

Electronic Supplementary Information

Synthesis of Ferrocene Amides and Esters from Aminoferrocene and 2-Substituted Ferrocenecarboxylic Acid and the Properties thereof

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Experimental procedures and characterization of the compounds

*Aminoferrocene (1).*¹

To a stirred, cooled (-78 °C) solution of ferrocene (1.86 g, 10.0 mmol) and *t*-BuOK (112 mg, 1.0 mmol) in THF (90 mL) was added *t*-BuLi (10.5 mL of a 1.9 M in pentane solution, 20.0 mmol) over 20 min. The reaction was stirred for 1 h at -78 °C and subsequently treated with a solution of I₂ (5.08 g, 20.0 mmol) in THF (40 mL). The mixture was stirred overnight at room temperature before addition of an aqueous saturated solution of Na₂S₂O₃ (20 mL) and extraction with ethyl acetate (3 × 100 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was taken up in pentane (180 mL) and repeatedly washed with a saturated aqueous solution of FeCl₃ until the aqueous layer no longer took on the blue-green color of ferrocenium.^{1b} The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/heptane: 1/99) gave **iodoferrocene** (2.65 g, 85%) as a brown solid (mp = 48 °C). ¹H NMR (CDCl₃, 300 MHz): δ = 4.16 (br m, 2H), 4.20 (br s, 5H), 4.42 (br m, 2H). ¹³C NMR (CDCl₃, 75 MHz): δ = 39.8, 68.9 (2C), 71.1 (5C), 74.6 (2C). These values are consistent with those reported in the literature.²

To a stirred solution of iodoferrocene (1.56 g, 5.0 mmol) and phthalimide (920 mg, 6.25 mmol) in CH₃CN (25 mL) was added Cu₂O (894 mg, 6.25 mmol). The mixture was refluxed for 36 h and then the solvent was removed under reduced pressure. The solid was dissolved in ethyl acetate (70 mL) and then filtered on celite[®]. The filtrate was successively washed with 2 M NaOH (2 × 50 mL), brine (2 × 50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/heptane: 8/92) gave ***N*-ferrocenylphthalimide** (1.39 g, 84%) as a red solid (mp = 150 °C). ¹H NMR (CDCl₃, 300 MHz): δ = 4.27 (br m, 7H), 5.07 (br m, 2H), 7.74 (br m, 2H), 7.87 (br, 2H). ¹³C NMR (CDCl₃, 75 MHz): δ = 62.9 (2C), 65.6 (2C), 69.6 (5C), 88.7, 123.3 (2C), 132.0 (2C), 134.2 (2C), 167.1 (2C). These values are consistent with those reported in the literature.³

To a stirred, cooled (0 °C) solution of *N*-ferrocenylphthalimide (1.66 g, 5.0 mmol) in CH₂Cl₂ (15 mL) was added hydrazine monohydrate (2.50 g, 50.0 mmol). The reaction was stirred for 1 h at room temperature and then filtered on celite[®]. The filtrate was dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/heptane: 67/33) gave **aminoferrocene (1)**, 1.39 g, 83%) as a brown solid (mp = 154 °C). ¹H NMR (CDCl₃, 300 MHz): δ = 2.82 (br s, 2H), 3.83 (br m, 2H), 3.99 (br m, 2H), 4.09 (br s, 5H). ¹³C NMR (CDCl₃, 75 MHz): δ = 58.6 (2C), 63.7 (2C), 69.1 (5C), 106.6. These values are consistent with those reported in the literature.⁴

3-Amino-3-deoxy-N-(tert-butoxycarbonyl)-1,2-O-isopropylidene-α-D-ribofuranic acid (SAA-1).

Methyl 3-amino-3-deoxy-N-(tert-butoxycarbonyl)-1,2-O-isopropylidene-α-D-ribofuranate was prepared according to the literature.⁵ White solid (mp = 118 °C). [α]_D (20 °C) = +43.8 (*c* 1.5, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.33 (s, 3H), 1.43 (s, 9H), 1.53 (s, 3H), 3.74 (br m, 3H), 4.19 (br m, 2H), 4.62 (t, 1H, *J* = 3.5 Hz), 5.08 (br d, 1H, *J* = 8.2 Hz), 5.95 (d, 1H, *J* = 3.5 Hz). ¹³C NMR (75 MHz, CDCl₃): δ = 26.4, 26.6, 28.2 (3C), 52.6, 56.5, 77.1, 78.9, 80.2, 104.6, 113.0, 154.9, 169.8. HRMS (ESI): calcd for C₁₄H₂₃NO₇Na [M+Na]⁺ 340.1372, found 340.1373.

To a stirred, cooled (0 °C) solution of methyl 3-amino-3-deoxy-N-(tert-butoxycarbonyl)-1,2-O-isopropylidene-α-D-ribofuranate (317 mg, 1.0 mmol) in THF/MeOH/H₂O 3/1/1 (25 mL) was added LiOH·H₂O (126 mg, 3.0 mmol). After 1 h at 0 °C, the reaction mixture was acidified to pH 2 with 1 M HCl and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with brine (30 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/heptane: 6/4) gave **3-amino-3-deoxy-N-(tert-butoxycarbonyl)-1,2-O-isopropylidene-α-D-ribofuranic acid (SAA-1)**, 227 mg, 75%) as a white solid (mp = 68 °C). [α]_D (20 °C) = +28.0 (*c* 1.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.33 (s, 3H), 1.41 (s, 9H), 1.52 (s, 3H), 4.21 (d, 1H, *J* = 9.3 Hz), 4.48 (br m, 1H), 4.63 (br m, 1H), 5.26 (d, 1H, *J* = 9.3 Hz), 5.94 (br s, 1H,), 7.03 (br s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ = 26.4, 26.7, 28.2 (3C), 55.9, 76.9, 79.1, 81.1, 104.5, 113.0, 155.6, 171.6. HRMS (ESI): calcd for C₁₃H₂₁NO₇Na [M+Na]⁺ 326.1216, found 326.1217.

Xylofuranoid sugar amino acid SAA-4.

The **corresponding methyl ester** was prepared according to the literature.⁵ White solid (mp = 218 °C). $[\alpha]_D$ (20 °C) = -19.4 (*c* 1.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.30 (s, 6H), 1.42 (s, 9H), 1.48 (s, 3H), 1.52 (s, 3H), 3.79 (s, 3H), 4.36 (dd, 1H, *J* = 4.3 and 7.3 Hz), 4.53 (d, 1H, *J* = 3.5 Hz), 4.62 (br s, 2H), 4.74 (br d, 1H, *J* = 3.8 Hz), 4.81 (m, 2H), 5.89 (d, 1H, *J* = 3.3 Hz), 6.00 (d, 1H, *J* = 3.5 Hz), 6.81 (br m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 26.0, 26.1, 26.4, 26.6, 28.2 (3C), 52.7, 56.3, 57.7, 76.8, 78.3, 80.2, 83.6, 84.3, 104.5, 104.8, 112.6, 112.7, 155.0, 166.9, 168.7. HRMS (ESI): calcd for C₂₂H₃₄N₂O₁₁Na [M+Na]⁺ 525.2060, found 525.2058.

To a stirred, cooled (0 °C) solution of the corresponding methyl ester (503 mg, 1.0 mmol) in THF/MeOH/H₂O 3/1/1 (25 mL) was added LiOH·H₂O (126 mg, 3.0 mmol). After 1 h at 0 °C, the reaction mixture was acidified to pH 2 with 1 M HCl and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with brine (30 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/heptane: 7/3) gave **SAA-4** (332 mg, 68%) as a white solid (mp = 152 °C). $[\alpha]_D$ (20 °C) = -37.2 (*c* 3.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.25 (s, 6H), 1.41 (s, 9H), 1.44 (s, 3H), 1.47 (s, 3H), 4.47 (m, 3H), 4.67 (d, 1H, *J* = 3.7 Hz), 4.83 (d, 1H, *J* = 3.5 Hz), 4.92 (d, 1H, *J* = 10.1 Hz), 5.48 (d, 1H, *J* = 9.6 Hz), 5.94 (d, 1H, *J* = 2.9 Hz), 5.98 (d, 1H, *J* = 3.2 Hz), 6.95 (d, 1H, *J* = 10.1 Hz), 8.36 (br s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 26.2, 26.3, 26.6, 26.7, 28.1 (3C), 28.2, 56.2, 58.7, 79.5, 83.2, 83.8, 84.1, 104.8, 105.2, 112.8, 113.0, 157.4, 166.8, 171.4. HRMS (ESI): calcd for C₂₁H₃₂N₂O₁₁Na [M+Na]⁺ 511.1904, found 511.1902.

Xylofuranoid sugar amino acid SAA-5.

To a stirred, cooled (0 °C) solution of the corresponding methyl ester (503 mg, 1.0 mmol) in THF/MeOH/H₂O 3/1/1 (25 mL) was added LiOH·H₂O (126 mg, 3.0 mmol). After 1 h at 0 °C, the reaction mixture was acidified to pH 2 with 1 M HCl and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with brine (30 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/heptane: 7/3) gave **SAA-5**

(332 mg, 63%) as a white solid (mp = 78 °C). ¹H NMR (300 MHz, CDCl₃): δ = 1.24 (s, 3H), 1.34 (s, 3H), 1.42 (s, 9H), 1.51 (s, 3H), 1.55 (s, 3H), 4.10-5.01 (m, 5H), 6.00 (br m, 2H), 6.68 (br s, 1H), 7.20 (d, 1H, *J* = 8.2 Hz). ¹³C NMR (75 MHz, CDCl₃): δ = 26.4, 26.6, 26.8, 26.9, 28.4 (3C), 29.8, 54.5, 58.4, 76.8, 78.9, 79.3, 84.4, 104.9, 105.3, 112.9, 113.5, 155.4, 168.7, 171.5. HRMS (ESI): calcd for C₂₁H₃₂N₂O₁₁Na [M+Na]⁺ 511.1904, found 511.1903.

Ferrocene Carboxamide FcC-0.

FcC-0 was prepared from aminoferrocene (**1**) and Boc-Trp-OH according to the general procedure for peptidic coupling. Purification by flash chromatography on silica gel (EtOAc/CH₂Cl₂: 1/9) gave **FcC-0** (322 mg, 66%) as a yellow solid (mp = 210 °C). [α]_D (20 °C) = +2.4 (*c* 2.3, CHCl₃). ¹H NMR (CDCl₃, 300 MHz): δ = 1.46 (br s, 9H), 3.19 (br s, 2H), 4.39 (br s, 5H), 4.64 (br s, 2H), 5.08 (br s, 3H), 6.58 (br s, 1H), 6.98 (br s, 1H), 7.16 (br s, 1H), 7.39 (br s, 1H), 7.64 (br d, 1H, *J* = 6.7 Hz), 8.23 (br s, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ = 28.2, 28.4 (3C), 55.5, 61.8, 62.1, 66.7 (2C), 72.0 (5C), 80.4, 95.3, 110.1, 111.5, 118.7, 119.7, 122.2, 123.4, 127.3, 136.3, 155.7, 169.8. HRMS (ESI): calcd for C₂₆H₂₉FeN₃O₃Na [M+Na]⁺ 510.1456, found 510.1450.

Ferrocene Carboxamide FcC-1.

FcC-1 was prepared from aminoferrocene (**1**) and **SAA-1** according to the general procedure for peptidic coupling. Purification by flash chromatography on silica gel (EtOAc/CH₂Cl₂: 1/9) gave **FcC-1** (301 mg, 62%) as a yellow solid (mp = 196 °C). [α]_D (20 °C) = +8.3 (*c* 2.4, CHCl₃). ¹H NMR (300 MHz, 340 K, C₆D₆): δ = 1.03 (br s, 3H), 1.23 (br s, 3H), 1.47 (br s, 9H), 3.90 (br m, 2H), 4.15-4.39 (br m, 8H), 4.62 (br s, 1H), 4.81 (br s, 1H), 5.09 (br s, 1H), 5.34 (br s, 1H). ¹³C NMR (75 MHz, 340 K, C₆D₆): δ = 26.3, 26.6, 28.4 (3C), 57.4, 61.5, 61.6, 64.7, 65.0, 69.8 (5C), 77.6, 79.5, 79.9, 94.7, 104.2, 113.0, 155.4, 166.5. HRMS (ESI): calcd for C₂₃H₃₀FeN₂O₆Na [M+Na]⁺ 509.1351, found 509.1352.

Ferrocene Carboxamide FcC-2.

FcC-2 was prepared from aminoferrocene (**1**) and **SAA-2** according to the general procedure for peptidic coupling. Purification by flash chromatography on silica gel (EtOAc/CH₂Cl₂: 1/9) gave **FcC-2**

(292 g, 60%) as a yellow solid (mp = 242 °C). $[\alpha]_D$ (20 °C) = -6.5 (*c* 1.6, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.28 (br s, 3H), 1.49 (br s, 3H), 1.52 (br s, 9H), 4.08 (br s, 2H), 4.62 (br s, 2H), 4.94-5.50 (br m, 7H), 5.83 (br m, 3H), 6.82 (br s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 26.4, 26.8, 28.5 (3C), 57.9, 61.8 (2C), 62.4 (2C), 68.0, 74.0 (5C), 79.4, 80.6, 84.3, 105.6, 112.7, 154.7, 164.4. HRMS (ESI): calcd for C₂₃H₃₀FeN₂O₆Na [M+Na]⁺ 509.1351, found 509.1353.

Ferrocene Carboxamide FcC-3.

FcC-3 was prepared from aminoferrocene (**1**) and **SAA-3** according to the general procedure for peptidic coupling. Purification by flash chromatography on silica gel (EtOAc/CH₂Cl₂: 2/8) gave **FcC-3** (416 mg, 62%) as a yellow solid (mp = 120 °C). $[\alpha]_D$ (20 °C) = -5.4 (*c* 1.8, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.25 (br s, 3H), 1.35 (br s, 3H), 1.44 (br s, 3H), 1.54 (br s, 3H), 1.78 (br s, 9H), 4.09-4.73 (br m, 7H), 5.02 (br s, 6H), 5.65-6.07 (br m, 6H), 6.91 (br m, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 26.4, 26.5, 26.6, 26.7, 28.1 (3C), 54.1, 54.2, 60.6 (2C), 63.6 (2C), 68.7 (5C), 75.9, 77.4, 78.2, 78.5, 78.7, 95.5, 104.3, 104.5, 111.9, 112.1, 154.7, 166.1, 167.7. HRMS (ESI): calcd for C₃₁H₄₁FeN₃O₁₀Na [M+Na]⁺ 694.2039, found 694.2041.

Ferrocene Carboxamide FcC-4.

FcC-4 was prepared from aminoferrocene (**1**) and **SAA-4** according to the general procedure for peptidic coupling. Purification by flash chromatography on silica gel (EtOAc/CH₂Cl₂: 1/9) gave **FcC-4** (102 mg, 63%) as a yellow solid (mp = 260 °C). $[\alpha]_D$ (20 °C) = -2.6 (*c* 2.1, CHCl₃). ¹H NMR (300 MHz, 340 K, CDCl₃): δ = 1.31 (br. s, 6H), 1.43 (br. s, 6H), 1.48 (br. s, 9H), 4.24-4.80 (br m, 10H), 5.20-6.20 (br. m, 7H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 26.2, 26.3, 26.7, 26.8, 28.2 (3C), 52.3, 53.2, 55.3, 55.6, 57.0, 57.7, 68.9 (5C), 78.1, 78.5, 78.6, 83.4, 83.9, 84.0, 104.6, 104.8, 111.3, 111.6, 154.9, 166.5, 169.0. HRMS (ESI): calcd for C₃₁H₄₁FeN₃O₁₀Na [M+Na]⁺ 694.2039, found 694.2040.

Ferrocene Carboxamide FcC-5.

FcC-5 was prepared from aminoferrocene (**1**) and **SAA-5** according to the general procedure for peptidic coupling. Purification by flash chromatography on silica gel (EtOAc/CH₂Cl₂: 2/8) gave **FcC-5**

(423 mg, 63%) as a yellow solid (mp = 168 °C). $[\alpha]_D$ (20 °C) = -4.3 (*c* 2.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.23-1.54 (br m, 21H), 4.19-4.84 (br m, 13H), 5.88-5.97 (br m, 4H), 6.95-6.99 (br m, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 26.2, 26.3, 26.6, 26.7, 28.3 (3C), 54.2, 54.3, 61.8 (2C), 65.3 (2C), 72.8 (5C), 78.3, 78.6, 78.9, 79.0, 80.4, 84.2, 104.7, 105.0, 112.7, 113.2, 154.9, 167.3, 168.9. HRMS (ESI): calcd for C₃₁H₄₁FeN₃O₁₀Na [M+Na]⁺ 694.2039, found 694.2040.

Ferrocene Carboxamide FcC-6.

FcC-6 was prepared from **FcC-0**, after Boc deprotection by TFA in CH₂Cl₂ at 0 °C, and Boc-Trp-OH according to the general procedure for peptidic coupling. Purification by flash chromatography on silica gel (EtOAc/CH₂Cl₂: 1/9) gave **FcC-6** (424 mg, 63%) as a yellow solid (mp = 128 °C). $[\alpha]_D$ (20 °C) = -2.7 (*c* 2.0, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.06 (br s, 9H), 2.30 (br m, 1H), 3.04-3.52 (br m, 3H), 4.12-4.24 (br m, 7H), 4.34-4.80 (br m, 2H), 4.99-5.06 (br m, 2H), 6.42 (br s, 2H), 6.54-6.73 (br m, 2H), 7.03-7.20 (br m, 4H), 7.30-7.49 (br m, 2H), 7.63-7.82 (br m, 2H), 8.69-9.41 (br m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ = 25.6, 26.8, 27.8 (3C), 54.2, 55.7, 60.7, 62.2, 65.6, 66.0, 72.8 (5C), 80.7, 95.8, 108.8, 109.3, 111.7, 111.9, 117.8, 118.9, 119.7, 120.1, 122.3, 122.8, 123.8 (2C), 127.2, 127.5, 136.2, 136.8, 156.1, 169.4, 172.1. HRMS (ESI): calcd for C₃₇H₃₉FeN₅O₄Na [M+Na]⁺ 696.2249, found 696.2252.

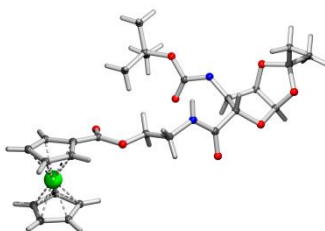
2-(Tert-butoxycarbonylamino)ethyl ferrocenecarboxylate.

To a stirred, cooled (0 °C) solution of ferrocenecarboxylic acid (230 mg, 1.0 mmol), *N*-Boc-ethanolamine (161 mg, 1.0 mmol) and DMAP (146 mg, 1.2 mmol) in CH₂Cl₂ (10 mL) was added DCC (248 mg, 1.2 mmol). The mixture was refluxed for 12 h and then filtered on celite[®]. Purification by flash chromatography on silica gel (EtOAc/heptane: 1/9) gave **2-(tert-butoxycarbonylamino)ethyl ferrocenecarboxylate** (299 mg, 80%) as a yellow solid (mp = 174 °C). ¹H NMR (CDCl₃, 300 MHz): δ = 1.44 (s, 9H), 3.47 (br m, 2H), 4.22 (s, 5H), 4.27 (t, 2H, *J* = 5.3 Hz), 4.42 (br s, 2H), 4.84 (br m, 3H). The ¹H NMR spectra is as described previously.⁶ ¹³C NMR (CDCl₃, 75 MHz): δ = 28.5 (3C), 40.1,

63.2, 69.9 (5C), 70.3 (2C), 70.7, 71.6 (2C), 79.6, 155.9, 171.9. HRMS (ESI): calcd for C₁₈H₂₃FeNO₄Na [M+Na]⁺ 396.0874, found 396.0871.

Ferrocene Ester FcE-1.

FcE-1 was prepared from **2-(tert-butoxycarbonylamino)ethyl ferrocenecarboxylate**, after Boc deprotection by TFA in CH₂Cl₂ at 0 °C, and **SAA-1** according to the general procedure for peptidic coupling. Purification by flash chromatography on silica gel (EtOAc/heptane: 3/9) gave **FcE-1** (363 mg, 65%) as a red solid (mp = 186 °C). [α]_D (20 °C) = +31.6 (c 1.2, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.31 (s, 3H), 1.42 (s, 9H), 1.49 (s, 3H), 3.49-3.72 (m, 2H), 4.17 (s, 5H), 4.08-4.31 (m, 4H), 4.38 (t, 2H, *J* = 1.8 Hz), 4.66 (br m, 1H), 4.78 (t, 2H, *J* = 1.8 Hz), 5.16 (d, 1H, *J* = 7.9 Hz), 5.84 (d, 1H, *J* = 3.3 Hz), 6.79 (br s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 26.5, 26.7, 28.3 (3C), 38.4, 56.9, 62.8, 69.9 (5C), 70.2, 70.3 (2C), 70.5, 71.6 (2C), 79.3, 80.2, 103.9, 113.3, 155.1, 169.1, 171.8. HRMS (ESI): calcd for C₂₆H₃₄FeN₂O₈Na [M+Na]⁺ 581.1562, found 581.1579. **Crystal data for FcE-1 (CCDC 1475360):** C₂₆H₃₃FeN₂O₈, M = 557.39, orthorhombic, P 2₁2₁2₁, a = 9.2335(5), b = 11.2140(5), c = 25.4777(13) Å, V = 2638.1(2) Å³, Z = 4, d = 1.403 g cm⁻³, μ = 0.623 mm⁻¹. A final refinement on F² with 5562 unique intensities and 262 parameters converged at wR(F²) = 0.2636 (R(F) = 0.1015) for 4081 observed reflections with I > 2σ(I).



Ferrocene Ester FcE-4.

FcE-4 was prepared from **2-(tert-butoxycarbonylamino)ethyl ferrocenecarboxylate**, after Boc deprotection by TFA in CH₂Cl₂ at 0 °C, and **SAA-4** according to the general procedure for peptidic coupling. Purification by flash chromatography on silica gel (EtOAc/heptane: 1/1) gave **FcE-4** (461 mg, 62%) as a red solid (mp = 190 °C). [α]_D (20 °C) = -14.6 (c 2.6, CHCl₃). ¹H NMR (300 MHz,

CDCl₃): δ = 1.29-1.49 (m, 12H), 1.45 (s, 9H), 3.40-3.80 (m, 2H), 4.25 (s, 5H), 4.38-4.46 (m, 4H), 4.63-4.85 (m, 6H), 5.14 (br s, 1H), 5.94 (m, 2H), 6.75 (br s, 1H), 6.93 (br s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 26.3, 26.4, 26.9 (2C), 28.4 (3C), 38.5, 56.4, 58.3, 63.1, 69.9 (5C), 70.3 (2C), 71.7, 71.8 (2C), 78.9, 79.5, 80.2, 84.0, 84.3, 105.0, 105.4, 112.7, 112.9, 155.5, 167.5, 168.0, 172.2. HRMS (ESI): calcd for C₃₄H₄₅FeN₃O₁₂Na [M+Na]⁺ 766.2245, found 766.2244.

2-Iodoferrocenecarboxylic acid (racemic mixture) (rac-7).

To a stirred, cooled (0 °C) solution of **racemic methyl 2-iodoferrocenecarboxylate**⁷ (370 mg, 1.0 mmol) in THF/MeOH/H₂O 3/1/1 (25 mL) was added LiOH·H₂O (126 mg, 3.0 mmol). After 1 h at 0 °C, the reaction mixture was acidified to pH 2 with 1 M HCl and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with brine (30 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/heptane: 4/6) gave **rac-7** (292 mg, 82%) as a yellow solid (mp = 198 °C). ¹H NMR (CDCl₃, 300 MHz): δ = 4.30 (br s, 5H), 4.53 (br m, 1H), 4.78 (br m, 1H), 4.96 (br m, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ = 39.7, 70.3, 71.3, 73.1, 73.3 (5C), 80.7, 177.1. HRMS (ESI): calcd for C₁₁H₉FeIO₂Na [M+Na]⁺ 378.8894, found 378.8894.

(S_P)-2-Iodoferrocenecarboxylic acid (S_P-7).

To a stirred, cooled (0 °C) solution of **(S_P)-3-O-(2-iodoferrocenecarbonyl)-1,2:5,6-di-O-isopropylidene- α -D-glucofuranose**⁸ (598 mg, 1.0 mmol) in THF/MeOH/H₂O 3/1/1 (25 mL) was added LiOH·H₂O (126 mg, 3.0 mmol). After 1 h at 0 °C, the reaction mixture was acidified to pH 2 with 1 M HCl and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with brine (30 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/heptane: 4/6) gave **S_P-7** (292 mg, 80%) as a yellow solid (mp = 198 °C). The analyses were found identical to those previously reported.⁹

N-(Ethoxycarbonylmethyl)-2-iodoferrocenecarboxamide (racemic mixture) (rac-8).

rac-8 was prepared from **rac-7** and H-Gly-OEt·HCl according to the general procedure for peptidic coupling. Purification by flash chromatography on silica gel (EtOAc/CH₂Cl₂: 2/8) gave **rac-8** (370 mg,

84%) as a red solid (mp = 98 °C). ¹H NMR (CDCl₃, 300 MHz): δ = 1.33 (t, 3H, *J* = 7.1 Hz), 4.10-4.34 (m, 4H), 4.28 (s, 5H), 4.42 (dd, 1H, *J* = 2.6 and 2.6 Hz), 4.62 (dd, 1H, *J* = 1.6 and 1.6 Hz), 4.89 (dd, 1H, *J* = 1.6 and 2.6 Hz), 6.97 (br s, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ = 14.3, 39.5, 41.6, 61.6, 69.6, 71.5, 73.0 (5C), 75.8, 78.8, 169.1, 170.1. HRMS (ESI): calcd for C₁₅H₁₆FeINO₃Na [M+Na]⁺ 463.9422, found 463.9444.

N-(Ethoxycarbonylmethyl)-2-((tert-butoxycarbonylamino)methyl)carbonyloxyferrocene-carboxamide (racemic mixture) (rac-9).

To a stirred solution of **rac-8** (441 mg, 1.0 mmol) and Cu₂O (114 mg, 0.8 mmol) in CH₃CN (10 mL) was added Boc-Gly-OH (210 mg, 1.2 mmol). The mixture was refluxed for 3 h and then the solvent was removed under reduced pressure. The crude residue was taken up in Et₂O (20 mL) and the organic mixture was successively washed with an aqueous saturated solution of NH₄Cl (20 mL), water (20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/CH₂Cl₂: 3/7) gave **rac-9** (244 mg, 50%) as a red solid (mp = 58 °C). ¹H NMR (CDCl₃, 300 MHz): δ = 1.31 (br m, 3H), 1.46 (s, 9H), 4.12-4.28 (m, 12H), 4.69 (br m, 1H), 4.84 (br m, 1H), 5.48 (br s, 1H), 7.12 (br s, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ = 14.1, 28.3 (3C), 41.4, 43.1, 61.4, 64.8, 65.0, 68.2, 69.8, 71.2 (5C), 80.2, 114.1, 156.2, 168.3, 169.3, 170.3. HRMS (ESI): calcd for C₂₂H₂₈FeN₂O₇Na [M+Na]⁺ 511.1144, found 511.1140.

(S_P)-N-(Ethoxycarbonylmethyl)-2-iodoferrocenecarboxamide (S_P-8).

S_P-8 was prepared from **S_P-7** and H-Gly-OEt·HCl according to the general procedure for peptidic coupling. Purification by flash chromatography on silica gel (EtOAc/heptane: 2/8) gave **S_P-8** (370 mg, 84%) as a red solid (mp = 98 °C). [α]_D (20 °C) = +5.0 (*c* 1.0, CHCl₃). ¹H NMR (CDCl₃, 300 MHz): δ = 1.31 (t, 3H, *J* = 7.0 Hz), 4.08-4.31 (m, 4H), 4.27 (s, 5H), 4.40 (br m, 1H), 4.62 (br m, 1H), 4.88 (br m, 1H), 7.00 (br s, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ = 14.3, 39.5, 41.6, 61.6, 69.7, 71.5, 73.0 (5C), 75.9, 78.8, 169.1, 170.1. HRMS (ESI): calcd for C₁₅H₁₆FeINO₃Na [M+Na]⁺ 463.9422, found 463.9444.

(S_P)-N-(Ethoxycarbonylmethyl)-2-((tert-butoxycarbonylamino)methyl)carbonyloxy)ferrocene-carboxamide (S_P-9).

To a stirred solution of **S_P-8** (441 mg, 1.0 mmol) and Cu₂O (114 mg, 0.8 mmol) in CH₃CN (10 mL) was added Boc-Gly-OH (210 mg, 1.2 mmol). The mixture was refluxed for 3 h and then the solvent was removed under reduced pressure. The crude residue was taken up in Et₂O (20 mL) and the organic mixture was successively washed with an aqueous saturated solution of NH₄Cl (20 mL), water (20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/heptane: 3/7) gave **S_P-9** (244 mg, 50%) as a red solid (mp = 58 °C). [α]_D (20 °C) = +5.0 (c 1.0, CHCl₃). ¹H NMR (CDCl₃, 300 MHz): δ = 1.32 (br m, 3H), 1.46 (s, 9H), 4.12-4.28 (m, 12H), 4.69 (br m, 1H), 4.84 (br m, 1H), 5.48 (br s, 1H), 7.12 (br s, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ = 14.1, 28.3 (3C), 41.4, 43.1, 61.4, 64.8, 65.0, 68.2, 69.8, 71.2 (5C), 80.2, 114.1, 156.2, 168.3, 169.3, 170.3. HRMS (ESI): calcd for C₂₂H₂₈FeN₂O₇Na [M+Na]⁺ 511.1144, found 511.1140.

2-(Tert-butoxycarbonylamino)ethyl 2-iodoferrocenecarboxylate (racemic mixture) (rac-10).

To a stirred, cooled (0 °C) solution of **rac-7** (356 mg, 1.0 mmol), *N*-Boc-ethanolamine (161 mg, 1.0 mmol) and DMAP (146 mg, 1.2 mmol) in CH₂Cl₂ (10 mL) was added DCC (248 mg, 1.2 mmol). The mixture was refluxed for 12 h and then filtered on celite[®]. Purification by flash chromatography on silica gel (EtOAc/heptane: 2/8) gave **rac-10** (419 mg, 84%) as a red solid (mp = 88 °C). ¹H NMR (CDCl₃, 300 MHz): δ = 1.44 (s, 9H), 3.52 (dt, 2H, *J* = 5.3 and 5.3 Hz), 4.22 (s, 5H), 4.32 (t, 2H, *J* = 5.3 Hz), 4.45 (dd, 1H, *J* = 2.6 and 2.6 Hz), 4.70 (dd, 1H, *J* = 1.5 and 2.6 Hz), 4.88 (dd, 1H, *J* = 1.5 and 1.5 Hz), 5.00 (br m, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ = 28.5 (3C), 39.8, 63.6, 69.9, 70.5, 70.9, 72.5, 72.9 (5C), 79.7, 80.0, 155.8, 170.3. HRMS (ESI): calcd for C₁₈H₂₂FeINO₄Na [M+Na]⁺ 521.9841, found 521.9848.

2-(Tert-butoxycarbonylamino)ethyl 2-((tert-butoxycarbonylamino)methyl)carbonyloxy)ferrocene-carboxylate (racemic mixture) (rac-11).

To a stirred solution of **rac-10** (499 mg, 1.0 mmol) and Cu₂O (114 mg, 0.8 mmol) in CH₃CN (10 mL) was added Boc-Gly-OH (210 mg, 1.2 mmol). The mixture was refluxed for 3 h and then the solvent was removed under reduced pressure. The crude residue was taken up in Et₂O (20 mL) and the organic mixture was successively washed with an aqueous saturated solution of NH₄Cl (20 mL), water (20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/heptane: 2/8) gave **rac-11** (295 mg, 54%) as a red solid (mp = 130 °C). ¹H NMR (CDCl₃, 300 MHz): δ = 1.45 (s, 18 H), 3.44 (br m, 2H), 3.94-4.43 (m, 5H), 4.28 (s, 5H), 4.57-4.64 (br m, 2H), 5.14 (br m, 1H), 5.32 (br m, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ = 28.4 (3C), 28.5 (3C), 40.0, 42.7, 63.2, 63.4, 65.3, 65.8, 66.8, 71.4 (5C), 79.8, 80.2, 115.0, 156.0 (2C), 170.0, 170.4. HRMS (ESI): calcd for C₂₅H₃₄FeN₂O₈Na [M+Na]⁺ 569.1562, found 569.1562.

(S_P)-2-(Tert-butoxycarbonylamino)ethyl 2-iodoferrocenecarboxylate (S_P-10).

To a stirred, cooled (0 °C) solution of **S_P-7** (356 mg, 1.0 mmol), *N*-Boc-ethanolamine (161 mg, 1.0 mmol) and DMAP (146 mg, 1.2 mmol) in CH₂Cl₂ (10 mL) was added DCC (248 mg, 1.2 mmol). The mixture was refluxed for 12 h and then filtered on celite[®]. Purification by flash chromatography on silica gel (EtOAc/CH₂Cl₂: 2/8) gave **S_P-10** (419 mg, 84%) as a red solid (mp = 88 °C). [α]_D (20 °C) = -6.3 (*c* 2.6, CHCl₃). ¹H NMR (CDCl₃, 300 MHz): δ = 1.43 (s, 9H), 3.50 (br m, 2H), 4.20 (s, 5H), 4.30 (br m, 2H), 4.44 (br m, 1H), 4.68 (br m, 1H), 4.86 (br m, 1H), 5.02 (br m, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ = 28.5 (3C), 39.8, 63.6, 69.9, 70.5, 70.8, 72.5, 72.9 (5C), 79.6, 80.0, 155.8, 170.3. HRMS (ESI): calcd for C₁₈H₂₂FeINO₄Na [M+Na]⁺ 521.9841, found 521.9848.

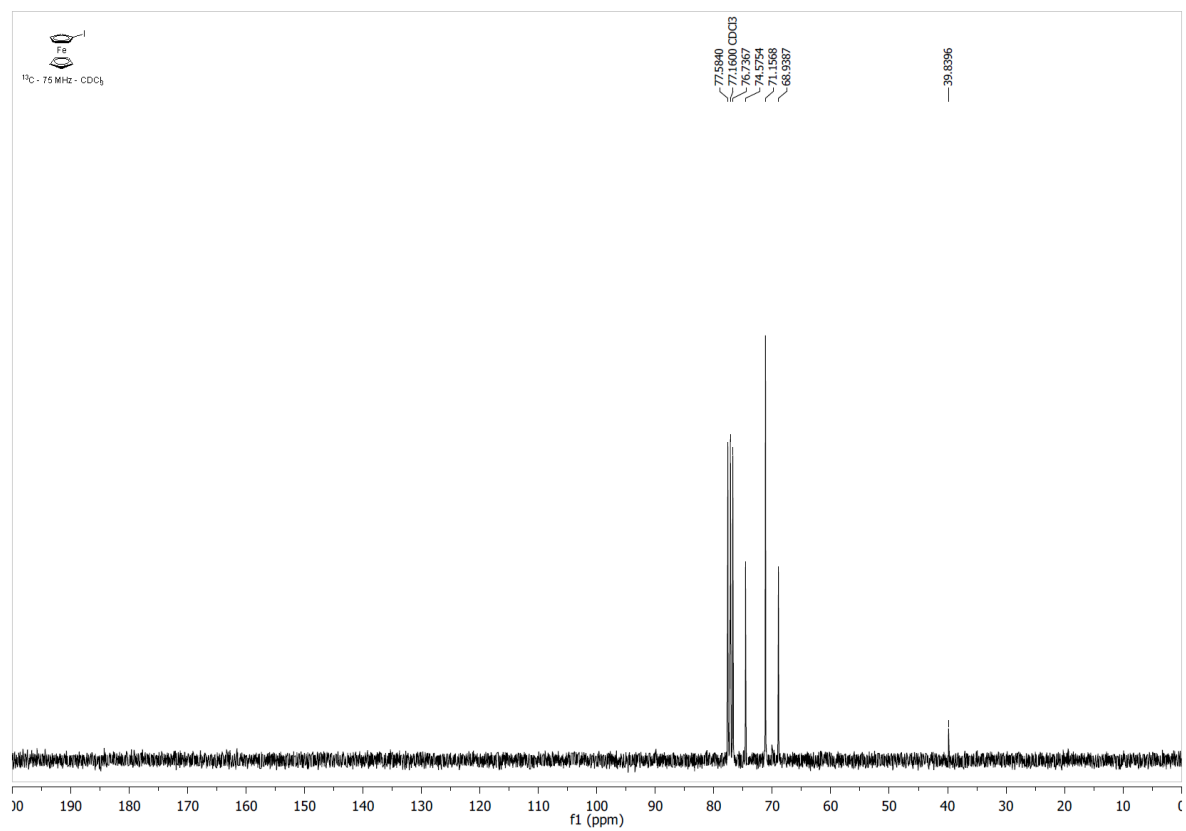
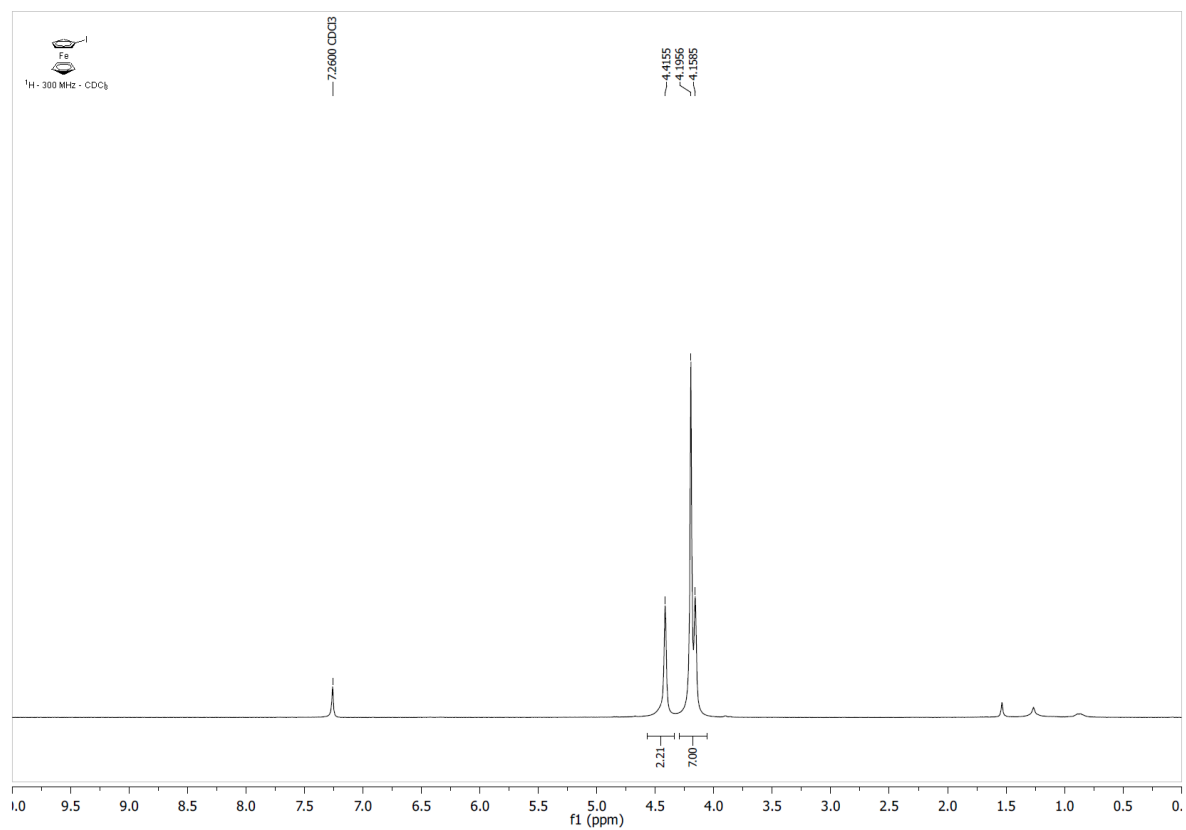
(S_P)-2-(Tert-butoxycarbonylamino)ethyl 2-((tert-butoxycarbonylamino)methyl)carbonyloxyferrocenecarboxylate (S_P-11).

To a stirred solution of **S_P-10** (499 mg, 1.0 mmol) and Cu₂O (114 mg, 0.8 mmol) in CH₃CN (10 mL) was added Boc-Gly-OH (210 mg, 1.2 mmol). The mixture was refluxed for 3 h and then the solvent was removed under reduced pressure. The crude residue was taken up in Et₂O (20 mL) and the organic mixture was successively washed with an aqueous saturated solution of NH₄Cl (20 mL), water (20 mL),

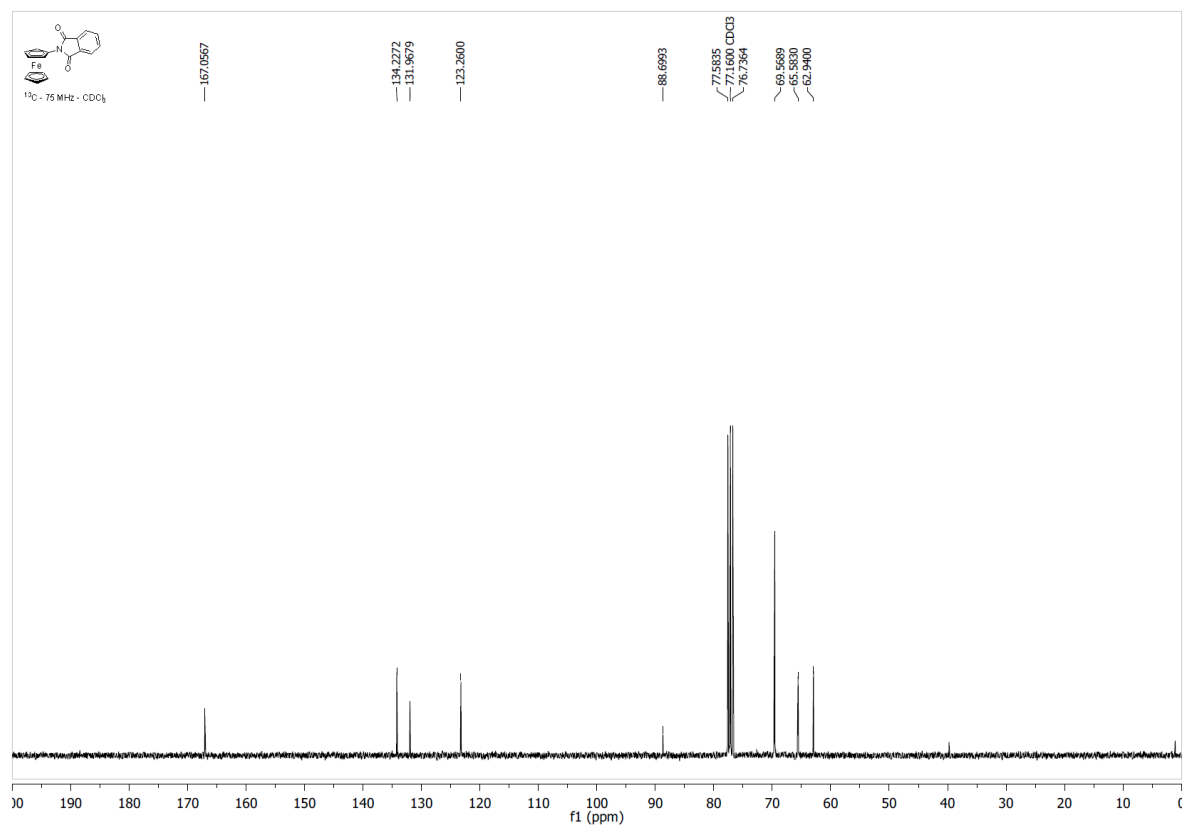
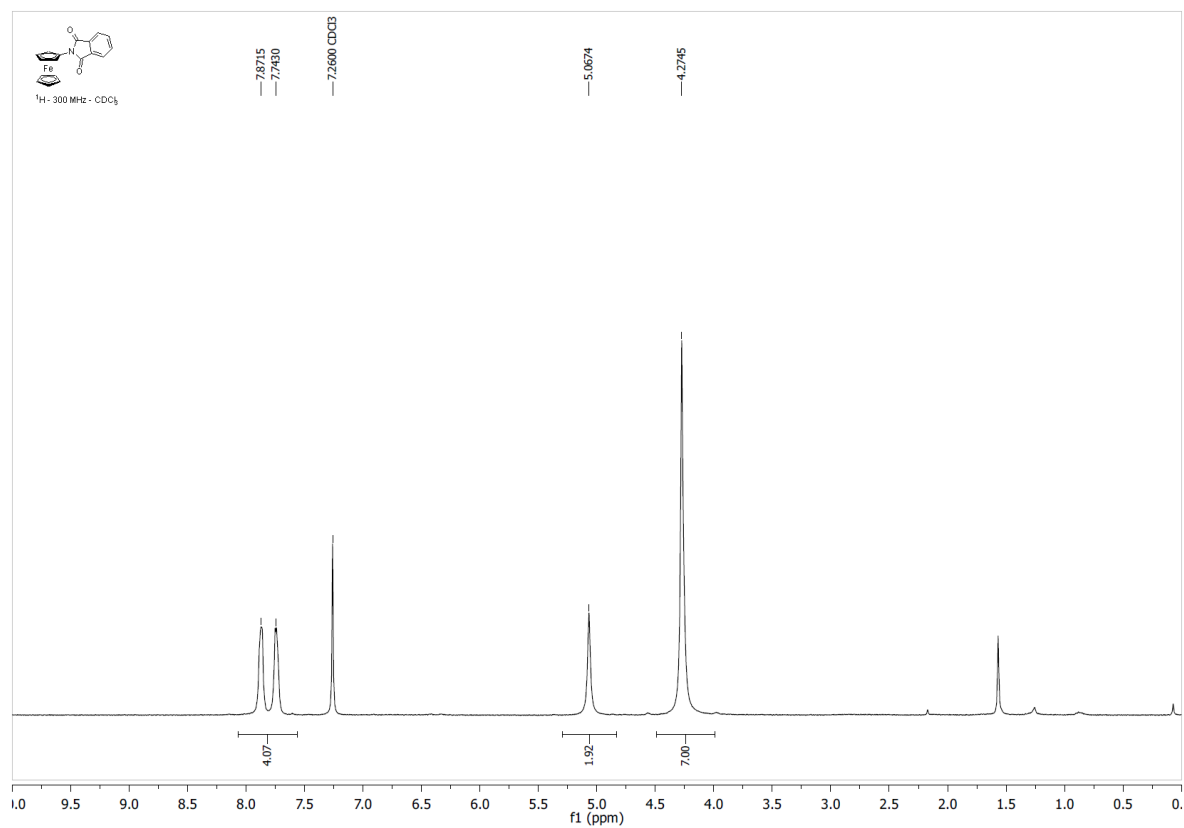
dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/heptane: 2/8) gave **Sp-11** (459 mg, 54%) as a red solid (mp = 130 °C). $[\alpha]_D$ (20 °C) = +28.0 (*c* 0.5, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ = 1.45 (s, 9 H), 1.46 (s, 9 H), 3.45 (br m, 2H), 3.94-4.43 (m, 5H), 4.29 (s, 5H), 4.58-4.65 (br m, 2H), 5.12 (br m, 1H), 5.29 (br m, 1H). ^{13}C NMR (CDCl_3 , 75 MHz): δ = 28.4 (3C), 28.5 (3C), 40.0, 42.7, 63.2, 63.4, 65.3, 65.8, 66.8, 71.4 (5C), 79.8, 80.2, 115.0, 156.0 (2C), 170.0, 170.4. HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{34}\text{FeN}_2\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 569.1562, found 569.1562.

It is worth noting that the broad peaks observed for carboxamide-containing ferrocenes are a feature of such compounds, and can change as a function of the solvent and concentration.¹⁰

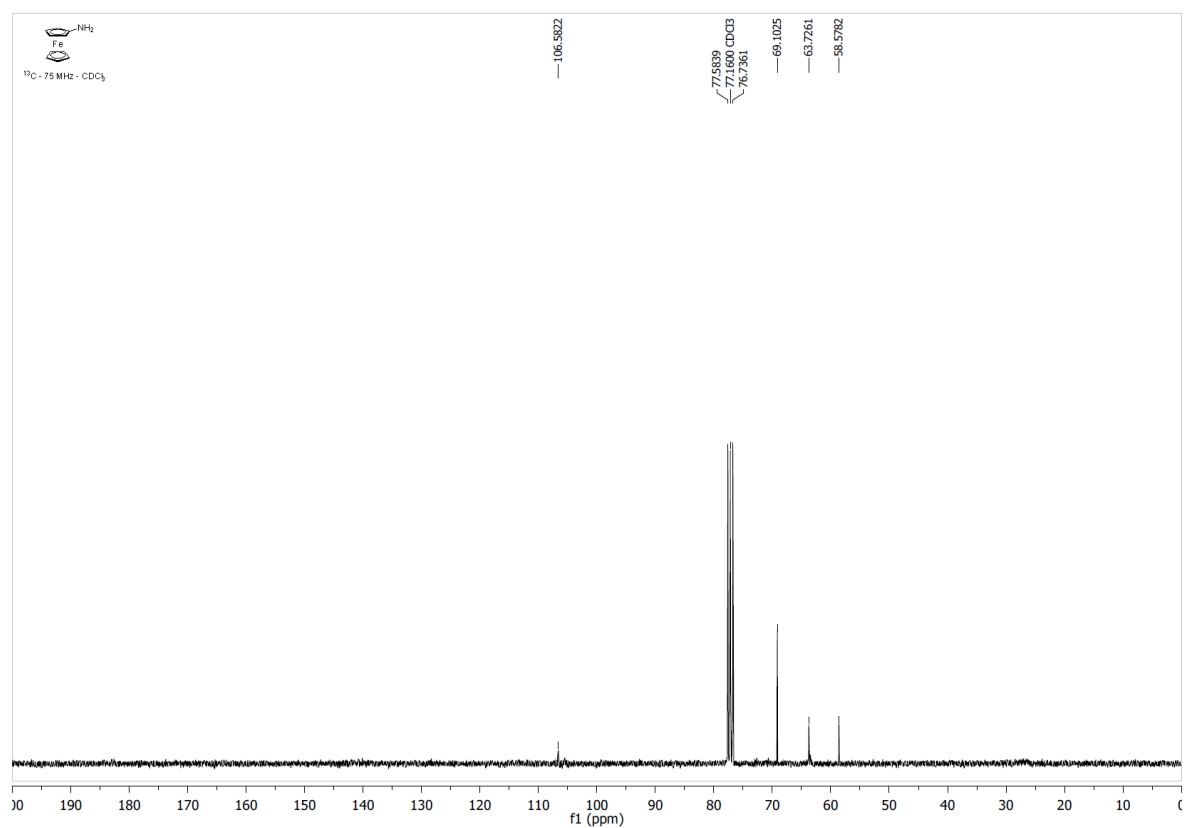
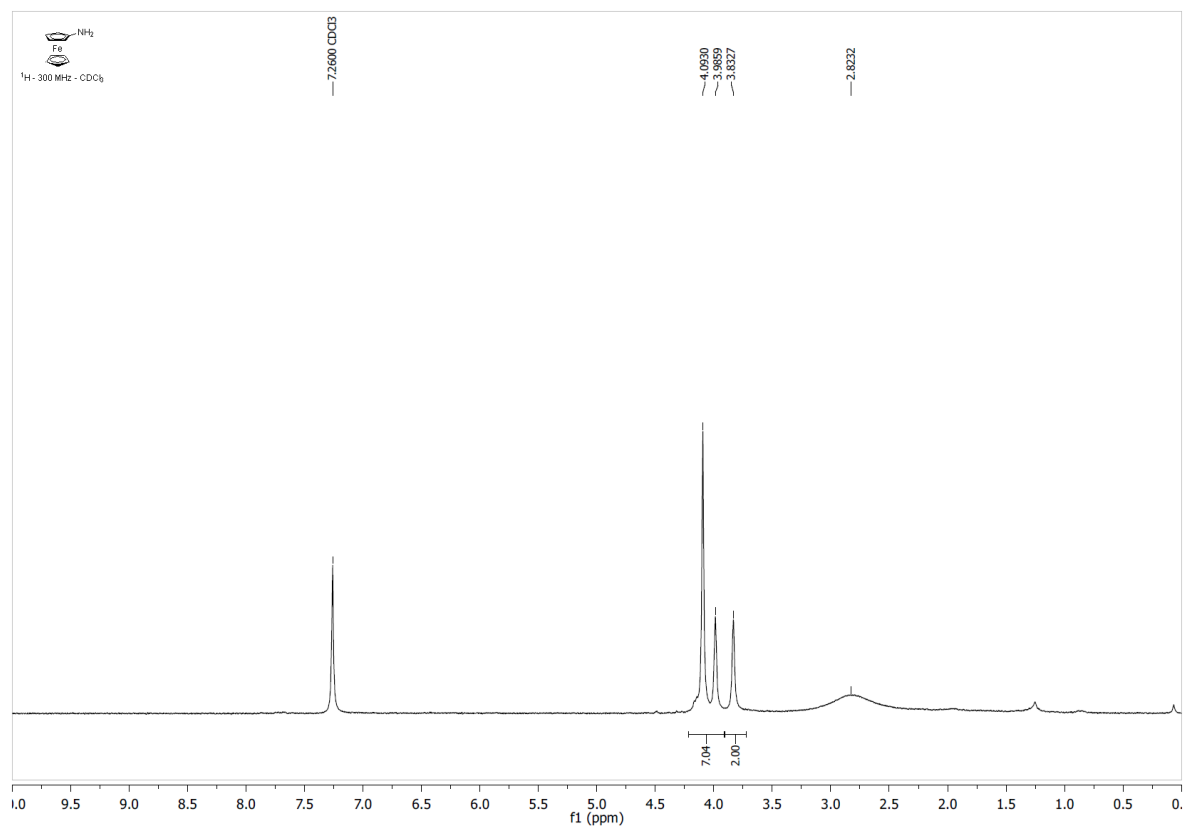
Iodoferrocene



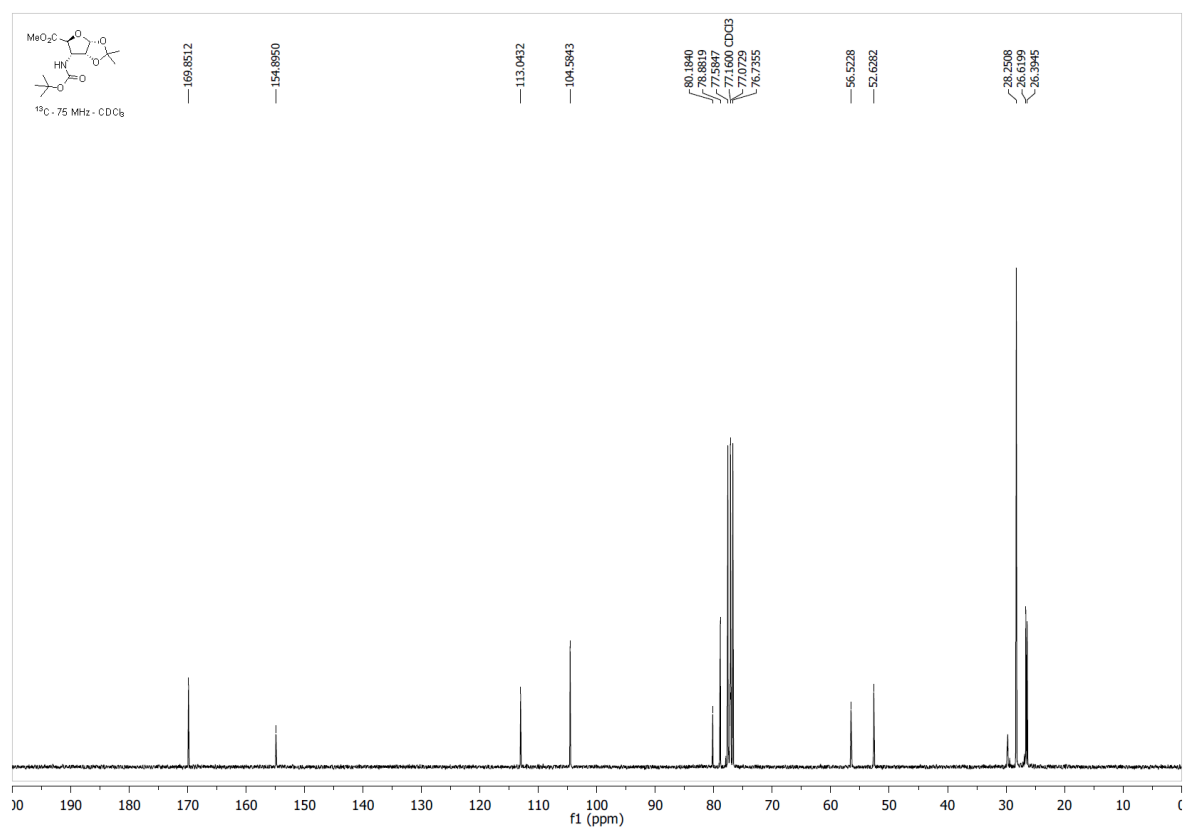
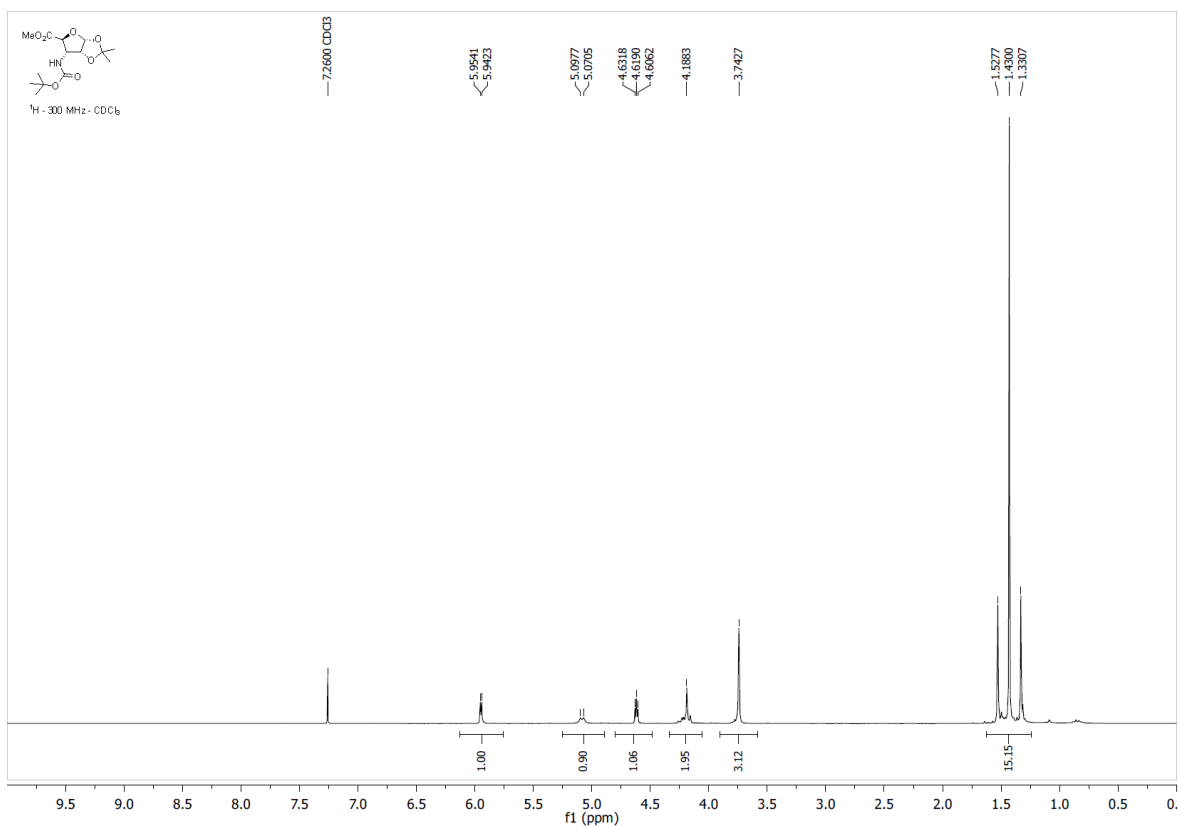
N-Ferrocenylphthalimide



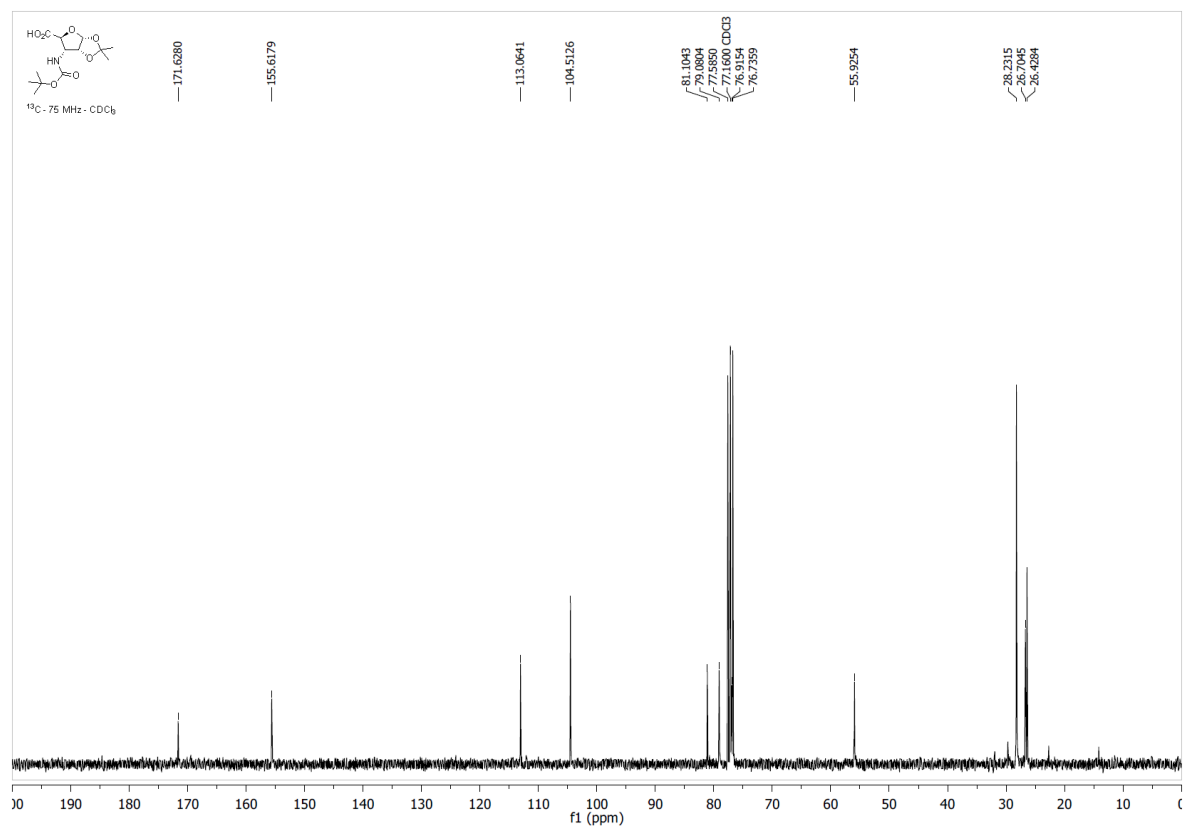
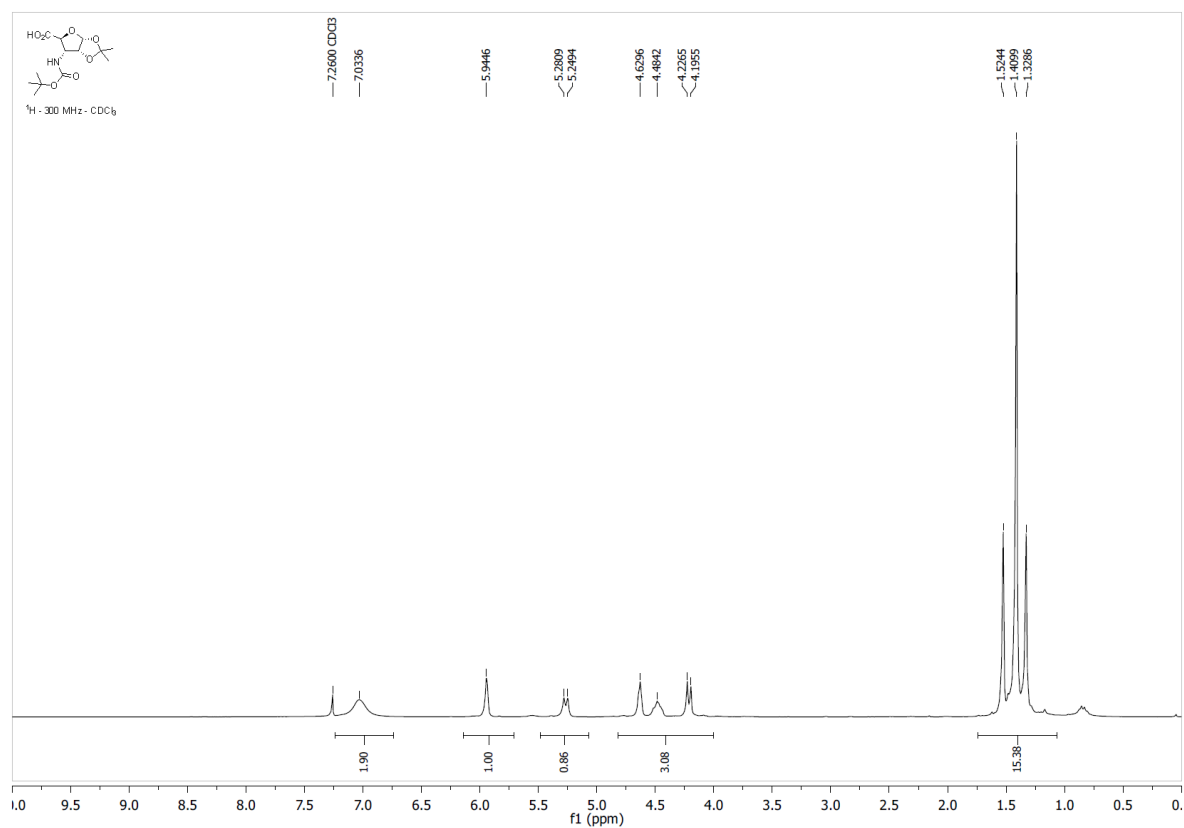
Aminoferrocene



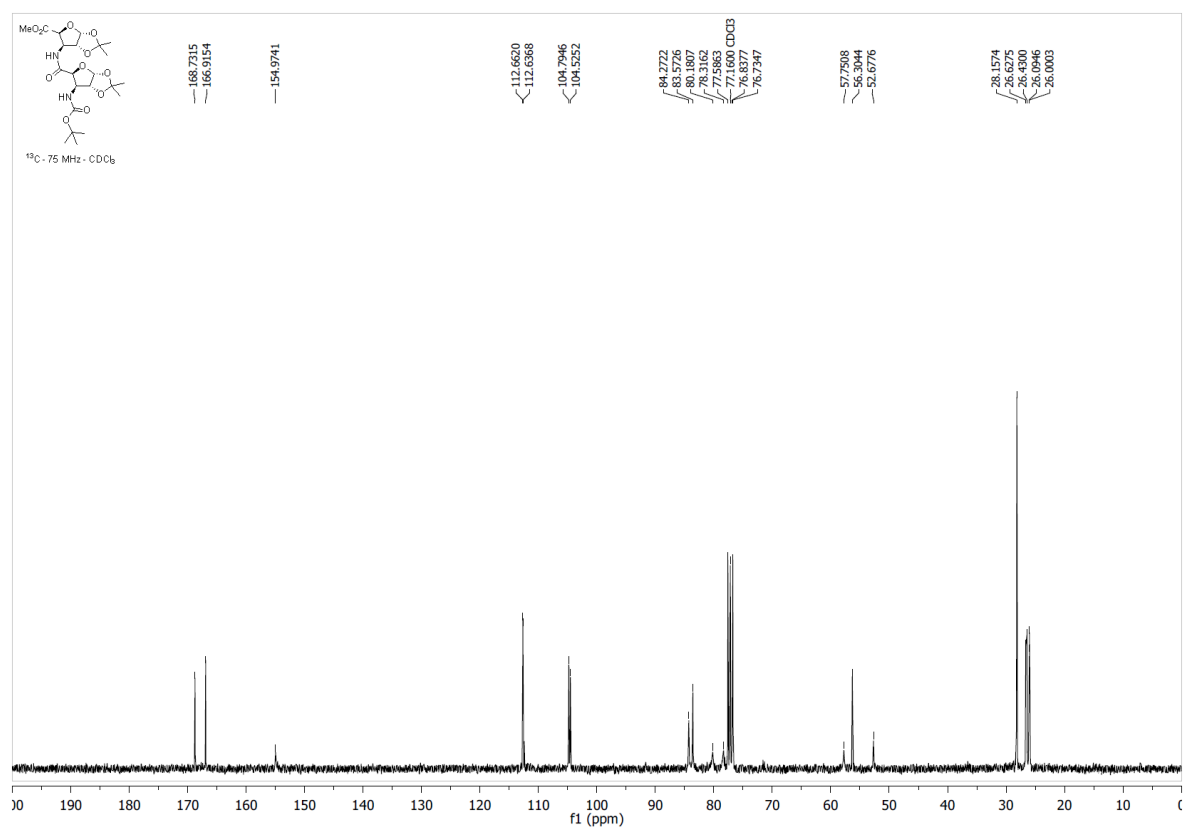
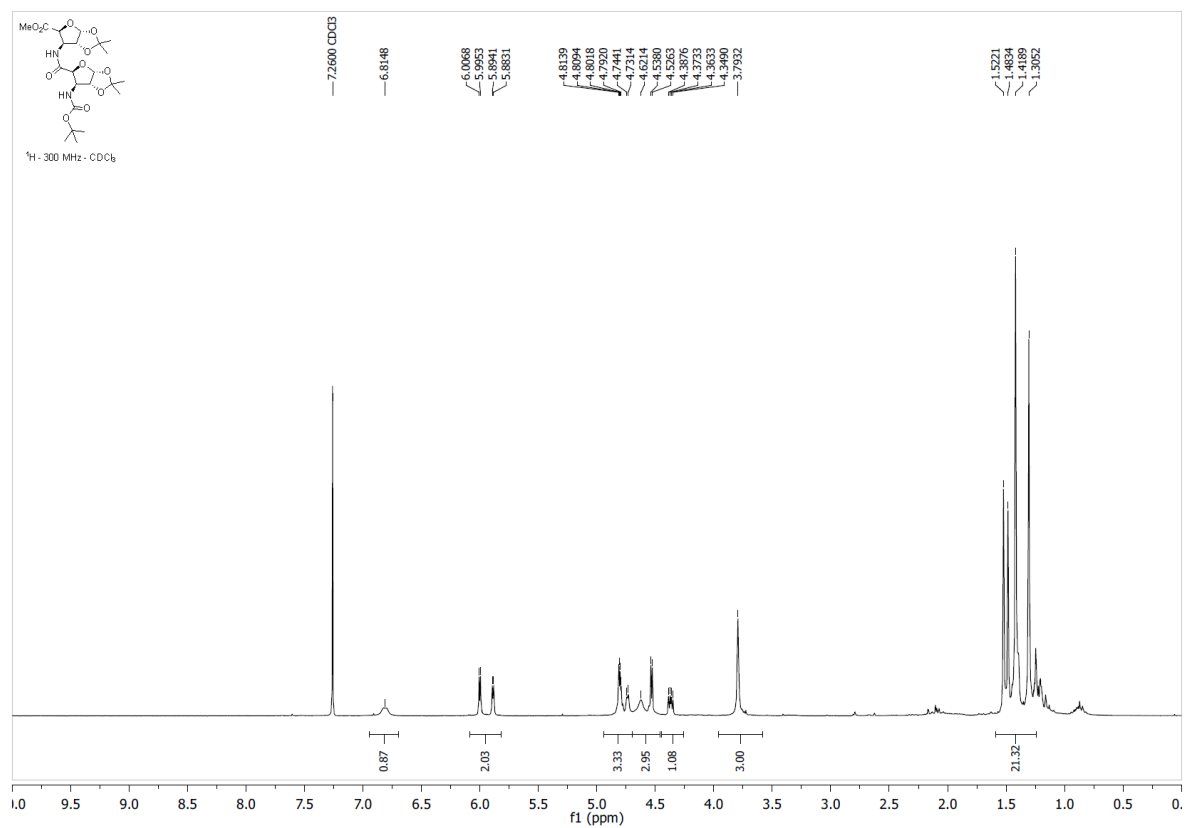
Methyl 3-amino-3-deoxy-*N*-(*tert*-butoxycarbonyl)-1,2-*O*-isopropylidene- α -D-ribofuranate



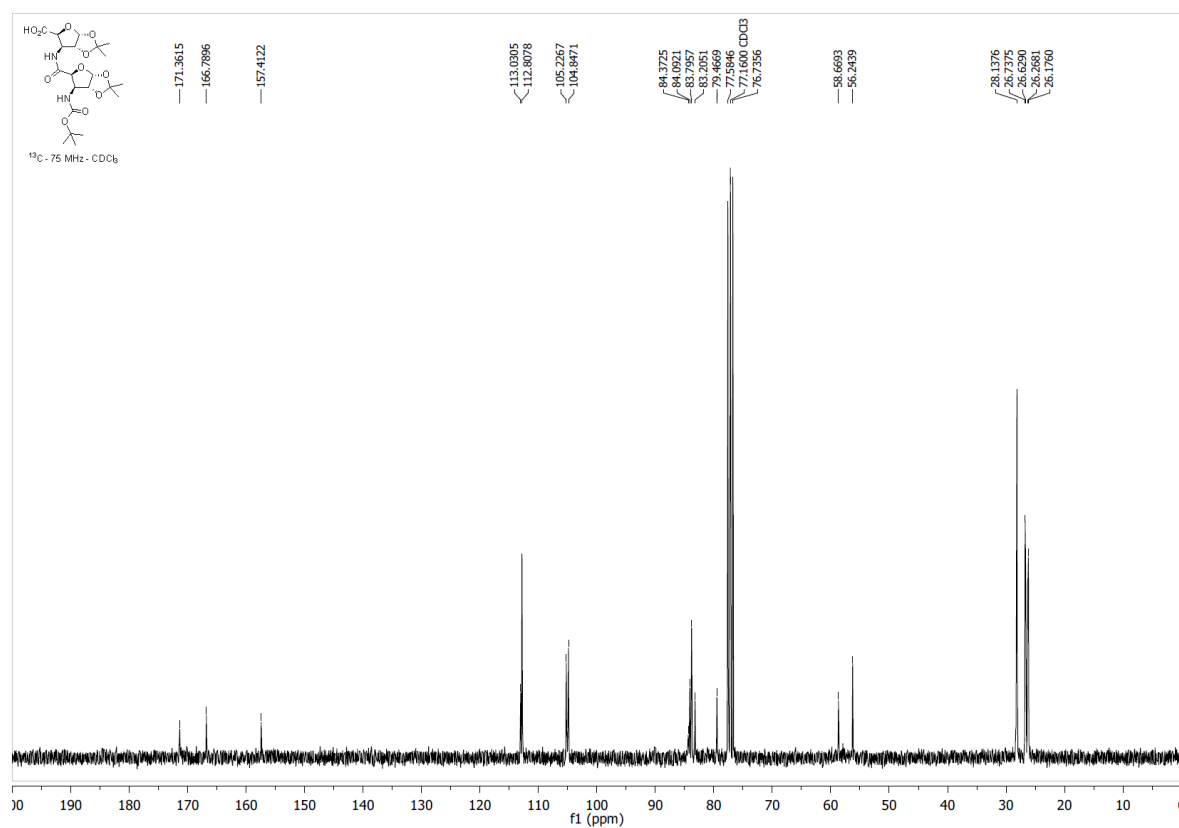
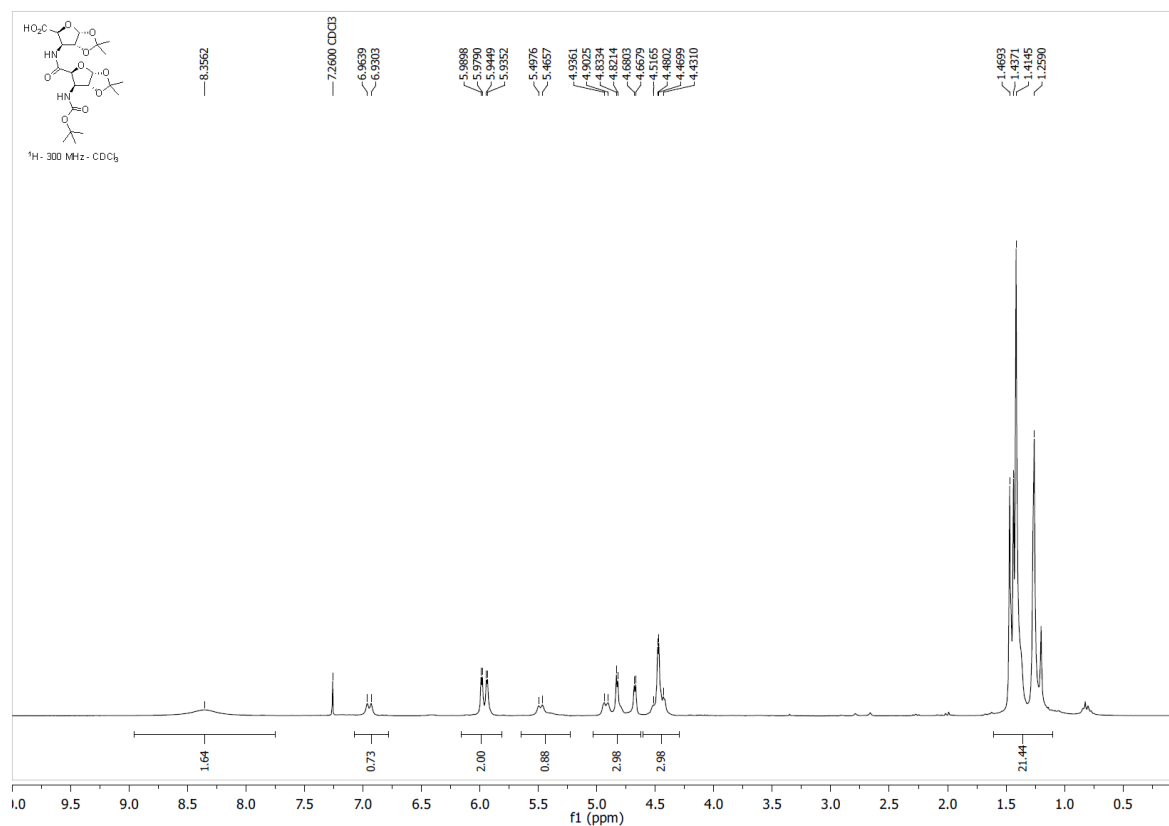
3-Amino-3-deoxy-*N*-(*tert*-butoxycarbonyl)-1,2-*O*-isopropylidene- α -D-ribofuranic acid (SAA-1)



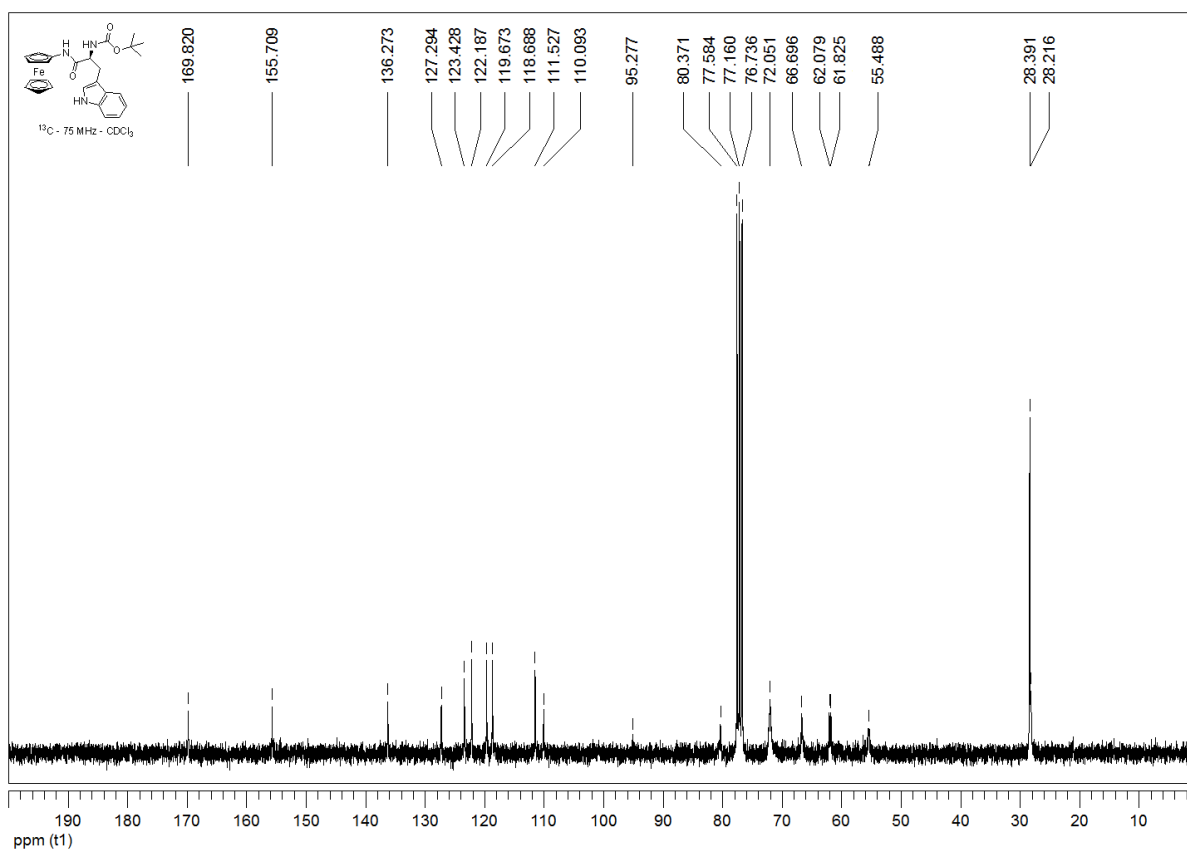
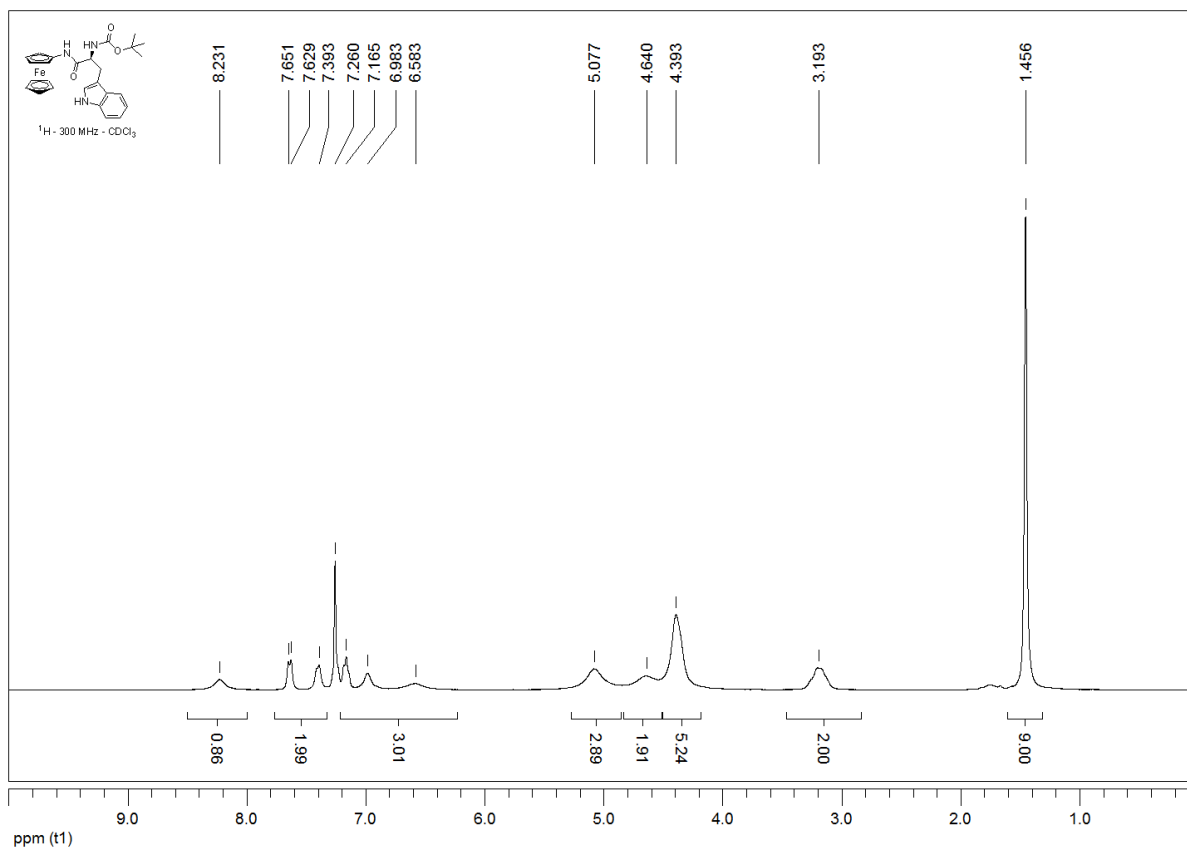
Methyl ester of xylofuranoid sugar amino acid SAA-4



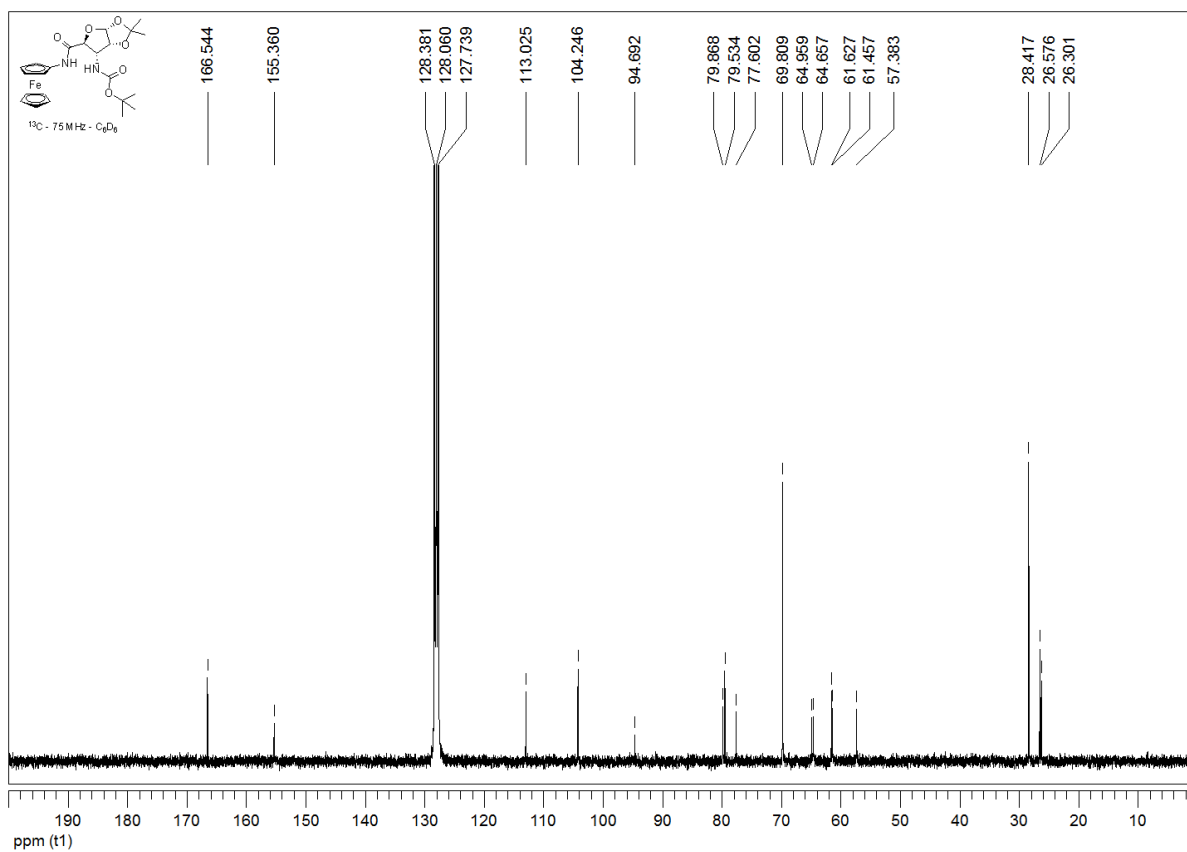
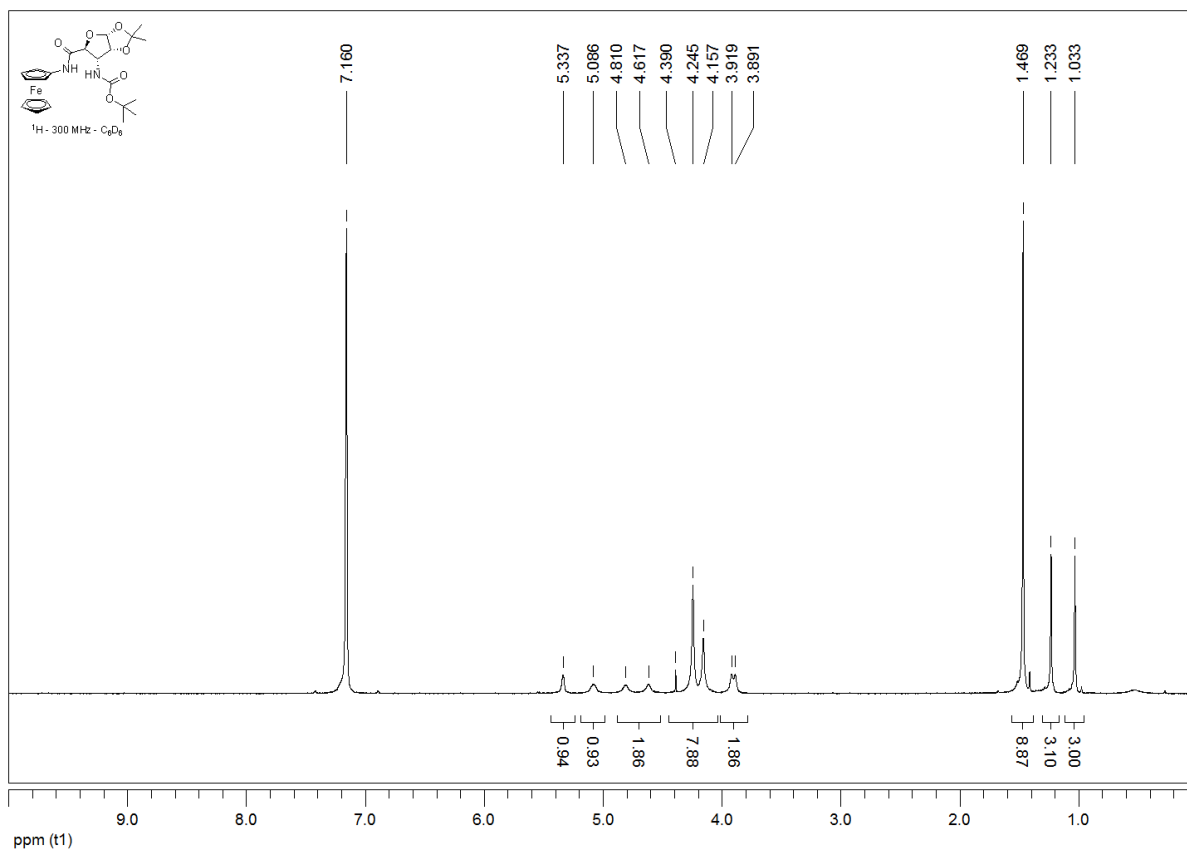
Xylofuranoid sugar amino acid SAA-4



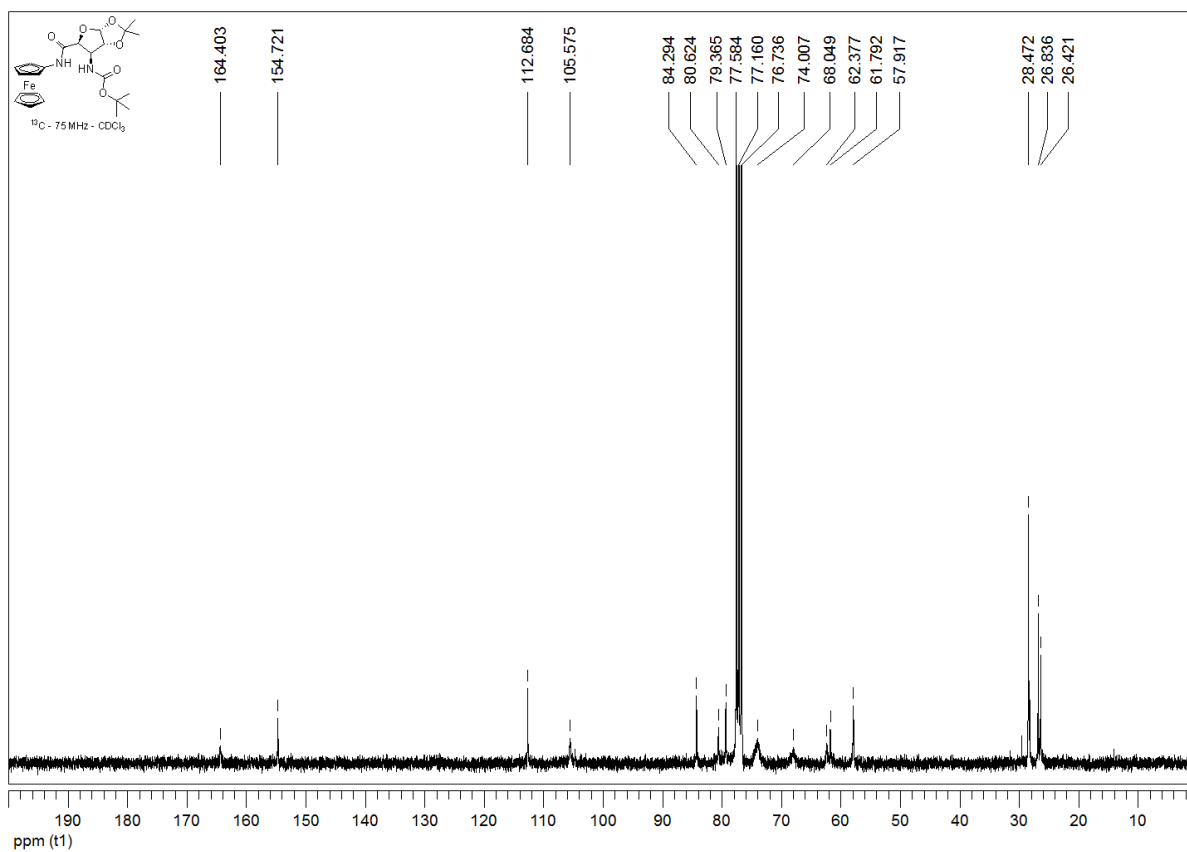
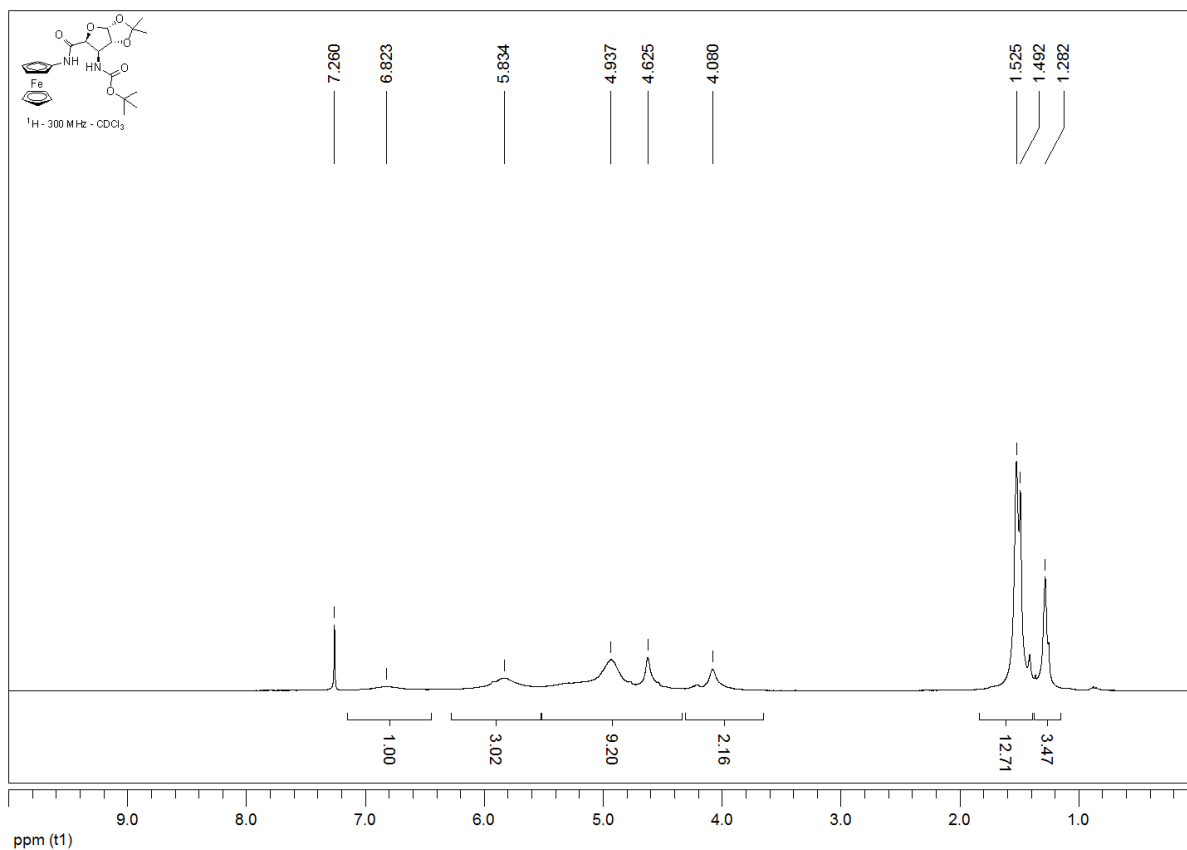
Ferrocene carboxamide FcC-0



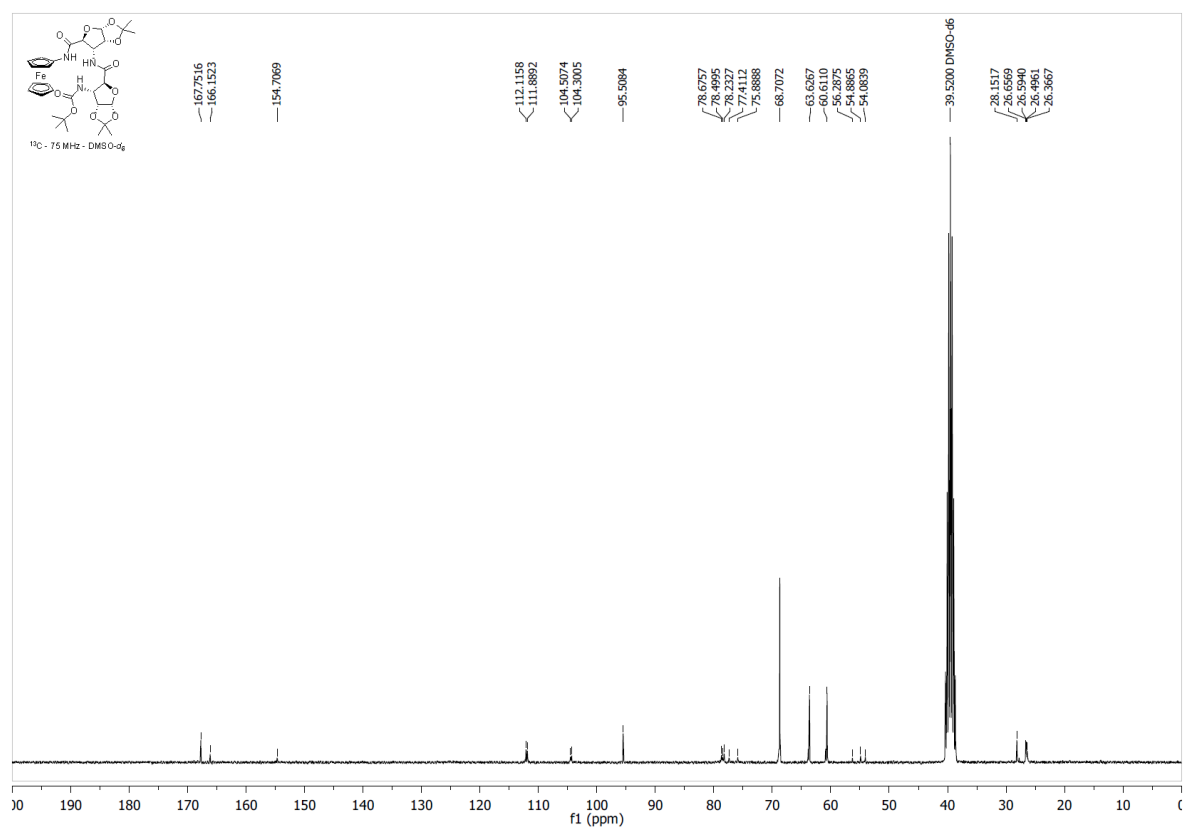
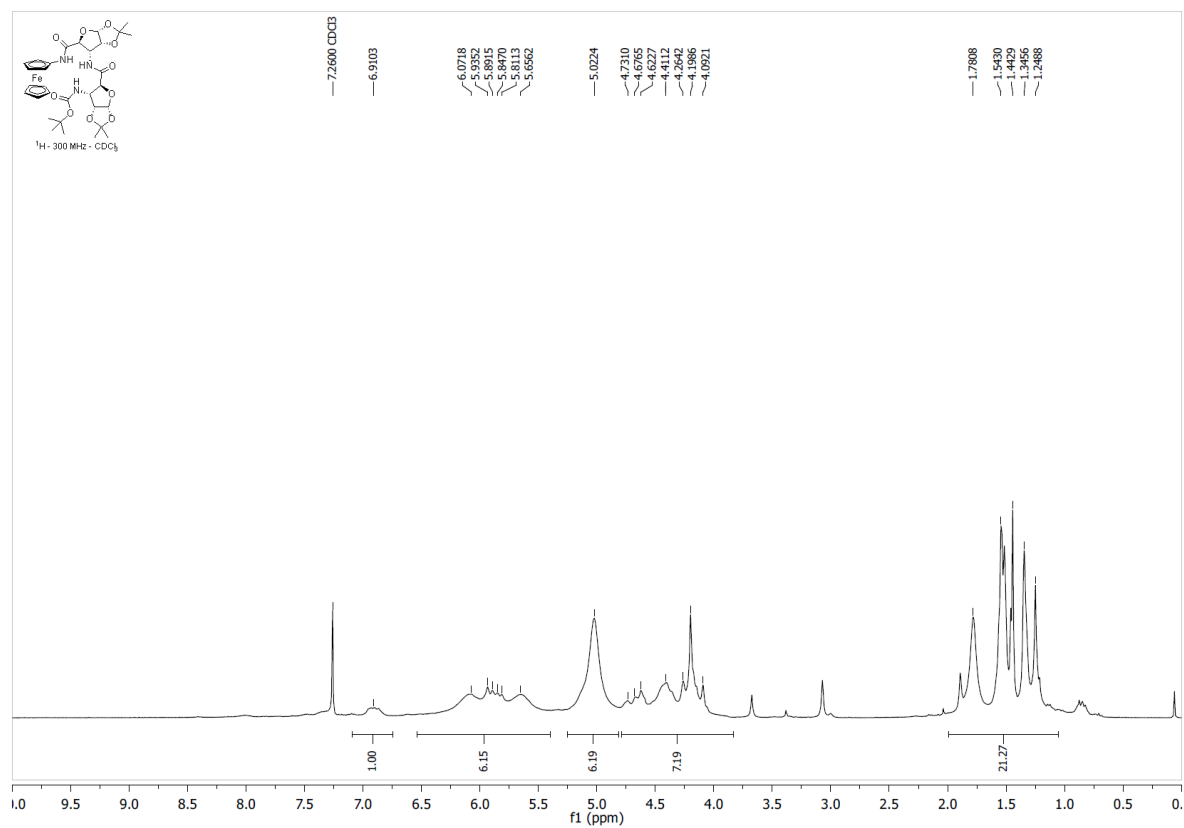
Ferrocene carboxamide FcC-1



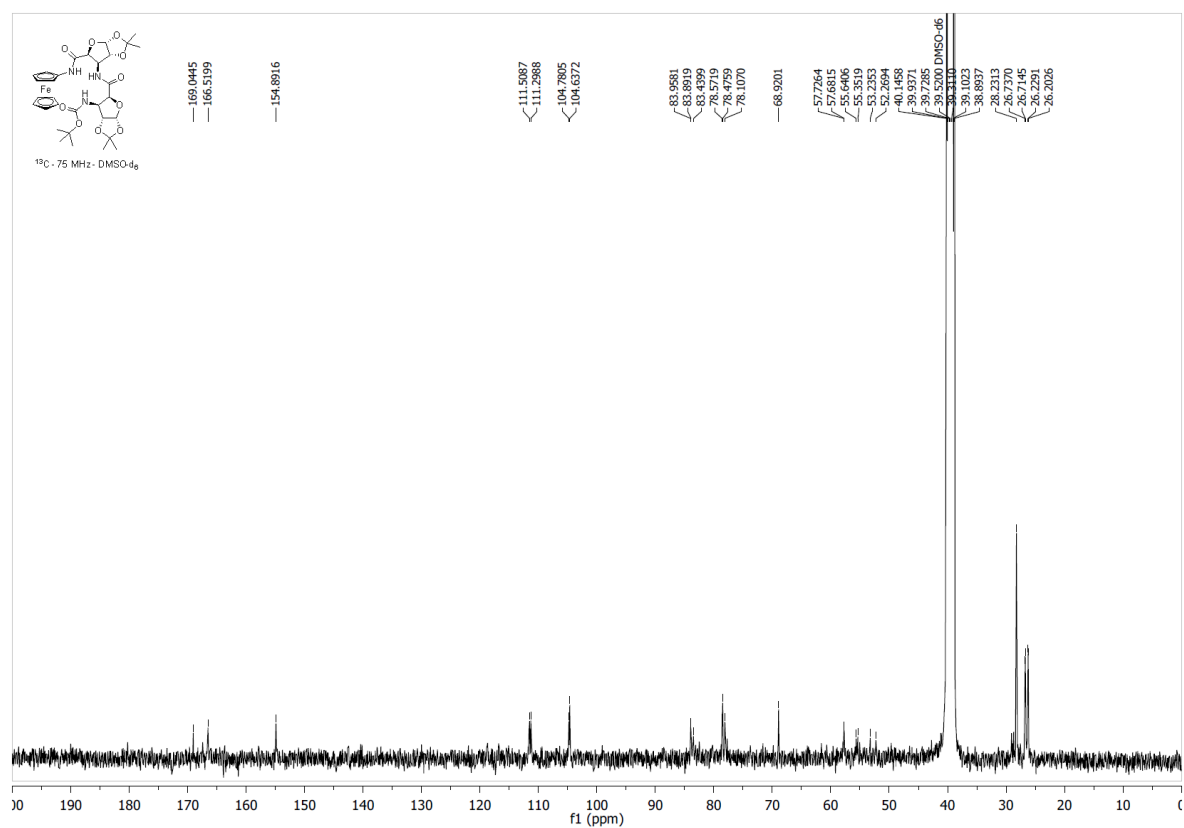
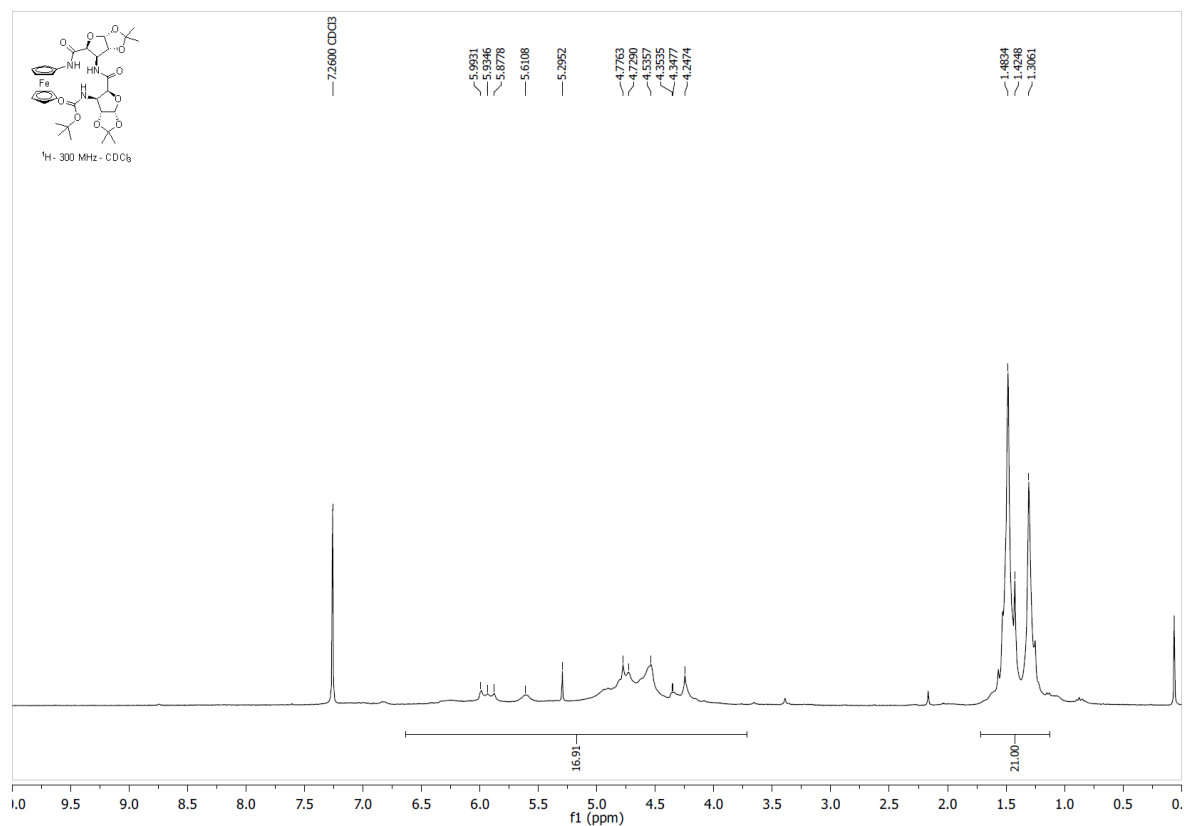
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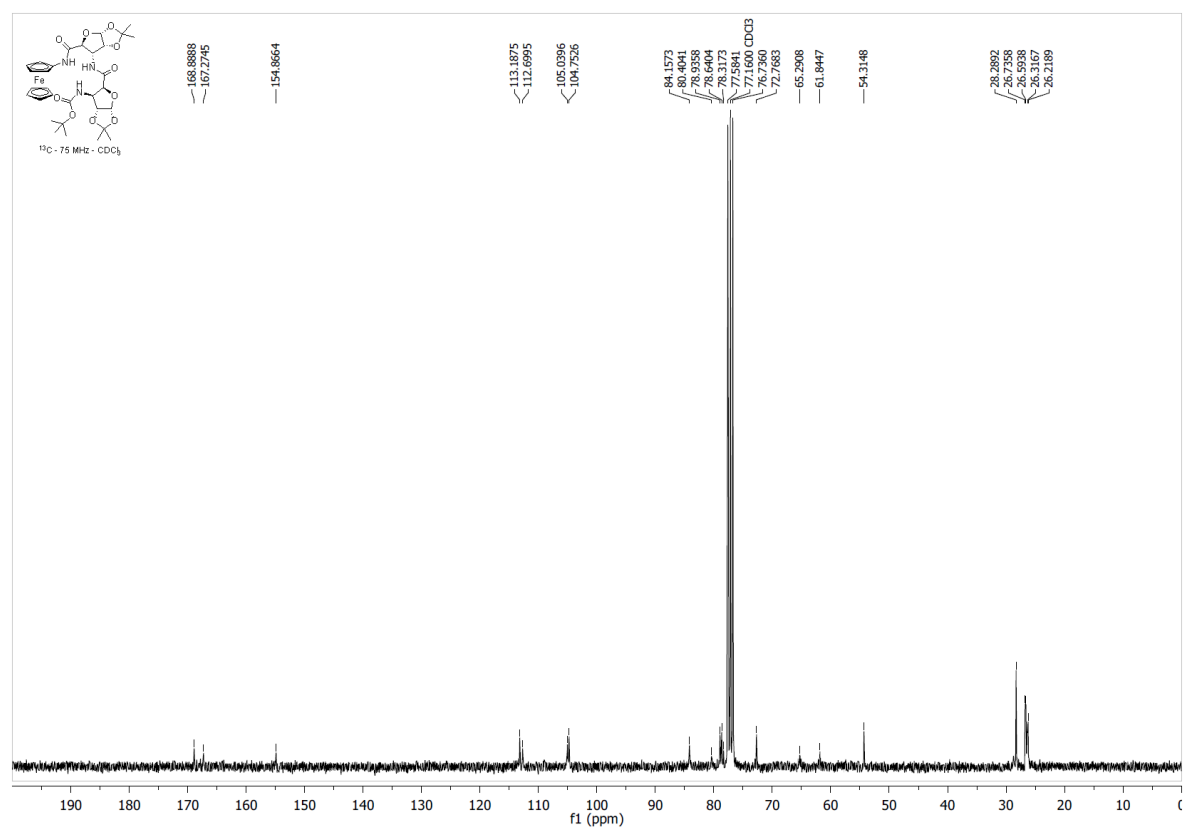
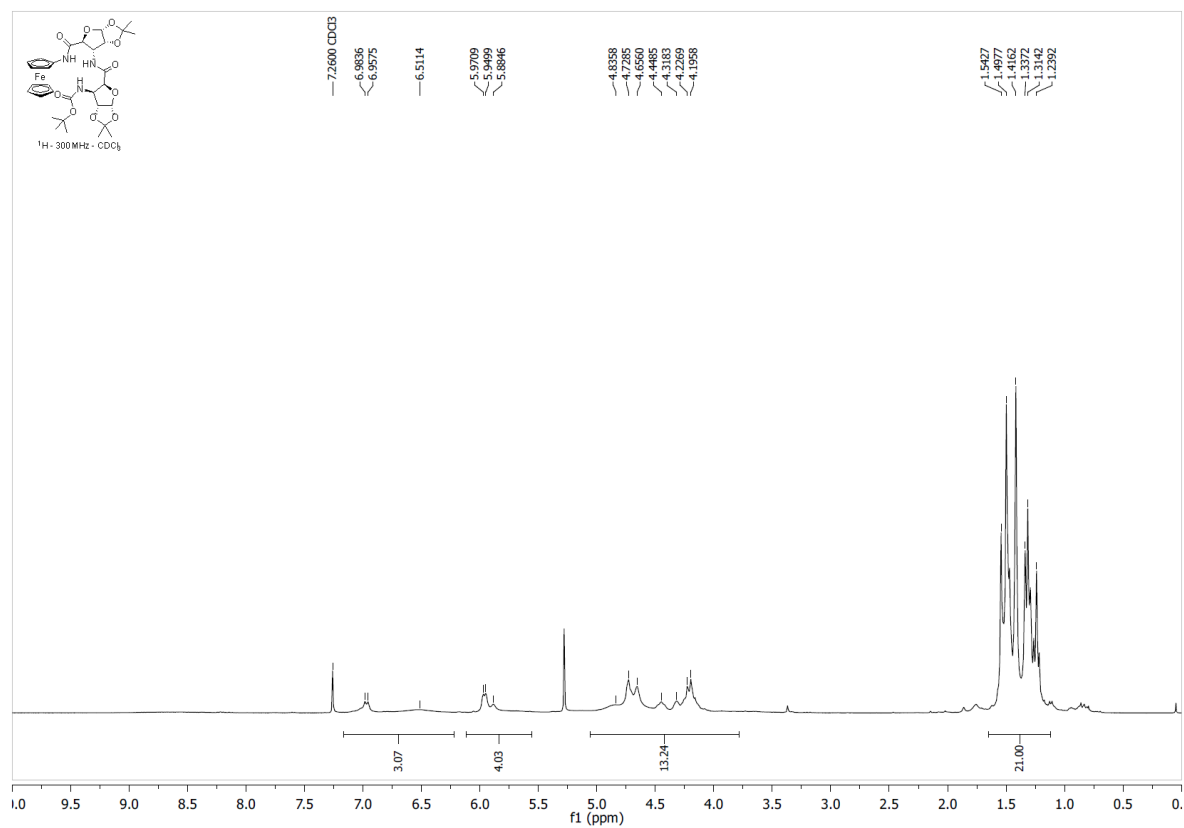
Ferrocene carboxamide FcC-3



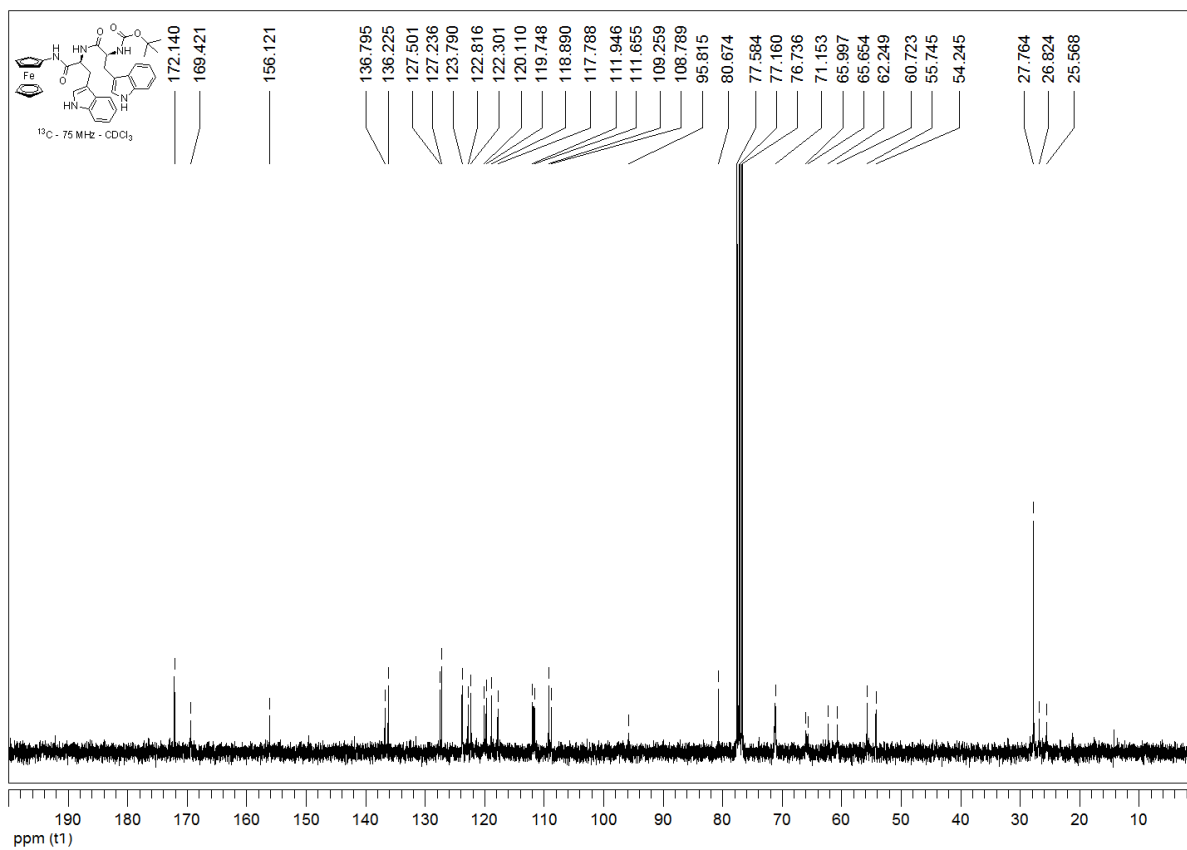
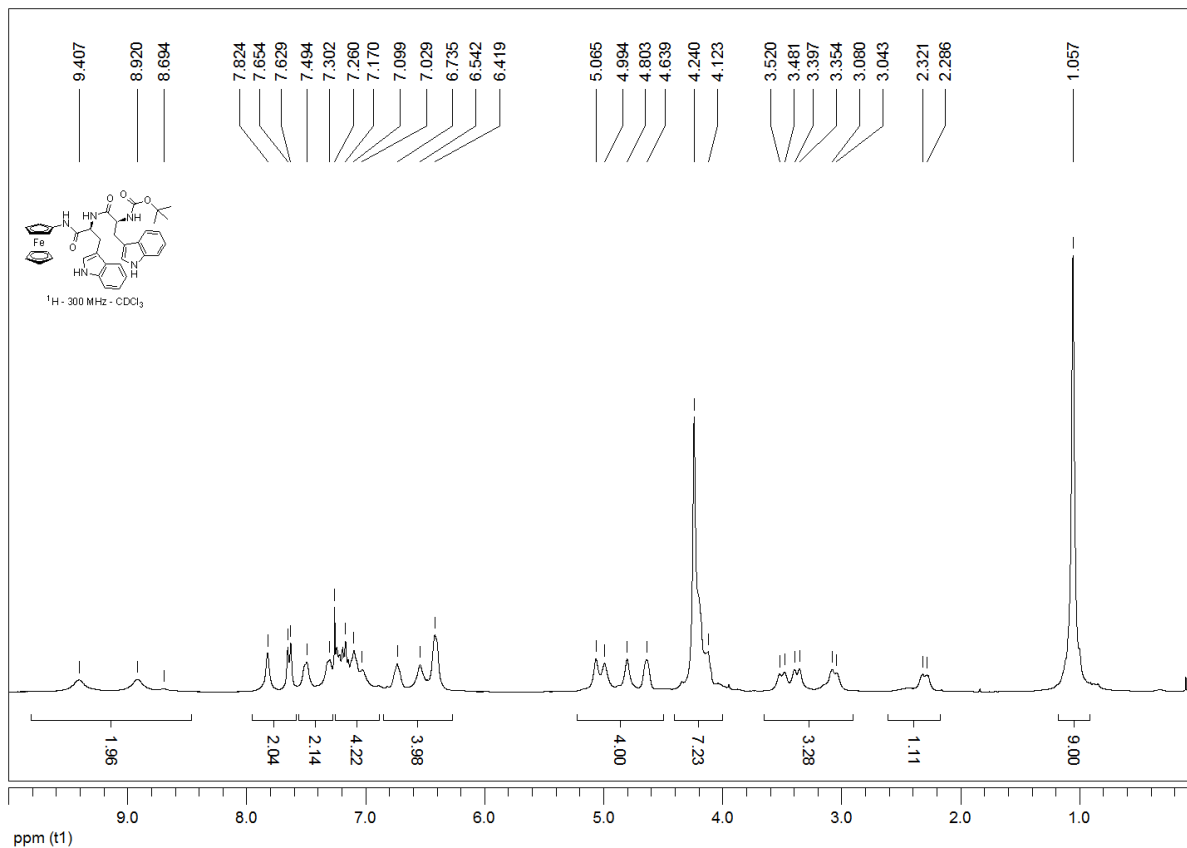
Ferrocene carboxamide FcC-4



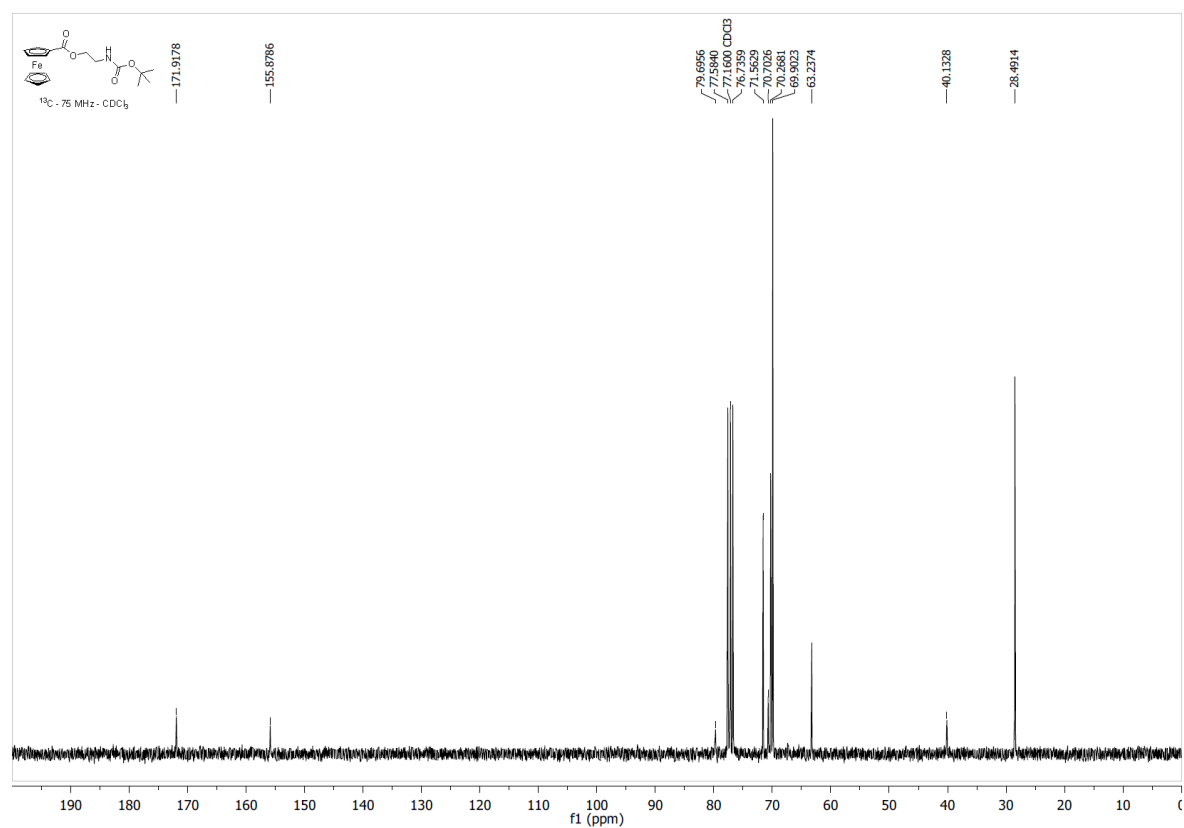
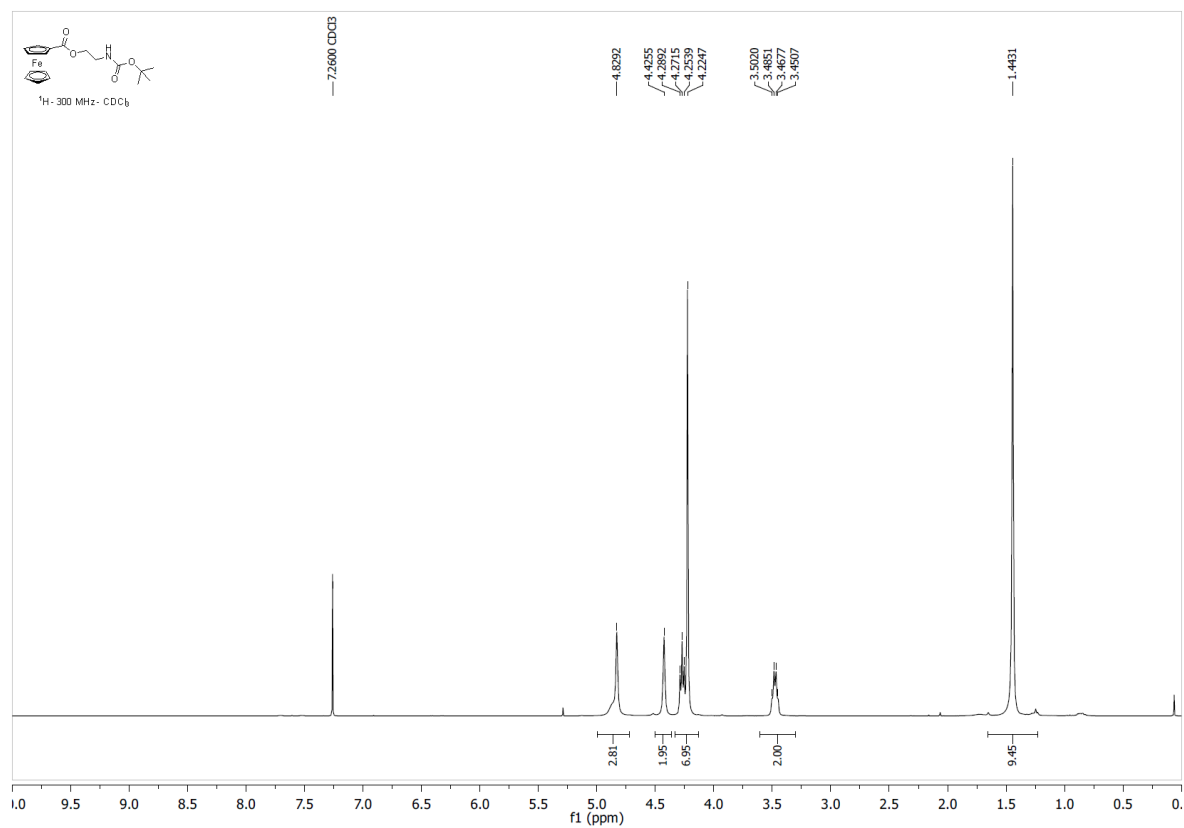
Ferrocene carboxamide FcC-5



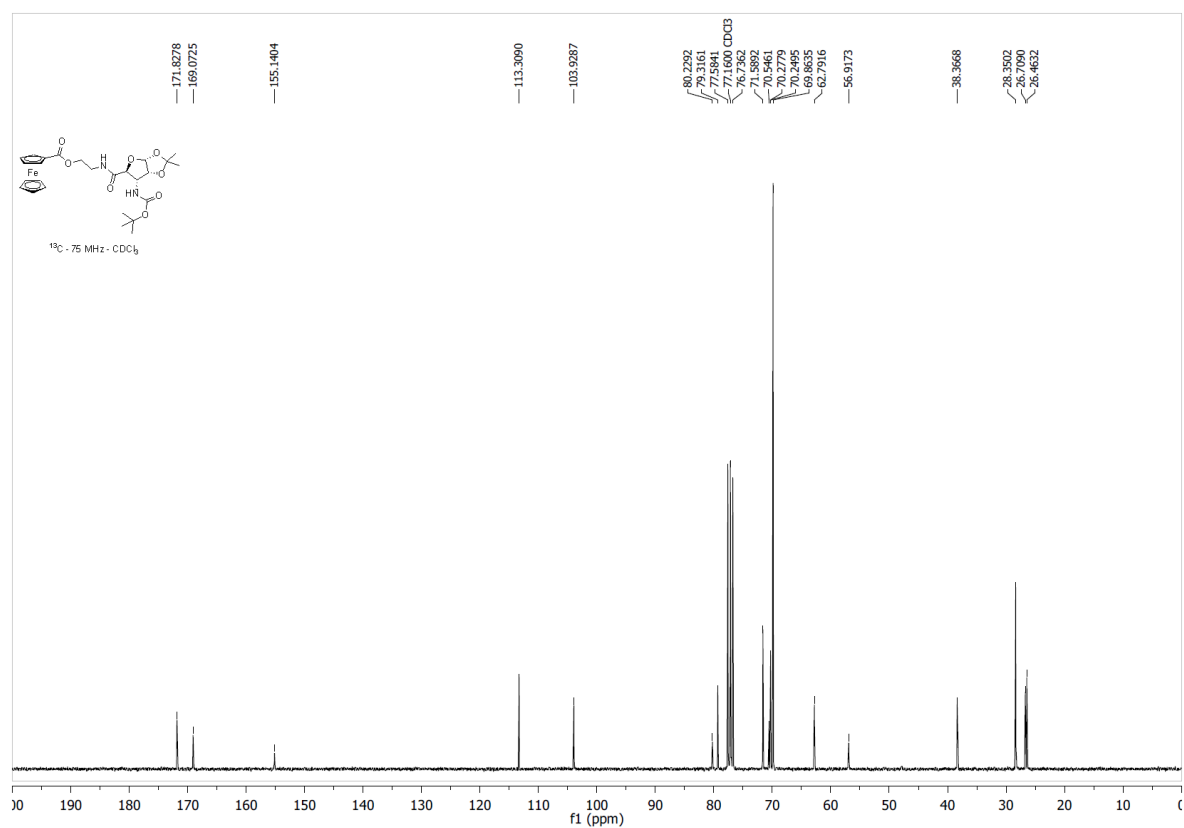
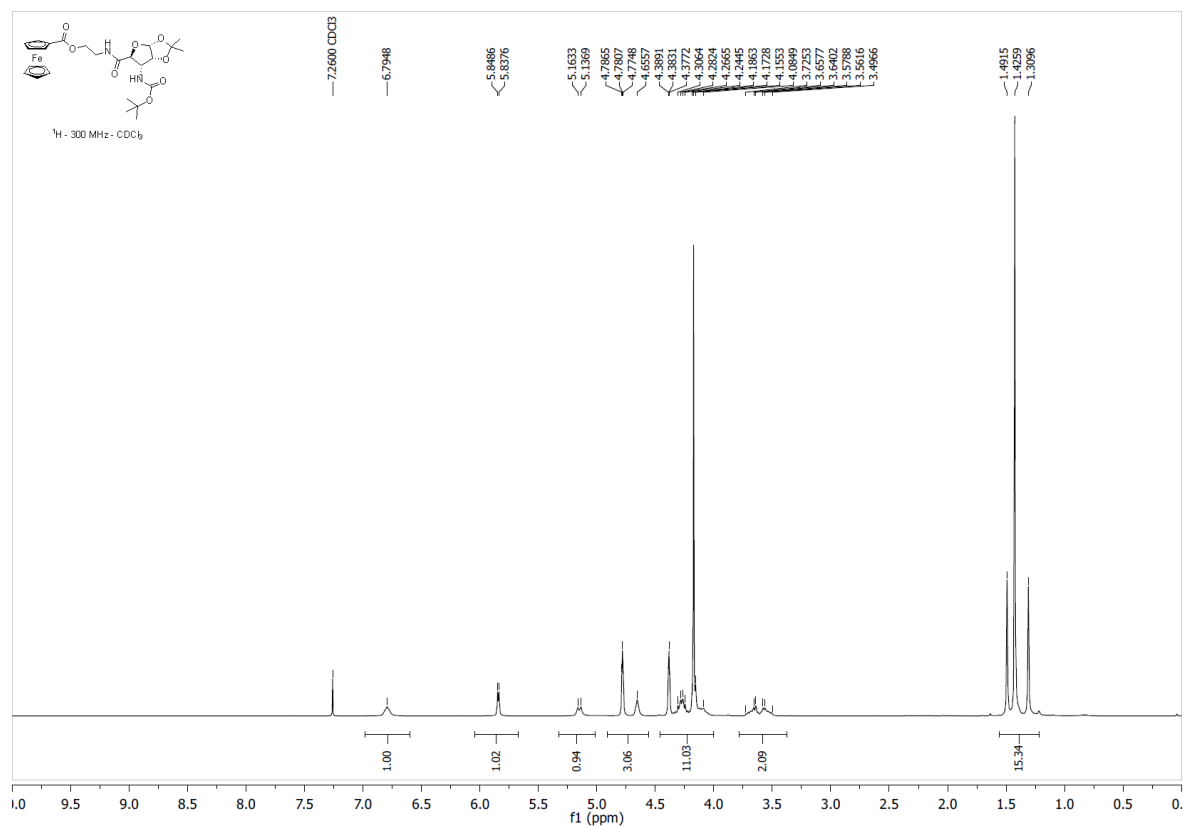
Ferrocene carboxamide FcC-6



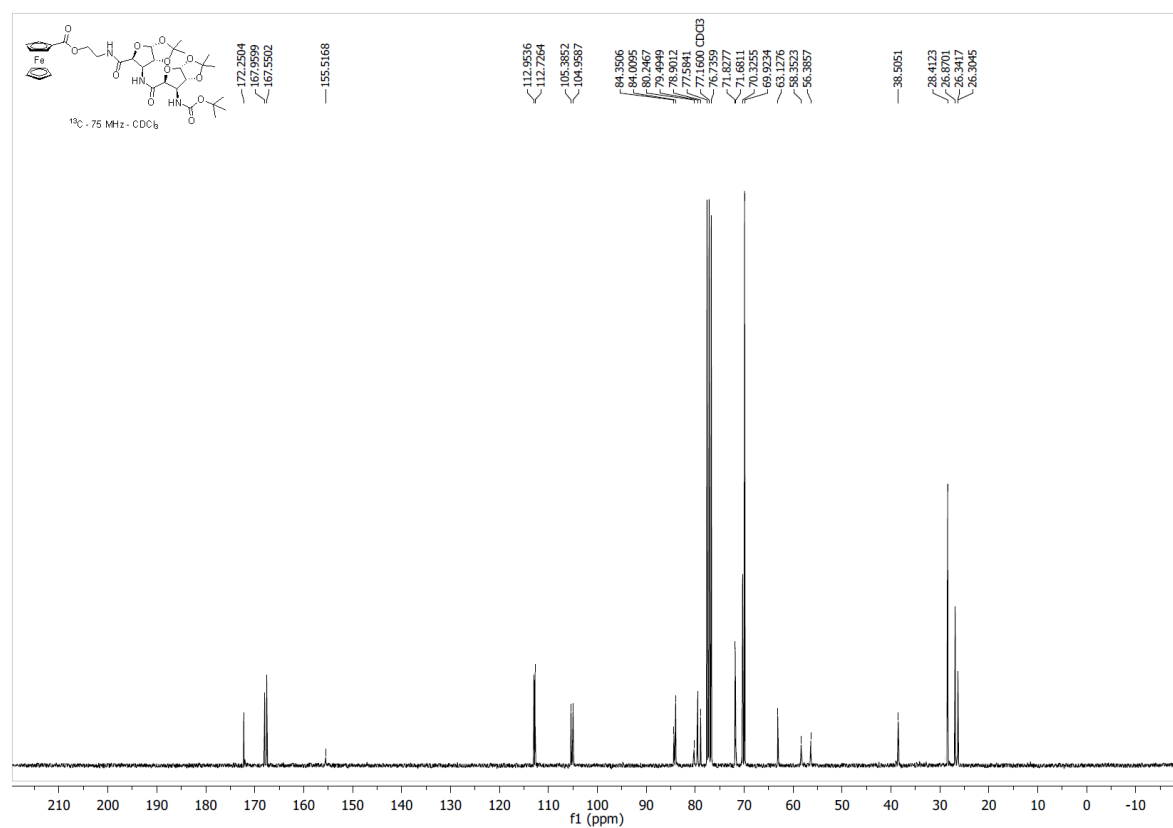
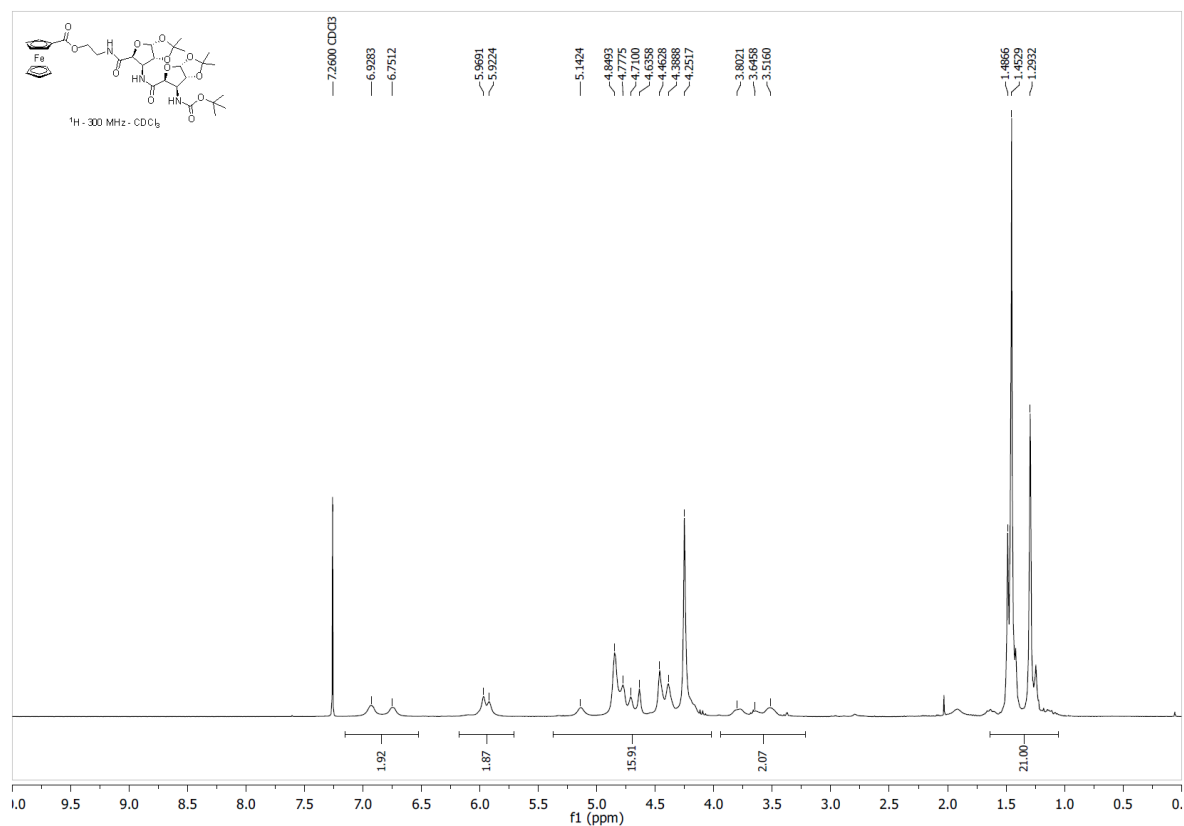
2-(*Tert*-butoxycarbonylamino)ethyl ferrocenecarboxylate



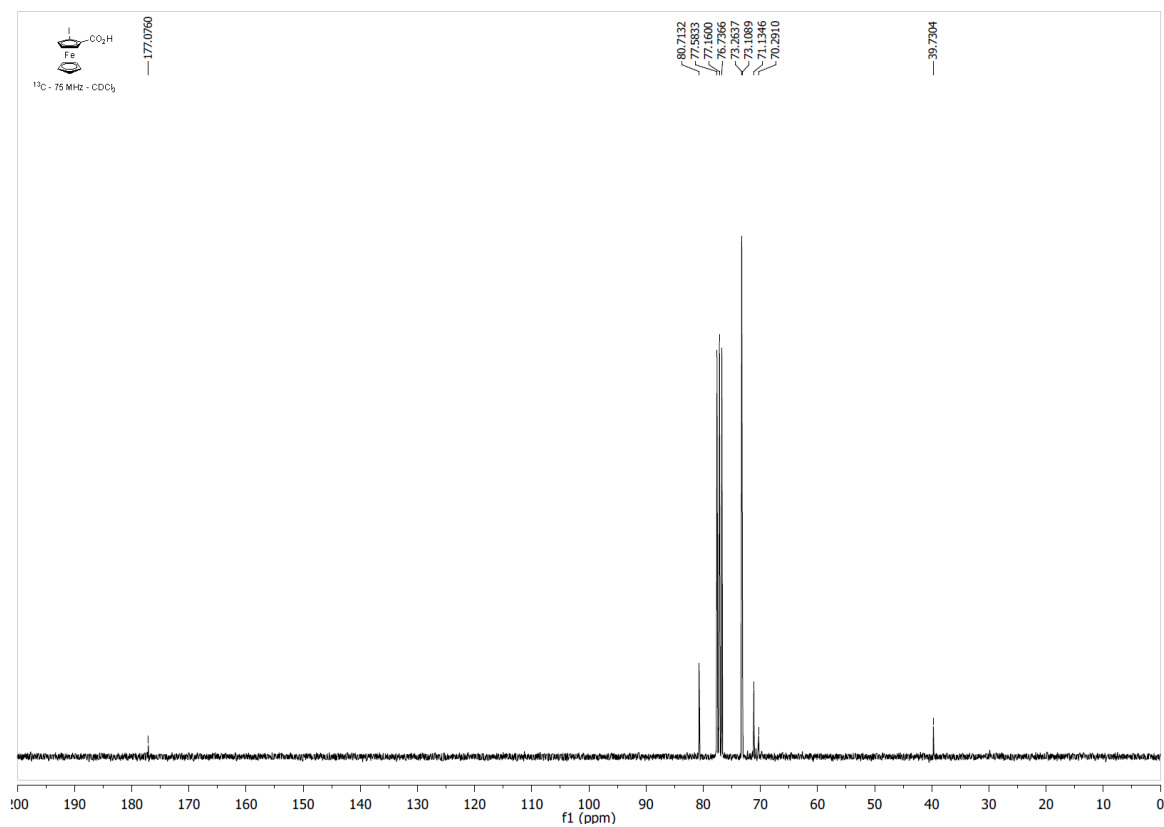
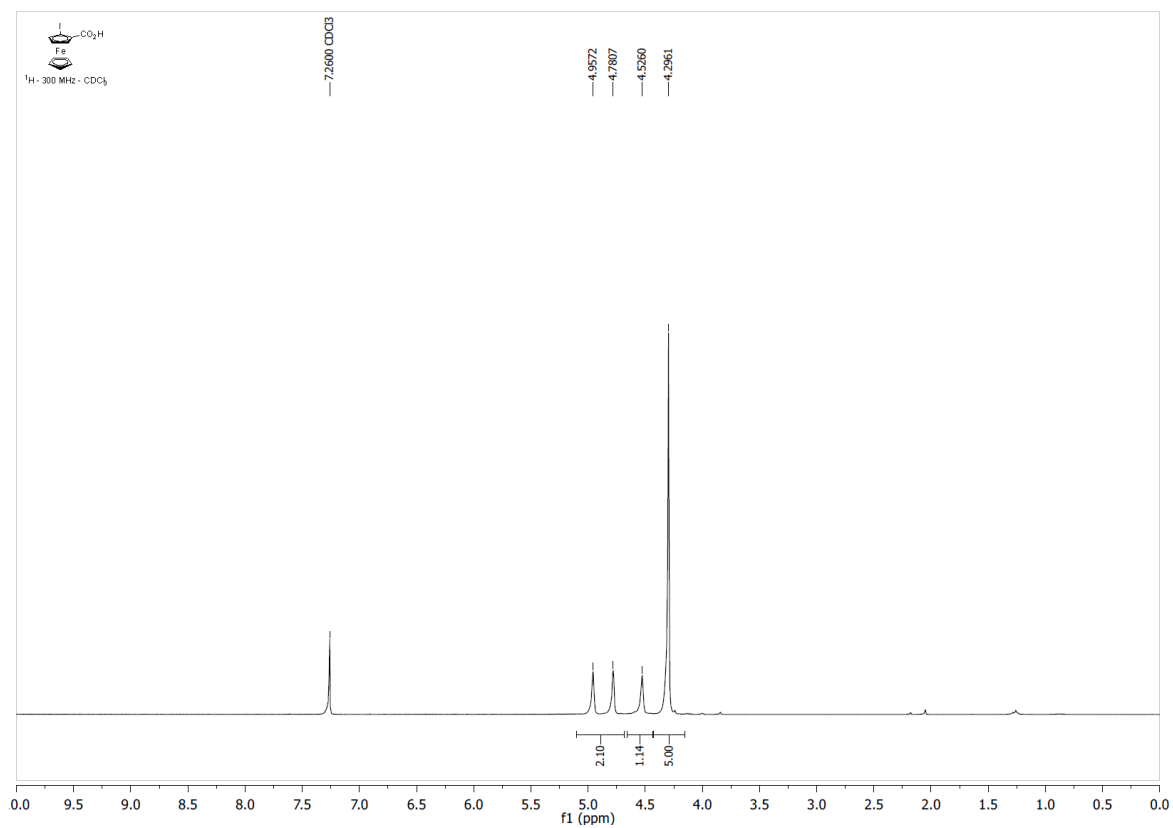
Ferrocene Ester FcE-1



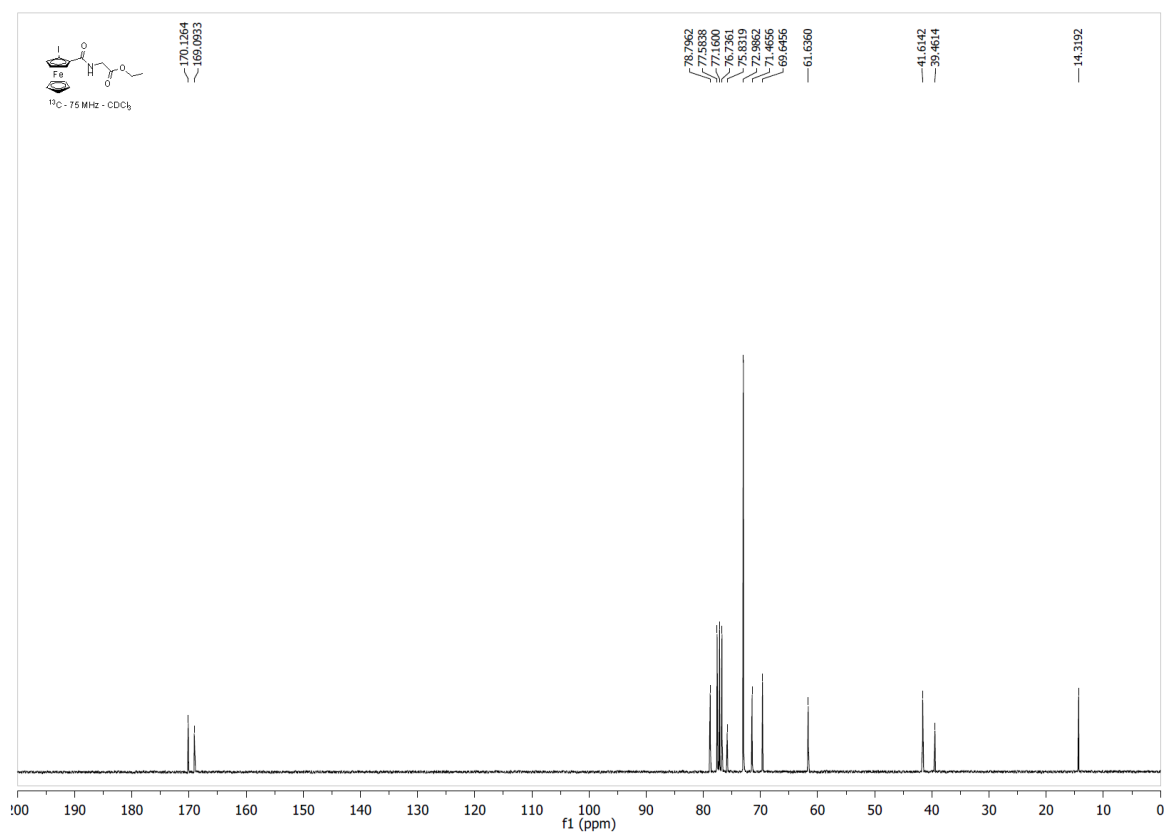
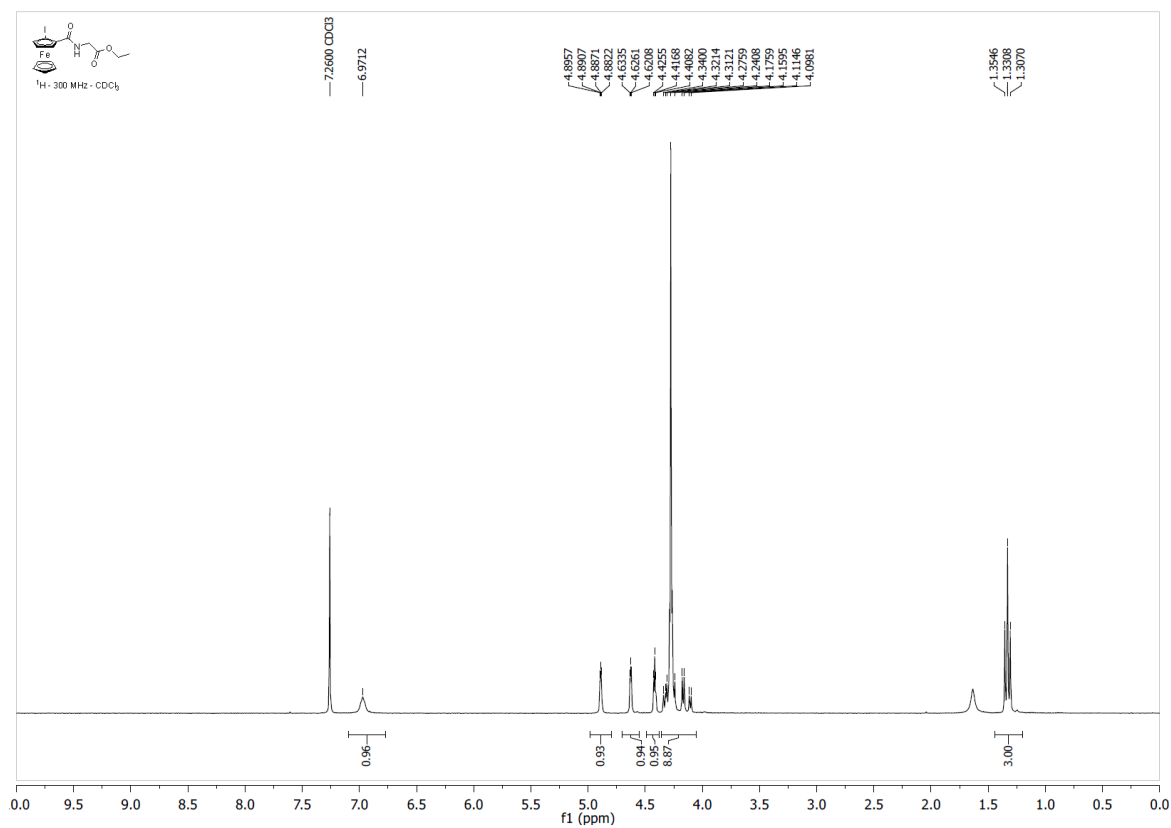
Ferrocene Ester FcE-4



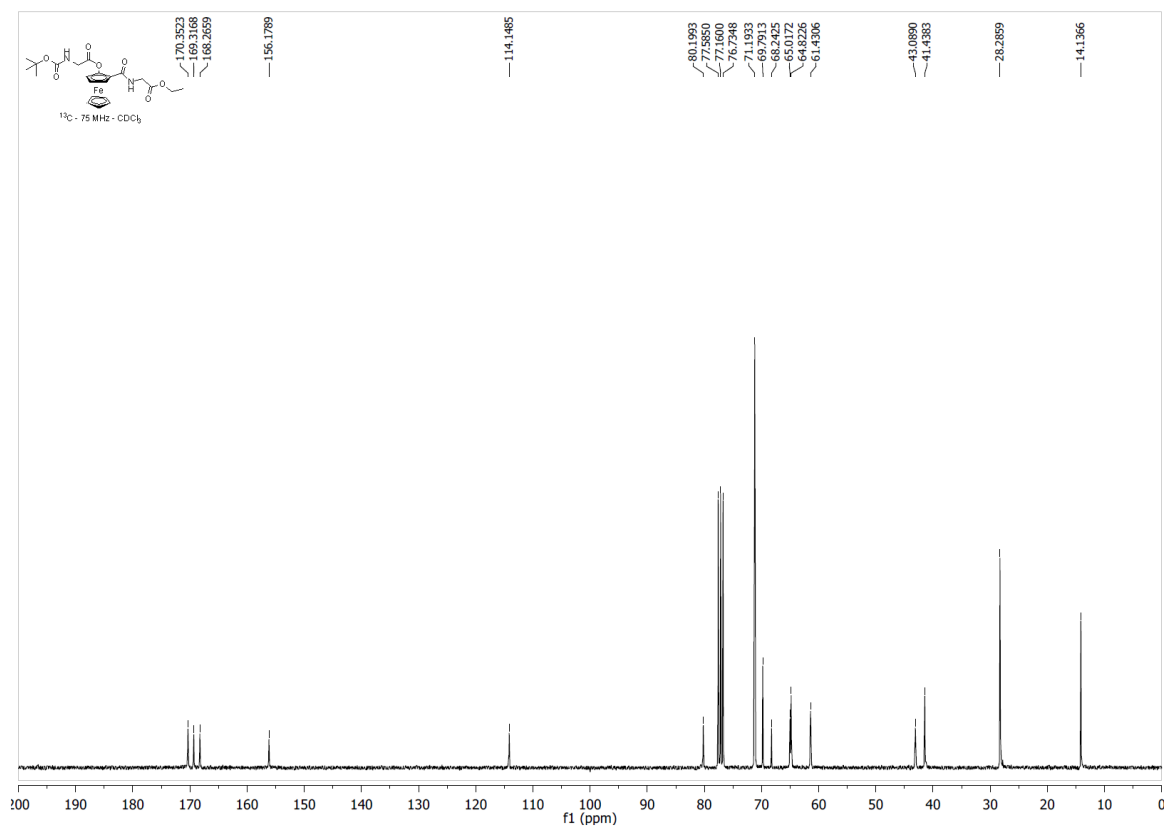
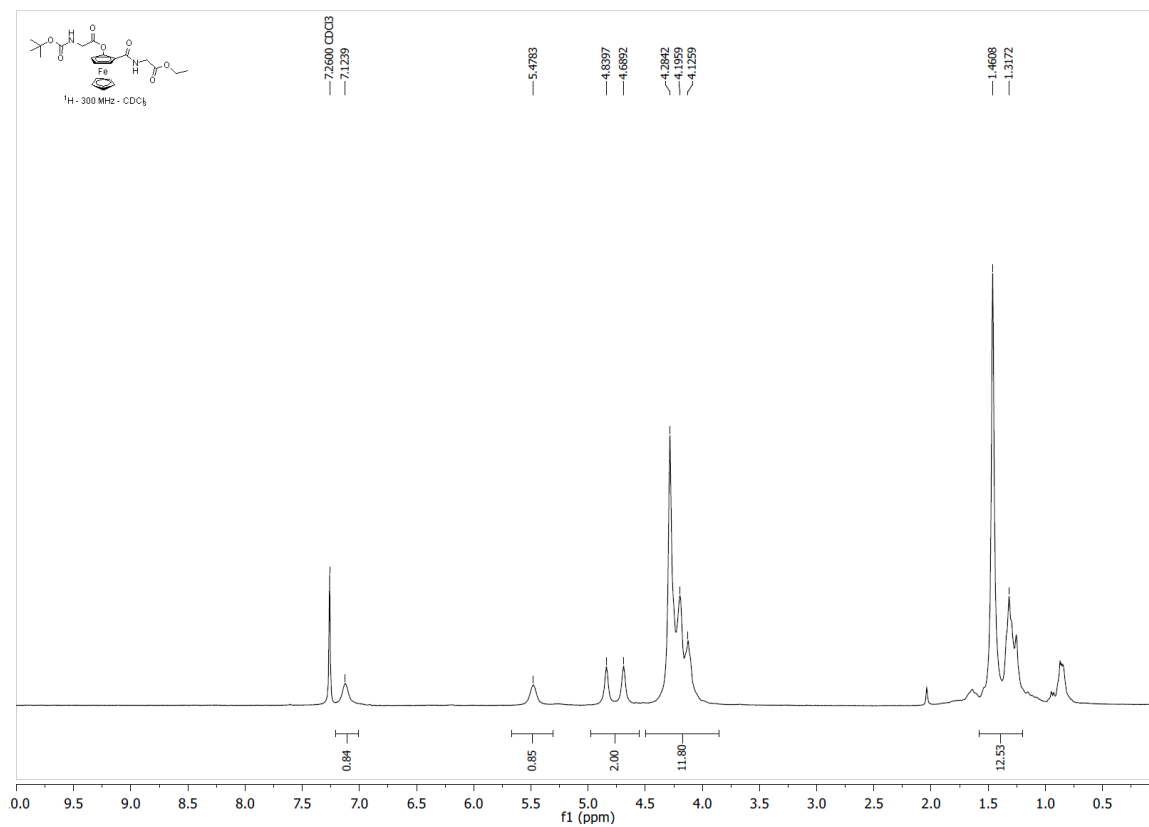
2-Iodoferrocenecarboxylic acid (racemic mixture) (*rac*-7)



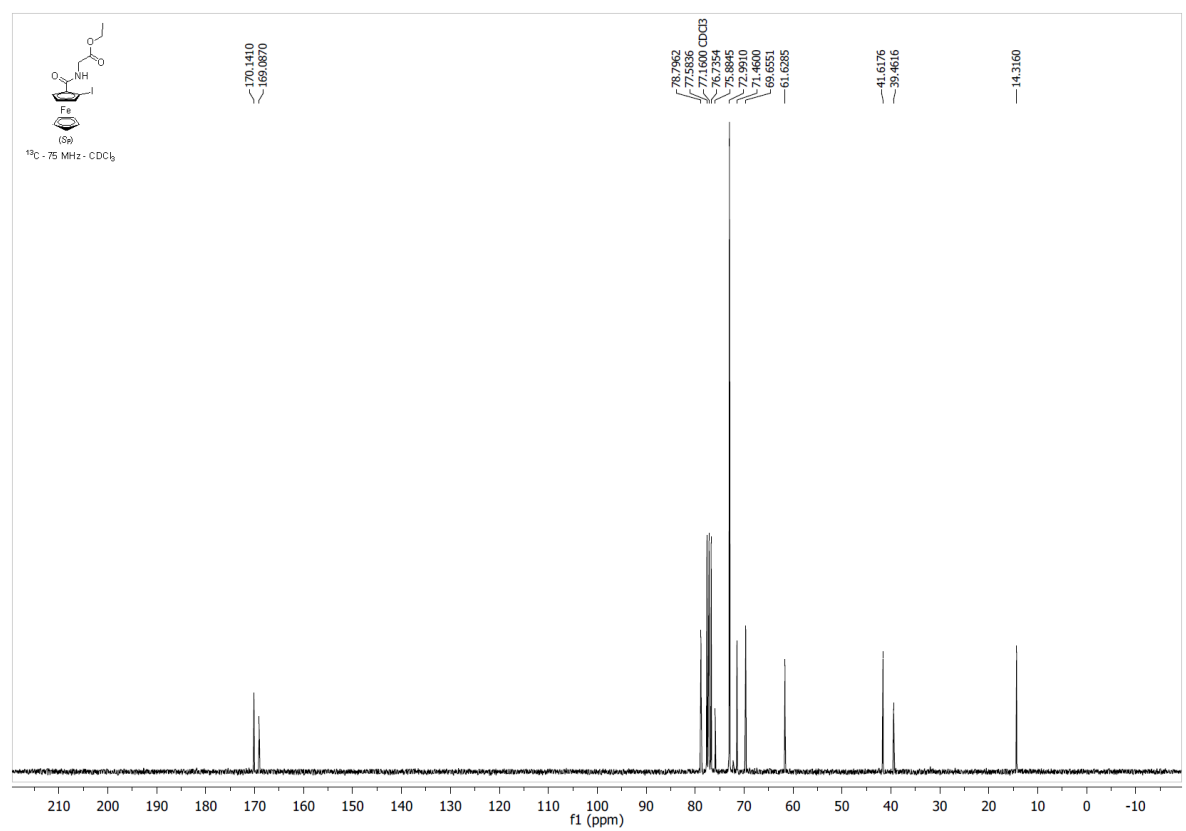
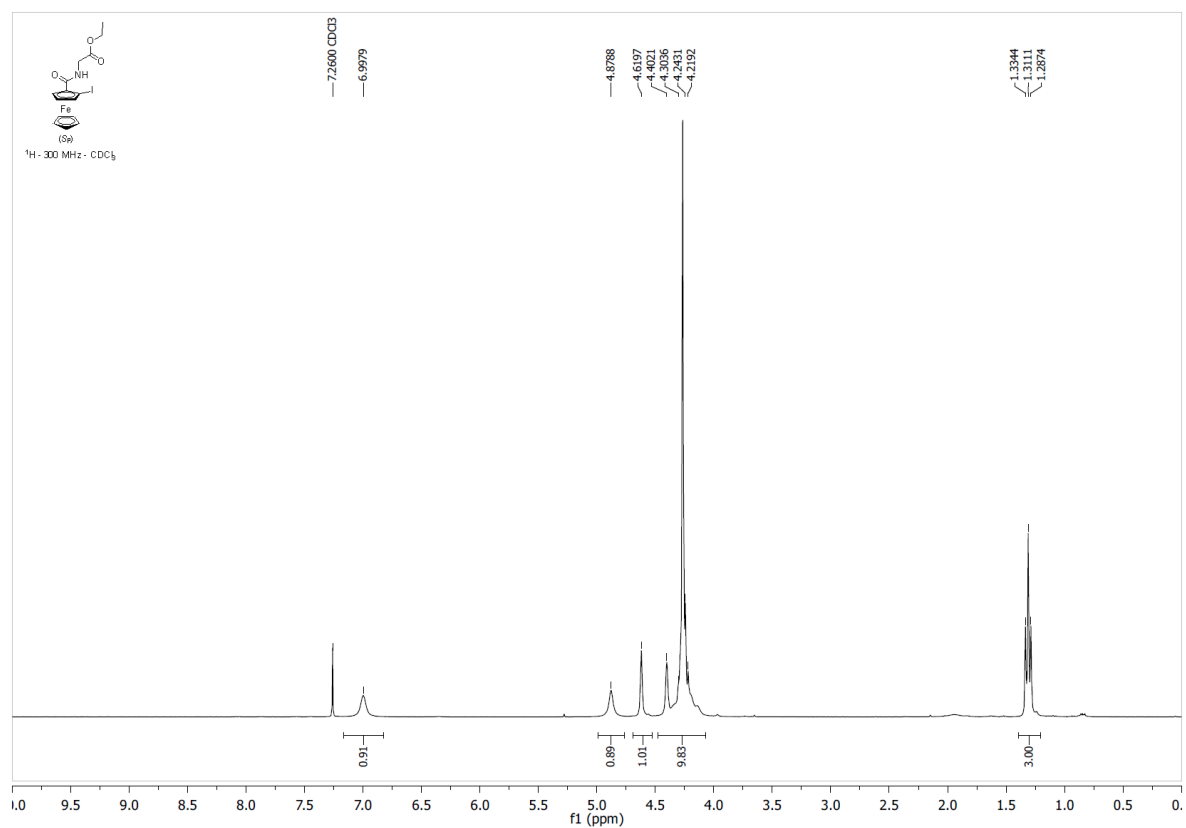
N-(Ethoxycarbonylmethyl)-2-iodoferrocenecarboxamide (racemic mixture) (*rac*-8)



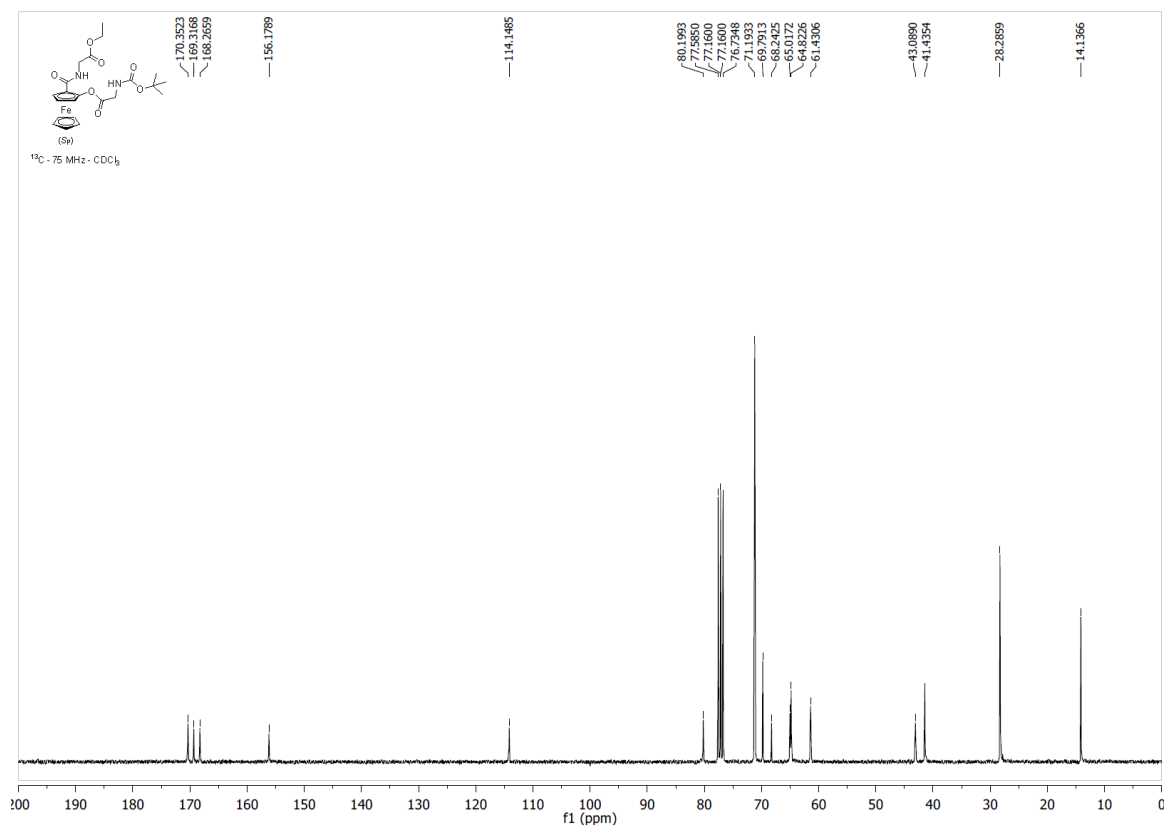
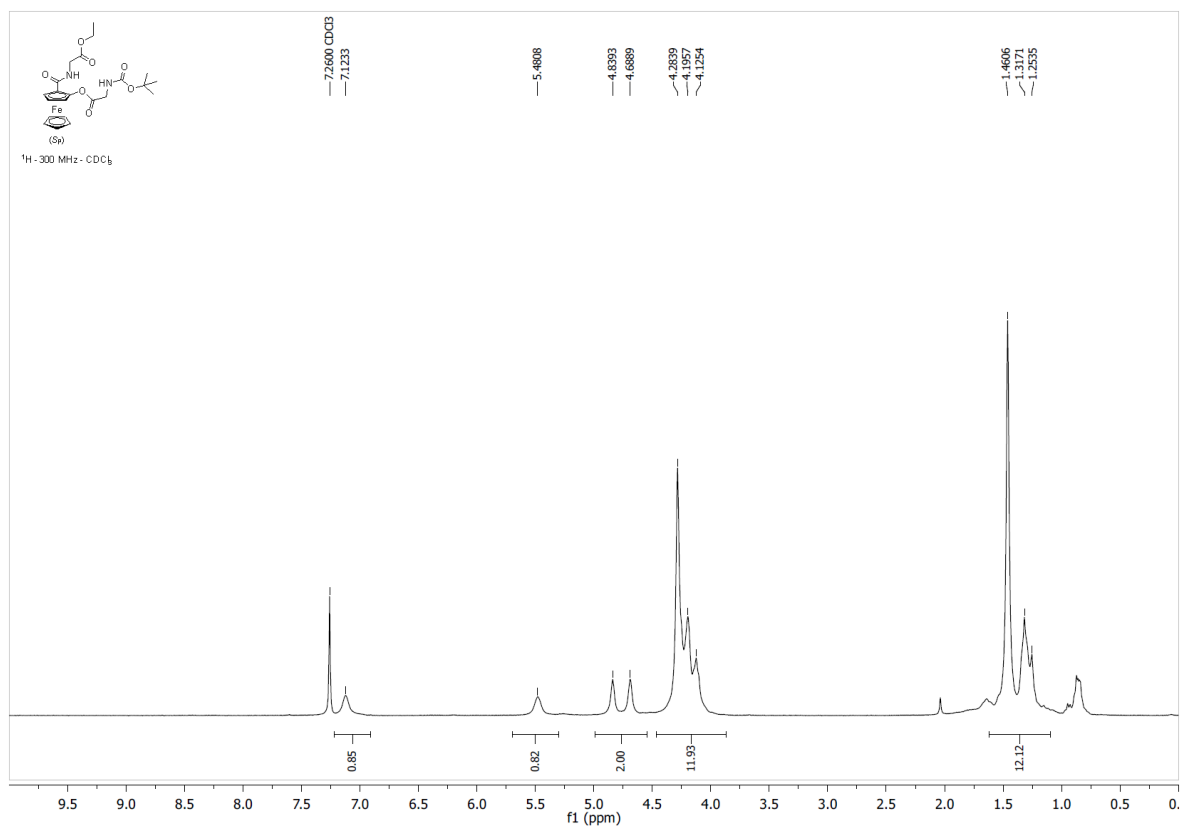
***N*-(Ethoxycarbonylmethyl)-2-((*tert*-butoxycarbonylaminoethyl)carboxyloxy)ferrocene-carboxamide (racemic mixture) (*rac*-9)**



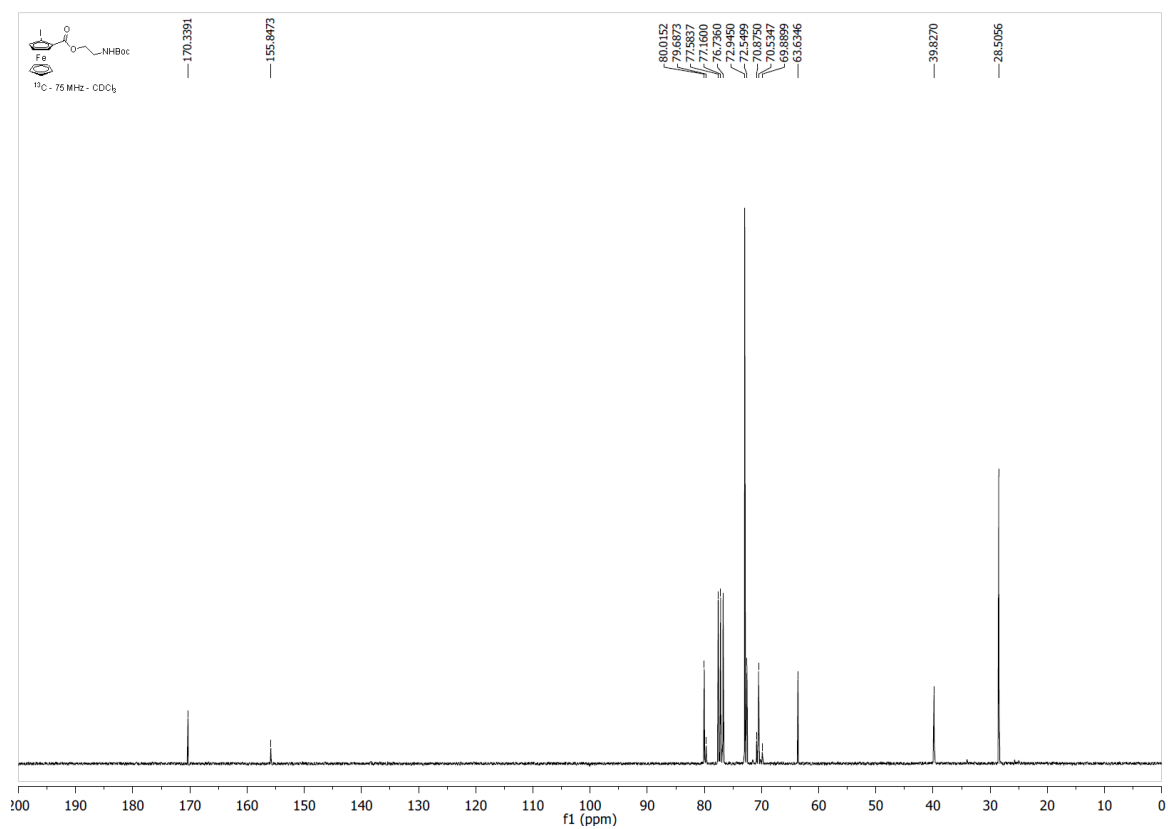
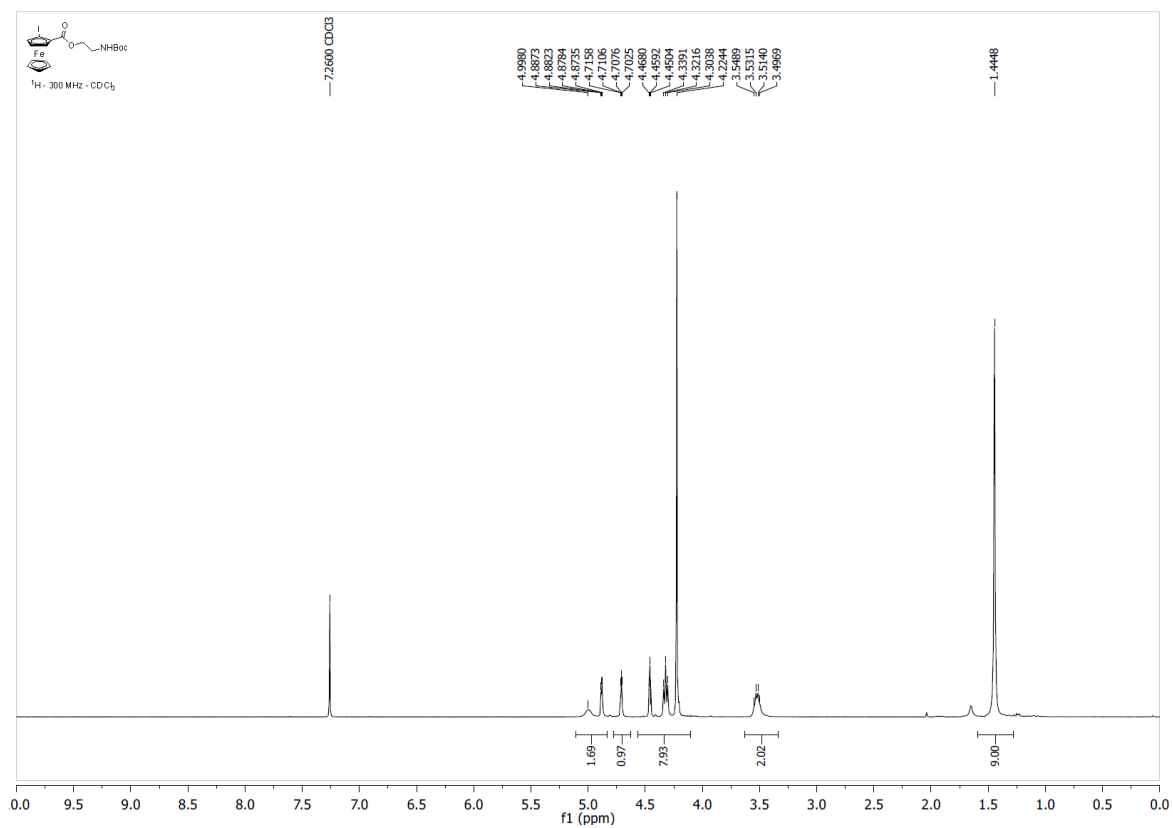
(*S_p*)-*N*-(Ethoxycarbonylmethyl)-2-iodoferrocenecarboxamide (*S_p*-8)



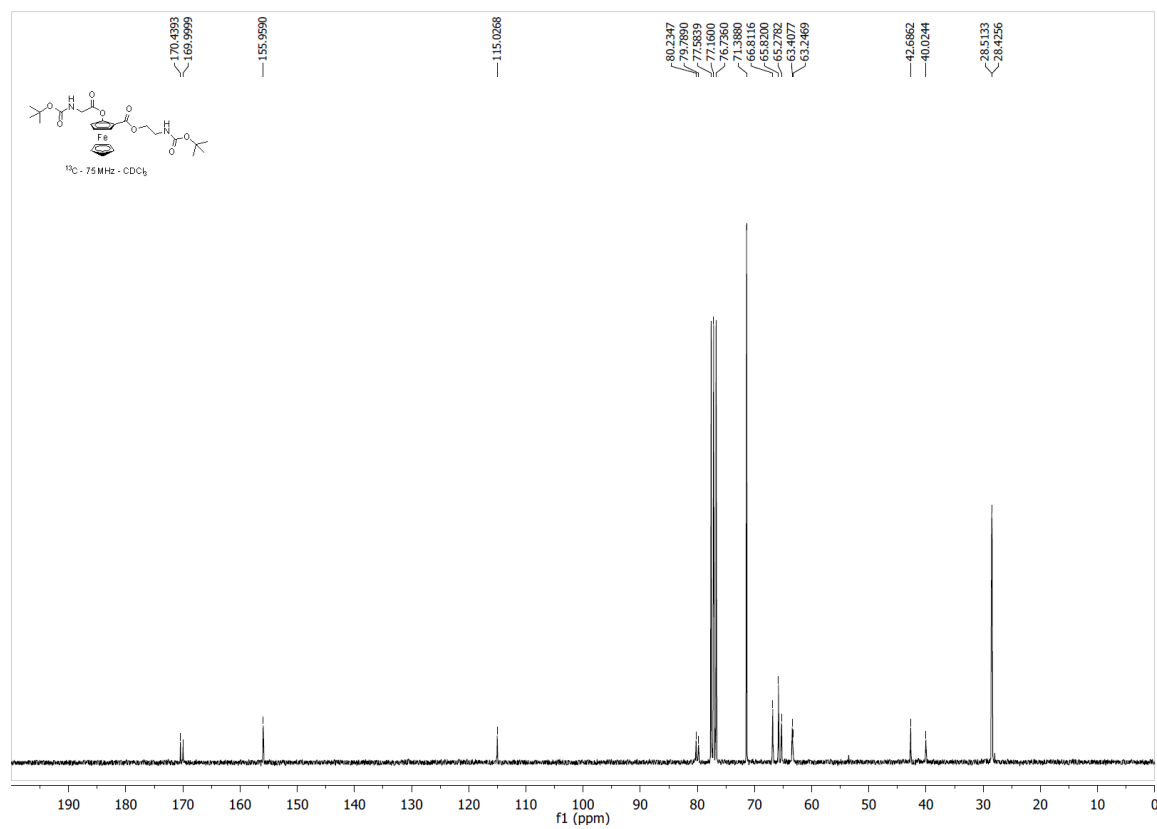
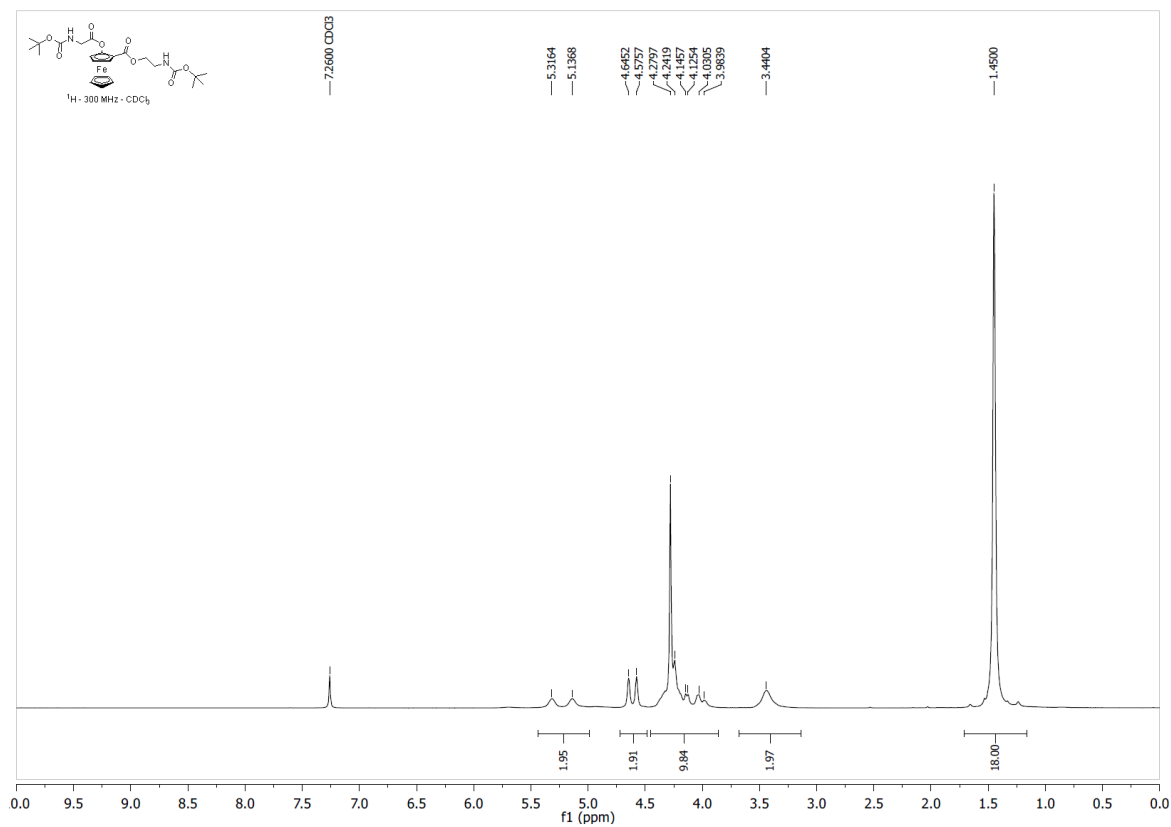
(*S_P*)-*N*-(Ethoxycarbonylmethyl)-2-((*tert*-butoxycarbonylaminoethyl)carboxyloxy)ferrocene-carboxamide (*S_P*-9)



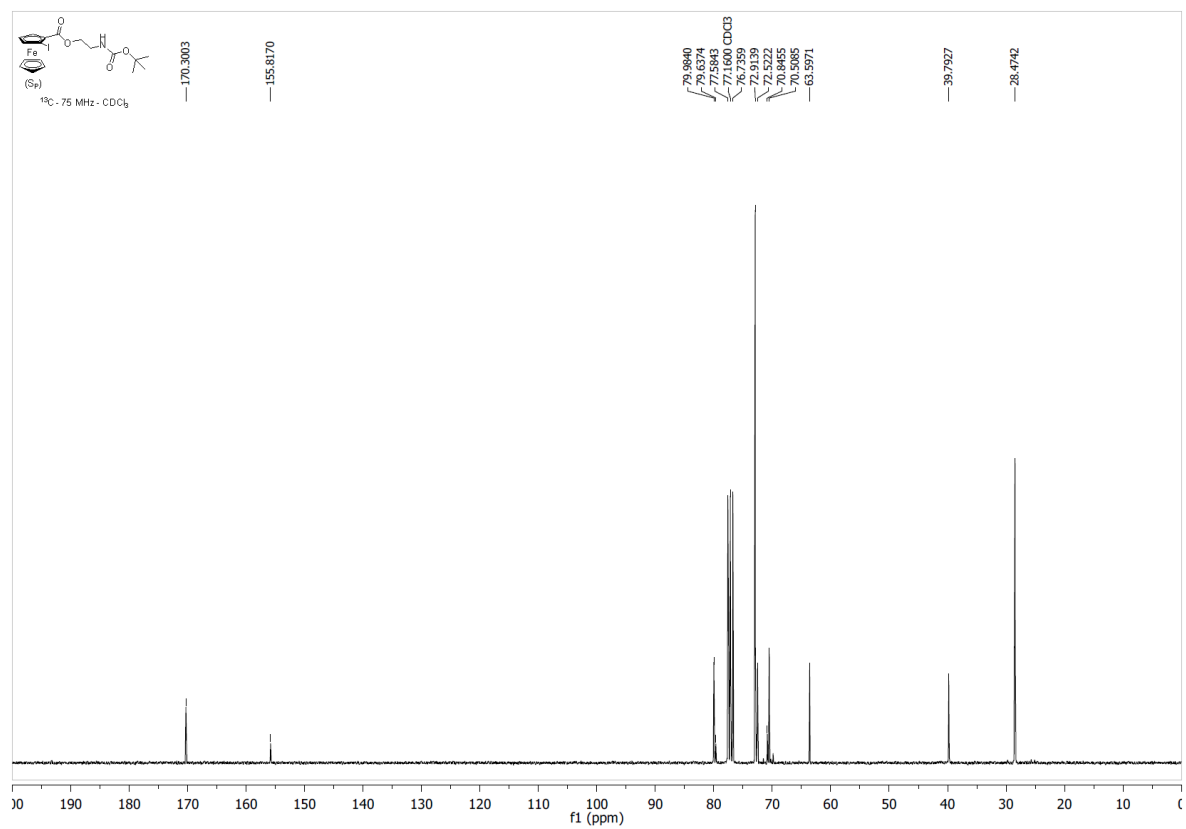
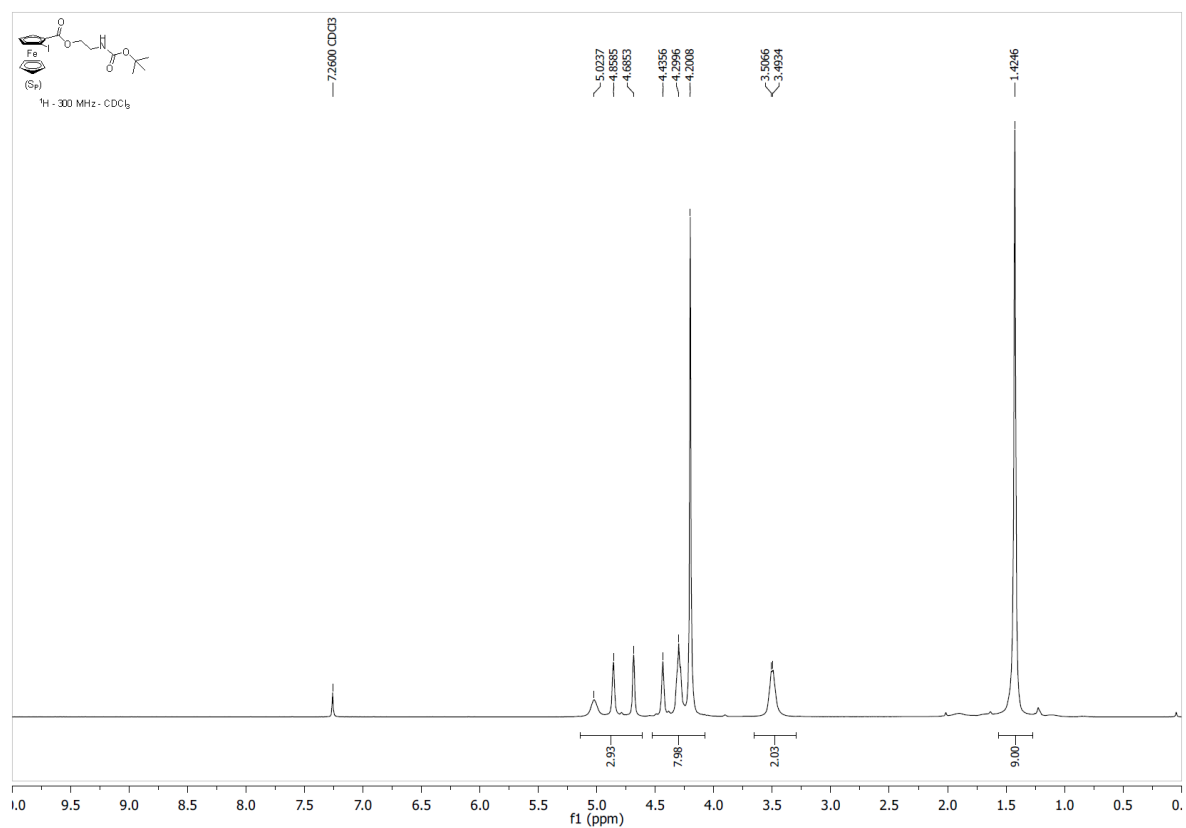
2-(*Tert*-butoxycarbonylamino)ethyl 2-iodoferrocenecarboxylate (racemic mixture) (*rac*-10)



2-(*Tert*-butoxycarbonylamino)ethyl 2-((*tert*-butoxycarbonylaminoethyl)carboxyloxy)ferrocene-carboxylate (racemic mixture) (*rac*-11)

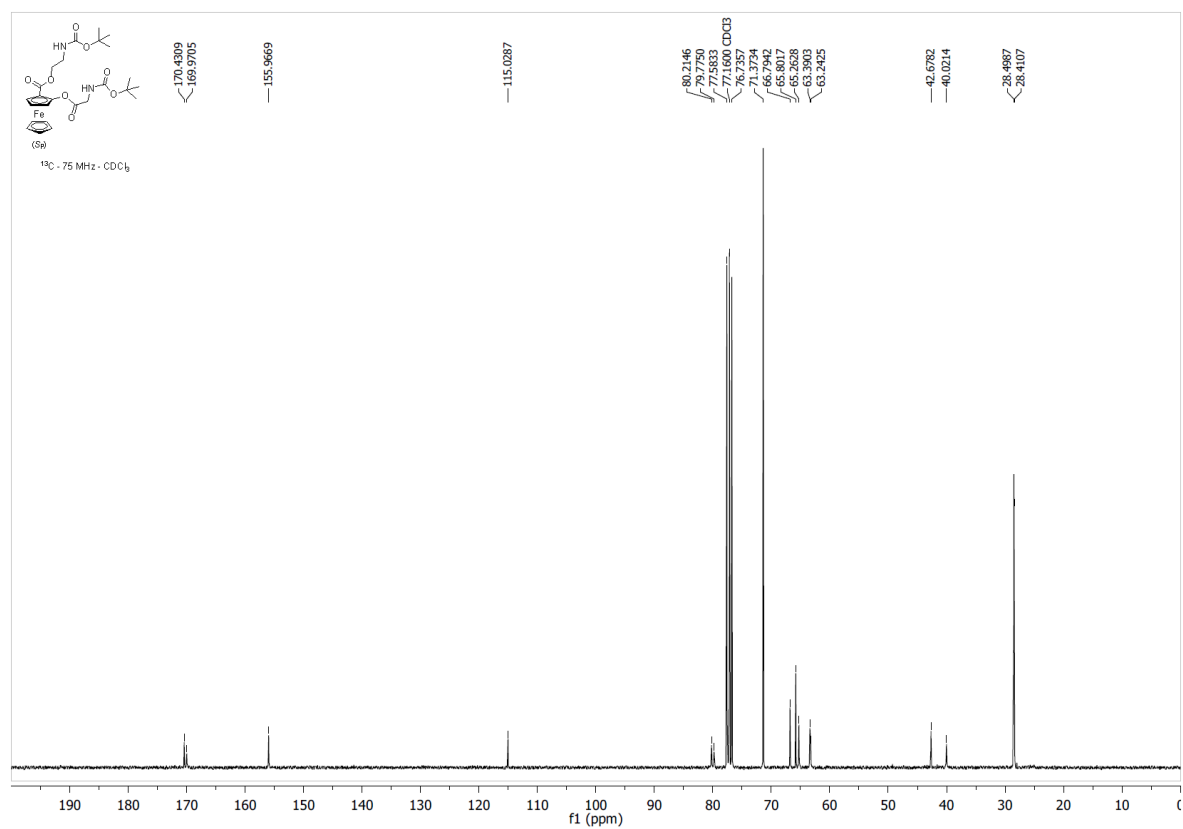
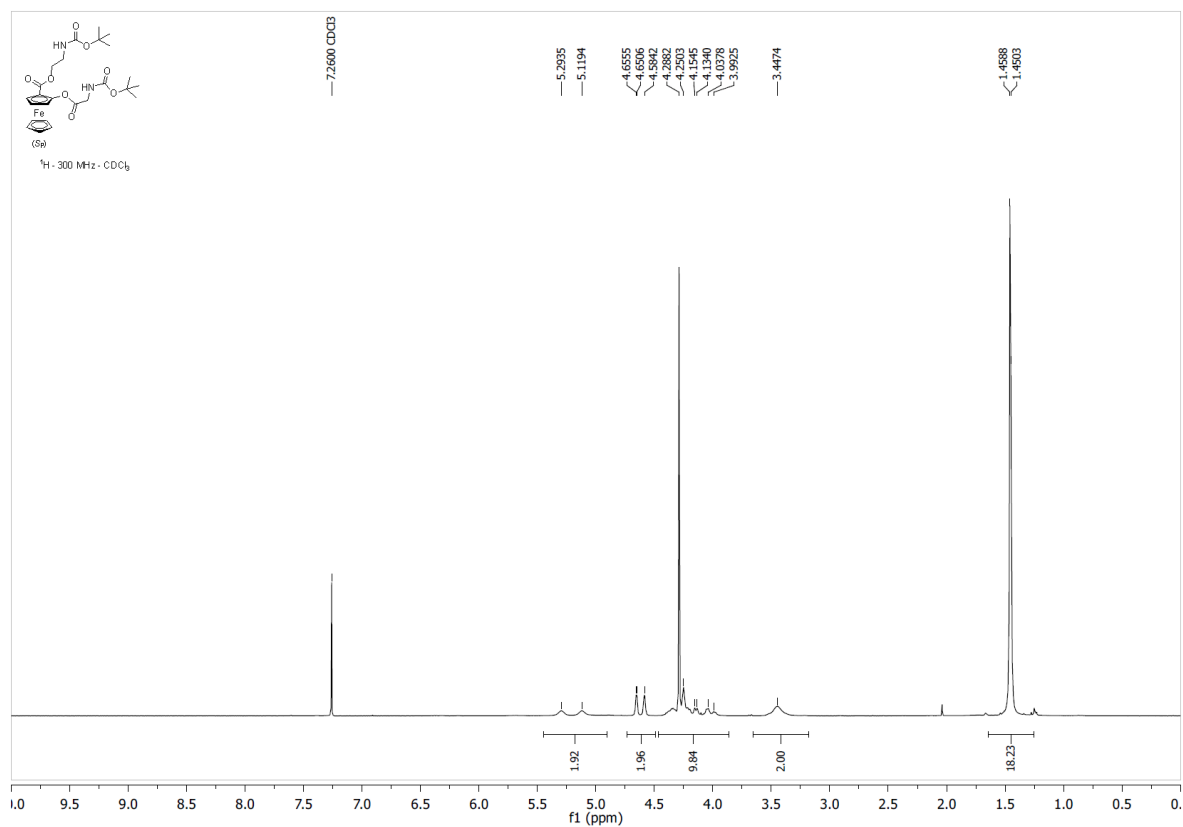


(S_P)-2-(Tert-butoxycarbonylamino)ethyl 2-iodoferrocenecarboxylate (S_P-10)



(S_P)-2-(Tert-butoxycarbonylamino)ethyl ferrocenecarboxylate (S_P-11)

2-((tert-butoxycarbonylamino)methyl)carboxy)-



Cyclic voltammetry of ferrocene derivatives **FcE-1**, **FcE-4**, S_p -9,
rac-11 and S_p -11 at a GC electrode

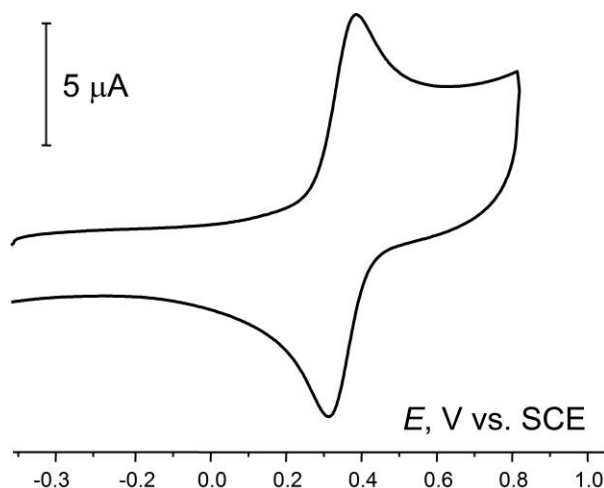


Figure S1. Cyclic voltammogram of oxidation of **FcE-1** (1.9 mmol L^{-1}) at a stationary GC disk electrode in $\text{CH}_3\text{CN} / 0.1 \text{ M Bu}_4\text{NBF}_4$. Scan rate $\nu = 100 \text{ mV s}^{-1}$. $T = 22 \text{ }^\circ\text{C}$.

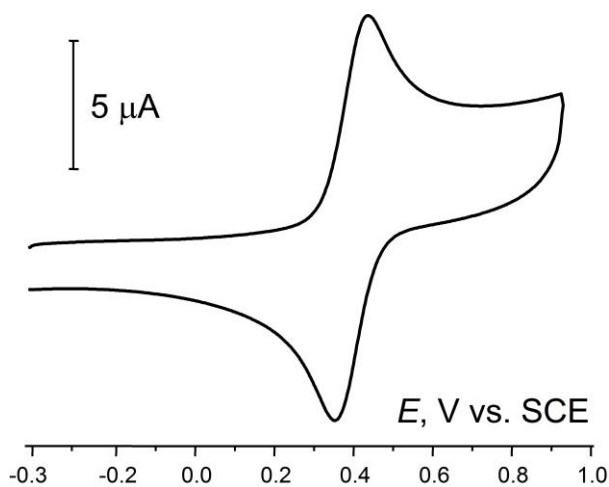


Figure S2. Cyclic voltammogram of oxidation of **FcE-4** (2 mmol L^{-1}) at a GC stationary disk electrode in $\text{CH}_3\text{CN} / 0.1 \text{ M Bu}_4\text{NBF}_4$. Scan rate $\nu = 100 \text{ mV s}^{-1}$. $T = 20 \text{ }^\circ\text{C}$.

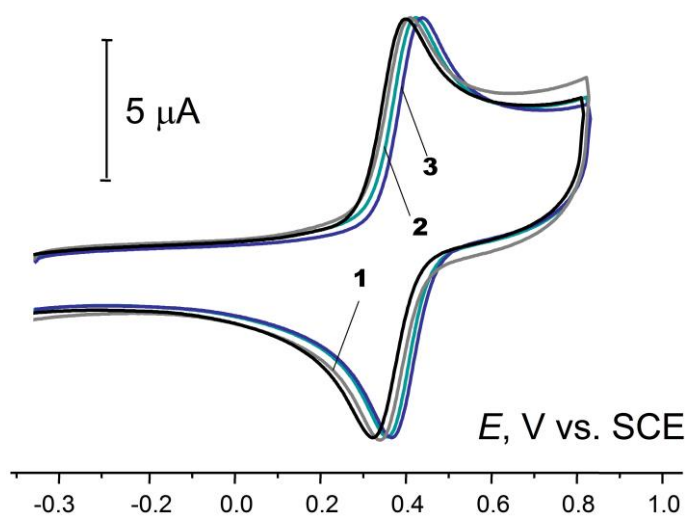


Figure S3. Cyclic voltammogram of oxidation of S_p -9 (2 mmol L^{-1}) at a stationary GC disk electrode in $\text{CH}_3\text{CN} / 0.1 \text{ M Bu}_4\text{NBF}_4$. (1), (2) and (3) - the responses of S_p -9 in the presence of L-glutamic acid, L-histidine and L-phenylalanine (all at 5 mmol L^{-1}), respectively. Scan rate $\nu = 100 \text{ mV s}^{-1}$. $T = 20 \text{ }^\circ\text{C}$.

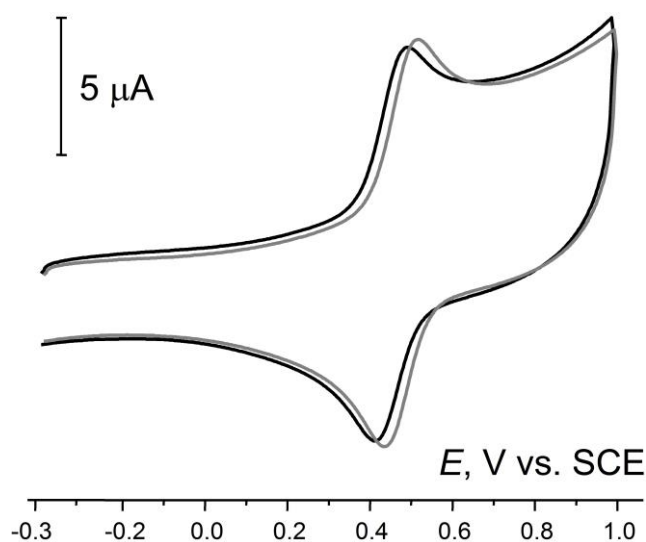


Figure S4. Cyclic voltammogram of oxidation of rac -11 (1.8 mmol L^{-1}) at a stationary GC disk electrode in $\text{CH}_3\text{CN} / 0.1 \text{ M Bu}_4\text{NBF}_4$. Scan rate $\nu = 100 \text{ mV s}^{-1}$. $T = 22 \text{ }^\circ\text{C}$. Grey line: in the presence of L-phenylalanine (4.5 mmol L^{-1}).

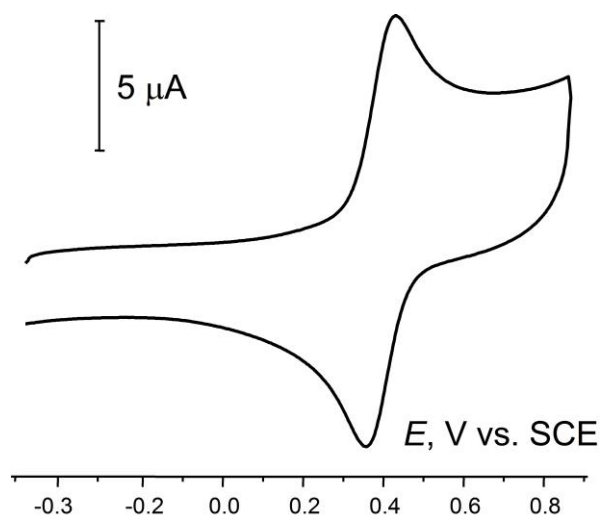


Figure S5. Cyclic voltammogram of oxidation of S_p -**11** (2 mmol L^{-1}) at a stationary GC disk electrode in $\text{CH}_3\text{CN} / 0.1 \text{ M Bu}_4\text{NBF}_4$. Scan rate $\nu = 100 \text{ mV s}^{-1}$. $T = 22 \text{ }^\circ\text{C}$.

In vitro antibacterial and antifungal activities. Applying the agar plate diffusion technique,¹¹ the compounds were screened *in vitro* for their bactericidal activity against Gram-positive bacteria (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia Coli*), and for their fungicidal activity against *Candida albicans*. In this method, a standard 5 mm diameter sterilized filter paper disc impregnated with the compound (0.3 mg/0.1 ml of DMF) was placed on an agar plate seeded with the test organism. The plates were incubated for 24 h at 37 °C for bacteria and 28 °C for fungi. The zone of inhibition of bacterial and fungi growth around the disc was observed.

In vitro antiproliferative (MCF-7) activities. The compounds were tested against breast carcinoma cell line MCF-7. The method applied is similar to that reported by Skehan et al.¹² using 20 sulforhodamine-B stain (SRB). Cells were plated in 96-multiwell plate (104 cells/well) for 24 h before treatment with the test compound to allow attachment of cell to the wall of the plate. Different concentrations of the compound under test (0, 1.0, 2.5, 5.0, and 10 mg/mL) were added to the cell monolayer in triplicate wells in individual dose, and monolayer cells were incubated with the compounds for 48 h at 37 °C and in atmosphere of 5% CO₂. After 48 h, cells were fixed, washed and stained with SRB stain, excess stain was washed with acetic acid, and attached stain was recovered with Tris-EDTA buffer. Color intensity was measured in an ELISA reader, and the relation between surviving fraction and drug concentration is plotted to get the survival curve of the tumor cell line after the specified compound and the IC₅₀ was calculated.

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