

## SUPPORTING INFORMATION

### Reprogramming RiPP Scaffolds through Skeletal Editing Unlocks Chemical Space

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## General Experimental

Reagents were purchased from commercial sources (Bide, Energy, TCI, and Sigma-Aldrich) and used without further purification unless otherwise stated. Yields refer to chromatographically unless otherwise stated. Reactions were monitored by LC/MS and thin layer chromatography (TLC). TLC was performed using 0.2-0.25 mm silica plates, and using short-wave UV light as the visualizing agent, phosphomolybdic acid with  $\text{Ce}(\text{SO}_4)_2$ , or  $\text{KMnO}_4$  via heat as developing agents. NMR spectra were recorded on Bruker AVII 400 and JEOL 600 instruments and are calibrated using residual undeuterated solvent ( $\text{CHCl}_3$  at 7.26 ppm  $^1\text{H}$  NMR, 77.16 ppm  $^{13}\text{C}$  NMR). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was performed using 230-400 mesh silica gel, and PTLC was performed using 0.2-0.25 mm silica plates. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments.

## Abbreviations

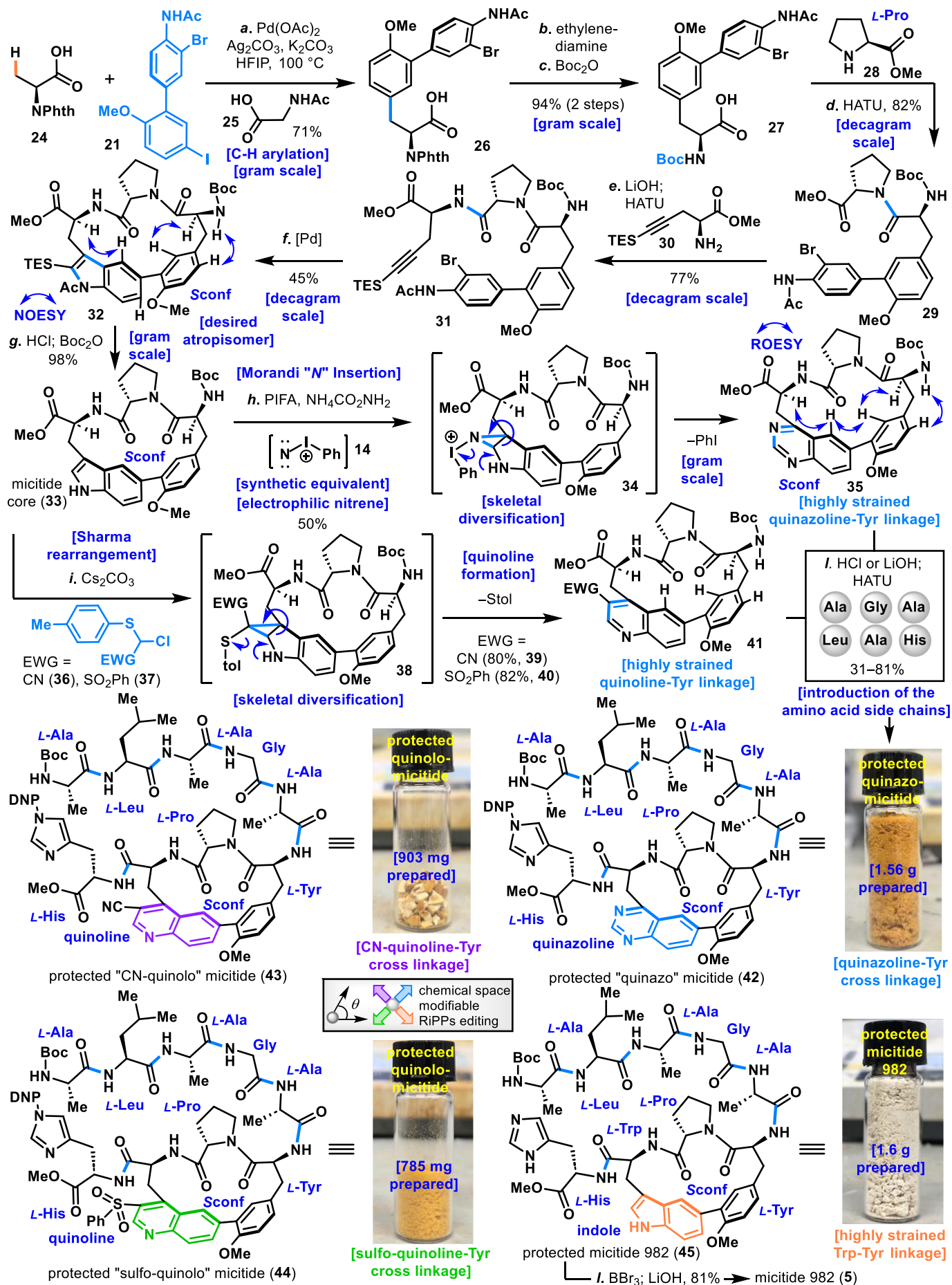
Ac	acetyl
aq.	aqueous
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
cat.	catalyst
DFT	density functional theory
DIPEA	<i>N</i> -diisopropylethylamine
DMSO	dimethyl sulfoxide
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
Ph	phenyl
$\text{PPh}_3$	triphenylphosphine
rt	25 °C
TFA	trifluoroacetic acid
THF	tetrahydrofuran
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
Phth	Phthalimide
Phg	Phenylglycine
DNP	Dinitrophenyl
AQ	Aminoquinoline

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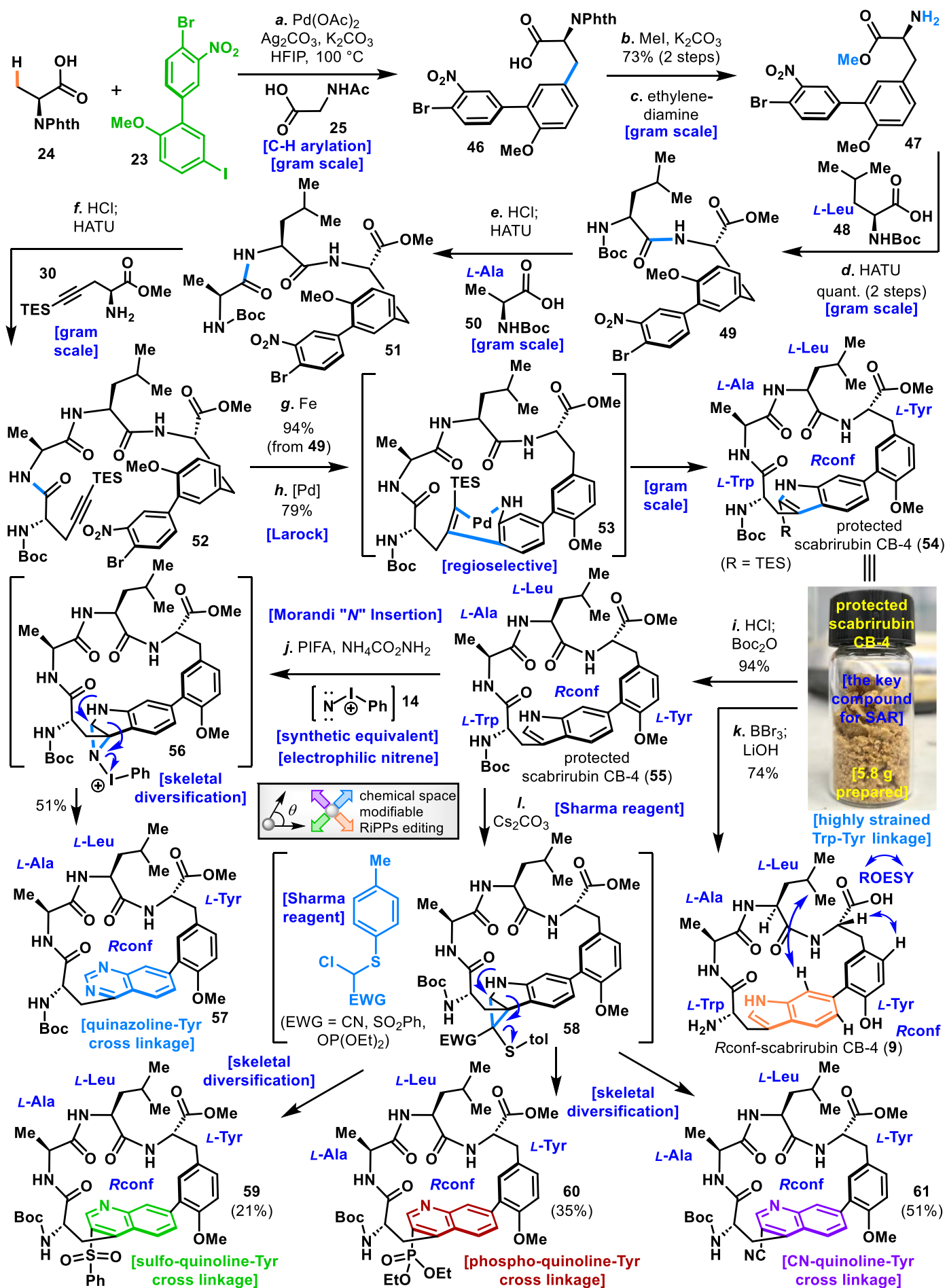
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# Synthetic route

Scheme S1. Total synthesis of micitide 982 (1) and its skeletal diversification.

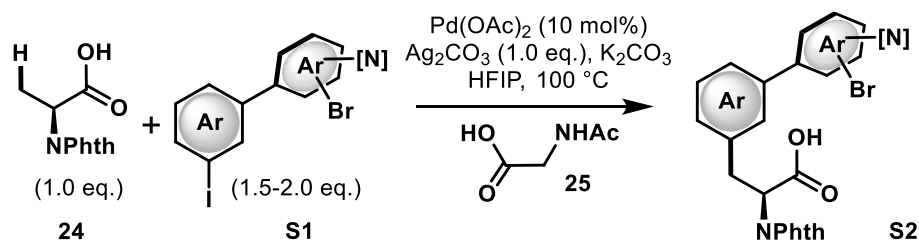


**Scheme S2.** Total synthesis of *R*<sub>conf</sub>-scabrirubin CB-4 (**9**) and its skeletal diversification.



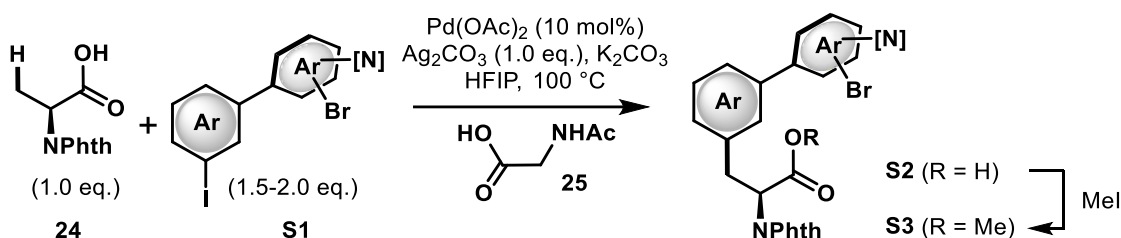
## C-H Arylation (General Procedure A)

Biaryl iodide **21** was prepared according to the procedure previously reported by our group.<sup>2</sup>



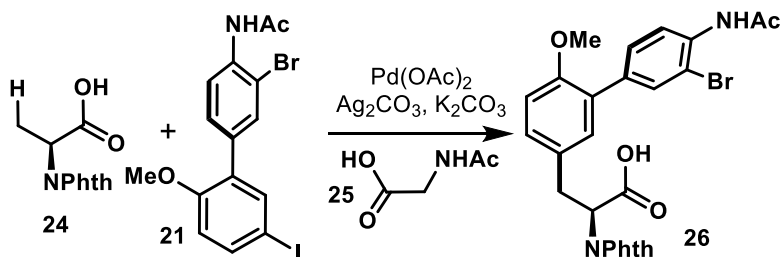
A mixture of Pht-Ala-OH **24** (1.0 eq.), aryl iodide **S1** (1.5 eq.), Pd(OAc)<sub>2</sub> (0.1 eq.), Ag<sub>2</sub>CO<sub>3</sub> (1.0 eq.), Ac-Gly-OH (0.3 eq.) and K<sub>2</sub>CO<sub>3</sub> (0.5 eq.), HFIP (0.1 M) in a sealed tube was heated at 100 °C with vigorous stirring for 12 hours. The reaction mixture was cooled to 25 °C, quenched with 1N HCl aq., and diluted with EtOAc. The mixture was filtered through Celite, and the aqueous phase was extracted with EtOAc three times. The organic phase was combined and dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was purified by preparative thin-layer chromatography or silica gel column chromatography.

## C-H Arylation and One-Pot Methyl Esterification (General Procedure B)



A mixture of Pht-Ala-OH **24** (1.0 eq.), aryl iodide **S1** (1.5 eq.), Pd(OAc)<sub>2</sub> (224.5 mg, 1.0 mmol, 0.1 eq.), Ag<sub>2</sub>CO<sub>3</sub> (1.38 g, 5.0 mmol, 1.0 eq.), Ac-Gly-OH (234 mg, 2.0 mmol, 0.4 eq.) and K<sub>2</sub>CO<sub>3</sub> (345 mg, 2.5 mmol, 0.5 eq.), HFIP (50 mL) in a sealed tube was heated at 100 °C with vigorous stirring for 12 hours. The reaction mixture was cooled to 25 °C and directly evaporated under vacuum. To the residue, K<sub>2</sub>CO<sub>3</sub> (5 eq.), acetone (0.1 M), MeI (30 eq.) were added sequentially, and the reaction was stirred at 25 °C for 2 h. The reaction was quenched with water, extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under vacuum. The residue was purified by preparative thin-layer chromatography or silica gel column chromatography.

## Synthesis of micitide 982 core



On 5.0 mmol scale, **General Procedure A** was followed with aryl iodide **21**. Purification by silica gel column chromatography (EtOAc:Hexane 1:2 to 4:1) gave the title compound **26**. (1.89 g, 71% yield)

## Compound 26

**Physical State:** off-white solid

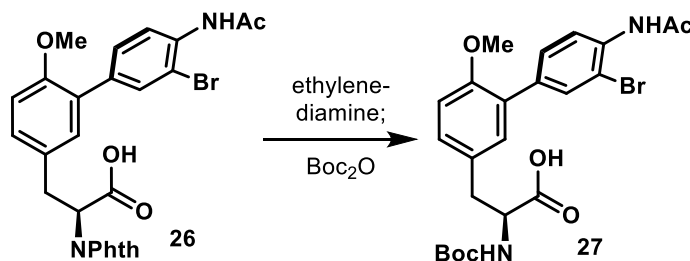
**<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):** δ 9.46 (s, 1H), 7.81 (s, 4H), 7.39 (m, 2H), 6.94 (m, 4H), 5.06 (s, 1H), 3.62 (s, 3H), 3.28 (m, 3H), 2.05 (s, 3H).

**<sup>13</sup>C NMR (151 MHz, DMSO-*d*<sub>6</sub>):** δ 170.64, 169.15, 167.80, 155.14, 137.01, 135.52, 133.09, 131.34, 131.12, 130.24, 130.18, 129.07, 127.82, 127.00, 123.91, 117.85, 112.18, 79.70, 55.99, 53.87, 33.60, 23.76.

**HRMS (ESI-TOF):** calculated for C<sub>26</sub>H<sub>21</sub>BrN<sub>2</sub>NaO<sub>6</sub><sup>+</sup> [M+Na]<sup>+</sup>: 559.0475, found: 559.0484.

**TLC:** R<sub>f</sub> = 0.2 (10:1 DCM:Methanol, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>25</sup><sub>D</sub>:** -68.6 (*c* = 0.1, CHCl<sub>3</sub>)



Compound **26** (1.89 g, 3.5 mmol, 1.0 eq.) was dissolved in *n*-BuOH (35 mL), and ethylenediamine (2.35 mL, 35.2 mmol, 10.0 eq.) was added. The reaction was stirred at 25 °C for 15 h. The reaction mixture was directly concentrated under reduced pressure to give the crude. The crude was dissolved in THF (35 mL), H<sub>2</sub>O (3.5 mL). NaHCO<sub>3</sub> (2.06 g, 24.5 mmol, 7.0 eq.) and (Boc)<sub>2</sub>O (4.0 mL, 17.5 mmol, 5.0 eq.) were added sequentially. The reaction mixture was stirred at 25 °C for 3 h and quenched by saturated *aq.* NH<sub>4</sub>Cl, extracted with DCM/MeOH = 10:1 for three times. The organic layers were combined and washed with saturated *aq.* NaCl, over Na<sub>2</sub>SO<sub>4</sub>. Organic layers were concentrated under reduced pressure and purified by silica gel chromatography to give compound **27** (1.54 g, 94% yield over two steps).

*Note:* A total of 21 g compound **27** was obtained.

## Compound 27

**Physical State:** colorless oil

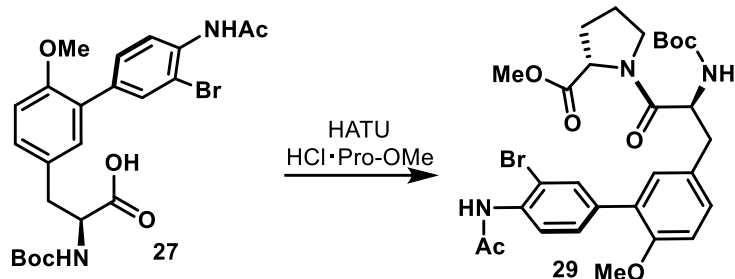
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, a mixture of two rotamers, A:B = 3:1, Signals of the major rotamer are reported.):** δ 8.23 (d, *J* = 8.2 Hz, 1H): 7.66 (m, 2H), 7.42 (m, 1H), 7.08 (m, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 5.13 (d, *J* = 7.1 Hz, 1H), 4.47 (m, 1H), 3.74 (s, 3H), 3.06 (m, 2H), 2.21 (s, 3H), 1.34 (s, 9H).

**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>, a mixture of two rotamers, A:B = 3:1, Signals of the major rotamer are reported.):** 175.42, 168.97, 155.50, 135.88, 134.23, 133.00, 132.41, 131.77, 130.07, 129.61, 128.57, 128.39, 121.79, 113.26, 111.48, 55.69, 54.57, 37.08, 28.40, 24.78.

**HRMS (ESI-TOF):** calculated for C<sub>23</sub>H<sub>27</sub>BrN<sub>2</sub>NaO<sub>6</sub><sup>+</sup> [M+Na]<sup>+</sup>: 529.0945, found: 529.0953.

**TLC:** R<sub>f</sub> = 0.5 (only EtOAc, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>25</sup><sub>D</sub>:** +38.8 (*c* = 1.0, CHCl<sub>3</sub>)



To the mixture of compound **27** (11.6 g, 23.1 mmol, 1.0 eq.), methyl L-prolinate (5.75 g, 34.7 mmol, 1.5 eq.), DIPEA (20.4 mL, 116 mmol, 5.0 eq.), was added HATU (13.2 g, 34.7 mmol, 1.5 eq.). The reaction mixture was stirred at for 3 h and quenched with *aq.* 0.5 M HCl, extracted with EtOAc three times. The organic layers were combined and washed with saturated *aq.* NaCl. The organic layers were concentrated under reduced pressure to give and purified by silica gel chromatography to give compound **29** (11.7 g, 82%).

### Compound 29

**Physical State:** white solid

**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 60 °C a mixture of two rotamers, A:B = 4:1):** δ 9.26 (s, 1H), 7.59 (m, 5H), 7.19 (s, 1H), 7.02 (d, *J* = 9.0 Hz, 1H), 6.70 (m, 1H), 4.39 (m, 2H), 3.76 (s, 3H), 3.62 (s, 3H), 3.54 (m, 1H), 2.93 (m, 1H), 2.78 (dd, *J* = 13.3, 9.1 Hz, 1H), 2.17 (m, 1H), 2.11 (s, 3H), 1.93 (m, 2H), 1.83 (m, 1H), 1.29 (s, 9H).

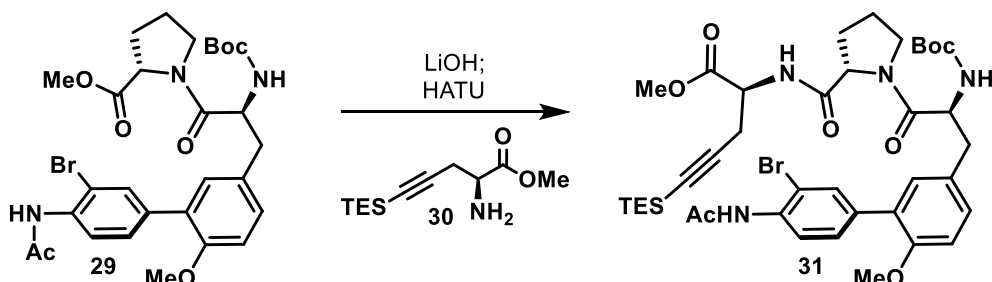
**<sup>3</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>, 60 °C, a mixture of two rotamers, A:B = 4:1):** δ 172.00, 169.99, 168.40, 154.74, 136.66, 134.99, 133.25, 132.65, 132.54, 132.23, 131.74, 131.72, 131.35, 131.25, 129.99, 129.82, 128.64, 128.52, 128.41, 127.27, 125.94, 116.97, 111.70, 78.95, 78.00, 58.47, 58.34, 55.58, 53.29, 51.92, 51.45, 46.28, 45.89, 35.74, 30.59, 28.35, 27.92, 24.46, 23.04, 21.46.

**HRMS (ESI-TOF):** calculated for C<sub>29</sub>H<sub>36</sub>BrN<sub>3</sub>NaO<sub>7</sub><sup>+</sup> [M+Na]<sup>+</sup>: 640.1629, found: 640.1633.

**TLC:** R<sub>f</sub> = 0.7 (only EtOAc, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>25</sup><sub>D</sub>:** -18.5 (*c* = 1.0, CHCl<sub>3</sub>)

*Note:* Due to rotamerism at room temperature, NMR spectra for structural assignment were recorded at 60 °C in DMSO-*d*<sub>6</sub>. However, even at this elevated temperature, the rotamers remained partially unresolved. Signals of the major rotamers were reported.



Compound **29** (20.0 g, 32.4 mmol, 1.0 eq.) was dissolved in THF/MeOH/H<sub>2</sub>O = 1:1:1 (600 mL), then LiOH·H<sub>2</sub>O (8.16 g, 194 mmol, 6.0 eq.) was added, the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was acidified with *aq.* 0.5M HCl gradually and extracted with DCM/MeOH = 10:1 three times. The organic layers were combined and washed with saturated *aq.* NaCl. The organic layers were concentrated under reduced pressure to give the crude. The crude was dissolved in DMF (320 mL), compound **30** (15.1 g, 42.5 mmol, 1.3 eq.), DIPEA (28.9 mL, 162 mmol, 5.0 eq.), and HATU (18.5 g, 48.6 mmol, 1.5 eq.) were added sequentially. The reaction mixture was stirred at 25 °C for 1.5 h, quenched by saturated *aq.*

0.5 M HCl, extracted with Hexane:EtOAc = 1:1 three times, the organic layers were combined and washed with saturated *aq.* NaCl. The organic layers were concentrated under reduced pressure and purified by silica gel chromatography to give compound **31** (26.8 g, 77% yield). The characteristics data were identical to those previously reported by our group, obtained via a different synthetic route.<sup>2</sup>

### Compound 31

**Physical State:** white solid

**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 60 °C, a mixture of two rotamers, A:B = 4:1, Signals of the major rotamer are reported.):** δ 9.25 (s, 1H), 7.97 (d, *J* = 7.1 Hz, 1H), 7.60 (m, 4H), 7.26 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.69 (m, 1H), 4.44 (s, 3H), 3.76 (s, 3H), 3.62 (m, 5H), 2.77 (m, 4H), 2.11 (s, 3H), 1.99 (m, 3H), 1.28 (s, 9H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.54 (q, *J* = 7.6 Hz, 6H).

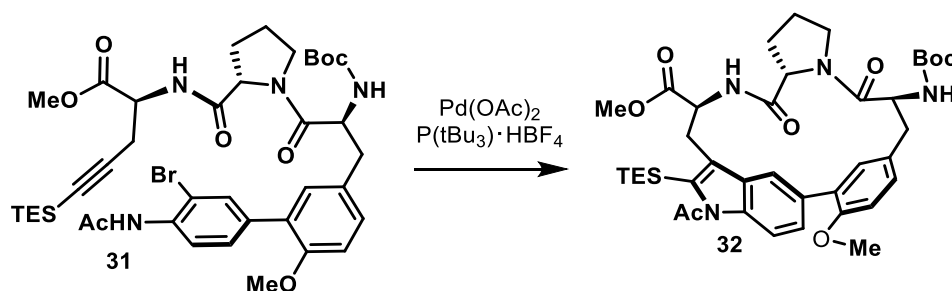
**<sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>, 60 °C, a mixture of two rotamers, A:B = 4:1, Signals of the major rotamer are reported.):** δ 171.30, 170.40, 170.26, 168.37, 154.71, 136.64, 135.00, 132.63, 131.74, 131.71, 131.35, 131.25, 131.19, 130.09, 129.95, 128.61, 128.53, 128.41, 127.25, 125.94, 116.96, 111.74, 103.40, 83.70, 77.93, 59.29, 55.58, 53.40, 51.69, 51.27, 46.56, 35.80, 28.61, 27.92, 24.28, 23.04, 22.44, 6.97, 3.85.

**HRMS (ESI-TOF):** calculated for C<sub>40</sub>H<sub>55</sub>BrN<sub>4</sub>NaO<sub>8</sub>Si<sup>+</sup> [M+Na]<sup>+</sup>: 849.2865, found: 849.2870.

**TLC:** R<sub>f</sub> = 0.6 (3:2 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>25</sup><sub>D</sub>:** +10.2 (*c* = 0.1, CHCl<sub>3</sub>)

*Note:* Due to rotamerism at room temperature, NMR spectra for structural assignment were recorded at 60 °C in DMSO-*d*<sub>6</sub>. However, even at this elevated temperature, the rotamers remained partially unresolved. Signals of the major rotamers were reported.



The reaction was conducted following the previously reported procedure. The characteristic data were identical to those previously reported.<sup>2</sup>

### Compound 32

**Physical State:** white solid

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 7.82 (d, *J* = 8.8 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.41 (s, 1H), 7.34 (s, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.79 (m, 1H), 5.17 (m, 1H), 4.93 (t, *J* = 9.1 Hz, 1H), 4.78 (t, *J* = 7.5 Hz, 1H), 4.45 (m, 1H), 3.81 (s, 3H), 3.77 (m, 1H), 3.72 (m, 1H), 3.68 (s, 3H), 3.65 (m, 1H), 3.14 (dd, *J* = 13.6, 6.7 Hz, 1H), 3.05 (m, 2H), 2.82 (s, 3H), 2.21 (m, 1H), 2.08 (m, 1H), 1.96 (m, 2H), 1.71 (m, 1H), 1.41 (s, 9H), 0.92 (t, *J* = 7.5 Hz, 9H), 0.85 (m, 6H).

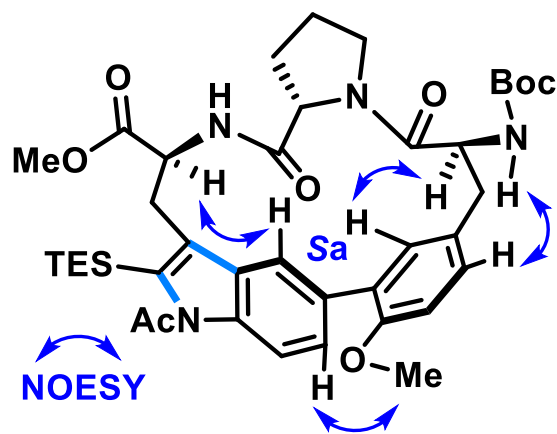
**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>):** 173.43, 171.46, 169.73, 169.60, 155.48, 155.45, 136.07, 135.27, 133.72, 133.28, 132.55, 132.02, 130.88, 129.14, 127.40, 127.20, 121.21, 112.70, 110.50, 79.49, 59.95, 55.57, 52.52, 52.49, 51.48, 47.30, 35.85, 30.13, 29.37, 28.47, 26.62, 25.01, 8.27, 6.39.

**HRMS (ESI-TOF):** calculated for C<sub>40</sub>H<sub>54</sub>N<sub>4</sub>NaO<sub>8</sub>Si<sup>+</sup> [M+Na]<sup>+</sup>: 769.3603, found: 769.3612.

**TLC:** R<sub>f</sub> = 0.3 (1:1 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

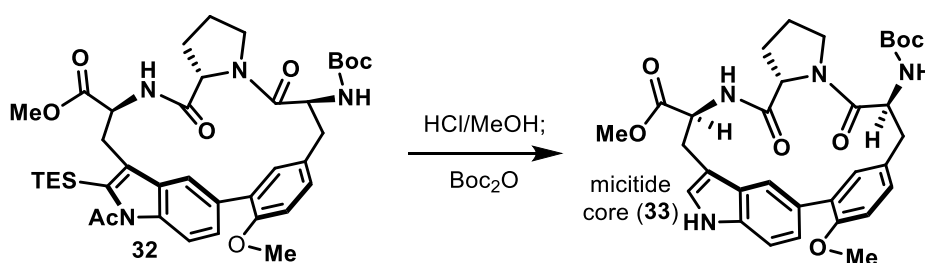
**[α]<sup>25</sup><sub>D</sub>:** -36.2 (*c* = 0.1, CHCl<sub>3</sub>)

## Key NOESY correlation of micitide core (32)



32 (CDCl<sub>3</sub>, NOESY, 600 MHz)

## Skeletal Editing of Micitide Core



Compound **32** (5.64 g, 7.56 mmol, 1.0 equiv.) was dissolved in MeOH (140

mL, 0.05 M), and SO<sub>2</sub>Cl<sub>2</sub> (20 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 25 °C for 2h. Then, the mixture was directly concentrated under reduced pressure to give the crude primary amine. The crude was then dissolved in the THF:sat. NaHCO<sub>3</sub> aq. 10:1 (140 mL, 0.05 M). Boc<sub>2</sub>O (18.8 g, 86.1 mmol, 11.4 equiv.) was added and the reaction was stirred for 2h at 25 °C. After confirming the full conversion of the primary amine by LC/MS, the reaction was diluted with H<sub>2</sub>O (200 mL) and extracted with EtOAc three times. The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give the crude. The crude was purified by flash column chromatography to give the compound **33** (4.39 g, 98%).

### Compound 33

**Physical State:** white solid

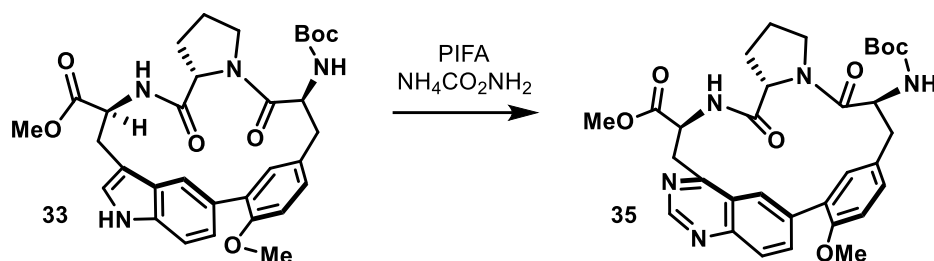
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.18 (s, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.59 – 7.43 (m, 2H), 7.36 (s, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.92 (s, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.84 – 6.78 (m, 1H), 5.28 (d, *J* = 8.2 Hz, 1H), 4.86 (t, *J* = 7.9 Hz, 1H), 4.78 (t, *J* = 5.7 Hz, 1H), 4.51 (d, *J* = 5.1 Hz, 1H), 3.85 – 3.74 (m, 4H), 3.75 – 3.62 (m, 4H), 3.26 (dd, *J* = 14.9, 6.3 Hz, 1H), 3.19 – 3.07 (m, 2H), 3.02 (d, *J* = 15.0 Hz, 1H), 2.13 (d, *J* = 24.8 Hz, 1H), 2.09 – 2.01 (m, 1H), 2.00 – 1.82 (m, 2H), 1.43 (s, 9H).

**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** δ 173.81, 171.19, 169.83, 155.49, 155.44, 135.58, 134.17, 132.16, 130.90, 129.99, 129.73, 128.49, 126.96, 124.34, 121.53, 121.02, 114.42, 110.61, 109.60, 79.43, 60.06, 55.57, 53.52, 52.40, 51.70, 47.17, 35.81, 31.05, 29.53, 28.44, 24.88.

**HRMS (ESI-TOF):** calculated for C<sub>32</sub>H<sub>38</sub>N<sub>4</sub>NaO<sub>7</sub><sup>+</sup> [M+Na]<sup>+</sup>: 613.2638, found: 613.2643.

**TLC:** R<sub>f</sub> = 0.6 (1:0 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>21</sup><sub>D</sub>:** +137.0 (*c* = 1.0, CHCl<sub>3</sub>)



In a culture tube equipped with a stirring bar, the compound **33** (1.77 g, 3.00 mmol, 1.0 eq.) and ammonium carbamate (2.34 g, 30 mmol, 10.0 equiv) were dissolved in MeOH (60 mL, 0.05 M). The resulting solution was cooled to 0 °C, and then PIFA (5.16 g, 12.0 mmol, 4.0 equiv) was added in one portion. The reaction was stirred at 0 °C for 1h and quenched with saturated aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The mixture was extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by silicagel column chromatography (EtOAc:Hexane:Et<sub>3</sub>N 33:66:1 to 100:0:1) to give the title compound **35** (910 mg, 50% yield)

### Compound 35

**Physical State:** white solid

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 9.19 (s, 1H), 8.36 (dd, *J* = 8.8, 1.8 Hz, 1H), 8.02 (d, *J* = 8.9 Hz, 1H), 7.99 (s, 0H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.12 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.84 (s, 1H), 5.13 (d, *J* = 6.4 Hz, 1H), 5.02 (t, *J* = 9.5 Hz, 1H), 4.81 (t, *J* = 7.7 Hz, 1H), 4.44 (dd, *J* = 7.9, 4.2 Hz, 1H), 3.90 – 3.78 (m, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 3.54 (dd, *J* = 13.3, 10.0 Hz, 1H), 3.21 (dd, *J* = 13.6, 7.0 Hz, 1H), 3.15 – 3.07 (m, 1H), 2.22 – 2.14 (m, 2H), 2.06 – 1.97 (m, 2H), 1.44 (s, 9H).

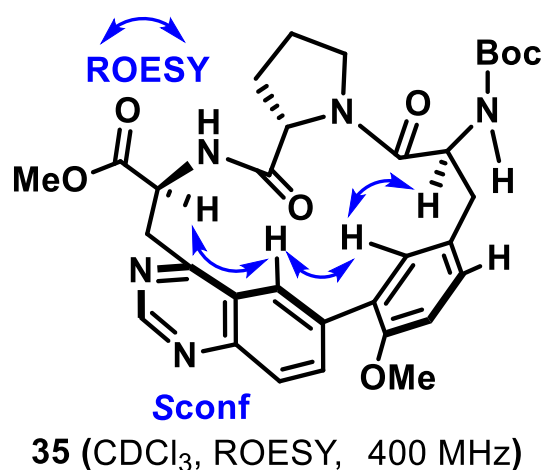
**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** δ 172.17, 171.33, 170.13, 167.01, 155.67, 155.38, 153.99, 149.56, 139.26, 136.90, 133.89, 132.25, 128.35, 127.59, 127.41, 125.09, 123.40, 110.76, 79.68, 60.29, 55.63, 52.80, 51.56, 47.43, 40.14, 35.65, 29.51, 28.49, 25.22, 25.11.

**HRMS (ESI-TOF):** calculated for C<sub>32</sub>H<sub>37</sub>N<sub>5</sub>NaO<sub>7</sub><sup>+</sup> [M+Na]<sup>+</sup>: 626.2591, found: 626.2692.

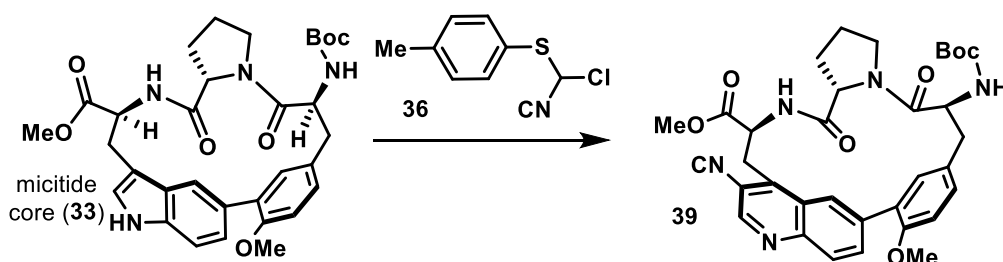
**TLC:** R<sub>f</sub> = 0.2 (10:1 EtOAc : Acetone, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>21</sup><sub>D</sub>:** +69.9 (*c* = 1.0, CHCl<sub>3</sub>)

## Key ROESY correlation of quinazomicitide core (35)



The conformation of the macrocycle was deduced to be *Sconf*.



To a solution of compound **33** (500 mg, 847  $\mu$ mol, 1.0 eq.) and Cs<sub>2</sub>CO<sub>3</sub> (966 mg, 2.96 mmol, 3.5 eq.) in THF (15 mL, 0.05 M), sulfenylcarbene precursor **36** (334 mg, 1.69 mmol, 2.0 eq.) was added portion-wise (0.5 equiv. every 1 h) at room temperature, and the resulting mixture was stirred for the next 5 h. The reaction was quenched with saturated aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by silica gel column chromatography (EtOAc:Hexane 1:4 to 2:1) to give the title compound **39** (425 mg, 80% yield)

### Compound 39

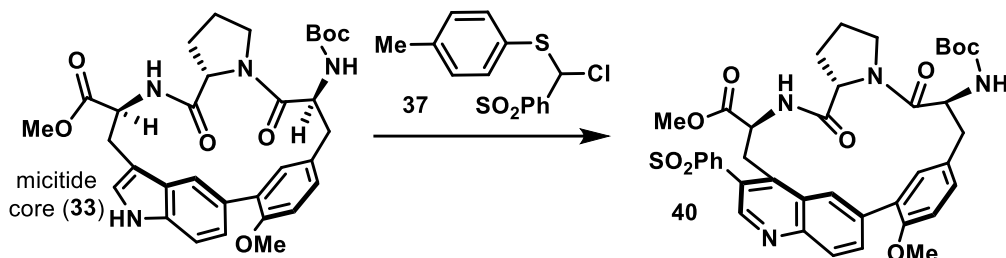
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  8.95 (s, 1H), 8.29 (dd,  $J$  = 8.9, 1.7 Hz, 1H), 8.13 (d,  $J$  = 8.8 Hz, 1H), 7.93 (d,  $J$  = 1.8 Hz, 1H), 7.59 – 7.43 (m, 2H), 7.12 (dd,  $J$  = 8.4, 2.2 Hz, 1H), 6.92 (d,  $J$  = 8.4 Hz, 1H), 5.29 (d,  $J$  = 8.5 Hz, 1H), 4.97 (ddd,  $J$  = 9.8, 6.4, 4.8 Hz, 1H), 4.82 (t,  $J$  = 7.8 Hz, 1H), 4.40 (dd,  $J$  = 7.8, 4.2 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.79 – 3.73 (m, 2H), 3.70 – 3.62 (m, 2H), 3.20 (dd,  $J$  = 13.6, 7.1 Hz, 1H), 3.11 – 3.03 (m, 1H), 2.36 – 1.72 (m, 4H), 1.42 (s, 9H).

**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):**  $\delta$  171.14, 170.87, 169.01, 154.78, 154.74, 148.90, 148.41, 147.37, 139.26, 134.87, 132.92, 131.82, 131.51, 131.41, 128.35, 128.00, 127.88, 127.26, 126.88, 124.36, 123.41, 116.36, 110.02, 106.58, 78.96, 59.34, 54.88, 52.67, 50.78, 50.53, 46.73, 35.09, 35.00, 28.76, 27.76, 24.34.

**HRMS (ESI-TOF):** calculated for C<sub>34</sub>H<sub>37</sub>N<sub>5</sub>NaO<sub>7</sub><sup>+</sup> [M+Na]<sup>+</sup>: 650.2591, found: 650.2591.

**TLC:** R<sub>f</sub> = 0.7 (2:1 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[ $\alpha$ ]<sup>21</sup><sub>D</sub>:** +36.6 ( $c$  = 1.0, CHCl<sub>3</sub>)



To a solution of compound **33** (1.00 g, 1.69 mmol, 1.0 eq.) and  $\text{Cs}_2\text{CO}_3$  (2.76 g, 8.47 mmol, 5.0 eq.) in THF (17 mL, 0.1 M), sulfenylcarbene precursor **37** (1.32 g, 4.24 mmol, 2.5 eq.) was added portion-wise (0.5 equiv. every 1 h) at room temperature, and the resulting mixture was stirred for the next 5 h. The reaction was quenched with saturated aq.  $\text{Na}_2\text{S}_2\text{O}_3$ , extracted with EtOAc (30 mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by silica gel column chromatography (EtOAc:Hexane 1:3 to 2:1) to give the title compound **40** (1.02 mg, 82% yield)

### Compound 40

**$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  9.40 (s, 1H), 8.28 (dd,  $J = 8.8, 1.6$  Hz, 1H), 8.13 (d,  $J = 8.8$  Hz, 1H), 8.03 (s, 0H), 7.83 (d,  $J = 8.0$  Hz, 1H), 7.82 (s, 1H), 7.55 – 7.42 (m, 4H), 7.31 (d,  $J = 10.2$  Hz, 1H), 7.12 (dd,  $J = 8.4, 2.2$  Hz, 1H), 6.87 (d,  $J = 8.4$  Hz, 1H), 5.22 (d,  $J = 8.7$  Hz, 1H), 5.04 (t,  $J = 9.8$  Hz, 1H), 4.82 (t,  $J = 7.8$  Hz, 1H), 4.59 (dd,  $J = 13.3, 10.9$  Hz, 1H), 4.39 (dd,  $J = 7.8, 4.8$  Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.74 – 3.64 (m, 2H), 3.53 (d,  $J = 13.3$  Hz, 1H), 3.18 (dd,  $J = 13.5, 7.4$  Hz, 1H), 3.07 (d,  $J = 13.5$  Hz, 1H), 2.14 – 1.99 (m, 2H), 1.96 – 1.81 (m, 2H), 1.39 (s, 9H).

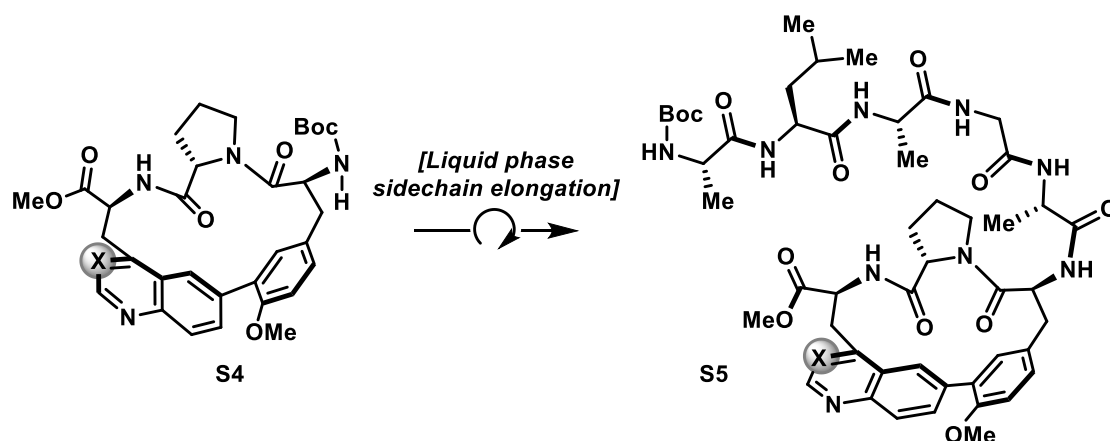
**$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):**  $\delta$  171.39, 171.03, 169.91, 155.46, 155.32, 148.74, 147.92, 145.07, 142.15, 139.76, 135.42, 133.54, 132.27, 132.20, 129.52, 128.92, 128.31, 127.50, 127.06, 126.11, 124.91, 110.56, 79.58, 60.18, 55.49, 52.76, 52.51, 51.47, 47.41, 35.86, 32.10, 29.19, 28.36, 25.06.

**HRMS (ESI-TOF):** calculated for  $\text{C}_{39}\text{H}_{42}\text{N}_4\text{NaO}_9\text{S}^+$  [ $\text{M}+\text{Na}$ ] $^+$ : 765.2570, found: 765.2573.

**TLC:**  $R_f = 0.7$  (2:1 EtOAc : Hexane,  $\text{Ce}_2(\text{SO}_4)_3$  in phosphomolybdic acid).

**$[\alpha]^{21}_D$ :**  $-12.1$  ( $c = 0.5$ ,  $\text{CHCl}_3$ )

### Sidechain Elongation of the Micitide Core Analogues (General Procedure C)

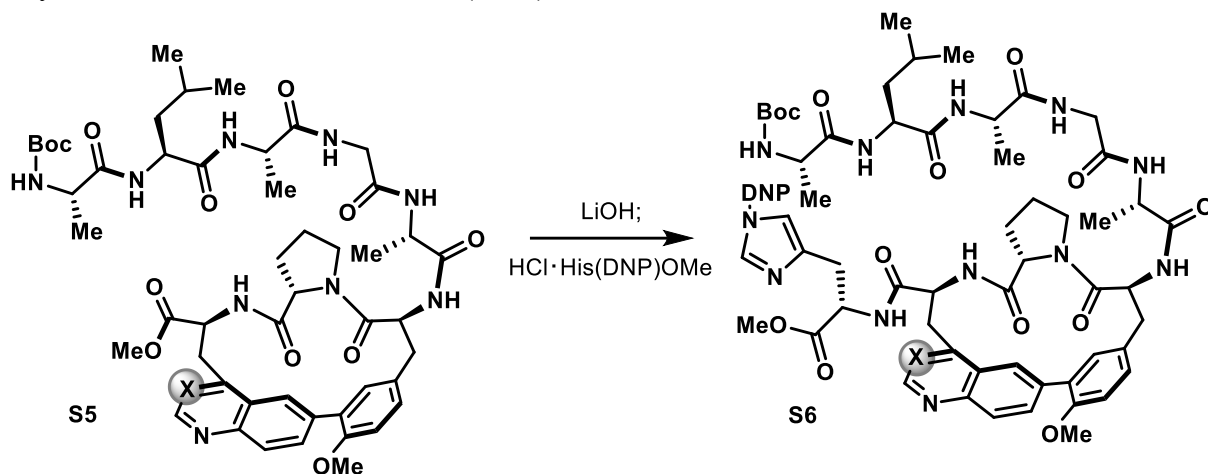


#### 1) Elongation towards the N-terminal

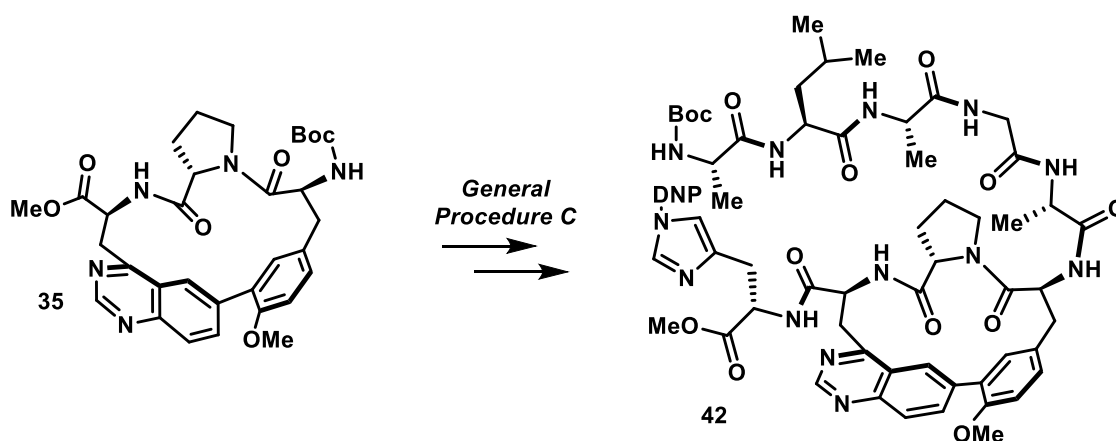
5 amino acids attached to the *N*-terminal of the micitide core was introduced by repeating the following procedure; The Boc-protected amine (**S4**, 1.0 eq.) was dissolved in DCM (0.1 M). 4.0 M HCl in 1,4-dioxane (0.4 M) was added dropwise. The reaction mixture was stirred at 25 °C for 2 h. The solvent was removed

under reduced pressure to give the crude. The crude was dissolved in DMF (0.1 M), corresponding carboxylic acid (3.0 eq.), DIPEA (6.0 eq.), and HATU (2.0 eq.) were added sequentially. The reaction was stirred at 25 °C for 2 h and quenched by saturated *aq.* NH<sub>4</sub>Cl and extracted with EtOAc three times. The organic layers were combined, washed with saturated *aq.* NaHCO<sub>3</sub> three times. The organic layers were concentrated under reduced pressure to give the coupled product. Following this procedure, L-Ala-OH, Gly-OH, L-Ala-OH, L-Leu-OH, and L-Ala-OH were introduced sequentially.

## 2) Hydrolysis and introduction of NH<sub>2</sub>-His(DNP)-OMe



The crude methyl ester **S5** was dissolved in THF/MeOH/H<sub>2</sub>O = 1/1/1 (0.1 M). LiOH·H<sub>2</sub>O (6 eq.) was added. The reaction was stirred at 25 °C for 0.5 h and acidified with *aq.* 0.5 M HCl. The solvent was removed under reduced pressure to give the crude. The crude was then dissolved in DMF (0.1 M). ClH<sub>3</sub>N-His(DNP)-OMe (1.5 eq.), DIPEA (6.0 eq.), and HATU (2 eq.) were added sequentially. The reaction was stirred at 25 °C for 2 h and quenched by saturated *aq.* NH<sub>4</sub>Cl, extracted with EtOAc three times. Organic layers were concentrated under reduced pressure and purified by silica gel chromatography to give the coupled product **S6**.



On 1.49 mmol scale, **General Procedure C** was followed with quinazoline containing micitide core **35**. Purification by silica gel column chromatography (EtOAc:Hexane 4:1 to Acetone:EtOAc 1:20) gave the title compound **42**. (1.56 g, 81% yield from **35**)

### Compound 42

**<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):** δ 9.03 (s, 1H), 8.87 (s, 1H), 8.58 (s, 1H), 8.38 (t, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 6.8 Hz, 1H), 7.91 (s, 2H), 7.82 (t, *J* = 3.7 Hz, 1H), 7.46 (d, *J* = 6.4 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.13 (s, 1H), 7.05 (t, *J* = 6.4 Hz, 1H), 5.05 (s, 1H), 4.90 – 4.79 (m, 3H), 4.59 – 4.52 (m, 1H), 4.39 (dd, *J* = 14.6, 7.4 Hz, 2H), 4.28 (d, *J* = 12.9 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 1H), 3.85 (s, 3H), 3.81

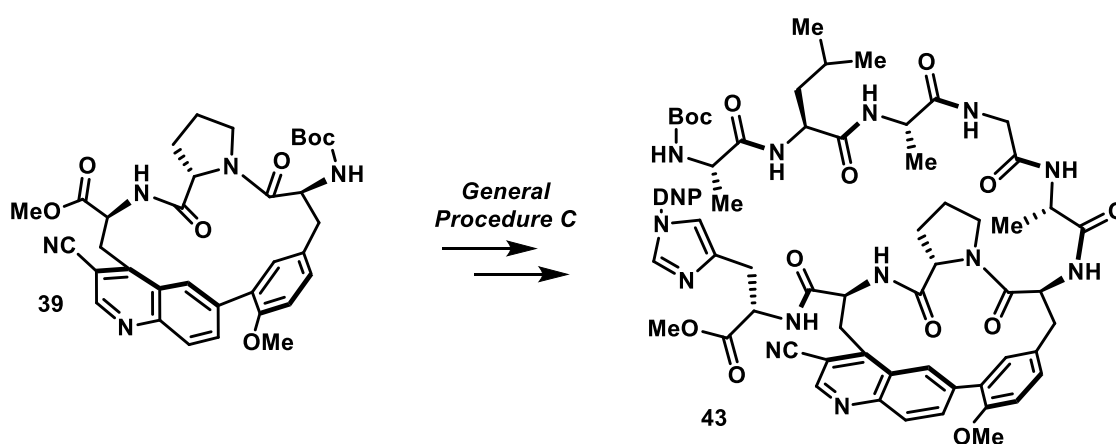
(d,  $J = 62.7$  Hz, 5H), 3.79 (s, 3H), 3.69 – 3.53 (m, 1H), 3.28 – 3.07 (m, 4H), 1.91 – 1.84 (m, 2H), 1.74 – 1.65 (m, 2H), 1.63 – 1.56 (m, 2H), 1.44 (s, 9H), 1.38 (d,  $J = 7.1$  Hz, 3H), 1.41 – 1.32 (m, 1H), 1.30 (d,  $J = 6.4$  Hz, 6H), 0.93 (d,  $J = 6.9$  Hz, 3H), 0.90 (d,  $J = 6.9$  Hz, 3H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):**  $\delta$  174.27, 173.28, 172.70, 172.19, 171.55, 170.78, 170.21, 169.32, 168.56, 168.23, 155.92, 155.00, 152.47, 148.14, 146.56, 143.58, 138.92, 137.81, 136.76, 136.55, 133.96, 132.85, 131.97, 128.99, 128.53, 127.53, 127.01, 126.78, 125.51, 124.85, 122.55, 120.38, 117.38, 110.24, 78.69, 77.18, 69.50, 65.62, 64.75, 62.25, 54.13, 51.82, 51.20, 51.03, 50.30, 49.78, 49.00, 48.52, 41.46, 39.59, 38.39, 38.17, 34.09, 32.72, 31.05, 29.57, 28.84, 28.74, 28.46, 28.06, 26.70, 24.05, 23.74, 23.52, 22.88, 22.01, 21.72, 21.49, 19.92, 16.07, 15.98, 15.57, 12.44, 12.38, 9.36.

**HRMS (ESI-TOF):** calculated for  $\text{C}_{61}\text{H}_{75}\text{N}_{15}\text{NaO}_{17}^+$   $[\text{M}+\text{Na}]^+$ : 1312.5363, found: 1312.5363.

**TLC:**  $R_f = 0.2$  (1:10 MeOH:EtOAc,  $\text{Ce}_2(\text{SO}_4)_3$  in phosphomolybdic acid).

**$[\alpha]^{21}_D$ :** +124.2 ( $c = 0.5$ , MeOH)



On 0.960 mmol scale, **General Procedure C** was followed with micitide core **39**. Purification by silica gel column chromatography (EtOAc:Hexane 4:1 to Acetone:EtOAc 1:20) gave the title compound **43**. (903 mg, 72% yield from **43**)

### Compound 43

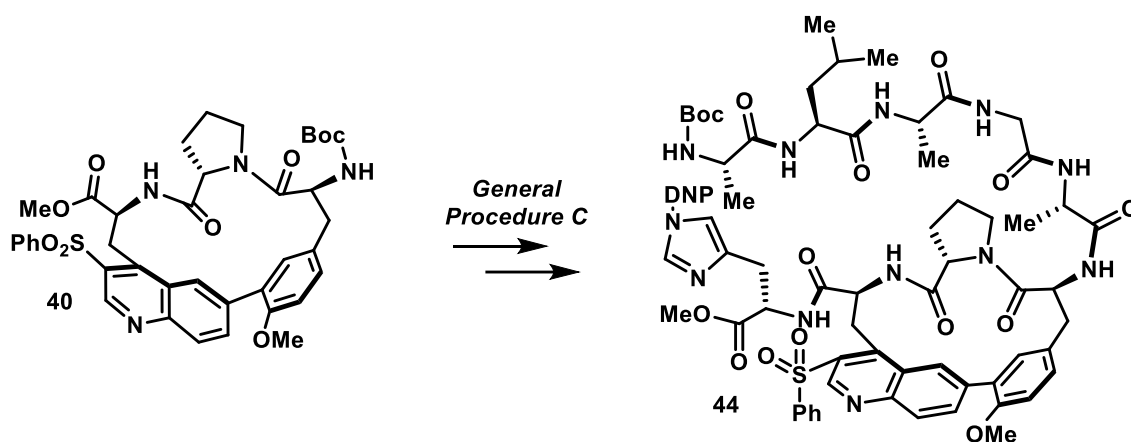
**$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):**  $\delta$  9.23 (d,  $J = 9.5$  Hz, 1H), 8.98 (s, 1H), 8.91 (d,  $J = 2.6$  Hz, 1H), 8.62 (dd,  $J = 8.8, 2.6$  Hz, 1H), 8.31 (d,  $J = 7.9$  Hz, 1H), 8.26 (dd,  $J = 8.8, 1.6$  Hz, 1H), 8.18 – 8.14 (m, 1H), 8.12 – 8.05 (m, 2H), 8.01 (d,  $J = 6.8$  Hz, 1H), 7.98 – 7.92 (m, 2H), 7.89 (d,  $J = 8.8$  Hz, 1H), 7.79 (d,  $J = 8.2$  Hz, 1H), 7.51 (br,  $J = 2.1$  Hz, 1H), 7.39 (d,  $J = 7.4$  Hz, 1H), 7.10 – 7.07 (m, 2H), 7.02 (d,  $J = 8.5$  Hz, 1H), 6.97 (d,  $J = 7.4$  Hz, 1H), 4.85 – 4.75 (m, 2H), 4.65 (q,  $J = 6.9$  Hz, 1H), 4.48 (dd,  $J = 8.5, 4.6$  Hz, 1H), 4.36 – 4.14 (m, 4H), 4.00 – 3.89 (m, 1H), 3.78 (s, 3H), 3.76 – 3.63 (m, 5H), 3.62 (s, 3H), 3.21 – 3.12 (m, 1H), 2.95 – 2.81 (m, 3H), 2.11 – 1.91 (m, 1H), 1.83 – 1.73 (m, 1H), 1.64 – 1.57 (m, 2H), 1.48 – 1.40 (m, 2H), 1.36 (s, 9H), 1.23 (d,  $J = 5.1$  Hz, 3H), 1.22 – 1.20 (m, 4H), 1.15 (d,  $J = 7.1$  Hz, 3H), 0.85 (d,  $J = 6.4$  Hz, 3H), 0.82 (d,  $J = 6.1$  Hz, 3H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ ):**  $\delta$  172.59, 172.34, 171.96, 171.75, 171.61, 171.12, 170.90, 169.55, 169.44, 168.24, 167.67, 155.01, 154.81, 149.74, 149.34, 147.04, 146.05, 143.20, 138.72, 138.61, 138.53, 136.92, 136.89, 134.37, 134.31, 133.09, 132.28, 129.27, 129.24, 128.54, 128.51, 128.29, 127.79, 126.91, 124.90, 124.22, 121.10, 117.07, 116.74, 116.44, 110.98, 106.95, 78.05, 69.58, 65.57, 58.77, 55.35, 51.80, 51.79, 51.70, 51.64, 50.60, 50.53, 49.55, 48.24, 46.62, 41.69, 34.61, 33.07, 30.50, 29.77, 29.61, 29.55, 28.92, 28.12, 27.93, 24.33, 23.79, 23.05, 22.94, 22.21, 22.07, 21.27, 17.90, 17.69, 17.61.

**HRMS (ESI-TOF):** calculated for  $\text{C}_{63}\text{H}_{75}\text{N}_{15}\text{NaO}_{17}^+$   $[\text{M}+\text{Na}]^+$ : 1336.5363, found: 1336.5363.

TLC:  $R_f = 0.7$  (1:10 MeOH:EtOAc,  $Ce_2(SO_4)_3$  in phosphomolybdic acid).

$[\alpha]^{21}_D$ : +52.2 ( $c = 1.0$ , MeOH)



On 0.960 mmol scale, **General Procedure C** was followed with micitide core **40**. Purification by silica gel column chromatography (EtOAc:Hexane 4:1 to Acetone:EtOAc 1:20) gave the title compound **44**. (785 mg, 40% yield from **40**)

#### Compound **44**

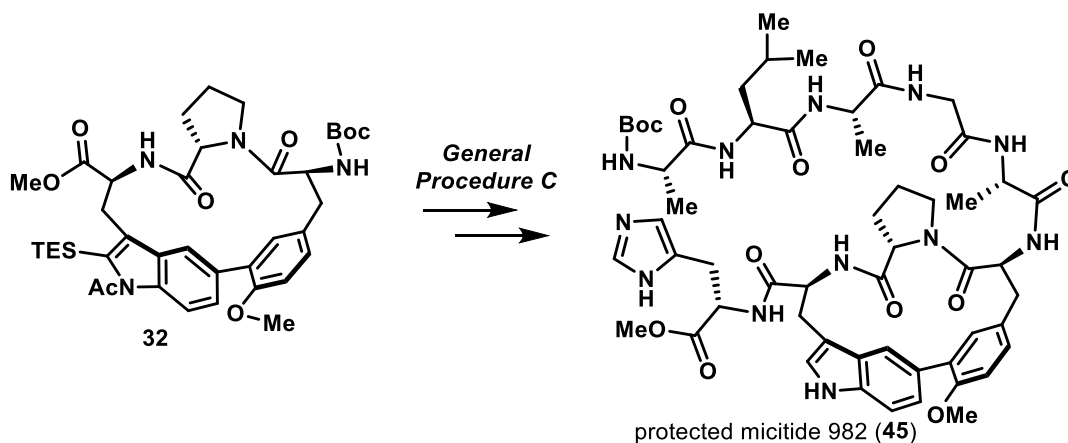
$^1H$  NMR (400 MHz,  $CD_3OD$ ):  $\delta$  8.95 (s, 2H), 8.69 – 8.60 (m, 3H), 8.00 – 7.84 (m, 10H), 7.24 – 7.12 (m, 2H), 4.79 – 4.72 (m, 2H), 4.45 – 4.12 (m, 4H), 4.12 – 3.99 (m, 1H), 3.87 – 3.76 (m, 3H), 3.73 (s, 6H), 3.69 – 3.66 (m, 3H), 3.25 – 3.11 (m, 2H), 3.05 – 2.91 (m, 4H), 1.72 – 1.51 (m, 6H), 1.45 (s, 9H), 1.37 – 1.26 (m, 10H), 0.98 – 0.87 (m, 6H).

$^{13}C$  NMR (101 MHz,  $CD_3OD$ ):  $\delta$  174.68, 174.49, 172.79, 172.67, 172.13, 172.11, 171.34, 169.44, 160.28, 156.02, 155.05, 146.61, 146.52, 143.75, 143.62, 143.58, 137.90, 137.79, 136.72, 136.41, 134.14, 134.02, 129.38, 129.20, 129.09, 128.78, 127.75, 127.60, 126.80, 120.46, 120.38, 118.12, 117.45, 117.33, 110.76, 78.80, 68.96, 65.64, 56.50, 54.14, 52.03, 51.63, 51.47, 50.88, 39.34, 38.24, 38.15, 36.68, 34.85, 32.73, 31.05, 29.56, 29.42, 29.36, 28.76, 28.05, 26.71, 24.27, 23.78, 23.51, 22.87, 22.00, 21.51, 21.47, 20.40, 19.92, 19.44, 19.22, 18.44, 16.34, 15.89, 15.44.

HRMS (ESI-TOF): calculated for  $C_{68}H_{81}N_{14}O_{19}S^+$   $[M+H]^+$ : 1429.5523, found: 1429.5524.

TLC:  $R_f = 0.6$  (1:10 MeOH:EtOAc,  $Ce_2(SO_4)_3$  in phosphomolybdic acid).

$[\alpha]^{21}_D$ : +20.0 ( $c = 1.0$ , MeOH)



On 4.98 mmol scale, **General Procedure C** was followed with micitide core **40**. In case of micitide core **32**, histidine methyl ester dihydrochloride was used instead of ClH<sub>3</sub>N-His(DNP)-OMe, using the same amide coupling conditions. purification by silica gel column chromatography (EtOAc:Hexane 4:1 to MeOH:EtOAc 1:4) gave the title compound **44**. (1.67 g, 31% yield from **32**) The characteristics data were identical to those previously reported by our group, obtained via a different synthetic route.<sup>2</sup>

*Note: Boc removal after the introduction of Gly was conducted using the following conditions to remove the acetyl group on the indole ring:*

*The Boc-protected amine was dissolved in MeOH (150 mL). SOCl<sub>2</sub> (20.5 mL) was added dropwise at 0 °C. The reaction mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure to give the ammonium salt.*

### Protected micitide 982 (45)

**Physical State:** white solid

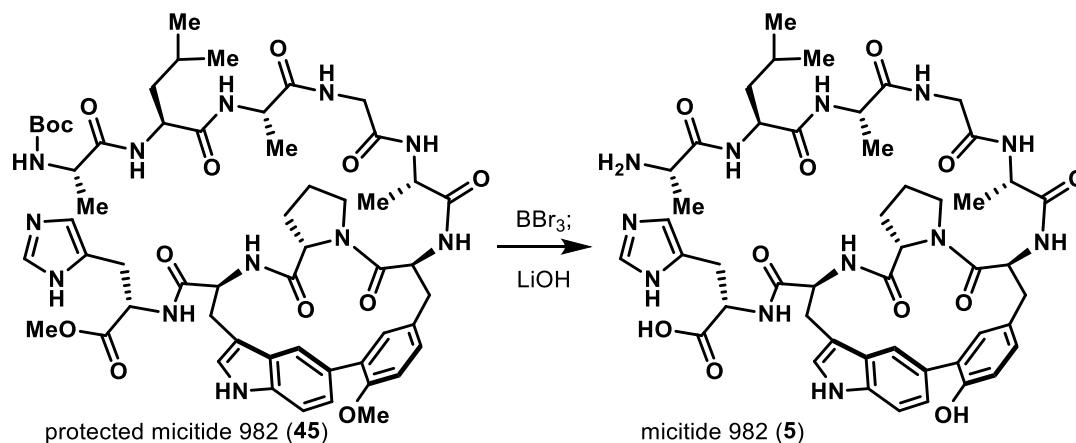
**<sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD):** δ 7.91 – 6.80 (m, 8H), 4.67 (dd, *J* = 8.2, 5.0 Hz, 1H), 4.38 – 4.33 (m, 2H), 4.28 – 4.22 (m, 2H), 4.08 – 4.02 (m, 2H), 3.93 – 3.75 (m, 6H), 3.71 (s, 6H), 3.25 – 3.15 (m, 2H), 3.13 – 3.04 (m, 2H), 1.74 – 1.67 (m, 2H), 1.64 – 1.54 (m, 2H), 1.44 (s, 9H), 1.33 – 1.28 (m, 10H), 0.95 (d, *J* = 6.6 Hz, 6H).

**<sup>13</sup>C NMR (151 MHz, CD<sub>3</sub>OD):** 176.62, 176.44, 175.64, 175.54, 174.99, 174.88, 172.27, 171.46, 171.36, 157.97, 156.97, 135.55, 135.52, 132.14, 118.84, 118.79, 80.72, 53.56, 53.51, 53.33, 53.06, 52.11, 51.97, 51.33, 51.11, 50.56, 43.54, 41.37, 41.30, 41.17, 28.72, 28.53, 28.36, 25.82, 25.74, 23.46, 21.94, 21.87, 17.99, 17.84, 17.63, 17.42, 9.25.

**HRMS (ESI-TOF):** calculated for C<sub>55</sub>H<sub>75</sub>N<sub>12</sub>O<sub>13</sub><sup>+</sup> [M+H]<sup>+</sup>: 1111.5571, found: 1111.5576.

**TLC:** R<sub>f</sub> = 0.5 (EtOAc:*n*BuOH:AcOH:H<sub>2</sub>O 9:9:1:1, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>25</sup><sub>D</sub>:** -27.8 (*c* = 0.1, MeOH)



Compound **45** (80.0 mg, 72.0  $\mu\text{mL}$ , 1.0 eq.) was dissolved in DCM (15 mL, 0.05 M),  $\text{BBr}_3$  (1M in DCM, 1.4 mL, 1.4 mmol, 20 eq.) was added dropwise at 0 °C under  $\text{N}_2$ , the reaction was stirred at 25 °C for 1 h, checked by LC-MS and quenched by MeOH dropwise at 0 °C, then it was concentrated under reduced pressure to give the residue. The residue was dissolved in THF/ $\text{H}_2\text{O}$ /MeOH = 1:1:1 (6.0 mL), LiOH (200 mg, 4.77 mmol, 66.2 eq.) was added, checked by LC-MS, the reaction was stirred at 25 °C for 2 h, acidified with 0.5 M HCl to adjust the pH = 3, the solvents was removed under reduced pressure and the residue was purified by C18 silica gel (manual reverse-phase silica gel) using  $\text{H}_2\text{O}$  followed by MeOH/ $\text{H}_2\text{O}$ /TFA = 40:60:1 as the mobile phase to give micitide 982 (**1**) (57.3 mg, 81% yield). The characterization data were identical to those reported in the isolation paper by Li *et al.*<sup>1</sup> and to those previously reported by our group.<sup>2</sup>

### Compound 5 (micitide 982)

**Physical State:** white solid

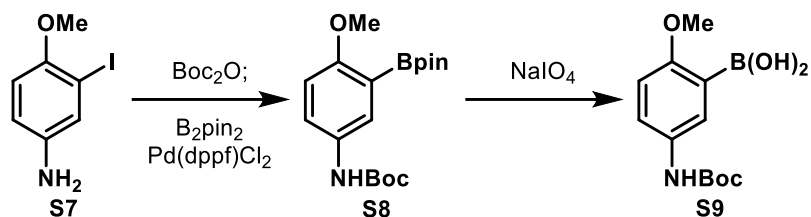
**$^1\text{H}$  NMR (600 MHz, DMSO-*d*6):**  $\delta$  10.70 (brs, 1H), 9.15 (s, 1H), 8.86 (d,  $J = 9.4$  Hz, 1H), 8.69 (m, 1H), 8.43 (d,  $J = 7.9$  Hz, 1H), 8.14 (s, 1H), 8.14 (d,  $J = 4.0$  Hz, 1H), 8.07 (d,  $J = 7.1$  Hz, 1H), 7.76 (d,  $J = 7.9$  Hz, 1H), 7.65 (dd,  $J = 8.7, 1.2$  Hz, 1H), 7.35 (s, 1H), 7.30 (s, 1H), 7.28 (d,  $J = 8.2$  Hz, 1H), 7.22 (brs, 1H), 7.08 (d,  $J = 7.4$  Hz, 1H), 6.99 (d,  $J = 2.2$  Hz, 1H), 6.74 (m, 1H), 6.74 (m, 1H), 4.76 (t,  $J = 7.6$  Hz, 1H), 4.63 (dd,  $J = 7.7, 3.4$  Hz, 1H), 4.57 (m, 1H), 4.52 (m, 1H), 4.35 (m, 1H), 4.25 (qd,  $J = 6.5, 2.7$  Hz, 1H), 4.25 (qd,  $J = 6.5, 2.7$  Hz, 1H), 3.86 (q,  $J = 7.3$  Hz, 1H), 3.79 (dd,  $J = 15.4, 6.1$  Hz, 2H), 3.66 (m, 2H), 3.61 (dd,  $J = 15.5, 6.7$  Hz, 1H), 3.22 (dd,  $J = 15.2, 6.1$  Hz, 1H), 3.08 – 2.99 (m, 2H), 3.07 – 2.85 (m, 2H), 2.82 (m, 1H), 2.05 – 1.68 (m, 2H), 2.00 – 1.91 (m, 2H), 1.64 (m, 1H), 1.48 (m, 2H), 1.34 (d,  $J = 6.9$  Hz, 3H), 1.23 (d,  $J = 7.3$  Hz, 3H), 1.23 (d,  $J = 7.3$  Hz, 3H), 0.90 (d,  $J = 6.3$  Hz, 3H), 0.87 (d,  $J = 6.4$  Hz, 3H),

**$^{13}\text{C}$  NMR (151 MHz, DMSO-*d*6):** 173.0, 172.5, 172.3, 172, 171.9, 171.6, 169.8, 168.9, 168.3, 153.2, 135.7, 134.1, 133.5, 130.1, 130, 129.5, 128.2, 127.1, 126.0, 123.6, 122.7, 120.1, 116.4, 115.5, 113.8, 110.1, 59.1, 54.0, 51.5, 51.3, 51.0, 49.0, 48.8, 48.4, 47, 42.2, 40.7, 35.1, 31.2, 29.7, 26.5, 24.6, 24.4, 23.4, 21.7, 18.2, 18.2, 17.5.

**HRMS (ESI-TOF):** calculated for  $\text{C}_{48}\text{H}_{62}\text{N}_{12}\text{O}_{11}^+ [\text{M}+2\text{H}]^{2+}$ : 492.2409, found: 492.2425.

**$[\alpha]^{25}_{\text{D}}$ :**  $-54.4$  ( $c = 0.1$ , MeOH)

## Synthesis of Scabrirubin CB-4



A mixture of aniline **S7** (15.0 g, 60.2 mmol, 1.0 eq.) and  $\text{Boc}_2\text{O}$  (19.8 g, 90.4 mmol, 1.5 eq.) was heated at 80 °C under vacuum. After completion of the reaction, confirmed by TLC, the mixture was cooled down to 25 °C. To the crude, KOAc (17.7 g, 181 mmol, 3.0 equiv.),  $\text{B}_2\text{pin}_2$  (18.3 g, 72.2 mmol, 1.2 equiv.) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (2.20 g, 3.01 mmol, 0.05 equiv.) were added. The flask was evacuated and backfilled with  $\text{N}_2$  three times. Dry DMSO (200 mL, 0.2 M) was added, and the reaction was stirred in a preheated oil bath set to 90 °C. After 6h, the reaction was cooled to 25 °C. The crude mixture was then diluted with water (1000 mL) and extracted with EtOAc (500 mL) three times. The organic phase was combined, washed with brine (1000 mL) three times, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under vacuum. The crude mixture was filtered through a pad of silica gel (EtOAc:Hexane 1:3) to give crude **S8**. The crude **S8** was dissolved in acetone/water = 1:1 (300 mL, 0.2 M), then  $\text{NaIO}_4$  (38.6 g, 181 mmol, 3.0 equiv.) and  $\text{NH}_4\text{OAc}$  (27.8 g, 361 mmol, 6.0 equiv.) were added. The reaction was stirred at 25 °C for 15h and quenched with 1N HCl aq. (500 mL). The aqueous phase was extracted with EtOAc (500 mL) three times. The organic phase was combined, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under vacuum. The residue was triturated with EtOAc:Hexane 1:2 and dried under vacuum to yield boronic acid **S9** as a white solid. (9.76 g, 61% from **S7**)

### Compound **S9**

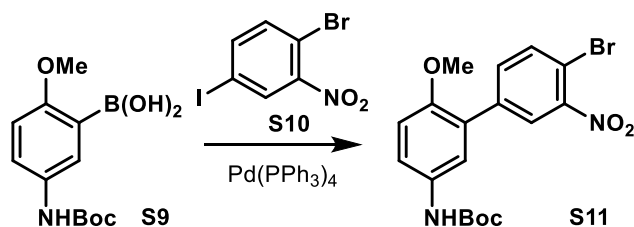
**Physical State:** white solid

**$^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{OD}$ , mixture of rotamers, A:B = 3:2):**  $\delta$  7.57 (s, 1H, B), 7.45 (d,  $J = 7.2$  Hz, 1H, B), 7.38 (d,  $J = 8.8$  Hz, 1H, A), 7.19 (s, 1H, A), 6.91 (d,  $J = 8.6$  Hz, 1H, B), 6.88 (d,  $J = 8.8$  Hz, 1H, A), 3.85 (s, 3H, B), 3.77 (s, 3H, A), 1.50 (s, 9H).

**$^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_3\text{OD}$ , mixture of rotamers, A:B = 3:2):**  $\delta$  160.23, 157.39, 154.45, 132.17, 132.11, 110.08, 109.89, 79.28, 54.64, 27.42.

**HRMS (ESI-TOF):** calculated for  $\text{C}_{12}\text{H}_{18}\text{BNNaO}_5^+ [\text{M}+\text{Na}]^+$ : 290.1176, found: 290.1175.

**TLC:**  $R_f = 0.6$  (2:1 EtOAc : Hexane,  $\text{Ce}_2(\text{SO}_4)_3$  in phosphomolybdic acid).



To a solution of compound **S9** (9.76 g, 36.5 mmol, 1.0 equiv.) in Dioxane: $\text{H}_2\text{O}$  2:1 (180 mL, 0.2 M) was added aryl iodide **S10** (14.3 g, 43.8 mmol, 1.2 equiv.),  $\text{K}_2\text{CO}_3$  (25.2 g, 183 mmol, 5.0 equiv.) and  $\text{Pd}(\text{PPh}_3)_4$  (2.11 g, 1.83 mmol, 0.05 equiv.). The reaction was stirred at 80 °C for 6 h, then the reaction mixture was allowed to cool to 25 °C, diluted with water, extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under vacuum. The crude was purified by silica gel chromatography (hexane:EtOAc 10:1 to 2:1) to give compound **S11** (10.4 g, 67% yield).

## Compound S11

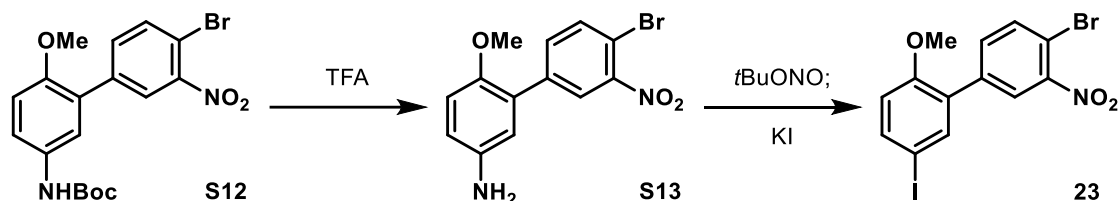
**Physical State:** pale yellow solid

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.02 (d, *J* = 2.1 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.57 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.39 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.54 (s, 1H), 3.79 (s, 3H), 1.51 (s, 9H).

**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** δ 152.49, 151.62, 148.82, 138.22, 133.86, 133.57, 131.34, 126.48, 125.94, 120.75, 120.09, 112.01, 111.37, 79.97, 55.30, 27.73.

**HRMS (CI-TOF):** calculated for C<sub>18</sub>H<sub>20</sub>BrN<sub>2</sub>O<sub>5</sub><sup>+</sup> [M+H]<sup>+</sup>: 423.0556, found: 423.0557.

**TLC:** R<sub>f</sub> = 0.4 (1:9 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).



To a solution of **S12** (10.4 g, 24.6 mmol, 1.0 equiv.) in DCM (120 mL, 0.2 M), TFA (30 mL, 0.8 M) was added. The reaction mixture was stirred at 25 °C for 1 h. The solvent and TFA were removed under reduced pressure to give crude. To a solution of the crude and *p*TsOH·H<sub>2</sub>O (18.7 g, 98.2 mmol, 4.0 equiv.) in MeCN (130 mL, 0.2 M), *t*BuONO (4.4 mL, 36.8 mmol, 1.5 equiv.) was added dropwise at 0 °C. The reaction was stirred at 0 °C for 1 h, then KI (24.4 g, 14.7 mmol, 6.0 equiv.) in H<sub>2</sub>O (30 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 25 °C for 4 h, quenched by saturated *aq.* NaHCO<sub>3</sub> and saturated *aq.* Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, extracted with DCM three times. The organic layers were combined and washed with saturated *aq.* Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. Organic layers were concentrated under reduced pressure and purified by silica gel chromatography (hexane:EtOAc 10:1 to 2:1) to give compound **23** (10.6 g, 76%).

## Compound 23

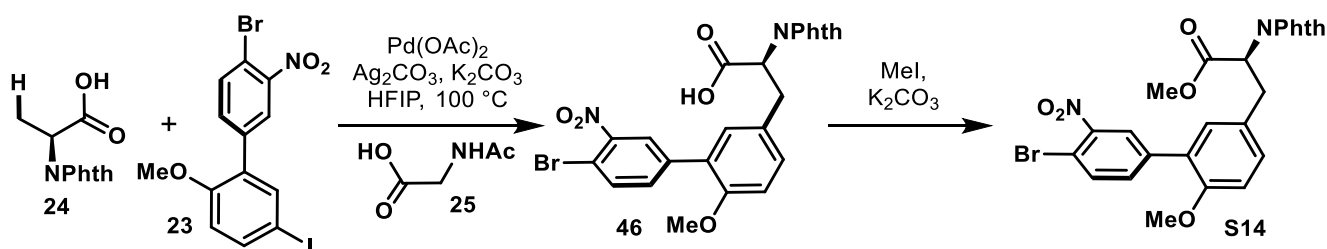
**Physical State:** colorless solid

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.99 (d, *J* = 2.1 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.66 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.58 (d, *J* = 2.3 Hz, 1H), 7.54 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 3.81 (s, 3H).

**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>):** δ 152.49, 151.62, 148.82, 138.22, 133.86, 133.57, 131.34, 126.48, 125.94, 120.75, 120.09, 112.01, 111.37, 79.97, 55.30, 27.73.

**HRMS (CI-TOF):** calculated for C<sub>13</sub>H<sub>9</sub>BrINO<sub>3</sub><sup>+</sup> [M+H]<sup>+</sup>: 433.8889, found: 433.8890.

**TLC:** R<sub>f</sub> = 0.5 (1:3 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).



On 14.0 mmol scale, **General Procedure B** was followed with aryl iodide **23**. Purification by silica gel column chromatography (EtOAc:Hexane 10:1 to 2:1) gave the title compound **S14** as a colorless solid. (5.50 g, 73%)

### Compound S14

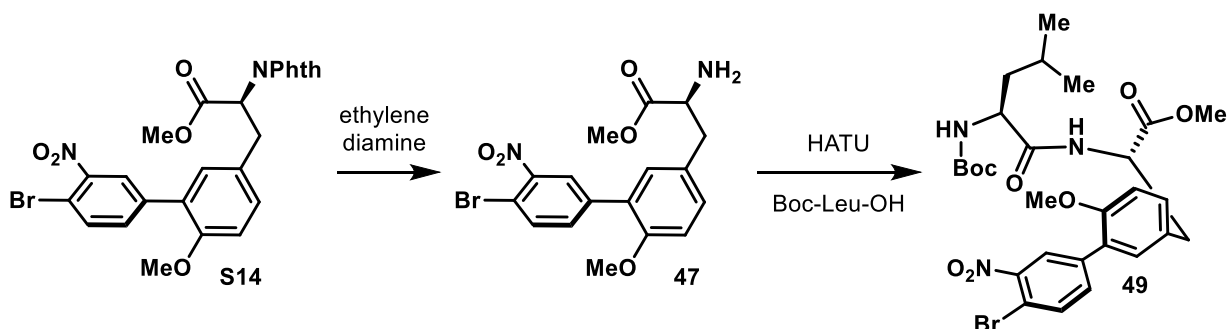
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.6, 3.0 Hz, 3H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.20 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 5.14 (dd, *J* = 11.1, 5.4 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.62 – 3.47 (m, 2H).

**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** δ 168.58, 166.83, 154.45, 138.19, 133.71, 133.35, 130.84, 130.12, 129.95, 128.63, 126.16, 125.67, 122.95, 111.80, 110.92, 54.92, 52.56, 52.36, 33.07.

**HRMS (CI-TOF):** calculated for C<sub>25</sub>H<sub>20</sub>BrN<sub>2</sub>O<sub>7</sub><sup>+</sup> [M+Na]<sup>+</sup>: 539.0454, found: 539.0449.

**TLC:** R<sub>f</sub> = 0.7 (1:1 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>21</sup><sub>D</sub>:** –108.5 (*c* = 1.0, CHCl<sub>3</sub>)



Compound **S14** (5.50 g, 10.2 mmol, 1.0 eq.) was dissolved in *n*-BuOH (70 mL, 0.2 M), and ethylenediamine (5.8 mL, 102 mmol, 10 eq.) was added. The reaction was stirred at 25 °C for 15 h. The reaction mixture was diluted with toluene (15 mL) and directly concentrated under reduced pressure to give the crude. To the crude, Boc-Leu-OH (16.2 g, 70.0 mmol, 6.9 eq.), and DIPEA (15 mL, 84 mmol, 8.2 eq.), was added HATU (26.6 g, 70 mmol, 6.9 eq.). The reaction mixture was stirred at for 3 h and quenched with *aq.* 0.5 M HCl, extracted with EtOAc three times. The organic layers were combined and washed with saturated *aq.* NaCl. The organic layers were concentrated under reduced pressure to give and purified by silica gel chromatography (EtOAc:Hexane 9:1 to 1:3) to give compound **49** (6.05 g, quant.).

### Compound 49

**<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, 60 °C):** δ 8.01 (dd, *J* = 3.6, 1.9 Hz, 1H), 7.79 (d, *J* = 3.4 Hz, 1H), 7.66 (ddd, *J* = 8.3, 3.5, 2.0 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 2H), 7.04 (d, *J* = 3.8 Hz, 1H), 4.08 – 3.95 (m, 2H), 3.81 (s, 3H), 3.31 (s, 3H), 3.19 – 3.09 (m, 1H), 2.98 (ddd, *J* = 13.1, 8.3, 3.8 Hz, 1H), 1.74 – 1.63 (m, 1H), 1.60 – 1.49 (m, 2H), 1.45 (s, 9H), 0.99 – 0.90 (m, 6H).

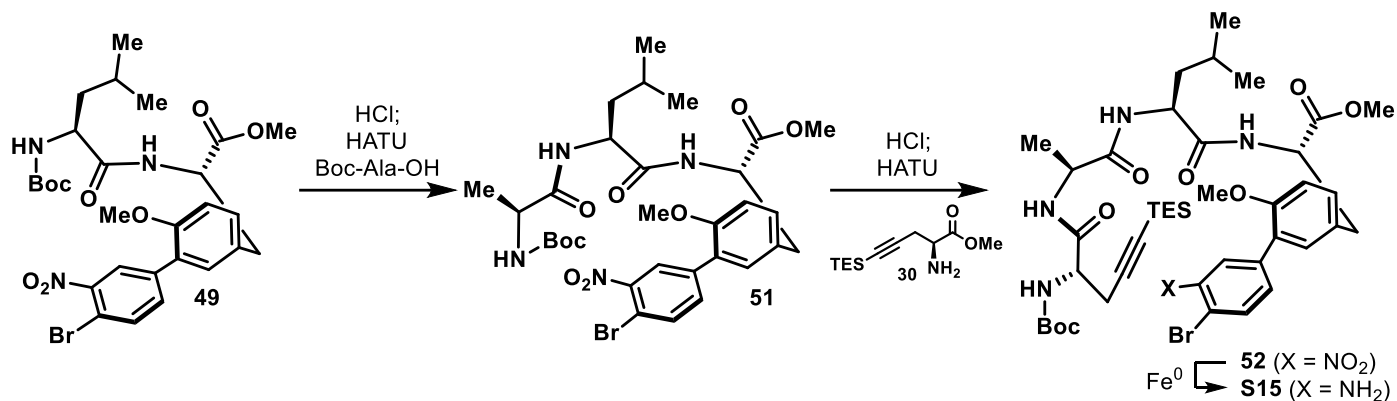
**<sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD, 60 °C):** δ 174.71, 174.08, 172.12, 156.36, 155.48, 149.96, 139.48, 134.10, 133.90, 130.86, 129.73, 126.81, 125.77, 111.78, 111.24, 79.48, 54.99, 54.55, 53.96, 53.63, 41.17, 40.70, 38.80, 38.71, 38.49, 36.51, 27.41, 27.36, 24.65, 24.52, 22.06, 22.00, 21.89, 20.68, 20.62.

**HRMS (ESI-TOF):** calculated for C<sub>27</sub>H<sub>36</sub>BrN<sub>3</sub>NaO<sub>7</sub><sup>+</sup> [M+Na]<sup>+</sup>: 616.1634, found: 616.1631.

**TLC:** R<sub>f</sub> = 0.6 (2:1 Acetone : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>21</sup><sub>D</sub>:** –91.3 (*c* = 1.0, CHCl<sub>3</sub>)

*Note: Due to rotamerism at room temperature, NMR spectra for structural assignment were recorded at 60 °C in CD<sub>3</sub>OD. However, even at this elevated temperature, the rotamers remained partially unresolved.*



Compound **49** (6.03 g, 9.71 mmol, 1.0 eq.) was dissolved in DCM (100 mL, 0.1 M), 4.0 M HCl in 1,4-dioxane (25 mL, 0.4 M) was added. The reaction was stirred at 25 °C for 1 h. The solvent was removed under reduced pressure to give the crude. The crude was dissolved in DMF (50 mL, 0.2 M), Boc-Ala-OH (5.51 g, 29.1 mmol, 3.0 eq.), DIPEA (10.2 mL, 58.3 mmol, 6.0 eq.), and HATU (7.38 g, 19.4 mmol, 2.0 eq.) were added sequentially. The reaction was stirred at 25 °C for 8 h and quenched by saturated *aq.* NH<sub>4</sub>Cl, extracted with EtOAc three times. The organic layers were combined and washed with saturated *aq.* NaHCO<sub>3</sub>. Organic layers were concentrated under reduced pressure to give the crude **51**. The crude **51** was dissolved in DCM (100 mL, 0.1 M), 4.0 M HCl in 1,4-dioxane (25 mL, 0.4 M) was added. The reaction was stirred at 25 °C for 1 h. The solvent was removed under reduced pressure to give the crude. The crude was dissolved in DMF (50 mL, 0.2 M), and compound **30** (7.38 g, 19.4 mmol, 2.0 eq.), DIPEA (10.2 mL, 58.3 mmol, 6.0 eq.), and HATU (7.38 g, 19.4 mmol, 2.0 eq.) were added sequentially. The reaction was stirred at 25 °C for 8 h and quenched by saturated *aq.* NH<sub>4</sub>Cl, extracted with EtOAc three times. The organic layers were combined and washed with saturated *aq.* NaHCO<sub>3</sub>. Organic layers were concentrated under reduced pressure to give the crude **52**. The crude was dissolved in EtOH (100 mL, 0.1 M) and H<sub>2</sub>O (50 mL, 0.2 M). Iron powder (5.42 g, 97.1 mmol, 10 equiv) was added, and the solution was heated at 50 °C. After 8 h, the mixture was filtered through a pad of Celite®, washed with DCM:MeOH 10:1, and neutralized with saturated aqueous NaHCO<sub>3</sub>. The solution was extracted with DCM:MeOH 10:1 (3 x 500 mL). The extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude was purified via flash column chromatography (DCM:MeOH 1:0 to 20:1) to afford aniline **S15** (7.99 g, 94% yield from **49**).

### Compound S15

**<sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD, 60 °C):** δ 7.31 (d, *J* = 8.2 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.94 (d, *J* = 2.1 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.67 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.63 (dd, *J* = 8.6, 5.4 Hz, 1H), 4.38 (dt, *J* = 9.2, 4.5 Hz, 1H), 4.26 (q, *J* = 7.0 Hz, 1H), 4.13 (dd, *J* = 8.9, 4.8 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.11 (dd, *J* = 14.1, 5.4 Hz, 1H), 2.96 (dd, *J* = 14.1, 8.7 Hz, 1H), 2.70 (dd, *J* = 17.2, 4.7 Hz, 1H), 2.57 (dd, *J* = 17.1, 8.9 Hz, 1H), 1.58 (tt, *J* = 8.0, 5.5 Hz, 2H), 1.43 (s, 9H), 1.33 (d, *J* = 7.1 Hz, 1H), 1.25 (d, *J* = 7.2 Hz, 3H), 0.98 – 0.94 (m, 9H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.59 – 0.50 (m, 6H).

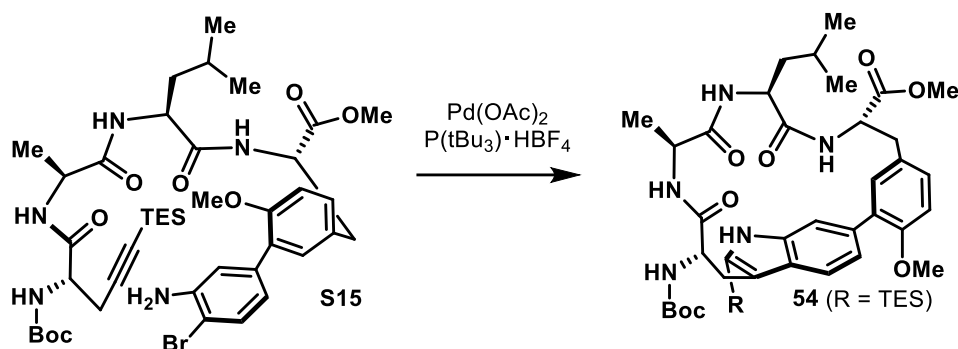
**<sup>13</sup>C NMR (151 MHz, CD<sub>3</sub>OD, 60 °C):** δ 173.22, 173.12, 172.01, 171.79, 156.54, 155.51, 144.63, 138.86, 131.37, 131.01, 129.96, 129.21, 128.89, 120.12, 116.98, 111.46, 107.26, 103.28, 79.68, 54.83, 53.96, 53.88, 51.76, 51.45, 49.28, 40.64, 36.10, 27.42, 24.46, 22.58, 22.06, 20.70, 16.86, 6.55, 4.03.

**HRMS (ESI-TOF):** calculated for C<sub>42</sub>H<sub>63</sub>BrN<sub>5</sub>O<sub>8</sub>Si<sup>+</sup> [M+H]<sup>+</sup>: 872.3629, found: 872.3625.

**TLC:** R<sub>f</sub> = 0.4 (2:1 Acetone : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sub>D</sub><sup>21</sup>:** –143.5 (*c* = 1.0, CHCl<sub>3</sub>)

Note: Due to rotamerism at room temperature, NMR spectra for structural assignment were recorded at 60 °C in CD<sub>3</sub>OD. However, even at this elevated temperature, the rotamers remained partially unresolved.



A round-bottom flask was charged with a magnetic stirring bar, compound **S15** (8.06 g, 9.20 mmol, 1.0 equiv.), Pd(OAc)<sub>2</sub> (1.04 g, 4.62 mmol, 0.5 equiv.), *t*Bu<sub>3</sub>P·HBF<sub>4</sub> (2.68 g, 9.20 mmol, 1.0 equiv.), and DIPEA (16 mL, 92.5 mmol, 10.0 equiv.), purged with N<sub>2</sub> three times. The reaction mixture was stirred at 110 °C under nitrogen for 12 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography (EtOAc:hexane 3:1 to 9:1) to give the compound **54** (5.76 g, 79% yield).

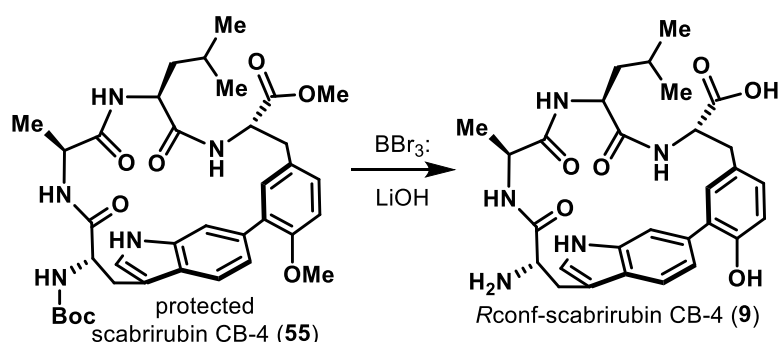
#### Compound 54

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.03 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.55 (s, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.04 – 6.85 (m, 3H), 6.36 (d, *J* = 7.9 Hz, 1H), 5.89 (d, *J* = 5.4 Hz, 1H), 5.43 (s, 1H), 5.32 (d, *J* = 7.9 Hz, 1H), 4.77 (ddd, *J* = 7.9, 6.1, 4.3 Hz, 1H), 4.39 (d, *J* = 39.5 Hz, 2H), 4.05 (d, *J* = 6.6 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.43 (dd, *J* = 14.1, 3.7 Hz, 1H), 3.28 – 3.13 (m, 2H), 2.97 (dd, *J* = 13.0, 6.6 Hz, 1H), 1.47 (s, 9H), 1.48 – 1.39 (m, 11H), 1.33 – 1.23 (m, 1H), 0.98 (q, *J* = 9.8 Hz, 6H), 0.94 – 0.88 (m, 6H), 0.73 (d, *J* = 6.1 Hz, 3H).  
**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** δ 171.32, 170.98, 170.35, 170.21, 154.66, 137.78, 134.42, 132.65, 132.44, 130.60, 129.63, 127.41, 126.77, 120.23, 119.53, 119.13, 114.94, 111.32, 110.90, 79.27, 55.12, 52.65, 51.94, 51.35, 48.94, 39.80, 35.98, 28.41, 27.67, 23.87, 22.35, 20.88, 16.49, 6.82, 3.00.

**HRMS (ESI-TOF):** calculated for C<sub>42</sub>H<sub>61</sub>N<sub>5</sub>NaO<sub>8</sub>Si<sup>+</sup> [M+Na]<sup>+</sup>: 814.4187, found: 814.4182.

**TLC:** R<sub>f</sub> = 0.6 (2:1 Acetone : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sub>D</sub><sup>21</sup>:** –41.2 (*c* = 1.0, CHCl<sub>3</sub>)



Compound **55** (100 mg, 0.123 mmol, 1.0 equiv.) was dissolved in DCM (2.5 mL, 0.05 M), 1.8 mL of BBr<sub>3</sub> (1M in DCM, 1.8 mmol, 15 eq.) was added dropwise at 0 °C under N<sub>2</sub>, the reaction was stirred at 25 °C. After 2h. the reaction was quenched by dropwise addition of MeOH (10 mL) at 0 °C, then it was concentrated under reduced pressure to give the residue. The residue was dissolved in THF/H<sub>2</sub>O/MeOH = 1:1:1 (3.0 mL, 0.03 M),

LiOH (155 mg, 3.68 mmol, 30 eq.) was added. The reaction was stirred at 25 °C for 2 h, acidified with 0.5 M HCl to adjust the pH = 3, the solvents were removed under reduced pressure, and the residue was purified by C18 silica gel (MeOH:H<sub>2</sub>O:TFA 10:90:1 to 75:25:1) to give the title compound **9** (49.9 mg, 74% yield).

### Compound **9**

**<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):** δ 10.88 (d, *J* = 2.4 Hz, 1H), 9.33 (s, 1H), 8.39 (s, 2H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.66 (d, *J* = 1.4 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.37 (d, *J* = 2.3 Hz, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.14 (dd, *J* = 8.3, 1.5 Hz, 1H), 6.91 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.51 (d, *J* = 7.7 Hz, 1H), 4.36 (ddd, *J* = 11.5, 8.4, 3.3 Hz, 1H), 4.08 (ddt, *J* = 11.6, 6.8, 4.6 Hz, 2H), 3.83 (dd, *J* = 10.1, 3.7 Hz, 1H), 3.24 (dd, *J* = 13.7, 10.9 Hz, 1H), 3.13 (dd, *J* = 13.8, 3.9 Hz, 1H), 2.99 (dd, *J* = 14.7, 3.3 Hz, 1H), 2.94 – 2.84 (m, 1H), 1.35 – 1.25 (m, 1H), 1.20 – 1.14 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.97 – 0.89 (m, 1H), 0.77 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.5 Hz, 3H).

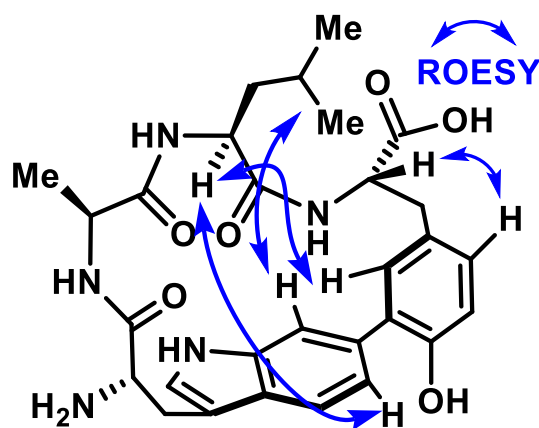
**<sup>13</sup>C NMR (151 MHz, DMSO-*d*<sub>6</sub>):** δ 171.32, 170.98, 170.35, 170.21, 154.66, 137.78, 134.42, 132.65, 132.44, 130.60, 129.63, 127.41, 126.77, 120.23, 119.53, 119.13, 114.94, 111.32, 110.90, 79.27, 55.12, 52.65, 51.94, 51.35, 48.94, 39.80, 35.98, 28.41, 27.67, 23.87, 22.35, 20.88, 16.49, 6.82, 3.00.

**HRMS (ESI-TOF):** calculated for C<sub>29</sub>H<sub>36</sub>N<sub>5</sub>O<sub>6</sub><sup>+</sup> [M+H]<sup>+</sup>: 550.2666, found: 550.2671.

**TLC:** R<sub>f</sub> = 0.6 (2:1 Acetone : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

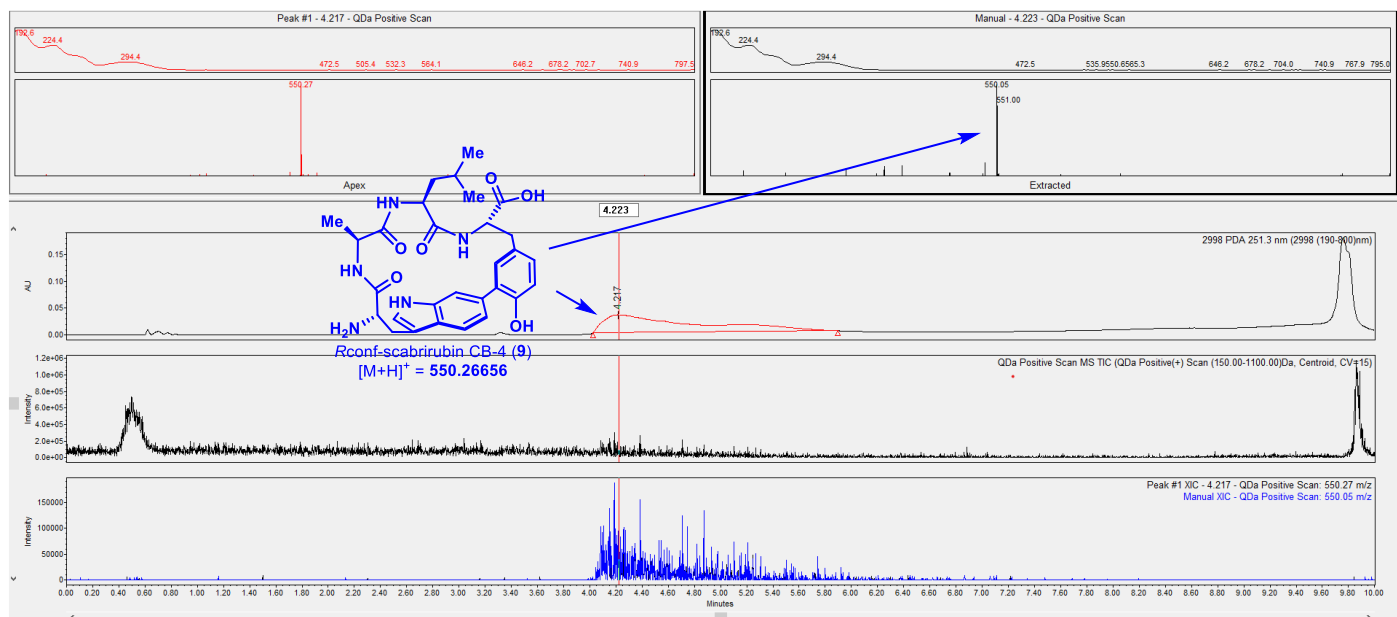
**[α]<sup>25</sup><sub>D</sub>:** -16.2 (*c* = 0.1, MeOH)

### Key NOESY Correlation of *Rconf*-scabrirubin CB-4



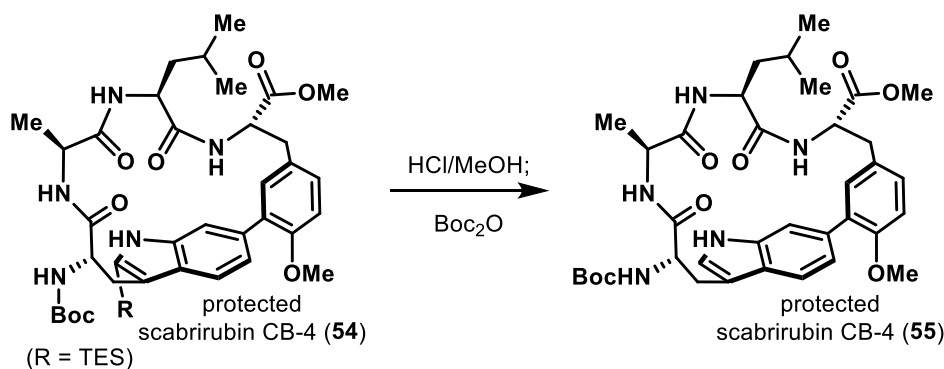
*Rconf*-scabrirubin CB-4 (**9**)  
(DMSO-*d*<sub>6</sub>, ROESY, 400 MHz)

## LC-MS trace of synthetic scabrirubin CB-4



cc

## Skeletal Editing of Scabrirubin CB-4



Compound **54** (1.23 g, 1.55 mmol, 1.0 equiv.) was dissolved in MeOH (14 mL, 0.1 M) and cooled to 0 °C using an ice bath. SO<sub>2</sub>Cl<sub>2</sub> (2mL) was added dropwise at 0 °C, and the reaction was stirred at 0 °C. After 2h. the reaction was directly concentrated under vacuum to give the residue. The residue was dissolved in DCM (15 mL, 0.1 M). Et<sub>3</sub>N (1.1 mL, 7.75 mmol, 5.0 eq.) and Boc<sub>2</sub>O (0.43 mL, 1.86 mmol, 1.2 eq.) were added sequentially. The reaction was stirred at 25 °C for 1h, then quenched with saturated aq. NH<sub>4</sub>Cl, extracted with EtOAc three times. The organic layers were combined and washed with brine. Organic layers were concentrated under reduced pressure to give the crude. The crude was purified by silicagel column chromatography (EtOAc:Hexane 1:3 to 1:3) to give the title compound **55** (982 mg, 94% yield)

### Compound **55**

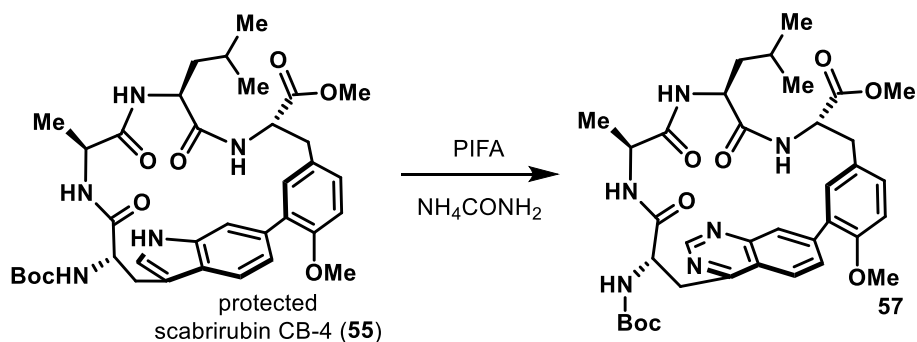
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.54 (s, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.48 (s, 1H), 7.10 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.01 (s, 1H), 6.97 – 6.84 (m, 3H), 6.34 (s, 1H), 6.13 (s, 1H), 5.99 (d, *J* = 5.3 Hz, 1H), 5.34 (s, 1H), 4.78 (dt, *J* = 7.6, 4.8 Hz, 1H), 4.39 (s, 1H), 4.08 (dd, *J* = 13.9, 7.4 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.41 (dd, *J* = 14.4, 3.7 Hz, 1H), 3.26 (dd, *J* = 14.1, 4.7 Hz, 1H), 3.08 (q, *J* = 13.4 Hz, 2H), 1.51 – 1.45 (m, 2H), 1.45 (s, 9H), 1.35 (s, 1H), 1.29 (d, *J* = 6.4 Hz, 3H), 0.80 (d, *J* = 5.8 Hz, 3H), 0.75 (d, *J* = 5.7 Hz, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.96, 170.72, 170.54, 170.02, 154.73, 154.43, 135.73, 134.36, 132.20, 131.07, 127.40, 126.76, 125.61, 123.22, 120.67, 119.18, 111.84, 111.00, 109.34, 79.40, 55.24, 52.75, 51.97, 51.36, 48.48, 40.57, 35.45, 29.08, 27.71, 23.93, 22.10, 21.31, 16.89.

HRMS (ESI-TOF): calculated for  $\text{C}_{36}\text{H}_{47}\text{N}_5\text{NaO}_8^+$   $[\text{M}+\text{Na}]^+$ : 700.3322, found: 700.3319.

TLC:  $R_f$  = 0.4 (2:1 EtOAc : Hexane,  $\text{Ce}_2(\text{SO}_4)_3$  in phosphomolybdic acid).

$[\alpha]^{21}_D$ : -36.9 ( $c$  = 0.1, MeOH)



In a culture tube equipped with a stirring bar, the compound **55** (60 mg, 88.6  $\mu\text{mol}$ , 1.0 eq.) and ammonium carbamate (69.2 mg, 886  $\mu\text{mol}$ , 10.0 equiv) were dissolved in MeOH (1.7 mL, 0.05 M). The resulting solution was cooled to 0  $^\circ\text{C}$ , and then PIFA (152 mg, 354  $\mu\text{mol}$ , 4.0 equiv) was added in one portion. The reaction was stirred at 0  $^\circ\text{C}$  for 1h and quenched with saturated aq.  $\text{Na}_2\text{S}_2\text{O}_3$ . The mixture was extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 9:1) to give the title compound **57** (31.2 mg, 51% yield)

### Compound 57

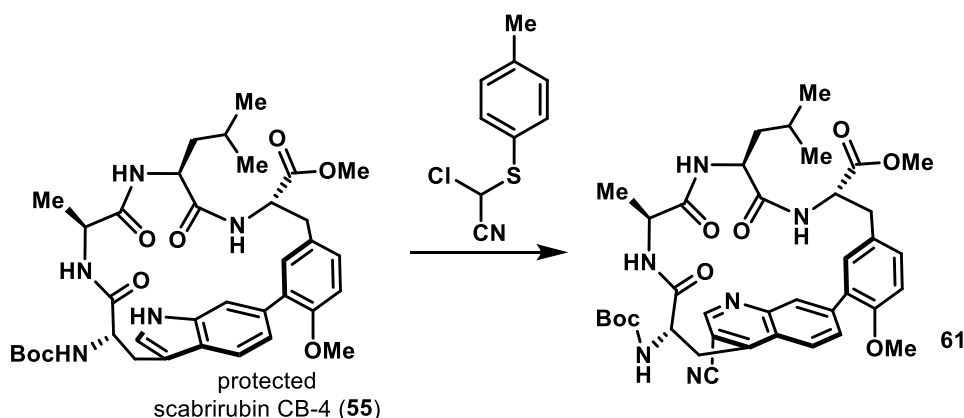
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.23 (s, 1H), 8.15 (s, 1H), 8.13 (s, 1H), 7.72 (d,  $J$  = 8.8 Hz, 1H), 7.09 – 7.04 (m, 1H), 7.05 (d,  $J$  = 7.3 Hz, 1H), 6.95 (d,  $J$  = 8.5 Hz, 1H), 6.36 (s, 1H), 6.13 (s, 1H), 5.97 (s, 1H), 5.75 (s, 1H), 4.80 (t,  $J$  = 7.7 Hz, 1H), 4.58 (s, 1H), 4.13 – 4.03 (m, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.69 – 3.57 (m, 1H), 3.22 (dd,  $J$  = 14.2, 4.4 Hz, 1H), 3.10 (dd,  $J$  = 14.1, 5.4 Hz, 1H), 2.29 – 1.82 (m, 2H), 1.48 – 1.45 (m, 1H), 1.44 (s, 9H), 1.12 (d,  $J$  = 7.1 Hz, 3H), 0.85 (d,  $J$  = 5.8 Hz, 3H), 0.81 (d,  $J$  = 5.8 Hz, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.58, 171.25, 170.27, 170.23, 155.43, 154.36, 154.27, 150.26, 145.17, 145.15, 134.25, 130.46, 129.99, 129.03, 128.85, 127.91, 125.25, 123.27, 111.34, 80.42, 55.65, 53.16, 52.63, 52.21, 49.34, 41.30, 36.11, 29.71, 28.30, 24.65, 22.74, 21.93, 17.36.

HRMS (ESI-TOF): calculated for  $\text{C}_{36}\text{H}_{46}\text{N}_6\text{NaO}_8^+$   $[\text{M}+\text{Na}]^+$ : 713.3275, found: 713.3280.

TLC:  $R_f$  = 0.6 (1:0 EtOAc : Hexane,  $\text{Ce}_2(\text{SO}_4)_3$  in phosphomolybdic acid).

$[\alpha]^{21}_D$ : -40.0 ( $c$  = 0.1,  $\text{CDCl}_3$ )



To a solution of compound **55** (30 mg, 44.3  $\mu\text{mol}$ , 1.0 eq.) and  $\text{Cs}_2\text{CO}_3$  (50.5 mg, 155  $\mu\text{mol}$ , 3.5 eq.) in THF (1 mL, 0.05 M), 2-chloro-2-(p-tolylthio)acetonitrile (13.1 mg, 66.5  $\mu\text{mol}$ , 1.5 eq.) was added portion-wise (0.5 equiv. every 1 h) at room temperature, and the resulting mixture was stirred for next 4 h. The reaction was quenched with saturated aq.  $\text{Na}_2\text{S}_2\text{O}_3$ , extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 3:1) to give the title compound **61** (16.1 mg, 51% yield)

### Compound 61

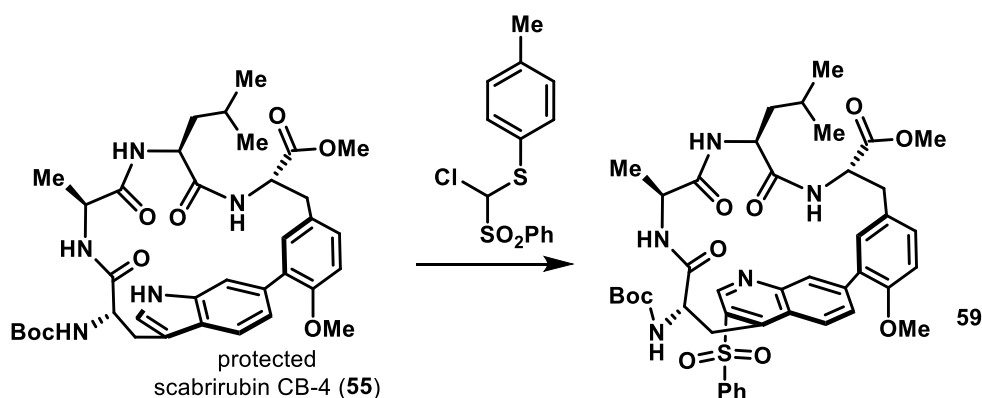
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.91 (s, 1H), 8.27 (s, 1H), 8.22 (d,  $J = 8.6$  Hz, 1H), 7.80 (d,  $J = 8.5$  Hz, 1H), 7.32 (s, 1H), 7.03 (d,  $J = 8.2$  Hz, 1H), 6.95 (d,  $J = 8.3$  Hz, 1H), 6.13 (d,  $J = 19.2$  Hz, 2H), 5.66 (s, 1H), 5.56 (s, 1H), 4.84 (s, 1H), 4.54 (q,  $J = 9.6$  Hz, 1H), 3.98 (m, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.23 (dd,  $J = 14.6, 5.5$  Hz, 1H), 3.11 (dd,  $J = 14.6, 4.7$  Hz, 1H), 1.48 (s, 11H), 1.26 (s, 1H), 1.13 (d,  $J = 6.7$  Hz, 3H), 0.92 (d,  $J = 5.8$  Hz, 3H), 0.89 (d,  $J = 5.2$  Hz, 3H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):**  $\delta$  171.00, 170.19, 169.53, 168.24, 154.79, 154.59, 149.49, 147.93, 142.67, 134.16, 132.26, 130.74, 130.26, 129.09, 128.51, 126.93, 124.01, 123.95, 116.10, 110.49, 106.34, 86.52, 55.00, 52.57, 52.27, 52.00, 48.05, 40.36, 35.39, 34.32, 27.69, 24.05, 22.14, 21.25, 17.04.

**HRMS (ESI-TOF):** calculated for  $\text{C}_{38}\text{H}_{46}\text{N}_6\text{NaO}_8^+$   $[\text{M}+\text{Na}]^+$ : 737.3275, found: 737.3272.

**TLC:**  $R_f = 0.7$  (3:1 EtOAc : Hexane,  $\text{Ce}_2(\text{SO}_4)_3$  in phosphomolybdic acid).

**$[\alpha]_D^{21}$ :**  $-97.4$  ( $c = 0.5$ ,  $\text{CDCl}_3$ )



To a solution of compound **55** (30 mg, 44.3  $\mu\text{mol}$ , 1.0 eq.) and  $\text{Cs}_2\text{CO}_3$  (50.5 mg, 155  $\mu\text{mol}$ , 3.5 eq.) in THF (1 mL, 0.05 M), (chloro(phenylsulfonyl)methyl)(p-tolyl)sulfane (27.6 mg, 88.6  $\mu\text{mol}$ , 2.0 eq.) was added portion-wise (0.5 equiv. every 1 h) at room temperature, and the resulting mixture was stirred for next 4 h.

The reaction was quenched with saturated aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 3:1) to give the title compound **59** (7.7 mg, 21% yield)

### Compound 59

**<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, 60 °C):** δ 10.35 (s, 1H), 8.46 (d, *J* = 15.4 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.10 (ddd, *J* = 12.2, 8.1, 3.8 Hz, 5H), 6.99 (d, *J* = 8.2 Hz, 1H), 4.61 – 4.51 (m, 1H), 4.30 (q, *J* = 6.5 Hz, 1H), 4.20 (q, *J* = 5.9 Hz, 1H), 3.97 – 3.88 (m, 1H), 3.85 – 3.80 (m, 3H), 3.77 (s, 6H), 3.23 – 3.13 (m, 2H), 3.14 – 3.01 (m, 2H), 1.58 (d, *J* = 5.5 Hz, 2H), 1.48 – 1.44 (m, 10H), 1.02 – 0.98 (m, 3H), 0.88 (d, *J* = 6.3 Hz, 3H), 0.82 (d, *J* = 6.1 Hz, 3H).

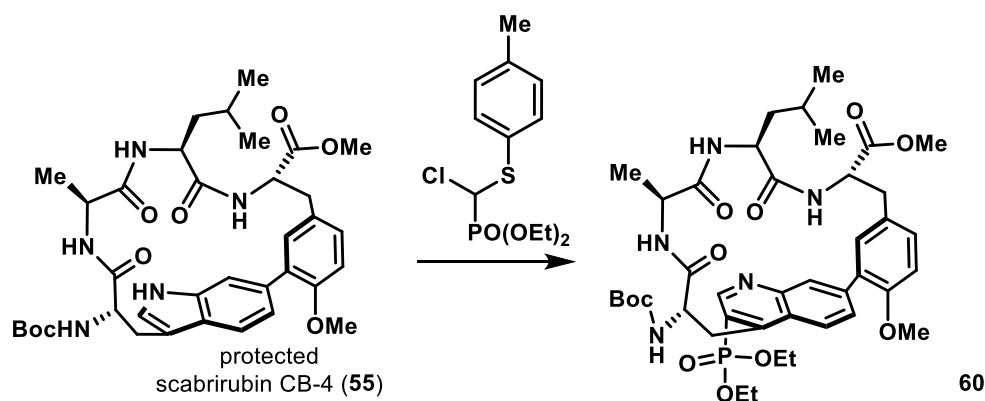
**<sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD, 60 °C):** δ 172.29, 171.41, 171.22, 170.95, 154.63, 147.80, 147.29, 142.68, 136.25, 133.07, 132.64, 132.28, 131.59, 129.53, 128.82, 128.40, 127.92, 127.22, 126.78, 125.69, 125.00, 123.80, 120.02, 118.09, 111.56, 110.57, 110.40, 108.71, 69.34, 54.16, 53.04, 50.84, 50.80, 50.67, 39.77, 39.67, 34.44, 28.72, 26.93, 26.76, 26.64, 23.63, 23.49, 21.45, 21.28, 20.18, 20.01, 15.74.

**HRMS (ESI-TOF):** calculated for C<sub>43</sub>H<sub>51</sub>N<sub>5</sub>NaO<sub>10</sub>S<sup>+</sup> [M+Na]<sup>+</sup>: 852.3254, found: 852.3251.

**TLC:** R<sub>f</sub> = 0.4 (3:1 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>21</sup><sub>D</sub>:** –173.0 (*c* = 0.5, CDCl<sub>3</sub>)

*Note: Due to rotamerism at room temperature, NMR spectra for structural assignment were recorded at 60 °C in CD<sub>3</sub>OD. However, even at this elevated temperature, the rotamers remained partially unresolved. Signals of the major isomer were reported.*



To a solution of compound **55** (30 mg, 44.3 μmol, 1.0 eq.) and Cs<sub>2</sub>CO<sub>3</sub> (50.5 mg, 155 μmol, 3.5 eq.) in THF (1 mL, 0.05 M), diethyl (chloro(p-tolylthio)methyl)phosphonate (27.6 mg, 88.6 μmol, 2.0 eq.) was added portion-wise (0.5 equiv. every 1 h) at room temperature, and the resulting mixture was stirred for next 4 h. The reaction was quenched with saturated aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 10:1) to give the title compound **60** (12.8 mg, 35% yield)

### Compound 60

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 9.16 (d, *J* = 5.3 Hz, 1H), 8.39 (d, *J* = 1.8 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 1H), 7.75 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.04 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.39 (s, 1H), 6.28 (s,

1H), 5.89 (s, 1H), 5.83 (s, 1H), 4.89 (dt,  $J = 8.5, 5.0$  Hz, 1H), 4.39 – 4.04 (m, 9H), 3.89 (s, 3H), 3.81 (s, 3H), 3.24 (dd,  $J = 14.3, 4.4$  Hz, 1H), 3.10 (dd,  $J = 14.3, 5.1$  Hz, 1H), 1.50 – 1.28 (m, 18H), 1.17 (d,  $J = 5.9$  Hz, 3H), 0.90 (d,  $J = 6.2$  Hz, 3H), 0.88 (d,  $J = 6.4$  Hz, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.91, 170.48, 170.47, 170.25, 155.10, 155.00, 151.38, 151.25, 148.52, 141.26, 133.68, 130.46, 129.77, 129.37, 129.06, 128.33, 127.29, 125.03, 110.72, 99.36, 76.60, 62.26, 62.20, 62.13, 62.08, 56.48, 54.96, 52.42, 52.17, 51.94, 48.63, 40.36, 35.79, 31.30, 29.07, 29.03, 28.74, 27.62, 25.60, 24.06, 22.15, 22.07, 21.39, 16.42, 15.81, 15.75, 15.69, 13.50.

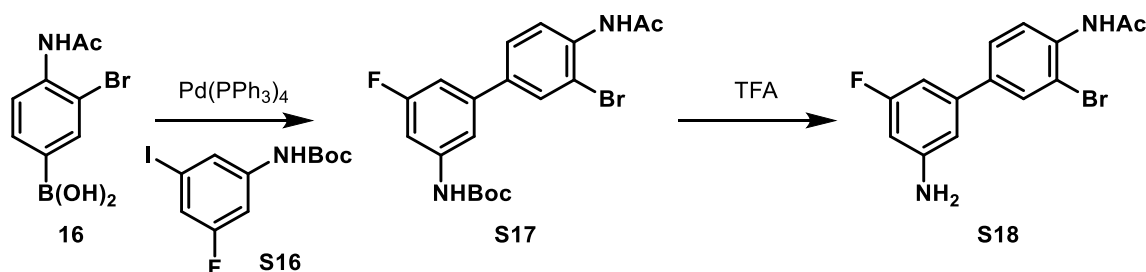
HRMS (ESI-TOF): calculated for  $\text{C}_{41}\text{H}_{56}\text{N}_5\text{NaO}_{11}\text{P}^+$   $[\text{M}+\text{Na}]^+$ : 848.3612, found: 848.3615.

TLC:  $R_f = 0.4$  (10:1 EtOAc : Hexane,  $\text{Ce}_2(\text{SO}_4)_3$  in phosphomolybdic acid).

$[\alpha]_D^{21}$ :  $-40.0$  ( $c = 0.1$ ,  $\text{CDCl}_3$ )

## Substrate Scope of CH arylation

Biaryl iodides correspond to compound **63**, **64**, **66**, and **67** were prepared according to the procedure described previously.<sup>2</sup>



Boronic acid **16** was prepared according to the procedure previously reported by our group.<sup>2</sup> To a solution of compound **16** (8.32 g, 32 mmol, 1.2 eq.) in toluene/ $\text{H}_2\text{O}$ / $\text{EtOH}$  (4:2:1, 140 mL) was added compound **S16** (9.0 g, 26.7 mmol, 1.0 eq.),  $\text{K}_2\text{CO}_3$  (18.5 g, 134 mmol, 5.0 eq.) and  $\text{Pd}(\text{PPh}_3)_4$  (1.54 g, 1.33 mmol, 0.05 eq.). The reaction was stirred at 80 °C under nitrogen atmosphere for 6 h, checked by LC-MS, then it was cooled to 25 °C and diluted with water, extracted with EtOAc for three times and the organic layers were combined, washed with saturated *aq.* NaCl, over  $\text{Na}_2\text{SO}_4$ , and removed under reduced pressure to give the residue, the residue was purified by silica gel chromatography to give compound **S17** (11.3 g, 42% yield). To a solution of compound **S17** (4.74 g, 11.2 mmol, 1.0 eq.) in DCM (50 mL) was added TFA (11.2 mL), the reaction was stirred at 25 °C for 3 h, the solvent and excess TFA were removed under reduced pressure, quenched by saturated *aq.*  $\text{NaHCO}_3$ , extracted with DCM/ $\text{MeOH}$  (10:1) for three times, over  $\text{Na}_2\text{SO}_4$ , and removed under reduced pressure to give the compound **S18** in quantitative yield.

## Compound S9

Physical State: yellow oil

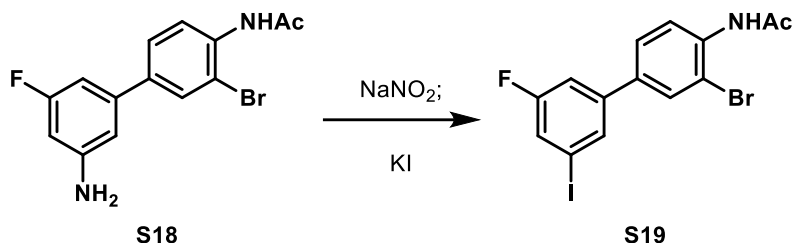
$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.29 (d,  $J = 8.2$  Hz, 1H), 7.65 (m, 2H), 7.39 (m, 1H), 6.55 (m, 2H), 6.32 (dd,  $J = 10.4, 2.1$  Hz, 1H), 3.92 (br, 2H), 2.22 (s, 3H).

$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.51, 164.24 (d,  $J = 243.3$  Hz), 148.69 (d,  $J = 11.5$  Hz), 141.84 (d,  $J = 9.9$  Hz), 137.49, 135.22, 130.51, 126.85, 122.13, 113.75, 109.09, 103.75 (d,  $J = 22.8$  Hz), 101.22 (d,  $J = 24.8$  Hz), 24.90.

$^{19}\text{F}$  NMR (565 MHz,  $\text{CDCl}_3$ ):  $\delta$  -112.56.

HRMS (ESI-TOF): calculated for  $\text{C}_{14}\text{H}_{13}\text{BrFN}_2\text{O}^+$   $[\text{M}+\text{H}]^+$ : 323.0190, found: 323.0196.

TLC:  $R_f = 0.7$  (1:1 EtOAc : Hexane,  $\text{Ce}_2(\text{SO}_4)_3$  in phosphomolybdic acid).



To a solution of the compound **S18** (3.6 g, 11.2 mmol, 1.0 eq.) in MeCN (100 mL) at 0 °C was added *p*TsOH·H<sub>2</sub>O (8.51 g, 44.7 mmol, 4.0 eq.), NaNO<sub>2</sub> (1.0 g, 14.5 mmol, 1.3 eq.) in H<sub>2</sub>O (20 mL) sequentially. The reaction was stirred at 25 °C for 3 h, then the KI (12.1 g, 72.7 mmol, 6.5 eq.) in H<sub>2</sub>O (20 mL) was added dropwise at 0 °C, the reaction was stirred at 25 °C for 12 h, checked by LC-MS, quenched by saturated *aq.* NaHCO<sub>3</sub> and saturated *aq.* Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, extracted with EtOAc for three times, the organic layers were combined, washed with saturated *aq.* NaCl and removed under reduced pressure to give the residue, the residue was purified by silica gel chromatography to give compound **S19** (2.7 g, 56%).

### Compound S19

**Physical State:** white solid

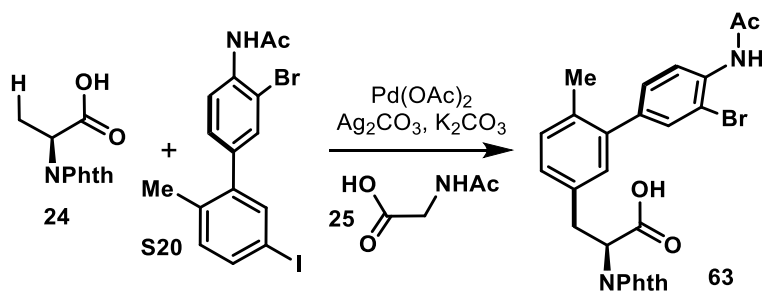
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 8.43 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 2.1 Hz, 1H), 7.65 (t, *J* = 1.4 Hz, 2H), 7.46 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.40 (ddd, *J* = 7.7, 2.2, 1.5 Hz, 1H), 7.18 (m, 1H), 2.26 (s, 3H).

**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>):** δ 168.37, 162.65 (d, *J* = 252.0 Hz), 142.91 (d, *J* = 7.9 Hz), 135.94, 135.27, 131.81 (d, *J* = 2.6 Hz), 130.58, 127.08, 123.88 (d, *J* = 23.7 Hz), 121.98, 113.68, 113.54, 94.11 (d, *J* = 8.6 Hz), 25.02.

**<sup>19</sup>F NMR (565 MHz, CDCl<sub>3</sub>):** δ -110.28.

**HRMS (ESI-TOF):** calculated for C<sub>14</sub>H<sub>11</sub>BrFINO<sup>+</sup> [M+H]<sup>+</sup>: 433.9047, found: 433.9056.

**TLC:** R<sub>f</sub> = 0.3 (1:5 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).



On 0.2 mmol scale, **General Procedure A** was followed with aryl iodide **S20**. Purification by preparative thin-layer chromatography (MeOH:EtOAc 1:20) gave the title compound **63**. (41.7 mg, 40% yield)

### Compound 63

**Physical State:** yellow oil

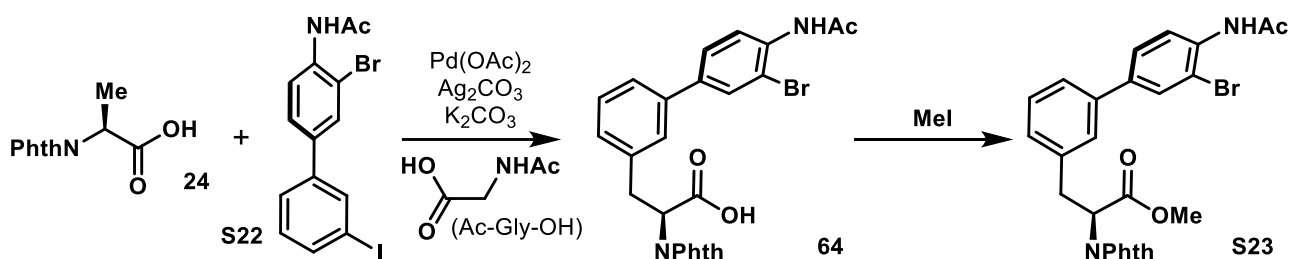
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 8.17 (d, *J* = 8.3 Hz, 1H), 7.69 (m, 2H), 7.61 (d, *J* = 5.3 Hz, 3H), 7.13 (s, 1H), 6.99 (t, *J* = 7.3 Hz, 2H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.78 (s, 1H), 4.98 (s, 1H), 3.59 (m, 3H), 2.24 (s, 3H), 2.07 (s, 3H).

**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>):** 168.52, 167.82, 139.80, 138.94, 134.21, 133.73, 132.41, 131.63, 130.76, 130.19, 129.09, 128.28, 123.54, 121.37, 112.85, 29.79, 24.94, 20.01.

**HRMS (ESI-TOF):** calculated for C<sub>26</sub>H<sub>21</sub>BrN<sub>2</sub>NaO<sub>5</sub><sup>+</sup> [M+Na]<sup>+</sup>: 543.0526, found: 543.0533.

**TLC:** R<sub>f</sub> = 0.2 (10:1 EtOAc : MeOH, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>25</sup><sub>D</sub>:** -99.8 (*c* = 0.1, CHCl<sub>3</sub>)



On 0.2 mmol scale, **General Procedure B** was followed with aryl iodide **S22**. Purification by preparative thin-layer chromatography (EtOAc:Hexane 1:2) gave the title compound **23** (62.2 mg, 82% yield).

### Compound S23

**Physical State:** white solid

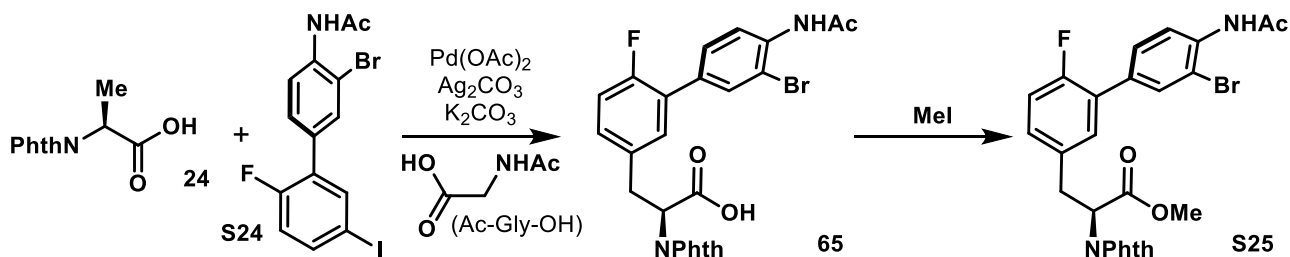
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.30 (d, *J* = 8.6 Hz, 1H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.62 (s, 1H), 7.54 (d, *J* = 2.1 Hz, 1H), 7.35 – 7.22 (m, 4H), 7.17 (dt, *J* = 7.3, 1.7 Hz, 1H), 5.20 (dd, *J* = 11.1, 5.4 Hz, 1H), 3.80 (s, 3H), 3.69 – 3.54 (m, 2H), 2.25 (s, 3H).

**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** δ 169.27, 167.45, 139.37, 137.45, 134.26, 131.54, 130.43, 129.19, 128.21, 127.36, 126.91, 125.50, 123.56, 121.88, 53.17, 52.99, 34.65.

**HRMS (ESI-TOF):** calculated for C<sub>26</sub>H<sub>21</sub>BrN<sub>2</sub>NaO<sub>5</sub><sup>+</sup> [M+Na]<sup>+</sup>: 543.0532, found: 543.0528.

**TLC:** R<sub>f</sub> = 0.5 (1:1 EtOAc:Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>21</sup><sub>D</sub>:** -106.7 (*c* = 1.0, CHCl<sub>3</sub>)



On 0.2 mmol scale, **General Procedure B** was followed with aryl iodide **S24**. Purification by preparative thin-layer chromatography (EtOAc:Hexane 1:2) gave the title compound **S25** (56.0 mg, 76% yield).

### Compound S25

**Physical State:** white solid

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.32 (d, *J* = 8.5 Hz, 1H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.64 (s, 1H), 7.55 – 7.40 (m, 1H), 7.25 (d, *J* = 9.2 Hz, 1H), 7.21 – 7.06 (m, 2H), 6.97 (dd, *J* = 10.4, 8.1 Hz, 1H), 5.15 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.79 (s, 3H), 3.67 – 3.49 (m, 2H), 2.25 (s, 3H).

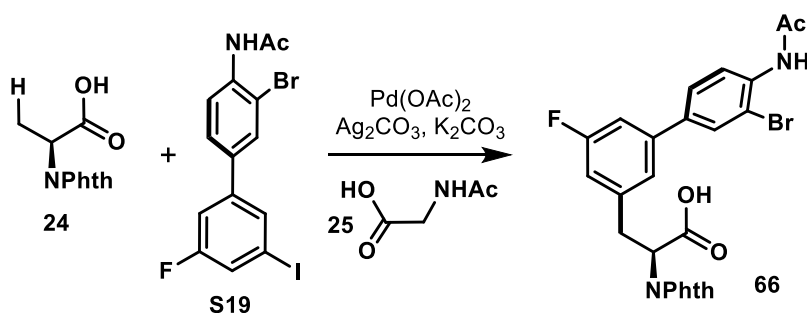
**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** δ 168.48, 166.80, 159.18, 156.71, 134.46, 133.74, 132.33, 131.68 (d, *J* = 6.7 Hz), 131.62, 130.82, 130.14 (d, *J* = 3.5 Hz), 129.17 (d, *J* = 8.5 Hz), 128.21 (d, *J* = 3.0 Hz), 123.00, 120.78, 115.81 (d, *J* = 22.9 Hz), 52.46, 52.39, 33.28, 24.31.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -120.45.

**HRMS (ESI-TOF):** calculated for C<sub>26</sub>H<sub>20</sub>BrFN<sub>2</sub>NaO<sub>5</sub><sup>+</sup> [*M*+Na]<sup>+</sup>: 561.0437, found: 561.0436.

**TLC:** R<sub>f</sub> = 0.5 (1:1 EtOAc:Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sub>D</sub><sup>21</sup>:** -78.4 (*c* = 1.0, CHCl<sub>3</sub>)



On 0.2 mmol scale, **General Procedure A** was followed with aryl iodide **S19**. Purification by preparative thin-layer chromatography (MeOH:EtOAc 1:20) gave the title compound **66** (68.1 mg, 65% yield).

### Compound 66

**Physical State:** yellow oil

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 8.22 (s, 1H), 7.71 (m, 2H), 7.61 (m, 3H), 7.45 (s, 1H), 7.21 (d, *J* = 7.4 Hz, 1H), 7.00 (s, 1H), 6.92 (d, *J* = 9.4 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.12 (m, 2H), 3.48 (m, 2H), 2.23 (s, 3H).

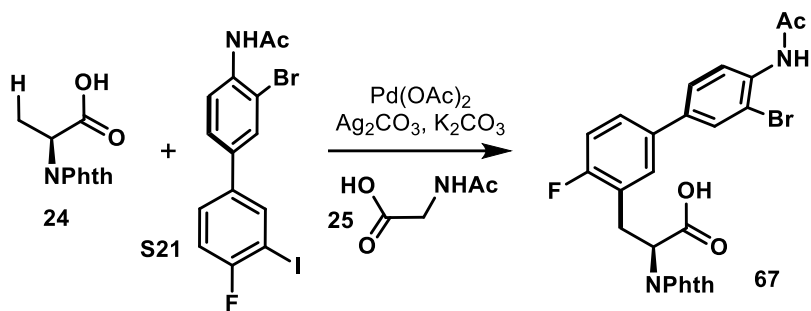
**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>):** 172.91, 168.80, 167.72, 163.10 (d, *J* = 246.9 Hz), 141.29, 140.19, 136.80, 135.17, 134.38, 131.50, 130.46, 126.91, 123.65, 123.05, 122.11, 115.11 (d, *J* = 21.5 Hz), 113.71, 112.36 (d, *J* = 22.6 Hz), 53.20, 34.57, 24.90.

**HRMS (ESI-TOF):** calculated for C<sub>25</sub>H<sub>18</sub>BrFN<sub>2</sub>NaO<sub>5</sub><sup>+</sup> [*M*+Na]<sup>+</sup>: 547.0275, found: 547.0282.

**<sup>19</sup>F NMR (565 MHz, CDCl<sub>3</sub>):** δ -112.332.

**TLC:** R<sub>f</sub> = 0.2 (10:1 EtOAc Methanol, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sub>D</sub><sup>25</sup>:** -43.4 (*c* = 0.1, CHCl<sub>3</sub>)



On 0.2 mmol scale, **General Procedure A** was followed with aryl iodide **S21**. Purification by preparative thin-layer chromatography (MeOH:EtOAc 1:20) gave the title compound **67** (10.0 mg, 19% yield).

### Compound 67

**Physical State:** yellow oil

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.21 (d, *J* = 8.4 Hz, 1H), 7.84 (dd, *J* = 5.3, 3.1 Hz, 1H), 7.73 (m, 3H), 7.64 (m, 2H), 7.38 (s, 1H), 7.18 (m, 2H), 6.98 (t, *J* = 9.0 Hz, 1H), 5.18 (d, *J* = 8.3 Hz, 1H), 4.78 (s, 1H), 3.56 (m, 2H), 2.25 (s, 3H).

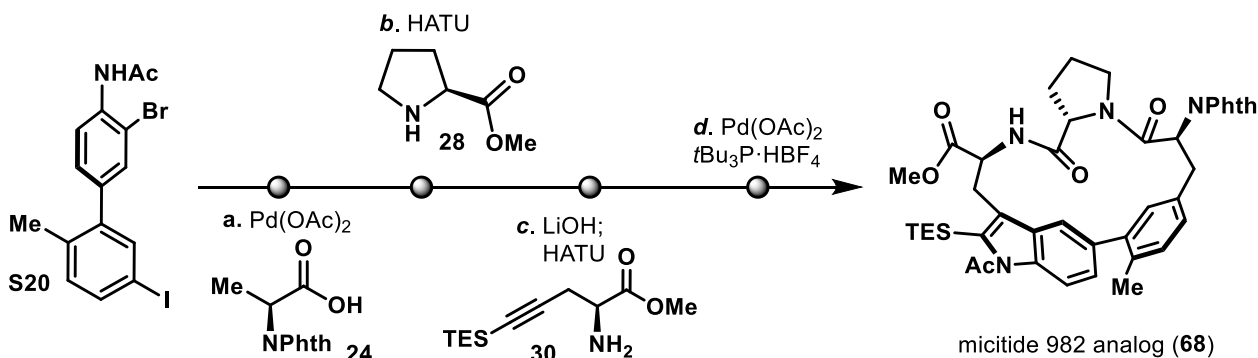
**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** 172.97, 168.65, 167.55, 161.25 (d, *J* = 248.1 Hz), 137.20, 135.31, 134.66, 131.94, 131.56, 130.30, 129.78, 127.42, 126.77, 124.63 (d, *J* = 16.0 Hz), 123.62, 122.09, 115.93 (d, *J* = 22.3 Hz), 113.65, 28.91, 24.89, 15.25.

**HRMS (ESI-TOF):** calculated for C<sub>25</sub>H<sub>18</sub>BrFN<sub>2</sub>NaO<sub>5</sub><sup>+</sup> [M+Na]<sup>+</sup>: 547.0275, found: 547.0282.

**<sup>19</sup>F NMR (565 MHz, CDCl<sub>3</sub>)** δ -119.31.

**TLC:** R<sub>f</sub> = 0.2 (10:1 EtOAc : MeOH, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>25</sup><sub>D</sub>:** -13.0 (*c* = 0.1, CHCl<sub>3</sub>)



On 5.0 mmol scale, **General Procedure A** was followed with aryl iodide **S20**. After completion of the CH arylation, the crude was directly used in the subsequent amide coupling right after the removal of the solvent under vacuum. The crude was dissolved in DMF (50 mL, 0.1 M), then L-Proline methyl ester (2.48 g, 15 mmol, 3.0 eq.), HATU (3.8 g, 10.0 mmol, 2.0 eq.) and DIPEA (4.43 mL, 25.0 mmol, 5.0 eq.) was added, the reaction was stirred at for 2 h. The reaction was quenched by saturated *aq.* NH<sub>4</sub>Cl, extracted with EtOAc for three times. The organic layers were combined, washed with 1N HCl *aq.*, and concentrated under vacuum to give the crude. The crude was dissolved in THF/MeOH/H<sub>2</sub>O = 1:1:1 (50 mL, 0.1 M), and LiOH·H<sub>2</sub>O (1.26 g, 30.0 mmol, 6.0 eq.) was added, the reaction was stirred at 25 °C for 1 h. The reaction was quenched by the addition of 1N HCl *aq.* and extracted with DCM/MeOH = 10:1 for three times. The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum. The crude was then dissolved in DMF (50 mL, 0.1 M), compound **30** (1.33 g, 5.50 mmol, 1.1 eq.), HATU (3.80 g, 10.0 mmol, 2.0 eq.), and DIPEA (1.8

mL, 25.0 mmol, 5.0 eq.) were added sequentially. The reaction was stirred at 25 °C for 1.5 h, quenched by saturated *aq.* NH<sub>4</sub>Cl and extracted with EtOAc three times. The organic layers were combined, washed with 1N HCl *aq.*, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum to give the residue. The residue was filtered through a pad of silicagel (EtOAc:Hexane 2:1) to give the crude. The crude was dissolved in toluene (250 mL, 0.02 M), Pd(OAc)<sub>2</sub> (554 mg, 2.47 mmol, 0.5 eq.), *t*Bu<sub>3</sub>P·HBF<sub>4</sub> (1.43 g, 4.94 mmol, 1.0 eq.) and DIPEA (8.6 mL, 49.4 mmol, 10.0 eq.) was added. The reaction was stirred at 110 °C under nitrogen for 12 h. The solvent was removed under reduced pressure to give the residue, the residue was purified by silica gel chromatography to give the compound **68** (1.31 g, 39% yield from aryl iodide **S20**).

### Compound 68

**Physical State:** colorless solid

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.91 (s, 1H), 7.91 – 7.85 (m, 2H), 7.76 (dd, *J* = 5.5, 2.6 Hz, 2H), 7.70 (s, 1H), 7.60 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 2.2 Hz, 2H), 5.05 (t, *J* = 8.8 Hz, 1H), 4.98 (dd, *J* = 11.7, 2.1 Hz, 1H), 4.45 (dt, *J* = 8.6, 2.4 Hz, 1H), 4.22 (t, *J* = 11.5 Hz, 1H), 3.83 – 3.72 (m, 1H), 3.64 (s, 3H), 3.52 (ddd, *J* = 10.5, 8.2, 3.1 Hz, 1H), 3.28 (d, *J* = 14.7 Hz, 1H), 3.11 (td, *J* = 9.4, 6.8 Hz, 1H), 2.81 (s, 3H), 2.69 (dd, *J* = 12.5, 2.1 Hz, 1H), 2.47 (s, 3H), 2.18 – 1.89 (m, 3H), 1.66 – 1.49 (m, 1H), 0.96 – 0.76 (m, 15H).

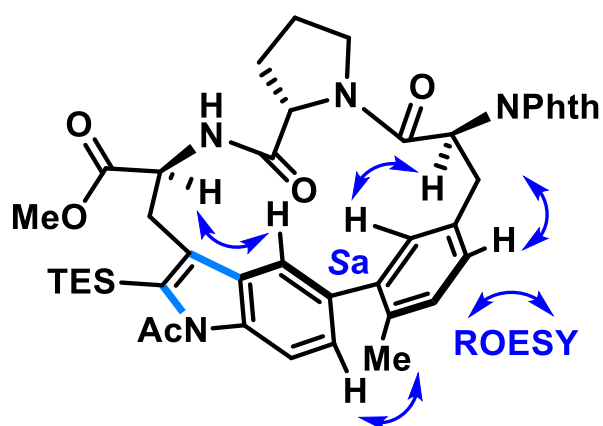
**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** δ 172.74, 170.98, 169.43, 167.10, 165.76, 139.78, 136.37, 136.19, 136.03, 135.09, 134.45, 134.17, 133.39, 133.00, 131.54, 131.40, 131.05, 128.08, 125.60, 123.67, 122.83, 112.57, 61.10, 54.41, 52.23, 52.03, 46.99, 36.21, 31.03, 29.05, 26.52, 25.01, 20.94, 8.20, 6.05.

**HRMS (ESI-TOF):** calculated for C<sub>43</sub>H<sub>48</sub>N<sub>4</sub>NaO<sub>7</sub>Si<sup>+</sup> [*M*+Na]<sup>+</sup>: 783.3190 found: 783.3187.

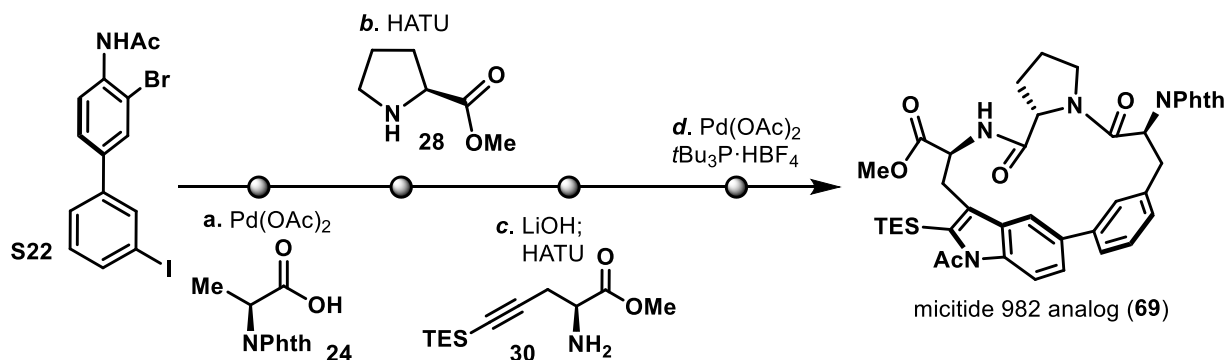
**TLC:** R<sub>f</sub> = 0.5 (2:1 EtOAc:Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>21</sup><sub>D</sub>:** +50.9 (*c* = 1.0, CHCl<sub>3</sub>)

### Key ROESY Correlations of Compound 68



**68** (CDCl<sub>3</sub>, 400 MHz)



On 4.0 mmol scale, **General Procedure A** was followed with aryl iodide **S22**. After completion of the CH arylation, the crude was directly used in the subsequent amide coupling right after the removal of the solvent under vacuum. The crude was dissolved in DMF (40 mL, 0.1 M), then L-Proline methyl ester (1.98 g, 12 mmol, 3.0 eq.), HATU (3.04 g, 8.00 mmol, 2.0 eq.) and DIPEA (3.5 mL, 20 mmol, 5.0 eq.) was added, the reaction was stirred at for 2 h. The reaction was quenched by saturated *aq.* NH<sub>4</sub>Cl, extracted with EtOAc for three times. The organic layers were combined, washed with 1N HCl *aq.*, and concentrated under vacuum to give the crude. The crude was dissolved in THF/MeOH/H<sub>2</sub>O = 1:1:1 (40 mL, 0.1 M), and LiOH·H<sub>2</sub>O (1.01 g, 24.0 mmol, 6.0 eq.) was added, the reaction was stirred at 25 °C for 1 h. The reaction was quenched by the addition of 1N HCl *aq.* and extracted with DCM/MeOH = 10:1 for three times. The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum. The crude was then dissolved in DMF (40 mL, 0.1 M), compound **30** (1.06 g, 4.40 mmol, 1.1 eq.), HATU (3.04 g, 8.00 mmol, 2.0 eq.), and DIPEA (3.5 mL, 20.0 mmol, 5.0 eq.) were added sequentially. The reaction was stirred at 25 °C for 1.5 h, quenched by saturated *aq.* NH<sub>4</sub>Cl and extracted with EtOAc three times. The organic layers were combined, washed with 1N HCl *aq.*, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum to give the residue. The residue was filtered through a pad of silicagel (EtOAc:Hexane 2:1) to give the crude. The crude was dissolved in toluene (200 mL, 0.02 M), Pd(OAc)<sub>2</sub> (450 mg, 2.01 mmol, 0.50 eq.), *t*Bu<sub>3</sub>P·HBF<sub>4</sub> (1.16 g, 4.01 mmol, 1.0 eq.) and DIPEA (7.0 mL, 40.1 mmol, 10 eq.) was added. The reaction was stirred at 110 °C under nitrogen for 12 h. The solvent was removed under reduced pressure to give the residue, the residue was purified by silica gel chromatography to give the compound **69** (810 mg, 30% yield from aryl iodide **69**).

## Compound 69

**Physical State:** white solid

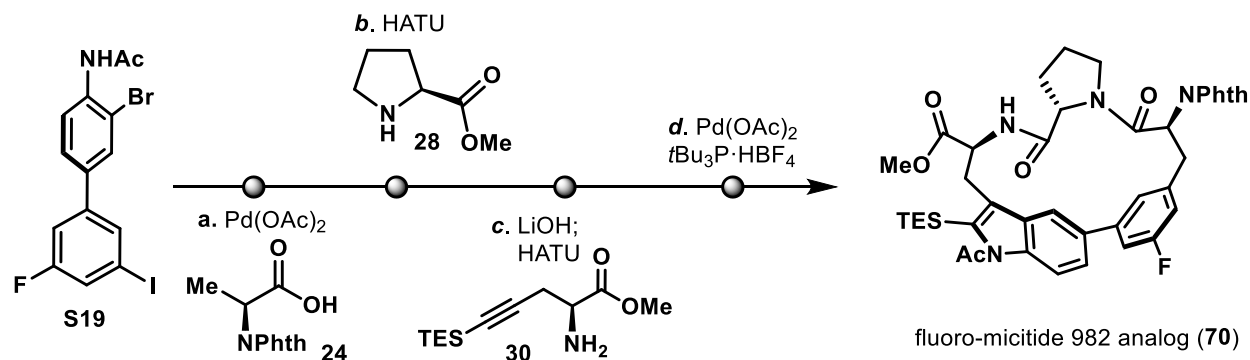
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.35 (s, 1H), 7.88 (m, 2H), 7.77 (m, 2H), 7.69 – 7.54 (m, 4H), 7.40 (brs, 1H), 7.27 (m, 1H), 5.02 (d, *J* = 11.5 Hz, 1H), 4.95 (t, *J* = 10.5 Hz, 1H), 4.57 (d, *J* = 8.1 Hz, 1H), 4.39 (t, *J* = 12.3 Hz, 1H), 3.77 (brs, 1H), 3.63 (s, 3H), 3.31 (d, *J* = 14.8 Hz, 1H), 3.07 (s, 1H), 2.78 (s, 3H), 2.66 (d, *J* = 12.6 Hz, 1H), 2.27 – 1.97 (m, 2H), 1.77 (s, 1H), 1.39 – 1.08 (m, 2H), 0.84 – 0.60 (m, 15H).

**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** δ 172.17, 170.50, 168.74, 166.34, 165.23, 139.06, 137.32, 135.84, 134.66, 133.83, 132.53, 130.90, 130.85, 129.94, 128.24, 127.62, 124.17, 123.06, 122.10, 118.72, 113.34, 60.50, 53.33, 51.75, 51.60, 46.36, 36.02, 29.98, 28.62, 25.91, 24.29, 7.45, 5.28.

**HRMS (ESI-TOF):** calculated for C<sub>42</sub>H<sub>46</sub>N<sub>4</sub>NaO<sub>7</sub>Si<sup>+</sup> [M+Na]<sup>+</sup>: 769.3033, found: 769.3033.

**TLC:** R<sub>f</sub> = 0.5 (2:1 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sub>D</sub><sup>21</sup>:** +77.3 (*c* = 1.0, CHCl<sub>3</sub>)



On 5.0 mmol scale, **General Procedure A** was followed with aryl iodide **S19**. After completion of the CH arylation, the crude was directly used in the subsequent amide coupling right after the removal of the solvent under vacuum. The crude was dissolved in DMF (50 mL, 0.1 M), then L-Proline methyl ester (2.48 g, 15 mmol, 3.0 eq.), HATU (3.8 g, 10.0 mmol, 2.0 eq.) and DIPEA (4.43 mL, 25.0 mmol, 5.0 eq.) was added, the reaction was stirred at for 2 h. The reaction was quenched by saturated *aq.* NH<sub>4</sub>Cl, extracted with EtOAc for three times. The organic layers were combined, washed with 1N HCl *aq.*, and concentrated under vacuum to give the crude. The crude was dissolved in THF/MeOH/H<sub>2</sub>O = 1:1:1 (50 mL, 0.1 M), and LiOH·H<sub>2</sub>O (1.26 g, 30.0 mmol, 6.0 eq.) was added, the reaction was stirred at 25 °C for 1 h. The reaction was quenched by the addition of 1N HCl *aq.* and extracted with DCM/MeOH = 10:1 for three times. The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum. The crude was then dissolved in DMF (50 mL, 0.1 M), compound **30** (1.33 g, 5.50 mmol, 1.1 eq.), HATU (3.80 g, 10.0 mmol, 2.0 eq.), and DIPEA (1.8 mL, 25.0 mmol, 5.0 eq.) were added sequentially. The reaction was stirred at 25 °C for 1.5 h, quenched by saturated *aq.* NH<sub>4</sub>Cl and extracted with EtOAc three times. The organic layers were combined, washed with 1N HCl *aq.*, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum to give the residue. The residue was filtered through a pad of silicagel (EtOAc:Hexane 2:1) to give the crude. The crude was dissolved in toluene (170 mL, 0.03 M), Pd(OAc)<sub>2</sub> (380 mg, 1.69 mmol, 0.34 eq.), *t*Bu<sub>3</sub>P·HBF<sub>4</sub> (982 mg, 3.38 mmol, 0.68 eq.) and DIPEA (5.9 mL, 33.8 mmol, 6.8 eq.) was added. The reaction was stirred at 110 °C under nitrogen for 12 h. The solvent was removed under reduced pressure to give the residue, the residue was purified by silica gel chromatography to give the compound **70** (897 mg, 23% yield from aryl iodide **S19**).

## Compound 70

**Physical State:** white solid

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 8.14 (s, 1H), 7.86 (m, 4H), 7.75 (m, 2H), 7.57 (m, 2H), 7.27 (d, *J* = 10.2 Hz, 1H), 6.96 (d, *J* = 9.1 Hz, 1H), 5.02 (dd, *J* = 11.5, 1.6 Hz, 1H), 4.95 (t, *J* = 9.1 Hz, 1H), 4.57 (dd, *J* = 8.1, 2.5 Hz, 1H), 4.44 (t, *J* = 12.1 Hz, 1H), 3.76 (m, 1H), 3.64 (m, 1H), 3.61 (s, 3H), 3.29 (d, *J* = 14.5 Hz, 1H), 3.07 (m, 1H), 2.74 (s, 3H), 2.60 (m, 1H), 2.17 (m, 1H), 2.03 (m, 2H), 1.78 (m, 1H), 0.65 (m, 12H), 0.56 (m, 3H).

**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>):** δ 172.82, 170.27 (d, *J* = 261.9 Hz), 166.96, 165.75, 164.19, 162.57, 141.87 (d, *J* = 8.1 Hz), 139.94 (d, *J* = 7.7 Hz), 136.83, 136.68, 134.59, 134.11, 133.22, 131.59, 126.21, 123.78, 122.71, 119.51, 114.83 (d, *J* = 21.3 Hz), 114.10, 111.72 (d, *J* = 22.0 Hz), 61.34, 53.77, 52.37, 52.28, 47.19, 36.48, 30.81, 29.51, 26.59, 24.92, 8.09, 5.85.

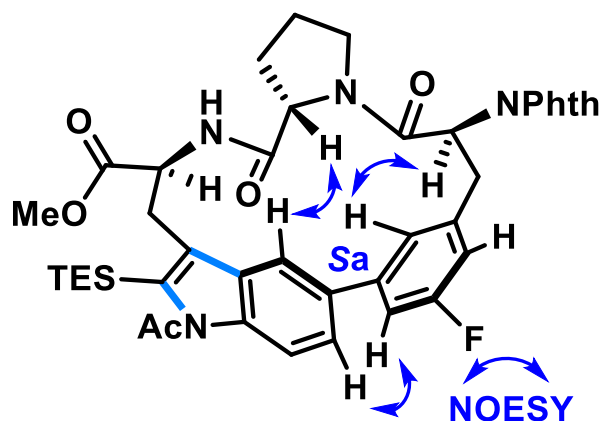
**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -113.96.

**HRMS (ESI-TOF):** calculated for C<sub>42</sub>H<sub>46</sub>BrFN<sub>4</sub>NaO<sub>7</sub>Si<sup>+</sup> [M+Na]<sup>+</sup>: 867.2195, found: 867.2205.

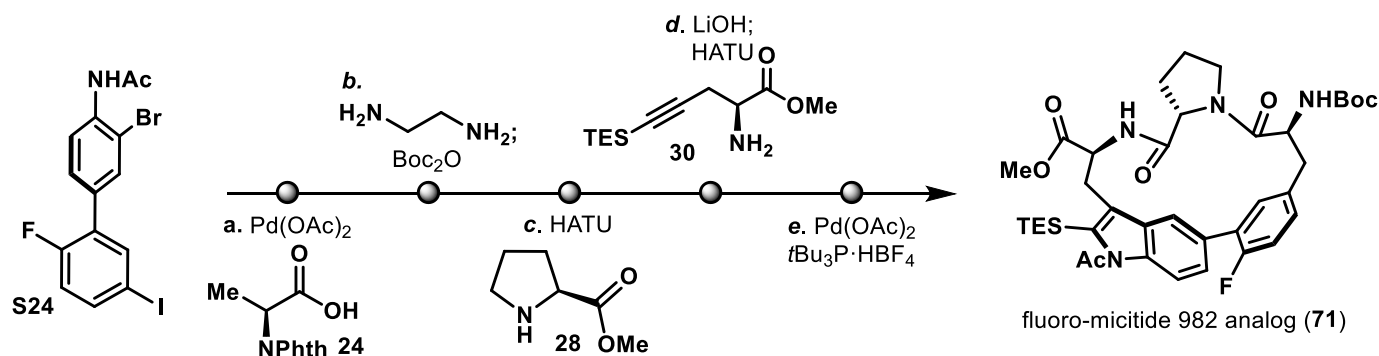
**TLC:** R<sub>f</sub> = 0.7 (7:3 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>25</sup><sub>D</sub>:** -71.6 (*c* = 0.2, CHCl<sub>3</sub>)

## Key ROESY Correlations of Compound 70



70 (CDCl<sub>3</sub>, 600 MHz)



On a 5.0 mmol scale, **General Procedure A** was followed with aryl iodide **S24**. After completion of the CH arylation, the crude was directly used in the subsequent reaction right after the removal of the solvent under vacuum. The crude was dissolved in *n*-BuOH (50 mL, 0.1 M), and ethylenediamine (3.3 mL, 50 mmol, 10.0 eq.) was added. The reaction was stirred at 25 °C for 15 h. The reaction mixture was directly concentrated under reduced pressure to give the crude. The crude was dissolved in THF (50 mL, 0.1 M), saturated *aq.* NaHCO<sub>3</sub> (5 mL, 1.0 M), and (Boc)<sub>2</sub>O (8.0 mL, 35.0 mmol, 7.0 eq.) were added sequentially. The reaction mixture was stirred at 25 °C for 3 h and quenched by 1N HCl *aq.*, extracted with DCM/MeOH = 10:1 three times. The organic layers were combined and washed with saturated *aq.* NaCl, and dried over Na<sub>2</sub>SO<sub>4</sub>. Organic layers were concentrated under reduced pressure and filtered through a pad of silicagel (EtOAc:Hexane 1:10 to 1:0) to give a crude. The crude was dissolved in DMF (50 mL, 0.1 M), then L-Proline methyl ester (2.48 g, 15 mmol, 3.0 eq.), HATU (3.8 g, 10.0 mmol, 2.0 eq.) and DIPEA (4.43 mL, 25.0 mmol, 5.0 eq.) was added, the reaction was stirred at for 2 h. The reaction was quenched by saturated *aq.* NH<sub>4</sub>Cl, extracted with EtOAc for three times. The organic layers were combined, washed with 1N HCl *aq.*, and concentrated under vacuum to give the crude. The crude was dissolved in THF/MeOH/H<sub>2</sub>O = 1:1:1 (50 mL, 0.1 M), and LiOH·H<sub>2</sub>O (1.26 g, 30.0 mmol, 6.0 eq.) was added, the reaction was stirred at 25 °C for 1 h. The reaction was quenched by the addition of 1N HCl *aq.* and extracted with DCM/MeOH = 10:1 for three times. The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum. The crude was then dissolved in DMF (50 mL, 0.1 M), compound **30** (1.33 g, 5.50 mmol, 1.1 eq.), HATU (3.80 g, 10.0 mmol, 2.0 eq.), and DIPEA (1.8 mL, 25.0 mmol, 5.0 eq.) were added sequentially. The reaction was stirred at 25 °C for 2 h, quenched by saturated *aq.* NH<sub>4</sub>Cl and extracted with EtOAc three times. The organic layers were combined, washed with 1N HCl *aq.*, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum to give the residue. The residue was filtered

through a pad of silicagel (EtOAc:Hexane 2:1) to give the crude. The crude was dissolved in toluene (250 mL, 0.02 M), Pd(OAc)<sub>2</sub> (554 mg, 2.47 mmol, 0.5 eq.), *t*Bu<sub>3</sub>P·HBF<sub>4</sub> (1.43 g, 4.94 mmol, 1.0 eq.) and DIPEA (8.6 mL, 49.4 mmol, 10.0 eq.) was added. The reaction was stirred at 110 °C under nitrogen for 12 h. The solvent was removed under reduced pressure to give the residue, the residue was purified by silica gel chromatography to give the compound **71** (1.14 g, 31% yield from aryl iodide **71**). The characteristics data were identical to those previously reported by our group.<sup>2</sup>

## Compound 71

**Physical State:** white solid

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 7.77 – 7.70 (m, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.02 – 6.88 (m, 2H), 5.49 – 5.40 (m, 1H), 4.97 (t, *J* = 9.3 Hz, 1H), 4.85 (t, *J* = 7.4 Hz, 1H), 4.36 (t, *J* = 6.5 Hz, 1H), 3.83 – 3.73 (m, 1H), 3.73 – 3.62 (m, 3H), 3.22 – 3.13 (m, 1H), 3.09 (d, *J* = 13.6 Hz, 1H), 2.97 (d, *J* = 14.4 Hz, 1H), 2.84 (s, 3H), 2.10 (dd, *J* = 12.9, 6.7 Hz, 1H), 1.95 – 1.86 (m, 2H), 1.77 (d, *J* = 12.4 Hz, 1H), 1.32 (s, 9H), 0.92 (dt, *J* = 92.4, 7.3 Hz, 9H), 0.87 (q, *J* = 7.3 Hz, 2H).

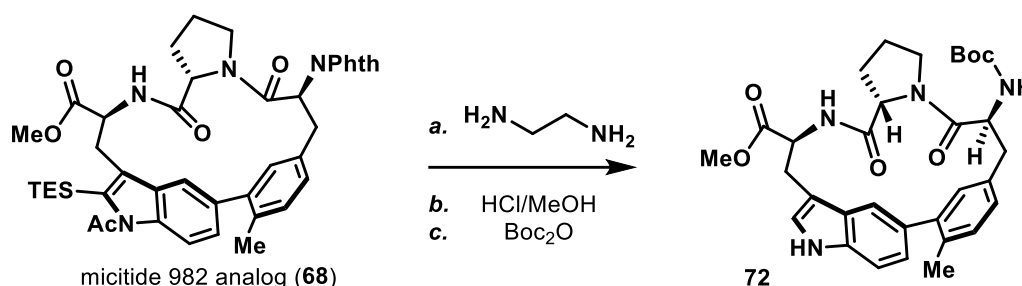
**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>):** δ = 173.52, 171.58, 169.59, 169.49, 159.90, 158.26, 155.46, 136.48, 135.90, 133.39, 132.74, 131.77, 131.38, 131.10, 130.71, 127.51, 127.43, 126.54, 126.49, 120.95, 115.14, 114.99, 113.38, 79.55, 60.14, 52.57, 52.26, 51.35, 47.43, 35.87, 30.08, 29.48, 28.34, 26.62, 26.02, 24.97, 8.25, 6.31.

**<sup>19</sup>F NMR (565 MHz, CDCl<sub>3</sub>):** δ -121.97.

**HRMS (ESI-TOF):** calculated for C<sub>39</sub>H<sub>51</sub>FN<sub>4</sub>NaO<sub>7</sub>Si<sup>+</sup> [M+Na]<sup>+</sup>: 757.3409, found: 757.3405.

**TLC:** R<sub>f</sub> = 0.6 (1:1 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>25</sup><sub>D</sub>:** 51.4 (*c* = 0.2, MeOH)



Compound **68** (840 mg, 1.10 mmol, 1.0 eq.) was dissolved in *n*-BuOH (11 mL, 0.1 M), and ethylenediamine (0.73 mL, 11 mmol, 10 eq.) was added. The reaction was stirred at 25 °C for 15 h. The reaction mixture was diluted with toluene (20 mL) and directly concentrated under reduced pressure to give the crude. The crude was dissolved in MeOH (22 mL, 0.05 M), and SO<sub>2</sub>Cl<sub>2</sub> (4.4 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 25 °C for 2h. Then, the mixture was directly concentrated under reduced pressure to give the crude primary amine. The crude was then dissolved in the THF:saturated *aq.* NaHCO<sub>3</sub> 10:1 (22 mL, 0.05 M). Boc<sub>2</sub>O (1.77 mL, 7.70 mmol, 7 equiv.) was added and the reaction was stirred for 2h at 25 °C. After confirming the full conversion of the primary amine by LC/MS, the reaction was diluted with H<sub>2</sub>O (200 mL) and extracted with EtOAc three times. The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give the crude. The crude was purified by flash column chromatography (EtOAc:Hexane 1:4 to 4:1) to give the compound **72** (630 mg, 99% yield).

## Compound 72

**Physical State:** white solid

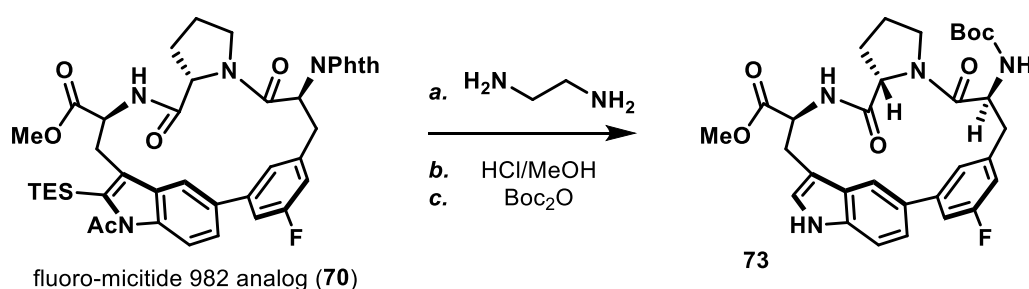
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.25 (s, 1H), 7.43 (s, 1H), 7.27 (dd, *J* = 6.4, 1.8 Hz, 2H), 7.25 – 7.21 (m, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 6.98 – 6.94 (m, 2H), 6.86 (t, *J* = 8.3 Hz, 1H), 5.28 (d, *J* = 8.5 Hz, 1H), 4.83 – 4.73 (m, 2H), 4.53 (dd, *J* = 8.3, 3.2 Hz, 1H), 3.84 – 3.75 (m, 1H), 3.72 (s, 3H), 3.71 – 3.63 (m, 1H), 3.24 (dd, *J* = 15.0, 5.7 Hz, 1H), 3.17 (dd, *J* = 13.5, 6.3 Hz, 1H), 3.10 (dd, *J* = 13.5, 2.1 Hz, 1H), 3.03 – 2.93 (m, 1H), 2.40 (s, 3H), 2.25 – 1.89 (m, 4H), 1.45 (s, 9H).

**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** δ 173.10, 170.51, 169.19, 154.77, 141.34, 134.71, 132.95, 132.73, 132.32, 131.43, 129.41, 127.97, 126.40, 123.05, 121.25, 120.88, 113.98, 108.88, 78.86, 59.41, 53.14, 51.84, 51.15, 46.49, 35.57, 30.34, 28.90, 27.81, 25.33, 24.20, 20.24.

**HRMS (ESI-TOF):** calculated for C<sub>32</sub>H<sub>38</sub>N<sub>4</sub>NaO<sub>6</sub><sup>+</sup> [M+Na]<sup>+</sup>: 597.2689, found: 597.2686.

**TLC:** R<sub>f</sub> = 0.6 (1:0 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sub>D</sub><sup>21</sup>:** +84.1 (*c* = 1.0, CHCl<sub>3</sub>)



Compound **70** (507 mg, 0.663 mmol, 1.0 eq.) was dissolved in *n*-BuOH (6 mL, 0.1 M), and ethylenediamine (0.44 mL, 6.6 mmol, 10 eq.) was added. The reaction was stirred at 25 °C for 15 h. The reaction mixture was diluted with toluene (15 mL) and directly concentrated under reduced pressure to give the crude. The crude was dissolved in MeOH (12 mL, 0.05 M), and SO<sub>2</sub>Cl<sub>2</sub> (2.4 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 25 °C for 2h. Then, the mixture was directly concentrated under reduced pressure to give the crude primary amine. The crude was then dissolved in the THF:saturated *aq.* NaHCO<sub>3</sub> 10:1 (12 mL, 0.05 M). Boc<sub>2</sub>O (1.1 mL, 4.6 mmol, 7 equiv.) was added and the reaction was stirred for 2h at 25 °C. After confirming the full conversion of the primary amine by LC/MS, the reaction was diluted with H<sub>2</sub>O (200 mL) and extracted with EtOAc three times. The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give the crude. The crude was purified by flash column chromatography (EtOAc:Hexane 1:4 to 4:1) to give the compound **73** (371 mg, 97% yield).

## Compound 73

**Physical State:** white solid

**<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):** δ 7.56 (s, 1H), 7.52 (dd, *J* = 8.6, 4.9 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.09 (d, *J* = 5.4 Hz, 1H), 7.06 – 6.98 (m, 2H), 4.87 (d, *J* = 11.4 Hz, 1H), 4.80 – 4.75 (m, 1H), 4.67 – 4.59 (m, 1H), 3.88 – 3.80 (m, 2H), 3.74 (s, 3H), 3.42 (dt, *J* = 13.4, 6.3 Hz, 1H), 3.18 (t, *J* = 6.0 Hz, 2H), 3.04 (d, *J* = 15.1 Hz, 1H), 2.80 (d, *J* = 6.5 Hz, 1H), 2.27 – 1.93 (m, 4H), 1.44 (s, 9H).

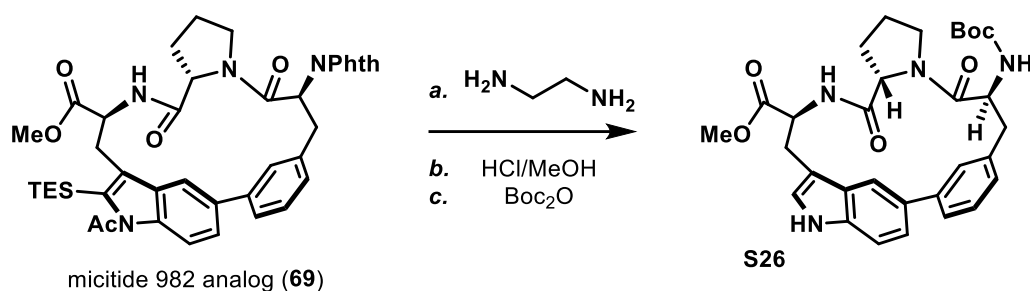
**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** δ 172.59, 171.74, 169.19, 157.27, 155.01, 135.83, 133.06, 130.03, 128.98, 126.29, 125.81, 122.00, 121.93, 121.77, 119.21, 114.15, 113.92, 113.30, 109.46, 78.93, 59.24, 52.49, 50.75, 34.41, 29.40, 28.64, 26.62, 23.85.

**<sup>19</sup>F NMR (377 MHz, CD<sub>3</sub>OD):** δ -123.39.

**HRMS (ESI-TOF):** calculated for C<sub>31</sub>H<sub>35</sub>FN<sub>4</sub>NaO<sub>6</sub><sup>+</sup> [M+Na]<sup>+</sup>: 601.2438, found: 601.2437.

TLC:  $R_f = 0.5$  (1:0 EtOAc : Hexane,  $Ce_2(SO_4)_3$  in phosphomolybdic acid).

$[\alpha]^{21}_D$ : +92.1 ( $c = 1.0$ ,  $CHCl_3$ )



Compound **69** (200 mg, 0.268 mmol, 1.0 eq.) was dissolved in *n*-BuOH (5 mL, 0.1 M), and ethylenediamine (0.18 mL, 2.7 mmol, 10 eq.) was added. The reaction was stirred at 25 °C for 15 h. The reaction mixture was diluted with toluene (15 mL) and directly concentrated under reduced pressure to give the crude. The crude was dissolved in MeOH (5 mL, 0.1 M), and  $SO_2Cl_2$  (1.0 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 25 °C for 2h. Then, the mixture was directly concentrated under reduced pressure to give the crude primary amine. The crude was then dissolved in the THF:saturated *aq.*  $NaHCO_3$  10:1 (5.5 mL, 0.1 M).  $Boc_2O$  (0.43 mL, 1.9 mmol, 7.0 equiv.) was added and the reaction was stirred for 2h at 25 °C. After confirming the full conversion of the primary amine by LC/MS, the reaction was diluted with  $H_2O$  (200 mL) and extracted with EtOAc three times. The organic layers were combined, dried over  $Na_2SO_4$ , and concentrated under reduced pressure to give the crude. The crude was purified by flash column chromatography (EtOAc:Hexane 1:4 to 4:1) to give the compound **S26** (148 mg, 99% yield).

### Compound **S26**

**Physical State:** white solid

**$^1H$  NMR (600 MHz,  $CDCl_3$ ):**  $\delta$  8.08 (s, 1H), 7.65 (s, 1H), 7.56 (s, 1H), 7.50 (d,  $J = 7.2$  Hz, 1H), 7.44 (dd,  $J = 8.4, 1.9$  Hz, 1H), 7.36 – 7.28 (m, 1H), 7.30 (t,  $J = 7.6$  Hz, 1H), 5.20 (s, 1H), 5.04 – 4.95 (m, 1H), 4.82 (ddd,  $J = 8.2, 5.4, 2.7$  Hz, 1H), 4.58 – 4.51 (m, 1H), 3.91 – 3.84 (m, 1H), 3.73 (t,  $J = 3.2$  Hz, 1H), 3.72 (s, 3H), 3.30 – 3.16 (m, 3H), 3.06 – 3.00 (m, 1H), 2.25 – 2.19 (m, 1H), 2.13 – 2.07 (m, 1H), 2.04 – 1.93 (m, 2H), 1.41 (s, 9H).

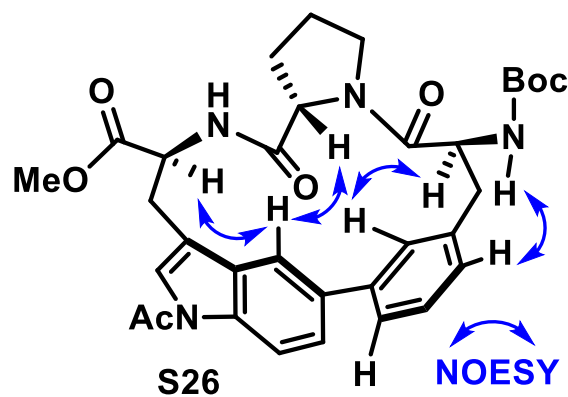
**$^{13}C$  NMR (151 MHz,  $CDCl_3$ ):**  $\delta$  173.84, 171.45, 169.93, 155.49, 141.90, 136.06, 134.99, 132.85, 130.52, 128.75, 127.90, 127.35, 125.31, 122.04, 121.32, 119.46, 114.47, 111.03, 79.53, 60.23, 53.08, 52.53, 51.81, 47.32, 36.59, 31.22, 29.58, 28.47, 25.06.

**HRMS (ESI-TOF):** calculated for  $C_{31}H_{36}N_4NaO_6^+$   $[M+Na]^+$ : 583.2533, found: 583.2535.

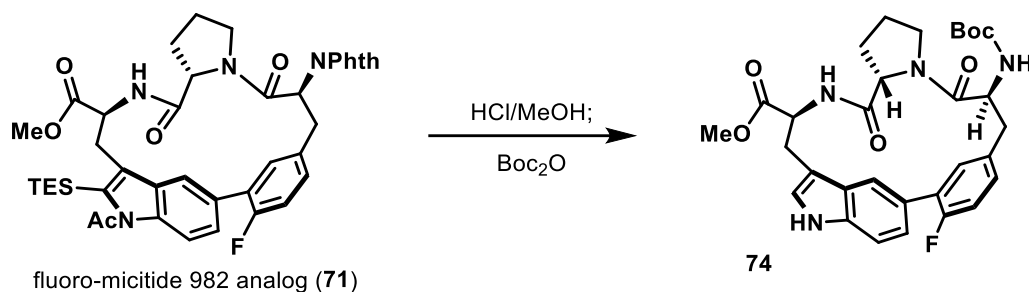
TLC:  $R_f = 0.6$  (1:0 EtOAc : Hexane,  $Ce_2(SO_4)_3$  in phosphomolybdic acid).

$[\alpha]^{21}_D$ : +169.6 ( $c = 1.0$ ,  $CHCl_3$ )

## Key NOESY Correlations of Compound S26



S26 (CDCl<sub>3</sub>, 400 MHz)



Compound **71** (651 mg, 0.886 mmol, 1.0 eq.) was dissolved in MeOH (18 mL, 0.05 M), and SO<sub>2</sub>Cl<sub>2</sub> (3.6 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 25 °C for 2h. Then, the mixture was directly concentrated under reduced pressure to give the crude primary amine. The crude was then dissolved in the THF:saturated *aq.* NaHCO<sub>3</sub> 10:1 (36 mL, 0.05 M). Boc<sub>2</sub>O (1.8 mL, 6.2 mmol, 7 equiv.) was added and the reaction was stirred for 2h at 25 °C. After confirming the full conversion of the primary amine by LC/MS, the reaction was diluted with H<sub>2</sub>O (100 mL) and extracted with EtOAc three times. The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give the crude. The crude was purified by flash column chromatography (EtOAc:Hexane 1:4 to 4:1) to give the compound **74** (487 mg, 95% yield).

### Compound 74

**Physical State:** white solid

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 7.52 (s, 2H), 7.45 (dd, *J* = 5.2, 2.6 Hz, 1H), 7.28 (d, *J* = 5.3 Hz, 1H), 7.14 (s, 1H), 7.02 – 6.92 (m, 1H), 6.97 – 6.87 (m, 2H), 5.31 (t, *J* = 17.1 Hz, 1H), 4.93 – 4.84 (m, 1H), 4.78 (t, *J* = 7.4 Hz, 1H), 4.45 (s, 1H), 3.74 (s, 3H), 3.74 – 3.65 (m, 2H), 3.27 – 3.06 (m, 3H), 2.99 (t, *J* = 15.5 Hz, 1H), 2.17 – 1.80 (m, 4H), 1.37 (s, 9H).

**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>):** δ 173.92, 171.44, 169.63, 159.98, 158.34, 155.50, 136.01, 133.98, 130.68, 130.20, 129.24, 127.14, 123.56, 121.99, 120.77, 114.97, 114.51, 110.38, 79.62, 60.19, 54.47, 54.44, 53.25, 52.50, 51.63, 47.32, 38.70, 35.82, 31.11, 29.65, 28.44, 24.91.

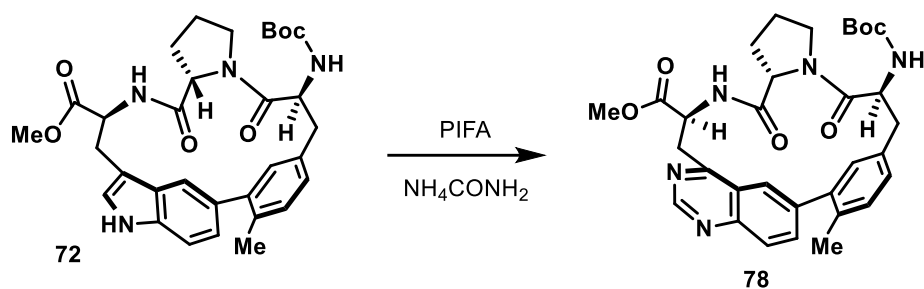
**<sup>19</sup>F NMR (565 MHz, CDCl<sub>3</sub>):** δ -122.22.

**HRMS (ESI-TOF):** calculated for C<sub>31</sub>H<sub>35</sub>FN<sub>4</sub>NaO<sub>6</sub><sup>+</sup> [M+Na]<sup>+</sup>: 601.2438, found: 601.2440.

**TLC:** R<sub>f</sub> = 0.5 (1:0 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>21</sup><sub>D</sub>:** +286.5 (*c* = 1.0, CHCl<sub>3</sub>)

## Skeletal Editing Employing Unnatural Micitide Core



In a culture tube equipped with a stirring bar, compound **72** (21.3 mg, 37.1  $\mu\text{mol}$ , 1.0 eq.) and ammonium carbamate (29.0 mg, 371  $\mu\text{mol}$ , 10.0 equiv) were dissolved in MeOH (2 mL, 0.02 M). The resulting solution was cooled to 0 °C, and then PIFA (63.8 mg, 148  $\mu\text{mol}$ , 4.0 equiv) was added in one portion. The reaction was stirred at 0 °C for 1h and quenched with saturated aq.  $\text{Na}_2\text{S}_2\text{O}_3$ . The mixture was extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 9:1) to give the title compound **78** (13.4 mg, 61% yield)

### Compound **78**

**Physical State:** white solid

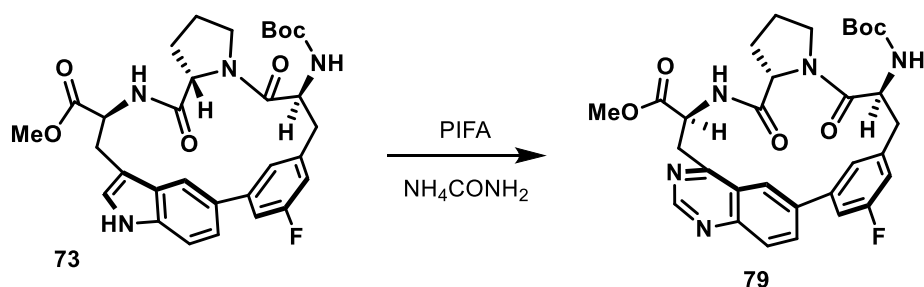
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , A mixture of rotamers A:B = 2.4:1, Signals of the major rotamer were reported):**  $\delta$  9.21 (s, 9H), 8.13 (s, 1H), 8.04 (d,  $J = 4.2$  Hz, 1H), 7.54 (s, 1H), 7.23 (d,  $J = 8.3$  Hz, 1H), 6.96 – 6.85 (m, 2H), 5.16 (d,  $J = 9.5$  Hz, 1H), 4.84 (q,  $J = 8.5$  Hz, 1H), 4.46 (dd,  $J = 7.9, 4.6$  Hz, 1H), 3.86 (dd,  $J = 13.8, 4.7$  Hz, 2H), 3.76 (s, 3H), 3.66 (d,  $J = 1.1$  Hz, 1H), 3.55 (dd,  $J = 12.9, 10.3$  Hz, 1H), 3.32 (dd,  $J = 13.4, 7.3$  Hz, 1H), 3.16 (dd,  $J = 36.2, 13.2$  Hz, 2H), 2.35 (s, 3H), 2.10 – 1.98 (m, 2H), 1.80 – 1.61 (m, 2H), 1.44 (s, 9H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ , A mixture of rotamers A:B = 2.4:1):**  $\delta$  171.25, 170.60, 169.14, 166.47, 160.85, 153.62, 153.46, 149.19, 148.67, 141.21, 139.15, 135.15, 132.41, 130.01, 129.16, 127.15, 125.60, 125.21, 123.30, 122.71, 117.13, 112.13, 79.21, 79.00, 66.18, 59.80, 59.55, 52.19, 52.12, 50.91, 50.80, 50.51, 46.82, 46.70, 40.06, 39.28, 35.47, 35.33, 33.38, 29.77, 29.08, 28.83, 27.77, 27.70, 24.65, 24.48, 23.14, 22.34, 19.95.

**HRMS (ESI-TOF):** calculated for  $\text{C}_{32}\text{H}_{37}\text{N}_5\text{NaO}_6$   $[\text{M}+\text{Na}]^+$ : 610.2642, found: 610.2643.

**TLC:**  $R_f = 0.6$  (1:0 EtOAc : Hexane,  $\text{Ce}_2(\text{SO}_4)_3$  in phosphomolybdic acid).

**$[\alpha]_D^{21}$ :** +160.2 ( $c = 0.5$ ,  $\text{CHCl}_3$ )



In a culture tube equipped with a stirring bar, compound **73** (41.4 mg, 71.6  $\mu\text{mol}$ , 1.0 eq.) and ammonium carbamate (55.6 mg, 712  $\mu\text{mol}$ , 10.0 equiv) were dissolved in MeOH (4 mL, 0.02 M). The resulting solution was cooled to 0 °C, and then PIFA (122 mg, 28.5  $\mu\text{mol}$ , 4.0 equiv) was added in one portion. The reaction was stirred at 0 °C for 1h and quenched with saturated aq.  $\text{Na}_2\text{S}_2\text{O}_3$ . The mixture was extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced

pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 9:1) to give the title compound **79** (25.3 mg, 60% yield)

### Compound 79

**Physical State:** white solid

**<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):** δ 9.13 (s, 1H), 8.37 – 8.29 (m, 1H), 8.16 (s, 1H), 8.08 (d, *J* = 9.1 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.23 – 7.12 (m, 2H), 5.08 (d, *J* = 9.8 Hz, 1H), 4.85 – 4.77 (m, 1H), 4.55 (dd, *J* = 8.4, 5.3 Hz, 1H), 3.99 (d, *J* = 13.7 Hz, 1H), 3.89 – 3.80 (m, 2H), 3.70 (s, 3H), 3.66 – 3.54 (m, 1H), 3.30 – 3.13 (m, 2H), 2.38 – 2.25 (m, 1H), 2.22 – 2.10 (m, 1H), 2.09 – 1.99 (m, 1H), 1.99 – 1.91 (m, 1H), 1.45 (s, 9H).

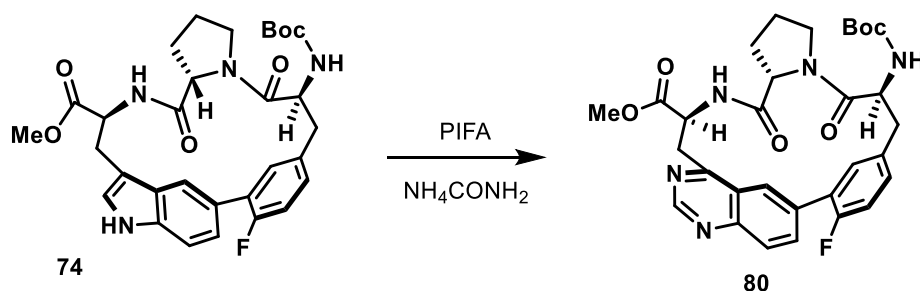
**<sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD):** δ 171.80, 170.50, 169.17, 167.97, 159.73, 152.86, 148.45, 135.95, 135.24, 135.17, 132.93, 132.03, 131.95, 127.04, 125.72 (d, *J* = 15.2 Hz), 124.48, 122.40, 114.53 (d, *J* = 23.3 Hz), 78.99, 59.37, 50.95, 50.58, 38.77, 34.35, 28.52, 26.61, 24.10.

**<sup>19</sup>F NMR (565 MHz, CD<sub>3</sub>OD):** δ -122.62.

**HRMS (ESI-TOF):** calculated for C<sub>31</sub>H<sub>34</sub>FN<sub>5</sub>NaO<sub>6</sub><sup>+</sup> [M+Na]<sup>+</sup>: 614.2391, found: 610.2394.

**TLC:** R<sub>f</sub> = 0.5 (1:0 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sub>D</sub><sup>21</sup>:** +91.9 (*c* = 0.5, CHCl<sub>3</sub>)



In a culture tube equipped with a stirring bar, compound **74** (41.2 mg, 71.2 μmol, 1.0 eq.) and ammonium carbamate (55.6 mg, 712 μmol, 10.0 equiv) were dissolved in MeOH (4 mL, 0.02 M). The resulting solution was cooled to 0 °C, and then PIFA (122 mg, 28.5 μmol, 4.0 equiv) was added in one portion. The reaction was stirred at 0 °C for 1h and quenched with saturated aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The mixture was extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 9:1) to give the title compound **80** (20.1 mg, 48% yield)

### Compound 80

**Physical State:** white solid

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 9.22 (s, 1H), 8.26 (dd, *J* = 8.6, 3.6 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 8.06 (s, 1H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.32 (dd, *J* = 11.8, 7.4 Hz, 1H), 7.15 – 7.02 (m, 2H), 5.29 (q, *J* = 5.7 Hz, 1H), 5.07 (t, *J* = 9.8 Hz, 1H), 4.86 (t, *J* = 7.7 Hz, 1H), 4.41 (dd, *J* = 7.6, 4.8 Hz, 1H), 3.85 – 3.75 (m, 3H), 3.76 (s, 3H), 3.51 (ddd, *J* = 13.0, 10.1, 2.2 Hz, 1H), 3.26 (dd, *J* = 13.6, 7.1 Hz, 1H), 3.14 (d, *J* = 13.6 Hz, 1H), 2.16 (d, *J* = 13.7 Hz, 2H), 1.94 (d, *J* = 11.7 Hz, 2H), 1.39 (s, 9H).

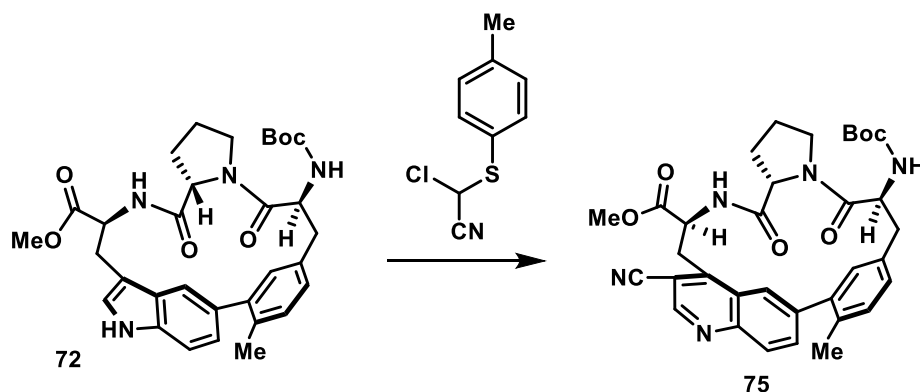
**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** δ 171.47, 170.79, 169.11, 166.52, 159.71, 157.25, 154.66, 153.64, 148.97, 135.70, 134.96, 132.91, 132.09, 130.75, 128.04, 125.94, 124.39, 122.62, 114.90, 114.68, 79.08, 59.63, 52.11, 50.72, 50.58, 46.82, 39.61, 35.01, 28.93, 27.70, 24.46.

**<sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>):** δ -121.16.

**HRMS (ESI-TOF):** calculated for C<sub>31</sub>H<sub>34</sub>FN<sub>5</sub>NaO<sub>6</sub><sup>+</sup> [M+Na]<sup>+</sup>: 614.2391, found: 610.2396.

**TLC:**  $R_f = 0.5$  (1:0 EtOAc : Hexane,  $Ce_2(SO_4)_3$  in phosphomolybdic acid).

**$[\alpha]^{21}_D$ :** +103.2 ( $c = 0.1$ ,  $CHCl_3$ )



To a solution of compound **72** (43.8 mg, 76.3  $\mu\text{mol}$ , 1.0 eq.) and  $Cs_2CO_3$  (125 mg, 382  $\mu\text{mol}$ , 5.0 eq.) in THF (2 mL, 0.05 M), 2-chloro-2-(p-tolylthio)acetonitrile (22.5 mg, 152  $\mu\text{mol}$ , 1.5 eq.) was added portion-wise (0.5 equiv. every 1 h) at room temperature, and the resulting mixture was stirred for next 4 h. The reaction was quenched with saturated aq.  $Na_2S_2O_3$ , extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 3:1) to give the title compound **75** (40.2 mg, 63% yield)

### Compound **75**

**Physical State:** pale yellow solid

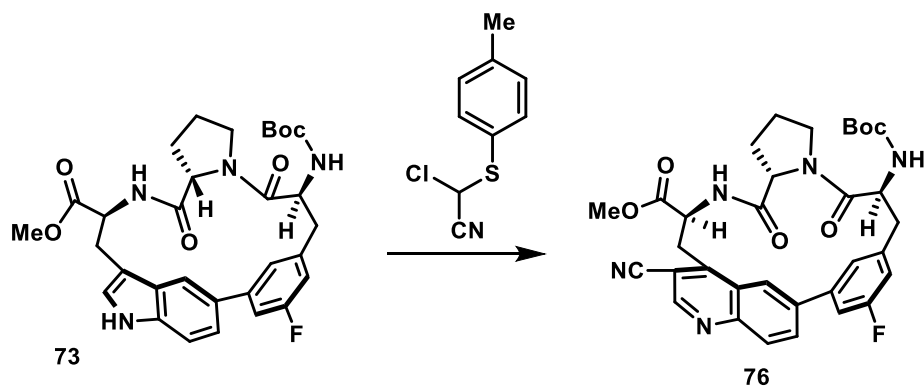
**$^1H$  NMR (400 MHz,  $CDCl_3$ , a mixture of two rotamers A:B = 2.2:1, Signals of the major rotamers were reported):**  $\delta$  8.98 (s, 1H), 8.25 (d,  $J = 8.7$  Hz, 1H), 8.14 (s, 1H), 8.09 (d,  $J = 8.7$  Hz, 1H), 7.24 – 6.88 (m, 3H), 5.19 (d,  $J = 7.7$  Hz, 1H), 4.84 (q,  $J = 7.4$  Hz, 1H), 4.50 – 4.40 (m, 1H), 3.83 (s, 3H), 3.82 (s, 2H), 3.71 (t,  $J = 9.5$  Hz, 2H), 3.32 (dd,  $J = 13.9, 7.0$  Hz, 1H), 3.18 (d,  $J = 13.3$  Hz, 1H), 3.13 – 3.04 (m, 1H), 2.27 (s, 3H), 2.19 (d,  $J = 10.9$  Hz, 2H), 2.01 (s, 2H), 1.43 (s, 9H).

**$^{13}C$  NMR (101 MHz,  $CDCl_3$ , a mixture of two rotamers A:B = 2.2:1):**  $\delta$   $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  170.94, 170.77, 170.59, 170.53, 169.19, 169.06, 163.25, 160.81, 154.62, 154.57, 149.14, 148.85, 148.76, 148.68, 147.83, 147.33, 141.99, 140.42, 140.35, 140.00, 138.68, 137.60, 137.52, 133.90, 133.09, 132.17, 132.11, 131.06, 130.71, 130.10, 129.95, 128.69, 125.50, 125.47, 124.53, 124.50, 124.28, 122.61, 117.34, 117.13, 116.29, 116.15, 112.47, 112.25, 107.34, 106.88, 79.26, 79.07, 69.85, 66.18, 59.75, 59.36, 52.85, 52.78, 50.89, 50.76, 50.62, 50.26, 46.85, 46.68, 38.09, 35.77, 35.55, 35.49, 35.21, 33.38, 31.30, 29.77, 29.07, 28.79, 28.74, 28.71, 28.49, 28.28, 27.77, 27.69, 24.65, 24.42, 23.85, 23.14, 22.34, 22.07, 20.03.

**HRMS (ESI-TOF):** calculated for  $C_{34}H_{37}N_5NaO_6^+$   $[M+Na]^+$ : 634.2642, found: 634.2643.

**TLC:**  $R_f = 0.5$  (3:1 EtOAc : Hexane,  $Ce_2(SO_4)_3$  in phosphomolybdic acid).

**$[\alpha]^{21}_D$ :** +115.9 ( $c = 1.0$ ,  $CHCl_3$ )



To a solution of compound **73** (43.8 mg, 76.3  $\mu\text{mol}$ , 1.0 eq.) and  $\text{Cs}_2\text{CO}_3$  (125 mg, 382  $\mu\text{mol}$ , 5.0 eq.) in THF (2 mL, 0.05 M), 2-chloro-2-(p-tolylthio)acetonitrile (30.1 mg, 152  $\mu\text{mol}$ , 2.0 eq.) was added portion-wise (0.5 equiv. every 1 h) at room temperature, and the resulting mixture was stirred for next 4 h. The reaction was quenched with saturated aq.  $\text{Na}_2\text{S}_2\text{O}_3$ , extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 3:1) to give the title compound **76** (27.2 mg, 58% yield)

### Compound 76

**Physical State:** pale yellow solid

**$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):**  $\delta$  9.00 (s, 1H), 8.28 – 8.06 (m, 3H), 7.70 – 7.60 (m, 1H), 7.25 – 7.10 (m, 2H), 5.03 (d,  $J = 9.0$  Hz, 1H), 4.80 (d,  $J = 7.1$  Hz, 1H), 4.57 (dd,  $J = 8.8, 5.1$  Hz, 1H), 3.90 – 3.79 (m, 4H), 3.77 (s, 3H), 3.31 – 3.20 (m, 1H), 3.19 – 3.08 (m, 1H), 2.32 (dt,  $J = 12.6, 7.5$  Hz, 1H), 2.23 – 2.12 (m, 1H), 2.12 – 2.00 (m, 1H), 2.01 – 1.94 (m, 1H), 1.48 (s, 9H).

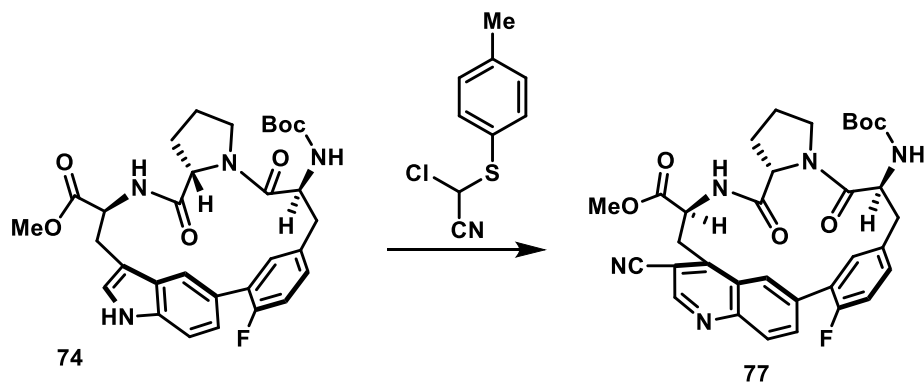
**$^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_3\text{OD}$ ):**  $\delta$  172.33, 170.93, 169.71, 157.89, 155.64, 150.76, 149.68, 147.73, 136.85, 133.89 (d,  $J = 7.6$  Hz), 133.43, 132.58 (d,  $J = 8.2$  Hz), 131.86, 129.17, 125.06, 124.36, 116.24, 115.16 (d,  $J = 23.1$  Hz), 108.00, 79.65, 59.93, 52.09, 51.48, 51.24, 35.44, 35.15, 29.10, 27.29, 27.26, 24.70.

**$^{19}\text{F}$  NMR (377 MHz,  $\text{CD}_3\text{OD}$ ):**  $\delta$  -122.30.

**HRMS (ESI-TOF):** calculated for  $\text{C}_{33}\text{H}_{34}\text{FN}_5\text{NaO}_6^+$  [ $\text{M}+\text{Na}$ ] $^+$ : 638.2391, found: 638.2391.

**TLC:**  $R_f = 0.5$  (3:1 EtOAc : Hexane,  $\text{Ce}_2(\text{SO}_4)_3$  in phosphomolybdic acid).

**$[\alpha]_D^{25}$ :** +98.5 ( $c = 0.3$ ,  $\text{CHCl}_3$ )



To a solution of compound **74** (43.8 mg, 76.3  $\mu\text{mol}$ , 1.0 eq.) and  $\text{Cs}_2\text{CO}_3$  (125 mg, 382  $\mu\text{mol}$ , 5.0 eq.) in THF (2 mL, 0.05 M), 2-chloro-2-(p-tolylthio)acetonitrile (30.1 mg, 152  $\mu\text{mol}$ , 2.0 eq.) was added portion-wise (0.5 equiv. every 1 h) at room temperature, and the resulting mixture was stirred for next 4 h. The reaction was

quenched with saturated aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 3:1) to give the title compound **77** (46.6 mg, 57% yield)

### Compound 77

**Physical State:** pale yellow solid

**<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):** δ 8.99 (s, 1H), 8.20 (s, 2H), 8.01 (s, 1H), 7.60 (dd, *J* = 7.8, 2.1 Hz, 1H), 7.50 (d, *J* = 10.0 Hz, 1H), 7.16 – 7.03 (m, 2H), 5.30 (d, *J* = 8.4 Hz, 1H), 5.01 (dt, *J* = 10.0, 5.7 Hz, 1H), 4.86 (t, *J* = 7.7 Hz, 1H), 4.38 (dd, *J* = 7.6, 4.9 Hz, 1H), 3.83 (s, 3H), 3.82 – 3.72 (m, 2H), 3.67 (d, *J* = 5.9 Hz, 2H), 3.33 – 3.22 (m, 1H), 3.15 – 3.06 (m, 1H), 2.23 – 1.88 (m, 4H), 1.39 (s, 9H).

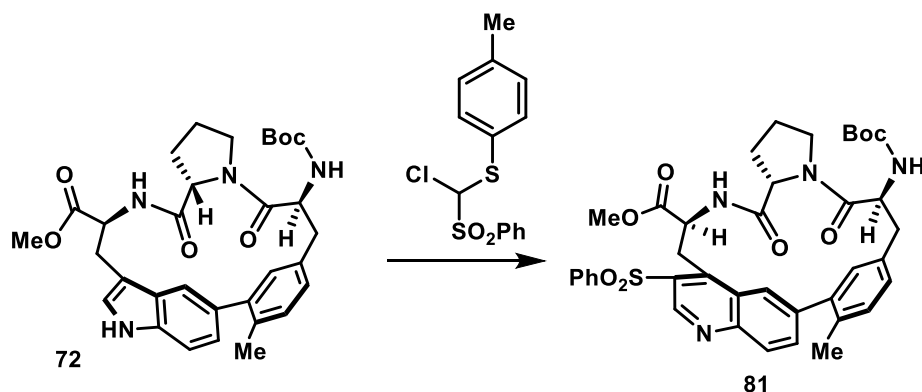
**<sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD):** δ 170.97, 170.67, 169.06, 159.66, 157.19, 154.65, 148.86 (d, *J* = 9.2 Hz), 147.61, 136.44, 133.57 (d, *J* = 8.0 Hz), 132.74, 132.32 (d, *J* = 8.5 Hz), 130.80, 129.58, 124.41, 123.56, 116.21, 114.91 (d, *J* = 22.5 Hz), 107.03, 79.15, 59.58, 52.86, 50.70, 50.38, 46.83, 35.35, 35.10, 28.85, 27.70, 24.45.

**<sup>19</sup>F NMR (565 MHz, CD<sub>3</sub>OD):** δ -124.57.

**HRMS (ESI-TOF):** calculated for C<sub>33</sub>H<sub>34</sub>FN<sub>5</sub>NaO<sub>6</sub><sup>+</sup> [M+Na]<sup>+</sup>: 638.2391, found: 638.2394.

**TLC:** R<sub>f</sub> = 0.5 (3:1 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sub>D</sub><sup>21</sup>:** +90.1 (*c* = 0.3, CHCl<sub>3</sub>)



To a solution of compound **72** (43.8 mg, 76.3 μmol, 1.0 eq.) and Cs<sub>2</sub>CO<sub>3</sub> (125 mg, 382 μmol, 5.0 eq.) in THF (2 mL, 0.05 M), (chloro(phenylsulfonyl)methyl)(p-tolyl)sulfane (47.6 mg, 152 μmol, 2.0 eq.) was added portion-wise (0.5 equiv. every 1 h) at room temperature, and the resulting mixture was stirred for next 4 h. The reaction was quenched with saturated aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 3:1) to give the title compound **81** (28.8 mg, 52% yield)

### Compound 81

**Physical State:** pale yellow solid

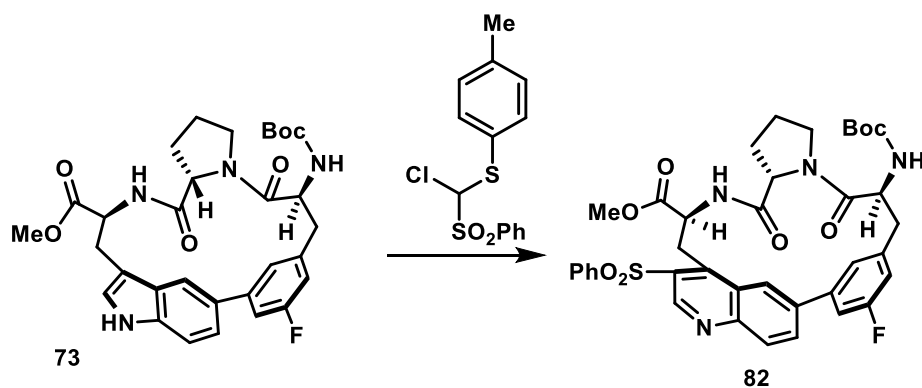
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>. A mixture of rotamers A:B = 2.6:1, Signals of the major rotamers were reported):** δ 8.99 (s, 1H), 8.20 (s, 2H), 8.01 (s, 1H), 7.60 (dd, *J* = 7.8, 2.1 Hz, 1H), 7.50 (d, *J* = 10.0 Hz, 1H), 7.16 – 7.03 (m, 2H), 5.30 (d, *J* = 8.4 Hz, 1H), 5.01 (dt, *J* = 10.0, 5.7 Hz, 1H), 4.86 (t, *J* = 7.7 Hz, 1H), 4.38 (dd, *J* = 7.6, 4.9 Hz, 1H), 3.83 (s, 3H), 3.82 – 3.72 (m, 2H), 3.67 (d, *J* = 5.9 Hz, 2H), 3.33 – 3.22 (m, 1H), 3.15 – 3.06 (m, 1H), 2.23 – 1.88 (m, 4H), 1.39 (s, 9H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, A mixture of rotamers A:B = 2.6:1) : δ 170.97, 170.67, 169.06, 159.66, 157.19, 154.65, 148.86 (d, *J* = 9.2 Hz), 147.61, 136.44, 133.57 (d, *J* = 8.0 Hz), 132.74, 132.32 (d, *J* = 8.5 Hz), 130.80, 129.58, 124.41, 123.56, 116.21, 114.91 (d, *J* = 22.5 Hz), 107.03, 79.15, 59.58, 52.86, 50.70, 50.38, 46.83, 35.35, 35.10, 28.85, 27.70, 24.45.

HRMS (ESI-TOF): calculated for C<sub>39</sub>H<sub>42</sub>N<sub>4</sub>NaO<sub>8</sub>S<sup>+</sup> [M+Na]<sup>+</sup>: 749.2621, found: 749.2617.

TLC: R<sub>f</sub> = 0.5 (3:1 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

[α]<sup>21</sup><sub>D</sub>: +36.2 (*c* = 0.5, CHCl<sub>3</sub>)



To a solution of compound **73** (43.8 mg, 76.3 μmol, 1.0 eq.) and Cs<sub>2</sub>CO<sub>3</sub> (125 mg, 382 μmol, 5.0 eq.) in THF (2 mL, 0.05 M), (chloro(phenylsulfonyl)methyl)(p-tolyl)sulfane (47.6 mg, 152 μmol, 2.0 eq.) was added portion-wise (0.5 equiv. every 1 h) at room temperature, and the resulting mixture was stirred for next 4 h. The reaction was quenched with saturated aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 3:1) to give the title compound **82** (14.5 mg, 27% yield)

## Compound 82

**Physical State:** pale yellow solid

<sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD): δ 9.35 (s, 1H), 8.20 (s, 1H), 8.13 (d, *J* = 14.4 Hz, 2H), 7.93 (s, 2H), 7.68 – 7.58 (m, 1H), 7.62 – 7.52 (m, 3H), 7.19 – 7.15 (m, 1H), 7.13 – 7.06 (m, 1H), 5.04 (d, *J* = 11.3 Hz, 1H), 4.76 (d, *J* = 7.7 Hz, 1H), 4.62 – 4.55 (m, 1H), 4.50 (t, *J* = 4.4 Hz, 3H), 3.85 – 3.78 (m, 1H), 3.77 – 3.69 (m, 1H), 3.65 (s, 3H), 3.59 (dd, *J* = 13.9, 1.7 Hz, 1H), 3.23 – 3.17 (m, 1H), 3.11 – 3.05 (m, 1H), 2.25 – 2.19 (m, 1H), 2.17 – 2.06 (m, 1H), 1.98 – 1.92 (m, 1H), 1.91 – 1.84 (m, 1H), 1.39 (s, 9H).

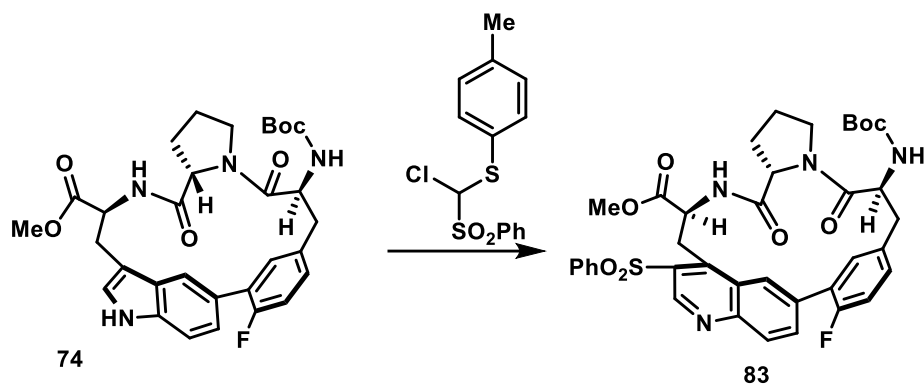
<sup>13</sup>C NMR (151 MHz, CD<sub>3</sub>OD) : δ 172.41, 170.79, 169.91, 160.01, 158.37, 155.73, 148.43, 148.14, 146.51, 141.92, 137.02, 134.07 (d, *J* = 7.5 Hz), 133.83, 133.51, 133.21, 132.62, 131.97, 129.61, 129.22, 127.12, 126.16, 124.84, 115.22 (d, *J* = 22.6 Hz), 79.69, 60.01, 52.62, 51.66, 51.52, 35.23, 31.58, 29.05, 27.32, 24.77.

<sup>19</sup>F NMR (565 MHz, CD<sub>3</sub>OD): δ -122.19.

HRMS (ESI-TOF): calculated for C<sub>38</sub>H<sub>39</sub>FN<sub>4</sub>NaO<sub>8</sub>S<sup>+</sup> [M+Na]<sup>+</sup>: 753.2370, found: 753.2371.

TLC: R<sub>f</sub> = 0.5 (3:1 EtOAc : Hexane, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

[α]<sup>21</sup><sub>D</sub>: +71.2 (*c* = 0.3, CHCl<sub>3</sub>)



To a solution of compound **74** (43.8 mg, 76.3  $\mu\text{mol}$ , 1.0 eq.) and  $\text{Cs}_2\text{CO}_3$  (125 mg, 382  $\mu\text{mol}$ , 5.0 eq.) in THF (2 mL, 0.05 M), (chloro(phenylsulfonyl)methyl)(p-tolyl)sulfane (47.6 mg, 152  $\mu\text{mol}$ , 2.0 eq.) was added portion-wise (0.5 equiv. every 1 h) at room temperature, and the resulting mixture was stirred for next 4 h. The reaction was quenched with saturated aq.  $\text{Na}_2\text{S}_2\text{O}_3$ , extracted with EtOAc (5mL) three times. The organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 3:1) to give the title compound **83** (12.4 mg, 22% yield)

### Compound **83**

**Physical State:** pale yellow solid

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  9.41 (s, 1H), 8.21 (s, 2H), 8.12 (s, 1H), 7.84 (d,  $J = 8.0$  Hz, 2H), 7.64 (d,  $J = 7.6$  Hz, 1H), 7.55 (t,  $J = 7.3$  Hz, 2H), 7.49 (dd,  $J = 8.3, 6.4$  Hz, 3H), 7.15 – 7.07 (m, 1H), 7.06 – 6.99 (m, 1H), 5.27 – 5.20 (m, 1H), 5.07 (t,  $J = 10.4$  Hz, 1H), 4.86 (t,  $J = 7.8$  Hz, 1H), 4.64 (t,  $J = 13.7$  Hz, 1H), 4.37 – 4.29 (m, 1H), 3.77 (s, 3H), 3.75 – 3.72 (m, 1H), 3.60 – 3.49 (m, 1H), 3.24 (dd,  $J = 13.5, 7.3$  Hz, 1H), 3.15 – 3.07 (m, 1H), 2.09 – 1.69 (m, 4H), 1.34 (s, 9H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):**  $\delta$  170.69, 170.47, 169.08, 159.65, 157.19, 154.64, 148.22, 147.81, 144.49, 141.32, 136.31, 133.47 (d,  $J = 7.7$  Hz), 133.05, 132.67, 132.24, 132.12 (d,  $J = 8.4$  Hz), 129.44, 129.01, 126.44, 125.52, 124.43, 114.68 (d,  $J = 22.7$  Hz), 79.05, 59.73, 52.22, 51.73, 50.60, 46.88, 35.15, 28.64, 27.63, 24.42.

**$^{19}\text{F}$  NMR (376 MHz,  $\text{CD}_3\text{OD}$ ):**  $\delta$  -121.04.

**HRMS (ESI-TOF):** calculated for  $\text{C}_{38}\text{H}_{39}\text{FN}_4\text{NaO}_8\text{S}^+$   $[\text{M}+\text{Na}]^+$ : 753.2370, found: 753.2371.

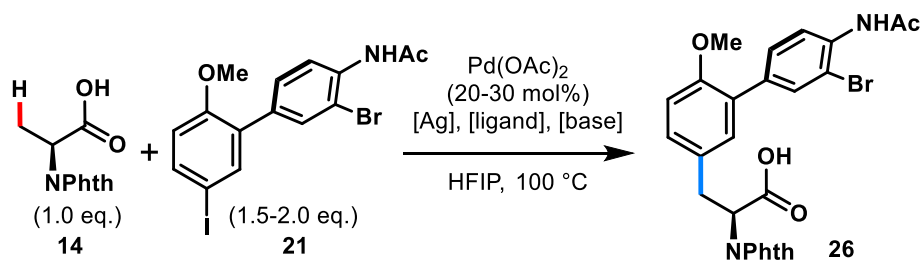
**TLC:**  $R_f = 0.5$  (3:1 EtOAc : Hexane,  $\text{Ce}_2(\text{SO}_4)_3$  in phosphomolybdic acid).

**$[\alpha]_D^{21}$ :** +51.8 ( $c = 0.3$ ,  $\text{CHCl}_3$ )

## Reaction optimization and discussion

### Optimization table of carboxylate-assisted C-H activation

Table S1. Conditions screening of carboxylate-assisted C-H activation

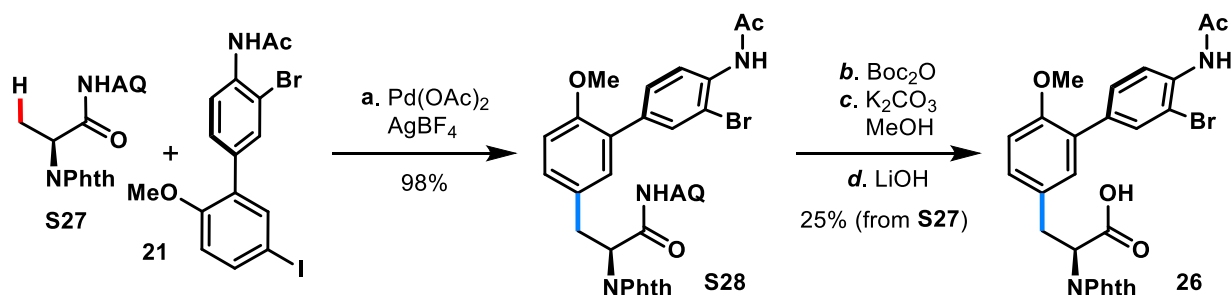


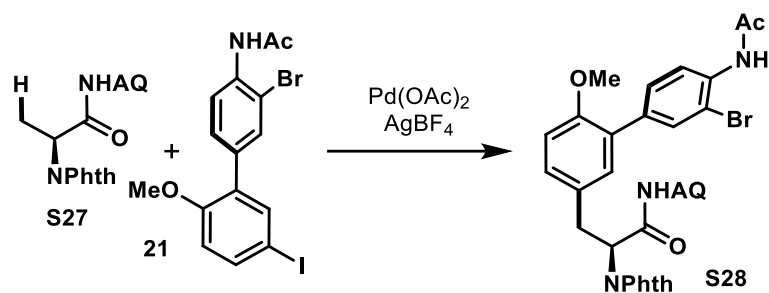
entry	[Ag] 1.0 eq.	[ligand] 0.6 eq.	[base] 0.5 eq.	yield <sup>a</sup>
1	Ag <sub>2</sub> CO <sub>3</sub>	Ac-L-Phe-OH	K <sub>2</sub> CO <sub>3</sub>	60%
2	Ag <sub>2</sub> CO <sub>3</sub>	Ac-L-Leu-OH	K <sub>2</sub> CO <sub>3</sub>	67%
3	Ag <sub>2</sub> CO <sub>3</sub>	Ac-L-isoLeu-OH	K <sub>2</sub> CO <sub>3</sub>	70%
4	Ag <sub>2</sub> CO <sub>3</sub>	Ac-L-Phe-OH	K <sub>2</sub> CO <sub>3</sub>	71%
5	Ag <sub>2</sub> CO <sub>3</sub>	Ac-L-Ala-OH	K <sub>2</sub> CO <sub>3</sub>	73%
6 <sup>b</sup>	Ag <sub>2</sub> CO <sub>3</sub>	Ac-L-Val-OH	K <sub>2</sub> CO <sub>3</sub>	75%
7	Ag <sub>2</sub> CO <sub>3</sub>	Ac-D-Leu-OH	K <sub>2</sub> CO <sub>3</sub>	65%
8	Ag <sub>2</sub> CO <sub>3</sub>	Ac-D-Phe-OH	K <sub>2</sub> CO <sub>3</sub>	63%
9 <sup>b</sup>	Ag <sub>2</sub> CO <sub>3</sub>	Ac-Gly-OH	K <sub>2</sub> CO <sub>3</sub>	89%
10 <sup>c</sup>	Ag <sub>2</sub> CO <sub>3</sub>	Ac-Gly-OH	K <sub>2</sub> CO <sub>3</sub>	71%
11	Ag <sub>2</sub> CO <sub>3</sub>	Boc-Gly-OH	K <sub>2</sub> CO <sub>3</sub>	trace
-----				
12	AgBF <sub>4</sub>	Ac-Gly-OH	K <sub>2</sub> CO <sub>3</sub>	15%
13	AgOAc	Ac-Gly-OH	K <sub>2</sub> CO <sub>3</sub>	61%
-----				
14	Ag <sub>2</sub> CO <sub>3</sub>	Ac-Gly-OH	Na <sub>2</sub> CO <sub>3</sub>	42%
15	Ag <sub>2</sub> CO <sub>3</sub>	Ac-Gly-OH	Rb <sub>2</sub> CO <sub>3</sub>	64%
16	Ag <sub>2</sub> CO <sub>3</sub>	Ac-Gly-OH	KOAc	61%
17	Ag <sub>2</sub> CO <sub>3</sub>	Ac-Gly-OH	NaOAc	38%

<sup>a</sup> Isolated yields. <sup>b</sup> 0.2 mmol scale. <sup>c</sup> Reaction was carried out on 1.1 g of **19** (5 mmol scale). 20 mol% Pd(OAc)<sub>2</sub>, 0.4 eq. Ac-Gly-OH, 1.5 eq. **18** and 50 mL HFIP were used for this scale.

### Aminoquinoline-directed C-H activation

Scheme S3. Overview of aminoquinoline-directed C-H activation





The compound **21** (104 mg, 0.3 mmol, 1.0 eq.) and compound **S27** was dissolved in *t*AmylOH (5 mL). Pd(OAc)<sub>2</sub> (8.98 mg, 0.04 mmol, 0.2 eq.), AgBF<sub>4</sub> (58.4 mg, 0.3 mmol, 1.0 eq.) were added. The reaction mixture was stirred at 80 °C under nitrogen for 24 h. The reaction mixture was concentrated under reduced pressure and purified by preparative thin-layer chromatography (EtOAc:Acetone 10:1) to give the compound **S28** (130 mg, 98% yield).

**Physical State:** white solid

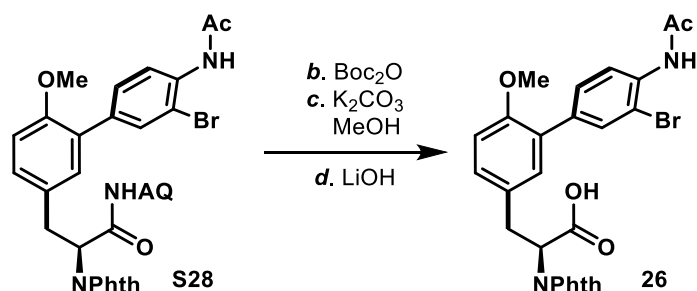
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.43 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 2.1 Hz, 1H), 7.65 (t, *J* = 1.4 Hz, 2H), 7.46 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.40 (ddd, *J* = 7.7, 2.2, 1.5 Hz, 1H), 7.18 (m, 1H), 2.26 (s, 3H).

**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** δ 168.21, 167.94, 166.41, 155.35, 148.32, 138.48, 136.26, 134.34, 133.84, 132.71, 131.62, 131.23, 129.61, 129.39, 128.97, 128.65, 127.85, 127.29, 123.62, 122.04, 121.64, 121.13, 116.78, 111.59, 56.48, 55.56, 33.91, 24.91.

**HRMS (ESI-TOF):** calculated for C<sub>35</sub>H<sub>27</sub>BrN<sub>4</sub>NaO<sub>5</sub><sup>+</sup> [M+Na]<sup>+</sup>: 685.1063, found: 685.1065.

**TLC:** R<sub>f</sub> = 0.5 (10:1 EtOAc : Acetone, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sub>D</sub><sup>25</sup>:** +68.2 (*c* = 1.0, CHCl<sub>3</sub>)



The compound **S28** (3.32 g, 5.00 mmol, 1.0 eq.) was dissolved in MeCN (60 mL, 0.083 M). DMAP (611 mg, 5.0 mmol, 1.0 eq.), DIPEA (5.0 mL, 29 mmol, 5.7 eq.), and Boc<sub>2</sub>O (25 mL, 110 mmol, 22 eq.) were added sequentially. The reaction mixture was stirred at 70 °C for 12h and quenched with saturated NH<sub>4</sub>Cl *aq.*, extracted with DCM (100 mL) three times. The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the crude. The crude was dissolved in MeOH (50 mL, 0.1 M). To this solution, K<sub>2</sub>CO<sub>3</sub> (7.20 g, 36.2 mmol, 5.0 eq.) was added, and the reaction was stirred at 25 °C for 4 h. The reaction was quenched with 1N HCl *aq.* and extracted with EtOAc (100 mL) three times. The organic layers were combined, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give the crude. The crude was dissolved in THF/MeOH/H<sub>2</sub>O = 1:1:1 (60 mL, 0.083 M), then LiOH·H<sub>2</sub>O (1.26 g, 30.0 mmol, 6.0 eq.) was added. The reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was acidified with 0.5M HCl *aq.* and extracted with DCM/MeOH = 10:1 three times. The organic layers were combined and washed with brine. The organic layers were concentrated under reduced pressure to give the crude. The crude was purified by silica gel column chromatography (EtOAc:Hexane 9:1 to 2:1) to give the title compound **26** (619 mg, 25% yield). The characteristic data were identical to the compound synthesized using carboxylate-assisted C-H activation.

## Compound 26

**Physical State:** off-white solid

**<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):** δ 9.46 (s, 1H), 7.81 (s, 4H), 7.39 (m, 2H), 6.94 (m, 4H), 5.06 (s, 1H), 3.62 (s, 3H), 3.28 (m, 3H), 2.05 (s, 3H).

**<sup>13</sup>C NMR (151 MHz, DMSO-*d*<sub>6</sub>):** δ 170.64, 169.15, 167.80, 155.14, 137.01, 135.52, 133.09, 131.34, 131.12, 130.24, 130.18, 129.07, 127.82, 127.00, 123.91, 117.85, 112.18, 79.70, 55.99, 53.87, 33.60, 23.76.

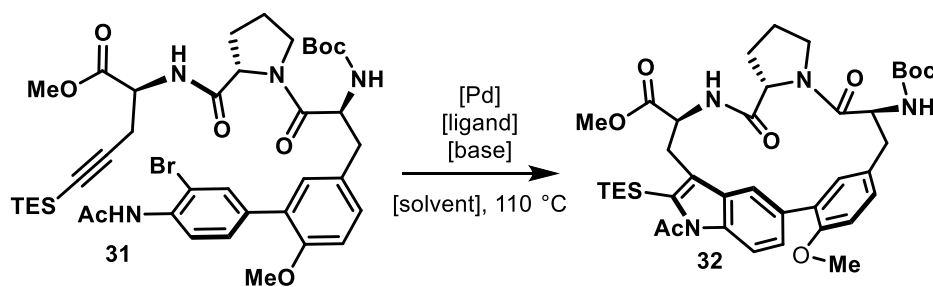
**HRMS (ESI-TOF):** calculated for C<sub>26</sub>H<sub>21</sub>BrN<sub>2</sub>NaO<sub>6</sub><sup>+</sup> [M+Na]<sup>+</sup>: 559.0475, found: 559.0484.

**TLC:** R<sub>f</sub> = 0.2 (10:1 DCM:Methanol, Ce<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in phosphomolybdic acid).

**[α]<sup>25</sup><sub>D</sub>:** -68.6 (*c* = 0.1, CHCl<sub>3</sub>)

## Optimization table of Larock cyclization

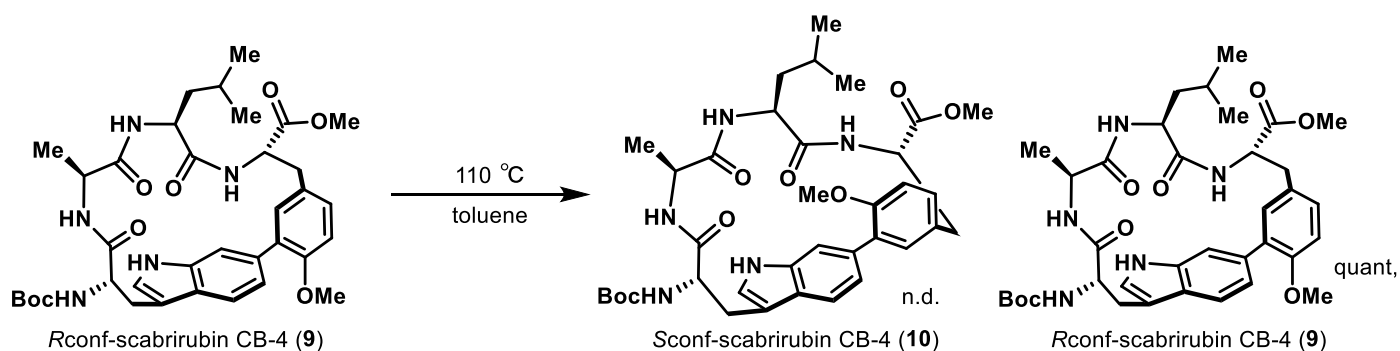
**Table S2.** Conditions screening of Larock cyclization



entry	[Pd] 0.5 eq.	[ligand] 1.0 eq.	[base] 10 eq.	[solvent] 1 mL	yield <sup>a</sup>
1	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub>	DIPEA	PhMe	22%
2	Pd(OAc) <sub>2</sub>	PCy <sub>3</sub>	DIPEA	PhMe	51%
3	Pd(OAc) <sub>2</sub>	P(OMe) <sub>3</sub>	DIPEA	PhMe	0%
4	Pd(OAc) <sub>2</sub>	dppe (0.5)	DIPEA	PhMe	31%
5	Pd(OAc) <sub>2</sub>	dppf (0.5)	DIPEA	PhMe	29%
-----					
6	Pd( <i>t</i> Bu <sub>3</sub> P) <sub>2</sub>	—	DIPEA	PhMe	35%
7	Pd(OAc) <sub>2</sub>	<i>t</i> Bu <sub>3</sub> P·HBF <sub>4</sub>	DIPEA	PhMe	59%
8 <sup>b</sup>	Pd(OAc) <sub>2</sub>	<i>t</i> Bu <sub>3</sub> P·HBF <sub>4</sub>	DIPEA	PhMe	45%
9	Pd(OAc) <sub>2</sub>	<i>t</i> Bu <sub>3</sub> P·HBF <sub>4</sub>	Cy <sub>2</sub> NMe	PhMe	50%
10	Pd(OAc) <sub>2</sub>	<i>t</i> Bu <sub>3</sub> P·HBF <sub>4</sub>	DBU	PhMe	30%
11	Pd(OAc) <sub>2</sub>	<i>t</i> Bu <sub>3</sub> P·HBF <sub>4</sub>	K <sub>2</sub> CO <sub>3</sub>	PhMe	42%
12	Pd(OAc) <sub>2</sub>	<i>t</i> Bu <sub>3</sub> P·HBF <sub>4</sub>	Cs <sub>2</sub> CO <sub>3</sub>	PhMe	trace
13	Pd(OAc) <sub>2</sub>	<i>t</i> Bu <sub>3</sub> P·HBF <sub>4</sub>	NaOAc	PhMe	36%

<sup>a</sup> Isolated yields. <sup>b</sup> The reaction was performed on 18.2 g scale. PhMe (0.06 M) were used for this scale.

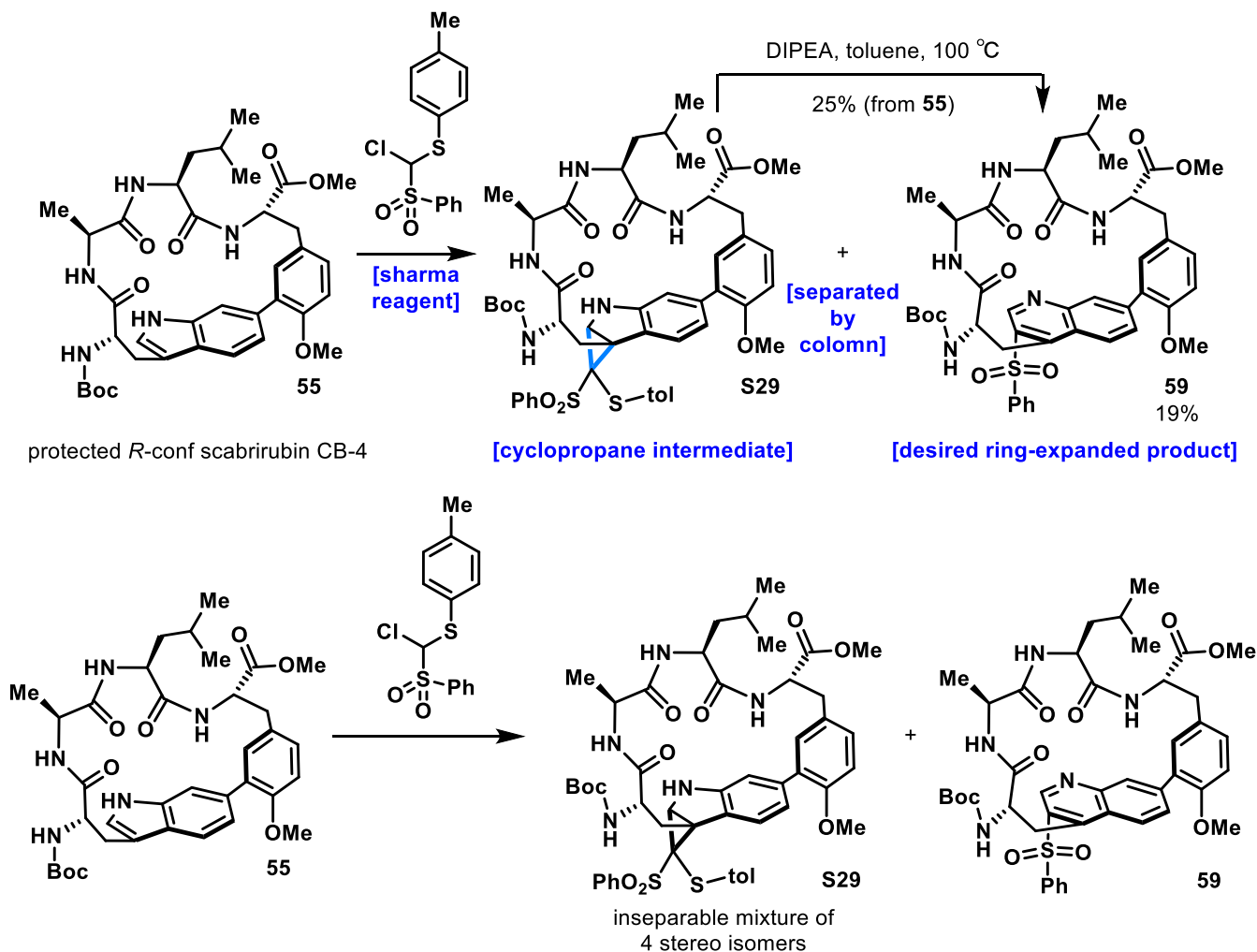
## Assessment of the thermodynamic stability of protected *R*-conf scabrirubin CB-4 (55)



The compound **9** (10.3 mg, 15.2  $\mu\text{mol}$ , 1.0 eq.) was dissolved in toluene (2 mL, 7.6 mM) and the solution was heated at 110 °C for 12h. The solvent was removed under reduced pressure, and the crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 2:1) to recover the starting material **9** (10.2 mg, quant.). The conformational isomer **10** was not observed.

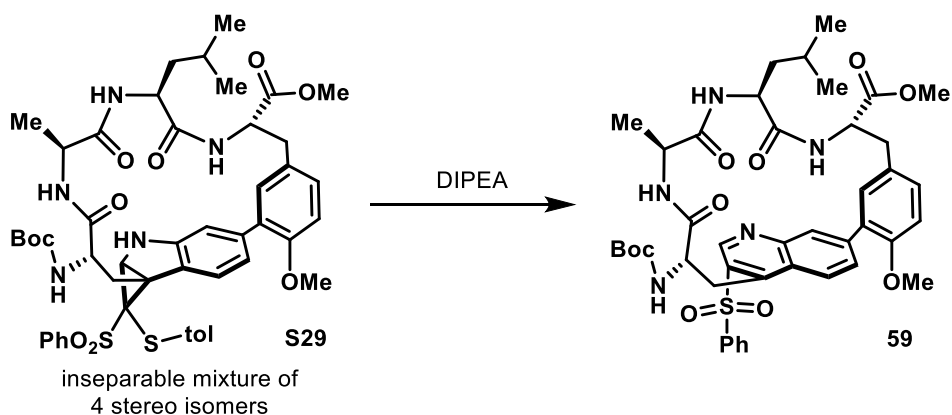
## Skeletal editing of scabrirubin core: stepwise procedure

**Scheme S4.** Overview of aminoquinoline-directed C-H activation.



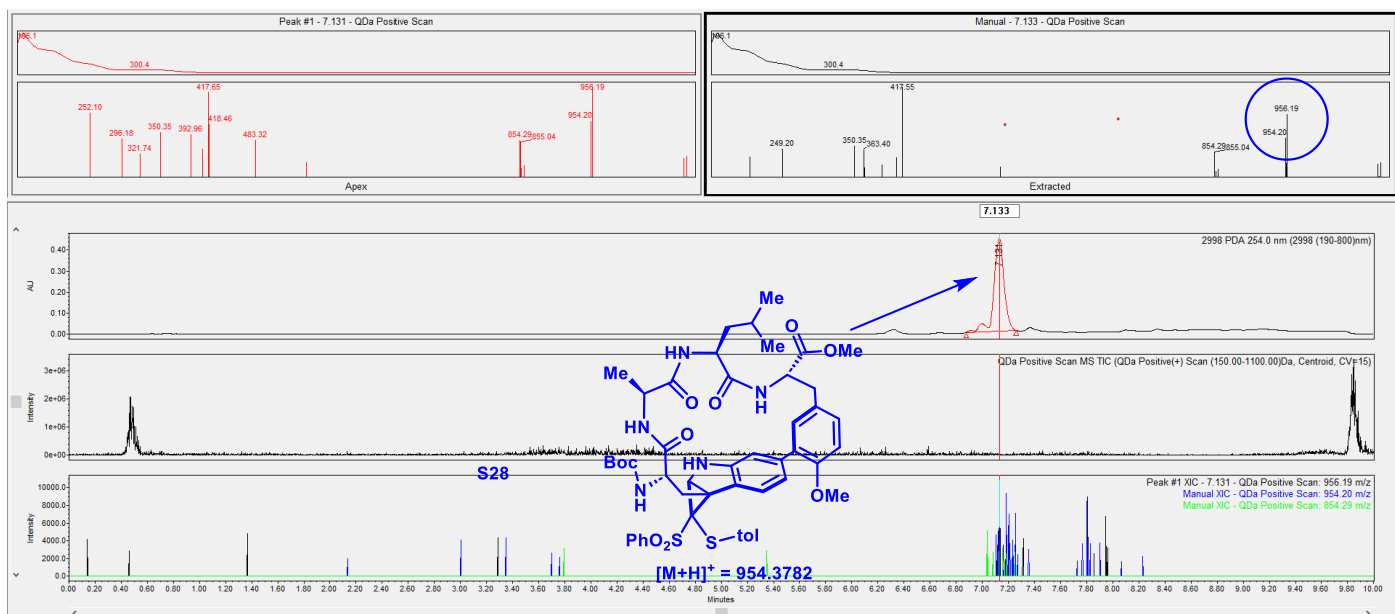
To a solution of compound **55** (100 mg, 148  $\mu\text{mol}$ , 1.0 eq.) and  $\text{Cs}_2\text{CO}_3$  (241 mg, 738  $\mu\text{mol}$ , 5.0 eq.) in THF (1.5 mL, 0.1 M), (chloro(phenylsulfonyl)methyl(*p*-tolyl)sulfane (92.1 mg, 295  $\mu\text{mol}$ , 2.0 eq.) was added portion-wise (0.5 equiv. every 1 h) at room temperature, and the resulting mixture was stirred for the next 4 h. The reaction was quenched with saturated aq.  $\text{Na}_2\text{S}_2\text{O}_3$ , extracted with EtOAc (5mL) three times. The

organic layers were combined and washed with brine and concentrated under reduced pressure to give the crude. The crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 3:1) to give the compound **59** (23.3 mg, 19% yield), along with the fraction containing cyclopropane intermediate **S28** (67.7 mg), which was obtained as an inseparable mixture of 4 stereoisomers.



The obtained fraction containing cyclopropane intermediate **S29** (67.7 mg) was dissolved in toluene (2 mL), and DIPEA (0.2 mL) was added. The solution was heated at 100 °C until the compound **S29** is completely consumed, judged by TLC. The solvent was evaporated, and the crude was purified by preparative thin-layer chromatography (EtOAc:Hexane 3:1) to give the compound **59** (30.6 mg, 25% yield from compound **55**). The characterization data were identical to those of compound **59** originally obtained in the previous step.

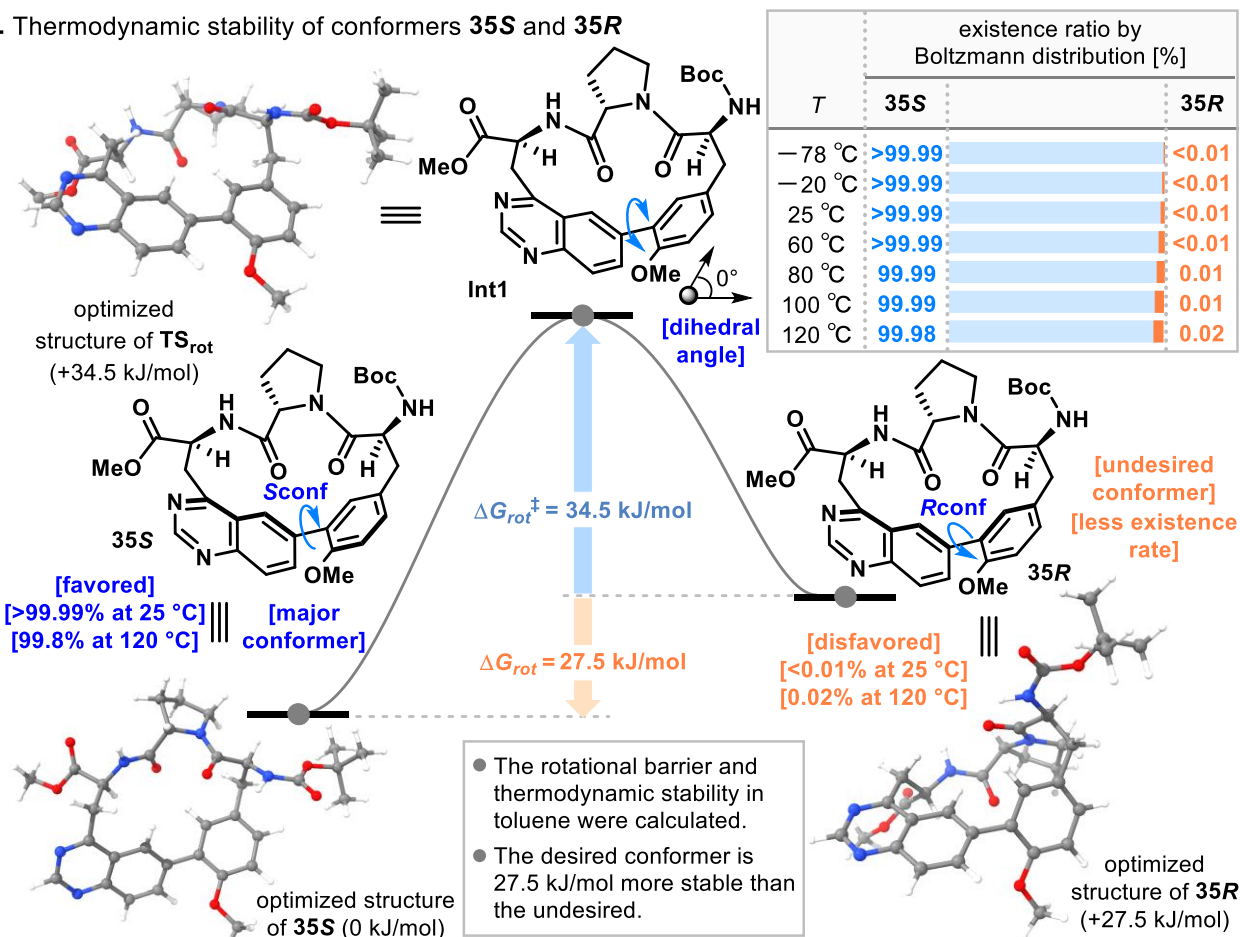
## LC-MS spectrum of cyclopropane intermediate **S29**



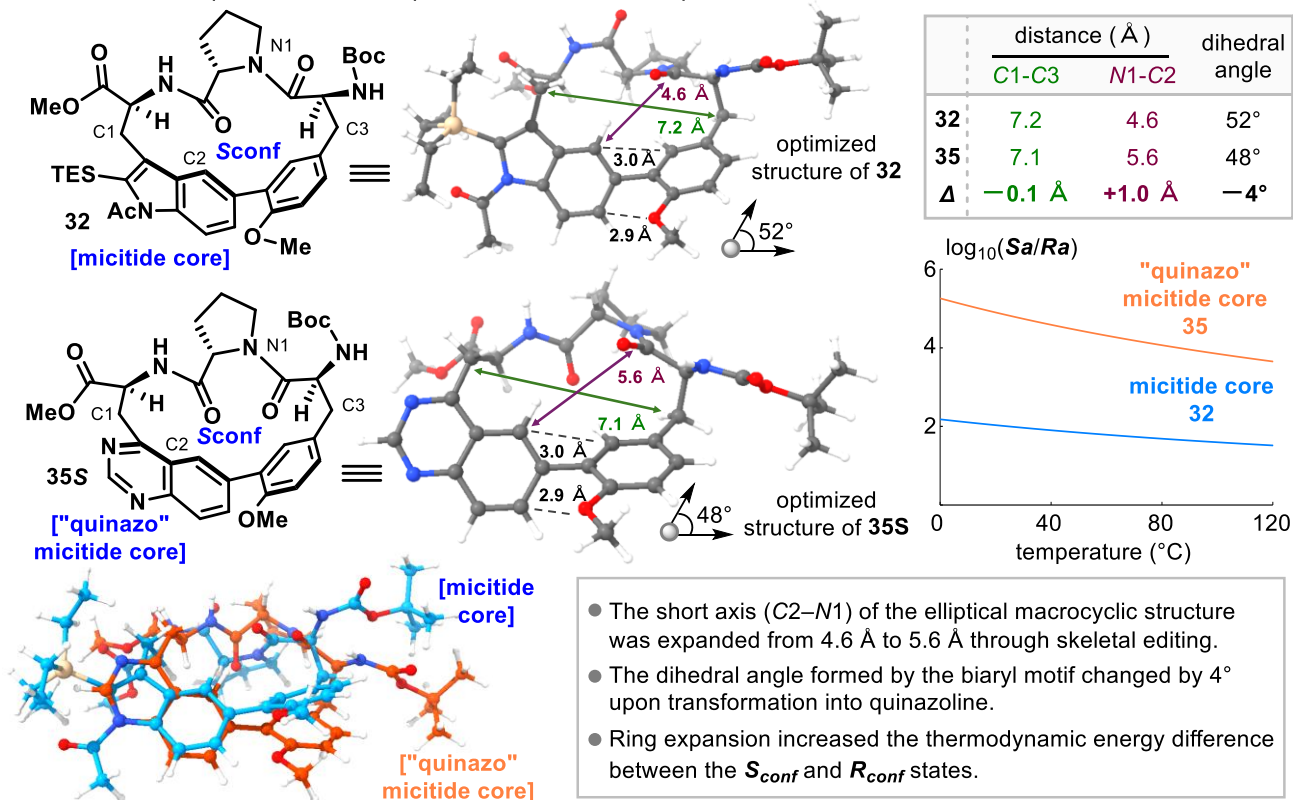
**Figure S1.** LC-MS spectrum of cyclopropane intermediate **S29**.

## Computational Details

### A. Thermodynamic stability of conformers **35S** and **35R**



### B. Structural comparison of DFT-Optimized micitide and "quinazo" micitide cores



**Figure S2.** (A) Thermodynamic stability of conformers **35S** and **35R**. (B) Structural comparison of DFT-optimized structures.

Equilibrium structures and a transition state were optimized employing GRRM23<sup>3-5</sup> with Gaussian 16, Revision C.02,<sup>6</sup> at the  $\omega$ B97X-D/def2-SVP level of theory in conjunction with the SMD solvation model (methanol) at 298.15 K. Subsequent vibrational frequency analyses were performed at the  $\omega$ B97X-D/def2-TZVP level with the SMD solvation model (methanol) to evaluate the Gibbs free energy at 298.15 K. The visualization was conducted by UCSF ChimeraX version 1.9.<sup>7,8</sup>

**Table S3.** Summary of the DFT calculations

	Free energy (hartree)	Relative free energy (hartree)	Relative free energy (kJ/mol)
Compound- <b>35S</b>	-2039.494037	0	0
Compound- <b>Int1</b>	-2039.479568	0.014469125	37.98868677
Compound- <b>35R</b>	-2039.482872	0.011164835	29.31327395

## Cartesian Coordinates

### Compound-35S

```

C   -1.912412849580   3.486379636046  -2.152935426064
C    0.050131378709   1.995278807415  -1.597368903561
C   -3.258740158463   3.639034269604  -2.494722533042
C   -1.382449007802   2.191248306237  -1.950856866661
C   -2.239930529180   1.093337015403  -2.063685178320
C   -4.081809761049   2.520342903298  -2.613226360109
C   -3.594467173711   1.231368634620  -2.389232273292
H   -1.833196540169   0.092047374363  -1.896708480660
H   -3.680451898827   4.629862177305  -2.663397819146
H   -5.129309913727   2.666598525923  -2.890974277495
C   -4.517343937542   0.041767370306  -2.449987093445
C    0.410952554853   1.152677442188  -0.564274559440
C    1.077329547300   2.656167440402  -2.334618955398
C    2.401101801450   2.498673676461  -2.016023259441
C    1.777000662860   0.959603824056  -0.222750111446
C    2.782308824736   1.657854948368  -0.938865631535
H    0.798631048602   3.301397803225  -3.169129693944
H    3.185052250607   3.012611913078  -2.575704092590
H   -0.373141199036   0.651071502472   0.007528457566
H   -3.963118917151  -0.858991593248  -2.753336156777
C   -5.241474129377  -0.252298843833  -1.103187861263
H   -5.297995390293   0.214668702941  -3.204354468068
C   -4.248408899378  -0.825284684456  -0.101558033160
N   -5.824165188558   0.922801679123  -0.498302774561
H   -6.038119056991  -0.981348865821  -1.297657128410
O   -3.611134042786  -0.076724737800   0.643855274121
N   -4.062237370210  -2.154251695518  -0.096916161519
C   -4.722269309538  -3.159377971590  -0.939889582772
C   -3.010622183193  -2.720525514109   0.731687533655

```

C	-3.820305177003	-4.384208429296	-0.800554402327
C	-3.224195819915	-4.236646661177	0.598867820554
H	-4.800840958489	-2.824246215725	-1.982288478390
H	-5.738488486125	-3.358113980939	-0.561847600162
C	-1.647111011228	-2.304083717195	0.181619208495
H	-2.290432313228	-4.797504786797	0.743991767081
H	-3.022637681189	-4.347003762987	-1.557170884248
H	-4.375581122563	-5.322020289616	-0.934444916409
H	-3.941901744036	-4.563462004428	1.366188974019
O	-1.472842054863	-2.094775325692	-1.015384308131
N	-0.664045751098	-2.225307461707	1.096040130214
H	-0.870362594299	-2.438950508616	2.067193318906
C	0.692481704847	-1.924720152242	0.734359447477
H	0.670747152487	-1.628048947958	-0.325071110825
C	1.276928339245	-0.771286087789	1.587291368259
C	1.553665904619	-3.177864215288	0.796614384690
O	2.784774790085	-2.927868030401	0.387406443606
O	1.166007538023	-4.262560629783	1.161060065081
C	3.721000837399	-4.003771598059	0.410584137135
H	0.430362151838	-0.160656427911	1.931346542893
H	1.785969765679	-1.164067226127	2.477438533224
C	2.238138721396	0.097390276810	0.823757304725
N	3.515147046332	0.028128432791	1.130274692512
H	-5.226823711267	1.439381753114	0.141419754404
C	-6.900764753731	1.594833238356	-0.968304682982
O	-1.067257498771	4.526096672770	-1.980868196666
C	-1.540908512762	5.842975812997	-2.160952322965
O	-7.243038819997	2.687705081516	-0.543536794602
O	-7.526923286744	0.902115480297	-1.920103925585
C	-8.687186810104	1.407248744913	-2.647720414072
C	-9.848934107237	1.647042231646	-1.688515871041
C	-8.300683047240	2.660800746881	-3.426221553596
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## Compound 35R

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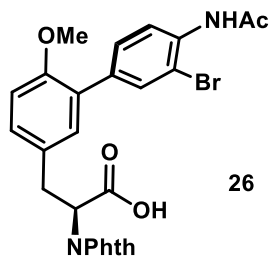
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C	0.549626136908	0.963072295139	-5.744589792277
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## Reference

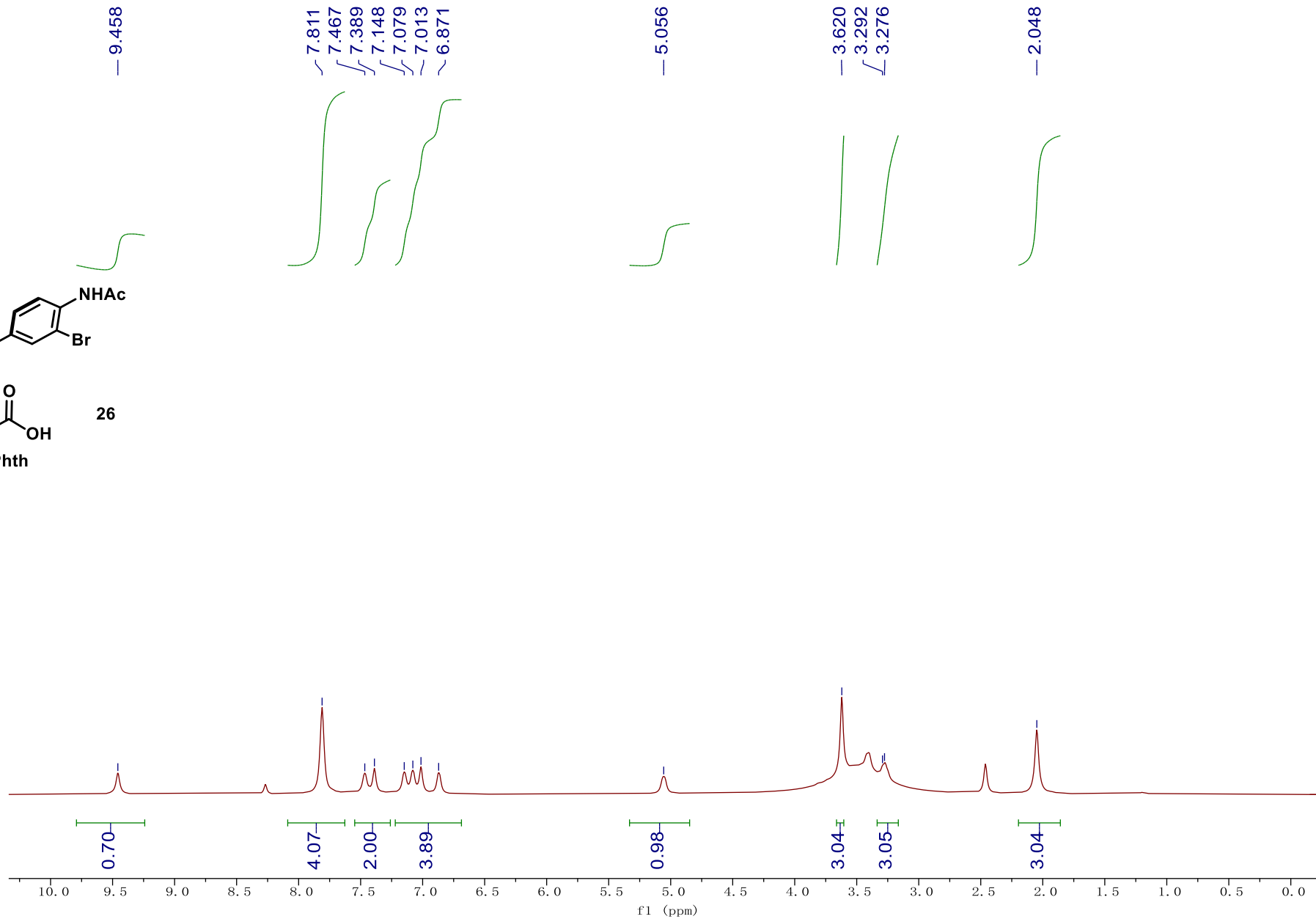
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- (5) Maeda, S.; Ohno, K.; Morokuma, K. Systematic Exploration of the Mechanism of Chemical Reactions: The Global Reaction Route Mapping (GRRM) Strategy Using the ADDF and AFIR Methods. *Phys. Chem. Chem. Phys.* **2013**, *15* (11), 3683–3701.
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# **NMR Spectrums**

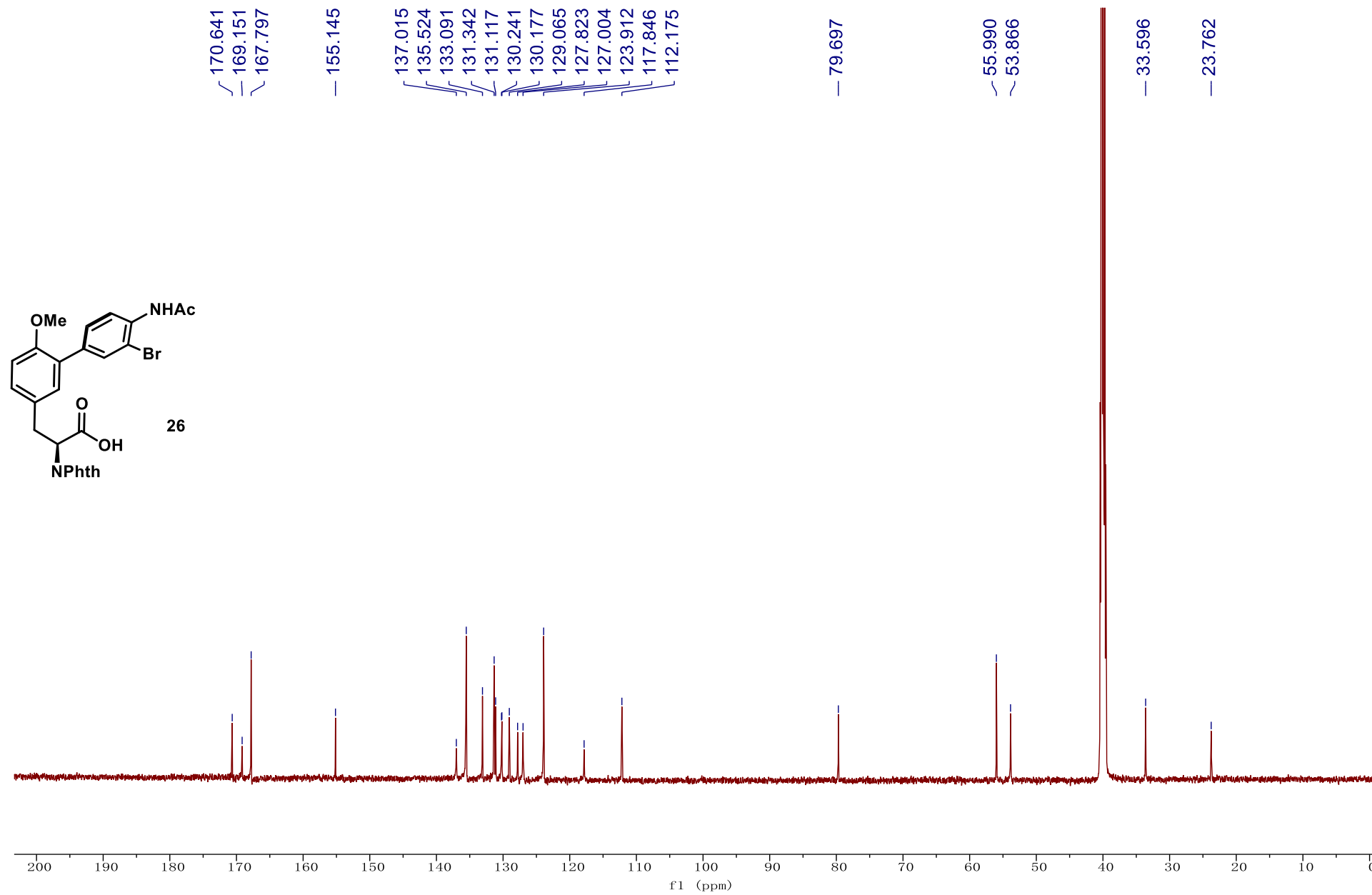
Compound 26 <sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>)



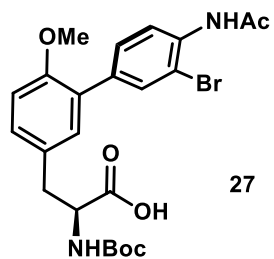
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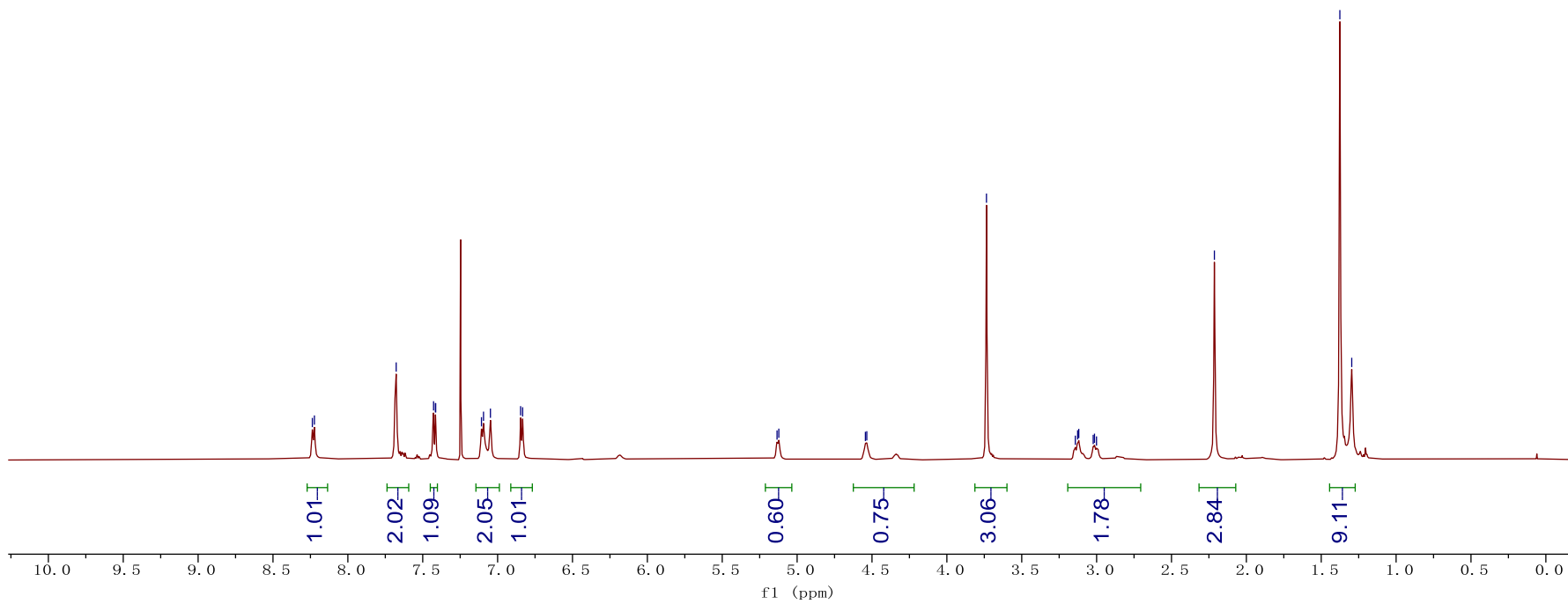
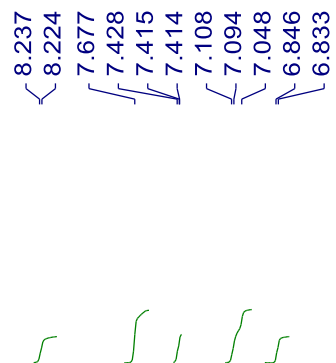
Compound 26 <sup>13</sup>C NMR (151 MHz, DMSO-*d*<sub>6</sub>)



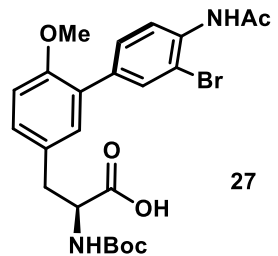
Compound 27 <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)



A mixture of two rotamers.  
A:B = 3:1



Compound 27 <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)

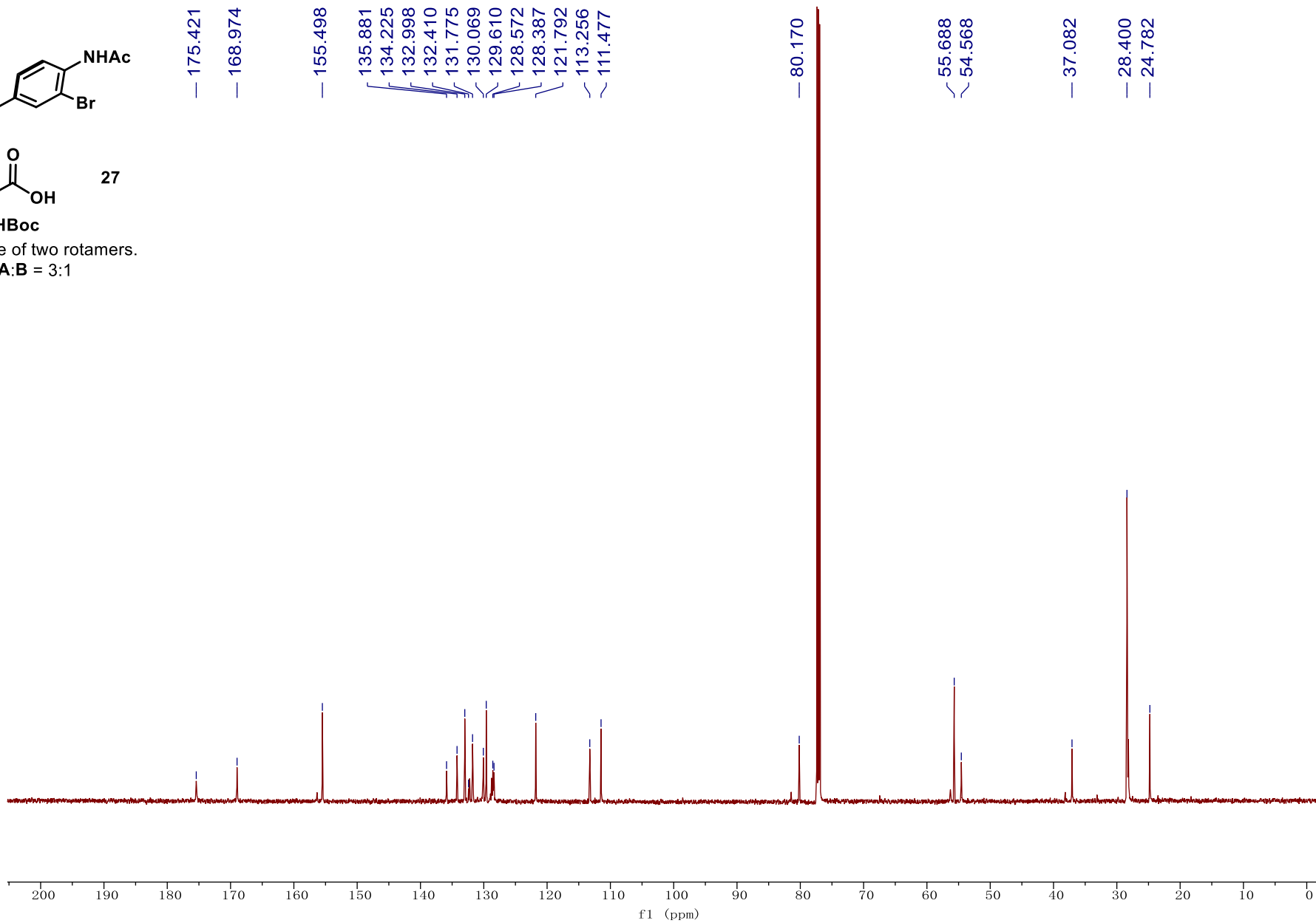


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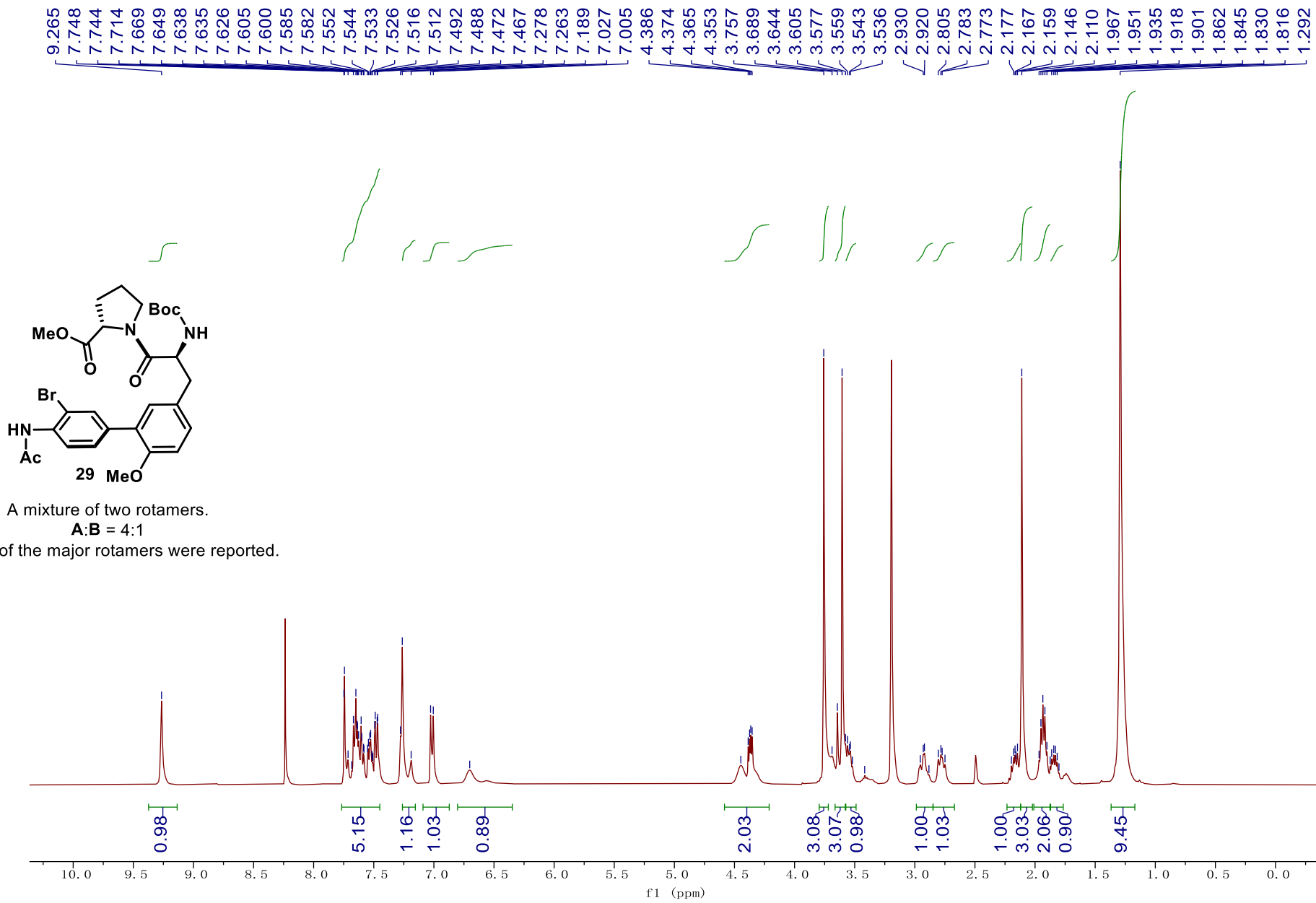
A mixture of two rotamers.  
A:B = 3:1

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131.775  
130.069  
129.610  
128.572  
128.387  
121.792  
113.256  
111.477

— 80.170  
55.688  
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— 24.782



Compound 29 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 60 °C)

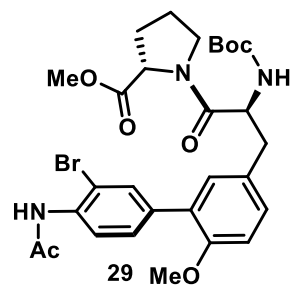


A mixture of two rotamers.

**A:B = 4:1**

Signals of the major rotamers were reported.

Compound 29 <sup>13</sup>C NMR (101 MHz, DMSO-d<sub>6</sub>, 60 °C)

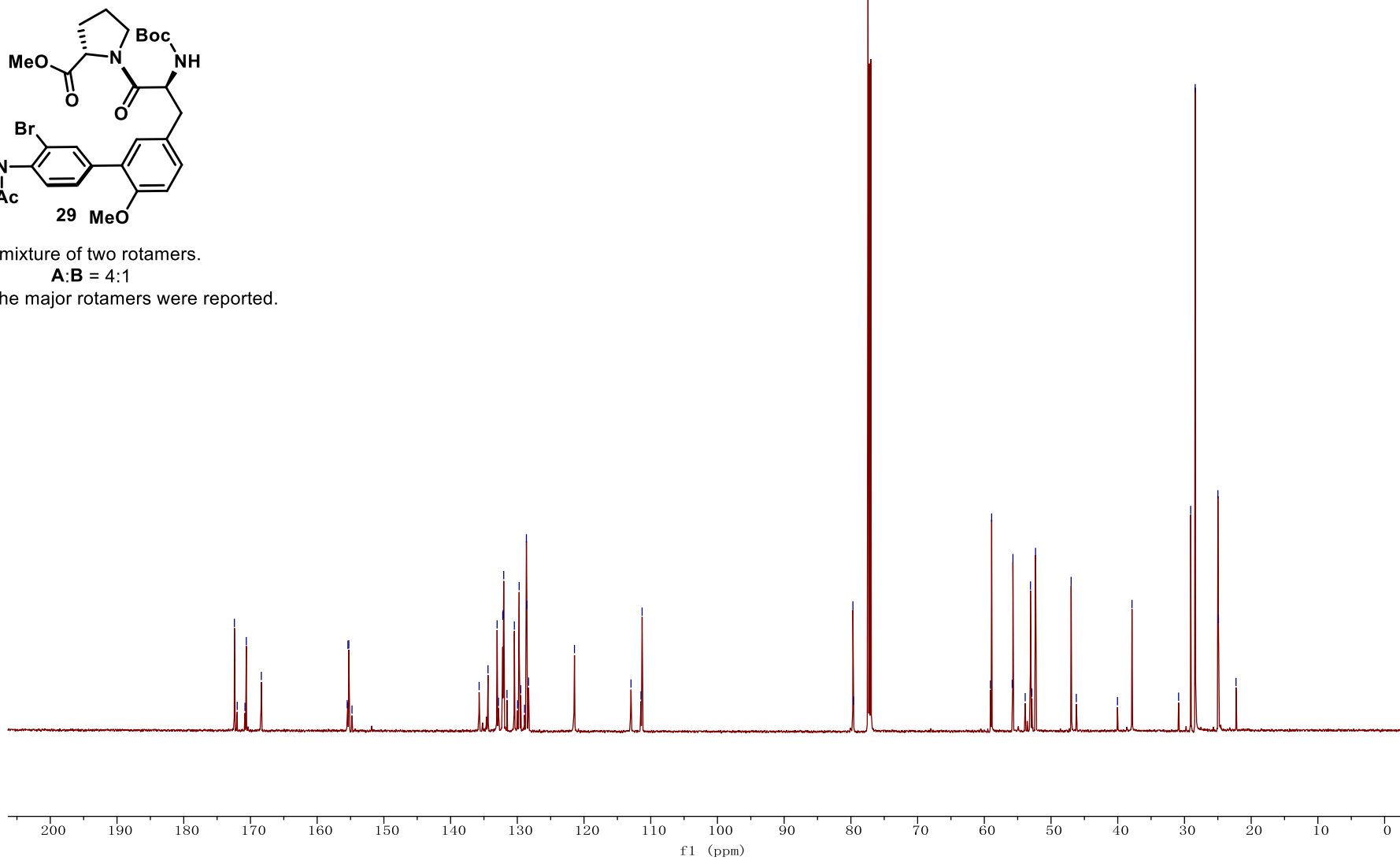


A mixture of two rotamers.

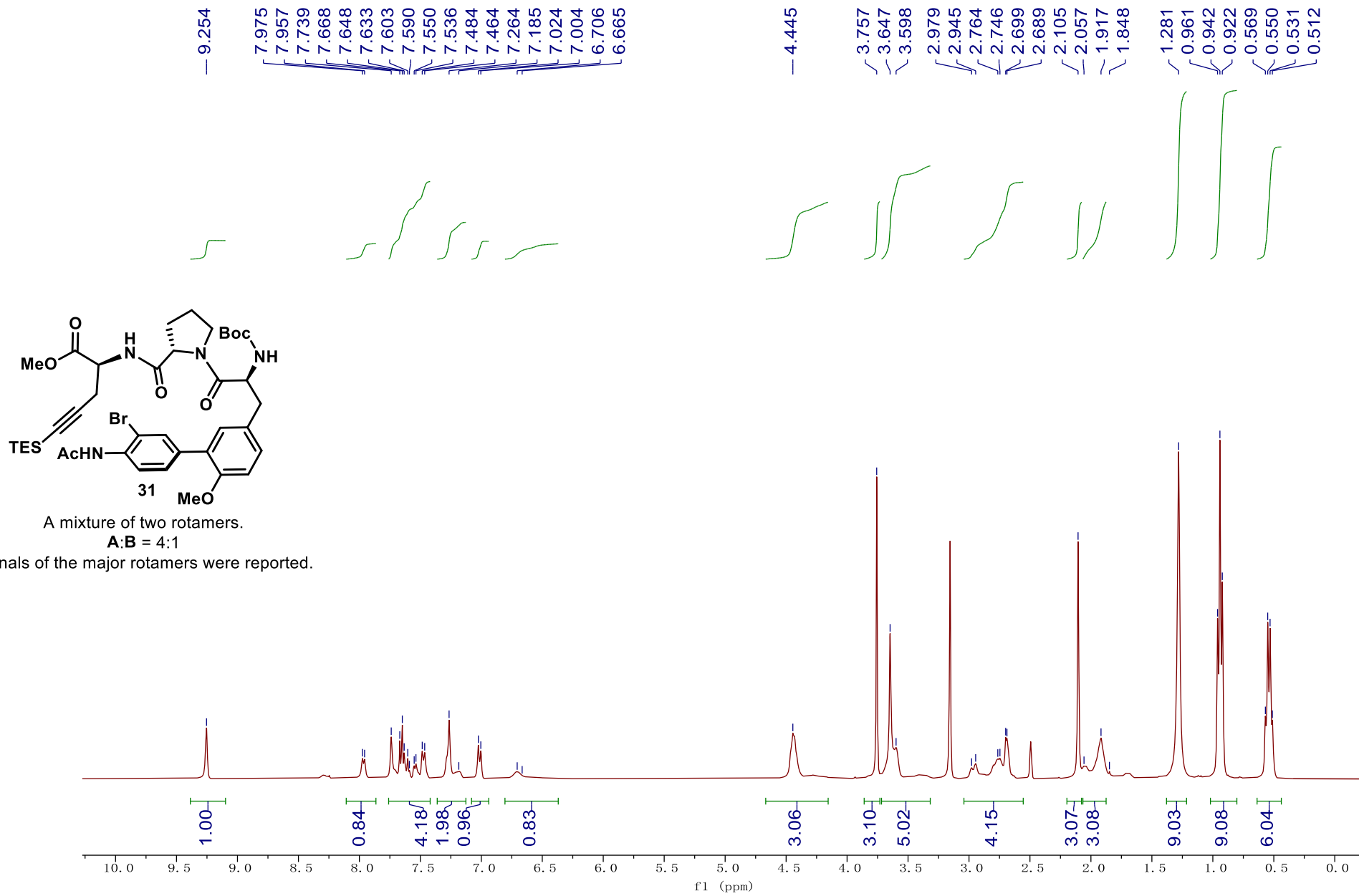
A:B = 4:1

Signals of the major rotamers were reported.

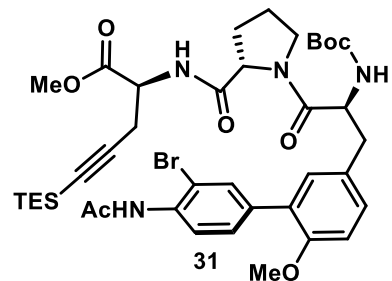
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129.964  
129.723  
129.475  
128.915  
128.637  
128.558  
128.308  
121.433  
112.959  
111.464  
111.294  
79.697  
79.598  
59.082  
58.901  
55.821  
55.711  
53.875  
53.080  
52.872  
52.322  
46.988  
46.207  
40.042  
37.865  
30.879  
29.066  
28.392  
24.988  
24.906  
22.267



Compound 31 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 60 °C)



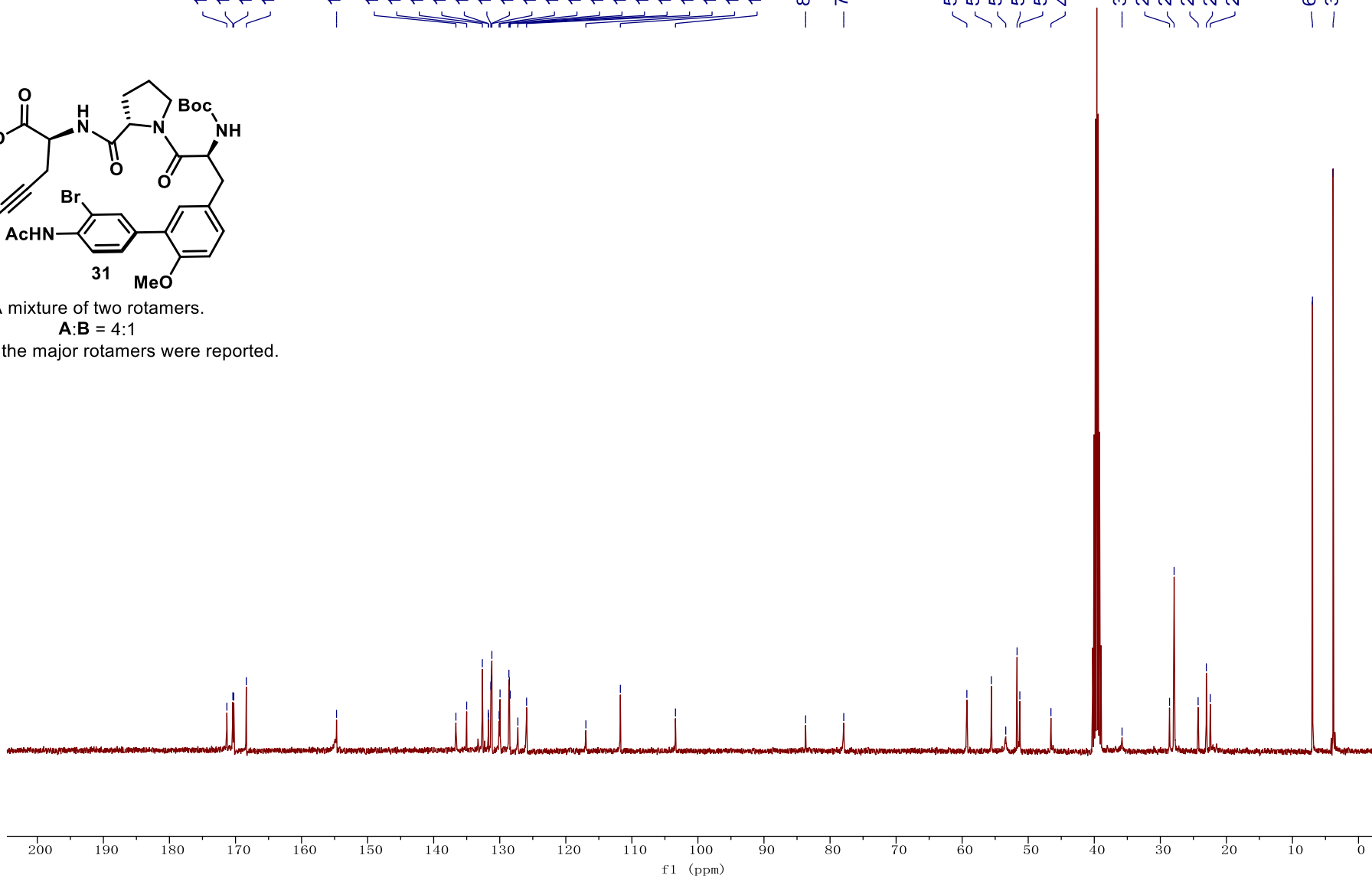
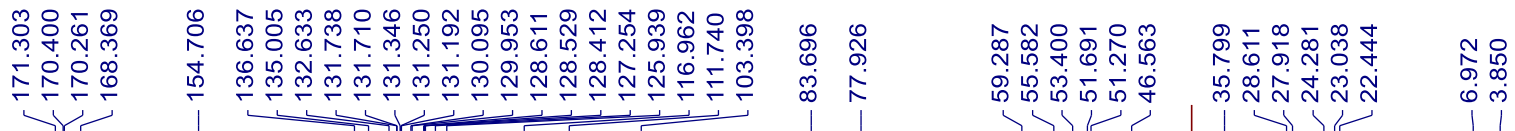
Compound 31 <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>, 60 °C)



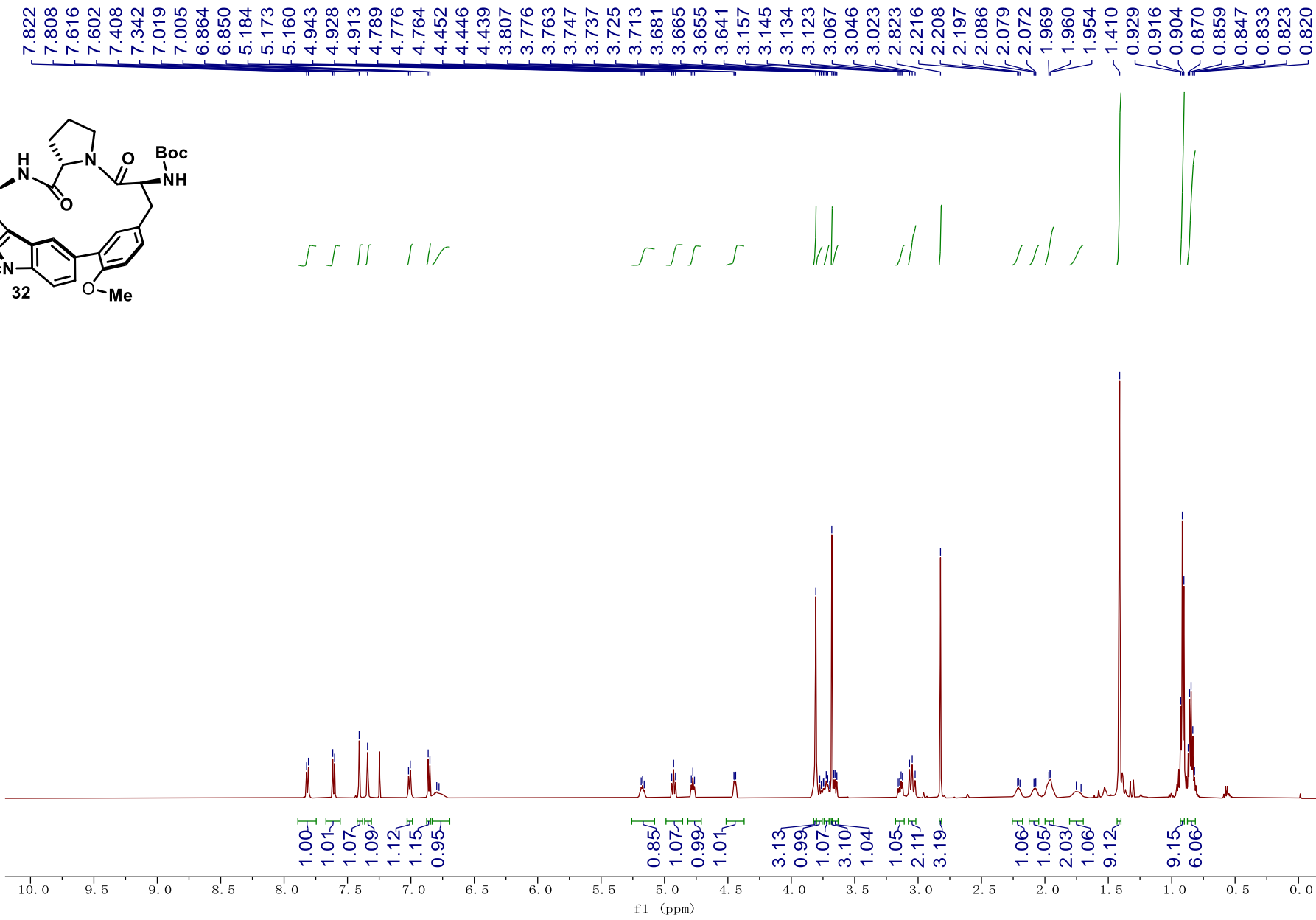
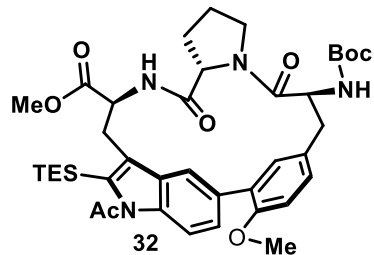
A mixture of two rotamers.

**A:B** = 4:1

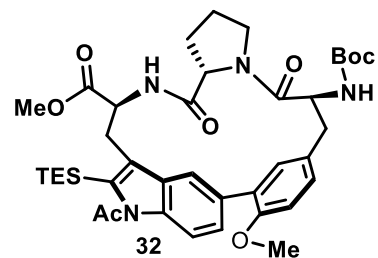
Signals of the major rotamers were reported.



Compound 32 <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)



Compound 32 <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)



173.433  
171.461  
169.733  
169.604

155.482  
155.452  
136.066  
135.266  
133.717  
133.284  
132.551  
132.025  
130.879  
129.137  
127.398  
127.205  
121.213

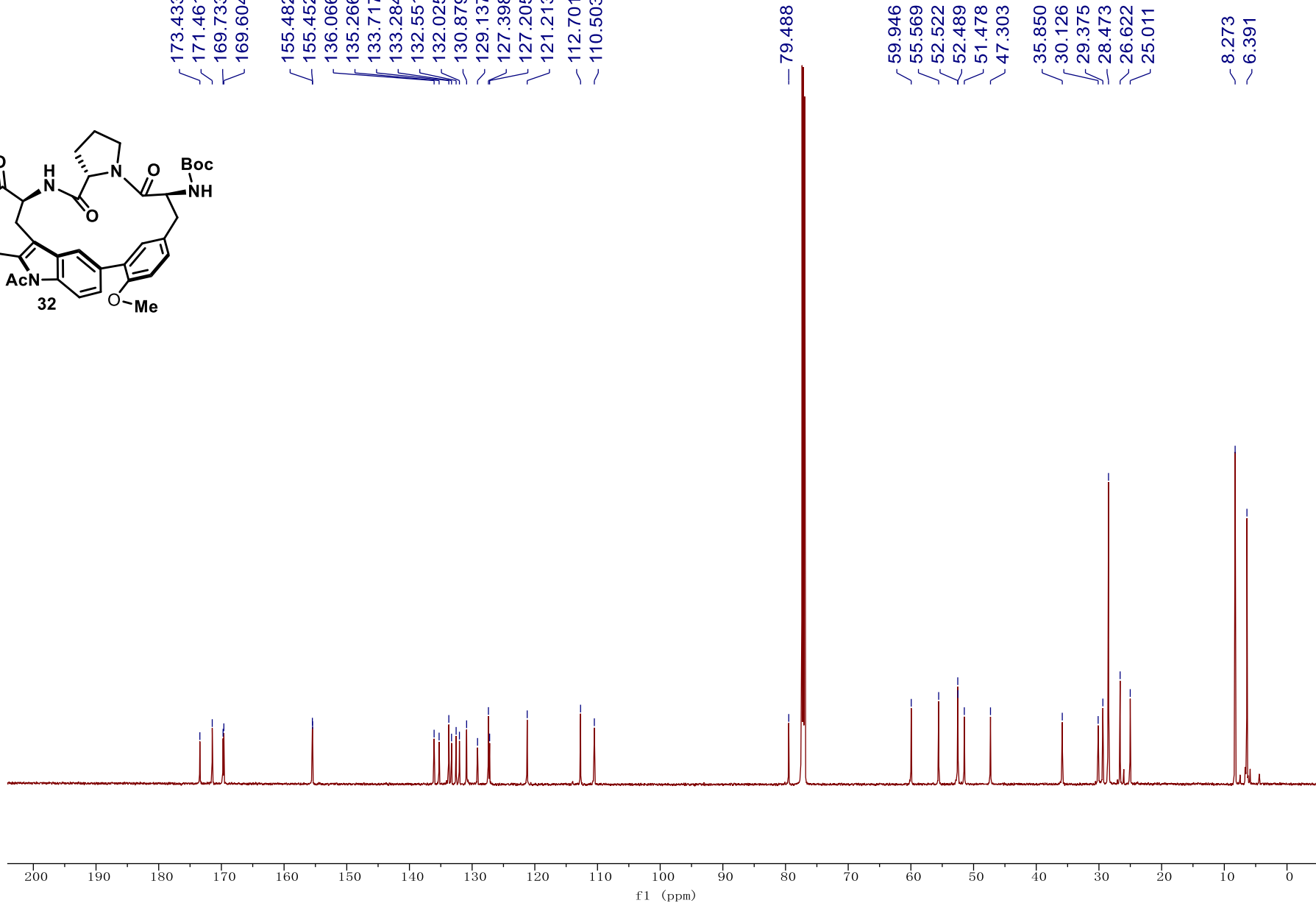
112.701  
110.503

79.488

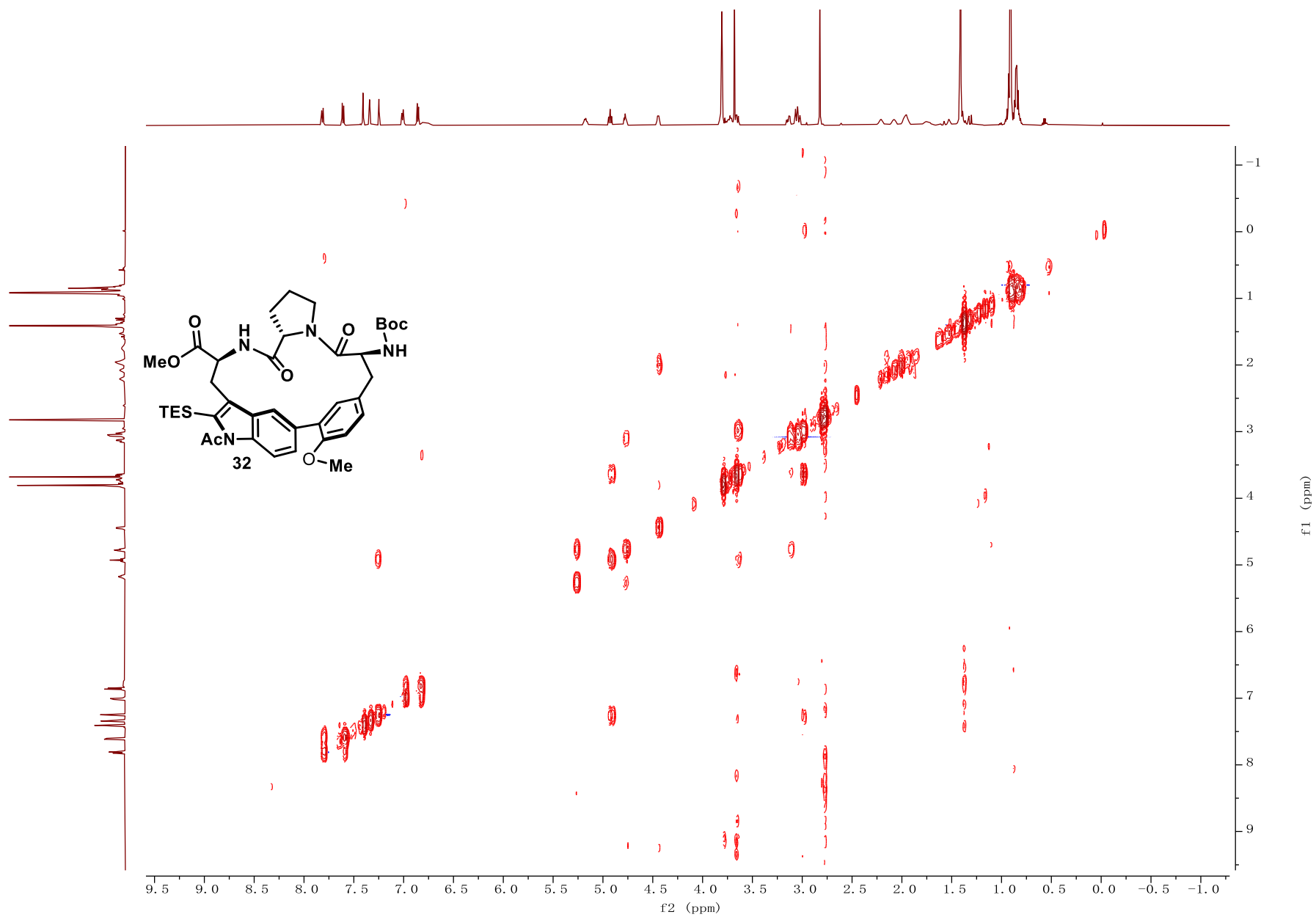
59.946  
55.569  
52.522  
52.489  
51.478  
47.303

35.850  
30.126  
29.375  
28.473  
26.622  
25.011

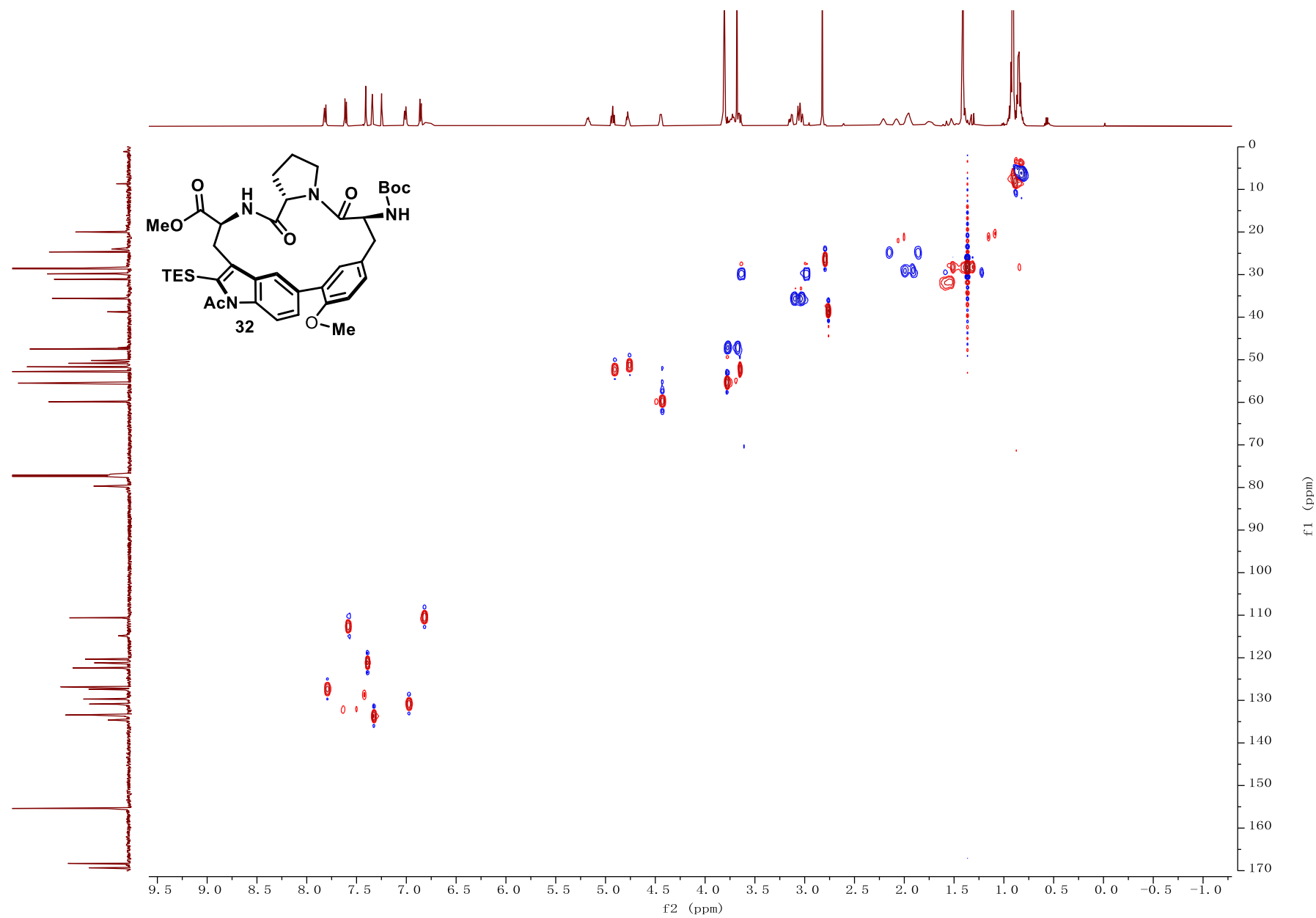
8.273  
6.391



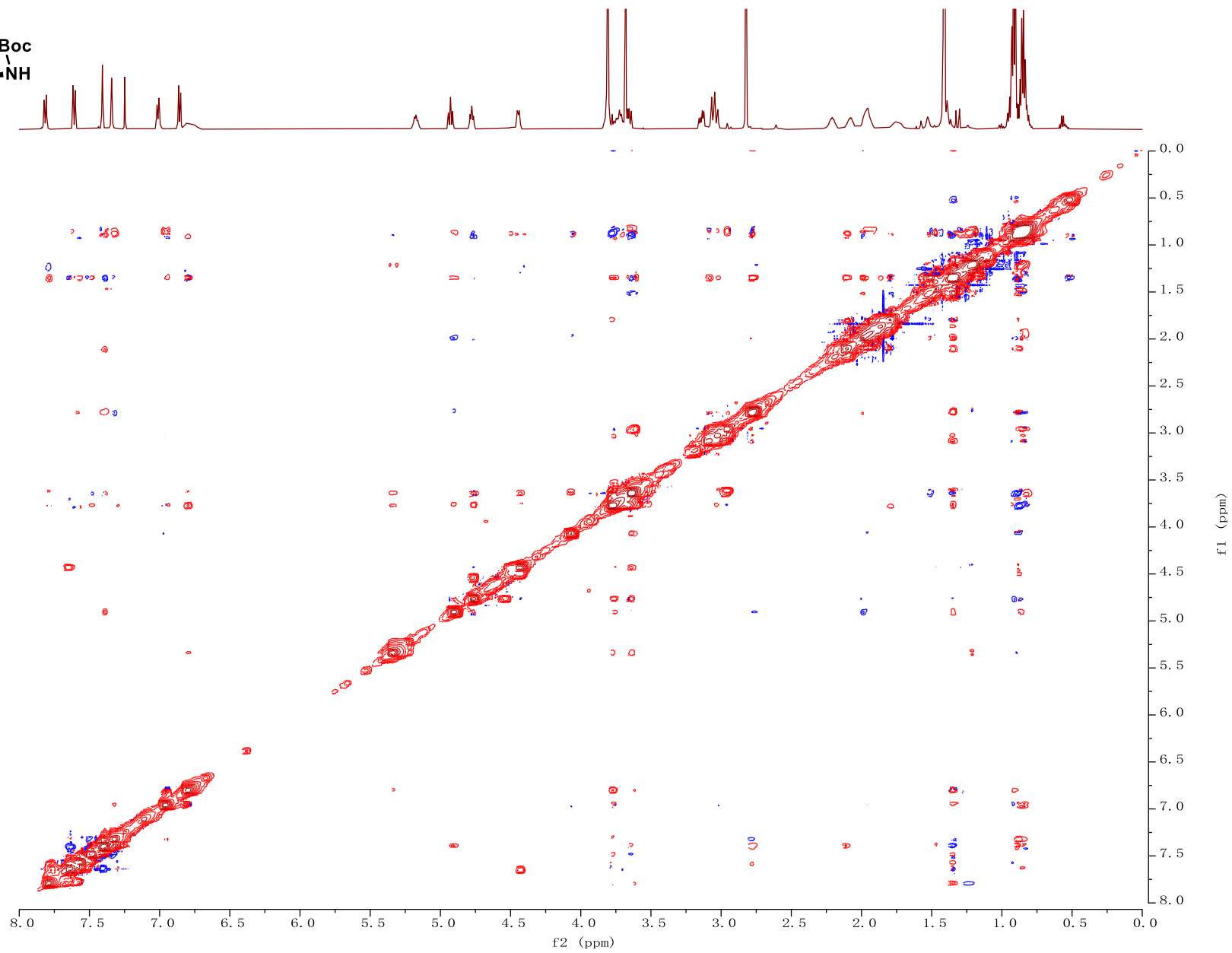
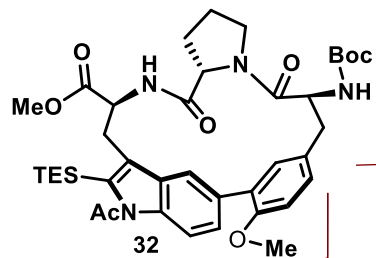
Compound 32  $^1\text{H}$ - $^1\text{H}$  COSY NMR (600 MHz,  $\text{CDCl}_3$ )



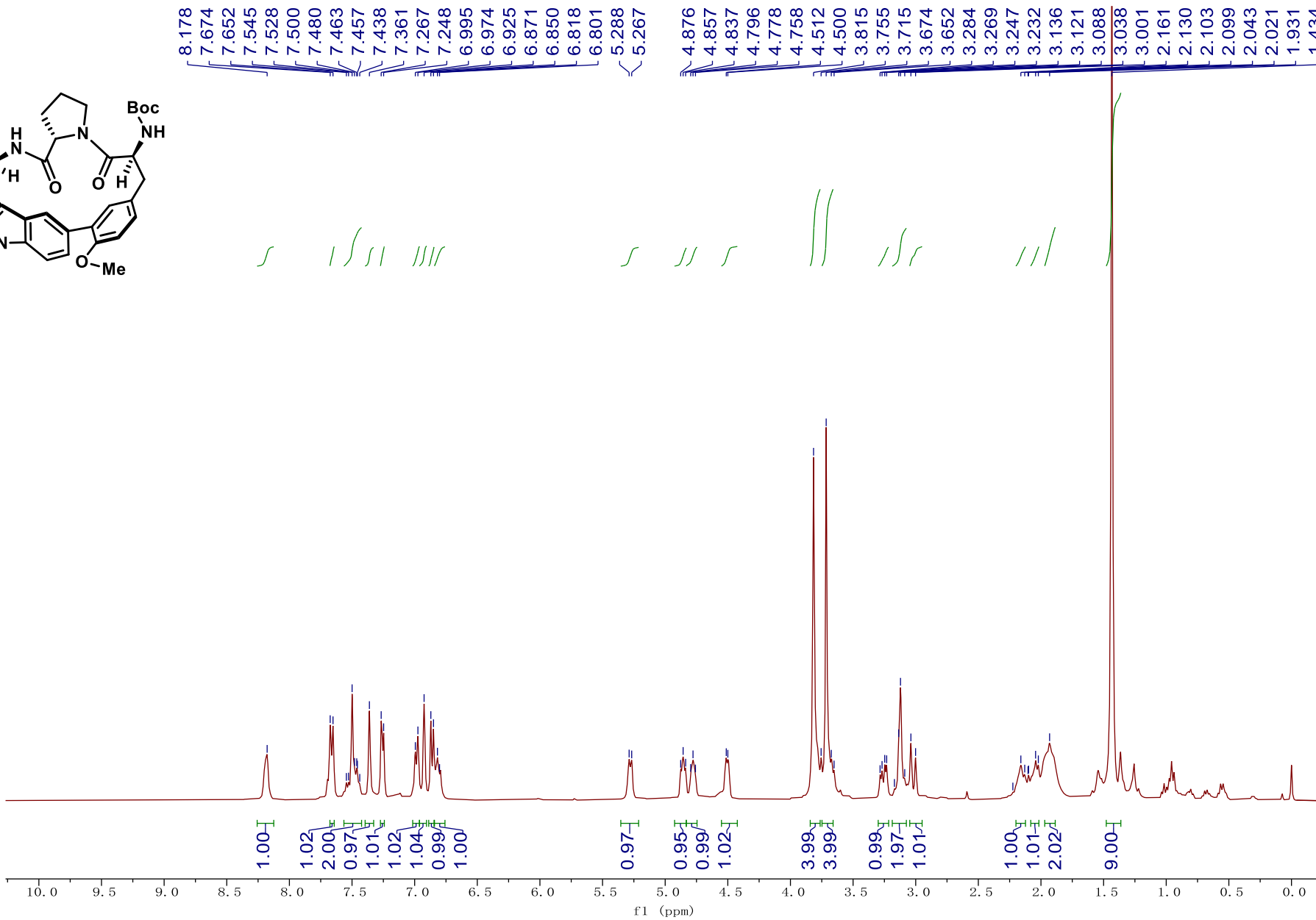
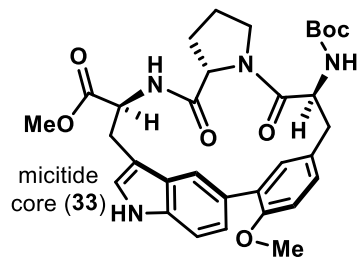
Compound 32  $^1\text{H}$ - $^{13}\text{C}$  HSQC NMR (600 MHz,  $\text{CDCl}_3$ )



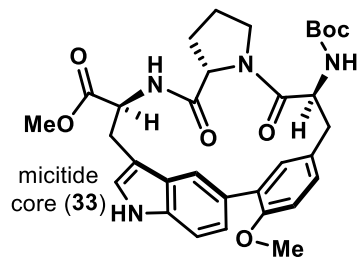
Compound 32  $^1\text{H}$ - $^1\text{H}$  NOESY NMR (600 MHz,  $\text{CDCl}_3$ )



Compound 33 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



Compound 33 <sup>1</sup>H NMR (101 MHz, CDCl<sub>3</sub>)



173.814  
171.193  
169.834

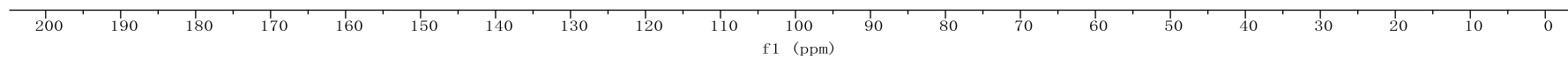
155.494  
155.445

135.583  
134.174  
132.162  
130.898  
129.989  
129.734  
128.489  
126.965  
124.338  
121.534  
121.018  
114.417  
110.608  
109.604

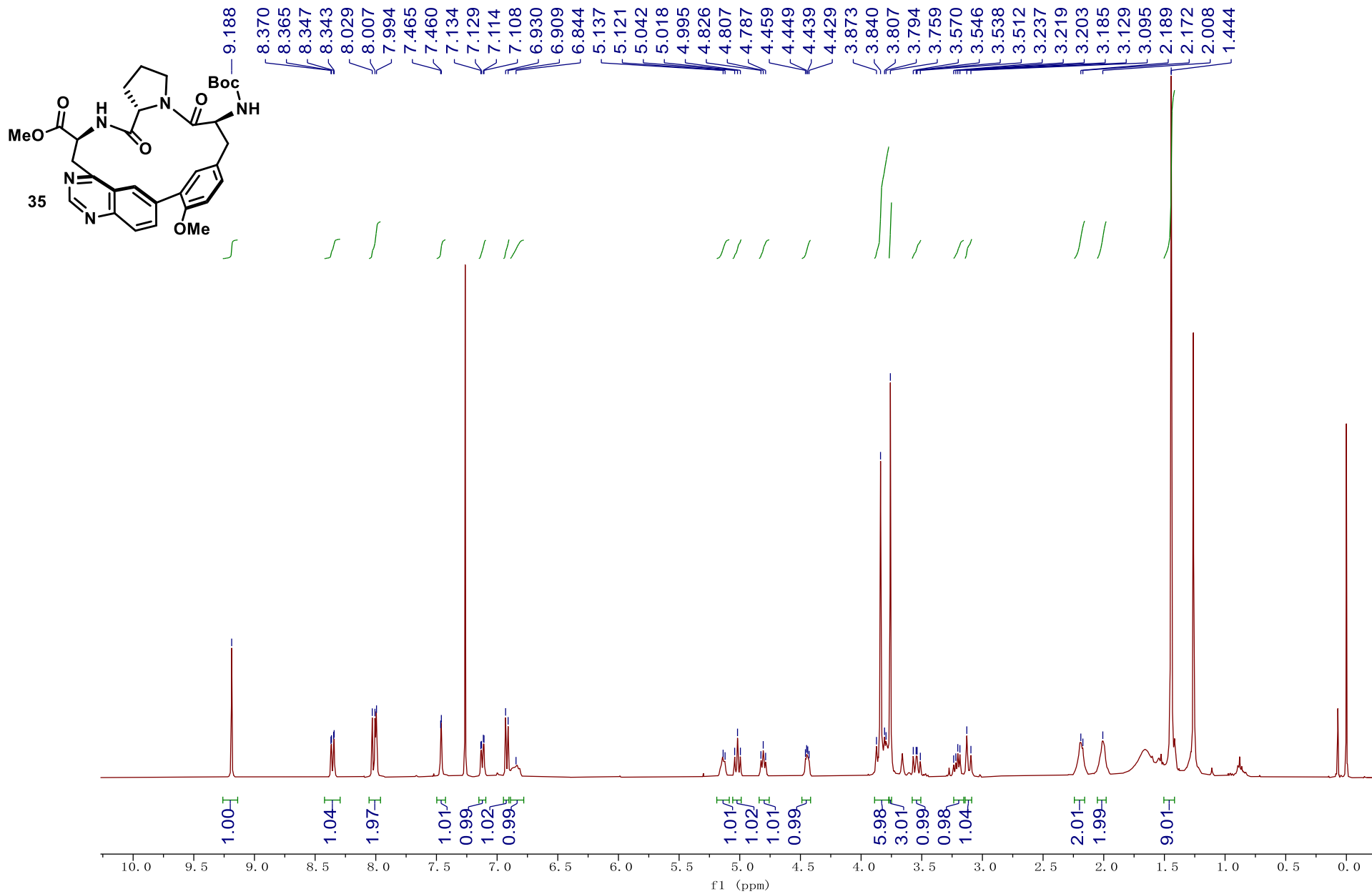
79.432

60.061  
55.571  
53.519  
52.403  
51.699  
47.174

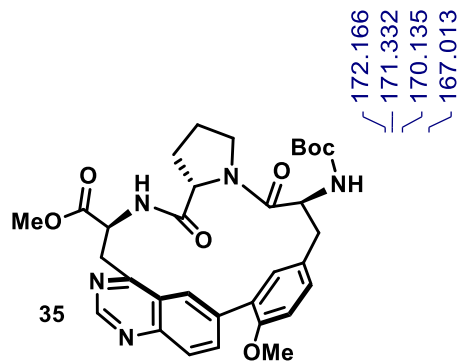
35.813  
31.048  
29.530  
28.444  
24.881



Compound 35 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

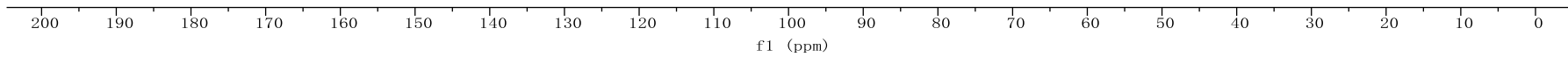


Compound 35 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

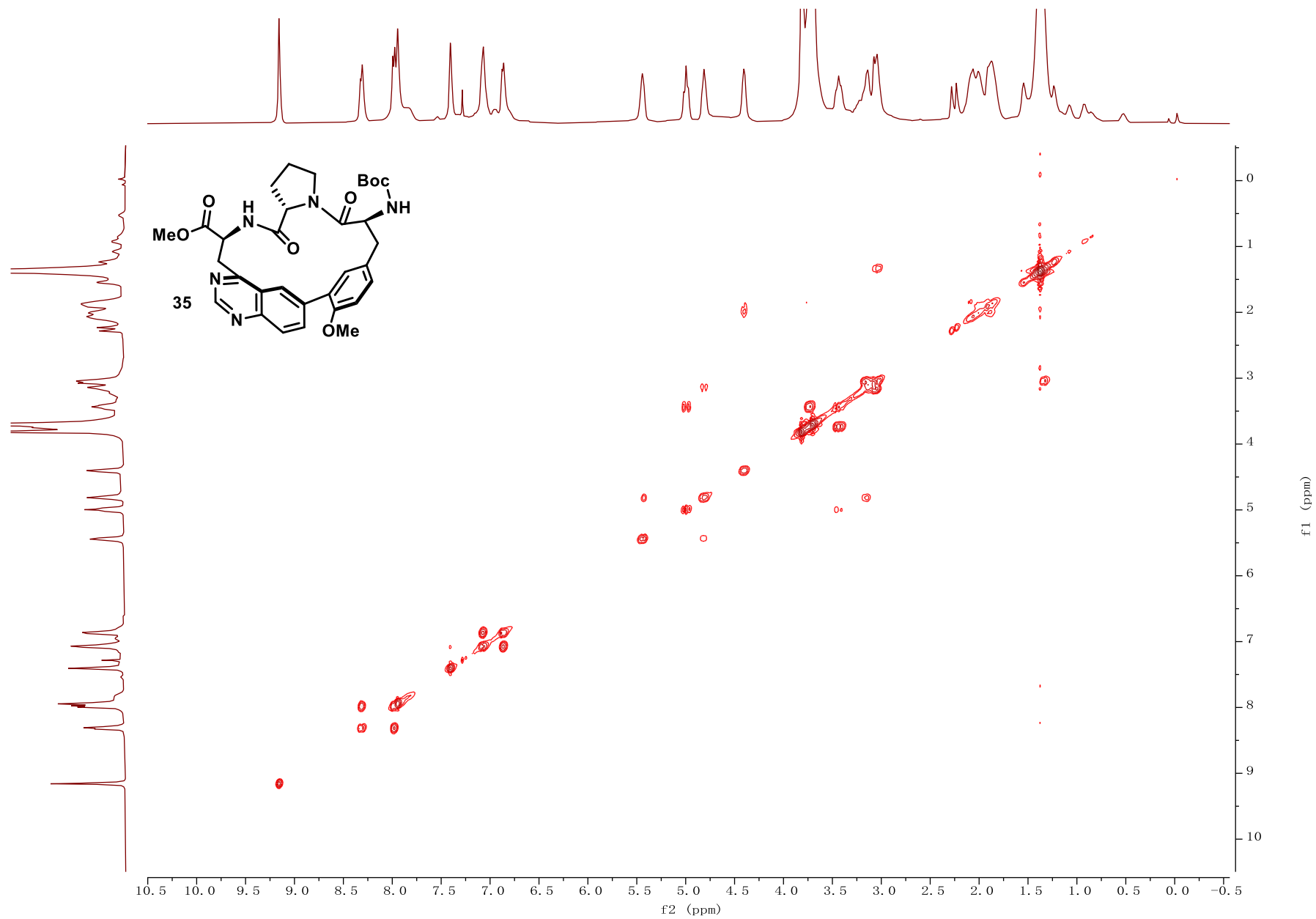


- 172.166
- 171.332
- 170.135
- 167.013
- 155.674
- 155.384
- 153.994
- 149.562
- 139.261
- 136.896
- 133.886
- 132.250
- 128.353
- 127.590
- 127.414
- 125.092
- 123.402
- 110.757

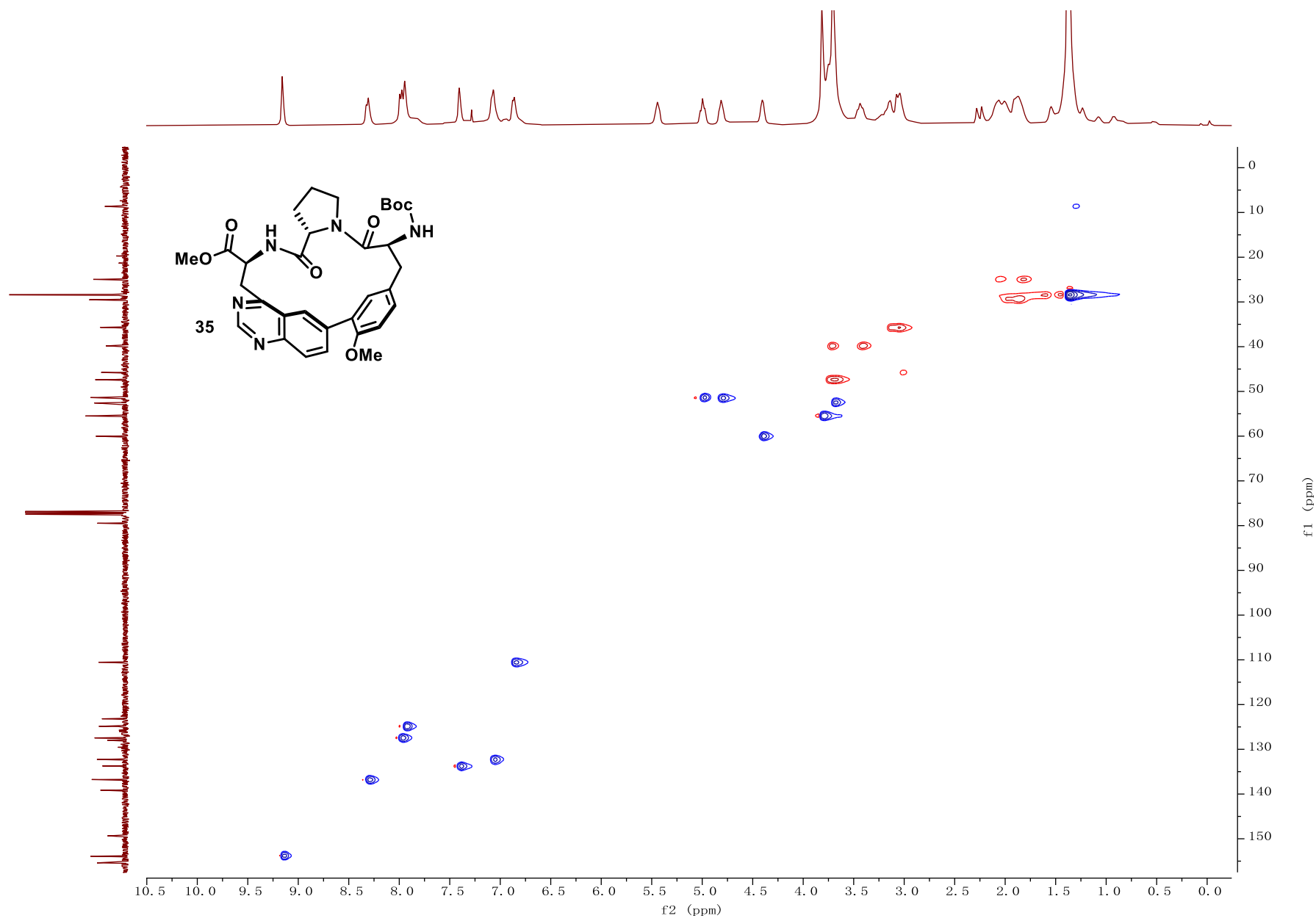
- 79.676
- 60.295
- 55.628
- 52.801
- 51.562
- 47.427
- 40.140
- 35.652
- 29.515
- 28.485
- 25.220
- 25.107



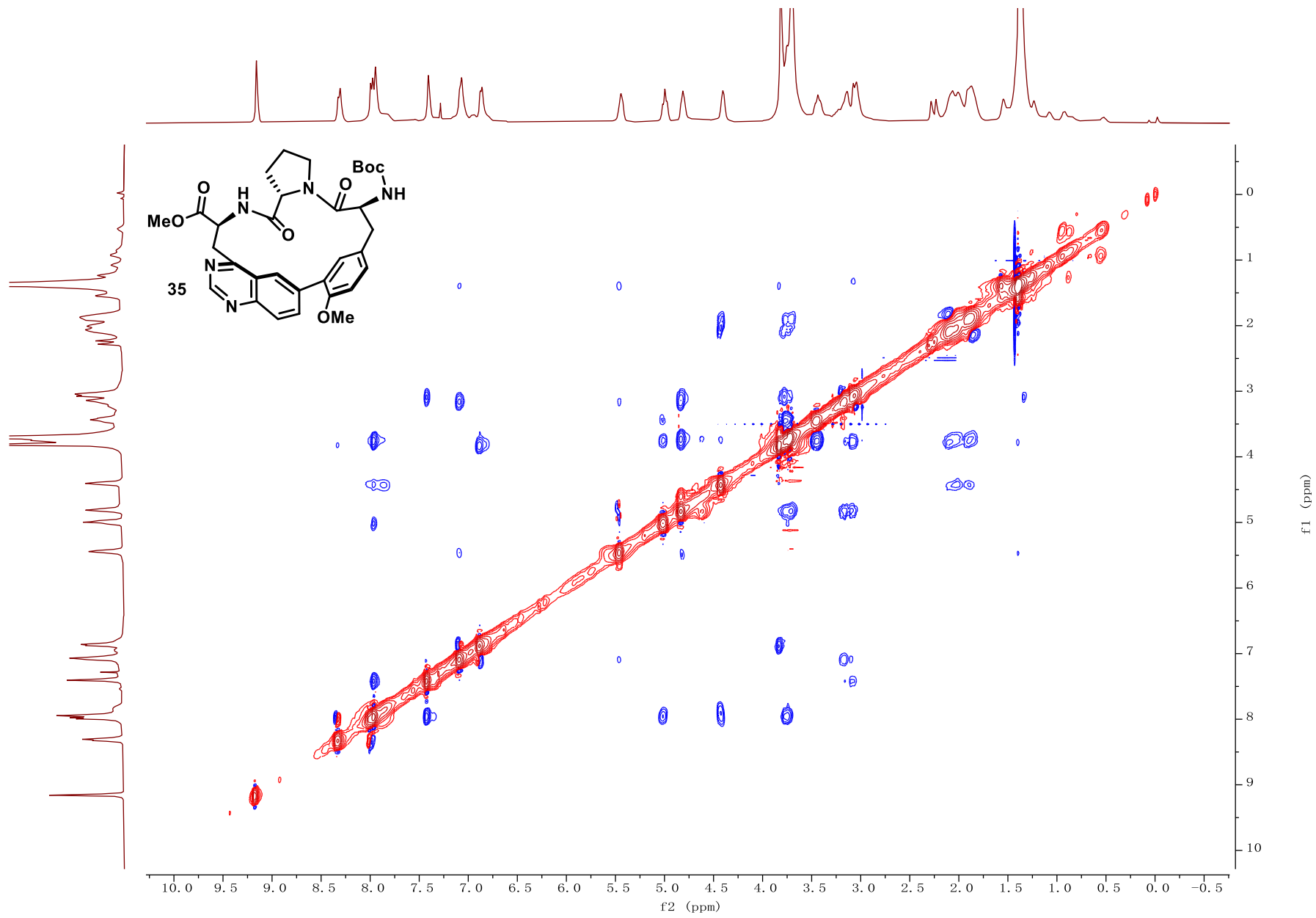
Compound 35  $^1\text{H}$ - $^1\text{H}$  COSY (400 MHz,  $\text{CDCl}_3$ )



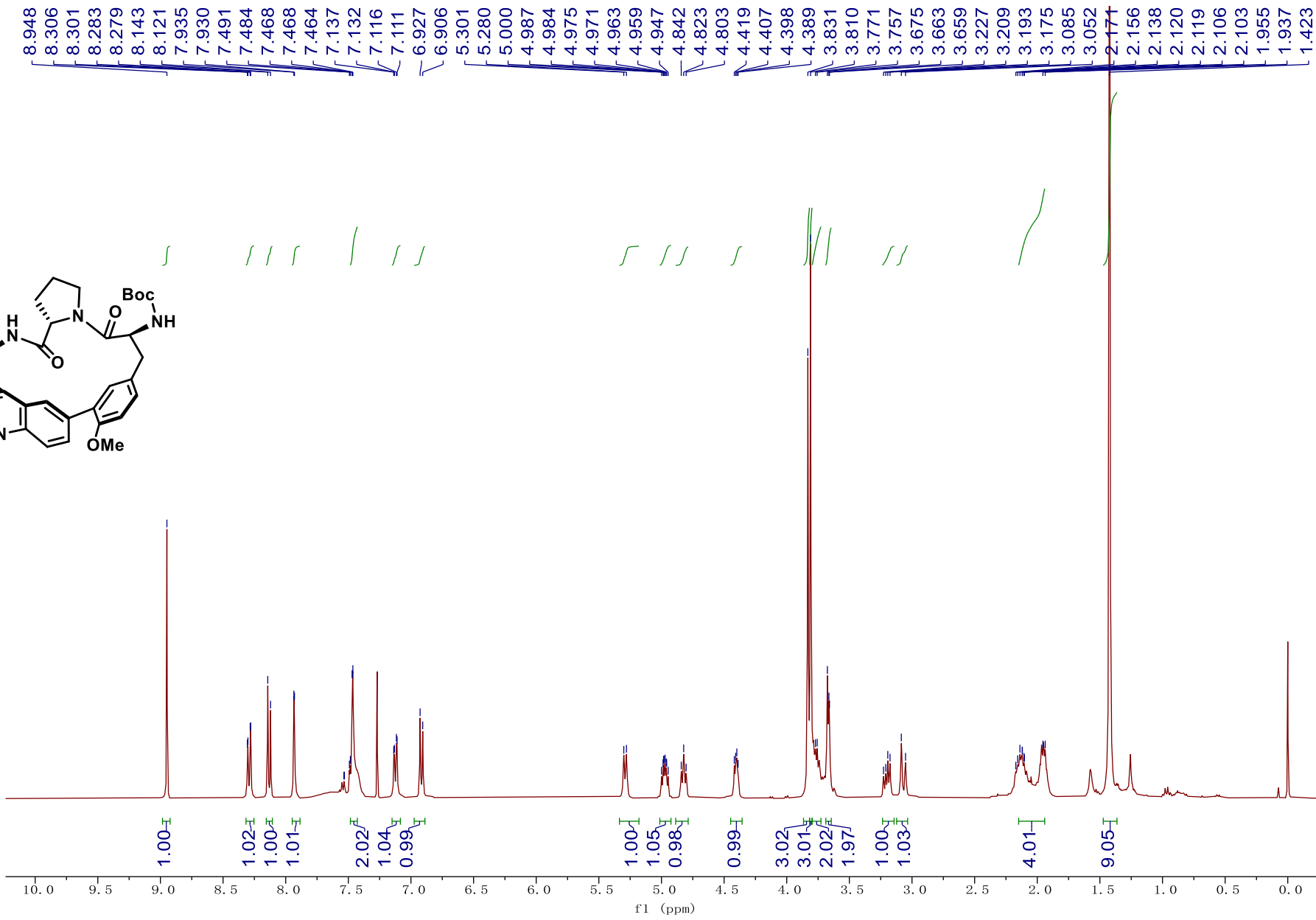
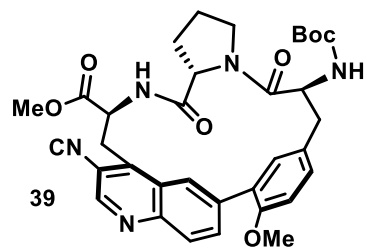
Compound 35  $^1\text{H}$ - $^{13}\text{C}$  HSQC (400 MHz,  $\text{CDCl}_3$ )



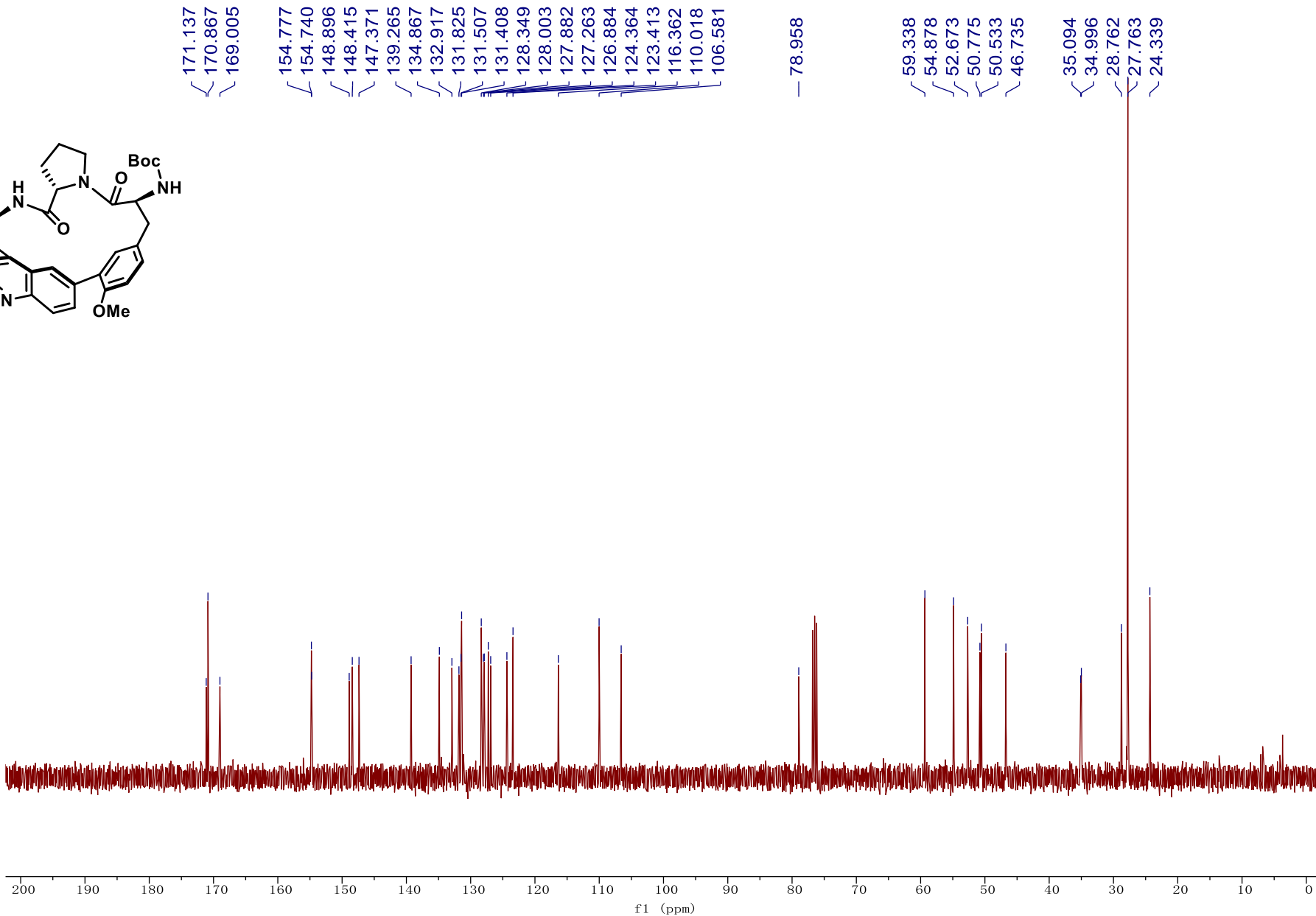
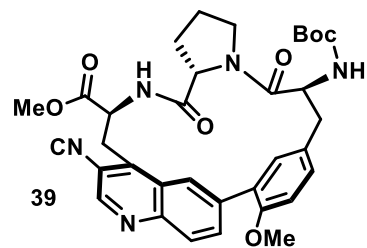
Compound 35  $^1\text{H}$ - $^1\text{H}$  ROESY (400 MHz,  $\text{CDCl}_3$ )



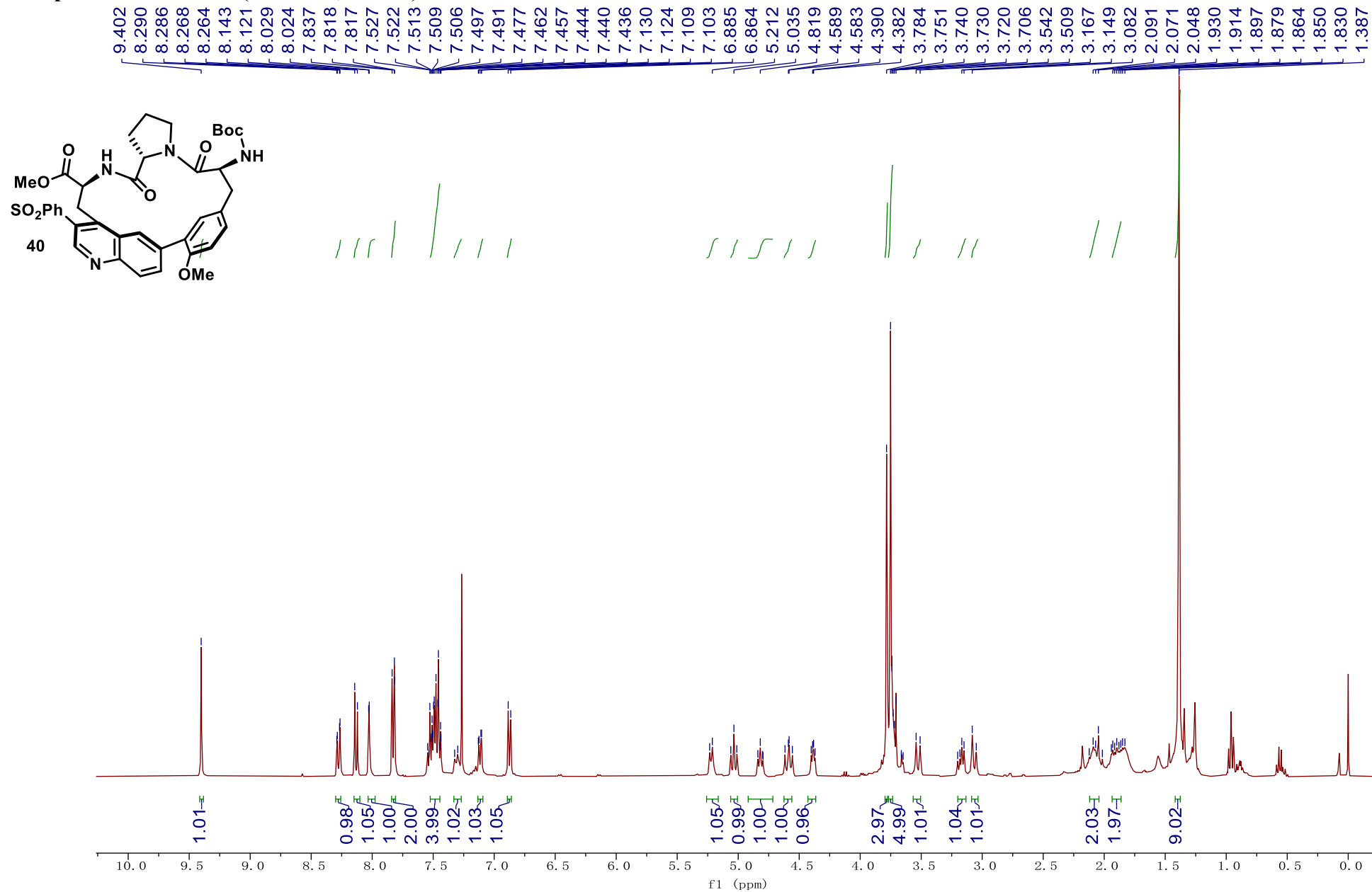
Compound 39 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



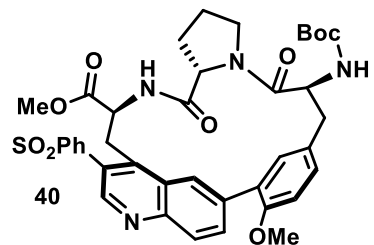
Compound 39 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



Compound 40 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



Compound 40 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

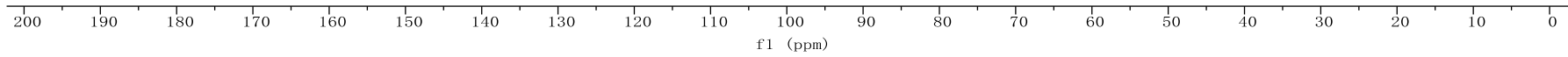


171.395  
171.027  
169.909  
155.460  
155.322  
148.736  
147.918  
145.075  
142.150  
139.761  
135.421  
133.542  
132.268  
132.195  
129.523  
128.916  
128.311  
127.503  
127.064  
126.113  
124.906  
— 110.560

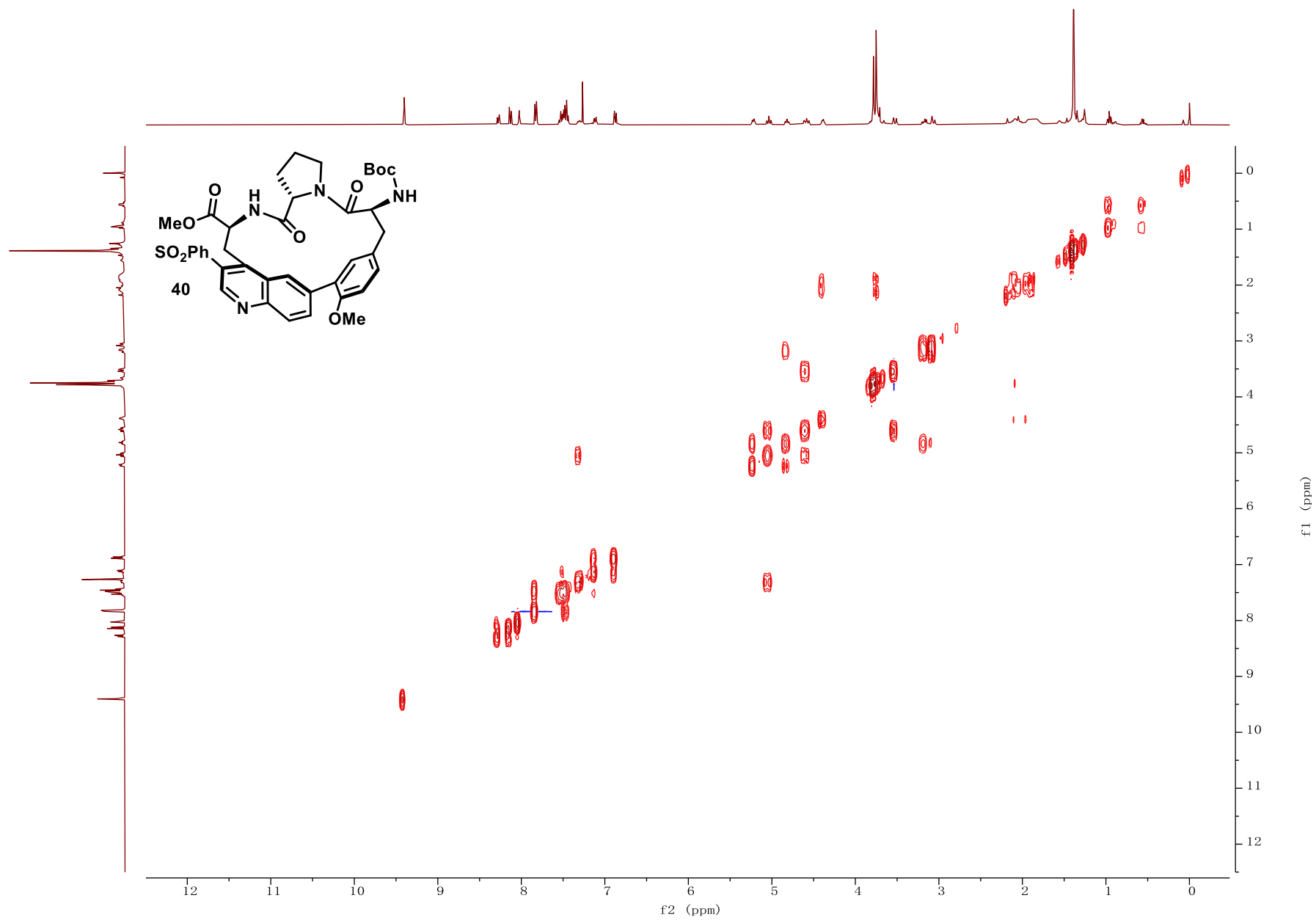
— 79.583

60.175  
55.493  
52.757  
52.509  
51.470  
47.408

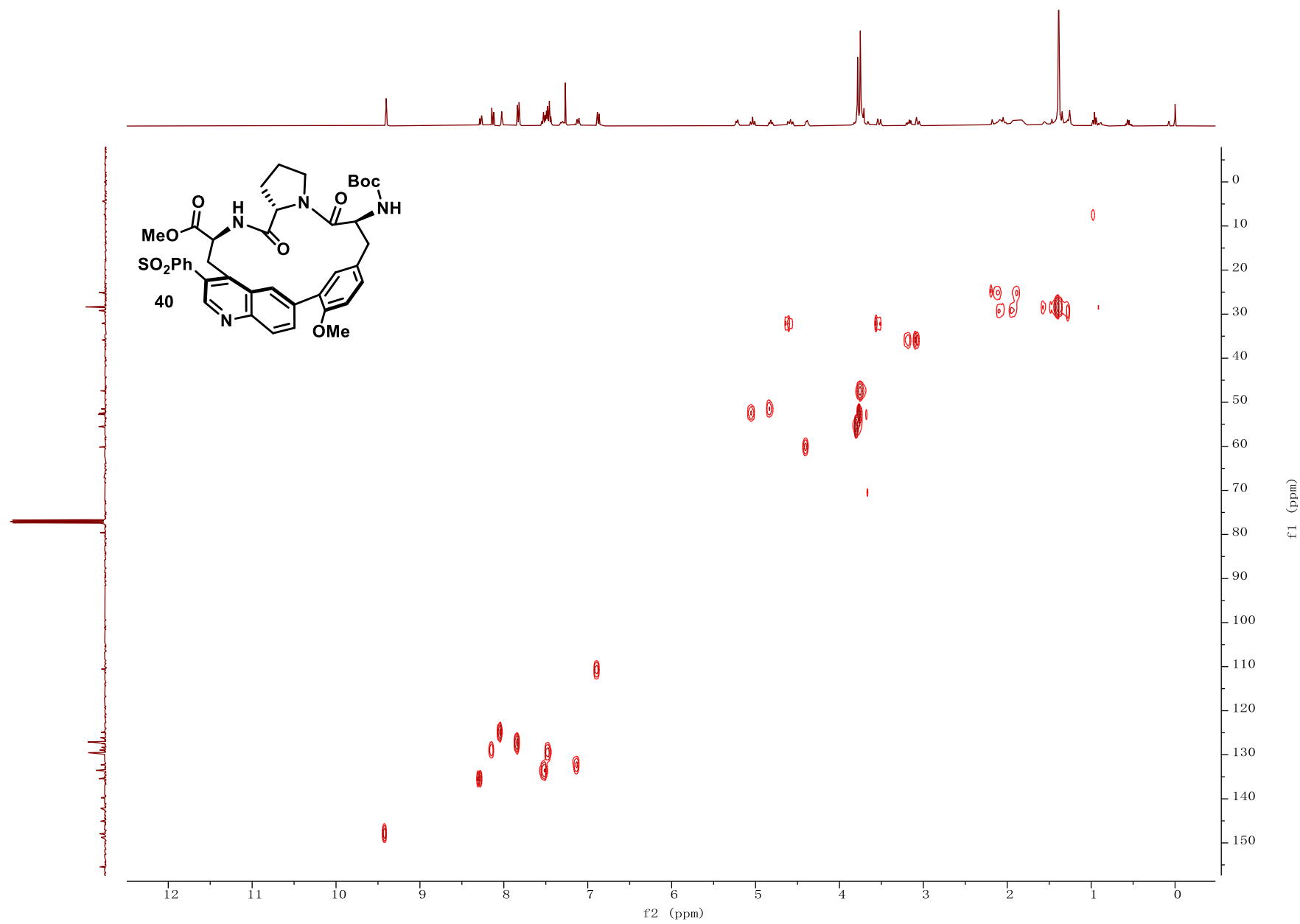
35.858  
32.099  
29.190  
28.364  
25.063



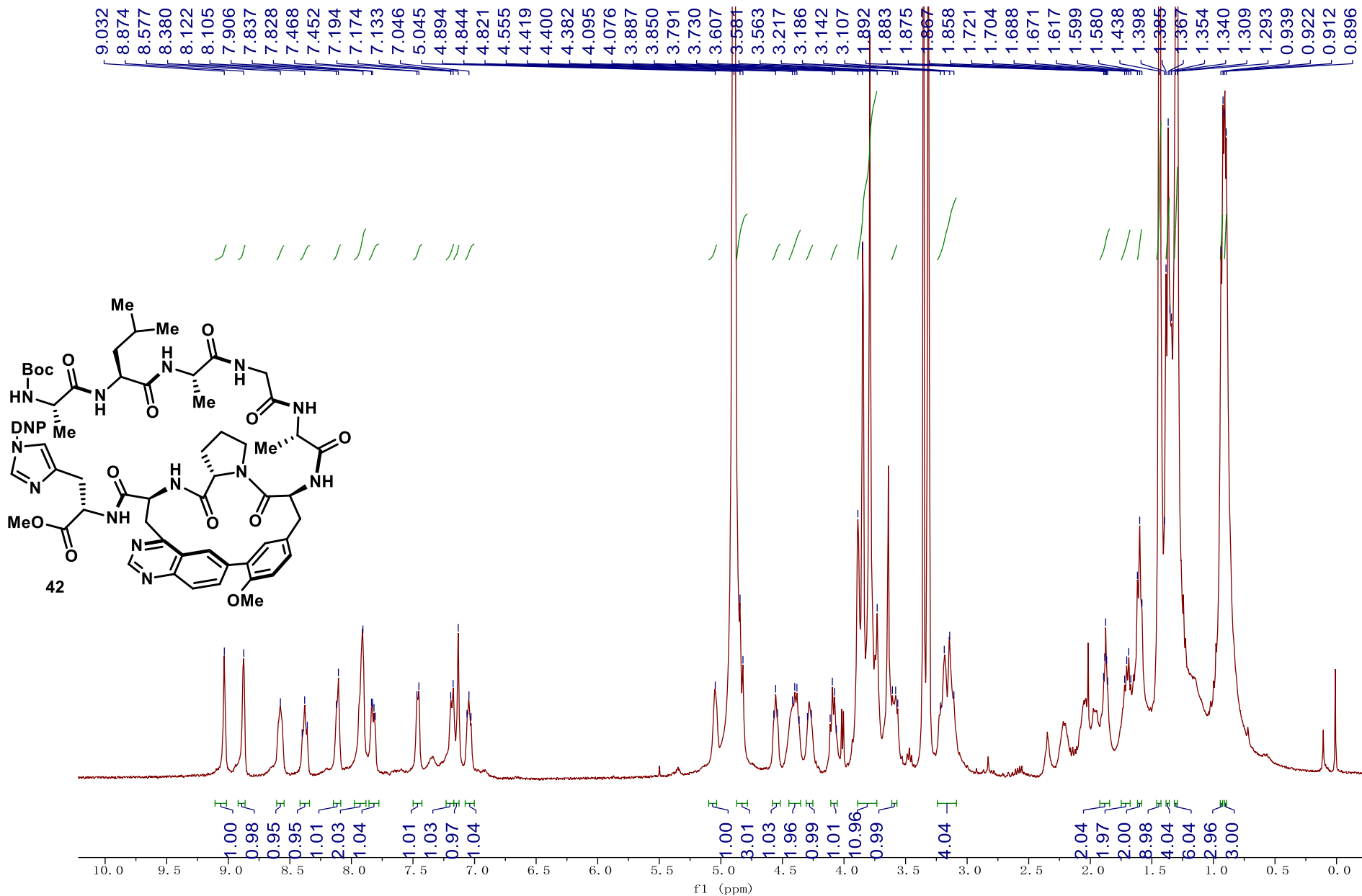
Compound 40  $^1\text{H}$ - $^1\text{H}$  COSY NMR (400 MHz,  $\text{CDCl}_3$ )



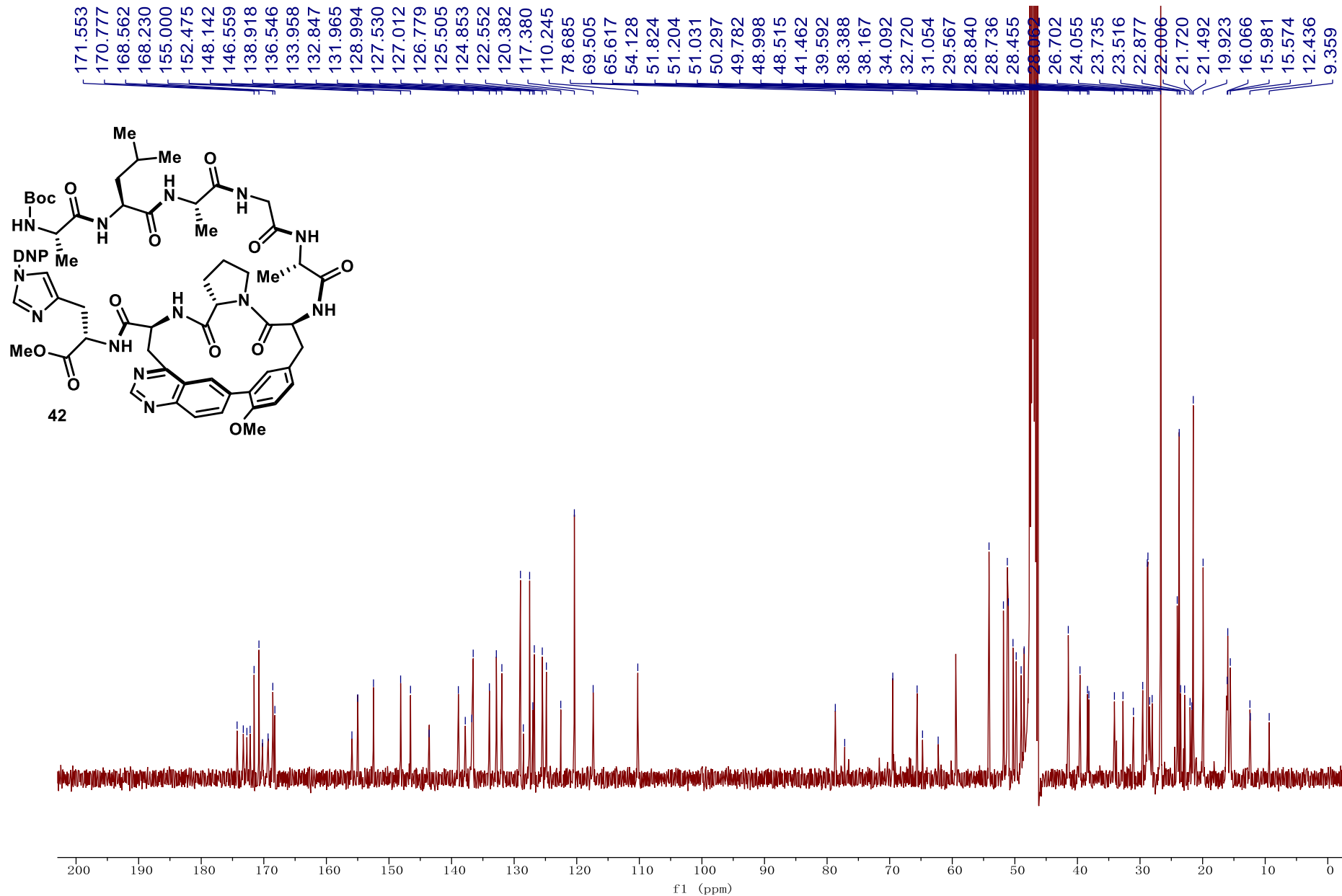
Compound 40  $^1\text{H}$ - $^{13}\text{C}$  HSQC NMR (400 MHz,  $\text{CDCl}_3$ )



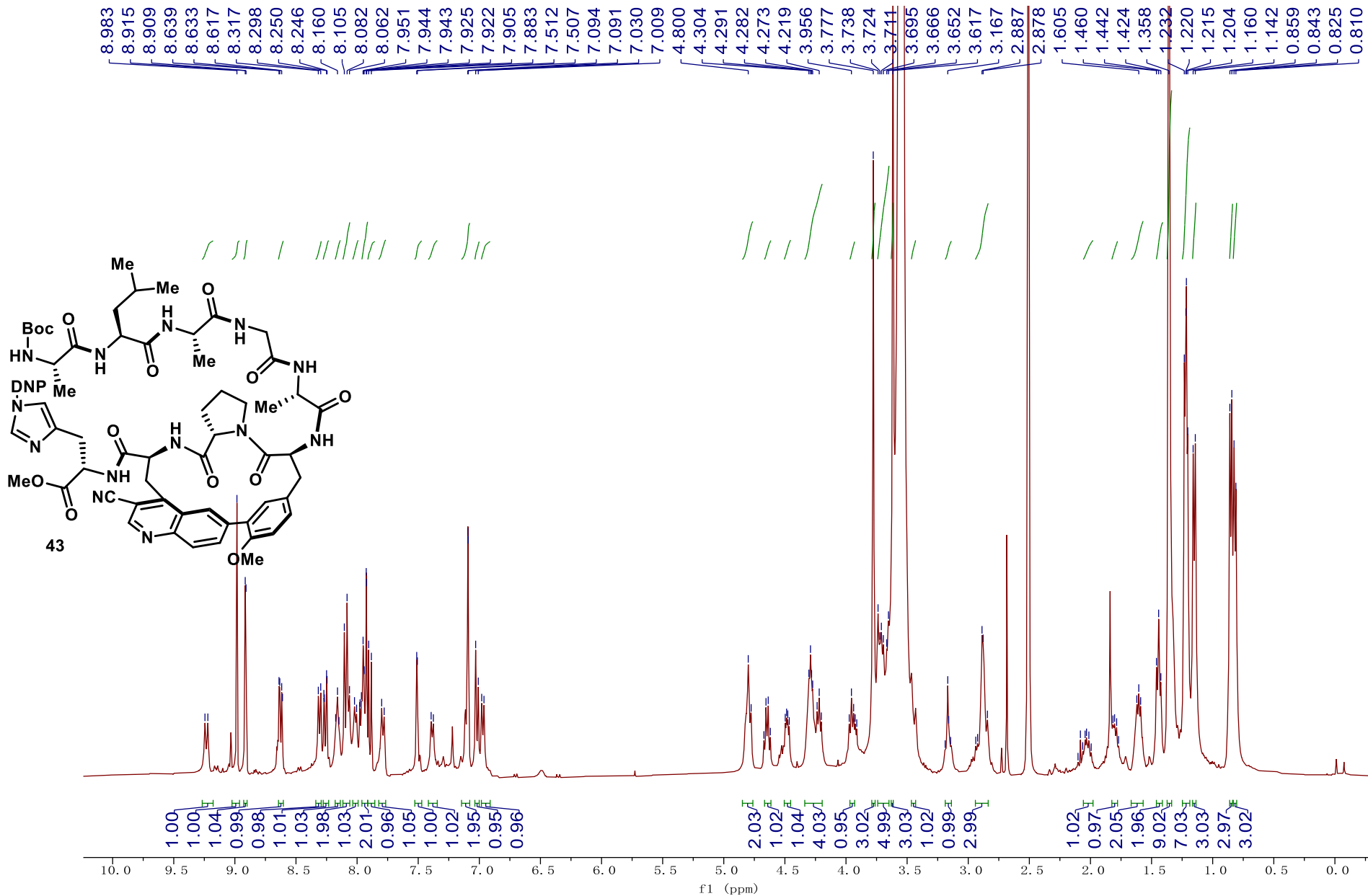
Compound 42 <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)



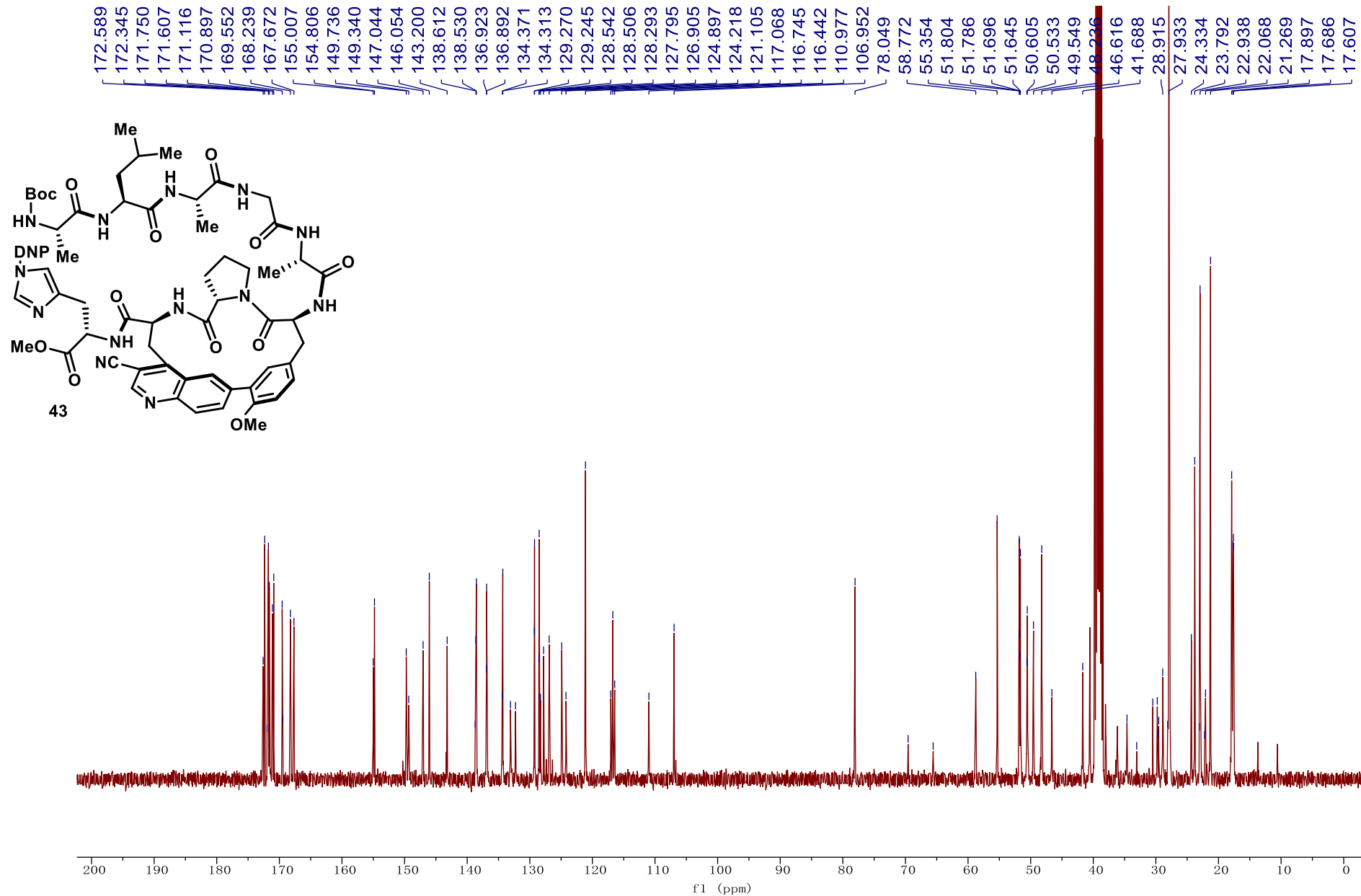
Compound 42 <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD)



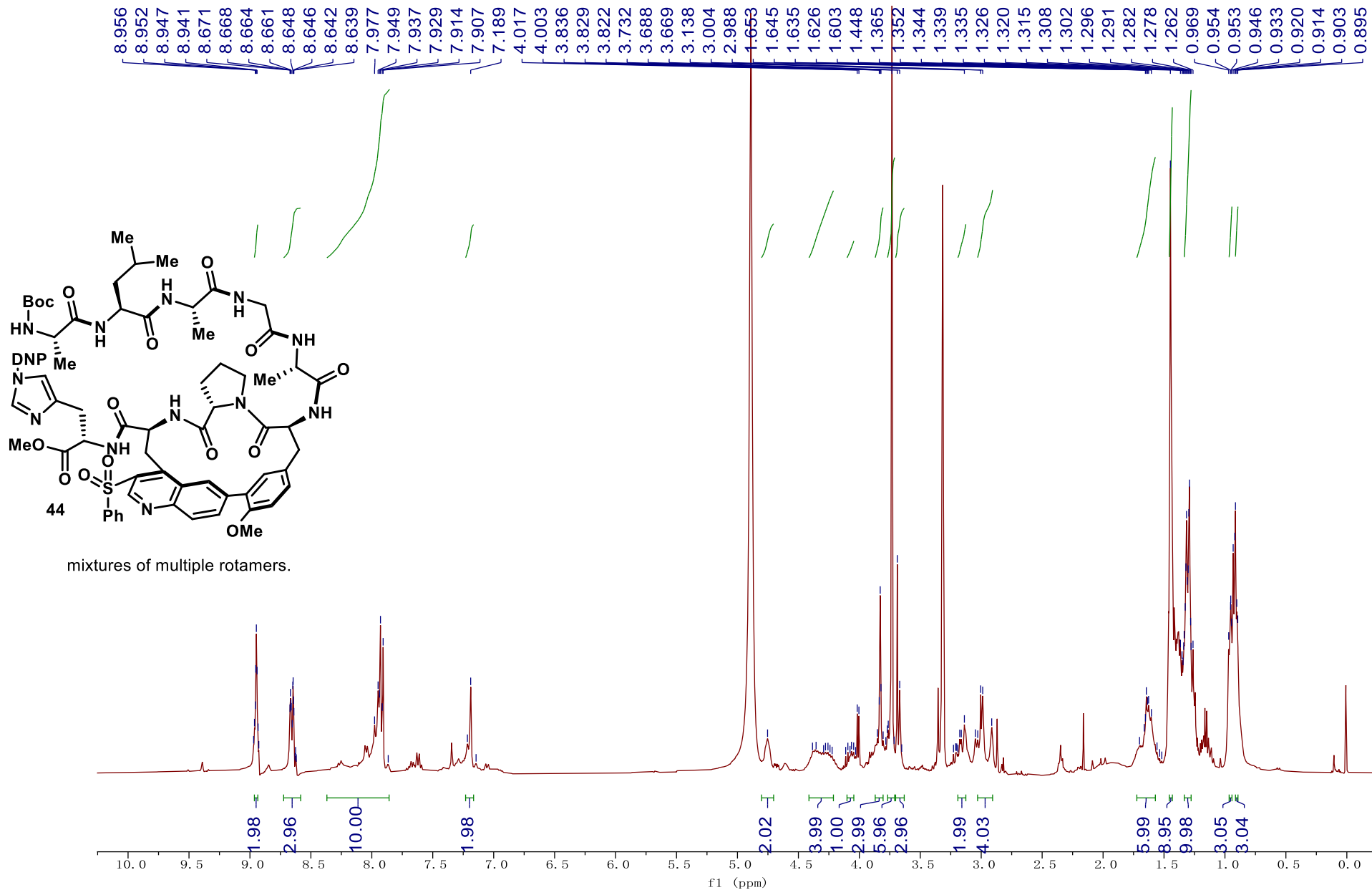
Compound 43 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)



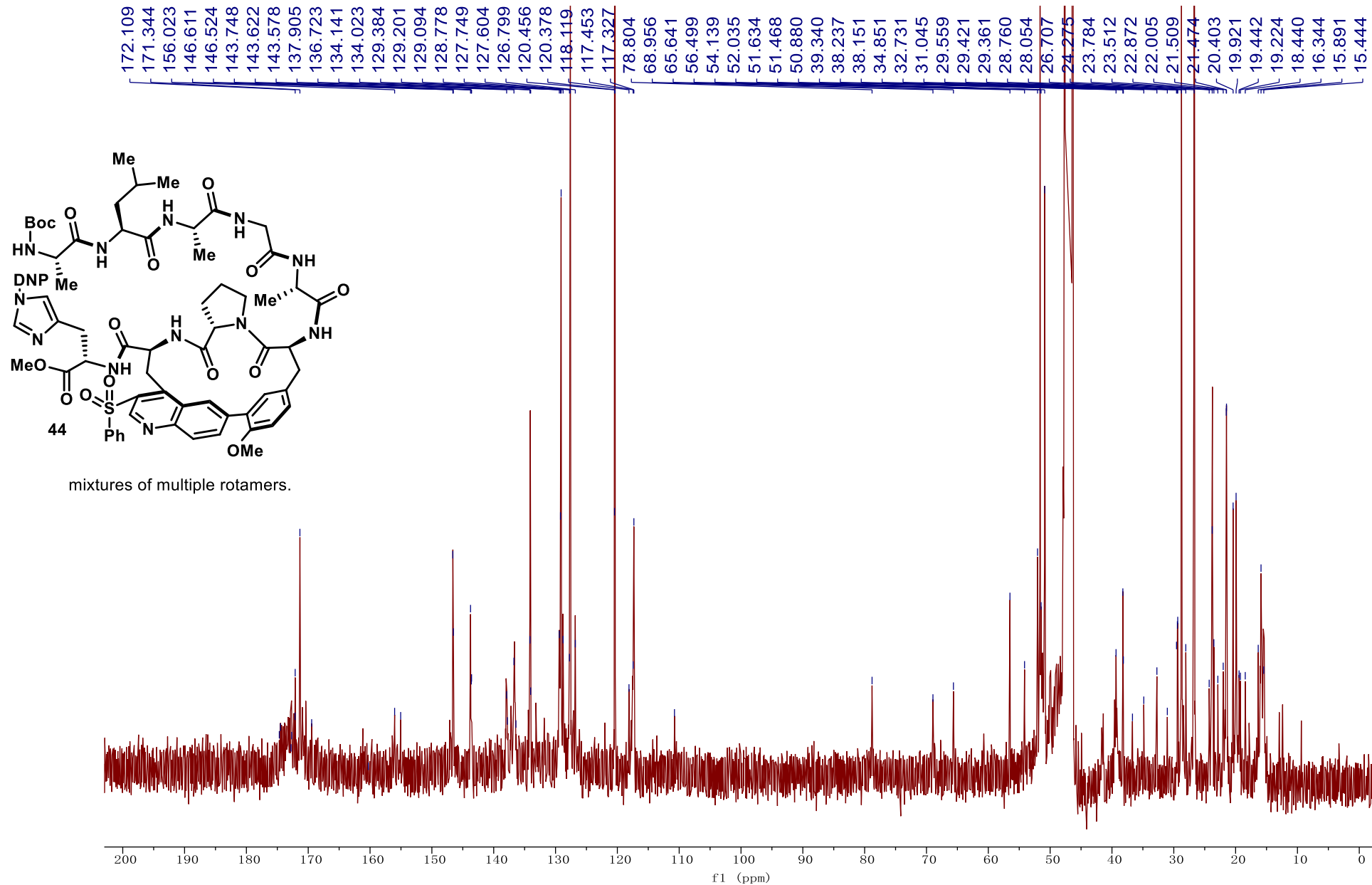
Compound 43 <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)



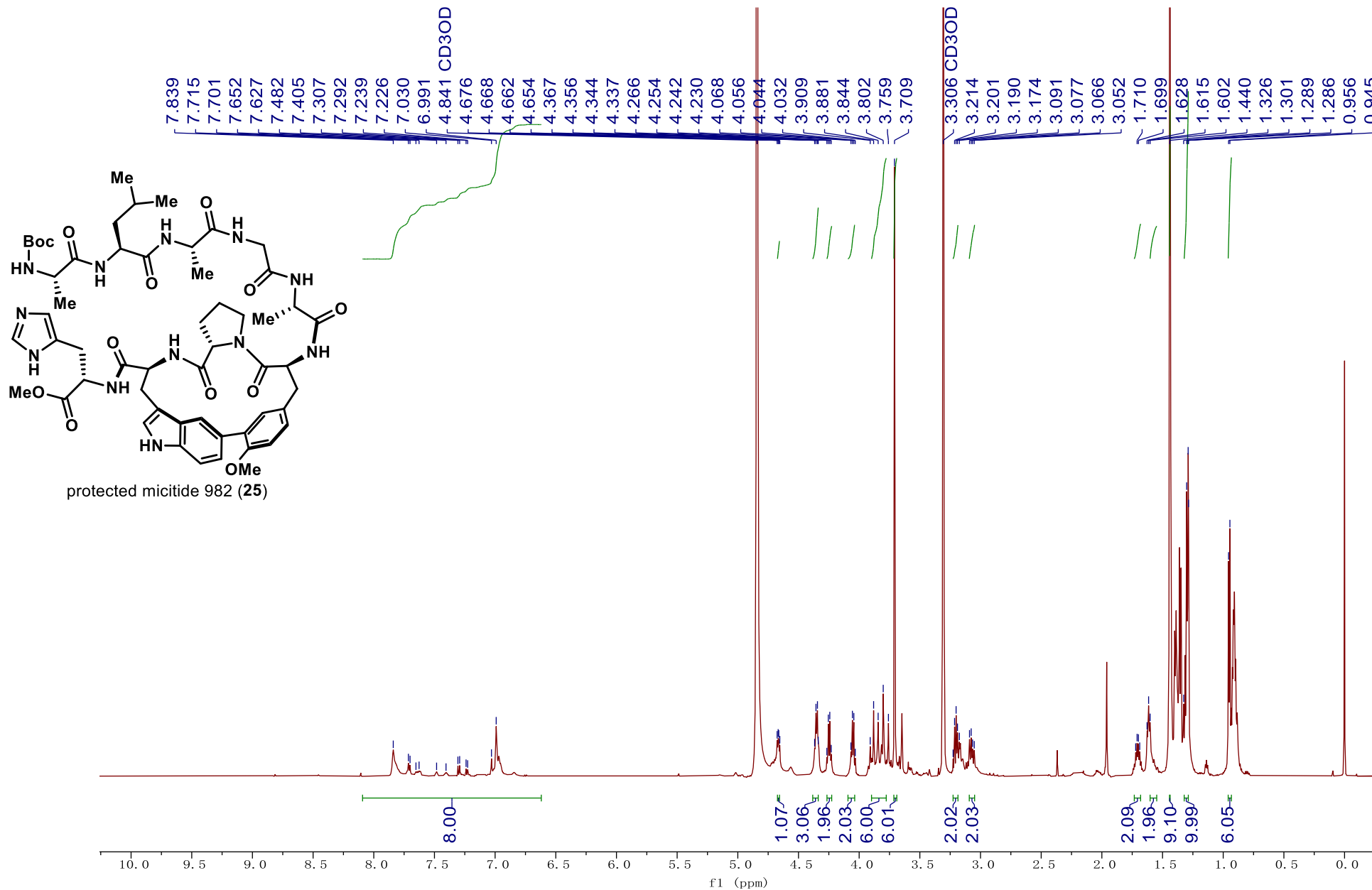
Compound 44 <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)



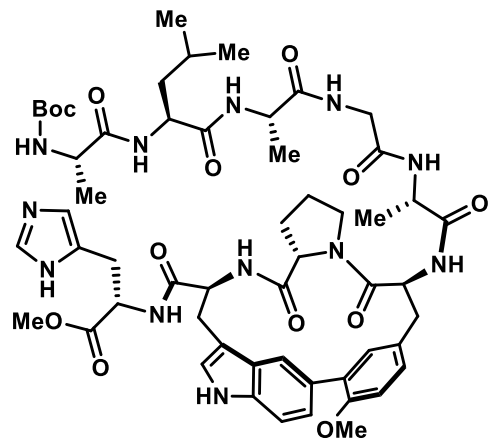
Compound 44 <sup>13</sup>C NMR (101 MHz, DMSO-d<sub>6</sub>)



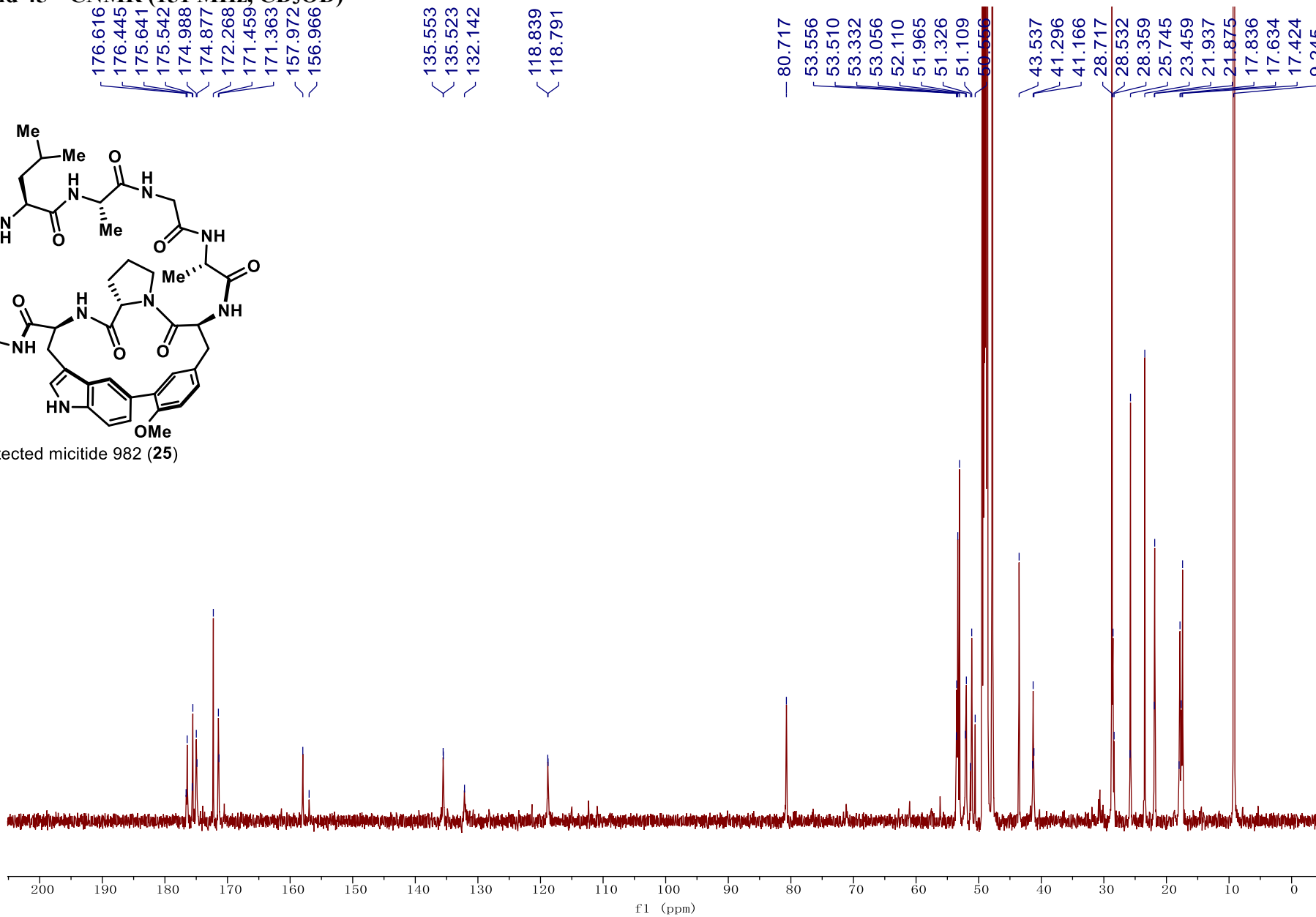
Compound 45 <sup>1</sup>HNMR (600 MHz, CD<sub>3</sub>OD)



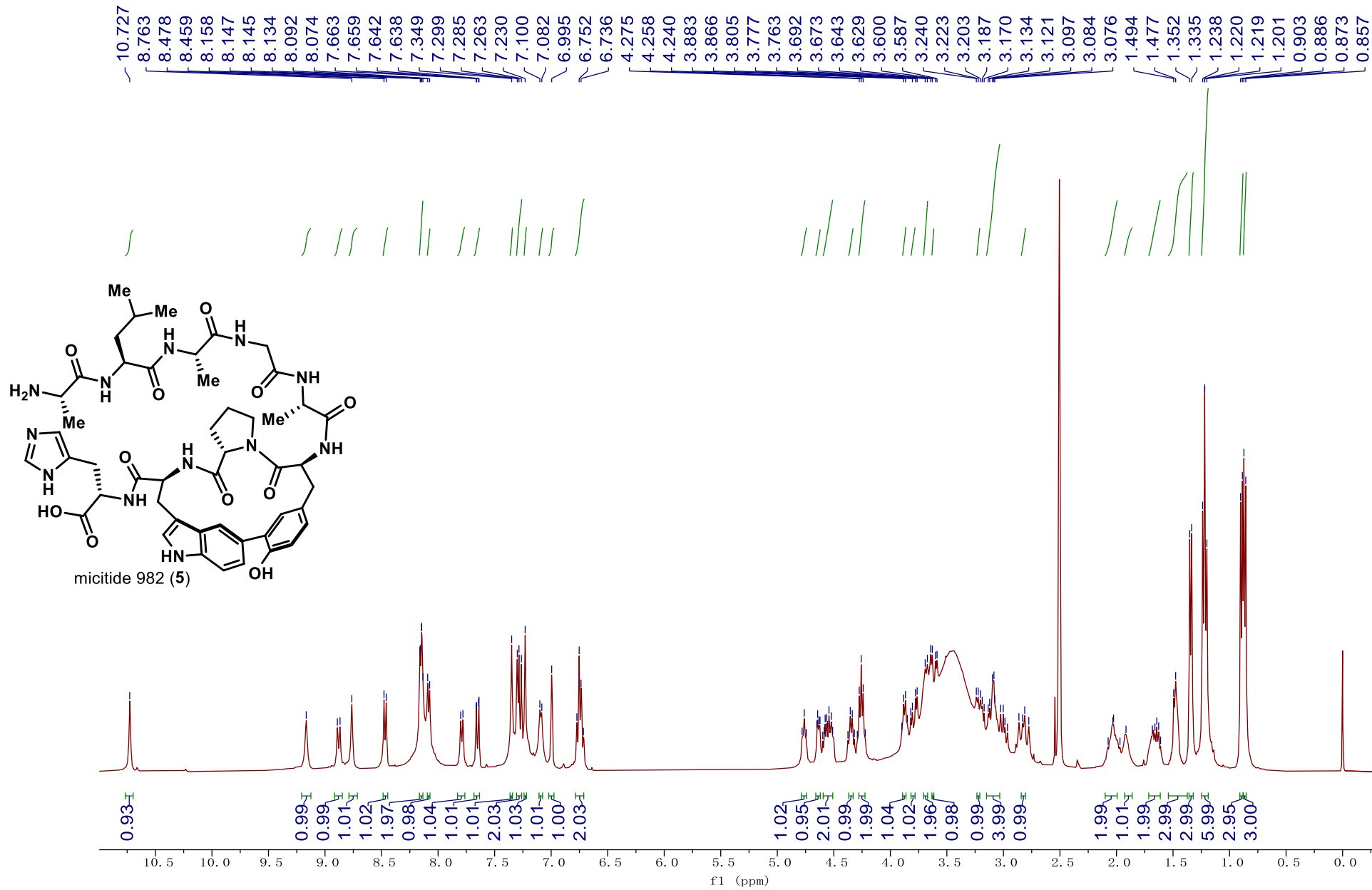
Compound 45 <sup>13</sup>CNMR (151 MHz, CD<sub>3</sub>OD)



protected micitide 982 (25)

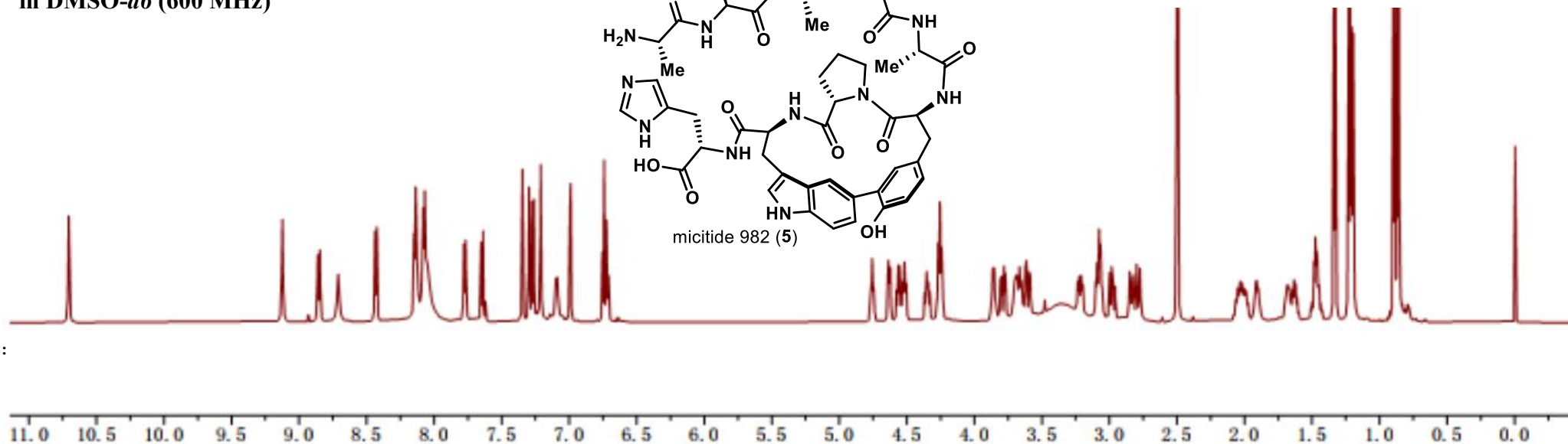
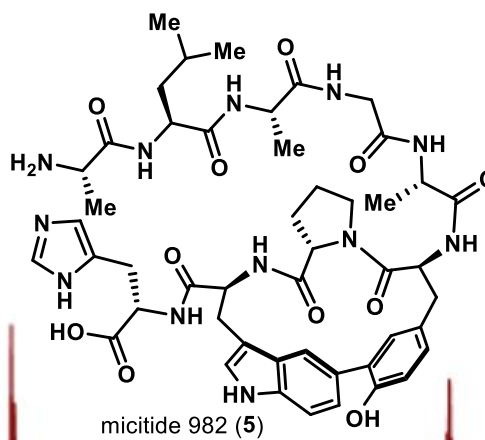


Compound 5 <sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>)

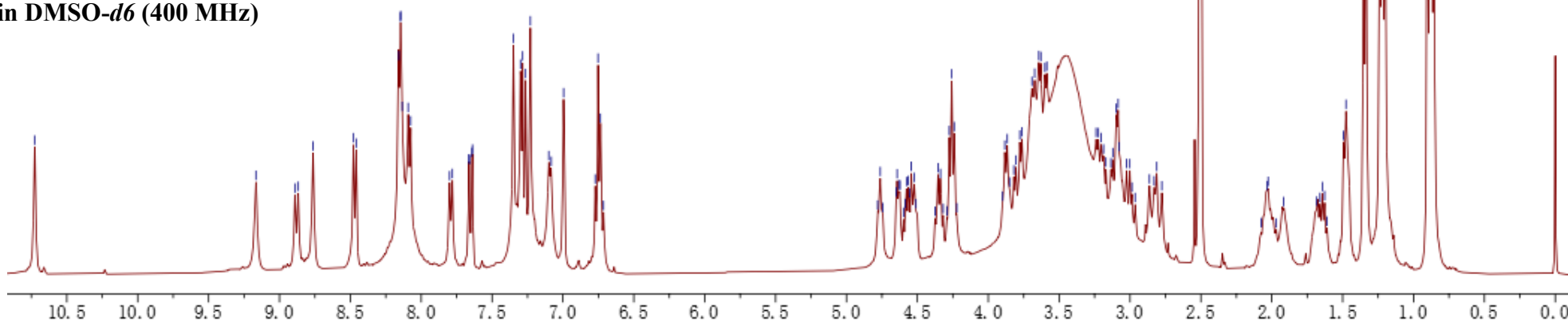


<sup>1</sup>HNMR Comparison of Micitide 982 (1) <sup>[1, 2]</sup>

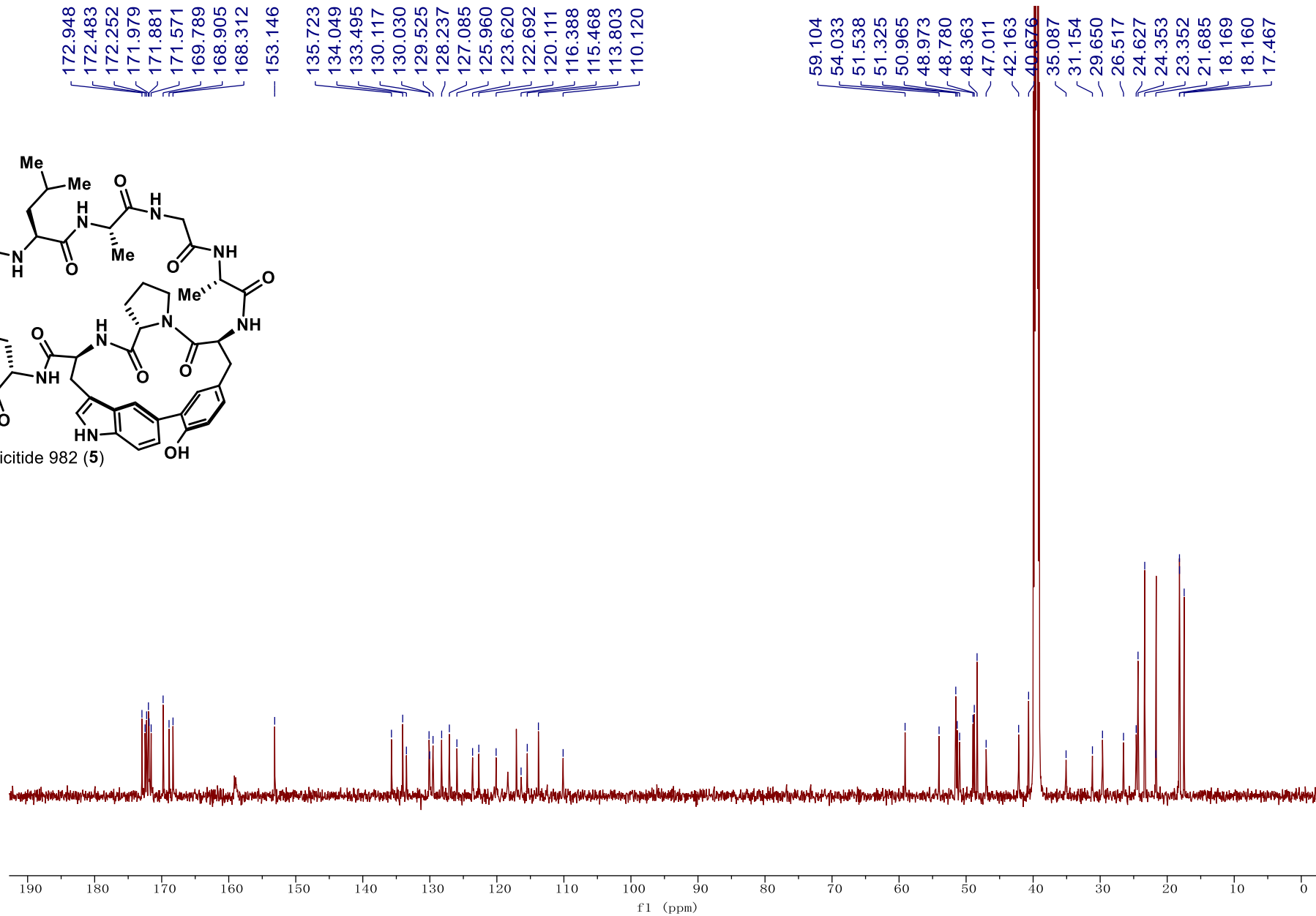
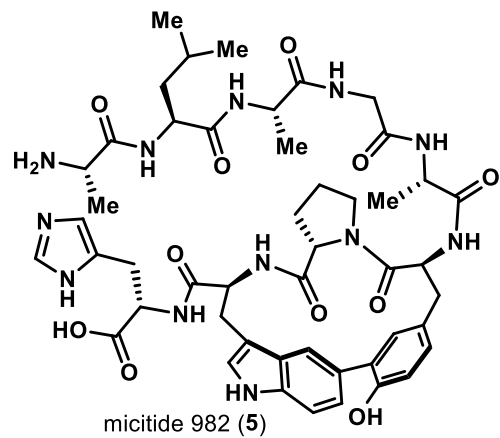
Reported<sup>1</sup>  
in DMSO-*d*<sub>6</sub> (600 MHz)



Synthetic (This work)  
in DMSO-*d*<sub>6</sub> (400 MHz)

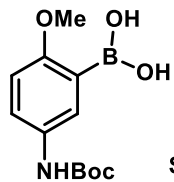


Compound 5 <sup>13</sup>CNMR (151 MHz, DMSO-*d*<sub>6</sub>)





Compound S9 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD)



mixture of rotamers  
A:B = 3:2

7.568  
7.459  
7.447  
7.383  
7.369  
7.188  
6.915  
6.901  
6.871  
6.856

1 1 1 1 1 1 1 1 1 1

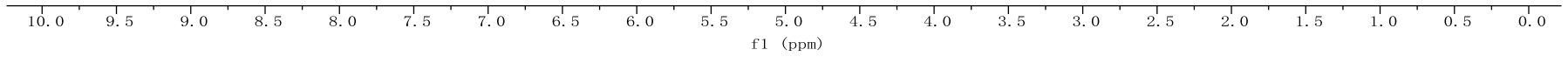
3.852  
3.771

1.503

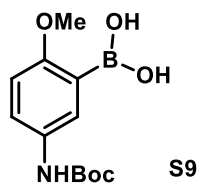
0.40  
0.38  
0.57  
0.60  
0.43  
0.61

1.20  
1.79

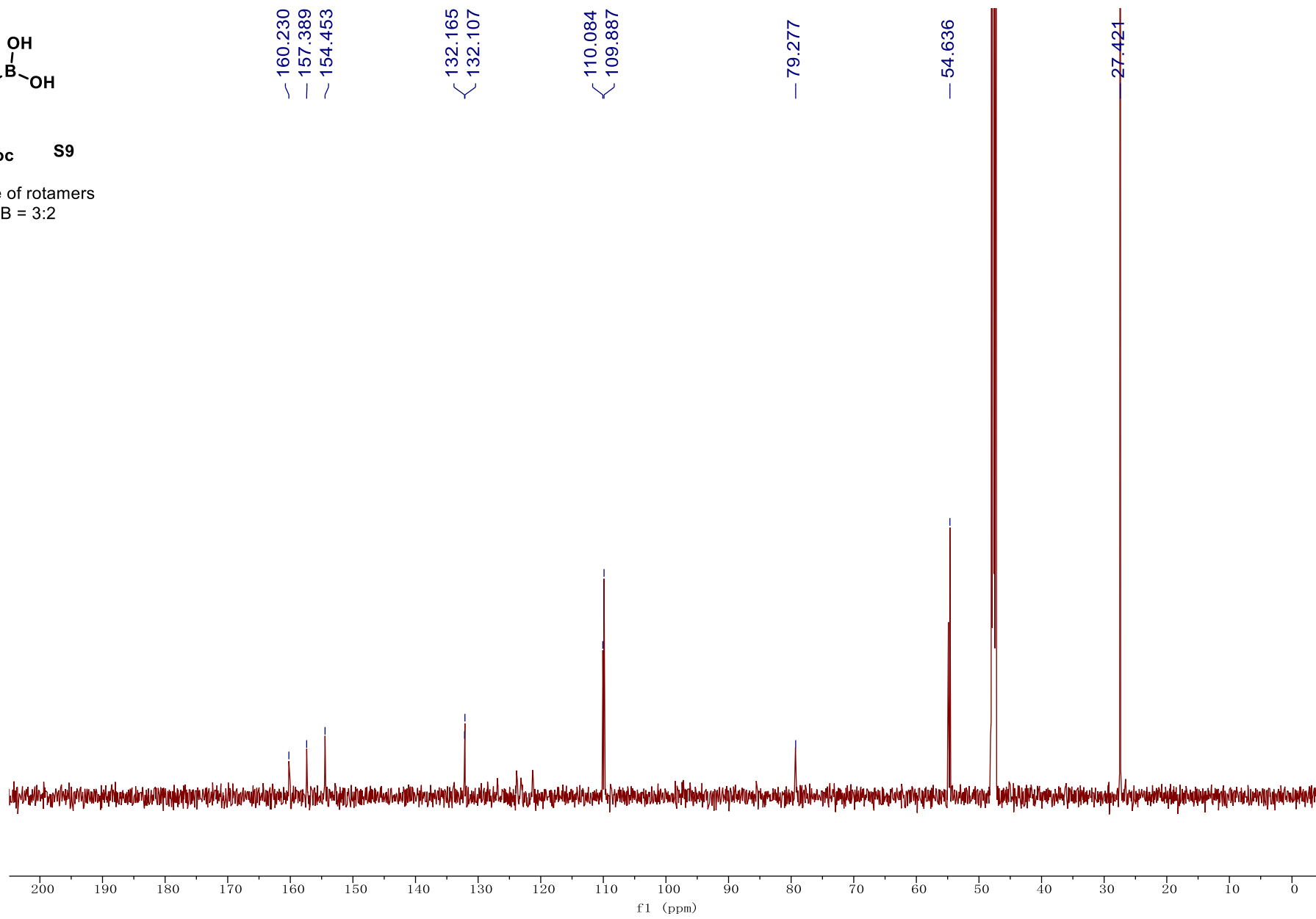
8.97



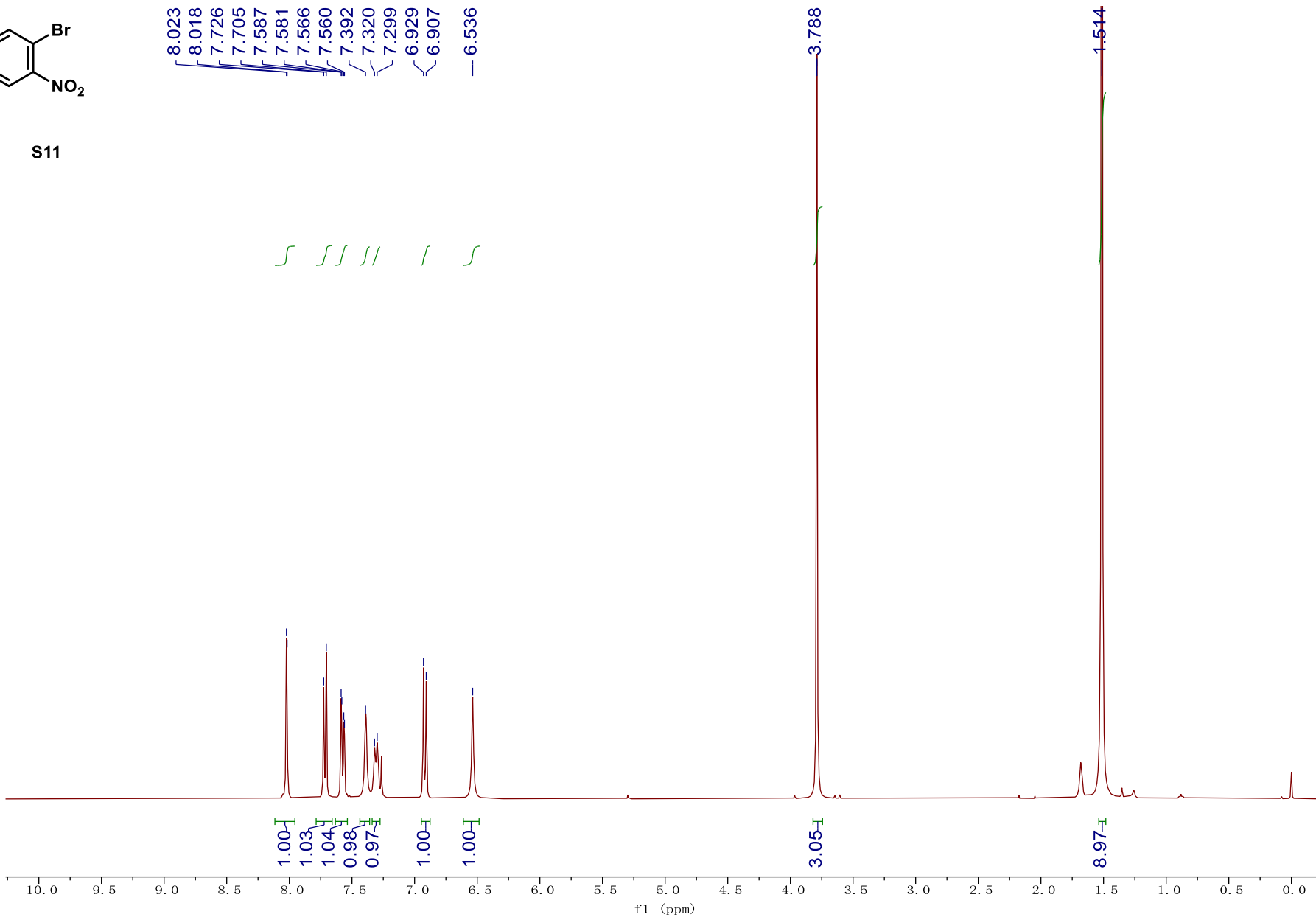
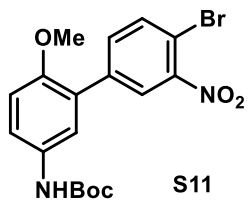
Compound S3 <sup>13</sup>C NMR (151 MHz, CD<sub>3</sub>OD)



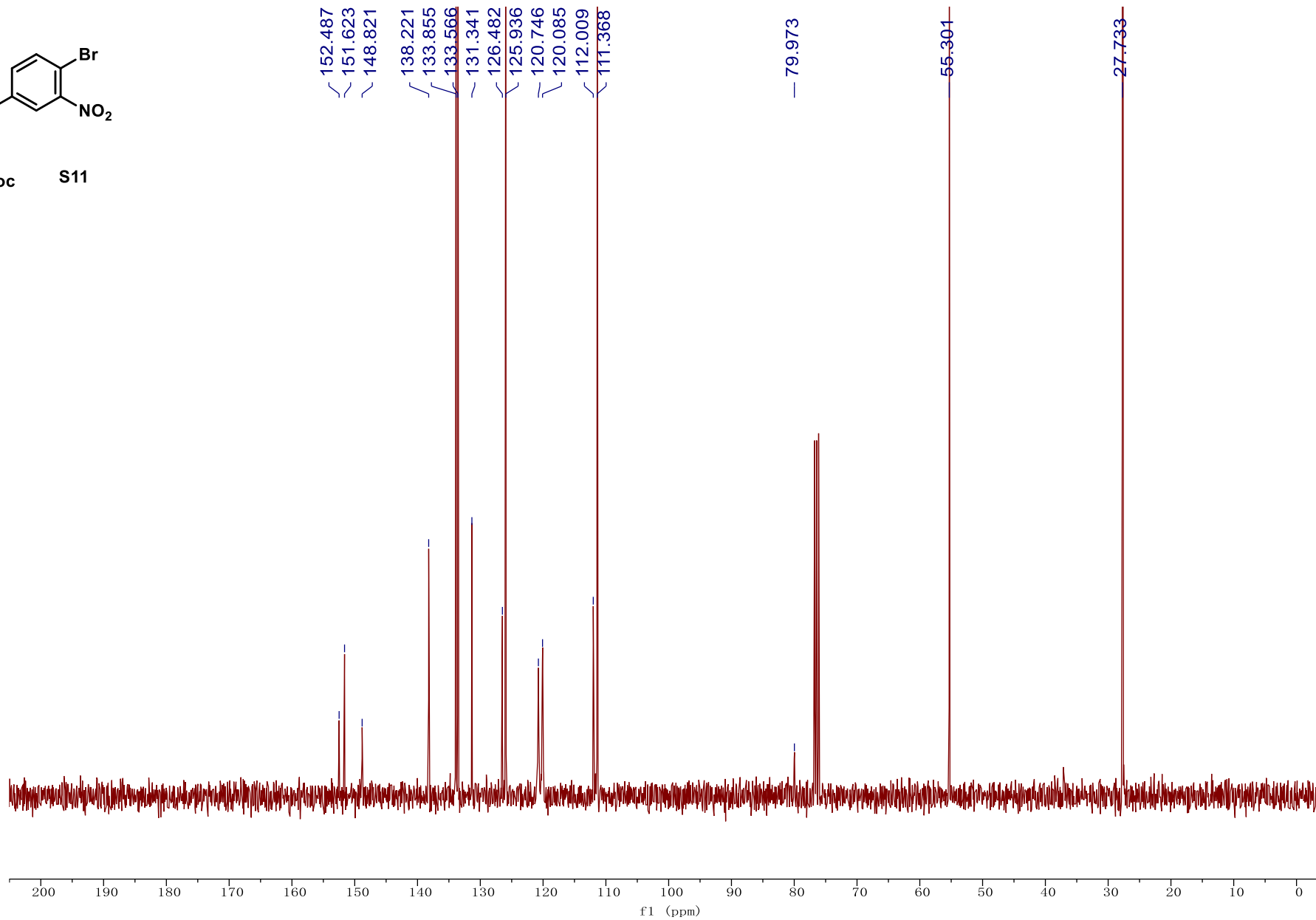
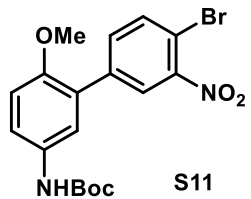
mixture of rotamers  
A:B = 3:2



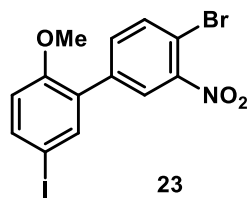
Compound S11 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



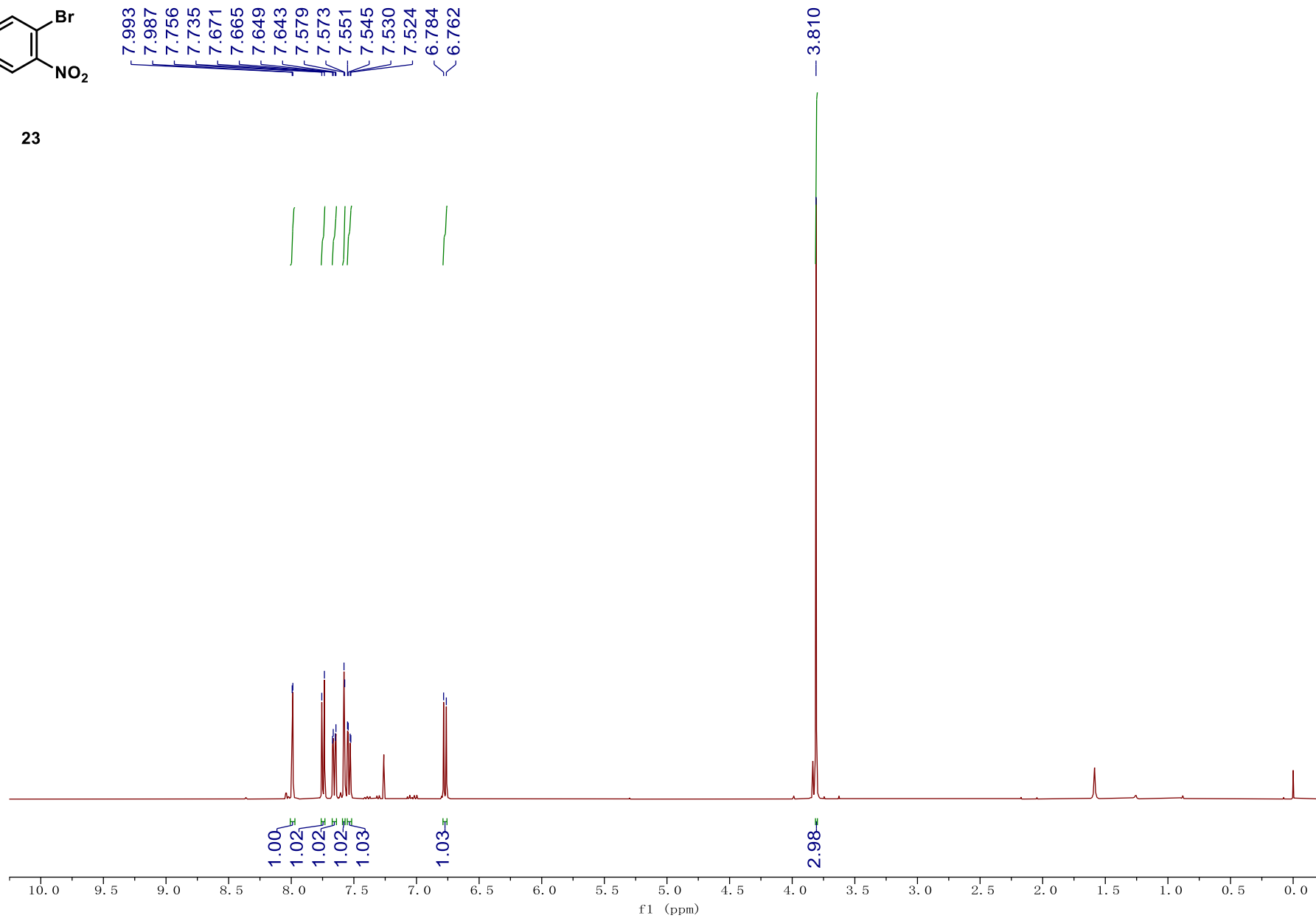
Compound S11 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



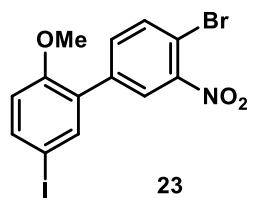
Compound 23 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



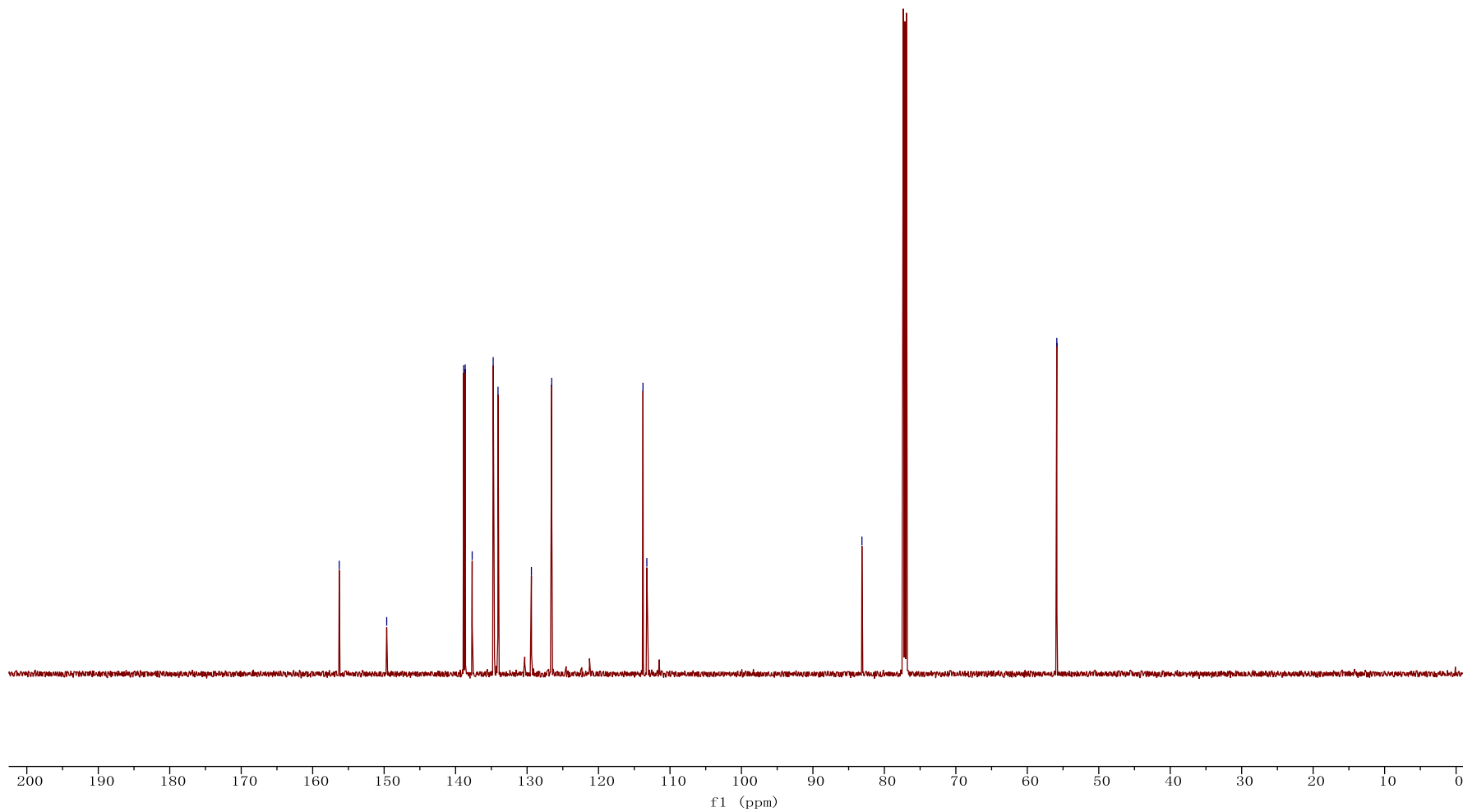
7.993  
7.987  
7.756  
7.735  
7.671  
7.665  
7.649  
7.643  
7.579  
7.573  
7.551  
7.545  
7.530  
7.524  
6.784  
6.762



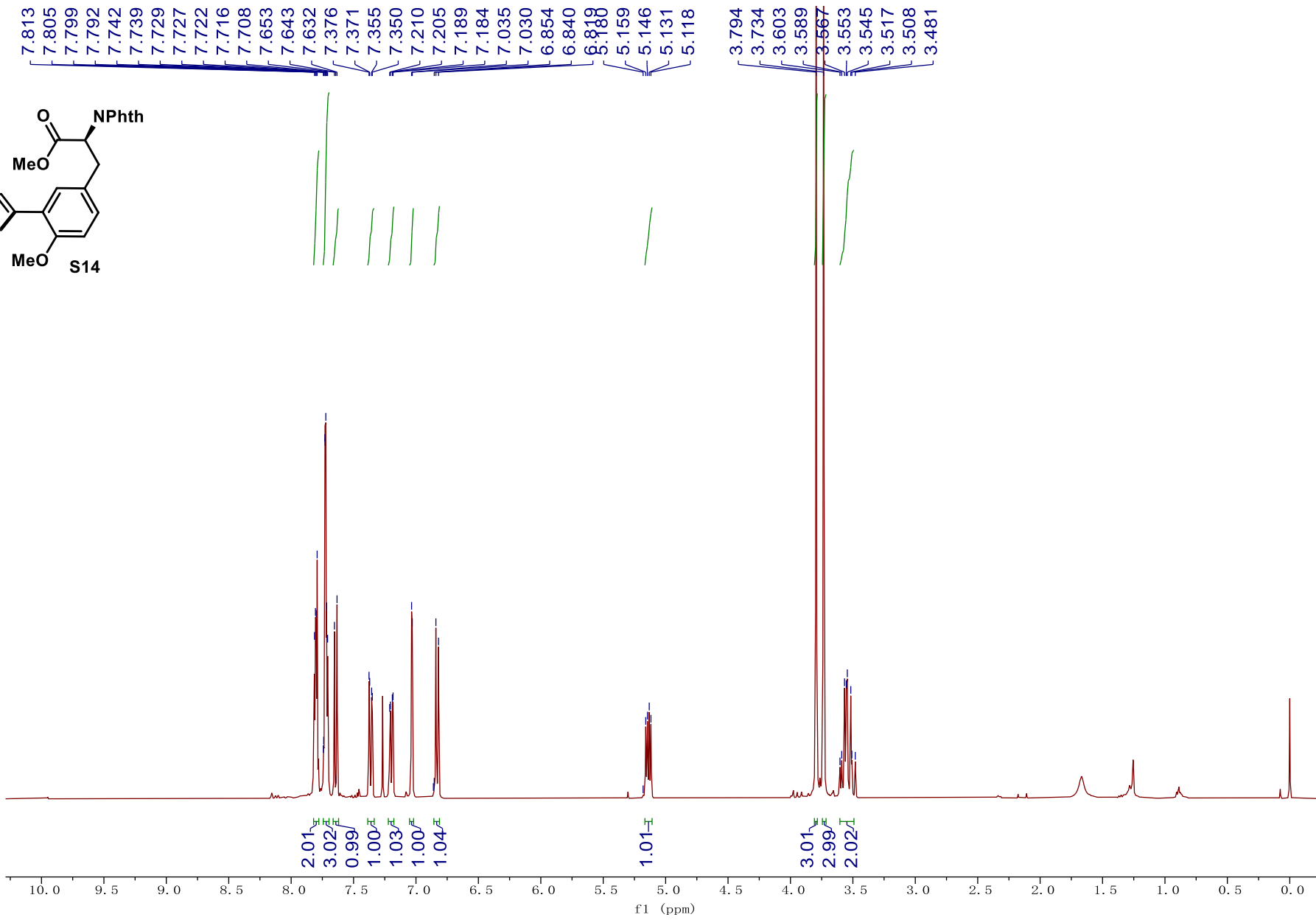
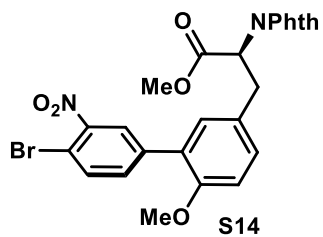
Compound 23 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



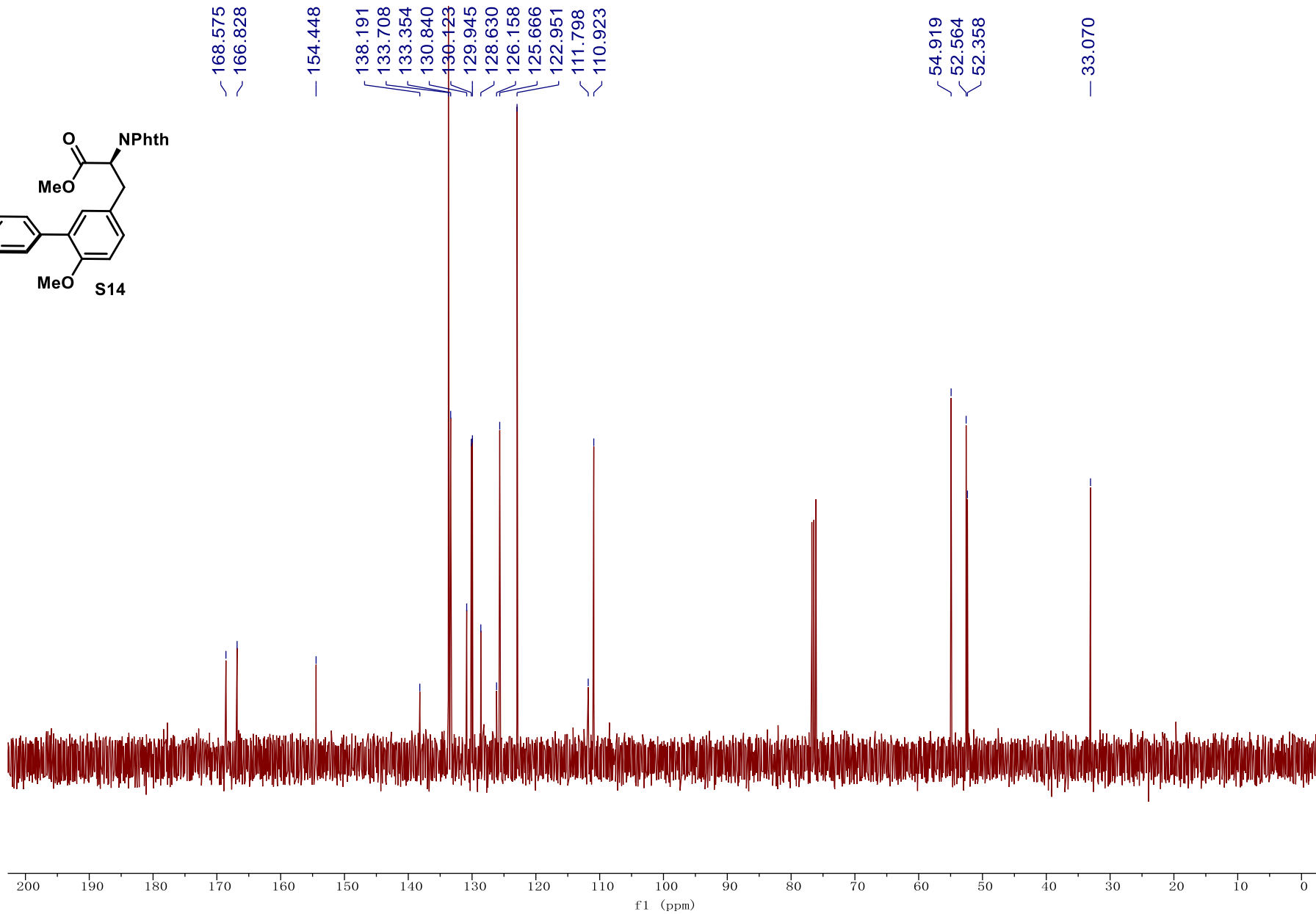
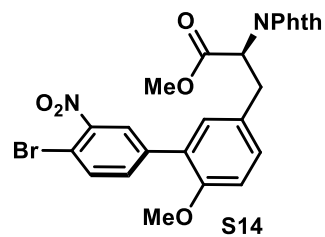
- 156.282
- 149.638
- 138.872
- 138.656
- 137.680
- 134.740
- 134.068
- 129.392
- 126.552
- 113.780
- 113.242
- 83.138
- 55.871



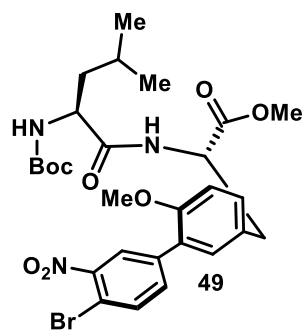
Compound S14 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



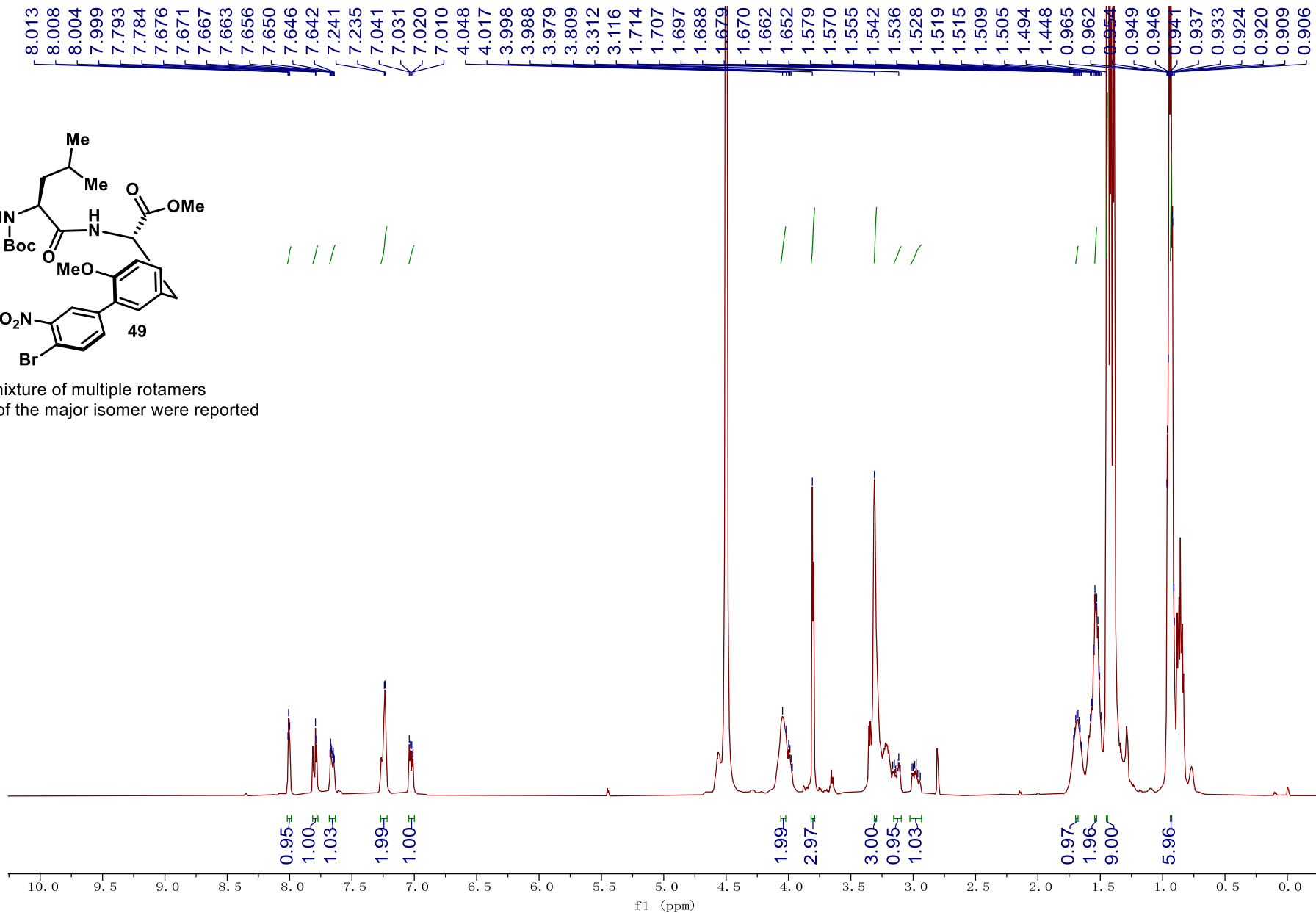
Compound S14 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



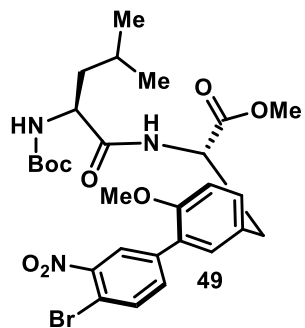
Compound 49 (400 MHz, CD<sub>3</sub>OD, 60 °C)



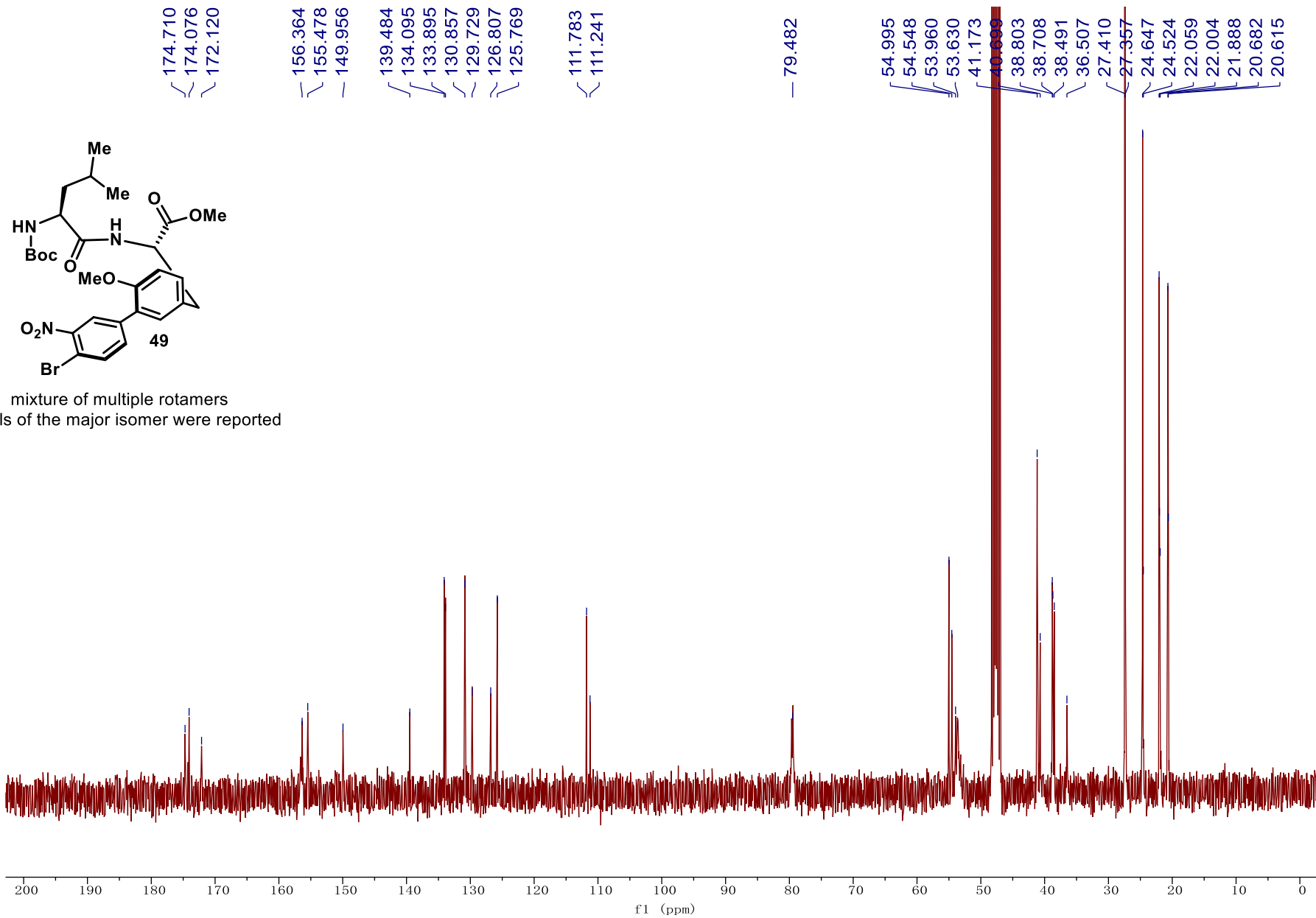
mixture of multiple rotamers  
signals of the major isomer were reported



Compound 49 <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD, 60 °C)

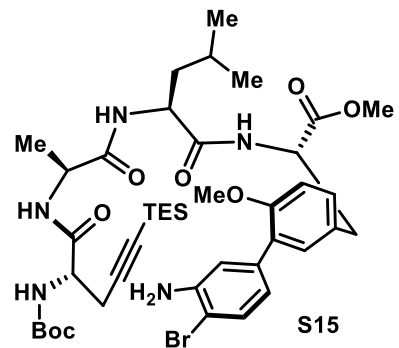


mixture of multiple rotamers  
signals of the major isomer were reported

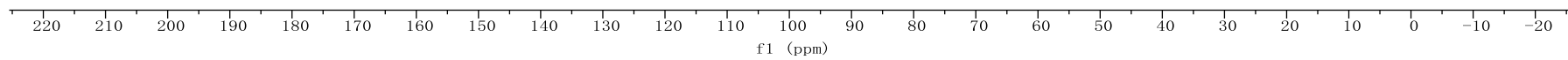




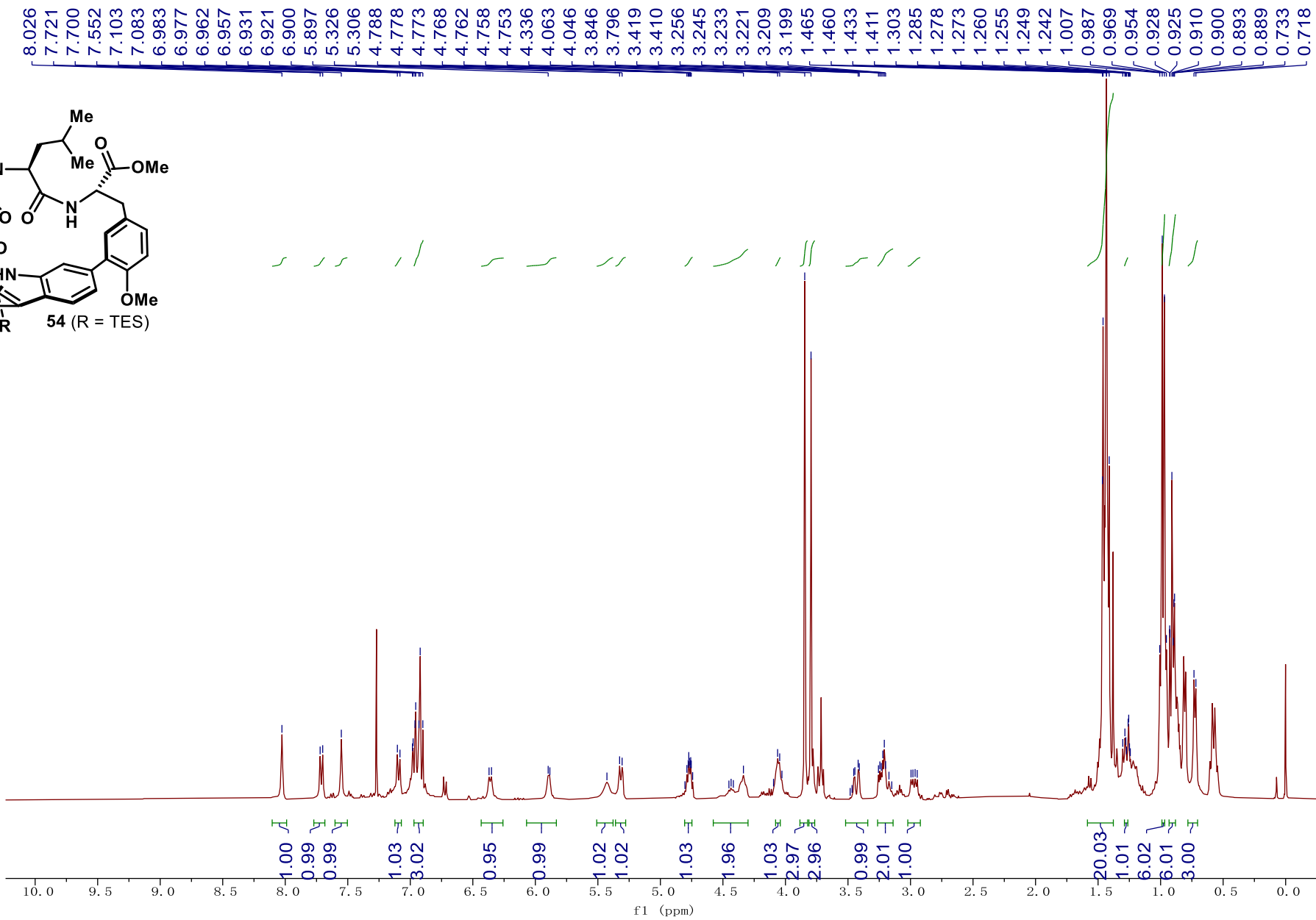
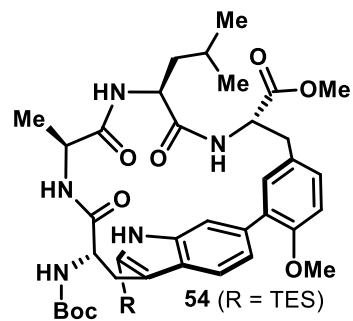
Compound S15 <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD, 60 °C)



- 173.215
- 173.121
- 172.009
- 171.788
- 156.539
- 155.512
- 144.633
- 138.857
- 131.370
- 131.014
- 129.955
- 129.214
- 128.893
- 120.115
- 116.983
- 111.462
- 107.263
- 103.275
- 79.685
- 54.833
- 53.962
- 53.882
- 51.759
- 51.454
- 49.284
- 40.639
- 36.098
- 27.418
- 24.455
- 22.580
- 22.062
- 20.700
- 16.856
- 6.553
- 4.031

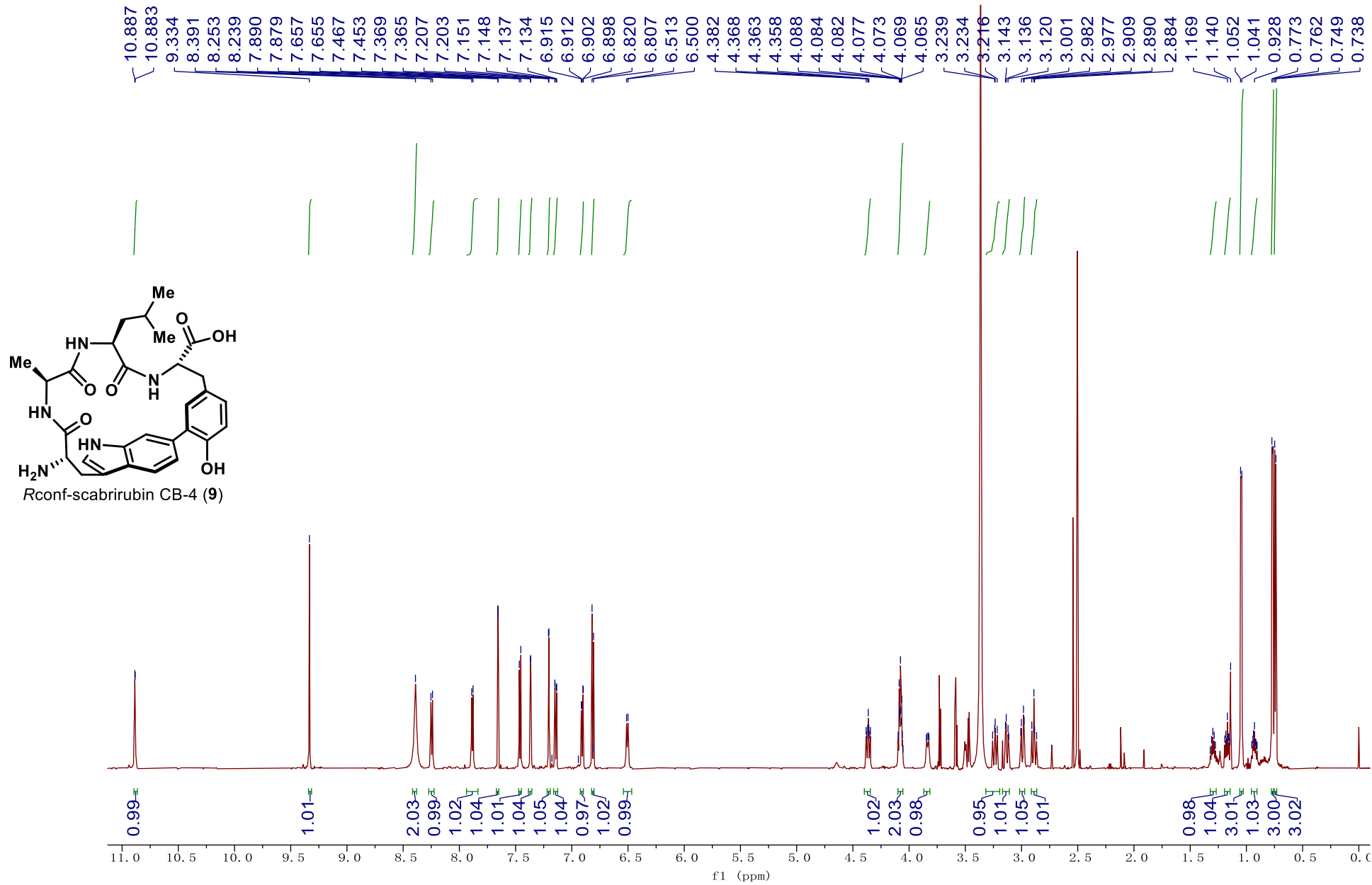


Compound 54 (400 MHz, CDCl<sub>3</sub>)

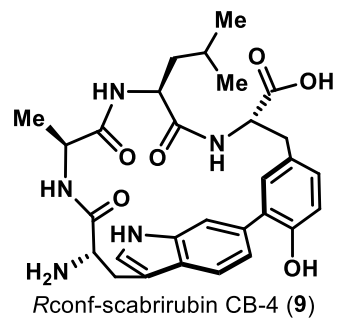




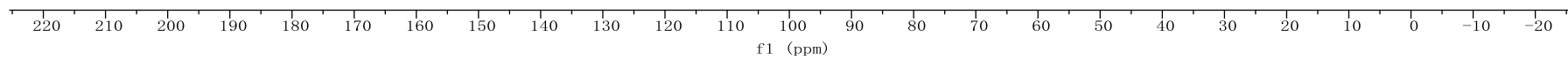
Compound 9 <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)



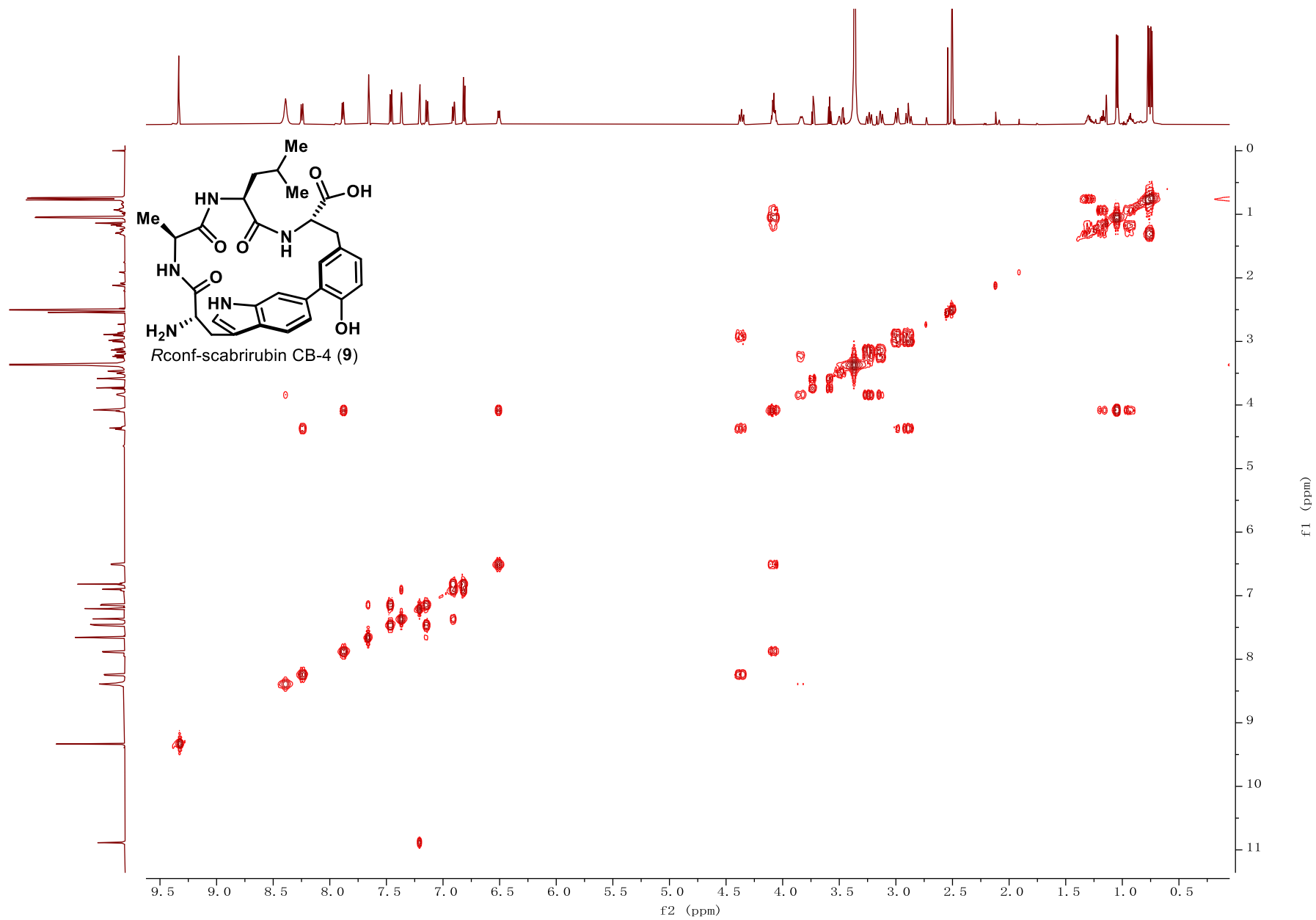
Compound 9 <sup>13</sup>C NMR (151 MHz, DMSO-*d*<sub>6</sub>)



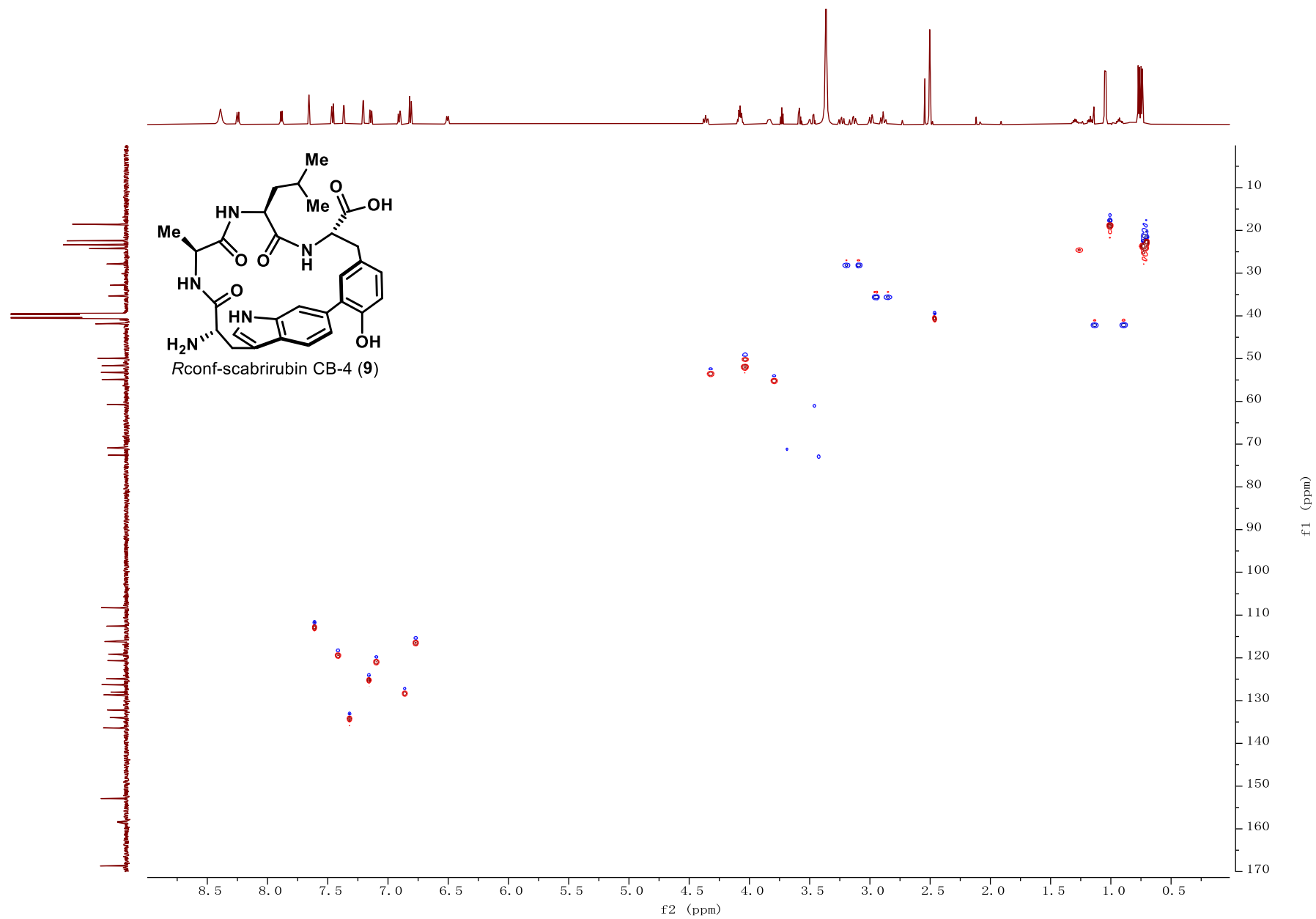
173.741  
171.257  
170.098  
168.671  
— 152.899  
136.379  
133.936  
132.172  
128.737  
128.635  
128.018  
126.265  
124.903  
120.638  
119.122  
116.199  
112.588  
108.265  
72.586  
70.895  
60.735  
54.875  
53.244  
51.686  
49.933  
41.849  
35.927  
32.846  
27.870  
24.285  
23.391  
22.432  
18.555



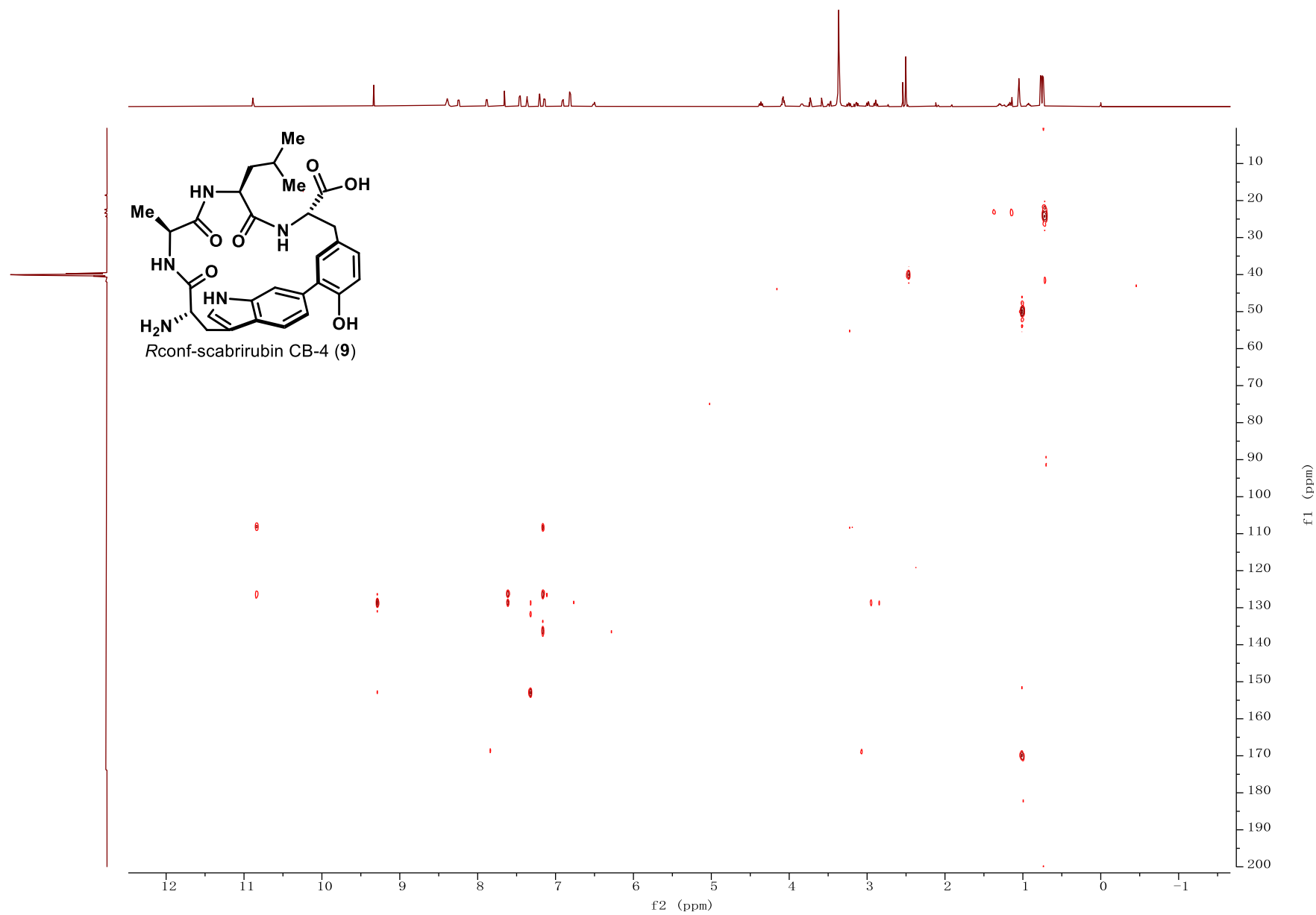
Compound 9  $^1\text{H}$ - $^1\text{H}$  COSY NMR (400 MHz,  $\text{DMSO-}d_6$ )



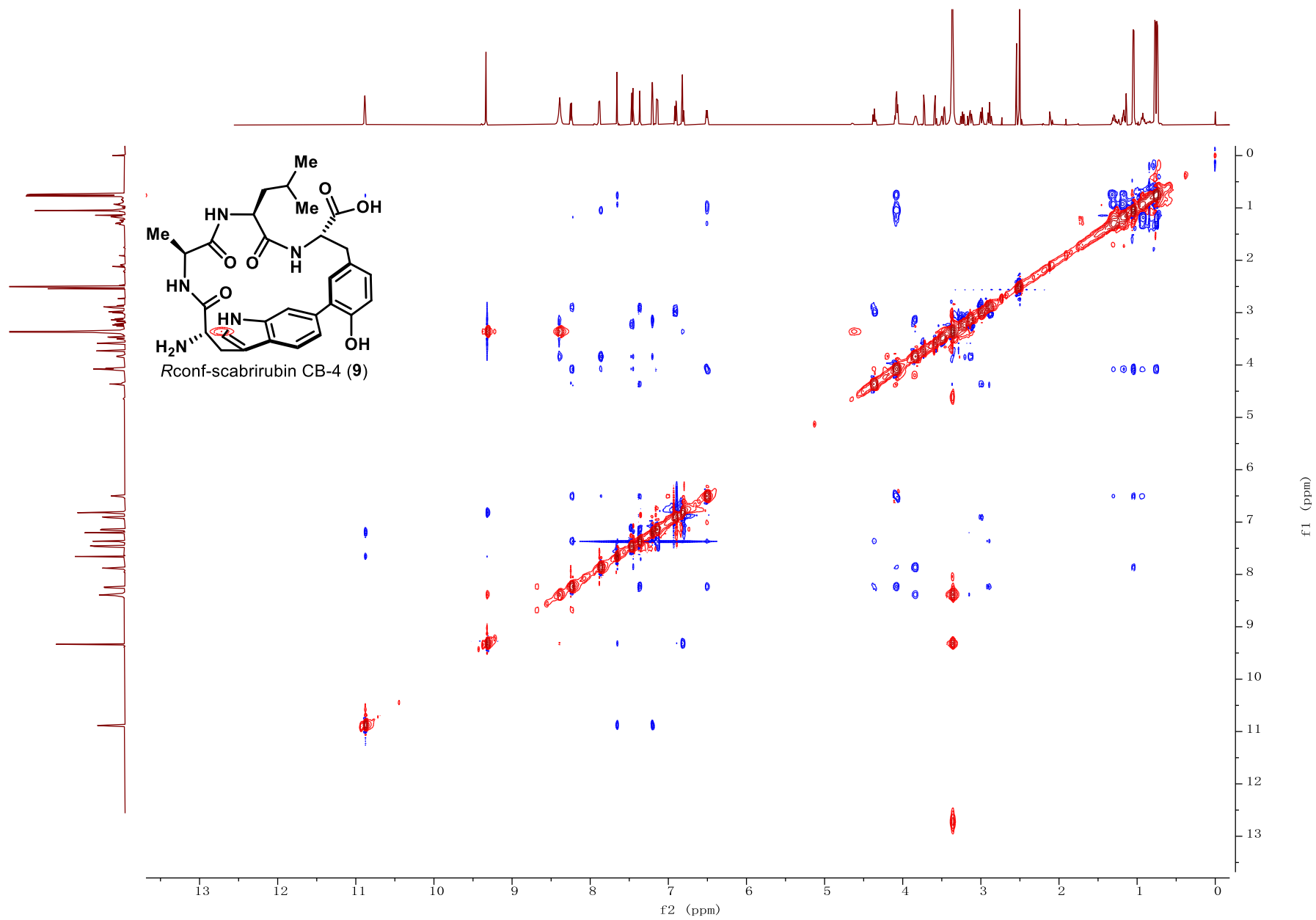
Compound 9  $^1\text{H}$ - $^{13}\text{C}$  HSQC NMR (600 MHz,  $\text{DMSO-}d_6$ )



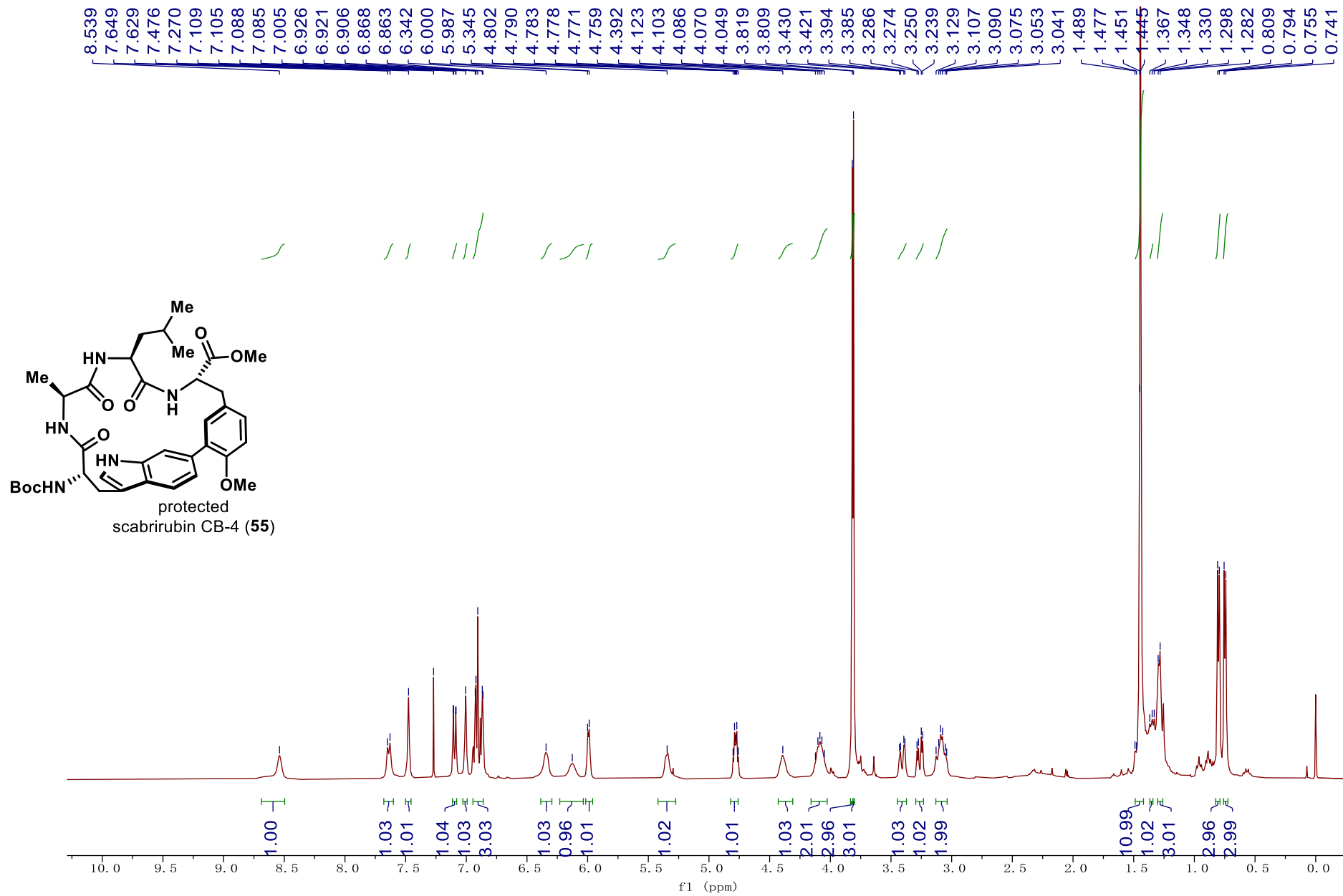
Compound 9  $^1\text{H}$ - $^{13}\text{C}$  HMBC NMR (600 MHz,  $\text{DMSO-}d_6$ )



Compound 9  $^1\text{H}$ - $^1\text{H}$  ROESY NMR (400 MHz,  $\text{DMSO-}d_6$ )

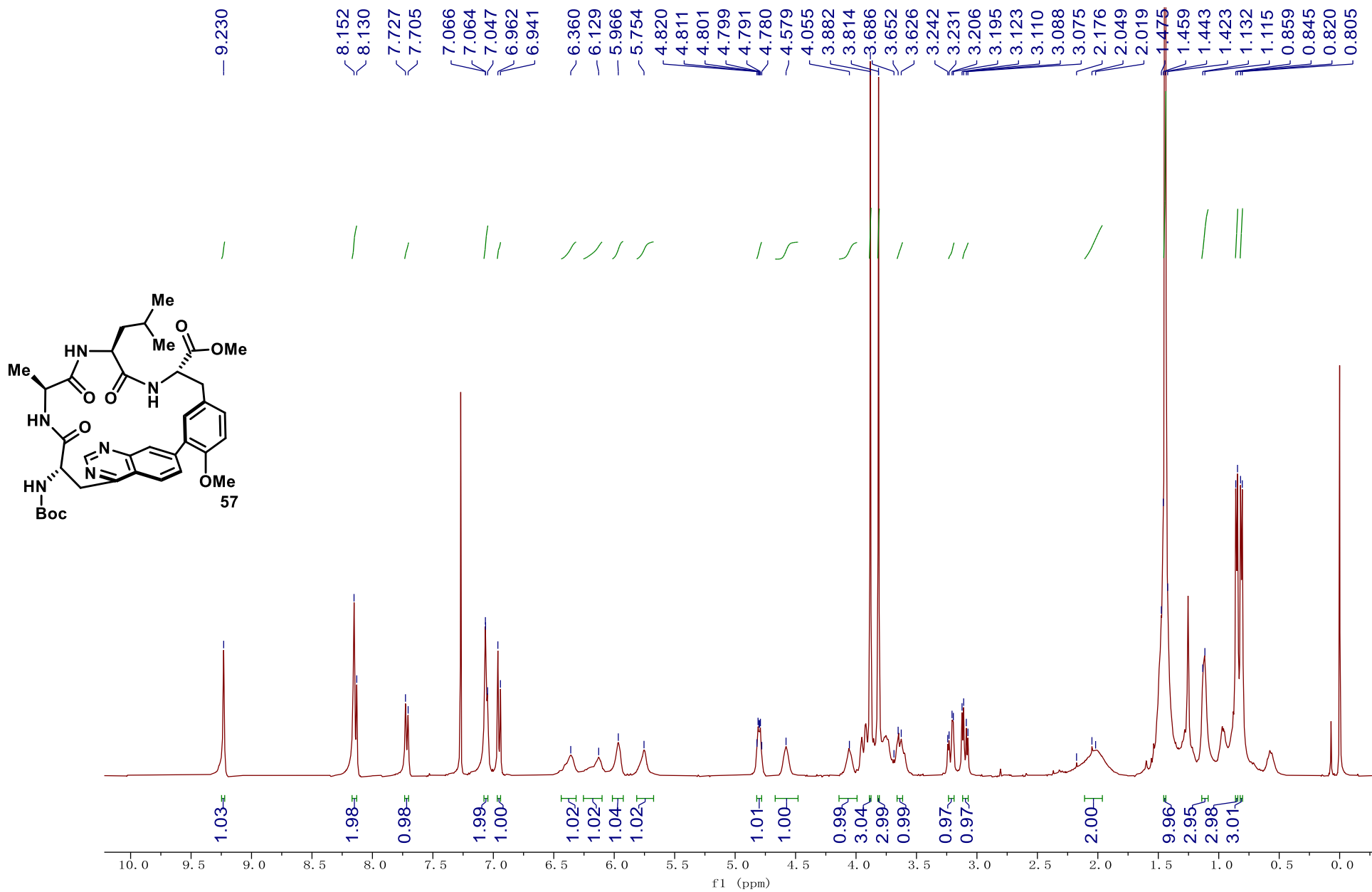


Compound 55 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

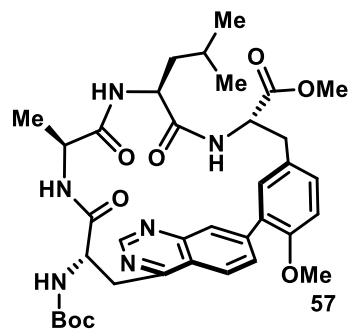




Compound 57 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



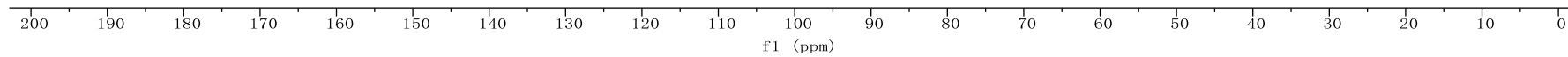
Compound 57 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



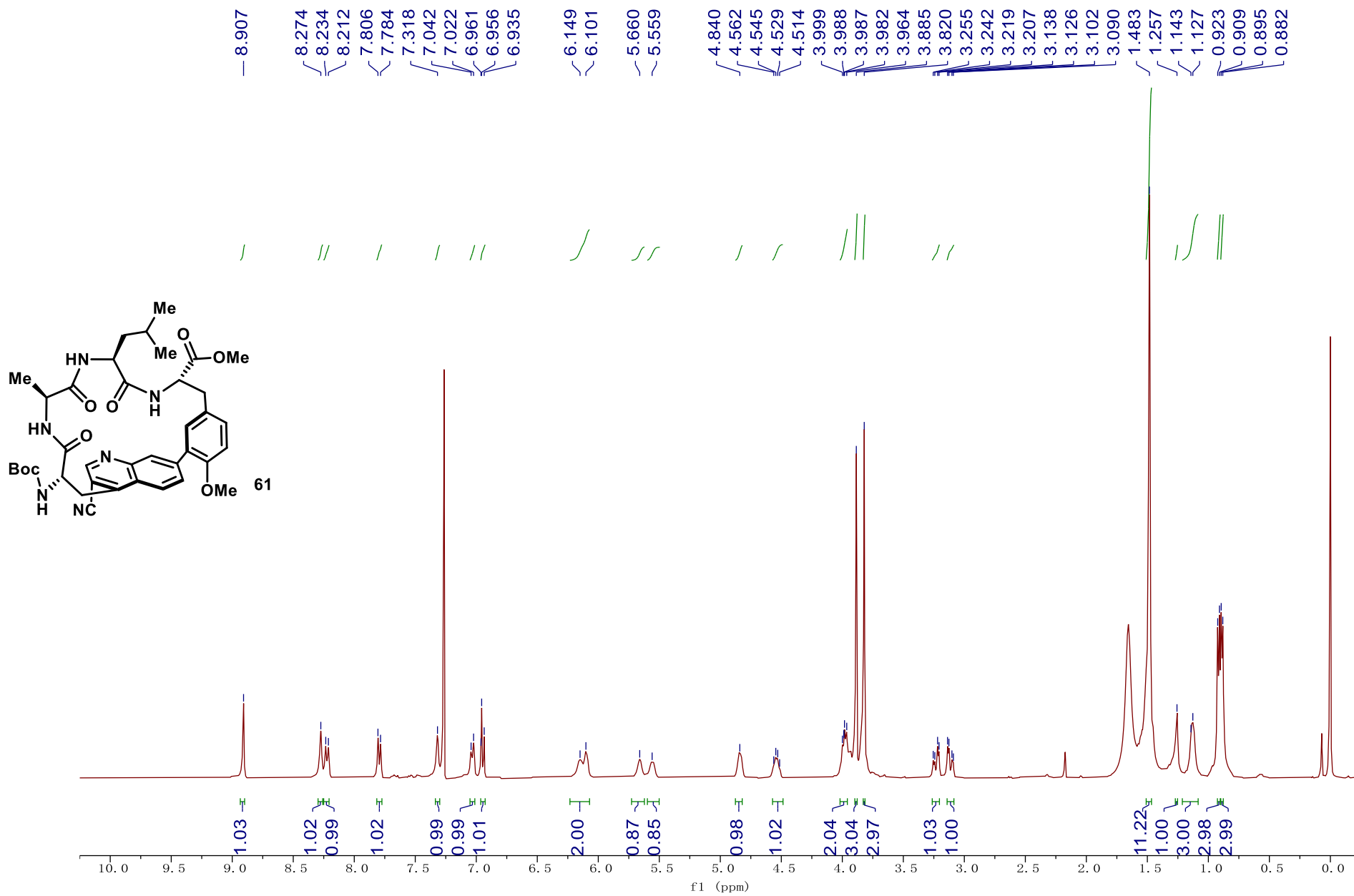
171.576  
171.252  
170.266  
170.230  
155.431  
154.363  
154.267  
150.264  
145.174  
145.147  
134.250  
130.464  
129.989  
129.028  
128.846  
127.909  
125.250  
123.271  
111.337

80.424

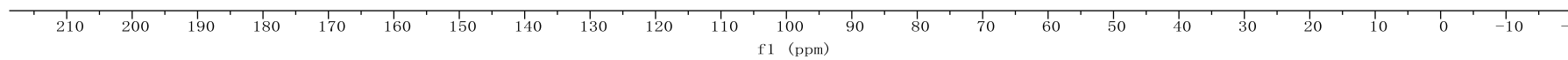
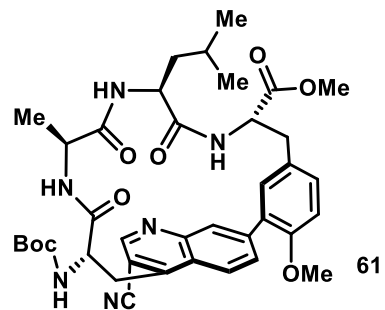
55.645  
53.158  
52.628  
52.206  
49.342  
41.296  
36.109  
29.711  
28.303  
24.646  
22.740  
21.927  
17.357



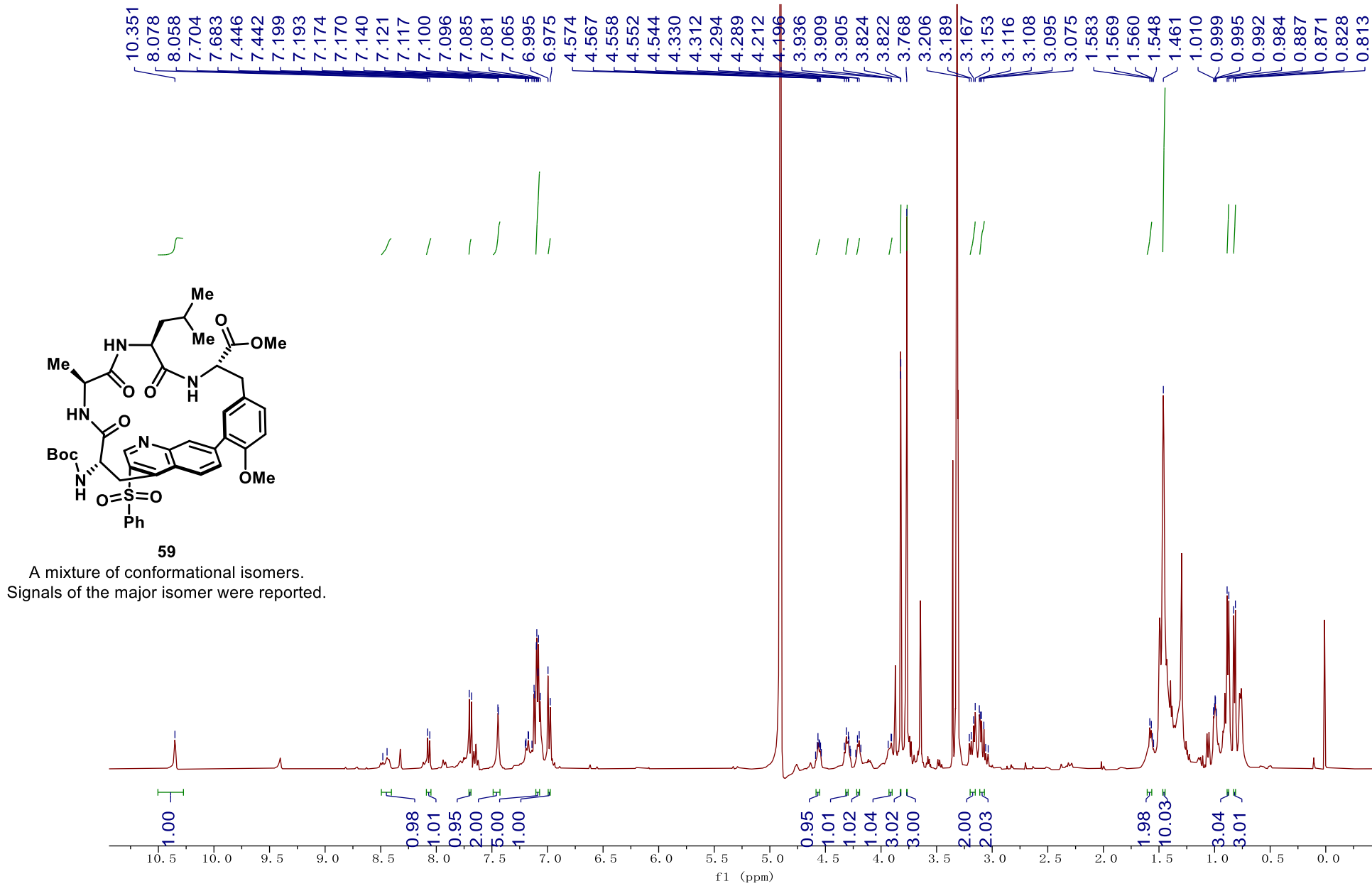
Compound 61 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



Compound 61 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



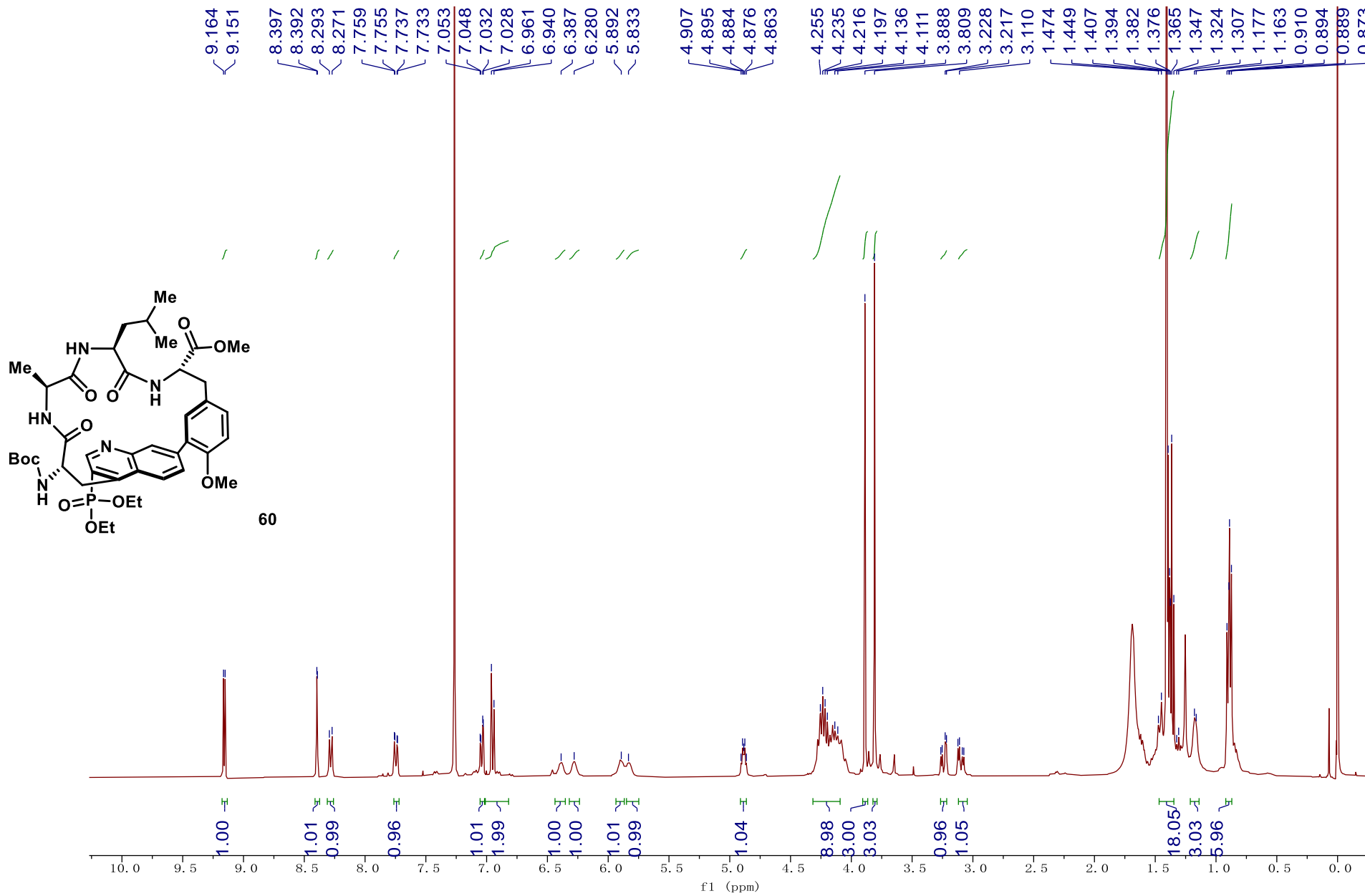
Compound 59 <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, 60 °C)



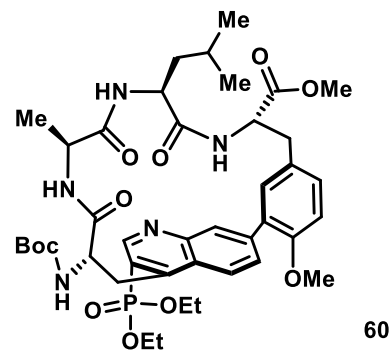
59  
A mixture of conformational isomers.  
Signals of the major isomer were reported.



Compound 60 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



Compound 60 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

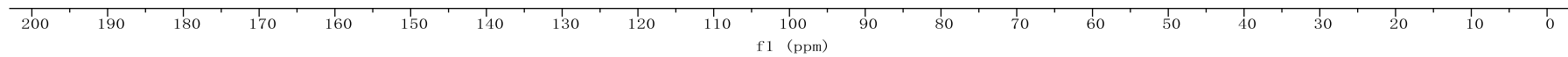


170.908  
170.479  
170.468  
170.250  
155.102  
154.999  
151.377  
151.255  
148.519  
— 141.262  
133.678  
130.460  
129.768  
129.375  
129.059  
128.334  
127.289  
125.032  
— 110.715

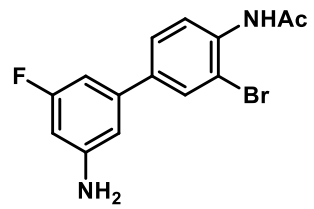
— 99.363

76.599  
62.260  
62.204  
62.133  
62.078  
56.476  
54.958  
52.421  
52.173  
51.940  
48.630

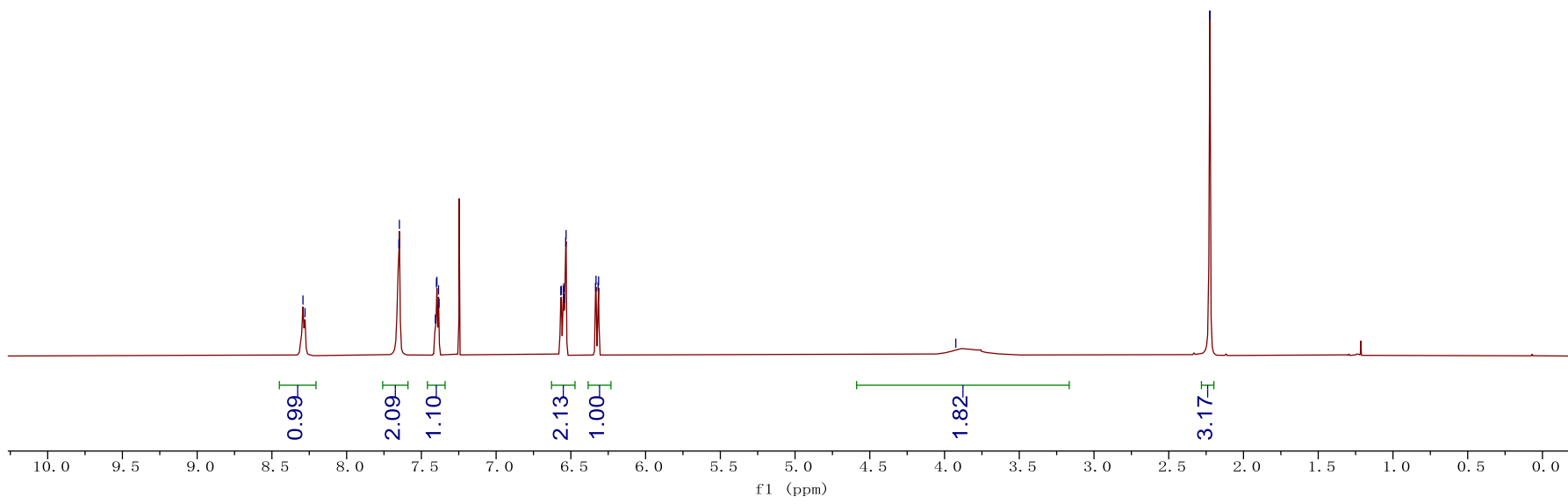
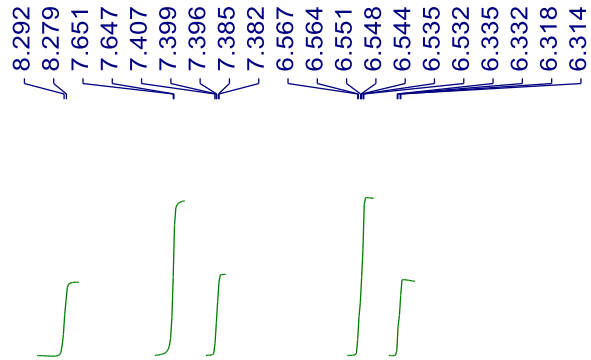
40.360  
35.786  
29.075  
29.032  
27.621  
25.601  
24.058  
22.148  
21.395  
16.423  
15.812  
15.750  
15.687



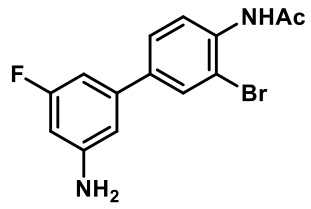
Compound S18 <sup>1</sup>HNMR (600 MHz, CDCl<sub>3</sub>)



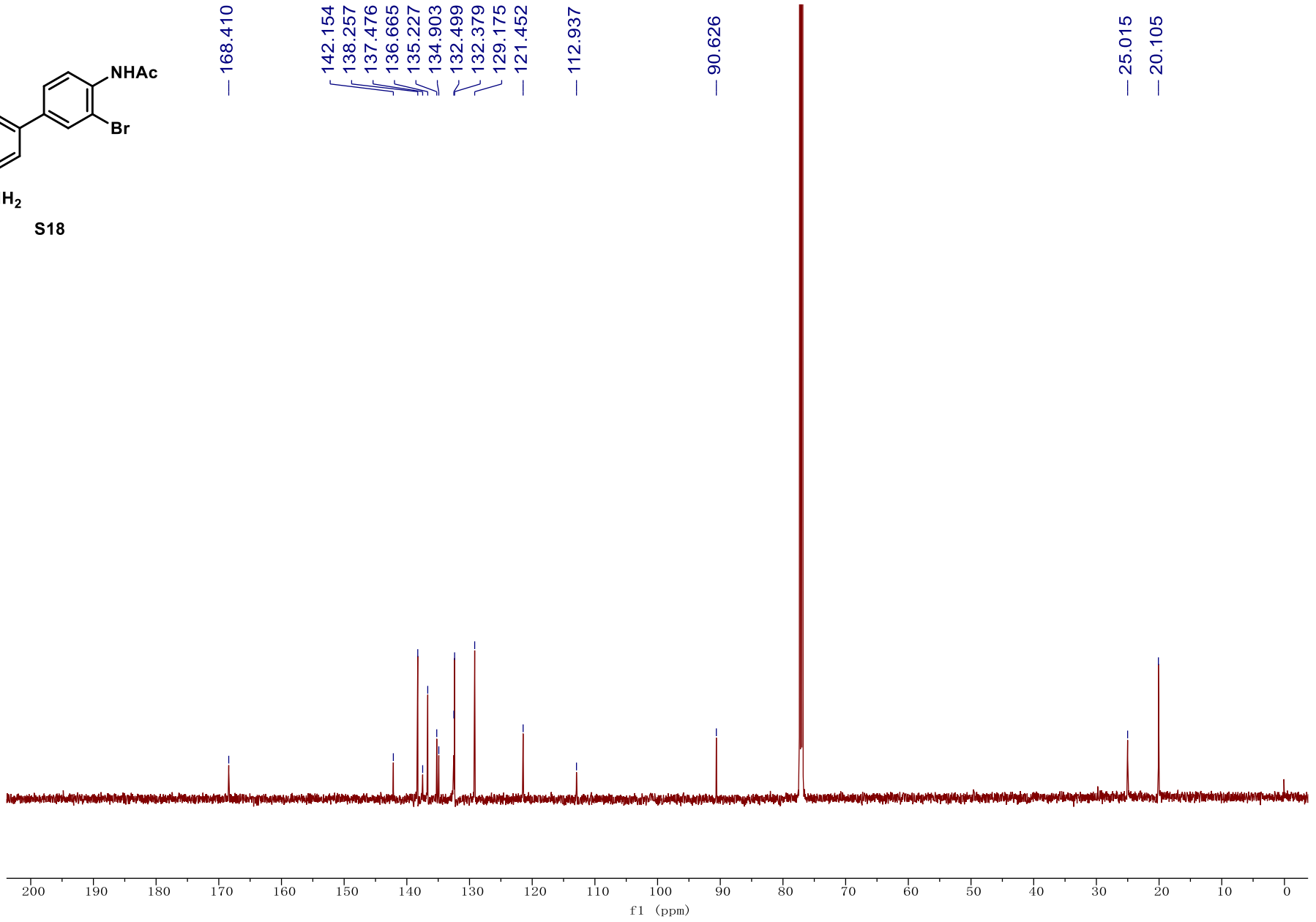
S18



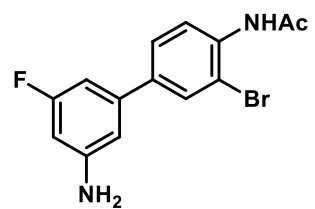
Compound S18 <sup>13</sup>CNMR (151 MHz, CDCl<sub>3</sub>)



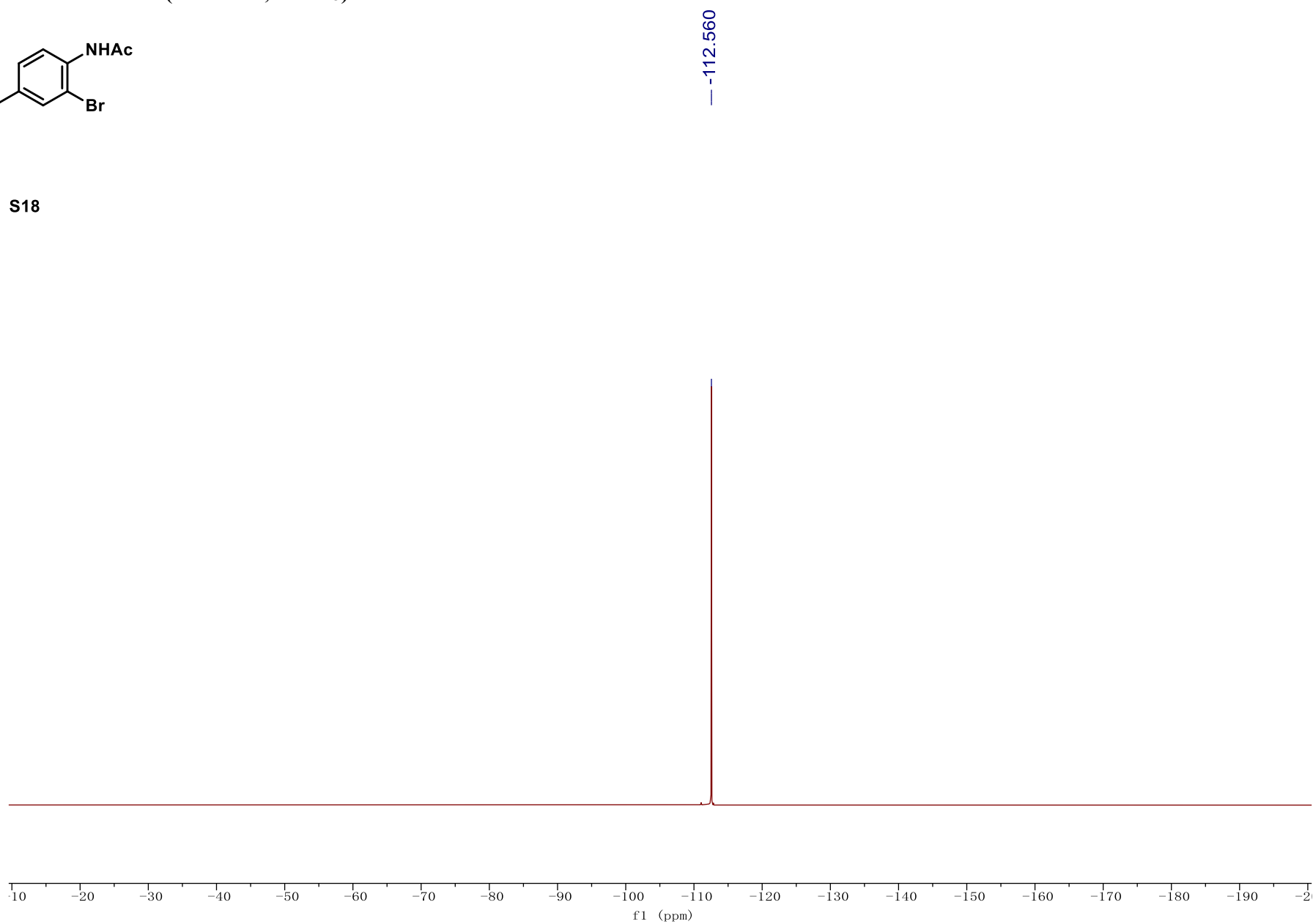
S18



Compound S18  $^{19}\text{F}$  NMR (565 MHz,  $\text{CDCl}_3$ )

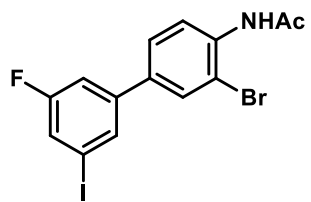


S18



S133

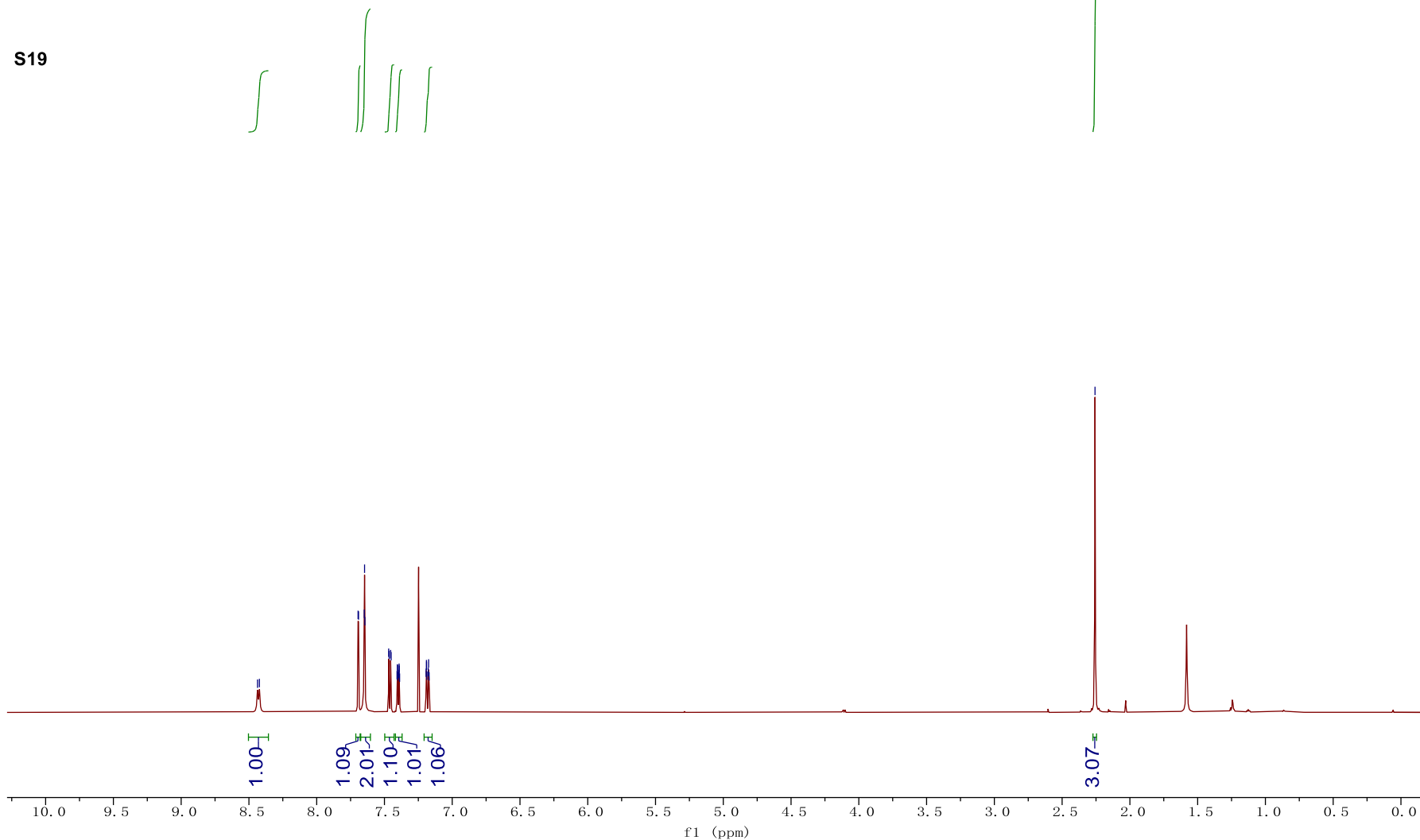
Compound S19 <sup>1</sup>HNMR (600 MHz, CDCl<sub>3</sub>)



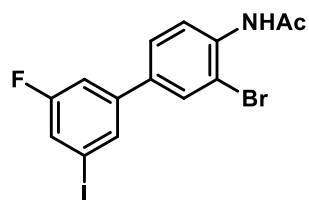
S19

8.437  
8.423  
7.695  
7.691  
7.649  
7.647  
7.644  
7.469  
7.465  
7.455  
7.451  
7.407  
7.405  
7.403  
7.401  
7.394  
7.392  
7.391  
7.388  
7.193  
7.190  
7.189  
7.187  
7.177  
7.174  
7.170

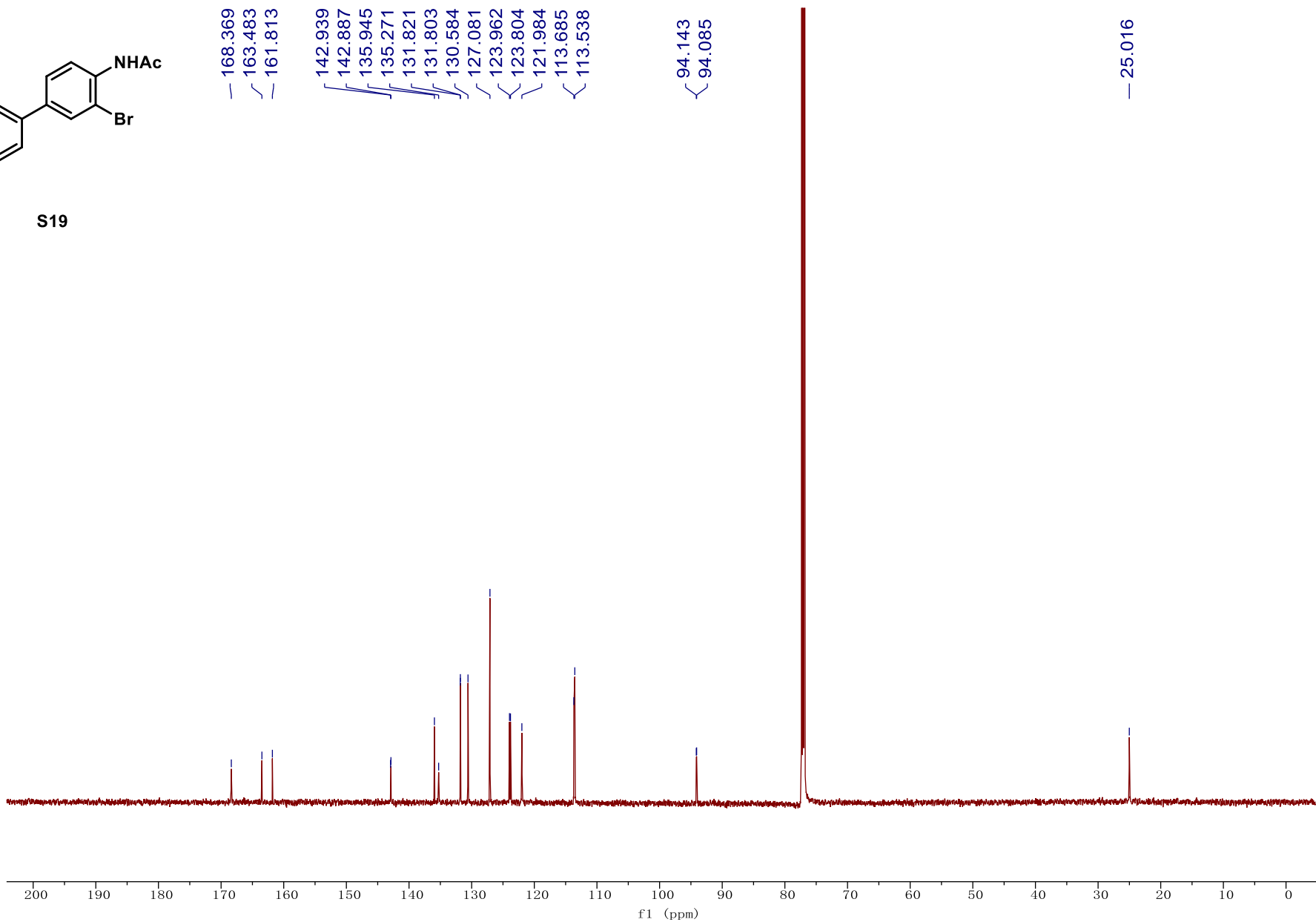
2.257



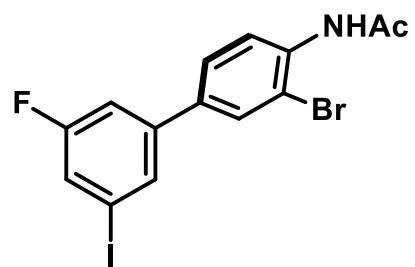
Compound S19 <sup>13</sup>CNMR (151 MHz, CDCl<sub>3</sub>)



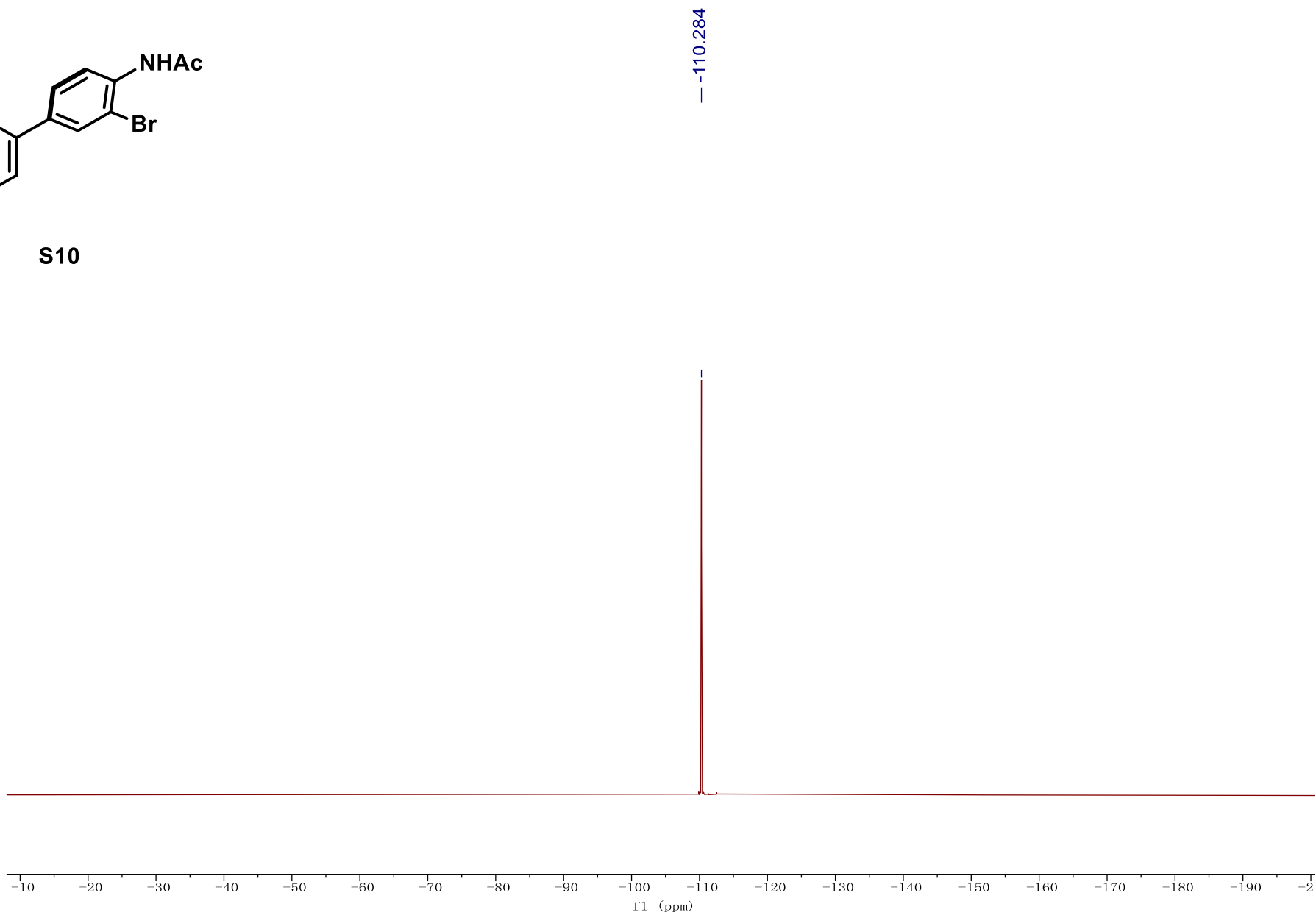
S19



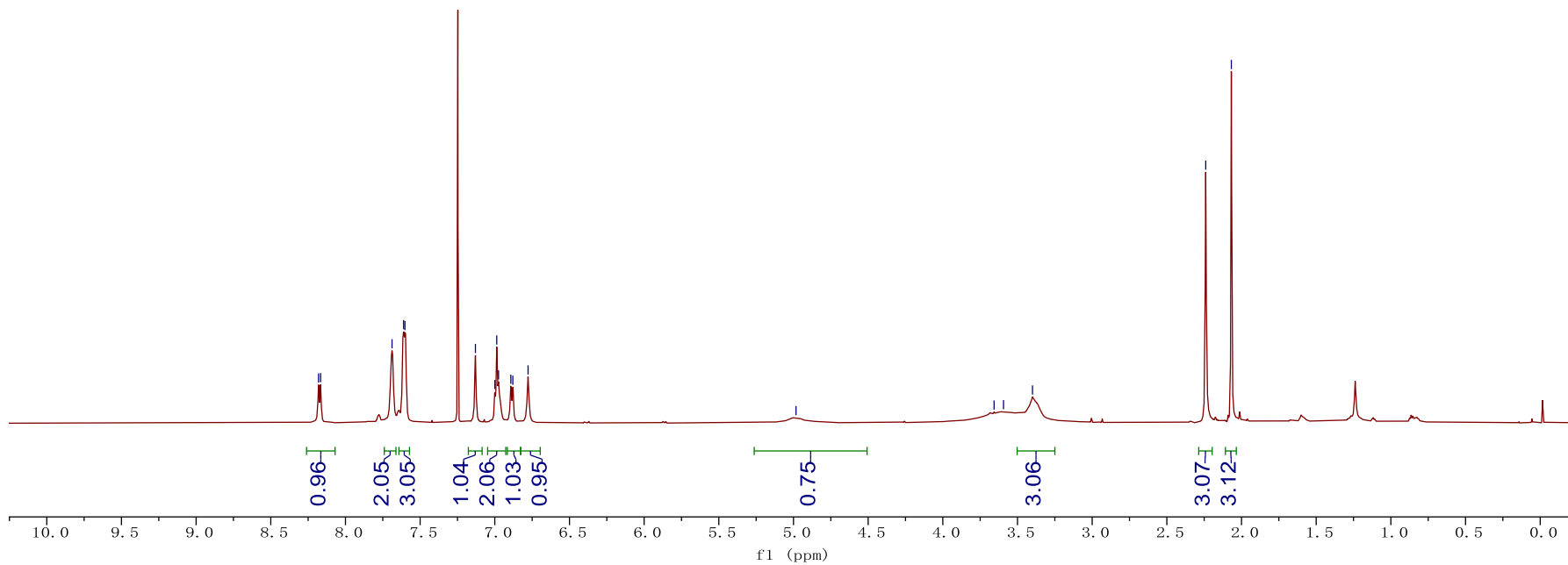
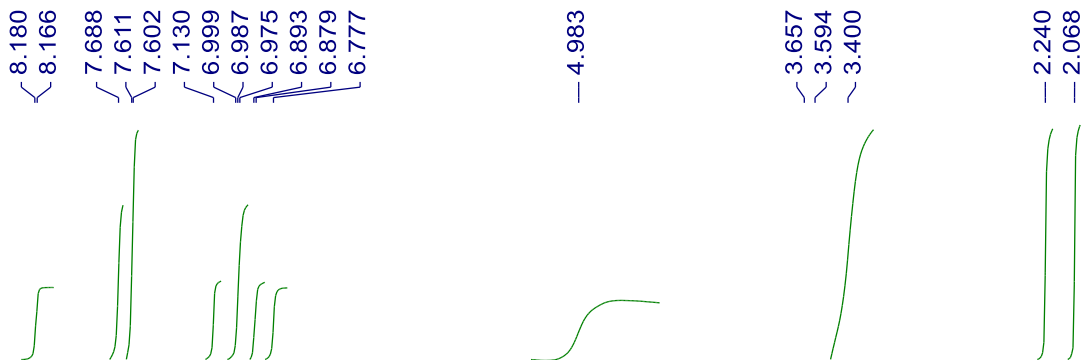
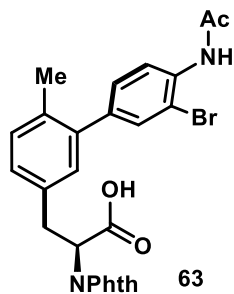
Compound S10 <sup>19</sup>F NMR (565 MHz, CDCl<sub>3</sub>)



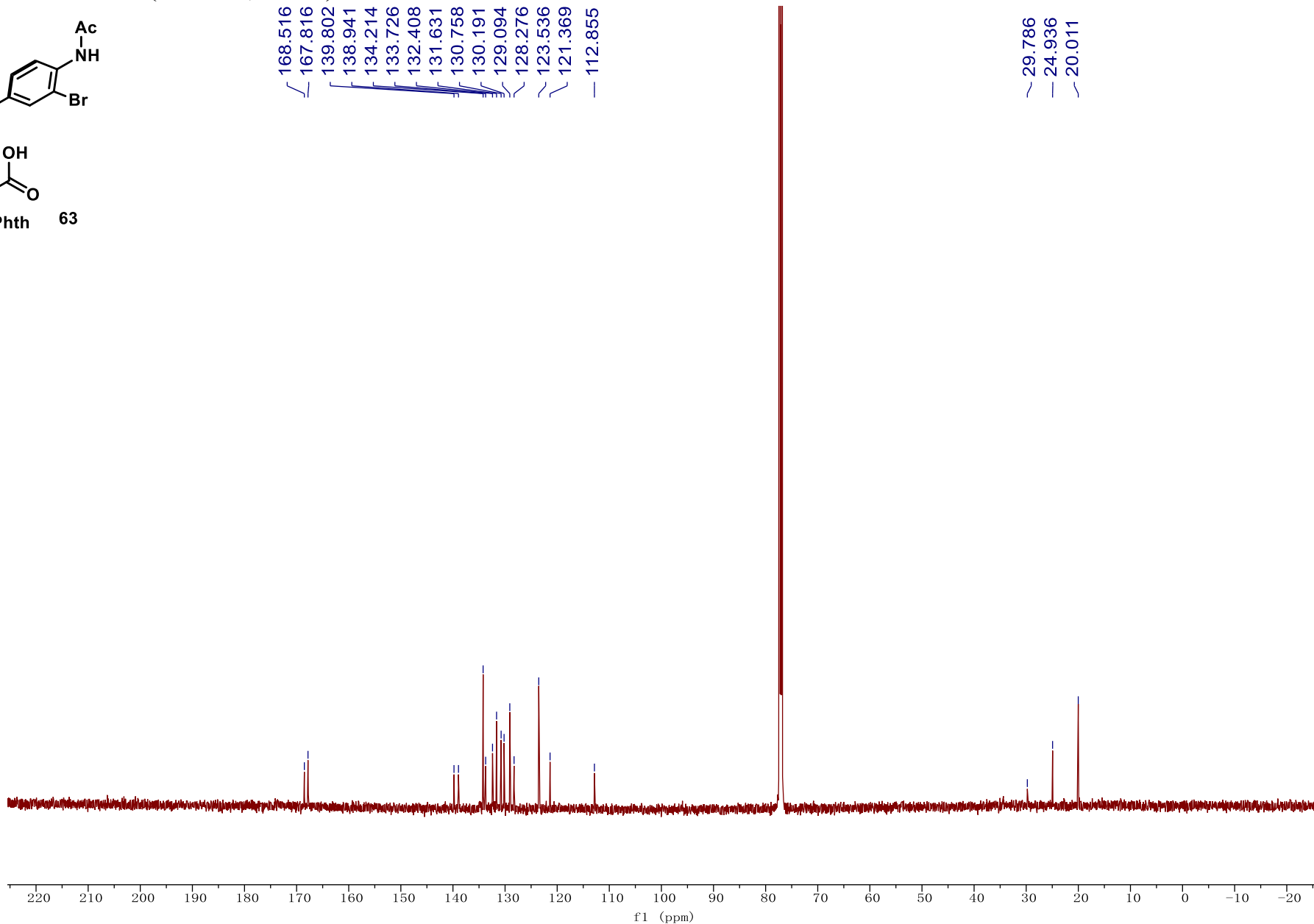
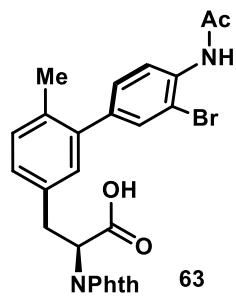
S10



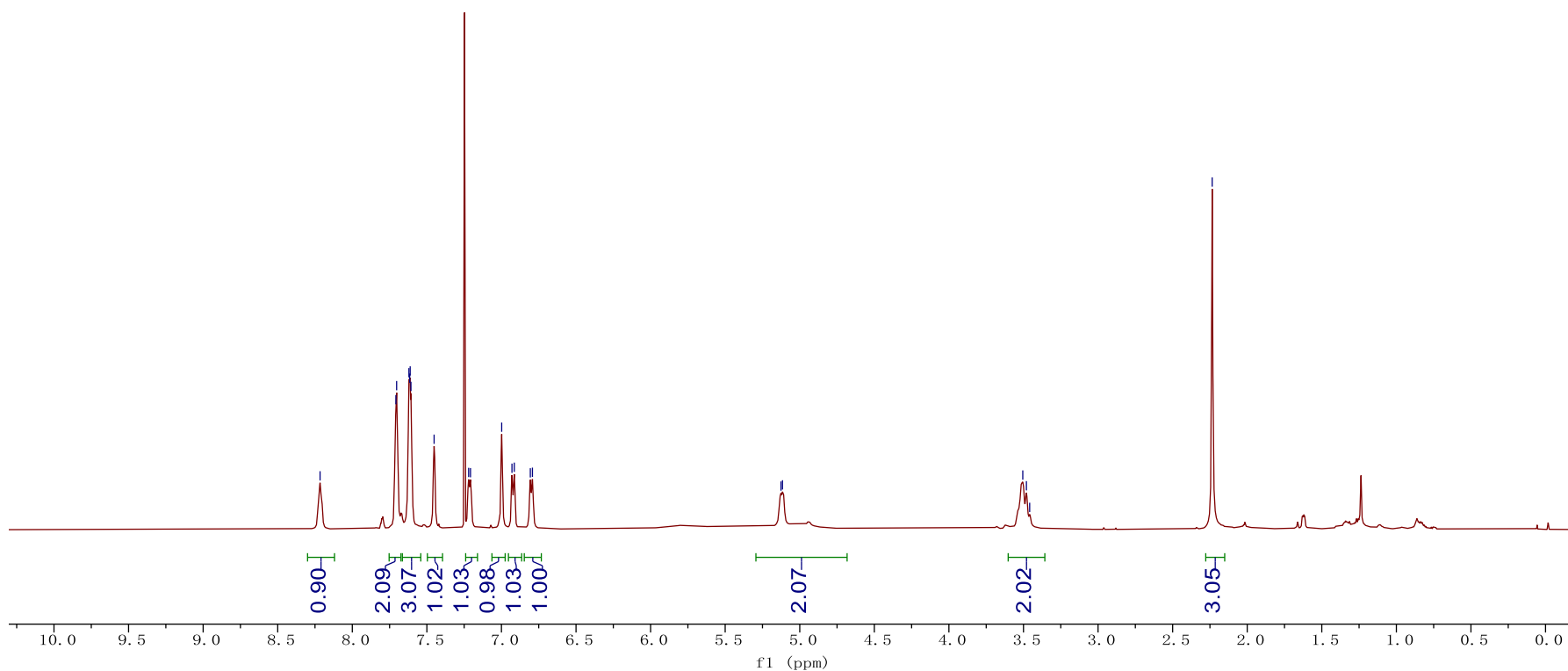
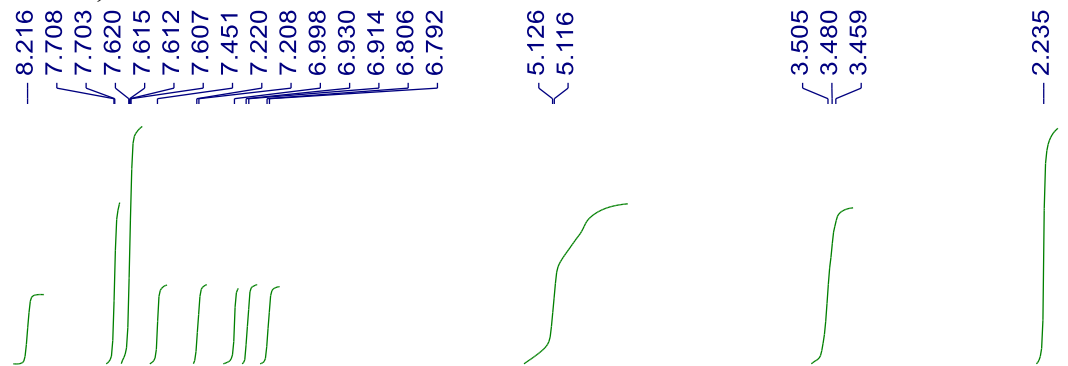
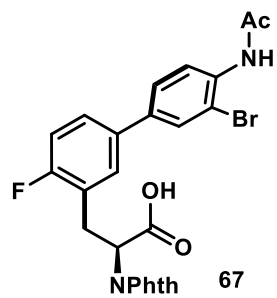
Compound 63 <sup>1</sup>HNMR (600 MHz, CDCl<sub>3</sub>)



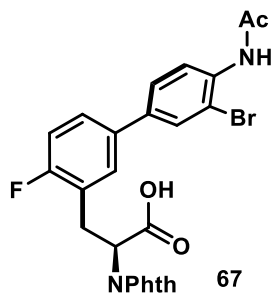
Compound 63 <sup>13</sup>CNMR (151 MHz, CDCl<sub>3</sub>)



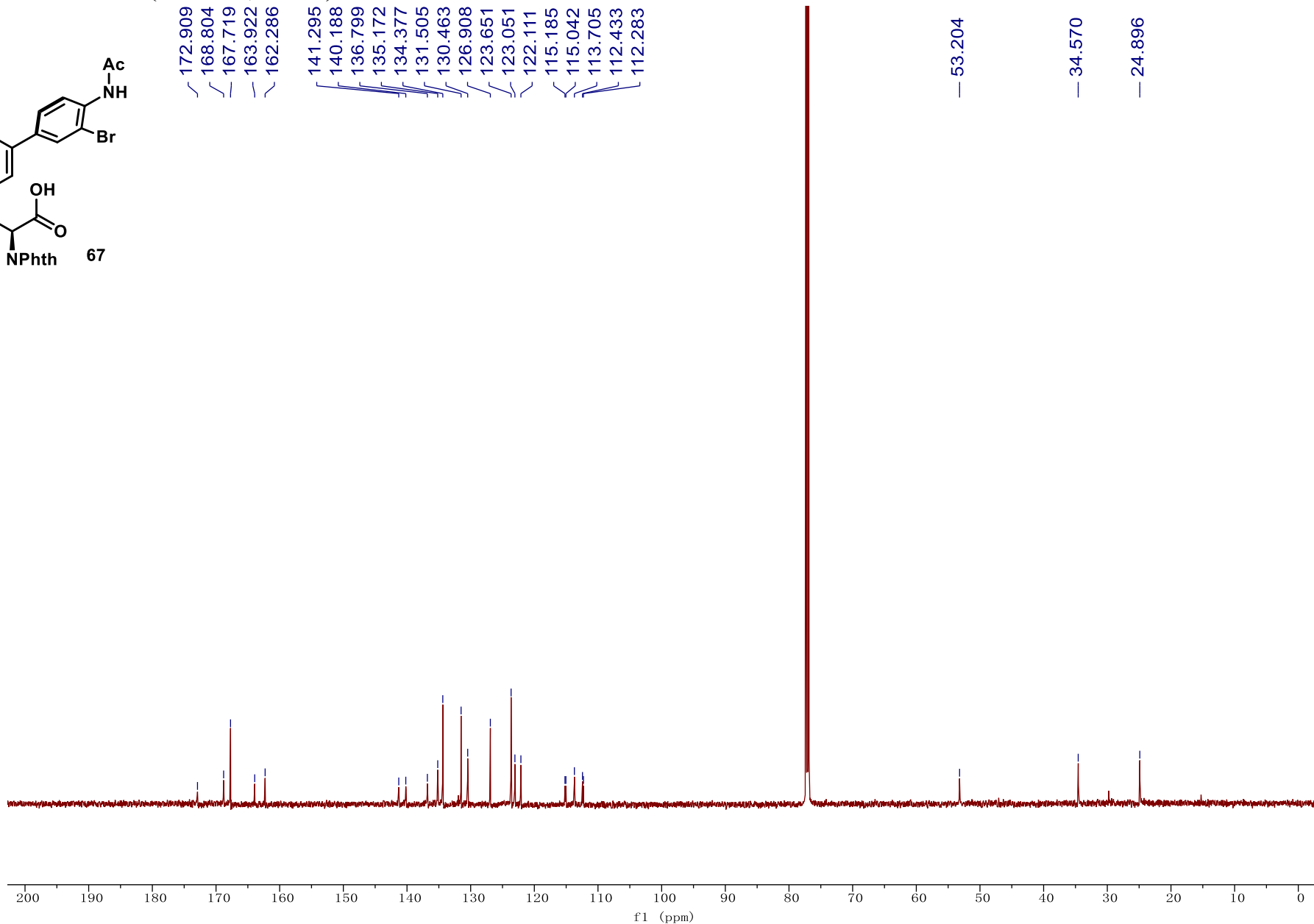
Compound 67 <sup>1</sup>HNMR (600 MHz, CDCl<sub>3</sub>)



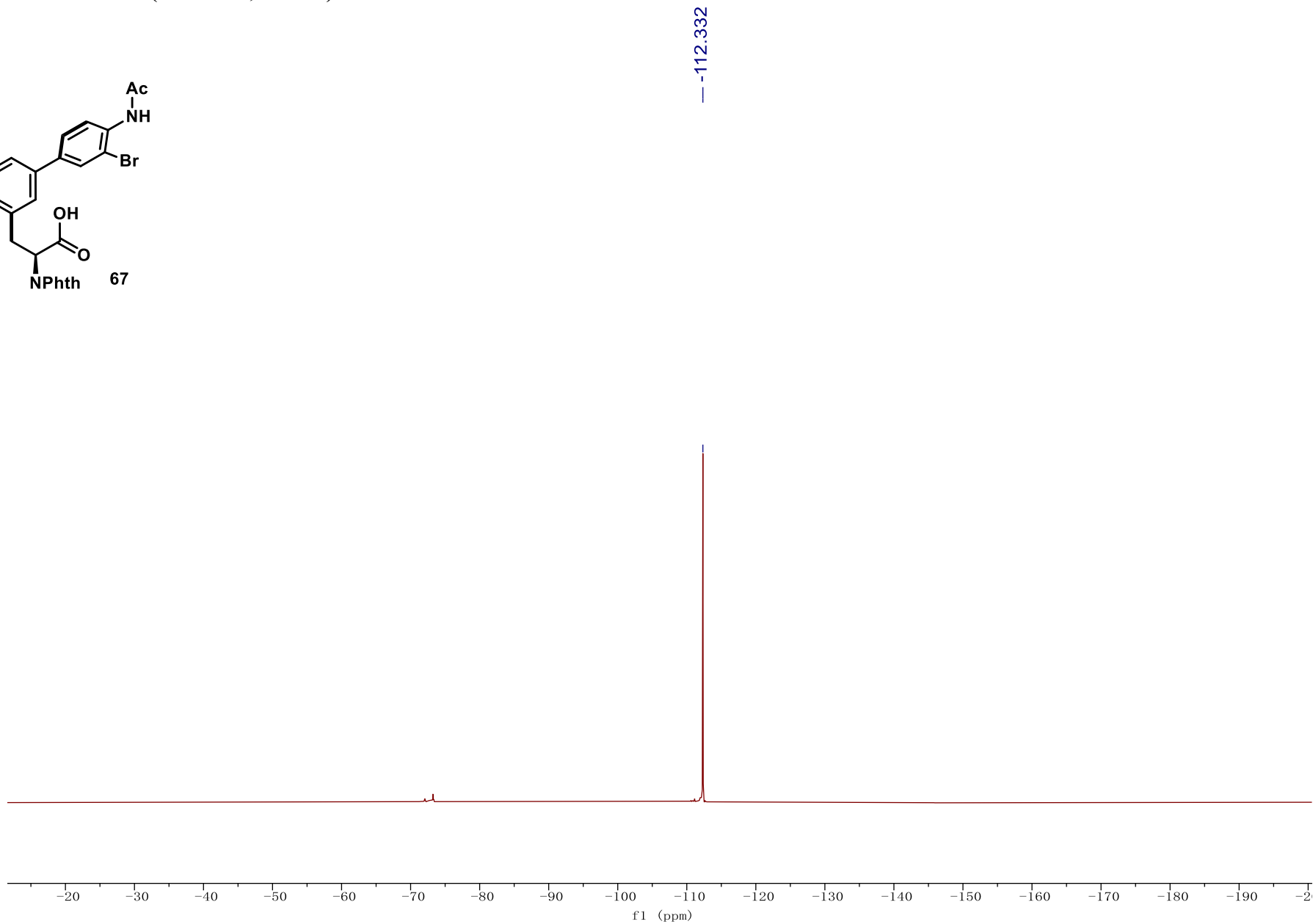
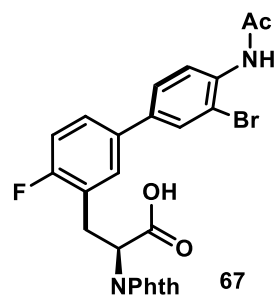
Compound 67 <sup>13</sup>CNMR (151 MHz, CDCl<sub>3</sub>)



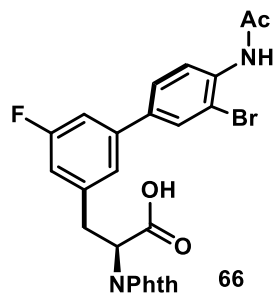
- 172.909
- 168.804
- 167.719
- 163.922
- 162.286
- 141.295
- 140.188
- 136.799
- 135.172
- 134.377
- 131.505
- 130.463
- 126.908
- 123.651
- 123.051
- 122.111
- 115.185
- 115.042
- 113.705
- 112.433
- 112.283



Compound 67  $^{19}\text{F}$  NMR (565 MHz,  $\text{CDCl}_3$ )



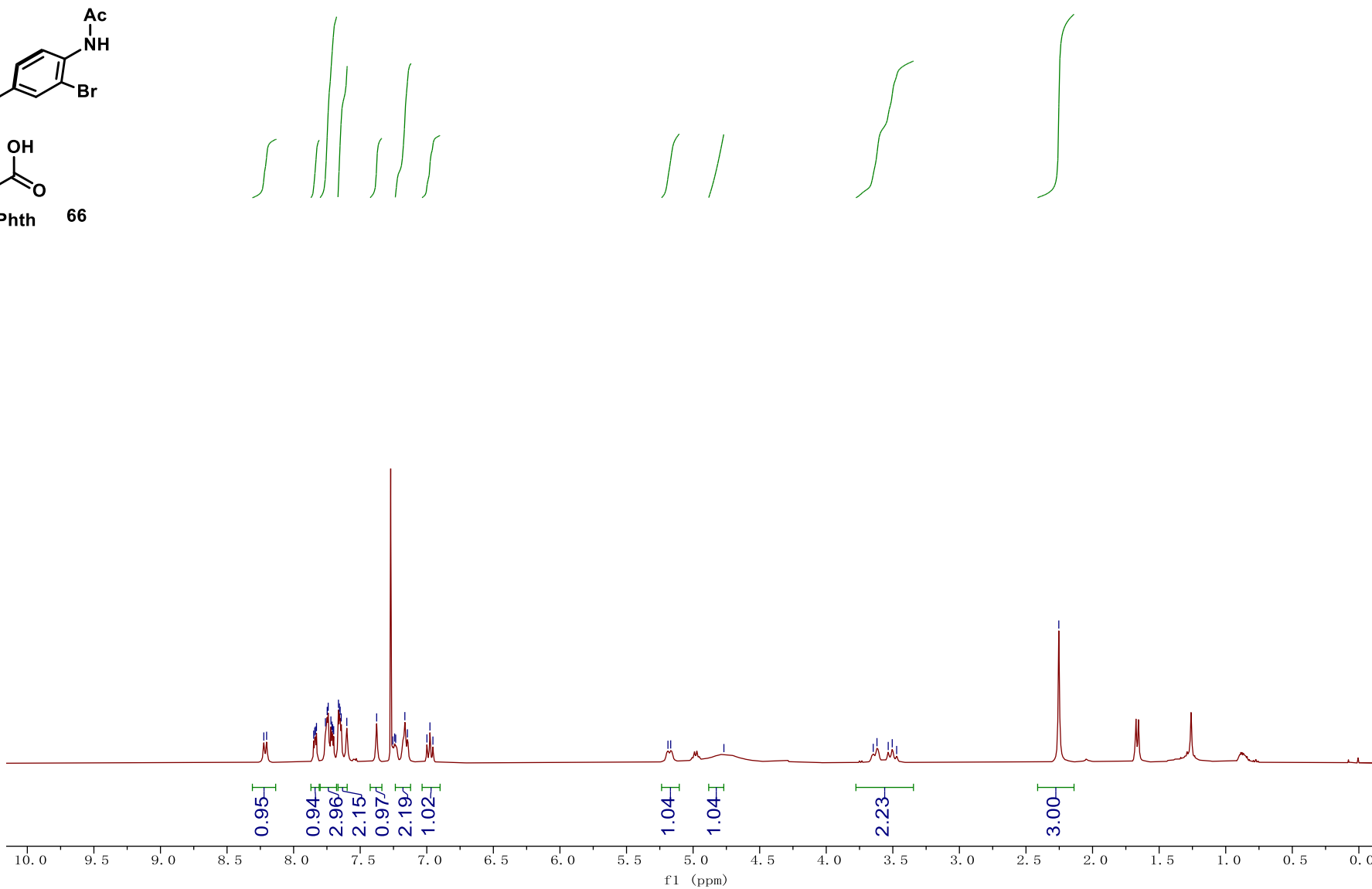
Compound 66 <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>)



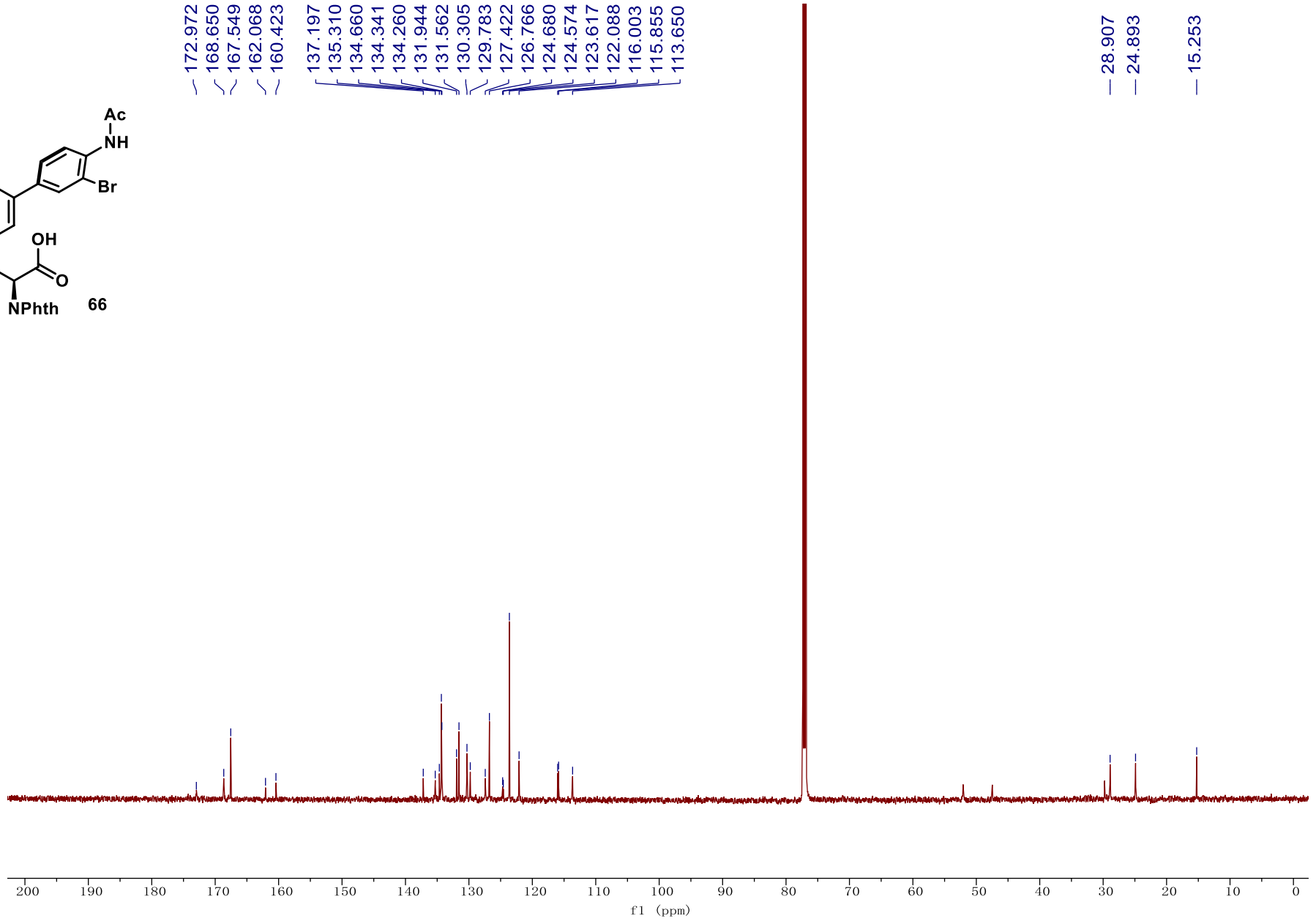
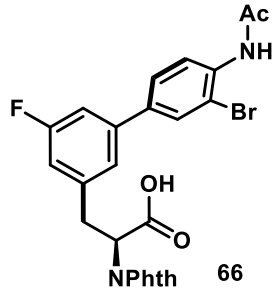
8.224  
8.203  
7.849  
7.842  
7.836  
7.828  
7.761  
7.748  
7.740  
7.720  
7.712  
7.707  
7.699  
7.663  
7.656  
7.650  
7.643  
7.601  
7.376  
7.255  
7.241  
7.233  
7.165  
7.145  
6.999  
6.976  
6.954  
5.189  
5.168  
4.769

3.647  
3.619  
3.535  
3.504  
3.471

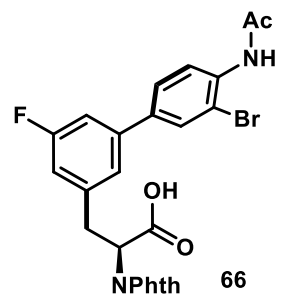
2.253



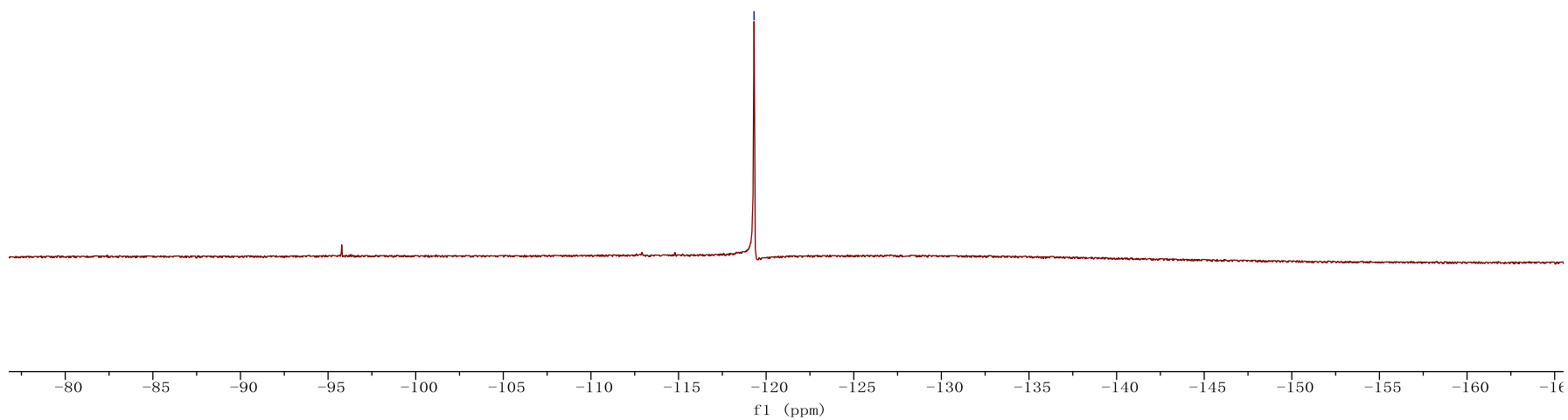
Compound 66 <sup>13</sup>CNMR (101 MHz, CDCl<sub>3</sub>)



Compound 66  $^{19}\text{F}$  NMR (565 MHz,  $\text{CDCl}_3$ )

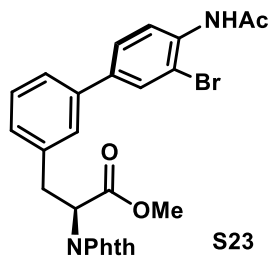


— -119.308

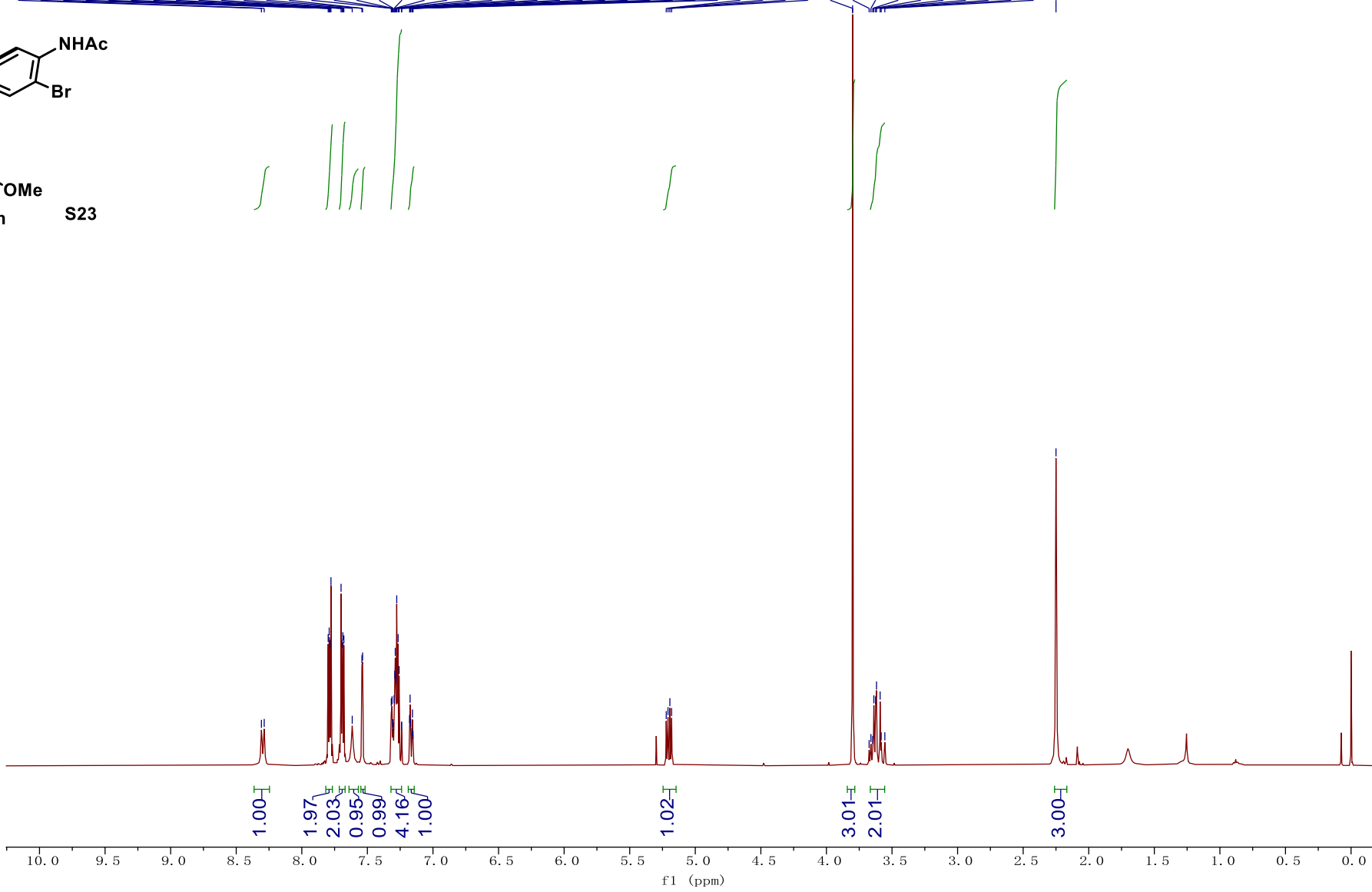


S144

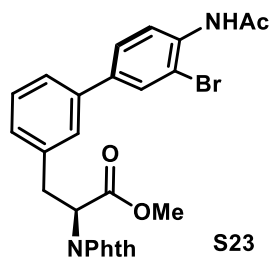
Compound S23 <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>)



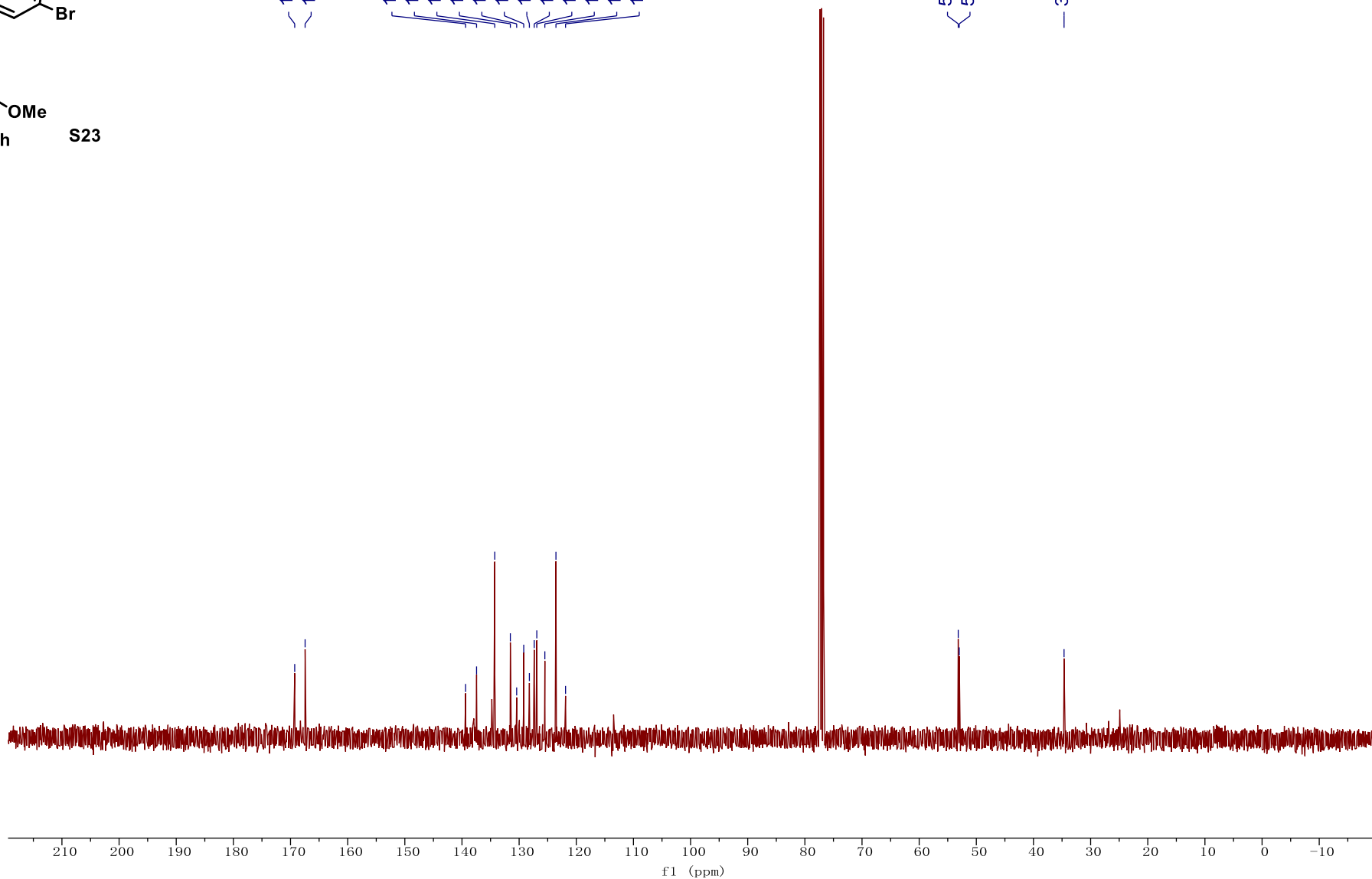
8.308  
8.287  
7.799  
7.791  
7.785  
7.778  
7.701  
7.693  
7.687  
7.679  
7.616  
7.542  
7.536  
7.318  
7.312  
7.306  
7.302  
7.296  
7.291  
7.287  
7.283  
7.276  
7.266  
7.258  
7.240  
7.238  
7.178  
7.174  
7.170  
7.161  
7.156  
7.152  
5.221  
5.208  
5.194  
5.180  
3.800  
3.674  
3.661  
3.647  
3.639  
3.625  
3.618  
3.591  
3.583  
3.555  
2.250



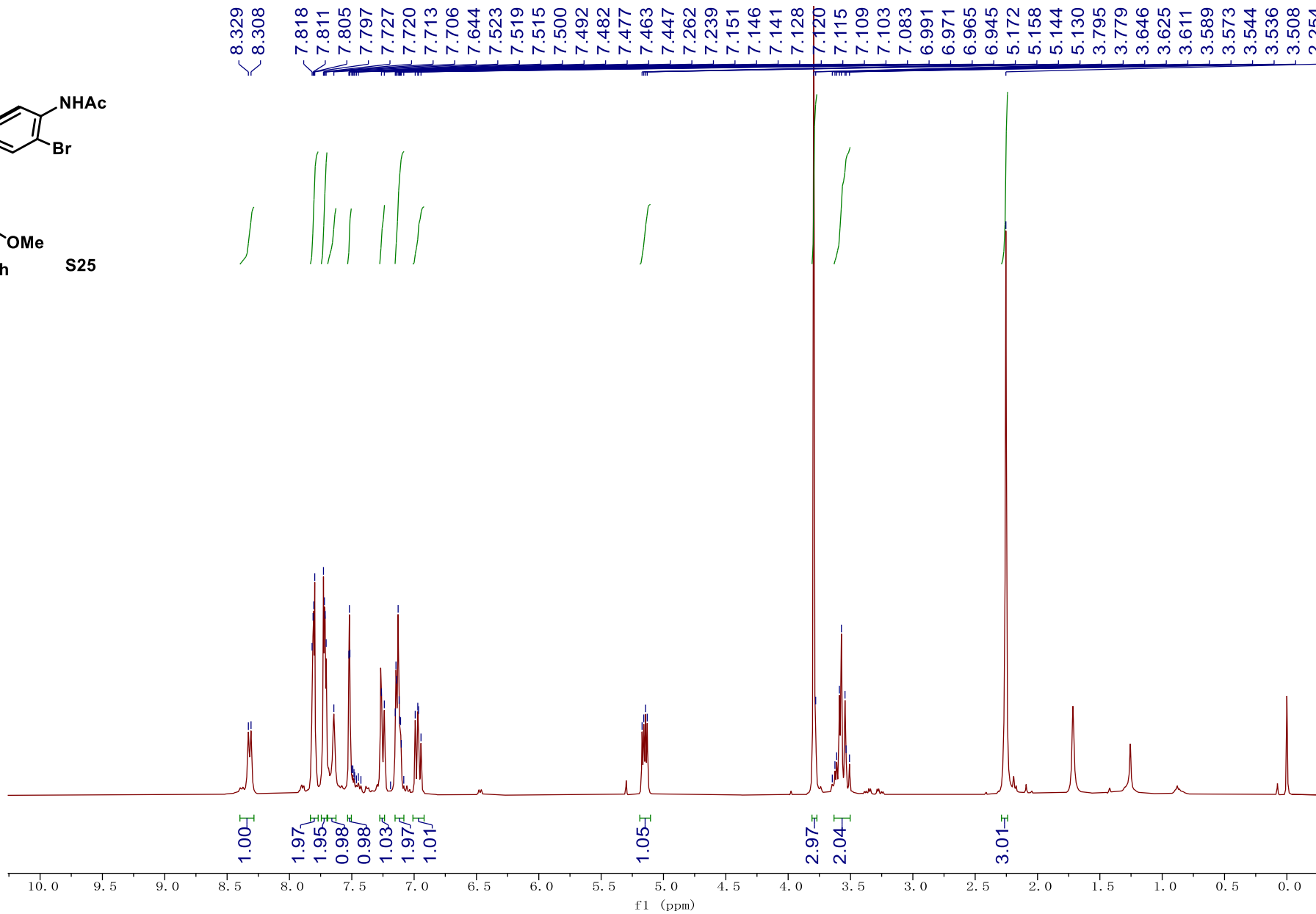
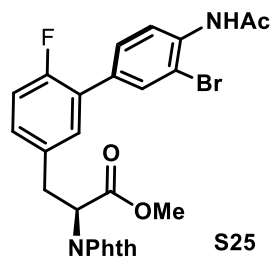
Compound S23 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



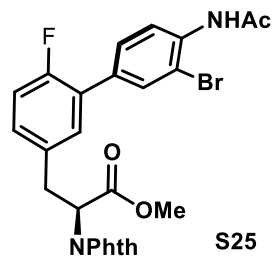
169.269  
167.451  
139.365  
137.448  
134.264  
131.536  
130.429  
129.194  
128.209  
127.363  
126.907  
125.499  
123.557  
121.876  
53.167  
52.987  
34.648



Compound S25 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



Compound S25 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

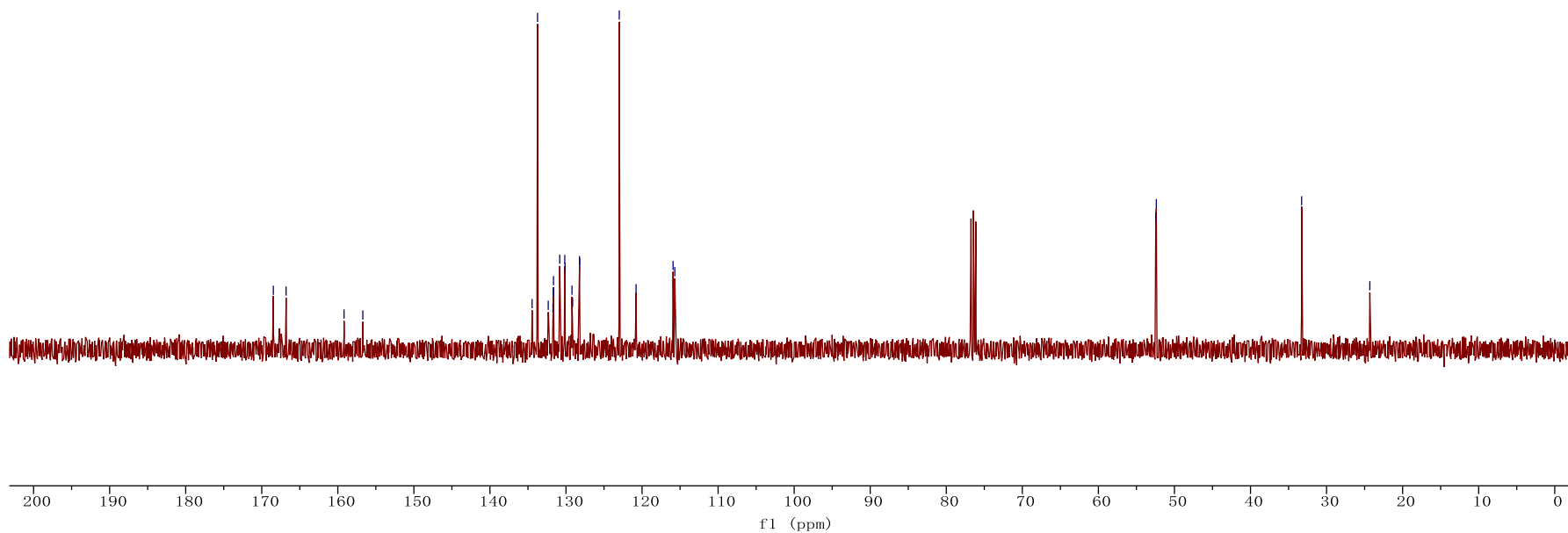


168.477  
166.799  
159.177  
156.712  
134.456  
133.741  
132.334  
131.711  
131.645  
131.617  
130.821  
130.156  
130.122  
129.212  
129.128  
128.223  
128.193  
122.997  
120.785  
115.922  
115.694

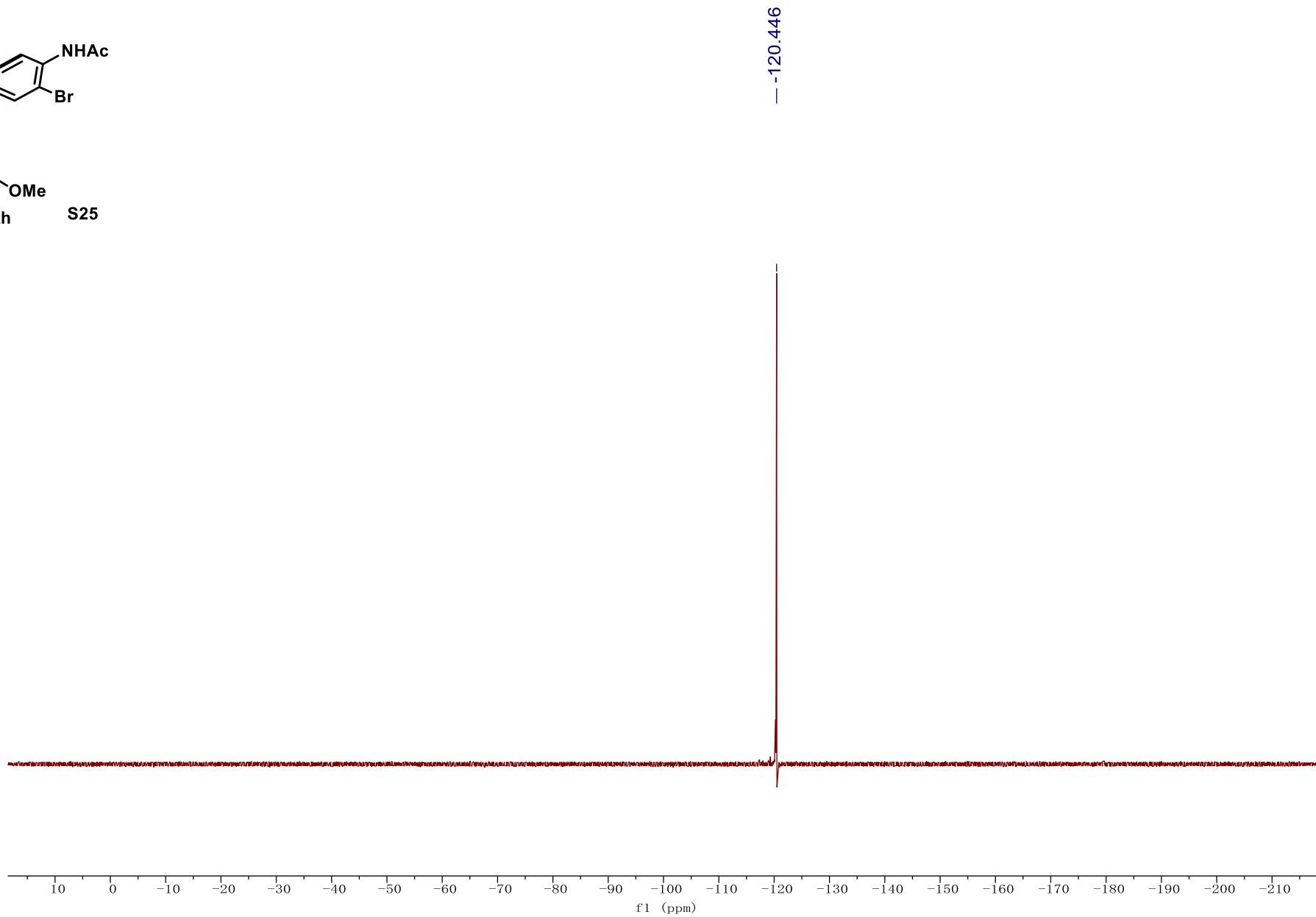
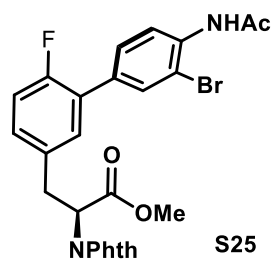
52.457  
52.386

33.275

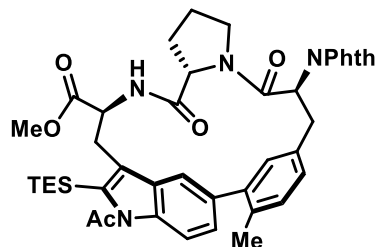
24.310



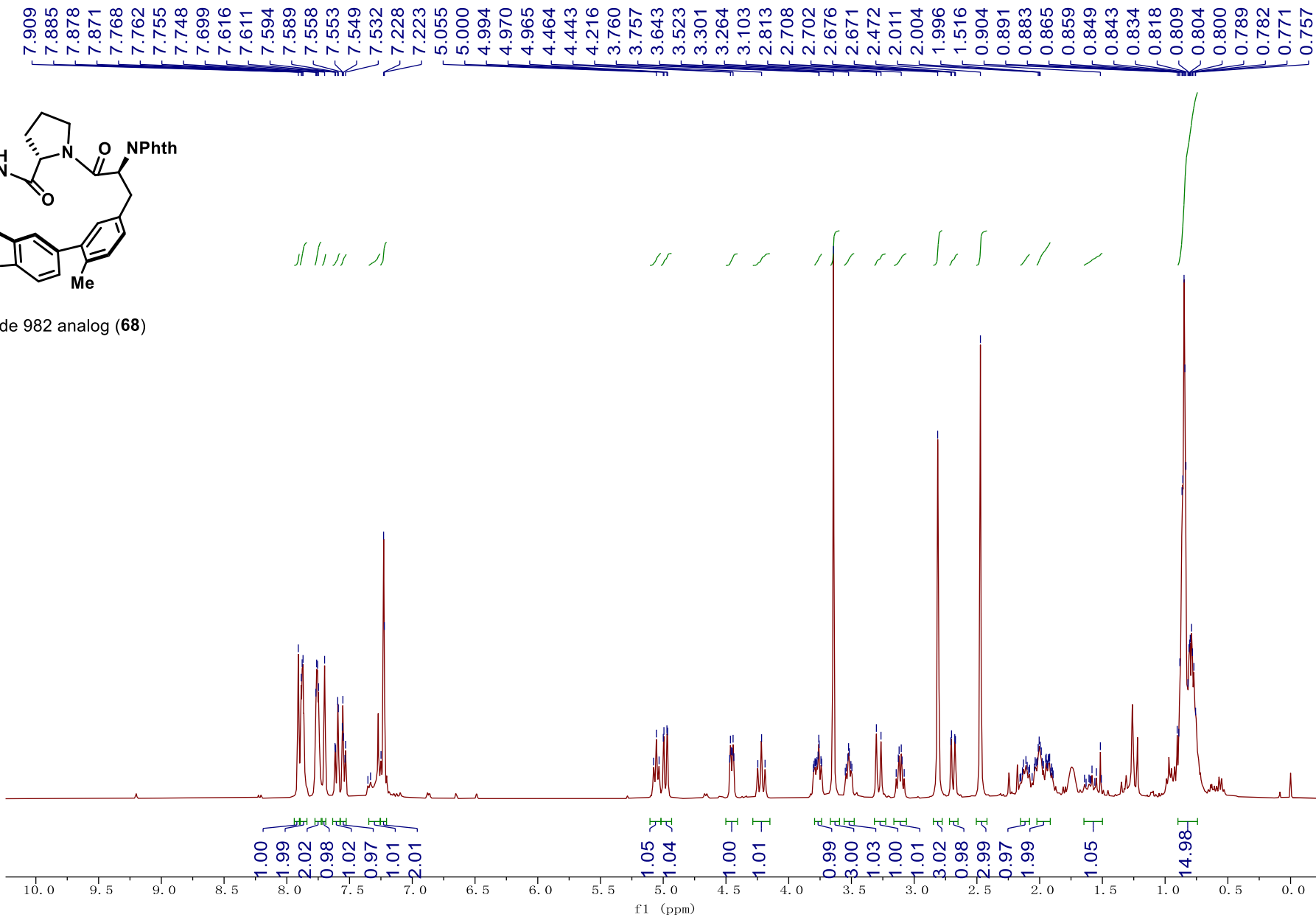
Compound S25  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )



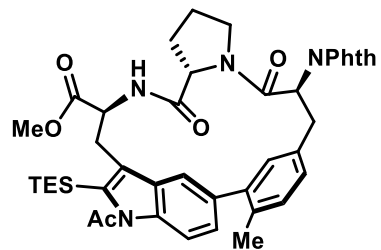
Compound 68 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



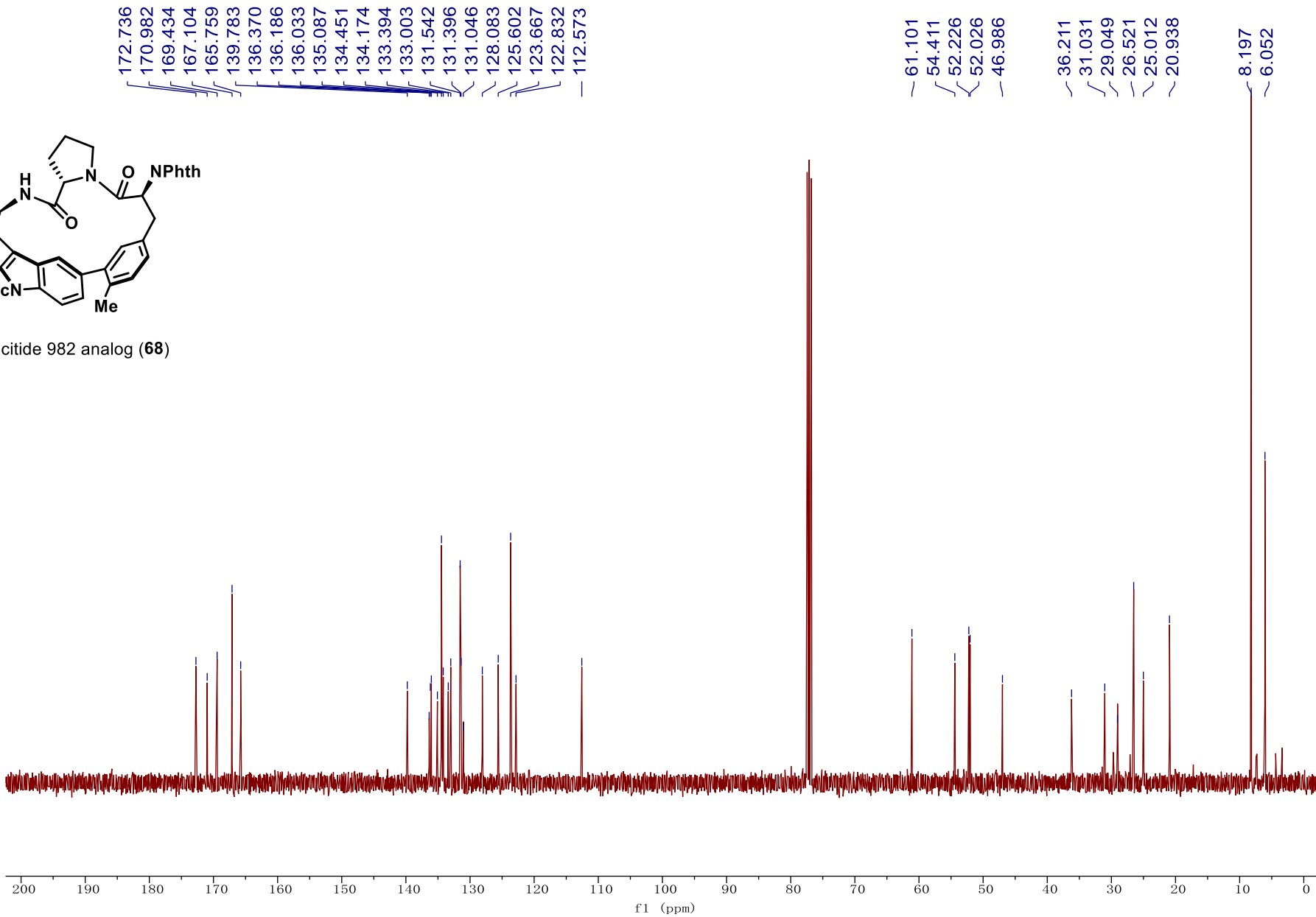
micitide 982 analog (**68**)



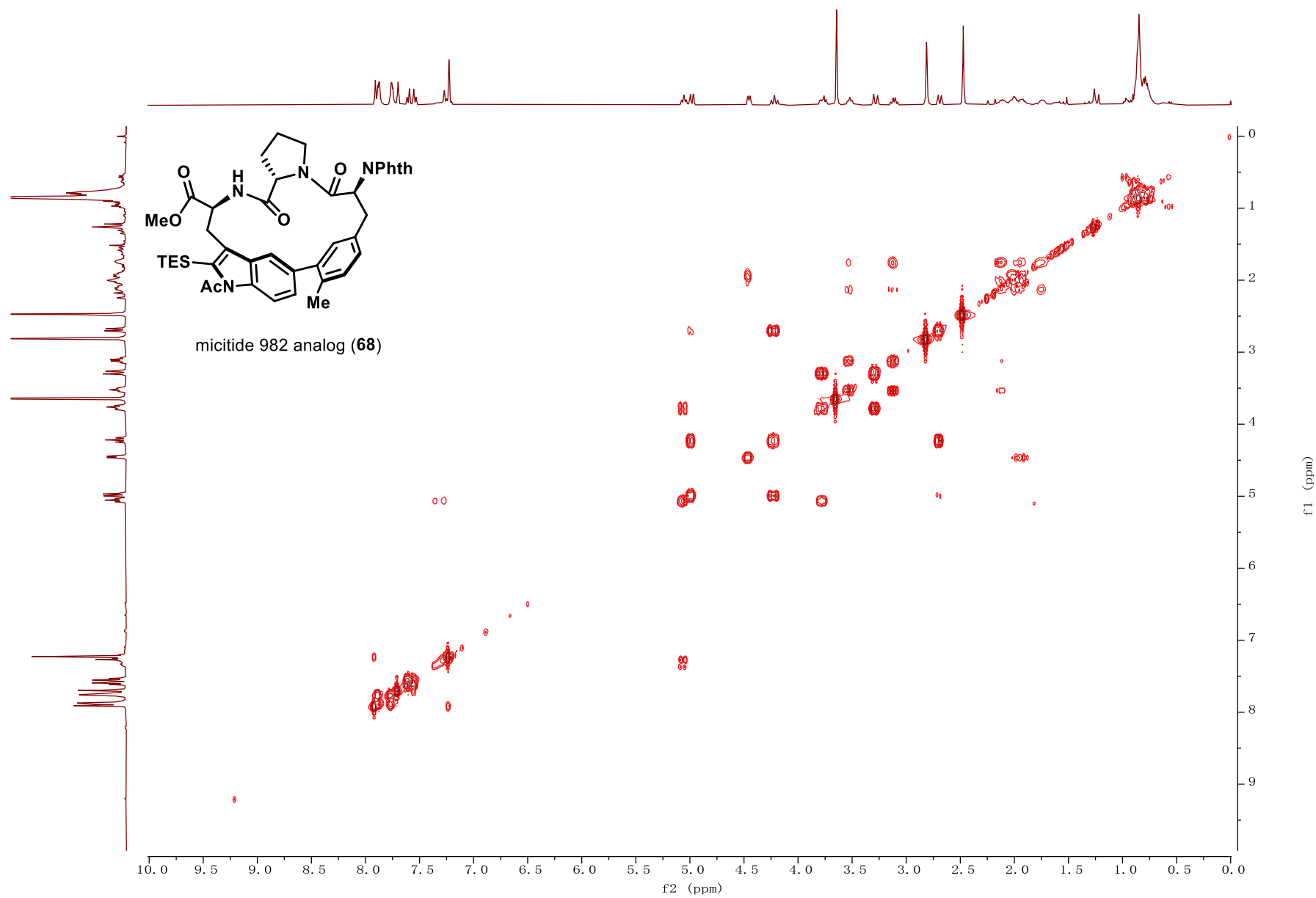
Compound 68 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



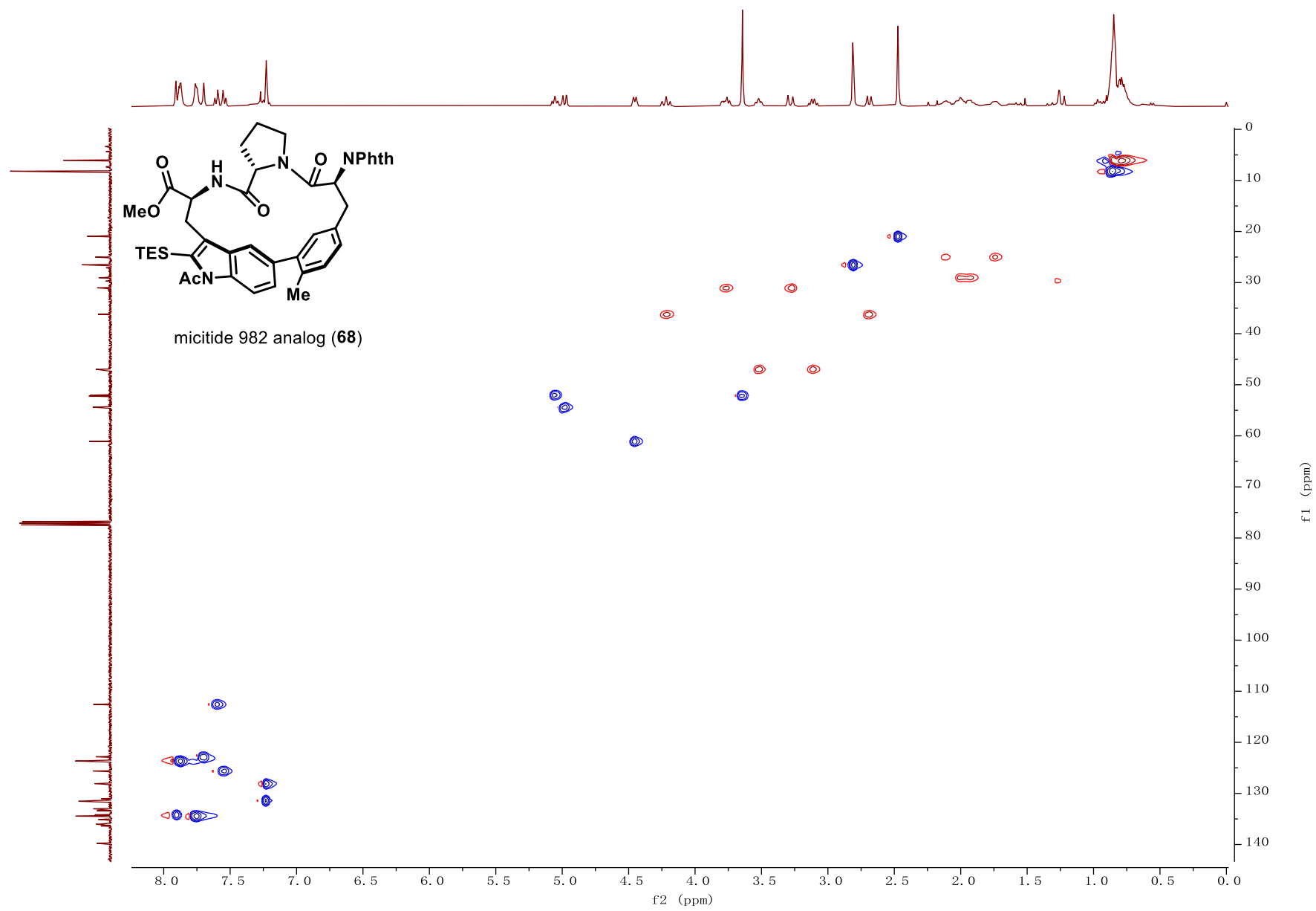
micitide 982 analog (**68**)



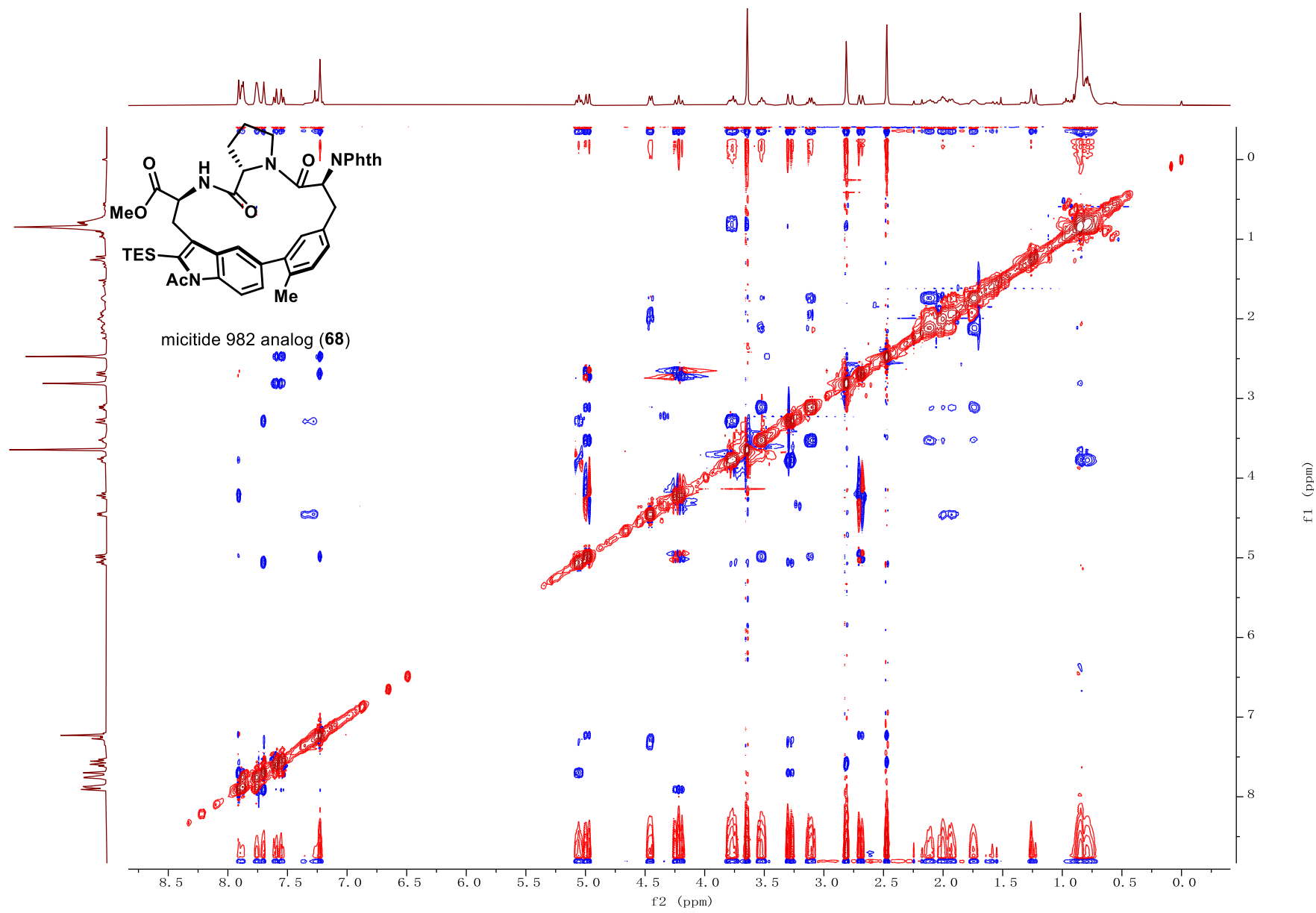
Compound 68  $^1\text{H}$ - $^1\text{H}$  COSY NMR (400 MHz,  $\text{CDCl}_3$ )



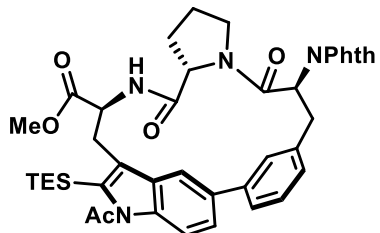
Compound 68  $^1\text{H}$ - $^{13}\text{C}$  HSQC NMR (400 MHz,  $\text{CDCl}_3$ )



Compound 68  $^1\text{H}$ - $^1\text{H}$  ROESY NMR (400 MHz,  $\text{CDCl}_3$ )



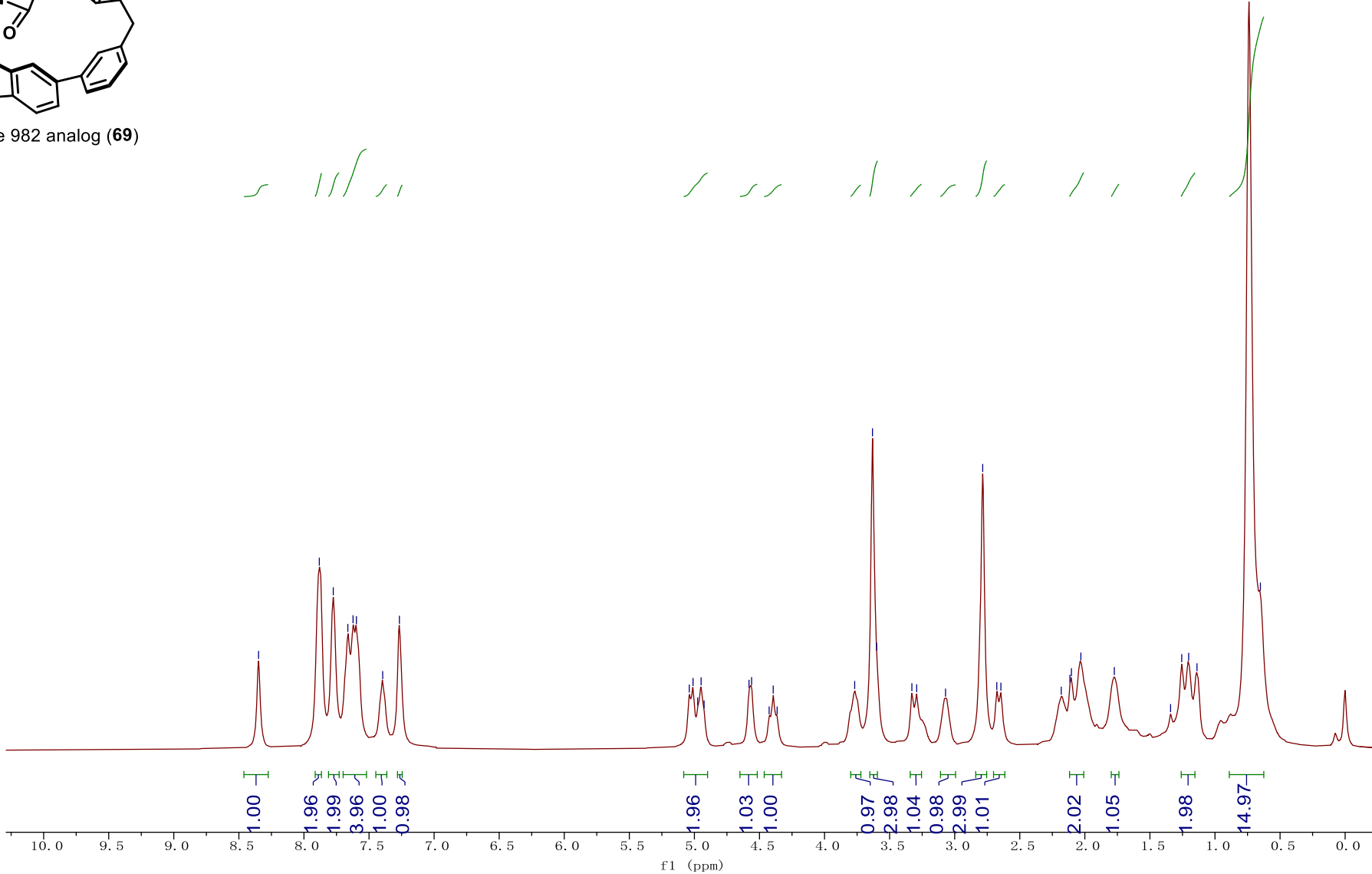
Compound 69 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



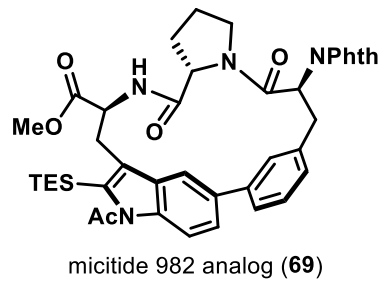
micitide 982 analog (69)

8.349  
7.882  
7.775  
7.663  
7.623  
7.597  
7.395  
7.267

5.039  
5.011  
4.975  
4.949  
4.926  
4.580  
4.560  
4.426  
4.394  
4.364  
3.768  
3.632  
3.600  
3.329  
3.292  
3.070  
2.785  
2.676  
2.645  
2.181  
2.115  
2.103  
2.031  
1.773  
1.341  
1.256  
1.202  
1.138  
0.739  
0.651



Compound 69 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



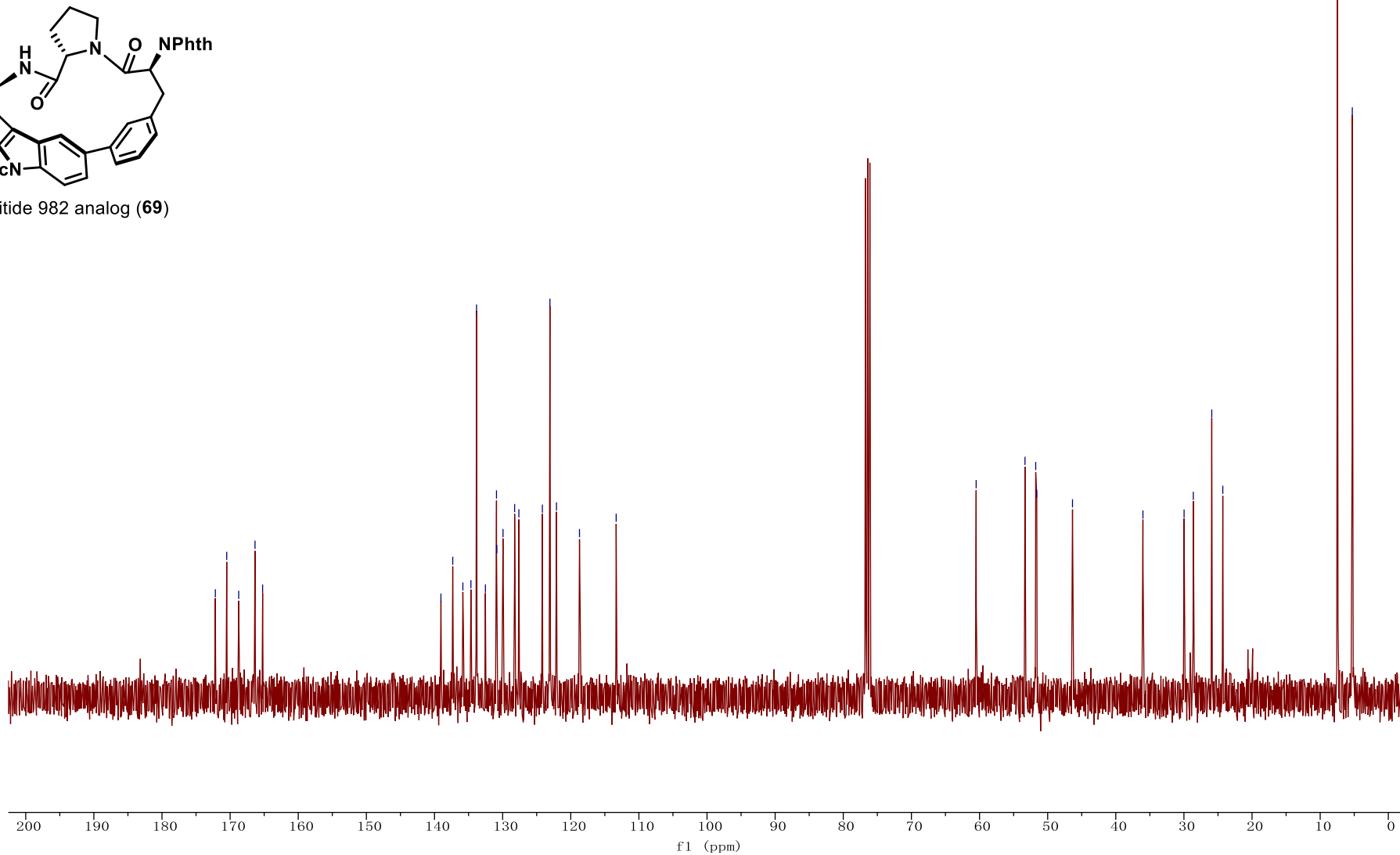
172.167  
170.496  
168.739  
166.344  
165.228

139.056  
137.322  
135.838  
134.656  
133.830  
132.531  
130.901  
130.854  
129.945  
128.240  
127.616  
124.167  
123.057  
122.097  
118.717  
113.336

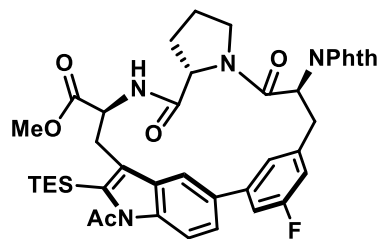
60.496  
53.326  
51.754  
51.597  
46.355

36.017  
29.977  
28.621  
25.915  
24.292

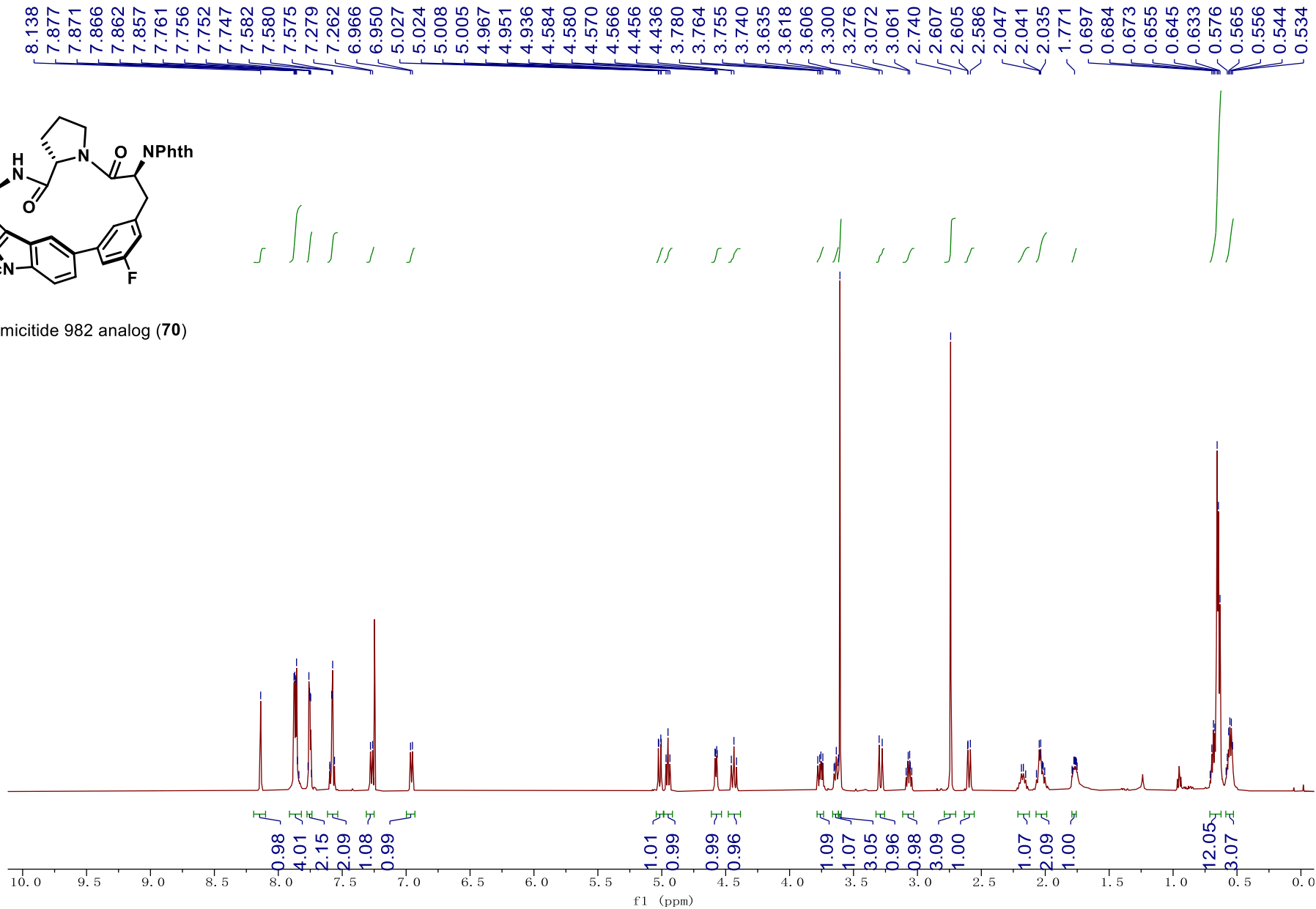
7.452  
5.284



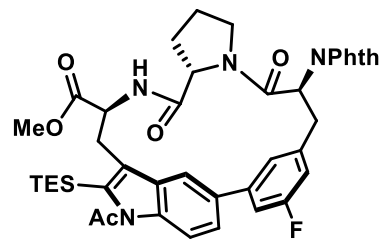
Compound 70 <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)



fluoro-micitide 982 analog (**70**)



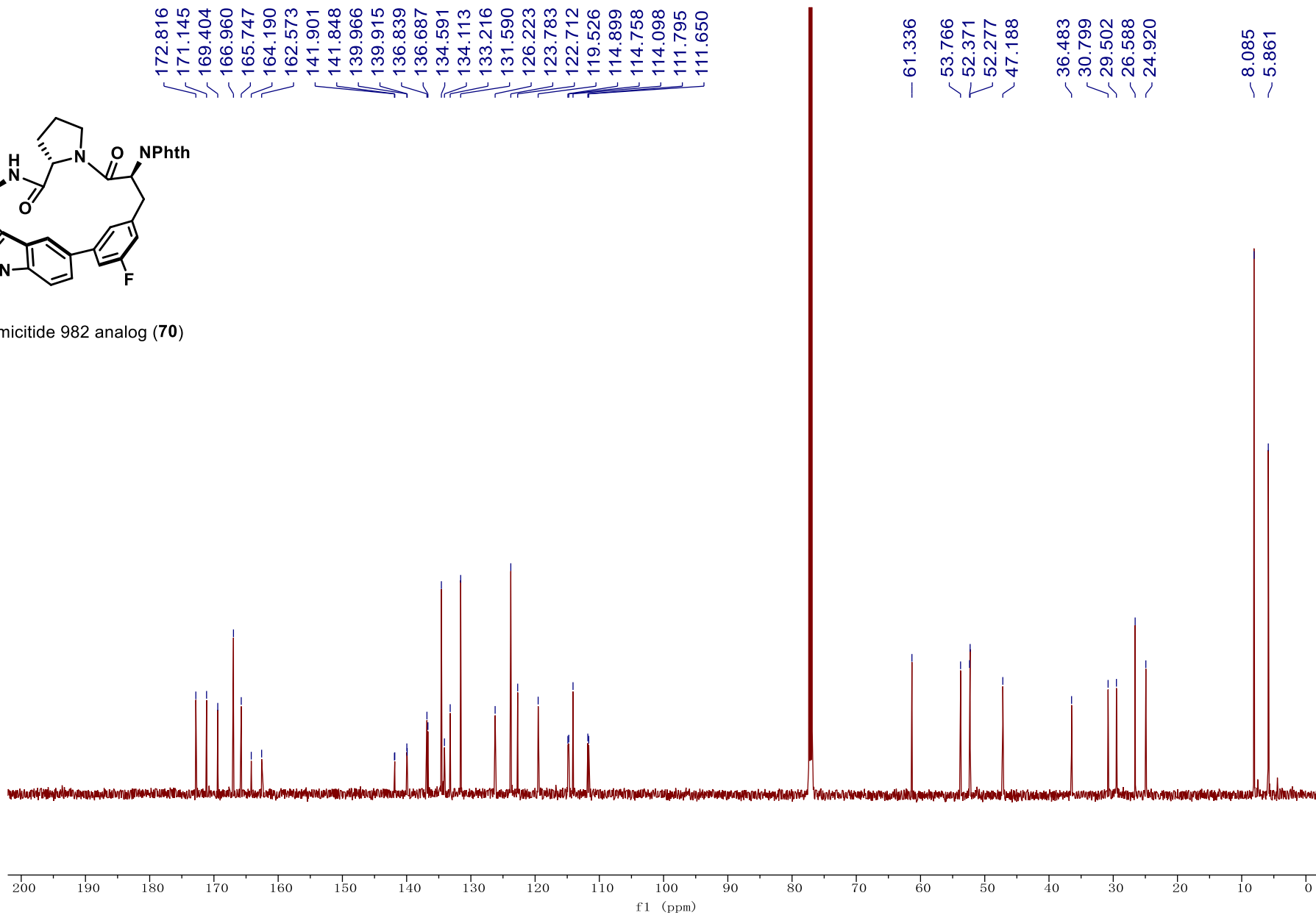
Compound 70 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



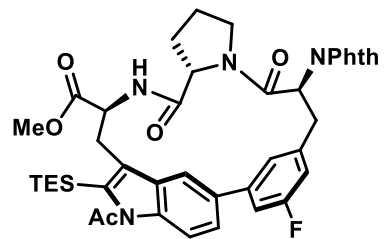
fluoro-micitide 982 analog (**70**)

172.816  
171.145  
169.404  
166.960  
165.747  
164.190  
162.573  
141.901  
141.848  
139.966  
139.915  
136.839  
136.687  
134.591  
134.113  
133.216  
131.590  
126.223  
123.783  
122.712  
119.526  
114.899  
114.758  
114.098  
111.795  
111.650

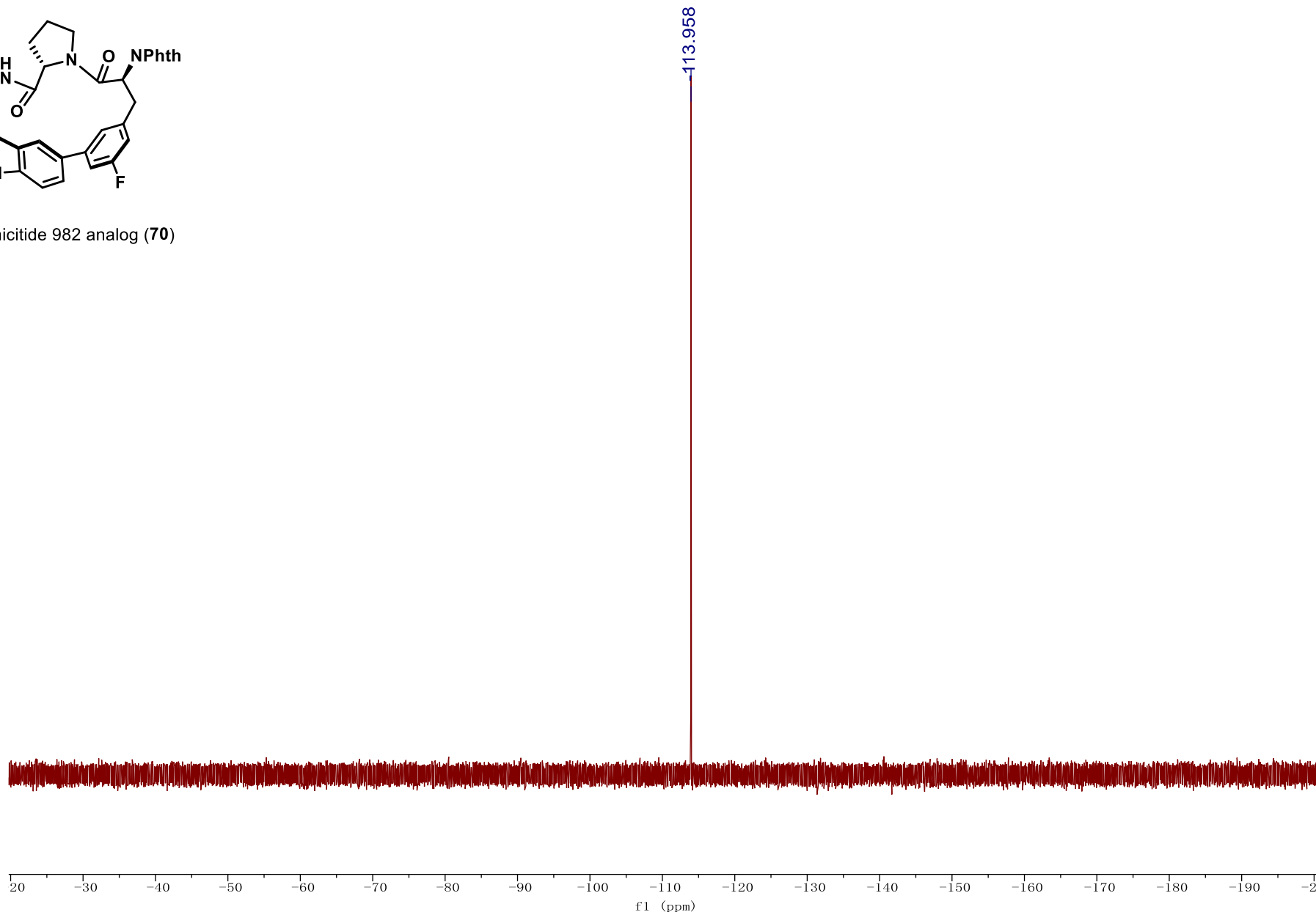
61.336  
53.766  
52.371  
52.277  
47.188  
36.483  
30.799  
29.502  
26.588  
24.920  
8.085  
5.861



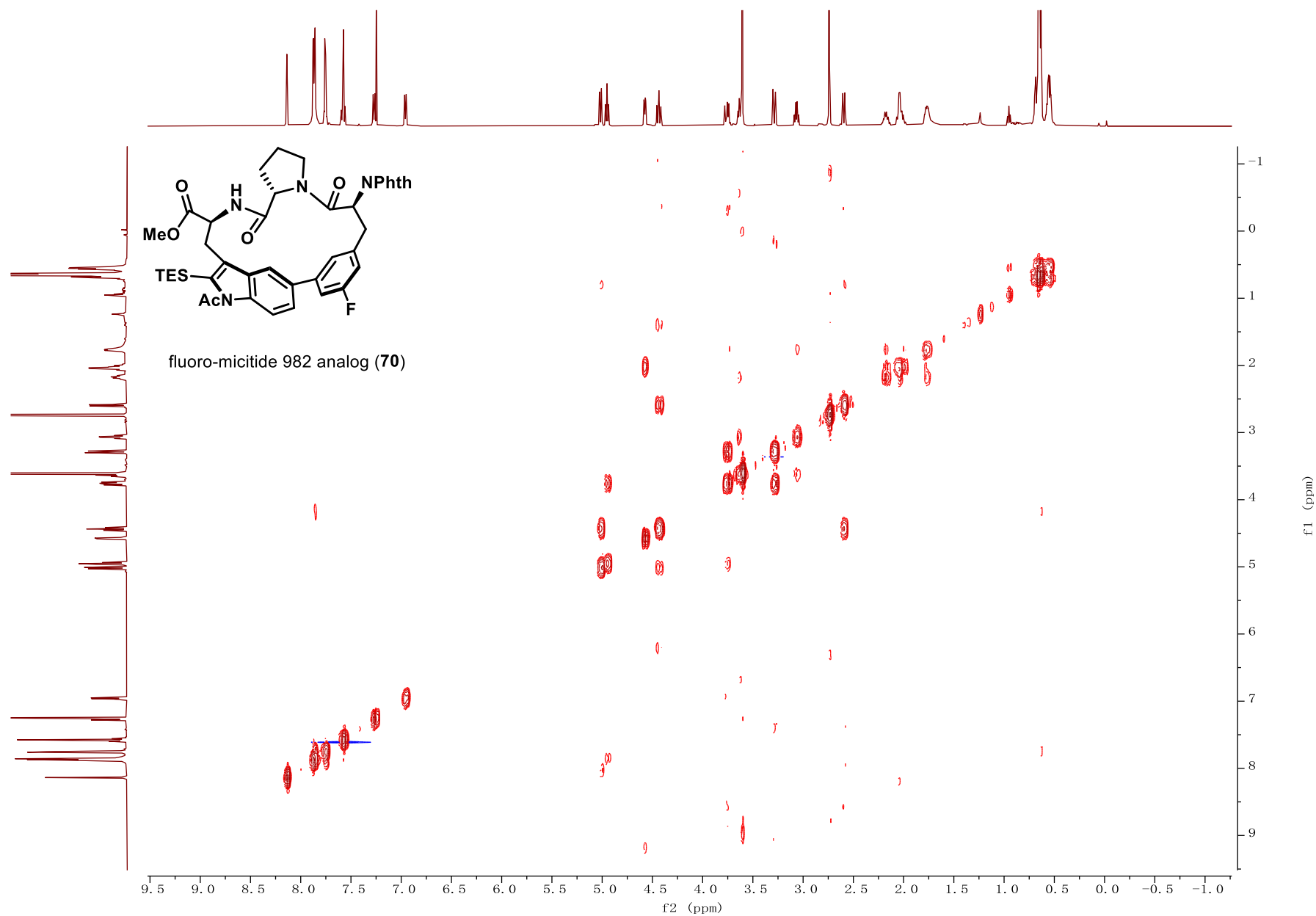
Compound 70  $^{13}\text{C}$  NMR (376 MHz,  $\text{CDCl}_3$ )



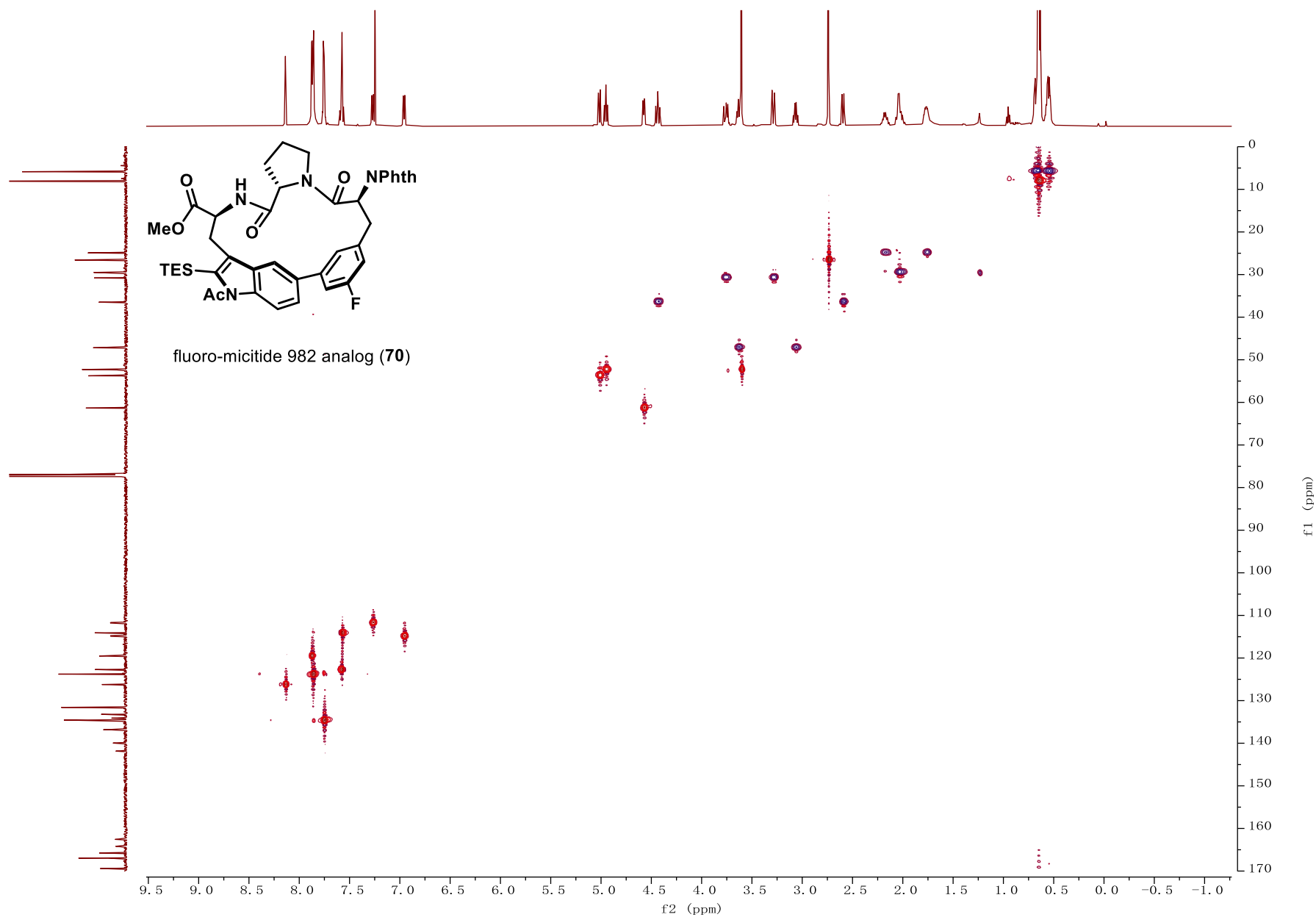
fluoro-micitide 982 analog (**70**)



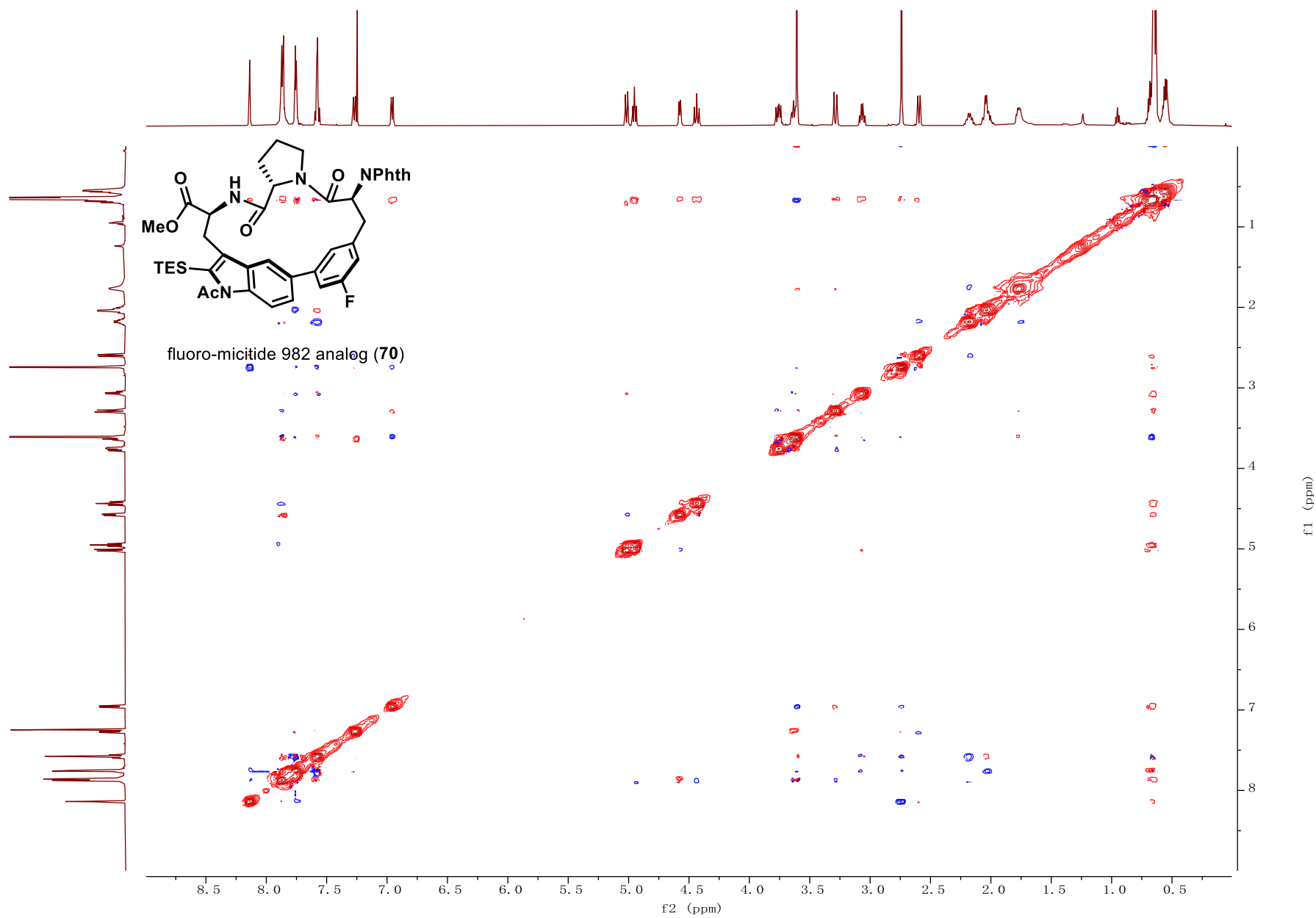
Compound 70  $^1\text{H}$ - $^1\text{H}$  COSY NMR (600 MHz,  $\text{CDCl}_3$ )



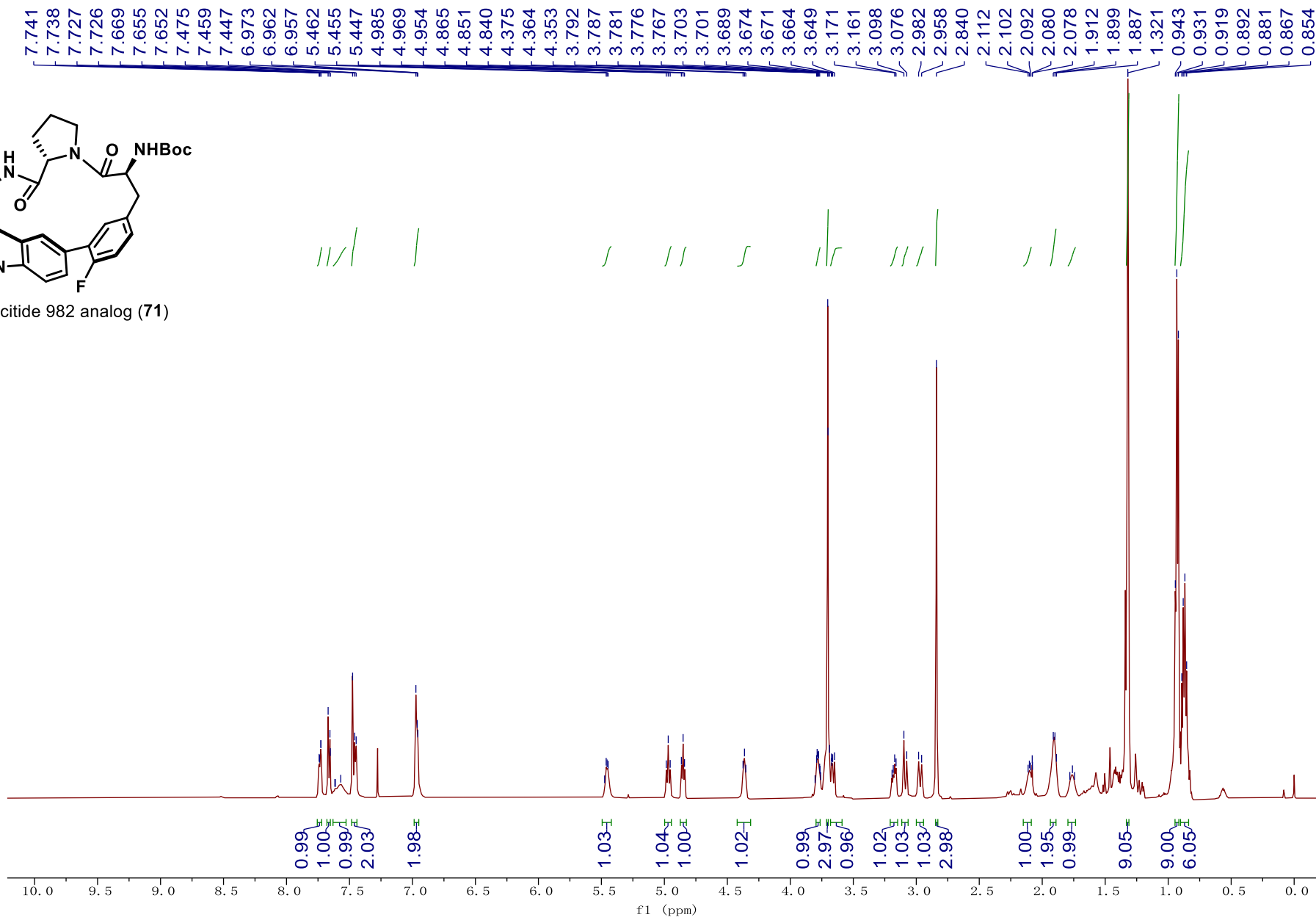
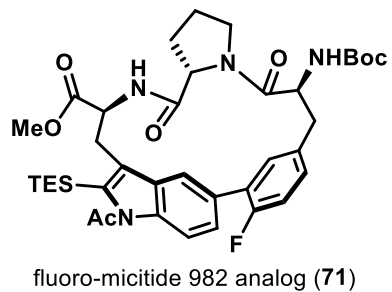
Compound 70  $^1\text{H}$ - $^{13}\text{C}$  HSQC NMR (400 MHz,  $\text{CDCl}_3$ )



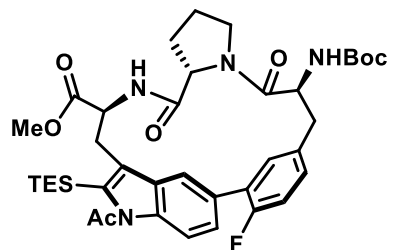
Compound 70  $^1\text{H}$ - $^1\text{H}$  NOESY NMR (400 MHz,  $\text{CDCl}_3$ )



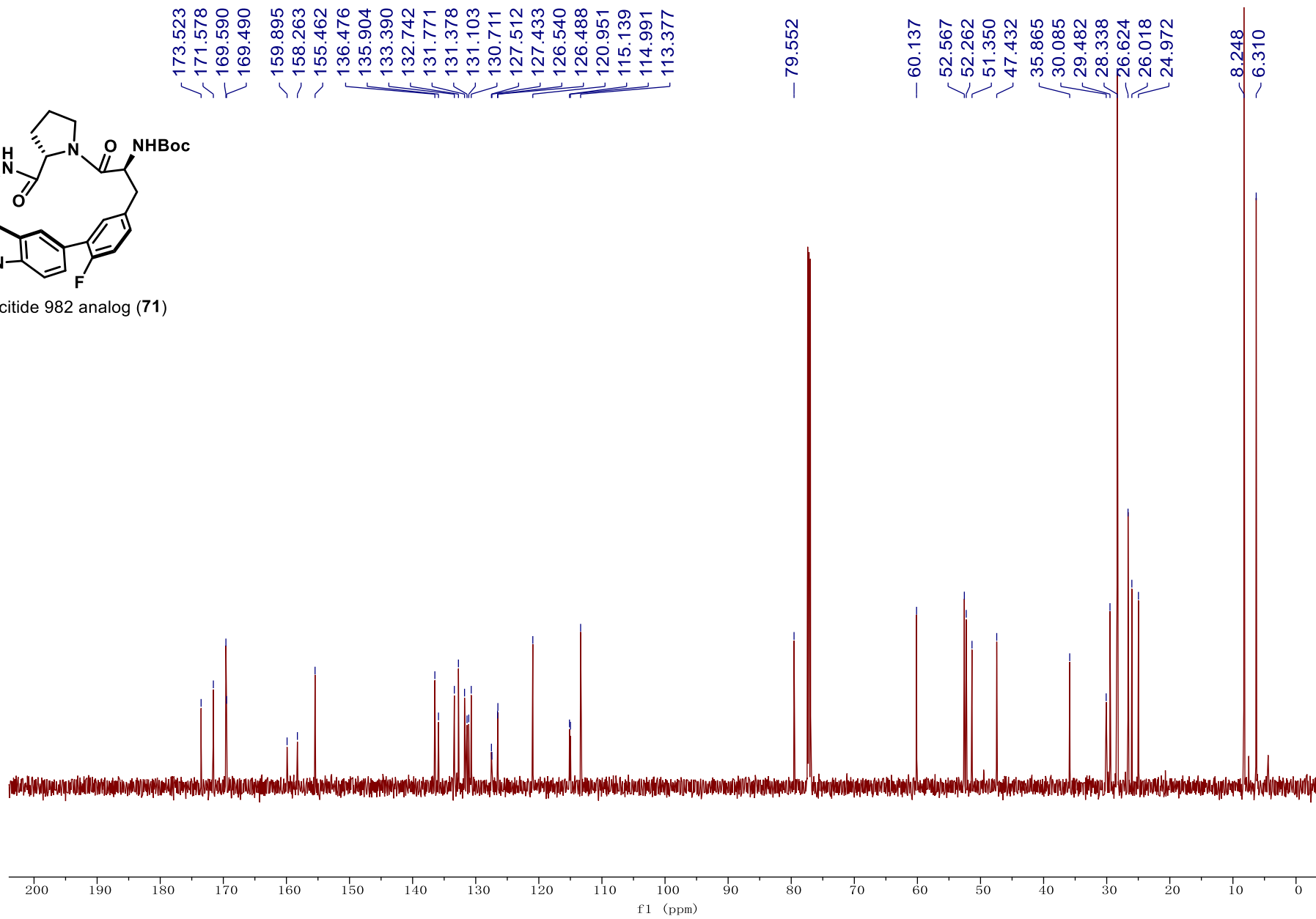
Compound 71 <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)



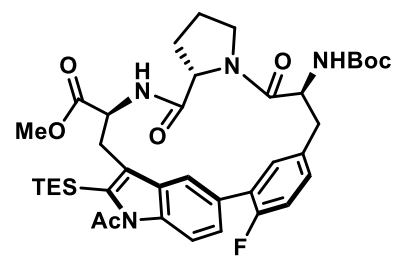
Compound 71 <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)



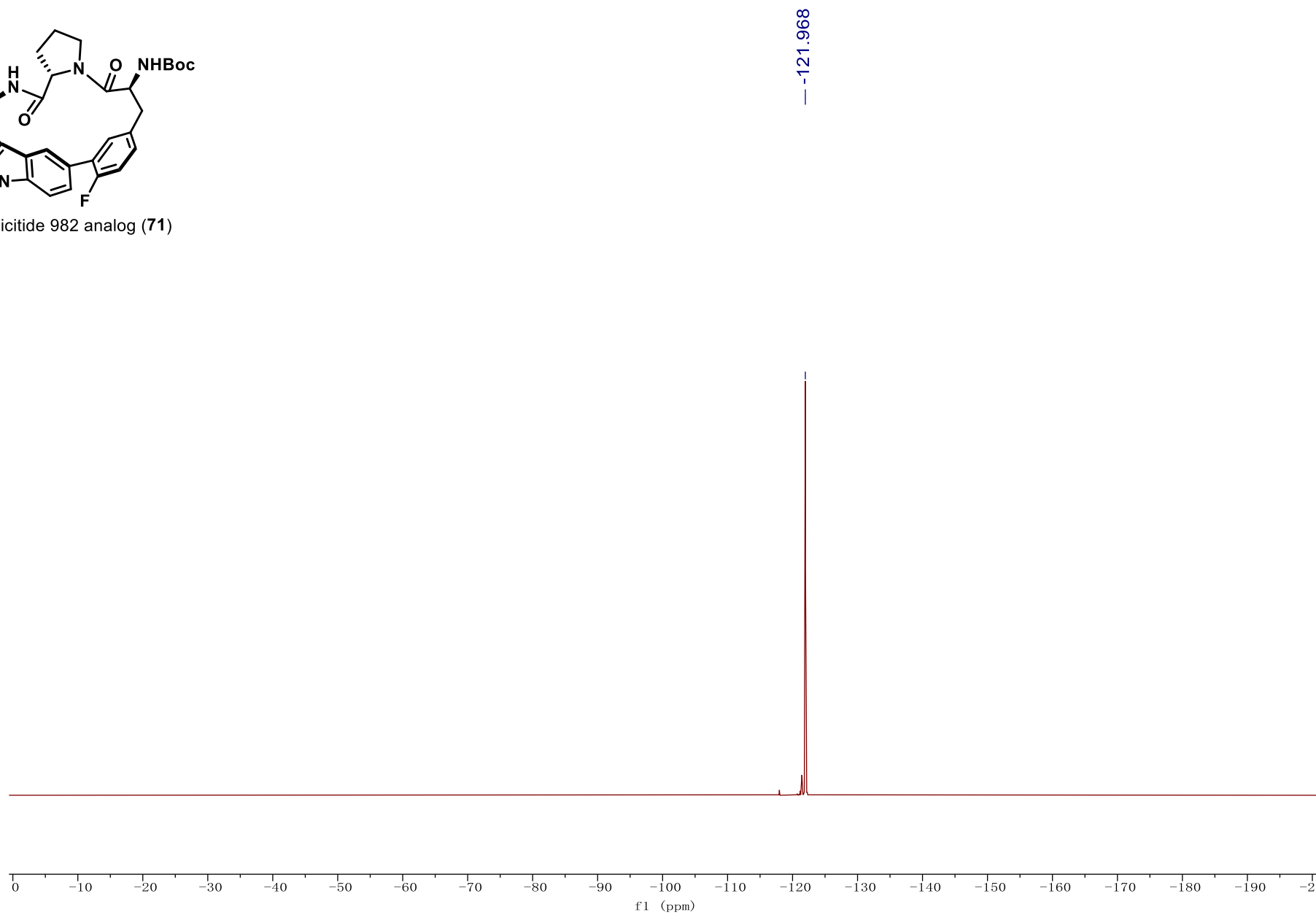
fluoro-micitide 982 analog (71)



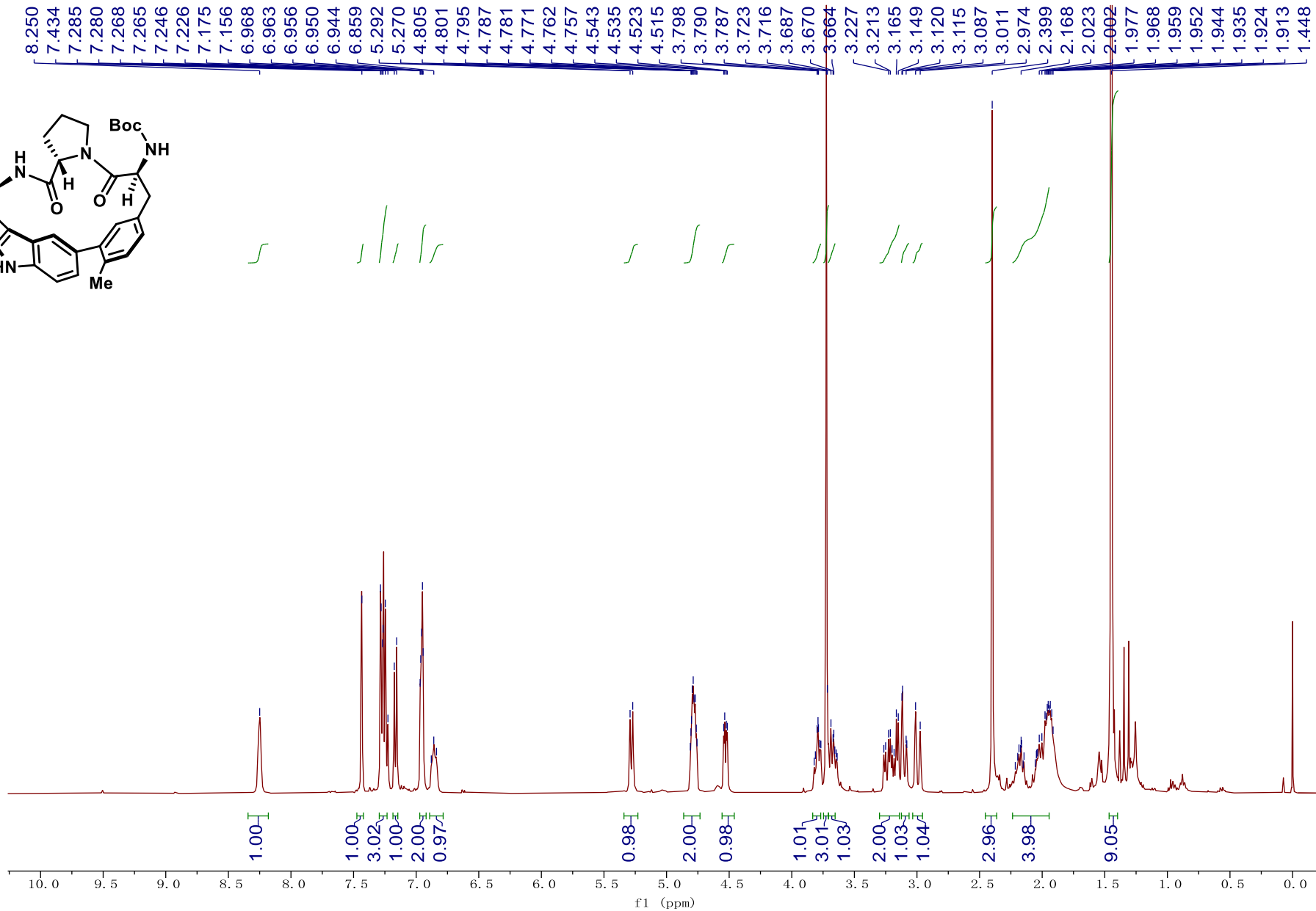
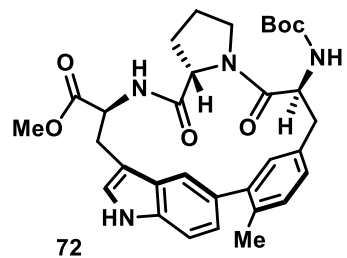
Compound 71  $^{19}\text{F}$  NMR (565 MHz,  $\text{CDCl}_3$ )



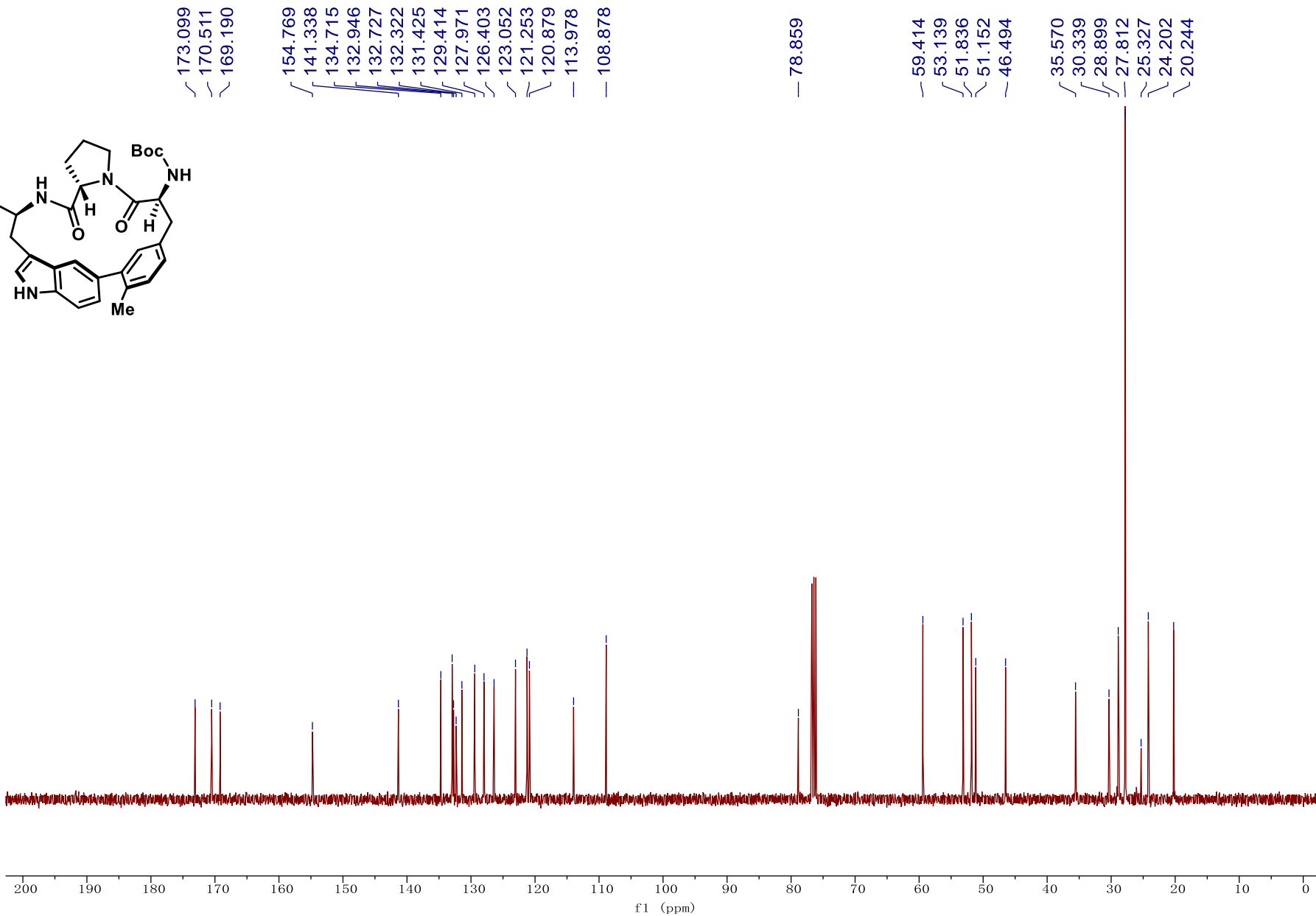
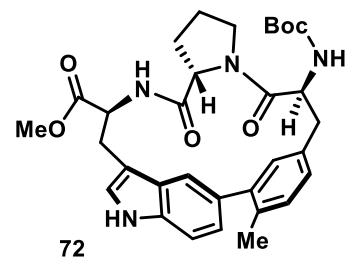
fluoro-micitide 982 analog (71)



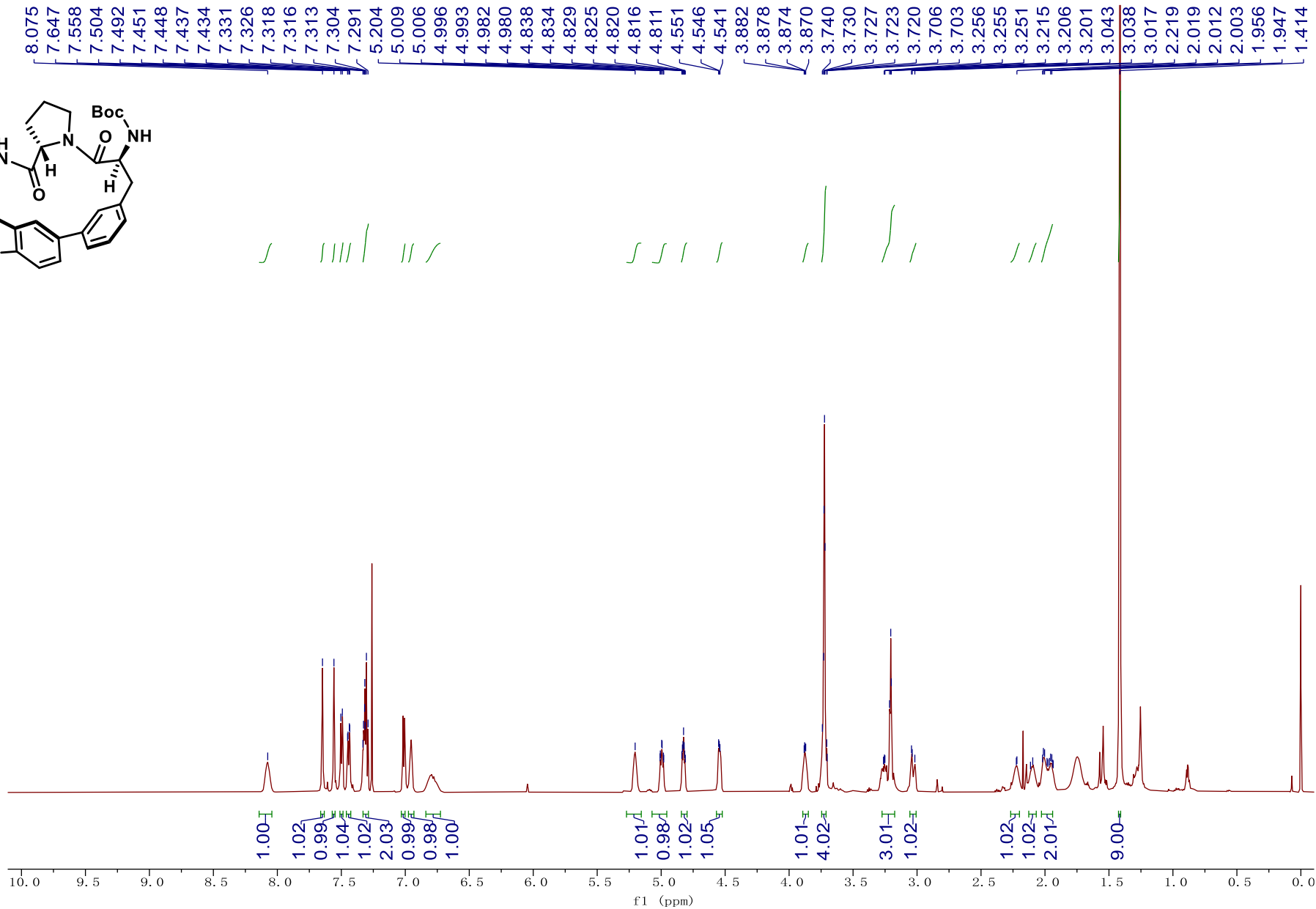
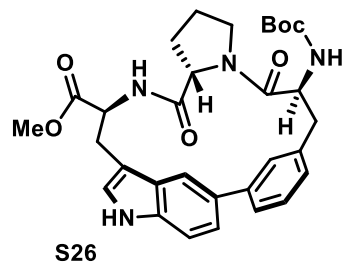
Compound 72 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



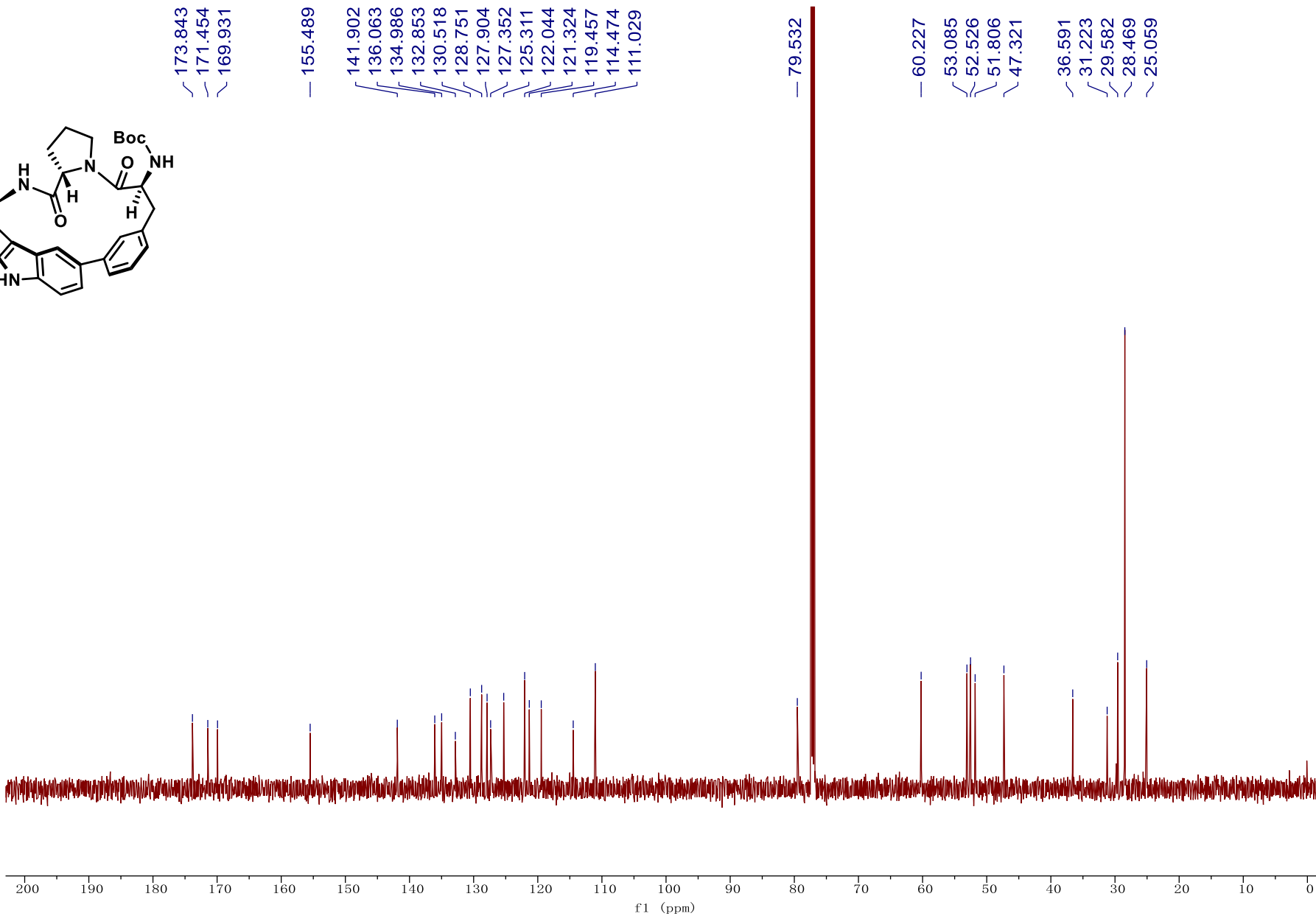
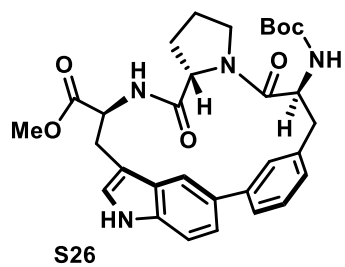
Compound 72 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



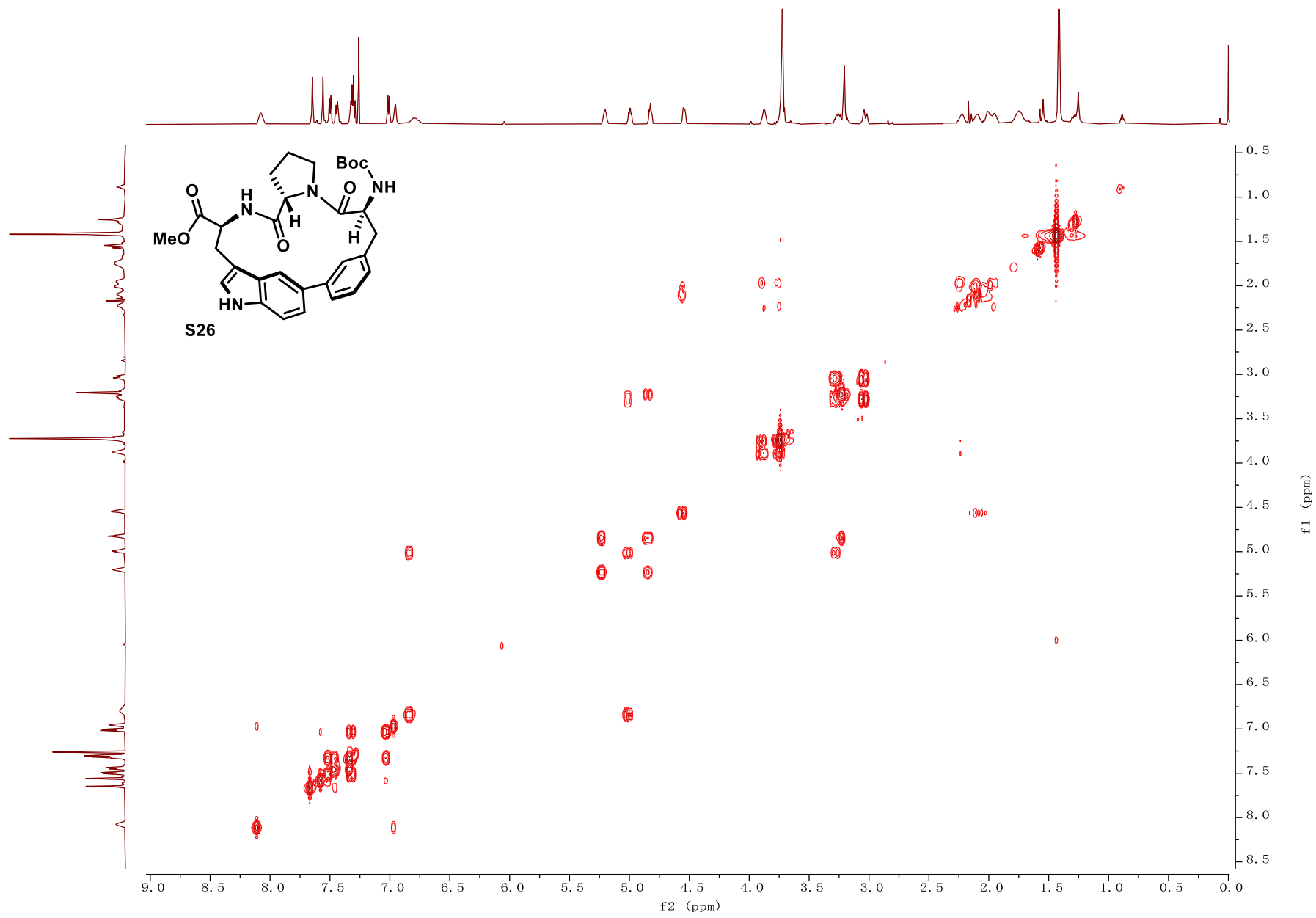
Compound S26 <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)



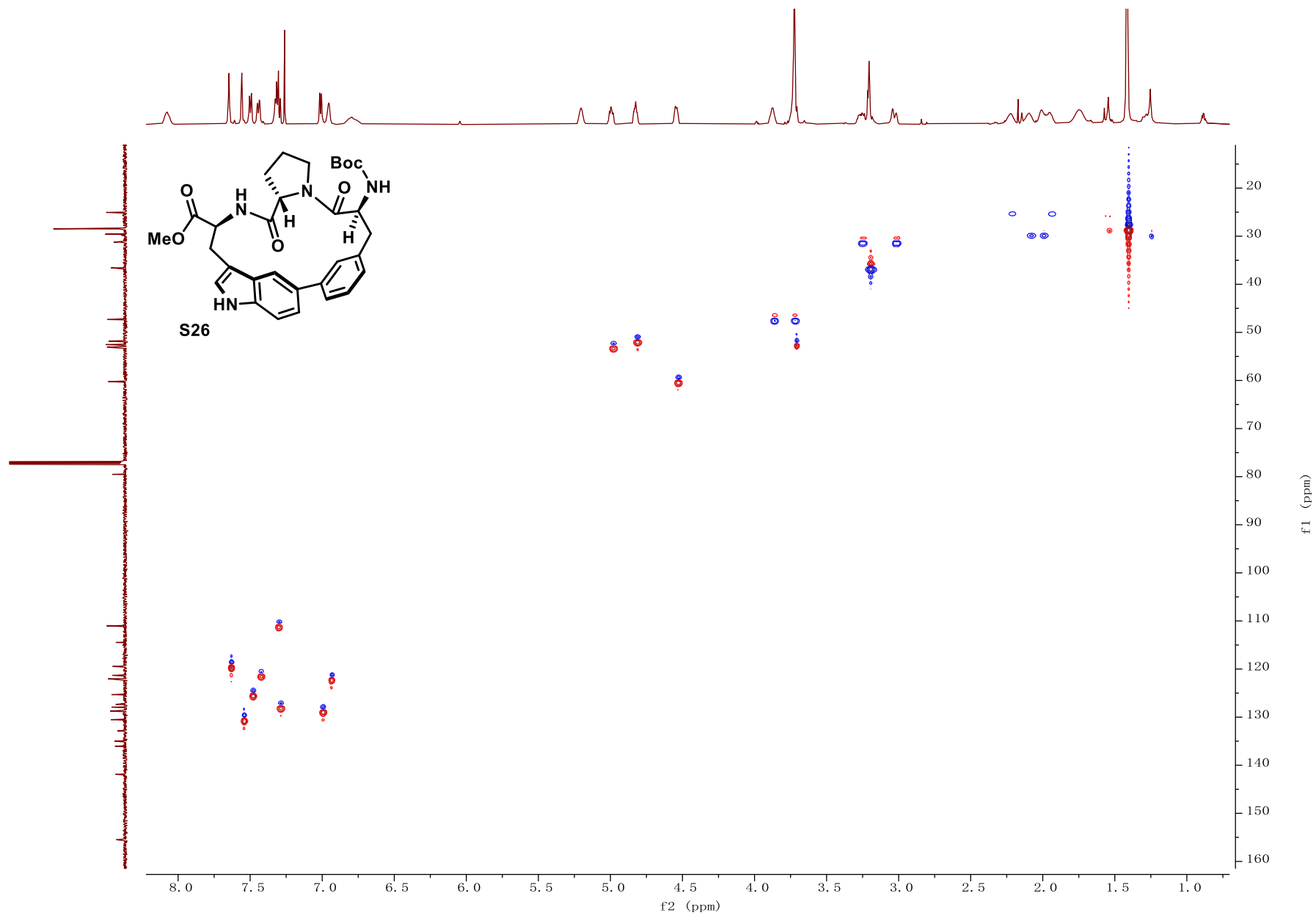
Compound S26 <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)



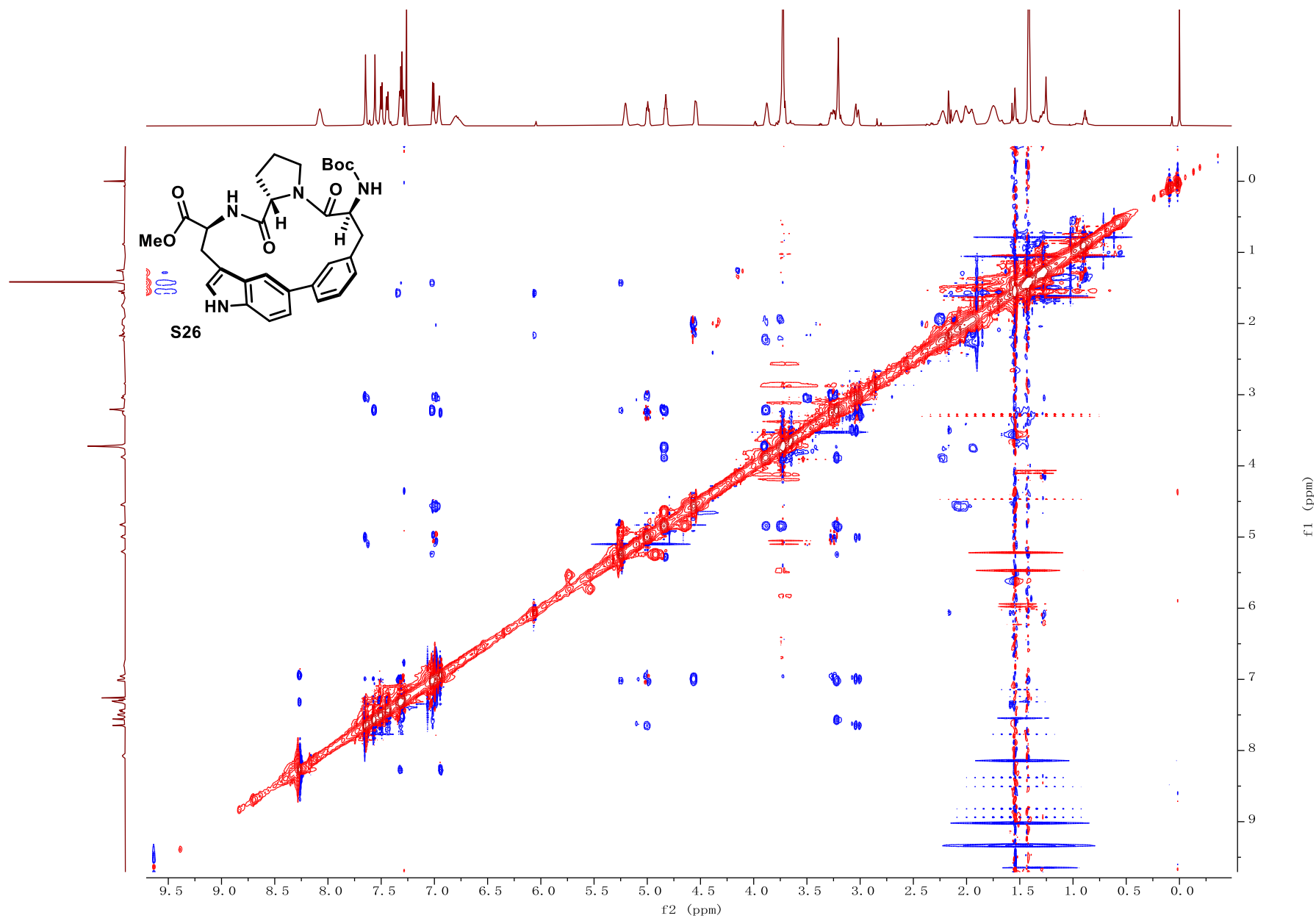
Compound S26  $^1\text{H}$ - $^1\text{H}$  COSY NMR (400 MHz,  $\text{CDCl}_3$ )



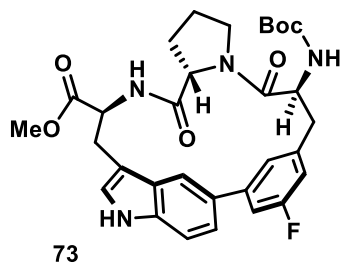
Compound S26  $^1\text{H}$ - $^{13}\text{C}$  HSQC NMR (400 MHz,  $\text{CDCl}_3$ )



Compound S26  $^1\text{H}$ - $^1\text{H}$  NOESY NMR (400 MHz,  $\text{CDCl}_3$ )

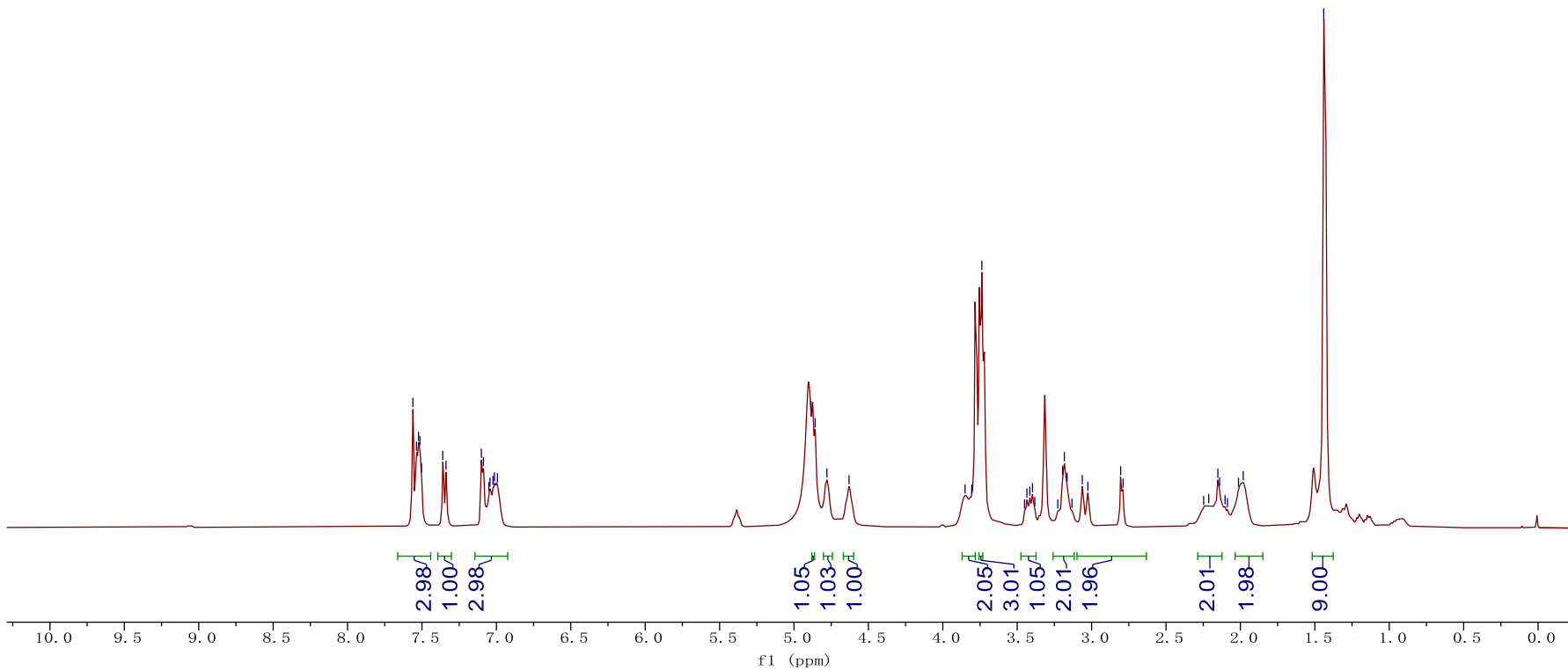
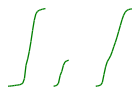


Compound 73 <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)

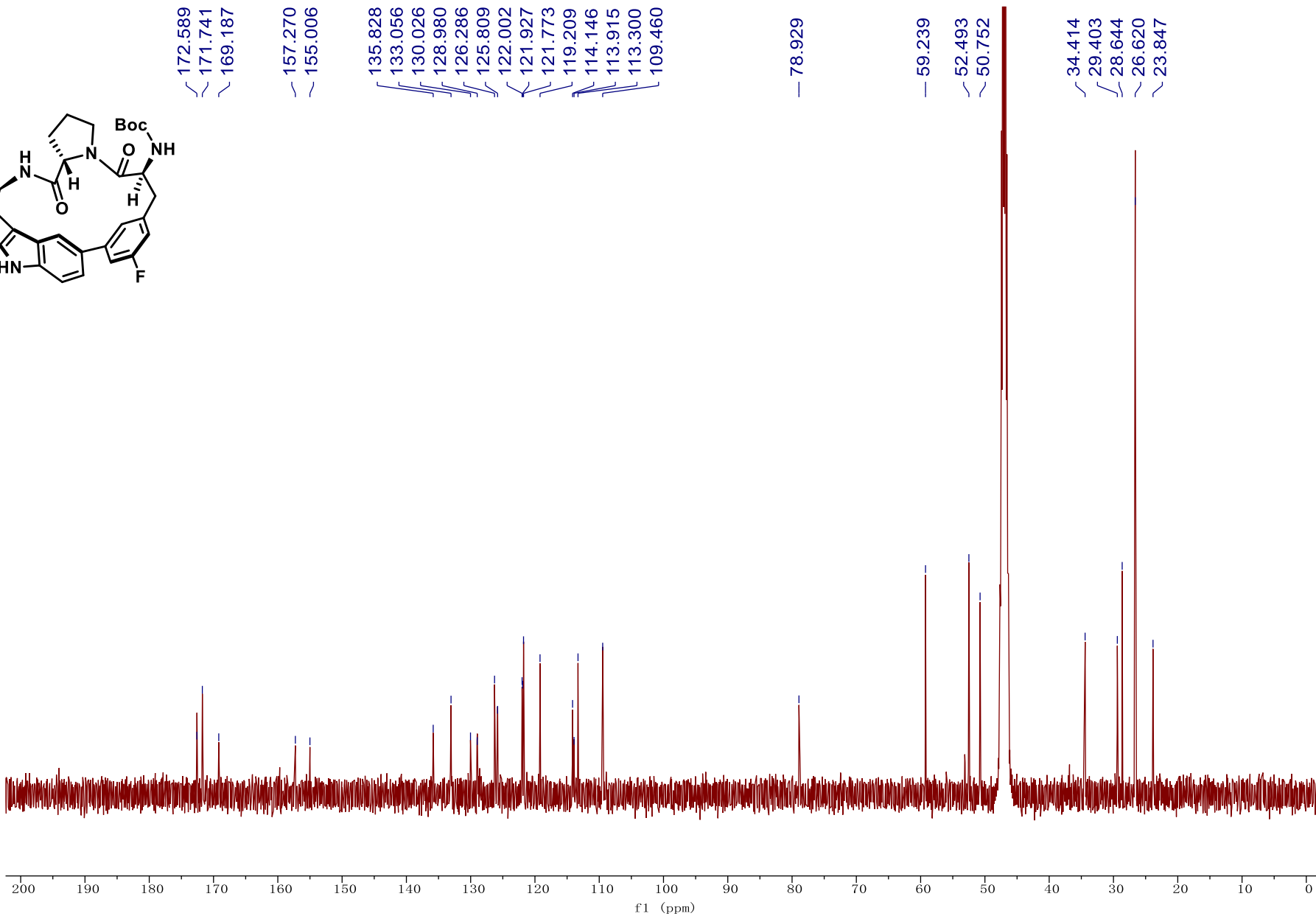
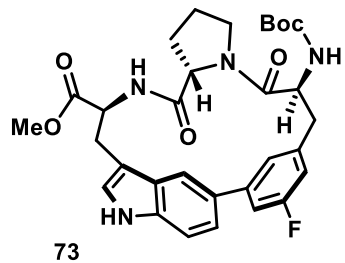


7.561  
7.537  
7.523  
7.514  
7.503  
7.360  
7.339  
7.101  
7.087  
7.051  
7.043  
7.023  
7.013  
6.993

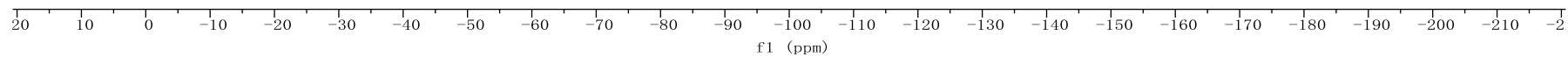
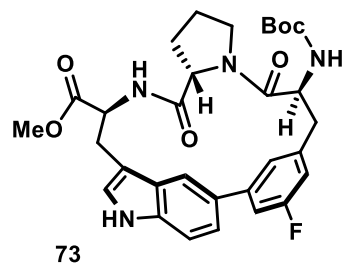
4.886  
4.858  
4.779  
4.630  
3.851  
3.806  
3.738  
3.451  
3.434  
3.415  
3.397  
3.382  
3.227  
3.195  
3.183  
3.165  
3.132  
3.063  
3.025  
2.805  
2.789  
2.247  
2.213  
2.152  
2.140  
2.103  
2.087  
2.013  
1.981  
1.440



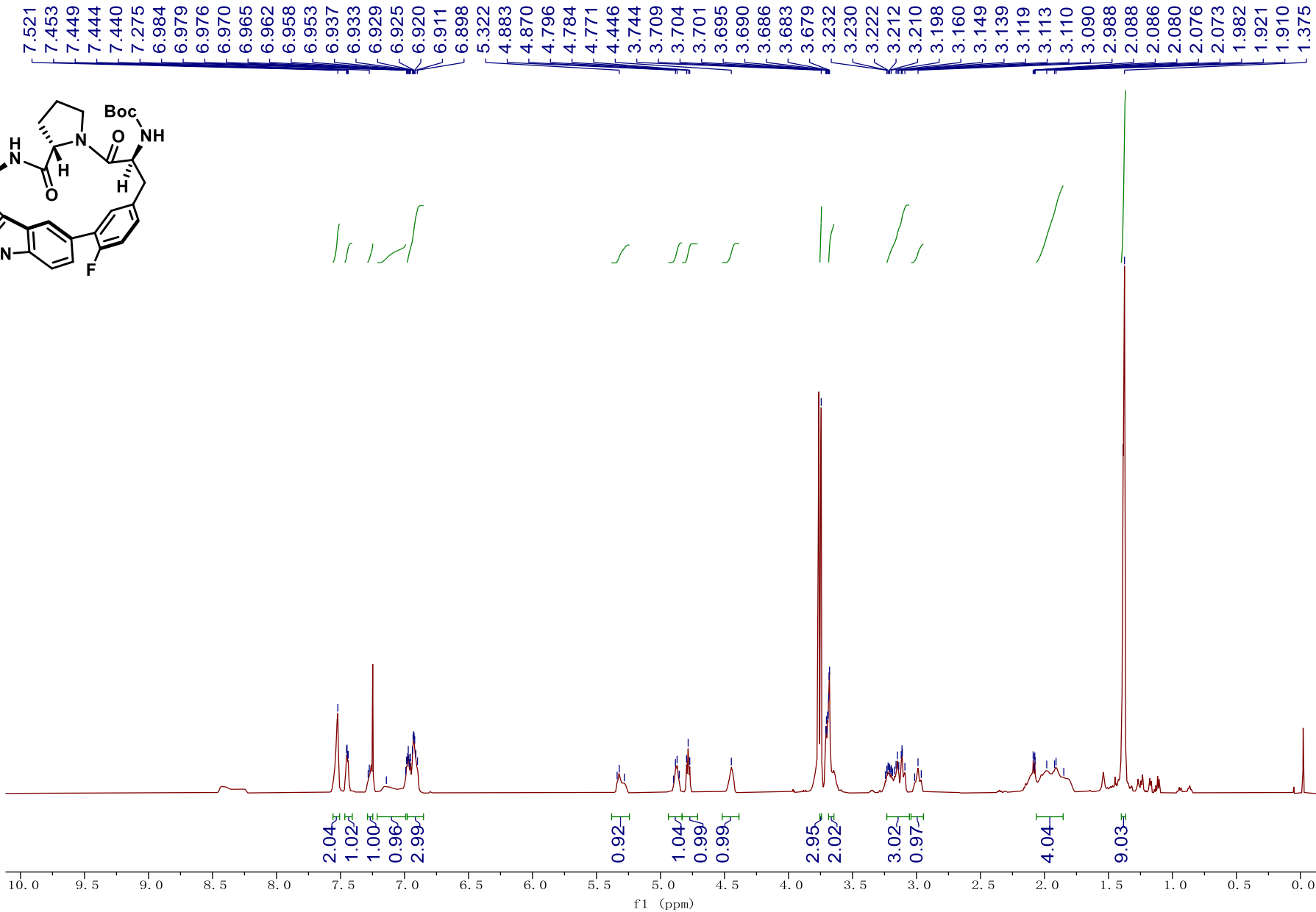
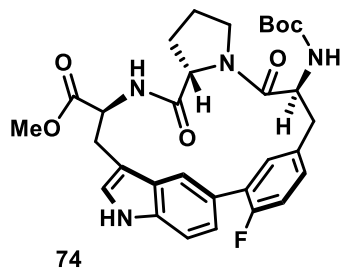
Compound 73 <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD)



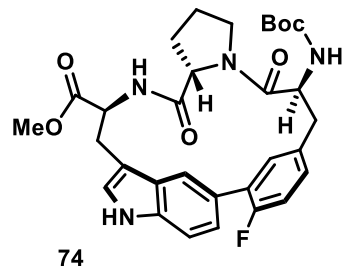
Compound 73  $^{19}\text{F}$  NMR (377 MHz,  $\text{CD}_3\text{OD}$ )



Compound 74 <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)

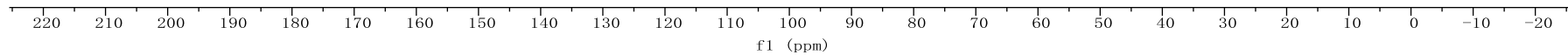


Compound 74 <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)

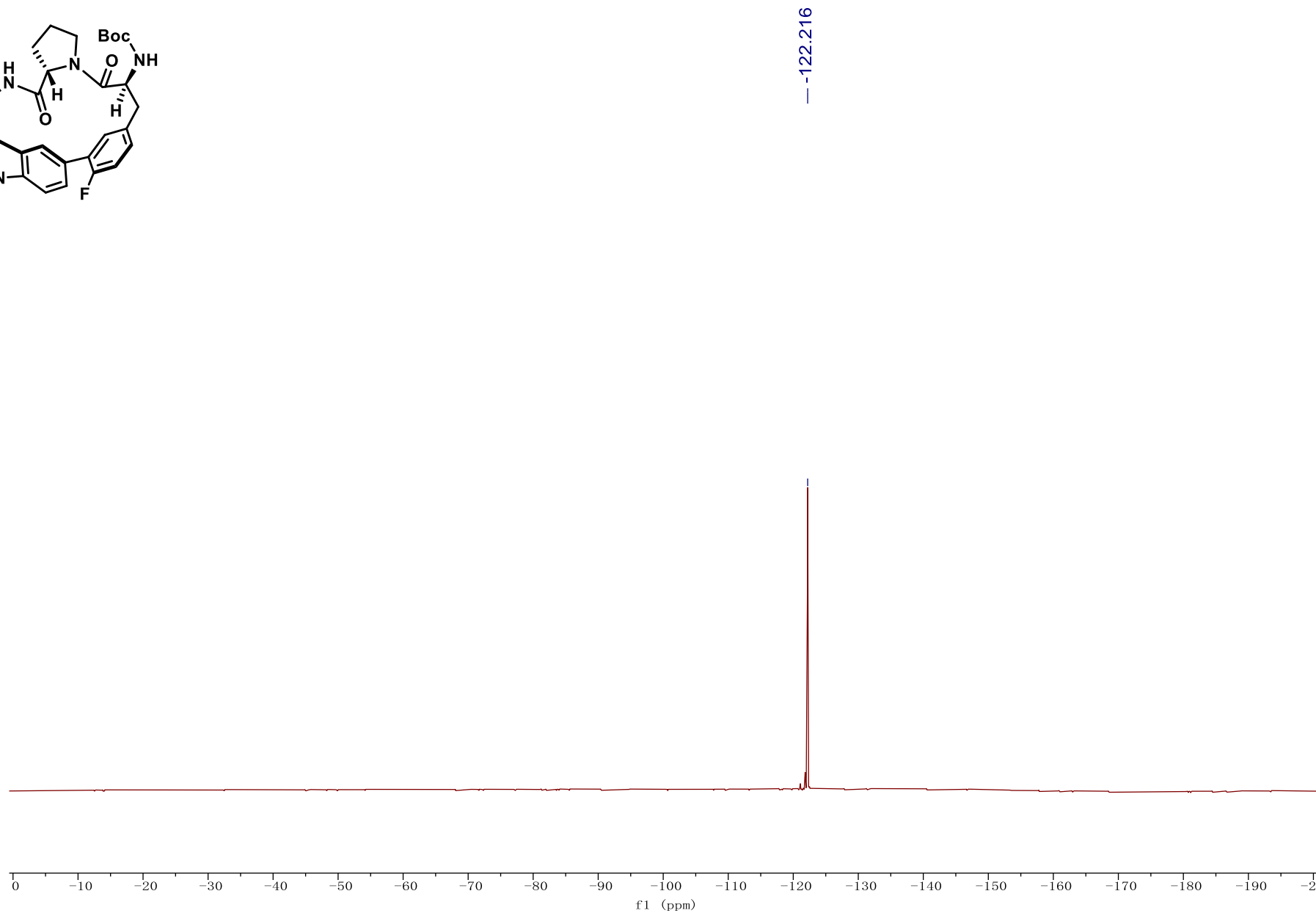
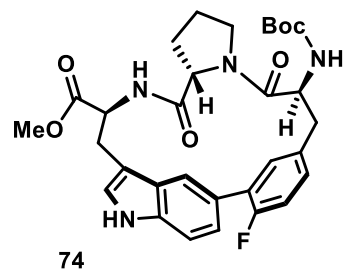


173.922  
171.438  
169.629  
159.983  
158.340  
155.500  
136.009  
133.978  
130.675  
130.198  
129.238  
127.143  
123.557  
121.993  
120.770  
114.967  
114.511  
110.375

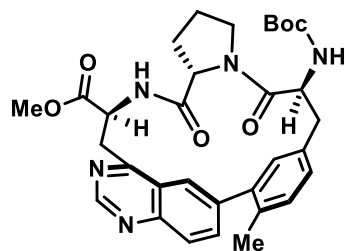
79.617  
60.185  
54.474  
54.435  
53.253  
52.503  
51.632  
47.315  
38.703  
35.821  
31.107  
29.650  
28.444  
24.913



Compound 74  $^{19}\text{F}$  NMR (575 MHz,  $\text{CDCl}_3$ )

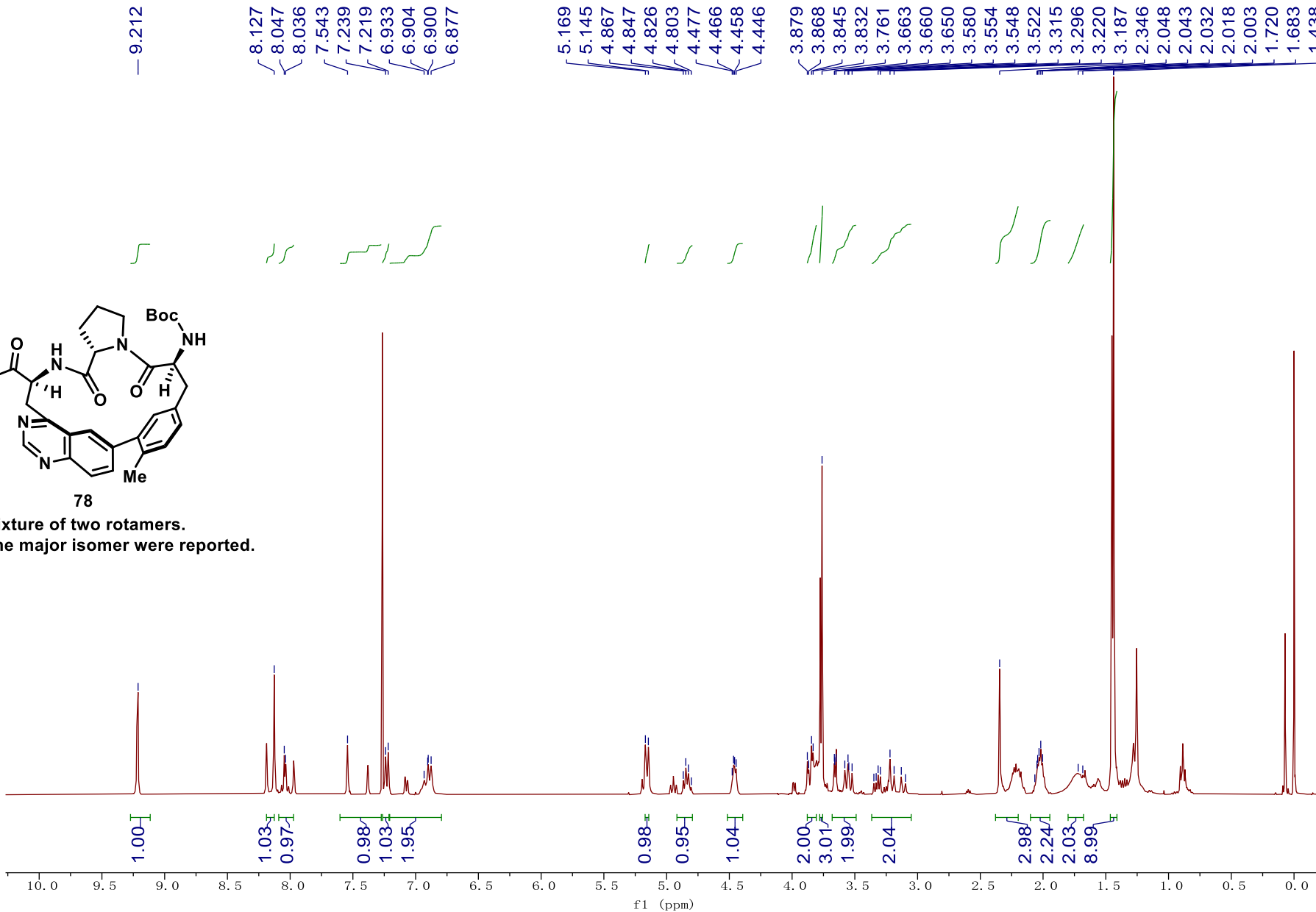


Compound 78 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

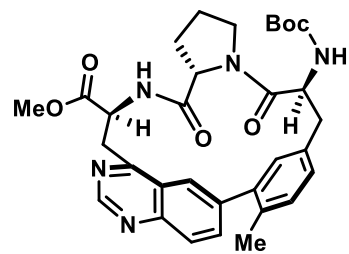


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mixture of two rotamers.  
signals of the major isomer were reported.

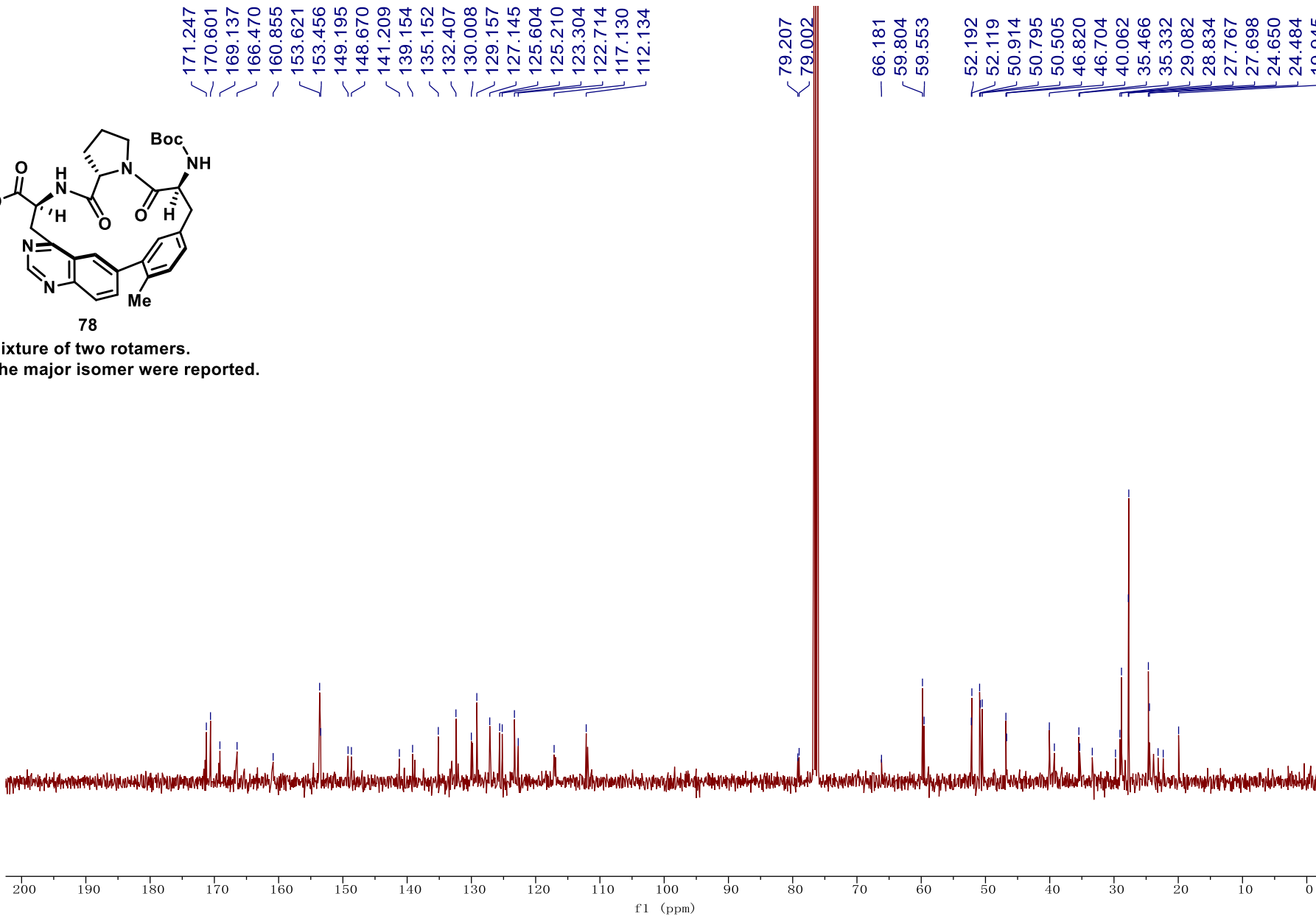


Compound 78 <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)

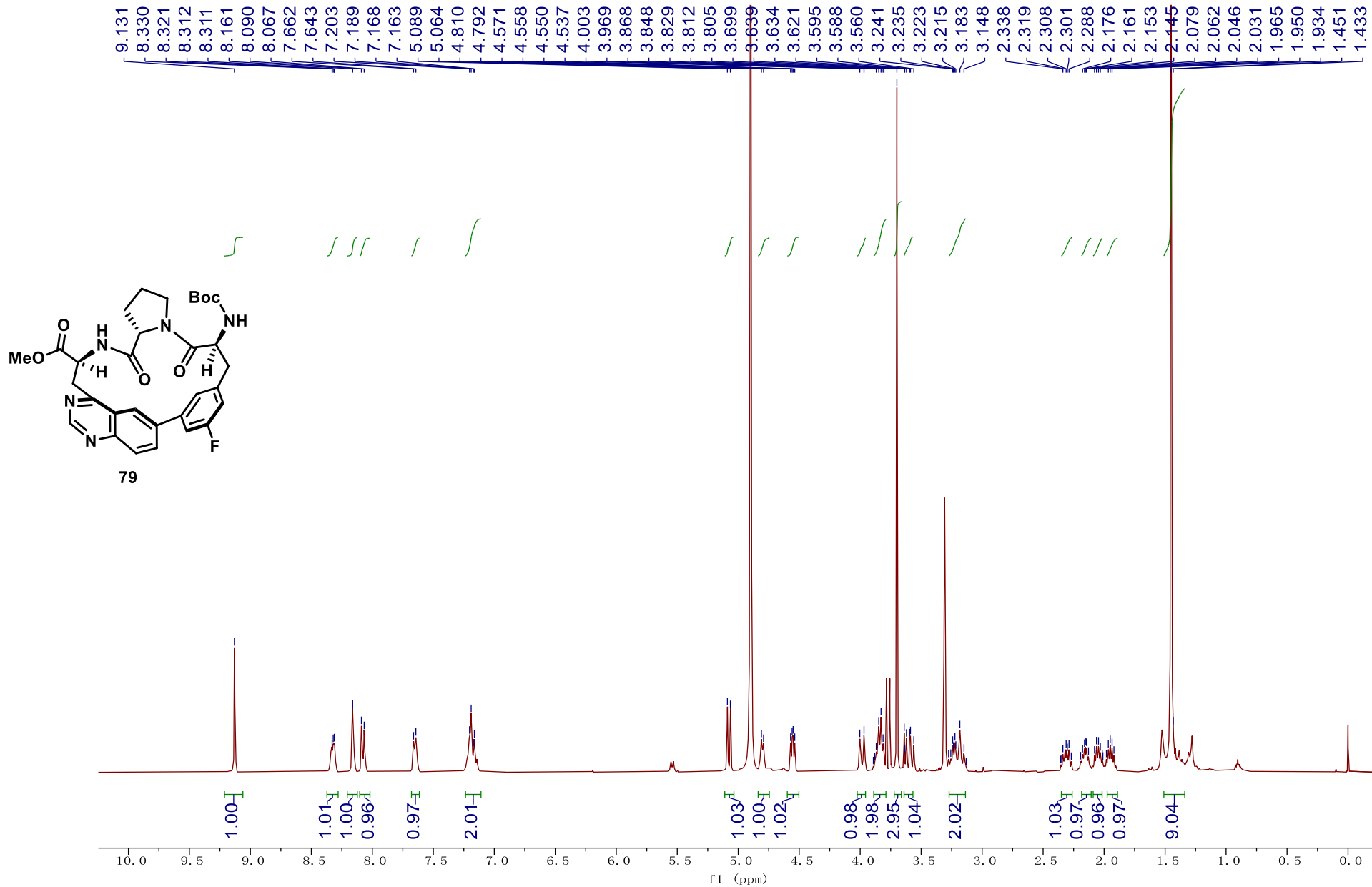


78

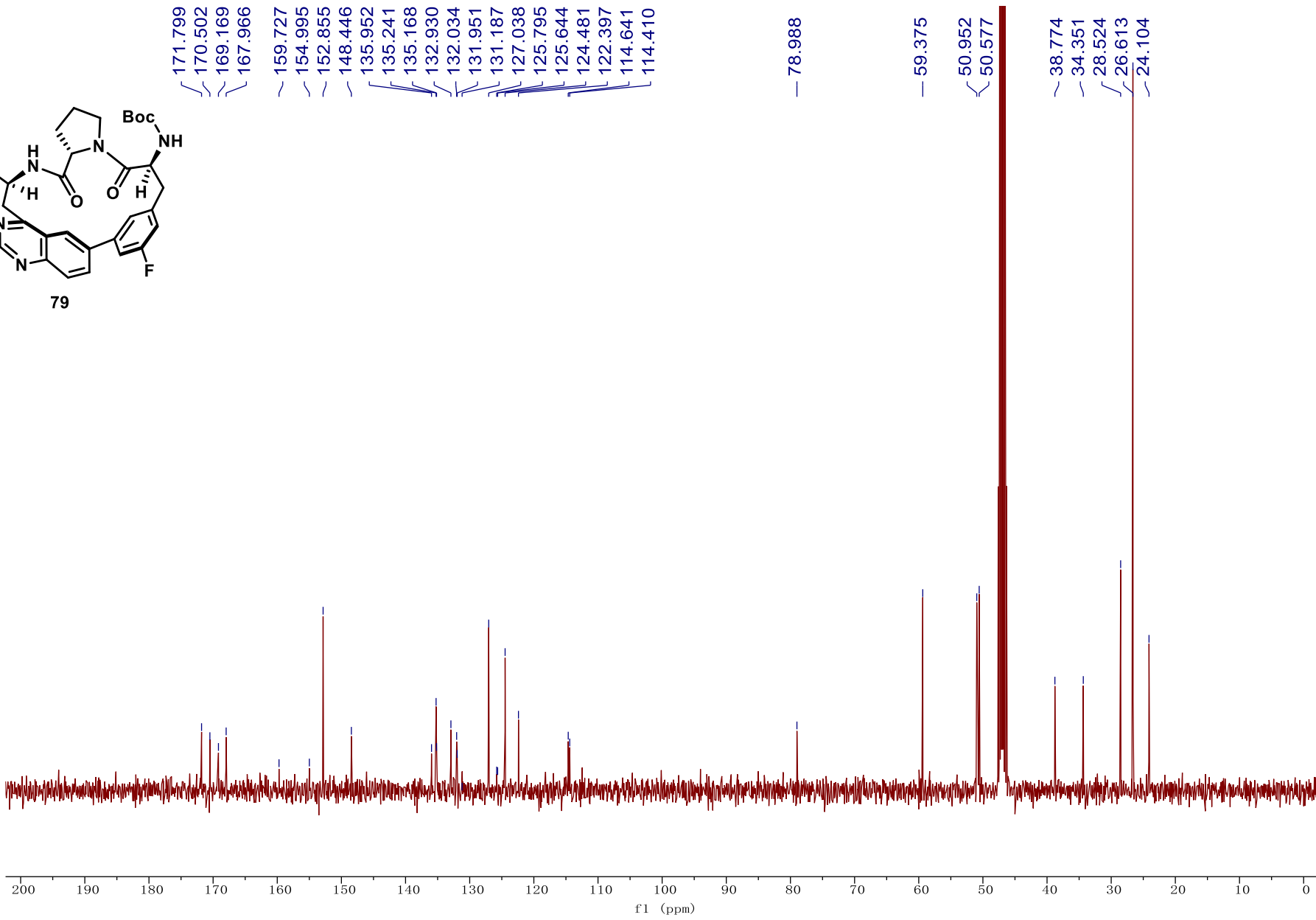
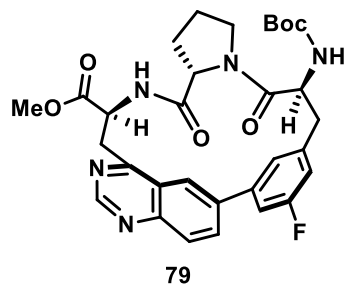
mixture of two rotamers.  
signals of the major isomer were reported.



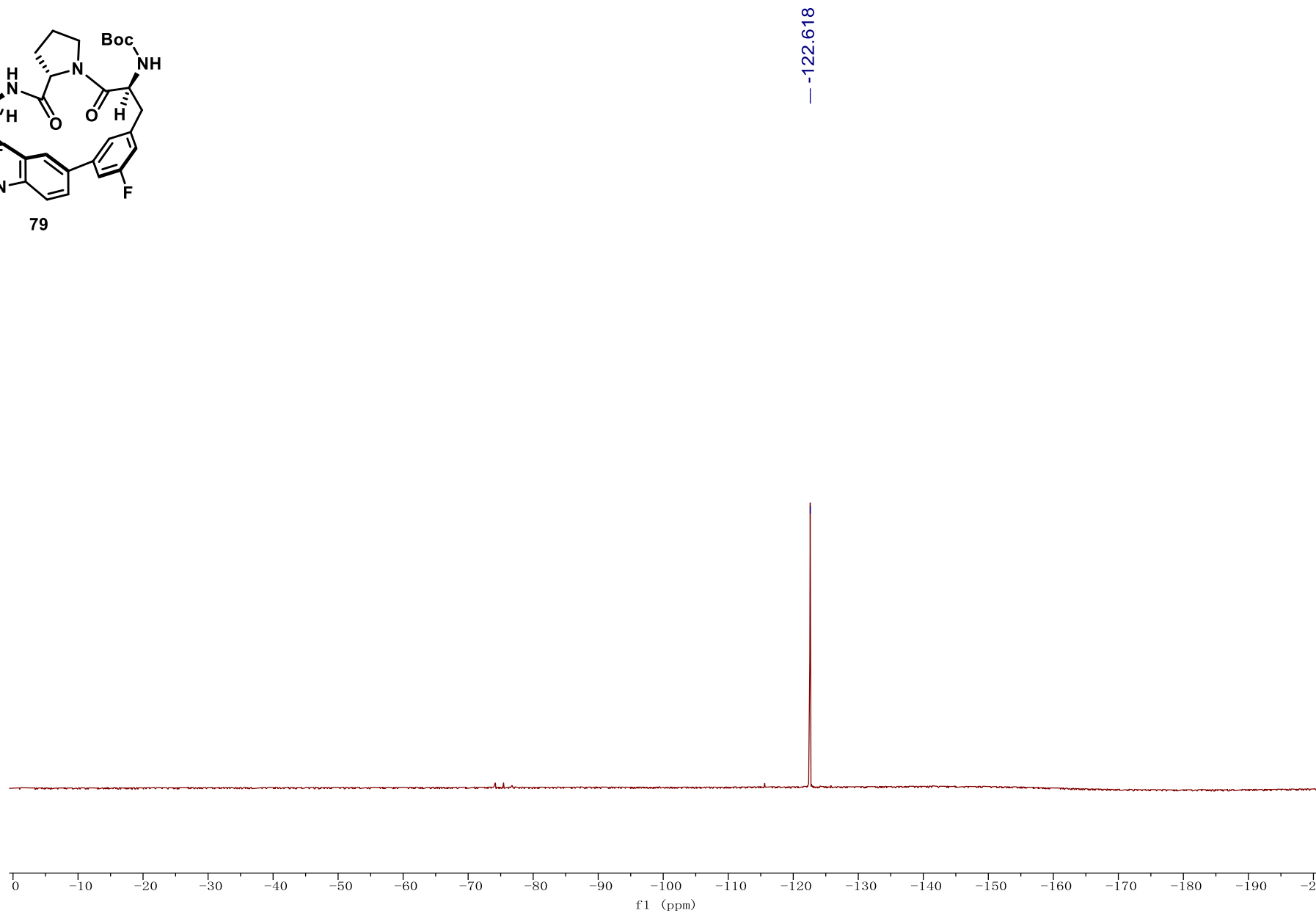
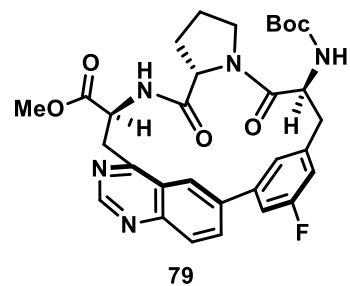
Compound 79 <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)



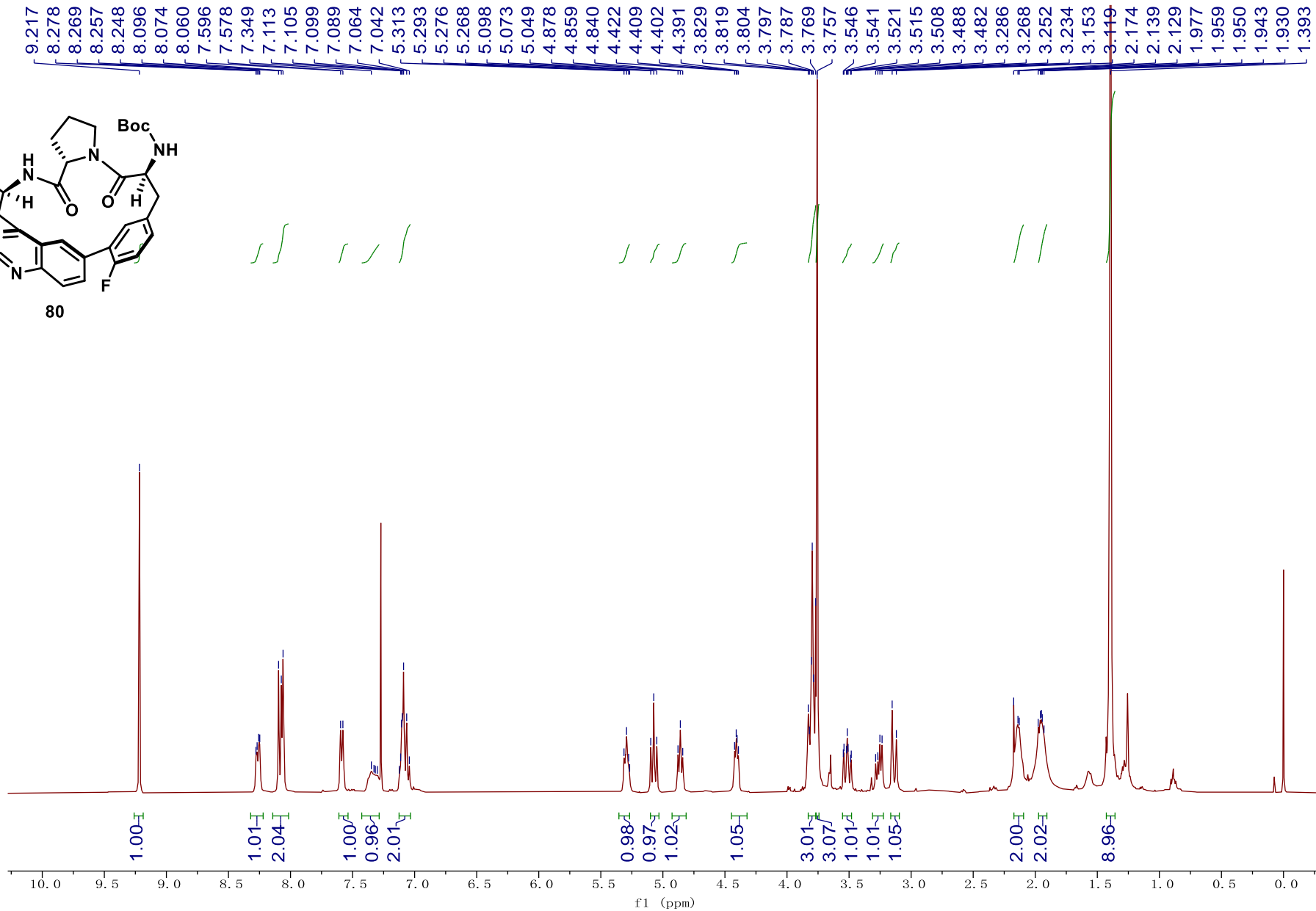
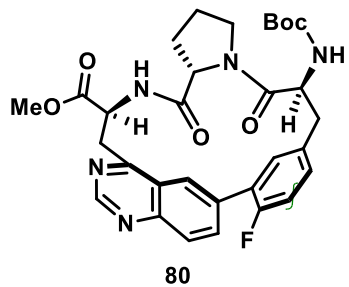
Compound 79 <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD)



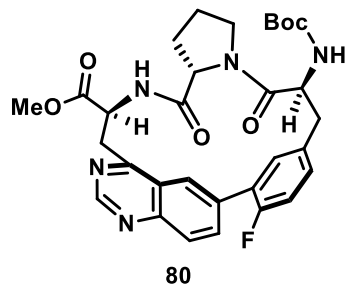
Compound 79 <sup>19</sup>F NMR (565 MHz, CD<sub>3</sub>OD)



Compound 80 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



Compound 80 <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)



171.470  
170.791  
169.108  
166.519  
159.712  
157.248  
154.656  
153.639  
148.969  
135.705  
134.959  
132.910  
132.094  
130.748  
128.037  
125.939  
124.394  
122.625  
114.900  
114.677

79.078

59.633

52.108

50.724

50.584

46.818

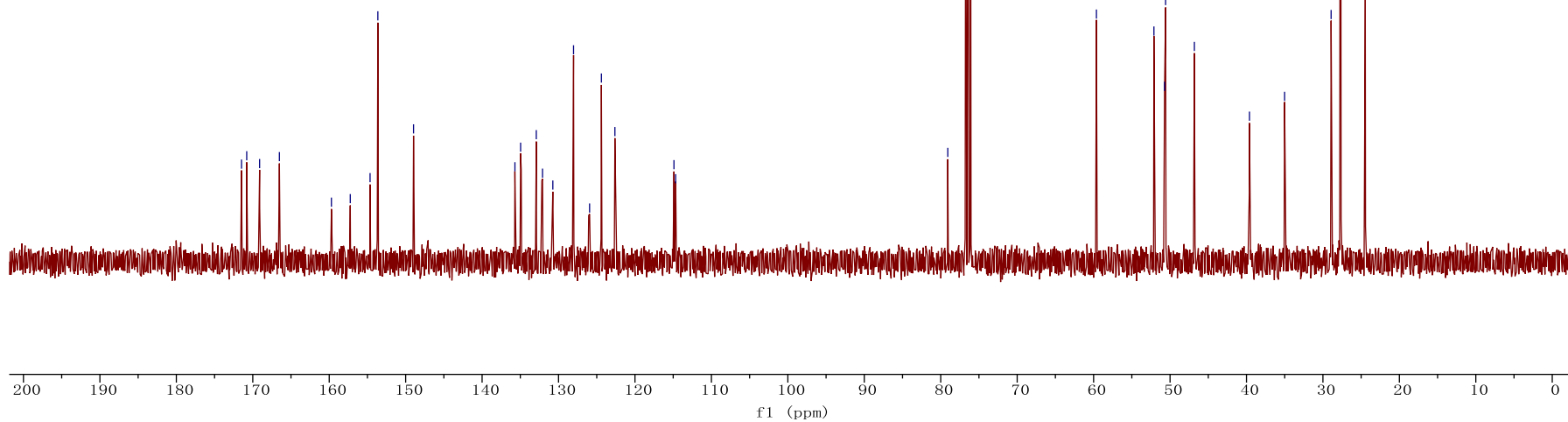
39.611

35.014

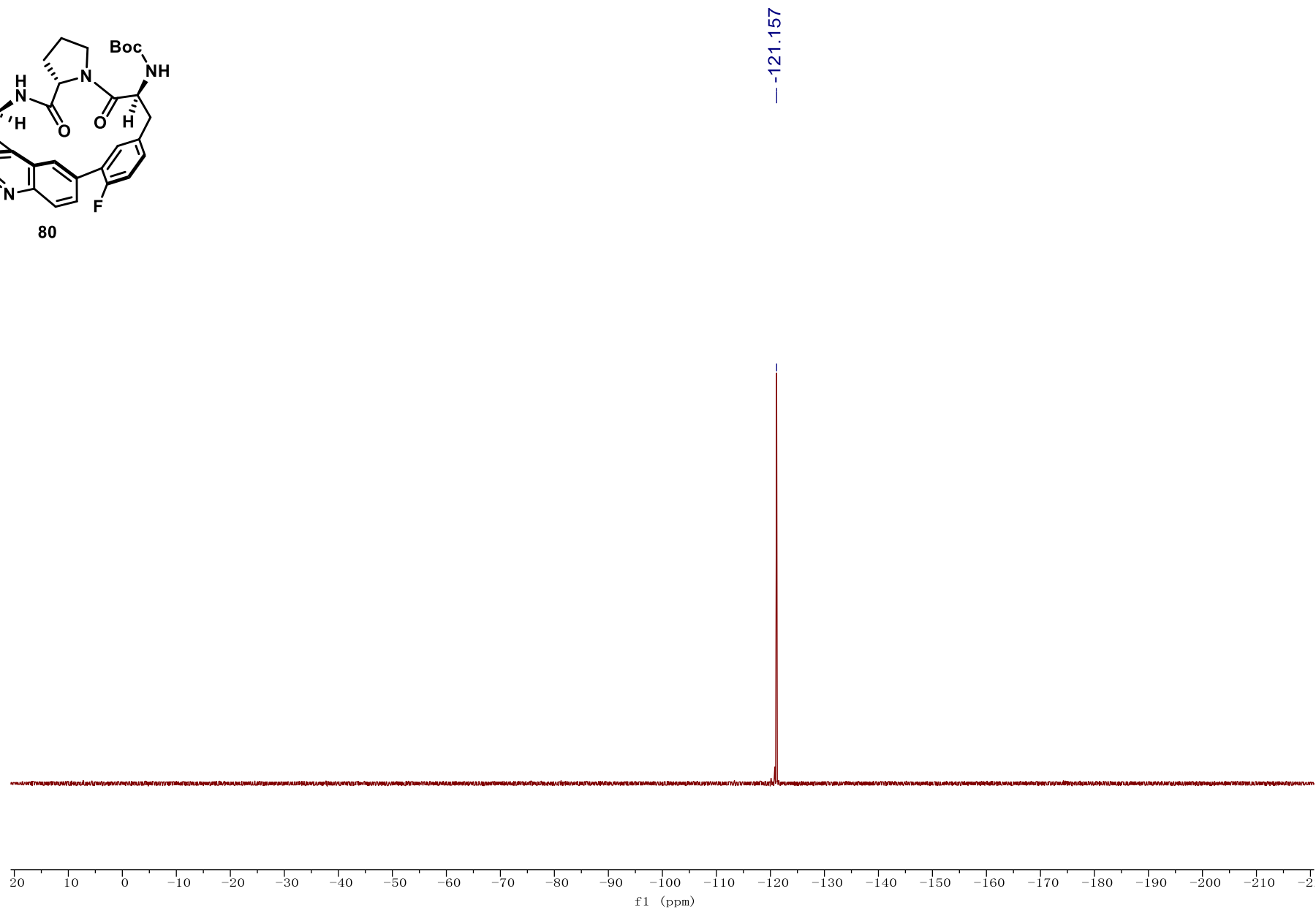
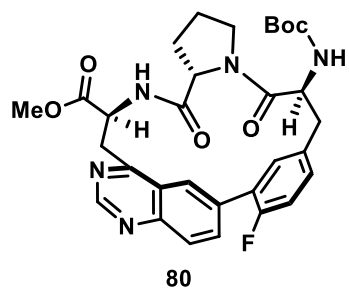
28.930

27.701

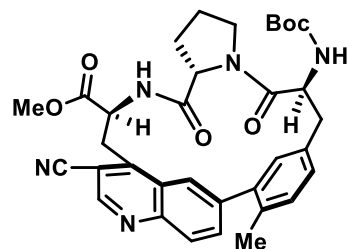
24.460



Compound 80  $^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ )

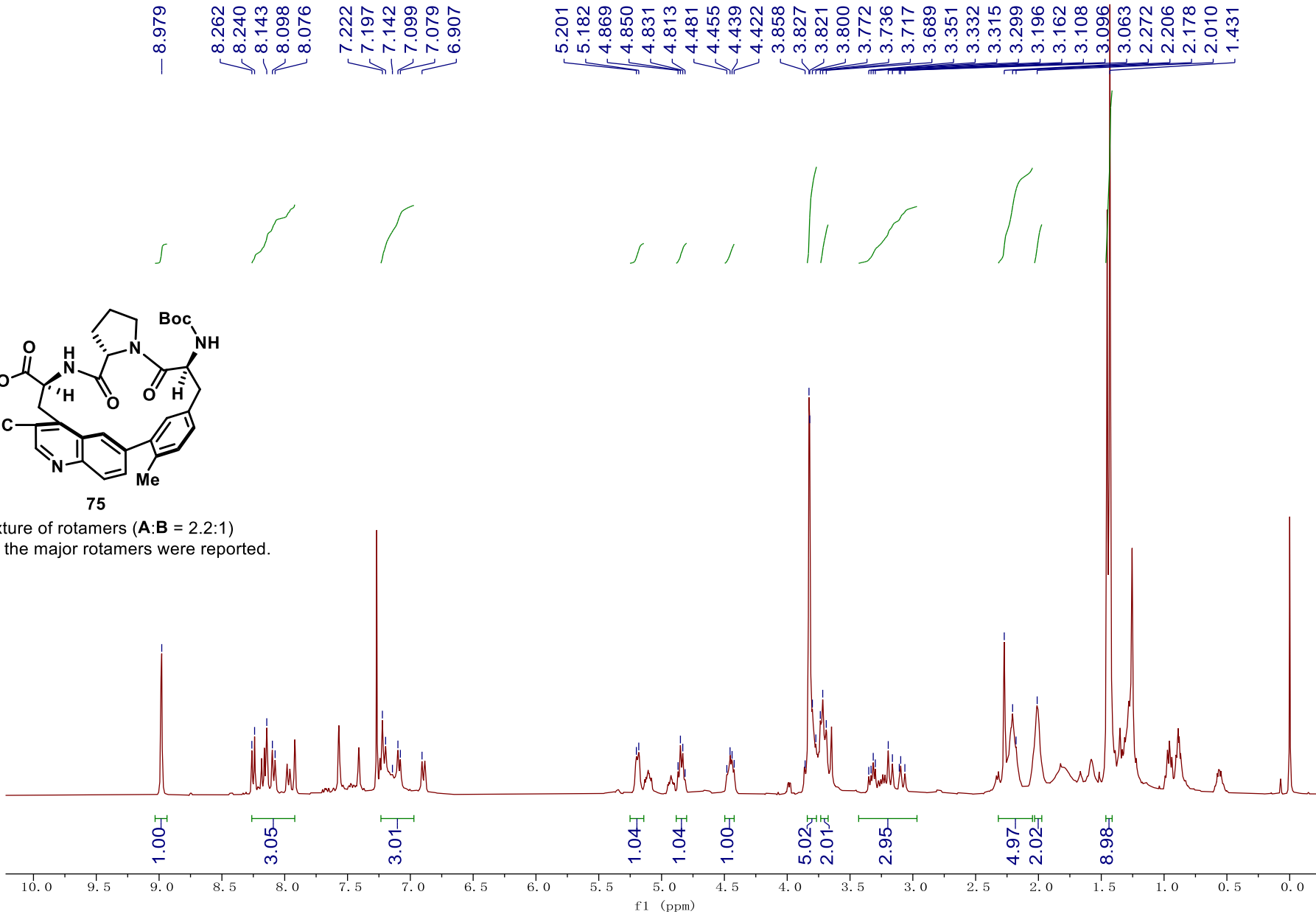


Compound 75 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

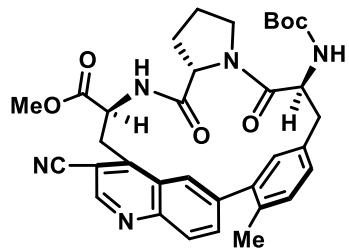


75

A mixture of rotamers (A:B = 2.2:1)  
 Signals of the major rotamers were reported.

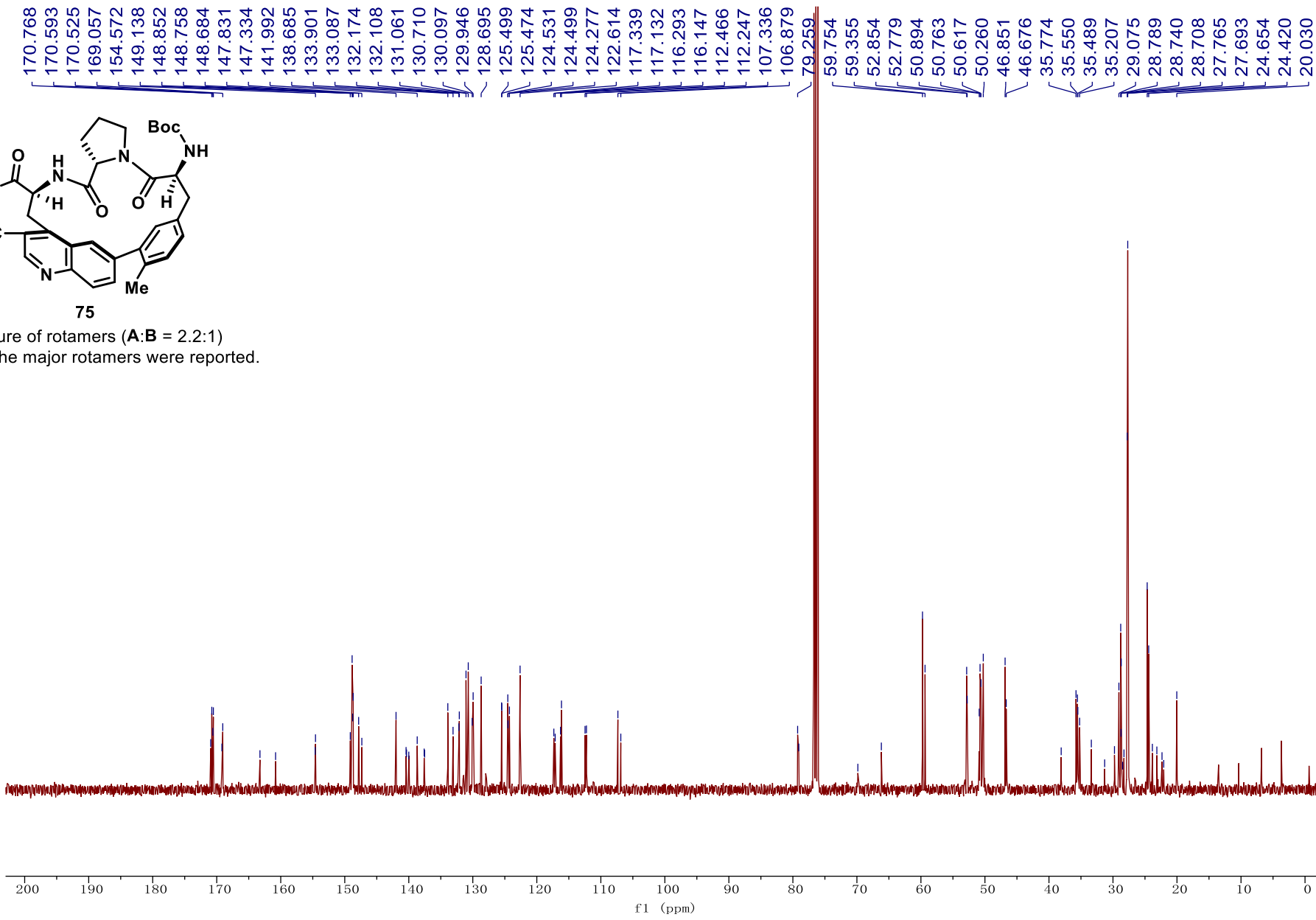


Compound 75 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

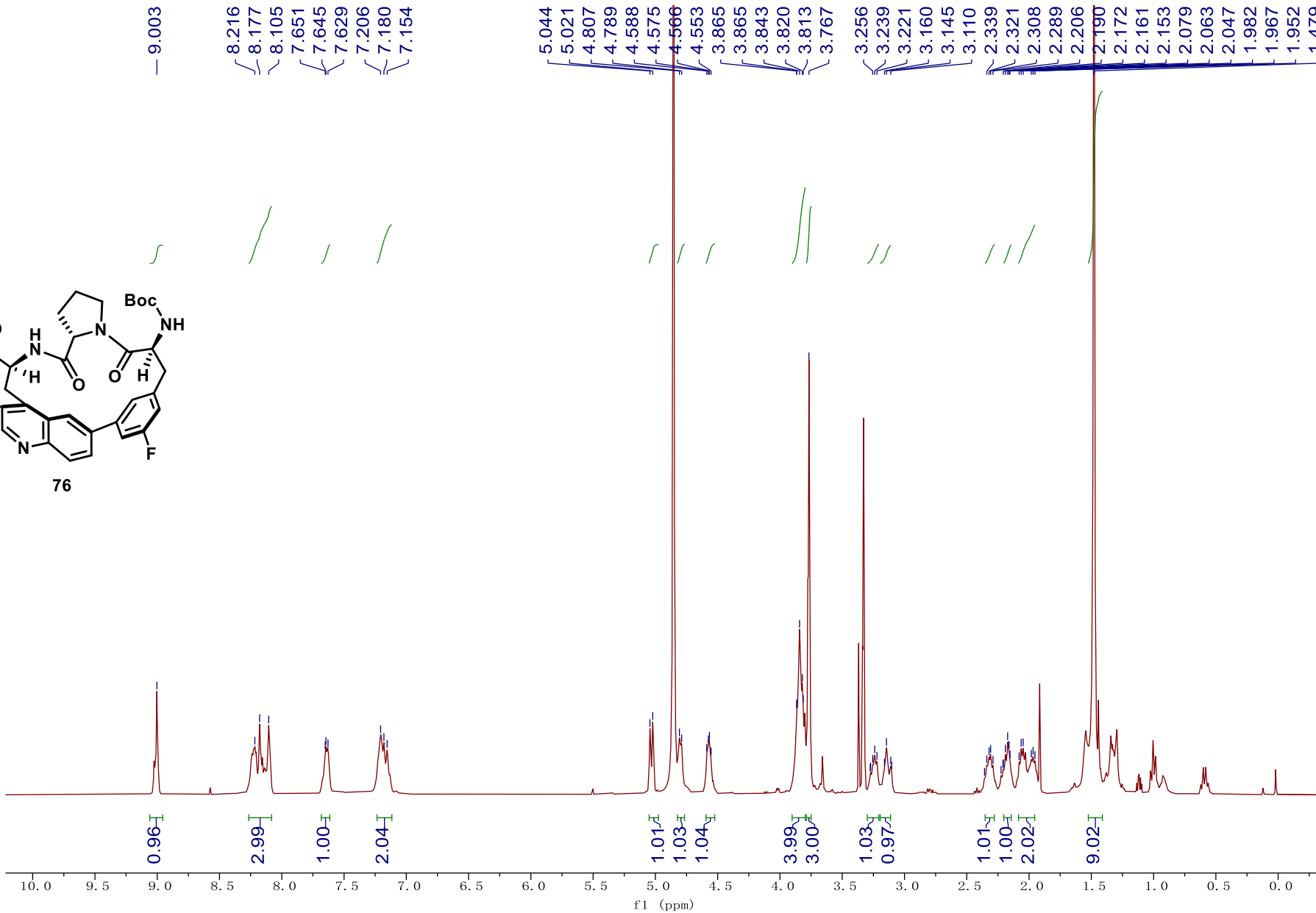
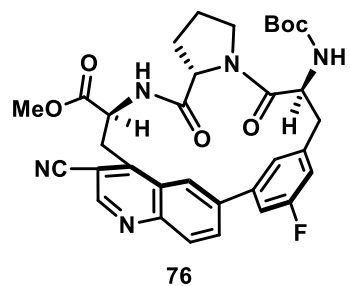


75

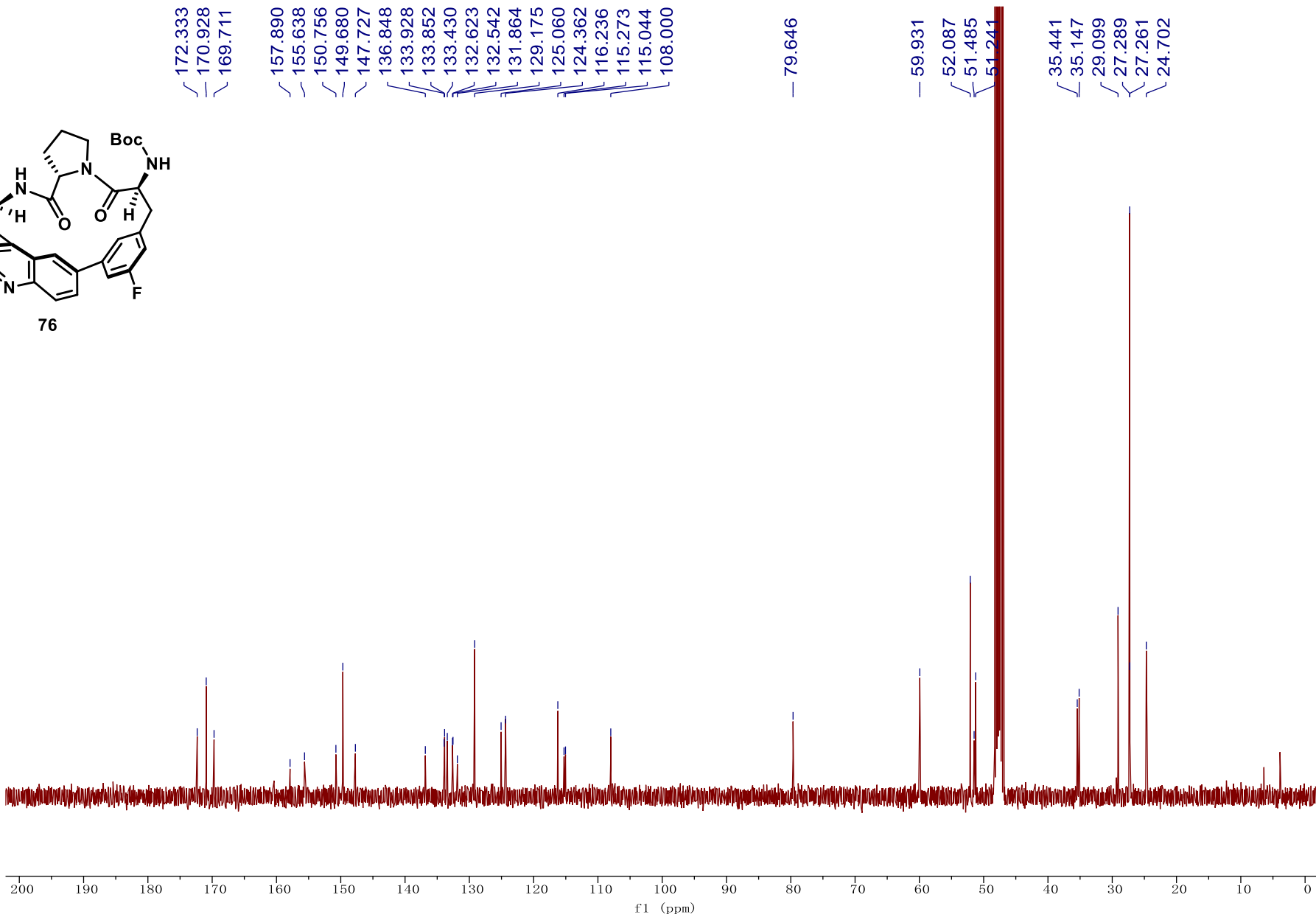
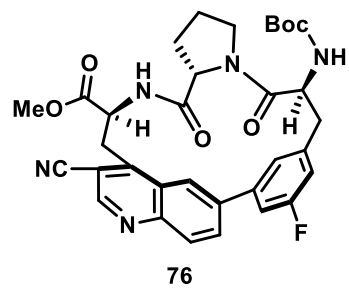
A mixture of rotamers (A:B = 2.2:1)  
 Signals of the major rotamers were reported.



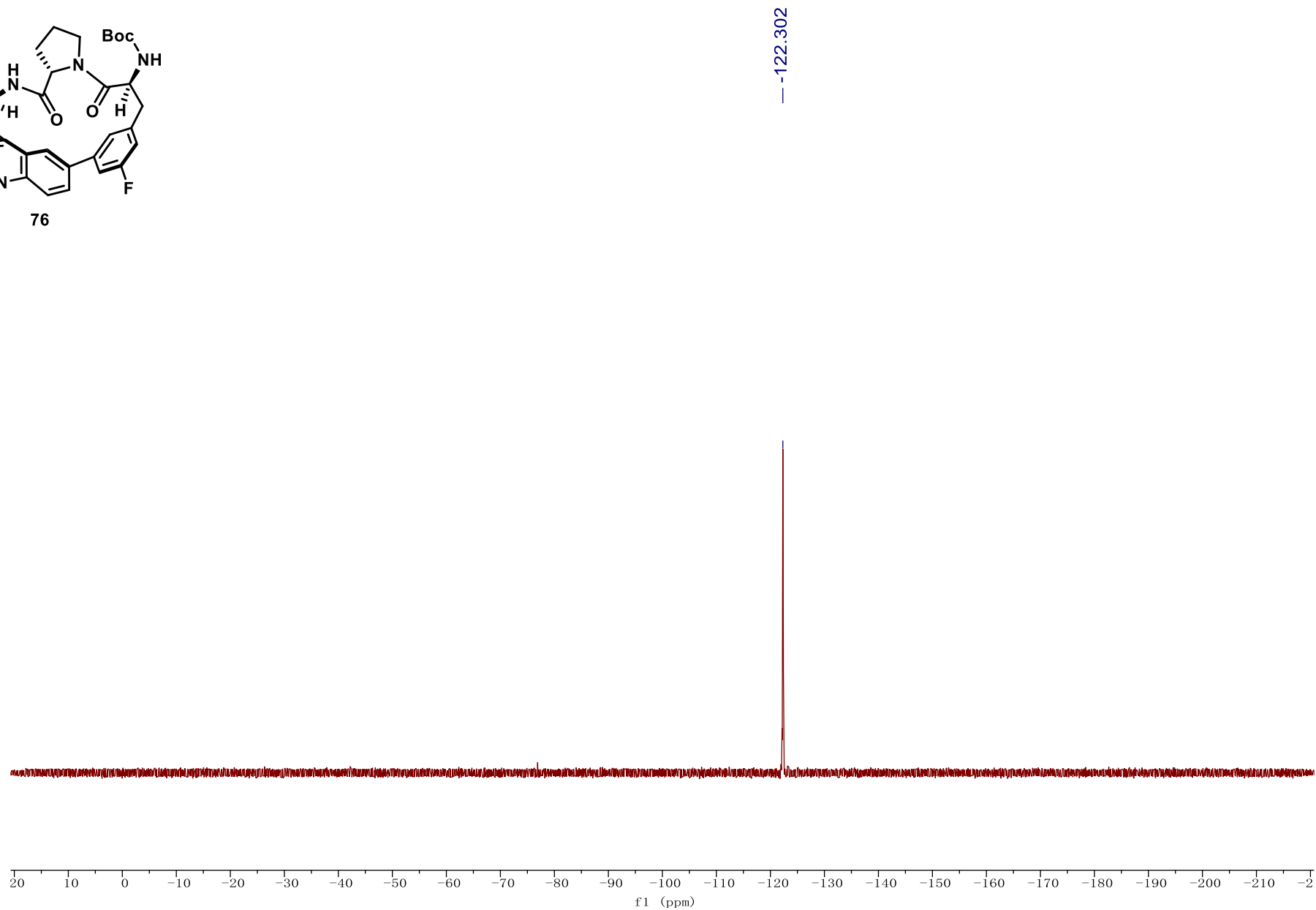
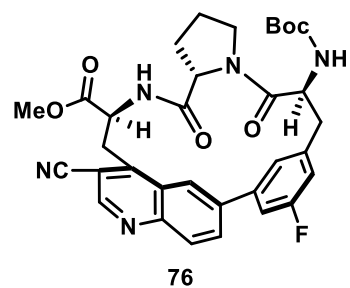
Compound 76 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



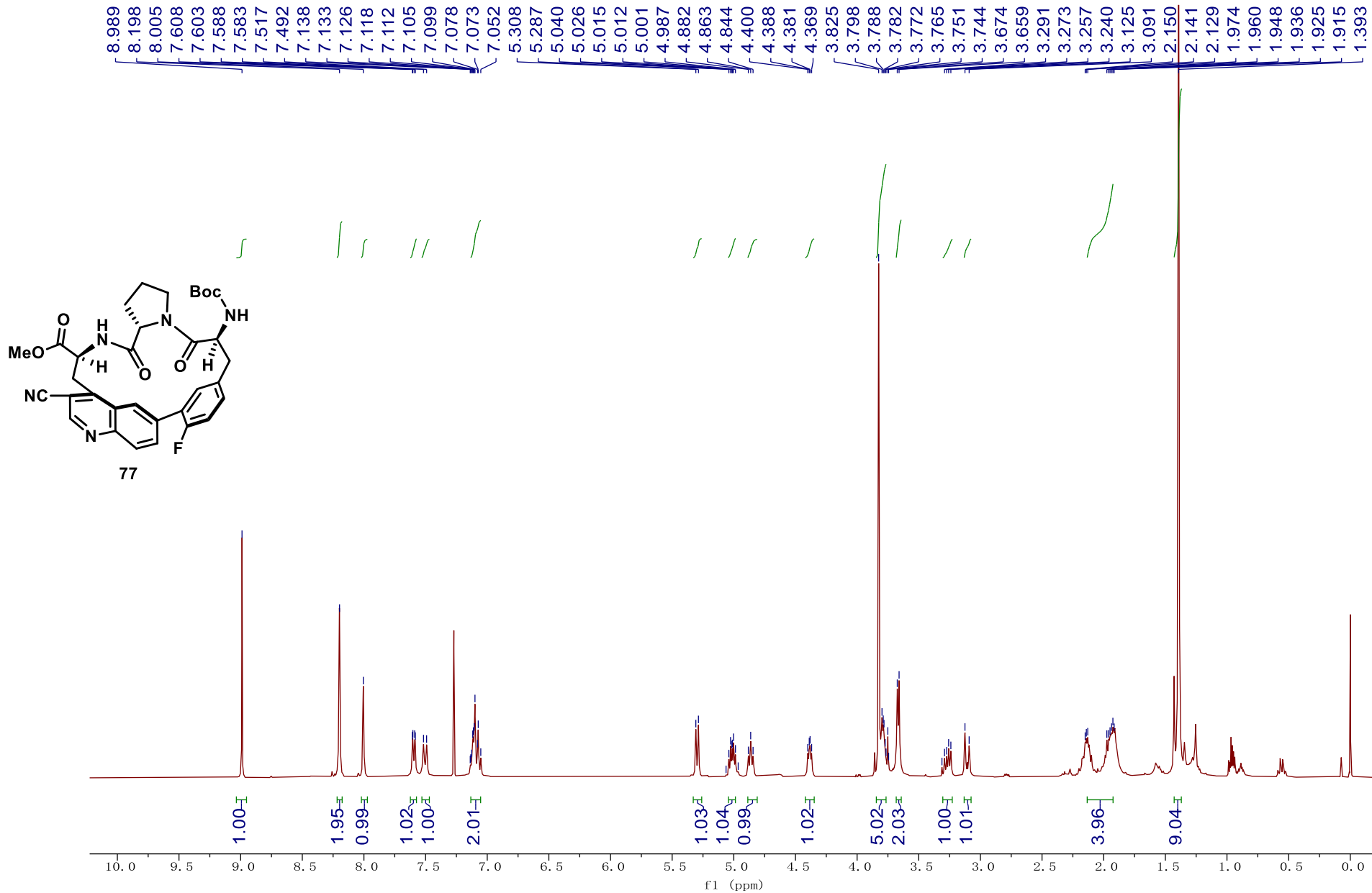
Compound 76 <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD)



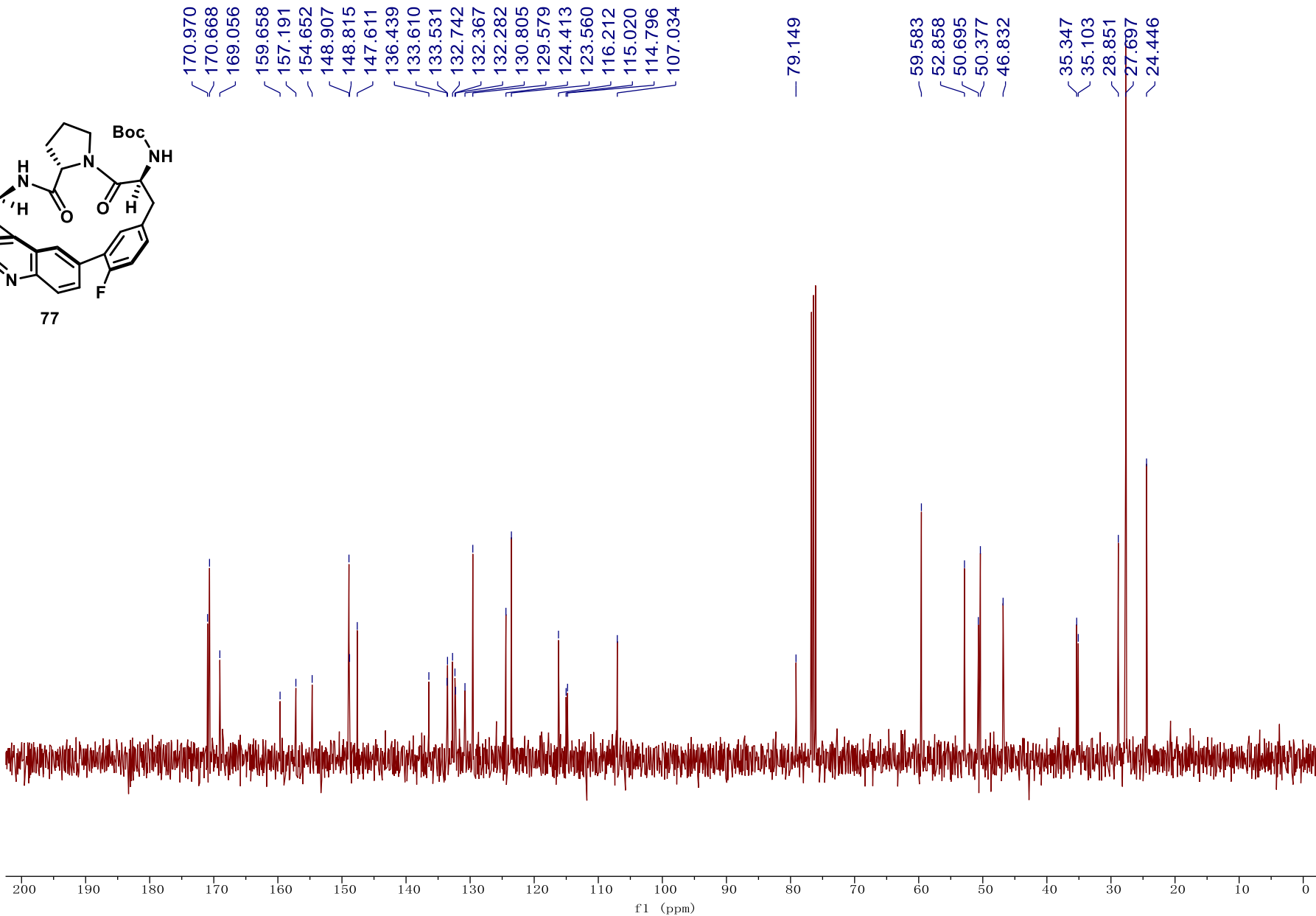
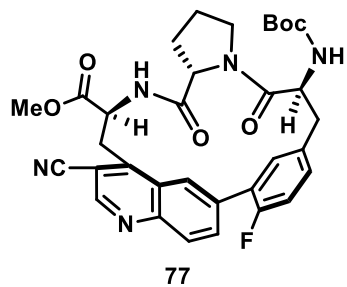
Compound 76  $^{19}\text{F}$  NMR (575 MHz,  $\text{CD}_3\text{OD}$ )



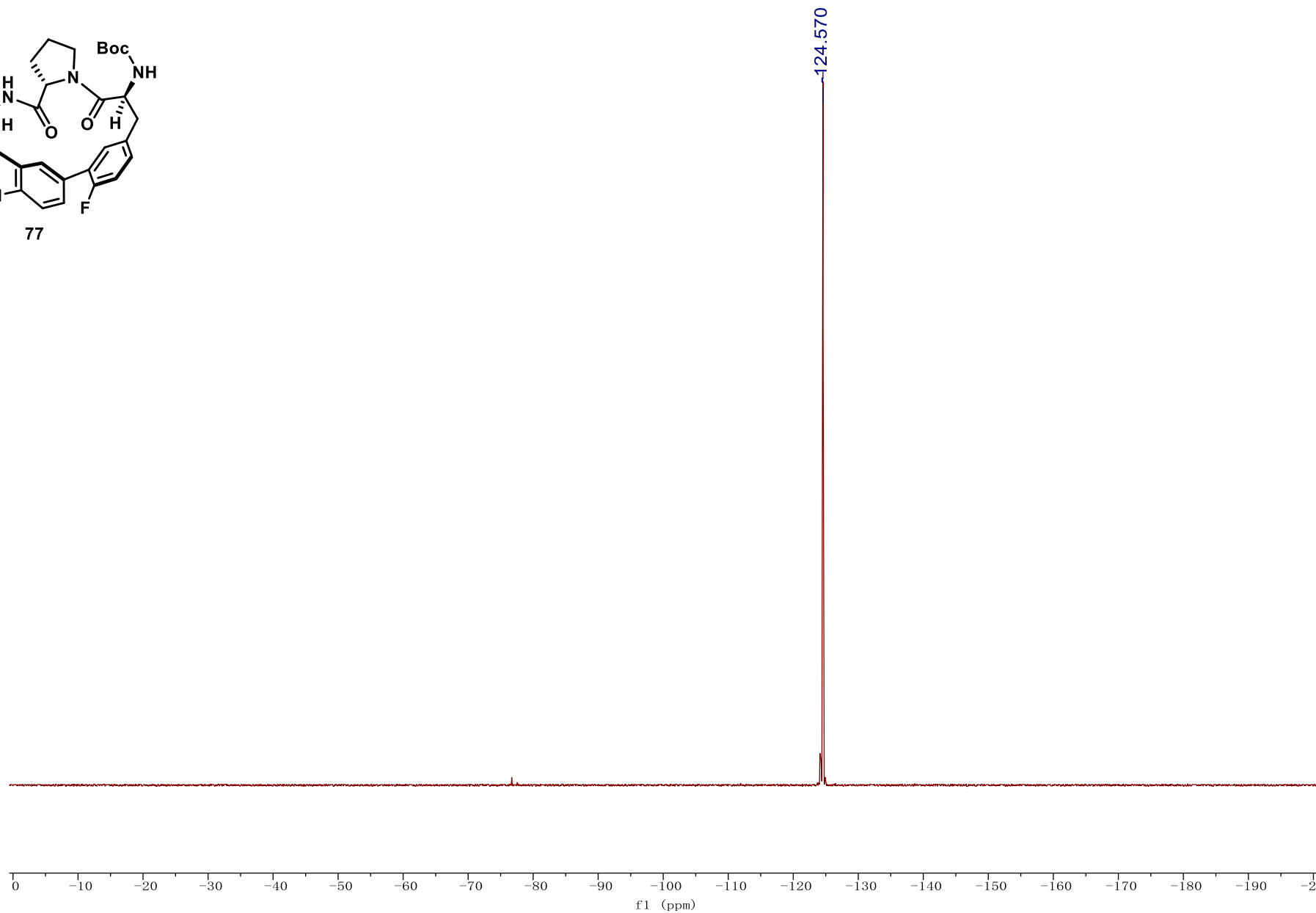
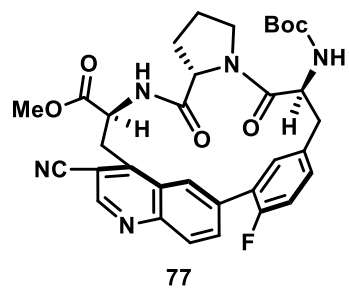
Compound 77 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



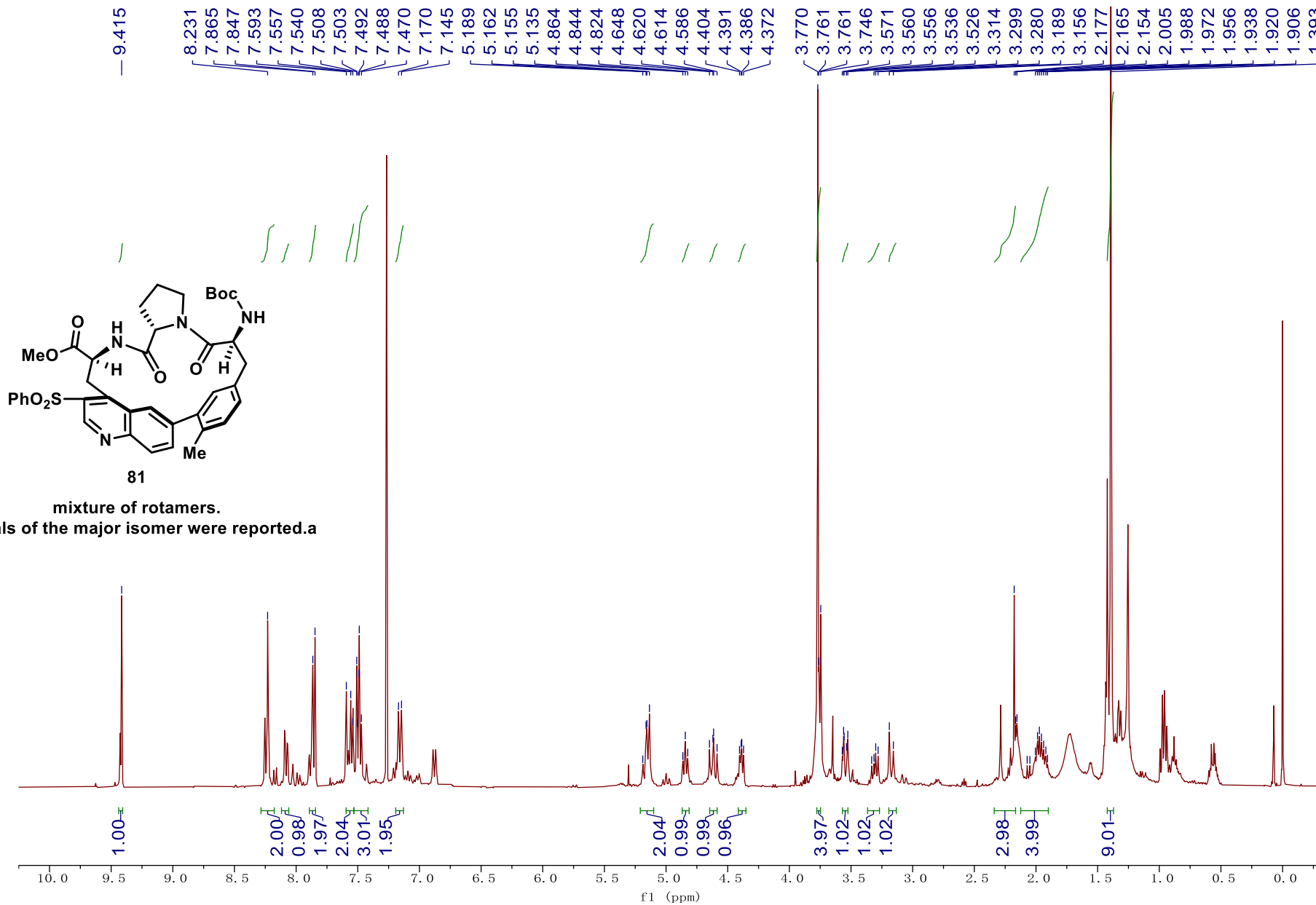
Compound 77 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



Compound 77  $^{19}\text{F}$  NMR (575 MHz,  $\text{CDCl}_3$ )

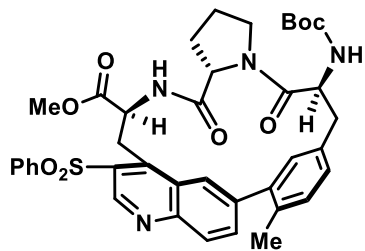


Compound 81 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



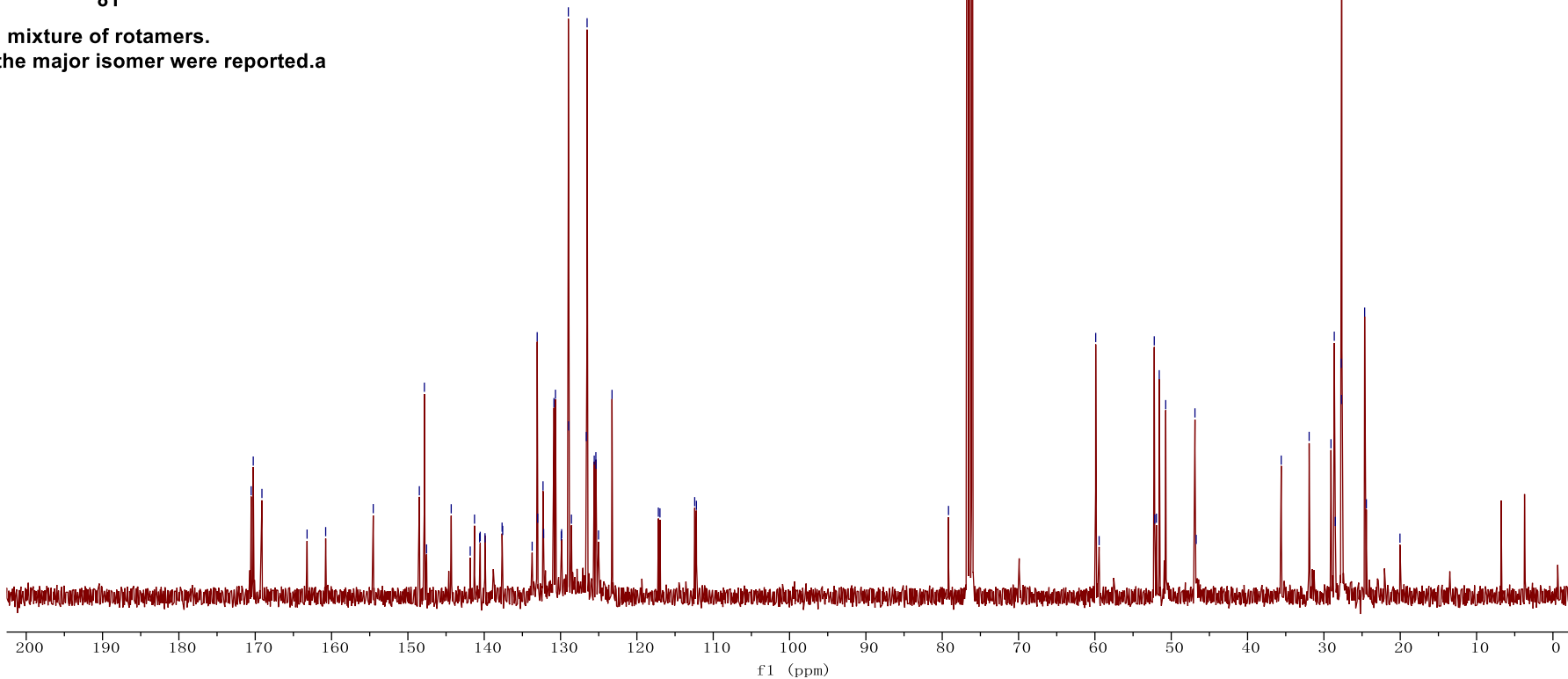
Compound 81 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

170.531  
170.259  
169.122  
163.209  
160.770  
154.539  
148.499  
147.839  
147.548  
144.324  
141.272  
140.602  
140.524  
139.897  
137.660  
137.583  
133.724  
133.060  
132.999  
132.295  
132.219  
130.866  
130.668  
129.913  
129.861  
128.980  
128.935  
128.576  
126.621  
126.523  
125.587  
125.374  
125.348  
125.024  
123.258  
117.187  
116.978  
112.426  
112.206  
79.178  
59.895  
59.447  
52.224  
52.163  
51.937  
51.569  
50.724  
46.892  
46.728  
35.591  
31.934  
29.077  
28.641  
28.506  
27.737  
27.710  
27.657  
24.663  
24.437  
20.035

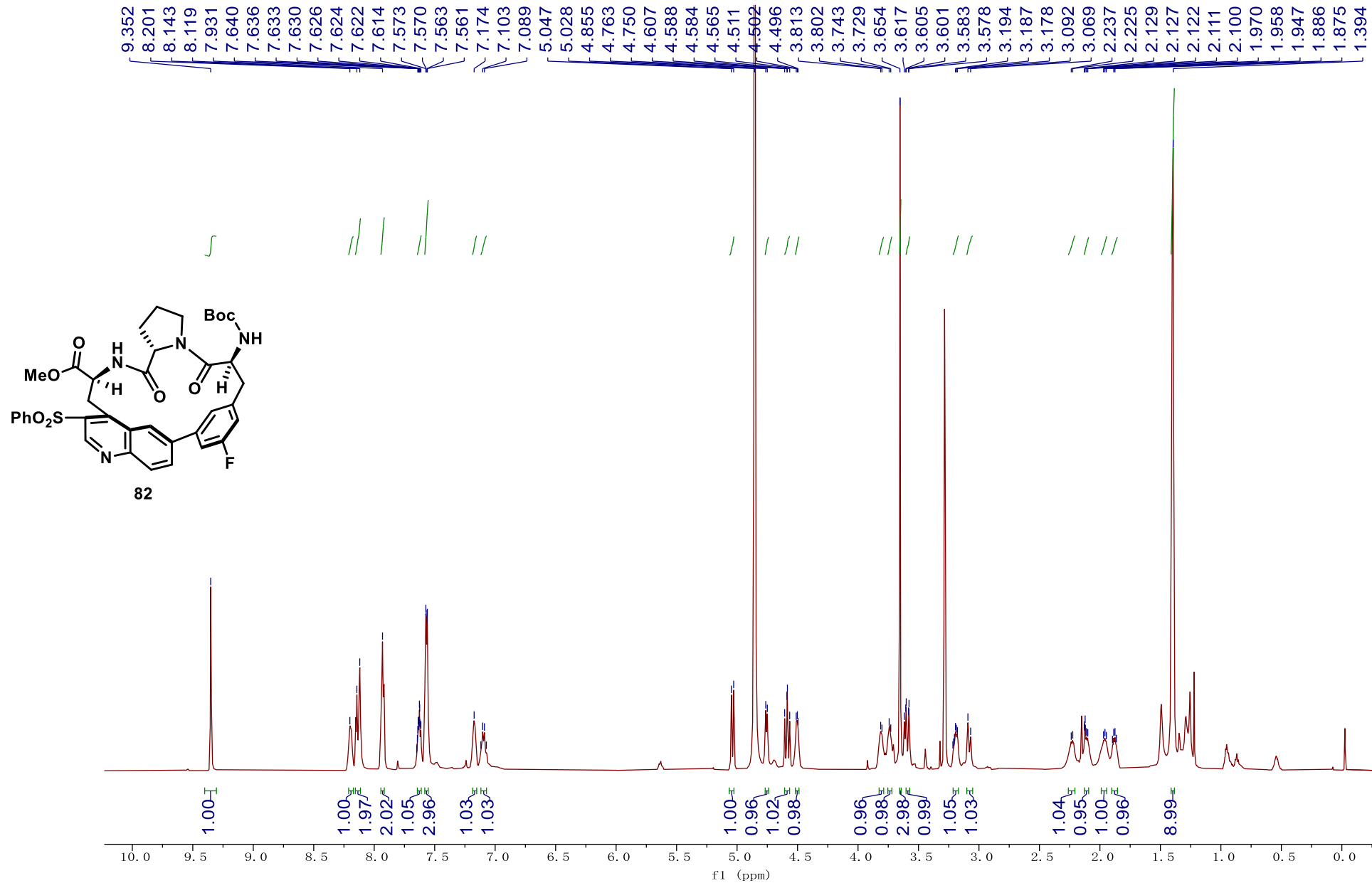


81

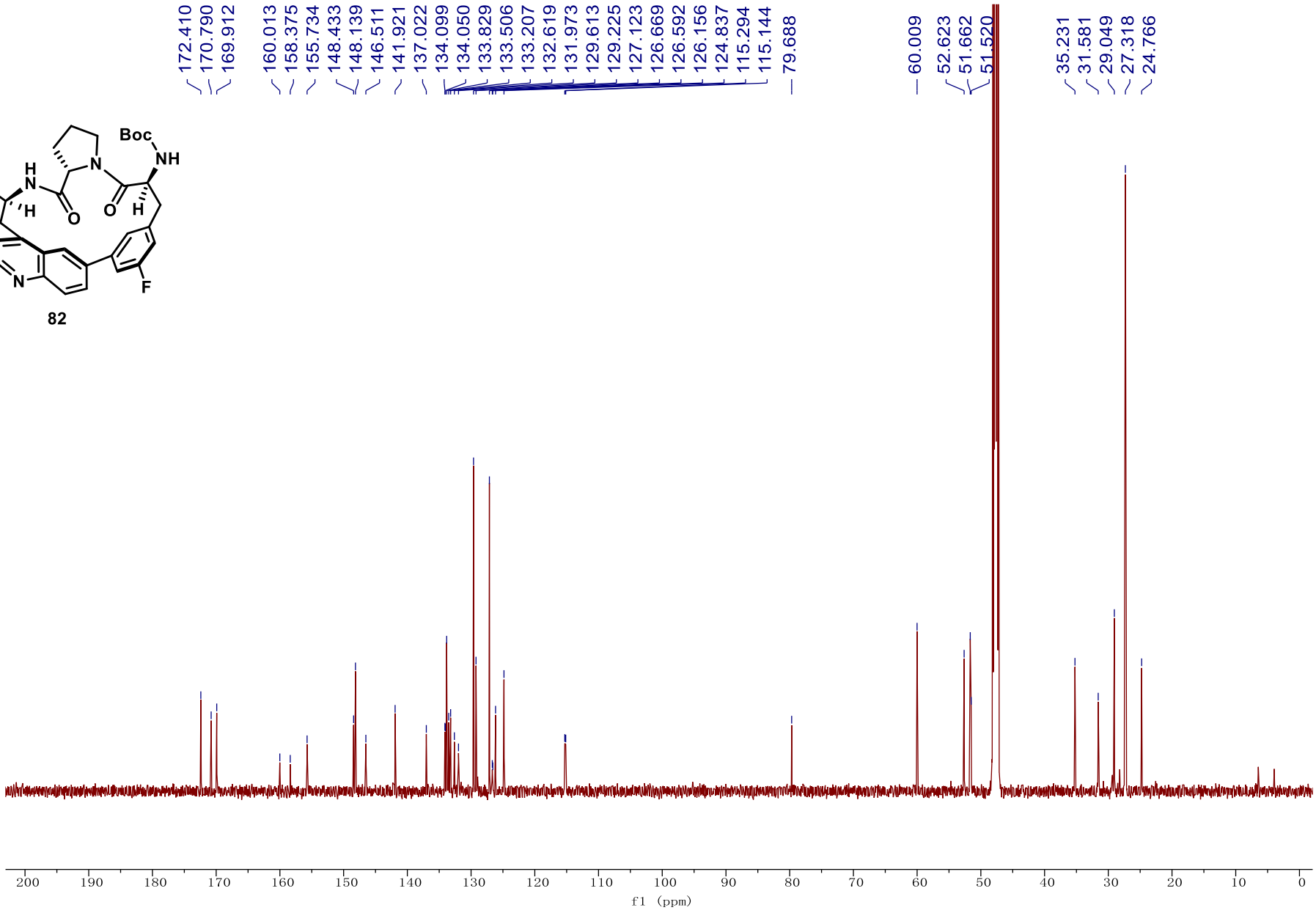
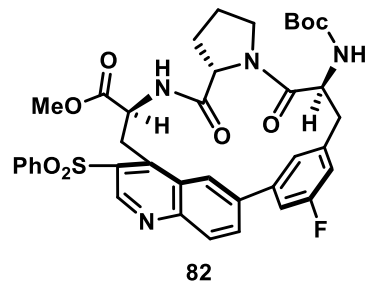
mixture of rotamers.  
signals of the major isomer were reported.a



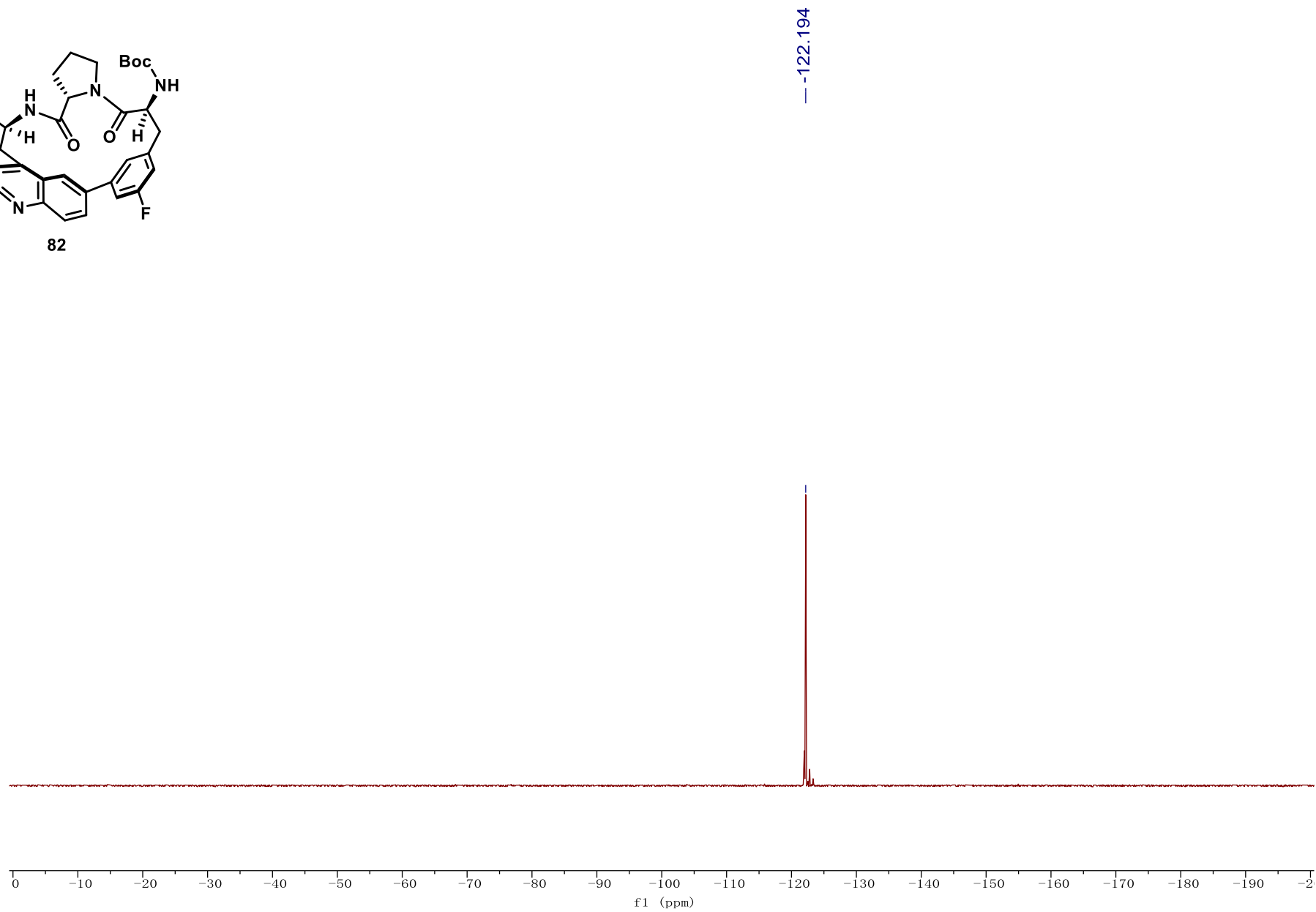
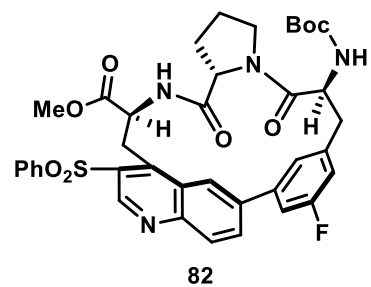
Compound 82 <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD)



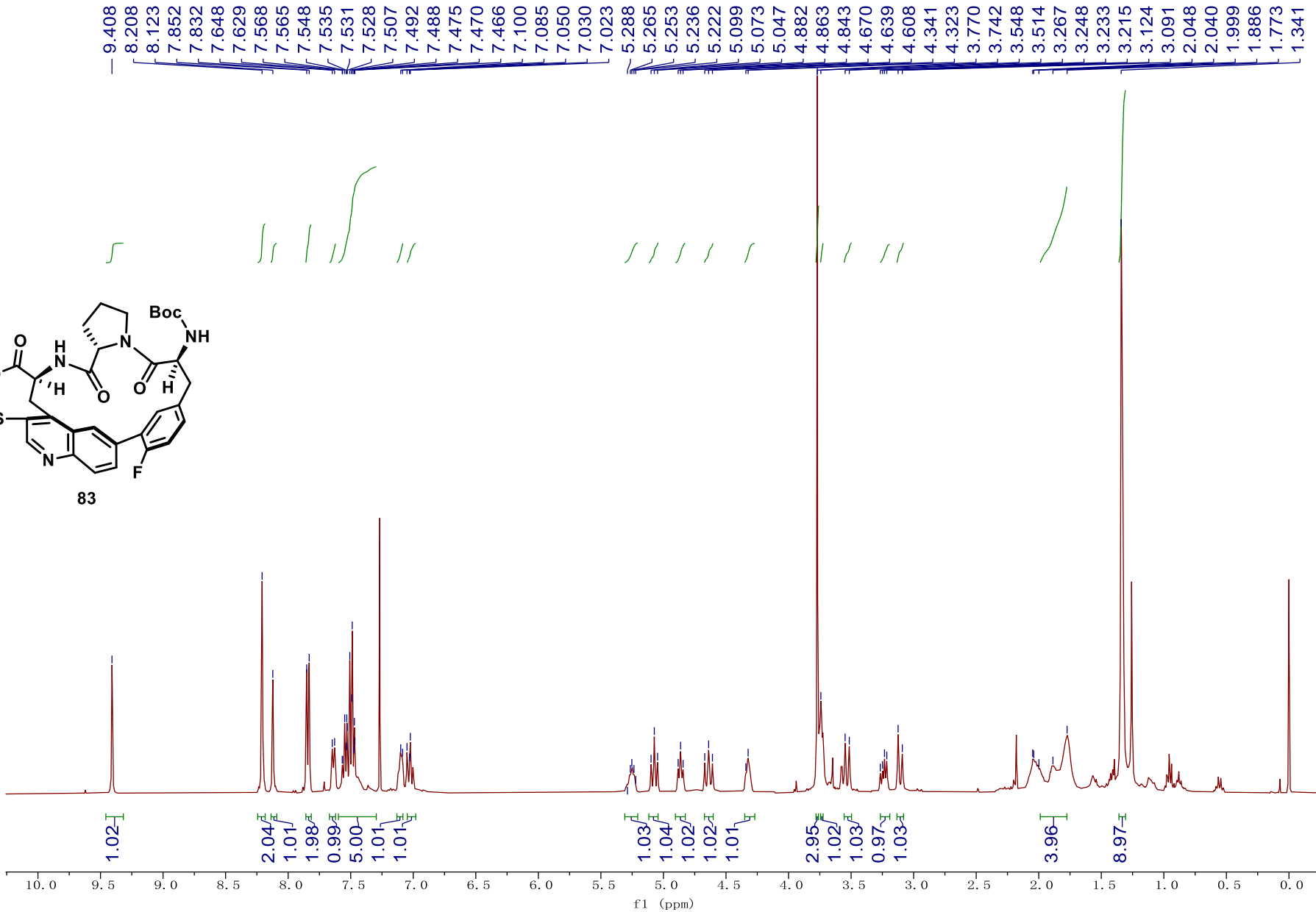
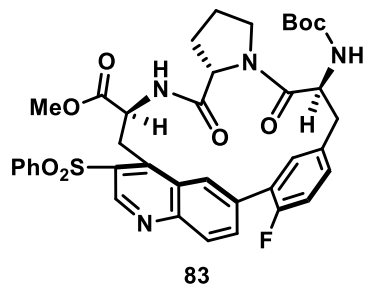
Compound 82 <sup>13</sup>C NMR (151 MHz, CD<sub>3</sub>OD)



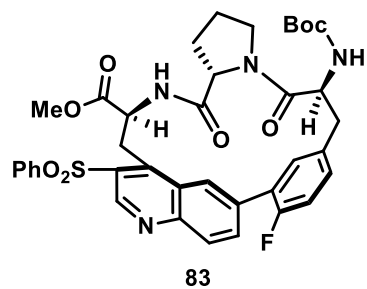
Compound 82  $^{19}\text{F}$  NMR (575 MHz,  $\text{CD}_3\text{OD}$ )



Compound 83 <sup>1</sup>H NMR(400 MHz, CD<sub>3</sub>OD)



Compound 83 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



170.691  
170.470  
169.076  
159.651  
157.188  
154.639  
148.219  
147.815  
144.490  
141.317  
136.315  
133.507  
133.431  
133.053  
132.672  
132.244  
132.163  
132.080  
130.860  
129.445  
129.005  
126.441  
125.520  
124.434  
114.792  
114.566

79.052

59.732

52.220

51.732

50.600

46.877

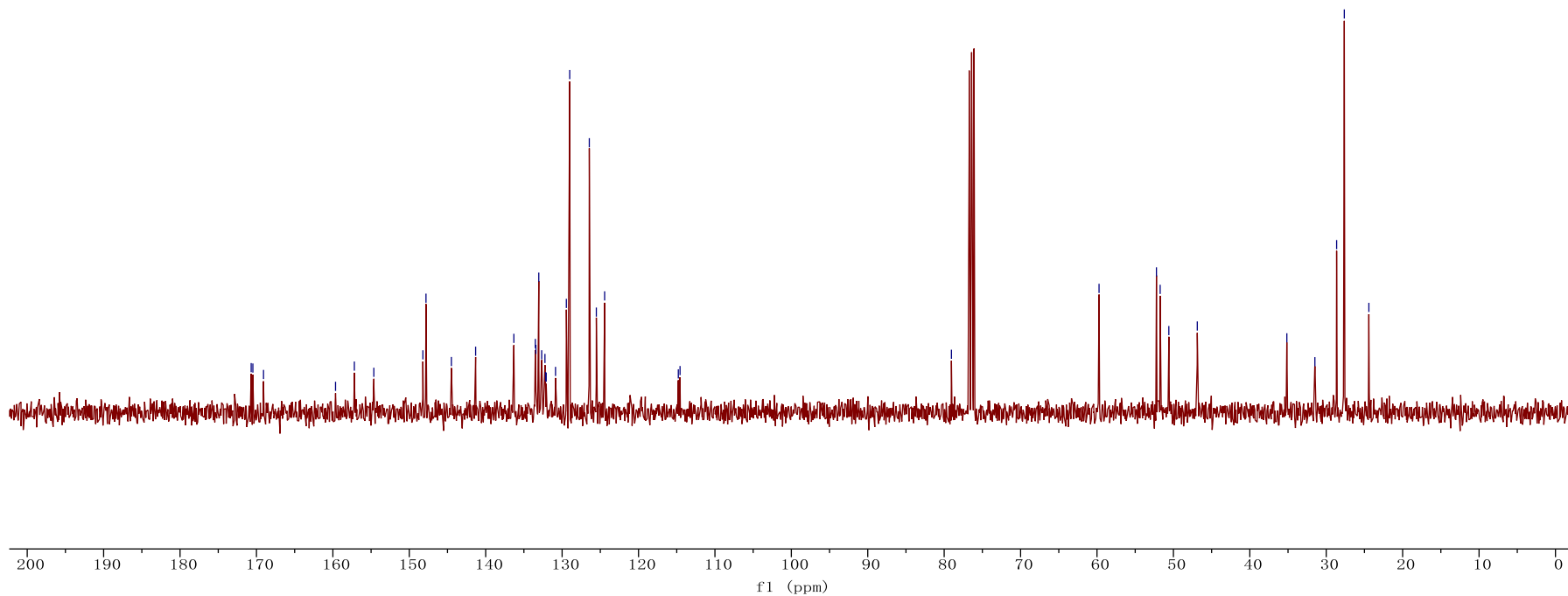
35.152

31.485

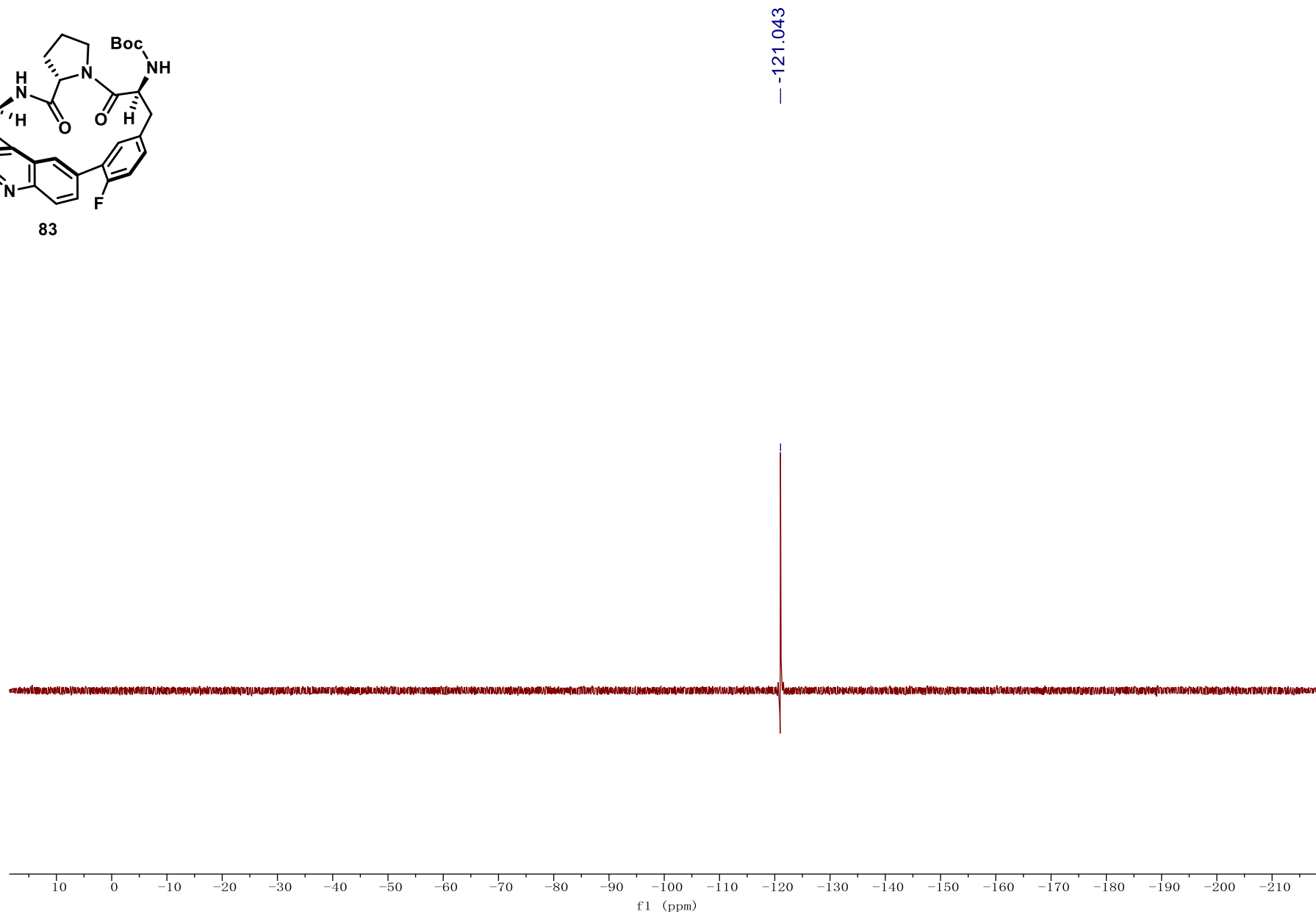
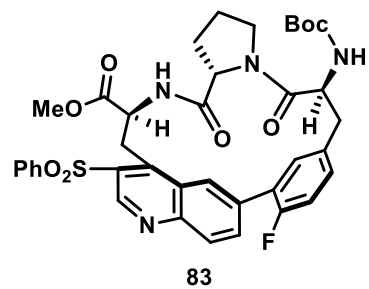
28.640

27.635

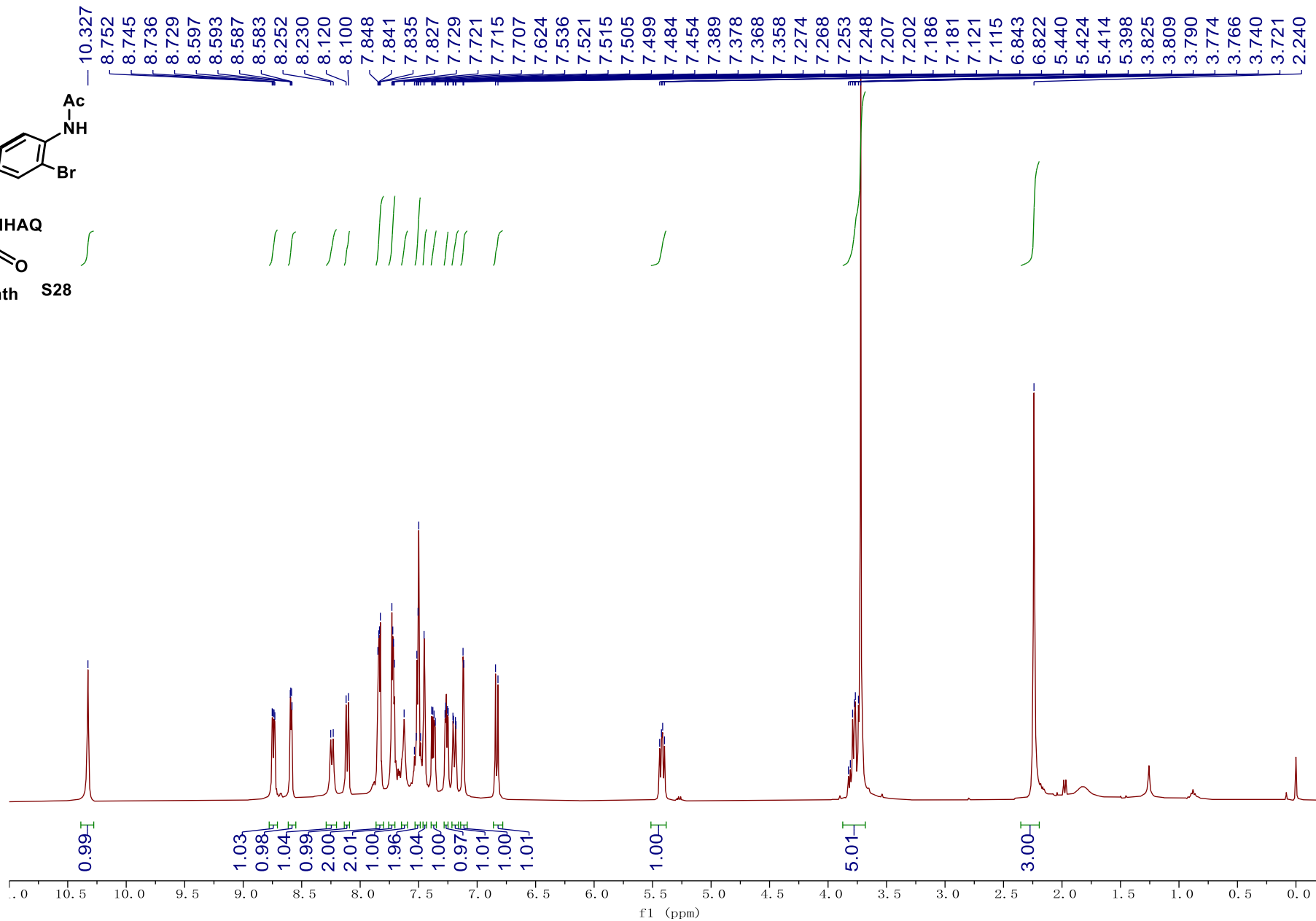
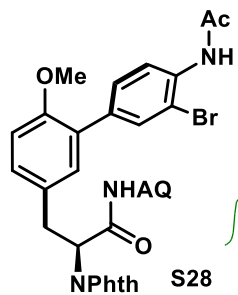
24.421



Compound 83  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )

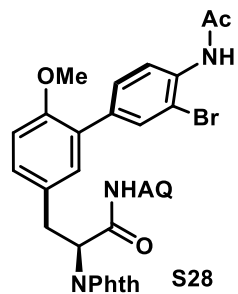


Compound S28 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



S203

Compound S28 <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



168.213  
167.940  
166.408  
— 155.351  
— 148.325  
— 138.477  
136.258  
134.338  
133.841  
132.715  
131.622  
131.227  
129.610  
129.394  
128.966  
128.647  
127.854  
127.290  
123.624  
122.041  
121.641  
121.125  
116.780  
111.586

56.481  
55.562

— 33.911

— 24.914

