Supporting Information

TFPN-mediated racemization/epimerization-free amide and peptide bond formation

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Contents

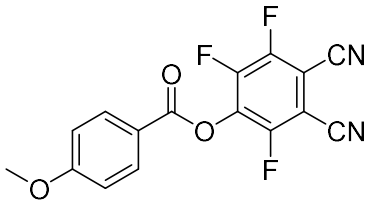
General information

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). $^{1}H/^{13}C\{H\}$ NMR spectra were recorded on Bruker Avance 300 MHz and Bruker AMX 300 MHz spectrometer at 300/75 MHz, respectively, in $CDCl_3$ unless otherwise stated, using either TMS or the undeuterated solvent residual signal as the reference. $CDCl_3$ 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 $^{13}C\{H\}$ 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. Flash column chromatography purification of compounds was carried out by gradient elution using ethyl acetate (EA) in light petroleum ether (PE). 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.

Synthesis of acyl fluorides

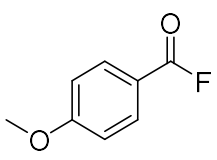
In a round bottom flask, 4-methoxybenzoic acid (**1a**, 0.20 mmol), TFPN (**2a**, 0.24 mmol) was dissolved in DMF (1 mL), then DIPEA (0.24 mmol) was added to the solution and reaction mixture was stirred at room temperature until 4-methoxybenzoic acid was fully consumed. After the reaction was finished, water (10 mL) was added followed by EtOAc (3 x 10 mL). Combined organic layers were washed with brine (1 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by silica gel chromatography to afford the 4-methoxybenzoyl fluoride (**4a**) in 93% yield.

3,4-dicyano-2,5,6-trifluorophenyl 4-methoxybenzoate (3a)



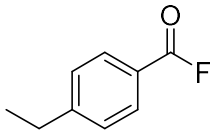
White solid, 92% yield, R_f = 0.3 (PE/EA = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.9 Hz, 2H), 7.03 (d, *J* = 8.9 Hz, 2H), 3.93 (s, 3H). ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 165.4, 161.1, 154.0 (dt, *J* = 264.5, 3.4 Hz), 149.7 (ddd, *J* = 265.5, 14.0, 3.7 Hz), 148.4 (ddd, *J* = 266.9, 13.7, 4.9 Hz), 134.6 (tt, *J* = 16.0, 2.9 Hz), 133.4, 117.7, 114.5, 108.8 (dt, *J* = 10.3, 2.9 Hz), 102.7 (dt, *J* = 16.3, 2.6 Hz), 100.8 (ddd, *J* = 17.9, 4.6, 1.8 Hz), 55.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.15 – -117.83 (d, *J* = 8.8 Hz), -127.02 (dd, *J* = 21.0, 11.0 Hz), -131.00 (dd, *J* = 21.0, 8.4 Hz). (s, 1F). HRMS m/z (ESI) calcd for $C_{16}H_8F_3N_2O_3^+$ $[M+H]^+$: 333.0482, found: 333.0486.

4-methoxybenzoyl fluoride (4a) [1]



Colorless oil, 93% yield, R_f = 0.5 (PE/EA = 10:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, J = 9.0 Hz, 2H), 7.15 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 165.5, 157.1 (d, J = 338.9 Hz), 134.0 (d, J = 4.1 Hz), 115.9 (d, J = 61.5 Hz), 115.2, 56.2. ^{19}F NMR (376 MHz, DMSO-d_6) δ 16.0 (s, 1F).

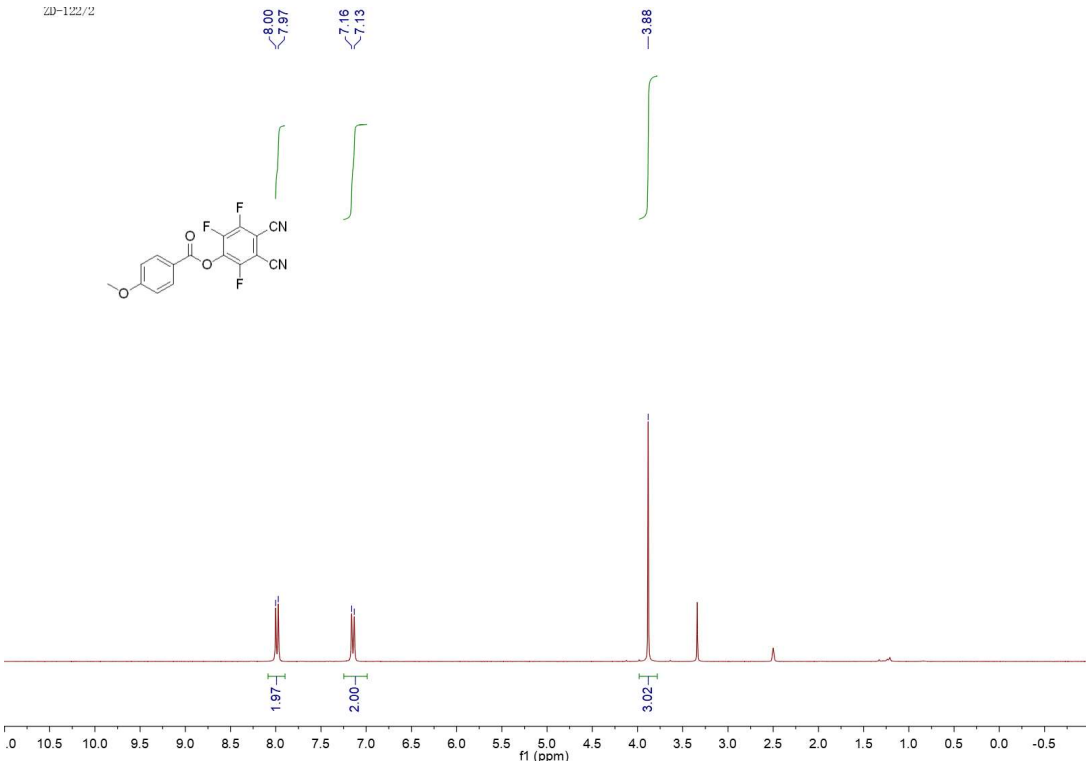
4-ethylbenzoyl fluoride (4b) [2]



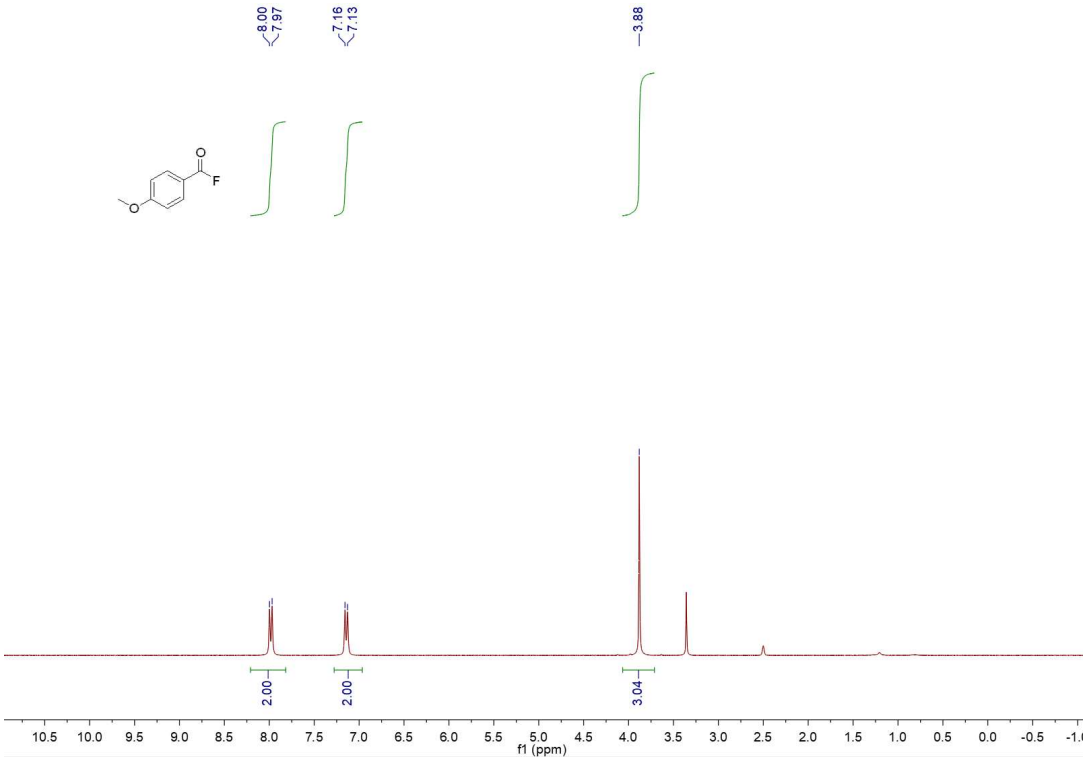
Colorless oil, 95% yield, R_f = 0.5 (PE/EA = 10:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 7.9 Hz, 1H), 2.73 (q, J = 7.6 Hz, 2H), 1.21 (t, J = 7.6 Hz, 3H). ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 157.3 (d, J = 342.2 Hz), 153.2, 131.72 (d, J = 4.0 Hz), 129.2, 121.7 (d, J = 60.6 Hz), 28.6, 15.2. ^{19}F NMR (376 MHz, DMSO-d_6) δ 18.0 (s, 1F).

(a) ^{1}H NMR study of acyl fluoride formation and (b) Proposed mechanism for the deoxyfluorination intermediate formation

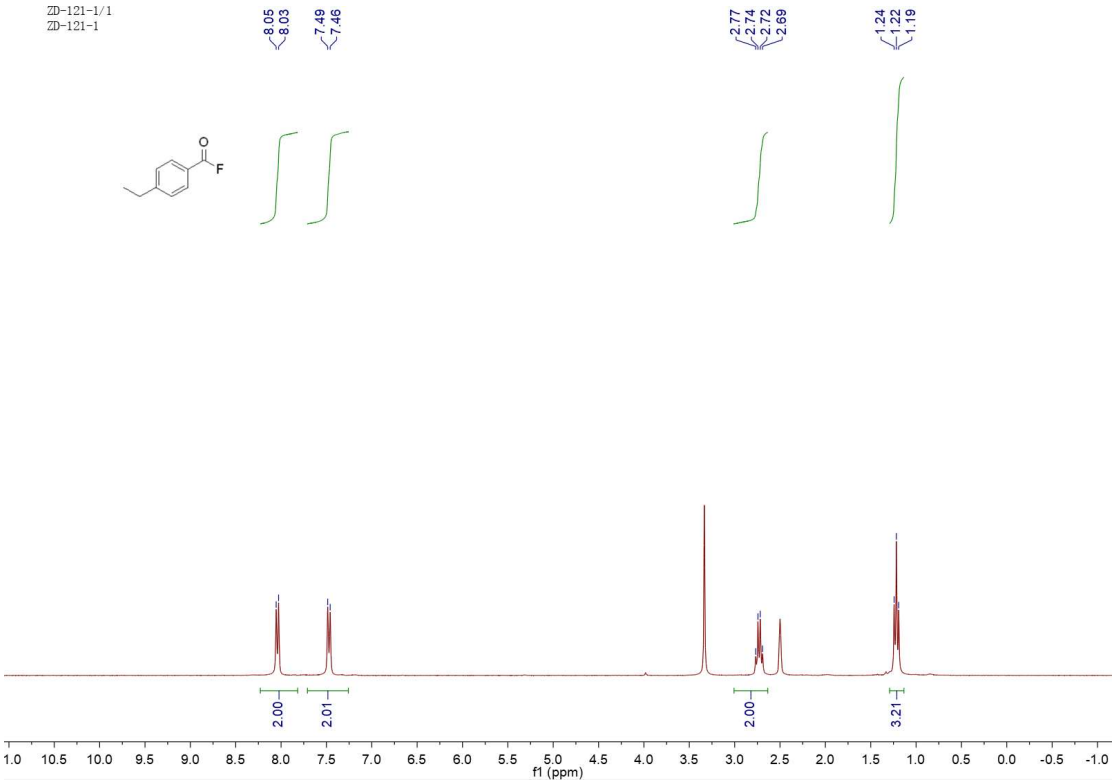
^{1}H NMR spectra of 3a



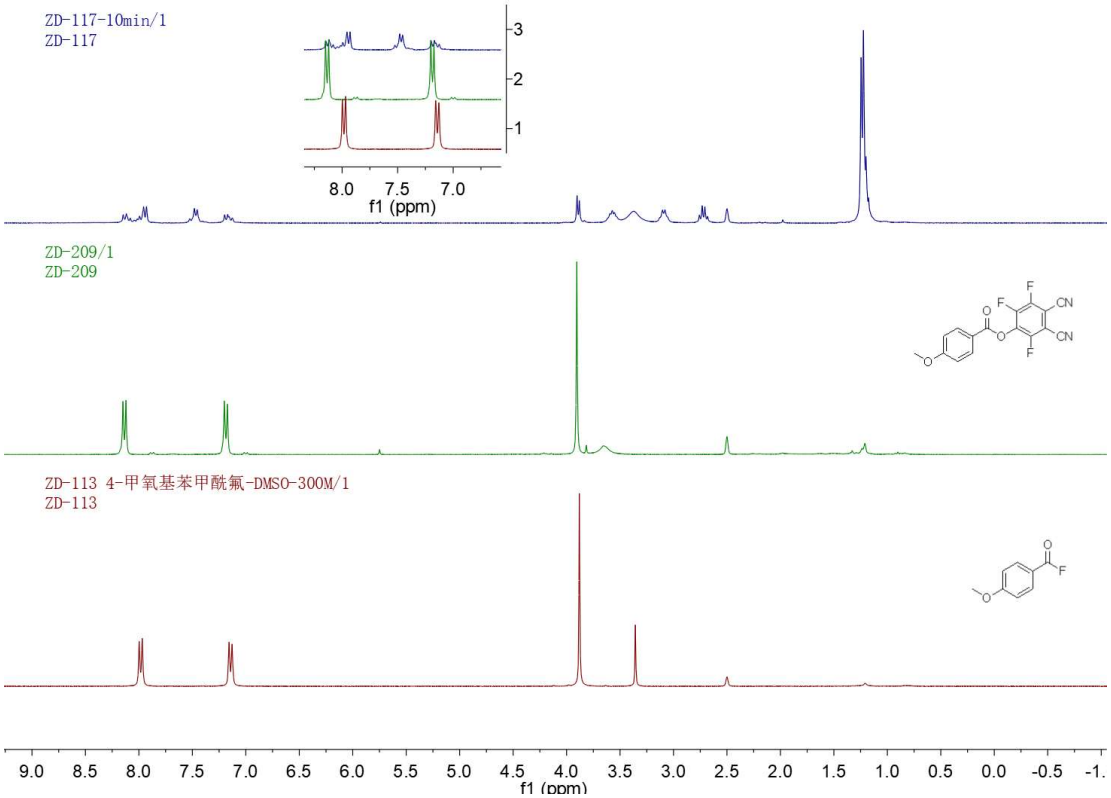
^{1}H NMR spectra of 4a



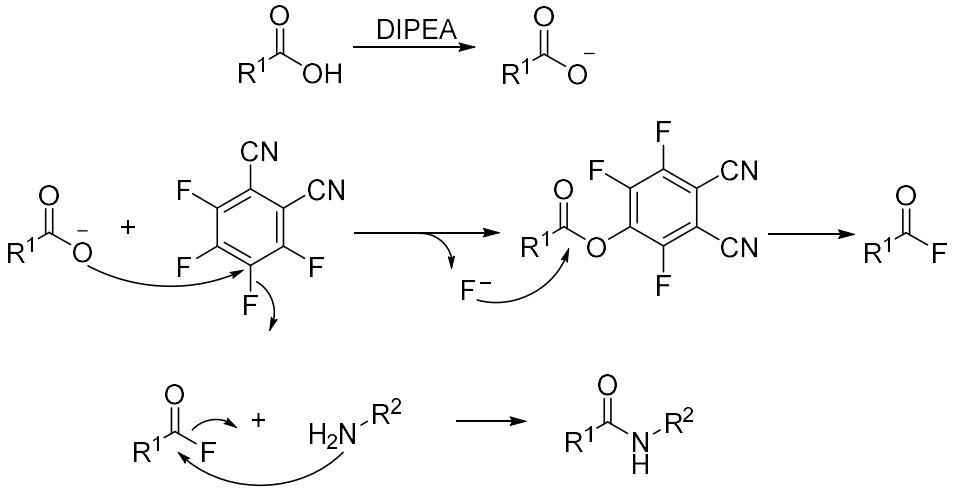
^{1}H NMR spectra of 4b



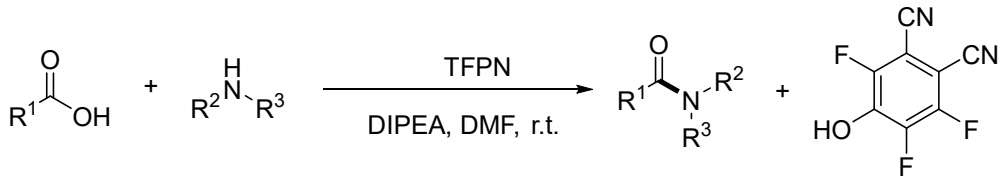
Acyl fluoride formation reaction monitored by ^{1}H NMR



(b) Proposed mechanism for the deoxyfluorination intermediate formation



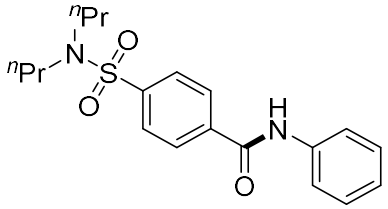
General procedure for the challenge amide formation



1 **5** **6** **6-1**

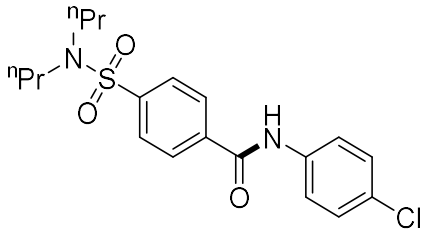
To a mixture of compound **1** (0.30 mmol) and TFPN (0.36 mmol) in DMF (1 mL) was added the DIPEA (0.36 mmol). The reaction solution was stirred at room temperature for 10 min. Then amine **5** (0.36 mmol) was added to the above solution and the reaction mixture was stirred at room temperature under air until the acyl fluoride intermediate was fully consumed. After these reactions were finished, water (20 mL) was added followed by EtOAc (3 x 10 mL), and the layers were separated. Combined organic layers were washed with brine (1 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by silica gel chromatography to afford **6** and **6-1**.

4-(*N*,*N*-dipropylsulfamoyl)-*N*-phenylbenzamide (6a) [3]



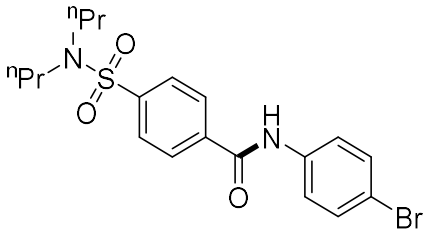
White solid, 99% yield, R_f = 0.3 (PE/EA = 4:1). ^{1}H NMR 8.67 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.69 (t, *J* = 8.8 Hz, 4H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 3.05 (t, *J* = 7.7 Hz, 4H), 1.52 (h, *J* = 7.5 Hz, 4H), 0.85 (t, *J* = 7.4 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 165.0, 142.4, 138.9, 137.9, 129.0, 128.1, 127.1, 124.8, 120.4, 50.0, 21.9, 11.1.

***N*-(4-chlorophenyl)-4-(*N*,*N*-dipropylsulfamoyl)benzamide (6b)** [4]



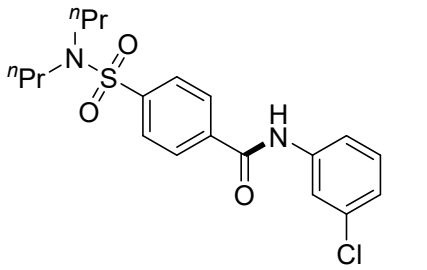
Yellow solid, 98% yield, R_f = 0.3 (PE/EA = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 4H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.27 (s, 1H), 3.22 – 2.86 (m, 4H), 1.53 (q, *J* = 7.5 Hz, 4H), 0.86 (t, *J* = 7.4 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 164.9, 142.5, 138.7, 136.5, 129.8, 129.1, 128.0, 127.2, 121.5, 50.0, 21.9, 11.1.

_N_-(4-bromophenyl)-4-(_N,N_-dipropylsulfamoyl)benzamide (6c) [5]



Yellow solid, 98% yield, R_f = 0.3 (PE/EA = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.64 (dd, *J* = 8.4, 2.0 Hz, 4H), 7.46 (d, *J* = 8.5 Hz, 2H), 3.05 (t, *J* = 7.6 Hz, 4H), 1.52 (h, *J* = 7.2 Hz, 4H), 0.85 (t, *J* = 7.4 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 164.9, 142.4, 138.7, 137.1, 132.0, 128.1, 127.1, 121.8, 117.4, 50.0, 21.9, 11.2.

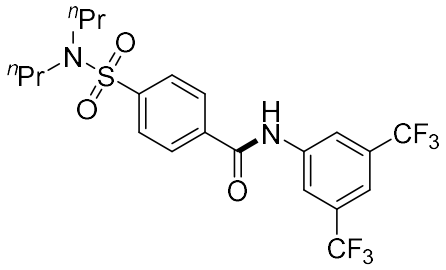
_N_-(3-chlorophenyl)-4-(_N,N_-dipropylsulfamoyl)benzamide (6d) [6]



White solid, 90% yield, R_f = 0.25 (PE/EA = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.86 (t, *J* = 8.1 Hz, 3H), 7.64 (d, *J* = 8.1 Hz, 3H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.13

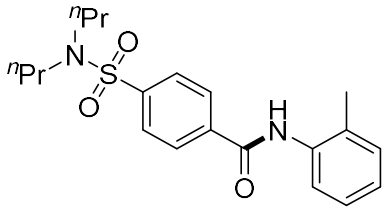
(d, *J* = 7.0 Hz, 1H), 3.06 (t, *J* = 7.6 Hz, 4H), 1.54 (h, *J* = 7.4 Hz, 4H), 0.87 (t, *J* = 7.4 Hz, 6H). $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 165.1, 142.4, 139.2, 138.7, 134.6, 130.0, 128.1, 127.1, 124.7, 120.3, 118.3, 50.0, 22.0, 11.2.

_N_-(3,5-bis(trifluoromethyl)phenyl)-4-(_N,N_-dipropylsulfamoyl)benzamide (6e)



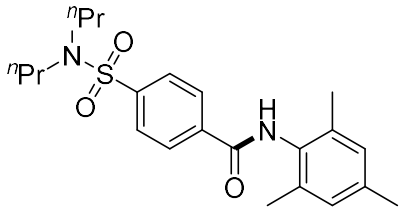
White solid, 99% yield, R_f = 0.3 (PE/EA = 5:1). ^1H NMR (300 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.33 (s, 2H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.65 (s, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 3.06 (d, *J* = 7.5 Hz, 5H), 1.55 (h, *J* = 7.4 Hz, 4H), 0.86 (t, *J* = 7.4 Hz, 6H). $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 165.7, 142.2, 139.8, 138.6, 132.3 (q, *J* = 33.3 Hz), 128.3, 127.2, 123.2 (d, *J* = 272.8 Hz), 119.9 (d, *J* = 3.2 Hz), 117.8, 50.2, 22.0, 11.1. HRMS m/z (ESI) calcd for $C_{21}H_{23}F_6N_2O_3S^+$ $[M+H]^+$: 497.1328, found: 497.1317.

4-(_N,N_-dipropylsulfamoyl)-_N_-(o-tolyl)benzamide (6f)



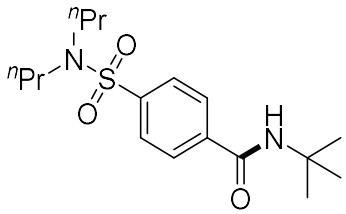
White solid, 99% yield, R_f = 0.3 (PE/EA = 5:1). ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.2 Hz, 2H), 7.95 – 7.83 (m, 3H), 7.79 (s, 1H), 7.34 – 7.23 (m, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 3.22 – 3.00 (m, 4H), 2.36 (s, 3H), 1.62 – 1.48 (m, 4H), 0.89 (t, *J* = 7.4 Hz, 6H). $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 164.4, 143.2, 138.4, 135.2, 130.7, 129.8, 127.8, 127.5, 127.0, 126.0, 123.5, 50.0, 22.0, 17.9, 11.2. HRMS m/z (ESI) calcd for $C_{20}H_{27}N_2O_3S^+$ $[M+H]^+$: 375.1737, found: 375.1729.

4-(_N,N_-dipropylsulfamoyl)-_N_-mesitylbenzamide (6g)



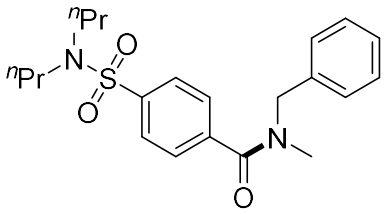
White solid, 90% yield, R_f = 0.3 (PE/EA = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.62 (s, 1H), 6.94 (s, 2H), 3.20 – 3.01 (m, 4H), 2.30 (s, 3H), 2.23 (s, 6H), 1.55 (p, *J* = 7.4 Hz, 4H), 0.88 (t, *J* = 7.4 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 164.9, 142.9, 138.1, 137.5, 135.2, 130.8, 129.1, 128.0, 127.3, 50.0, 22.0, 21.0, 18.4, 11.2. HRMS m/z (ESI) calcd for $C_{22}H_{31}N_2O_3S^+$ $[M+H]^+$: 403.2050, found: 403.2037.

_N_-(tert-butyl)-4-(_N,N_-dipropylsulfamoyl)benzamide (6h) [7]



White solid, 99% yield, R_f = 0.3 (PE/EA = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 2H), 6.25 (s, 1H), 3.11 – 2.92 (m, 4H), 1.60 – 1.37 (m, 13H), 0.83 (t, *J* = 7.3 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 165.7, 142.1, 139.5, 127.6, 127.0, 52.0, 49.9, 28.7, 21.9, 11.1.

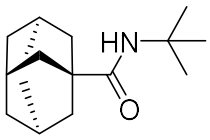
_N_-benzyl-4-(_N,N_-dipropylsulfamoyl)-N-methylbenzamide (6i)



White solid, 99% yield, R_f = 0.4 (PE/EA = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.71 (m, 2H), 7.63 – 7.50 (m, 2H), 7.47 – 7.22 (m, 4H), 7.19 – 7.06 (m, 1H), 4.61 (s, 2H), 3.17 – 2.76 (m, 7H), 1.69 – 1.44 (m, 4H), 1.00 – 0.75 (m, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 170.7, 170.0, 141.2, 140.0, 139.9, 136.5, 135.9, 130.5, 129.0, 128.8, 128.2, 127.9, 127.7, 127.6, 127.4, 127.3, 126.6, 55.0, 50.8, 50.1, 49.9, 36.9, 33.4, 22.1,

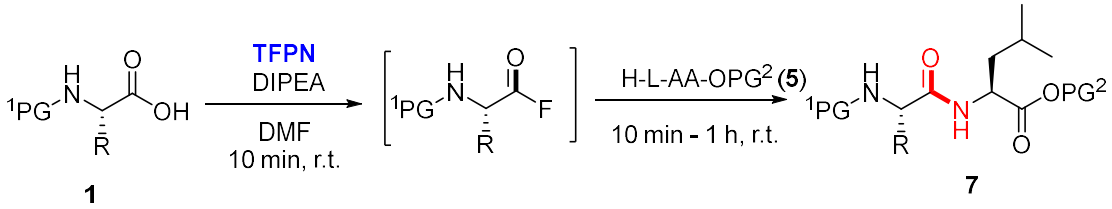
21.9, 11.2. HRMS m/z (ESI) calcd for $C_{21}H_{29}N_2O_3S^+$ $[M+H]^+$: 389.1893, found: 389.1880

_N_-(tert-butyl)adamantane-1-carboxamide (6j) [8]



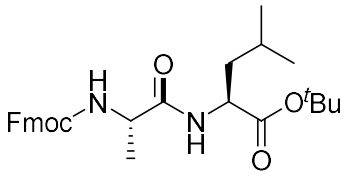
White solid, 92% yield, R_f = 0.4 (PE/EA = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 (s, 1H), 2.07 – 1.96 (m, 3H), 1.85 – 1.75 (m, 6H), 1.75 – 1.60 (m, 6H), 1.31 (s, 9H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 177.4, 50.5, 40.8, 39.3, 36.5, 28.8, 28.2.

General procedure for the synthesis of peptides



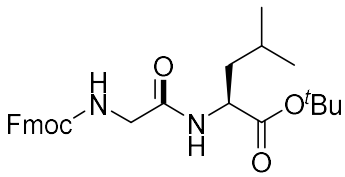
To a mixture of compound **1** (0.30 mmol) and **TFPN** (0.36 mmol) in DMF (1 mL) was added the DIPEA (0.36 mmol). The reaction solution was stirred at room temperature for 10 min. Then amine **5** (0.36 mmol) was added to the above solution and the reaction mixture was stirred at room temperature under air until the acyl fluoride intermediate was fully consumed. After these reactions were finished, water (20 mL) was added followed by EtOAc (3 x 10 mL), and the layers were separated. Combined organic layers were washed with brine (1 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by silica gel chromatography to afford **7**.

tert-butyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-alanyl-L-leucinate (7a) [9]



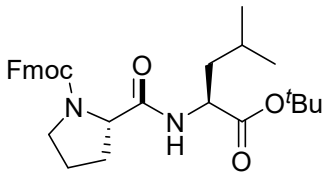
Yellow solid, 95% yield, R_f = 0.55 (PE/EA = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.5 Hz, 2H), 7.51 (d, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 2H), 6.41 (d, *J* = 8.2 Hz, 1H), 5.49 (d, *J* = 7.8 Hz, 1H), 4.48 – 4.36 (m, 1H), 4.36 – 4.17 (m, 3H), 4.13 (t, *J* = 7.1 Hz, 1H), 1.62 – 1.48 (m, 2H), 1.47 – 1.25 (m, 13H), 0.83 (d, *J* = 5.7 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 171.9, 171.8, 155.9, 143.8, 141.3, 127.7, 127.1, 125.1, 120.0, 82.0, 67.1, 51.5, 50.4, 47.1, 41.7, 28.0, 24.9, 22.8, 22.1, 18.9.

tert-butyl (((9H-fluoren-9-yl)methoxy)carbonyl)glycyl-L-leucinate (7b) [9]



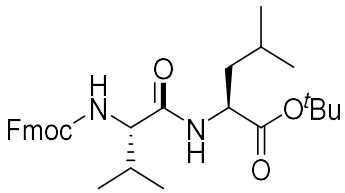
White solid, 97% yield, R_f = 0.55 (PE/EA = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.32 (d, *J* = 7.4 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 1H), 5.80 (t, *J* = 5.5 Hz, 1H), 4.56 (td, *J* = 8.5, 4.9 Hz, 1H), 4.40 (d, *J* = 7.1 Hz, 2H), 4.23 (t, *J* = 7.1 Hz, 1H), 3.96 (d, *J* = 5.5 Hz, 2H), 1.77 – 1.51 (m, 3H), 1.47 (s, 9H), 0.94 (dd, *J* = 6.3, 2.4 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 172.2, 168.8, 156.7, 143.8, 141.3, 127.7, 127.1, 125.1, 120.0, 82.1, 67.3, 51.4, 47.0, 44.4, 41.7, 28.0, 24.9, 22.8, 22.0.

(9H-fluoren-9-yl)methyl (S)-2-(((S)-1-(tert-butoxy)-4-methyl-1-oxopentan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (7c) [8]



White solid, 93% yield, R_f = 0.5 (PE/EA = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.35 – 7.13 (m, 4H), 6.99 – 6.18 (m, 1H), 4.56 – 4.22 (m, 4H), 4.23 – 4.08 (m, 1H), 3.62 – 3.26 (m, 2H), 2.33 – 2.05 (m, 1H), 2.02 – 1.74 (m, 3H), 1.61 – 1.47 (m, 2H), 1.46 – 1.19 (m, 10H), 0.81 (d, *J* = 5.8 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 171.8, 171.2, 156.0, 143.8, 141.3, 127.7, 127.1, 125.1, 120.0, 81.7, 67.8, 61.1, 60.4, 51.6, 47.2, 47.0, 42.0, 41.6, 31.4, 28.3, 28.0, 25.0, 24.7, 23.6, 22.8, 22.2.

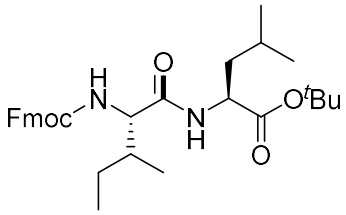
tert-butyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-valyl-L-leucinate (7d) [8]



White solid, 91% yield, R_f = 0.4 (PE/EA = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.7 Hz, 2H), 6.45 (d, *J* = 8.2 Hz, 1H), 5.57 (d, *J* = 9.0 Hz, 1H), 4.48 – 4.29 (m, 2H), 4.23 (dd, *J* = 10.5, 7.0 Hz, 1H), 4.12 (t, *J* = 7.1 Hz, 1H), 4.06 – 3.96 (m, 1H), 2.10 – 1.93 (m,

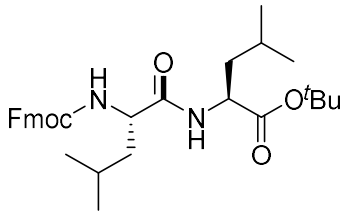
1H), 1.65 – 1.45 (m, 2H), 1.45 – 1.23 (m, 10H), 0.95 – 0.69 (m, 12H). $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 171.9, 171.0, 156.4, 143.9, 143.8, 141.3, 127.7, 127.1, 125.2, 125.1, 120.0, 119.9, 81.9, 67.1, 60.2, 51.5, 47.1, 41.6, 31.5, 28.0, 24.9, 22.7, 22.1, 19.2, 18.0.

tert-butyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-isoleucyl-L-leucinate (7e) [8]



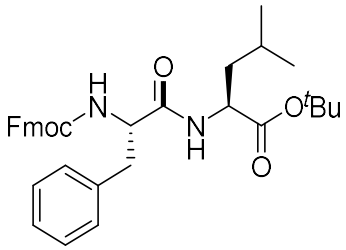
Yellow solid, 92% yield, R_f = 0.3 (PE/EA = 3:1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.5 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 2H), 6.47 (d, *J* = 8.1 Hz, 1H), 5.59 (d, *J* = 9.0 Hz, 1H), 4.48 – 4.28 (m, 2H), 4.27 – 4.18 (m, 1H), 4.16 – 4.06 (m, 1H), 4.03 (t, *J* = 8.1 Hz, 1H), 1.84 – 1.68 (m, 1H), 1.64 – 1.22 (m, 13H), 1.15 – 0.99 (m, 1H), 0.95 – 0.67 (m, 12H). $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 171.8, 171.0, 156.3, 143.9, 143.8, 141.3, 127.7, 127.1, 125.2, 125.1, 120.0, 119.9, 81.8, 67.1, 59.5, 51.5, 47.1, 41.6, 37.8, 28.0, 24.9, 22.7, 22.1, 15.4, 11.4.

tert-butyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-leucyl-L-leucinate (7f) [8]



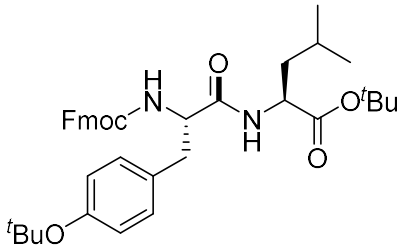
White solid, 99% yield, R_f = 0.3 (PE/EA = 5:1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.4 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 2H), 6.46 (d, *J* = 7.8 Hz, 1H), 5.42 (d, *J* = 8.4 Hz, 1H), 4.53 – 4.43 (m, 1H), 4.44 – 4.29 (m, 2H), 4.29 – 4.13 (m, 2H), 1.77 – 1.49 (m, 6H), 1.45 (s, 9H), 0.94 (d, *J* = 4.5 Hz, 6H), 0.90 (d, *J* = 5.4 Hz, 6H). $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 171.8, 171.8, 156.2, 143.9, 143.7, 141.3, 127.7, 127.1, 125.1, 120.0, 120.0, 81.9, 67.1, 53.4, 51.5, 47.1, 41.7, 28.0, 24.9, 24.6, 23.0, 22.7, 22.1.

tert-butyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-phenylalanyl-L-leucinate (7g)[8]



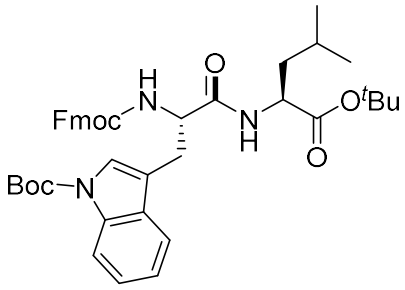
White solid, 92% yield, R_f = 0.3 (PE/EA = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 6.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.25 – 7.03 (m, 7H), 6.39 (s, 1H), 5.46 (s, 1H), 4.51 – 4.26 (m, 3H), 4.18 (t, *J* = 8.6 Hz, 1H), 4.12 – 4.02 (m, 1H), 2.99 (d, *J* = 6.5 Hz, 2H), 1.53 – 1.42 (m, 2H), 1.42 – 1.27 (m, 10H), 0.79 (t, *J* = 4.8 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 171.7, 170.5, 155.9, 143.8, 143.7, 141.3, 136.3, 129.5, 128.6, 127.7, 127.1, 127.0, 125.2, 125.1, 120.0, 82.0, 67.1, 55.9, 51.5, 47.1, 41.8, 38.6, 28.0, 24.8, 22.7, 22.1.

tert-butyl ((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-(tert-butoxy)phenyl)propanoyl)-L-leucinate (7h)



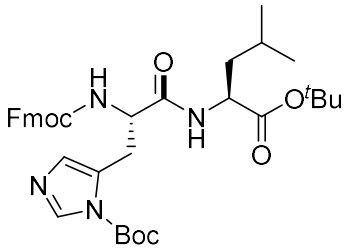
White solid, 91% yield, R_f = 0.75 (PE/EA = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 2H), 7.47 (dd, *J* = 7.4, 2.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.1 Hz, 2H), 6.26 (d, *J* = 8.0 Hz, 1H), 5.37 (d, *J* = 8.3 Hz, 1H), 4.46 – 4.28 (m, 3H), 4.24 (d, *J* = 7.4 Hz, 1H), 4.10 (t, *J* = 6.9 Hz, 1H), 2.96 (t, *J* = 6.6 Hz, 2H), 1.54 – 1.42 (m, 2H), 1.42 – 1.29 (m, 10H), 1.22 (s, 9H), 0.80 (dd, *J* = 6.0, 3.5 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 171.6, 170.4, 155.9, 154.4, 143.8, 143.7, 141.3, 131.0, 129.9, 127.7, 127.1, 125.1, 125.1, 124.2, 120.0, 82.0, 78.4, 67.1, 55.9, 51.5, 47.1, 41.7, 37.8, 28.8, 28.0, 24.8, 22.7, 22.1. HRMS m/z (ESI) calcd for $C_{38}H_{49}N_2O_6^+$ $[M+H]^+$: 629.3585, found: 629.3577.

tert-butyl 3-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(((S)-1-(tert-butoxy)-4-methyl-1-oxopentan-2-yl)amino)-3-oxopropyl)-1H-indole-1-carboxylate (7i) [10]



White solid, 93% yield, R_f = 0.75 (PE/EA = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 6.1 Hz, 3H), 7.28 (q, *J* = 5.7, 4.1 Hz, 2H), 7.24 – 7.09 (m, 4H), 6.25 (dd, *J* = 7.9, 4.3 Hz, 1H), 5.58 (d, *J* = 8.0 Hz, 1H), 4.50 (q, *J* = 7.2 Hz, 1H), 4.39 – 4.18 (m, 3H), 4.09 (t, *J* = 7.2 Hz, 1H), 3.28 – 2.97 (m, 2H), 1.54 (s, 9H), 1.48 – 1.38 (m, 2H), 1.39 – 1.24 (m, 10H), 0.77 (dd, *J* = 5.9, 2.7 Hz, 7H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 171.4, 170.5, 156.0, 149.5, 143.8, 143.7, 141.3, 135.5, 130.3, 127.7, 127.1, 125.2, 125.1, 124.7, 124.6, 122.8, 120.0, 119.1, 115.4, 115.3, 83.6, 81.9, 67.3, 54.7, 51.7, 47.1, 41.7, 28.4, 28.2, 28.0, 24.8, 22.7, 22.2.

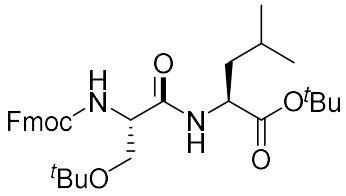
tert-butyl 5-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(((S)-1-(tert-butoxy)-4-methyl-1-oxopentan-2-yl)amino)-3-oxopropyl)-1H-imidazole-1-carboxylate (7j) [8]



White solid, 96% yield, R_f = 0.4 (PE/EA = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.68 (d, *J* = 7.5 Hz, 2H), 7.63 – 7.48 (m, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 7.0 Hz, 2H), 6.62 (d, *J* = 7.5 Hz, 1H), 4.50 (d, *J* = 6.3 Hz, 1H), 4.40 – 4.22 (m, 3H), 4.19 (d, *J* = 7.4 Hz, 1H), 3.09 (dd, *J* = 14.8, 5.0 Hz, 1H), 2.89 (dd,

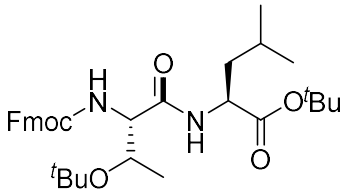
J = 14.9, 5.9 Hz, 1H), 1.51 (s, 9H), 1.44 – 1.22 (m, 12H), 0.77 (t, *J* = 6.0 Hz, 6H). $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 171.6, 170.5, 156.2, 146.8, 143.9, 141.2, 139.1, 136.7, 127.7, 127.1, 125.2, 119.9, 114.9, 85.7, 81.7, 67.3, 54.7, 51.4, 47.1, 41.5, 30.3, 27.9, 27.8, 24.6, 22.8, 21.8.

tert-butyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-O-(tert-butyl)-L-seryl-L-leucinate (7k) [11]



White solid, 98% yield, R_f = 0.25 (PE/EA = 4:1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.0 Hz, 2H), 7.69 – 7.53 (m, 2H), 7.40 (t, *J* = 6.8 Hz, 2H), 7.32 (t, *J* = 6.9 Hz, 2H), 7.28 – 7.19 (m, 1H), 5.79 (s, 1H), 4.60 – 4.33 (m, 3H), 4.25 (d, *J* = 5.9 Hz, 2H), 3.91 – 3.76 (m, 1H), 3.40 (t, *J* = 7.7 Hz, 1H), 1.70 – 1.57 (m, 2H), 1.54 (s, 1H), 1.46 (s, 9H), 1.22 (s, 9H), 0.95 (d, *J* = 4.8 Hz, 6H). $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 171.6, 169.9, 156.0, 143.9, 143.8, 141.3, 127.7, 127.1, 125.1, 120.0, 81.7, 74.3, 67.1, 61.8, 54.3, 51.6, 47.1, 41.9, 28.0, 27.4, 24.9, 22.8, 22.1.

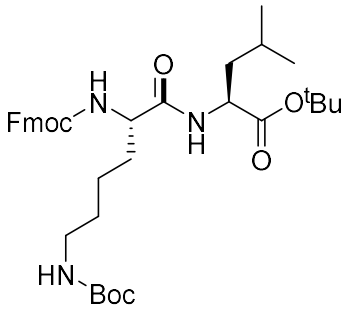
tert-butyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-O-(tert-butyl)-L-threonyl-L-leucinate (7l)



Yellow solid, 97% yield, R_f = 0.5 (PE/EA = 4:1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 3H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 2H), 5.96 (d, *J* = 4.8 Hz, 1H), 4.49 – 4.23 (m, 3H), 4.22 – 3.98 (m, 3H), 1.66 – 1.50 (m, 2H), 1.51 – 1.32 (m, 10H), 1.22 (s, 9H), 1.05 (d, *J* = 6.2 Hz, 3H), 0.88 (t, *J* = 6.3 Hz, 6H). $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 171.5, 169.2, 156.1, 144.0, 143.7, 141.3, 141.3, 127.7, 127.1, 125.2, 120.0, 120.0, 81.6, 75.6, 66.9, 66.8, 58.3, 51.9, 47.2, 41.4,

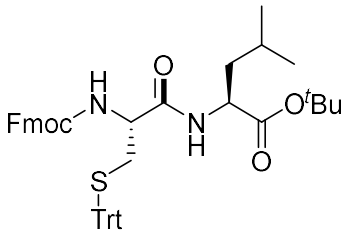
28.2, 28.0, 25.1, 22.8, 22.1, 16.5. HRMS m/z (ESI) calcd for $C_{33}H_{47}N_2O_6^+$ $[M+H]^+$: 567.3429, found: 567.3409.

tert-butyl N2-(((9H-fluoren-9-yl)methoxy)carbonyl)-N6-(tert-butoxycarbonyl)-L-lysyl-L-leucinate (7m) [12]



White solid, 99% yield, R_f = 0.3 (PE/EA = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 2H), 6.63 (d, *J* = 8.1 Hz, 1H), 5.68 (d, *J* = 8.3 Hz, 1H), 4.78 (d, *J* = 6.1 Hz, 1H), 4.53 – 4.41 (m, 1H), 4.36 (d, *J* = 7.2 Hz, 2H), 4.29 – 4.15 (m, 2H), 3.23 – 2.95 (m, 2H), 1.85 (p, *J* = 6.5 Hz, 1H), 1.74 – 1.57 (m, 3H), 1.43 (d, *J* = 6.3 Hz, 23H), 0.89 (d, *J* = 5.8 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 171.9, 171.5, 156.2, 143.9, 143.7, 141.3, 127.7, 127.1, 125.1, 120.0, 120.0, 81.9, 79.1, 67.1, 54.5, 51.5, 47.1, 41.4, 39.9, 32.4, 29.5, 28.4, 28.0, 24.9, 22.7, 22.3, 22.0.

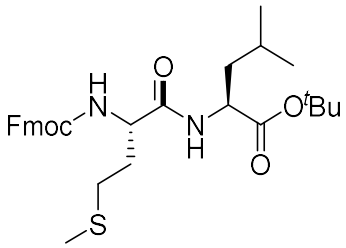
tert-butyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-L-cysteinyl-L-leucinate (7n) [13]



Yellow solid, 96% yield, R_f = 0.5 (PE/EA = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.7 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 2H), 7.78 – 7.60 (m, 3H), 7.50 – 7.10 (m, 19H), 4.42 – 4.10 (m, 4H), 4.05 (q, *J* = 7.7 Hz, 1H), 2.44 – 2.27 (m, 2H), 1.62 – 1.37 (m, 3H), 1.27 (s, 9H), 0.80 (dd, *J* = 17.4, 6.3 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 171.4,

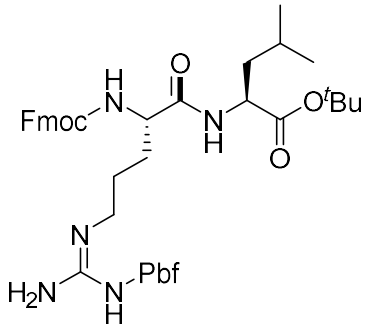
169.6, 155.9, 144.4, 143.8, 143.7, 141.3, 129.6, 128.1, 127.8, 127.1, 126.9, 125.1, 120.0, 81.9, 67.3, 67.1, 54.0, 51.6, 47.1, 41.7, 33.9, 27.9, 24.9, 22.7, 22.2.

tert-butyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-methionyl-L-leucinate (7o)



White solid, 97% yield, R_f = 0.4 (PE/EA = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.35 – 7.23 (m, 2H), 6.80 (d, *J* = 8.1 Hz, 1H), 5.87 (d, *J* = 8.3 Hz, 1H), 4.56 – 4.32 (m, 4H), 4.22 (d, *J* = 7.2 Hz, 1H), 2.61 (t, *J* = 7.3 Hz, 2H), 2.18 – 1.90 (m, 5H), 1.72 – 1.58 (m, 2H), 1.57 – 1.38 (m, 10H), 0.92 (d, *J* = 5.7 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 171.7, 170.9, 156.1, 143.8, 143.7, 141.3, 127.7, 127.1, 125.1, 125.1, 120.0, 120.0, 81.9, 67.1, 53.5, 51.6, 47.1, 41.5, 32.0, 29.9, 28.0, 24.9, 22.7, 22.1, 15.1. HRMS m/z (ESI) calcd for $C_{30}H_{41}N_2O_5S^+$ $[M+H]^+$: 541.2731, found: 541.2715.

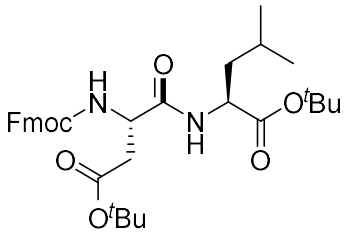
tert-butyl ((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(((Z)-amino ((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran)-5-sulfonamido)methylene) amino)pentanoyl)-L-leucinate (7p)



Colorless oil, 80% yield, R_f = 0.4 (PE/EA = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$ δ 7.72 (d, *J* = 7.5 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 3H), 7.25 (d, *J* = 8.0 Hz, 3H), 6.38 (s, 2H), 6.09 (d, *J* = 8.2 Hz, 2H), 4.48 – 4.26 (m, 4H), 4.13 (t, *J* = 7.0 Hz, 1H), 3.24 (s, 2H), 2.89 (s, 2H), 2.59 (s, 3H), 2.51 (s, 3H), 2.06 (s, 3H), 2.00 – 1.89 (m,

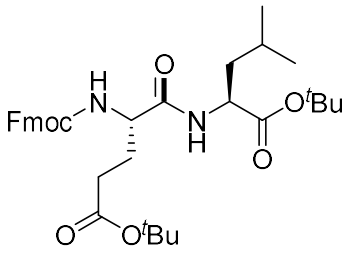
1H), 1.80 – 1.68 (m, 1H), 1.68 – 1.49 (m, 5H), 1.41 (d, J = 2.7 Hz, 15H), 0.83 (d, J = 6.2 Hz, 6H). $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 172.5, 172.1, 158.7, 156.4, 143.9, 143.7, 141.2, 141.2, 138.4, 132.9, 132.3, 127.7, 127.1, 125.2, 124.6, 119.9, 117.5, 86.4, 81.9, 67.1, 60.4, 53.9, 51.9, 47.0, 43.2, 40.5, 28.6, 28.0, 25.1, 24.8, 22.7, 21.8, 19.4, 18.0, 14.2, 12.5. HRMS m/z (ESI) calcd for $C_{44}H_{60}N_5O_8S^+$ $[M+H]^+$: 818.4157, found: 818.4140.

tert-butyl ((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(tert-butoxy)-4-oxobutanoyl)-L-leucinate (7q)



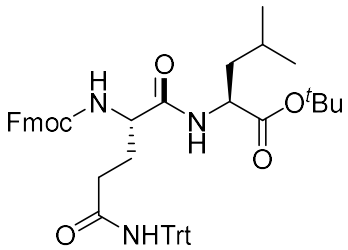
Colorless oil, 95% yield, R_f = 0.3 (PE/EA = 4:1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 7.4 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.22 (t, J = 7.4 Hz, 2H), 6.87 (d, J = 8.2 Hz, 1H), 5.97 (d, J = 8.4 Hz, 1H), 4.49 (q, J = 6.6 Hz, 1H), 4.44 – 4.26 (m, 3H), 4.14 (t, J = 7.1 Hz, 1H), 2.85 (dd, J = 17.3, 4.3 Hz, 1H), 2.54 (dd, J = 17.2, 6.8 Hz, 1H), 1.66 – 1.29 (m, 21H), 0.84 (d, J = 6.0 Hz, 6H). $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 171.5, 171.4, 170.2, 156.0, 143.8, 143.7, 141.3, 127.8, 127.1, 125.1, 120.0, 81.9, 81.8, 67.3, 51.6, 51.0, 47.1, 41.6, 37.7, 28.0, 28.0, 24.8, 22.9, 22.0. HRMS m/z (ESI) calcd for $C_{33}H_{44}N_2NaO_7^+$ $[M+Na]^+$: 603.3041, found: 603.3027.

tert-butyl (S)-4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(((S)-1-(tert-butoxy)-4-methyl-1-oxopentan-2-yl)amino)-5-oxopentanoate (7r)



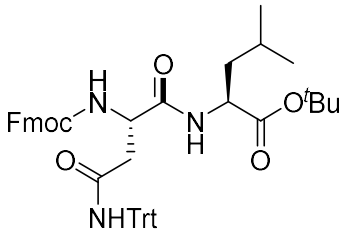
Yellow oil, 93% yield, R_f = 0.7 (PE/EA = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.4 Hz, 2H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 6.77 (d, *J* = 7.8 Hz, 1H), 5.79 (d, *J* = 7.6 Hz, 1H), 4.54 – 4.41 (m, 1H), 4.36 (d, *J* = 7.1 Hz, 2H), 4.32 – 4.25 (m, 1H), 4.21 (t, *J* = 7.1 Hz, 1H), 2.54 – 2.35 (m, 2H), 2.20 – 2.02 (m, 1H), 2.02 – 1.92 (m, 1H), 1.74 – 1.60 (m, 2H), 1.58 – 1.32 (m, 20H), 0.92 (d, *J* = 5.6 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 173.0, 171.6, 170.9, 156.1, 143.9, 143.7, 141.3, 141.3, 127.7, 127.1, 125.1, 120.0, 81.9, 81.0, 67.1, 53.9, 51.7, 47.1, 41.5, 31.6, 28.6, 28.1, 28.0, 24.9, 22.8, 22.0. HRMS m/z (ESI) calcd for $C_{34}H_{47}N_2O_7^+$ $[M+H]^+$: 595.3378, found:595.3362.

tert-butyl N^2-(((9H-fluoren-9-yl)methoxy)carbonyl)-N^5-trityl-L-glutaminyl-L-leucinate (7s)



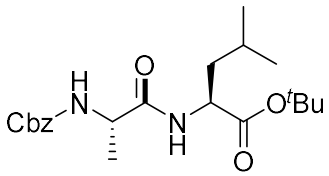
Yellow solid, 91% yield, R_f = 0.3 (PE/EA = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.5 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.26 – 7.09 (m, 17H), 7.06 (s, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 5.79 (d, *J* = 7.2 Hz, 1H), 4.26 (d, *J* = 6.9 Hz, 3H), 4.18 – 4.07 (m, 1H), 4.08 – 3.96 (m, 1H), 2.44 (t, *J* = 6.5 Hz, 2H), 2.09 – 1.82 (m, 3H), 1.55 – 1.38 (m, 2H), 1.33 (s, 9H), 0.77 (d, *J* = 5.9 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 172.0, 171.9, 171.2, 156.1, 144.6, 143.9, 143.8, 141.3, 141.3, 128.7, 128.0, 127.7, 127.1, 127.0, 125.2, 120.0, 81.7, 70.7, 67.0, 53.5, 51.7, 47.2, 40.7, 33.4, 30.1, 28.0, 24.8, 22.8, 21.8. HRMS m/z (ESI) calcd for $C_{49}H_{54}N_3O_6^+$ $[M+H]^+$: 780.4007, found: 780.3986.

tert-butyl N^2-(((9H-fluoren-9-yl)methoxy)carbonyl)-N^4-trityl-L-asparaginyl-L-leucinate (7t)



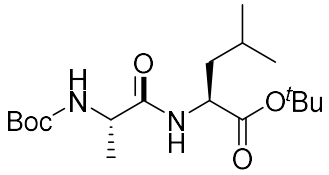
White solid, 90% yield, R_f = 0.4 (PE/EA = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.4 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.44 (d, *J* = 7.4 Hz, 2H), 7.38 – 7.10 (m, 19H), 7.03 (s, 1H), 6.49 (d, *J* = 7.4 Hz, 1H), 4.67 – 4.54 (m, 1H), 4.49 – 4.32 (m, 3H), 4.22 (t, *J* = 7.2 Hz, 1H), 3.10 (d, *J* = 15.2 Hz, 1H), 2.72 (dd, *J* = 15.6, 6.4 Hz, 1H), 1.71 – 1.54 (m, 2H), 1.53 – 1.36 (m, 10H), 0.91 (d, *J* = 4.9 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 170.9, 170.2, 155.8, 143.8, 143.3, 143.2, 140.8, 140.8, 128.2, 127.5, 127.2, 126.6, 124.7, 119.5, 81.1, 70.4, 66.8, 51.4, 50.6, 46.6, 40.5, 38.0, 27.5, 24.4, 22.2, 21.6. HRMS m/z (ESI) calcd for $C_{48}H_{52}N_3O_6^+$ $[M+H]^+$: 766.3851, found:766.3839.

tert-butyl ((benzyloxy)carbonyl)-L-alanyl-L-leucinate (7u) [14]



White solid, 95% yield, R_f = 0.2 (PE/EA = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 6.70 (d, *J* = 6.1 Hz, 1H), 5.65 (d, *J* = 6.5 Hz, 1H), 5.08 (s, 2H), 4.52 – 4.40 (m, 1H), 4.39 – 4.21 (m, 1H), 1.68 – 1.53 (m, 2H), 1.50 – 1.40 (m, 10H), 1.36 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 5.5 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 172.0, 171.8, 155.8, 136.2, 128.5, 128.1, 127.9, 81.8, 66.8, 51.4, 50.3, 41.5, 27.9, 24.8, 22.7, 22.0, 18.8.

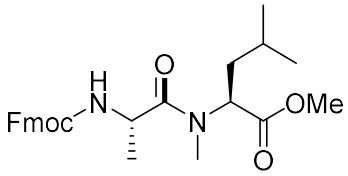
tert-butyl (tert-butoxycarbonyl)-L-alanyl-L-leucinate (7v) [15]



White solid, 91% yield, R_f = 0.55 (PE/EA = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (d, *J* = 7.6 Hz, 1H), 5.15 (d, *J* = 7.2 Hz, 1H), 4.44 (q, *J* = 8.3 Hz, 1H), 4.17 (s, 1H), 1.69

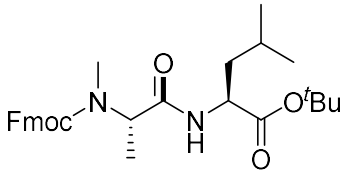
– 1.50 (m, 3H), 1.42 (s, 9H), 1.41 (s, 9H), 1.32 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.0 Hz, 6H).^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 172.2, 171.9, 155.4, 81.7, 79.9, 51.3, 49.9, 41.7, 28.3, 27.9, 24.8, 22.8, 22.0, 18.3.

methyl N-((((9H-fluoren-9-yl)methoxy)carbonyl)-L-alanyl)-N-methyl-L-leucinate (7w)



White solid, 93% yield, R_f = 0.25 (PE/EA = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 5.85 (d, *J* = 8.0 Hz, 1H), 5.39 – 5.24 (m, 1H), 4.72 (p, *J* = 7.1 Hz, 1H), 4.36 (d, *J* = 7.3 Hz, 2H), 4.21 (t, *J* = 7.3 Hz, 1H), 3.70 (s, 3H), 2.98 (s, 3H), 1.81 – 1.66 (m, 2H), 1.58 – 1.45 (m, 1H), 1.40 (d, *J* = 6.8 Hz, 3H), 0.94 (t, *J* = 6.8 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 173.4, 172.0, 155.6, 144.0, 143.8, 141.3, 127.7, 127.1, 125.2, 125.2, 120.0, 67.0, 54.7, 52.3, 47.3, 47.2, 36.9, 31.0, 24.9, 23.2, 21.4, 18.6. HRMS m/z (ESI) calcd for $C_{26}H_{33}N_2O_5^+$ $[M+H]^+$: 453.2384, found: 453.2371.

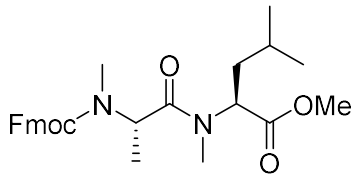
tert-butyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-methyl-L-alanyl-L-leucinate (7x)



Yellow oil, 94% yield, R_f = 0.65 (PE/EA = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 6.38 (s, 1H), 4.81 (s, 1H), 4.56 – 4.39 (m, 3H), 4.26 (t, *J* = 6.8 Hz, 1H), 2.84 (s, 3H), 1.68 – 1.52 (m, 2H), 1.50 – 1.39 (m, 10H), 1.34 (d, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 5.4 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 171.8, 170.6, 157.0, 143.8, 141.3, 127.8,

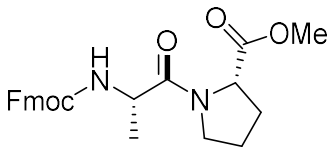
127.1, 124.9, 120.0, 81.9, 67.9, 54.4, 51.3, 47.2, 41.6, 29.6, 28.0, 25.0, 22.8, 22.0, 13.7. HRMS m/z (ESI) calcd for $C_{29}H_{38}N_2NaO_5^+$ $[M+H]^+$: 517.2673, found:517.2665.

methyl N-(N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-methyl-L-alanyl)-N-methyl-L-leucinate (7y)



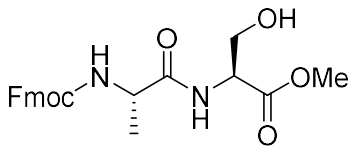
Yellow oil, 94% yield, R_f = 0.6 (PE/EA = 4:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89 (d, *J* = 7.3 Hz, 2H), 7.63 (t, *J* = 6.8 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.38 – 7.29 (m, 2H), 5.09 – 4.48 (m, 3H), 4.47 – 4.09 (m, 2H), 3.61 (s, 3H), 2.87 – 2.54 (m, 3H), 2.51 – 2.34 (m, 2H), 1.87 – 1.51 (m, 2H), 1.35 – 1.21 (m, 1H), 1.11 (d, *J* = 6.7 Hz, 2H), 0.99 – 0.73 (m, 7H). ^{13}C{H} NMR (75 MHz, DMSO-d_6) δ 172.0, 171.8, 171.5, 170.5, 155.5, 144.2, 141.3, 128.1, 128.0, 127.5, 125.3, 125.2, 125.1, 120.6, 120.5, 66.9, 56.8, 55.0, 52.4, 51.5, 51.1, 47.4, 38.2, 37.1, 31.4, 29.7, 29.5, 29.1, 28.7, 24.9, 24.8, 23.6, 23.2, 21.8, 21.4, 14.9, 14.6. HRMS m/z (ESI) calcd for $C_{27}H_{35}N_2O_5^+$ $[M+H]^+$: 467.2540, found: 467.2532.

methyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-alanyl-L-prolinate (7z) [16]



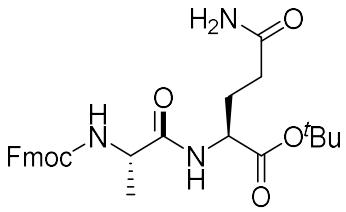
Colorless oil, 91% yield, R_f = 0.2 (PE/EA = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.5 Hz, 2H), 7.49 (dd, *J* = 7.5, 2.9 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 2H), 5.77 (d, *J* = 8.0 Hz, 1H), 4.54 – 4.37 (m, 2H), 4.31 – 4.16 (m, 2H), 4.10 (t, *J* = 7.2 Hz, 1H), 3.69 – 3.38 (m, 5H), 2.20 – 2.02 (m, 1H), 2.01 – 1.75 (m, 3H), 1.32 (d, *J* = 6.8 Hz, 3H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 172.3, 171.3, 155.7, 143.9, 143.8, 141.2, 127.7, 127.1, 125.2, 119.9, 67.0, 58.8, 52.3, 48.3, 47.1, 46.8, 28.9, 24.9, 18.3.

methyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-alanyl-L-serinate (7aa)



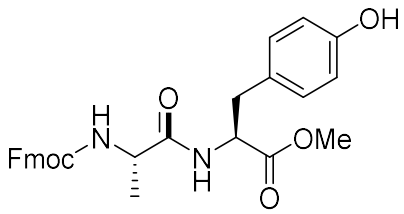
Colorless oil, 90% yield, R_f = 0.2 (PE/EA = 1:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (d, J = 7.7 Hz, 1H), 7.89 (d, J = 7.5 Hz, 2H), 7.79 – 7.67 (m, 2H), 7.56 (d, J = 7.7 Hz, 1H), 7.42 (t, J = 7.4 Hz, 2H), 7.34 (d, J = 7.4 Hz, 2H), 5.09 (t, J = 5.5 Hz, 1H), 4.40 – 4.32 (m, 1H), 4.30 – 4.13 (m, 4H), 3.77 – 3.68 (m, 1H), 3.62 (s, 4H), 1.23 (d, J = 7.1 Hz, 3H). ^{13}C NMR (75{H} MHz, DMSO-d_6) δ 172.9, 171.1, 155.7, 143.9, 143.8, 140.7, 127.7, 127.1, 125.3, 120.1, 65.6, 61.3, 54.6, 51.9, 49.7, 46.7, 18.3. HRMS m/z (ESI) calcd for $C_{22}H_{25}N_2O_6^+$ $[M+H]^+$: 413.1707, found: 413.1717.

tert-butyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-alanyl-L-glutaminate (7ab) [8]



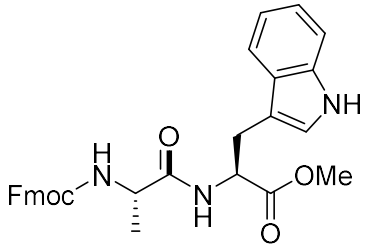
White solid, 93% yield, R_f = 0.3 (PE/EA = 4:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.13 (d, J = 7.2 Hz, 1H), 7.82 (d, J = 7.4 Hz, 2H), 7.73 – 7.61 (m, 2H), 7.47 (d, J = 7.7 Hz, 1H), 7.35 (t, J = 7.3 Hz, 2H), 7.31 – 7.19 (m, 3H), 6.75 (s, 1H), 4.18 (d, J = 6.7 Hz, 3H), 4.10 – 3.93 (m, 2H), 2.10 (t, J = 7.5 Hz, 2H), 1.87 (dd, J = 14.9, 7.3 Hz, 1H), 1.73 (dt, J = 13.9, 8.0 Hz, 1H), 1.32 (s, 9H), 1.19 (d, J = 7.0 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6) δ 173.8, 173.2, 171.4, 156.1, 144.4, 144.2, 141.2, 128.1, 127.5, 125.8, 120.5, 80.9, 66.1, 52.8, 50.1, 47.1, 31.6, 28.0, 27.1, 18.7.

methyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-alanyl-L-tyrosinate (7ac)



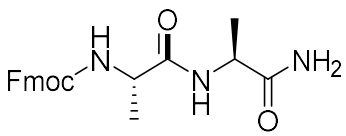
White solid, 99% yield, R_f = 0.2 (PE/EA = 1:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.93 (s, 1H), 8.45 – 8.23 (m, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.75 (t, *J* = 6.8 Hz, 2H), 7.63 – 7.48 (m, 2H), 7.50 – 7.26 (m, 5H), 7.30 – 7.16 (m, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.59 (q, *J* = 7.1 Hz, 1H), 4.42 – 4.09 (m, 4H), 3.58 (s, 3H), 3.30 – 3.04 (m, 2H), 1.27 (d, *J* = 7.0 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6) δ 173.0, 172.3, 156.3, 155.9, 144.2, 144.1, 141.0, 130.3, 127.9, 127.4, 127.3, 125.6, 120.4, 115.4, 65.9, 54.3, 52.1, 50.0, 47.0, 36.2, 18.5. HRMS m/z (ESI) calcd for $C_{28}H_{29}N_2O_6^+$ $[M+H]^+$: 489.2020, found: 489.2010.

methyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-alanyl-L-tryptophanate (7ad)



White solid, 90% yield, R_f = 0.3 (PE/EA = 2:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.93 (s, 1H), 8.46 – 8.22 (m, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.75 (t, *J* = 6.9 Hz, 2H), 7.54 (dd, *J* = 12.6, 7.9 Hz, 2H), 7.37 (dq, *J* = 15.7, 7.5 Hz, 5H), 7.23 (s, 0H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.59 (q, *J* = 7.1 Hz, 1H), 4.39 – 4.08 (m, 4H), 3.58 (s, 3H), 3.30 – 3.03 (m, 2H), 1.27 (d, *J* = 7.1 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6) δ 173.2, 172.7, 156.1, 144.4, 144.2, 141.2, 136.5, 128.1, 127.5, 125.8, 124.2, 121.4, 120.5, 118.9, 118.4, 111.9, 109.7, 66.1, 53.6, 52.3, 50.2, 47.1, 27.5, 18.7. HRMS m/z (ESI) calcd for $C_{30}H_{30}N_3O_5^+$ $[M+H]^+$: 512.2180, found: 512.2173.

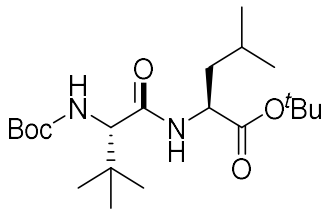
(9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-amino-1-oxopropan-2-yl)amino)-1-oxopropan-2-yl)carbamate (7ae)



White solid, 91% yield, R_f = 0.3 (PE/EA = 4:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.90 (d, *J* = 6.2 Hz, 2H), 7.73 (s, 2H), 7.64 (s, 1H), 7.53 – 7.21 (m, 5H), 7.09

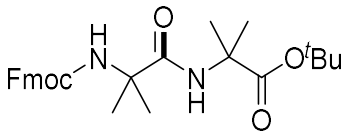
(s, 1H), 4.39 – 4.11 (m, 4H), 4.05 (s, 1H), 1.31 – 1.10 (m, 6H); $^{13}C\{H\}$ NMR (75 MHz, DMSO-d_6) δ 174.6, 172.6, 156.3, 144.2, 141.1, 128.1, 127.5, 125.7, 120.6, 66.1, 50.6, 48.4, 47.0, 18.7, 18.3. HRMS m/z (ESI) calcd for $C_{21}H_{23}N_3NaO_4^+$ $[M+H]^+$: 404.1581, found: 404.1574.

tert-butyl ((S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-L-leucinate (7af)



Yellow solid, 94% yield, R_f = 0.55 (PE/EA = 5:1). ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 (d, *J* = 8.3 Hz, 1H), 5.24 (d, *J* = 9.5 Hz, 1H), 4.56 – 4.40 (m, 1H), 3.81 (d, *J* = 9.5 Hz, 1H), 1.69 – 1.53 (m, 2H), 1.52 – 1.46 (m, 1H), 1.44 (s, 9H), 1.41 (s, 9H), 0.99 (s, 9H), 0.91 (d, *J* = 5.9 Hz, 6H). $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 171.7, 170.5, 155.8, 81.8, 79.6, 62.5, 51.4, 41.9, 34.5, 28.3, 27.9, 26.5, 24.8, 22.7, 22.1. HRMS m/z (ESI) calcd for $C_{21}H_{41}N_2O_5^+$ $[M+H]^+$: 401.3010, found:401.2999.

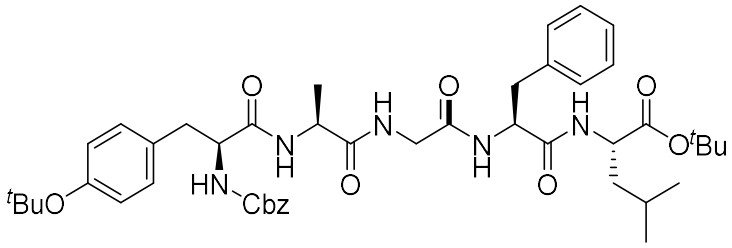
tert-butyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-methylpropanamido)-2-methylpropanoate (7ag) [8]



White solid, 91% yield, R_f = 0.4 (PE/EA = 3:1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.4 Hz, 2H), 7.62 (d, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 6.95 (s, 1H), 5.66 (s, 1H), 4.40 (d, *J* = 6.2 Hz, 2H), 4.22 (t, *J* = 6.7 Hz, 1H), 1.54 (s, 12H), 1.46 (s, 9H). $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 173.8, 173.3, 155.0, 143.9, 141.3, 127.7, 127.1, 125.1, 120.0, 81.6, 66.5, 56.9, 56.8, 47.2, 27.8, 25.3, 24.2.

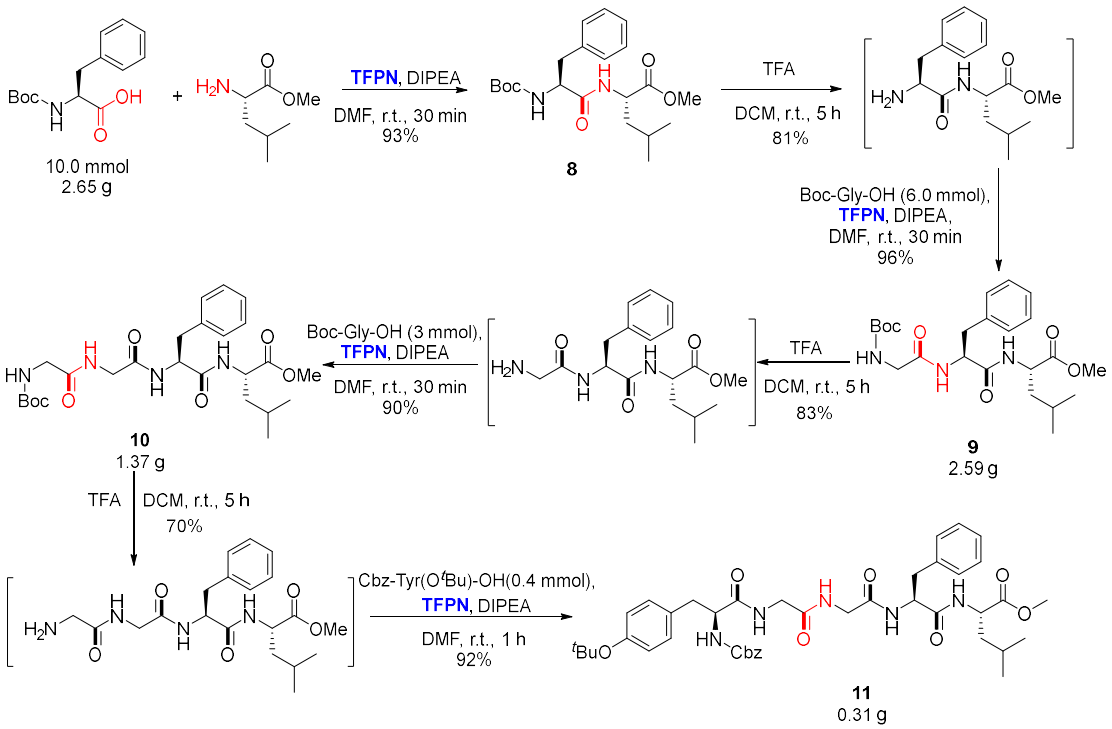
Leuphasyl (*L*-Ala) (7ah)

A 10 mL round-bottomed flask was charged with **1ah** (Cbz-*L*-Tyr(O^{t}Bu)-*L*-Ala-Gly-OH, 0.30 mmol), **TFPN** (0.36 mmol), DIPEA (0.36 mmol) and DMF (1 mL). The reaction solution was stirred at room temperature for 10 min. Then amine **5** (NH_2-*L*-Phe-*L*-Leu-O^{t}Bu, 0.36 mmol) was added to the above solution and the reaction mixture was stirred at room temperature under air until the acyl fluoride intermediate was fully consumed. After these reactions were finished, water (20 mL) was added followed by EtOAc (3 x 10 mL), and the layers were separated. Combined organic layers were washed with brine (1 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by silica gel chromatography to afford **7ah**.



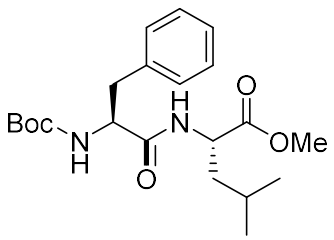
White solid, 92% yield, R_f = 0.3 (DCM/MeOH = 10:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 – 7.47 (m, 3H), 7.39 – 7.23 (m, 5H), 7.25 – 6.87 (m, 8H), 6.81 (d, *J* = 7.2 Hz, 2H), 6.64 (s, 1H), 5.31 (s, 1H), 5.13 (d, *J* = 12.3 Hz, 2H), 5.00 (d, *J* = 12.4 Hz, 1H), 4.83 (s, 1H), 4.52 (s, 2H), 3.90 (d, *J* = 16.6 Hz, 1H), 3.23 – 2.77 (m, 4H), 2.10 – 1.84 (m, 1H), 1.70 – 1.54 (m, 2H), 1.49 – 1.36 (m, 12H), 1.27 (s, 9H), 0.95 – 0.79 (m, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 172.8, 172.1, 171.4, 170.7, 168.5, 156.5, 154.2, 136.9, 136.6, 131.8, 130.0, 129.7, 128.4, 128.3, 128.0, 127.9, 126.7, 124.1, 81.8, 78.3, 66.8, 56.2, 53.8, 51.5, 48.6, 43.2, 42.0, 39.7, 28.9, 28.1, 25.0, 22.7, 22.6, 20.7. HRMS m/z (ESI) calcd for $C_{45}H_{62}N_5O_9^+$ $[M+H]^+$: 816.4542, found: 816.4536.

The synthesis of protected Leu-enkephalin



Boc-*L*-Phe-*L*-Leu-OMe (8) [17]:

A 10 mL round-bottomed flask was charged with **Boc-*L*-Phe-OH** (10 mmol, 2.65 g), **TFPN** (11 mmol), DIPEA (12 mmol) and DMF (15 mL). The reaction solution was stirred at room temperature for 10 min. Then amine **5** (NH_2-*L*-Leu-OMe, 12 mmol) was added to the above solution and the reaction mixture was stirred at room temperature under air until the acyl fluorides intermediates was fully consumed. After these reactions were finished, water (50 mL) was added followed by EtOAc (3 x 20 mL) and the layers were separated. Combined organic layers was washed with brine (1 x 30 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by silica gel chromatography to afford **8 (**93%, 3.65g**)**.

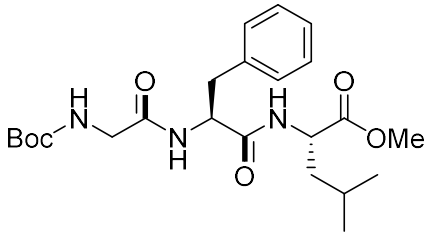


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.14 (m, 5H), 6.28 (s, 1H), 5.02 (s, 1H), 4.69 – 4.49 (m, 1H), 4.45 – 4.25 (m, 1H), 3.69 (s, 3H), 3.07 (d, *J* = 6.4 Hz, 2H), 1.64 – 1.45 (m, 3H), 1.42 (s, 9H), 0.90 (t, *J* = 5.0 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 172.8, 170.9, 155.4, 136.6, 129.4, 128.6, 126.9, 80.2, 55.6, 52.3, 50.7, 41.6, 38.0, 28.2, 24.6, 22.8, 21.9.

Boc-Gly-*L*-Phe-*L*-Leu-OMe (9) [17]:

8 (7.2 mmol, 2.82 g) was dissolved in 10 mL of DCM and TFA (6 mL) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 4 h. After the reaction was finished, the solvent was removed under reduced pressure. Then $NaHCO_3$ (30 mL, 2 M) was added and extracted with DCM (3 x 20 mL). The combined organic layers were washed with water (50 mL), brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was used for further reaction without purification.

A 10 mL round-bottomed flask was charged with **Boc-Gly-OH** (6.0 mmol, 1.05 g), **TFPN** (6.6 mmol), DIPEA (7.2 mmol), and DMF (15 mL). The reaction solution was stirred at room temperature for 10 min. Then the crude amine (6.6 mmol) was added to the above solution and the reaction mixture was stirred at room temperature under air until the acyl fluoride intermediate was fully consumed. After these reactions were finished, water (40 mL) was added followed by EtOAc (3 x 20 mL), and the layers were separated. Combined organic layers were washed with brine (1 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by silica gel chromatography to afford **9 (**96%, 2.59 g**)**.

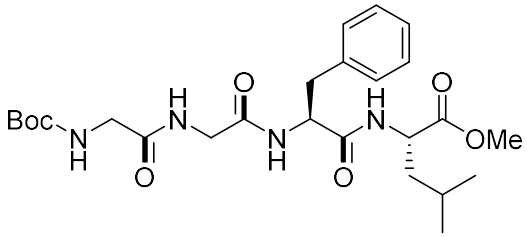


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 3H), 7.23 – 7.17 (m, 2H), 6.95 – 6.72 (m, 1H), 6.69 – 6.38 (m, 1H), 5.22 (s, 1H), 4.73 (d, *J* = 6.0 Hz, 1H), 4.62 – 4.44 (m, 1H), 3.77 (s, 2H), 3.69 (s, 3H), 3.22 – 2.91 (m, 2H), 1.66 – 1.47 (m, 4H), 1.43 (s, 9H), 0.88 (d, *J* = 4.2 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 172.8, 170.5, 169.5, 156.1, 136.4, 129.5, 128.7, 127.2, 80.5, 54.2, 52.4, 51.0, 44.5, 41.3, 38.2, 28.4, 24.8, 22.8, 22.0.

Boc-Gly-Gly-*L*-Phe-*L*-Leu-OMe (10) [17]:

9 (3.6 mmol, 1.12 g) was dissolved in 5 mL of DCM and TFA (3 mL) was added dropwise at 0 ℃. The mixture was allowed to warm to room temperature and stirred for 4 h. After the reaction was finished, the solvent was removed under reduced pressure. Then $NaHCO_3$ (20 mL, 2 M) was added and extracted with DCM (3 x 15 mL). The combined organic layers were washed with water (30 mL), brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was used for further reaction without purification.

A 10 mL round-bottomed flask was charged with **Boc-Gly-OH** (3.0 mmol, 0.53 g), **TFPN** (3.3 mmol), DIPEA (3.6 mmol), and DMF (15 mL). The reaction solution was stirred at room temperature for 10 min. Then the crude amine (3.6 mmol) was added to the above solution and the reaction mixture was stirred at room temperature under air until the acyl fluoride intermediate was fully consumed. After these reactions were finished, water (30 mL) was added followed by EtOAc (3 x 20 mL), and the layers were separated. Combined organic layers were washed with brine (1 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by silica gel chromatography to afford **10 (**90%, 1.37 g**)**.

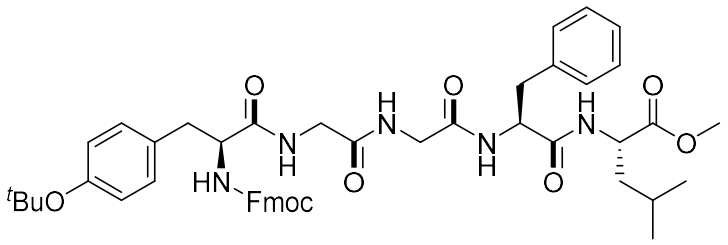


^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.54 (m, 3H), 7.30 – 7.06 (m, 5H), 5.90 (s, 1H), 5.04 (s, 1H), 4.59 (s, 1H), 4.18 – 3.84 (m, 4H), 3.71 (s, 3H), 3.24 – 3.05 (m, 1H), 2.96 (s, 1H), 1.71 – 1.56 (m, 3H), 1.45 (s, 9H), 0.90 (s, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 173.1, 171.4, 169.9, 168.6, 156.2, 136.5, 129.4, 128.3, 126.8, 79.8, 54.2, 52.2, 50.9, 43.7, 42.9, 40.9, 39.0, 28.4, 24.8, 22.7, 21.9.

Fmoc-*L*-Tyr(O^{t}Bu)-Gly-Gly-*L*-Phe-*L*-Leu-OMe (11):

10 (0.48 mmol, 0.243 g) was dissolved in 1 mL of DCM, and TFA (1 mL) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 4 h. After the reaction was finished, the solvent was removed under reduced pressure. Then $NaHCO_3$ (10 mL, 2 M) was added and extracted with DCM (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was used for further reaction without purification.

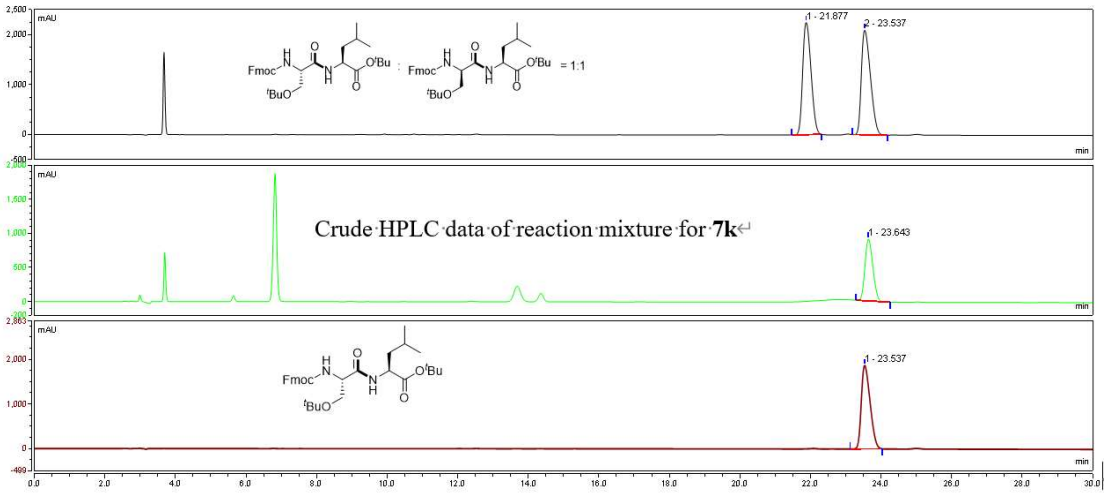
A 10 mL round-bottomed flask was charged with Fmoc-*L*-Tyr(O^{t}Bu)-OH (0.4 mmol, 0.15 g), **TFPN** (0.44 mmol), DIPEA (0.48 mmol) and DMF (1 mL). The reaction solution was stirred at room temperature for 10 min. Then the crude amine (0.48 mmol) was added to the above solution and the reaction mixture was stirred at room temperature under air until the acyl fluoride intermediate was fully consumed. After these reactions were finished, water (20 mL) was added followed by EtOAc (3 x 10 mL) and the layers were separated. Combined organic layers were washed with brine (1 x 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by silica gel chromatography to afford **14** (92%, 0.31 g**)**.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 – 7.92 (m, 3H), 7.69 (d, *J* = 7.8 Hz, 3H), 7.57 (d, *J* = 7.0 Hz, 1H), 7.47 – 7.14 (m, 5H), 7.13 – 6.87 (m, 8H), 6.75 (d, *J* = 7.7 Hz, 2H), 5.34 (s, 1H), 5.01 (s, 1H), 4.69 (s, 1H), 4.61 – 4.44 (m, 1H), 4.45 – 4.03 (m, 6H), 3.29 (s, 3H), 3.19 – 2.79 (m, 4H), 1.64 – 1.34 (m, 3H), 1.15 (s, 9H), 0.78 (s, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 172.9, 172.0, 170.6, 168.5, 168.1, 156.3, 154.1, 144.2, 143.8, 141.2, 136.4, 131.5, 130.0, 129.6, 128.1, 127.6, 127.0, 126.6, 125.6, 125.3, 123.9, 119.8, 78.1, 67.3, 55.5, 53.9, 51.8, 50.6, 46.9, 43.7, 43.3, 41.6, 39.9, 39.6, 28.7, 24.8, 22.6, 22.3. HRMS m/z (ESI) calcd for $C_{48}H_{58}N_5O_9^+$ $[M+H]^+$: 848.4229, found: 848.4224.

HPLC studies for determining epimerization with Ser, Asn, Asp

HPLC Studies for Determining Racemization of 7k



HPLC condition: Chiralpak®IC 250 × 4.6 mm column; hexanes (solvent A): isopropanol (solvent B); isocratic 15% solvent B in 30 min; flow rate = 1.0 mL/min; detection wavelength = 254 nm.

(1) Mixed HPLC data of **7k** and **7k**'

Peak No	RT (min)	Area (%)	Area	Height (mAU)
1	21.877	49.64	615.1429	2250.94
2	23.537	50.36	624.0292	2095.08
Total:		100.00	1239.1721	4346.02

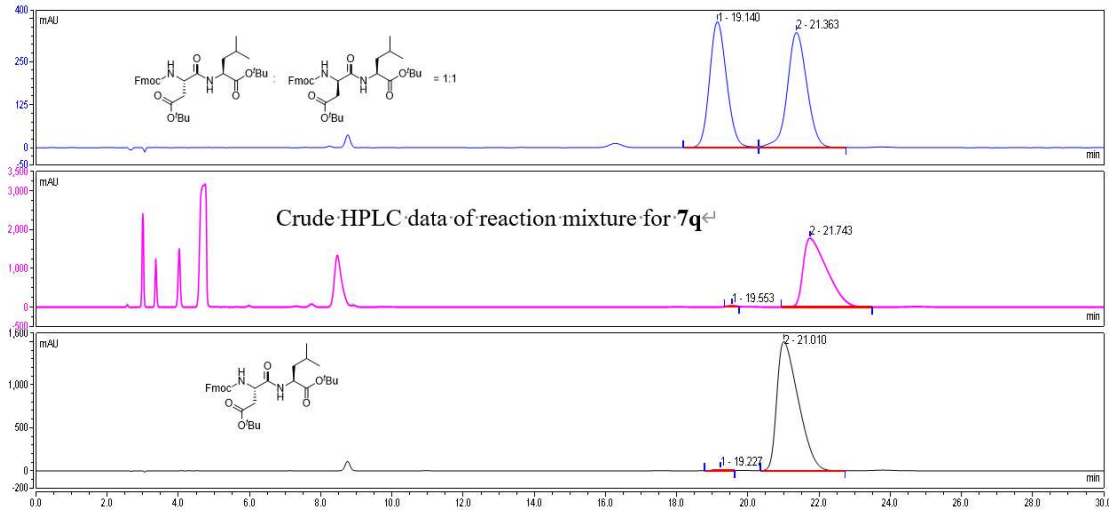
(2) Crude HPLC data of reaction mixture for preparing compound **7k**

Peak No	RT (min)	Area (%)	Area	Height (mAU)
1	23.643	100.00	236.0804	910.23
Total:		100.00	236.0804	910.23

(3) Pure HPLC data of **7k**

Peak No	RT (min)	Area (%)	Area	Height (mAU)
1	23.537	100.00	538.4030	1875.91
Total:		100.00	538.4030	1875.91

HPLC Studies for Determining Racemization of 7q



HPLC condition: Chiralpak®IC 250 × 4.6 mm column; hexanes (solvent A): isopropanol (solvent B); isocratic 15% solvent B in 35 min; flow rate = 1.0 mL/min; detection wavelength = 254 nm.

(1) Mixed HPLC data of **7q** and **7q**'

Peak No	RT (min)	Area (%)	Area	Height (mAU)
1	19.140	48.95	203.2103	365.79
2	21.363	51.05	211.9121	334.10
Total:		100.00	415.1224	699.89

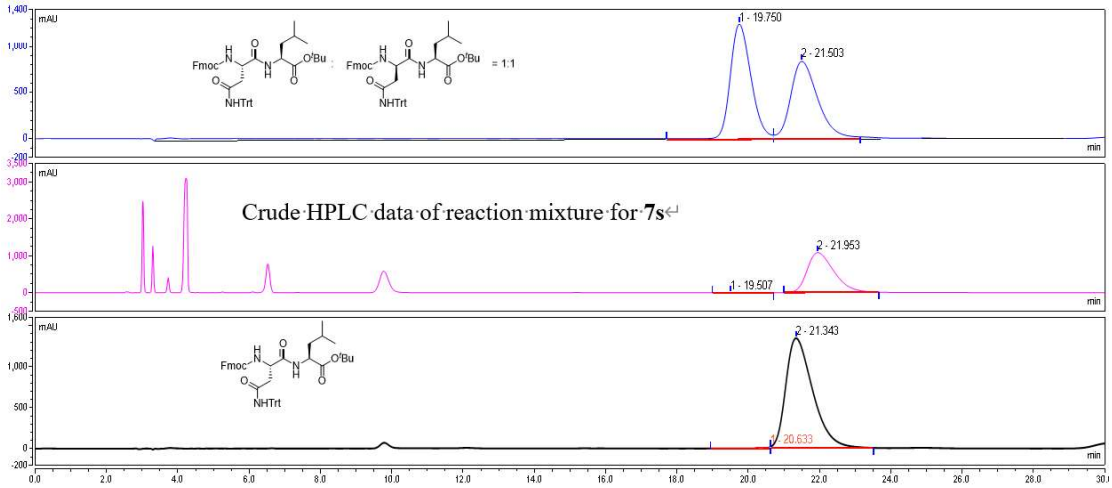
(2) Crude HPLC data of reaction mixture for preparing compound **7q**

Peak No	RT (min)	Area (%)	Area	Height (mAU)
1	19.553	0.40	5.4583	22.92
2	21.743	99.60	1367.4906	1778.45
Total:		100.00	1372.9489	1801.37

(3) Pure HPLC data of **7q**

Peak No	RT (min)	Area (%)	Area	Height (mAU)
1	19.227	0.49	5.1248	11.54
2	21.010	99.51	1045.5387	1499.59
Total:		100.00	1050.6635	1511.13

HPLC Studies for Determining Racemization of 7t



HPLC condition: Chiralpak®IC 250 × 4.6 mm column; hexanes (solvent A): isopropanol (solvent B); isocratic 15% solvent B in 35 min; flow rate = 1.0 mL/min; detection wavelength = 254 nm.

(1) Mixed HPLC data of **7t** and **7t**'

Peak No	RT (min)	Area (%)	Area	Height (mAU)
1	19.750	53.13	853.7111	1248.72
2	21.503	46.87	753.2121	844.08
Total:		100.00	1606.9232	2092.80

(2) Crude HPLC data of reaction mixture for preparing compound **7t**

Peak No	RT (min)	Area (%)	Area	Height (mAU)
1	19.507	0.04	0.3512	0.85
2	21.953	99.96	937.0125	1078.06
Total:		100.00	937.3637	1078.92

(3) Pure HPLC data of **7t**

Peak No	RT (min)	Area (%)	Area	Height (mAU)
1	20.633	0.02	0.2424	19.25
2	21.343	99.98	1172.9898	1341.83
Total:		100.00	1173.2322	1361.08

Procedures for the synthesis of peptides on resin (SPPS)

General procedure for incorporating the first amino acid on the solid support (2-CTC resin)

2-CTC resin (39.0 mg, 0.03 mmol) with a loading of 0.77 mmol/g was placed in a 5.0 mL fritted syringe, and the resin was swollen in DCM (2 mL) for 30 min. Then the syringe was drained, and Fmoc-Gly-OH (0.09 mmol 3.0 equiv.), DIPEA (18.2 mg, 6.0 equiv.), and 2 mL of a 1:1 DMF/DCM mixture (v/v) were added to the fritted syringe. The loading reaction was left to proceed for 2 h at room temperature before the syringe was drained. Then, the resin was washed with DMF (4 × 2 mL) and DCM (4 × 2 mL).

General procedure for incorporating the first amino acid on the solid support (MBHA resin)

MBHA resin (0.03 mmol) with a loading of 0.79 mmol/g was placed in a 5.0 mL fritted syringe. The resin was successively swollen in DCM (2 mL) for 30 min, then drained and treated with a solution (2 mL) of piperidine: DMF (20:80, v/v, 20% piperidine in DMF) for 5 min before being drained. The solution was added again for 15 min, then drained and the resin was washed with DMF (4 × 2 mL) and DCM (4 × 2 mL). A 5 mL tube was charged with Fmoc-Xaa-OH (0.09 mmol), TFPN (0.09 mmol), DIPEA (0.11 mmol), and DMF (1 mL). The reaction solution was reacted at room temperature for 10 min. Then this solution was added to the fritted syringe. The loading reaction was left to proceed until the resin gave a negative color test. Then, the resin was washed with DMF (4 × 2.0 mL) and DCM (4 × 2.0 mL) before being drained.

General procedure for removing Fmoc-protection group

The solution of 20% piperidine in DMF (1 mL) was added to the fritted syringe to react for 5 min before being drained. A further 1 mL of 20% piperidine was added to react for 15 min. Then, the resin was again carefully washed with DMF (4 × 2 mL) and DCM (4 × 2 mL) before being drained.

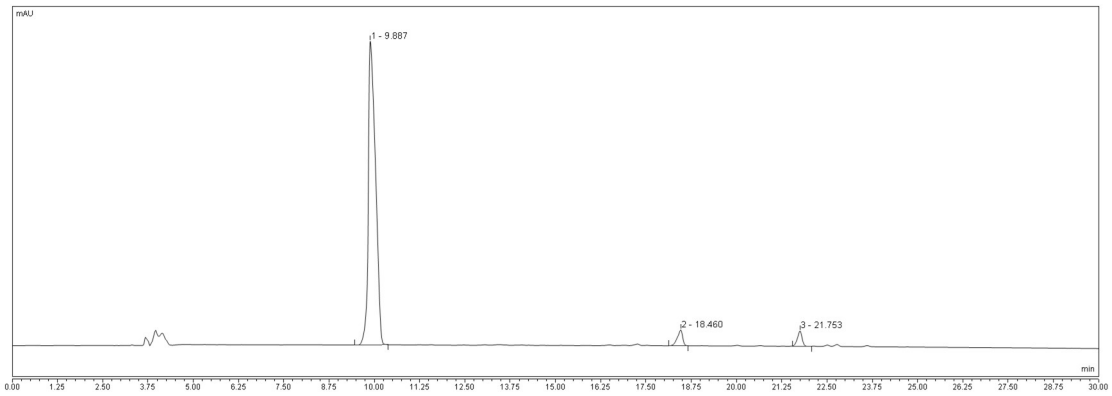
General procedure for peptide elongation

A 5 mL tube was charged with Fmoc-Xaa-OH (0.09 mmol), TFPN (0.09 mmol), DIPEA (0.11 mmol), and DMF (1 mL). The reaction solution was reacted at room temperature for 10 min. Then this solution was added to the fritted syringe. The loading reaction was left to proceed until the resin gave a negative color test. Then, the resin was washed with DMF (4 × 2.0 mL) and DCM (4 × 2.0 mL) before being drained.

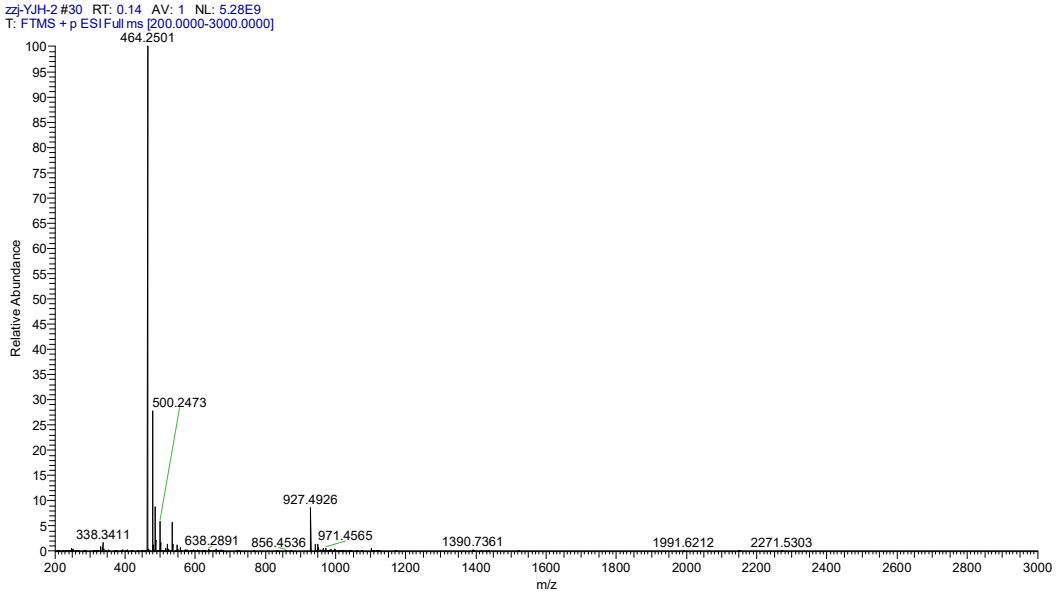
General procedure of resin cleavage

The resin was washed with DCM (4 × 2 mL) and diethyl ether (4 × 2 mL) immediately after synthesis was completed. Cleavage was then performed with 0.5 mL of a freshly prepared TFA/TIS/H_2O (95:2.5:2.5) solution for 2 h. The resin was then filtered and washed with pure TFA (2 × 0.5 mL). After combining the TFA solution, TFA was removed by Nitrogen, the residue was washed by ice-cold ether (4 × 5 mL) and dissolved in MeCN/H_2O (1:1, 3 mL). This solution was analyzed by analytical RP-HPLC subsequently.

NH_2-Ala-Ala-Val-Gly-Phe-OH (12): HRMS m/z (ESI) calcd for $C_{22}H_{34}N_5O_6^+$ $[M+H]^+$: 464.2504, found: 464.2501.

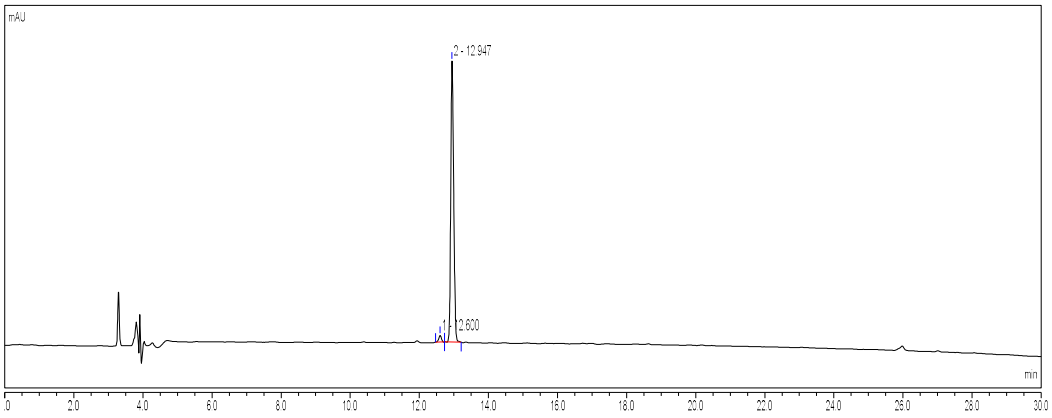


HPLC condition: Jupiter 5μm C18 4.6 × 250 mm^2 column; 0.05% TFA (v/v) in H_2O (solvent A), 0.05% TFA (v/v) in MeCN (solvent B); gradient 10%-100% (solvent B) in 30 min; flow rate = 1.0 mL/min; detection wavelength = 214 nm.

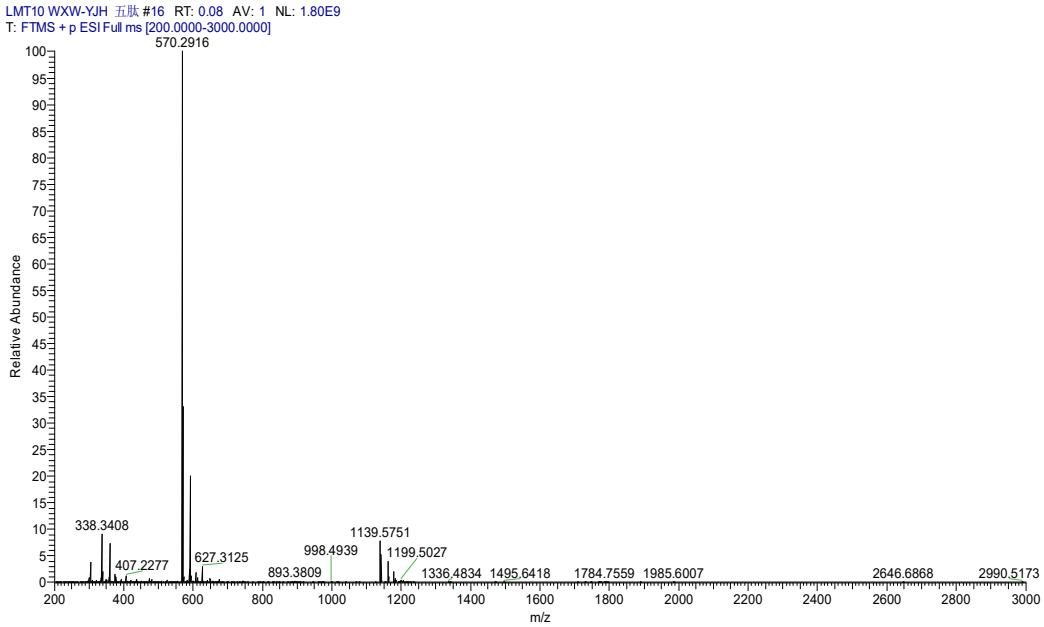


Peak No	RT (min)	Area (%)	Area
1	9.887	93.50	452.9561
2	18.460	3.55	17.1751
3	21.753	2.95	14.3003
Total		100.00	484.4316

NH_2-Tyr-Ala-Gly-Phe-Leu-OH (13): HRMS m/z (ESI) calcd for $C_{29}H_{40}N_5O_7^+$ $[M+H]^+$: 570.2922, found: 570.2916.

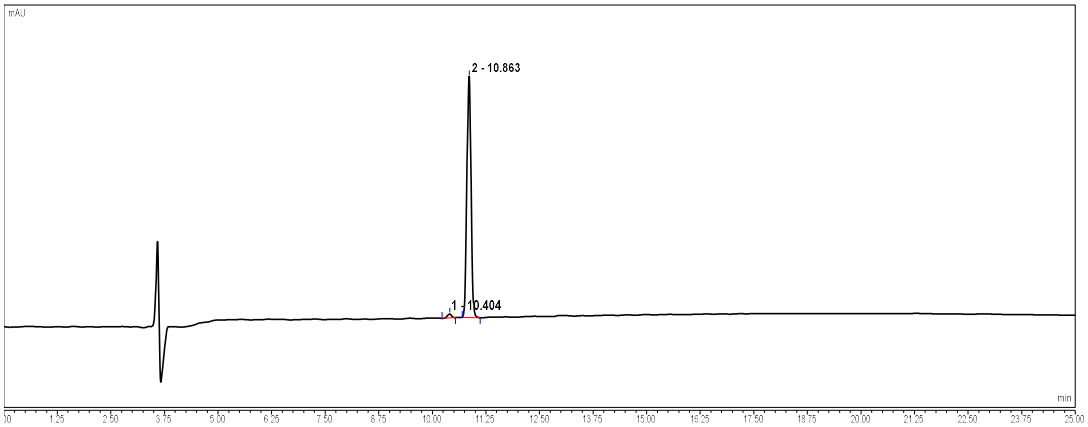


HPLC condition: Jupiter 5μm C18 4.6 × 250 mm^2 column; 0.05% TFA (v/v) in H_2O (solvent A), 0.05% TFA (v/v) in MeCN (solvent B); gradient 10%-100% (solvent B) in 30 min; flow rate = 1.0 mL/min; detection wavelength = 214 nm.

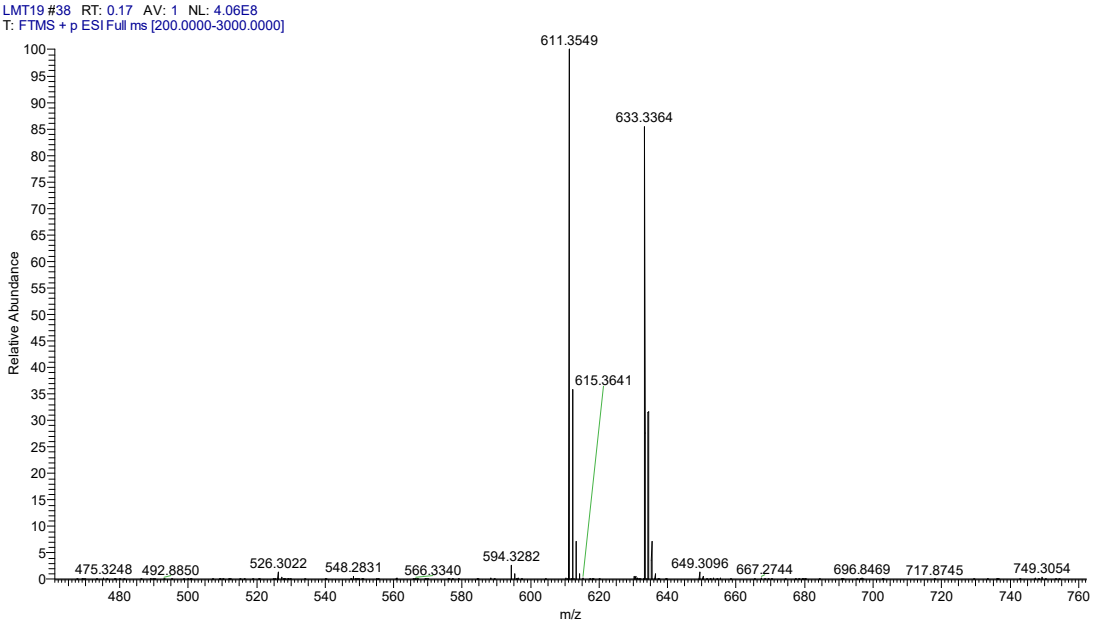


Peak No	RT (min)	Area (%)	Area
1	12.600	1.97	0.6548
2	12.947	98.03	32.5899
Total		100.00	33.2447

NH_2-Tyr-Aib-Aib-Phe-Leu-NH_2 (14): HRMS m/z (ESI) calcd for $C_{32}H_{47}N_6O_6^+$ $[M+H]^+$: 611.3552, found: 611.3549.

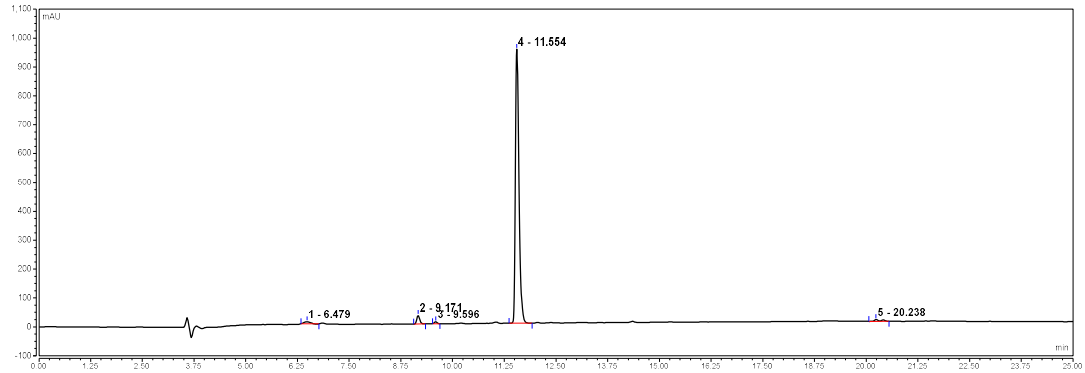


HPLC condition: Jupiter 5μm C18 4.6 × 250 mm^2 column; 0.05% TFA (v/v) in H_2O (solvent A), 0.05% TFA (v/v) in MeCN (solvent B); gradient 10%-100% (solvent B) in 30 min; flow rate = 1.0 mL/min; detection wavelength = 214 nm.

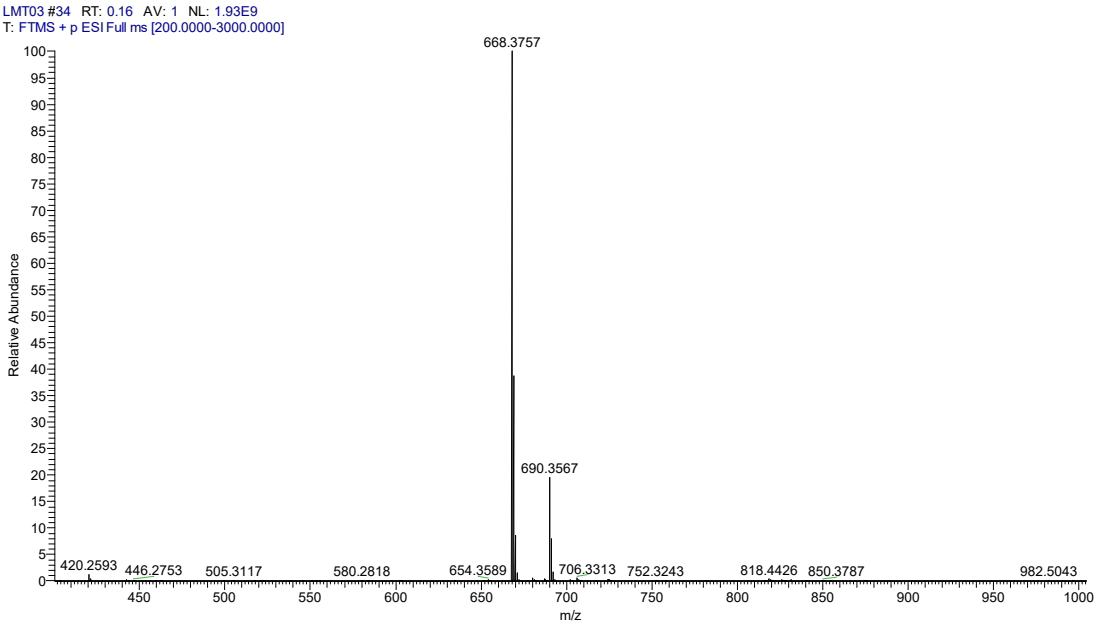


Peak No	RT (min)	Area (%)	Area
1	10.404	1.55	0.538
2	10.863	98.45	34.135
Total:		100.00	34.673

NH_2-Me-Ala-Tyr-Me-Ala-Gly-Phe-Leu-NH_2 (15): HRMS m/z (ESI) calcd for $C_{34}H_{50}N_7O_7^+$ $[M+H]^+$: 668.3766, found: 668.3757.

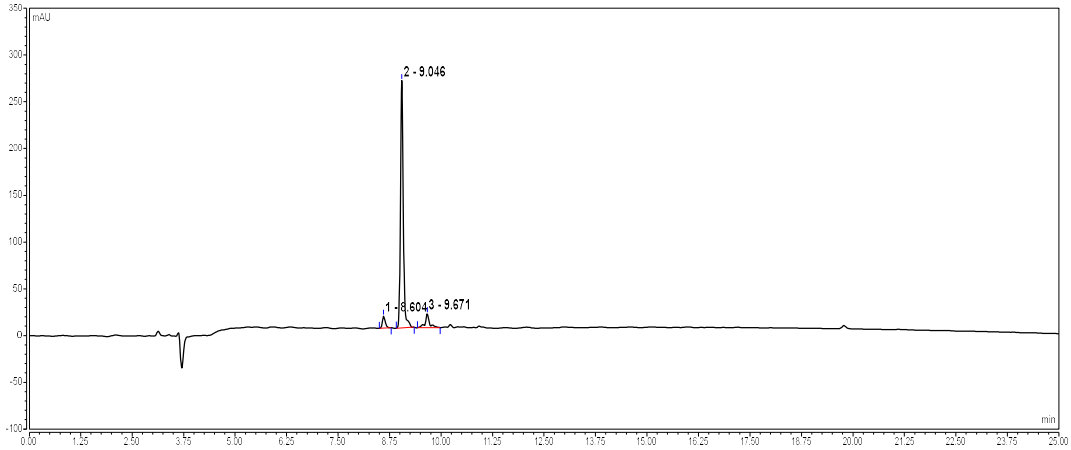


HPLC condition: Jupiter 5μm C18 4.6 × 250 mm^2 column; 0.05% TFA (v/v) in H_2O (solvent A), 0.05% TFA (v/v) in MeCN (solvent B); gradient 10%-100% (solvent B) in 30 min; flow rate = 1.0 mL/min; detection wavelength = 214 nm.

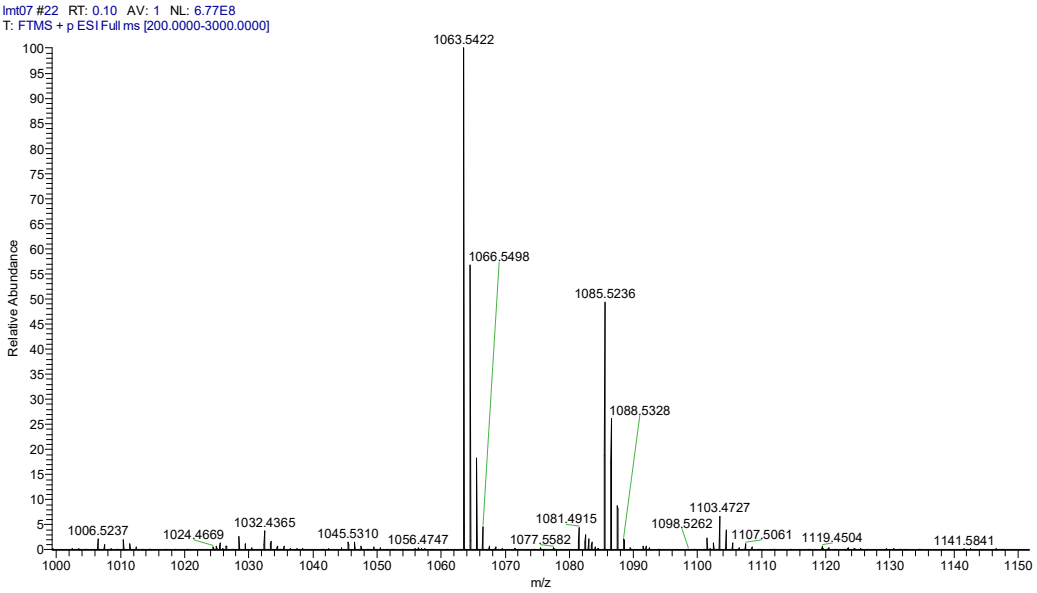


Peak No	RT (min)	% Area	Area
1	6.479	1.17	1.172
2	9.171	2.44	2.438
3	9.596	0.51	0.506
4	11.554	94.74	94.550
5	20.238	1.13	1.129
Total:		100.00	99.795

NH_2-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-OH (16): HRMS m/z (ESI) calcd for $C_{47}H_{75}N_{12}O_{16}^+$ $[M+H]^+$: 1063.5419, found: 1063.5422.



HPLC condition: Jupiter 5μm C18 4.6 × 250 mm^2 column; 0.05% TFA (v/v) in H_2O (solvent A), 0.05% TFA (v/v) in MeCN (solvent B); gradient 10%-100% (solvent B) in 30 min; flow rate = 1.0 mL/min; detection wavelength = 214 nm.



Peak No	RT (min)	% Area	Area
1	8.604	4.33	1.040
2	9.046	88.26	21.226
3	9.671	7.41	1.782
Total:		100.00	24.048

NMR spectrum

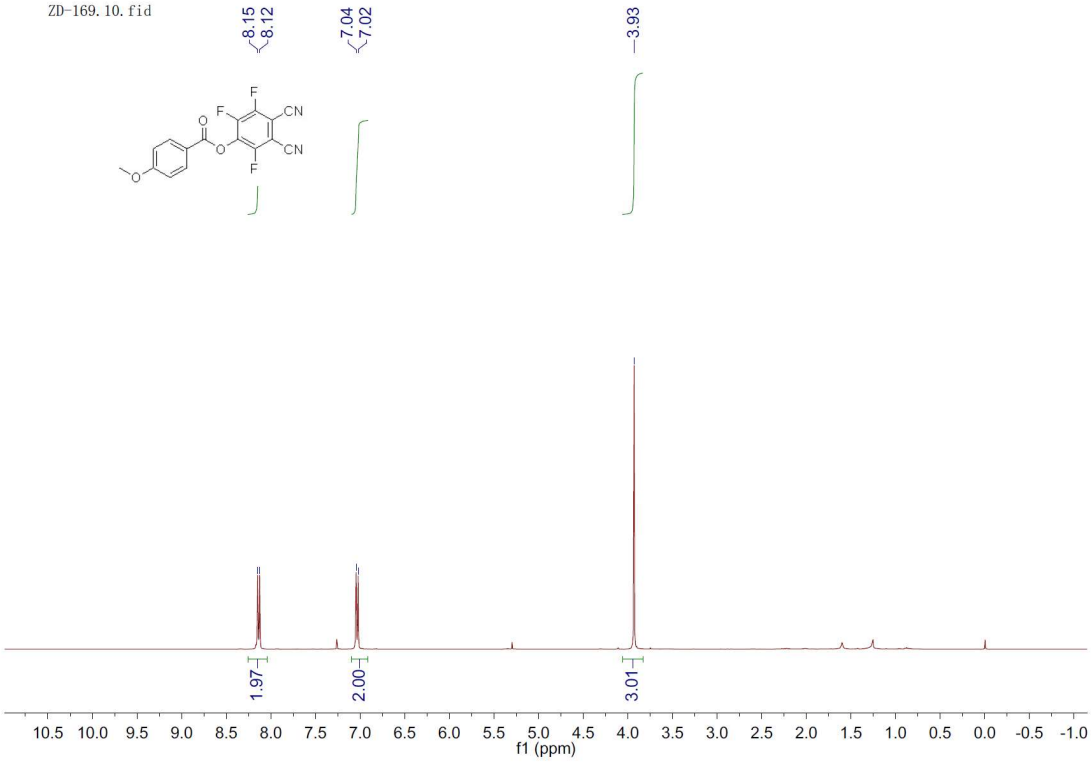


Figure S1. ^{1}H NMR of compound **3a** in DMSO-d_6, 400 MHz for ^{1}H NMR.

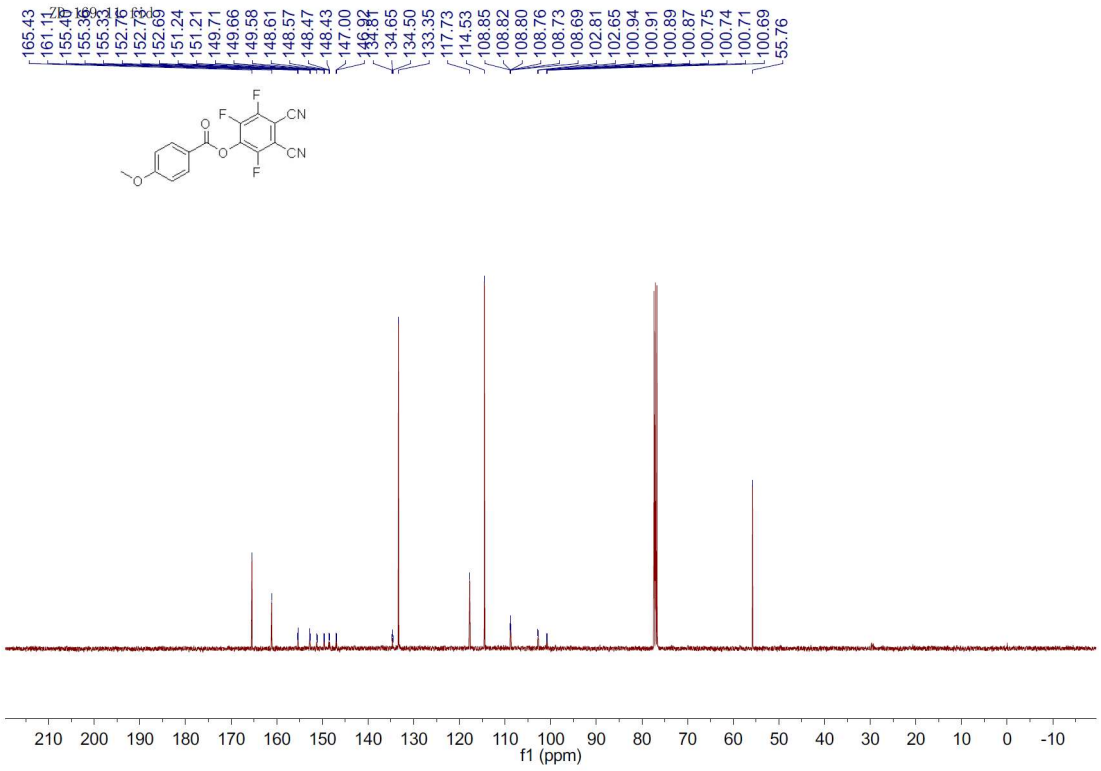


Figure S2. ^{13}C NMR of compound **3a** in DMSO-d_6, 100 MHz for ^{13}C NMR.

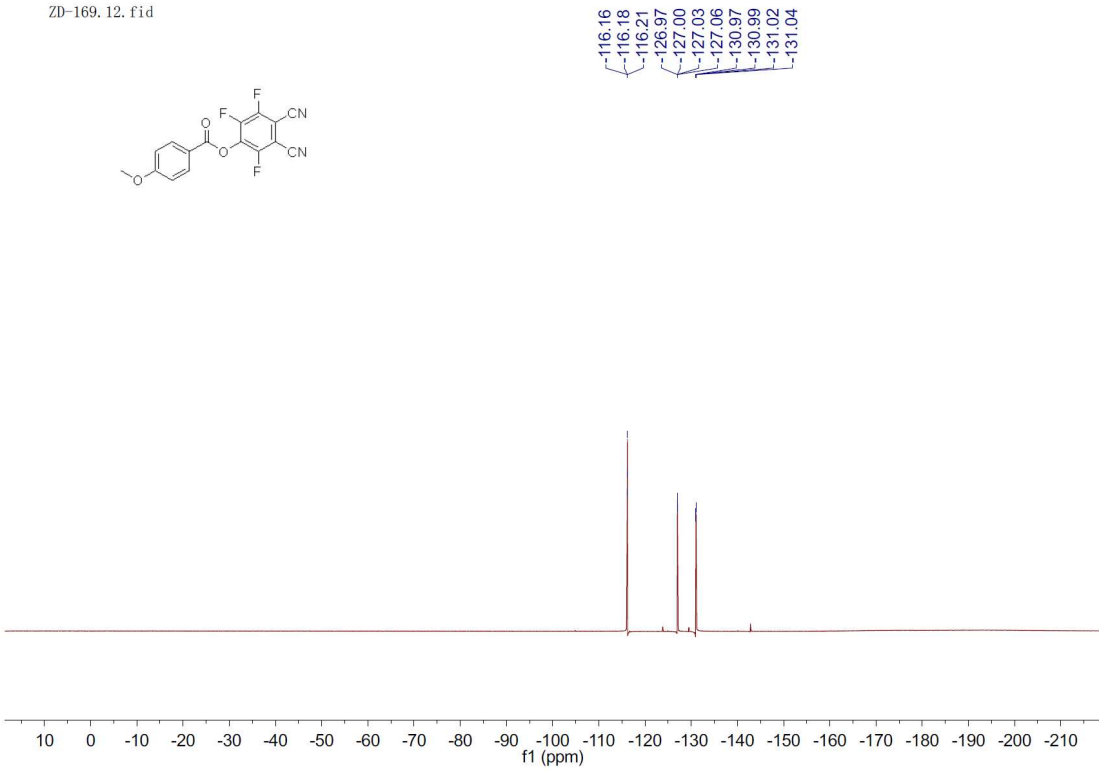


Figure S3. ^{13}F NMR of compound **3a** in DMSO-d_6, 376 MHz for ^{13}F NMR.

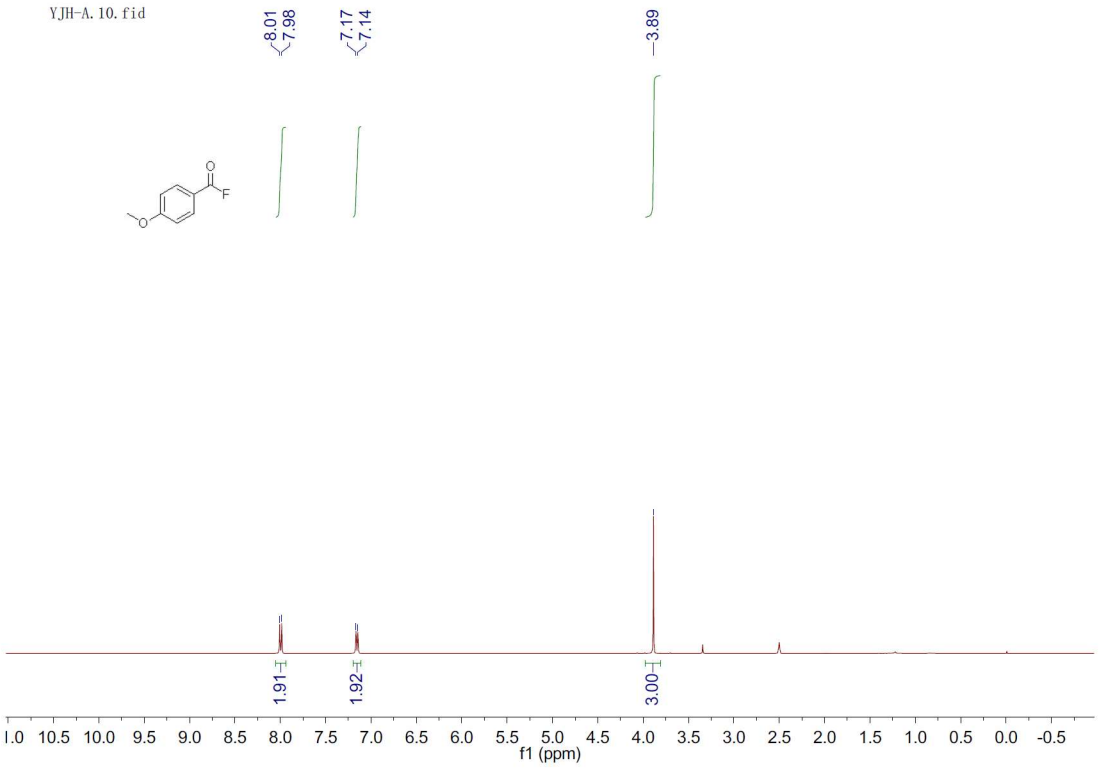


Figure S4. ^{1}H NMR of compound **4a** in DMSO-d_6, 400 MHz for ^{1}H NMR.

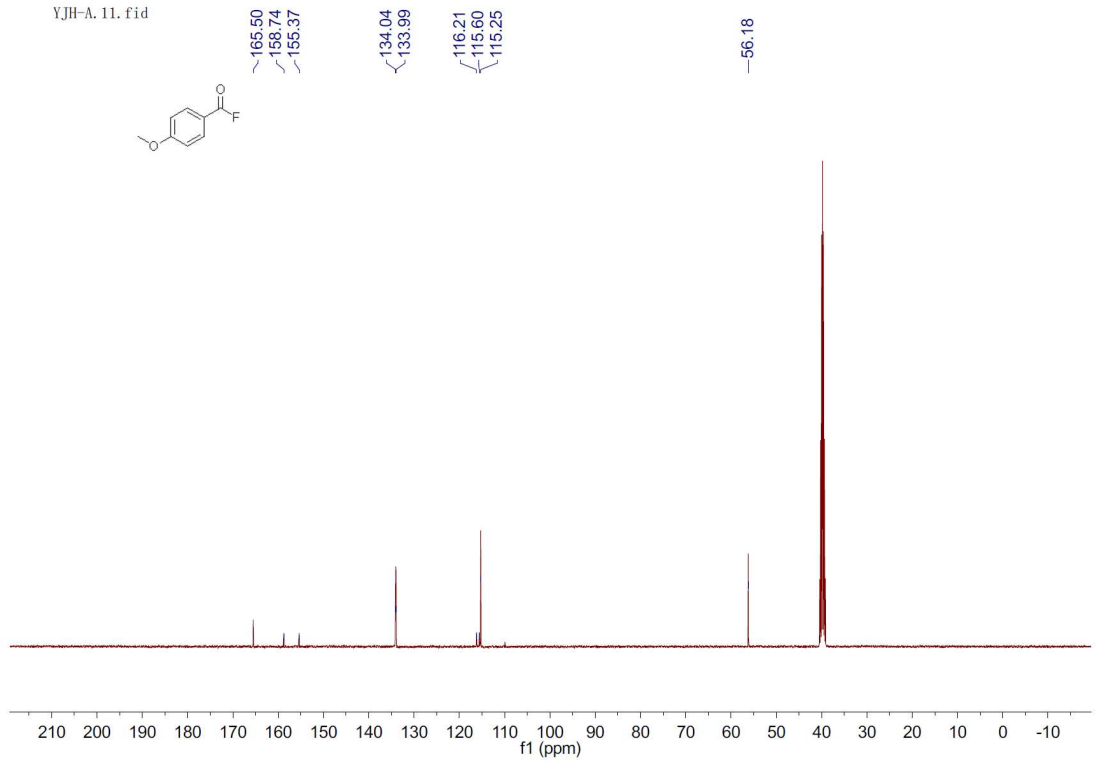


Figure S5. ^{13}C NMR of compound **4a** in DMSO-d_6, 100 MHz for ^{13}C NMR.

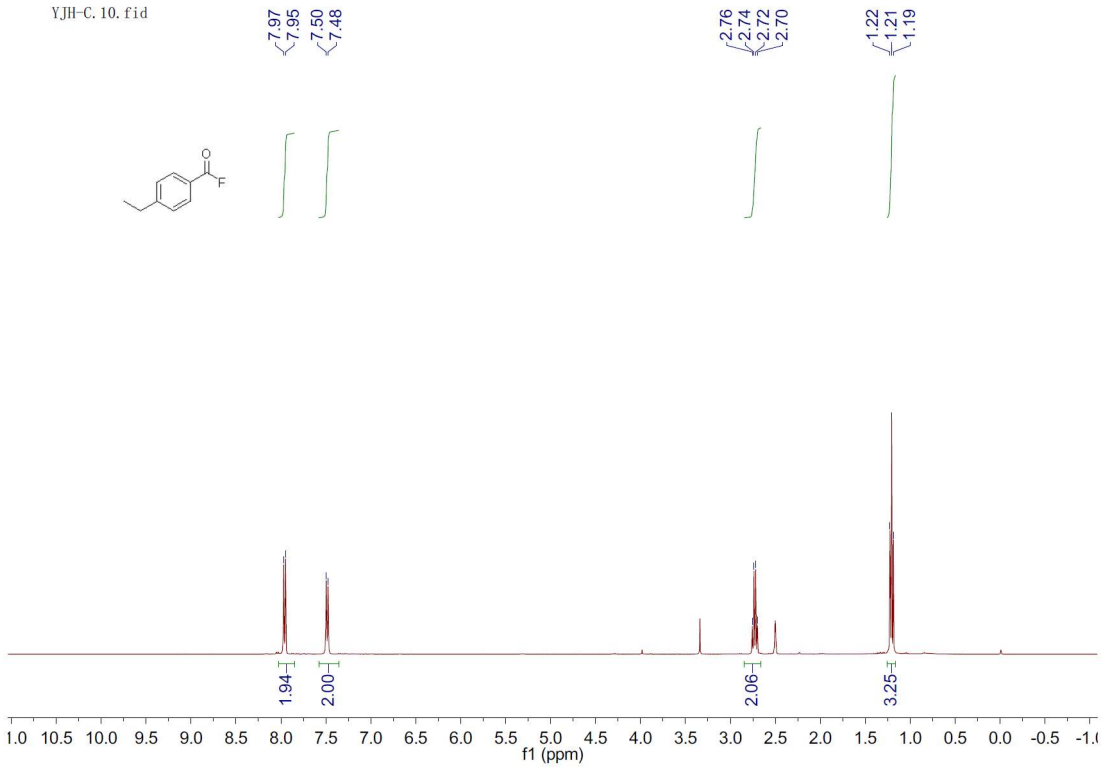


Figure S6. ^{1}H NMR of compound **4b** in DMSO-d_6, 400 MHz for ^{1}H NMR.

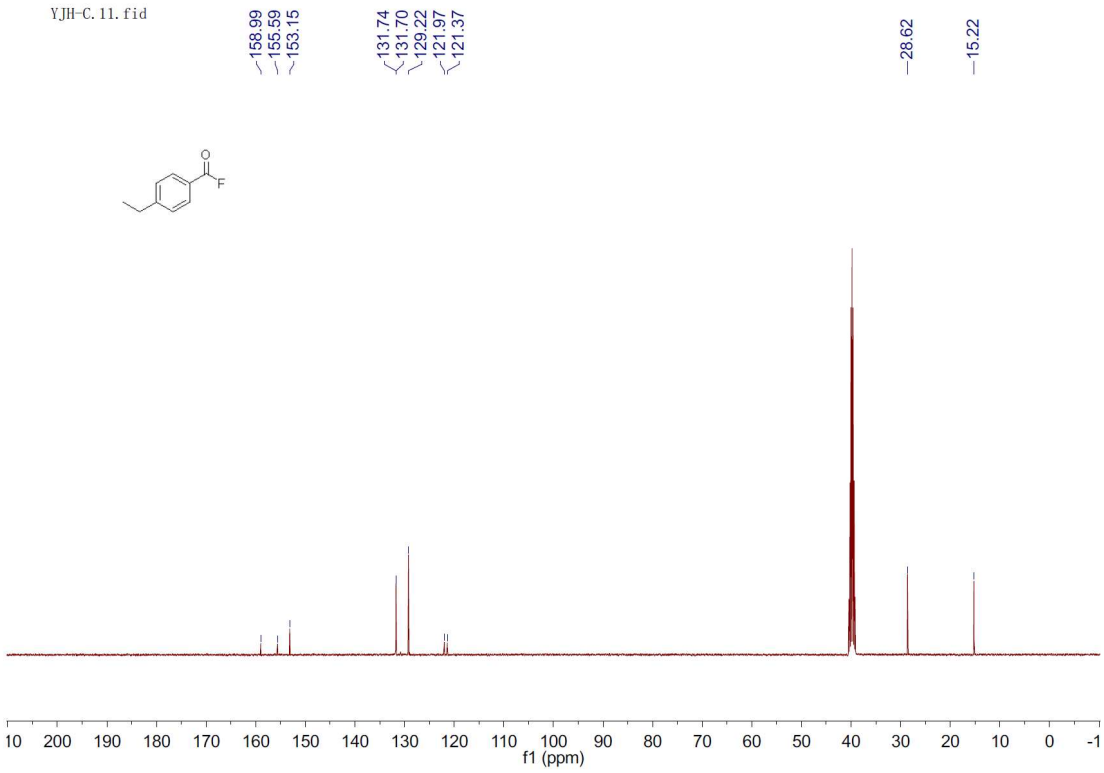


Figure S7. ^{13}C NMR of compound **4b** in DMSO-d_6, 100 MHz for ^{13}C NMR.

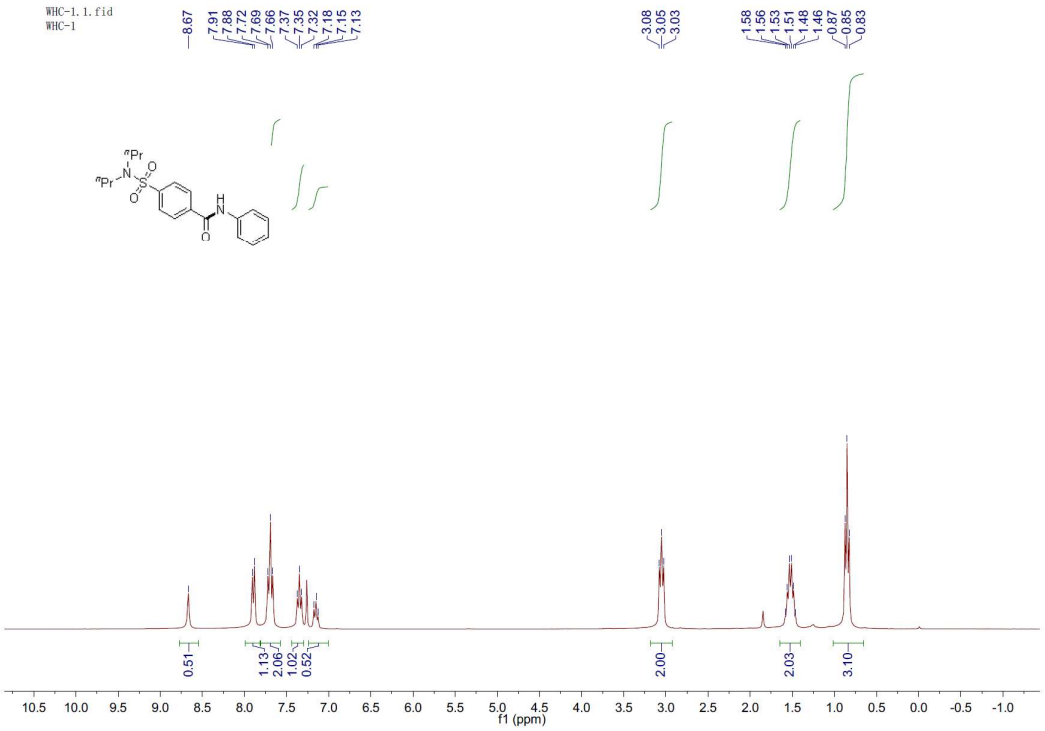


Figure S8. ^{1}H NMR of compound **6a** in $CDCl_3$, 300 MHz for ^{1}H NMR.

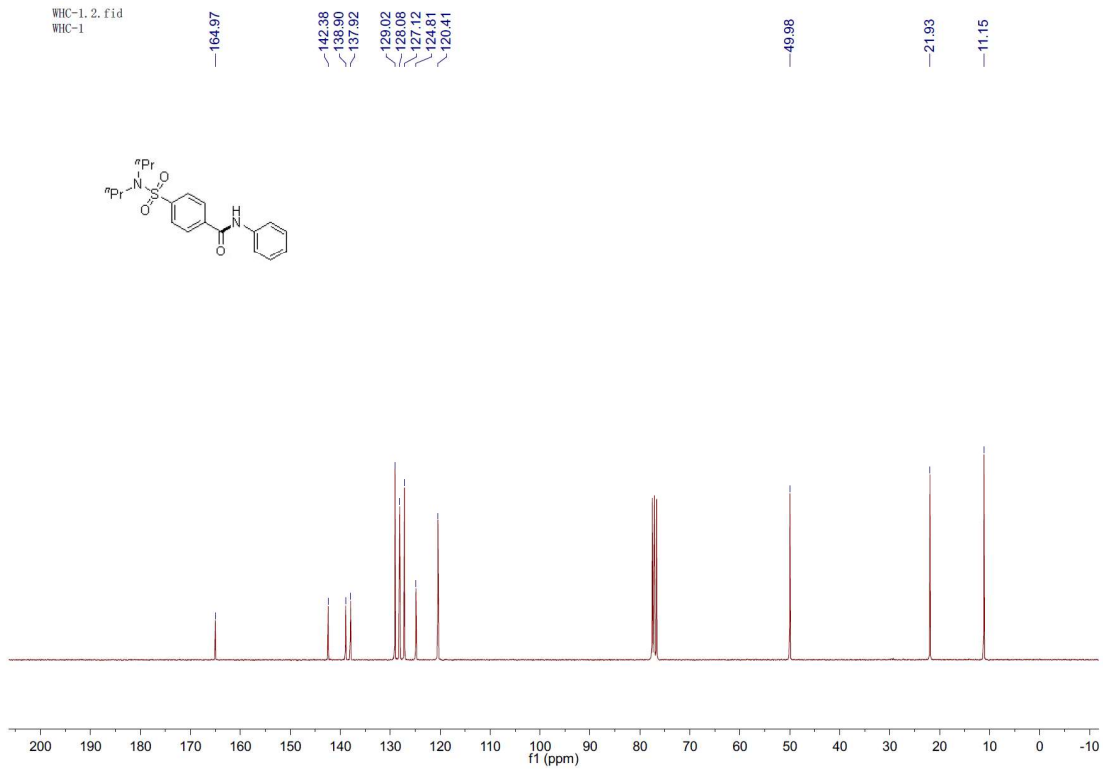


Figure S9. ^{13}C NMR of compound **6a** in $CDCl_3$, 75 MHz for ^{13}C NMR.

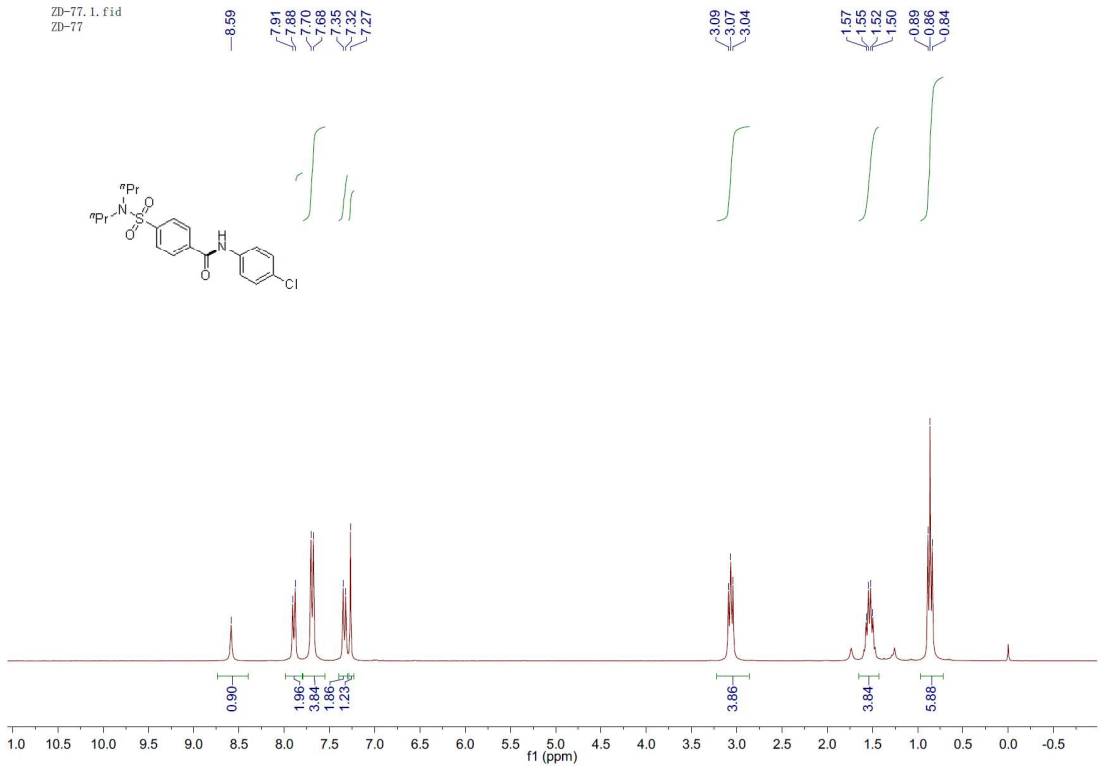


Figure S10. ^{1}H NMR of compound **6b** in $CDCl_3$, 300 MHz for ^{1}H NMR.

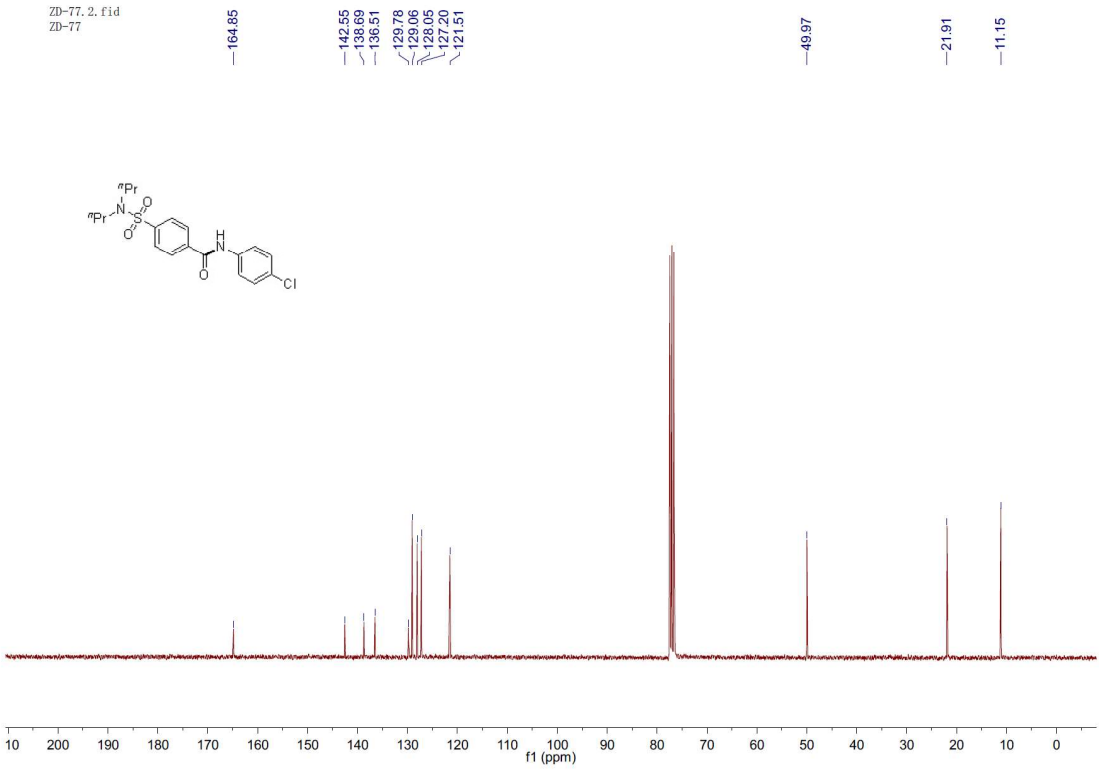


Figure S11. ^{13}C NMR of compound **6b** in $CDCl_3$, 75 MHz for ^{13}C NMR.

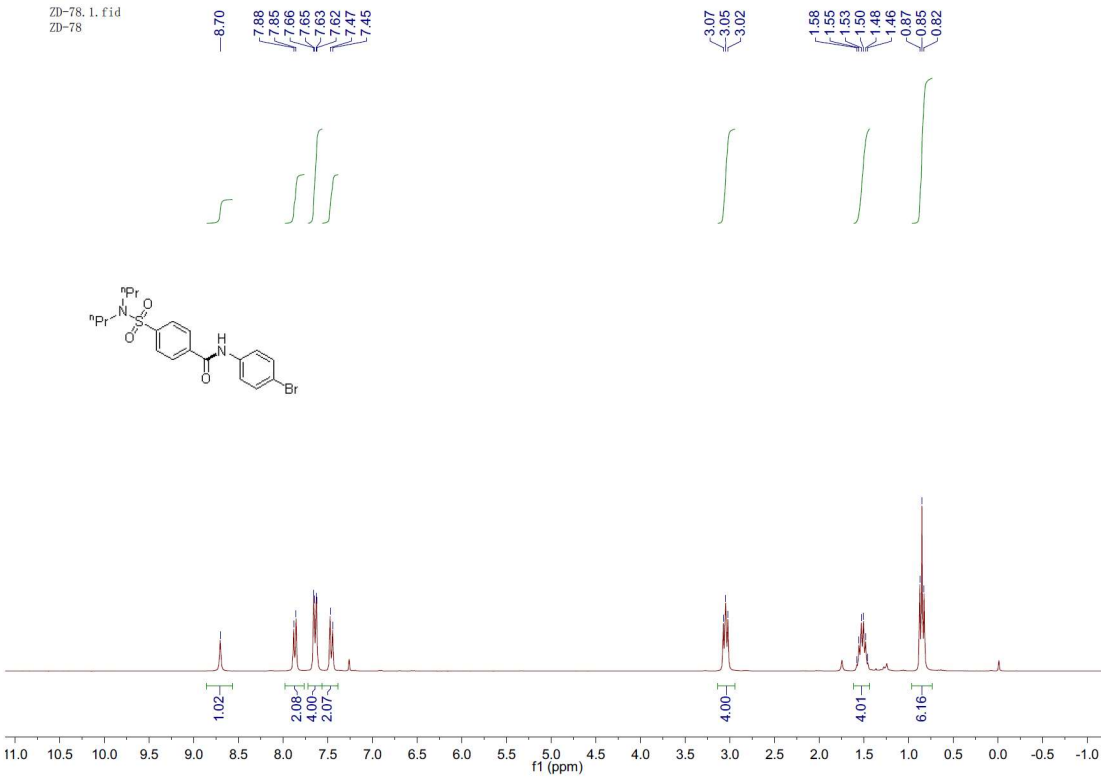


Figure S12. ^{1}H NMR of compound **6c** in $CDCl_3$, 300 MHz for ^{1}H NMR.

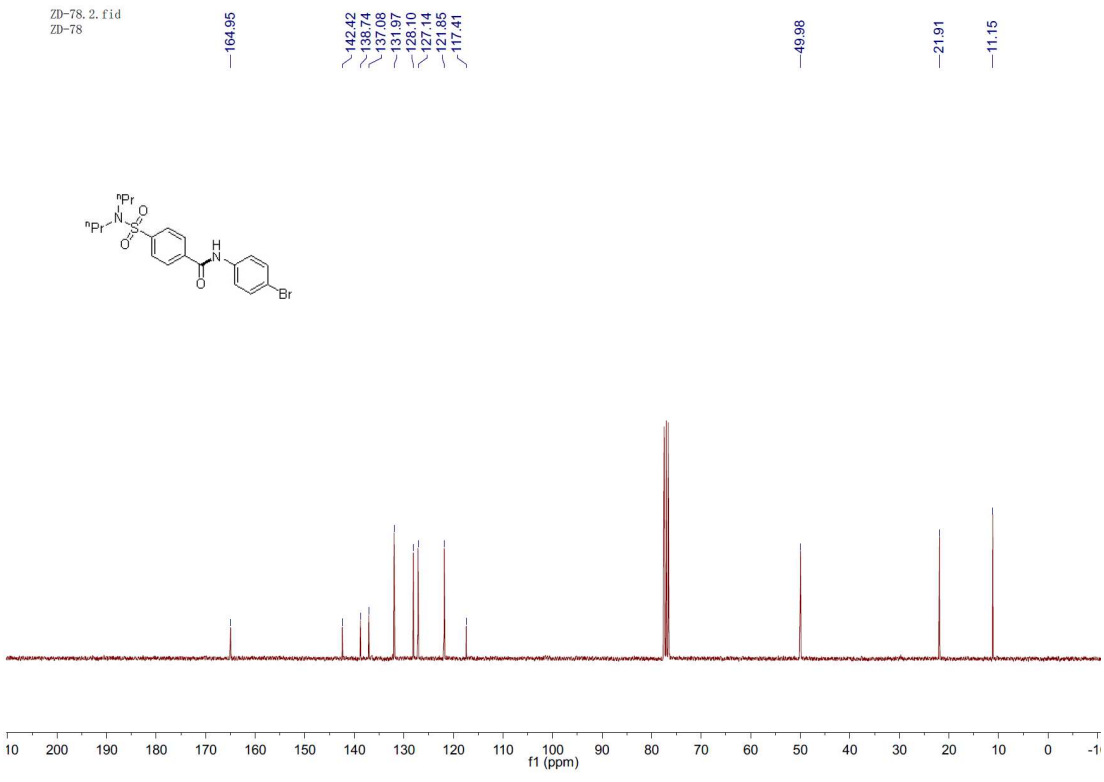


Figure S13. ^{13}C NMR of compound **6c** in $CDCl_3$, 75 MHz for ^{13}C NMR.

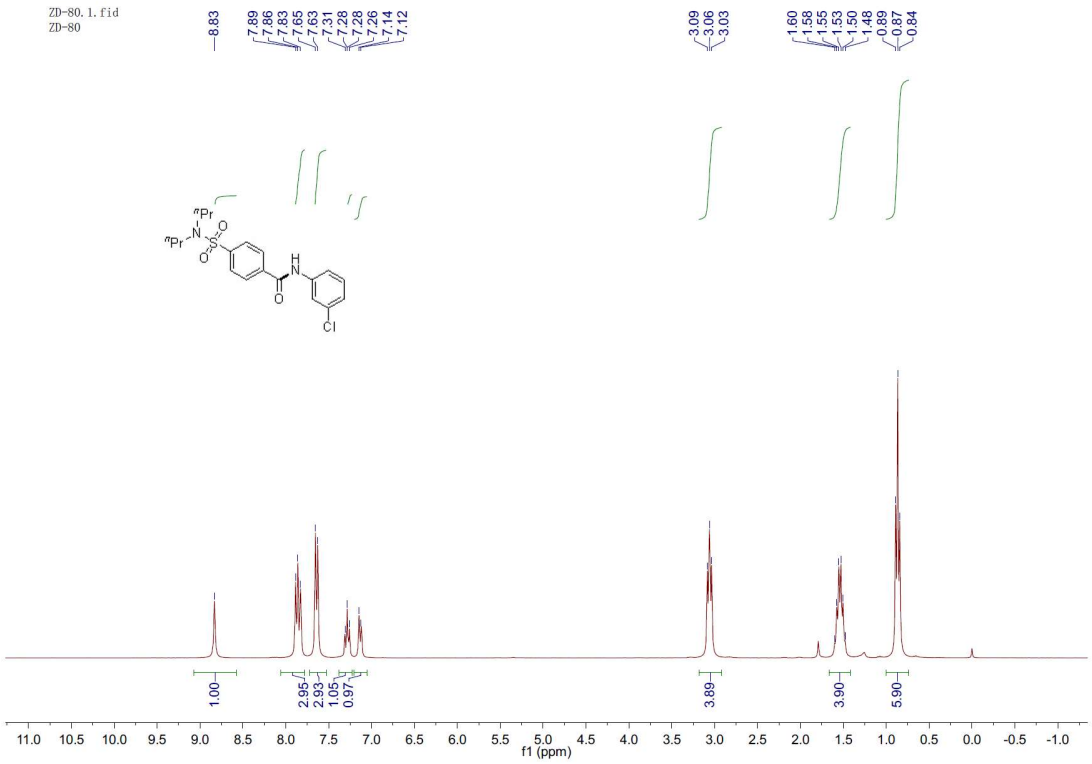


Figure S14. ^{1}H NMR of compound **6d** in $CDCl_3$, 300 MHz for ^{1}H NMR.

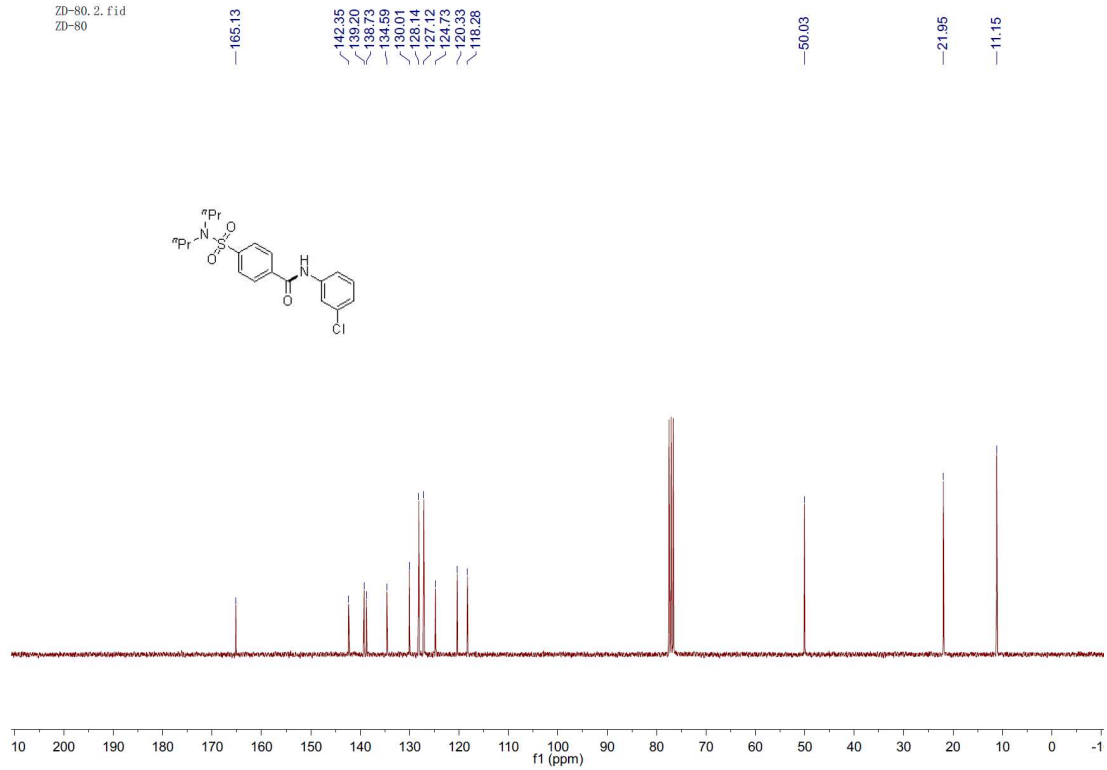


Figure S15. ^{13}C NMR of compound **6d** in $CDCl_3$, 75 MHz for ^{13}C NMR.

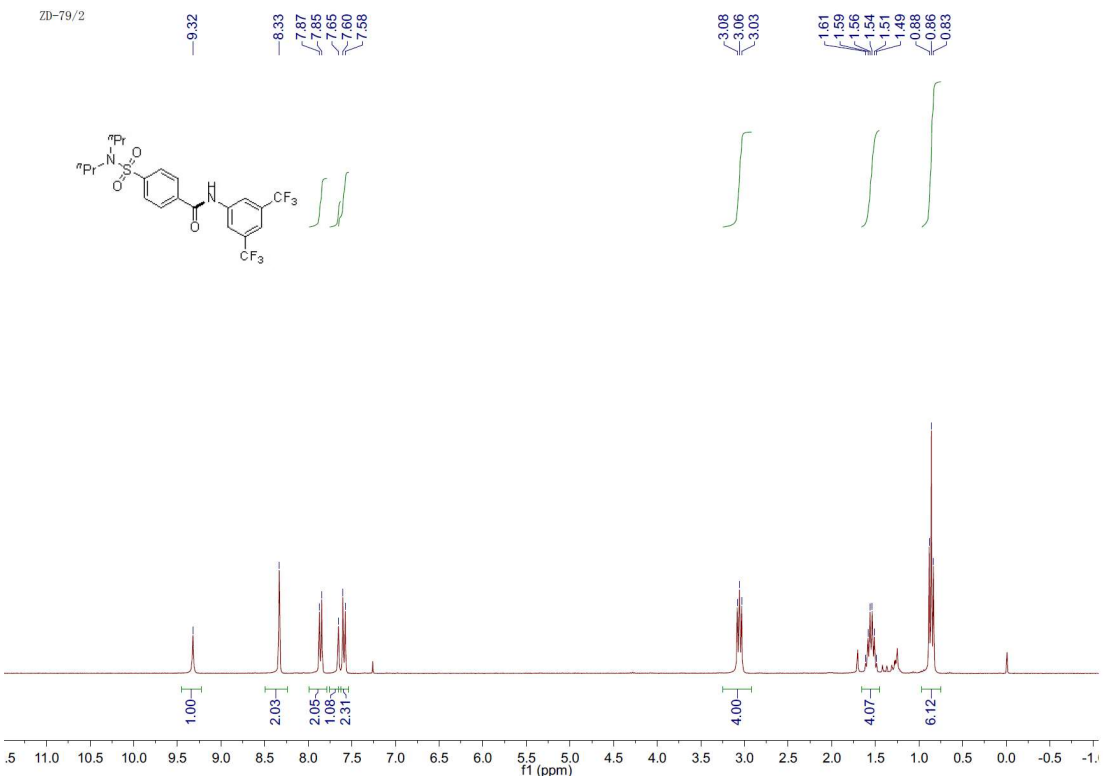


Figure S16. ^{1}H NMR of compound **6e** in $CDCl_3$, 300 MHz for ^{1}H NMR.

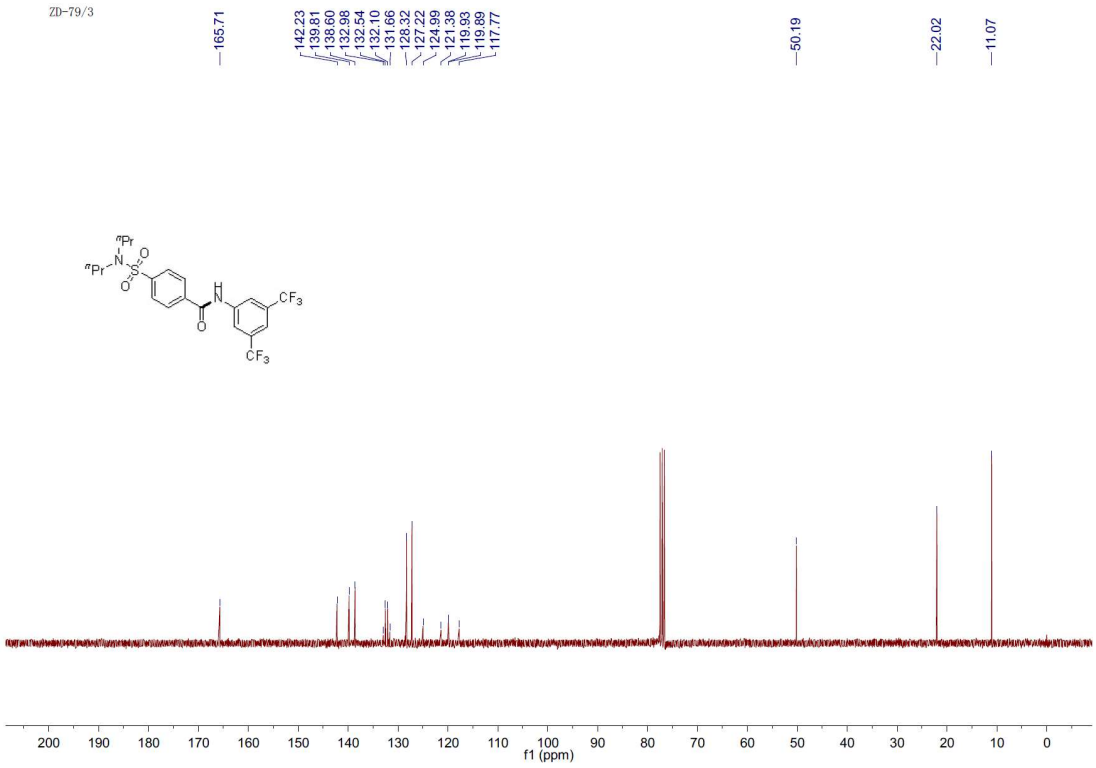


Figure S17. ^{13}C NMR of compound **6e** in $CDCl_3$, 75 MHz for ^{13}C NMR.

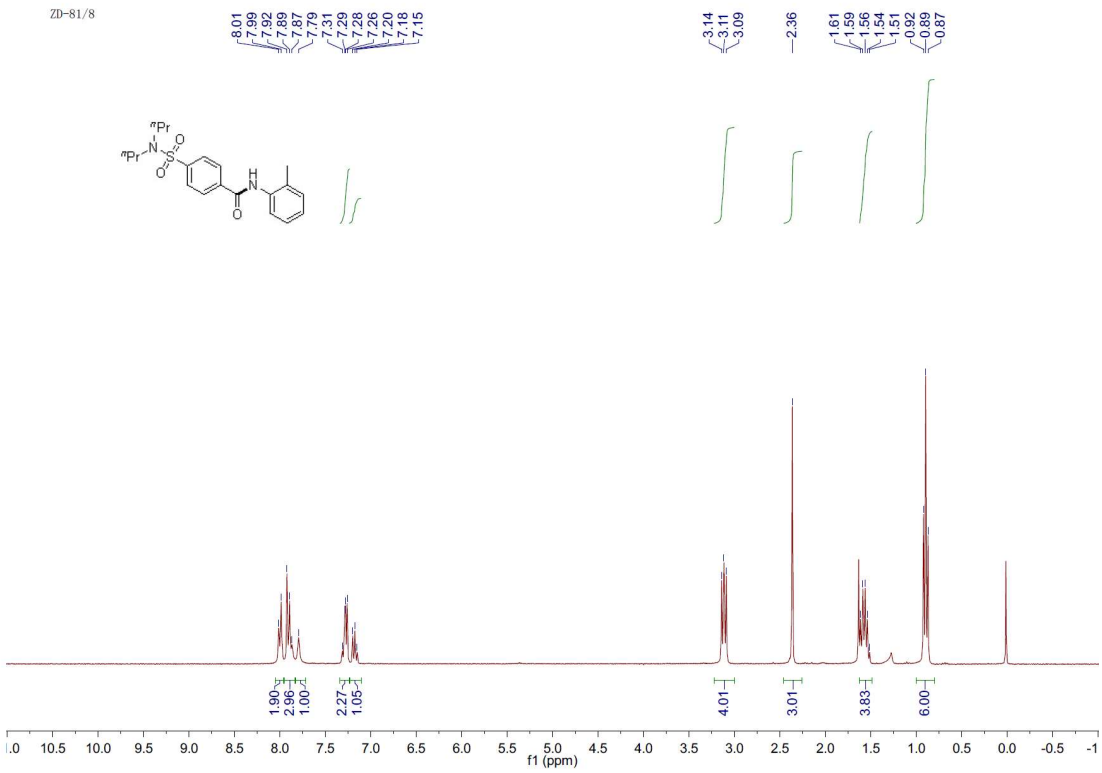


Figure S18. ^{1}H NMR of compound **6f** in $CDCl_3$, 300 MHz for ^{1}H NMR.

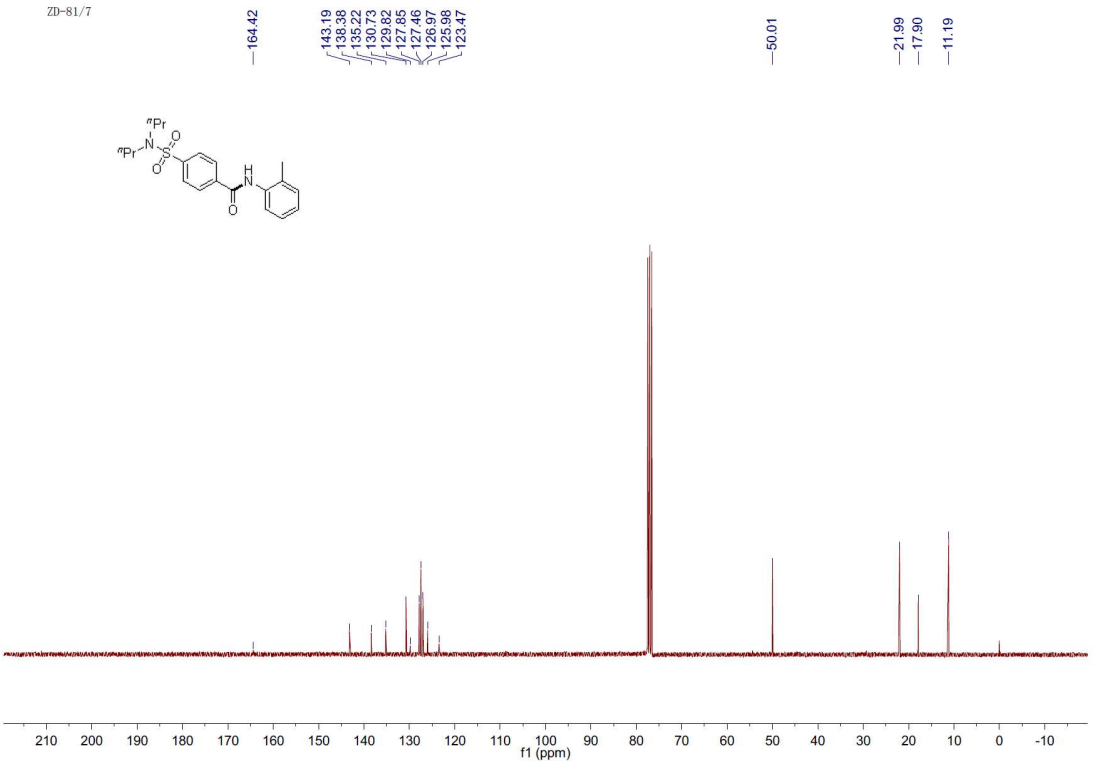


Figure S19. ^{13}C NMR of compound **6f** in $CDCl_3$, 75 MHz for ^{13}C NMR.

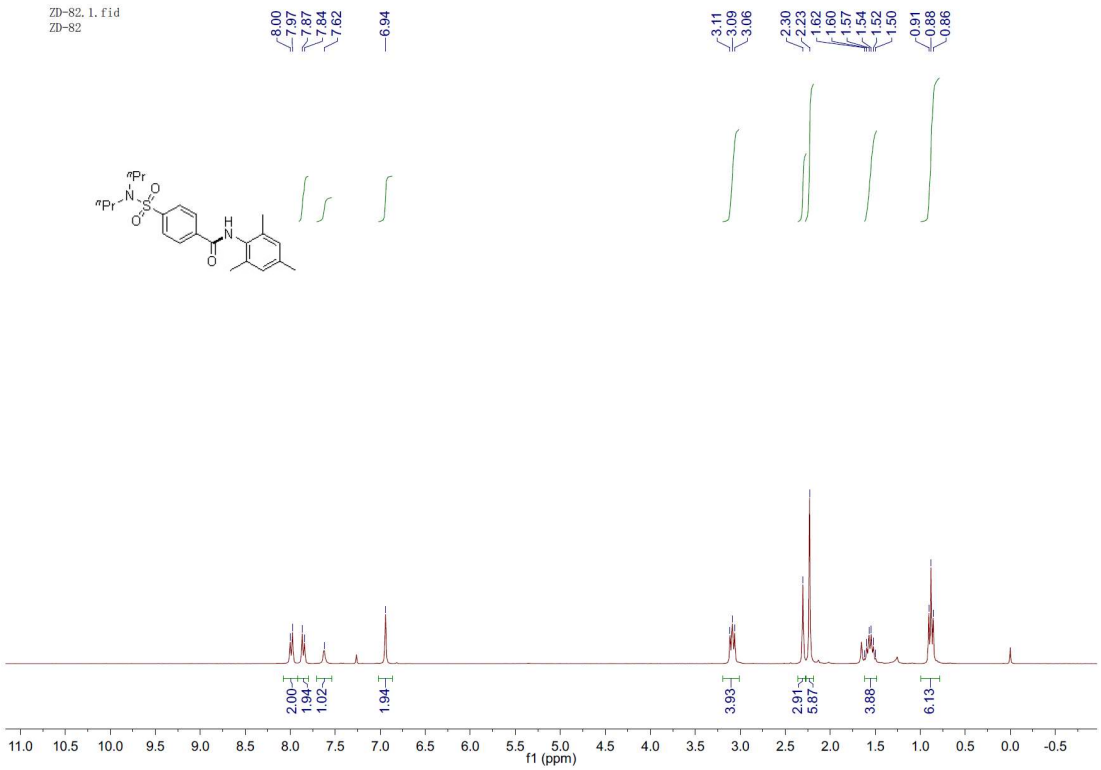


Figure S10. ^{1}H NMR of compound **6g** in $CDCl_3$, 300 MHz for ^{1}H NMR.

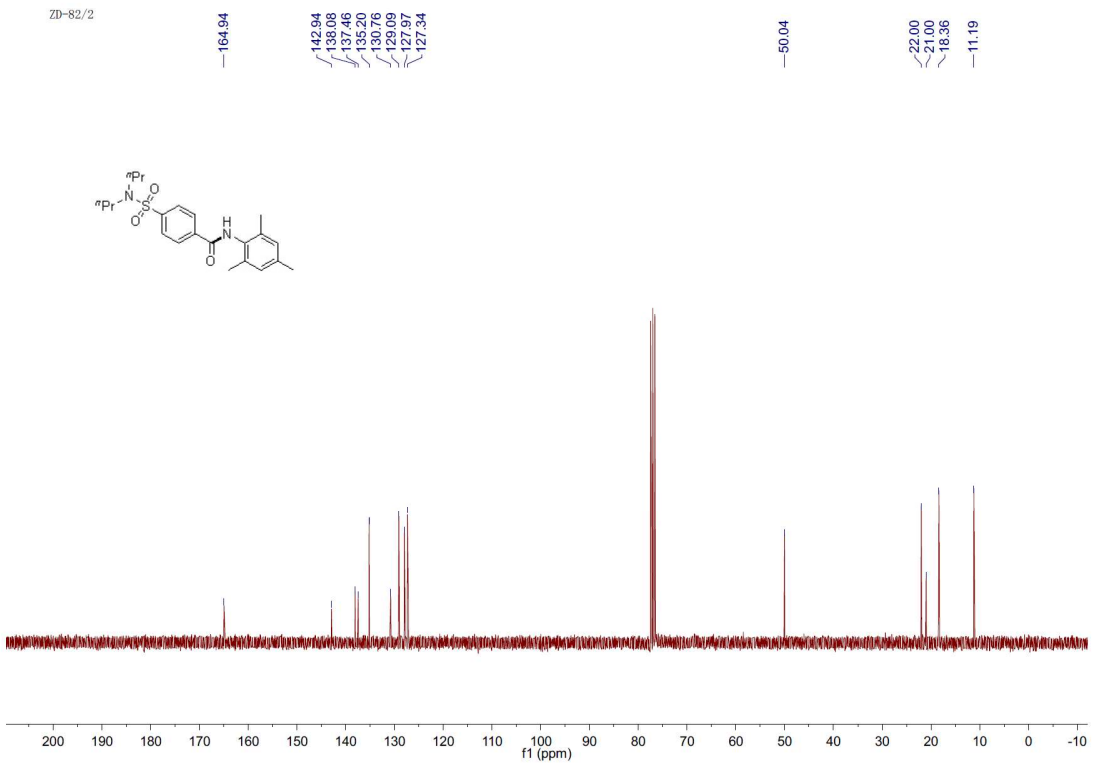


Figure S21. ^{13}C NMR of compound **6g** in $CDCl_3$, 75 MHz for ^{13}C NMR.

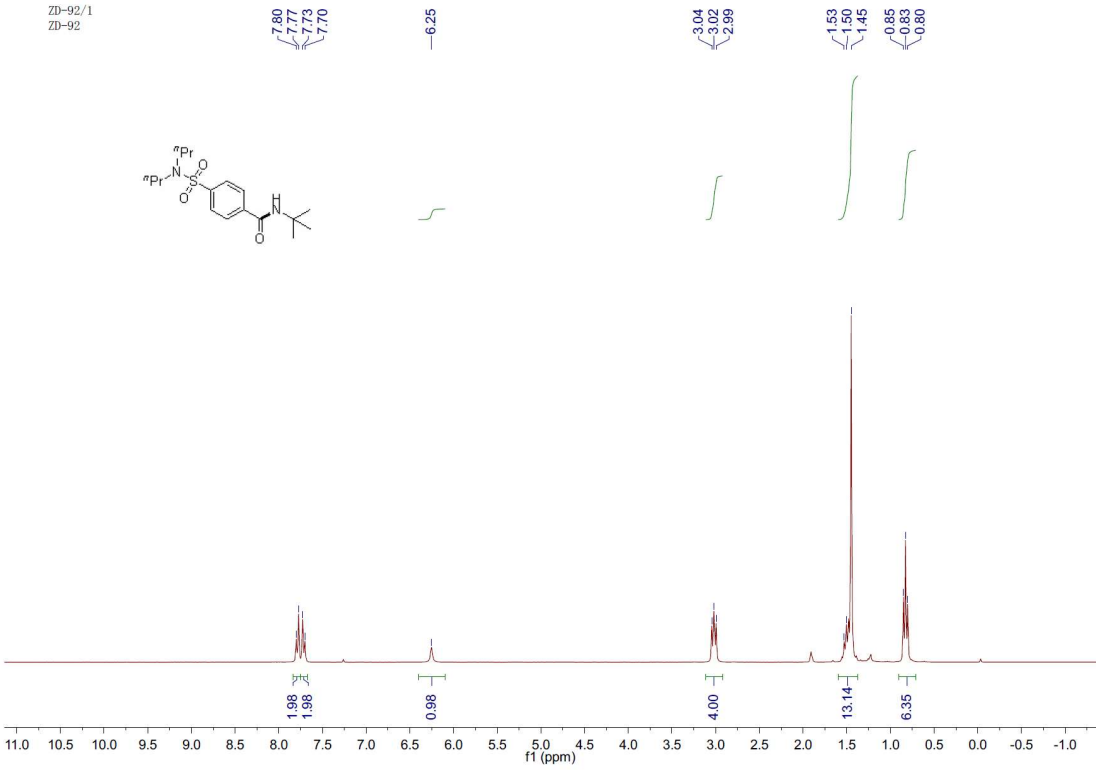


Figure S22. ^{1}H NMR of compound **6h** in $CDCl_3$, 300 MHz for ^{1}H NMR.

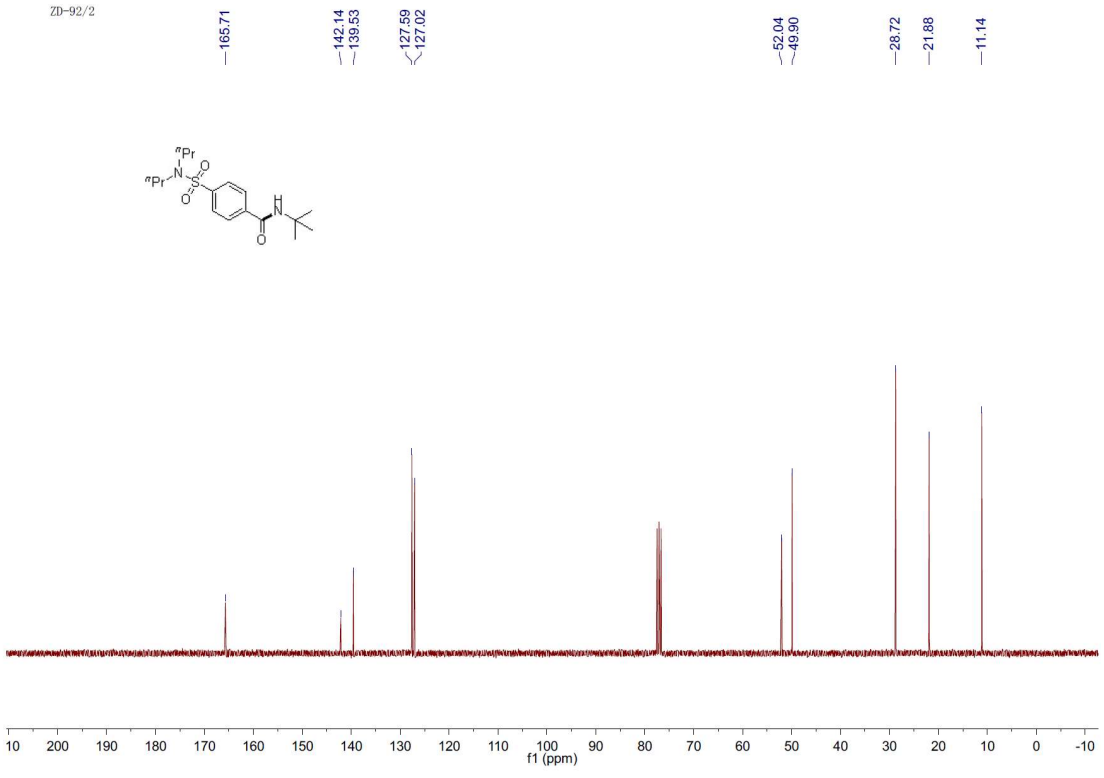


Figure S23. ^{13}C NMR of compound **6h** in $CDCl_3$, 75 MHz for ^{13}C NMR.

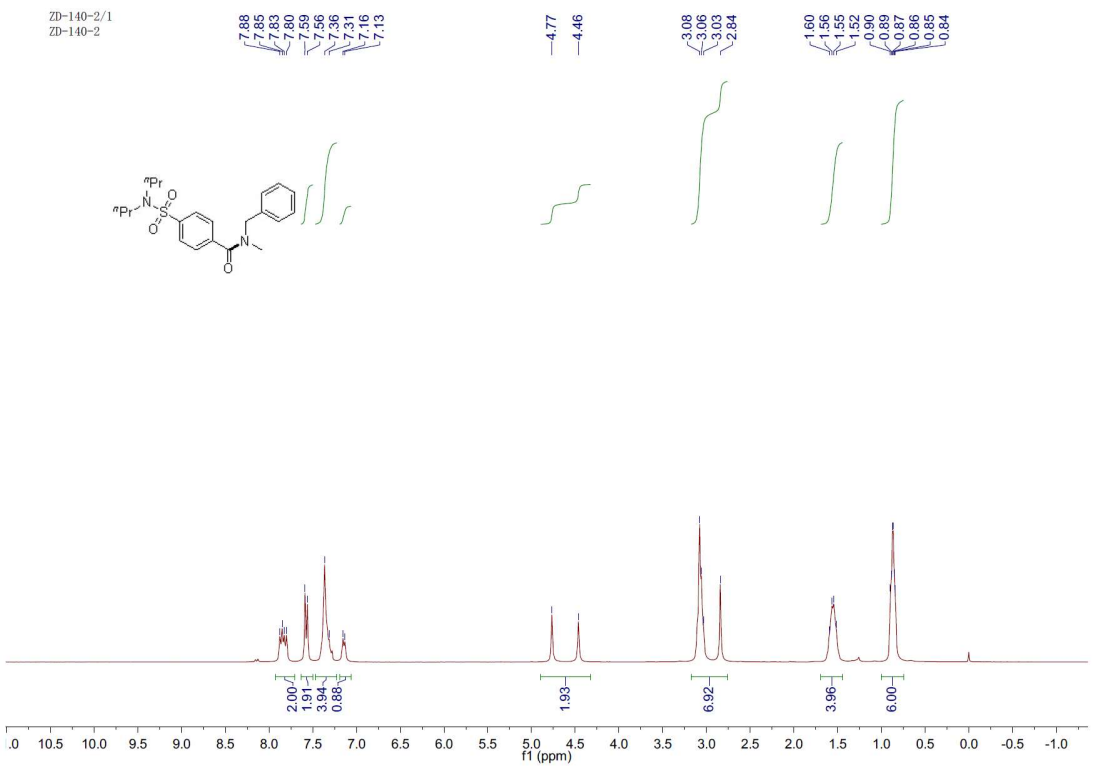


Figure S24. ^{1}H NMR of compound **6i** in $CDCl_3$, 300 MHz for ^{1}H NMR.

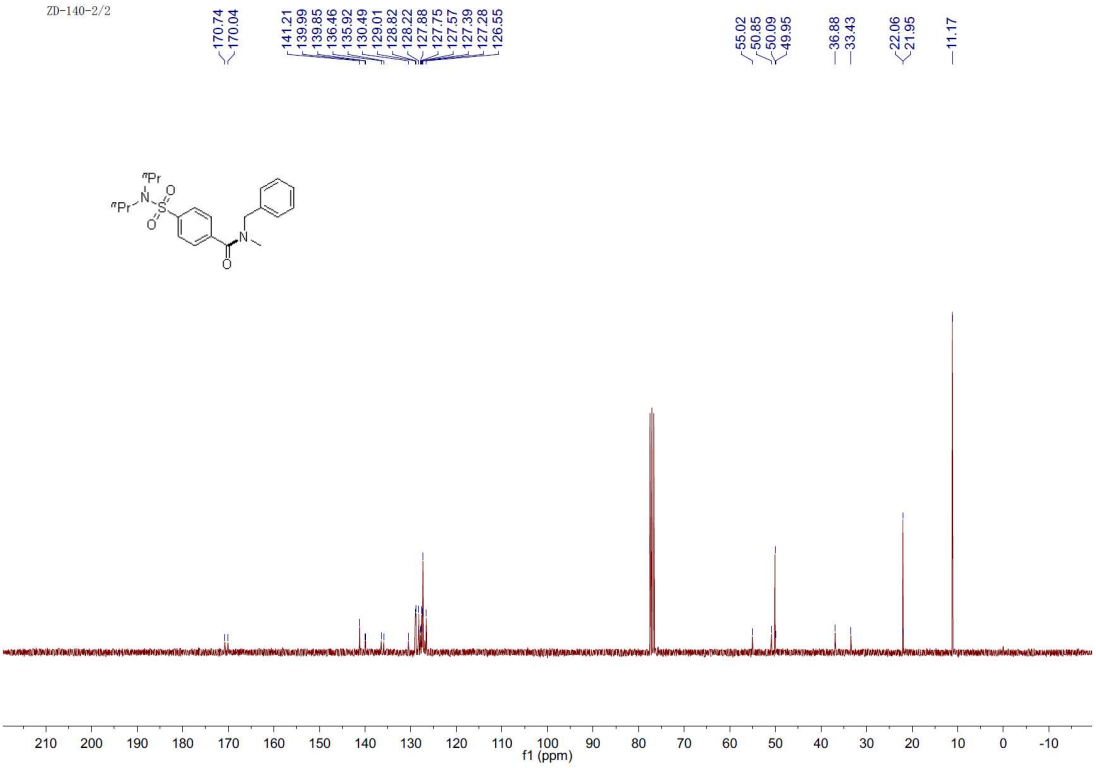


Figure S25. ^{13}C NMR of compound **6i** in $CDCl_3$, 75 MHz for ^{13}C NMR.

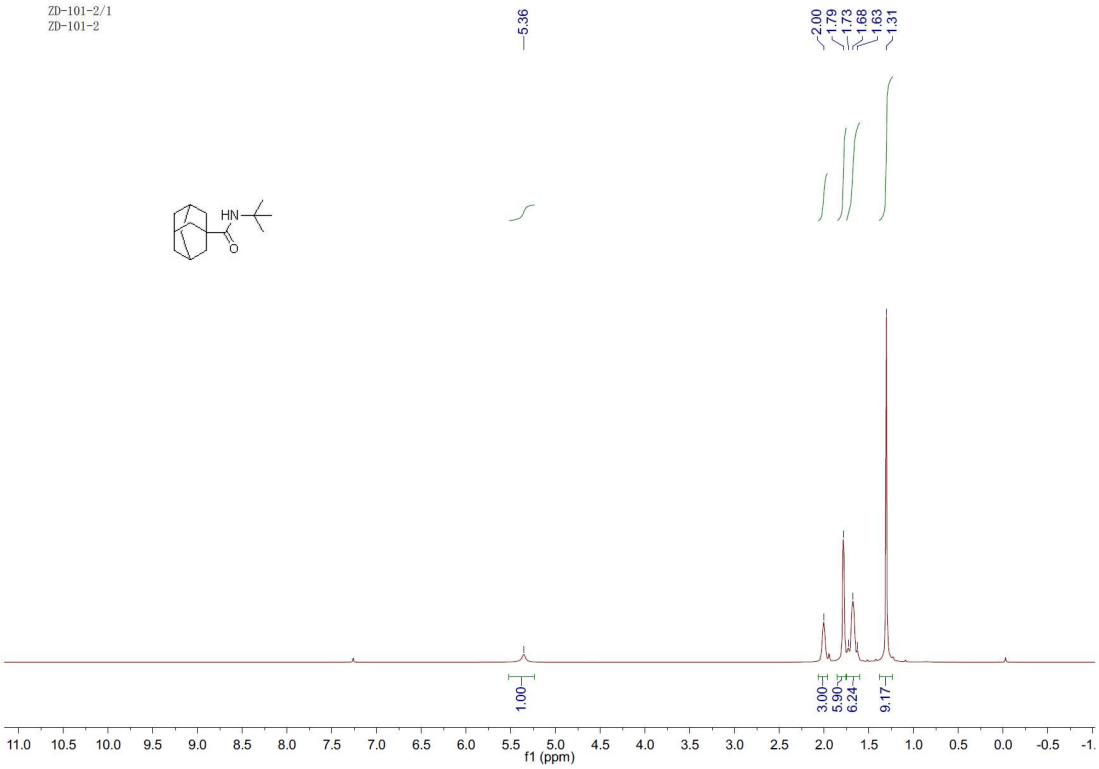


Figure S26. ^{1}H NMR of compound **6j** in $CDCl_3$, 300 MHz for ^{1}H NMR.

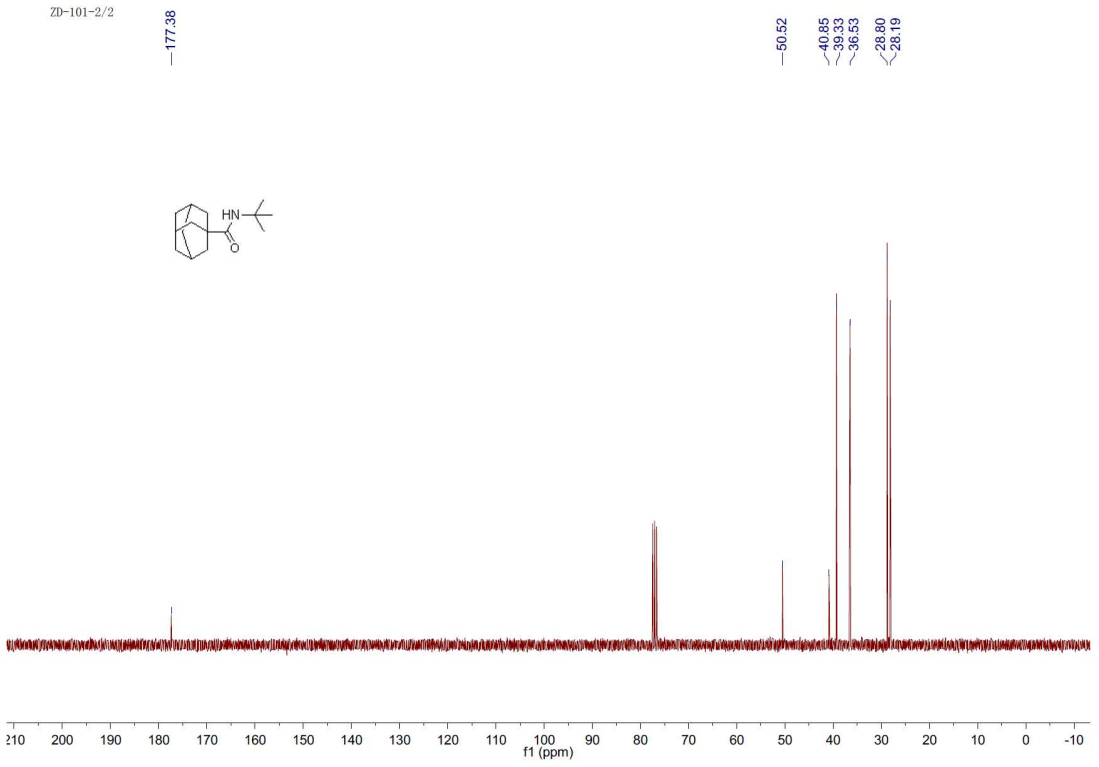


Figure S27. ^{13}C NMR of compound **6j** in $CDCl_3$, 75 MHz for ^{13}C NMR.

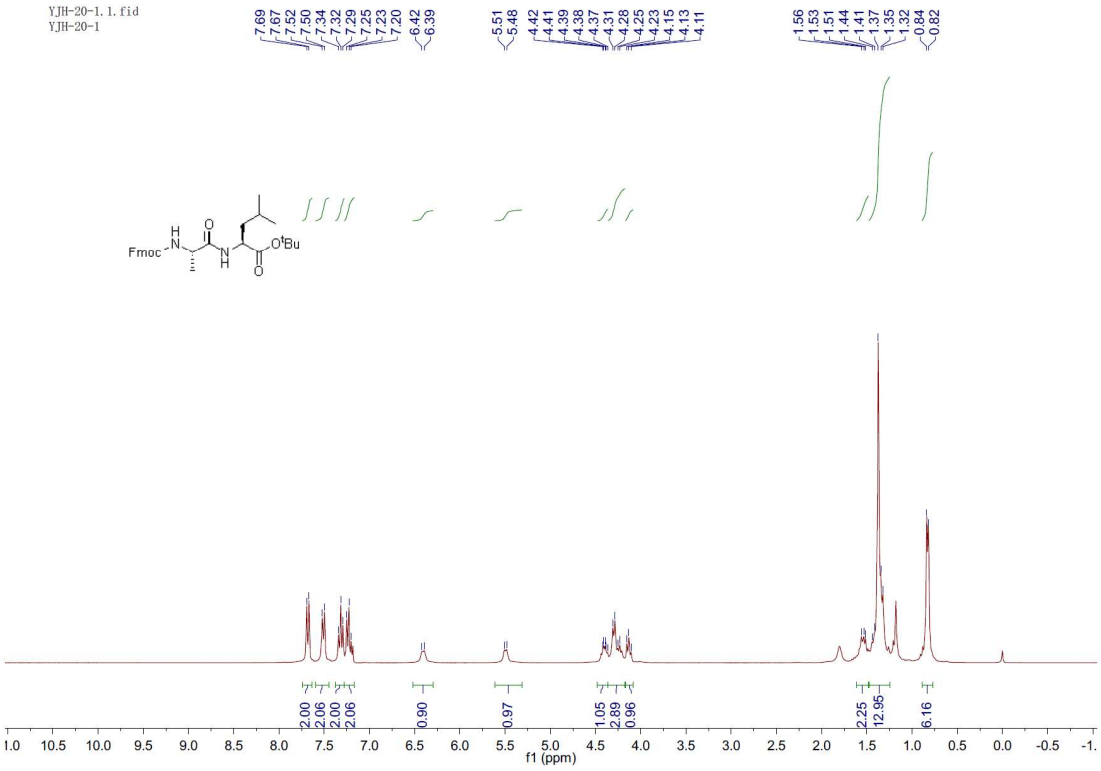


Figure S28. ^{1}H NMR of compound **7a** in $CDCl_3$, 300 MHz for ^{1}H NMR.

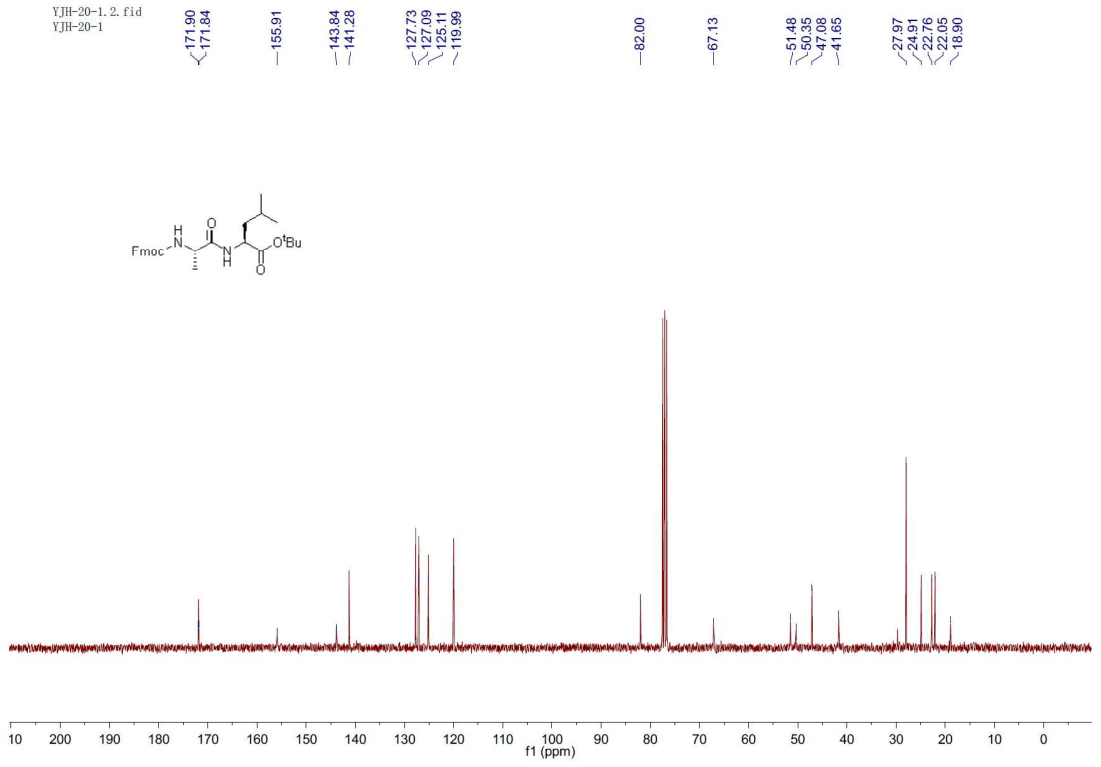


Figure S29. ^{13}C NMR of compound **7a** in $CDCl_3$, 75 MHz for ^{13}C NMR.

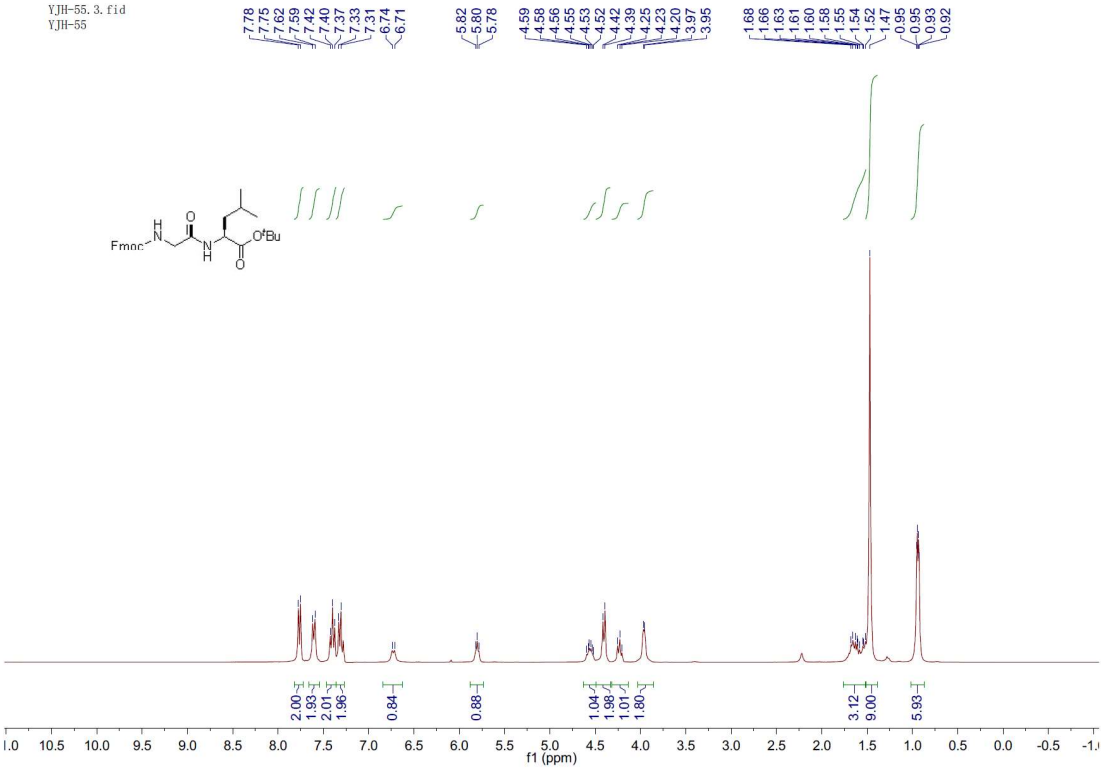


Figure S30. ^{1}H NMR of compound **7b** in $CDCl_3$, 300 MHz for ^{1}H NMR.

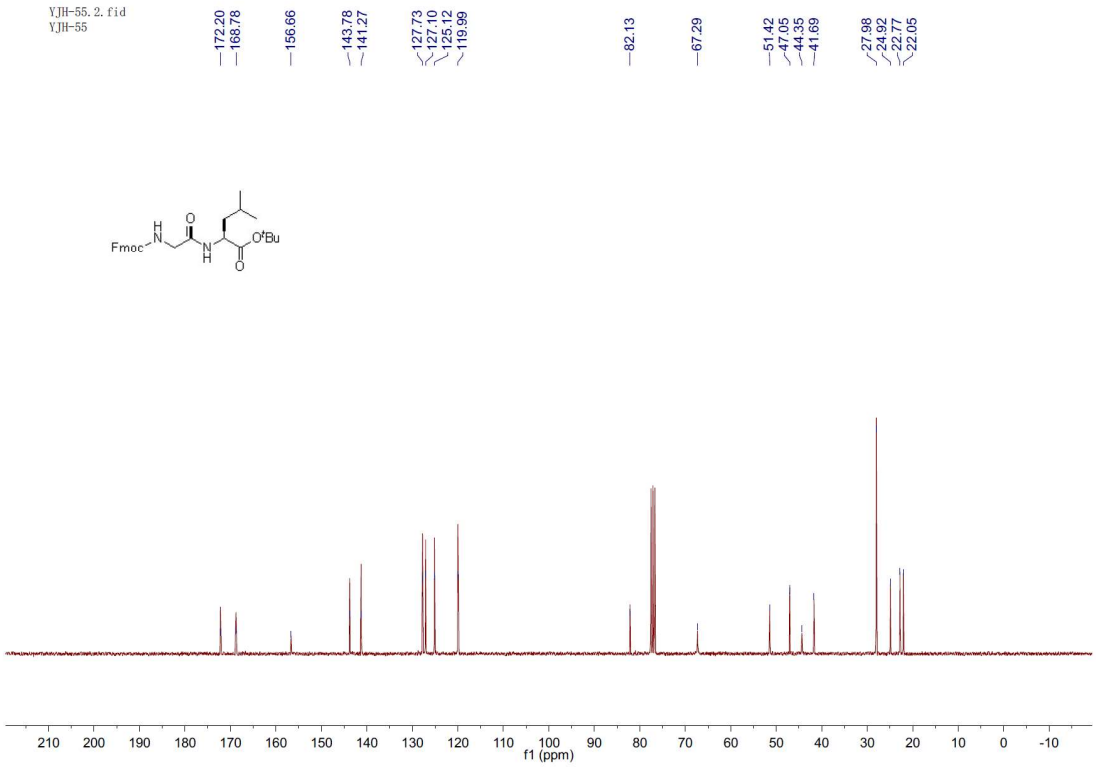


Figure S31. ^{13}C NMR of compound **7b** in $CDCl_3$, 75 MHz for ^{13}C NMR.

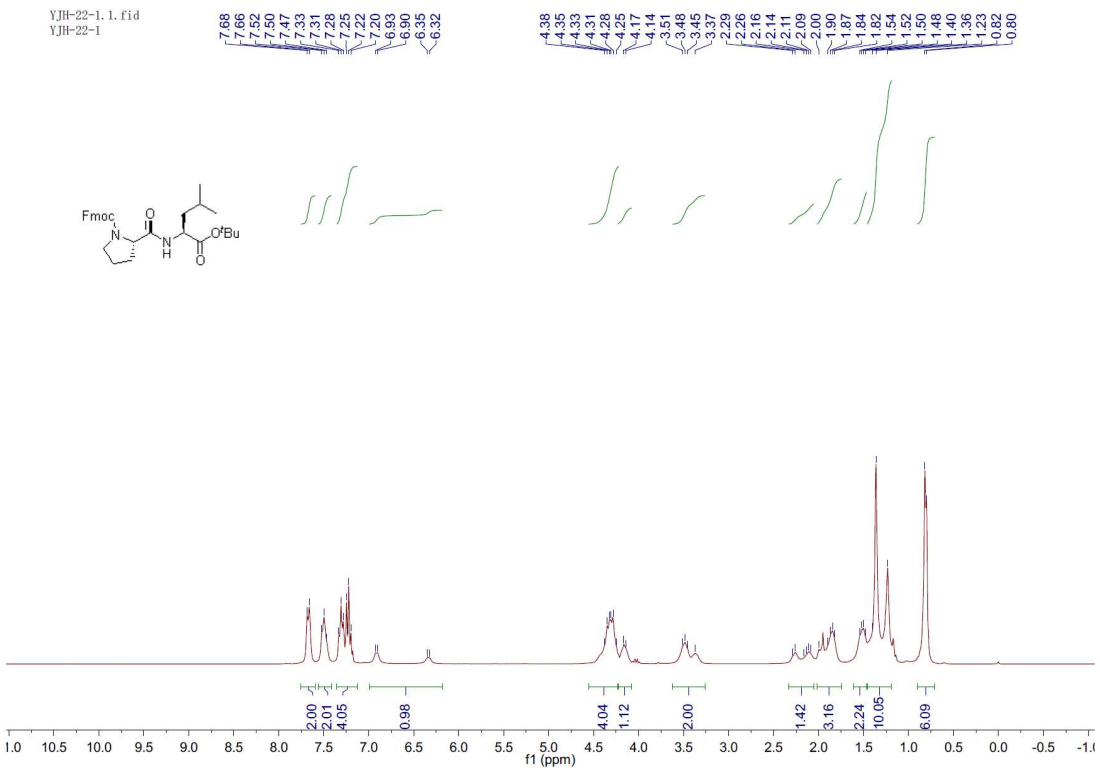


Figure S32. ^{1}H NMR of compound **7c** in $CDCl_3$, 300 MHz for ^{1}H NMR.

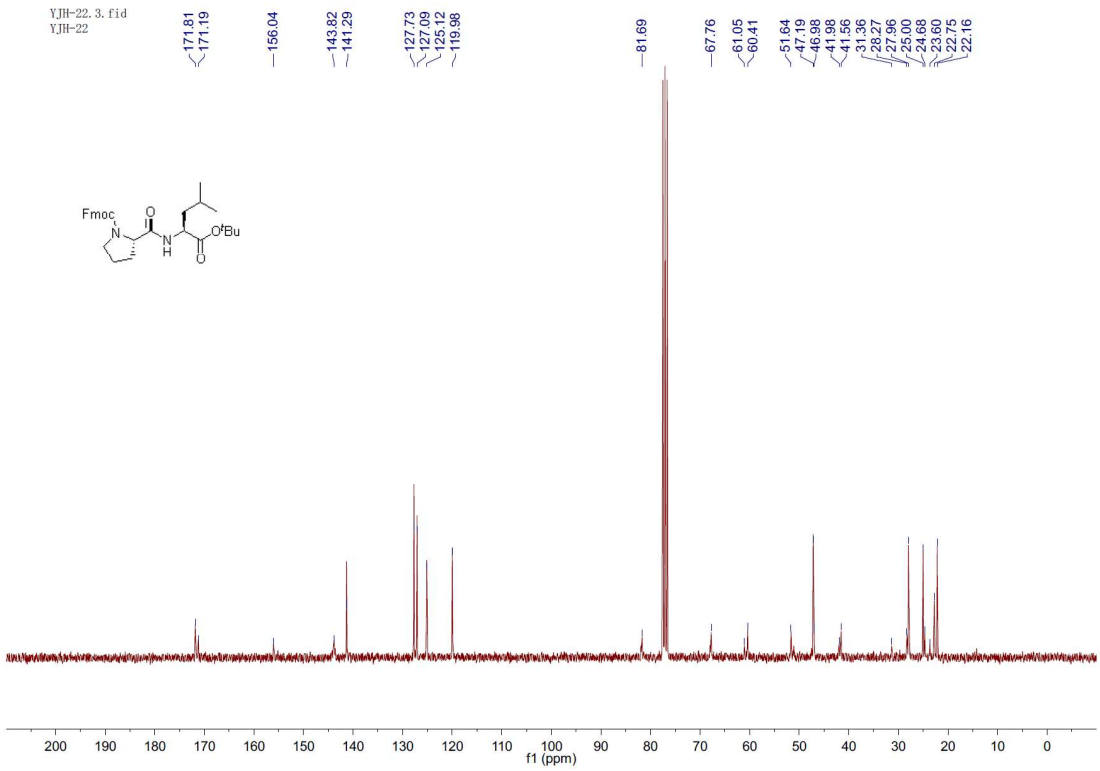


Figure S33. ^{13}C NMR of compound **7c** in $CDCl_3$, 75 MHz for ^{13}C NMR.

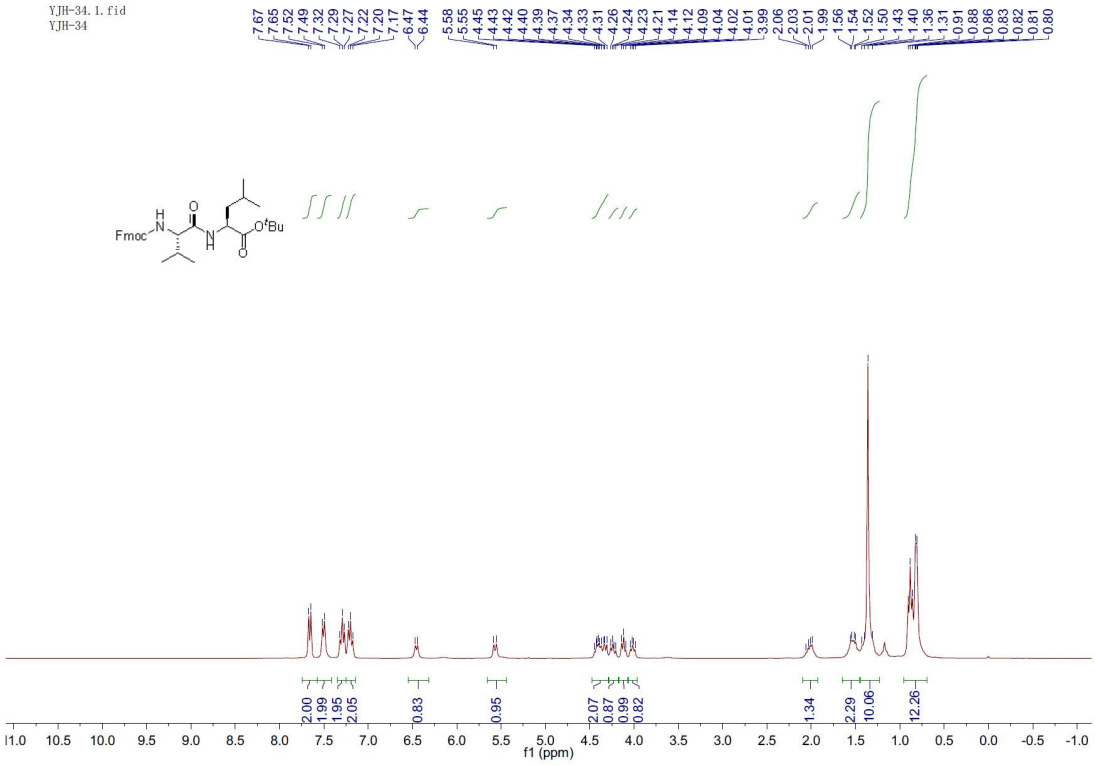


Figure S34. ^{1}H NMR of compound **7d** in $CDCl_3$, 300 MHz for ^{1}H NMR.

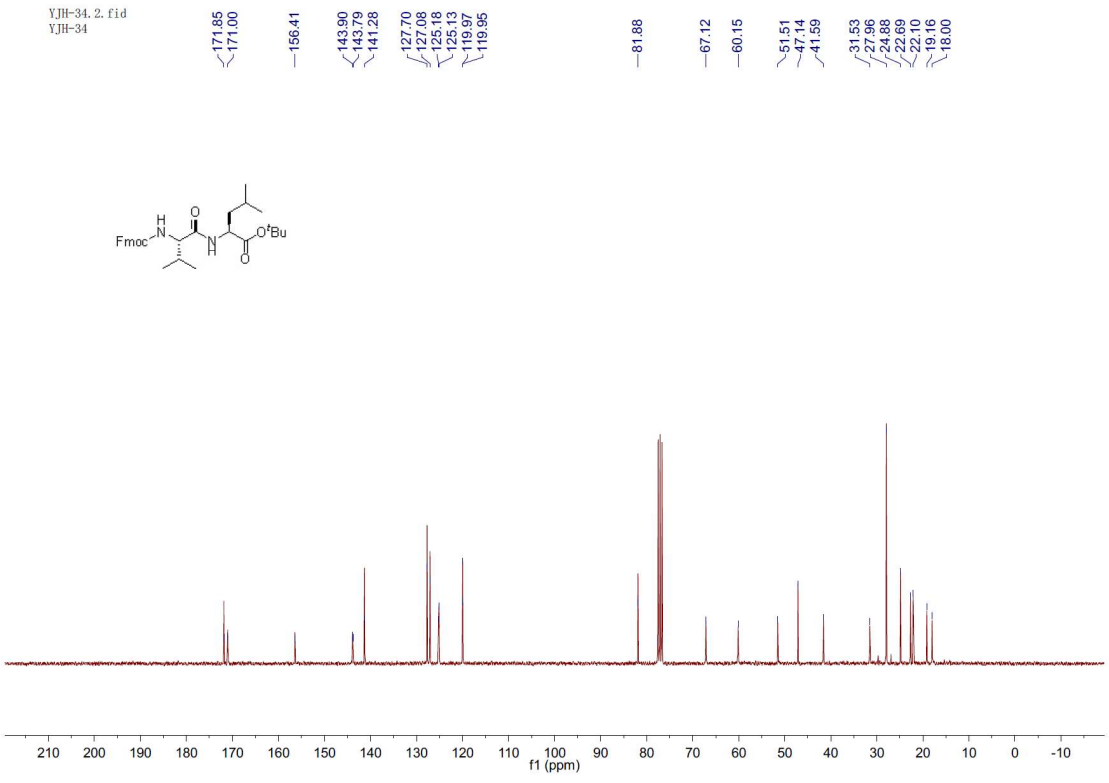


Figure S35. ^{13}C NMR of compound **7d** in $CDCl_3$, 75 MHz for ^{13}C NMR.

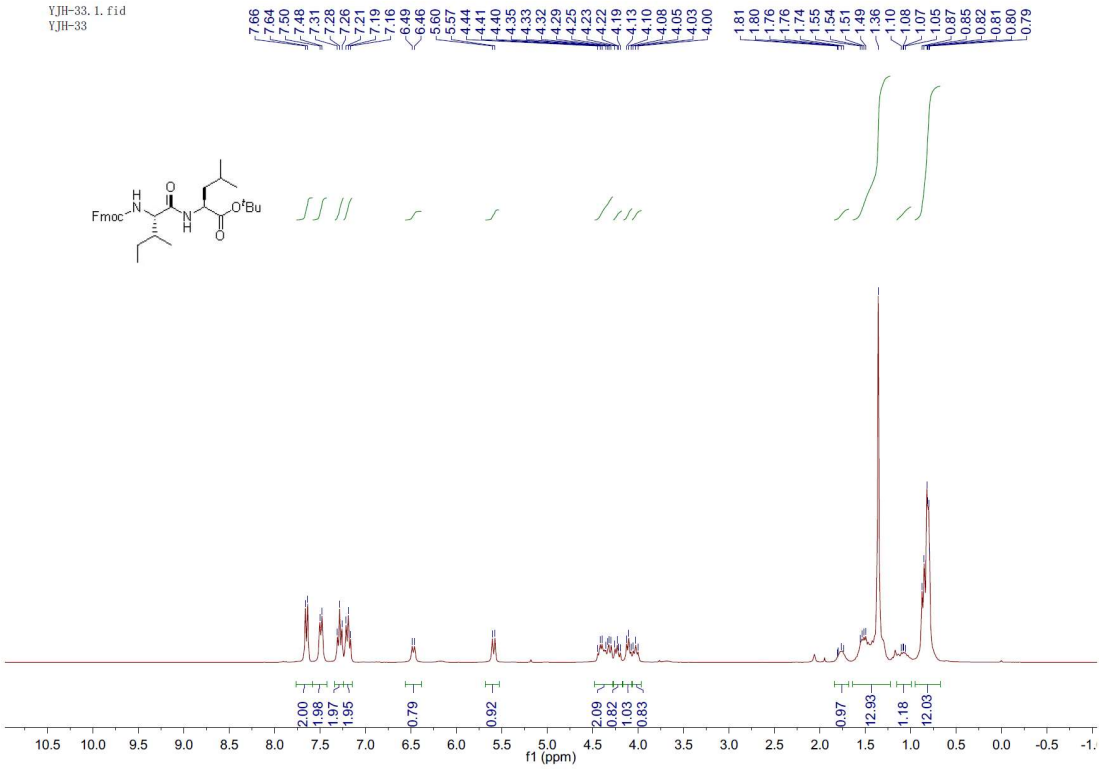


Figure S36. ^{1}H NMR of compound **7e** in $CDCl_3$, 300 MHz for ^{1}H NMR.

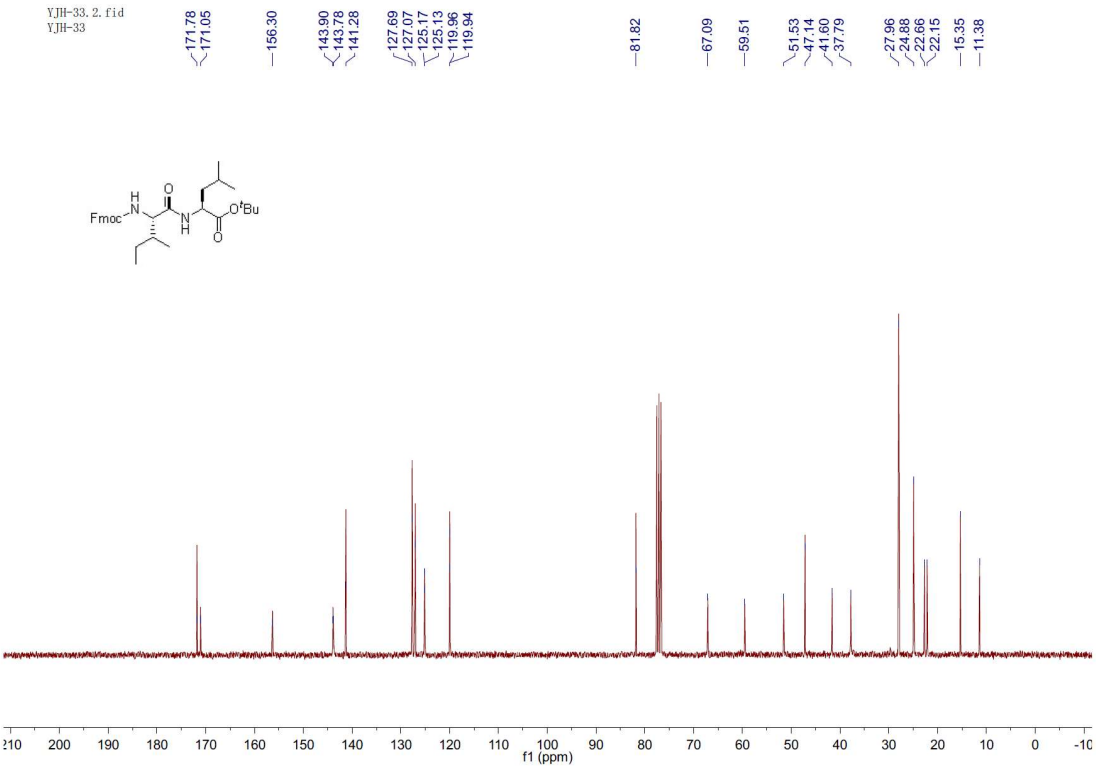


Figure S37. ^{13}C NMR of compound **7e** in $CDCl_3$, 75 MHz for ^{13}C NMR.

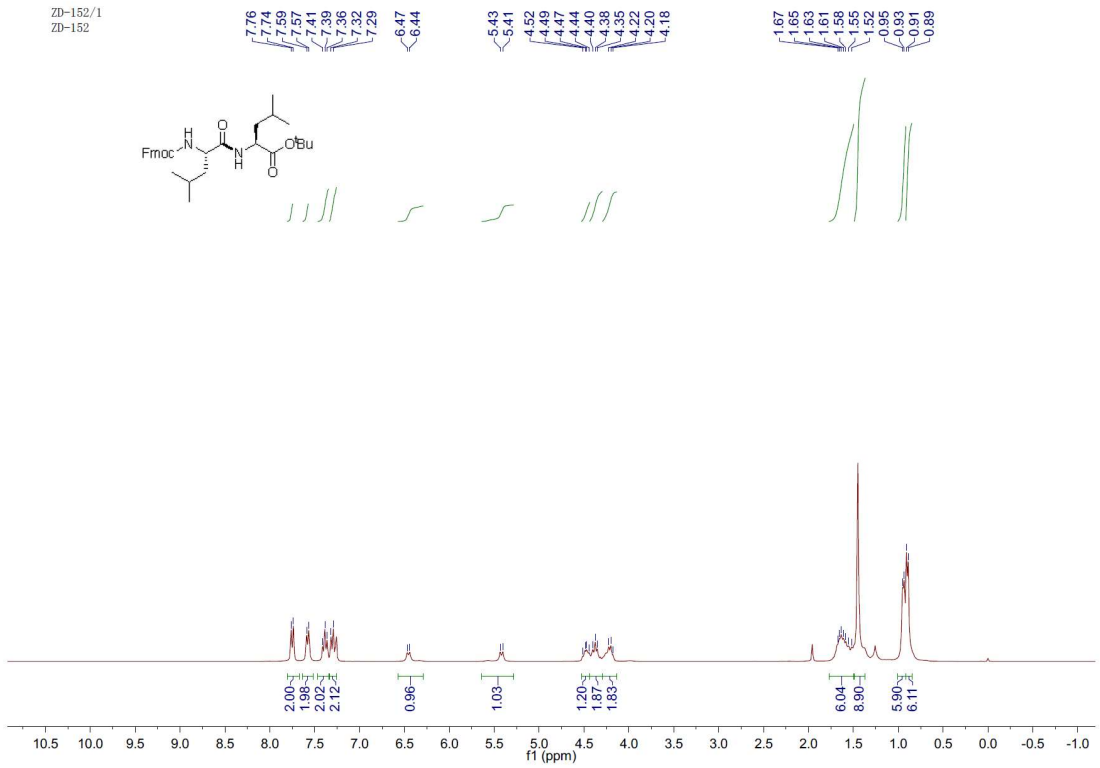


Figure S38. ^{1}H NMR of compound **7f** in $CDCl_3$, 300 MHz for ^{1}H NMR.

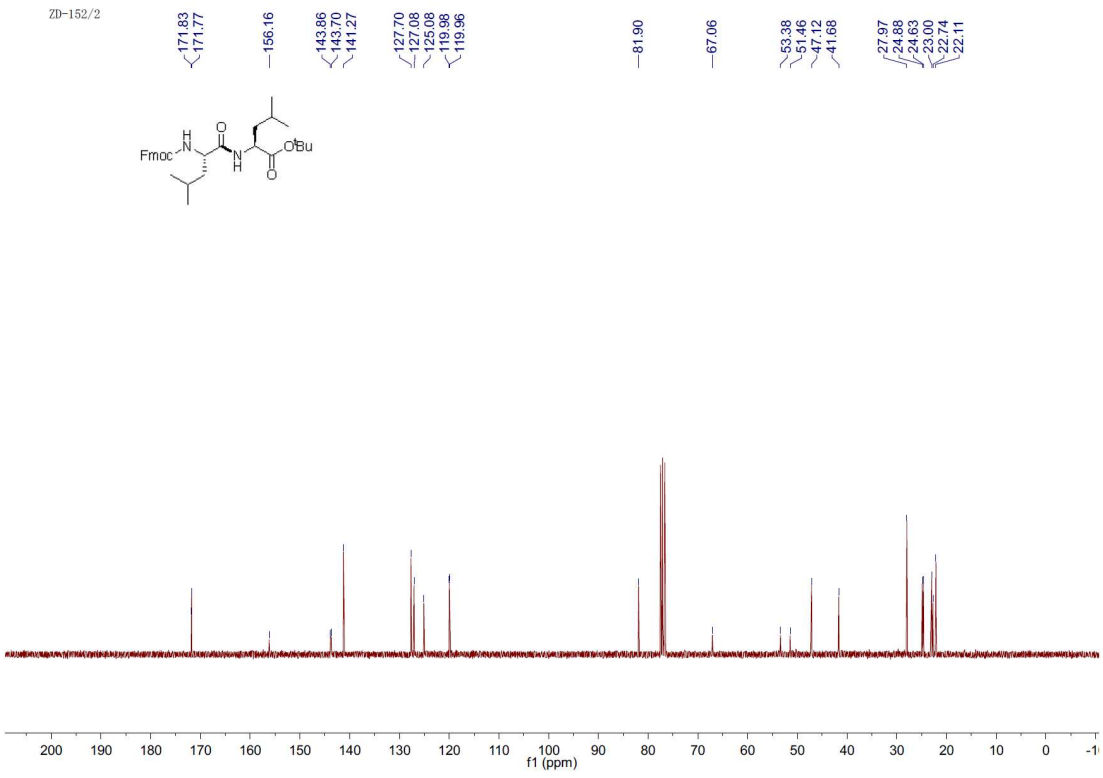


Figure S39. ^{13}C NMR of compound **7f** in $CDCl_3$, 75 MHz for ^{13}C NMR.

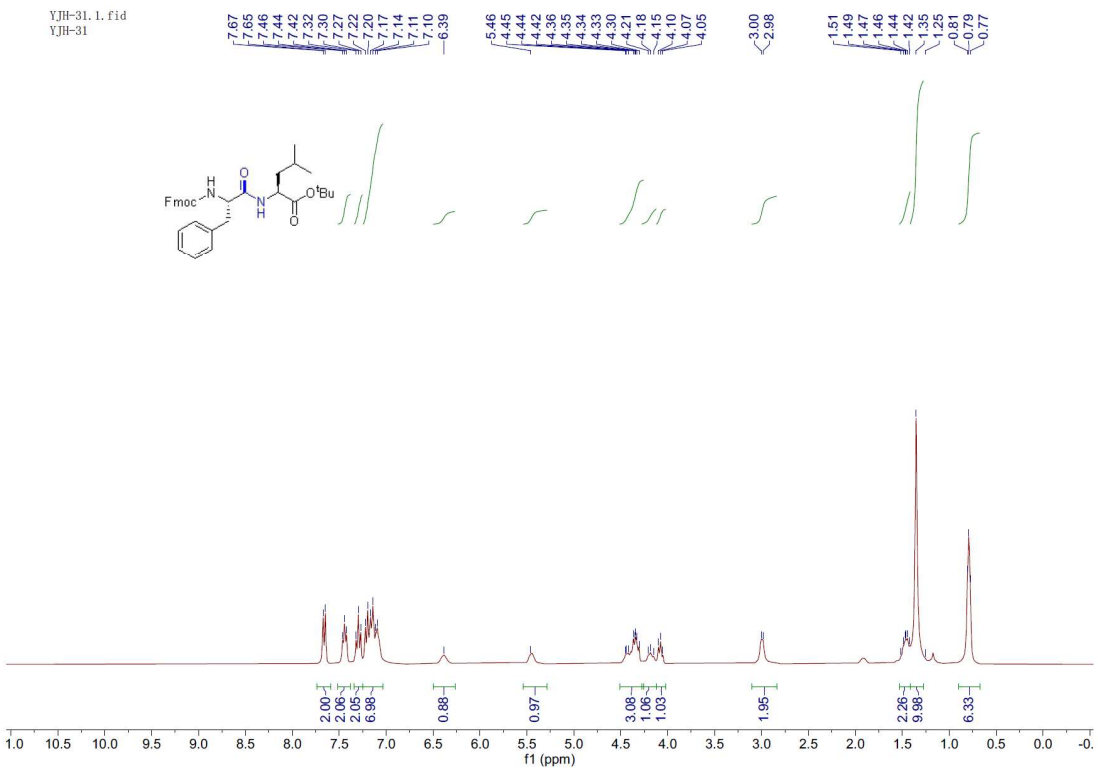


Figure S40. ^{1}H NMR of compound **7g** in $CDCl_3$, 300 MHz for ^{1}H NMR.

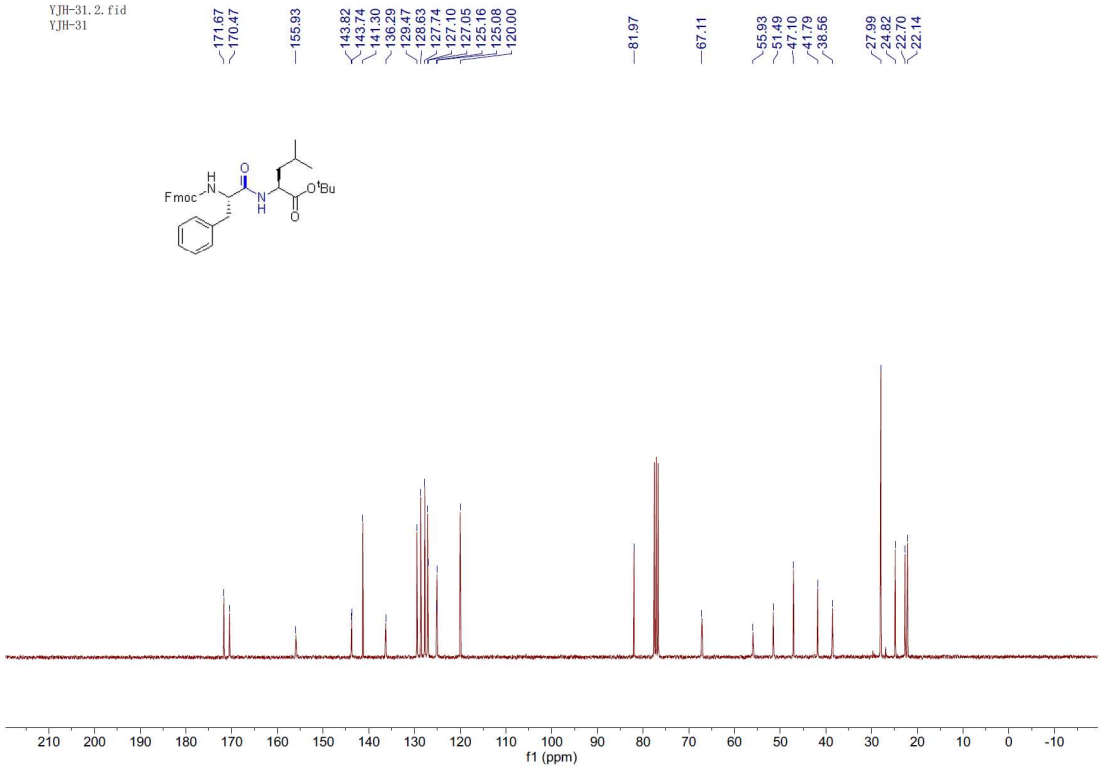


Figure S41. ^{13}C NMR of compound **7g** in $CDCl_3$, 75 MHz for ^{13}C NMR.

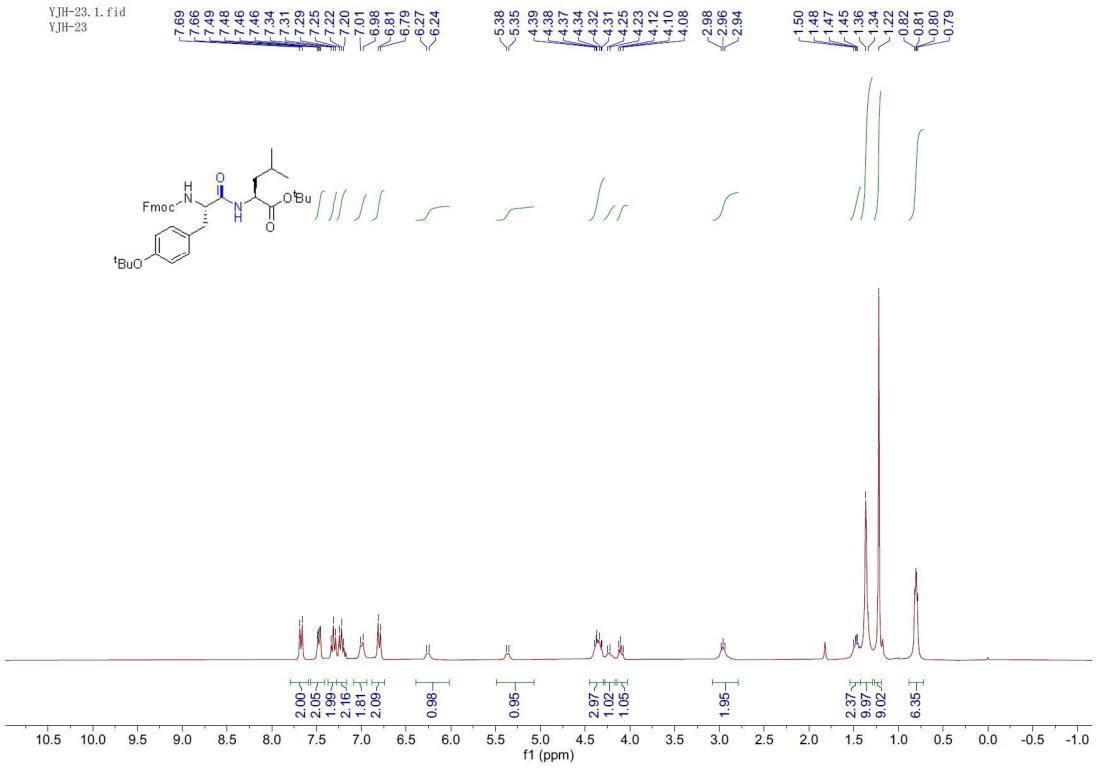


Figure S42. ^{1}H NMR of compound **7h** in $CDCl_3$, 300 MHz for ^{1}H NMR.

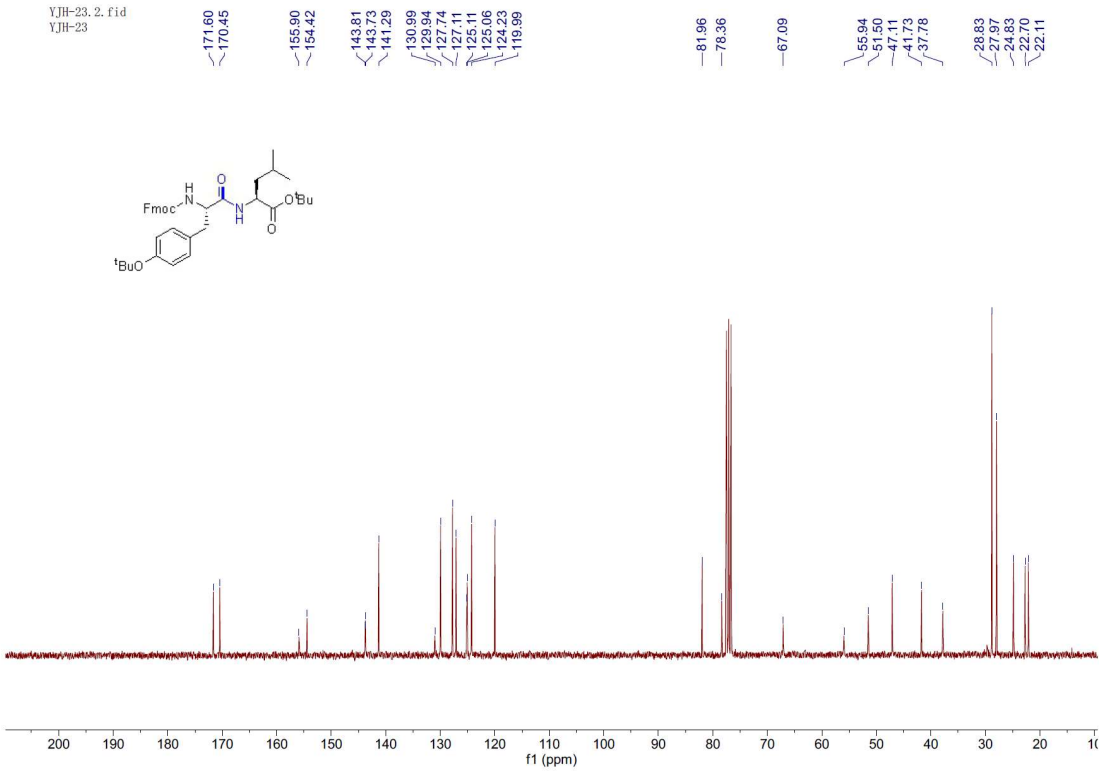


Figure S43. ^{13}C NMR of compound **7h** in $CDCl_3$, 75 MHz for ^{13}C NMR.

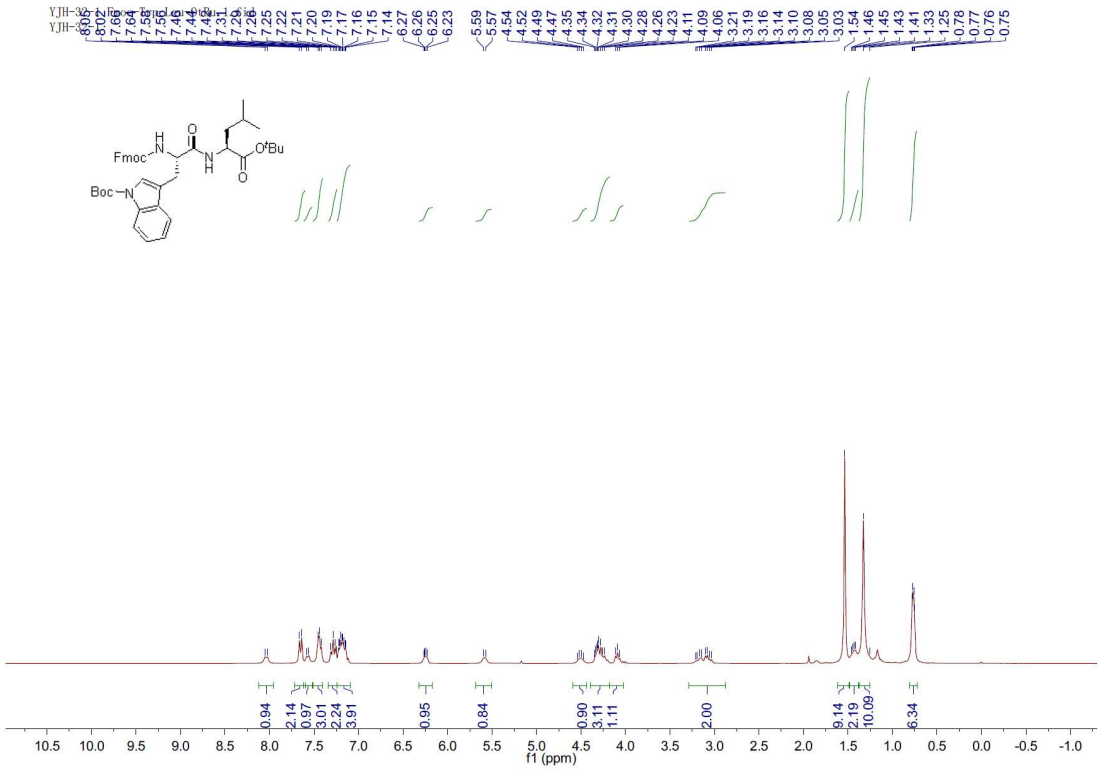


Figure S44. ^{1}H NMR of compound **7i** in $CDCl_3$, 300 MHz for ^{1}H NMR.

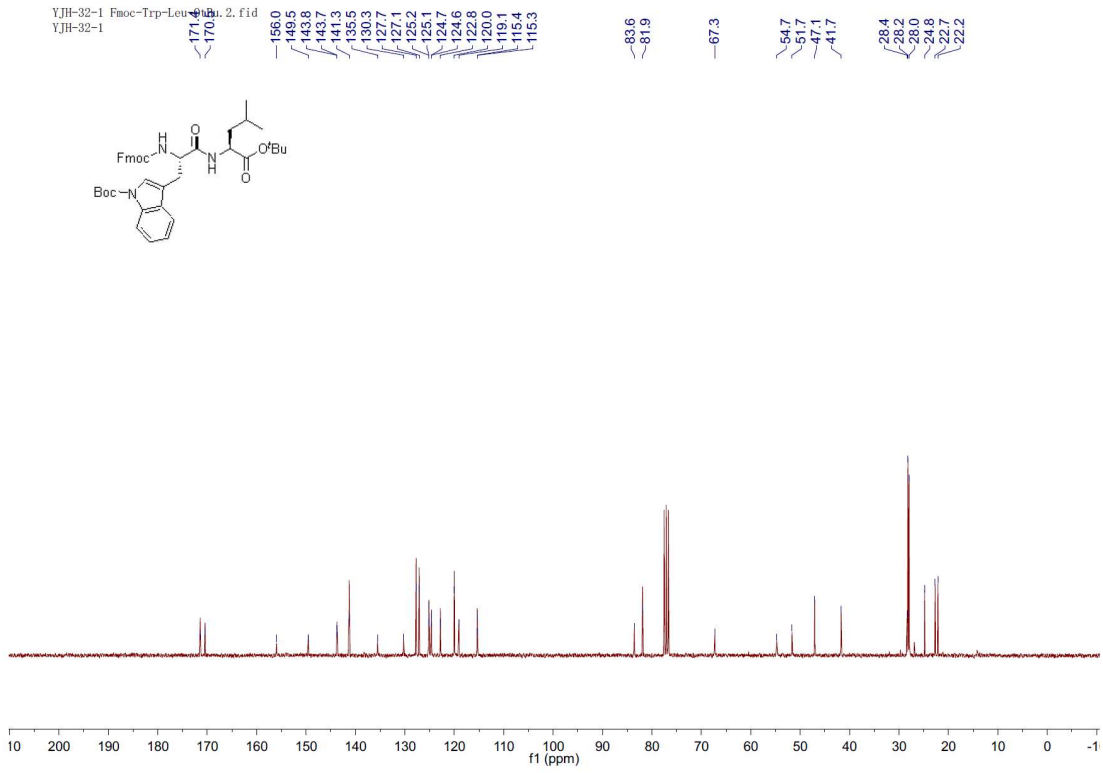


Figure S45. ^{13}C NMR of compound **7i** in $CDCl_3$, 75 MHz for ^{13}C NMR.

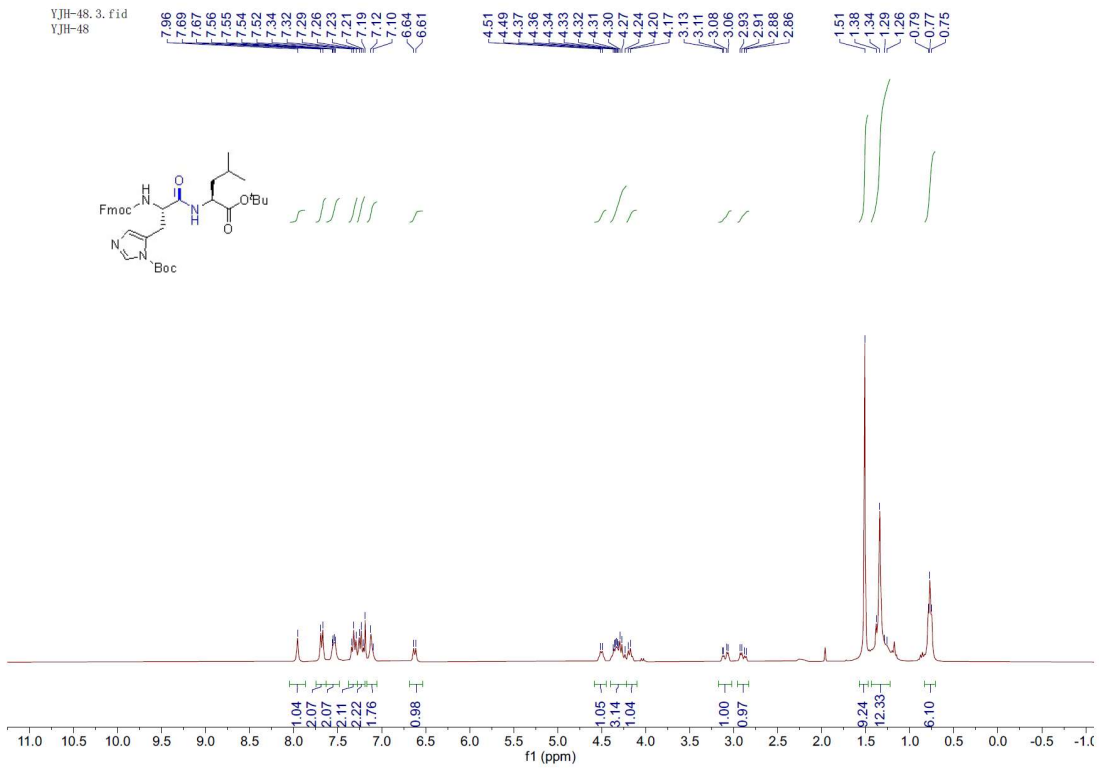


Figure S46. ^{1}H NMR of compound **7j** in $CDCl_3$, 300 MHz for ^{1}H NMR.

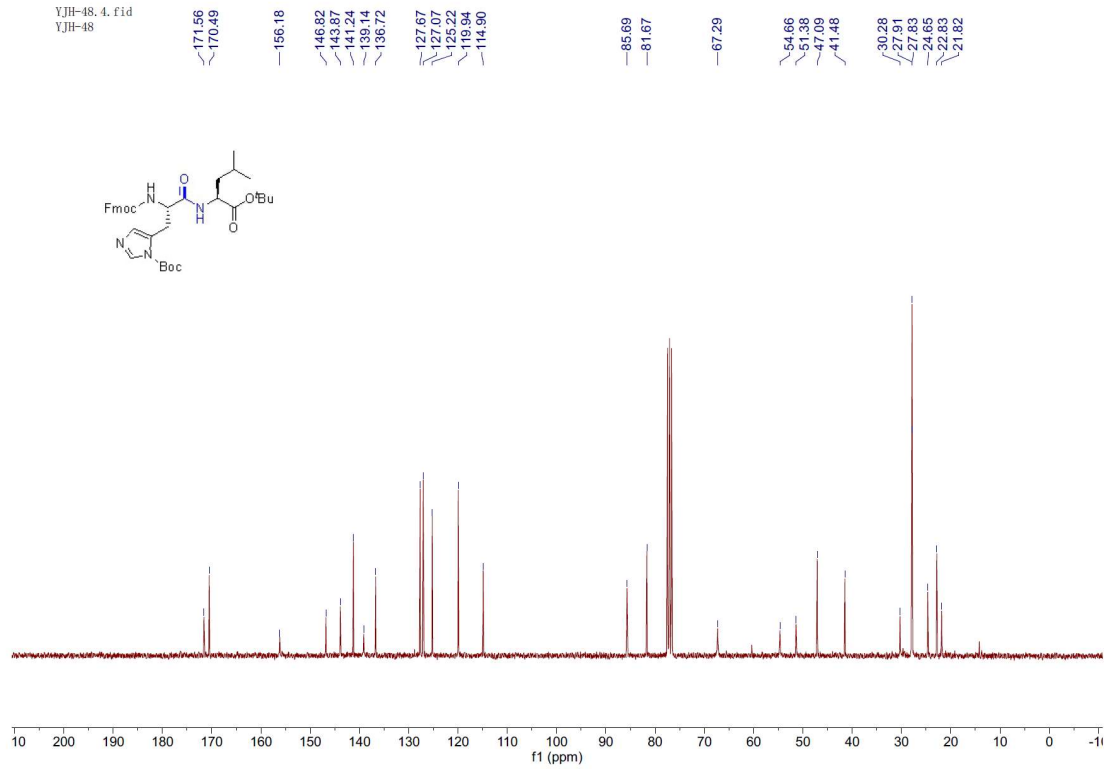


Figure S47. ^{13}C NMR of compound **7j** in $CDCl_3$, 75 MHz for ^{13}C NMR.

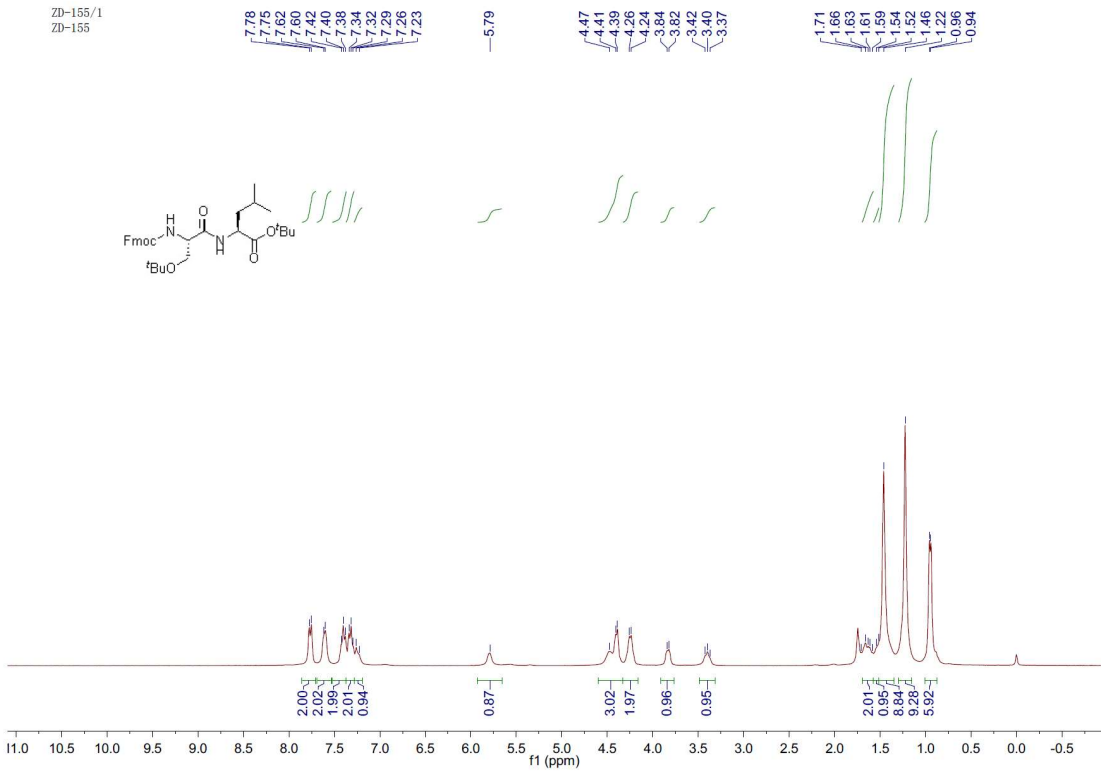


Figure S48. ^{1}H NMR of compound **7k** in $CDCl_3$, 300 MHz for ^{1}H NMR.

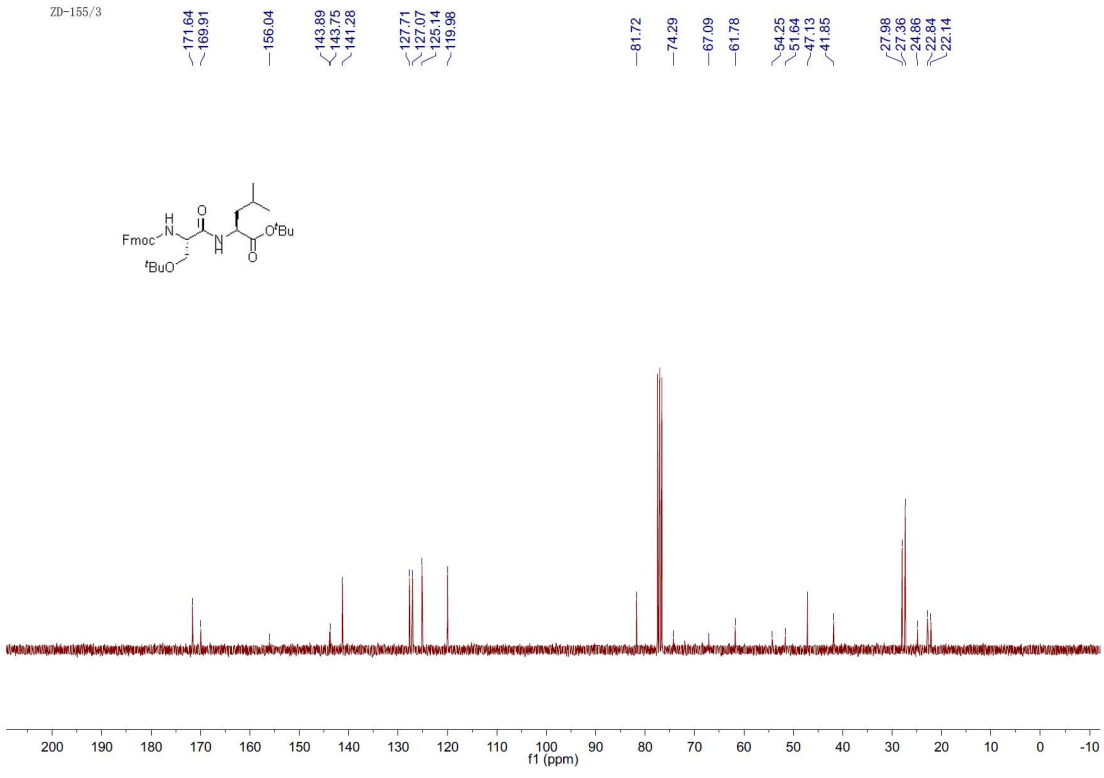


Figure S49. ^{13}C NMR of compound **7k** in $CDCl_3$, 75 MHz for ^{13}C NMR.

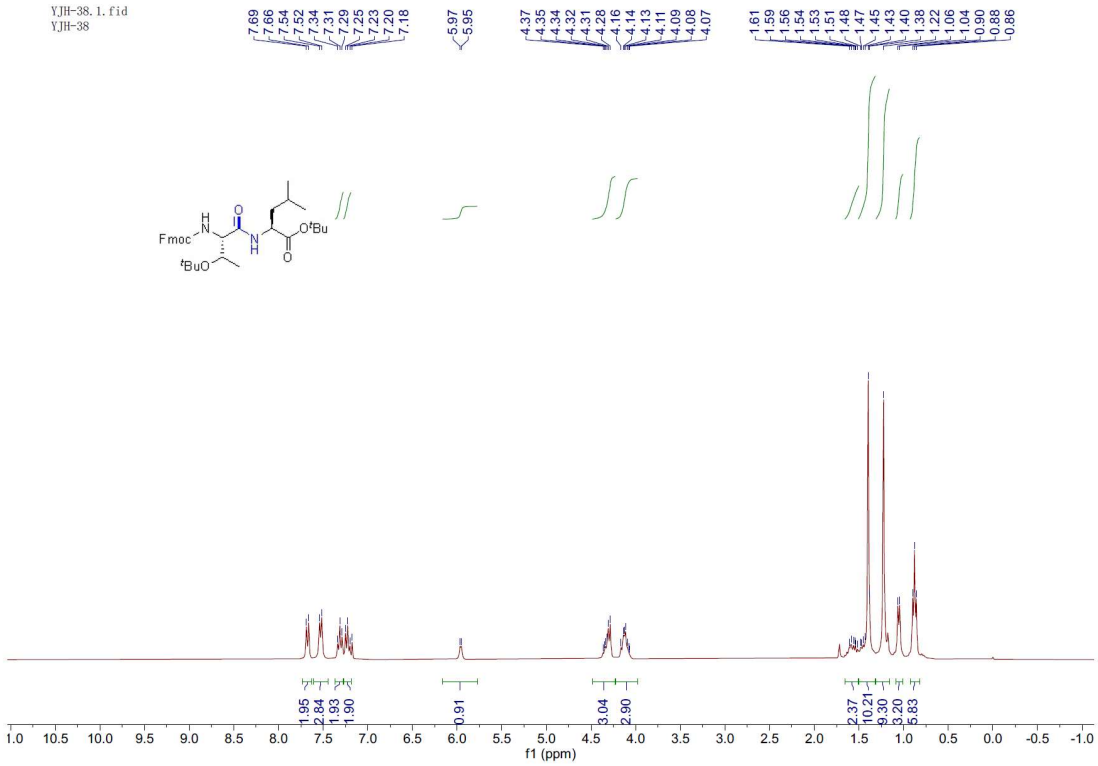


Figure S50. ^{1}H NMR of compound **7l** in $CDCl_3$, 300 MHz for ^{1}H NMR.

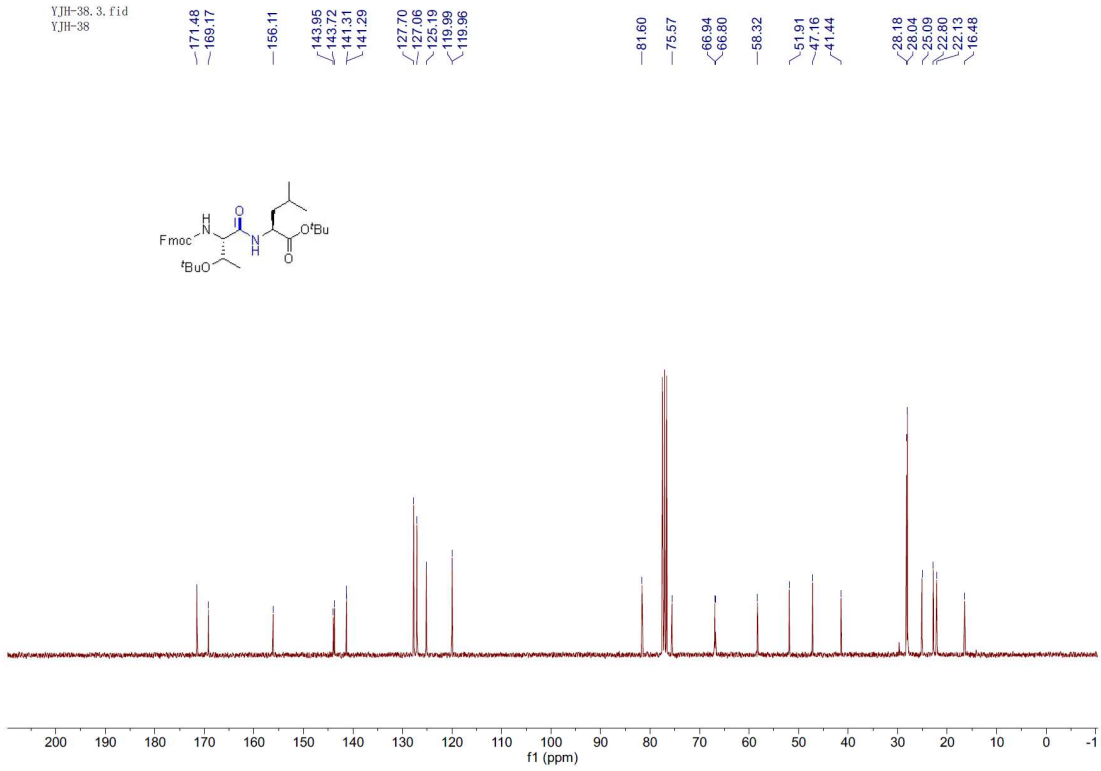


Figure S51. ^{13}C NMR of compound **7l** in $CDCl_3$, 75 MHz for ^{13}C NMR.

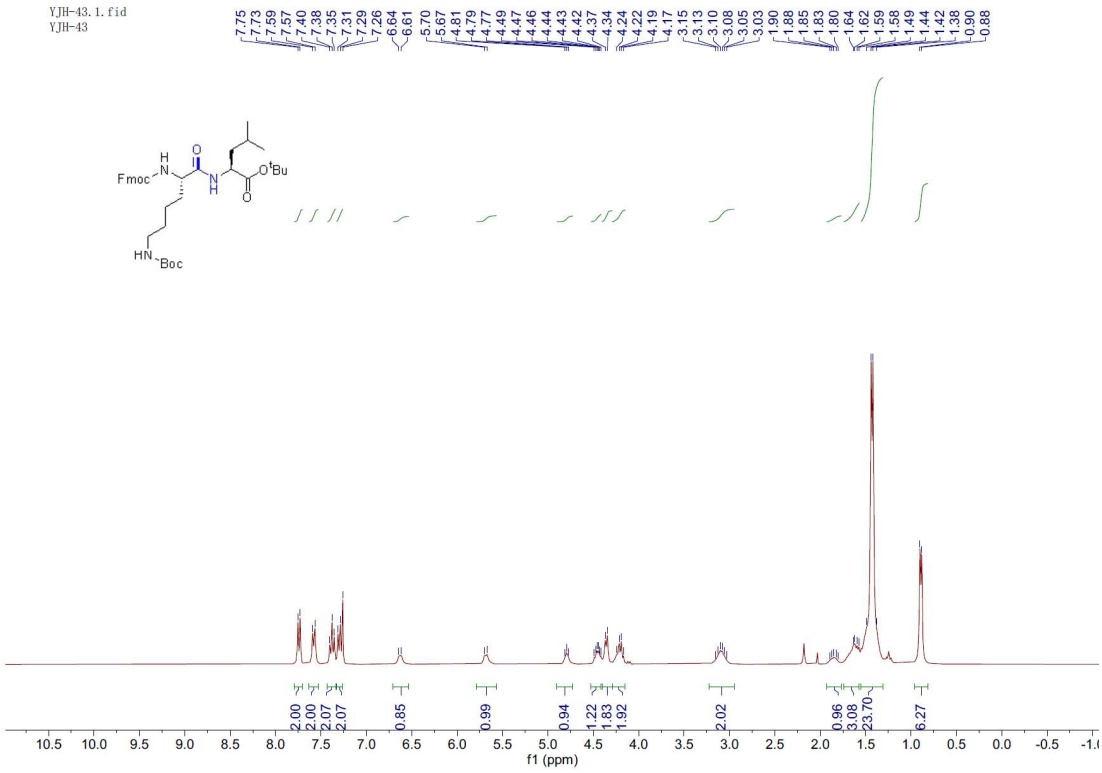


Figure S52. ^{1}H NMR of compound **7m** in $CDCl_3$, 300 MHz for ^{1}H NMR.

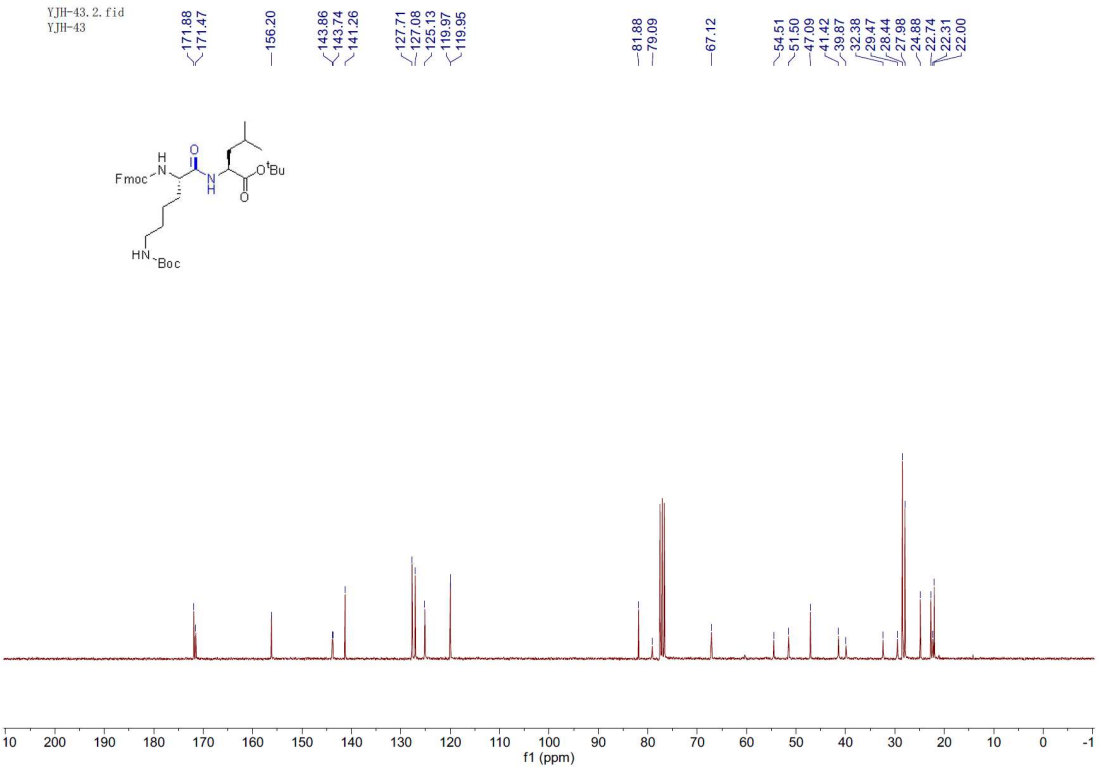


Figure S53. ^{13}C NMR of compound **7m** in $CDCl_3$, 75 MHz for ^{13}C NMR.

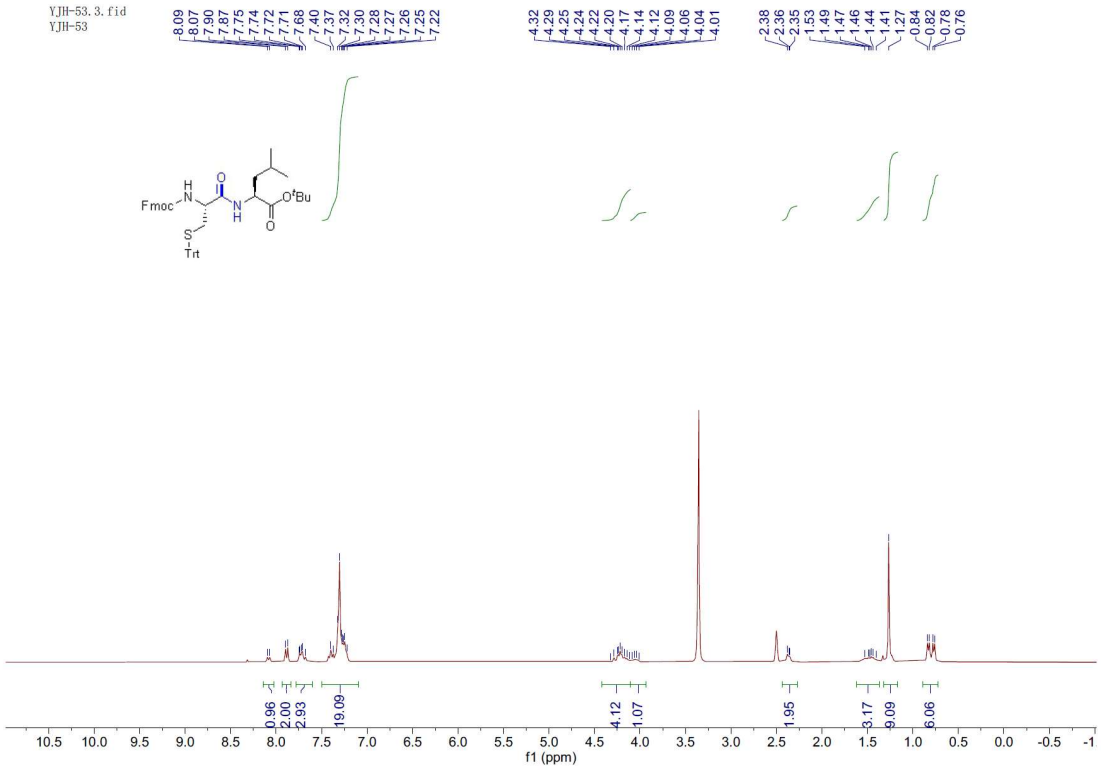


Figure S54. ^{1}H NMR of compound **7n** in $CDCl_3$, 300 MHz for ^{1}H NMR.

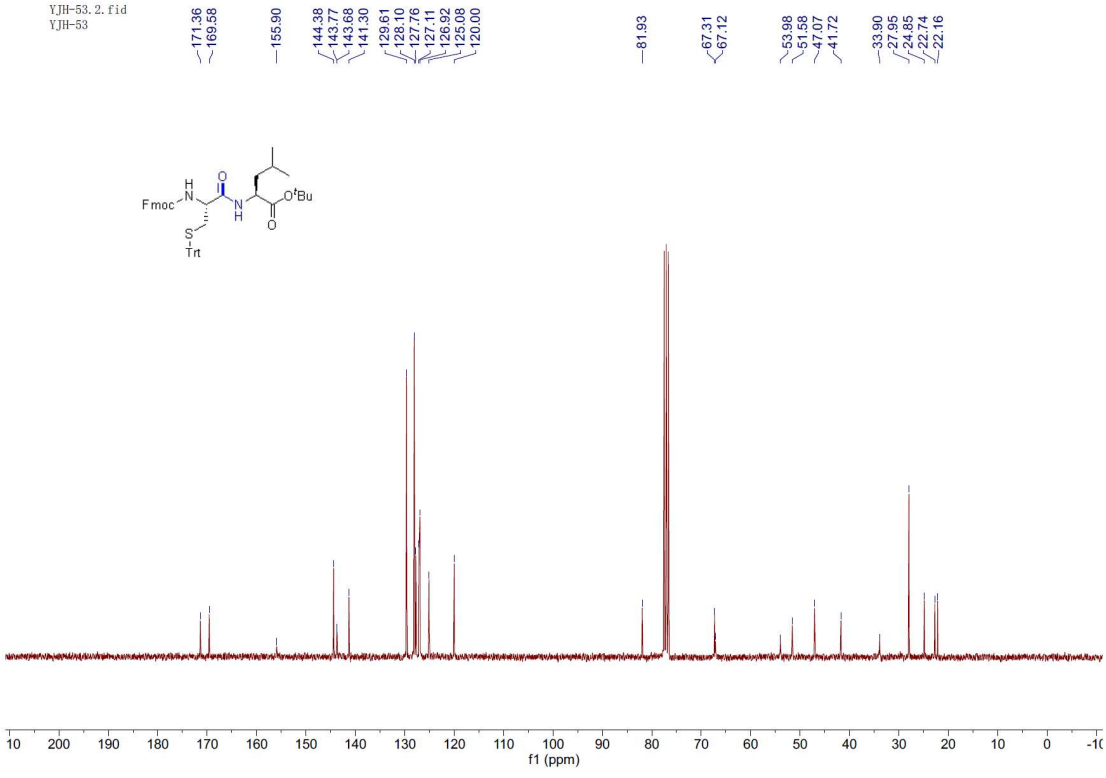


Figure S55 ^{13}C NMR of compound **7n** in $CDCl_3$, 75 MHz for ^{13}C NMR.

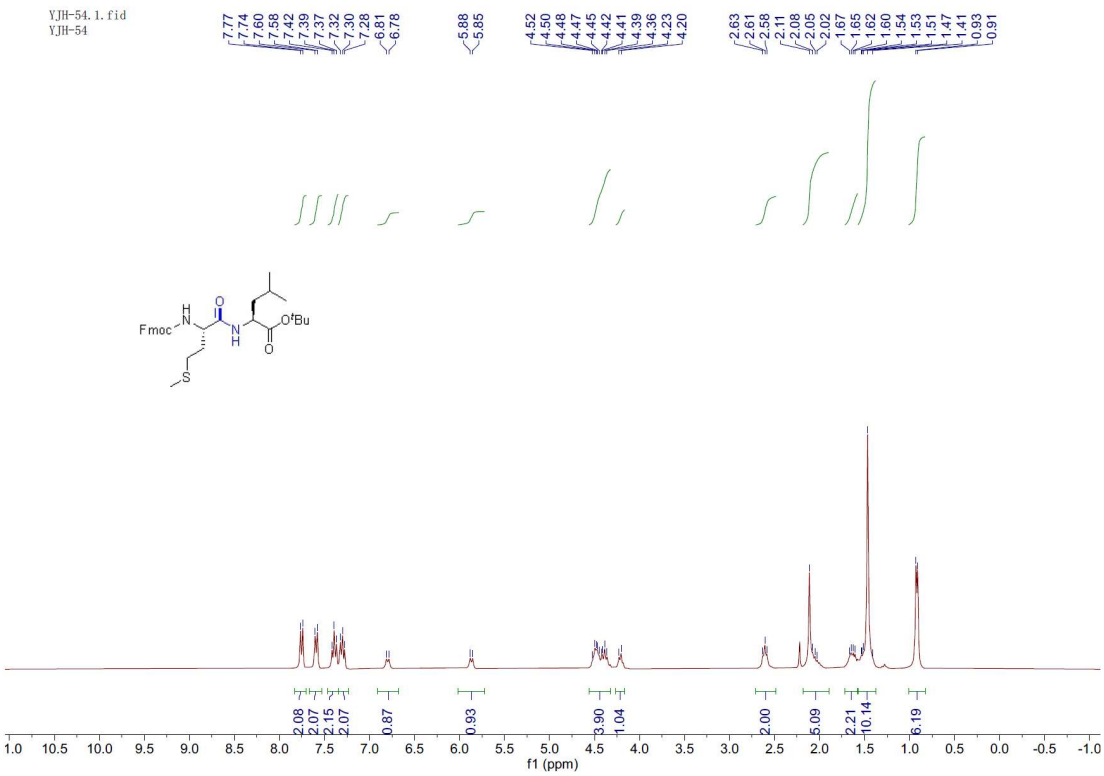


Figure S56. ^{1}H NMR of compound **7o** in $CDCl_3$, 300 MHz for ^{1}H NMR.

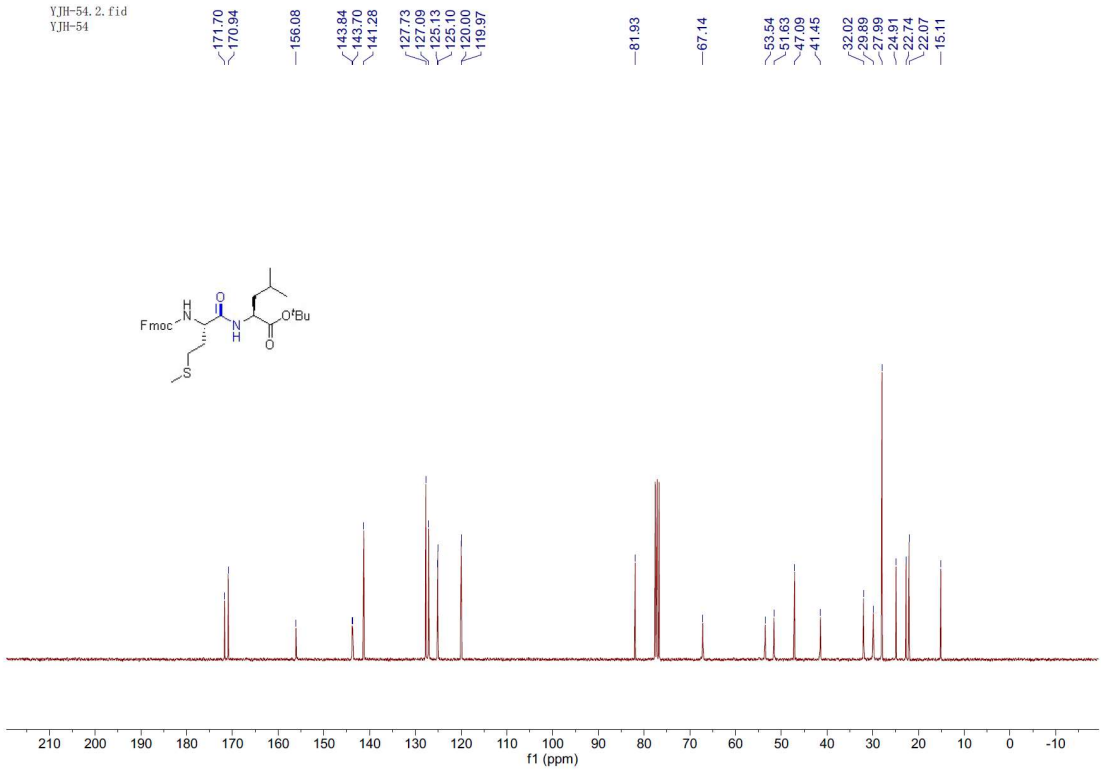


Figure S57. ^{13}C NMR of compound **7o** in $CDCl_3$, 75 MHz for ^{13}C NMR.

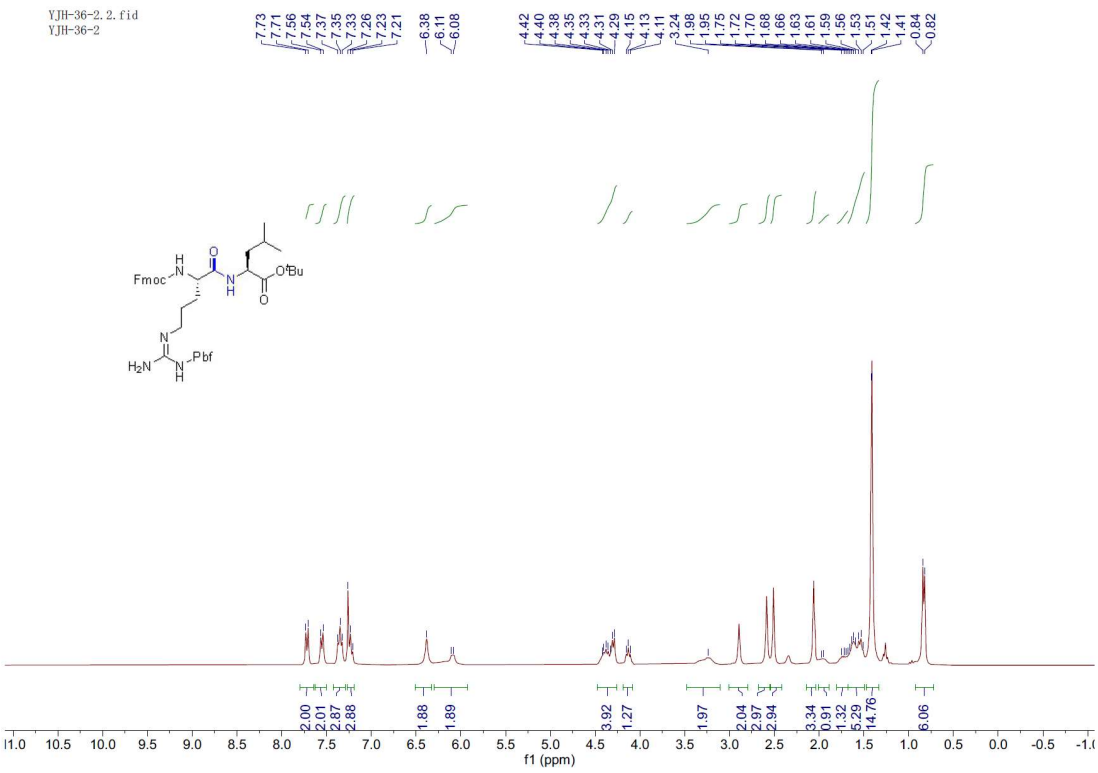


Figure S58. ^{1}H NMR of compound **7p** in $CDCl_3$, 300 MHz for ^{1}H NMR.

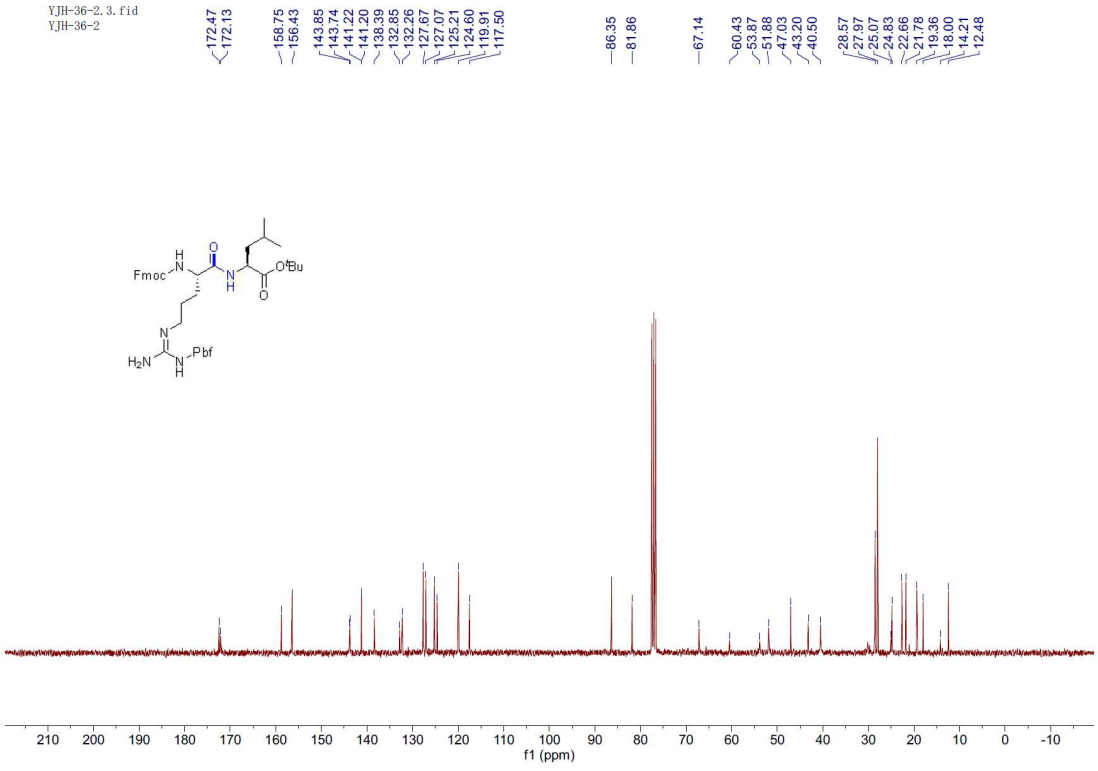


Figure S59. ^{13}C NMR of compound **7p** in $CDCl_3$, 75 MHz for ^{13}C NMR.

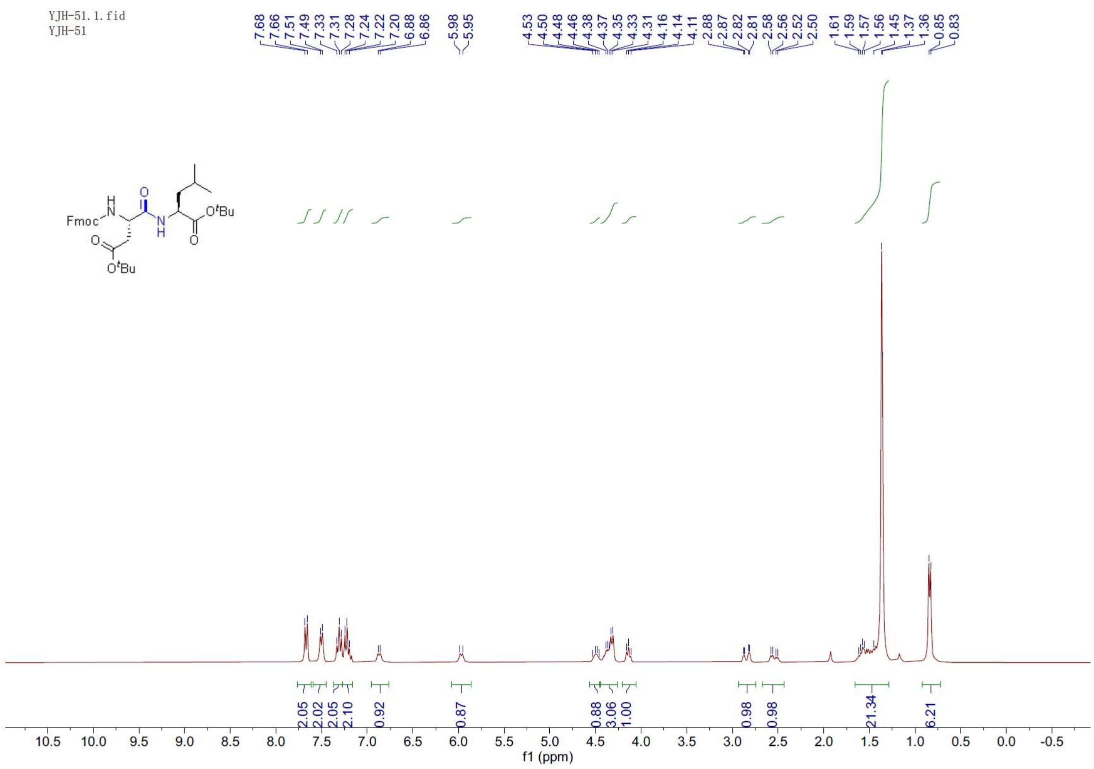


Figure S60. ^{1}H NMR of compound **7q** in $CDCl_3$, 300 MHz for ^{1}H NMR.

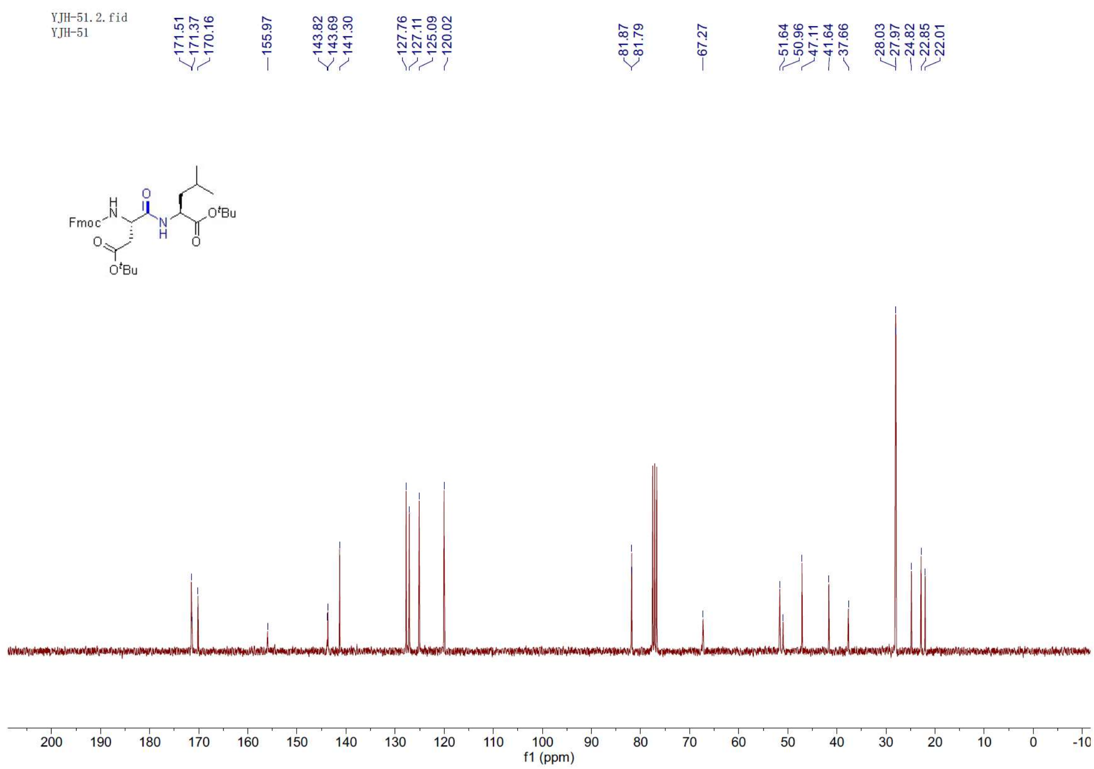


Figure S61. ^{13}C NMR of compound **7q** in $CDCl_3$, 75 MHz for ^{13}C NMR.

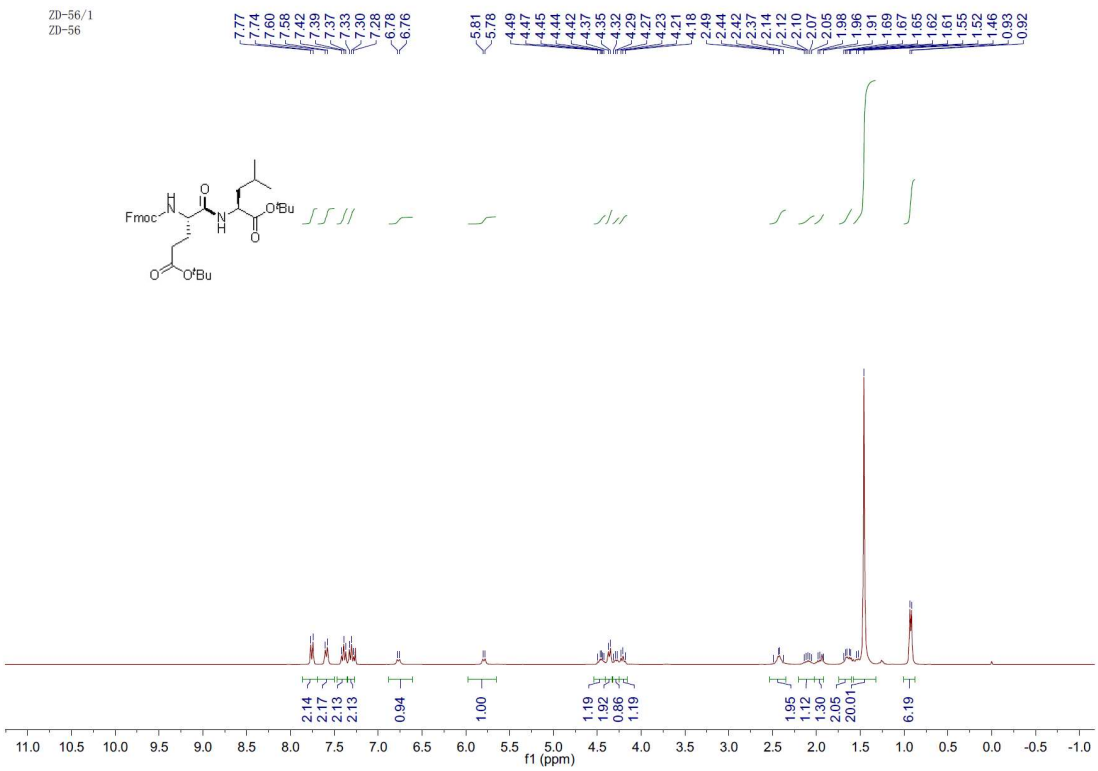


Figure S62. ^{1}H NMR of compound **7r** in $CDCl_3$, 300 MHz for ^{1}H NMR.

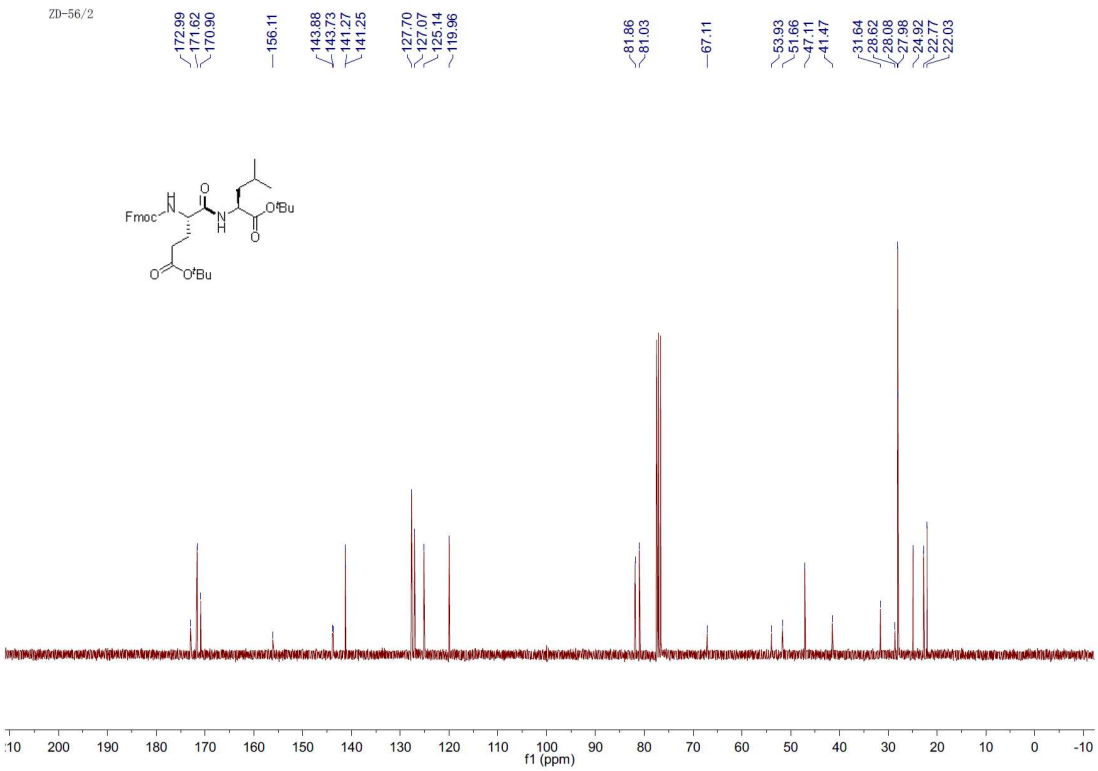


Figure S63. ^{13}C NMR of compound **7r** in $CDCl_3$, 75 MHz for ^{13}C NMR.

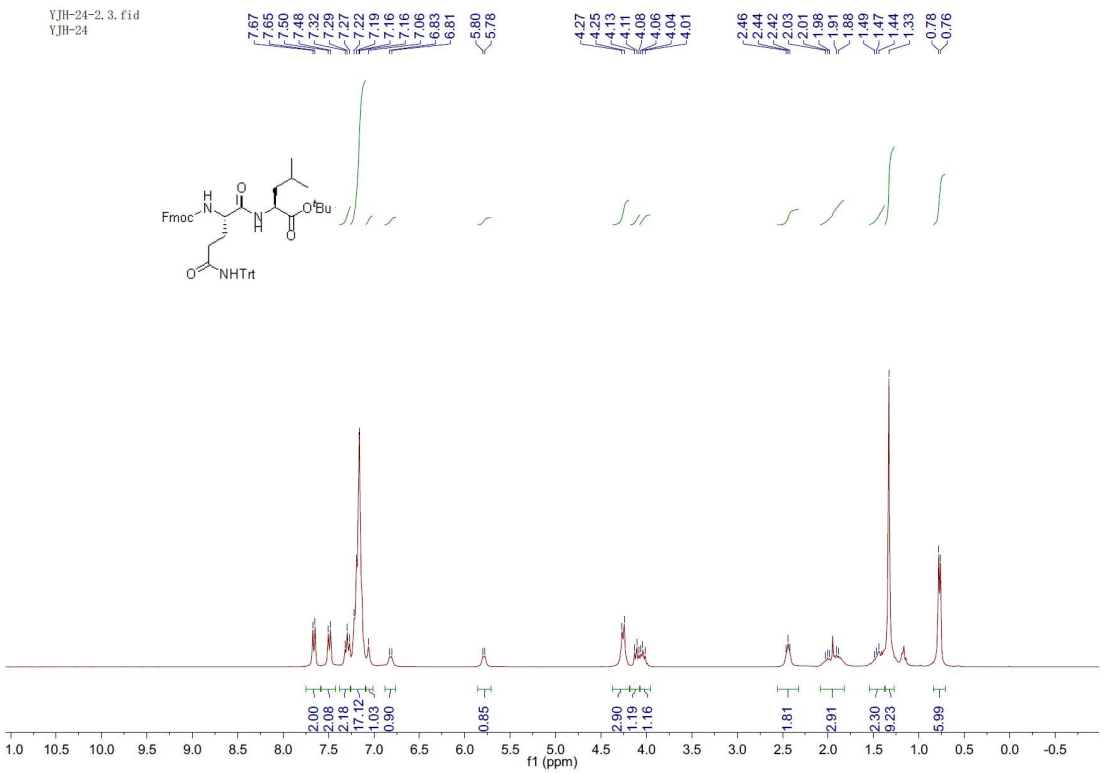


Figure S64. ^{1}H NMR of compound **7s** in $CDCl_3$, 300 MHz for ^{1}H NMR.

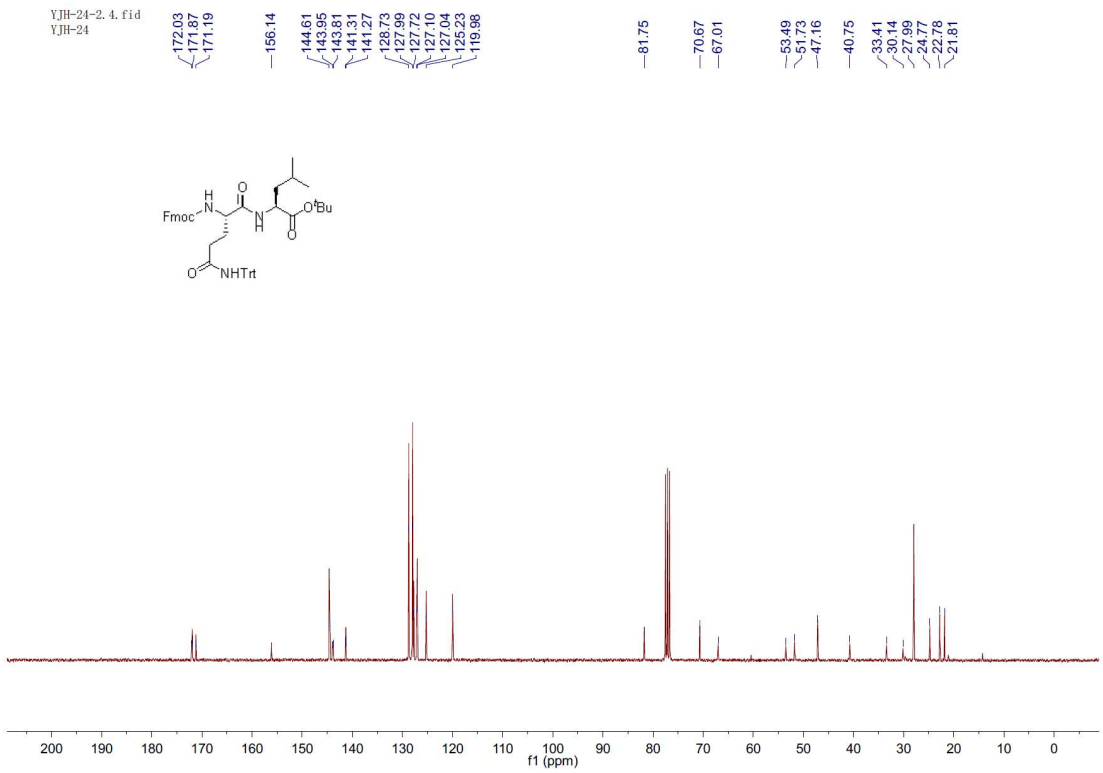


Figure S65. ^{13}C NMR of compound **7s** in $CDCl_3$, 75 MHz for ^{13}C NMR.

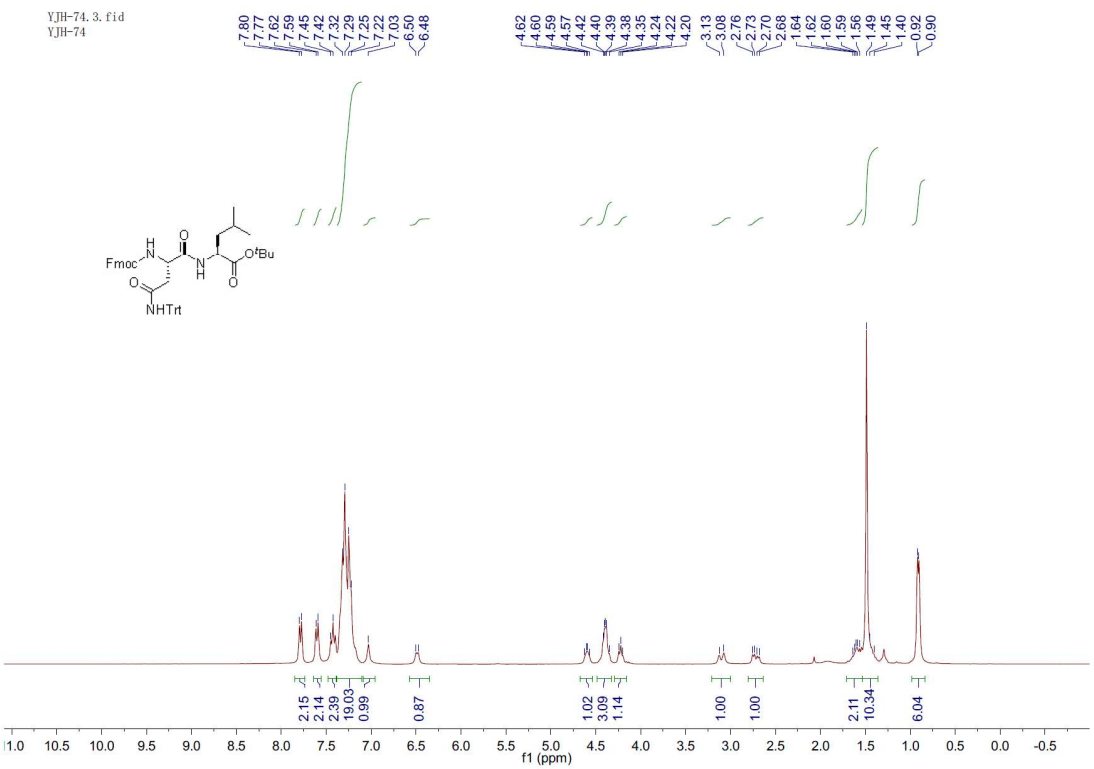


Figure S66. ^{1}H NMR of compound **7t** in $CDCl_3$, 300 MHz for ^{1}H NMR.

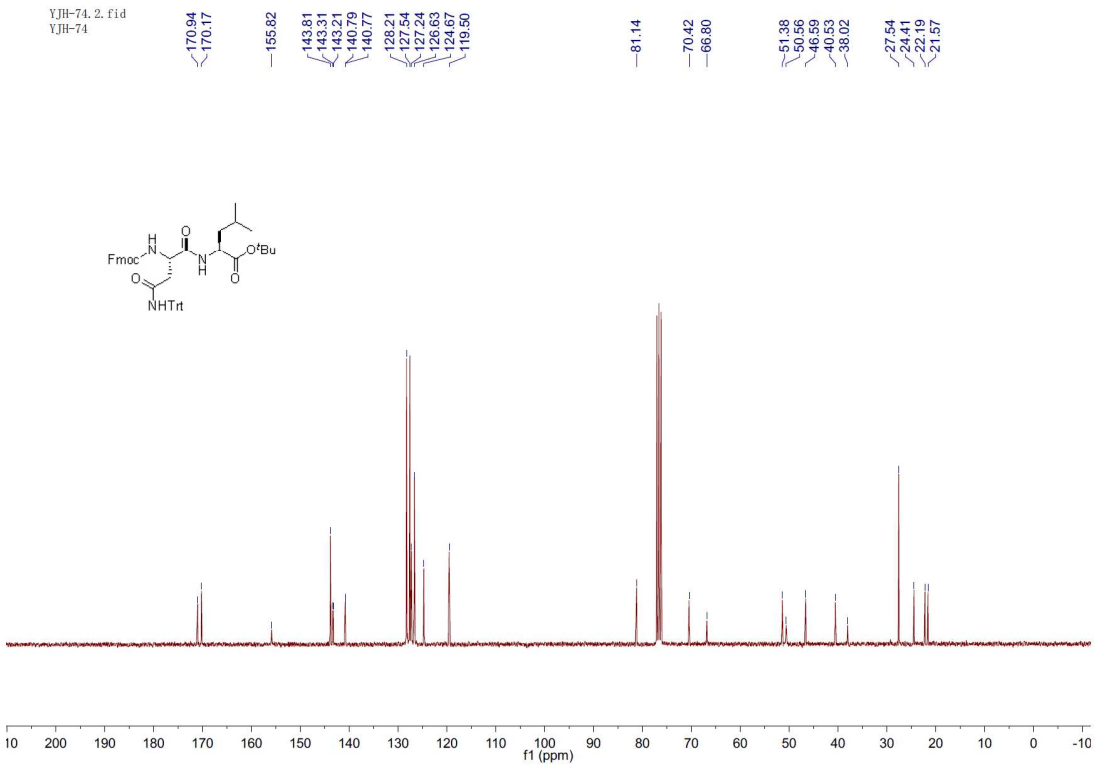


Figure S67. ^{13}C NMR of compound **7t** in $CDCl_3$, 75 MHz for ^{13}C NMR.

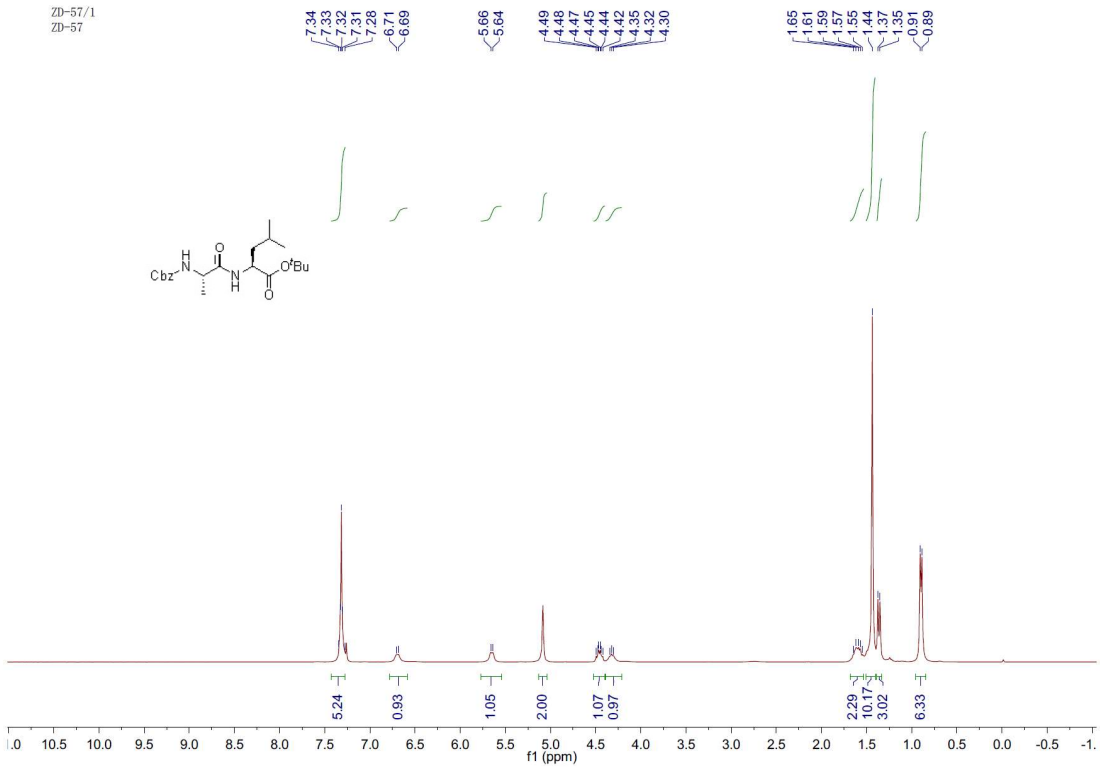


Figure S68. ^{1}H NMR of compound **7u** in $CDCl_3$, 300 MHz for ^{1}H NMR.

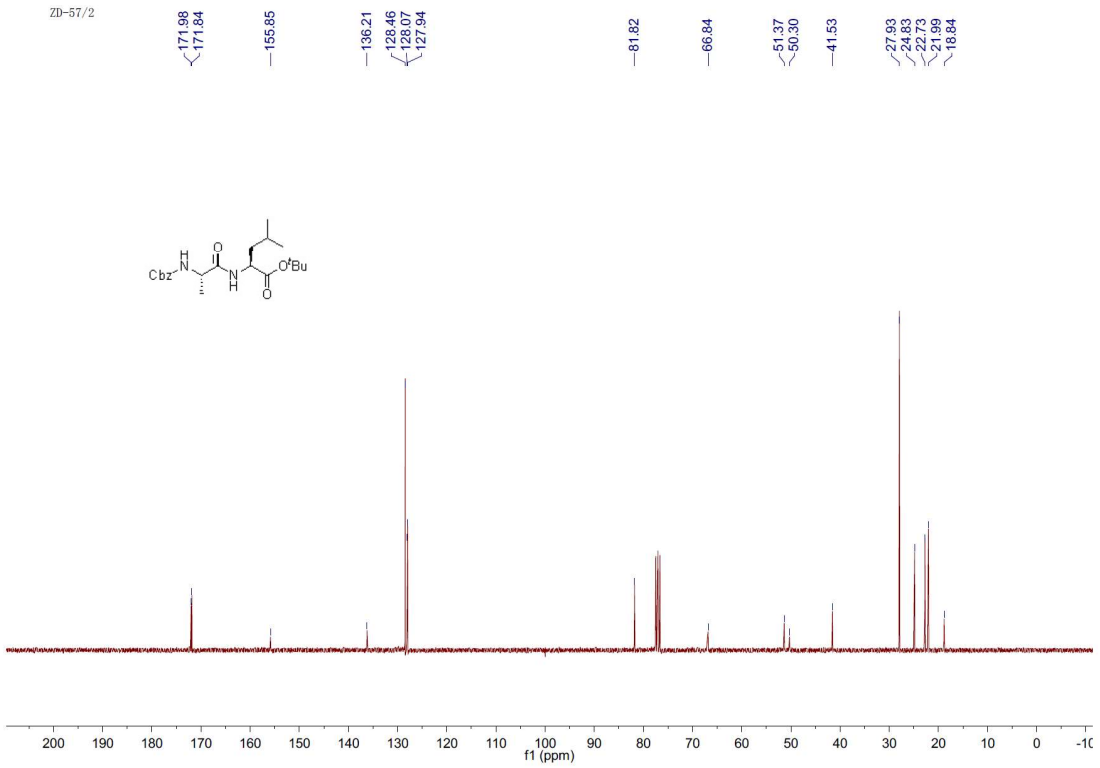


Figure S69. ^{13}C NMR of compound **7u** in $CDCl_3$, 75 MHz for ^{13}C NMR.

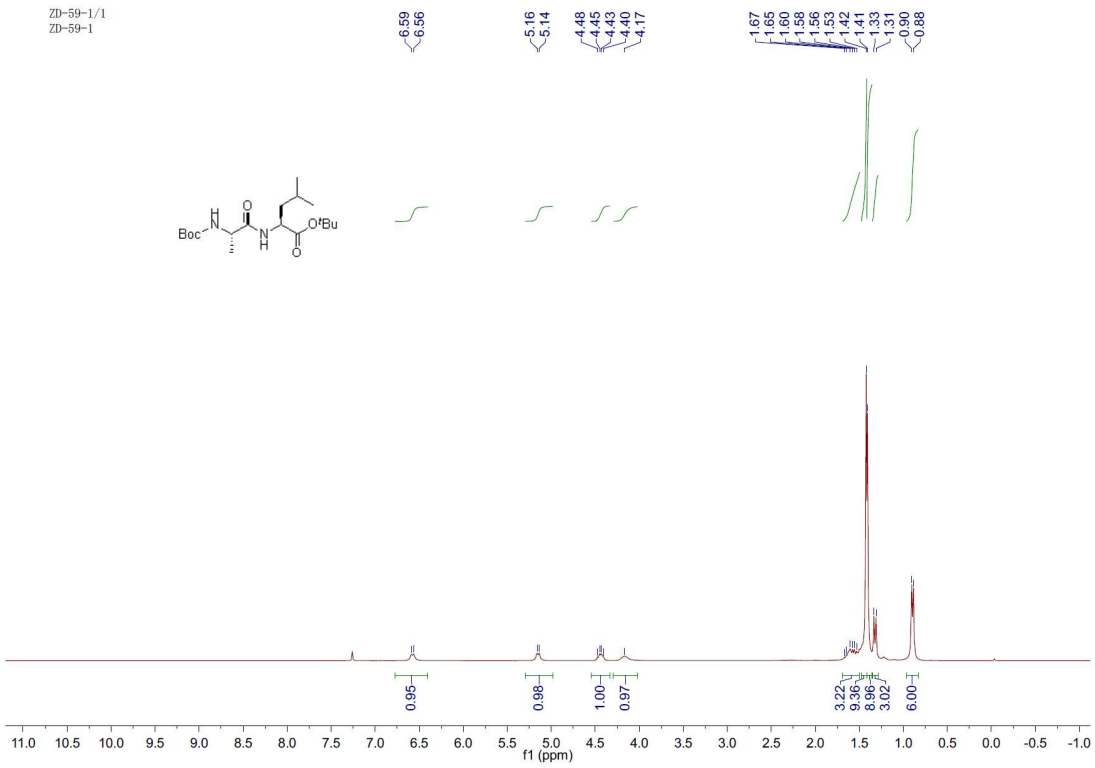


Figure S70. ^{1}H NMR of compound **7v** in $CDCl_3$, 300 MHz for ^{1}H NMR.

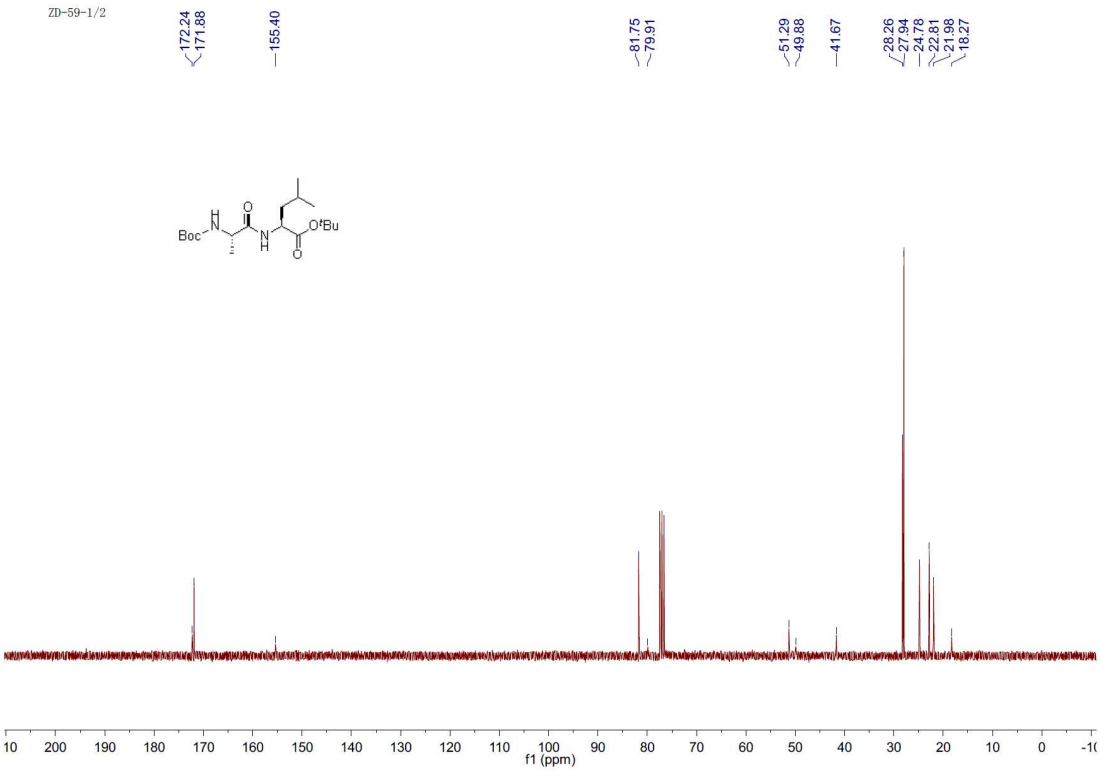


Figure S71. ^{13}C NMR of compound **7v** in $CDCl_3$, 75 MHz for ^{13}C NMR.

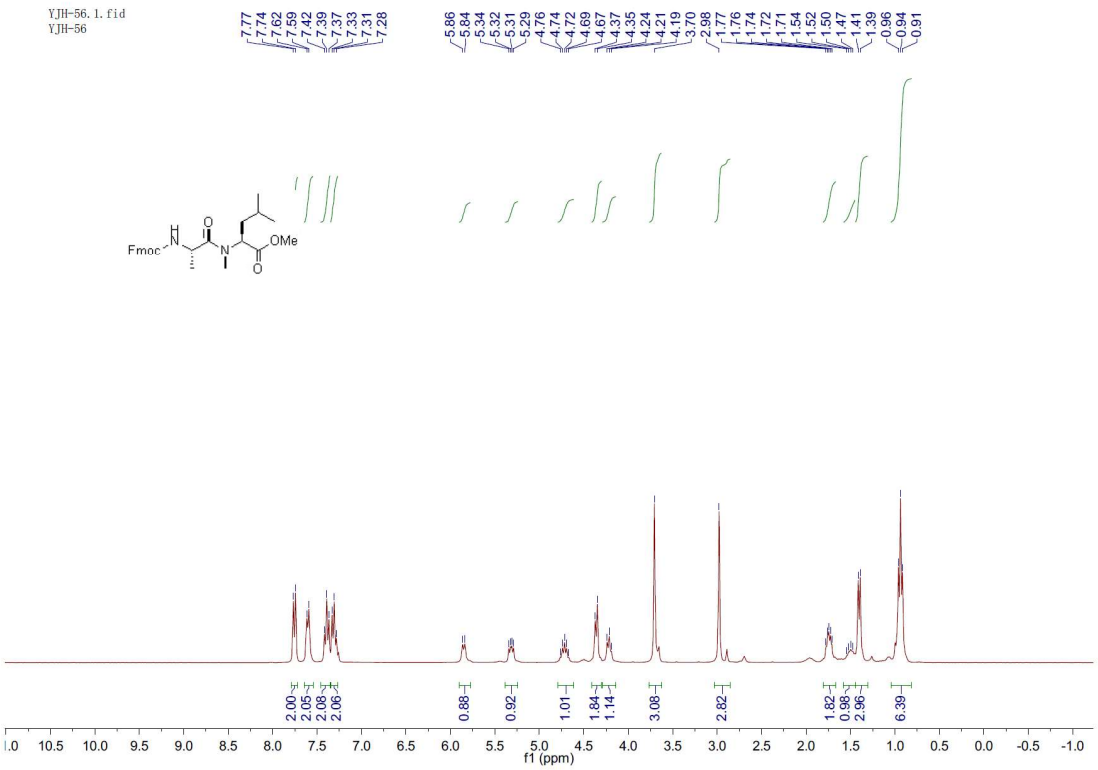


Figure S72. ^{1}H NMR of compound **7w** in $CDCl_3$, 300 MHz for ^{1}H NMR.

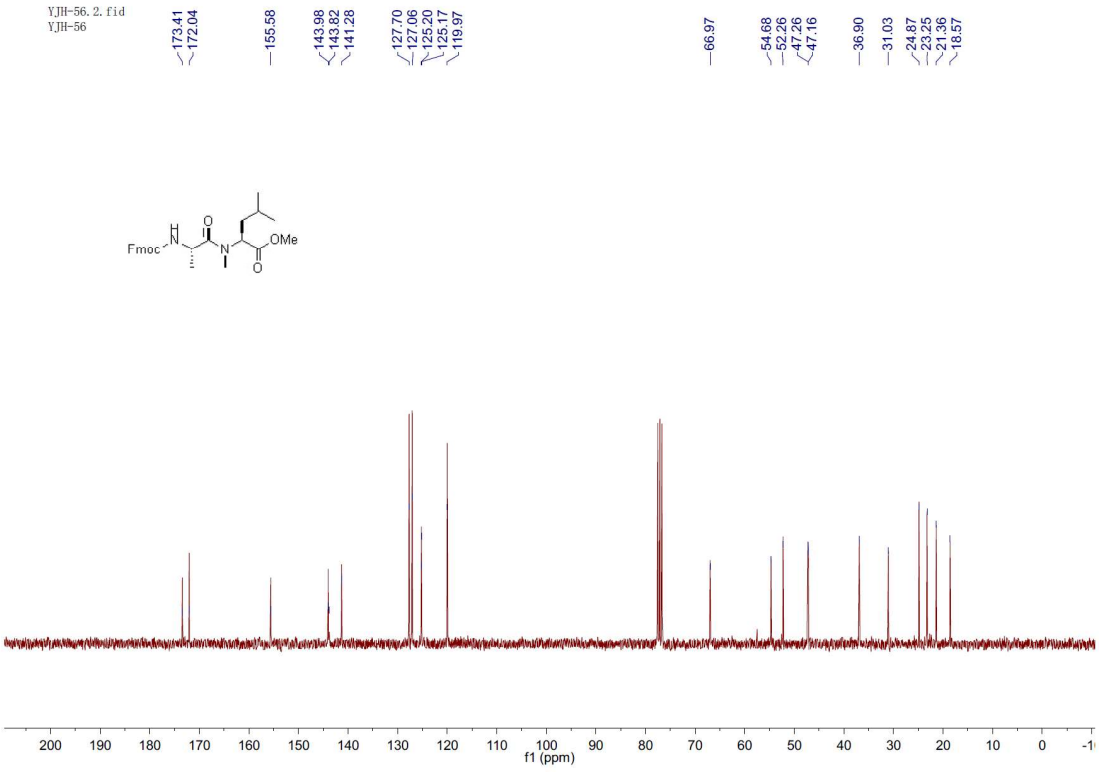


Figure S73. ^{13}C NMR of compound **7w** in $CDCl_3$, 75 MHz for ^{13}C NMR.

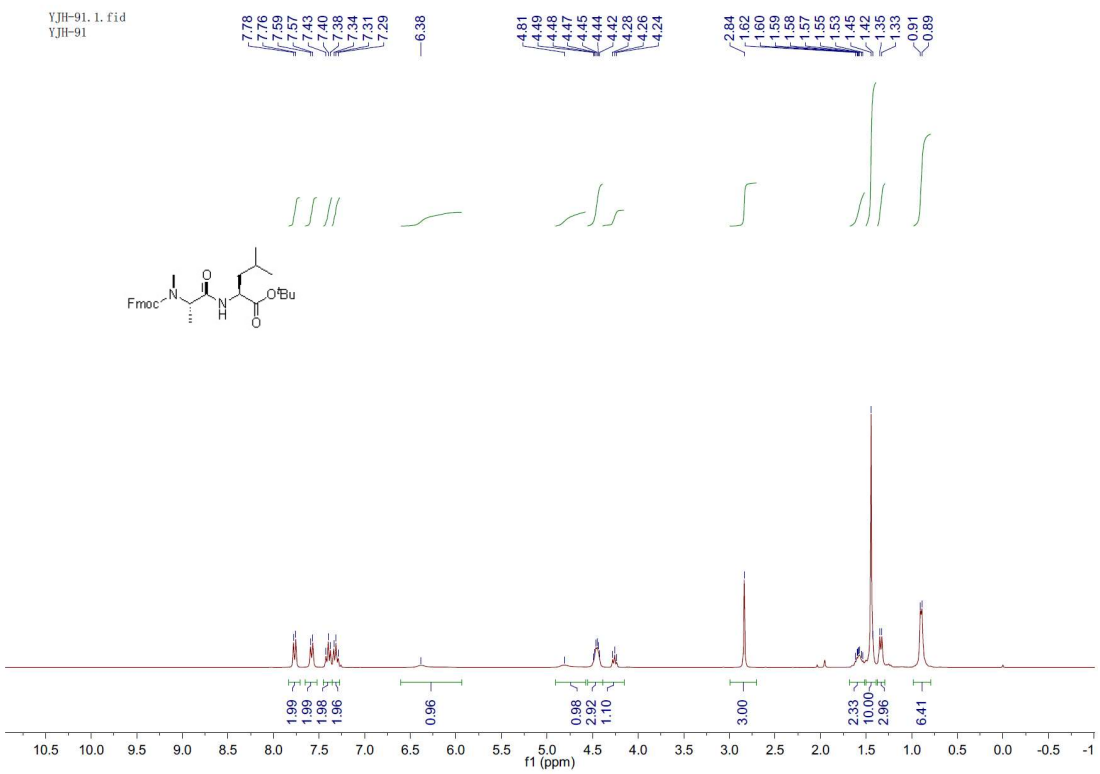


Figure S74. ^{1}H NMR of compound **7x** in $CDCl_3$, 300 MHz for ^{1}H NMR.

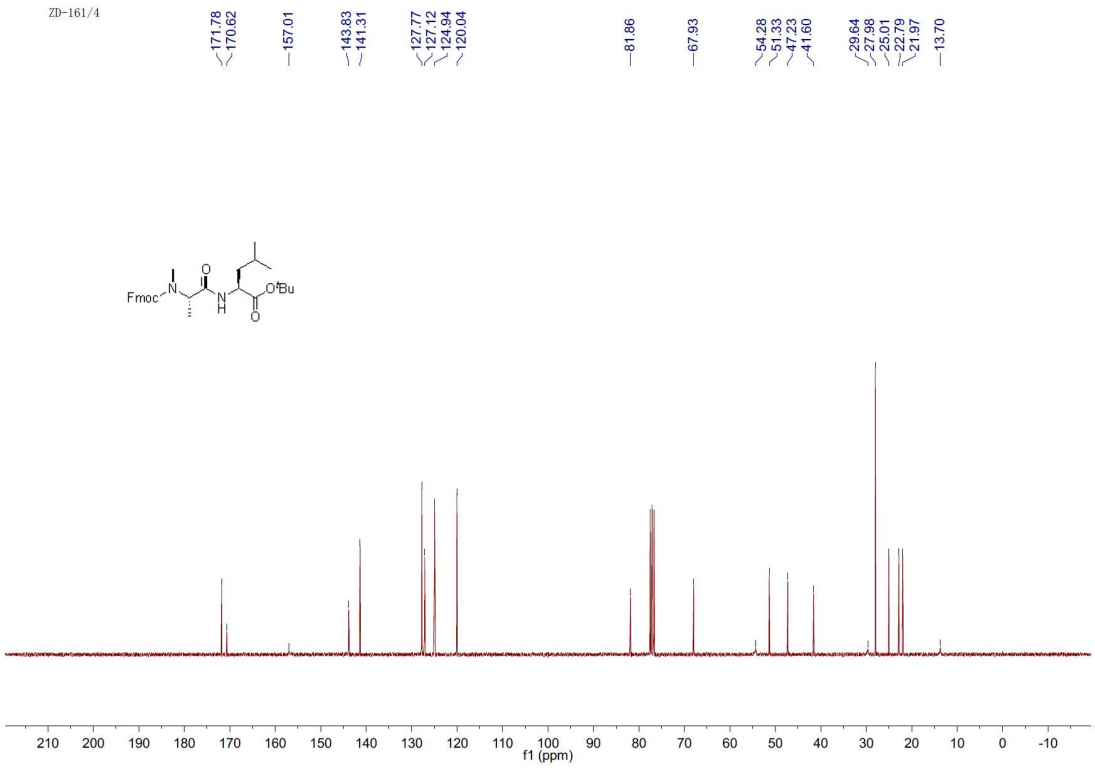


Figure S75. ^{13}C NMR of compound **7x** in $CDCl_3$, 75 MHz for ^{13}C NMR.

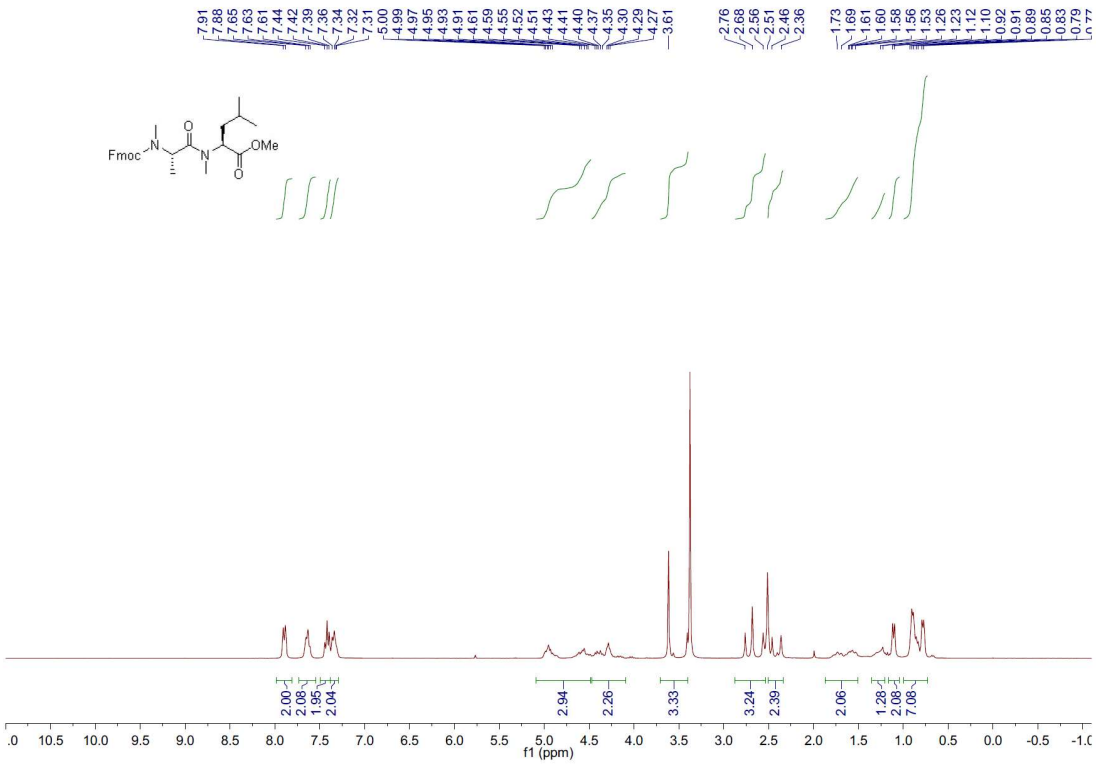


Figure S76. ^{1}H NMR of compound **7y** in DMSO-d_6, 300 MHz for ^{1}H NMR.

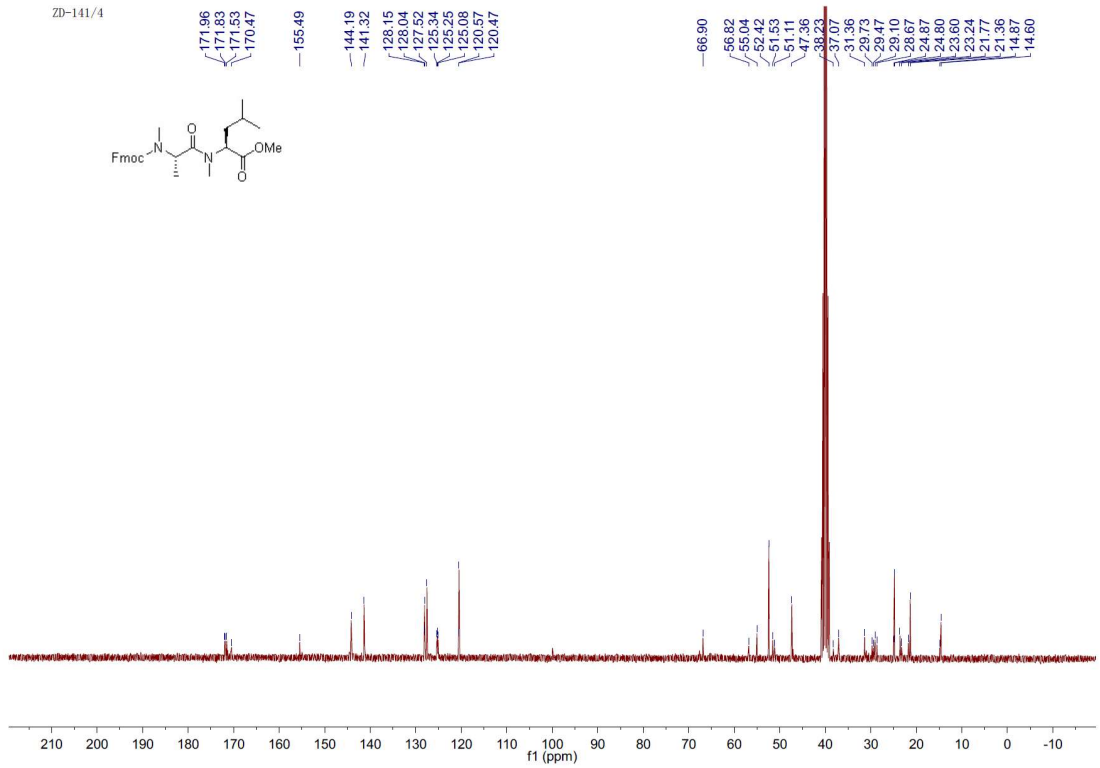


Figure S77. ^{13}C NMR of compound **7y** in DMSO-d_6, 75 MHz for ^{13}C NMR.

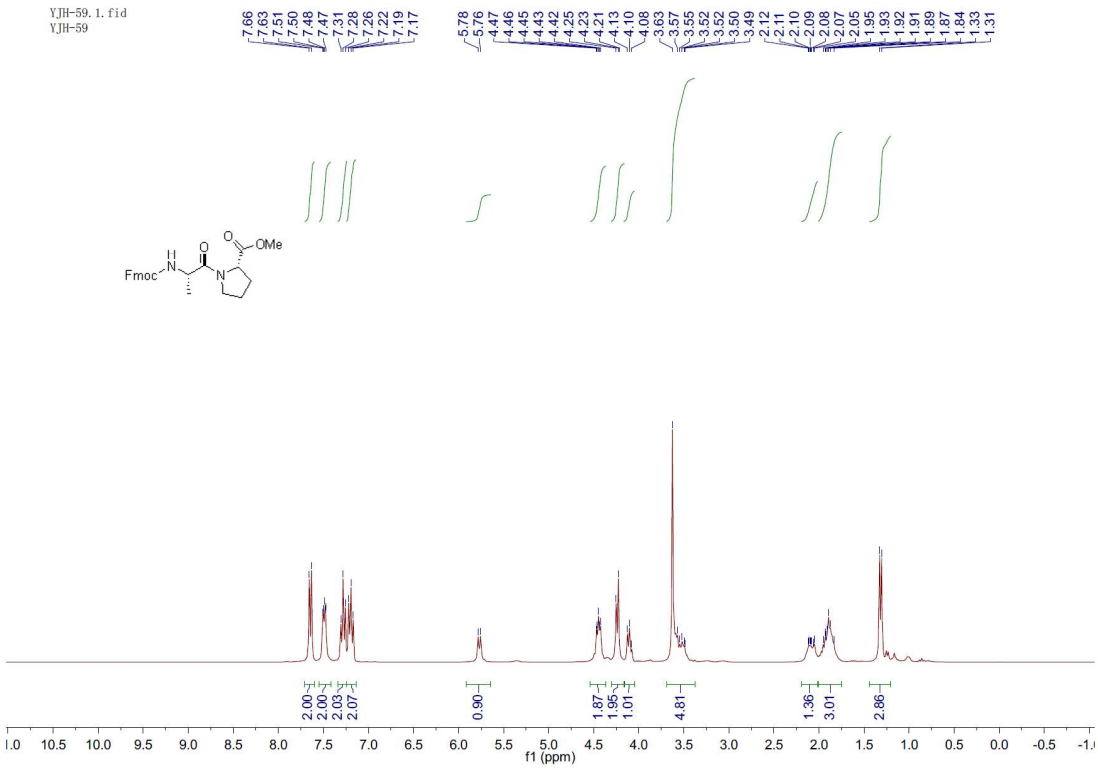


Figure S78. ^{1}H NMR of compound **7z** in $CDCl_3$, 300 MHz for ^{1}H NMR.

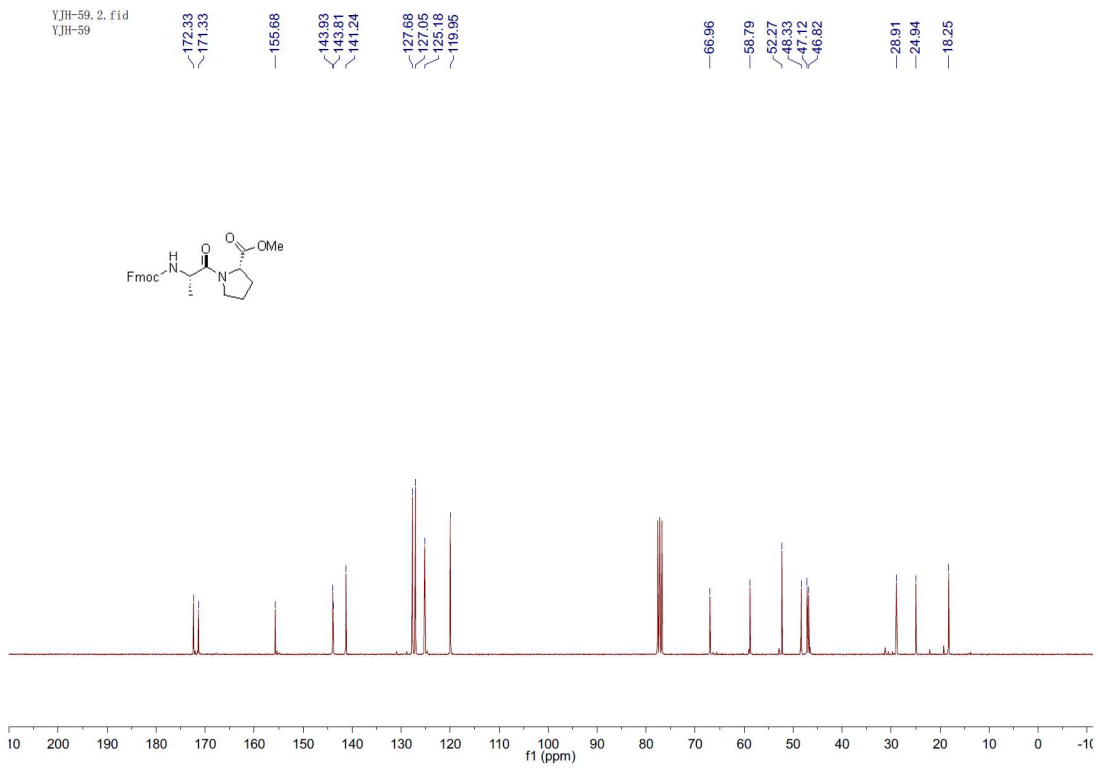


Figure S79. ^{13}C NMR of compound **7z** in $CDCl_3$, 75 MHz for ^{13}C NMR.

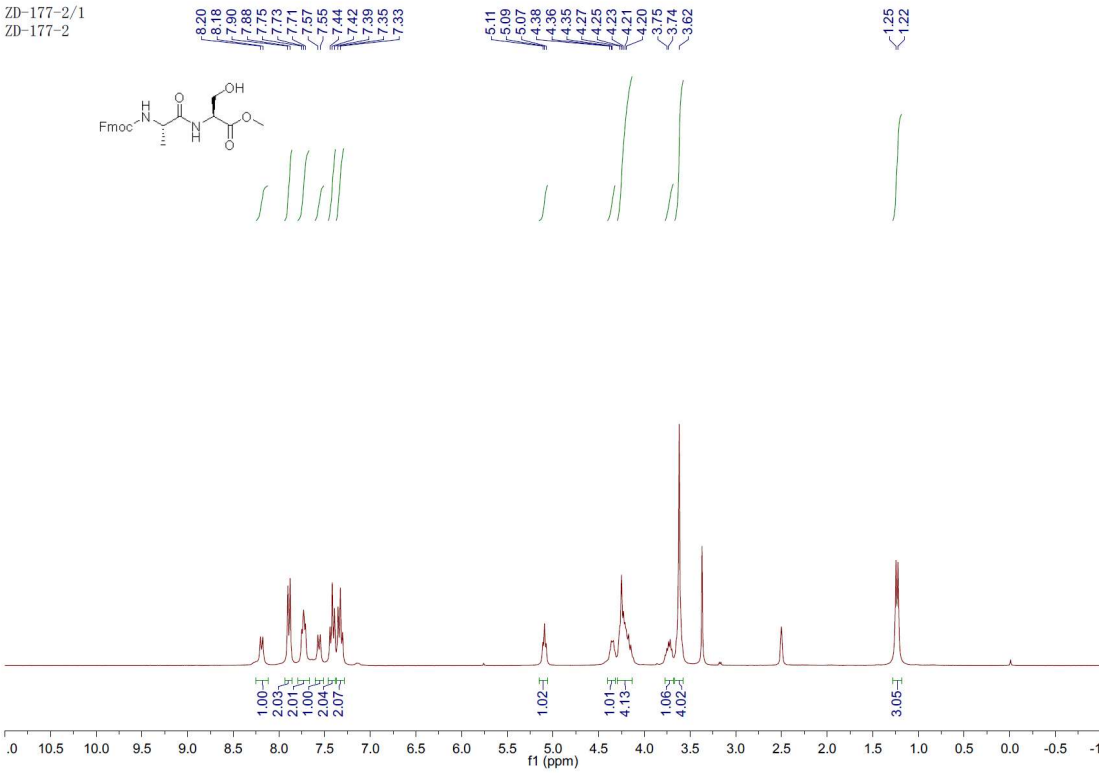


Figure S80. ^{1}H NMR of compound **7aa** in $CDCl_3$, 300 MHz for ^{1}H NMR.

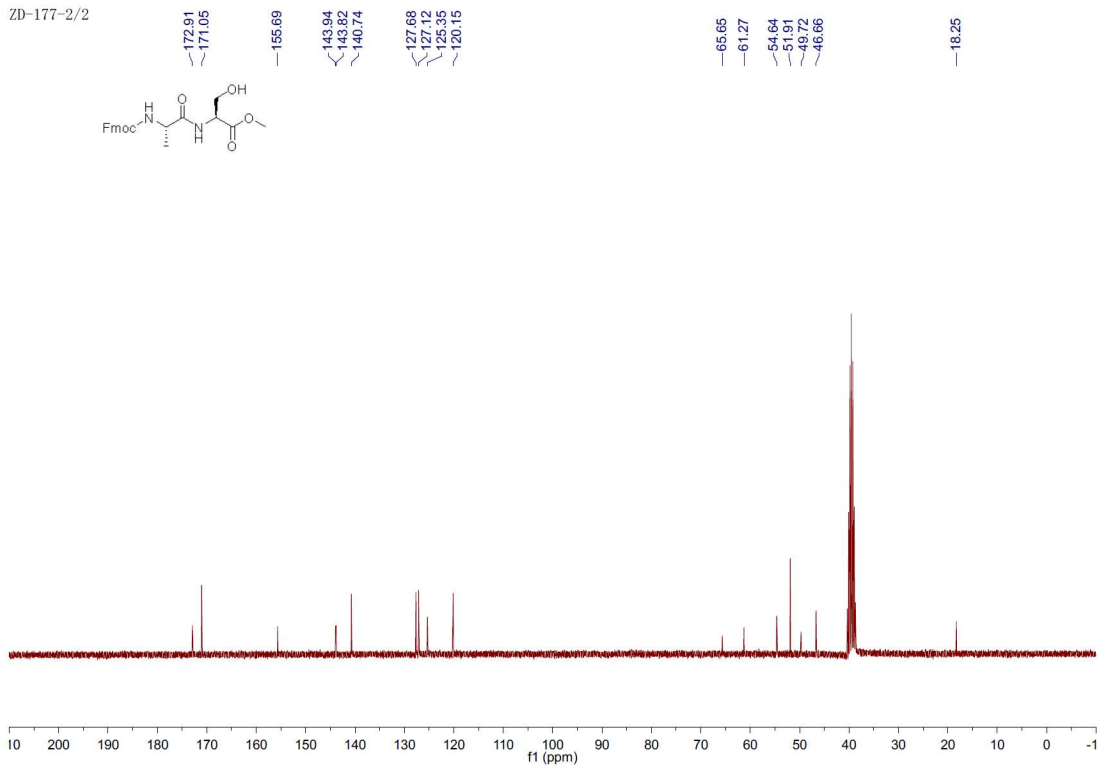


Figure S81. ^{13}C NMR of compound **7aa** in $CDCl_3$, 75 MHz for ^{13}C NMR.

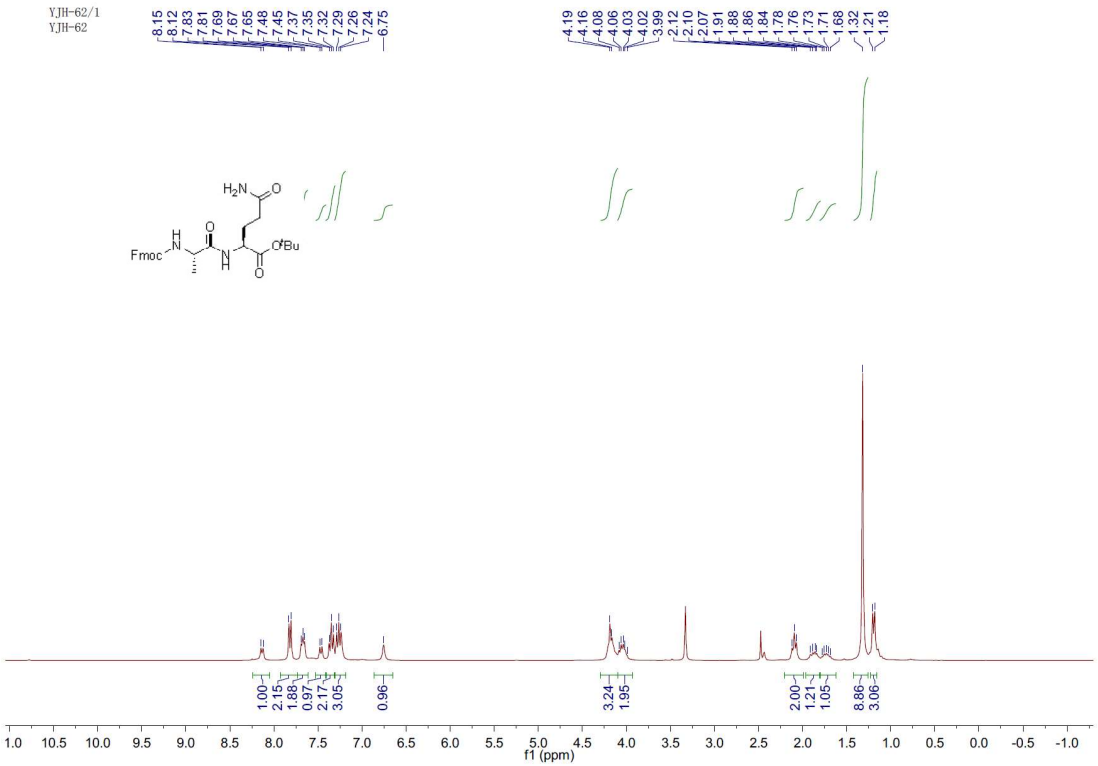


Figure S82. ^{1}H NMR of compound **7ab** in $CDCl_3$, 300 MHz for ^{1}H NMR.

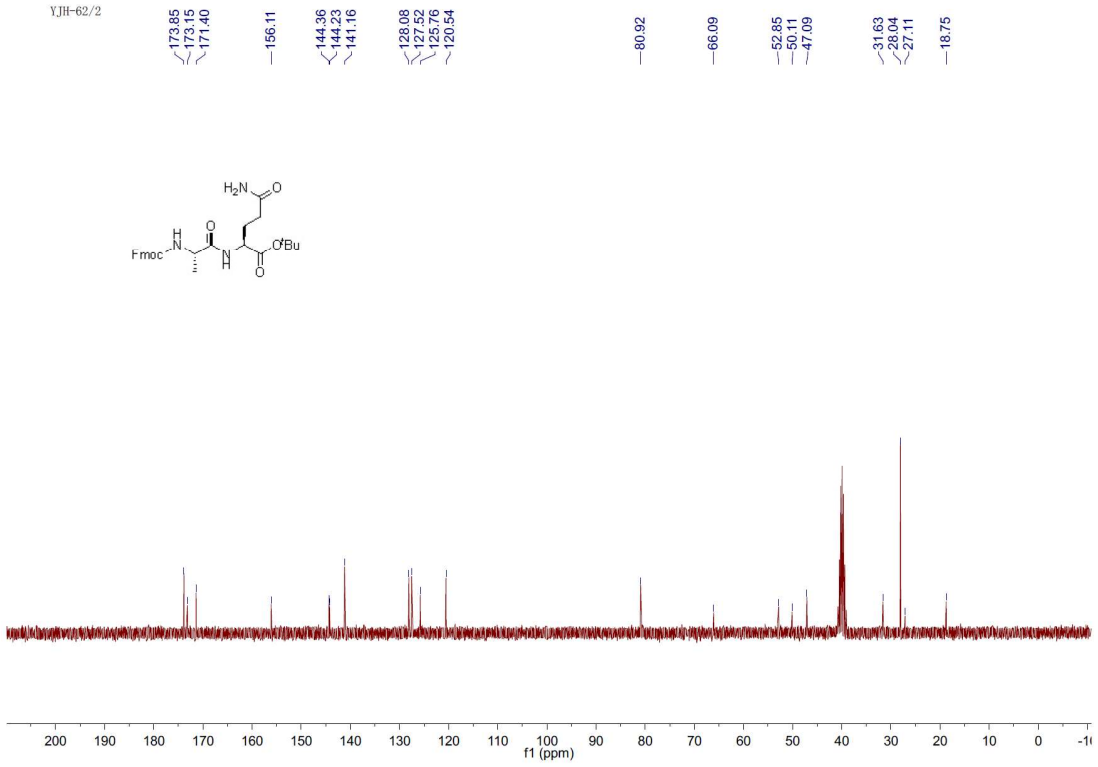


Figure S83. ^{13}C NMR of compound **7ab** in $CDCl_3$, 75 MHz for ^{13}C NMR.

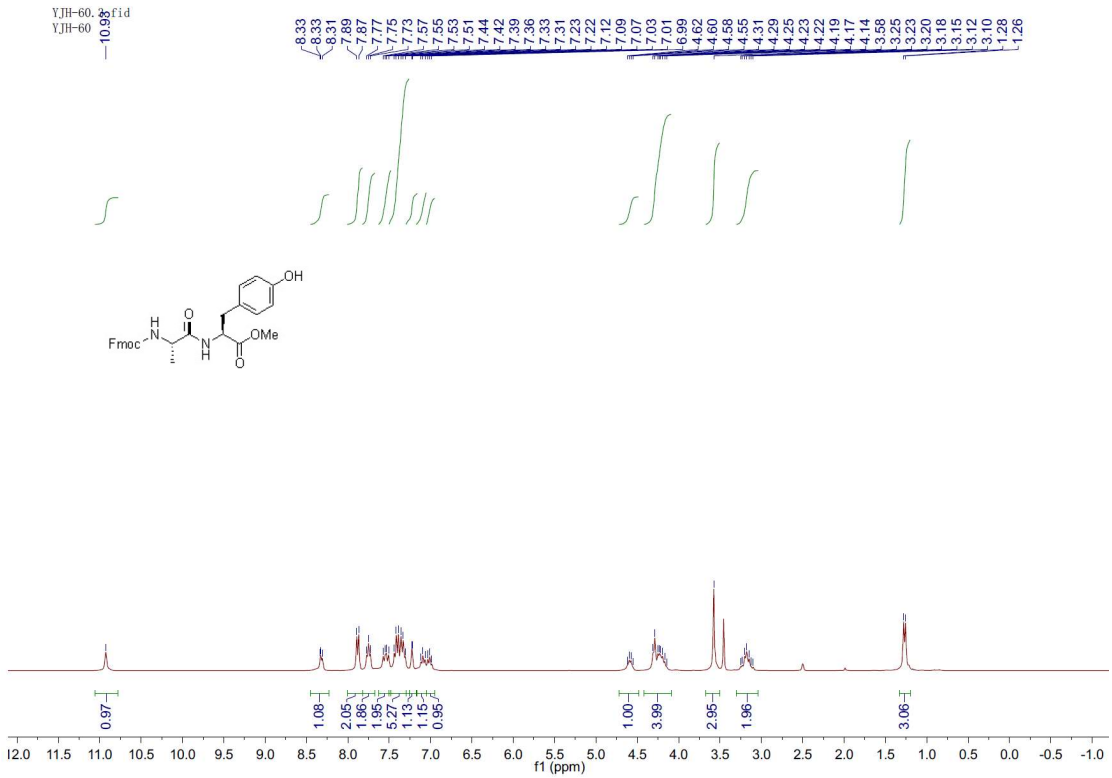


Figure S84. ^{1}H NMR of compound **7ac** in DMSO-d_6, 300 MHz for ^{1}H NMR.

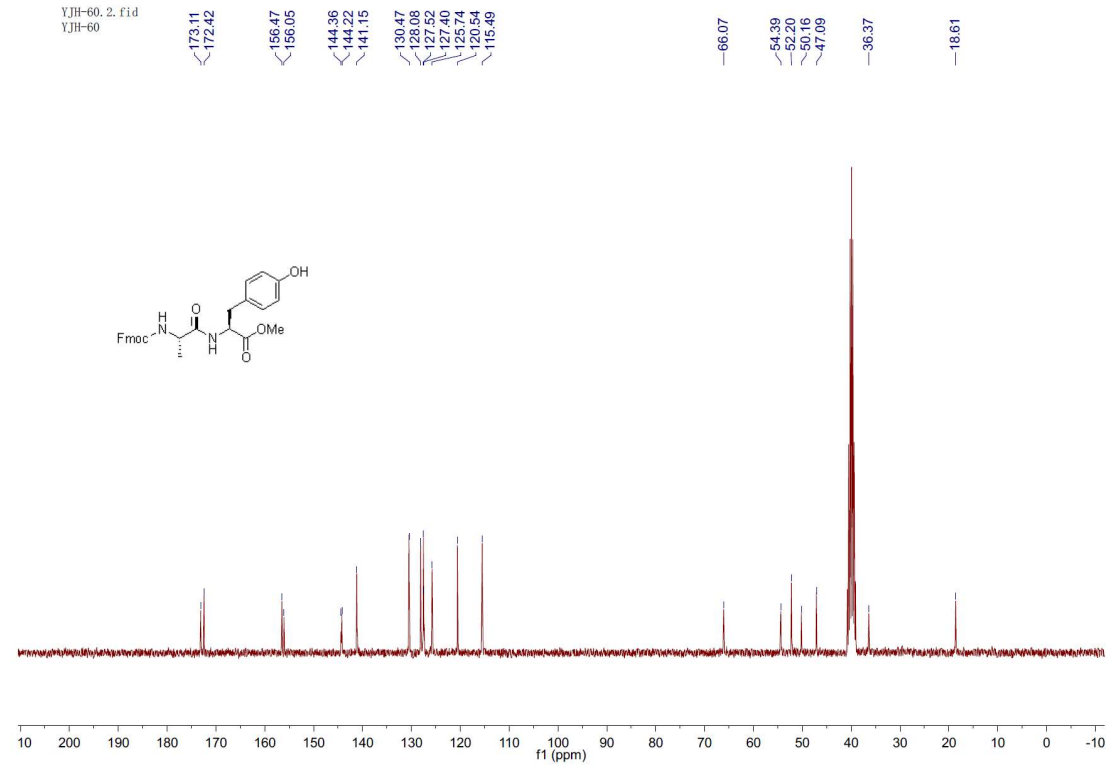


Figure S85. ^{13}C NMR of compound **7ac** in DMSO-d_6, 75 MHz for ^{13}C NMR.

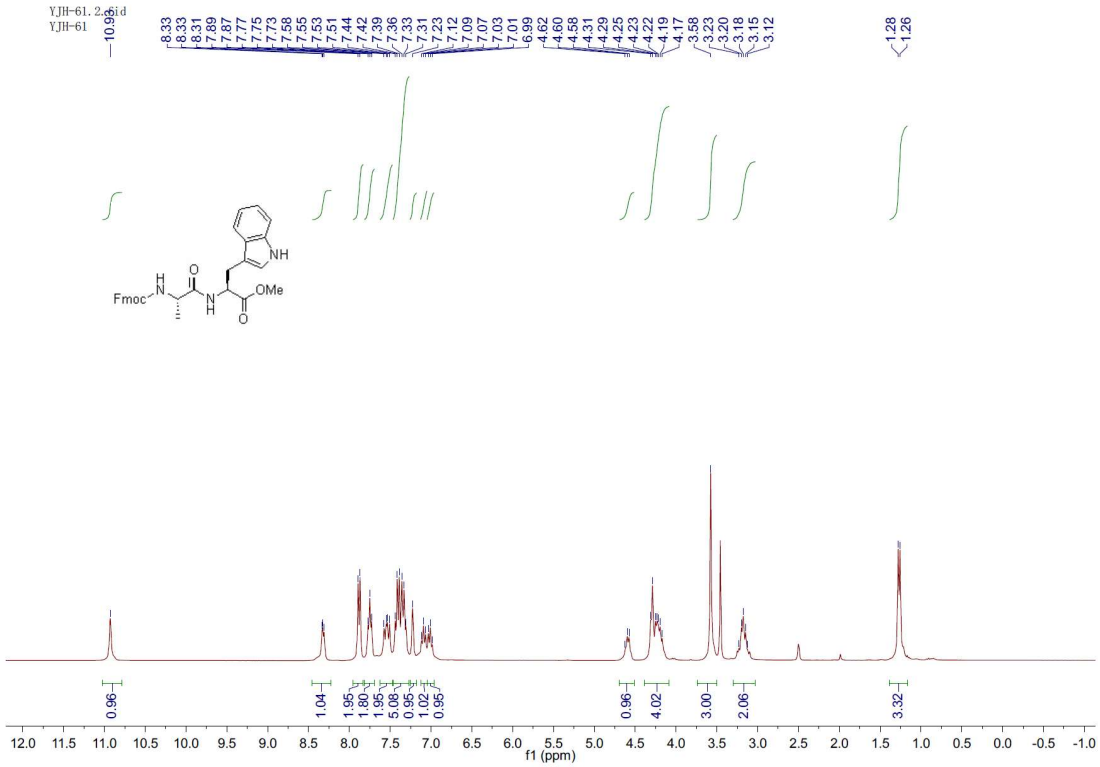


Figure S86. ^{1}H NMR of compound **7ad** in DMSO-d_6, 300 MHz for ^{1}H NMR.

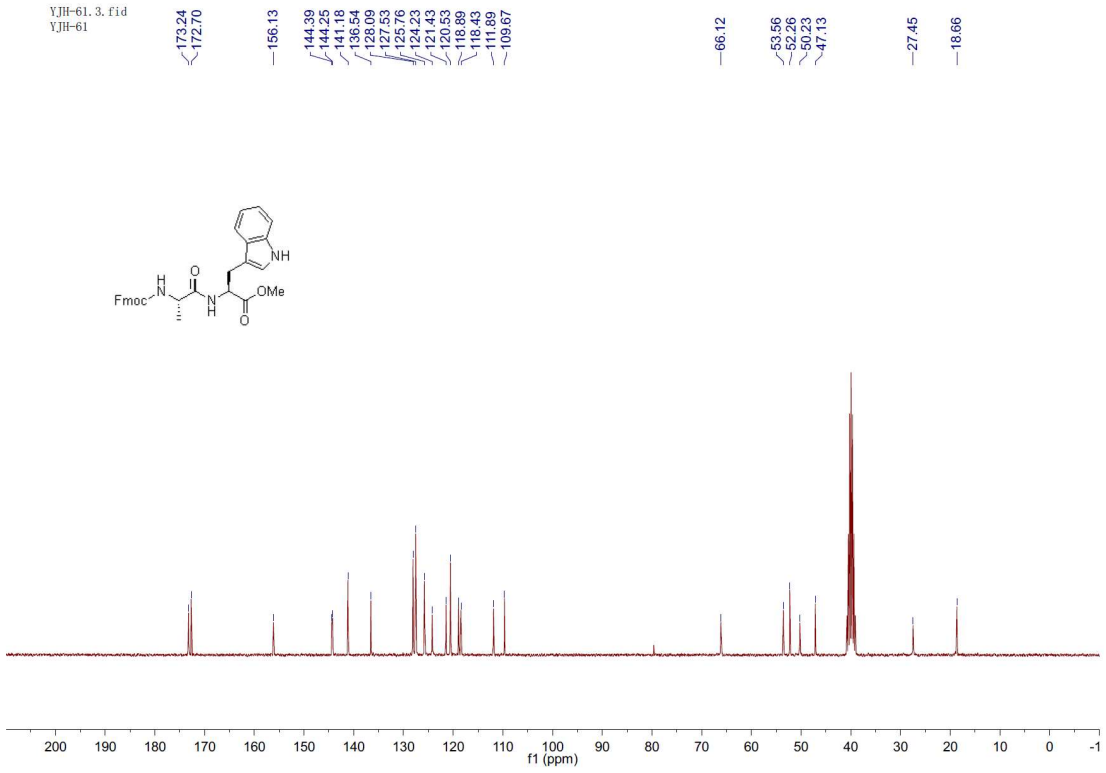


Figure S87. ^{13}C NMR of compound **7ad** in DMSO-d_6, 75 MHz for ^{13}C NMR.

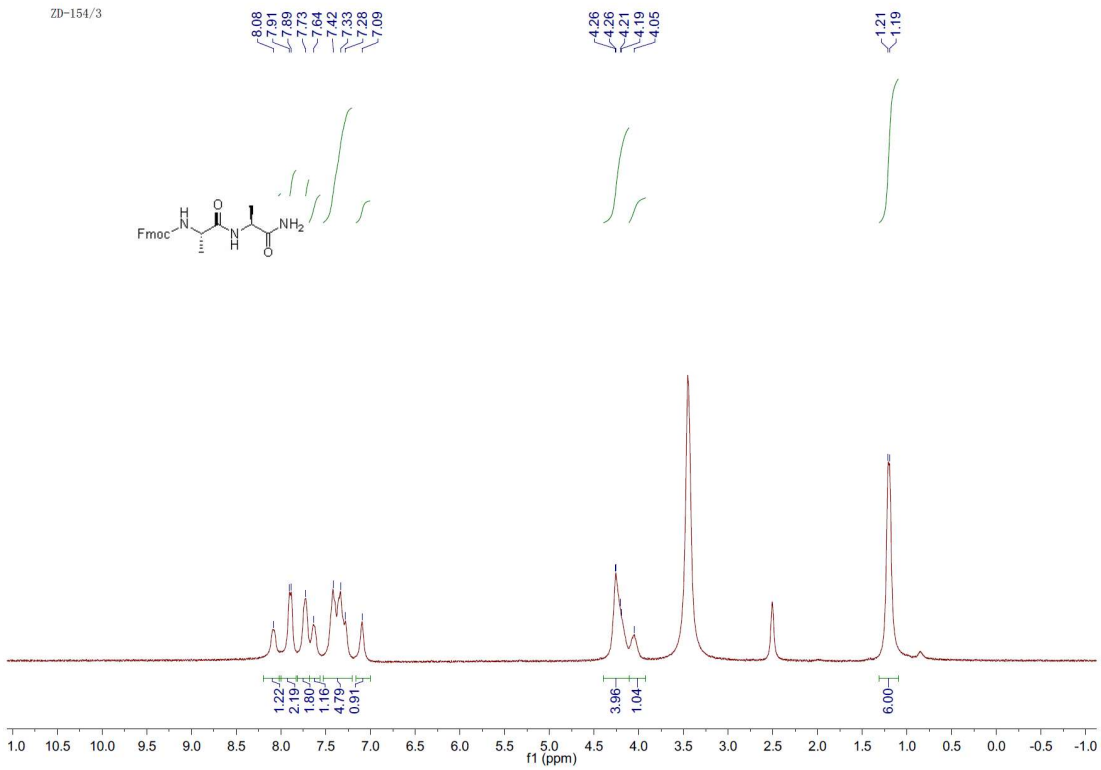


Figure S88. ^{1}H NMR of compound **7ae** in DMSO-d_6, 300 MHz for ^{1}H NMR.

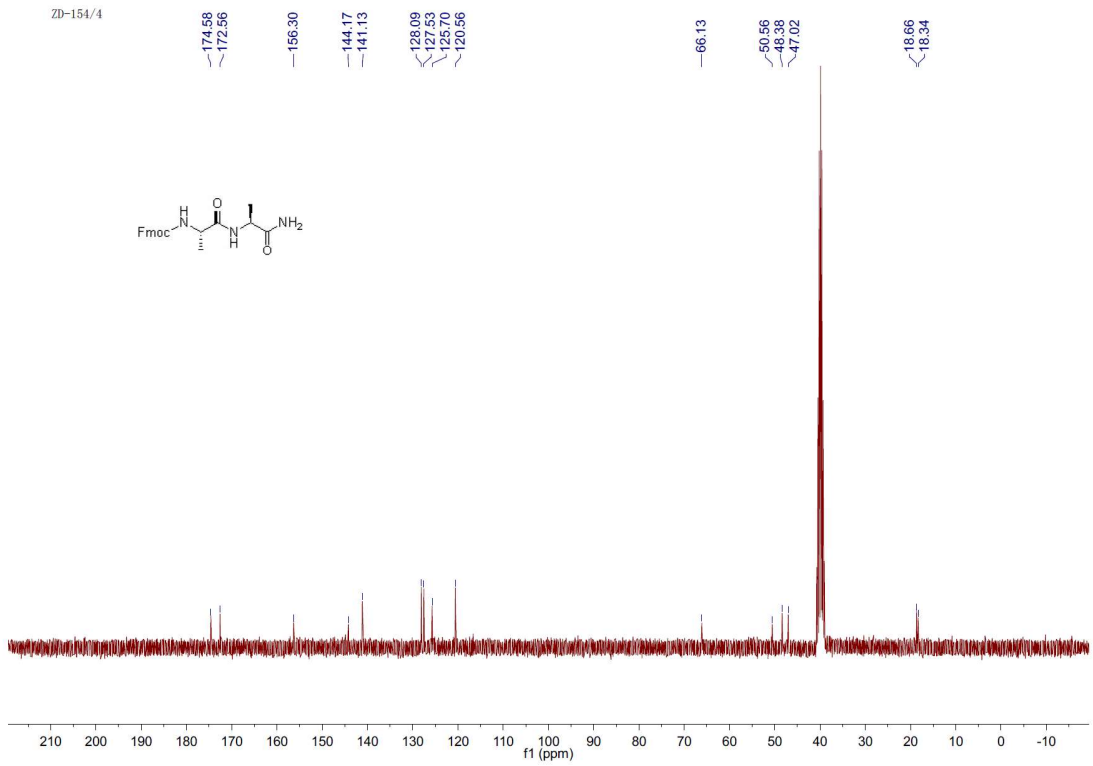


Figure S89. ^{13}C NMR of compound **7ae** in DMSO-d_6, 75 MHz for ^{13}C NMR.

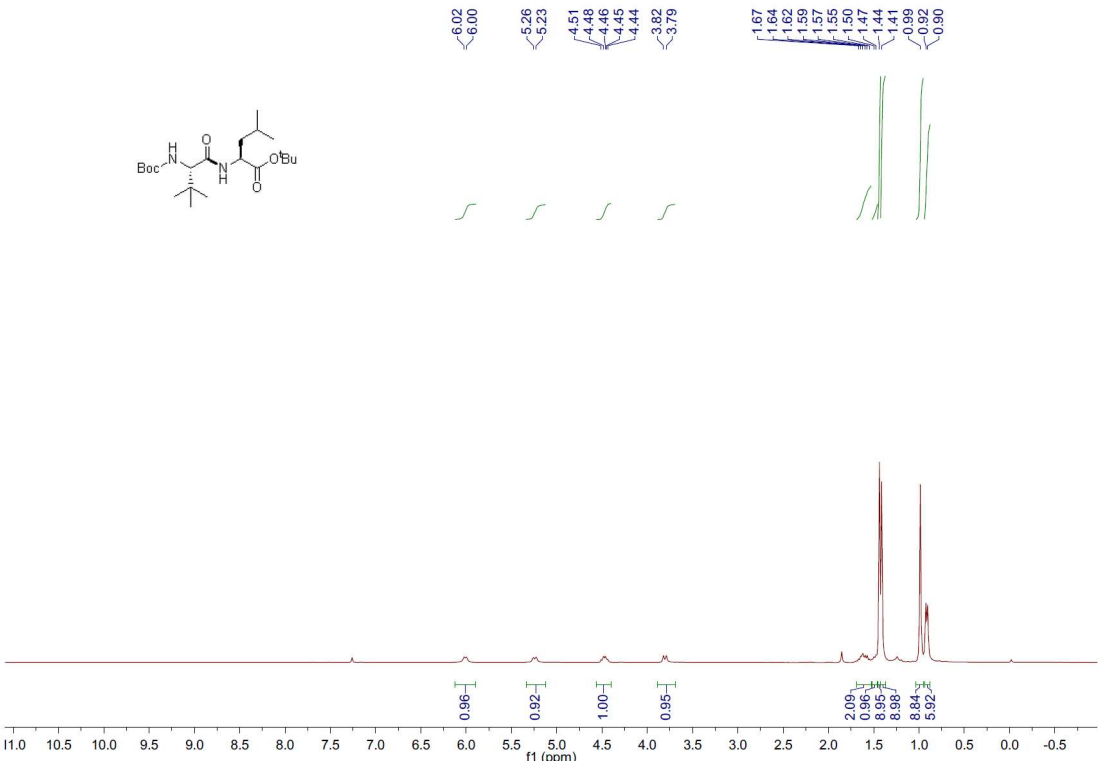


Figure S90. ^{1}H NMR of compound **7af** in $CDCl_3$, 300 MHz for ^{1}H NMR.

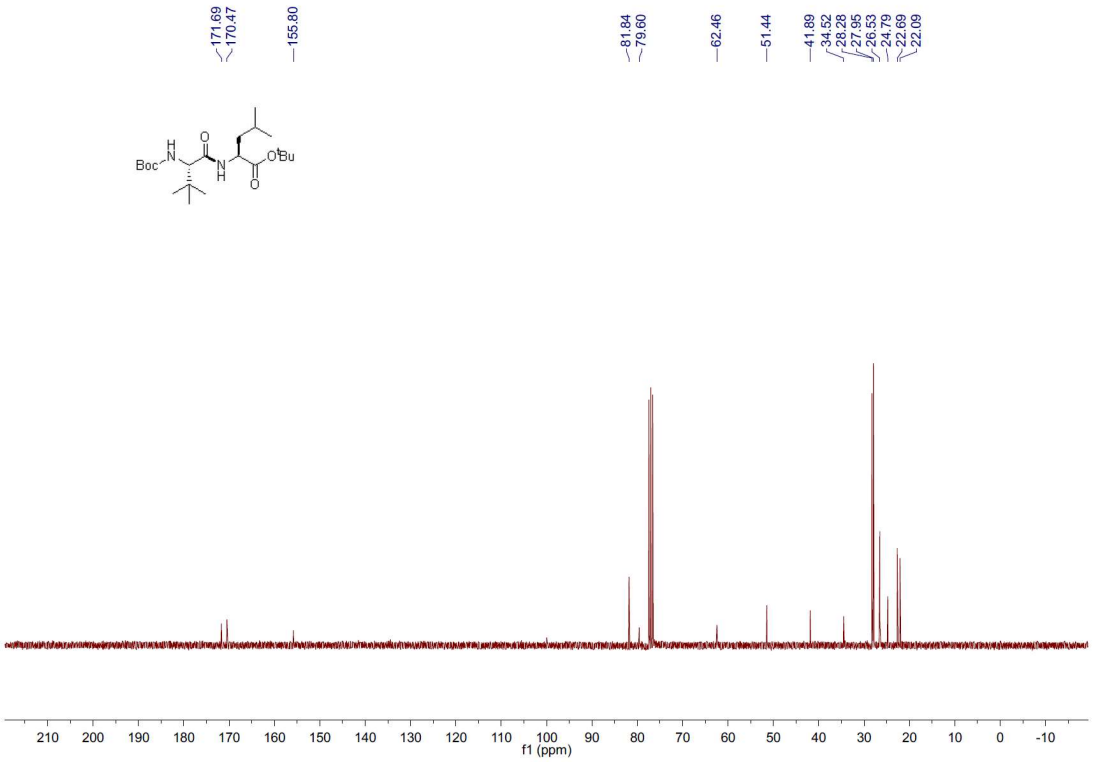


Figure S91. ^{13}C NMR of compound **7af** in $CDCl_3$ 75 MHz for ^{13}C NMR.

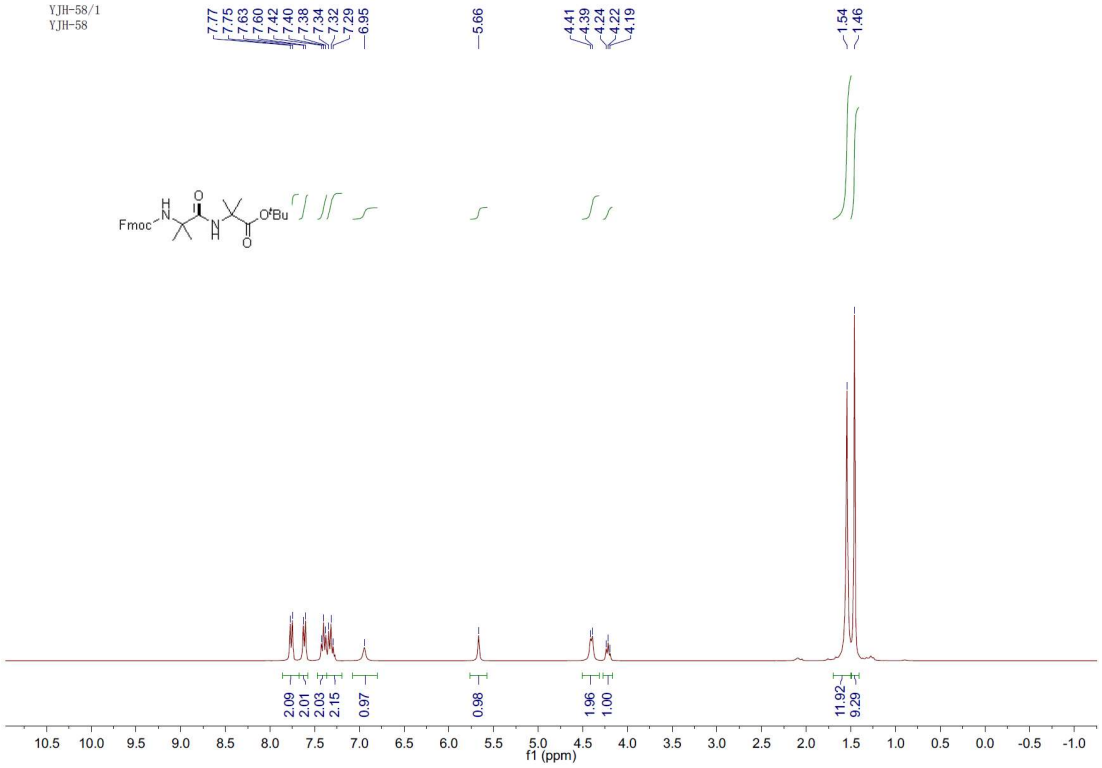


Figure S92. ^{1}H NMR of compound **7ag** in $CDCl_3$, 300 MHz for ^{1}H NMR.

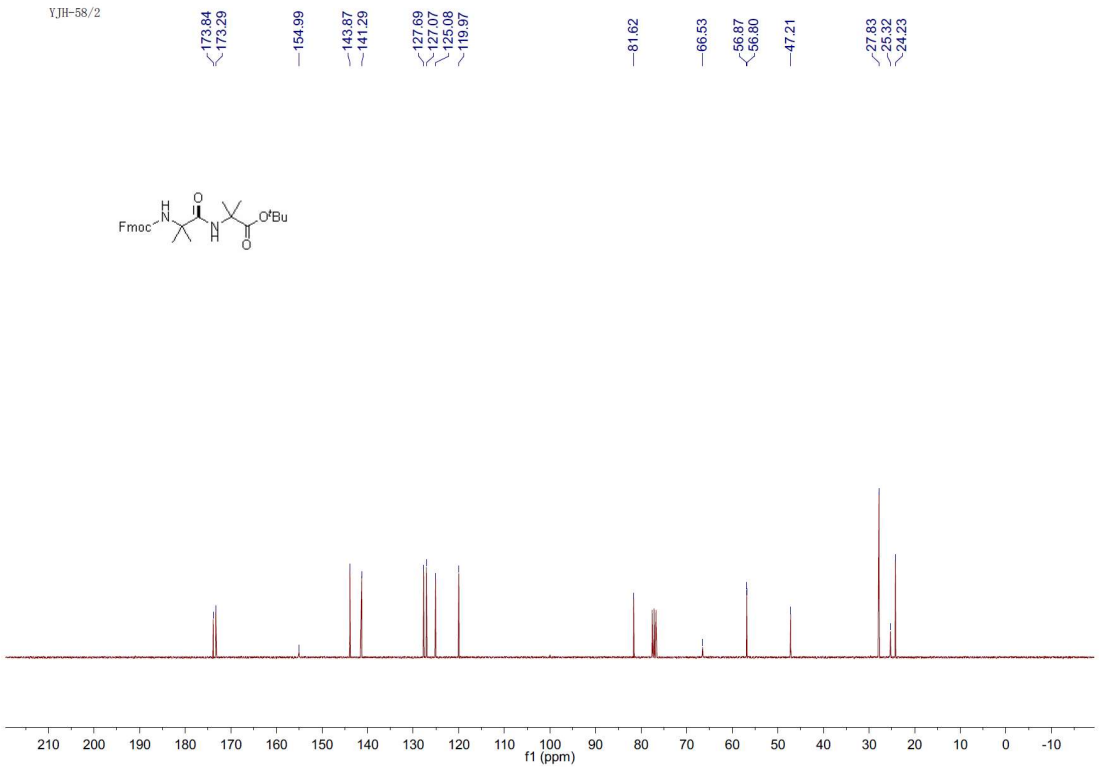


Figure S93. ^{13}C NMR of compound **7ag** in $CDCl_3$, 75 MHz for ^{13}C NMR.

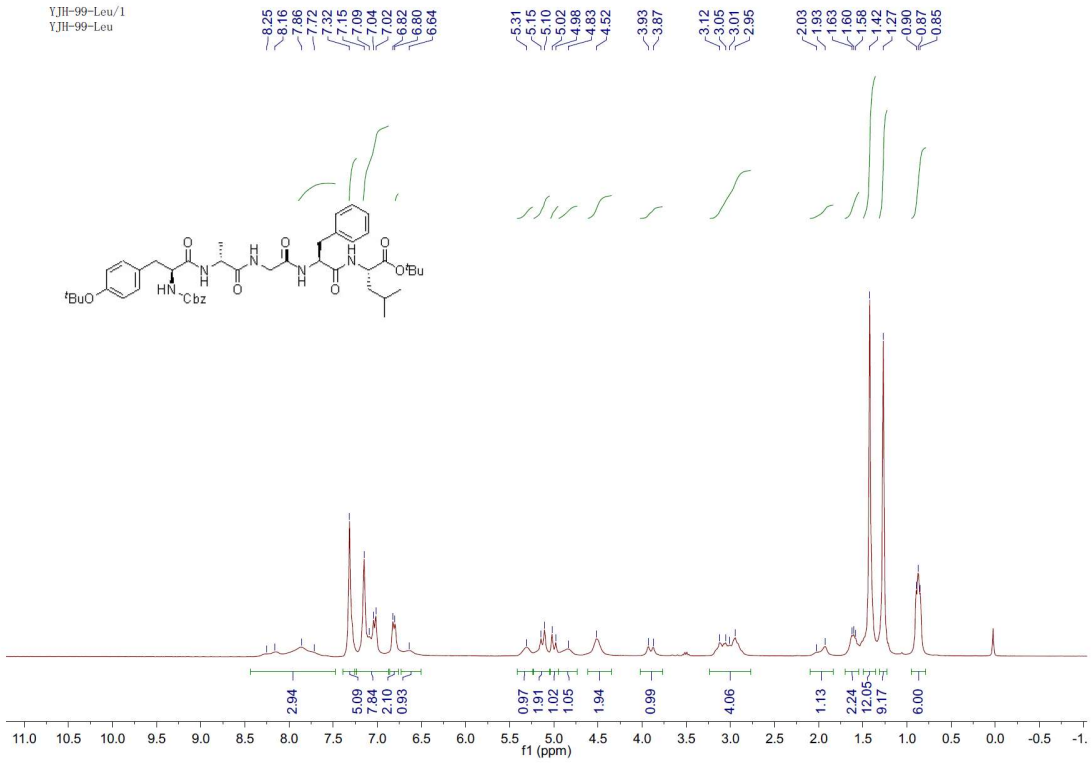


Figure S94. ^{1}H NMR of compound **7ah** in $CDCl_3$, 300 MHz for ^{1}H NMR.

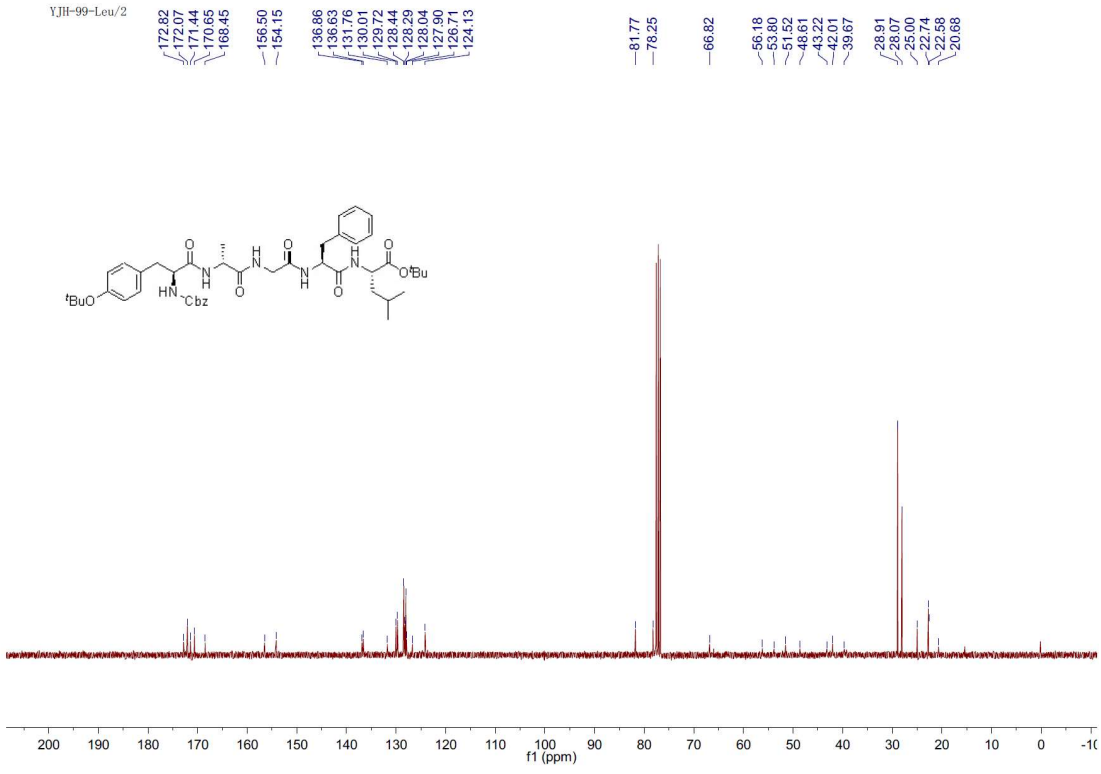


Figure S95. ^{13}C NMR of compound **7ah** in $CDCl_3$, 75 MHz for ^{13}C NMR.

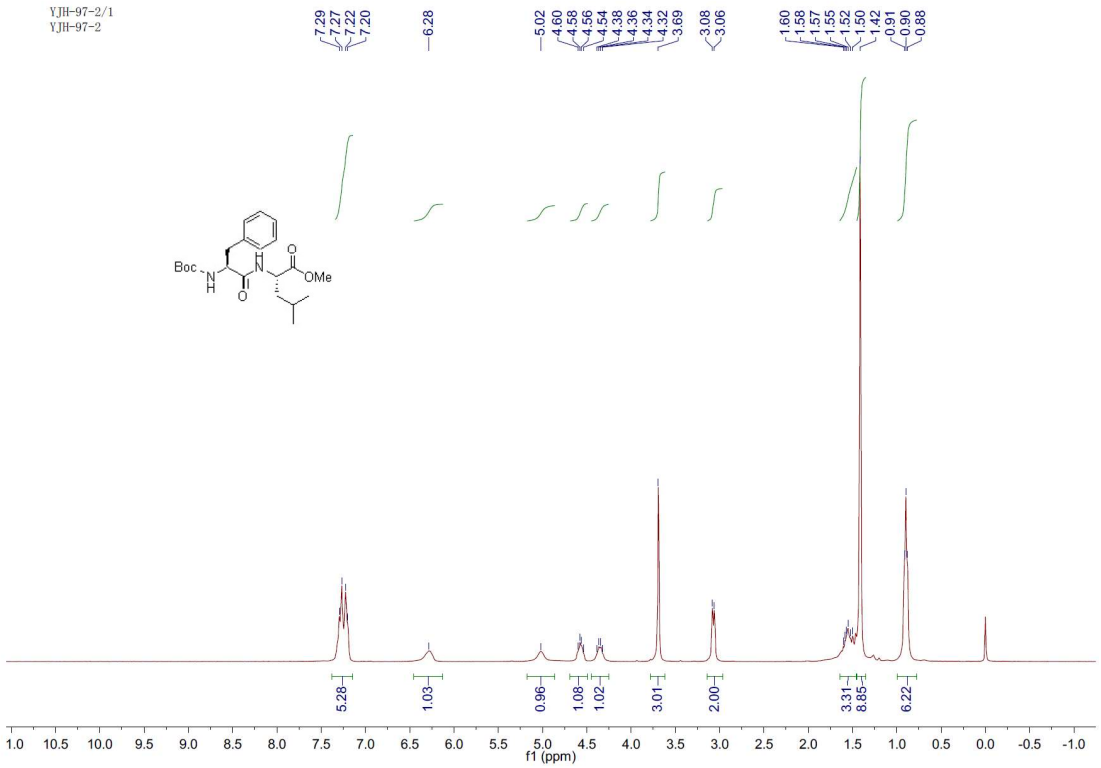


Figure S96. ^{1}H NMR of compound **8** in $CDCl_3$, 300 MHz for ^{1}H NMR.

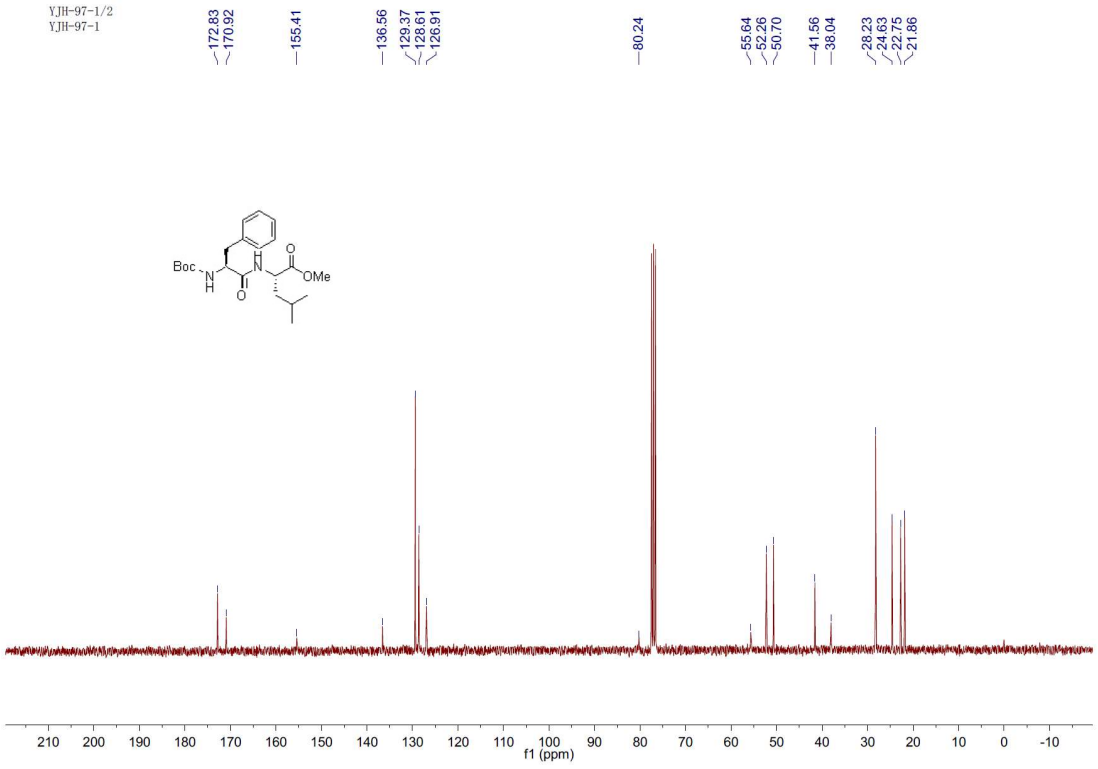


Figure S97. ^{13}C NMR of compound **8** in $CDCl_3$, 75 MHz for ^{13}C NMR.

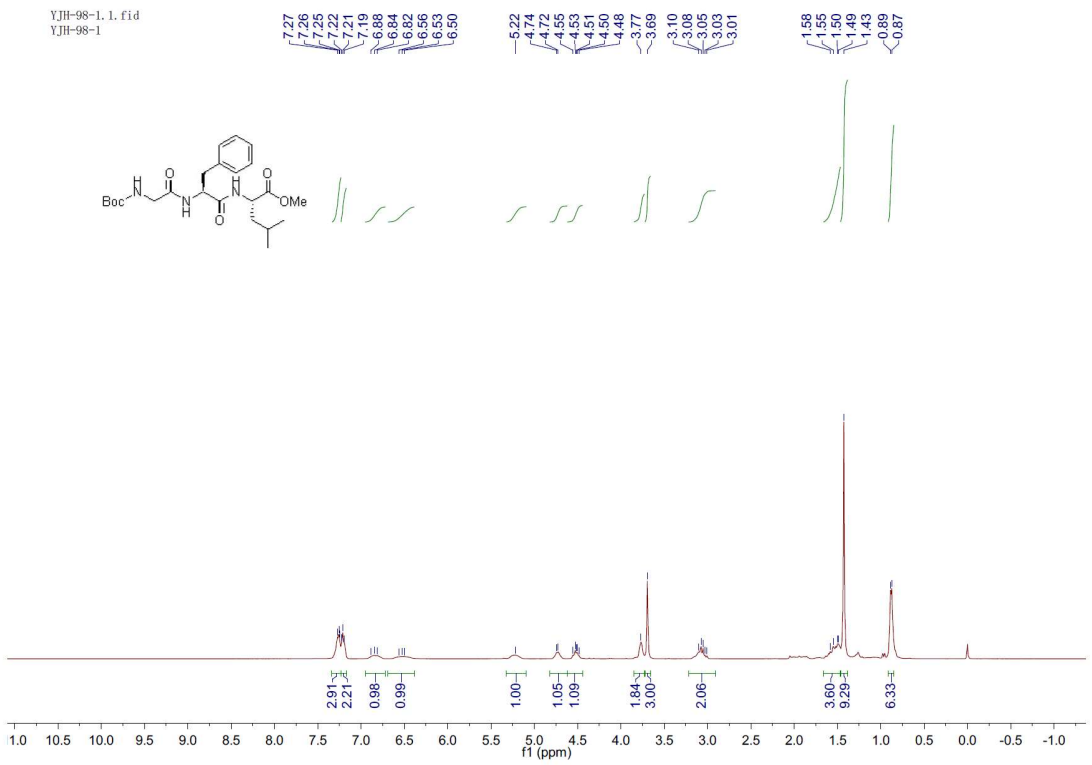


Figure S98. ^{1}H NMR of compound **10** in $CDCl_3$, 300 MHz for ^{1}H NMR.

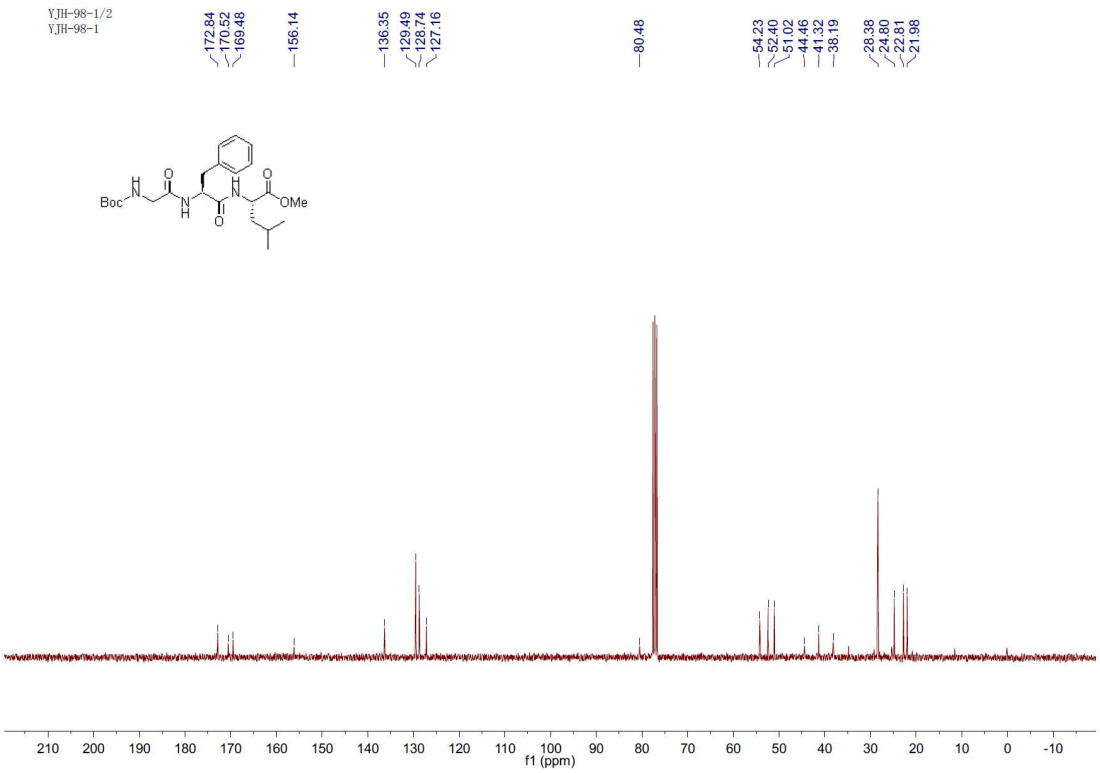


Figure S99. ^{13}C NMR of compound **10** in $CDCl_3$, 75 MHz for ^{13}C NMR.

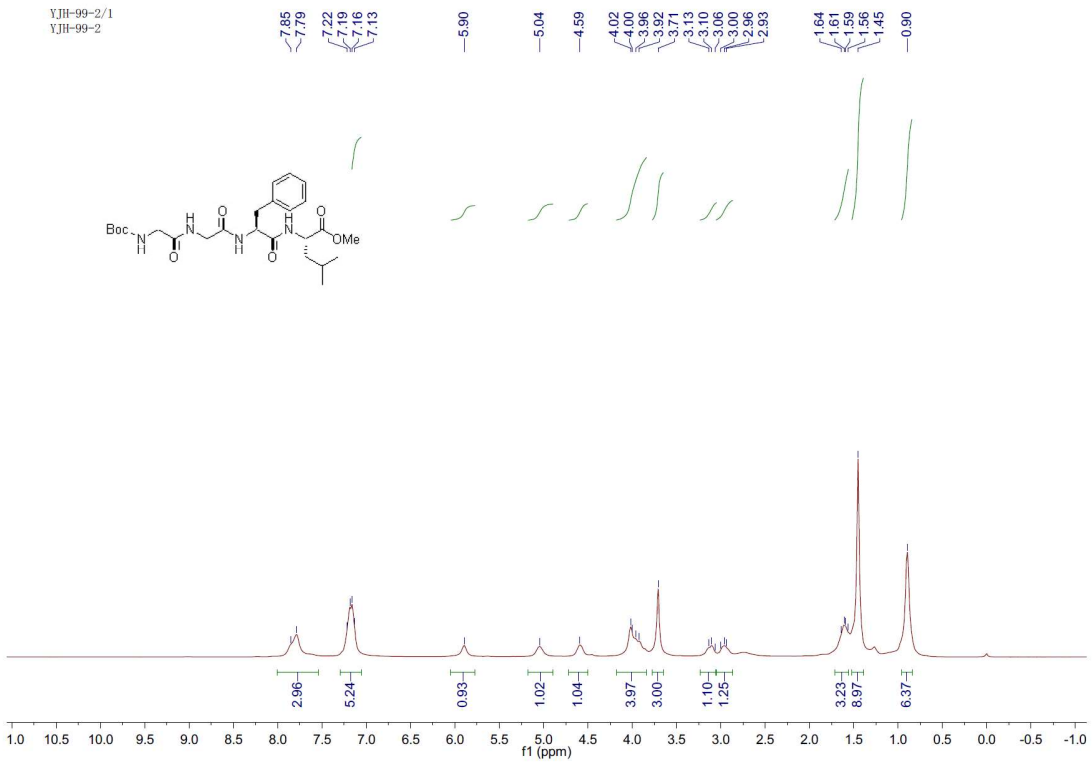


Figure S100. ^{1}H NMR of compound **12** in $CDCl_3$, 300 MHz for ^{1}H NMR.

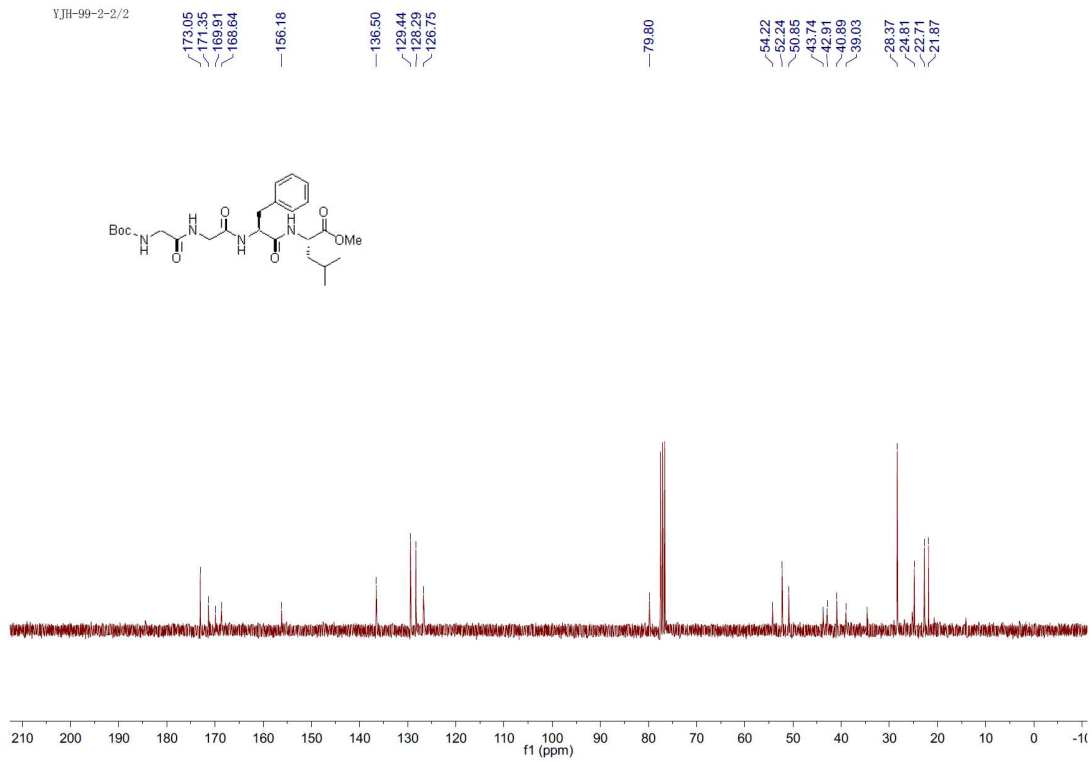


Figure S101. ^{13}C NMR of compound **12** in $CDCl_3$, 75 MHz for ^{13}C NMR.

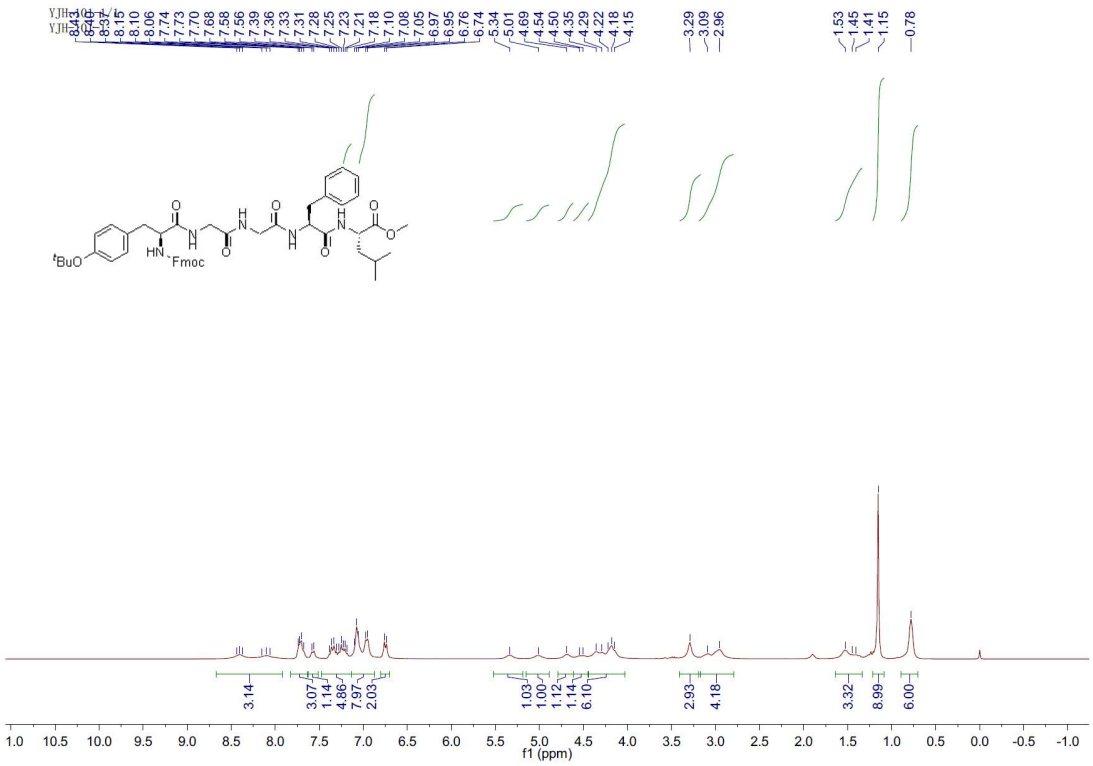


Figure S102. ^{1}H NMR of compound **14** in $CDCl_3$, 300 MHz for ^{1}H NMR.

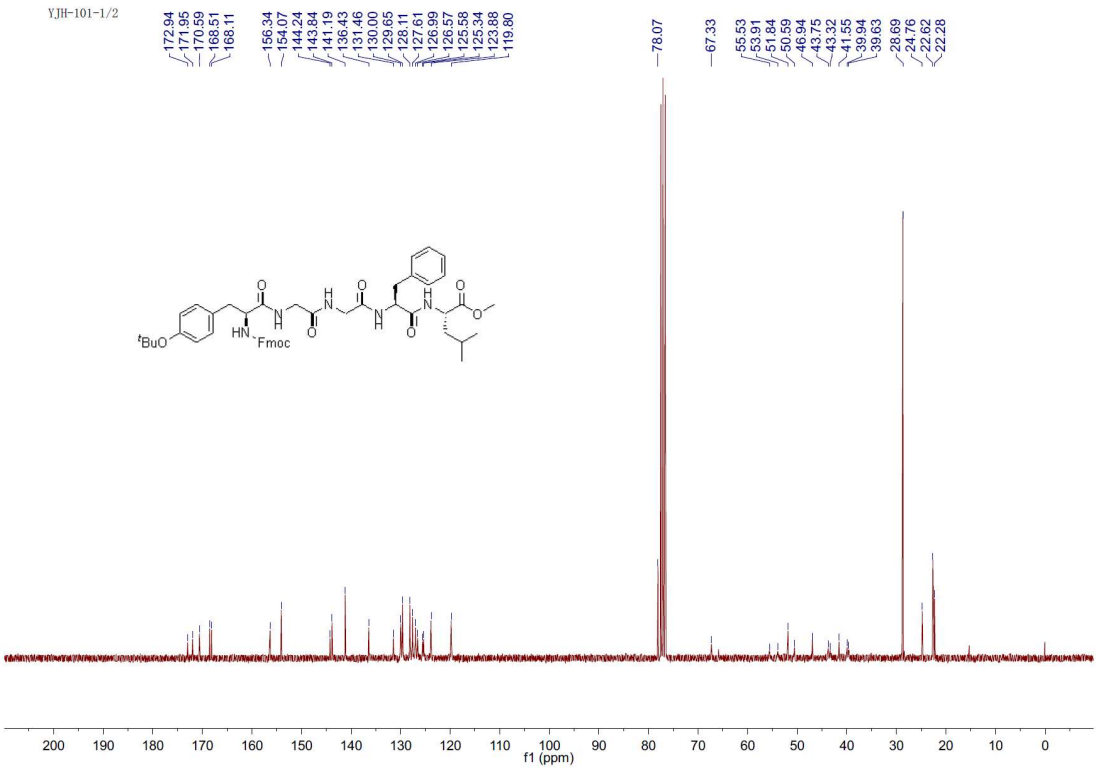


Figure S103. ^{13}C NMR of compound **14** in $CDCl_3$, 75 MHz for ^{13}C NMR.

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