

# Electrochemical Synthesis of Unnatural Amino Acids Embedding 5- and 6-Membered Heteroaromatics

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## General Experimental Information

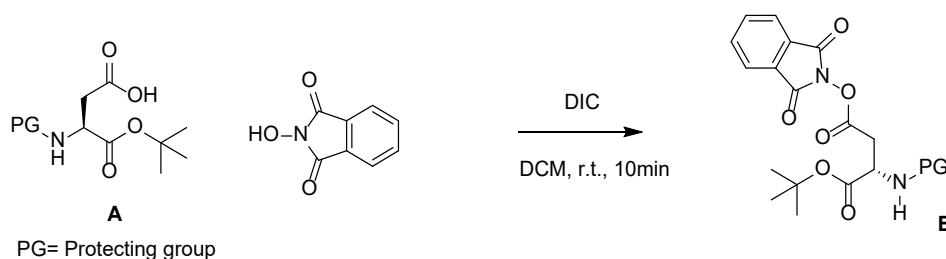
Reagents and dry solvents have been purchased from available commercial suppliers (Merk, Activate Scientific, ABCR etc.) and used as received.

All electrochemical synthesis experiments were performed with commercially available ElectraSyn 2.0 and standard equipment unless otherwise stated. Yields refer to chromatographically and spectroscopically (<sup>1</sup>H NMR or LCMS) homogeneous material, unless otherwise stated. Purifications were performed by flash chromatography on a Biotage SP1 purification system or equivalent MPLC (ISOLERA ONE Flash Chromatography and ISOLERA SELEKT flash chromatography) using Biotage Columns (ULTRA SNAP- or HC-SFAR-cartridges: Silica, Silica-NH and C18). Solvents were removed from crude reaction mixtures with Biotage V-10 Touch Evaporator. UPLC-MS analyses were performed on an Acquity UPCL Water instrument (CSH C18 column 50mm x 2.1mm 1.7μm, maintained at 40°C). The completion of the reactions and the composition of the reaction mixtures were established by LC-MS analyses. Crude was diluted to exactly 10 mL with methanol (MeOH), 50 μL have been picked up and added in a UPLC vial with a calibrated pipette. Volume was brought to 1 mL with MeOH and the sample was injected in the LC-MS.

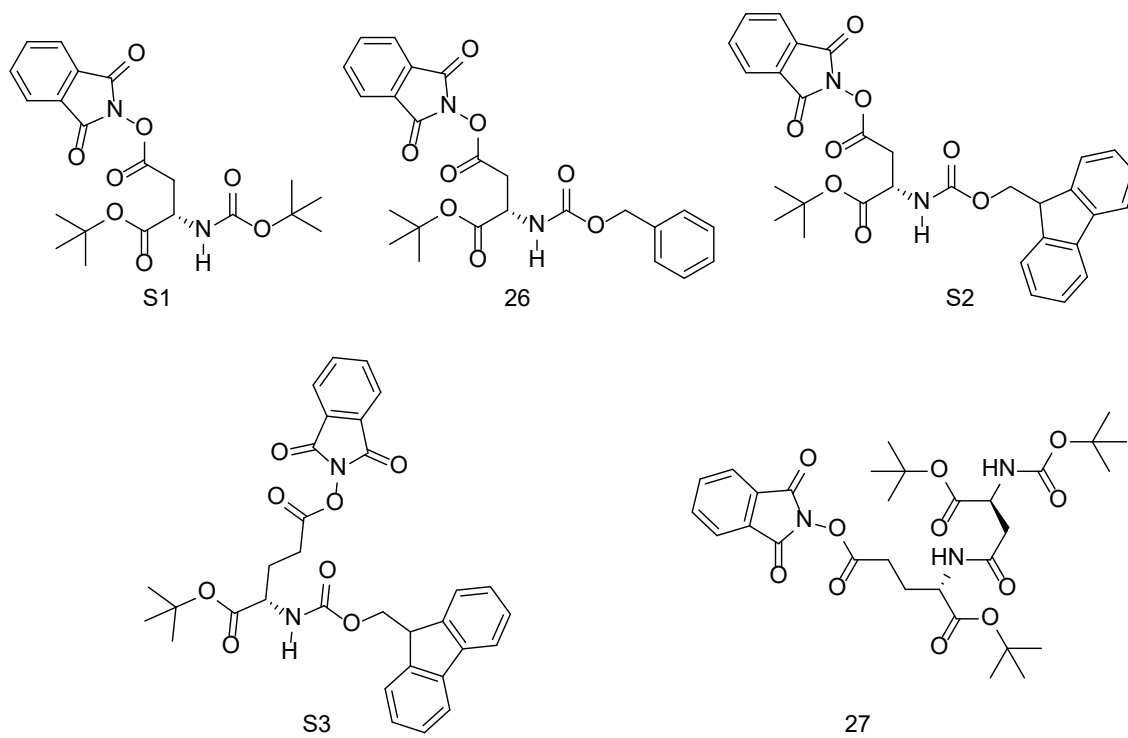
NMR spectra were recorded on a Varian 400MHz spectrometer; all spectra were acquired at 28°C (301.15 K). The following notation was used to report NMR spectra: s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, q = quadruplet, m = multiplet.

HRMS analysis were performed using a Thermo Fisher Scientific Q Exactive mass spectrometer equipped with a HESI (Heated Electrospray Ionisation) ion source coupled with a Thermo Fisher Scientific Vanquish chromatographer. Samples were analysed in positive ESI (ES<sup>+</sup>) ion mode, using a FIA (flow injection analysis) technique and processed with Excalibur (Thermo) software.

## General Procedure 1: Synthesis of NHPI Redox Active Esters

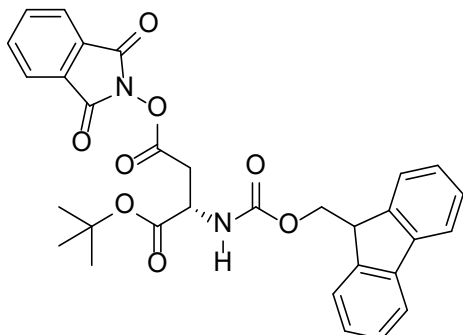


To a stirring solution of carboxylic acid **A** (1.0 equiv.), N-hydroxyphthalimide (1.0 equiv.) in DCM (0.3M), N,N'-diisopropylcarbodiimide (1.3 eq) was added via syringe. The reaction mixture was vigorously stirred until complete (monitored by UPLC-MS, 10 minutes). Upon completion, the mixture was triturated with MTBE, and filtered. The mother liquor was concentrated under vacuum and was directly purified via silica gel column chromatography to afford the activated ester. Redox-active esters shown below S1,<sup>1</sup> S2,<sup>2</sup> S3<sup>3</sup> have previously been reported in the literature. Refer to these references for characterization. For newly reported redox active esters 26 and 27, the second one was not isolated due to the instability of the NHPI ester motif.

**Table S1 – NHPI Redox Active Esters**

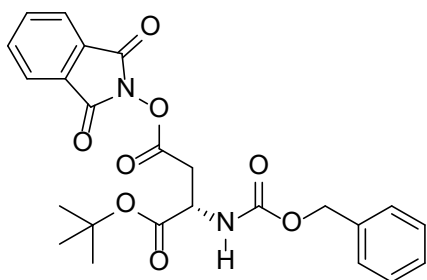
## General Supporting Information for NHPI Redox Active Esters

### Compound S1:



Following the General Procedure 1 with 3S)-3-(9H-fluoren-9-ylmethoxycarbonylamino)-4-[(2-methylpropan-2-yl)oxy]-4-oxobutanoic acid (10 g, 24.30 mmol), *N*-hydroxyphthalimide (3.96 g, 24.30 mmol) and diisopropylmethanediimine (4.89 ml, 31.6 mmol) in DCM (80 ml) was stirring for 10 minutes afforded 13 g (96%) of the title compound after purification by column chromatography Heptane:EtOAc from 100:0 to 20:80 in gradient elution.

The spectroscopical data were in agreement with those reported in literature [1]

**Compound 26:**

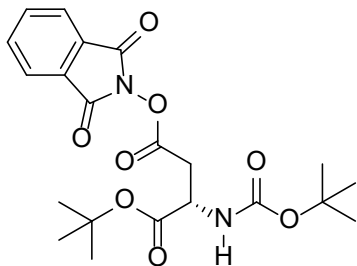
To a solution of (3S)-3-amino-4-[(2-methylpropan-2-yl)oxy]-4-oxobutanoic acid (1 g, 5.29 mmol) in dry DCM (20 mL), TEA (0.737 mL, 5.29 mmol) and N-(benzyloxycarbonyloxy)succinimide (1.449 g, 5.81 mmol) were added and stirred overnight. Then, N-hydroxyphthalimide (0.862 g, 5.29 mmol) and N,N'-diisopropylcarbodiimide (0.834 mL, 5.29 mmol) were added and the reaction was stirred overnight. The reaction was diluted with 200 mL of DCM and the organic layers were washed with saturated NaHCO<sub>3</sub> aqueous solution (100 mL). The organic phase was dried over sodium sulfate and the solvent removed under reduced pressure. The crude was purified by silica gel flash chromatography (Biotage SNAP 50 g) starting from heptane:ethyl acetate 100:0 to 1:1 in gradient elution affording 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) ((benzyloxy)carbonyl)-L-aspartate (1.2 g, 2.56 mmol, 48.5 % yield).

**Physical State:** white-yellow solid

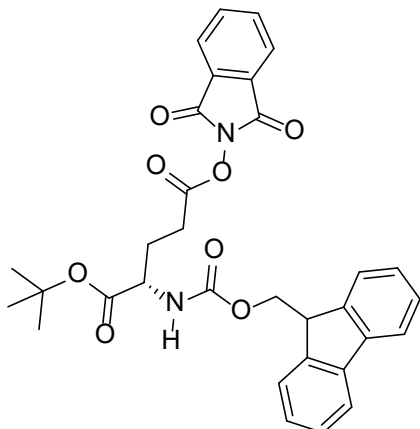
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ ppm 7.89 (2 H, m), 7.80 (2 H, m), 7.37 (5 H, m), 5.82 (1 H, br d, J=7.78 Hz), 5.16 (2 H, m), 4.67 (1 H, dt, J=7.71, 4.55 Hz), 3.35 (1 H, dd, J=17.17, 4.25 Hz), 3.28 (1 H, dd, J=17.17, 4.65 Hz), 1.49 (9 H, s)

**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>):** δ ppm 168.29 (1 C, s), 167.25 (1 C, s), 161.52 (2 C, s), 155.89 (1 C, s), 136.11 (1 C, s), 134.82 (2 C, s), 128.77 (1 C, s), 128.47 (2 C, s), 128.10 (2 C, s), 128.02 (2 C, s), 124.02 (2 C, s), 83.55 (1 C, s), 67.14 (1 C, s), 50.53 (1 C, s), 34.11 (1 C, s), 27.70 (3 C, s)

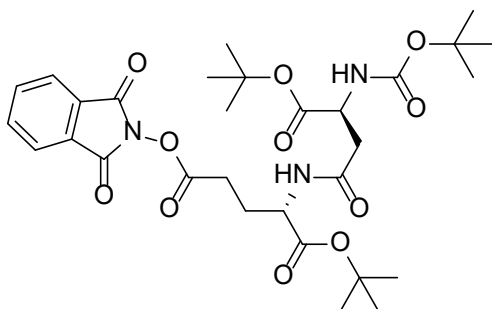
**HMRS** calculated for : C<sub>24</sub>H<sub>24</sub>O<sub>8</sub>N<sub>2</sub>, [M+H]<sup>+</sup>: 468.1527 Found: 468.1528

**Compound S2:**

Following the General Procedure 1 with To a stirring solution of (3S)-4-[(2-methylpropan-2-yl)oxy]-3-[(2-methylpropan-2-yl)oxycarbonylamino]-4-oxobutanoic acid (3 g, 10.37 mmol), N-hydroxyphthalimide (1.691 g, 10.37 mmol) in DCM (30 ml). was stirring for 10 minutes 4.50g (100%) of the title compound after purification by column chromatography Heptane:EtOAc from 100:0 to 20:80 in gradient elution. The spectroscopical data were in agreement with those reported in literature [2]

**Compound S3:**

Following the General Procedure 1 with (4S)-4-(9H-fluoren-9-ylmethoxycarbonylamino)-5-[(2-methylpropan-2-yl)oxy]-5-oxopentanoic acid (5 g, 11.75 mmol), N-hydroxyphthalimide (1.917 g, 11.75 mmol) and N-hydroxyphthalimide (1.917 g, 11.75 mmol) in DCM (35 ml) was stirring for 10 minutes afforded 6.7 g (100%) of the title compound after purification by column chromatography Heptane:EtOAc from 100:0 to 20:80 in gradient elution. The spectroscopical data were in agreement with those reported in literature [3]

**Compound 27:**

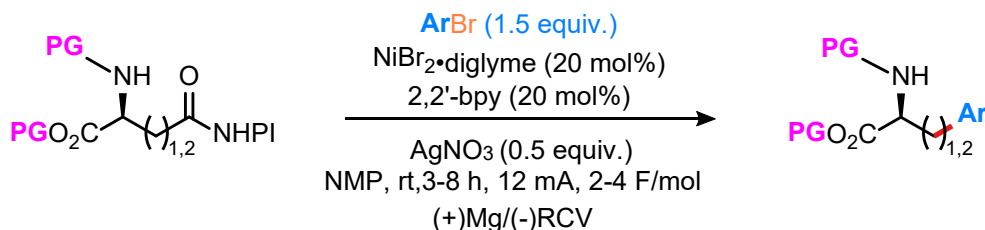
**Step1:** To a solution of (3S)-4-[(2-methylpropan-2-yl)oxy]-3-[(2-methylpropan-2-yl)oxycarbonylamino]-4-oxobutanoic acid (0.877 g, 3.03 mmol) (3S)-4-[(2-methylpropan-2-yl)oxy]-3-[(2-methylpropan-2-yl)oxycarbonylamino]-4-oxobutanoic acid (0.877 g, 3.03 mmol) in DMF, HATU (1.729 g, 4.55 mmol) and DIPEA (0.530 ml, 3.03 mmol) were added and the solution was stirred for 10 min. Then, a solution of 5-O-benzyl 1-O-tert-butyl (2S)-2-aminopentanedioate;hydrochloride (1 g, 3.03 mmol) in 5 ml of DMF was added and the reaction was stirred for 10 min. Then, the crude was concentrated until 5 mL volume and purified by C18 flash chromatography ((H<sub>2</sub>O/ACN)) 95:5 +0.1% HCOOH};{(ACN/H<sub>2</sub>O) 95:5 + HCOOH 0.1 %} from 100:0 to 0:100 affording 5-benzyl 1-(tert-butyl) ((S)-4-(tert-butoxy)-3-((tert-butoxycarbonyl)amino)-4-oxobutanoyl)-L-glutamate (1.2 g, 2.125 mmol, 70.1 % yield) as a brown pale solid.

**Step2:** to a solution of 5-benzyl 1-(tert-butyl) ((S)-4-(tert-butoxy)-3-((tert-butoxycarbonyl)amino)-4-oxobutanoyl)-L-glutamate (1 g, 1.771 mmol) in ACN, Pd/C 10% 50% wet (0.188 g, 1.771 mmol) was added and the reaction was stirred under hydrogen atmosphere for 10 min. Then, the catalyst was removed by filtration through a celite pad. Then, the solvent was removed affording (S)-5-(tert-butoxy)-4-((S)-4-(tert-butoxy)-3-((tert-butoxycarbonyl)amino)-4-oxobutanamido)-5-oxopentanoic acid as a white solid.

**Step3:** Following the General Procedure 1 with To a solution of (S)-5-(tert-butoxy)-4-((S)-4-(tert-butoxy)-3-((tert-butoxycarbonyl)amino)-4-oxobutanamido)-5-oxopentanoic acid (600 mg, 1.264

mmol) in dry DCM, N-hydroxyphthalimide (0.282 ml, 1.517 mmol) and N,N'-diisopropylcarbodiimide (1.517 mmol) were added and the solution was stirred for 1h. Then, the reaction was concentrated to half volume was concentrated to dryness and dissolved in 12.6 mL of NMP affording a 0.1M solution of (S)-5-(tert-butoxy)-4-((S)-4-(tert-butoxy)-3-((tert-butoxycarbonyl)amino)-4-oxobutanamido)-5-oxopentanoic acid.

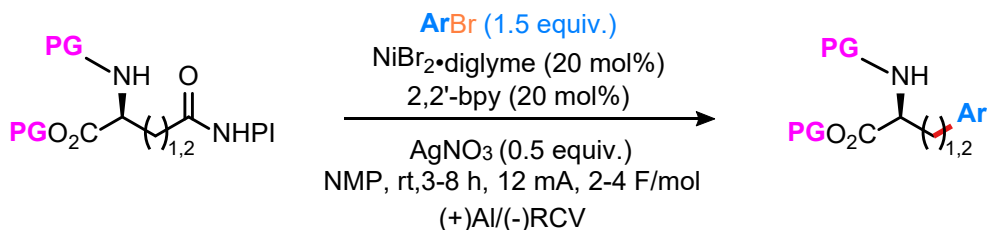
## General Procedure 2: Ag-Ni Electrocatalytic Decarboxylative Arylation (0.7 mmol scale)



To a 8 mL ElectraSyn 2.0 vial, redox active **2** (0.7 mmol, 1 eq), **1** (1.1 mmol, 1.5 eq), NiBr<sub>2</sub> diglyme (0.14 mmol, 0.2 eq), and 2,2'-bipyridine (0.14 mmol, 0.2eq) were mixed together. Anhydrous NMP (7 ml) via syringe and the vials were allowed to stir until a clear solution was formed. The vial was closed with an ElectraSyn 2.0 vial cap with a Mg sacrificial anode (WE) and a 100 ppi RVC cathode (3 mm x 7 mm x 51 mm) (CE) or Ni foam (CE) and placed on an IKA ElectraSyn 2.0 stir plate and electrolysis was set to 12 mA, 0,7mmol, 3 F/mol providing 6 A/m<sup>2</sup> current density. At this point, AgNO<sub>3</sub> (0.36 mmol, 0.5eq) was added.

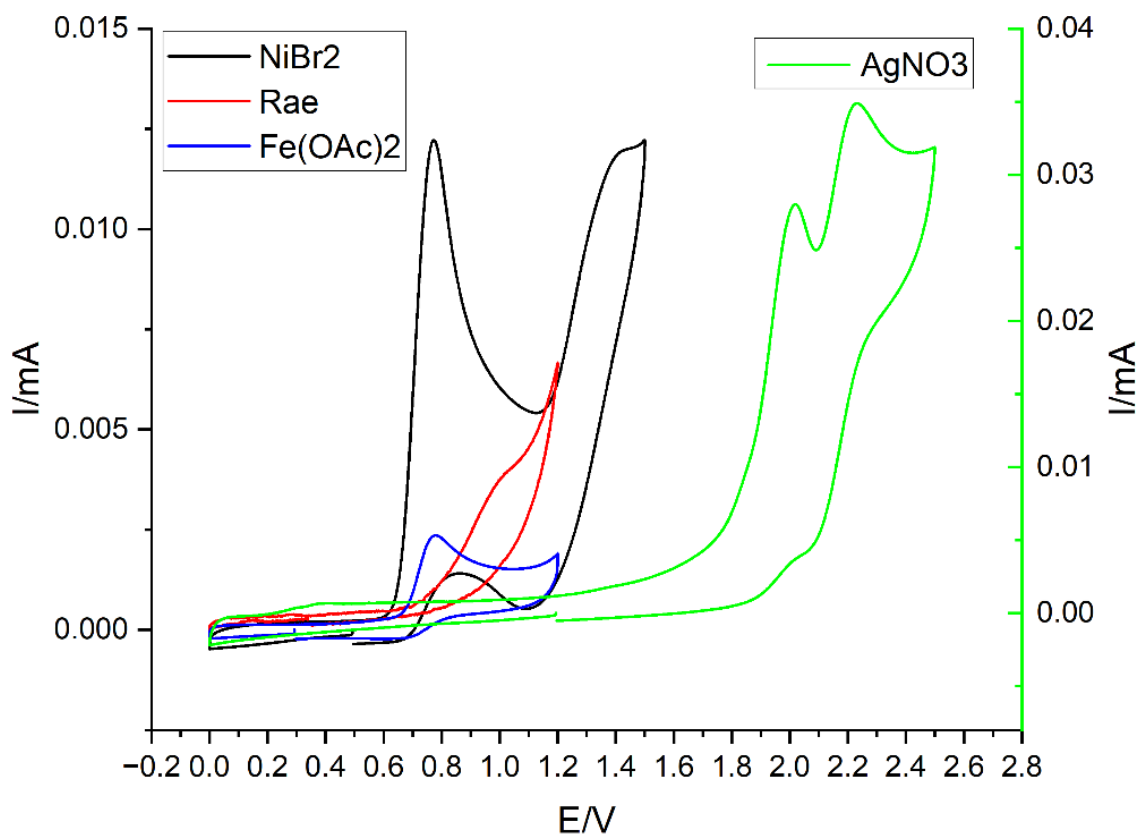
After completion of the reaction, the electrodes were washed in ACN and concentrated under vacuum. The crude was purified with two different purification: inverse phase: column C18, H<sub>2</sub>O:ACN:HCOOC (95:5:0.1)/ACN:H<sub>2</sub>O:HCOOH (95:5:0.1) from 100:0 to 0:100, the fraction mixture was concentrated at the vacuum. Second purification was made in direct phase, via silica column Heptane:EtOAc 100:0 to 0:100 to afford desired product.

## General Procedure 2a: Ag-Ni Electrocatalytic Decarboxylative Arylation (0.7 mmol scale), with WE: Aluminium

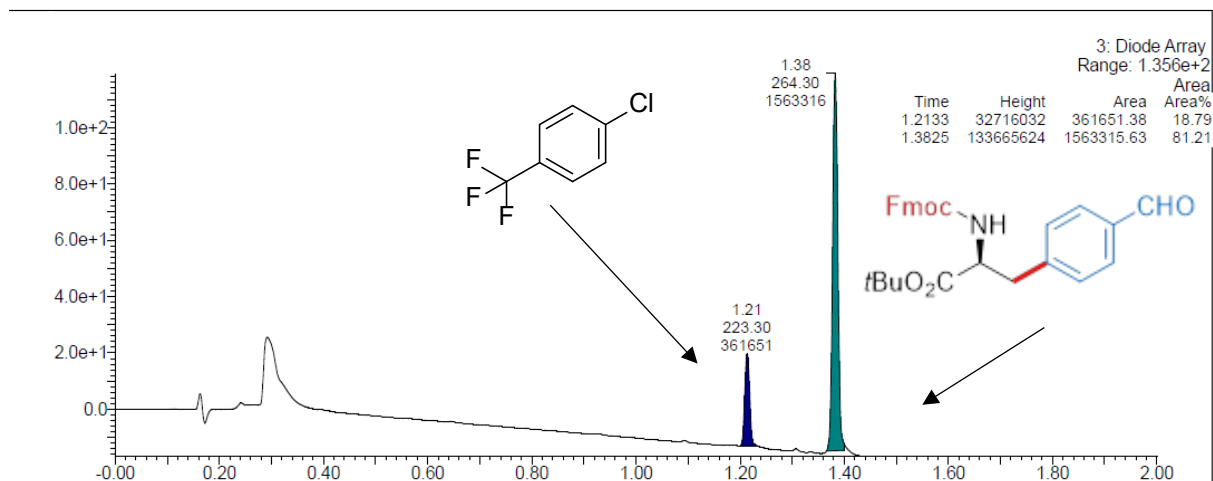


The commercial available Al electrode is activated by immersion in a 6N aqueous solution of HCl for 30 minutes then the electrode is washed first with water 10mL and then 10mL of acetone. After drying the electrode is ready to be used. To an oven dried 8 mL ElectraSyn 2.0 vial, redox active **2** (0.7 mmol, 1 eq), **1** (1.1 mmol, 1.5 eq), NiBr<sub>2</sub> diglyme (0.14 mmol, 0.2 eq), and 2,2'-bipyridine (0.14 mmol, 0.2eq) were all directly added as solids/oils. Anhydrous NMP (7 ml) via syringe. The contents of the vial were allowed to stir until all solids were dissolved (roughly 10 minutes). AgNO<sub>3</sub> (0.36 mmol, 0.5eq) was then added to the reaction mixture directly as a solid. The vial was closed with an ElectraSyn 2.0 vial cap with a Al sacrificial anode (WE) and a 100 ppi RVC cathode (3 mm x 7 mm x 51 mm) (CE) or Ni foam (CE). The vial was then placed on an IKA ElectraSyn 2.0 stir plate and electrolysis was set to 12 mA, 0.7mmol, 3 F/mol providing 6 A/m<sup>2</sup> current density.

After completion of the reaction, the electrodes were washed in ACN and concentrated under vacuum. The crude was purified with two different purification: inverse phase: column C18, H<sub>2</sub>O:ACN:HCOOC (95:5:0.1)/ACN:H<sub>2</sub>O:HCOOH (95:5:0.1) from 100:0 to 0:100, the fraction mixture was concentrated at the vacuum. Second purification was made in direct phase, via silica column Heptane:EtOAc 100:0 to 0:100 to afford desired product.

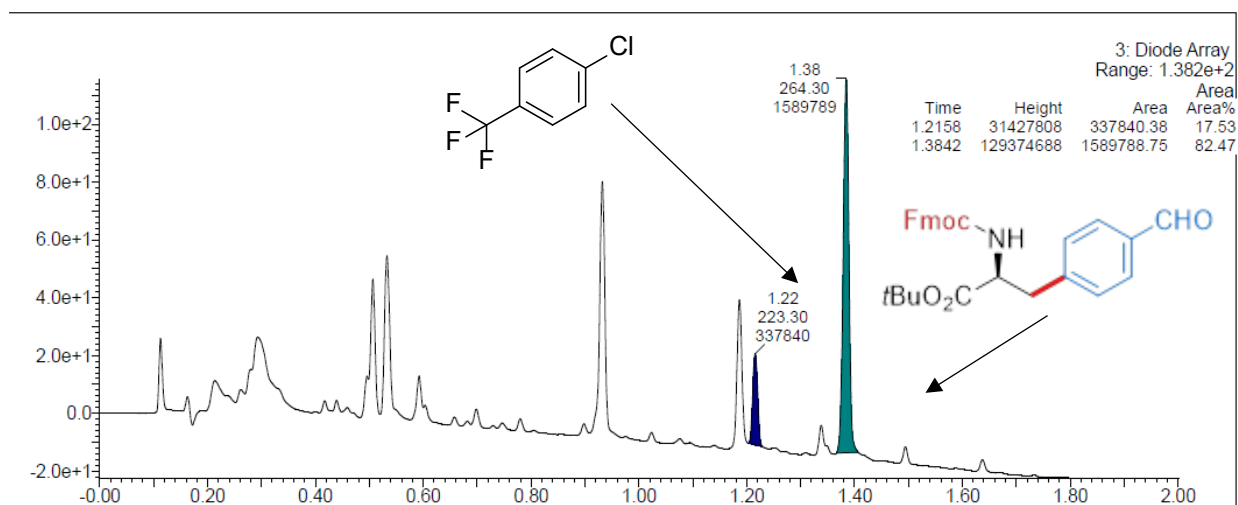
**Cyclic Voltammetry characterization:**

**Figure 1.** Cyclic voltammetry curves of the different species. Species concentration of each compound: 2 mM in 0.08 M TBAPF<sub>6</sub>/CH<sub>3</sub>CN electrolyte solution. Working electrode: GC disk (3 mm diameter); Sweep rate: 0.05 Vs<sup>-1</sup>; T=25 °C; Reference Electrode: Ag/AgCl/KCl(3M).

**Internal Standard method:**

Peak area Standard: 19, Peak area Product: 81

Peak area Ratio: 4.26



Peak area Standard: 17.5, Peak area Product: 82.5

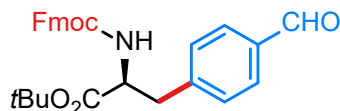
Peak area Ratio: 4.71

$$18.57:4.26=X:4.71 \rightarrow X=20.53 \rightarrow m=X*V=20.53*3.5=71.87\text{mg}$$

**UPLC method:** Acquity CSH C18 column 50mm x 2.1mm 1.7 $\mu$ m, maintained at 40°C; Mobile Phase: Eluent B (ACN) in Eluent A (water +0.1% HCOOH) from 1% to 99.9% within 1.5 min. Flow rate: 1 mL/min. Wavelength: 210-400 nm DAD. UPLC + Waters PDA + Waters QDA.

## Procedures and Characterization of Ag-Ni Electrocatalytic Decarboxylative Arylation Products

### Compound 2



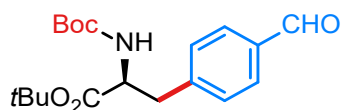
Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (400 mg, 0.719 mmol), 4-bromobenzaldehyde (199 mg, 1.078 mmol) in NMP (7 mL) for 3.0 F/mol afforded 95 mg (28%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):**  $\delta$  ppm 9.99 (1 H, s), 7.79 (2 H, m), 7.79 (2 H, m), 7.58 (2 H, dd,  $J=7.34, 3.62$  Hz), 7.42 (2 H, t,  $J=7.47$  Hz), 7.33 (2 H, m), 7.33 (2 H, m), 5.35 (1 H, br d,  $J=7.67$  Hz), 4.59 (1 H, br dt,  $J=7.67, 6.14$  Hz), 4.47 (1 H, m), 4.38 (1 H, m), 4.22 (1 H, t,  $J=6.69$  Hz), 3.18 (2 H, br t,  $J=7.02$  Hz), 1.42 (8 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)**  $\delta$  ppm 191.80 (1 C, s), 170.06 (1 C, s), 155.43 (1 C, s), 143.77 (1 C, s), 143.64 (1 C, s), 143.48 (1 C, s), 141.30 (2 C, s), 135.22 (1 C, s), 130.21 (2 C, s), 129.74 (2 C, s), 127.72 (2 C, s), 127.02 (2 C, s), 125.01 (1 C, s), 124.94 (1 C, s), 119.99 (2 C, s), 82.85 (1 C, s), 66.83 (1 C, s), 54.83 (1 C, s), 47.15 (1 C, s), 38.61 (1 C, s), 27.94 (3 C, s)

**HRMS:** calculated for C<sub>29</sub>H<sub>30</sub>O<sub>5</sub>N [M+H]<sup>+</sup>: 472.2118 Found: 472.2121

**Compound 3**

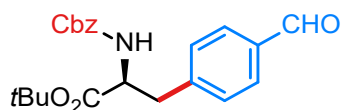
Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxisoindolin-2-yl) (tert-butoxycarbonyl)-L-aspartate (400 mg, 0.921 mmol), 4-bromobenzaldehyde (256 mg, 1.381 mmol) in NMP (7 mL) for 3.0 F/mol afforded 185mg (57%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 10.00 (1 H, s), 7.82 (2 H, m, J=8.11 Hz), 7.37 (2 H, m, J=8.11 Hz), 5.05 (1 H, d, J=7.45 Hz), 4.50 (1 H, q, J=6.80, 6.36 Hz), 3.14 (2 H, m), 1.43 (9 H, s), 1.41 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C):** δ ppm 191.89 (1 C, s), 154.95 (1 C, s), 143.92 (1 C, s), 135.16 (1 C, s), 131.20 (1 C, s), 130.24 (2 C, s), 129.73 (2 C, s), 82.52 (2 C, s), 54.58 (1 C, s), 38.86 (1 C, s), 28.29 (3 C, s), 27.95 (3 C, s)

**HRMS:** calculated for C<sub>19</sub>H<sub>28</sub>O<sub>5</sub>N [M+H]<sup>+</sup>: 350.1962 Found: 350.1968

**Compound 4**

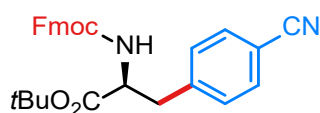
Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) ((benzyloxy)carbonyl)-L-aspartate (400 mg, 0.854 mmol), 4-bromobenzaldehyde (237 mg, 1.281 mmol) in NMP (7 mL) for 3.0 F/mol afforded 118 mg (36%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 9.99 (1 H, s), 7.79 (2 H, d, J=8.11 Hz), 7.35 (7 H, m), 5.31 (1 H, m), 5.10 (2 H, m), 4.57 (1 H, m), 3.17 (2 H, m), 1.40 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C):** δ ppm 191.83 (1 C, s), 170.05 (1 C, s), 155.47 (1 C, s), 143.51 (1 C, s), 136.20 (1 C, s), 135.22 (1 C, s), 130.21 (2 C, s), 129.76 (2 C, s), 128.53 (2 C, s), 128.23 (1 C, s), 128.12 (2 C, s), 82.80 (1 C, s), 66.95 (1 C, s), 54.92 (1 C, s), 38.71 (1 C, s), 27.93 (3 C, s)

**HRMS:** calculated for C<sub>22</sub>H<sub>26</sub>O<sub>5</sub>N [M+H]<sup>+</sup>: 384.1805 Found: 384.1805

**Compound 5**

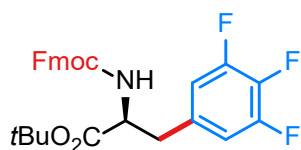
Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (400 mg, 0.719 mmol), 4-bromobenzonitrile (196 mg, 1.078 mmol) in NMP (7 mL) for 3.0 F/mol afforded 160 mg (48%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 7.79 (2 H, br d, J=7.45 Hz), 7.57 (2 H, m), 7.57 (2 H, m), 7.43 (2 H, t, J=7.45 Hz), 7.33 (2 H, t, J=7.33 Hz), 7.24 (2 H, br d, J=7.89 Hz), 5.30 (1 H, m), 4.52 (2 H, m), 4.39 (1 H, m), 4.21 (1 H, m), 3.14 (2 H, m), 1.42 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C):** δ ppm 169.90 (1 C, s), 155.43 (1 C, s), 143.77 (1 C, s), 141.38 (1 C, s), 132.09 (2 C, s), 130.33 (2 C, s), 127.78 (2 C, s), 127.06 (1 C, s), 124.99 (4 C, s), 120.04 (2 C, s), 118.74 (1 C, s), 110.93 (1 C, s), 83.05 (1 C, s), 66.79 (1 C, s), 54.75 (1 C, s), 47.19 (1 C, s), 38.55 (1 C, s), 27.97 (3 C, s)

**HRMS:** calculated for C<sub>29</sub>H<sub>29</sub>O<sub>4</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 469.2122 Found: 469.2122

**Compound 6**

Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (400 mg, 0.719 mmol), 1-bromo-3,4,5-trifluorobenzene (0.129 ml, 1.078 mmol) in NMP (7 mL) for 3.0 F/mol afforded 140 mg (40%).

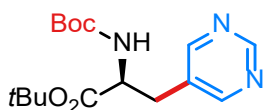
**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 7.76 (2 H, br d, J=7.45 Hz), 7.57 (2 H, dd, J=7.45, 3.51 Hz), 7.39 (2 H, m), 7.31 (2 H, m), 6.75 (2 H, br t, J=7.13 Hz), 5.32 (1 H, br d, J=7.45 Hz), 4.47 (2 H, m), 4.37 (1 H, m), 4.20 (1 H, t, J=6.58 Hz), 3.00 (2 H, br t, J=5.81 Hz), 1.43 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)** δ ppm 169.78 (1 C, s), 155.43 (1 C, s), 150.90 (2 C, ddd, J=249.68, 9.73, 4.58 Hz), 143.77 (1 C, s), 143.55 (1 C, s), 141.32 (2 C, s), 138.84 (1 C, dt, J=250.82, 15.35 Hz), 132.47 (1 C, br d, J=6.10 Hz), 127.75 (2 C, s), 127.06 (1 C, s), 127.02 (1 C, s), 125.00 (1 C, s), 124.89 (1 C, s), 120.02 (2 C, s), 113.53 (2 C, br dd, J=15.26, 5.34 Hz), 83.12 (1 C, s), 66.89 (1 C, s), 54.78 (1 C, s), 47.15 (1 C, s), 37.72 (1 C, s), 27.96 (3 C, s)

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)** δ ppm -134.60 (2 F, br dd, J=20.44, 8.18 Hz), -162.75 (1 F, tt, J=20.40, 6.10 Hz)

**HRMS:** calculated for C<sub>28</sub>H<sub>27</sub>O<sub>4</sub>NF<sub>3</sub> [M+H]<sup>+</sup>: 498.1887 Found: 498.1887

**Compound 7**

Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxisoindolin-2-yl) (tert-butoxycarbonyl)-L-aspartate (500 mg, 1.151 mmol) and 5-bromopyrimidine (274 mg, 1.726 mmol) in NMP (8 mL) for 3.0 F/mol afforded 156 mg (42%).

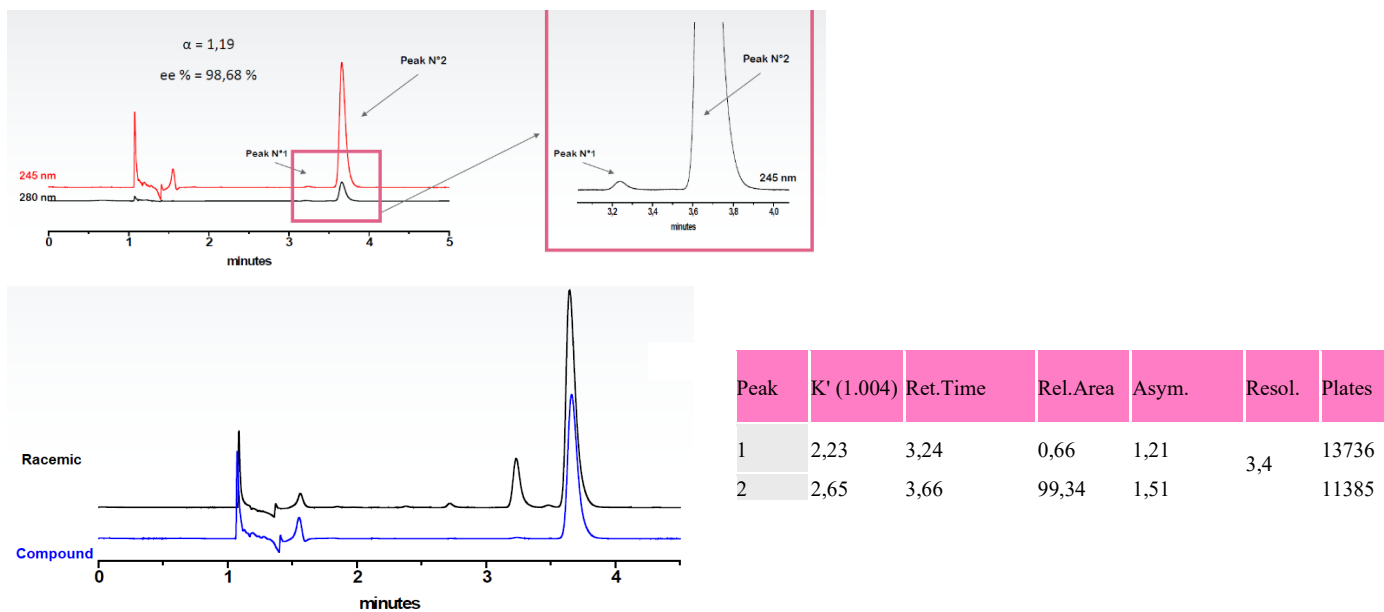
**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz)** δ 9.09 (s, 1H), 8.56 (s, 2H), 5.1-5.2 (m, 1H), 4.44 (br d, 1H, J=5.9 Hz), 3.14 (br dd, 1H, J=5.9, 14.0 Hz), 3.00 (br dd, 1H, J=5.3, 14.0 Hz), 1.41 (s, 18H)

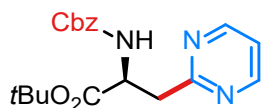
**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)** δ ppm 169.75 (1 Cq), 157.52 (2 CH), 157.36 (1 CH), 154.90 (1 Cq), 130.15 (1 Cq), 83.12 (1 Cq), 80.17 (1 Cq), 54.09 (1 CH), 33.25 (1 CH<sub>2</sub>), 28.21 (3 CH<sub>3</sub>), 27.92 (3 CH<sub>3</sub>)

**HRMS:** calculated for C<sub>16</sub>H<sub>26</sub>O<sub>4</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 324.1918 Found: 324.1917

For this compound chiral analysis was performed and it result with an optical purity of 98,68% see figure below. The partial racemization of compound 1 was obtained under this condition: NaHMDS 1M in THF (2eq), THF at 0°C for 1 hour obtaining compound 1 pure with an optical purity of 68% ee.



Instrumen: UltiMate®3000 RS UHPLCSystemDionex, Software:Chromleon7.2.9, Column:ChiralpakIC100 x 3 mm L. x I.D.; 1.6 µm, Detection:UV at 245nm, T column:35°C, Flow rate: 0.4 mL/min  
 Mobile Phases: A Hex/EtOH/MeOH90/5/5 + 0.1% Triethylamine  
 B Hex/EtOH/MeOH50/25/25 + 0.1% Triethylamine  
 Samples:DissolvedinB, InjectionVolume: 2.0 µL, ISOCRATIC, A/B 90 10

**Compound 8**

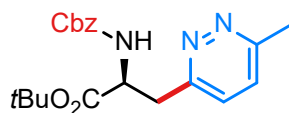
Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) ((benzyloxy)carbonyl)-L-aspartate (500 mg, 1.067 mmol), 2-bromopyrimidine (255 mg, 1.601 mmol) in NMP (8 mL) for 3.0 F/mol afforded 52 mg (14%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 8.63 (2 H, d, J=4.99 Hz), 7.35 (5 H, s), 7.14 (1 H, t, J=4.92 Hz), 6.18 (1 H, br d, J=8.66 Hz), 5.10 (2 H, s), 4.78 (1 H, dt, J=8.80, 4.99 Hz), 3.58 (1 H, dd, J=15.92, 5.50 Hz), 3.43 (1 H, dd, J=15.99, 4.55 Hz), 1.35 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)** δ ppm 170.31 (1 Cq), 167.42 (1 Cq), 156.83 (2 CH), 156.05 (1 Cq), 136.40 (1 Cq), 128.40 (2 CH), 128.08 (2 CH), 128.00 (1 CH), 118.96 (1 CH), 81.75 (1 Cq), 66.76 (1 CH<sub>2</sub>), 52.72 (1 CH), 40.74 (1 CH<sub>2</sub>), 27.75 (3 CH<sub>3</sub>)

**HRMS:** calculated for C<sub>19</sub>H<sub>24</sub>O<sub>4</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 358.1761 Found: 358.1760

**Compound 9**

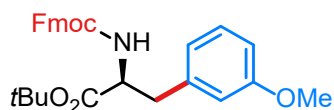
Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) ((benzyloxy)carbonyl)-L-aspartate (500 mg, 1.067 mmol), 3-bromo-6-methylpyridazine (277 mg, 1.601 mmol) in NMP (8 mL) for 3.0 F/mol afforded 80 mg (21%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 7.32 (5 H, m), 7.22 (2 H, m), 6.00 (1 H, br d, J=8.11 Hz), 5.08 (2 H, s), 4.67 (1 H, br d, J=19.29 Hz), 3.43 (2 H, br dd, J=8.00, 5.81 Hz), 2.67 (3 H, s), 1.37 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)** δ ppm 169.94 (1 Cq), 158.42 (1 Cq), 156.97 (1 Cq), 155.91 (1 Cq), 136.32 (1 Cq), 128.38 (2 CH), 127.97 (1 CH), 127.93 (2 CH), 127.12 (1 CH), 126.91 (1 CH), 82.31 (1 Cq), 66.70 (1 CH<sub>2</sub>), 53.55 (1 CH), 37.54 (1 CH<sub>2</sub>), 27.81 (3 CH<sub>3</sub>), 21.93 (1 CH<sub>3</sub>)

**HRMS:** calculated for C<sub>20</sub>H<sub>26</sub>O<sub>4</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 372.1918 Found: 372.1916

**Compound 10**

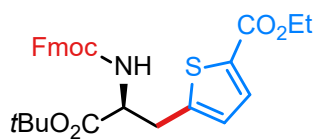
Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (600 mg, 1.078 mmol), 3-iodoanisole (0.064 ml, 0.539 mmol) in NMP (8 mL) for 3.0 F/mol afforded 115 mg (45%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 7.78 (2 H, d, J=7.45 Hz), 7.58 (2 H, t, J=7.34 Hz), 7.41 (2 H, t, J=7.45 Hz), 7.32 (2 H, tt, J=7.45, 1.86 Hz), 7.21 (1 H, t, J=7.78 Hz), 6.76 (1 H, m), 6.74 (1 H, m), 6.78 (1 H, m), 5.30 (1 H, d, J=7.32 Hz), 4.57 (1 H, br dt, J=7.89, 6.14 Hz), 0.00 (1 H, dd, J=10.42, 7.45 Hz), 4.34 (1 H, dd, J=10.30, 7.02 Hz), 4.23 (1 H, m), 3.78 (3 H, s), 3.09 (2 H, d, J=5.92 Hz), 1.44 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)** δ ppm 170.56 (1 Cq), 159.61 (1 Cq), 155.53 (1 Cq), 143.88 (1 Cq), 143.82 (1 Cq), 141.27 (2 Cq), 137.56 (1 Cq), 129.38 (1 CH), 127.66 (2 CH), 127.03 (2 CH), 125.16 (1 CH), 125.10 (1 CH), 121.89 (1 CH), 119.95 (2 CH), 115.27 (1 CH), 112.33 (1 CH), 82.38 (1 Cq), 66.98 (1 CH<sub>2</sub>), 55.14 (1 CH<sub>3</sub>), 54.99 (1 CH), 47.16 (1 CH), 38.41 (1 CH<sub>2</sub>), 27.98 (3 CH<sub>3</sub>)

**HRMS:** calculated for C<sub>29</sub>H<sub>32</sub>O<sub>5</sub>N [M+H]<sup>+</sup>: 474.2275 Found: 474.2272

**Compound 11**

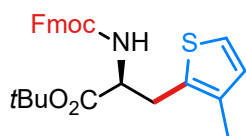
Following the General Procedure 2 with 1 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (300 mg, 0.539 mmol), ethyl 5-bromothiophene-2-carboxylate (190 mg, 0.809 mmol) in NMP (6 mL) for 3.0 F/mol afforded 95 mg (30%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** )  $\delta$  ppm 7.78 (2 H, d,  $J=7.67$  Hz), 7.62 (1 H, m), 7.61 (2 H, m), 7.41 (2 H, m), 7.34 (1 H, s), 6.80 (1 H, m), 6.79 (1 H, br d,  $J=3.51$  Hz), 5.49 (1 H, br d,  $J=7.23$  Hz), 4.57 (1 H, dt,  $J=7.23, 5.04$  Hz), 4.49 (1 H, br dd,  $J=10.41, 7.34$  Hz), 4.33 (3 H, m), 4.26 (1 H, m), 3.40 (1 H, dd,  $J=14.69, 5.26$  Hz), 3.36 (1 H, dd,  $J=15.13, 4.82$  Hz), 1.47 (9 H, s), 1.36 (3 H, t,  $J=7.13$  Hz)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)**  $\delta$  ppm 169.43 (1 Cq), 162.01 (1 Cq), 155.47 (1 Cq), 145.21 (1 Cq), 143.78 (1 Cq), 143.72 (1 Cq), 141.29 (2 Cq), 133.20 (1 CH), 133.04 (1 CH), 127.70 (2 CH), 127.63 (1 Cq), 127.08 (1 Cq), 127.03 (1 Cq), 125.15 (1 Cq), 125.07 (1 Cq), 119.97 (2 Cq), 83.15 (1 Cq), 67.08 (1 CH<sub>2</sub>), 61.04 (1 CH<sub>2</sub>), 54.55 (1 CH), 47.12 (1 CH), 32.92 (1 CH<sub>2</sub>), 27.95 (3 CH<sub>3</sub>), 14.30 (1 CH<sub>3</sub>)

**HRMS:** calculated for C<sub>29</sub>H<sub>32</sub>O<sub>6</sub>NS [M+H]<sup>+</sup>: 522.1945 Found: 522.1946

**Compound 12**

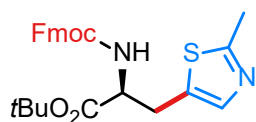
Following the General Procedure 2 with 1 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) (9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (400 mg, 0.719 mmol), 2-bromo-3-methylthiophene (191 mg, 1.078 mmol) in NMP (6 mL) for 3.0 F/mol afforded 84mg (25%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 7.78 (2 H, d, J=7.45 Hz), 7.60 (2 H, m), 7.41 (2 H, t, J=7.34 Hz), 7.32 (2 H, t, J=7.42 Hz), 7.09 (1 H, d, J=5.04 Hz), 6.80 (1 H, d, J=5.04 Hz), 5.43 (1 H, br d, J=7.89 Hz), 4.55 (1 H, m), 4.39 (2 H, m), 4.23 (1 H, m), 3.29 (2 H, br dd, J=14.58, 5.59 Hz), 2.17 (3 H, s), 1.46 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C) :** δ ppm 170.20 (1 C, s), 155.56 (1 C, s), 143.82 (2 C, s), 141.28 (2 C, s), 135.29 (1 C, s), 131.01 (1 C, s), 129.83 (1 C, s), 127.67 (2 C, s), 127.04 (2 C, s), 125.13 (2 C, s), 122.84 (1 C, s), 119.95 (2 C, s), 82.66 (1 C, s), 67.03 (1 C, s), 55.01 (1 C, s), 47.14 (1 C, s), 30.49 (1 C, s), 27.95 (3 C, s), 13.86 (1 C, s)

**HRMS:** calculated for C<sub>27</sub>H<sub>30</sub>O<sub>4</sub>NS [M+H]<sup>+</sup>: 464.1890 Found: 464.1893

**Compound 13**

Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (300 mg, 0.539 mmol), 5-bromo-2-methylthiazole (144 mg, 0.809 mmol), in NMP (7 mL) for 3.0 F/mol afforded 105 mg (42%).

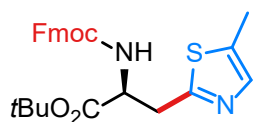
This scope was also obtained by large-scale reaction (3g of RAE) using carousel IKA equipment leading to the obtainment of 1.22g of product, with a yield of 49%.

**Physical State:** yellow solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 7.78 (2 H, d, J=7.45 Hz), 7.61 (2 H, br d, J=7.02 Hz), 7.42 (2 H, t, J=7.42 Hz), 7.34 (3 H, m), 5.47 (1 H, br d, J=7.02 Hz), 4.53 (1 H, br d, J=6.36 Hz), 4.48 (1 H, br dd, J=10.41, 7.56 Hz), 4.37 (1 H, dd, J=10.52, 7.23 Hz), 4.25 (1 H, t, J=7.02 Hz), 3.34 (2 H, br dd, J=12.83, 4.49 Hz), 2.68 (3 H, s), 1.47 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)** δ ppm 169.56 (1 C, s), 166.03 (1 C, s), 155.49 (1 C, s), 143.77 (2 C, s), 141.29 (2 C, s), 141.17 (1 C, s), 131.37 (1 C, s), 127.71 (2 C, s), 127.04 (2 C, s), 125.11 (1 C, s), 125.05 (1 C, s), 119.98 (2 C, s), 83.12 (1 C, s), 67.06 (1 C, s), 54.47 (1 C, s), 47.13 (1 C, s), 29.78 (1 C, s), 28.01 (3 C, s), 19.20 (1 C, s)

**HRMS:** calculated for C<sub>26</sub>H<sub>29</sub>O<sub>4</sub>N<sub>2</sub>S [M+H]<sup>+</sup>: 465.1843 Found: 465.1841

**Compound 14**

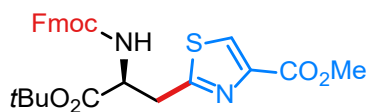
Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (500 mg, 0.898 mmol), 5-bromo-2-methyl-1,3-thiazole (240 mg, 1.348 mmol), in NMP (7 mL) for 3.0 F/mol afforded 13 mg (5%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 7.77 (2 H, d, J=7.45 Hz), 7.62 (2 H, m), 7.41 (2 H, m), 7.36 (1 H, s), 7.31 (2 H, m), 6.07 (1 H, br d, J=8.11 Hz), 4.66 (1 H, dt, J=7.89, 5.04 Hz), 4.37 (2 H, m), 4.26 (1 H, m), 3.50 (2 H, ddd, J=28.00, 15.60, 5.20 Hz), 2.44 (3 H, s), 1.44 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)** δ ppm 169.55 (1 Cq), 155.89 (1 Cq), 143.86 (2 Cq), 141.26 (2 Cq), 134.02 (1 Cq), 127.66 (2 CH), 127.04 (2 CH), 125.24 (2 CH), 119.93 (2 CH), 82.66 (1 Cq), 67.19 (1 CH<sub>2</sub>), 53.67 (1 CH), 47.13 (1 CH), 34.93 (1 CH<sub>2</sub>), 27.91 (3 CH<sub>3</sub>), 11.93 (1 CH<sub>3</sub>)

**HRMS:** calculated for C<sub>26</sub>H<sub>29</sub>O<sub>4</sub>N<sub>2</sub>S [M+H]<sup>+</sup>: 465.1843 Found: 465.1843

**Compound 15**

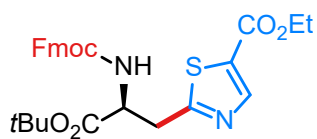
Following the General Procedure 2 with 1 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (400 mg, 0.719 mmol),methyl 2-bromo-1,3-thiazole-4-carboxylate (239 mg, 1.078 mmol) in NMP (6 mL) for 3.0 F/mol afforded 106 mg (29%).

**Physical State:** yellow solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 8.11 (1 H, s), 7.77 (2 H, d, J=7.45 Hz), 7.60 (2 H, br dd, J=6.80, 4.38 Hz), 7.41 (2 H, t, J=7.34 Hz), 7.31 (2 H, t, J=7.45 Hz), 5.77 (1 H, br d, J=7.45 Hz), 4.65 (1 H, br dt, J=7.45, 6.14 Hz), 4.40 (2 H, m), 4.23 (1 H, m), 3.93 (3 H, s), 3.59 (2 H, br dd, J=18.85, 5.48 Hz), 1.45 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C):** δ ppm 169.27 (1 C, s), 165.89 (1 C, s), 161.63 (1 C, s), 155.70 (1 C, s), 146.56 (1 C, s), 143.76 (1 C, s), 141.28 (1 C, s), 128.07 (1 C, s), 127.69 (2 C, s), 127.06 (2 C, s), 125.10 (2 C, s), 119.97 (2 C, s), 83.18 (1 C, s), 77.20 (1 C, s), 76.81 (1 C, s), 67.11 (1 C, s), 53.80 (1 C, s), 52.35 (1 C, s), 47.12 (1 C, s), 35.75 (1 C, s), 31.87 (1 C, s), 29.01 (1 C, s), 27.89 (3 C, s), 22.68 (1 C, s), 14.10 (1 C, s)

**HRMS:** calculated for C<sub>27</sub>H<sub>29</sub>O<sub>6</sub>N<sub>2</sub>S [M+H]<sup>+</sup>: 509.1741 Found: 509.1741

**Compound 16**

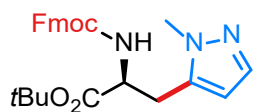
Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (320 mg, 0.575 mmol), ethyl 2-bromothiazole-5-carboxylate (204 mg, 0.862 mmol) in NMP (6 mL) for 3.0 F/mol afforded 87 mg (29%).

**Physical State:** yellow solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 8.30 (1 H, s), 7.77 (2 H, d, J=7.45 Hz), 7.61 (2 H, dd, J=7.34, 3.40 Hz), 7.41 (2 H, m), 7.32 (2 H, t, J=7.44 Hz), 5.96 (1 H, br d, J=7.67 Hz), 4.70 (1 H, br dt, J=7.23, 5.04 Hz), 4.37 (2 H, m), 4.39 (2 H, d, J=9.87 Hz), 4.26 (1 H, m), 3.59 (2 H, br dd, J=9.10, 4.93 Hz), 1.47 (9 H, br s), 1.38 (3 H, t, J=7.13 Hz)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)** δ ppm 171.00 (1 C, s), 169.15 (1 C, s), 161.06 (1 C, s), 155.78 (1 C, s), 147.78 (1 C, s), 143.81 (1 C, s), 143.76 (1 C, s), 141.27 (2 C, s), 129.85 (1 C, s), 127.69 (2 C, s), 127.05 (2 C, s), 125.15 (2 C, s), 119.96 (2 C, s), 83.02 (1 C, s), 67.23 (1 C, s), 61.68 (1 C, s), 53.42 (1 C, s), 47.10 (1 C, s), 35.63 (1 C, s), 27.89 (3 C, s), 14.25 (1 C, s)

**HRMS:** calculated for C<sub>28</sub>H<sub>31</sub>O<sub>6</sub>N<sub>2</sub>S [M+H]<sup>+</sup>: 523.1897 Found: 523.1899

**Compound 17**

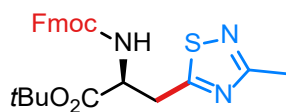
Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (350 mg, 0.629 mmol), 5-bromo-1-methyl-1H-pyrazole (152 mg, 0.943 mmol) in NMP (6 mL) for 3.0 F/mol afforded 25 mg (9%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):**  $\delta$  ppm 7.77 (2 H, d,  $J=7.45$  Hz), 7.58 (2 H, d,  $J=7.45$  Hz), 7.41 (3 H, m), 7.32 (2 H, m), 6.06 (1 H, s), 5.41 (1 H, d,  $J=7.45$  Hz), 4.54 (1 H, dt,  $J=7.02, 5.92$  Hz), 4.43 (2 H, m), 4.22 (1 H, m), 3.79 (3 H, s), 3.16 (2 H, br d,  $J=5.70$  Hz), 1.44 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)**  $\delta$  ppm 169.78 (1 Cq), 155.59 (1 Cq), 143.73 (1 Cq), 143.59 (1 Cq), 141.31 (2 Cq), 138.10 (1 CH), 137.21 (1 Cq), 127.75 (2 CH), 127.07 (2 CH), 124.96 (2 CH), 120.01 (2 CH), 105.79 (1 CH), 83.12 (1 Cq), 66.98 (1 CH<sub>2</sub>), 53.62 (1 CH), 47.13 (1 CH), 36.35 (1 CH<sub>3</sub>), 28.51 (1 CH<sub>2</sub>), 27.91 (3 CH<sub>3</sub>)

**HRMS:** calculated for C<sub>26</sub>H<sub>30</sub>O<sub>4</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 448.2231 Found: 448.2229

**Compound 18**

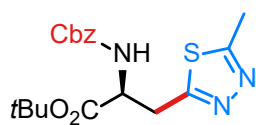
Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (400 mg, 0.719 mmol), 5-bromo-3-methyl-1,2,4-thiadiazole (193 mg, 1.078 mmol), in NMP (7 mL) for 3.0 F/mol afforded 74 mg (23%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 7.77 (2 H, d, J=7.45 Hz), 7.61 (2 H, dd, J=7.23, 2.85 Hz), 7.41 (2 H, t, J=7.34 Hz), 7.32 (2 H, t, J=7.44 Hz), 5.86 (1 H, br d, J=6.80 Hz), 4.69 (1 H, m), 4.42 (2 H, br dd, J=16.55, 7.34 Hz), 4.25 (1 H, m), 3.64 (2 H, br s), 2.66 (3 H, s), 1.43 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)** δ ppm 185.56 (1 C, s), 173.14 (1 C, s), 168.96 (1 C, s), 155.75 (1 C, s), 143.77 (1 C, s), 143.68 (1 C, s), 141.30 (2 C, s), 127.73 (2 C, s), 127.06 (2 C, s), 125.06 (2 C, s), 119.99 (2 C, s), 83.21 (1 C, s), 67.18 (1 C, s), 53.12 (1 C, s), 47.12 (1 C, s), 33.32 (1 C, s), 27.95 (3 C, s), 18.72 (1 C, s)

**HRMS:** calculated for C<sub>25</sub>H<sub>28</sub>O<sub>4</sub>N<sub>3</sub>S [M+H]<sup>+</sup>: 466.1795 Found: 466.1795

**Compound 19**

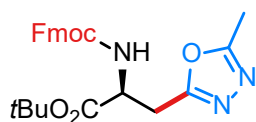
Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) ((benzyloxy)carbonyl)-L-aspartate (500 mg, 1.067 mmol), 2-bromo-5-methyl-1,3,4-thiadiazole (287 mg, 1.601 mmol) in NMP (7 mL) for 3.0 F/mol afforded 53 mg (13%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 7.36 (5 H, m), 5.78 (1 H, br d, J=7.02 Hz), 5.13 (2 H, s), 4.65 (1 H, dt, J=7.02, 5.04 Hz), 3.60 (2 H, m), 2.75 (3 H, s), 1.43 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)** δ ppm 169.02 (1 C, s), 165.71 (1 C, s), 164.85 (1 C, s), 155.76 (1 C, s), 136.17 (1 C, s), 128.51 (2 C, s), 128.17 (1 C, s), 128.08 (2 C, s), 83.23 (1 C, s), 67.05 (1 C, s), 53.33 (1 C, s), 32.54 (1 C, s), 27.86 (3 C, s), 15.55 (1 C, s)

**HRMS:** calculated for C<sub>18</sub>H<sub>28</sub>O<sub>4</sub>N<sub>3</sub>S [M+H]<sup>+</sup>: 378.1482 Found: 378.1482

**Compound 20**

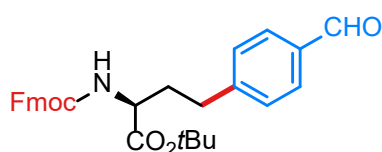
Following the General Procedure 2 with 1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-aspartate (300 mg, 0.539 mmol), 2-bromo-5-methyl-1,3,4-oxadiazole (132 mg, 0.809 mmol) in NMP (6 mL) for 3.0 F/mol afforded 20 mg (8%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 7.77 (2 H, d, J=7.45 Hz), 7.60 (2 H, d, J=7.45 Hz), 7.41 (2 H, t, J=7.43 Hz), 7.32 (2 H, t, J=7.43 Hz), 5.80 (1 H, br d, J=7.89 Hz), 4.71 (1 H, br dt, J=7.89, 5.48 Hz), 4.39 (2 H, d, J=7.02 Hz), 4.24 (1 H, m), 3.37 (2 H, m), 2.51 (3 H, s), 1.45 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C)** δ ppm 168.86 (1 Cq), 164.11 (1 Cq), 163.33 (1 Cq), 155.69 (1 Cq), 143.72 (2 Cq), 141.28 (2 Cq), 127.72 (2 CH), 127.07 (2 CH), 125.12 (2 CH), 119.98 (2 CH), 83.40 (1 Cq), 67.30 (1 CH<sub>2</sub>), 51.81 (1 CH), 47.07 (1 CH), 28.68 (1 CH<sub>2</sub>), 27.83 (3 CH<sub>3</sub>), 10.93 (1 CH<sub>3</sub>)

**HRMS:** calculated for C<sub>25</sub>H<sub>28</sub>O<sub>5</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 450.2023 Found: 450.2023

**Compound 21**

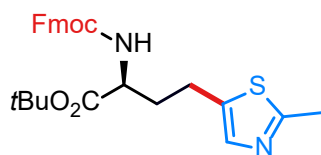
Following the General Procedure 2 with 1-(tert-butyl) 5-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-glutamate (400 mg, 0.701 mmol), 4-bromobenzaldehyde (195 mg, 1.052 mmol) in NMP (7 mL) for 3.0 F/mol afforded 115mg (33%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 9.98 (1 H, s), 7.82 (2 H, d, J=8.11 Hz), 7.78 (2 H, m), 7.61 (2 H, br d, J=6.80 Hz), 7.36 (6 H, m), 5.40 (1 H, d, J=7.89 Hz), 4.43 (2 H, br d, J=6.36 Hz), 4.34 (1 H, m), 4.24 (1 H, m), 2.75 (2 H, m), 2.08 (2 H, m), 1.50 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C):** δ ppm 191.84 (1 C, s), 171.14 (1 C, s), 155.81 (1 C, s), 143.85 (2 C, s), 141.31 (2 C, s), 134.75 (2 C, s), 130.03 (2 C, s), 129.06 (2 C, s), 127.71 (2 C, s), 127.03 (2 C, s), 125.03 (2 C, s), 119.98 (2 C, s), 82.56 (1 C, s), 66.89 (1 C, s), 53.99 (1 C, s), 47.19 (1 C, s), 34.24 (1 C, s), 31.71 (1 C, s), 28.01 (3 C, s)

**HRMS:** calculated for C<sub>30</sub>H<sub>32</sub>O<sub>5</sub>N [M+H]<sup>+</sup>: 486.2275 Found: 486.2278

**Compound 22**

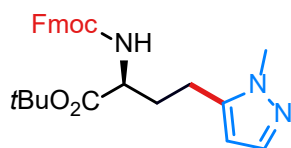
Following the General Procedure 2 with 1 1-(tert-butyl) 5-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-glutamate (400mg, 0.701 mmol), 5-bromo-2-methyl-1,3-thiazole (187 mg, 1.052 mmol) in NMP (7 mL) for 3.0 F/mol afforded 166 mg (50%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 7.77 (2 H, br d, J=7.45 Hz), 7.61 (2 H, br d, J=7.02 Hz), 7.41 (2 H, td, J=7.23, 3.95 Hz), 7.32 (3 H, m), 5.40 (1 H, br d, J=7.89 Hz), 4.43 (2 H, br t, J=6.36 Hz), 4.33 (1 H, br d, J=5.26 Hz), 4.23 (1 H, t, J=6.90 Hz), 2.82 (2 H, m), 2.67 (3 H, s), 2.19 (1 H, m), 1.96 (1 H, m), 1.49 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C):** δ ppm 171.02 (1 C, s), 164.80 (1 C, s), 155.85 (1 C, s), 143.86 (1 C, s), 143.69 (1 C, s), 141.30 (2 C, s), 139.09 (1 C, s), 137.32 (1 C, s), 127.70 (2 C, s), 127.03 (2 C, s), 125.01 (2 C, s), 119.97 (2 C, s), 82.61 (1 C, s), 66.91 (1 C, s), 53.79 (1 C, s), 47.21 (1 C, s), 34.77 (1 C, s), 28.00 (3 C, s), 22.97 (1 C, s), 19.18 (1 C, s)

**HRMS:** calculated for C<sub>27</sub>H<sub>31</sub>O<sub>4</sub>N<sub>2</sub>S [M+H]<sup>+</sup>: 479.1999 Found: 479.1999

**Compound 23**

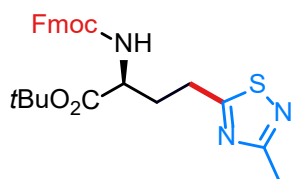
Following the General Procedure 2 with 1-(tert-butyl) 5-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-glutamate (400mg, 0.701 mmol), 5-bromo-1-methyl-1H-pyrazole (113 mg, 0.701 mmol) in NMP (7 mL) for 3.0 F/mol afforded 86 mg (27%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):**  $\delta$  ppm 7.77 (2 H, br d,  $J=7.23$  Hz), 7.60 (2 H, m), 7.40 (3 H, m), 7.32 (2 H, m), 6.06 (1 H, s), 5.46 (1 H, br d,  $J=7.67$  Hz), 4.44 (2 H, br d,  $J=6.80$  Hz), 4.36 (1 H, br d,  $J=5.26$  Hz), 4.23 (1 H, t,  $J=6.91$  Hz), 3.78 (3 H, s), 2.65 (2 H, m), 2.20 (1 H, m), 1.99 (1 H, m), 1.50 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C):**  $\delta$  ppm 170.97 (1 C, s), 155.87 (1 C, s), 143.82 (1 C, s), 143.64 (1 C, s), 141.28 (1 C, s), 141.28 (1 C, s), 138.07 (1 C, s), 127.69 (2 C, s), 127.01 (2 C, s), 124.98 (2 C, s), 119.97 (2 C, s), 119.97 (1 C, s), 104.15 (1 C, s), 82.67 (1 C, s), 66.88 (1 C, s), 53.87 (1 C, s), 47.16 (1 C, s), 36.06 (1 C, s), 31.63 (1 C, s), 27.99 (3 C, s), 21.40 (1 C, s)

**HRMS:** calculated for C<sub>27</sub>H<sub>32</sub>O<sub>4</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 462.2387 Found: 462.2388

**Compound 24**

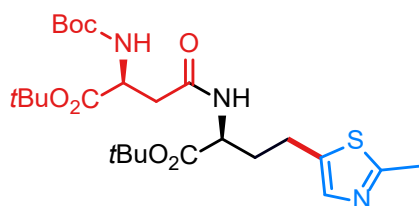
Following the General Procedure 2 with 1-(tert-butyl) 5-(1,3-dioxoisindolin-2-yl) (((9H-fluoren-9-yl)methoxy)carbonyl)-L-glutamate (400mg, 0.701 mmol), 5-bromo-3-methyl-1,2,4-thiadiazole (126 mg, 0.701 mmol) in NMP (7 mL) for 3.0 F/mol afforded 90 mg (27%).

**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):**  $\delta$  ppm 7.77 (2 H, br d,  $J=7.45$  Hz), 7.60 (2 H, br d,  $J=7.23$  Hz), 7.40 (2 H, m), 7.32 (2 H, m), 5.57 (1 H, br d,  $J=7.67$  Hz), 4.41 (3 H, m), 4.23 (1 H, m), 3.13 (2 H, m), 2.66 (3 H, s), 2.38 (1 H, m), 2.16 (1 H, br d,  $J=8.77$  Hz), 1.49 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C):**  $\delta$  ppm 189.97 (1 C, s), 173.35 (1 C, s), 170.66 (1 C, s), 155.97 (1 C, s), 143.83 (1 C, s), 143.67 (1 C, s), 141.31 (1 C, s), 141.31 (1 C, s), 127.72 (2 C, s), 127.05 (1 C, s), 125.07 (1 C, s), 125.01 (1 C, s), 119.98 (2 C, s), 82.84 (1 C, s), 66.96 (1 C, s), 53.82 (1 C, s), 47.20 (1 C, s), 32.10 (1 C, s), 27.99 (3 C, s), 27.13 (1 C, s), 18.77 (1 C, s)

**HRMS:** calculated for C<sub>26</sub>H<sub>30</sub>O<sub>4</sub>N<sub>3</sub>S [M+H]<sup>+</sup>: 480.1952 Found: 480.1953

**Compound 25**

Following the General Procedure 2 with 5-bromo-2-methyl-1,3-thiazole (172 mg, 0.968 mmol), a 0.1 M solution of 1-(tert-butyl) 5-(1,3-dioxisoindolin-2-yl) ((S)-4-(tert-butoxy)-3-((tert-butoxycarbonyl)amino)-4-oxobutanoyl)-L-glutamate in NMP (6mL, 0.6 mmol) in NMP (1 mL) for 3.0 F/mol afforded 123 mg (36%).

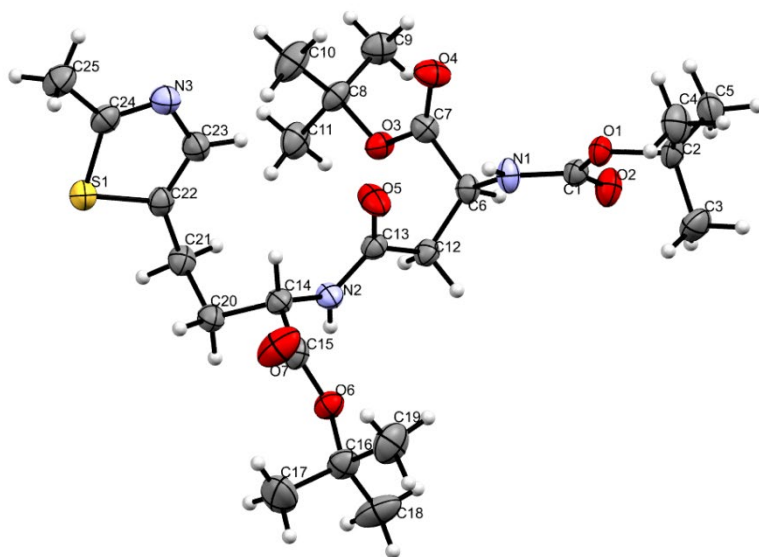
**Physical State:** white solid

**<sup>1</sup>H NMR (CHLOROFORM-d, 400 MHz):** δ ppm 7.31 (1 H, m), 6.23 (1 H, br d, J=7.45 Hz), 5.69 (1 H, br d, J=7.89 Hz), 4.52 (1 H, td, J=7.51, 5.15 Hz), 4.41 (1 H, m), 2.78 (4 H, m), 2.66 (3 H, s), 2.17 (1 H, m), 1.93 (1 H, m), 1.48 (9 H, s), 1.45 (9 H, s), 1.44 (9 H, s)

**<sup>13</sup>C NMR (101 MHz, CHLOROFORM-d, 77.00 ppm, 25°C):** δ ppm 170.81 (1 C, s), 170.32 (1 C, s), 169.85 (1 C, s), 164.82 (1 C, s), 155.66 (1 C, s), 138.92 (1 C, s), 137.36 (1 C, s), 82.71 (1 C, s), 82.08 (1 C, s), 79.72 (1 C, s), 52.15 (1 C, s), 50.89 (1 C, s), 38.15 (1 C, s), 34.74 (1 C, s), 28.29 (3 C, s), 27.96 (3 C, s), 27.89 (3 C, s), 23.01 (1 C, s), 19.13 (1 C, s)

**HRMS:** calculated for C<sub>25</sub>H<sub>42</sub>O<sub>7</sub>N<sub>3</sub>S [M+H]<sup>+</sup>: 528.2738 Found: 528.2741

## Single-crystal X-ray diffraction (SC-XRD) analysis



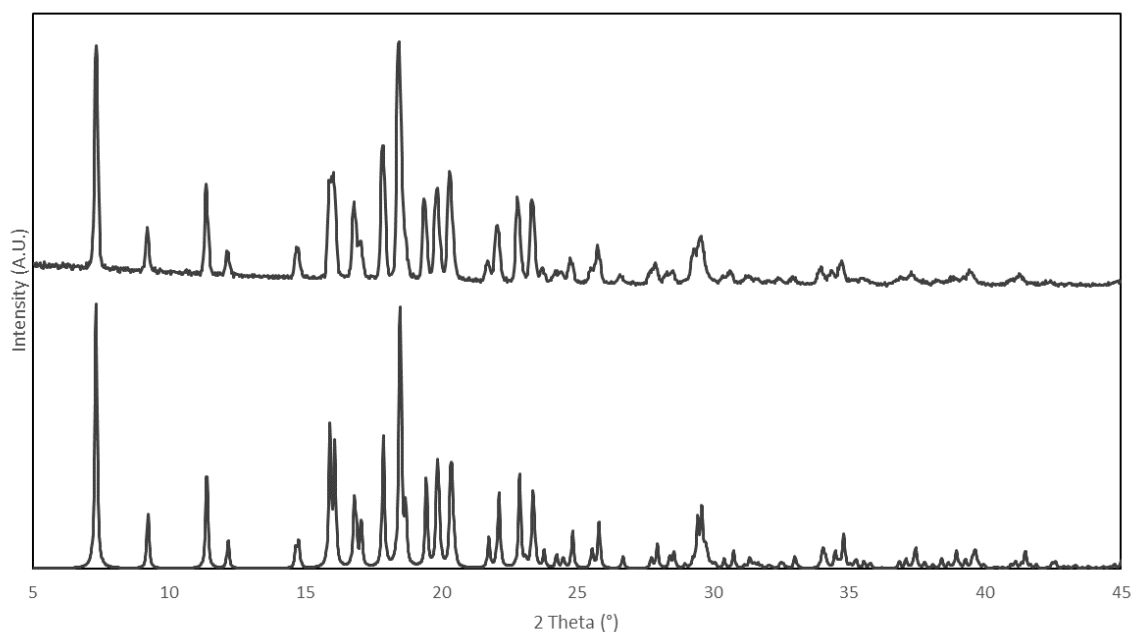
Crystals of compound **25** suitable for SC-XRD analysis were grown by slow evaporation of an acetonitrile solution. Data were collected at 200 K with a Bruker D8 Venture diffractometer equipped with a Photon II detector, using a CuK $\alpha$  microfocus radiation source ( $\lambda = 1.54184 \text{ \AA}$ ). Data reduction was performed with APEX4. Absorption correction was applied using the program SADABS. The structures were solved by intrinsic phasing with the program SHELXT.<sup>4</sup> Fourier analysis and refinement were performed by the full-matrix least-squares method based on  $F^2$  using SHELXL implemented in Olex2 software.<sup>5,6</sup> Non-H atoms were refined with anisotropic displacement parameters, H atoms were placed in calculated positions and refined with a riding model. The absolute configuration was determined by the synthesis and fixed during refinement. Crystallographic data for compounds **25** (2293382) have been deposited with the Cambridge Crystallographic Data Centre.

**Crystal data and structure refinement for 25**

<i>Empirical formula</i>	C <sub>25</sub> H <sub>41</sub> N <sub>3</sub> O <sub>7</sub> S
<i>Formula weight</i>	527.67
<i>Temperature/K</i>	200.00
<i>Crystal system</i>	triclinic
<i>Space group</i>	P1
<i>a/Å</i>	6.1057(2)
<i>b/Å</i>	9.7397(3)
<i>c/Å</i>	12.1590(4)
<i>α/°</i>	85.1960(10)
<i>β/°</i>	84.2900(10)
<i>γ/°</i>	80.1340(10)
<i>Volume/Å<sup>3</sup></i>	707.20(4)
<i>Z</i>	1
<i>ρ<sub>calc</sub>/cm<sup>3</sup></i>	1.239
<i>μ/mm<sup>-1</sup></i>	1.399
<i>F(000)</i>	284.0
<i>Crystal size/mm<sup>3</sup></i>	0.15 × 0.1 × 0.04
<i>Radiation</i>	CuKα (λ = 1.54178)
<i>2θ range for data collection/°</i>	12.184 to 149.132
<i>Index ranges</i>	-7 ≤ h ≤ 7, -11 ≤ k ≤ 12, -15 ≤ l ≤ 15
<i>Reflections collected</i>	23543
<i>Independent reflections</i>	5318 [R <sub>int</sub> = 0.0375, R <sub>sigma</sub> = 0.0323]
<i>Data/restraints/parameters</i>	5318/3/335
<i>Goodness-of-fit on F<sup>2</sup></i>	1.094
<i>Final R indexes [I &gt;= 2σ (I)]</i>	R <sub>1</sub> = 0.0294, wR <sub>2</sub> = 0.0739
<i>Final R indexes [all data]</i>	R <sub>1</sub> = 0.0298, wR <sub>2</sub> = 0.0742
<i>Largest diff. peak/hole / e Å<sup>-3</sup></i>	0.13/-0.19
<i>Flack parameter</i>	0.123(5)

## X-ray powder diffraction (XRPD) analysis of **25**

XRPD pattern was collected on a Panalytical Empyrean instrument equipped with a CuK $\alpha$  radiation source and PIXcel detector. The sample was placed on Si zero background sample holder. The measurement was performed in Bragg-Brentano geometry with a 2Theta scan in the range 3-45°, step size 0.026°, counting time 100s, soller slit 0.02 rad, divergence slit 1/8°, antiscatter slit 1/4°.

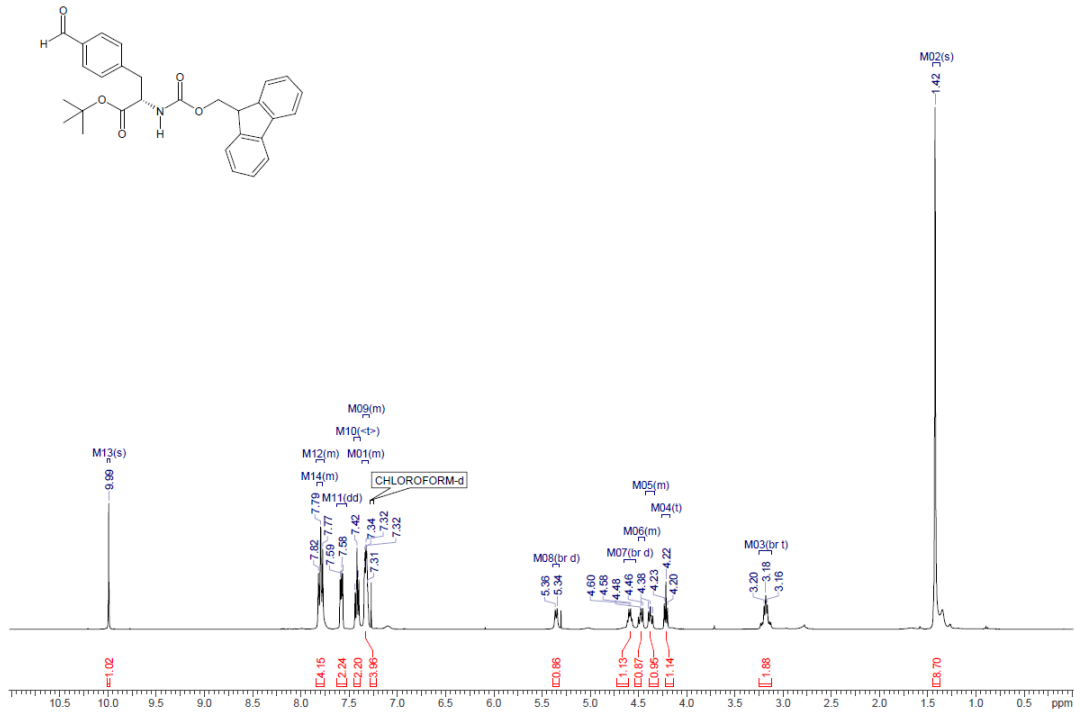
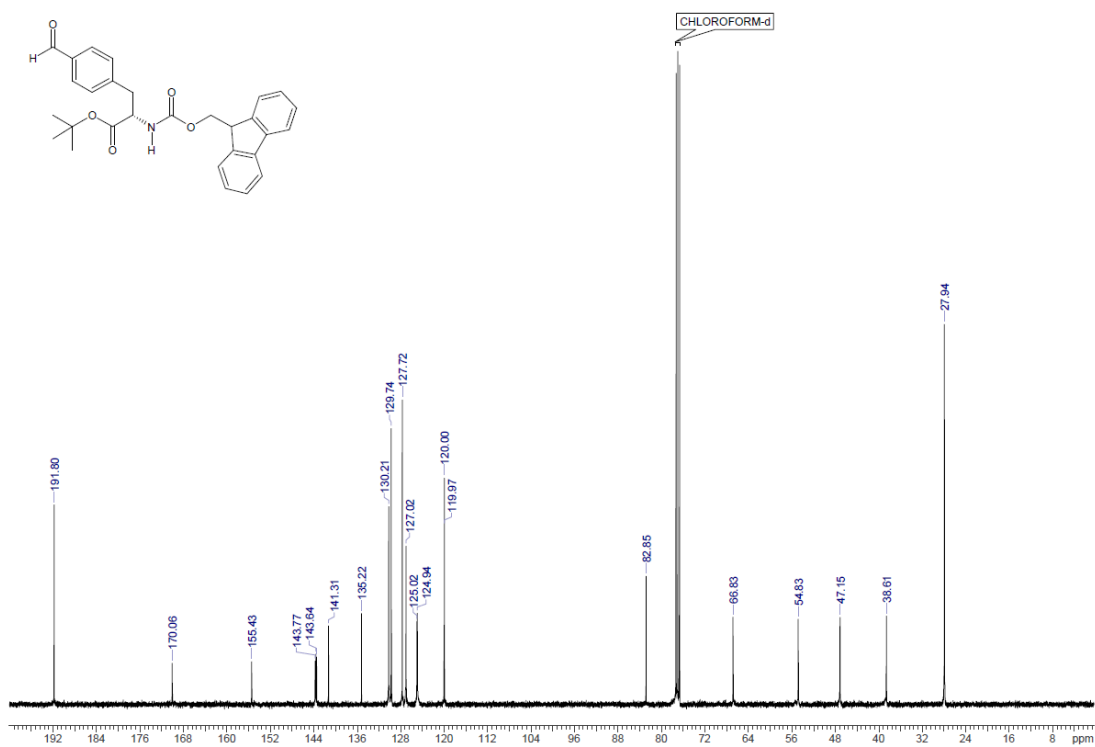


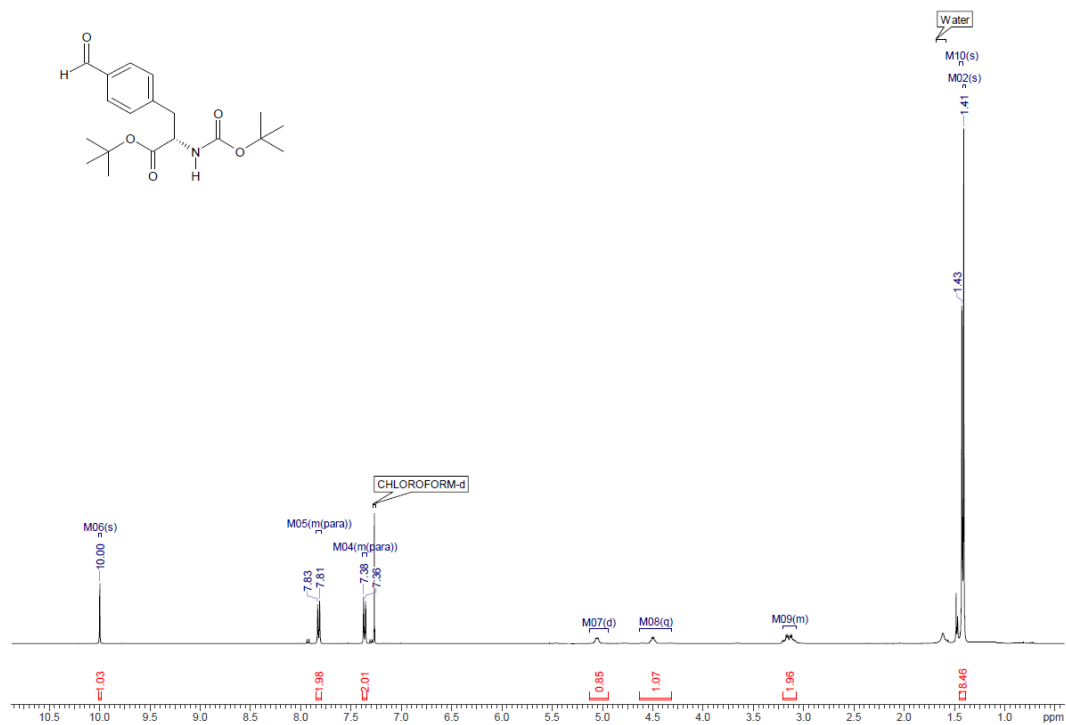
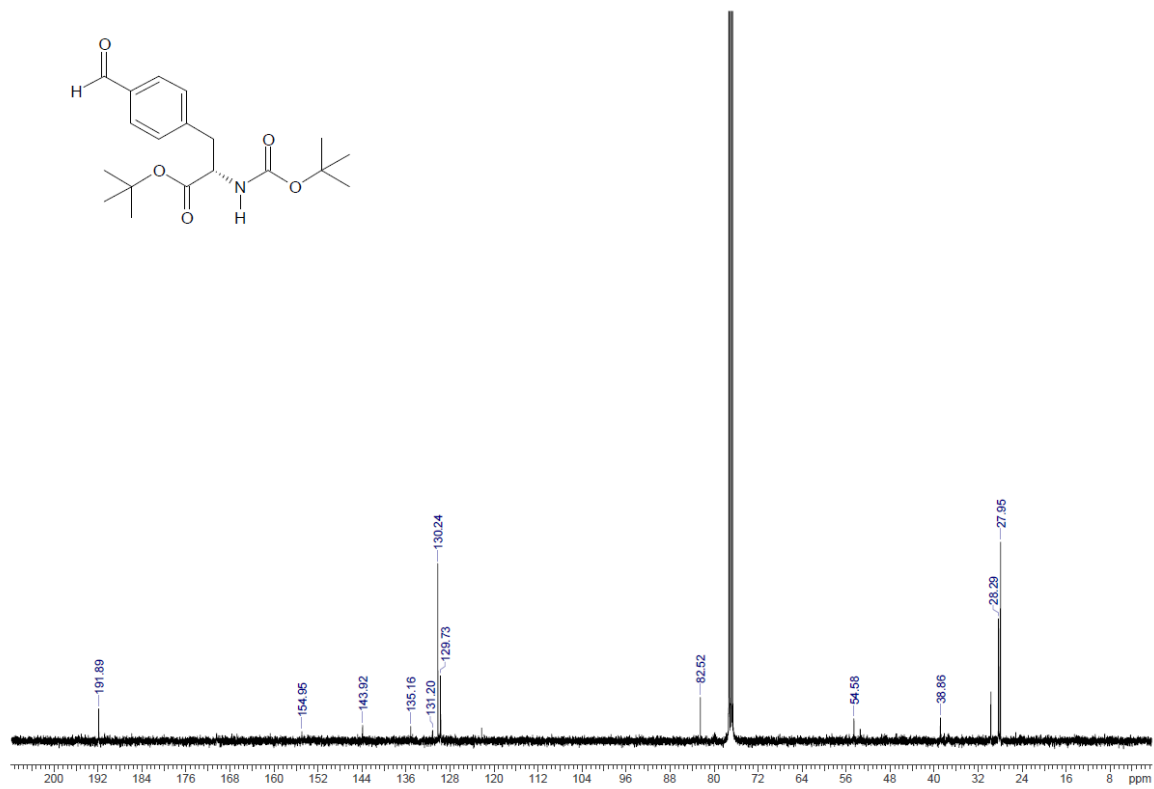
Experimental XRPD pattern of bulk **25** (top) and calculated pattern from the crystal structure (bottom), with the correspondence between the two showing that the structure is representative of the bulk material; the XRPD pattern was calculated with Mercury.<sup>7</sup>

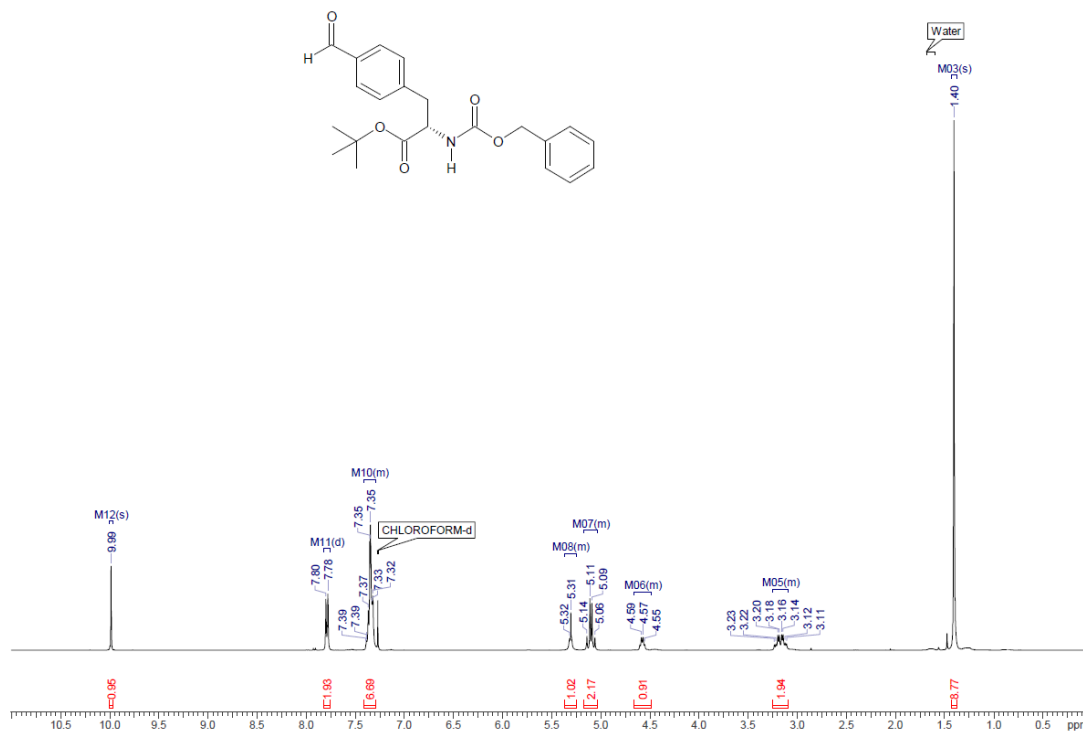
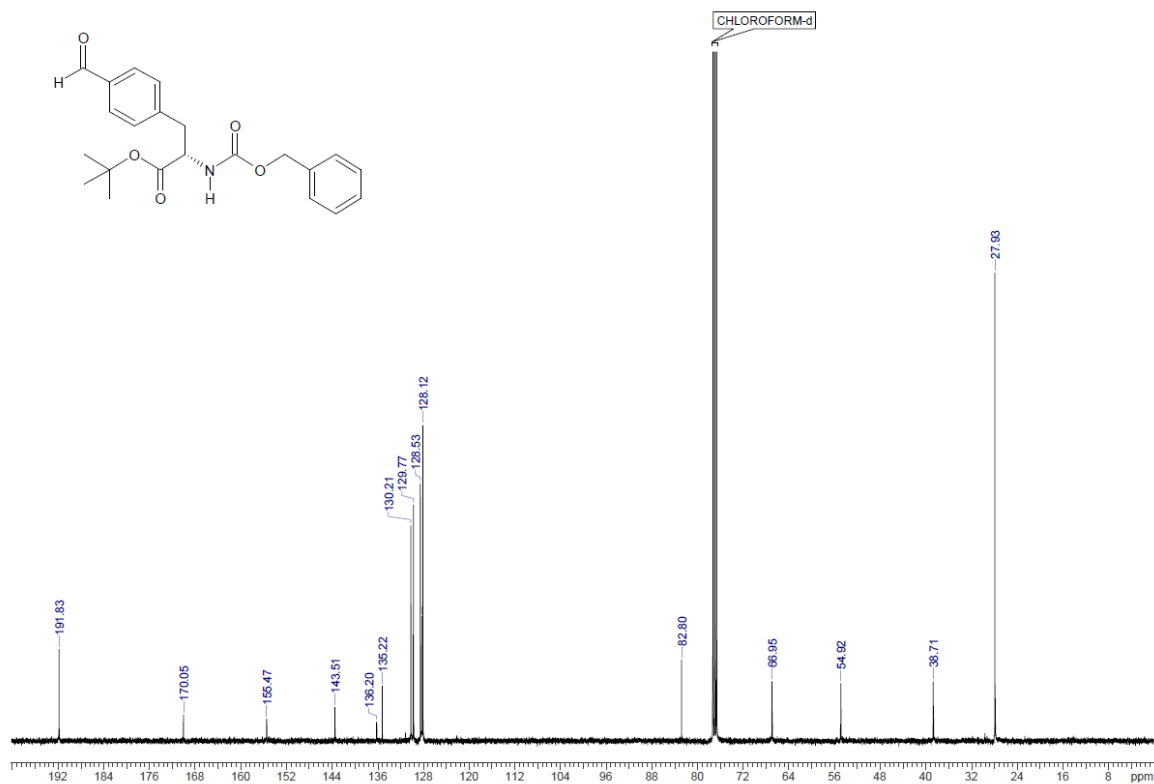
**References:**

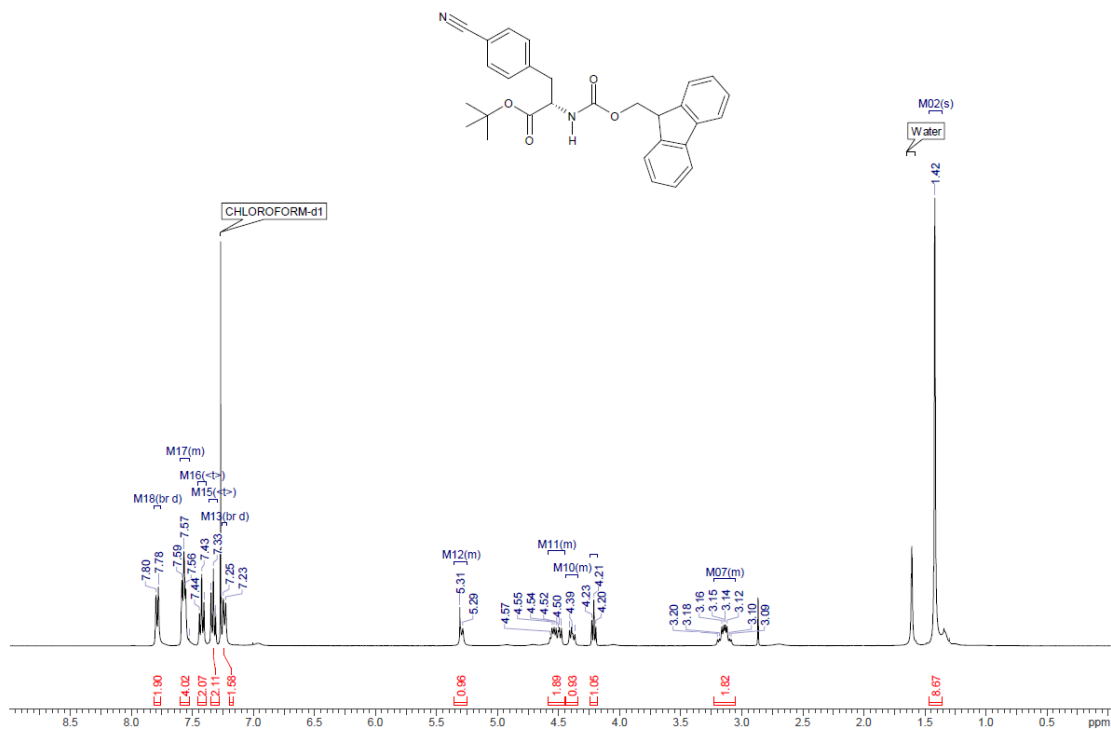
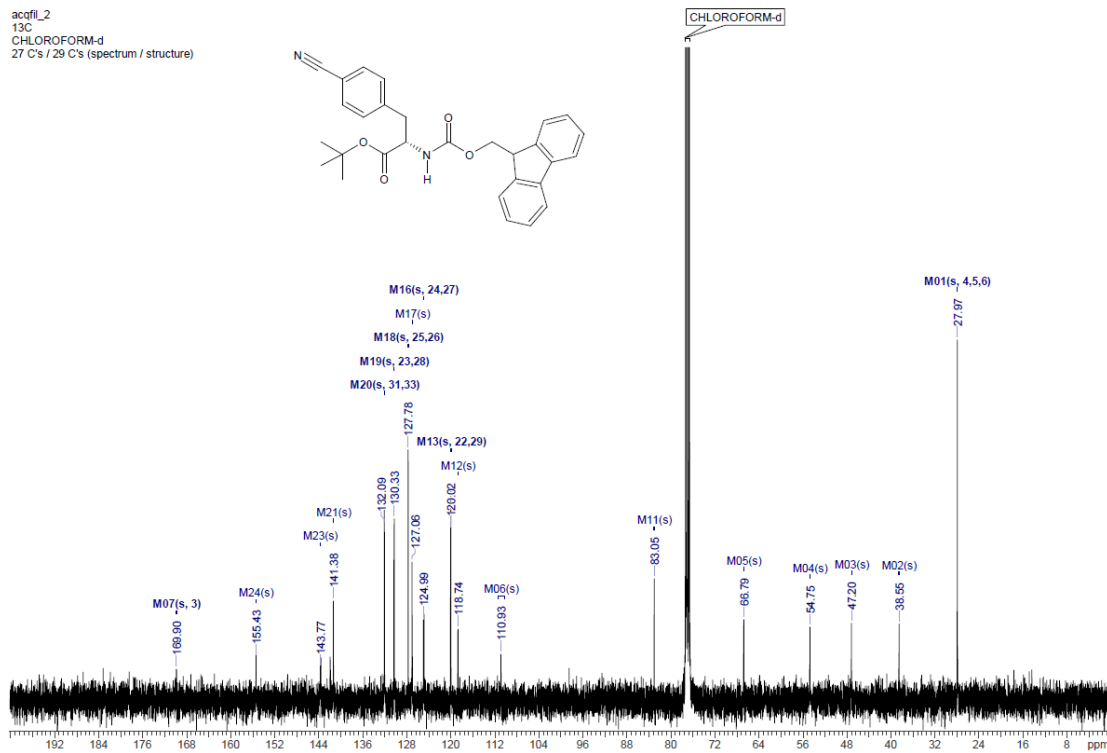
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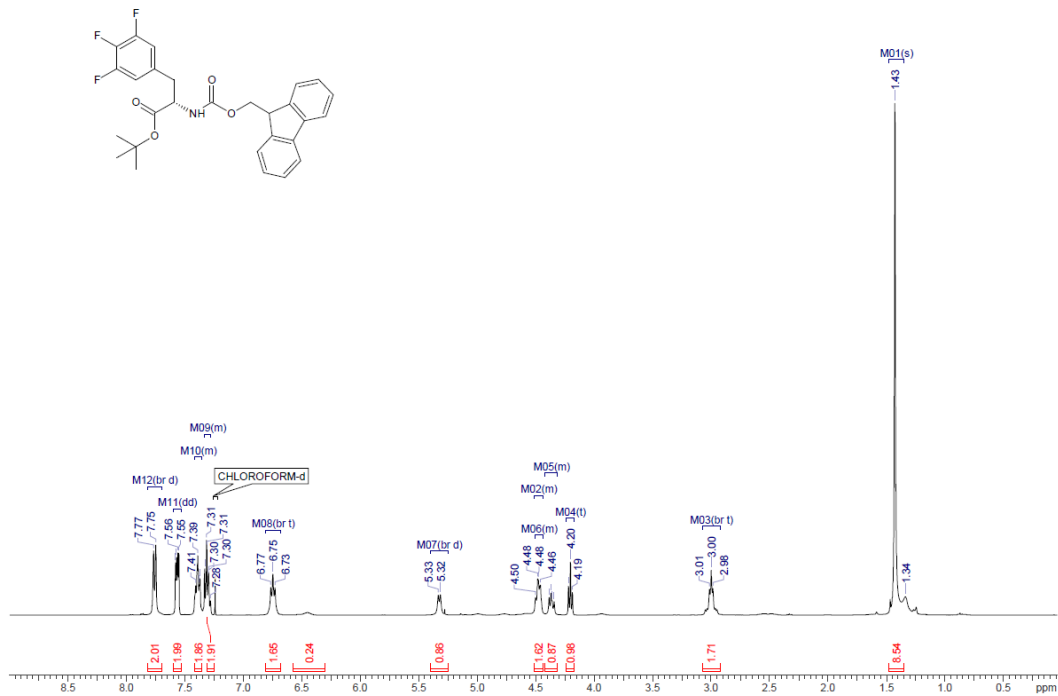
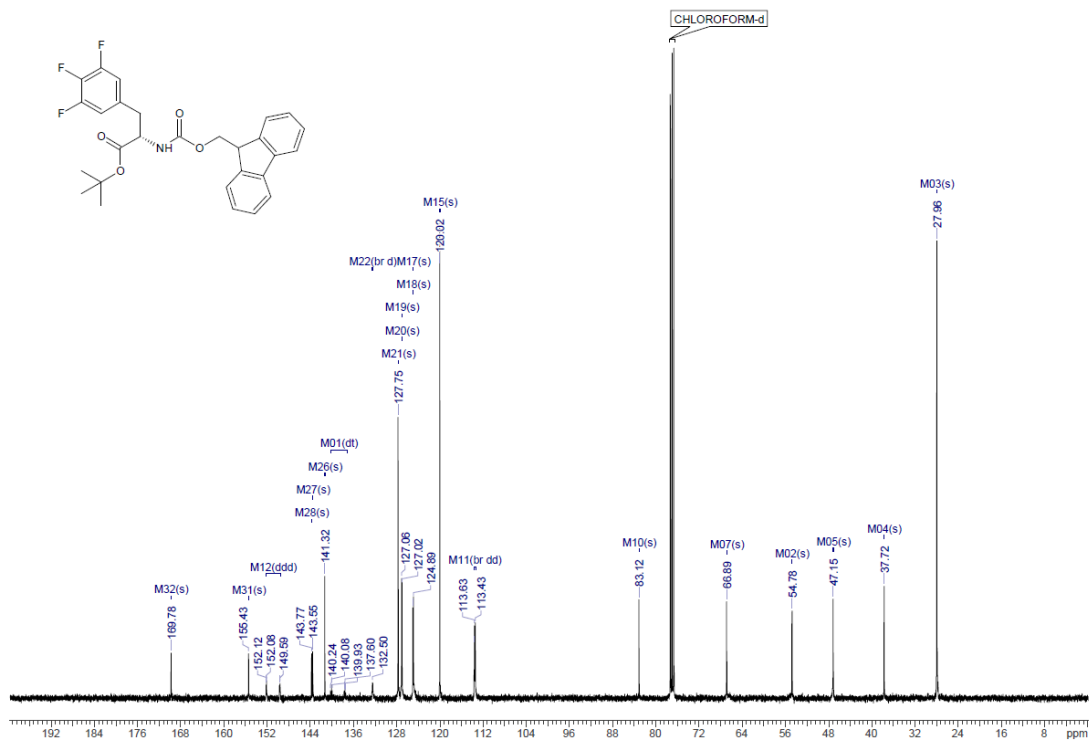
## NMR spectra

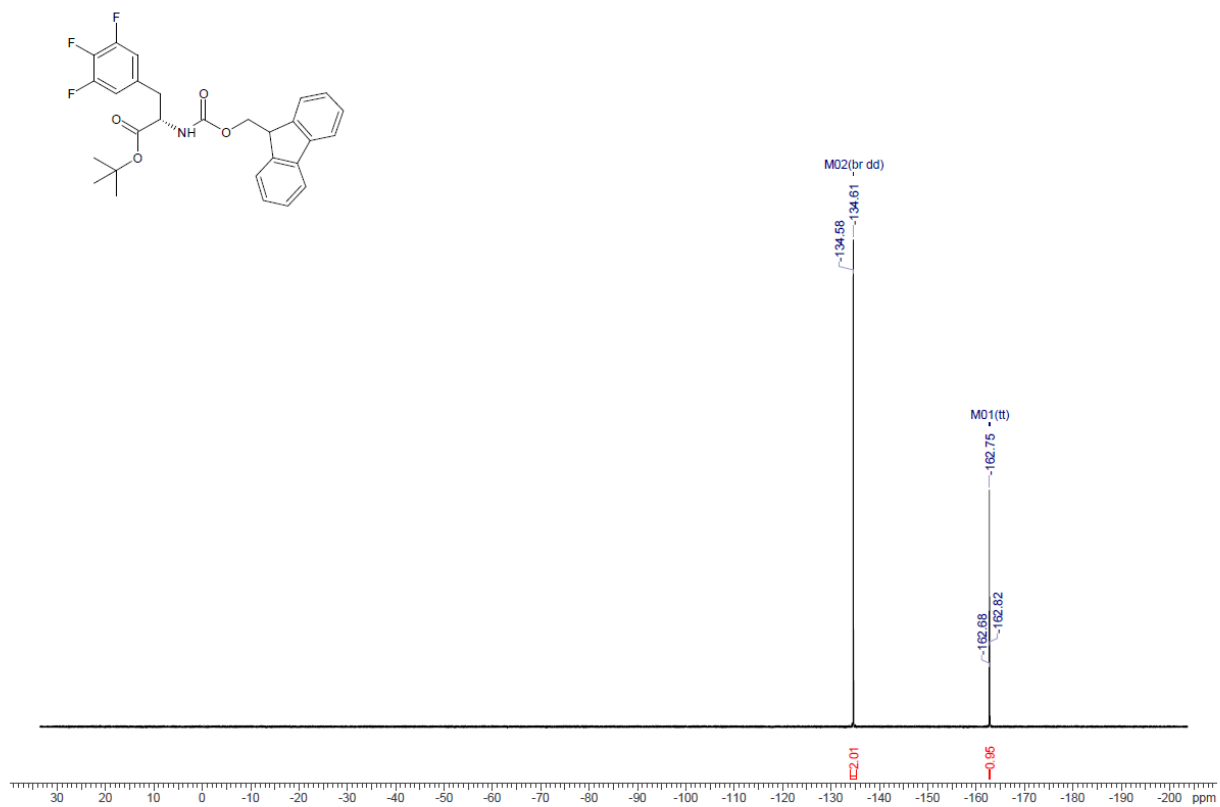
Compound 2 <sup>1</sup>H-NMR:Compound 2 <sup>13</sup>C-NMR:

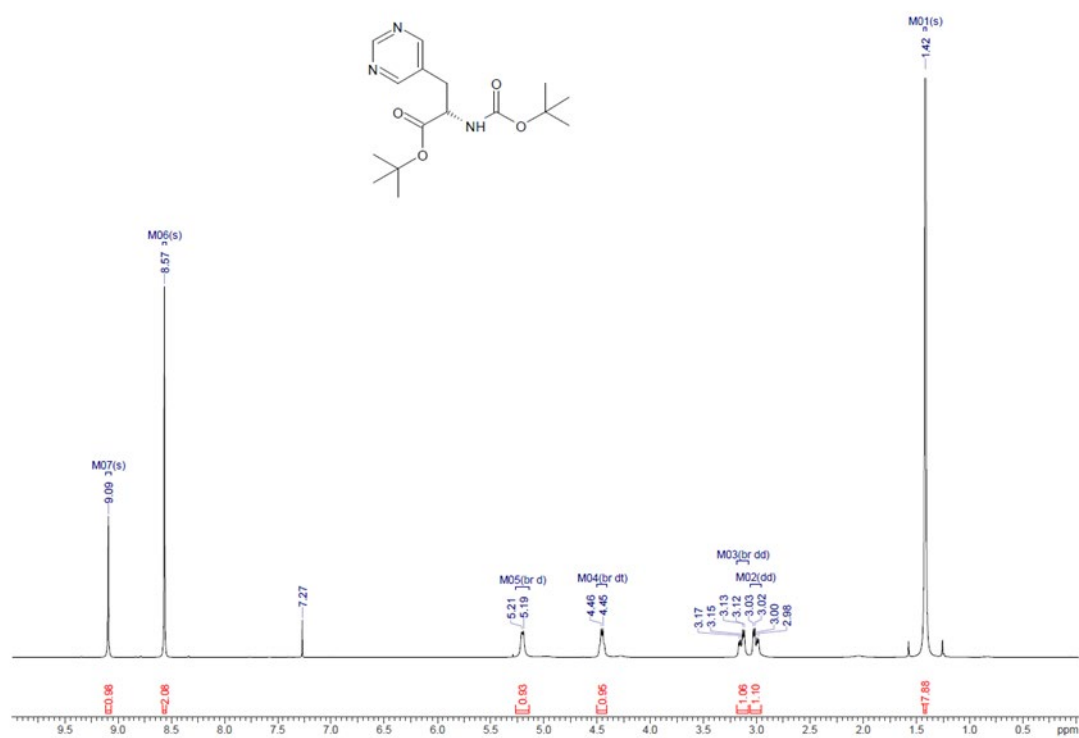
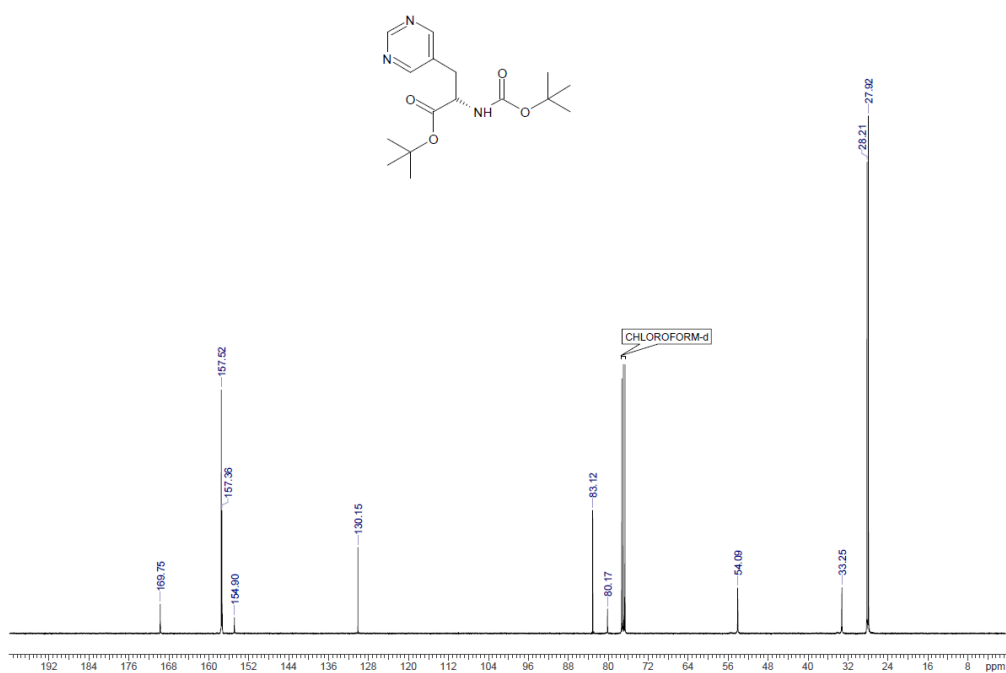
Compound 3 <sup>1</sup>H-NMR:Compound 3 <sup>13</sup>C-NMR:

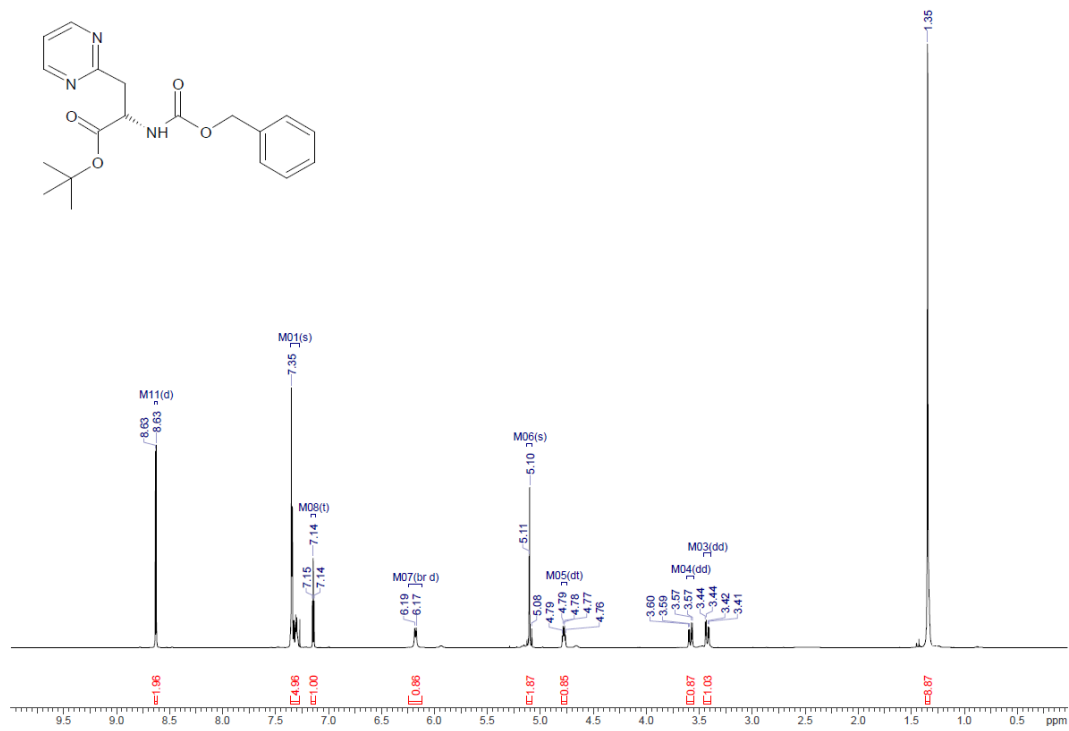
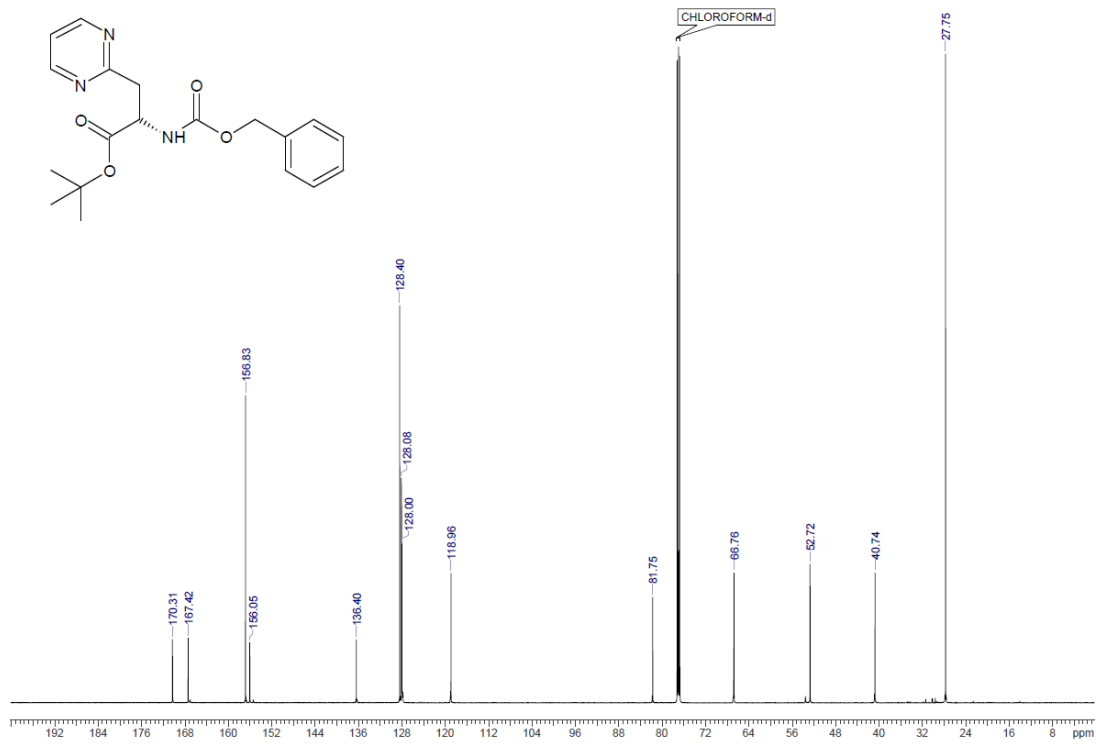
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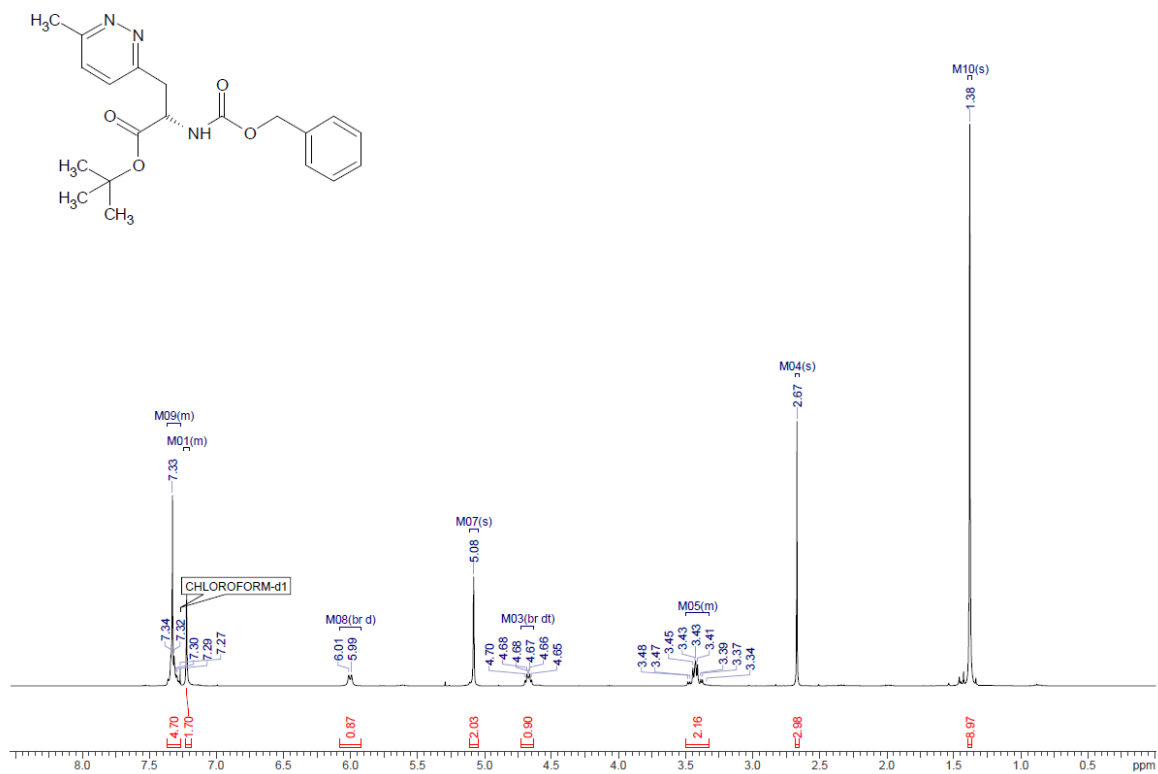
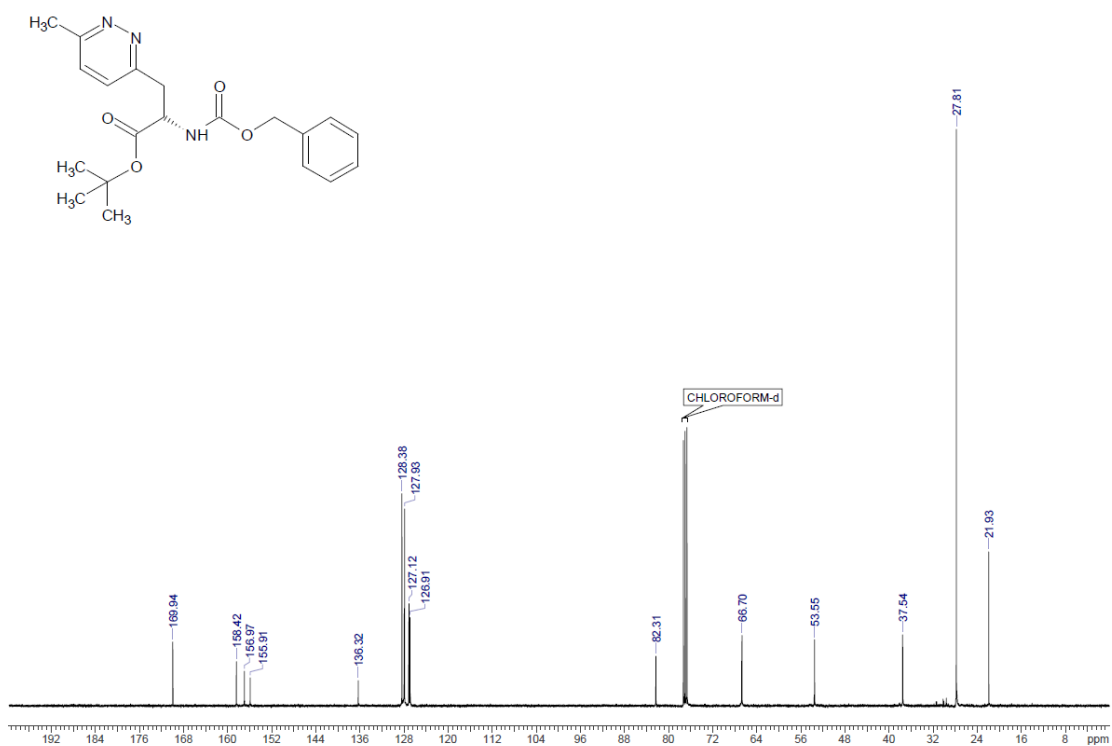
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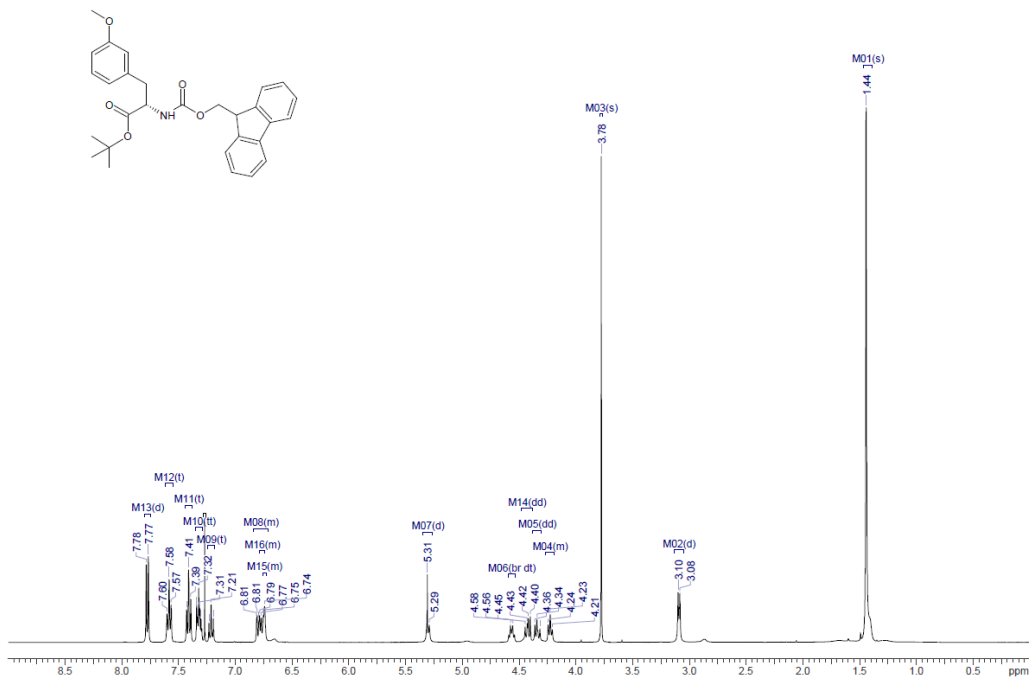
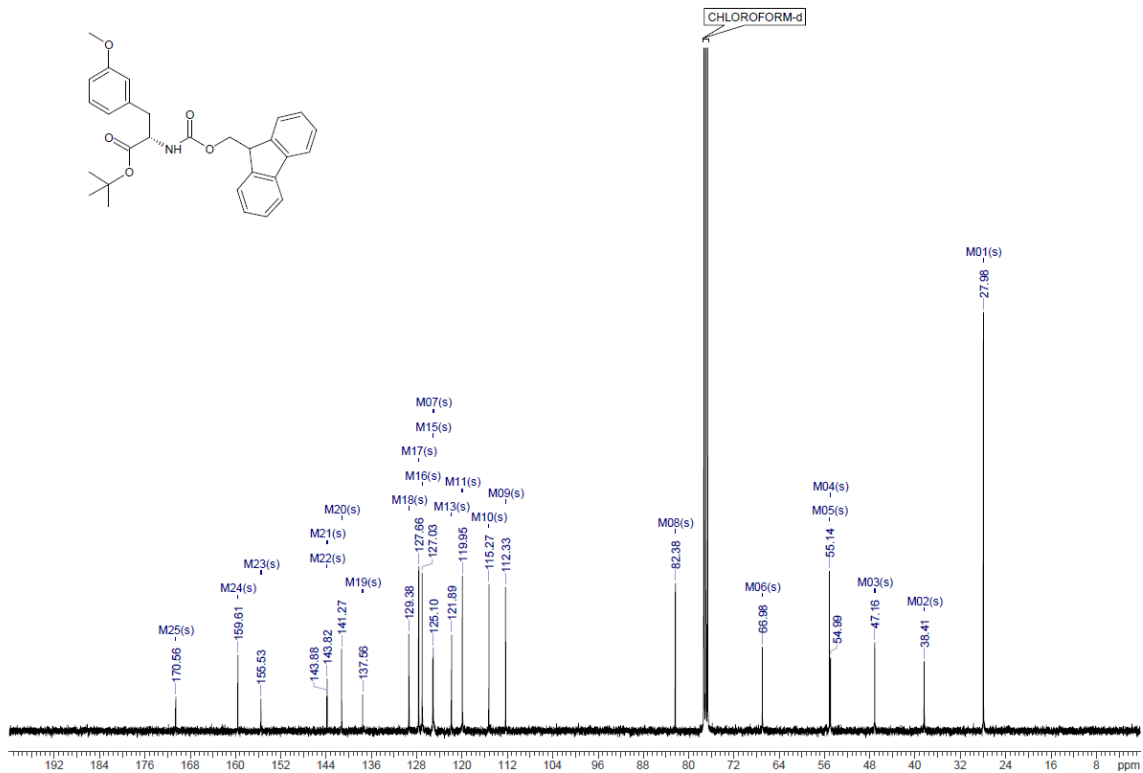
Compound 6 <sup>1</sup>H-NMR:Compound 6 <sup>13</sup>C-NMR:

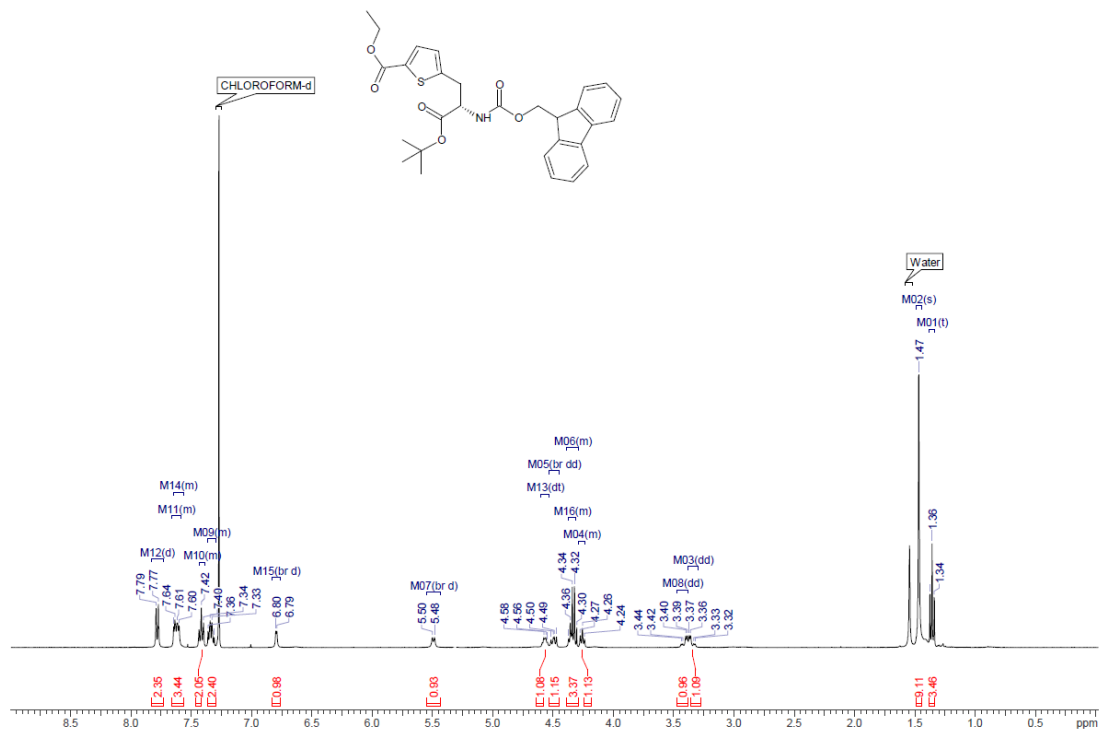
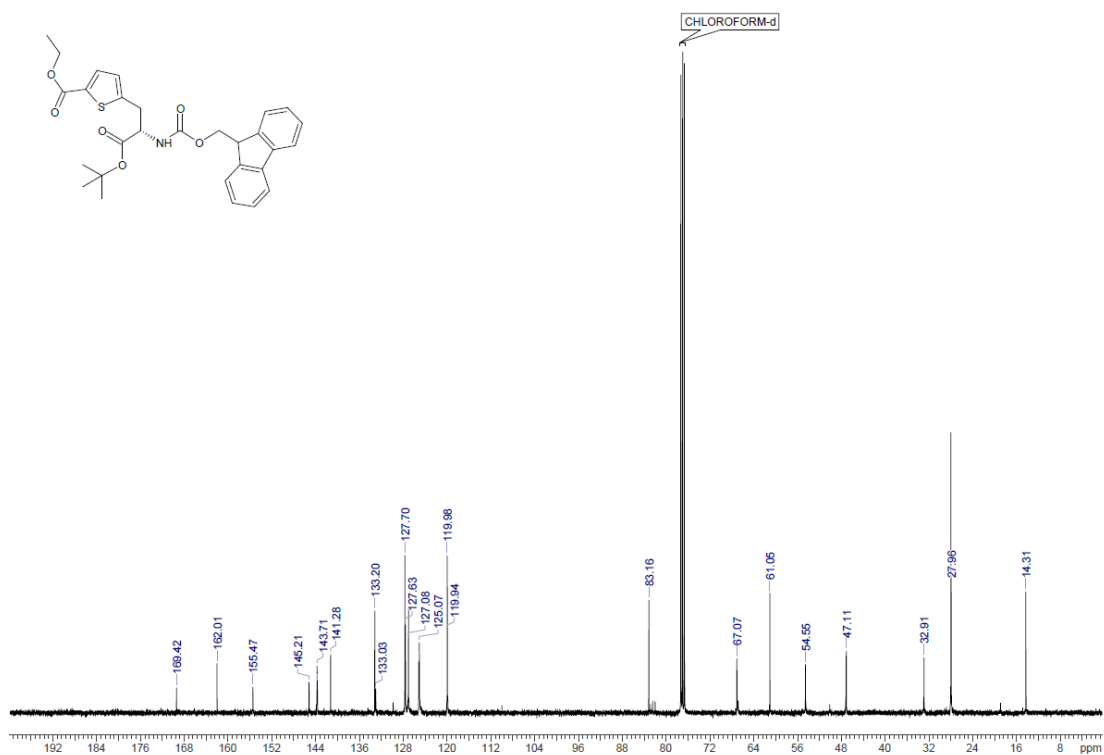
**Compound 6  $^{19}\text{F}$ -NMR:**

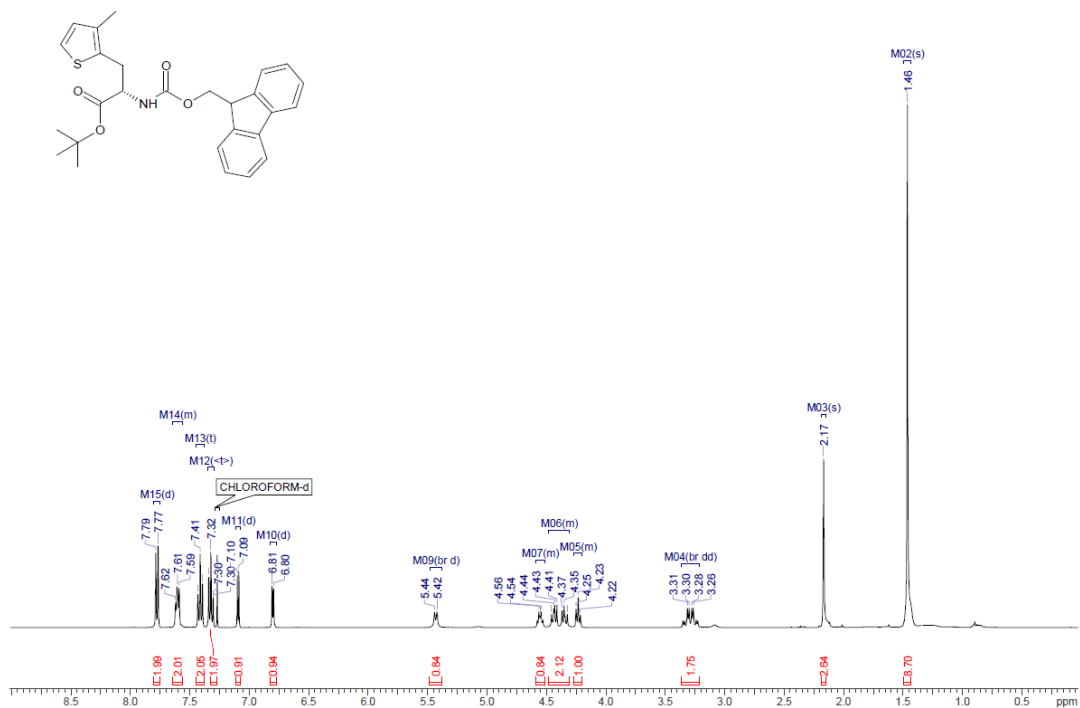
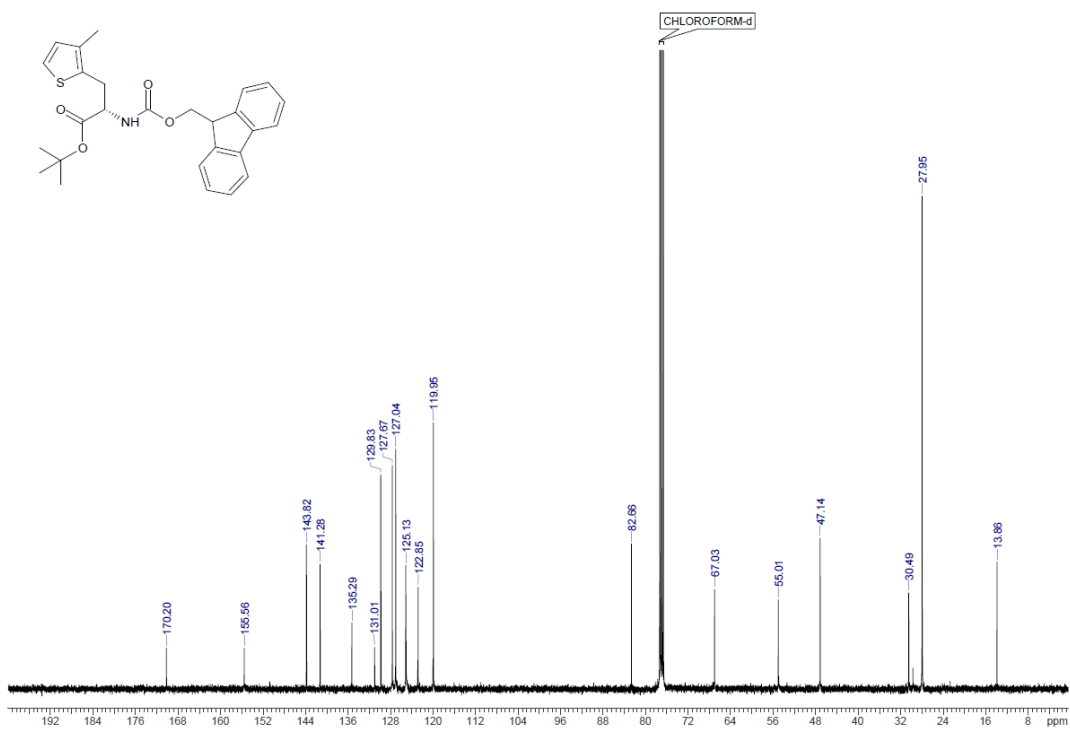
Compound 7  $^1\text{H-NMR}$ :Compound 7  $^{13}\text{C-NMR}$ :

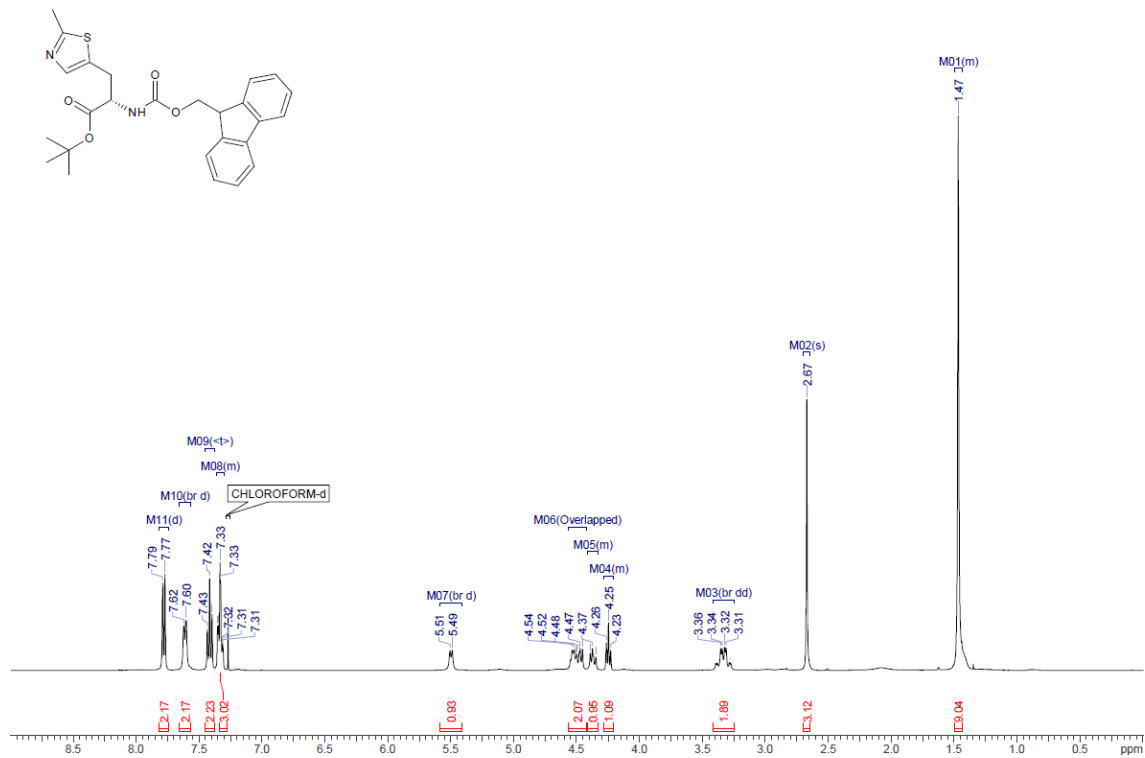
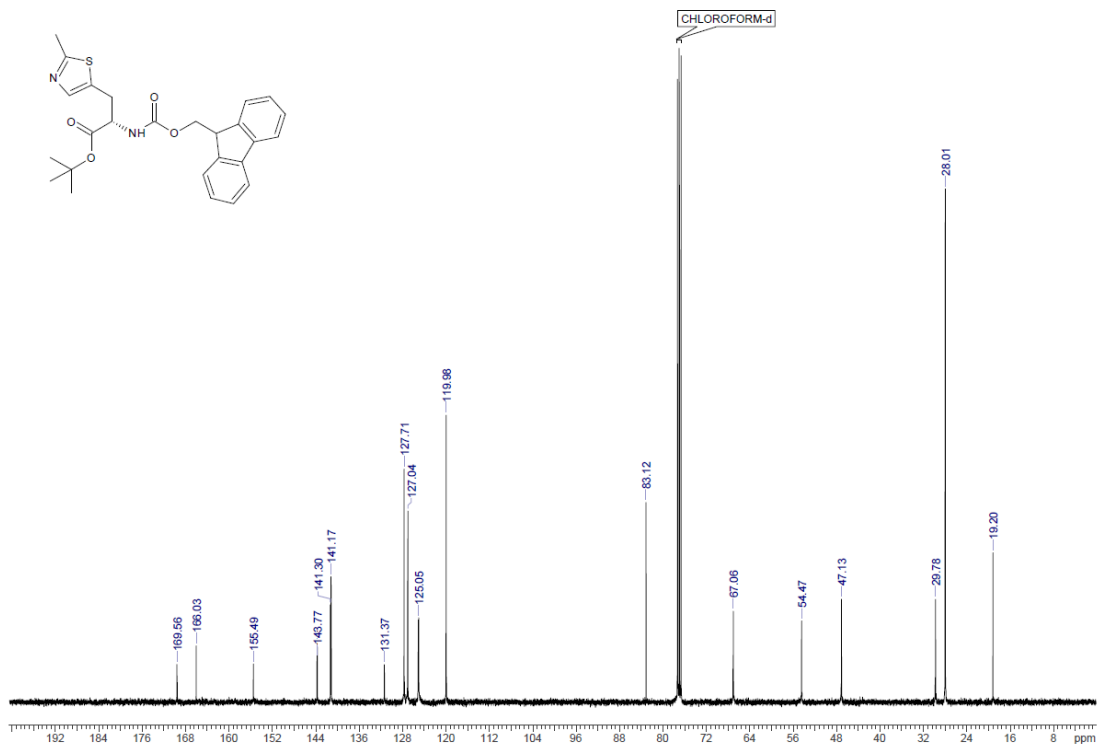
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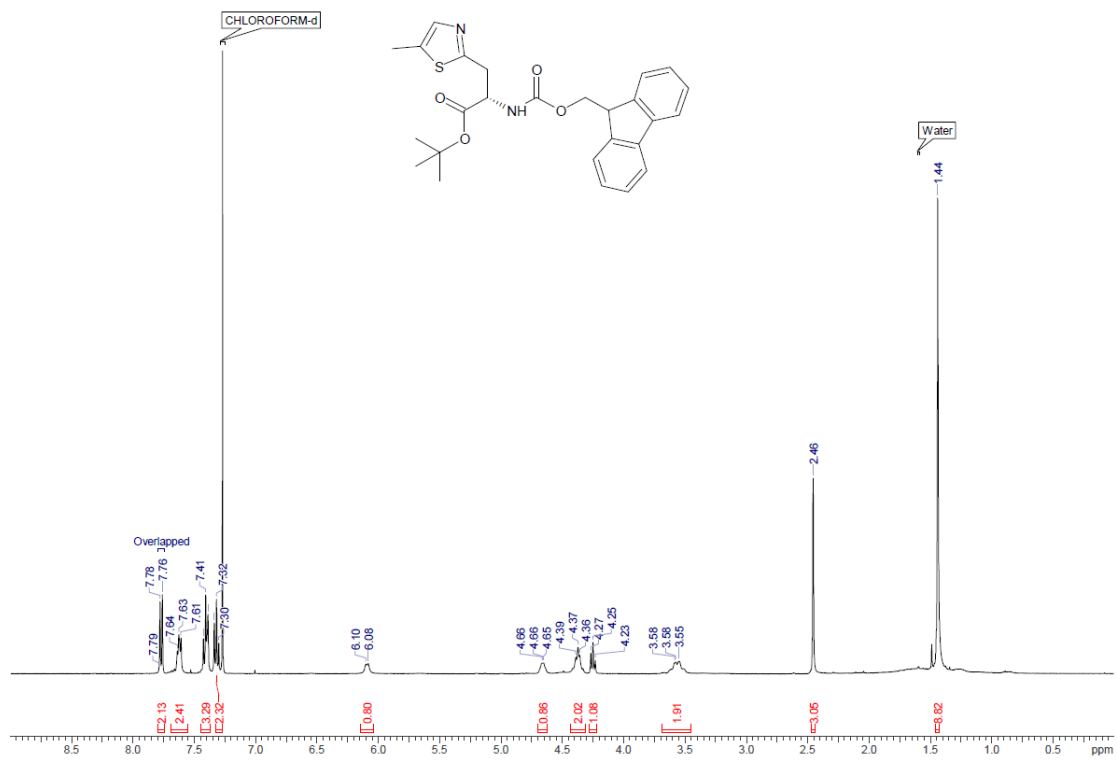
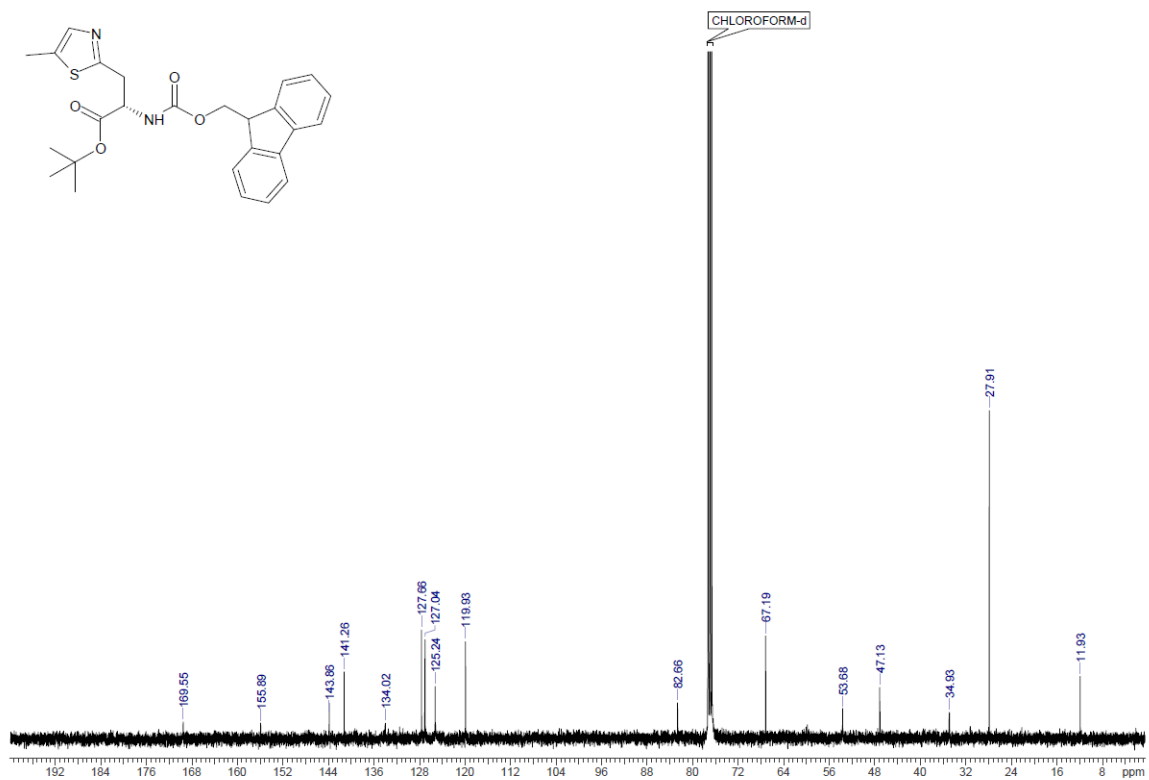
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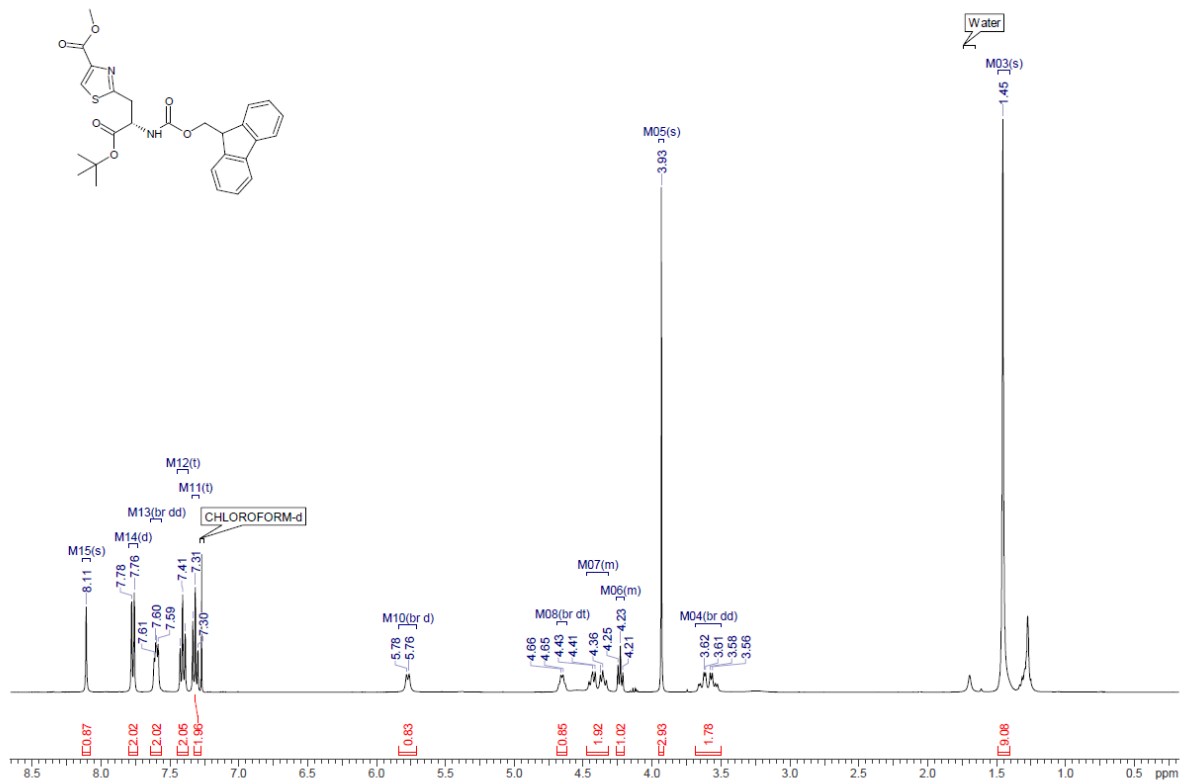
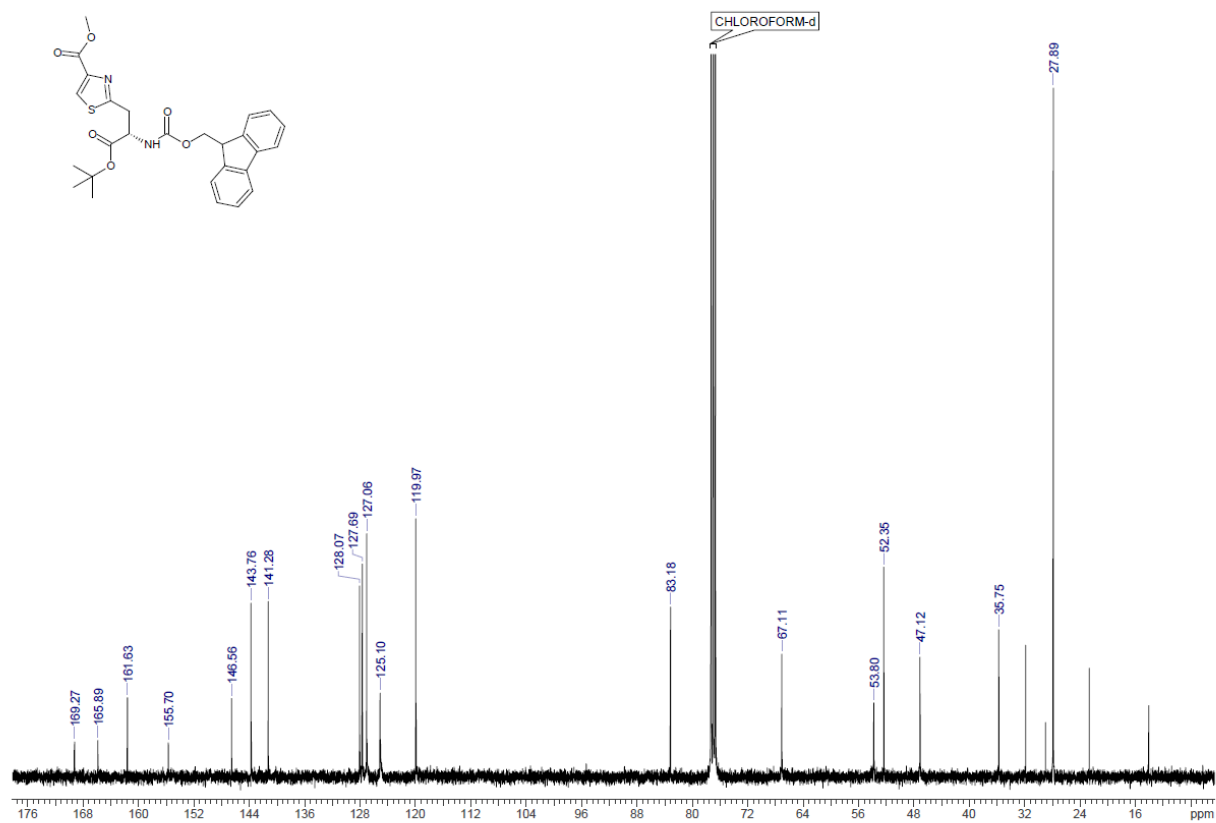
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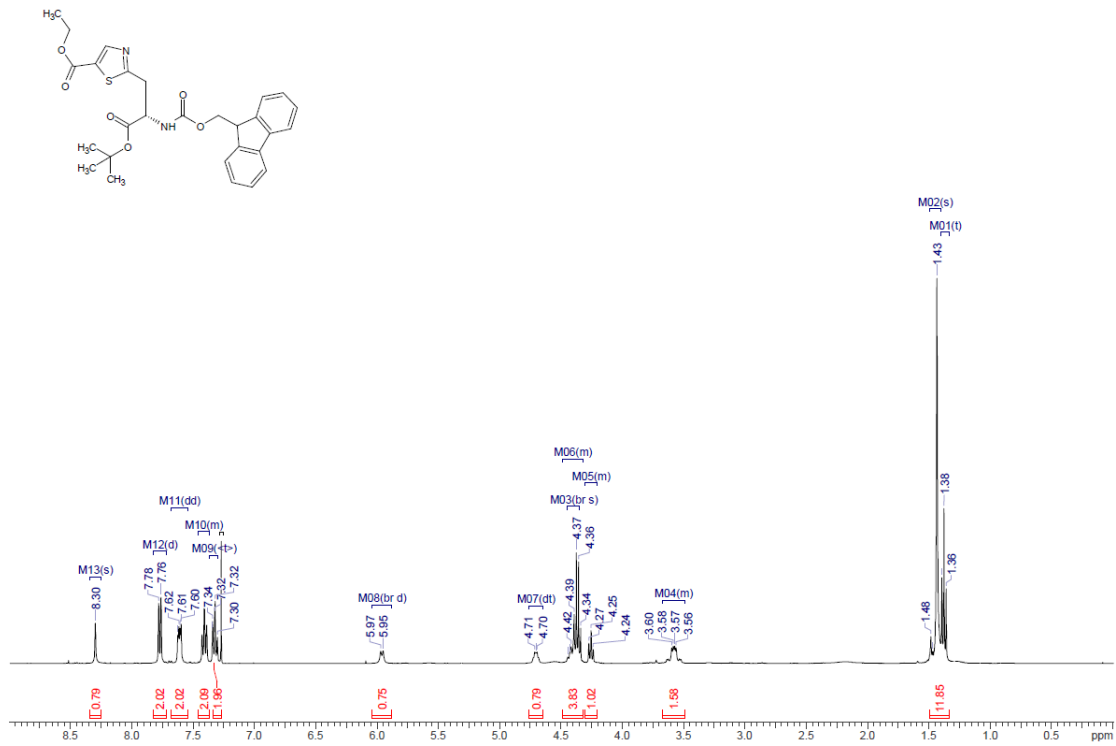
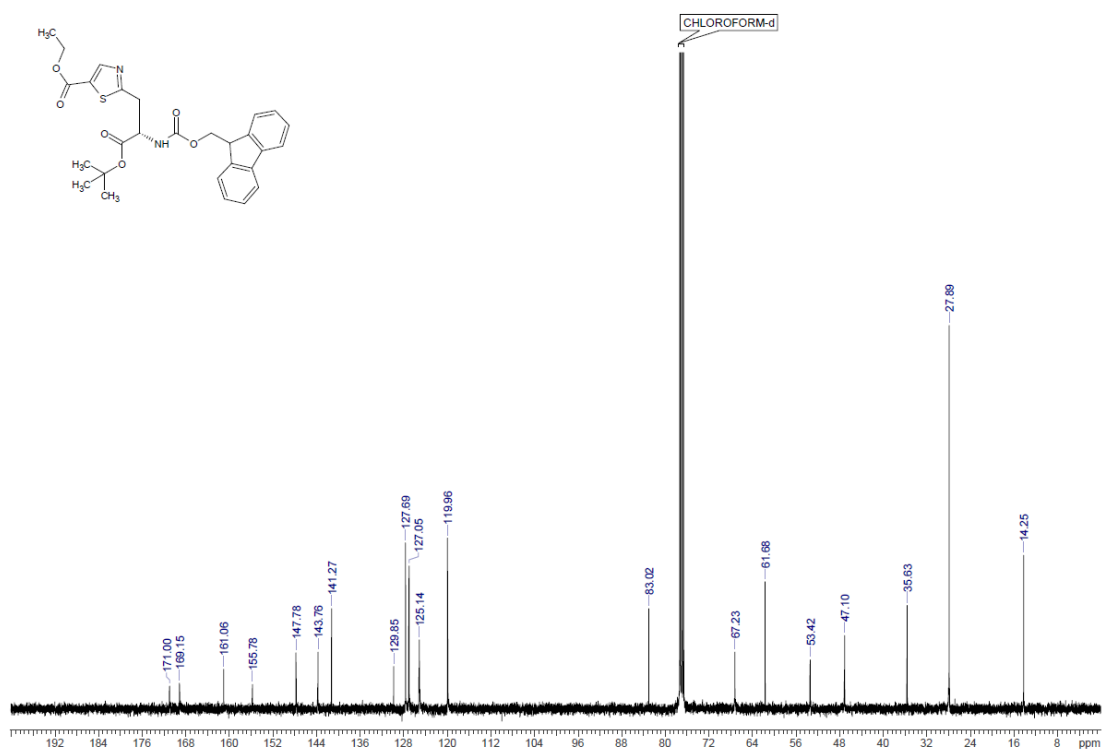
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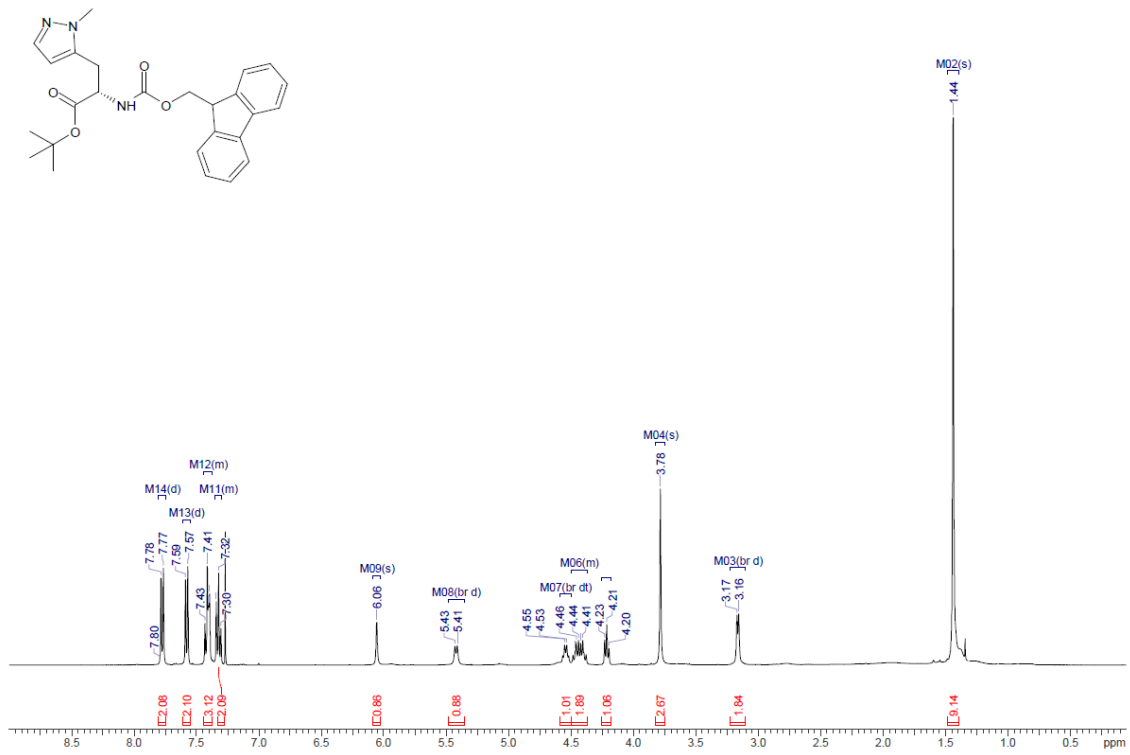
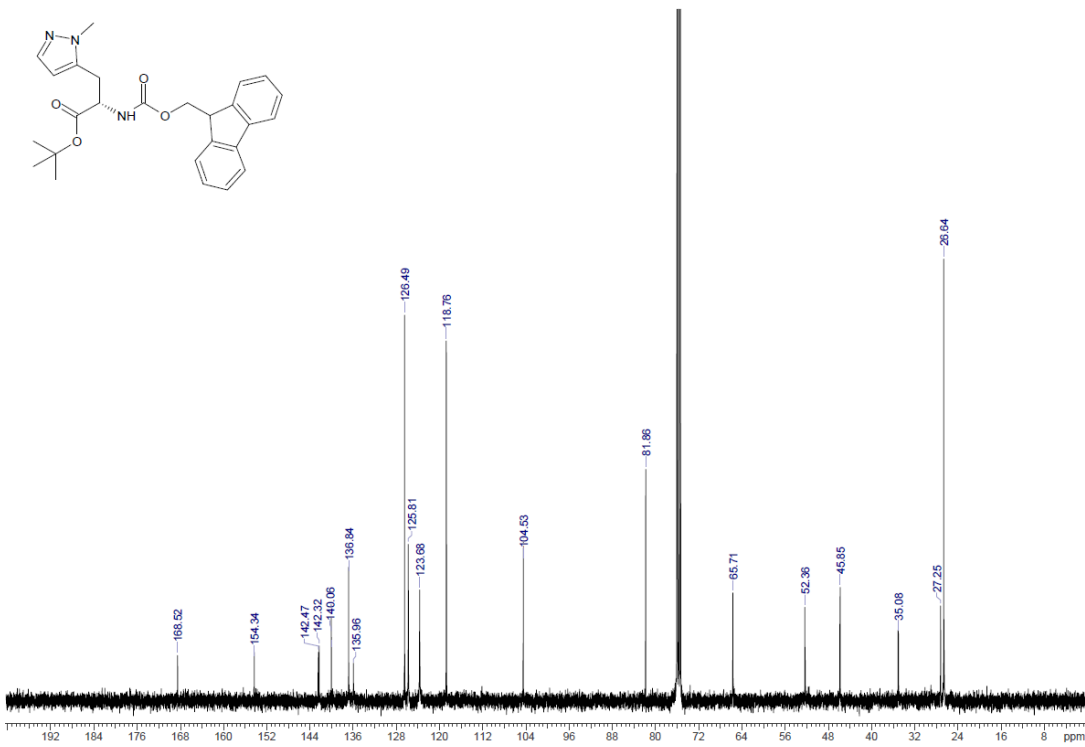
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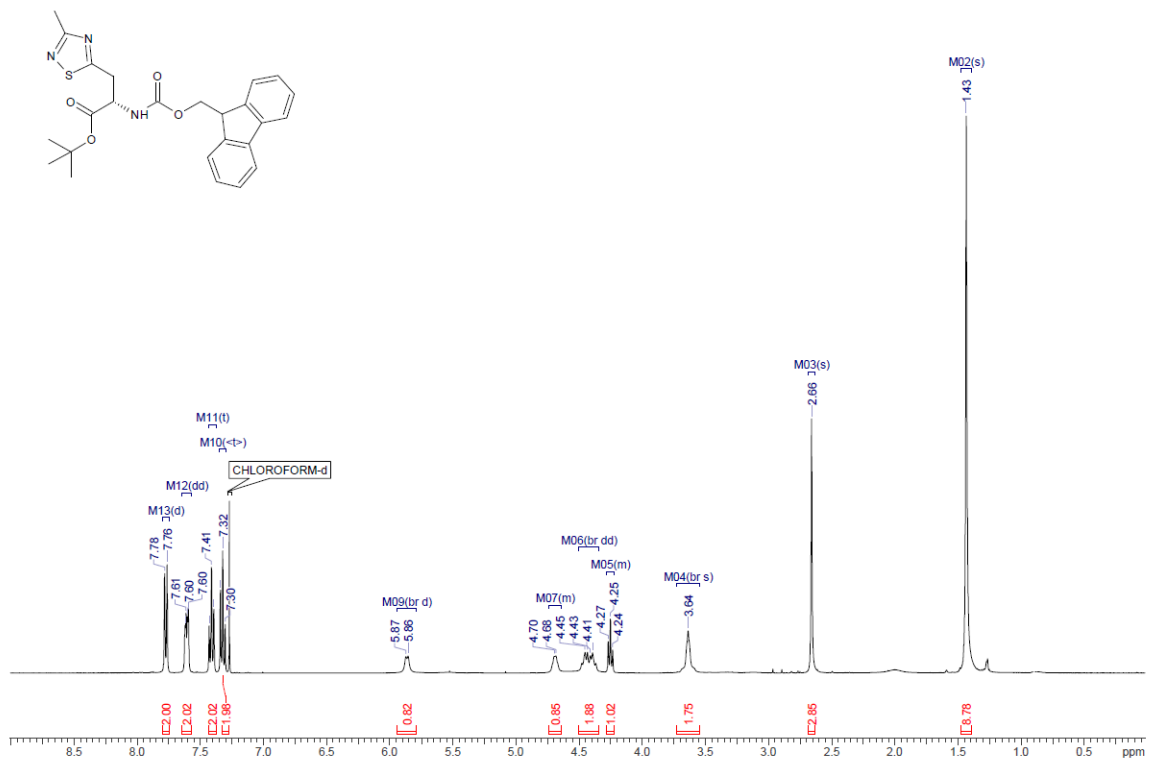
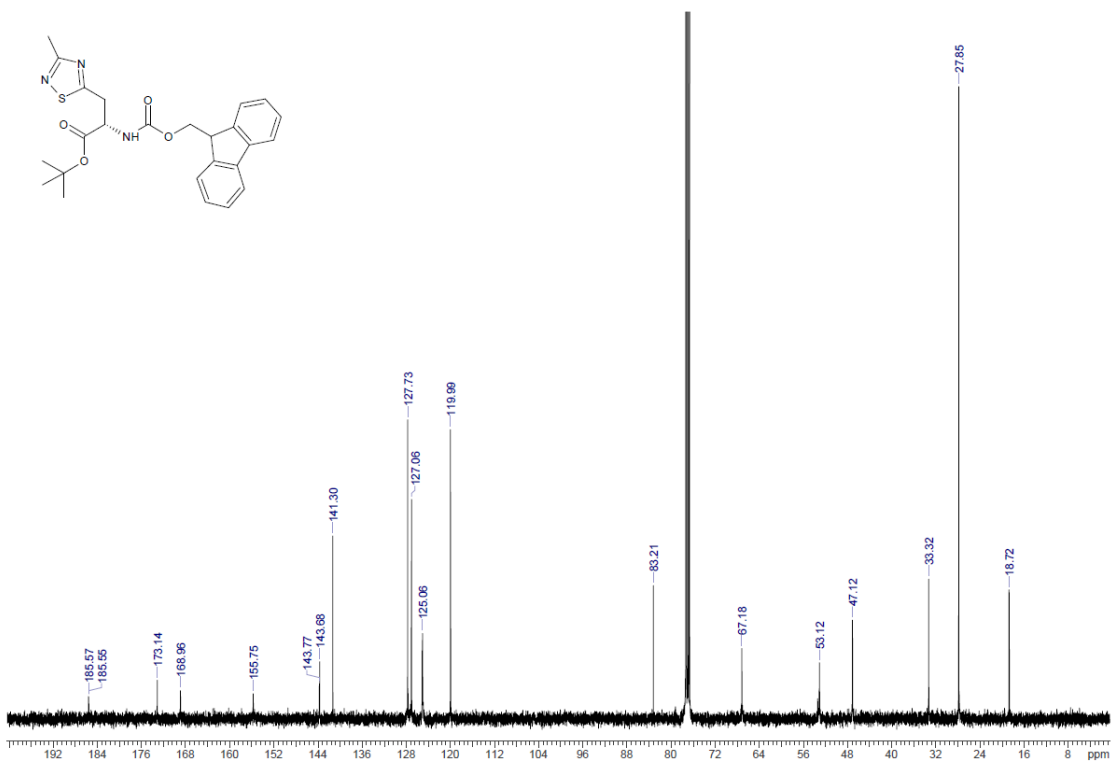
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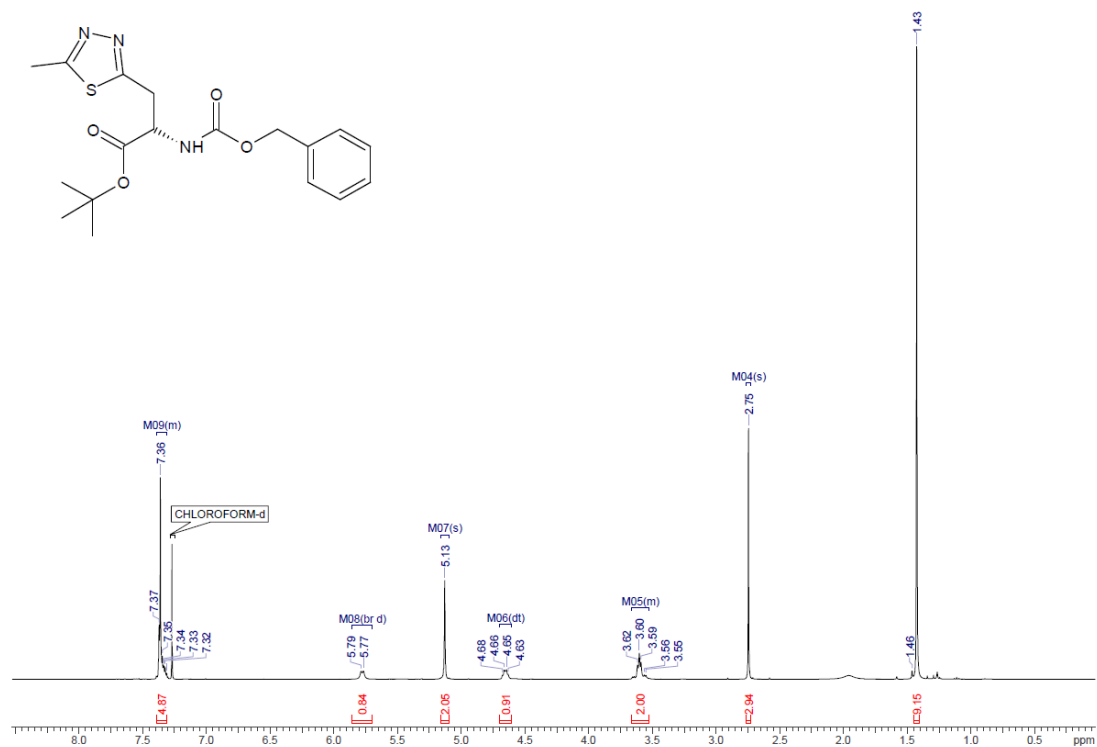
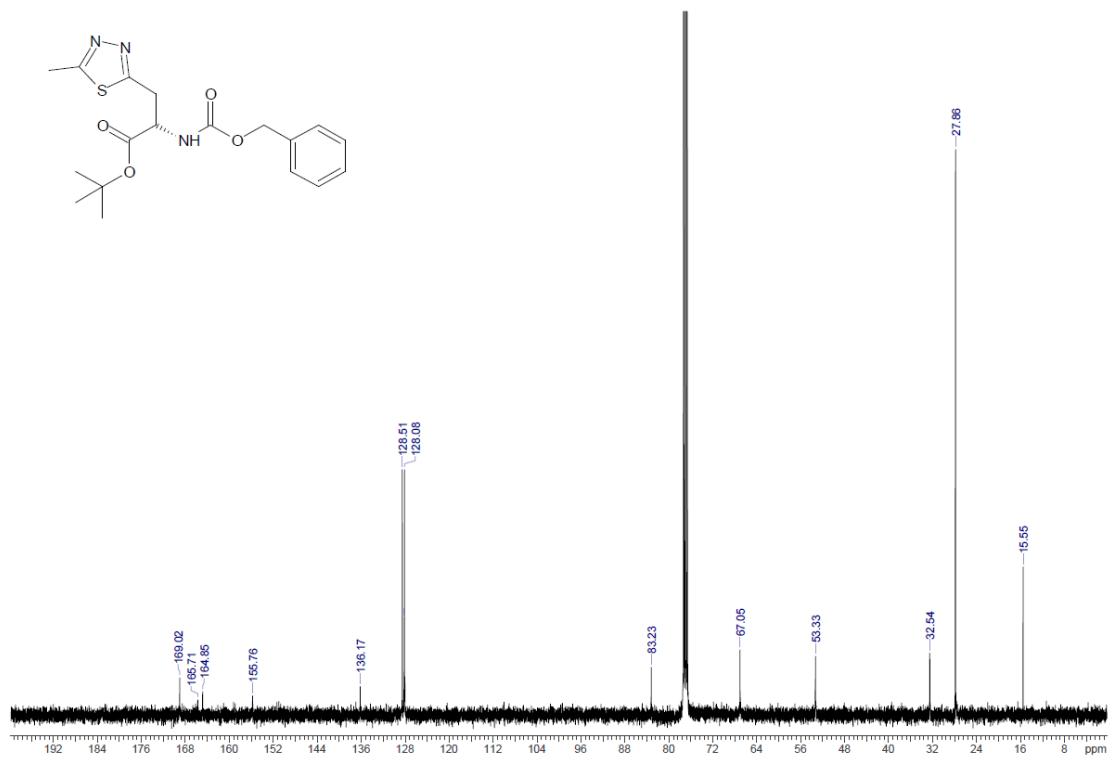
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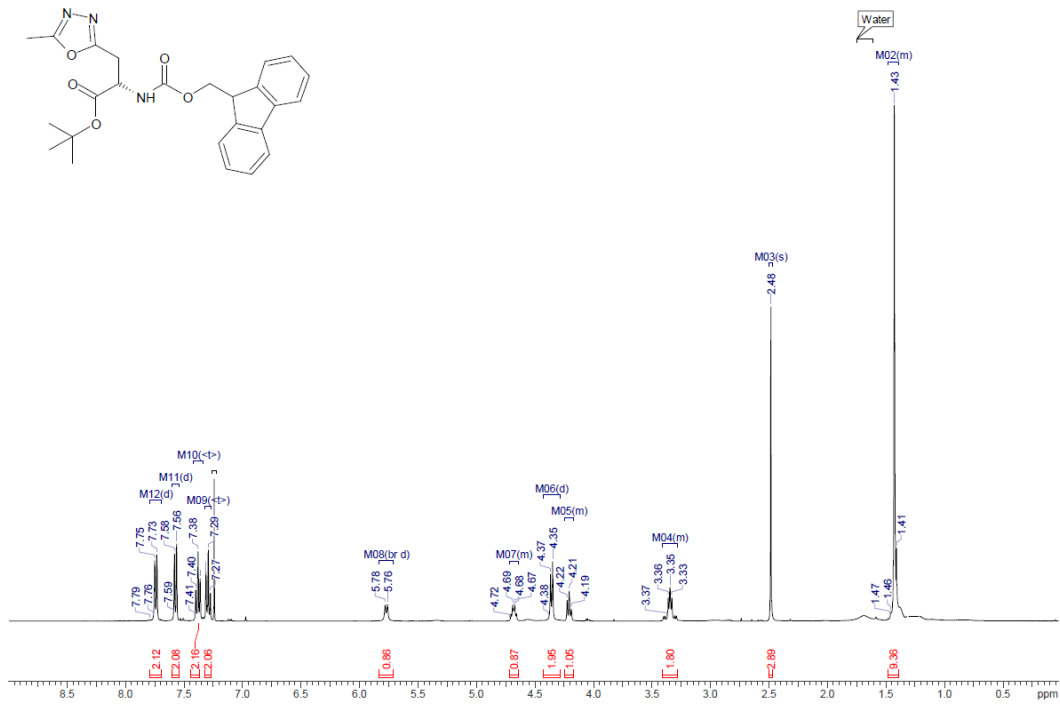
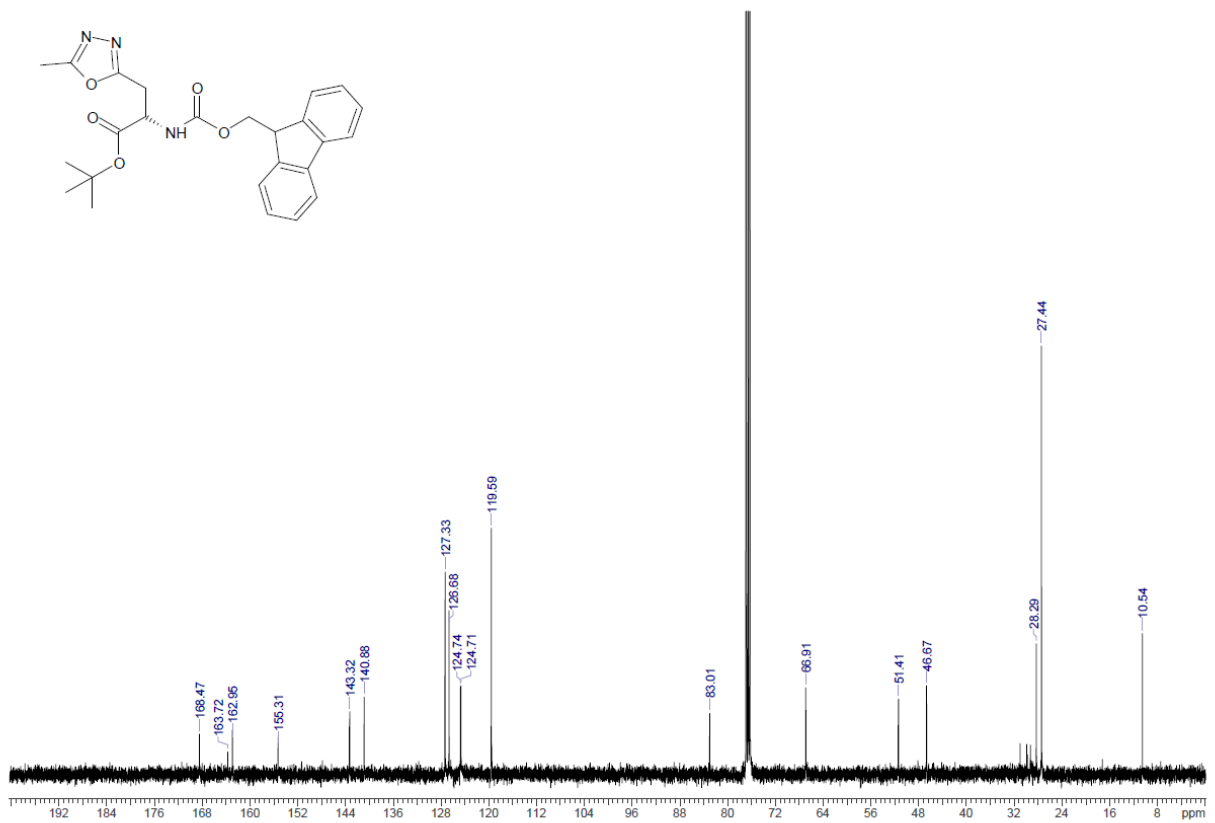
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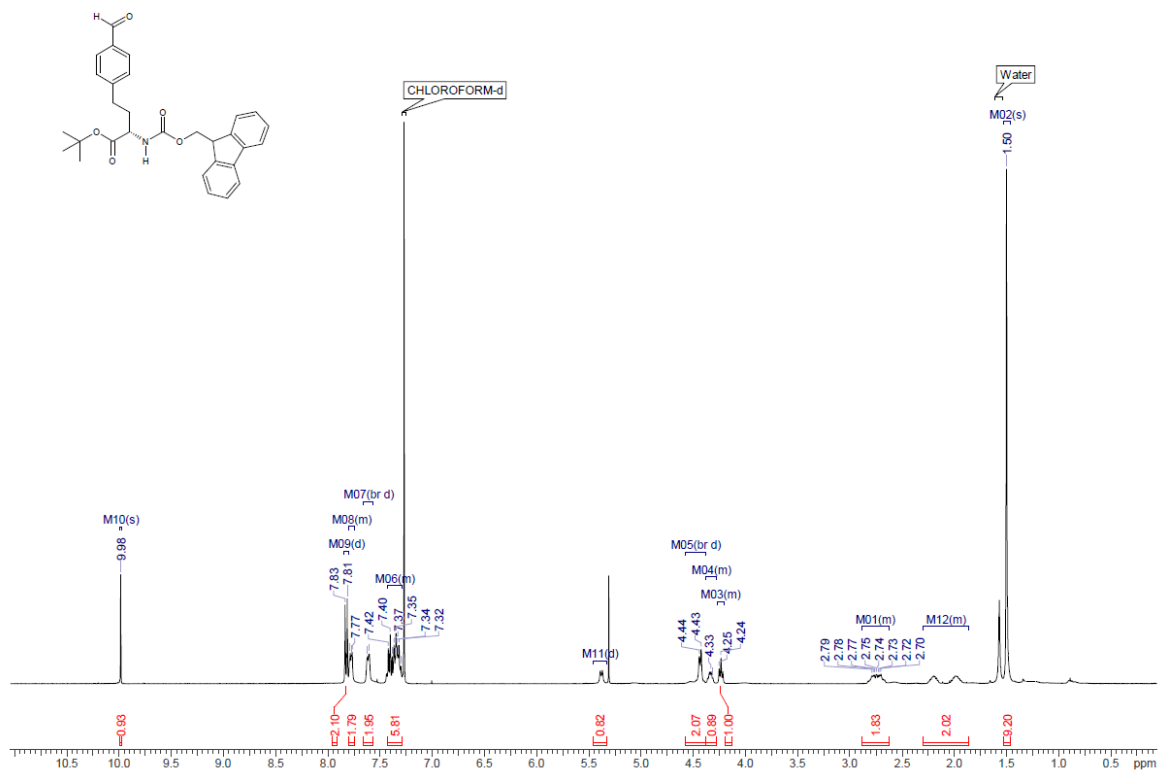
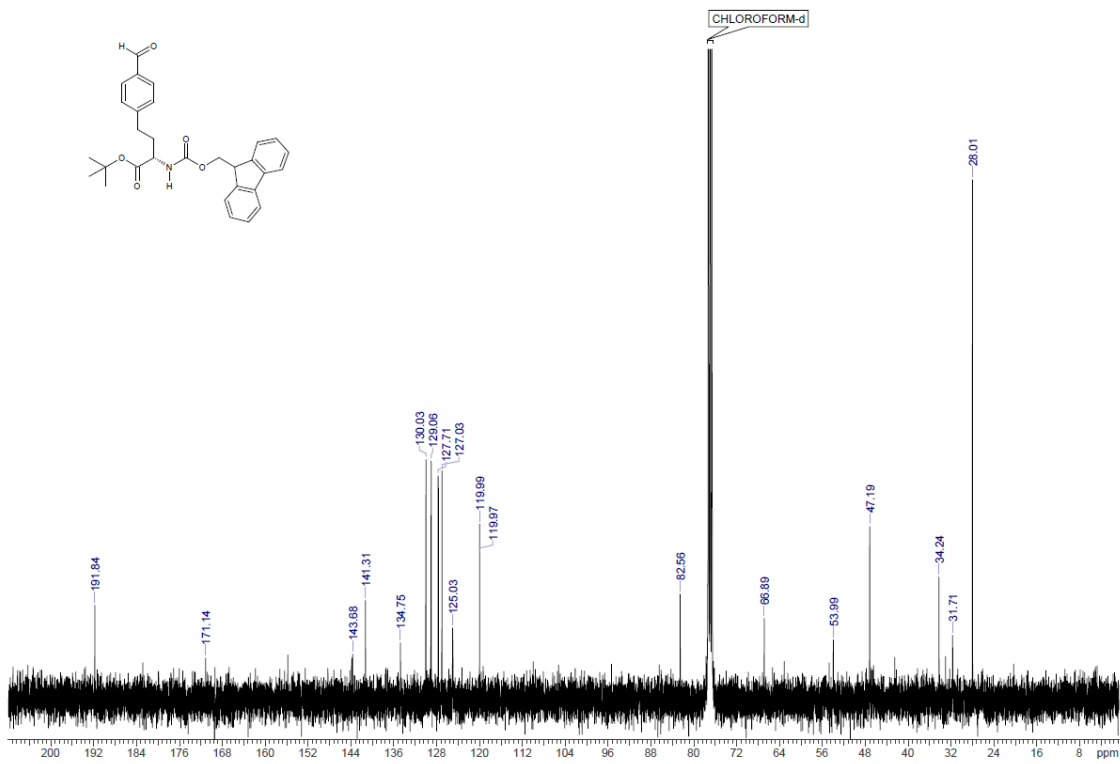
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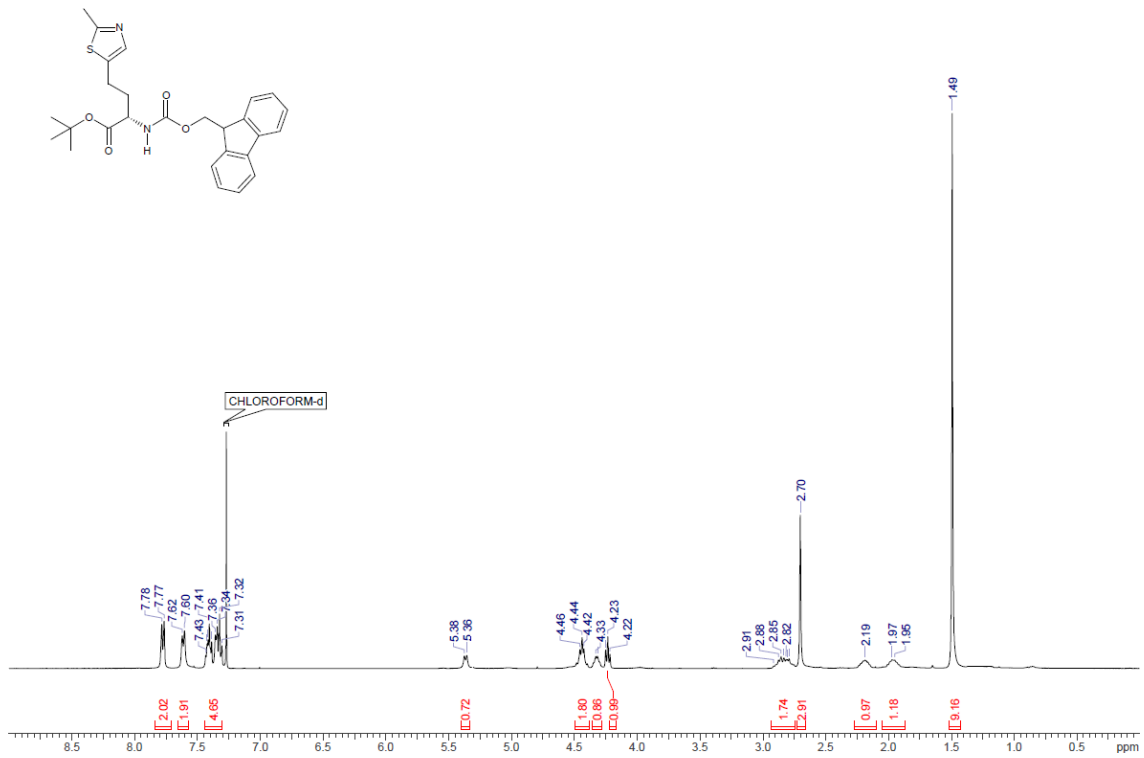
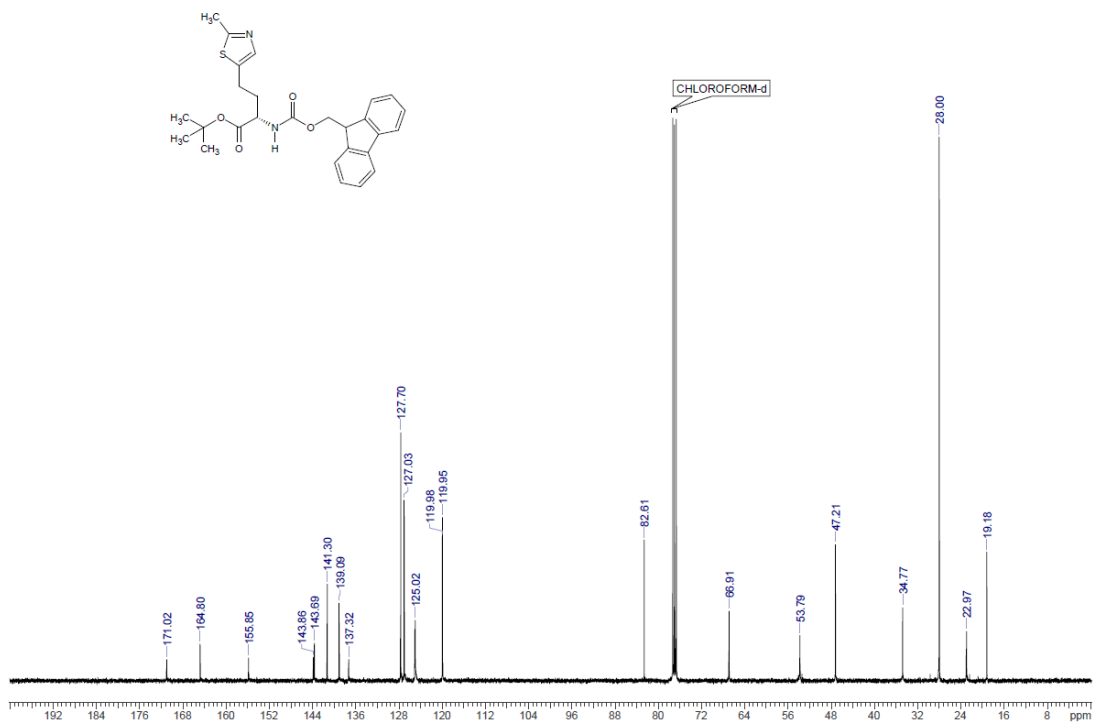
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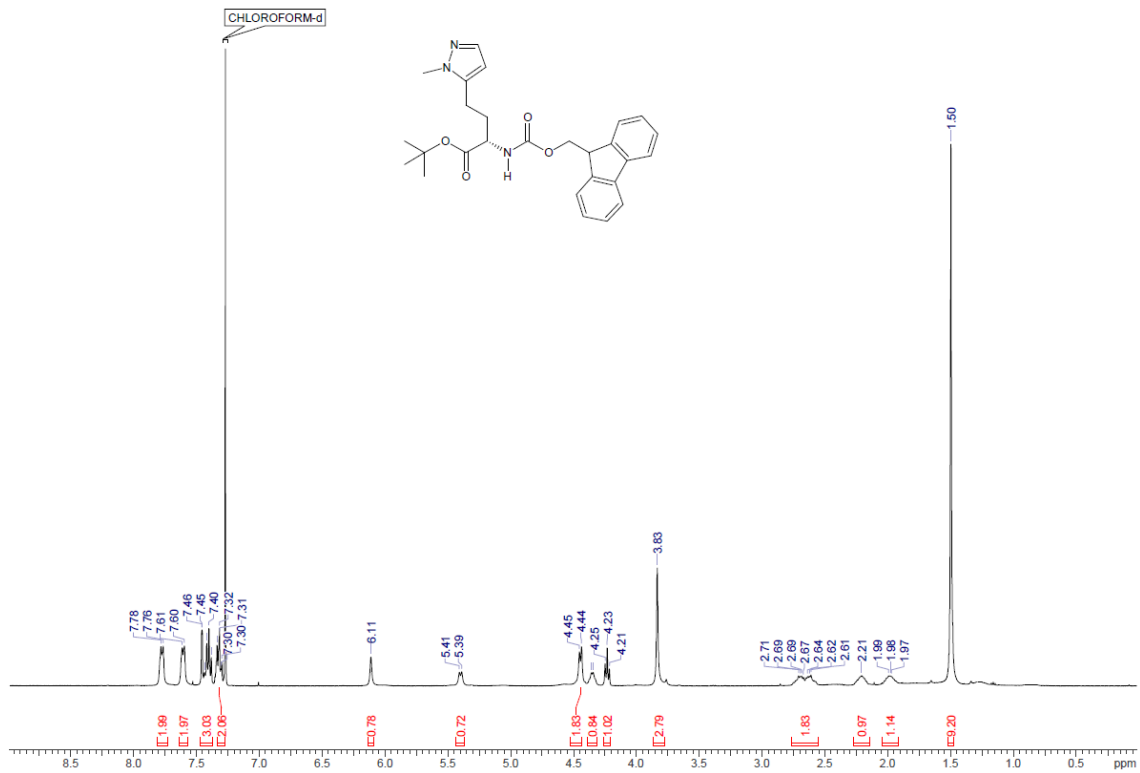
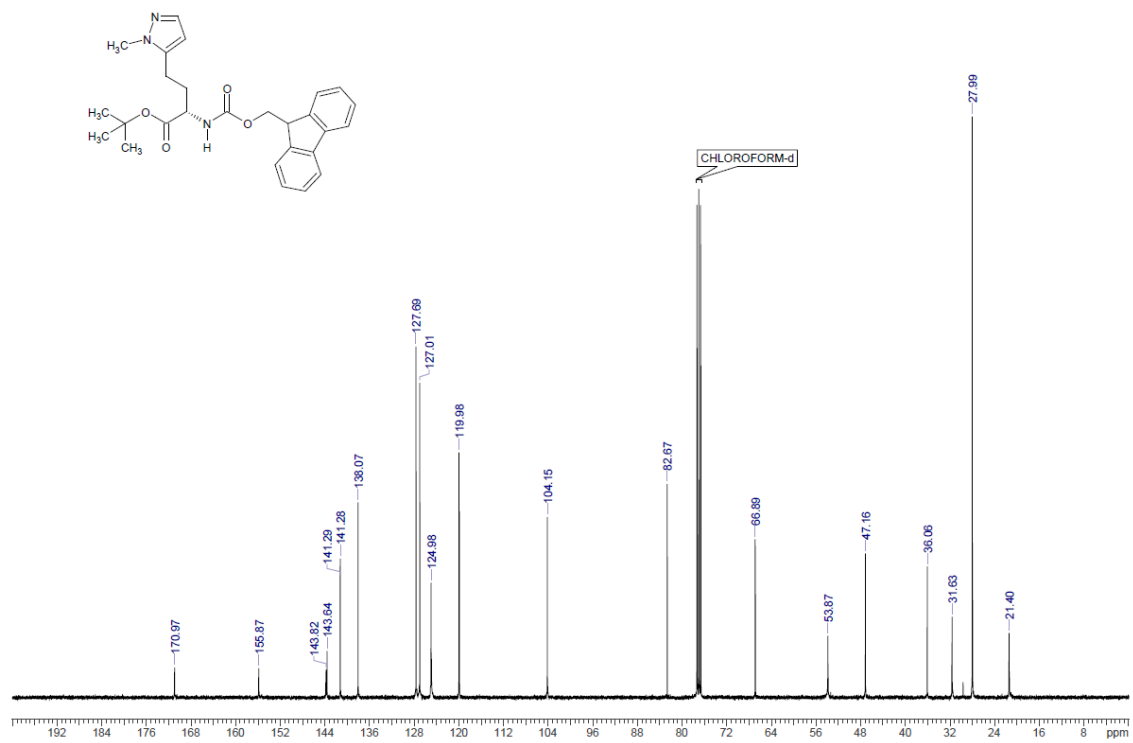
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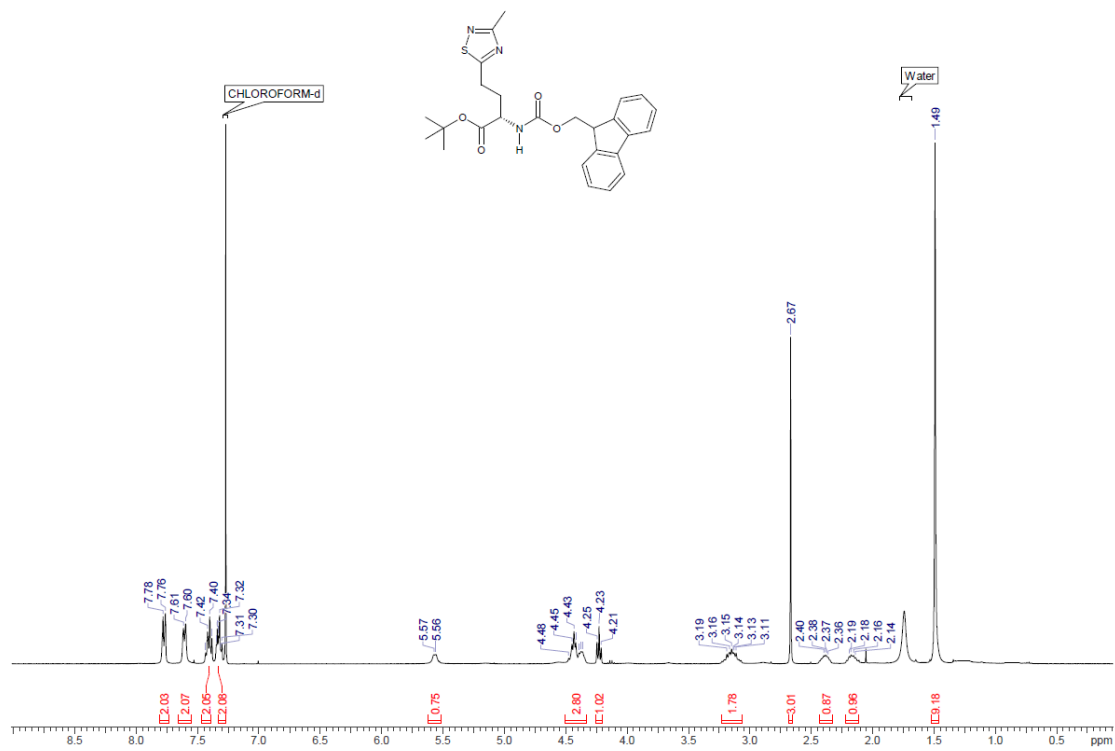
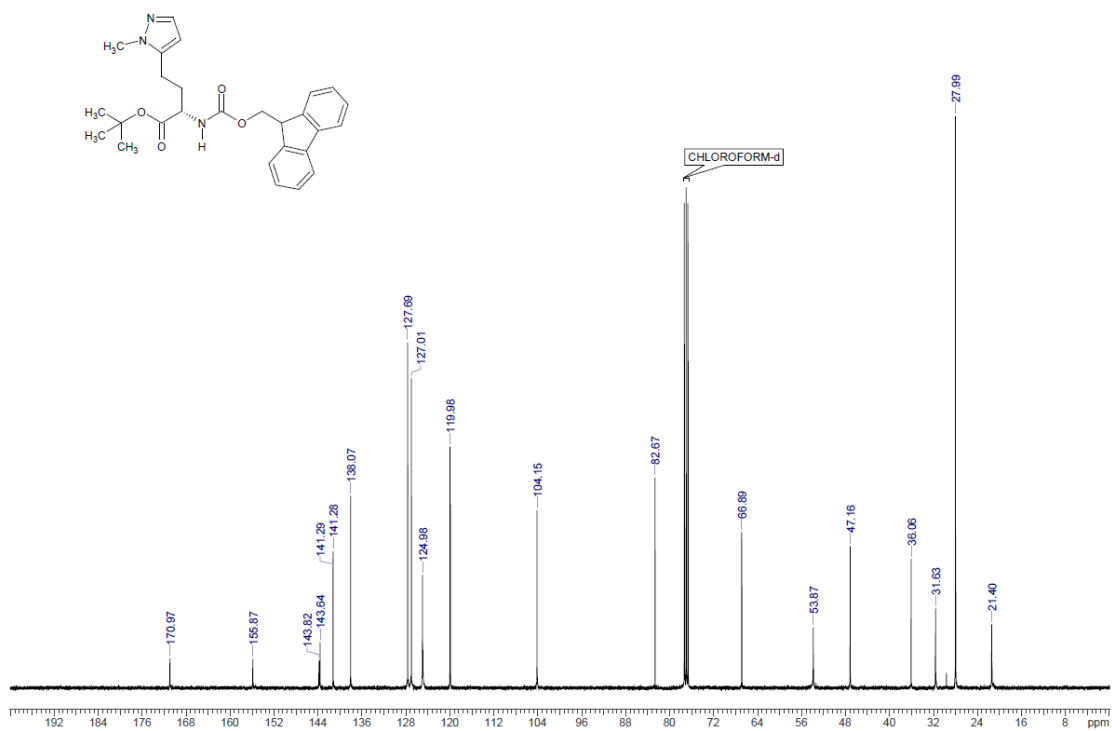
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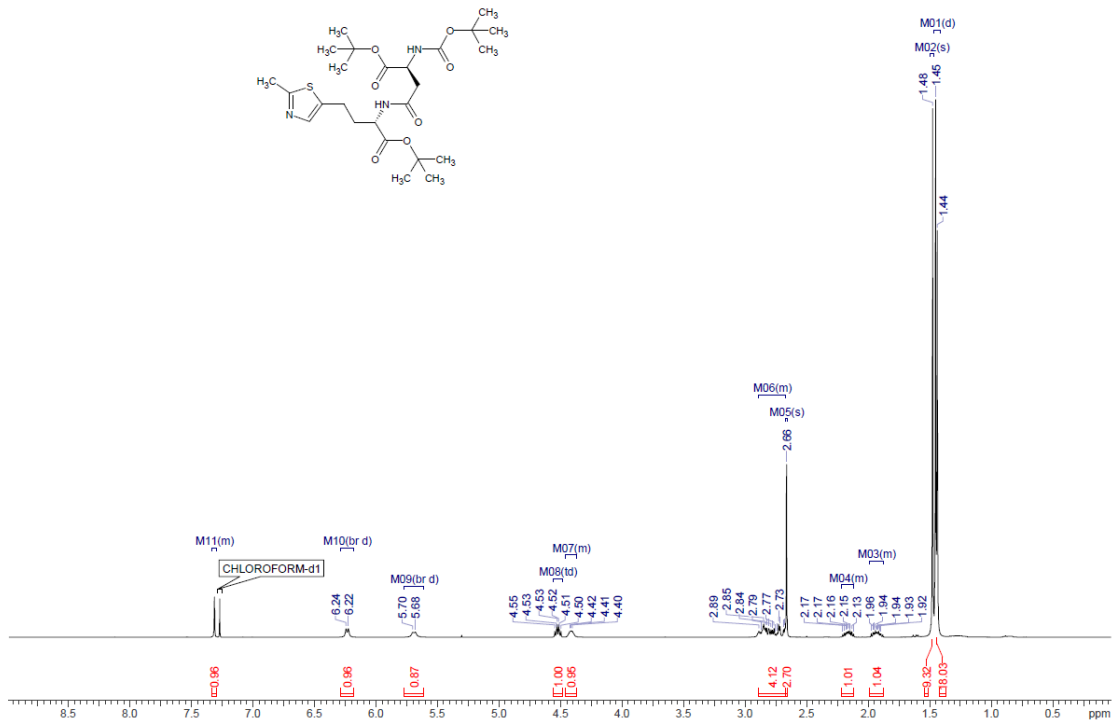
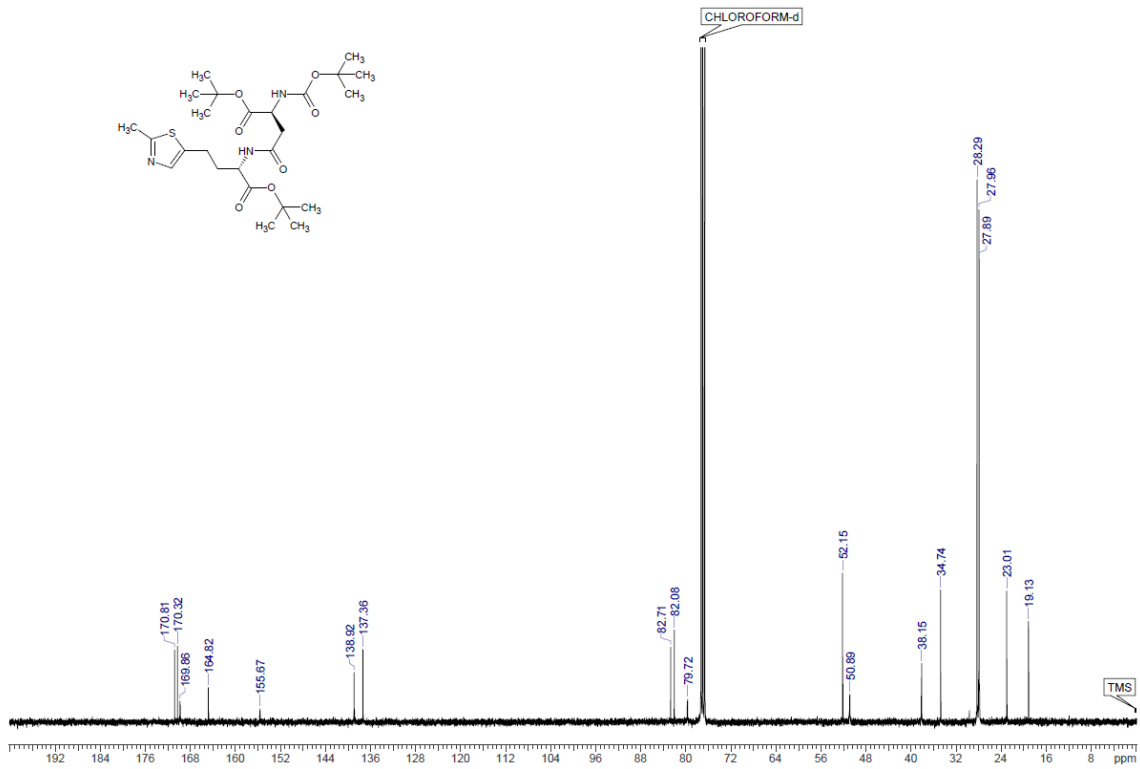
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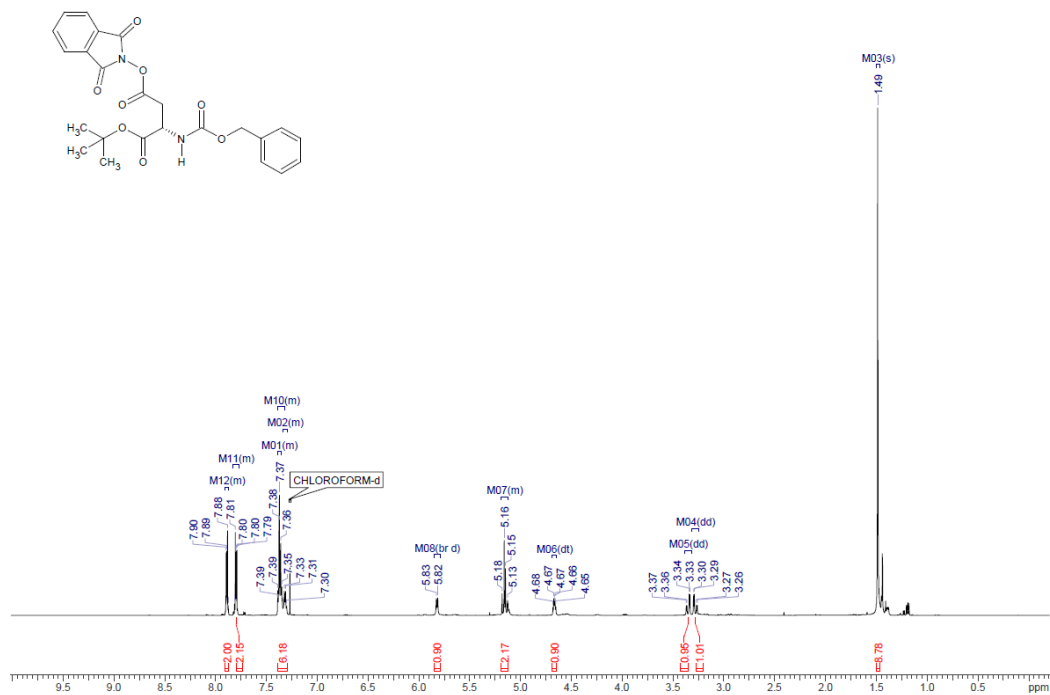
Compound 21 <sup>1</sup>H-NMR:Compound 21 <sup>13</sup>C-NMR:

Compound 22 <sup>1</sup>H-NMR:Compound 22 <sup>13</sup>C-NMR:

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Compound 24 <sup>1</sup>H-NMR:Compound 24 <sup>13</sup>C-NMR:

Compound 25 <sup>1</sup>H-NMR:Compound 25 <sup>13</sup>C-NMR:

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