Supporting Information

Water-Removable Ynamide Coupling Reagent for Racemization-Free Syntheses of Peptides, Amides, and Esters

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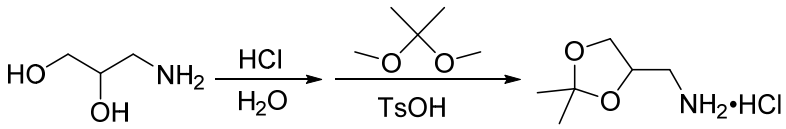
1. General Information

Unless otherwise stated, all components as well as reagents and solvents were bought from commercial suppliers (Leyan, Energy Chemical) and used without further purification. TLC analysis was performed using commercially prepared silica gel plates, and visualization was affected at ultraviolet light (254 nm). ^{1}H and ^{13}C spectra were recorded on a Bruker (400 MHz for ^{1}H and 100 MHz for ^{13}C respectively) instrument, and are internally referenced to residual solvent signals, $CDCl_3$ referenced at δ 7.26 and 77.00 ppm, DMSO-d_6 referenced at δ 2.50 and 39.8 ppm. Data for ^{1}H is reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), broad peaks (br), coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz) and no special nomenclature is used for equivalent carbons. HRMS (ESI) spectra were obtained by the electrospray ionization time-of-flight (ESI-TOF) mass spectrometry. Analytical HPLC was performed on an UltiMate 3000 HPLC system with appropriate columns and elution conditions.

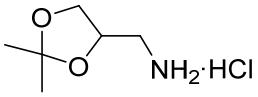
2. Synthesis of water-removable ynamide

The synthesis of (2,2-dimethyl-1,3-dioxolan-4-yl)methanamine hydrochloride



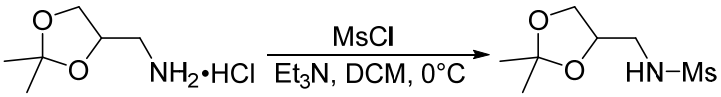
In a round bottom flask, 3-aminopropane-1,2-diol (100 mmol, 1.0 equiv.) was dissolved in water (20 mL). The pH value of the solution was adjusted to 1 with 3 M HCl. The reaction mixture was stirred for 20 min at room temperature and then was concentrated under vacuum. Upon completion, the obtained mixture were gradually added 2,2-dimethoxypropane (100 mL), and TsOH (4 mmol, 0.04 equiv.). After the reflux of crude mixture for 1 h, the solid was collected by filtering and washing with acetone to get (2,2-dimethyl-1,3-dioxolan-4-yl)methanamine hydrochloride (15.9 g, 95% yield).

(2,2-dimethyl-1,3-dioxolan-4-yl)methanamine hydrochloride



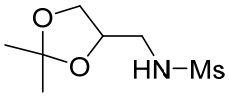
^{1}H NMR (400 MHz, DMSO) δ 8.30 (s, 3H), 4.31 (p, *J* = 6.1 Hz, 1H), 4.04 (dd, *J* = 8.7, 6.5 Hz, 1H), 3.77 (dd, *J* = 8.7, 5.7 Hz, 1H), 2.97 (dd, *J* = 13.0, 4.1 Hz, 1H), 2.80 (dd, *J* = 13.0, 7.7 Hz, 1H), 1.38 (s, 3H), 1.29 (s, 3H).^{13}C NMR (100 MHz, DMSO) δ = 109.1, 72.1, 66.2, 41.4, 26.7, 25.3.

The synthesis of *N*-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)methanesulfonamide



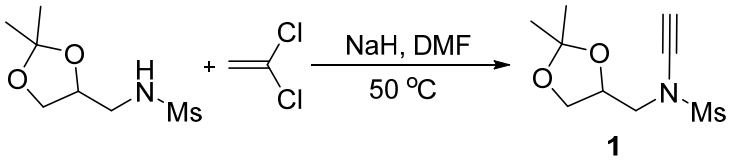
In a round bottom flask, (2,2-dimethyl-1,3-dioxolan-4-yl)methanamine hydrochloride (8.8 g, 52.5 mmol, 1.05 equiv.) was dissolved in DCM (150 mL) and Et_3N (21 mL, 150 mmol, 3 equiv.) was added. After cooling to 0°C, MsCl (3.87 mL, 50 mmol, 1.0 equiv.) was added drop-wise and the temperature was allowed to rise to 25°C. After 24 h, the reaction mixture was acidified with 0.5 M citric acid. The crude mixture was dried with $MgSO_4$, filtered, concentrated under vacuum to give 9.93 g of *N*-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)methanesulfonamide, yellow liquid, 95% yield.

***N*-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)methanesulfonamide**



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (s, 1H), 4.28 (qd, *J* = 6.3, 3.9 Hz, 1H), 4.07 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.75 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.34 (ddd, *J* = 13.3, 6.7, 3.8 Hz, 1H), 3.23 – 3.16 (m, 1H), 3.00 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 109.9, 74.5, 66.6, 45.6, 40.7, 26.9, 25.3.

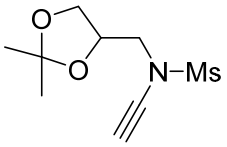
The synthesis of *N*-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-*N*-ethynylmethanesulfonamide (1)



1

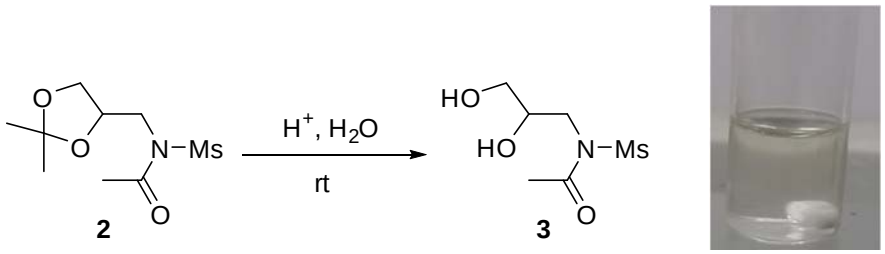
N-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)methanesulfonamide (20 mmol, 4.2 g), NaH (60 mmol, 1.44 g)，1,1-dichloroethene (40 mmol, 3.12 mL) and DMF (50 mL) were combined in a round bottom flask. The reaction mixture was stirred at 50 °C for another 3 h and then cooled to room temperature. The mixture was concentrated and dried under vacuum and the residue was purified by silica gel chromatography to afford **1** as a white solid (4.34 g, 93% yield).

***N*-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-*N*-ethynylmethanesulfonamide (1)**



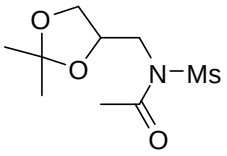
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 – 4.43 (m, 1H), 4.12 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.80 (dd, *J* = 8.8, 5.1 Hz, 1H), 3.74 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.43 (dd, *J* = 14.1, 4.5 Hz, 1H), 3.20 (s, 3H), 2.87 (s, 1H), 1.47 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 110.3, 75.5, 73.1, 66.8, 60.1, 54.1, 38.7, 27.0, 25.5. HRMS (ESI) m/z calcd. for $C_9H_{16}NO_4S$ $[M+H]^+$: 234.0795, found: 234.0793. MP = 73 - 77°C.

3. The hydrolysis of the byproduct



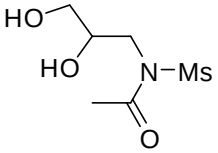
2 (1.25 mmol, 0.314 g) was added in 1 mL HCl/H_2O (4 M). The reaction mixture was stirred 5 min. The mixture was concentrated and dried under vacuum and the residue was purified by silica gel chromatography to afford **3**. Colorless liquid, 0.19 g, 90% yield.

***N*-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-*N*-(methylsulfonyl)acetamide (2)**



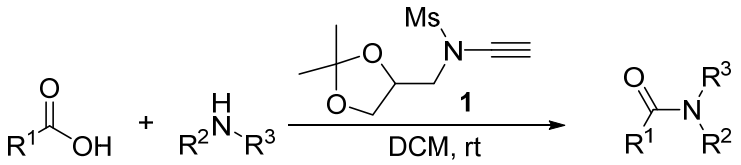
Colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (dh, *J* = 9.3, 3.5 Hz, 1H), 4.11 (dd, *J* = 8.7, 6.6 Hz, 1H), 3.96 (dd, *J* = 15.1, 3.4 Hz, 1H), 3.89 (dd, *J* = 15.1, 8.0 Hz, 1H), 3.71 (dd, *J* = 8.8, 5.8 Hz, 1H), 3.37 (s, 3H), 2.45 (s, 3H), 1.46 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.4, 110.2, 74.2, 67.2, 49.5, 42.6, 26.6, 25.3, 25.0. HRMS (ESI) m/z calcd. for $C_9H_{17}NO_5S$ $[M+H]^+$: 251.0827, found: 251.0831.

***N*-(2,3-dihydroxypropyl)-*N*-(methylsulfonyl)acetamide (3)**



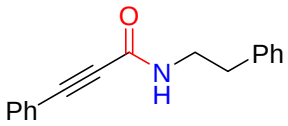
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (s, 1H), 4.26 – 3.68 (m, 3H), 3.41 – 3.03 (m, 3H), 2.95 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.6, 68.8, 65.8, 45.8, 40.6, 21.1. HRMS (ESI) m/z calcd. for $C_6H_{13}NO_5S$ $[M+H]^+$: 211.0514, found: 211.0519.

4. General procedure for the syntheses of amides and peptides



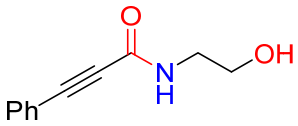
Acid (0.5 mmol), ynamide coupling reagent **1** (0.55 mmol) and DCM (3.0 mL) were combined together and stirred for hours. Then amine (0.55 mmol) was added to the above solution and the reaction mixture was stirred at room temperature under air until *α*-acyloxyenamide intermediate was fully consumed. The reaction mixture was diluted with DCM or EA (20 mL), and the organic layer was vigorously shaken for 2 min with 0.2-1 M HCl (20 mL), followed by washing with sat. $NaHCO_3$ (15 mL) and H_2O (15 mL). The organic solution was dried with $MgSO_4$, filtered, concentrated under vacuum to collect product with high purity.

N-phenethyl-3-phenylpropiolamide (6a)



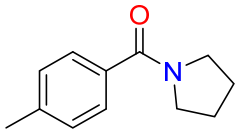
White solid, 92% yield, R_f = 0.4 (PE/EA = 4:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.1 Hz, 2H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 4H), 7.27 – 7.21 (m, 3H), 6.06 (s, 1H), 3.66 – 3.56 (m, 2H), 2.88 (t, *J* = 7.0 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.5, 138.6, 132.6, 130.1, 128.9, 128.8, 128.6, 126.8, 120.3, 84.8, 83.2, 41.1, 35.5.

N-(2-hydroxyethyl)-3-phenylpropiolamide (6b)



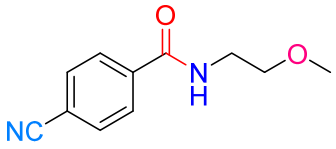
White solid, 90% yield, R_f = 0.25 (PE/EA = 1:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.0 Hz, 2H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 2H), 6.83 (t, *J* = 5.9 Hz, 1H), 3.80 – 3.75 (m, 2H), 3.52 (q, *J* = 5.4 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.5, 132.6, 130.3, 128.6, 120.2, 85.6, 82.9, 61.5, 42.7.

pyrrolidin-1-yl(p-tolyl)methanone (6c)



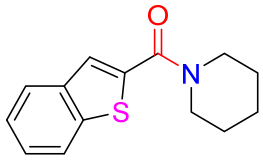
White solid, 90% yield, R_f = 0.3 (PE/EA = 4:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 3.64 (t, *J* = 6.7 Hz, 2H), 3.44 (t, *J* = 6.3 Hz, 2H), 2.37 (s, 3H), 1.94 (q, *J* = 6.2 Hz, 2H), 1.87 (q, *J* = 6.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.9, 140.0, 134.4, 128.9, 127.3, 49.7, 46.3, 26.5, 24.6, 21.5.

4-cyano-*N*-(2-methoxyethyl)benzamide (6d)



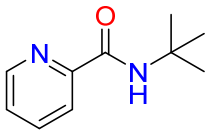
Yellow solid, 94% yield, R_f = 0.25 (PE/EA = 3:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 6.77 (s, 1H), 3.66 (q, *J* = 5.0 Hz, 2H), 3.60 – 3.55 (m, 2H), 3.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.8, 138.5, 132.5, 127.8, 118.1, 115.1, 70.9, 58.9, 40.0.

benzo[b]thiophen-2-yl(piperidin-1-yl)methanone (6e)



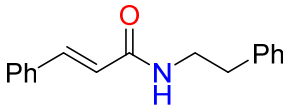
Faint yellow solid, 90% yield, R_f = 0.6 (PE/EA = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.80 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.44 (s, 1H), 7.38 (dt, *J* = 6.0, 3.5 Hz, 2H), 3.71 – 3.64 (m, 4H), 1.73 – 1.62 (m, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.8, 140.2, 138.8, 137.4, 125.6, 124.8, 124.7, 124.6, 122.4, 26.3, 24.7.

***N*-(*tert*-butyl)picolinamide (6f)**



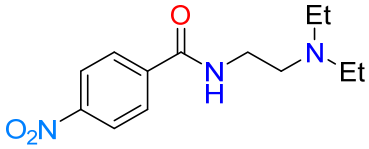
White solid, 88% yield, R_f = 0.6 (PE/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.7 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.01 (s, 1H), 7.83 (td, *J* = 7.7, 1.5 Hz, 1H), 7.40 (dd, *J* = 7.5, 4.8 Hz, 1H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.6, 151.0, 147.9, 137.5, 126.0, 121.8, 51.1, 28.9.

_N_-phenethylcinnamamide (6g)



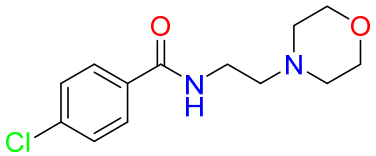
White solid, 90% yield, R_f = 0.35 (PE/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 15.6 Hz, 1H), 7.46 (dd, *J* = 6.4, 2.5 Hz, 2H), 7.37 – 7.28 (m, 5H), 7.23 (t, *J* = 9.5 Hz, 3H), 6.35 (d, *J* = 15.6 Hz, 1H), 5.86 (s, 1H), 3.65 (q, *J* = 6.8 Hz, 2H), 2.88 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.0, 141.1, 139.0, 134.9, 129.7, 128.9, 128.9, 128.8, 127.9, 126.7, 120.8, 41.0, 35.8.

_N_-(2-(diethylamino)ethyl)-4-nitrobenzamide (6h)



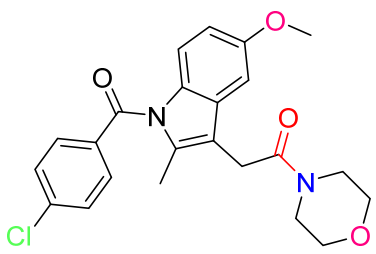
White solid, 98% yield, R_f = 0.3 (DCM/MeOH = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.7 Hz, 2H), 7.96 (d, *J* = 8.7 Hz, 2H), 3.52 (q, *J* = 5.3 Hz, 2H), 2.69 (t, *J* = 5.9 Hz, 2H), 2.60 (q, *J* = 7.1 Hz, 4H), 1.05 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.3, 149.6, 140.4, 128.2, 123.9, 51.3, 46.9, 37.6, 11.9.

4-chloro-_N_-(2-morpholinoethyl)benzamide (6i)



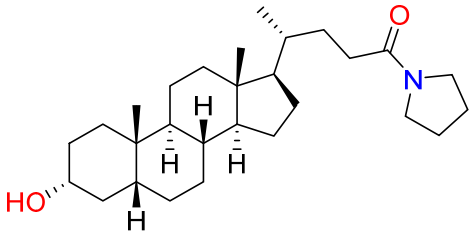
White solid, 97% yield, R_f = 0.2 (PE/EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 6.84 (s, 1H), 3.77 – 3.71 (m, 4H), 3.54 (q, *J* = 5.6 Hz, 2H), 2.60 (t, *J* = 6.0 Hz, 2H), 2.55 – 2.47 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.5, 137.7, 133.1, 128.9, 128.5, 67.1, 57.0, 53.5, 36.2.

2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)-1-morpholinoethan-1-one (6j)



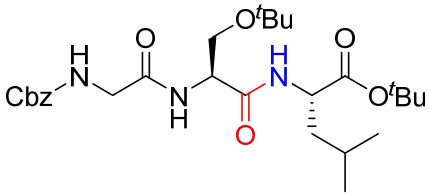
White solid, 93% yield, R_f = 0.3 (PE/EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.65 (dd, *J* = 9.0, 2.1 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 2H), 3.68 – 3.62 (m, 4H), 3.59 – 3.55 (m, 2H), 3.55 – 3.49 (m, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.9, 168.3, 156.1, 139.4, 135.3, 133.9, 131.3, 130.9, 130.7, 129.2, 115.0, 113.1, 111.6, 101.6, 67.0, 66.6, 55.8, 46.4, 42.5, 30.2, 13.5.

(*R*)-4-((*3R,5R,8R,9S,10S,13R,14S,17R*)-3-hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-1-(pyrrolidin-1-yl)pentan-1-one (6k)



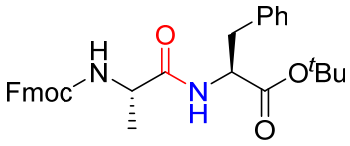
White solid, 85% yield, R_f = 0.3 (PE/EA = 3:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (tt, *J* = 10.9, 4.4 Hz, 1H), 3.43 (dt, *J* = 13.7, 6.8 Hz, 4H), 2.39 – 2.06 (m, 4H), 1.94 (q, *J* = 6.8 Hz, 3H), 1.88 – 1.83 (m, 3H), 1.82 – 1.74 (m, 3H), 1.68 – 1.48 (m, 3H), 1.45 – 1.04 (m, 16H), 1.01 – 0.92 (m, 4H), 0.92 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.4, 71.8, 56.6, 56.2, 46.7, 45.7, 42.8, 42.2, 40.5, 40.3, 36.5, 35.9, 35.7, 35.5, 34.7, 31.8, 31.0, 30.6, 28.3, 27.3, 26.5, 26.2, 24.5, 24.3, 23.5, 20.9, 18.6, 12.1.

Cbz-Gly-Ser(O^{t}Bu)-Leu-O^{t}Bu (9a)



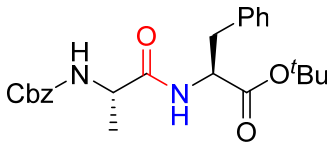
White solid, 95% yield, R_f = 0.4 (PE/EA = 3:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 6H), 6.98 (d, *J* = 6.9 Hz, 1H), 5.72 (d, *J* = 5.8 Hz, 1H), 5.17 – 5.08 (m, 2H), 4.46 (dd, *J* = 8.5, 5.4 Hz, 2H), 3.90 (dd, *J* = 10.2, 4.2 Hz, 2H), 3.82 – 3.72 (m, 1H), 3.38 – 3.32 (m, 1H), 1.72 – 1.50 (m, 3H), 1.45 (s, 9H), 1.20 (s, 9H), 0.93 (dd, *J* = 6.4, 4.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.7, 169.9, 169.1, 156.8, 136.3, 128.6, 128.2, 128.1, 81.8, 74.4, 67.2, 61.4, 52.9, 51.8, 44.6, 41.8, 28.1, 27.4, 24.9, 22.9, 22.2.

Fmoc-Ala-Phe-O^{t}Bu (9b)



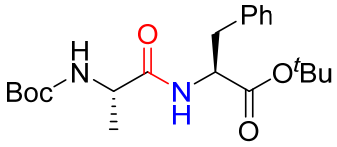
White solid, 87% yield, R_f = 0.6 (PE/EA = 3:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.0 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.24 – 7.10 (m, 5H), 6.69 – 6.48 (m, 1H), 5.60 – 5.40 (m, 1H), 4.73 (q, *J* = 6.1 Hz, 1H), 4.39 (dd, *J* = 10.3, 7.3 Hz, 1H), 4.36 – 4.22 (m, 2H), 4.19 (t, *J* = 7.0 Hz, 1H), 3.08 (h, *J* = 8.0, 7.2 Hz, 2H), 1.38 (s, 9H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.8, 170.4, 155.9, 143.9, 141.4, 136.1, 129.6, 128.4, 127.8, 127.2, 127.0, 125.2, 120.1, 82.5, 67.2, 53.7, 50.5, 47.2, 38.1, 28.0, 18.9.

Cbz-Ala-Phe-O^{t}Bu (9c)



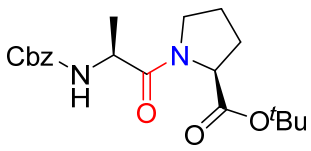
White solid, 94% yield, R_f = 0.4 (PE/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 7.26 – 7.19 (m, 3H), 7.13 (d, *J* = 6.8 Hz, 2H), 6.69 – 6.45 (m, 1H), 5.51 – 5.34 (m, 1H), 5.10 (t, *J* = 9.4 Hz, 2H), 4.72 (q, *J* = 6.2 Hz, 1H), 4.34 – 4.16 (m, 1H), 3.11 – 3.03 (m, 2H), 1.40 (s, 9H), 1.33 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.8, 170.4, 155.9, 136.3, 136.1, 129.6, 128.6, 128.4, 128.2, 128.1, 127.0, 82.5, 67.1, 53.7, 50.6, 38.1, 28.0, 18.7.

Boc-Ala-Phe-O^{t}Bu (9d)



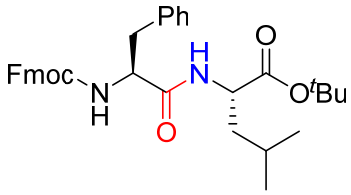
White solid, 90% yield, R_f = 0.6 (PE/EA = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dt, *J* = 13.1, 6.8 Hz, 3H), 7.15 (d, *J* = 6.8 Hz, 2H), 6.60 (s, 1H), 5.05 (s, 1H), 4.71 (q, *J* = 6.2 Hz, 1H), 4.15 (s, 1H), 3.13 – 3.04 (m, 2H), 1.43 (s, 9H), 1.39 (s, 9H), 1.32 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.2, 170.4, 155.4, 136.2, 129.6, 128.4, 127.0, 82.4, 80.1, 53.7, 50.3, 38.2, 28.4, 28.0, 18.6.

Cbz-Ala-Pro-O^{t}Bu (9e)



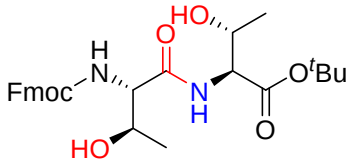
Glassy oil, 92% yield, R_f = 0.3 (PE/EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H), 5.74 (d, *J* = 7.8 Hz, 1H), 5.07 (s, 2H), 4.49 (p, *J* = 7.1 Hz, 1H), 4.39 (dd, *J* = 8.6, 4.4 Hz, 1H), 3.65 (dt, *J* = 10.0, 6.4 Hz, 1H), 3.60 – 3.48 (m, 1H), 2.21 – 2.13 (m, 1H), 2.04 – 1.89 (m, 3H), 1.43 (s, 9H), 1.37 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.0, 170.9, 155.7, 136.6, 128.5, 128.5, 128.0, 128.0, 127.9, 81.4, 59.7, 48.3, 46.9, 29.0, 28.0, 24.9, 18.4.

Fmoc-Phe-Leu-O^{t}Bu (9f)



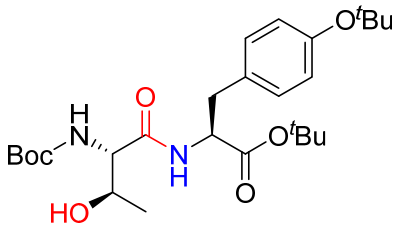
White solid, 93% yield, R_f = 0.4 (PE/EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.53 (t, *J* = 6.8 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.31 – 7.15 (m, 7H), 6.36 (s, 1H), 5.47 (s, 1H), 4.55 – 4.38 (m, 3H), 4.33 – 4.22 (m, 1H), 4.17 (t, *J* = 6.8 Hz, 1H), 3.08 (s, 2H), 1.59 – 1.50 (m, 2H), 1.44 (s, 9H), 0.88 (t, *J* = 5.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.7, 170.4, 156.0, 143.9, 143.8, 141.4, 136.4, 129.5, 128.7, 127.8, 127.2, 127.1, 125.2, 125.1, 120.1, 82.0, 67.2, 56.0, 51.6, 47.2, 41.9, 38.6, 28.1, 24.9, 22.8, 22.2.

Fmoc-Thr-Thr-O^{t}Bu (9g)



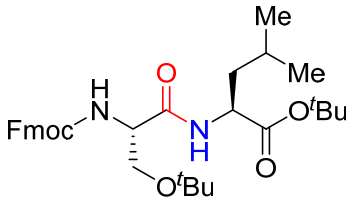
White solid, 85% yield, R_f = 0.3 (PE/EA = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 6.6 Hz, 2H), 7.45 – 7.32 (m, 3H), 7.30 – 7.25 (m, 2H), 6.27 – 6.09 (m, 1H), 4.47 – 4.43 (m, 1H), 4.43 – 4.38 (m, 1H), 4.37 – 4.21 (m, 4H), 4.19 (t, *J* = 7.0 Hz, 1H), 1.45 (s, 9H), 1.21 – 1.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.3, 170.1, 156.9, 143.9, 143.7, 141.4, 127.8, 127.2, 125.2, 125.2, 120.1, 82.9, 68.3, 67.5, 67.4, 59.2, 58.6, 47.2, 28.1, 20.3, 18.2.

Boc-Thr-Tyr(O^{t}Bu)-O^{t}Bu (9h)



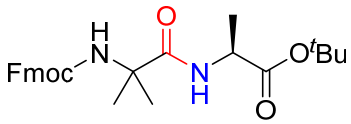
Glassy solid, 92% yield, R_f = 0.3 (PE/EA = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 5.48 (d, *J* = 7.4 Hz, 1H), 4.69 (q, *J* = 6.2 Hz, 1H), 4.34 – 4.26 (m, 1H), 4.09 (d, *J* = 7.3 Hz, 1H), 3.32 (s, 1H), 3.05 – 2.98 (m, 2H), 2.15 (s, 1H), 1.45 (s, 9H), 1.38 (s, 9H), 1.32 (s, 9H), 1.16 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.9, 170.4, 156.3, 154.5, 131.0, 130.0, 124.2, 82.5, 80.3, 78.5, 67.1, 58.4, 54.0, 37.6, 28.9, 28.4, 28.0, 18.3.

Fmoc-Ser(O^{t}Bu)-Leu-O^{t}Bu (9i)



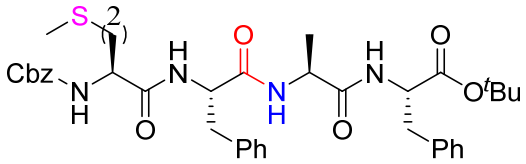
White solid, 93% yield, R_f = 0.4 (PE/EA = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 6.9 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.22 (s, 1H), 5.80 (s, 1H), 4.49 (s, 1H), 4.42 – 4.36 (m, 2H), 4.23 (t, *J* = 7.1 Hz, 2H), 3.83 (dd, *J* = 8.3, 3.4 Hz, 1H), 3.40 (t, *J* = 8.0 Hz, 1H), 1.76 – 1.59 (m, 3H), 1.58 – 1.47 (m, 3H), 1.45 (s, 9H), 1.22 (s, 9H), 0.95 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.7, 170.0, 156.1, 144.0, 143.9, 141.4, 127.8, 127.1, 125.2, 120.0, 81.8, 74.3, 67.2, 61.9, 54.4, 51.7, 47.2, 42.0, 28.1, 27.4, 25.0, 22.9, 22.2.

Fmoc-Aib-Ala-O^{t}Bu (9j)



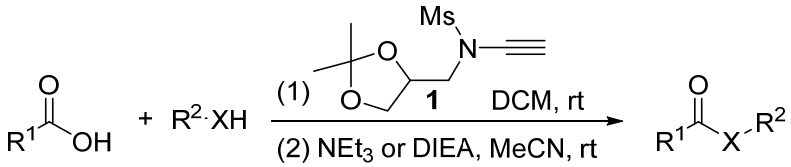
White solid, 93% yield, R_f = 0.4 (PE/EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.61 – 7.57 (m, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 6.74 (s, 1H), 5.52 (s, 1H), 4.45 – 4.35 (m, 3H), 4.20 (t, *J* = 6.7 Hz, 1H), 1.53 (s, 6H), 1.44 (s, 9H), 1.35 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.8, 172.2, 155.1, 144.0, 144.0, 141.4, 127.8, 127.2, 125.1, 125.1, 120.1, 82.1, 66.7, 56.8, 49.0, 47.3, 28.1, 25.7, 25.3, 18.5.

Cbz-Met-Phe-Ala-Phe-O^{t}Bu (9k)



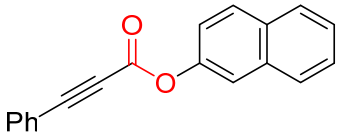
White solid, 95% yield, R_f = 0.4 (PE/EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.4 Hz, 1H), 7.77 (d, *J* = 6.9 Hz, 1H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.23 – 7.03 (m, 15H), 6.36 (d, *J* = 8.3 Hz, 1H), 5.08 – 4.99 (m, 2H), 4.94 – 4.87 (m, 1H), 4.82 (d, *J* = 12.4 Hz, 1H), 4.73 – 4.62 (m, 2H), 2.96 – 2.87 (m, 4H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.98 – 1.91 (m, 4H), 1.86 – 1.79 (m, 1H), 1.28 – 1.23 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.0, 171.5, 170.8, 170.4, 156.3, 136.6, 136.5, 136.5, 129.7, 129.6, 129.5, 128.5, 128.5, 128.5, 128.4, 128.4, 128.1, 128.0, 126.9, 126.9, 82.2, 66.9, 54.2, 54.1, 53.9, 48.7, 39.6, 38.3, 33.2, 30.1, 28.0, 19.7, 15.4. HRMS (ESI) m/z calcd. for $C_{38}H_{48}N_4NaO_7S[M+Na]^+$: 727.3136, found: 727.3132.

5. General procedure for the syntheses of esters and thioesters



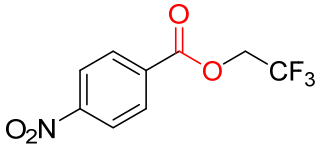
Acid (0.5 mmol), **1** (0.55 mmol) and DCM (3.0 mL) were combined together and stirred for hours. After acid was completely consumed, then the solvent was removed under vacuum. The mixture was dissolved in MeCN (3.0 mL), phenol (1.1 equiv.) or alcohol (1 - 3 equiv.) and NEt_3 (0.2 equiv.) or DIEA (0.2 equiv.) were added in sequence. After the intermediate was fully consumed, the solvent was removed under vacuum. The reaction mixture was diluted with DCM or EA (20 mL), the organic layer was vigorously shaken for 2 min with 0.2-1 M HCl (20 mL), followed by washing with sat. $NaHCO_3$ (15 mL) and H_2O (15 mL). The organic solution was dried with $MgSO_4$, filtered, concentrated under vacuum to collect product with high purity.

naphthalen-2-yl 3-phenylpropiolate (11a)



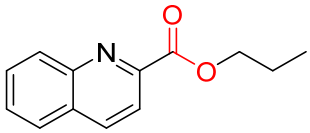
White solid, 95% yield, R_f = 0.65 (PE/EA = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 20.9, 9.9 Hz, 3H), 7.70 – 7.58 (m, 3H), 7.48 (dt, *J* = 14.2, 7.4 Hz, 3H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.6, 147.9, 133.8, 133.3, 131.8, 131.2, 129.7, 128.8, 127.9, 127.9, 126.9, 126.1, 120.8, 119.4, 118.7, 89.0, 80.5.

2,2,2-trifluoroethyl 4-nitrobenzoate (11b)



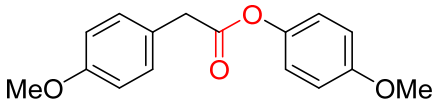
Glassy oil, 96% yield, R_f = 0.6 (PE/EA = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 6.9 Hz, 2H), 8.26 (d, *J* = 9.0 Hz, 2H), 4.76 (q, *J* = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.3, 151.3, 133.8, 131.3, 123.9, 123.0($J_{C\text{-}F}$= 277.1 Hz), 61.6 ($J_{C\text{-}F}$ = 37.1 Hz).

propyl quinoline-2-carboxylate (11c)



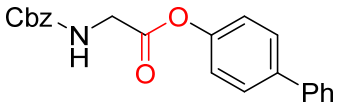
White solid, 93% yield, R_f = 0.6 (PE/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 10.3, 8.9 Hz, 2H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.78 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.64 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 4.46 (t, *J* = 6.9 Hz, 2H), 1.94 – 1.86 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.5, 148.4, 147.8, 137.3, 130.9, 130.3, 129.4, 128.6, 127.6, 121.1, 67.8, 22.2, 10.5.

4-methoxyphenyl 2-(4-methoxyphenyl)acetate (11d)



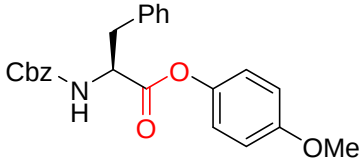
White solid, 87% yield, R_f = 0.45 (PE/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 3.78 – 3.75 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.8, 159.0, 157.4, 144.4, 130.4, 125.7, 122.3, 114.5, 114.3, 55.7, 55.4, 40.6.

[1,1'-biphenyl]-4-yl ((benzyloxy)carbonyl)glycinate (11e)



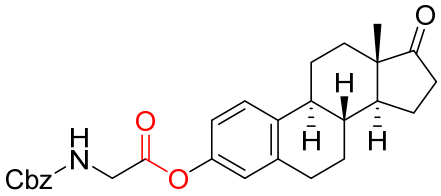
White solid, 95% yield, R_f = 0.5 (PE/EA = 5:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.69 (dd, *J* = 19.0, 7.8 Hz, 4H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.44 – 7.27 (m, 6H), 7.22 (d, *J* = 8.1 Hz, 2H), 5.11 (s, 2H), 4.12 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 169.2, 156.6, 149.8, 139.3, 138.0, 136.9, 128.9, 128.3, 127.8, 127.8, 127.7, 127.5, 126.7, 122.0, 65.7, 42.5. HRMS (ESI) m/z calcd. for $C_{22}H_{20}NNaO_4$ $[M+Na]^+$: 384.1206, found: 384.1203.

4-methoxyphenyl ((benzyloxy)carbonyl)-*L*-phenylalaninate (11f)



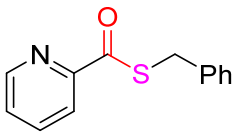
White solid, 94% yield, R_f = 0.5 (PE/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.19 (m, 10H), 6.91 – 6.81 (m, 4H), 5.38 (s, 1H), 5.11 (s, 2H), 4.87 (q, *J* = 5.7 Hz, 1H), 3.76 (s, 3H), 3.23 (d, *J* = 5.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6, 157.5, 155.8, 143.8, 136.3, 135.6, 129.5, 128.8, 128.6, 128.3, 128.2, 127.4, 122.1, 114.6, 67.2, 55.6, 55.1, 38.4.

(*8R,9S,13S,14S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl ((benzyloxy)carbonyl)glycinate (11g)



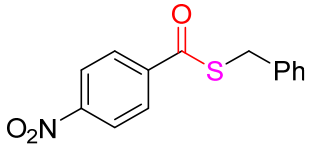
White solid, 85% yield, R_f = 0.4 (PE/EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 6H), 6.91 – 6.72 (m, 2H), 5.46 (s, 1H), 5.14 (s, 2H), 4.20 (d, *J* = 5.5 Hz, 2H), 2.94 – 2.84 (m, 2H), 2.50 (dd, *J* = 18.9, 8.7 Hz, 1H), 2.42 – 2.34 (m, 1H), 2.30 – 2.22 (m, 1H), 2.18 – 1.94 (m, 4H), 1.65 – 1.41 (m, 6H), 0.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.0, 156.4, 148.2, 138.2, 137.8, 136.2, 128.6, 128.2, 128.1, 126.5, 121.3, 118.4, 67.2, 50.4, 47.9, 44.1, 43.0, 38.0, 35.8, 31.6, 29.4, 26.3, 25.8, 21.6, 13.8. HRMS (ESI) m/z calcd. for $C_{28}H_{31}NNaO_5[M+Na]^+$: 484.2094, found: 484.2090.

***S*-benzyl pyridine-2-carbothioate (11h)**



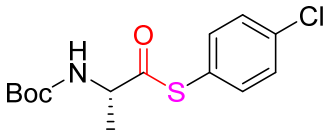
White solid, 87% yield, R_f = 0.4 (PE/EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.7 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.83 (td, *J* = 7.7, 1.6 Hz, 1H), 7.50 – 7.46 (m, 1H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.26 – 7.21 (m, 1H), 4.28 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 193.1, 152.0, 149.2, 137.7, 137.3, 129.1, 128.7, 127.9, 127.3, 120.6, 33.3.

***S*-benzyl 4-nitrobenzothioate (11i)**



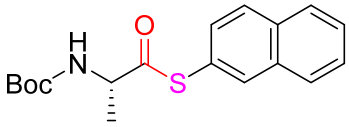
White solid, 87% yield, R_f = 0.65 (PE/EA = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.9 Hz, 2H), 8.10 (d, *J* = 8.9 Hz, 2H), 7.32 (ddt, *J* = 22.8, 14.6, 7.4 Hz, 5H), 4.36 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.9, 150.7, 141.5, 136.7, 129.1, 128.9, 128.4, 127.8, 124.0, 34.0.

_S_-(4-chlorophenyl) (_S_)-2-((_tert_-butoxycarbonyl)amino)propanethioate (11j)



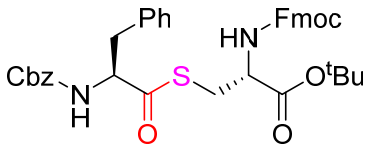
White solid, 89% yield, R_f = 0.5 (PE/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 5.04 (s, 1H), 4.58 – 4.35 (m, 1H), 1.49 (s, 9H), 1.43 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.8, 155.0, 136.0, 136.0, 129.6, 126.0, 80.7, 56.5, 28.5, 18.7.

_S_-(naphthalen-2-yl) (_S_)-2-((_tert_-butoxycarbonyl)amino)propanethioate (11k)



White solid, 94% yield, R_f = 0.6 (PE/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.87 – 7.79 (m, 3H), 7.54 – 7.47 (m, 2H), 7.43 (d, *J* = 8.3 Hz, 1H), 5.10 (s, 1H), 4.65 – 4.43 (m, 1H), 1.50 (s, 9H), 1.46 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.3, 155.1, 134.7, 133.7, 133.5, 131.1, 128.9, 128.0, 127.9, 127.2, 126.7, 124.7, 80.6, 56.5, 28.5, 18.8.

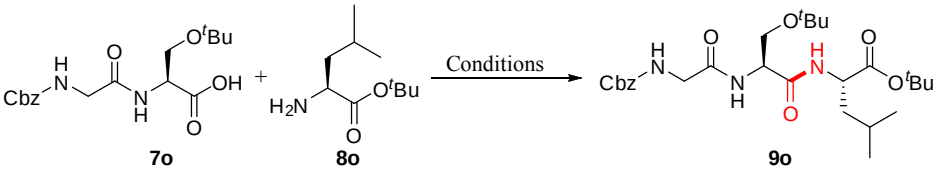
***tert*-butyl**
_N_-(((9H-fluoren-9-yl)methoxy)carbonyl)-_S_-(((benzyloxy)carbonyl)-_L_-phenylalanyl)-_L_-cysteinate (11l)



White solid, 84% yield, R_f = 0.35 (PE/EA = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 6.7 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.33 – 7.20 (m, 10H), 7.10 (d, *J* = 6.9 Hz, 2H), 5.61 – 5.41 (m, 1H), 5.25 – 5.14 (m, 1H), 5.06 (s, 2H), 4.71 (q, *J* = 7.5 Hz, 1H), 4.56 – 4.48 (m, 1H), 4.45 – 4.32 (m, 2H), 4.23 (t, *J* = 6.9 Hz, 1H), 3.58 – 3.41 (m, 1H), 3.30 (dd, *J* = 13.8, 5.6 Hz, 1H), 3.13 (dd, *J* = 14.1, 5.3 Hz,

1H), 2.98 (dd, *J* = 14.0, 7.6 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.6, 169.0, 155.7, 144.0, 143.9, 141.4, 136.1, 135.4, 129.3, 128.9, 128.6, 128.3, 128.1, 127.8, 127.4, 127.2, 125.3, 120.1, 83.2, 67.3, 61.8, 54.1, 47.3, 38.4, 31.2, 28.0. HRMS (ESI) m/z calcd. for $C_{39}H_{41}N_2NaO_7S[M+Na]^+$: 703.2448, found: 703.2441.

6. HPLC studies of epimerization/racemization

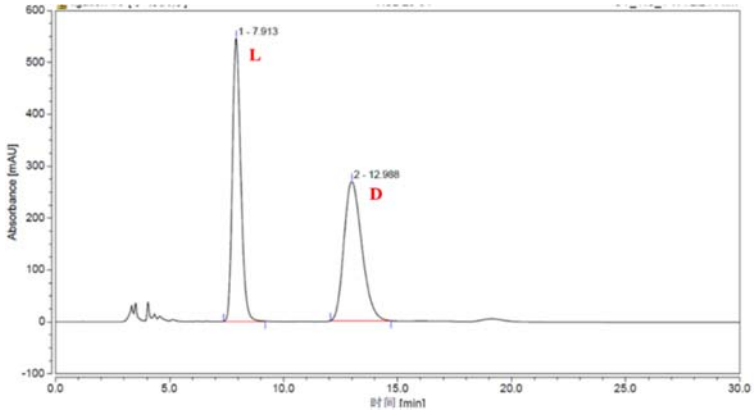


7o **8o** **9o**

Entry	Coupling reagent	Additive	Time	*dr*[b]	yield[c]
1	EDCI	--	1 h	53:47	80%
2	EDCI	HOSu	1 h	72:28	86%
3	EDCI	HOBt	1 h	91:9	91%
4	EDCI	HOAt	1 h	93:7	91%
5	EDCI	Oxyma	1 h	91:9	86%
6	HBTU	DIEA	1 h	90:10	90%
7	HATU	DIEA	1 h	96:4	92%
8	TBTU	DIEA	1 h	92:8	91%
9	COMU	DIEA	1 h	95:5	92%
10	**1**	--	48 h	>99:1	95%
11[d]	**1**	--	7 h	>99:1	93%

[a] Reaction conditions: **7o** (0.2 mmol), **8o** (0.22 mmol), coupling reagent (0.22 mmol), additive (0.22 mmol), DIEA (*N*,*N*-Diisopropylethylamine) (0.4 mmol), DCM(1 mL); [b] The diastereomeric ratios (*dr*) were determined by HPLC; [c] isolated yield; [d] DMF was used as the solvent for the aminolysis step.

Cbz–Gly-*DL*-Ser(O^{t}Bu)-Leu-O^{t}Bu

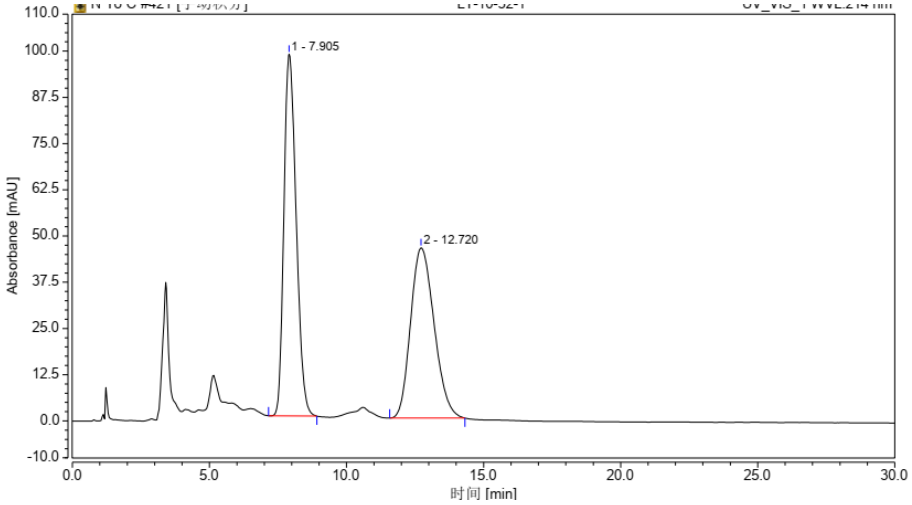


HPLC condition: chiral IC 250 × 4.6 mm^2 column; isocratic elution of 30% isopropanol in hexanes; flow rate = 1.0 mL/min; detection wavelength = 214 nm.

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	48.64	321.149	7.913	545.923
2	51.36	244.090	12.988	268.690
Total:	100	475.239		814.612

Cbz–Gly-Ser(O^{t}Bu)-Leu-O^{t}Bu (EDCI)

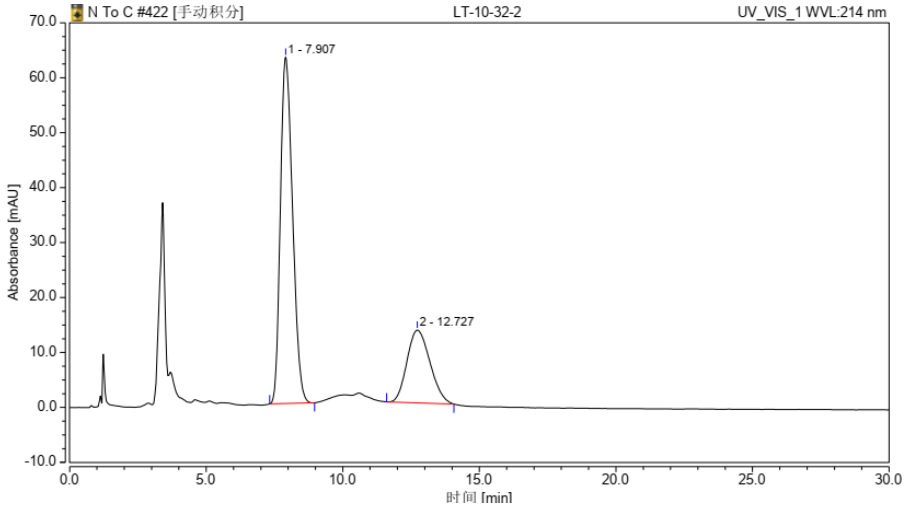


Crude HPLC

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	52.56	50.786	7.905	97.853
2	47.44	45.830	12.720	46.056
Total:	100	96.615		143.909

Cbz–Gly-Ser(O^{t}Bu)-Leu-O^{t}Bu (EDCI-HOSu)

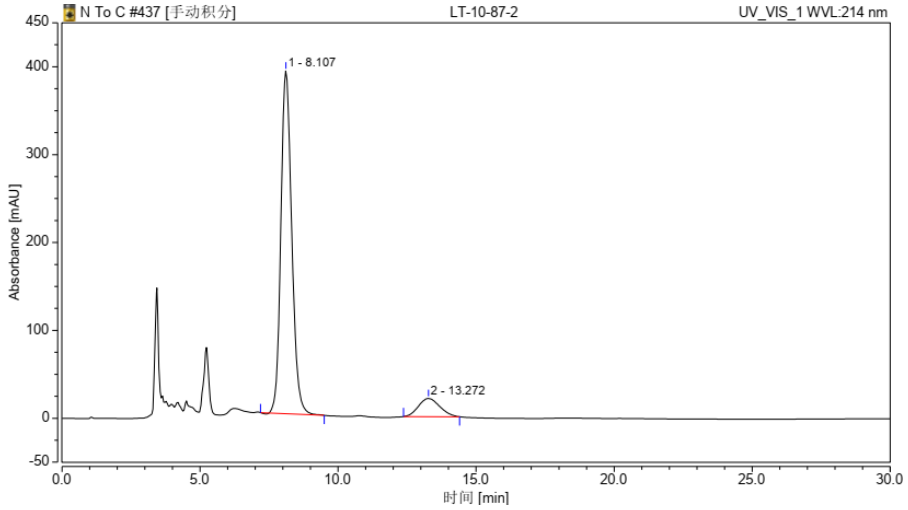


Crude HPLC

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	71.67	32.636	7.907	63.027
2	28.33	12.898	12.727	13.224
Total:	100	45.534		76.251

Cbz–Gly-Ser(O^{t}Bu)-Leu-O^{t}Bu (EDCI-HOBt)

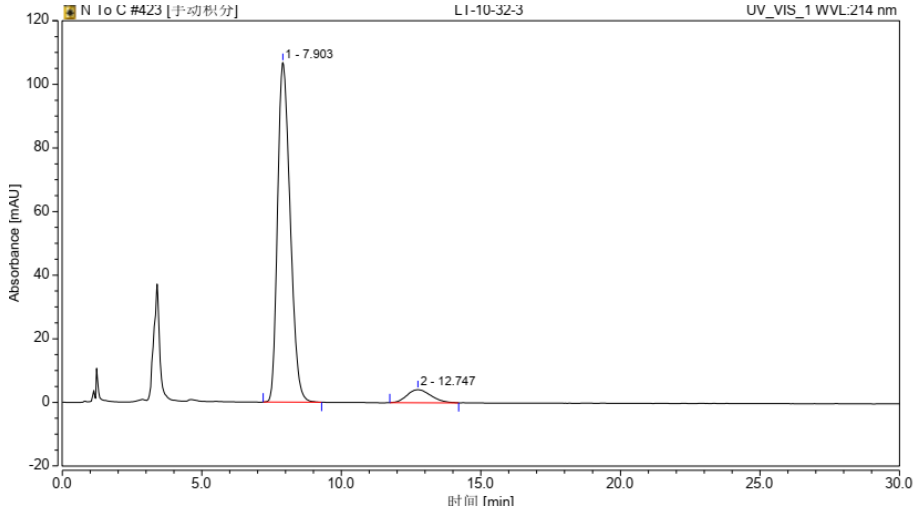


Crude HPLC

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	90.53	177.332	8.107	390.017
2	9.47	18.549	13.272	20.642
Total:	100	195.881		410.659

Cbz–Gly-Ser(O^{t}Bu)-Leu-O^{t}Bu (EDCI-HOAt)

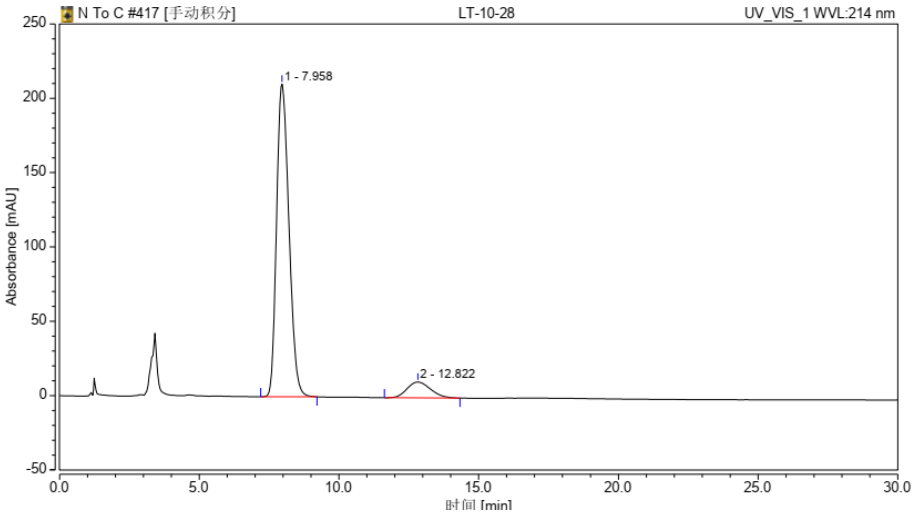


Crude HPLC

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	93.22	56.085	7.903	106.861
2	6.78	4.076	12.747	4.109
Total:	100	60.161		110.971

Cbz–Gly-Ser(O^{t}Bu)-Leu-O^{t}Bu (EDCI-Oxyma)

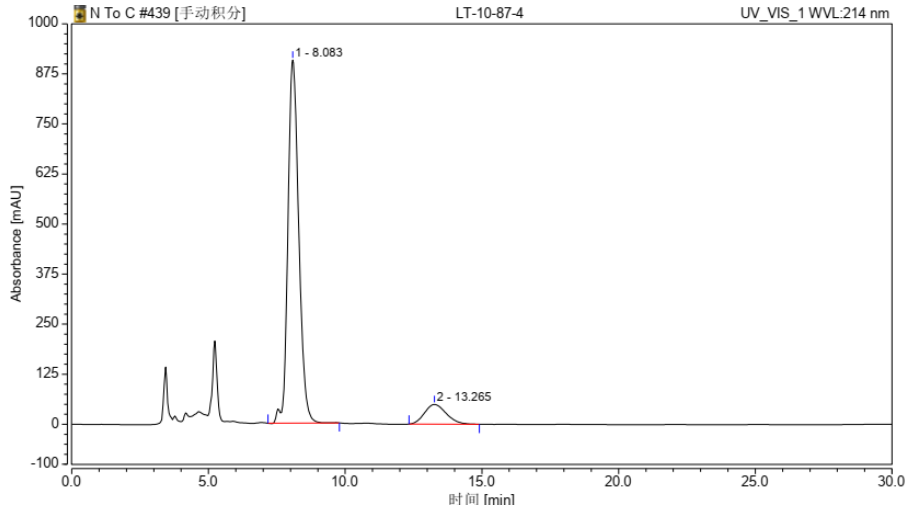


Crude HPLC

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	91.21	108.154	7.958	210.325
2	8.79	10.428	12.822	10.699
Total:	100	118.582		211.023

Cbz–Gly-Ser(O^{t}Bu)-Leu-O^{t}Bu (HBTU)

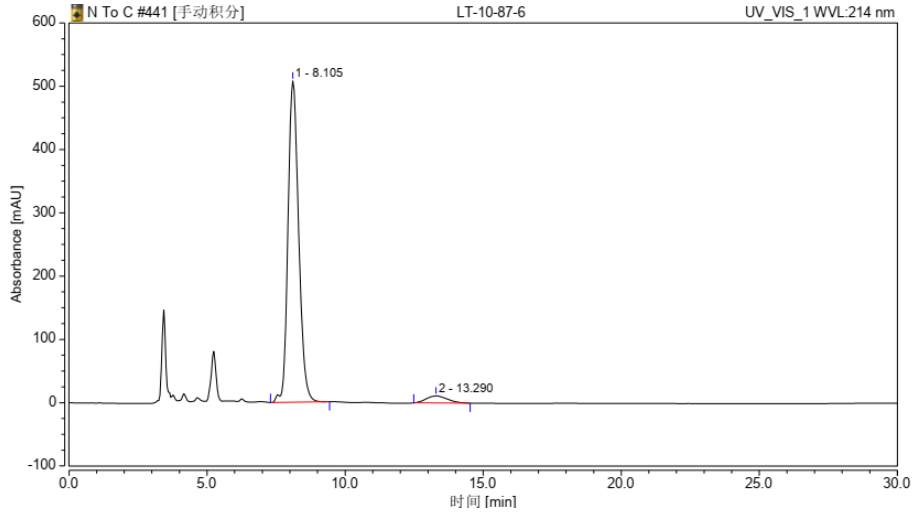


Crude HPLC

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	90.19	416.947	8.083	906.602
2	9.81	45.366	13.265	49.097
Total:	100	462.313		955.699

Cbz–Gly-Ser(O^{t}Bu)-Leu-O^{t}Bu (HATU)

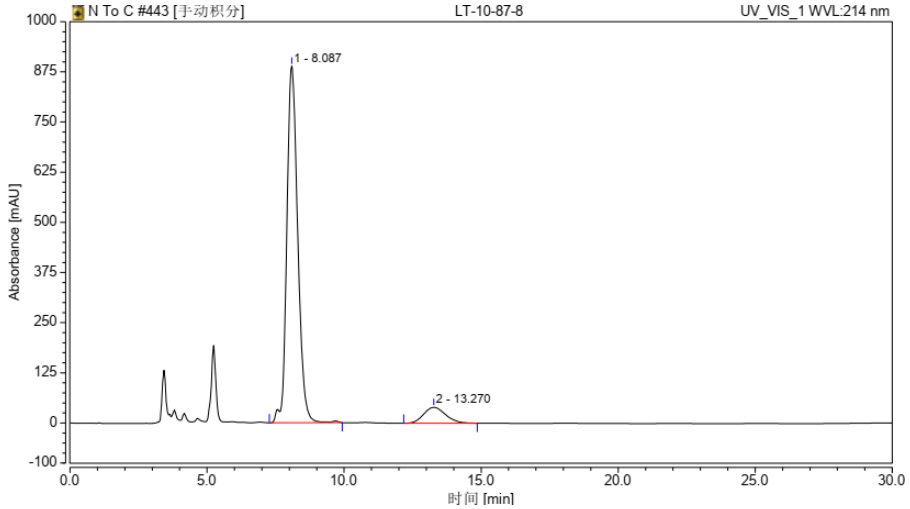


Crude HPLC

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	95.85	227.783	8.105	507.768
2	4.15	9.863	13.290	11.142
Total:	100	237.646		518.142

Cbz–Gly-Ser(O^{t}Bu)-Leu-O^{t}Bu (TBTU)

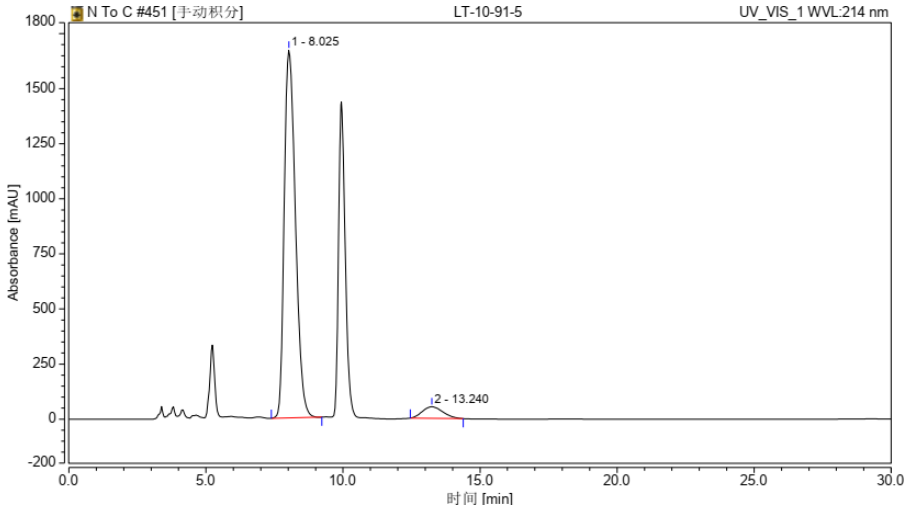


Crude HPLC

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	91.77	410.775	8.087	888.989
2	8.23	36.855	13.270	39.612
Total:	100	447.630		928.601

Cbz–Gly-Ser(O^{t}Bu)-Leu-O^{t}Bu (COMU)

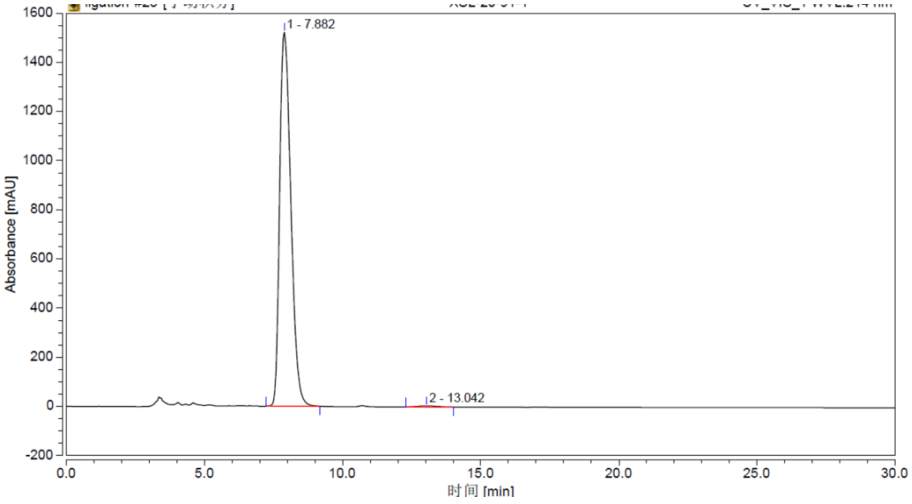


Crude HPLC

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	94.57	792.379	8.025	1669.897
2	5.43	45.459	13.240	52.225
Total:	100	837.838		1722.123

Cbz–Gly-Ser(O^{t}Bu)-Leu-O^{t}Bu (Ynamide 1)

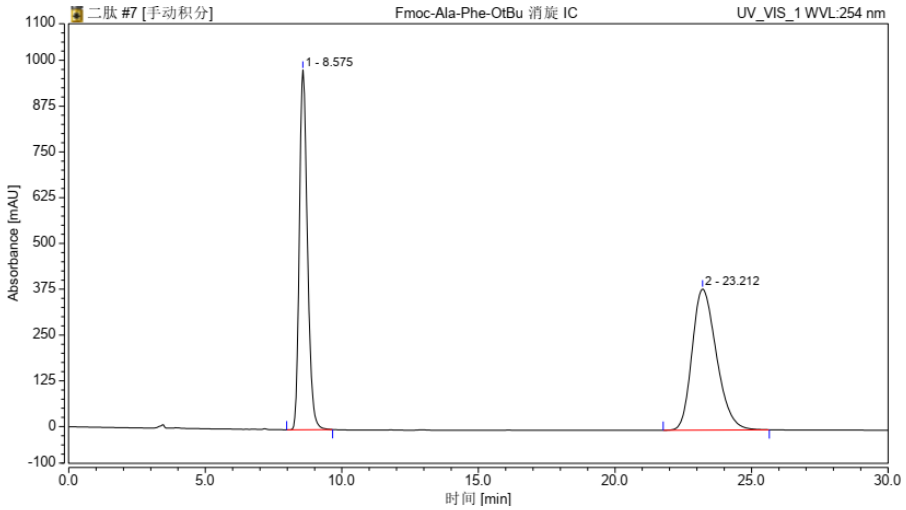


Crude HPLC

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	99.52	712.905	7.882	1521.523
2	0.48	3.430	13.042	4.230
Total:	100	716.335		1525.753

Fmoc-*DL*-Ala-Phe-O^{t}Bu

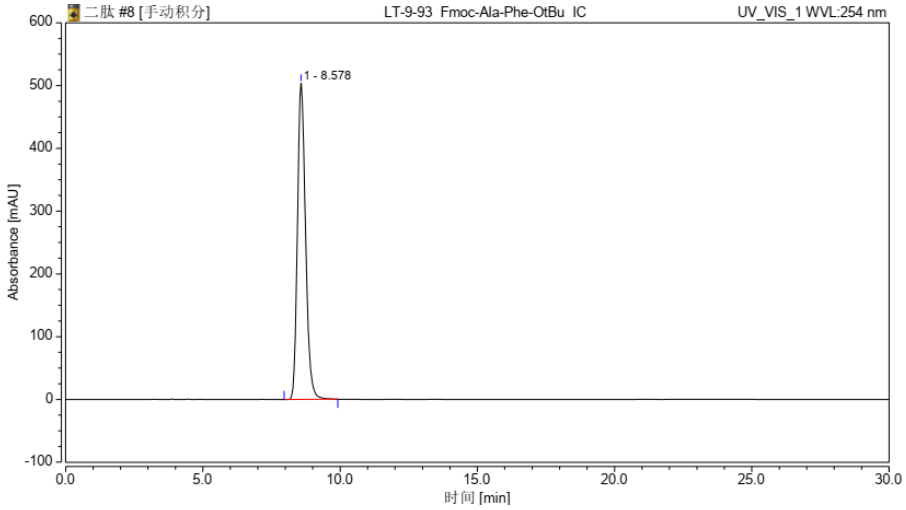


HPLC condition: chiral IC 250 × 4.6 mm^2 column; isocratic elution of 20% isopropanol in hexanes; flow rate = 1.0 mL/min; detection wavelength = 254 nm.

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	45.85	337.086	8.575	981.685
2	54.15	398.140	23.212	385.149
Total:	100	735.225		1366.834

Fmoc-Ala-Phe-O^{t}Bu (9a)

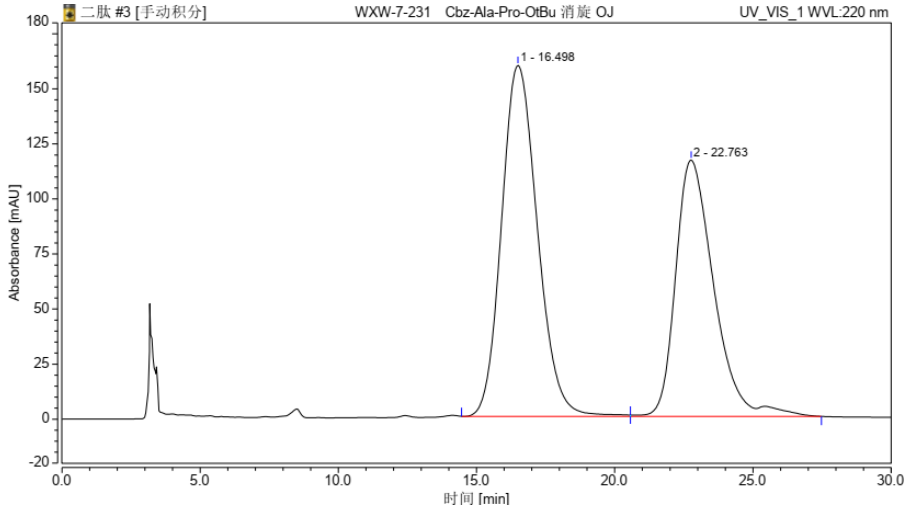


Crude HPLC

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	100	172.888	8.578	503.935
Total:	100	172.888		503.935

Cbz-*DL*-Ala-Pro-O^{t}Bu

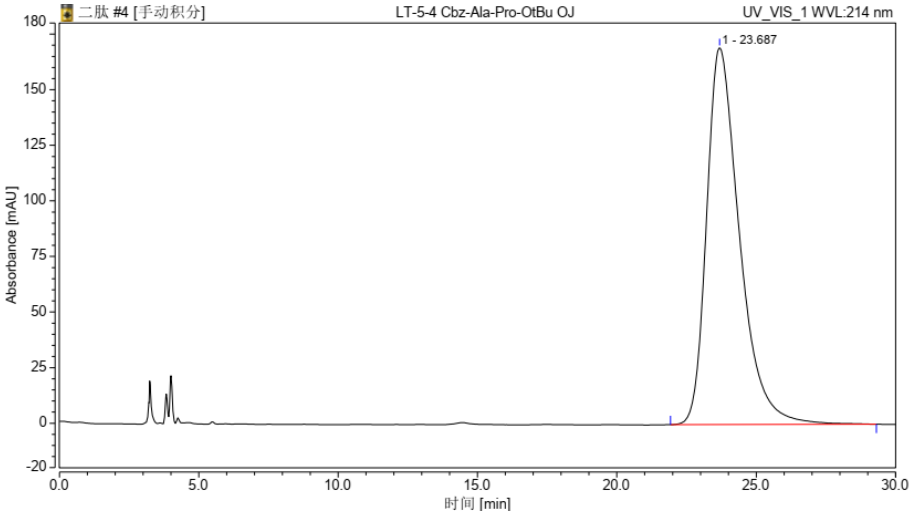


HPLC condition: chiral OJ 250 × 4.6 mm^2 column; isocratic elution of 5% isopropanol in hexanes; flow rate = 1.0 mL/min; detection wavelength = 220 nm.

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	56.26	240.009	16.498	159.377
2	43.74	186.628	22.763	116.420
Total:	100	735.225		426.638

Cbz-Ala-Pro-O^{t}Bu (9e)

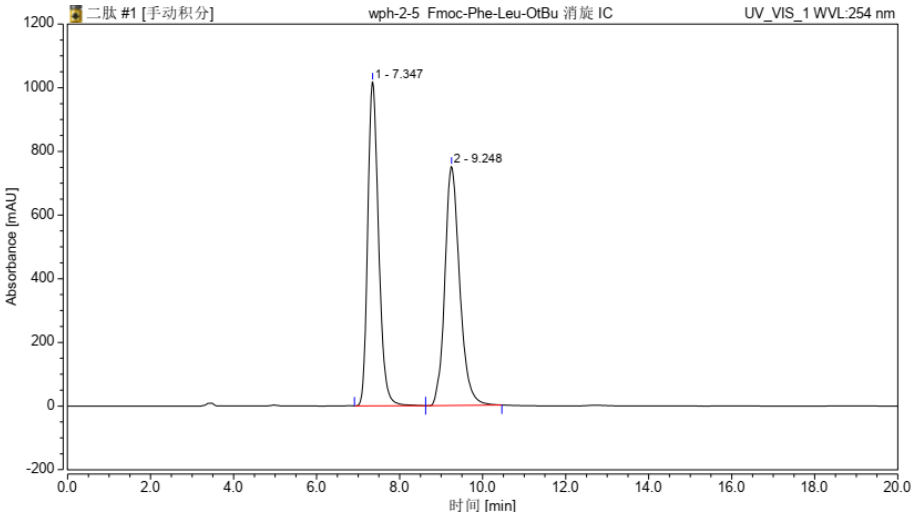


Crude HPLC

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	100	231.782	23.687	169.509
Total:	100	231.782		169.509

Fmoc-*DL*-Phe-Leu-O^{t}Bu

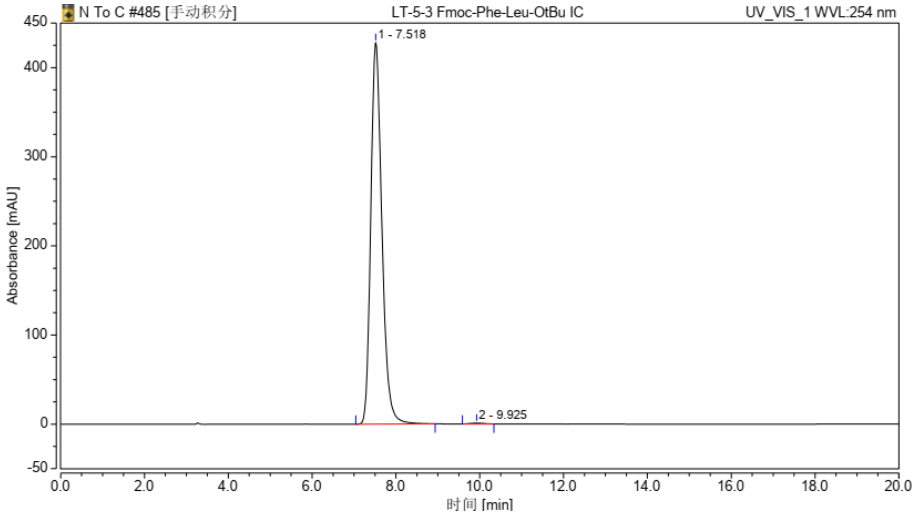


HPLC condition: chiral IC 250 × 4.6 mm^2 column; isocratic elution of 10% isopropanol in hexanes; flow rate = 1.0 mL/min; detection wavelength = 254 nm.

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	49.77	307.994	7.347	1017.952
2	50.23	310.853	9.248	751.876
Total:	100	618.846		1769.828

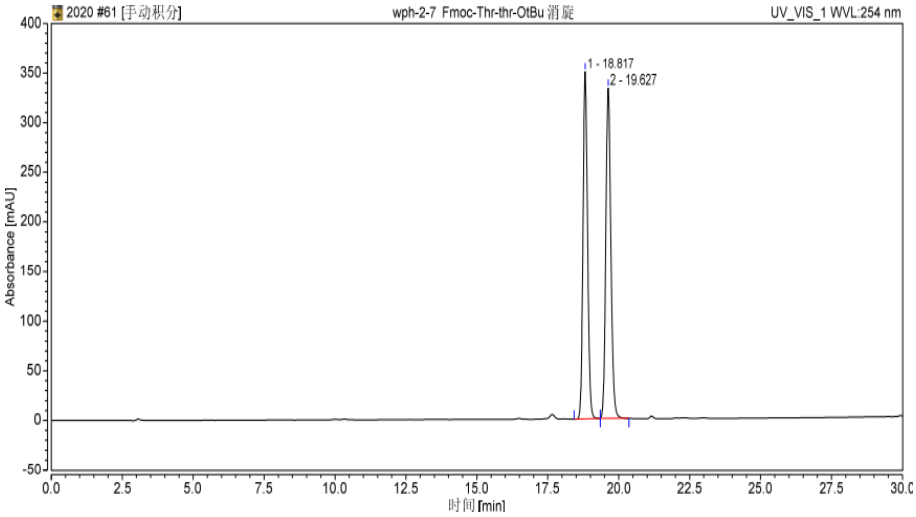
Fmoc-Phe-Leu-O^{t}Bu (9d)



Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	99.72	131.547	7.518	428.021
2	0.28	0.368	9.925	1.001
Total:	100	131.915		429.022

Fmoc-*DL*-Thr-Thr-O^{t}Bu

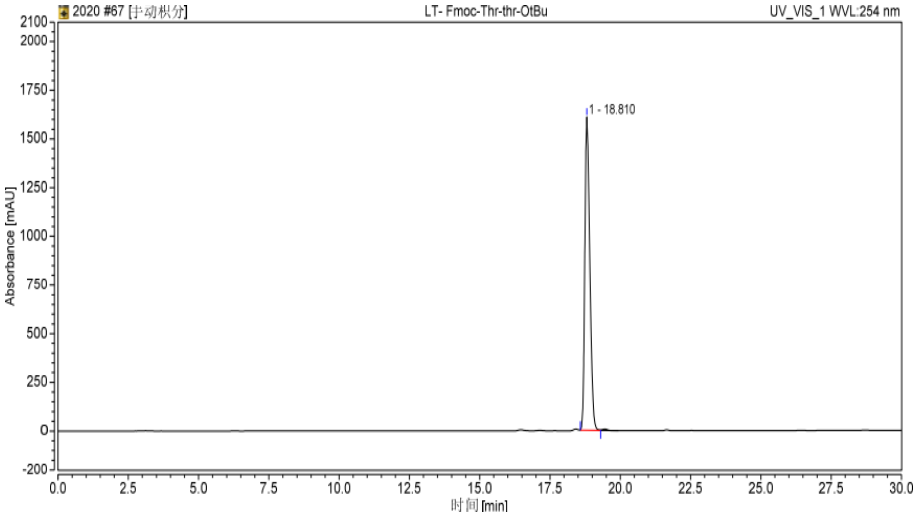


HPLC condition: Chiral MD(2)-RH 5u 4.6 × 250 mm^2 column; 0.045% TFA (v/v) in water (solvent A), 0.039% TFA (v/v) and 10% H_2O in acetonitrile (solvent B); gradient 10-100% (solvent B) in 30 min; flow rate = 1.0 mL/min; detection wavelength = 254 nm.

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	48.59	64.867	18.817	349.546
2	51.41	68.634	19.627	332.579
Total:	100	133.501		682.125

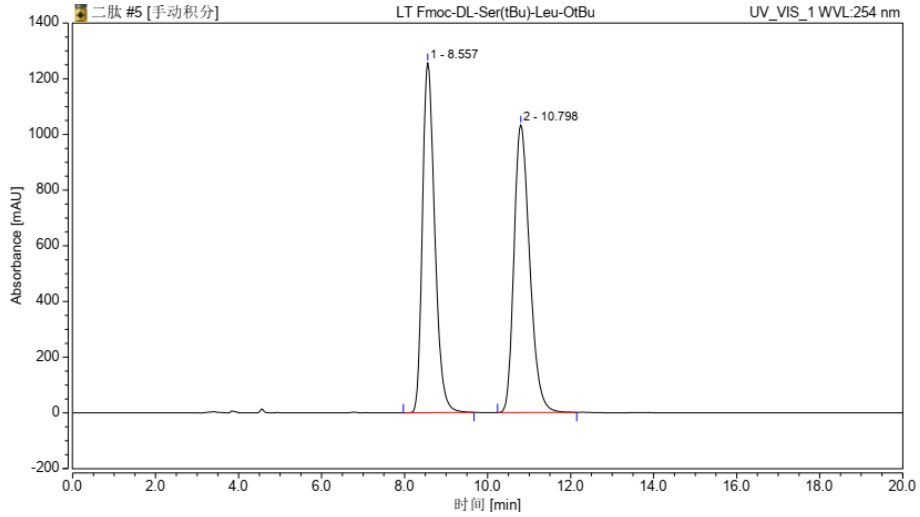
Fmoc-Thr-Thr-O^{t}Bu (9f)



Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	100	329.102	18.810	1607.778
Total:	100	329.102		1607.778

Fmoc-*DL*-Ser(O^{t}Bu)-Leu-O^{t}Bu

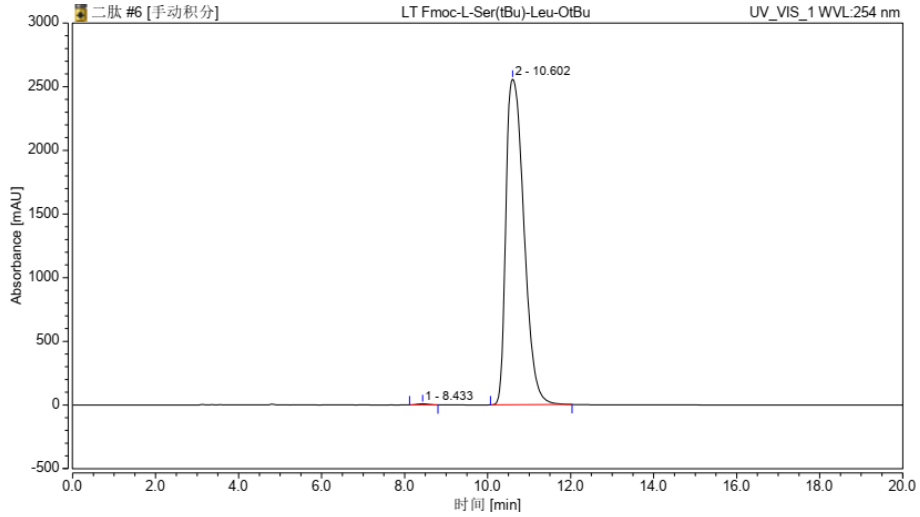


HPLC condition: chiral IC 250 × 4.6 mm^2 column; isocratic elution of 10% isopropanol in hexanes; flow rate = 1.0 mL/min; detection wavelength = 254 nm.

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	48.80	431.879	8.557	1257.412
2	51.20	453.069	10.798	1033.367
Total:	100	884.948		2290.779

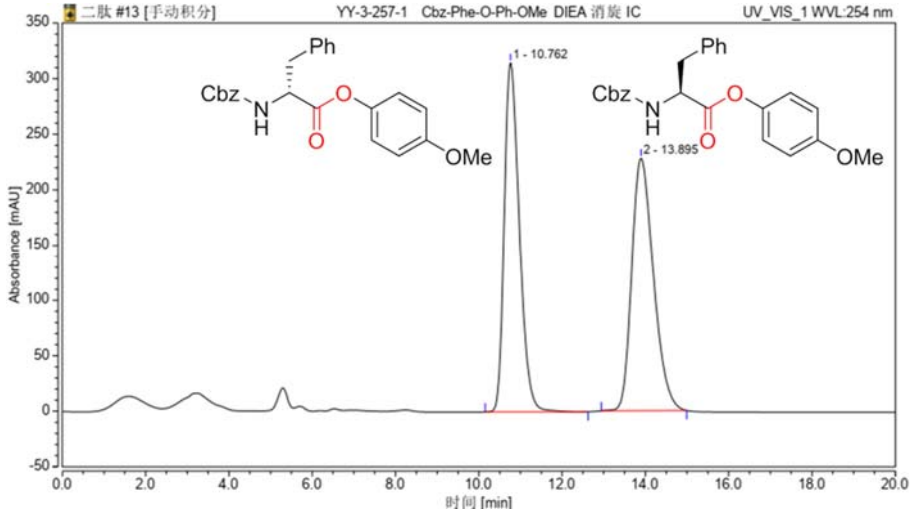
Fmoc-Ser(O^{t}Bu)-Leu-O^{t}Bu (9h)



Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	0.19	8.193	8.433	8.193
2	99.81	2557.867	10.602	2557.867
Total:	100	2566.059		2566.059

11f (D) and 11f (L)

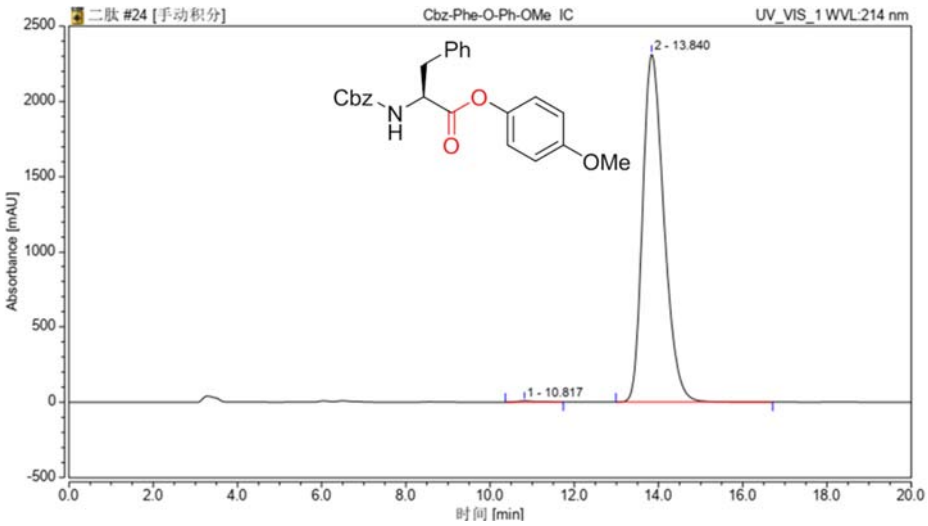


HPLC condition: chiral IC 250 × 4.6 mm^2 column; isocratic elution of 30% isopropanol in hexanes; flow rate = 1.0 mL/min; detection wavelength = 254 nm.

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	49.03	132.348	10.762	314.969
2	50.97	137.579	13.895	228.060
Total:	100	269.926		543.030

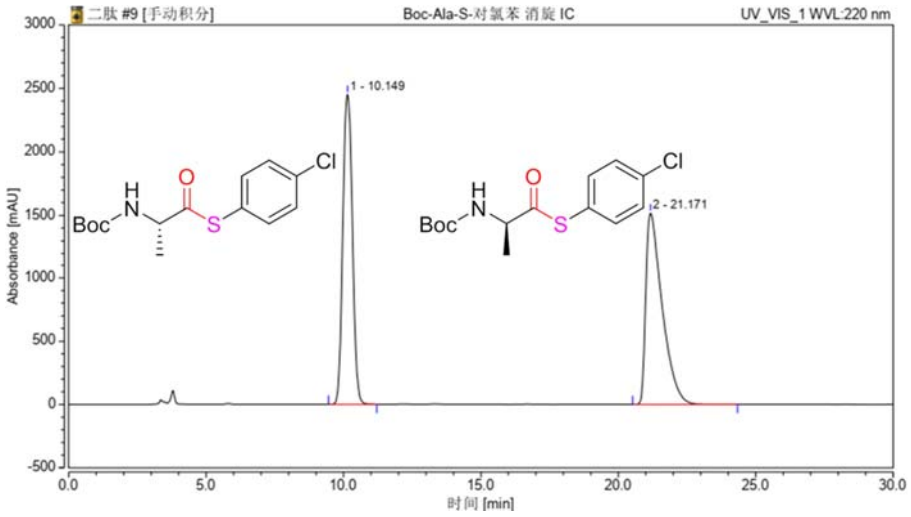
11f



Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	0.30	4.004	10.817	7.537
2	99.70	1353.053	13.840	2312.765
Total:	100	1357.057		2320.302

11j (L) and 11j (D)

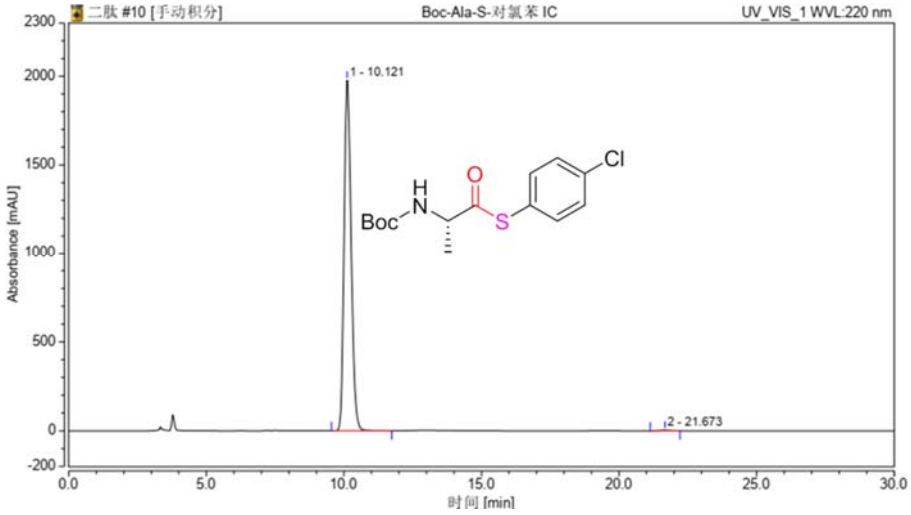


HPLC condition: chiral IC 250 × 4.6 mm^2 column; isocratic elution of 5% isopropanol in hexanes; flow rate = 1.0 mL/min; detection wavelength = 220 nm.

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	48.67	989.935	10.149	2452.158
2	51.33	1044.071	21.171	1520.742
Total:	100	2034.007		3978.900

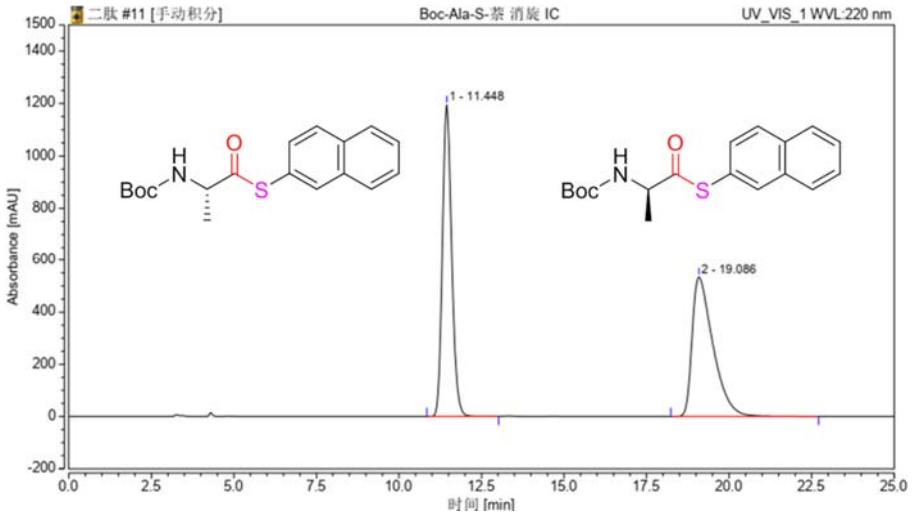
11j



Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	99.64	586.793	10.121	1977.042
2	0.36	2.125	21.673	3.888
Total:	100	588.917		1980.930

11k (L) and 11k (D)

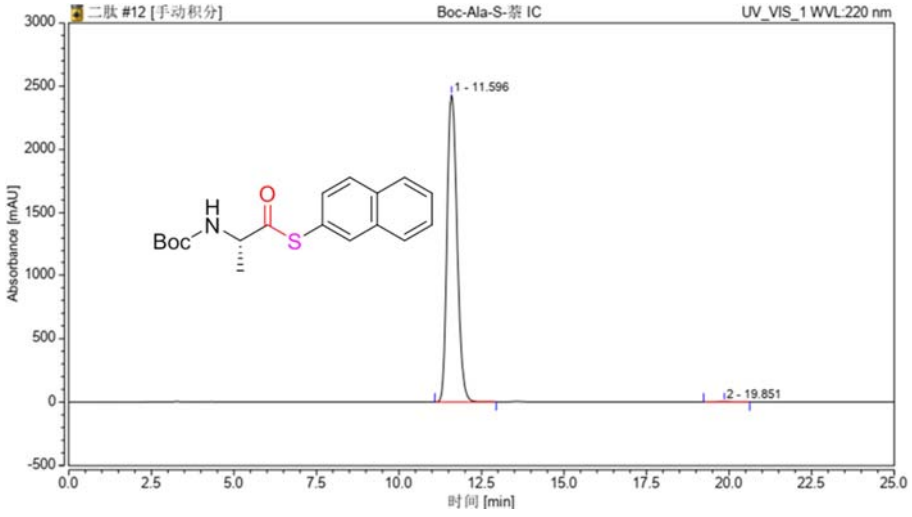


HPLC condition: chiral IC 250 × 4.6 mm^2 column; isocratic elution of 10% isopropanol in hexanes; flow rate = 1.0 mL/min; detection wavelength = 220 nm.

Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	49.89	389.251	11.448	1194.894
2	50.11	391.014	19.086	534.695
Total:	100	780.264		1729.589

11k

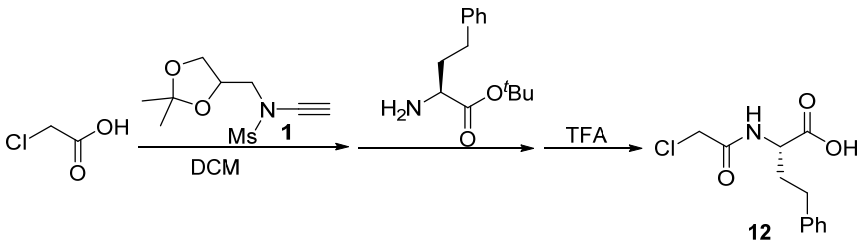


Peak Info

Peak No	% Area	Area	RT (min)	Height (mAV)
1	99.87	854.132	11.596	2429.329
2	0.13	1.140	19.851	1.794
Total:	100	855.272		2431.123

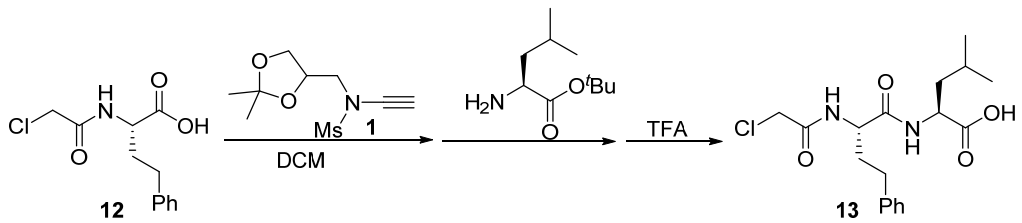
7. The procedure for the synthesis of Carfilzomib

The synthesis of **12**:



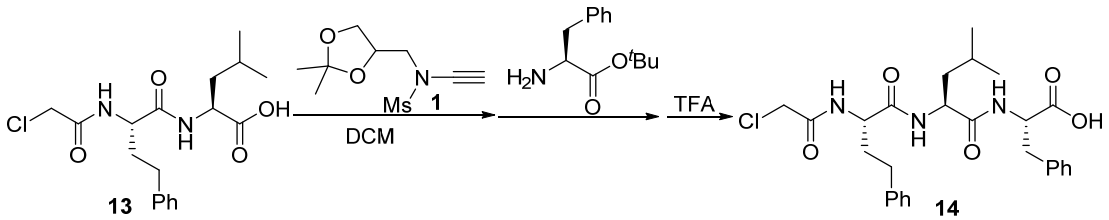
Chloroacetic acid (5 mmol), **1** (6 mmol) and DCM (10 mL) were added to a round-bottom flask and stirred at 35 °C for 30 min. Then H-Hpa-O^{t}Bu (5.5 mmol) was added for 5 h to obtain dipeptide butyl acetate. TFA (20 mL) was added to the reaction mixture stirred for hours to remove the *tert*-butyl group and the mixture was concentrated to dryness under vacuum. The dry residue was then dissolved in 50 mL EA and washed with H_2O for two times and dried with $MgSO_4$. After concentrated, 3 mL EA was added to dissolve the sample and recrystallized by ice ethyl ether. Precipitate appeared, and the white precipitate was filtered and dried to afford the pure product **12**. White solid, 93% yield.

The synthesis of **13**:



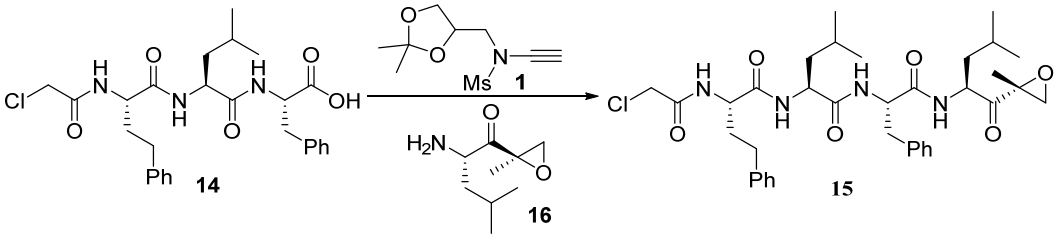
12 (4 mmol), **1** (5 mmol) and DCM (15 mL) were added to a clean round-bottom flask and stirred at 35 °C for 3 h. Then H-Leu-O^{t}Bu (4.4 mmol) was added for 12 h to obtain tripeptide butyl acetate. TFA (20 mL) was added to the system and stirred for hours to remove the *tert*-butyl group , then the mixture was concentrated to dryness under vacuum. The dry residue was then dissolved in 50 mL EA and washed with H_2O for two times and dried with $MgSO_4$. After concentrated, 3 mL EA was added to dissolve the sample and recrystallized by ice ethyl ether. Precipitate appeared, and the white precipitate was filtered and dried to afford the pure product **13**. White solid, 94% yield.

The synthesis of **14:**



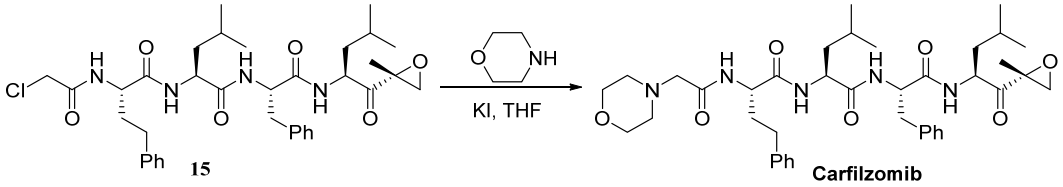
13 (3 mmol), **1** (5 mmol) and DCM (15 mL) were added to a clean round-bottom flask and stirred at 35 ° C for 7 h. Then H-Phe-O^{t}Bu (4 mmol) was added for 14 h to obtain tetrapeptide butyl acetate. TFA (20 mL) was added to the system and stirred for hours to remove the *tert*-butyl group, then mixture was concentrated to dryness under vacuum. The dry residue was then dissolved in 50 mL EA and washed with H_2O for two times and dried with $MgSO_4$. After concentrated, 3 mL EA was added to dissolve the sample and recrystallized by ethyl ether. Precipitate appeared, and the white precipitate was filtered and dried to afford the pure product **14**. White solid, 92% yield.

The synthesis of **15**:



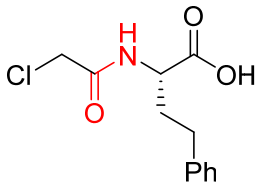
14 (2 mmol), **1** (4 mmol) and DCM (10 mL) were added to a clean round-bottom flask and stirred at 35 ° C for 12 h. Then **16** was added for 36 h and the solvent was removed under vacuum, and 1 M HCl (20 mL) was added. The solution was extracted with EA (30 mL). The organic layer was washed with 1 M HCl (20 mL), H_2O (20 mL) and dried with $MgSO_4$. After concentrated, 3 mL EA was added to dissolve the sample and recrystallized by ethyl ether. Precipitate appeared, and the white precipitate was filtered and dried to afford the pure product **15**. White solid, 88% yield.

The synthesis of **Carfizomib**:



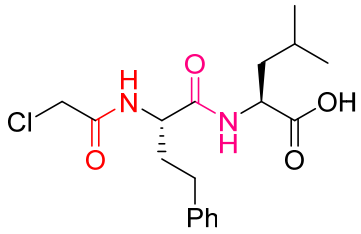
15 (0.5 mmol), morpholine (0.75 mmol), KI (0.5 mmol) and THF(5 mL) were added into a clean reaction tube and stirred at room temperature under nitrogen atmosphere for 12 h. Upon completion, the reaction mixture was washed with water and extracted with EA. After drying with $MgSO_4$, and then recrystallize with EA and petroleum ether to obtain carfilzomib (0.495 mmol), white solid, 99% yield.

(*S*)-2-(2-chloroacetamido)-4-phenylbutanoic acid



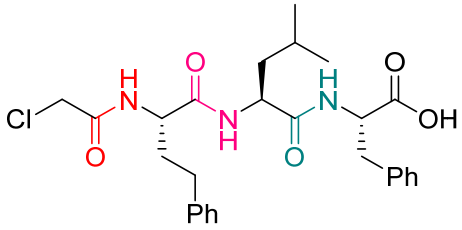
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, J = 7.7 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 4.22 – 4.09 (m, 3H), 2.62 (tt, J = 15.5, 7.3 Hz, 2H), 2.01 (ddt, J = 13.8, 7.2, 3.1 Hz, 1H), 1.91 (ddt, J = 17.9, 9.1, 4.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 173.1, 166.1, 140.9, 128.4, 128.4, 126.0, 51.7, 42.4, 32.7, 31.3.

((*S*)-2-(2-chloroacetamido)-4-phenylbutanoyl)-*L*-leucine



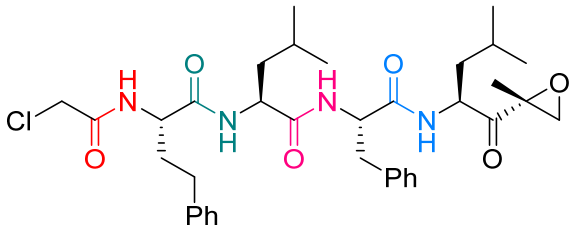
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (d, J = 8.0 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.20 – 7.16 (m, 3H), 4.44 – 4.36 (m, 1H), 4.27 – 4.21 (m, 1H), 4.15 (d, J = 2.0 Hz, 2H), 2.60 (t, J = 8.2 Hz, 2H), 1.97 – 1.81 (m, 2H), 1.70 – 1.61 (m, 1H), 1.59 – 1.49 (m, 2H), 0.91 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 173.9, 171.0, 165.7, 141.5, 128.3, 128.2, 125.8, 52.3, 50.3, 42.6, 39.7, 34.5, 31.1, 24.3, 22.9, 21.3.

((*S*)-2-(2-chloroacetamido)-4-phenylbutanoyl)-*L*-leucyl-*L*-phenylalanine



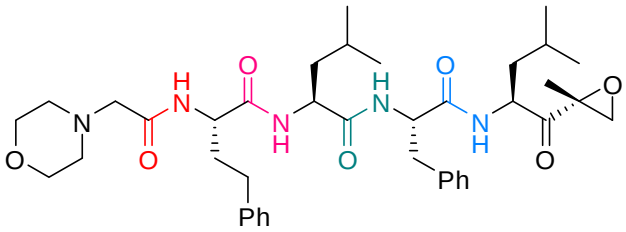
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (d, J = 7.6 Hz, 1H), 8.15 (d, J = 7.8 Hz, 1H), 8.10 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 7.4 Hz, 2H), 7.22 – 7.15 (m, 7H), 7.12 – 7.07 (m, 1H), 4.49 – 4.41 (m, 1H), 4.40 – 4.32 (m, 2H), 4.18 – 4.10 (m, 2H), 3.05 (dd, J = 14.0, 4.7 Hz, 1H), 2.95 – 2.89 (m, 1H), 2.60 – 2.51 (m, 2H), 1.93 – 1.75 (m, 2H), 1.64 – 1.55 (m, 1H), 1.43 (t, J = 6.9 Hz, 2H), 0.86 (dd, J = 18.5, 6.5 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.7, 171.8, 170.6, 165.8, 141.4, 137.4, 129.0, 128.3, 128.3, 128.1, 126.3, 125.8, 53.2, 52.6, 50.9, 42.6, 40.8, 36.6, 34.3, 31.3, 24.1, 23.0, 21.7.

(*S*)-2-((*S*)-2-(2-chloroacetamido)-4-phenylbutanamido)-4-methyl-*N*-((*S*)-1-(((*S*)-4-methyl-1-((*R*)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)pentanamide



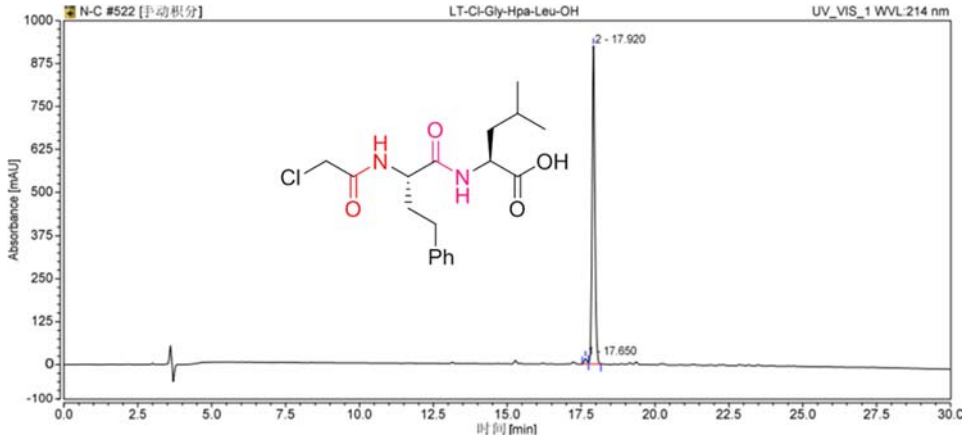
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, J = 7.4 Hz, 1H), 7.28 (t, J = 7.4 Hz, 2H), 7.20 – 7.12 (m, 7H), 7.09 – 7.05 (m, 1H), 4.56 (td, J = 8.6, 5.0 Hz, 1H), 4.39 – 4.25 (m, 3H), 4.13 (d, J = 4.9 Hz, 2H), 3.11 (d, J = 5.2 Hz, 1H), 3.01 – 2.93 (m, 2H), 2.75 (dd, J = 14.0, 9.0 Hz, 1H), 2.60 – 2.51 (m, 2H), 1.92 – 1.84 (m, 1H), 1.82 – 1.75 (m, 1H), 1.67 – 1.60 (m, 1H), 1.56 – 1.49 (m, 1H), 1.41 – 1.29 (m, 7H), 0.86 (t, J = 7.2 Hz, 6H), 0.81 (dd, J = 6.3, 3.3 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 208.1, 171.4, 171.0, 170.7, 165.9, 141.4, 137.4, 129.1, 128.3, 128.2, 127.9, 126.1, 125.8, 58.8, 52.9, 52.6, 51.5, 51.2, 49.3, 42.6, 40.7, 38.5, 37.5, 34.1, 31.3, 24.5, 24.1, 23.1, 23.0, 21.6, 21.0, 16.4.

Carfilzomib



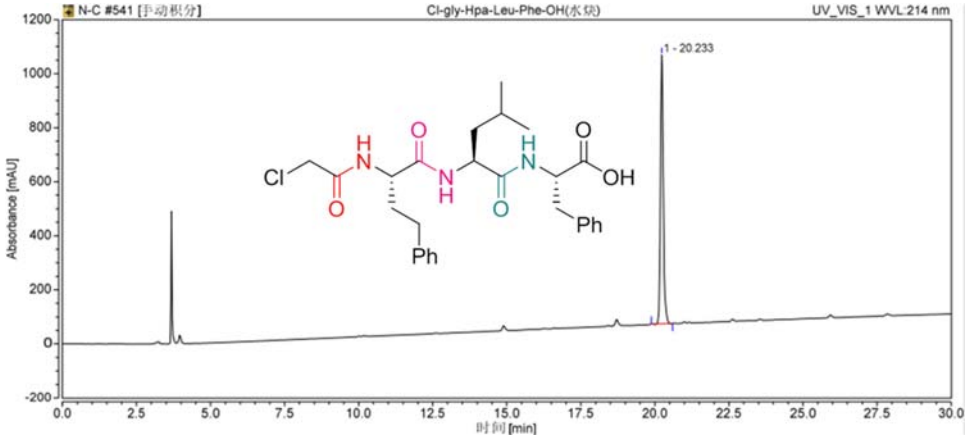
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, J = 6.8 Hz, 1H), 8.09 (d, J = 7.7 Hz, 1H), 7.97 (d, J = 7.7 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.33 – 7.23 (m, 2H), 7.23 – 7.02 (m, 8H), 4.61 – 4.49 (m, 1H), 4.43 – 4.32 (m, 2H), 4.32 – 4.23 (m, 1H), 3.71 – 3.51 (m, 4H), 3.41 – 3.32 (m, 1H), 3.12 (d, J = 4.2 Hz, 1H), 3.06 – 2.85 (m, 4H), 2.81 – 2.70 (m, 1H), 2.57 – 2.51 (m, 1H), 2.47 – 2.38 (m, 4H), 1.93 – 1.76 (m, 2H), 1.69 – 1.59 (m, 1H), 1.55 – 1.47 (m, 1H), 1.43 – 1.28 (m, 7H), 0.89 – 0.83 (m, 6H), 0.83 – 0.76 (m, 6H). ^{13}C NMR (100 MHz, DMSO) δ 208.2, 171.5, 171.0, 170.9, 168.8, 141.5, 137.4, 129.1, 128.3, 128.2, 127.9, 126.1, 125.8, 66.1, 61.3, 58.8, 53.2, 53.0, 51.8, 51.5, 51.1, 49.2, 40.8, 38.5, 37.4, 34.3, 31.4, 24.5, 24.1, 23.2, 23.0, 21.6, 21.0, 16.4.

HPLC of 13



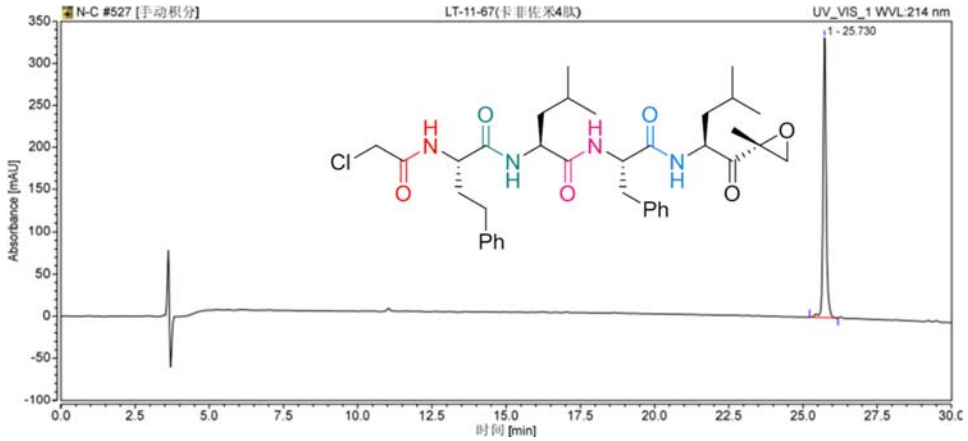
HPLC condition: Jupiter 5μm C18 4.6 × 250 mm^2 column; 0.045% TFA (v/v) in water (solvent A), 0.039% TFA (v/v) and 10% H_2O in acetonitrile (solvent B); gradient 10-100% (solvent B) in 30 min; flow rate = 1.0 mL/min; detection wavelength = 214 nm, t_R = 17.920 min.

HPLC of 14



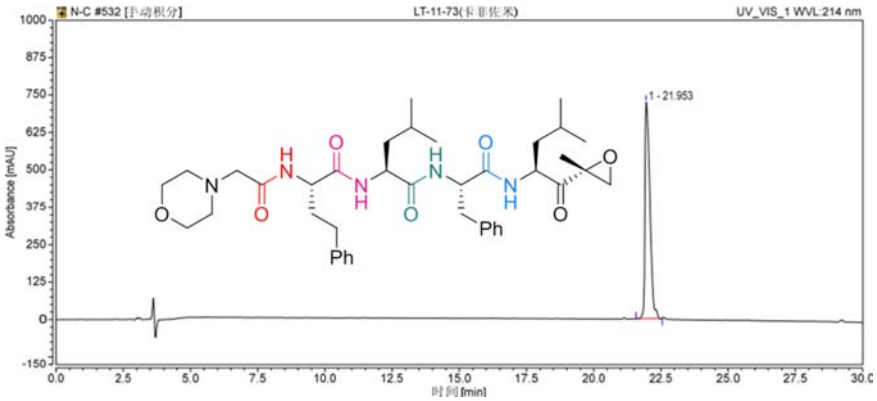
HPLC condition: Jupiter 5μm C18 4.6 × 250 mm^2 column; 0.045% TFA (v/v) in water (solvent A), 0.039% TFA (v/v) and 10% H_2O in acetonitrile (solvent B); gradient 10-100% (solvent B) in 30 min; flow rate = 1.0 mL/min; detection wavelength = 214 nm, t_R = 20.233 min.

HPLC of 15



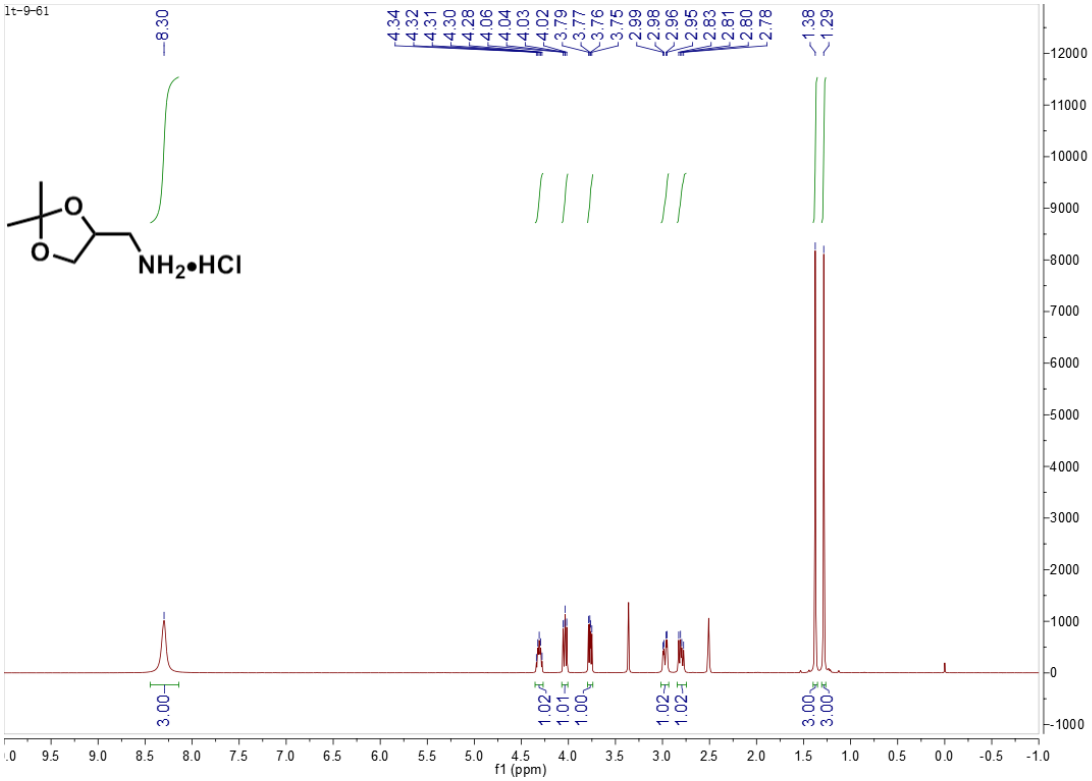
HPLC condition: Jupiter 5μm C18 4.6 × 250 mm^2 column; 0.045% TFA (v/v) in water (solvent A), 0.039% TFA (v/v) and 10% H_2O in acetonitrile (solvent B); gradient 10-100% (solvent B) in 30 min; flow rate = 1.0 mL/min; detection wavelength = 214 nm, t_R = 25.730 min.

HPLC of Carfilzomib

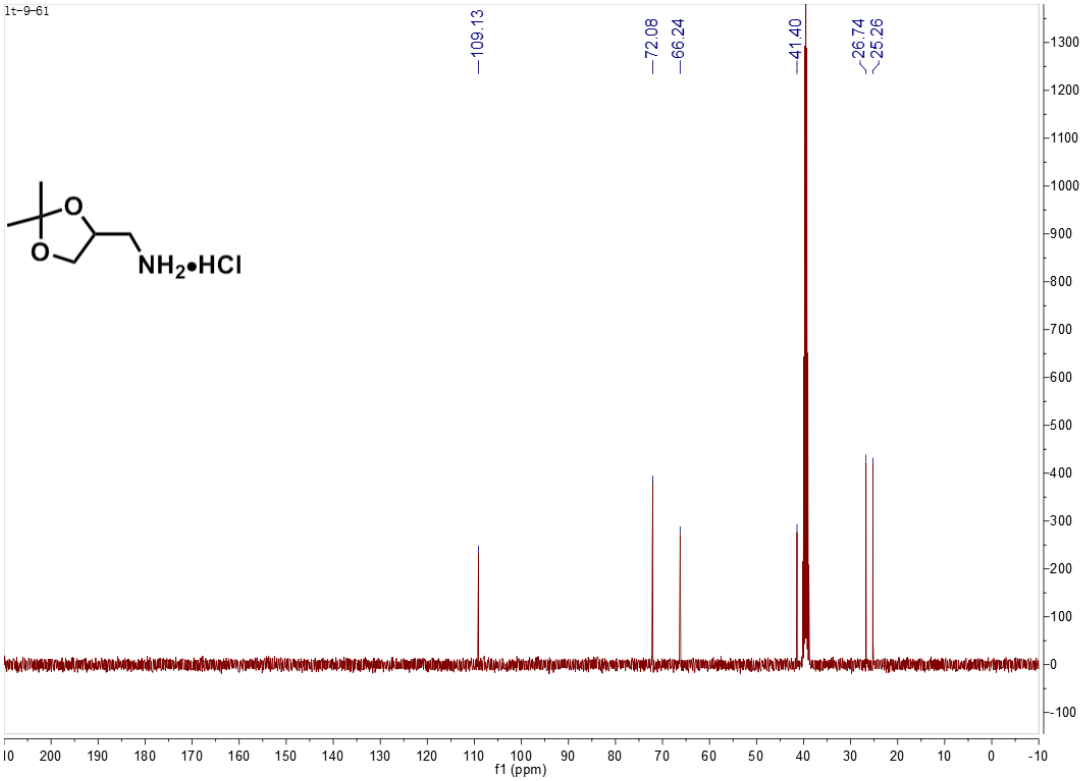


HPLC condition: Jupiter 5μm C18 4.6 × 250 mm^2 column; 0.045% TFA (v/v) in water (solvent A), 0.039% TFA (v/v) and 10% H_2O in acetonitrile (solvent B); gradient 10-100% (solvent B) in 30 min; flow rate = 1.0 mL/min; detection wavelength = 214 nm, t_R = 21.953 min.

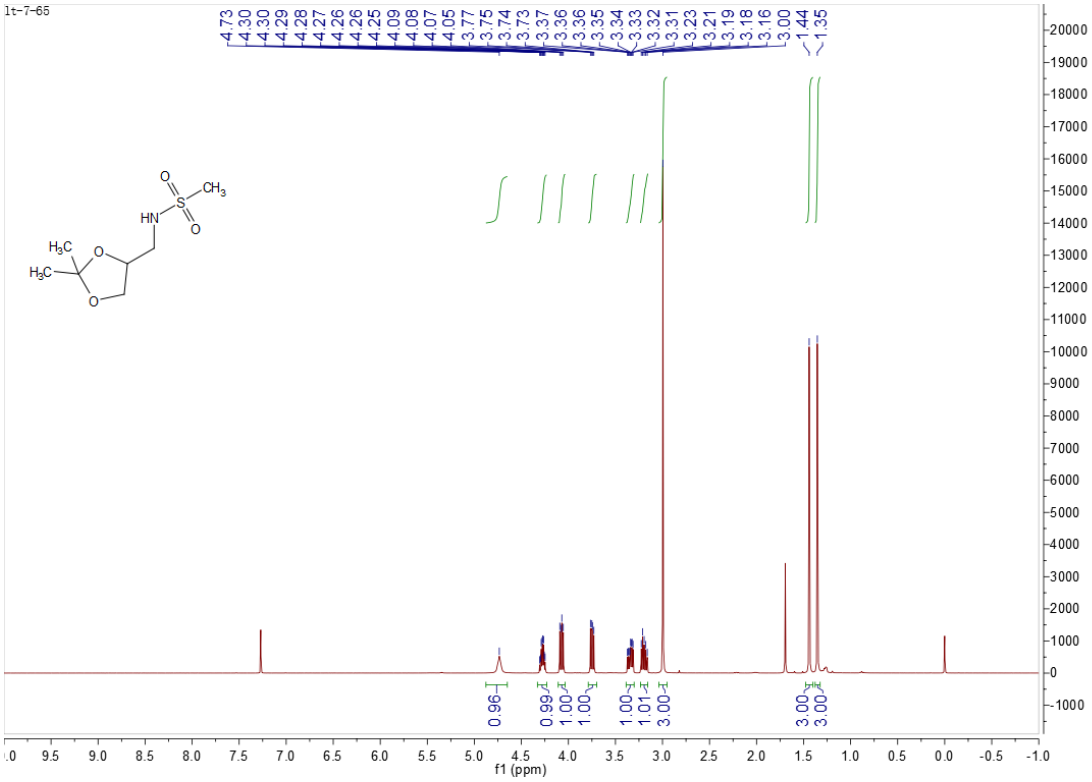
NMR Spectrum



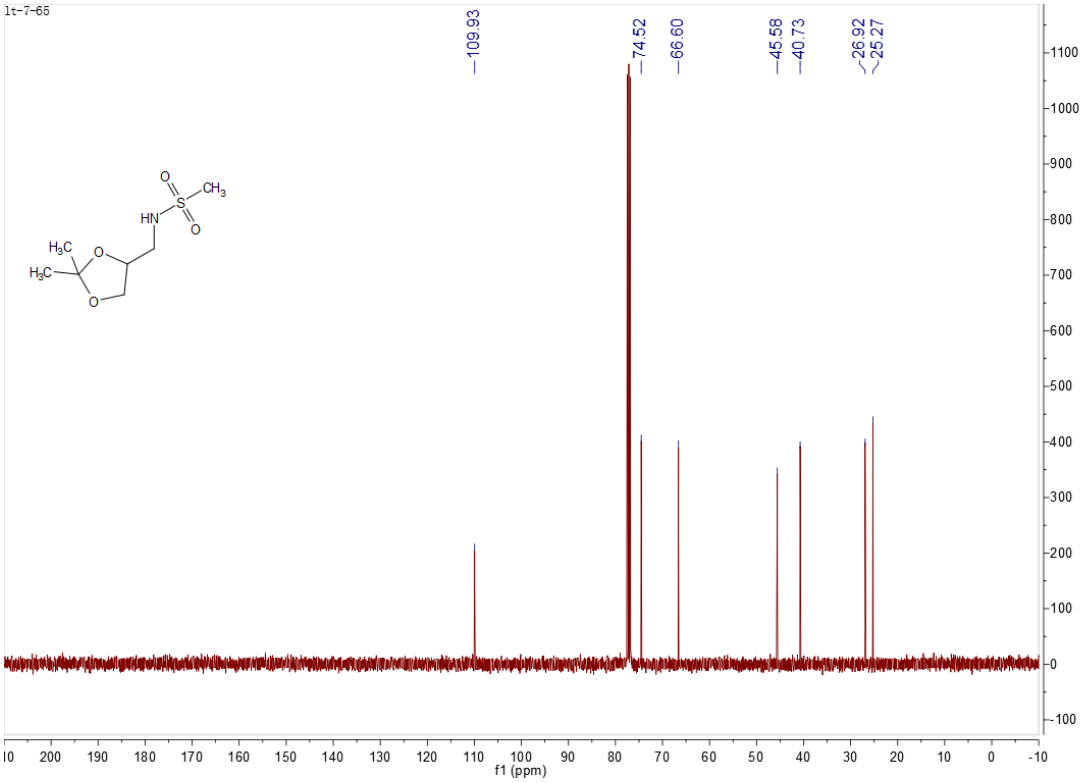
^{1}H NMR(400 Mz) spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methanamine hydrochloride in DMSO-d_6



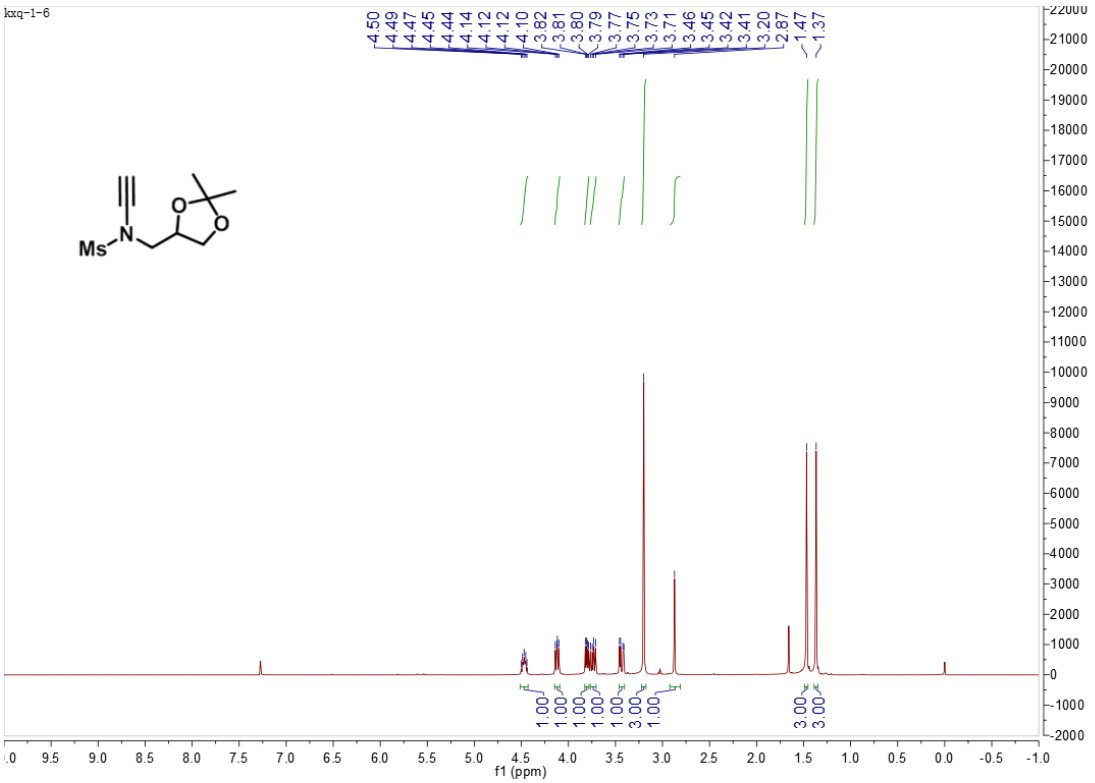
^{13}C NMR(100 Mz) spectrum of (2,2-dimethyl-1,3-dioxolan-4-yl)methanamine hydrochloride in DMSO-d_6



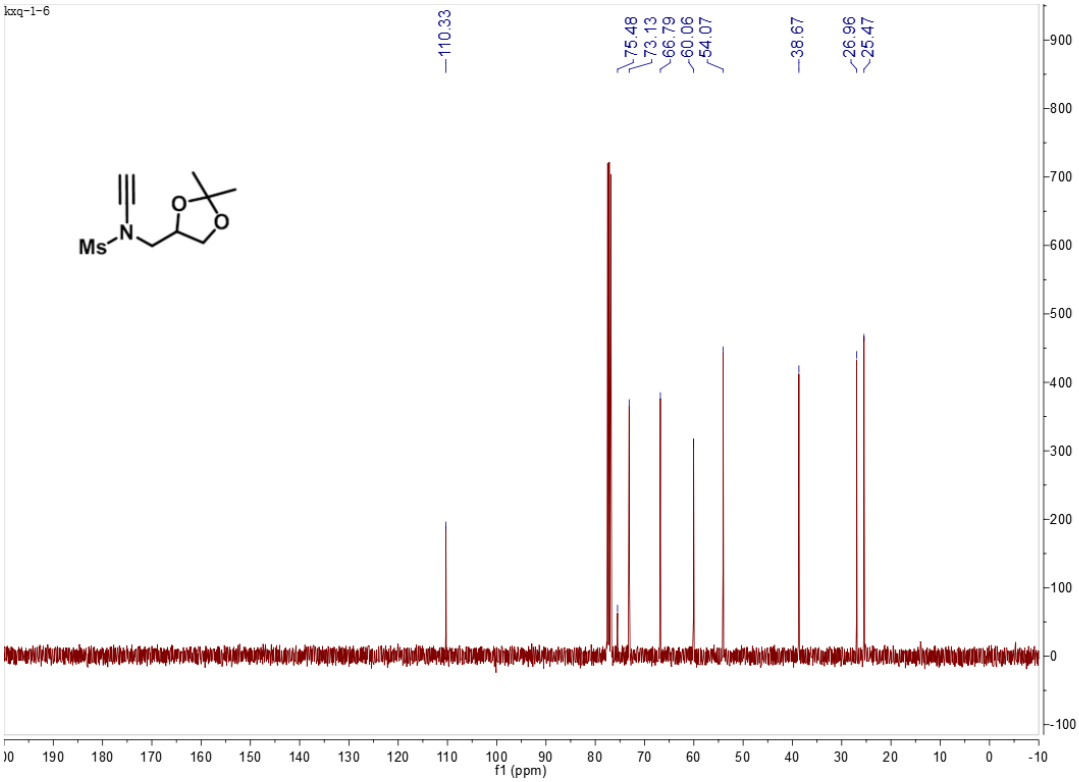
^{1}H NMR(400 Mz) spectrum of
N-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)methanesulfonamide in $CDCl_3$



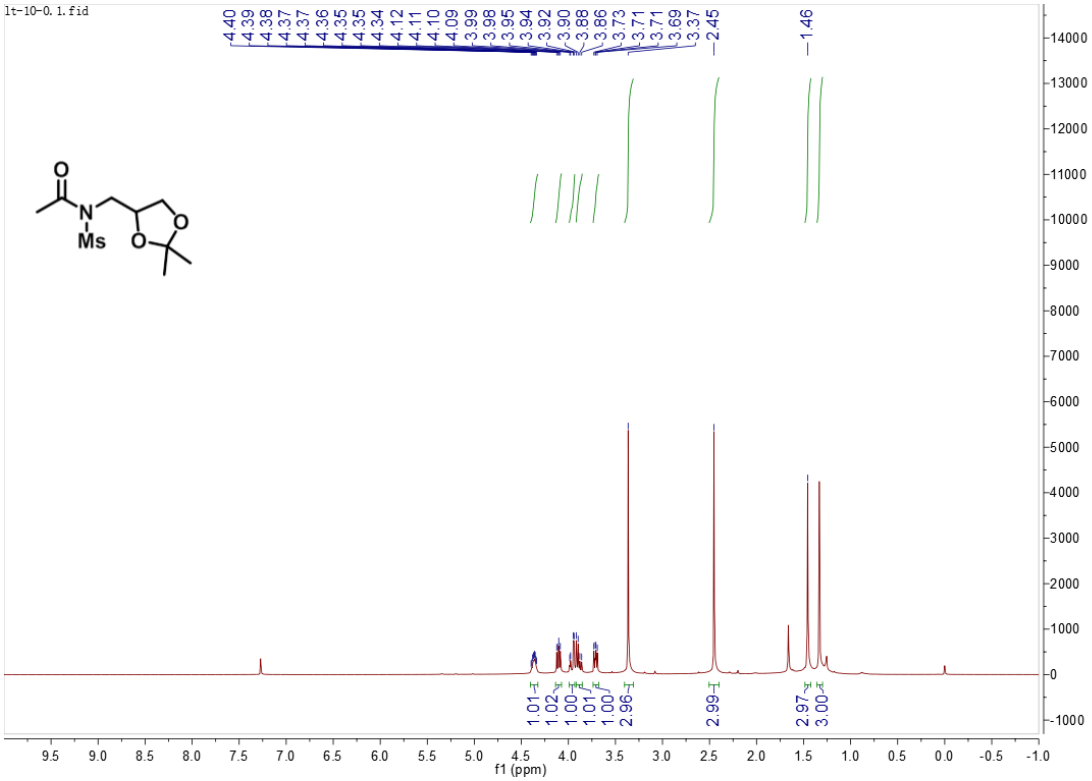
^{13}C NMR(100 Mz) spectrum of
N-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)methanesulfonamide in $CDCl_3$



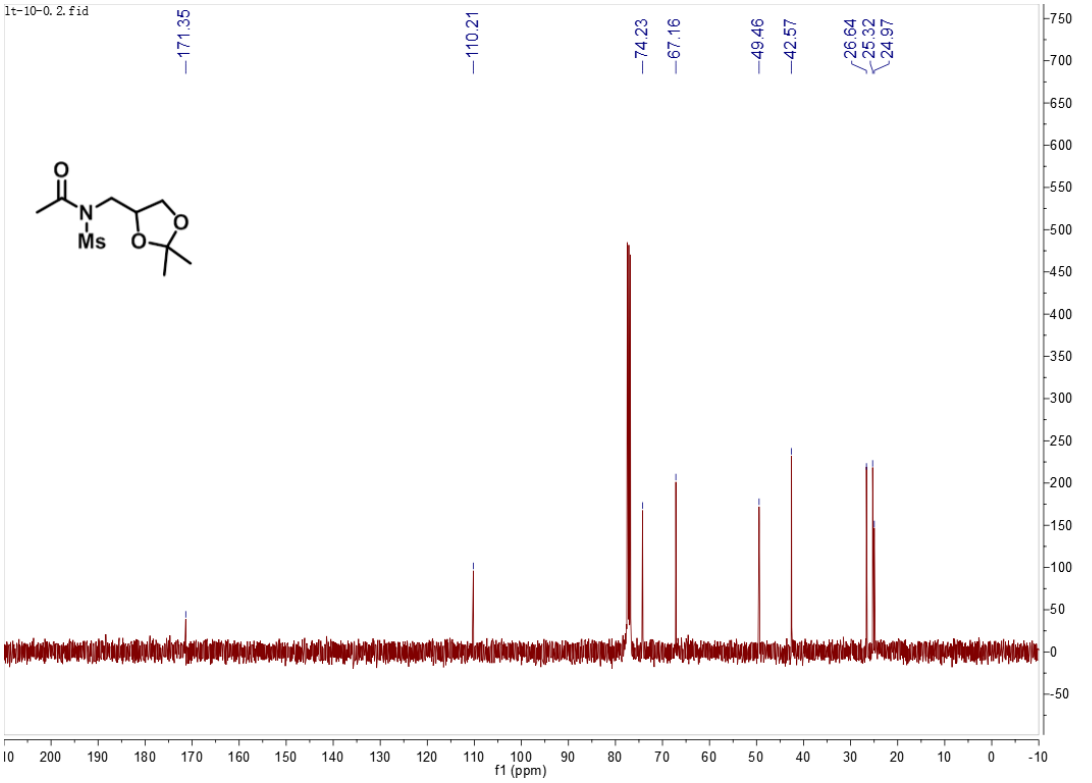
^{1}H NMR(400 Mz) spectrum of compound **1** in $CDCl_3$



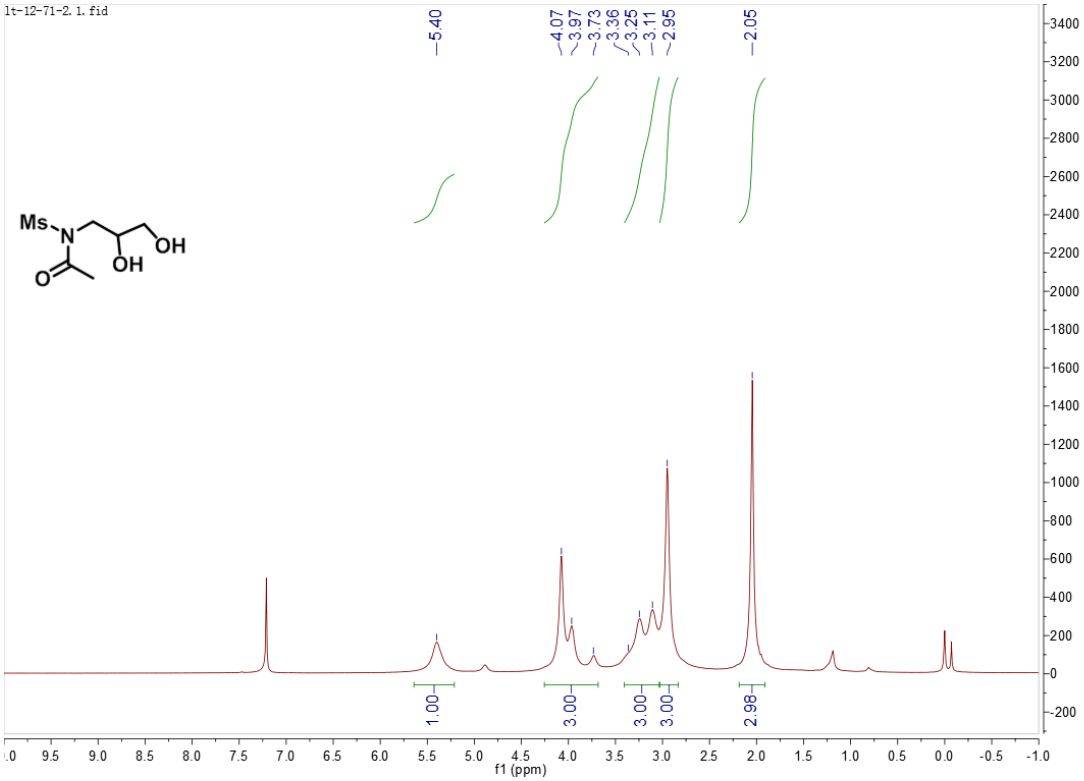
^{13}C NMR(100 Mz) spectrum of compound **1** in $CDCl_3$



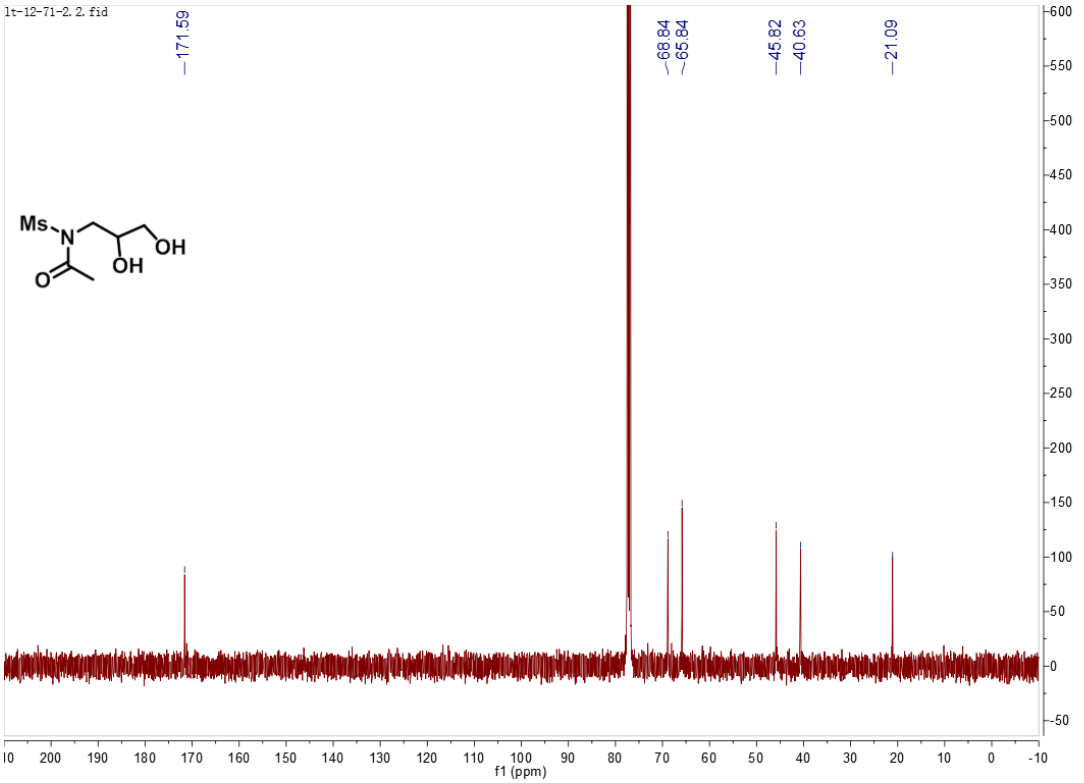
^{1}H NMR(400 Mz) spectrum of compound **2** in $CDCl_3$



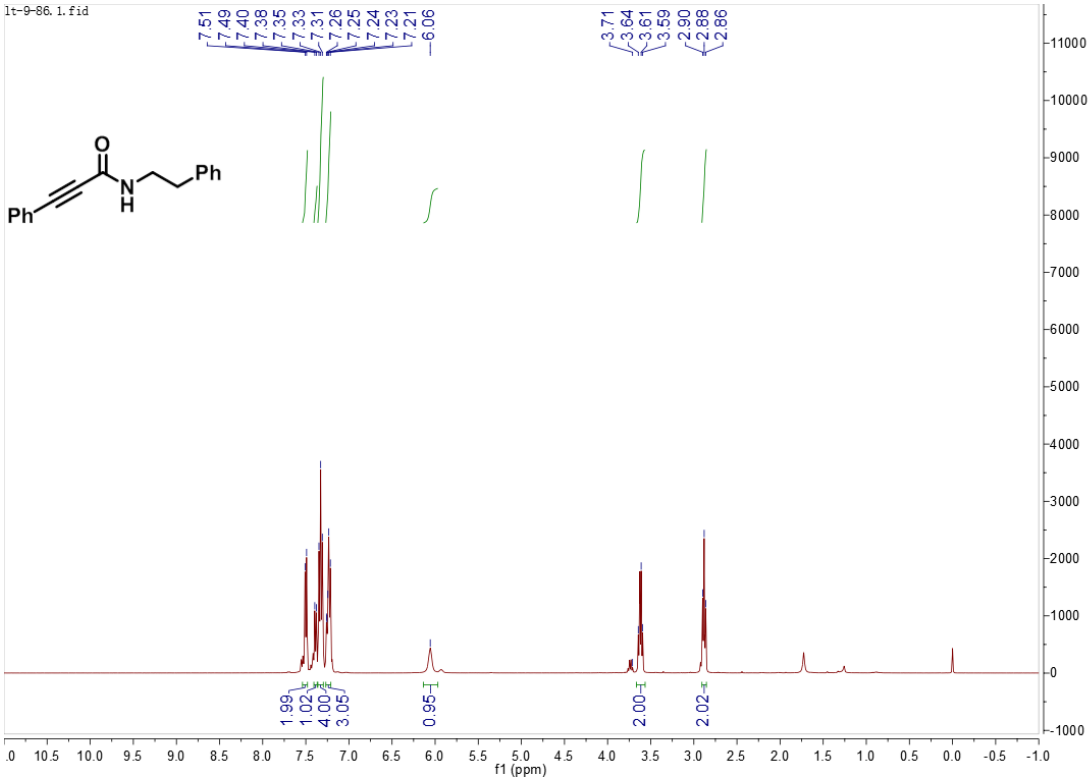
^{13}C NMR(100 Mz) spectrum of compound **2** in $CDCl_3$



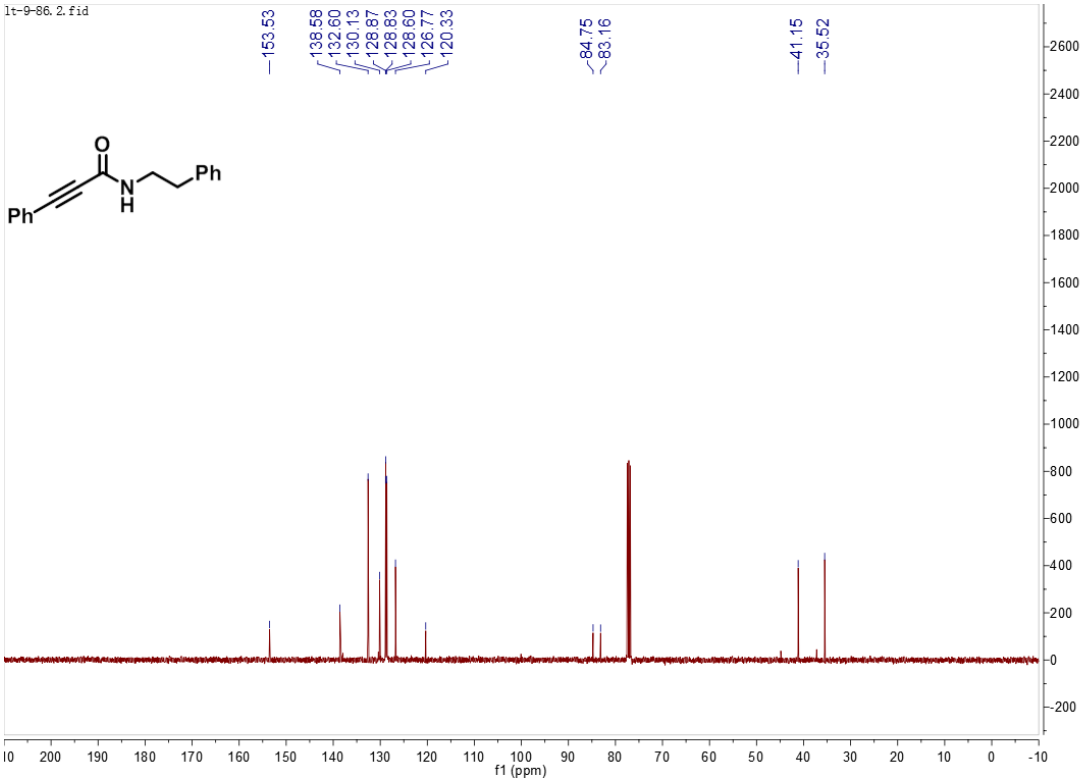
^{1}H NMR(400 Mz) spectrum of compound **3** in $CDCl_3$



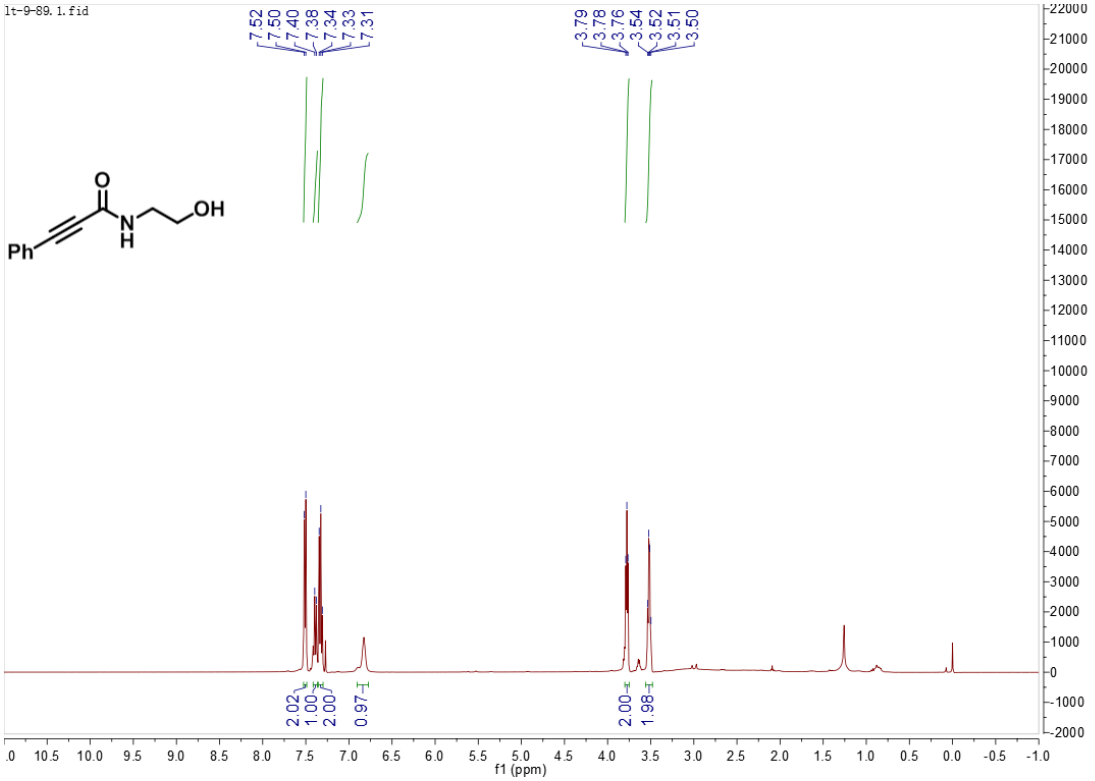
^{13}C NMR(100 Mz) spectrum of compound **3** in $CDCl_3$



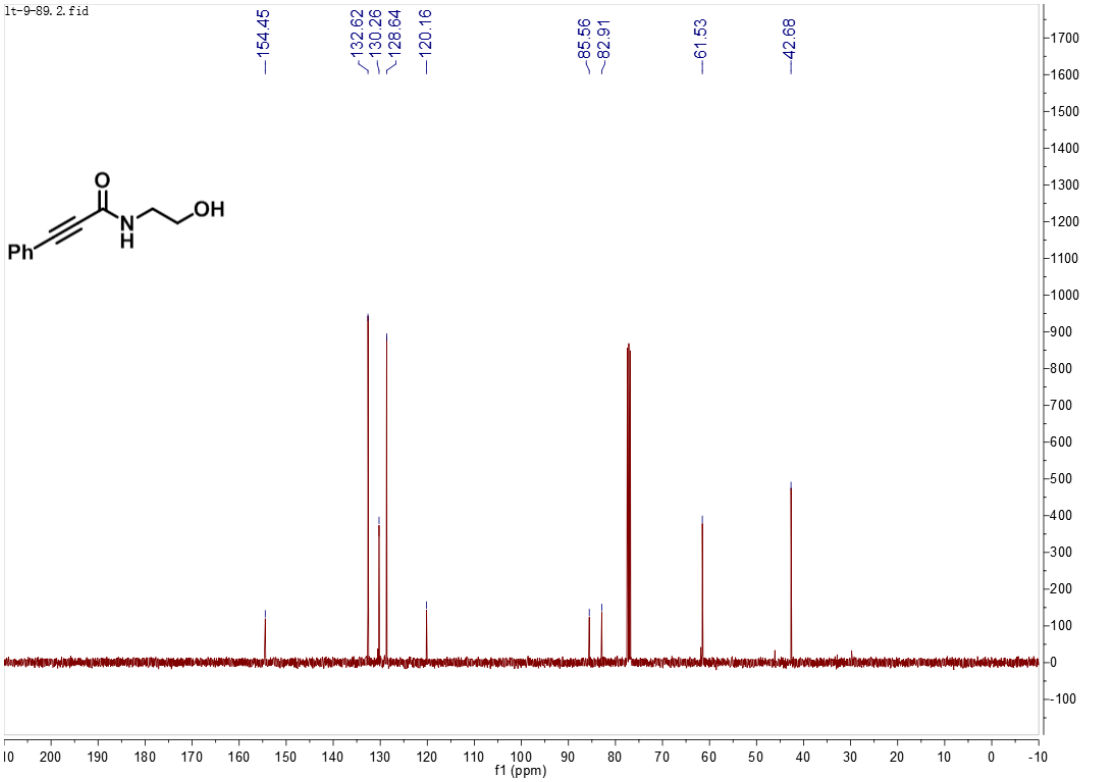
^{1}H NMR(400 Mz) spectrum of compound **6a** in $CDCl_3$



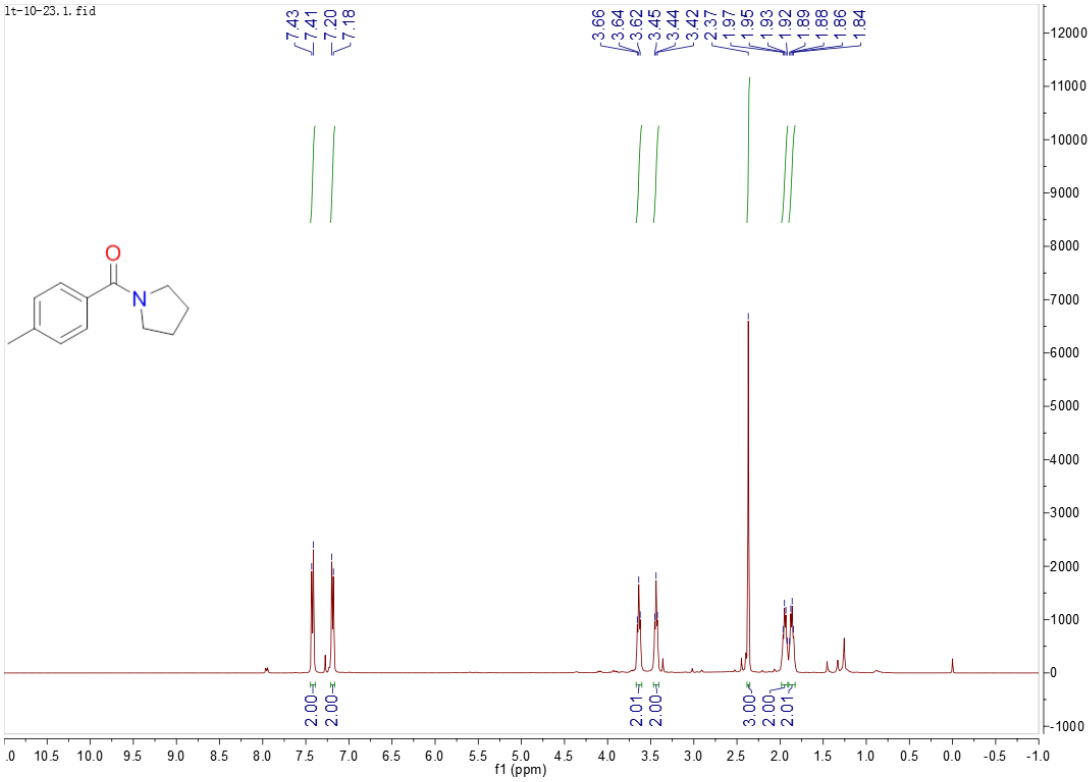
^{13}C NMR(100 Mz) spectrum of compound **6a** in $CDCl_3$



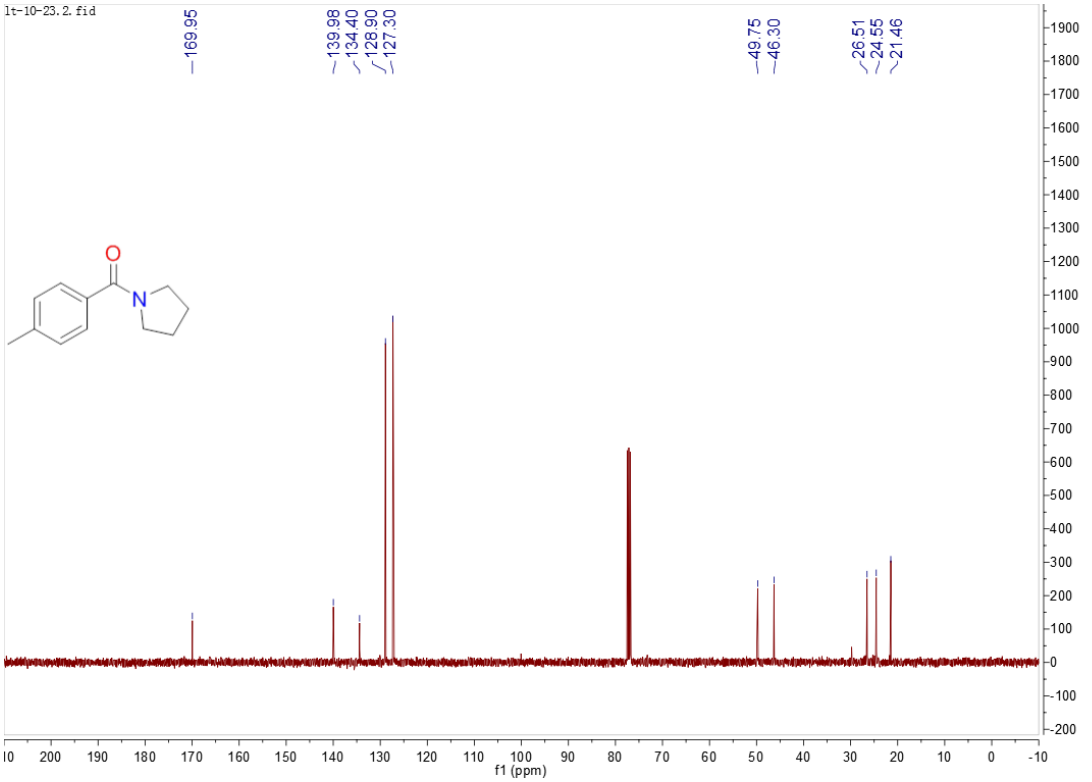
^{1}H NMR(400 Mz) spectrum of compound **6b** in $CDCl_3$



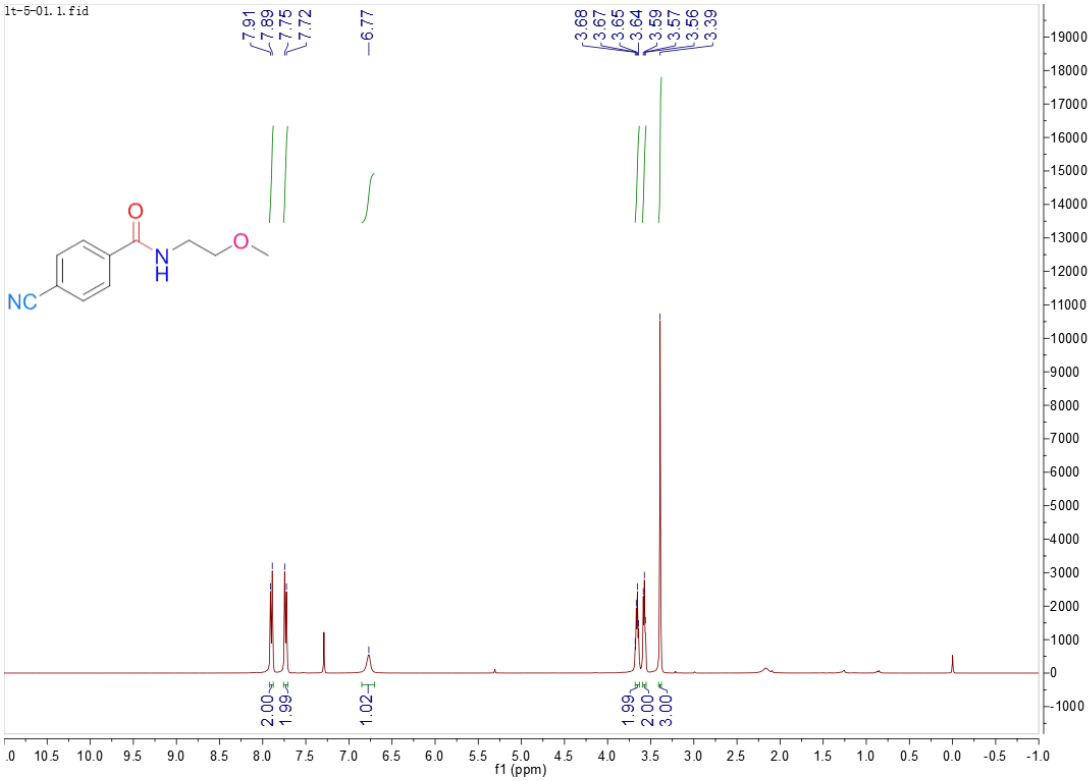
^{13}C NMR(100 Mz) spectrum of compound **6b** in $CDCl_3$



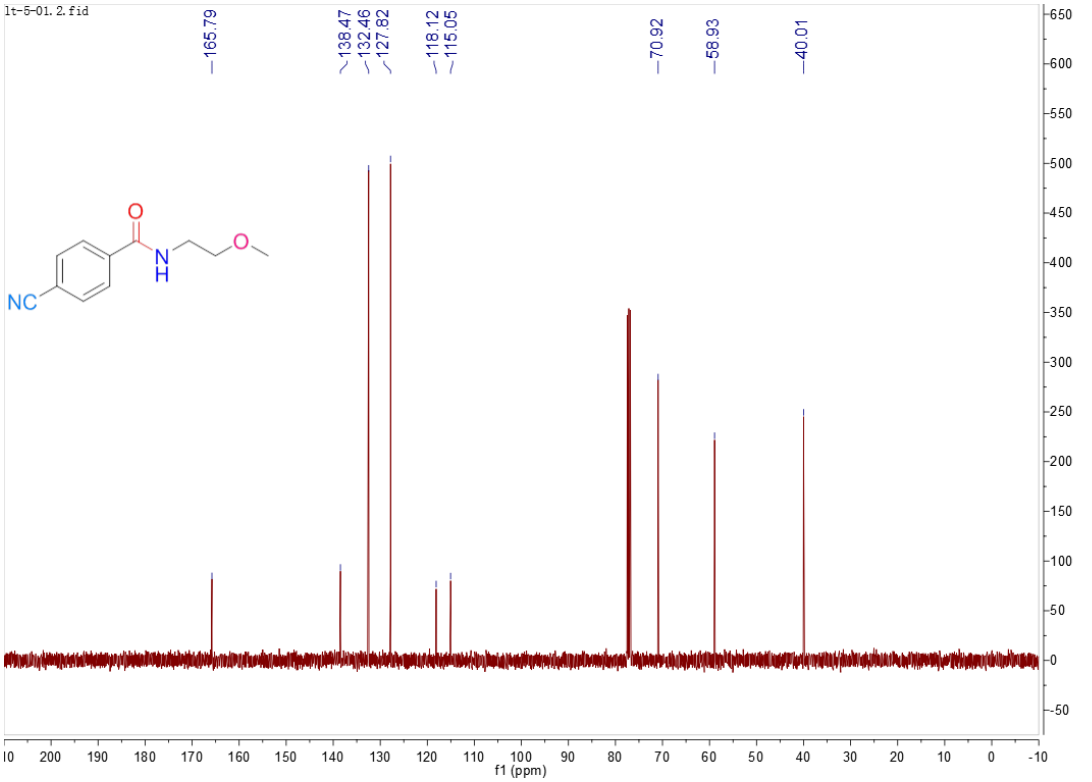
^{1}H NMR(400 Mz) spectrum of compound **6c** in $CDCl_3$



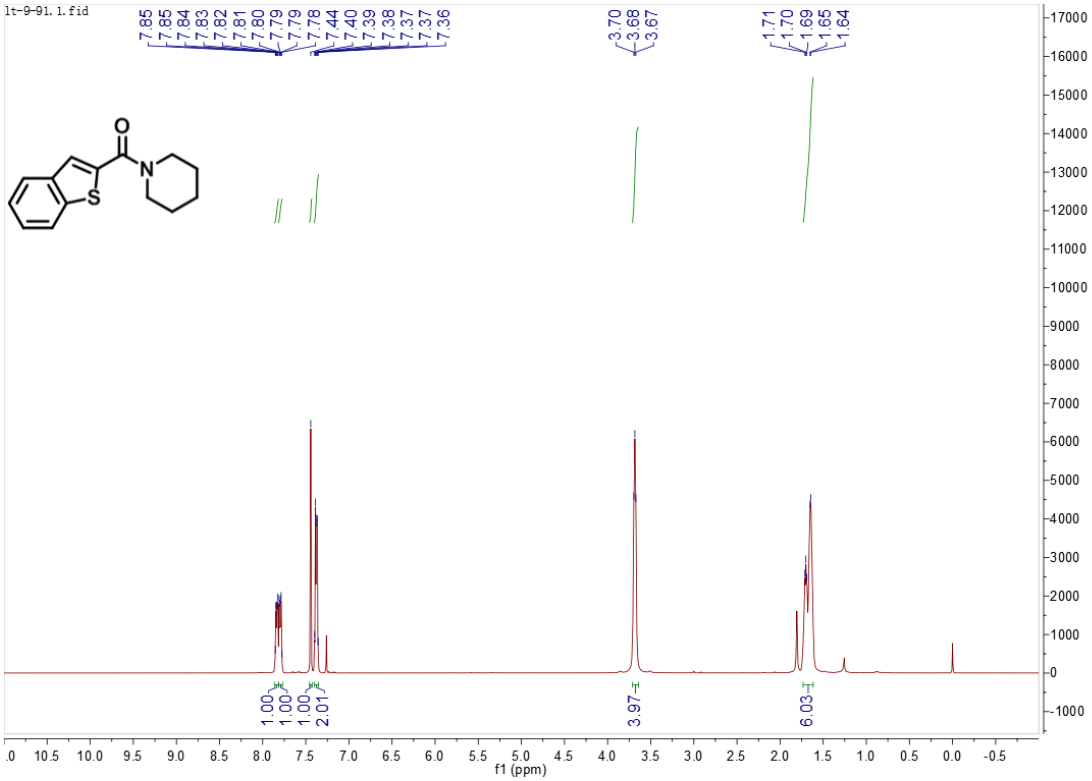
^{13}C NMR(100 Mz) spectrum of compound **6c** in $CDCl_3$



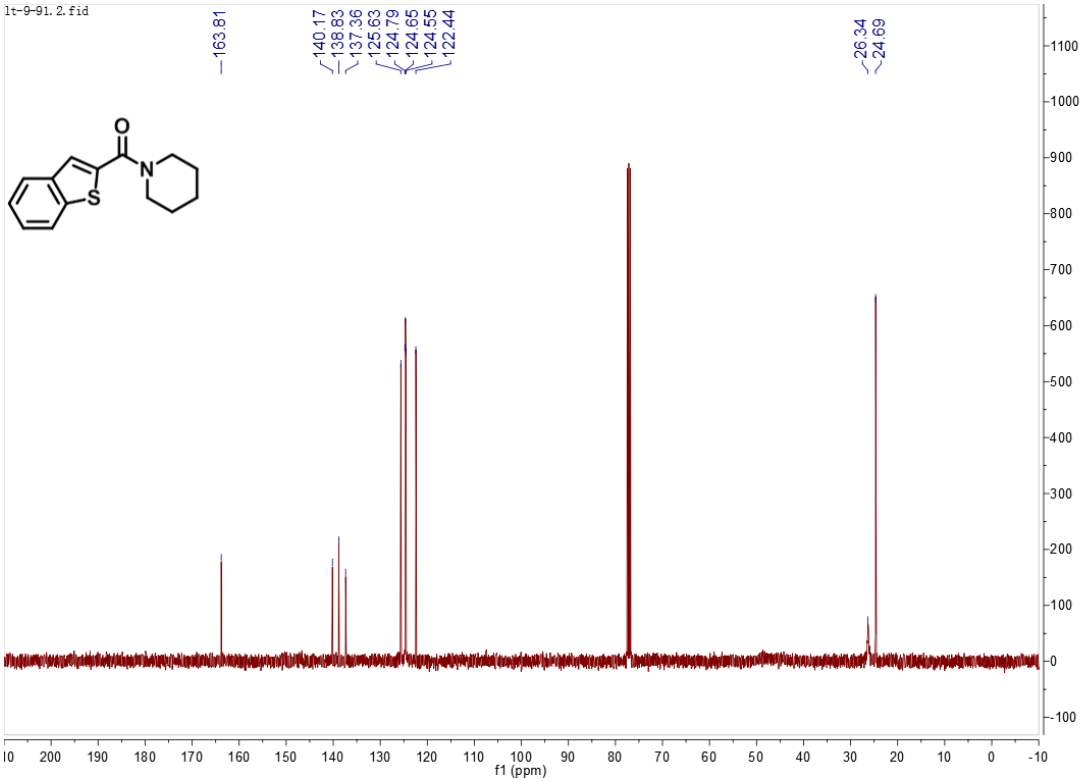
^{1}H NMR(400 Mz) spectrum of compound **6d** in $CDCl_3$



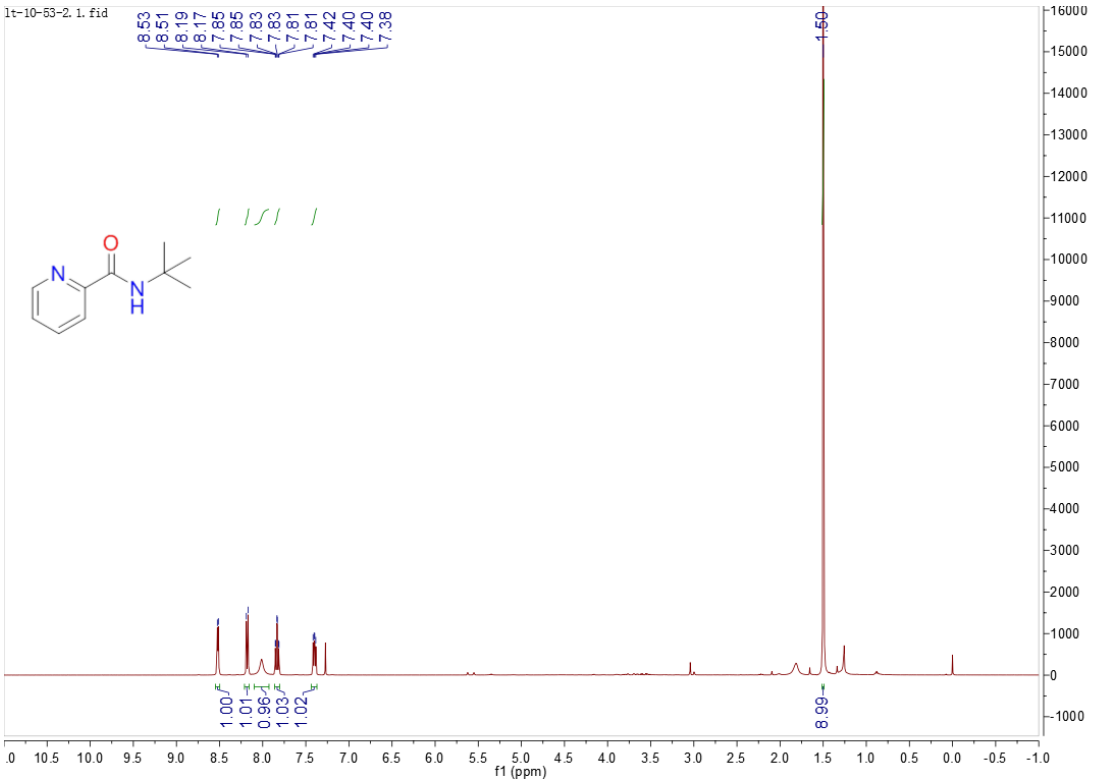
^{13}C NMR(100 Mz) spectrum of compound **6d** in $CDCl_3$



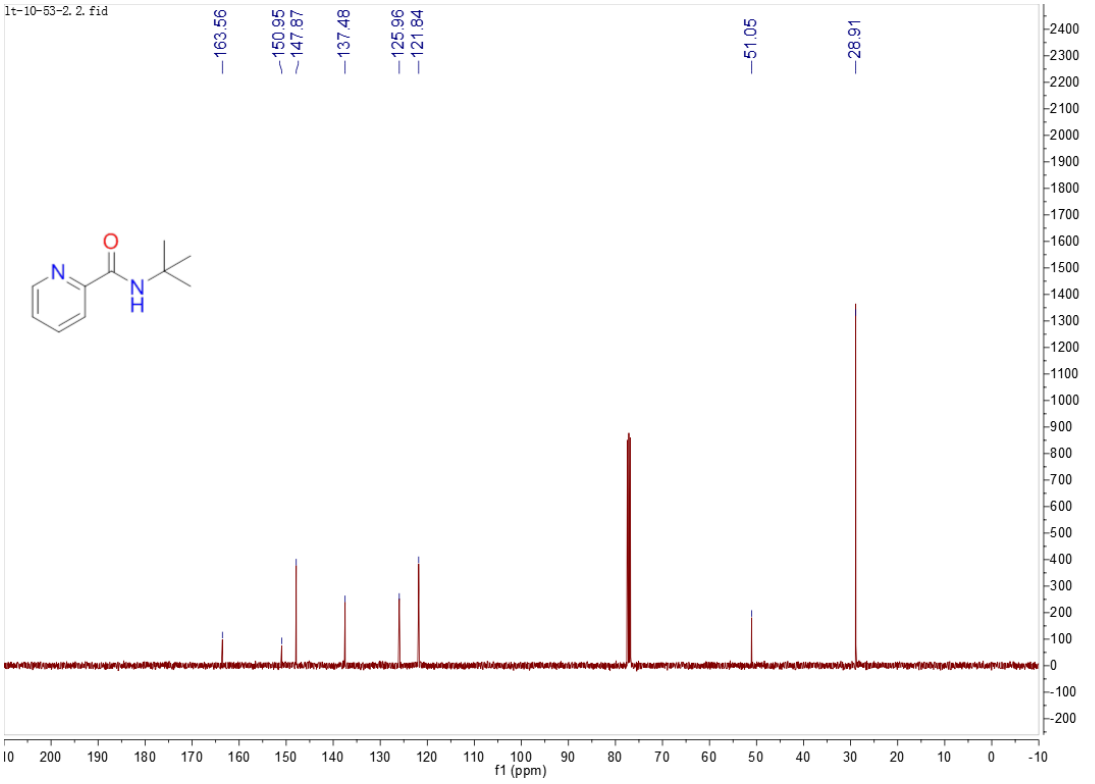
^{1}H NMR(400 Mz) spectrum of compound **6e** in $CDCl_3$



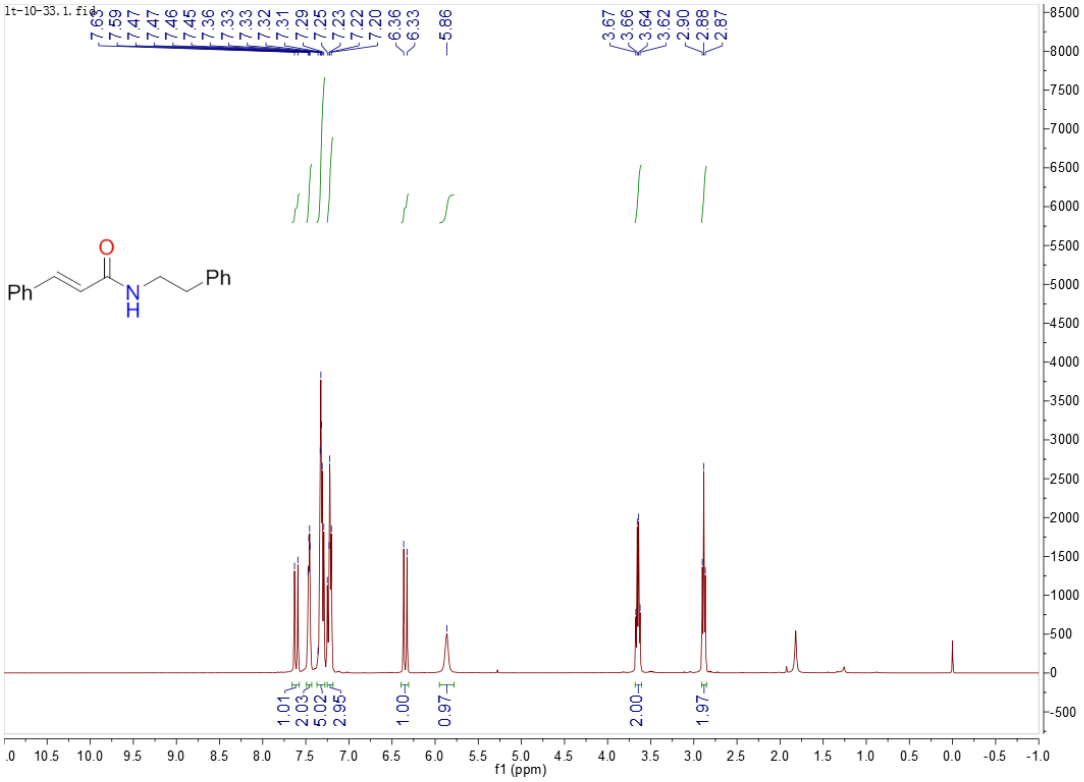
^{13}C NMR(100 Mz) spectrum of compound **6e** in $CDCl_3$



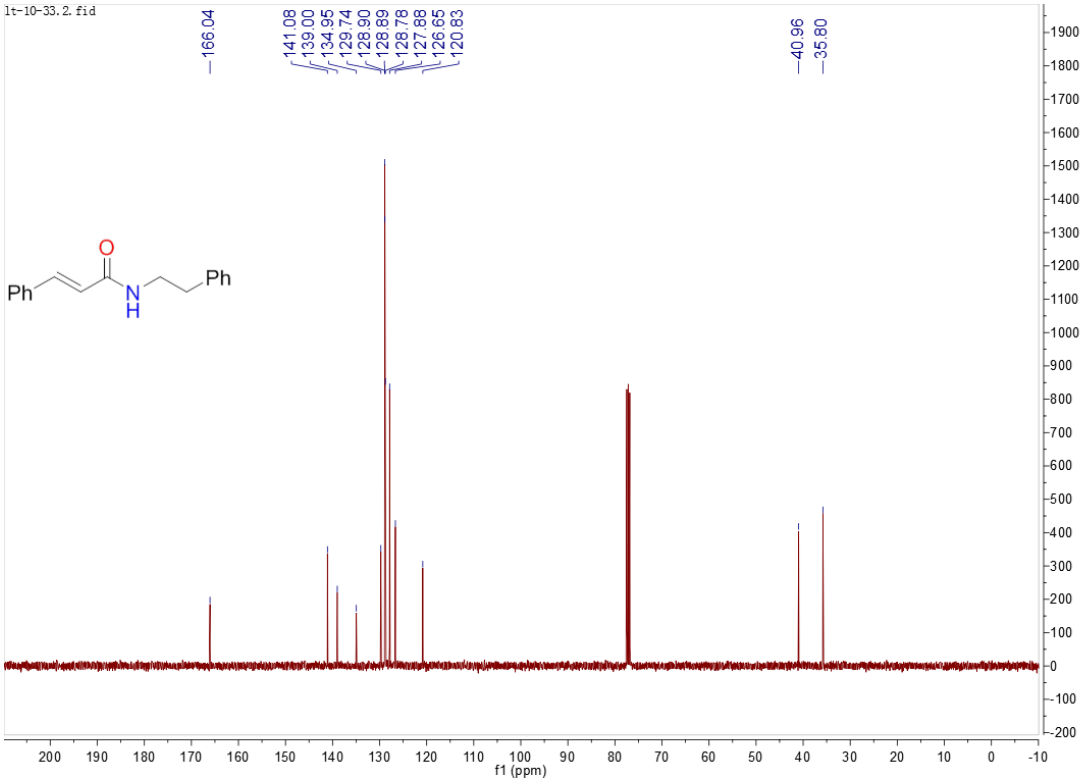
^{1}H NMR(400 Mz) spectrum of compound **6f** in $CDCl_3$



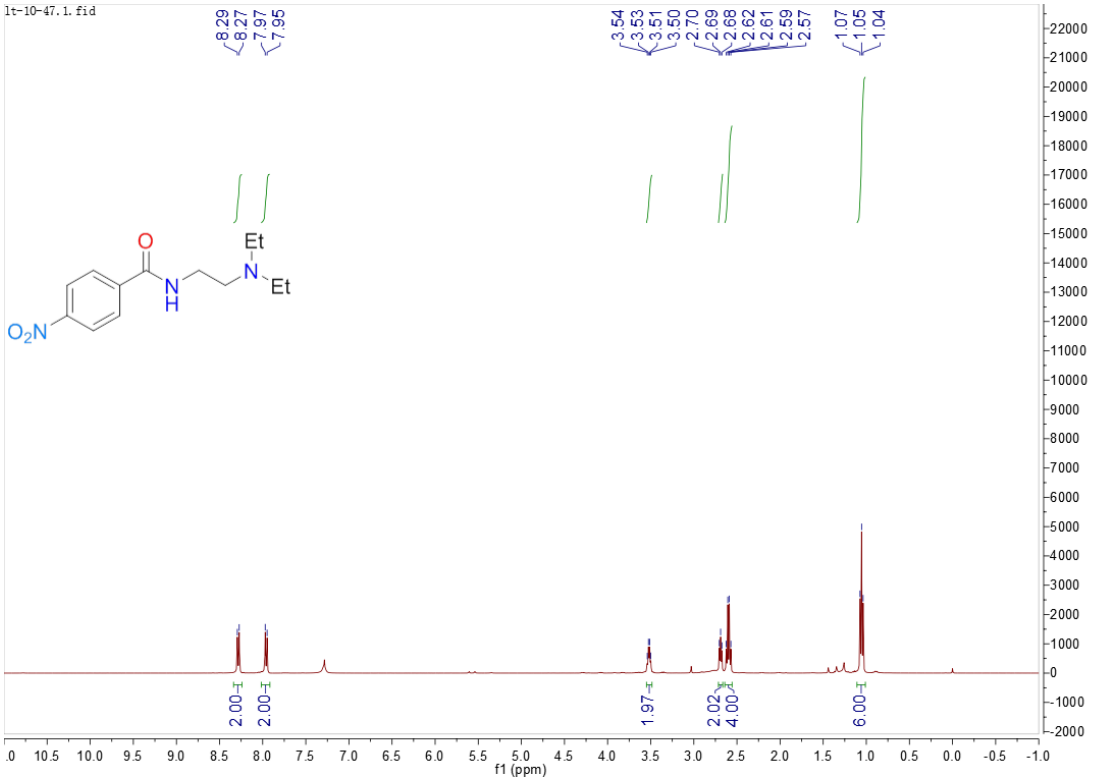
^{13}C NMR(100 Mz) spectrum of compound **6f** in $CDCl_3$



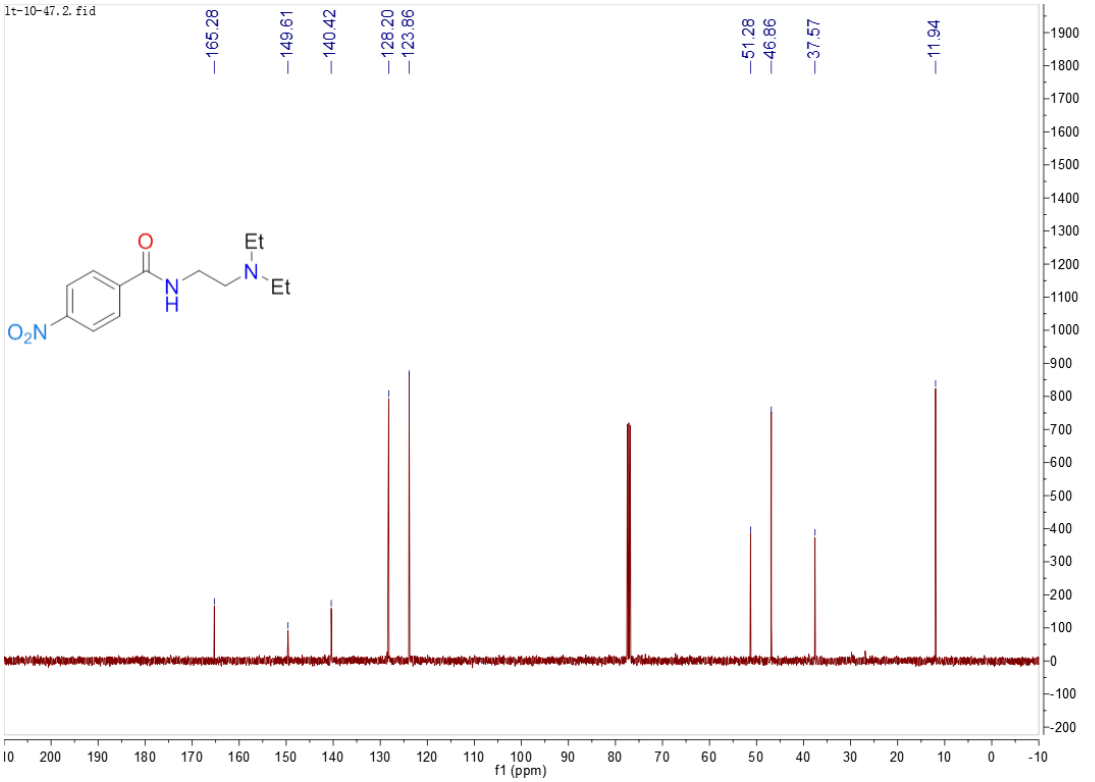
^{1}H NMR(400 Mz) spectrum of compound **6g** in $CDCl_3$



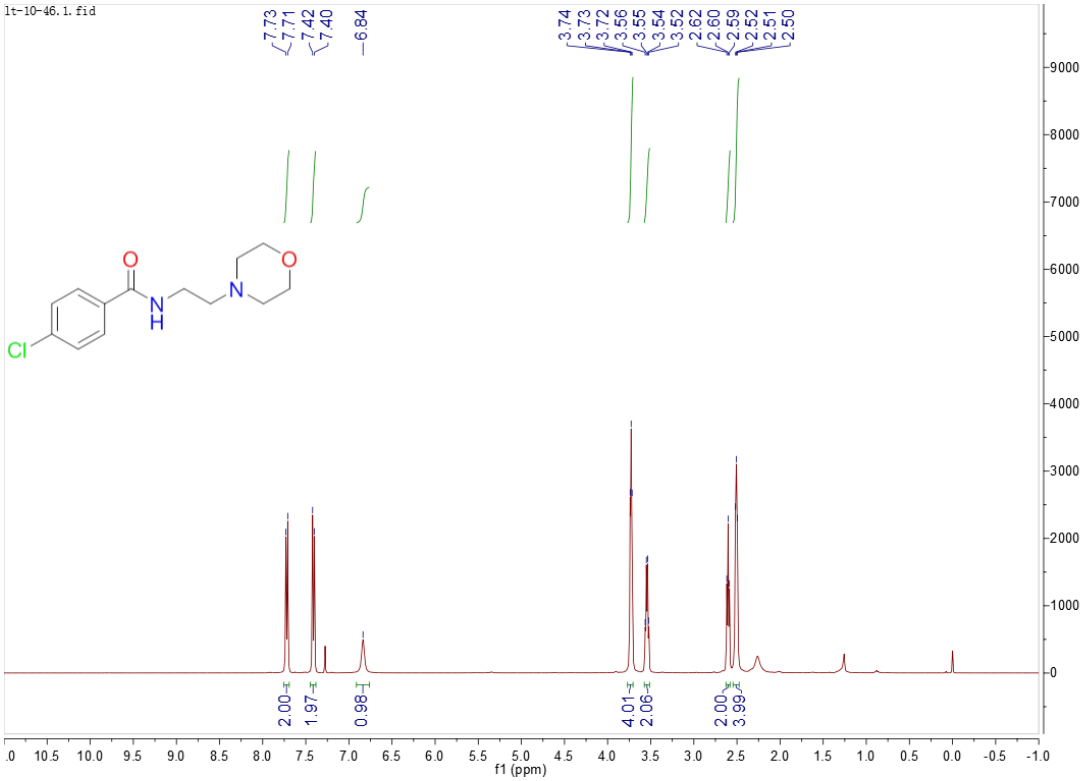
^{13}C NMR(100 Mz) spectrum of compound **6g** in $CDCl_3$



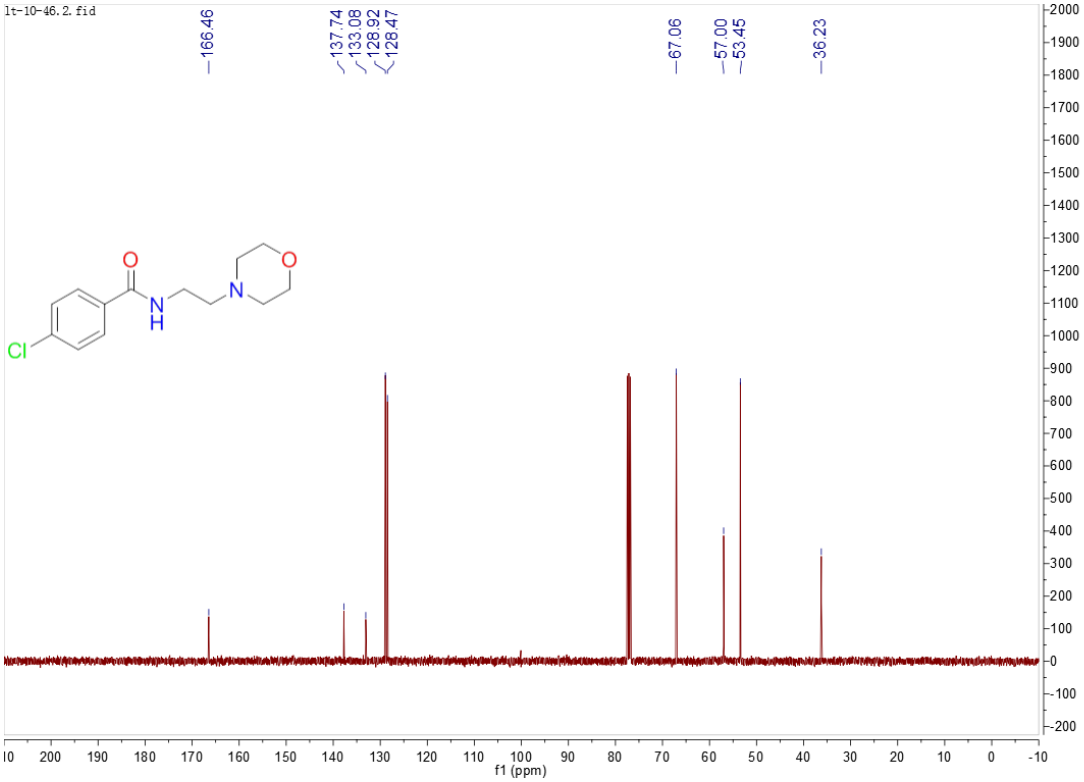
^{1}H NMR(400 Mz) spectrum of compound **6h** in $CDCl_3$



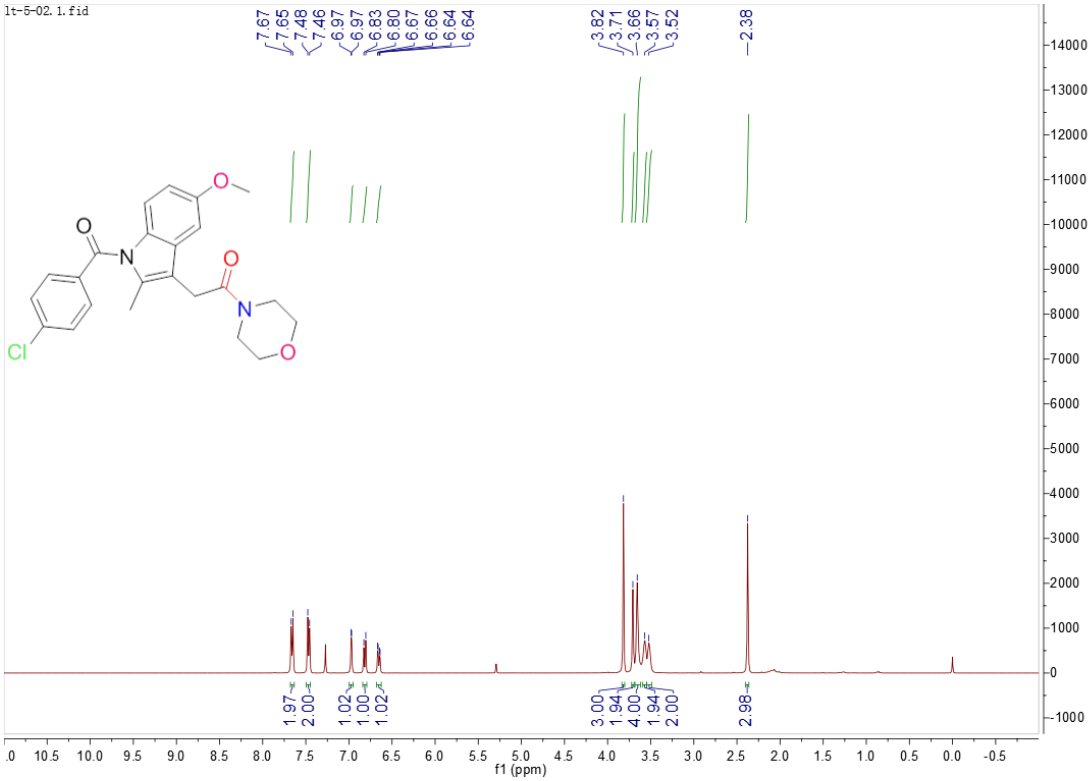
^{13}C NMR(100 Mz) spectrum of compound **6h** in $CDCl_3$



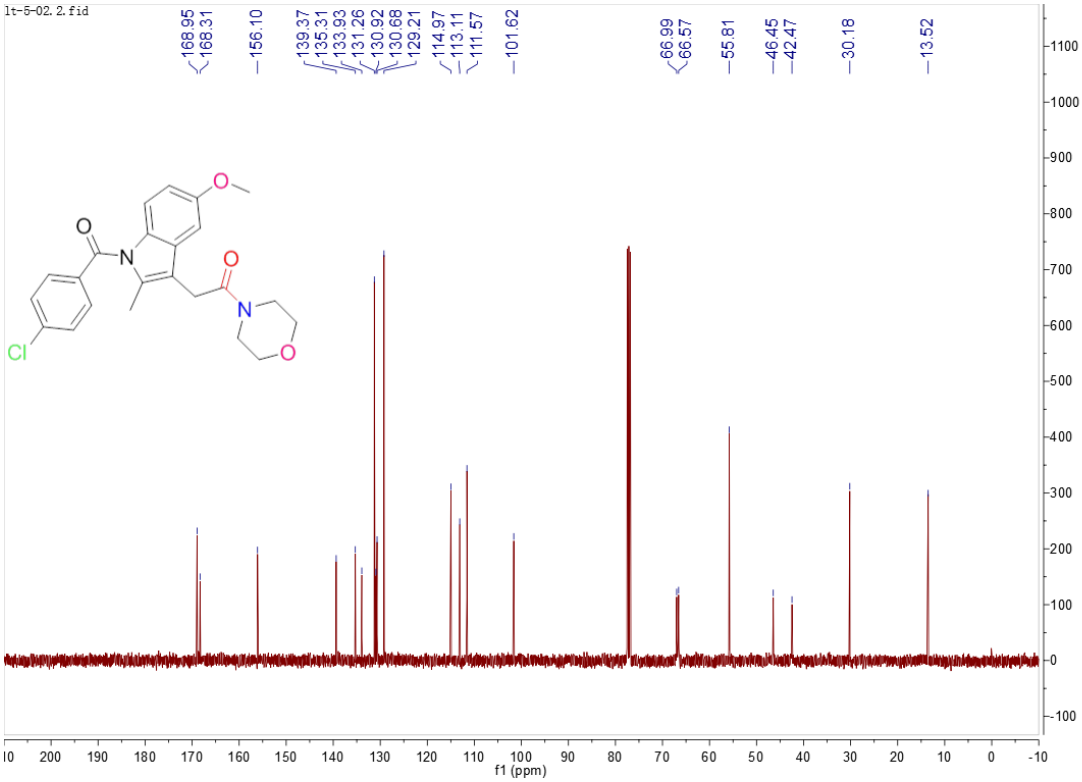
^{1}H NMR(400 Mz) spectrum of compound **6i** in $CDCl_3$



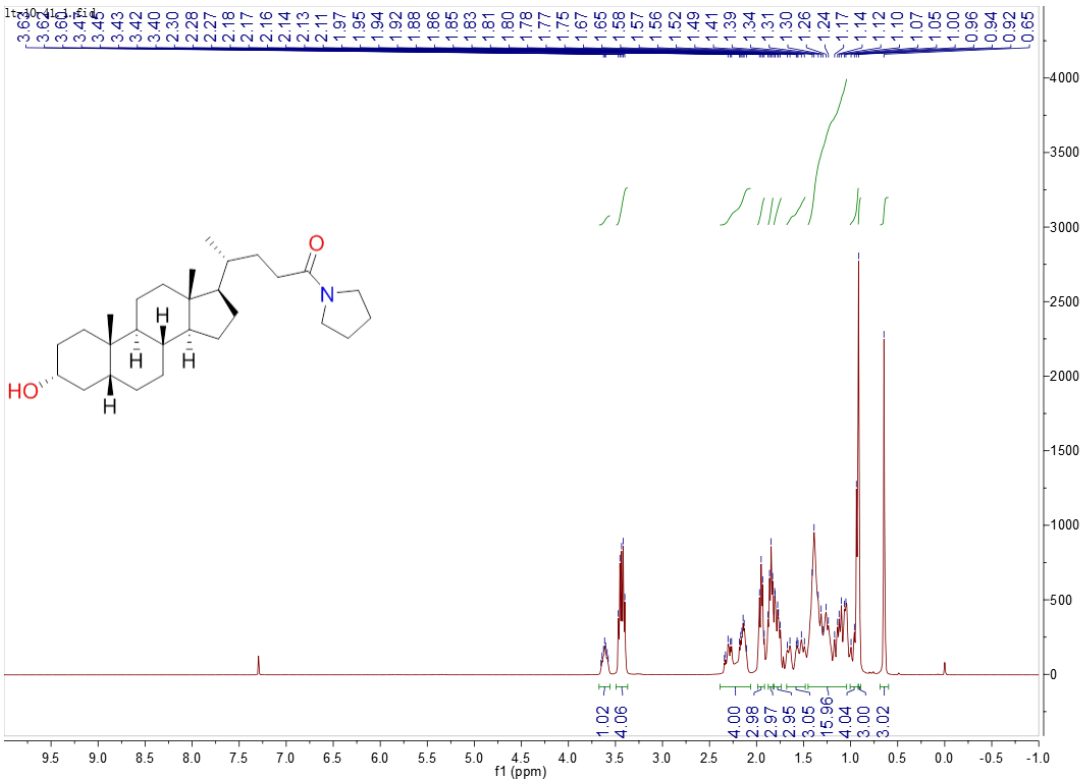
^{13}C NMR(100 Mz) spectrum of compound **6i** in $CDCl_3$



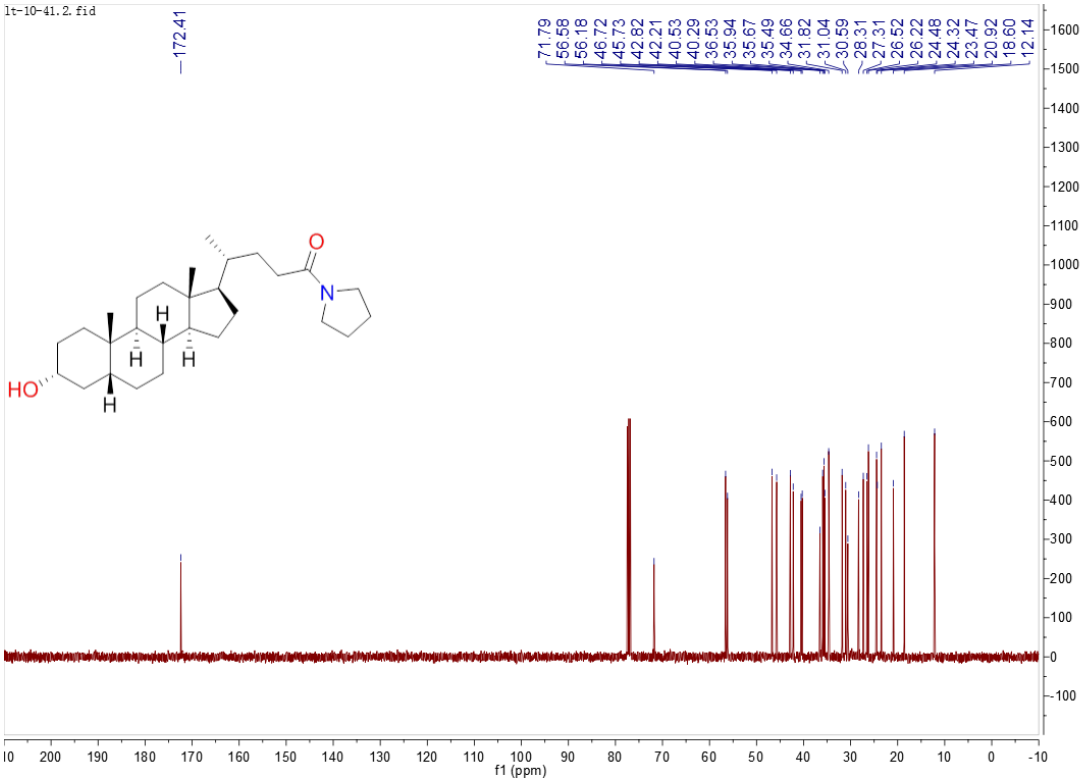
^{1}H NMR(400 Mz) spectrum of compound **6j** in $CDCl_3$



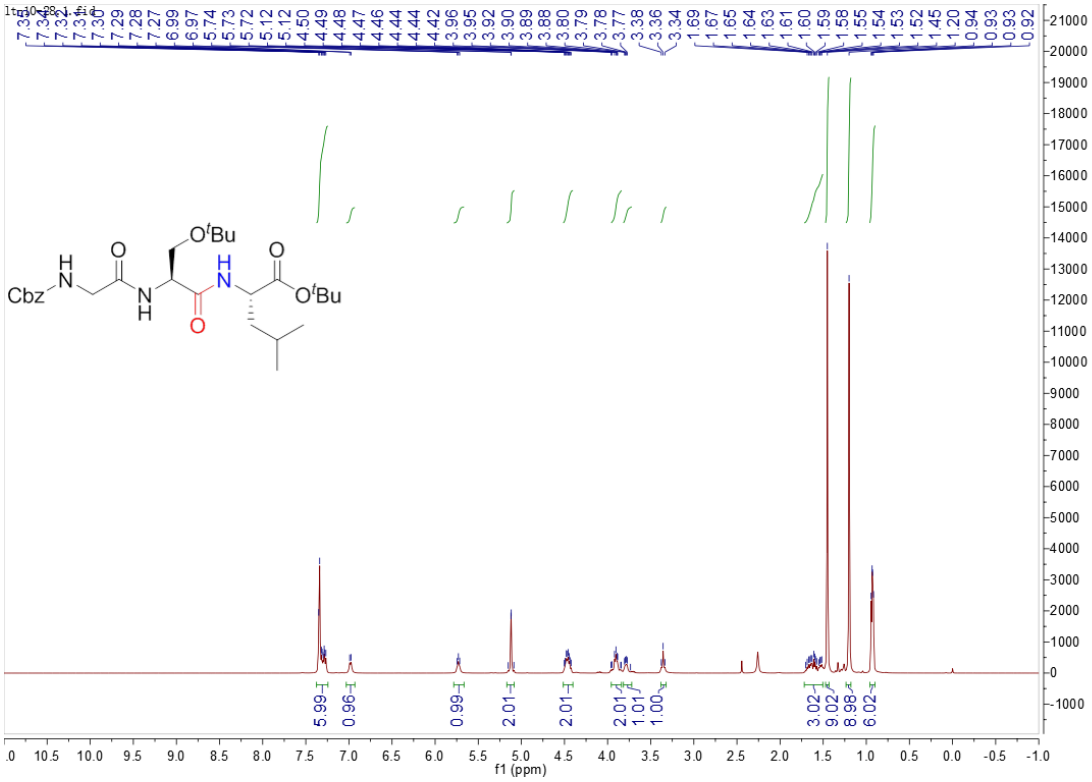
^{13}C NMR(100 Mz) spectrum of compound **6j** in $CDCl_3$



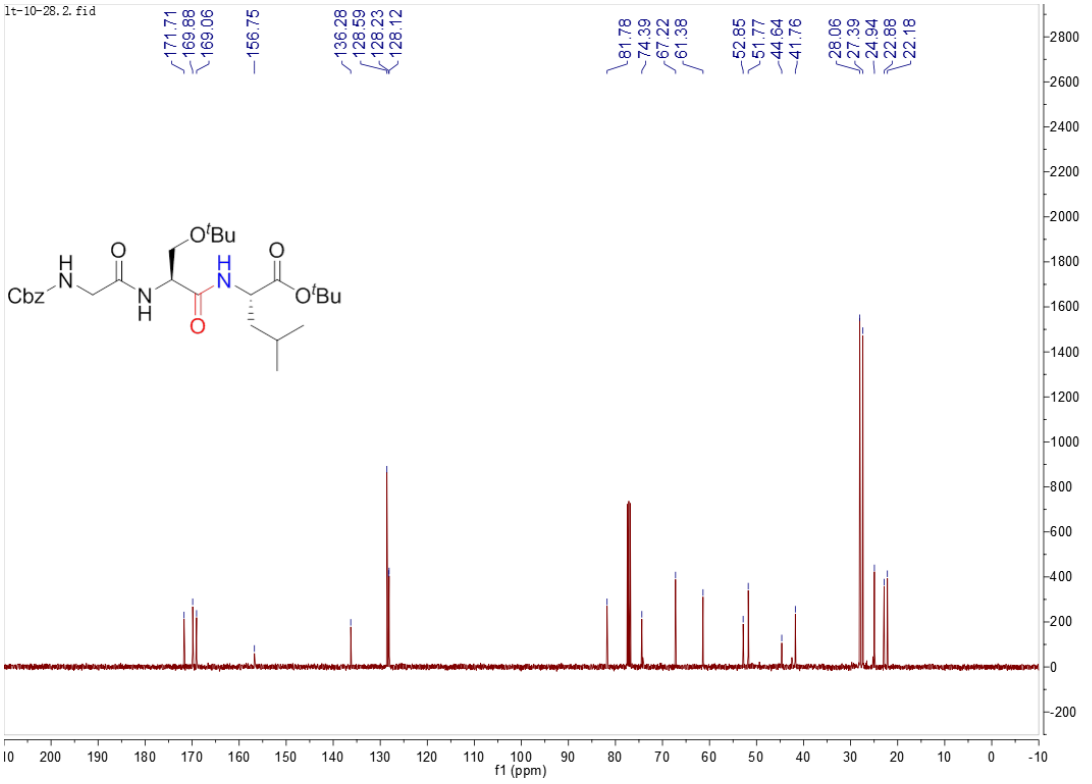
^{1}H NMR(400 Mz) spectrum of compound **6k** in $CDCl_3$



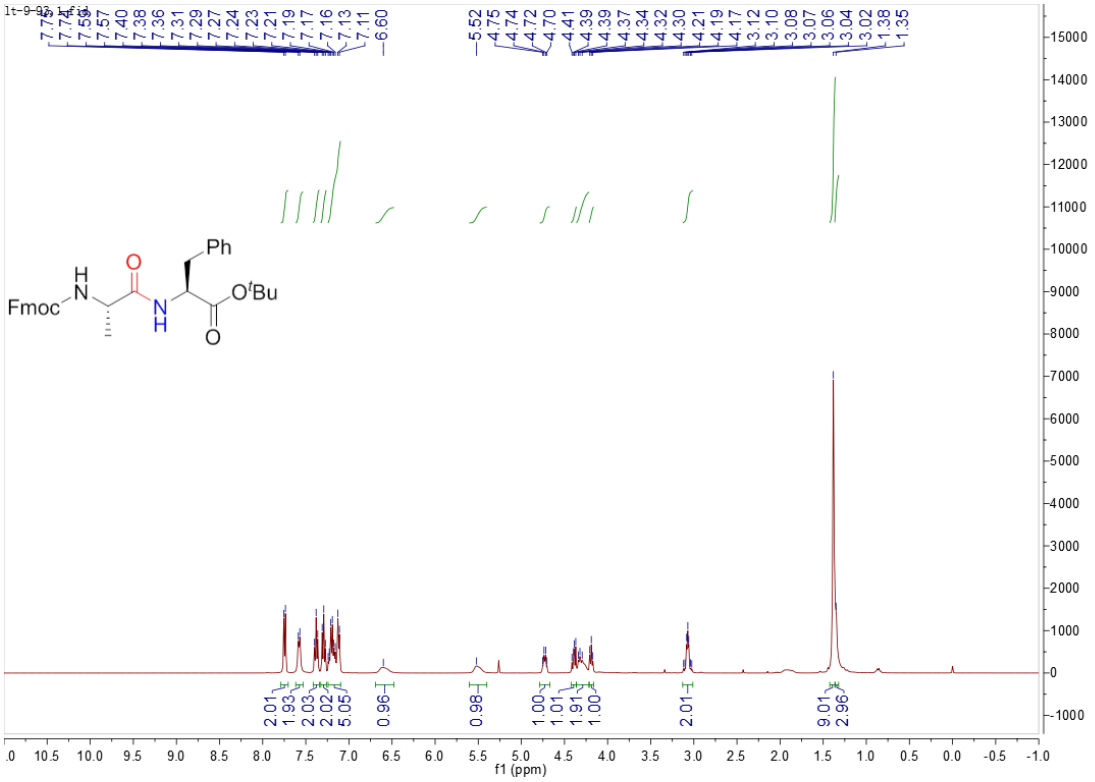
^{13}C NMR(100 Mz) spectrum of compound **6k** in $CDCl_3$



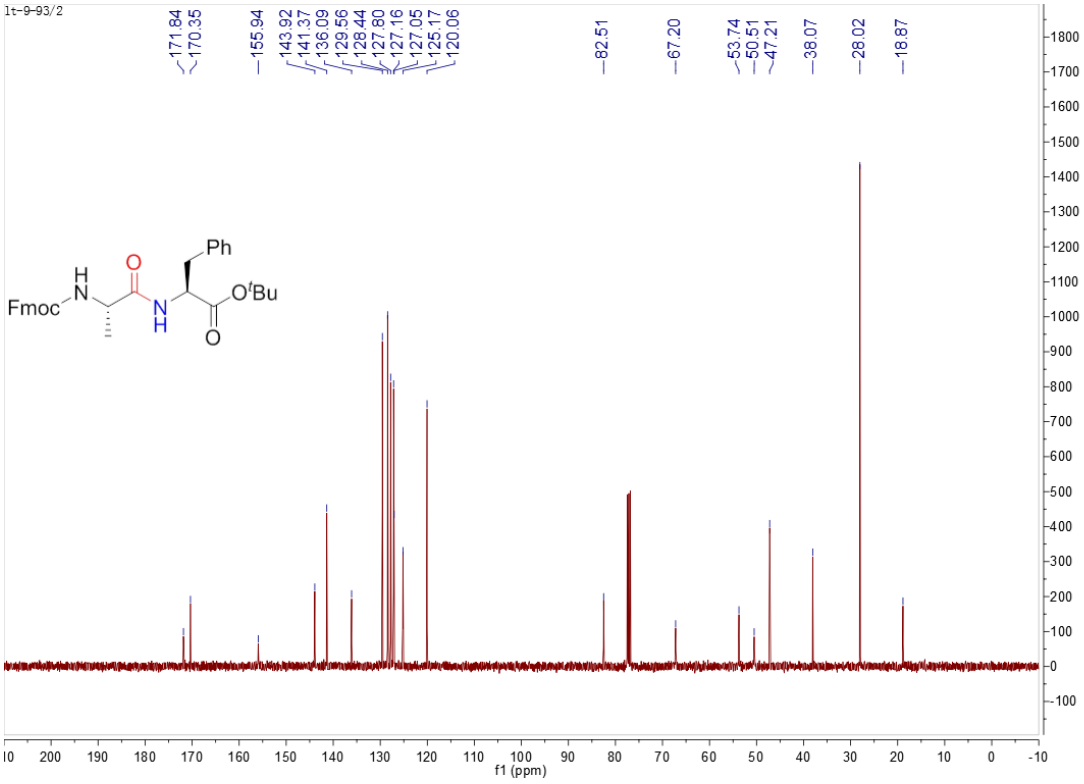
^{1}H NMR(400 Mz) spectrum of **9a** in $CDCl_3$



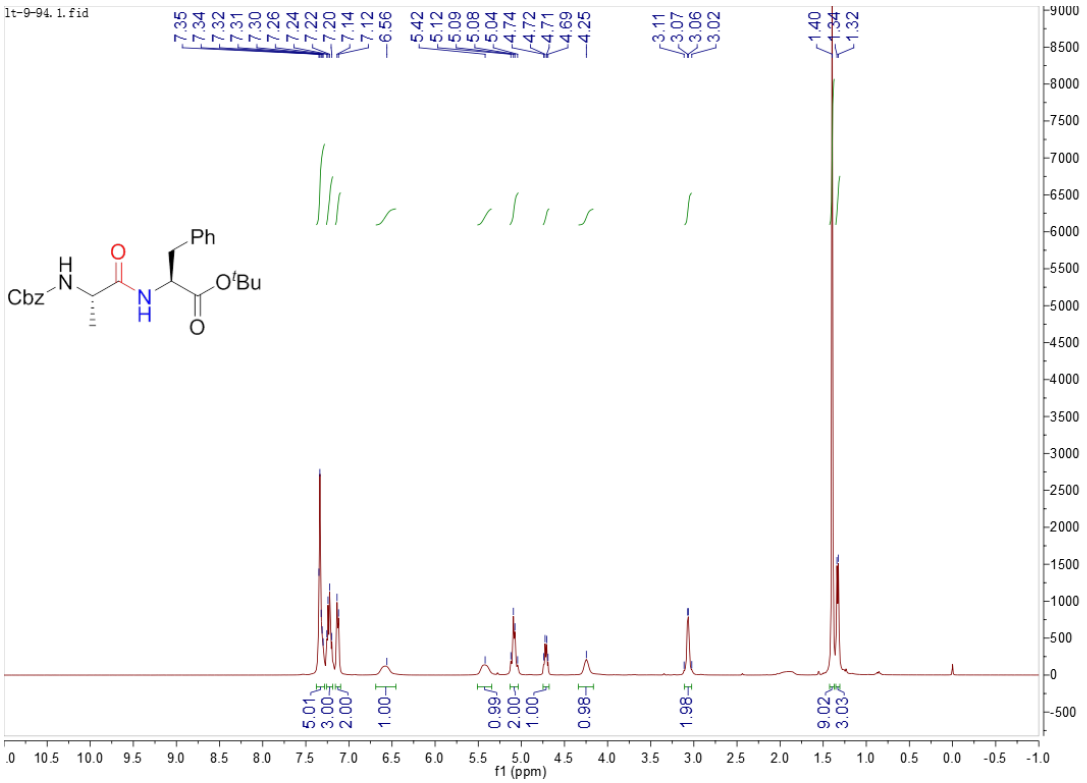
^{13}C NMR(100 Mz) spectrum of **9a** in $CDCl_3$



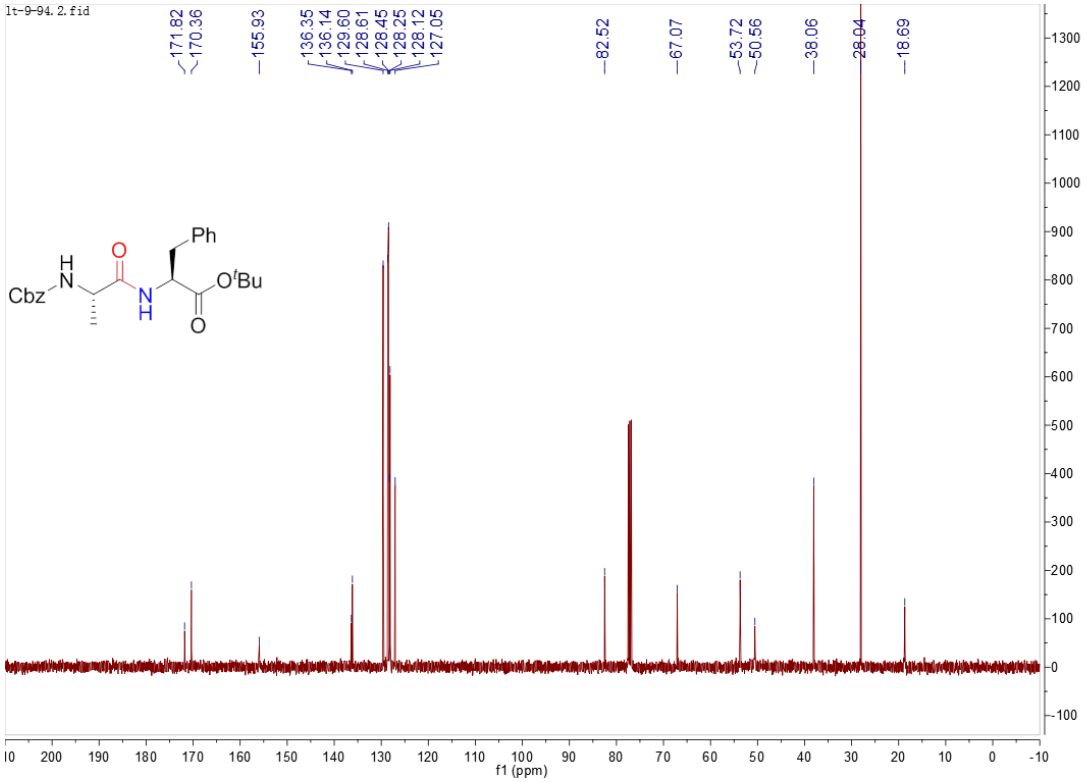
^{1}H NMR(400 Mz) spectrum of compound **9b** in $CDCl_3$



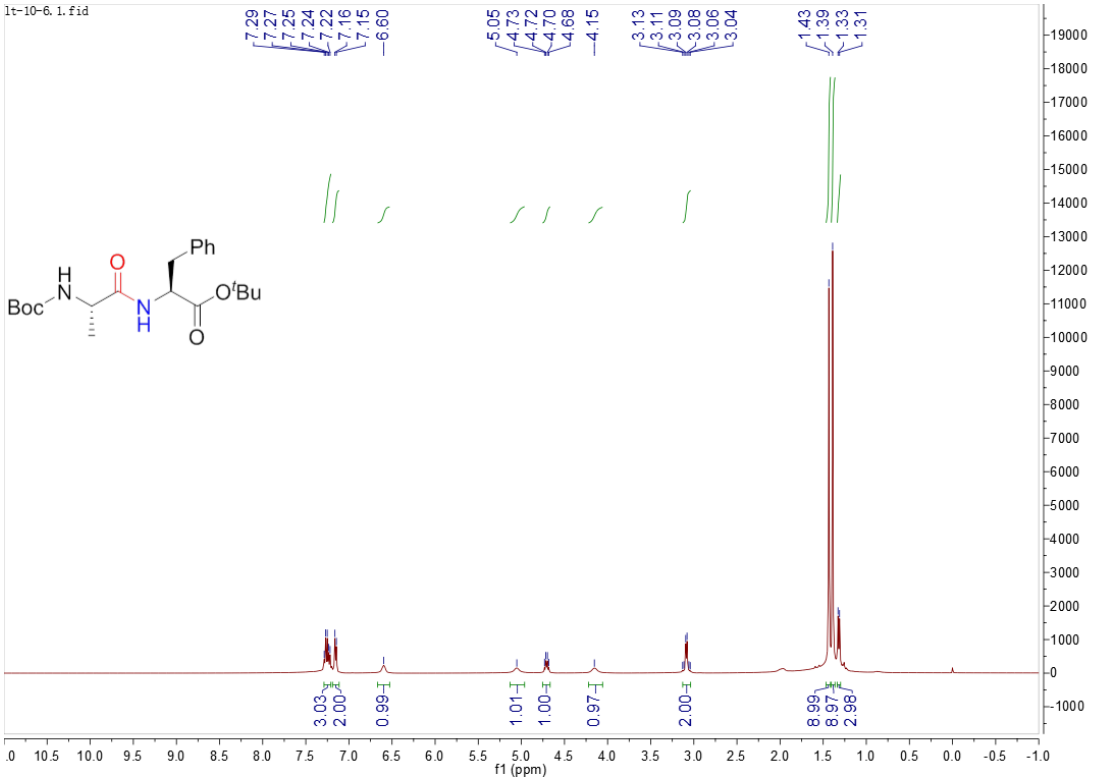
^{13}C NMR(100 Mz) spectrum of compound **9b** in $CDCl_3$



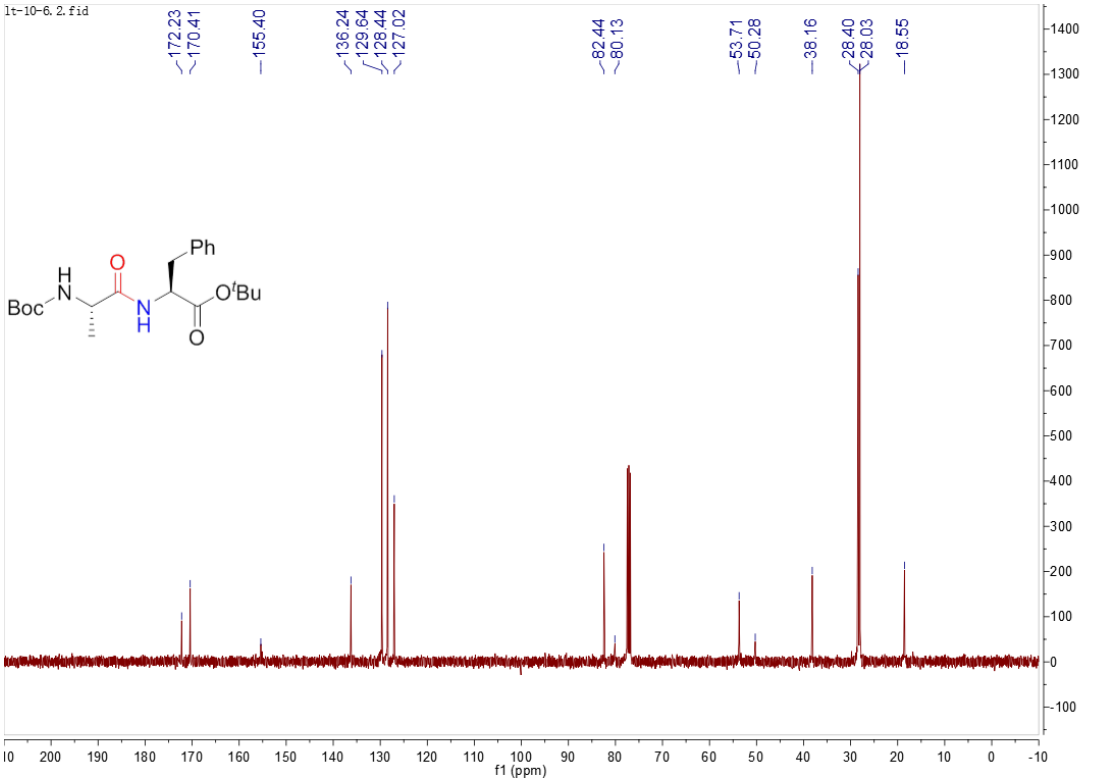
^{1}H NMR(400 Mz) spectrum of compound **9c** in $CDCl_3$



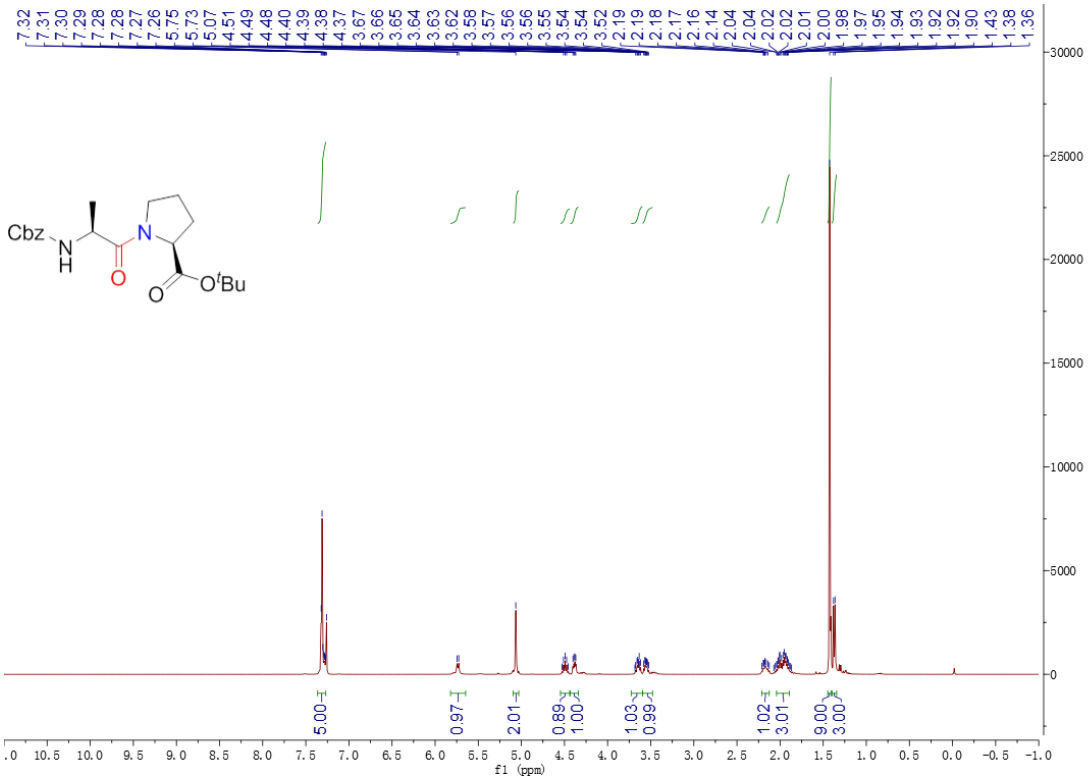
^{13}C NMR(100 Mz) spectrum of compound **9c** in $CDCl_3$



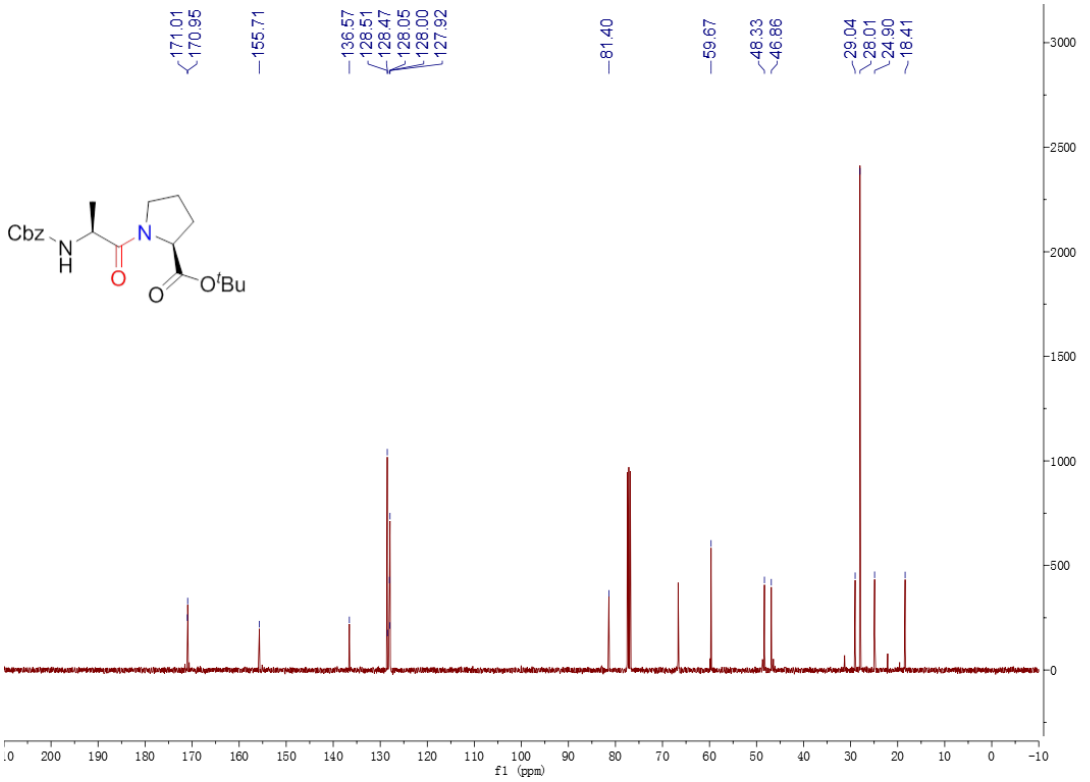
^{1}H NMR(400 Mz) spectrum of compound **9d** in $CDCl_3$



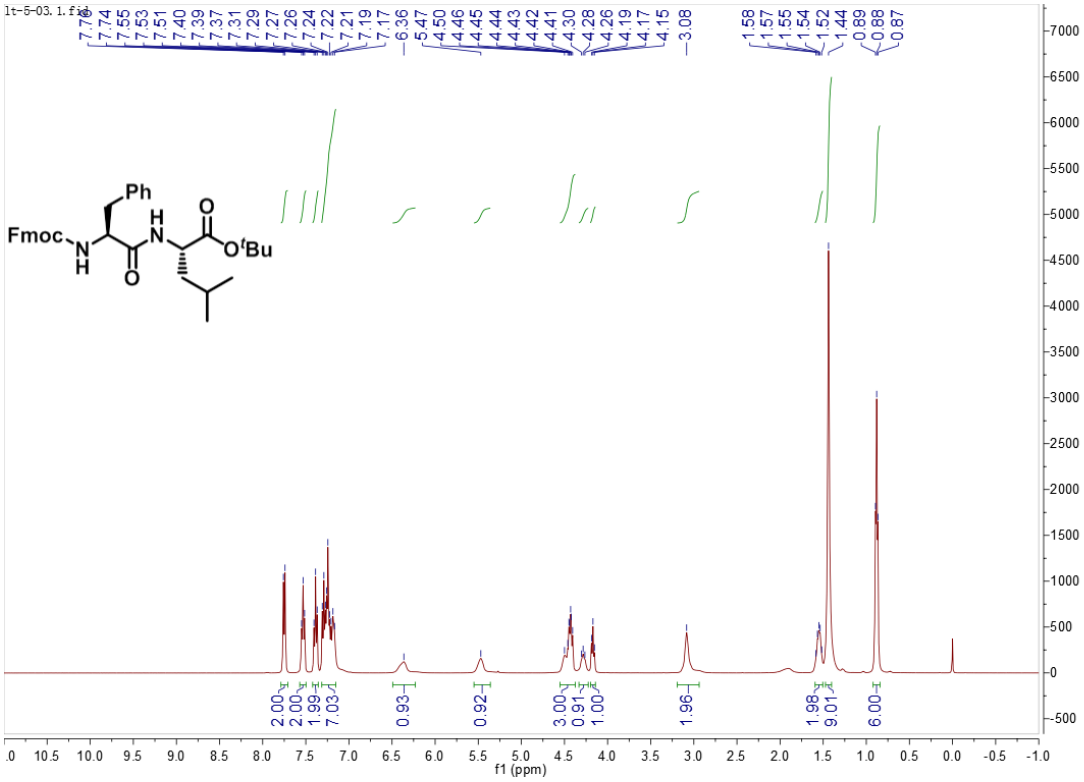
^{13}C NMR(100 Mz) spectrum of compound **9d** in $CDCl_3$



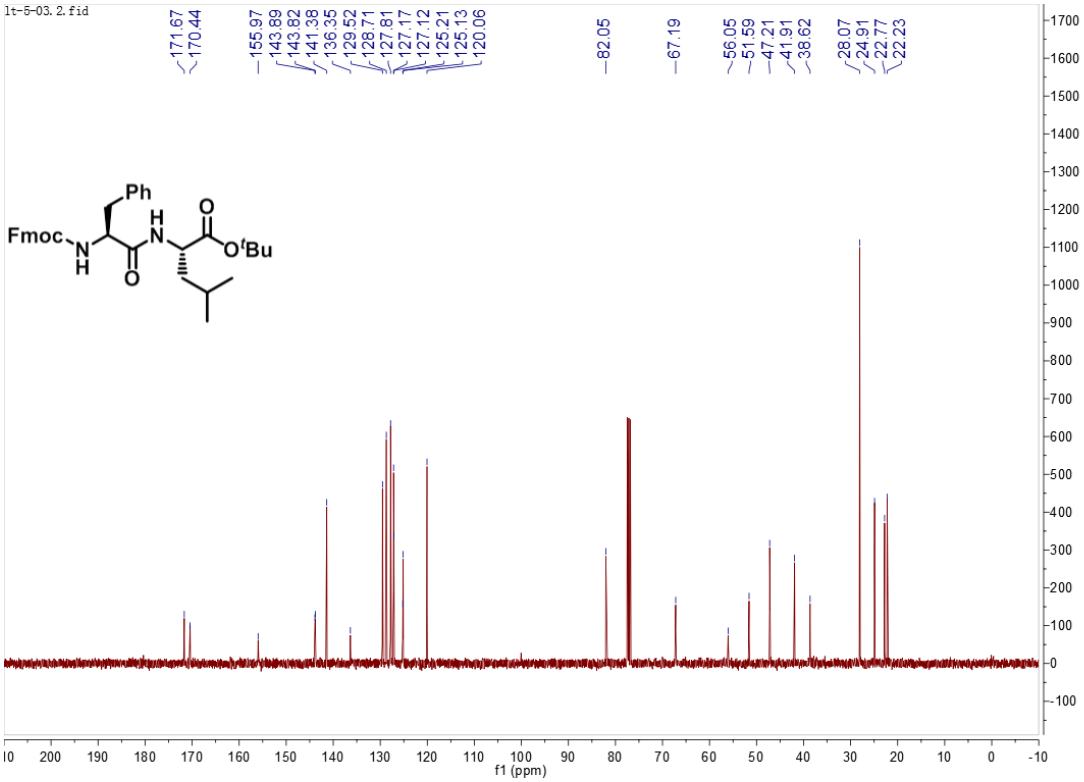
^{1}H NMR(400 Mz) spectrum of compound **9e** in $CDCl_3$



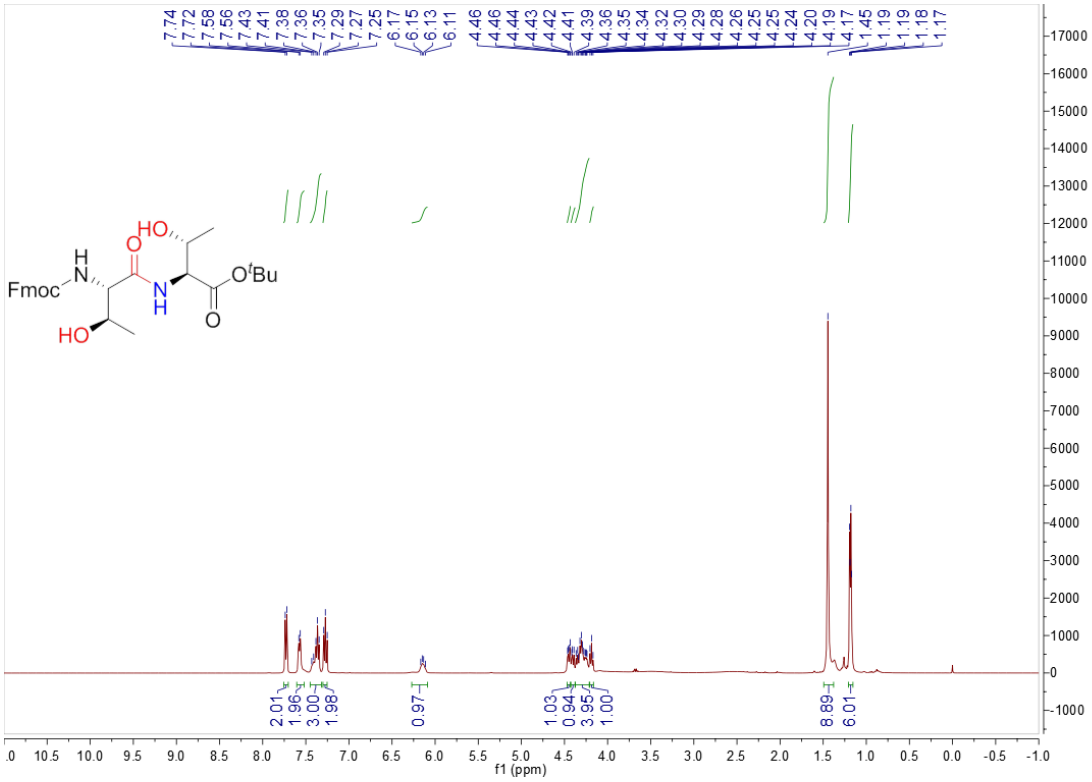
^{13}C NMR(100 Mz) spectrum of compound **9e** in $CDCl_3$



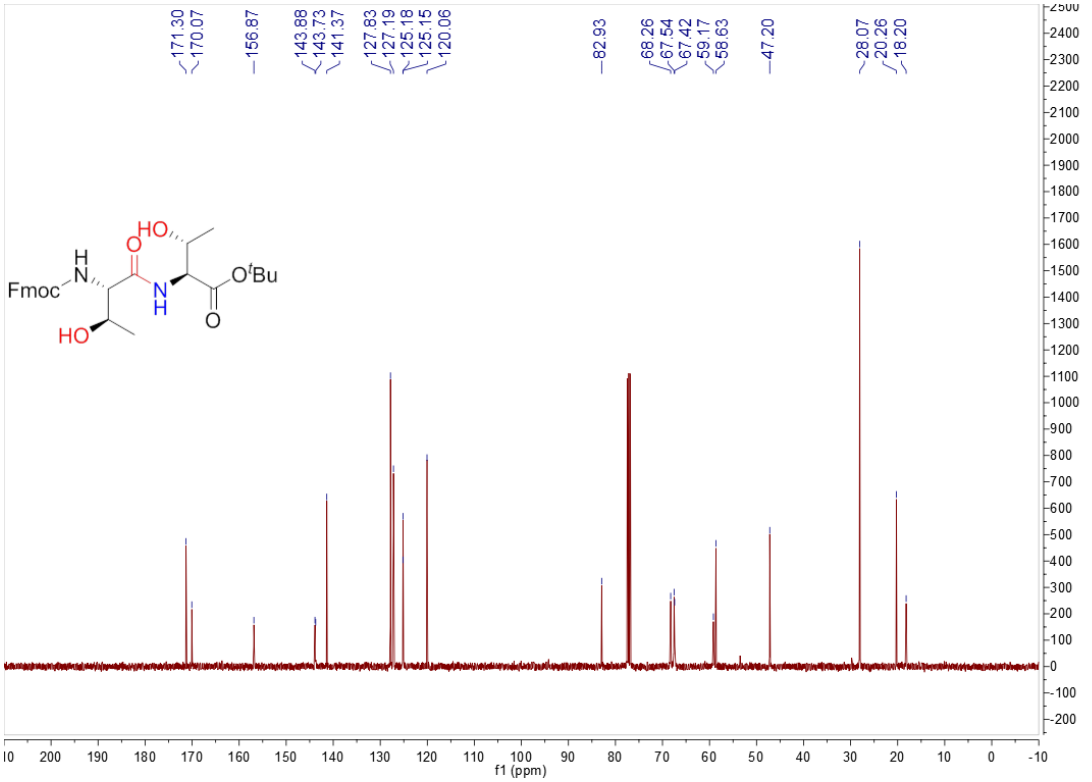
^{1}H NMR(400 Mz) spectrum of compound **9f** in $CDCl_3$



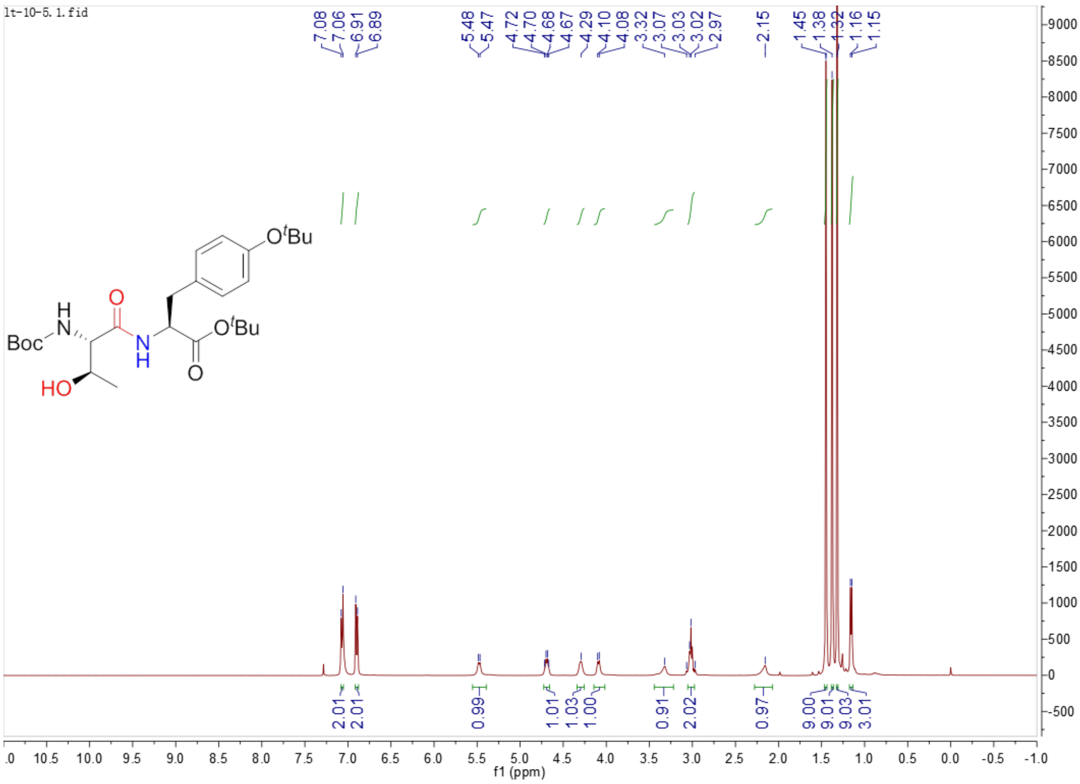
^{13}C NMR(100 Mz) spectrum of compound **9f** in $CDCl_3$



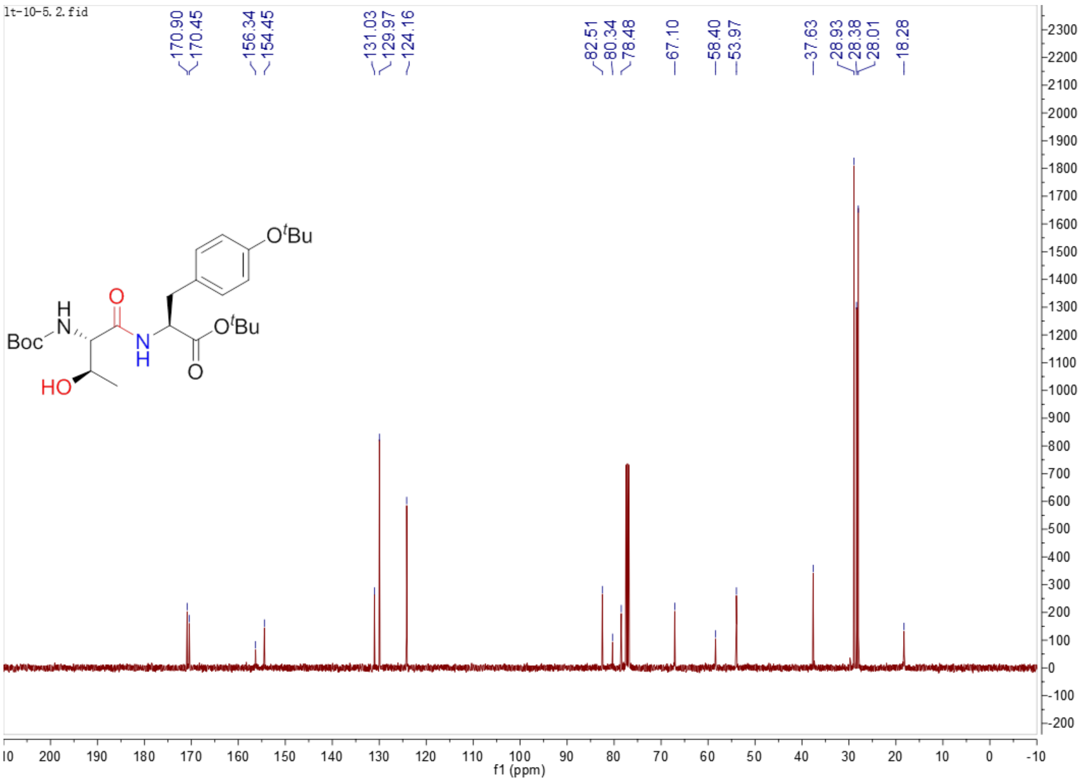
^{1}H NMR(400 Mz) spectrum of compound **9g** in $CDCl_3$



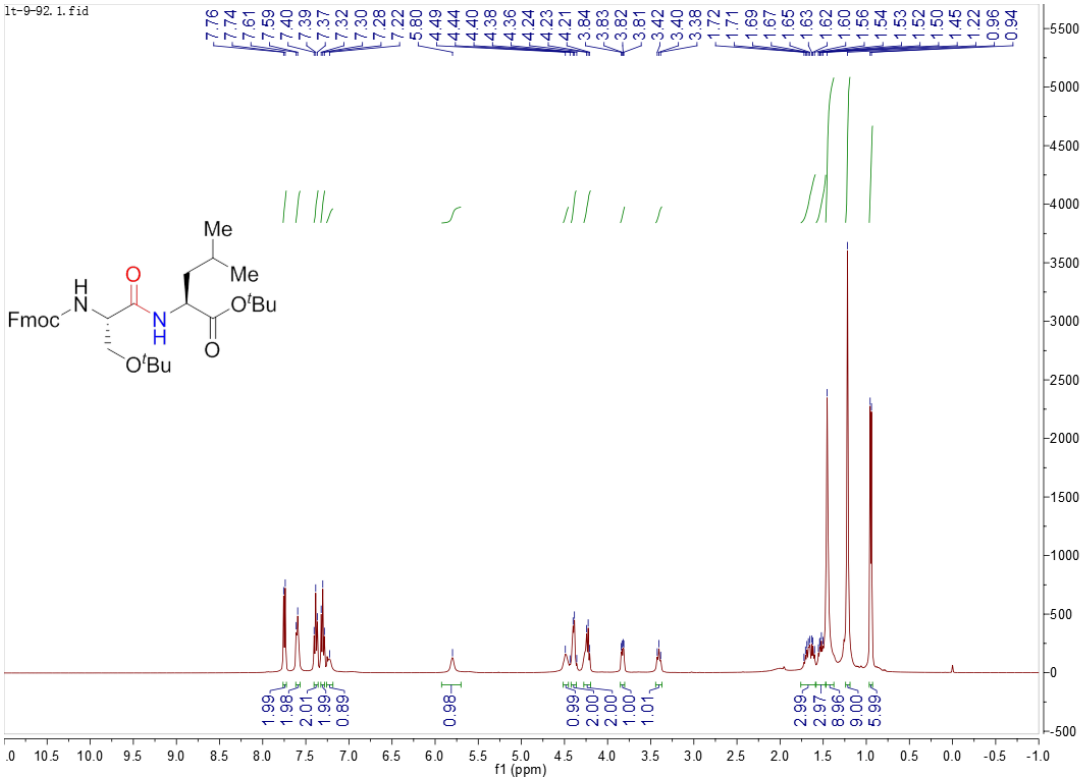
^{13}C NMR(100 Mz) spectrum of compound **9g** in $CDCl_3$



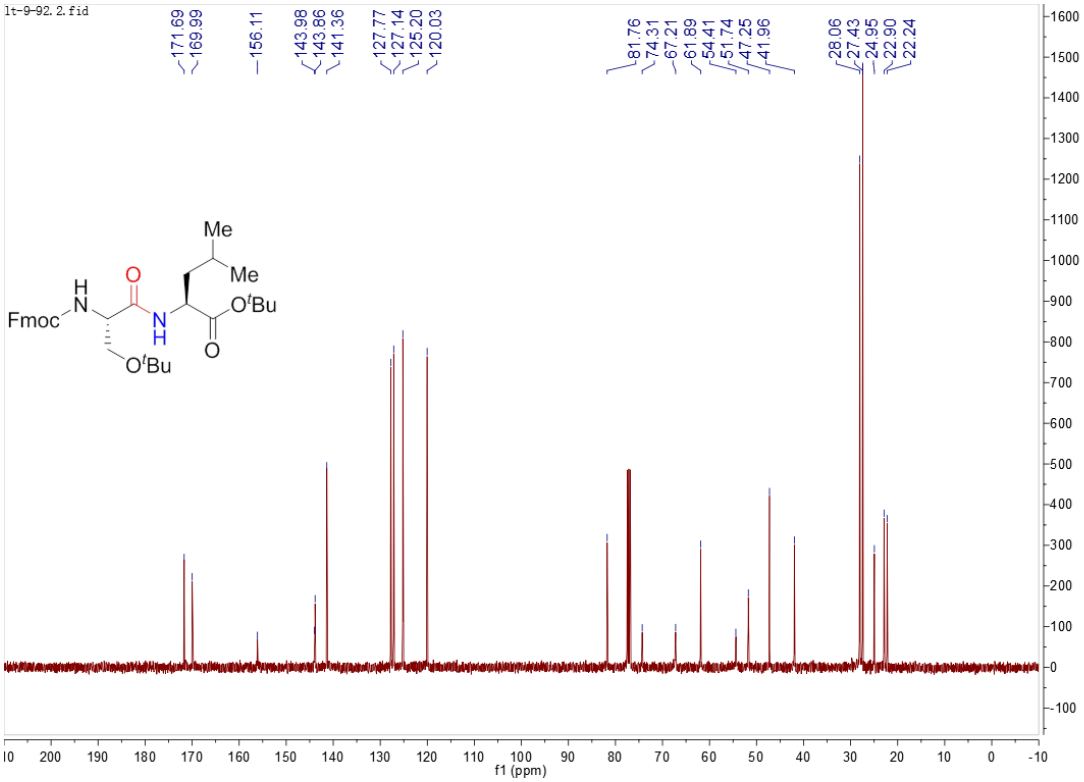
^{1}H NMR(400 Mz) spectrum of compound **9h** in $CDCl_3$



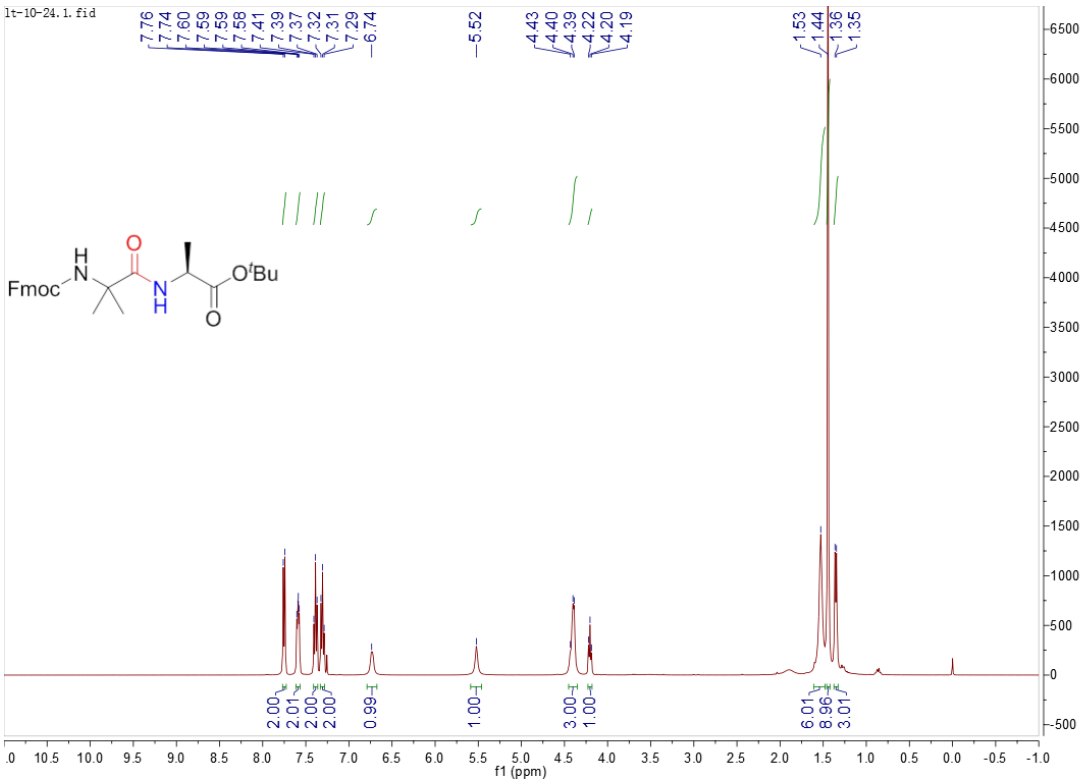
^{13}C NMR(100 Mz) spectrum of compound **9h** in $CDCl_3$



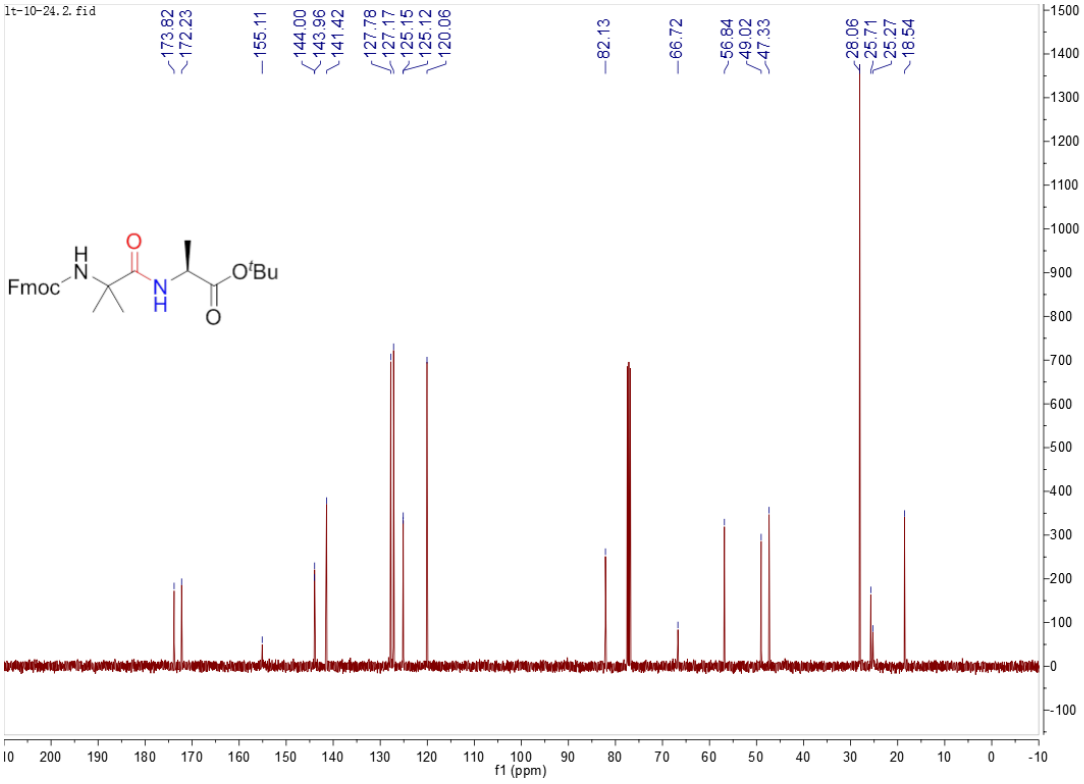
^{1}H NMR(400 Mz) spectrum of compound **9i** in $CDCl_3$



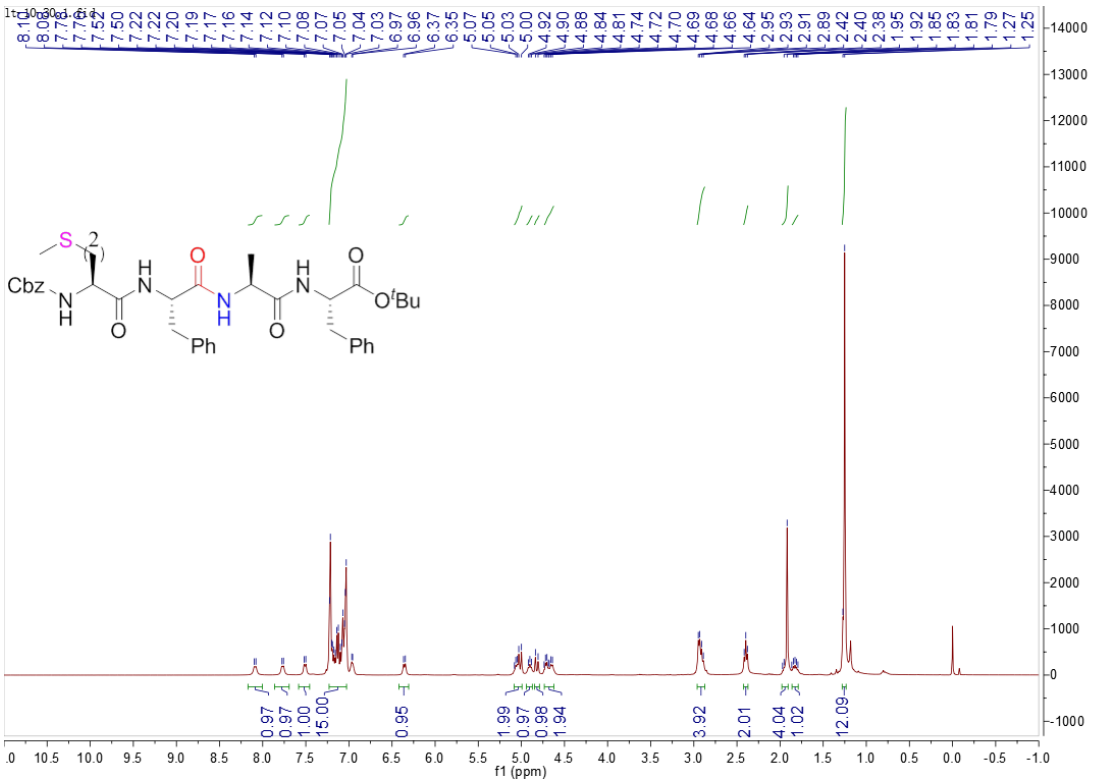
^{13}C NMR(100 Mz) spectrum of compound **9i** in $CDCl_3$



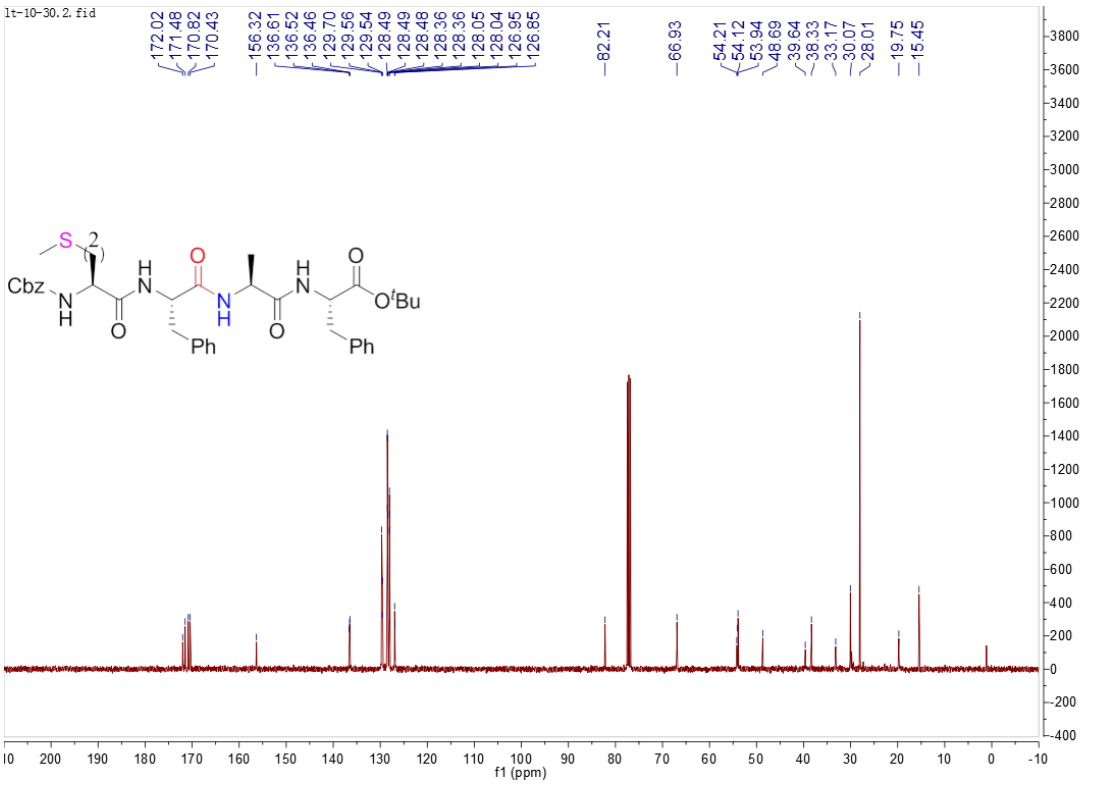
^{1}H NMR(400 Mz) spectrum of compound **9j** in $CDCl_3$



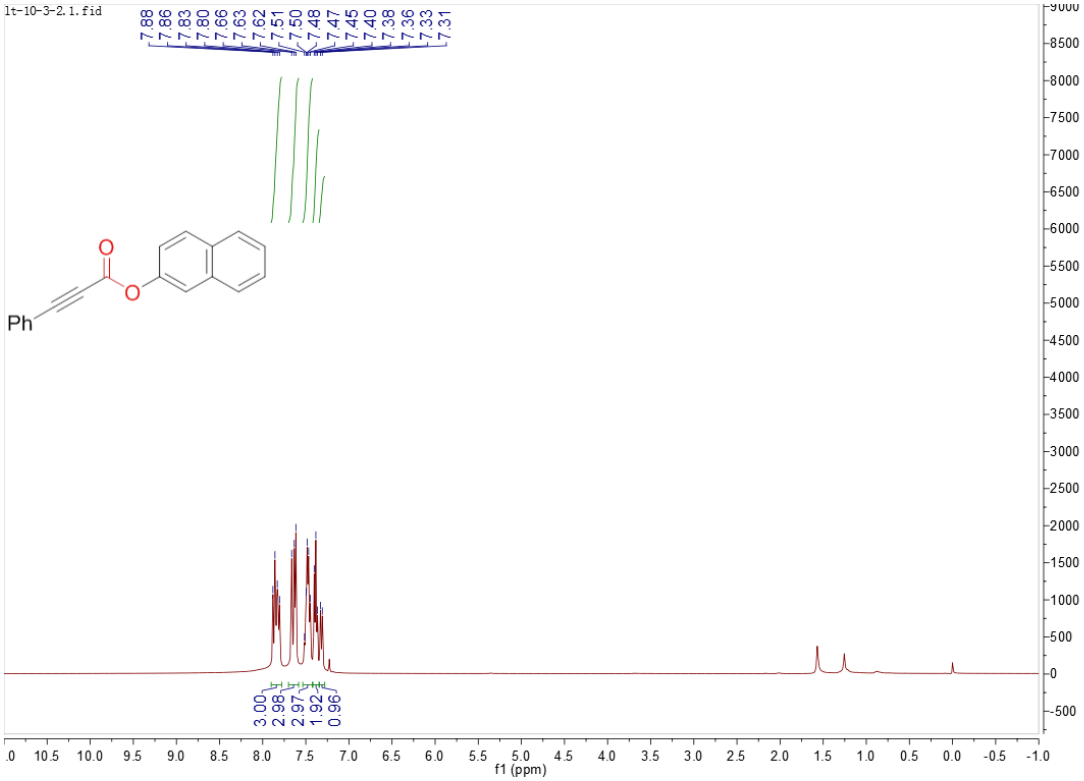
^{13}C NMR(100 Mz) spectrum of compound **9j** in $CDCl_3$



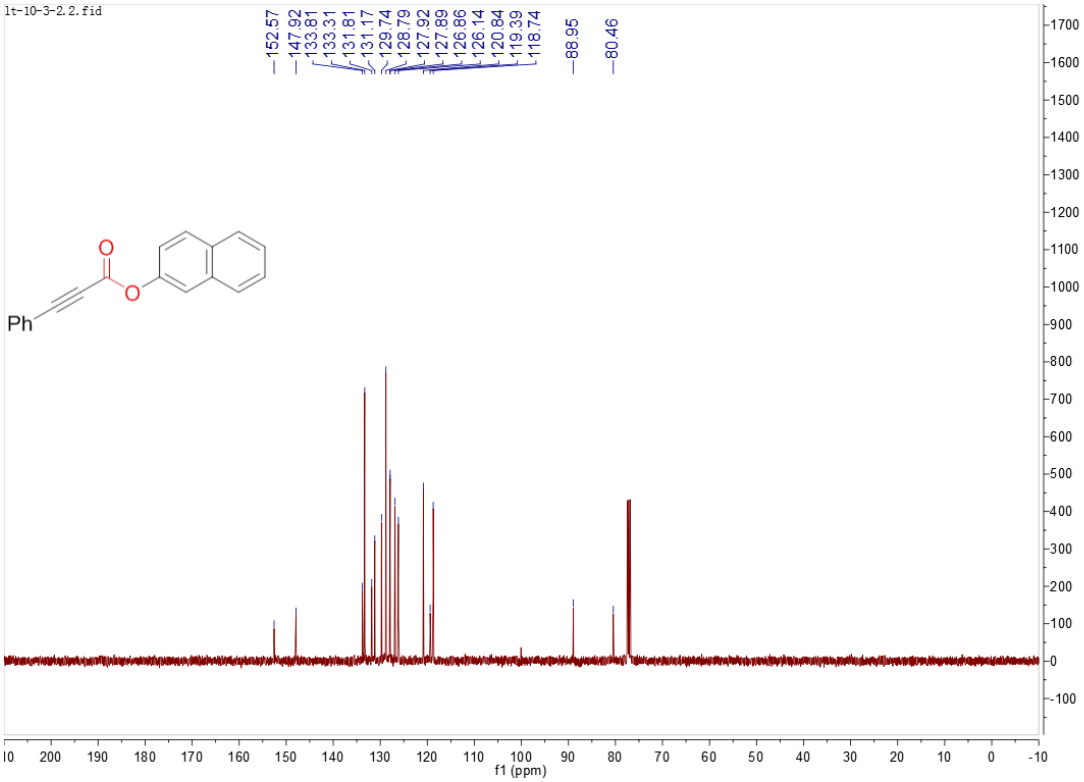
^{1}H NMR(400 Mz) spectrum of compound **9k** in $CDCl_3$



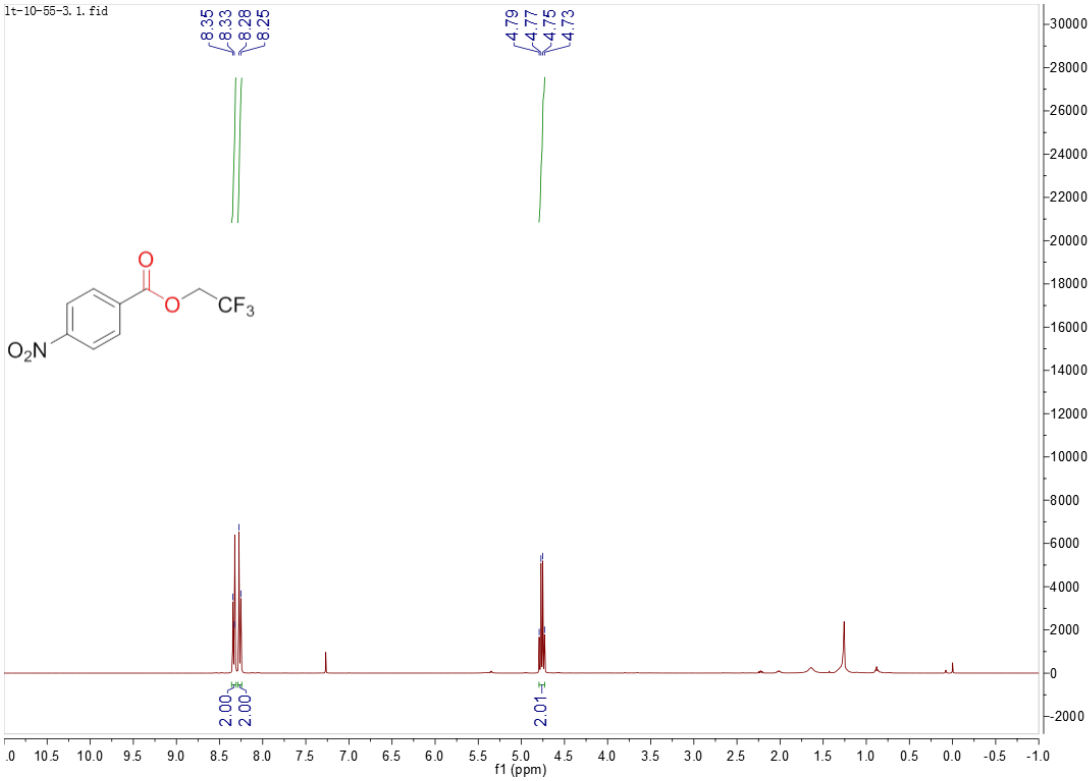
^{13}C NMR(100 Mz) spectrum of compound **9k** in $CDCl_3$



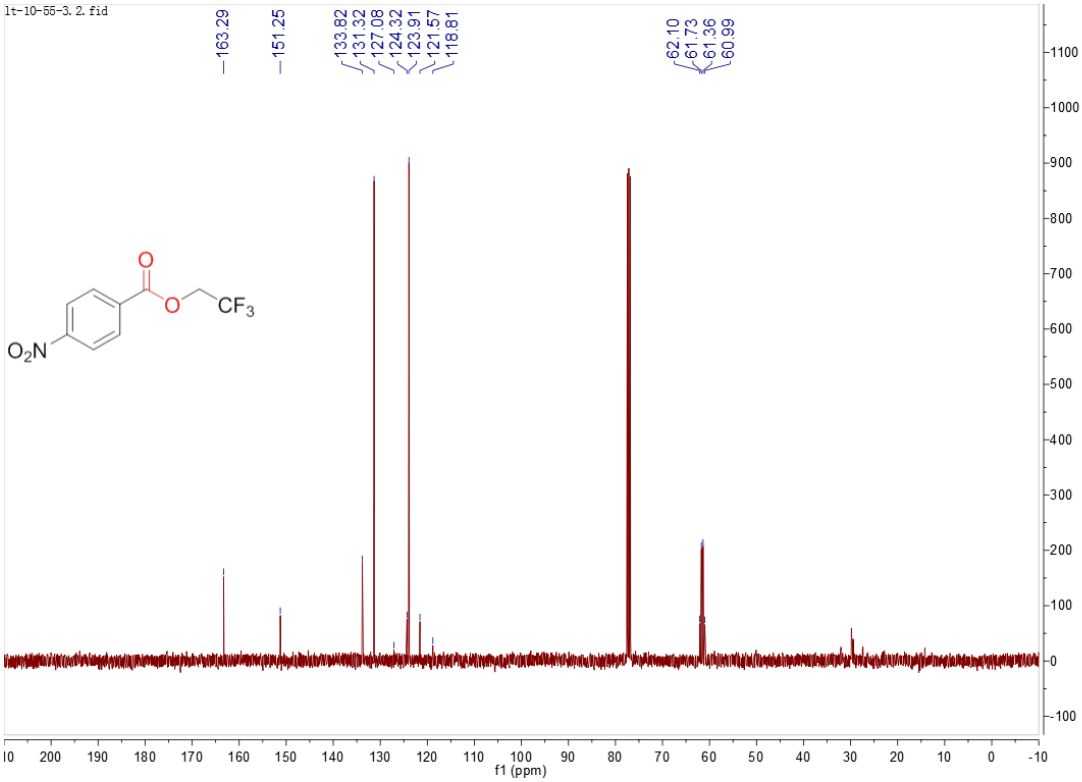
^{1}H NMR(400 Mz) spectrum of compound **11a** in $CDCl_3$



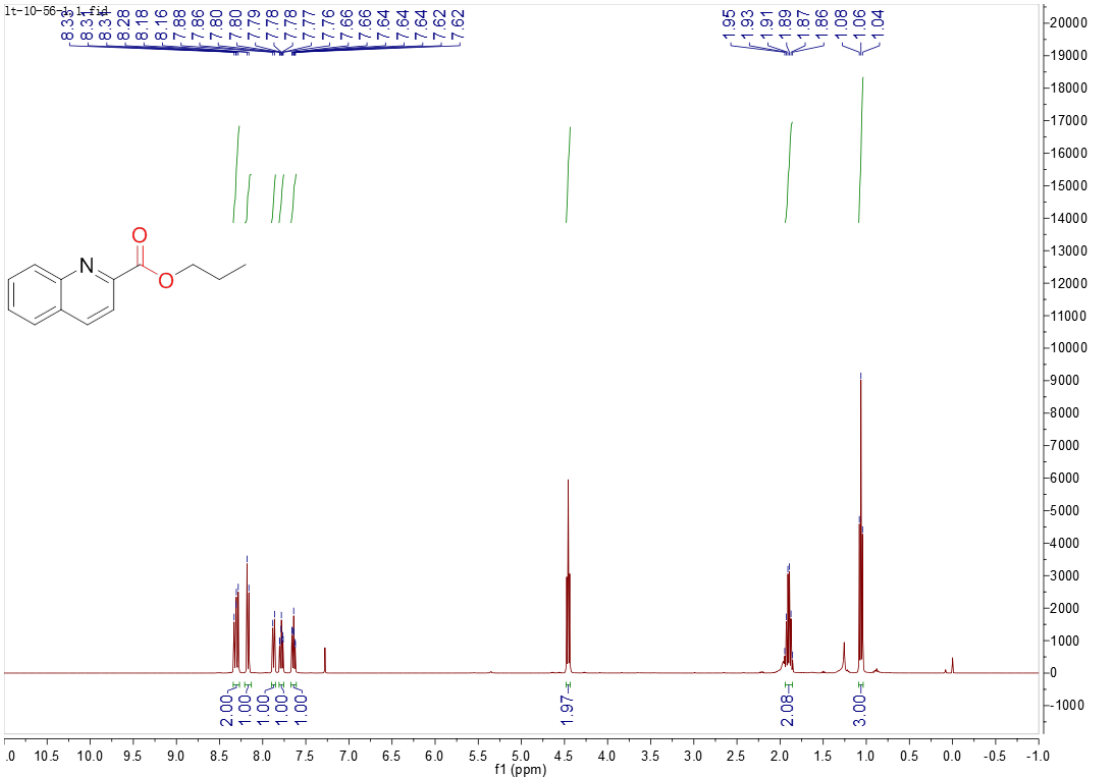
^{13}C NMR(100 Mz) spectrum of compound **11a** in $CDCl_3$



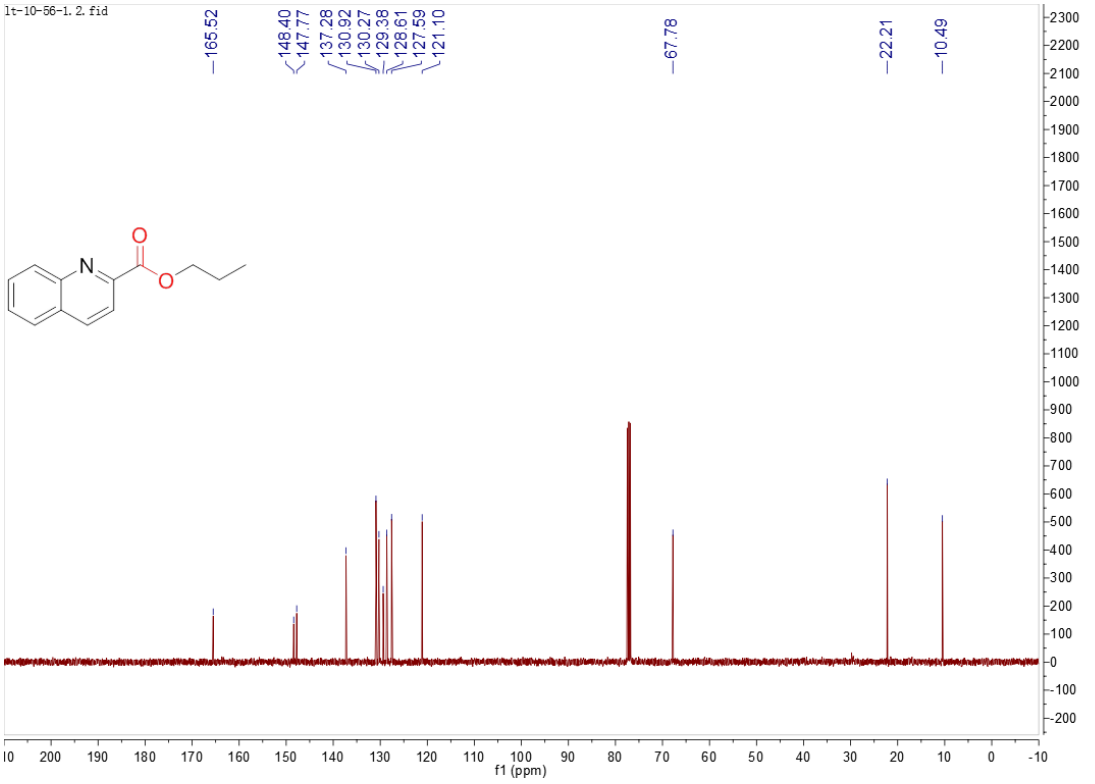
^{1}H NMR(400 Mz) spectrum of compound **11b** in $CDCl_3$



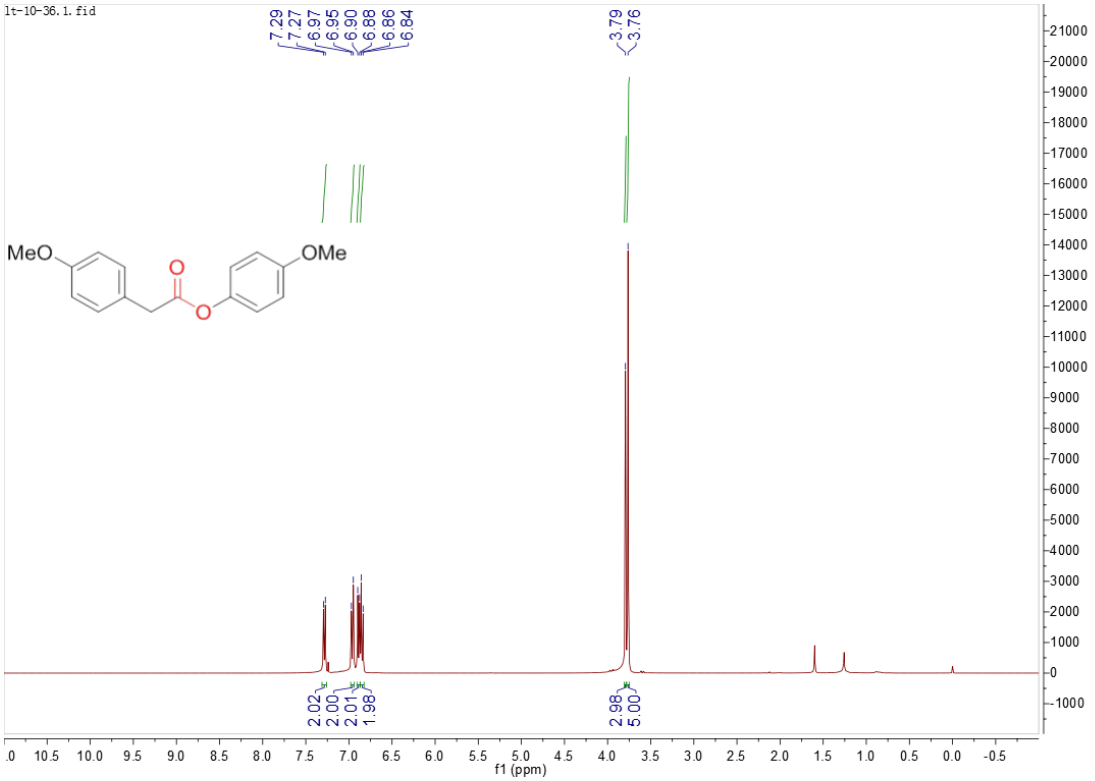
^{13}C NMR(100 Mz) spectrum of compound **11b** in $CDCl_3$



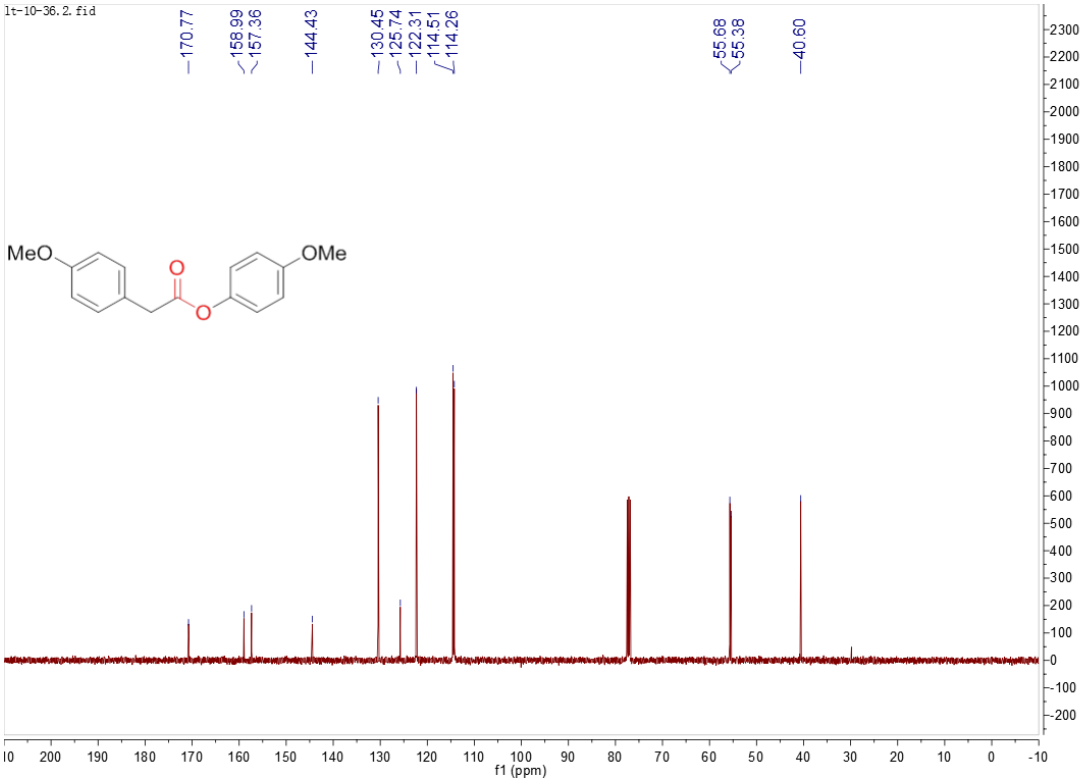
^{1}H NMR(400 Mz) spectrum of compound **11c** in $CDCl_3$



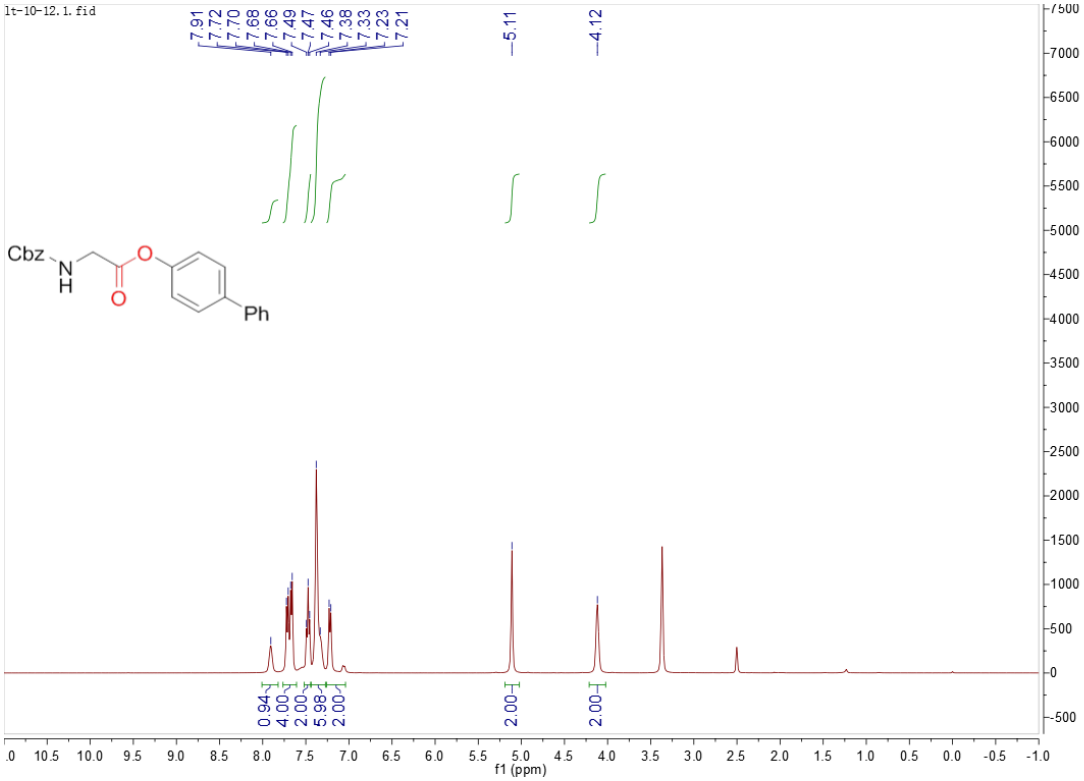
^{13}C NMR(100 Mz) spectrum of compound **11c** in $CDCl_3$



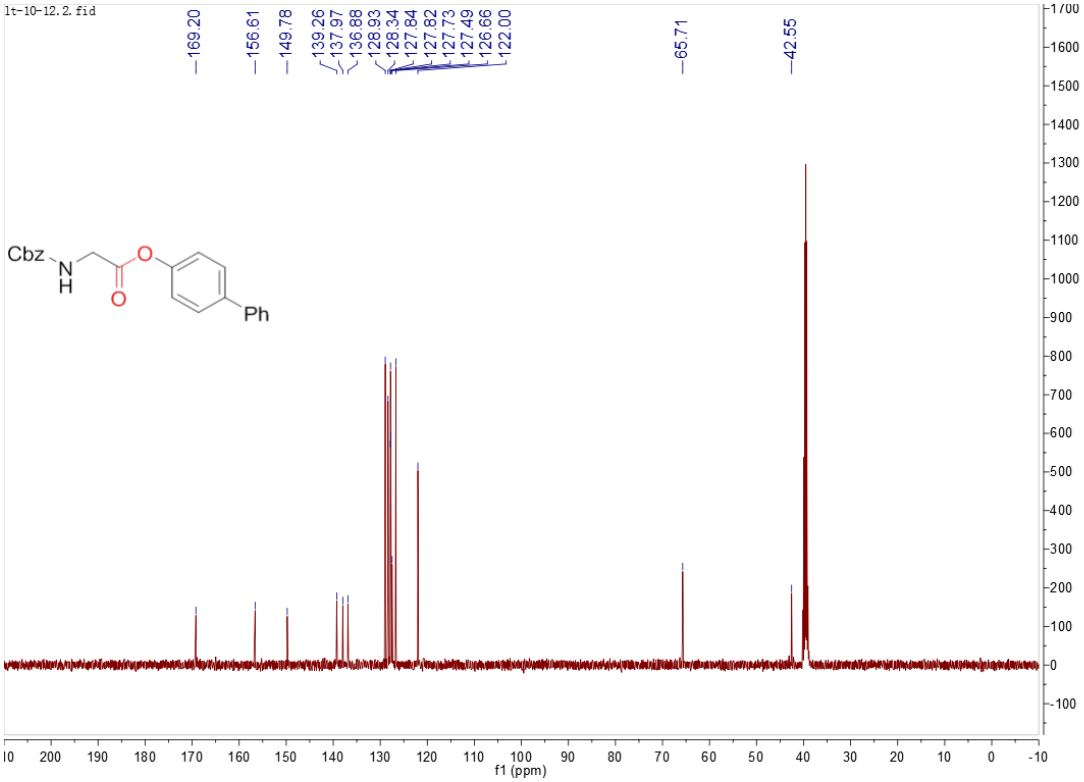
^{1}H NMR(400 Mz) spectrum of compound **11d** in $CDCl_3$



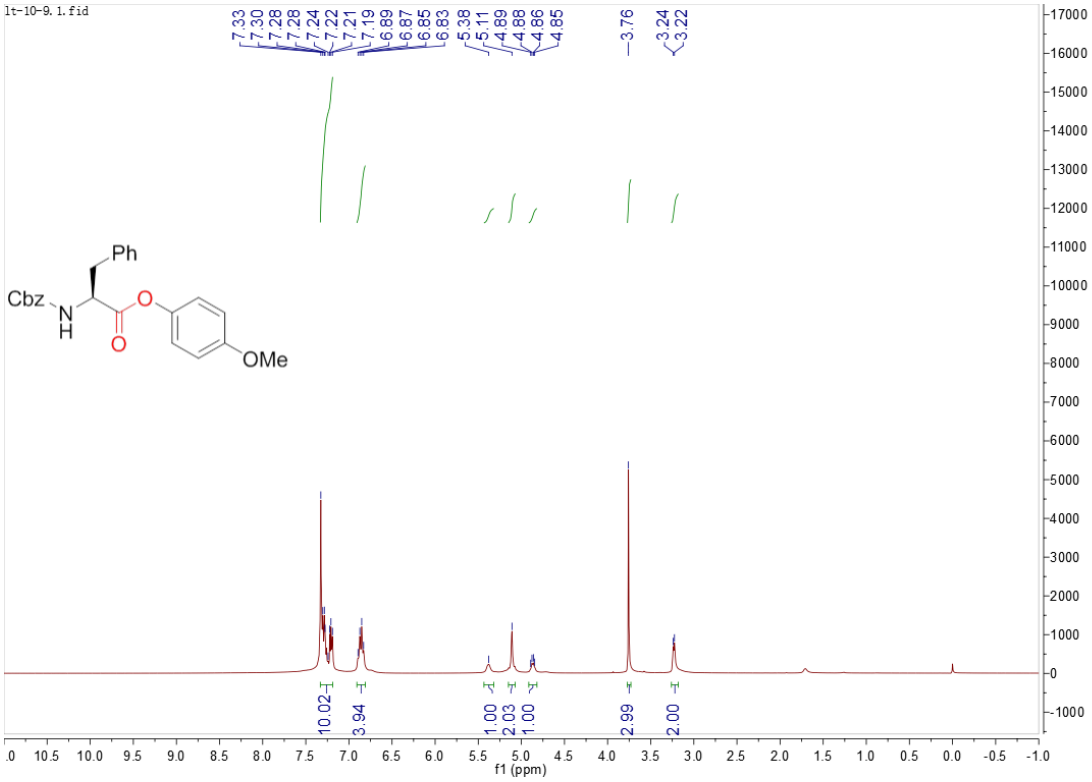
^{13}C NMR(100 Mz) spectrum of compound **11d** in $CDCl_3$



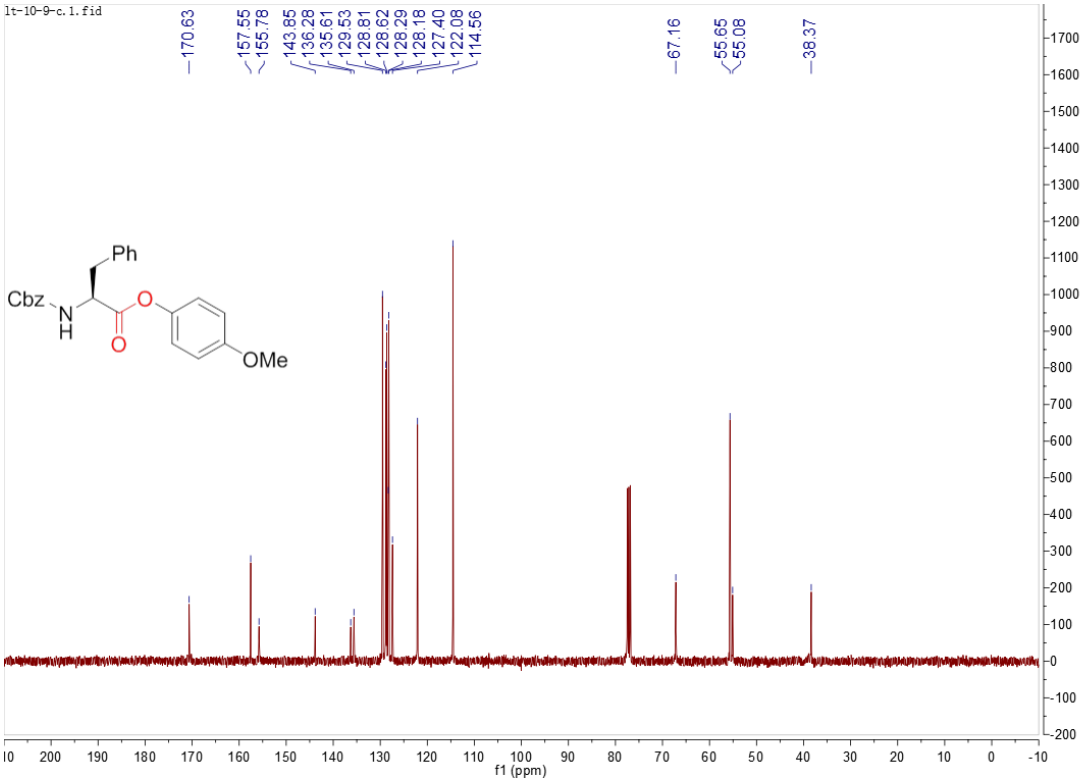
^{1}H NMR(400 Mz) spectrum of compound **11e** in DMSO-d_6



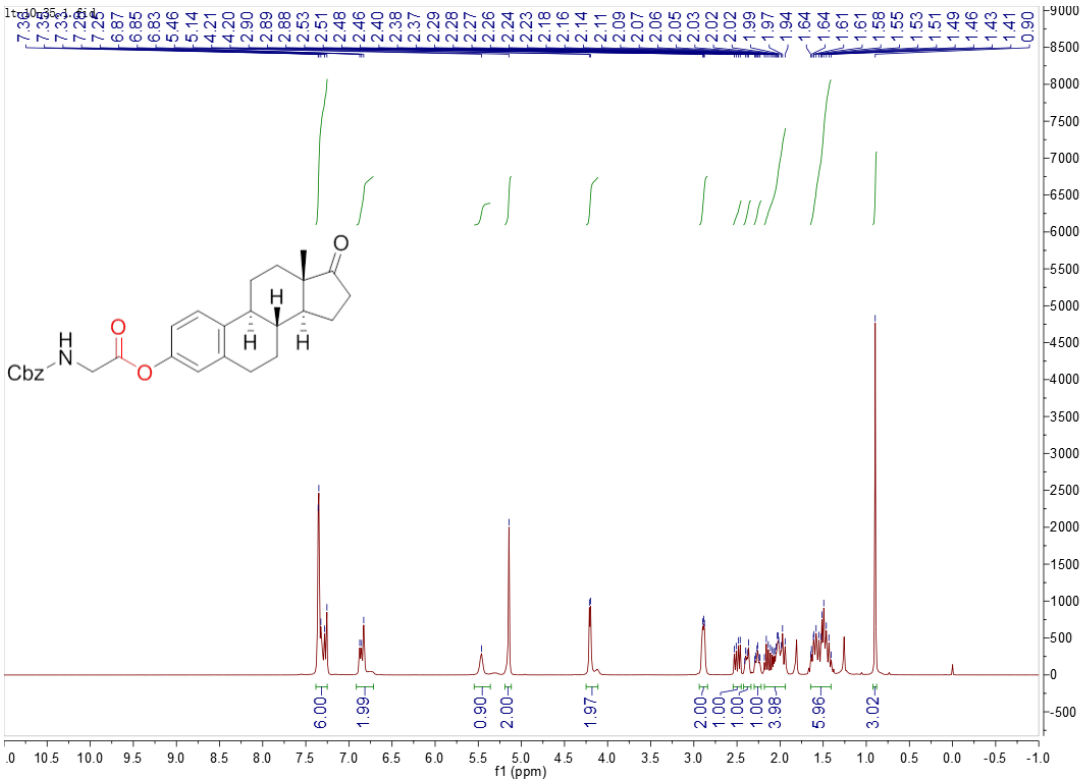
^{13}C NMR(100 Mz) spectrum of compound **11e** in DMSO-d_6



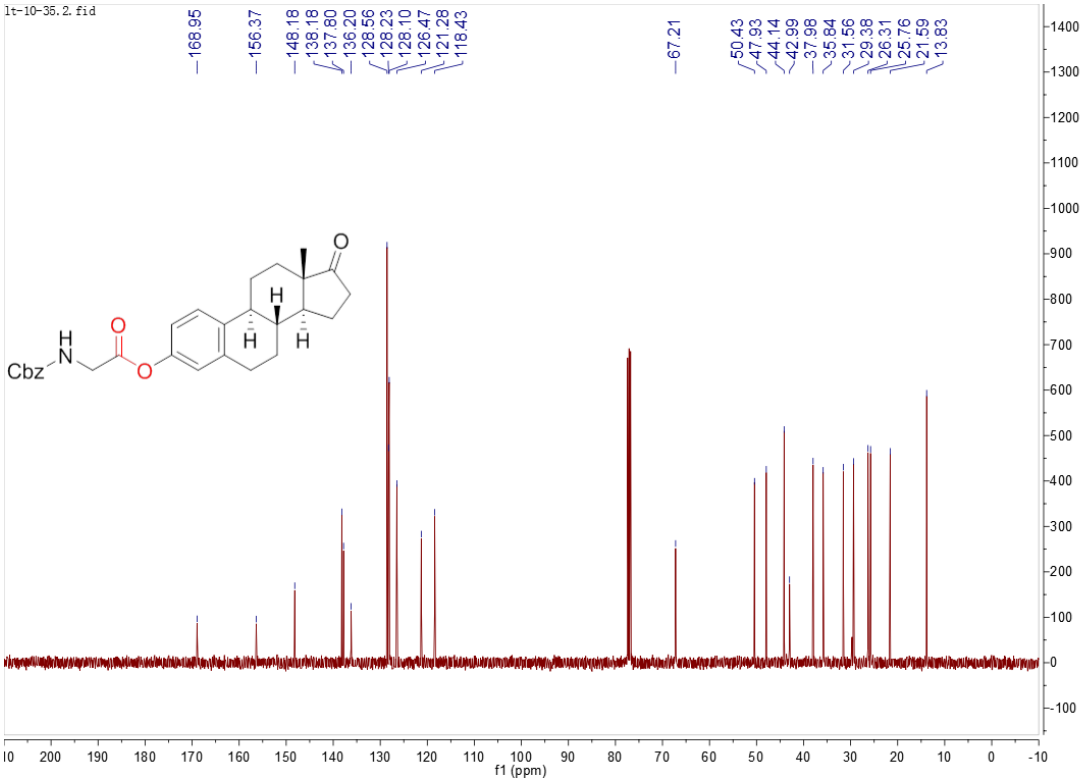
^{1}H NMR(400 Mz) spectrum of compound **11f** in $CDCl_3$



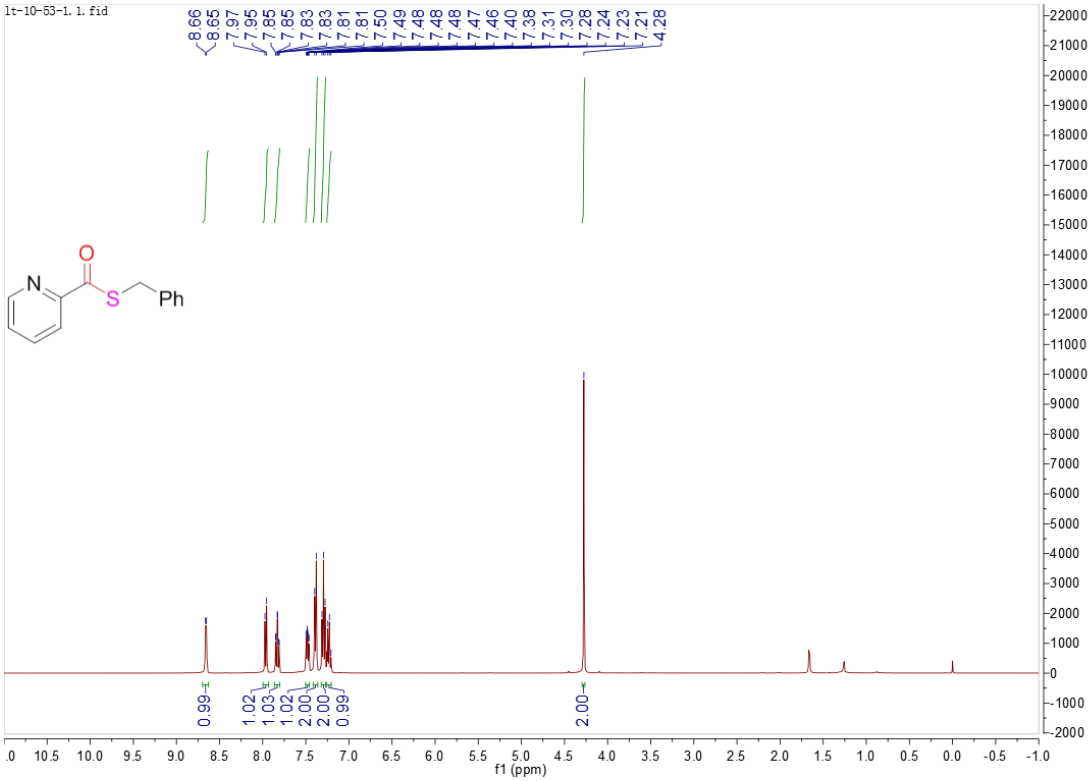
^{13}C NMR(100 Mz) spectrum of compound **11f** in $CDCl_3$



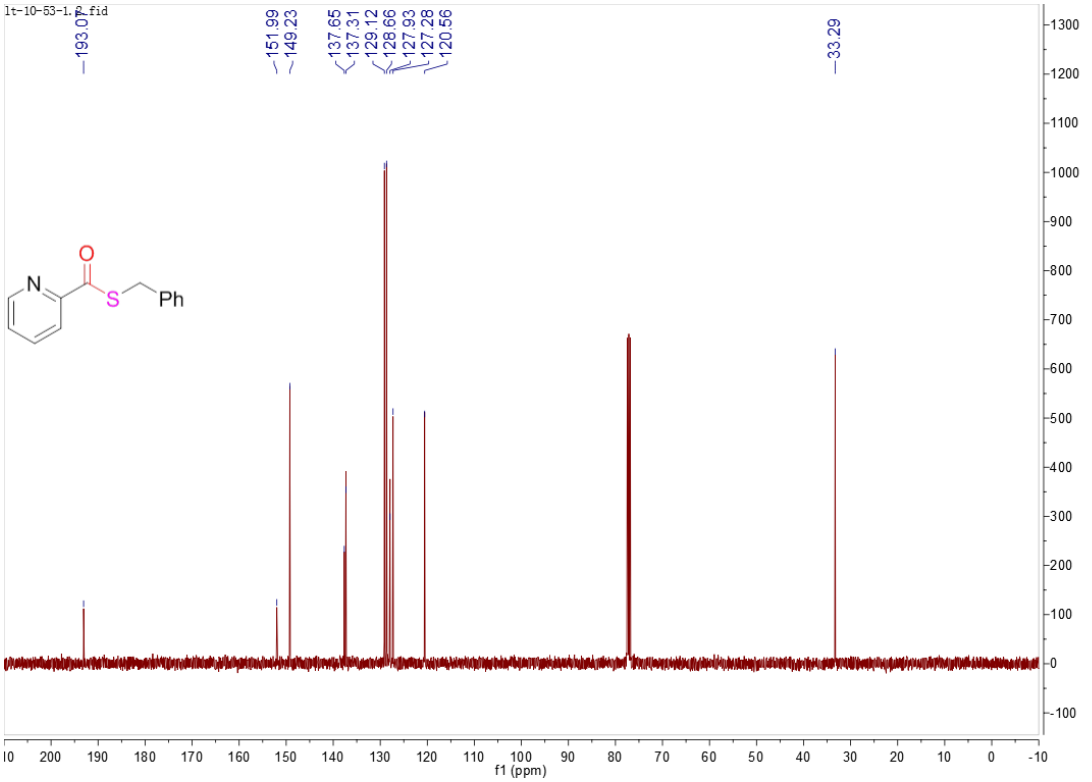
^{1}H NMR(400 Mz) spectrum of compound **11g** in $CDCl_3$



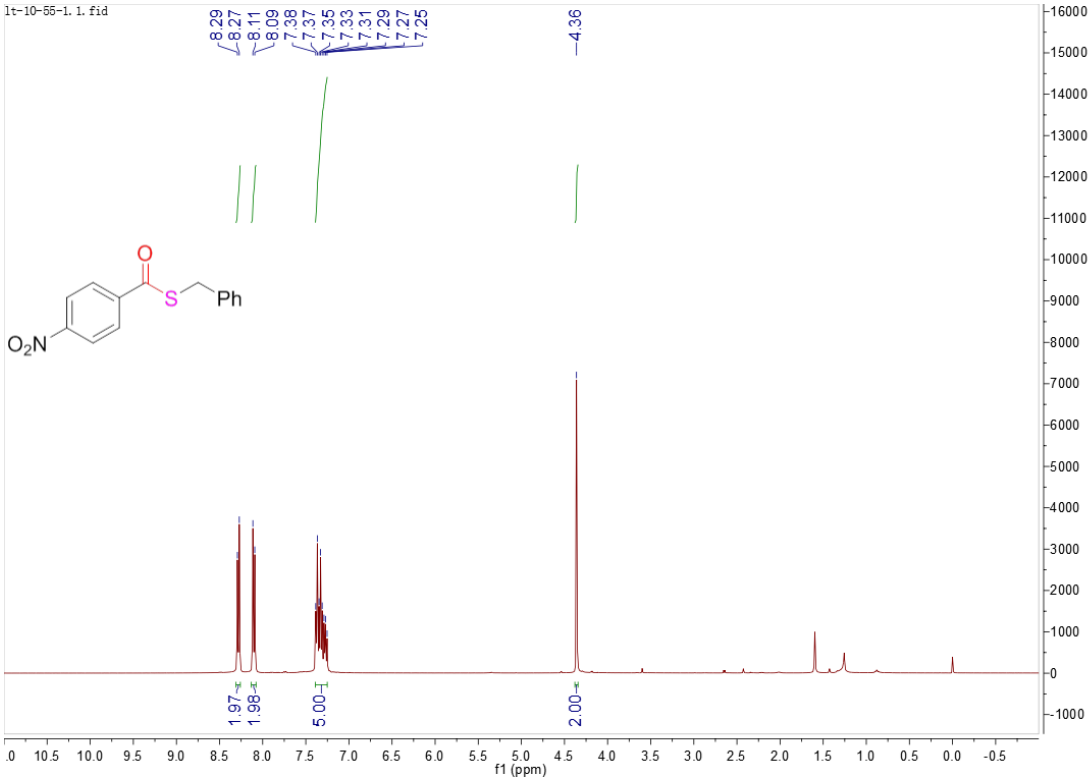
^{13}C NMR(100 Mz) spectrum of compound **11g** in $CDCl_3$



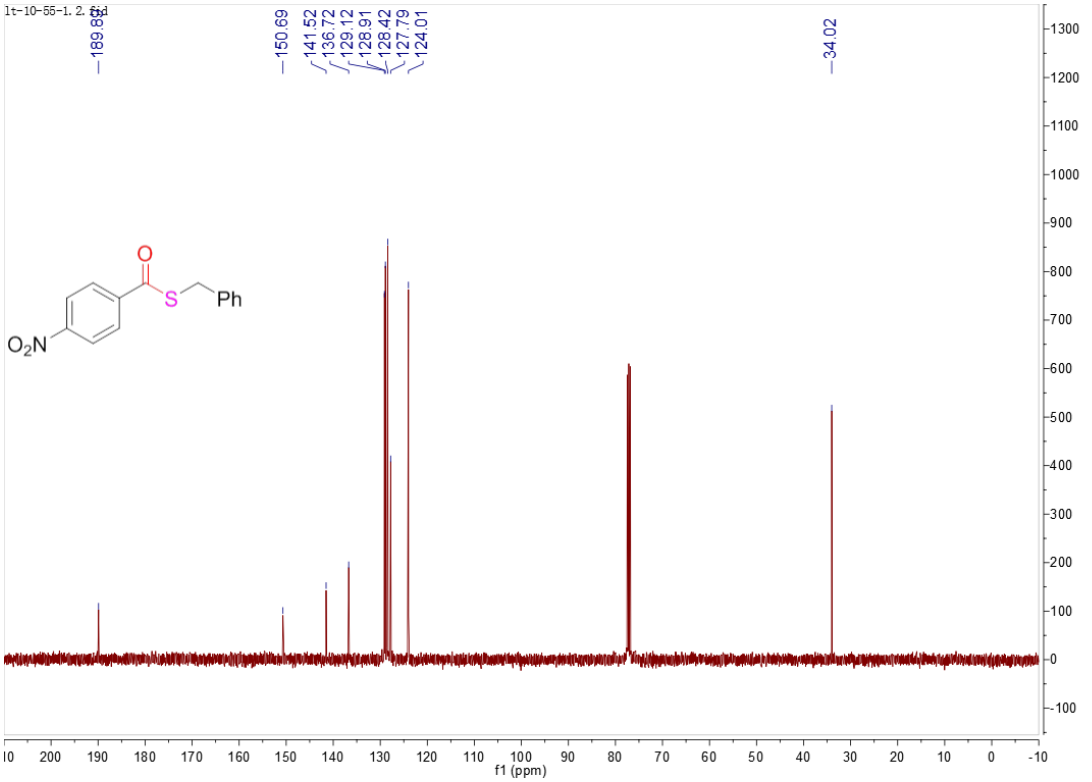
^{1}H NMR(400 Mz) spectrum of compound **11h** in $CDCl_3$



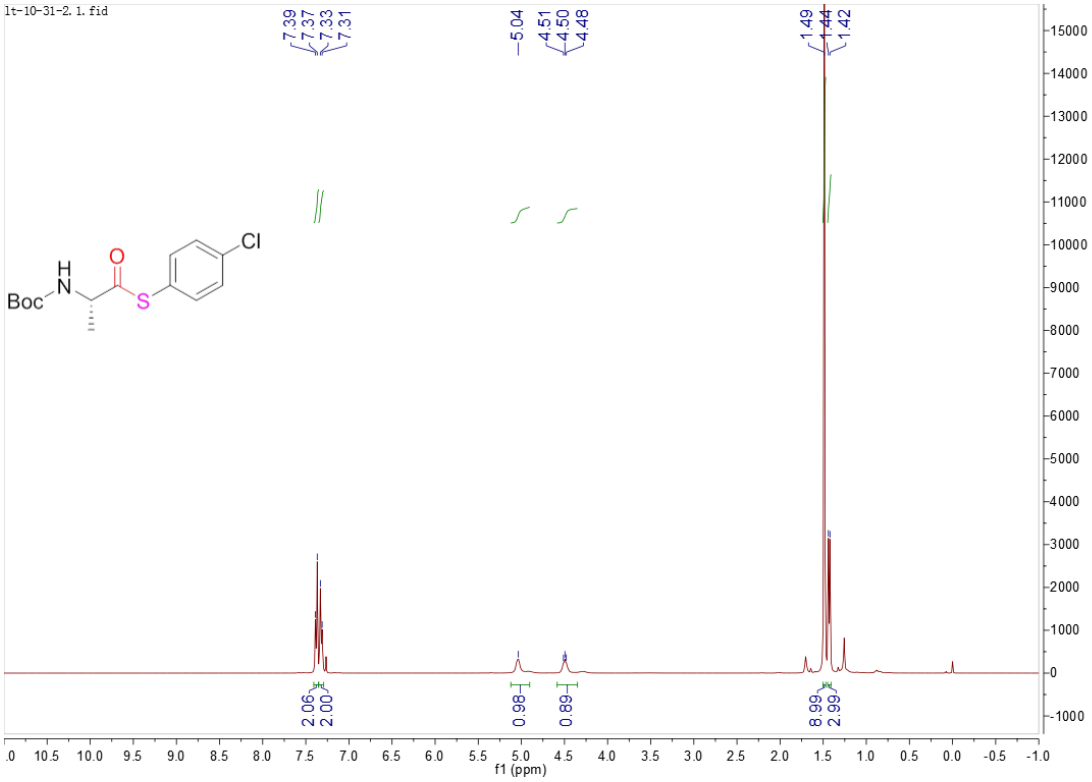
^{13}C NMR(100 Mz) spectrum of compound **11h** in $CDCl_3$



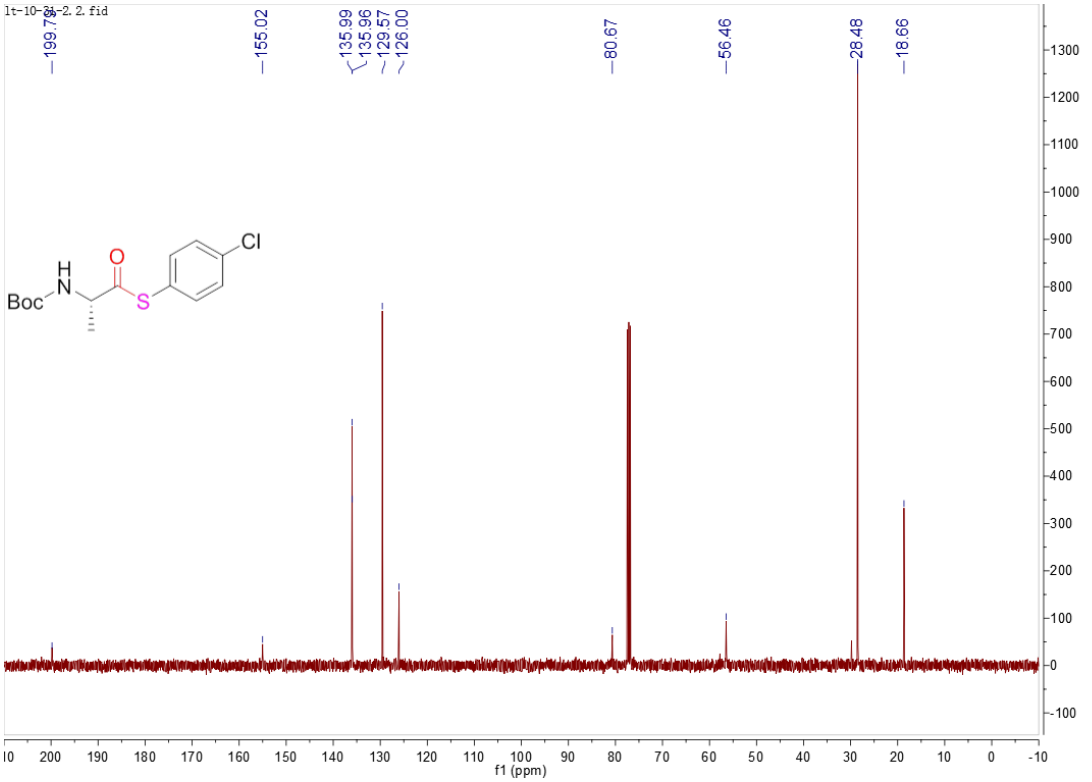
^{1}H NMR(400 Mz) spectrum of compound **11i** in $CDCl_3$



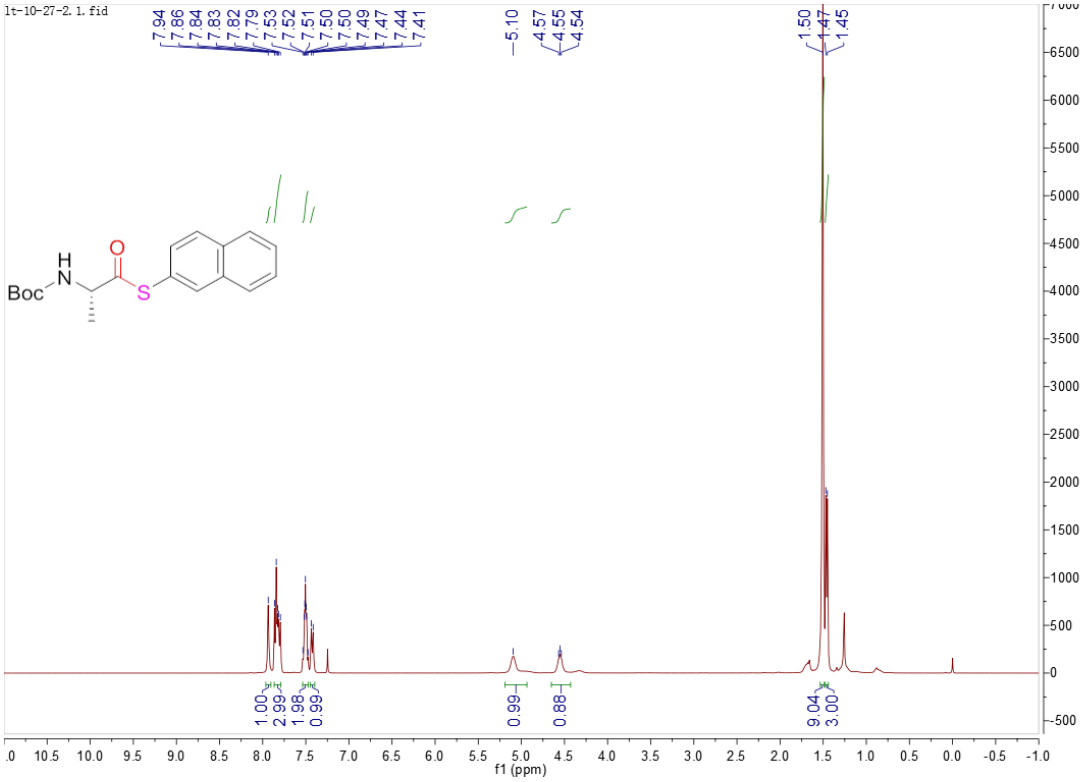
^{13}C NMR(100 Mz) spectrum of compound **11i** in $CDCl_3$



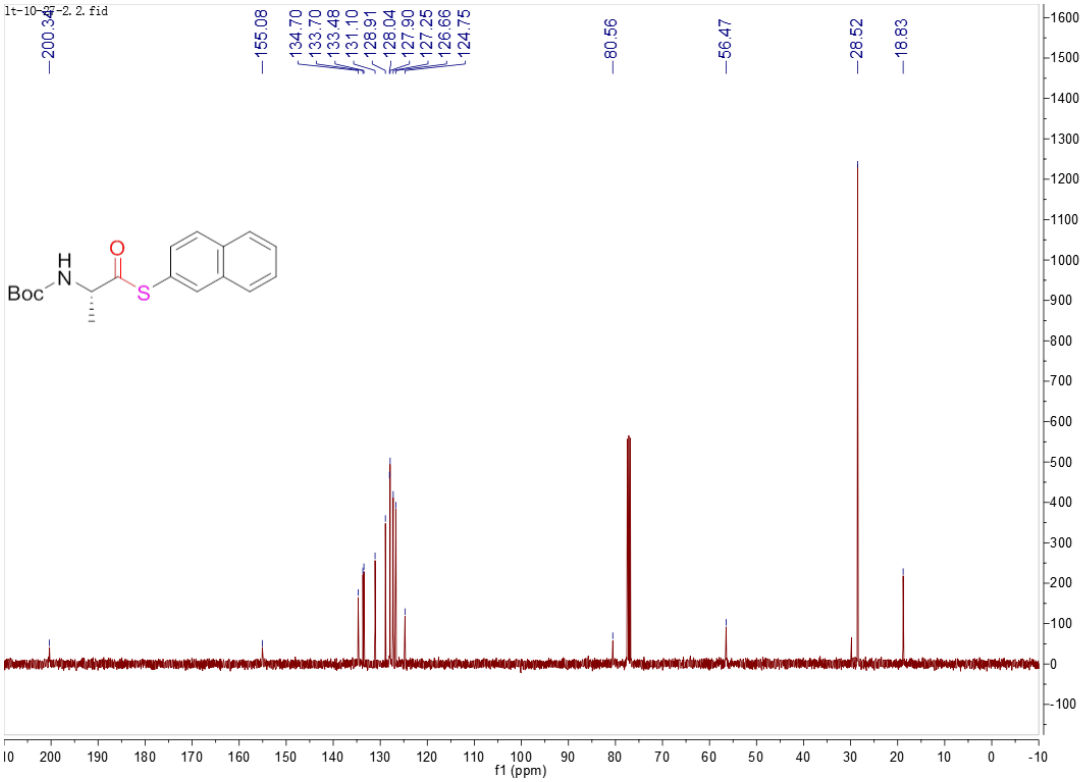
^{1}H NMR(400 Mz) spectrum of compound **11j** in $CDCl_3$



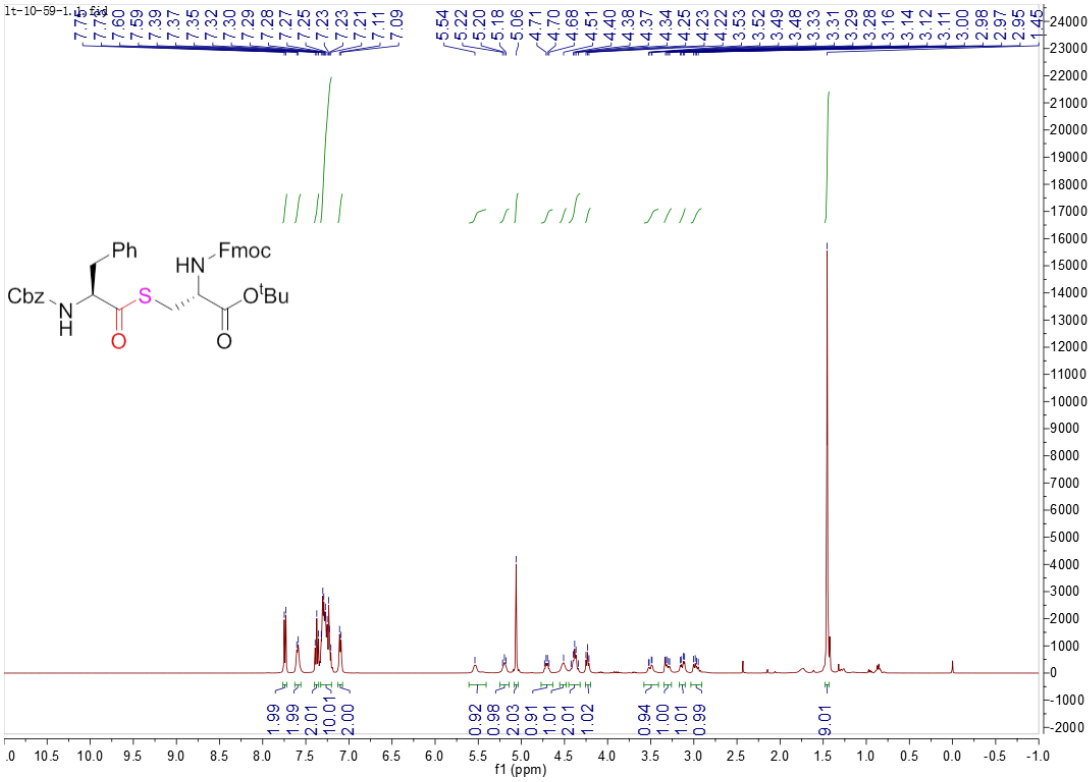
^{13}C NMR(100 Mz) spectrum of compound **11j** in $CDCl_3$



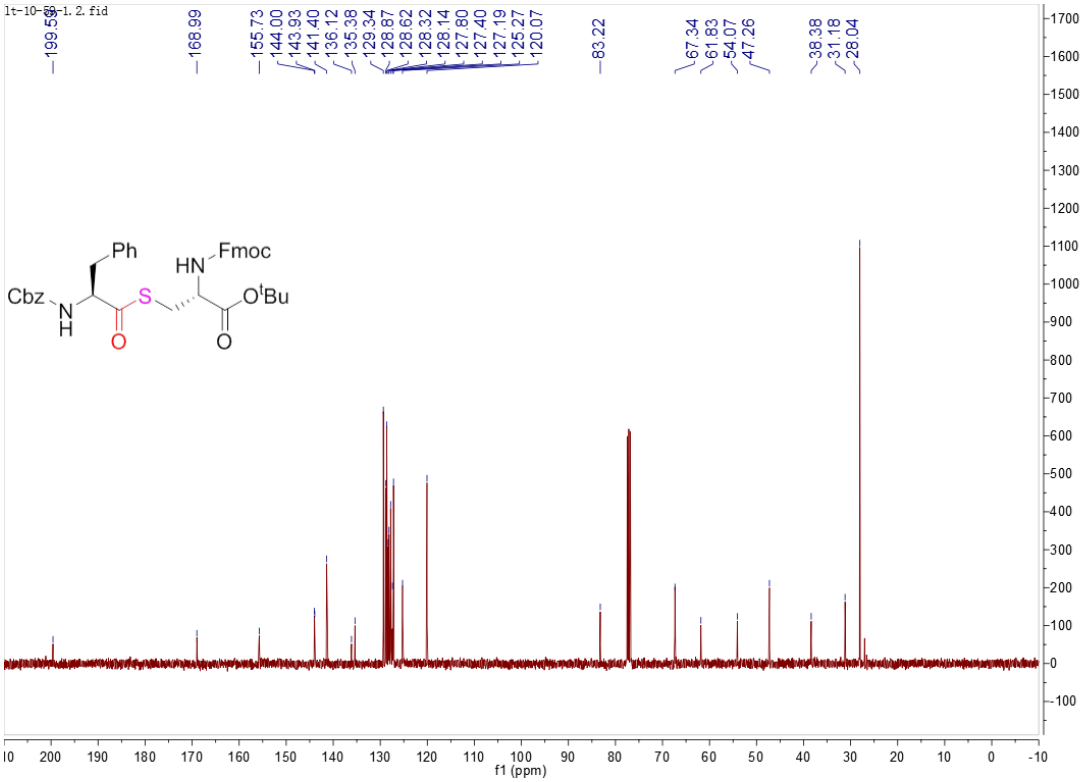
^{1}H NMR(400 Mz) spectrum of compound **11k** in $CDCl_3$



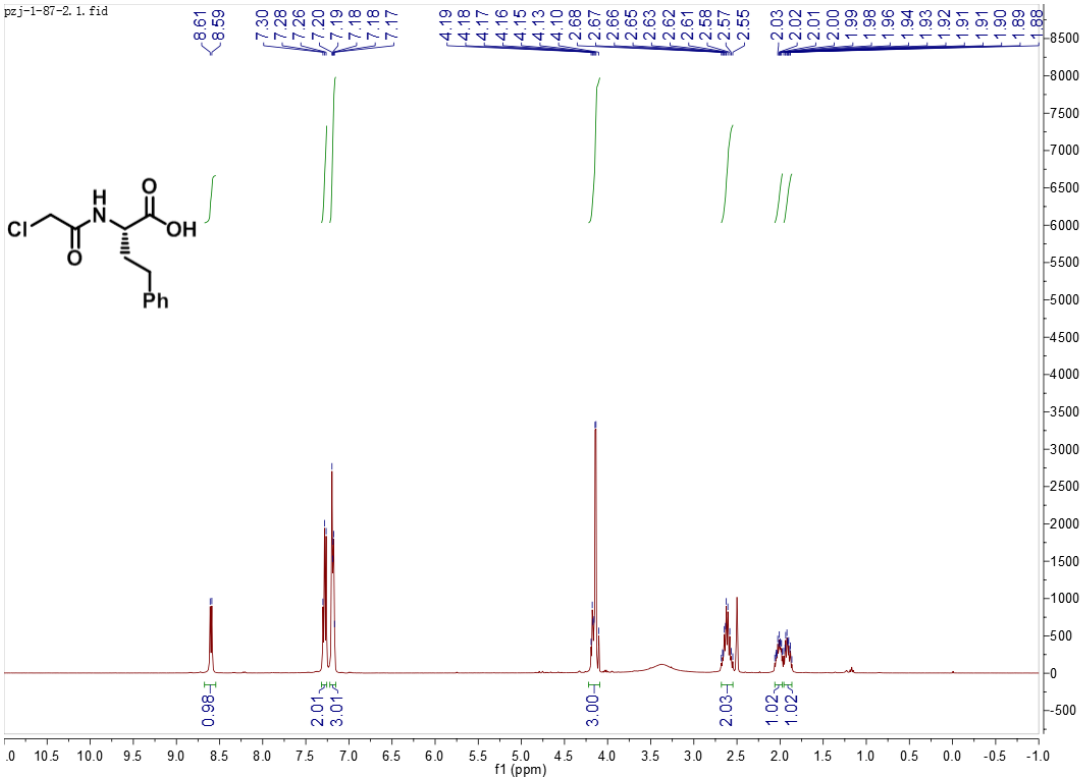
^{13}C NMR(100 Mz) spectrum of compound **11k** in $CDCl_3$



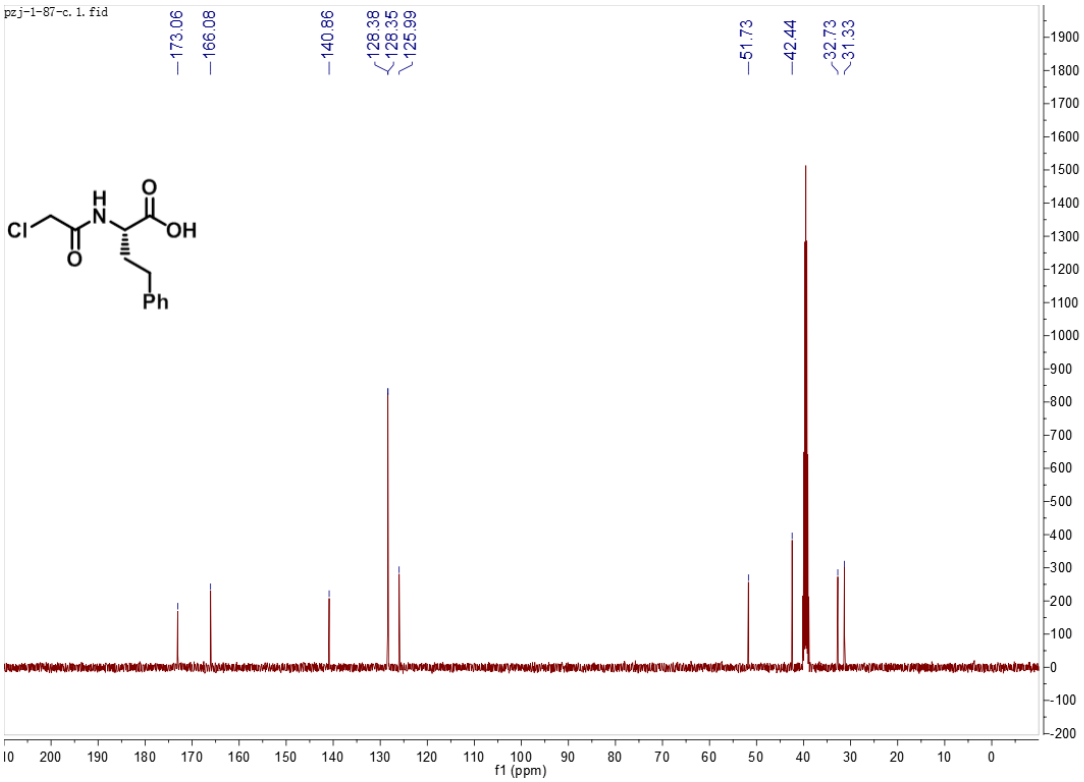
^{1}H NMR(400 Mz) spectrum of compound **11l** in $CDCl_3$



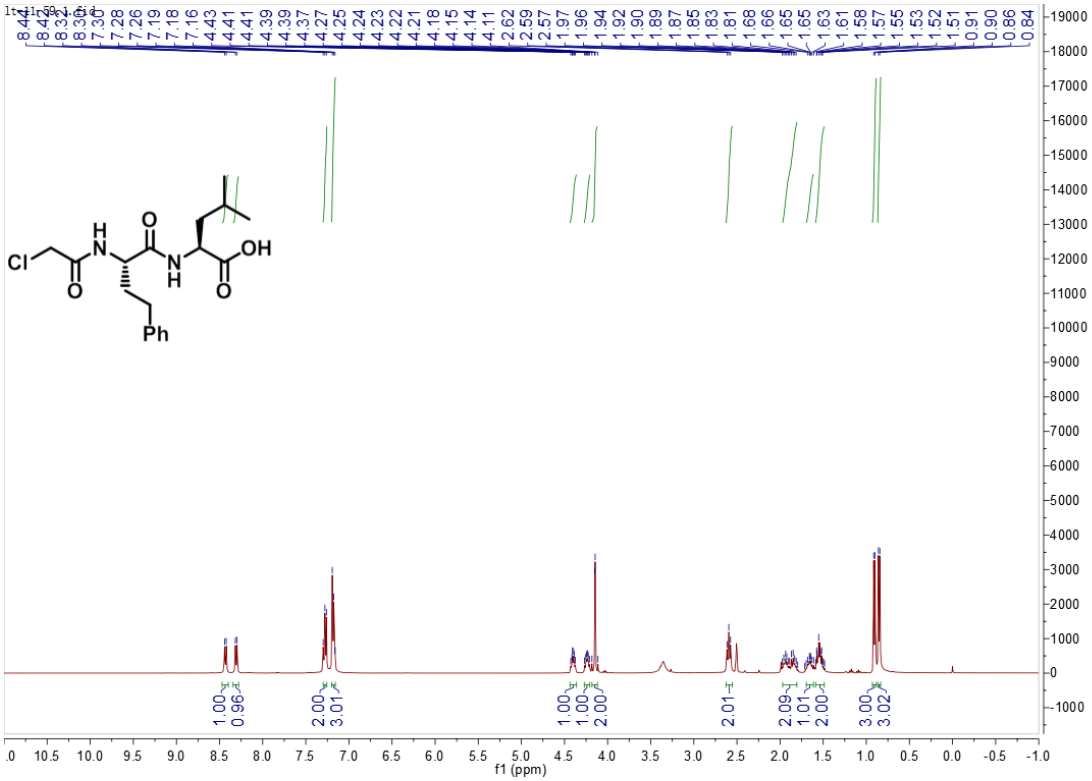
^{13}C NMR(100 Mz) spectrum of compound **11l** in $CDCl_3$



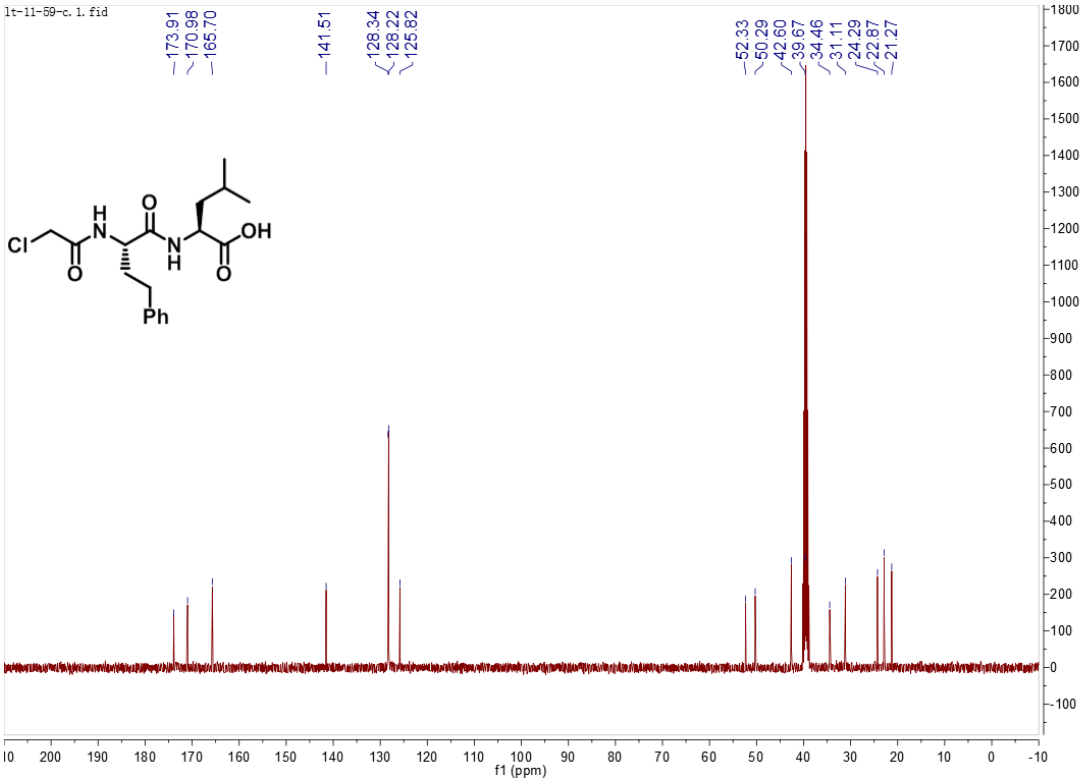
^{1}H NMR(400 Mz) spectrum of compound **12** in DMSO-d_6



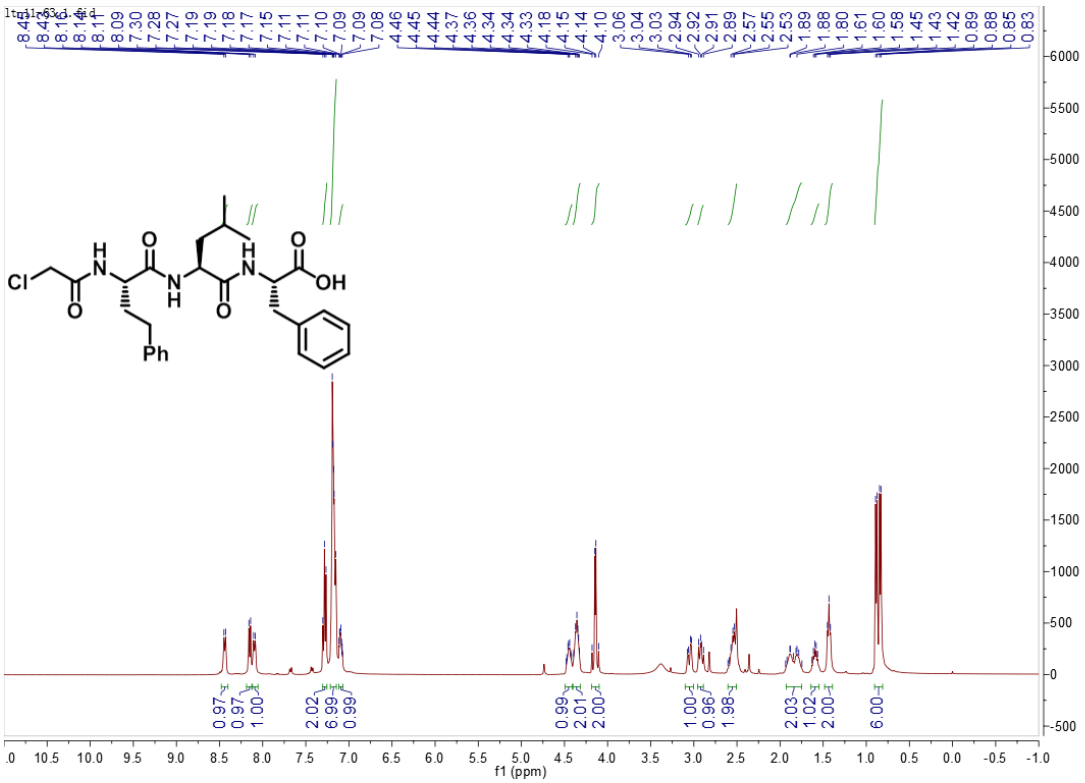
^{13}C NMR(100 Mz) spectrum of compound **12** in DMSO-d_6



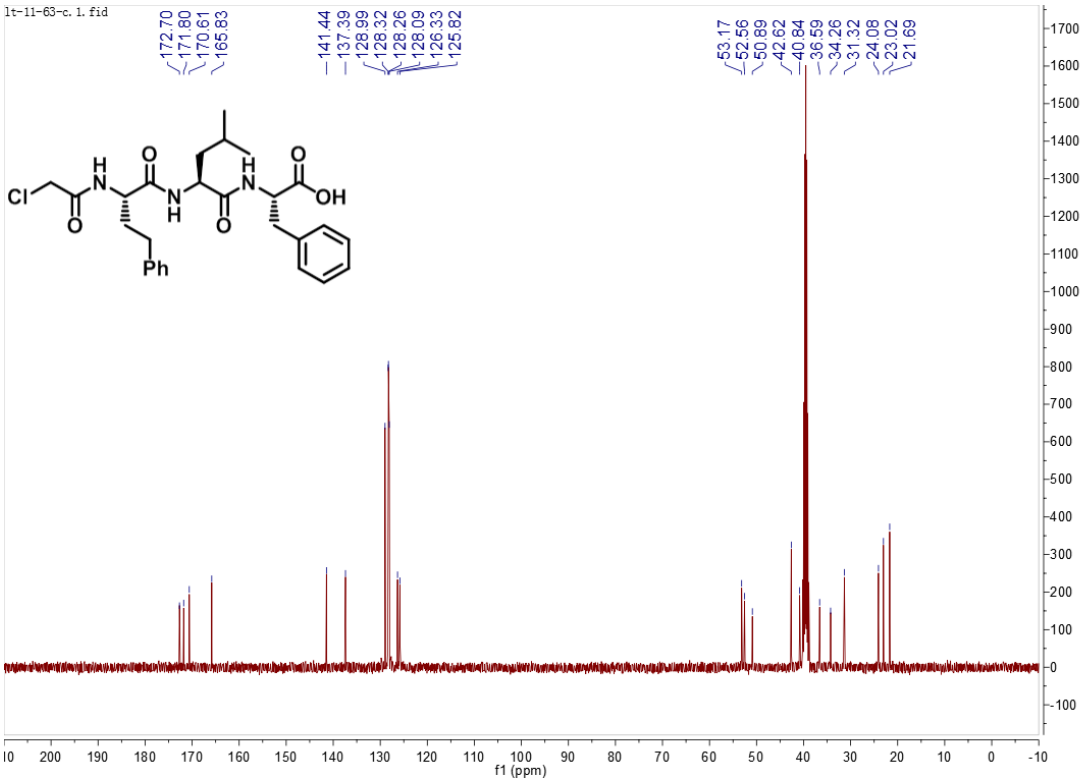
^{1}H NMR(400 Mz) spectrum of compound **13** in DMSO-d_6



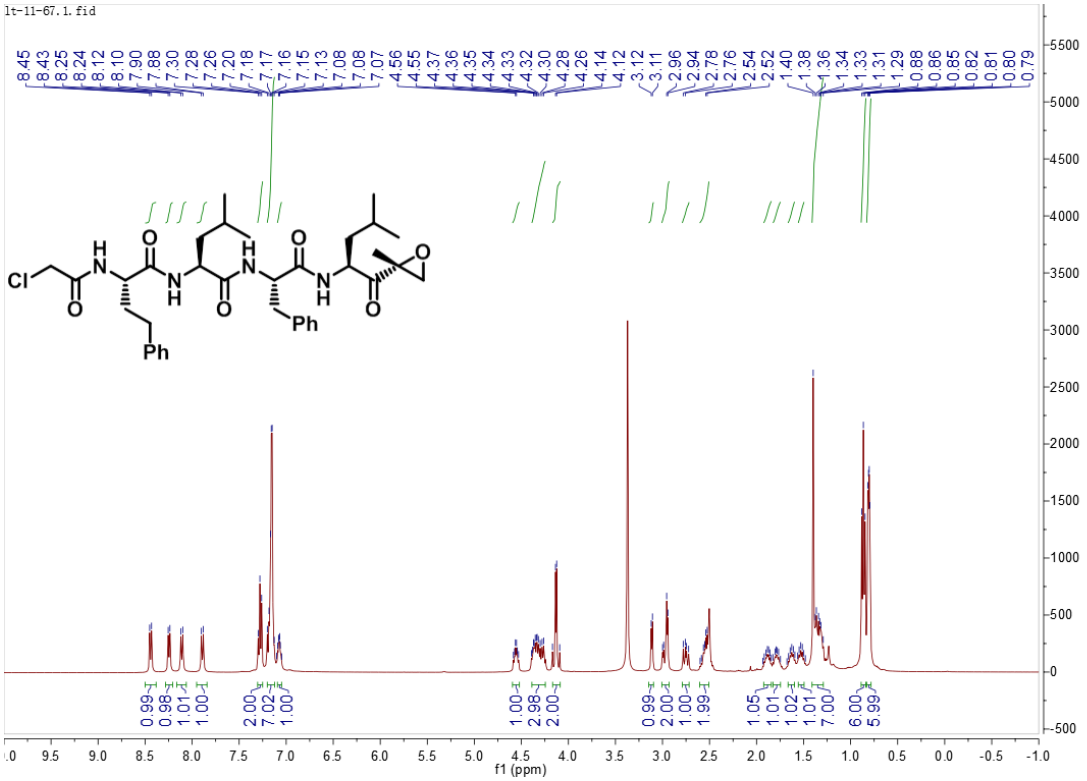
^{13}C NMR(100 Mz) spectrum of compound **13** in DMSO-d_6



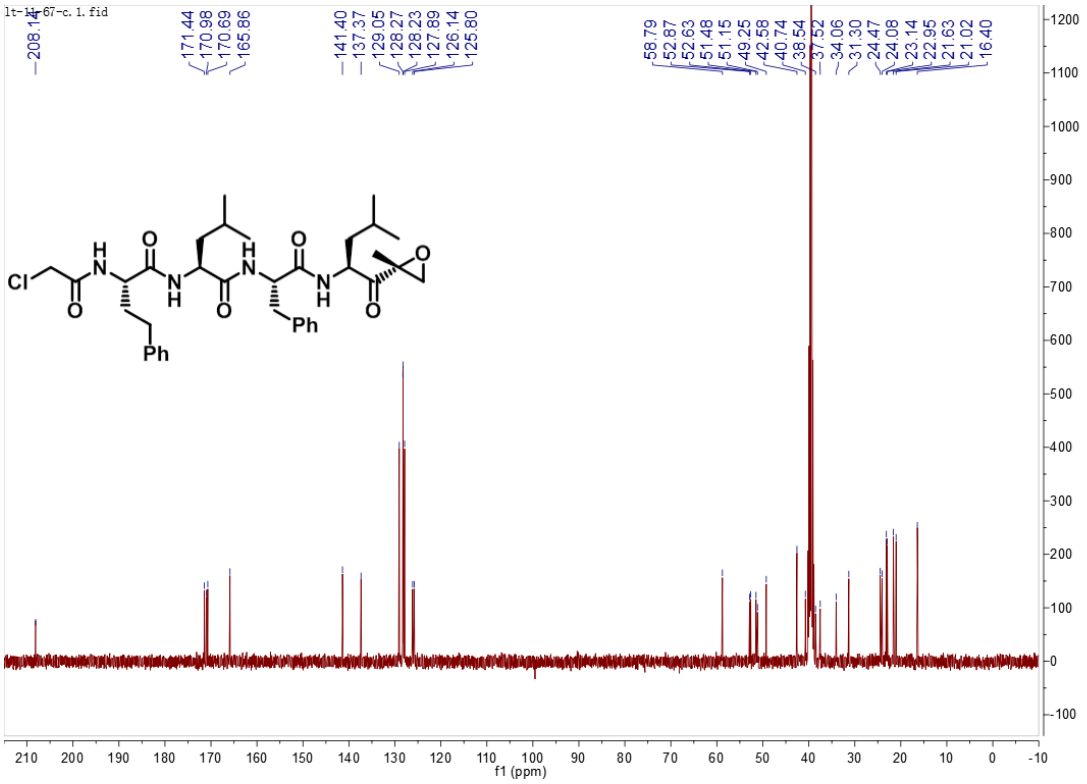
^{1}H NMR(400 Mz) spectrum of compound **14** in DMSO-d_6



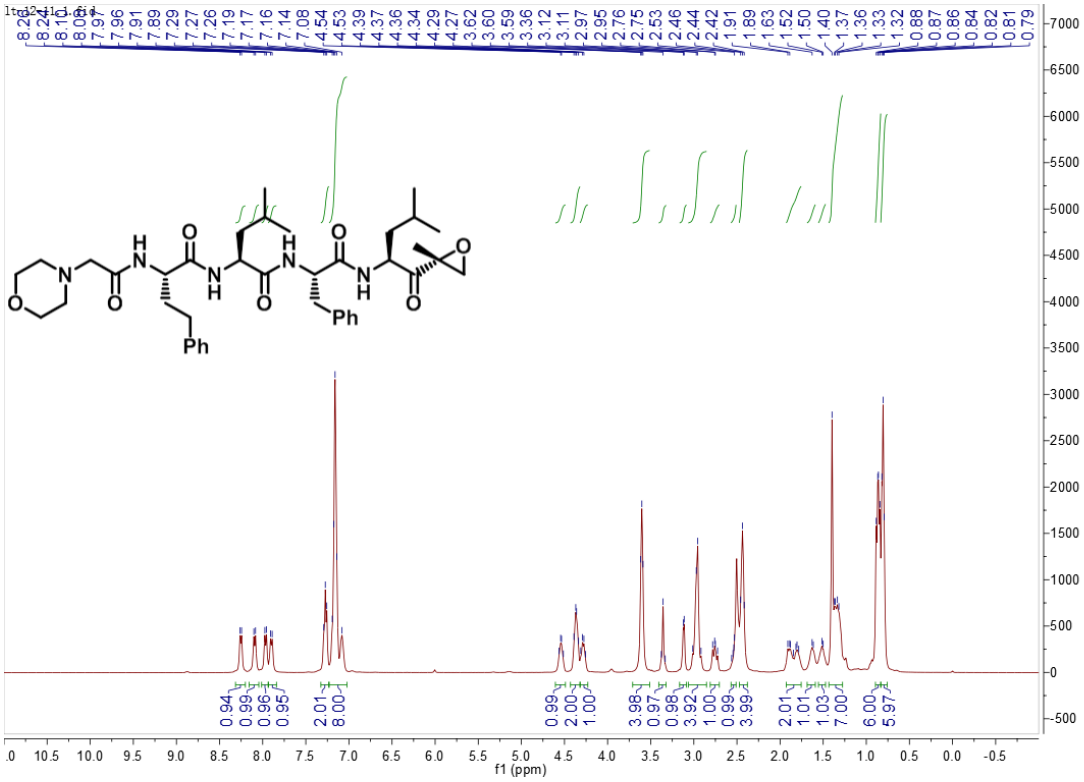
^{13}C NMR(100 Mz) spectrum of compound **14** in DMSO-d_6



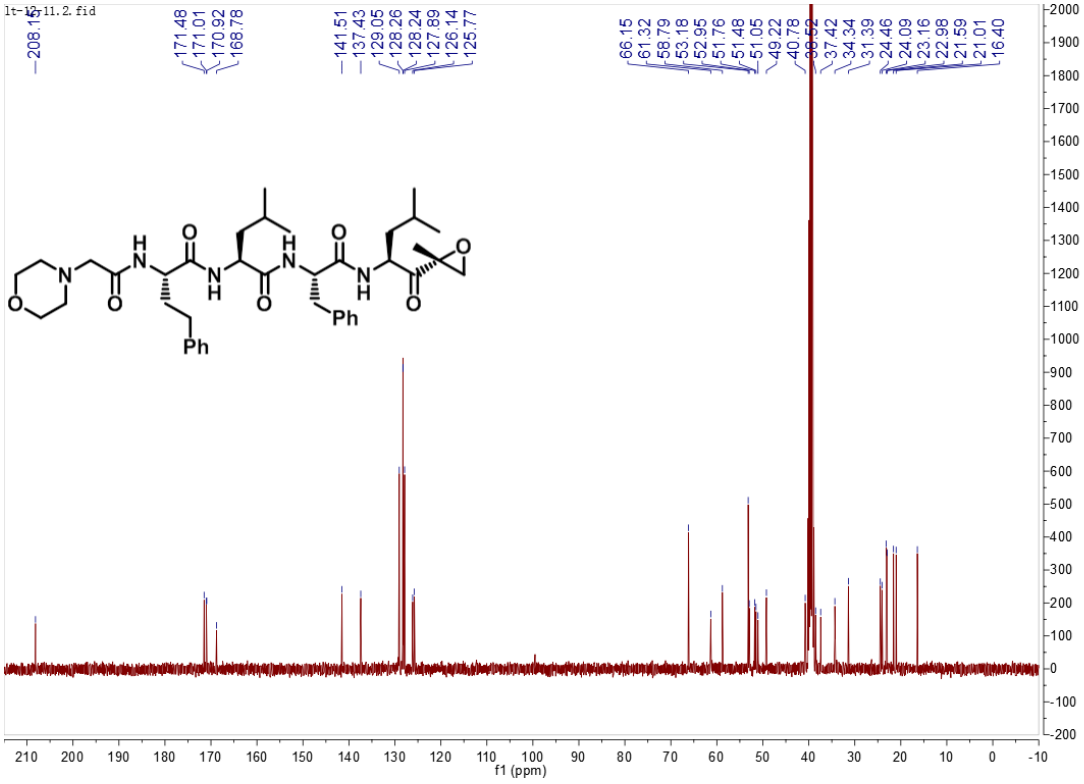
^{1}H NMR(400 Mz) spectrum of compound **15** in DMSO-d_6



^{13}C NMR(100 Mz) spectrum of compound **15** in DMSO-d_6



^{1}H NMR(400 Mz) spectrum of **Carfilzomib** in DMSO-d_6



^{13}C NMR(100 Mz) spectrum of **Carfilzomib** in DMSO-d_6