

Supporting Information

One-pot Synthesis of Tetrahydro-pyrrol benzodiazepines and Tetrahydropyrrol benzodiazepinons Through the sequence of 1,3-Dipolar cycloaddition/*N*-Alkylation/Staudinger/Aza-Wittig reaction

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1. General information

Chemicals and solvents were purchased from Sijama, TCI and Oakwood. ^1H (400 MHz) and ^{13}C NMR spectra (101 MHz) were recorded on a 400 MHz Agilent NMR spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26, dmsO δ 2.50), carbon (chloroform δ 77.0, dmsO δ 39.53). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). LC-MS were performed on an Agilent 2100 system. A C_{18} column (5.0 μm , 6.0 x 50 mm) was used for the separation. The mobile phases were methanol and water both containing 0.05% trifluoroacetic acid. A linear gradient was used to increase from 25:75 v/v methanol/water to 100% methanol over 7.0 min at a flow rate of 0.7 mL/min. UV detections were conducted at 210 nm, 254 nm and 365 nm. Low resolution mass spectra were recorded in APCI (atmospheric pressure chemical ionization). Flash chromatography separations were performed on YAMAZEN AI-580 flash column system with Agela silica gel columns (230-400 μm mesh) and Angela Flash/Cheetah System with Venusil PrepG C_{18} column (10 μm , 120 \AA , 21.2 mm x 250 mm).

2. General procedures for one-pot synthesis of **7** and **10**

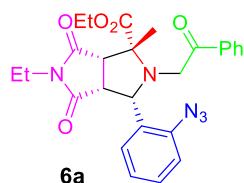
*General procedures for one-pot synthesis of tetrahydro-pyrrolo[1,2-d][1,4]benzodiazepine **7**:*

A solution of 2-azidobenzaldehyde **1** (0.5 mmol), amino ester **2** (0.6 mmol) and maleimide **3** (0.55 mmol) in CH_3CN (2 mL) with Et_3N (0.75 mmol) were heated at 125 $^\circ\text{C}$ for 30 min under microwave in a sealed vial. Then bromide ketone **5** (1.5 mmol) and K_2CO_3 (1 mmol) was added into the pyrrolidine **4** containing mixture followed by heating at 120 $^\circ\text{C}$ for 2 h. Upon the completion of the reaction as monitored by LC-MS, PPh_3 (0.6 mmol) was added to the mixture and then heated at 105 $^\circ\text{C}$ for 6 h. The concentrated reaction mixture was separated with a Flash chromatography system (YAMAZEN AI-580 flash column system) or a semi-preparative HPLC with a C_{18} column (Angela HP-100 pre-LC system) to afford purified major diastereomer of product **7**.

*General procedures for one-pot synthesis of tetrahydro-pyrrolo[1,2-d][1,4]benzodiazepinone **10**:*

A solution of 2-azidobenzaldehyde **1** (0.5 mmol), amino ester **2** (0.6 mmol) and maleimide **3** (0.55 mmol) in CH_3CN (2 mL) with Et_3N (0.75 mmol) were heated at 125 $^\circ\text{C}$ for 30 min under microwave in a sealed vial. The phenylglyoxylic acid **8a** (0.5 mmol) and Et_3N (0.5 mmol) were then added into the mixture, followed by addition of 2,4,6-trichloro-1,3,5-triazine (TCT)/ CH_3CN solution (0.5 mmol/1mL), the mixture was stirred at room temperature for 30 min. Upon the completion of the reaction as monitored by LC-MS, PPh_3 (0.6 mmol) was added to the mixture and then heated at 105 $^\circ\text{C}$ for 6 h. The concentrated reaction mixture was separated with a Flash chromatography system (YAMAZEN AI-580 flash column system) or a semi-preparative HPLC with a C_{18} column (Angela HP-100 pre-LC system) to afford purified major diastereomer of product **10**.

3. Characterization of intermediate 6a, products 7 and 10

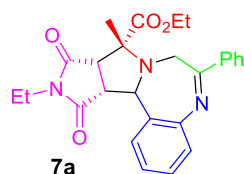


ethyl (1*R*,3*S*,3*aR*,6*aS*)-3-(2-azidophenyl)-5-ethyl-1-methyl-4,6-dioxo-2-(2-oxo-2-phenylethyl)octahydroindolo[3,4-*c*]pyrrole-1-carboxylate (**6a**):

White solid, 90% yield.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.82 – 7.78 (m, 2H), 7.49 – 7.44 (m, 1H), 7.33 (dd, $J = 10.8, 4.7$ Hz, 2H), 7.27 – 7.24 (m, 1H), 7.20 (td, $J = 7.7, 1.5$ Hz, 1H), 7.07 (d, $J = 7.9$ Hz, 1H), 6.84 (t, $J = 7.4$ Hz, 1H), 5.43 (d, $J = 10.2$ Hz, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 4.09 (s, 2H), 3.66 (dd, $J = 10.2, 8.2$ Hz, 1H), 3.31 (dd, $J = 13.3, 7.1$ Hz, 1H), 3.25 (d, $J = 8.2$ Hz, 1H), 3.19 (dd, $J = 13.4, 7.1$ Hz, 1H), 1.59 (s, 3H), 1.33 (t, $J = 7.2$ Hz, 3H), 0.93 (t, $J = 7.2$ Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 198.35 (s), 175.19 (s), 174.41 (s), 172.06 (s), 138.99 (s), 136.01 (s), 133.08 (s), 129.17 (s), 128.48 (d, $J = 18.0$ Hz), 128.00 (d, $J = 6.8$ Hz), 124.30 (s), 118.06 (s), 70.05 (s), 61.43 (s), 59.10 (s), 54.88 (s), 52.35 (s), 46.85 (s), 33.72 (s), 30.87 (s), 20.78 (s), 14.05 (s), 12.77 (s).



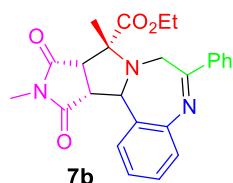
ethyl (9*R*,9*aS*,12*aR*)-11-ethyl-9-methyl-10,12-dioxo-6-phenyl-7,9,9*a*,10,11,12,12*a*,12*b*-octahydrobenzo[*ff*]pyrrolo[3',4':3,4]pyrrolo[1,2-*d*][1,4]diazepine-9-carboxylate (**7a**):

White solid, 85% yield. MP: 116-117°C.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.70 – 7.65 (m, 2H), 7.40 – 7.34 (m, 1H), 7.23 – 7.15 (m, 3H), 7.11 (dd, $J = 7.4, 1.6$ Hz, 1H), 7.05 – 6.97 (m, 2H), 4.21 (d, $J = 5.2$ Hz, 1H), 4.10 – 4.01 (m, 2H), 3.82 (t, $J = 9.8$ Hz, 1H), 3.77 – 3.69 (m, 3H), 3.14 (d, $J = 7.9$ Hz, 1H), 3.03 (dd, $J = 7.9, 5.2$ Hz, 1H), 1.57 (s, 3H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.16 (dd, $J = 8.3, 6.0$ Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 198.42 (s), 175.51 (s), 171.17 (s), 162.24 (s), 144.75 (s), 135.57 (s), 132.55 (s), 131.01 (s), 130.17 (s), 128.45 (s), 127.68 (s), 125.78 (s), 124.21 (s), 122.34 (s), 70.30 (s), 61.84 (s), 59.11 (s), 55.38 (s), 55.03 (s), 39.68 (s), 35.02 (s), 18.20 (s), 13.83 (s), 12.89 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_4$ 446.2080, found 446.2085



ethyl (9*R*,9*aS*,12*aR*)-9,11-dimethyl-10,12-dioxo-6-phenyl-7,9,9*a*,10,11,12,12*a*,12*b*-octahydrobenzo[*ff*]pyrrolo[3',4':3,4]pyrrolo[1,2-*d*][1,4]diazepine-9-carboxylate (**7b**):

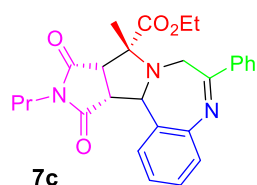
White solid, 83% yield. MP: 141-142.5°C.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.67 – 7.60 (m, 2H), 7.41 – 7.35 (m, 1H), 7.27 – 7.17 (m, 3H), 7.14 – 7.08

(m, 2H), 7.01 (td, $J = 7.4, 1.3$ Hz, 1H), 4.26 (d, $J = 5.2$ Hz, 1H), 4.08 – 4.00 (m, 1H), 3.98 – 3.90 (m, 1H), 3.86 (d, $J = 15.9$ Hz, 1H), 3.67 (d, $J = 15.8$ Hz, 1H), 3.17 (s, 4H), 3.07 (dd, $J = 7.7, 5.2$ Hz, 1H), 1.56 (s, 3H), 1.08 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (101 MHz, cdCl_3) δ 198.20 (s), 175.93 (s), 171.29 (s), 163.07 (s), 144.64 (s), 135.52 (s), 132.70 (s), 130.86 (s), 130.23 (s), 128.33 (s), 127.80 (s), 125.89 (s), 124.40 (s), 122.60 (s), 70.30 (s), 61.82 (s), 59.00 (s), 55.73 (s), 54.17 (s), 39.72 (s), 30.88 (s), 26.22 (s), 18.36 (s), 13.72 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_4$ 432.1923, found 432.1927



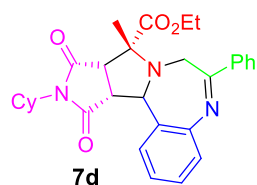
ethyl (9R,9aS,12aR)-9-methyl-10,12-dioxo-6-phenyl-11-propyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (7c):

White solid, 63% yield. MP: 102-104°C.

^1H NMR (400 MHz, cdCl_3) δ 7.65 (dt, $J = 8.4, 1.5$ Hz, 2H), 7.39 – 7.34 (m, 1H), 7.19 (tdd, $J = 8.1, 7.6, 1.7$ Hz, 3H), 7.07 (ddd, $J = 19.6, 7.6, 1.4$ Hz, 2H), 6.98 (td, $J = 7.4, 1.3$ Hz, 1H), 4.20 (d, $J = 5.2$ Hz, 1H), 4.08 – 3.96 (m, 2H), 3.83 (d, $J = 15.7$ Hz, 1H), 3.73 – 3.65 (m, 2H), 3.57 (ddd, $J = 13.0, 8.4, 7.1$ Hz, 1H), 3.13 (d, $J = 7.9$ Hz, 1H), 3.03 (dd, $J = 7.9, 5.2$ Hz, 1H), 1.77 – 1.67 (m, 2H), 1.56 (s, 3H), 1.12 (t, $J = 7.2$ Hz, 3H), 0.96 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (101 MHz, cdCl_3) δ 198.38 (s), 175.72 (s), 171.21 (s), 162.44 (s), 144.77 (s), 135.56 (s), 132.58 (s), 130.94 (s), 130.14 (s), 128.43 (s), 127.71 (s), 125.85 (s), 124.22 (s), 122.40 (s), 70.23 (s), 61.80 (s), 59.07 (s), 55.43 (s), 54.76 (s), 41.54 (s), 39.64 (s), 20.81 (s), 18.25 (s), 13.78 (s), 11.40 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{30}\text{N}_3\text{O}_4$ 460.2236, found 460.2234



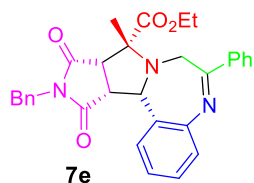
ethyl (9R,9aS,12aR)-11-cyclohexyl-9-methyl-10,12-dioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (7d):

White solid, 80% yield. MP: 106-108.5°C.

^1H NMR (400 MHz, cdCl_3) δ 7.74 (dt, $J = 8.4, 1.5$ Hz, 2H), 7.38 – 7.33 (m, 1H), 7.18 – 7.13 (m, 3H), 7.07 (dd, $J = 7.5, 1.2$ Hz, 1H), 6.98 – 6.92 (m, 2H), 4.19 – 4.09 (m, 4H), 3.78 (d, $J = 3.5$ Hz, 2H), 3.07 (d, $J = 8.0$ Hz, 1H), 2.92 (dd, $J = 8.0, 5.2$ Hz, 1H), 2.41 – 2.24 (m, 2H), 1.86 (t, $J = 10.7$ Hz, 2H), 1.77 – 1.67 (m, 3H), 1.56 (s, 3H), 1.35 (dddd, $J = 16.6, 10.4, 5.4, 2.2$ Hz, 3H), 1.27 – 1.22 (m, 3H).

^{13}C NMR (101 MHz, cdCl_3) δ 198.71 (s), 175.37 (s), 171.15 (s), 162.19 (s), 144.79 (s), 135.61 (s), 132.38 (s), 130.96 (s), 130.03 (s), 128.56 (s), 127.57 (s), 125.72 (s), 123.96 (s), 121.84 (s), 70.31 (s), 61.88 (s), 59.09 (s), 55.73 (s), 55.24 (s), 53.03 (s), 39.14 (s), 29.15 (s), 28.12 (s), 25.92 (d, $J = 17.5$ Hz), 25.24 (s), 18.14 (s), 14.02 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{30}\text{H}_{34}\text{N}_3\text{O}_4$ 500.2549, found 500.2556



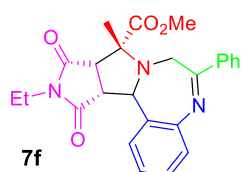
ethyl (9R,9aS,12aR,12bS)-11-benzyl-9-methyl-10,12-dioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (7e):

White solid, 88% yield. MP: 194-197°C.

¹H NMR (400 MHz, cdcl₃) δ 7.70 – 7.64 (m, 2H), 7.50 – 7.45 (m, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.33 – 7.19 (m, 6H), 7.14 (ddd, *J* = 10.7, 7.6, 1.4 Hz, 2H), 7.01 (td, *J* = 7.4, 1.4 Hz, 1H), 4.95 (d, *J* = 14.1 Hz, 1H), 4.81 (d, *J* = 14.1 Hz, 1H), 4.28 (d, *J* = 5.3 Hz, 1H), 4.01 – 3.86 (m, 3H), 3.71 (d, *J* = 15.8 Hz, 1H), 3.17 (d, *J* = 8.0 Hz, 1H), 3.07 (dd, *J* = 7.9, 5.3 Hz, 1H), 1.58 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (101 MHz, cdcl₃) δ 198.26 (s), 175.44 (s), 171.23 (s), 162.03 (s), 144.69 (s), 136.31 (s), 135.59 (s), 132.69 (s), 130.80 (s), 130.15 (s), 128.79 (s), 128.42 (d, *J* = 7.9 Hz), 127.86 (s), 127.63 (s), 126.21 (s), 124.44 (s), 122.65 (s), 70.23 (s), 61.79 (s), 59.00 (s), 55.59 (s), 54.16 (s), 43.09 (s), 40.01 (s), 18.56 (s), 13.76 (s).

HRMS (ESI-TOF, *m/z*): [M+H]⁺ calculated for C₃₁H₃₀N₃O₄ 508.2236, found 508.2240



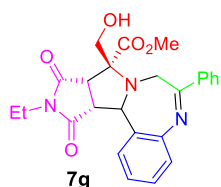
methyl (9R,9aS,12aR)-11-ethyl-9-methyl-10,12-dioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (7f):

White solid, 85% yield. MP: 113-114.5°C.

¹H NMR (400 MHz, cdcl₃) δ 7.65 (dt, *J* = 8.5, 1.5 Hz, 2H), 7.40 – 7.34 (m, 1H), 7.26 – 7.17 (m, 3H), 7.11 (ddd, *J* = 10.4, 7.7, 1.3 Hz, 2H), 7.01 (td, *J* = 7.4, 1.3 Hz, 1H), 4.25 (d, *J* = 5.2 Hz, 1H), 3.86 (d, *J* = 15.8 Hz, 1H), 3.78 – 3.66 (m, 3H), 3.54 (s, 3H), 3.13 (d, *J* = 7.9 Hz, 1H), 3.03 (dd, *J* = 7.9, 5.2 Hz, 1H), 1.57 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (101 MHz, cdcl₃) δ 198.45 (s), 175.68 (s), 171.59 (s), 162.34 (s), 144.74 (s), 135.53 (s), 132.62 (s), 130.96 (s), 130.22 (s), 128.35 (s), 127.76 (s), 125.87 (s), 124.31 (s), 122.37 (s), 70.32 (s), 58.98 (s), 55.41 (s), 54.57 (s), 52.34 (s), 50.78 (s), 39.57 (s), 35.19 (s), 18.27 (s), 12.72 (s).

HRMS (ESI-TOF, *m/z*): [M+H]⁺ calculated for C₂₅H₂₆N₃O₄ 432.1923, found 432.1922



methyl (9S,9aS,12aR)-11-ethyl-9-(hydroxymethyl)-10,12-dioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (7g):

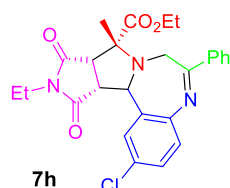
White solid, 68% yield. MP: 171-172.5°C.

¹H NMR (400 MHz, dmsO) δ 7.49 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.40 (ddd, *J* = 5.7, 4.0, 1.6 Hz, 2H), 7.37 –

7.29 (m, 3H), 7.26 (ddd, $J = 7.8, 4.5, 1.3$ Hz, 2H), 7.19 (td, $J = 7.4, 1.3$ Hz, 1H), 6.72 (d, $J = 2.9$ Hz, 1H), 5.05 (d, $J = 5.8$ Hz, 1H), 4.33 (d, $J = 11.7$ Hz, 1H), 4.17 (d, $J = 11.7$ Hz, 1H), 3.58 (s, 5H), 3.37 – 3.32 (m, 1H), 3.16 (dd, $J = 9.7, 6.5$ Hz, 1H), 2.73 (d, $J = 14.8$ Hz, 1H), 2.32 (dd, $J = 14.8, 2.9$ Hz, 1H), 1.11 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (101 MHz, dms o) δ 175.21 (s), 170.50 (s), 163.51 (s), 144.71 (s), 144.07 (s), 130.98 (s), 129.82 (s), 128.33 (s), 126.03 (s), 125.76 (s), 124.59 (d, $J = 11.7$ Hz), 95.38 (s), 67.48 (s), 58.25 (s), 56.61 (s), 52.73 (s), 51.33 (s), 49.67 (s), 34.84 (s), 12.93 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_5$ 448.1872, found 448.1876



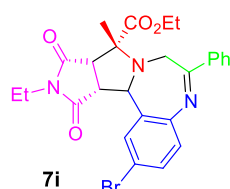
*ethyl (9R,9a*S*,12aR)-2-chloro-11-ethyl-9-methyl-10,12-dioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[*f*]pyrrolo[3',4':3,4]pyrrolo[1,2-*d*][1,4]diazepine-9-carboxylate (7h):*

White solid, 77% yield. MP: 155-157°C.

^1H NMR (400 MHz, cdcl_3) δ 7.76 – 7.71 (m, 2H), 7.42 – 7.36 (m, 1H), 7.24 – 7.19 (m, 2H), 7.15 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.09 (d, $J = 2.3$ Hz, 1H), 6.94 (d, $J = 8.4$ Hz, 1H), 4.20 (d, $J = 5.2$ Hz, 1H), 4.12 – 4.05 (m, 2H), 3.83 (d, $J = 15.8$ Hz, 1H), 3.79 – 3.67 (m, 3H), 3.14 (d, $J = 7.9$ Hz, 1H), 3.01 (dd, $J = 7.8, 5.2$ Hz, 1H), 1.56 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.21 – 1.17 (m, 3H).

^{13}C NMR (101 MHz, cdcl_3) δ 198.39 (s), 175.31 (s), 171.01 (s), 162.54 (s), 143.34 (s), 135.57 (s), 132.67 (s), 130.76 (s), 129.99 (s), 129.18 (s), 128.43 (s), 127.84 (s), 126.83 (s), 123.95 (s), 70.40 (s), 61.96 (s), 58.70 (s), 55.26 (s), 54.91 (s), 39.52 (s), 35.12 (s), 18.39 (s), 13.87 (s), 12.83 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{26}\text{H}_{27}\text{ClN}_3\text{O}_4$ 480.1690, found 480.1687



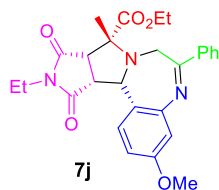
*ethyl (9R,9a*S*,12aR)-2-bromo-11-ethyl-9-methyl-10,12-dioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[*f*]pyrrolo[3',4':3,4]pyrrolo[1,2-*d*][1,4]diazepine-9-carboxylate (7i):*

White solid, 75% yield. MP: 160-162°C.

^1H NMR (400 MHz, cdcl_3) δ 7.73 (dt, $J = 8.5, 1.6$ Hz, 2H), 7.41 – 7.35 (m, 1H), 7.29 (dd, $J = 8.4, 2.3$ Hz, 1H), 7.24 – 7.18 (m, 3H), 6.87 (d, $J = 8.4$ Hz, 1H), 4.17 (d, $J = 5.2$ Hz, 1H), 4.08 (qd, $J = 7.2, 1.5$ Hz, 2H), 3.81 (d, $J = 15.8$ Hz, 1H), 3.77 – 3.67 (m, 3H), 3.13 (d, $J = 7.9$ Hz, 1H), 3.00 (dd, $J = 7.8, 5.2$ Hz, 1H), 1.55 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.19 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (101 MHz, cdcl_3) δ 198.35 (s), 175.31 (s), 170.99 (s), 162.60 (s), 143.78 (s), 135.57 (s), 133.62 (s), 133.00 (s), 132.64 (s), 128.46 (s), 127.82 (s), 127.20 (s), 124.34 (s), 116.82 (s), 70.42 (s), 61.97 (s), 58.65 (s), 55.13 (d, $J = 18.0$ Hz), 39.52 (s), 35.14 (s), 21.02 (s), 18.32 (s), 13.87 (s), 12.82 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{26}\text{H}_{27}\text{BrN}_3\text{O}_4$ 524.1185, found 524.1189



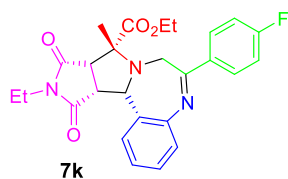
ethyl (9R,9aS,12aR,12bS)-11-ethyl-3-methoxy-9-methyl-10,12-dioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (7j):

White solid, 67% yield. MP: 121-123°C.

$^1\text{H NMR}$ (400 MHz, cdCl_3) δ 7.69 (dd, $J = 8.3, 1.3$ Hz, 2H), 7.37 – 7.31 (m, 1H), 7.16 (dd, $J = 11.0, 4.7$ Hz, 2H), 6.95 (d, $J = 8.2$ Hz, 1H), 6.55 – 6.48 (m, 2H), 4.06 (pd, $J = 6.9, 3.3$ Hz, 3H), 3.77 – 3.66 (m, 7H), 3.09 (d, $J = 7.9$ Hz, 1H), 2.98 (dd, $J = 7.8, 5.2$ Hz, 1H), 1.53 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.17 (t, $J = 7.2$ Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, cdCl_3) δ 221.18 (s), 198.37 (s), 175.56 (s), 171.21 (s), 162.82 (s), 161.18 (s), 145.93 (s), 135.56 (s), 132.46 (s), 131.65 (s), 128.48 (s), 127.47 (s), 114.35 (s), 110.81 (s), 110.14 (s), 70.23 (s), 61.84 (s), 58.82 (s), 55.60 (s), 55.23 (d, $J = 19.2$ Hz), 40.08 (s), 35.03 (s), 17.80 (s), 13.86 (s), 12.89 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{30}\text{N}_3\text{O}_5$ 476.2185, found 476.2182



ethyl (9R,9aS,12aR,12bS)-11-ethyl-6-(4-fluorophenyl)-9-methyl-10,12-dioxo-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (7k):

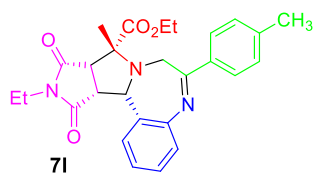
White solid, 74% yield. MP: 131-133°C.

$^1\text{H NMR}$ (400 MHz, cdCl_3) δ 7.77 – 7.70 (m, 2H), 7.15 (td, $J = 7.6, 1.6$ Hz, 1H), 7.05 (dd, $J = 7.4, 1.5$ Hz, 1H), 6.99 – 6.90 (m, 2H), 6.77 (t, $J = 8.8$ Hz, 2H), 4.09 (qd, $J = 7.2, 2.4$ Hz, 2H), 3.98 (d, $J = 5.2$ Hz, 1H), 3.79 – 3.66 (m, 4H), 3.11 (d, $J = 7.9$ Hz, 1H), 2.99 (dd, $J = 7.9, 5.2$ Hz, 1H), 1.55 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.20 (t, $J = 7.2$ Hz, 3H).

$^{19}\text{F NMR}$ (376 MHz, cdCl_3) δ -106.01 (s).

$^{13}\text{C NMR}$ (101 MHz, cdCl_3) δ 196.51 (s), 175.35 (s), 171.16 (s), 166.43 (s), 163.91 (s), 162.09 (s), 144.72 (s), 131.98 (d, $J = 2.9$ Hz), 131.57 – 131.14 (m), 130.31 (s), 125.56 (s), 124.08 (s), 121.99 (s), 114.56 (s), 114.35 (s), 70.45 (s), 61.97 (s), 59.74 (s), 56.47 (s), 55.09 (s), 39.55 (s), 35.09 (s), 17.36 (s), 13.90 (s), 12.88 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{26}\text{H}_{27}\text{FN}_3\text{O}_4$ 464.1986, found 464.1989



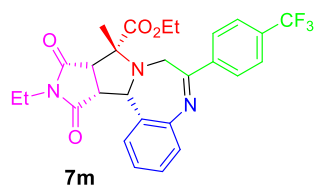
ethyl (9R,9aS,12aR,12bS)-11-ethyl-9-methyl-10,12-dioxo-6-(p-tolyl)-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (7l):

White solid, 80% yield. MP: 127-129°C.

^1H NMR (400 MHz, cdCl_3) δ 7.56 (d, $J = 8.2$ Hz, 2H), 7.26 – 7.21 (m, 1H), 7.12 (dd, $J = 7.6, 1.5$ Hz, 2H), 7.02 – 6.96 (m, 3H), 4.27 (d, $J = 5.2$ Hz, 1H), 4.06 – 3.96 (m, 2H), 3.83 (d, $J = 15.8$ Hz, 1H), 3.80 – 3.69 (m, 2H), 3.66 (d, $J = 15.8$ Hz, 1H), 3.12 (d, $J = 7.9$ Hz, 1H), 3.03 (dd, $J = 7.9, 5.2$ Hz, 1H), 2.30 (s, 3H), 1.55 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.11 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (101 MHz, cdCl_3) δ 198.03 (s), 175.58 (s), 171.19 (s), 162.39 (s), 144.74 (s), 143.33 (s), 133.21 (s), 130.93 (s), 130.10 (s), 128.49 (s), 125.83 (s), 124.24 (s), 122.61 (s), 70.18 (s), 61.75 (s), 58.84 (s), 55.55 (s), 54.21 (s), 39.74 (s), 34.98 (s), 21.60 (s), 18.55 (s), 13.79 (s), 12.89 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{30}\text{N}_3\text{O}_4$ 460.2236, found 460.2232



ethyl (9R,9aS,12aR,12bS)-11-ethyl-9-methyl-10,12-dioxo-6-(4-(trifluoromethyl)phenyl)-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (7m):

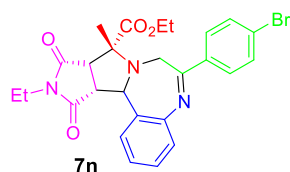
Gray solid, 63% yield. MP: 112-114°C.

^1H NMR (400 MHz, cdCl_3) δ 7.79 (dd, $J = 8.7, 0.7$ Hz, 2H), 7.40 – 7.34 (m, 2H), 7.18 – 7.12 (m, 1H), 7.04 (dd, $J = 7.4, 1.7$ Hz, 1H), 6.98 (td, $J = 7.4, 1.3$ Hz, 1H), 6.87 (dd, $J = 7.8, 1.2$ Hz, 1H), 4.17 – 4.07 (m, 2H), 3.96 (d, $J = 5.2$ Hz, 1H), 3.80 – 3.67 (m, 4H), 3.13 (d, $J = 7.9$ Hz, 1H), 3.00 (dd, $J = 7.9, 5.2$ Hz, 1H), 1.58 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H).

^{19}F NMR (376 MHz, cdCl_3) δ -63.20 (s).

^{13}C NMR (101 MHz, cdCl_3) δ 197.35 (s), 175.25 (s), 171.12 (s), 161.98 (s), 144.75 (s), 137.96 (s), 133.40 (s), 133.08 (s), 131.24 (s), 130.50 (s), 128.94 (s), 125.70 (s), 124.29 (dd, $J = 13.6, 9.8$ Hz), 121.77 (s), 70.43 (s), 62.08 (s), 59.88 (s), 56.75 (s), 55.03 (s), 39.45 (s), 35.16 (s), 17.22 (s), 13.91 (s), 12.84 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{27}\text{F}_3\text{N}_3\text{O}_4$ 514.1954, found 514.1958



ethyl (9R,9aS,12aR)-6-(4-bromophenyl)-11-ethyl-9-methyl-10,12-dioxo-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (7n):

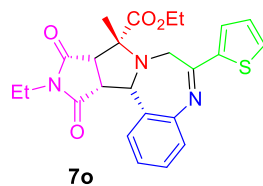
Canary yellow solid, 75% yield. MP: 144-146°C.

^1H NMR (400 MHz, cdCl_3) δ 7.59 – 7.54 (m, 2H), 7.28 – 7.24 (m, 2H), 7.20 – 7.16 (m, 1H), 7.05 (dd, $J = 7.7, 1.6$ Hz, 1H), 6.98 (ddd, $J = 7.9, 5.2, 1.3$ Hz, 2H), 4.12 – 4.04 (m, 2H), 3.99 (d, $J = 5.2$ Hz, 1H), 3.81 – 3.73 (m, 2H), 3.72 – 3.64 (m, 2H), 3.12 (d, $J = 7.9$ Hz, 1H), 3.01 (dd, $J = 7.9, 5.2$ Hz, 1H), 1.56 (s, 3H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.20 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (101 MHz, cdCl_3) δ 197.09 (s), 175.33 (s), 171.10 (s), 162.09 (s), 144.73 (s), 134.20 (s), 131.54 (s), 131.23 (s), 130.74 (s), 130.34 (d, $J = 17.6$ Hz), 129.68 (s), 127.51 (s), 125.70 (s), 124.13 (s), 121.98 (s), 70.37 (s), 61.99 (s), 59.76 (s), 56.32 (s), 55.13 (s), 39.55 (s), 35.13 (s), 17.38 (s), 13.90 (s).

12.90 (s).

HRMS (ESI-TOF, m/z): $[M+H]^+$ calculated for $C_{26}H_{27}BrN_3O_4$ 524.1185, found 524.1182



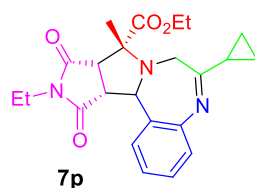
ethyl (9R,9aS,12aR,12bS)-11-ethyl-9-methyl-10,12-dioxo-6-(thiophen-2-yl)-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (7o):

Brownish yellow solid, 64% yield. MP: 102-104.5°C.

1H NMR (400 MHz, $cdCl_3$) δ 7.98 (dd, $J = 3.8, 1.1$ Hz, 1H), 7.37 (dd, $J = 4.9, 1.1$ Hz, 1H), 7.19 – 7.11 (m, 2H), 6.98 (ddd, $J = 7.3, 6.1, 1.4$ Hz, 2H), 6.88 (dd, $J = 4.9, 3.8$ Hz, 1H), 4.15 – 4.07 (m, 3H), 3.77 (dddd, $J = 14.3, 10.9, 7.1, 3.5$ Hz, 2H), 3.65 (s, 2H), 3.12 (d, $J = 7.9$ Hz, 1H), 3.02 (dd, $J = 7.9, 5.2$ Hz, 1H), 1.54 (s, 3H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.22 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (101 MHz, $cdCl_3$) δ 191.11 (s), 175.42 (s), 171.21 (s), 162.07 (s), 144.46 (s), 142.41 (s), 134.38 (s), 133.21 (s), 131.01 (s), 130.24 (s), 127.53 (s), 125.45 (s), 124.31 (s), 122.17 (s), 70.55 (s), 62.01 (s), 59.60 (s), 56.41 (s), 55.16 (s), 39.67 (s), 35.12 (s), 17.98 (s), 13.97 (s), 12.90 (s).

HRMS (ESI-TOF, m/z): $[M+H]^+$ calculated for $C_{24}H_{26}N_3O_4S$ 452.1644, found 452.1650



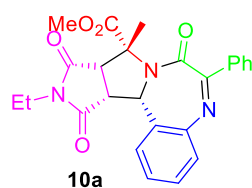
ethyl (9R,9aS,12aR)-6-cyclopropyl-11-ethyl-9-methyl-10,12-dioxo-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (7p):

White solid, 74% yield. MP: 115-117°C.

1H NMR (400 MHz, $cdCl_3$) δ 7.37 – 7.31 (m, 2H), 7.09 (dd, $J = 7.4, 0.5$ Hz, 1H), 7.05 – 7.00 (m, 1H), 4.25 – 4.15 (m, 1H), 4.09 – 4.01 (m, 1H), 3.87 (d, $J = 5.3$ Hz, 1H), 3.81 – 3.73 (m, 2H), 3.22 – 3.12 (m, 3H), 3.06 (dd, $J = 7.9, 5.3$ Hz, 1H), 2.25 – 2.17 (m, 1H), 1.50 (s, 3H), 1.29 – 1.18 (m, 6H), 0.71 – 0.63 (m, 1H), 0.55 – 0.46 (m, 1H), 0.19 (tdd, $J = 8.2, 6.3, 4.1$ Hz, 1H), -0.09 – -0.18 (m, 1H).

^{13}C NMR (101 MHz, $cdCl_3$) δ 210.75 (s), 175.36 (s), 171.12 (s), 162.39 (s), 145.12 (s), 130.86 (s), 130.25 (s), 125.96 (s), 124.55 (s), 122.41 (s), 70.72 (s), 61.81 (s), 60.17 (s), 58.65 (s), 54.79 (s), 39.61 (s), 35.06 (s), 17.53 (s), 16.73 (s), 14.01 (s), 12.73 (s), 11.71 (s), 11.29 (s).

HRMS (ESI-TOF, m/z): $[M+H]^+$ calculated for $C_{23}H_{28}N_3O_4$ 410.2080, found 410.2083



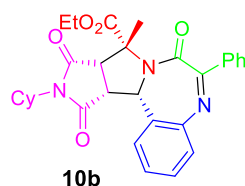
methyl (9R,9aS,12aR,12bS)-11-ethyl-9-methyl-7,10,12-trioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (10a):

White solid, 84% yield. MP: 154-156°C.

¹H NMR (400 MHz, cdcl₃) δ 8.38 (s, 1H), 7.90 – 7.81 (m, 2H), 7.67 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.44 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.20 (s, 1H), 7.17 – 7.12 (m, 1H), 7.05 – 6.97 (m, 4H), 4.82 (s, 1H), 3.54 (s, 3H), 3.44 (qd, *J* = 13.4, 7.1 Hz, 2H), 1.86 (s, 3H), 0.58 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (101 MHz, cdcl₃) δ 174.12 (s), 173.15 (s), 172.07 (s), 156.04 (s), 147.23 (s), 136.48 (s), 135.17 (s), 132.11 (s), 130.00 (s), 128.59 (dd, *J* = 25.8, 8.0 Hz), 127.89 – 127.32 (m), 125.70 (s), 124.56 (s), 118.72 (s), 81.50 (s), 65.32 (s), 63.34 (s), 52.73 (s), 33.60 (s), 25.53 (s), 11.89 (s).

HRMS (ESI-TOF, *m/z*): [M+H]⁺ calculated for C₂₅H₂₄N₃O₅ 446.1716, found 446.1715



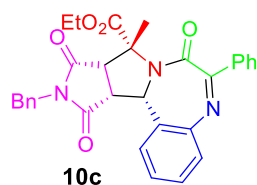
ethyl (9R,9aS,12aR,12bS)-11-cyclohexyl-9-methyl-7,10,12-trioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (10b):

White solid, 83% yield. MP: 162-164°C.

¹H NMR (400 MHz, cdcl₃) δ 8.37 (s, 1H), 7.92 – 7.80 (m, 2H), 7.70 – 7.62 (m, 1H), 7.42 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.26 (d, *J* = 2.3 Hz, 1H), 7.14 (ddd, *J* = 8.6, 3.8, 1.8 Hz, 1H), 7.03 – 6.90 (m, 4H), 5.17 (s, 1H), 4.23 – 4.13 (m, 1H), 4.00 – 3.84 (m, 2H), 1.96 (dt, *J* = 12.2, 8.8 Hz, 2H), 1.84 (s, 3H), 1.71 – 1.51 (m, 3H), 1.26 – 1.02 (m, 7H), 0.69 (d, *J* = 12.1 Hz, 1H).

¹³C NMR (101 MHz, cdcl₃) δ 174.23 (s), 173.42 (s), 171.67 (s), 156.41 (s), 147.07 (s), 136.27 (s), 135.37 (s), 129.77 (s), 128.55 (d, *J* = 15.1 Hz), 127.73 (d, *J* = 5.2 Hz), 127.40 (s), 125.40 (s), 124.42 (s), 118.77 (s), 81.54 (s), 65.35 (s), 62.91 (s), 62.06 (s), 51.44 (s), 27.90 (s), 27.53 (s), 25.86 – 25.29 (m), 25.09 (s), 13.83 (s).

HRMS (ESI-TOF, *m/z*): [M+H]⁺ calculated for C₃₀H₃₂N₃O₅ 514.2342, found 514.2345



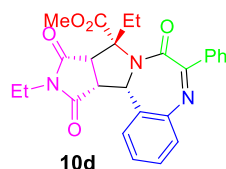
ethyl (9R,9aS,12aR,12bS)-11-benzyl-9-methyl-7,10,12-trioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (10c):

White solid, 83% yield. MP: 149-151°C.

¹H NMR (400 MHz, cdcl₃) δ 8.43 (s, 1H), 7.91 – 7.83 (m, 2H), 7.67 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.48 – 7.42 (m, 1H), 7.19 (s, 1H), 7.12 – 7.04 (m, 4H), 7.03 – 6.98 (m, 2H), 6.97 – 6.88 (m, 4H), 4.94 (s, 1H), 4.61 (d, *J* = 14.5 Hz, 1H), 4.52 (d, *J* = 14.5 Hz, 1H), 3.98 – 3.90 (m, 1H), 3.75 – 3.66 (m, 1H), 1.84 (s, 3H), 0.92 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, cdcl₃) δ 174.16 (s), 173.20 (s), 171.46 (s), 156.03 (s), 147.21 (s), 136.56 (s), 135.66 (s), 135.00 (s), 129.93 (s), 128.75 (d, *J* = 10.7 Hz), 128.20 (d, *J* = 3.0 Hz), 127.94 (s), 127.50 (d, *J* = 7.3 Hz), 127.03 (s), 125.85 (s), 124.62 (s), 118.75 (s), 81.65 (s), 65.38 (s), 63.40 (s), 62.02 (s), 42.44 (s), 25.59 (s), 13.66 (s).

HRMS (ESI-TOF, *m/z*): [M+H]⁺ calculated for C₃₁H₂₈N₃O₅ 522.2029, found 522.2026



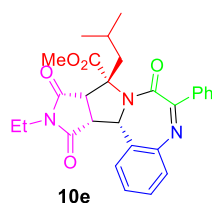
methyl (9R,9aS,12aR,12bS)-9,11-diethyl-7,10,12-trioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (10d):

White solid, 80% yield. MP: 145-147°C.

¹H NMR (400 MHz, cdcl₃) δ 8.39 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.67 (ddd, *J* = 8.3, 7.0, 1.5 Hz, 1H), 7.46 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.30 (s, 1H), 7.18 – 7.11 (m, 1H), 7.01 (dt, *J* = 8.7, 4.8 Hz, 4H), 4.25 (s, 1H), 3.55 (s, 3H), 3.49 – 3.37 (m, 2H), 2.71 (dd, *J* = 13.2, 7.5 Hz, 1H), 2.04 – 1.96 (m, 1H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.57 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (101 MHz, cdcl₃) δ 173.94 (s), 173.33 (s), 170.81 (s), 156.00 (s), 147.21 (s), 137.00 (s), 135.13 (s), 130.06 (s), 128.76 (d, *J* = 2.4 Hz), 127.75 – 127.36 (m), 125.64 (s), 124.58 (s), 118.48 (s), 81.16 (s), 68.77 (s), 64.13 (s), 52.51 (s), 33.62 (s), 30.98 (s), 11.87 (s), 8.51 (s).

HRMS (ESI-TOF, *m/z*): [M+H]⁺ calculated for C₂₆H₂₆N₃O₅ 460.1872, found 460.1875



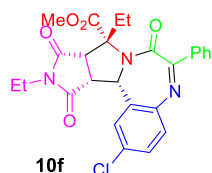
methyl (9R,9aS,12aR,12bS)-11-ethyl-9-isobutyl-7,10,12-trioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (10e):

White solid, 77% yield. MP: 160-162.5°C.

¹H NMR (400 MHz, cdcl₃) δ 8.44 (s, 1H), 7.90 (dd, *J* = 14.9, 7.8 Hz, 2H), 7.72 – 7.66 (m, 1H), 7.51 – 7.45 (m, 1H), 7.34 (s, 1H), 7.12 (dd, *J* = 9.8, 4.3 Hz, 1H), 7.05 – 6.97 (m, 4H), 4.79 (s, 1H), 3.54 (s, 3H), 3.47 – 3.38 (m, 2H), 2.70 (dd, *J* = 13.5, 5.6 Hz, 1H), 1.92 (dd, *J* = 13.5, 6.4 Hz, 1H), 1.69 (dt, *J* = 12.9, 6.4 Hz, 1H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.58 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, cdcl₃) δ 173.85 (s), 173.44 (s), 171.40 (s), 156.00 (s), 147.18 (s), 137.28 (s), 135.20 (s), 130.09 (s), 128.87 (s), 128.65 (s), 127.60 (dd, *J* = 24.8, 16.1 Hz), 125.67 (s), 124.56 (s), 118.59 (s), 81.01 (s), 67.83 (s), 64.83 (s), 52.48 (s), 50.63 (s), 46.32 (s), 33.62 (s), 24.70 (s), 24.25 (s), 23.32 (s), 11.89 (s).

HRMS (ESI-TOF, *m/z*): [M+H]⁺ calculated for C₂₈H₃₀N₃O₅ 488.2185, found 488.2187



methyl (9R,9aS,12aR,12bS)-2-chloro-9,11-diethyl-7,10,12-trioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (10f):

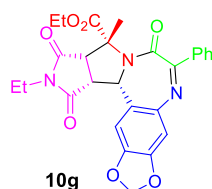
White solid, 70% yield. MP: 173-175°C.

¹H NMR (400 MHz, cdcl₃) δ 8.31 (d, *J* = 3.1 Hz, 1H), 7.86 (d, *J* = 2.5 Hz, 1H), 7.83 – 7.78 (m, 1H),

7.60 (dd, $J = 8.9, 2.5$ Hz, 1H), 7.52 (s, 1H), 7.16 (dd, $J = 10.3, 4.3$ Hz, 1H), 7.04 (dd, $J = 9.6, 5.9$ Hz, 2H), 6.98 (d, $J = 7.4$ Hz, 2H), 5.03 (s, 1H), 3.57 (s, 3H), 3.48 – 3.41 (m, 2H), 2.73 – 2.63 (m, 1H), 2.03 – 1.93 (m, 1H), 0.94 (t, $J = 7.5$ Hz, 3H), 0.57 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, cdCl_3) δ 173.87 (s), 173.59 (s), 170.82 (s), 156.23 (s), 145.61 (s), 136.02 (s), 135.10 (s), 130.59 (s), 129.92 (s), 129.09 (s), 128.76 (s), 127.46 (d, $J = 8.2$ Hz), 126.30 (s), 119.67 (s), 81.12 (s), 68.91 (s), 64.21 (s), 52.57 (s), 50.70 (s), 33.69 (s), 30.97 (s), 11.84 (s), 8.54 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{26}\text{H}_{25}\text{ClN}_3\text{O}_5$ 494.1483, found 494.1488



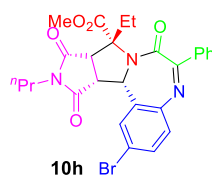
ethyl (9R,9aS,12aR,12bS)-11-ethyl-9-methyl-7,10,12-trioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (10g):

White solid, 62% yield. MP: 151-153°C.

^1H NMR (400 MHz, cdCl_3) δ 8.23 (s, 1H), 7.22 (s, 1H), 7.17 – 7.13 (m, 2H), 7.11 (s, 1H), 7.05 (t, $J = 7.8$ Hz, 2H), 7.02 – 6.98 (m, 2H), 6.10 (dd, $J = 2.6, 1.2$ Hz, 2H), 4.63 (s, 1H), 4.12 – 4.06 (m, 1H), 3.96 (dd, $J = 10.7, 7.1$ Hz, 1H), 3.47 – 3.37 (m, 2H), 1.86 (s, 3H), 1.05 (t, $J = 7.1$ Hz, 3H), 0.47 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (101 MHz, cdCl_3) δ 173.91 (s), 173.13 (s), 171.65 (s), 154.97 (s), 150.76 (s), 146.07 (s), 145.21 (s), 135.37 (d, $J = 9.7$ Hz), 128.63 (s), 127.52 (d, $J = 17.4$ Hz), 121.55 (s), 116.31 (s), 105.37 (s), 104.50 (s), 101.68 (s), 81.56 (s), 65.04 (s), 63.46 (s), 61.92 (s), 33.46 (s), 25.61 (s), 13.73 (s), 12.42 (s), 11.84 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{26}\text{N}_3\text{O}_7$ 504.1771, found 504.1766



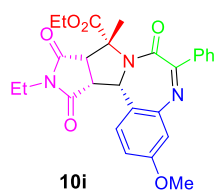
methyl (9R,9aS,12aR,12bS)-2-bromo-9-ethyl-7,10,12-trioxo-6-phenyl-11-propyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (10h):

White solid, 72% yield. MP: 145-147°C.

^1H NMR (400 MHz, cdCl_3) δ 8.33 (s, 1H), 8.03 (s, 1H), 7.73 (s, 3H), 7.15 (dd, $J = 11.4, 4.2$ Hz, 1H), 7.05 (t, $J = 7.7$ Hz, 2H), 7.01 – 6.97 (m, 2H), 5.47 (s, 1H), 3.57 (s, 3H), 3.33 – 3.26 (m, 2H), 2.73 – 2.64 (m, 1H), 1.96 (td, $J = 14.7, 7.2$ Hz, 1H), 1.10 – 0.98 (m, 2H), 0.93 (d, $J = 7.5$ Hz, 3H), 0.59 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (101 MHz, cdCl_3) δ 174.19 (s), 173.84 (s), 170.86 (s), 156.72 (s), 145.87 (s), 135.92 (s), 135.20 (s), 133.11 (s), 130.74 (s), 129.31 (s), 128.69 (s), 127.45 (d, $J = 14.5$ Hz), 126.86 (s), 119.64 (s), 117.66 (s), 81.14 (s), 69.10 (s), 64.26 (s), 52.56 (s), 50.48 (s), 40.53 (s), 30.98 (s), 20.17 (s), 11.05 (s), 8.53 (s).

HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{27}\text{BrN}_3\text{O}_5$ 552.1134, found 552.1130



ethyl (9R,9aS,12aR,12bS)-11-ethyl-3-methoxy-9-methyl-7,10,12-trioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (10i):

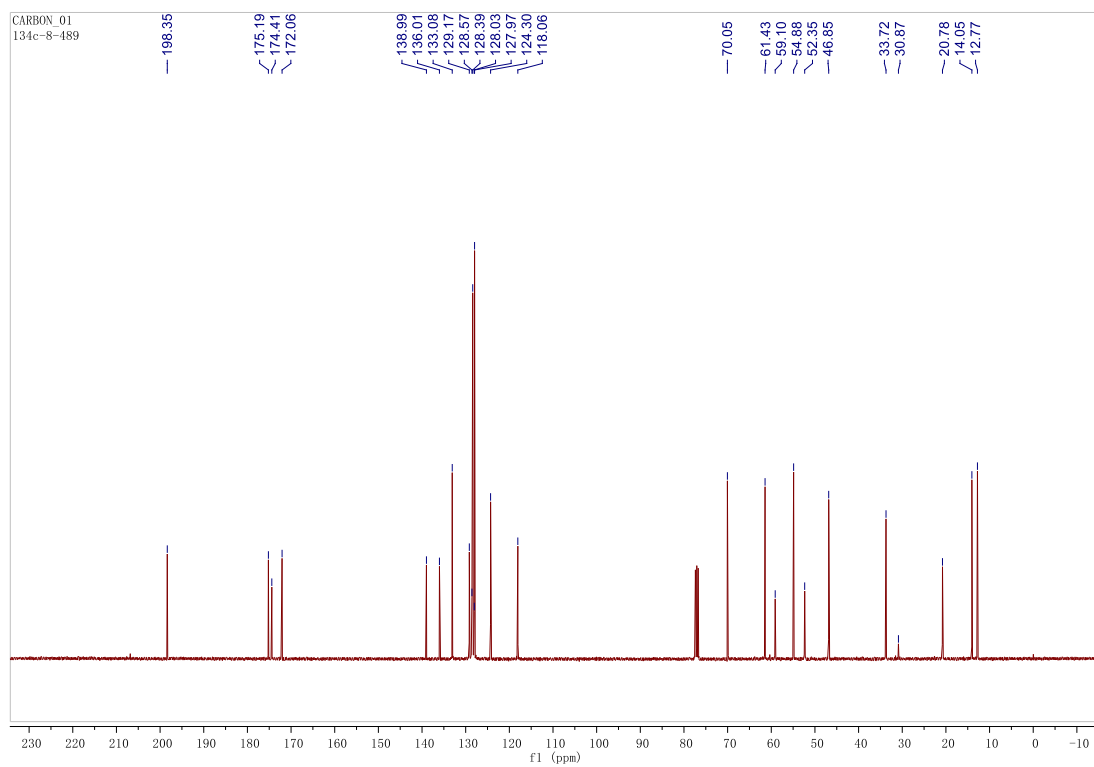
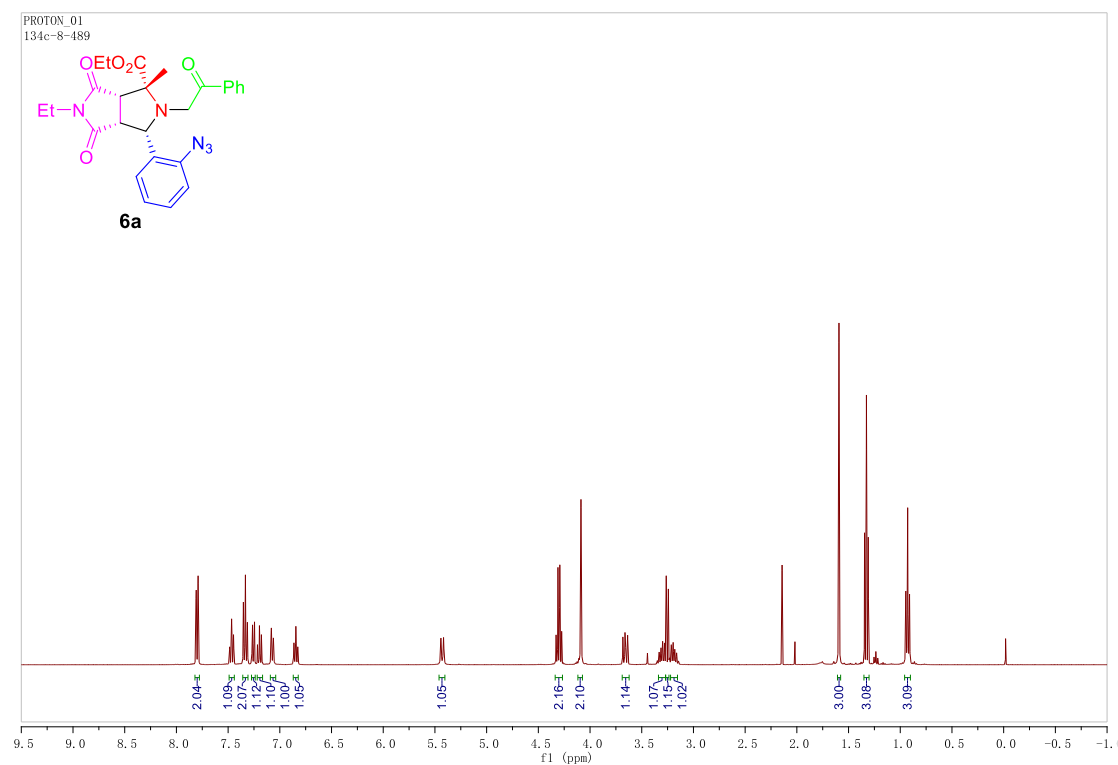
White solid, 67% yield. MP: 148-150°C.

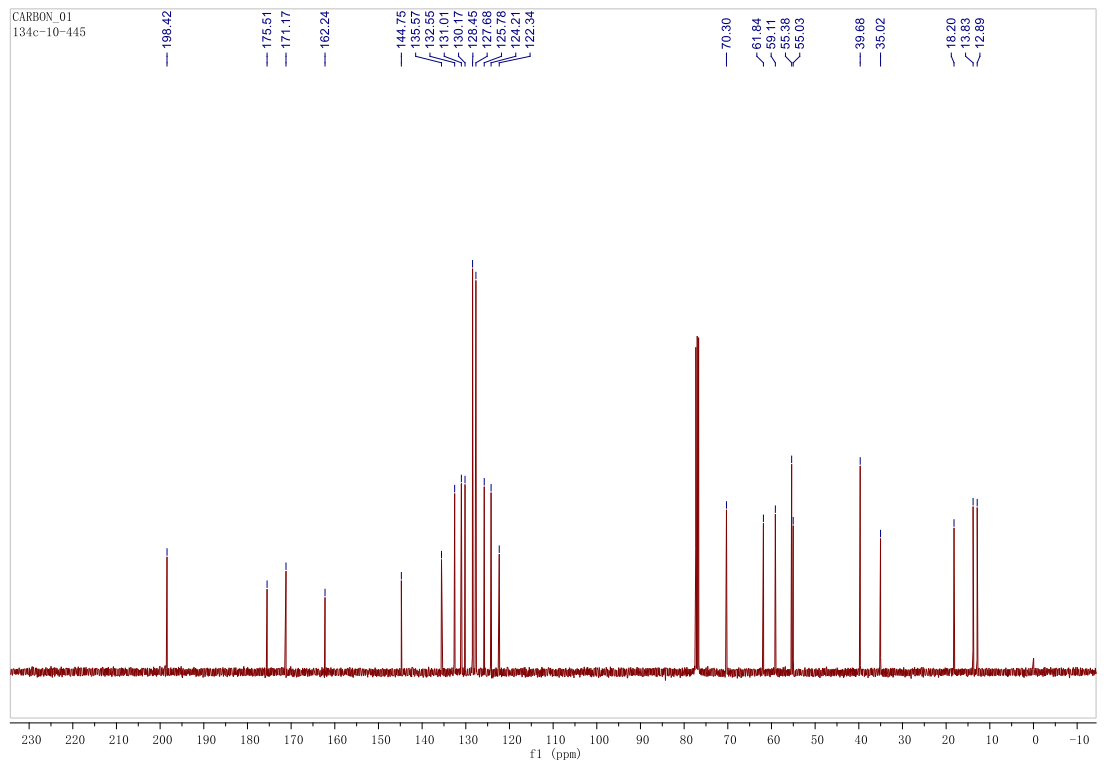
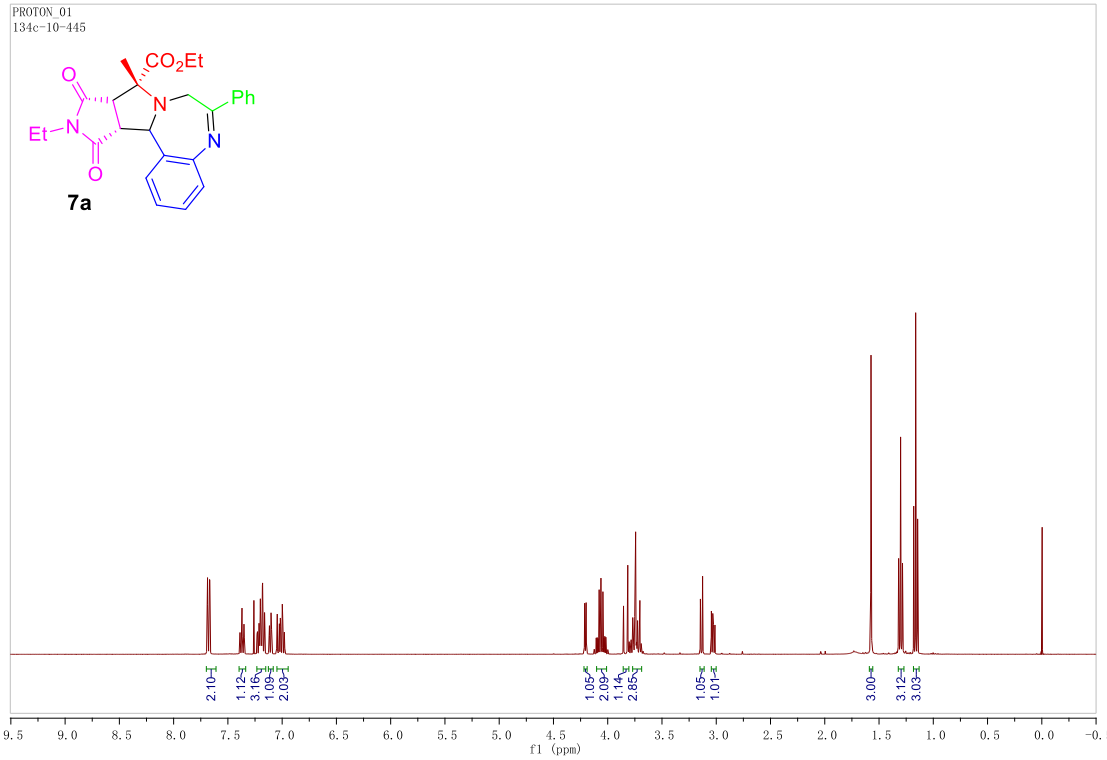
^1H NMR (400 MHz, cdCl_3) δ 8.30 (s, 1H), 7.72 (d, $J = 8.9$ Hz, 1H), 7.25 – 7.24 (m, 1H), 7.17 – 7.12 (m, 1H), 7.11 – 6.94 (m, 6H), 4.61 (s, 1H), 4.10 – 4.04 (m, 1H), 3.98 – 3.94 (m, 1H), 3.93 (s, 3H), 3.51 – 3.37 (m, 2H), 1.86 (s, 3H), 1.04 (t, $J = 7.1$ Hz, 3H), 0.48 (t, $J = 7.1$ Hz, 3H).

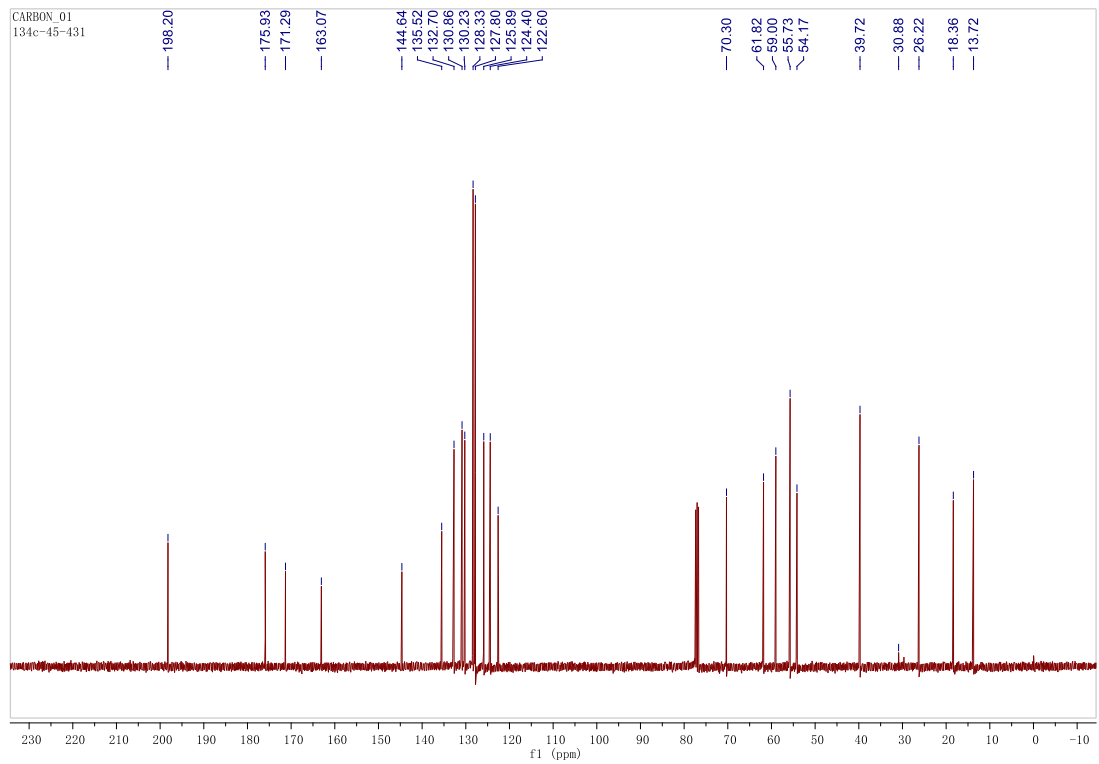
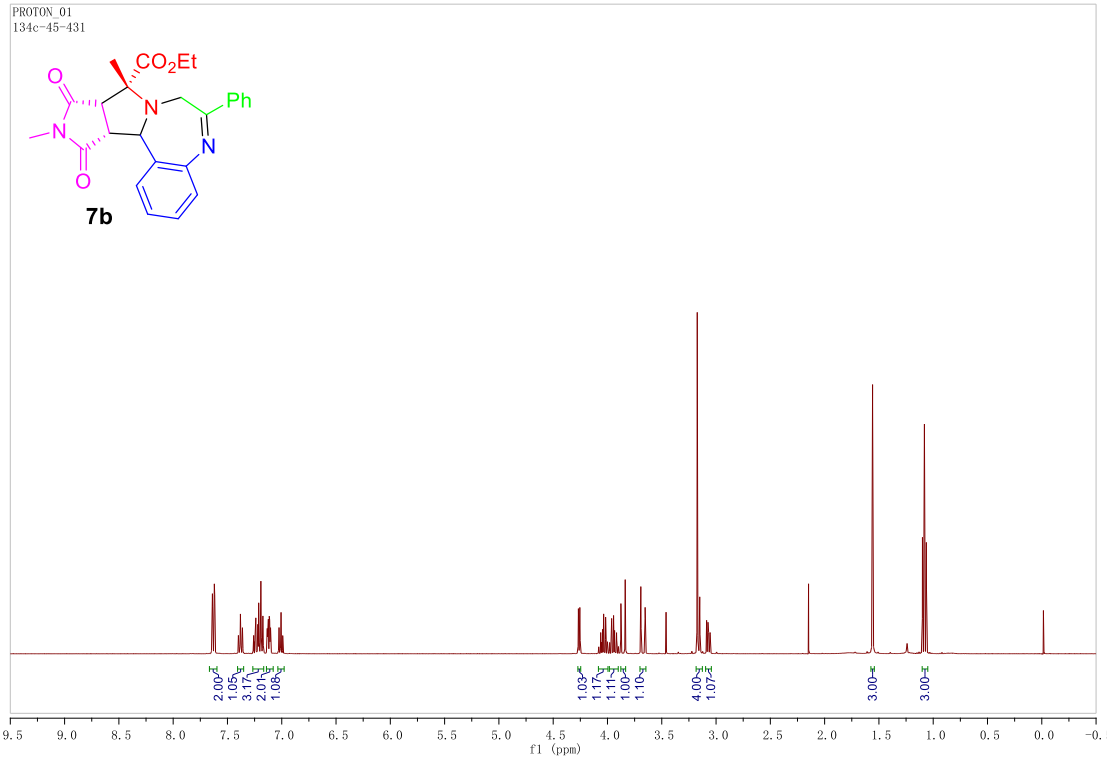
^{13}C NMR (101 MHz, cdCl_3) δ 174.17 (s), 173.07 (s), 171.62 (s), 161.29 (s), 156.56 (s), 149.09 (s), 136.10 (s), 135.32 (s), 129.67 (s), 128.64 (s), 127.53 (d, $J = 16.3$ Hz), 120.41 (s), 116.54 (s), 116.02 (s), 107.10 (s), 81.54 (s), 65.05 (s), 63.30 (s), 61.91 (s), 55.54 (s), 33.52 (s), 25.60 (s), 13.72 (s), 11.83 (s).

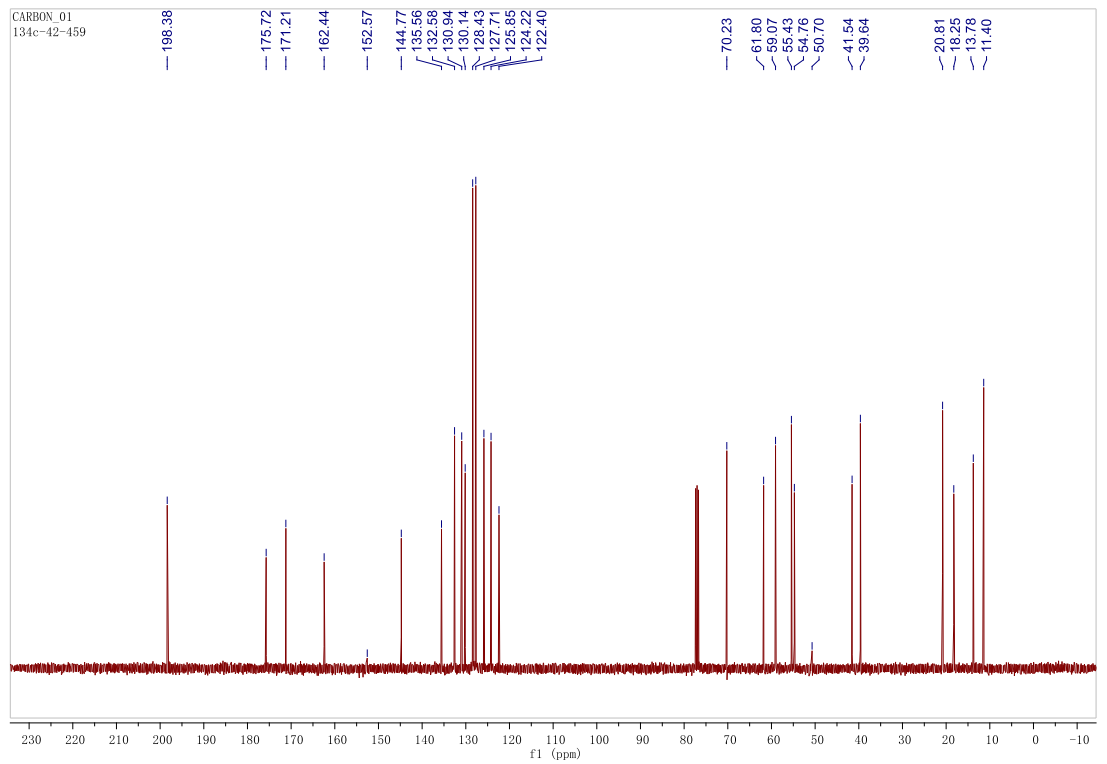
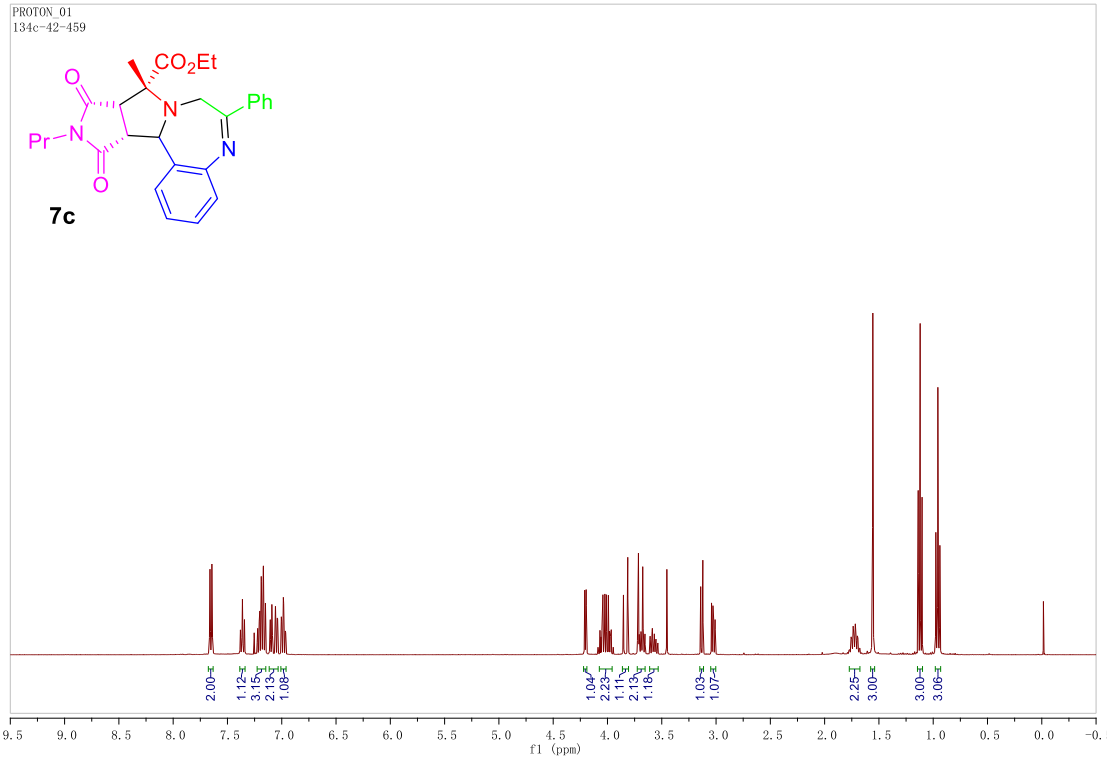
HRMS (ESI-TOF, m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{28}\text{N}_3\text{O}_6$ 490.1978, found 490.1974

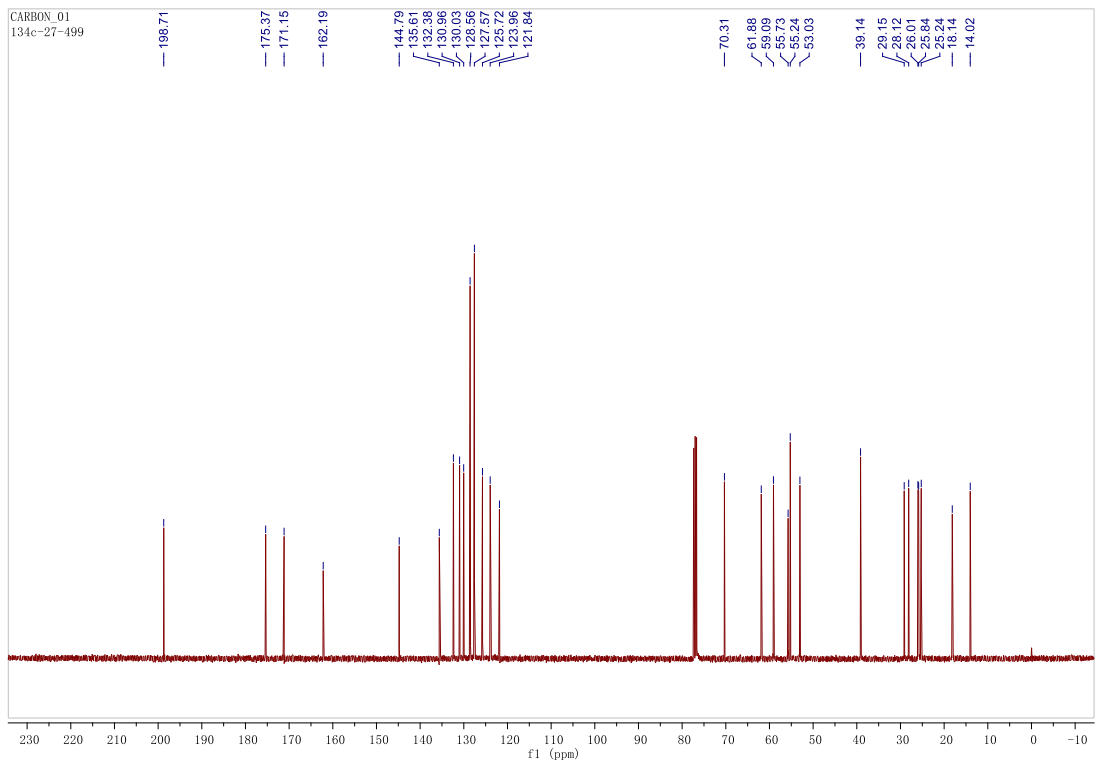
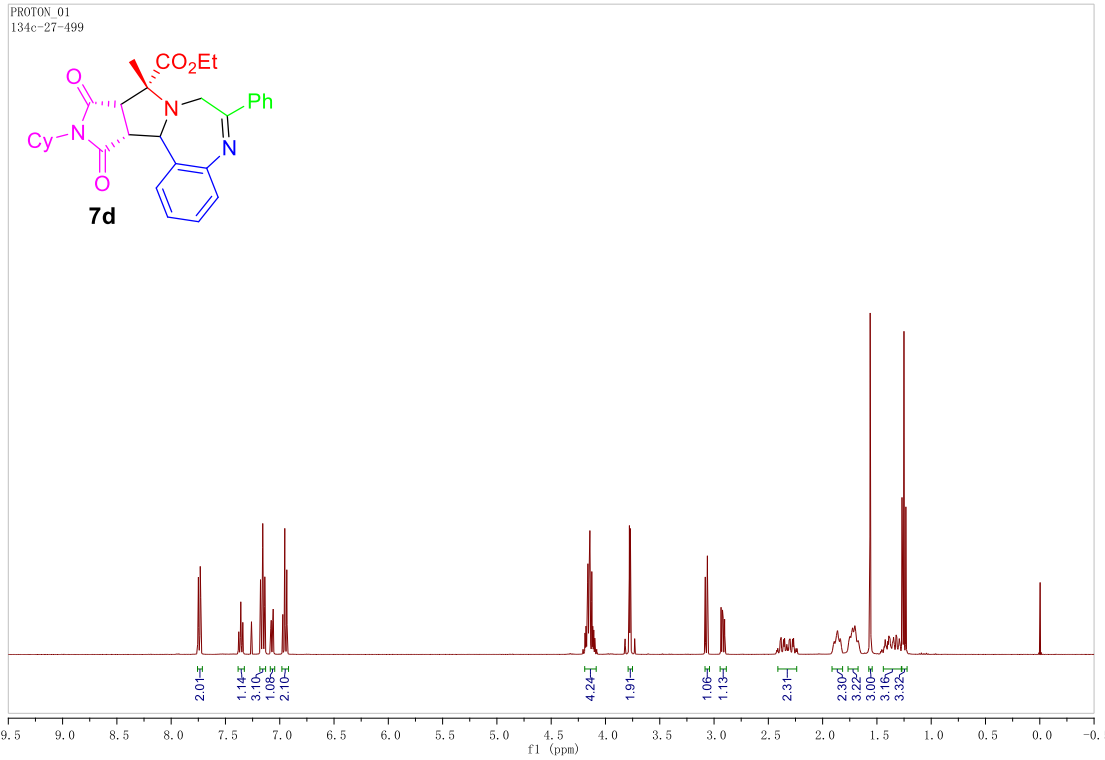
4. NMR spectra of products 6a, 7 and 10

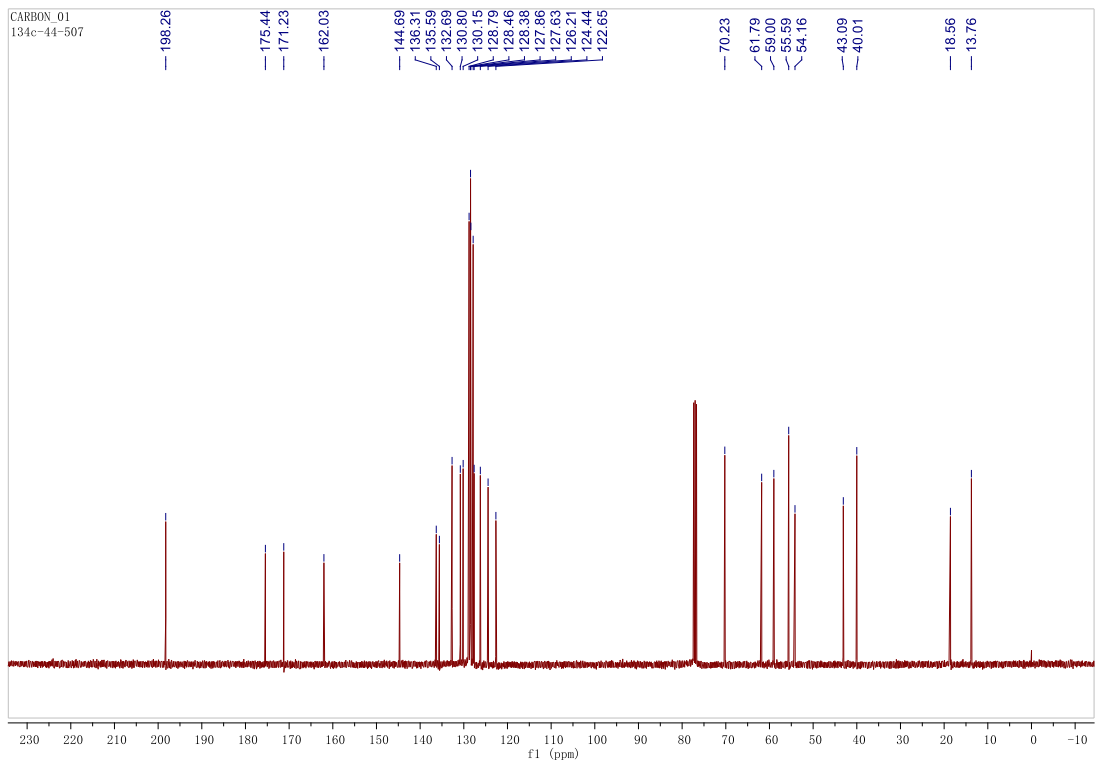
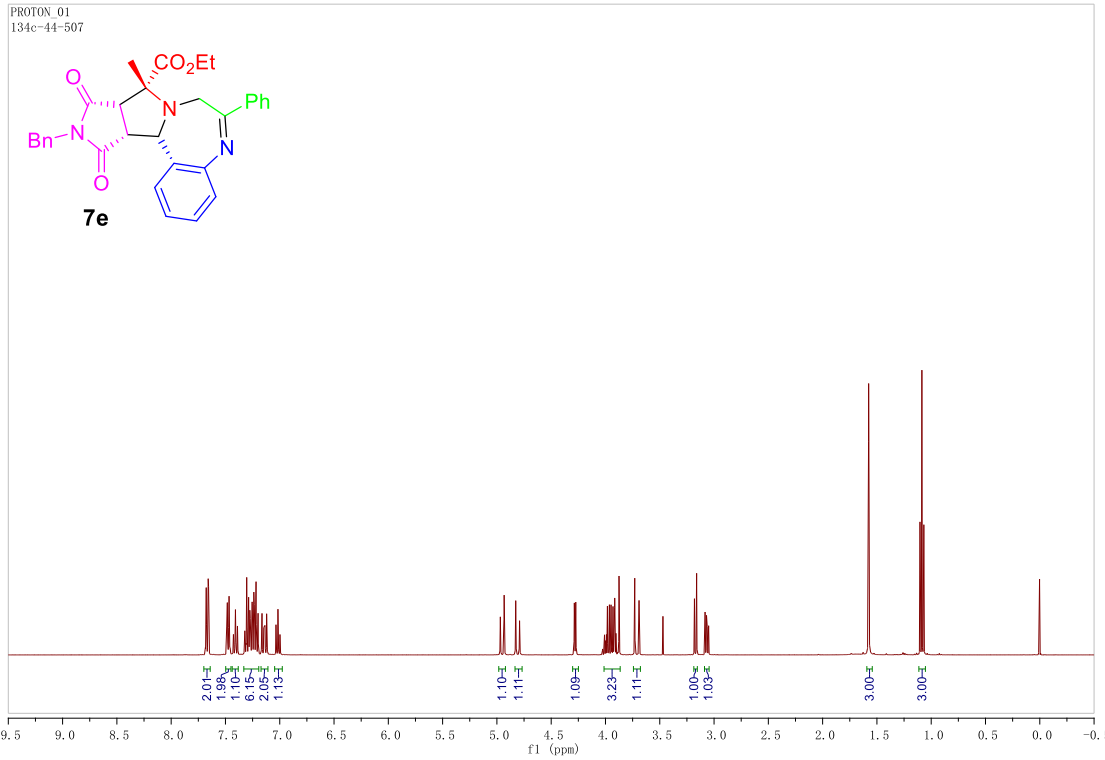


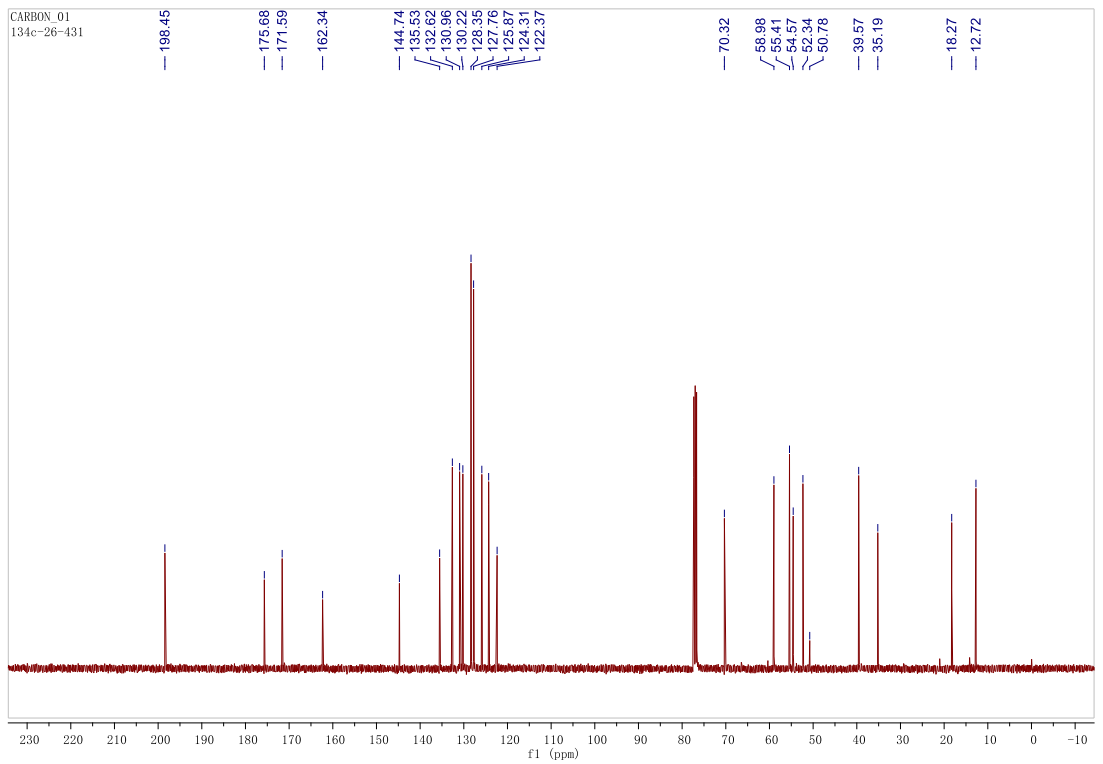
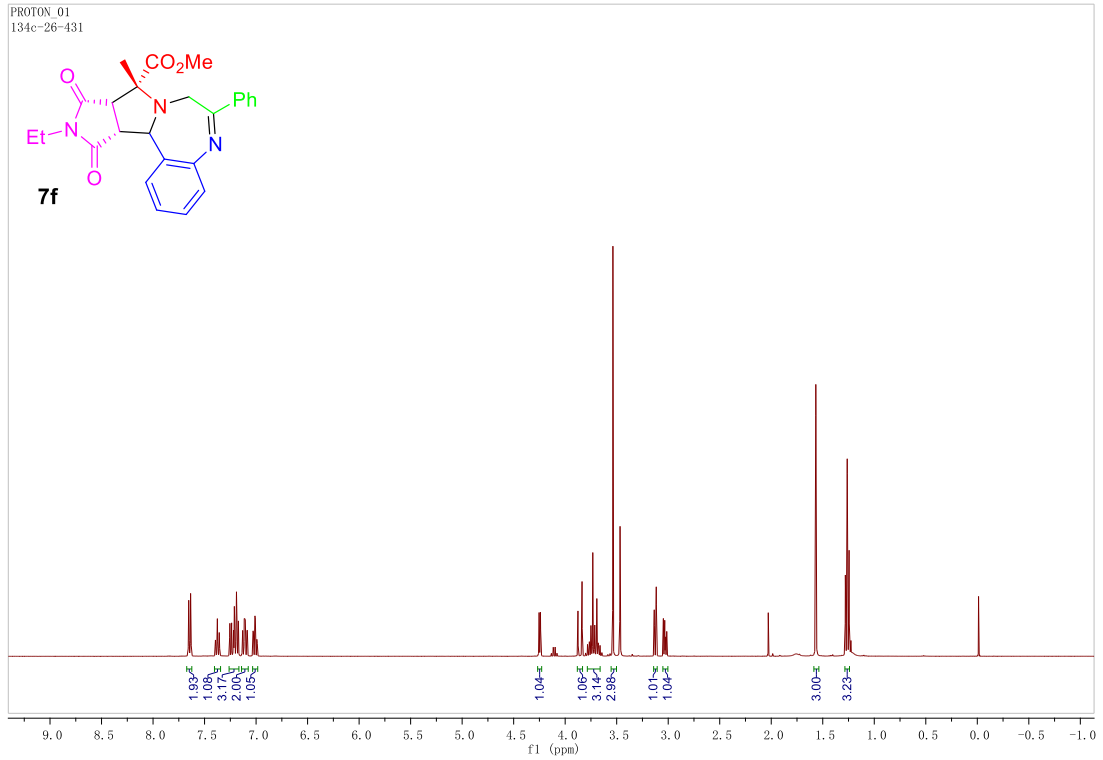


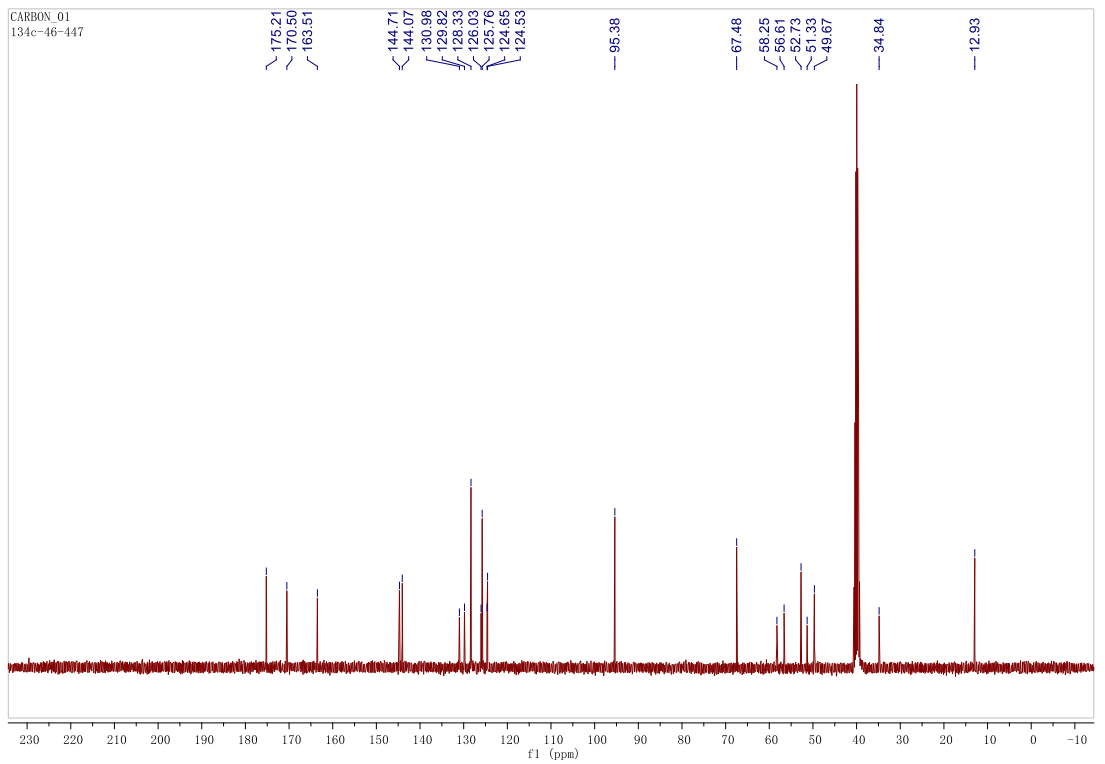
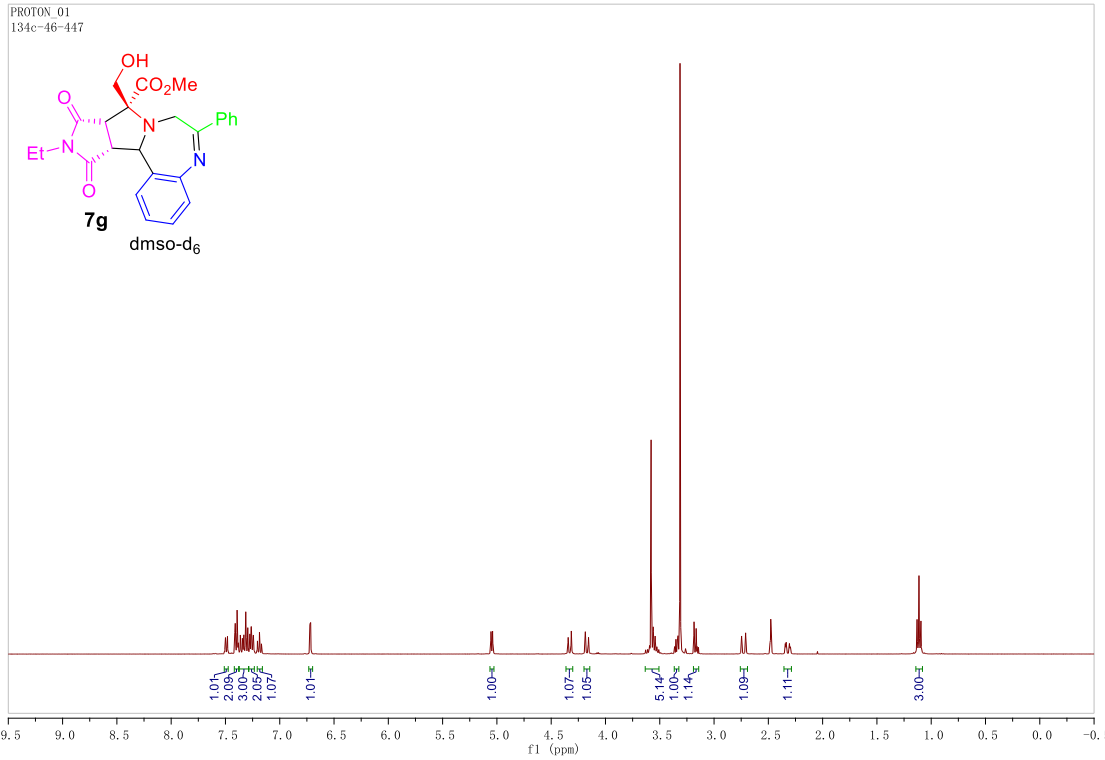


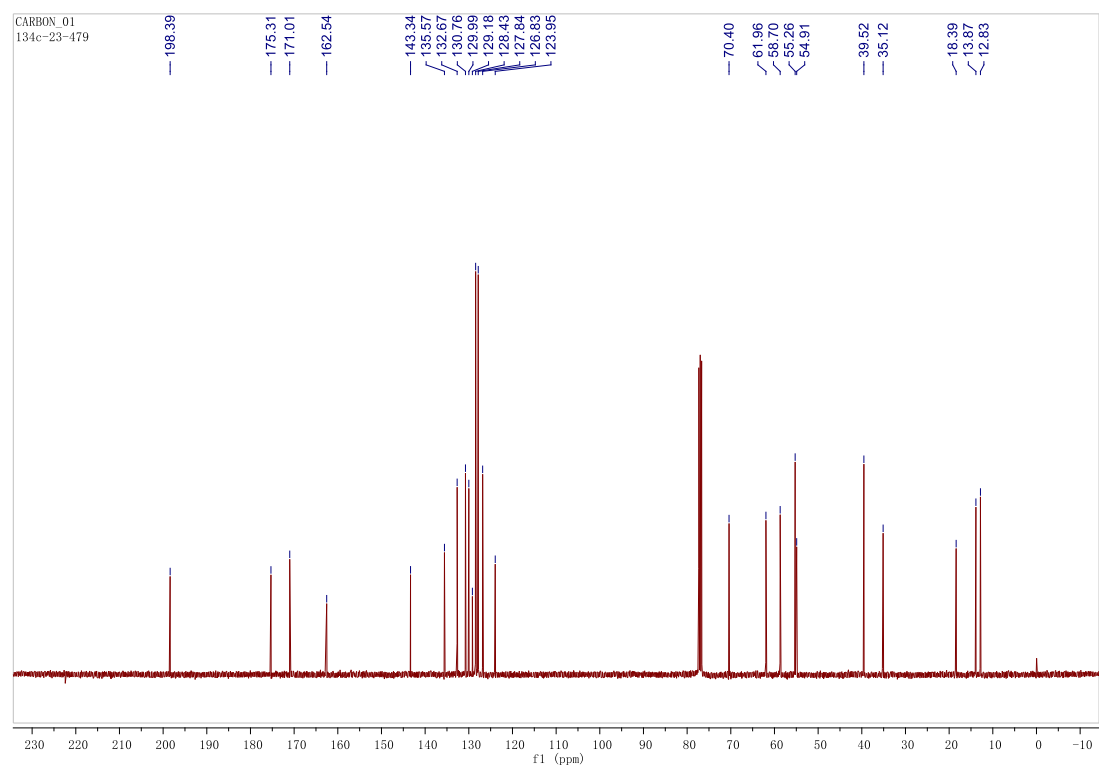
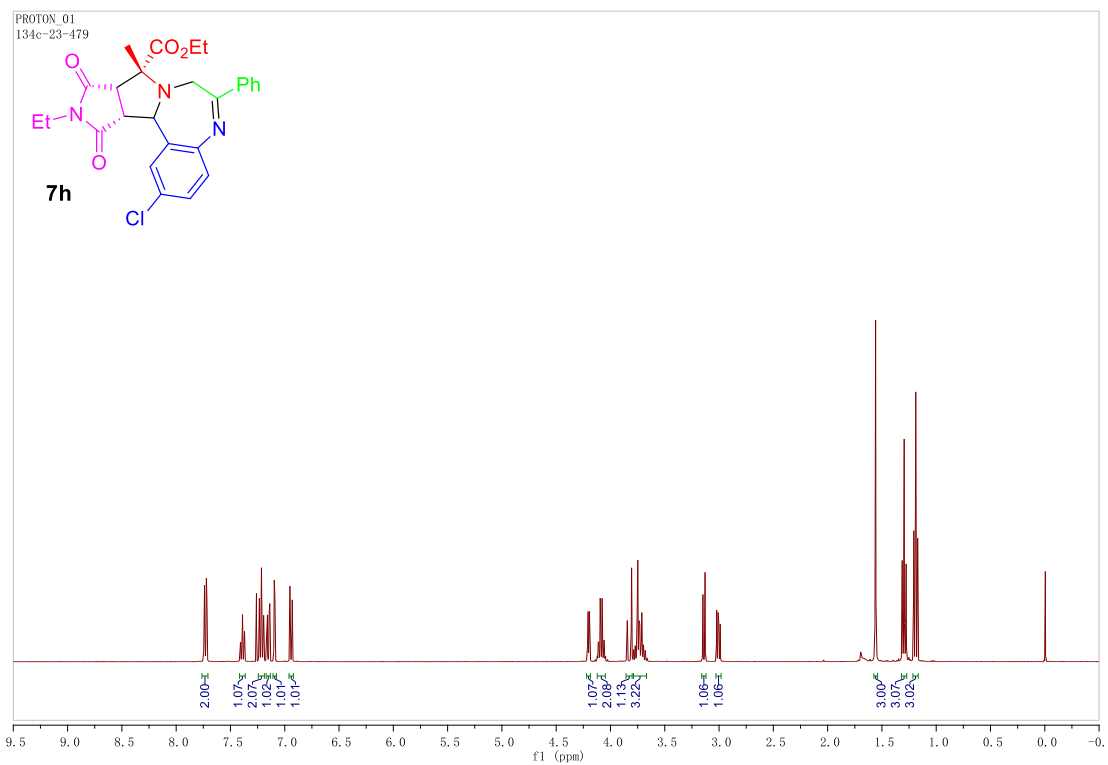




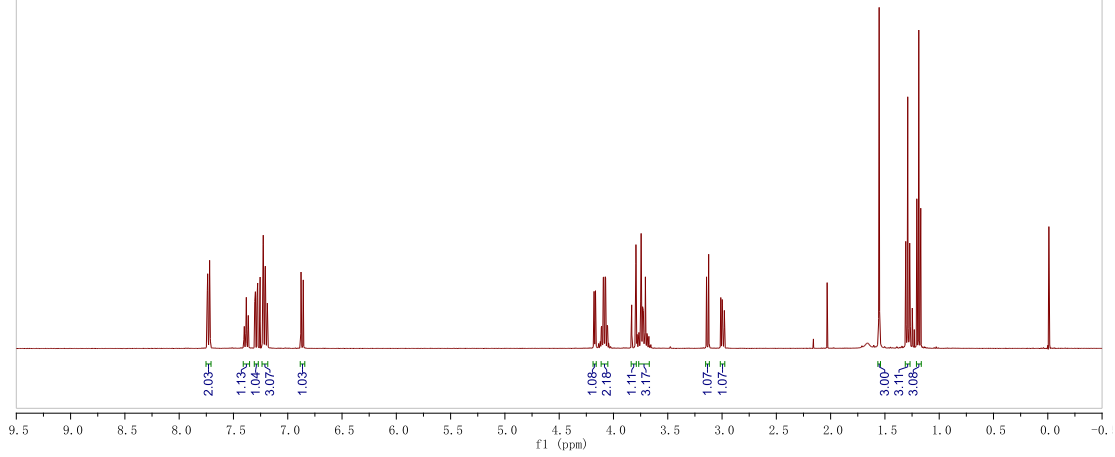
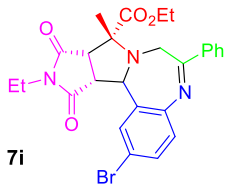




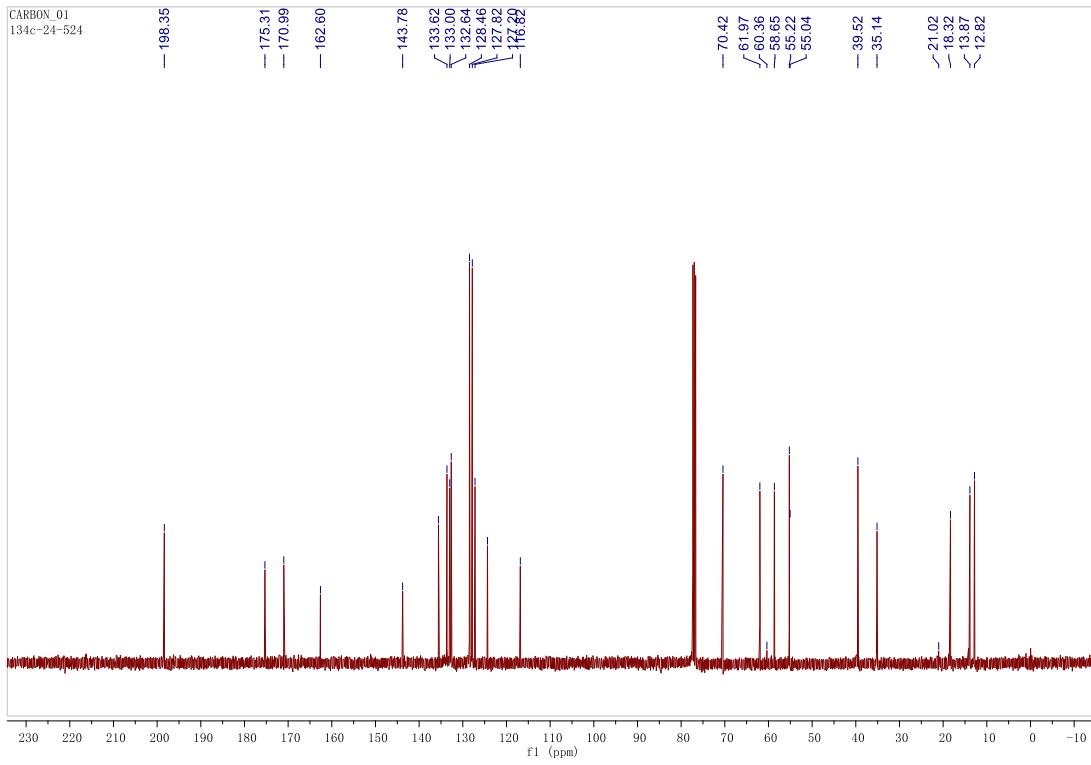


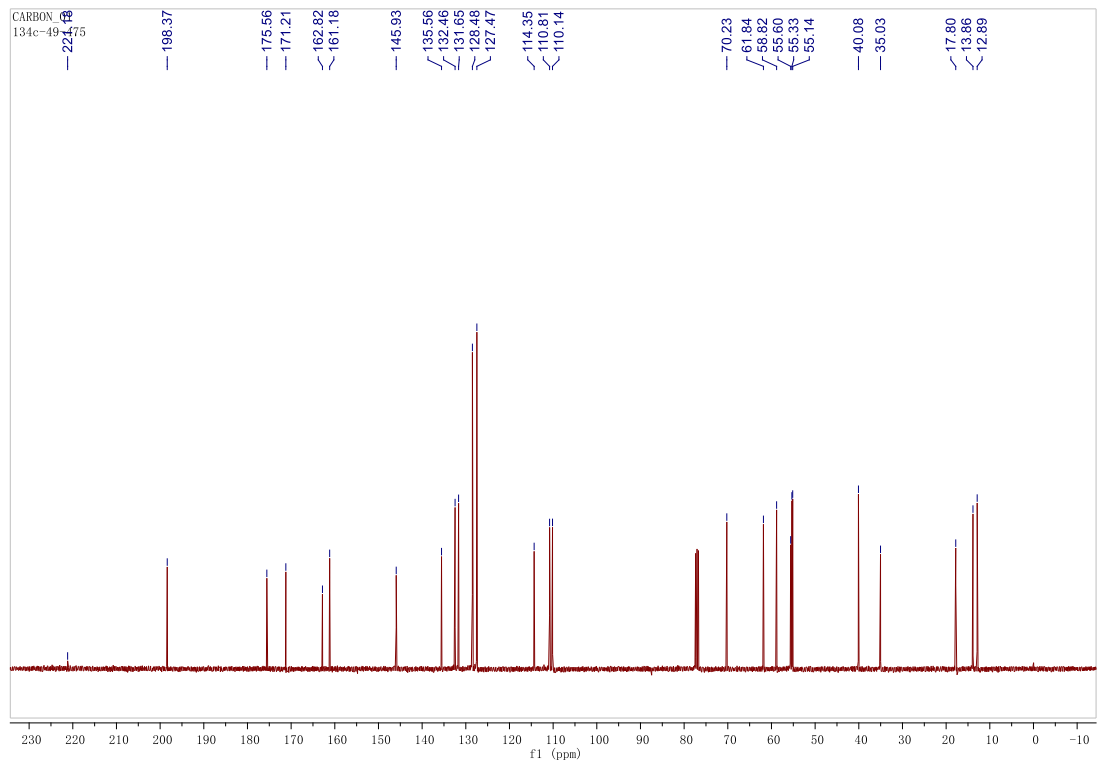
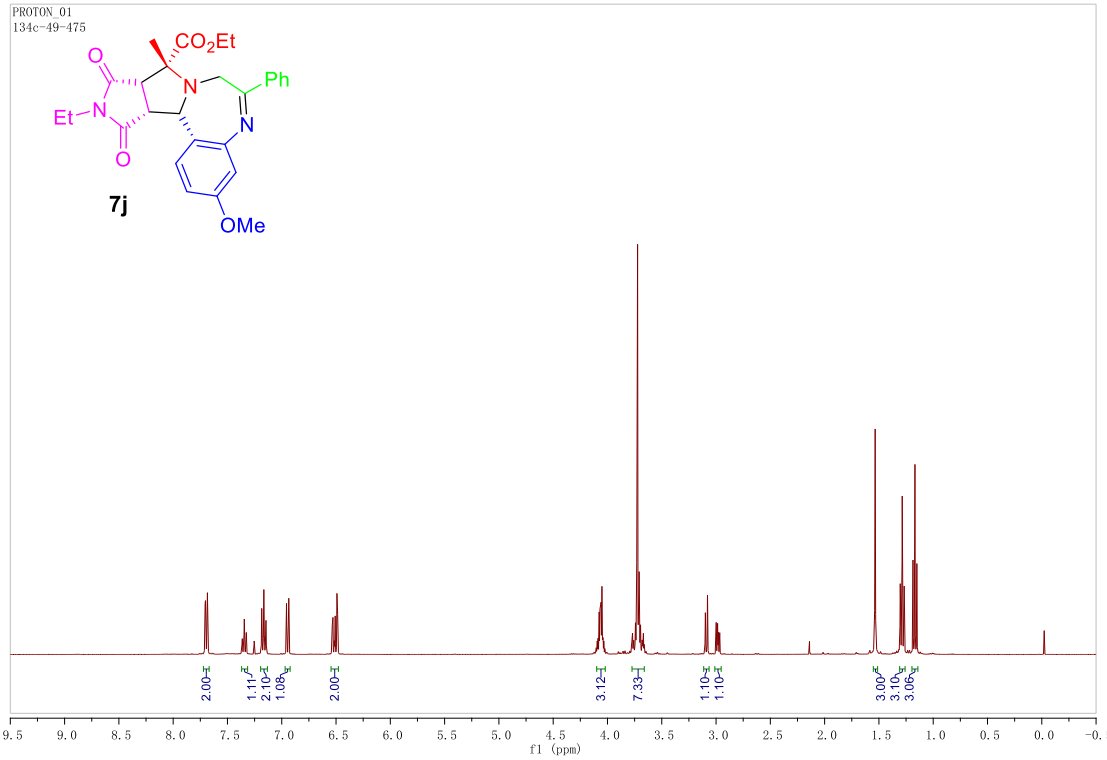


PROTON 01
134c-24-524

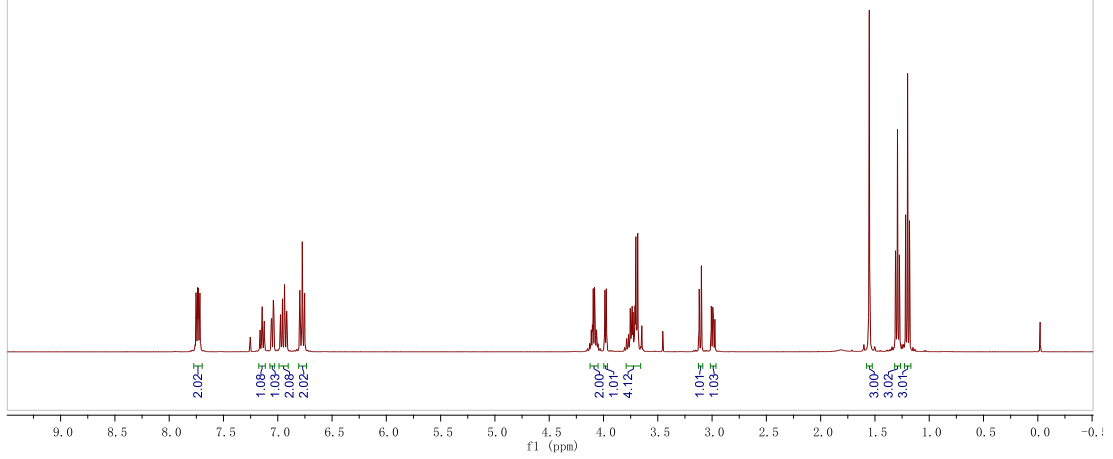
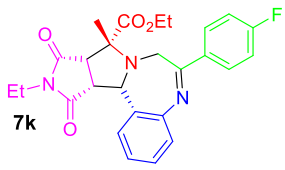


CARBON 01
134c-24-524

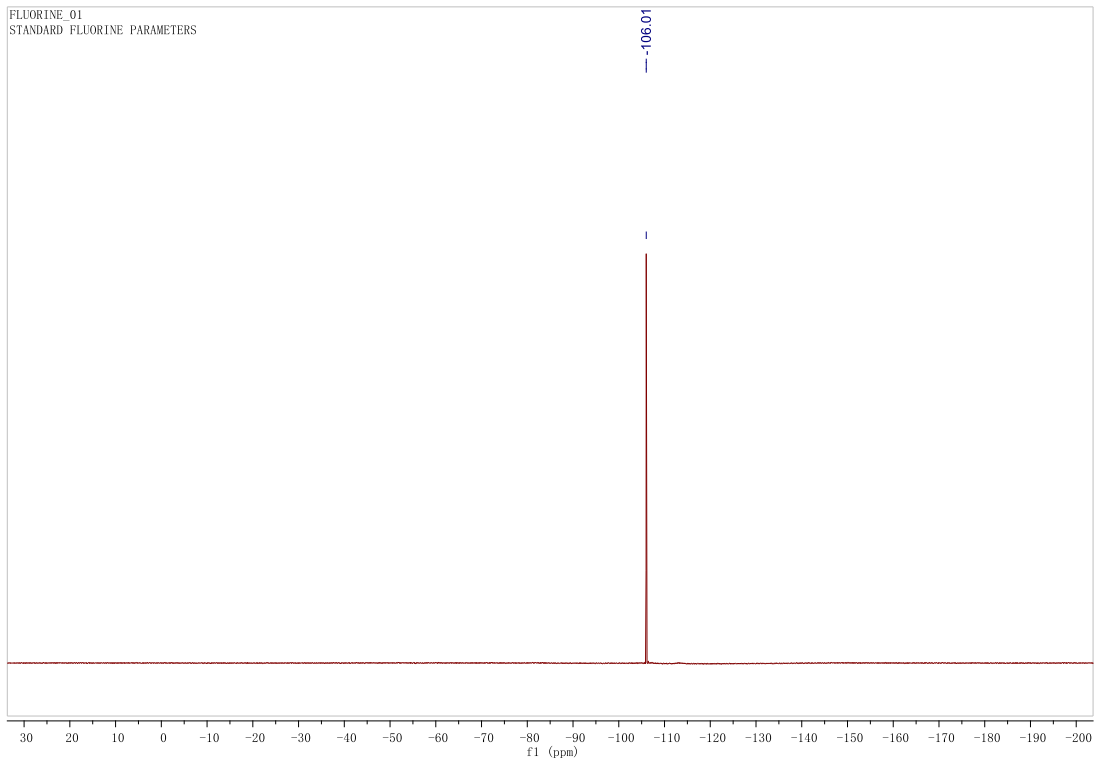


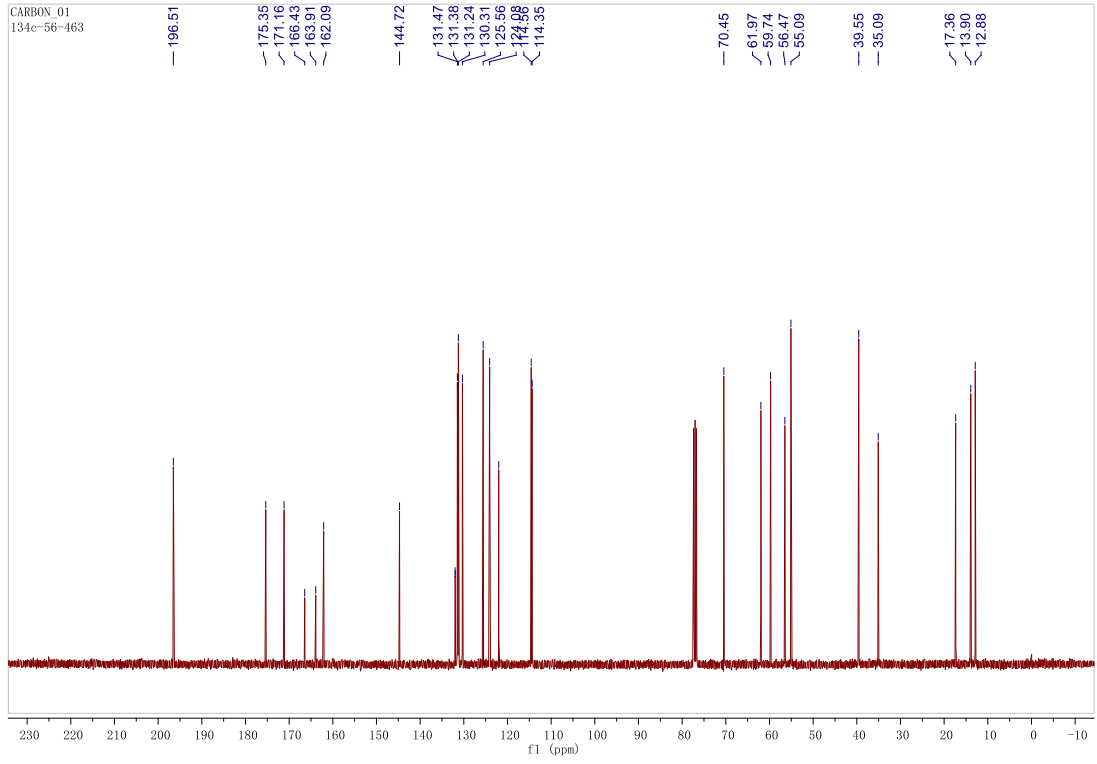


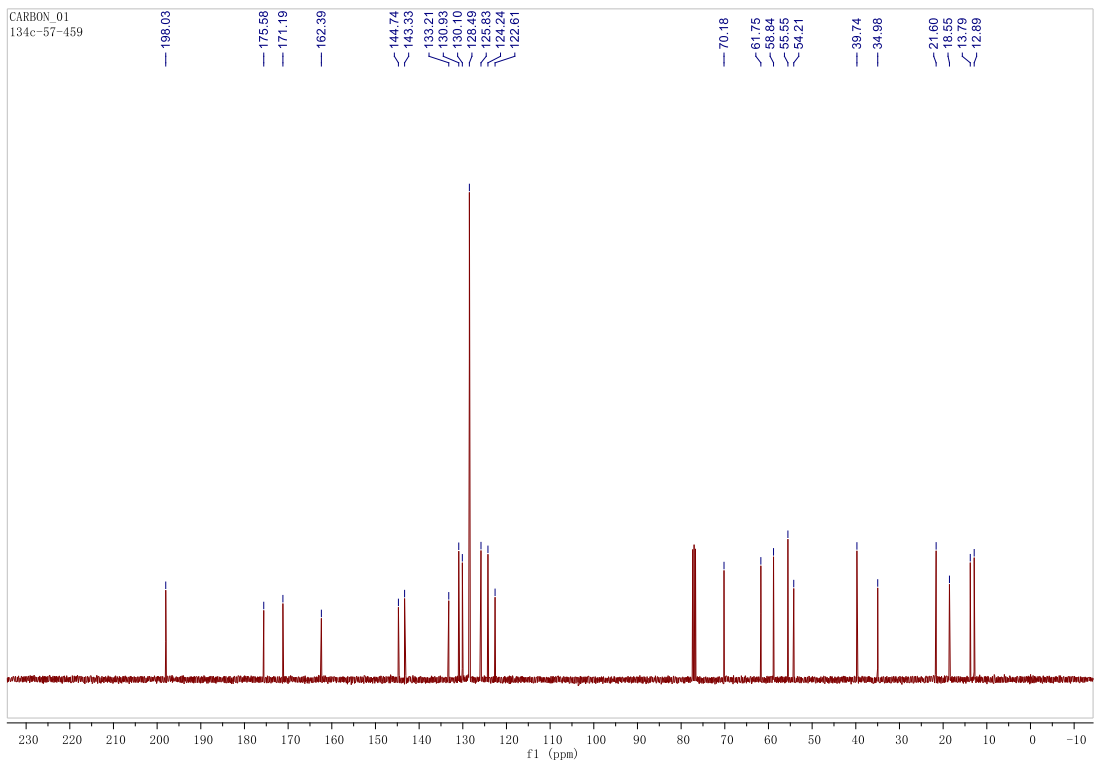
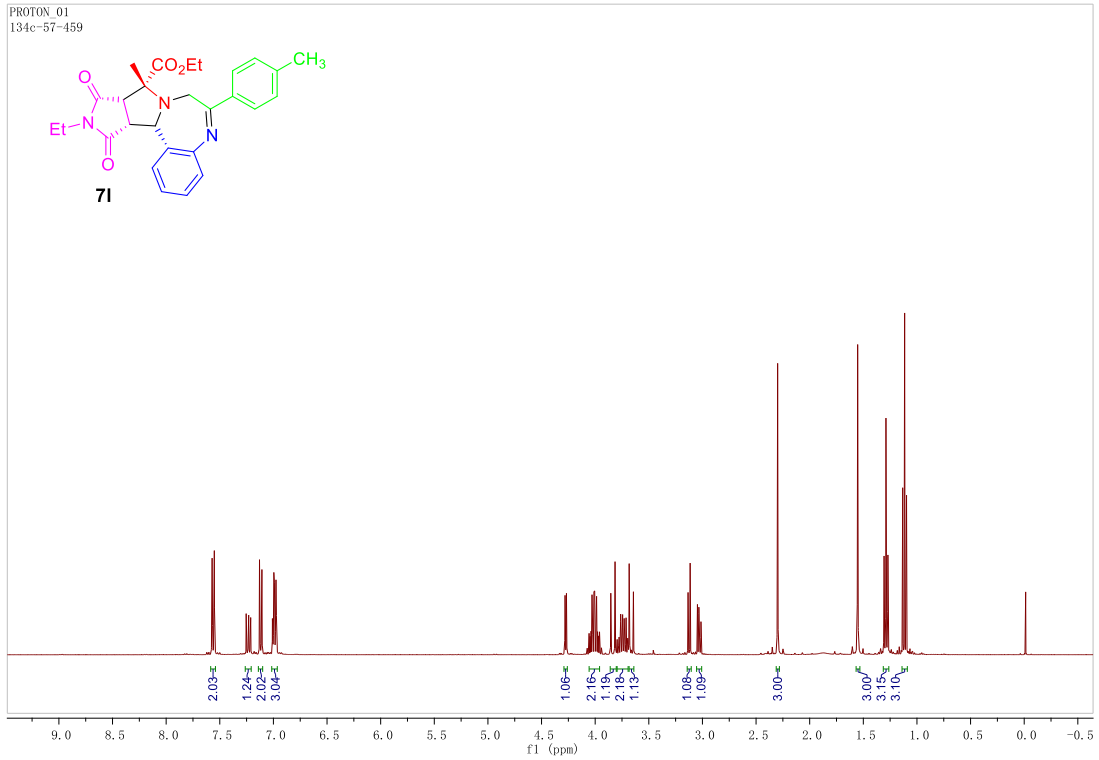
PROTON 01
134c-56-463



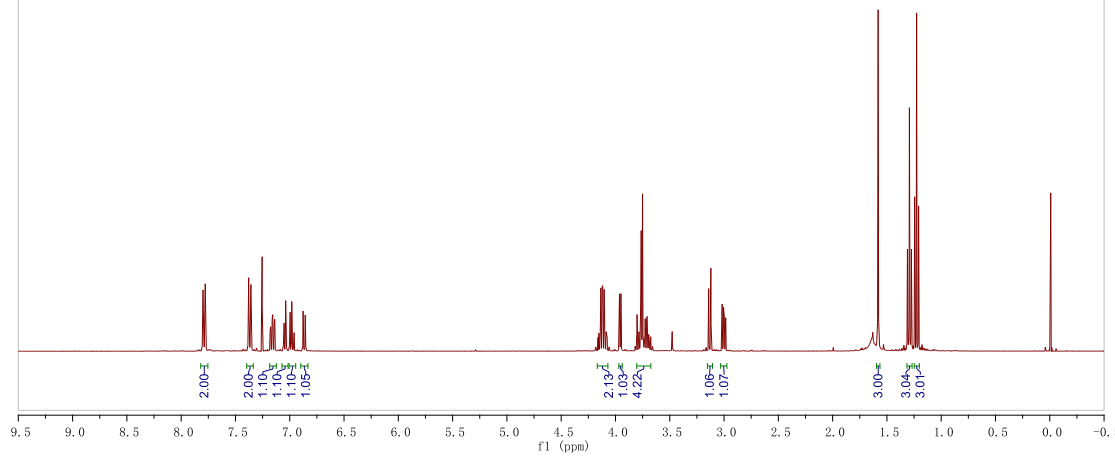
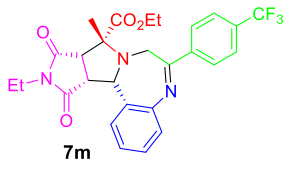
FLUORINE 01
STANDARD FLUORINE PARAMETERS



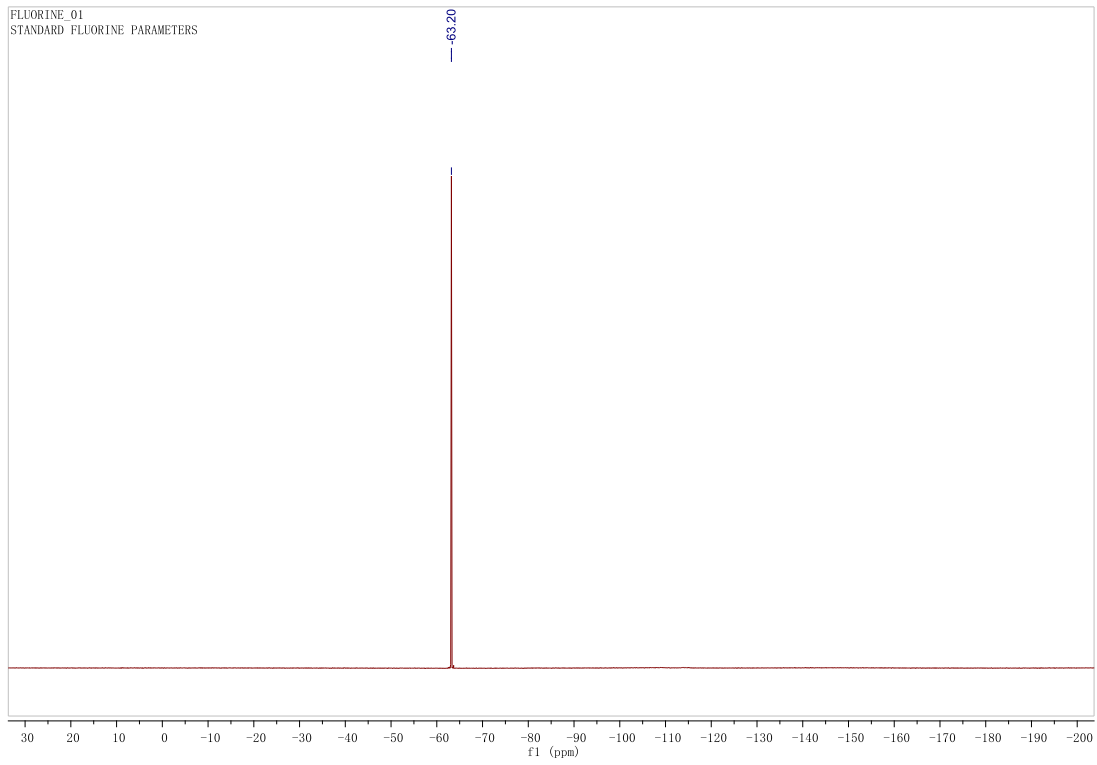


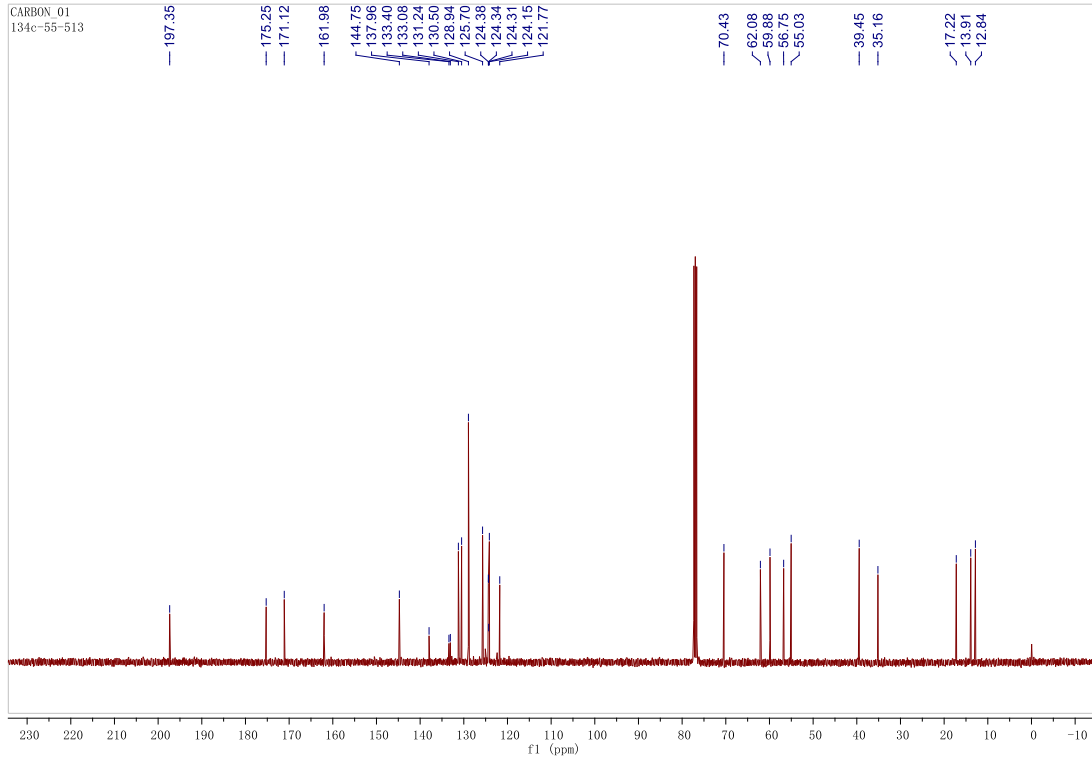


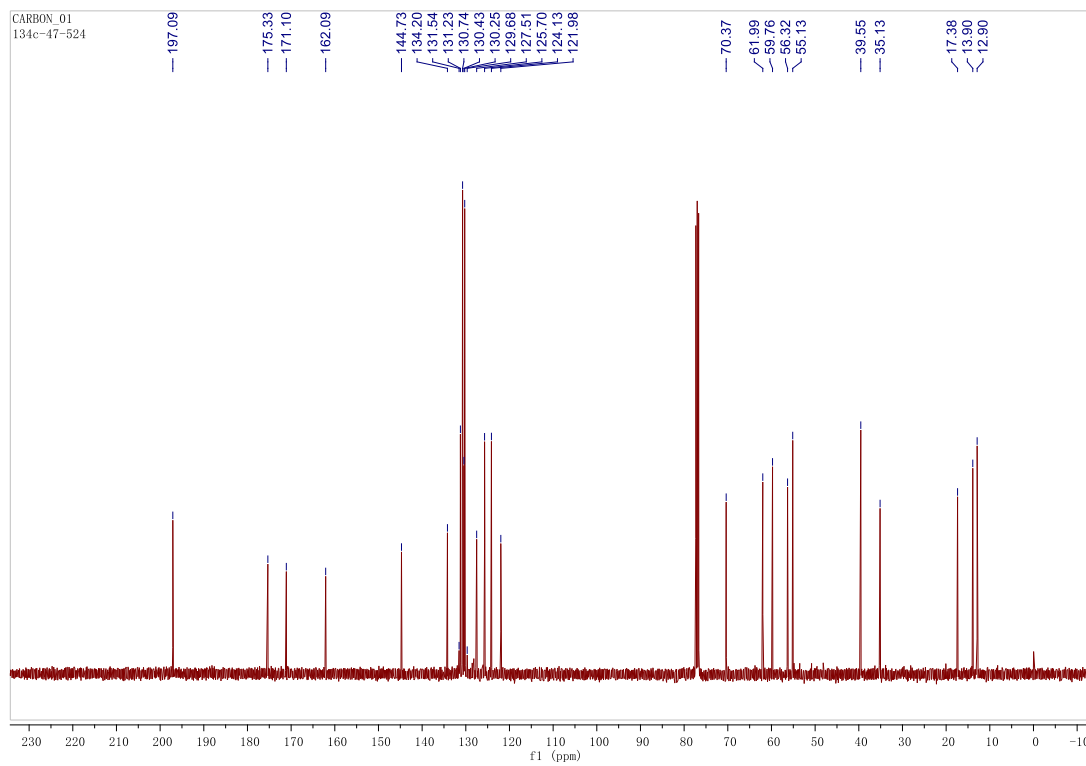
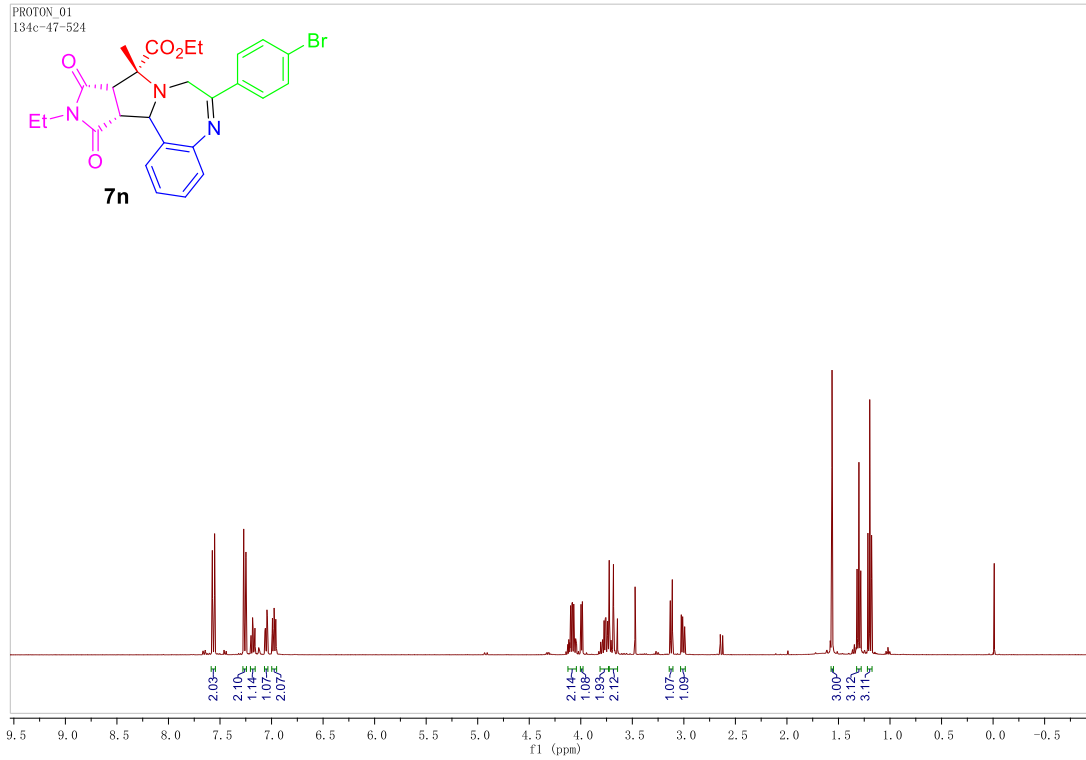
PROTON 01
134c-55-513

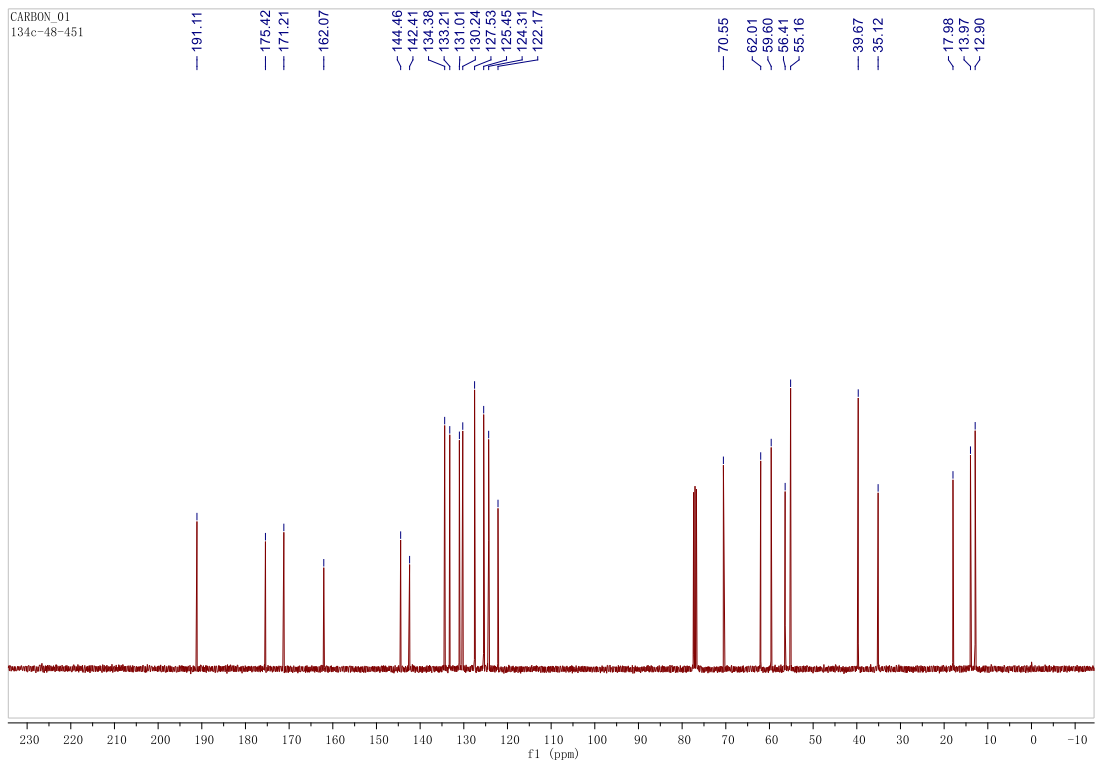
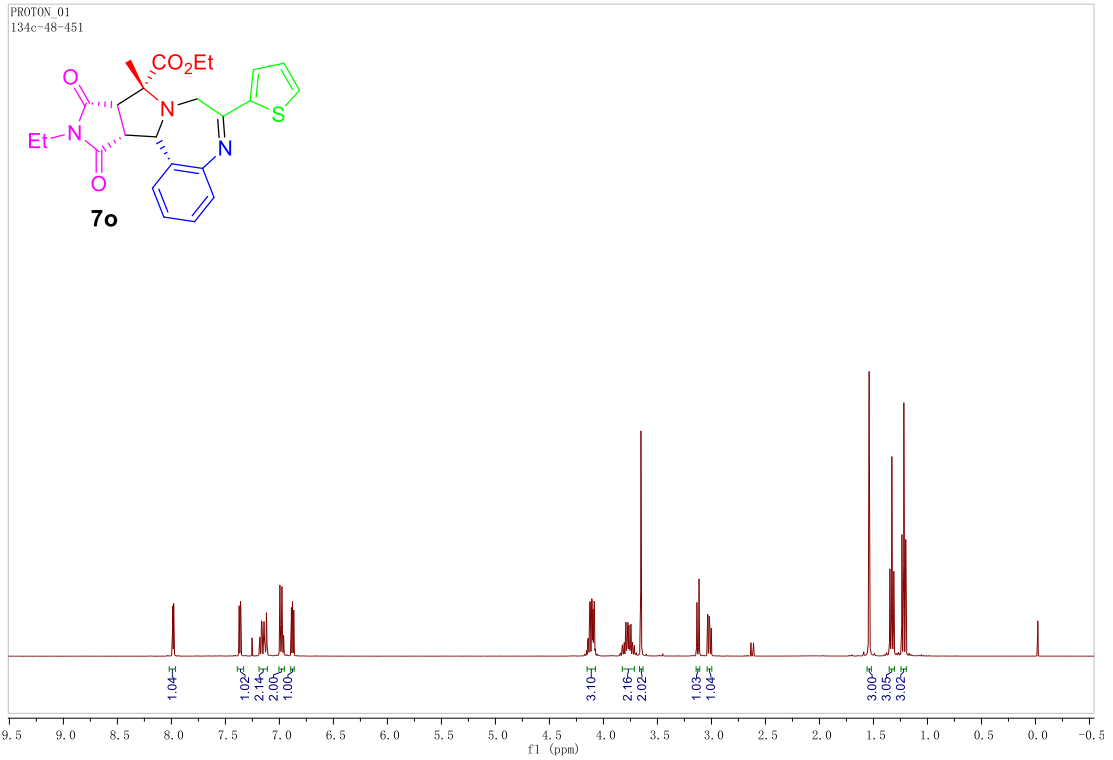


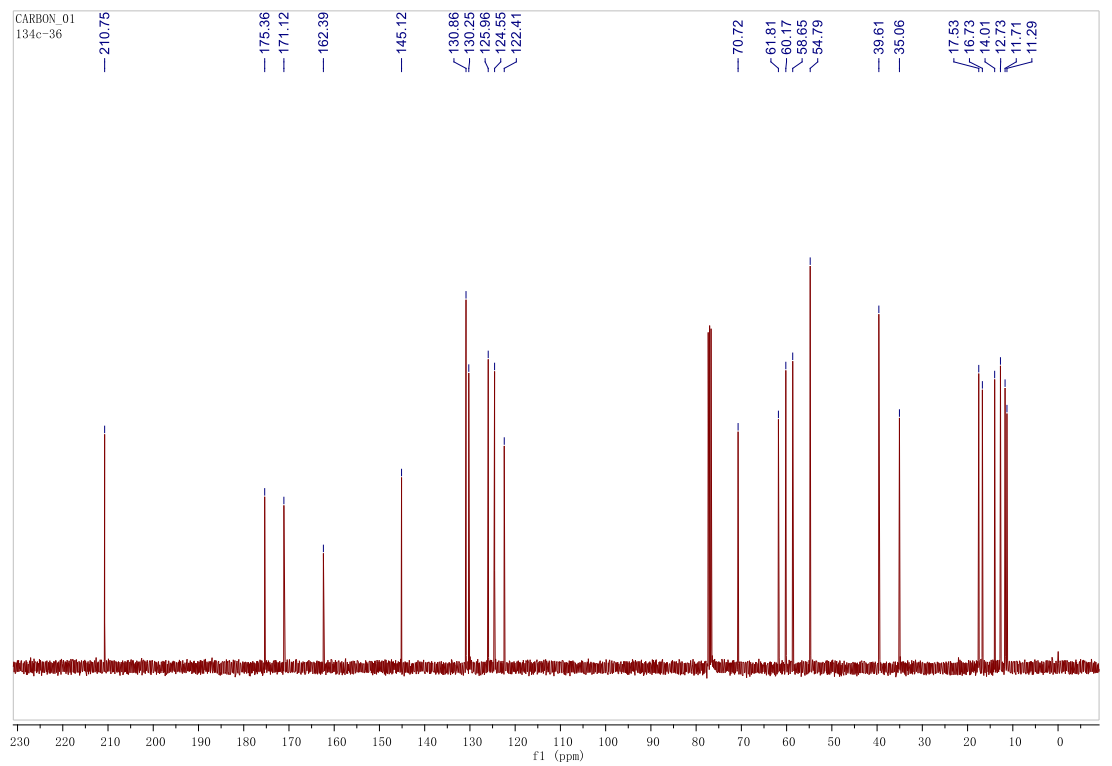
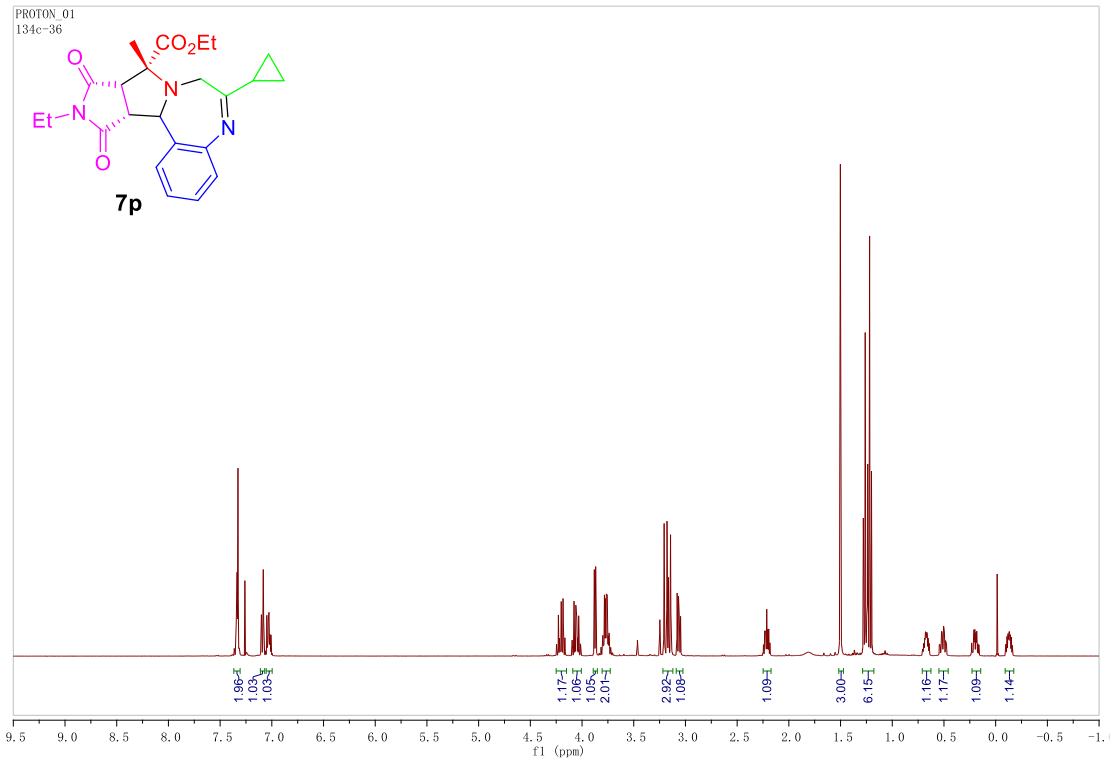
FLUORINE 01
STANDARD FLUORINE PARAMETERS

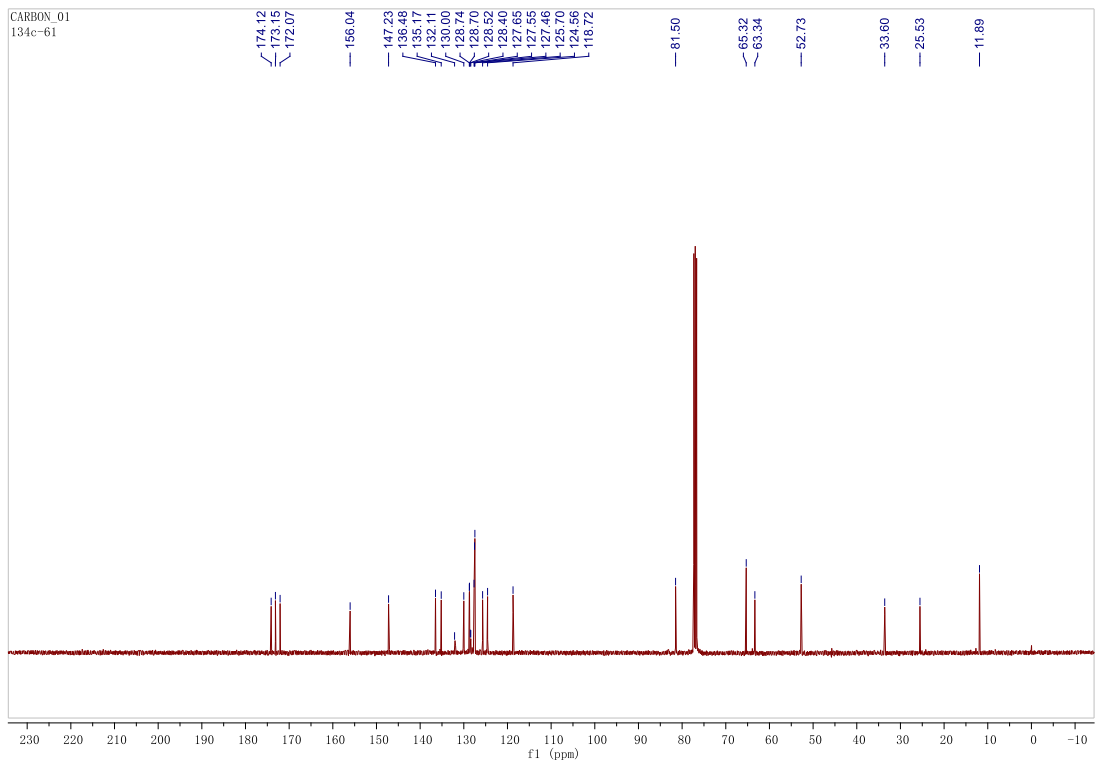
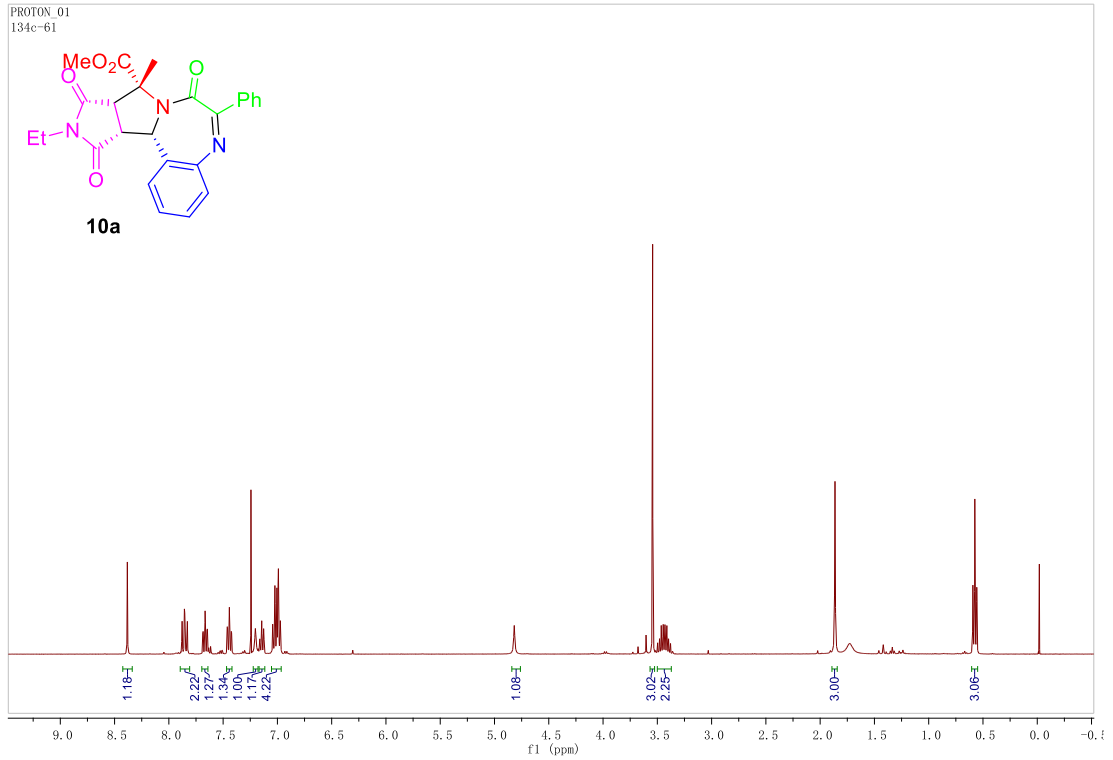




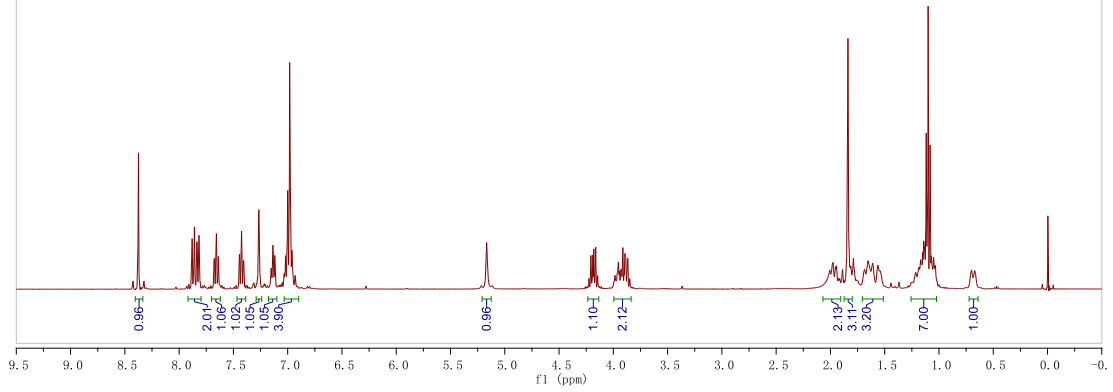
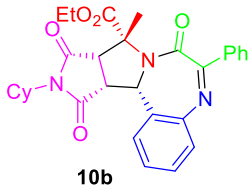




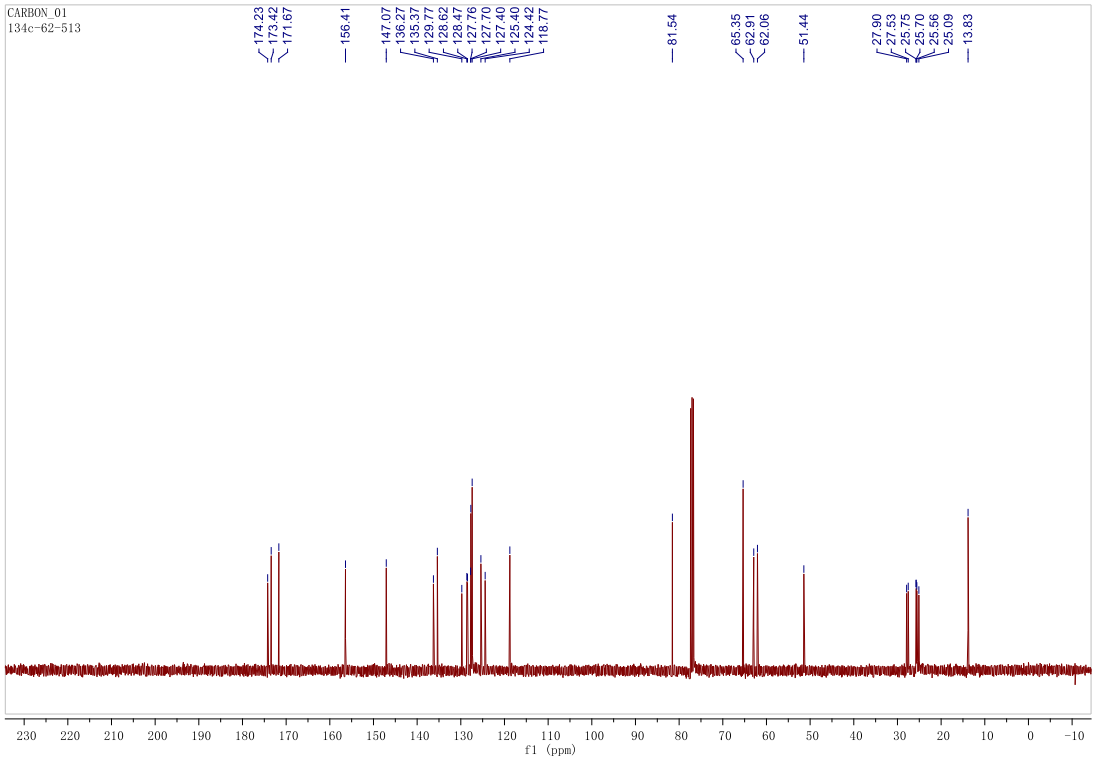


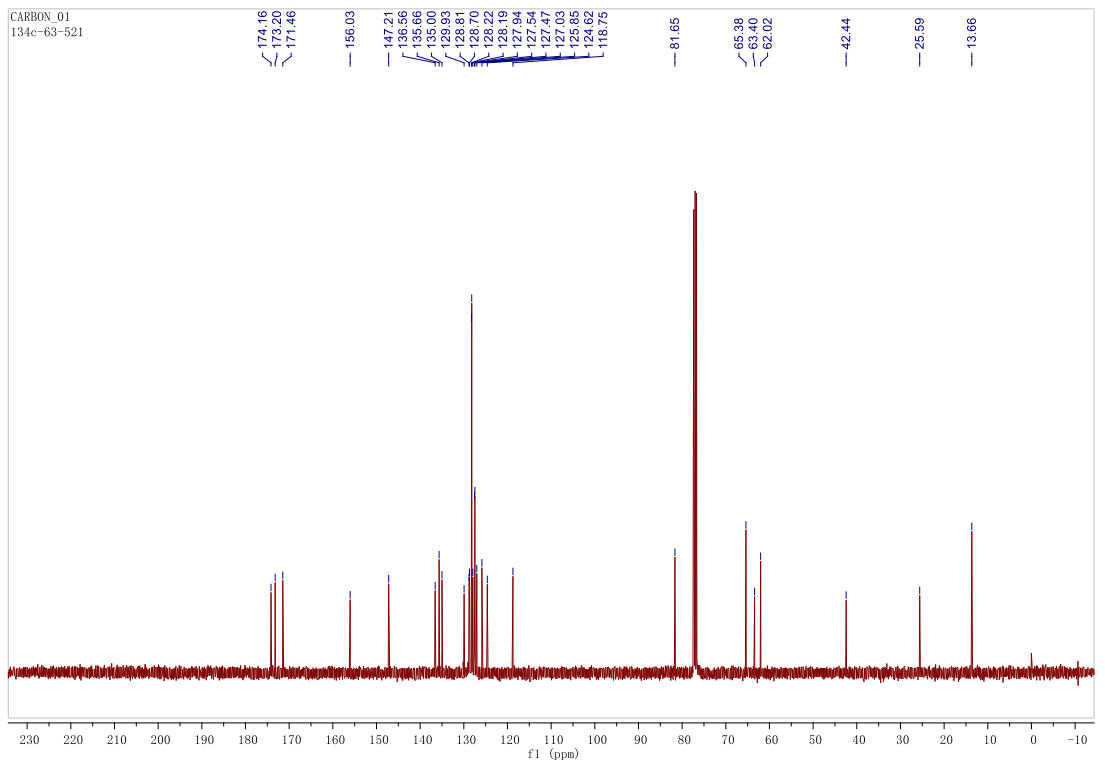
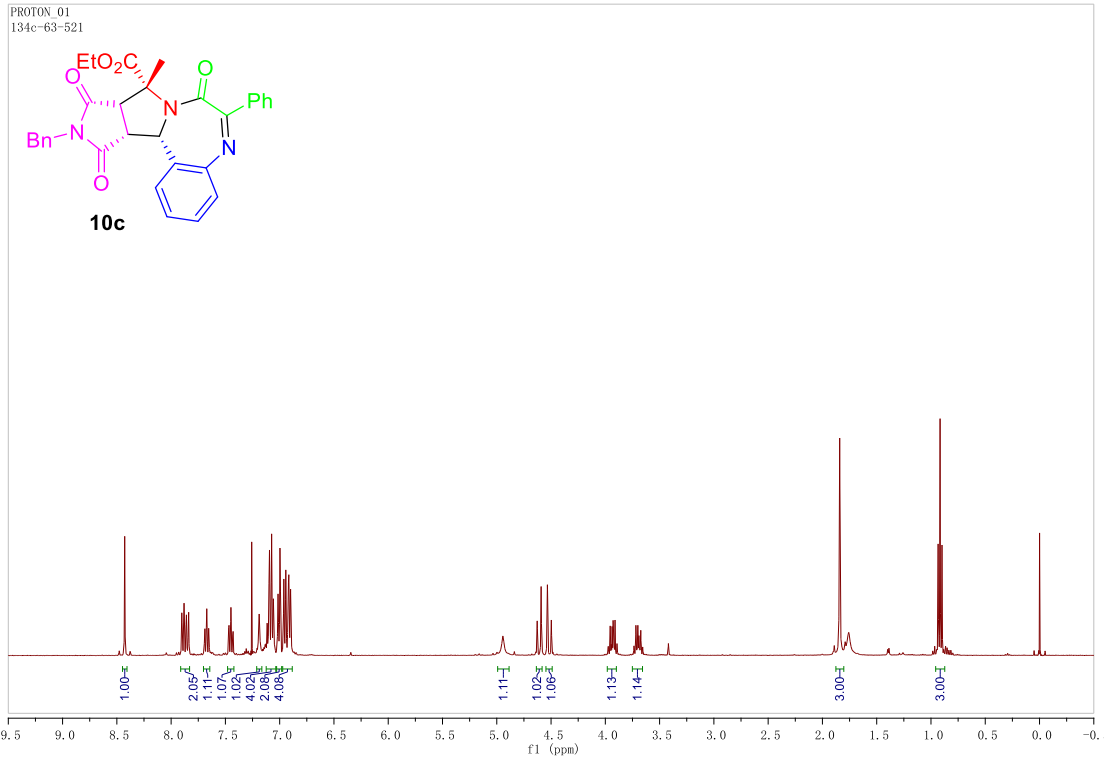


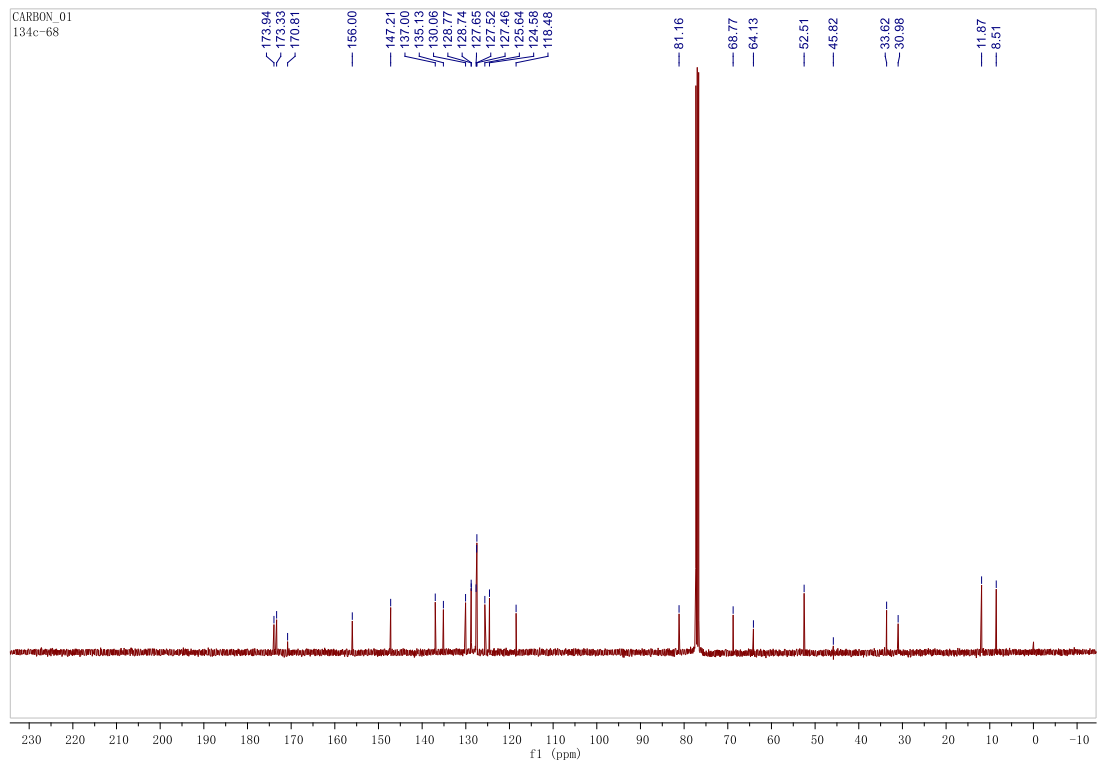
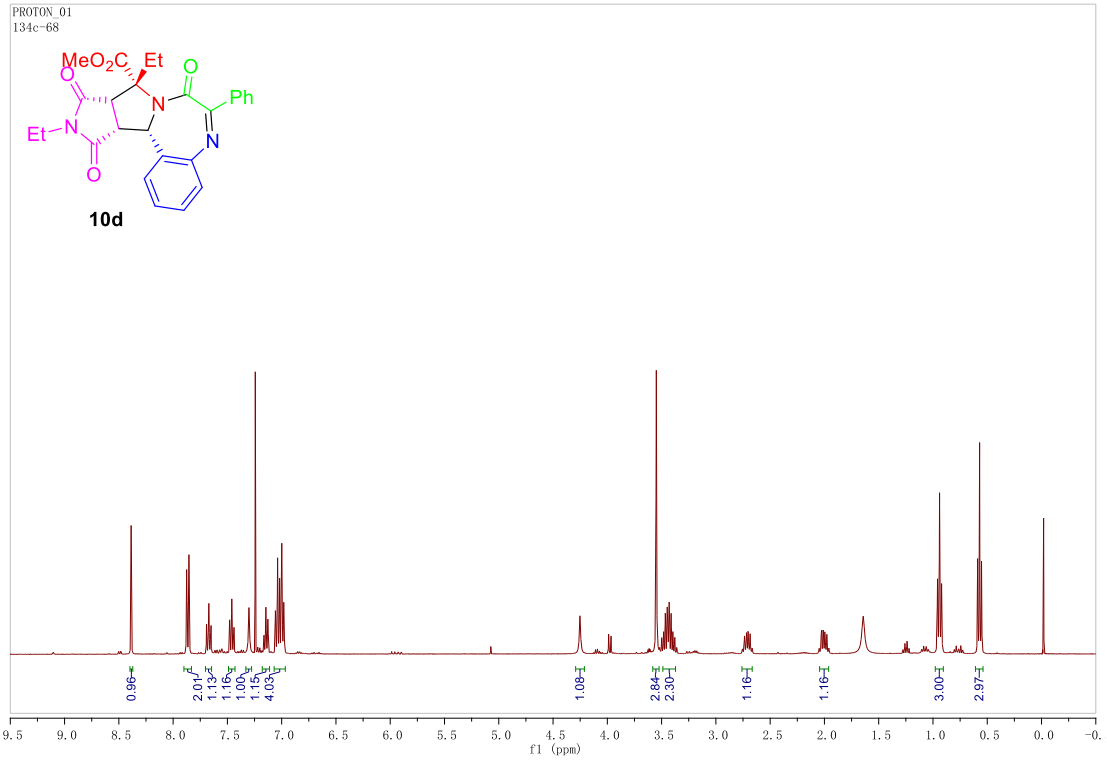
PROTON 01
134c-62-513

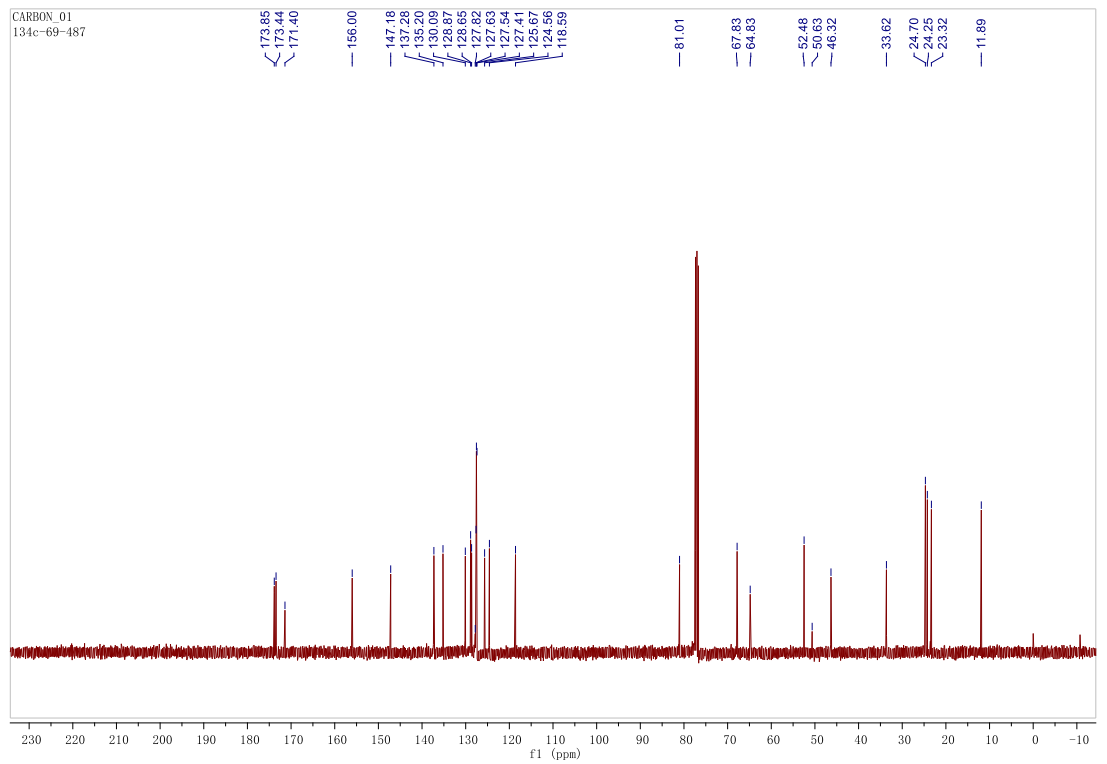
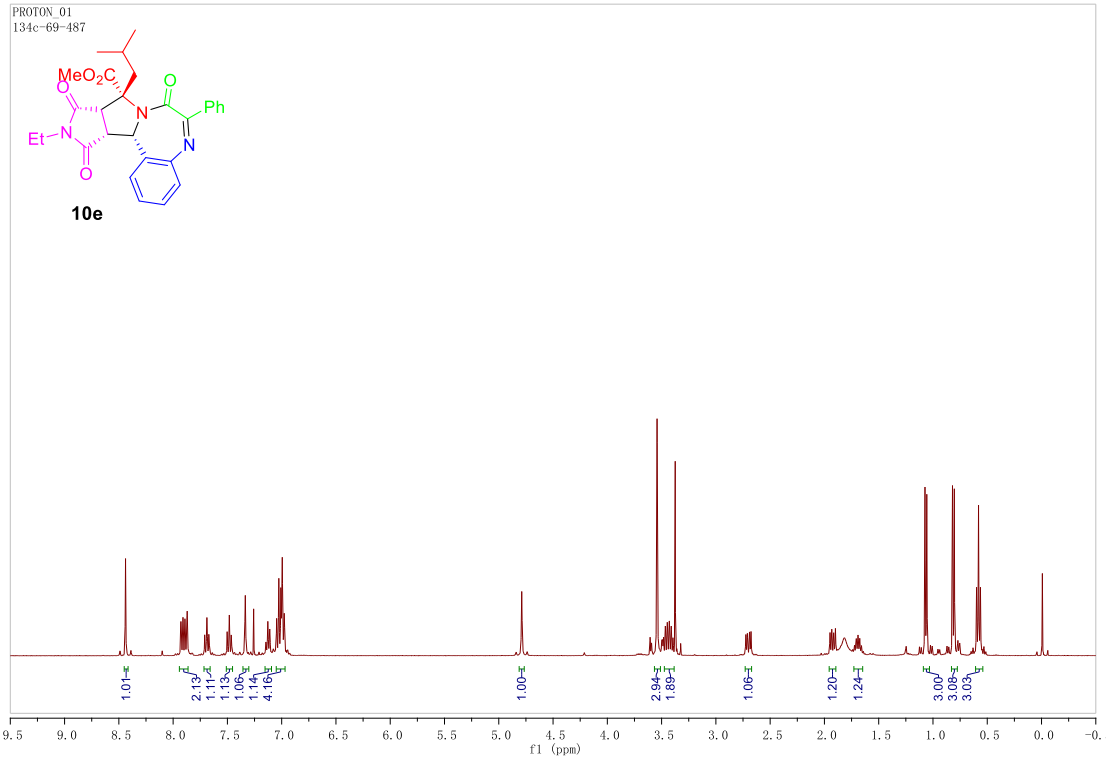


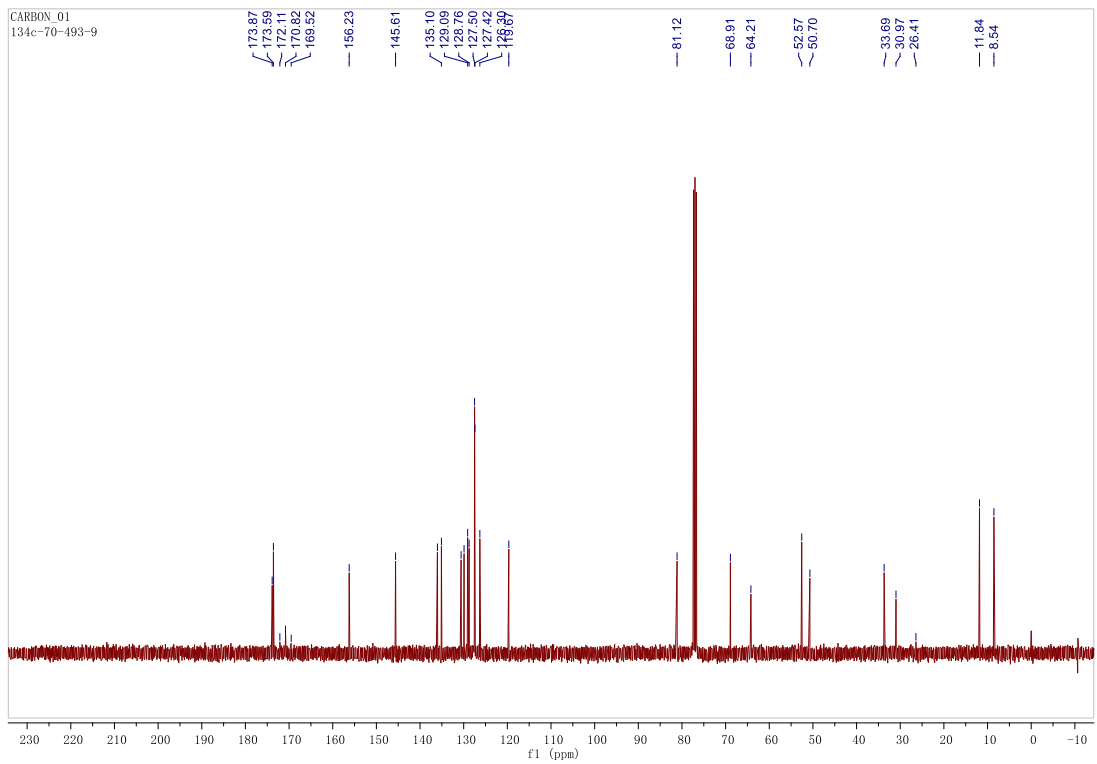
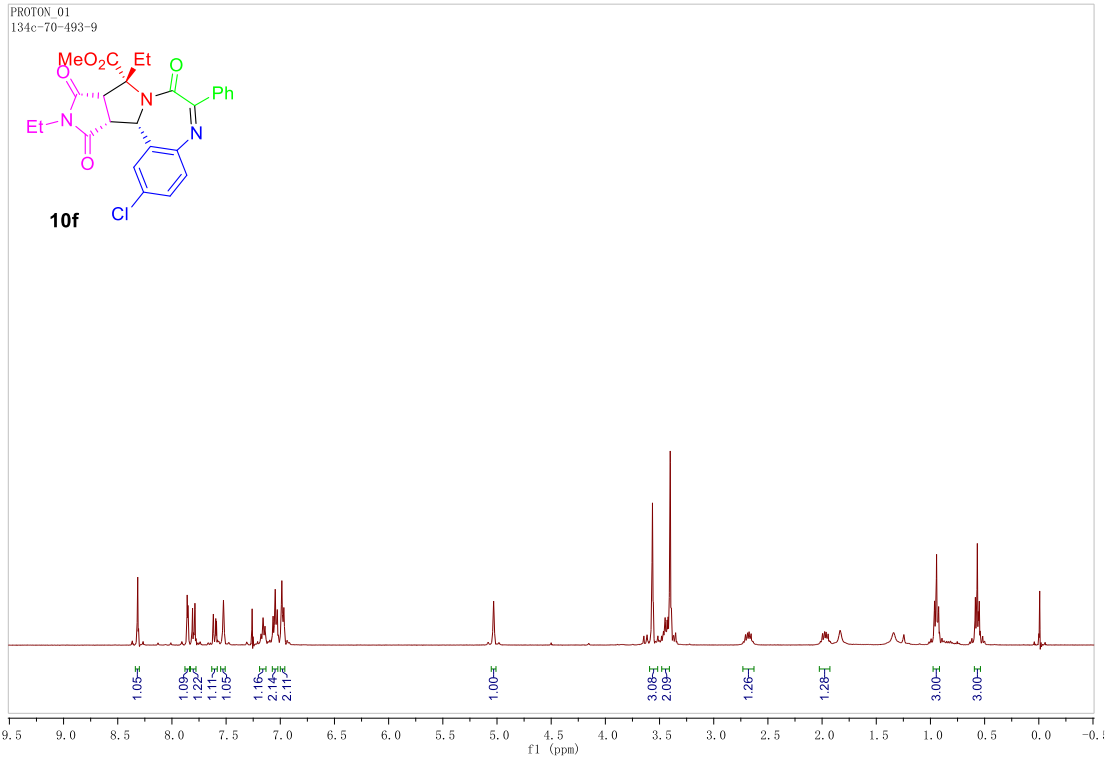
CARBON 01
134c-62-513

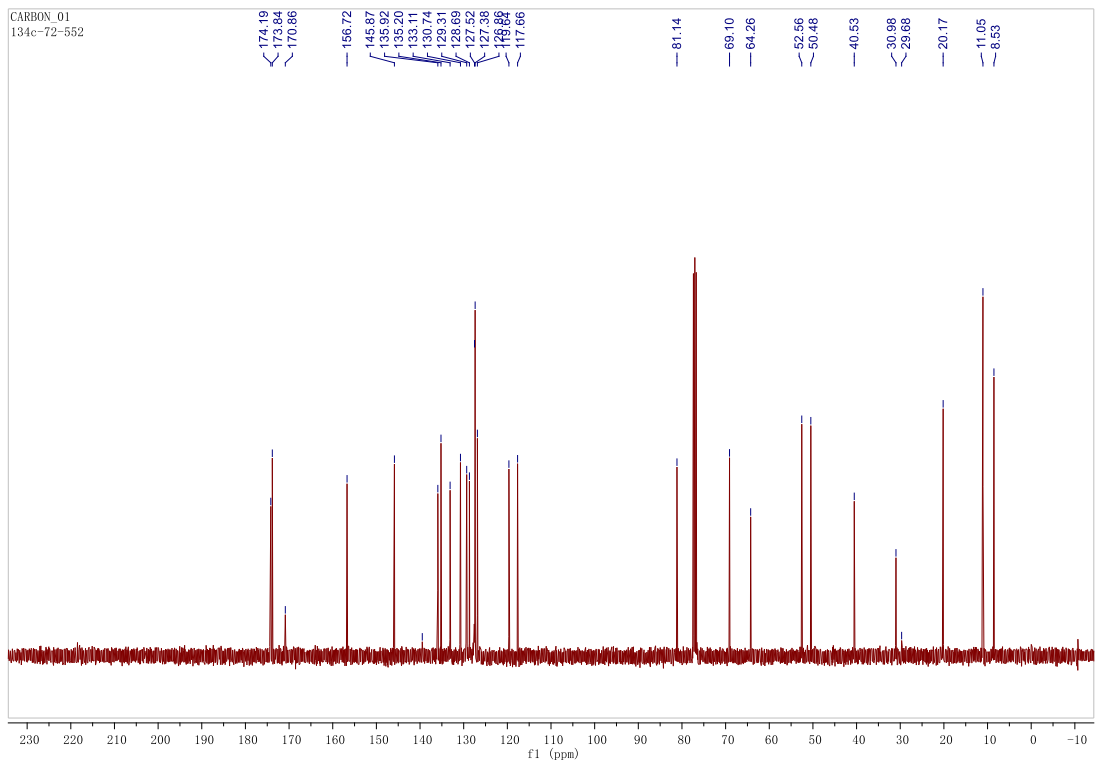
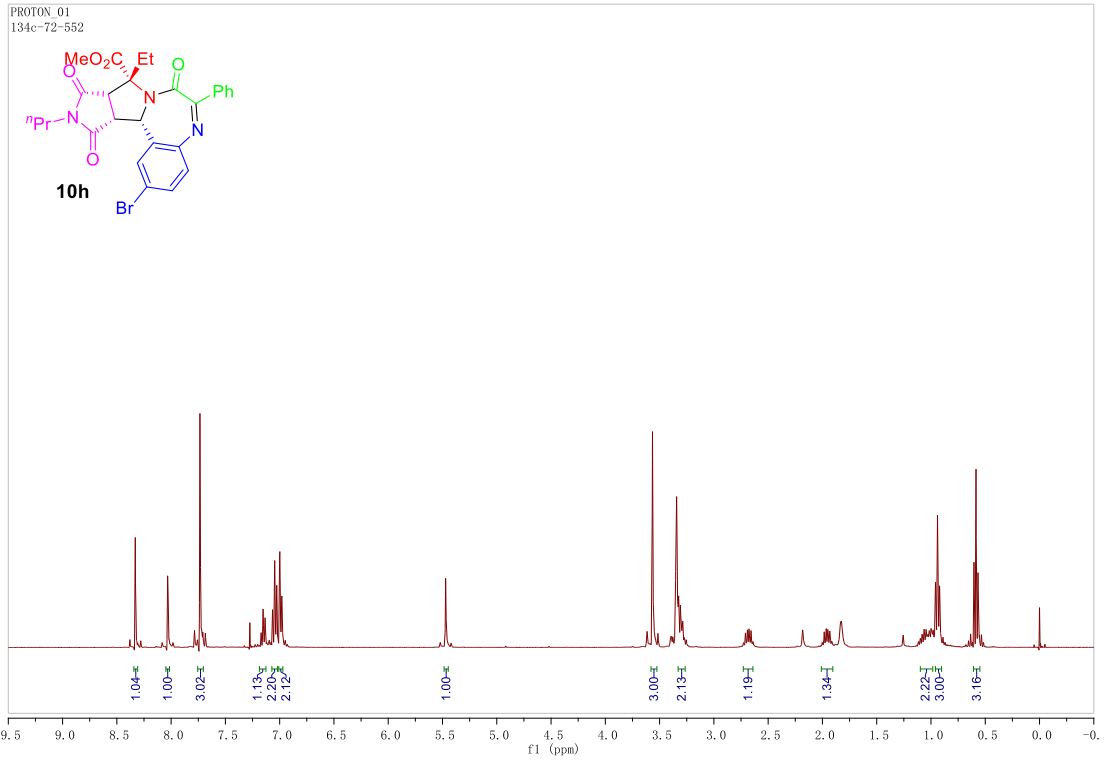


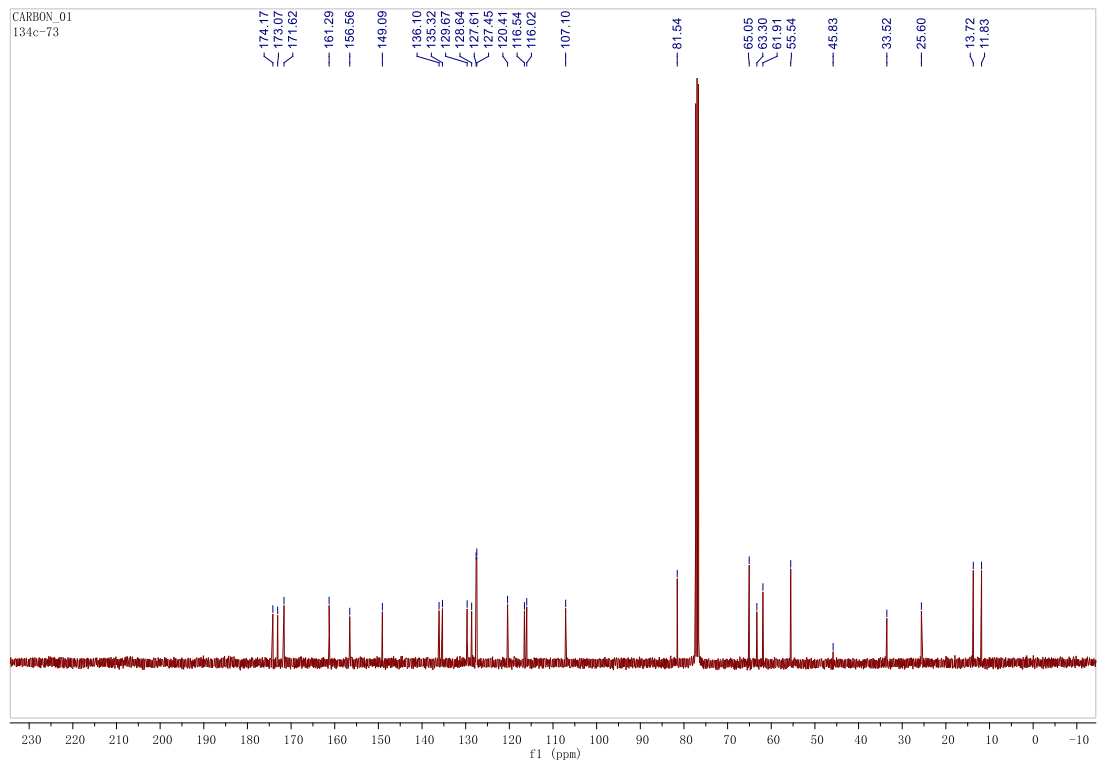
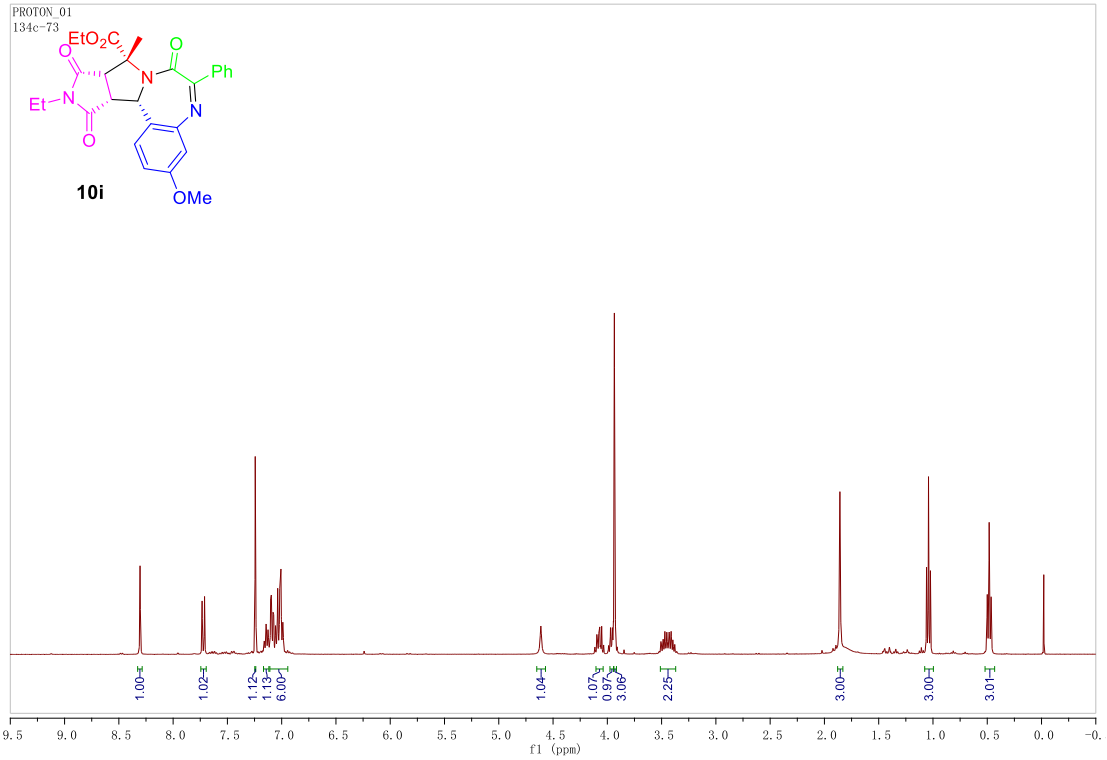












5. Green chemistry metrics analysis

The following formulae were used for calculating Atom Economy (AE), Atom Efficiency (AEf), Carbon Efficiency (CE), Reaction Mass Efficiency (RME), Optimum Efficiency (OE), Mass Productivity (MP), Mass Intensity (MI) and Process Mass Intensity (PMI), E factor, Solvent and Water Intensity (SI and WI).¹⁻¹⁴

$$AE = \frac{\text{Molecular weight of product}}{\text{Total molecular weight of reactants}} \times 100$$

$$AEf = AE \times \text{yield}\%$$

$$CE = \frac{\text{Amount of carbon in the product}}{\text{Total carbon present in reactants}} \times 100$$

$$RME = \frac{\text{Mass of isolated product}}{\text{Total mass of reactants}} \times 100$$

$$OE = \frac{RME}{AE} \times 100$$

$$MI = \frac{\text{Total mass of input material in a process or process step}}{\text{Mass of product}}$$

$$PMI = \frac{\text{Total mass of input material in the whole process}}{\text{Mass of product}}$$

$$MP = \frac{1}{PMI} \times 100$$

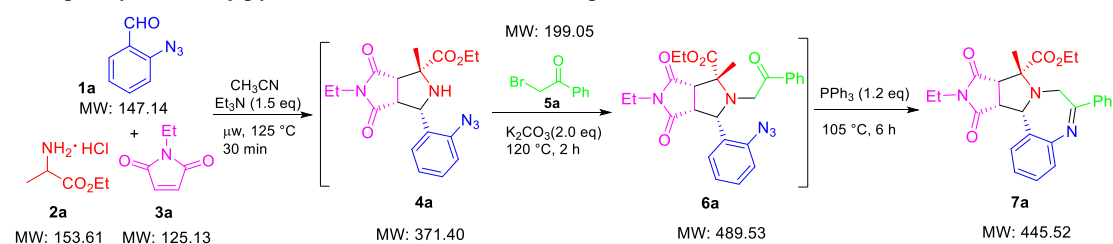
$$E \text{ Factor} = PMI - 1$$

$$SI = \frac{\text{Total mass of solvents excl. water in the whole process}}{\text{Mass of product}}$$

$$WI = \frac{\text{Total mass of water used in the whole process}}{\text{Mass of product}}$$

5.1 One-pot process

One-pot synthesis of pyrrolo[1,2-d][1,4]benzodiazepine **7a**:



This is a one-pot synthesis with only one step of separation for the final product.

Experimental procedures:

A solution of 2-azidobenzaldehyde **1a** (73.6 mg, 0.5 mmol), L-alanine ethyl ester **2a** (92.2 mg, 0.6

mmol) and N-ethylmaleimide **3a** (68.8 mg, 0.55 mmol) in CH₃CN (2 mL) with Et₃N (76.0mg, 0.75 mmol) were heated at 125 °C for 30 min under microwave in a sealed vial. Then phenacyl bromide **5a** (298.5 mg, 1.5 mmol) and K₂CO₃ (138.2 mg, 1 mmol) was added into the pyrrolidine **4a** containing mixture followed by heating at 120 °C for 2 h. Upon the completion of the reaction as monitored by LC-MS, PPh₃ (157.2 mg, 0.6 mmol) was added to the mixture and then heated at 105 °C for 6 h. The concentrated reaction mixture was separated on YAMAZEN AI-580 flash column system to afford product **7a** 189.3 mg (85% yield).

Materials used for metrics calculations: 2-azidobenzaldehyde **1a** (73.6 mg, 0.5 mmol), L-alanine ethyl ester **2a** (92.2 mg, 0.6 mmol) and N-ethylmaleimide **3a** (68.8 mg, 0.55 mmol), CH₃CN (1580 mg, 2 mL), Et₃N (76.0 mg, 0.75 mmol), phenacyl bromide **5a** (298.5 mg, 1.5 mmol), K₂CO₃ (138.2 mg, 1 mmol), PPh₃ (157.2 mg, 0.6 mmol), and product **7a** 189.3 mg (0.425 mmol).

$$AE(7a) = \frac{445.52}{147.14 + 153.61 + 125.13 + 199.05} \times 100 = 71$$

$$AEf(7a) = 71 \times 85\% = 60$$

$$CE(7a) = \frac{26 \times 0.425}{7 \times 0.5 + 5 \times 0.6 + 6 \times 0.55 + 8 \times 1.5} \times 100 = 51$$

$$RME(7a) = \frac{189.3}{73.6 + 92.2 + 68.8 + 298.5} \times 100 = 36$$

$$OE(7a) = \frac{36}{71} \times 100 = 51$$

$$PMI(7a) = \frac{73.6 + 92.2 + 68.8 + 1580 + 76.0 + 298.5 + 138.2 + 157.2}{189.3} = 13$$

$$MP(7a) = \frac{1}{13} \times 100 = 7.7$$

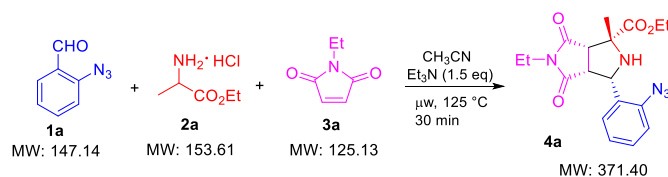
$$E \text{ Factor}(7a) = 13 - 1 = 12$$

$$SI(7a) = \frac{1580 + 76}{189.3} = 8.7$$

$$WI(7a) = \frac{0}{189.3} = 0$$

5.2 Three-step isolated process

Step 1: Synthesis of ethyl (1R,3S,3aR,6aS)-3-(2-azidophenyl)-5-ethyl-1-methyl-4,6-dioxoocta-hydro-pyrrolo[3,4-c]pyrrole-1-carboxylate (**4a**)



Experimental procedures:

A solution of 2-azidobenzaldehyde **1a** (73.6 mg, 0.5 mmol), L-alanine ethyl ester **2a** (92.2 mg, 0.6

mmol) and N-ethylmaleimide **3a** (68.8 mg, 0.55 mmol) in CH₃CN (2 mL) with Et₃N (76.0mg, 0.75 mmol) were heated at 125 °C for 30 min under microwave in a sealed vial. The concentrated reaction mixture was separated on YAMAZEN AI-580 flash column system to afford pyrrolidine **4a** 168.8 mg (91% yield).

Materials used for metrics calculations: 2-azidobenzaldehyde **1a** (73.6 mg, 0.5 mmol), L-alanine ethyl ester **2a** (92.2 mg, 0.6 mmol) and N-ethylmaleimide **3a** (68.8 mg, 0.55 mmol), CH₃CN (1580 mg, 2 mL), Et₃N (76.0 mg, 0.75 mmol) and pyrrolidine **4a** 168.8 mg (0.455 mmol).

$$AE(4a) = \frac{371.4}{147.14 + 153.61 + 125.13} \times 100 = 87$$

$$AEf(4a) = 87 \times 91\% = 79$$

$$CE(4a) = \frac{18 \times 0.455}{7 \times 0.5 + 5 \times 0.6 + 6 \times 0.55} \times 100 = 83$$

$$RME(4a) = \frac{168.8}{73.6 + 92.2 + 68.8} \times 100 = 72$$

$$OE(4a) = \frac{72}{87} \times 100 = 81$$

$$MI(4a) = \frac{73.6 + 92.2 + 68.8 + 1580 + 76}{168.8} = 11$$

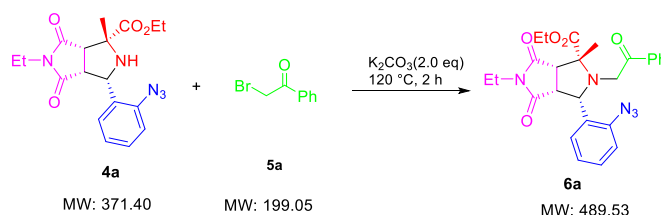
$$MP(4a) = \frac{1}{11} \times 100 = 9.1$$

$$E \text{ Factor}(4a) = 11 - 1 = 10$$

$$SI(4a) = \frac{1580 + 76}{168.8} = 9.8$$

$$WI(4a) = \frac{0}{168.8} = 0$$

Step 2: Synthesis of ethyl (1R,3S,3aR,6aS)-3-(2-azidophenyl)-5-ethyl-1-methyl-4,6-dioxo-2-(2-oxo-2-phenylethyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**6a**)



Experimental procedures:

A solution of pyrrolidine **4a** (168.8 mg, 0.455 mmol), phenacyl bromide **5a** (271.6 mg, 1.36 mmol) and K₂CO₃ (125.6 mg, 0.91 mmol) in CH₃CN (2 mL) was heated at 120 °C for 2 h. The concentrated reaction mixture was separated on YAMAZEN AI-580 flash column system to afford amino ketone **6a** 200.5 mg (90% yield).

Materials used for metrics calculations: pyrrolidine **4a** (168.8 mg, 0.455 mmol), phenacyl bromide

5a (271.6 mg, 1.36 mmol), K₂CO₃ (125.6 mg, 0.91 mmol), CH₃CN (1580 mg, 2 mL) and amino ketone **6a** (200.5 mg, 0.40 mmol).

$$AE(6a) = \frac{489.53}{371.4 + 199.05} \times 100 = 85.8$$

$$AEf(6a) = 85.8 \times 90\% = 77$$

$$CE(6a) = \frac{26 \times 0.40}{18 \times 0.455 + 8 \times 1.36} \times 100 = 54$$

$$RME(6a) = \frac{200.5}{168.8 + 271.6} \times 100 = 45$$

$$OE(6a) = \frac{45}{85.8} \times 100 = 52$$

$$MI(6a) = \frac{168.8 + 271.6 + 125.6 + 1580}{200.5} = 10.7$$

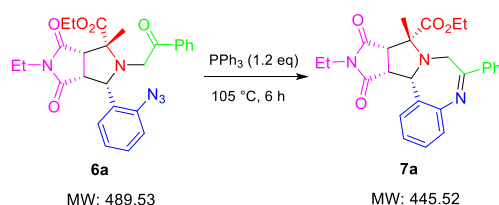
$$MP(6a) = \frac{1}{10.7} \times 100 = 9.3$$

$$E \text{ Factor}(6a) = 10.7 - 1 = 9.7$$

$$SI(6a) = \frac{1580}{200.5} = 7.9$$

$$WI(6a) = \frac{0}{200.5} = 0$$

Step 3: Synthesis of ethyl (9R,9aS,12aR,12bS)-11-ethyl-9-methyl-10,12-dioxo-6-phenyl-7,9,9a,10,11,12,12a,12b-octahydrobenzo[f]pyrrolo[3',4':3,4]pyrrolo[1,2-d][1,4]diazepine-9-carboxylate (7a)



Experimental procedures:

A solution of amino ketone **6a** (200.5 mg, 0.40 mmol) and PPh₃ (125.8 mg, 0.48 mmol) in CH₃CN (2 mL) was heated at 105 °C for 6 h. The concentrated reaction mixture was separated on YAMAZEN AI-580 flash column system to afford product **7a** 153.2 mg (85% yield).

Materials used for metrics calculations: amino ketone **6a** (200.5 mg, 0.40 mmol), PPh₃ (125.8 mg, 0.48 mmol), CH₃CN (1580 mg, 2 mL), product **7a** (153.2 mg, 0.344 mmol).

$$AE(7a) = \frac{445.52}{489.53} \times 100 = 91$$

$$AEf(7a) = 91 \times 85\% = 77$$

$$CE(7a) = \frac{26 \times 0.344}{26 \times 0.40} \times 100 = 86$$

$$RME(7a) = \frac{153.2}{200.5} \times 100 = 76$$

$$OE(7a) = \frac{76}{91} \times 100 = 83$$

$$MI(7a) = \frac{200.5 + 125.8 + 1580}{153.2} = 12.4$$

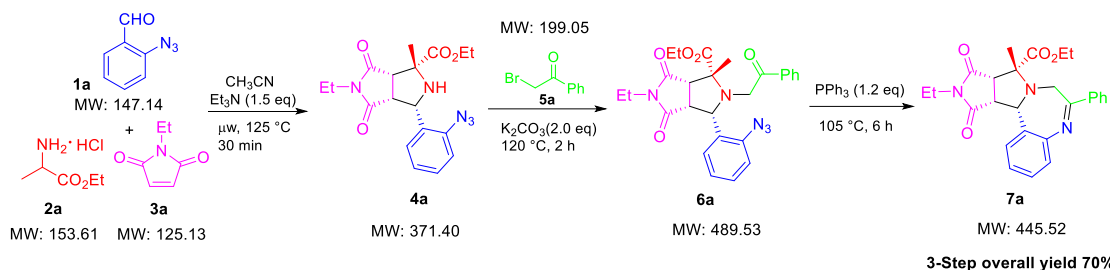
$$MP(7a) = \frac{1}{12.4} \times 100 = 8$$

$$E \text{ Factor}(7a) = 12.4 - 1 = 11.4$$

$$SI(7a) = \frac{1580}{153.2} = 10.3$$

$$WI(7a) = \frac{0}{153.2} = 0$$

Cumulative metrics for compound 7a:



$$AE(7a \text{ cumulative}) = \frac{445.2}{147.14 + 153.61 + 125.13 + 199.05} = 71$$

$$AEf(7a \text{ cumulative}) = 71 \times 70\% = 50$$

$$CE(7a \text{ cumulative}) = \frac{26 \times 0.344}{7 \times 0.5 + 5 \times 0.6 + 6 \times 0.55 + 8 \times 1.36} \times 100 = 43$$

$$RME(7a \text{ cumulative}) = \frac{153.2}{73.6 + 92.2 + 68.8 + 271.6} = 30$$

$$OE(7a \text{ cumulative}) = \frac{30}{71} \times 100 = 42$$

$$PMI(7a \text{ cumulative}) = \frac{73.6 + 92.2 + 68.8 + 1580 \times 3 + 76 + 271.6 + 125.6 + 125.8}{153.2} = 36$$

$$MP(7a \text{ cumulative}) = \frac{1}{36} \times 100 = 2.7$$

$$E \text{ Factor}(7a \text{ cumulative}) = 36 - 1 = 35$$

$$SI(7a \text{ cumulative}) = \frac{1580 \times 3 + 76}{153.2} = 31.4$$

$$WI(7a \text{ cumulative}) = \frac{0}{153.2} = 0$$

6. References for green metrics

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