Supporting Information

Intermolecular Sulfur Atom Transfer Cascade Enabled Late-Stage Introduction of Sulfilimines into Peptides

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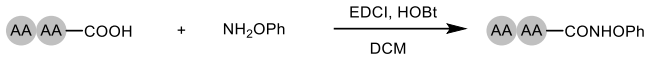
1. General information

All commercially available reagents were used without further purification unless otherwise stated. All solvents were purified and dried according to standard methods prior to use. Trifluoroacetic acid (TFA), triisopropylsilane (TIPS), *N,N*-diisopropylethylamine (DIPEA), *N*-Ethyl-*N'*-(3-dimethyl-aminopropyl)carbodiimide hydrochloride (EDCI), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU), 1-Hydroxybenzotriazole (HOBt) and Fmoc-amino acids were purchased from Energy Chemical and GL Biochem, and were used without further purification. Solid phase peptide synthesis was performed on rink amide-MBHA resin (100-200 mesh, 0.43 mmol/g, crosslinked polystyrene) and 2-Chlorotrityl chloride resin (100-200 mesh, 0.97mmol/g) manually. ^{1}H, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker instrument (300 MHz, 75 MHz and 282 MHz respectively) and internally referenced to tetramethylsilane signal or residual protio solvent signals. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet or unresolved, coupling constant (s) in Hz, integration). Data for ^{13}C NMR and ^{19}F NMR are reported in terms of chemical shift (δ, ppm). High resolution mass spectra (HRMS) were obtained by the ESI ionization sources. The LC-MS were performed on Thermo Scientific Orbitrap IQ-X Tribrid using a ACQUITY UPLC® BEH C18 Column (1.7 μm, 2.1 × 50 mm) at a flow rate of 0.3 mL/min. Semi-preparative HPLC was performed on Hanbon Sci.& Tech system using Dubhe C18 column (10 μm, 20 × 250 mm) at a flow rate of 10.0 mL/min. Analytical HPLC was performed on Waters e2695 using a XTerra® RP 18 Column. (5 μm, 4.6 × 250 mm) at a flow rate of 1.0 mL/min. Linear gradients using A: MeCN (0.1% CF_3COOH) and B: H_2O (0.1% CF_3COOH) were run over varying periods of time.

2. Preparation of starting materials

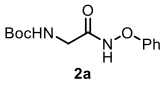
2.1 Amino acids and peptides derivatives

General procedure for the synthesis of amino acids and peptides derivatives



O-phenylhydroxylamine was prepared according to the previous reports.[1] Amino acids or peptides (1.0 equiv.), EDCI (1.2 equiv.) and HOBt (1.2 equiv.) were added to a round-bottom flask, DCM (0.2-1 M) was added and the mixture was stirred at ice-water bath for 30 min. Then O-phenylhydroxylamine (1.0 equiv.) was added. The reaction mixtures were stirred at room temperature and monitored by TLC. Upon starting materials were completed consumed, the reaction was dissolved with DCM, washed with saturated citric acid aqueous solution (2 × 50 mL), saturated sodium bicarbonate aqueous solution (2 × 50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography to give the product.

***tert*-butyl (2-oxo-2-(phenoxyamino)ethyl)carbamate (2a)**



2a

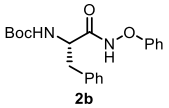
White solid was obtained by chromatography on silica gel (eluted: PE:EtOAc = 4:1), 1 mmol scale, 162 mg, 62% yield.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.87 (s, 1H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 3H), 5.34 (s, 1H), 3.93 (d, *J* = 8.3 Hz, 2H), 1.44 (s, 9H).

^{13}C NMR (75 MHz, Chloroform-d) δ 168.03, 159.12, 156.52, 129.55, 123.23, 113.08, 80.88, 42.39, 28.23.

HRMS (ESI) $C_{13}H_{18}N_2NaO_4$ $[M+Na]^+$ Calcd: 289.1159, Found: 289.1153.

***tert*-butyl (*S*)-(1-oxo-1(phenoxyamino)-3-phenylpropan-2-yl)carbamate (2b)**



2b

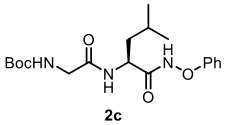
White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 4:1), 13 mmol scale, 2618 mg, 56% yield.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.64 (s, 1H), 7.36 – 7.21 (m, 6H), 7.16 (d, *J* = 7.6 Hz, 2H), 6.97 (t, *J* = 7.3 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 5.26 (d, *J* = 8.6 Hz, 1H), 4.46 (d, *J* = 8.4 Hz, 1H), 3.11 (t, *J* = 7.3 Hz, 2H), 1.37 (s, 9H).

^{13}C NMR (75 MHz, Chloroform-d) δ 169.25, 158.94, 155.71, 135.94, 129.37, 129.20, 128.66, 126.95, 122.74, 112.95, 80.70, 53.46, 38.19, 28.13.

HRMS (ESI) $C_{20}H_{24}N_2NaO_4$ $[M+Na]^+$ Calcd: 379.1628, Found: 379.1617.

***tert*-butyl (*S*)-(2-((4-methyl-1-oxo-1-(phenoxyamino)pentan-2-yl)amino)-2-oxoethyl)carbamate (2c)**



2c

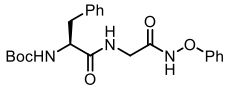
White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 4:1), 4 mmol scale, 958 mg, 63% yield.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.40 – 7.21 (m, 2H), 7.01 (dd, J = 13.3, 7.7 Hz, 4H), 4.34 (t, J = 7.7 Hz, 1H), 3.68 – 3.46 (m, 2H), 1.70 – 1.49 (m, 3H), 1.38 (s, 9H), 0.90 (dd, J = 17.1, 6.2 Hz, 6H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 169.51, 169.26, 159.39, 155.82, 129.41, 122.29, 112.74, 78.03, 48.98, 43.10, 28.14, 24.10, 22.79, 21.57.

HRMS (ESI) $C_{19}H_{29}N_3NaO_5$ $[M+Na]^+$ Calcd: 402.1999, Found: 402.1984.

***tert*-butyl (*S*)-(1-oxo-1-((2-oxo-2-(phenoxyamino)ethyl)amino)-3-phenylpropan-2-yl)carbamate (2d)**



2d

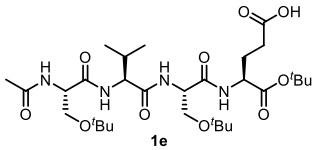
White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1), 1.5 mmol scale, 320 mg, 53% yield.

^{1}H NMR (300 MHz, Chloroform-d) δ 10.30 (s, 1H), 7.33 – 7.20 (m, 5H), 7.17 (d, J = 7.2 Hz, 2H), 7.02 (d, J = 8.1 Hz, 4H), 5.17 (d, J = 3.9 Hz 1H), 4.30 (t, J = 6.8 Hz, 1H), 4.18 – 3.76 (m, 2H), 3.03 (ddd, J = 45.2, 13.8, 7.2 Hz, 2H), 1.31 (s, 9H).

^{13}C NMR (75 MHz, Chloroform-d) δ 172.67, 159.15, 156.01, 136.05, 130.90, 129.48, 129.12, 128.80, 127.20, 123.04, 113.17, 81.09, 65.56, 56.58, 30.54, 28.13.

HRMS (ESI): $C_{22}H_{27}N_3O_5Na$ $[M+Na]^+$ Calcd: 436.1843, Found: 436.1833.

(5*S*,8*S*,11*S*,14*S*)-5-acetamido-14-(*tert*-butoxycarbonyl)-11-(*tert*-butoxymethyl)-8-isopropyl-2,2-dimethyl-6,9,12-trioxo-3-oxa-7,10,13-triazaheptadecan-17-oic acid (1e)



1e

Light yellow solid was obtained from 2-chlorotrityl chloride resin that cleavage by 20% HFIP in DCM (1 mmol resin loading, 10 steps, 511 mg, 81% yield).

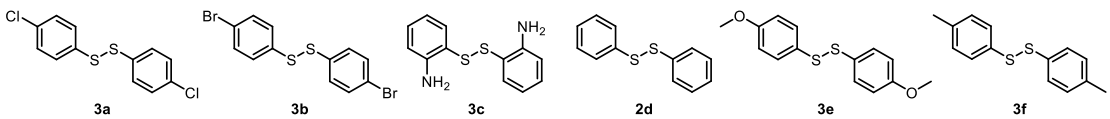
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.10 – 7.91 (m, 3H), 7.70 (d, J = 8.9 Hz, 1H), 4.46 – 4.31 (m, 2H), 4.27 (t, J = 7.8 Hz, 1H), 4.20 – 4.08 (m, 1H), 3.53 – 3.34 (m, 4H), 2.25 (t, J = 7.8 Hz, 2H), 2.03 – 1.89 (m, 2H), 1.88 (s, 3H), 1.82 – 1.72 (m, 1H), 1.39 (s, 9H), 1.10 (s, 18H), 0.89 – 0.75 (m, 6H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 173.85, 170.52, 169.77, 169.50, 169.35, 80.59, 72.78, 61.82, 57.37, 53.41, 53.15, 51.99, 35.79, 30.98, 29.89, 27.57, 27.15, 26.45, 22.52, 19.20, 17.98.

HRMS (ESI): $C_{30}H_{55}N_4O_{10}$ $[M+H]^+$ Calcd: 631.3913, Found: 631.3924.

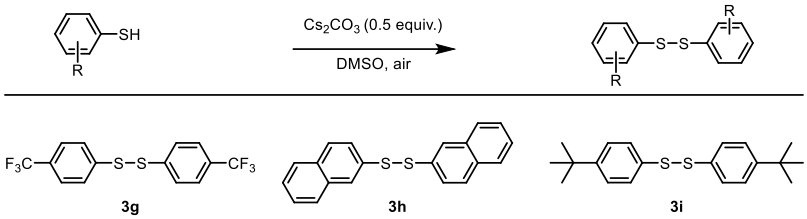
2.2 Diaryl disulfides

These diaryl disulfides are commercially available



3a 3b 3c 2d 3e 3f

General Procedure A for the Synthesis of diaryl disulfides

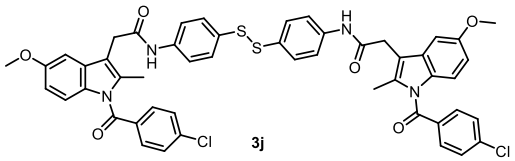


To an oven-dried Schlenk vial equipped with a magnetic stir bar was charged with thiophenols (0.1 mmol, 1.0 equiv.), Cs_2CO_3 (0.025 mmol), DMSO (1 mL, 0.1 M) and stirred for 30 min under air. The reaction solution could be used directly without any purification and treatment.

General procedure B for the synthesis of diaryl disulfides

To an oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 4,4'-dithiodianiline (1.0 equiv.), HATU (2.4 equiv.), DMF (0.1-0.5 M) and stirred at room temperature for 30 min, then carboxylic acids (2.0 equiv.) were added and stirred at room temperature. The reaction was monitored by TLC until starting materials were completed consumed. The crude reaction mixture was dissolved with 50 mL DCM, washed with saturated citric acid aqueous solution (2 × 50 mL), saturated sodium bicarbonate aqueous solution (2 × 50 mL) and brine (50 mL). In this process, the product appears as precipitation, filtrated and washed with DCM, dried over at 40℃ to give the product.

***N,N'*-(disulfanediylbis(4,1-phenylene))bis(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetamide) (3j)**



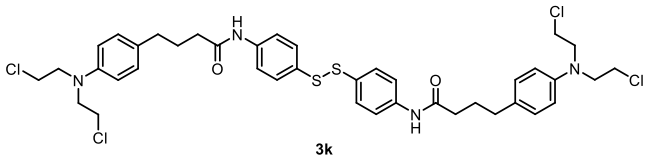
Light yellow solid, 6 mmol scale, 4719 mg, 85% yield.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.39 (s, 2H), 7.73 – 7.59 (m, 12H), 7.45 (d, J = 8.4 Hz, 4H), 7.19 (d, J = 2.5 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 6.71 (dd, J = 9.0, 2.5 Hz, 2H), 3.76 (d, J = 7.4 Hz, 10H), 2.29 (s, 6H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 168.69, 167.85, 155.56, 139.27, 137.62, 135.45, 134.17, 131.16, 130.85, 130.26, 130.04, 129.73, 129.05, 119.98, 114.60, 113.91, 111.17, 101.93, 55.42, 32.02, 13.42.

HRMS (ESI) $C_{50}H_{40}Cl_2N_4NaO_6S_2$ $[M+Na]^+$ Calcd: 949.1659, Found: 949.1633.

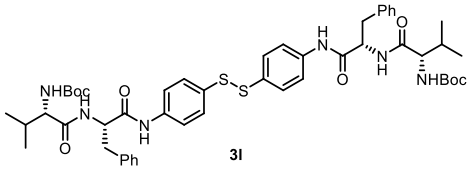
***N,N'*-(disulfanediylbis(4,1-phenylene))bis(4-(4-(bis(2-chloroethyl)amino)phenyl)butanamide) (3k)**



White solid, 2 mmol scale, 904 mg, 52% yield.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.41 (s, 8H), 7.20 (s, 2H), 7.07 (d, *J* = 8.2 Hz, 4H), 6.61 (d, *J* = 8.2 Hz, 4H), 3.76 – 3.49 (m, 16H), 2.60 (t, *J* = 7.4 Hz, 4H), 2.33 (t, *J* = 7.4 Hz, 4H), 2.08 – 1.88 (m, 4H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 171.23, 144.34, 137.65, 131.91, 130.22, 129.99, 129.67, 120.26, 112.09, 53.49, 40.50, 36.77, 33.89, 26.98.
HRMS (ESI) $C_{40}H_{46}Cl_4N_4NaO_2S_2$ $[M+Na]^+$ Calcd: 841.1709, Found: 841.1713.

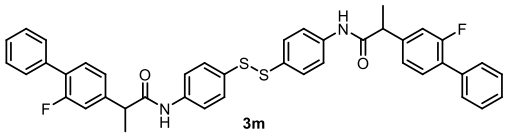
di-*tert*-butyl ((2*S*,2'*S*)-(((2*S*,2'*S*)-((disulfanediylbis(4,1-phenylene))bis(azanediyl))bis(1-oxo-3-phenylpropane-1,2-diyl))bis(azanediyl))bis(3-methyl-1-oxobutane-1,2-diyl))dicarbamate (3l)



3l

White solid, 2 mmol scale, 788 mg, 41% yield. (2.4 equiv. HOBt was added to the reaction)
^{1}H NMR (300 MHz, DMSO-d_6) δ 10.22 (s, 2H), 8.11 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 4H), 7.44 (d, *J* = 8.7 Hz, 4H), 7.33 – 7.13 (m, 10H), 6.68 (d, *J* = 8.9 Hz, 2H), 4.71 (q, *J* = 7.9, 7.5 Hz, 2H), 3.75 (t, *J* = 8.0 Hz, 2H), 3.09 – 2.82 (m, 4H), 1.84 (q, *J* = 6.8 Hz, 2H), 1.36 (s, 18H), 0.72 (dd, *J* = 10.4, 6.7 Hz, 12H).
^{13}C NMR (75 MHz, DMSO-d_6) δ 171.79, 171.42, 170.32, 170.22, 155.76, 155.45, 138.76, 137.64, 137.35, 130.06, 129.23, 128.14, 126.43, 120.32, 120.10, 78.25, 59.98, 55.04, 54.94, 54.64, 37.76, 37.40, 30.56, 30.07, 28.22, 28.15, 19.14, 18.94, 18.27, 18.15.
HRMS (ESI) $C_{50}H_{64}N_6NaO_8S_2$ $[M+Na]^+$ Calcd: 963.4119, Found: 963.4100.

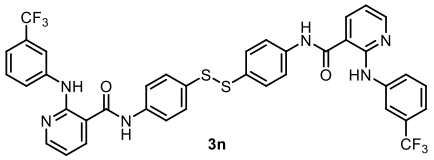
***N,N'*-(disulfanediylbis(4,1-phenylene))bis(2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide) (3m)**



3m

White solid, 2.05 mmol, 827 mg, 64% yield.
^{1}H NMR (300 MHz, DMSO-d_6) δ 10.29 (s, 2H), 7.62 (d, *J* = 8.7 Hz, 4H), 7.55 – 7.38 (m, 16H), 7.31 (d, *J* = 3.4 Hz, 2H), 7.28 (s, 2H), 3.89 (q, *J* = 6.9 Hz, 2H), 1.45 (d, *J* = 6.9 Hz, 6H).
^{13}C NMR (75 MHz, DMSO-d_6) δ 171.83, 160.49, 157.23, 143.54, 143.44, 139.25, 134.90, 130.73, 130.68, 130.08, 129.77, 128.73, 128.69, 128.59, 127.77, 126.76, 126.58, 123.82, 123.77, 119.96, 115.08, 114.77, 45.49, 18.37.
^{19}F NMR (282 MHz, DMSO-d_6) δ -118.43.
HRMS (ESI) $C_{38}H_{26}F_6N_6NaO_2S_2$ $[M+Na]^+$ Calcd: 799.1355, Found: 799.1326.

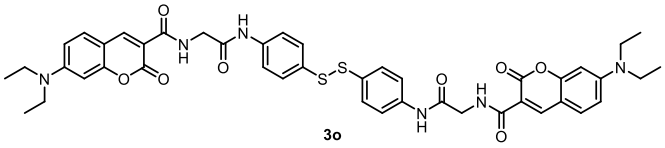
***N,N'*-(disulfanediylbis(4,1-phenylene))bis(2-((3-(trifluoromethyl)phenyl)amino)nicotinamide) (3n)**



White solid, 1.77 mmol scale, 885 mg, 64% yield.

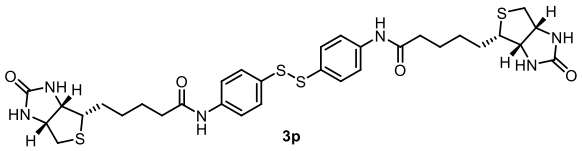
^{1}H NMR (300 MHz, DMSO-d_6) δ 10.64 (s, 2H), 10.38 (s, 2H), 8.42 (dd, *J* = 4.9, 1.7 Hz, 2H), 8.25 (dd, *J* = 7.8, 1.8 Hz, 4H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.7 Hz, 4H), 7.61 – 7.48 (m, 6H), 7.30 (d, *J* = 7.3 Hz, 2H), 7.02 (dd, *J* = 7.7, 4.8 Hz, 2H).
^{13}C NMR (75 MHz, DMSO-d_6) δ 166.53, 153.84, 150.79, 140.95, 138.62, 138.08, 130.85, 129.77, 129.71, 129.54, 123.12, 122.54, 117.83, 115.26, 114.55, 113.02.
^{19}F NMR (282 MHz, DMSO-d_6) δ -61.15.
HRMS (ESI) $C_{38}H_{26}F_6N_6NaO_2S_2$ $[M+Na]^+$ Calcd: 799.1355, Found: 799.1326.

***N,N′*-(((disulfanediylbis(4,1-phenylene))bis(azanediyl))bis(2-oxoethane-2,1-diyl))bis(7-diethylamino)-2-oxo-2*H*-chromene-3-carboxamide) (3o)**



Yellow solid, 5 mmol scale, 1764 mg, 41% yield.
^{1}H NMR (300 MHz, DMSO-d_6) δ 10.26 (s, 2H), 9.08 (t, *J* = 5.3 Hz, 2H), 8.68 (s, 2H), 7.69 (d, *J* = 9.0 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 4H), 7.46 (d, *J* = 8.7 Hz, 4H), 6.81 (dd, *J* = 9.1, 2.3 Hz, 2H), 6.63 (d, *J* = 2.3 Hz, 2H), 4.17 (d, *J* = 5.3 Hz, 4H), 3.49 (q, *J* = 6.9 Hz, 8H), 1.14 (t, *J* = 7.0 Hz, 12H).
^{13}C NMR (75 MHz, DMSO-d_6) δ 167.58, 162.41, 161.61, 157.34, 152.54, 147.89, 138.98, 131.69, 130.15, 129.70, 119.86, 110.17, 108.95, 107.63, 95.89, 44.36, 43.34, 12.33.
HRMS (ESI) $C_{44}H_{44}N_6NaO_8S_2$ $[M+Na]^+$ Calcd: 871.2554, Found: 871.2525.

***N,N′*-(disulfanediylbis(4,1-phenylene))bis(5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide) (3p)**

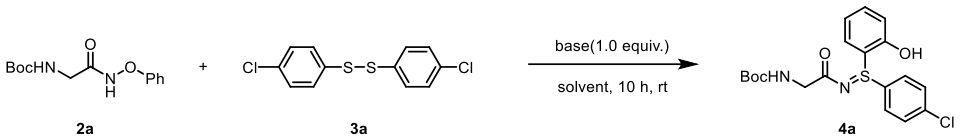


Light brown solid, 2 mmol scale, 1017 mg, 73% yield.
^{1}H NMR (300 MHz, DMSO-d_6) δ 10.04 (s, 2H), 7.61 (d, *J* = 8.6 Hz, 4H), 7.43 (d, *J* = 8.5 Hz, 4H), 6.43 (d, *J* = 23.8 Hz, 4H), 4.31 (dd, *J* = 7.7, 5.0 Hz, 2H), 4.14 (ddd, *J* = 7.5, 4.5, 1.7 Hz, 2H), 3.17 – 3.05 (m, 2H), 2.82 (dd, *J* = 12.4, 5.0 Hz, 2H), 2.58 (d, *J* = 12.4 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 4H), 1.70 – 1.43 (m, 8H), 1.42 – 1.23 (m, 4H).
^{13}C NMR (75 MHz, DMSO-d_6) δ 171.40, 162.76, 139.52, 130.17, 129.30, 119.74, 61.04, 59.21, 55.38, 39.87, 36.24, 28.21, 28.08, 25.05.
^{13}C NMR (75 MHz, DMSO-d_6) δ 171.39, 162.75, 139.51, 130.16, 129.29, 119.73, 61.04, 59.20, 55.38, 36.24, 28.21, 28.08, 25.05.
HRMS (ESI) $C_{32}H_{40}N_6NaO_4S_4$ $[M+Na]^+$ Calcd: 723.1886, Found: 723.1857.

3. General procedure for N=S bond coupling reaction

3.1 Optimization of reaction conditions (Method A)

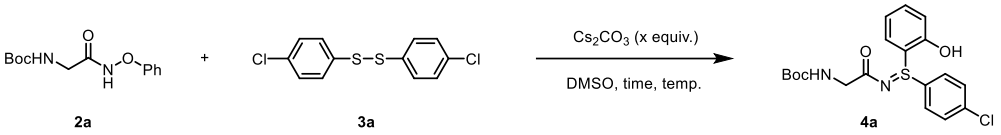
Table S1: Optimization of solvent and additives



entry	solvent	base	yield[a] (%)
1	CH_3CN	CsOAc	41[b]
2	CH_3CN	Cs_2CO_3	71
3[c]	CH_3CN	Cs_2CO_3	64
4	CH_3CN	Na_2CO_3	trace
5	CH_3CN	quinine	trace
6	CH_3CN	Et_3N	trace
7	$CHCl_3$	Cs_2CO_3	0
8	DCM	Cs_2CO_3	0
9	DCE	Cs_2CO_3	0
10	Tol	Cs_2CO_3	0
11	EtOAc	Cs_2CO_3	0
12	MeOH	Cs_2CO_3	0
13	**DMSO**	**Cs_2CO_3**	**83(75[b])**
14	DMSO	CsOAc	61

[a]Unless otherwise stated, the reaction was carried out with 0.05 mmol **2a**, 0.05 mmol **3a** and 0.05 mmol basic additives in 1 mL solvent at room temperature for 10 h. Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield after column chromatography was given. [c]50 mg 4 Å MS was added.

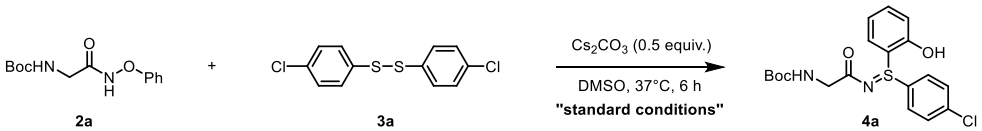
Table S2: Optimization of temperature, reaction time and base loading



entry	Cs_2CO_3 (x equiv.)	time (h)	temp. (°C)	yield[a] (%)
1	0	10	rt	0
2	2	10	rt	48
3	1	10	rt	83(75[b])
4	**0.5**	**10**	**rt**	**90**
5	0.5	6	rt	79
6	**0.5**	**6**	**37**	**90(85[b])**
7	0.3	6	37	74
8	0.1	6	37	52
9[c]	0.5	6	37	89

[a]Unless otherwise stated, the reaction was carried out with 0.05 mmol **2a**, 0.05 mmol **3a** and x equiv. Cs_2CO_3 in 1 mL DMSO. Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield after column chromatography was given. [c]DMF instead of DMSO.

Table S3: Optimization of control experiments under standard reaction conditions



entry	change from the "standard conditions"	yield (%)
1	standard conditions	90
2	without Cs_2CO_3	0
3	under Ar	90
4	2 equiv. 4-Chlorothiophenol instead of **3a**	90
5	DMF instead of DMSO	89

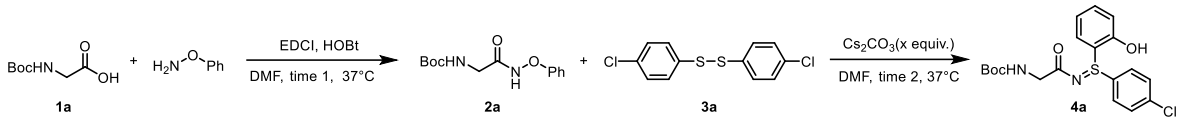
"standard conditions": the reaction was carried out with 0.05 mmol **2a**, 0.05 mmol **3a** and 0.025 mmol Cs_2CO_3 in 1 mL DMSO at 37°C for 6 h. Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

General procedure (Method A)

To an oven-dried 10 mL test tube with a stirring bar was added amino acid or peptides derivatives **2** (0.05 mmol), diaryl disulfide derivatives **3** (0.05 mmol) and Cs_2CO_3 (0.025 mmol,). Then DMSO (1 mL) was added and the mixture was stirred at 37°C. The reaction was monitored by TLC until starting materials were completed consumed. The crude reaction mixture was diluted with EtOAc (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was washed with EtOAc (2 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residues were purified by column chromatography on silica gel to give the product.

3.2 Optimization of one pot two-steps reaction conditions (Method B)

Table S4: Optimization of reaction time and base loading



1a 2a 3a 4a

entry	Cs_2CO_3 (x equiv.)	time 1 (h)	time 2 (h)	yield (%)
1	1.2	0	6	0
2	1.2	4	6	41
3	1.7	4	6	42
4	1.7	6	6	44
5	**1.7**	**6**	**12**	**53**

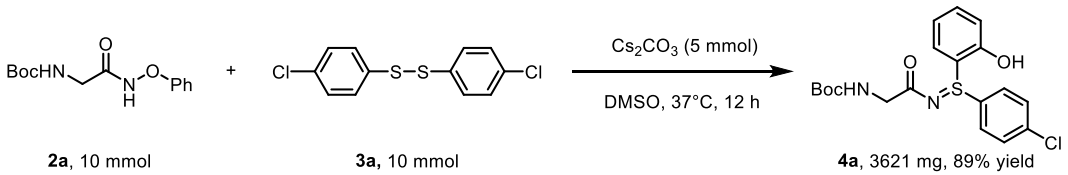
Reaction conditions: Boc-Glycine **1a** (0.1 mmol), phenoxyamine (0.1 mmol), EDCI (0.12 mmol) and HOBt (0.12 mmol) in 2 mL DMF at 37 ℃ under air for time 1, then 4,4'-dichlorodiphenyl disulfide **3a** (0.1 mmol) and Cs_2CO_3 (x equiv.) were added and stirred for time 2. Yield was determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

General procedure for one pot two-steps reaction (Method B)

To an oven-dried 10 mL test tube with a stirring bar was added amino acids or peptides **1** (0.1 mmol), EDCI (0.12 mmol) and HOBt (0.12 mmol). Then O-phenylhydroxylamine (0.1 mmol) in DMF (2 mL) were added and the mixture was stirred at 37℃ for 6 h. Subsequently, 4,4'-dichlorodiphenyl disulfide **3** (0.1 mmol) and Cs_2CO_3 (0.17 mmol) were added to the reaction mixture and stirred at 37℃. The reaction was monitored by TLC until starting materials were completed consumed. The crude reaction mixture was diluted with EtOAc (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was washed with EtOAc (2 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residues were purified by column chromatography on silica gel to give the product.

3.3 General procedure for scale-up experiment

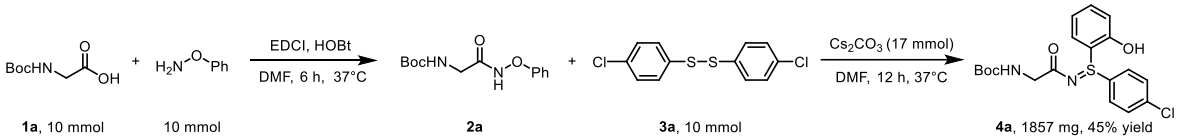
Method A:



2a, 10 mmol **3a,** 10 mmol **4a**, 3621 mg, 89% yield

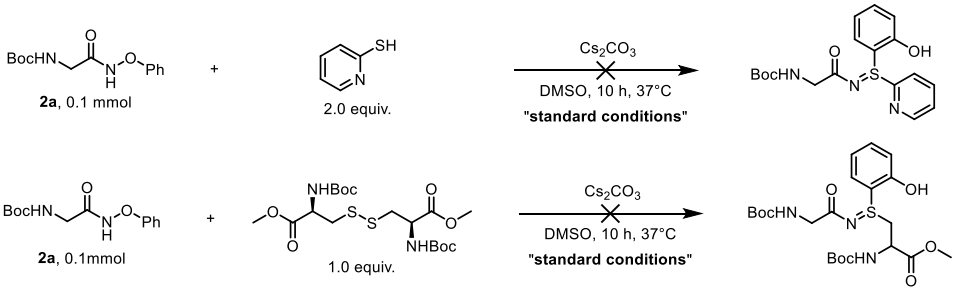
To an oven-dried 100 mL round bottom flask with a stirring bar was added **2a** (10 mmol), **3a** (10 mmol), Cs_2CO_3 (5 mmol) and DMSO (20 mL). The reaction mixture was stirred at 37℃ for 12 h and monitored by TLC. Upon starting materials were completed consumed, The crude reaction mixture was diluted with EtOAc (100 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was washed with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (2 × 100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residues were purified by column chromatography on silica gel (PE: EtOAc = 2:1) to give the product **4a**.

Method B:



To an oven-dried 100 mL round bottom flask with a stirring bar was added Boc-Gly-OH **1a** (10 mmol), EDCI (12 mmol), HOBt (12 mmol), DMF (20 mL) and stirred for 10 min, then NH_2OPh (10 mmol) in DMF (5 mL) was added and the mixture was stirred at 37℃ for 6 h. Subsequently, 4,4'-dichlorodiphenyl disulfide **3a** (10 mmol) and Cs_2CO_3 (17 mmol) were added to the reaction mixture and stirred at 37℃ for 12 h. The reaction was monitored by TLC until starting materials were completed consumed. The crude reaction mixture was diluted with EtOAc (100 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was washed with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (2 × 100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residues were purified by column chromatography on silica gel (PE: EtOAc = 2:1) to give the product **4a**.

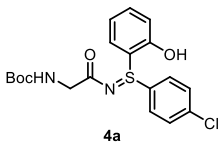
3.4 Heteroaryl thiols and dialkyl disulfides experiment



Under "**standard conditions**", 2-Mercaptopyridine and (Boc-*L*-Cys-OMe)$_2$ were not reacted with **2a**.

3.5 Characterization of products

***tert*-butyl (2-(((4-chlorophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-2-oxoethyl)carbamate (4a)**



White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).

Method A, 0.05 mmol scale, 17.3 mg, 85% yield.

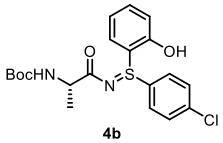
Method B, 10 mmol scale, 1.9 g, 45 % yield.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.59 (s, 1H), 7.69 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.34 (t, *J* = 7.9 Hz, 2H), 6.91 (t, *J* = 7.6 Hz, 2H), 5.23 (s, 1H), 4.03 (d, *J* = 5.4 Hz, 2H), 1.45 (s, 9H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 179.07, 159.72, 155.86, 138.61, 134.28, 133.59, 130.04, 128.78, 127.79, 120.35, 119.32, 115.77, 79.50, 45.36, 28.30.

HRMS (ESI) $C_{19}H_{22}ClN_2O_4S$ $[M+H]^+$ Calcd: 409.0983, Found: 409.0982.

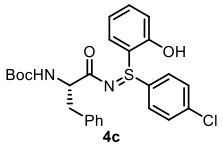
***tert*-butyl ((2*S*)-1-(((4-chlorophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-1-oxopropan-2-yl)carbamate (4b)**



4b

Light yellow solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method B, 0.1 mmol scale, 25.1 mg, 59% yield.
^{1}H NMR (300 MHz, Chloroform-d) δ 7.67 (t, J = 8.4 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 7.34 (t, J = 7.2 Hz, 2H), 7.02 – 6.84 (m, 2H), 5.32 – 5.15 (m, 1H), 4.42 (d, J = 8.5 Hz, 1H), 1.44 (d, J = 4.1 Hz, 12H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 182.57, 182.34, 160.11, 159.68, 155.28, 138.73, 134.67, 134.54, 133.88, 130.18, 129.08, 128.61, 120.51, 120.30, 120.13, 115.05, 79.39, 51.60, 28.36, 20.03, 19.81.
HRMS (ESI) $C_{20}H_{24}ClN_2O_4S$ $[M+H]^+$ Calcd: 423.1140, Found: 423.1133.

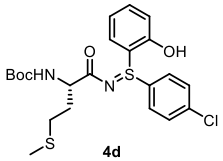
***tert*-butyl ((2*S*)-1-(((4-chlorophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (4c)**



4c

White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1 to 1:1).
Method A, 0.05 mmol scale, 18.3 mg, 73% yield.
Method B, 0.1 mmol scale, 25.8 mg, 52% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.50 (s, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.46 (t, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.33 – 7.24 (m, 2H), 7.24 – 7.09 (m, 5H), 6.96 – 6.77 (m, 2H), 5.21 (t, *J* = 7.8 Hz, 1H), 4.79 – 4.62 (m, 1H), 3.22 – 3.03 (m, 2H), 1.43 (s, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 180.89, 180.67, 159.58, 159.20, 155.18, 138.68, 138.53, 137.11, 137.05, 134.51, 134.42, 133.59, 133.32, 130.10, 130.02, 129.38, 128.87, 128.73, 128.30, 128.16, 126.48, 120.34, 120.19, 119.74, 115.34, 114.98, 79.43, 56.70, 56.59, 39.60, 28.34.
HRMS (ESI) $C_{26}H_{28}ClN_2O_4S$ $[M+H]^+$ Calcd 499.1453, Found: 499.1446.

***tert*-butyl ((2*S*)-1-(((4-chlorophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (4d)**

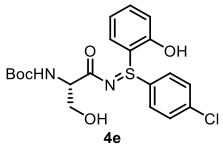


4d

White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method B, 0.1 mmol scale, 24.6 mg, 51% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.69 (dd, *J* = 10.9, 8.6 Hz, 2H), 7.46 (dd, *J* = 8.8, 2.6 Hz, 2H), 7.44 – 7.27 (m, 2H), 7.05 – 6.84 (m, 2H), 5.36 – 5.20 (m, 1H), 4.51 (d, *J* = 3.6 Hz, 1H), 2.64 – 2.42 (m, 2H), 2.28 – 2.12 (m, 1H), 2.06 (d, *J* = 5.2 Hz, 3H), 2.04 – 1.89 (m, 1H), 1.44 (d, *J* = 2.8 Hz, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 181.42, 158.17, 155.50, 138.56, 134.38, 134.08, 133.40, 130.06, 130.01, 128.88, 127.25, 120.31, 118.77, 116.42, 79.46, 55.33, 33.40, 30.17, 28.26, 15.40.

HRMS (ESI) $C_{22}H_{28}ClN_2O_4S$ $[M+H]^+$ Calcd: 483.1174, Found: 483.1168.

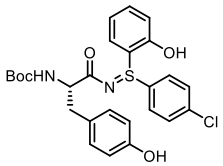
***tert*-butyl ((2*S*)-1-(((4-chlorophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (4e)**



4e

Light yellow solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method B, 0.1 mmol scale, 12.1 mg, 28% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.75 – 7.65 (m, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.30 (m, 2H), 7.04 – 6.81 (m, 2H), 5.63 (d, *J* = 7.4 Hz, 1H), 4.48 (s, 1H), 4.09 – 3.83 (m, 2H), 1.45 (s, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 179.98, 158.76, 156.04, 138.74, 134.63, 134.49, 133.05, 130.17, 128.76, 128.02, 120.45, 119.49, 79.88, 64.63, 57.56, 44.15, 38.51, 28.31.
HRMS (ESI) $C_{20}H_{24}ClN_2O_5S$ $[M+H]^+$ Calcd 439.1089, Found: 439.1085.

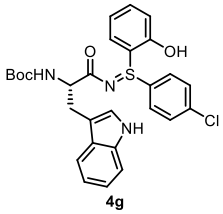
***tert*-butyl ((2*S*)-1-(((4-chlorophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (4f)**



4f

White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method B, 0.1 mmol scale, 24.8 mg, 48% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.12 – 6.73 (m, 5H), 6.69 – 6.53 (m, 2H), 5.37 – 5.21 (m, 1H), 4.74 – 4.60 (m, 1H), 3.13 – 2.94 (m, 2H), 1.44 (d, *J* = 7.5 Hz, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 181.16, 158.91, 155.45, 155.06, 138.61, 134.57, 134.45, 133.30, 130.38, 130.09, 130.05, 128.84, 128.71, 128.42, 128.17, 120.47, 119.90, 119.61, 115.36, 115.27, 79.78, 56.89, 38.73, 28.34.
HRMS (ESI) $C_{26}H_{28}ClN_2O_5S$ $[M+H]^+$ Calcd: 515.1402, Found: 515.1391.

***tert*-butyl ((2S)-1-(((4-chlorophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate (4g)**

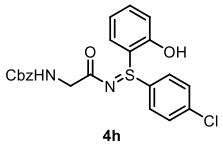


4g

Light yellow solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method B, 0.1 mmol scale, 20.1 mg, 37% yield.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.50 (s, 1H), 8.43 – 8.13 (m, 1H), 7.58 (dd, *J* = 13.4, 7.8 Hz, 1H), 7.46 – 7.27 (m, 4H), 7.22 (t, *J* = 8.2 Hz, 3H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.98 – 6.92 (m, 1H), 6.91 – 6.74 (m, 2H), 5.35 (d, *J* = 7.9 Hz, 1H), 4.86 – 4.72 (m, 1H), 3.43 – 3.22 (m, 2H), 1.43 (s, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 181.55, 181.17, 159.62, 159.10, 155.38, 138.51, 138.28, 135.92, 134.32, 133.85, 133.17, 130.01, 129.87, 128.81, 128.45, 128.33, 127.86, 122.72, 121.87, 121.75, 120.23, 120.07, 119.68, 119.39, 119.21, 118.96, 115.53, 114.56, 111.13, 110.97, 79.42, 56.32, 29.67, 29.14, 28.37.
HRMS (ESI) $C_{28}H_{29}ClN_3O_4S$ $[M+H]^+$ Calcd: 538.1562, Found: 538.1549.

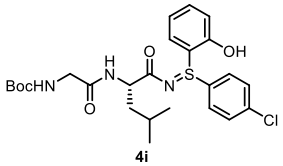
benzyl (2-(((4-chlorophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-2-oxoethyl)carbamate (4h)



4h

White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method B, 0.1 mmol scale, 23.1 mg, 52% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.61 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.37 (m, 3H), 7.37 – 7.27 (m, 6H), 6.93 (dd, *J* = 13.8, 7.5 Hz, 2H), 5.46 (t, *J* = 5.1 Hz, 1H), 5.13 (s, 2H), 4.10 (d, *J* = 5.4 Hz, 2H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 178.41, 159.58, 156.28, 138.92, 136.46, 134.65, 133.66, 130.25, 128.76, 128.64, 128.44, 128.02, 120.48, 120.21, 114.73, 66.83, 45.60.
HRMS (ESI) $C_{22}H_{20}ClN_2O_4S$ $[M+H]^+$ Calcd: 443.0827, Found: 443.0824.

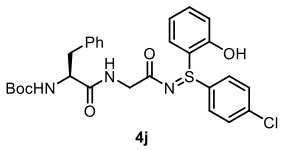
***tert*-butyl (2-(((2*S*)-1-(((4-chlorophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-4-methyl-1-oxopentan-2-yl)amino)-2-oxoethyl)carbamate (4i)**



4i

Light yellow solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method A, 0.1 mmol scale, 34.0 mg, 65% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.68 (t, *J* = 8.1 Hz, 2H), 7.47 – 7.39 (m, 2H), 7.39 – 7.30 (m, 2H), 7.03 – 6.77 (m, 3H), 5.34 (t, *J* = 5.6 Hz, 1H), 4.77 (td, *J* = 8.7, 4.6 Hz, 1H), 3.86 (dd, *J* = 16.3, 10.2 Hz, 2H), 1.77 – 1.52 (m, 3H), 1.42 (s, 9H), 0.93 (d, *J* = 5.7 Hz, 6H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 181.64, 181.56, 168.93, 159.73, 159.40, 155.94, 138.75, 134.51, 134.45, 134.06, 133.91, 130.18, 128.81, 128.61, 120.41, 120.28, 120.22, 119.94, 115.28, 113.22, 80.00, 52.98, 42.85, 42.71, 28.24, 24.96, 22.92, 22.04.
HRMS (ESI) $C_{25}H_{33}ClN_3O_5S$ $[M+H]^+$ Calcd: 522.1824, Found: 522.1815.

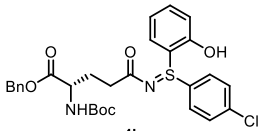
***tert*-butyl ((2*S*)-1-((2-(((4-chlorophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (4j)**



4j

Light brown solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 1:1).
Method A, 0.05 mmol scale, 20.6 mg, 74% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.89 (s, 1H), 7.66 (dd, *J* = 8.7, 1.9 Hz, 2H), 7.45 (dd, *J* = 8.6, 1.2 Hz, 2H), 7.42 – 7.35 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.15 (m, 5H), 7.00 – 6.88 (m, 2H), 6.76 (q, *J* = 5.6 Hz, 1H), 5.11 (d, *J* = 3.9 Hz,1H), 4.44 (d, *J* = 5.4 Hz, 1H), 4.25 – 3.96 (m, 2H), 3.22 – 2.93 (m, 2H), 1.35 (d, *J* = 2.8 Hz, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 177.68, 171.24, 159.14, 155.39, 138.93, 136.71, 134.63, 133.32, 130.23, 129.24, 128.86, 128.50, 128.42, 126.75, 120.55, 119.90, 115.05, 80.03, 55.65, 44.19, 28.17.
HRMS (ESI) $C_{28}H_{31}ClN_3O_5S$ $[M+H]^+$ Calcd: 556.1667, Found: 556.1655.

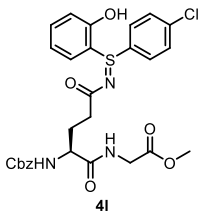
benzyl N^2-(*tert*-butoxycarbonyl)-N^5-((4-chlorophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)-*L*-glutaminate (4k)



4k

Yellow solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method B, 0.1 mmol scale, 27.4 mg, 48% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.38 – 7.27 (m, 7H), 6.99 – 6.85 (m, 2H), 5.35 (d, *J* = 8.3 Hz, 1H), 5.22 – 5.09 (m, 2H), 4.39 (tt, *J* = 8.5, 4.4 Hz, 1H), 2.64 – 2.42 (m, 2H), 2.32 – 2.15 (m, 1H), 2.04 (dq, *J* = 14.5, 7.8 Hz, 1H), 1.41 (s, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 181.97, 172.37, 159.69, 159.63, 155.41, 138.62, 135.32, 134.39, 134.02, 130.12, 128.81, 128.72, 128.66, 128.50, 128.26, 128.16, 120.29, 120.09, 120.05, 114.89, 114.80, 79.76, 66.97, 53.32, 53.26, 33.32, 33.26, 28.59, 28.24, 27.72.
HRMS (ESI) $C_{29}H_{32}ClN_2O_6S$ $[M+H]^+$ Calcd: 571.1664, Found: 571.1652.

methyl N^2-((benzyloxy)carbonyl)-N^5-((4-chlorophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)-*L*-glutaminylglycinate (4l)

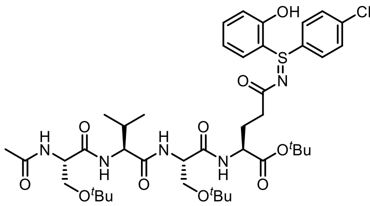


4l

Light yellow solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method B, 0.1 mmol scale, 27.3 mg, 47% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.72 – 7.62 (m, 2H), 7.48 – 7.40 (m, 3H), 7.40 – 7.27 (m, 6H), 7.04 – 6.97 (m, 1H), 6.96 – 6.88 (m, 1H), 6.08 (dd, *J* = 12.6, 7.3 Hz, 1H), 5.18 – 5.00 (m, 2H), 4.43 –

4.24 (m, 1H), 4.16 – 3.90 (m, 2H), 3.72 (d, *J* = 2.9 Hz, 3H), 2.80 – 2.55 (m, 2H), 2.12 (d, *J* = 7.5 Hz, 2H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 182.92, 182.80, 171.82, 171.70, 170.01, 160.06, 159.96, 156.19, 138.84, 138.78, 136.36, 136.26, 134.70, 134.62, 134.03, 130.36, 130.24, 129.28, 129.16, 128.81, 128.47, 128.05, 127.97, 120.57, 120.44, 114.23, 114.12, 66.88, 66.84, 54.31, 52.28, 41.13, 33.28, 29.18.
HRMS (ESI) $C_{28}H_{29}ClN_3O_7S$ [M+H]$^+$ Calcd: 586.1409, Found: 586.1392.

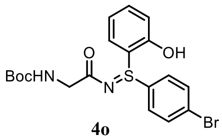
***tert*-butyl (*Z*)-*N*^{2}-(N-N-acetyl-O-(*tert*-butyl)-*L*-seryl-*L*-valyl-O-(*tert*-butyl)-*L*-seryl)-*N*^{5}-((4-chlorophenyl)(2-hydroxyphenyl)-l^4-sulfaneylidene)-*L*-glutaminate (4m)**



4m

White solid was obtained by chromatography on silica gel (eluted: DCM:MeOH = 20:1).
Method B, 0.1 mmol scale, 32.1 mg, 37% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 8.5 Hz, 2H), 7.50 – 7.28 (m, 5H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.97 – 6.79 (m, 3H), 4.47 (s, 3H), 4.39 – 4.29 (m, 1H), 3.84 – 3.73 (m, 2H), 3.37 (q, *J* = 8.0, 7.5 Hz, 2H), 2.61 – 2.36 (m, 2H), 2.23 (dd, *J* = 13.8, 7.1 Hz, 2H), 2.09 – 1.95 (m, 4H), 1.45 (s, 9H), 1.22 (s, 9H), 1.17 (s, 9H), 0.95 (dd, *J* = 14.0, 6.8 Hz, 6H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 182.05, 170.91, 170.52, 170.43, 170.32, 169.83, 159.85, 138.67, 134.42, 130.14, 128.82, 128.75, 120.35, 114.75, 81.86, 74.47, 74.03, 61.45, 61.31, 58.94, 52.98, 52.73, 33.28, 30.72, 28.72, 27.92, 27.36, 27.27, 23.05, 19.35, 17.60.
HRMS (ESI) $C_{42}H_{63}ClN_5O_{10}S$ [M+H]$^+$ Calcd: 864.3979, Found: 864.4018.

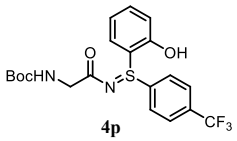
***tert*-butyl (2-(((4-bromophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-2-oxoethyl)carbamate (4o)**



4o

White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method A, 0.05 mmol scale, 19.1 mg, 84% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.73 (s, 1H), 7.65 – 7.56 (m, 4H), 7.45 – 7.37 (m, 1H), 7.30 (d, *J* = 1.6 Hz, 1H), 7.01 – 6.87 (m, 2H), 5.18 (s, 1H), 4.02 (d, *J* = 5.4 Hz, 2H), 1.45 (s, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 178.92, 159.85, 155.81, 134.70, 134.47, 133.18, 128.88, 128.80, 127.25, 120.41, 114.41, 79.55, 45.25, 28.34.
HRMS (ESI) $C_{19}H_{22}BrN_2O_4S$ [M+H]$^+$ Calcd: 453.0478, Found: 453.0473.

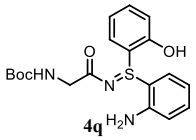
***tert-butyl* (2-(((2-hydroxyphenyl)(4-(trifluoromethyl)phenyl)-l^4-sulfanylidene)amino)-2-oxoethyl)carbamate (4p)**



4p

White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method A, 0.05 mmol scale, 15.6 mg, 71% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.64 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.50 – 7.33 (m, 2H), 7.06 – 6.90 (m, 2H), 5.18 (s, 1H), 4.05 (d, *J* = 5.5 Hz, 2H), 1.46 (s, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 179.19, 160.03, 155.86, 139.56, 135.03, 129.09, 127.66, 126.95, 126.90, 120.56, 113.94, 79.64, 45.30, 28.34.
^{19}F NMR (282 MHz, Chloroform-d) δ -63.15.
HRMS (ESI) $C_{20}H_{22}F_3N_2O_4S$ $[M+H]^+$ Calcd: 443.1247, Found: 443.1245.

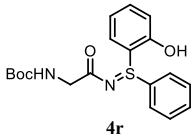
***tert*-butyl (2-(((2-aminophenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-2-oxoethyl)carbamate (4q)**



4q

White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method A, 0.05 mmol scale, 15.8 mg, 81% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.45 – 7.38 (m, 1H), 7.31 – 7.20 (m, 3H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.78 – 6.67 (m, 2H), 5.17 (s, 1H), 3.97 (d, *J* = 3.0 Hz, 2H), 1.44 (s, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 178.79, 159.94, 155.71, 148.21, 134.10, 129.89, 129.13, 120.36, 120.24, 119.01, 117.93, 116.76, 112.70, 79.49, 45.01, 28.32.
HRMS (ESI) $C_{19}H_{24}N_3O_4S$ $[M+H]^+$ Calcd: 390.1482, Found: 390.1480.

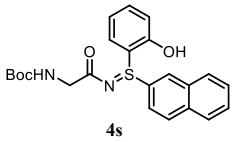
***tert*-butyl (2-(((2-hydroxyphenyl)(phenyl)-l^4-sulfanylidene)amino)-2-oxoethyl)carbamate (4r)**



4r

White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method A, 0.05 mmol scale, 15.6 mg, 83% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.83 (s, 1H), 7.77 – 7.69 (m, 2H), 7.53– 7.45 (m, 3H), 7.44– 7.36 (m, 1H), 7.31 (d, *J* = 7.1 Hz, 1H), 7.03– 6.87 (m, 2H), 5.20 (s, 1H), 4.03 (d,*J* = 5.3 Hz, 2H), 1.45 (s, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 178.72, 160.13, 155.81, 135.31, 134.54, 132.35, 129.98, 129.25, 127.37, 120.52, 120.29, 114.75, 79.51, 45.28, 28.40.
HRMS (ESI) $C_{19}H_{23}N_2O_4S$ $[M+H]^+$ Calcd 375.1373, Found: 375.1371.

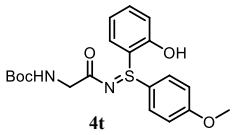
***tert*-butyl (2-(((2-hydroxyphenyl)(naphthalen-2-yl)-l^4-sulfanylidene)amino)-2-oxoethyl)carbamate (4s)**



4s

White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method A, 0.05 mmol scale, 16.0 mg, 75% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.10 (s, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.33 (d,*J* = 7.4 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.94 (d,*J* = 8.6 Hz, 1H), 7.71– 7.56 (m, 3H), 7.41 – 7.32 (m, 1H), 7.08 (t,*J* = 8.1 Hz, 2H), 6.84 – 6.74 (m, 1H), 5.19 (s, 1H), 4.03 (d, *J* = 5.3 Hz, 2H), 1.44 (s, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 178.67, 159.79, 155.73, 134.29, 133.97, 133.37, 129.99, 129.05, 128.65, 128.45, 127.74, 127.27, 125.80, 122.57, 120.78, 120.54, 116.00, 79.39, 45.20, 28.36.
HRMS (ESI) $C_{23}H_{25}N_2O_4S$ $[M+H]^+$ Calcd 425.1530, Found: 425.1526.

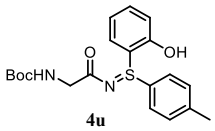
***tert*-butyl (2-(((2-hydroxyphenyl)(4-methoxyphenyl)-l^4-sulfanylidene)amino)-2-oxoethyl)carbamate (4t)**



4t

White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method A, 0.05 mmol scale, 13.2 mg, 65% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.21 (s, 1H), 7.70 (d, *J* = 8.9 Hz, 2H), 7.45 – 7.36 (m, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 7.05 – 6.93 (m, 3H), 6.89 (t, *J* = 7.4 Hz, 1H), 5.17 (s, 1H), 3.99 (d, *J* = 5.3 Hz, 2H), 3.82 (s, 3H), 1.44 (s, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 178.32, 162.89, 160.06, 155.74, 134.21, 129.73, 129.12, 126.29, 120.57, 120.21, 115.48, 79.39, 55.63, 45.15, 28.35.
HRMS (ESI) $C_{20}H_{25}N_2O_5S$ $[M+H]^+$ Calcd: 405.1479, Found: 405.1476.

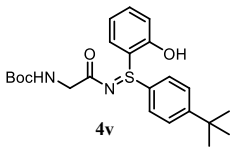
***tert*-butyl (2-(((2-hydroxyphenyl)(p-tolyl)-l^4-sulfanylidene)amino)-2-oxoethyl)carbamate (4u)**



4u

White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method A, 0.05 mmol scale, 14.8 mg, 76% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.06 (s, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.46 – 7.37 (m, 1H), 7.31 – 7.23 (m, 3H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 5.18 (s, 1H), 4.01 (d, *J* = 5.3 Hz, 2H), 2.38 (s, 3H), 1.44 (s, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 178.49, 160.15, 155.76, 143.32, 134.36, 132.17, 130.69, 129.24, 127.44, 120.57, 120.22, 114.80, 79.40, 45.19, 28.35, 21.45.
HRMS (ESI) $C_{20}H_{25}N_2O_4S$ $[M+H]^+$ Calcd: 389.1530, Found: 389.1528.

***tert*-butyl (2-(((4-(*tert*-butyl)phenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-2-oxoethyl)carbamate (4v)**



4v

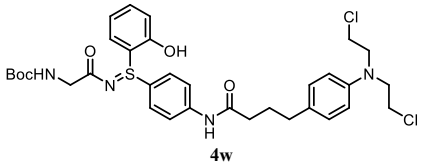
White solid was obtained by chromatography on silica gel (eluted: PE: EtOAc = 2:1).
Method A, 0.05 mmol scale, 10.9 mg, 51% yield.

^{1}H NMR (300 MHz, Chloroform-d) δ 11.94 (s, 1H), 7.65 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.6 Hz, 2H), 7.44 – 7.36 (m, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H), 5.20 (s, 1H), 4.02 (d, J = 5.3 Hz, 2H), 1.45 (s, 9H), 1.29 (s, 9H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 178.47, 160.10, 156.22, 155.76, 134.30, 132.04, 129.18, 127.28, 127.14, 120.41, 120.18, 114.52, 79.41, 45.19, 35.08, 30.99, 28.34.

HRMS (ESI) $C_{23}H_{31}N_2O_4S$ $[M+H]^+$ Calcd: 431.1999, Found: 431.1995.

***tert*-butyl (2-(((4-(4-(4-(bis(2-chloroethyl)amino)phenyl)butanamido)phenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-2-oxoethyl)carbamate (4w)**



4w

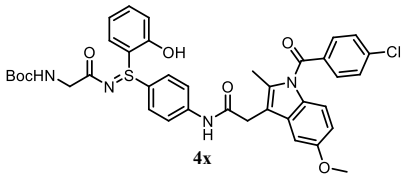
Colorless oil was obtained by chromatography on silica gel (eluted: DCM:MeOH = 40:1).
Method A, 0.1 mmol scale, 35.0mg, 52% yield.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.73 (s, 1H), 8.69 (s, 1H), 7.60 – 7.42 (m, 4H), 7.41 – 7.28 (m, 2H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.89 (t, *J* = 7.7 Hz, 1H), 6.58 (d, *J* = 8.1 Hz, 2H), 5.19 (s, 1H), 3.95 (d, *J* = 5.6 Hz, 2H), 3.62 (dq, *J* = 14.2, 8.2, 7.5 Hz,8H), 2.57 (t, *J* = 7.6 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.03 – 1.91 (m, 2H), 1.42 (s, 9H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 178.69, 172.03, 159.20, 155.91, 144.30, 142.46, 134.22, 131.64, 130.36, 129.64, 128.70, 128.44, 120.43, 120.34, 119.94, 114.87, 112.07, 79.69, 53.47, 45.34, 40.48, 36.71, 33.97, 28.31, 26.96.

HRMS (ESI) $C_{33}H_{40}Cl_2N_4NaO_5S$ $[M+H]^+$ Calcd: 697.1989, Found 697.1991.

***tert*-butyl (2-(((4-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetamido)phenyl)(2-hydroxyphenyl)-l^4-sulfanylidene)amino)-2-oxoethyl)carbamate (4x)**



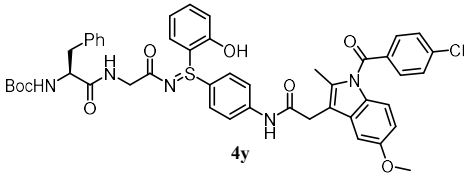
4x

Light yellow solid was obtained by chromatography on silica gel (eluted: DCM:MeOH = 40:1).
Method A, 0.05 mmol scale, 27.1 mg, 74% yield.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.86 (s, 1H), 8.29 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.55 – 7.43 (m, 6H), 7.40 – 7.31 (m, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 6.99 – 6.92 (m, 2H), 6.90 – 6.81 (m, 2H), 6.68 (dd, *J* = 9.0, 2.5 Hz, 1H), 5.21 (s, 1H), 3.98 (d, *J* = 5.6 Hz, 2H), 3.78 (s, 5H), 2.41 (s, 3H), 1.42 (s, 9H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 178.68, 168.85, 168.27, 159.62, 156.25, 155.86, 141.69, 139.56, 136.71, 134.31, 133.46, 131.16, 130.90, 130.25, 129.69, 129.19, 128.94, 128.29, 120.75, 120.31, 115.11, 114.58, 112.06, 111.90, 101.10, 79.59, 55.72, 45.27, 33.25, 28.33, 13.37.
HRMS (ESI) C38H38ClN4O7S [M+H]+ Calcd: 729.2144, Found: 729.2133.

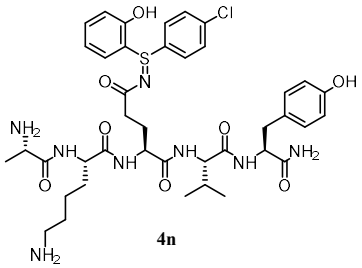
***tert*-butyl ((2*S*)-1-((2-(((4-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetamido)phenyl)(2-hdroxyphenyl)-l^4-sulfanylidene)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (4y)**



4y

Light yellow solid was obtained by chromatography on silica gel (eluted: DCM:MeOH = 40:1). Method A, 0.05 mmol scale, 27.1 mg, 62% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.83 (s, 1H), 7.97 (s, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.60 – 7.42 (m, 6H), 7.44 – 7.32 (m, 1H), 7.26 – 7.11 (m, 5H), 7.02 – 6.90 (m, 2H), 6.90 – 6.80 (m,= 2H), 6.79 – 6.64 (m, 2H), 5.09 (s, 1H), 4.41 (s, 1H), 4.21 – 3.89 (m, 2H), 3.78 (d, *J* = 4.0 Hz, 5H),= 3.22 – 2.90 (m, 2H), 2.42 (s, 3H), 1.32 (s, 9H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 177.45,= 171.24, 168.71, 168.26, 159.59, 156.31, 141.58, 139.65, 136.77, 134.43, 133.39, 131.19, 130.92,= 130.10, 129.46, 129.22, 128.98, 128.53, 126.78, 120.76, 120.41, 115.18, 112.05, 111.88, 100.98,= 80.05, 55.74, 44.15, 38.51, 33.30, 28.18, 13.34. **HRMS** (ESI) $C_{47}H_{47}ClN_5O_8S$ [M+H]+ Calcd:= 876.2828, Found: 876.2799.

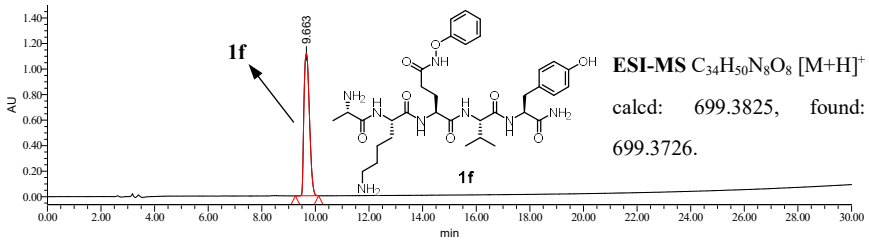
Compound **4n (**sama as **5a**, see below**)**



4n

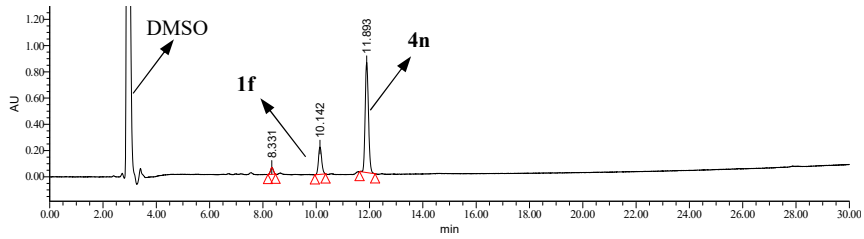
White solid was obtained by after purified by semi preparative HPLC, Method A, 0.025 mmol scale, 9.7mg, 46% yield.
^{1}H NMR (300 MHz, Deuterium Oxide) δ 7.42 (d, *J* = 10.3 Hz, 4H), 7.27 (dd, *J* = 19.8, 8.5 Hz, 2H), 6.92 (d, *J* = 10.7 Hz, 4H), 6.61 (s, 2H), 4.44 (s, 1H), 4.38 – 4.20 (m, 2H), 4.04 (s, 2H), 2.90 (s, 3H), 2.69 (s, 1H), 2.45 (s, 2H), 1.92 (d, *J* = 30.3 Hz, 3H), 1.65 (d, *J* = 28.8 Hz, 4H), 1.39 (d, *J* = 24.6 Hz, 6H), 0.73 (s, 6H).
^{13}C NMR (75 MHz, Deuterium Oxide) δ 180.27, 175.20, 173.17, 172.61, 172.51, 170.61, 163.51, 163.04, 162.57, 156.00, 154.37, 139.32, 135.94, 130.35, 129.67, 129.59, 127.96, 122.12, 121.59, 118.25, 117.26, 115.32, 114.38, 59.24, 54.59, 53.58, 52.91, 48.82, 39.10, 36.28, 32.48, 30.50, 30.24, 27.19, 26.31, 22.00, 18.27, 17.46, 16.55.
ESI-MS $C_{40}H_{54}ClN_8O_8S$ $[M+H]^+$ calcd: 841.3469, found: 841.3353.

a)



ESI-MS $C_{34}H_{50}N_8O_8$ $[M+H]^+$ calcd: 699.3825, found: 699.3726.

b)

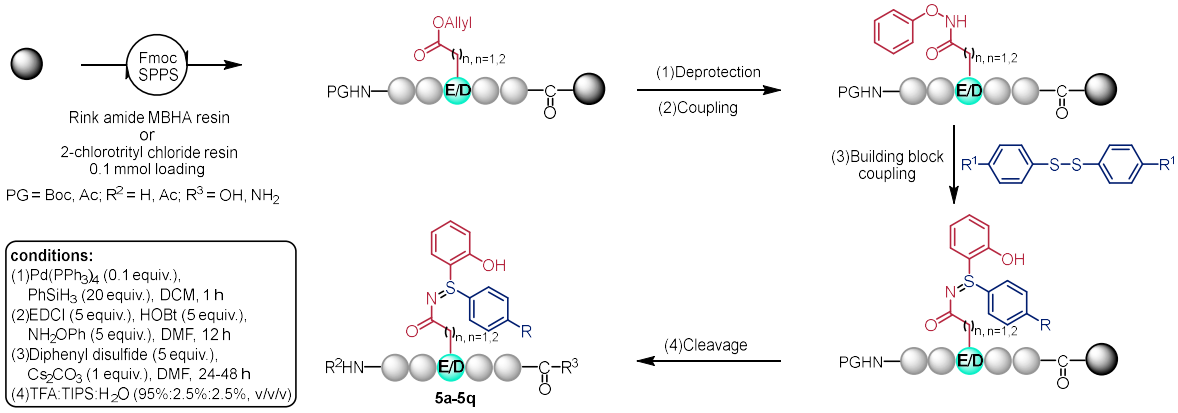


#	Retention Time	Area	Height	% Area
1	8.331	387876	52114	4.14
2	10.142	1742063	208596	18.60
3	11.893	7233831	835793	77.25

Figure S1: a) HPLC trace spectrum of the **1f**. b) HPLC trace spectrum of the crude reaction between **1f** and **3a** in DMSO solution.

4. General procedure for modification of peptides on resin

The general process is as follows:



4.1 Modification of peptides on Rink amide MBHA resin

General solid phase loading procedure

Into a 20 mL filtration syringe was added rink amide MBHA resin (0.1 mmol, 1.0 equiv., substitution = 0.37 mmol/g). The resin was swollen in dry DCM for 30 min then washed with DMF (3 × 10 mL). Deprotection was treated with a solution of DBU:piperidine:DMF (3%:3%:94%) for 5 min followed by repeat this procedure again for 15 min. Then the resin was drained and rinsed with DMF (3 × 10 mL). A solution of Fmoc-AA-OH (0.3 mmol, 3.0 equiv.), HBTU (0.3 mmol, equiv.), HOBt (0.3 mmol, 3.0 equiv.) and DIPEA (0.6 mmol, 6.0 equiv.) in DMF (10 mL) was added to the resin. The reaction mixture was stirred at room temperature for 1 h and then washed by DMF (3 × 10mL). Peptides were elongated by repeating the deprotection and coupling steps. Using Boc-AA-OH for the last amino acid or capping the last amino acid with acetyl.

General acetyl capping procedure

A 10 mL solution of acetic anhydride in pyridine (1:9 v/v) was added to the resin and the mixture shaken for 10 min. The resin was drained and rinsed with DMF (3 × 10 mL).

General deallylation of Allyl

A solution of $Pd(PPh_3)_4$ (0.01 mmol, 0.1 equiv.) and $PhSiH_3$ (2 mmol, 20 equiv.) in dry DCM (10 mL) was added to the resin. The resin was shaken for 1 h then washed with DCM (3 × 10 mL), DMF (3 × 10 mL).

Coupling of phenoxyamine

A solution of HOBt (5.0 equiv.) and EDCI (5.0 equiv.) in DMF (9 mL) was added to the resin and shaken for 30 min. Then a solution of phenoxyamine (5.0 equiv.) in DMF (1 mL) was added to the resin. The reaction mixture was shaken at room temperature for 12 h and then washed by DMF (3 × 10 mL).

General procedure for on-resin N-S bond coupling reaction

Diphenyl disulfide derivatives (5.0 equiv.), Cs_2CO_3 (1.0 equiv.) and DMF (10 mL) were added to the resin, and shaken at roomtemp for 24 – 48 h. The reaction mixture was then expelled and the resin washed thoroughly with DMF (4 × 10 mL).

General procedure for resin cleavage and product purification

After completion of synthesis, the resin was thoroughly rinsed with DMF (3 × 10 mL), DCM (2 ×

10 mL), MeOH (1 × 10 mL), DCM (1 × 10 mL) and MeOH (2 × 10 mL). The resin was treated with a solution of TFA/TIPS/H_2O (9.5 mL/0.25 mL/0.25 mL, rt, 3 h). The cleavage solution was expelled into a 100 mL round-bottom flask and the resin washed with TFA (2 × 2 mL). The combined solutions were concentrated under reduced pressure and the crude residue was treated with cold Et_2O. The crude peptide product was collected as a solid. The crude product was resuspended in a mixture of H_2O/acetonitrile and immediately purified by Semi preparative HPLC using a linear gradient as specified.

4.2 Modification of peptides on 2-chlorotrityl chloride resin

Into a 20 mL filtration syringe was added 2-chlorotrityl chloride resin (0.1 mmol, 1.0 equiv., substitution = 0.97 mmol/g). The resin was swollen in dry DCM for 30 min followed by a solution of the Fmoc amino acid (0.3 mmol, 3 equiv.) and DIPEA (0.6 mmol, 6 equiv.) in DCM (10 mL). After two hour of shaking, 0.5 mL DIPEA and 1 mL MeOH was added and the mixture agitated for 30 minutes. The resin was then drained, rinsed with DCM (3 × 10 mL) and DMF (3 × 10 mL). Deprotection was treated with a solution of DBU:piperidine:DMF (3%:3%:94%) for 5 min followed by repeat this procedure again for 15 min. Then the resin was drained and rinsed with DMF (3 × 10 mL). Peptides were elongated by repeating the coupling and deprotection steps. Using Boc-amino acids for the last amino acid or capping the last amino acid with acetyl.

Except for the coupling of the first amino acid, other procedures are the same as the Rink amide MBHA resin.

4.3 Method for analyzing the purities

Analyzing the purities was carried out on a Waters e2695 using a XBridge® Peptide BEH C18 column (130 Å, 10 μm, 4.6 mm × 250 mm). Linear gradients using A: MeCN (0.1% CF_3COOH) and B: H_2O (0.1% CF_3COOH).

Time (min)	A (%)	B (%)	Flow (mL/min)
0	5	95	1
30	95	5	1
30.5	100	0	1
35	100	0	1
35.5	5	95	1
40	5	95	1

4.4 Method for UPLC-MS analysis

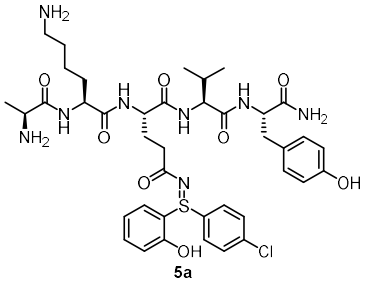
UPLC-MS analysis was carried out on Thermo Scientific Orbitrap IQ-X Tribrid using a ACQUITY UPLC® BEH C18 Column (1.7 μm, 2.1 × 50 mm) at a flow rate of 0.3 mL/min. Linear gradients using A: MeCN (0.1% HCOOH) and B: H_2O (0.1% HCOOH).

Time (min)	A (%)	B (%)	Flow (mL/min)
0	1	99	0.3
10	70	30	0.3
10.5	100	0	0.3
12	100	0	0.3
12.5	1	99	0.3

The progress of the crude reaction was checked by cleavage of a small portion of resin beads followed by UPLC-MS analysis. **5a_Raw** - **5q_Raw** represent the corresponding peptide before sulfimidation modification (see below).

4.6 Characterization of products

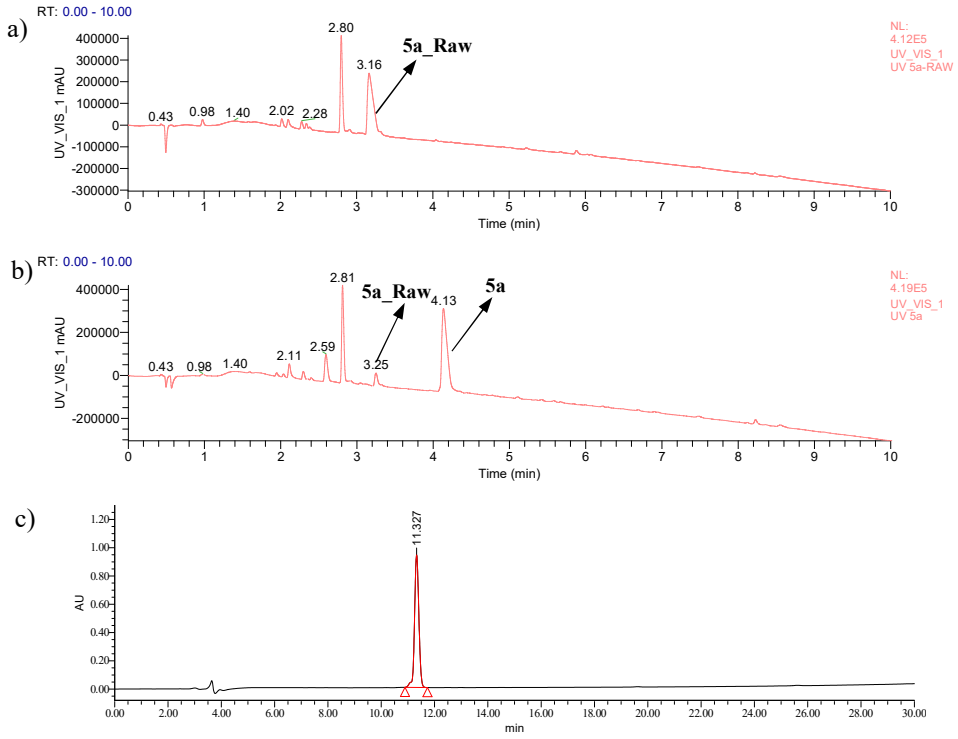
Compound **5a**



5a

According to the general procedure for modification of peptides on the resin, **5a** was obtained as a white solid (14 steps from resin loading, 31.3 mg, 37% isolated yield), >99.00% purity.

ESI-MS $C_{40}H_{54}ClN_8O_8S$ $[M+H]^+$ calcd: 841.3469, found: 841.3353.



#	Rentention time (min)	Area	Height	% Area
1	11.327	10540174	938152	>99

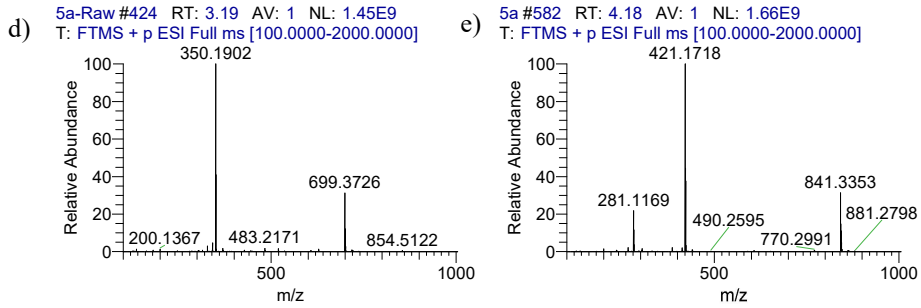
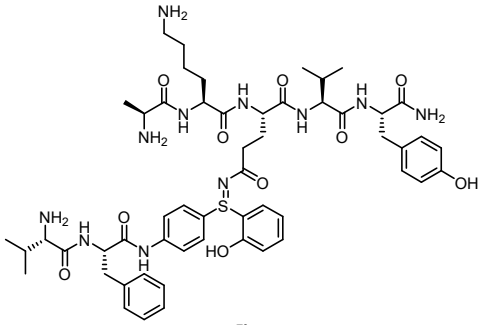


Figure S2: a) UPLC-MS chromatogram of **5a_Raw**. b) UPLC-MS chromatogram of the crude reaction between **5a-Raw** and **3a** with 1equiv. Cs_2CO_3. c) Liquid chromatograph spectrum of **5a**. d) Mass spectrum of **5a_Raw** (Calculated $[M+H]^+$: 699.3825; Observed $[M+H]^+$: 699.3726). e) Mass spectrum of **5a** (Calculated $[M+H]^+$: 841.3469; Observed $[M+H]^+$: 841.3353).

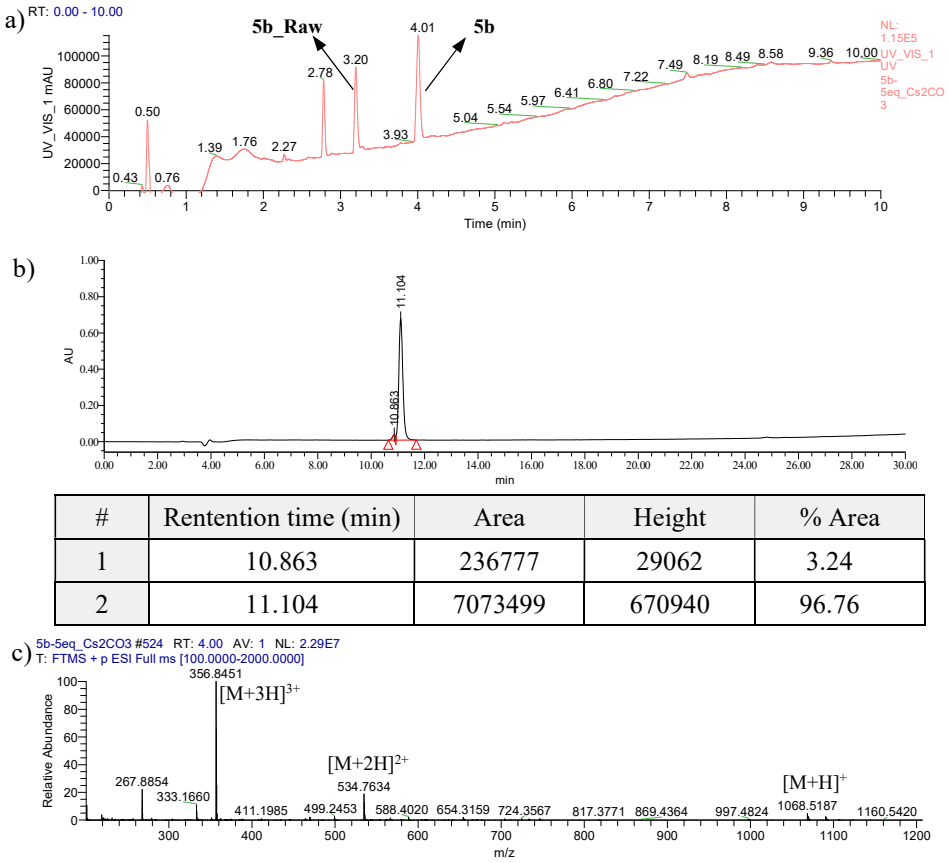
Compound **5b**



5b

According to the general procedure for modification of peptides on the resin, **5b** was obtained as a white solid (14 steps from resin loading, 22.5 mg, 21% isolated yield), 96.76% purity.

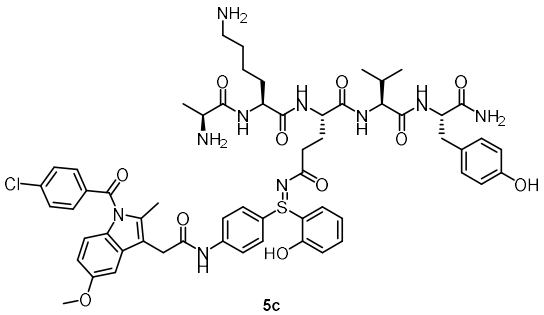
ESI-MS $C_{54}H_{74}N_{11}O_{10}S$ $[M+H]^+$ calcd: 1068.5336, found: 1068.5187.



#	Rentention time (min)	Area	Height	% Area
1	10.863	236777	29062	3.24
2	11.104	7073499	670940	96.76

Figure S3: a) UPLC-MS chromatogram of the crude reaction between **5b_Raw** and **3l** with 5 equiv. Cs_2CO_3. b) Liquid chromatograph spectrum of **5b**. c) Mass spectrum of **5b** (Calculated Mass $[M+H]^+$: 1068.5336; Observed Mass $[M+H]^+$: 1068.5187).

Compound **5c**

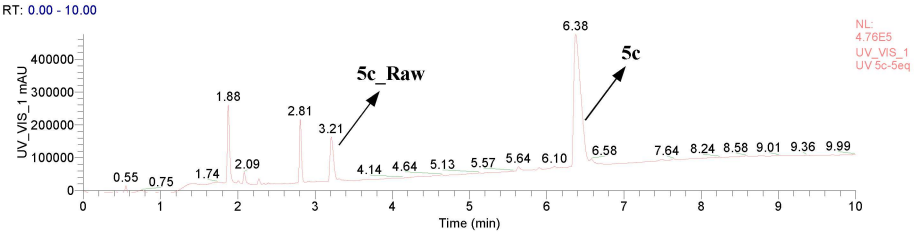


5c

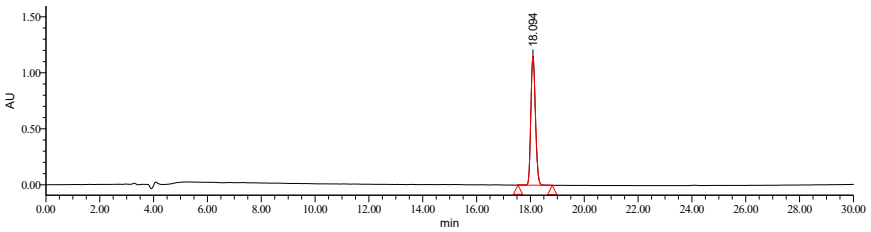
According to the general procedure for modification of peptides on the resin, **5c** was obtained as a white solid (14 steps from resin loading, 28.8 mg, 25% isolated yield), >99% purity.

^{1}H NMR (300 MHz, Deuterium Oxide) δ 7.39 – 7.11 (m, 6H), 6.95 (s, 5H), 6.89 – 6.72 (m, 3H), 6.68 (t, J = 8.6 Hz, 2H), 6.44 – 6.29 (m, 2H), 4.44 – 4.31 (m, 3H), 4.24 – 4.17 (m, 1H), 4.11 – 3.94 (m, 2H), 3.85 – 3.69 (m, 2H), 3.53 (d, J = 5.9 Hz, 1H), 2.97 – 2.70 (m, 3H), 2.66 (t, J = 7.6 Hz, 3H), 2.54 – 2.38 (m, 1H), 2.29 – 2.05 (m, 2H), 1.91 (q, J = 6.6 Hz, 1H), 1.67 (dd, J = 22.7, 8.2 Hz, 3H), 1.41 (dt, J = 26.6, 7.7 Hz, 4H), 1.19 (d, J = 7.1 Hz, 3H), 1.11 (s, 2H), 0.76 – 0.57 (m, 6H), 0.50 (s, 6H). **ESI-MS** $C_{59}H_{70}ClN_{10}O_{11}S$ $[M+H]^+$ calcd: 1161.4630, found: 1161.4463.

a)



b)



#	Rentention time (min)	Area	Height	% Area
1	18.094	13574353	1148725	>99

c)

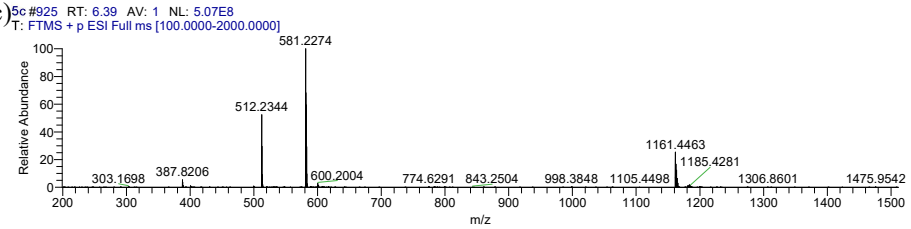
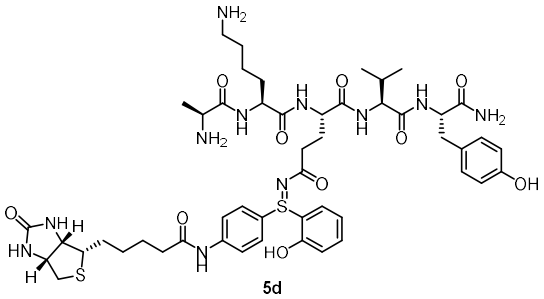


Figure S4: a) UPLC-MS chromatogram of the crude reaction between **5c_Raw** and **3j** with 5 equiv. Cs_2CO_3. b) Liquid chromatograph spectrum of **5c**. c) Mass spectrum of **5c** (Calculated Mass $[M+H]^+$: 1161.4630; Observed Mass $[M+H]^+$: 1161.4463).

Compound **5d**

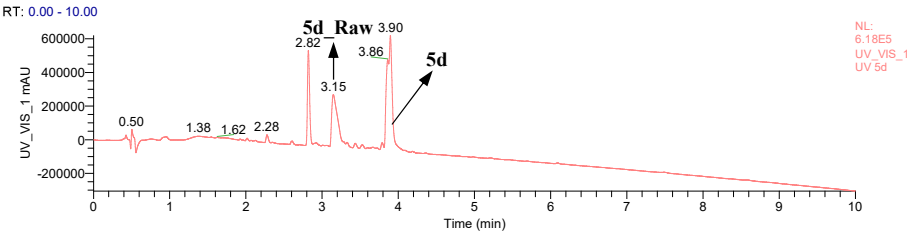


5d

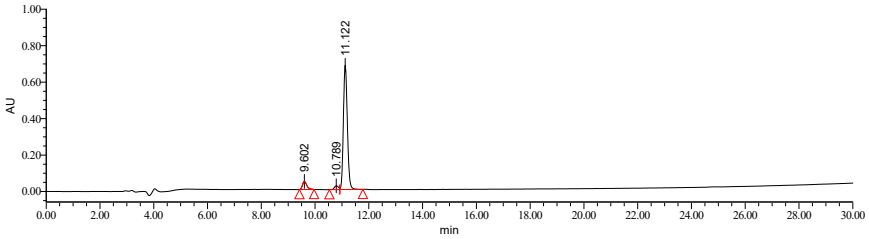
According to the general procedure for modification of peptides on the resin, **5d** was obtained as a white solid (14 steps from resin loading, 23.3 mg, 22% isolated yield), 90.72% purity.

ESI-MS $C_{50}H_{70}N_{11}O_{10}S_2$ $[M+H]^+$ calcd: 1048.4744, found: 1048.4594.

a)



b)



#	Rentention time (min)	Area	Height	% Area
1	9.602	498122	44774	6.45
2	10.789	218610	20746	2.83
3	11.122	7007292	681360	90.72

c)

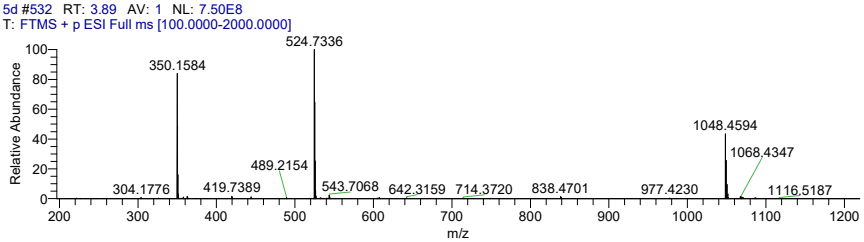
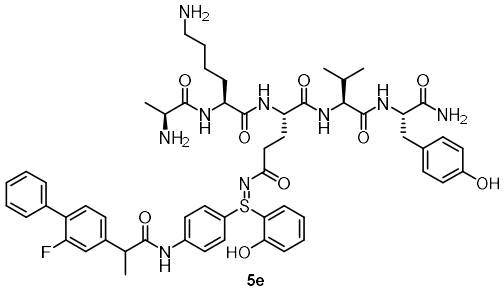


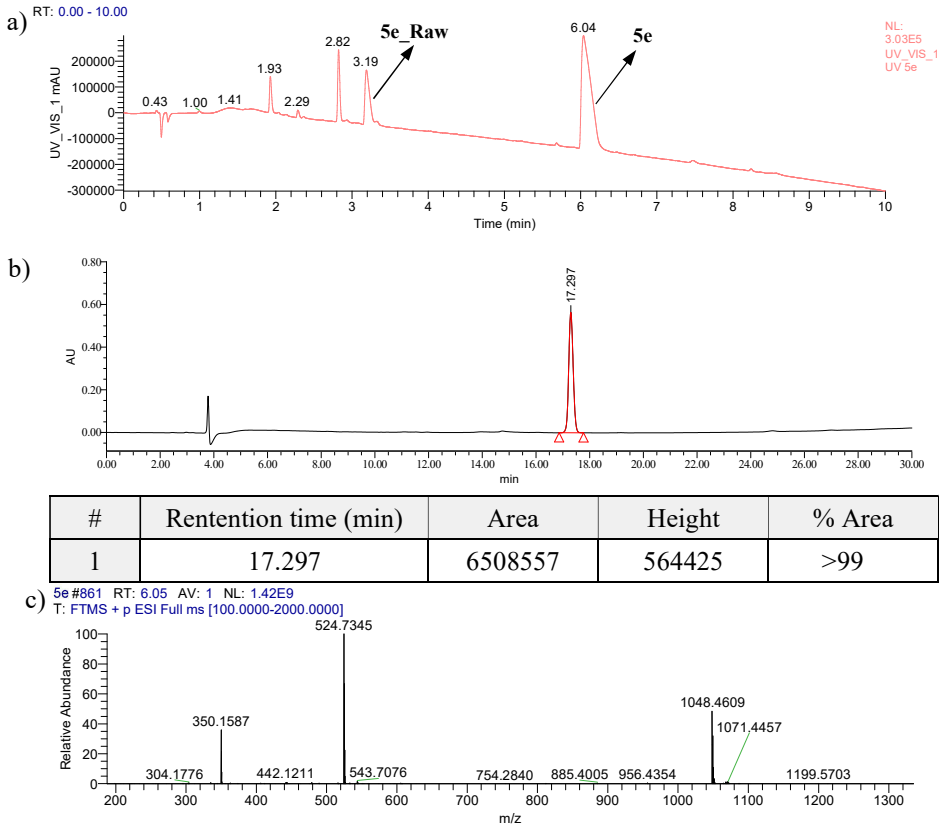
Figure S5: a) UPLC-MS chromatogram of the crude reaction between **5d_Raw** and **3p** with 5 equiv. Cs_2CO_3. b) Liquid chromatograph spectrum of **5d**. c) Mass spectrum of **5d** (Calculated Mass $[M+H]^+$: 1048.4744; Observed Mass $[M+H]^+$: 1048.4594).

Compound **5e**



According to the general procedure for modification of peptides on the resin, **5e** was obtained as a white solid (14 steps from resin loading, 26.0 mg, 25% isolated yield), >99.00% purity.

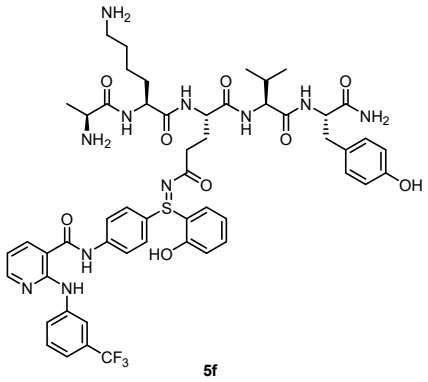
ESI-MS $C_{55}H_{67}FN_9O_9S$ $[M+H]^+$ calcd: 1048.4761, found: 1048.4609.



#	Rentention time (min)	Area	Height	% Area
1	17.297	6508557	564425	>99

Figure S6: a) UPLC-MS chromatogram of the crude reaction between **5e_Raw** and **3m** with 5 equiv. Cs_2CO_3. b) Liquid chromatograph spectrum of **5e**. c) Mass spectrum of **5e** (Calculated Mass $[M+H]^+$: 1048.4761; Observed Mass $[M+H]^+$: 1048.4609).

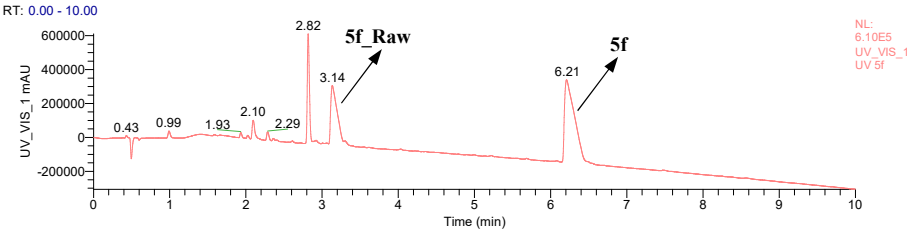
Compound **5f**



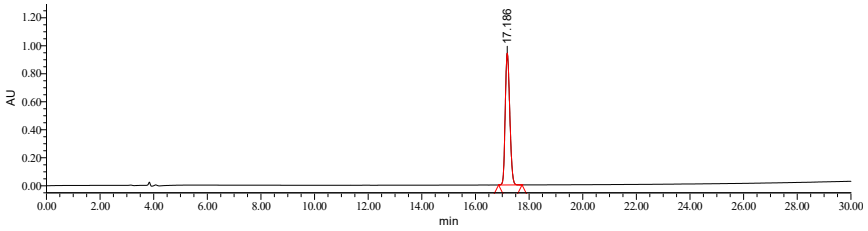
5f

According to the general procedure for modification of peptides on the resin, **5f** was obtained as a white solid (14 steps from resin loading, 20.9 mg, 19% isolated yield), >99.00% purity.
ESI-MS $C_{53}H_{63}F_3N_{11}O_9S$ $[M+H]^+$ calcd: 1086.4478, found: 1086.4314.

a)



b)



#	Rentention time (min)	Area	Height	% Area
1	17.186	11086548	941776	>99

c)

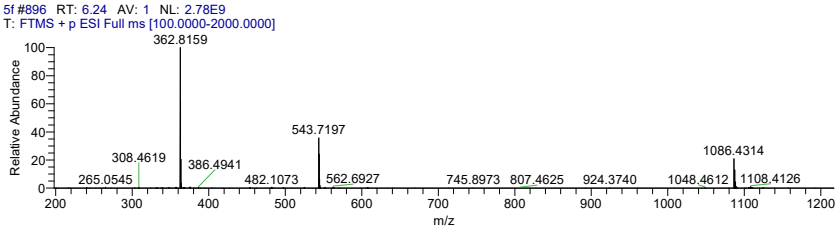
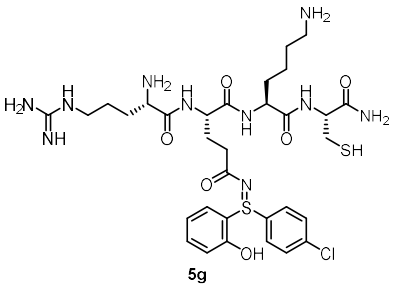


Figure S7: a) UPLC-MS chromatogram of the crude reaction between **5f_Raw** and **3n** with 5 equiv. Cs_2CO_3. b) Liquid chromatograph spectrum of **5f**. c) Mass spectrum of **5f** (Calculated Mass $[M+H]^+$: 1086.4478; Observed Mass $[M+H]^+$: 1086.4314).

Compound **5g**



5g

According to the general procedure for modification of peptides on the resin, **5g** was obtained as a white solid (12 steps from resin loading, 14.8 mg, 19% isolated yield), was slowly degraded in solution at room temperature.

ESI-MS $C_{32}H_{48}ClN_{10}O_6S_2$ $[M+H]^+$ calcd: 767.2883, found: 767.2783.

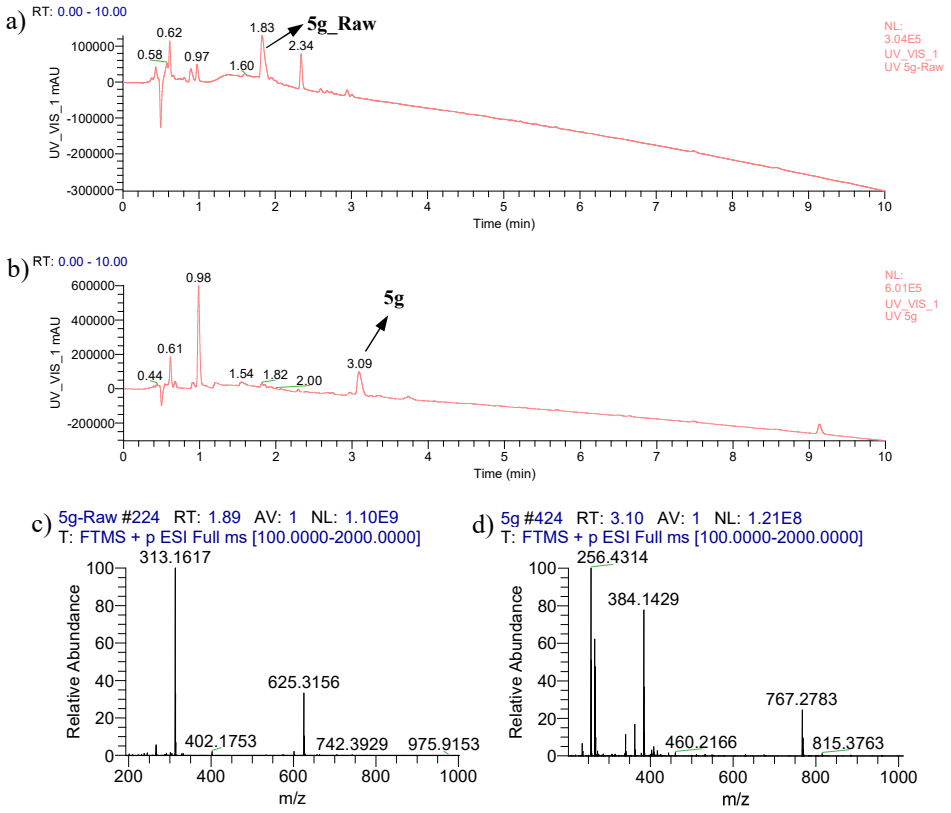
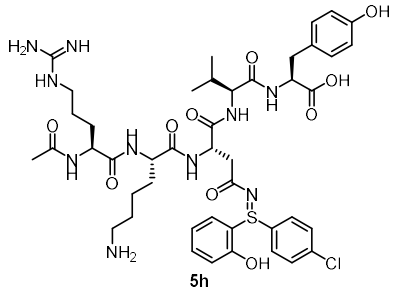


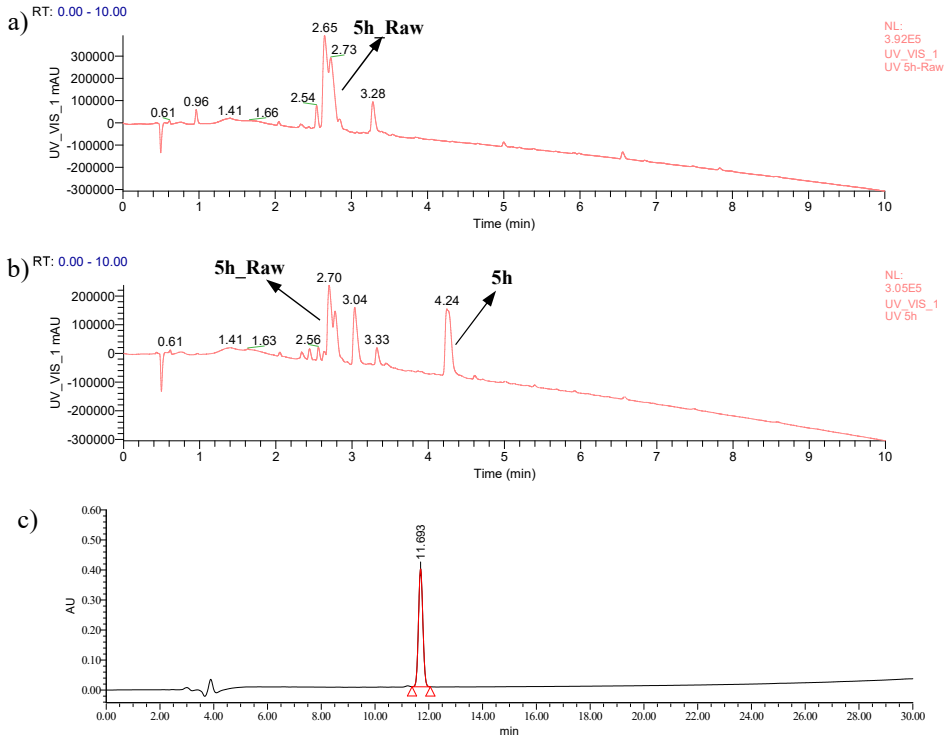
Figure S8: a) UPLC-MS chromatogram of **5g_Raw**. b) UPLC-MS chromatogram of the crude reaction between **5g-Raw** and **3a** with 1 equiv. Cs_2CO_3. c) Mass spectrum of **5g_Raw** (Calculated Mass $[M+H]^+$: 625.3239; Observed Mass $[M+H]^+$: 625.3156). d) Mass spectrum of **5g** (Calculated Mass $[M+H]^+$: 767.2883; Observed Mass $[M+H]^+$: 767.2783).

Compound **5h**



According to the general procedure for modification of peptides on the resin, **5h** was obtained as a white solid (15 steps from resin loading, 20.2 mg, 20% isolated yield), >99% purity.

ESI-MS $C_{44}H_{60}ClN_{10}O_{10}S$ $[M+H]^+$ calcd: 955.3898, found: 955.3760.



#	Rentention time (min)	Area	Height	% Area
1	11.693	4476838	392834	>99

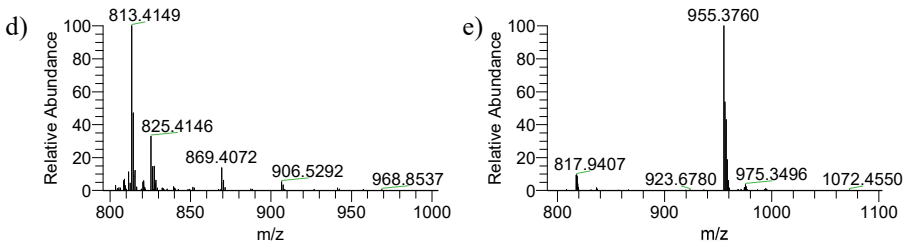
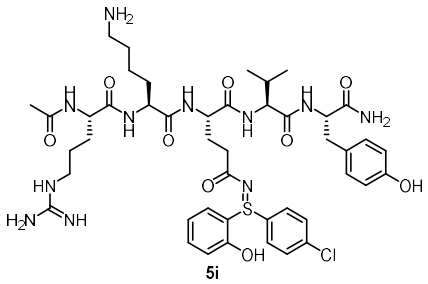


Figure S9: a) UPLC-MS chromatogram of **5h_Raw**. b) UPLC-MS chromatogram of the crude reaction between **5h_Raw** and **3a** with 1 equiv. Cs_2CO_3. c) Liquid chromatograph spectrum of **5h**. d) Mass spectrum of **5h_Raw** (Calculated Mass $[M+H]^+$: 813.4254; Observed Mass $[M+H]^+$: 813.4149). e) Mass spectrum of **5h** (Calculated Mass $[M+H]^+$: 955.3898; Observed Mass $[M+H]^+$: 955.3760).

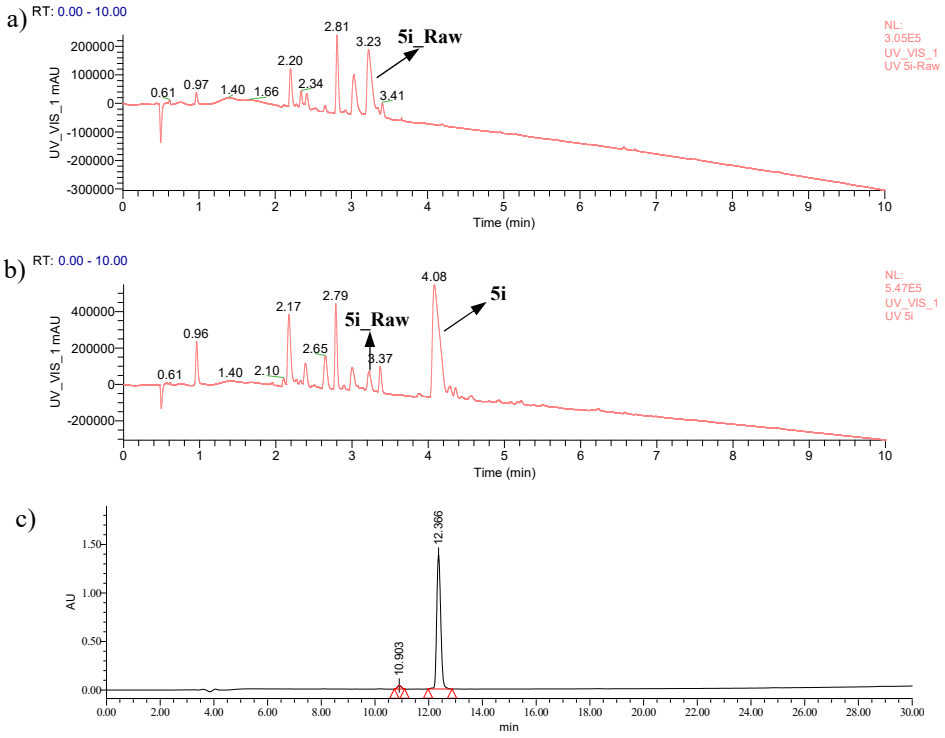
Compound **5i**



5i

According to the general procedure for modification of peptides on the resin, **5i** was obtained as a white solid (16 steps from resin loading, 31.8 mg, 33% isolated yield), 97.49% purity.

ESI-MS $C_{45}H_{63}ClN_{11}O_9S$ $[M+H]^+$ calcd: 968.4214, found: 968.4069.



#	Rentention time (min)	Area	Height	% Area
1	10.903	368194	36142	2.51
2	12.366	14305479	1384636	97.49

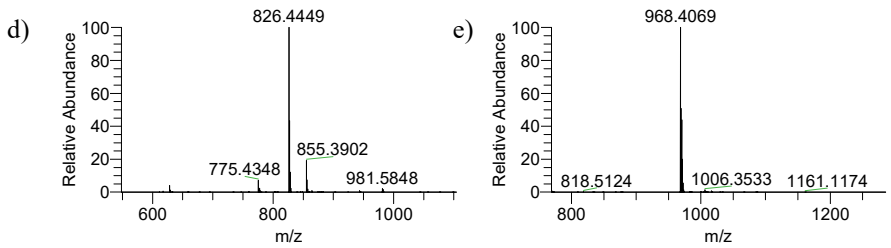
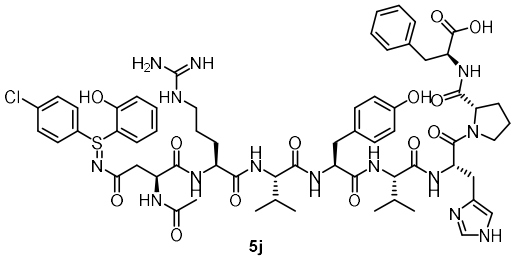


Figure S10: a) UPLC-MS chromatogram of **5i_Raw**. b) UPLC-MS chromatogram of the crude reaction between **5i_Raw** and **3a** with 1 equiv. Cs_2CO_3. c) Liquid chromatograph spectrum of **5i**. d) Mass spectrum of **5i_Raw** (Calculated Mass $[M+H]^+$: 826.4570; Observed Mass $[M+H]^+$: 826.4449). e) Mass spectrum of **5i** (Calculated Mass $[M+H]^+$: 968.4214; Observed Mass $[M+H]^+$: 968.4069).

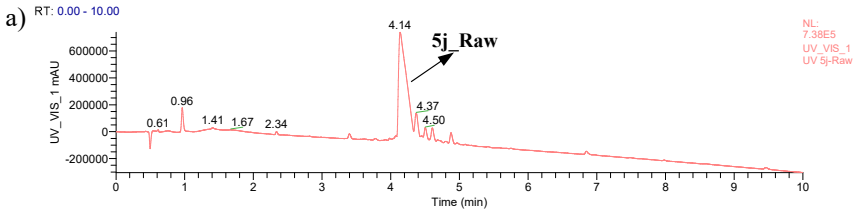
Compound **5j**

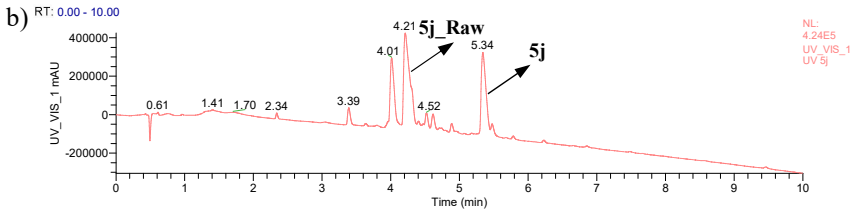


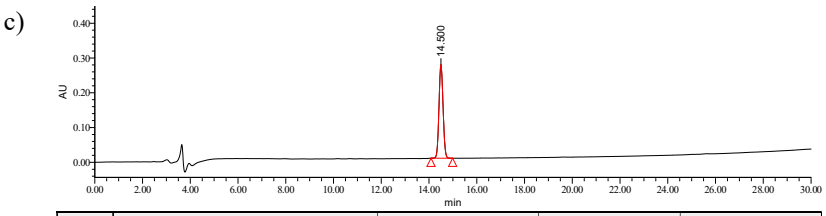
5j

According to the general procedure for modification of peptides on the resin, **5j** was obtained as a white solid (14 steps from resin loading, 18.4 mg, 14% isolated yield), >99% purity.

^{1}H NMR (300 MHz, Deuterium Oxide) δ 8.27 (s, 1H), 7.26 (dd, J = 21.0, 8.2 Hz, 6H), 7.09 – 6.87 (m, 6H), 6.78 (dd, J = 26.2, 9.5 Hz, 4H), 6.41 (d, J = 8.0 Hz, 2H), 4.40 – 4.21 (m, 3H), 4.13 – 3.92 (m, 2H), 3.73 – 3.58 (m, 2H), 2.95 – 2.45 (m, 10H), 1.94 – 1.81 (m, 1H), 1.69 (s, 3H), 1.69 – 1.30 (m, 9H), 1.31 – 1.06 (m, 3H), 1.06 – 0.90 (m, 2H), 0.62 – 0.30 (m, 12H). **ESI-MS** $C_{63}H_{80}ClN_{14}O_{13}S$ $[M+H]^+$ calcd: 1307.5434, found: 1307.5237.







#	Rentention time (min)	Area	Height	% Area
1	14.500	3197482	268736	>99

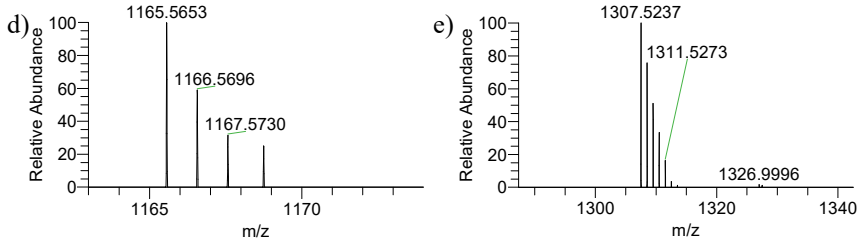
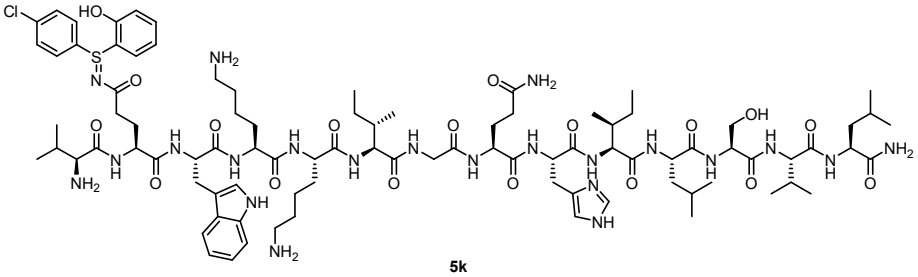


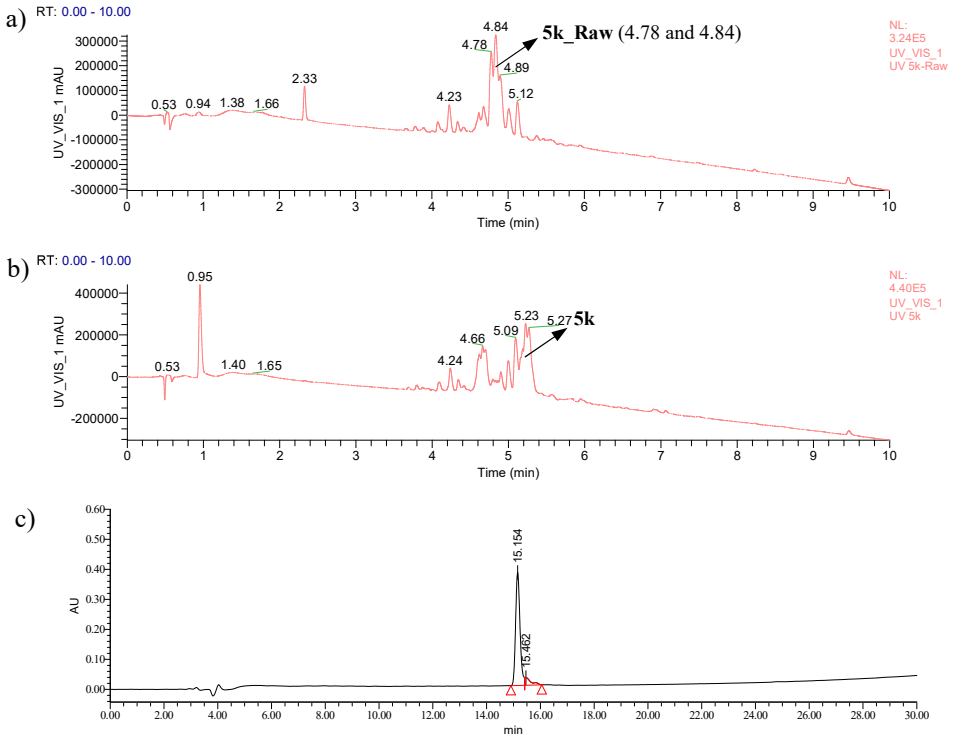
Figure S11: a) UPLC-MS chromatogram of **5j_Raw**. b) UPLC-MS chromatogram of the crude reaction between **5j_Raw** and **3a** with 1 equiv. Cs_2CO_3. c) Liquid chromatograph spectrum of **5j**. d) Msss spectrum of **5j_Raw** (Calculated $[M+H]^+$: 1165.5790; Observed $[M+H]^+$: 1165.5653). e) Mass spectrum of **5j** (Calculated $[M+H]^+$: 1307.5434; Observed $[M+H]^+$: 1307.5237).

Compound **5k**



According to the general procedure for modification of peptides on the resin, **5k** was obtained as a white solid (14 steps from resin loading, 24.1 mg, 13% isolated yield), 91.44% purity.

ESI-MS $C_{90}H_{138}ClN_{22}O_{18}S$ $[M+H]^+$ calcd: 1881.9964, found: 1881.9708.



#	Rentention time (min)	Area	Height	% Area
1	15.154	4309095	376700	91.44
2	15.462	403544	25314	8.56

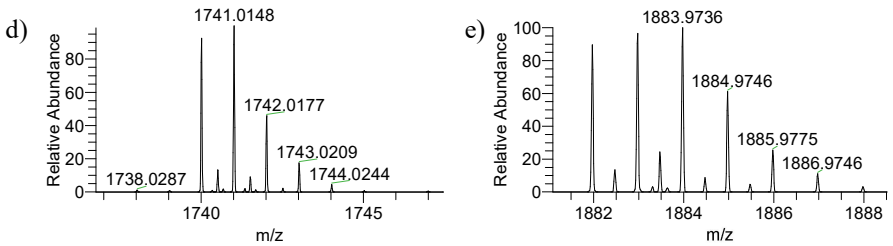
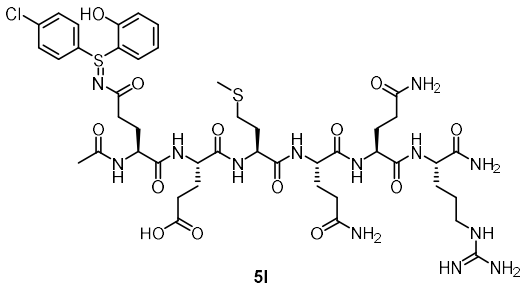


Figure S12: a) UPLC-MS chromatogram of **5k_Raw**. b) UPLC-MS chromatogram of the crude reaction between **5k_Raw** and **3a** with 1 equiv. Cs_2CO_3. c) Liquid chromatograph spectrum of **5k**. d) Msss spectrum of **5k_Raw** (Calculated Mass $[M+H]^+$: 1740.0320; Observed Mass $[M+H]^+$: 1740.0081). e) Mass spectrum of **5k** (Calculated Mass $[M+H]^+$: 1881.9964; Observed Mass $[M+H]^+$: 1881.9708).

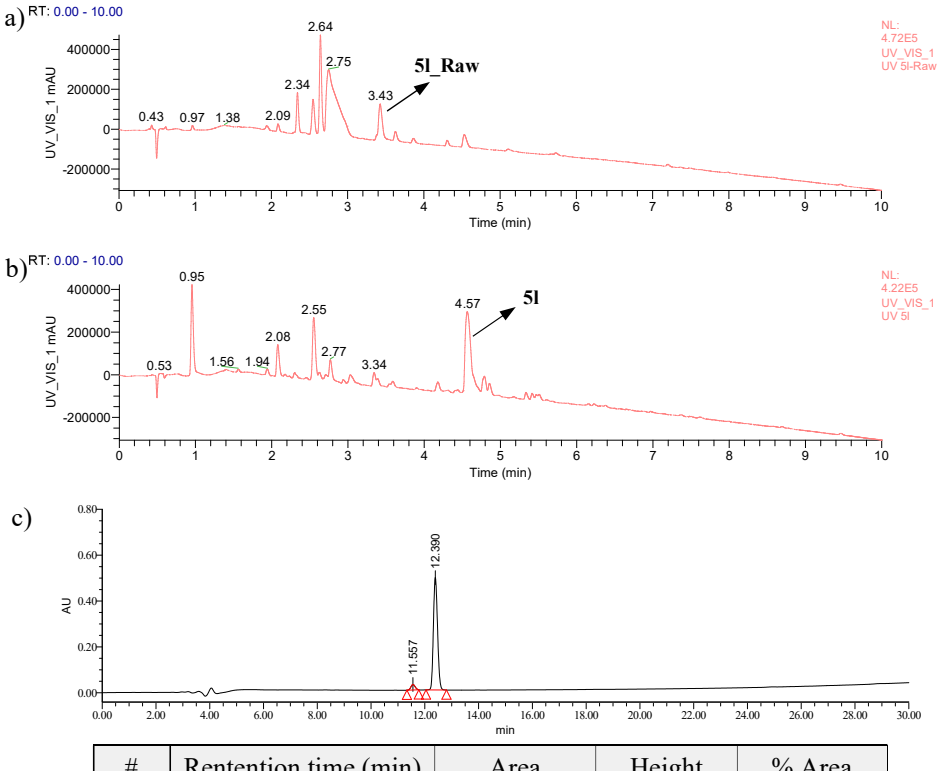
Compound **5l**



5l

According to the general procedure for modification of peptides on the resin, **5l** was obtained as a white solid (18 steps from resin loading, 38.1 mg, 35% isolated yield), 95.16% purity.

ESI-MS $C_{45}H_{65}ClN_{13}O_{13}S_2$ $[M+H]^+$ calcd: 1094.3950, found: 1094.3798.



#	Rentention time (min)	Area	Height	% Area
1	11.557	267067	24169	4.84
2	12.390	5249733	490584	95.16

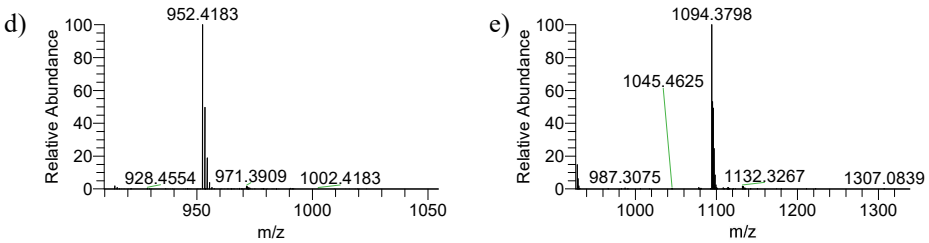
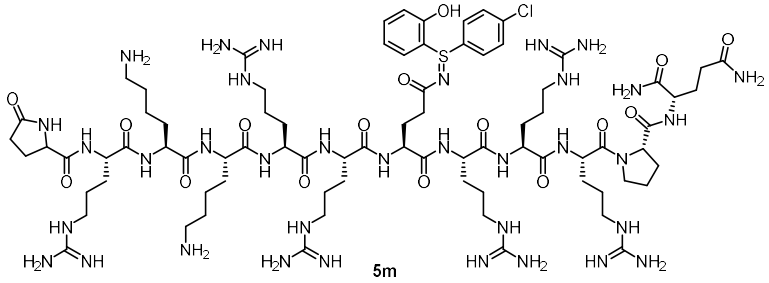


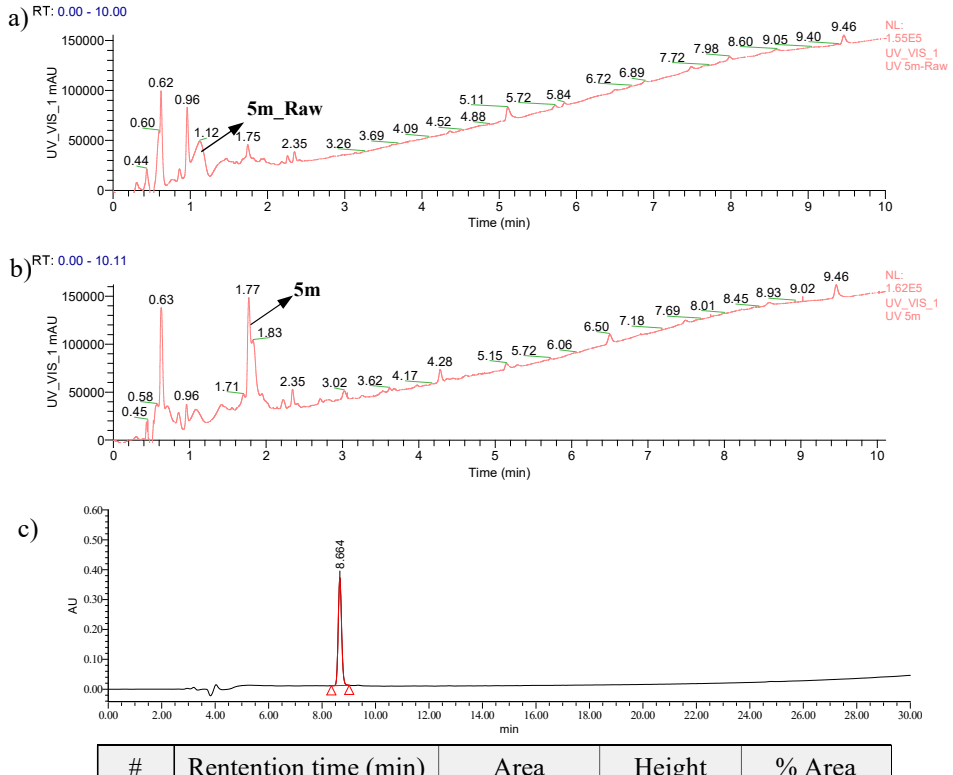
Figure S13: a) UPLC-MS chromatogram of **5l_Raw**. b) UPLC-MS chromatogram of the crude reaction between **5l_Raw** and **3a** with 1 equiv. Cs_2CO_3. c) Liquid chromatograph spectrum of **5l**. d) Msss spectrum of **5l_Raw** (Calculated Mass $[M+H]^+$: 952.4306; Observed Mass $[M+H]^+$: 952.4183). e) Mass spectrum of **5l** (Calculated Mass $[M+H]^+$:; Observed Mass $[M+H]^+$: 1094.3798).

Compound **5m**



According to the general procedure for modification of peptides on the resin, **5m** was obtained as a white solid (28 steps from resin loading, 14.5 mg, 15% isolated yield), >99% purity.

ESI-MS $C_{80}H_{136}ClN_{35}O_{16}S$ $[M+2H]^{2+}$ calcd: 955.0152, found: 955.0018.



#	Rentention time (min)	Area	Height	% Area
1	8.664	3170955	360335	>99

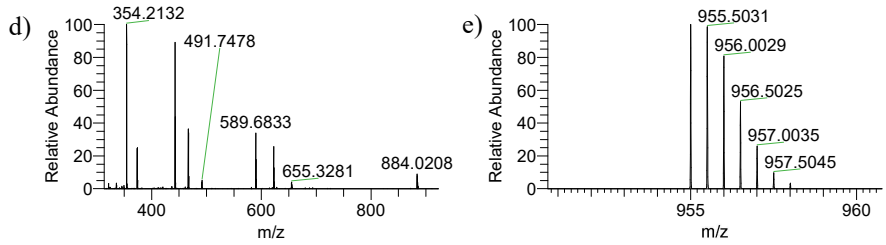
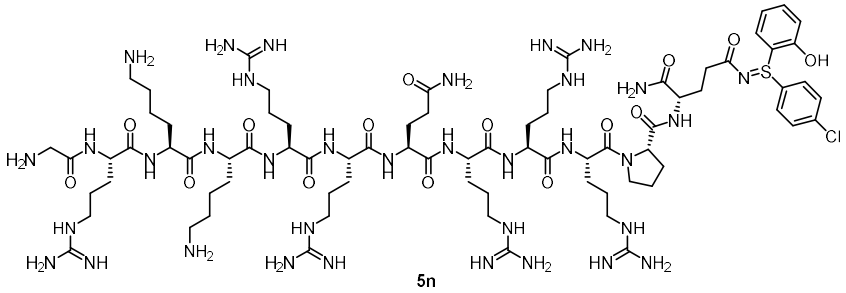


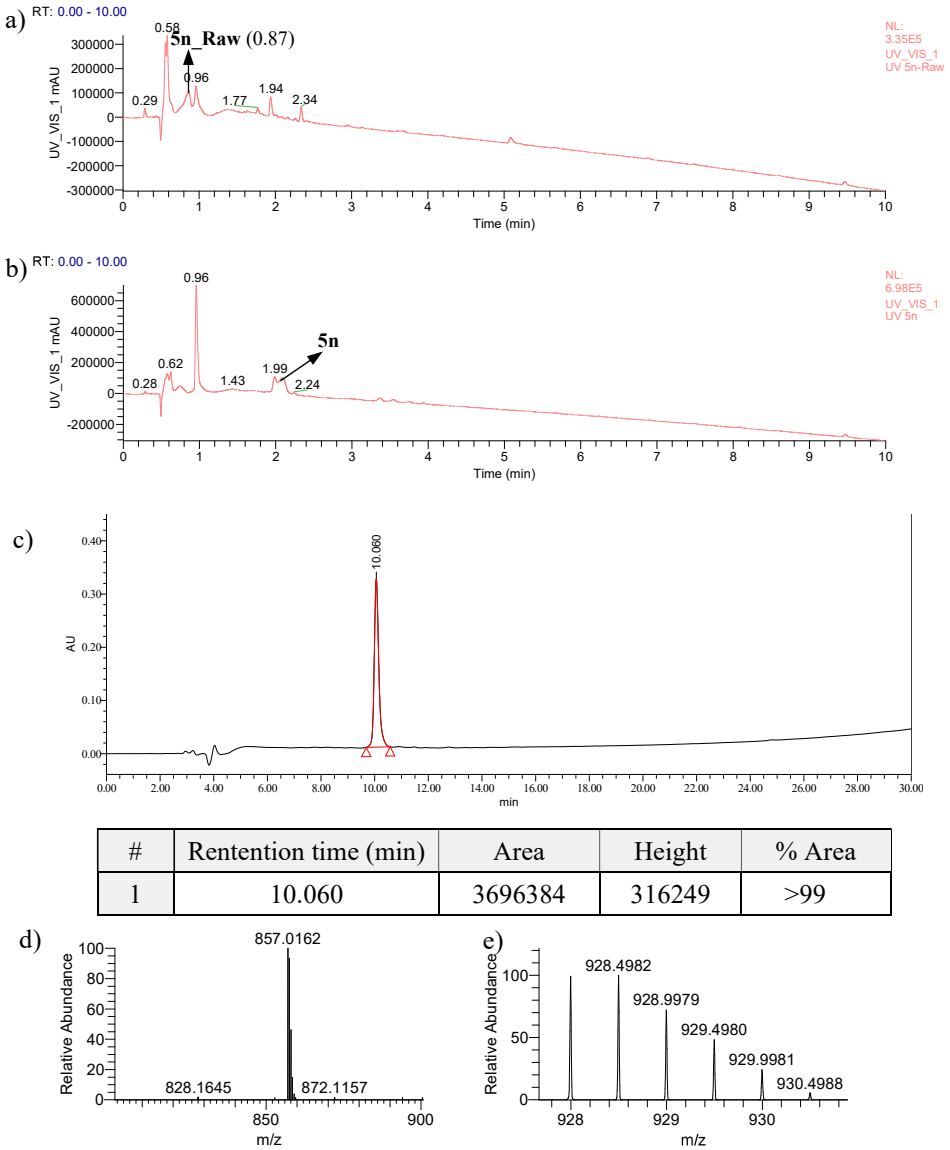
Figure S14: a) UPLC-MS chromatogram of **5m_Raw**. b) UPLC-MS chromatogram of the crude reaction between **5m_Raw** and **3a** with 1 equiv. Cs_2CO_3. c) Liquid chromatograph spectrum of **5m**. d) Msss spectrum of **5m_Raw** (Calculated Mass $[M+2H]^{2+}$: 884.0330; Observed Mass $[M+2H]^{2+}$: 884.0208). e) Mass spectrum of **5m** (Calculated Mass $[M+2H]^{2+}$: 955.0152; Observed Mass $[M+2H]^{2+}$: 955.0018).

Compound **5n**



According to the general procedure for modification of peptides on the resin, **5n** was obtained as a white solid (28 steps from resin loading, 20.6 mg, 11% isolated yield), >99% purity.

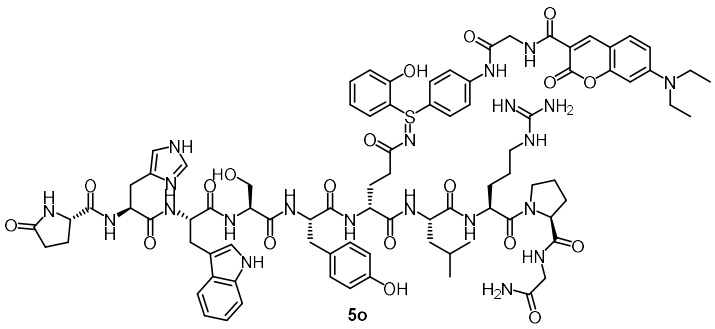
ESI-MS $C_{77}H_{134}ClN_{35}O_{15}S$ $[M+2H]^{2+}$, calcd: 928.0099, found: 927.9969.



#	Rentention time (min)	Area	Height	% Area
1	10.060	3696384	316249	>99

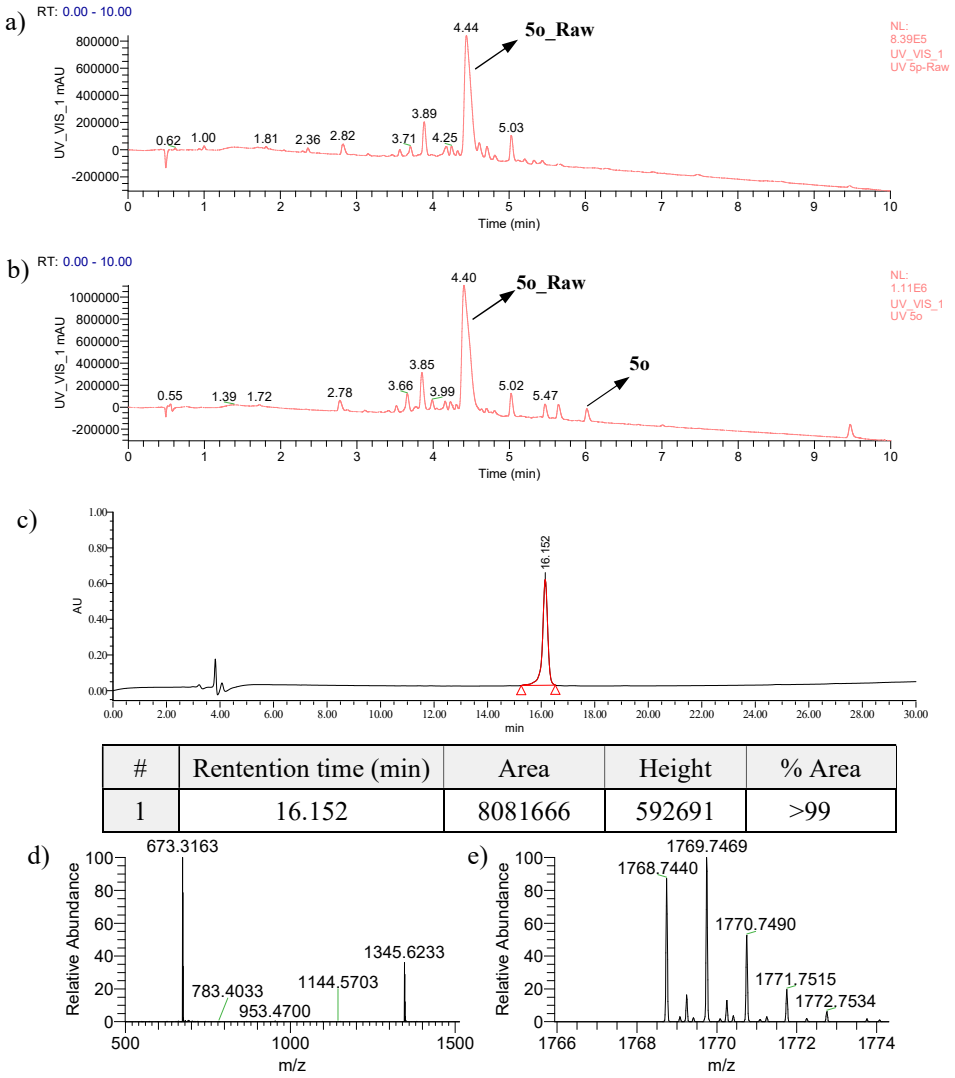
Figure S15: a) UPLC-MS chromatogram of **5n_Raw**. b) UPLC-MS chromatogram of the crude reaction between **5n_Raw** and **3a** with 1 equiv. Cs_2CO_3. c) Liquid chromatograph spectrum of **5n**. d) Msss spectrum of **5n_Raw** (Calculated $[M+2H]^{2+}$: 857.0277; Observed $[M+2H]^{2+}$: 857.0162). e) Mass spectrum of **5n** (Calculated $[M+2H]^{2+}$: 928.0099; Observed $[M+2H]^{2+}$: 927.9969).

Compound **5o**



According to the general procedure for modification of peptides on the resin, **5o** was obtained as a yellow solid (24 steps from resin loading, 5.8 mg, 3% isolated yield), >99% purity.

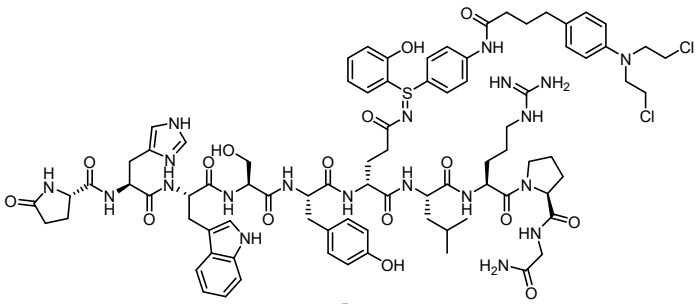
ESI-MS $C_{86}H_{106}N_{21}O_{19}S$ $[M+H]^+$ calcd: 1768.7690, found: 1768.7740.



#	Rentention time (min)	Area	Height	% Area
1	16.152	8081666	592691	>99

Figure S16: a) UPLC-MS chromatogram of **5o_Raw**. b) UPLC-MS chromatogram of the crude reaction between **5o_Raw** and **3o** with 5 equiv. Cs_2CO_3. c) Liquid chromatograph spectrum of **5o**. d) Msss spectrum of **5o_Raw** (Calculated Mass $[M+H]^+$: 1345.6437; Observed Mass $[M+H]^+$: 1345.6233). e) Mass spectrum of **5o** (Calculated Mass $[M+H]^+$: 1768.7690; Observed Mass $[M+H]^+$: 1768.7440).

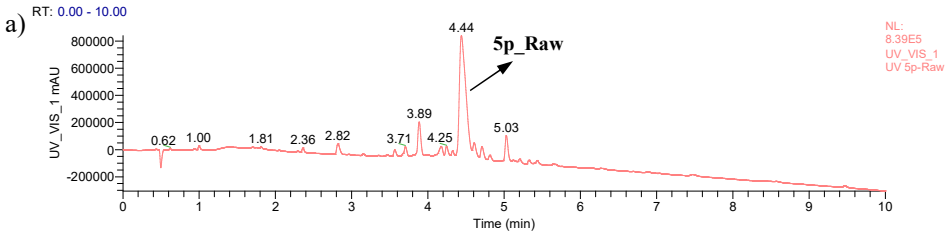
Compound **5p**

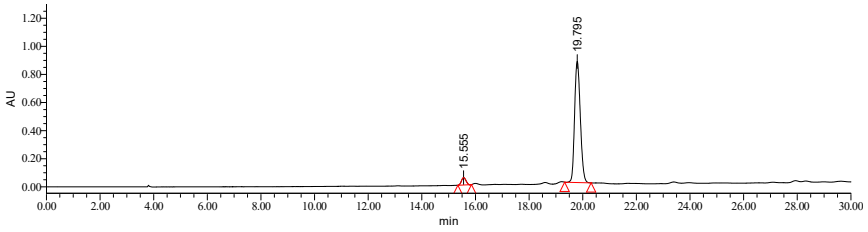


5p

According to the general procedure for modification of peptides on the resin, **5p** was obtained as a white solid (24 steps from resin loading, 19.5 mg, 10% isolated yield), 95.39% purity.

ESI-MS $C_{84}H_{107}Cl_2N_{20}O_{16}S$ $[M+H]^+$ calcd: 1753.7267, found: 1753.7021.





#	Rentention time (min)	Area	Height	% Area
1	15.555	618145	4.61	4.61
2	19.795	12785036	95.39	95.39

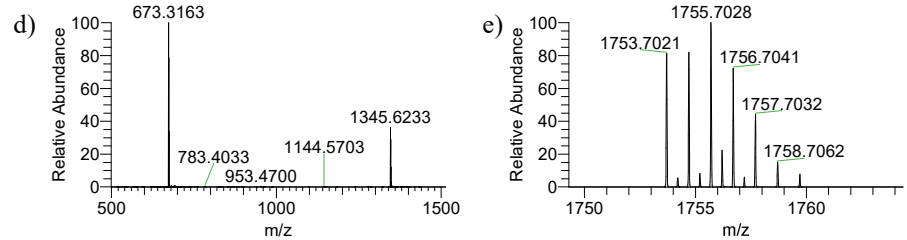
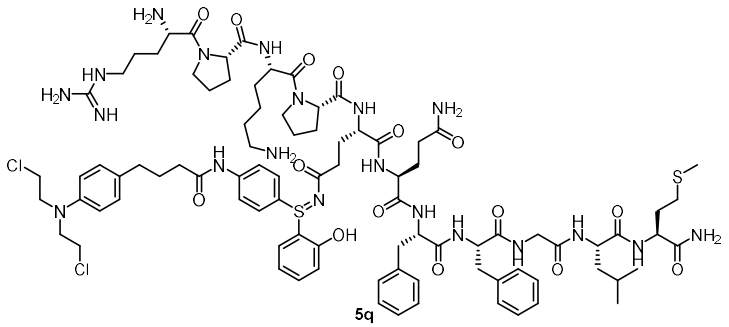


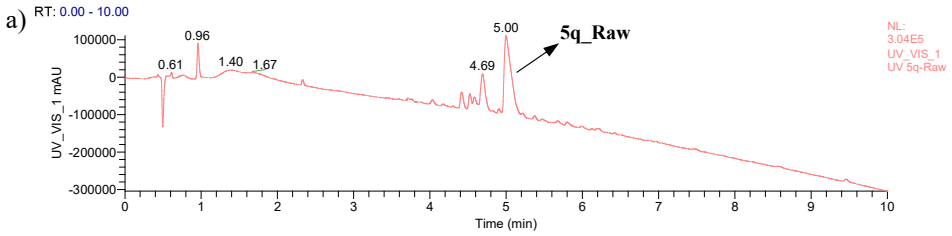
Figure S17: a) UPLC-MS chromatogram of **5p_Raw**. b) UPLC-MS chromatogram of the crude reaction between **5p_Raw** and **3k** with 5 equiv. Cs_2CO_3. c) Liquid chromatograph spectrum of **5p**. d) Msss spectrum of **5p_Raw** (Calculated Mass $[M+H]^+$: 1345.6437; Observed Mass $[M+H]^+$: 1345.6233). e) Mass spectrum of **5p** (Calculated Mass $[M+H]^+$: 1753.7267; Observed Mass $[M+H]^+$: 1753.7021).

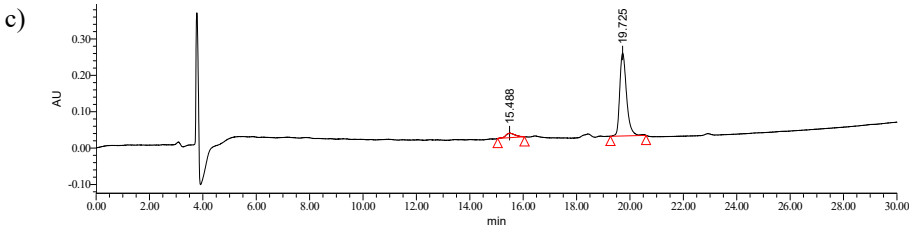
Compound **5q**



According to the general procedure for modification of peptides on the resin, **5q** w was obtained as a white solid (26 steps from resin loading, 42.8 mg, 23% isolated yield), 93.06% purity.

ESI-MS $C_{89}H_{125}Cl_2N_{20}O_{15}S_2$ $[M+H]^+$ calcd: 1847.8447, found: 1847.8180.





#	Rentention time (min)	Area	Height	% Area
1	15.488	299312	4.61	6.94
2	19.725	4012224	95.39	93.06

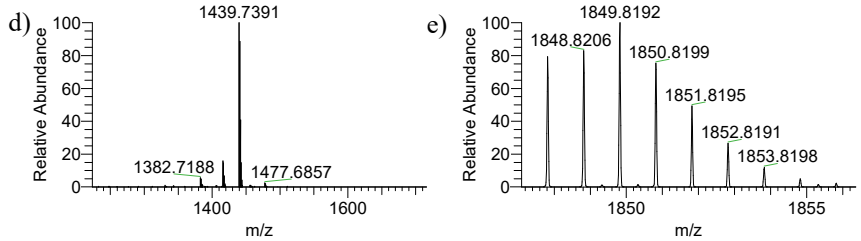
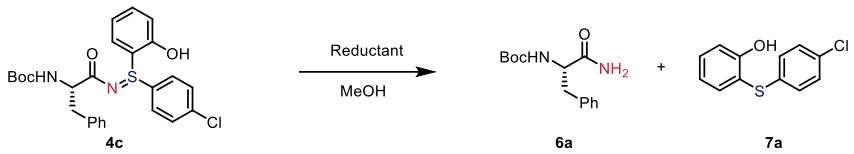


Figure S18: a) UPLC-MS chromatogram of **5q_Raw**. b) UPLC-MS chromatogram of the crude reaction between **5q_Raw** and **3k** with 5 equiv. Cs_2CO_3. c) Liquid chromatograph spectrum of **5q**. d) Msss spectrum of **5q_Raw** (Calculated Mass $[M+H]^+$: 1439.7617; Observed Mass $[M+H]^+$: 1439.7391). e) Mass spectrum of **5q** (Calculated Mass $[M+H]^+$: 1847.8447; Observed Mass $[M+H]^+$: 1847.8180).

5. Deconjugation of modified products

Chang, Toste, and co-workers have reported that peptides stapled by sulfimide linkers were decomposed into starting peptide under reductive conditions.[2] Therefore, we take research on the decomposition of the products.

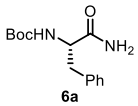
5.1 Deconjugation of products 4c



Entry	Reductant	Time (h)	Conversion[a] (%)
1	DTT (5 eq)	3	100 (98[b])
2	GSH (5 eq)	3	0[c]
3	TCEP (5 eq)	3	0[c]
4	Cys (5 eq)	3	100
5	Cys (3 eq)	24	100

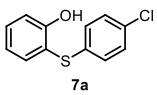
[a]The reaction was carried out with 0.1 mmol **4c**, 0.5 mmol reductant in 1 mL MeOH at room temperature. [b]Isolated yield of **6a** (98%) and **7a** (94%). [c]MeOH/PBS (v/v = 1:1) instead of MeOH.

***tert*-butyl (*S*)-(1-amino-1-oxo-3-phenylpropan-2-yl)carbamate (6a)**



White solid was obtained by chromatography on silica gel (eluted: DCM:MeOH = 20:1).
0.1 mmol scale, 26.0 mg, 98% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.36 – 7.17 (m, 5H), 6.17 (s, 1H), 5.98 (s, 1H), 5.27 (d, *J* = 8.3 Hz, 1H), 4.42 (d, *J* = 8.7 Hz, 1H), 3.19 – 2.87 (m, 2H), 1.39 (s, 9H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 174.05, 155.43, 136.64, 129.28, 128.57, 126.87, 80.14, 38.48, 28.22.
HRMS (ESI) $C_{14}H_{21}N_2O_3$ $[M+H]^+$ Calcd: 265.1547, Found 265.1546.

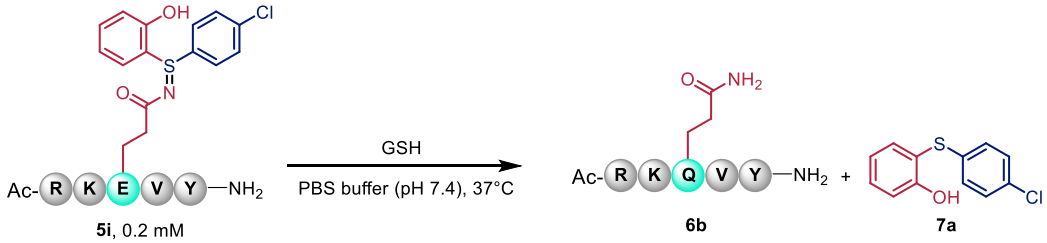
2-((4-chlorophenyl)thio)phenol (7a)



Colorless oil was obtained by chromatography on silica gel (eluted: PE: EtOAc = 20:1).
0.1 mmol scale, 22.1 mg, 94% yield.
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.43 – 7.34 (m, 2H), 7.23 – 7.15 (m, 4H), 7.07 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.03 – 6.91 (m, 6H), 6.44 (s, 2H).
^{13}C NMR (75 MHz, Chloroform-*d*) δ 157.15, 136.80, 134.42, 132.54, 132.11, 129.28, 128.09, 121.43, 115.90, 115.72.
HRMS (ESI) $C_{12}H_8ClOS$ $[M-H]^-$ Calcd: 234.9989, Found 234.9990.

5.2 Deconjugation of water-solubility products

Deconjugation rates and stability of products 5i



PBS buffer (pH 7.4)

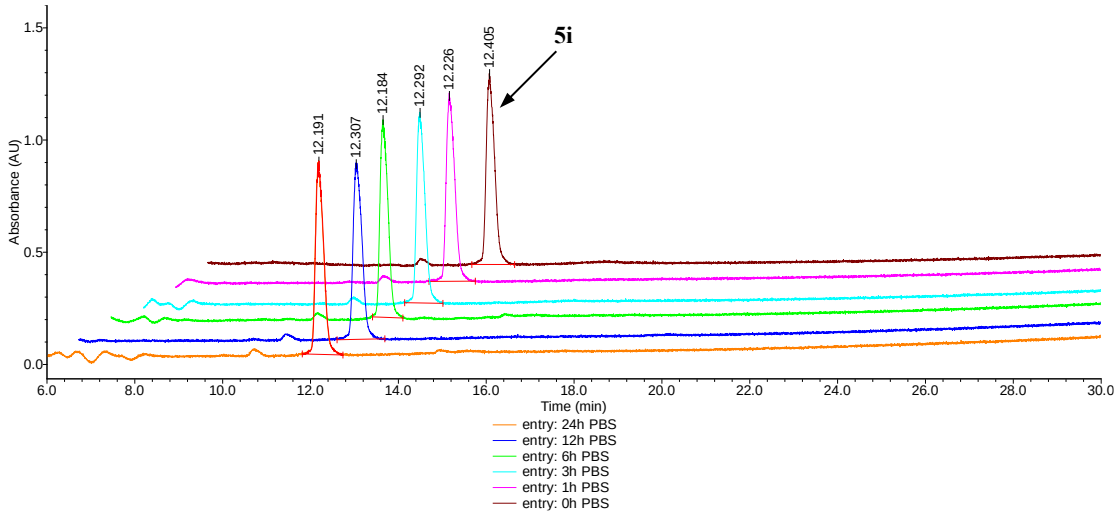
To a solution of PBS buffer (pH 7.4, 5 mL), **5i** (1 μmol, 0.97 mg) was added and the resulting mixture was incubated at 37°C. The reaction mixture was analyzed by HPLC (monitored at 220 nm, method: linear gradient B/(A+B) = 5-95% over 0-30 min, A: H_2O + 0.1% CF_3COOH, B: MeCN + 0.1% CF_3COOH) at 0 h, 1 h, 3 h, 6 h, 12 h and 24 h respectively. The residual amount of product was calculated by HPLC peak areas. The residual amount of product at different times was calculated as follows:

$$\text{Residual amount (\%)} = \text{Area (x h)} / \text{Area (0 h)} \times 100\%$$

Area (x h) and Area (0 h) refer to the following HPLC peak areas (λ = 220 nm), respectively.:

Area (x h): peak areas of **5i** in the mixture at different times.

Area (0 h): peak areas of **5i** in the mixture at 0 h.

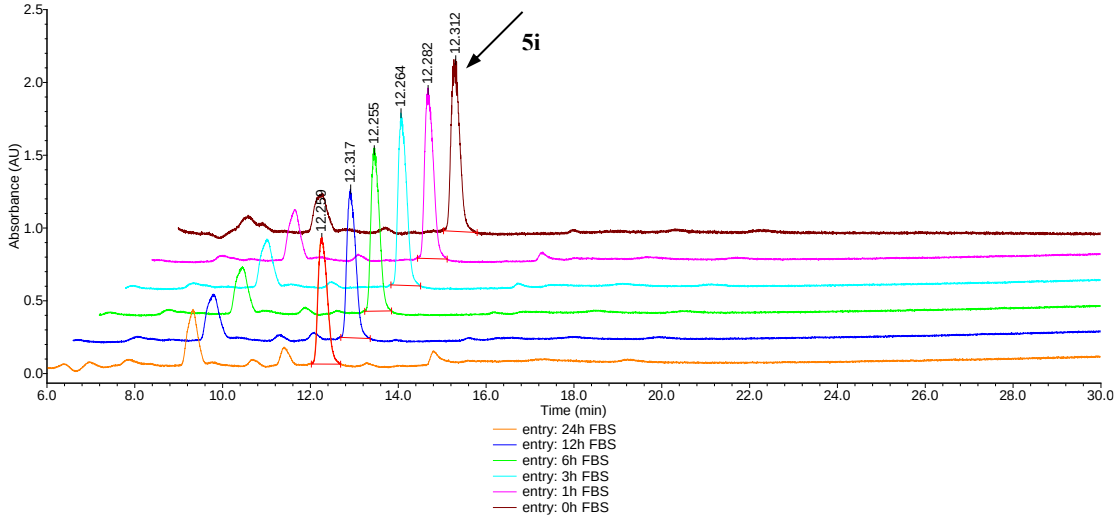


#	Retention Time	Area	Residual amount (%)
0 h	12.405	11215426	100
1 h	12.226	11224548	100
3 h	12.292	11205464	99.9
6 h	12.184	11175261	99.6
12 h	12.307	11083716	98.8
24 h	12.191	11130315	99.2

Figure S19. Time course study of the stability of **5i** in PBS buffer (pH 7.4).

FBS

To a solution of **5i** (1 μmol, 0.97 mg) in PBS buffer (pH 7.4, 100 μL), 1.9 mL FBS was added and the resulting mixture was incubated at 37℃. Take out 100 μL of reaction solution at 0 h, 1 h, 3 h, 6 h, 12 h, 24 h respectively and added 100 μL ice acetonitrile, shocked and treaded with centrifugation (10000 r/min, 10 min), the supernate was analyzed by HPLC (monitored at 220 nm, method: linear gradient B/(A+B) = 5-95% over 0-30 min, A: H_2O + 0.1% CF_3COOH, B: MeCN + 0.1% CF_3COOH). The results indicated that no deconjugation had occurred. 0%, 1%, 2%, 6%, 14%, 23% of **5i** were hydrolyzed by enzymes after 0 h, 1 h, 3 h, 6 h, 12 h and 24 h respectively.

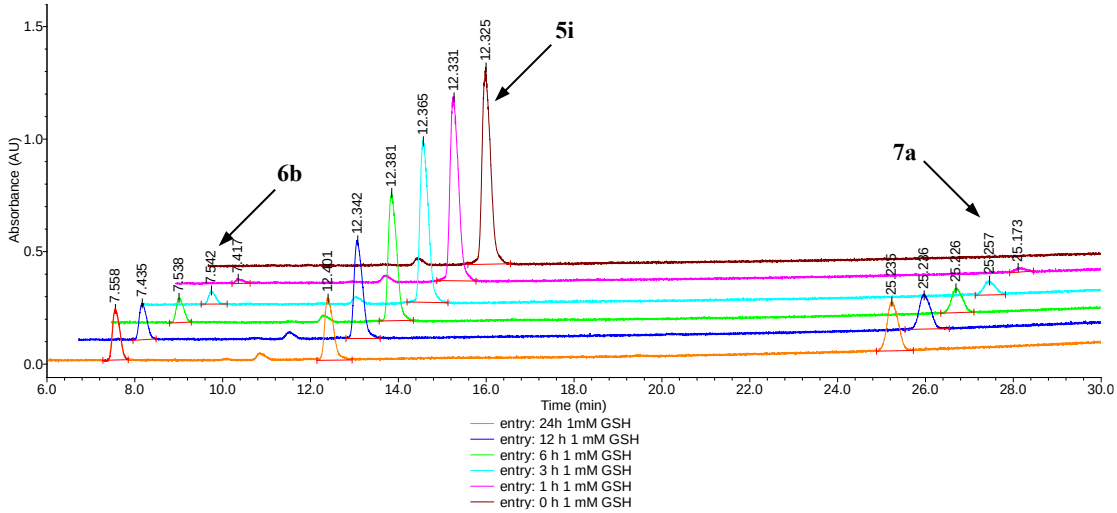


#	Retention Time	Area	Residual amount (%)
0 h	12.312	15821115	100
1 h	12.282	15714620	99.3
3 h	12.264	15647950	98.9
6 h	12.255	14800381	93.5
12 h	12.317	14075552	89.0
24 h	12.259	12572896	79.5

Figure S20. Time course study of the stability of **5i** in FBS.

1 mM GSH

To a solution of **5i** (1 μmol, 0.97 mg) in PBS buffer (pH 7.4, 5 mL), GSH (1.5 mg, 5 μmol) was added and the resulting mixture was incubated at 37℃. The reaction mixture was analyzed by HPLC (monitored at 220 nm, method: linear gradient B/(A+B) = 5-95% over 0-30 min, A: H_2O + 0.1% CF_3COOH, B: MeCN + 0.1% CF_3COOH) at 0 h, 1 h, 3 h, 6 h, 12 h and 24 h respectively. The deconjugation yield was 0 %, 6%, 18%, 35%, 50% and 69% respectively.

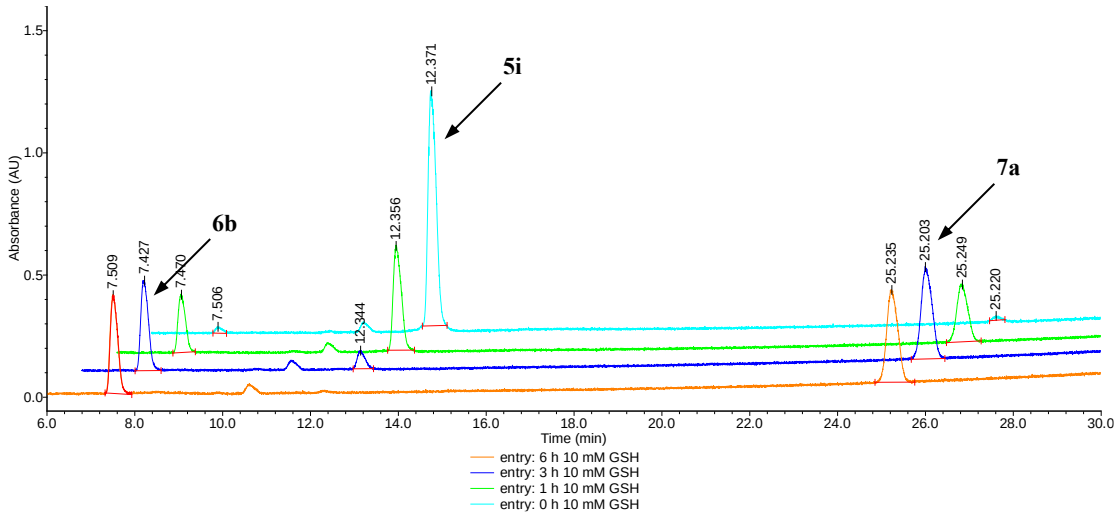


#	Retention Time	Area	Residual amount (%)
0 h	12.325	11550490	100
1 h	12.331	10988225	95.1
3 h	12.365	9592073	83
6 h	12.381	7556086	65.4
12 h	12.342	5908520	51.2
24 h	12.401	3823989	33.1

Figure S21. Time course study of the deconjugation of **5i** in 1 mM GSH.

10 mM GSH

To a solution of **5i** (1 μmol, 0.97 mg) in PBS buffer (pH 7.4, 5 mL), GSH (15.4 mg, 50 μmol) was added and the resulting mixture was incubated at 37°C. The reaction mixture was analyzed by HPLC (monitored at 220 nm, method: linear gradient B/(A+B) = 5-95% over 0-30 min, A: H_2O + 0.1% CF_3COOH, B: MeCN + 0.1% CF_3COOH) at 0 h, 1 h, 3 h, 6 h, 12 h and 24 h respectively. The deconjugation yield was 0 %, 56%, 93%, 100% after 0 h, 1 h, 3 h and 6 h respectively.



#	Retention Time	Area	Residual amount (%)
0 h	12.371	12239821	100
1 h	12.356	5433602	44.4
3 h	12.344	879090	7.2
6 h	-	0	0

Figure S22. Time course study of the deconjugation of **5i** in 10 mM GSH.

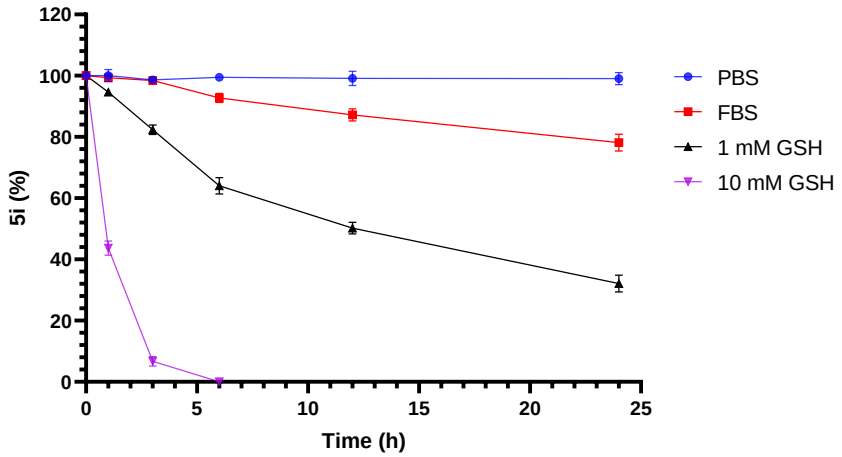


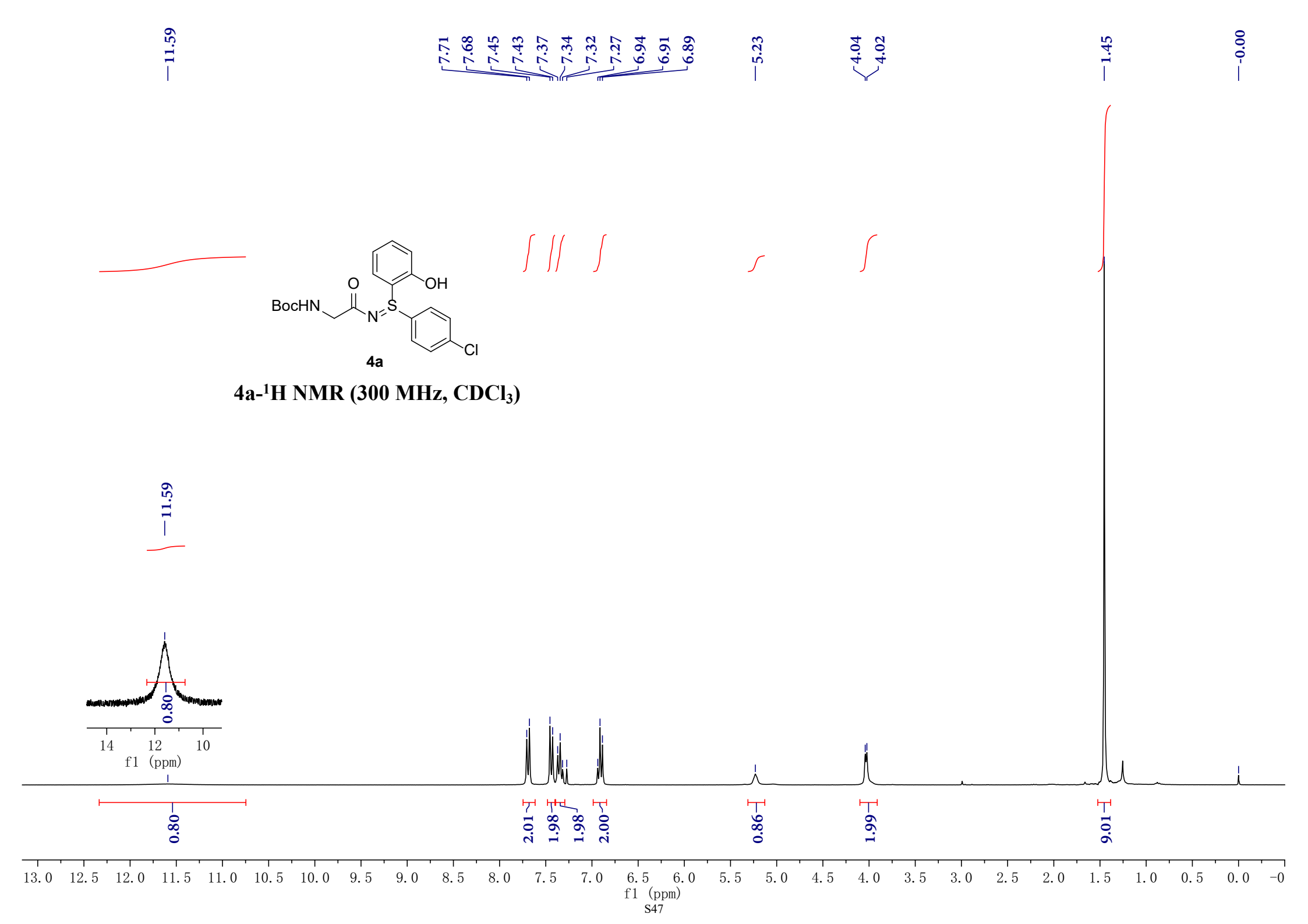
Figure S23. Time course study of the stability of **5i** under different conditions. Blue: **5i** in PBS buffer (pH 7.4) solution, red: **5i** in FBS solution, black: **5i** in 1 mM GSH of PBS buffer (pH 7.4) solution, purple: **5i** in 10 mM GSH of PBS buffer (pH 7.4) solution. The reaction mixture was analyzed by HPLC (monitored at 220 nm, method: linear gradient B/(A+B) = 5-95% over 0-30 min, A: H_2O + 0.1% CF_3COOH, B: MeCN + 0.1% CF_3COOH) at 0 h, 1 h, 3 h, 6 h, 12 h and 24 h respectively.

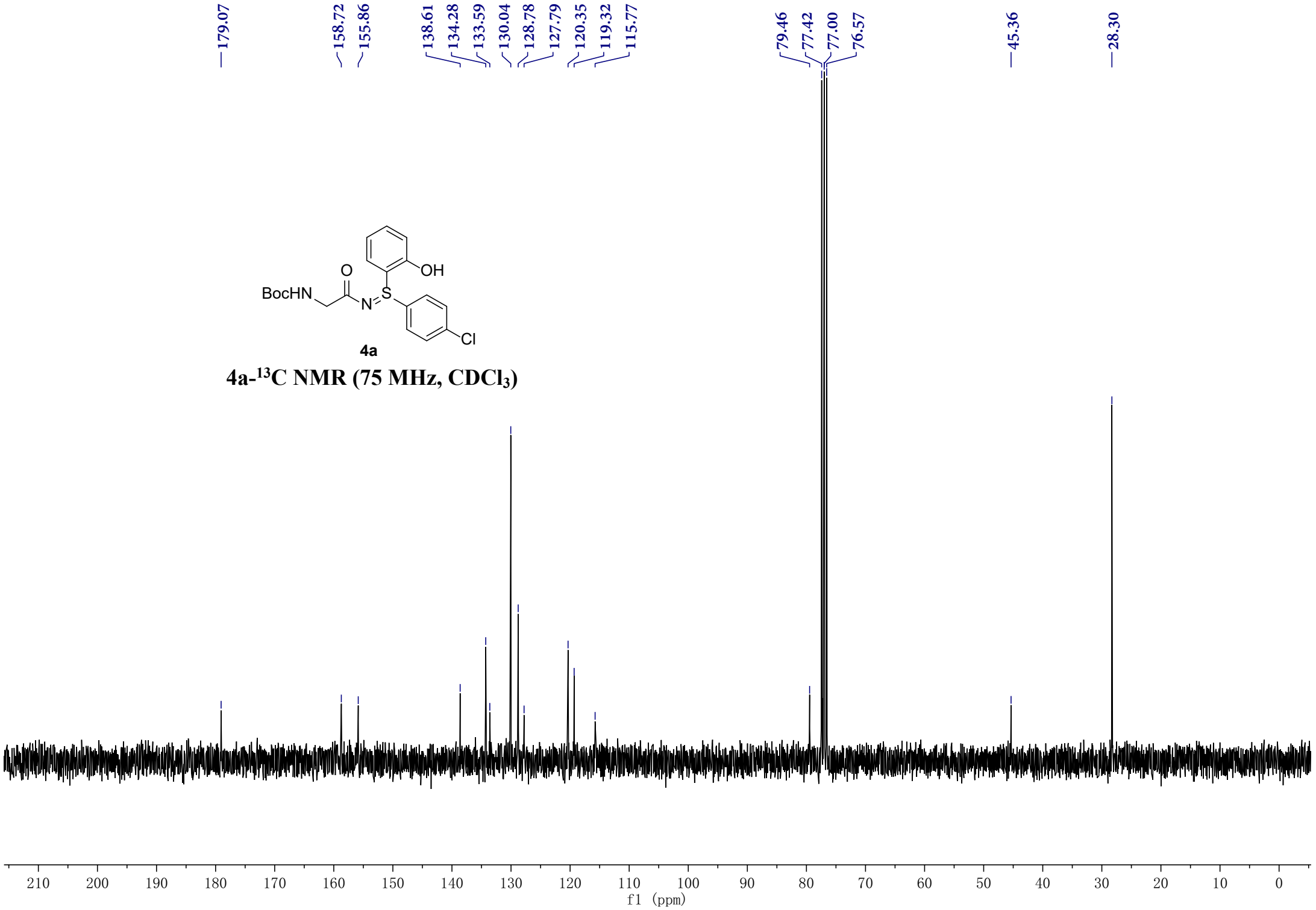
6. References

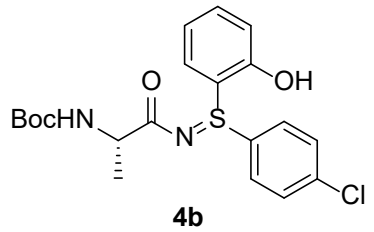
(1) Petrassi, H. M., Sharpless, K. B. & Kelly, J. W. The copper-mediated cross-coupling of phenylboronic acids and N-hydroxyphthalimide at room temperature: synthesis of aryloxyamines. *Org. Lett.* **2001**, *3*, 139-142.

(2) Christian, A. H.; Jia, S.; Cao, W.; Zhang, P.; Meza, A. T.; Sigman, M. S.; Chang, C. J.; Toste, F. D. A Physical Organic Ap-proach to Tuning Reagents for Selective and Stable Methionine Bio-conjugation. *J. Am. Chem. Soc.* **2019**, *141*, 12657-12662.

7. NMR spectra

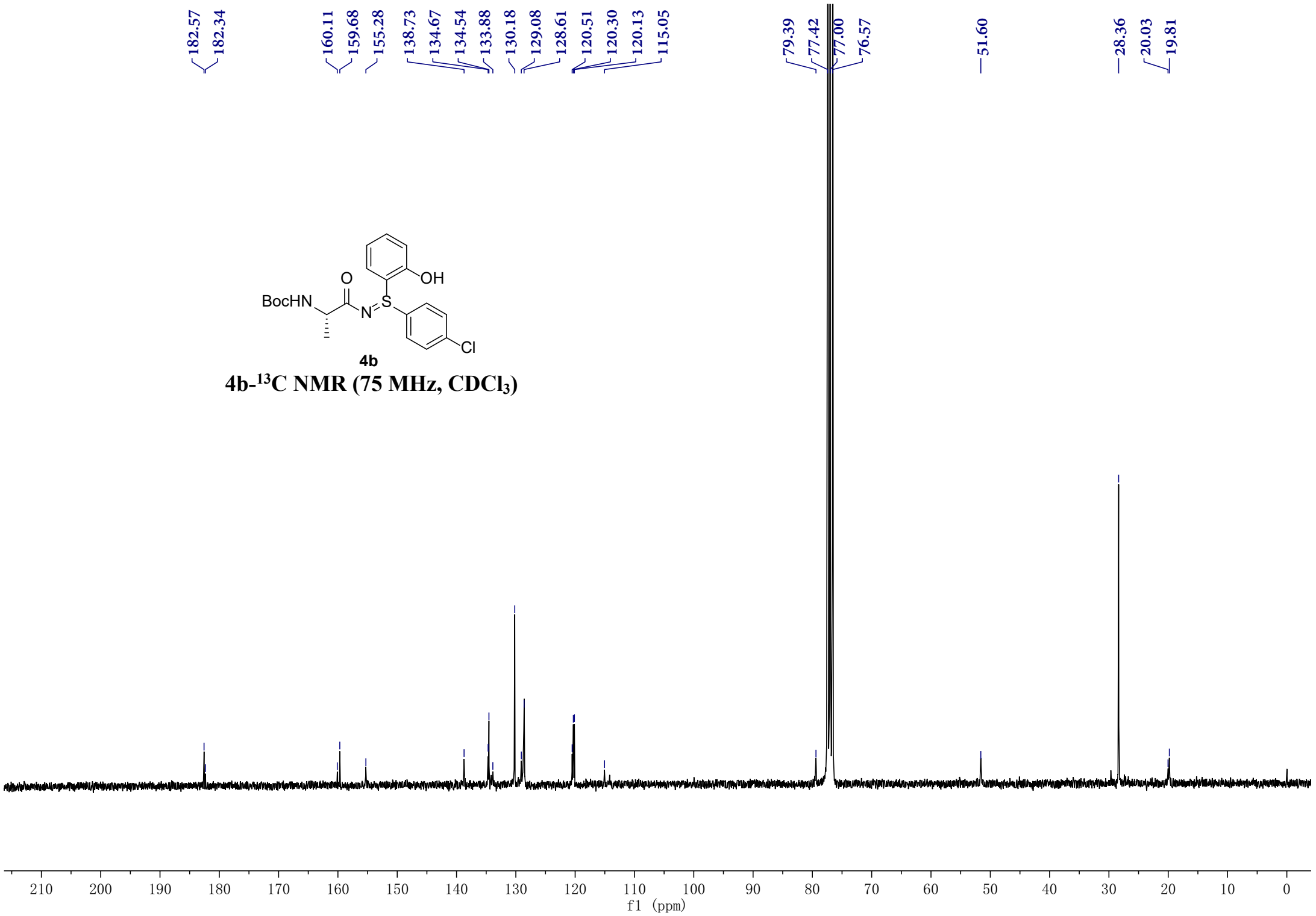

11.59
7.71
7.68
7.45
7.43
7.37
7.34
7.32
7.27
6.94
6.91
6.89
5.23
4.04
4.02
1.45
-0.00
O
OH
BocHN
N
S
Cl
4a
4a-1H NMR (300 MHz, CDCl3)
11.59
0.80
14
12
10
f1 (ppm)
0.80
2.01
1.98
1.98
2.00
0.86
1.99
9.01
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)


179.07
158.72
155.86
138.61
134.28
133.59
130.04
128.78
127.79
120.35
119.32
115.77
79.46
77.42
77.00
76.57
45.36
28.30
O
OH
BocHN
N
S
Cl
4a
4a-13C NMR (75 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



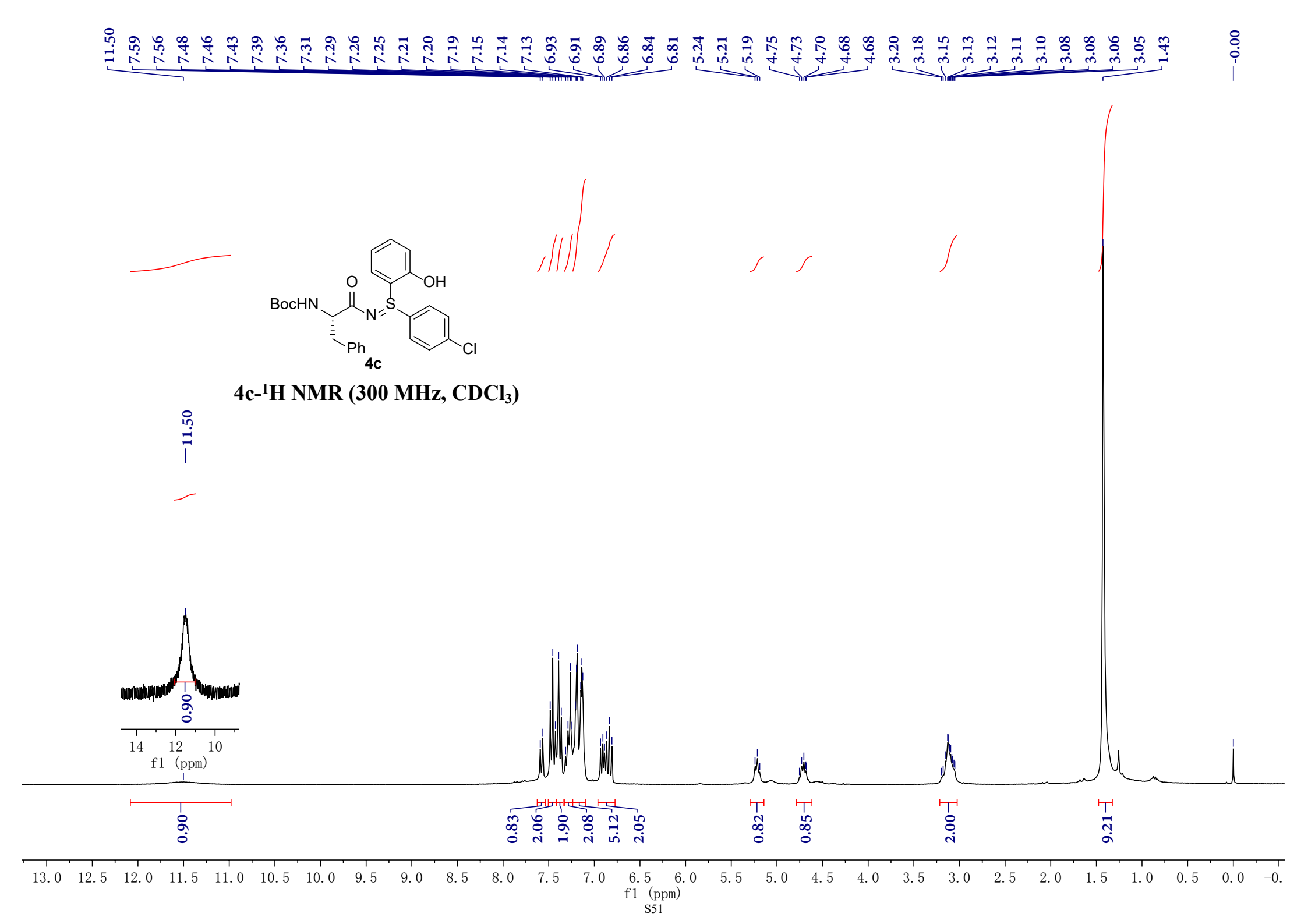
4b

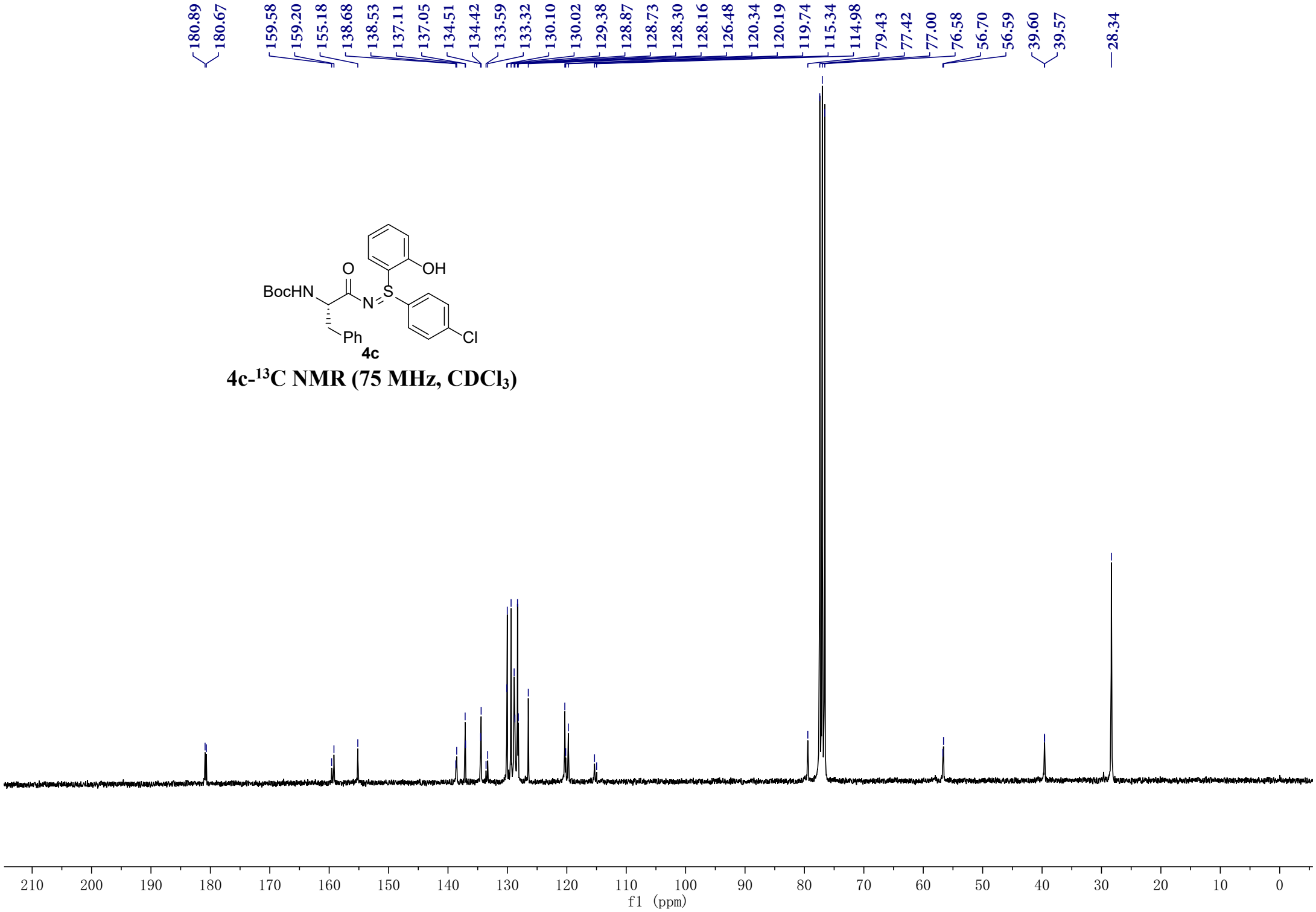
4b-^{1}H NMR (300 MHz, $CDCl_3$)



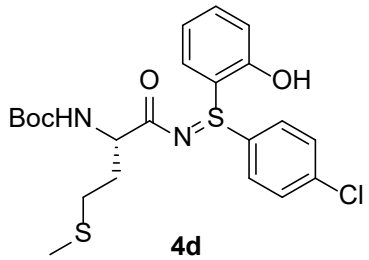
4b

4b-^{13}C NMR (75 MHz, $CDCl_3$)


11.50
7.59
7.56
7.48
7.46
7.43
7.39
7.36
7.31
7.29
7.26
7.25
7.21
7.20
7.19
7.15
7.14
7.13
6.93
6.91
6.89
6.86
6.84
6.81
5.24
5.21
5.19
4.75
4.73
4.70
4.68
4.68
3.20
3.18
3.15
3.13
3.12
3.11
3.10
3.08
3.08
3.06
3.05
1.43
-0.00
O
OH
BocHN
N
S
Ph
Cl
4c
4c-1H NMR (300 MHz, CDCl3)
11.50
0.90
14
12
10
f1 (ppm)
0.90
0.83
2.06
1.90
2.08
5.12
2.05
0.82
0.85
2.00
9.21
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.
f1 (ppm)

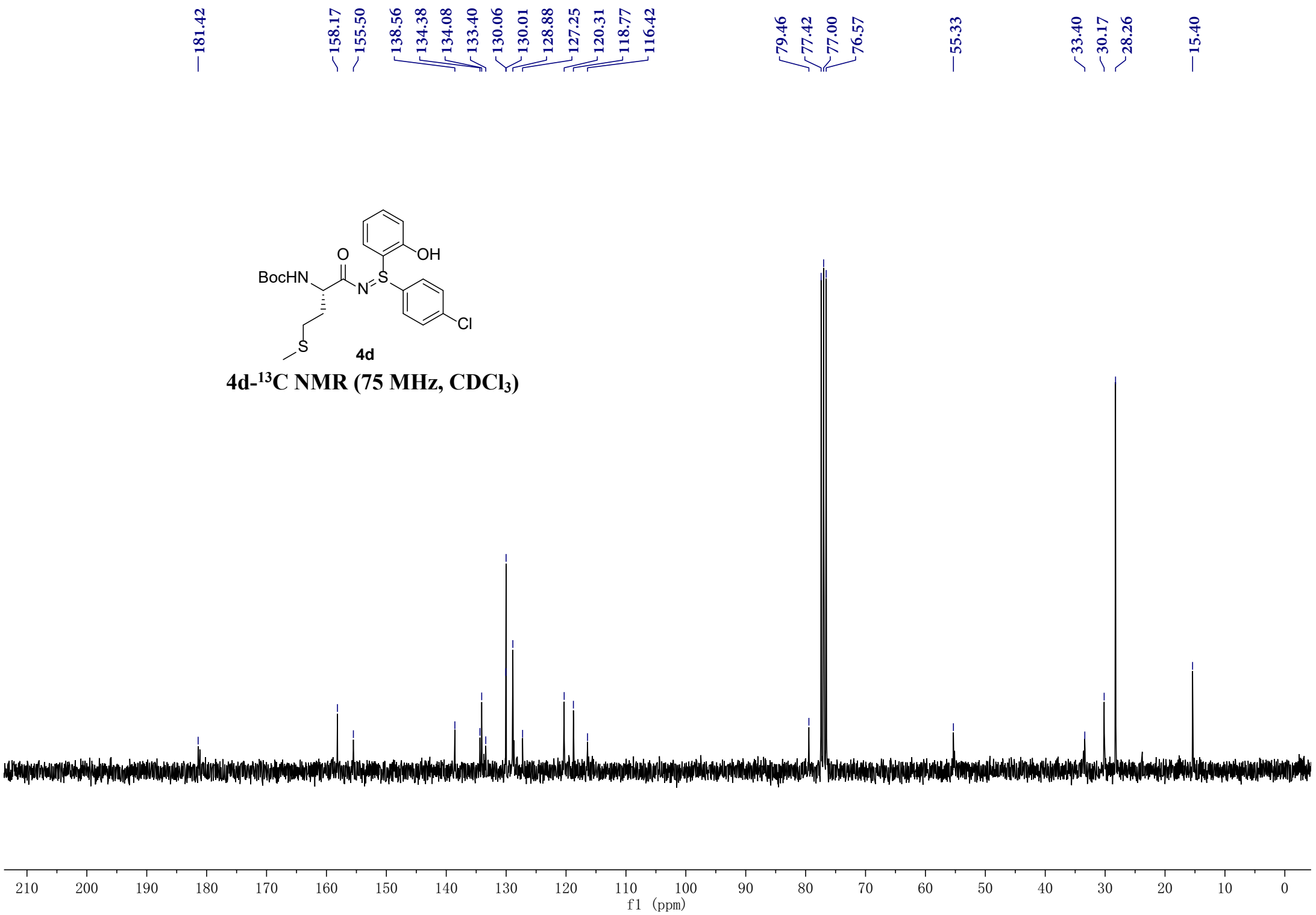


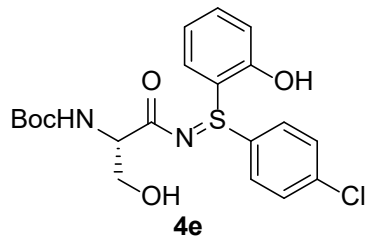
4c-^{13}C NMR (75 MHz, $CDCl_3$)



4d

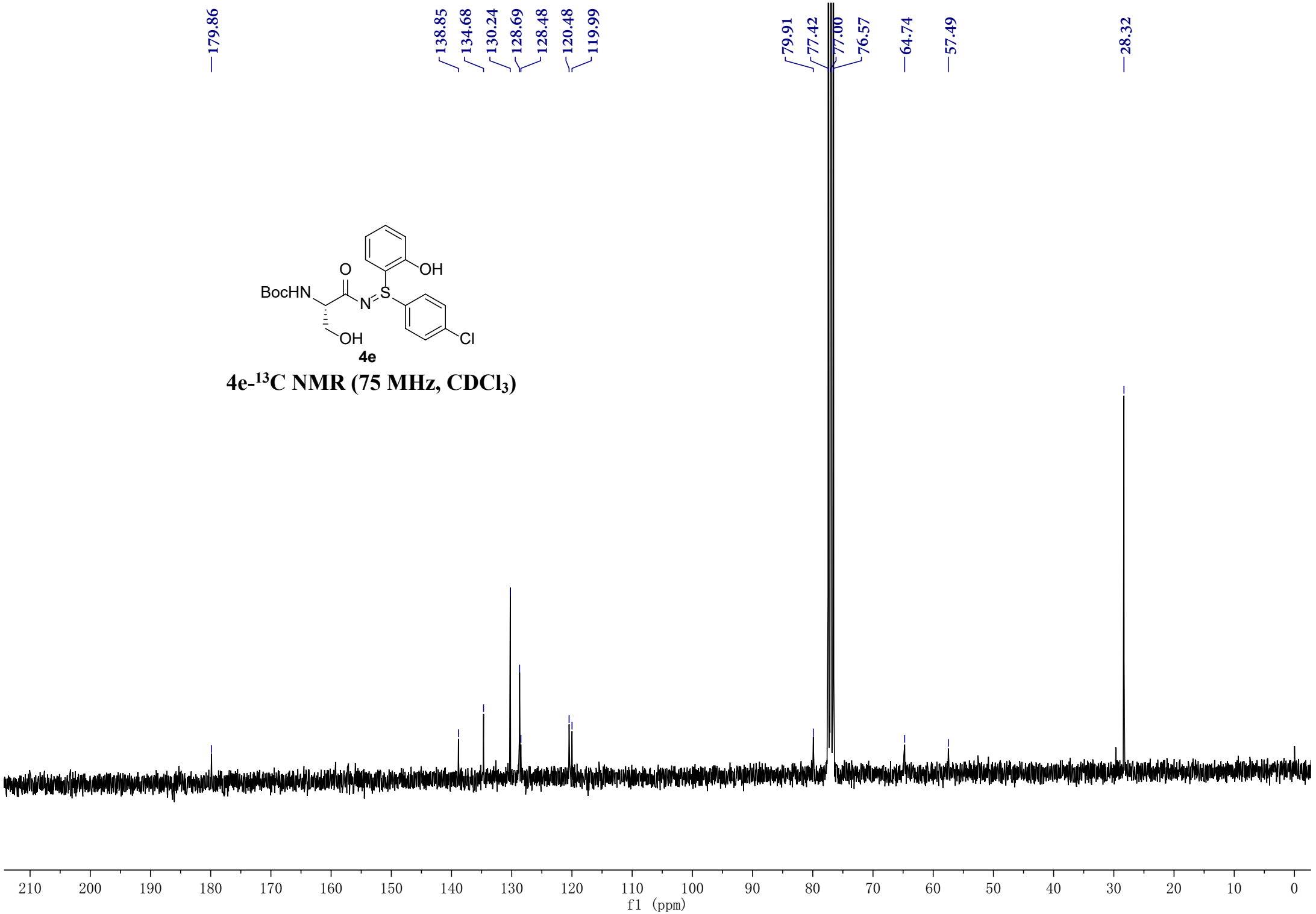
4d-^{1}H NMR (300 MHz, $CDCl_3$)


181.42
158.17
155.50
138.56
134.38
134.08
133.40
130.06
130.01
128.88
127.25
120.31
118.77
116.42
79.46
77.42
77.00
76.57
55.33
33.40
30.17
28.26
15.40
BocHN
O
N
S
OH
Cl
S
4d
4d-13C NMR (75 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

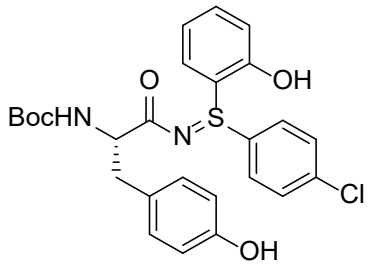


4e

4e-^{1}H NMR (300 MHz, $CDCl_3$)

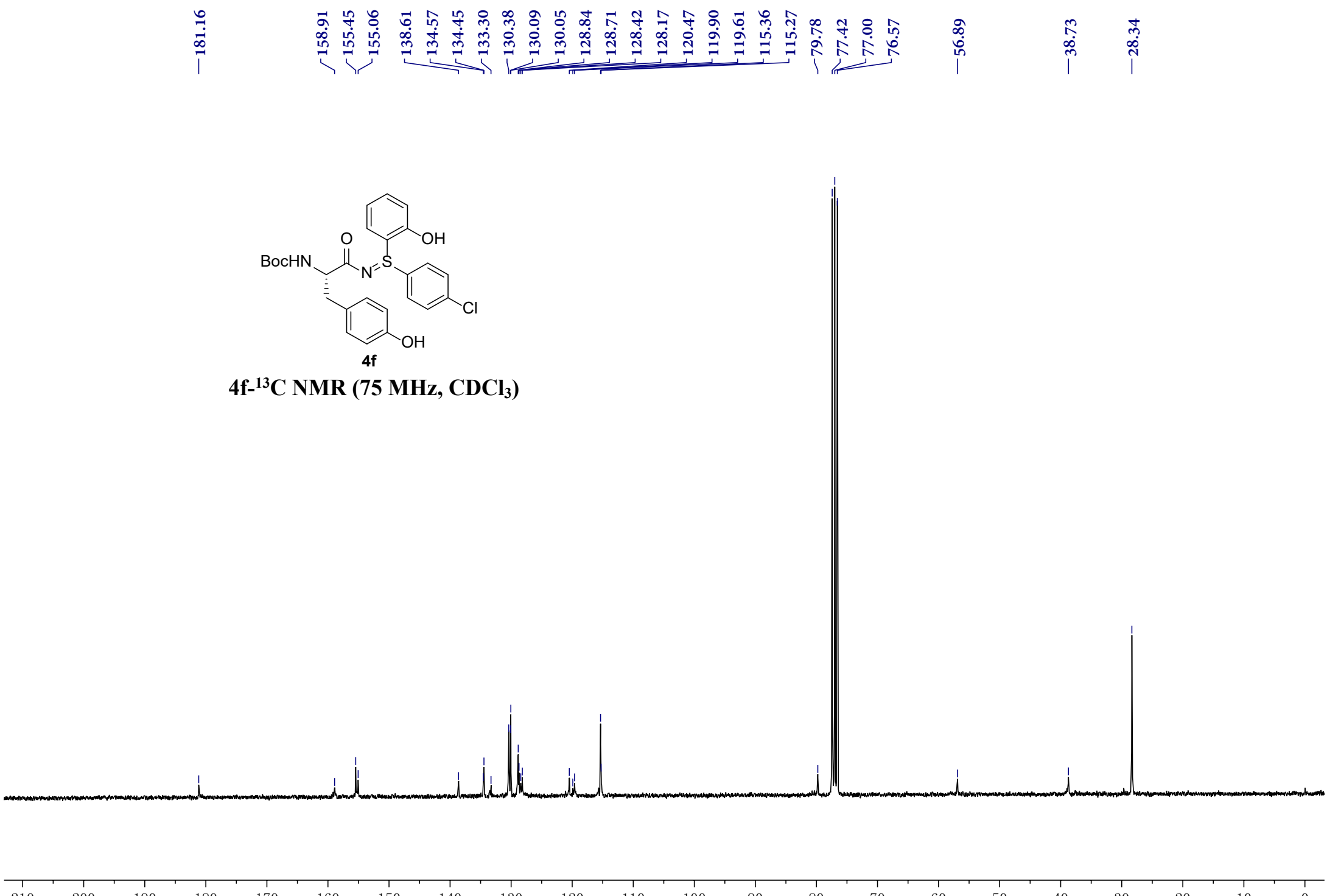


4e-^{13}C NMR (75 MHz, $CDCl_3$)

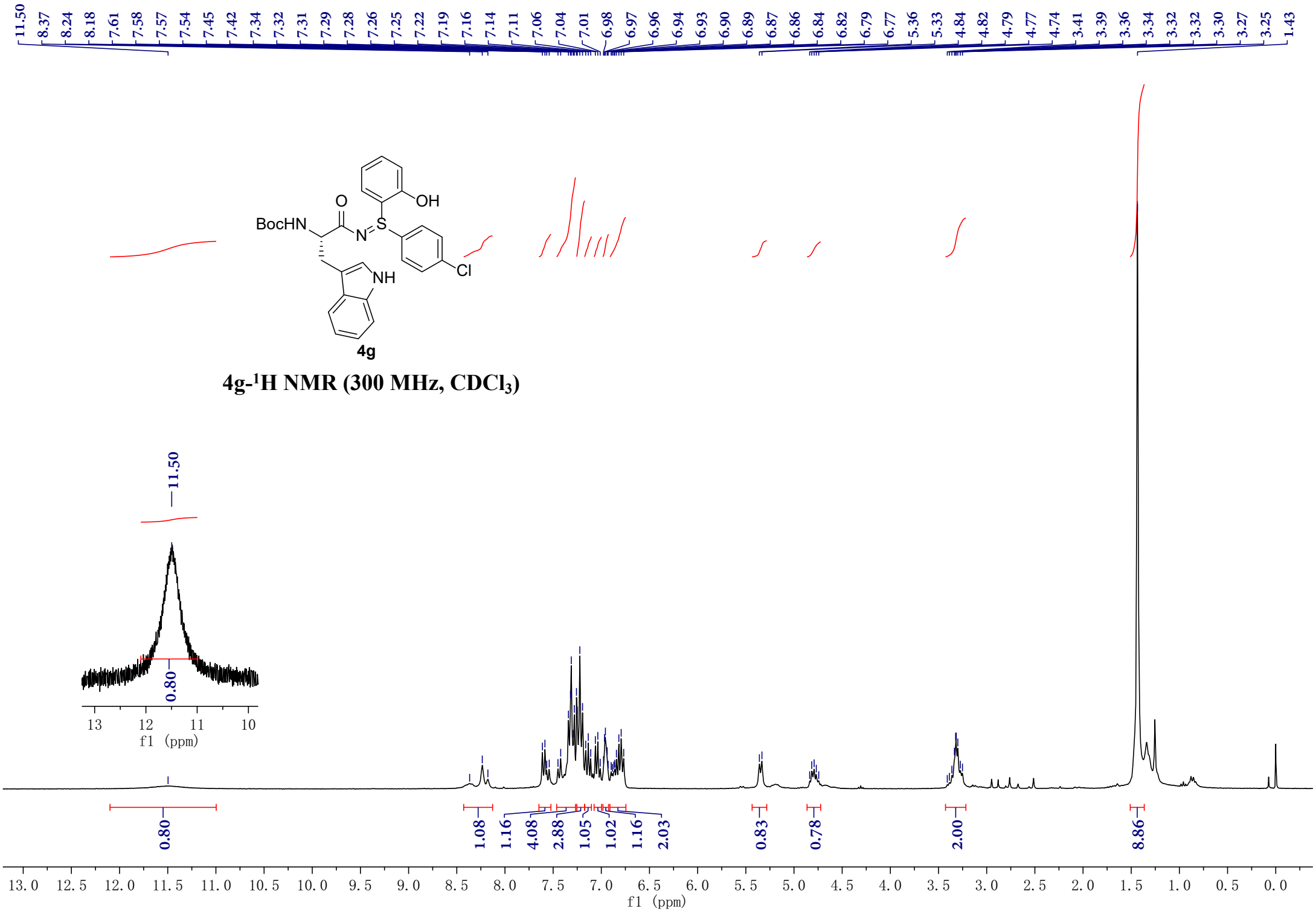


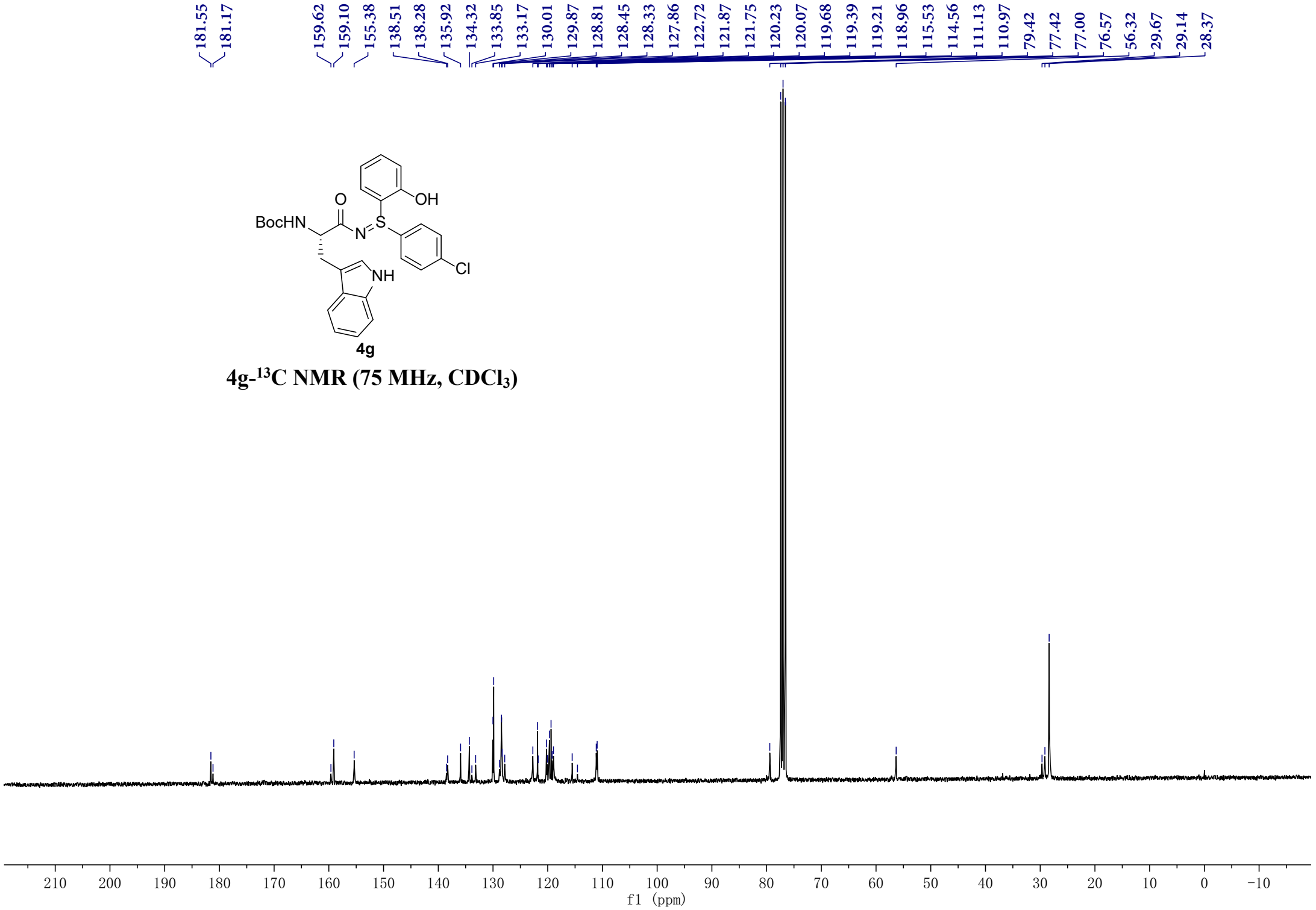
4f

4f-^{1}H NMR (300 MHz, $CDCl_3$)

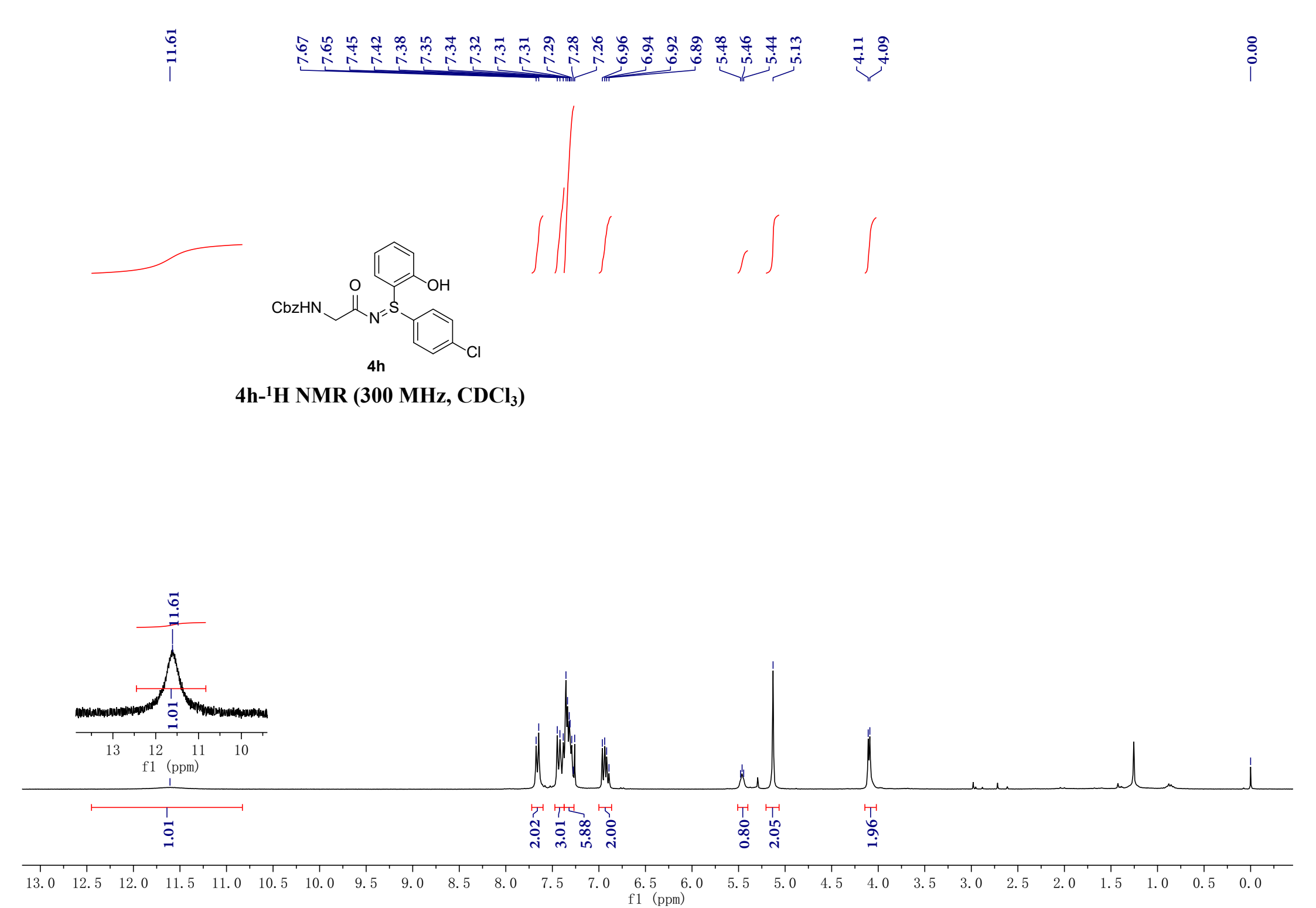


4f-^{13}C NMR (75 MHz, $CDCl_3$)

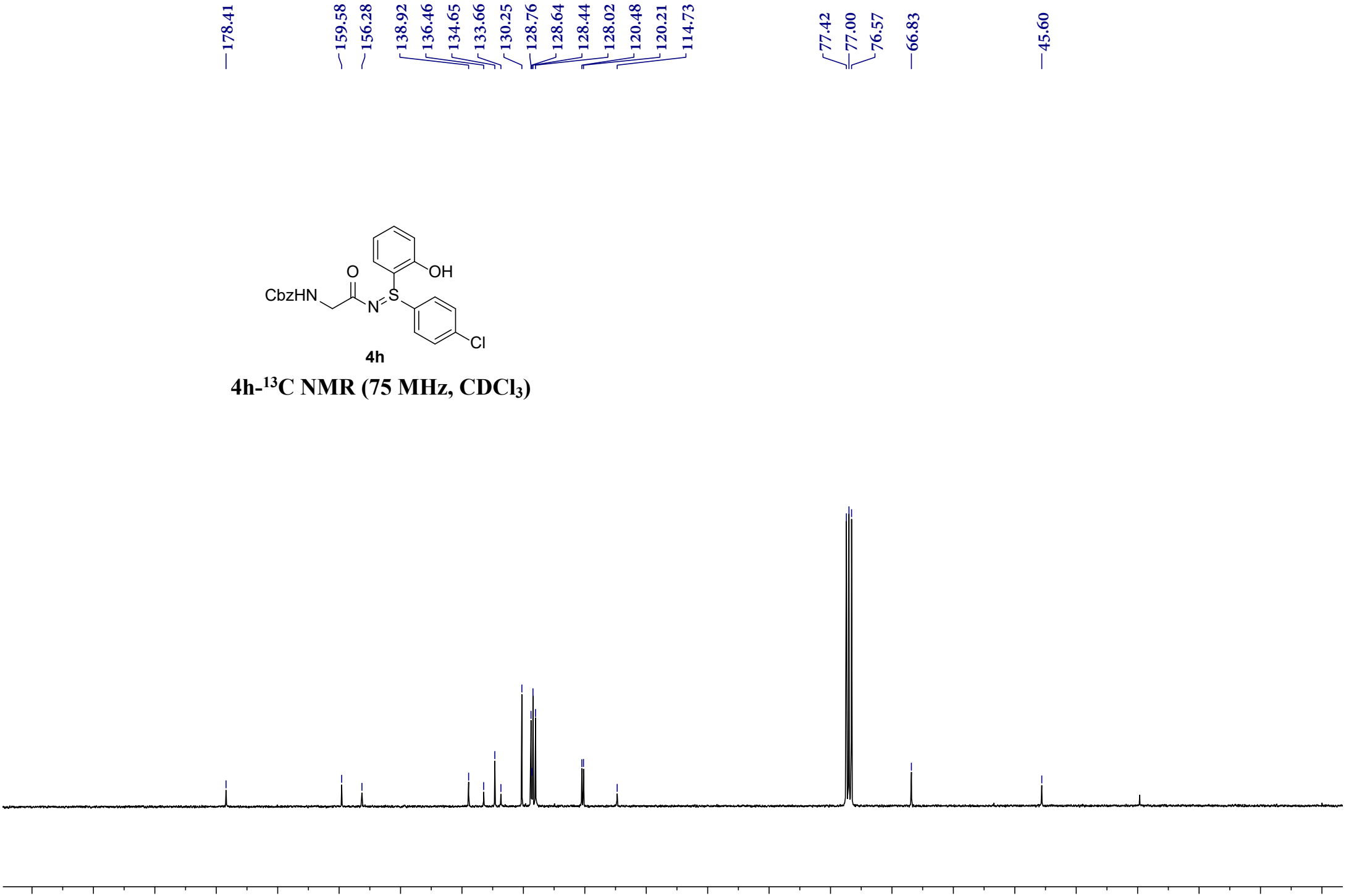

11.50 8.37 8.24 8.18 7.61 7.58 7.57 7.54 7.45 7.42 7.34 7.32 7.31 7.29 7.28 7.26 7.25 7.22 7.19 7.16 7.14 7.11 7.06 7.04 7.01 6.98 6.97 6.96 6.94 6.93 6.90 6.89 6.87 6.86 6.84 6.82 6.79 6.77 5.36 5.33 4.84 4.82 4.79 4.77 4.74 3.41 3.39 3.36 3.34 3.32 3.32 3.30 3.27 3.25 1.43
BocHN
O
N
S
OH
Cl
NH
4g
4g-1H NMR (300 MHz, CDCl3)
11.50
0.80
13 12 11 10
f1 (ppm)
0.80 1.08 1.16 4.08 2.88 1.05 1.02 1.16 2.03 0.83 0.78 2.00 8.86
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



4g-^{13}C NMR (75 MHz, $CDCl_3$)

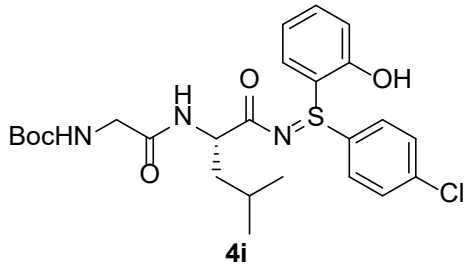


4h-^{1}H NMR (300 MHz, $CDCl_3$)



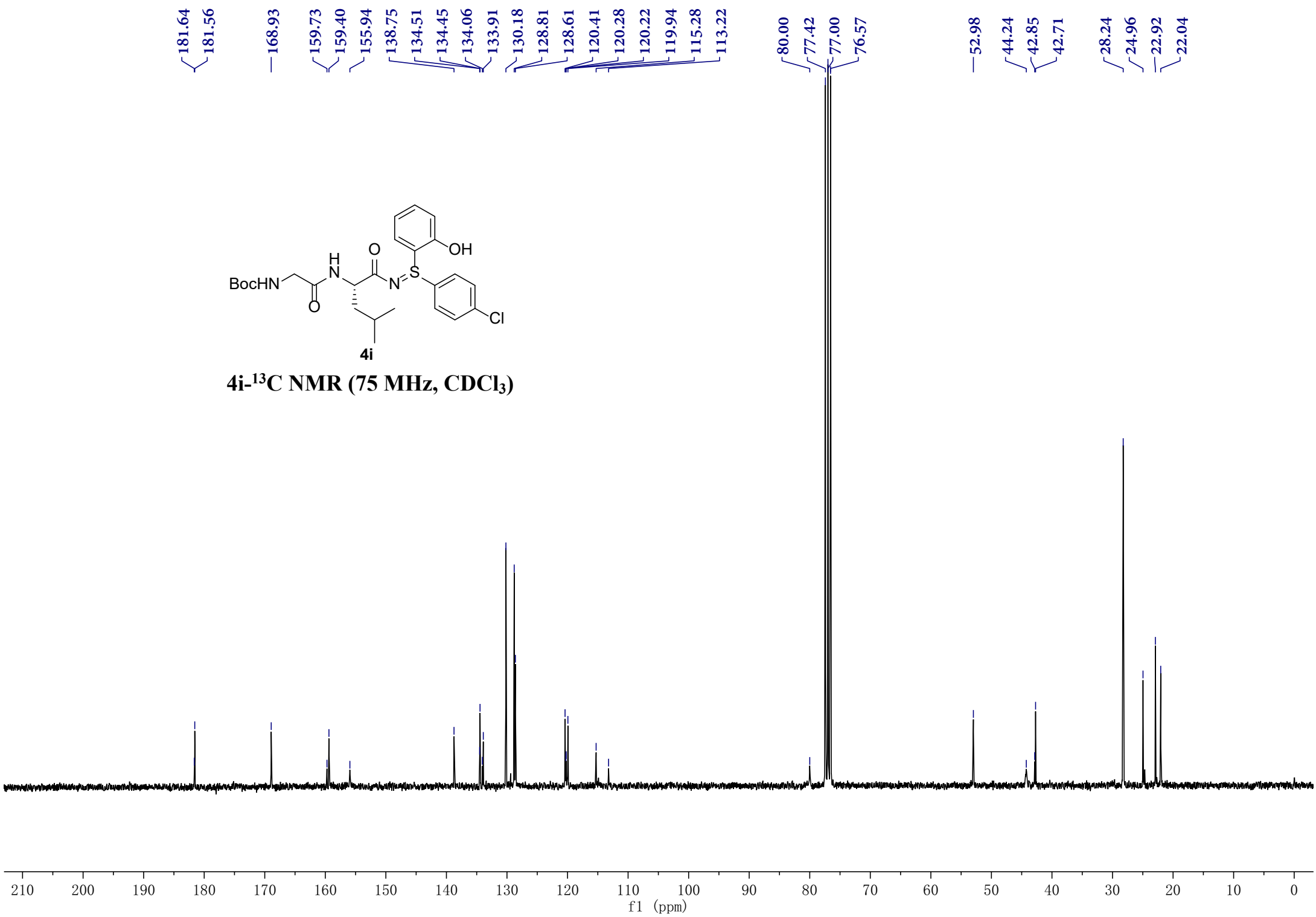
4h

4h-^{13}C NMR (75 MHz, $CDCl_3$)

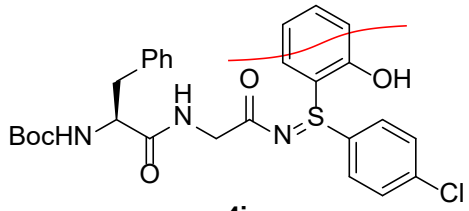


4i

4i-^{1}H NMR (300 MHz, $CDCl_3$)

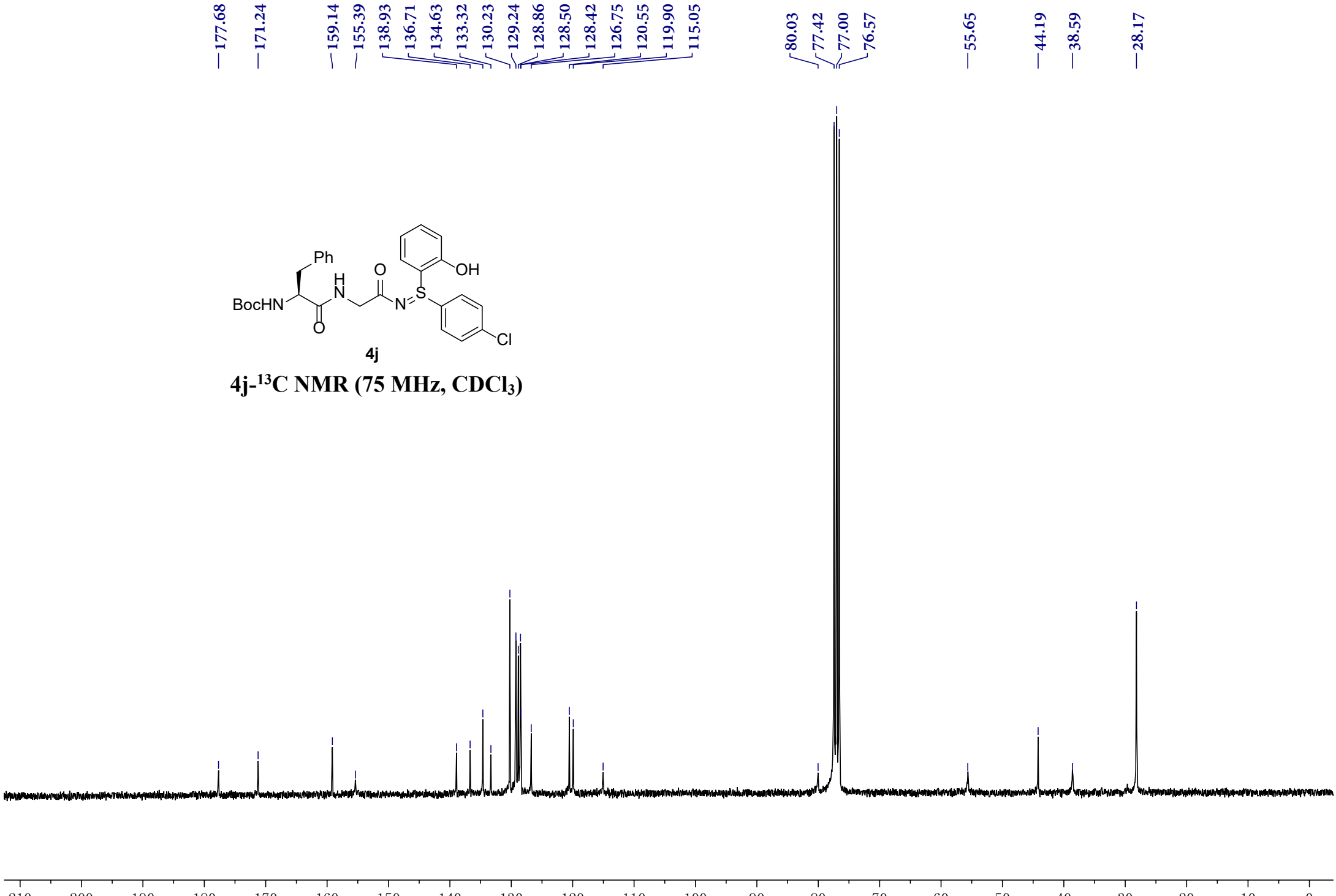


4i-^{13}C NMR (75 MHz, $CDCl_3$)



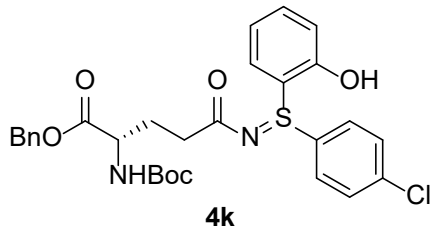
4j

4j-^{1}H NMR (300 MHz, $CDCl_3$)



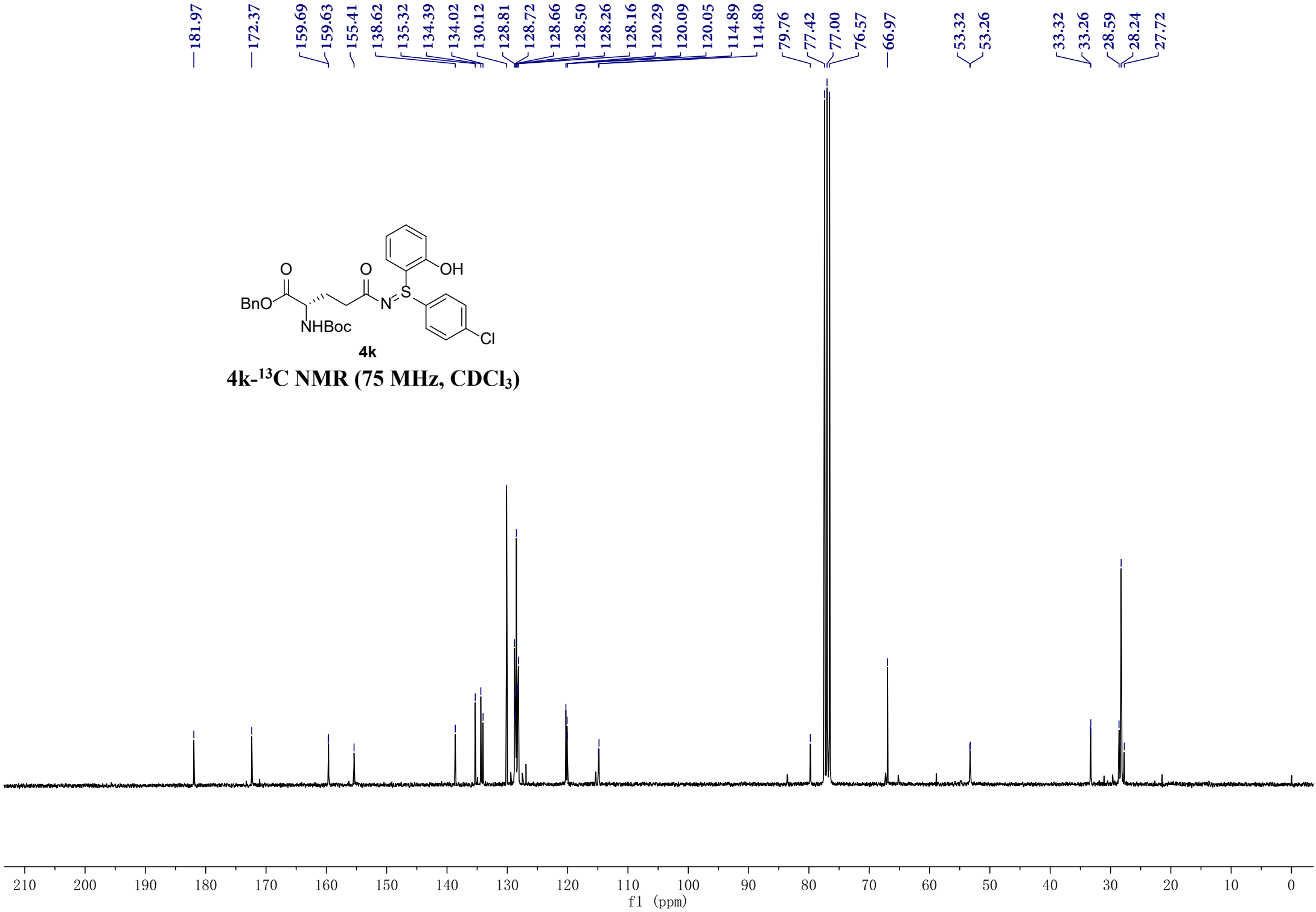
4j

4j-^{13}C NMR (75 MHz, $CDCl_3$)

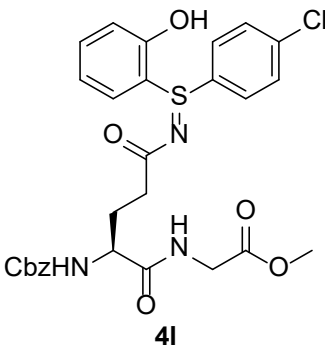


4k

4k-^{1}H NMR (300 MHz, $CDCl_3$)

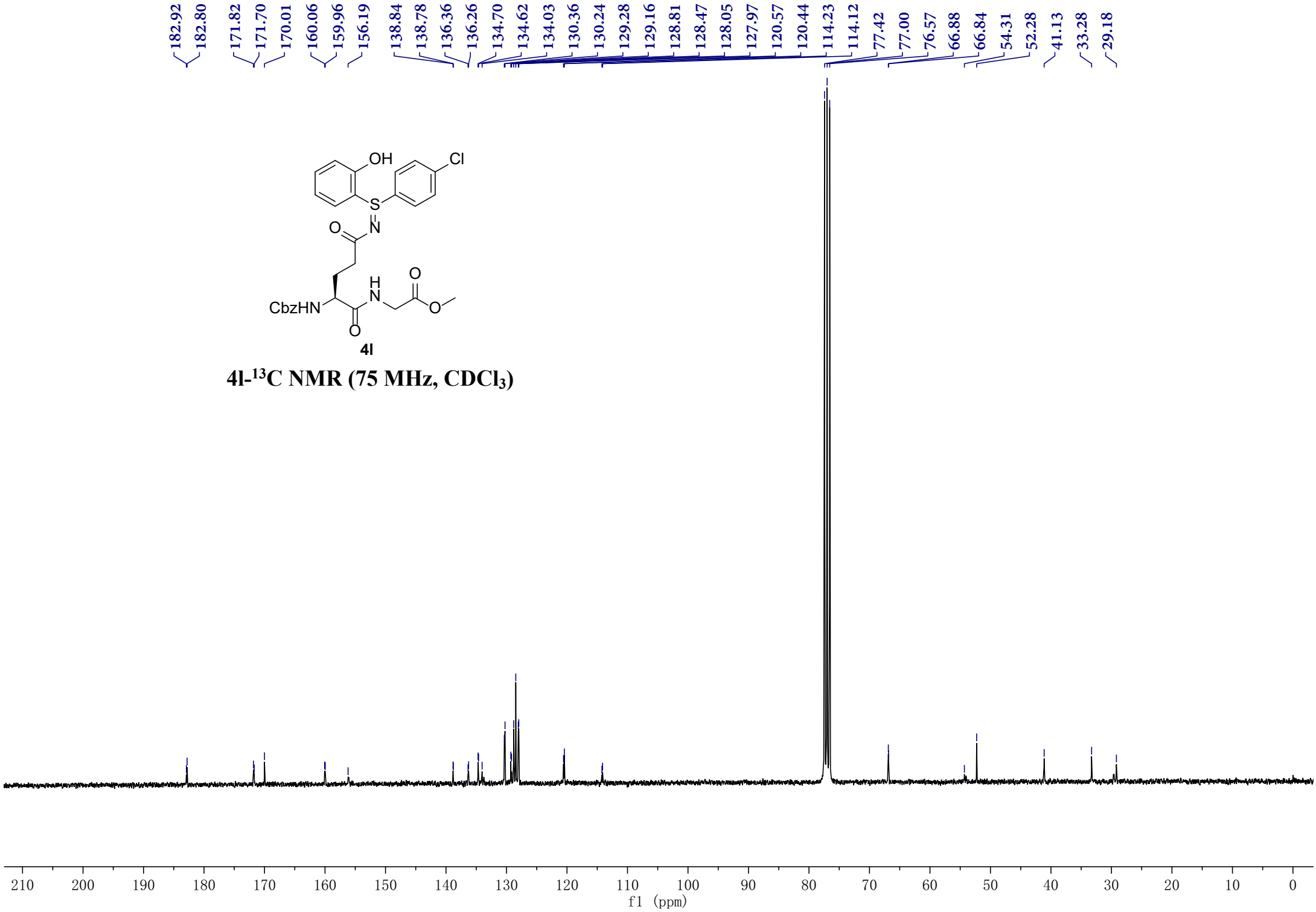


4k-^{13}C NMR (75 MHz, $CDCl_3$)



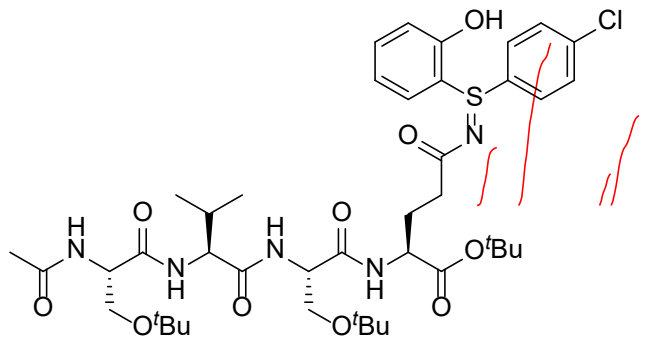
4l

4l-^{1}H NMR (300 MHz, $CDCl_3$)



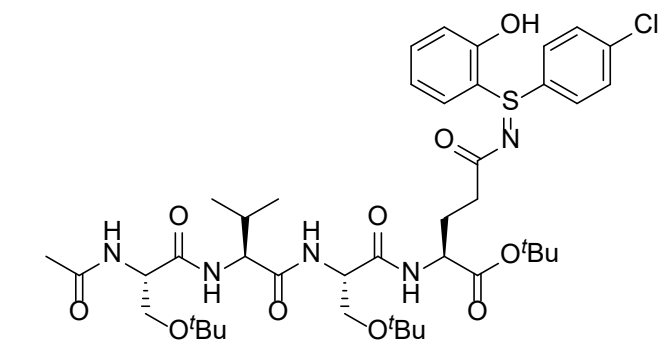
4l

4l-^{13}C NMR (75 MHz, $CDCl_3$)



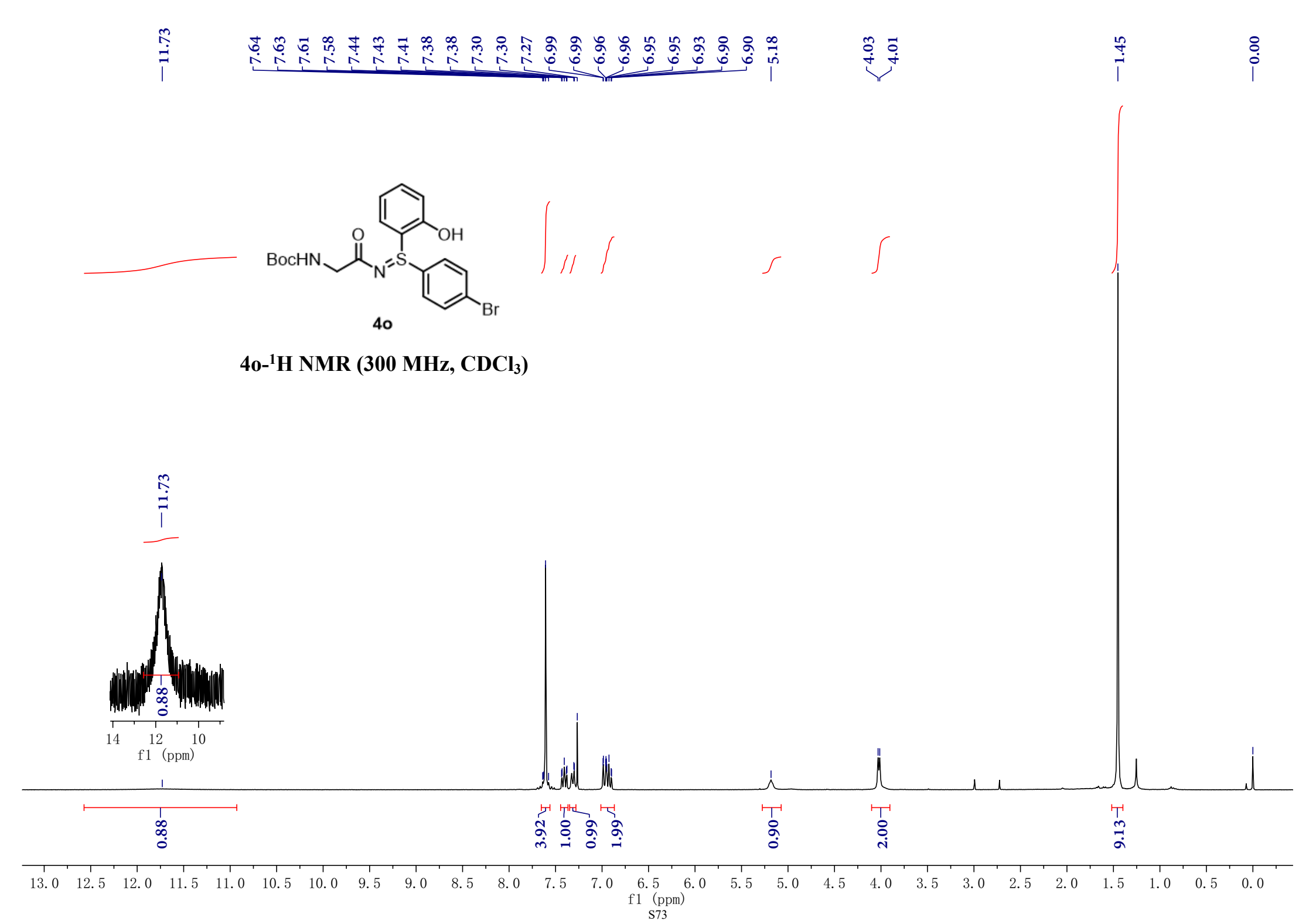
4m

4m-^{1}H NMR (300 MHz, $CDCl_3$)

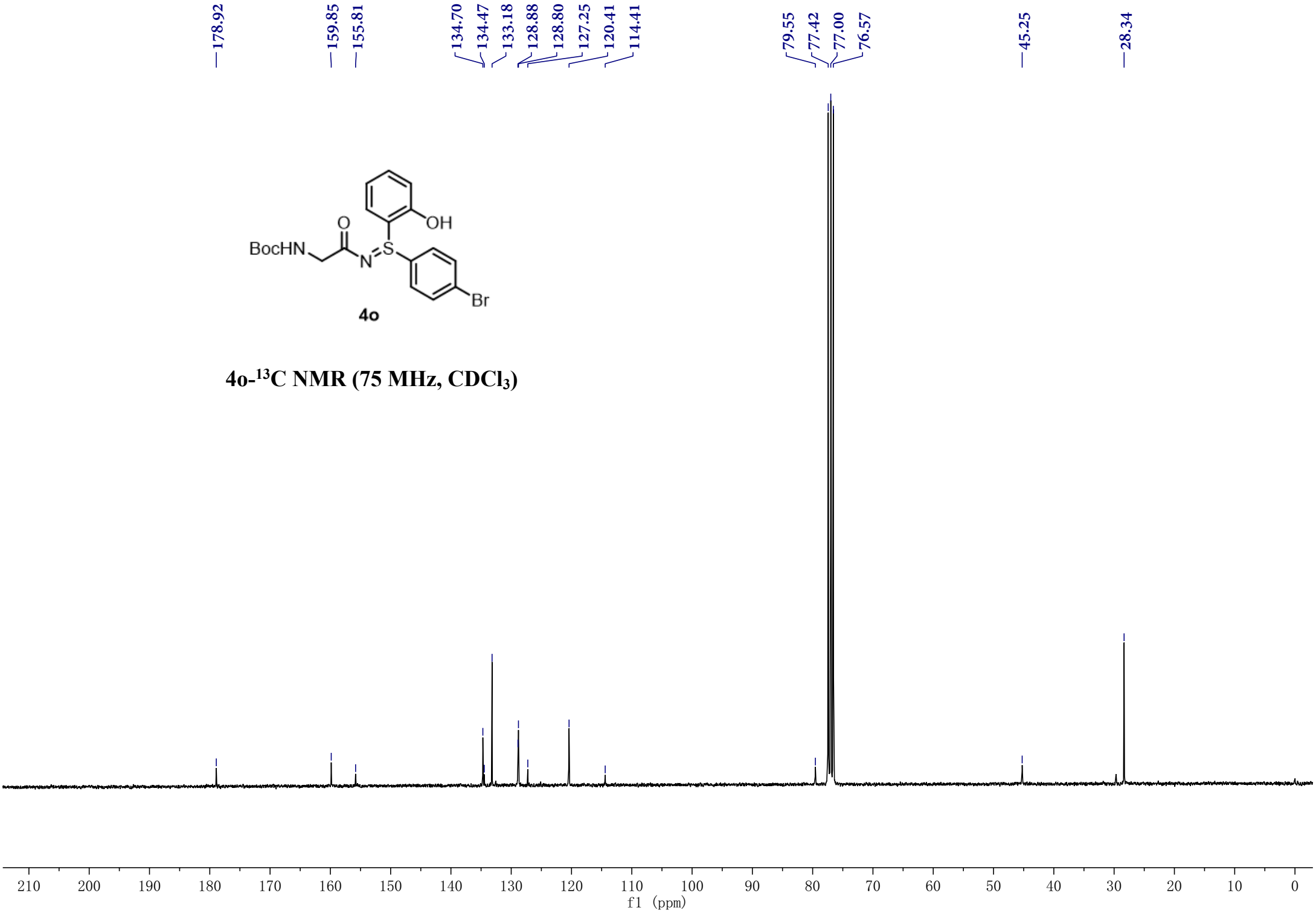


4m

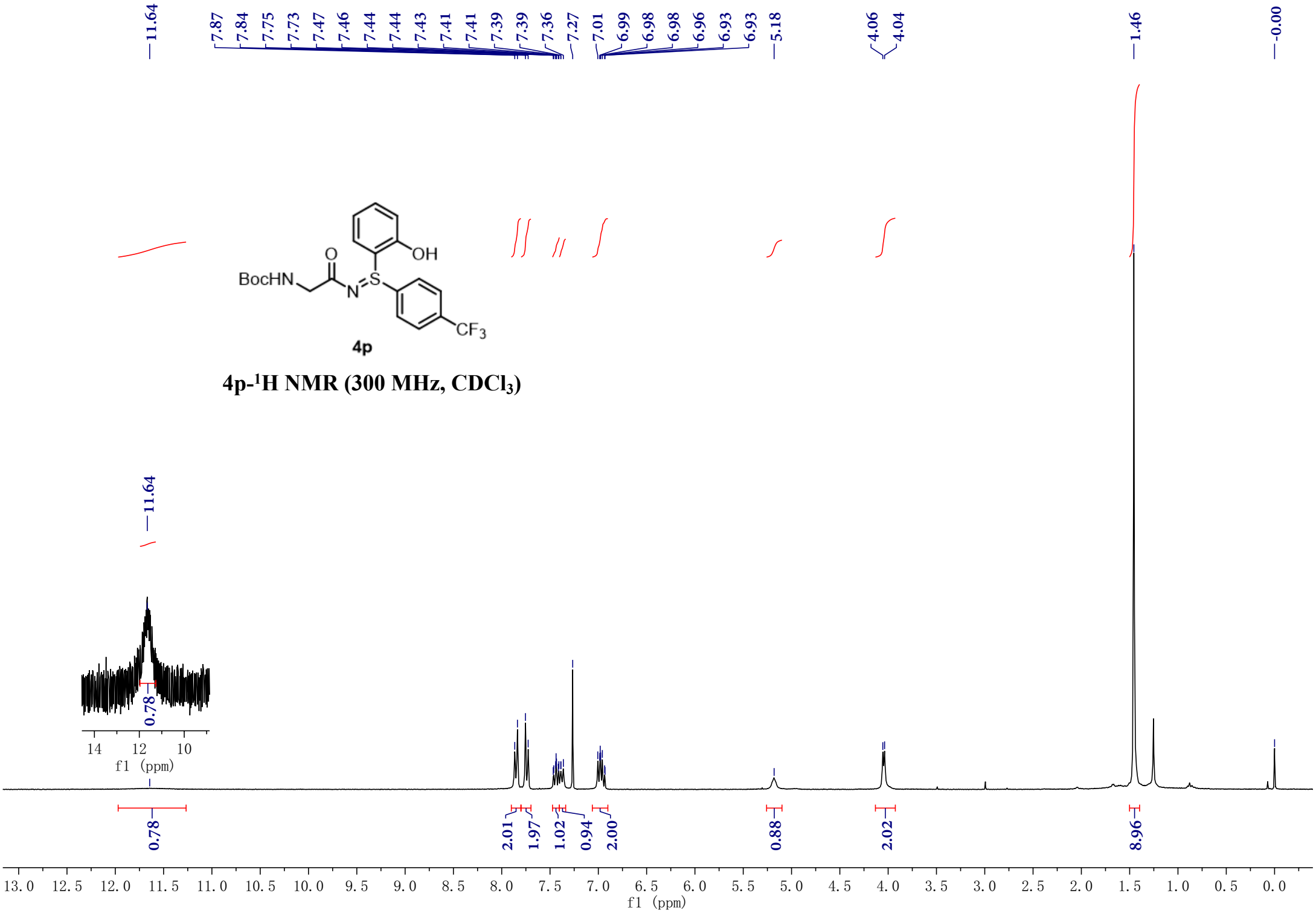
4m-^{13}C NMR (75 MHz, $CDCl_3$)



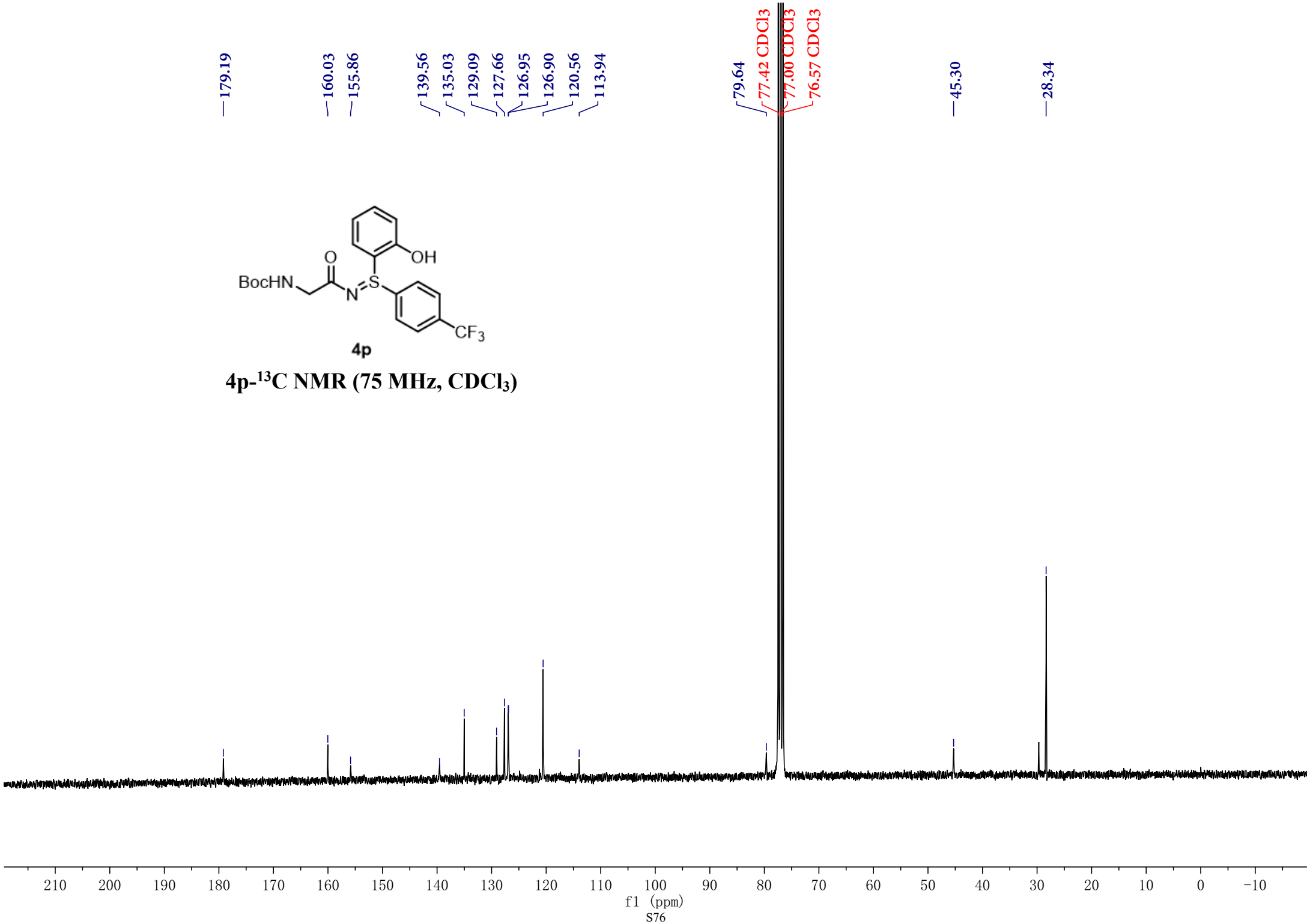
4o-^{1}H NMR (300 MHz, $CDCl_3$)



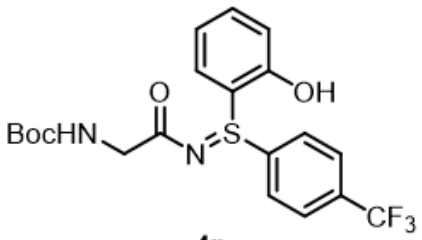
4o-^{13}C NMR (75 MHz, $CDCl_3$)



4p-^{1}H NMR (300 MHz, $CDCl_3$)

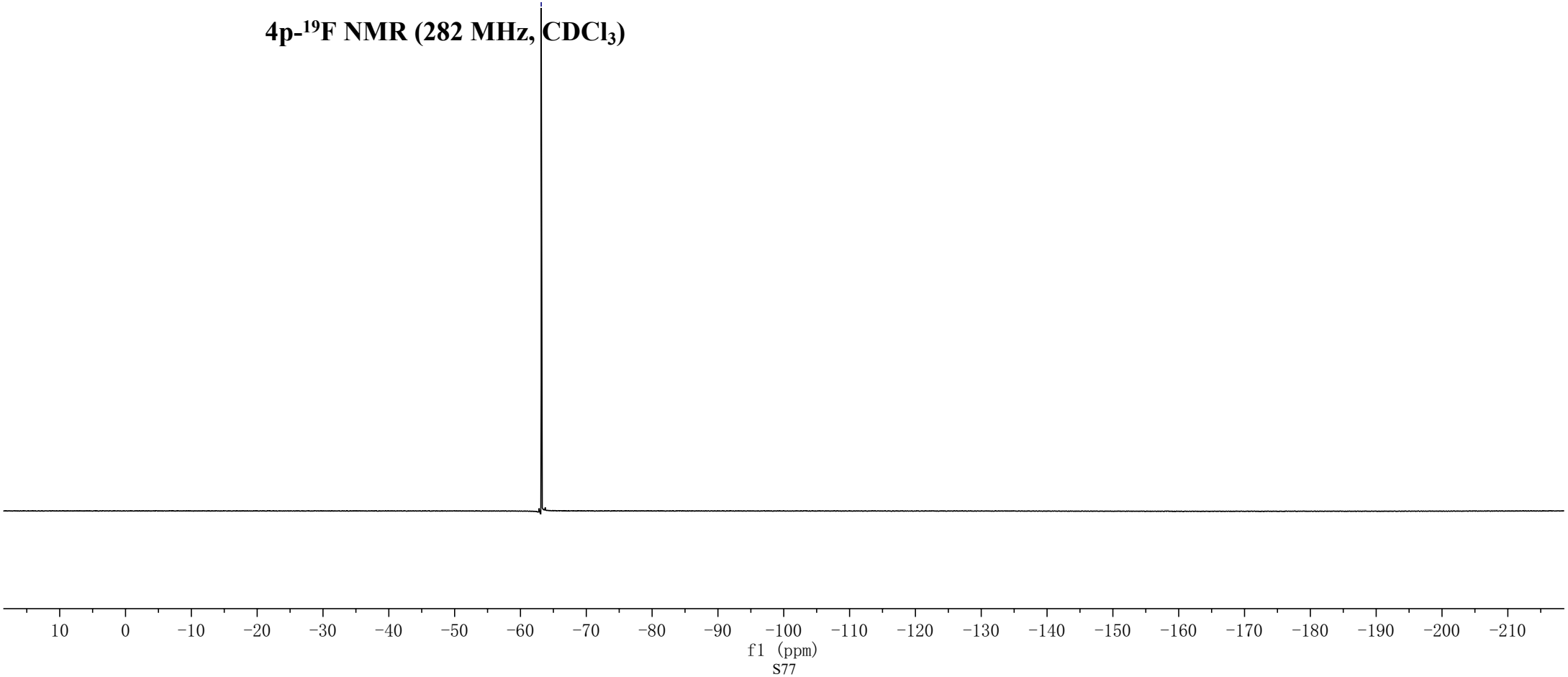


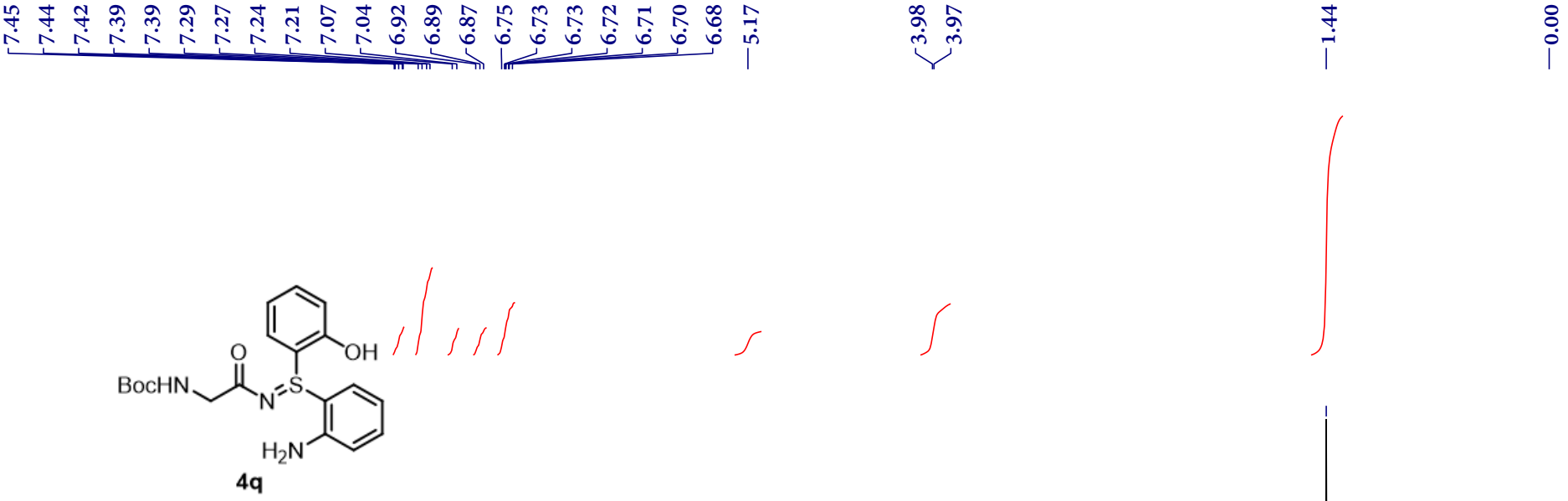
4p-^{13}C NMR (75 MHz, $CDCl_3$)



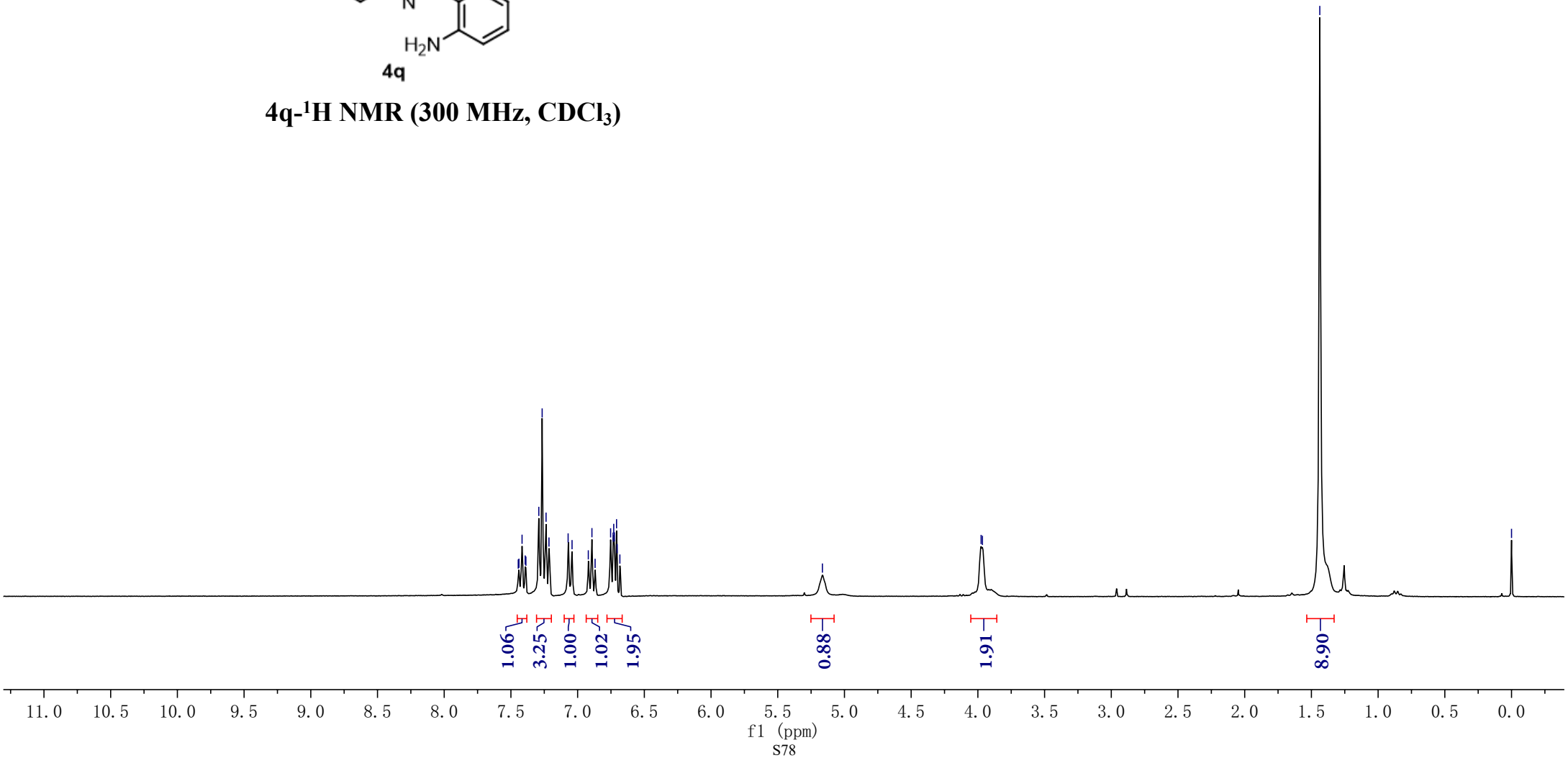
4p

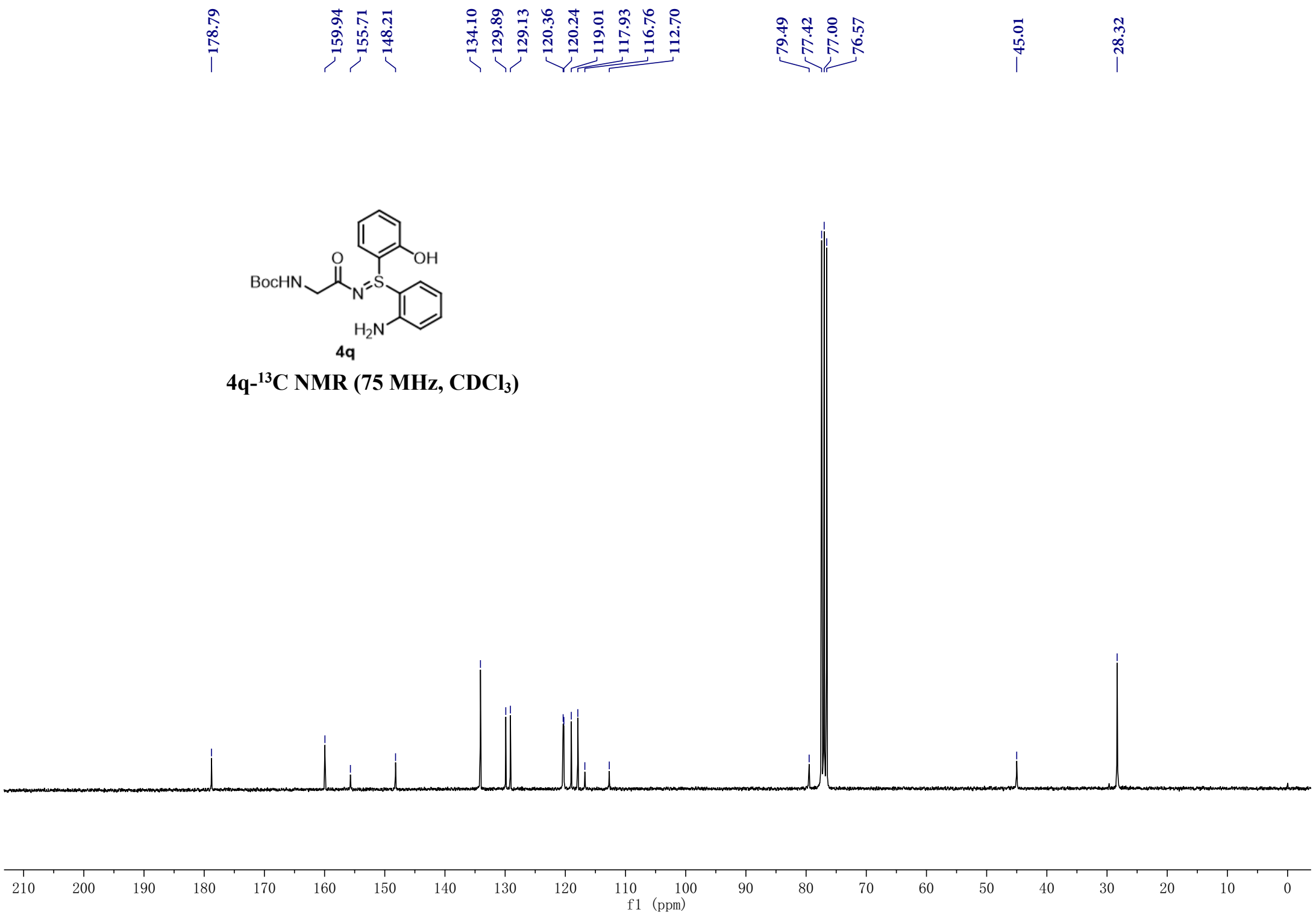
4p-^{19}F NMR (282 MHz, $CDCl_3$)



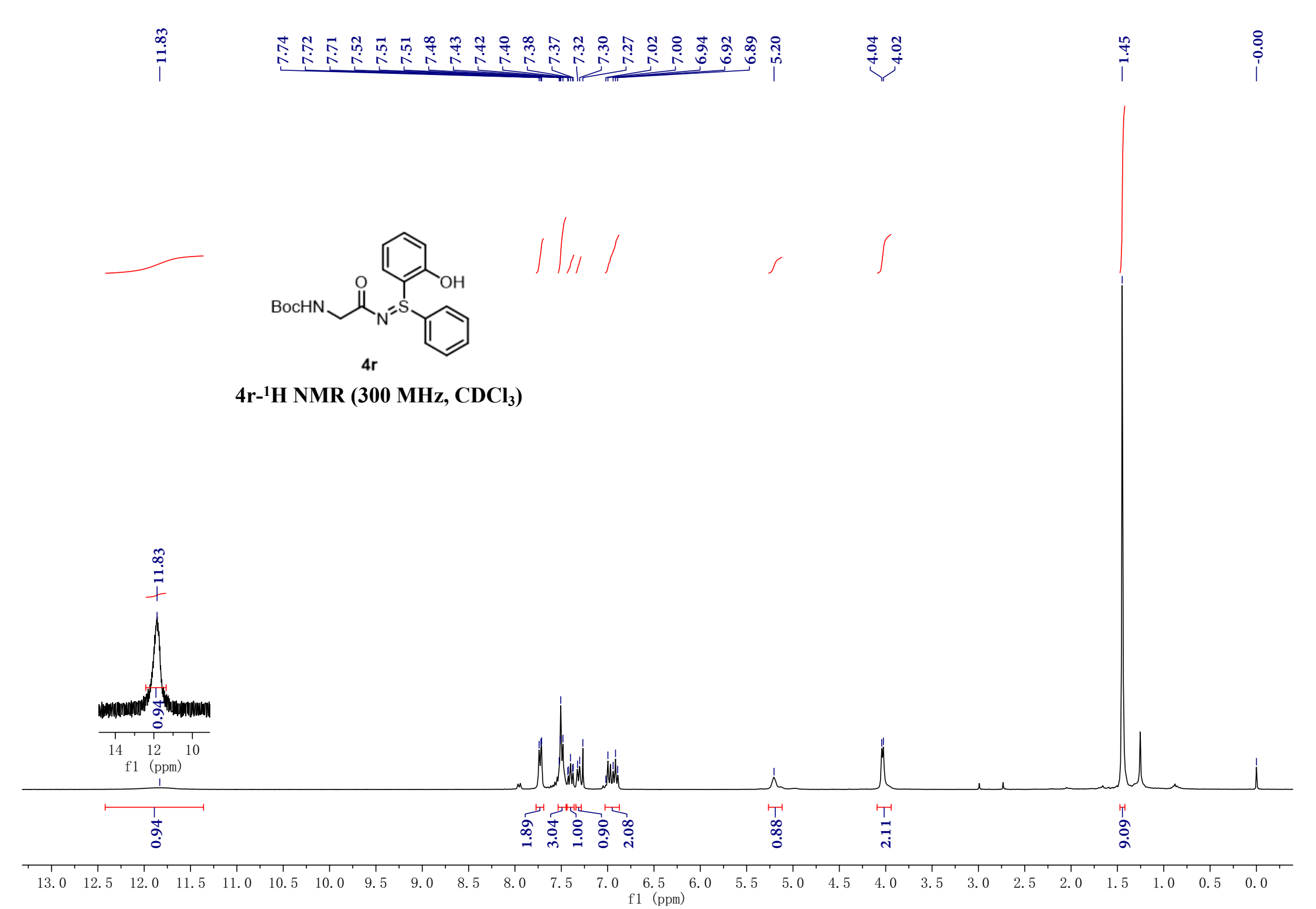


4q-^{1}H NMR (300 MHz, $CDCl_3$)

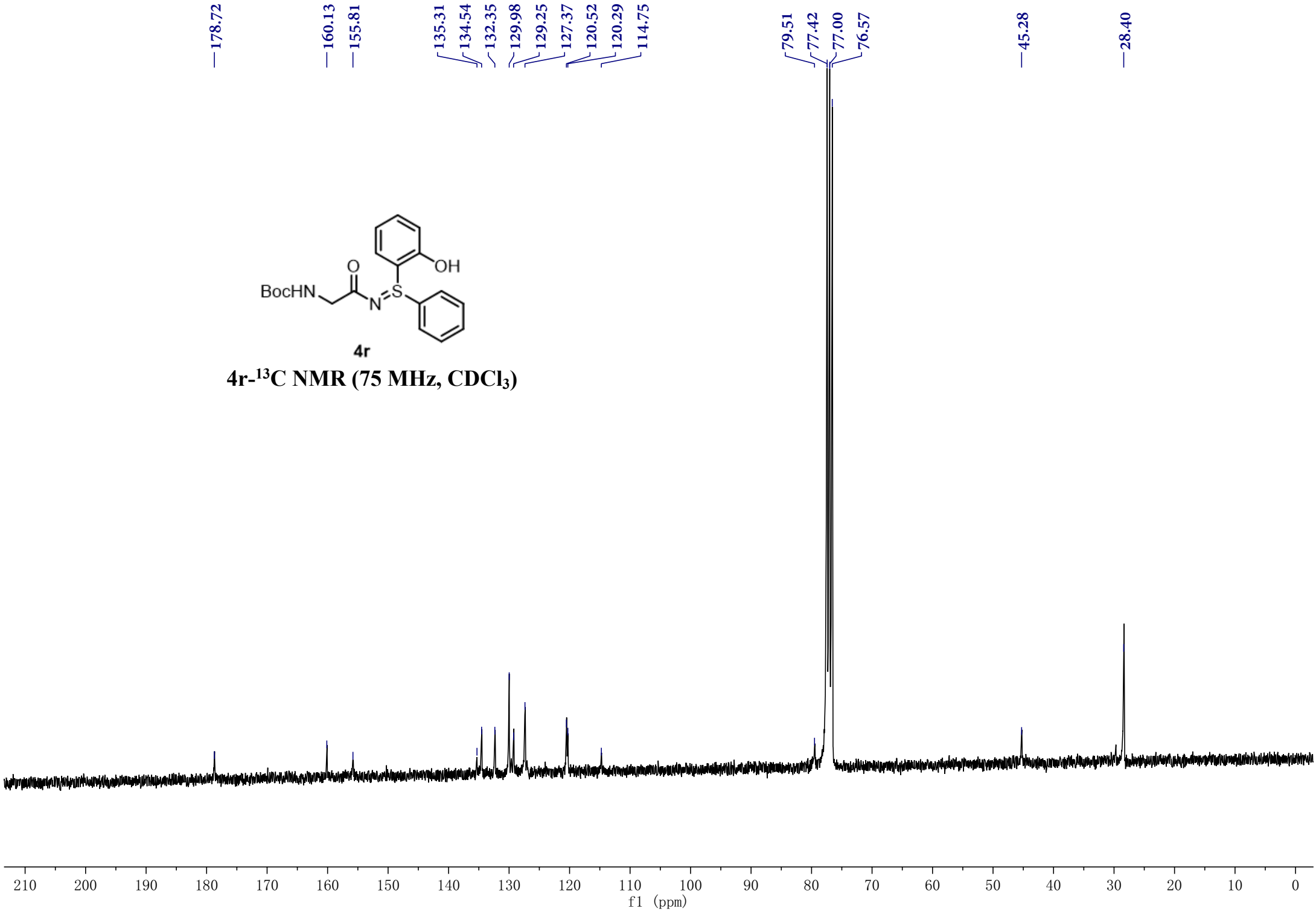




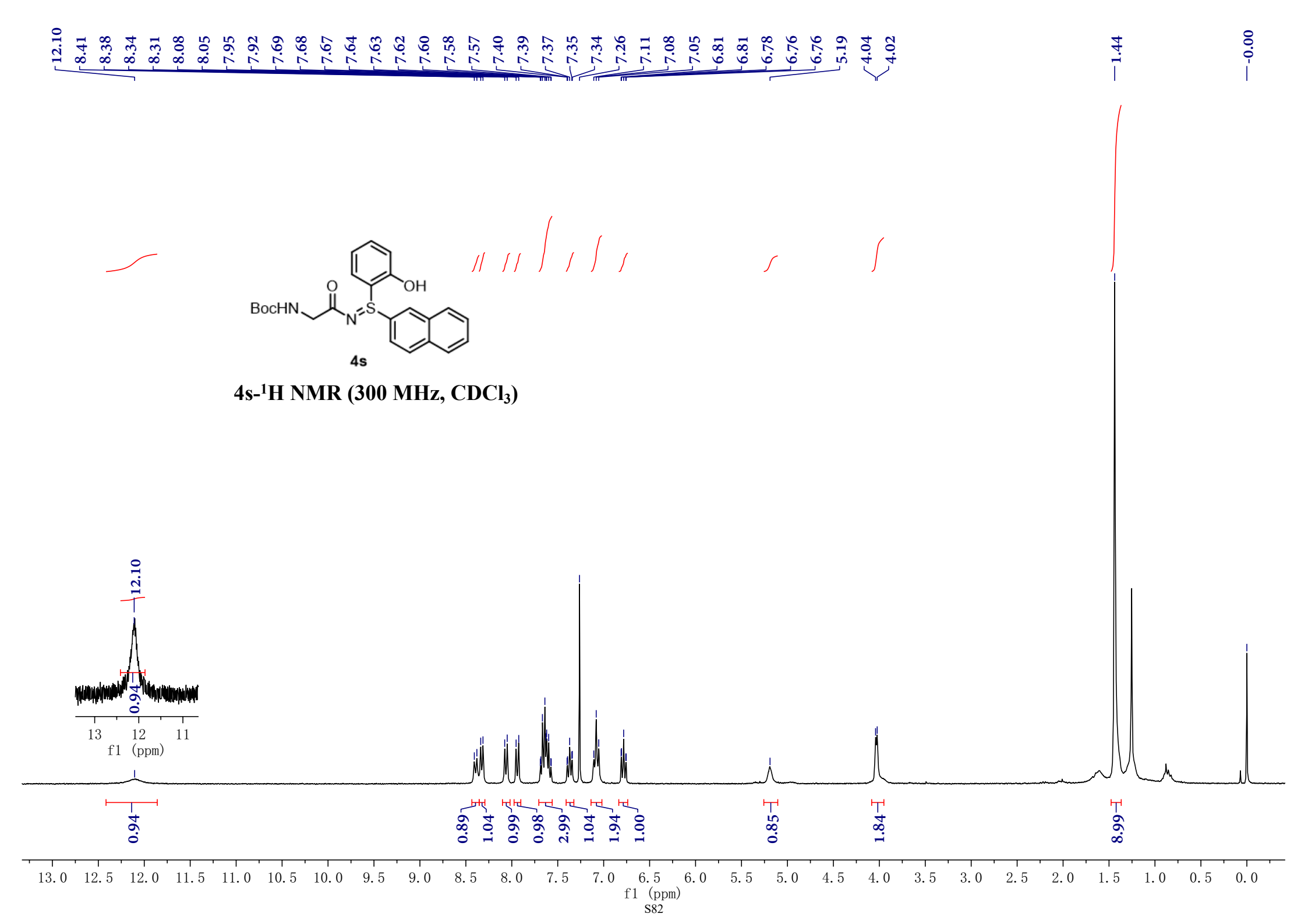
4q-^{13}C NMR (75 MHz, $CDCl_3$)

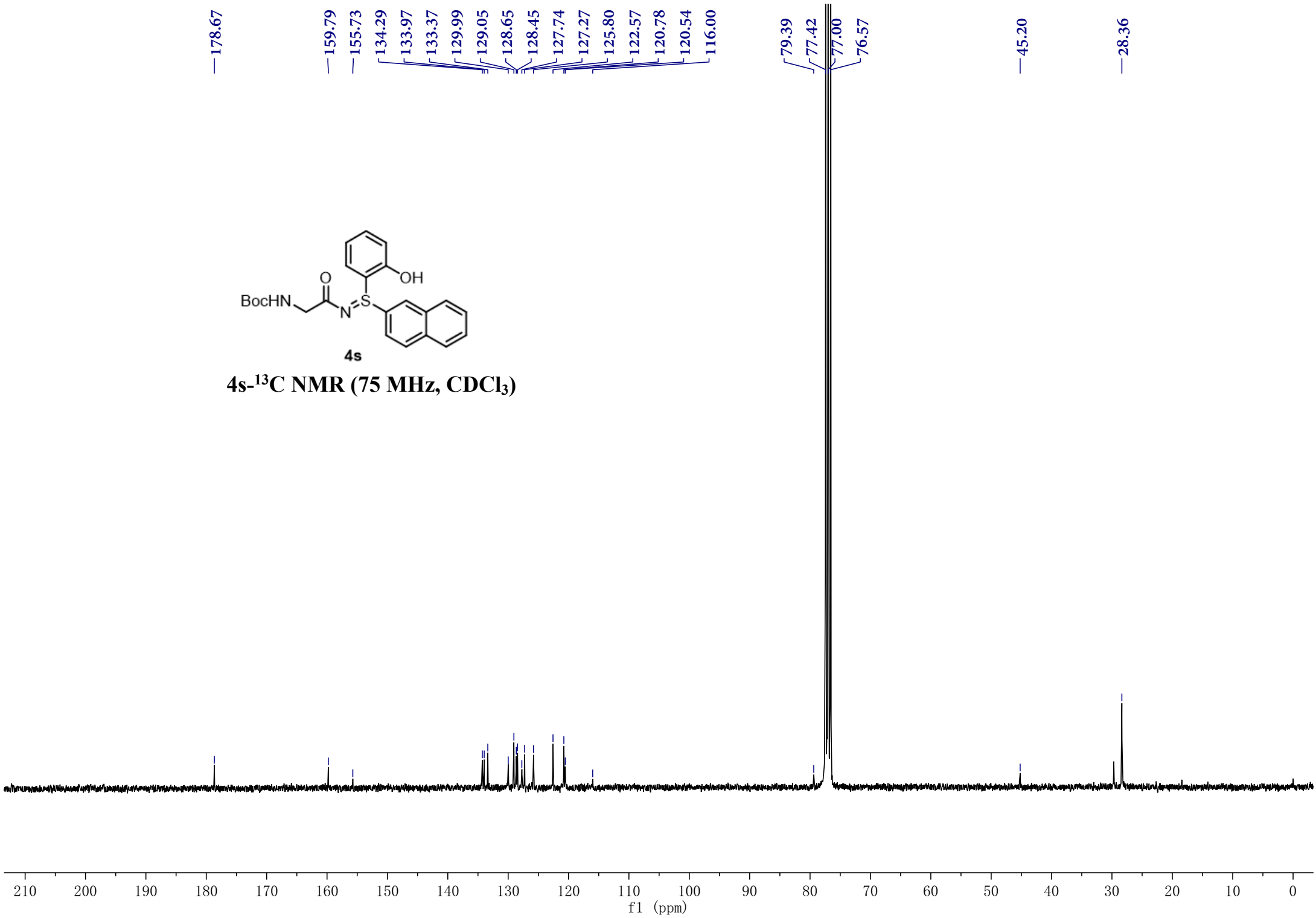


4r-^{1}H NMR (300 MHz, $CDCl_3$)

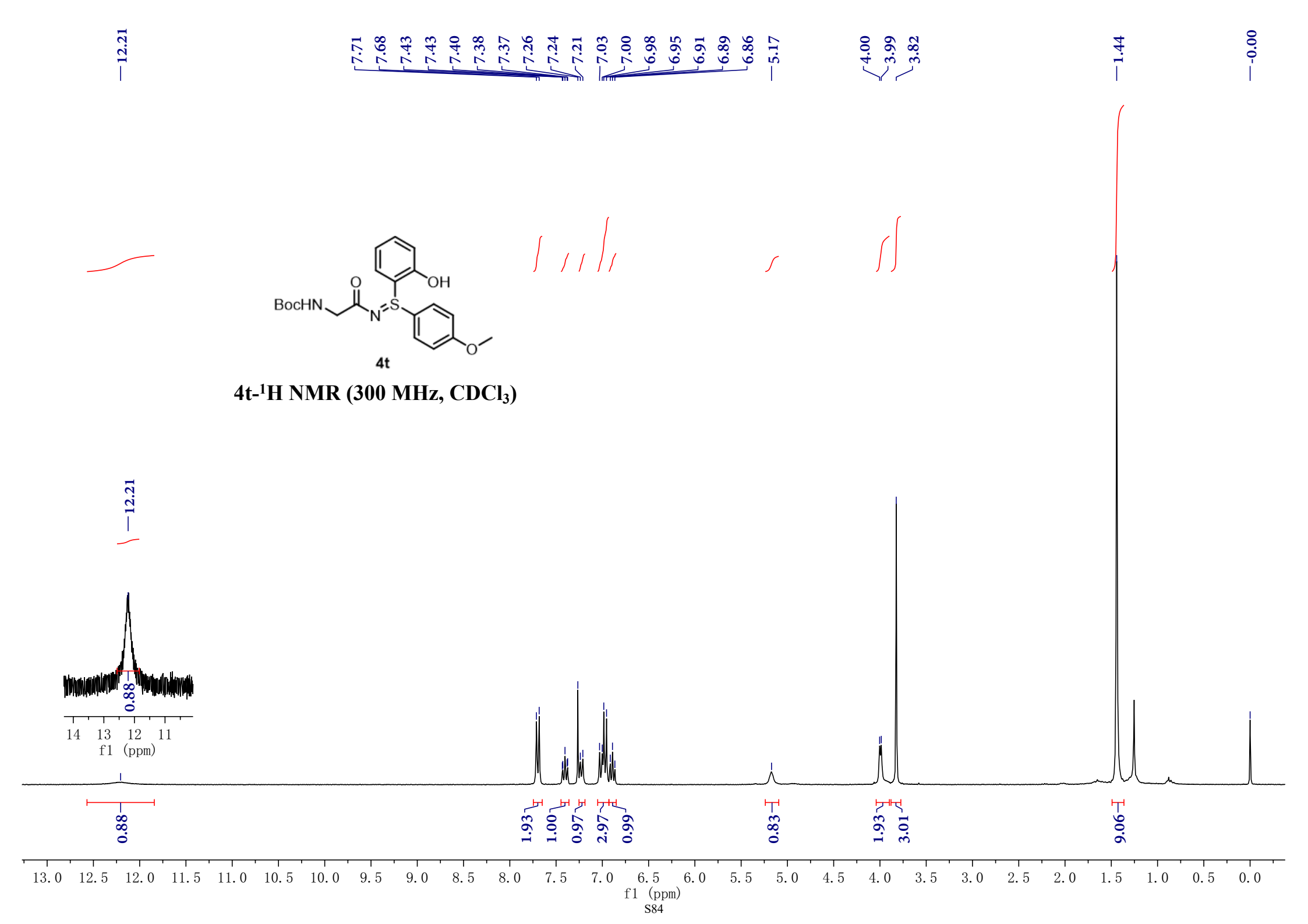


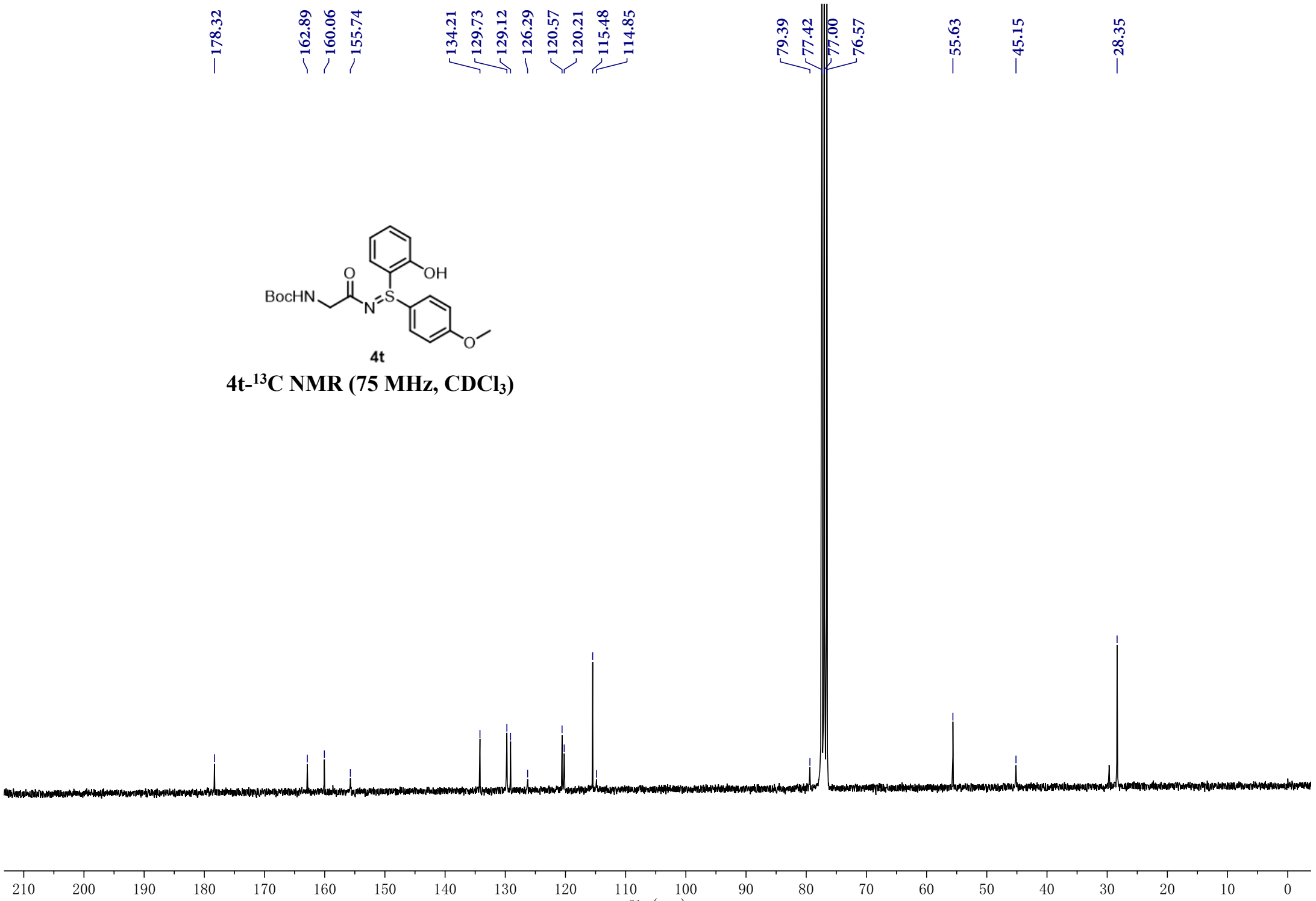
4r-^{13}C NMR (75 MHz, $CDCl_3$)


12.10
8.41
8.38
8.34
8.31
8.08
8.05
7.95
7.92
7.69
7.68
7.67
7.64
7.63
7.62
7.60
7.58
7.57
7.40
7.39
7.37
7.35
7.34
7.26
7.11
7.08
7.05
6.81
6.81
6.78
6.76
6.76
5.19
4.04
4.02
1.44
-0.00
BocHN
O
N
S
OH
4s
4s-1H NMR (300 MHz, CDCl3)
12.10
0.94
13
12
11
f1 (ppm)
0.94
0.89
1.04
0.99
0.98
2.99
1.04
1.94
1.00
0.85
1.84
8.99
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

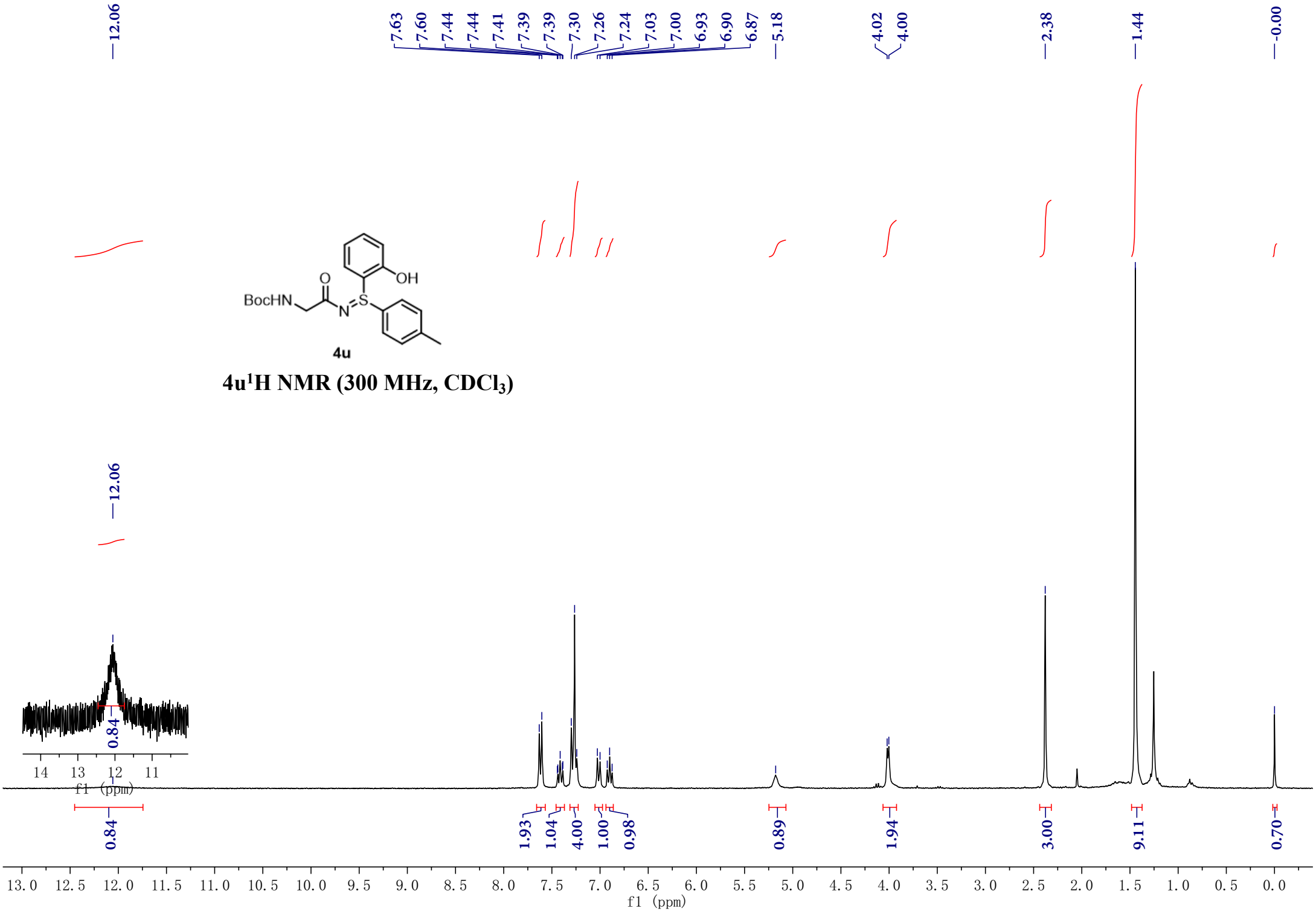


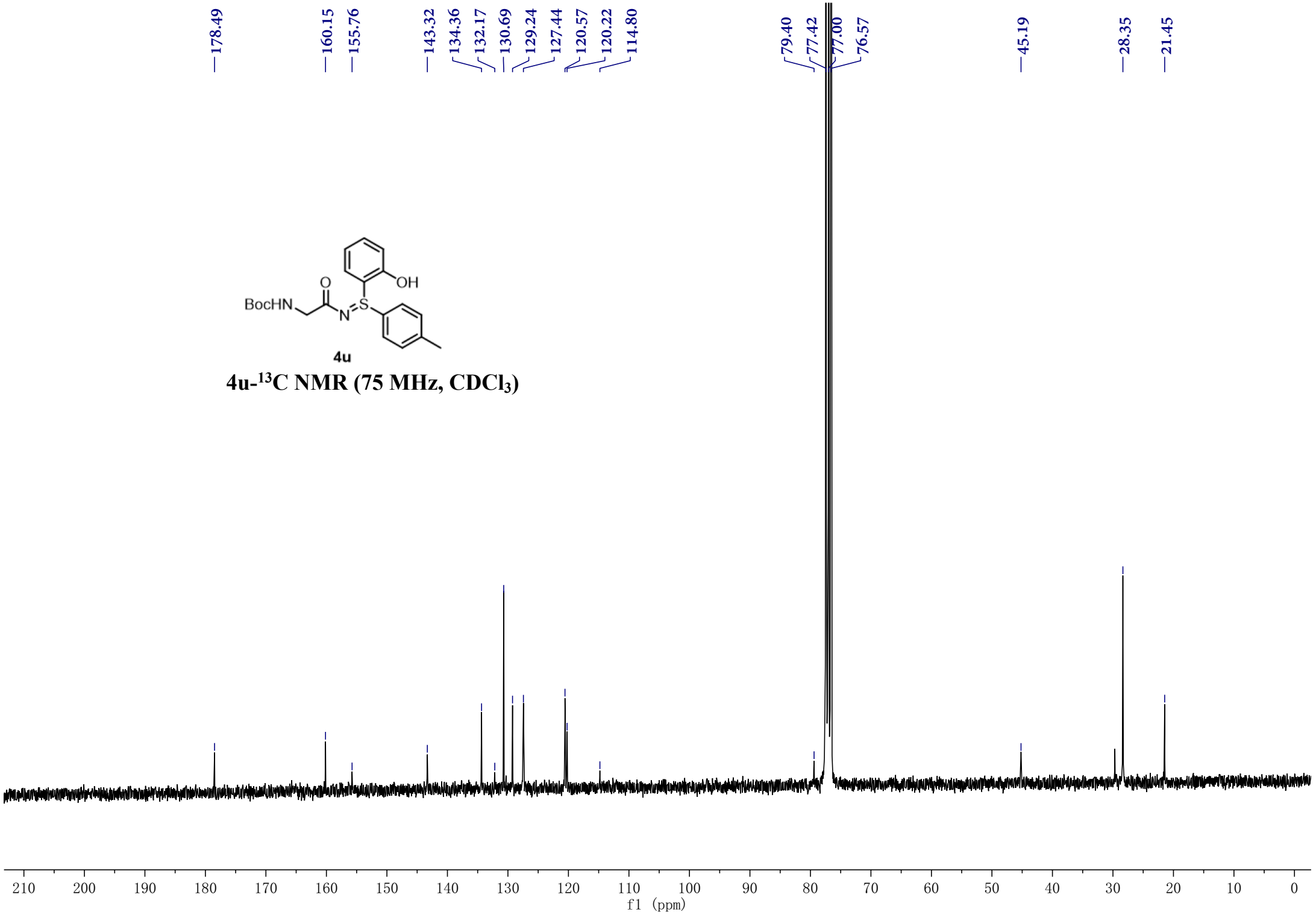
4s-^{13}C NMR (75 MHz, $CDCl_3$)


12.21
7.71
7.68
7.43
7.43
7.40
7.38
7.37
7.26
7.24
7.21
7.03
7.00
6.98
6.95
6.91
6.89
6.86
5.17
4.00
3.99
3.82
1.44
-0.00
BocHN
O
N
S
OH
O
4t
4t-1H NMR (300 MHz, CDCl3)
0.88
1.93
1.00
0.97
2.97
0.99
0.83
1.93
3.01
9.06
f1 (ppm)

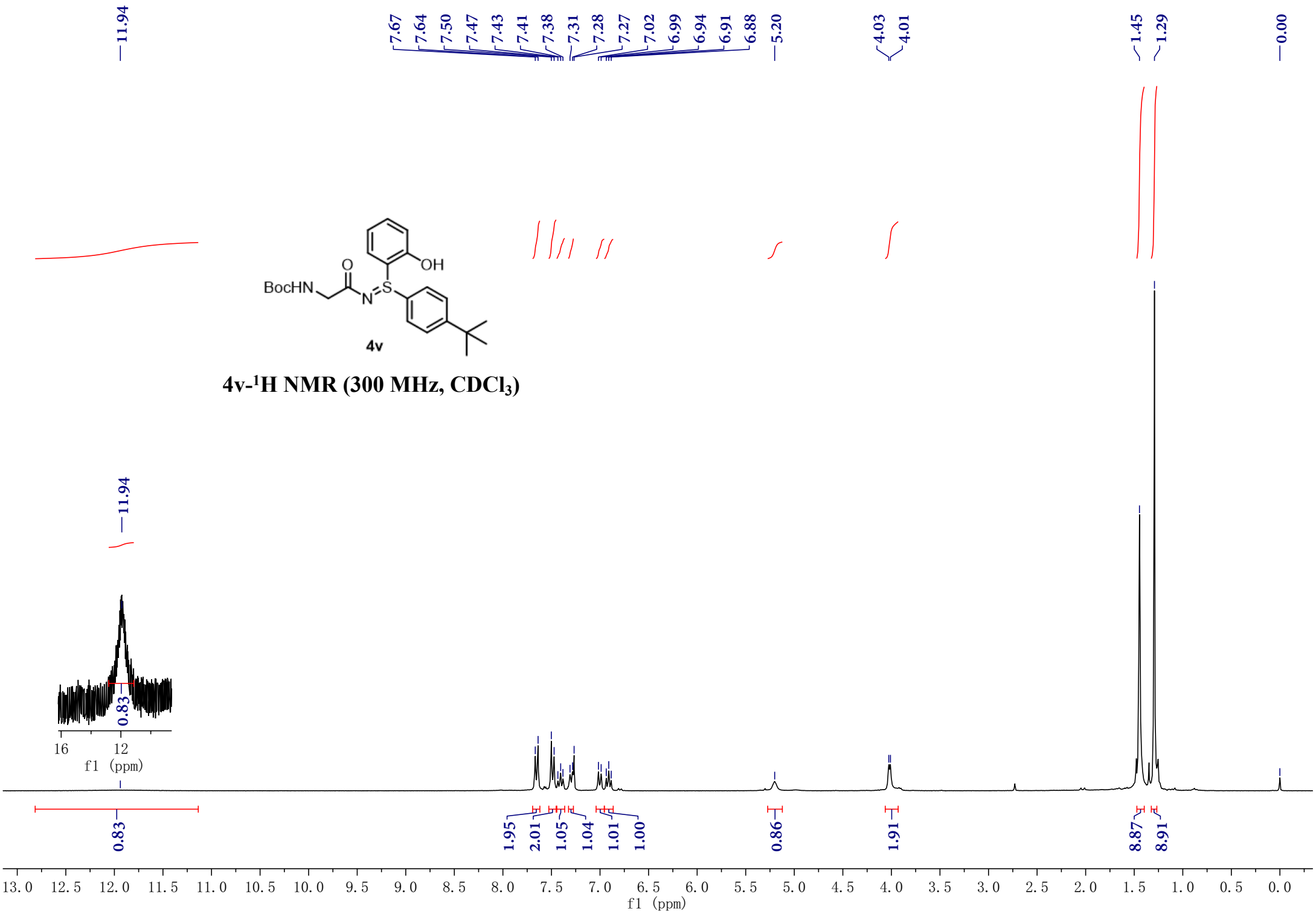


4t-^{13}C NMR (75 MHz, $CDCl_3$)

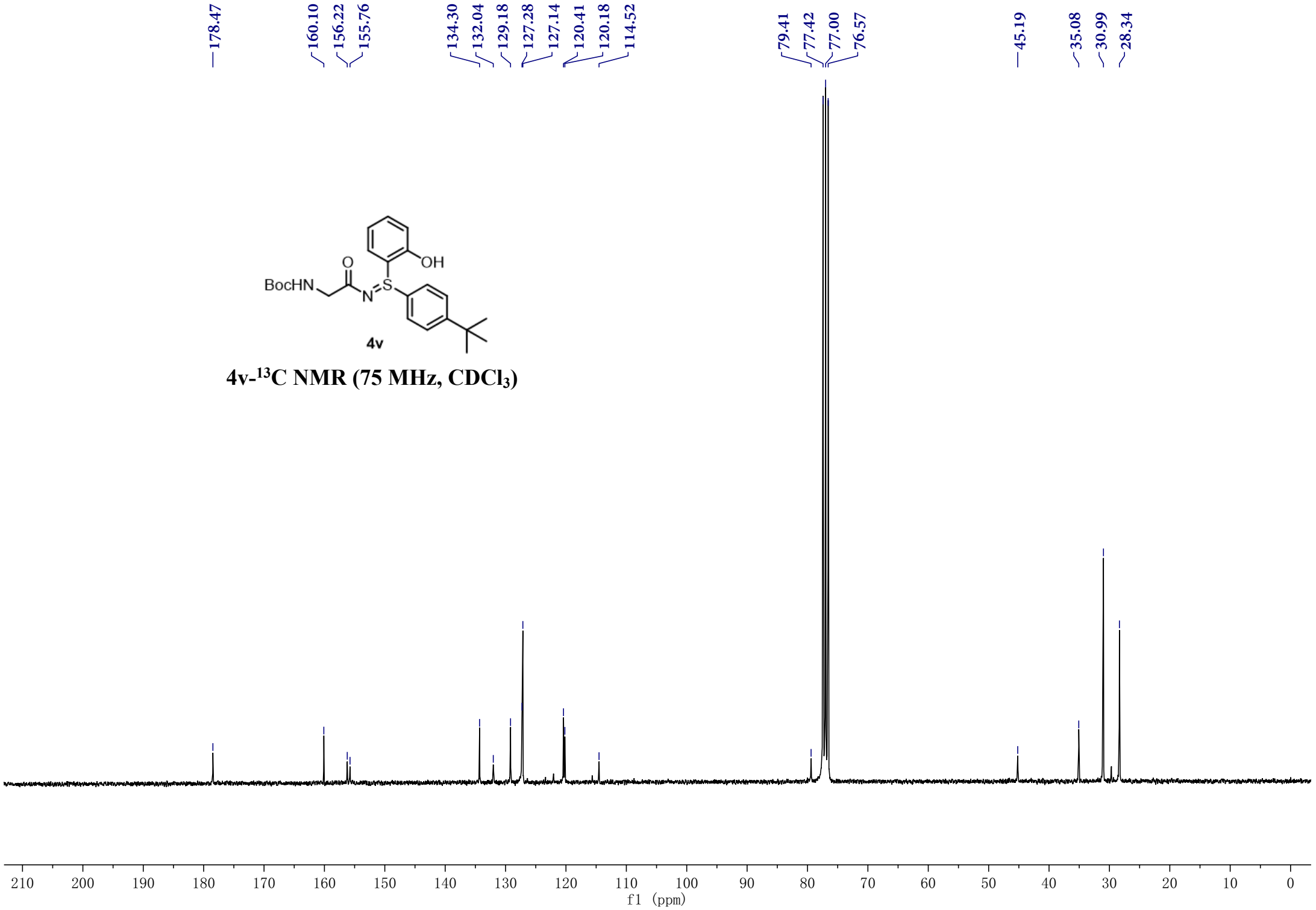

12.06
7.63
7.60
7.44
7.44
7.41
7.39
7.39
7.30
7.26
7.24
7.03
7.00
6.93
6.90
6.87
5.18
4.02
4.00
2.38
1.44
-0.00
BocHN
O
N
S
OH
4u
4u ¹H NMR (300 MHz, CDCl₃)
12.06
0.84
14 13 12 11
f1 (ppm)
0.84
1.93
1.04
4.00
1.00
0.98
0.89
1.94
3.00
9.11
0.70
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



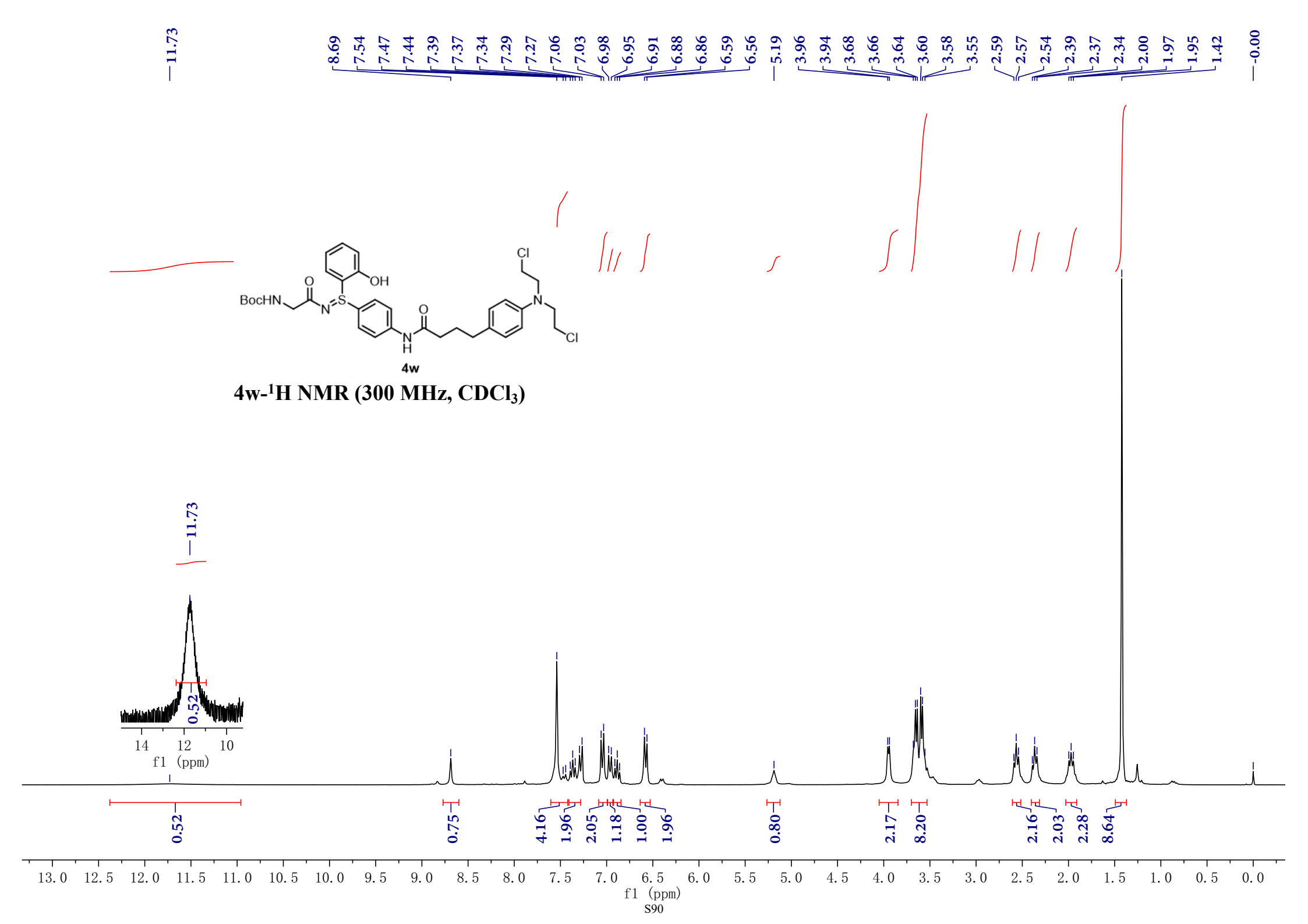
4u-^{13}C NMR (75 MHz, $CDCl_3$)

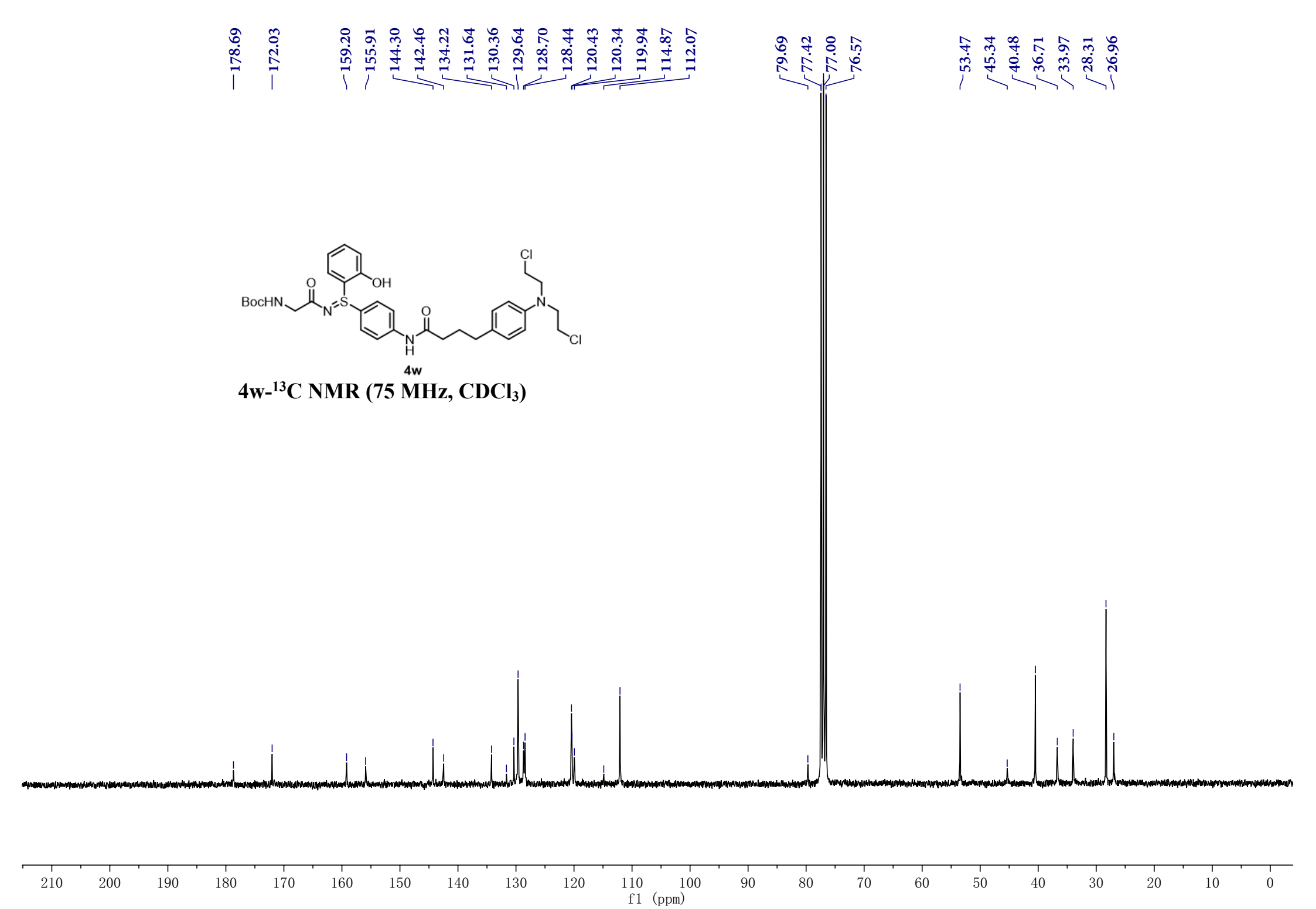


4v-^{1}H NMR (300 MHz, $CDCl_3$)



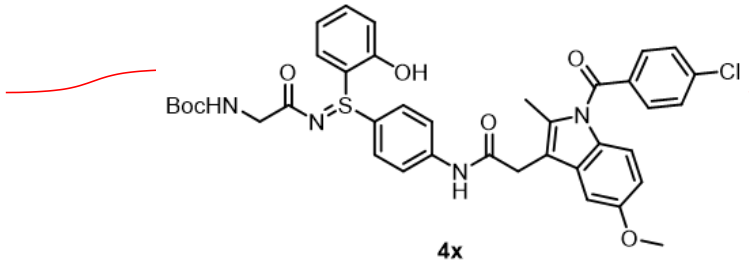
4v-^{13}C NMR (75 MHz, $CDCl_3$)


11.73
8.69
7.54
7.47
7.44
7.39
7.37
7.34
7.29
7.27
7.06
7.03
6.98
6.95
6.91
6.88
6.86
6.59
6.56
5.19
3.96
3.94
3.68
3.66
3.64
3.60
3.58
3.55
2.59
2.57
2.54
2.39
2.37
2.34
2.00
1.97
1.95
1.42
-0.00
BocHN
O
N
S
OH
O
N
H
Cl
N
Cl
4w
4w-1H NMR (300 MHz, CDCl3)
11.73
0.52
14
12
10
f1 (ppm)
0.52
0.75
4.16
1.96
2.05
1.18
1.00
1.96
0.80
2.17
8.20
2.16
2.03
2.28
8.64
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



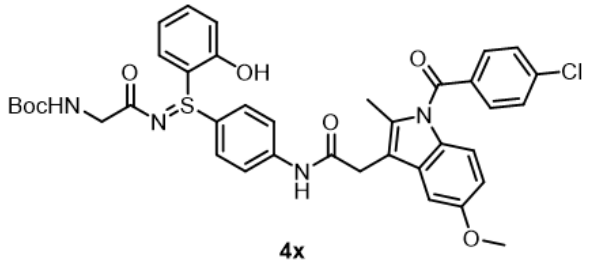
4w

4w-^{13}C NMR (75 MHz, $CDCl_3$)



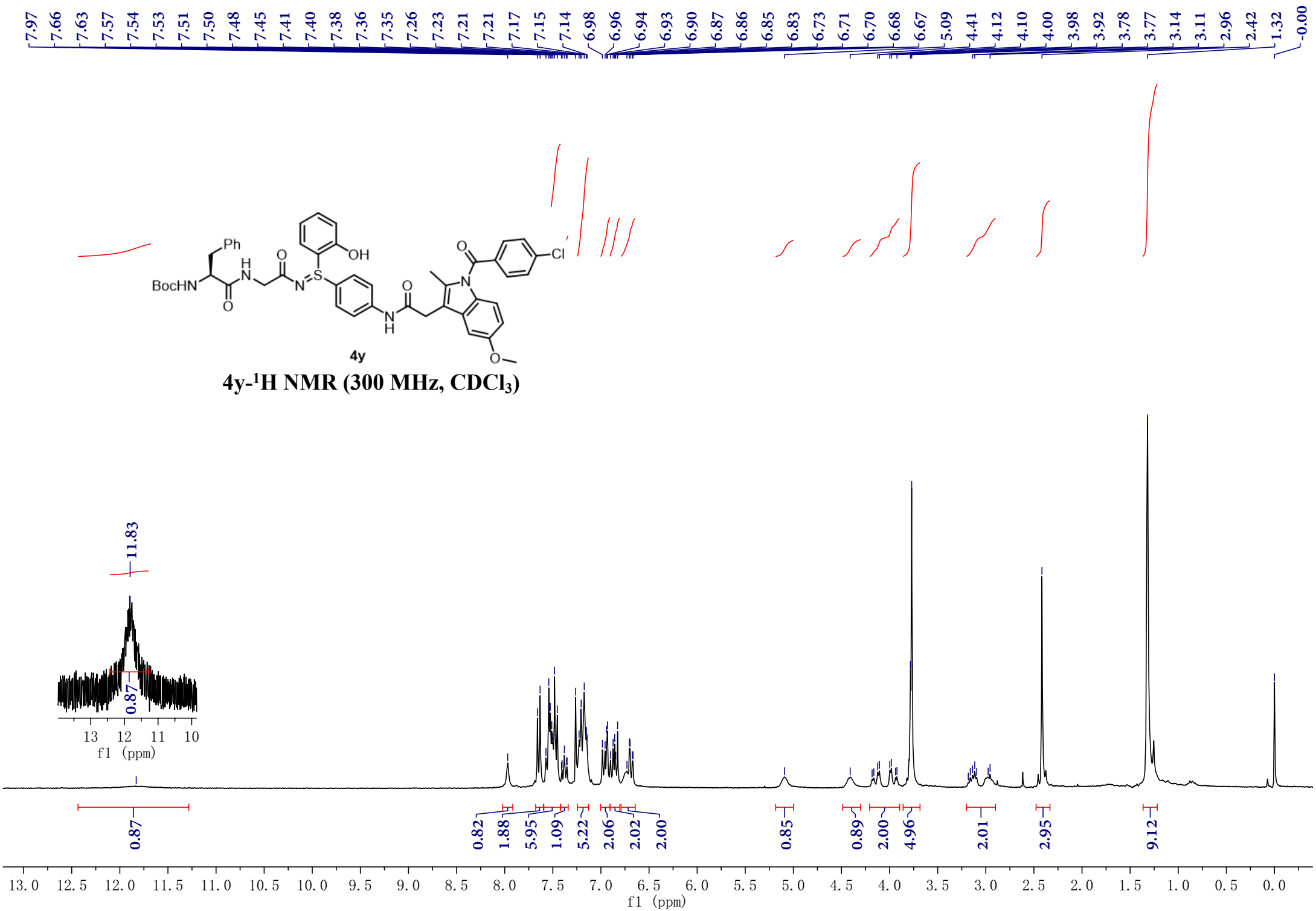
4x

4x-^{1}H NMR (300 MHz, $CDCl_3$)

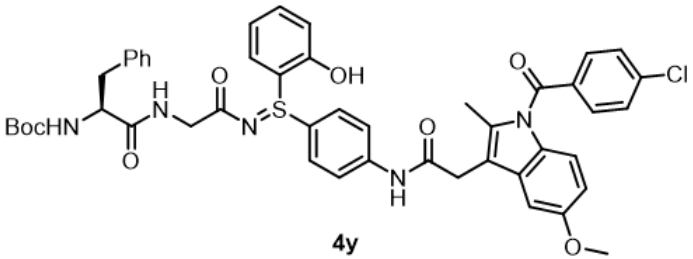


4x

4x-^{13}C NMR (75 MHz, $CDCl_3$)

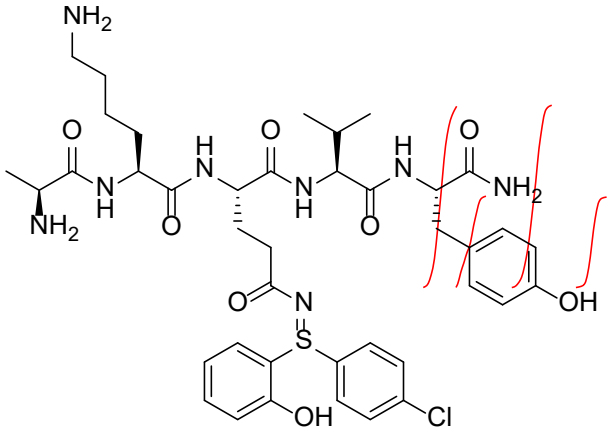


4y-^{1}H NMR (300 MHz, $CDCl_3$)



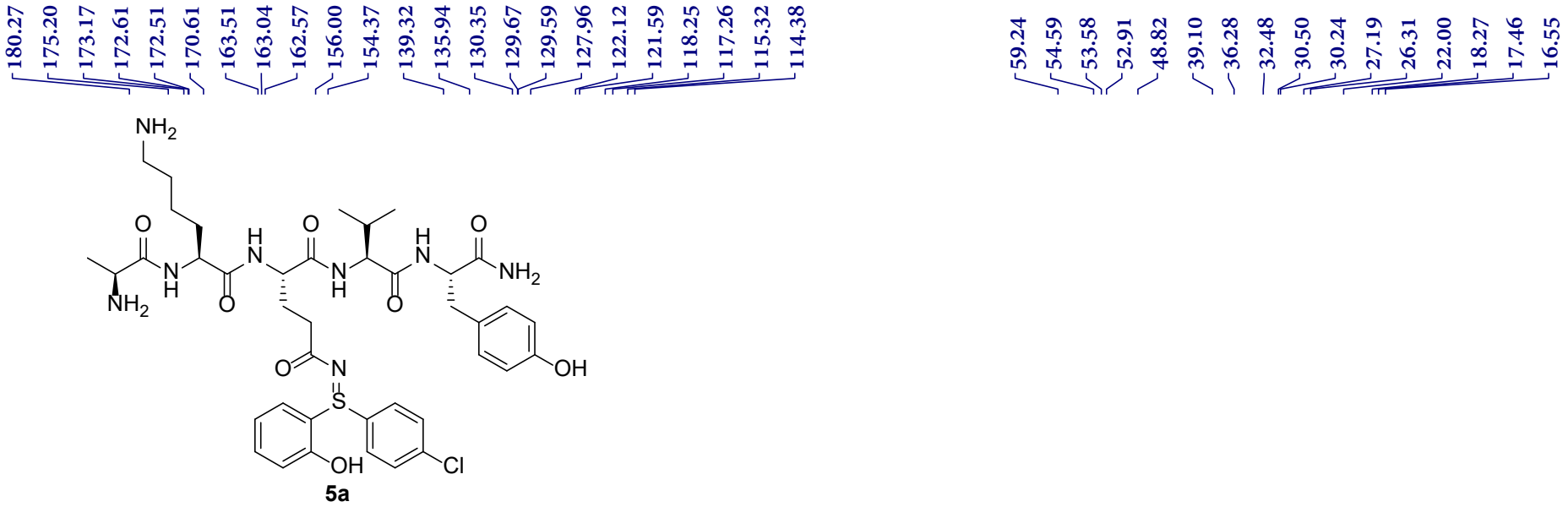
4y

4y-^{13}C NMR (75 MHz, $CDCl_3$)



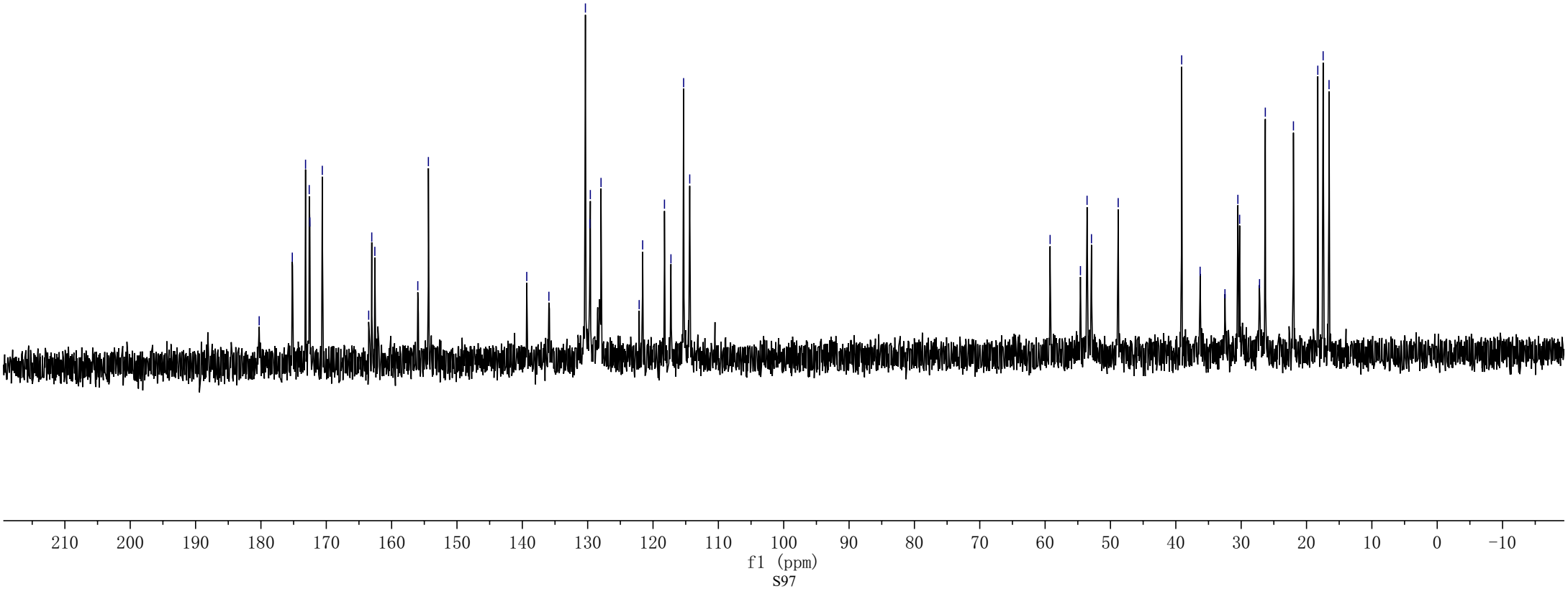
5a

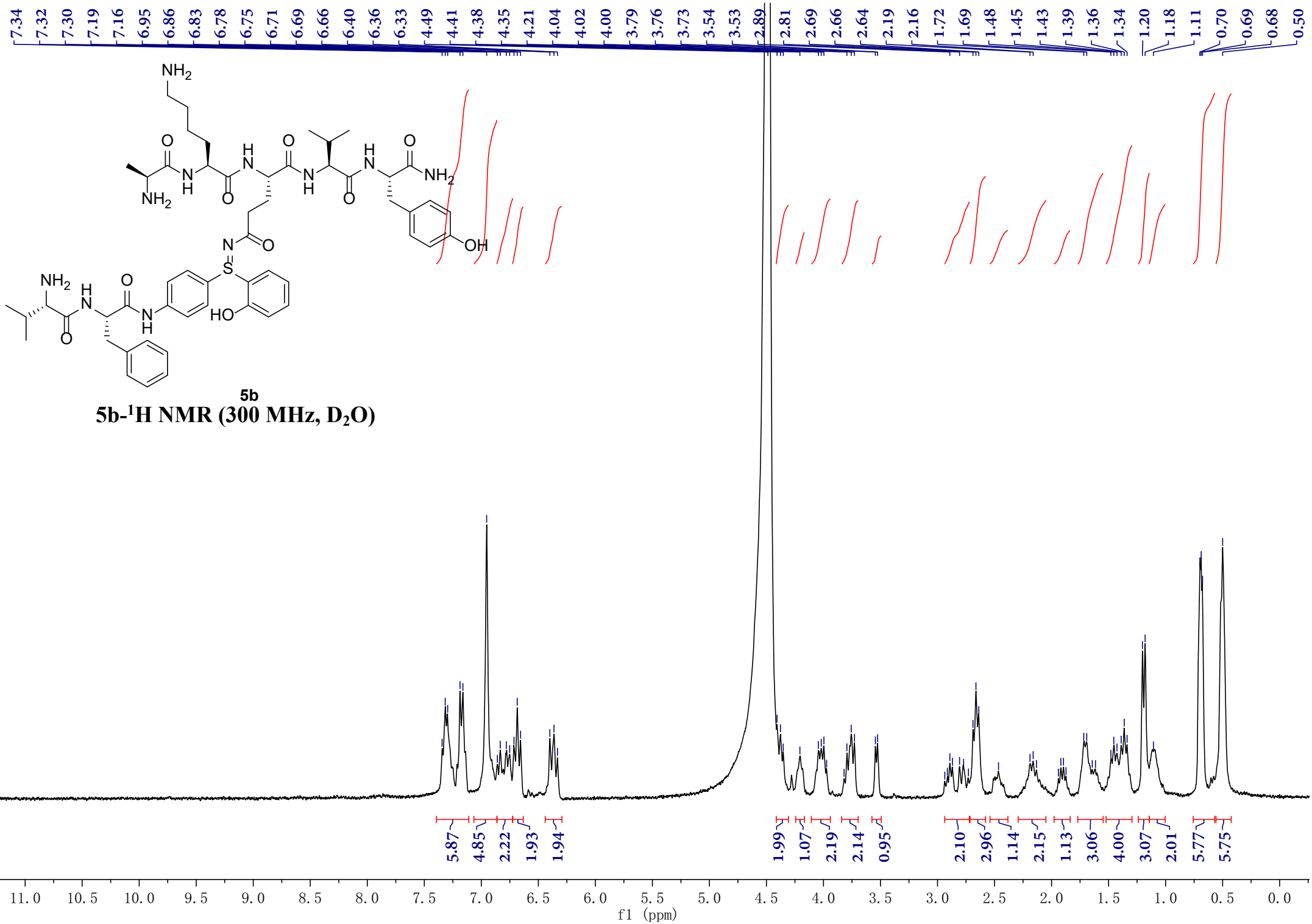
5a (4n)-^{1}H NMR (300 MHz, D_2O)



5a

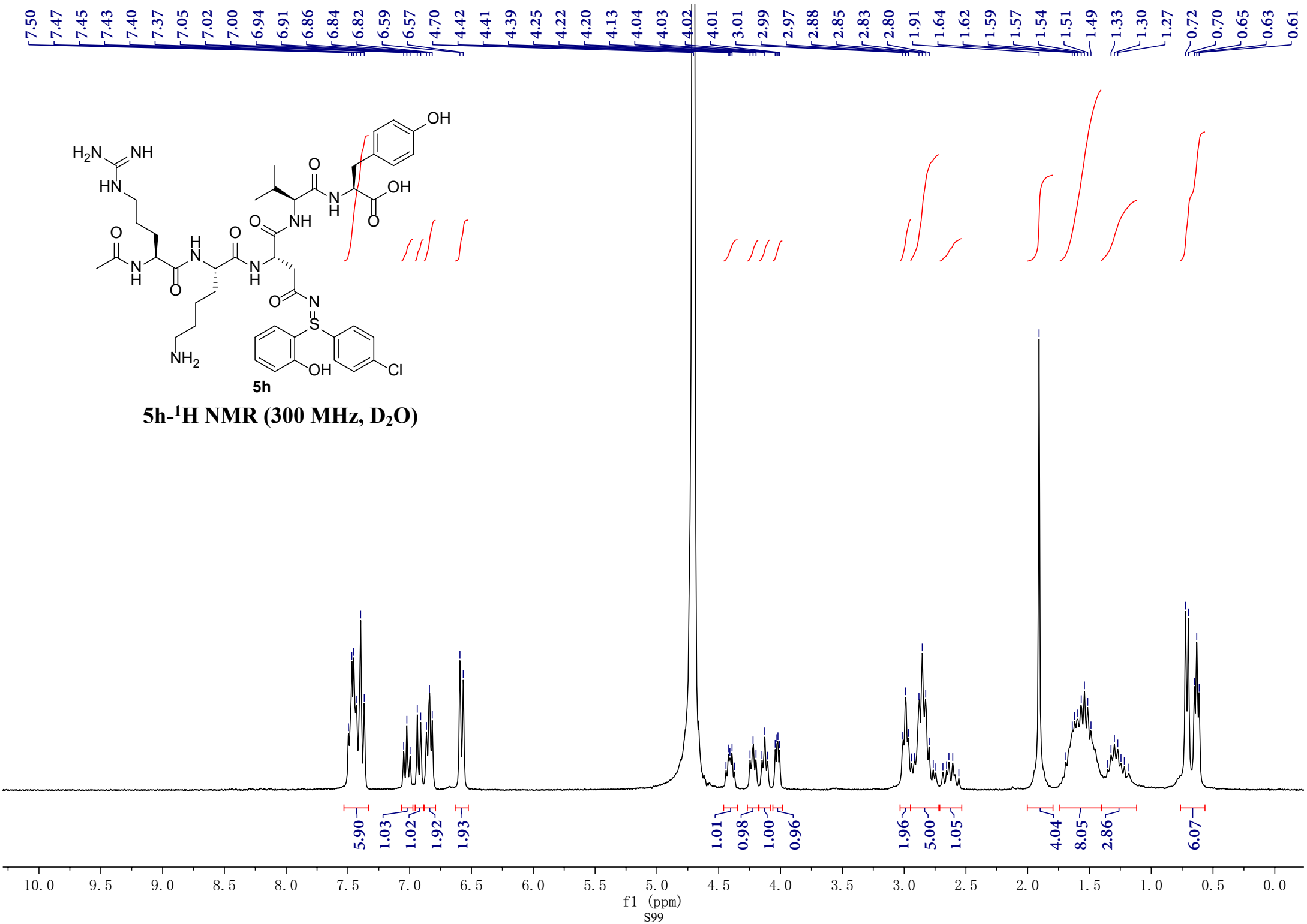
5a (4n)-^{13}C NMR (75 MHz, D_2O)





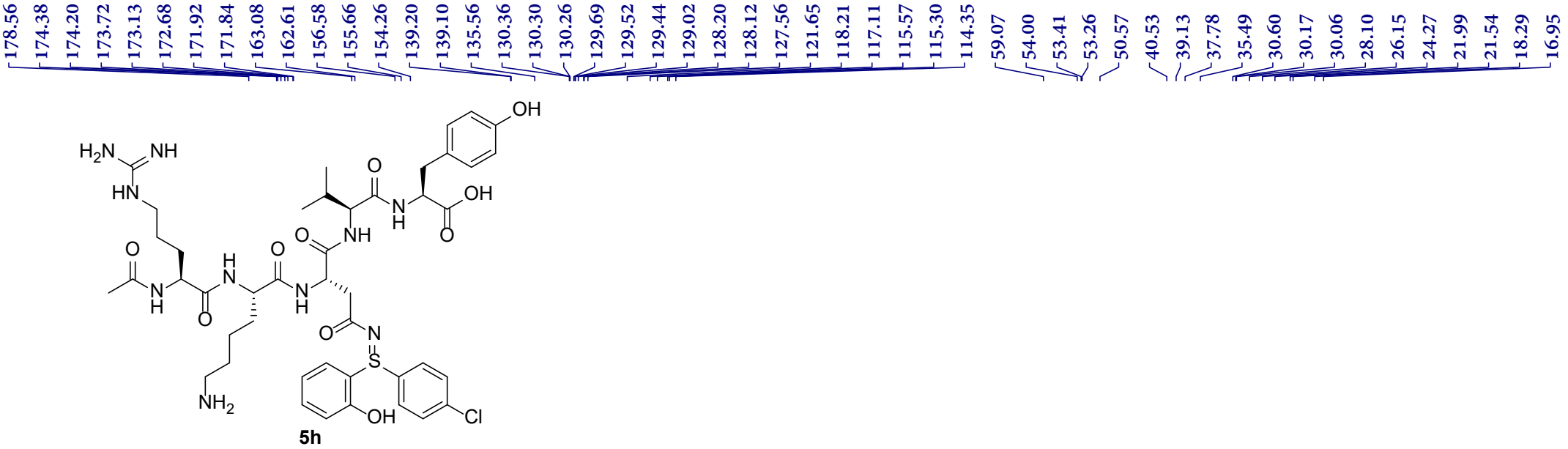
5b

5b-^{1}H NMR (300 MHz, D_2O)

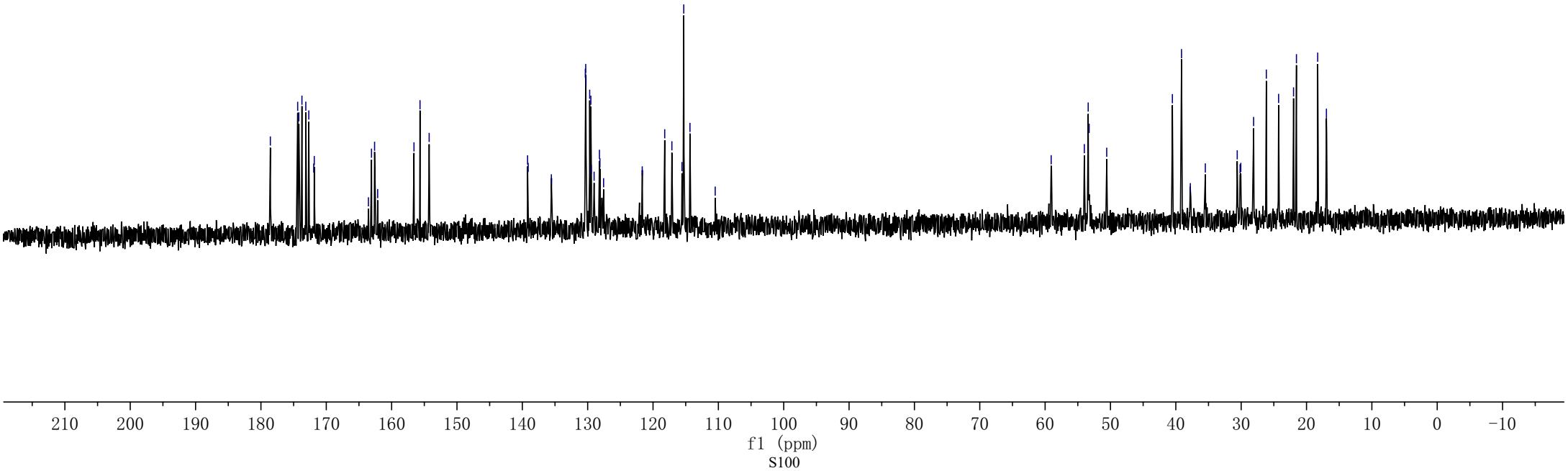


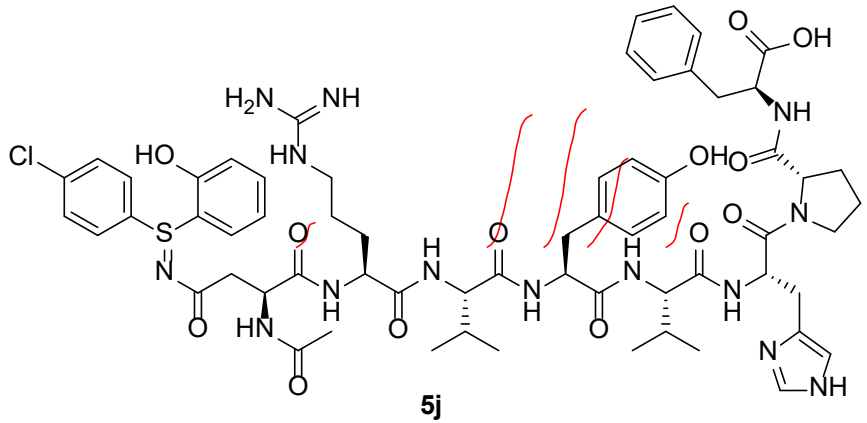
5h

5h-^{1}H NMR (300 MHz, D_2O)



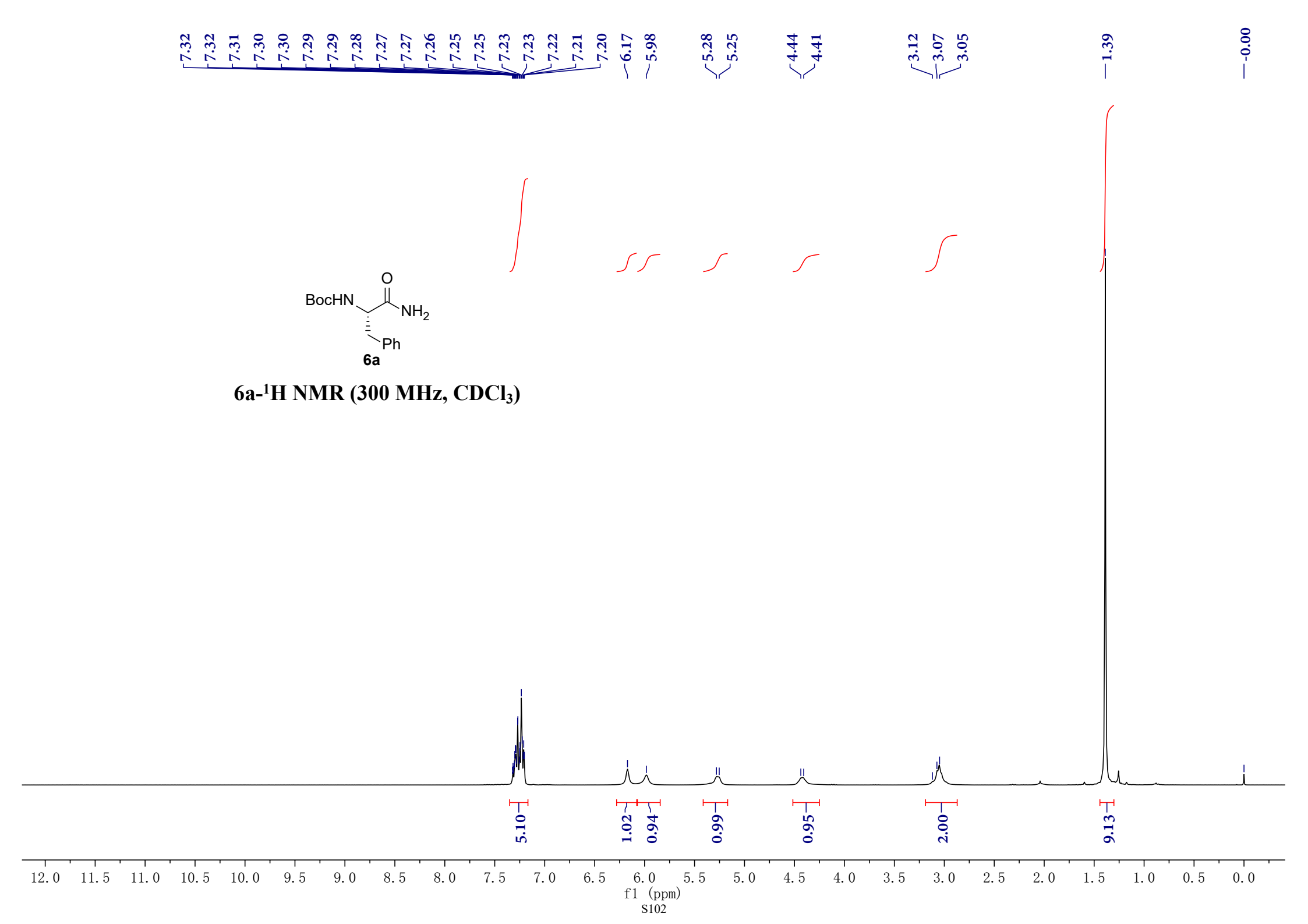
5h-^{13}C NMR (75 MHz, D_2O)



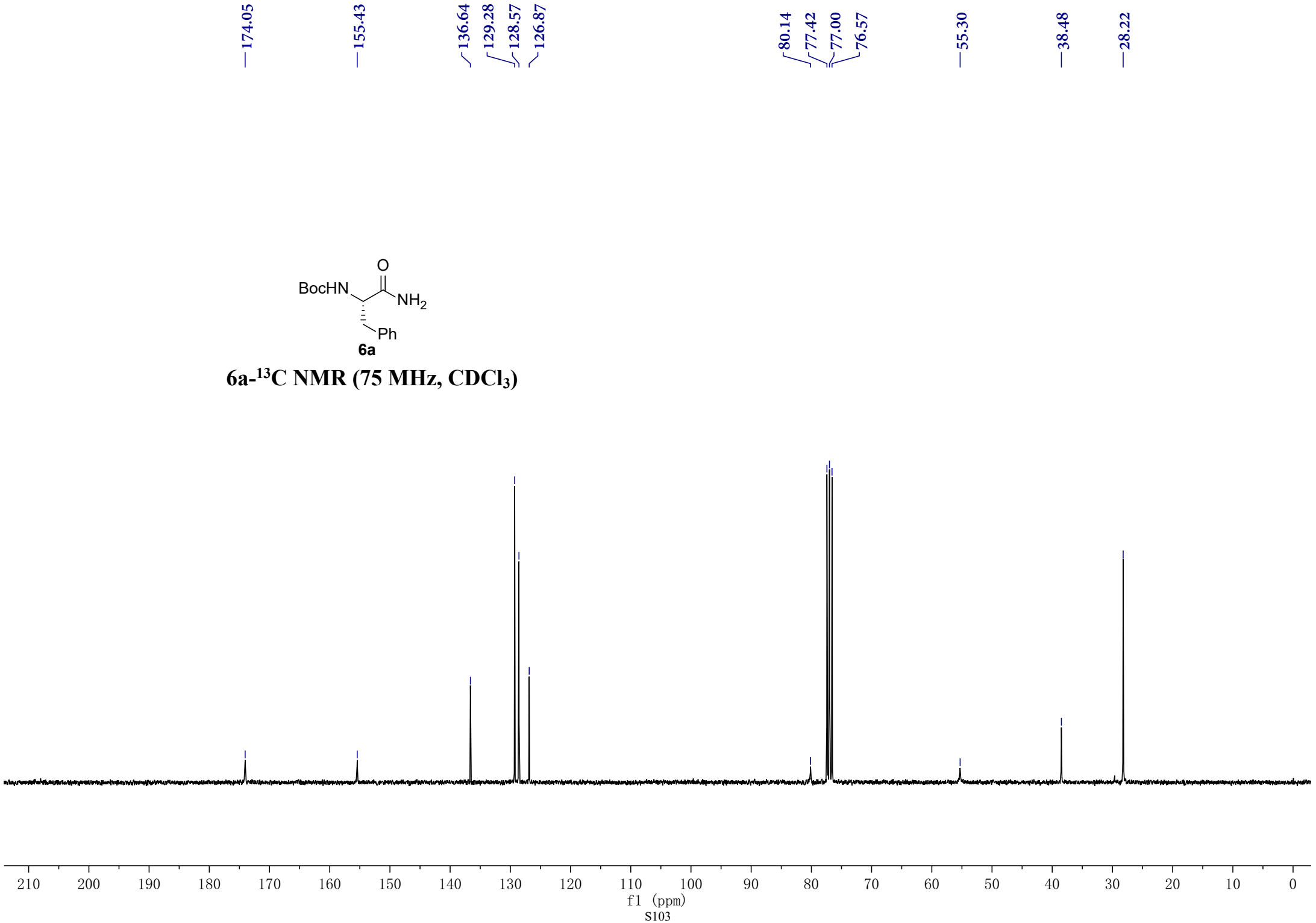


5j

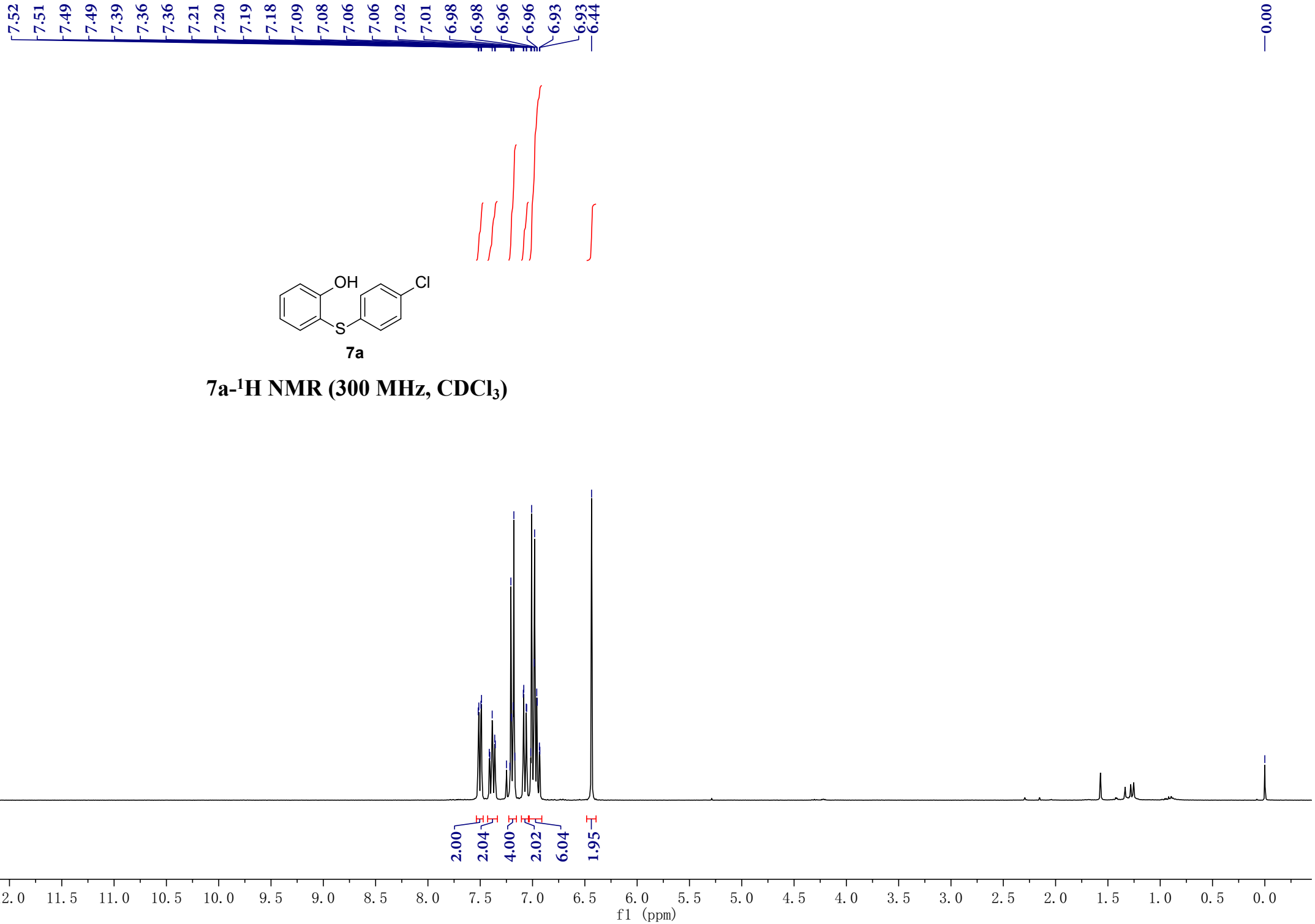
5j-^{1}H NMR (300 MHz, D_2O)



6a-^{1}H NMR (300 MHz, $CDCl_3$)

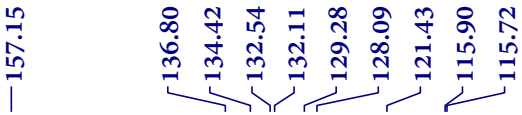


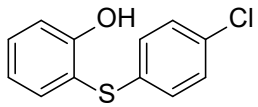
6a-^{13}C NMR (75 MHz, $CDCl_3$)



7a

7a-^{1}H NMR (300 MHz, $CDCl_3$)





7a

7a-^{13}C NMR (75 MHz, $CDCl_3$)