Supplementary Information

Fe(II)-complexation of tripodal hexapeptide ligands with three bidentate triazolylpyridines: induction of metal-centred chirality by peptide macrocyclization

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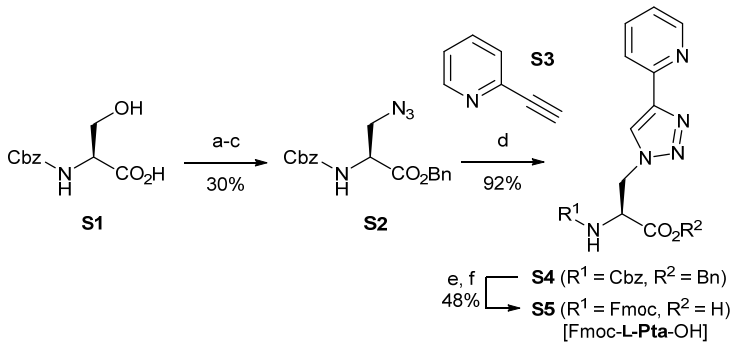
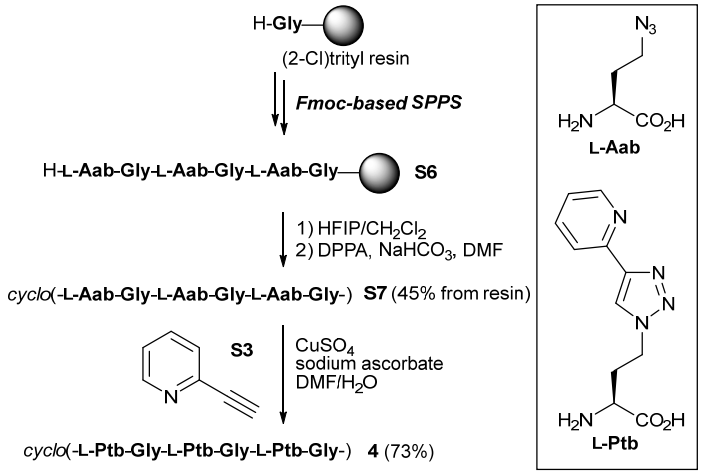
Experimental section

Synthesis. Initially, we prepared Fmoc-L-Pta-OH (**S5**) as a building block for triazolylpyridine-containing peptides (Scheme S1). A Mitsunobu reaction of Cbz-L-Ser-OH (**S1**) provided an α-amino-β-lactone intermediate, which was subjected to NaN_3-mediated nucleophilic ring opening to afford a L-β-azidoalanine derivative **S2**.[S1] Huisgen cycloaddition between azide **S2** and 2-ethynylpyridine **S3** led to the formation of the 2-(1*H*-1,2,3-triazol-4-yl)pyridine scaffold.[S2] Subsequent manipulations, including deprotection followed by Fmoc protection, provided the desired amino acid **S5**. Using this amino acid, we synthesised peptides **1** and **2** by standard Fmoc-based solid-phase peptide synthesis (SPPS) on (2-Cl)Trt resin followed by diphenylphosphoryl azide (DPPA)-mediated macrocyclization.[S3,S4] A reference open-chain peptide **2L** was also designed and synthesised in a similar manner on Novasyn TGR resin.



Scheme S1. Synthesis of Fmoc-protected pyridine-triazole-containing amino acid (Fmoc-L-Pta-OH, **S5**). *Reagents and conditions*: a) DEAD, Ph_3P, THF; b) NaN_3, DMF; c) BnBr, Et_3N; d) **6**, $CuSO_4$, sodium ascorbate, DMF/H_2O; e) H_2, Pd/C, THF; f) Fmoc-OSu, (^{i}Pr)$_2$NEt, MeCN/H_2O.

For the preparation of peptide **4**, the coupling of the Fmoc-protected L-Ptb by standard SPPS conditions failed. Therefore, we initially prepared the cyclic peptide scaffold using Fmoc-L-Aab-OH [L-Aab: (*S*)-2-amino-4-azidobutyric acid] (Scheme S2). After cleavage from (2-Cl)Trt resin and DPPA-mediated cyclisation, Huisgen cycloaddition of the azide groups in the cyclic hexapeptide **S7** with **S3** at the final step provided three triazolylpyridine moieties in peptide **4**.



Scheme S2. Synthesis of (*S*)-2-amino-4-[4-(pyridine-2-yl)-1,2,3-triazol-1-yl]butyric acid (L-Ptb)-containing cyclic hexapeptide (**4**).

Synthetic general method. ^{1}H NMR spectra were recorded using a JEOL ECA-500 spectrometer. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane or solvent residual peak (CH_3CN) as an internal standard. ^{13}C NMR spectra were referenced to the residual peak as an internal standard. Exact mass (HRMS) spectra were recorded on a JMS-700 mass spectrometer. The mass spectra of peptides and peptide-Fe(II) complexes were measured on AXIMA CFR plus (Shimadzu) and Quattro micro^{TM} API with ESCi Multi-mode ionization source (Waters). Optical rotations were measured with a JASCO P-1020 polarimeter. For column chromatography, Wakogel C-200E or C-300E (Wako) was employed. For analytical HPLC, a COSMOSIL 5C18-ARII column (4.6 × 250 mm, Nacalai Tesque Inc., Kyoto, Japan) was employed with a linear gradient of CH_3CN containing 0.1% (v/v) TFA at a flow rate of 1 cm^3 min^{-1}, and the eluting products were detected by UV at 220 or 254 nm. Preparative HPLC was performed using a COSMOSIL 5C18-ARII column (20 or 10 × 250 mm, Nacalai Tesque Inc.) with a linear gradient of CH_3CN containing 0.1 % (v/v) TFA at a flow rate of 8 or 4 cm^3 min^{-1}, respectively. For the analysis and purification of peptide **S7**, MeOH/H_2O were used as mobile phase of HPLC.

Benzyl (*S*)-3-azido-2-[*N*-(benzyloxycarbonyl)amino]propanoate (S2). To a solution of triphenylphosphine (Ph_3P, 12.1 g, 46.0 mmol) and diethyl azodicarboxylate (DEAD, 2.2 mol dm^{-3} in toluene, 20.9 cm^3, 46.0 mmol) in THF (100 cm^3), Cbz-L-Ser-OH (**S1**) (10 g, 41.8 mmol) in THF (100 cm^3) was added dropwise at 0 °C and this mixture was stirred for 4.5 hr at room temperature. After additional Ph_3P (2.19 g, 8.35 mmol) and DEAD (3.80 cm^3, 8.36 mmol) were added, the mixture was stirred for 2.5 hr. After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) to provide crude lactone. To a solution of lactone in DMF (209 cm^3),

NaN_3 (2.72 g, 41.8 mmol) was added. After the mixture was stirred for 9.75 hr at room temperature, benzyl bromide (BnBr, 14.9 cm^3, 125.4 mmol) and Et_3N (11.6 cm^3, 83.6 mmol) were added and the reaction was continued for 3 hr. Additional BnBr (5.0 cm^3, 41.8 mmol) was added and the mixture was stirred for 2.5 hr. After concentration, the residue was extracted with EtOAc, and the whole was washed with H_2O and brine, and dried over Na_2SO_4. Purification by column chromatography over silica gel with *n*-hexane–EtOAc (6:1) followed by recrystallization from *n*-hexane gave the azide **S2** as colorless fibrous crystals (4.34 g, 30% in 3 steps): mp 43–44°C; IR (neat) ν_{max}/cm^{-1}: 3329 (NH), 2106 (N_3) 1720 (C=O); $[\alpha]^{32}_D$ 12.5 (*c* 0.93, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.76 (2H, d, *J* 3.4), 4.58-4.55 (1H, m), 5.13 (2H, s), 5.22 (2H, s), 5.63 (1H, d, *J* 7.4), 7.39-7.30 (10H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.6, 54.0, 67.3, 67.9, 128.1 (2C), 128.3, 128.4 (2C), 128.6 (2C), 128.7 (3C), 134.8, 135.9, 155.6, 169.3; *Anal.* calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.81; found: C, 61.05; H, 5.14; N, 15.82.

Benzyl (*S*)-2-[*N*-(benzyloxycarbonyl)amino]-3-[4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl]propanoate (S4). To a solution of compound **S2** (3.51 g, 9.91 mmol), $CuSO_4$ pentahydrate (0.742 g, 2.97 mmol) and ascorbic acid sodium salt (1.18 g, 5.94 mmol) in DMF–H_2O (4:1, 110 cm^3), 2-ethynylpyridine (**S3**) (1.10 cm^3, 10.9 mmol) was added, and the mixture was stirred for 2 hr at room temperature. After concentration under reduced pressure, the residue was extracted with EtOAc. The whole was washed with 5% EDTA and H_2O, and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with *n*-hexane–EtOAc (1:1) to provide the triazole **S4** (4.18 g, 92%) as a colorless powder: mp 125-126°C (from $CHCl_3$-*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 3336 (NH), 1718 (C=O); $[\alpha]^{32}_D$ 16.4 (*c* 0.93, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.82-4.88 (2H, m), 4.92-5.00 (1H, m), 5.08-5.16 (2H, m), 5.16-5.24 (2H, m), 5.78 (1H, d, *J* 6.2), 7.23 (1H, ddd, *J* 8.0, 4.6, 1.1), 7.28-7.37 (10H, m), 7.77 (1H, ddd, *J* 8.0, 8.0, 1.7), 8.03 (1H, s), 8.13 (1H, d, *J* 8.0), 8.58 (1H, d, *J* 4.6); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 51.0, 54.2, 67.4, 68.3, 120.2, 122.9, 123.3, 128.0 (2C), 128.3, 128.5 (2C), 128.66 (2C), 128.70 (3C), 134.5, 135.8, 136.8, 148.4, 149.4, 149.9, 155.7, 168.5; *Anal*. calcd for $C_{25}H_{23}N_5O_4$: C, 65.64; H, 5.07; N, 15.31; found: C, 65.49; H, 5.14; N, 15.28.

(*S*)-2-{*N*-[(9*H*-Fluoren-9-yl)methoxycarbonyl]amino}-3-[4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl]propanoic acid (Fmoc-L-Pta-OH, S5). Compound **S4** (4.00 g, 8.74 mmol) was treated with 10% Pd/C (1.74 g) in THF (44.0 cm^3) under H_2 atmosphere at room temperature, and the mixture was stirred for 7 hr. 1N HCl (10.0 cm^3) was added to the mixture, and then the Pd/C was removed by filtration. After concentration under reduced pressure, the residue was dissolved in MeCN–H_2O (1:1, 174 cm^3)

and adjusted to pH 8 by (^{i}Pr)$_2$EtN (5.35 cm^3, 31.5 mmol). Fmoc-OSu (3.24 g, 9.62 mmol) in MeCN (117 cm^3) was added and the mixture was stirred for 2 hr. The reaction mixture was acidified with 1N HCl to pH 2. After concentration under reduced pressure, the residue was extracted with EtOAc and washed with 1N HCl and H_2O, and dried over Na_2SO_4. After concentration under reduced pressure, the residue was purified by column chromatography over silica gel with $CHCl_3$–MeOH–AcOH (10:0:0 to 9:1:0.5) followed by recrystallization from Et_2O to provide the acid **S5** (1.90g, ca. 48%) as a colorless powder: mp. 192–194 °C; IR (neat) ν_{max}/cm^{-1}: 3308 (NH), 1721 (C=O); $[\alpha]^{26}_D$ –28.4 (*c* 0.80, DMSO); ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 4.13-4.29 (3H, m), 4.55-4.64 (1H, m), 4.72 (1H, dd, *J* 13.7, 9.6), 4.89 (1H, dd, *J* 13.7, 4.3), 7.20-7.46 (5H, m), 7.62 (2H, dd, *J* 18.5, 7.5), 7.83-7.96 (4H, m), 8.03 (1H, d, *J* 8.1), 8.53-8.65 (2H, m), 13.34 (1H, br s); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 46.5, 49.7, 54.2, 65.8, 119.3, 120.1 (2C), 122.9, 123.9, 125.1, 125.2, 127.0 (2C), 127.6 (2C), 137.2, 140.6 (2C), 143.6 (2C), 147.1, 149.6, 149.9, 155.8, 170.7; HRMS (FAB): *m/z* calcd for $C_{25}H_{22}N_5O_4$ $[M + H]^+$ 456.1666; found: 456.1659.

2-(1-Methyl-*1H*-1,2,3-triazol-4-yl)pyridine (3). According to the reported procedure,[S5] the triazole (**3**) was obtained as colorless fibrous crystals in 38% yield: mp. 108-109 °C (EtOAc-*n*-hexane); IR (neat) 3142 (aromatic CH), 1603, 1571 (aromatic C=C, C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.17 (3H, s), 7.23 (1H, ddd, *J* 7.7, 5.1, 1.1), 7.78 (1H, ddd, *J* 8.0, 7.7, 1.7), 8.12 (1H, s), 8.15-8.19 (1H, m), 8.57-8.60 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 36.8, 120.2, 122.8, 122.9, 136.9, 148.7, 149.4, 150.2; *Anal*. calcd for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98; found: C, 59.73; H,5.02; N, 34.92.

***cyclo*(-L-Pta-L-Pta-L-Pta-Gly-Gly-Gly-) (1).** The linear peptide resin was constructed by Fmoc-based solid-phase synthesis on H-Gly-(2-Cl)Trt resin (0.89 mmol g^{-1}, 112.4 mg, 0.10 mmol). Fmoc-Gly-OH (0.50 mmol) and Fmoc-L-Pta-OH (0.30 mmol) were coupled using DIC-HOBt (equivalent of Fmoc-amino acid) in DMF. Completion of each coupling reaction was ascertained using the Kaiser ninhydrin test. The Fmoc-protecting group was removed by treating the resin with 20% piperidine in DMF for 20 min. The resulting protected peptide resin was subjected to HFIP–CH_2Cl_2 (2:8, 20 cm^3) treatment at room temperature for 2 hr. After filtration of the residual resin, the filtrate was concentrated under reduced pressure to give a crude linear peptide. To a mixture of the resulting linear peptide in DMF (100 cm^3), DPPA (0.053 cm^3, 0.25 mmol) and $NaHCO_3$ (42.0 mg, 0.50 mmol) were added at –40 °C. The mixture was stirred for 0.5 hr at this temperature and for 19 hr with warming to room temperature. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC to afford the title compound as colorless freeze-dried powder (26.3 mg, 23% from H-Gly-(2-Cl)Trt resin): $[\alpha]^{28}_D$ –59.6 (*c* 0.11, DMSO); ^{1}H-NMR (DMSO-d_6) δ: 3.49-

3.63 (2H, m), 3.67 (1H, dd, *J* 16.6, 5.2), 3.73 (1H, dd, *J* 16.0, 5.7), 3.83 (1H, dd, *J* 16.6, 6.3), 3.97 (1H, dd, *J* 16.3, 6.6), 4.62-4.97 (8H, m), 5.04 (1H, dd, *J* 14.0, 4.3), 7.39-7.47 (3H, m), 7.94-8.14 (8H, m), 8.51 (1H, d, *J* 8.0), 8.57 (1H, d, *J* 6.9), 8.59-8.66 (5H, m), 8.69-8.75 (2H, m), 8.76 (1H, s); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 42.3 (2C), 43.0, 49.8 (2C), 50.0, 53.7, 54.0, 54.2, 120.0, 120.07, 120.15, 123.3, 123.4 (2C), 124.3, 124.5, 124.8, 138.3, 138.5, 138.6, 146.10, 146.15, 146.3, 148.5, 148.6, 148.7, 148.9 (2C), 149.0, 168.6, 168.77, 168.84, 169.2, 169.3, 169.5; MALDI-TOFMS: *m/z* calcd for $C_{36}H_{37}N_{18}O_6$ $[M + H]^+$ 817.31; found: 817.30.

***cyclo*(-L-Pta-Gly-L-Pta-Gly-L-Pta-Gly-) (2).** By the identical procedure for the synthesis of peptide **1**, peptide **2** was obtained as colorless freeze-dried powder (15.6 mg, 13% from H-Gly-(2-Cl)Trt resin): $[\alpha]^{27}_D$ –66.9 (*c* 0.11, DMSO); ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 3.52 (3H, dd, *J* 16.6, 3.4), 3.96 (3H, dd, *J* 16.6, 6.9), 4.76-4.82 (3H, m), 4.82-4.90 (3H, m), 4.99 (3H, dd, *J* 14.3, 4.0), 7.40 (3H, dd, *J* 7.6, 4.6), 7.98 (3H, ddd, *J* 7.6, 7.6, 1.1), 8.10 (3H, d, *J* 7.6), 8.35 (3H, d, *J* 7.4), 8.39-8.41 (3H, m), 8.54 (3H, s), 8.62 (3H, d, *J* 4.6); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 42.7 (3C), 49.8 (3C), 52.8 (3C), 120.0 (3C), 123.3 (3C), 124.6 (3C), 138.4 (3C), 146.1 (3C), 148.7 (3C), 149.0 (3C), 168.9 (3C), 169.4 (3C); ^{1}H-NMR [500 MHz, D_2O/CD_3CN (1:1)] δ: 3.67 (3H, d, *J* 17.5), 4.09 (3H, d, *J* 17.5), 4.97 (9H, br s), 7.59 (3H, ddd, *J* 7.4, 5.5, 1.7), 8.15-8.25 (6H, m), 8.48 (3H, s), 8.57 (3H, d, *J* 5.5); ^{13}C-NMR [125 MHz, D_2O/CD_3CN (1:1)] δ: 42.2 (3C), 49.6 (3C), 52.4 (3C), 122.1 (3C), 124.6 (3C), 125.8 (3C), 142.3 (3C), 143.0 (3C), 145.3 (3C), 145.5 (3C), 169.8 (3C), 170.5 (3C); MALDI-TOFMS: *m/z* calcd for $C_{36}H_{37}N_{18}O_6$ $[M + H]^+$ 817.31; found: 817.26.

Fe(II)-*cyclo*(-L-Pta-Gly-L-Pta-Gly-L-Pta-Gly-) [Fe(II)-2]. Peptide **2** (1.35 mg) and $FeSO_4 \cdot 7H_2O$ (0.387 mg, 1.2 eq.) were dissolved in D_2O/CD_3CN (1:1). ^{1}H-NMR [500 MHz, D_2O/CD_3CN (1:1)] δ: 3.65 (3H, d, *J* 17.2), 4.38 (3H, d, *J* 14.7), 4.49 (3H, d, *J* 17.2), 5.21 (3H, dd, *J* 14.7, 4.6), 5.39-5.50 (3H, m), 7.31-7.42 (6H, m), 8.08 (3H, ddd, *J* 7.8, 7.8, 1.2), 8.21 (3H, d, *J* 7.8), 8.91 (3H, s).; ^{13}C-NMR [125 MHz, D_2O/CD_3CN (1:1)] δ: 42.8 (3C), 51.0 (3C), 52.3 (3C), 122.0 (3C), 125.7 (3C), 127.8 (3C), 139.0 (3C), 148.8 (3C), 152.1 (3C), 153.9 (3C), 169.3 (3C), 170.5 (3C).

Ac-L-Pta-Gly-L-Pta-Gly-L-Pta-Gly-NH_2 (2L). The peptide resin was constructed by Fmoc-based solid-phase synthesis on NovaSyn TGR resin (0.21 mmol g^{-1}, 384.6 mg, 0.10 mmol) by the identical procedure for the synthesis of peptide **1**. The resin was subjected to *N*-terminus acetylation using acetic anhydride (0.0951 cm^3, 1.0 mmol) and pyridine (0.0806 cm^3, 1.0 mmol). The resin was treated with TFA/triisopropylsilane/H_2O (95:2.5:2.5, 4.0 cm^3) at room temperature for 2 hr. After filtration of the residual resin, the filtrate was poured into ice-cold-Et_2O. The precipitation was washed with ice-cold

Et_2O three times. HPLC purification gave the linear peptide **2L** as white freeze-dried powder. (48.7 mg, 32% from NovaSyn TGR resin): $[\alpha]^{27}_D$ –2.25 (*c* 0.11, DMSO); ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 1.79 (3H, s), 3.64-3.77 (4H, m), 3.77-3.86 (2H, m), 4.54-4.73 (3H, m), 4.76-4.95 (6H, m), 7.15 (1H, s), 7.29 (1H, s), 7.38-7.43 (3H, m), 7.95-8.01 (3H, m), 8.05-8.10 (3H, m), 8.37 (1H, d, *J* 8.0), 8.41-8.49 (4H, m), 8.54 (1H, t, *J* 5.7), 8.56 (1H, s), 8.59 (1H, s), 8.59-8.63 (4H, m); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 22.5, 42.1, 42.15, 42.22, 50.60, 50.64 (2C), 52.68, 52.75, 52.8, 119.9, 120.05, 120.07, 123.3 (3C), 124.3, 124.5 (2C), 138.3, 138.48, 138.53, 145.87, 145.94, 146.0, 148.5, 148.6, 148.7, 148.88, 148.94, 149.0, 168.5, 168.7, 168.9, 169.01, 169.03, 169.9, 170.5; ^{1}H-NMR [500 MHz, D_2O/CD_3CN (1:1)] δ: 1.91 (3H, s), 3.79-3.98 (6H, m), 4.77-5.05 (9H, m), 7.77-7.86 (3H, m), 8.22-8.32 (3H, m), 8.38-8.48 (3H, m), 8.62-8.74 (6H, m); ^{13}C-NMR [125 MHz, D_2O/CD_3CN (1:1)] δ: 21.6, 41.8, 42.3 (2C), 50.2, 50.3, 50.4, 52.6 (3C), 123.1 (2C), 123.3, 125.2 (3C), 126.3, 126.5, 126.6, 140.6, 140.8 (2C), 142.8, 143.1 (2C), 143.6, 143.8 (2C), 144.8, 144.9, 145.1, 169.3, 169.6, 169.9, 170.6, 170.7, 172.9, 173.2; MALDI-TOFMS: *m/z* calcd for $C_{38}H_{42}N_{19}O_7$ $[M + H]^+$ 876.35; found: 876.28.

***cyclo*(-L-Aab-Gly-L-Aab-Gly-L-Aab-Gly-) (S7).** By the identical procedure for the synthesis of peptide **1**, the peptide **S7** was obtained using Fmoc-L-Aab-OH as a colorless freeze-dried powder (49.6 mg, 45% from H-Gly-(2-Cl)Trt resin): $[\alpha]^{28}_D$ –54.2 (*c* 0.12, DMSO); ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 1.80-1.90 (3H, m), 2.00-2.11 (3H, m), 3.27-3.44 (6H, m), 3.62 (3H, dd, *J* 16.4, 5.4), 3.88 (3H, dd, *J* 16.4, 5.7), 4.18-4.26 (3H, m), 8.13 (3H, d, *J* 7.4), 8.19 (3H, dd, *J* 5.4, 5.7); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 29.9 (3C), 42.8 (3C), 47.5 (3C), 50.4 (3C), 169.1 (3C), 171.0 (3C); MALDI-TOFMS: *m/z* calcd for $C_{18}H_{27}N_{15}NaO_6$ $[M + Na]^+$ 572.21; found: 572.13.

***cyclo*(-L-Ptb-Gly-L-Ptb-Gly-L-Ptb-Gly-) (4).** To a solution of peptide **S7** (30.4 mg, 55.3 μmol), $CuSO_4 \cdot 5H_2O$ (13.8 mg, 55.3 μmol) and sodium L-ascorbate (22.0 mg, 111 μmol) in DMF/H_2O (4:1, 1.84 cm^3), was added 2-ethynylpyridine (0.0336 cm^3, 332 μmol). The mixture was stirred for 22 hr at room temperature. HPLC purification provided the L-Ptb-containing peptide **4** as a pale yellow freeze-dried powder (48.3 mg, 73%): $[\alpha]^{25}_D$ –34.1 (*c* 0.95, MeOH); ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 2.19-2.30 (3H, m), 2.49-2.58 (3H, m), 3.63 (3H, dd, *J* 16.0, 5.1), 3.98 (3H, dd, *J* 16.0, 5.1), 4.13-4.24 (3H, m), 4.42-4.56 (6H, m), 7.36-7.48 (3H, m), 7.95-8.04 (3H, m), 8.04-8.13 (3H, m), 8.21 (3H, dd, *J* 5.1, 5.1), 8.31 (3H, d, *J* 7.4), 8.60-8.65 (3H, m), 8.67 (3H, s); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 31.3 (3C), 42.9 (3C), 46.7 (3C), 50.2 (3C), 120.0 (3C), 123.3 (3C), 124.0 (3C), 138.5 (3C), 146.0 (3C), 148.6 (3C), 149.0 (3C), 169.3 (3C), 170.8 (3C); MALDI-TOFMS: *m/z* calcd for $C_{39}H_{43}N_{18}O_6$ $[M + H]^+$ 859.36; found: 859.37.

CD spectra. CD spectra were recorded on a JASCO J-720 circular dichroism spectrometer at 20 °C. Peptide and $FeSO_4$ (0.2 mM each) were dissolved in MeCN/H_2O (1:1).

^{1}H-DOSY spectra. ^{1}H-DOSY experiments were perfomed on a Bruker Avance I 600 spectrometer using a standerd stimulated echo pulse sequence with biopolar gradient pulses at 25 °C. The pseudo-2D spectra were analyzed by a DOSY analysis module integrated in a topspin 2.1 software.

UV-vis spectra. UV-vis spectra were recorded on a Shimadzu UV-2450 UV-vis spectrophotometer at room temprature. Peptide (0.125 mM) and $FeSO_4$ (0.125 mM) were dissolved in MeCN/H_2O (1:1). To obtain the Job's plot of peptide **2** and Fe(II), peptide and $FeSO_4$ (0.2 mM total concentration) were dissolved in H_2O. Absorbance at 420 nm was recorded at room temperature.

Isothermal titration calorimetry (ITC). ITC experiments were carried out on Microcal Auto-iTC200 at 25 °C and the data were analysed using Origin 7.0. Each ligand in 50 mM MES buffer (pH 6.0) was titrated with $FeSO_4 \cdot 7H_2O$ in H_2O. As a control experiment, 50 mM MES buffer solution without peptide was titrated with $FeSO_4$ solution to exclude the possible background heat by dilution.

Reference

S1 L. D. Arnold, R. G. May and J. C. Vederas, *J. Am. Chem. Soc.*, 1988, **110**, 2237–2241.

S2 S. S. Bag, S. Jana and M. K. Pradhan, *Bioorg. Med. Chem.*, 2016, **24**, 3579–3595.

S3 K. Kobayashi, S. Oishi, Y. Kobayashi, H. Ohno, H. Tsutsumi, Y. Hata and N. Fujii, *Bioorg. Med. Chem.*, 2012, **20**, 2651–2655.

S4 Y. Kobayashi, S. Oishi, K. Kobayashi, H. Ohno, H. Tsutsumi, Y. Hata and N. Fujii, *Bioorg. Med. Chem.,* 2013, **21**, 4296–4300.

S5 S. D. Gabriel and A. Thomas, PCT Int. Appl. 2012, WO 2012062623 A1.

Fig. S1. Job's plot of peptide **2** with Fe(II) in H_2O at room temperature at 420 nm absorption.

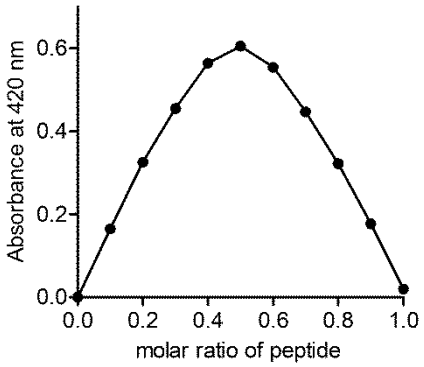
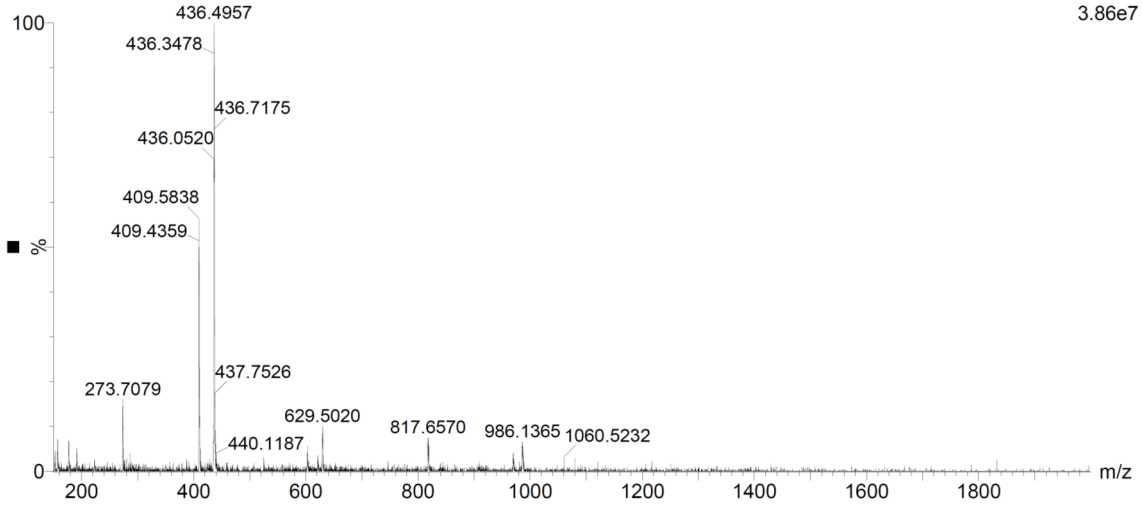


Fig. S2. Mass spectra of Fe(II)–**2** (a) and Fe(II)–**2L** (b) complexes.

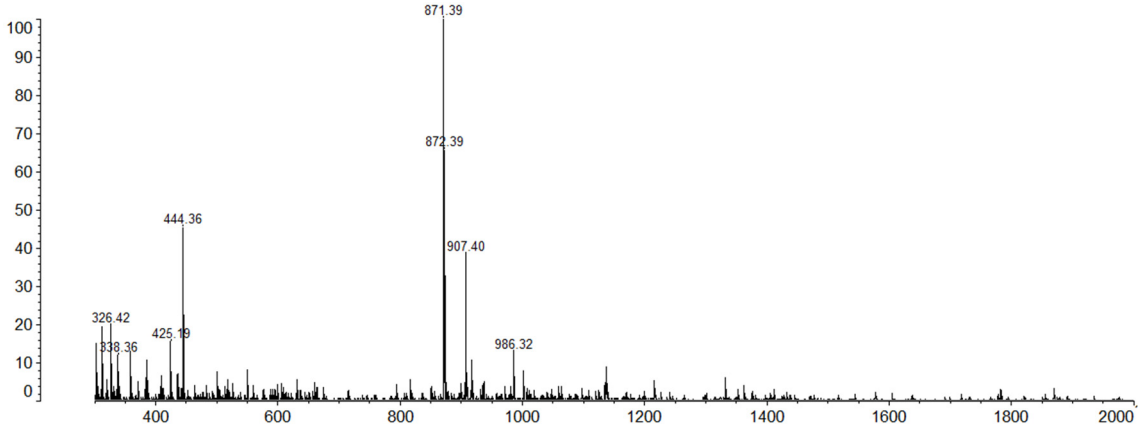
(a)

ESI-MS spectrum of Fe(II)–**2**



In the electrospray ionisation mass spectroscopy (ESI-MS) analysis, an *m/z* value of $[M+Fe]^{2+}$ (436.5) was detected.

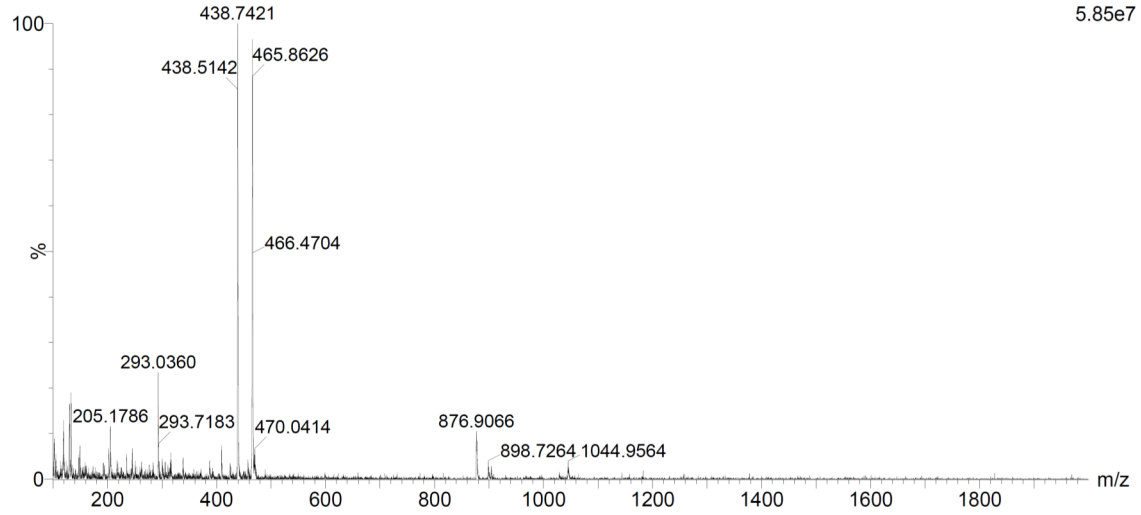
MALDI TOF-MS spectrum of Fe(II)–**2**



Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOFMS) analysis also suggested the presence of the complex as a $[M+Fe-H]^{+}$ ion (871.39).

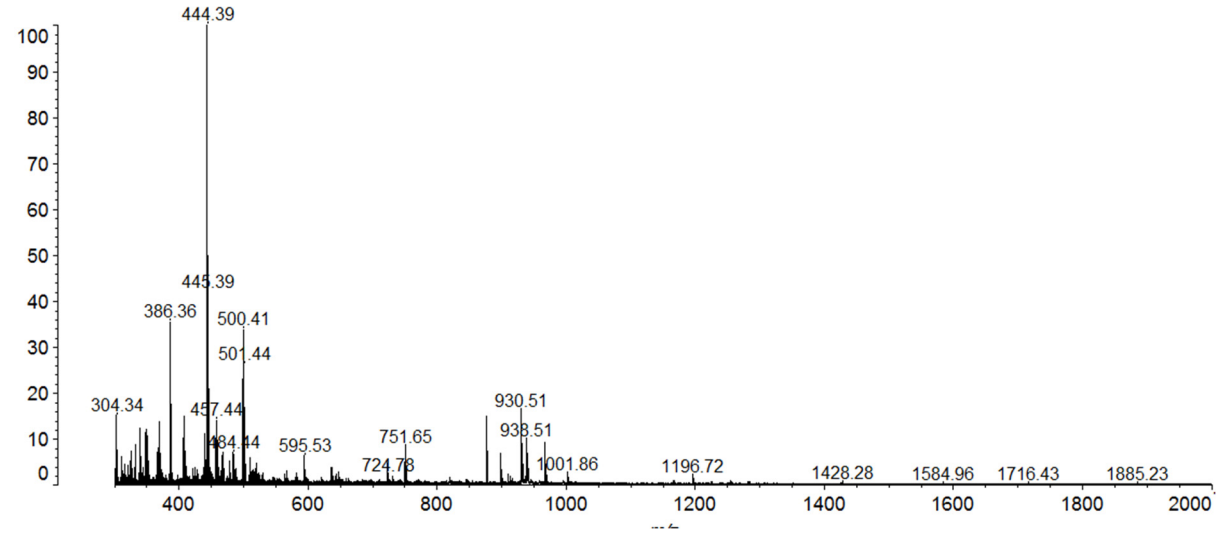
(b)

ESI-MS spectrum of Fe(II)–**2L**



In ESI-MS analysis, an *m/z* value of $[M+Fe]^{2+}$ (465.6) was detected.

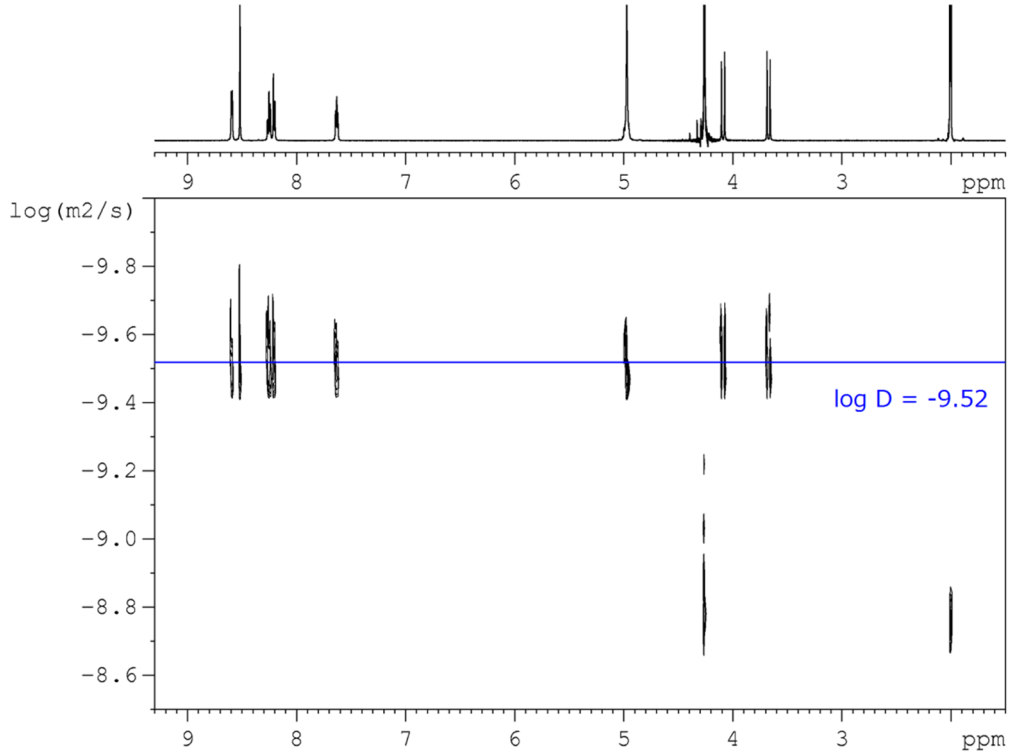
MALDI TOF-MS spectrum of Fe(II)–**2L**



In MALDI-TOFMS analysis, an *m/z* value of $[M+Fe-H]^{+}$ ion (930.51) was detected as a minor peak.

Fig. S3. ^{1}H-DOSY spectra of peptide **2** (a) and its Fe(II) complex (b) in D_2O/CD_3CN (1:1).

(a)



(b)

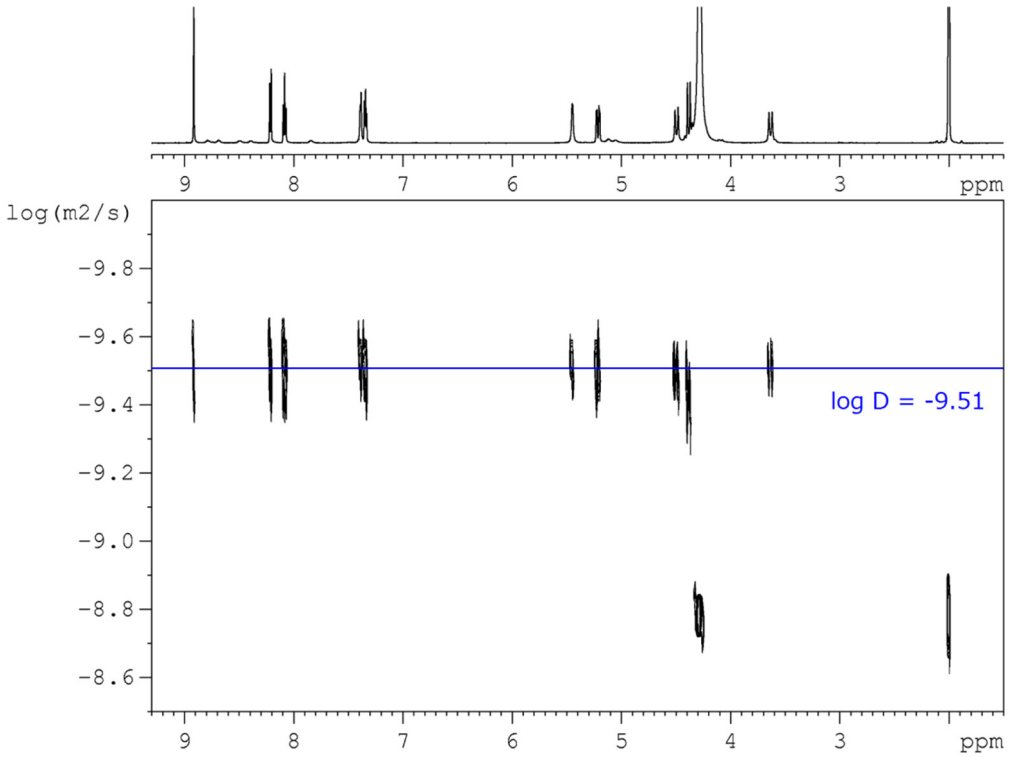


Fig. S4. ^{1}H-NMR spectra of L-Pta-containing peptide **2L** (a) and its Fe(II) complex (b) in D_2O/CD_3CN (1:1).

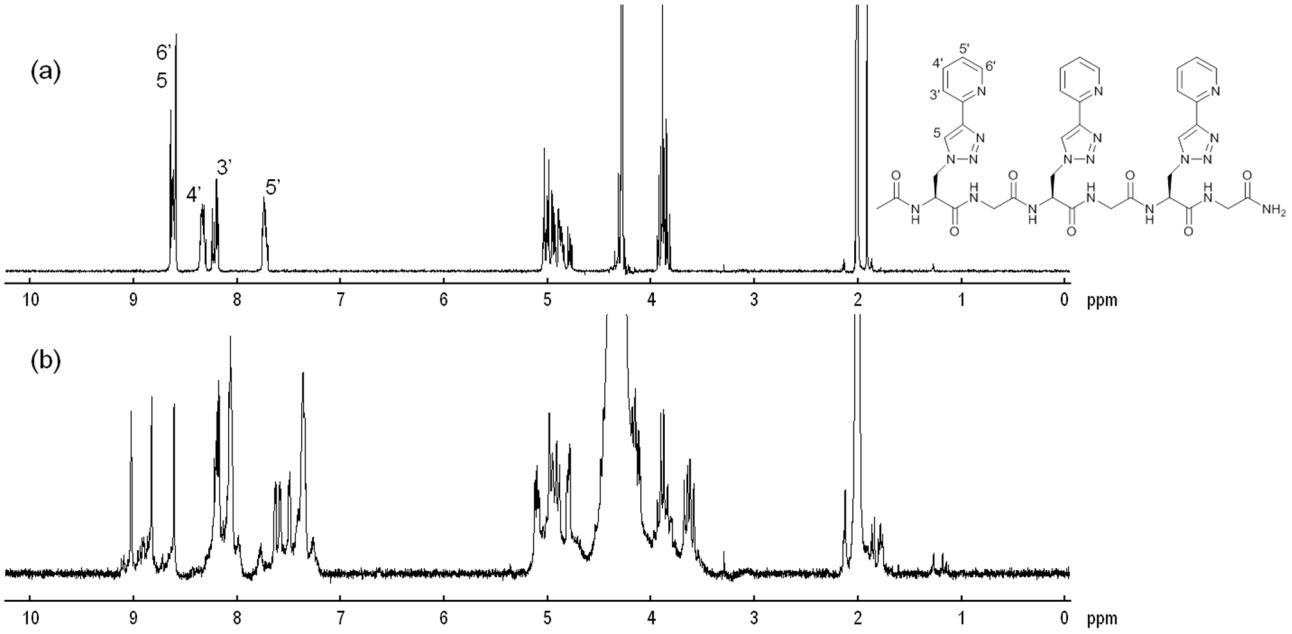
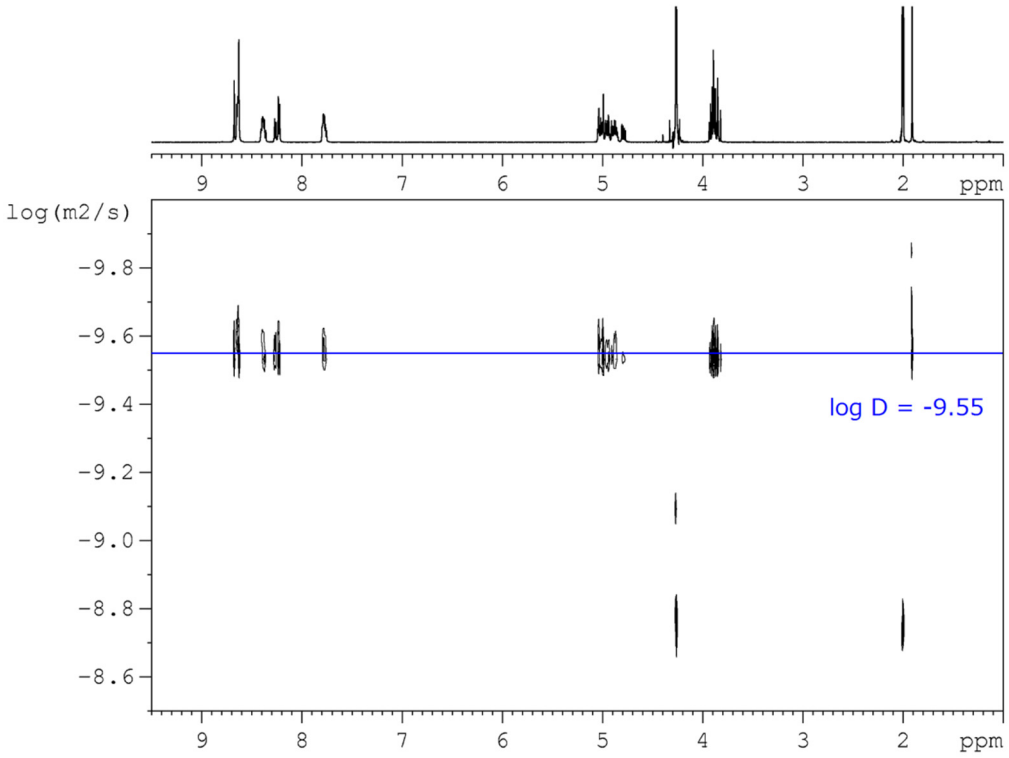


Fig. S5. DOSY spectra of peptide **2L** (a) and its Fe(II) complex (b) in D_2O/CD_3CN (1:1).

(a)



(b)

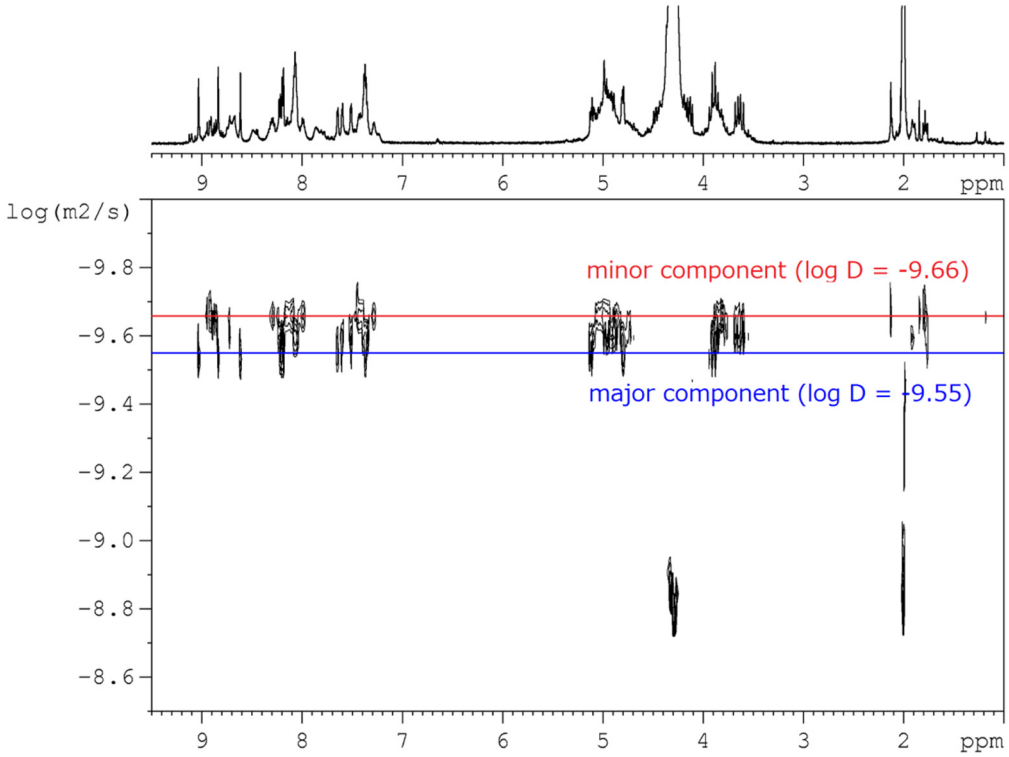


Fig. S6. Spectral data of L-Ptb-containing peptide Fe(II)–**4** complex. UV-vis absorption spectra (a); and CD spectra (b).

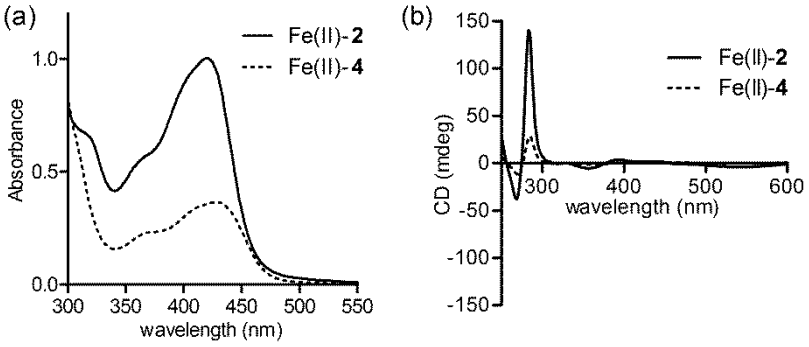


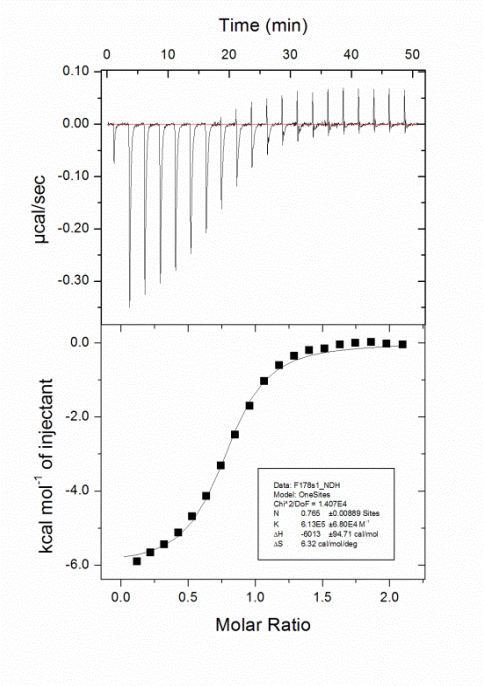
Table S1. The affinity between peptides and Fe(II), and ITC conditions.

Compound [a]	K_a (M^{-1})	K_d (M)	ligand conc (mM)	Fe(II) conc (mM)
2	6.13×10^{5}	1.6×10^{-6}	0.05	0.5
2L	1.41×10^{6}	7.1×10^{-7}	0.045	0.45
4	2.23×10^{4}	4.5×10^{-5}	0.1	4.0

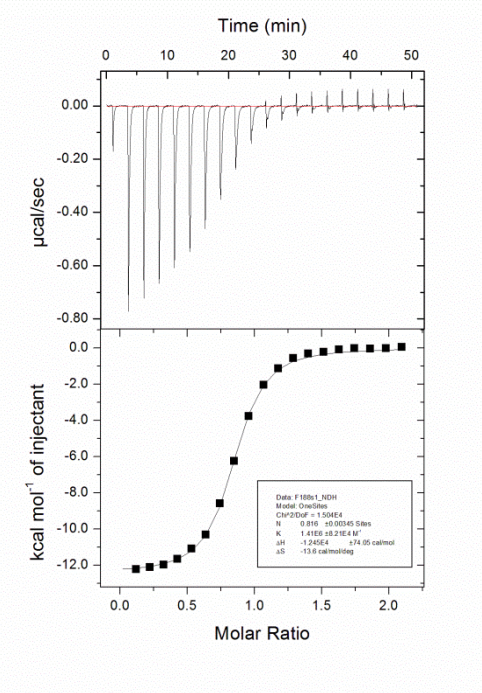
[a] The data of peptide **1** were not obtained because of the low solubility in MES buffer.

Fig. S7. ITC data and titration curves.

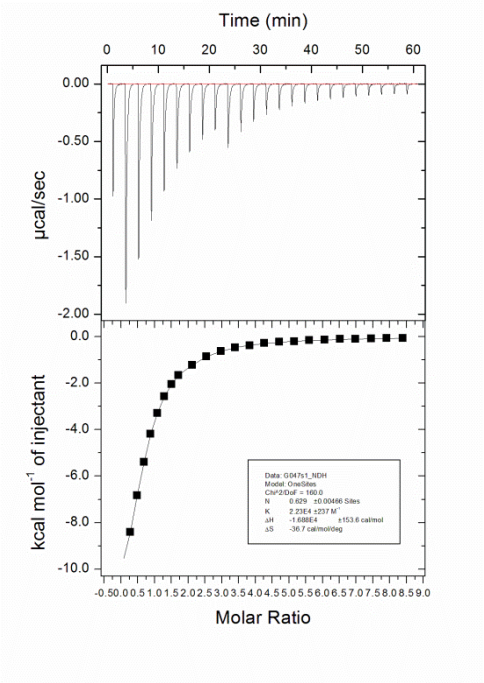
Peptide **2**

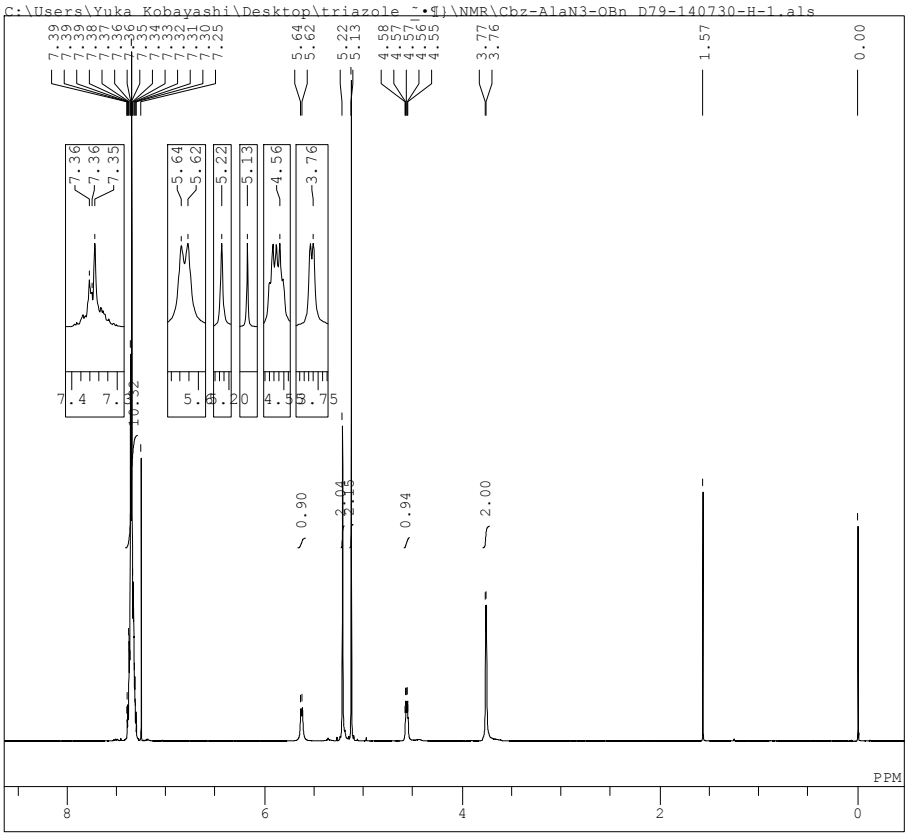


Peptide **2L**



Peptide **4**





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DATIM 2014-07-30 16:21:56
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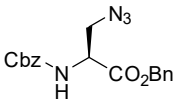
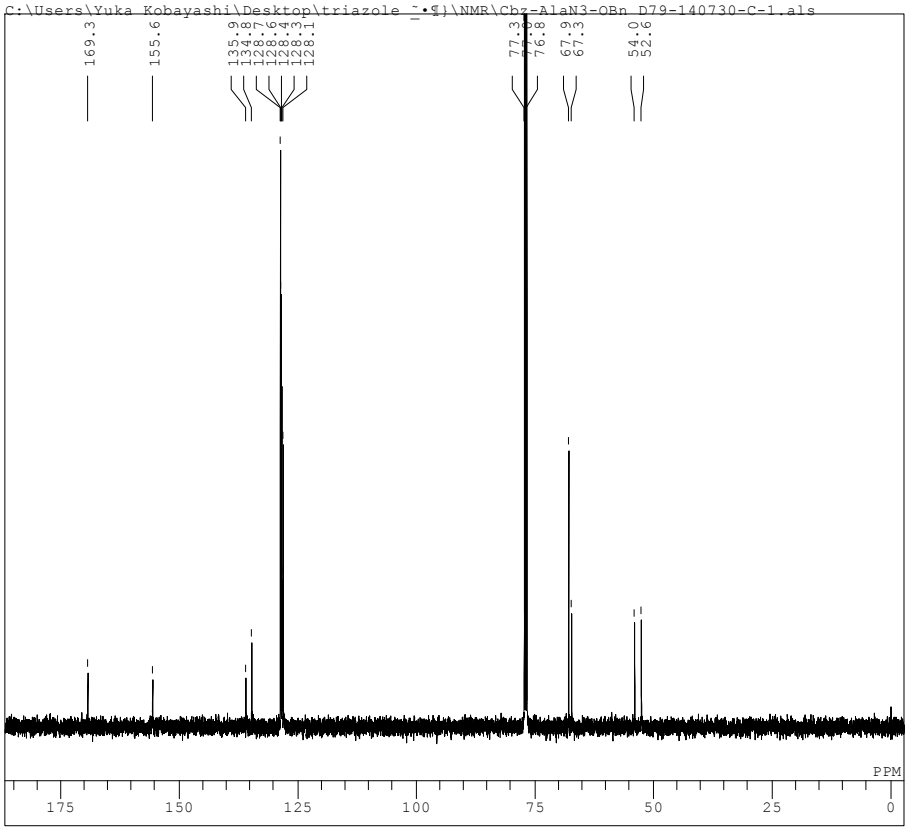
EXMOD single_pulse.ex2
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.39 Hz
SCANS 16
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.82 usec
IRNUC 1H
CTEMP 25.2 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 44



S2



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EXMOD single_pulse_dec
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.06 Hz
SCANS 512
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.50 usec
IRNUC 1H
CTEMP 24.9 c
SLVNT CDCL3
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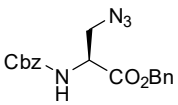
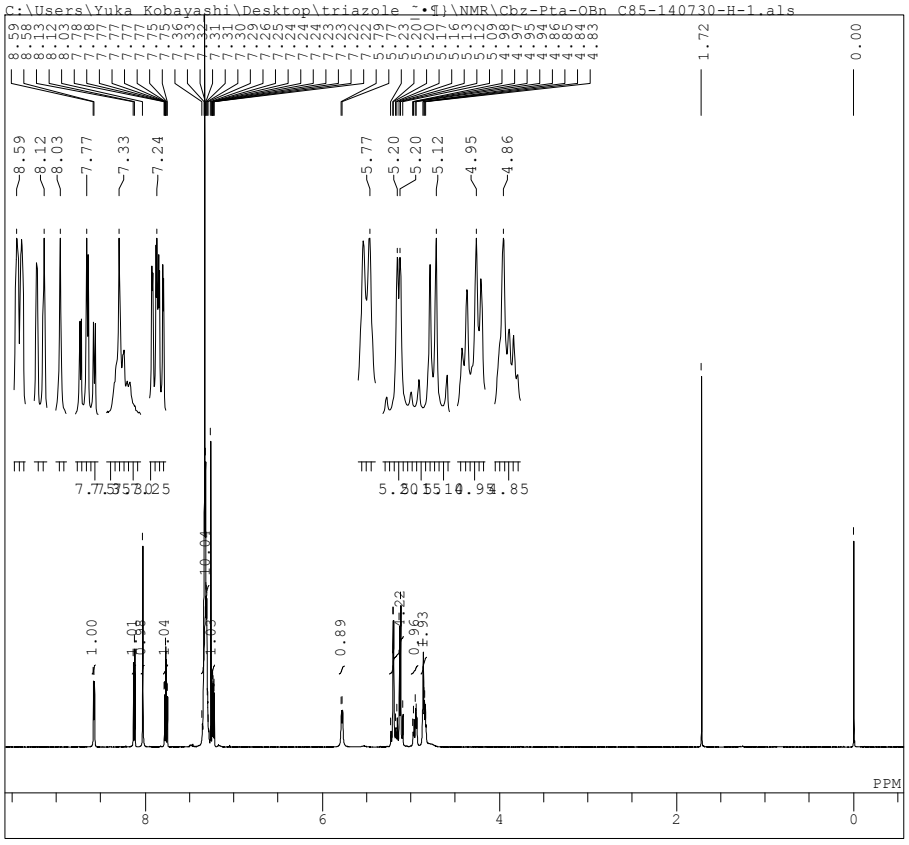
BF 1.20 Hz
RGAIN 52



S2

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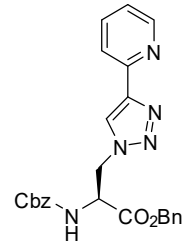
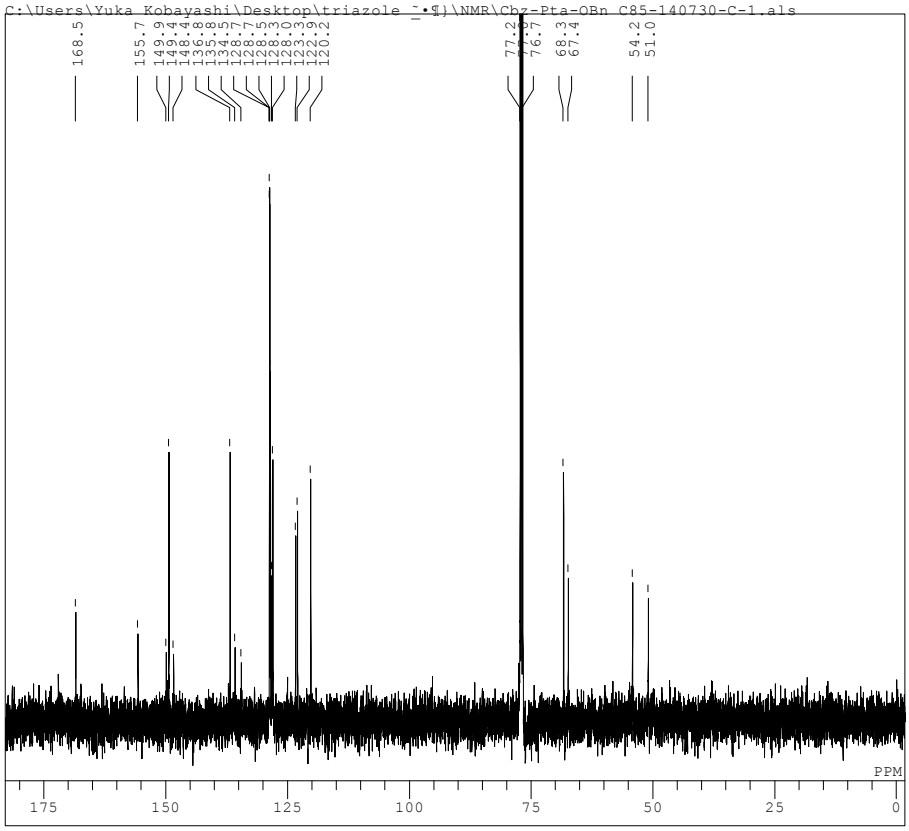
COMNT single pulse
DATIM 2014-07-30 18:22:10
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         13107
FREQU       7507.39 Hz
SCANS            16
ACQTM        1.7459 sec
PD           5.0000 sec
PW1             6.82 usec
IRNUC 1H
CTEMP          24.0 c
SLVNT CDCL3
EXREF           0.00 ppm
BF              0.12 Hz
RGAIN             44
```



S4

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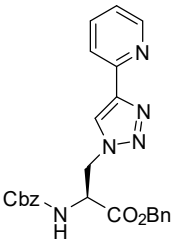
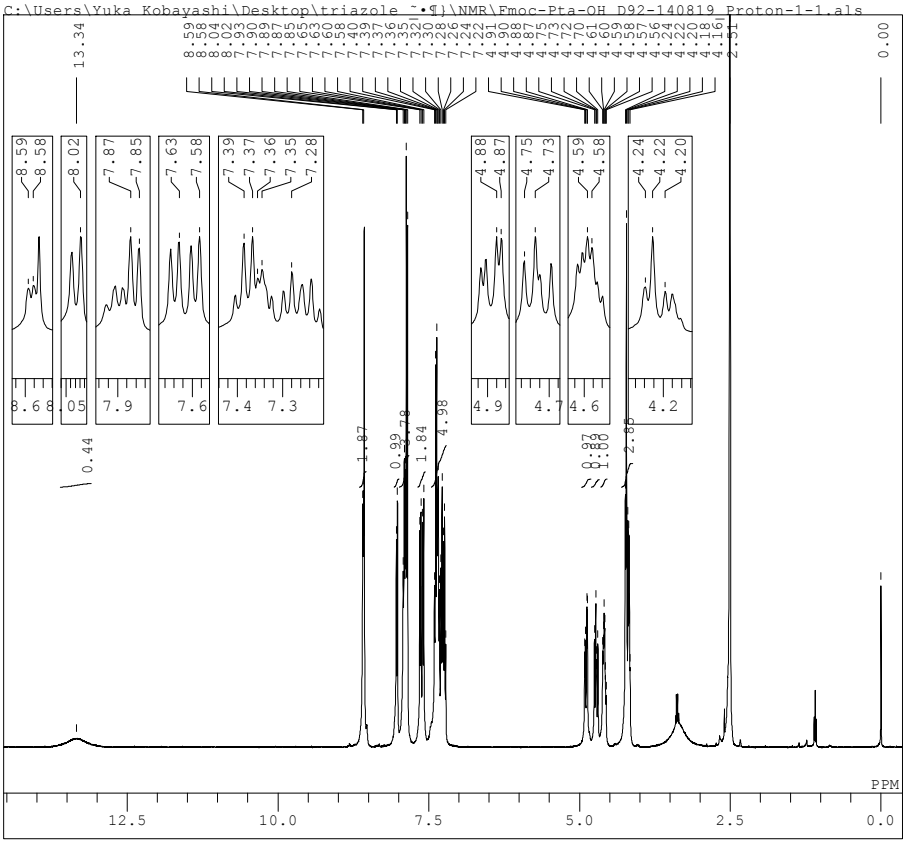
OBSET          7.87 KHz
OBFIN          4.21 Hz
POINT         26214
FREQU      31446.06 Hz
SCANS            300
ACQTM        0.8336 sec
PD           2.0000 sec
PW1             3.50 usec
IRNUC 1H
CTEMP          24.3 c
SLVNT CDCL3
EXREF          77.00 ppm
BF              1.20 Hz
RGAIN             54
```



S4

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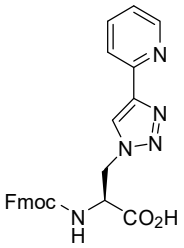
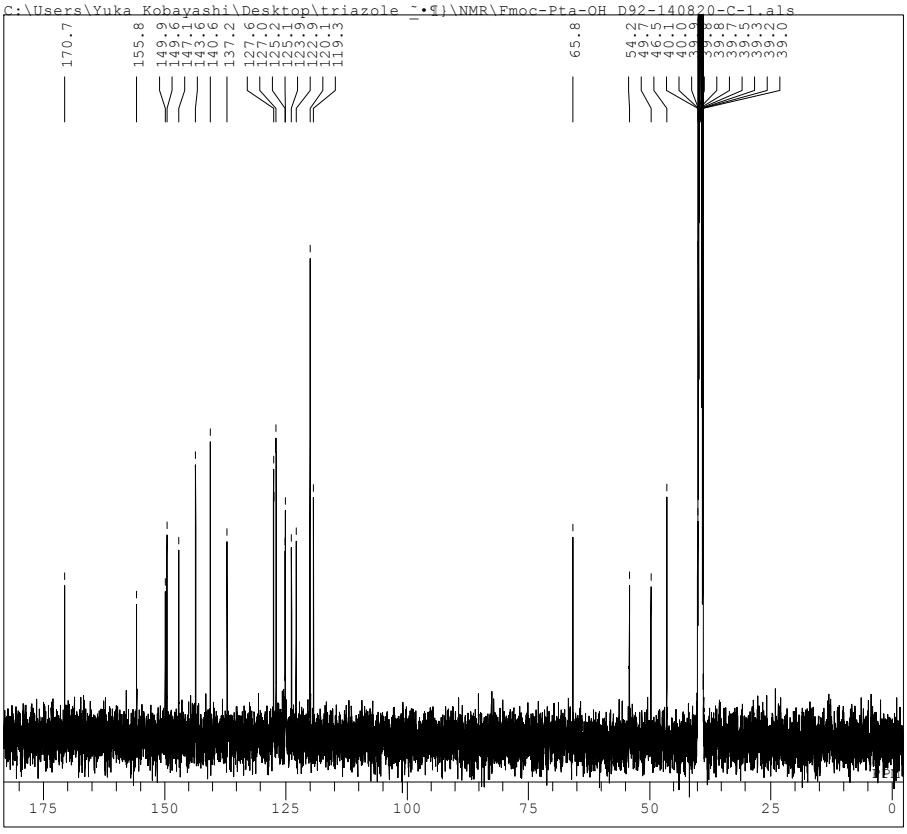
COMNT single pulse
DATIM 2014-08-19 15:04:46
OBNUC 1H
EXMOD proton.jxp
OBFRQ       399.78 MHz
OBSET         4.19 KHz
OBFIN         7.29 Hz
POINT        13107
FREQU      7598.78 Hz
SCANS            8
ACQTM       1.7249 sec
PD          5.0000 sec
PW1           3.06 usec
IRNUC 1H
CTEMP         22.8 c
SLVNT DMSO
EXREF         0.00 ppm
BF            0.12 Hz
RGAIN           34
```



Fmoc-Pta-OH (**S5**)

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EXMOD single_pulse_dec
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OBSET         7.87 KHz
OBFIN         4.21 Hz
POINT        26214
FREQU      31446.06 Hz
SCANS          600
ACQTM       0.8336 sec
PD          2.0000 sec
PW1           3.50 usec
IRNUC 1H
CTEMP         24.2 c
SLVNT DMSO
EXREF        39.50 ppm
BF            1.20 Hz
RGAIN           56
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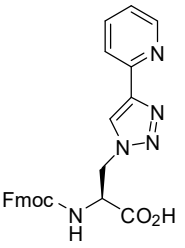
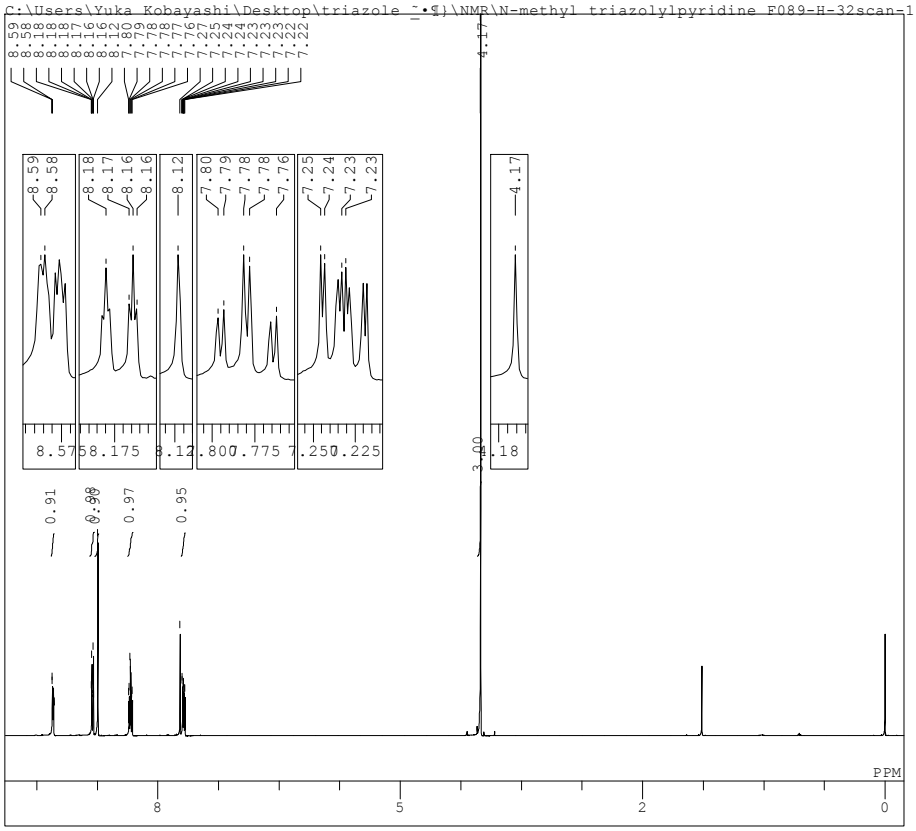


Fmoc-Pta-OH (**S5**)



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OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.39 Hz
SCANS 32
ACQTM 1.7459 sec
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IRNUC 1H
CTEMP 21.0 c
SLVNT CDCL3
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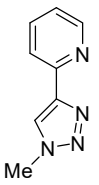
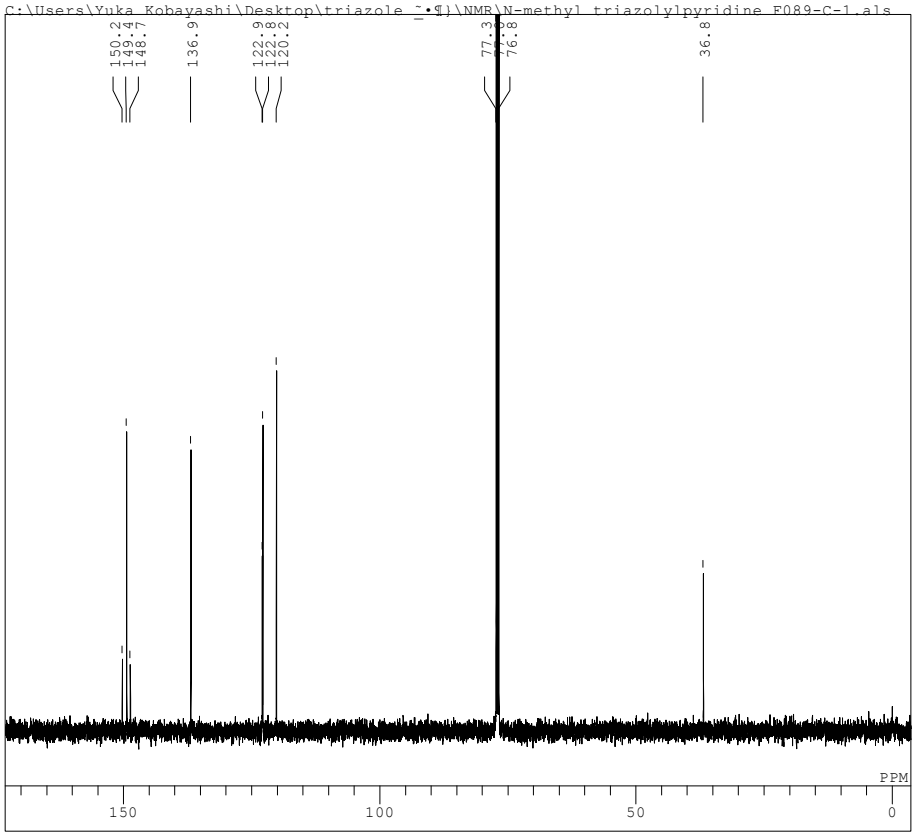
BF 0.12 Hz
RGAIN 46



3



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OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.06 Hz
SCANS 400
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PD 2.0000 sec
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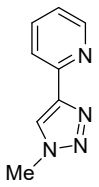
RGAIN 54



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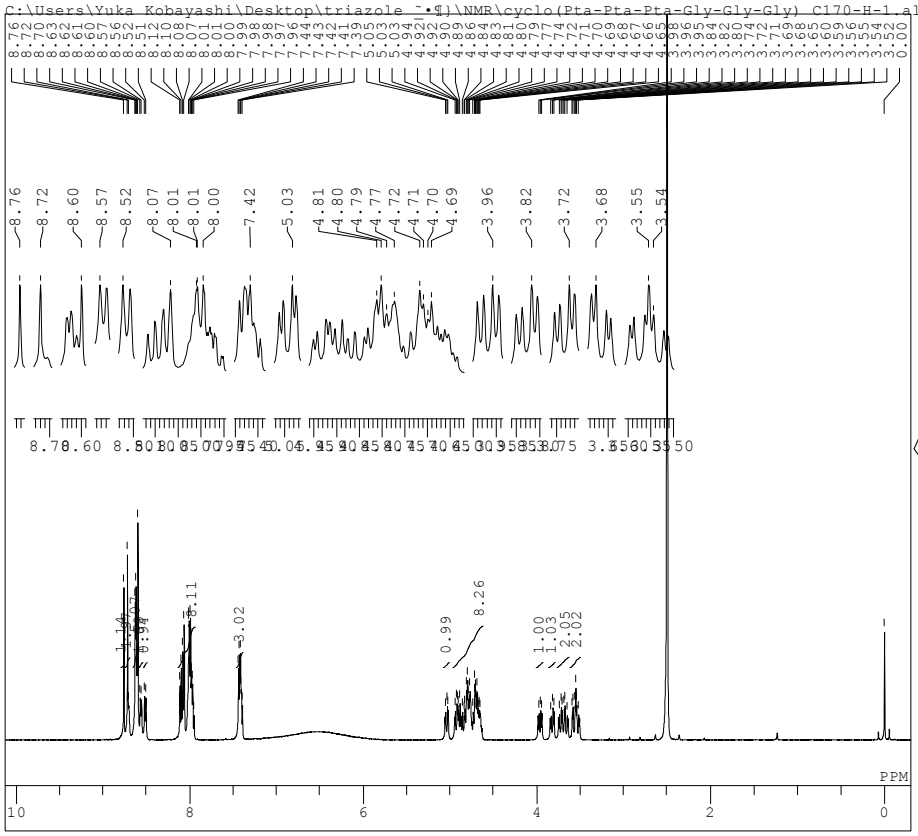


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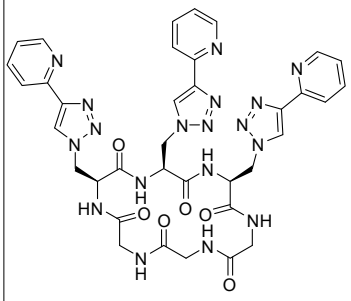
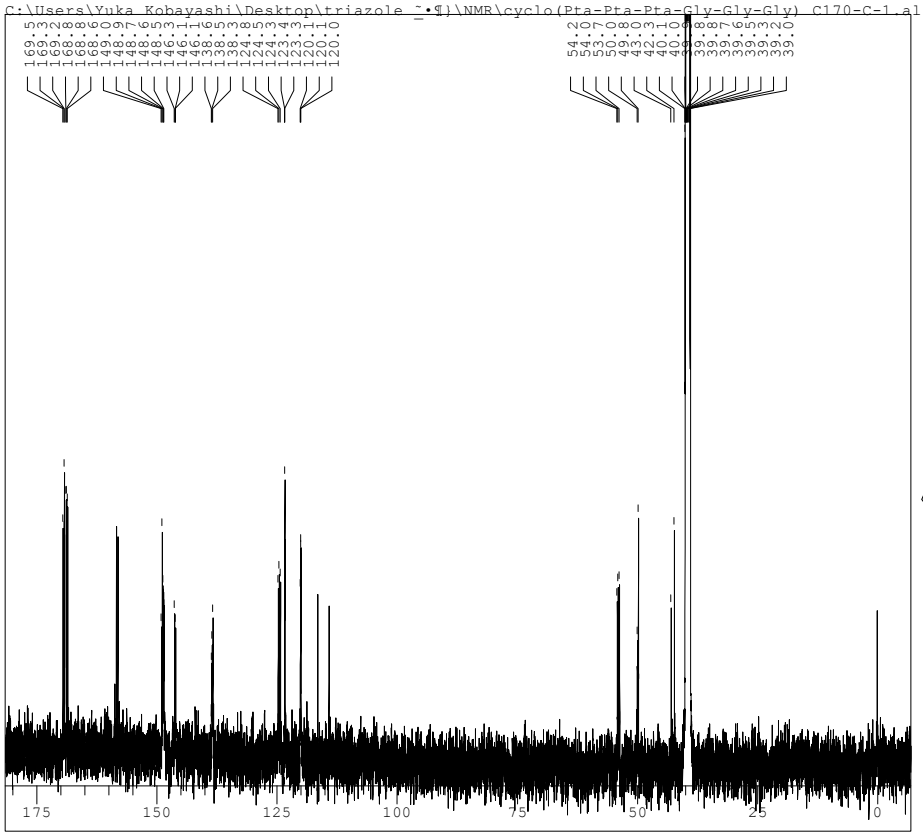
OBSET           2.41 KHz
OBFIN           6.01 Hz
POINT          13107
FREQU        7507.39 Hz
SCANS             24
ACQTM         1.7459 sec
PD            5.0000 sec
PW1              6.82 usec
IRNUC 1H
CTEMP            24.0 c
SLVNT DMSO
EXREF            0.00 ppm
BF               0.12 Hz
RGAIN              46
```



cyclo(-Pta-Pta-Pta-Gly-Gly-Gly-) (**1**)

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EXMOD single_pulse_dec
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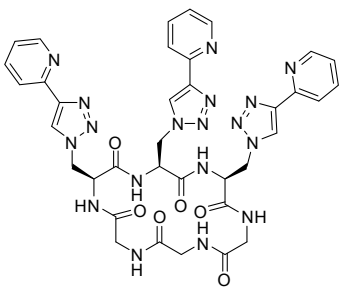
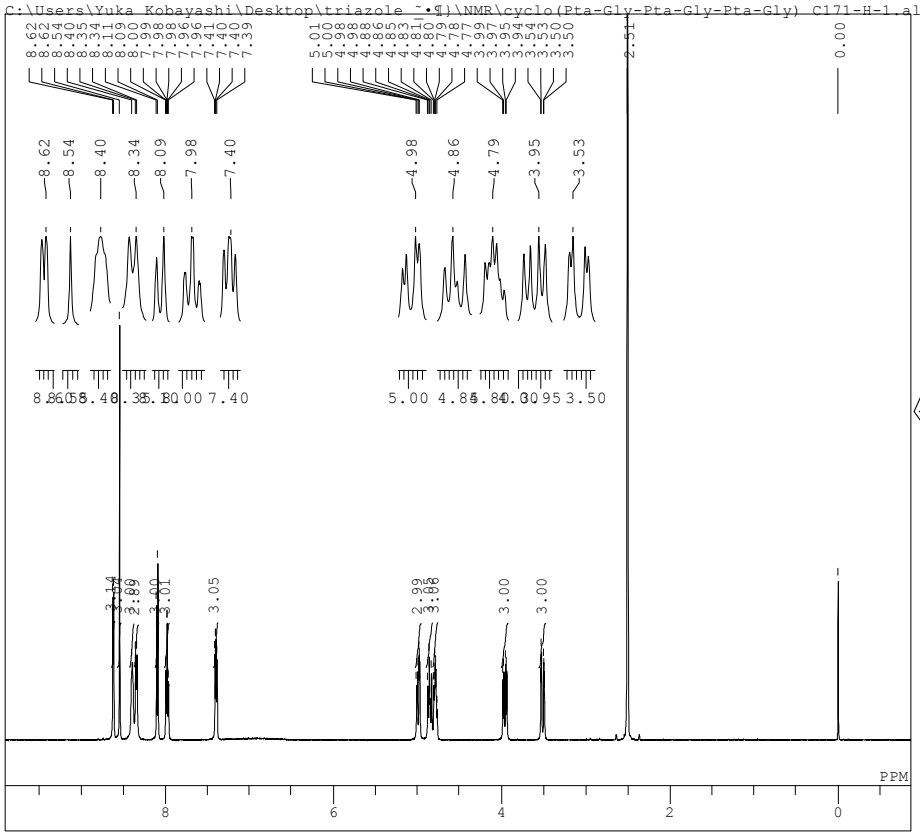
OBSET           7.87 KHz
OBFIN           4.21 Hz
POINT          26214
FREQU       31446.06 Hz
SCANS           5500
ACQTM         0.8336 sec
PD            2.0000 sec
PW1              3.50 usec
IRNUC 1H
CTEMP            23.7 c
SLVNT DMSO
EXREF           39.50 ppm
BF               1.20 Hz
RGAIN              52
```



cyclo(-Pta-Pta-Pta-Gly-Gly-Gly-) (**1**)




```
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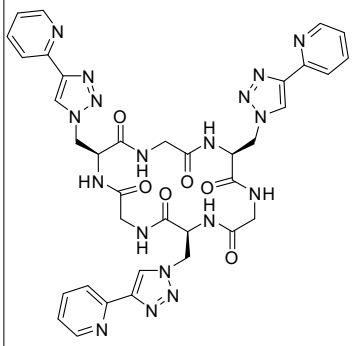
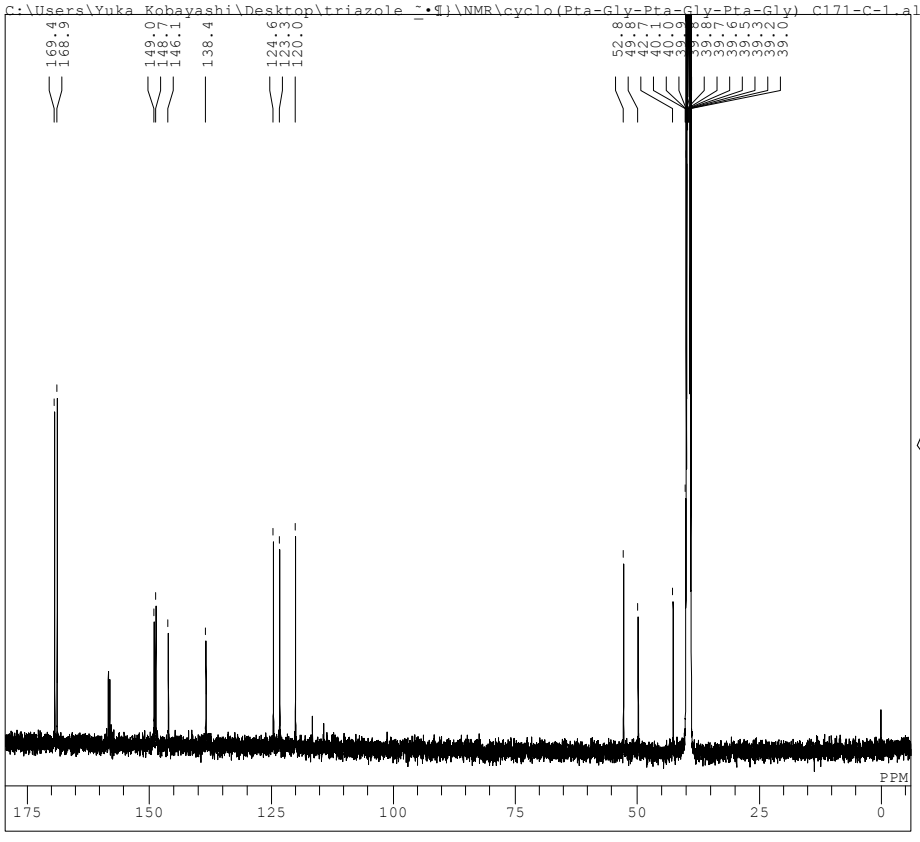
EXMOD single_pulse.ex2
OBFRQ         500.16 MHz
OBSET           2.41 KHz
OBFIN           6.01 Hz
POINT          13107
FREQU        7507.39 Hz
SCANS             8
ACQTM          1.7459 sec
PD             5.0000 sec
PW1              6.50 usec
IRNUC 1H
CTEMP           22.1 c
SLVNT DMSO
EXREF           0.00 ppm
BF              0.12 Hz
RGAIN             46
```



cyclo(-Pta-Gly-Pta-Gly-Pta-Gly-) (**2**)
in DMSO




```
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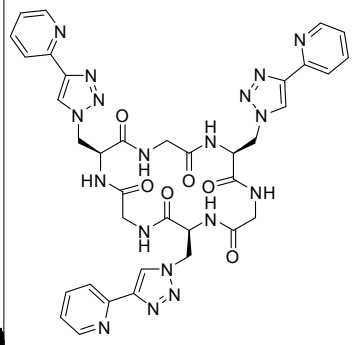
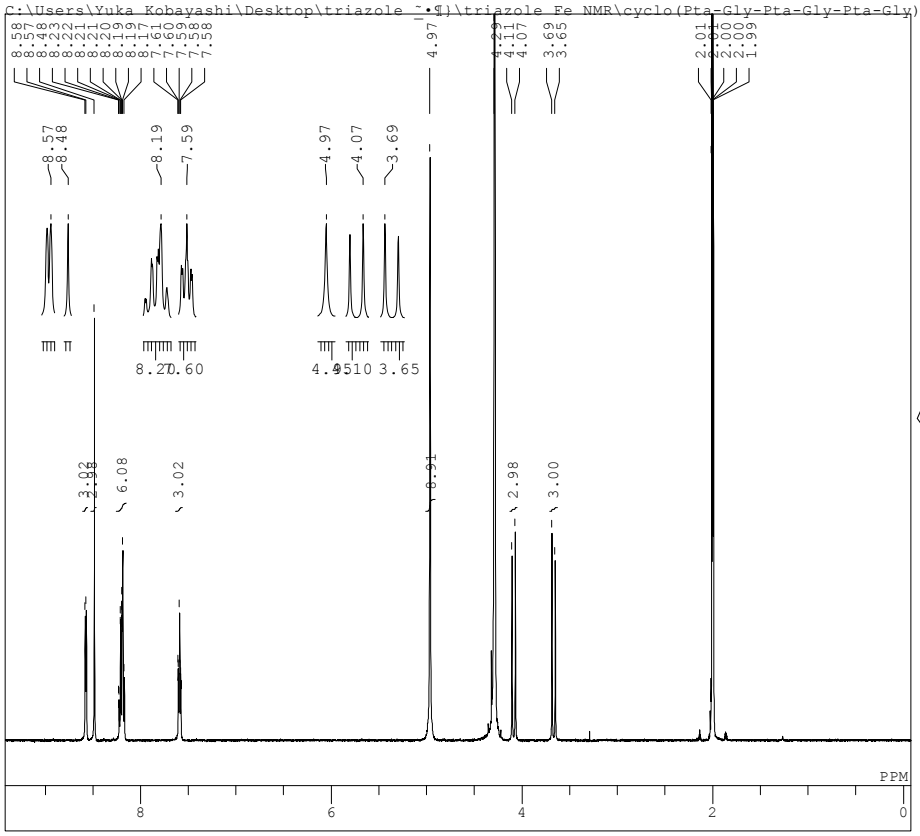
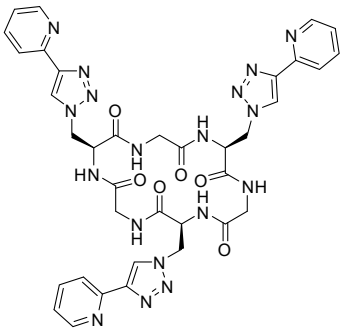
COMNT single pulse decoupled ga
DATIM 2014-02-15 05:17:19
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ         125.77 MHz
OBSET           7.87 KHz
OBFIN           4.21 Hz
POINT          26214
FREQU       31446.06 Hz
SCANS           8500
ACQTM         0.8336 sec
PD            2.0000 sec
PW1              3.73 usec
IRNUC 1H
CTEMP           22.6 c
SLVNT DMSO
EXREF          39.50 ppm
BF              1.20 Hz
RGAIN             52
```



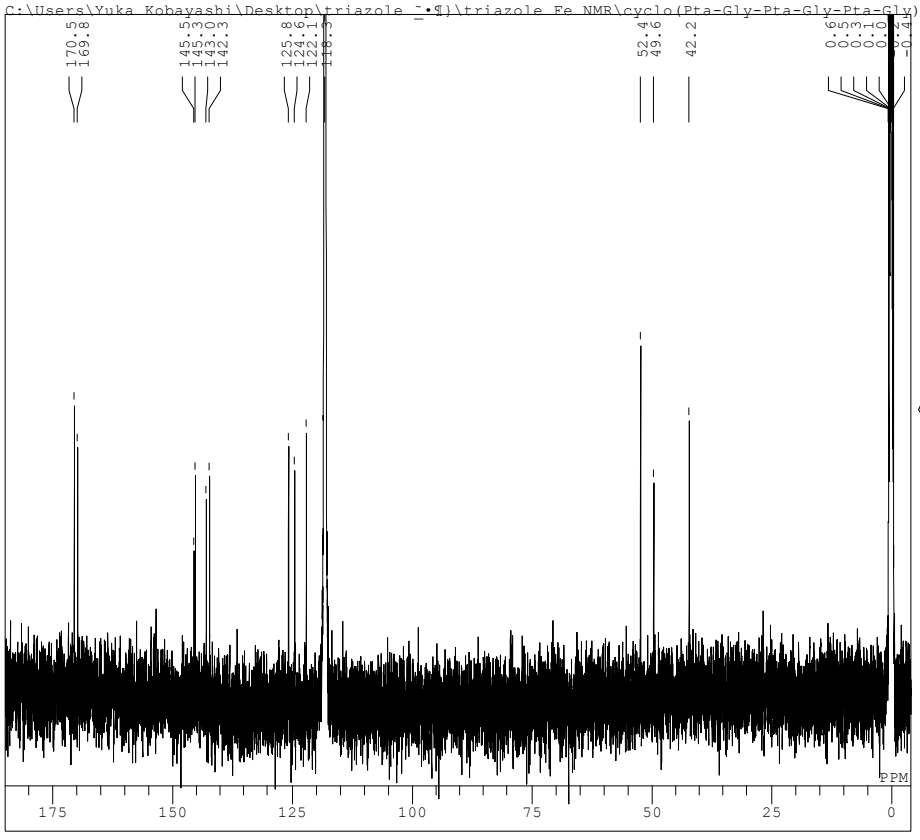
cyclo(-Pta-Gly-Pta-Gly-Pta-Gly-) (**2**)
in DMSO



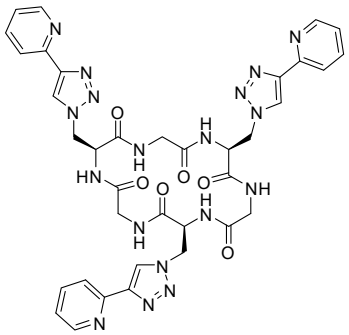

```
DFILE G063-H-no-Fe-1.als
COMNT single_pulse
DATIM 2017-05-27 20:32:57
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ         500.16 MHz
OBSET           2.41 KHz
OBFIN           6.01 Hz
POINT          13107
FREQU        7507.39 Hz
SCANS             32
ACQTM          1.7459 sec
PD             5.0000 sec
PW1               7.15 usec
IRNUC 1H
CTEMP            20.8 c
SLVNT CD3CN
EXREF             2.00 ppm
BF                0.12 Hz
RGAIN               50
```



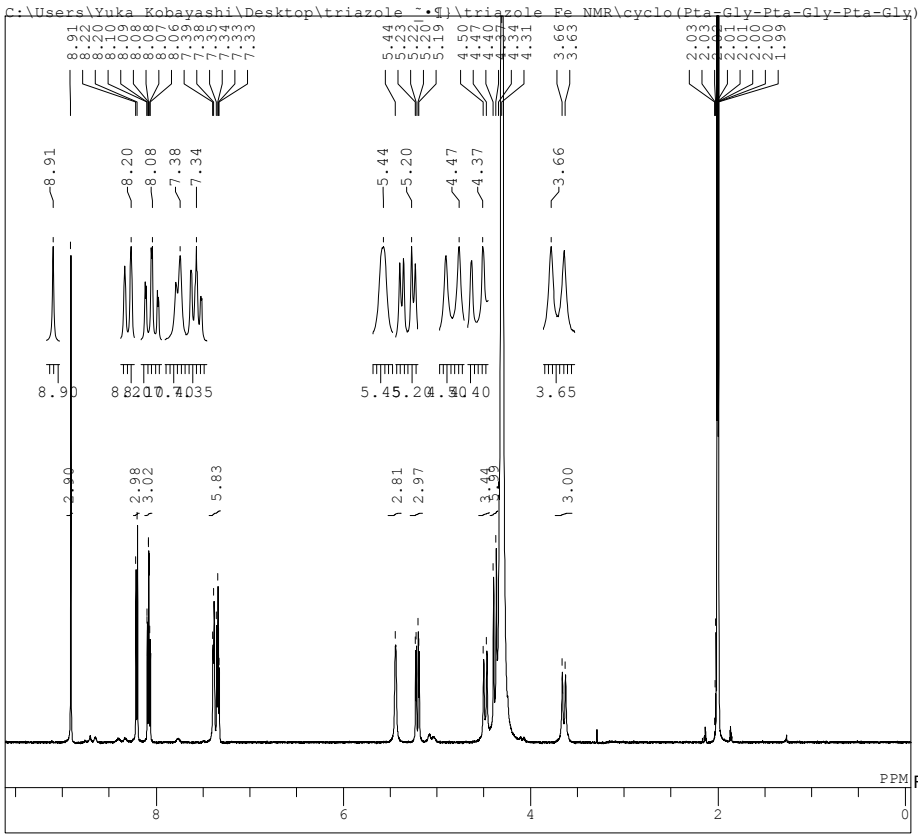
cyclo(-Pta-Gly-Pta-Gly-Pta-Gly-) (**2**)
in CD_3CN/D_2O

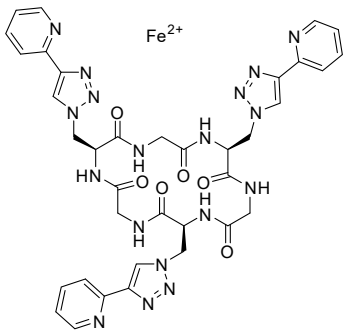



```
DFILE G063-C-no-Fe-1.als
COMNT
DATIM 2017-05-28 04:25:48
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ         125.77 MHz
OBSET           7.87 KHz
OBFIN           4.21 Hz
POINT          26214
FREQU       31446.06 Hz
SCANS          10000
ACQTM          0.8336 sec
PD             2.0000 sec
PW1               3.67 usec
IRNUC 1H
CTEMP            22.0 c
SLVNT CD3CN
EXREF           118.26 ppm
BF                1.20 Hz
RGAIN               56
```

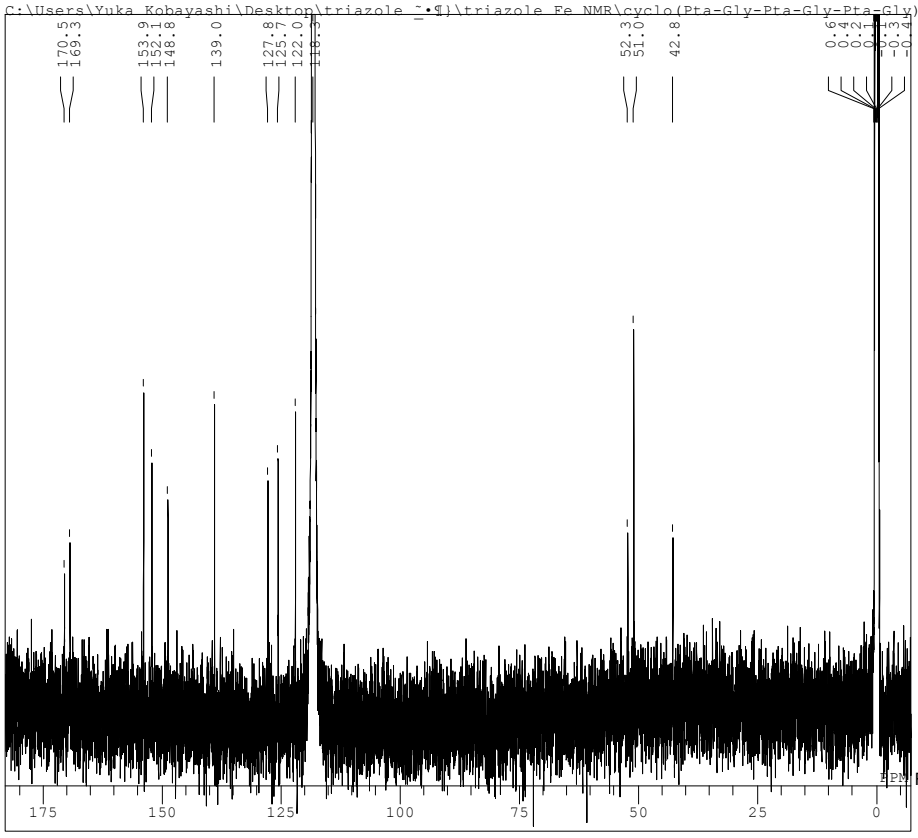


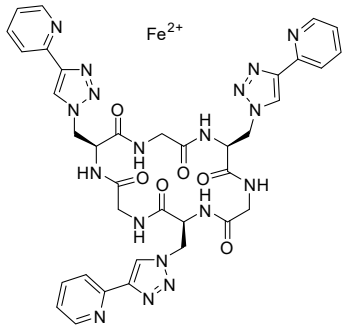
cyclo(-Pta-Gly-Pta-Gly-Pta-Gly-) (**2**)
in CD_3CN/D_2O



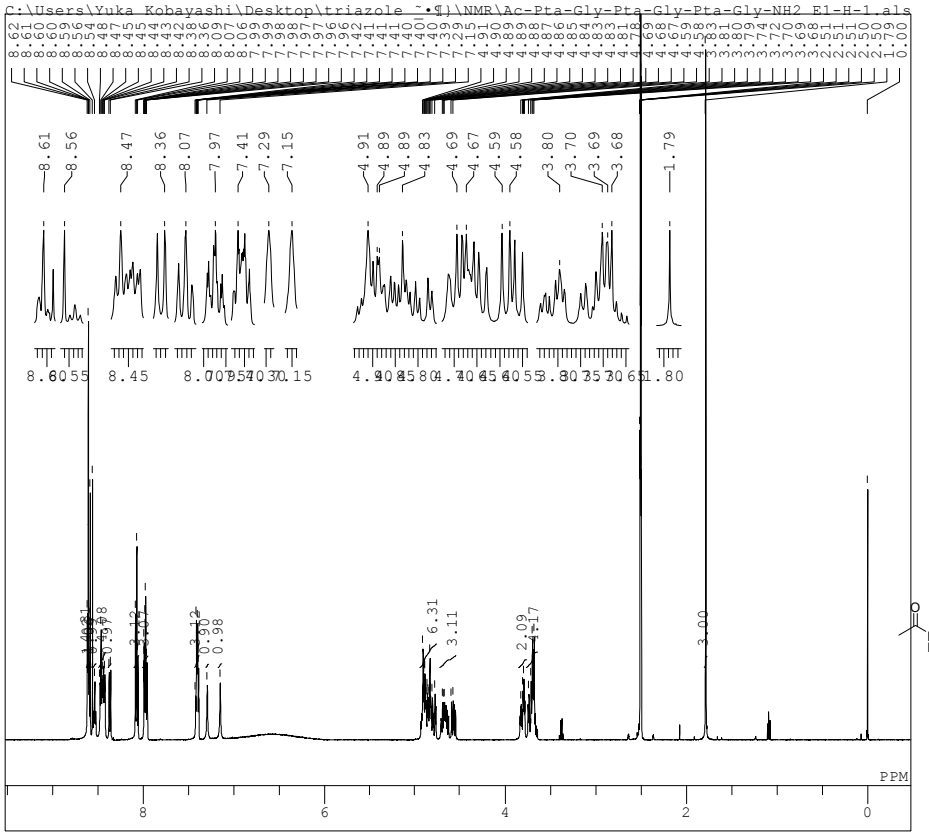


Fe(II)-*cyclo*(-Pta-Gly-Pta-Gly-Pta-Gly-) (**2**)
in CD_3CN/D_2O

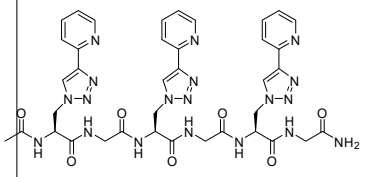




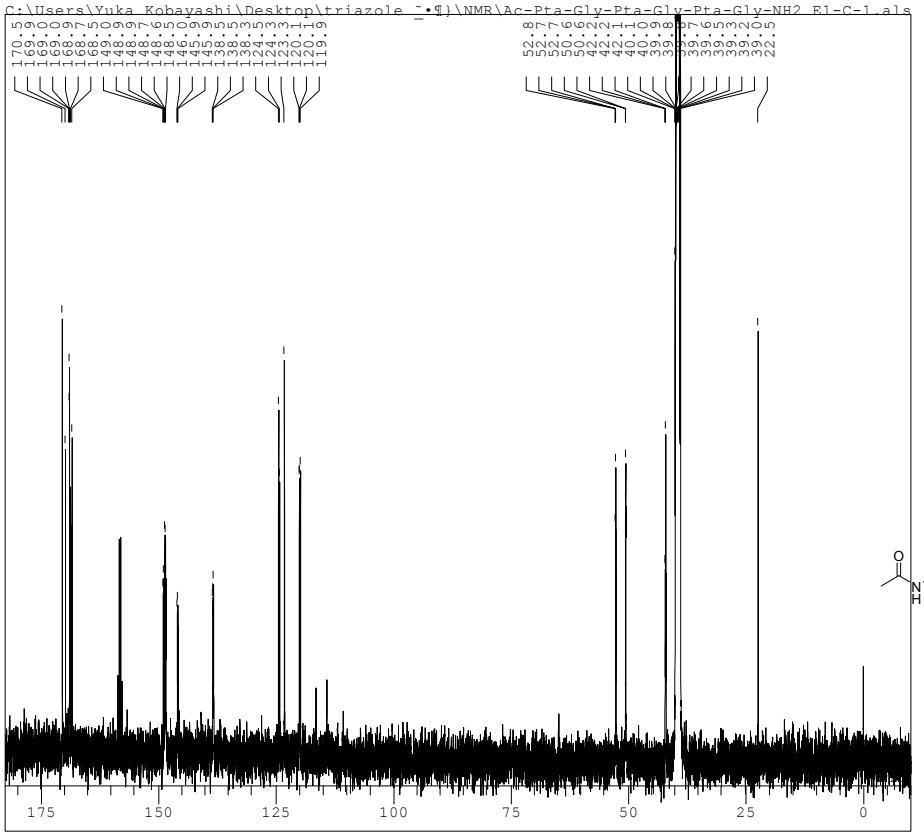
Fe(II)-*cyclo*(-Pta-Gly-Pta-Gly-Pta-Gly-) (**2**)
in CD_3CN/D_2O



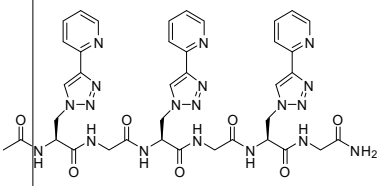

```
DFILE Ac-Pta-Gly-Pta-Gly-Pta-Gly
COMNT single pulse
DATIM 2014-07-28 22:27:30
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ        500.16 MHz
OBSET          2.41 KHz
OBFIN          6.01 Hz
POINT         13107
FREQU       7507.39 Hz
SCANS             8
ACQTM        1.7459 sec
PD           5.0000 sec
PW1             6.82 usec
IRNUC 1H
CTEMP          25.5 c
SLVNT DMSO
EXREF          0.00 ppm
BF             0.12 Hz
RGAIN            44
```



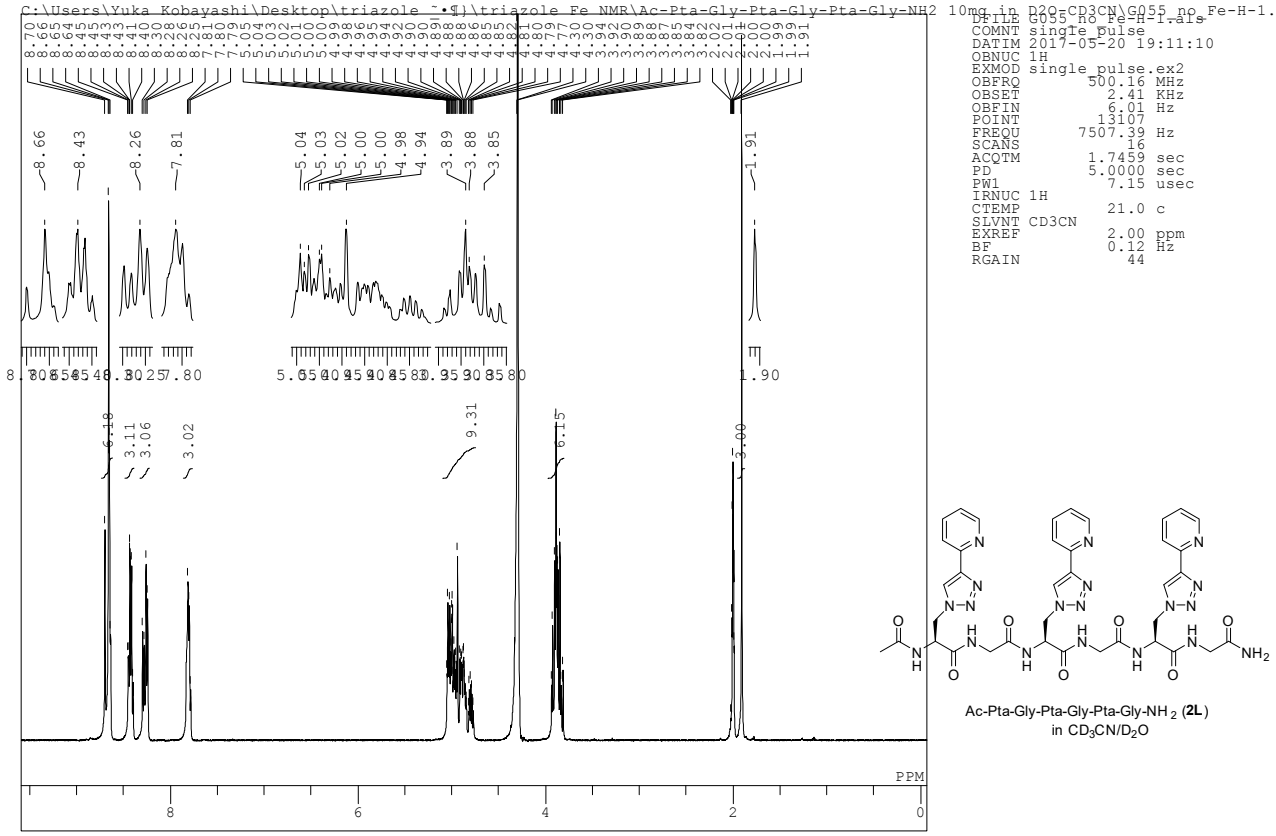
Ac-Pta-Gly-Pta-Gly-Pta-Gly-NH_2 (**2L**)
in DMSO

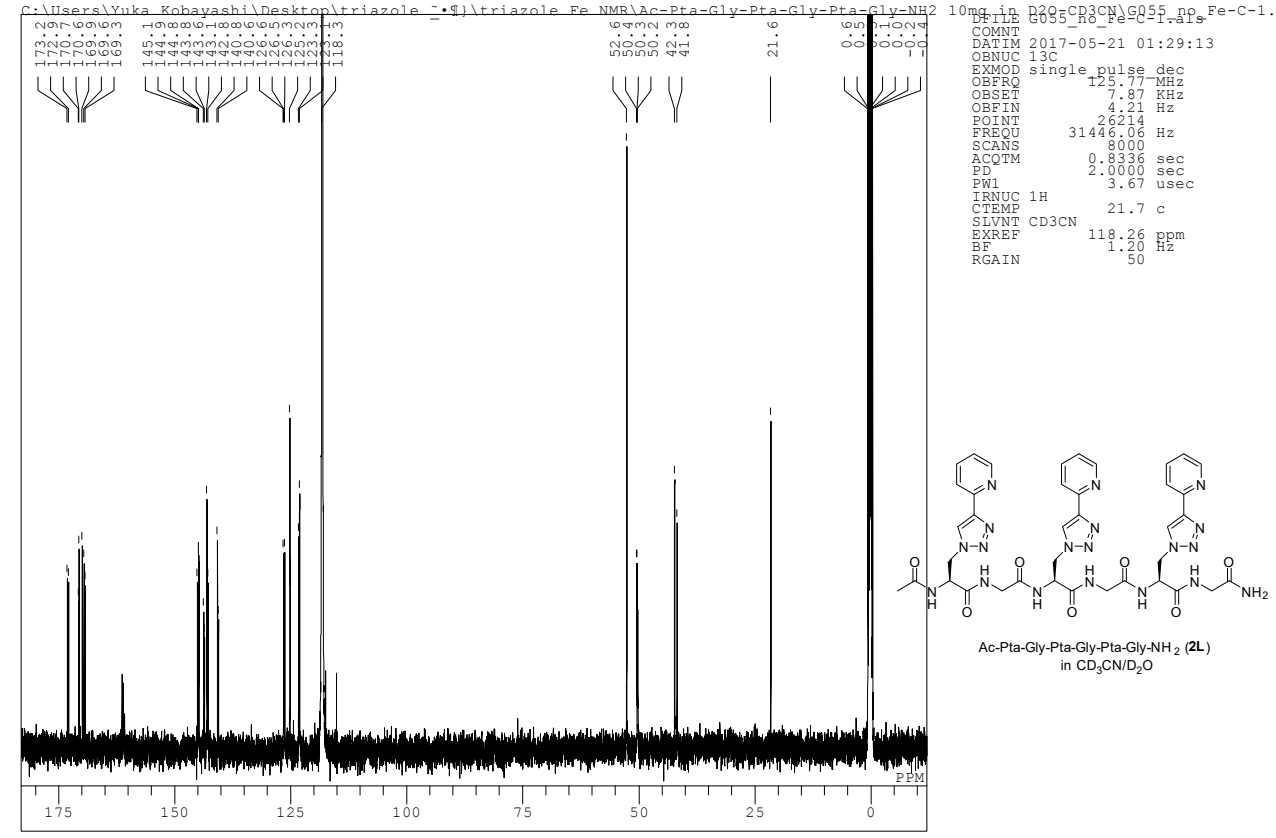


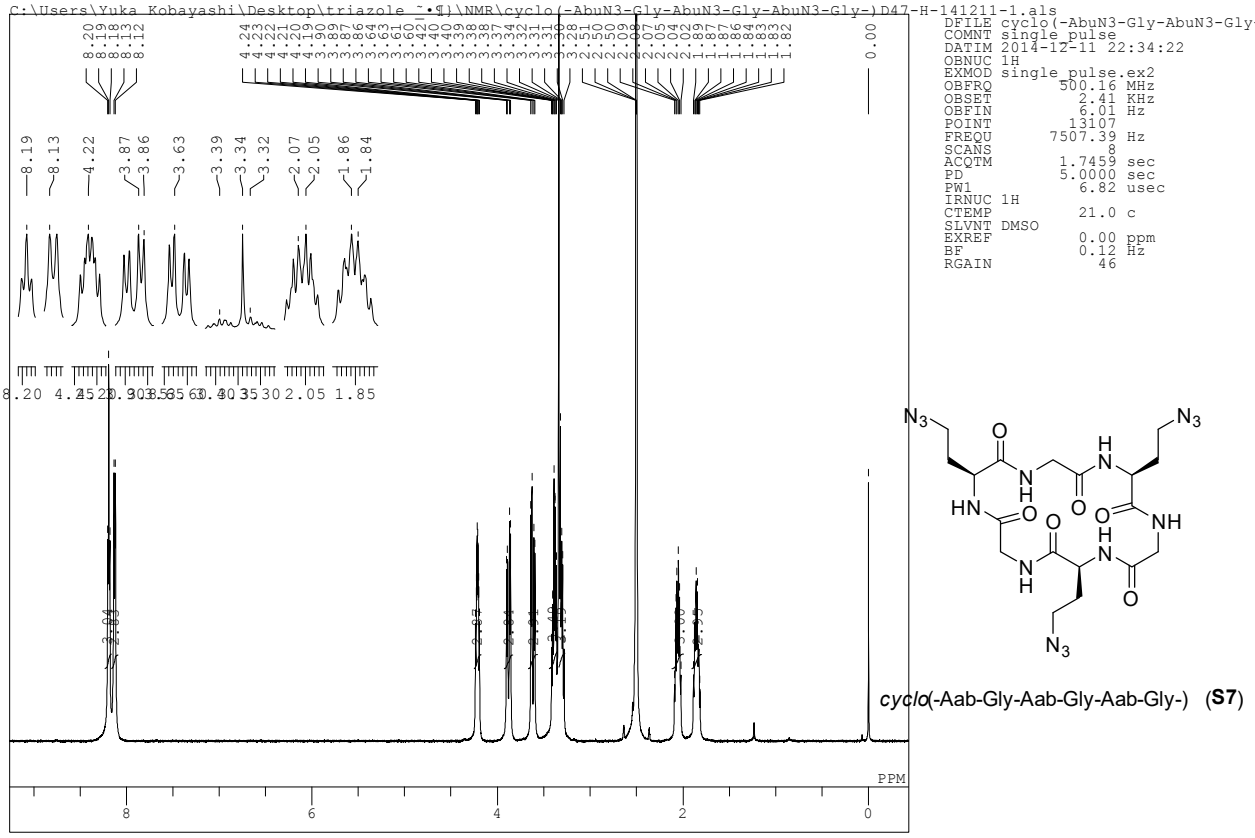

```
DFILE Ac-Pta-Gly-Pta-Gly-Pta-Gly
COMNT single_pulse_decoupled ga
DATIM 2014-07-29 03:14:13
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ       125.77 MHz
OBSET         7.87 KHz
OBFIN         4.21 Hz
POINT        26214
FREQU     31446.06 Hz
SCANS         6000
ACQTM       0.8336 sec
PD          2.0000 sec
PW1            3.50 usec
IRNUC 1H
CTEMP         24.6 c
SLVNT DMSO
EXREF         39.50 ppm
BF             1.20 Hz
RGAIN            56
```



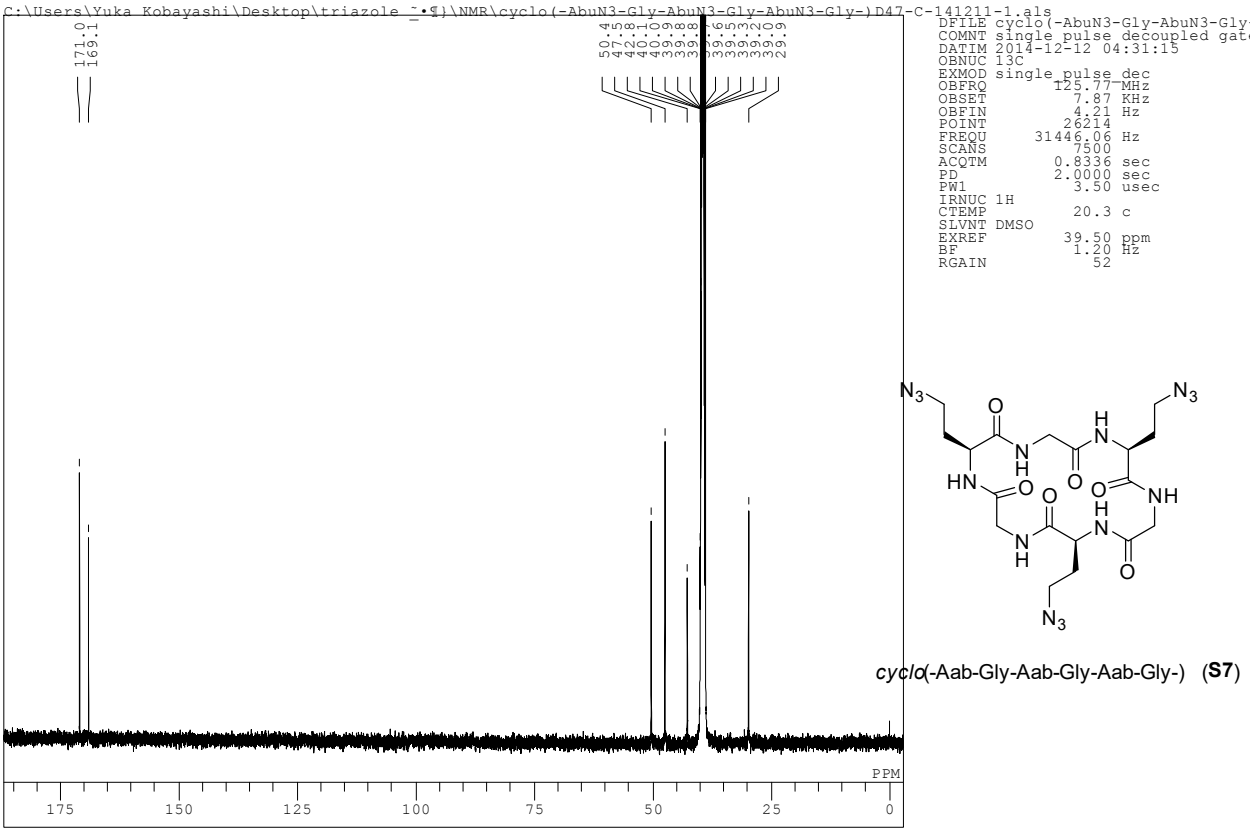
Ac-Pta-Gly-Pta-Gly-Pta-Gly-NH_2 (**2L**)
in DMSO


C:\Users\Yuka Kobayashi\Desktop\triazole ~•¶\triazole Fe NMR\Ac-Pta-Gly-Pta-Gly-Pta-Gly-NH2 10mg in D2O=CD3CN\G055_no_Fe-H-1.
DFILE G055_no_Fe-H-1.rals
COMNT single_pulse
DATIM 2017-05-20 19:11:10
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.39 Hz
SCANS 16
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 7.15 usec
IRNUC 1H
CTEMP 21.0 c
SLVNT CD3CN
EXREF 2.00 ppm
BF 0.12 Hz
RGAIN 44
PPM
Ac-Pta-Gly-Pta-Gly-Pta-Gly-NH2 (2L)
in CD3CN/D2O

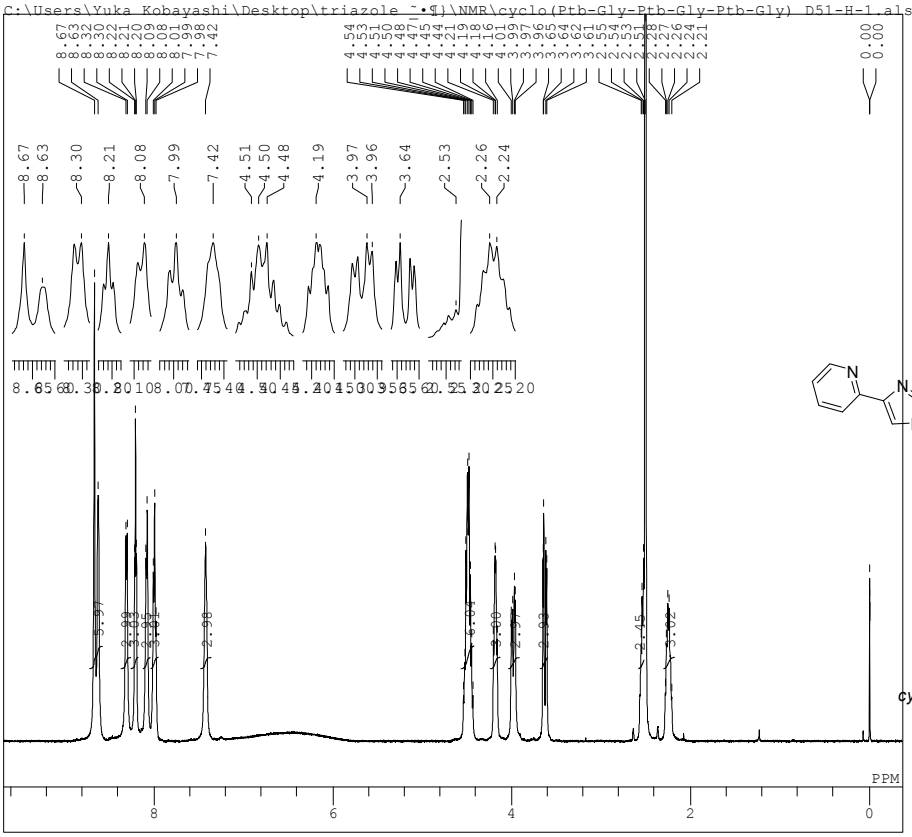

C:\Users\Yuka Kobayashi\Desktop\triazole ~•¶\triazole Fe NMR\Ac-Pta-Gly-Pta-Gly-Pta-Gly-NH2 10mg in D2O=CD3CN\G055_no_Fe-C-1.
DFILE G055_no_Fe-C-1.rals
COMNT
DATIM 2017-05-21 01:29:13
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.06 Hz
SCANS 8000
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.67 usec
IRNUC 1H
CTEMP 21.7 c
SLVNT CD3CN
EXREF 118.26 ppm
BF 1.20 Hz
RGAIN 50
PPM
Ac-Pta-Gly-Pta-Gly-Pta-Gly-NH2 (2L)
in CD3CN/D2O



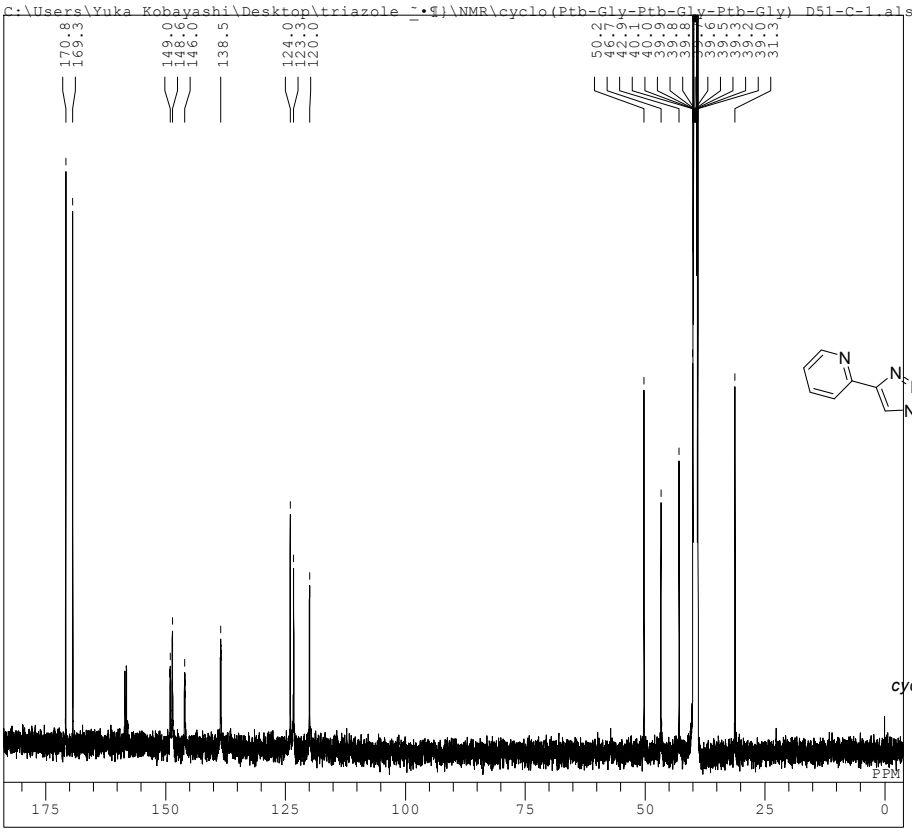
cyclo(-Aab-Gly-Aab-Gly-Aab-Gly-) (**S7**)



cyclo(-Aab-Gly-Aab-Gly-Aab-Gly-) (**S7**)



cyclo(-Ptb-Gly-Ptb-Gly-Ptb-Gly-) (**4**)



cyclo(-Ptb-Gly-Ptb-Gly-Ptb-Gly-) (**4**)