Supplementary Information

Modular Assembly of Bioisosteric Bridged Aza-frameworks via Strained Ring Release

Haotian Jiang,[1†] Yuxia Dai,[2†] Kai Tang,[1] Bo Pan,[1] Hongming Jin,[2*] Xiangyang Chen,[1*]& Yangyang Yang[1*]

[1]Frontiers Science Center for Transformative Molecules, State Key Laboratory of Synergistic Chem-Bio Synthesis, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University; Shanghai 200240, China.

[2]Jiangsu Key Laboratory of Drug Target Research and Drug Discovery of Neurodegenerative Disease, School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, China.

*Corresponding author. Email: yangyang.yang@sjtu.edu.cn, chenxiangyang@sjtu.edu.cn, hmjin@njucm.edu.cn

†These authors contributed equally to this work.

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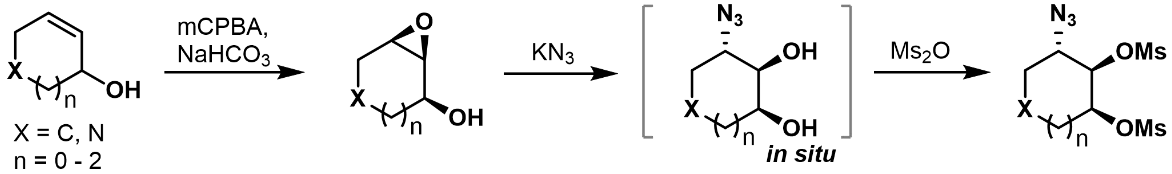
General Materials and Methods

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. All reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Solvents for chromatography were used as supplied by GENERAL-REAGENT®. Reactions were monitored by thin layer chromatography (TLC). TLC was performed with 0.25 mm Merck glass plates (silica gel 60 F254) using shortwave UV light as the visualizing agent, $KMnO_4$, cerium ammonium molybdate (Hanessian's stain), phosphomolybdic acid and heat as developing agents. SiliaFlash® P60 silica gel (particle size: 40–63 μm, 230–400 mesh) was used for flash column chromatography. NMR spectra were recorded on a Bruker AVANCE NEO 400 MHz and Bruker AVANCE NEO 500 MHz. The spectra were calibrated by using residual undeuterated solvents (for ^{1}H NMR) and deuterated solvents (for ^{13}C NMR) as internal references: undeuterated chloroform (δH = 7.26 ppm) and $CDCl_3$ (δC = 77.16 ppm); undeuterated methanol (δH = 3.31 ppm) and methanol-d_4 (δC = 49.00 ppm); undeuterated DMSO-d_6 (δH = 2.50 ppm) and DMSO-d_6 (δC = 39.60 ppm). The following abbreviations areused to designate multiplicities: s = singlet, d = doublet, t = triplet, g= quartet, m = multiplet, br = broad. Melting points (m.p.) were recorded on an SGW X-4B apparatus. Specific rotations were recorded on Anton Paar MCP 5500. High-resolution mass spectra (HRMS) were recorded on a Waters G2-XS/APGC.

General Procedures

General Procedure for Preparation of Azabicycloalkane Precursors

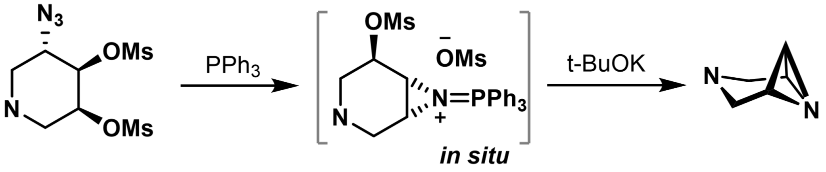


To a flame dried flask equipped with a stirrer bar was added allyl alcohol compounds (1.0 equiv.), $NaHCO_3$ (1.0 equiv.) and DCM (0.5–1.0 M), the reaction system was backfilled with argon three times. The mixture was cooled to 0 °C, mCPBA (1.5 equiv.) was added dropwise via syringe as a solution in DCM (0.5 M). The mixture was then stirred at 0 °C/ room temperature until the completion of the reaction showed by TLC analysis (usually 3–12 h). Water and sat. aq. Na_2SO_3 were added, and the mixture was extracted with EA and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, and the resulting crude was purified by flash column chromatography on silica gel to afford the epoxides.

A flask was charged with epoxides (1.0 equiv.), $MgSO_4$ (4.0 equiv.), KN_3 (4.0 equiv.) and water (0.5 M). The mixture was then stirred at 50 °C until the completion of the reaction showed by TLC analysis (usually 6–12 h). The reaction solution was extracted with EA. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was used directly in further reactions.

To a flame dried flask equipped with a stirrer bar was added azide compounds (1.0 equiv.), triethylamine (4.0 equiv.) and DCM (0.5 M) and the reaction was backfilled with argon three times. The mixture was then cooled to 0 °C, methanesulfonic anhydride (5.0 equiv.) was added dropwise via syringe as a solution in DCM (1.0 M). The mixture was then stirred at room temperature until the completion of the reaction showed by TLC analysis (usually 3 h). The reaction solution was washed with sat. aq. $NaHCO_3$ and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by crystallization to afford the mesylate compounds.

General Procedure A for Preparation of azabicycloalkanes

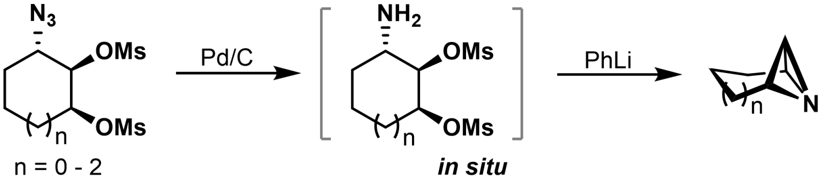


To a flame dried, screw-capped vial equipped with a stirrer bar was added PPh_3 (1.0 equiv.) and MeCN (0.2 M), the reaction vial was backfilled with argon three times. Mesylate compounds (1.0 equiv.) were added dropwise via syringe as a solution in MeCN (0.1 M). The mixture was then stirred at room temperature until the completion of the reaction showed by TLC analysis (usually 3 h). After solvent removed under reduced pressure, the crude product of phosphonium salt was used directly in further reactions.

To a flame dried, screw-capped vial equipped with a stirrer bar was added the crude phosphonium salt (1.0 equiv.) and DCM (0.1 M). The mixture was cooled to -78 °C, t-BuOK (1.5 equiv.) was added dropwise via syringe as a solution in THF (1.0 M). The mixture was then stirred at 0 °C until the completion of the reaction showed by TLC analysis (usually 3 h). The solvent was removed under vacuum and the crude product was purified by sublimation to afford the azabicycloalkanes products.

Note: To eliminate the detrimental effect of triphenylphosphine oxide in subsequent reactions, the phosphonium intermediate was hydrolyzed to an aziridine intermediate using 1M NaOH. After purification of the resulting aziridine compound via flash column chromatography, ring condensation was promoted using potassium tert-butoxide to afford the corresponding azatricycloalkane products.

General Procedure B for Preparation of azabicycloalkanes



To a flame dried, screw-capped vial equipped with a stirrer bar was added mesylate compounds (1.0 equiv.), Pd/C (20-30%) and methanol (0.2 M), the reaction vial was backfilled with hydrogen three times. The mixture was then stirred at room temperature until the completion of the reaction showed by TLC analysis (usually 12 h). After filtration and solvent removed under reduced pressure, the crude product was used directly in further reactions.

To a flame dried, screw-capped vial equipped with a stirrer bar was added the hydrogenated product (1.0 equiv.) and THF (0.1 M). The mixture was cooled to -78 °C, PhLi (2.0 equiv.) was added dropwise via syringe as a solution in Et_2O (0.2 M). The mixture was then stirred at 0 °C until the completion of the reaction showed by TLC analysis (usually 3 h). The solvent was carefully removed under reduced pressure (35 °C 160 mbar) to give the crude product, which was used directly in further reactions.

Reaction Optimizations

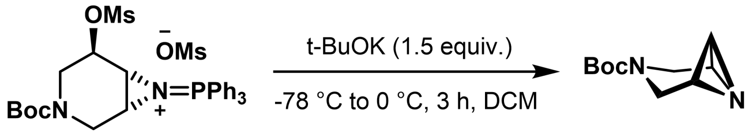


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Table S1. Optimization details of compound 9 to compound 10.

Entry	Deviation from above	Yield (%)[a]
1	None	85
2	LiHMDS in place of t-BuOK	trace
3	MeLi in place of t-BuOK	trace
4	PhLi in place of t-BuOK	12
5	n-BuLi in place of t-BuOK	trace
6	LDA in place of t-BuOK	trace
8	t-BuONa in place of t-BuOK	35
8	Ether in place of DCM	21
9	THF in place of DCM	62
10	with 2.0 equiv. t-BuOK	70

[a] Yield determined by NMR.

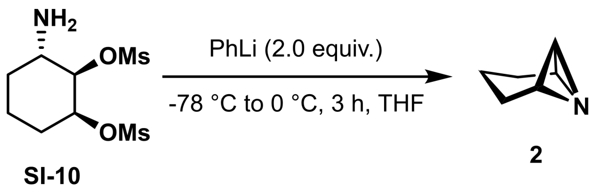

Table S2. Optimization details of compound SI-10 to compound 2.

Entry	Deviation from above	Yield (%)[a]
1	None	72
2	LiHMDS in place of PhLi	45
3	MeLi in place of PhLi	54
4	PhLi in place of PhLi	58
5	n-BuLi in place of PhLi	40
6	t-BuOK in place of PhLi	trace
7	NaH in place of PhLi	ND[b]
8	DBU in place of PhLi	ND
9	KOH in place of PhLi	trace
10	NaOMe in place of PhLi	trace
11	LDA in place of PhLi	47
12	PhLi in place of PhLi	69
13	Reaction performed for 1 h	33
14	Reaction performed for 12 h	20
15	Reaction performed for 24 h	trace

[a] Yield determined by NMR.

[b] Not detected.

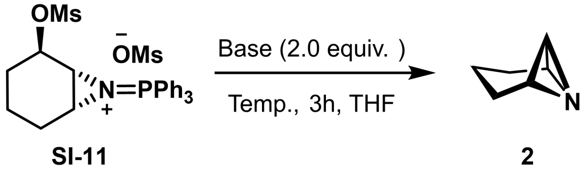

Table S3. Optimization details of compound SI-11 to compound 2.

Entry	Base	Temp.	Yield (%)[a]
1	0.2 M LiHMDS	-78 to 0 °C	ND[b]
2	0.2 M MeLi	-78 to 0 °C	ND
3	0.2 M PhLi	-78 to 0 °C	ND
4	0.2 M n-BuLi	-78 to 0 °C	ND
5	1.0 M LDA	-78 to 0 °C	ND
6	1.0 M t-BuOK	-78 to 0 °C	ND
7	t-BuONa	-78 to 0 °C	ND
8	KOH	Reflux	ND
9	NaOMe	25 °C	ND

[a] Yield determined by NMR.

[b] Not detected.

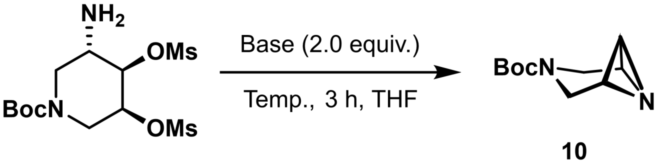

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Table S4. Optimization details for the synthesis of compound 10.

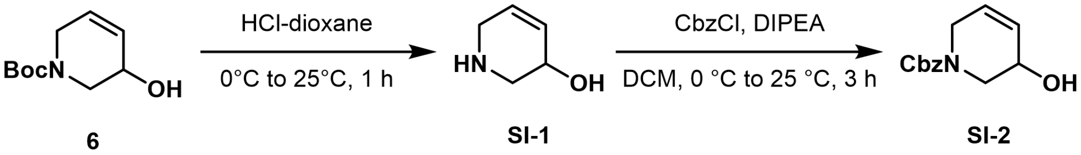
Entry	Base	Temp.	Yield (%)[a]
1	0.2 M LiHMDS	-78 to 0 °C	ND[b]
2	0.2 M MeLi	-78 to 0 °C	ND
3	0.2 M PhLi	-78 to 0 °C	trace
4	0.2 M n-BuLi	-78 to 0 °C	ND
5	1.0 M LDA	-78 to 0 °C	ND
6	1.0 M t-BuOK	-78 to 0 °C	trace
7	t-BuONa	-78 to 0 °C	ND
8	KOH	Reflux	ND
9	NaOMe	25 °C	ND

[a] Yield determined by NMR.

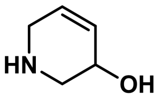
[b] Not detected.

Experimental Procedures and Characterization Data

Procedure for Preparation of 1



Compound SI-1



1,2,3,6-tetrahydropyridin-3-ol **(SI-1)**

HCl-dioxane (56.3 mL, 4M, 225 mmol, 3.0 equiv.) was added to 1-Boc-3-hydroxy-1,2,3,6-tetrahydro-pyridine (**6**) (15.0 g, 75 mmol, 1.0 equiv.) in a 250 mL vial at 0 °C and stirred at 25 °C for 1 hour. The reaction solution was filtered through a Büchner funnel and rinsed with 1,4-dioxane to afford 6.68g (90%) of the title compound **SI-1**.

Physical State: yellow solid.

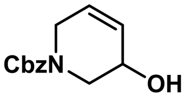
m.p. 99-100 °C.

^{1}H NMR (500 MHz, Methanol-*d*$_4$): δ 6.06 (ddt, *J* = 10.6, 4.5, 2.2 Hz, 1H), 5.90 (dtd, *J* = 10.5, 3.2, 1.0 Hz, 1H), 4.36 (tdt, *J* = 4.0, 2.7, 1.3 Hz, 1H), 3.67 (dq, *J* = 4.0, 2.0 Hz, 2H), 3.33 (dd, *J* = 12.3, 3.5 Hz, 1H), 3.24 (dd, *J* = 12.7, 4.0 Hz, 1H).

^{13}C NMR (126 MHz, Methanol-*d*$_4$): δ 128.24, 122.03, 59.06, 47.29, 41.54.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_5H_{10}NO^+$ 100.0762, found 100.0759.

Compound SI-2



benzyl 3-hydroxy-3,6-dihydropyridine-1(2H)-carboxylate **(SI-2)**

To a solution of **SI-1** (5.0 g, 50 mmol, 1.0 equiv.) in DCM (100 mL) was added DIPEA (34.8 mL, 200 mmol, 4.0 equiv.) and the reaction vessel was backfilled with argon three times.

After cooling the mixture to 0 °C, CbzCl (10.5 mL, 75 mmol, 1.5 equiv.) was added dropwise via syringe, and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. To the reaction solution, sat. aq. NH_4Cl (50 mL) was added. The mixture was extracted with DCM (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 8.74 g (75%) of the title compound **SI-2**.

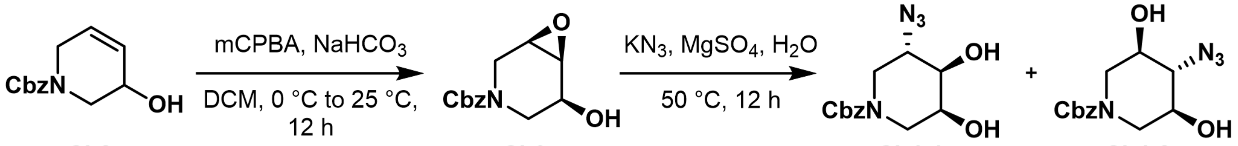
Physical State: colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 5H), 5.91 (dd, J = 10.3, 3.1 Hz, 1H), 5.81 (d, J = 33.7 Hz, 1H), 5.15 (s, 2H), 4.21 (d, J = 27.3 Hz, 1H), 4.02 (d, J = 16.1 Hz, 1H), 3.88 (d, J = 19.4 Hz, 1H), 3.76 – 3.44 (m, 2H), 2.53 – 2.05 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.83, 136.52, 128.54, 128.11, 127.97, 127.38, 126.45, 67.36, 63.45, 47.96, 47.63, 43.36.

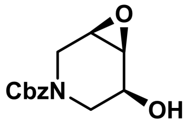
HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{15}NNaO_3^+$ 256.0950, found 256.0949.

TLC: R_f = 0.3 (2:1 hexanes : ethyl acetate).



SI-2 SI-3 SI-4-1 SI-4-2

Compound SI-3



***benzyl (1R,5S,6S)-5-hydroxy-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate* (SI-3)**

To a solution of **SI-2** (23.3 g, 100 mmol, 1.0 equiv.) in DCM (100 mL) was added $NaHCO_3$ (8.4 g, 100 mmol, 1.0 equiv.) and the reaction vessel was backfilled with argon three times. After cooling the mixture to 0 °C, 3-chloroperbenzoic acid (85%; 30.35 g, 150 mmol, 1.5 equiv.) was added dropwise via syringe as a solution in DCM (300 mL), and the reaction solution was stirred at 25 °C for 12 hours under an argon atmosphere. Half of the solvent was evaporated. To the reaction solution, sat. aq. Na_2SO_3 (40 mL) was added. The mixture was extracted with DCM (3×200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 19.92 g (80%) of the title compound **SI-3**.

Physical State: colorless oil.

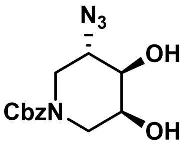
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.23 (m, 5H), 5.09 (s, 2H), 4.07 – 3.94 (m, 1H), 3.93 – 3.65 (m, 2H), 3.67 – 3.45 (m, 2H), 3.43 – 3.31 (m, 2H), 3.07 – 2.92 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.45, 136.30, 128.56, 128.20, 127.98, 67.51, 64.94, 54.26, 53.34, 52.90, 43.94, 43.52, 41.34.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{15}NNaO_4^+$ 272.0899, found 272.0898.

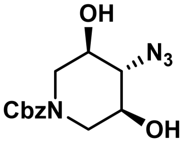
TLC: $R_f = 0.3$ (2:1 hexanes : ethyl acetate).

Compound SI-4-1



benzyl (3S,4R,5S)-3-azido-4,5-dihydroxypiperidine-1-carboxylate **(SI-4-1)**

Compound SI-4-2



benzyl (3R,4r,5S)-4-azido-3,5-dihydroxypiperidine-1-carboxylate **(SI-4-2)**

To a solution of **SI-3** (5.0 g, 20 mmol, 1.0 equiv.) in water (100 mL) were added $MgSO_4$ (9.6 g, 80 mmol, 4.0 equiv.) and potassium azide (6.5 g, 80 mmol, 4.0 equiv.). The reaction solution was stirred at 50 °C for 12 hours. The reaction solution was extracted with EA (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 3.85 g (66%) of the title compound **SI-4-1** and 1.28 g (22%)

of the title compound **SI-4-2**.

SI-4-1:

Physical State: white solid.

m.p. 105-106 °C.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.40 – 7.29 (m, 5H), 5.14 (d, *J* = 9.6 Hz, 2H), 4.26 – 3.91 (m, 3H), 3.70 (d, *J* = 11.9 Hz, 1H), 3.57 (s, 1H), 3.46 – 3.33 (m, 1H), 3.21 (s, 1H), 3.10 (dd, *J* = 14.2, 2.3 Hz, 1H), 2.87 (d, *J* = 37.7 Hz, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 156.10, 136.14, 128.59, 128.25, 127.92, 77.32, 77.06, 76.81, 73.36, 67.86, 67.26, 59.38, 47.26, 45.20.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{13}H_{16}N_4NaO_4^+$ 315.1069, found 315.1069.

TLC: R*f* = 0.3 (1:1 hexanes : ethyl acetate).

SI-4-2:

Physical State: white solid.

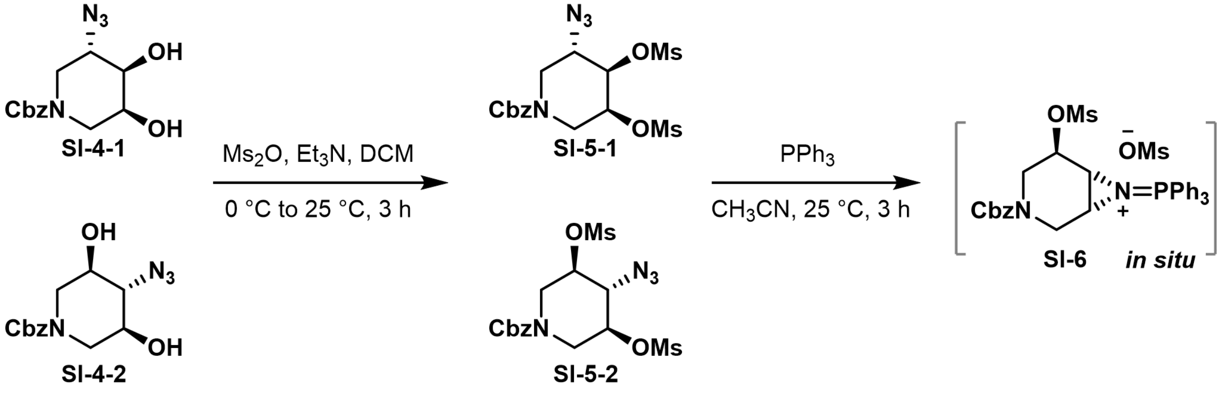
m.p. 170-172 °C.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.43 – 7.25 (m, 5H), 5.64 – 5.55 (m, 2H), 5.06 (s, 2H), 4.09 – 3.89 (m, 2H), 3.26 – 3.11 (m, 3H), 2.72 – 2.51 (m, 2H).

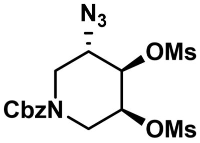
^{13}C NMR (101 MHz, DMSO-*d*$_6$): δ 154.70, 137.15, 128.92, 128.41, 128.08, 72.44, 68.30, 67.01, 48.85.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{13}H_{16}N_4NaO_4^+$ 315.1069, found 315.1067.

TLC: R*f* = 0.2 (1:1 hexanes : ethyl acetate).



Compound SI-5-1



benzyl (3S,4R,5S)-3-azido-4,5-bis((methylsulfonyl)oxy)piperidine-1-carboxylate **(SI-5-1)**

To a solution of **SI-4-1** (2.92 g, 10 mmol, 1.0 equiv.) in DCM (50 mL) was added Et_3N (5.55 mL, 40 mmol, 4.0 equiv.) and the reaction vessel was backfilled with argon three times. After cooling the mixture to 0 °C, methanesulfonic anhydride (8.7 g, 50 mmol, 5.0 equiv.) was added dropwise via syringe as a solution in DCM (50 mL), and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. The reaction solution was washed with sat. aq. $NaHCO_3$ (30 mL) and extracted with DCM (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 3.85 g (86%) of the title compound **SI-5-1**.

Physical State: colorless oil.

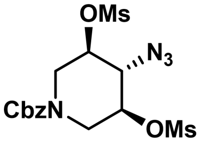
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 – 7.29 (m, 5H), 5.16 (d, J = 2.4 Hz, 2H), 5.03 (d, *J* = 42.7 Hz, 1H), 4.68 – 4.19 (m, 3H), 3.99 – 3.84 (m, 1H), 3.19 (s, 4H), 3.02 (d, *J* = 35.7 Hz, 4H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.29, 135.84, 128.64, 128.41, 128.17, 79.21, 78.27, 75.54, 74.53, 68.24, 56.89, 56.34, 46.75, 45.82, 45.58, 45.41, 38.82, 38.63, 38.41.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{20}N_4NaO_8S_2^+$ 471.0620, found 471.0620.

TLC: R_f = 0.3 (2:1 hexanes : ethyl acetate).

Compound SI-5-2



benzyl (3R,4r,5S)-4-azido-3,5-bis((methylsulfonyl)oxy)piperidine-1-carboxylate **(SI-5-2)**

To a solution of **SI-4-2** (2.92 g, 10 mmol, 1.0 equiv.) in DCM (50 mL) was added Et_3N (5.55

mL, 40 mmol, 4.0 equiv.) and the reaction vessel was backfilled with argon three times. After cooling the mixture to 0 °C, methanesulfonic anhydride (8.7 g, 50 mmol, 5.0 equiv.) was added dropwise via syringe as a solution in DCM (50 mL), and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. The reaction solution was washed with sat. aq. $NaHCO_3$ (30 mL) and extracted with DCM (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 3.94 g (88%) of the title compound **SI-5-2**.

Physical State: colorless oil.

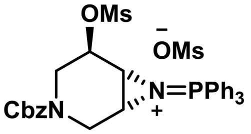
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.28 (m, 5H), 5.15 (s, 2H), 4.50 (dd, *J* = 13.9, 4.9 Hz, 2H), 4.38 (s, 2H), 3.71 (t, *J* = 9.0 Hz, 1H), 3.12 (s, 6H), 3.08 – 2.96 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.42, 135.74, 128.65, 128.41, 128.03, 74.98, 68.17, 65.25, 46.27, 38.49.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{20}N_4NaO_8S_2^+$ 471.0620, found 471.0619.

TLC: R*f* = 0.3 (2:1 hexanes : ethyl acetate).

Compound SI-6



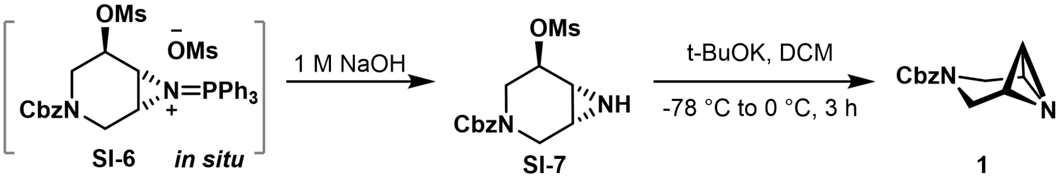
(1R,5R,6R)-3-((benzyloxy)carbonyl)-5-((methylsulfonyl)oxy)-7-(triphenyl-λ^5-phosphaneylidene) -3,7-diazabicyclo[4.1.0]heptan-7-ium$^+$methanesulfonate$^-$ **(SI-6)**

The reaction vessel was added a solution of PPh_3 (2.62 g, 10 mmol, 1.0 equiv.) in MeCN (50 mL) and backfilled with argon three times. The solution of **SI-5-1/SI-5-2** (3.13 g, 10 mmol, 1.0 equiv.) in MeCN (100 mL) was added dropwise via syringe, and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo and directly used for the next step. Yield: 92% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard). *Note: the mixture was used directly* *without separation.*

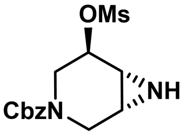
Physical State: colorless oil.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{36}N_2O_8PS_2^+$ 683.1651, found 683.1649.

TLC: $R_f = 0.4$ (10:1 dichloromethane : methanol).



Compound SI-7



***benzyl (1R,5R,6R)-5-((methylsulfonyl)oxy)-3,7-diazabicyclo[4.1.0]heptane-3-carboxylate* (SI-7)**

To a solution of **SI-6** (6.3 g, 9.2 mmol, 1.0 equiv.) in DCM (20 mL) was added 1 M NaOH aq. (20 mL). The reaction solution was stirred at 25 °C for 5 minutes and the mixture was extracted with DCM (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (dichloromethane: ether, 1:1) on silica gel to afford 2.55 g (82%) of the title compound **SI-7**.

Physical State: colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.28 (m, 5H), 5.30 – 4.95 (m, 3H), 4.17 – 3.85 (m, 2H), 3.56 (t, J = 15.0 Hz, 1H), 3.33 (dd, J = 27.4, 14.5 Hz, 1H), 3.07 (s, 1.5H), 2.85 (s, 1.5H), 2.70 – 2.49 (m, 2H). *Note: Two isomers with a 2:3 ratio, attributed to rotational isomerization of amide, were observed.*

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.78, 155.35, 136.47, 128.57, 128.15, 127.93, 74.89, 73.95, 67.46, 67.37, 42.25, 42.06, 41.93, 41.49, 38.97, 38.45, 30.62, 30.42, 28.28, 27.87.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{19}N_2O_5S^+$ 327.1015, found 327.1014.

TLC: R_f = 0.3 (1:1 dichloromethane : ether).

Compound 1

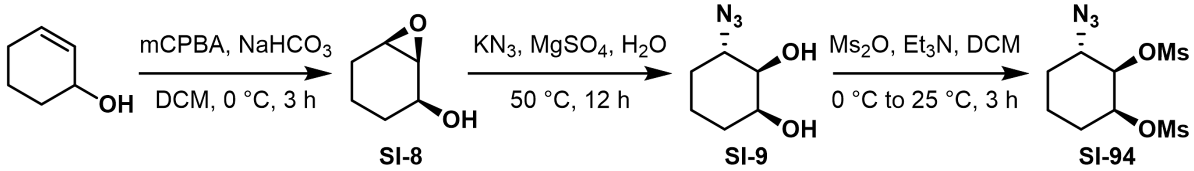
benzyl 1,4-diazatricyclo[4.1.0.0^{2,7}]heptane-4-carboxylate **(1)**

The reaction vessel was added a solution of **SI-7** (326 mg, 1 mmol, 1.0 equiv.) in DCM (10 mL) and backfilled with argon three times. After cooling the mixture to -78 °C, t-BuOK (1.0 mol/L, THF, 1.5 mL, 1.5 mmol, 1.5 equiv.) was added dropwise via syringe, and the reaction solution was stirred at 0 ℃ for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo, after dissolution in MeCN and filtration via diatomaceous earth, the crude product was used directly in further reactions. Yield: 78% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard).

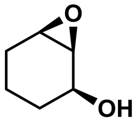
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.26 (m, 5H), 5.13 (d, J = 2.4 Hz, 2H), 3.70 (dq, J = 13.9, 2.5 Hz, 2H), 3.26 – 3.12 (m, 4H), 2.73 (p, J = 2.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.16, 136.50, 128.53, 128.13, 127.99, 67.12, 58.15, 57.79, 36.72, 36.34, 25.87.

Procedure for Preparation of 2



Compound SI-8



(1S,2S,6R)-7-oxabicyclo[4.1.0]heptan-2-ol **(SI-8)**

To a solution of cyclohex-2-en-1-ol (19.6 g, 200 mmol, 1.0 equiv.) in DCM (200 mL) was added $NaHCO_3$ (16.8 g, 200 mmol, 1.0 equiv.). The reaction vessel was then backfilled with argon three times. After cooling the mixture to 0 °C, 3-chloroperbenzoic acid (85%; 60.7 g, 300 mmol, 1.5 equiv.) was added dropwise via syringe as a solution in DCM (400 mL), and the reaction solution was stirred at 0 °C for 3 hours under an argon atmosphere before warmed to room temperature. Half of the solvent was evaporated. To the reaction solution, sat. aq. Na_2SO_3 (80 mL) was added. The mixture was then extracted with DCM (3×200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 18.47 g (81%) of the title compound **SI-8**.

Physical State: colorless oil.

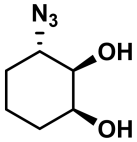
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.86 (ddd, *J* = 8.2, 5.2, 2.5 Hz, 1H), 3.31 (s, br., 1H), 3.18 (ddd, *J* = 6.6, 4.5, 2.7 Hz, 2H), 1.71 – 1.62 (m, 2H), 1.50 – 1.37 (m, 2H), 1.36 – 1.26 (m, 1H), 1.19 – 1.04 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ67.32, 55.59, 55.23, 28.29, 22.82, 18.85.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_6H_{10}NaO_2^+$ 137.0578, found 137.0579.

TLC: R_f = 0.3 (3:1 hexanes : ethyl acetate).

Compound SI-9



(1S,2R,3S)-3-azidocyclohexane-1,2-diol **(SI-9)**

To a solution of **SI-8** (11.4 g, 100 mmol, 1.0 equiv.) in water (200 mL) were added $MgSO_4$ (30.0 g, 250 mmol, 2.5 equiv.) and potassium azide (20.3 g, 250 mmol, 2.5 equiv.). The reaction solution was stirred at 50 °C for 12 hours. The reaction solution was extracted with EA (3×300 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by crystallization (ether/methanol) to afford 13.03 g (83%) of the title compound **SI-9**.

Physical State: white solid.

m.p. 70-71 °C.

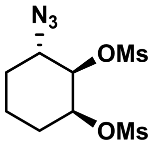
^{1}H NMR (400 MHz, CDCl$_3$): δ 4.01 (q, *J* = 3.4 Hz, 1H), 3.84 (s, br., 1H), 3.59 (td, *J* = 10.1, 4.3 Hz, 1H), 3.47 (s, br., 1H), 3.38 (dd, *J* = 9.4, 2.9 Hz, 1H), 1.96 (dq, *J* = 13.3, 5.1, 4.5 Hz, 1H), 1.83 (dd, *J* = 14.2, 4.4 Hz, 1H), 1.65 (qt, *J* = 12.6, 3.7 Hz, 1H), 1.50 (dt, *J* = 13.7, 4.0 Hz, 1H), 1.40 (tt, *J* = 13.4, 3.6 Hz, 1H), 1.28 (qd, *J* = 12.3, 3.9 Hz, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 74.75, 69.54, 61.92, 30.11, 29.17, 18.20.

HRMS (*m/z*): $[M-N_2+H]^+$ calcd for $C_6H_{12}NO_2^+$ 130.0868, found 130.0866.

TLC: R_f = 0.3 (1:1 hexanes : ethyl acetate).

Compound SI-94



(1S,2R,3S)-3-azidocyclohexane-1,2-diyl dimethanesulfonate **(SI-94)**

To a solution of **SI-9** (7.85 g, 50 mmol, 1.0 equiv.) in DCM (200 mL) was added Et_3N (27.7 mL, 200 mmol, 4.0 equiv.). The reaction vessel was then backfilled with argon three times. After cooling the mixture to 0 °C, methanesulfonic anhydride (43.5 g, 250 mmol, 5.0 equiv.) was added dropwise via syringe as a solution in DCM (200 mL), and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. The reaction solution was washed with sat. aq. $NaHCO_3$ (100 mL) and extracted with DCM (3×200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by crystallization (ether/methanol) to afford 12.52 g (80%) of the title compound **SI-94**.

Physical State: white solid.

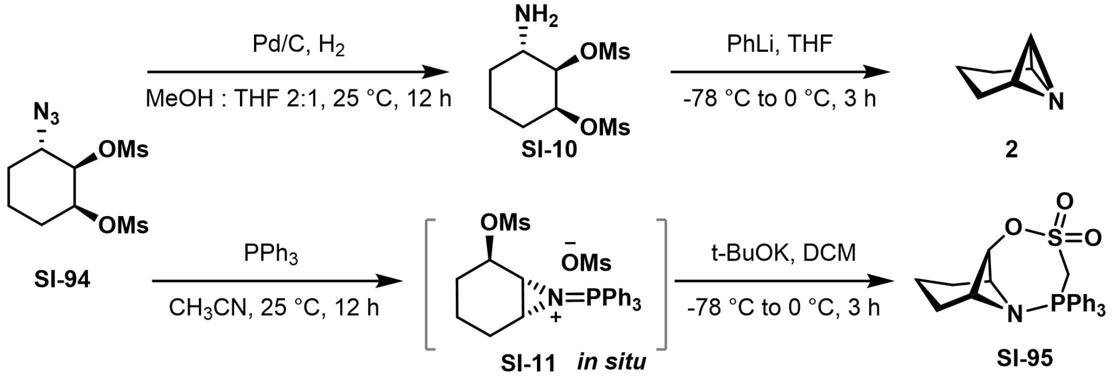
m.p. 83-85 ℃.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.08 (dt, *J* = 4.9, 2.6 Hz, 1H), 4.41 (dd, *J* = 9.7, 3.0 Hz, 1H), 3.87 (td, *J* = 10.0, 5.0 Hz, 1H), 3.18 (s, 3H), 3.12 (s, 3H), 2.24 – 2.13 (m, 2H), 1.86 – 1.58 (m, 3H), 1.49 – 1.39 (m, 1H).

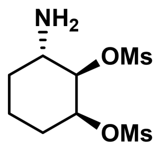
^{13}C NMR (101 MHz, $CDCl_3$): δ 81.00, 79.36, 59.00, 38.53, 38.41, 29.66, 29.46, 17.54.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_8H_{15}N_3NaO_6S_2^+$ 336.0300, found 336.0297.

TLC: R_f = 0.3 (3:1 hexanes : ethyl acetate).



Compound SI-10



***(1S,2R,3S)-3-aminocyclohexane-1,2-diyl dimethanesulfonate* (SI-10)**

To a solution of **SI-94** (3.13 g, 10 mmol, 1.0 equiv.) in MeOH (50mL) and THF (25mL) was added 30% Pd/C (940 mg), and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was purified by flash column chromatography (dichloromethane: methanol, 20:1) on silica gel to afford 2.44 g (85%) of the title compound **SI-10**.

Physical State: white solid.

m.p. 112-114 °C.

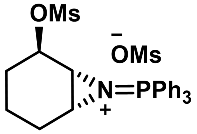
^{1}H NMR (500 MHz, CDCl$_3$): δ 5.14 (dd, *J* = 4.7, 2.5 Hz, 1H), 4.30 (dd, *J* = 9.6, 2.9 Hz, 1H), 3.22-3.16 (m, 4H), 3.09 (s, 3H), 2.20 – 2.12 (m, 1H), 2.04 – 1.97 (m, 1H), 1.76 – 1.59 (m, 3H), 1.40 (s, 2H), 1.31 – 1.19 (m, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 84.99, 79.30, 48.82, 38.66, 38.52, 32.94, 30.21, 18.29.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_8H_{18}NO_6S_2^+$ 288.0576, found 288.0575.

TLC: R_f = 0.3 (20:1 dichloromethane : methanol).

Compound SI-11



(1R,2R,6R)-2-((methylsulfonyl)oxy)-7-(triphenyl-λ^5-phosphaneylidene)-7-azabicyclo[4.1.0] heptan-7-ium$^+$methanesulfonate$^-$ **(SI-11)**

The reaction vessel was added a solution of PPh$_3$ (2.62 g, 10 mmol, 1.0 equiv.) in MeCN (50 mL) and backfilled with argon three times. The solution of **SI-94** (3.13 g, 10 mmol, 1.0 equiv.) in MeCN (100 mL) was added dropwise via syringe, and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo and directly used for the next step. Yield: 83% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard).

Physical State: colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.87 – 7.61 (m, 15H), 5.26 – 5.17 (m, 1H), 3.12 (s, 3H), 2.88 – 2.82 (m, 1H), 2.82 – 2.78 (m, 1H), 2.60 (s, 3H), 2.19 (tt, *J* = 15.2, 4.8 Hz, 2H), 1.94 (tt, *J* = 10.9, 4.4 Hz, 1H), 1.66 (hept, *J* = 4.4 Hz, 2H), 1.53 – 1.39 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 136.05, 136.02, 133.54, 133.44, 130.70, 130.57, 118.42, 117.43, 74.13, 74.08, 41.34, 41.26, 39.98, 39.90, 39.43, 38.14, 27.06, 22.95, 14.57.

^{31}P NMR (162 MHz, CDCl$_3$): δ 49.08.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{26}H_{31}NO_6PS_2^+$ 548.1330, found 548.1331.

TLC: R$_f$ = 0.5 (10:1 dichloromethane : methanol).

Compound 2

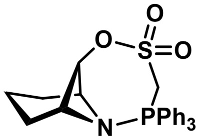
1-azatricyclo[4.1.0.0^{2,7}]heptane **(2)**

The reaction vessel was added a solution of **SI-10** (2.87 g, 10 mmol, 1.0 equiv.) in THF (100 mL) and backfilled with argon three times. After cooling the mixture to -78 °C, PhLi (0.2 mol/L, ether solution, 100 mL, 20 mmol, 2.0 equiv.) was added dropwise via syringe, and the reaction solution was stirred at 0 °C for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo (35 °C, 160 mbar), after dissolution in MeCN and filtration via diatomaceous earth, the crude product was used directly in further reactions. Yield: 69% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard).

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.12 (dt, *J* = 3.0, 1.4 Hz, 2H), 2.57 (p, *J* = 1.9 Hz, 1H), 1.60 – 1.49 (m, 4H), 1.41 – 1.37 (m, 1H), 1.35 – 1.28 (m, 1H). *Note: The ^{1}H NMR of the crude was made.*

Note: Preparation of 0.2 mol/L PhLi solution in ether: Prepared a 250 mL dried vial and backfilled with argon three times and added anhydrous ether (80 mL) dropwise via syringe. After cooling the mixture to 0 °C, 1 mol/L PhLi (20 mL, 20mmol) was added dropwise via syringe.

Compound SI-95

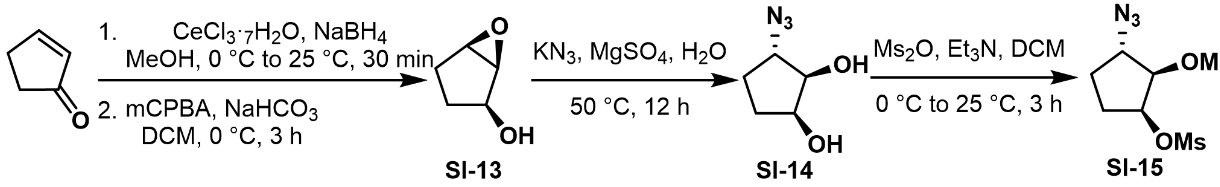


(1R,2r,7s,8S)-3,3,3-triphenyl-6-oxa-5-thia-2-aza-3λ^5-phosphatricyclo[5.4.0.0^{2,8}]undecane 5,5-dioxide **(SI-95)**

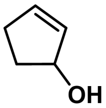
The reaction vessel was added a solution of **SI-11**(547 mg, 1 mmol, 1.0 equiv.) in DCM (10 mL) and backfilled with argon three times. After cooling the mixture to -78 °C, t-BuOK (1.0 mol/L, THF, 1.5 mL, 1.5 mmol, 1.5 equiv.) was added dropwise via syringe, and the reaction solution was stirred at 0 ℃ for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo to afford the title compound **SI-95**. Yield: 70% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.71 – 7.49 (m, 15H), 4.84 (p, *J* = 2.8 Hz, 1H), 3.44 (d, *J* = 13.4 Hz, 1H), 3.33 (dd, *J* = 13.4, 7.1 Hz, 1H), 3.06 (dddd, *J* = 19.8, 10.4, 8.7, 4.1 Hz, 1H), 2.57 (ddd, *J* = 10.4, 6.8, 3.6 Hz, 1H), 2.10 (dt, *J* = 14.9, 2.4 Hz, 1H), 1.73 (qd, *J* = 5.1, 1.9 Hz, 1H), 1.65 – 1.35 (m, 4H). *Note: The ^{1}H NMR of the crude was made.*

Procedure for Preparation of 3



Compound SI-12



cyclopent-2-en-1-ol **(SI-12)**

To a solution of 2-cyclopenten-1-one (10.25 g, 125 mmol, 1.0 equiv.) in MeOH (300 mL) was added cerium(III) chloride heptahydrate (30.8 g, 125 mmol, 1.0 equiv.) and stirred to dissolve it. After cooling the mixture to 0 °C, $NaBH_4$ (9.5 g, 250 mmol, 2 equiv.) was added slowly in 30 minutes, and the reaction solution was stirred at 25 ℃ for 30 minutes. To the reaction solution, sat. aq. NaCl (100 mL) was added and concentrated in vacuo (35 ℃, 80 mbar), and then extracted with ether (3×300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo (35 °C, 80 mbar) to afford 8.40 g (80%) of the title compound **SI-12**.

Physical State: colorless oil.

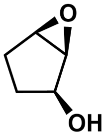
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (dtd, *J* = 5.7, 2.3, 1.1 Hz, 1H), 5.72 (dq, *J* = 6.1, 2.1 Hz, 1H), 4.74 (ddp, *J* = 7.3, 3.6, 1.1 Hz, 1H), 3.28 (s, 1H), 2.40 (tddd, *J* = 11.0, 6.6, 4.8, 2.8 Hz, 1H), 2.24 – 2.05 (m, 2H), 1.65 – 1.52 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 134.58, 133.31, 77.08, 32.95, 30.92.

HRMS (*m/z*): $[M-H]^-$ calcd for $C_5H_7O^-$ 83.0497, found 83.0498.

TLC: R_f = 0.3 (5:1 hexanes : ethyl acetate).

Compound SI-13



(1S,2S,5R)-6-oxabicyclo[3.1.0]hexan-2-ol **(SI-13)**

To a solution of **SI-12** (8.4 g, 100 mmol, 1.0 equiv.) in DCM (100 mL) was added $NaHCO_3$ (8.4 g, 100 mmol, 1 equiv.). The reaction vessel was then backfilled with argon three times. After cooling the mixture to 0 °C, 3-chloroperbenzoic acid (85%; 30.4 g, 150 mmol, 1.5 equiv.) was added dropwise via syringe as a solution in DCM (200 mL), and the reaction solution was stirred at 0 °C for 3 hours under an argon atmosphere before warmed to room temperature. Half of the solvent was evaporated. To the reaction solution, sat. aq. Na_2SO_3 (40 mL) was added. The mixture was then extracted with DCM (3×200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 6.30 g (63%) of the title compound **SI-13**.

Physical State: colorless oil.

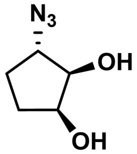
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (td, J = 8.1, 1.5 Hz, 1H), 3.50 – 3.38 (m, 2H), 2.70 (s, br., 1H), 2.06 (dd, J = 14.4, 8.4 Hz, 1H), 1.90 (dt, J = 13.0, 8.2 Hz, 1H), 1.62 (dddd, J = 14.3, 10.1, 8.5, 1.3 Hz, 1H), 1.23 (ddd, J = 10.3, 4.4, 2.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ73.50, 58.92, 56.22, 26.84, 25.91.

HRMS (*m/z*): $[M-H]^-$ calcd for $C_5H_7O_2^-$ 99.0446, found 99.0445.

TLC: R_f = 0.3 (1:1 hexanes : ethyl acetate).

Compound SI-14



(1S,2R,3S)-3-azidocyclopentane-1,2-diol **(SI-14)**

To a solution of **SI-13** (5.0 g, 50 mmol, 1.0 equiv.) in water (100 mL) were added $MgSO_4$ (18.0 g, 150 mmol, 3.0 equiv.) and potassium azide (12.2 g, 150 mmol, 3.0 equiv.). The reaction solution was stirred at 50 °C for 12 hours. The reaction solution was extracted with EA (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 4.43 g (62%) of the title compound **SI-14**.

Physical State: colorless oil.

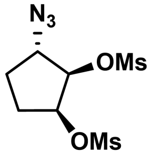
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10 (dt, *J* = 7.8, 3.9 Hz, 1H), 3.95 (s, br., 1H), 3.87 – 3.75 (m, 2H), 3.54 (s, br., 1H), 2.23 – 2.09 (m, 1H), 2.03 (ddt, *J* = 15.5, 10.9, 5.7 Hz, 1H), 1.74 – 1.61 (m, 1H), 1.50 (ddt, *J* = 13.6, 9.9, 6.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 78.30, 71.47, 65.64, 28.96, 25.71.

HRMS (*m/z*): $[M\text{-}N_2+H]^+$ calcd for $C_5H_{10}NO_2^+$ 116.0712, found 116.0711.

TLC: R$_f$ = 0.3 (1:1 hexanes : ethyl acetate).

Compound SI-15



(1S,2R,3S)-3-azidocyclopentane-1,2-diyl dimethanesulfonate **(SI-15)**

To a solution of **SI-14** (4.3 g, 30 mmol, 1.0 equiv.) in DCM (100 mL) was added Et_3N (16.6 mL, 120 mmol, 4.0 equiv.). The reaction vessel was then backfilled with argon three times. After cooling the mixture to 0 °C, methanesulfonic anhydride (26.1 g, 150 mmol, 5.0 equiv.) was added dropwise via syringe as a solution in DCM (100 mL), and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. The reaction solution was washed with sat. aq. $NaHCO_3$ (60 mL) and extracted with DCM (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by crystallization (ether/methanol) to afford 5.38 g (60%) of the title compound **SI-15**.

Physical State: white solid.

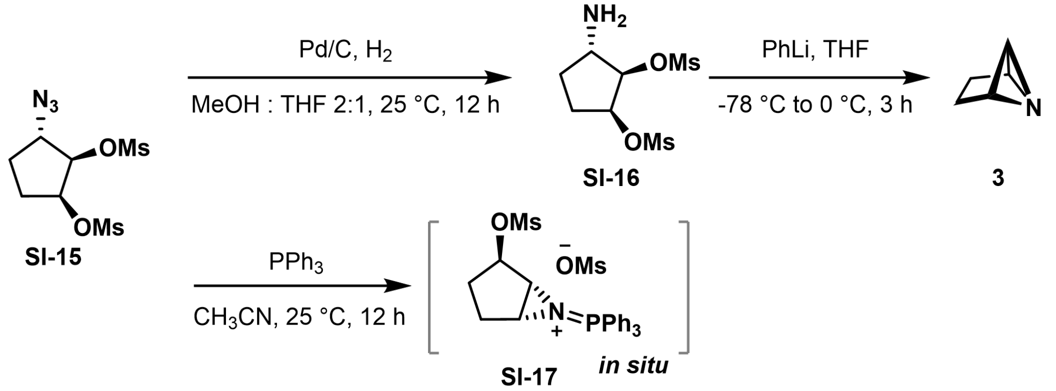
m.p. 51-53 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.08 (td, *J* = 5.3, 2.8 Hz, 1H), 4.67 (dd, *J* = 7.8, 4.4 Hz, 1H), 4.20 (dt, *J* = 9.1, 7.3 Hz, 1H), 3.15 (s, 3H), 3.08 (s, 3H), 2.42 – 2.31 (m, 1H), 2.24 (ddt, *J* = 16.3, 11.3, 5.8 Hz, 1H), 2.11 (dddd, *J* = 15.3, 10.0, 5.4, 2.7 Hz, 1H), 1.67 (dddd, *J* = 13.9, 10.5, 6.9, 5.4 Hz, 1H).

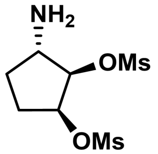
^{13}C NMR (126 MHz, CDCl$_3$): δ 82.57, 79.45, 62.37, 38.52, 38.51, 27.59, 24.76.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_7H_{13}N_3NaO_6S_2^+$ 322.0143, found 322.0142.

TLC: R$_f$ = 0.3 (3:1 hexanes : ethyl acetate).



Compound SI-16



***(1S,2R,3S)-3-aminocyclopentane-1,2-diyl dimethanesulfonate* (SI-16)**

To a solution of **SI-15** (600 mg, 2 mmol, 1.0 equiv.) in MeOH (10mL) and THF (5mL) was added 30% Pd/C (180 mg), and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was purified by flash column chromatography (dichloromethane: methanol, 10:1) on silica gel to afford 453.2 mg (83%) of the title compound **SI-16**.

Physical State: white solid.

m.p. 108-110 °C.

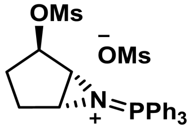
^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 5.09 (dt, *J* = 6.1, 4.2 Hz, 1H), 4.59 (dd, *J* = 6.8, 4.4 Hz, 1H), 3.34 – 3.29 (m, 1H), 3.27 (s, 3H), 3.18 (s, 3H), 2.21 – 2.12 (m, 1H), 2.06 (dddd, *J* = 13.5, 10.1, 8.5, 5.1 Hz, 1H), 1.81 (dddd, *J* = 14.1, 10.1, 6.3, 4.0 Hz, 1H), 1.30 (ddt, *J* = 13.3, 10.3, 6.6 Hz, 1H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 90.57, 85.15, 59.23, 43.05, 42.97, 32.79, 32.09.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_7H_{16}NO_6S_2^+$ 274.0419, found 274.0419.

TLC: $R_f = 0.3$ (10:1 dichloromethane : methanol).

Compound SI-17



(1R,2R,5R)-2-((methylsulfonyl)oxy)-6-(triphenyl-λ^5-phosphaneylidene)-6-azabicyclo[3.1.0] hexan-6-ium$^+$methanesulfonate$^-$ **(SI-17)**

The reaction vessel was added a solution of PPh_3 (262 mg, 1 mmol, 1.0 equiv.) in MeCN (5 mL) and backfilled with argon three times. The solution of **SI-15** (300 mg, 1 mmol, 1.0 equiv.) in MeCN (10 mL) was added dropwise via syringe, and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo and directly used for the next step. Yield: 78% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard).

Physical State: colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.87 – 7.65 (m, 15H), 5.56 (d, J = 4.3 Hz, 1H), 3.40 (dd, J = 15.2, 4.1 Hz, 1H), 3.23 (ddd, J = 13.5, 4.0, 1.8 Hz, 1H), 3.17 (s, 3H), 2.56 (s, 3H), 2.33 – 2.19 (m, 2H), 2.17 – 2.04 (m, 2H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 136.09, 136.06, 133.31, 133.20, 130.81, 130.68, 118.80, 117.81, 80.57, 80.50, 53.57, 45.58, 39.43, 38.42, 28.25, 25.49.

^{31}P NMR (162 MHz, CDCl$_3$): δ 46.05.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{29}NO_6PS_2^+$ 534.1174, found 534.1173.

TLC: $R_f = 0.3$ (10:1 dichloromethane : methanol).

Note: The product in DCM (10 mL) was added t-BuOK (1.0 mol/L, THF, 1.5 mL, 1.5 mmol, 1.5 equiv.) dropwise via syringe at -78 °C, and the reaction solution was stirred at 0 °C for 3 hours under an argon atmosphere. But the compound ***3*** *was not obtained.*

Compound 3

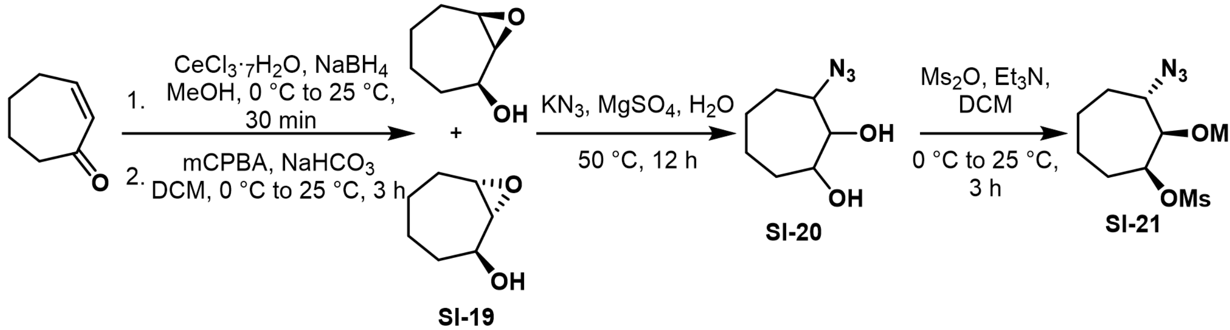
***1-azatricyclo[3.1.0.0^{2,6}]hexane* (3)**

The reaction vessel was added a solution of **SI-16** (273 mg, 1 mmol, 1.0 equiv.) in THF (10 mL) and backfilled with argon three times. After cooling the mixture to -78 °C, PhLi (0.2 mol/L, ether solution, 10 mL, 2 mmol, 2.0 equiv.) was added dropwise via syringe, and the reaction solution was stirred at 0 °C for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo (35 °C, 160 mbar). After dissolution in MeCN and filtration via diatomaceous earth, the crude product was used directly in further reactions. Yield: 65% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard).

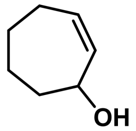
^{1}H NMR (500 MHz, CDCl$_3$): δ 2.77 (s, 1H), 2.45 (s, 1H), 1.50 – 1.45 (m, 1H), 1.39 – 1.33 (m, 1H). *Note: The ^{1}H NMR of the crude was made.*

Note: Preparation of 0.2 mol/L PhLi solution in ether: Prepared a 250 mL dried vial and backfilled with argon three times and added anhydrous ether (80 mL). After cooling the mixture to 0 °C, 1 mol/L PhLi (20 mL, 20mmol) was added dropwise via syringe.

Procedure for Preparation of 4



Compound SI-18



cyclohept-2-en-1-ol **(SI-18)**

To a solution of 2-cyclohepten-1-one (11.0 g, 100 mmol, 1.0 equiv.) in MeOH (300 mL) was added cerium(III) chloride heptahydrate (24.6 g, 100 mmol, 1.0 equiv.) and stirred to dissolve it. After cooling the mixture to 0 °C, $NaBH_4$ (7.6 g, 200 mmol, 2.0 equiv.) was added slowly in 30 minutes, and the reaction solution was stirred at 25 °C for 30 minutes. To the reaction solution, sat. aq. NaCl (60 mL) was added. The mixture was concentrated in vacuo (35 °C, 80 mbar), and then extracted with ether (3×200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo (35 °C, 80 mbar) to afford 9.52 g (85%) of the title compound **SI-18**.

Physical State: colorless oil.

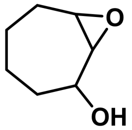
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 – 5.61 (m, 2H), 4.36 – 4.25 (m, 1H), 3.01 (s, br., 1H), 2.16 – 2.04 (m, 1H), 2.00 – 1.90 (m, 1H), 1.88 – 1.74 (m, 2H), 1.62 – 1.48 (m, 3H), 1.33 – 1.22 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.20, 129.66, 71.91, 36.59, 28.60, 26.96, 26.69.

HRMS (*m/z*): $[M-H]^-$ calcd for $C_7H_{11}O^-$ 111.0810, found 111.0809.

TLC: R_f = 0.3 (5:1 hexanes : ethyl acetate).

Compound SI-19



8-oxabicyclo[5.1.0]octan-2-ol **(SI-19)**

To a solution of **SI-18** (9.5 g, 85 mmol, 1.0 equiv.) in DCM (100 mL) was added $NaHCO_3$ (7.14 g, 85 mmol, 1.0 equiv.), and the reaction vessel was backfilled with argon three times. After cooling the mixture to 0 °C, 3-chloroperbenzoic acid (85%; 25.8 g, 128 mmol, 1.5 equiv.) was added dropwise via syringe as a solution in DCM (200 mL), and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. Half of the solvent was evaporated. To the reaction solution, sat. aq. Na_2SO_3 (40 mL) was added. The mixture was extracted with DCM (3×200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 9.25 g (85%) of the title compound **SI-19**.

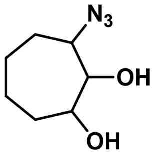
Physical State: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01 (ddd, *J* = 10.7, 3.6, 1.1 Hz, 1H), 3.90 – 3.77 (m, 0.5H), 3.27 – 3.22 (m, 1H), 3.14 (td, *J* = 5.3, 4.8, 1.5 Hz, 1H), 3.10 – 3.01 (m, 1H), 2.66 (s, br., 1.5H), 2.29 – 2.14 (m, 1.5H), 1.84 – 1.29 (m, 10.5H), 0.94 (dtt, *J* = 14.8, 12.5, 2.7 Hz, 1H). *Note: dr = 2:1*

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_7H_{12}NaO_2^+$ 151.0735, found 151.0735.

TLC: R_f = 0.3 (2:1 hexanes : ethyl acetate).

Compound SI-20



3-azidocycloheptane-1,2-diol **(SI-20)**

To a solution of **SI-19** (3.84 g, 30 mmol, 1.0 equiv.) in water (90 mL) were added $MgSO_4$

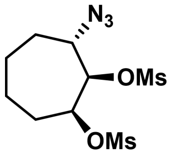
(10.8 g, 90 mmol, 3.0 equiv.) and potassium azide (7.29 g, 90 mmol, 3.0 equiv.). The reaction solution was stirred at 50 °C for 12 hours. The reaction solution was extracted with EA (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 4.10 g (80%) of the title compound **SI-20**. *Note: the mixture was used directly without separation.*

Physical State: colorless oil.

HRMS (*m/z*): $[M-N_2+H]^+$ calcd for $C_7H_{14}NO_2^+$ 144.1025, found 144.1026.

TLC: $R_f = 0.3$ (2:1 hexanes : ethyl acetate).

Compound SI-21



***(1S,2R,3S)-3-azidocyclopentane-1,2-diyl dimethanesulfonate* (SI-21)**

To a solution of **SI-20** (4.1 g, 24 mmol, 1.0 equiv.) in DCM (50 mL) was added Et_3N (13.3 mL, 96 mmol, 4.0 equiv.), and the reaction vessel was backfilled with argon three times. After cooling the mixture to 0 °C, methanesulfonic anhydride (20.9 g, 120 mmol, 5.0 equiv.) was added dropwise via syringe as a solution in DCM (50 mL), and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. The reaction solution was washed with sat. aq. $NaHCO_3$ (50 mL) and extracted with DCM (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by crystallization (ether/methanol) to afford 5.49 g (70%) of the title compound **SI-21**.

Physical State: white solid.

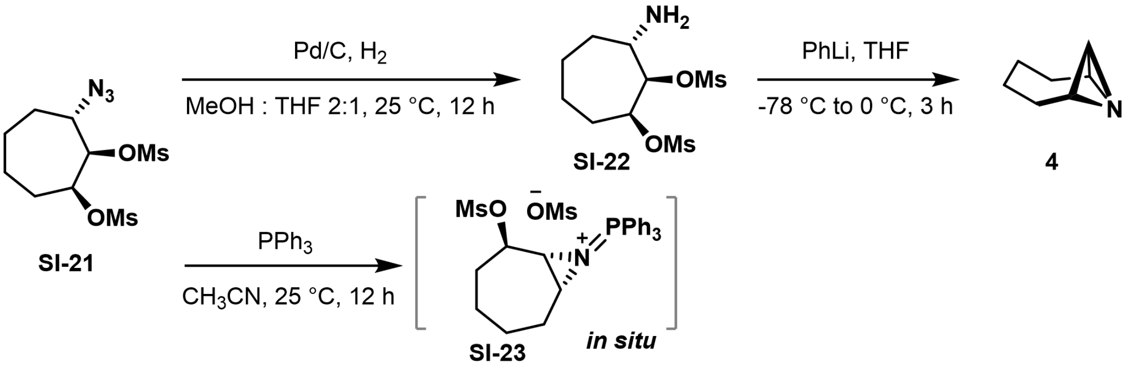
m.p. 122-123 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.13 (dt, *J* = 8.1, 1.9 Hz, 1H), 4.59 (dd, *J* = 8.0, 1.7 Hz, 1H), 3.90 (ddd, *J* = 8.1, 6.7, 4.5 Hz, 1H), 3.17 (s, 3H), 3.12 (s, 3H), 2.34 – 2.18 (m, 1H), 2.11 – 2.00 (m, 1H), 1.91 – 1.62 (m, 6H).

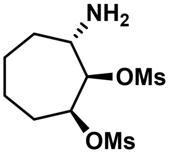
^{13}C NMR (126 MHz, CDCl$_3$): δ 85.11, 81.54, 62.64, 38.68, 38.23, 29.31, 28.63, 22.11, 21.45.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_9H_{17}N_3NaO_6S_2^+$ 350.0456, found 350.0455.

TLC: R$_f$ = 0.3 (5:1 hexanes : ethyl acetate).



Compound SI-22



***(1S,2R,3S)-3-aminocycloheptane-1,2-diyl dimethanesulfonate* (SI-22)**

To a solution of **SI-21** (500 mg, 1.5 mmol, 1.0 equiv.) in MeOH (10mL) and THF (5mL) was added 20% Pd/C (100 mg), and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was purified by flash column chromatography (dichloromethane: methanol, 20:1) on silica gel to afford 361.2 mg (80%) of the title compound **SI-22**.

Physical State: colorless oil.

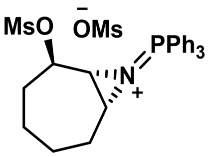
^{1}H NMR (500 MHz, CDCl$_3$): δ 5.19 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.55 (dd, *J* = 7.4, 1.8 Hz, 1H), 3.27 (td, *J* = 7.7, 4.4 Hz, 1H), 3.16 (s, 3H), 3.09 (s, 3H), 2.19 (ddt, *J* = 13.9, 10.2, 5.4 Hz, 1H), 1.92 (ddd, *J* = 13.3, 7.3, 3.9 Hz, 1H), 1.88 – 1.79 (m, 1H), 1.75 (ddt, *J* = 12.8, 9.5, 4.3 Hz, 2H), 1.72 – 1.56 (m, 4H), 1.48 (dt, *J* = 15.8, 8.2 Hz, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 88.43, 80.98, 52.10, 38.75, 38.47, 32.80, 28.58, 22.43, 21.94.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_9H_{20}NO_6S_2^+$ 302.0732, found 302.0734.

TLC: R_f = 0.3 (20:1 dichloromethane : methanol).

Compound SI-23



(1R,2R,7R)-2-((methylsulfonyl)oxy)-8-(triphenyl-λ^5-phosphaneylidene)-8-azabicyclo [5.1.0] octan-8-ium$^+$methanesulfonate$^-$ **(SI-23)**

The reaction vessel was added a solution of PPh_3 (2.62 g, 10 mmol, 1.0 equiv.) in MeCN (50 mL), and backfilled with argon three times. The solution of **SI-21** (3.27 g, 10 mmol, 1.0 equiv.) in MeCN (100 mL) was added dropwise via syringe, and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo and directly used for the next step. Yield: 80% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard).

Physical State: colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 – 7.58 (m, 15H), 5.02 (t, J = 7.7 Hz, 1H), 3.22 (s, 1H), 2.98 (s, 3H), 2.79 – 2.60 (m, 2H), 2.50 (s, 3H), 2.40 – 2.30 (m, 1H), 2.04 – 1.90 (m, 2H), 1.74 – 1.57 (m, 2H), 1.52 – 1.30 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 134.18, 134.16, 131.62, 131.54, 128.83, 128.72, 116.62, 115.83, 79.01, 78.98, 48.18, 43.90, 43.84, 39.66, 39.60, 37.52, 37.23, 31.08, 27.14, 27.12, 23.44, 21.90.

^{31}P NMR (202 MHz, CDCl3): δ 46.90.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{33}NO_6PS_2^+$ 562.1487, found 562.1482.

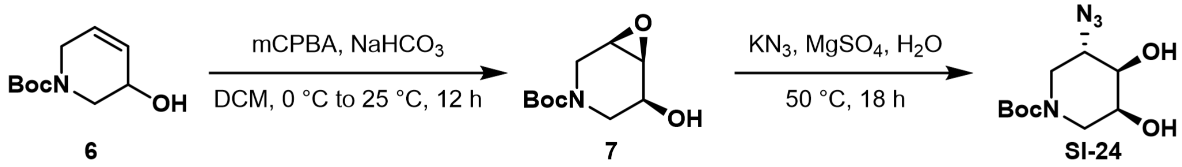
TLC: R_f = 0.3 (20:1 dichloromethane : methanol).

Compound 4

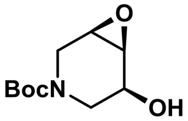
1-azatricyclo[5.1.0.0^{2,8}]octane **(4)**

The reaction vessel was added a solution of **SI-22** (60.2 mg, 0.2 mmol, 1.0 equiv.) in THF (2.0 mL) and backfilled with argon three times. After cooling the mixture to -78 °C, PhLi (0.2 mol/L, ether solution, 2.0 mL, 0.4 mmol, 2.0 equiv.) was added dropwise via syringe, and the reaction solution was stirred at 0 °C for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo (35 °C, 160 mbar). After dissolution in MeCN and filtration via diatomaceous earth, the crude product was used directly in further reactions. Yield: 25% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard). *Note: the mixture was used directly without separation.*

Procedure for Preparation of 10



Compound 7



tert-butyl (1R,5S,6S)-5-hydroxy-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate **(7)**

To a solution of **6** (19.9 g, 100 mmol, 1.0 equiv.) in DCM (100 mL) was added $NaHCO_3$ (8.4 g, 100 mmol, 1.0 equiv.) and the reaction vessel was backfilled with argon three times. After cooling the mixture to 0 °C, 3-chloroperbenzoic acid (85%; 30.35 g, 150 mmol, 1.5 equiv.) was added dropwise via syringe as a solution in DCM (200 mL), and the reaction solution was stirred at 25 ℃ for 12 hours under an argon atmosphere. Half of the solvent was evaporated. To the reaction solution, sat. aq. Na_2SO_3 (40 mL) was added. The mixture was extracted with DCM (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 18.49 g (86%) of the title compound **7**.

Physical State: colorless oil.

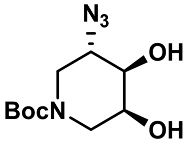
^{1}H NMR (500 MHz, CDCl$_3$): δ 3.98 (s, 1H), 3.90 – 3.56 (m, 2H), 3.52 (d, *J* = 15.3 Hz, 1H), 3.40 (q, *J* = 3.1 Hz, 2H), δ 2.93 (dd, *J* = 13.1, 8.5 Hz, 1H)., 1.40 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 154.70, 80.44, 65.05, 54.20, 53.71, 53.12, 44.32, 43.14, 41.58, 40.75, 28.32.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{10}H_{17}NNaO_4^+$ 238.1055, found 238.1055.

TLC: R_f = 0.3 (2:1 hexanes : ethyl acetate).

Compound SI-24



***tert*-butyl (3S,4R,5S)-3-azido-4,5-dihydroxypiperidine-1-carboxylate** **(SI-24)**

To a solution of **7** (10.75 g, 50 mmol, 1.0 equiv.) in water (100 mL) were added $MgSO_4$ (15.0 g, 125 mmol, 2.5 equiv.) and potassium azide (10.2 g, 125 mmol, 2.5 equiv.). The reaction solution was stirred at 50 °C for 18 hours. The reaction solution was extracted with EA (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 11.22 g (87%) of the title compound **SI-24**.

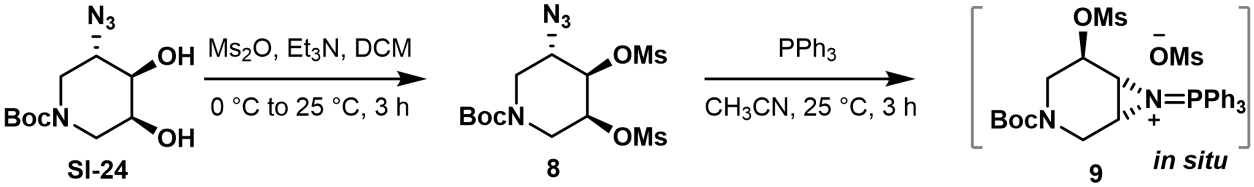
Physical State: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 – 3.78 (m, 3H), 3.75 – 3.40 (m, 4H), 3.27 – 2.37 (m, 2H), 1.45 (s, 9H).

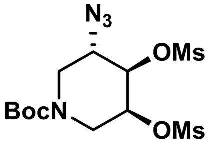
^{13}C NMR (101 MHz, $CDCl_3$): δ 155.50, 80.91, 73.03, 67.05, 59.48, 46.34, 44.85, 28.30.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{10}H_{18}N_4NaO_4^+$ 281.1226, found 281.1226.

TLC: R_f = 0.2 (2:1 hexanes : ethyl acetate).



Compound 8



***tert*-butyl (3S,4R,5S)-3-azido-4,5-bis((methylsulfonyl)oxy)piperidine-1-carboxylate** **(8)**

To a solution of **SI-24** (7.74 g, 30 mmol, 1.0 equiv.) in DCM (100 mL) was added Et_3N (16.6 mL, 120 mmol, 4.0 equiv.) and the reaction vessel was backfilled with argon three times.

After cooling the mixture to 0 °C, methanesulfonic anhydride (26.1 g, 150 mmol, 5.0 equiv.) was added dropwise via syringe as a solution in DCM (100 mL), and the reaction solution was stirred at 25 °C under an argon atmosphere for 3 hours. The reaction solution was washed with sat. aq. $NaHCO_3$ (30 mL) and extracted with DCM (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 10.68 g (86%) of the title compound **8**.

Physical State: colorless oil.

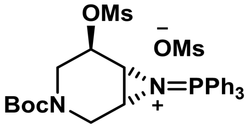
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.10 – 4.87 (m, 1H), 4.75 – 4.36 (m, 2.4H), 4.28 – 4.01 (m, 0.6H), 3.91 (td, *J* = 9.9, 5.0 Hz, 1H), 3.37 – 3.22 (m, 0.4H), 3.21 (s, 3H), 3.18 – 3.15 (m, 0.4H), 3.14 (s, 3H), 3.12 – 3.04 (m, 0.6H), 2.74 – 2.57 (m, 0.6H), 1.49 (s, 9H). *Note: Two isomers with a 2:3 ratio, attributed to rotational isomerization of amide, were observed.*

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.30, 81.68, 79.82, 78.28, 76.31, 74.57, 57.04, 56.32, 47.00, 45.20, 44.59, 38.75, 38.51, 38.36, 28.04.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{22}N_4NaO_8S_2^+$ 437.0777, found 437.0776.

TLC: R_f = 0.3 (3:1 hexanes : ethyl acetate).

Compound 9



(1R,5R,6R)-3-(tert-butoxycarbonyl)-5-((methylsulfonyl)oxy)-7-(triphenyl-λ^5-phosphaneylidene)-3,7-diazabicyclo[4.1.0]heptan-7-ium$^+$methanesulfonate$^-$ **(9)**

The reaction vessel was added a solution of PPh_3 (2.62 g, 10 mmol, 1.0 equiv.) in MeCN (50 mL) and backfilled with argon three times. The solution of **8** (3.13 g, 10 mmol, 1.0 equiv.) in MeCN (100 mL) was added dropwise via syringe, and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo and directly used for the next step. Yield: 83% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard).

Physical State: colorless oil.

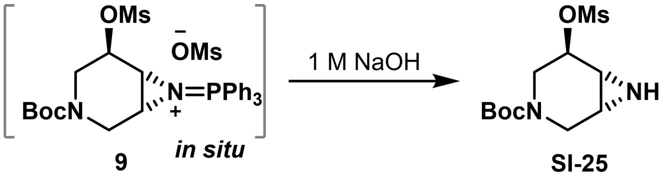
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.59 (m, 15H), 5.07 (dt, *J* = 26.4, 7.2 Hz, 1H), 4.28 (dd, *J* = 22.8, 15.3 Hz, 1H), 4.06 (dd, *J* = 13.8, 5.7 Hz, 0.5H), 3.94 (dd, *J* = 14.3, 5.2 Hz, 0.5H), 3.80 (d, *J* = 15.7 Hz, 0.5H), 3.72 (d, *J* = 15.4 Hz, 0.5H), 3.56 (dd, *J* = 15.2, 6.0 Hz, 0.5H), 3.31 (dd, *J* = 14.0, 8.2 Hz, 0.5H), 3.23 – 3.08 (m, 2.5H), 3.08 – 2.92 (m, 2.5H), 2.54 (s, 3H), 1.35 (s, 4.5H), 1.28 (s, 4.5H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.50, 135.29, 135.27, 133.76, 133.67, 132.07, 131.99, 130.16, 130.06, 128.55, 128.45, 121.38, 120.56, 80.98, 69.46, 53.96, 49.96, 46.84, 46.76, 39.49, 38.19, 37.81, 29.27, 27.90. *Note: Two isomers with a 1:1 ratio, attributed to rotational isomerization of amide, were observed.*

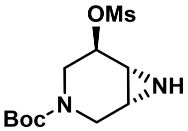
^{31}P NMR (202 MHz, $CDCl_3$): δ 39.89.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{38}N_2O_8PS_2^+$ 649.1807, found 649.1805.

TLC: R_f = 0.3 (10:1 dichloromethane : methanol).



Compound SI-25



tert-butyl (1R,5R,6R)-5-((methylsulfonyl)oxy)-3,7-diazabicyclo[4.1.0]heptane-3-carboxylate (SI-25)

To a solution of **9** (5.4 g, 8.3 mmol, 1.0 equiv.) in DCM (20 mL) was added 1 M NaOH aq. (20 mL). The reaction solution was stirred at 25 °C for 5 minutes and the mixture was extracted with DCM (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4

and concentrated in vacuo. The crude product was purified by flash column chromatography (dichloromethane: ether, 5:1) on silica gel to afford 1.94 g (80%) of the title compound **SI-25**.

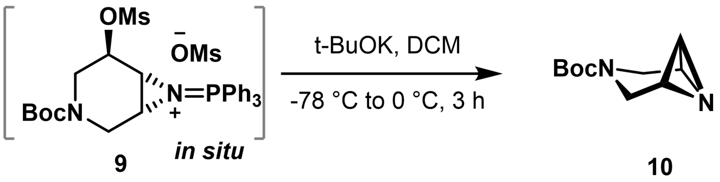
Physical State: colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ 5.03 (d, J = 38.2 Hz, 1H), 4.07 – 3.75 (m, 2H), 3.48 (d, J = 14.2 Hz, 1H), 3.34 – 3.15 (m, 1H), 3.09 (s, 3H), 2.56 (dd, J = 43.8, 23.9 Hz, 2H), 1.44 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 155.06, 154.75, 80.28, 75.24, 74.36, 62.71, 42.60, 42.13, 41.36, 40.71, 38.97, 38.67, 30.69, 28.35.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{11}H_{21}N_2O_5S^+$ 293.1171, found 293.1173.

TLC: R_f = 0.3 (5:1 dichloromethane : ether).



Compound 10

***tert-butyl 1,4-diazatricyclo[4.1.0.0^{2,7}]heptane-4-carboxylate* (10)**

The reaction vessel was added a solution of **9** (648 mg, 1 mmol, 1.0 equiv.) in DCM (10 mL) and backfilled with argon three times. After cooling the mixture to -78 °C, t-BuOK (1.0 mol/L, THF, 1.5 mL, 1.5 mmol, 1.5 equiv.) was added dropwise via syringe, and the reaction solution was stirred at 0 °C for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo, the compound can be purified by sublimation (60 °C, 5*10^{-2} Pa). Yield: 71%.

The crude product was also used directly in further reactions. Yield: 83% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard).

Physical State: colorless solid.

m.p. 104-106 °C.

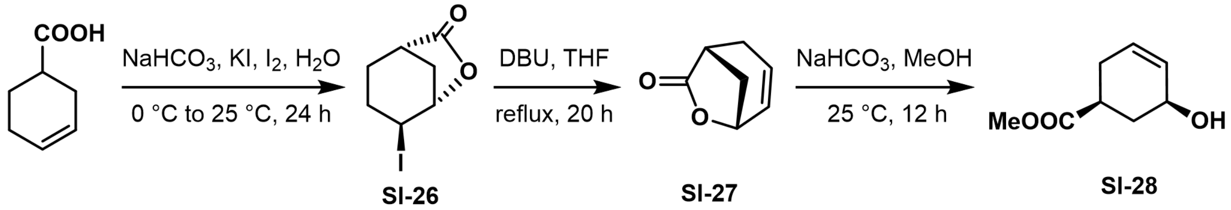
^{1}H NMR (500 MHz, CDCl$_3$): δ 3.62 (dd, J = 20.9, 13.7 Hz, 2H), 3.26 – 3.05 (m, 4H), 2.72 (p, J

= 2.0 Hz, 1H), 1.45 (s, 9H).

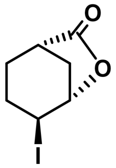
^{13}C NMR (126 MHz, CDCl$_3$): δ 154.60, 79.93, 58.24, 57.90, 36.97, 35.87, 28.39, 25.86.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{10}H_{17}N_2O_2^+$ 197.1290, found 197.1295.

Procedure for Preparation of SI-96



Compound SI-26



(1S,4S,5S)-4-iodo-6-oxabicyclo[3.2.1]octan-7-one **(SI-26)**

SI-26 was prepared according to the previously reported procedure[1]. A suspension of naphthenic acid (6.3 g, 50 mmol, 1.0 equiv.) in water (140 mL) was cooled to 0 °C before $NaHCO_3$ (12.6 g, 150 mmol, 3.0 equiv.) was added slowly. The mixture was then backfilled with argon three times. KI (49.8 g, 300 mmol, 6.0 equiv.) and I_2 (12.7 g, 50 mmol, 1.0 equiv.) were added dropwise via syringe as a solution in water (120 mL) at 0 °C, and the mixture was stirred at 25 °C under an argon atmosphere for 24 hours. The reaction solution was washed with sat. aq. NaS_2O_3 (20mL) and extracted with DCM (3×100 mL). The combined organic layers were dried over Na_2SO_4, protected from light, concentrated in vacuo and quickly in high vacuo to afford 11.34 g (90%) of the title compound **SI-26**.

Physical State: colorless solid.

m.p. 132-133 °C.

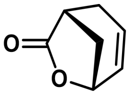
^{1}H NMR (500 MHz, CDCl$_3$): δ 4.81 (dd, J = 5.9, 4.1 Hz, 1H), 4.59 – 4.39 (m, 1H), 2.78 (d, J = 12.3 Hz, 1H), 2.66 (td, J = 5.2, 3.0 Hz, 1H), 2.48 – 2.34 (m, 2H), 2.11 (dd, J = 16.4, 5.3 Hz, 1H), 1.89 (tdd, J = 12.9, 5.3, 2.1 Hz, 1H), 1.81 (dtd, J = 11.4, 5.4, 3.4 Hz, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 177.79, 80.24, 38.62, 34.52, 29.73, 23.78, 23.13.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_7H_{10}IO_2^+$ 252.9725, found 252.9723.

TLC: R_f = 0.3 (5:1 hexanes : ethyl acetate).

Compound SI-27



(1R,5R)-6-oxabicyclo[3.2.1]oct-3-en-7-one **(SI-27)**

SI-27 was prepared according to the previously reported procedure [1]. To a solution of **SI-26** (11.3 g, 44.8 mmol, 1.0 equiv.) in THF (100 mL) was added DBU (10 mL, 67.2 mmol, 1.5 equiv.) and the mixture was refluxed under an argon atmosphere for 20 hours. The reaction mixture was cooled down to room temperature, transferred with Et_2O (200 mL) into a separation funnel and extracted with aq. HCl (100 mL, 0.5 M) and brine (100 mL). The aqueous layers were extracted with Et_2O (3×200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate 3:1) on silica gel to afford 5.0 g (90%) of the title compound **SI-27**.

Physical State: colorless oil.

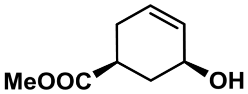
^{1}H NMR (500 MHz, CDCl$_3$): δ 6.17 (ddd, J = 9.9, 5.4, 2.5 Hz, 1H), 5.79 (dt, J = 8.6, 3.4 Hz, 1H), 4.70 (t, J = 5.4 Hz, 1H), 2.85 (t, J = 5.3 Hz, 1H), 2.51 – 2.31 (m, 3H), 2.04 (d, J = 11.2 Hz, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 179.43, 130.27, 129.31, 73.31, 38.02, 34.41, 29.11.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_7H_9O_2^+$ 125.0603, found 125.0600.

TLC: R_f = 0.3 (5:1 hexanes : ethyl acetate).

Compound SI-28



methyl (1S,5S)-5-hydroxycyclohex-3-ene-1-carboxylate **(SI-28)**

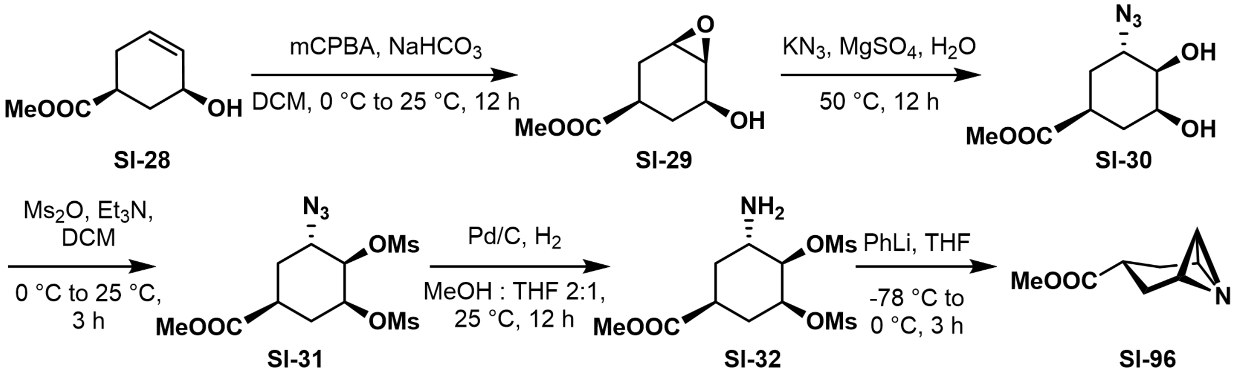
SI-28 was prepared according to the previously reported procedure [1]. To a suspension of $NaHCO_3$ (3.4 g, 40.3 mmol, 1.0 equiv.) in MeOH (100 mL) was added **SI-27** (5.0 g, 40.3 mmol, 1.0 equiv.). The mixture was then backfilled with argon three times and stirred at 25 °C under an argon atmosphere for 12 hours. The solvent was evaporated and added DCM (60 mL). The mixture was washed with water (100 mL) and brine (100 mL). The aqueous layers were extracted with DCM (2×100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate 2:1) on silica gel to afford 6.04 g (96%) of the title compound **SI-28**.

Physical State: colorless oil.

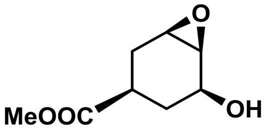
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 – 5.67 (m, 2H), 4.27 (tdd, *J* = 8.2, 3.5, 1.6 Hz, 1H), 3.67 (s, 3H), 2.75 – 2.63 (m, 1H), 2.31 – 2.22 (m, 3H), 1.70 (ddd, *J* = 12.8, 10.8, 8.1 Hz, 1H).

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_8H_{12}NaO_3^+$ 179.0684, found 179.0683.

TLC: R_f = 0.3 (2:1 hexanes : ethyl acetate).



Compound SI-29



methyl (1R,3R,5S,6S)-5-hydroxy-7-oxabicyclo[4.1.0]heptane-3-carboxylate **(SI-29)**

To a solution of **SI-28** (4.68 g, 30 mmol, 1.0 equiv.) in DCM (50 mL) was added $NaHCO_3$ (2.52 g, 30 mmol, 1.0 equiv.). The reaction vessel was backfilled with argon three times. After cooling the mixture to 0 °C, 3-chloroperbenzoic acid (85%; 9.1 g, 45 mmol, 1.5 equiv.) was added dropwise via syringe as a solution in DCM (100 mL), and the reaction solution was stirred at 25 °C for 12 hours under an argon atmosphere. Half of the solvent was evaporated. To the reaction solution, sat. aq. Na_2SO_3 (15 mL) was added. The mixture was extracted with DCM (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 3.35 g (65%) of the title compound **SI-29**.

Physical State: white solid.

m.p. 58-60 °C.

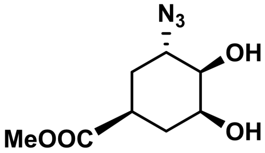
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (ddd, *J* = 9.9, 5.7, 1.9 Hz, 1H), 3.58 (s, 3H), 3.38 (s, br., 1H), 3.28 – 3.14 (m, 2H), 2.39 – 2.24 (m, 1H), 2.07 – 1.92 (m, 2H), 1.86 (dddt, *J* = 12.6, 5.5, 2.6, 1.1 Hz, 1H), 1.57 – 1.42 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.58, 67.52, 55.43, 53.65, 51.95, 38.14, 29.91, 25.21.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_8H_{12}NaO_4^+$ 195.0633, found 195.0633.

TLC: R_f = 0.3 (1:1 hexanes : ethyl acetate).

Compound SI-30



methyl (1S,3S,4R,5S)-3-azido-4,5-dihydroxycyclohexane-1-carboxylate **(SI-30)**

To a solution of **SI-29** (1.72 g, 10 mmol, 1.0 equiv.) in water (30 mL) were added $MgSO_4$ (3.0 g, 25 mmol, 2.5 equiv.) and potassium azide (2.0 g, 25 mmol, 2.5 equiv.). The reaction solution was stirred at 50 ℃ for 12 hours. The reaction solution was extracted with EA (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 1.29 g (60%) of the title compound **SI-30**.

Physical State: colorless oil.

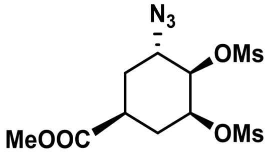
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (dt, *J* = 6.6, 3.4 Hz, 1H), 3.93 – 3.84 (m, 1H), 3.71 (s, 3H), 3.56 (dd, *J* = 7.6, 3.0 Hz, 1H), 3.03 (s, br., 2H), 2.71 (ddd, *J* = 11.2, 6.2, 4.9 Hz, 1H), 2.23 (tt, *J* = 20.5, 5.7 Hz, 2H), 1.81 (ddd, *J* = 14.0, 5.2, 3.5 Hz, 1H), 1.62 (ddd, *J* = 13.6, 8.7, 4.7 Hz, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 175.47, 73.09, 68.41, 59.76, 52.21, 36.24, 31.04, 28.83.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_8H_{13}N_3NaO_4^+$ 238.0804, found 238.0802.

TLC: R$_f$ = 0.3 (1:1 hexanes : ethyl acetate).

Compound SI-31



methyl (1S,3S,4R,5S)-3-azido-4,5-bis((methylsulfonyl)oxy)cyclohexane-1-carboxylate **(SI-31)**

To a solution of **SI-30** (1.3 g, 6 mmol, 1.0 equiv.) in DCM (30 mL) was added Et_3N (3.3 mL, 24 mmol, 4.0 equiv.). The reaction vessel was then backfilled with argon three times. After cooling the mixture to 0 °C, methanesulfonic anhydride (5.22 g, 30 mmol, 5.0 equiv.) was added dropwise via syringe as a solution in DCM (30 mL), and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. The reaction solution was washed with sat. aq. $NaHCO_3$ (30 mL) and extracted with DCM (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel and crystallization (ether/methanol) to afford 1.56 g (70%) of the title compound **SI-31**.

Physical State: white solid.

m.p. 94-95 °C.

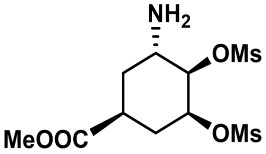
^{1}H NMR (400 MHz, CDCl$_3$): δ 5.00 (dt, *J* = 6.7, 3.2 Hz, 1H), 4.54 (d, *J* = 7.7 Hz, 1H), 4.20 (td, *J* = 8.3, 4.1 Hz, 1H), 3.73 (s, 3H), 3.16 (s, 3H), 3.07 (s, 3H), 2.80 (t, *J* = 5.6 Hz, 1H), 2.52 (s, br., 1H), 2.41 (s, br., 1H), 2.11 – 1.98 (m, 1H), 1.71 (s, br., 1H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 173.12, 79.18, 57.46, 52.49, 38.47, 38.46, 35.17, 30.51, 28.81, 26.94.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{10}H_{17}N_3NaO_8S_2^+$ 394.0355, found 394.0355.

TLC: R$_f$ = 0.3 (3:1 hexanes : ethyl acetate).

Compound SI-32



methyl (1S,3S,4R,5S)-3-amino-4,5-bis((methylsulfonyl)oxy)cyclohexane-1-carboxylate **(SI-32)**

To a solution of **SI-31** (372 mg, 1.0 mmol, 1.0 equiv.) in MeOH (5mL) and THF (2.5mL) was added 30% Pd/C (110 mg) and the reaction vessel was backfilled with hydrogen three times . The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was purified by flash column chromatography (dichloromethane: methanol, 10:1) on silica gel to afford 276.0 mg (80%) of the title compound **SI-32**.

Physical State: white solid.

m.p. 53-54 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.20 (dt, *J* = 7.8, 3.1 Hz, 1H), 4.52 (dd, *J* = 7.4, 2.9 Hz, 1H), 3.72 (s, 3H), 3.60 (td, *J* = 7.5, 4.0 Hz, 1H), 3.17 (s, 3H), 3.07 (s, 3H), 2.87 (ddd, *J* = 11.7, 7.0, 4.8 Hz, 1H), 2.56 – 2.42 (m, 1H), 2.28 (dd, *J* = 13.3, 7.3 Hz, 1H), 2.13 – 1.99 (m, 1H), 1.61 (s, 2H), 1.59 – 1.54 (m, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 173.86, 82.07, 52.20, 50.49, 47.82, 38.50, 38.45, 35.42, 31.18, 30.54.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{10}H_{20}NO_8S_2^+$ 346.0630, found 346.0628.

TLC: R$_f$ = 0.3 (20:1 dichloromethane : methanol).

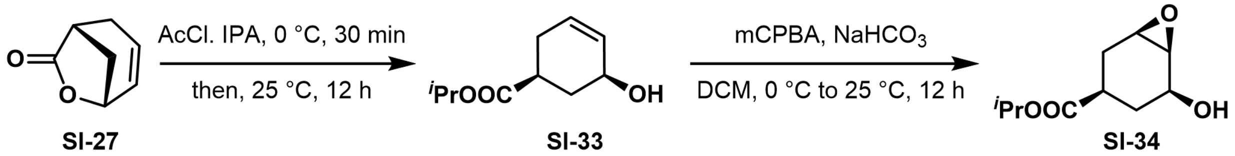
Compound SI-96

methyl (2R,4r,6S,7s)-1-azatricyclo[4.1.0.0^{2,7}]heptane-4-carboxylate **(SI-96)**

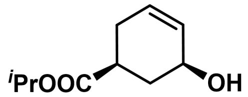
The reaction vessel was added a solution of **SI-32** (34.5 mg, 0.1 mmol, 1.0 equiv.) in THF (1.0 mL) and backfilled with argon three times. After cooling the mixture to -78 °C, PhLi (0.2

mol/L, ether solution, 1.0 mL, 0.2 mmol, 2.0 equiv.) was added dropwise via syringe, and the reaction solution was stirred at 0 °C for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo (35 °C, 160 mbar), After dissolution in MeCN and filtration via diatomaceous earth, the crude product was used directly in further reactions. Yield: 39% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard). *Note: the mixture was used directly without separation.*

Procedure for Preparation of 12



Compound SI-33



isopropyl (1S,5S)-5-hydroxycyclohex-3-ene-1-carboxylate **(SI-33)**

SI-33 was prepared according to the previously reported procedure [2]. Isopropanol (20 mL) was placed in a 100 mL vial and the vial was backfilled with argon three times. Acetyl chloride (1.7 mL, 24 mmol, 1.2 equiv.) was added dropwise at 0 °C, and the mixture was stirred at 25 °C under an argon atmosphere for 30 minutes. Added **SI-27** (2.5 g, 20 mmol, 1.0 equiv.) dropwise via syringe as a solution in isopropanol (20 mL) and stirred for 12 hours under an argon atmosphere. The solvent was evaporated and added DCM (30 mL). The mixture was washed with water and brine (2×20 mL). The aqueous layers were extracted with DCM (2×30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate 3:1) on silica gel to afford 3.09 g (84%) of the title compound **SI-33**.

Physical State: white solid.

m.p. 78-79 °C.

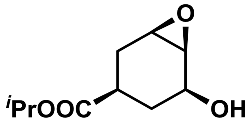
^{1}H NMR (400 MHz, CDCl$_3$): δ 5.74 (s, 2H), 5.00 (hept, J = 6.3 Hz, 1H), 4.27 (ddt, J = 7.8, 5.9, 3.0 Hz, 1H), 2.65 (dtd, J = 10.5, 7.2, 3.2 Hz, 1H), 2.26 (ddt, J = 8.1, 4.7, 3.1 Hz, 3H), 1.71 (ddd, J = 12.9, 10.6, 7.9 Hz, 1H), 1.22 (dd, J = 6.3, 2.9 Hz, 6H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 174.82, 130.87, 126.87, 67.97, 66.00, 38.07, 34.14, 27.42, 21.74.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{10}H_{17}O_3^+$ 185.1178, found 185.1176.

TLC: R_f = 0.3 (3:1 hexanes : ethyl acetate).

Compound SI-34



isopropyl (1R,3R,5S,6S)-5-hydroxy-7-oxabicyclo[4.1.0]heptane-3-carboxylate **(SI-34)**

To a solution of **SI-33** (1.84 g, 10 mmol, 1.0 equiv.) in DCM (30 mL) was added $NaHCO_3$ (840 mg, 10 mmol, 1.0 equiv.). The reaction vessel was backfilled with argon three times. After cooling the mixture to 0 °C, 3-chloroperbenzoic acid (85%; 3.0 g, 15 mmol, 1.5 equiv.) was added dropwise via syringe as a solution in DCM (60 mL), and the reaction solution was stirred at 25 °C for 12 hours under an argon atmosphere. Half of the solvent was evaporated. To the reaction solution, sat. aq. Na_2SO_3 (5.0 mL) was added. The mixture was extracted with DCM (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 1.34 g (67%) of the title compound **SI-34**.

Physical State: white solid.

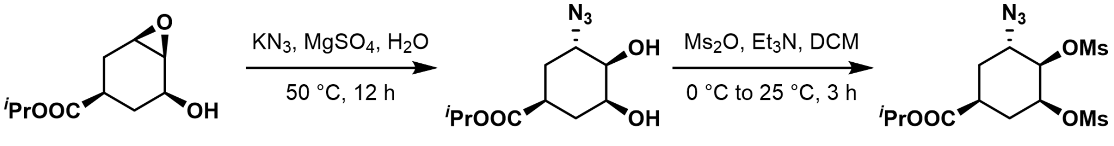
m.p. 47-49 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.95 (hept, *J* = 6.3 Hz, 1H), 4.02 (ddd, *J* = 9.4, 5.8, 2.1 Hz, 1H), 3.42 – 3.17 (m, 2H), 2.85 (s, br., 1H), 2.45 – 2.22 (m, 1H), 2.05 (ddd, *J* = 7.5, 4.3, 1.4 Hz, 2H), 1.90 (ddd, *J* = 12.9, 5.8, 2.9 Hz, 1H), 1.58 (ddd, *J* = 12.9, 11.5, 9.3 Hz, 1H), 1.18 (dd, *J* = 6.3, 3.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.67, 68.13, 67.53, 55.36, 53.85, 38.42, 30.17, 25.34, 21.68.

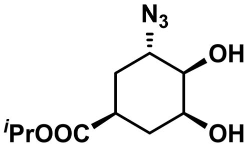
HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{10}H_{16}NaO_4^+$ 223.0946, found 223.0944.

TLC: R_f = 0.3 (1:1 hexanes : ethyl acetate).



SI-34 **SI-35** **SI-36**

Compound SI-35



isopropyl (1S,3S,4R,5S)-3-azido-4,5-dihydroxycyclohexane-1-carboxylate **(SI-35)**

To a solution of **SI-34** (1.98 g, 10 mmol, 1.0 equiv.) in water (30 mL) were added $MgSO_4$ (4.8 g, 40 mmol, 4.0 equiv.) and potassium azide (4.24 g, 40 mmol, 4.0 equiv.). The reaction solution was stirred at 50 °C for 12 hours. The reaction solution was extracted with EA (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 1.46 g (60%) of the title compound **SI-35**.

Physical State: colorless oil.

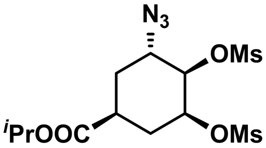
^{1}H NMR (400 MHz, CDCl$_3$): δ 5.01 (hept, J = 6.3 Hz, 1H), 3.99 (ddd, J = 8.2, 6.4, 3.6 Hz, 1H), 3.89 – 3.80 (m, 1H), 3.64 – 3.47 (m, 1H), 3.08 (d, J = 4.8 Hz, 1H), 2.91 (d, J = 5.4 Hz, 1H), 2.67 (p, J = 5.6 Hz, 1H), 2.38 – 2.07 (m, 2H), 1.80 (ddd, J = 14.1, 5.3, 3.7 Hz, 1H), 1.62 (ddd, J = 13.7, 8.8, 4.8 Hz, 1H), 1.24 (d, J = 6.3 Hz, 6H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 174.68, 73.21, 68.62, 68.41, 59.85, 36.74, 30.95, 29.03, 21.70, 21.66.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{10}H_{17}N_3NaO_4^+$ 226.1117, found 226.1117.

TLC: R_f = 0.2 (1:1 hexanes : ethyl acetate).

Compound SI-36



***isopropyl (1S,3S,4R,5S)-3-azido-4,5-bis((methylsulfonyl)oxy)cyclohexane-1-carboxylate* (SI-36)**

To a solution of **SI-35** (1.46 g, 6 mmol, 1.0 equiv.) in DCM (30 mL) was added Et_3N (3.3 mL, 24 mmol, 4.0 equiv.) and the reaction vessel was backfilled with argon three times. After cooling the mixture to 0 °C, methanesulfonic anhydride (5.22 g, 30 mmol, 5.0 equiv.) was added dropwise via syringe as a solution in DCM (30 mL), and the reaction solution was stirred at 25 °C for 3 hours under an argon atmosphere. To the reaction solution, washed with sat. aq. $NaHCO_3$ (30 mL) and the mixture was extracted with DCM (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (dichloromethane: ether, 100:1) on silica gel to afford 1.75 g (73%) of the title compound **SI-36**.

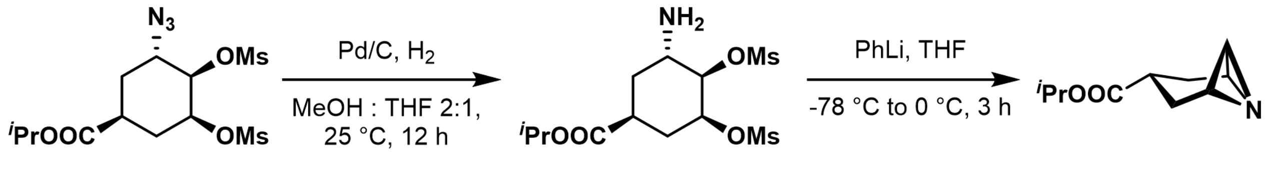
Physical State: colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.08 – 4.92 (m, 2H), 4.67 – 4.56 (m, 1H), 4.22 (td, *J* = 7.0, 3.8 Hz, 1H), 3.15 (s, 3H), 3.07 (s, 3H), 2.78 – 2.68 (m, 1H), 2.32 (d, *J* = 36.3 Hz, 2H), 2.08 (dt, *J* = 14.4, 4.3 Hz, 1H), 1.80 (d, *J* = 12.6 Hz, 1H), 1.25 (dd, *J* = 9.7, 6.3 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.12, 78.37, 76.36, 69.20, 58.07, 38.56, 38.47, 35.63, 30.01, 28.21, 21.73, 21.65.

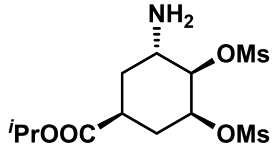
HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{21}N_3NaO_8S_2^+$ 422.0668, found 422.0668.

TLC: R_f = 0.4 (30:1 dichloromethane : ether).



SI-36 **SI-37** **12**

Compound SI-37



***isopropyl (1S,3S,4R,5S)-3-amino-4,5-bis((methylsulfonyl)oxy)cyclohexane-1-carboxylate* (SI-37)**

To a solution of **SI-36** (400 mg, 1.0 mmol, 1.0 equiv.) in MeOH (5mL) and THF (2.5mL) was added 30% Pd/C (120 mg) and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was purified by flash column chromatography (dichloromethane: methanol, 10:1) on silica gel to afford 298.4 mg (80%) of the title compound **SI-37**.

Physical State: colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.20 (dt, *J* = 8.8, 3.4 Hz, 1H), 4.98 (hept, *J* = 6.3 Hz, 1H), 4.57 (dd, *J* = 6.3, 3.0 Hz, 1H), 3.58 (td, *J* = 6.4, 3.8 Hz, 1H), 3.13 (s, 3H), 3.06 (s, 3H), 2.82 (tt, *J* = 8.8, 4.6 Hz, 1H), 2.32 (dt, *J* = 17.0, 8.9 Hz, 1H), 2.21 – 2.11 (m, 1H), 2.07 (dt, *J* = 13.6, 4.3 Hz, 1H), 1.61 (dt, *J* = 14.0, 5.3 Hz, 1H), 1.50 (s, 2H), 1.23 (t, *J* = 6.3 Hz, 6H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 172.91, 81.54, 76.58, 68.66, 48.48, 38.58, 38.56, 35.79, 30.64, 30.15, 21.74, 21.71.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{12}H_{24}NO_8S_2^+$ 374.0943, found 374.0942.

TLC: R$_f$ = 0.4 (10:1 dichloromethane : methanol).

Compound 12

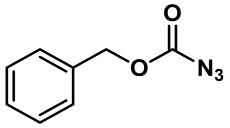
***isopropyl (2R,4r,6S,7s)-1-azatricyclo[4.1.0.0^{2,7}]heptane-4-carboxylate* (12)**

The reaction vessel was added a solution of **SI-37** (37.3 mg, 0.1 mmol, 1.0 equiv.) in THF (1.0 mL) and backfilled with argon three times. After cooling the mixture to -78 °C, PhLi (0.2 mol/L, ether solution, 1.0 mL, 0.2 mmol, 2.0 equiv.) was added dropwise via syringe, and the reaction solution was stirred at 0 ℃ for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo), after dissolution in MeCN and filtration via diatomaceous earth, the crude product was used directly in further reactions. Yield: 43% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard).

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.02 (tt, *J* = 11.9, 6.2 Hz, 1H), 3.15 (dd, *J* = 6.3, 2.1 Hz, 1H), 3.12 – 3.09 (m, 2H), 2.58 (p, *J* = 1.9 Hz, 1H), 2.05 (ddd, *J* = 15.3, 4.8, 2.5 Hz, 2H), 1.84 – 1.77 (m, 2H), 1.24 (d, *J* = 6.3 Hz, 6H). *Note: The ^{1}H NMR of the crude was made.*

Procedure of Substrate Precursors

Compound SI-90



benzyl carbonazidate **(SI-90)**

SI-90 was prepared according to the previously reported procedure[3]. To a solution of CbzCl (341 mg, 2 mmol, 1.0 equiv.) in acetone (10 mL) was added potassium azide (194 mg, 2.4 mmol, 1.2 equiv.). The mixture was backfilled with argon three times, and then stirred under an argon atmosphere at 25 °C for 1 hours. The reaction solution was concentrated in vacuo to afford 247.8 mg (70%) of the title compound **SI-90**.

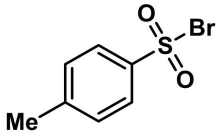
Physical State: colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.42 – 7.34 (m, 5H), 5.23 (s, 2H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 157.51, 134.39, 128.92, 128.73, 128.58, 70.12.

TLC: R_f = 0.3 (50:1 hexanes : ethyl acetate).

Compound SI-91



4-methylbenzenesulfonyl bromide **(SI-91)**

SI-91 was prepared according to the previously reported procedure[4]. To a solution of 4-methylbenzenesulfonhydrazide (372 mg, 2 mmol, 1.0 equiv.) in MeCN (10 mL) was added NBS (712 mg, 4 mmol, 2.0 equiv.) and the reaction vessel was backfilled with argon three times, and then stirred under an argon atmosphere at 25 °C for 2 hours. The reaction solution was concentrated in vacuo and the crude product was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 282.0 mg (60%) of the title compound **SI-91**.

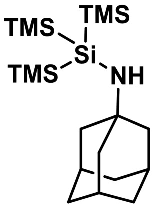
Physical State: brown yellow solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.87 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 2.48 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 146.86, 144.59, 130.18, 126.54, 21.88.

TLC: R$_f$ = 0.3 (10:1 hexanes : ethyl acetate).

Compound SI-92



N-(adamantan-1-yl)-1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)trisilan-2-amine **(SI-92)**

SI-92 was prepared according to the previously reported procedure[5]. DCM (30 mL) was placed in a 100 mL oven-dried round bottom flask. The flask was backfilled with argon three times, and trifluoromethanesulfonic acid (0.93 mL, 10.5 mmol, 1.05 equiv.) was added via syringe. After cooling the mixture to 0 °C, tris(trimethylsilyl)silane (3.08 mL, 10 mmol, 1.0 equiv.) was added dropwise via syringe, and the reaction solution was stirred at 25 °C for 1 hours under an argon atmosphere. After cooling the mixture to 0 °C, 1-adamantylamine (1.59 g, 10.5 mmol, 1.05 equiv.) and DIPEA (2.61 mL, 15 mmol, 1.5 equiv.) were added and stirred at 25 °C for 12 hours under an argon atmosphere. The reaction solution was concentrated in vacuo and the resulting white solid was resuspended in hexanes (10 mL). The mixture was filtered and concentrated in vacuo. The crude product was purified by crystallization (dichloromethane/methanol) to afford 2.38 g (60%) of the title compound **SI-92**.

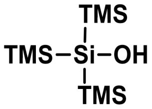
Physical State: white solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.07 – 2.01 (m, 3H), 1.66 – 1.57 (m, 6H), 1.55 (d, *J* = 3.1 Hz, 6H), 0.17 (s, 27H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 47.90, 46.22, 35.68, 29.43, 0.00.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{19}H_{44}NSi_4^+$ 398.2551, found 398.2552.

Compound SI-93



1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)trisilan-2-ol **(SI-93)**

SI-93 was prepared according to the previously reported procedure[6]. To a solution of tris(trimethylsilyl)silane (0.3 mL, 1 mmol, 1.0 equiv.) in Et_2O (1.0 mL) was added 2-bromopropane (0.2 mL, 2 mmol, 2.0 equiv.) dropwise under air. The reaction vessel was capped under air with a rubber septum and irradiated with a Kessil Blue LED lamp (450 nm, 6 cm distance, maximum power). The mixture was stirred at 25 °C for 4 hours. After irradiation, the septum was punctured to allow for slow gap evolution. Then NaOH (1.0 mL, 2.5 M) solution was added, and the mixture was stirred at 25 °C under air for 12 hours. The reaction mixture was diluted with Et_2O (1.0 mL) and extracted with Et_2O (3×2.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford 211.2 mg (80%) of the title compound **SI-93**.

Physical State: colorless oil.

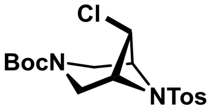
^{1}H NMR (400 MHz, CDCl$_3$): δ 0.18 (s, 27H).

^{13}C NMR (101 MHz, CDCl$_3$): δ -0.00.

HRMS (*m/z*): $[M-H]^-$ calcd for $C_9H_{27}OSi_4^-$ 263.1139, found 263.1139.

Experimental Procedures and Characterization Data of Substrates

Compound 15



tert-butyl (1R,5S,7r)-7-chloro-6-tosyl-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate **(15)**

To a solution of **10** (19.6 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) was added TosCl (38.0 mg, 0.2 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 25.5 mg (66%) of the title compound **15**.

Physical State: white solid.

m.p. 150-151 °C.

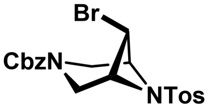
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 4.78 (t, J = 6.2 Hz, 1H), 4.50 – 4.39 (m, 2H), 3.75 (ddd, J = 13.0, 8.0, 2.6 Hz, 2H), 3.66 (ddd, J = 12.6, 5.5, 1.4 Hz, 2H), 2.45 (s, 3H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.86, 144.75, 135.62, 130.06, 127.61, 80.31, 64.76, 64.55, 50.47, 44.78, 44.21, 28.42, 21.66.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{23}ClN_2NaO_4S^+$ 409.0965, found 409.0964.

TLC: R_f = 0.5 (5:1 hexanes : ethyl acetate).

Compound 16



benzyl (1R,5S,7r)-7-bromo-6-tosyl-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate **(16)**

To a solution of **1** (23 mg, 0.1 mmol, 1.0 equiv.) in DCM (1.0 mL) was added TosBr (35.3 mg, 0.15 mmol, 1.5 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 26.9 mg (58%) of the title compound **16**.

Physical State: white solid.

m.p. 131-133 °C.

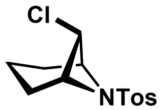
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.73 (m, 2H), 7.41 – 7.27 (m, 7H), 5.16 (s, 2H), 4.94 (t, *J* = 6.2 Hz, 1H), 4.48 (ddddd, *J* = 14.0, 6.4, 4.8, 2.7, 1.7 Hz, 2H), 3.87 (td, *J* = 12.1, 2.7 Hz, 2H), 3.79 (ddd, *J* = 12.8, 4.7, 1.7 Hz, 2H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.43, 144.85, 136.39, 135.46, 130.07, 128.54, 128.13, 127.83, 127.62, 67.35, 64.21, 63.97, 45.91, 45.78, 41.28, 21.64.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{21}BrN_2NaO_4S^+$ 487.0303, found 487.0304.

TLC: R_f = 0.3 (3:1 hexanes : ethyl acetate).

Compound 17



(1R,5S,7r)-7-chloro-6-tosyl-6-azabicyclo[3.1.1]heptane **(17)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) was added TosCl (38.0 mg, 0.2 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3 × 1.0 mL).

The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 18.9 mg (66%) of the title compound **17**.

Physical State: white solid.

m.p. 81-82 °C.

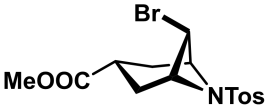
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 4.56 (t, *J* = 6.3 Hz, 1H), 4.38 (dq, *J* = 6.0, 4.0 Hz, 2H), 2.44 (s, 3H), 2.13 (ddt, *J* = 13.4, 9.2, 3.6 Hz, 2H), 2.02 (ddd, *J* = 14.4, 9.2, 6.2 Hz, 2H), 1.94 – 1.78 (m, 2H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 144.18, 136.32, 129.98, 127.43, 68.07, 53.45, 23.10, 21.62, 13.72.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{13}H_{16}ClNNaO_2S^+$ 308.0488, found 308.0486.

TLC: R_f = 0.4 (10:1 hexanes : ethyl acetate).

Compound 18



***methyl (1R,3r,5S,7r)-7-bromo-6-tosyl-6-azabicyclo[3.1.1]heptane-3-carboxylate* (18)**

The reaction vessel was added a solution of **SI-32** (34.5 mg, 0.1 mmol, 1.0 equiv.) in THF (1.0 mL) and backfilled with argon three times. After cooling the mixture to -78 °C, PhLi (0.2 mol/L, ether solution, 1.0 mL, 0.2 mmol, 2.0 equiv.) was added dropwise via syringe, and the reaction solution was stirred at 0 °C for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo, after dissolution in MeCN and filtration via diatomaceous earth, the crude product was used directly in further reactions. Yield: 39% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard). To the resulting filtrate was added TosBr (23.5 mg, 0.1 mmol, 1.0 equiv.) and then the mixture was stirred at 25 °C for 18 hours and evaporated in vacuo. The residue was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 9.1 mg (60%) of the title compound **18**.

Physical State: white solid.

m.p. 142-144 °C.

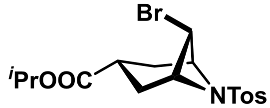
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 4.76 (t, *J* = 6.4 Hz, 1H), 4.44 (t, *J* = 5.4 Hz, 2H), 3.72 (s, 3H), 3.17 (p, *J* = 9.1 Hz, 1H), 2.55 – 2.38 (m, 7H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 174.20, 144.52, 135.95, 130.10, 127.44, 66.67, 52.08, 46.70, 32.39, 26.90, 21.65.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{15}H_{18}BrNNaO_4S^+$ 410.0038, found 410.0039.

TLC: R$_f$ = 0.3 (5:1 hexanes : ethyl acetate).

Compound 19



***isopropyl (1R,3r,5S,7r)-7-bromo-6-tosyl-6-azabicyclo[3.1.1]heptane-3-carboxylate* (19)**

The reaction vessel was added a solution of **SI-37** (37.3 mg, 0.1 mmol, 1.0 equiv.) in THF (1.0 mL) and backfilled with argon three times. After cooling the mixture to -78 °C, PhLi (0.2 mol/L, ether solution, 1.0 mL, 0.2 mmol, 2.0 equiv.) was added dropwise via syringe, and the reaction solution was stirred at 0 ℃ for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo, after dissolution in MeCN and filtration via diatomaceous earth, the crude product was used directly in further reactions. Yield: 43% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard). To the resulting filtrate was added TosBr (23.5 mg, 0.1 mmol, 1.0 equiv.) and then the mixture was stirred at 25 °C for 18 hours and evaporated in vacuo. The residue was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 11.6 mg (65%) of the title compound **19**.

Physical State: white solid.

m.p. 127-128 °C.

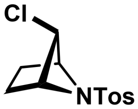
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 5.05 (hept, *J* = 6.3 Hz, 1H), 4.78 (t, *J* = 6.3 Hz, 1H), 4.48 – 4.41 (m, 2H), 3.11 (p, *J* = 9.1 Hz, 1H), 2.55 – 2.36 (m, 7H), 1.24 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 173.24, 144.46, 136.01, 130.07, 127.45, 68.16, 66.76, 46.75, 32.61, 26.94, 21.81, 21.65.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{17}H_{22}BrNNaO_4S^+$ 438.0351, found 438.0349.

TLC: R$_f$ = 0.3 (5:1 hexanes : ethyl acetate).

Compound 20



(1R,4S,6r)-6-chloro-5-tosyl-5-azabicyclo[2.1.1]hexane **(20)**

To a solution of **3** (8.1 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) was added TosCl (38.0 mg, 0.2 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3 × 1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 17.9 mg (66%) of the title compound **20**.

Physical State: white solid.

m.p. 85-86 °C.

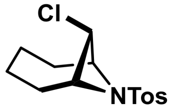
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.35 – 4.33 (m, 2H), 4.29 (tt, *J* = 2.8, 1.3 Hz, 1H), 2.43 (s, 3H), 2.26 – 2.20 (m, 2H), 2.07 – 2.02 (m, 2H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 144.04, 137.35, 129.65, 127.34, 72.38, 53.51, 23.79, 21.60.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{12}H_{14}ClNNaO_2S^+$ 294.0331, found 294.0334.

TLC: R$_f$ = 0.4 (10:1 hexanes : ethyl acetate).

Compound 21



***(1R,6S,8r)-8-chloro-7-tosyl-7-azabicyclo[4.1.1]octane* (21)**

The reaction vessel was added a solution of **SI-22** (60.2 mg, 0.2 mmol, 1.0 equiv.) in THF (2.0 mL) and backfilled with argon three times. After cooling the mixture to -78 °C, PhLi (0.2 mol/L, ether solution, 2.0 mL, 0.4 mmol, 2.0 equiv.) was added dropwise via syringe, and the reaction solution was stirred at 0 °C for 3 hours under an argon atmosphere. The reaction solution was concentrated in vacuo (35 °C, 160 mbar). Yield: 25% (determined by ^{1}H NMR of the crude reaction mixture using dibromomethane as an internal standard). After dissolution in MeCN and filtration via diatomaceous earth, the crude product was used directly in further reactions. To the resulting filtrate was added TosCl (95 mg, 0.5 mmol, 1.0 equiv.) and then the mixture was stirred at 25 °C for 18 hours and evaporated in vacuo. The residue was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 9.0 mg (60%) of the title compound **21**.

Physical State: white solid.

m.p. 131-132 °C.

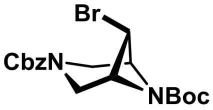
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.47 – 4.40 (m, 2H), 4.38 – 4.29 (m, 1H), 2.46 (s, 3H), 2.02 – 1.82 (m, 8H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 144.22, 134.95, 130.03, 127.51, 67.79, 52.54, 27.92, 23.15, 21.64.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{14}H_{18}ClNNaO_2S^+$ 322.0644, found 322.0645.

TLC: R$_f$ = 0.3 (10:1 hexanes : ethyl acetate).

Compound 22



***3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-bromo-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarbo-xylate* (22)**

To a solution of **1** (1.15 g, 5 mmol, 1.0 equiv.) in MeCN (50 mL) were added LiBr (2.18 g, 25 mmol, 5.0 equiv.) and Boc$_2$O (2.18 g, 10 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×50 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 1.77 g (86%) of the title compound **22**.

Physical State: white solid.

m.p. 98-99 °C.

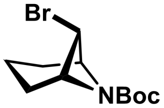
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.38 – 7.27 (m, 5H), 5.20 (d, *J* = 12.5 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 4.66 (t, *J* = 5.9 Hz, 1H), 4.29 (dt, *J* = 6.4, 3.5 Hz, 1H), 4.23 (dt, *J* = 6.6, 3.5 Hz, 1H), 4.18 – 4.08 (m, 2H), 3.57 – 3.50 (m, 2H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 155.83, 155.77, 136.56, 128.51, 128.04, 127.79, 81.53, 67.19, 62.45, 62.07, 42.53, 42.20, 40.88, 28.09.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{18}H_{23}BrN_2NaO_4^+$ 433.0739, found 433.0737.

TLC: R_f = 0.3 (10:1 hexanes : ethyl acetate).

Compound 23



tert-butyl (1R,5S,7r)-7-bromo-6-azabicyclo[3.1.1]heptane-6-carboxylate **(23)**

To a solution of **2** (950 mg, 10 mmol, 1.0 equiv.) in MeCN (50 mL) were added LiBr (4.34 g, 50 mmol, 5.0 equiv.) and Boc$_2$O (4.36 g, 20 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×50 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 20:1) on silica gel to afford 2.18 g (79%) of the title compound **23**.

Physical State: white solid.

m.p. 84-85 °C.

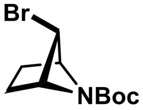
^{1}H NMR (500 MHz, CDCl$_3$): δ 4.71 (t, *J* = 6.0 Hz, 1H), 4.23 (s, 2H), 2.28 (s, br., 2H), 1.91 (t, *J* = 8.4 Hz, 1H), 1.94 (t, *J* = 8.2 Hz, 1H), 1.81 – 1.70 (m, 1H), 1.64 – 1.51 (m, 1H), 1.47 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 156.68, 80.12, 45.97, 28.28, 12.95. *Note: NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{11}H_{18}BrNNaO_2^+$ 298.0419, found 298.0421.

TLC: R$_f$ = 0.3 (20:1 hexanes : ethyl acetate).

Compound 24



tert-butyl (1R,4S,6r)-6-bromo-5-azabicyclo[2.1.1]hexane-5-carboxylate **(24)**

To a solution of **3** (8.1 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) were added LiBr (54.2 mg, 0.5 mmol, 5.0 equiv.) and Boc$_2$O (43.6 mg, 0.2 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 20:1) on silica gel to afford 21.7 mg (83%) of the title compound **24**.

Physical State: white solid.

m.p. 132-133 °C.

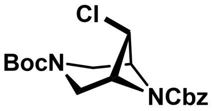
^{1}H NMR (500 MHz, CDCl$_3$): δ 4.22 (d, *J* = 2.8 Hz, 2H), 4.13 (tt, *J* = 2.8, 1.3 Hz, 1H), 2.01 (d, *J* = 8.6 Hz, 2H), 1.91 (d, *J* = 9.0 Hz, 2H), 1.44 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 157.51, 80.94, 68.84, 43.62, 28.11, 23.97.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{10}H_{16}BrNNaO_2^+$ 284.0262, found 284.0264.

TLC: R$_f$ = 0.3 (20:1 hexanes : ethyl acetate).

Compound 25



6-benzyl 3-(tert-butyl) (1R,5S,7r)-7-chloro-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate (25)

To a solution of **10** (19.6 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) was added CbzCl (34 mg, 0.2 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 21.2 mg (58%) of the title compound **25**.

Physical State: white solid.

m.p. 91-93 °C.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.40 – 7.30 (m, 5H), 5.15 (d, *J* = 12.2 Hz, 1H), 5.10 (d, *J* = 12.2

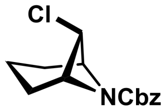
Hz, 1H), 4.62 (t, $J = 5.9$ Hz, 1H), 4.39 (dt, $J = 6.4, 3.5$ Hz, 1H), 4.32 (dt, $J = 6.5, 3.5$ Hz, 1H), 4.01 – 3.95 (m, 2H), 3.45 (dd, $J = 12.8, 6.8$ Hz, 2H), 1.47 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 156.12, 155.24, 135.80, 128.65, 128.41, 128.17, 80.17, 67.55, 63.14, 62.78, 49.42, 41.45, 41.13, 28.41.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{18}H_{23}ClN_2NaO_4^+$ 389.1244, found 389.1242.

TLC: $R_f = 0.3$ (5:1 hexanes : ethyl acetate).

Compound 26



benzyl (1R,5S,7r)-7-chloro-6-azabicyclo[3.1.1]heptane-6-carboxylate **(26)**

To a solution of **2** (19 mg, 0.2 mmol, 1.0 equiv.) in MeCN (1.0 mL) was added CbzCl (68 mg, 0.4 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 38.1 mg (72%) of the title compound **26**.

Physical State: colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.40 – 7.29 (m, 5H), 5.14 (s, 2H), 4.64 (t, $J = 6.0$ Hz, 1H), 4.35 – 4.32 (m, 2H), 2.19 (s, br., 2H), 1.92 (t, $J = 7.0$ Hz, 1H), 1.89 (t, $J = 6.0$ Hz, 1H), 1.78 – 1.68 (m, 1H), 1.50 (dddd, $J = 14.6, 9.8, 7.3, 2.3$ Hz, 1H).

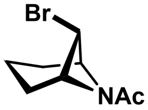
^{13}C NMR (126 MHz, CDCl$_3$): δ 156.89, 136.41, 128.55, 128.21, 128.11, 67.03, 52.65, 13.19.

Note: NCH and NCHCH$_2$ were not observed.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{14}H_{16}ClNNaO_2^+$ 288.0767, found 288.0768.

TLC: $R_f = 0.3$ (5:1 hexanes : ethyl acetate).

Compound 27



1-((1R,5S,7r)-7-bromo-6-azabicyclo[3.1.1]heptan-6-yl)ethan-1-one **(27)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in MeCN (0.5 mL) was added acetyl bromide (40.2 mg, 0.2 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×0.5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 11.3 mg (52%) of the title compound **27**.

Physical State: colorless oil.

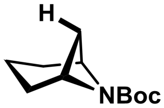
^{1}H NMR (500 MHz, CDCl$_3$): δ 4.76 (t, *J* = 6.1 Hz, 1H), 4.51 (q, *J* = 4.8 Hz, 1H), 4.39 (q, *J* = 4.8 Hz, 1H), 2.32 (dt, *J* = 12.6, 7.7 Hz, 1H), 2.18 – 2.05 (m, 2H), 1.99 – 1.91 (m, 4H), 1.87 – 1.77 (m, 1H), 1.68 – 1.57 (m, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 170.00, 66.77, 64.12, 45.46, 23.45, 21.75, 20.03, 13.31.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_8H_{12}BrNNaO^+$ 240.0000, found 240.0002.

TLC: R_f = 0.2 (2:1 hexanes : ethyl acetate).

Compound 28



tert-butyl (1R,5S)-6-azabicyclo[3.1.1]heptane-6-carboxylate **(28)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in THF (0.5 mL) was added $LiAlH_4$ (7.6 mg, 0.2 mmol, 2 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 3 hours under an argon atmosphere. Then Boc_2O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×0.5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 20:1) on silica gel to afford 10.2 mg (52%) of the title compound **28**.

Physical State: colorless oil.

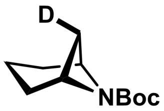
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.07 (s, br., 2H), 2.42 (dtt, *J* = 7.8, 6.3, 1.5 Hz, 1H), 2.33 (s, br., 1H), 2.20 (s, br., 1H), 1.98 – 1.84 (m, 1H), 1.74 – 1.59 (m, 3H), 1.46 (s, 9H), 1.36 (d, *J* = 8.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.59, 79.06, 28.91, 28.49, 14.24. *Note: NCH and NCH_2 were not observed.*

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{19}NNaO_2^+$ 220.1313, found 220.1312.

TLC: R_f = 0.4 (20:1 hexanes : ethyl acetate).

Compound 29



***tert-butyl (1R,5S,7r)-6-azabicyclo[3.1.1]heptane-6-carboxylate-7-d* (29)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in THF (0.5 mL) was added $LiAlD_4$ (8.4 mg, 0.2 mmol, 2 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 3 hours under an argon atmosphere. Then Boc_2O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×0.5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 20:1) on silica gel to afford 8.3 mg (42%) of the title compound **29**.

Physical State: colorless oil.

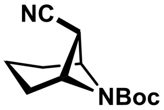
^{1}H NMR (500 MHz, CDCl$_3$): δ 4.06 (s, 2H), 2.40 (t, *J* = 6.4 Hz, 1H), 2.27 (s, 2H), 1.96 – 1.85 (m, 1H), 1.72 – 1.61 (m, 3H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 156.60, 79.05, 28.55 (t, J = 21.4 Hz), 28.49, 14.25. *Note: NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{18}DNNaO_2^+$ 221.1376, found 221.1376.

TLC: R_f = 0.4 (20:1 hexanes : ethyl acetate).

Compound 30



tert-butyl (1R,5S,7r)-7-cyano-6-azabicyclo[3.1.1]heptane-6-carboxylate **(30)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in MeCN (0.5 mL) were added Boc$_2$O (43.6 mg, 0.2 mmol, 2.0 equiv.) and TMSCN (49.5 mg, 0.5 mmol, 5.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×0.5 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 10.4 mg (47%) of the title compound **30**.

Physical State: white solid.

m.p. 99-101 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.28 (s, br. 2H), 3.50 – 3.42 (m, 1H), 2.40 (s, br., 2H), 2.06 – 1.88 (m, 3H), 1.75 – 1.62 (m, 1H), 1.47 (s, 9H).

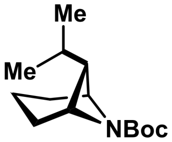
^{13}C NMR (101 MHz, CDCl$_3$): δ 156.64, 117.19, 80.50, 29.98, 28.25, 13.36. *Note: NCH and*

$NCHCH_2$ were not observed.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{18}N_2NaO_2^+$ 245.1266, found 245.1267.

TLC: R_f = 0.4 (10:1 hexanes : ethyl acetate).

Compound 31



tert-butyl (1R,5S,7r)-7-isopropyl-6-azabicyclo[3.1.1]heptane-6-carboxylate **(31)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in THF (0.5 mL) were added $Cu(OTf)_2$ (3.6 mg, 0.01 mmol, 0.1 equiv.) and iPr·MgCl·LiCl (1.0 M, THF, 0.1 mL, 0.1 mmol, 1.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 3 hours under an argon atmosphere. Then Boc_2O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with sat. aq. NH_4Cl (0.5 mL) and extracted with DCM (3×0.5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 20:1) on silica gel to afford 18.4 mg (77%) of the title compound **31**.

Physical State: colorless oil.

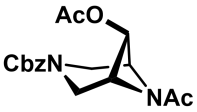
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.02 (s, 1H), 3.97 (s, 1H), 2.24 (s, br., 1H), 2.17 – 2.06 (m, 2H), 1.73 – 1.64 (m, 2H), 1.62 – 1.54 (m, 3H), 1.45 (s, 9H),0.81 (d, J = 5.2 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.46, 78.93, 62.92, 61.69, 46.38, 28.39, 23.62, 20.34, 19.74, 19.27, 14.04.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{14}H_{25}NNaO_2^+$ 262.1783, found 262.1785.

TLC: R_f = 0.3 (20:1 hexanes : ethyl acetate).

Compound 32



benzyl (1R,5S,7r)-7-acetoxy-6-acetyl-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate **(32)**

To a solution of **1** (23.0 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) was added Ac_2O (41.4 mg, 0.3 mmol, 3.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:2) on silica gel to afford 12.9 mg (39%) of the title compound **32**.

Physical State: colorless oil.

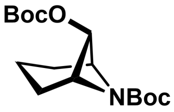
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 – 7.29 (m, 5H), 5.23 – 5.10 (m, 3H), 4.72 – 4.48 (m, 2H), 4.16 – 4.02 (m, 1H), 3.93 – 3.83 (m, 1H), 3.49 – 3.37 (m, 2H), 2.09 – 2.01 (m, 3H), 2.00 – 1.89 (m, 3H). *Note: a mixture of isomers, attribute to rotational isomerization of amides, was observed.*

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.68, 170.10, 156.08, 155.67, 136.32, 128.56, 128.23, 128.16, 128.01, 127.86, 67.42, 67.37, 63.12, 62.95, 62.83, 62.71, 59.91, 59.73, 42.98, 42.92, 42.08, 41.57, 29.71, 20.63, 20.56.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{20}N_2NaO_5^+$ 355.1270, found 355.1272.

TLC: R_f = 0.2 (1:2 hexanes : ethyl acetate).

Compound 33



tert-butyl (1R,5S,7r)-7-((tert-butoxycarbonyl)oxy)-6-azabicyclo[3.1.1]heptane-6-carboxylate

(33)

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) were added K_2CO_3 (41.4 mg, 0.3 mmol, 3.0 equiv.) and Boc_2O (43.6 mg, 0.2 mmol, 3.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 20.7 mg (66%) of the title compound **33**.

Physical State: colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.89 (t, J = 5.9 Hz, 1H), 4.29 (s, br., 2H), 2.18 (s, br., 2H), 1.82 – 1.63 (m, 3H), 1.59 – 1.51 (m, 1H), 1.49 (s, 9H), 1.47 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 157.13, 152.45, 82.82, 79.71, 66.55, 28.32, 27.71, 13.97. *Note: NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{27}NNaO_5^+$ 336.1787, found 336.1788.

TLC: R_f = 0.3 (10:1 hexanes : ethyl acetate).

Compound 34

***3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-methoxy-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate* (34)**

To a solution of **1** (460 mg, 2 mmol, 1.0 equiv.) in MeOH (20 mL) was added HBr (48%, 337.1 mg, 2.0 mmol, 1.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc_2O (872.4 mg, 4.0 mmol, 2.0 equiv.) and K_2CO_3 (552.2 mg, 4.0 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo.

The residue was diluted with water and extracted with DCM (3×20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 514.0 mg (71%) of the title compound **34**.

Physical State: colorless oil.

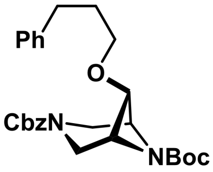
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.26 (m, 5H), 5.17 (d, J = 12.5 Hz, 1H), 5.11 (d, J = 12.4 Hz, 1H), 4.24 (s, 1H), 4.19 (s, 1H), 4.04 (s, br., 2H), 4.00 (t, J = 5.6 Hz, 1H), 3.34 (s, 3H), 3.29 (t, J = 12.7 Hz, 2H), 1.38 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.81, 156.09, 136.75, 128.45, 127.93, 127.83, 80.76, 69.47, 66.96, 57.12, 28.12. *Note: NCH and $NCHCH_2$ were not observed.*

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{26}N_2NaO_5^+$ 385.1739, found 385.1741.

TLC: R_f = 0.3 (5:1 hexanes : ethyl acetate).

Compound 35



***3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-(3-phenylpropoxy)-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate* (35)**

To a solution of **1** (23 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) were added TfOH (0.2 mol/L, MeCN solution, 0.5 mL, 0.1 mmol, 1.0 equiv.) and phenylpropanol (27.2 mg, 0.2 mmol, 2.0 equiv.) at -35 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc_2O (43.6 mg, 0.2 mmol, 2.0 equiv.) and DIPEA (25.8 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 14.4 mg (31%) of the title compound **35**.

Physical State: colorless oil.

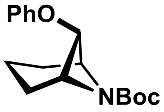
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.24 (m, 7H), 7.20 – 7.13 (m, 3H), 5.21 – 5.10 (m, 2H), 4.22 (s, 1H), 4.17 (s, 1H), 4.08 – 4.04 (m, 3H), 3.45 (td, J = 6.5, 3.5 Hz, 2H), 3.36 – 3.29 (m, 2H), 2.68 – 2.62 (m, 2H), 1.89 (dq, J = 8.4, 6.5 Hz, 2H), 1.39 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.36, 136.78, 128.47, 128.43, 128.39, 127.93, 127.79, 125.97, 80.73, 69.02, 68.30, 66.97, 32.14, 31.12, 28.13. *Note: CO, NCH and $NCHCH_2$ were not observed.*

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{27}H_{34}N_2NaO_5^+$ 489.2365, found 489.2365.

TLC: R_f = 0.3 (3:1 hexanes : ethyl acetate).

Compound 36



tert-butyl (1R,5S,7r)-7-phenoxy-6-azabicyclo[3.1.1]heptane-6-carboxylate **(36)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in toluene (1.0 mL) was added phenol (18.8 mg, 0.2 mmol, 2.0 equiv.) at 25 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc_2O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 20.5 mg (71%) of the title compound **36**.

Physical State: white solid.

m.p. 76-78 °C.

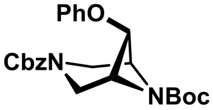
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.33 – 7.26 (m, 2H), 6.98 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 2H), 4.72 (t, *J* = 5.7 Hz, 1H), 4.41 (s, br., 2H), 2.16 (s, br., 2H), 1.86 – 1.71 (m, 3H), 1.57 (s, 1H), 1.49 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 157.34, 157.04, 129.68, 121.53, 114.88, 79.66, 67.97, 28.37, 14.35. *Note: NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{17}H_{23}NNaO_3^+$ 312.1576, found 312.1575.

TLC: R$_f$ = 0.2 (5:1 hexanes : ethyl acetate).

Compound 37



***3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-phenoxy-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate* (37)**

To a solution of **1** (23 mg, 0.1 mmol, 1.0 equiv.) in toluene (1.0 mL) was added phenol (18.8 mg, 0.2 mmol, 2.0 equiv.) at 25 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc$_2$O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K$_2$CO$_3$ (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 20.8 mg (49%) of the title compound **37**.

Physical State: white solid.

m.p. 127-128 °C.

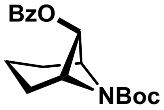
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.36 – 7.25 (m, 7H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 2H), 5.18 (d, *J* = 12.5 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 4.80 (t, *J* = 5.6 Hz, 1H), 4.46 (s, br., 1H), 4.41 (s, br., 1H), 4.11 (s, br., 2H), 3.39 (dd, *J* = 12.4, 5.4 Hz, 2H), 1.41 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 156.57, 156.12, 136.64, 129.82, 128.48, 127.98, 127.80, 122.16, 114.89, 81.13, 67.07, 65.86, 28.13. *Note: NCH, NCH$_2$ and a CO were not observed.*

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{24}H_{28}N_2NaO_5^+$ 447.1896, found 447.1896.

TLC: R$_f$ = 0.3 (3:1 hexanes : ethyl acetate).

Compound 38



***tert-butyl (1R,5S,7r)-7-(benzoyloxy)-6-azabicyclo[3.1.1]heptane-6-carboxylate* (38)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in toluene (1.0 mL) was added benzoic acid (18.3 mg, 0.15 mmol, 1.5 equiv.) at 25 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc$_2$O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 25.7 mg (81%) of the title compound **38**.

Physical State: white solid.

m.p. 98-100 °C.

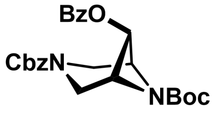
^{1}H NMR (500 MHz, CDCl$_3$): δ 8.08 – 8.03 (m, 2H), 7.64 – 7.57 (m, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 5.29 (t, *J* = 5.9 Hz, 1H), 4.43 (s, 2H), 2.27 (s, br., 2H), 1.85 – 1.76 (m, 3H), 1.70 – 1.60 (m, 1H), 1.49 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 165.59, 157.07, 133.50, 129.63, 129.44, 128.61, 79.79, 65.43, 64.80, 63.73, 28.35, 20.68, 19.86, 14.01.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{18}H_{23}NNaO_4^+$ 340.1525, found 340.1524.

TLC: R$_f$ = 0.3 (5:1 hexanes : ethyl acetate).

Compound 39



3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-(benzoyloxy)-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate **(39)**

To a solution of **1** (46 mg, 0.2 mmol, 1.0 equiv.) in toluene (2.0 mL) was added benzoic acid (36.6 mg, 0.3 mmol, 1.5 equiv.) at 25 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc$_2$O (87.2 mg, 0.4 mmol, 2.0 equiv.) and K_2CO_3 (55.2 mg, 0.4 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×2.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 78.6 mg (87%) of the title compound **39**.

Physical State: white solid.

m.p. 121-124 °C.

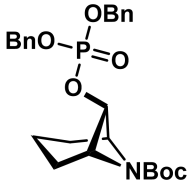
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.95 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.60 (tt, *J* = 7.1, 1.3 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.35 – 7.27 (m, 5H), 5.37 (t, *J* = 5.8 Hz, 1H), 5.17 (d, *J* = 12.5 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 4.48 (s, br. 1H), 4.44 (s, br. 1H), 4.28 – 4.09 (m, 2H), 3.45 (d, *J* = 12.7 Hz, 1H), 3.40 (d, *J* = 12.5 Hz, 1H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 165.47, 156.21, 156.07, 136.56, 133.84, 129.72, 128.72, 128.66, 128.50, 128.02, 127.72, 81.25, 67.13, 63.10, 28.14. *Note: NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{25}H_{28}N_2NaO_6^+$ 475.1845, found 475.1844.

TLC: R$_f$ = 0.3 (5:1 hexanes : ethyl acetate).

Compound 40



tert-butyl (1R,5S,7r)-7-((bis(benzyloxy)phosphoryl)oxy)-6-azabicyclo[3.1.1]heptane-6-carboxylate **(40)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in toluene (1.0 mL) was added dibenzyl phosphate (55.6 mg, 0.2 mmol, 2.0 equiv.) at 25 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc_2O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 20.8 mg (44%) of the title compound **40**.

Physical State: colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.41 – 7.31 (m, 10H), 5.12 – 5.01 (m, 4H), 4.71 (q, J = 6.0 Hz, 1H), 4.08 (s, br. 2H), 2.06 (s, br., 2H), 1.71 – 1.57 (m, 4H), 1.44 (s, 9H).

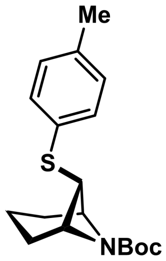
^{13}C NMR (126 MHz, CDCl$_3$): δ 135.51, 128.78, 128.70, 128.01, 79.81, 69.68, 69.63, 66.66, 28.29, 13.85. *Note: NCO, NCH and NCHCH$_2$ were not observed.*

^{31}P NMR (202 MHz, CDCl3): δ -1.90.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{25}H_{32}NNaO_6P^+$ 496.1865, found 496.1864.

TLC: R_f = 0.3 (3:1 hexanes : ethyl acetate).

Compound 41



tert-butyl (1R,5S,7r)-7-(p-tolylthio)-6-azabicyclo[3.1.1]heptane-6-carboxylate **(41)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in THF (1.0 mL) was added 4-methoxybenzenethiol (28.0 mg, 0.2 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc_2O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 18.5 mg (58%) of the title compound **41**.

Physical State: white solid.

m.p. 72-74 °C.

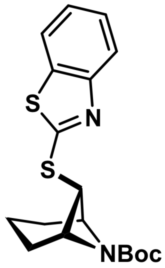
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 – 7.16 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 4.27 (s, br. 2H), 4.08 (t, *J* = 6.1 Hz, 1H), 2.31 (s, 3H), 2.19 (s, br., 2H), 1.92 – 1.84 (m, 2H), 1.78 – 1.83 (m, 1H), 1.58 – 1.67 (m, 1H), 1.47 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.77, 136.52, 131.73, 129.89, 129.82, 79.66, 47.05, 28.35, 21.00, 13.76. *Note: NCH and $NCHCH_2$ were not observed.*

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{25}NNaO_2S^+$ 342.1504, found 342.1503.

TLC: R_f = 0.3 (10:1 hexanes : ethyl acetate).

Compound 42



***tert-butyl (1R,5S,7r)-7-(benzo[d]thiazol-2-ylthio)-6-azabicyclo[3.1.1]heptane-6-carbox-ylate* (42)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in THF (1.0 mL) was added 2-benzothiazolethiol (28.0 mg, 0.2 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc_2O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 23.9 mg (66%) of the title compound **42**.

Physical State: white solid.

m.p. 118-119 °C.

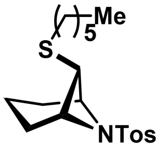
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.86 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 4.80 (t, *J* = 6.2 Hz, 1H), 4.46 (s, 2H), 2.35 (s, br., 1H), 2.28 (s, br., 1H), 1.86 – 1.75 (m, 3H), 1.69 – 1.60 (m, 1H), 1.49 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 164.57, 156.57, 153.21, 135.17, 126.22, 124.50, 121.80, 120.98, 79.93, 65.06, 63.86, 45.15, 28.37, 21.60, 20.90, 13.54.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{22}N_2NaO_2S_2^+$ 385.1020, found 385.1021.

TLC: R*f* = 0.3 (3:1 hexanes : ethyl acetate).

Compound 43



(1R,5S,7r)-7-(hexylthio)-6-tosyl-6-azabicyclo[3.1.1]heptane **(43)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in THF (1.0 mL) was added 1-hexanethiol (23.6 mg, 0.2 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then TosCl (38.0 mg, 0.2 mmol, 2.0 equiv.) was added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 22.7 mg (62%) of the title compound **43**.

Physical State: colorless oil.

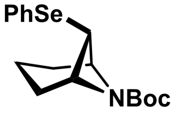
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.33 – 4.26 (m, 2H), 3.58 (t, *J* = 6.4 Hz, 1H), 2.44 (s, 3H), 2.30 (t, *J* = 7.4 Hz, 2H), 2.17 – 2.08 (m, 2H), 1.98 – 1.77 (m, 4H), 1.42 – 1.31 (m, 2H), 1.33 – 1.18 (m, 6H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 143.69, 136.88, 129.76, 127.46, 67.85, 48.01, 32.65, 31.36, 30.46, 28.39, 24.09, 22.54, 21.58, 14.37, 14.04.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{29}NNaO_2S_2^+$ 390.1537, found 390.1539.

TLC: R_f = 0.3 (10:1 hexanes : ethyl acetate).

Compound 44



tert-butyl (1R,5S,7r)-7-(phenylselanyl)-6-azabicyclo[3.1.1]heptane-6-carboxylate **(44)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in THF (1.0 mL) was added phenylselenol (28.0 mg, 0.2 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc_2O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 21.8 mg (62%) of the title compound **44**.

Physical State: white solid.

m.p. 66-67 °C.

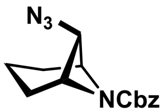
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.47 – 7.41 (m, 2H), 7.27 – 7.24 (m, 3H), 4.28 (s, 2H), 4.25 (dd, J = 12.4, 6.9 Hz, 1H), 2.30 (s, br., 2H), 1.93 – 1.83 (m, 2H), 1.84 – 1.73 (m, 1H), 1.70 – 1.57 (m, 1H), 1.47 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 156.54, 132.61, 129.81, 129.29, 127.17, 79.68, 44.65, 28.36, 13.64. *Note: NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{17}H_{23}NNaO_2Se^+$ 376.0792, found 376.0793.

TLC: R_f = 0.3 (10:1 hexanes : ethyl acetate).

Compound 45



benzyl (1R,5S,7r)-7-azido-6-azabicyclo[3.1.1]heptane-6-carboxylate **(45)**

To a solution of **2** (19 mg, 0.2 mmol, 1.0 equiv.) in MeCN (1.0 mL) was added $CbzN_3$ (70.8 mg, 0.4 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 30.5 mg (56%) of the title compound **45**.

Physical State: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.27 (m, 5H), 5.13 (s, 2H), 4.38 – 4.28 (m, 3H), 2.14 (s, br., 2H), 1.81 – 1.68 (m, 3H), 1.49 – 1.41 (m, 1H).

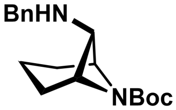
^{13}C NMR (101 MHz, $CDCl_3$): δ 157.02, 136.49, 128.53, 128.16, 128.09, 66.88, 55.83, 13.65.

Note: NCH and NCHCH$_2$ were not observed.

HRMS (*m/z*): $[M-N_2+Na]^+$ calcd for $C_{14}H_{16}N_2NaO_2^+$ 267.1109, found 267.1111.

TLC: $R_f = 0.3$ (5:1 hexanes : ethyl acetate).

Compound 46



***tert-butyl (1R,5S,7r)-7-(benzylamino)-6-azabicyclo[3.1.1]heptane-6-carboxylate* (46)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) was added TfOH (0.2 mol/L, MeCN solution, 0.5 mL, 0.1 mmol, 1.0 equiv.) and benzylamine (21.4 mg, 0.2 mmol, 2.0 equiv.) at -35 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc_2O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 10.3 mg (34%) of the title compound **46**.

Physical State: colorless oil.

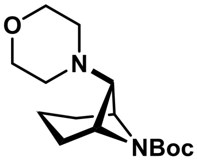
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.36 – 7.23 (m, 5H), 4.12 (s, 1H), 4.07 (s, 1H), 3.73 (s, 2H), 3.56 (t, J = 6.0 Hz, 1H), 2.21 (s, br., 1H), 2.08 (s, br., 1H), 1.73 – 1.53 (m, 5H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 157.51, 139.92, 128.56, 128.25, 127.31, 79.23, 53.70, 51.72, 28.38, 14.00. *Note: NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{18}H_{27}N_2O_2^+$ 303.2073, found 303.2071.

TLC: R$_f$ = 0.3 (5:1 hexanes : ethyl acetate).

Compound 47



tert-butyl (1R,5S,7r)-7-morpholino-6-azabicyclo[3.1.1]heptane-6-carboxylate **(47)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) were added TfOH (0.2 mol/L, MeCN solution, 0.5 mL, 0.1 mmol, 1.0 equiv.) and morpholine (17.4 mg, 0.2 mmol, 2.0 equiv.) at -35 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc$_2$O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K$_2$CO$_3$ (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 19.7 mg (70%) of the title compound **47**.

Physical State: white solid.

m.p. 143-144 °C.

^{1}H NMR (500 MHz, CDCl$_3$): δ 4.09 (s, 1H), 4.03 (s, 1H), 3.70 (t, J = 4.7 Hz, 4H), 2.83 (t, J = 5.8 Hz, 1H), 2.29 – 2.23 (m, 4H), 2.12 (s, br., 1H), 1.98 (s, br., 1H), 1.88 – 1.77 (m, 1H), 1.74 –

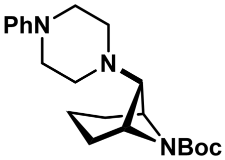
1.63 (m, 2H), 1.56 – 1.48 (m, 1H), 1.46 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 157.50, 79.28, 66.55, 62.97, 61.77, 60.06, 50.69, 28.37, 20.52, 19.53, 15.08.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{15}H_{27}N_2O_3^+$ 283.2022, found 283.2024.

TLC: R$_f$ = 0.3 (5:1 hexanes : ethyl acetate).

Compound 48



tert-butyl (1R,5S,7r)-7-(4-phenylpiperazin-1-yl)-6-azabicyclo[3.1.1]heptane-6-carboxylate **(48)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) were added TfOH (0.2 mol/L, MeCN solution, 0.5 mL, 0.1 mmol, 1.0 equiv.) and 4-phenylpiperidine (32.2 mg, 0.2 mmol, 2.0 equiv.) at -35 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc$_2$O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K$_2$CO$_3$ (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 27.8 mg (78%) of the title compound **48**.

Physical State: white solid.

m.p. 106-108 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.25 (t, J = 7.5 Hz, 2H), 6.92 (d, J = 8.2 Hz, 2H)., 6.86 (t, J = 7.3 Hz, 1H), 4.13 (s, 1H), 4.08 (s, 1H), 3.20 (t, J = 5.0 Hz, 4H), 2.89 (t, J = 5.8 Hz, 1H), 2.43 (t, J = 5.0 Hz, 4H), 2.15 (s, br., 1H), 2.01 (s, br., 1H), 1.68 – 1.89 (m, 3H), 1.61 – 1.49 (m, 1H), 1.48

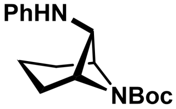
(s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 157.57, 151.34, 129.12, 119.76, 116.04, 79.27, 63.12, 61.92, 59.94, 50.22, 48.69, 28.41, 20.58, 19.59, 15.10.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{21}H_{32}N_3O_2^+$ 358.2495, found 358.2493.

TLC: R$_f$ = 0.3 (10:1 hexanes : ethyl acetate).

Compound 49



***tert-butyl (1R,5S,7r)-7-(phenylamino)-6-azabicyclo[3.1.1]heptane-6-carboxylate* (49)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) were added TfOH (0.2 mol/L, MeCN solution, 0.5 mL, 0.1 mmol, 1.0 equiv.) and aniline (18.6 mg, 0.2 mmol, 2.0 equiv.) at -35 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then Boc$_2$O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 22.8 mg (79%) of the title compound **49**.

Physical State: white solid.

m.p. 142-143 °C.

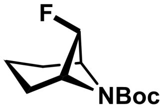
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.18 (t, J = 7.9 Hz, 2H), 6.75 (t, J = 7.3 Hz, 1H), 6.62 (d, J = 7.9 Hz, 2H), 4.31 (s, br., 2H), 4.12 (q, J = 6.0 Hz, 1H), 3.86 (d, J = 6.1 Hz, 1H), 2.31 (s, br., 1H), 2.16 (s, br., 1H), 1.79 – 1.63 (m, 1H), 1.65 – 1.57 (m, 3H), 1.49 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 157.36, 146.49, 129.45, 118.33, 113.09, 79.54, 64.48, 63.22, 49.30, 28.39, 19.99, 19.06, 13.82.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{24}N_2NaO_2^+$ 311.1735, found 311.1736.

TLC: R_f = 0.3 (10:1 hexanes : ethyl acetate).

Compound 50



tert-butyl (1R,5S,7r)-7-fluoro-6-azabicyclo[3.1.1]heptane-6-carboxylate **(50)**

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in MeCN (50 mL) were added LiBr (43.5 mg, 0.5 mmol, 5.0 equiv.) and Boc_2O (43.6 mg, 0.2 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. Then PPh_3 (2.62 mg, 0.01 mmol, 0.1 equiv.) and AgF (12.7 mg, 0.1 mmol, 1.0 equiv.) were added at 25 °C and the mixture was stirred for a further 6 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×0.5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 16.6 mg (77%) of the title compound **50**.

Physical State: white solid.

m.p. 50-51 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.03 (dt, J = 60.0, 5.8 Hz, 1H), 4.26 (s, br., 2H), 2.19 (s, br., 2H), 1.82 – 1.69 (m, 3H), 1.61 – 1.53 (m, 1H), 1.46 (s, 9H).

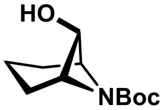
^{13}C NMR (126 MHz, $CDCl_3$): δ 157.29, 80.44 (d, J = 221.9 Hz), 79.85, 64.78, 28.30, 19.98, 14.11.

^{19}F NMR (471 MHz, $CDCl_3$): δ -198.99 (d, J = 60.4 Hz).

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{18}FNNaO_2^+$ 238.1219, found 238.1219.

TLC: R_f = 0.3 (10:1 hexanes : ethyl acetate).

Compound 51



tert-butyl (1R,5S,7r)-7-hydroxy-6-azabicyclo[3.1.1]heptane-6-carboxylate **(51)**

To a solution of **23** (276 mg, 1.0 mmol, 1.0 equiv.) in DMF (5.0 mL) was added $AgNO_2$ (258 mg, 2.0 mmol, 2.0 equiv.) at 0 °C and the mixture was stirred for 6 hours at 25 °C under an argon atmosphere and protected from light. After the reaction was completed, the reaction mixture was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in EtOH (5.0 mL), then 1 M NaOH (2.0 mL) was added at 25 °C, the reaction mixture was stirred at 25 °C for 3 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×3.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 115.0 mg (54%) of the title compound **51**.

Physical State: white solid.

m.p. 98-99 °C.

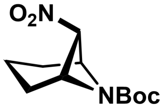
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.44 (q, *J* = 5.2 Hz, 1H), 4.13 (s, br., 2H), 2.67 (d, *J* = 4.9 Hz, 1H), 2.12 (s, br., 2H), 1.85 – 1.61 (m, 3H), 1.54 – 1.47 (m, 1H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.71, 79.49, 65.83, 64.87, 63.52, 28.35, 19.87, 19.15, 14.16.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{19}NNaO_3^+$236.1263, found 236.1263.

TLC: R_f = 0.3 (3:1 hexanes : ethyl acetate).

Compound 52



tert-butyl (1R,5S,7r)-7-nitro-6-azabicyclo[3.1.1]heptane-6-carboxylate **(52)**

52 was prepared according to the previously reported procedure[7-9]. To a solution of **23** (276 mg, 1.0 mmol, 1.0 equiv.) in Et_2O (5.0 mL) was added $AgNO_2$ (258 mg, 2.0 mmol, 2.0 equiv.) at 0 °C and the mixture was stirred for 12 hours at 25 °C under an argon atmosphere and protected from light. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×3.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 75.0 mg (31%) of the title compound **52**.

Physical State: white solid.

m.p. 128-130 °C.

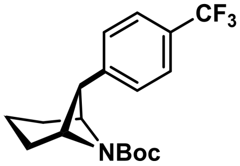
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.90 (t, J = 6.1 Hz, 1H), 4.49 (dt, J = 6.4, 1.8 Hz, 2H), 2.33 (s, br., 2H), 2.00 – 1.91 (m, 2H), 1.69 – 1.51 (m, 2H), 1.47 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.72, 80.84, 72.47, 63.99, 28.33, 20.58, 12.70.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{18}N_2NaO_4^+$ 265.1164, found 265.1165.

TLC: R_f = 0.3 (10:1 hexanes : ethyl acetate).

Compound 53



***tert-butyl (1R,5S,7s)-7-(4-(trifluoromethyl)phenyl)-6-azabicyclo[3.1.1]heptane-6-carboxylate* (53)**

A mixture of **23** (55.2 mg, 0.2 mmol, 2.0 equiv.), $CsCO_3$ (65.2 mg, 0.2 mmol, 2.0 equiv.), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (2.24 mg, 2 μmol, 0.02 equiv.), $Ni(dtbpy)Br_2$(2.45 mg, 5 μmol, 0.05 equiv.) was prepared in a 10 mL oven-dried tube. This reaction tube was backfilled with argon three times. To the mixture was added trifluorotoluene (2.0 mL, previously degassed by sparging with argon for 15 min). The mixture was stirred at 25 °C for 5 min and then placed in front of the

Kessil Blue LED photoreactor (450 nm, 100% light intensity) with fan cooling. The mixture was stirred under argon for 2 hours. While stirring and irradiating the reaction mixture, a solution of 4-bromobenzotrifluoride (22.5 mg, 0.1 mmol, 1.0 equiv.) and **SI-92** (63.5 mg, 0.16 mmol, 1.6 equiv.) in trifluorotoluene (1.0 mL, previously degassed by sparging with argon for 15 min) was added via syringe pump at a rate of 2.0 mL/h over 30 min. After complete addition, the mixture was irradiated for 90 min. After the reaction was completed, the reaction mixture was removed from the photoreactor, opened to air. To the mixture, EA (2.0 mL) and methanol (60 µL) were added. The reaction mixture was stirred at 25 °C for 1 hour and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 20.8 mg (61%) of the title compound **53**.

Physical State: white solid.

m.p. 74-75 °C.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.63 – 7.52 (m, 4H), 4.18 (q, *J* = 2.8 Hz, 1H), 4.04 (q, *J* = 3.2 Hz, 1H), 2.76 (s, 1H), 2.56 (ddt, *J* = 13.3, 8.6, 4.1 Hz, 1H), 2.39 (ddt, *J* = 13.2, 8.7, 5.1 Hz, 1H), 1.99 (dtt, *J* = 14.0, 8.8, 5.0 Hz, 1H), 1.87 (dddd, *J* = 19.0, 10.4, 5.1, 1.6 Hz, 2H), 1.77 (dtd, *J* = 14.0, 8.9, 4.7 Hz, 1H), 1.47 (s, 9H).

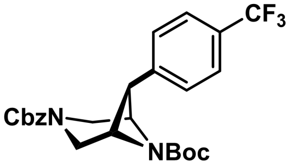
^{13}C NMR (126 MHz, CDCl$_3$): δ 157.04, 145.60,128.96 (q, *J* = 13.8 Hz)., 127.62, 125.41 (q, *J* = 4.0 Hz)., 79.62, 66.85, 65.12, 47.02, 28.44, 26.77, 25.46, 14.55. *Note: CF3 was not observed.*

^{19}F NMR (471 MHz, CDCl$_3$): δ -62.41.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{22}F_3NNaO_2^+$ 364.1500, found 364.1500.

TLC: R_f=0.3 (10:1 hexanes : ethyl acetate).

Compound 54



3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-(4-(trifluoromethyl)phenyl)-3,6-diazabicyclo[3.1.1] heptane-3,6-dicarboxylate **(54)**

A mixture of **22** (82.2 mg, 0.2 mmol, 2.0 equiv.), $CsCO_3$ (65.2 mg, 0.2 mmol, 2.0 equiv.), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (2.24 mg, 2 μmol, 0.02 equiv.), $Ni(dtbpy)Br_2$(2.45 mg, 5 μmol, 0.05 equiv.) was prepared in a 10 mL oven-dried tube. This reaction tube was backfilled with argon three times. To the mixture was added trifluorotoluene (2.0 mL, previously degassed by sparging with argon for 15 min). The mixture was stirred at 25 °C for 5 min and then placed in front of the Kessil Blue LED photoreactor (450 nm, 100% light intensity) with fan cooling. The mixture was stirred under argon for 2 hours. While stirring and irradiating the reaction mixture, a solution of 4-bromobenzotrifluoride (22.5 mg, 0.1 mmol, 1.0 equiv.) and **SI-92** (63.5 mg, 0.16 mmol, 1.6 equiv.) in trifluorotoluene (1.0 mL, previously degassed by sparging with argon for 15 min) was added via syringe pump at a rate of 2.0 mL/h over 30 min. After complete addition, the mixture was irradiated for 90 min. After the reaction was completed, the reaction mixture was removed from the photoreactor, opened to air. To the mixture, EA (2.0 mL) and methanol (60 μL) were added. The reaction mixture was stirred at 25 °C for 1 hour and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 19.0 mg (40%) of the title compound **54**.

Physical State: colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 – 7.55 (m, 4H), 7.40 – 7.31 (m, 5H), 5.20 (s, 2H), 4.36 – 4.03 (m, 4H), 3.61 (d, *J* = 11.5 Hz, 2H), 2.88 (s, 1H), 1.42 (s, 9H).

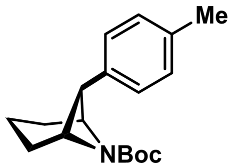
^{13}C NMR (126 MHz, $CDCl_3$): δ 156.53, 156.27, 143.42, 136.50, 129.71 (q, J = 32.6 Hz), 128.56, 128.13, 127.91, 127.59, 125.68 (q, *J* = 3.8 Hz), 124.11 (q, *J* = 272.1 Hz), 81.14, 67.28, 63.52, 62.09, 46.68, 45.77, 45.39, 28.24.

^{19}F NMR (471 MHz, $CDCl_3$): δ -62.52.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{25}H_{27}F_3N_2NaO_4^+$ 499.1821, found 499.1824.

TLC: R_f = 0.3 (3:1 hexanes : ethyl acetate).

Compound 55



tert-butyl (1R,5S,7s)-7-(p-tolyl)-6-azabicyclo[3.1.1]heptane-6-carboxylate **(55)**

A mixture of **23** (55.2 mg, 0.2 mmol, 2.0 equiv.), $CsCO_3$ (65.2 mg, 0.2 mmol, 2.0 equiv.), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (2.24 mg, 2 μmol, 0.02 equiv.), $Ni(dtbpy)Br_2$(4.89 mg, 10 μmol, 0.1 equiv.) was prepared in a 10 mL oven-dried tube. This reaction tube was backfilled with argon three times. To the mixture was added trifluorotoluene (2.0 mL, previously degassed by sparging with argon for 15 min). The mixture was stirred at 25 °C for 5 min and then placed in front of the Kessil Blue LED photoreactor (450 nm, 100% light intensity) with fan cooling. The mixture was stirred under argon for 2 hours. While stirring and irradiating the reaction mixture, a solution of 4-bromotoluene (17.1 mg, 0.1 mmol, 1.0 equiv.) and **SI-92** (63.5 mg, 0.16 mmol, 1.6 equiv.) in trifluorotoluene (1.0 mL, previously degassed by sparging with argon for 15 min) was added via syringe pump at a rate of 2.0 mL/h over 30 min. After complete addition, the mixture was irradiated for 90 min. After the reaction was completed, the reaction mixture was removed from the photoreactor, opened to air. To the mixture, EA (2.0 mL) and methanol (60 μL) were added. The reaction mixture was stirred at 25 °C for 1 hour and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 14.9 mg (52%) of the title compound **55**.

Physical State: colorless oil.

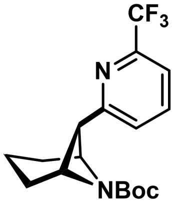
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 4.17 (q, *J* = 3.4 Hz, 1H), 4.01 (q, *J* = 3.2 Hz, 1H), 2.68 (s, 1H), 2.59 – 2.49 (m, 1H), 2.41 – 2.34 (m, 4H), 1.97 (dtt, *J* = 14.1, 9.1, 5.1 Hz, 1H), 1.90 – 1.79 (m, 2H), 1.74 (dtt, *J* = 13.8, 9.3, 4.9 Hz, 1H), 1.46 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.70, 139.06, 136.84, 129.76, 127.69, 79.80, 67.63, 65.76, 47.39, 29.07, 27.55, 26.26, 21.64, 15.25.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{25}NNaO_2^+$ 310.1783, found 310.1785.

TLC: R_f =0.3 (5:1 hexanes : ethyl acetate).

Compound 56



tert-butyl
***(1R,5S,7s)-7-(6-(trifluoromethyl)pyridin-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxylate* (56)**

A mixture of **23** (55.2 mg, 0.2 mmol, 2.0 equiv.), $CsCO_3$ (65.2 mg, 0.2 mmol, 2.0 equiv.), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (2.24 mg, 2 μmol, 0.02 equiv.), $Ni(dtbpy)Br_2$(2.45 mg, 5 μmol, 0.05 equiv.) was prepared in a 10 mL oven-dried tube. This reaction tube was backfilled with argon three times. To the mixture was added trifluorotoluene (2.0 mL, previously degassed by sparging with argon for 15 min). The mixture was stirred at 25 °C for 5 min and then placed in front of the Kessil Blue LED photoreactor (450 nm, 100% light intensity) with fan cooling. The mixture was stirred under argon for 2 hours. While stirring and irradiating the reaction mixture, a solution of 2-bromo-6-(trifluoromethyl)pyridine (22.6 mg, 0.1 mmol, 1.0 equiv.) and **SI-92** (63.5 mg, 0.16 mmol, 1.6 equiv.) in trifluorotoluene (1.0 mL, previously degassed by sparging with argon for 15 min) was added via syringe pump at a rate of 2.0 mL/h over 30 min. After complete addition, the mixture was irradiated for 90 min. After the reaction was completed, the reaction mixture was removed from the photoreactor, opened to air. To the mixture, EA (2.0 mL) and methanol (60 μL) were added. The reaction mixture was stirred at 25 °C for 1 hour and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 16.8 mg (49%) of the title compound **56**.

Physical State: yellow solid.

m.p. 104-106 °C.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.91 – 7.83 (m, 2H), 7.57 (t, *J* = 3.4 Hz, 1H), 4.28 (s, 1H), 4.17 (s, 1H), 3.08 (s, 1H), 2.61 – 2.49 (m, 1H), 2.38 (tt, *J* = 9.2, 4.3 Hz, 1H), 2.05 – 1.87 (m, 3H), 1.77 (qd, *J* = 9.3, 4.6 Hz, 1H), 1.47 (s, 9H).

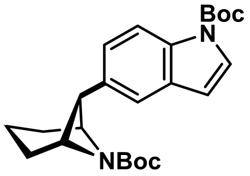
^{13}C NMR (126 MHz, CDCl$_3$): δ 162.34, 157.01, 147.41 (q, *J* = 34.3 Hz), 138.12, 123.69, 121.53 (q, *J* = 274.1 Hz), 118.53 (q, *J* = 2.8 Hz), 79.74, 66.26, 64.71, 48.69, 28.44, 26.33, 25.08, 14.54.

^{19}F NMR (471 MHz, CDCl$_3$): δ -67.97.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{17}H_{21}F_3N_2NaO_2^+$ 365.1453, found 365.1454.

TLC: R_f=0.3 (5:1 hexanes : ethyl acetate).

Compound 57



***tert-butyl (1R,5S,7s)-7-(1-(tert-butoxycarbonyl)-1H-indol-5-yl)-6-azabicyclo[3.1.1]heptane-6-carboxylate* (57)**

A mixture of **23** (55.2 mg, 0.2 mmol, 2.0 equiv.), $CsCO_3$ (65.2 mg, 0.2 mmol, 2.0 equiv.), Ir(dF(CF$_3$)ppy)$_2$(dtbpy)PF$_6$ (2.24 mg, 2 µmol, 0.02 equiv.) and Ni(dtbpy)Br$_2$(4.89 mg, 10 µmol, 0.1 equiv.) was prepared in a 10 mL oven-dried tube. This reaction tube was backfilled with argon three times. To the mixture was added trifluorotoluene (2.0 mL, previously degassed by sparging with argon for 15 min). The mixture was stirred at 25 °C for 5 min and then placed in front of the Kessil Blue LED photoreactor (450 nm, 100% light intensity) with fan cooling. The mixture was stirred under argon for 2 hours. While stirring and irradiating the reaction mixture, a solution of N-Boc-5-bromoindole (29.6 mg, 0.1 mmol, 1.0 equiv.) and **SI-92** (63.5 mg, 0.16 mmol, 1.6 equiv.) in trifluorotoluene (1.0 mL, previously degassed by sparging with argon for 15 min) was added via syringe pump at a rate of 2.0 mL/h over 30 min. After complete addition, the mixture was irradiated for 90 min. After the reaction was completed, the reaction mixture was removed from the photoreactor, opened to air. To the mixture, EA (2.0 mL) and methanol (60 μL) were added. The reaction mixture was stirred at 25 °C for 1 hour and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 23.5 mg (57%) of the title compound **57**.

Physical State: white solid.

m.p. 155-157 °C.

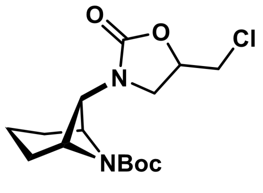
^{1}H NMR (500 MHz, CDCl$_3$): δ 8.07 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 1.8 Hz, 1H), 7.58 (d, J = 5.3 Hz, 1H), 7.36 (dd, J = 8.6, 1.8 Hz, 1H), 6.55 (d, J = 3.7 Hz, 1H), 4.23 (td, J = 3.5, 1.7 Hz, 1H), 4.05 (td, J = 3.4, 1.6 Hz, 1H), 2.81 (s, 1H), 2.61 – 2.52 (m, 1H), 2.44 – 2.34 (m, 1H), 1.99 (ddt, J = 13.8, 10.0, 4.3 Hz, 1H), 1.93 – 1.83 (m, 2H), 1.77 (ddt, J = 18.4, 9.1, 4.7 Hz, 1H), 1.67 (s, 9H), 1.48 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 157.25, 149.80, 135.88, 130.84, 127.63, 126.17, 123.94, 119.04, 115.05, 107.33, 83.60, 79.28, 67.33, 65.42, 47.17, 28.50, 28.22, 27.04, 25.77, 14.69.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{24}H_{32}N_2NaO_4^+$ 435.2260, found 435.2260.

TLC: R_f=0.3 (5:1 hexanes : ethyl acetate).

Compound 58



***tert-butyl (1R,5S,7s)-7-(5-(chloromethyl)-2-oxooxazolidin-3-yl)-6-azabicyclo[3.1.1]heptane-6-carboxylate* (58)**

A mixture of 5-chloromethyl-2-oxazolidinone (13.6 mg, 0.1 mmol, 1.0 equiv.), CuTC (9.55 mg, 0.05 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 0.05 mmol, 0.5 equiv.), 4-CzIPN (3.95 mg, 5 μmol, 0.05 equiv.) and MeCN (3.3 mL, 0.03 M) was prepared in a 10 mL tube. To the mixture was added 1,5-diazabicyclo[4.3.0]non-5-ene (24.8 mg, 0.2 mmol, 2.0 equiv.) and water (45 μL, 2.5 mmol, 25 equiv.). The resulting solution was stirred for 1-2 min under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, **23** (55.2 mg, 0.2 mmol, 2.0 equiv.) and **SI-93** (0.08 mL, 0.25 mmol, 2.5 equiv.) were added to the mixture, and then plugged the tube and inserted an 18G ventilation needle into the plug. The reaction tube was placed in front of the Kessil Blue LED photoreactor (450 nm, 25% light intensity) with fan cooling. The mixture was stirred under air for 12 hours. After 12 hours, MeOH (0.1 mL) was added. The resulting solution was stirred under air for 2 hours and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 18.2 mg (55%) of the title compound **58**.

Physical State: white solid.

m.p. 166-168 °C.

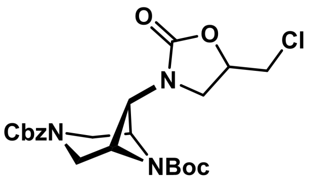
^{1}H NMR (500 MHz, CDCl$_3$): δ 4.78 (dq, *J* = 10.7, 5.5 Hz, 1H), 4.14 – 4.08 (m, 1H), 4.04 (s, 1H), 3.99 (q, *J* = 9.9 Hz, 1H), 3.78 – 3.67 (m, 4H), 2.49 (dp, *J* = 14.7, 4.9, 4.5 Hz, 1H), 2.32 (dt, *J* = 13.2, 4.6 Hz, 1H), 1.92 – 1.78 (m, 3H), 1.67 – 1.59 (m, 1H), 1.46 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 157.04, 156.95, 80.13, 71.94, 71.88, 65.04, 64.72, 63.57, 63.28, 56.39, 45.87, 45.77, 44.92, 44.80, 28.37, 25.75, 24.56, 13.98.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{15}H_{23}ClN_2NaO_4^+$ 353.1244, found 353.1245.

TLC: R$_f$=0.3 (2:1 hexanes : ethyl acetate).

Compound 59



3-benzyl 6-(tert-butyl)

***(1R,5S,7s)-7-(5-(chloromethyl)-2-oxooxazolidin-3-yl)-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate* (59)**

A mixture of 5-chloromethyl-2-oxazolidinone (13.6 mg, 0.1 mmol, 1.0 equiv.), CuTC (9.55 mg, 0.05 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 0.05 mmol, 0.5 equiv.), 4-CzIPN (3.95 mg, 5 μmol, 0.05 equiv.) and MeCN (3.3 mL, 0.03 M) was prepared in a 10 mL tube. To the mixture was added 1,5-diazabicyclo[4.3.0]non-5-ene (24.8 mg, 0.2 mmol, 2.0 equiv.) and water (45 μL, 2.5 mmol, 25 equiv.). The resulting solution was stirred for 1-2 min under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, **22** (82.2 mg, 0.2 mmol, 2.0 equiv.) and **SI-93** (0.08 mL, 0.25 mmol, 2.5 equiv.) were added to the mixture, and then plugged the tube and inserted an 18G ventilation needle into the plug. The reaction tube was placed in front of the Kessil Blue LED photoreactor (450 nm, 25% light intensity) with fan cooling. The mixture was stirred under air for 12 hours. After 12 hours, MeOH (0.1 mL) was added. The resulting solution was stirred under air for 2 hours and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 20.0 mg (43%) of the title compound **59**.

Physical State: white solid.

m.p. 130-131 °C.

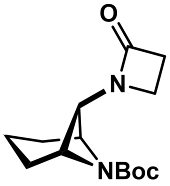
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.40 – 7.28 (m, 5H), 5.16 (s, 2H), 4.82 (dq, *J* = 9.7, 5.0 Hz, 1H), 4.31 – 4.06 (m, 4H), 4.01 (t, *J* = 9.1 Hz, 1H), 3.88 (d, *J* = 3.2 Hz, 1H), 3.78 (dd, *J* = 9.4, 5.7 Hz, 1H), 3.73 (d, *J* = 5.0 Hz, 2H), 3.61 – 3.50 (m, 2H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 156.78, 156.41, 156.08, 136.34, 128.55, 128.16, 127.96, 81.63, 71.94, 67.39, 55.54, 45.75, 44.78, 28.15. *Note: NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{22}H_{28}ClN_3NaO_6^+$ 488.1564, found 488.1565.

TLC: R*f* =0.3 (1:1 hexanes : ethyl acetate).

Compound 60



tert-butyl (1R,5S,7s)-7-(2-oxoazetidin-1-yl)-6-azabicyclo[3.1.1]heptane-6-carboxylate **(60)**

A mixture of 2-azetidinone (7.1 mg, 0.1 mmol, 1.0 equiv.), CuTC (9.55 mg, 0.05 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 0.05 mmol, 0.5 equiv.), 4-CzIPN (3.95 mg, 5 μmol, 0.05 equiv.) and MeCN (3.3 mL, 0.03 M) was prepared in a 10 mL tube. To the mixture was added 1,5-diazabicyclo[4.3.0]non-5-ene (24.8 mg, 0.2 mmol, 2.0 equiv.) and water (45 μL, 2.5 mmol, 25 equiv.). The resulting solution was stirred for 1-2 min under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, **23** (55.2 mg, 0.2 mmol, 2.0 equiv.) and **SI-93** (0.08 mL, 0.25 mmol, 2.5 equiv.) were added to the mixture, and then plugged the tube and inserted an 18G ventilation needle into the plug. The reaction tube was placed in front of the Kessil Blue LED photoreactor (450 nm, 25% light intensity) with fan cooling. The mixture was stirred under air for 12 hours. After 12 hours, MeOH (0.1 mL) was added. The resulting solution was stirred under air for 2 hours and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 14.9 mg (56%) of the title compound **60**.

Physical State: white solid.

m.p. 76-77 °C.

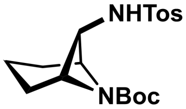
^{1}H NMR (400 MHz, CDCl$_3$): δ 4.09 (s, 1H), 4.05 (s, 1H), 3.64 (s, 1H), 3.47 (q, J = 4.4 Hz, 2H), 2.94 (t, J = 4.1 Hz, 2H), 2.43 (tt, J = 9.3, 4.2 Hz, 1H), 2.31 – 2.22 (m, 1H), 1.88 – 1.70 (m, 3H), 1.69 – 1.53 (m, 1H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 167.77, 156.99, 79.92, 65.27, 63.75, 53.65, 38.30, 36.23, 28.38, 25.46, 24.28, 14.19.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{14}H_{22}N_2NaO_3^+$ 289.1528, found 289.1530.

TLC: R_f=0.3 (1:1 hexanes : ethyl acetate).

Compound 61



tert-butyl (1R,5S,7s)-7-((4-methylphenyl)sulfonamido)-6-azabicyclo[3.1.1]heptane-6-carboxylate **(61)**

A mixture of tosylamide (17.1 mg, 0.1 mmol, 1.0 equiv.), Ir[dF(CF_3)ppy]$_2$[4,4'-d(CF_3)bpy]PF_6 (0.9 mg, 0.8 μmol, 0.008 equiv.) and MeCN (1.0 mL) was prepared in a 10 mL tube. To this tube was added 1,5-diazabicyclo[4.3.0]non-5-ene (12.4 mg, 0.1 mmol, 1.0 equiv.). The resulting solution was stirred for 5 minutes, after which LiOt-Bu (24 mg, 0.3 mmol, 3.0 equiv.) and H_2O (18 μL, 0.1 mmol, 10 equiv.) were added to the tube. This suspension was then sonicated under air for 1 minute until the mixture became homogeneous. Cu(TMHD)$_2$ (12.9 mg, 0.03 mmol, 0.3 equiv.) was then added to the tube, and the solution was stirred for 1-2 min under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, **23** (69 mg, 0.25 mmol, 2.5 equiv.) and **SI-92** (99 mg, 0.25 mmol, 2.5 equiv.) were added to the mixture. This reaction tube was plugged the tube and inserted an 18G ventilation needle into the plug. The tube was placed in front of the Kessil Blue LED photoreactor (450 nm, 25% light intensity) with fan cooling. The mixture was stirred under air for 4 hours. After 4 hours, to the mixture was added EA (2.0 mL). The resulting solution was stirred under air for 2 hours and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 12.8 mg (35%) of the title compound **61**.

Physical State: yellow solid.

m.p. 138-139 °C.

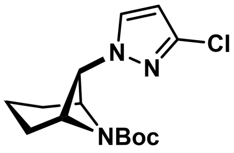
^{1}H (400 MHz, CDCl$_3$): δ 7.74 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.27 (d, J = 9.9 Hz, 1H), 3.73 (s, br., 1H), 3.53 (s, br., 1H), 3.27 (d, J = 9.9 Hz, 1H), 2.43 (s, 3H), 2.27 (s, br., 1H), 2.22 (s, br., 1H), 1.81 – 1.74 (m, 1H), 1.61 – 1.51 (m, 3H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 157.28, 143.87, 137.58, 129.95, 126.93, 80.06, 56.39, 28.31, 21.58, 14.20. *Note: NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{18}H_{26}N_2NaO_4S^+$ 389.1511, found 389.1513.

TLC: R$_f$ =0.3 (3:1 hexanes : ethyl acetate).

Compound 62



***tert-butyl (1R,5S,7s)-7-(3-chloro-1H-pyrazol-1-yl)-6-azabicyclo[3.1.1]heptane-6-carboxylate* (62)**

A mixture of 3-chloro-1H-pyrazole (10.2 mg, 0.1 mmol, 1.0 equiv.), CuTC (9.55 mg, 0.05 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 0.05 mmol, 0.5 equiv.), 4-CzIPN (3.95 mg, 5 µmol, 0.05 equiv.) and MeCN (3.3 mL, 0.03 M) was prepared in a 10 mL tube. To the mixture was added 1,5-diazabicyclo[4.3.0]non-5-ene (24.8 mg, 0.2 mmol, 2.0 equiv.) and water (45 µL, 2.5 mmol, 25 equiv.). The resulting solution was stirred for 1-2 min under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, **23** (55.2 mg, 0.2 mmol, 2.0 equiv.) and **SI-93** (0.08 mL, 0.25 mmol, 2.5 equiv.) were added to the mixture, and then plugged the tube and inserted an 18G ventilation needle into the plug. The reaction tube was placed in front of the Kessil Blue LED photoreactor (450 nm, 25% light intensity) with fan cooling. The mixture was stirred under air for 12 hours. After 12 hours, MeOH (0.1 mL) was added. The resulting solution was stirred under air for 2 hours and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 10.4 mg (35%) of the title compound **62**.

Physical State: yellow solid.

m.p. 115-116 °C.

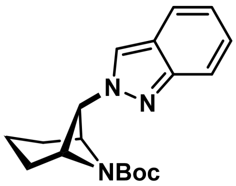
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.75 (s, 1H), 6.24 (s, 1H), 4.33 (s, 1H), 4.22 (s, 1H), 4.17 (s, 1H), 2.61 – 2.55 (m, 1H), 2.42 – 2.38 (m, 1H), 1.97 – 1.84 (m, 3H), 1.79 – 1.66 (m, 1H), 1.46 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 157.11, 139.29, 129.31, 105.48, 80.26, 66.76, 65.12, 63.91, 28.35, 25.93, 24.78, 14.25.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{14}H_{20}ClN_3NaO_2^+$ 320.1142, found 320.1140.

TLC: R$_f$=0.3 (5:1 hexanes : ethyl acetate).

Compound 63



tert-butyl (1R,5S,7s)-7-(2H-indazol-2-yl)-6-azabicyclo[3.1.1]heptane-6-carboxylate **(63)**

A mixture of 1H-indazole (11.8 mg, 0.1 mmol, 1.0 equiv.), CuTC (9.55 mg, 0.05 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 0.05 mmol, 0.5 equiv.), 4-CzIPN (3.95 mg, 5 μmol, 0.05 equiv.) and MeCN (3.3 mL, 0.03 M) was prepared in a 10 mL tube. To the mixture was added 1,5-diazabicyclo[4.3.0]non-5-ene (24.8 mg, 0.2 mmol, 2.0 equiv.) and water (45 μL, 2.5 mmol, 25 equiv.). The resulting solution was stirred for 1-2 min under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, **23** (55.2 mg, 0.2 mmol, 2.0 equiv.) and **SI-93** (0.08 mL, 0.25 mmol, 2.5 equiv.) were added to the mixture, and then plugged the tube and inserted an 18G ventilation needle into the plug. The reaction tube was placed in front of the Kessil Blue LED photoreactor (450 nm, 25% light intensity) with fan cooling. The mixture was stirred under air for 12 hours. After 12 hours, MeOH (0.1 mL) was added. The resulting solution was stirred under air for 2 hours and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 14.7 mg (47%)

of the title compound **63**.

Physical State: colorless oil.

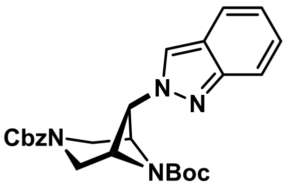
^{1}H NMR (500 MHz, CDCl$_3$): δ 8.05 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 3.6 Hz, 2H), 7.18 (dt, *J* = 7.9, 3.8 Hz, 1H), 4.78 – 4.72 (m, 2H), 4.33 (s, 1H), 2.72 – 2.65 (m, 1H), 2.57 – 2.50 (m, 1H), 2.06 – 1.95 (m, 3H), 1.88 – 1.81 (m, 1H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 157.17, 139.22, 133.08, 126.32, 125.06, 121.39, 120.93, 109.48, 79.75, 64.97, 63.90, 61.90, 28.39, 26.15, 24.97, 14.45.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{18}H_{23}N_3NaO_2^+$ 336.1688, found 336.1686.

TLC: R_f =0.3 (5:1 hexanes : ethyl acetate).

Compound 64



3-benzyl 6-(tert-butyl) (1R,5S,7s)-7-(2H-indazol-2-yl)-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate **(64)**

A mixture of 1H-indazole (11.8 mg, 0.1 mmol, 1.0 equiv.), CuTC (9.55 mg, 0.05 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 0.05 mmol, 0.5 equiv.), 4-CzIPN (3.95 mg, 5 μmol, 0.05 equiv.) and MeCN (3.3 mL, 0.03 M) was prepared in a 10 mL tube. To the mixture was added 1,5-diazabicyclo[4.3.0]non-5-ene (24.8 mg, 0.2 mmol, 2.0 equiv.) and water (45 μL, 2.5 mmol, 25 equiv.). The resulting solution was stirred for 1-2 min under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, **22** (82.2 mg, 0.2 mmol, 2.0 equiv.) and **SI-93** (0.08 mL, 0.25 mmol, 2.5 equiv.) were added to the mixture, and then plugged the tube and inserted an 18G ventilation needle into the plug. The reaction tube was placed in front of the Kessil Blue LED photoreactor (450 nm, 25% light intensity) with fan cooling. The mixture was stirred under air for 12 hours. After 12 hours, MeOH (0.1 mL) was added. The resulting solution was stirred under air for 2 hours and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 15.2 mg (34%) of the title compound **64**.

Physical State: white solid.

m.p. 122-124 °C.

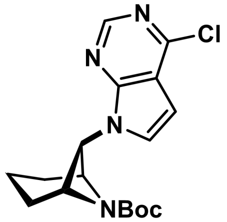
^{1}H NMR (500 MHz, CDCl$_3$): δ 8.08 (s, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.42 – 7.30 (m, 7H), 7.21 (t, *J* = 7.5 Hz, 1H), 5.21 (s, 2H), 4.81 (q, *J* = 3.6 Hz, 2H), 4.51 – 4.36 (m, 2H), 4.30 – 4.20 (m, 1H), 3.79 – 3.70 (m, 2H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 139.28, 136.38, 133.64, 128.59, 128.20, 127.97, 126.73, 125.16, 121.62, 121.31, 108.90, 81.22, 67.44, 59.84, 28.19. *Note: CO, NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{25}H_{28}N_4NaO_4^+$ 471.2008, found 471.2007.

TLC: R*f* =0.3 (3:1 hexanes : ethyl acetate).

Compound 65



tert-butyl (1R,5S,7s)-7-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-6-azabicyclo[3.1.1]heptane-6-carboxylate **(65)**

A mixture of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (15.3 mg, 0.1 mmol, 1.0 equiv.), CuTC (9.55 mg, 0.05 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 0.05 mmol, 0.5 equiv.), 4-CzIPN (3.95 mg, 5 μmol, 0.05 equiv.) and MeCN (3.3 mL, 0.03 M) was prepared in a 10 mL tube. To the mixture was added 1,5-diazabicyclo[4.3.0]non-5-ene (24.8 mg, 0.2 mmol, 2.0 equiv.) and water (45 μL, 2.5 mmol, 25 equiv.). The resulting solution was stirred for 1-2 min under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, **23** (55.2 mg, 0.2 mmol, 2.0 equiv.) and **SI-93** (0.08 mL, 0.25 mmol, 2.5 equiv.) were added to the mixture, and then plugged the tube and inserted an 18G ventilation needle into the plug. The reaction tube was placed in front of the Kessil Blue LED photoreactor (450 nm, 25% light intensity) with fan cooling. The mixture was stirred under air for 12 hours. After 12 hours, MeOH (0.1 mL) was added. The resulting solution was stirred under air for 2 hours and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 15.0 mg (43%) of the title compound **65**.

Physical State: yellow solid.

m.p. 138-139 °C.

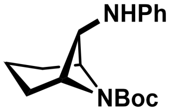
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.62 (d, *J* = 2.1 Hz, 1H), 7.85 (s, 1H), 6.67 (s, 1H), 4.73 (s, 1H), 4.33 (s, 1H), 4.19 (s, 1H), 2.67 (s, br., 1H), 2.48 (s, br., 1H), 2.10 – 1.99 (m, 3H), 1.82 – 1.73 (m, 1H), 1.50 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 157.06, 152.17, 151.45, 150.47, 127.25, 117.88, 100.03, 80.39, 67.30, 65.76, 56.41, 28.37, 26.13, 24.94, 14.23.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{17}H_{22}ClN_4O_2^+$ 349.1431, found 349.1431.

TLC: R$_f$=0.3 (3:1 hexanes : ethyl acetate).

Compound 66



***tert-butyl (1R,5S,7s)-7-(phenylamino)-6-azabicyclo[3.1.1]heptane-6-carboxylate* (66)**

A mixture of aniline (9.3 mg, 0.1 mmol, 1.0 equiv.), Ir[dF(CF$_3$)ppy]$_2$[4,4'-d(CF$_3$)bpy]PF$_6$ (0.9 mg, 0.8 μmol, 0.008 equiv.) and MeCN (1.0 mL) was prepared in a 10 mL tube. To this tube was added 1,5-diazabicyclo[4.3.0]non-5-ene (12.4 mg, 0.1 mmol, 1.0 equiv.). The resulting solution was stirred for 5 minutes, after which LiOt-Bu (24 mg, 0.3 mmol, 3.0 equiv.) and H$_2$O (18 μL, 0.1 mmol, 10 equiv.) were added to the tube. This suspension was then sonicated under air for 1 minute until the mixture became homogeneous. Cu(TMHD)$_2$ (12.9 mg, 0.03 mmol, 0.3 equiv.) was then added to the tube, and the solution was stirred for 1-2 min under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, **23** (69 mg, 0.25 mmol, 2.5 equiv.) and **SI-92** (99 mg, 0.25 mmol, 2.5 equiv.) were added to the mixture. This reaction tube was plugged the tube and inserted an 18G ventilation needle into the plug. The tube was placed in front of the Kessil Blue LED photoreactor (450 nm, 25% light intensity) with fan cooling. The mixture was stirred under air for 4 hours. After 4 hours, to the mixture was added EA (2.0 mL). The resulting solution was stirred under air for 2 hours and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ether, 1:1) on silica gel to afford 10.9 mg (38%) of the title compound **66**.

Physical State: yellow solid.

m.p. 193-194 °C.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.19 (t, *J* = 7.9 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 7.4 Hz, 2H), 4.35 (d, *J* = 7.0 Hz, 1H), 3.99 (s, br., 1H), 3.93 (s, br., 1H), 3.31 (d, *J* = 6.9 Hz, 1H), 2.54 – 2.46 (m, 1H), 2.40 – 2.31 (m, 1H), 1.95 – 1.77 (m, 3H), 1.73 – 1.64 (m, 1H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 157.90, 146.92, 129.38, 118.23, 113.50, 79.55, 66.10, 65.06, 56.94, 28.39, 25.92, 24.88, 14.61.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{17}H_{24}N_2NaO_2^+$ 311.1735, found 311.1733.

TLC: R$_f$ =0.3 (1:1 hexanes : ether).

Additional Data of Substrates

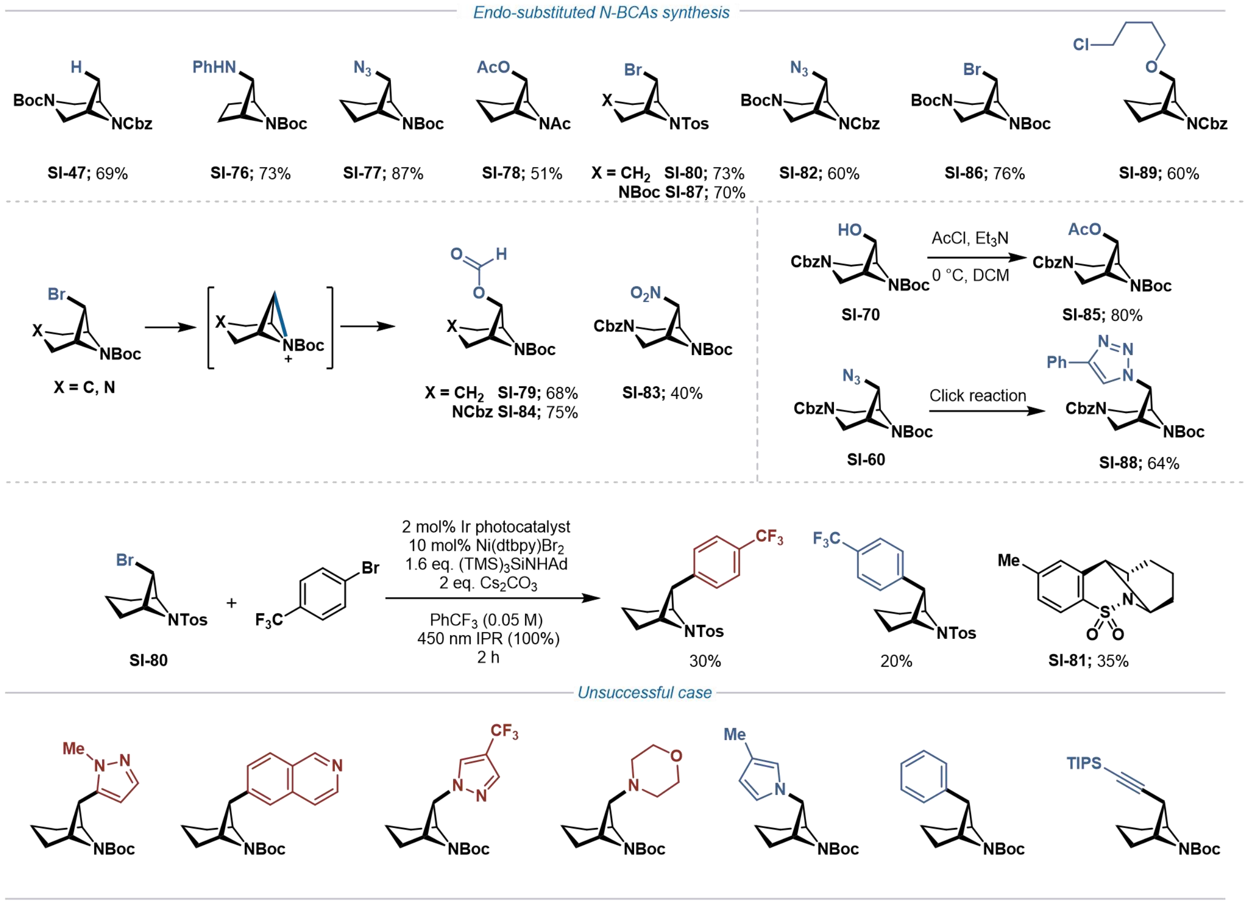


Fig. S1. Modular synthesis of N-BCAs by transformation of 1-azztricycloalkanes and unsuccessful cases.

Compound SI-47

6-benzyl 3-(tert-butyl) (1R,5S)-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate **(SI-47)**

To a solution of **10** (196 mg, 1.0 mmol, 1.0 equiv.) in MeOH (10 mL) was added 20% Pd/C and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DCM (5.0 mL). To the mixture were added DIPEA (193.5 mg, 1.5 mmol, 1.5 equiv.) and CbzCl (170 mg, 1.0 mmol, 1.0 equiv.) at 0 °C. The reaction mixture was stirred at 25 °C for 3 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×5.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 229.1 mg (69%) of the title compound **SI-47**.

Physical State: white solid.

m.p. 64-65 °C.

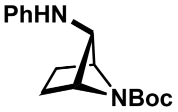
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.38 – 7.26 (m, 5H), 5.13 (d, *J* = 12.3 Hz, 1H), 5.06 (d, *J* = 12.3 Hz, 1H), 4.24 (s, 1H), 4.17 (s, 1H), 3.93 (s, br., 1H), 3.81 (s, br., 1H), 3.41 (d, *J* = 12.4 Hz, 1H), 3.39 – 3.34 (m, 1H), 2.62 – 2.55 (m, 1H), 1.45 (s, 9H), 1.43 (d, *J* = 8.8 Hz, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 156.23, 156.01, 136.29, 128.55, 128.17, 128.03, 79.89, 66.81, 58.64, 45.54, 28.70, 28.44.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}N_2NaO_4^+$ 355.1634, found 355.1636.

TLC: $R_f = 0.3$ (3:1 hexanes : ethyl acetate).

Compound SI-76



tert-butyl (1R,4S,6r)-6-(phenylamino)-5-azabicyclo[2.1.1]hexane-5-carboxylate **(SI-76)**

To a solution of **3** (8.1 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) were added TfOH (0.2 mol/L, MeCN solution, 0.5 mL, 0.1 mmol, 1.0 equiv.) and aniline (32.2 mg, 0.2 mmol, 2.0 equiv.) at -35 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. To the reaction mixture, Boc_2O (43.6 mg, 0.2 mmol, 2.0 equiv.) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.) were added at 0 °C. The mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 20.0 mg (73%) of the title compound **SI-76**.

Physical State: yellow solid.

m.p. 104-106 °C.

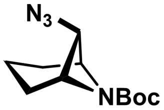
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.18 (t, J = 7.8 Hz, 2H), 6.75 (t, J = 7.3 Hz, 1H), 6.61 (d, J = 8.0 Hz, 2H), 4.24 (d, J = 2.7 Hz, 2H), 3.55 (t, J = 2.9 Hz, 1H), 1.87 (d, J = 9.2 Hz, 2H), 1.71 (d, J = 8.6 Hz, 2H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 158.39, 146.24, 129.41, 118.37, 112.82, 80.35, 66.05, 51.92, 28.19, 23.22.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{16}H_{22}N_2NaO_2^+$ 297.1579, found 297.1580.

TLC: R_f = 0.3 (10:1 hexanes : ethyl acetate).

Compound SI-77



tert-butyl (1R,5S,7r)-7-azido-6-azabicyclo[3.1.1]heptane-6-carboxylate **(SI-77)**

To a solution of **2** (95 mg, 1 mmol, 1.0 equiv.) in MeCN (20 mL) were added Boc$_2$O (436 mg, 2 mmol, 2.0 equiv.) and TMSN$_3$ (575 mg, 5 mmol, 5.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×10 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 207.1 mg (87%) of the title compound **SI-77**.

Physical State: colorless oil.

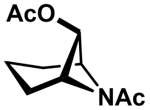
^{1}H NMR (500 MHz, CDCl$_3$): δ 4.31 (t, J = 6.1 Hz, 1H), 4.22 (s, 2H), 2.17 (s, br., 2H), 1.80 – 1.68 (m, 3H), 1.57 – 1.47 (m, 1H), 1.46 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 156.98, 79.84, 55.63, 28.31, 13.72. *Note: NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{11}H_{18}N_4NaO_2^+$ 261.1327, found 261.1329.

TLC: R$_f$ = 0.3 (5:1 hexanes : ethyl acetate).

Compound SI-78



(1R,5S,7r)-6-acetyl-6-azabicyclo[3.1.1]heptan-7-yl acetate (SI-78)

To a solution of **2** (9.5 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) was added Ac$_2$O (41.4 mg, 0.3 mmol, 3.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:2) on silica gel to afford 10.0 mg (51%) of the title compound **SI-78**.

Physical State: colorless oil.

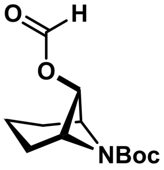
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.06 (t, J = 6.1 Hz, 1H), 4.55 (q, J = 4.6 Hz, 1H), 4.47 (q, J = 4.7 Hz, 1H), 2.30 – 2.21 (m, 1H), 2.12 (s, 3H), 2.08 – 2.00 (m, 1H), 1.95 (s, 3H), 1.79 – 1.69 (m, 3H), 1.67 – 1.60 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.46, 170.19, 65.83, 65.00, 62.72, 22.20, 20.78, 20.48, 20.13, 14.46.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{10}H_{15}NNaO_3^+$ 220.0950, found 220.0951.

TLC: R_f = 0.3 (1:2 hexanes : ethyl acetate).

Compound SI-79



tert-butyl (1R,5S,7r)-7-(formyloxy)-6-azabicyclo[3.1.1]heptane-6-carboxylate **(SI-79)**

To a solution of **23** (276 mg, 1.0 mmol, 1.0 equiv.) in DMF (5.0 mL) was added $AgNO_2$ (258 mg, 2.0 mmol, 2.0 equiv.) at 0 °C and the mixture was stirred for 6 hours at 25 °C under an argon atmosphere and protected from light. After the reaction was completed, the reaction mixture was concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 163.9 mg (68%) of the title compound **SI-79**.

Physical State: colorless oil.

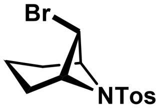
^{1}H NMR (500 MHz, CDCl$_3$): δ 8.08 (s, 1H), 5.15 (t, *J* = 6.0 Hz, 1H), 4.32 (s, 2H), 2.22 (s, 2H), 1.76 – 1.56 (m, 4H), 1.47 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 159.90, 157.01, 79.89, 64.89, 28.32, 13.84. *Note: NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{12}H_{19}NNaO_4^+$ 264.1212, found 264.1214.

TLC: R*$_f$* = 0.3 (2:1 hexanes : ethyl acetate).

Compound SI-80



(1R,5S,7r)-7-bromo-6-tosyl-6-azabicyclo[3.1.1]heptane **(SI-80)**

To a solution of **2** (190 mg, 2 mmol, 1.0 equiv.) in MeCN (10 mL) was added TosBr (680 mg, 4 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 481.8 mg (73%) of the title compound **SI-80**.

Physical State: white solid.

m.p. 93-95 °C.

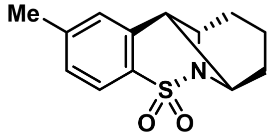
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 4.72 (t, *J* = 6.3 Hz, 1H), 4.43 – 4.36 (m, 2H), 2.44 (s, 3H), 2.24 – 2.12 (m, 2H), 2.12 – 2.00 (m, 2H), 1.92 – 1.80 (m, 2H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 144.23, 136.22, 130.00, 127.45, 67.85, 46.14, 24.34, 21.64, 13.39.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{13}H_{16}BrNNaO_2S^+$ 351.9983, found 351.9981.

TLC: R*$_f$* = 0.4 (10:1 hexanes : ethyl acetate).

Compound SI-81



(2r,3R,4s,9S)-6-methyl-3,4-dihydro-2,4,3-(epibutane[1,1,4]triyl)benzo[e][1,2]thiazine 1,1-dioxide **(SI-81)**

A mixture of **SI-80** (66 mg, 0.2 mmol, 2.0 equiv.), $CsCO_3$ (65.2 mg, 0.2 mmol, 2.0 equiv.), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (2.24 mg, 2 μmol, 0.02 equiv.) and $Ni(dtbpy)Br_2$(2.45 mg, 5 μmol, 0.05 equiv.) was prepared in a 10 mL oven-dried tube. This reaction tube was backfilled with argon three times. To the mixture was added trifluorotoluene (2.0 mL, previously degassed by sparging with argon for 15 min). The mixture was stirred at 25 °C for 5 min and then placed in front of the Kessil Blue LED photoreactor (450 nm, 100% light intensity) with fan cooling. The mixture was stirred under argon for 2 hours. While stirring and irradiating the reaction mixture, a solution of 4-bromobenzotrifluoride (22.5 mg, 0.1 mmol, 1.0 equiv.) and **SI-92** (63.5 mg, 0.16 mmol, 1.6 equiv.) in trifluorotoluene (1.0 mL, previously degassed by sparging with argon for 15 min) was added via syringe pump at a rate of 2.0 mL/h over 30 min. After complete addition, the mixture was irradiated for 90 min. After the reaction was completed, the reaction mixture was removed from the photoreactor, opened to air. To the mixture, EA (2.0 mL) and methanol (60 μL) were added. The reaction mixture was stirred at 25 °C for 1 hour and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 8.7 mg (35%) of the title compound **SI-81**.

Physical State: white solid.

m.p. 150-151 °C.

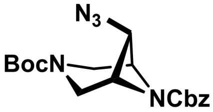
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.07 (s, 1H), 4.29 (s, 2H), 3.14 (s, 1H), 2.43 – 2.32 (m, 5H), 2.27 – 2.09 (m, 2H), 2.12 – 1.88 (m, 2H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 142.73, 140.29, 130.14, 130.09, 127.18, 125.70, 74.39, 46.59, 28.19, 21.63, 15.58.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{13}H_{15}NNaO_2S^+$ 272.0721, found 272.0723.

TLC: R$_f$ = 0.3 (5:1 hexanes : ethyl acetate).

Compound SI-82



***6-benzyl 3-(tert-butyl) (1R,5S,7r)-7-azido-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate* (SI-82)**

To a solution of **10** (39.2 mg, 0.2 mmol, 1.0 equiv.) in MeCN (1.0 mL) was added CbzN$_3$ (70.8 mg, 0.4 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 44.8 mg (60%) of the title compound **SI-82**.

Physical State: colorless oil.

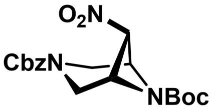
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.36 – 7.25 (m, 5H), 5.17 – 5.04 (m, 2H), 4.41 – 4.34 (m, 2H), 4.29 (dt, *J* = 6.6, 3.6 Hz, 1H), 3.92 (d, *J* = 12.4 Hz, 2H), 3.32 (dd, *J* = 12.6, 5.3 Hz, 2H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 156.31, 155.28, 135.90, 128.63, 128.35, 128.12, 80.10, 67.37, 62.13, 61.72, 53.76, 40.87 (br.), 28.41.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{18}H_{23}N_5NaO_4^+$ 396.1648, found 396.1648.

TLC: R$_f$ = 0.3 (5:1 hexanes : ethyl acetate).

Compound SI-83



***3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-nitro-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate* (SI-83)**

SI-83 was prepared according to the previously reported procedure[7-9]. To a solution of **22** (441 mg, 1.0 mmol, 1.0 equiv.) in Et_2O (5.0 mL) was added $AgNO_2$ (258 mg, 2.0 mmol, 2.0 equiv.) at 0 °C and the mixture was stirred for 12 hours at 25 °C under an argon atmosphere and protected from light. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×3.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 150.8 mg (40%) of the title compound **SI-83**.

Physical State: colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 – 7.26 (m, 5H), 5.31 (t, J = 5.6 Hz, 1H), 5.20 (d, J = 12.4 Hz, 1H), 5.13 (d, J = 12.3 Hz, 1H), 4.47 (dt, J = 6.3, 3.5 Hz, 1H), 4.41 (dt, J = 6.6, 3.6 Hz, 1H), 4.17 – 4.08 (m, 2H), 3.31 (dd, J = 12.8, 10.1 Hz, 2H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.82, 136.33, 128.55, 128.15, 127.93, 81.80, 68.23, 67.37, 61.49, 61.03, 40.51, 40.13, 28.07. *Note: a NCO was not observed.*

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{23}N_3NaO_6^+$ 400.1485, found 400.1483.

TLC: R_f = 0.3 (5:1 hexanes : ethyl acetate).

Compound SI-84

3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-(formyloxy)-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate **(SI-84)**

To a solution of **22** (411 mg, 1.0 mmol, 1.0 equiv.) in DMF (5.0 mL) was added $AgNO_2$ (258 mg, 2.0 mmol, 2.0 equiv.) at 0 °C and the mixture was stirred for 6 hours at 25 °C under an argon atmosphere and protected from light. After the reaction was completed, the reaction mixture was concentrated in vacuo. The crude product was was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 282.0 mg (75%) of the title compound **SI-84**.

Physical State: yellow oil.

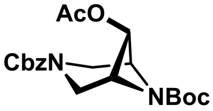
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.39 – 7.29 (m, 5H), 5.23 (t, J = 5.8 Hz, 1H), 5.22 – 5.10 (m, 2H), 4.39 (s, 1H), 4.34 (s, 1H), 4.23 – 4.04 (m, 2H), 3.32 (d, J = 8.3 Hz, 1H), 3.29 (d, J = 8.5 Hz, 1H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.58, 155.97, 136.48, 128.53, 128.11, 127.92, 81.36, 67.21, 62.49, 28.11. *Note: NCH, $NCHCH_2$ and a NCO were not observed.*

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{24}N_2NaO_6^+$ 399.1532, found 399.1530.

TLC: R_f = 0.3 (3:1 hexanes : ethyl acetate).

Compound SI-85



3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-acetoxy-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate **(SI-85)**

To a solution of **SI-70** (34.8 mg, 0.1 mmol, 1.0 equiv.) in DCM (1.0 mL) were added Et_3N (30.3 mg, 0.3 mmol, 3.0 equiv.) and acetyl chloride (11.7 mg, 0.15 mmol, 1.5 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 3 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×3.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 31.2 mg (80%) of the title compound **SI-85**.

Physical State: colorless oil.

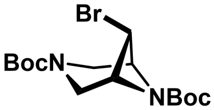
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.37 – 7.26 (m, 5H), 5.15 (q, *J* = 12.5 Hz, 2H), 5.08 (t, *J* = 5.8 Hz, 1H), 4.33 (s, 1H), 4.28 (s, 1H), 4.18 – 4.03 (m, 2H), 3.26 (dd, *J* = 12.5, 4.6 Hz, 2H), 2.04 (s, 3H), 1.37 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 170.03, 156.22, 156.01, 136.57, 128.50, 128.06, 127.84, 81.13, 67.11, 62.74, 61.50, 61.03, 40.80, 28.09, 20.56.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{20}H_{26}N_2NaO_6^+$ 413.1689, found 413.1687.

TLC: R$_f$ = 0.3 (3:1 hexanes : ethyl acetate).

Compound SI-86



di-tert-butyl (1R,5S,7r)-7-bromo-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate **(SI-86)**

To a solution of **10** (196 mg, 1 mmol, 1.0 equiv.) in MeCN (10 mL) were added LiBr (434 mg, 5 mmol, 5.0 equiv.) and Boc$_2$O (436 mg, 2 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×10 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 286.5 mg (76%) of the title compound **SI-86**.

Physical State: colorless oil.

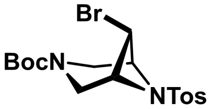
^{1}H NMR (500 MHz, CDCl$_3$): δ 4.63 (t, *J* = 5.8 Hz, 1H), 4.26 (s, 1H), 4.20 (dt, *J* = 6.4, 3.5 Hz, 1H), 4.05 (dd, *J* = 12.8, 3.5 Hz, 2H), 3.42 (dd, *J* = 12.7, 4.6 Hz, 2H), 1.46 (s, 9H), 1.44 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 156.01, 155.27, 81.39, 80.09, 62.59, 62.15, 41.87, 41.09, 28.38, 28.13.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{25}BrN_2NaO_4^+$ 399.0895, found 399.0893.

TLC: $R_f = 0.3$ (10:1 hexanes : ethyl acetate).

Compound SI-87



tert-butyl (1R,5S,7r)-7-bromo-6-tosyl-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate **(SI-87)**

To a solution of **10** (392 mg, 2 mmol, 1.0 equiv.) in MeCN (10 mL) was added TosBr (680 mg, 4 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 603.4 mg (70%) of the title compound **SI-87**.

Physical State: colorless oil.

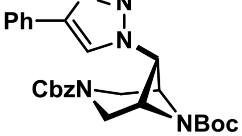
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.77 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.89 (t, J = 6.2 Hz, 1H), 4.49 – 4.41 (m, 2H), 3.81 – 3.65 (m, 4H), 2.44 (s, 3H), 1.46 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 154.85, 144.79, 135.50, 130.07, 127.63, 80.35, 64.35, 64.13, 45.99, 45.41, 41.37, 28.43, 21.66.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{23}BrN_2NaO_4S^+$ 453.0460, found 453.0462.

TLC: $R_f = 0.3$ (10:1 hexanes : ethyl acetate).

Compound SI-88



3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-(4-phenyl-1H-1,2,3-triazol-1-yl)-3,6-diazabicyclo[3.1.1] heptane-3,6-dicarboxylate **(SI-88)**

To a solution of **SI-60** (37.3 mg, 0.1 mmol, 1.0 equiv.) in THF (1.0 mL) were added DIPEA (25.8 mg, 0.2 mmol, 2.0 equiv.), phenylacetylene (15.3 mg, 0.15 mmol, 1.5 equiv.) and CuI (19.0 mg, 0.1 mmol, 1.0 equiv.) at 25 °C and the mixture was stirred for 12 hours at 25 °C under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 30.4 mg (64%) of the title compound **SI-88**.

Physical State: white solid.

m.p. 189-190 °C.

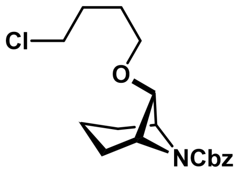
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.5 Hz, 2H), 7.71 (s, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.30 – 7.22 (m, 5H), 5.19 (t, *J* = 5.9 Hz, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 5.02 (d, *J* = 12.4 Hz, 1H), 4.70 (s, 2H), 4.16 (d, *J* = 12.4 Hz, 1H), 3.74 (d, *J* = 13.0 Hz, 1H), 3.60 (d, *J* = 13.3 Hz, 1H), 1.44 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.61, 148.17, 136.30, 129.85, 128.95, 128.58, 128.48, 128.03, 127.72, 125.88, 118.44, 81.89, 67.28, 51.32, 28.17. *Note: NCH, $NCHCH_2$ and a NCO were not observed.*

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{26}H_{29}N_5NaO_4^+$ 498.2117, found 498.2115.

TLC: R_f = 0.3 (3:1 hexanes : ethyl acetate).

Compound SI-89



benzyl (1R,5S,7r)-7-(4-chlorobutoxy)-6-azabicyclo[3.1.1]heptane-6-carboxylate **(SI-89)**

To a solution of **2** (19 mg, 0.2 mmol, 1.0 equiv.) in THF (1.0 mL) was added CbzCl (68 mg, 0.4 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 40.4 mg (60%) of the title compound **SI-89**.

Physical State: colorless oil.

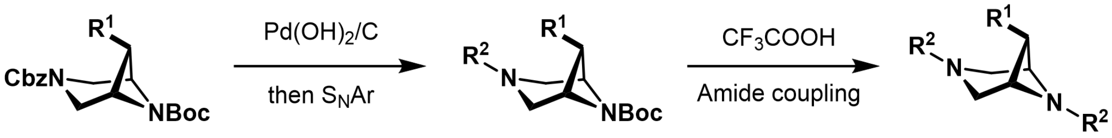
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.29 (m, 5H), 5.13 (s, 2H), 4.28 (s, 2H), 4.06 (t, J = 5.8 Hz, 1H), 3.58 (t, J = 6.6 Hz, 2H), 3.44 (t, J = 6.2 Hz, 2H), 2.13 (s, br., 1H), 2.02 (s, br., 1H), 1.92 – 1.83 (m, 2H), 1.78 – 1.66 (m, 5H), 1.52 – 1.41 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.48, 136.79, 128.48, 128.01, 127.98, 70.57, 68.31, 66.67, 44.84, 29.56, 27.11, 14.59. *Note: NCH and $NCHCH_2$ were not observed.*

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}ClNNaO_3^+$ 360.1342, found 360.1340.

TLC: R_f = 0.3 (5:1 hexanes : ethyl acetate).

General Procedure for Preparation of OXR antagonists



Step 1. To a flame dried, screw-capped vial equipped with a stirrer bar was added strain release products (1.0 equiv.), $Pd(OH)_2/C$ (20-30%) and methanol (0.2 M), the reaction vial was backfilled with hydrogen three times. The mixture was then stirred at room temperature until the completion of the reaction showed by TLC analysis (usually 12 h). After solvent removed under reduced pressure, the crude product was used directly in further reactions.

Step 2. To a flame dried, screw-capped vial equipped with a stirrer bar was added crude product (1.0 equiv.) and DMF (0.2 M). To the mixture was added DIPEA (2.0 equiv.) and aryl chlorinated (1.5 equiv.). The reaction mixture was stirred at 120 °C for 6 hours under an argon atmosphere. The solvent was removed under reduced pressure, and the resulting crude material was purified by flash column chromatography on silica gel to afford the S_NAr products.

Step 3. To a flame dried, screw-capped vial equipped with a stirrer bar was added S_NAr products (1.0 equiv.), DCM (0.2 M) and CF_3COOH (20 equiv.). The mixture was then stirred at room temperature until the completion of the reaction showed by TLC analysis (usually 2-3 h). After solvent removed under reduced pressure, the crude product was used directly in further reactions. To a flame dried, screw-capped vial equipped with a stirrer bar was added crude product (1.0 equiv.) and DMF (0.2 M). To the mixture was added DIPEA (5.0 equiv.), acid (1.1 equiv.) and HATU (1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. The solvent was removed under reduced pressure, and the resulting crude material was purified by flash column chromatography on silica gel to afford the OXR antagonists.

Experimental Procedures and Characterization Data of OXR antagonists

Compound SI-38

3-benzyl 6-(tert-butyl) (1R,5S)-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate **(SI-38)**

To a solution of **1** (230 mg, 1.0 mmol, 1.0 equiv.) in THF (10 mL) was added $LiAlH_4$ (76 mg, 2.0 mmol, 2 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 3 hours under an argon atmosphere. Then Boc_2O (436 mg, 2.0 mmol, 2.0 equiv.) and K_2CO_3 (276 mg, 2.0 mmol, 2.0 equiv.) were added at 0 °C and the mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with sat. aq. $NaHCO_3$ (3.0 mL) and extracted with DCM (3×5.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 162.7 mg (49%) of the title compound **SI-38**.

Physical State: colorless oil.

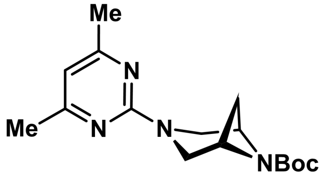
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 5H), 5.16 (d, J = 1.8 Hz, 2H), 4.14 (s, 1H), 4.10 (s, 1H), 3.99 (s, br., 2H), 3.43 (dd, J = 12.3, 1.5 Hz, 2H), 2.61 – 2.53 (m, 1H), 1.40 (s, 9H), 1.37 (d, J = 8.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.61, 156.23, 136.65, 128.50, 128.03, 127.85, 80.45, 67.06, 58.27, 45.69, 28.48, 28.28.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}N_2NaO_4^+$ 355.1634, found 355.1635.

TLC: R_f = 0.3 (10:1 hexanes : ethyl acetate).

Compound SI-39



***tert-butyl (1R,5S)-3-(4,6-dimethylpyrimidin-2-yl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate* (SI-39)**

To a solution of **SI-38** (132.8 mg, 0.4 mmol, 1.0 equiv.) in MeOH (4.0 mL) was added 20% $Pd(OH)_2/C$ and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (2.0 mL). To the mixture were added DIPEA (103.2 mg, 0.8 mmol, 2.0 equiv.) and 2-chloro-4,6-dimethylpyrimidine (85.2 mg, 0.6 mmol, 1.5 equiv.). The reaction mixture was stirred at 120 °C for 6 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×5.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 87.6 mg (72%) of the title compound **SI-39**.

Physical State: yellow oil.

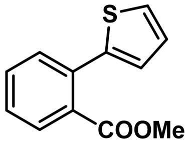
^{1}H NMR (500 MHz, Methanol-*d*$_4$): δ 6.44 (s, 1H), 4.24 – 4.16 (m, 4H), 3.55 (d, *J* = 12.3 Hz, 2H), 2.66 – 2.58 (m, 1H), 2.29 (s, 6H), 1.46 (d, *J* = 8.8 Hz, 1H), 1.33 (s, 9H).

^{13}C NMR (126 MHz, Methanol-*d*$_4$): δ 167.15, 161.74, 157.26, 109.07, 80.11, 59.01, 58.16, 46.07, 45.18, 28.73, 27.14, 22.54.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{25}N_4O_2^+$ 305.1978, found 305.1980.

TLC: R_f = 0.4 (3:1 hexanes : ethyl acetate).

Compound SI-40



methyl 2-(thiophen-2-yl)benzoate **(SI-40)**

To a solution of 2-bromobenzoic acid (1.01 g, 5 mmol, 1.0 equiv.) in MeOH (10 mL) was added concentrated sulfuric acid (1.33 mL, 25 mmol, 5.0 equiv.) and the reaction mixture was stirred at 80 °C for 3 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was extracted with DCM (3×20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was used directly in further reaction. To the resulting product were added 2-thiopheneboronic acid (640 mg, 5 mmol, 1.0 equiv.), K_2CO_3 (1.73g, 12.5 mmol, 2.5 equiv.), THF (10 mL), H_2O (5.0 mL) and $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol,0.01 equiv.) and the reaction mixture was stirred at 70 °C for 10 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 937.4 mg (86%) of the title compound **SI-40**.

Physical State: yellow oil.

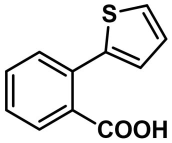
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.73 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.44 – 7.37 (m, 1H), 7.35 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.11 – 7.01 (m, 2H), 3.74 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 169.15, 142.06, 134.17, 131.75, 131.20, 131.02, 129.46, 127.74, 127.23, 126.30, 125.89, 52.23.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{10}NaO_2S^+$ 241.0299, found 241.0300.

TLC: R_f = 0.3(10:1 hexanes : ethyl acetate).

Compound SI-41



2-(thiophen-2-yl)benzoic acid **(SI-41)**

To a solution of **SI-40** (937 mg, 4.3 mmol, 1.0 equiv.) in EtOH (10 mL) was added NaOH (258 mg, 6.45 mmol, 1.5 equiv.) and the reaction mixture was stirred at 90 °C for 3 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was dissolved in distilled water (20 mL) and cooled to 10 °C and then added 1M HCl aq. (10 mL). The mixture was extracted with DCM (3×20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford 701.8 mg (80%) of the title compound **SI-41**.

Physical State: white solid.

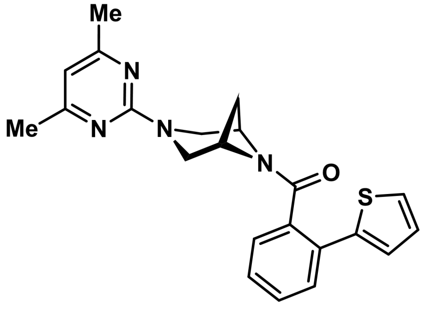
m.p. 83-84 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (ddd, *J* = 7.8, 1.5, 0.6 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.42 (ddd, *J* = 7.8, 7.2, 1.6 Hz, 1H), 7.36 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.14 – 7.03 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.39, 141.59, 135.15, 131.92, 131.83, 130.50, 130.18, 127.81, 127.28, 126.82, 126.11.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_8NaO_2S^+$ 227.0143, found 227.0144.

Compound 67



((1R,5S)-3-(4,6-dimethylpyrimidin-2-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl)(2-(thiophen-2-yl)phenyl)methanone **(67)**

To a solution of **SI-39** (60.8 mg, 0.2 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF_3COOH (0.1 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (129.0 mg, 1.0 mmol, 5.0 equiv.), 2-(2-thienyl)benzoic acid (44.9 mg, 0.22 mmol, 1.1 equiv.) and HATU (83.6 mg, 0.22 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 42.9 mg (55%) of the title compound **67**.

Physical State: yellow oil.

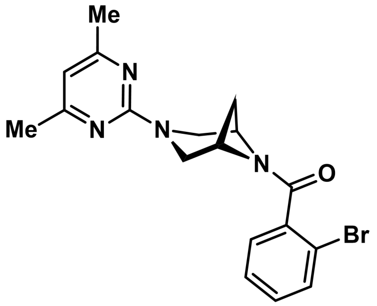
^{1}H NMR (500 MHz, Methanol-*d*$_4$): δ 7.57 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.49 (td, *J* = 7.4, 1.9 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.21 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.18 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.78 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.46 (s, 1H), 4.63 (ddt, *J* = 6.2, 4.1, 2.1 Hz, 1H), 4.09 – 4.05 (m, 2H), 3.81 (dd, *J* = 12.6, 1.9 Hz, 1H), 3.57 (dd, *J* = 12.6, 1.7 Hz, 1H), 3.30 – 3.28 (m, 1H), 2.51 (q, *J* = 6.9 Hz, 1H), 2.27 (s, 6H), 1.55 (d, *J* = 8.8 Hz, 1H).

^{13}C NMR (126 MHz, Methanol-*d*$_4$): δ 169.69, 167.03, 161.44, 140.55, 133.00, 131.74, 130.01, 129.70, 127.66, 127.59, 127.05, 126.37, 125.87, 109.25, 61.32, 58.06, 48.91, 47.56, 29.59, 22.50.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{23}N_4OS^+$ 391.1593, found 391.1591.

TLC: R_f = 0.3 (1:1 hexanes : ethyl acetate).

Compound SI-42



(2-bromophenyl)((1R,5S)-3-(4,6-dimethylpyrimidin-2-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl)methan-one **(SI-42)**

To a solution of **SI-39** (121.6 mg, 0.4 mmol, 1.0 equiv.) in DCM (1.5 mL) was added CF_3COOH (0.2 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (2.0 mL). To the mixture were added DIPEA (258.0 mg, 2.0 mmol, 5.0 equiv.), 2-bromobenzoic acid (88.4 mg, 0.44 mmol, 1.1 equiv.) and HATU (167.2 mg, 0.44 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×2.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 109.9 mg (71%) of the title compound **SI-42**.

Physical State: white solid.

m.p. 118-119 °C.

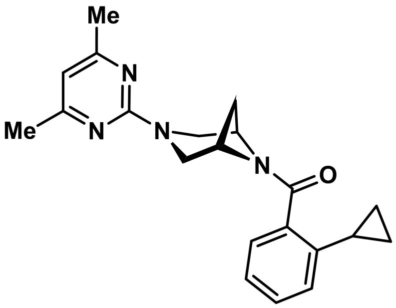
^{1}H NMR (500 MHz, Methanol-*d*$_4$): δ 7.70 – 7.63 (m, 1H), 7.45 (ddd, *J* = 7.9, 6.9, 1.2 Hz, 1H), 7.43 – 7.32 (m, 2H), 6.48 (s, 1H), 4.74 (ddt, *J* = 6.1, 4.0, 2.1 Hz, 1H), 4.29 (ddt, *J* = 6.3, 3.9, 2.0 Hz, 1H), 4.23 (ddd, *J* = 12.6, 2.4, 1.1 Hz, 1H), 3.93 (dd, *J* = 12.6, 1.9 Hz, 1H), 3.76 (dd, *J* = 12.8, 1.7 Hz, 1H), 3.64 (ddd, *J* = 12.8, 2.6, 1.2 Hz, 1H), 2.91 (dtt, *J* = 9.0, 6.6, 1.2 Hz, 1H), 2.30 (s, 6H), 1.72 (d, *J* = 8.9 Hz, 1H).

^{13}C NMR (126 MHz, Methanol-*d*$_4$): δ 168.57, 167.21, 161.64, 136.00, 133.13, 131.22, 128.36, 127.66, 118.87, 109.22, 61.59, 58.42, 48.94, 37.48, 29.44, 22.47.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{20}BrN_4O^+$ 387.0820, found 387.0820.

TLC: R$_f$ = 0.2 (2:1 hexanes : ethyl acetate).

Compound 68



(2-cyclopropylphenyl)((1R,5S)-3-(4,6-dimethylpyrimidin-2-yl)-3,6-diazabicyclo[3.1.1] heptan-6-yl)methanone **(68)**

To a solution of **SI-42** (38.7 mg, 0.1 mmol, 1.0 equiv.) in dioxane (1.0 mL) and H_2O (0.1 mL) were added K_2CO_3 (34.5 mg, 0.25 mmol, 2.5 equiv.), cyclopropylboronic acid (12.9 mg, 0.15 mmol, 1.5 equiv.) and [1,1'-Bis(diphenylphosphino)ferrocene] dichloro palladium (II) [Pd(dppf)Cl_2] (3.7 mg, 0.005 mmol, 0.05 equiv.). The reaction solution was backfilled with argon three times and stirred under an argon atmosphere at 100 °C for 12 hours. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 26.1 mg (75%) of the title compound **68**.

Physical State: yellow solid.

m.p. 202-204 °C.

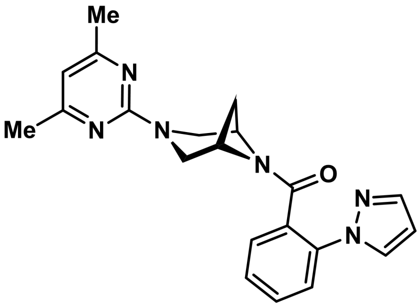
^{1}H NMR (500 MHz, Methanol-*d*$_4$): δ 7.35 (td, *J* = 7.6, 1.5 Hz, 1H), 7.26 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.20 (td, *J* = 7.5, 1.1 Hz, 1H), 6.92 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.48 (s, 1H), 4.71 (ddt, *J* = 6.2, 4.1, 2.1 Hz, 1H), 4.36 – 4.27 (m, 2H), 3.83 (dd, *J* = 12.6, 1.7 Hz, 1H), 3.64 (dd, *J* = 12.7, 1.7 Hz, 1H), 3.61 (dd, *J* = 13.1, 2.0 Hz, 1H), 2.88 (dtt, *J* = 8.8, 6.5, 1.2 Hz, 1H), 2.29 (s, 6H), 1.97 (tt, *J* = 8.2, 5.5 Hz, 1H), 1.66 (d, *J* = 8.9 Hz, 1H), 0.88 (dtt, *J* = 8.9, 6.4, 4.2 Hz, 1H), 0.71 (ddt, *J* = 8.5, 7.0, 4.8 Hz, 1H), 0.54 – 0.46 (m, 2H).

^{13}C NMR (126 MHz, Methanol-*d*$_4$): δ 172.56, 167.22, 161.69, 141.15, 134.43, 130.03, 126.43, 125.13, 123.69, 109.20, 61.44, 58.18, 48.66, 47.09, 29.28, 22.50, 11.67, 8.50, 8.27.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{21}H_{25}N_4O^+$ 349.2028, found 349.2026.

TLC: R$_f$ = 0.3 (2:1 hexanes : ethyl acetate).

Compound 69



(2-(1H-pyrazol-1-yl)phenyl)((1R,5S)-3-(4,6-dimethylpyrimidin-2-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl)methanone **(69)**

To a solution of **SI-42** (38.7 mg, 0.1 mmol, 1.0 equiv.) in toluene (1.0 mL) were added K_3PO_4 (53.8 mg, 0.25 mmol, 2.5 equiv.), pyrazole (10.2 mg, 0.15 mmol, 1.5 equiv.), CuI (1.9 mg, 0.01 mmol, 0.1 equiv.) and N,N'-dimethyl-1,2-cyclohexanediamine (2.84 mg, 0.02 mmol, 0.2 equiv.). The reaction solution was backfilled with argon three times and stirred under an argon atmosphere at 120 °C for 12 hours. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:3) on silica gel to afford 23.9 mg (64%) of the title compound **69**.

Physical State: colorless oil.

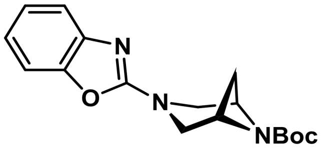
^{1}H NMR (500 MHz, Methanol-*d*$_4$): δ 7.91 (d, *J* = 2.3 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.55 – 7.44 (m, 2H), 7.22 (d, *J* = 1.8 Hz, 1H), 6.51 – 6.46 (m, 1H), 6.31 (t, *J* = 2.2 Hz, 1H), 4.62 (ddt, *J* = 6.2, 4.1, 2.1 Hz, 1H), 4.22 (ddt, *J* = 6.2, 4.1, 2.1 Hz, 1H), 4.17 – 4.11 (m, 1H), 3.86 (dd, *J* = 12.5, 2.0 Hz, 1H), 3.68 (d, *J* = 1.8 Hz, 0.3H), 3.65 (d, *J* = 1.8 Hz, 0.7H), 3.58 (dd, *J* = 12.6, 1.3 Hz, 1H), 2.75 – 2.65 (m, 1H), 2.29 (s, 6H), 1.64 (d, *J* = 8.7 Hz, 1H).

^{13}C NMR (126 MHz, Methanol-*d*$_4$): δ 168.65, 167.11, 161.71, 140.48, 137.52, 130.89, 129.70, 128.78, 128.47, 127.57, 123.82, 109.10, 106.97, 61.65, 58.17, 48.69, 47.32, 29.35, 22.49.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{21}H_{23}N_6O^+$ 375.1933, found 375.1935.

TLC: R$_f$ = 0.2 (1:2 hexanes : ethyl acetate).

Compound SI-43



***tert-butyl (1R,5S)-3-(benzo[d]oxazol-2-yl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate* (SI-43)**

To a solution of **SI-38** (132.8 mg, 0.4 mmol, 1.0 equiv.) in MeOH (4.0 mL) was added 20% $Pd(OH)_2/C$ and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in MeCN (2.0 mL). To the mixture were added K_2CO_3 (66.2 mg, 0.48 mmol, 1.2 equiv.) and 2-chlorobenzoxazole (61.2 mg, 0.4 mmol, 1.0 equiv.), the reaction mixture was stirred at 90 °C for 16 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×5.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 95.8 mg (76%) of the title compound **SI-43**.

Physical State: white solid.

m.p. 123-124 °C.

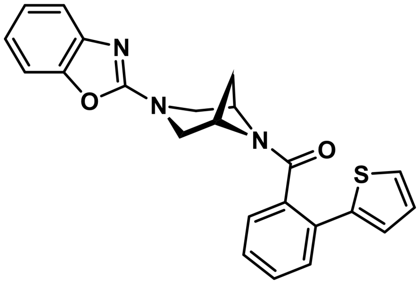
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.36 (d, *J* = 7.9 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.15 (td, *J* = 7.7, 1.2 Hz, 1H), 7.00 (td, *J* = 7.7, 1.3 Hz, 1H), 4.34 – 4.01 (m, 4H), 3.65 (d, *J* = 11.4 Hz, 2H), 2.67 (q, *J* = 7.2 Hz, 1H), 1.50 (d, *J* = 9.0 Hz, 1H), 1.37 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 162.14, 156.10, 148.86, 143.04, 124.02, 120.56, 116.35, 108.86, 80.67, 58.25, 57.56, 46.64, 45.55, 28.63, 28.26.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{22}N_3O_3^+$ 316.1661, found 316.1663.

TLC: R_f = 0.3 (2:1 hexanes : ethyl acetate).

Compound SI-44



((1R,5S)-3-(benzo[d]oxazol-2-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl)(2-(thiophen-2-yl)phenyl) methan-one **(SI-44)**

To a solution of **SI-43** (63 mg, 0.2 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF_3COOH (0.1 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (129.0 mg, 1.0 mmol, 5.0 equiv.), 2-(2-thienyl)benzoic acid (44.9 mg, 0.22 mmol, 1.1 equiv.) and HATU (83.6 mg, 0.22 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:2) on silica gel to afford 50.5 mg (63%) of the title compound **SI-44**.

Physical State: white solid.

m.p. 161-162 °C.

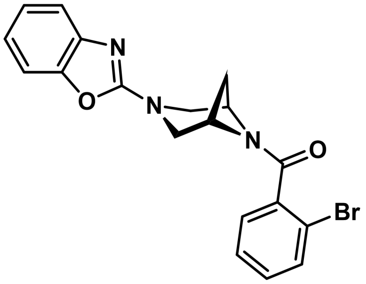
^{1}H NMR (500 MHz, Methanol-*d*$_4$): δ 7.59 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.52 (ddd, *J* = 7.9, 5.8, 3.0 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.32 (t, *J* = 8.1 Hz, 2H), 7.24 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.21 (td, *J* = 7.6, 1.1 Hz, 1H), 7.09 (td, *J* = 7.7, 1.3 Hz, 1H), 7.00 (d, *J* = 5.1 Hz, 1H), 6.71 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.68 (ddt, *J* = 5.9, 3.8, 2.0 Hz, 1H), 4.16 (dd, *J* = 11.5, 1.4 Hz, 1H), 4.15 – 4.09 (m, 1H), 3.81 (dd, *J* = 11.4, 1.8 Hz, 1H), 3.56 (dd, *J* = 11.6, 1.6 Hz, 1H), 3.33 – 3.29 (m, 1H), 2.65 (q, *J* = 7.2 Hz, 1H), 1.67 (d, *J* = 9.2 Hz, 1H).

^{13}C NMR (126 MHz, Methanol-*d*$_4$): δ 170.00, 161.81, 148.60, 142.06, 140.50, 132.83, 131.59, 130.14, 129.79, 127.78, 127.55, 127.06, 126.57, 126.03, 123.99, 120.79, 115.35, 108.68, 60.59, 57.32, 29.21.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{20}N_3O_2S^+$ 402.1276, found 402.1277.

TLC: R_f = 0.3 (1:2 hexanes : ethyl acetate).

Compound SI-45



((1R,5S)-3-(benzo[d]oxazol-2-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl)(2-bromophenyl) methanone **(SI-45)**

To a solution of **SI-43** (126 mg, 0.4 mmol, 1.0 equiv.) in DCM (1.5 mL) was added CF_3COOH (0.2 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (2.0 mL). To the mixture were added DIPEA (258.0 mg, 2.0 mmol, 5.0 equiv.), 2-bromobenzoic acid (88.4 mg, 0.44 mmol, 1.1 equiv.) and HATU (167.2 mg, 0.44 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×2.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 105.1 mg (66%) of the title compound **SI-45**.

Physical State: colorless oil.

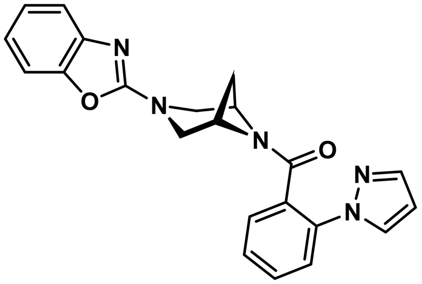
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.9 Hz, 1H), 7.39 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.34 – 7.31 (m, 2H), 7.30 – 7.22 (m, 2H), 7.18 (td, *J* = 7.7, 1.1 Hz, 1H), 7.04 (td, *J* = 7.7, 1.2 Hz, 1H), 4.79 (ddt, *J* = 5.9, 3.9, 2.1 Hz, 1H), 4.49 – 4.43 (m, 1H), 4.25 (ddt, *J* = 6.0, 3.9, 2.0 Hz, 1H), 3.92 (dd, *J* = 11.6, 1.9 Hz, 1H), 3.81 – 3.72 (m, 2H), 2.96 – 2.94 (m, 1H), 1.76 (d, *J* = 9.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 168.29, 161.90, 148.89, 142.82, 136.15, 133.48, 131.24, 128.55, 127.74, 124.15, 120.80, 119.46, 116.48, 108.96, 60.50, 57.48, 49.45, 47.63, 29.77.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{17}BrN_3O_2^+$ 398.0504, found 398.0505.

TLC: R_f = 0.2 (1:1 hexanes : ethyl acetate).

Compound SI-46



(2-(1H-pyrazol-1-yl)phenyl)((1R,5S)-3-(benzo[d]oxazol-2-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl)meth-anone **(SI-46)**

To a solution of **SI-45** (39.8 mg, 0.1 mmol, 1.0 equiv.) in toluene (1.0 mL) were added K_3PO_4 (53.8 mg, 0.25 mmol, 2.5 equiv.), pyrazole (10.2 mg, 0.15 mmol, 1.5 equiv.), CuI (1.9 mg, 0.01 mmol, 0.1 equiv.) and N,N'-dimethyl-1,2-cyclohexanediamine (2.84 mg, 0.02 mmol, 0.2 equiv.). The reaction solution was backfilled with argon three times and stirred under an argon atmosphere at 120 °C for 12 hours. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:4) on silica gel to afford 25.8 mg (67%) of the title compound **SI-46**.

Physical State: white solid.

m.p. 199-200 °C.

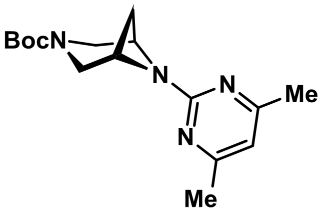
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.78 (d, *J* = 2.4 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.26 (t, *J* = 2.1 Hz, 1H), 4.64 (tt, *J* = 5.7, 2.3 Hz, 1H), 4.32 (dd, *J* = 11.5, 2.1 Hz, 1H), 4.15 (tt, *J* = 5.8, 2.2 Hz, 1H), 3.83 (dd, *J* = 11.6, 2.0 Hz, 1H), 3.75 (dd, *J* = 11.6, 2.2 Hz, 1H), 3.62 (dd, *J* = 11.7, 1.8 Hz, 1H), 2.68 (q, *J* = 7.0 Hz, 1H), 1.67 (d, *J* = 8.9 Hz, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 168.28, 162.06, 148.83, 142.90, 141.05, 137.82, 130.91, 129.99, 129.29, 128.48, 127.78, 124.57, 124.09, 120.65, 116.39, 108.87, 107.43, 60.54, 57.19, 49.01, 47.53, 29.49.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{20}N_5O_2^+$ 386.1617, found 386.1618.

TLC: $R_f = 0.2$ (1:3 hexanes : ethyl acetate).

Compound SI-48



***tert-butyl (1R,5S)-6-(4,6-dimethylpyrimidin-2-yl)-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate* (SI-48)**

To a solution of **SI-47** (132.8 mg, 0.4 mmol, 1.0 equiv.) in MeOH (4.0 mL) was added 20% $Pd(OH)_2/C$ and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (2.0 mL). To the mixture were added DIPEA (103.2 mg, 0.8 mmol, 2.0 equiv.) and 2-chloro-4,6-dimethylpyrimidine (85.2 mg, 0.6 mmol, 1.5 equiv.). The reaction mixture was stirred at 120 °C for 6 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×5.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 85.1 mg (70%) of the title compound **SI-48**.

Physical State: white solid.

m.p. 168-170 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.37 (s, 1H), 4.49 (ddt, J = 5.8, 3.9, 2.0 Hz, 1H), 4.41 (ddt, J =

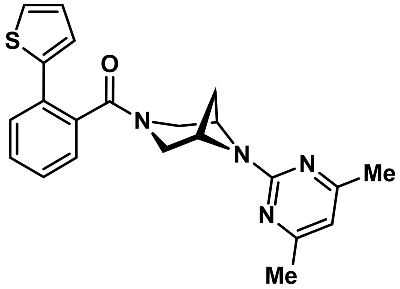
5.6, 3.5, 2.0 Hz, 1H), 3.98 (ddt, *J* = 12.2, 2.3, 1.3 Hz, 2H), 3.38 (td, *J* = 12.5, 1.8 Hz, 2H), 2.69 (dtt, *J* = 8.7, 6.2, 1.2 Hz, 1H), 2.29 (s, 6H), 1.55 (d, *J* = 8.5 Hz, 1H), 1.39 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 167.44, 162.22, 156.19, 111.08, 79.43, 58.28, 58.08, 44.44, 43.87, 28.72, 28.44, 24.00.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{16}H_{25}N_4O_2^+$ 305.1978, found 305.1976.

TLC: R$_f$ = 0.4 (3:1 hexanes : ethyl acetate).

Compound SI-49



((1R,5S)-6-(4,6-dimethylpyrimidin-2-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)(2-(thiophen-2-yl)phenyl) methanone **(SI-49)**

To a solution of **SI-48** (60.8 mg, 0.2 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF_3COOH (0.1 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (129.0 mg, 1.0 mmol, 5.0 equiv.), 2-(2-thienyl)benzoic acid (44.9 mg, 0.22 mmol, 1.1 equiv.) and HATU (83.6 mg, 0.22 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 46.0 mg (59%) of the title compound **SI-49**.

Physical State: colorless oil.

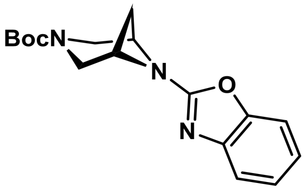
^{1}H NMR (500 MHz, Methanol-d_4): δ 7.57 (t, *J* = 7.3 Hz, 1H), 7.53 – 7.47 (m, 0.4H), 7.50 – 7.42 (m, 1H), 7.41 (td, *J* = 7.4, 1.3 Hz, 0.6H), 7.35 (td, *J* = 7.3, 1.4 Hz, 1H), 7.22 (dd, *J* = 3.7, 1.2 Hz, 0.4H), 7.16 (dd, *J* = 5.2, 1.1 Hz, 0.6H), 7.13 (dd, *J* = 5.1, 3.6 Hz, 0.4H), 6.91 (dd, *J* = 3.6, 1.2 Hz, 0.6H), 6.81 (dd, *J* = 7.6, 1.4 Hz, 0.4H), 6.70 (dd, *J* = 5.2, 3.6 Hz, 0.6H), 6.64 (s, 0.4H), 6.56 (s, 0.6H), 4.51 (dq, *J* = 5.3, 2.3 Hz, 0.6H), 4.45 (dt, *J* = 6.5, 3.5 Hz, 0.4H), 4.33 – 4.25 (m, 1H), 4.16 (dq, *J* = 7.4, 2.6 Hz, 0.4H), 4.04 (dt, *J* = 13.6, 1.8 Hz, 0.6H), 3.82 (dd, *J* = 13.5, 1.9 Hz, 0.6H), 3.72 (dd, *J* = 11.8, 1.7 Hz, 0.4H), 3.54 (dt, *J* = 11.9, 1.5 Hz, 0.6H), 3.41 (dd, *J* = 13.4, 1.4 Hz, 0.4H), 3.20 (dd, *J* = 11.8, 2.0 Hz, 0.6H), 2.88 (dd, *J* = 12.0, 1.5 Hz, 0.4H), 2.74 – 2.66 (m, 0.6H), 2.55 (q, *J* = 7.1 Hz, 0.4H), 2.31 (s, 6H), 1.65 (d, *J* = 8.8 Hz, 0.6H), 0.92 (d, *J* = 8.8 Hz, 0.4H). *Note: Two isomers with a 2:3 ratio, attributed to rotational isomerization of amide, were observed.*

^{13}C NMR (126 MHz, Methanol-d_4): δ 173.53, 173.23, 168.18, 167.81, 162.28, 161.13, 140.65, 140.27, 134.71, 134.37, 131.06, 130.65, 129.64, 129.51, 129.13, 128.96, 127.85, 127.73, 127.70, 127.24, 126.88, 126.52, 126.41, 126.13, 125.19, 111.65, 111.21, 58.00, 57.89, 57.61, 46.28, 46.14, 43.61, 43.46, 37.51, 28.47, 27.69, 22.42, 22.34.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{22}H_{23}N_4OS^+$ 391.1593, found 391.1591.

TLC: R$_f$ = 0.3 (1:1 hexanes : ethyl acetate).

Compound SI-50



***tert*-butyl (1R,5S)-6-(benzo[d]oxazol-2-yl)-3,6-diazabicyclo[3.1.1]heptane-3-carboxylate (SI-50)**

To a solution of **SI-47** (132.8 mg, 0.4 mmol, 1.0 equiv.) in MeOH (4.0 mL) was added 20% Pd(OH)$_2$/C and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in MeCN (2.0 mL). To the mixture were added K_2CO_3 (66.2 mg, 0.48 mmol, 1.2 equiv.) and 2-chlorobenzoxazole (61.2 mg, 0.4 mmol, 1.0 equiv.). The reaction mixture was stirred at 90 °C for 16 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×5.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 100.8 mg (80%) of the title compound **SI-50**.

Physical State: white solid.

m.p. 188-190 °C.

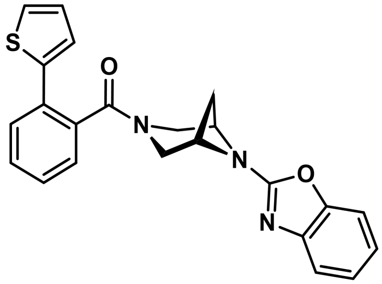
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.42 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.30 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.20 (td, *J* = 7.7, 1.1 Hz, 1H), 7.09 (td, *J* = 7.7, 1.3 Hz, 1H), 4.54 (ddt, *J* = 5.8, 3.8, 2.0 Hz, 1H), 4.48 (ddt, *J* = 5.7, 3.7, 2.0 Hz, 1H), 4.06 (ddd, *J* = 12.7, 2.2, 1.1 Hz, 1H), 3.97 (ddd, *J* = 12.8, 2.2, 1.2 Hz, 1H), 3.58 (dd, *J* = 12.8, 1.8 Hz, 1H), 3.53 (dd, *J* = 12.7, 1.8 Hz, 1H), 2.93 – 2.85 (m, 1H), 1.69 (d, *J* = 8.7 Hz, 1H), 1.40 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 160.49, 155.78, 149.11, 142.29, 124.10, 121.64, 117.11, 109.25, 80.12, 60.33, 60.07, 45.00, 44.75, 29.67, 28.37.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{22}N_3O_3^+$ 316.1661, found 316.1663.

TLC: $R_f = 0.3$ (2:1 hexanes : ethyl acetate).

Compound SI-51



((1R,5S)-6-(benzo[d]oxazol-2-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)(2-(thiophen-2-yl)phenyl) methan-one **(SI-51)**

To a solution of **SI-50** (63 mg, 0.2 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF_3COOH (0.1 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (129.0 mg, 1.0 mmol, 5.0 equiv.), 2-(2-thienyl)benzoic acid (44.9 mg, 0.22 mmol, 1.1 equiv.) and HATU (83.6 mg, 0.22 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:2) on silica gel to afford 52.1 mg (65%) of the title compound **SI-51**.

Physical State: white solid.

m.p. 172-173 °C.

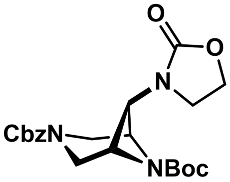
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 16.1, 7.7 Hz, 1H), 7.39 (q, *J* = 8.9 Hz, 2H), 7.31 (dq, *J* = 12.9, 7.2, 5.9 Hz, 2.5H), 7.23 (dt, *J* = 11.5, 7.8 Hz, 2H), 7.17 – 7.04 (m, 2H), 6.89 (d, *J* = 3.8 Hz, 0.5H), 6.22 (d, *J* = 5.1 Hz, 0.5H), 6.19 – 6.11 (m, 0.5H), 4.55 (dd, *J* = 6.1, 3.2 Hz, 0.5H), 4.49 (t, *J* = 4.9 Hz, 0.5H), 4.30 (dd, *J* = 6.0, 3.2 Hz, 0.5H), 4.19 (d, *J* = 13.2 Hz, 1H), 4.07 (q, *J* = 14.2 Hz, 1H), 3.84 (d, *J* = 12.3 Hz, 0.5H), 3.76 – 3.70 (m, 0.5H), 3.56 (d, *J* = 12.3 Hz, 0.5H), 3.23 (dd, *J* = 12.5, 2.1 Hz, 0.5H), 3.01 (dd, *J* = 12.5, 2.0 Hz, 0.5H), 2.87 (q, *J* = 7.0 Hz, 0.5H), 2.64 (q, J = 7.0 Hz, 0.5H), 1.69 (d, J = 8.8 Hz, 0.5H), 0.83 (d, J = 8.8 Hz, 0.5H). *Note: Two isomers with a 1:1 ratio, attributed to rotational isomerization of amide, were observed.*

^{13}C NMR (126 MHz, CDCl$_3$): δ 172.68, 172.60, 167.05, 166.93, 160.22, 159.59, 149.07, 148.90, 142.23, 142.19, 141.07, 139.86, 135.24, 134.71, 131.26, 129.57, 129.41, 128.37, 127.98, 127.79, 127.17, 127.07, 126.88, 126.46, 126.32, 125.75, 125.63, 124.22, 124.04, 121.87, 121.61, 117.53, 117.26, 109.33, 60.42, 59.91, 59.71, 59.52, 46.85, 46.61, 44.57, 43.98, 29.14, 14.22.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{23}H_{20}N_3O_2S^+$ 402.1276, found 402,1276.

TLC: R$_f$ = 0.3 (1:2 hexanes : ethyl acetate).

Compound SI-52



3-benzyl 6-(tert-butyl) (1R,5S,7s)-7-(2-oxooxazolidin-3-yl)-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate **(SI-52)**

A mixture of 2-oxazolidone (8.7 mg, 0.1 mmol, 1.0 equiv.), CuTC (9.55 mg, 0.05 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 0.05 mmol, 0.5 equiv.), 4-CzIPN (3.95 mg, 5 µmol, 0.05 equiv.) and MeCN (3.3 mL, 0.03 M) was prepared in a 10 mL tube. To this mixture was added 1,5-diazabicyclo[4.3.0]non-5-ene (24.8 mg, 0.2 mmol, 2.0 equiv.) and water (45 µL, 2.5 mmol, 25 equiv.). The resulting solution was stirred for 1-2 minutes under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, **22** (82.2 mg, 0.2 mmol, 2.0 equiv.) and **SI-93** (0.08 mL, 0.25 mmol, 2.5 equiv.) were added to the mixture, and then plugged the tube and inserted an 18G ventilation needle into the plug. The reaction tube was placed in front of a Kessil Blue LED photoreactor (450 nm, 25% light intensity) with fan cooling. The mixture was stirred under air for 12 hours. After 12 hours, MeOH (0.1 mL) was added. The resulting solution was stirred under air for 2 hours and then filtered through celite, rinsing with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 12.5 mg (30%) of the title compound **SI-52**.

Physical State: white solid.

m.p. 150-151 °C.

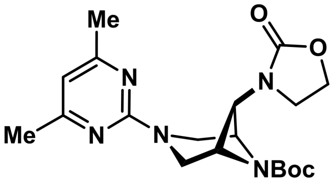
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.38 – 7.28 (m, 5H), 5.16 (s, 2H), 4.41 (t, *J* = 7.9 Hz, 2H), 4.31 – 3.99 (m, 4H), 3.90 – 3.84 (m, 3H), 3.55 (d, *J* = 11.5 Hz, 2H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 158.23, 156.13, 136.34, 128.55, 128.17, 127.93, 81.31, 67.38, 62.47, 55.61, 42.99, 28.15. *Note: NCH, NCHCH$_2$ and a NCO were not observed.*

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{21}H_{27}N_3NaO_6^+$ 440.1798, found 440.1799.

TLC: R_f = 0.3 (1:1 hexanes : ethyl acetate).

Compound SI-53



tert-butyl (1R,5S,7s)-3-(4,6-dimethylpyrimidin-2-yl)-7-(2-oxooxazolidin-3-yl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate **(SI-53)**

To a solution of **SI-52** (41.7 mg, 0.1 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added 20% Pd(OH)$_2$/C and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in MeCN (1.0 mL). To the mixture were added K$_2$CO$_3$ (16.5 mg, 0.12 mmol, 1.2 equiv.) and 2-chlorobenzoxazole (15.3 mg, 0.1 mmol, 1.0 equiv.). The reaction mixture was stirred at 90 °C for 16 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×2.0 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:2) on silica gel to afford 15.6 mg (40%) of the title compound **SI-53**.

Physical State: colorless oil.

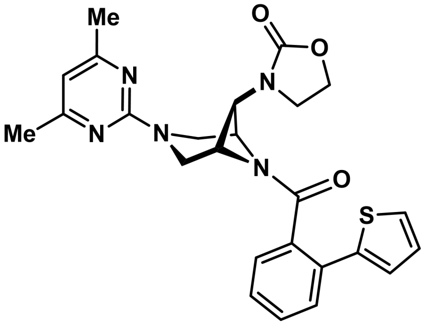
^{1}H NMR (500 MHz, CDCl$_3$): δ 6.35 (s, 1H), 4.42 (t, *J* = 7.9 Hz, 3H), 4.26 (s, 3H), 3.94 (m, 3H), 3.75 (d, *J* = 12.8 Hz, 2H), 2.31 (s, 6H), 1.34 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 166.87, 161.35, 158.28, 156.77, 109.86, 80.89, 62.44, 56.08, 43.08, 28.17, 24.05. *Note: NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{19}H_{28}N_5O_4^+$ 390.2141, found 390.2143.

TLC: R$_f$ = 0.3 (1:2 hexanes : ethyl acetate).

Compound 70



***3-((1R,5S,7s)-3-(4,6-dimethylpyrimidin-2-yl)-6-(2-(thiophen-2-yl)benzoyl)-3,6-diazabicyclo [3.1.1]heptan-7-yl)oxazolidin-2-one* (70)**

To a solution of **SI-53** (15.6 mg, 0.04 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF$_3$COOH (0.05 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (25.8 mg, 0.2 mmol, 5.0 equiv.), 2-bromobenzoic acid (9.0 mg, 0.044 mmol, 1.1 equiv.) and HATU (16.7 mg, 0.044 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over

Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:5) on silica gel to afford 9.9 mg (52%) of the title compound **70**.

Physical State: colorless oil.

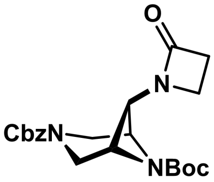
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J = 8.1 Hz, 1H), 7.48 – 7.41 (m, 1H), 7.34 (td, J = 7.4, 1.5 Hz, 1H), 7.24 (dd, J = 11.7, 4.1 Hz, 3H), 6.94 (dd, J = 5.1, 3.6 Hz, 1H), 6.39 (s, 1H), 4.57 (dt, J = 4.4, 2.1 Hz, 1H), 4.47 (dd, J = 12.7, 2.8 Hz, 1H), 4.27 (td, J = 8.8, 6.5 Hz, 1H), 4.19 (td, J = 8.8, 6.9 Hz, 1H), 3.98 (t, J = 3.9 Hz, 1H), 3.91 – 3.85 (m, 2H), 3.66 (d, J = 13.0 Hz, 1H), 3.55 (dd, J = 12.9, 2.9 Hz, 1H), 3.40 (td, J = 8.8, 6.8 Hz, 1H), 2.99 (q, J = 8.2 Hz, 1H), 2.30 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.10, 166.68, 158.00, 141.52, 133.70, 131.51, 130.46, 130.27, 128.23, 127.76, 127.74, 127.29, 125.84, 110.07, 63.74, 62.43, 60.83, 56.55, 48.25, 46.71, 42.03, 24.00.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{26}N_5O_3S^+$ 476.1756, found 476.1754.

TLC: $R_f = 0.3$ (1:5 hexanes : ethyl acetate).

Compound SI-54



3-benzyl 6-(tert-butyl) (1R,5S,7s)-7-(2-oxoazetidin-1-yl)-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate **(SI-54)**

A mixture of 2-azetidinone (7.1 mg, 0.1 mmol, 1.0 equiv.), CuTC (9.55 mg, 0.05 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 0.05 mmol, 0.5 equiv.), 4-CzIPN (3.95 mg, 5 μmol, 0.05 equiv.) and MeCN (3.3 mL, 0.03 M) was prepared in a 10 mL tube. To this mixture was added 1,5-diazabicyclo[4.3.0]non-5-ene (24.8 mg, 0.2 mmol, 2.0 equiv.) and water (45 μL, 2.5 mmol, 25 equiv.). The resulting solution was stirred for 1-2 minutes under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, **22** (82.2 mg, 0.2 mmol, 2.0 equiv.) and **SI-93** (0.08 mL, 0.25 mmol, 2.5 equiv.) were added to the mixture, and then plugged the tube and inserted an 18G ventilation needle into the plug. The reaction tube was placed in front of a Kessil Blue LED photoreactor (450 nm, 25% light intensity) with fan cooling. The mixture was stirred under air for 12 hours. After 12 hours, MeOH (0.1 mL) was added. The resulting solution was stirred under air for 2 hours and then filtered through celite, rinsing with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 24.1 mg (60%) of the title compound **SI-54**.

Physical State: yellow oil.

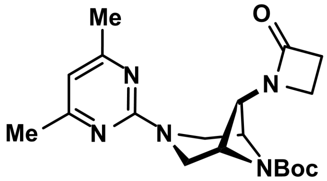
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.35 – 7.27 (m, 5H), 5.14 (s, 2H), 4.31 – 3.97 (m, 4H), 3.71 (s, 1H), 3.58 – 3.41 (m, 4H), 2.98 (t, J = 4.2 Hz, 2H), 1.39 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 167.72, 156.51, 156.10, 136.37, 128.53, 128.13, 127.92, 81.27, 67.32, 61.94, 60.91, 53.10, 45.35, 44.17, 38.44, 36.57, 28.15.

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{21}H_{27}N_3NaO_5^+$ 424.1848, found 424.1848.

TLC: R$_f$ = 0.3 (1:1 hexanes : ethyl acetate).

Compound SI-55



tert-butyl (1R,5S,7s)-3-(4,6-dimethylpyrimidin-2-yl)-7-(2-oxoazetidin-1-yl)-3,6-diazabicyclo [3.1.1]heptane-6-carboxylate **(SI-55)**

To a solution of **SI-54** (80.2 mg, 0.2 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added 20% Pd(OH)$_2$/C and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in MeCN (1.0 mL). To the mixture were added K_2CO_3 (33.1 mg, 0.24 mmol, 1.2 equiv.) and 2-chlorobenzoxazole (30.6 mg, 0.2 mmol, 1.0 equiv.). The reaction mixture was stirred at 90 °C for 16 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×2.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 44.8 mg (60%) of the title compound **SI-55**.

Physical State: white solid.

m.p. 144-145 °C.

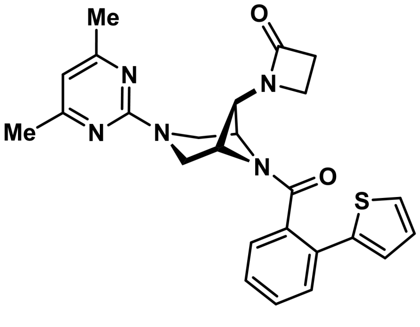
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.32 (s, 1H), 4.37 (d, J = 12.9 Hz, 1H), 4.24 (s, 3H), 3.78 (s, 1H), 3.64 (d, J = 12.8 Hz, 2H), 3.52 (s, br., 2H), 2.97 (t, J = 4.2 Hz, 2H), 2.27 (s, 6H), 1.31 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.77, 166.86, 161.38, 156.82, 109.83, 80.76, 62.66, 61.48, 53.52, 45.75, 44.78, 38.45, 36.47, 28.13, 24.03.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{28}N_5O_3^+$ 374.2192, found 374.2192.

TLC: R_f = 0.4 (1:1 hexanes : ethyl acetate).

Compound 71



1-((1R,5S,7s)-3-(4,6-dimethylpyrimidin-2-yl)-6-(2-(thiophen-2-yl)benzoyl)-3,6-diazabicyclo [3.1.1]heptan-7-yl)azetidin-2-one **(71)**

To a solution of **SI-55** (37.3 mg, 0.1 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF_3COOH (0.1 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (64.5 mg, 0.5 mmol, 5.0 equiv.), 2-bromobenzoic acid (22.1 mg, 0.11 mmol, 1.1 equiv.) and HATU (41.8 mg, 0.11 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (dichloromethane: methanol, 10:1) on silica gel to afford 17.9 mg (39%) of the title compound **71**.

Physical State: white solid.

m.p. 98-99 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.7 Hz, 1H), 7.43 (td, *J* = 7.6, 1.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 1.4 Hz, 1H), 7.23 (d, *J* = 3.6 Hz, 1H), 7.15 (d, *J* = 5.1 Hz, 1H), 6.85 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.38 (s, 1H), 4.62 (dt, *J* = 4.2, 2.1 Hz, 1H), 4.41 (dd, *J* = 12.8, 2.7 Hz, 1H), 4.06 (s, 1H), 3.81 (dd, *J* = 12.8, 1.7 Hz, 1H), 3.76 (s, 1H), 3.61 – 3.53 (m, 1H), 3.48 (dd, *J* = 13.0, 2.9 Hz, 1H), 3.17 (td, *J* = 5.3, 2.8 Hz, 1H), 2.96 – 2.92 (m, 1H), 2.87 (tdd, *J* = 14.7, 5.4, 2.8 Hz, 2H), 2.30 (s, 6H).

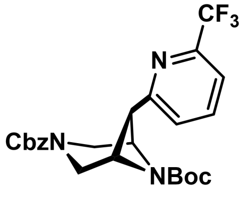
^{13}C NMR (126 MHz, $CDCl_3$): δ 172.01, 167.55, 141.16, 133.45, 131.68, 130.38, 130.21, 127.98, 127.84, 127.67, 127.13, 125.83, 110.03, 63.80, 61.01, 54.30, 48.00, 46.41, 37.81, 36.67, 23.99.

Note: C2 and C4 on pyrimidine were not observed.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{26}N_5O_2S^+$ 460.1807, found 460.1807.

TLC: R_f = 0.4 (10:1 dichloromethane : methanol).

Compound SI-56



3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-(6-(trifluoromethyl)pyridin-2-yl)-3,6-diazabicyclo[3.1.1] heptane-3,6-dicarboxylate **(SI-56)**

A mixture of **22** (82.2 mg, 0.2 mmol, 2.0 equiv.), $CsCO_3$ (65.2 mg, 0.2 mmol, 2.0 equiv.), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (2.24 mg, 2 μmol, 0.02 equiv.), $Ni(dtbpy)Br_2$(2.45 mg, 5 μmol, 0.05 equiv.) was prepared in a 10 mL oven-dried tube. This reaction tube was backfilled with argon three times. To the mixture was added trifluorotoluene (2.0 mL, previously degassed by sparging with argon for 15 min). The mixture was stirred at 25 °C for 5 min and then placed in front of the Kessil Blue LED photoreactor (450 nm, 100% light intensity) with fan cooling. The mixture was stirred under argon for 2 hours. While stirring and irradiating the reaction mixture, a solution of 2-bromo-6-(trifluoromethyl)pyridine (22.6 mg, 0.1 mmol, 1.0 equiv.) and **SI-92** (63.5 mg, 0.16 mmol, 1.6 equiv.) in trifluorotoluene (1.0 mL, previously degassed by sparging with argon for 15 min) was added via syringe pump at a rate of 2.0 mL/h over 30 min. After complete addition, the mixture was irradiated for 90 min. After the reaction was completed, the reaction mixture was removed from the photoreactor, opened to air. To the mixture, EA (2.0 mL) and methanol (60 μL) were added. The reaction mixture was stirred at 25 °C for 1 hour and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 19.1 mg (40%) of the title compound **SI-56**.

Physical State: colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (t, J = 7.8 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.39 – 7.29 (m, 5H), 5.19 (s, 2H), 4.43 – 4.26 (m, 3H), 4.18 – 4.06 (m, 1H), 3.66 (d, J = 12.4 Hz, 2H), 3.14 (s, 1H), 1.40 (s, 9H).

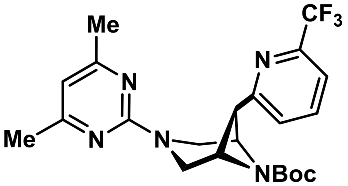
^{13}C NMR (126 MHz, $CDCl_3$): δ 160.02, 156.43, 147.82 (q, J = 34.6 Hz), 138.33, 136.54, 128.54, 128.37, 128.10, 127.88, 123.72, 121.39 (q, J = 274.4 Hz) 119.01 (q, J = 3.2 Hz), 81.15, 67.24, 62.61, 61.56, 47.77, 46.34, 45.11, 28.20.

^{19}F NMR (471 MHz, $CDCl_3$): δ -68.01.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{26}F_3N_3NaO_4^+$ 500.1773, found 500.1774.

TLC: $R_f = 0.3$ (3:1 hexanes : ethyl acetate).

Compound SI-57



tert-butyl (1R,5S,7r)-3-(4,6-dimethylpyrimidin-2-yl)-7-(6-(trifluoromethyl)pyridin-2-yl)-3,6-diazabicyclo [3.1.1]heptane-6-carboxylate **(SI-57)**

To a solution of **SI-56** (47.7 mg, 0.1 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added 20% $Pd(OH)_2/C$ and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in MeCN (1.0 mL). To the mixture were added K_2CO_3 (16.5 mg, 0.12 mmol, 1.2 equiv.) and 2-chlorobenzoxazole (15.3 mg, 0.1 mmol, 1.0 equiv.). The reaction mixture was stirred at 90 °C for 16 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×2.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 26.9 mg (60%) of the title compound **SI-57**.

Physical State: colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 – 7.85 (m, 2H), 7.60 (dd, J = 7.1, 1.5 Hz, 1H), 6.35 (s, 1H), 4.50 – 4.25 (m, 4H), 3.86 (d, J = 12.7 Hz, 2H), 3.22 (s, 1H), 2.32 (s, 6H), 1.35 (s, 9H).

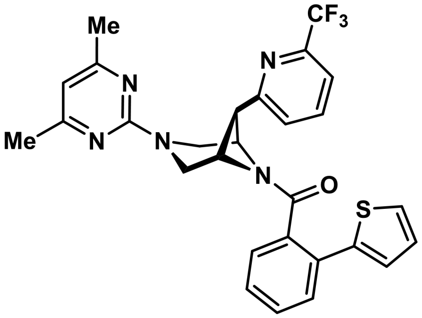
^{13}C NMR (126 MHz, $CDCl_3$): δ 166.85, 161.76, 160.84, 156.83, 147.71 (q, J = 34.5 Hz), 138.18, 123.81, 121.47 (q, J = 273.9 Hz), 118.82 (q, J = 3.1 Hz), 109.64, 80.57, 63.43, 62.18, 48.38, 46.80, 45.79, 28.21, 24.09.

^{19}F NMR (471 MHz, CDCl$_3$): δ -67.98.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{27}F_3N_5O_2^+$ 450.2117, found 450.2119.

TLC: R$_f$ = 0.3 (5:1 hexanes : ethyl acetate).

Compound 72



((1R,5S,7r)-3-(4,6-dimethylpyrimidin-2-yl)-7-(6-(trifluoromethyl)pyridin-2-yl)-3,6-diazabicyclo [3.1.1]heptan-6-yl)(2-(thiophen-2-yl)phenyl)methanone **(72)**

To a solution of **SI-57** (26.9 mg, 0.06 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF_3COOH (0.1 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (38.7 mg, 0.3 mmol, 5.0 equiv.), 2-bromobenzoic acid (13.5 mg, 0.066 mmol, 1.1 equiv.) and HATU (25.1 mg, 0.066 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 17.3 mg (54%) of the title compound **72**.

Physical State: white solid.

m.p. 87-88 °C.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.80 (t, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* =

7.7 Hz, 1H), 7.41 (td, *J* = 7.5, 1.7 Hz, 1H), 7.40 – 7.29 (m, 2H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.15 (d, *J* = 3.5 Hz, 1H), 7.00 (d, *J* = 5.0 Hz, 1H), 6.68 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.38 (s, 1H), 4.80 – 4.75 (m, 1H), 4.46 (dd, *J* = 12.7, 2.4 Hz, 1H), 4.37 – 4.32 (m, 1H), 4.00 (dd, *J* = 12.7, 1.8 Hz, 1H), 3.74 (d, *J* = 12.7 Hz, 1H), 3.55 (dd, *J* = 12.8, 2.7 Hz, 1H), 3.26 (s, 1H), 2.31 (d, *J* = 8.0 Hz, 6H).

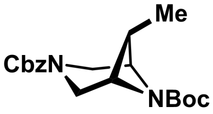
^{13}C NMR (126 MHz, CDCl$_3$): δ 171.22, 166.77, 161.51, 159.59, 147.77 (q, *J* = 34.5 Hz), 140.98, 138.31, 133.58, 131.68, 130.11, 129.99, 128.17, 127.85, 127.45, 126.87, 125.57, 124.01, 121.45 (q, *J* = 274.2 Hz), 118.84 (q, *J* = 2.8 Hz), 109.76, 64.05, 62.03, 49.18, 48.67, 47.66, 24.06.

^{19}F NMR (471 MHz, CDCl$_3$): δ -67.89.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{28}H_{25}F_3N_5OS^+$ 536.1732, found 536.1730.

TLC: R$_f$ = 0.3 (1:1 hexanes : ethyl acetate).

Compound SI-58



***3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-methyl-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate* (SI-58)**

A mixture of **22** (41.1 mg, 0.1 mmol, 1.0 equiv.), Ir(dF(CF$_3$)ppy)$_2$(dtbpy)PF$_6$ (1.12 mg, 1 μmol, 0.01 equiv.) and Ni(dtbpy)Br$_2$(2.45 mg, 5 μmol, 0.05 equiv.), TBAB (80.5 mg, 0.25 mmol, 2.5 equiv.), **SI-93** (39.6 mg, 0.15 mmol, 1.5 equiv.), K$_3$PO$_4$ (42.4 mg, 0.2 mmol, 2 equiv.) was prepared in a 10 mL oven-dried tube. This reaction tube was backfilled with argon three times. To the mixture was added MeCN (2.0 mL, previously degassed by sparging with argon for 15 min). The mixture was then added 4-methyl-benzenesulfonicacimethylester (37.2 mg, 0.2 mmol, 2 equiv.) and placed in front of the Kessil Blue LED photoreactor (450 nm, 100% light intensity) with fan cooling. The mixture was stirred under argon for 12 hours. After the reaction was completed, the reaction mixture was removed from the photoreactor, opened to air. To the mixture, EA (2.0 mL) was added and then filtered through celite, rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes : ethyl acetate, 5:1) on silica gel to afford 10.4 mg (30%) of the title compound **SI-58**.

Physical State: yellow oil.

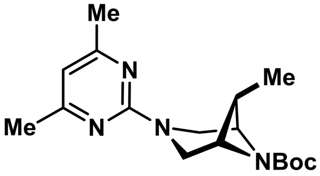
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.39 – 7.29 (m, 5H), 5.16 (s, 2H), 4.12 (dd, *J* = 24.4, 12.1 Hz, 1H), 3.95 (t, *J* = 14.1 Hz, 1H), 3.83 – 3.60 (m, 2H), 3.41 (d, *J* = 11.9 Hz, 2H), 1.77 (q, *J* = 6.8 Hz, 1H), 1.43 – 1.37 (m, 12H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 136.69, 128.49, 127.97, 127.77, 80.41, 67.02, 62.85, 62.01, 46.44, 45.30, 36.40, 28.28, 15.43. *Note: NCO were not observed.*

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{19}H_{26}N_2NaO_4^+$ 369.1790, found 369.1788.

TLC: R$_f$ = 0.3 (5:1 hexanes : ethyl acetate).

Compound SI-59



***tert*-butyl (1R,5S,7r)-3-(4,6-dimethylpyrimidin-2-yl)-7-methyl-3,6-diazabicyclo[3.1.1] heptane-6-carboxylate** (**SI-59**)

To a solution of **SI-58** (34.6 mg, 0.1 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added 20% Pd(OH)$_2$/C and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in MeCN (1.0 mL). To the mixture were added K$_2$CO$_3$ (16.5 mg, 0.12 mmol, 1.2 equiv.) and 2-chlorobenzoxazole (15.3 mg, 0.1 mmol, 1.0 equiv.). The reaction mixture was stirred at 90 °C for 16 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×2.0 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 13.0 mg (41%) of the title compound **SI-59**.

Physical State: colorless oil.

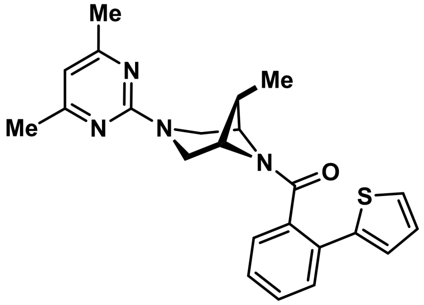
^{1}H NMR (500 MHz, CDCl$_3$): δ 6.31 (s, 1H), 4.29 – 4.23 (m, 1H), 4.13 (d, *J* = 12.5 Hz, 1H), 3.86 (s, 1H), 3.80 (s, 1H), 3.62 – 3.56 (m, 2H), 2.29 (s, 6H), 1.84 (q, *J* = 6.7 Hz, 1H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.35 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 166.74, 161.90, 157.58, 109.29, 79.85, 63.69, 62.72, 47.08, 46.13, 36.92, 28.29, 24.10, 15.63.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{17}H_{27}N_4O_2^+$ 319.2134, found 319.2137.

TLC: R$_f$ = 0.3 (3:1 hexanes : ethyl acetate).

Compound 73



***((1R,5S,7r)-3-(4,6-dimethylpyrimidin-2-yl)-7-methyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)(2-(thiophen-2-yl)phenyl)methanone* (73)**

To a solution of **SI-59** (13.0 mg, 0.04 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF$_3$COOH (0.1 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (26.5 mg, 0.21 mmol, 5.0 equiv.), 2-bromobenzoic acid (9.18mg, 0.045 mmol, 1.1 equiv.) and HATU (17.1 mg, 0.045 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over

Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 9.8 mg (59%) of the title compound **73**.

Physical State: white solid.

m.p. 61-62 °C.

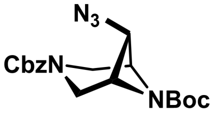
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.49 (d, *J* = 8.6 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.38 – 7.29 (m, 2H), 7.29 – 7.25 (m, 1H), 7.16 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.88 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.34 (s, 1H), 4.23 (dd, *J* = 12.5, 2.4 Hz, 1H), 4.18 (dt, *J* = 4.1, 2.1 Hz, 1H), 3.77 (dd, *J* = 12.5, 1.8 Hz, 1H), 3.53 (d, *J* = 12.6 Hz, 1H), 3.49 (dt, *J* = 4.1, 2.0 Hz, 1H), 3.35 (dd, *J* = 12.5, 2.5 Hz, 1H), 2.29 (d, *J* = 11.2 Hz, 6H), 1.88 (q, *J* = 6.6 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 170.72, 166.69, 161.62, 141.08, 134.20, 131.73, 129.98, 129.74, 127.92, 127.89, 127.70, 126.98, 125.69, 109.45, 65.14, 62.30, 49.28, 47.89, 37.25, 24.05, 14.68.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{23}H_{25}N_4OS^+$ 405.1749, found 405.1751.

TLC: R$_f$ = 0.3 (1:1 hexanes : ethyl acetate).

Compound SI-60



***3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-azido-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate* (SI-60)**

Procedure A: To a solution of **1** (23 mg, 0.1 mmol, 1.0 equiv.) in MeCN (1.0 mL) was added $BocN_3$ (28.6 mg, 0.2 mmol, 2.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 4:1) on silica gel to afford 22.8 mg (61%) of the title compound **SI-60**.

Procedure B: To a solution of **1** (460 mg, 2 mmol, 1.0 equiv.) in MeCN (20 mL) were added Boc_2O (872 mg, 4 mmol, 2.0 equiv.) and $TMSN_3$ (1.15 g, 10 mmol, 5.0 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 4:1) on silica gel to afford 678.9 mg (91%) of the title compound **SI-60**.

Physical State: white solid.

m.p. 77-79 °C.

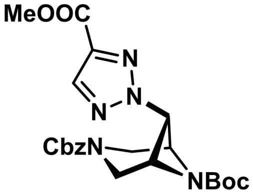
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.24 (m, 5H), 5.22 – 5.08 (m, 2H), 4.36 (t, *J* = 5.9 Hz, 1H), 4.32 – 4.17 (m, 2H), 4.03 (s, br., 2H), 3.36 (dd, *J* = 12.4, 5.6 Hz, 2H), 1.38 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.09, 155.89, 136.59, 128.49, 128.02, 127.84, 81.23, 67.13, 61.73, 61.31, 53.36, 40.90, 40.55, 28.10.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{23}N_5NaO_4^+$ 396.1648, found 396.1647.

TLC: R_f = 0.4 (4:1 hexanes : ethyl acetate).

Compound SI-61



3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-(4-(methoxycarbonyl)-1H-1,2,3-triazol-1-yl)-3,6-diazabicyclo[3.1.1] heptane-3,6-dicarboxylate **(SI-61)**

To a solution of **SI-60** (373 mg, 1.0 mmol, 1.0 equiv.) in THF (10 mL) were added DIPEA (258 mg, 2.0 mmol, 2.0 equiv.), methyl propiolate (126 mg, 1.5 mmol, 1.5 equiv.) and CuI (190 mg, 1.0 mmol, 1.0 equiv.) at 25 °C and the mixture was stirred at 25 °C under an argon atmosphere for 12 hours. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×5.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 329.0 mg (72%) of the title compound **SI-61**.

Physical State: yellow solid.

m.p. 146-148 °C.

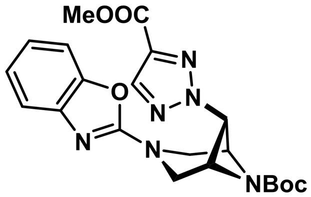
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.35 – 7.27 (m, 3H), 7.26 – 7.23 (m, 2H), 5.18 (t, *J* = 5.9 Hz, 1H), 5.10 (d, *J* = 12.5 Hz, 1H), 5.00 (d, *J* = 12.4 Hz, 1H), 4.72 – 4.67 (m, 2H), 4.13 (s, br., 1H), 4.11 (s, br., 1H), 3.94 (s, 3H), 3.65 (d, *J* = 13.1 Hz, 1H), 3.49 (d, *J* = 13.3 Hz, 1H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.63, 155.51, 155.34, 140.30, 136.17, 128.52, 128.09, 127.73, 126.58, 82.07, 67.37, 61.29, 52.39, 51.39, 40.63, 28.15.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{27}N_5NaO_6^+$ 480.1859, found 480.1859.

TLC: R_f = 0.4 (2:1 hexanes : ethyl acetate).

Compound SI-62



tert-butyl (1R,5S,7r)-3-(benzo[d]oxazol-2-yl)-7-(4-(methoxycarbonyl)-2H-1,2,3-triazol-2-yl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate **(SI-62)**

To a solution of **SI-61** (91.4 mg, 0.2 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added 20%

$Pd(OH)_2/C$ and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in MeCN (1.0 mL). To the mixture were added K_2CO_3 (33.1 mg, 0.24 mmol, 1.2 equiv.) and 2-chlorobenzoxazole (30.6 mg, 0.2 mmol, 1.0 equiv.). The reaction mixture was stirred at 90 °C for 16 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×2.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 59.8 mg (68%) of the title compound **SI-62**.

Physical State: colorless oil.

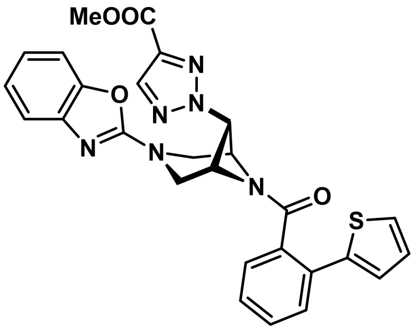
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.15 (td, J = 7.7, 1.1 Hz, 1H), 7.03 (td, J = 7.8, 1.2 Hz, 1H), 5.29 (t, J = 5.9 Hz, 1H), 4.85 (d, J = 5.9 Hz, 2H), 4.37 (d, J = 12.6 Hz, 2H), 3.89 (s, 3H), 3.83 (d, J = 12.7 Hz, 2H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.70, 160.53, 155.18, 148.84, 142.39, 140.38, 126.59, 124.18, 121.09, 116.64, 109.12, 82.35, 52.37, 51.52, 28.18. *Note: NCH and $NCHCH_2$ were not observed.*

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{25}N_6O_5^+$ 441.1886, found 441.1885.

TLC: R_f = 0.3 (1:1 hexanes : ethyl acetate).

Compound 74



methyl 2-((1R,5S,7r)-3-(benzo[d]oxazol-2-yl)-6-(2-(thiophen-2-yl)benzoyl)-3,6-diazabicyclo[3.

1.1]heptan-7-yl)-2H-1,2,3-triazole-4-carboxylate **(74)**

To a solution of **SI-62** (44.0 mg, 0.1 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF_3COOH (0.1 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (64.5 mg, 0.5 mmol, 5.0 equiv.), 2-bromobenzoic acid (22.1 mg, 0.11 mmol, 1.1 equiv.) and HATU (41.8 mg, 0.11 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (dichloromethane: methanol, 20:1) on silica gel to afford 24.7 mg (47%) of the title compound **74**.

Physical State: colorless oil.

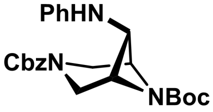
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.55 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.49 (td, *J* = 7.4, 1.6 Hz, 1H), 7.45 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.39 (td, *J* = 7.3, 1.4 Hz, 1H), 7.29 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.25 (d, *J* = 1.1 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.14 (td, *J* = 7.6, 1.1 Hz, 1H), 7.10 – 7.04 (m, 1H), 7.01 (td, *J* = 7.7, 1.3 Hz, 1H), 6.83 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.22 (s, 1H), 4.87 (t, *J* = 6.0 Hz, 1H), 4.55 (s, 1H), 4.32 (d, *J* = 11.5 Hz, 1H), 3.90 (d, *J* = 11.8 Hz, 1H), 3.82 (s, 3H), 3.67 (d, *J* = 12.6 Hz, 1H), 3.47 (d, *J* = 12.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.66, 160.47, 160.25, 148.76, 142.20, 140.41, 140.22, 132.67, 131.70, 130.78, 130.31, 128.35, 127.83, 127.80, 127.25, 126.71, 126.45, 124.19, 121.14, 116.54, 109.06, 63.12, 60.06, 52.30, 52.19, 44.53, 43.43.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{23}N_6O_4S^+$ 527.1501, found 527.1503.

TLC: R_f = 0.3 (20:1 dichloromethane : methanol).

Compound SI-63



3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-(phenylamino)-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate **(SI-63)**

To a solution of **1** (230 mg, 1.0 mmol, 1.0 equiv.) in MeCN (10 mL) were added TfOH (0.2 mol/L, MeCN solution, 5.0 mL, 1.0 mmol, 1.0 equiv.) and aniline (322 mg, 2.0 mmol, 2.0 equiv.) at -35 °C and the reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. To the reaction mixture, Boc_2O (436 mg, 2.0 mmol, 2.0 equiv.) and K_2CO_3 (276 mg, 2.0 mmol, 2.0 equiv.) were added at 0 °C. The mixture was stirred for a further 3 hours at 25 °C. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 346.9 mg (82%) of the title compound **SI-63**.

Physical State: yellow solid.

m.p. 115-116 °C.

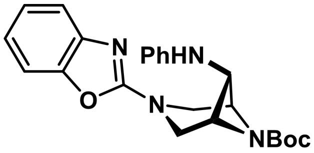
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.28 (m, 5H), 7.22 – 7.15 (m, 2H), 6.78 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 7.4 Hz, 2H), 5.22 – 5.11 (m, 2H), 4.37 (s, 1H), 4.32 (s, 1H), 4.26 (t, *J* = 5.7 Hz, 1H), 4.11 (s, br., 2H), 3.33 (t, *J* = 12.1 Hz, 2H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.17, 156.16, 145.88, 136.44, 129.54, 128.54, 128.11, 127.85, 119.01, 113.33, 80.95, 67.26, 47.81, 28.22. *Note: NCH and $NCHCH_2$ were not observed.*

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{29}N_3NaO_4^+$ 446.2056, found 446.2057.

TLC: R_f = 0.3 (5:1 hexanes : ethyl acetate).

Compound SI-64



tert-butyl (1R,5S,7r)-3-(benzo[d]oxazol-2-yl)-7-(phenylamino)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate **(SI-64)**

To a solution of **SI-63** (87.4 mg, 0.2 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added 20% $Pd(OH)_2/C$ and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in MeCN (1.0 mL). To the mixture were added K_2CO_3 (33.1 mg, 0.24 mmol, 1.2 equiv.) and 2-chlorobenzoxazole (30.6 mg, 0.2 mmol, 1.0 equiv.). The reaction mixture was stirred at 90 °C for 16 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×2.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 64.1 mg (79%) of the title compound **SI-64**.

Physical State: white solid.

m.p. 186-188 °C.

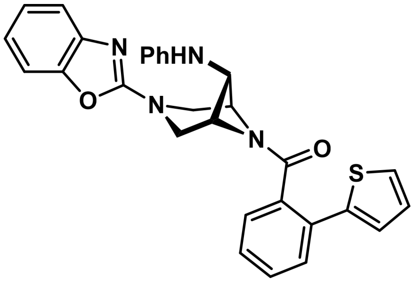
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.28 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.18 (dtt, *J* = 7.6, 4.9, 2.7 Hz, 3H), 7.04 (td, *J* = 7.8, 1.3 Hz, 1H), 6.79 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.70 – 6.63 (m, 2H), 4.48 (d, *J* = 5.4 Hz, 2H), 4.42 – 4.26 (m, 3H), 4.12 (dd, *J* = 7.1, 2.6 Hz, 1H), 3.61 (d, *J* = 12.2 Hz, 2H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.56, 156.10, 148.90, 145.94, 142.76, 129.55, 124.17, 120.89, 119.08, 116.43, 113.37, 109.04, 81.21, 48.13, 28.24. *Note: NCH and $NCHCH_2$ were not* *observed.*

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{27}N_4O_3^+$ 407.2083, found 407.2083.

TLC: $R_f = 0.3$ (2:1 hexanes : ethyl acetate).

Compound 75



((1R,5S,7r)-3-(benzo[d]oxazol-2-yl)-7-(phenylamino)-3,6-diazabicyclo[3.1.1]heptan-6-yl)(2-(thiophen-2-yl)phenyl)methanone **(75)**

To a solution of **SI-64** (42.0 mg, 0.1 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF_3COOH (0.1 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (64.5 mg, 0.5 mmol, 5.0 equiv.), 2-bromobenzoic acid (22.1 mg, 0.11 mmol, 1.1 equiv.) and HATU (41.8 mg, 0.11 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes : ethyl acetate, 1:1) on silica gel to afford 27.1 mg (55%) of the title compound **75**.

Physical State: colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J = 7.7 Hz, 1H), 7.50 – 7.36 (m, 4H), 7.31 (d, J = 3.6 Hz, 1H), 7.27 (s, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.12 – 7.00 (m, 4H), 6.80 (s, 1H), 6.73 (d, J = 7.5

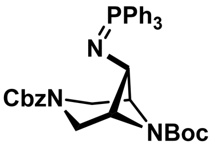
Hz, 1H), 6.53 (d, *J* = 7.9 Hz, 2H), 4.86 (s, 1H), 4.30 (dd, *J* = 12.1, 2.5 Hz, 1H), 4.03 (s, 2H), 3.78 (d, *J* = 12.0 Hz, 1H), 3.43 (s, 2H), 2.80 (s, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 169.28, 148.50, 145.46, 140.72, 133.45, 131.99, 131.47, 130.25, 130.10, 129.43, 128.15, 127.71, 127.68, 127.10, 126.36, 124.46, 121.28, 119.13, 116.13, 113.33, 109.13, 63.29, 59.97, 49.57, 44.83, 43.82. *Note: C2 on the benzoxazole were not observed.*

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{29}H_{25}N_4O_2S^+$ 493.1698, found 493.1697.

TLC: R$_f$ = 0.2 (1:1 hexanes : ethyl acetate).

Compound SI-65



***3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-((triphenyl-l5-phosphaneylidene)amino)-3,6-diazabicyclo[3.1.1] heptane-3,6-dicarboxylate* (SI-65)**

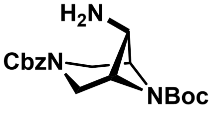
To a solution of **SI-60** (373 mg, 1.0 mmol, 1.0 equiv.) in MeCN (10 mL) was added PPh$_3$ (262 mg, 1.0 mmol, 1.0 equiv.) at 25 °C and stirring for a further 6 hours at 25 °C under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The resulting crude was purified by flash column chromatography (dichloromethane: methanol, 20:1) on silica gel to afford 509.9 mg (84%) of the title compound **SI-65**.

Physical State: colorless oil.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{36}H_{39}N_3O_4P^+$ 608.2678, found 608.2680.

TLC: R$_f$ = 0.3 (20:1 dichloromethane : methanol).

Compound SI-66



3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-amino-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate

(SI-66)

To a solution of **SI-65** (607.0 mg, 1.0 mmol, 1.0 equiv.) in THF (18 mL) was added H_2O (0.6 mL) at 25 °C. The mixture was stirred for 12 hours at 25 °C under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL).The resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:3) on silica gel to afford 295.0 mg (85%) of the title compound **SI-66**.

Physical State: colorless oil.

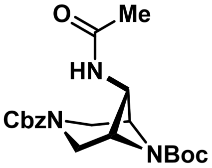
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.24 (m, 5H), 5.22 – 5.10 (m, 2H), 4.18 – 3.93 (m, 4H), 3.79 (t, J = 6.0 Hz, 1H), 3.37 (dd, J = 12.6, 8.7 Hz, 2H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.12, 136.50, 128.53, 128.08, 127.86, 80.61, 67.19, 62.57, 40.95, 47.13, 28.23. *Note: a NCO was not observed.*

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{25}N_3NaO_4^+$ 370.1743, found 370.1743.

TLC: R_f = 0.3 (1:3 hexanes : ethyl acetate).

Compound SI-67



3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-acetamido-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate **(SI-67)**

To a solution of **SI-65** (303.5 mg, 0.5 mmol, 1.0 equiv.) in DCM (3.0 mL) were added Et_3N (165 mg, 1.5 mmol, 3.0 equiv.) and acetyl chloride (58.9 mg, 0.75 mmol, 1.5 equiv.) at 0 °C and the reaction mixture was stirred at 25 °C for 3 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×3 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 173.1 mg (89%) of the title compound **SI-67**.

Physical State: white solid.

m.p. 131-132 °C.

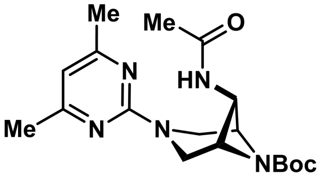
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.38 – 7.28 (m, 5H), 5.92 (d, *J* = 8.4 Hz, 1H), 5.20 (d, *J* = 12.3 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 4.84 (q, *J* = 6.8 Hz, 1H), 4.29 – 4.20 (m, 2H), 4.09 (d, *J* = 46.8 Hz, 2H), 3.32 (dd, *J* = 13.0, 6.5 Hz, 2H), 1.97 (s, 3H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 170.82, 156.25, 155.73, 136.20, 128.61, 128.49, 128.29, 127.86, 81.08, 67.44, 43.26, 28.20, 23.24. *Note: NCH and NCHCH$_2$ were not observed.*

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{20}H_{27}N_3NaO_5^+$ 412.1848, found 412.1848.

TLC: R$_f$ = 0.3 (3:1 hexanes : ethyl acetate).

Compound SI-68



tert-butyl (1R,5S,7r)-7-acetamido-3-(4,6-dimethylpyrimidin-2-yl)-3,6-diazabicyclo[3.1.1] heptane-6-carboxylate **(SI-68)**

To a solution of **SI-67** (77.8 mg, 0.2 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added 20% Pd(OH)$_2$/C and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (51.6 mg, 0.4 mmol, 2.0 equiv.) and 2-chloro-4,6-dimethylpyrimidine (42.6 mg, 0.3 mmol, 1.5 equiv.). The reaction mixture was stirred at 120 °C for 6 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×2.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:2) on silica gel to afford 48.4 mg (67%) of the title compound **SI-68**.

Physical State: yellow solid.

m.p. 191-192 °C.

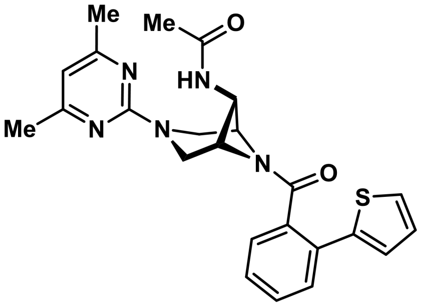
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.42 (s, 1H), 5.75 (d, J = 9.3 Hz, 1H), 4.99 (dt, J = 9.4, 6.0 Hz, 1H), 4.42 – 4.14 (m, 4H), 3.53 (d, J = 13.4 Hz, 2H), 2.34 (s, 6H), 1.95 (s, 3H), 1.37 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.59, 167.06, 161.47, 155.79, 110.30, 80.60, 43.68, 28.25, 24.08, 23.49. Note: NCH and $NCHCH_2$ were not observed.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{28}N_5O_3^+$ 362.2192, found 362,2192.

TLC: R_f = 0.3 (1:2 hexanes : ethyl acetate).

Compound 76



***N*-((1*R*,5*S*,7*r*)-3-(4,6-dimethylpyrimidin-2-yl)-6-(2-(thiophen-2-yl)benzoyl)-3,6-diazabicyclo[3.1.1] heptan-7-yl)acetamide** (**76**)

To a solution of **SI-68** (36.1 mg, 0.1 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF_3COOH (0.1 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (64.5 mg, 0.5 mmol, 5.0 equiv.), 2-bromobenzoic acid (22.1 mg, 0.11 mmol, 1.1 equiv.) and HATU (41.8 mg, 0.11 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (dichloromethane: methanol, 20:1) on silica gel to afford 29.1 mg (65%) of the title compound **76**.

Physical State: colorless oil.

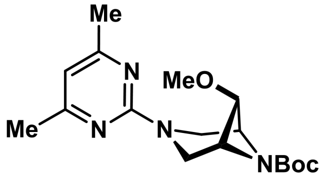
^{1}H NMR (500 MHz, Methanol-d_4): δ 7.59 (d, J = 7.7 Hz, 1H), 7.57 – 7.47 (m, 1H), 7.46 – 7.38 (m, 2H), 7.20 – 7.14 (m, 2H), 6.75 – 6.70 (m, 1H), 6.50 (s, 1H), 4.81 – 4.74 (m, 1H), 4.43 (t, J = 6.1 Hz, 1H), 4.23 – 4.15 (m, 2H), 3.65 (dd, J = 13.2, 1.5 Hz, 1H), 3.39 (d, J = 2.2 Hz, 2H), 2.30 (s, 6H), 1.88 (s, 3H).

^{13}C NMR (126 MHz, Methanol-d_4): δ 173.11, 170.23, 167.03, 160.80, 140.34, 132.95, 131.69, 130.17, 129.74, 127.69, 127.53, 127.03, 126.38, 125.91, 109.44, 63.91, 60.48, 45.63, 44.01, 42.94, 22.50, 20.72.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{26}N_5O_2S^+$ 448.1807, found 448.1808.

TLC: R_f = 0.4 (20:1 dichloromethane : methanol).

Compound SI-69



tert-butyl (1R,5S,7r)-3-(4,6-dimethylpyrimidin-2-yl)-7-methoxy-3,6-diazabicyclo[3.1.1] heptane-6-carboxylate **(SI-69)**

To a solution of **34** (72.4 mg, 0.2 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added 20% $Pd(OH)_2/C$ and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (51.6 mg, 0.4 mmol, 2.0 equiv.) and 2-chloro-4,6-dimethylpyrimidine (42.6 mg, 0.3 mmol, 1.5 equiv.). The reaction mixture was stirred at 120 °C for 6 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×2.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 2:1) on silica gel to afford 38.7 mg (58%) of the title compound **SI-69**.

Physical State: colorless oil.

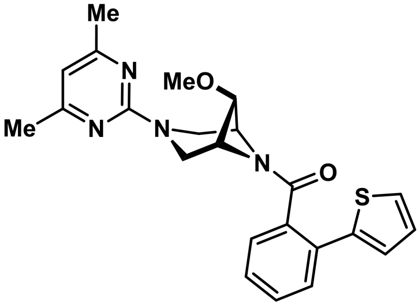
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.27 (s, 1H), 4.33 (d, *J* = 15.2 Hz, 4H), 4.04 (t, *J* = 5.6 Hz, 1H), 3.37 (s, 1H), 3.34 (s, 1H), 3.33 (s, 3H), 2.27 (s, 6H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ166.59, 161.41, 157.05, 109.12, 80.24, 70.12, 62.00, 57.00, 40.93, 28.09, 24.06.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{27}N_4O_3^+$ 335.2083, found 335.2082.

TLC: R_f = 0.4 (2:1 hexanes : ethyl acetate).

Compound 77



((1R,5S,7r)-3-(4,6-dimethylpyrimidin-2-yl)-7-methoxy-3,6-diazabicyclo[3.1.1]heptan-6-yl)(2-(thiophen-2-yl)phenyl)methanone **(77)**

To a solution of **SI-69** (33.4 mg, 0.1 mmol, 1.0 equiv.) in DCM (1.0 mL) was added

CF_3COOH (0.1 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (64.5 mg, 0.5 mmol, 5.0 equiv.), 2-bromobenzoic acid (22.1 mg, 0.11 mmol, 1.1 equiv.) and HATU (41.8 mg, 0.11 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:2) on silica gel to afford 25.2 mg (60%) of the title compound **77**.

Physical State: colorless oil.

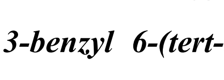
^{1}H NMR (500 MHz, Methanol-*d*$_4$): δ 7.58 (dd, J = 7.8, 1.3 Hz, 1H), 7.55 – 7.46 (m, 1H), 7.41 (td, J = 7.4, 1.3 Hz, 1H), 7.37 (dd, J = 7.6, 1.6 Hz, 1H), 7.23 (dd, J = 5.2, 1.2 Hz, 1H), 7.17 (dd, J = 3.6, 1.2 Hz, 1H), 6.77 (dd, J = 5.1, 3.6 Hz, 1H), 6.45 (s, 1H), 4.80 – 4.72 (m, 1H), 4.23 – 4.13 (m, 2H), 3.91 (t, J = 5.8 Hz, 1H), 3.51 (dd, J = 12.7, 1.1 Hz, 1H), 3.46 (dd, J = 12.8, 3.6 Hz, 1H), 3.31 – 3.26 (m, 4H), 2.28 (d, J = 16.1 Hz, 6H).

^{13}C NMR (126 MHz, Methanol-*d*$_4$): δ 170.64, 166.97, 160.72, 140.45, 133.21, 131.62, 130.06, 129.69, 127.67, 127.44, 127.09, 126.40, 125.92, 108.97, 70.40, 64.44, 61.16, 56.22, 43.57, 42.70, 22.48.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{25}N_4O_2S^+$ 421.1698, found 421.1699.

TLC: R_f = 0.3 (1:2 hexanes : ethyl acetate).

Compound SI-70



3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-hydroxy-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate

(SI-70)

To a solution of **22** (411 mg, 1.0 mmol, 1.0 equiv.) in DMF (5.0 mL) was added $AgNO_2$ (258 mg, 2.0 mmol, 2.0 equiv.) at 0 °C and the mixture was stirred for 6 hours at 25 °C under an argon atmosphere and protected from light. After the reaction was completed, the reaction mixture was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in EtOH (5.0 mL), Then 1 M NaOH (2.0 mL) was added at 25 °C, the reaction mixture was stirred at 25 °C for 3 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×3 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 208.8 mg (60%) of the title compound **SI-70**.

Physical State: yellow oil.

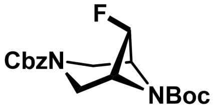
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 5H), 5.21 – 5.06 (m, 2H), 4.48 (t, *J* = 5.8 Hz, 1H), 4.21 – 3.97 (m, 4H), 3.42 (d, *J* = 12.2 Hz, 1H), 3.39 (d, *J* = 12.3 Hz, 1H), 1.39 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.73, 156.23, 136.62, 128.49, 128.00, 127.80, 80.81, 67.09, 62.76, 62.30, 61.86, 40.62, 28.16.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}N_2NaO_5^+$ 371.1583, found 371.1583.

TLC: $R_f = 0.3$ (1:1 hexanes : ethyl acetate).

Compound SI-71



***3-benzyl 6-(tert-butyl) (1R,5S,7r)-7-fluoro-3,6-diazabicyclo[3.1.1]heptane-3,6-dicarboxylate* (SI-71)**

To a solution of **SI-70** (69.6 mg, 0.2 mmol, 1.0 equiv.) in DCM (1.0 mL) was added pyridine (32.3 µL, 0.4 mmol, 2.0 equiv.). To the reaction solution was added DAST (52.8 µL, 0.4 mmol, 2.0 equiv.) under an argon atmosphere at -78 °C and stirred at 25 °C for 3 hours. The reaction solution was quenched with water and extracted with DCM (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 5:1) on silica gel to afford 49.0 mg (70%) of the title compound **SI-71**.

Physical State: white solid.

m.p. 80-81 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.39 – 7.25 (m, 5H), 5.22 – 5.00 (m, 3H), 4.32 (t, *J* = 4.5 Hz, 1H), 4.27 (q, *J* = 4.3, 3.9 Hz, 1H), 4.17 – 4.10 (m, 2H), 3.40 (dd, *J* = 12.5, 8.0 Hz, 2H), 1.39 (s, 9H).

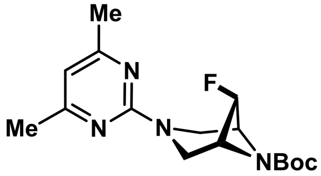
^{13}C NMR (101 MHz, CDCl$_3$): δ 155.95, 136.55, 128.50, 128.05, 127.89, 81.34, 78.39 (d, *J* = 233.2 Hz), 67.17, 61.96, 40.55, 28.09. *Note: a NCO was not observed.*

^{19}F NMR (377 MHz, CDCl$_3$): δ -201.70.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{23}FN_2NaO_4^+$ 373.1540, found 373.1540.

TLC: R_f = 0.4(5:1 hexanes : ethyl acetate).

Compound SI-72



tert-butyl (1R,5S,7r)-3-(4,6-dimethylpyrimidin-2-yl)-7-fluoro-3,6-diazabicyclo[3.1.1] heptane-6-carboxylate **(SI-72)**

To a solution of **SI-71** (35.0 mg, 0.1 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added 20% $Pd(OH)_2/C$ and the reaction vessel was backfilled with hydrogen three times. The reaction solution was stirred under a hydrogen atmosphere at 25 °C for 12 hours. The reaction solution was filtered through celite and concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in MeCN (1.0 mL). To the mixture were added K_2CO_3 (16.5 mg, 0.12 mmol, 1.2 equiv.) and 2-chlorobenzoxazole (15.3 mg, 0.1 mmol, 1.0 equiv.). The reaction mixture was stirred at 90 °C for 16 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with DCM (3×2.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 3:1) on silica gel to afford 12.9 mg (40%) of the title compound **SI-72**.

Physical State: colorless oil.

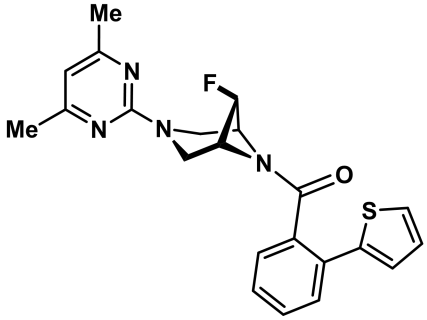
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.33 (s, 1H), 5.16 (dt, *J* = 58.6, 5.6 Hz, 1H), 4.52 – 4.31 (m, 4H), 3.49 (d, *J* = 12.7 Hz, 2H), 2.30 (s, 6H), 1.33 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.76, 161.33, 156.69, 156.64, 109.52, 80.83, 79.07 (d, *J* = 222.8 Hz), 62.46, 40.86, 28.07, 24.09.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{24}FN_4O_2^+$ 323.1883, found 323.1885.

TLC: R_f = 0.3 (3:1 hexanes : ethyl acetate).

Compound 78



((1R,5S,7r)-3-(4,6-dimethylpyrimidin-2-yl)-7-fluoro-3,6-diazabicyclo[3.1.1]heptan-6-yl)(2-(thiophen-2-yl)phenyl)methanone **(78)**

To a solution of **SI-72** (12.9 mg, 0.04 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF_3COOH (0.05 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DMF (1.0 mL). To the mixture were added DIPEA (25.8 mg, 0.2 mmol, 5.0 equiv.), 2-bromobenzoic acid (9.0 mg, 0.044 mmol, 1.1 equiv.) and HATU (16.7 mg, 0.044 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 10.9 mg (67%) of the title compound **78**.

Physical State: white solid.

m.p. 74-75 °C.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.51 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.43 (ddd, *J* = 7.8, 6.2, 2.6 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.21 (ddd, *J* = 6.3, 4.4, 1.2 Hz, 2H), 6.88 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.35 (s, 1H), 4.82 (ddt, *J* = 5.7, 4.3, 2.1 Hz, 1H), 4.65 (dt, *J* = 57.9, 5.7 Hz, 1H), 4.34 (dd, *J* = 12.8, 2.4 Hz, 1H), 4.09 – 4.04 (m, 1H), 3.68 – 3.58 (m, 2H), 3.44 (d, *J* = 13.0 Hz, 1H), 2.29 (d, *J* = 25.8 Hz, 6H).

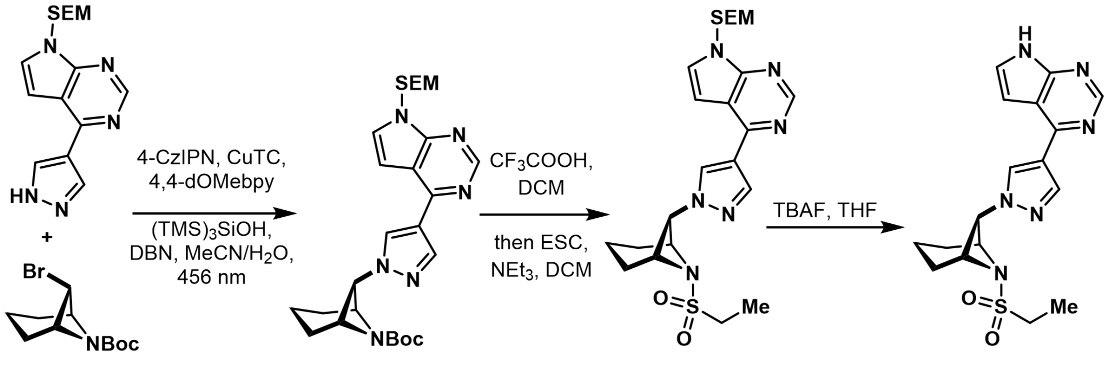
^{13}C NMR (126 MHz, CDCl$_3$): δ 169.89, 169.86, 160.85, 140.71, 133.67, 131.45, 130.11, 129.94, 128.03, 127.76, 127.70, 126.87, 126.18, 109.58, 78.97 (d, *J* = 230.2 Hz), 64.31 (d, *J* = 22.6 Hz), 61.27 (d, *J* = 22.8 Hz), 43.87, 42.97, 24.05.

^{19}F NMR (471 MHz, CDCl$_3$): δ -196.34.

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{22}FN_4OS^+$ 409.1498, found 409.1499.

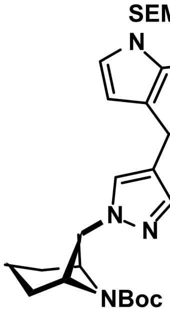
TLC: R_f = 0.3 (1:1 hexanes : ethyl acetate).

Experimental Procedures and Characterization Data of Novel Bioisostere of Azetidine



23 **SI-73** **SI-74** **79**

Compound SI-73



tert-butyl (1R,5S,7s)-7-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-6-azabicyclo[3.1.1]heptane-6-carboxylate **(SI-73)**

A mixture of 4-(1H-Pyrazol-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (31.5 mg, 0.1 mmol, 1.0 equiv.), CuTC (9.55 mg, 0.05 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 0.05 mmol, 0.5 equiv.), 4-CzIPN (3.95 mg, 5 μmol, 0.05 equiv.) and MeCN (3.3 mL, 0.03 M) was prepared in a 10 mL tube. To this mixture was added 1,5-diazabicyclo[4.3.0]non-5-ene (24.8 mg, 0.2 mmol, 2.0 equiv.) and water (45 μL, 2.5 mmol, 25 equiv.). The resulting solution was stirred for 1-2 minutes under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, **23**

(55.2 mg, 0.2 mmol, 2.0 equiv.) and **SI-93** (0.08 mL, 0.25 mmol, 2.5 equiv.) were added to the mixture, and then plugged the tube and inserted an 18G ventilation needle into the plug. The reaction tube was placed in front of a Kessil Blue LED photoreactor (450 nm, 25% light intensity) with fan cooling. The mixture was stirred under air for 12 hours. After 12 hours, MeOH (0.1 mL) was added. The resulting solution was stirred under air for 2 hours, filtered through celite and rinsed with EA. The filtrate was concentrated in vacuo and purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 22.4 mg (44%) of the title compound **SI-73**.

Physical State: pale yellow oil.

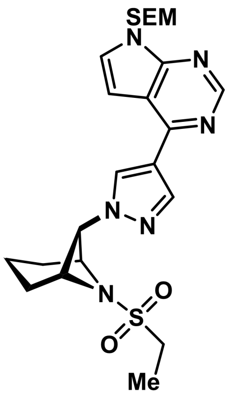
^{1}H NMR (500 MHz, CDCl$_3$): δ 8.86 (s, 1H), 8.66 (s, 1H), 8.28 (s, 1H), 7.40 (d, *J* = 3.7 Hz, 1H), 6.82 (d, *J* = 3.7 Hz, 1H), 5.67 (s, 2H), 4.44 (s, 1H), 4.35 (s, 1H), 4.33 (s, 1H), 3.58 – 3.51 (m, 2H), 2.65 (s, 1H), 2.48 (d, *J* = 14.4 Hz, 1H), 2.03 – 1.90 (m, 3H), 1.75 (td, *J* = 8.8, 3.7 Hz, 1H), 1.48 (s, 9H), 0.99 – 0.89 (m, 2H), -0.06 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 157.19, 152.20, 151.83, 139.38, 128.35, 128.17, 114.20, 111.27, 101.04, 80.31, 72.80, 66.90, 66.57, 65.61, 64.06, 28.38, 26.07, 24.85, 17.74, 14.28, -1.44. *Note: a NCO was not observed.*

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{26}H_{39}N_6O_3Si^+$ 511.2853, found 511.2855.

TLC: R$_f$ = 0.3 (1:1 hexanes : ethyl acetate).

Compound SI-74



***(1R,5S,7s)-6-(ethylsulfonyl)-7-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-6-azabicyclo[3.1.1]heptane* (SI-74)**

SI-74 was prepared according to the previously reported procedure[10]. To a solution of SI-73 (30 mg, 0.06 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF_3COOH (0.1 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DCM (1.0 mL). To the mixture were added Et_3N (50 μL, 0.36 mmol, 6.0 equiv.) and ethanesulfonyl chloride (11.6 mg, 0.09 mmol, 1.5 equiv.) The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:2) on silica gel to afford 19.0 mg (63%) of the title compound **SI-74**.

Physical State: colorless oil.

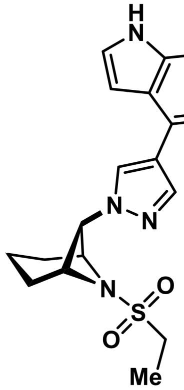
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.86 (s, 1H), 8.65 (s, 1H), 8.32 (s, 1H), 7.43 (d, J = 3.7 Hz, 1H), 6.83 (d, J = 3.7 Hz, 1H), 5.68 (s, 2H), 4.62 (d, J = 2.7 Hz, 2H), 4.35 (s, 1H), 3.59 – 3.52 (m, 2H), 3.05 (q, J = 7.4 Hz, 2H), 2.78 (dt, J = 9.6, 5.2 Hz, 2H), 2.31 – 2.18 (m, 1H), 2.04 (d, J = 8.4 Hz, 2H), 1.35 – 1.26 (m, 4H), 0.96 – 0.89 (m, 2H), -0.06 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 152.23, 139.75, 128.81, 126.08, 123.41, 114.15, 101.05, 84.29, 72.95, 70.39, 66.73, 65.23, 49.55, 26.60, 17.81, 14.61, 8.24, -1.38. *Note: NCN were not observed.*

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{35}N_6O_3SSi^+$ 503.2261, found 503.2260.

TLC: R_f = 0.3(1:2 hexanes : ethyl acetate).

Compound 79



***(1R,5S,7s)-7-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-6-(ethylsulfonyl)-6-azabicyclo [3.1.1]heptane* (79)**

To a solution of **SI-74** (19 mg, 0.04 mmol, 1.0 equiv.) in THF (1.0 mL) was added TBAF (1 M, THF solution, 0.4 mL, 0.4 mmol, 10 equiv.). The reaction solution was stirred under an argon atmosphere at 60 °C for 3 hours. The reaction solution was concentrated in vacuo. and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:3) on silica gel to afford 11.9 mg (80%) of the title compound **79**.

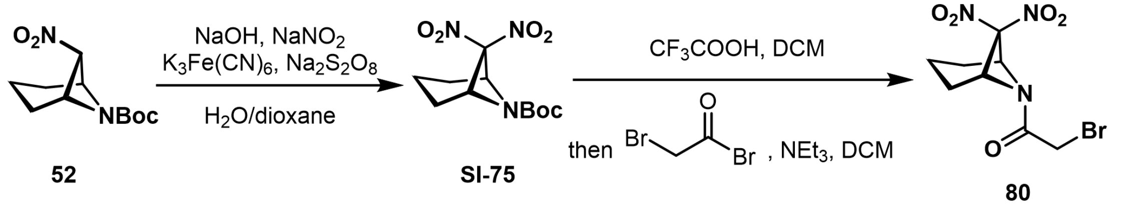
Physical State: colorless oil.

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 12.10 (s, 1H), 8.89 (s, 1H), 8.69 (s, 1H), 8.39 (s, 1H), 7.59 (dd, J = 3.6, 2.4 Hz, 1H), 7.05 (dd, J = 3.6, 1.7 Hz, 1H), 4.72 (d, J = 2.7 Hz, 2H), 4.49 (s, 1H), 3.05 (q, J = 7.3 Hz, 2H), 2.49 – 2.47 (m, 2H), 2.06 – 1.94 (m, 4H), 1.07 (t, J = 7.2 Hz, 3H).

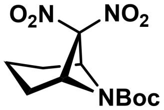
^{13}C NMR (126 MHz, DMSO-*d*$_6$): δ 152.59, 151.40, 150.36, 139.53, 130.22, 127.15, 121.70, 113.34, 100.36, 69.50, 64.36, 48.52, 26.15, 14.72, 8.48.

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{17}H_{21}N_6O_2S^+$ 373.1447, found 373.1449.

TLC: R*f* = 0.3(1:3 hexanes : ethyl acetate).



Compound SI-75



tert-butyl (1R,5S)-7,7-dinitro-6-azabicyclo[3.1.1]heptane-6-carboxylate **(SI-75)**

SI-75 was prepared according to the previously reported procedure[11]. To a solution of **52** (24.2 mg, 0.1 mmol, 1.0 equiv.) in H_2O (0.9 mL) and 1,4-dioxane (0.3 mL) was added NaOH(6.4 mg, 0.16 mmol, 1.6 equiv.) at 0 °C. To the mixture were added aqueous $NaNO_2$ solution (4.8 M, 95 μL, 0.46 mmol, 4.6 equiv.), aqueous $K_3Fe(CN)_6$ solution (0.3 M, 65.8 μL, 0.02 mmol, 0.2 equiv.) and solid $Na_2S_2O_8$ (26.2 mg, 0.11 mmol, 1.1 equiv.). The mixture was stirred at 25 °C for 12 hours. After the reaction was completed, the reaction mixture was extracted with DCM (3×3 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 10:1) on silica gel to afford 23.0 mg (80%) of the title compound **SI-75**.

Physical State: yellow oil.

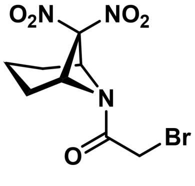
^{1}H NMR (500 MHz, CDCl$_3$): δ 4.92 (s, 2H), 2.59 (d, J = 74.0 Hz, 2H), 2.11 (ddd, J = 14.9, 8.9, 5.3 Hz, 2H), 1.67 – 1.59 (m, 2H), 1.47 (s, 9H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 154.92, 110.46, 82.13, 68.53, 67.70, 28.15, 22.93, 21.89, 12.04.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{17}N_3NaO_6^+$ 310.1015, found 310.1013.

TLC: R_f = 0.3(10:1 hexanes : ethyl acetate).

Compound 80



2-bromo-1-((1R,5S)-7,7-dinitro-6-azabicyclo[3.1.1]heptan-6-yl)ethan-1-one **(80)**

To a solution of **SI-75** (23 mg, 0.08 mmol, 1.0 equiv.) in DCM (1.0 mL) was added CF_3COOH (0.1 mL). The reaction solution was stirred under an argon atmosphere at 25 °C for 3 hours. The reaction solution was concentrated in vacuo. The crude product was directly in further reactions. The crude product from the previous step was dissolved in DCM (1.0 mL). To the mixture were added Et_3N (66.6 μL, 0.48 mmol, 6.0 equiv.) and bromoacetyl bromide (24.2 mg, 0.12 mmol, 1.5 equiv.) The reaction mixture was stirred at 25 °C for 12 hours under an argon atmosphere. After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with EA (3×1.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude was purified by flash column chromatography (hexanes: ethyl acetate, 1:1) on silica gel to afford 17.2 mg (70%) of the title compound **80**.

Physical State: colorless oil.

^{1}H NMR (400 MHz, Methanol-*d*$_4$): δ 5.45 (d, *J* = 4.6 Hz, 1H), 5.19 (d, *J* = 4.7 Hz, 1H), 3.95 – 3.81 (m, 2H), 2.64 – 2.42 (m, 2H), 2.17 (tt, *J* = 18.8, 7.2 Hz, 2H), 1.74 (ddq, *J* = 19.7, 9.7, 4.9 Hz, 1H), 1.55 (dtt, *J* = 15.0, 9.2, 5.7 Hz, 1H).

^{13}C NMR (126 MHz, Methanol-*d*$_4$): δ 166.67, 110.59, 70.60, 68.12, 25.42, 24.08, 23.57, 12.22.

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_8H_{10}BrN_3NaO_5^+$ 329.9702, found 329.9700.

TLC: R_f = 0.3(1:1 hexanes : ethyl acetate).

Antagonist test evaluation of OXR inhibitors

The objective of this study is to determine the potency and efficacy of compounds on HEK293/OX1R+Gq and HEK293/OX2R+Gq stable cell line under antagonist mode[12-14]. according

Reagent List

Name	Source	Cat#
DMEM	ATCC	ATCC® 30-2002
0.25% Trypsin-EDTA	Invitrogen	25200056
PBS pH 7.4	Invitrogen	10010023
Penicillin-Streptomycin	Invitrogen	15140122
PBS pH 7.4	Gibco	10010-023
Orexin A	MCE	HY-106224A
IP-ONE – Gq KIT	Cisbio	62IPAPEC

Consumables/Supplies List

LDV plate	Labcyte	LP-0200
384-well small volume white plate	Grenier	784075
10 cm dish	Corning	430167
15 cm dish	BIOFIL	TCD010150
25 mL pipette	Thermo	1163Y23
10 mL pipette	Thermo	1163Y22
Frozen pipe	Thermo	5151M88
15 mL centrifuge tube	Corning	430052
50 mL centrifuge tube	Corning	430829

Equipment

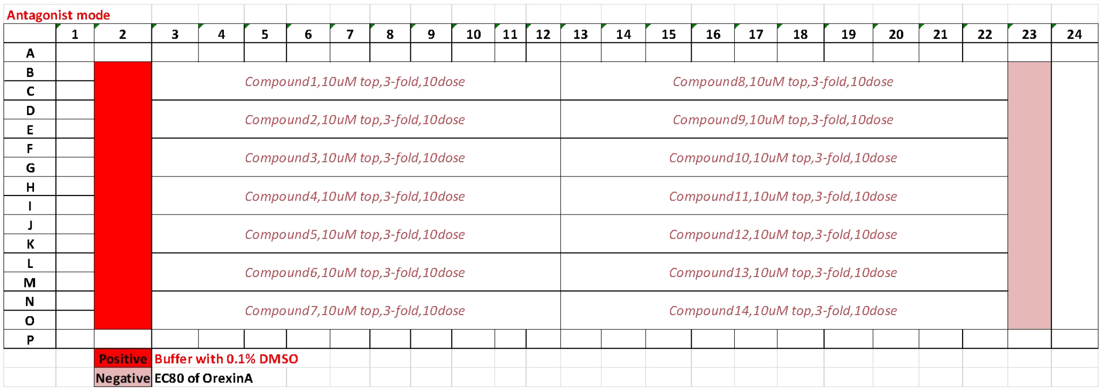
Automated cell counter	Count star

Envision	PerkinElmer
ECHO 550	LABCYTE

Cell line

Cell line	Clone No.	Medium
HEK293/OX1R+Gq	14	DMEM +10%FBS +1%PS+1000ug/mL G418
HEK293/OX2R+Gq	8	DMEM +10%FBS +1%PS+1000ug/mL G418

Plate Map



Antagonist mode

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
A																								
B			Compound1,10uM top,3-fold,10dose										Compound8,10uM top,3-fold,10dose											
C																								
D			Compound2,10uM top,3-fold,10dose										Compound9,10uM top,3-fold,10dose											
E																								
F			Compound3,10uM top,3-fold,10dose										Compound10,10uM top,3-fold,10dose											
G																								
H			Compound4,10uM top,3-fold,10dose										Compound11,10uM top,3-fold,10dose											
I																								
J			Compound5,10uM top,3-fold,10dose										Compound12,10uM top,3-fold,10dose											
K																								
L			Compound6,10uM top,3-fold,10dose										Compound13,10uM top,3-fold,10dose											
M																								
N			Compound7,10uM top,3-fold,10dose										Compound14,10uM top,3-fold,10dose											
O																								
P																								

Positive Buffer with 0.1% DMSO

Negative EC80 of OrexinA

Procedures

Compounds preparation

1) Solid compounds are solubilized in 100% DMSO to a stock solution of 10mM. Store at nitrogen gas tank (RT).

2) Compounds were diluted from 10mM to source concentration by DMSO.

3) 3- fold Serial dilute the compound in 384 LDV plate by Bravo (5uL compound to 10uL DMSO)

Cells collection

1) Cells from 15cm dish should be near 80% confluency before collection.

2) Remove culture medium and gently rinse flask using PBS.

3) Add 4mL 0.05% trypsin (0.25% trypsin-EDTA was diluted 5-fold by PBS), incubate the plate at 37 °C and 5% CO2 until cells are dislodged.

4) Add 8 mL of medium and pipette up and down until cells are homogeneously dispersed in the solution.

5) Spin the cell suspension at 1000 rpm for 5 min.

6) After centrifugation, discard the supernatant. Resuspend the cell pellet with 5.0 mL cell culture medium, incubate the centrifuge tube at 37 °C and 5% CO2 for two hours and then wash 2 times with PBS before using.

IP-1 HTRF assay

1) Calculate the volume of stimulation buffer needed to re-suspend the cell pellet, achieving an optimal cell density (15000 cells/well).

2) Add 15nL diluted compounds to assay plate (784075) by ECHO.

3) Seed 7uL the resuspension cells (15000 cells/well) to assay plate which contained 15nL compounds, and incubate 30min at 37°C.

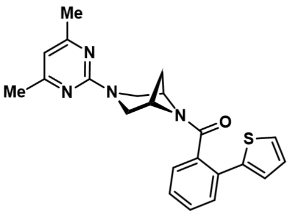
4) Add 7uL EC80 OrexinA to assay plate and incubate 2h at 37°C.

5) Add 3uL IP1-d2 (need dilute 20-fold before using) to assay plate, centrifuge 1000 rpm, 1 min.

6) 3uL Anti-IP1-Cryptate (need dilute 20-fold before using) to assay plate, centrifuge 1000 rpm, 1 min.

7) Read plate by Envision.

Bioactivity Results



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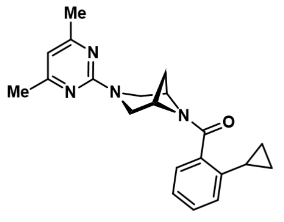

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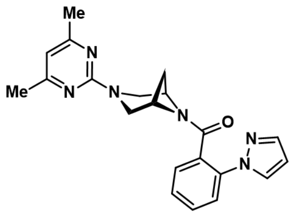

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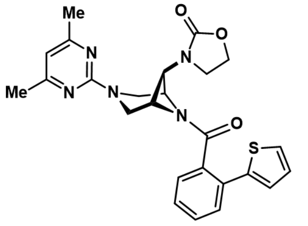

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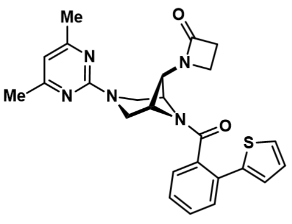

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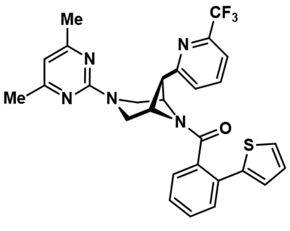

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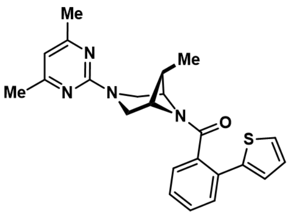

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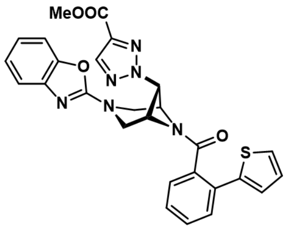

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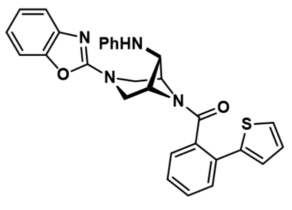

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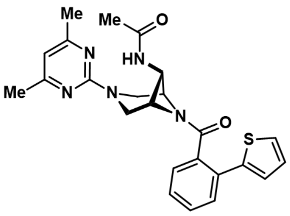

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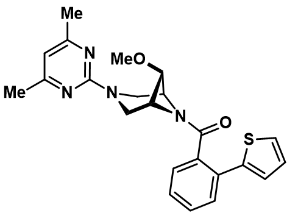

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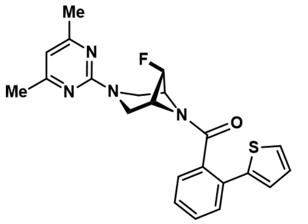

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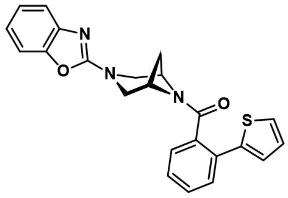
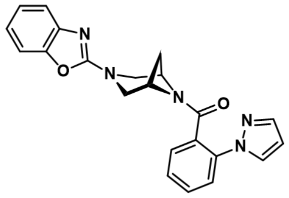
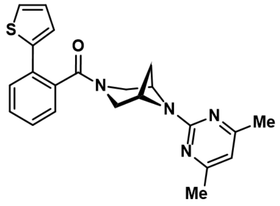


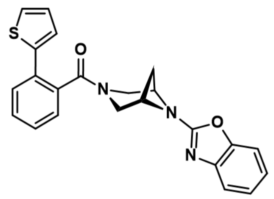
SI-44



SI-46



SI-49



SI-51

Fig. S2. All synthesized OXR antagonists.

Table S5. The bioactivity test results of synthesized compounds.

Compound #	HEK293 cell line	
	OX1R IC_{50} (nM)	OX2R IC_{50} (nM)
67	97	16
68	7697	242
69	>10000	583
70	8663	2140
71	725	135
72	119	178
73	91	10
74	>10000	>10000
75	197	>10000
76	>10000	>10000
77	2204	311
78	45	6
SI-44	65	194
SI-46	>10000	ND [a]
SI-49	809	25
SI-51	ND [a]	75

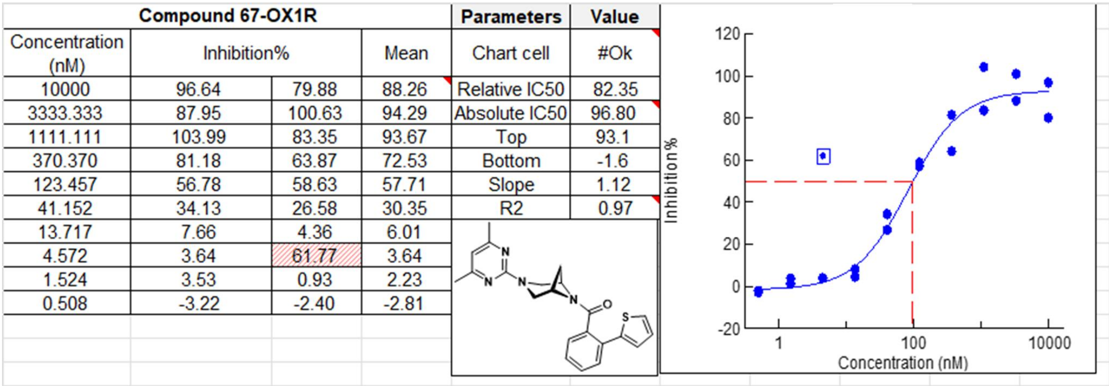
[a] Not determined.

Bioactivity Comparison

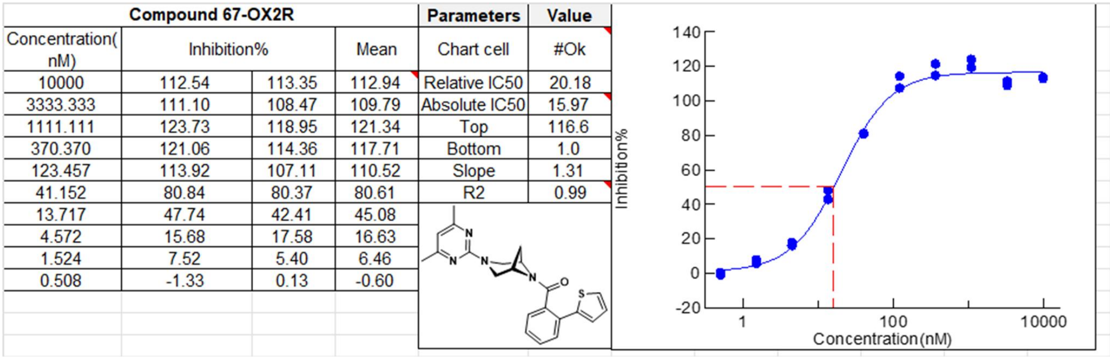
Table S6. Comparison of the biological activities between synthesized compounds and reference drugs.

Compound #	HEK293 cell line	
	OX1R IC_{50} (nM)	OX2R IC_{50} (nM)
67	97	16
73	91	10
78	45	6
SI-44	65	194
TCS-OX2-29	5050	205
ACT 462206	66	19
Seltorexant	465	15
Almorexant	11	8

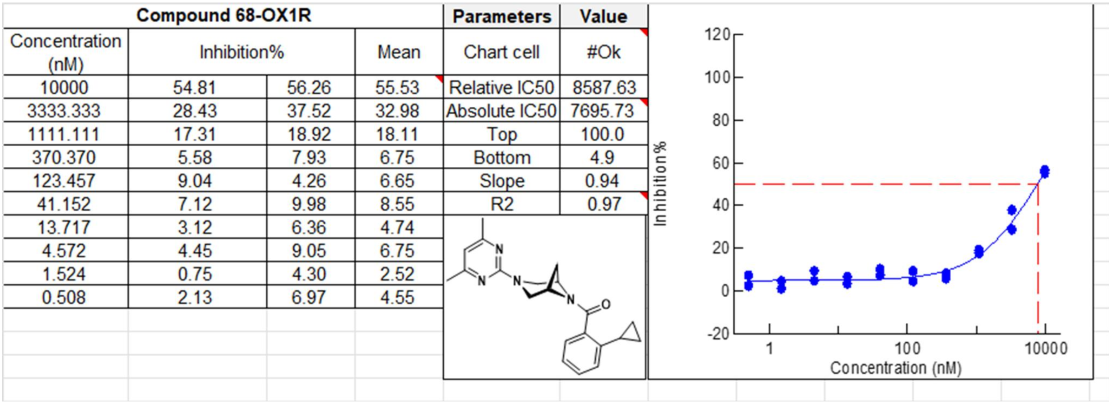
Data Analysis



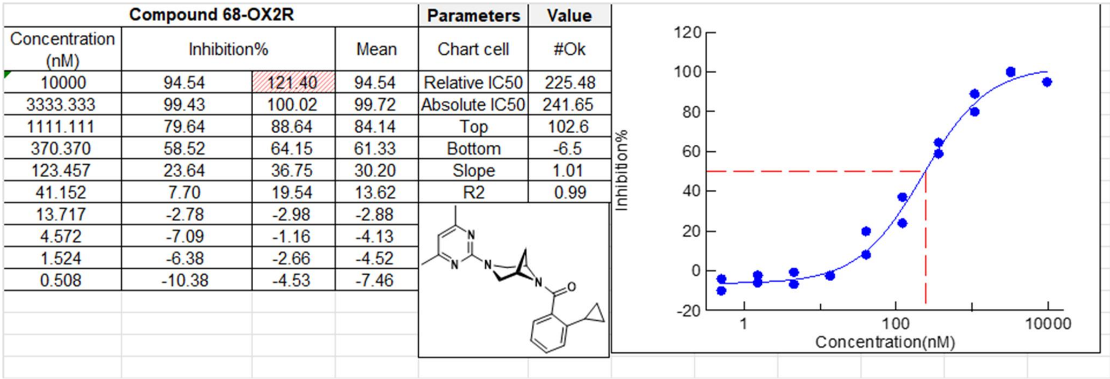
Compound 67-OX1R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	96.64	79.88	88.26	Relative IC50	82.35
3333.333	87.95	100.63	94.29	Absolute IC50	96.80
1111.111	103.99	83.35	93.67	Top	93.1
370.370	81.18	63.87	72.53	Bottom	-1.6
123.457	56.78	58.63	57.71	Slope	1.12
41.152	34.13	26.58	30.35	R2	0.97
13.717	7.66	4.36	6.01		
4.572	3.64	61.77	3.64		
1.524	3.53	0.93	2.23		
0.508	-3.22	-2.40	-2.81		



Compound 67-OX2R				Parameters	Value
Concentration(nM)	Inhibition%		Mean	Chart cell	#Ok
10000	112.54	113.35	112.94	Relative IC50	20.18
3333.333	111.10	108.47	109.79	Absolute IC50	15.97
1111.111	123.73	118.95	121.34	Top	116.6
370.370	121.06	114.36	117.71	Bottom	1.0
123.457	113.92	107.11	110.52	Slope	1.31
41.152	80.84	80.37	80.61	R2	0.99
13.717	47.74	42.41	45.08		
4.572	15.68	17.58	16.63		
1.524	7.52	5.40	6.46		
0.508	-1.33	0.13	-0.60		

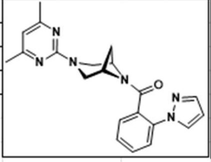


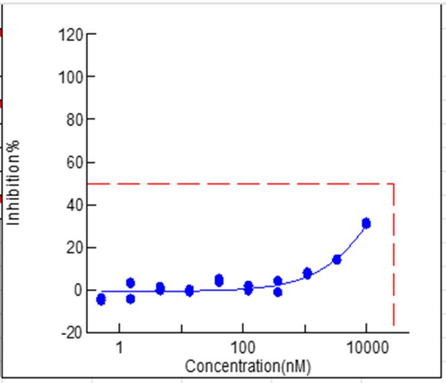
Compound 68-OX1R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	54.81	56.26	55.53	Relative IC50	8587.63
3333.333	28.43	37.52	32.98	Absolute IC50	7695.73
1111.111	17.31	18.92	18.11	Top	100.0
370.370	5.58	7.93	6.75	Bottom	4.9
123.457	9.04	4.26	6.65	Slope	0.94
41.152	7.12	9.98	8.55	R2	0.97
13.717	3.12	6.36	4.74		
4.572	4.45	9.05	6.75		
1.524	0.75	4.30	2.52		
0.508	2.13	6.97	4.55		



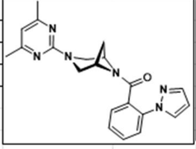
Compound 68-OX2R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	94.54	121.40	94.54	Relative IC50	225.48
3333.333	99.43	100.02	99.72	Absolute IC50	241.65
1111.111	79.64	88.64	84.14	Top	102.6
370.370	58.52	64.15	61.33	Bottom	-6.5
123.457	23.64	36.75	30.20	Slope	1.01
41.152	7.70	19.54	13.62	R2	0.99
13.717	-2.78	-2.98	-2.88		
4.572	-7.09	-1.16	-4.13		
1.524	-6.38	-2.66	-4.52		
0.508	-10.38	-4.53	-7.46		

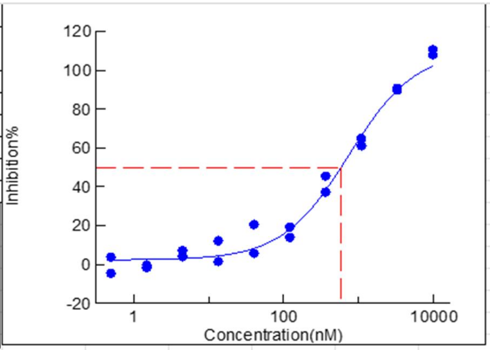
Compound 69-OX1R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	30.59	31.14	30.86	Relative IC50	>10000
3333.333	13.80	13.96	13.88	Absolute IC50	>10000
1111.111	7.79	6.93	7.36	Top	100.0
370.370	-1.35	3.80	1.23	Bottom	-0.7
123.457	1.61	-0.46	0.58	Slope	0.81
41.152	3.41	4.79	4.10	R2	0.94
13.717	-0.27	-1.20	-0.73		
4.572	1.14	-0.46	0.34		
1.524	-4.55	2.92	-0.82		
0.508	-5.24	-4.08	-4.66		



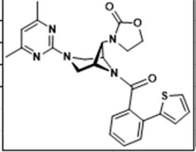


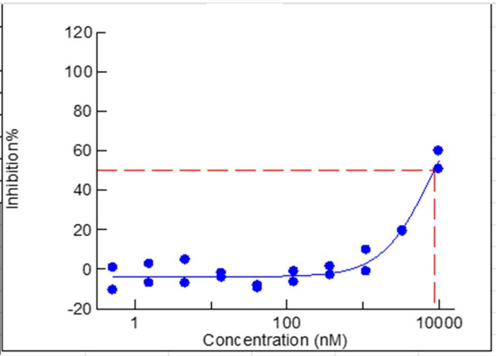
Compound 69-OX2R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	107.77	110.27	109.02	Relative IC50	740.68
3333.333	90.46	89.45	89.95	Absolute IC50	582.76
1111.111	64.60	60.83	62.72	Top	110.3
370.370	45.22	36.92	41.07	Bottom	2.3
123.457	13.58	18.96	16.27	Slope	0.98
41.152	5.49	20.20	12.84	R2	0.98
13.717	11.86	1.15	6.51		
4.572	3.74	6.79	5.27		
1.524	-2.07	-0.67	-1.37		
0.508	3.44	-4.91	-0.74		



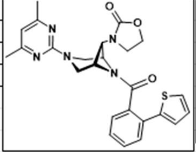


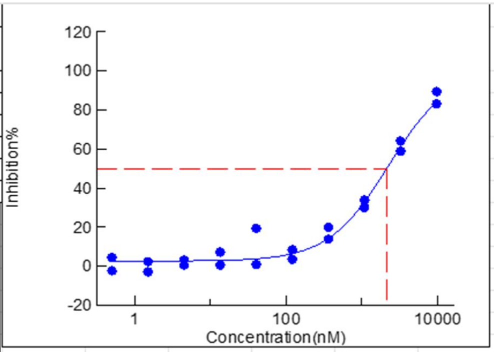
Compound 70-OX1R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	50.74	59.80	55.27	Relative IC50	8200.77
3333.333	19.14	19.67	19.41	Absolute IC50	8663.39
1111.111	-1.07	9.81	4.37	Top	100.0
370.370	-2.98	1.43	-0.77	Bottom	-3.8
123.457	-6.47	-1.03	-3.75	Slope	1.32
41.152	-8.24	-9.52	-8.88	R2	0.94
13.717	-4.21	-1.96	-3.08		
4.572	-7.04	4.83	-1.10		
1.524	-6.96	2.67	-2.15		
0.508	-10.54	0.82	-4.86		

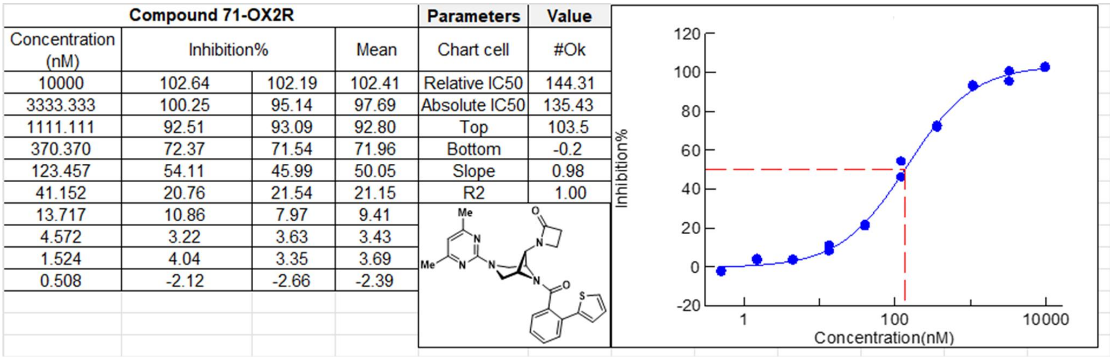




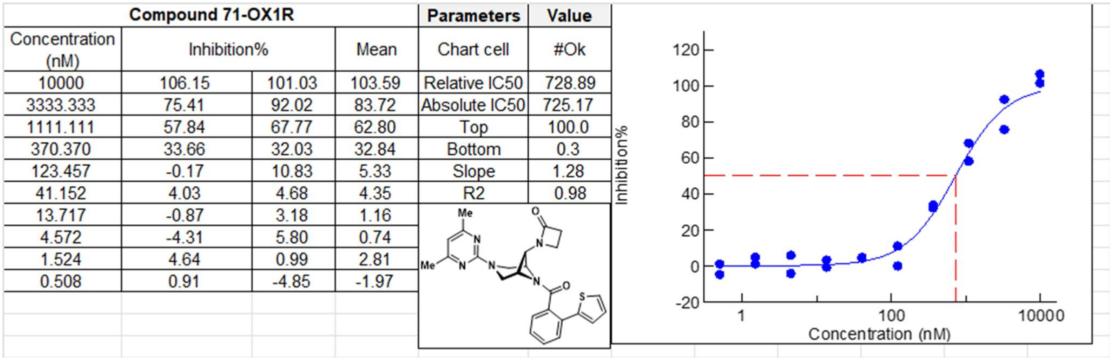
Compound 70-OX2R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	88.97	82.76	85.87	Relative IC50	2248.96
3333.333	58.57	63.75	61.16	Absolute IC50	2140.81
1111.111	29.67	33.52	31.60	Top	100.0
370.370	13.53	19.63	16.58	Bottom	2.6
123.457	3.18	8.15	5.66	Slope	1.09
41.152	0.55	19.00	9.78	R2	0.97
13.717	0.24	6.90	3.57		
4.572	0.22	2.87	1.54		
1.524	-3.23	2.06	-0.58		
0.508	-2.62	4.11	0.75		



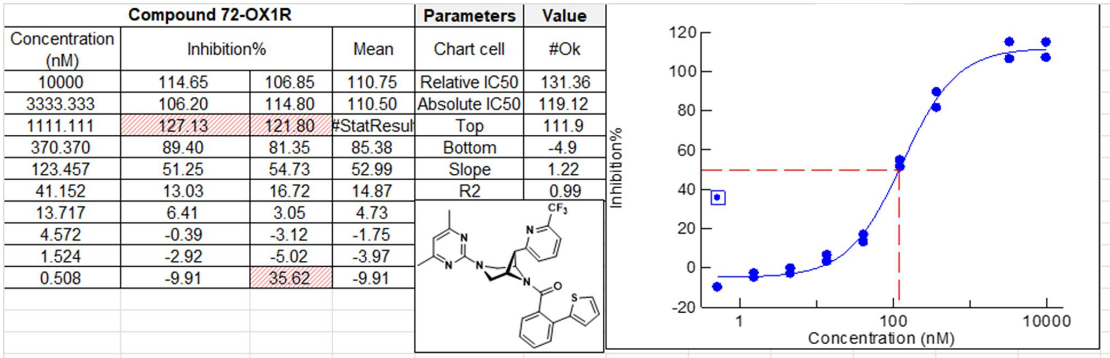




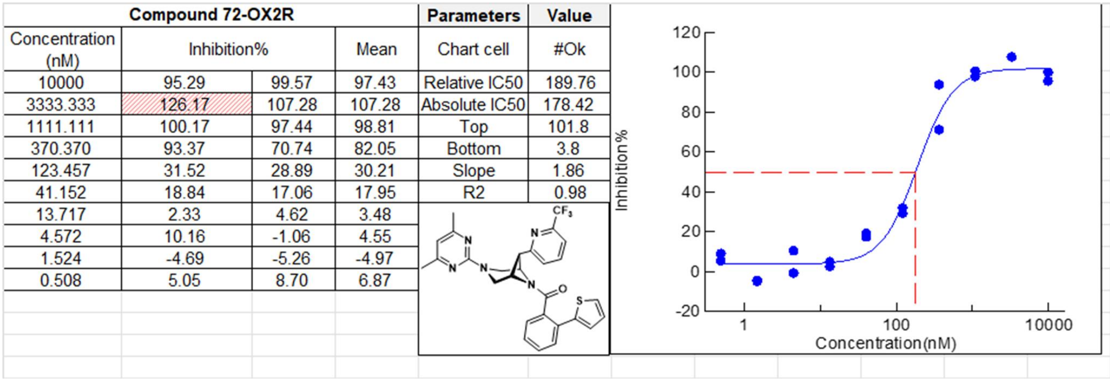
Compound 71-OX2R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	102.64	102.19	102.41	Relative IC50	144.31
3333.333	100.25	95.14	97.69	Absolute IC50	135.43
1111.111	92.51	93.09	92.80	Top	103.5
370.370	72.37	71.54	71.96	Bottom	-0.2
123.457	54.11	45.99	50.05	Slope	0.98
41.152	20.76	21.54	21.15	R2	1.00
13.717	10.86	7.97	9.41		
4.572	3.22	3.63	3.43		
1.524	4.04	3.35	3.69		
0.508	-2.12	-2.66	-2.39		



Compound 71-OX1R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	106.15	101.03	103.59	Relative IC50	728.89
3333.333	75.41	92.02	83.72	Absolute IC50	725.17
1111.111	57.84	67.77	62.80	Top	100.0
370.370	33.66	32.03	32.84	Bottom	0.3
123.457	-0.17	10.83	5.33	Slope	1.28
41.152	4.03	4.68	4.35	R2	0.98
13.717	-0.87	3.18	1.16		
4.572	-4.31	5.80	0.74		
1.524	4.64	0.99	2.81		
0.508	0.91	-4.85	-1.97		

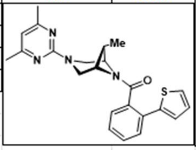


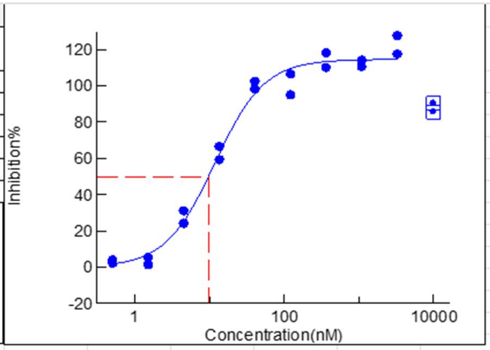
Compound 72-OX1R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	114.65	106.85	110.75	Relative IC50	131.36
3333.333	106.20	114.80	110.50	Absolute IC50	119.12
1111.111	127.13	121.80	#StatResul	Top	111.9
370.370	89.40	81.35	85.38	Bottom	-4.9
123.457	51.25	54.73	52.99	Slope	1.22
41.152	13.03	16.72	14.87	R2	0.99
13.717	6.41	3.05	4.73		
4.572	-0.39	-3.12	-1.75		
1.524	-2.92	-5.02	-3.97		
0.508	-9.91	35.62	-9.91		



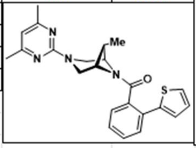
Compound 72-OX2R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	95.29	99.57	97.43	Relative IC50	189.76
3333.333	126.17	107.28	107.28	Absolute IC50	178.42
1111.111	100.17	97.44	98.81	Top	101.8
370.370	93.37	70.74	82.05	Bottom	3.8
123.457	31.52	28.89	30.21	Slope	1.86
41.152	18.84	17.06	17.95	R2	0.98
13.717	2.33	4.62	3.48		
4.572	10.16	-1.06	4.55		
1.524	-4.69	-5.26	-4.97		
0.508	5.05	8.70	6.87		

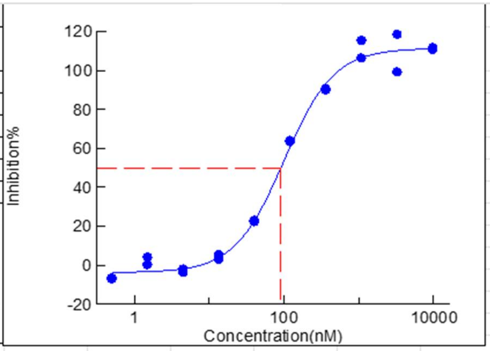
Compound 73-OX1R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	85.52	90.39	#StatResul	Relative IC50	11.71
3333.333	117.17	127.24	122.21	Absolute IC50	9.64
1111.111	110.22	113.81	112.02	Top	114.6
370.370	117.82	109.79	113.80	Bottom	0.0
123.457	94.64	106.16	100.40	Slope	1.32
41.152	102.18	97.96	100.07	R2	0.98
13.717	66.20	59.01	62.61		
4.572	23.82	30.69	27.25		
1.524	4.99	0.93	2.96		
0.508	1.85	3.74	2.80		



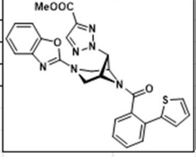


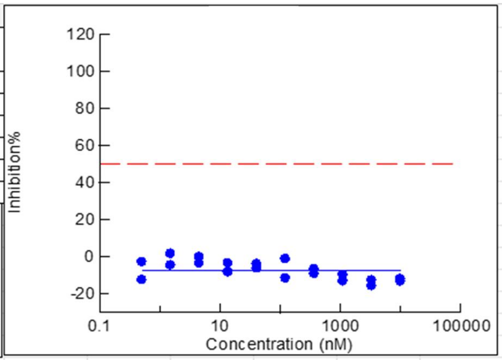
Compound 73-OX2R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	110.37	111.46	110.91	Relative IC50	100.95
3333.333	98.97	118.18	108.58	Absolute IC50	91.22
1111.111	106.13	115.11	110.62	Top	111.4
370.370	90.36	89.66	90.01	Bottom	-3.7
123.457	63.71	63.24	63.47	Slope	1.31
41.152	22.74	22.13	22.44	R2	0.99
13.717	2.69	5.19	3.94		
4.572	-3.88	-2.35	-3.12		
1.524	0.01	3.90	1.96		
0.508	-6.83	-7.33	-7.08		



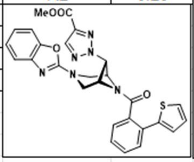


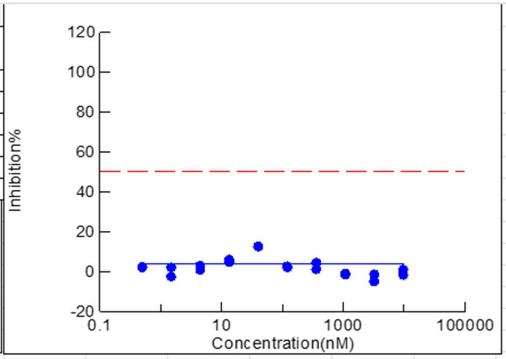
Compound 74-OX1R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	-13.28	-11.99	-12.63	Relative IC50	>10000
3333.333	-12.64	-15.74	-14.19	Absolute IC50	>10000
1111.111	-13.19	-9.76	-11.47	Top	100.0
370.370	-9.24	-6.78	-8.01	Bottom	-7.5
123.457	-11.69	-1.17	-6.43	Slope	3.00
41.152	-6.27	-3.87	-5.07	R2	0.00
13.717	-8.36	-3.54	-5.95		
4.572	-0.19	-3.65	-1.92		
1.524	-4.63	1.55	-1.54		
0.508	-12.50	-2.85	-7.68		

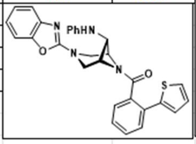


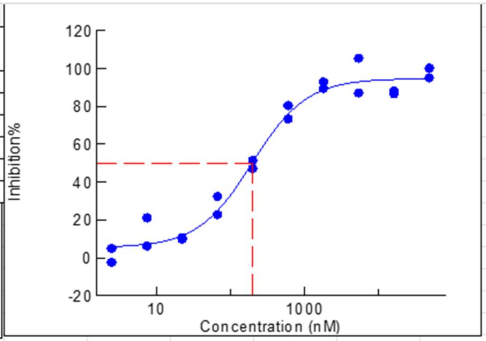


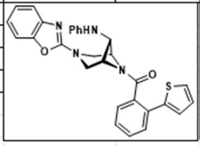
Compound 74-OX2R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	-2.02	0.70	-0.66	Relative IC50	>10000
3333.333	-1.69	-5.31	-3.50	Absolute IC50	>10000
1111.111	-1.28	-1.84	-1.56	Top	100.0
370.370	4.18	0.82	2.50	Bottom	4.1
123.457	2.37	1.80	2.09	Slope	0.30
41.152	12.09	12.46	12.27	R2	0.20
13.717	5.68	4.46	5.07		
4.572	2.69	0.49	1.59		
1.524	1.82	-2.84	-0.51		
0.508	2.04	1.70	1.87		

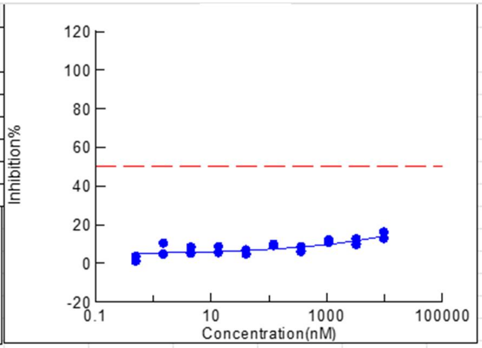


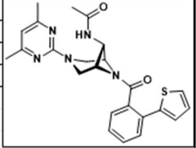


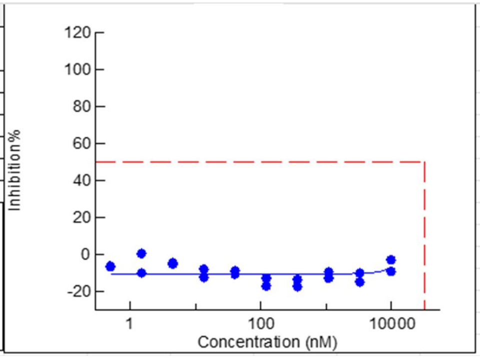
Compound 75-OX1R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
50000	99.92	94.84	97.38	Relative IC50	197.78
16666.667	87.89	86.36	87.12	Absolute IC50	197.16
5555.556	86.81	105.17	95.99	Top	94.8
1851.852	92.72	89.25	90.98	Bottom	5.4
617.284	73.11	80.19	76.65	Slope	1.18
205.761	51.20	46.86	49.03	R2	0.97
68.587	22.49	32.08	27.29		
22.862	9.54	10.28	9.91		
7.621	20.82	5.85	13.34		
2.540	4.59	-2.77	0.91		

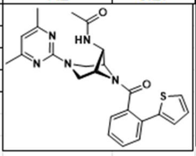


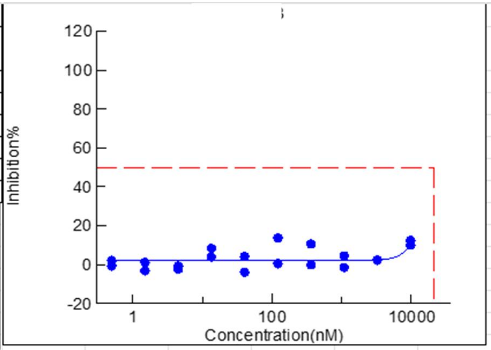
Compound 75-OX2R				Parameters	Value
Concentration(nM)	Inhibition%		Mean	Chart cell	#Ok
10000	15.89	12.52	14.20	Relative IC50	>10000
3333.333	9.42	12.37	10.90	Absolute IC50	>10000
1111.111	10.34	11.87	11.11	Top	100.0
370.370	5.77	8.23	7.00	Bottom	4.6
123.457	8.79	9.63	9.21	Slope	0.30
41.152	4.37	6.45	5.41	R2	0.64
13.717	5.24	8.28	6.76		
4.572	4.86	8.05	6.46		
1.524	4.44	10.14	7.29		
0.508	3.26	0.84	2.05		

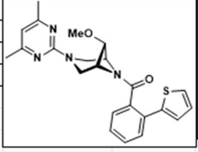


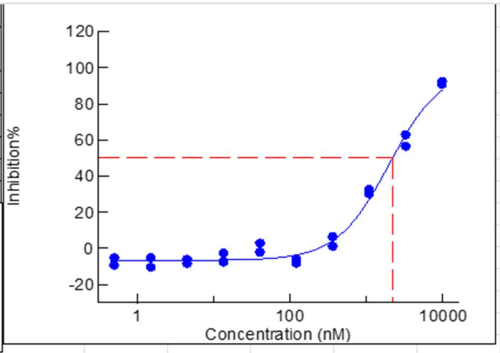
Compound 76-OX1R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	-3.12	-9.30	-6.21	Relative IC50	>10000
3333.333	-10.31	-15.08	-12.69	Absolute IC50	>10000
1111.111	-9.51	-12.96	-11.24	Top	100.0
370.370	-17.61	-13.71	-15.66	Bottom	-10.2
123.457	-17.17	-12.97	-15.07	Slope	3.00
41.152	-9.03	-10.87	-9.95	R2	0.07
13.717	-8.18	-12.60	-10.39		
4.572	-4.54	-5.47	-5.01		
1.524	0.34	-10.22	-4.94		
0.508	-6.86	-6.44	-6.65		

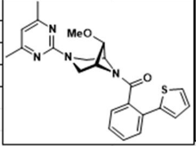


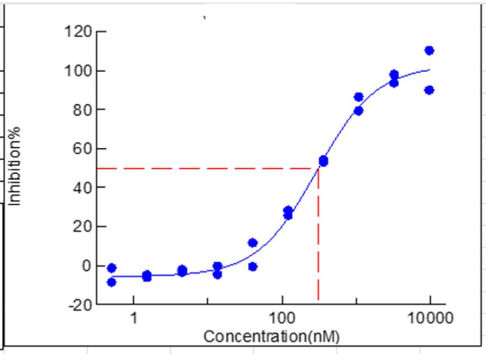
Compound 76-OX2R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	9.73	12.08	10.90	Relative IC50	>10000
3333.333	1.96	2.13	2.04	Absolute IC50	>10000
1111.111	-1.86	4.16	1.15	Top	100.0
370.370	10.25	-0.48	4.88	Bottom	1.9
123.457	13.34	0.16	6.75	Slope	3.00
41.152	-4.29	3.83	-0.23	R2	0.27
13.717	3.48	8.02	5.75		
4.572	-2.72	-1.07	-1.89		
1.524	-3.53	0.79	-1.37		
0.508	-1.00	1.71	0.35		

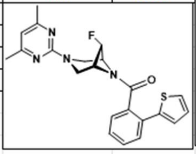


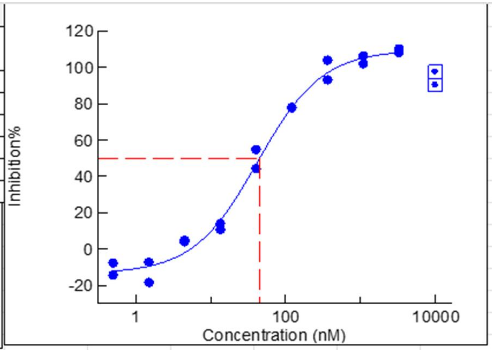
Compound 77-OX1R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	90.52	91.96	91.24	Relative IC50	1998.41
3333.333	62.56	56.18	59.37	Absolute IC50	2204.08
1111.111	32.29	29.82	31.05	Top	100.0
370.370	6.12	0.88	3.50	Bottom	-6.6
123.457	-6.34	-8.58	-7.46	Slope	1.27
41.152	2.55	-2.45	0.05	R2	0.99
13.717	-2.97	-7.75	-5.36		
4.572	-8.51	-6.46	-7.48		
1.524	-5.53	-10.68	-8.11		
0.508	-5.48	-9.57	-7.53		

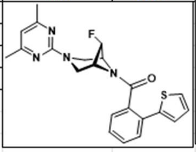


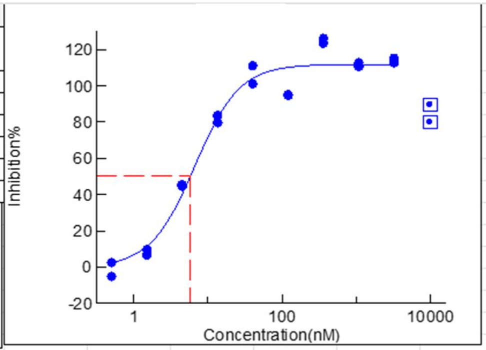
Compound 77-OX2R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	110.04	89.73	99.88	Relative IC50	296.39
3333.333	93.37	97.65	95.51	Absolute IC50	311.17
1111.111	86.17	79.11	82.64	Top	102.8
370.370	52.72	53.87	53.29	Bottom	-5.6
123.457	25.38	27.94	26.66	Slope	1.07
41.152	11.32	-0.87	5.23	R2	0.99
13.717	-0.63	-4.99	-2.81		
4.572	-3.72	-2.45	-3.08		
1.524	-5.10	-6.40	-5.75		
0.508	-1.68	-8.85	-5.26		



Compound 78-OX1R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	97.64	90.34	#StatResul	Relative IC50	42.34
3333.333	107.94	110.09	109.01	Absolute IC50	44.99
1111.111	101.71	106.15	103.93	Top	109.7
370.370	92.92	103.73	98.33	Bottom	-13.5
123.457	77.82	77.46	77.64	Slope	1.01
41.152	44.07	54.51	49.29	R2	0.99
13.717	10.39	13.77	12.08		
4.572	3.60	4.55	4.07		
1.524	-7.58	-18.79	-13.19		
0.508	-8.01	-14.71	-11.36		



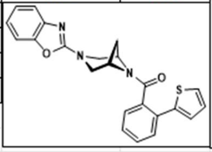
Compound 78-OX2R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	80.01	89.66	#StatResul	Relative IC50	6.66
3333.333	112.42	114.93	113.67	Absolute IC50	5.75
1111.111	110.34	112.43	111.38	Top	111.9
370.370	123.10	125.86	124.48	Bottom	0.0
123.457	94.74	94.37	94.55	Slope	1.45
41.152	100.84	110.77	105.81	R2	0.97
13.717	79.40	83.46	81.43		
4.572	44.26	45.16	44.71		
1.524	6.27	9.18	7.73		
0.508	2.12	-5.45	-1.67		

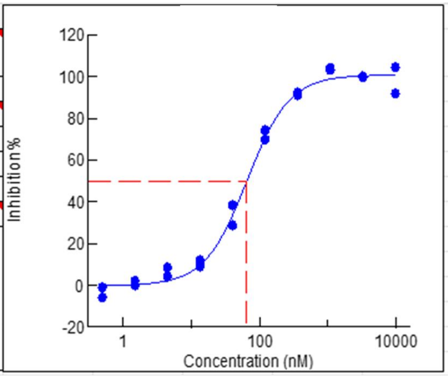


Compound SI-44-OX1R

Concentration (nM)	Inhibition%		Mean
10000	91.64	104.19	97.91
3333.333	99.29	99.84	99.56
1111.111	103.95	102.92	103.43
370.370	92.10	90.82	91.46
123.457	69.64	74.01	71.82
41.152	28.48	38.21	33.35
13.717	11.68	8.84	10.26
4.572	8.27	3.96	6.11
1.524	-0.29	1.83	0.77
0.508	-6.15	-1.23	-3.69

Parameters	Value
Chart cell	#Ok
Relative IC50	65.88
Absolute IC50	65.18
Top	100.8
Bottom	0.0
Slope	1.40
R2	0.99

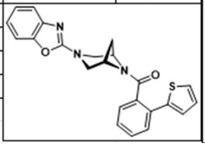


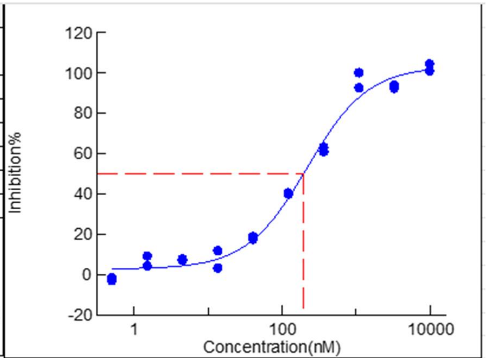


Compound SI-44-OX2R

Concentration (nM)	Inhibition%		Mean
10000	104.16	100.71	102.43
3333.333	92.07	93.70	92.88
1111.111	92.30	99.78	96.04
370.370	60.70	62.90	61.80
123.457	39.62	40.22	39.92
41.152	17.29	18.73	18.01
13.717	3.05	11.68	7.36
4.572	6.78	7.46	7.12
1.524	8.95	4.09	6.52
0.508	-3.14	-1.72	-2.43

Parameters	Value
Chart cell	#Ok
Relative IC50	217.56
Absolute IC50	193.60
Top	103.3
Bottom	2.9
Slope	1.06
R2	0.99

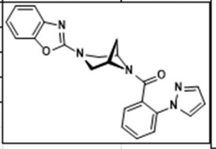


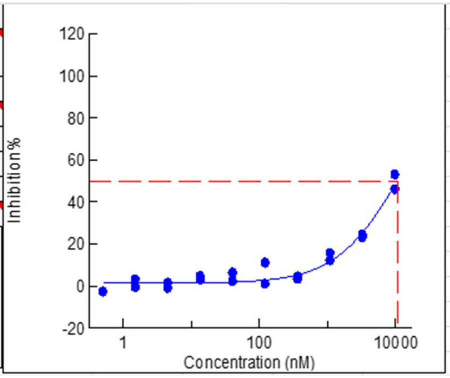


Compound SI-46-OX1R

Concentration (nM)	Inhibition%		Mean
10000	45.83	52.77	49.30
3333.333	22.82	24.23	23.53
1111.111	11.99	15.41	13.70
370.370	3.12	4.25	3.69
123.457	0.86	10.86	5.86
41.152	2.06	6.09	4.07
13.717	2.77	4.43	3.60
4.572	-1.25	1.25	0.00
1.524	-0.87	2.91	1.02
0.508	-2.84	-2.97	-2.91

Parameters	Value
Chart cell	#Ok
Relative IC50	>10000
Absolute IC50	>10000
Top	100.0
Bottom	1.4
Slope	0.93
R2	0.96

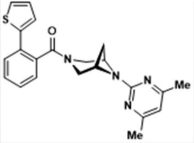


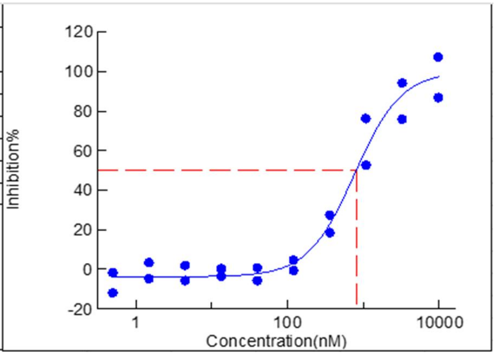


Compound SI-49-OX1R

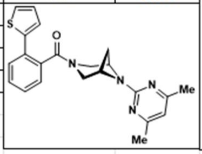
Concentration (nM)	Inhibition%		Mean
10000	86.52	106.94	96.73
3333.333	75.56	93.89	84.73
1111.111	52.35	75.96	64.16
370.370	18.24	27.09	22.66
123.457	-0.89	4.37	1.74
41.152	-6.03	0.44	-2.80
13.717	-3.81	-0.08	-1.95
4.572	-6.00	1.62	-2.19
1.524	-5.05	3.10	-0.98
0.508	-12.21	-2.01	-7.11

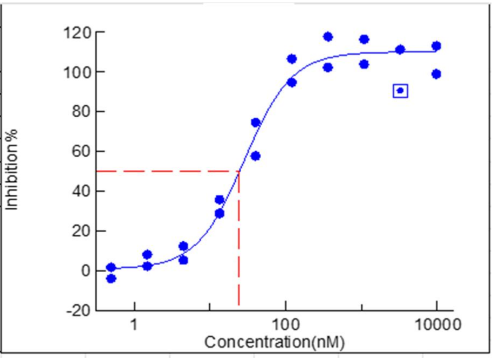
Parameters	Value
Chart cell	#Ok
Relative IC50	769.02
Absolute IC50	809.30
Top	100.0
Bottom	-3.7
Slope	1.41
R2	0.97



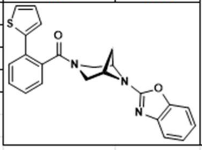


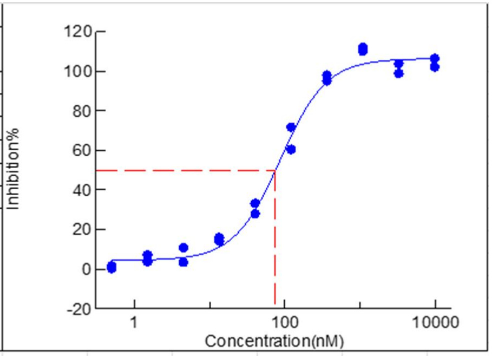
Compound SI-49-OX2R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	112.74	98.65	105.70	Relative IC50	28.46
3333.333	110.93	90.39	110.93	Absolute IC50	24.62
1111.111	116.17	103.54	109.85	Top	110.1
370.370	117.41	101.94	109.67	Bottom	0.8
123.457	106.29	94.47	100.38	Slope	1.39
41.152	74.30	57.44	65.87	R2	0.98
13.717	35.47	28.49	31.98		
4.572	12.11	5.05	8.58		
1.524	7.84	2.00	4.92		
0.508	1.41	-4.19	-1.39		





Compound SI-51-OX2R				Parameters	Value
Concentration (nM)	Inhibition%		Mean	Chart cell	#Ok
10000	101.71	106.19	103.95	Relative IC50	87.12
3333.333	103.45	98.54	100.99	Absolute IC50	75.04
1111.111	109.73	111.67	110.70	Top	106.3
370.370	94.65	97.74	96.20	Bottom	4.4
123.457	60.15	71.41	65.78	Slope	1.42
41.152	27.59	32.93	30.26	R2	0.99
13.717	13.77	15.63	14.70		
4.572	3.13	10.51	6.82		
1.524	3.44	6.91	5.18		
0.508	-0.03	1.37	0.67		





X-ray Crystallography

Compound 10

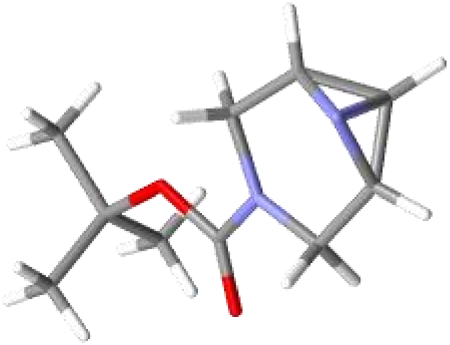


Table S7. Crystal data and structure refinement for compound 10.

Empirical formula	$C_{10}H_{16}N_2O_2$
Formula weight	196.25
Temperature/K	150.00
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	9.7882(2)
b/Å	10.5232(2)
c/Å	20.3801(4)
α/°	90
β/°	95.356(2)
γ/°	90
Volume/Å^3	2090.05(7)
Z	8
ρ_{calc}g/cm^3	1.247
μ/mm^{-1}	0.713
F(000)	848.0
Crystal size/mm^3	0.07 × 0.04 × 0.03
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	8.716 to 137.186
Index ranges	$-9 \le h \le 11$, $-12 \le k \le 12$, $-24 \le l \le 22$
Reflections collected	16909
Independent reflections	3690 [R_{int}= 0.0949, R_{sigma}= 0.0674]

Data/restraints/parameters	3690/0/259
Goodness-of-fit on F^2	1.035
Final R indexes [I>=2σ (I)]	R_1= 0.0531, wR_2= 0.1228
Final R indexes [all data]	R_1= 0.0874, wR_2= 0.1395
Largest diff. peak/hole / e $Å^{-3}$	0.17/-0.21

Table S8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound 10. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

x		y	z	U(eq)
C1	2503(3)	7431(2)	3492.1(12)	37.6(6)
C2	3053(3)	7020(2)	4153.3(12)	36.5(6)
C3	3807(3)	7353(2)	3195.7(12)	37.4(6)
C4	4579(3)	6119(2)	3178.0(12)	37.3(6)
C5	3753(3)	5757(2)	4270.4(11)	35.0(6)
C6	4321(3)	3963(2)	3553.4(11)	30.5(6)
C7	3927(3)	1870(2)	4033.4(12)	34.2(6)
C8	2930(3)	1448(2)	3461.7(13)	47.2(7)
C9	5362(3)	1347(2)	3989.0(14)	45.6(7)
C10	3400(3)	1509(2)	4682.4(13)	46.7(7)
N1	4125(2)	5226.2(17)	3657.4(9)	30.7(5)
N2	3764(2)	8070.1(18)	3826.8(11)	44.0(6)
O1	4731.9(19)	3536.4(15)	3055.6(8)	39.2(5)
O2	3970.5(18)	3275.6(14)	4070.7(7)	32.8(4)
C11	2358(3)	3595(3)	1627.4(16)	58.1(9)
C12	1768(3)	4394(2)	2107.9(14)	45.4(7)

Compound 17

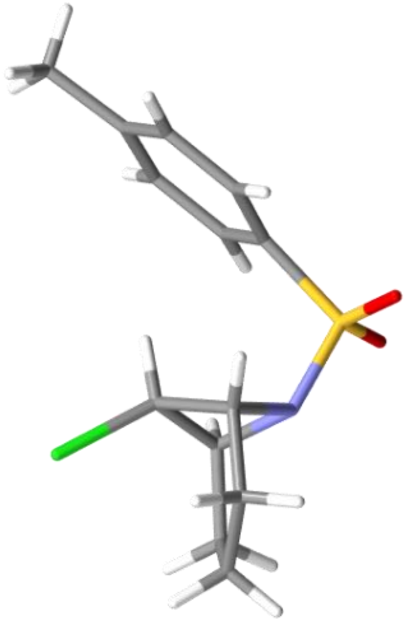


Table S9. Crystal data and structure refinement for compound 17.

Empirical formula	C13 H16 Cl N O2 S	
Formula weight	285.78	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.15160(10) Å	α= 90°.
	b = 12.0485(2) Å	β= 90°.
	c = 18.0168(3) Å	γ = 90°.
Volume	1335.36(4) Å^3	
Z	4	
Density (calculated)	1.421 Mg/m^3	
Absorption coefficient	3.945 mm^{-1}	
F(000)	600	
Crystal size	0.180 x 0.160 x 0.140 mm^3	
Theta range for data collection	4.415 to 76.160°.	
Index ranges	-5<=h<=7, -15<=k<=14, -22<=l<=22	

Reflections collected	13596
Independent reflections	2730 [R(int) = 0.0322]
Completeness to theta = 67.684°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.78167
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2730 / 0 / 165
Goodness-of-fit on F^2	1.104
Final R indices [I>2sigma(I)]	R1 = 0.0261, wR2 = 0.0689
R indices (all data)	R1 = 0.0271, wR2 = 0.0693
Absolute structure parameter	-0.019(7)
Extinction coefficient	0.0014(3)
Largest diff. peak and hole	0.214 and -0.272 e.Å^{-3}

Table S10. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for compound 17. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(12)	8633(4)	5368(2)	4998(1)	19(1)
C(11)	7507(4)	5584(2)	4344(1)	22(1)
C(10)	5490(4)	6109(2)	4352(1)	21(1)
C(9)	4633(4)	6443(2)	5033(1)	20(1)
C(8)	5713(4)	6226(2)	5694(1)	19(1)
C(5)	5525(4)	3829(2)	6803(1)	16(1)
C(7)	7703(4)	5677(2)	5671(1)	16(1)
C(1)	7965(4)	3062(2)	6164(1)	16(1)
S(1)	8930(1)	5224(1)	6505(1)	16(1)
Cl(1)	3733(1)	2228(1)	5803(1)	23(1)
N(1)	7953(3)	4002(2)	6724(1)	15(1)
O(1)	11196(3)	5059(1)	6356(1)	22(1)
C(2)	8271(4)	1998(2)	6603(1)	21(1)
O(2)	8253(3)	5952(1)	7091(1)	23(1)
C(6)	5550(4)	3330(2)	6017(1)	16(1)
C(3)	6648(4)	1904(2)	7254(2)	29(1)

C(13)	4248(5)	6300(2)	3639(1)	30(1)
C(4)	5238(4)	2948(2)	7397(1)	21(1)

Compound 51

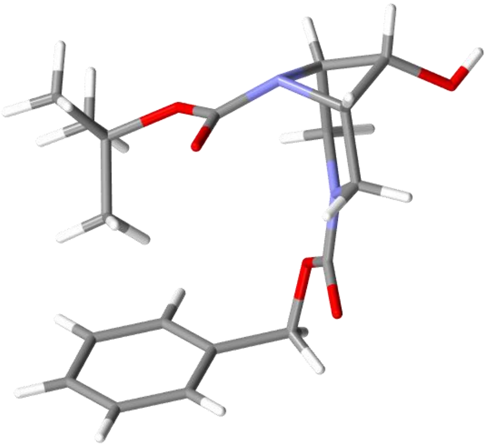


Table S11. Crystal data and structure refinement for compound 51.

Empirical formula	C18 H24 N2 O5	
Formula weight	348.39	
Temperature	99.9(4) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	Pbcn	
Unit cell dimensions	a = 31.6869(7) Å	α= 90°.
	b = 8.3611(2) Å	β= 90°.
	c = 13.8562(3) Å	γ = 90°.
Volume	3671.03(14) Å^3	
Z	8	
Density (calculated)	1.261 Mg/m^3	
Absorption coefficient	0.763 mm^{-1}	
F(000)	1488	
Crystal size	0.16 x 0.14 x 0.12 mm^3	
Theta range for data collection	2.789 to 76.030°.	
Index ranges	-38<=h<=39, -10<=k<=10, -17<=l<=13	
Reflections collected	42546	
Independent reflections	3793 [R(int) = 0.0810]	
Completeness to theta = 67.684°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.71129	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3793 / 0 / 231
Goodness-of-fit on F^2	1.185
Final R indices [I>2sigma(I)]	R1 = 0.1053, wR2 = 0.2635
R indices (all data)	R1 = 0.1103, wR2 = 0.2660
Extinction coefficient	0.00037(10)
Largest diff. peak and hole	0.500 and -0.401 e.Å^{-3}

Table S12. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for compound 51. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(8)	2995(1)	1965(5)	3099(3)	24(1)
C(12)	3635(1)	-102(6)	1808(3)	28(1)
C(11)	4601(2)	2731(7)	3971(5)	45(1)
C(2)	3223(1)	2343(6)	4781(3)	26(1)
O(2)	2804(1)	2347(4)	2362(2)	30(1)
N(2)	3398(1)	5204(5)	4865(3)	27(1)
C(17)	3622(2)	861(6)	983(3)	30(1)
C(1)	3292(1)	3753(5)	5438(3)	27(1)
O(1)	3209(1)	584(4)	3217(2)	28(1)
N(1)	3011(1)	2885(4)	3888(3)	24(1)
C(10)	3244(2)	-476(5)	2385(3)	28(1)
C(9)	4627(2)	5710(7)	3743(4)	41(1)
C(5)	2942(1)	5473(6)	4684(3)	28(1)
O(5)	2498(1)	3670(4)	5654(2)	31(1)
C(4)	2796(1)	4449(5)	3849(3)	27(1)
O(4)	4002(1)	4258(4)	4278(2)	32(1)
O(3)	3669(1)	6292(4)	3493(3)	34(1)
C(3)	3691(1)	5311(6)	4145(3)	28(1)
C(7)	2865(1)	4603(7)	5646(3)	31(1)
C(6)	4366(2)	4206(6)	3613(4)	32(1)
C(15)	4366(2)	508(6)	749(4)	38(1)
C(13)	4020(2)	-737(6)	2091(4)	35(1)

C(16)	3988(2)	1146(6)	468(4)	34(1)
C(14)	4385(2)	-440(7)	1574(4)	41(1)
C(18)	4220(2)	3957(7)	2576(4)	44(1)

Compound 52

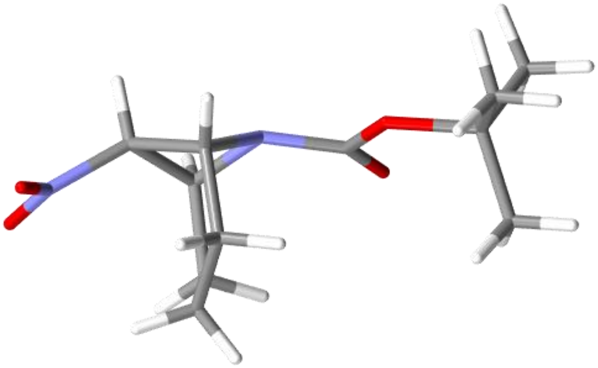


Table S13. Crystal data and structure refinement for compound 52.

Empirical formula	C11 H18 N2 O4	
Formula weight	242.27	
Temperature	99.9(4) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.1558(2) Å	α= 112.779(6)°.
	b = 10.2480(6) Å	β= 95.767(4)°.
	c = 10.3920(8) Å	γ = 90.343(4)°.
Volume	600.66(7) Å^3	
Z	2	
Density (calculated)	1.340 Mg/m^3	
Absorption coefficient	0.853 mm^{-1}	
F(000)	260	
Crystal size	0.2 x 0.18 x 0.15 mm^3	
Theta range for data collection	4.644 to 75.846°.	
Index ranges	-5<=h<=7, -12<=k<=12, -12<=l<=13	
Reflections collected	6872	
Independent reflections	2360 [R(int) = 0.0154]	
Completeness to theta = 67.684°	98.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.92365	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	2360 / 1 / 158
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0336, wR2 = 0.0857
R indices (all data)	R1 = 0.0360, wR2 = 0.0875
Extinction coefficient	0.0037(8)
Largest diff. peak and hole	0.320 and -0.240 e.Å^{-3}

Table S14. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for compound 52. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	9108(2)	690(1)	3702(1)	19(1)
O(1)	8067(1)	2892(1)	6181(1)	21(1)
N(1)	7046(2)	887(1)	4388(1)	17(1)
C(5)	5783(2)	-23(1)	3030(1)	18(1)
C(7)	6327(2)	2099(1)	5343(1)	18(1)
C(2)	9242(2)	1727(1)	2980(1)	21(1)
C(11)	6460(2)	4078(1)	8396(1)	24(1)
N(2)	8504(2)	-1422(1)	1261(1)	22(1)
O(2)	4414(1)	2351(1)	5443(1)	21(1)
C(4)	5200(2)	854(1)	2162(1)	20(1)
O(4)	7018(2)	-2068(1)	351(1)	31(1)
C(6)	7971(2)	-751(1)	2730(1)	19(1)
C(10)	10109(2)	4790(1)	7932(1)	26(1)
C(9)	6697(2)	5268(1)	6696(1)	26(1)
C(3)	7253(2)	1520(1)	1882(1)	25(1)
O(3)	10419(2)	-1341(1)	1053(1)	31(1)
C(8)	7765(2)	4277(1)	7313(1)	20(1)

Compound 55

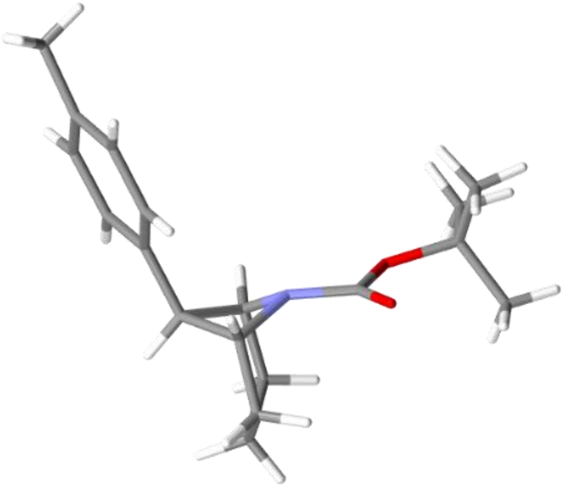


Table S15. Crystal data and structure refinement for compound 55.

Empirical formula	C18 H25 N O2	
Formula weight	287.39	
Temperature	100.0(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.4053(7) Å	α= 111.954(4)°.
	b = 10.2829(7) Å	β= 95.479(5)°.
	c = 13.1889(4) Å	γ = 95.811(7)°.
Volume	793.13(10) Å^3	
Z	2	
Density (calculated)	1.203 Mg/m^3	
Absorption coefficient	0.609 mm^{-1}	
F(000)	312	
Crystal size	0.15 x 0.12 x 0.1 mm^3	
Theta range for data collection	3.652 to 75.468°.	
Index ranges	-7<=h<=8, -12<=k<=12, -8<=l<=15	
Reflections collected	7712	
Independent reflections	3091 [R(int) = 0.0269]	
Completeness to theta = 67.684°	98.7 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	1.00000 and 0.88826
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3091 / 0 / 195
Goodness-of-fit on F^2	1.113
Final R indices [I>2sigma(I)]	R1 = 0.0499, wR2 = 0.1419
R indices (all data)	R1 = 0.0525, wR2 = 0.1445
Extinction coefficient	0.0064(15)
Largest diff. peak and hole	0.279 and -0.450 e.Å^{-3}

Table S16. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for compound 55. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(8)	10272(2)	3823(1)	3602(1)	20(1)
C(7)	8675(2)	2765(1)	3771(1)	20(1)
C(6)	8793(2)	-2265(1)	196(1)	25(1)
C(1)	9524(2)	1504(1)	3973(1)	21(1)
N(1)	9274(2)	783(1)	2750(1)	21(1)
O(1)	10469(2)	-1317(1)	2488(1)	26(1)
C(11)	13136(2)	5815(1)	3213(1)	23(1)
C(3)	5632(2)	844(1)	3969(1)	24(1)
C(9)	9554(2)	4729(2)	3119(1)	24(1)
C(5)	7534(2)	1600(1)	2652(1)	21(1)
C(12)	13851(2)	4926(1)	3706(1)	23(1)
C(14)	14674(2)	6820(2)	2956(1)	30(1)
C(2)	7892(2)	751(1)	4422(1)	23(1)
O(2)	8523(2)	-938(1)	1095(1)	25(1)
C(15)	9481(2)	-577(1)	2142(1)	22(1)
C(10)	10963(2)	5715(1)	2936(1)	25(1)
C(13)	12439(2)	3951(1)	3899(1)	22(1)
C(4)	5461(2)	860(1)	2798(1)	24(1)
C(16)	7653(3)	-3525(2)	359(1)	33(1)
C(18)	7711(3)	-2099(2)	-815(1)	33(1)
C(17)	11130(3)	-2358(2)	123(1)	34(1)

Compound 62

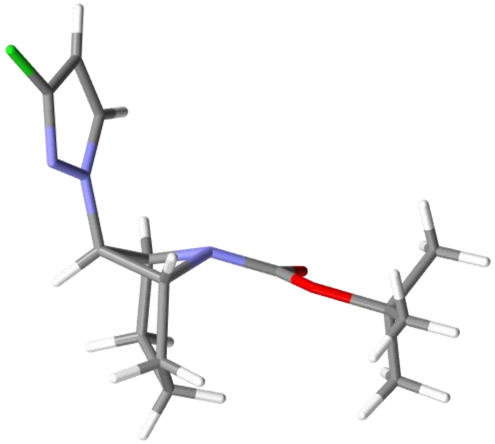


Table S17. Crystal data and structure refinement for compound 62.

Empirical formula	C14 H20 Cl N3 O2	
Formula weight	297.78	
Temperature	100.00(10) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 12.96965(18) Å	α= 90°.
	b = 10.71093(11) Å	β= 109.3503(15)°.
	c = 11.31514(15) Å	γ = 90°.
Volume	1483.07(4) Å^3	
Z	4	
Density (calculated)	1.334 Mg/m^3	
Absorption coefficient	2.330 mm^{-1}	
F(000)	632	
Crystal size	0.18 x 0.16 x 0.14 mm^3	
Theta range for data collection	3.612 to 75.870°.	
Index ranges	-15<=h<=16, -10<=k<=13, -13<=l<=14	
Reflections collected	16857	
Independent reflections	3019 [R(int) = 0.0316]	
Completeness to theta = 67.684°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.72363	

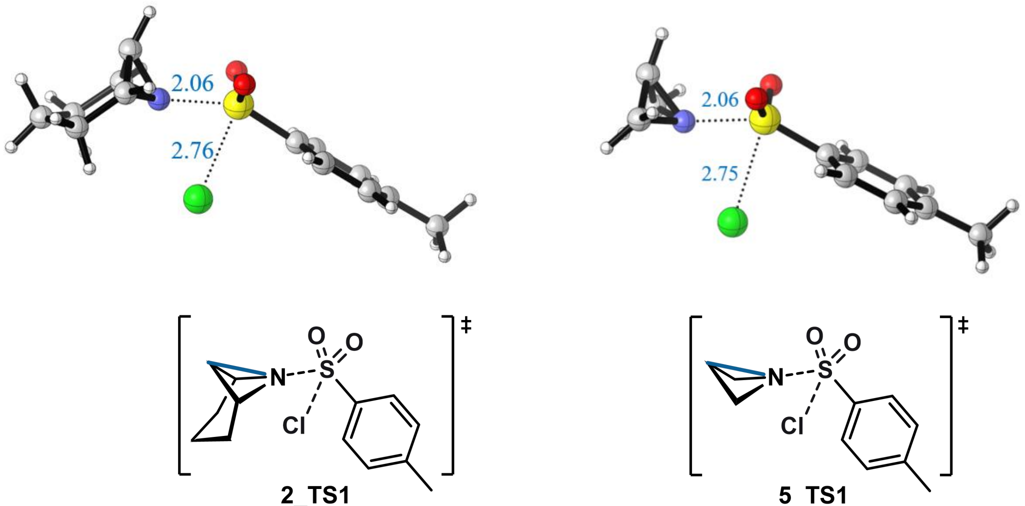
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3019 / 0 / 184
Goodness-of-fit on F^2	1.120
Final R indices [I>2sigma(I)]	R1 = 0.0359, wR2 = 0.0996
R indices (all data)	R1 = 0.0374, wR2 = 0.1009
Extinction coefficient	n/a
Largest diff. peak and hole	0.308 and -0.310 e.Å^{-3}

Table S18. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for compound 62. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	535(1)	835(1)	6409(1)	33(1)
O(1)	4220(1)	7267(1)	8584(1)	25(1)
N(1)	1245(1)	4231(1)	7003(1)	19(1)
C(1)	2396(1)	5457(1)	6034(1)	19(1)
O(2)	4606(1)	6080(1)	7095(1)	22(1)
N(2)	899(1)	3241(1)	6222(1)	22(1)
C(5)	1952(1)	6432(1)	7395(1)	19(1)
C(6)	1366(1)	5420(1)	6440(1)	18(1)
C(7)	1461(1)	3918(1)	8217(1)	22(1)
C(8)	1240(1)	2664(1)	8255(1)	25(1)
C(9)	903(1)	2311(1)	6999(1)	24(1)
C(10)	3976(1)	6506(1)	7740(1)	20(1)
C(11)	5730(1)	6553(1)	7348(1)	23(1)
C(4)	1717(1)	7710(1)	6760(1)	22(1)
C(2)	2264(1)	6508(1)	5076(1)	23(1)
N(3)	2990(1)	5900(1)	7332(1)	18(1)
C(3)	2206(1)	7781(1)	5691(1)	25(1)
C(13)	6115(1)	5787(1)	6442(2)	30(1)
C(14)	6417(1)	6282(2)	8702(1)	32(1)
C(12)	5691(1)	7932(1)	7032(1)	29(1)

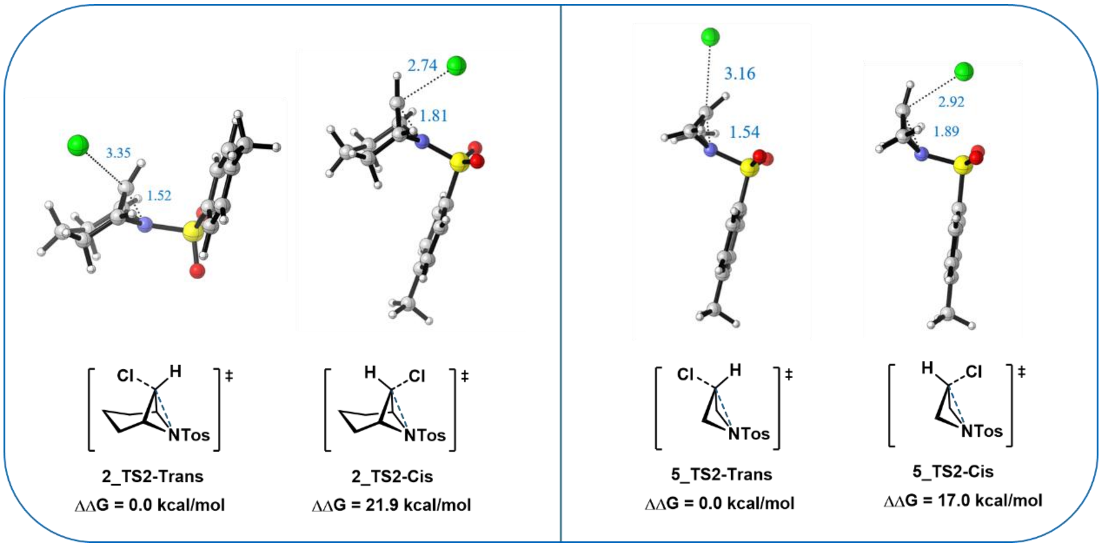
DFT calculations

All DFT calculations were performed with the Gaussian 16 package[15]. Geometry optimizations were performed with the B3LYP[16-17] functional by adding the D3 version of Grimme's dispersion with Becke-Johnson damping (GD3BJ)[18] and using the basis set of 6-31g(d,p)[19-20] with the SMD[21-22] solvation model for MeCN. Frequency analysis was conducted at the same level of theory to verify the stationary points to be minima or saddle points and to obtain zero-point vibrational energy (ZPVE) and thermal energy corrections under 298.15 K and 1 atm pressure. All transition states were confirmed to connect reactants and products by intrinsic reaction coordinate (IRC) calculations. Single-point solvation energies were calculated with the 6-311++G(d,p)[23-25] by using SMD solvation model with MeCN. Conformational searches on the transition states and intermediates were extensively performed using Grimme's programs XTB 6.4.0 and CREST 2.12[26-28]. Grimme[29] correction (frequency cut-off is 100 cm-1) for entropy is performed using GoodVibes v3.2[30]. Computed structures are illustrated using CYLView[31]. Unless otherwise noted, the relative energies reported in the text are Gibbs free energies with the solvent effect corrections. In addition, geometry optimization, frequency analysis and single point energy of open-shell local minimums are calculated with unrestricted DFT methods, while same computations for closed-shell structures were performed with restricted DFT methods.



2_TS1 **5_TS1**

Fig. S3. Optimized structures of TS1.



2_TS2-Trans
ΔΔG = 0.0 kcal/mol

2_TS2-Cis
ΔΔG = 21.9 kcal/mol

5_TS2-Trans
ΔΔG = 0.0 kcal/mol

5_TS2-Cis
ΔΔG = 17.0 kcal/mol

Fig. S4. Optimized trans/cis structures of TS2 for 2 and 5.

DFT: B3LYP-D3(BJ)/6-311++G(d,p)//B3LYP-D3(BJ)/6-31G(d,p)

BDE (kcal/mol)	1	2	3	4	5
ΔH_SPC	45	45	57	36	39
ΔH	46	46	58	36	39

DFT: PBE0-D3(BJ)/6-311++G(d,p)//PBE0-D3(BJ)/6-31G(d,p)

BDE (kcal/mol)	1	2	3	4	5
ΔH_SPC	47	47	59	37	41
ΔH	48	48	60	38	41

Fig. S5. Comparison of BDE by different DFT methods. *Notes: H_SPC (Enthalpy at the 6-311++G(d,p) basis set) and H (Enthalpy at the 6-31G(d,p) basis set); Methods: B3LYP-D3(BJ)/6-311++G(d,p)//B3LYP-D3(BJ)/6-31G(d,p).*

Table S19. The bond dissociation energies and other thermodynamic parameters.

Structure	E_SPC	E	H_SPC	T.qh-S	G(T)_SPC	qh-G(T)_SPC
1	-763.959597	-763.775035	-763.690684	0.056611	-763.751057	-763.747295
1_diradicals	-763.884406	-763.698679	-763.61841	0.058108	-763.680425	-763.676518
2	-288.826706	-288.76495	-288.679505	0.035201	-288.714699	-288.714706
2_diradicals	-288.751557	-288.688349	-288.607214	0.036687	-288.643893	-288.643901
3	-249.223997	-248.956684	-249.106609	0.032892	-249.139498	-249.139501
3_diradicals	-249.400482	-249.345068	-249.286556	0.034369	-249.32092	-249.320925
4	-328.147364	-328.077805	-327.970038	0.037973	-328.008035	-328.008012
4_diradicals	-328.087383	-328.016689	-327.913355	0.039401	-327.952746	-327.952756
5	-171.860631	-171.66168	-171.780387	0.029682	-171.810068	-171.810069
5_diradicals	-171.779805	-171.590637	-171.704303	0.033226	-171.738025	-171.737529

Notes: E_SPC= Single-point solvation energies; E= Electronic energies; T.qh-S = temperature and quasi-harmonically corrected entropy; H_SPC = enthalpy; G(T)_SPC = Gibbs free energy; qh-G(T)_SPC = Gibbs free energy with Grimme correction. Methods: B3LYP-D3(BJ)/6-311++G(d,p)//B3LYP-D3(BJ)/6-31G(d,p), with Grimme correction for entropy. All energies are in a.u.

Table S20. Energies and other thermodynamic parameters.

Structure	E_SPC	E	H_SPC	T.qh-S	G(T)_SPC	qh-G(T)_SPC
2_IM0	-1568.809743	-1568.586653	-1568.520069	0.065211	-1568.590953	-1568.585279
2_IM1	-1568.824482	-1568.597364	-1568.534238	0.063721	-1568.602161	-1568.597959
2_P-Cis	-1568.863488	-1568.639478	-1568.57134	0.060344	-1568.634153	-1568.631684
2_P-Trans	-1568.866563	-1568.642021	-1568.57474	0.060594	-1568.638165	-1568.635333
2_TS1	-1568.779035	-1568.555993	-1568.490491	0.0619	-1568.556081	-1568.552391
2_TS2-Cis	-1568.786419	-1568.559848	-1568.497852	0.062312	-1568.56414	-1568.560164
2_TS2-Trans	-1568.821766	-1568.59266	-1568.532301	0.062646	-1568.599139	-1568.594947
5_IM0	-1451.109885	-1450.087131	-1450.885993	0.060084	-1450.950537	-1450.946077

5_IM1	-1452.024996	-1451.819526	-1451.801587	0.061085	-1451.868265	-1451.862672
5_P-Cis	-1451.180972	-1450.152216	-1450.954959	0.056662	-1451.014806	-1451.011621
5_P-Trans	-1451.181926	-1450.154367	-1450.955809	0.056421	-1451.015449	-1451.01223
5_TS1	-1451.068166	-1450.033841	-1450.845405	0.056206	-1450.904206	-1450.901611
5_TS2-Cis	-1451.073373	-1450.02353	-1450.851775	0.057543	-1450.912661	-1450.909319
5_TS2-Trans	-1451.098446	-1450.037601	-1450.876072	0.057627	-1450.937067	-1450.933699

Notes: E_SPC= Single-point solvation energies; E= Electronic energies; T.qh-S = temperature and quasi-harmonically corrected entropy; H_SPC = enthalpy; G(T)_SPC = Gibbs free energy; qh-G(T)_SPC = Gibbs free energy with Grimme correction. Methods: B3LYP-D3(BJ)/6-311++G(d,p)/SMD(Acetonitrile)//B3LYP-D3(BJ)/6-31G(d,p)/SMD(Acetonitrile), with Grimme correction for entropy. All energies are in a.u.

Coordinates for all stationary points

31

1_diradicals Esp=-763.884406

C	-4.313894	-0.039019	0.012755
C	-3.213771	0.905574	-0.521407
C	-1.767004	-1.093112	0.109055
C	-3.152250	-1.646867	0.517122
H	-3.339084	1.028194	-1.603942
H	-3.289793	1.889377	-0.053766
H	-5.304188	0.394181	-0.158122
H	-1.398294	-1.657185	-0.756512
H	-1.058600	-1.217974	0.929729
H	-3.069092	-2.697627	0.811589
N	-4.052041	-1.358317	-0.641567
C	-3.911123	-0.635249	1.337340
H	-4.558951	-0.838928	2.182020
N	-1.905011	0.332719	-0.199005
C	-0.837839	1.180519	-0.215036
O	-0.900385	2.372743	-0.467601
O	0.314945	0.521855	0.088300
C	1.500272	1.340707	0.102576
H	1.463420	2.017625	-0.756527
H	1.503297	1.959478	1.005577
C	2.701849	0.436581	0.056420
C	3.800297	0.683131	0.883618
C	2.753469	-0.635161	-0.842741
C	4.939261	-0.119899	0.809188
H	3.763890	1.507121	1.591217
C	3.885346	-1.443775	-0.911405
H	1.896316	-0.836663	-1.477033
C	4.983540	-1.186262	-0.087644
H	5.786000	0.082981	1.457783
H	3.912963	-2.275062	-1.609497
H	5.866080	-1.816132	-0.143152

31

1 Esp=-763.959597

C	-4.300656	0.098285	-0.042715
C	-3.159343	0.946382	-0.554339
C	-1.764197	-1.054598	0.012991
C	-3.085701	-1.649161	0.448346
H	-3.234381	1.030555	-1.648916
H	-3.228659	1.958360	-0.148660
H	-5.278741	0.556445	-0.180224
H	-1.440702	-1.544203	-0.918290
H	-1.004624	-1.261886	0.769287
H	-3.014703	-2.697334	0.734706
N	-4.336713	-1.368127	-0.309735
C	-4.136101	-0.835568	1.085303
H	-4.804003	-1.070627	1.904771
N	-1.875994	0.387392	-0.155637
C	-0.793983	1.217115	-0.169787
O	-0.838589	2.414139	-0.402269
O	0.349025	0.537212	0.122109
C	1.545152	1.338866	0.159436
H	1.515496	2.044272	-0.676662
H	1.558913	1.927323	1.082490
C	2.734738	0.421103	0.080298
C	3.842946	0.633382	0.904044
C	2.766000	-0.627966	-0.846053
C	4.971398	-0.180987	0.799544
H	3.822405	1.439403	1.632674
C	3.887425	-1.448009	-0.944895
H	1.901217	-0.803108	-1.477741
C	4.995423	-1.224680	-0.124370
H	5.825794	-0.004816	1.445889
H	3.899120	-2.261591	-1.663979
H	5.869739	-1.863437	-0.203283

16

2_diradicals Esp=-288.751557

C	-0.743239	1.028132	-0.015019
C	0.789338	1.278754	-0.140829
C	1.547241	-0.000000	0.268538
C	0.789338	-1.278754	-0.140829
C	-0.743240	-1.028132	-0.015019
H	2.558453	-0.000001	-0.151306
H	1.000759	1.558317	-1.178539
H	1.078323	2.120908	0.497041
H	-1.311883	1.961162	-0.090362
H	1.000759	-1.558317	-1.178539
H	1.078322	-2.120909	0.497041
H	-1.311884	-1.961162	-0.090362

H	1.650816	-0.000000	1.358110
N	-1.050927	0.000000	-1.055242
C	-1.050305	0.000000	1.048063
H	-1.921979	0.000001	1.694178

16

2 Esp=-288.826706

C	-0.630967	1.100565	-0.019012
C	0.871598	1.254081	-0.181893
C	1.599835	-0.000000	0.311362
C	0.871598	-1.254081	-0.181893
C	-0.630967	-1.100565	-0.019012
H	2.649119	-0.000000	-0.000540
H	1.087254	1.439273	-1.242258
H	1.210893	2.138276	0.370042
H	-1.199034	2.029555	-0.063184
H	1.087254	-1.439273	-1.242258
H	1.210893	-2.138276	0.370042
H	-1.199034	-2.029555	-0.063184
H	1.587267	-0.000000	1.407469
N	-1.354968	0.000000	-0.722066
C	-1.225575	0.000000	0.771141
H	-2.082961	0.000000	1.434179

13

3_diradicals Esp=-249.400482

C	1.096979	0.782970	0.041787
H	1.521999	1.220177	0.949221
H	1.610602	1.206981	-0.825297
C	1.096980	-0.782968	0.041787
H	1.522002	-1.220174	0.949220
H	1.610604	-1.206977	-0.825297
C	-0.447994	1.000190	-0.047158
H	-0.806214	2.023972	-0.162537
N	-0.812057	-0.000000	-1.101373
C	-0.447991	-1.000191	-0.047158
H	-0.806210	-2.023974	-0.162537
C	-0.968328	-0.000001	0.966125
H	-0.946264	-0.000001	2.054541

13

3 Esp=-249.494666

C	1.184188	0.775805	0.044203
H	1.646061	1.199696	0.941296
H	1.694267	1.190583	-0.830501
C	1.184188	-0.775805	0.044203
H	1.646061	-1.199696	0.941297
H	1.694268	-1.190583	-0.830501
C	-0.313095	1.052602	-0.008278
H	-0.707746	2.057556	-0.124361
N	-1.019924	0.000000	-0.810678
C	-0.313096	-1.052602	-0.008278
H	-0.707746	-2.057556	-0.124362
C	-1.094121	-0.000000	0.671776
H	-2.014086	-0.000000	1.240131

19

4_diradicals Esp=-328.087383

C	0.947074	-1.099503	0.039729
C	-0.511022	-1.627278	0.119980
H	-0.677518	-1.982122	1.144154
H	-0.600909	-2.494588	-0.543350
C	-1.579372	-0.591536	-0.270192
H	-1.549699	-0.446285	-1.356712
H	-2.562373	-1.018203	-0.039286
N	1.090507	-0.156901	-1.107248
C	-1.451475	0.779738	0.415342
H	-1.303416	0.636444	1.492990
H	-2.395989	1.324008	0.298903
C	-0.323607	1.663557	-0.137422
H	-0.549772	1.966889	-1.166945
H	-0.248153	2.578129	0.462326
C	1.067194	0.980964	-0.141469
H	1.834371	1.736924	-0.363095
C	1.304294	0.014502	0.987491
H	2.068948	0.032278	1.757319
H	1.632446	-1.957828	-0.016319

19

4 Esp=-328.147364

C	0.933749	-1.121274	-0.100105
C	-0.502056	-1.617164	-0.113754
H	-0.513764	-2.550358	0.465209
H	-0.740894	-1.901954	-1.147813
C	-1.587500	-0.683944	0.415097
H	-2.553066	-1.196415	0.331700
H	-1.426305	-0.493322	1.484391

N	1.489601	0.078419	-0.800265
C	-1.628928	0.641114	-0.343007
H	-2.599555	1.130523	-0.201084
H	-1.533779	0.445028	-1.418720
C	-0.537906	1.614914	0.097289
H	-0.592663	2.511427	-0.532795
H	-0.744919	1.953538	1.122282
C	0.908097	1.138178	0.070051
H	1.581549	1.999840	0.070175
C	1.517510	-0.042478	0.714829
H	2.458790	-0.067686	1.255877
H	1.619613	-1.955630	-0.2697709

5_diradicals Esp=-171.973324

N	0.000000	-1.075714	-0.105066
C	-1.049057	-0.029816	0.040604
H	-1.795437	-0.051350	-0.770725
H	-1.612182	-0.161577	0.982436
C	-0.000000	1.042471	0.029120
C	1.049057	-0.029816	0.040604
H	1.612182	-0.161577	0.982436
H	1.795437	-0.051350	-0.770725
H	-0.000000	2.058820	-0.349928

9

5 Esp=-172.039214

N	0.000000	-0.391857	0.756932
C	-1.090586	-0.186518	-0.235608
H	-1.135631	-0.855198	-1.098955
H	-2.050571	0.047033	0.218205
C	0.000000	0.796835	-0.153313
C	1.090586	-0.186518	-0.235608
H	2.050571	0.047033	0.218205
H	1.135631	-0.855198	-1.098955
H	-0.000000	1.816532	0.210148

34

2_IM0 Esp=-1568.809743

C	2.780603	1.463032	0.502979
C	4.258598	1.808545	0.499700
C	5.110637	0.547653	0.326836
C	4.504058	-0.354306	-0.752268
C	2.996619	-0.440724	-0.599103
H	6.149624	0.800875	0.093546
H	4.445655	2.522084	-0.313516
H	4.511102	2.320327	1.435210
H	2.120938	2.230109	0.906989
H	4.728805	0.030624	-1.755664
H	4.929740	-1.362547	-0.696768
H	2.513774	-1.267651	-1.115602
H	5.116072	-0.001144	1.276009
N	2.171233	0.803960	-0.694271
C	2.299733	0.067724	0.602394
H	1.441812	-0.335036	1.126474
S	-1.287408	-1.843090	-0.439150
Cl	-0.715841	-2.303539	1.596095
O	-0.034803	-1.822711	-1.188659
O	-2.342667	-2.801337	-0.756383
C	-3.562351	3.725275	0.129413
C	-1.949481	-0.214712	-0.275566
C	-3.298192	-0.073484	0.060482
C	-3.807442	1.212446	0.194650
C	-2.991589	2.339865	0.005629
C	-1.640640	2.150757	-0.323878
C	-1.099770	0.876898	-0.465377
H	-3.929833	-0.941331	0.209431
H	-4.853774	1.345372	0.451018
H	-1.000145	3.015070	-0.471012
H	-0.049519	0.745333	-0.715938
H	-3.927348	4.073731	-0.844814
H	-4.406952	3.747148	0.823100
H	-2.805686	4.437486	0.469214

34

2_IM1 Esp=-1568.824482

C	-1.315090	-0.384644	1.339321
C	-2.366745	-1.149814	2.105085
C	-3.766828	-0.598596	1.808225
C	-3.957967	-0.328678	0.310628
C	-2.743688	0.354538	-0.269647
H	-4.534080	-1.284091	2.175092
H	-2.278010	-2.208610	1.839661
H	-2.131241	-1.061751	3.169989
H	-0.279296	-0.485796	1.651651
H	-4.133126	-1.251196	-0.252901
H	-4.819262	0.324047	0.139455

H	-2.838921	0.839617	-1.237376
H	-3.887268	0.347167	2.347597
N	-1.458406	-0.449782	-0.170467
C	-1.627278	0.848753	0.572073
H	-0.992847	1.725337	0.385598
S	-0.279147	-0.797971	-1.488359
Cl	0.035174	3.732680	-0.087932
O	-0.543474	-2.191456	-1.827131
O	-0.510325	0.277972	-2.446917
C	4.956872	-0.219381	1.457423
C	1.253878	-0.626194	-0.648486
C	1.777216	0.655538	-0.452134
C	2.974707	0.771227	0.244613
C	3.646194	-0.359102	0.735048
C	3.083473	-1.628850	0.523076
C	1.885259	-1.777247	-0.163145
H	1.256264	1.545472	-0.795854
H	3.391510	1.758957	0.414792
H	3.590915	-2.509568	0.903835
H	1.449868	-2.756661	-0.322540
H	5.790529	-0.352822	0.756812
H	5.059779	0.770910	1.908037
H	5.062799	-0.977969	2.237911

34

2_P-Cis Esp=-1568.863488

C	1.844793	-0.504767	-1.053210
C	0.757493	-1.545221	-1.315001
C	0.167395	-2.132833	0.003333
C	0.759083	-1.541883	1.319471
C	1.846142	-0.502181	1.053735
H	-0.913375	-1.977899	0.003775
H	-0.028777	-1.088364	-1.920220
H	1.201566	-2.338345	-1.925294
H	2.256729	-0.059917	-1.958732
H	-0.026458	-1.083410	1.924449
H	1.203816	-2.333475	1.931258
H	2.259274	-0.055120	1.957615
H	0.322103	-3.214098	0.004605
N	1.450265	0.481696	-0.000676
C	2.819944	-1.071252	0.000326
Cl	4.444861	-0.266748	-0.001707
S	0.218869	1.592487	-0.000695
O	0.352348	2.305729	1.278868
O	0.351270	2.304755	-1.280912
C	-5.224926	-1.135370	-0.001553
C	-1.393406	0.820623	0.000099
C	-2.009301	0.512644	-1.214938
C	-3.243633	-0.129810	-1.205301
C	-3.878110	-0.463096	0.001167
C	-3.244951	-0.126381	1.206306
C	-2.009705	0.516270	1.214920
H	-1.530903	0.777588	-2.150597
H	-3.725625	-0.373599	-2.147529
H	-3.727512	-0.367397	2.148830
H	-1.531986	0.783527	2.150274
H	-6.025659	-0.393014	-0.108365
H	-5.317488	-1.834800	-0.837438
H	-5.401168	-1.677968	0.930949
H	2.995205	-2.144992	0.001504

34

2_P-Trans Esp=-1568.866563

C	1.534463	0.175013	-1.056247
C	3.036592	0.295372	-1.302988
C	3.829131	0.010077	0.000213
C	3.036369	0.295487	1.303253
C	1.534282	0.175106	1.056268
H	4.093394	-1.050001	0.000282
H	3.332675	-0.416464	-2.078609
H	3.237031	1.298573	-1.690804
H	0.939697	0.051475	-1.961326
H	3.332320	-0.416279	2.078988
H	3.236740	1.298723	1.691015
H	0.939364	0.051656	1.961260
H	4.768750	0.568956	0.000268
N	1.351945	-0.898419	0.000041
C	1.031518	1.175976	-0.000077
S	0.010195	-1.900658	-0.000063
O	0.067928	-2.624015	-1.277726
O	0.067849	-2.624214	1.277490
C	-4.858780	1.738149	0.000068
C	-1.468085	-0.904546	-0.000028
C	-2.008612	-0.481929	1.217105

C	-3.101160	0.380270	1.206463
C	-3.661184	0.826489	0.000033
C	-3.101088	0.380447	-1.206427
C	-2.008539	-0.481754	-1.217130
H	-1.582577	-0.826458	2.152241
H	-3.527354	0.712806	2.148302
H	-3.527224	0.713122	-2.148243
H	-1.582443	-0.826140	-2.152290
H	-4.873803	2.375044	0.888798
H	-4.873932	2.374942	-0.888731
H	-5.786902	1.153075	0.000174
Cl	1.673089	2.873283	-0.000093
H	-0.050652	1.271495	-0.000176

34

2_TS1 Esp=-1568.779035

C	-2.923584	-0.411761	-1.119803
C	-3.848016	0.774425	-1.279244
C	-4.696417	0.971215	-0.016669
C	-3.843329	0.823408	1.249446
C	-2.919983	-0.368539	1.132731
H	-5.197278	1.942895	-0.034632
H	-3.233768	1.657252	-1.489022
H	-4.485280	0.606393	-2.153172
H	-2.465170	-0.822537	-2.015120
H	-3.227580	1.713258	1.421897
H	-4.477355	0.690256	2.131679
H	-2.459036	-0.744995	2.041754
H	-5.477461	0.202519	-0.000308
N	-1.959700	-0.366812	0.004671
C	-3.047964	-1.363971	0.025294
H	-2.867661	-2.430543	0.045558
S	0.042353	-0.854410	0.011720
O	-0.121740	-1.503121	1.327127
O	-0.122031	-1.538400	-1.285687
C	5.961220	0.634089	-0.011027
C	1.794750	-0.370447	0.004408
C	2.442505	-0.213702	-1.217042
C	3.795849	0.115691	-1.208634
C	4.493226	0.300932	-0.005863
C	3.797206	0.147103	1.202073
C	2.443854	-0.181812	1.220603
H	1.908459	-0.349154	-2.149246
H	4.317627	0.232611	-2.153951
H	4.320027	0.288610	2.143447
H	1.910821	-0.292529	2.156614
H	6.237532	1.199494	-0.905355
H	6.240028	1.216105	0.871763
H	6.564727	-0.282248	-0.003438
Cl	-0.194947	1.800191	-0.018696

34

2_TS2-Cis Esp=-1568.786419

C	1.615274	1.078592	1.095575
C	0.646185	2.244026	1.283750
C	0.585583	3.094171	-0.000278
C	0.645529	2.243444	-1.283948
C	1.614737	1.078112	-1.095750
H	-0.305980	3.726019	-0.000194
H	-0.328458	1.814713	1.537819
H	0.972358	2.853345	2.131598
H	1.948258	0.573836	2.000191
H	-0.329241	1.813998	-1.537300
H	0.971236	2.852381	-2.132248
H	1.947301	0.572967	-2.000302
H	1.452584	3.765710	-0.000649
N	1.157718	0.165002	0.000226
C	2.623051	1.219531	-0.000370
H	3.697971	1.283090	-0.000653
S	0.411728	-1.355038	0.000803
Cl	4.218415	-1.004100	-0.000972
O	0.744505	-1.976053	-1.280235
O	0.744306	-1.974785	1.282517
C	-5.403487	0.375968	-0.000841
C	-1.308968	-0.911637	0.000384
C	-1.956798	-0.699820	1.219518
C	-3.281714	-0.275291	1.207129
C	-3.962690	-0.057082	-0.000407
C	-3.281486	-0.276823	-1.207537
C	-1.956571	-0.701372	-1.219142
H	-1.435585	-0.866262	2.155280
H	-3.796969	-0.110122	2.148486
H	-3.796562	-0.112839	-2.149198
H	-1.435175	-0.869022	-2.154587

H	-6.065564	-0.498915	-0.000656
H	-5.641814	0.966436	0.888012
H	-5.641437	0.965738	-0.890262

34

2_TS2-Trans Esp=-1568.821766

C	2.005031	-0.563281	-1.191385
H	1.576246	-0.863473	-2.140405
C	3.110877	0.276289	-1.139999
H	3.546999	0.637722	-2.065645
C	3.670422	0.666300	0.087201
C	3.097339	0.190113	1.277084
H	3.522073	0.485227	2.231187
C	1.992275	-0.651980	1.256019
H	1.552309	-1.017070	2.176625
C	-1.369599	0.604496	0.611382
H	-0.414346	0.932359	1.005972
C	1.460019	-1.016733	0.014769
C	-2.437538	-0.653474	-0.965219
H	-2.324779	-1.317363	-1.817510
S	0.023740	-2.029955	-0.029138
N	-1.300219	-0.822463	0.032248
O	-0.149855	-2.657519	-1.336331
C	-3.802019	-0.520552	-0.333659
H	-4.008615	-1.439164	0.225631
H	-4.536882	-0.460798	-1.142242
O	-0.134004	-2.778650	1.211689
C	-1.412768	0.407973	-0.845442
H	-0.641813	0.666348	-1.557641
C	-3.869078	0.725039	0.559278
H	-4.764200	0.698673	1.184844
H	-3.942800	1.607961	-0.084383
C	4.879465	1.558196	0.126236
H	4.915814	2.215468	-0.746346
H	5.795409	0.954314	0.123190
H	4.892474	2.169442	1.032386
C	-2.611322	0.870187	1.424342
H	-2.525800	1.887470	1.813733
H	-2.616666	0.183726	2.277477
Cl	-1.018323	3.707623	-0.386053

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5_IM0 Esp=-1452.017483

C	-4.987276	-0.259515	0.640486
C	-4.251676	1.233224	-0.779507
H	-4.832490	-1.098989	1.314299
H	-3.449307	1.699445	-1.344331
N	-4.006019	-0.206232	-0.481249
C	-3.985772	0.816603	0.605336
H	-3.115911	0.984306	1.224887
S	-0.325725	-0.148619	-0.465956
Cl	-0.894392	-1.171336	1.342857
O	-0.613000	-1.080021	-1.552024
O	-0.961815	1.164217	-0.393632
C	5.649742	0.412315	0.283759
C	1.421482	0.013116	-0.241939
C	1.913293	1.141993	0.416014
C	3.288444	1.255114	0.586026
C	4.162942	0.262217	0.117263
C	3.627093	-0.861882	-0.530669
C	2.256072	-1.001585	-0.714079
H	1.241646	1.910185	0.780559
H	3.690943	2.127495	1.091106
H	4.293228	-1.637477	-0.895287
H	1.845525	-1.871412	-1.213220
H	6.079520	0.923010	-0.586986
H	5.892495	1.008931	1.166983
H	6.140477	-0.561000	0.367543
H	-5.265191	1.529370	-1.058681
H	-6.030061	-0.022801	0.417709

27

5_IM1 Esp=-1452.024996

S	0.440683	-1.704804	0.003979
O	0.664191	-2.376028	-1.270976
O	0.666409	-2.367632	1.282978
C	-4.663531	1.513910	0.000152
C	-1.055233	-0.785718	0.002208
C	-1.608706	-0.398141	1.226669
C	-2.775224	0.355670	1.209639
C	-3.385078	0.723712	-0.000656
C	-2.795049	0.321042	-1.209067
C	-1.627989	-0.433072	-1.223347
H	-1.141095	-0.680936	2.162523
H	-3.221329	0.665134	2.149338

H	-3.256585	0.603038	-2.149908
H	-1.175314	-0.742444	-2.158090
H	-4.707117	2.196212	0.853314
H	-4.775469	2.089882	-0.921882
H	-5.525057	0.838824	0.075580
Cl	2.332230	3.389571	-0.009777
C	2.517486	0.103519	1.135220
C	2.516331	0.098133	-1.139083
H	2.379471	-0.461713	2.051345
H	2.377574	-0.471394	-2.052430
N	1.642562	-0.366368	-0.000419
C	3.136700	-0.605055	-0.000556
H	3.535322	-1.611877	0.001614
H	2.554324	1.186834	-1.191336
H	2.555479	1.192452	1.182306

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5_P-Cis Esp=-1452.086060

C	1.764512	-0.437002	1.072486
H	0.818535	-0.791712	1.495115
H	2.445721	-0.134325	1.867628
O	0.378408	2.367765	-1.278709
Cl	4.100671	-1.579309	-0.000133
N	1.596804	0.586437	-0.000007
S	0.301212	1.648656	0.000062
C	2.292848	-1.407064	-0.000064
H	1.886230	-2.414183	-0.000063
O	0.378490	2.367670	1.278882
C	1.764432	-0.436968	-1.072546
C	-1.186142	0.668910	0.000069
C	-1.739662	0.260311	-1.216803
H	-1.307634	0.595796	-2.152544
C	-2.860378	-0.565381	-1.206069
H	-3.297129	-0.883290	-2.148087
C	-3.436168	-0.990976	0.000071
C	-2.860051	-0.565865	1.206157
H	-3.296527	-0.884140	2.148170
C	-1.739311	0.259882	1.216898
H	-1.307071	0.595027	2.152664
C	-4.665397	-1.859647	-0.000082
H	-5.572249	-1.242217	-0.006400
H	-4.705933	-2.491272	0.891580
H	-4.699671	-2.499746	-0.885997
H	0.818425	-0.791659	-1.495123
H	2.445589	-0.134266	-1.867723

27

5_P-Trans Esp=-1452.086956

C	-2.040899	0.384454	-1.076563
H	-2.731304	0.131174	-1.881245
H	-1.065263	0.669362	-1.481795
O	-0.854182	-2.507653	-1.280544
Cl	-1.787896	3.006519	0.001934
N	-1.959004	-0.649995	-0.001573
S	-0.730676	-1.796268	-0.001223
C	-2.540879	1.363675	-0.000116
H	-3.617825	1.513780	-0.000832
O	-0.857245	-2.509804	1.276571
C	-2.042547	0.382390	1.075200
C	0.815874	-0.914072	0.001160
C	1.396967	-0.542429	-1.215972
H	0.944864	-0.849344	-2.152018
C	2.572343	0.200958	-1.203432
H	3.034016	0.484128	-2.144825
C	3.175544	0.585169	0.004644
C	2.573388	0.196248	1.208751
H	3.034414	0.475217	2.151334
C	1.395995	-0.548608	1.217933
H	0.944596	-0.859029	2.153174
C	4.437296	1.405884	-0.002013
H	4.226170	2.435491	-0.315007
H	5.168598	0.998833	-0.707582
H	4.894133	1.443426	0.989992
H	-2.734045	0.127650	1.878472
H	-1.067350	0.666385	1.482265

27

5_TS1 Esp=-1451.983254

S	0.769937	-0.644134	0.041287
O	1.025581	-1.362787	-1.219069
O	1.028348	-1.191885	1.384016
C	-5.271071	0.146917	-0.014401
C	-1.018444	-0.354916	0.021175
C	-1.682308	-0.183885	1.232714
C	-3.064513	-0.021247	1.206537

C	-3.774399	-0.009280	-0.003772
C	-3.061366	-0.167630	-1.201269
C	-1.678790	-0.332669	-1.203638
H	-1.138642	-0.184092	2.169043
H	-3.600085	0.101517	2.143257
H	-3.594472	-0.159295	-2.147266
H	-1.133143	-0.446835	-2.131834
H	-5.611268	0.774136	0.814386
H	-5.618509	0.586472	-0.953245
H	-5.760312	-0.829383	0.092728
Cl	0.640325	2.095323	-0.112964
C	3.611623	0.355604	1.091691
C	3.609547	0.191769	-1.146202
H	3.248213	-0.019794	2.042759
H	3.243721	-0.317978	-2.031610
N	2.665932	0.146774	-0.016782
C	3.913487	-0.647992	0.039792
H	3.922268	-1.726723	0.119120
H	4.120095	1.140972	-1.296485
H	4.122073	1.316580	1.101080

27

5_TS2-Cis Esp=-1451.993686

C	1.897424	1.671357	1.102891
C	1.800486	1.699937	-1.108139
H	2.184331	1.034687	1.938671
H	2.012095	1.085594	-1.982707
N	1.058711	1.023880	0.023145
C	2.828117	1.694757	-0.045757
H	3.854408	1.344707	-0.093111
S	0.536067	-0.621815	0.020336
Cl	4.283922	-0.833714	-0.020645
O	0.933440	-1.203982	-1.260452
O	0.926252	-1.187875	1.310619
C	-5.460815	0.293693	-0.017253
C	-1.221317	-0.369698	0.009343
C	-1.897921	-0.233686	1.224558
C	-3.270164	-0.010932	1.202496
C	-3.971656	0.080273	-0.010231
C	-3.261187	-0.056729	-1.211957
C	-1.887847	-0.280357	-1.214571
H	-1.361969	-0.307076	2.163841
H	-3.807958	0.093487	2.139934
H	-3.791386	0.011697	-2.156854
H	-1.344542	-0.389965	-2.145965
H	-5.771732	0.947343	0.802734
H	-5.796290	0.729199	-0.961983
H	-5.984516	-0.661684	0.111647
H	1.452584	2.616961	1.419582
H	1.332007	2.653235	-1.361817

27

5_TS2-Trans Esp=-1452.022749

C	1.800742	0.558404	-1.559458
C	1.815980	-1.524450	-0.663763
H	1.787675	1.629385	-1.383865
H	1.814847	-2.133919	0.234140
N	1.036818	-0.241194	-0.536412
C	2.576612	-0.266653	-0.621561
H	3.213542	0.083128	0.180909
S	0.176360	0.374887	0.912737
Cl	5.706620	-0.080913	-0.256934
O	0.542587	-0.571647	1.959637
O	0.549007	1.783369	0.969014
C	-5.558664	-0.337722	-0.832595
C	-1.496219	0.171141	0.414044
C	-2.146331	1.237246	-0.213731
C	-3.462652	1.055662	-0.621653
C	-4.125331	-0.164051	-0.414591
C	-3.435877	-1.213960	0.214125
C	-2.120627	-1.061078	0.633663
H	-1.638573	2.181335	-0.372212
H	-3.985557	1.873130	-1.107512
H	-3.938885	-2.161853	0.377153
H	-1.594281	-1.873051	1.121760
H	-6.226667	-0.127789	0.011942
H	-5.823104	0.347575	-1.641718
H	-5.755446	-1.363333	-1.156536
H	1.609958	0.218839	-2.573868
H	1.625919	-2.028759	-1.607306

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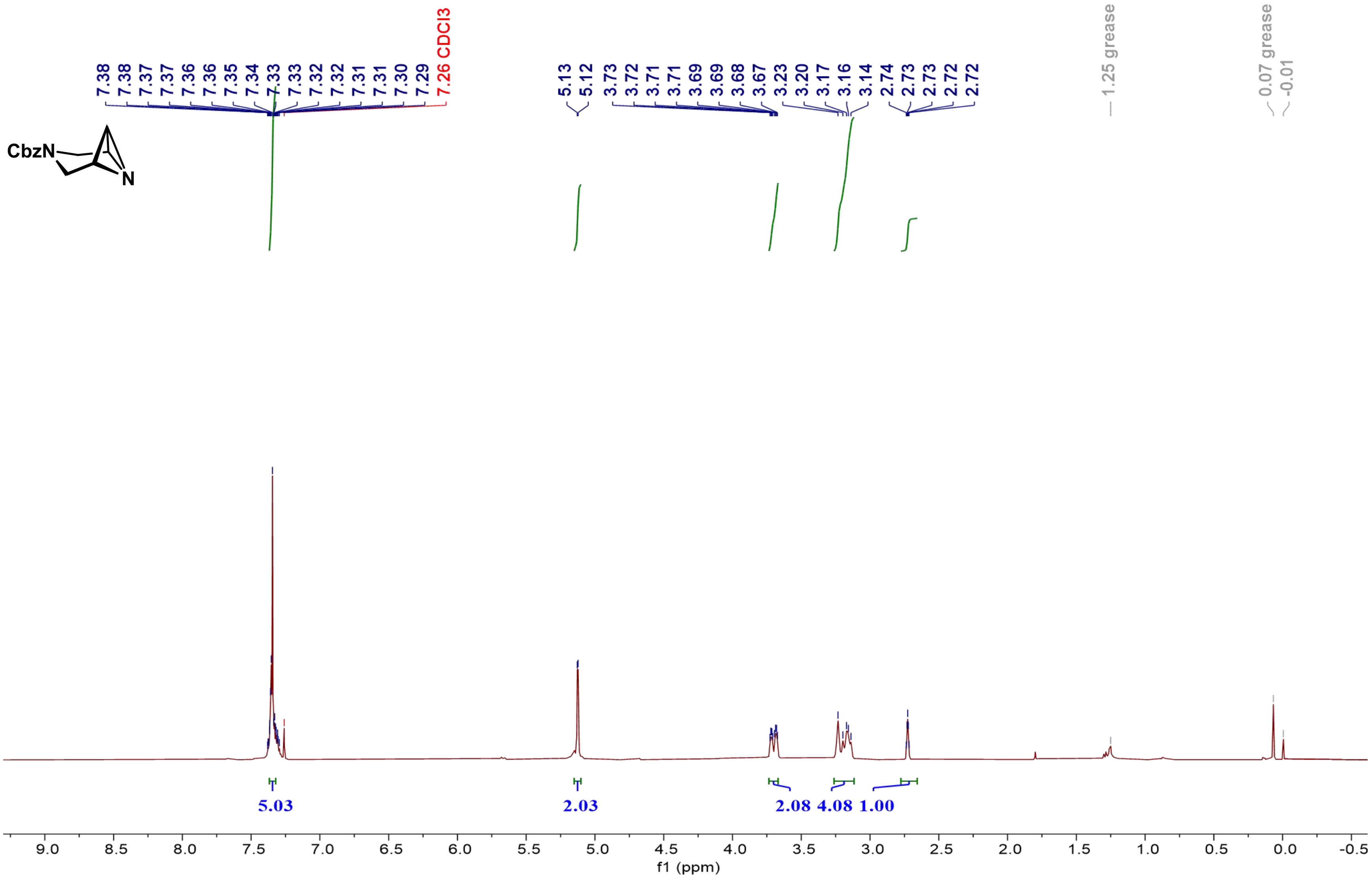
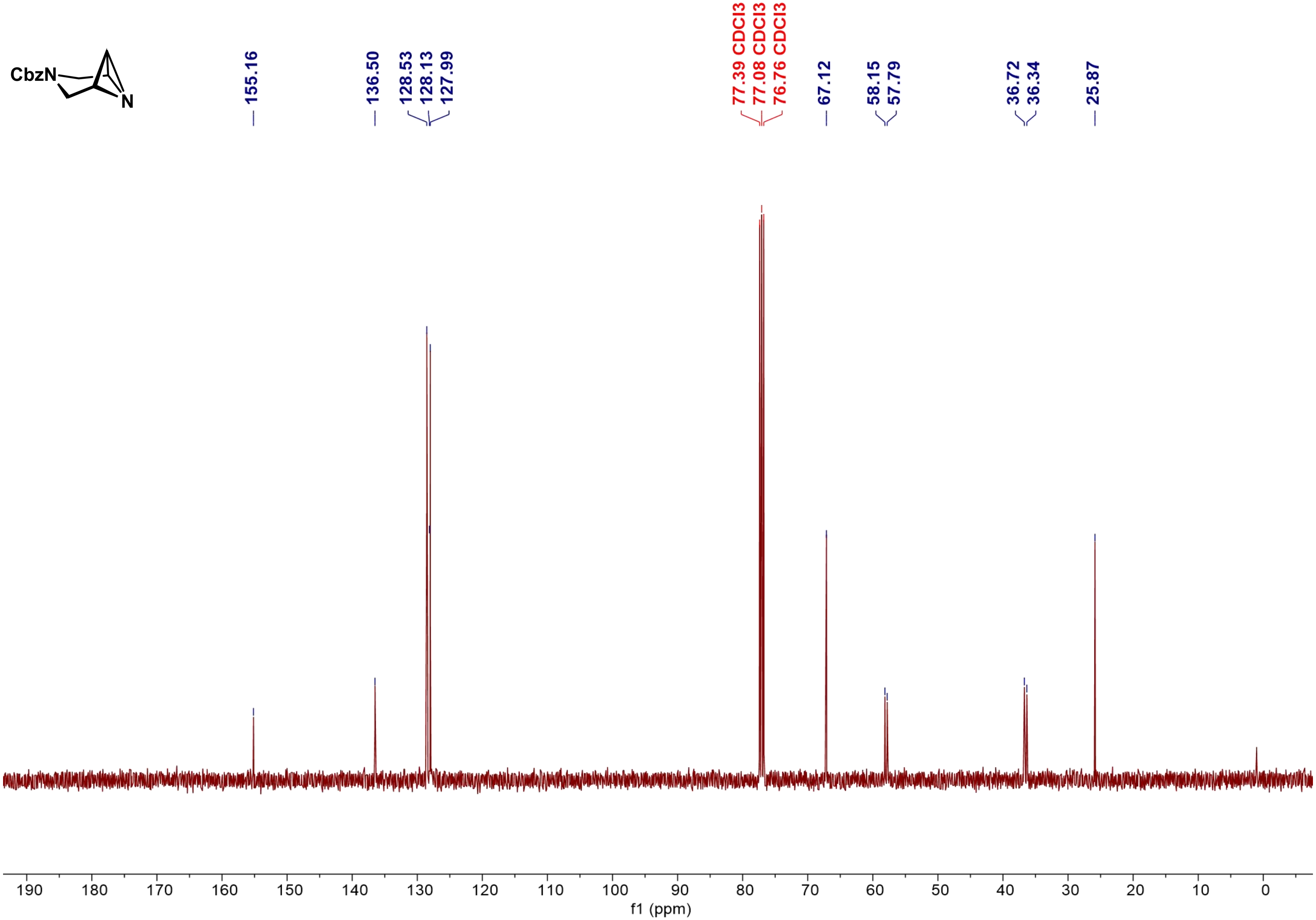
NMR Spectra

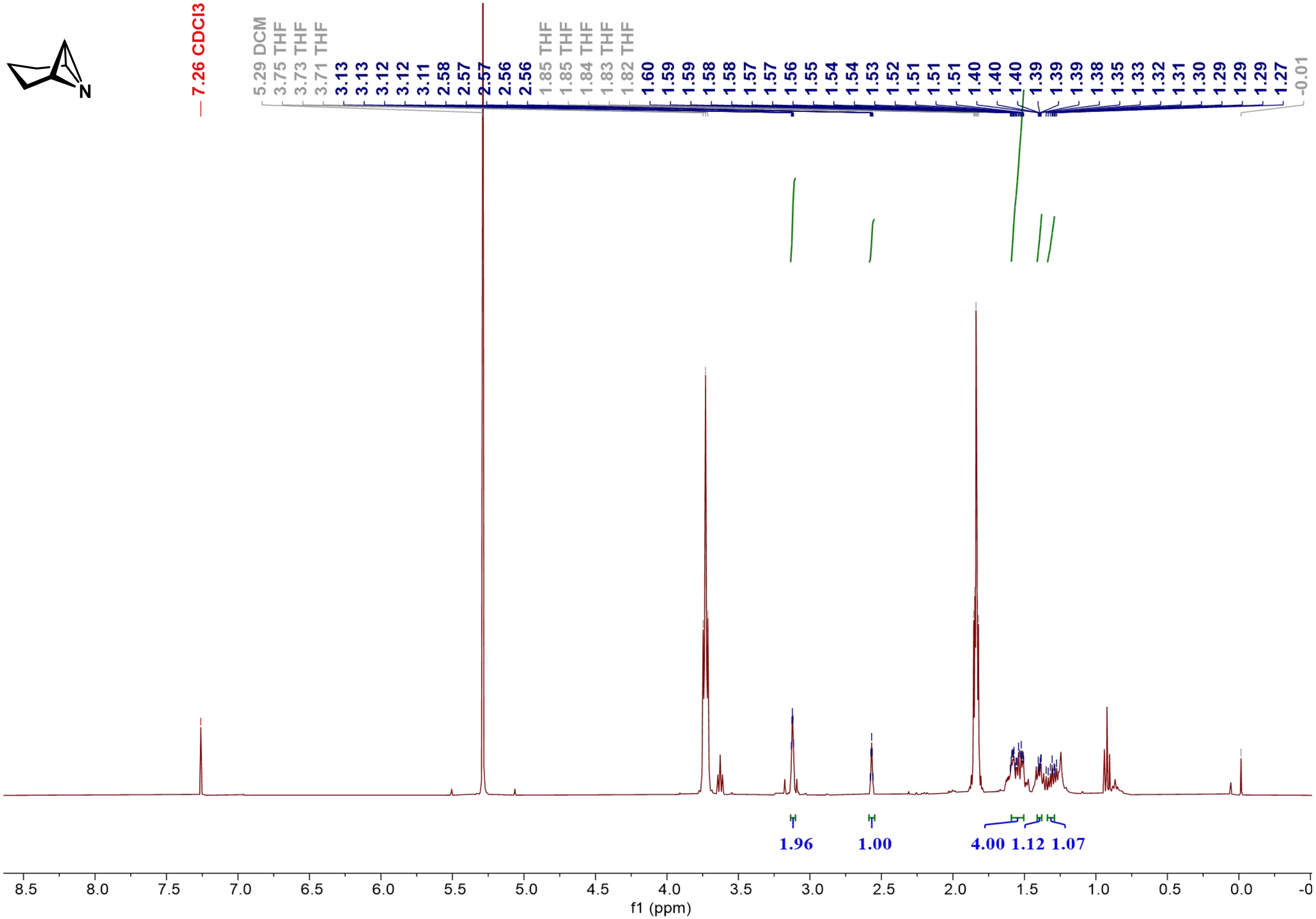
^{1}H NMR Spectrum of compound 1 (400 MHz, $CDCl_3$)



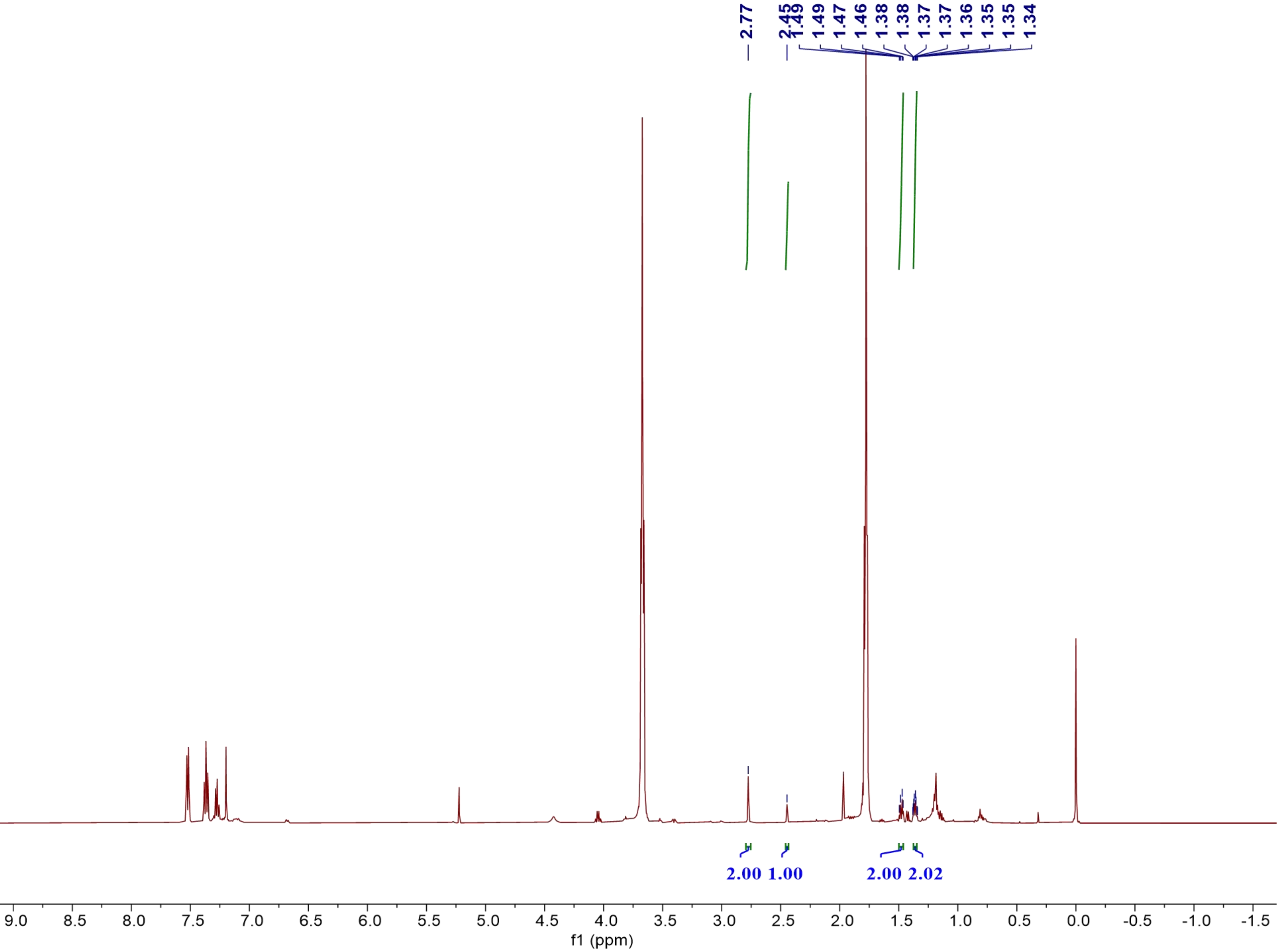
^{13}C NMR Spectrum of compound 1 (101 MHz, $CDCl_3$)



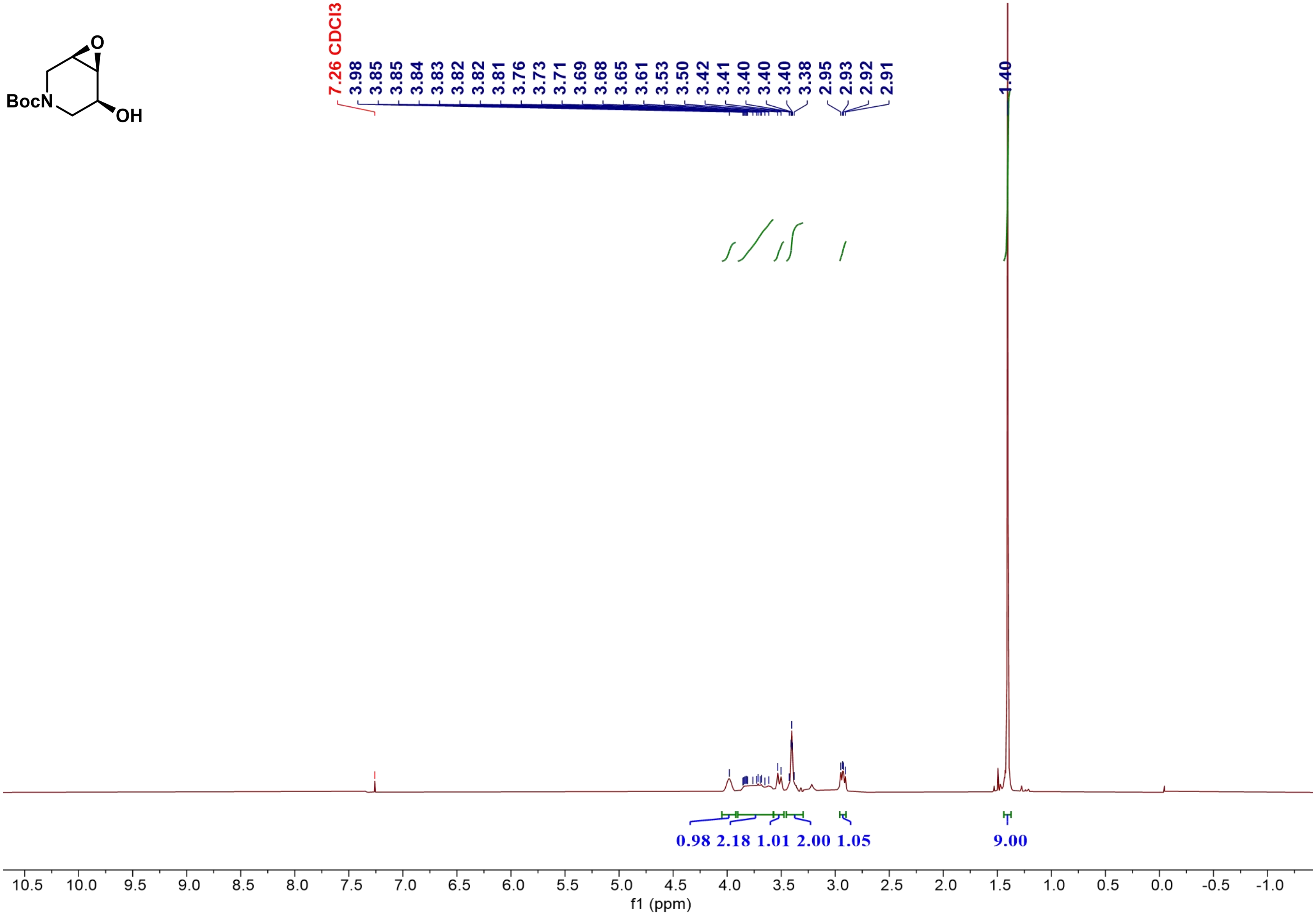
^{1}H NMR Spectrum of compound 2 (400 MHz, CDCl$_3$)



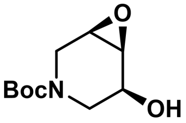
^{1}H NMR Spectrum of compound 3 (500 MHz, $CDCl_3$)

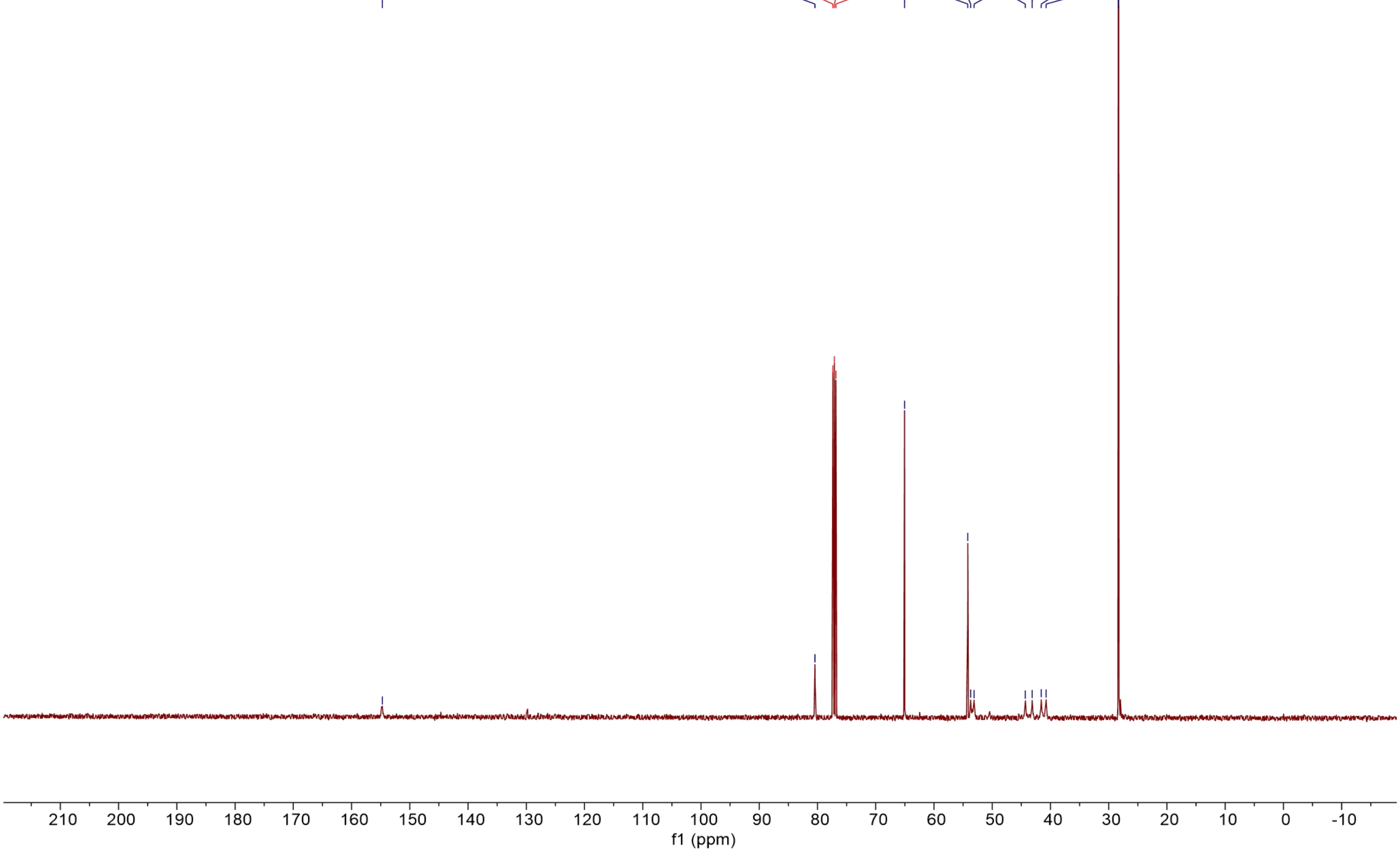


^{1}H NMR Spectrum of compound 7 (500 MHz, $CDCl_3$)

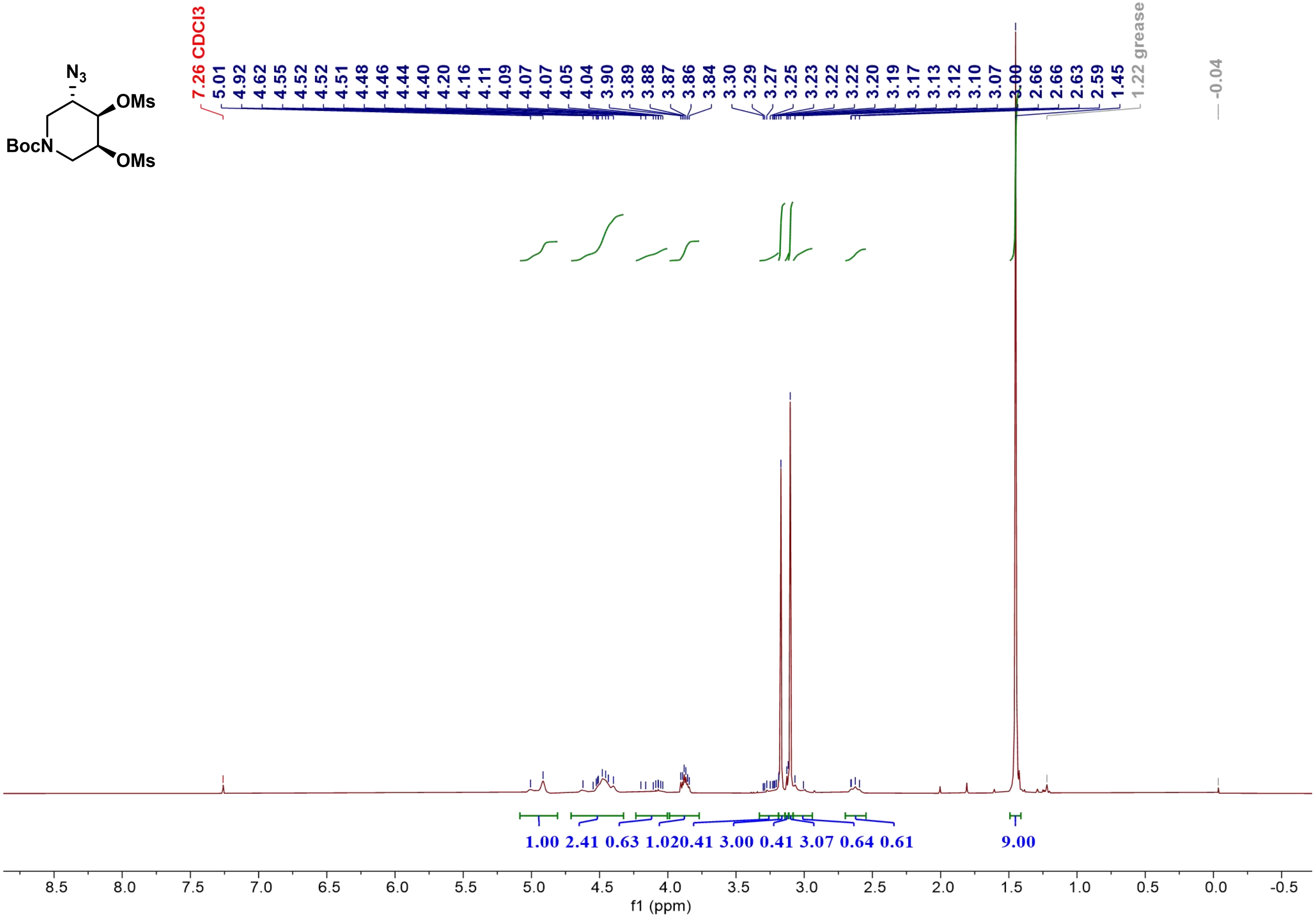


^{13}C NMR Spectrum of compound 7 (126 MHz, CDCl$_3$)

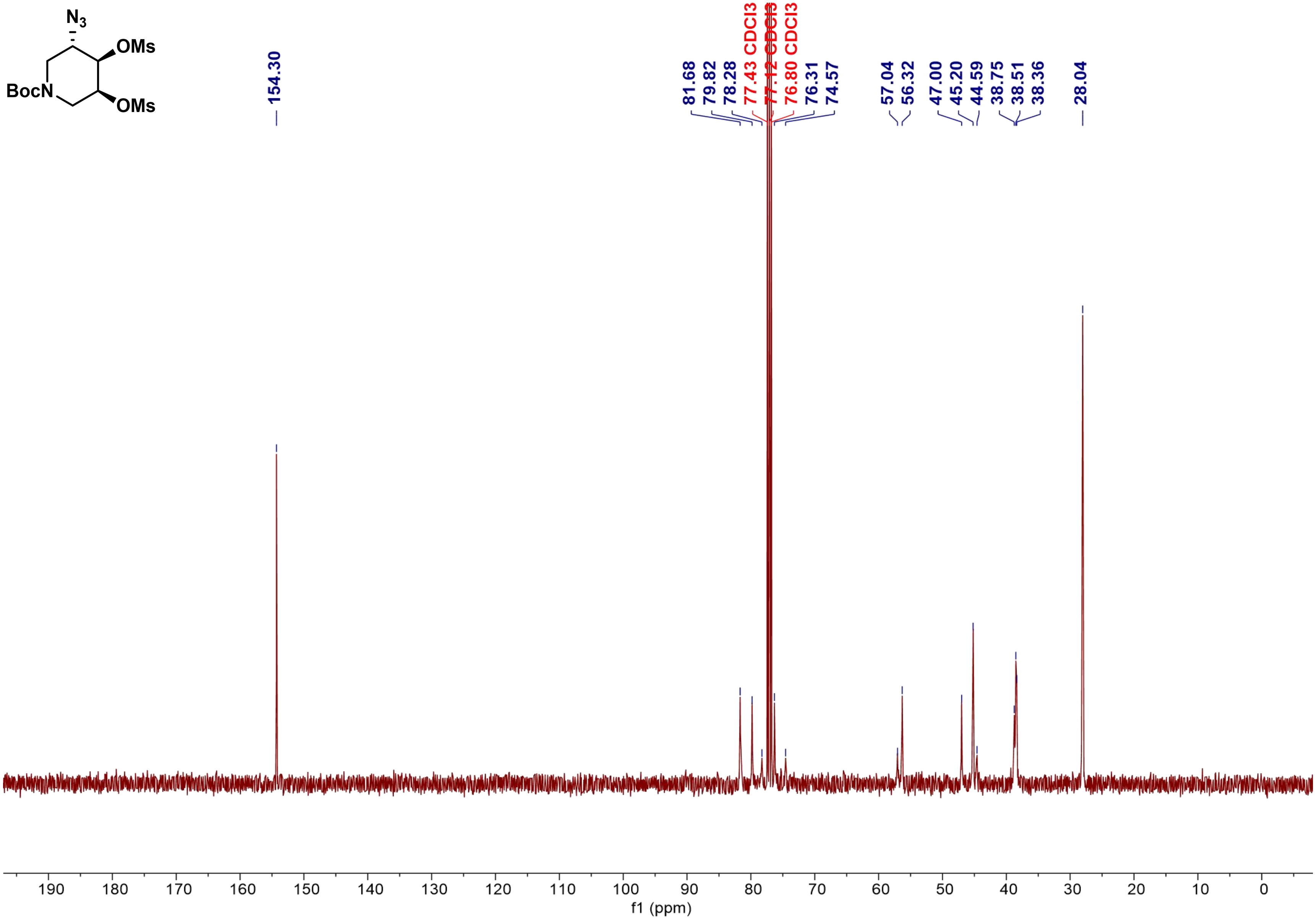




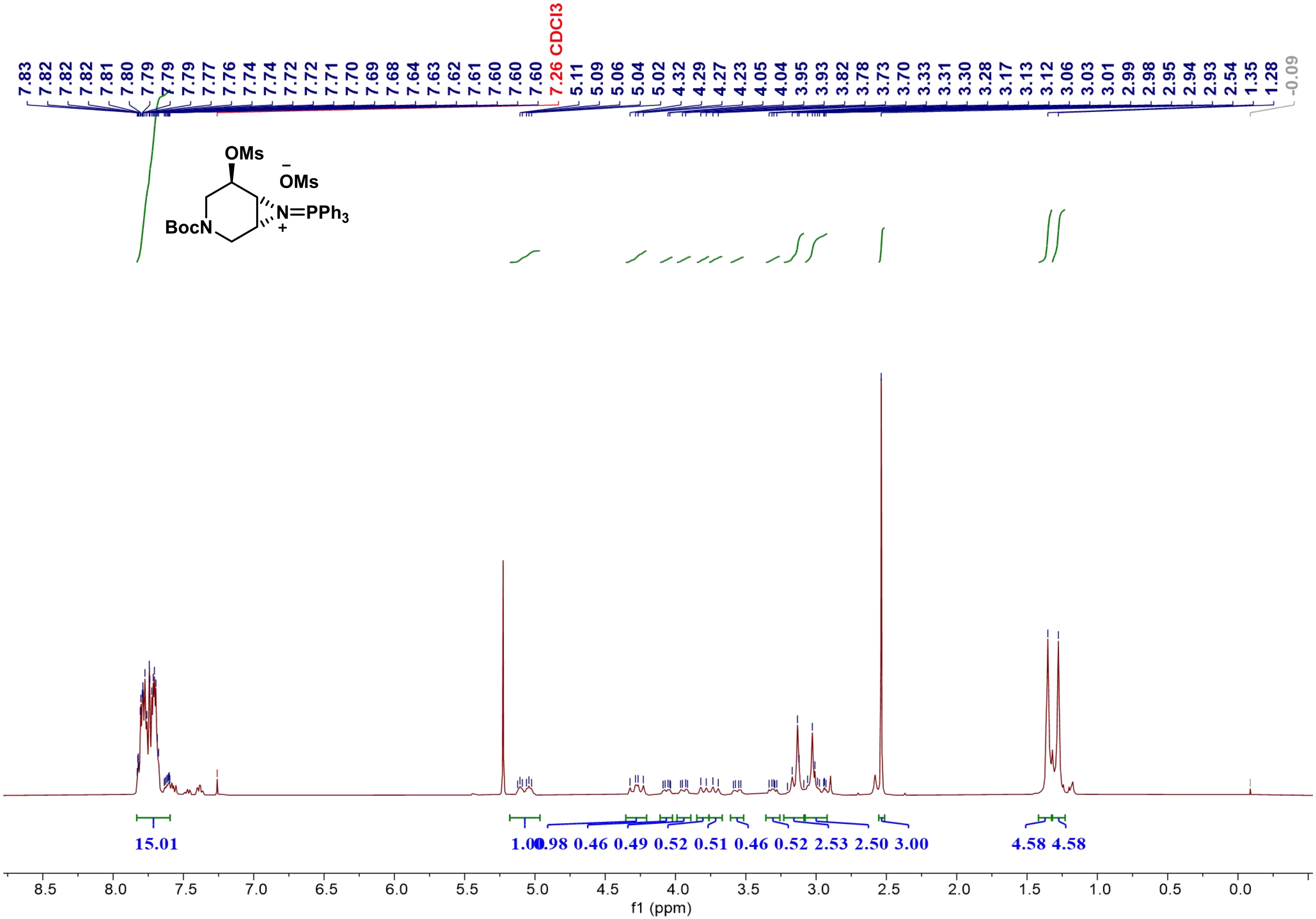
^{1}H NMR Spectrum of compound 8 (400 MHz, $CDCl_3$)



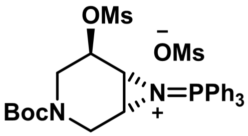
^{13}C NMR Spectrum of compound 8 (101 MHz, CDCl$_3$)

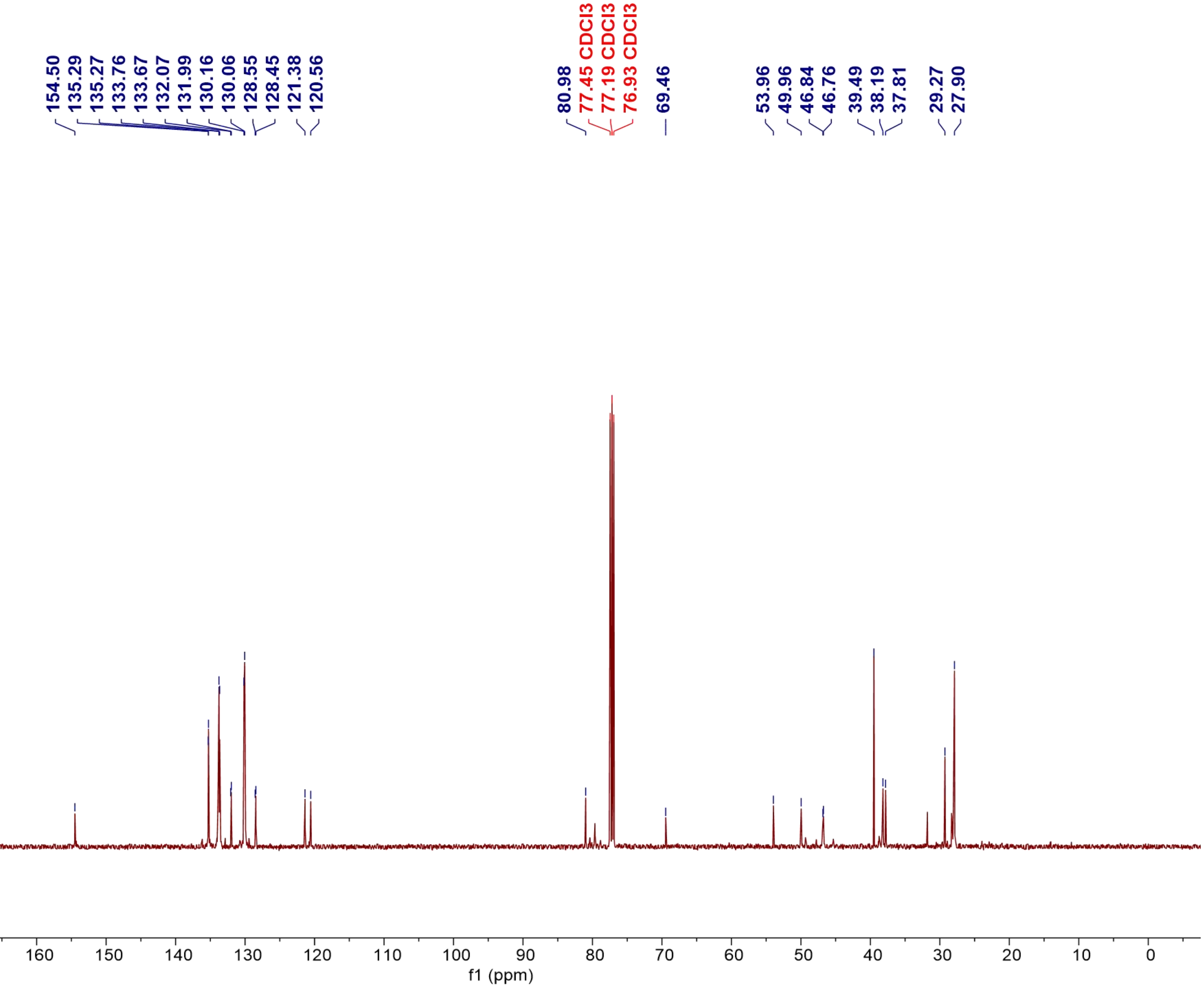


^{1}H NMR Spectrum of compound 9 (400 MHz, $CDCl_3$)

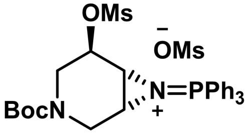


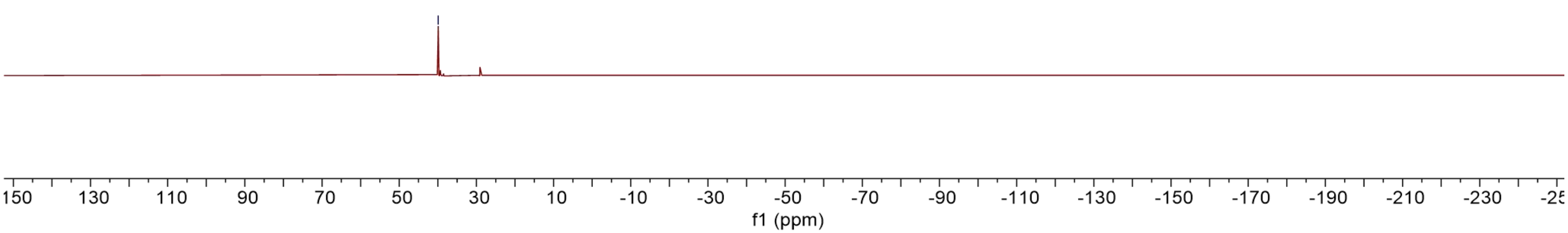
^{13}C NMR Spectrum of compound 9 (126 MHz, CDCl$_3$)



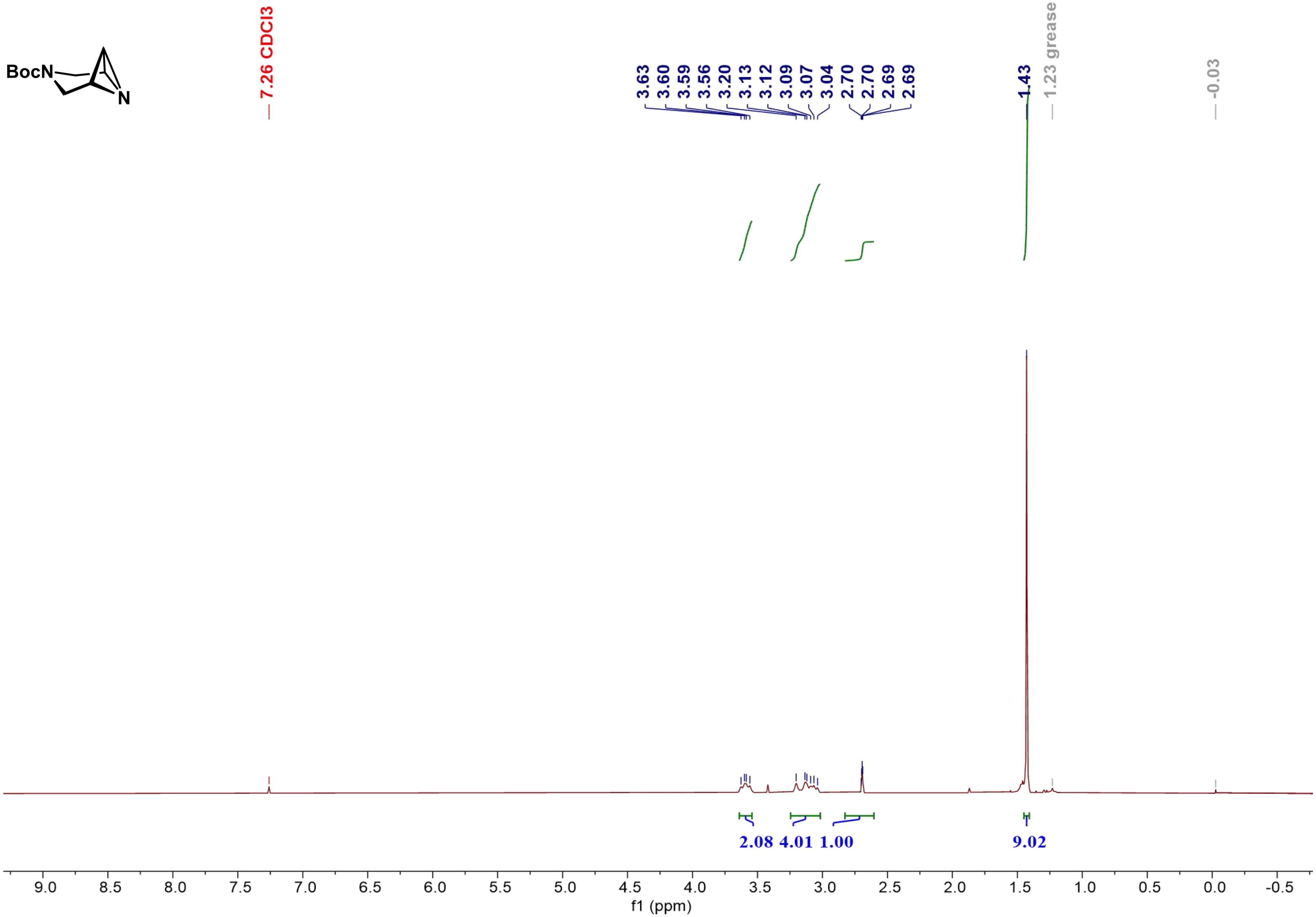


^{31}P NMR Spectrum of compound 9 (202 MHz, CDCl$_3$)

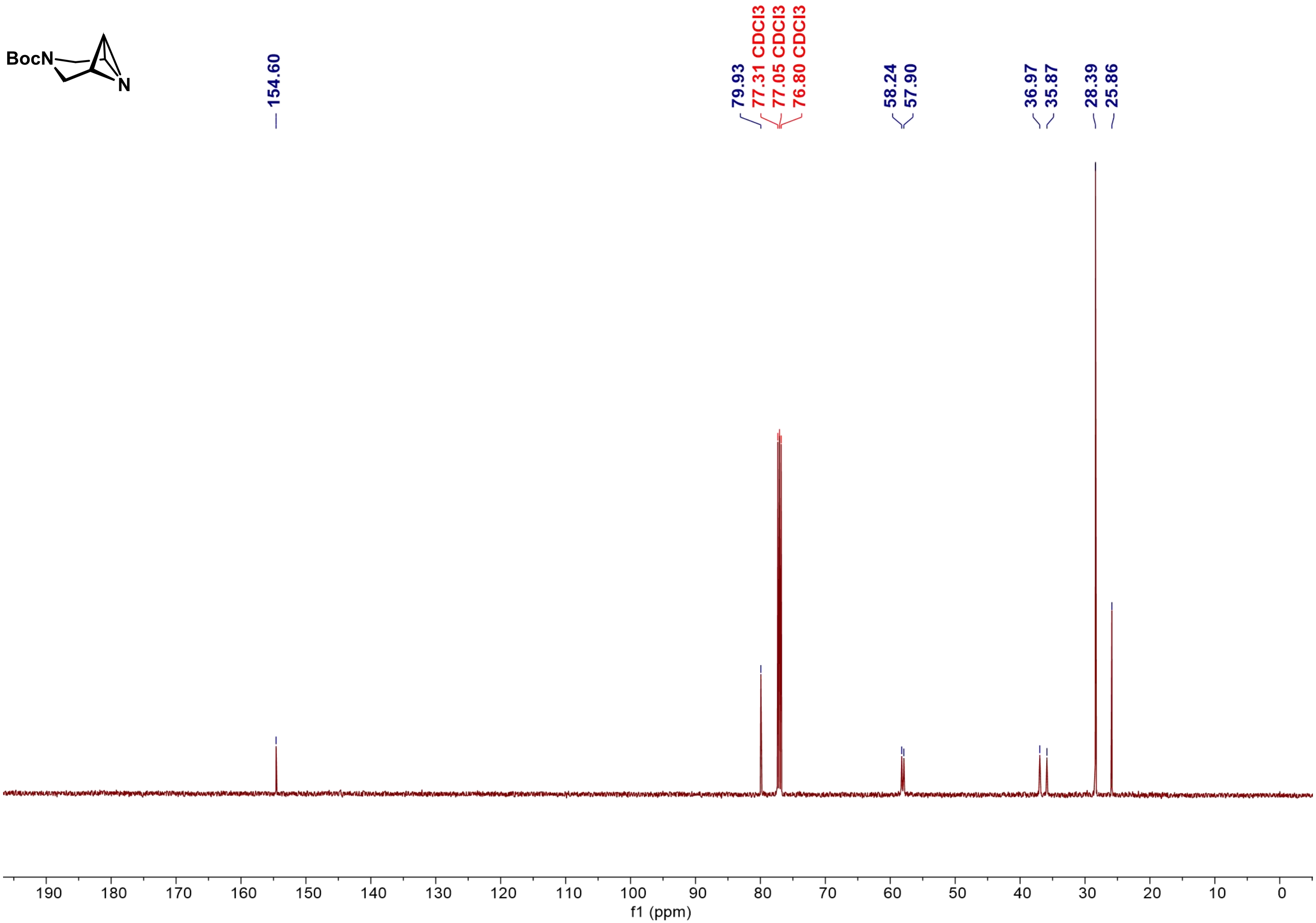




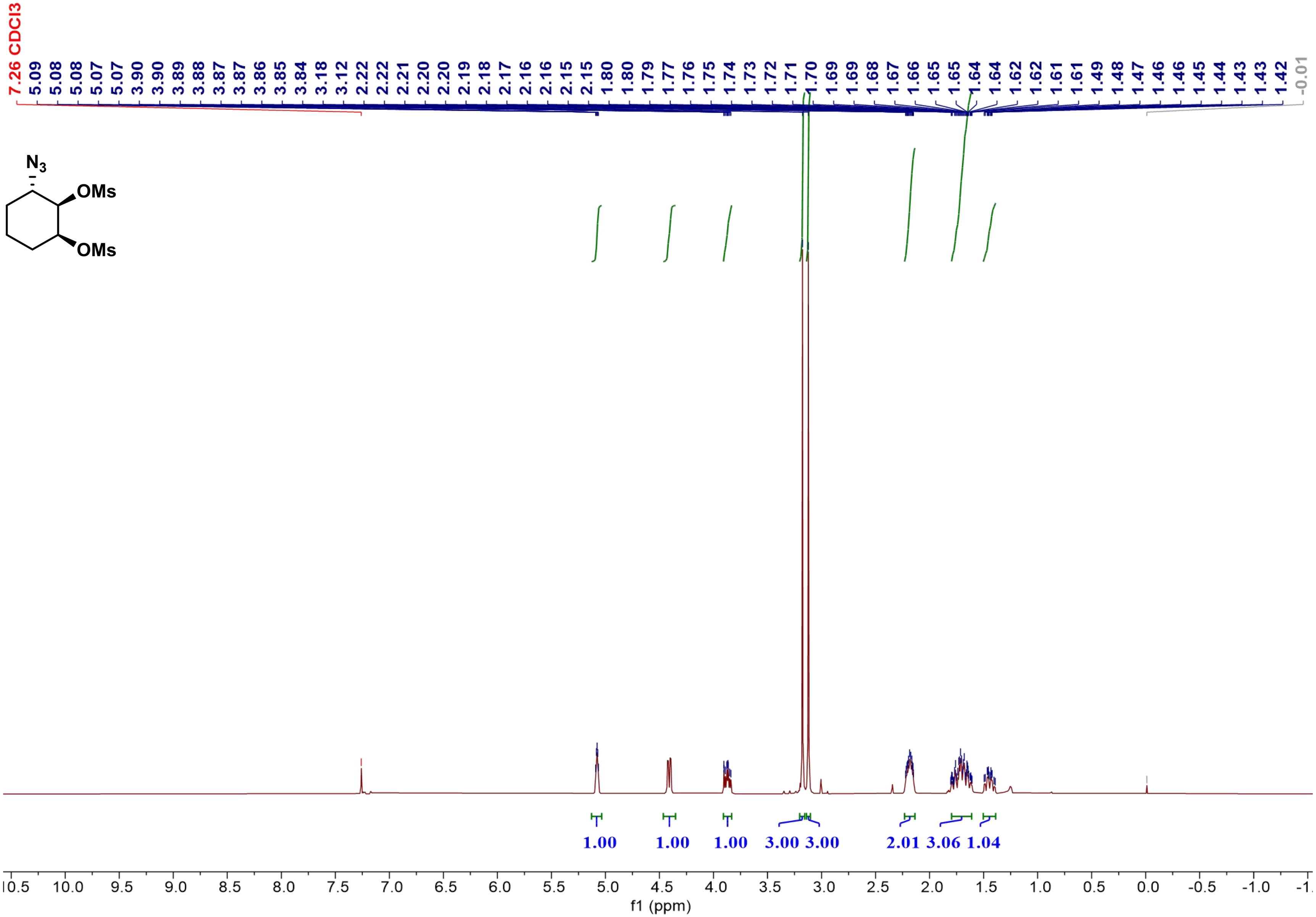
^{1}H NMR Spectrum of compound 10 (500 MHz, CDCl$_3$)



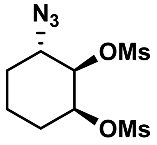
^{13}C NMR Spectrum of compound 10 (126 MHz, $CDCl_3$)

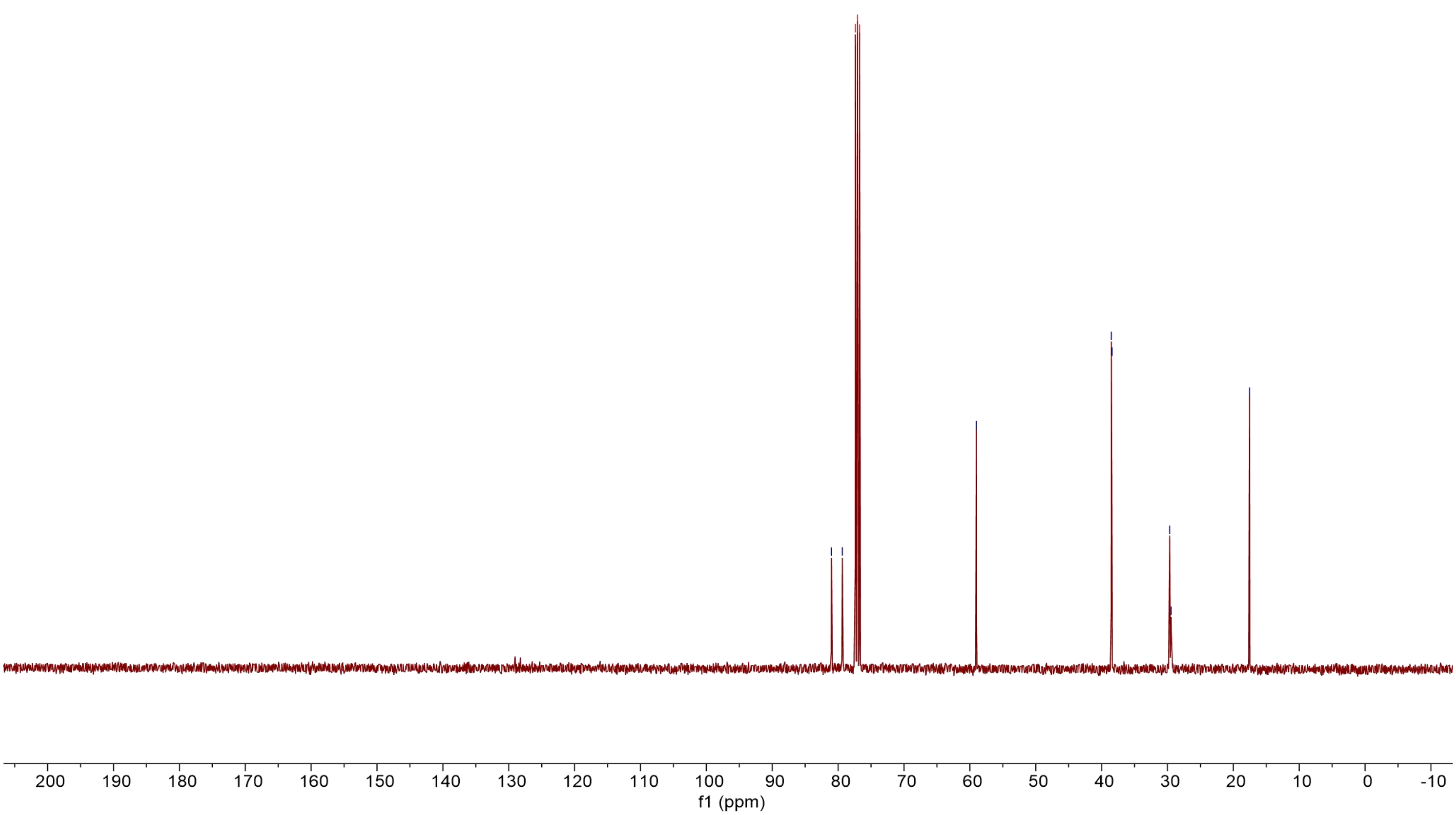


^{1}H NMR Spectrum of compound SI-94 (400 MHz, $CDCl_3$)

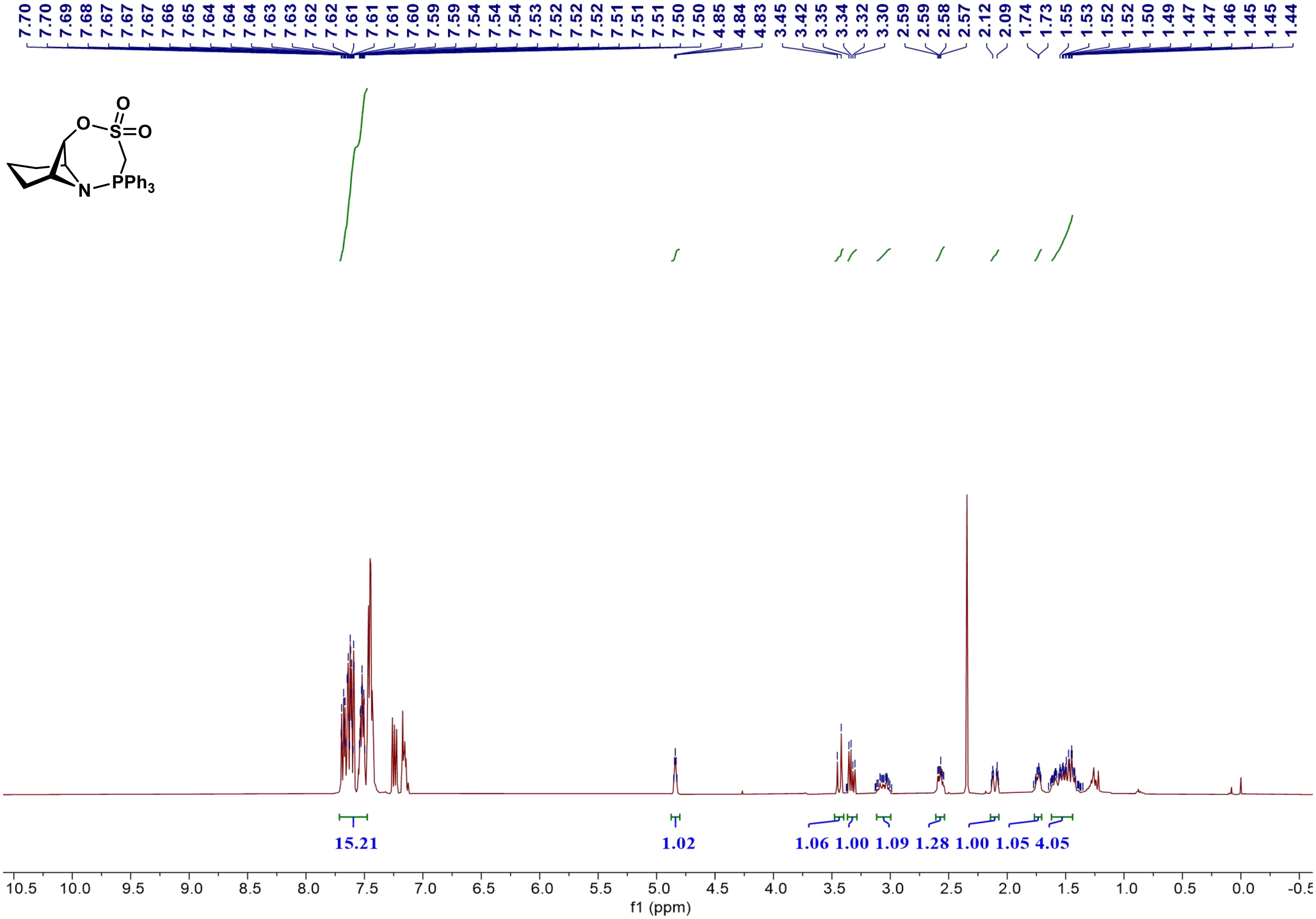


^{13}C NMR Spectrum of compound SI-94 (101 MHz, CDCl$_3$)

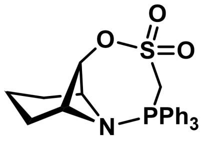


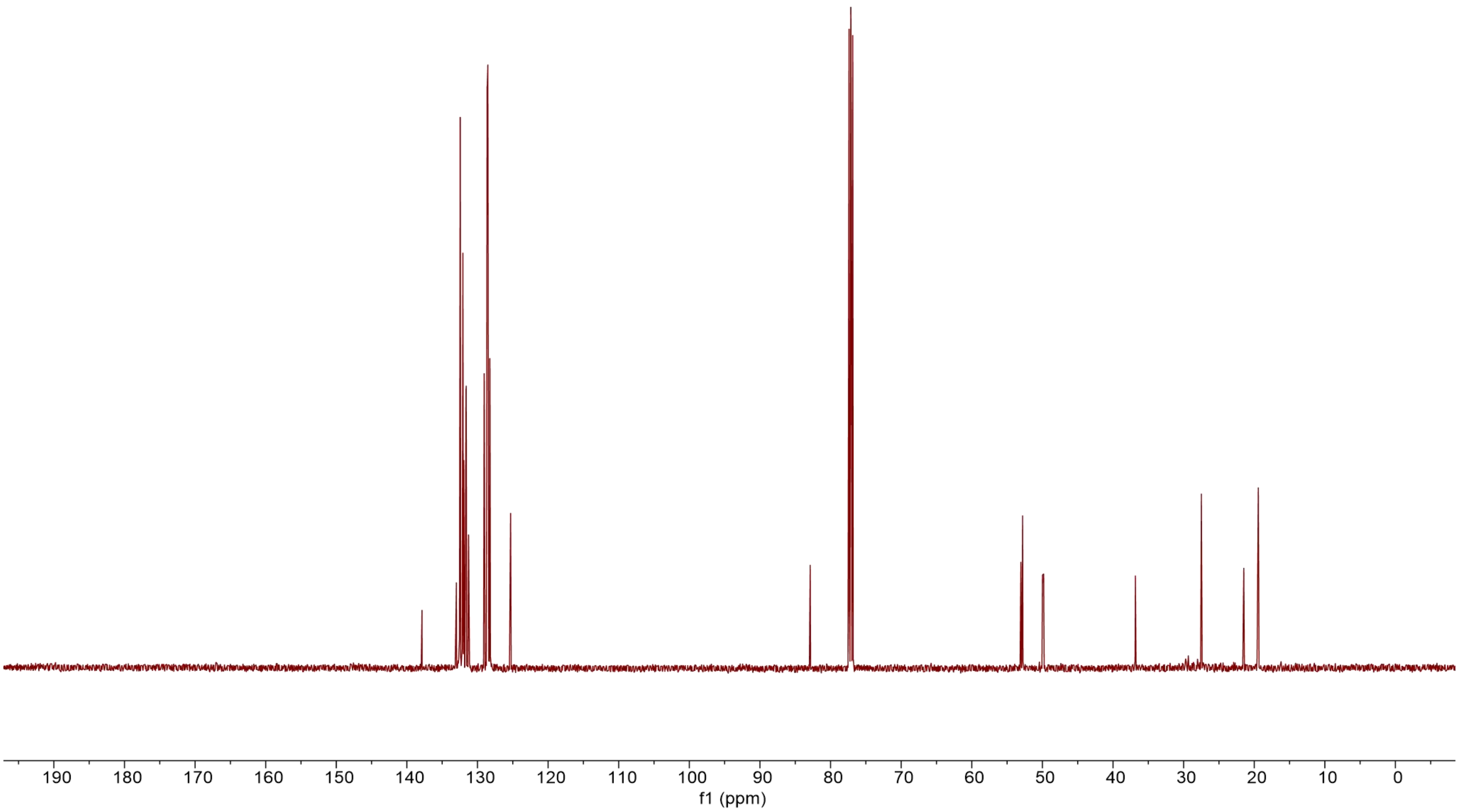


^{1}H NMR Spectrum of compound SI-95 (400 MHz, $CDCl_3$)

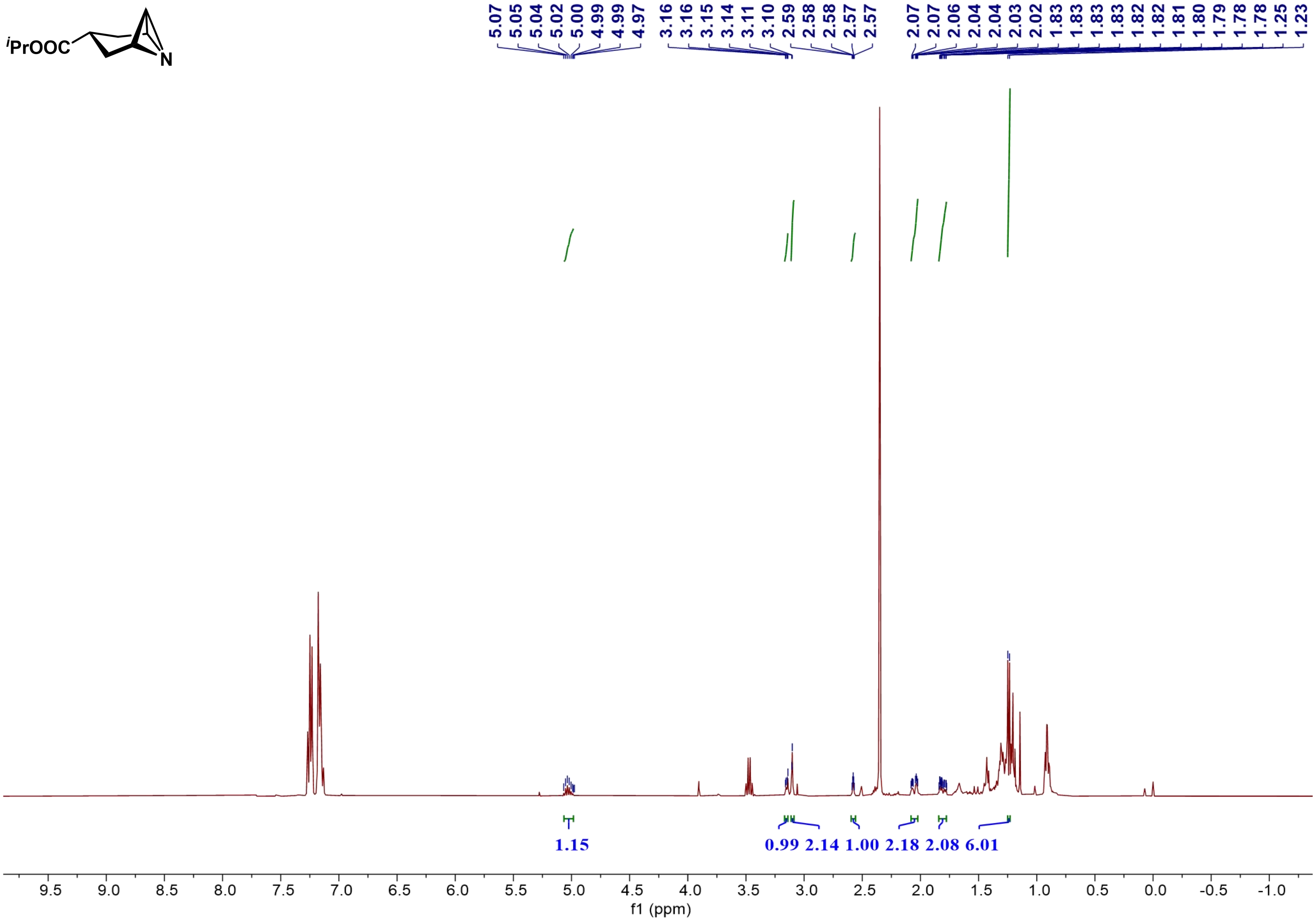


^{13}C NMR Spectrum of compound SI-95 (101 MHz, CDCl$_3$)

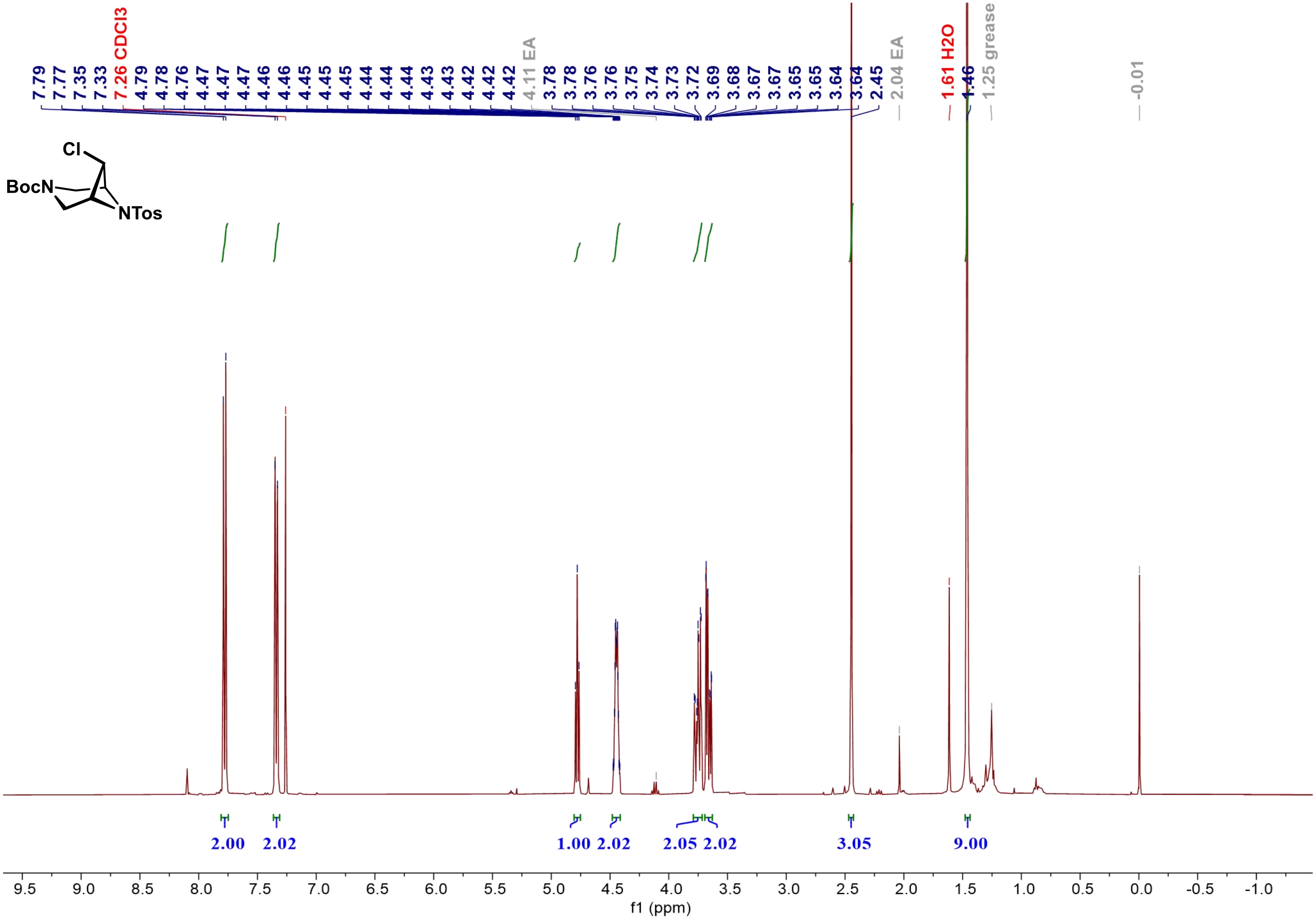




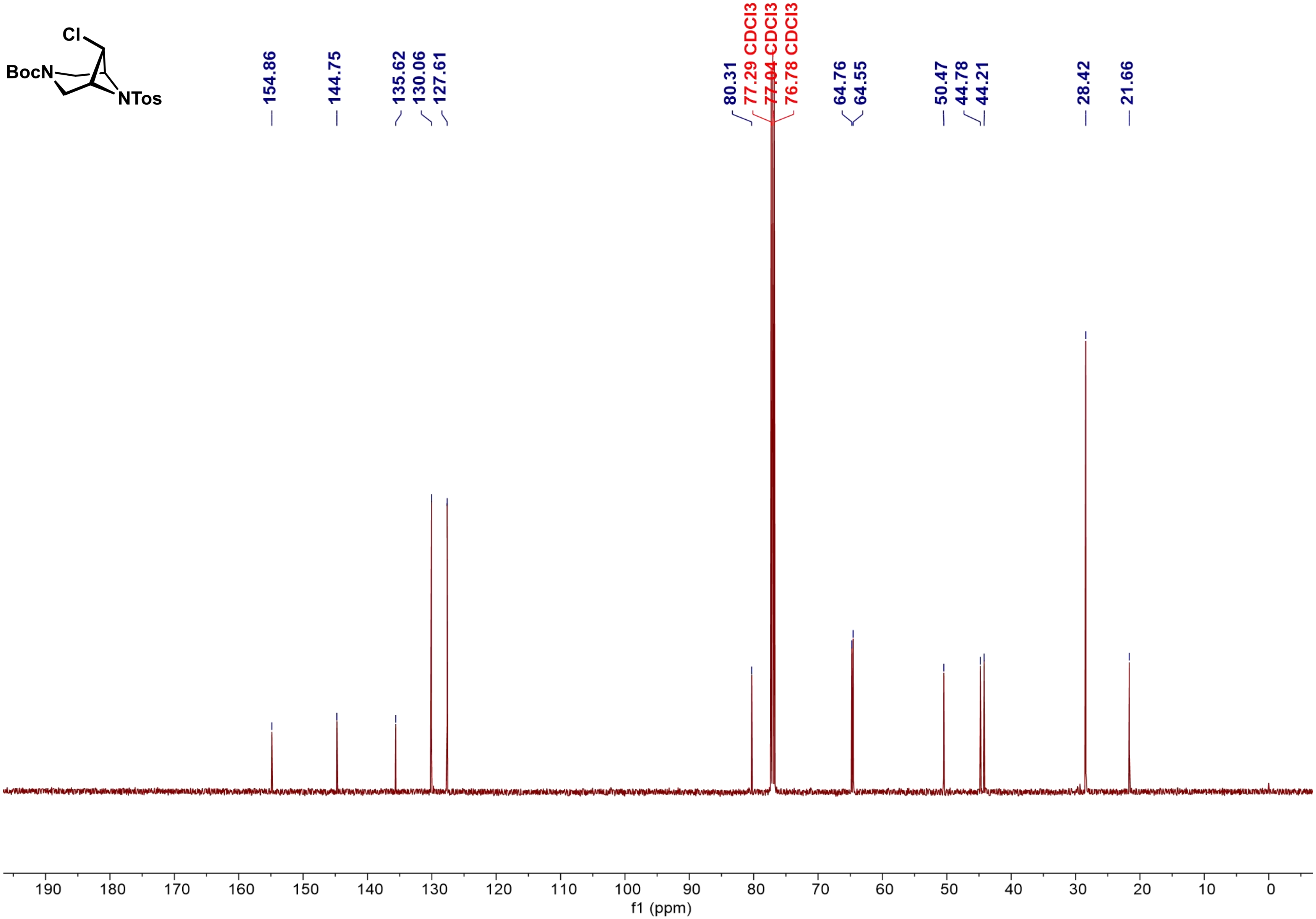
^{1}H NMR Spectrum of compound 12 (400 MHz, CDCl$_3$)



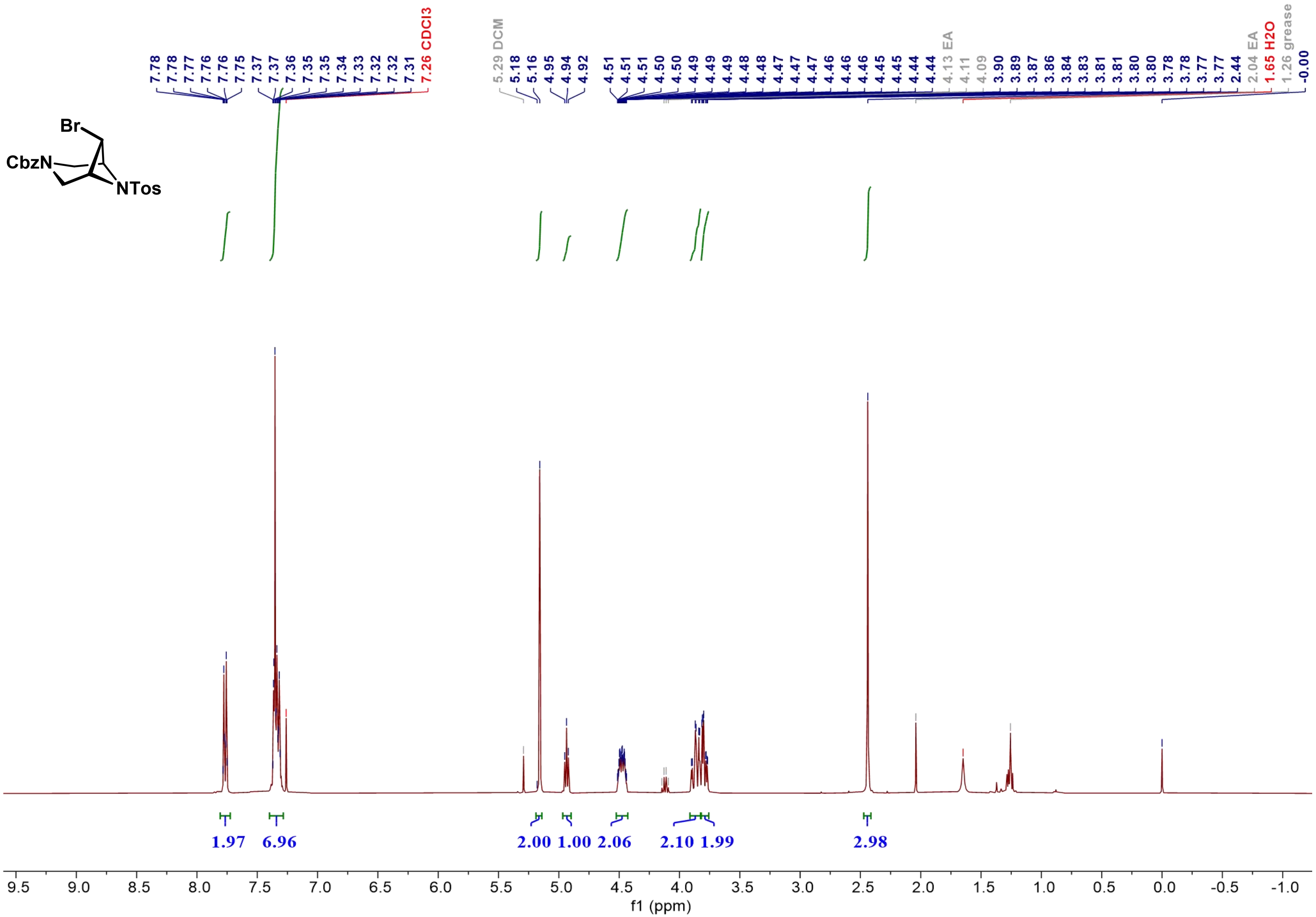
^{1}H NMR Spectrum of compound 15 (400 MHz, $CDCl_3$)



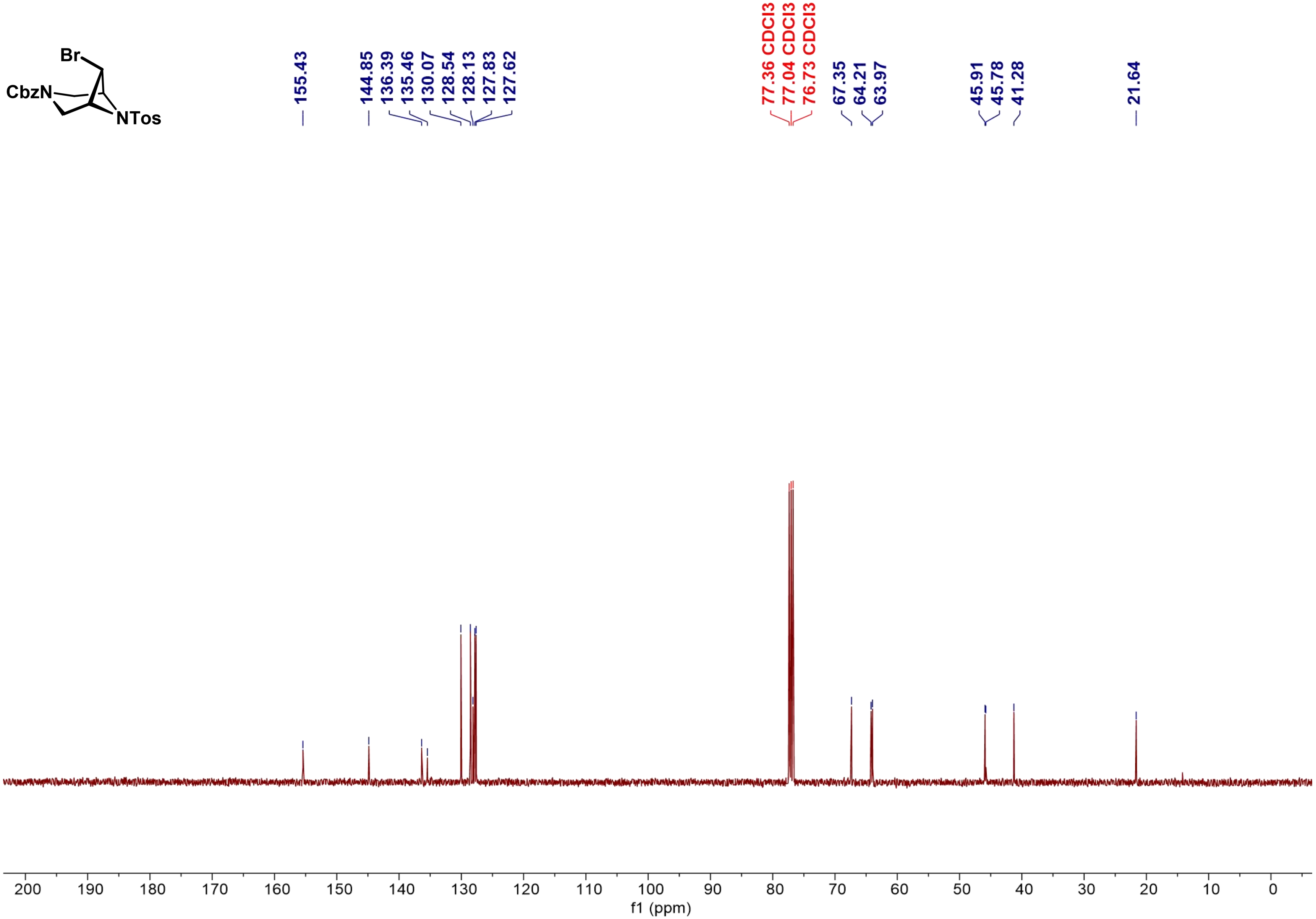
^{13}C NMR Spectrum of compound 15 (101 MHz, $CDCl_3$)



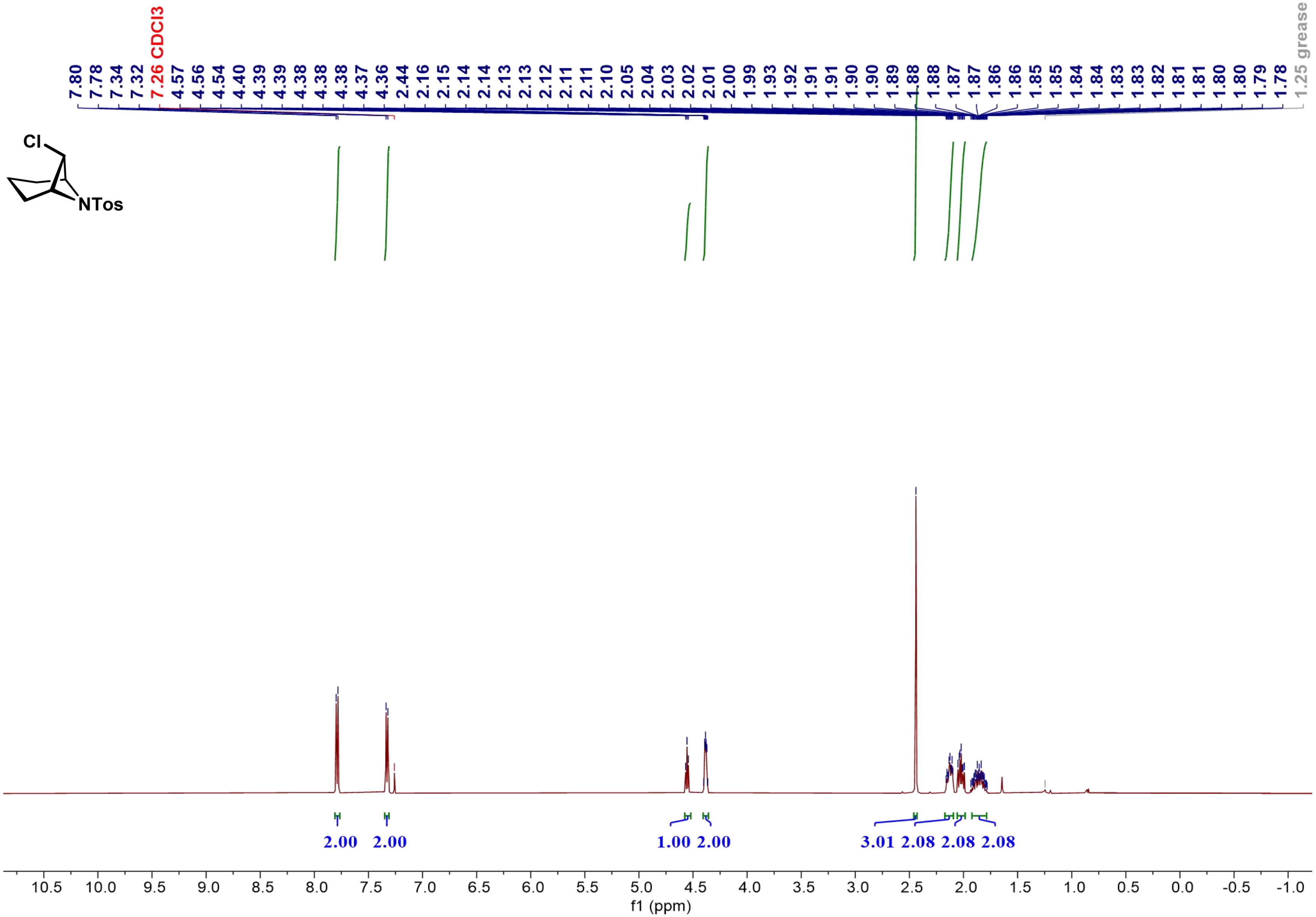
^{1}H NMR Spectrum of compound 16 (400 MHz, $CDCl_3$)



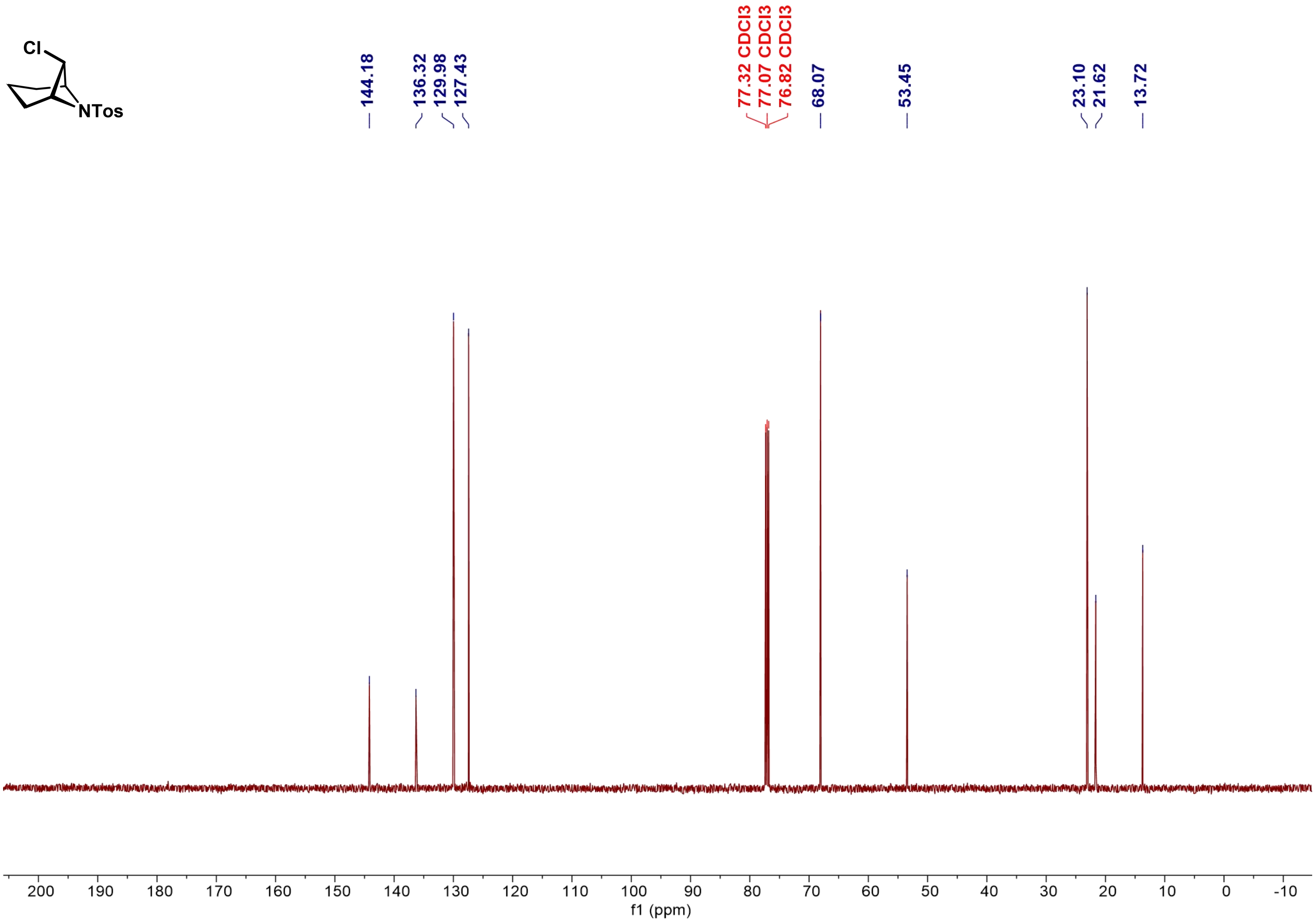
^{13}C NMR Spectrum of compound 16 (101 MHz, $CDCl_3$)



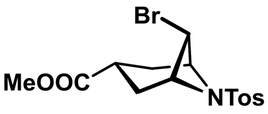
^{1}H NMR Spectrum of compound 17 (500 MHz, $CDCl_3$)

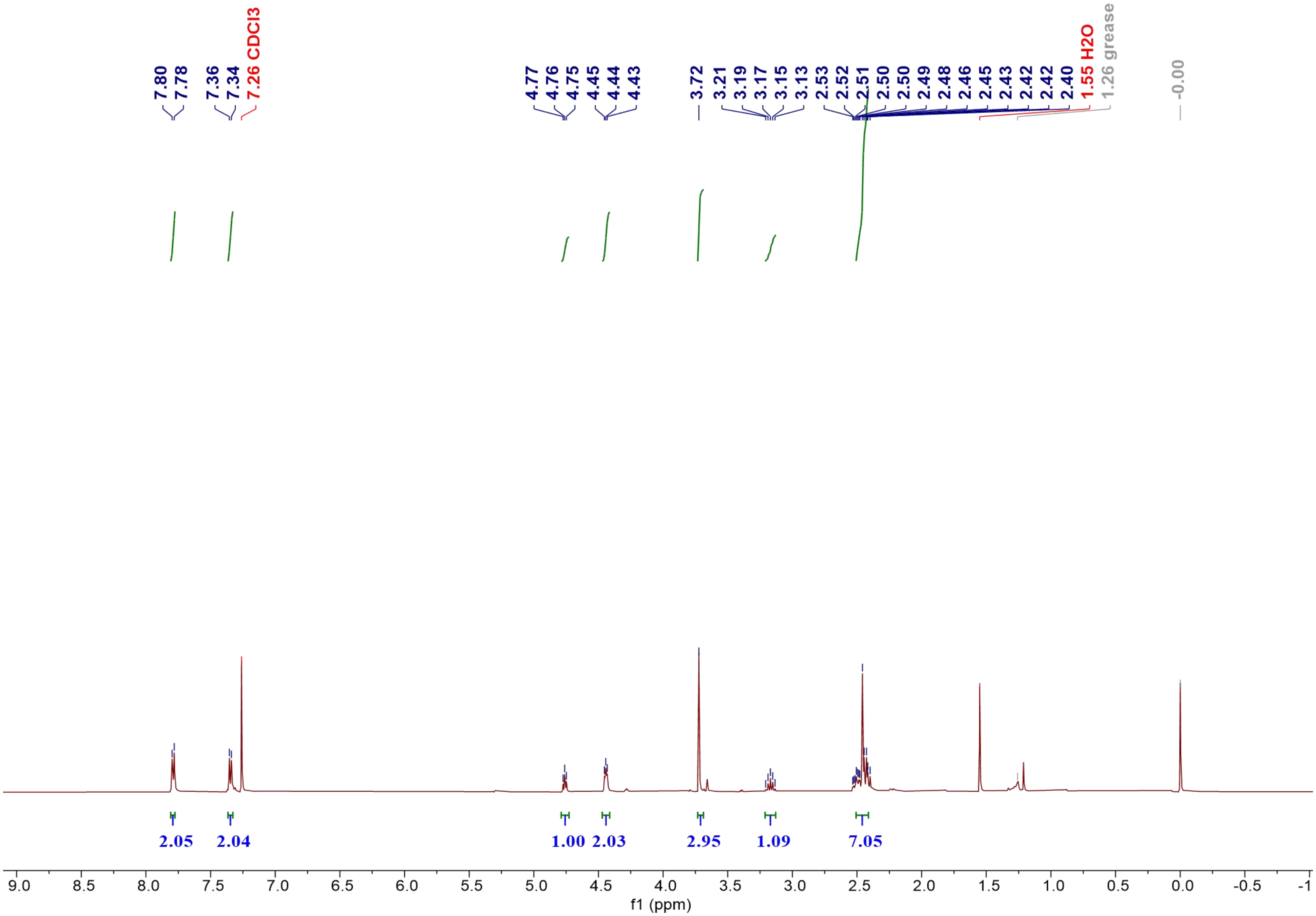


^{13}C NMR Spectrum of compound 17 (126 MHz, $CDCl_3$)

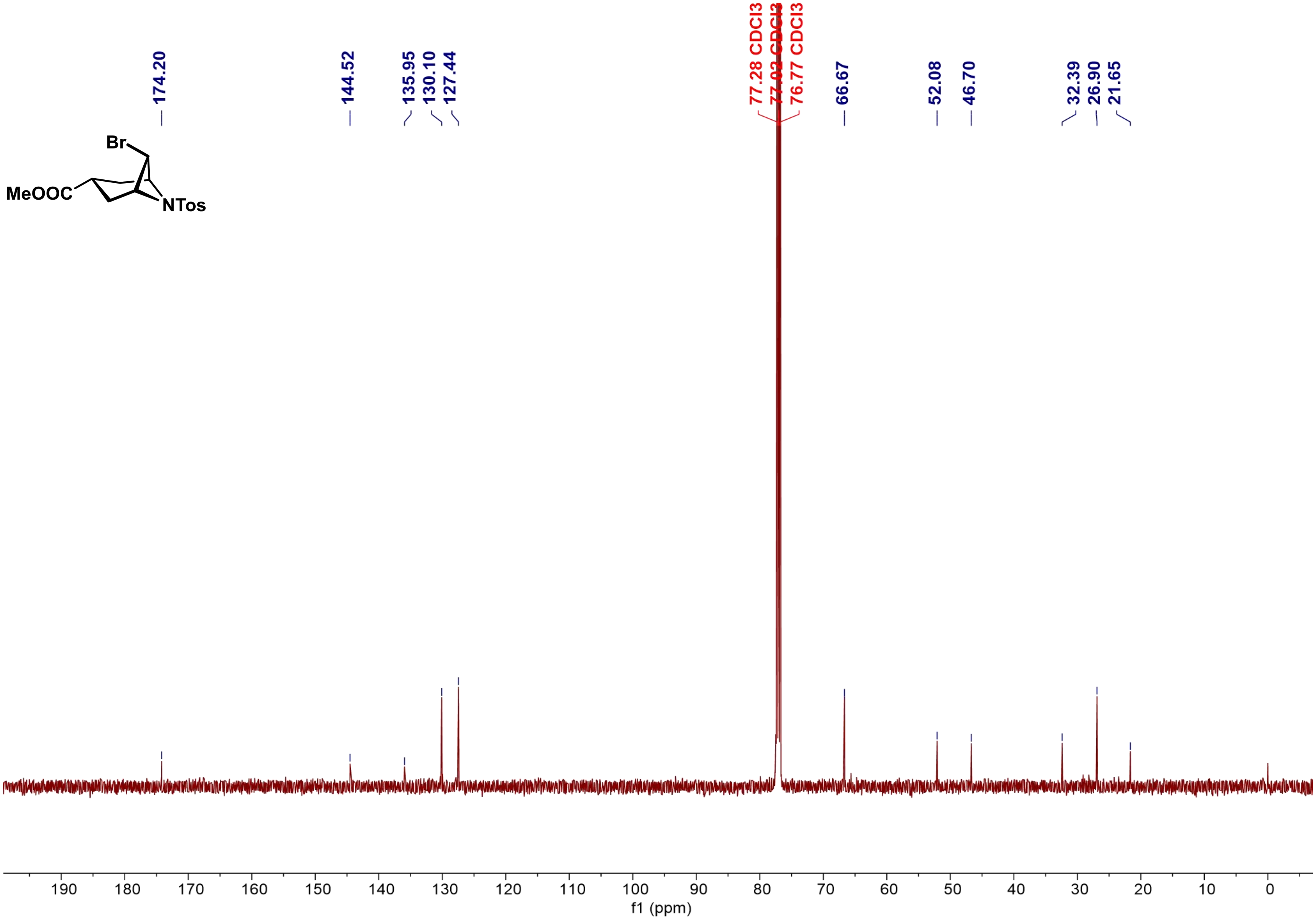


^{1}**H NMR Spectrum of compound 18 (500 MHz, CDCl$_3$)**

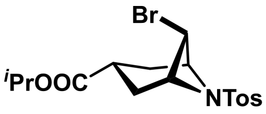


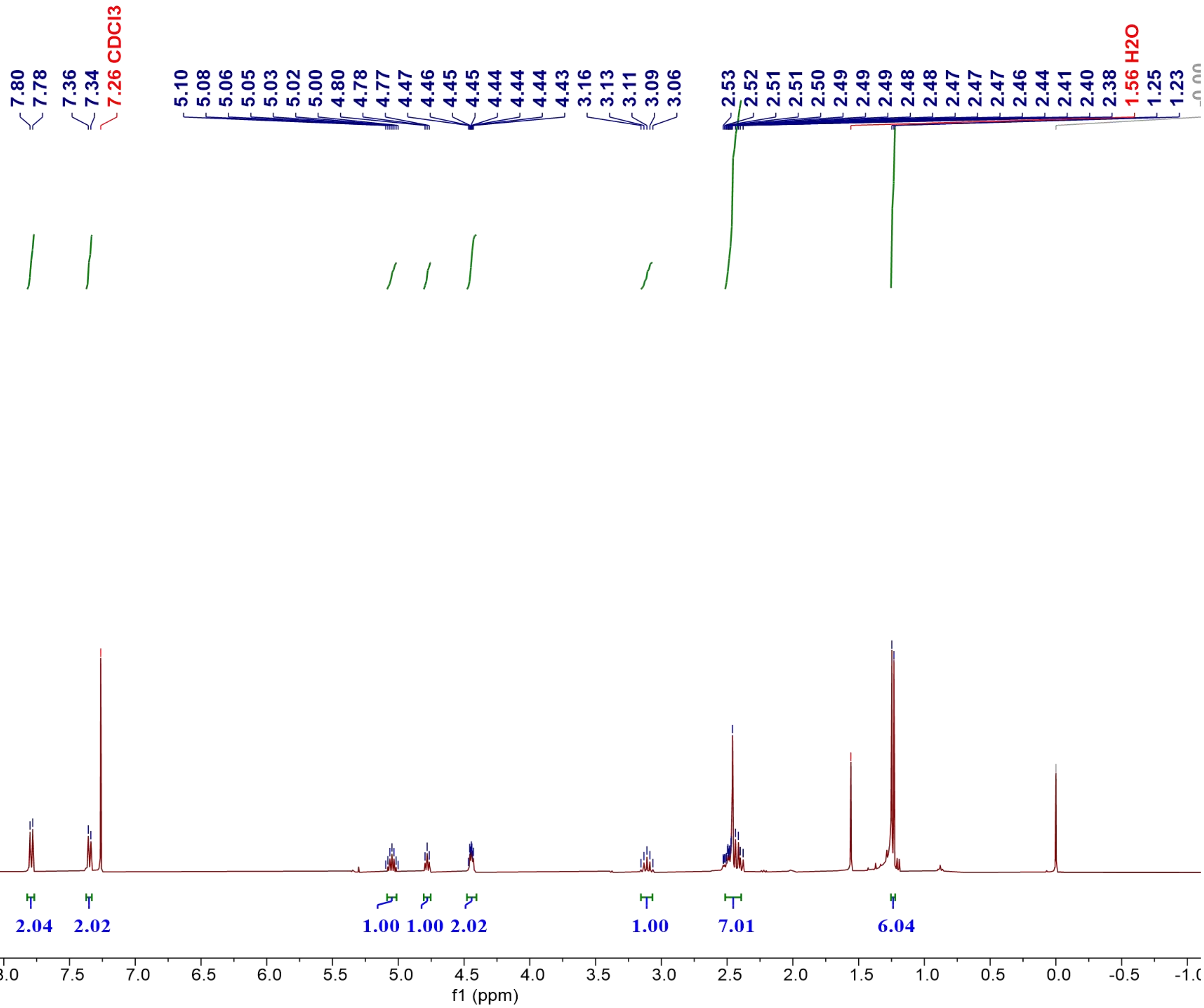

7.80
7.78
7.36
7.34
7.26 CDCl3
4.77
4.76
4.75
4.45
4.44
4.43
3.72
3.21
3.19
3.17
3.15
3.13
2.53
2.52
2.51
2.50
2.50
2.49
2.48
2.46
2.45
2.43
2.42
2.42
2.40
1.55 H2O
1.26 grease
-0.00
2.05
2.04
1.00
2.03
2.95
1.09
7.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

^{13}C NMR Spectrum of compound 18 (126 MHz, CDCl$_3$)

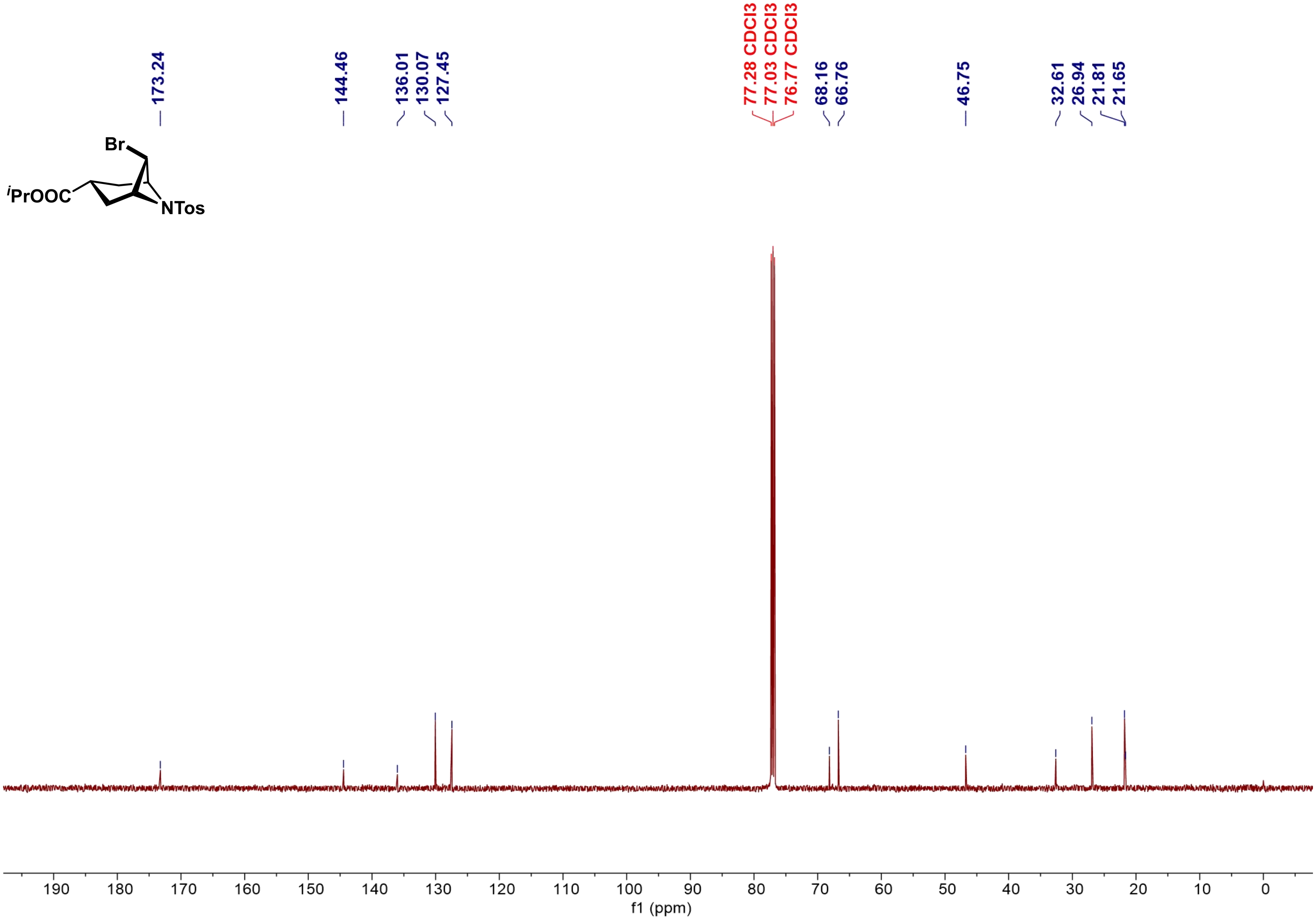


^{1}H NMR Spectrum of compound 19 (400 MHz, CDCl$_3$)

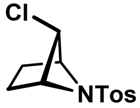


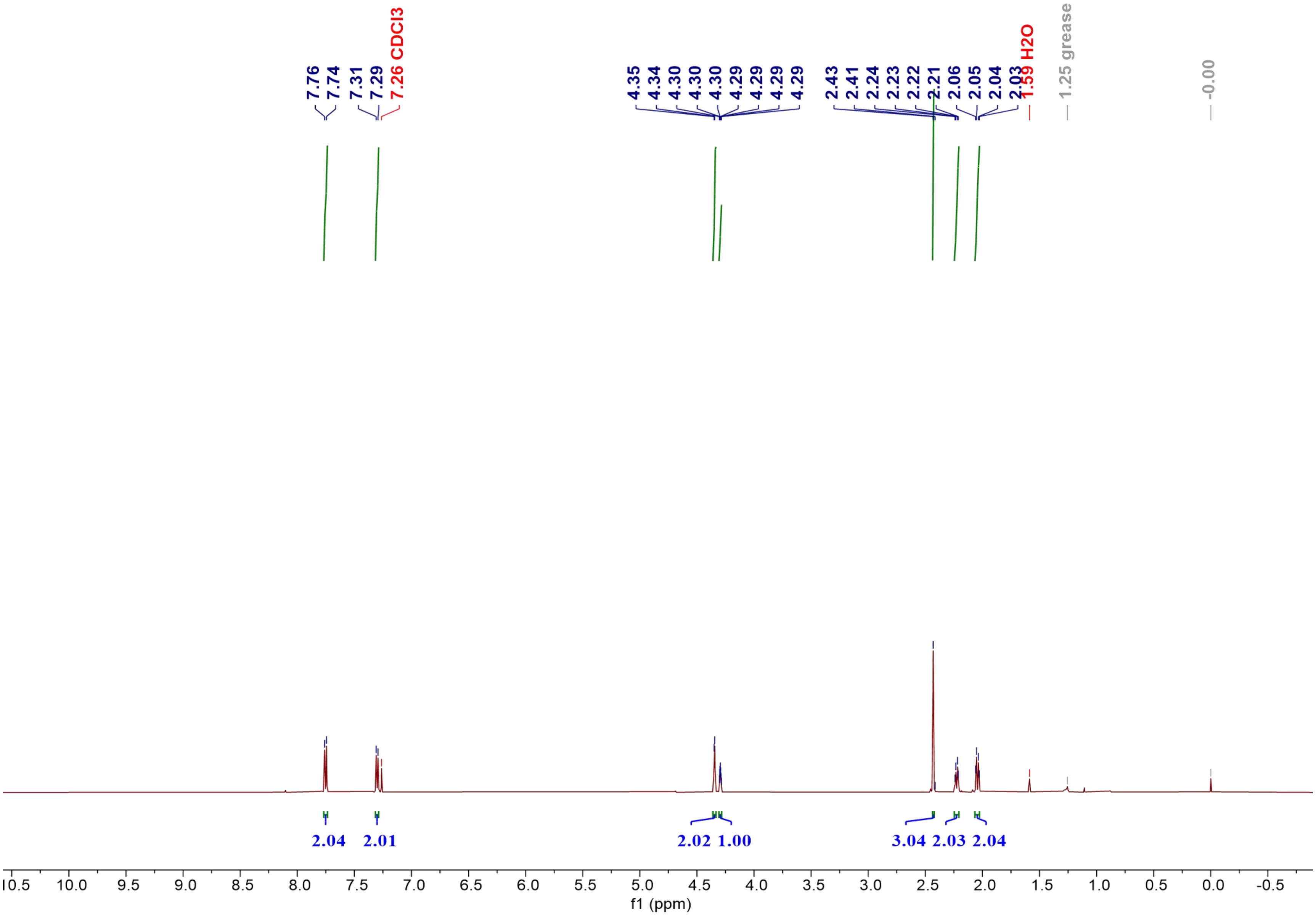


^{13}C NMR Spectrum of compound 19 (101 MHz, $CDCl_3$)



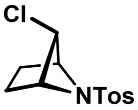
^{1}H NMR Spectrum of compound 20 (500 MHz, CDCl$_3$)

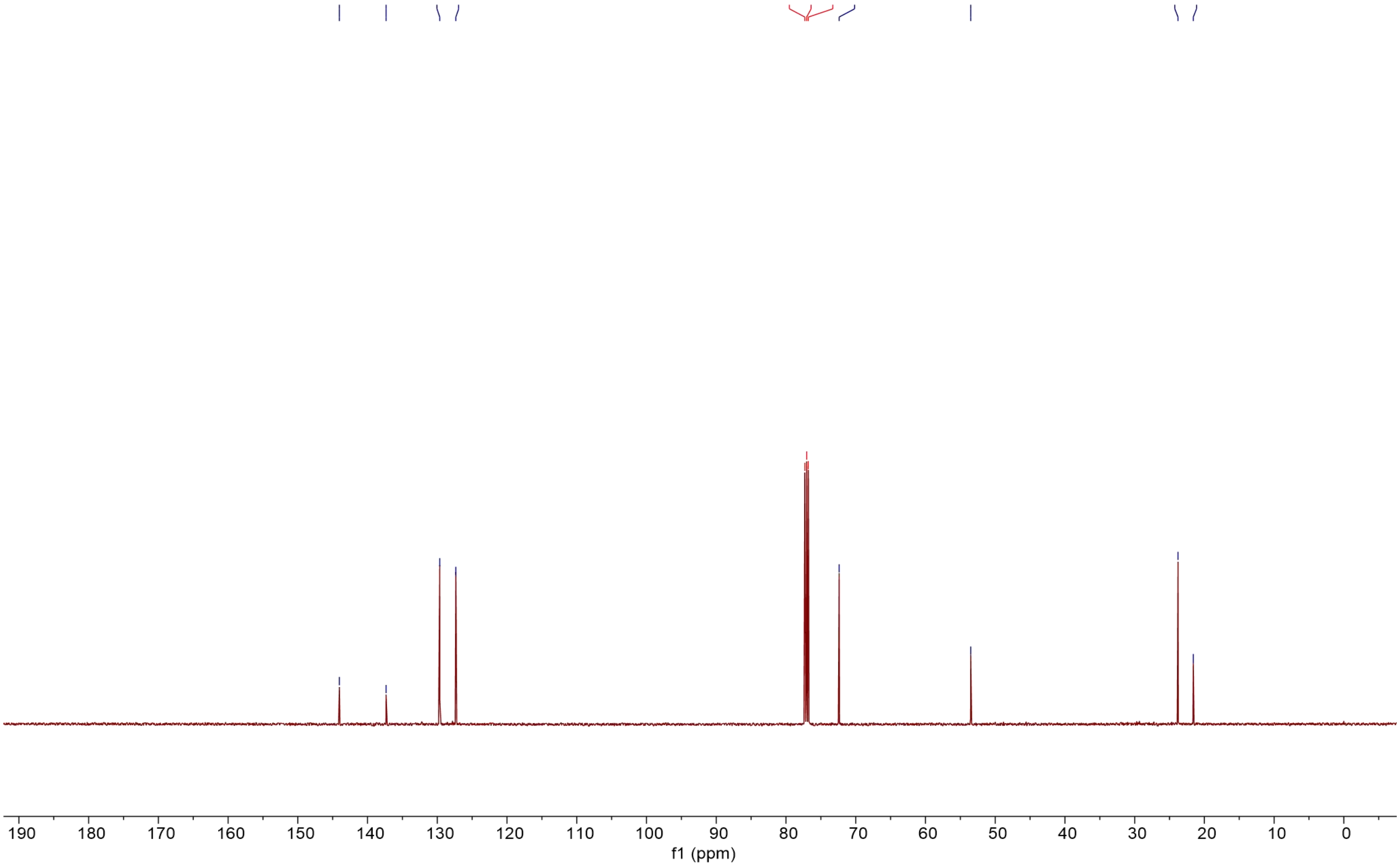




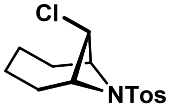
7.76
7.74
7.31
7.29
7.26 CDCl3
4.35
4.34
4.30
4.30
4.30
4.29
4.29
4.29
4.29
2.43
2.41
2.24
2.23
2.22
2.21
2.06
2.05
2.04
2.03
1.59 H2O
1.25 grease
-0.00
2.04
2.01
2.02
1.00
3.04
2.03
2.04
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

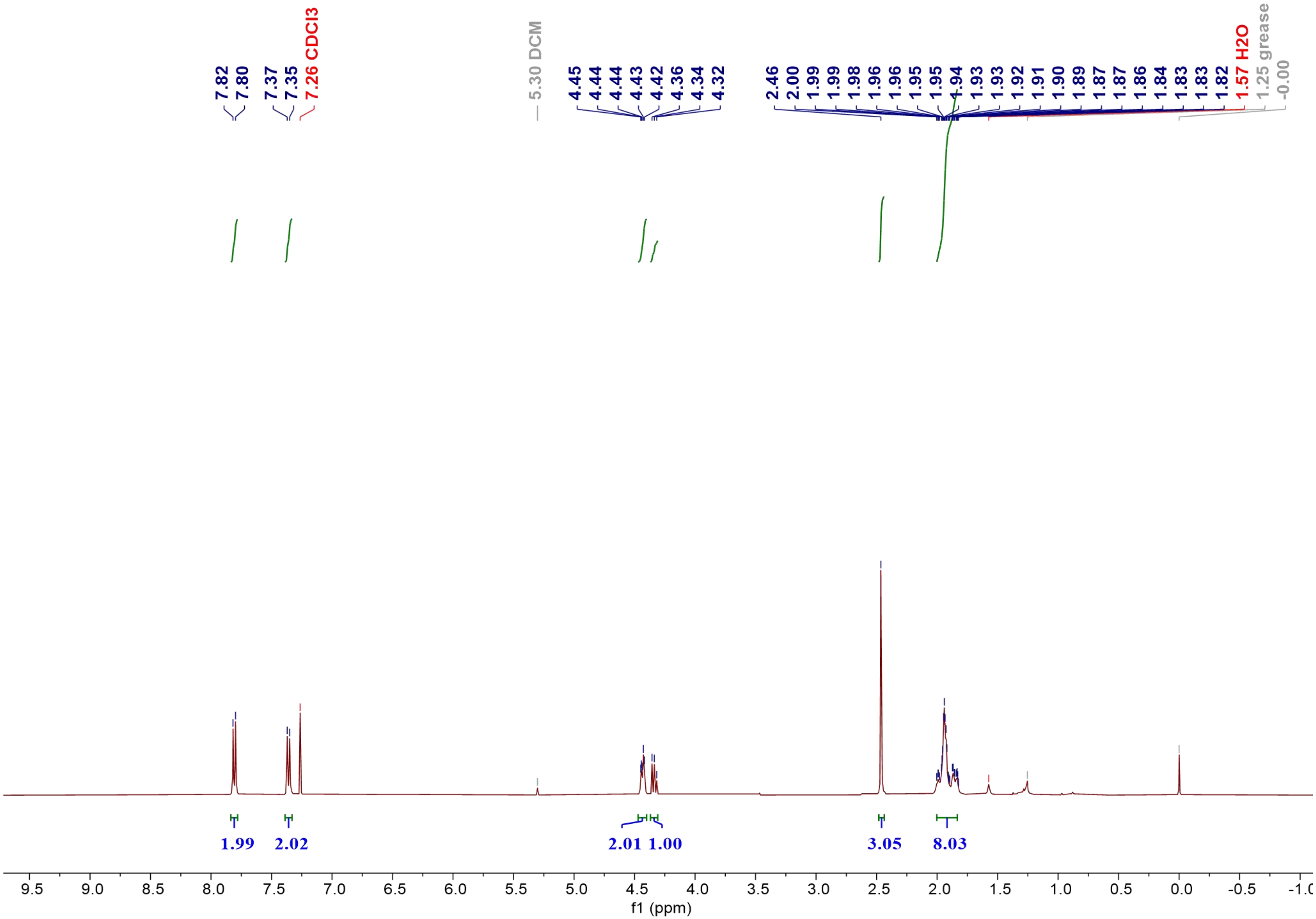
^{13}C NMR Spectrum of compound 20 (126 MHz, CDCl$_3$)



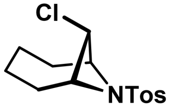


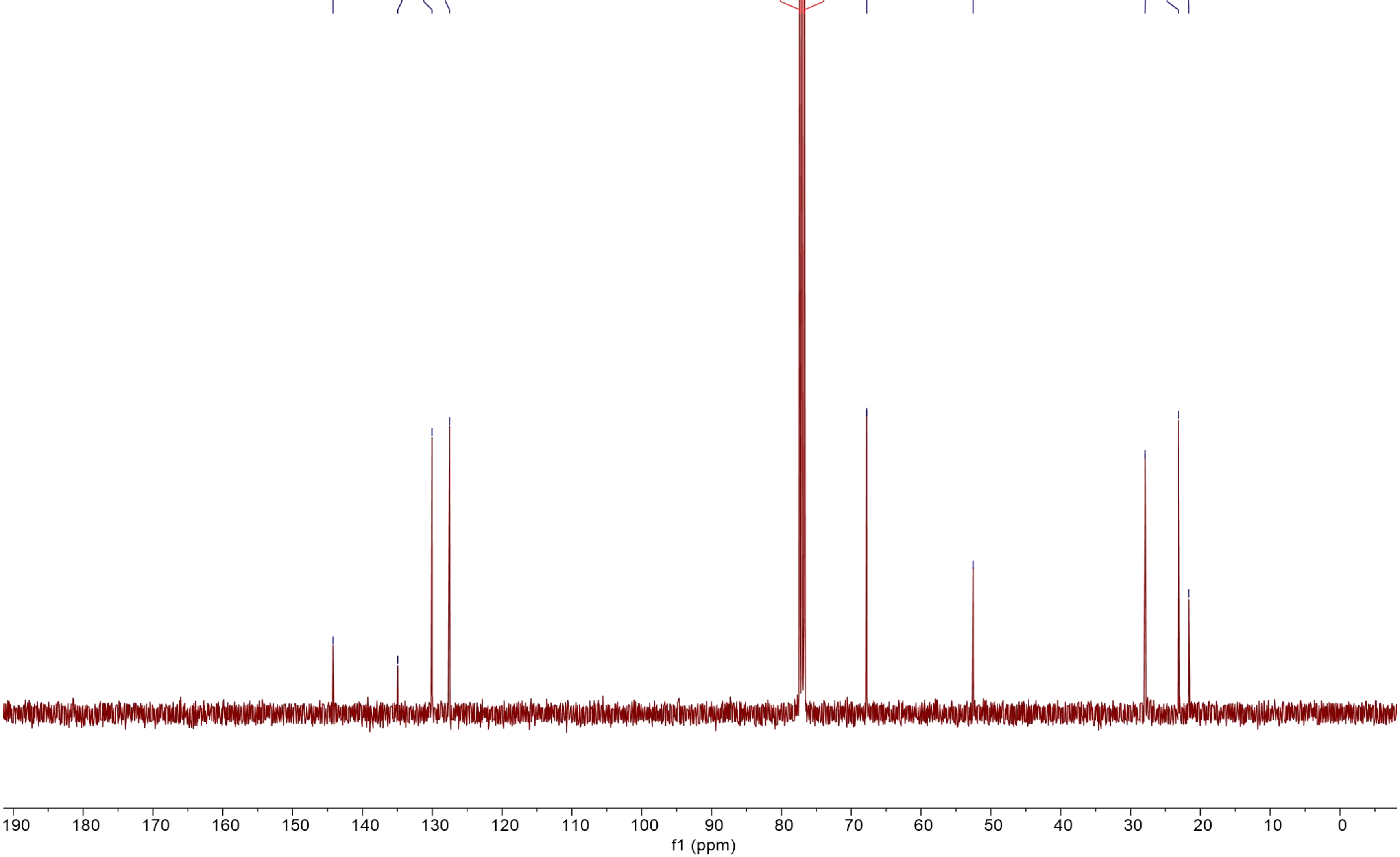
^{1}H NMR Spectrum of compound 21 (400 MHz, CDCl$_3$)



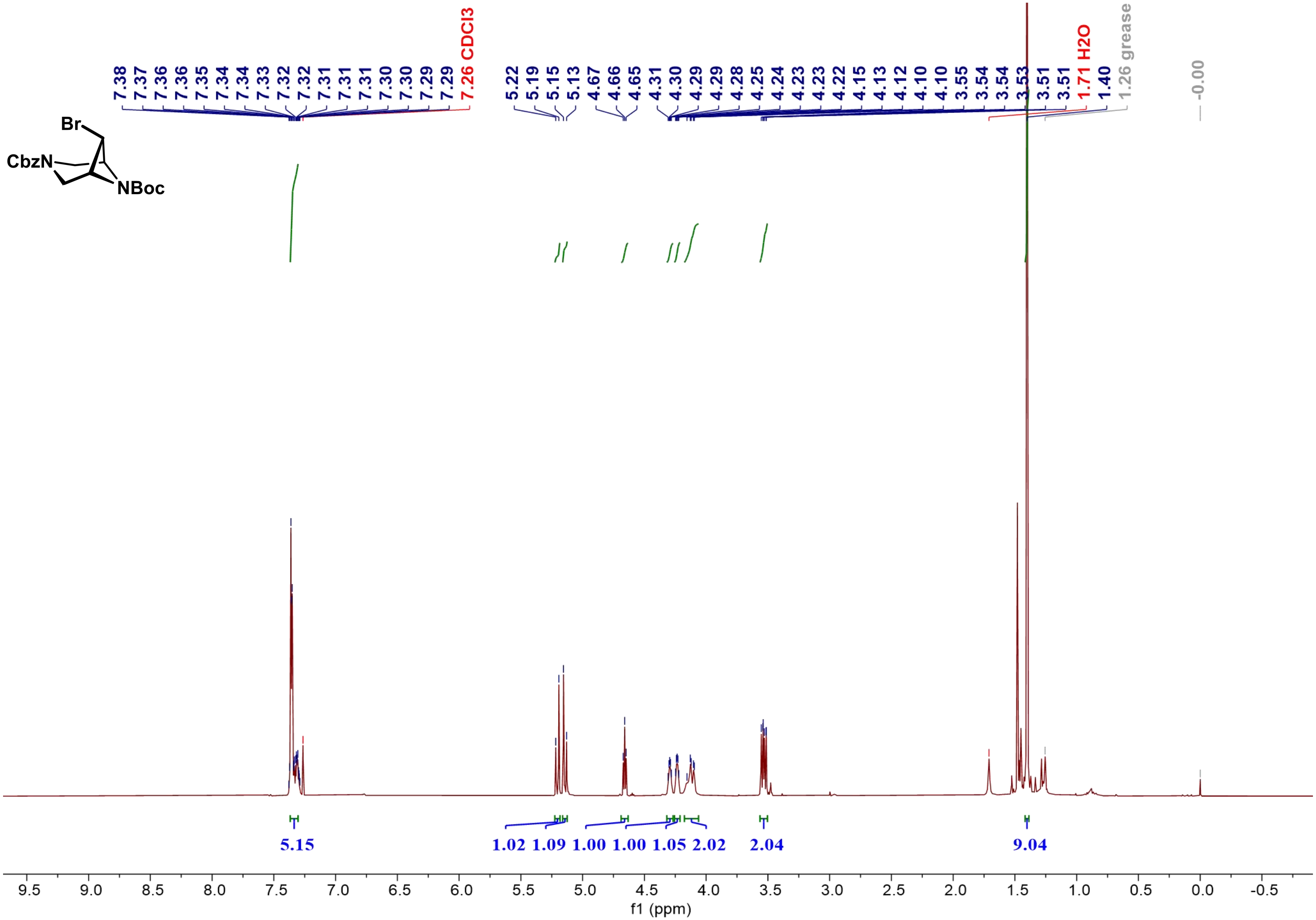

7.82
7.80
7.37
7.35
7.26 CDCl3
5.30 DCM
4.45
4.44
4.44
4.43
4.42
4.36
4.34
4.32
2.46
2.00
1.99
1.99
1.98
1.96
1.96
1.95
1.95
1.94
1.93
1.93
1.92
1.91
1.90
1.89
1.87
1.87
1.86
1.84
1.83
1.83
1.82
1.57 H2O
1.25 grease
-0.00
1.99
2.02
2.01
1.00
3.05
8.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

^{13}C NMR Spectrum of compound 21 (101 MHz, $CDCl_3$)

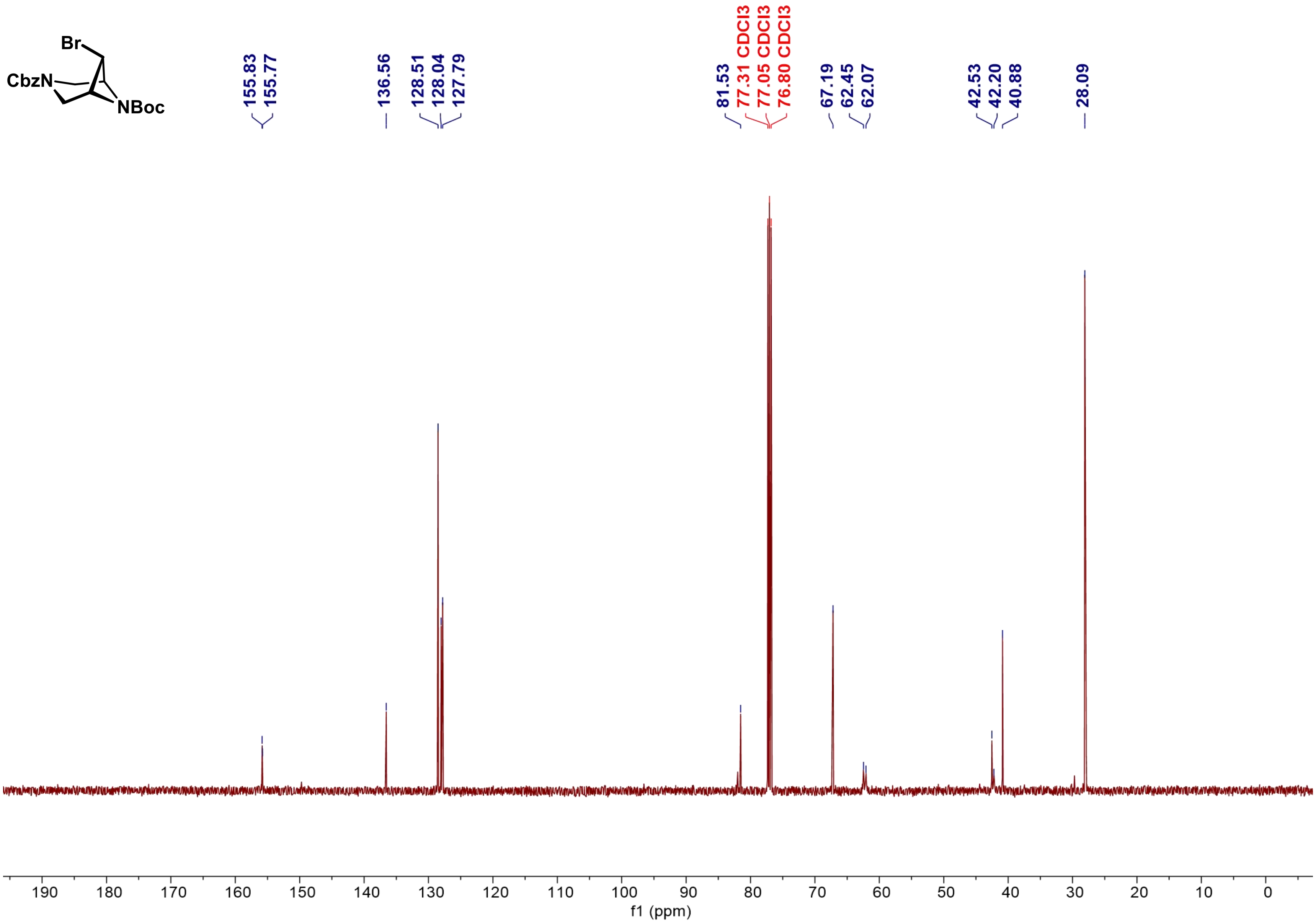




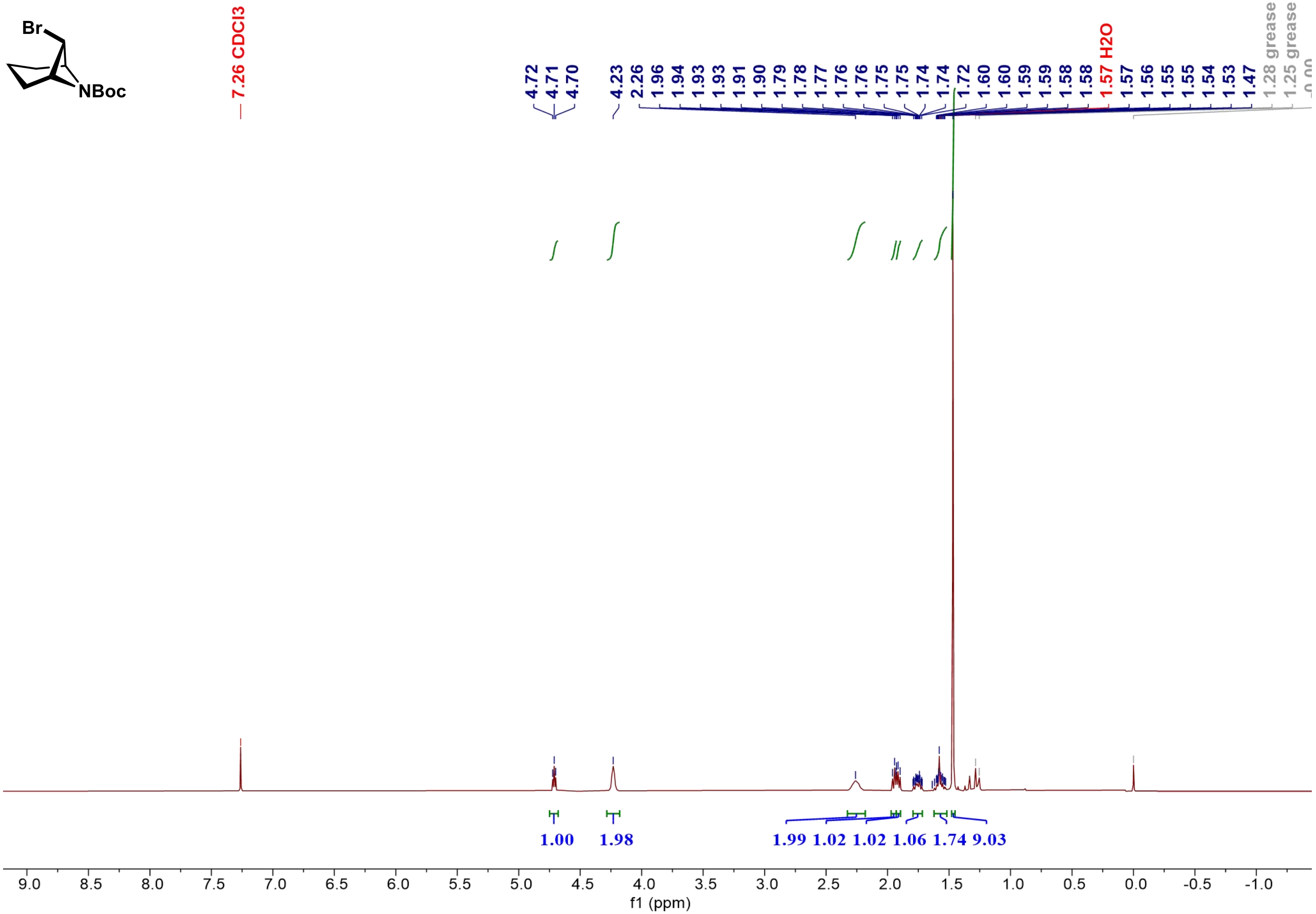
^{1}H NMR Spectrum of compound 22 (500 MHz, CDCl$_3$)



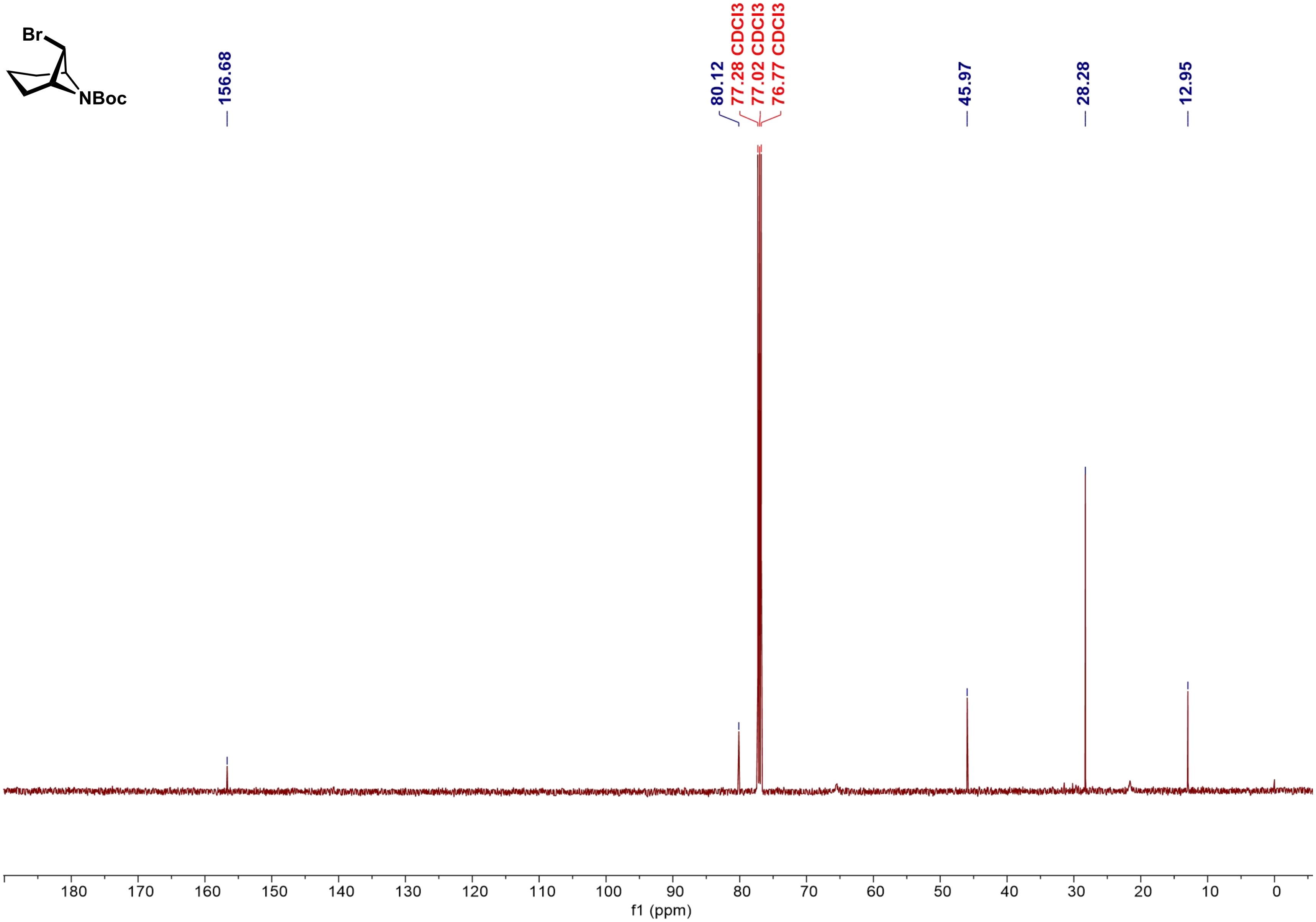
^{13}C NMR Spectrum of compound 22 (126 MHz, $CDCl_3$)



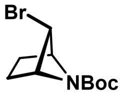
^{1}H NMR Spectrum of compound 23 (500 MHz, $CDCl_3$)

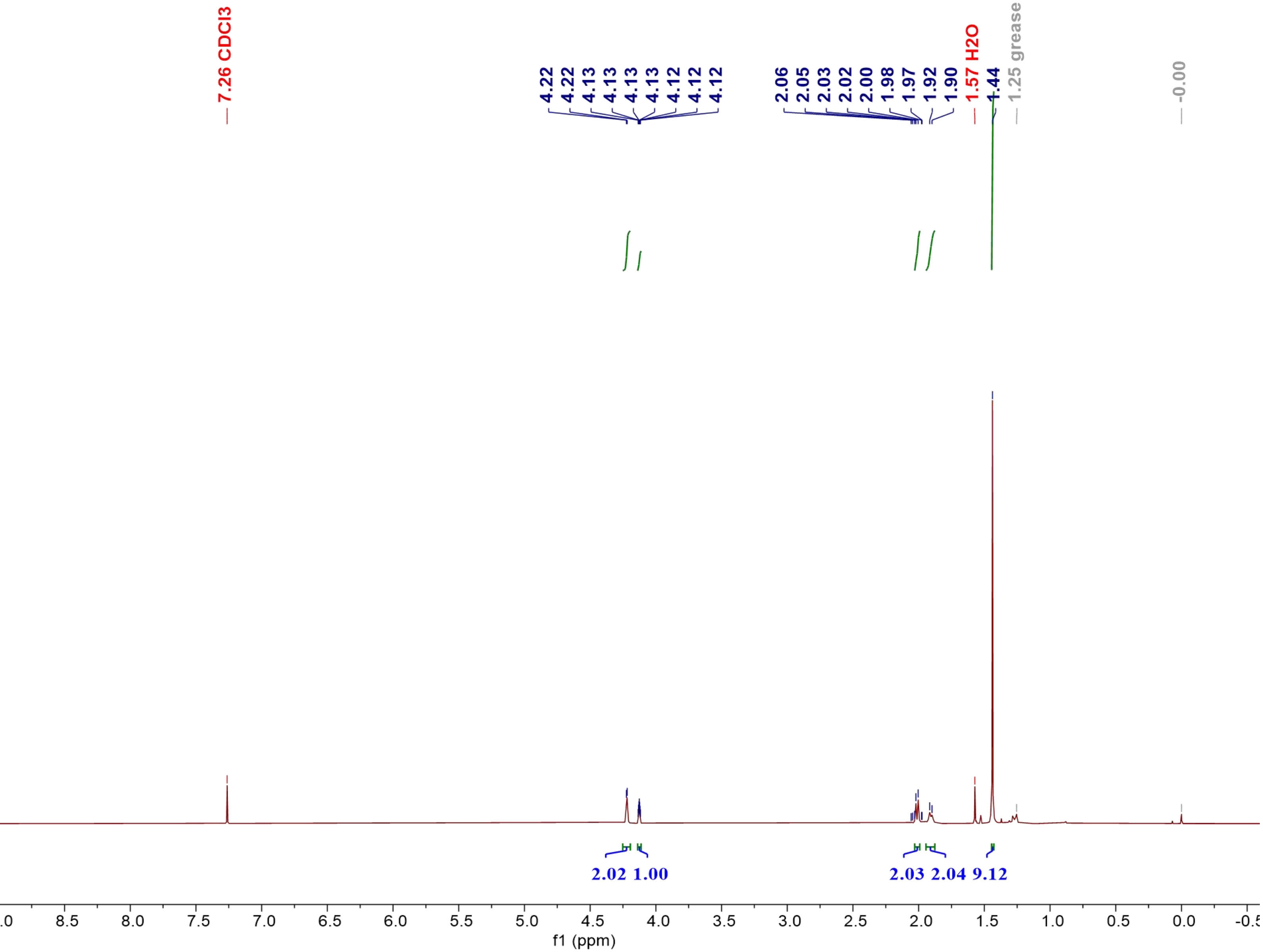


^{13}C NMR Spectrum of compound 23 (126 MHz, $CDCl_3$)

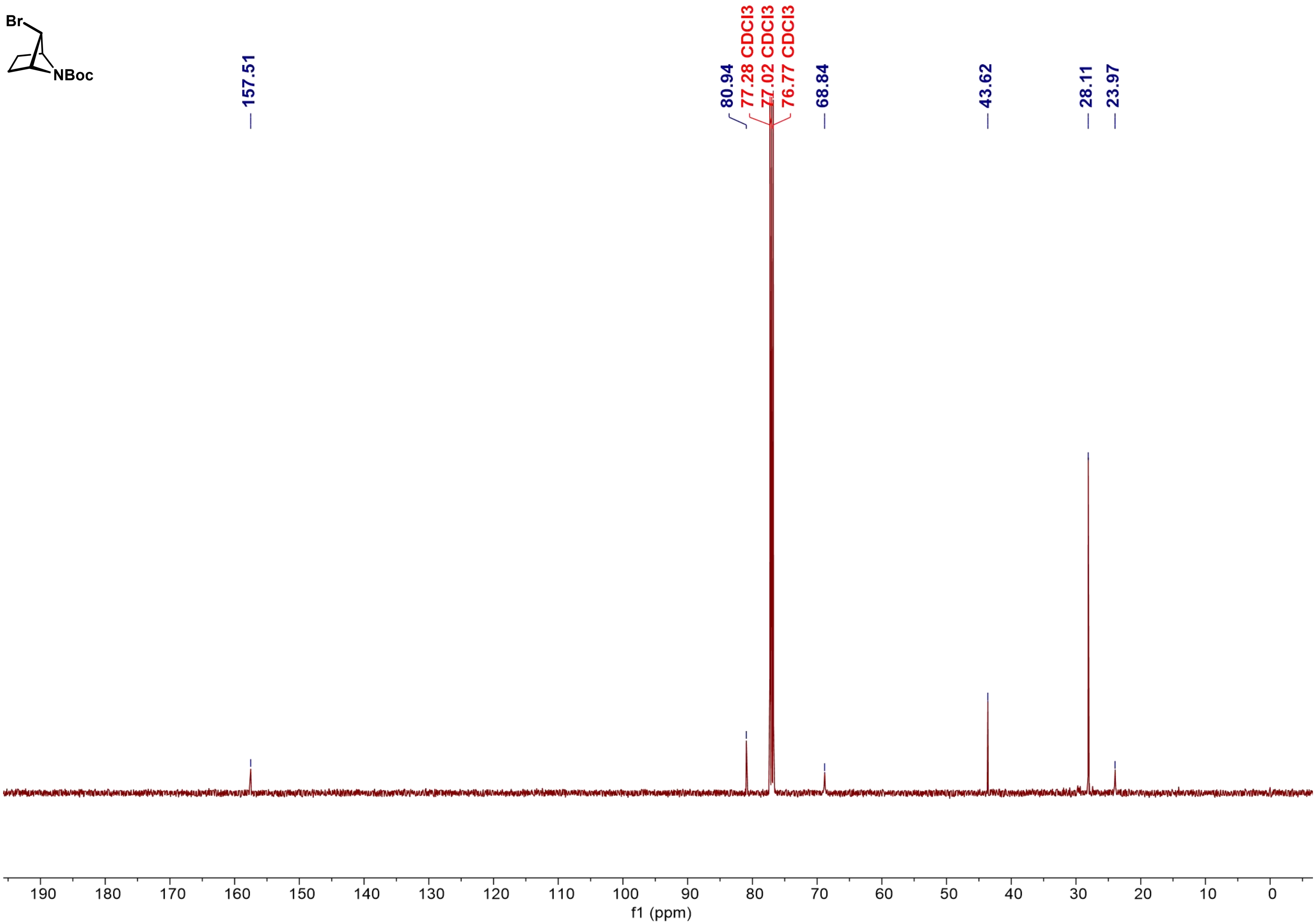


^{1}H NMR Spectrum of compound 24 (500 MHz, CDCl$_3$)

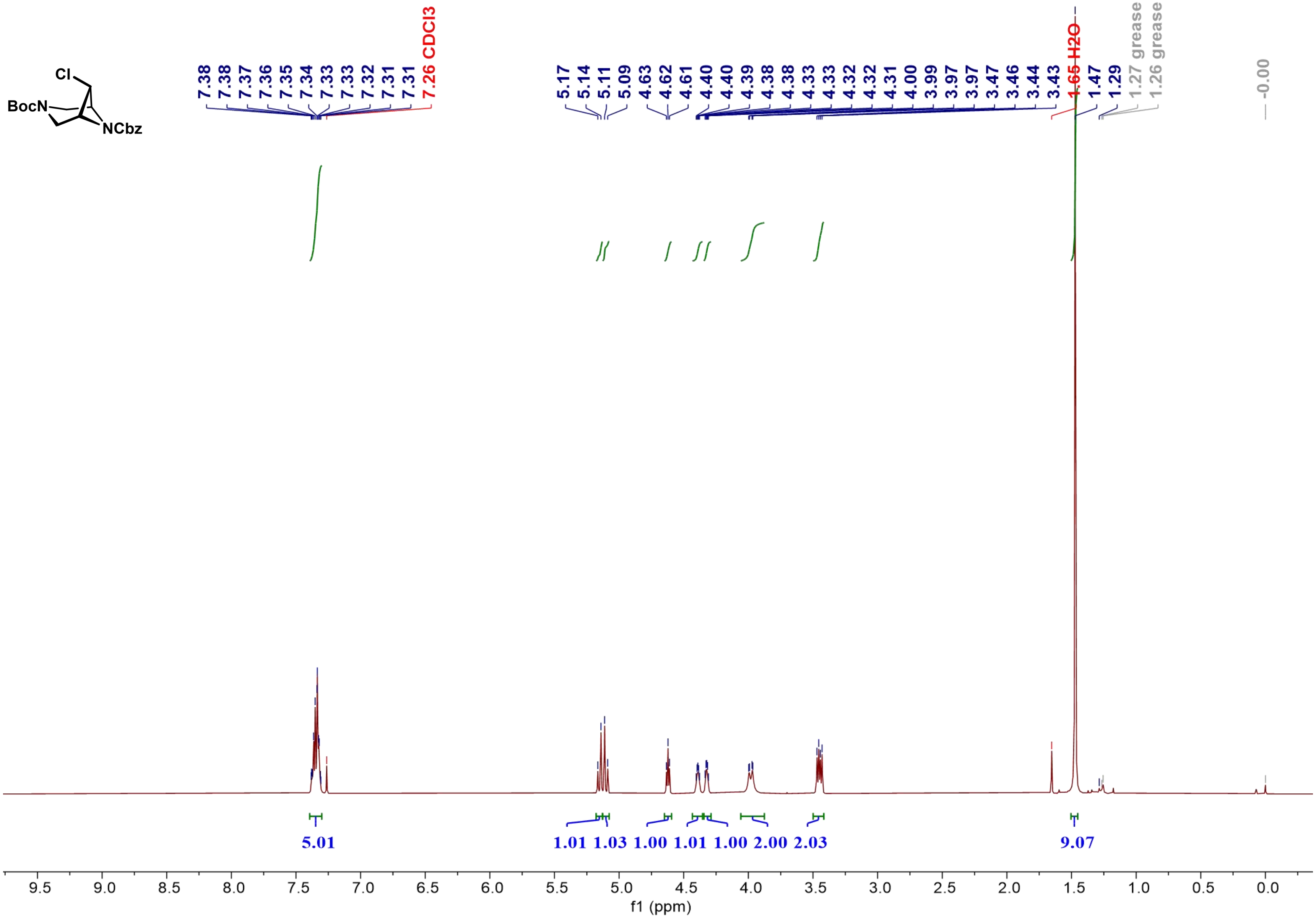




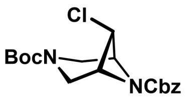
^{13}C NMR Spectrum of compound 24 (126 MHz, $CDCl_3$)

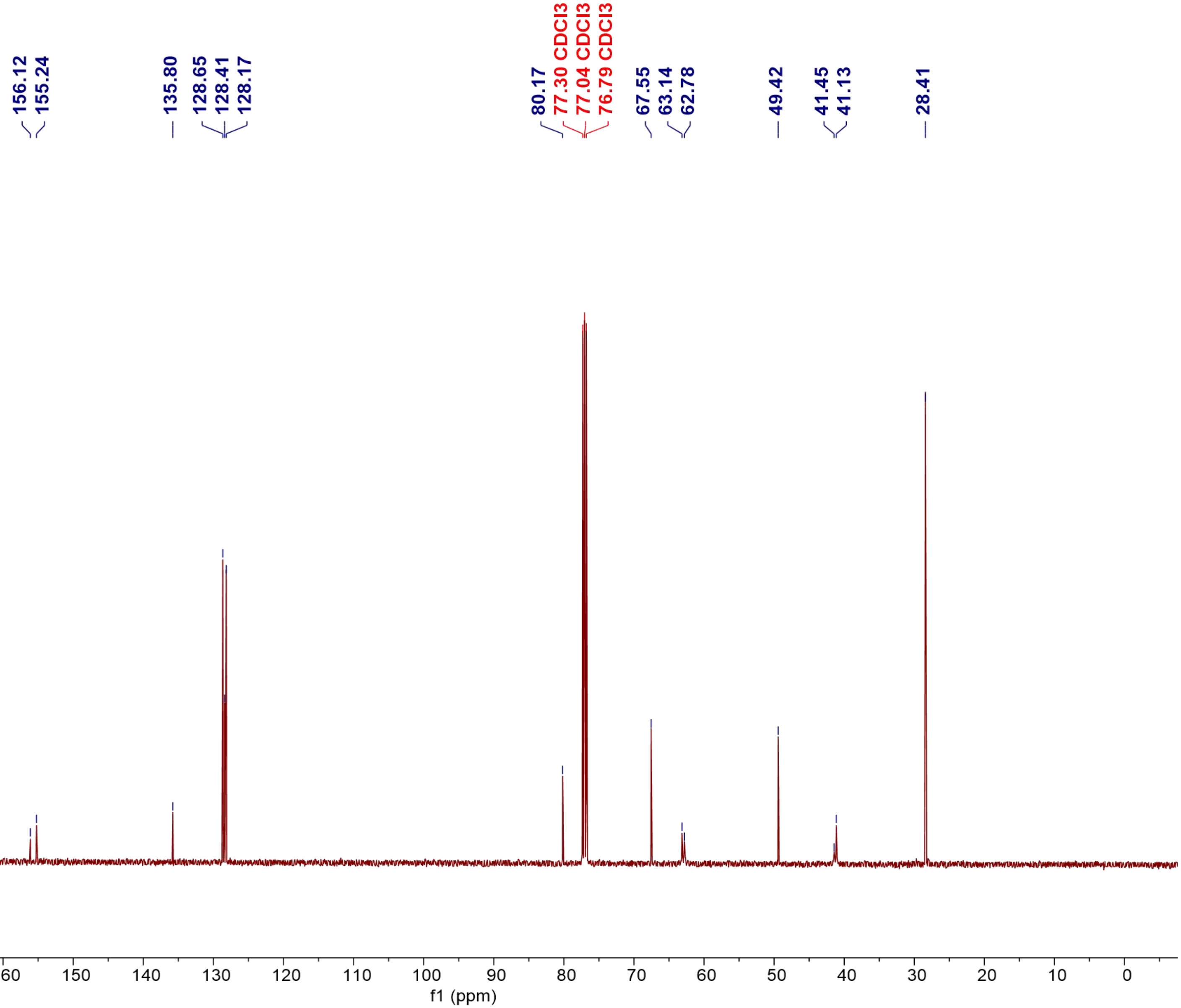


^{1}H NMR Spectrum of compound 25 (500 MHz, CDCl$_3$)

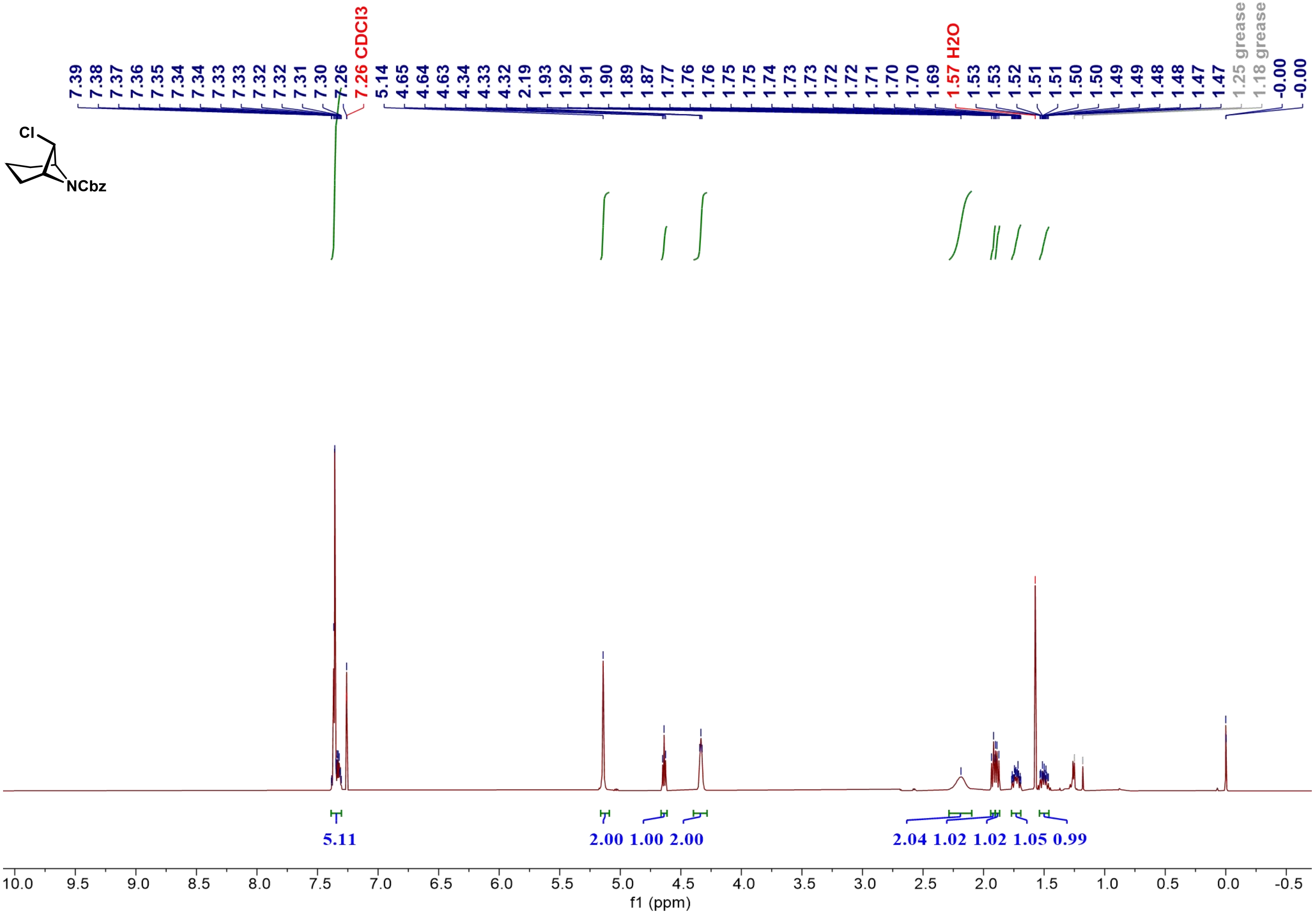


^{13}C NMR Spectrum of compound 25 (126 MHz, CDCl$_3$)

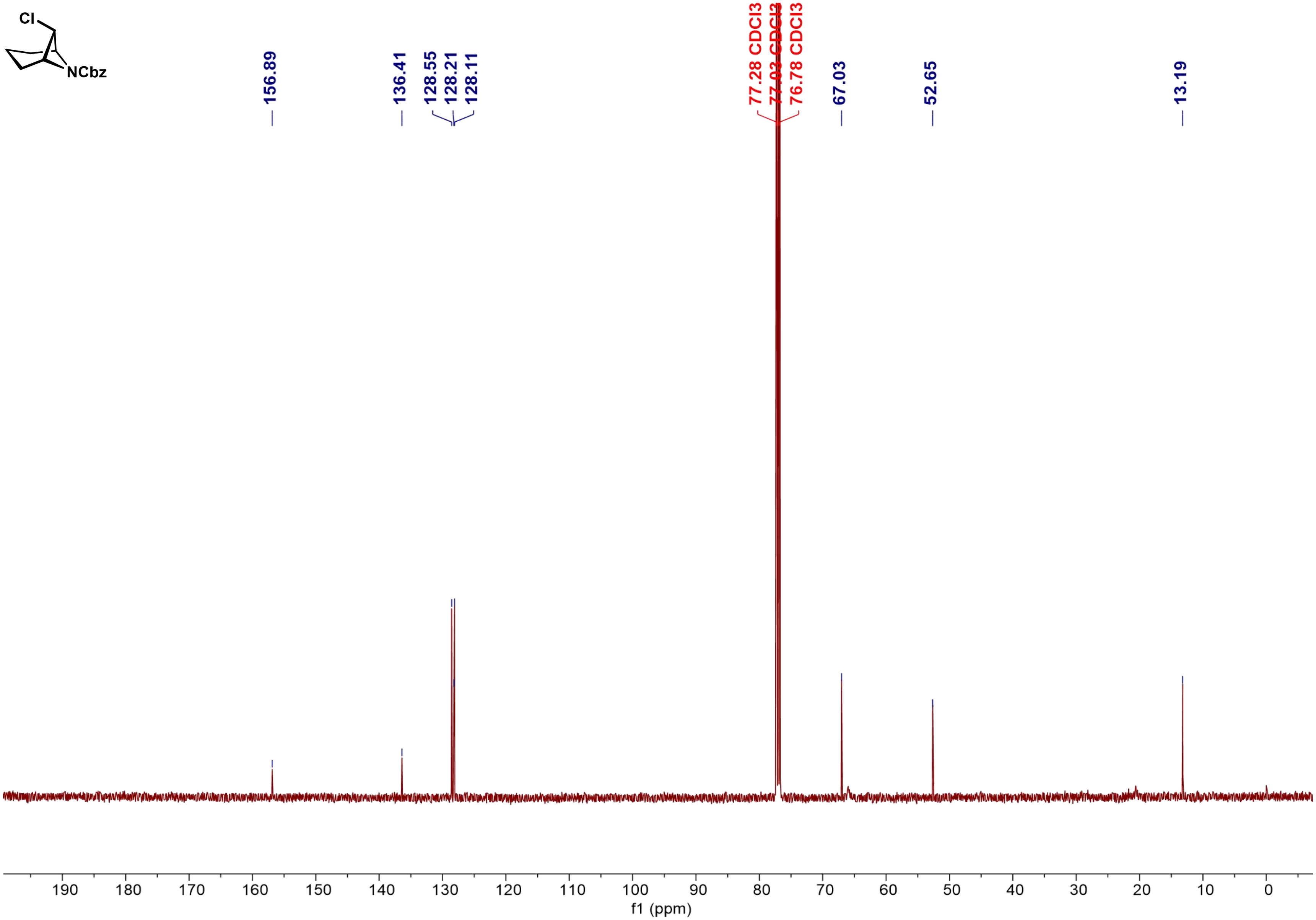




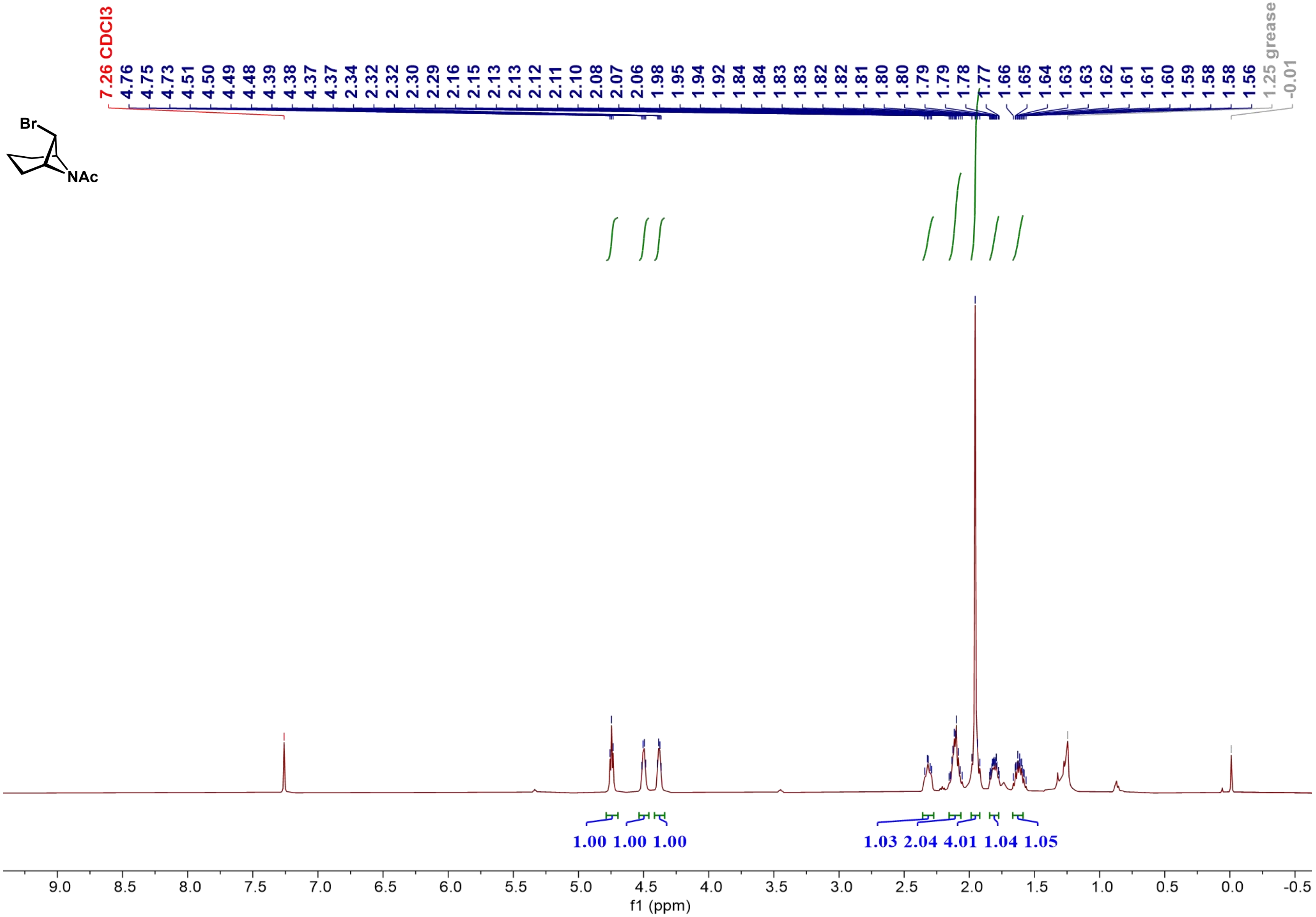
^{1}H NMR Spectrum of compound 26 (500 MHz, CDCl$_3$)



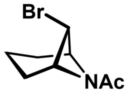
^{13}C NMR Spectrum of compound 26 (126 MHz, $CDCl_3$)

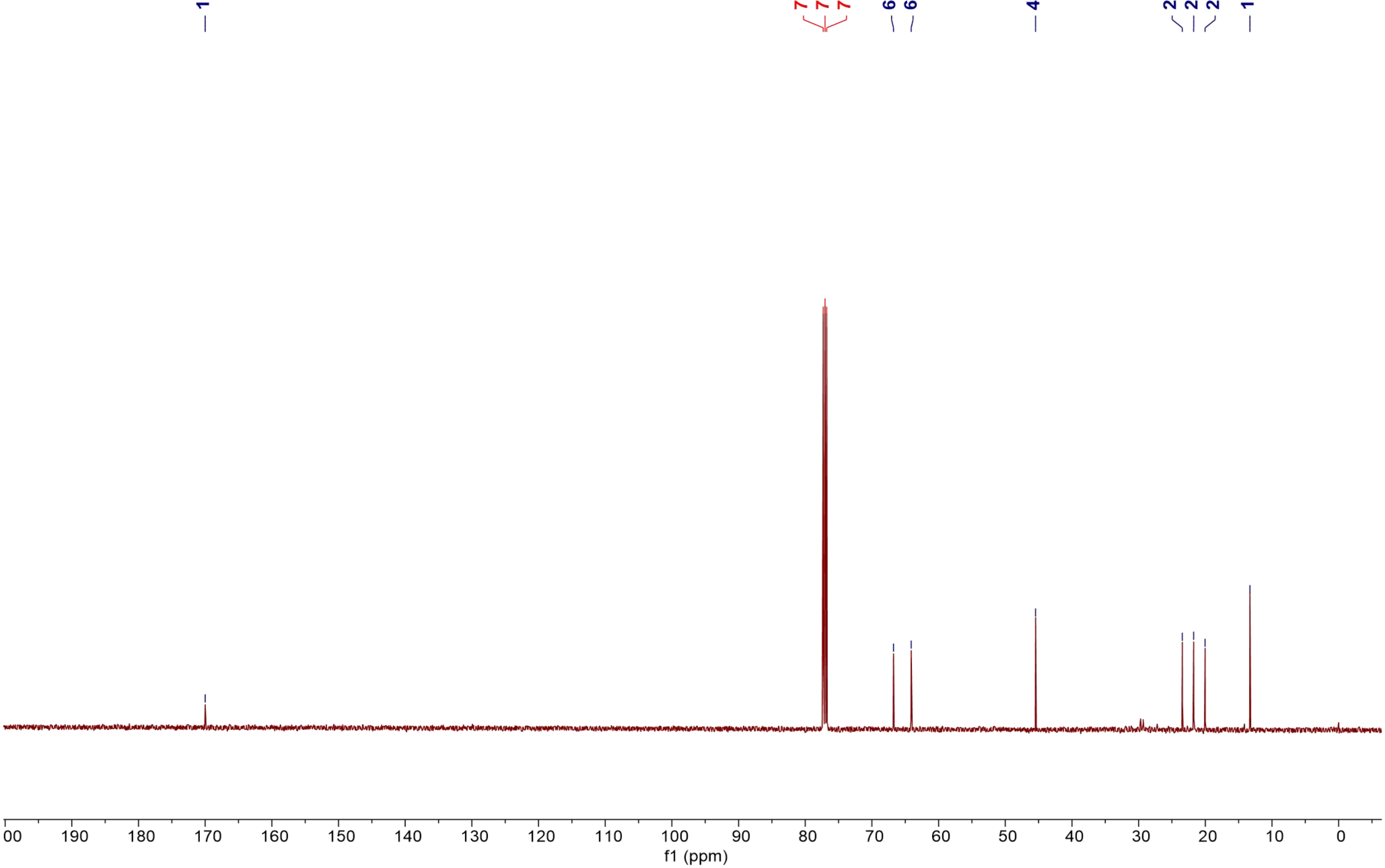


^{1}H NMR Spectrum of compound 27 (500 MHz, $CDCl_3$)

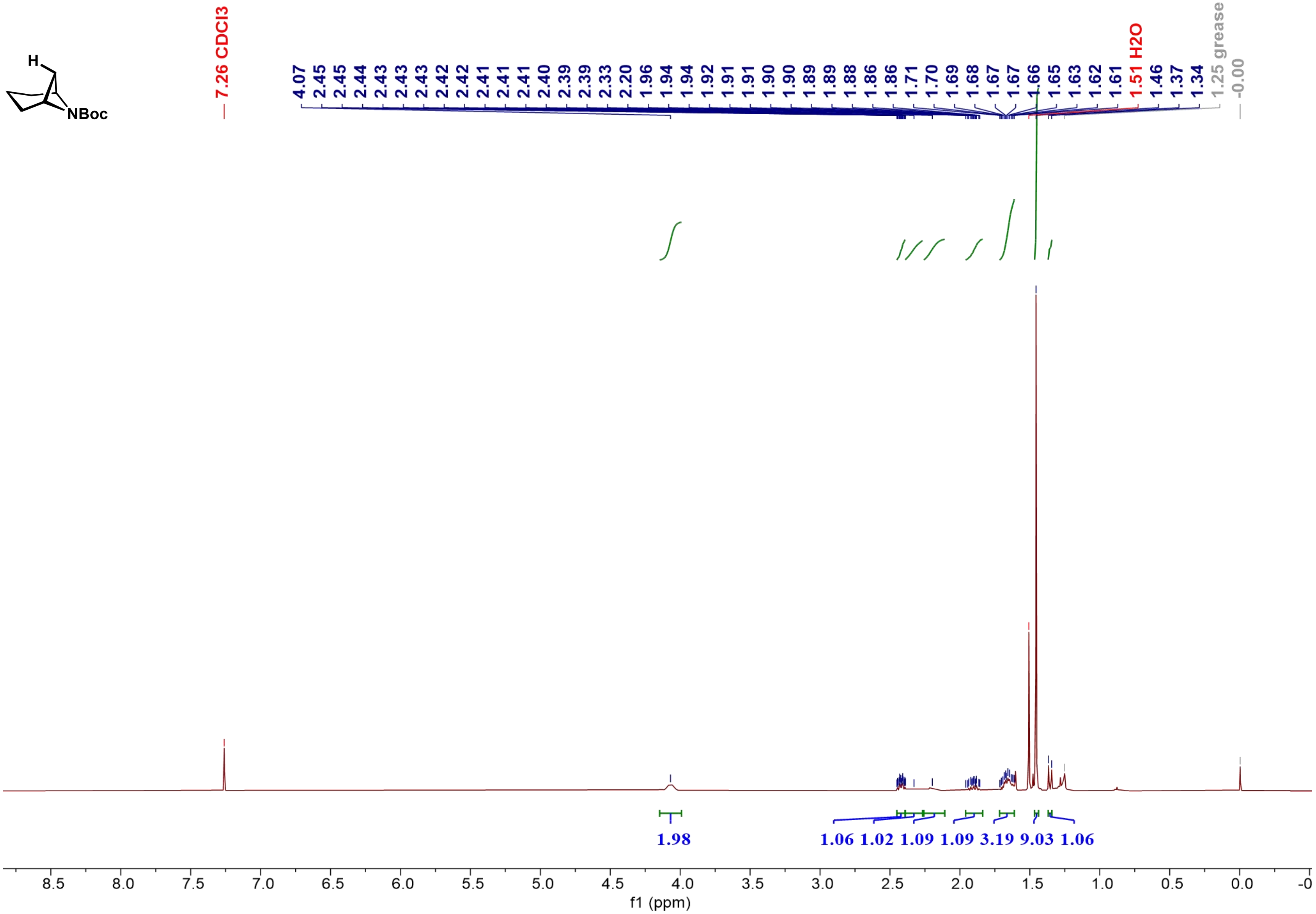


^{13}C NMR Spectrum of compound 27 (126 MHz, $CDCl_3$)

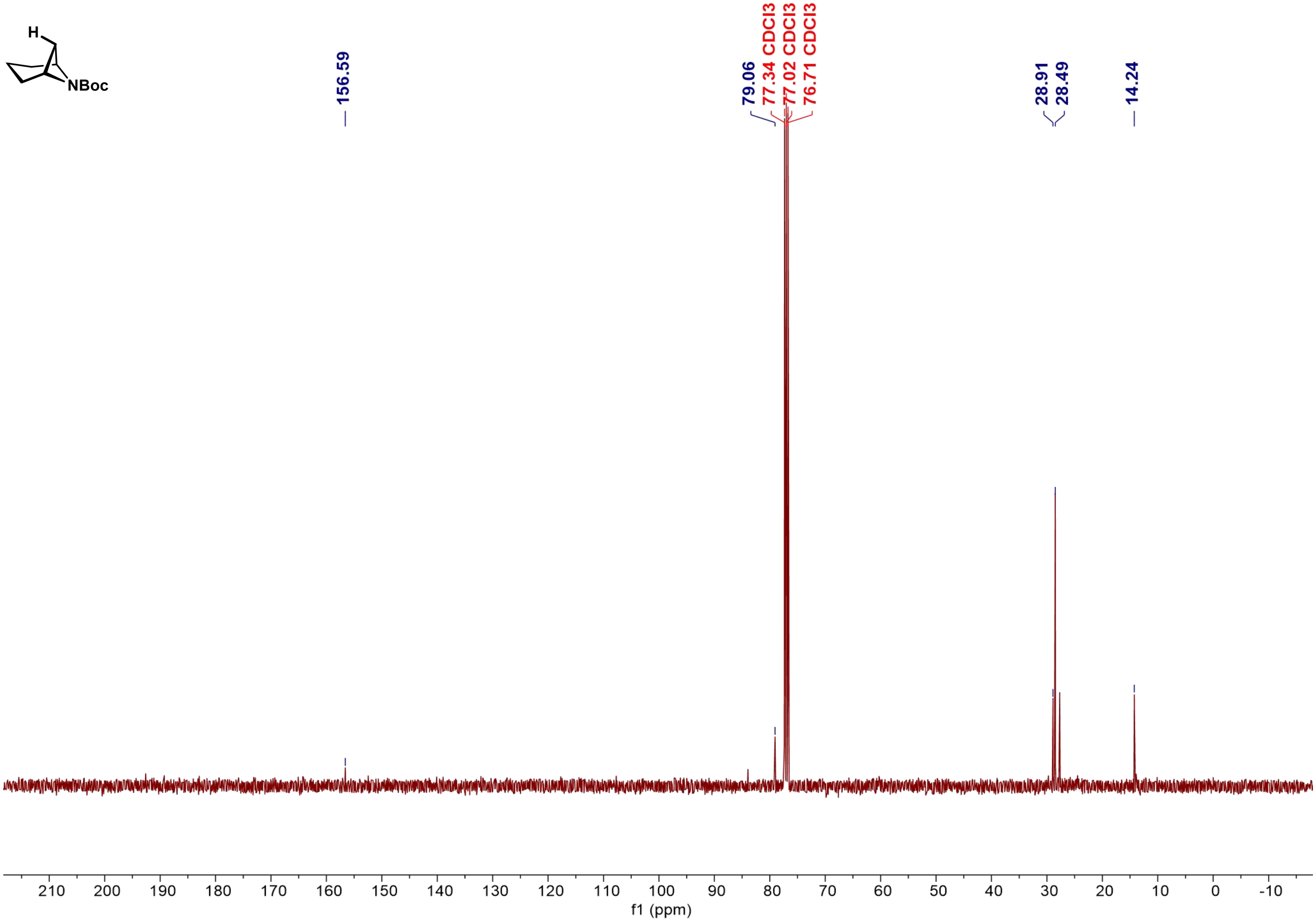




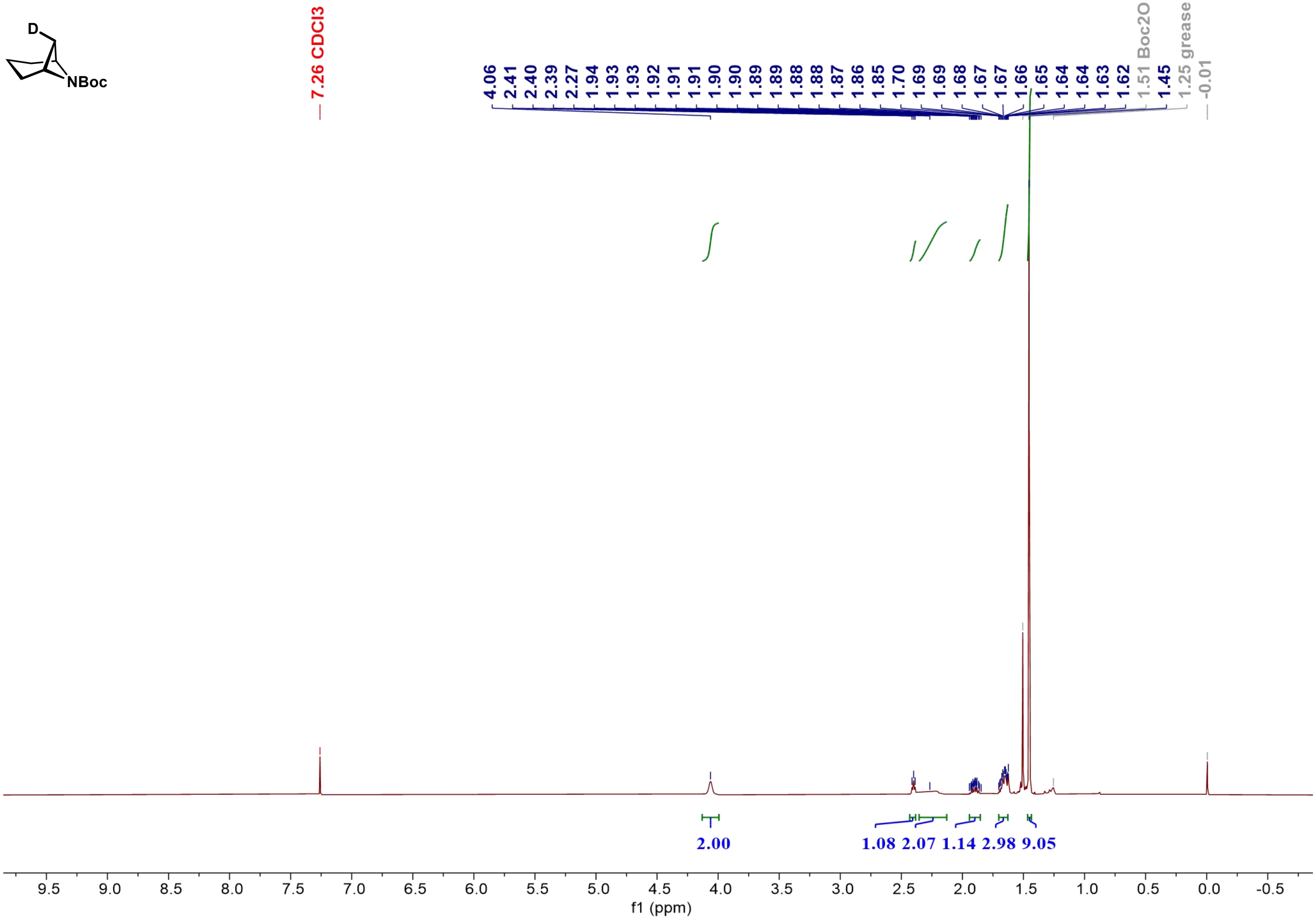
^{1}H NMR Spectrum of compound 28 (400 MHz, $CDCl_3$)



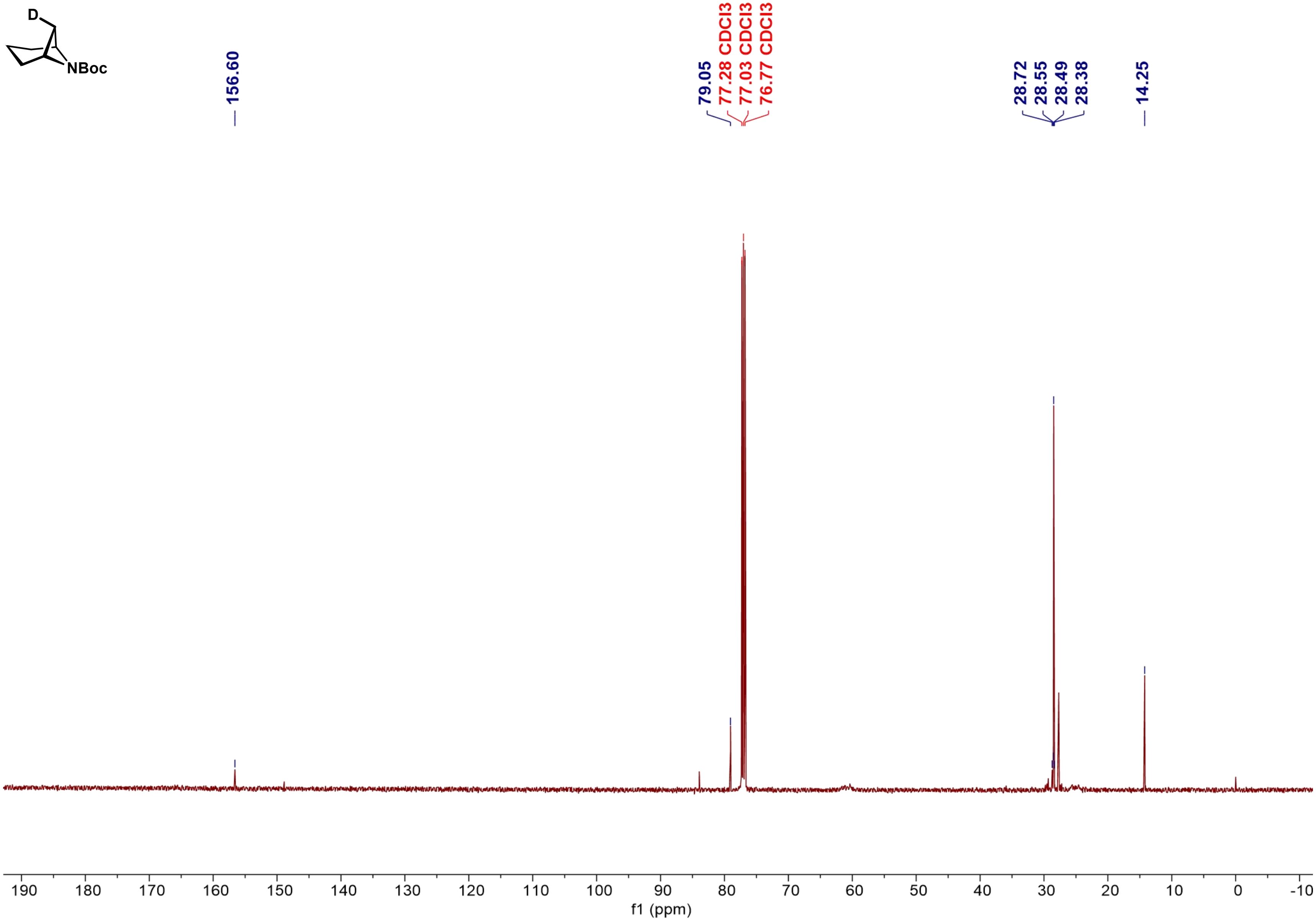
^{13}C NMR Spectrum of compound 28 (101 MHz, $CDCl_3$)



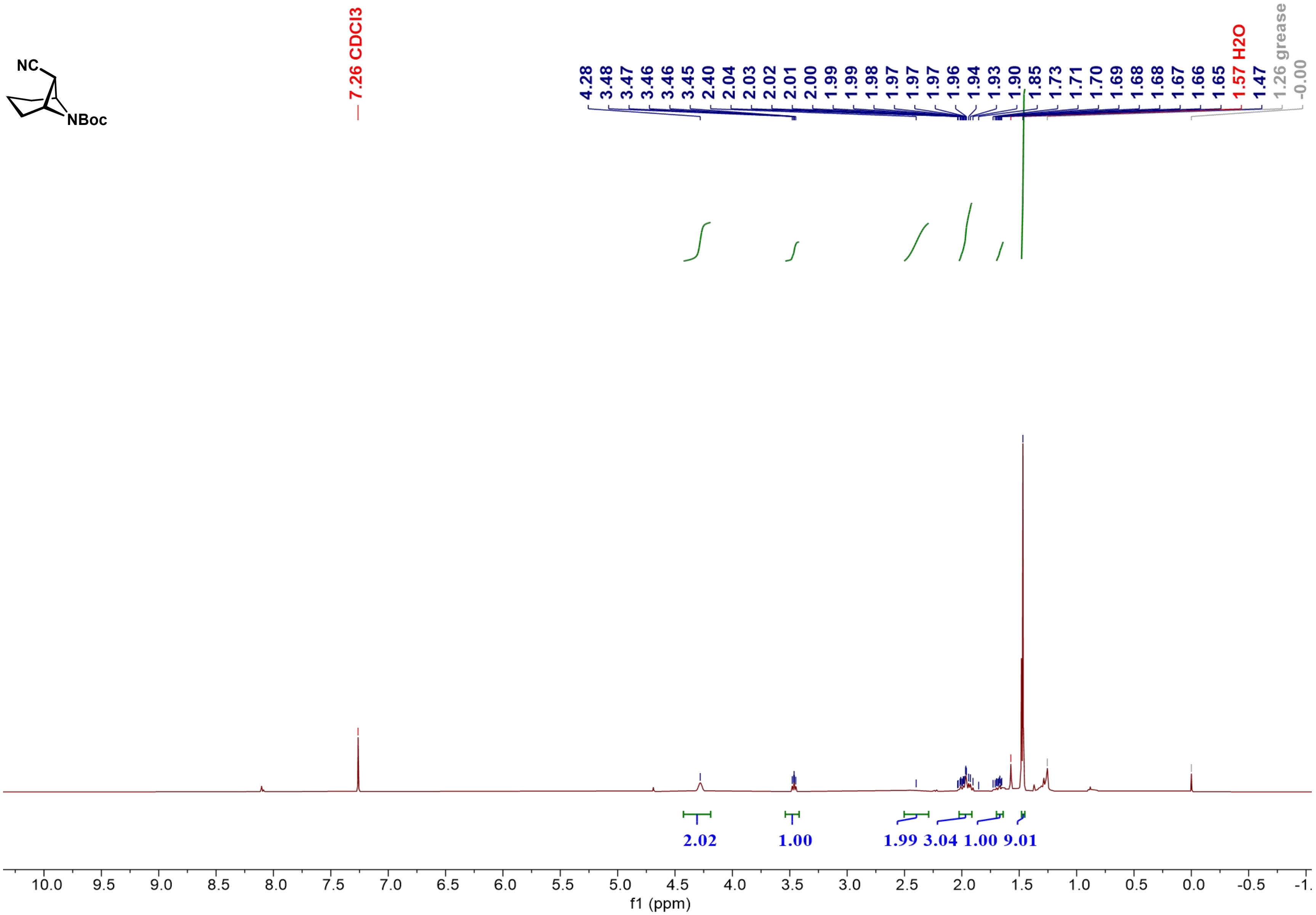
^{1}H NMR Spectrum of compound 29 (500 MHz, CDCl$_3$)



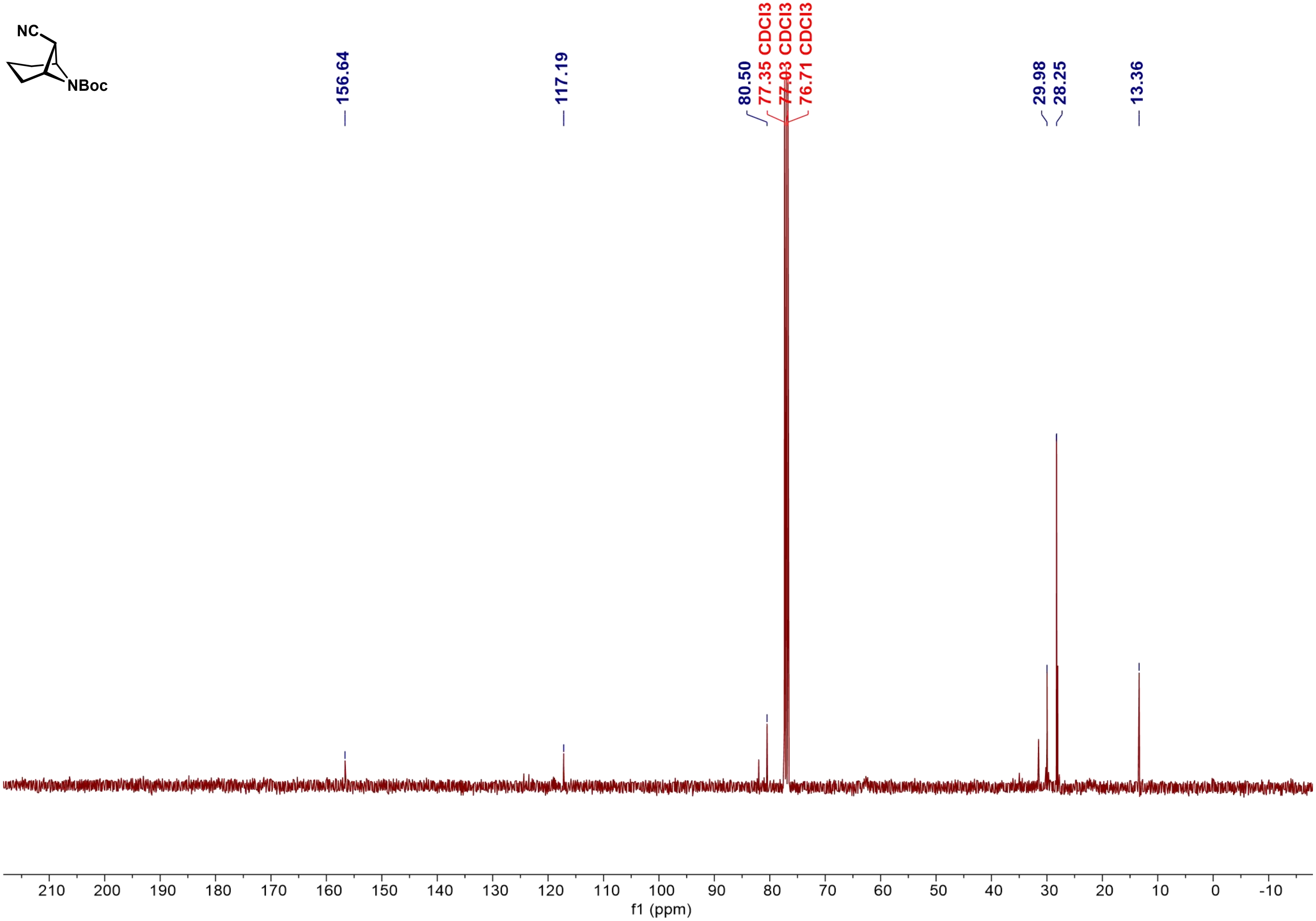
^{13}C NMR Spectrum of compound 29 (126 MHz, $CDCl_3$)



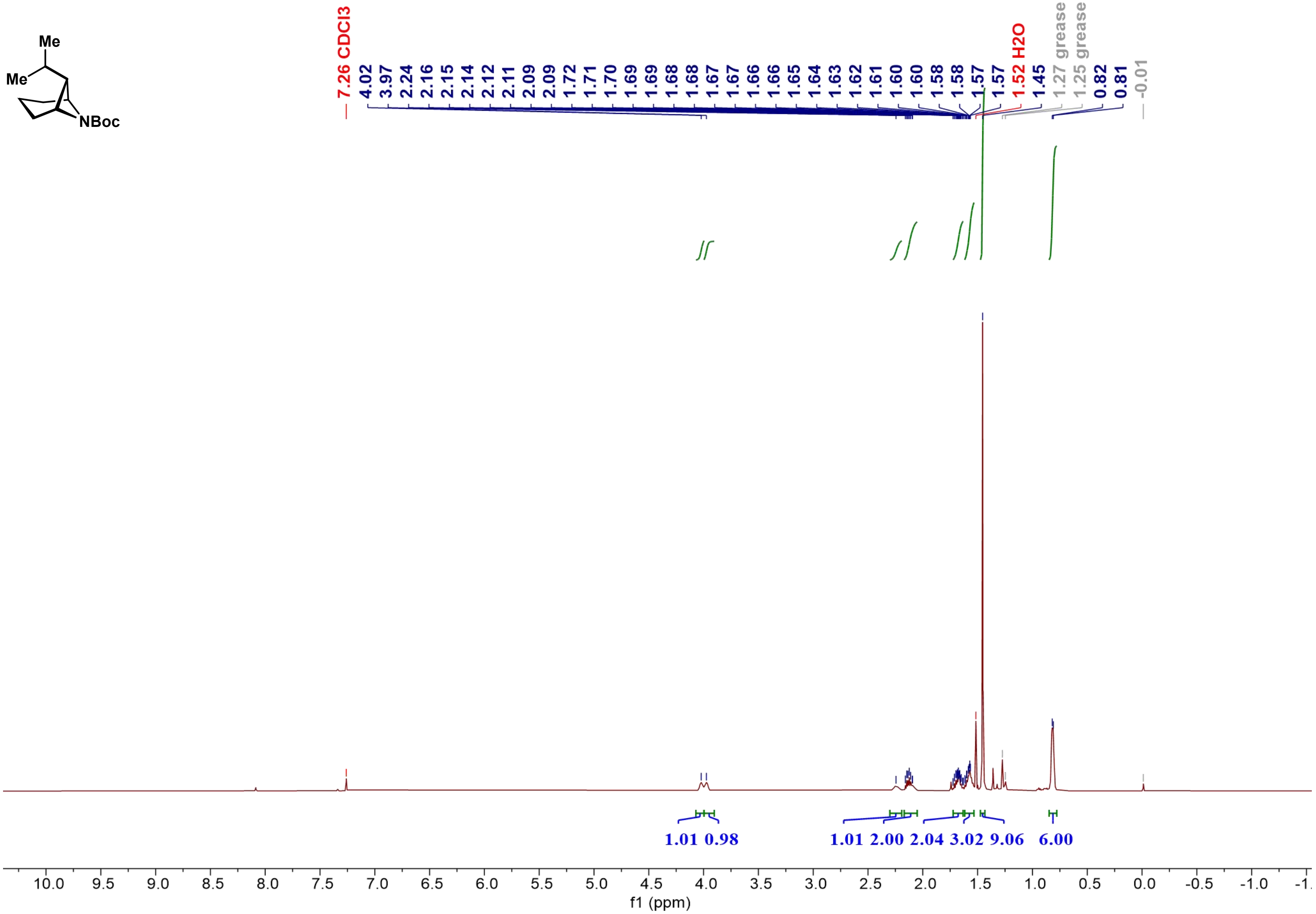
^{1}H NMR Spectrum of compound 30 (400 MHz, $CDCl_3$)



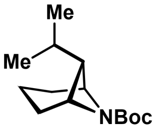
^{13}C NMR Spectrum of compound 30 (101 MHz, $CDCl_3$)

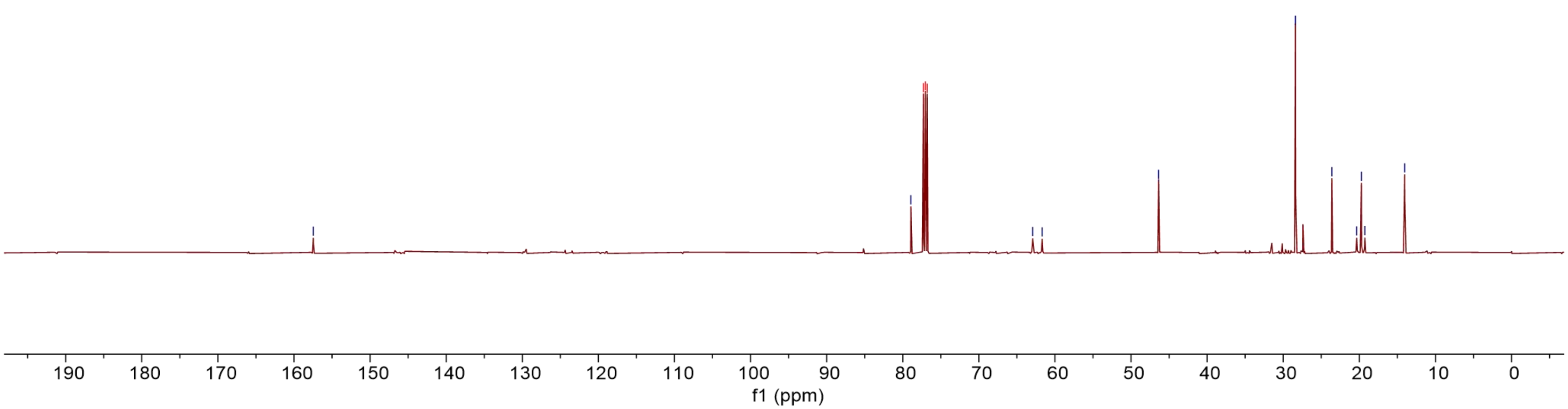


^{1}H NMR Spectrum of compound 31 (500 MHz, CDCl$_3$)

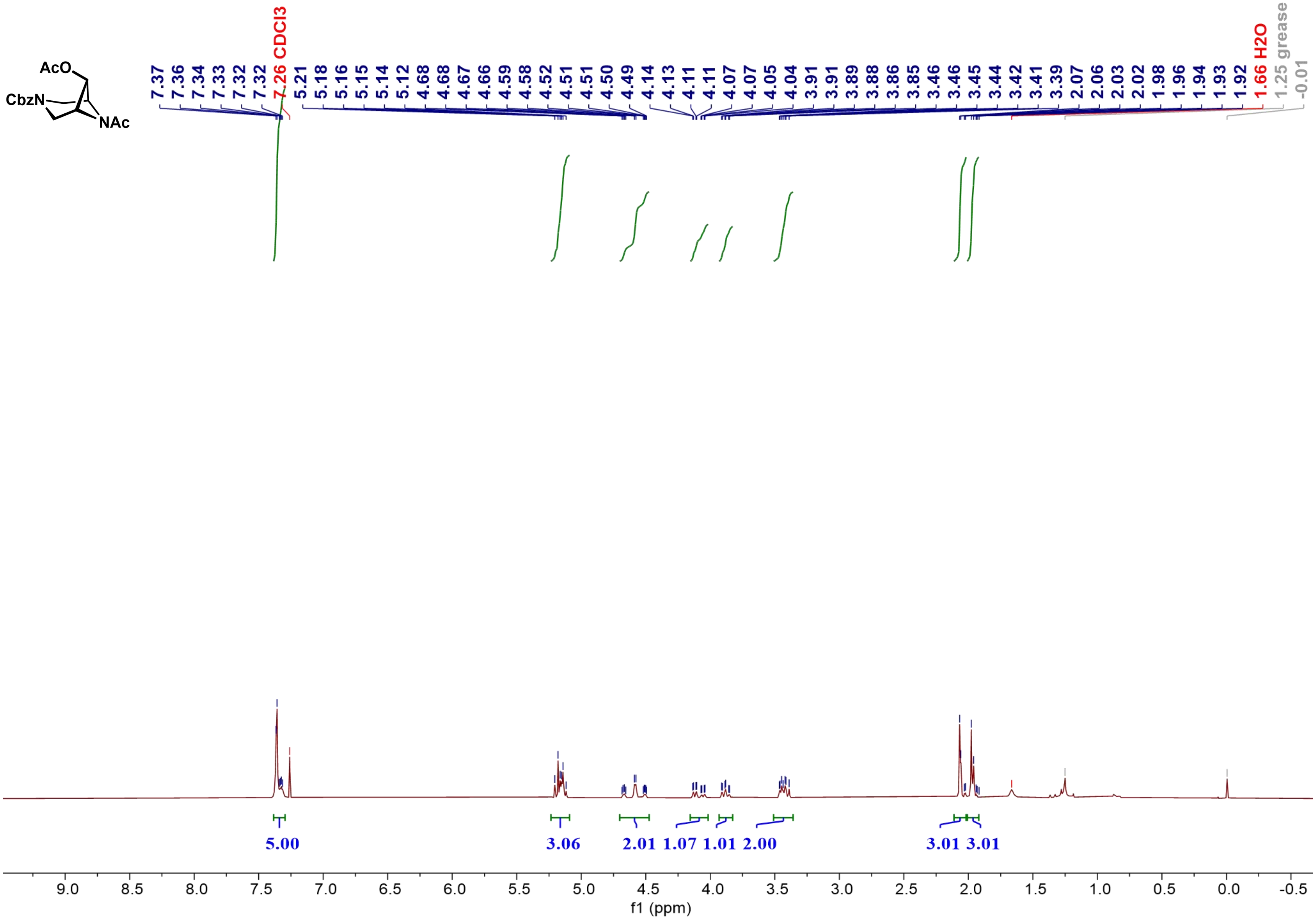


^{13}C NMR Spectrum of compound 31 (126 MHz, $CDCl_3$)

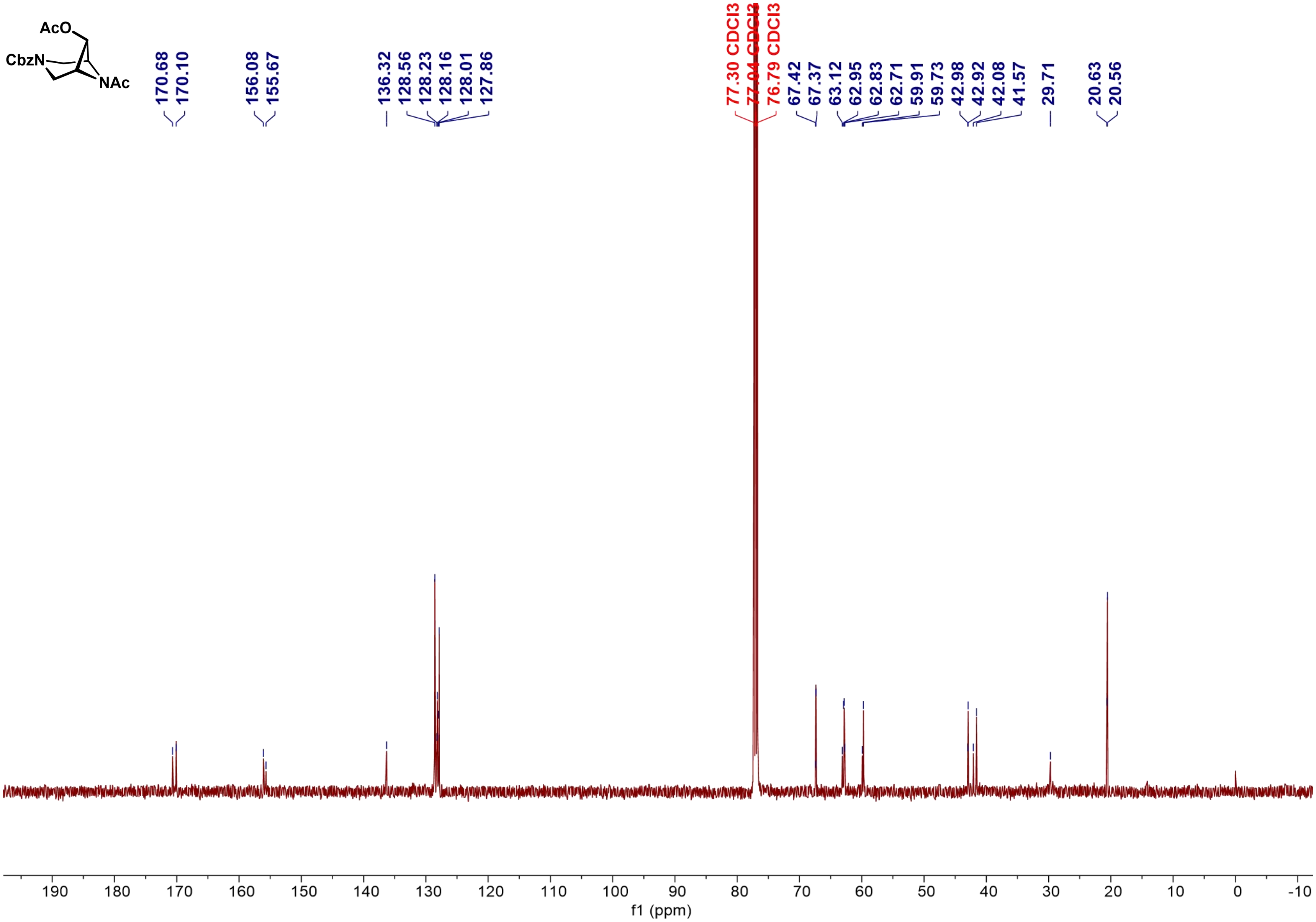




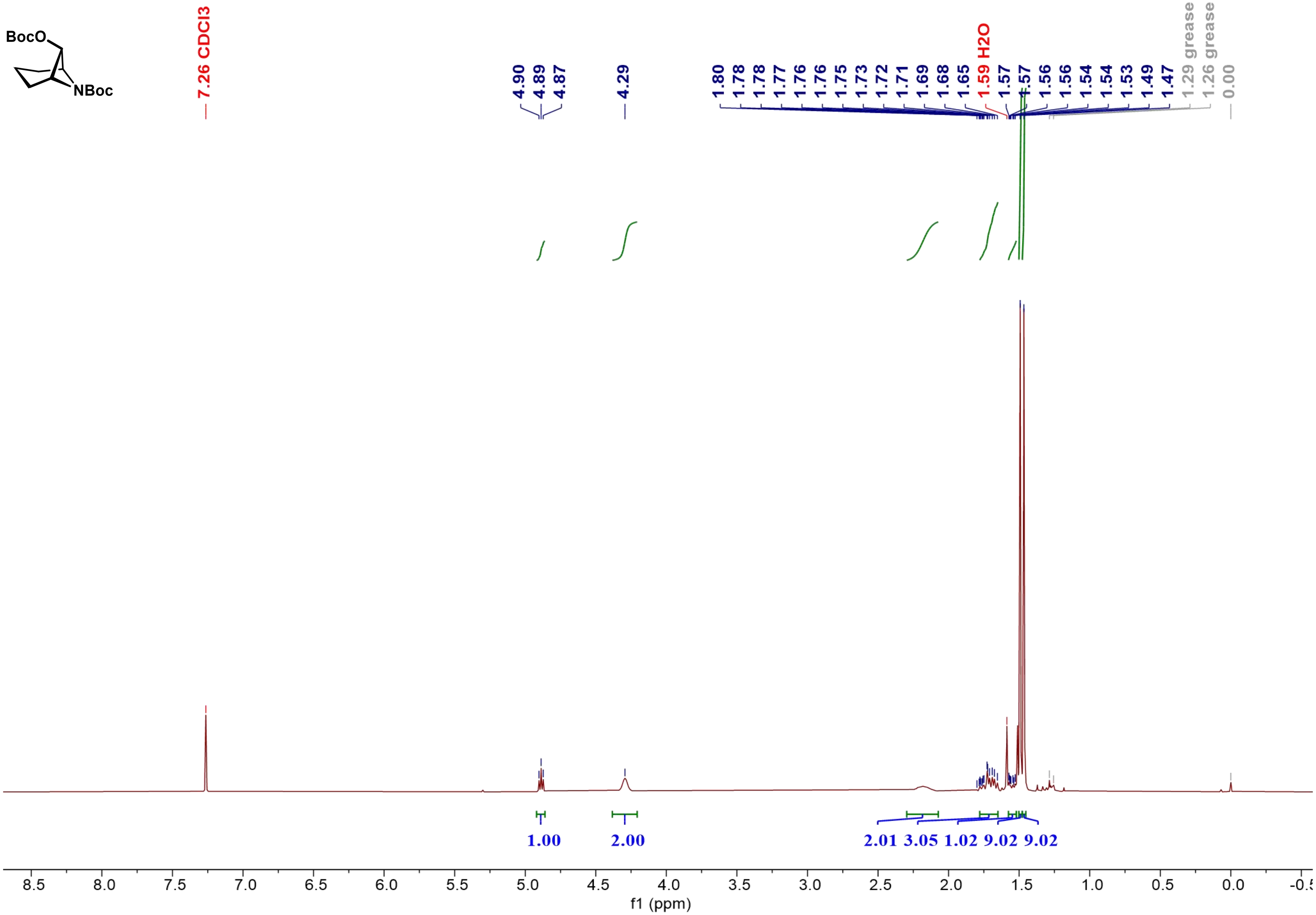
^{1}H NMR Spectrum of compound 32 (500 MHz, $CDCl_3$)



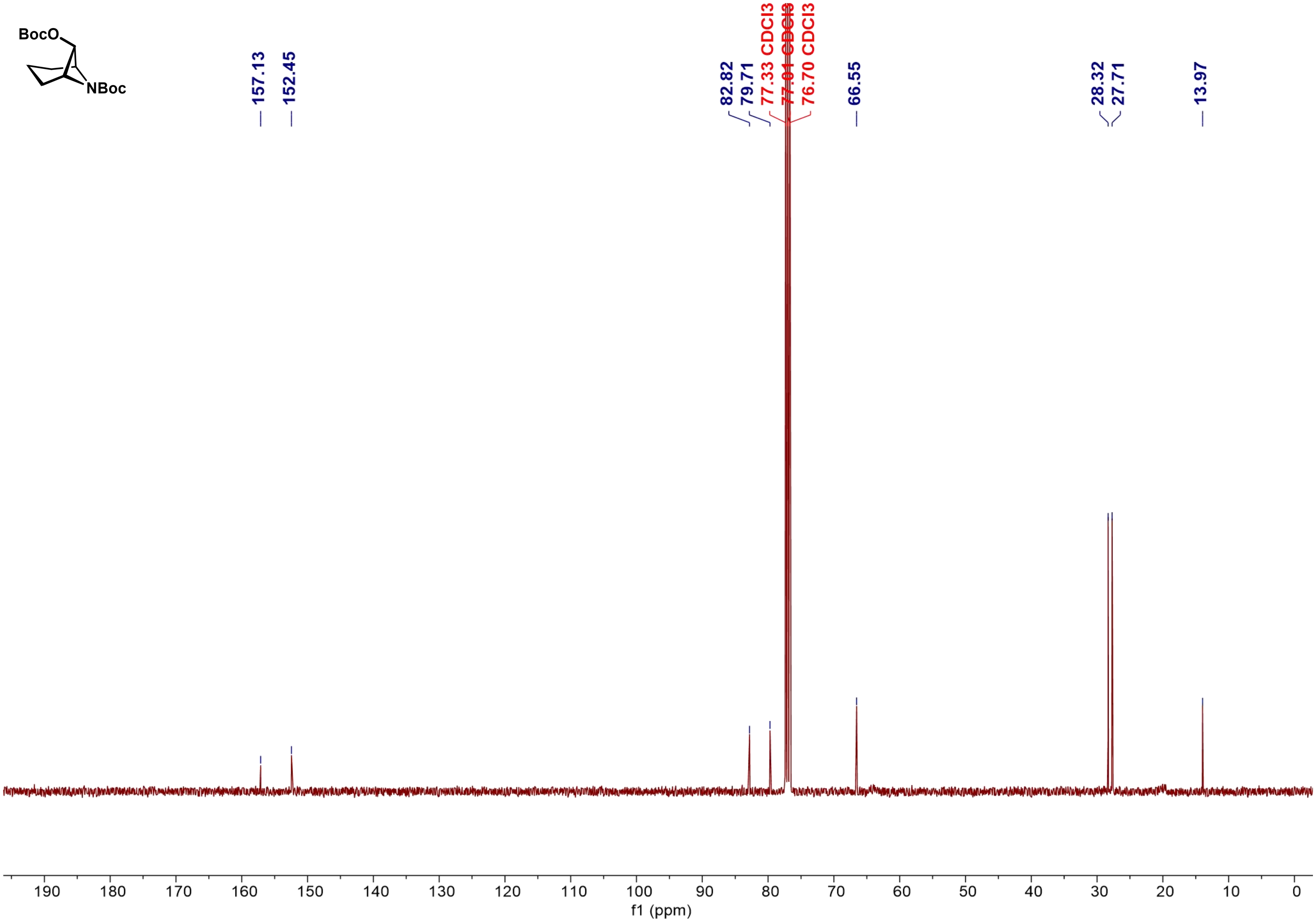
^{13}C NMR Spectrum of compound 32 (126 MHz, CDCl$_3$)



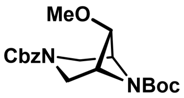
^{1}H NMR Spectrum of compound 33 (400 MHz, $CDCl_3$)

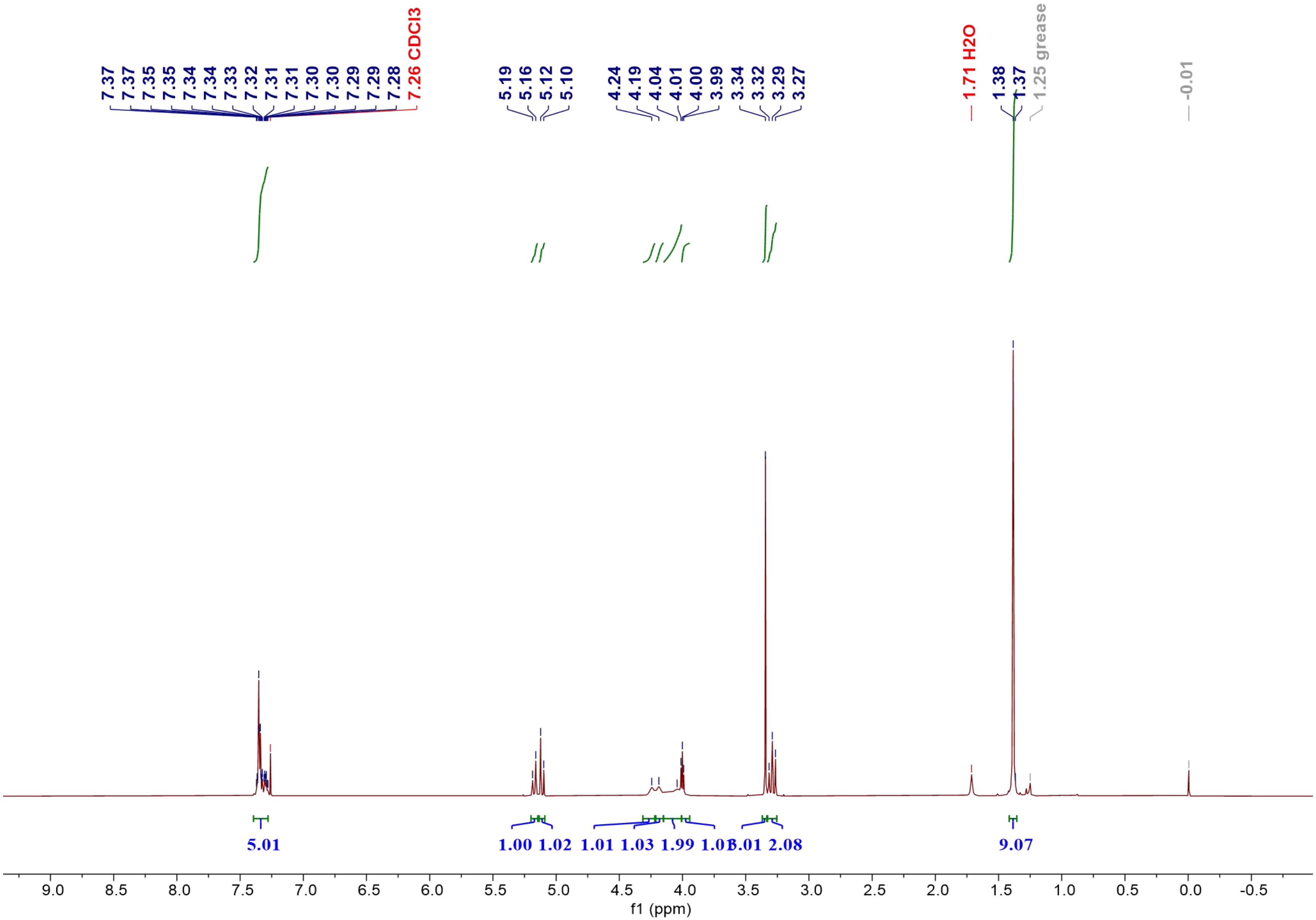


^{13}C NMR Spectrum of compound 33 (101 MHz, $CDCl_3$)

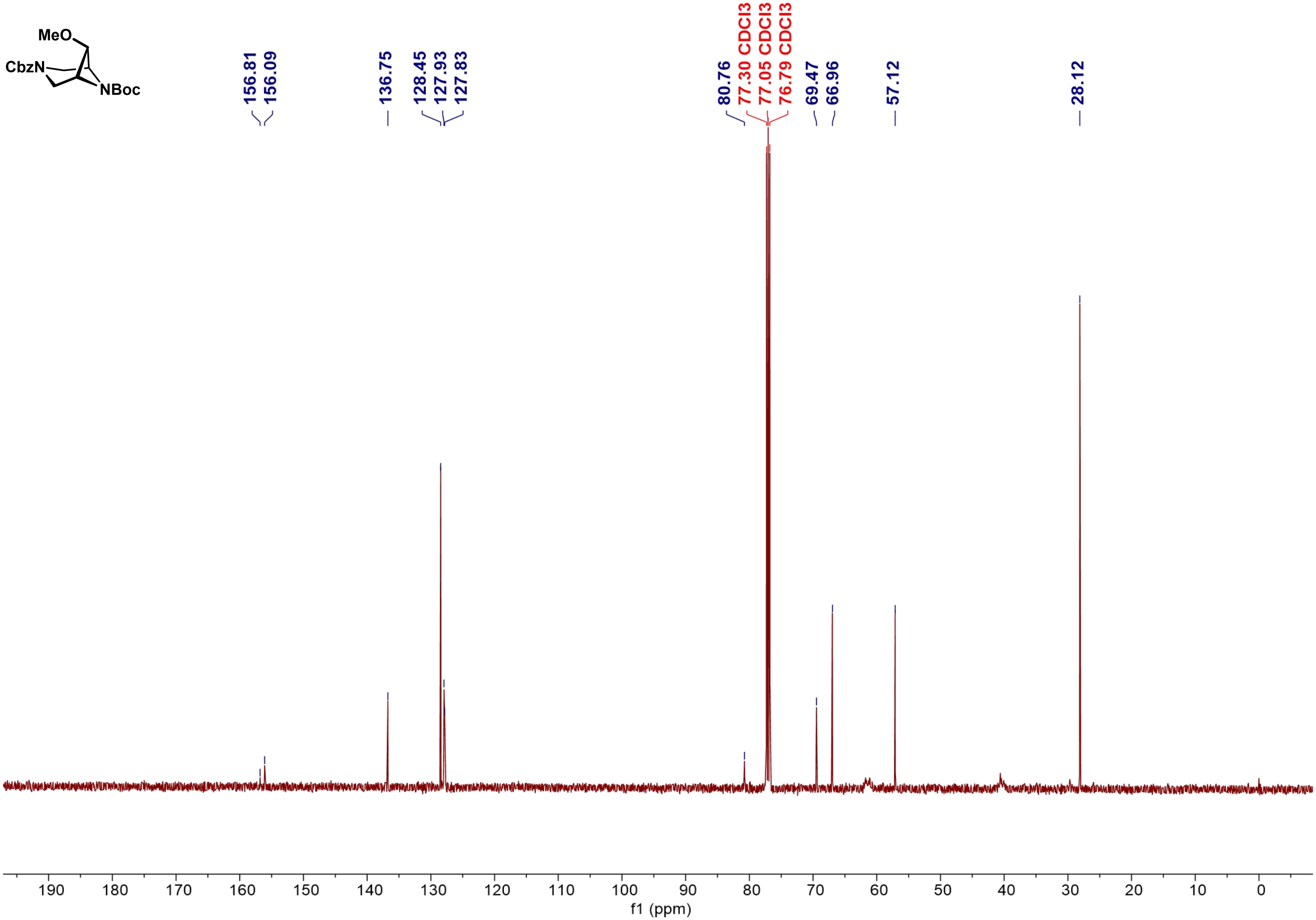


^{1}H NMR Spectrum of compound 34 (500 MHz, CDCl$_3$)

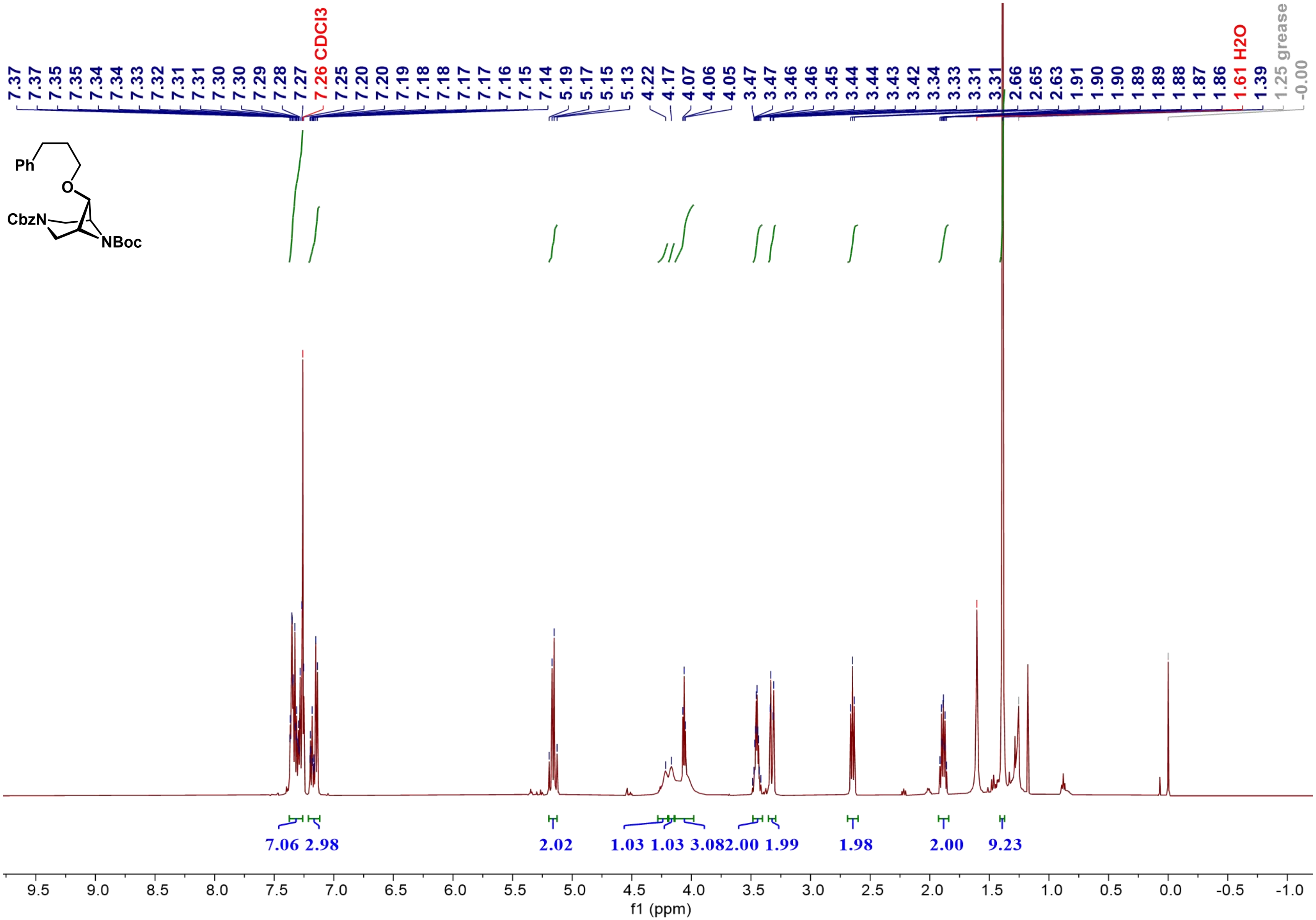



7.37
7.37
7.35
7.35
7.34
7.34
7.33
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.28
7.26 CDCl3
5.19
5.16
5.12
5.10
4.24
4.19
4.04
4.01
4.00
3.99
3.34
3.32
3.29
3.27
1.71 H2O
1.38
1.37
1.25 grease
-0.01
5.01
1.00
1.02
1.01
1.03
1.99
1.01
3.01
2.08
9.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

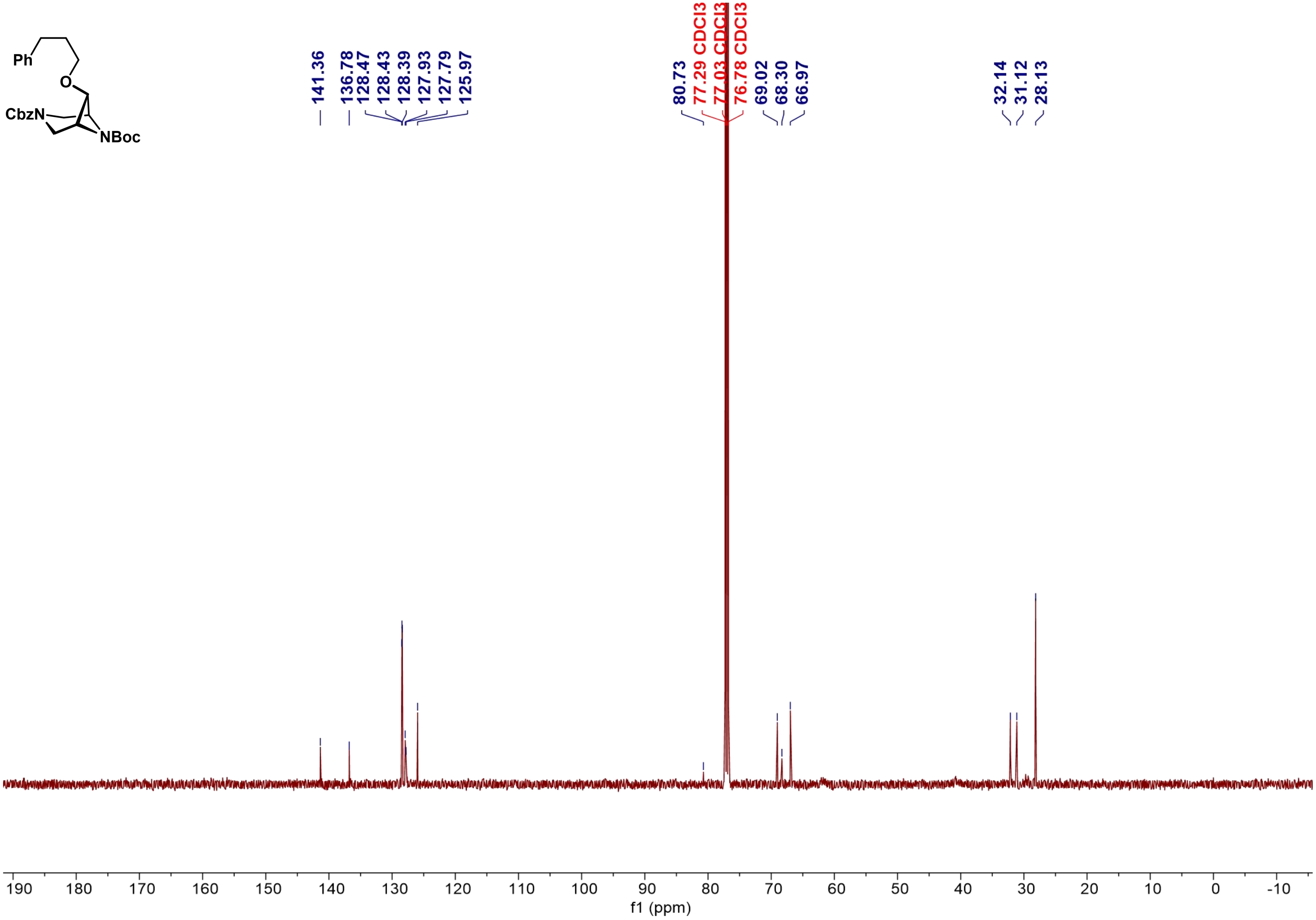
^{13}C NMR Spectrum of compound 34 (126 MHz, $CDCl_3$)



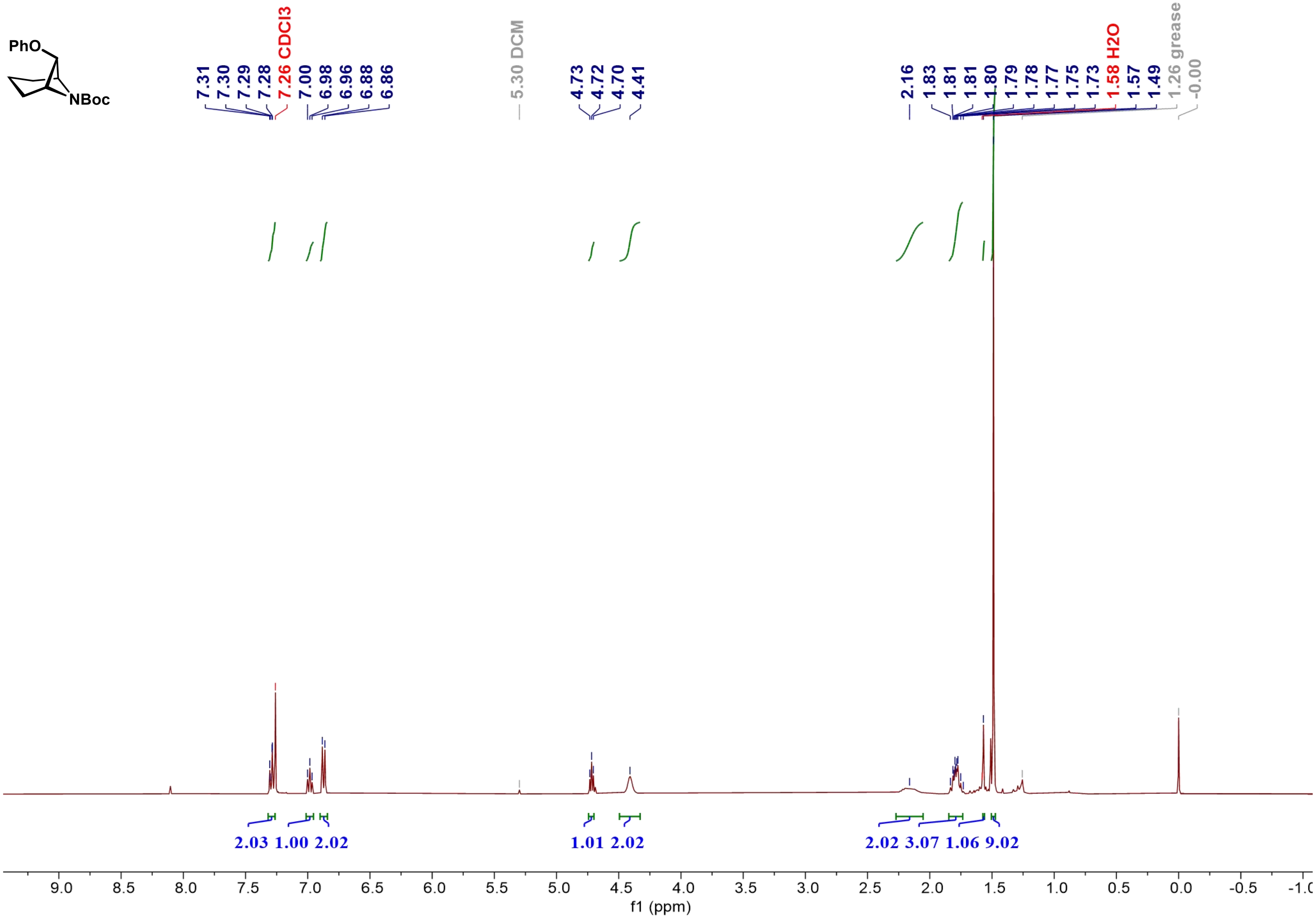
^{1}H NMR Spectrum of compound 35 (500 MHz, $CDCl_3$)



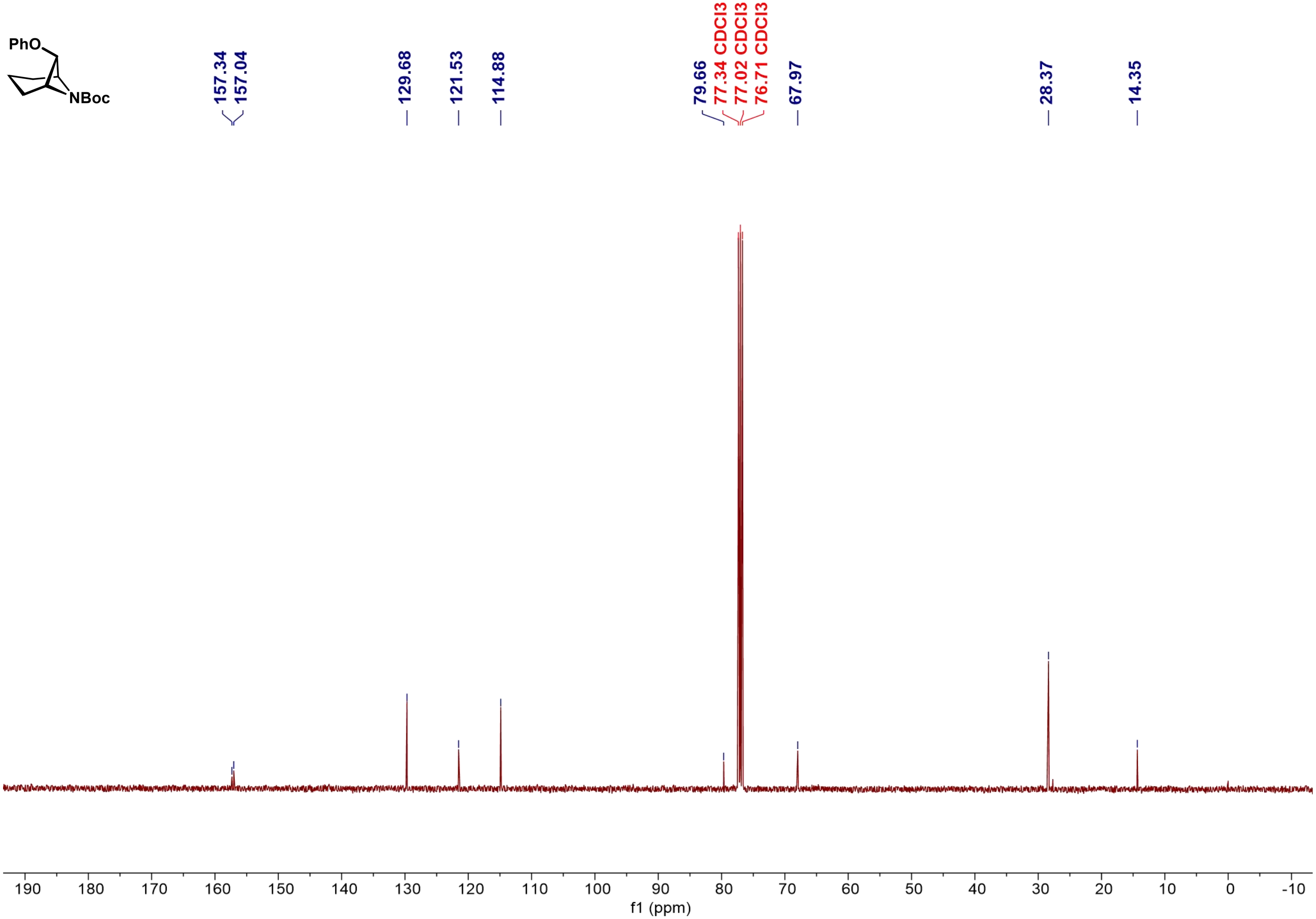
^{13}C NMR Spectrum of compound 35 (126 MHz, CDCl$_3$)



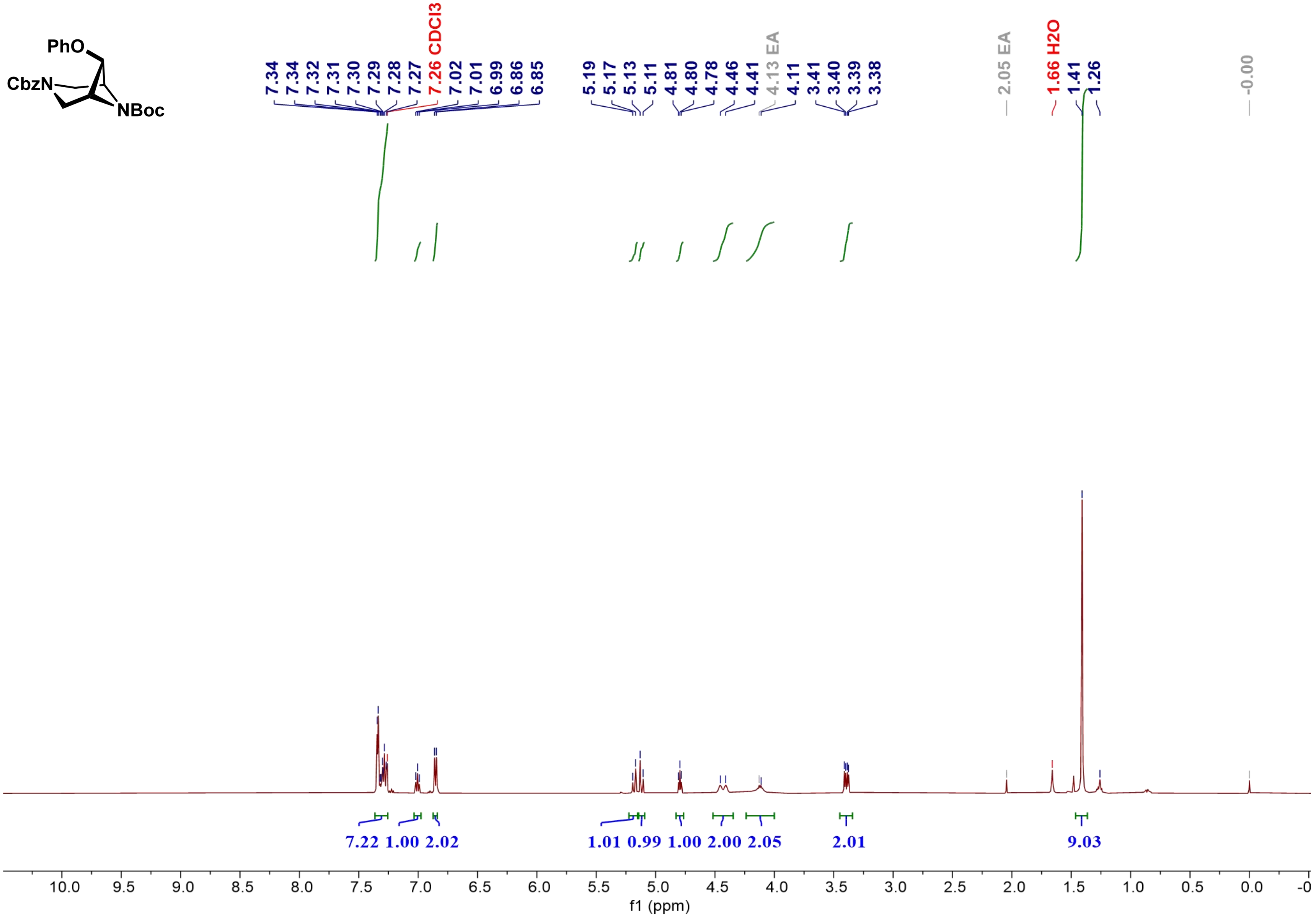
^{1}H NMR Spectrum of compound 36 (400 MHz, $CDCl_3$)



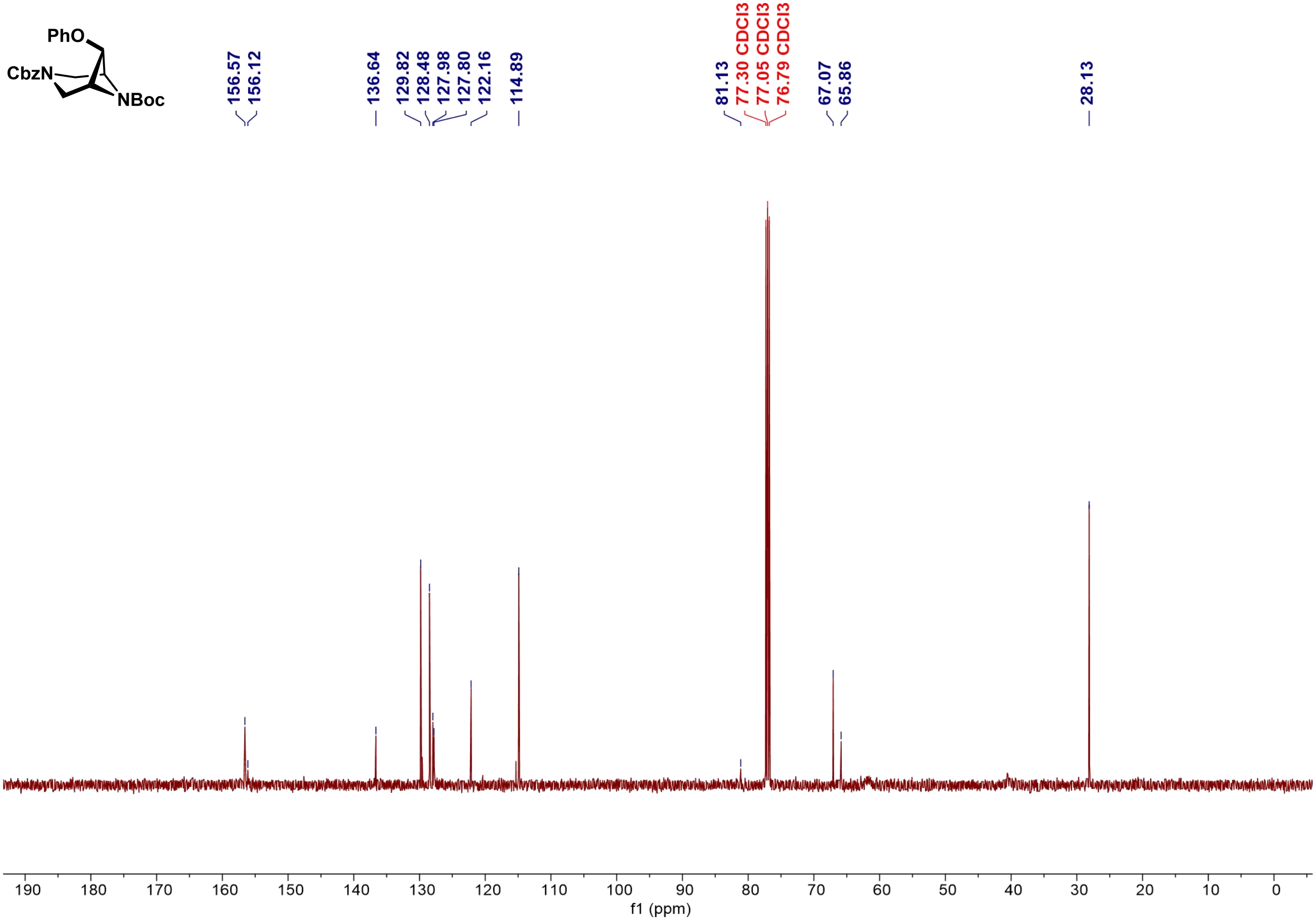
^{13}C NMR Spectrum of compound 36 (101 MHz, CDCl$_3$)



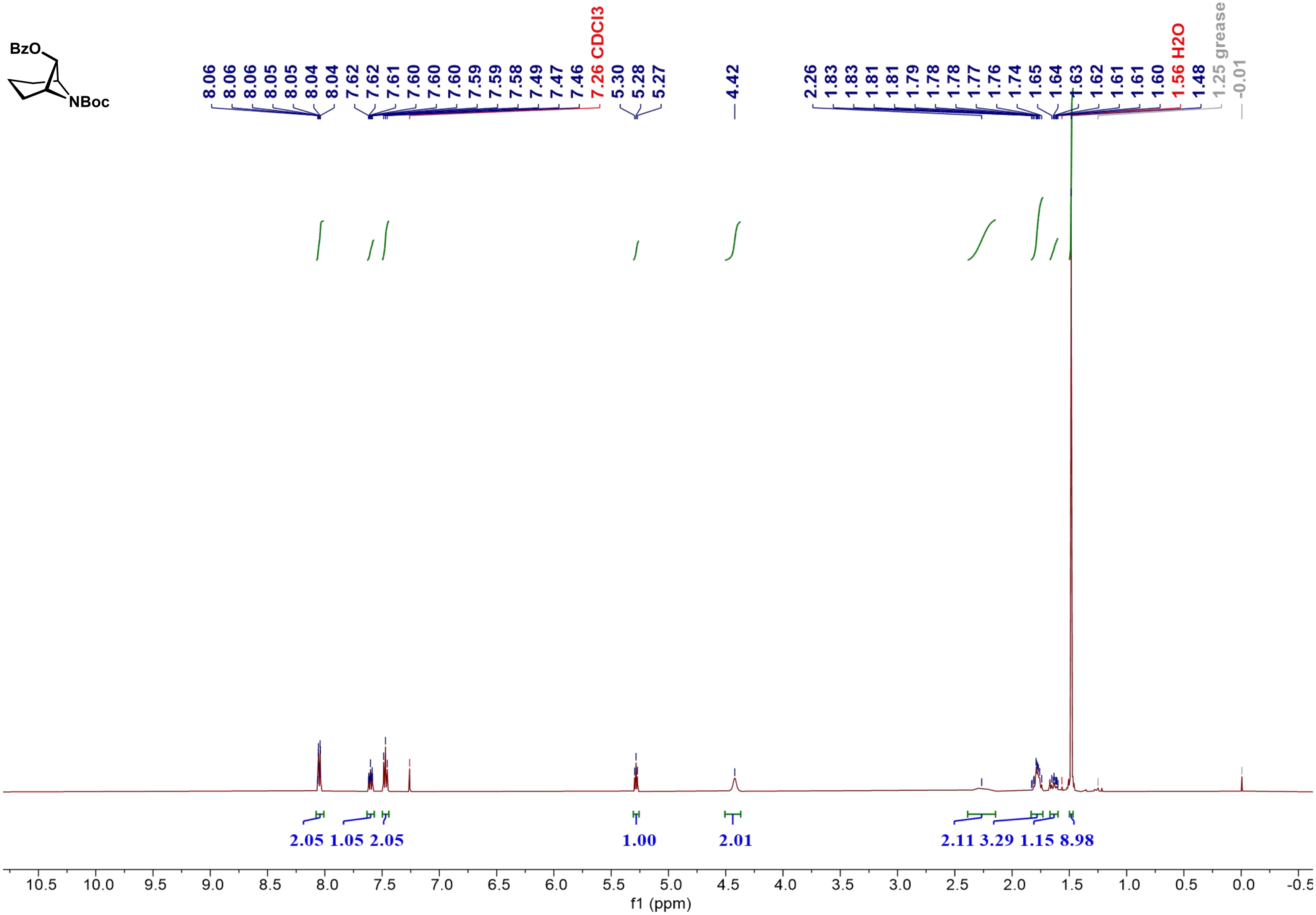
^{1}H NMR Spectrum of compound 37 (500 MHz, CDCl$_3$)



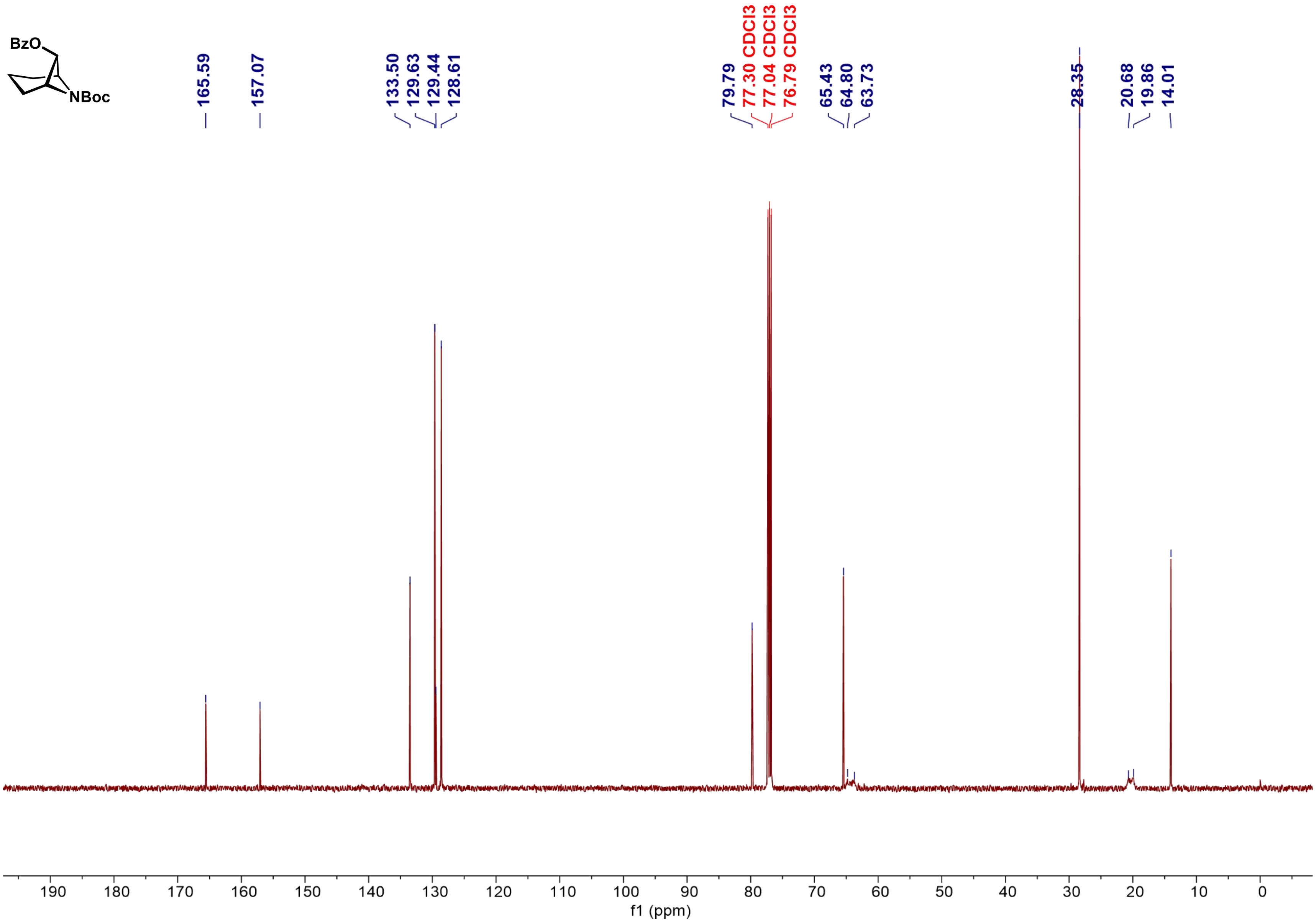
^{13}C NMR Spectrum of compound 37 (126 MHz, CDCl$_3$)



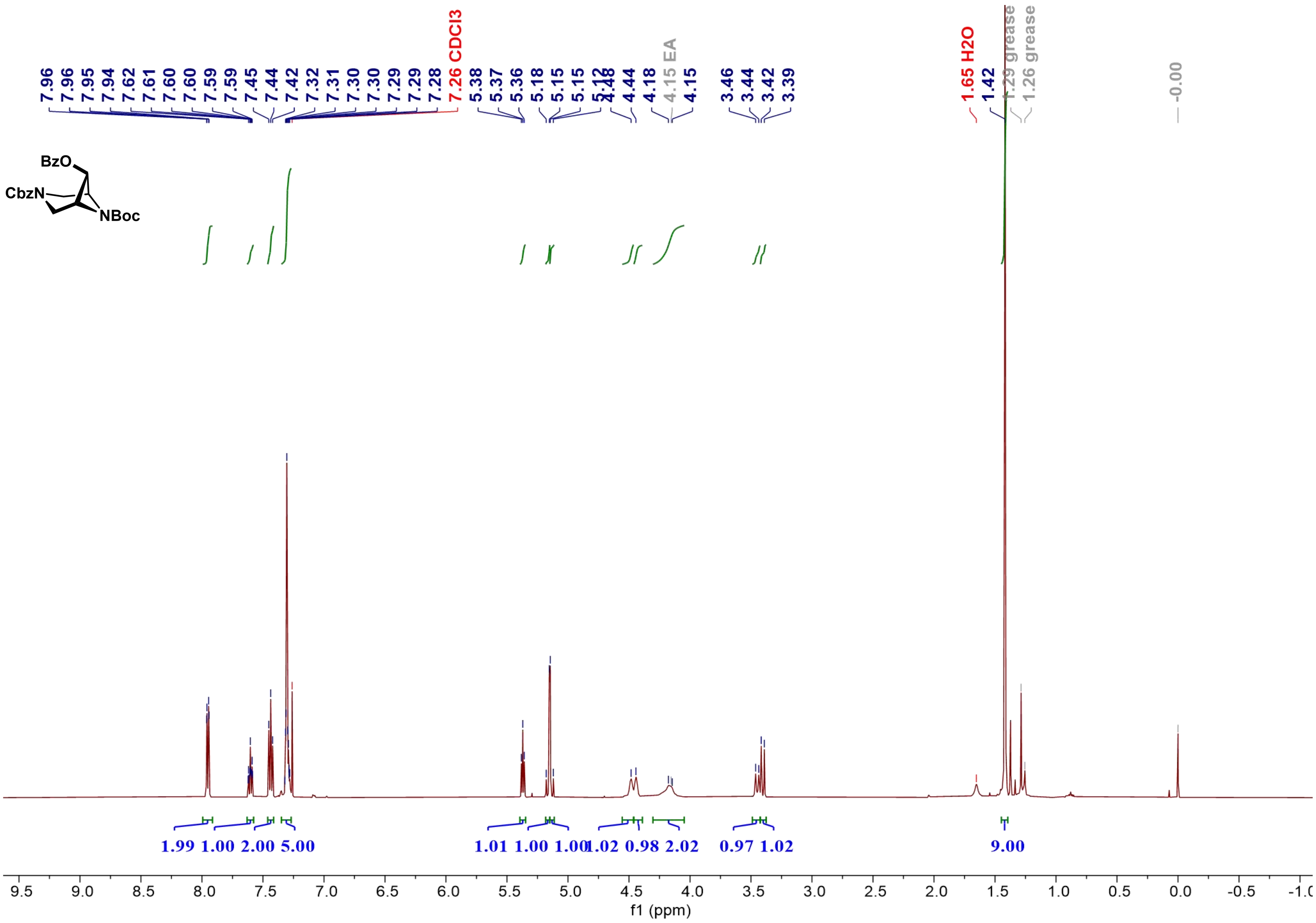
^{1}H NMR Spectrum of compound 38 (500 MHz, $CDCl_3$)



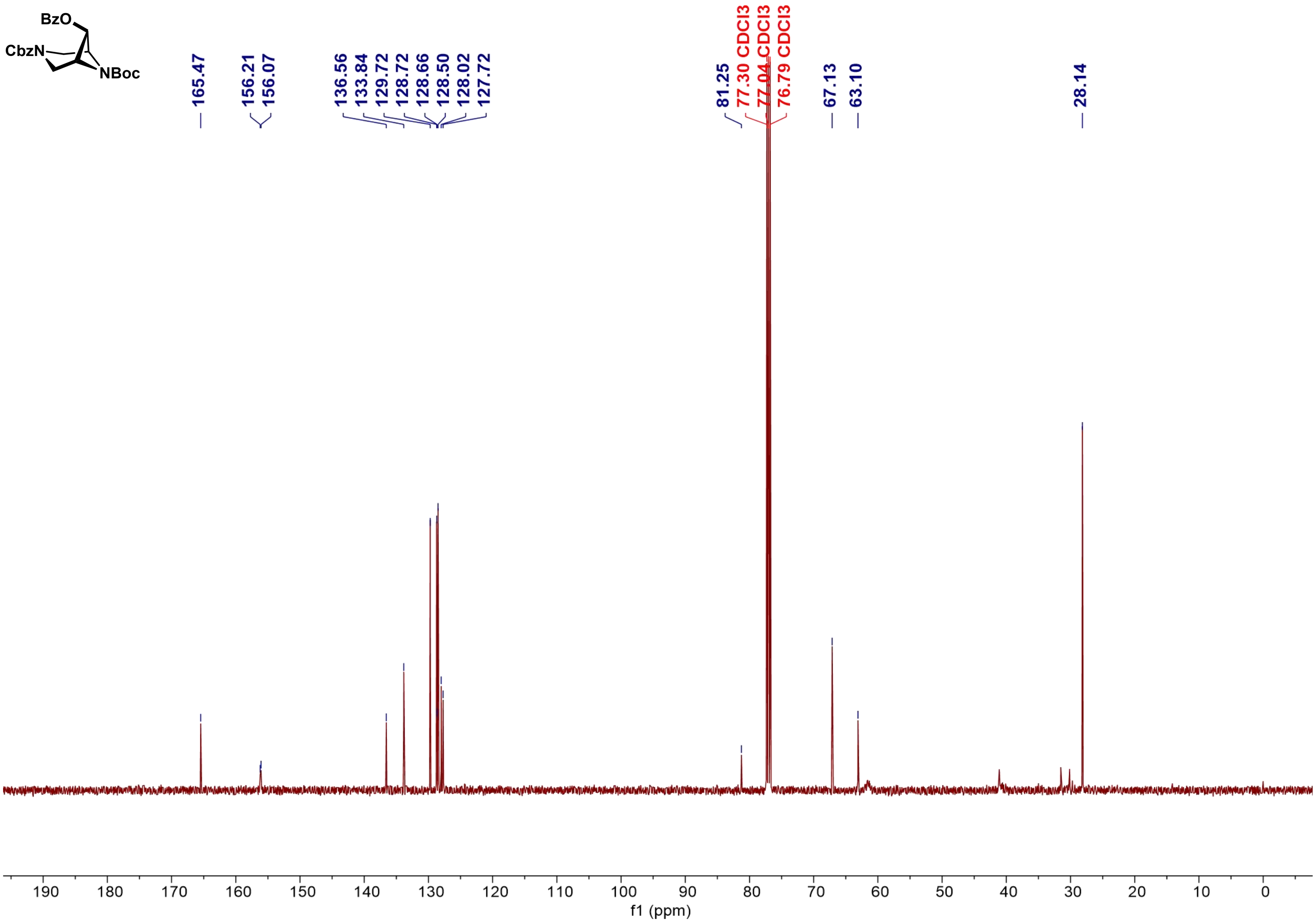
^{13}C NMR Spectrum of compound 38 (126 MHz, $CDCl_3$)



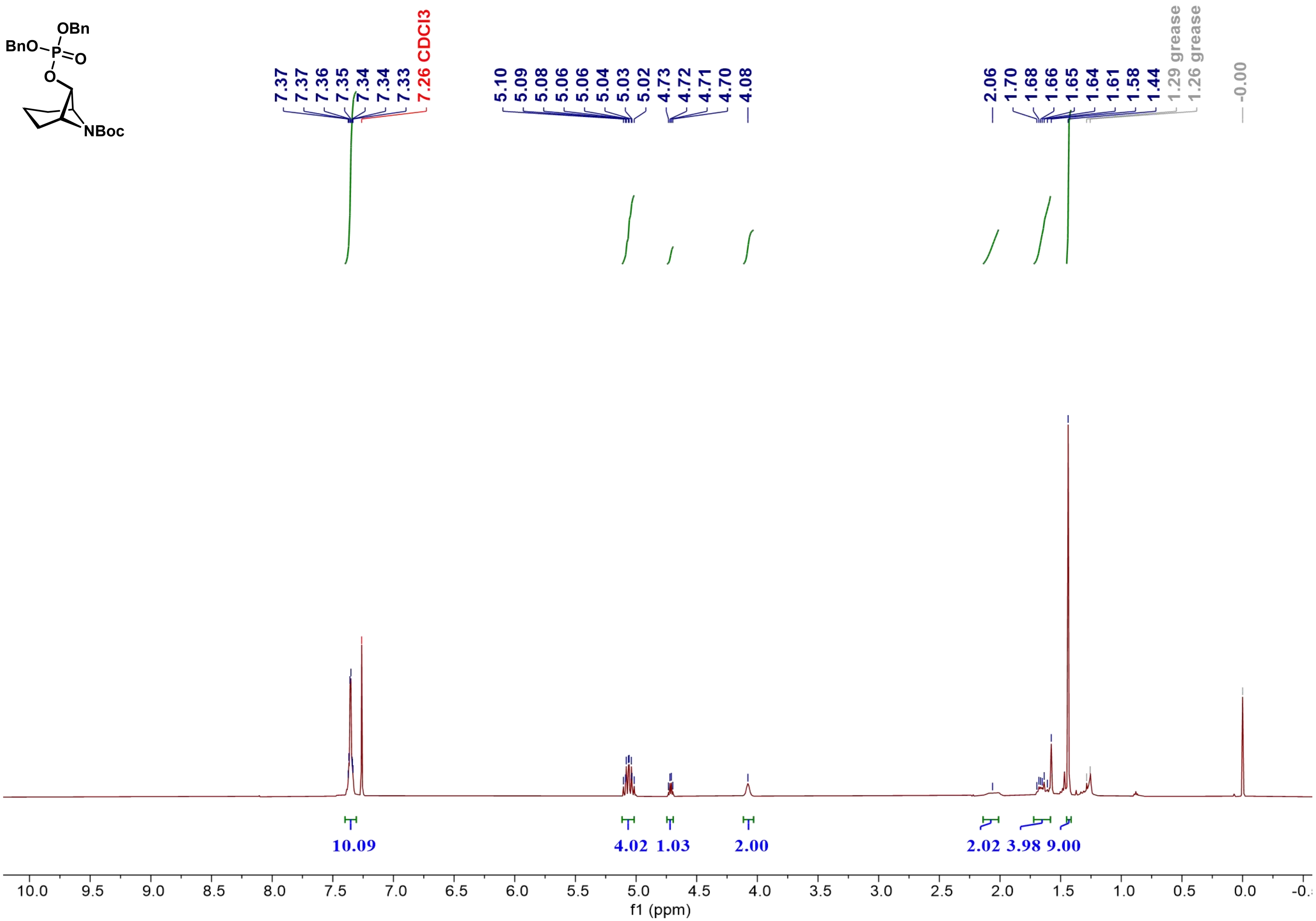
^{1}H NMR Spectrum of compound 39 (500 MHz, CDCl$_3$)



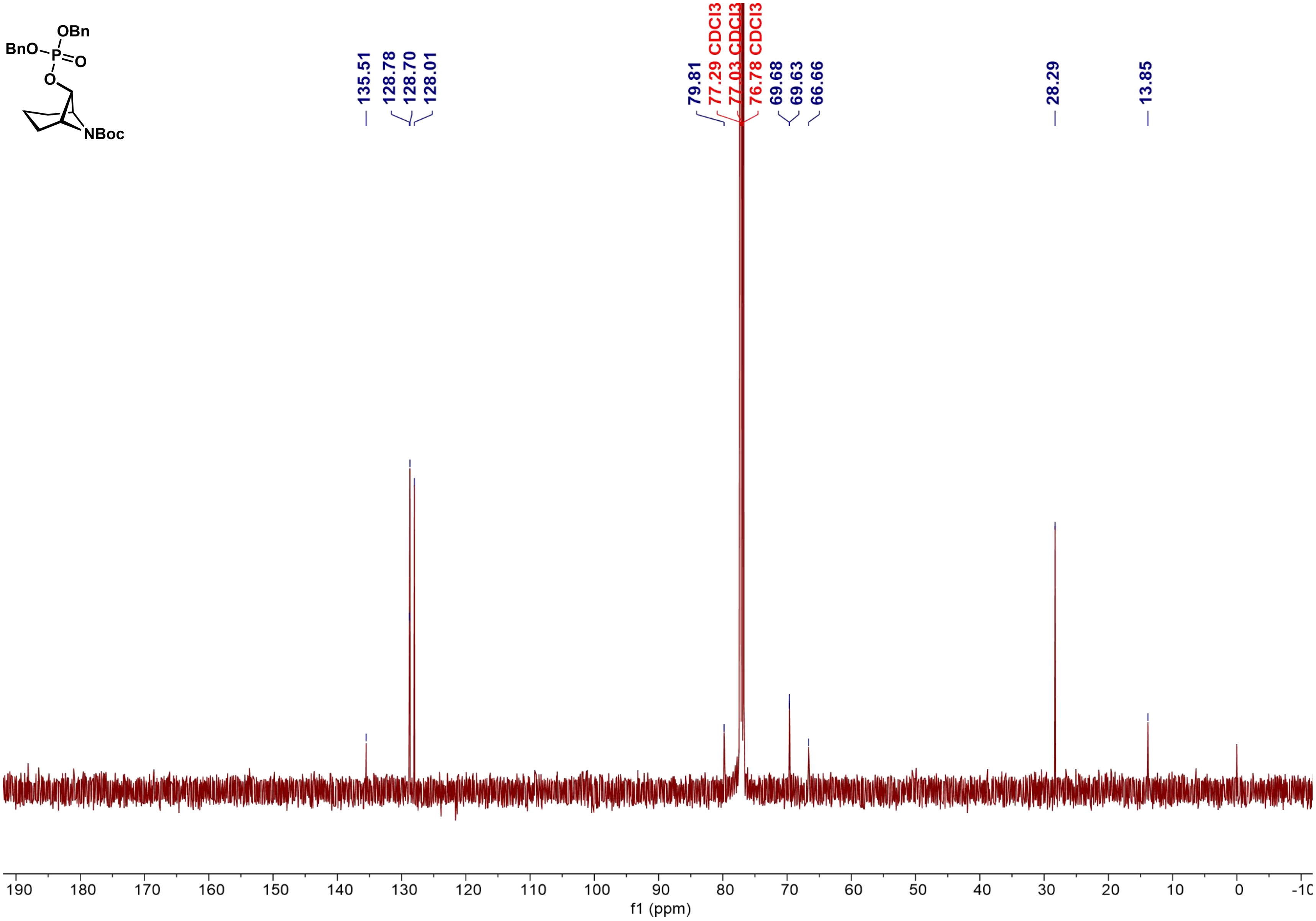
^{13}C NMR Spectrum of compound 39 (126 MHz, CDCl$_3$)



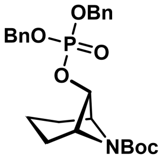
^{1}H NMR Spectrum of compound 40 (500 MHz, $CDCl_3$)

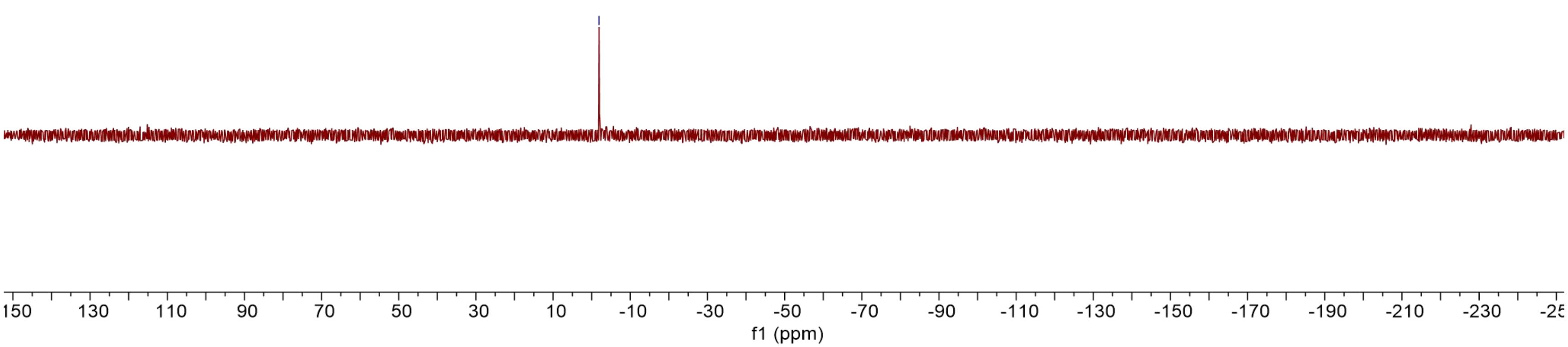


^{13}C NMR Spectrum of compound 40 (126 MHz, CDCl$_3$)

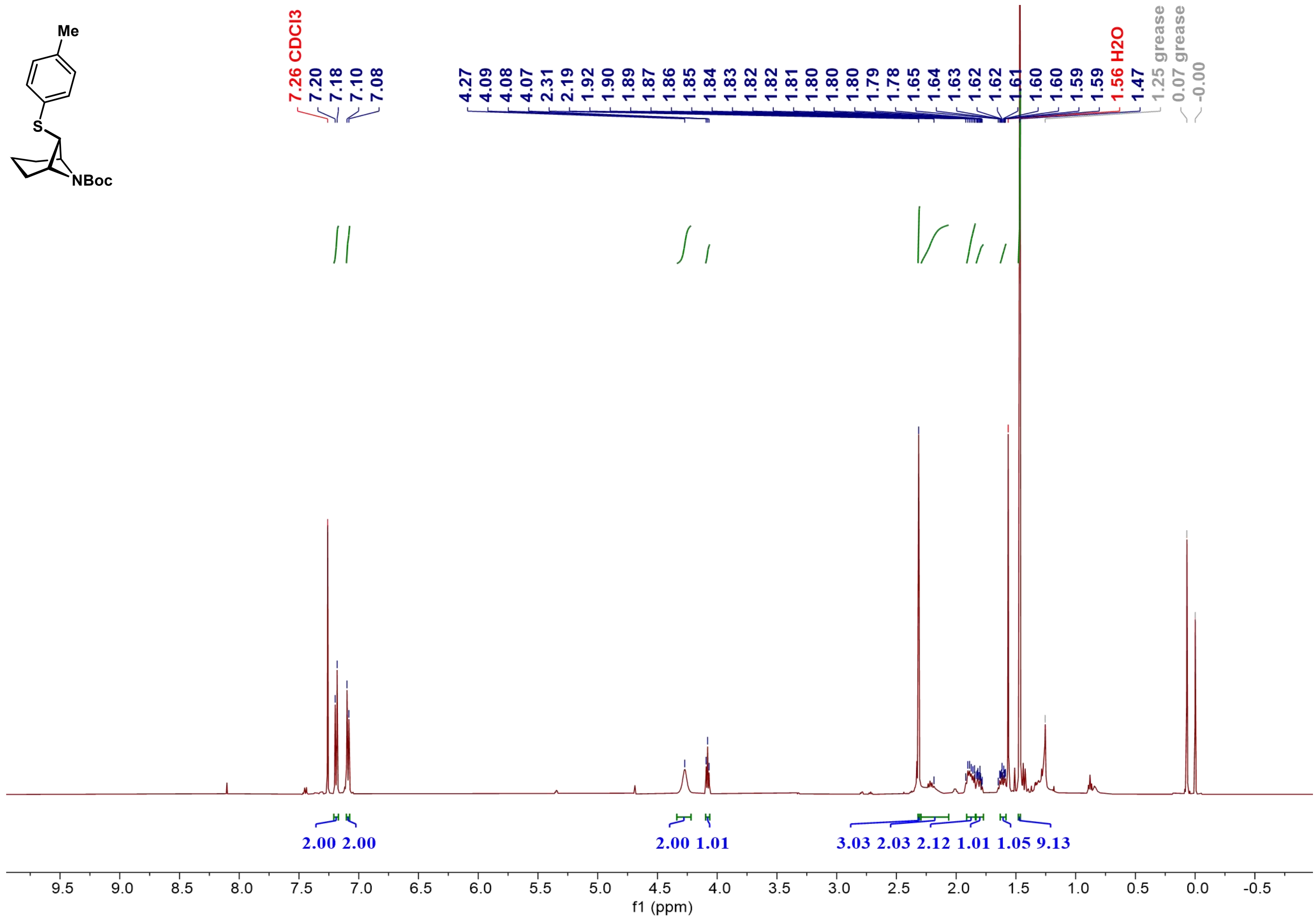


^{31}P NMR Spectrum of compound 40 (202 MHz, $CDCl_3$)

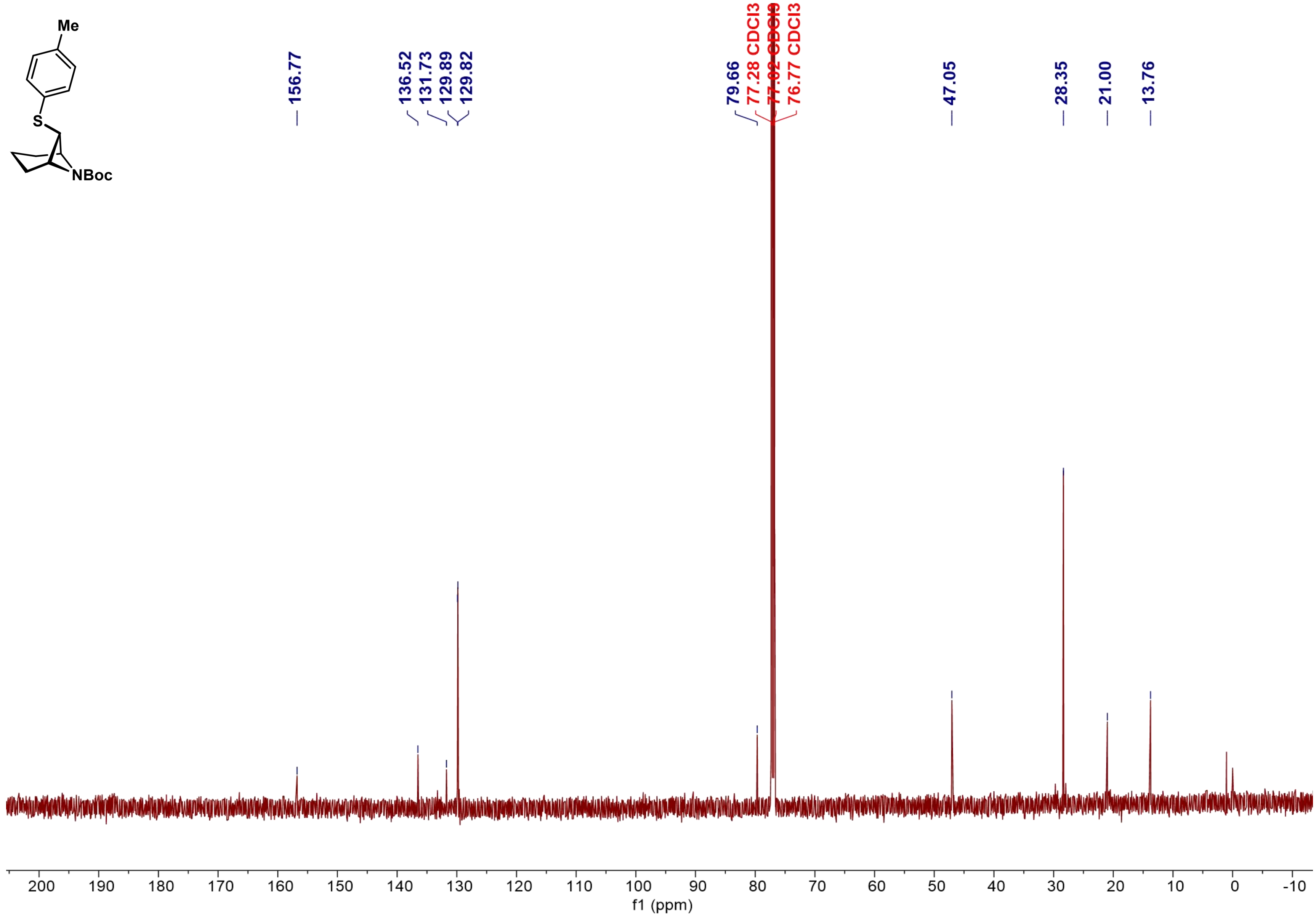




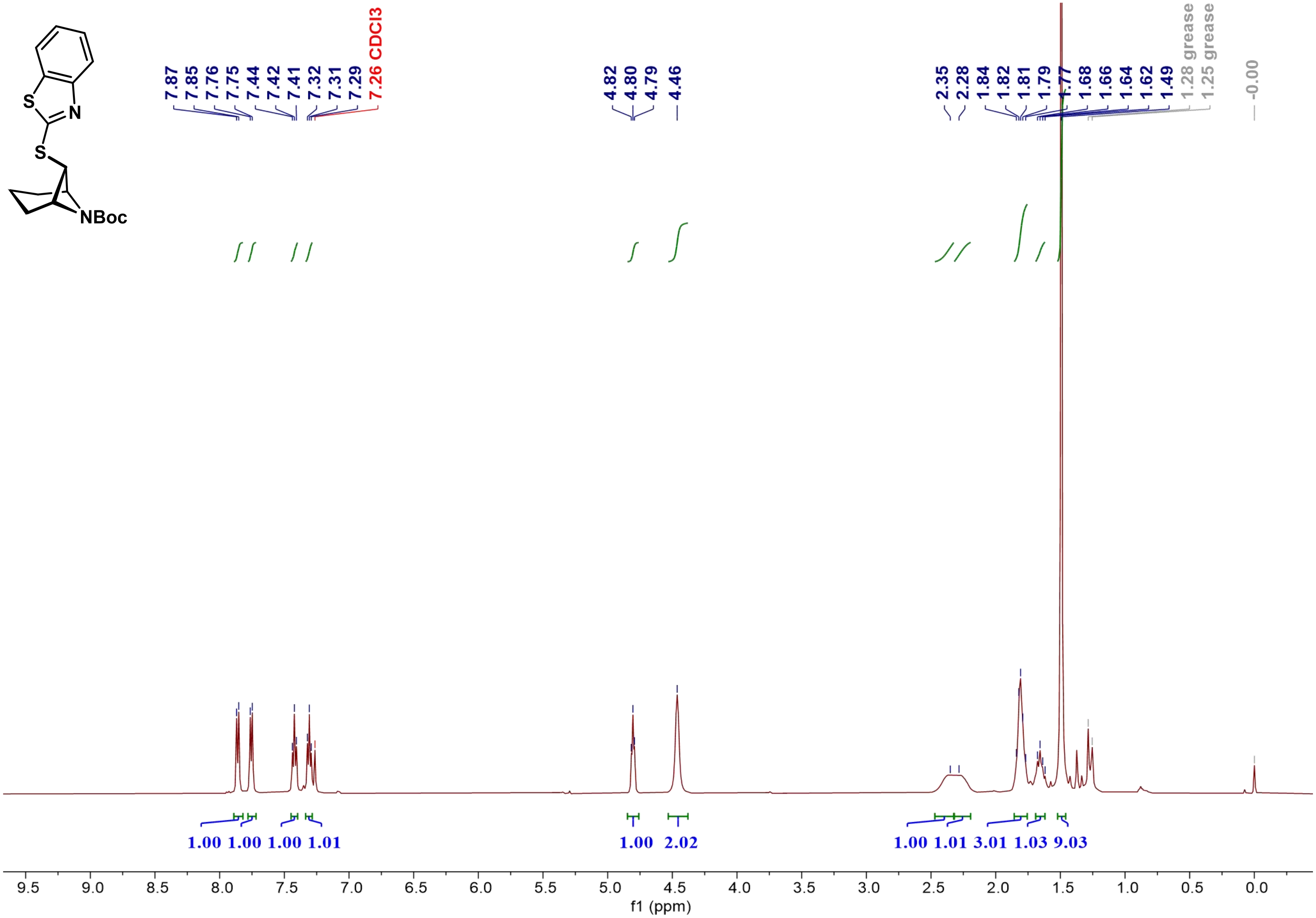
^{1}H NMR Spectrum of compound 41 (500 MHz, $CDCl_3$)



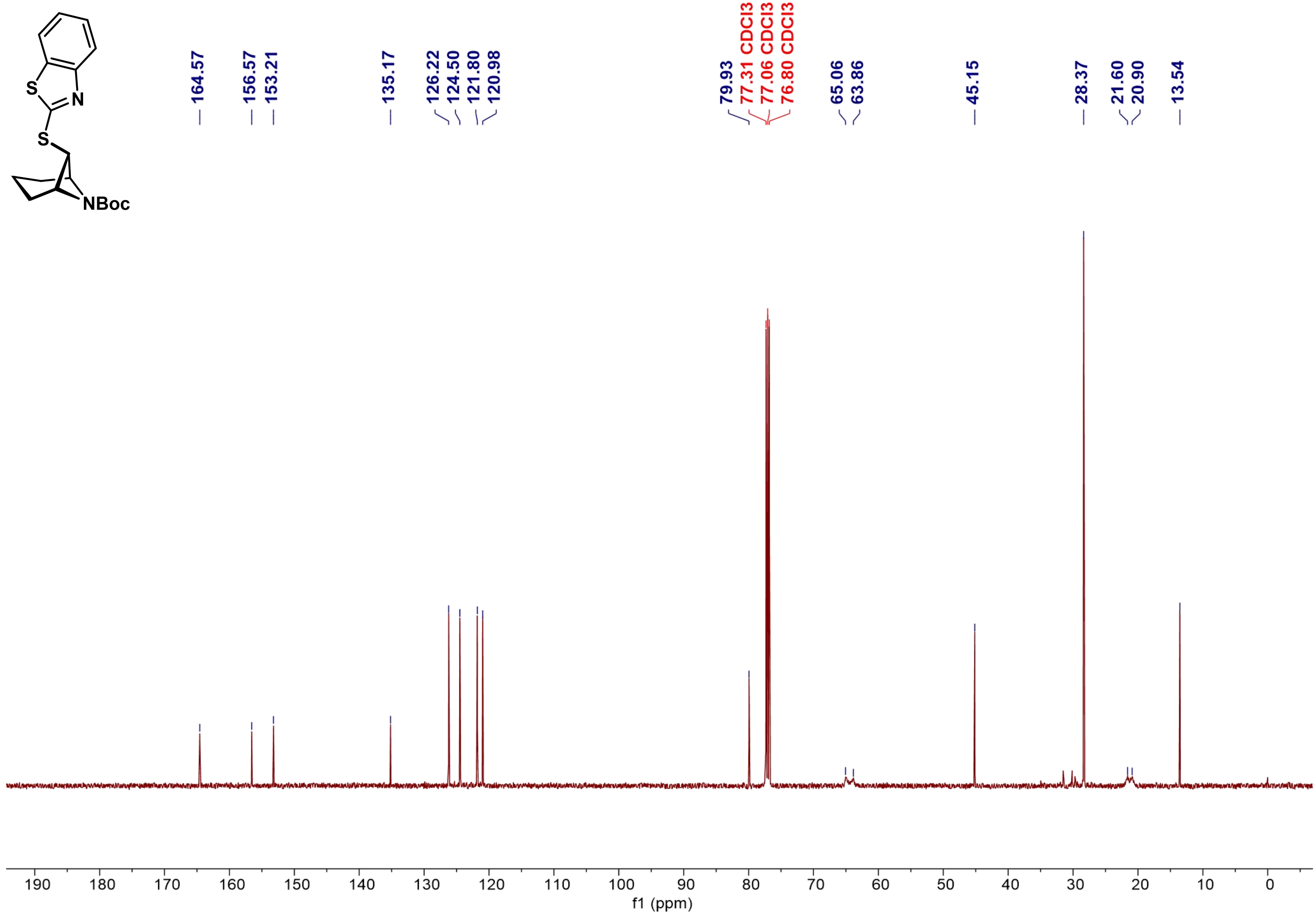
^{13}C NMR Spectrum of compound 41 (126 MHz, CDCl$_3$)



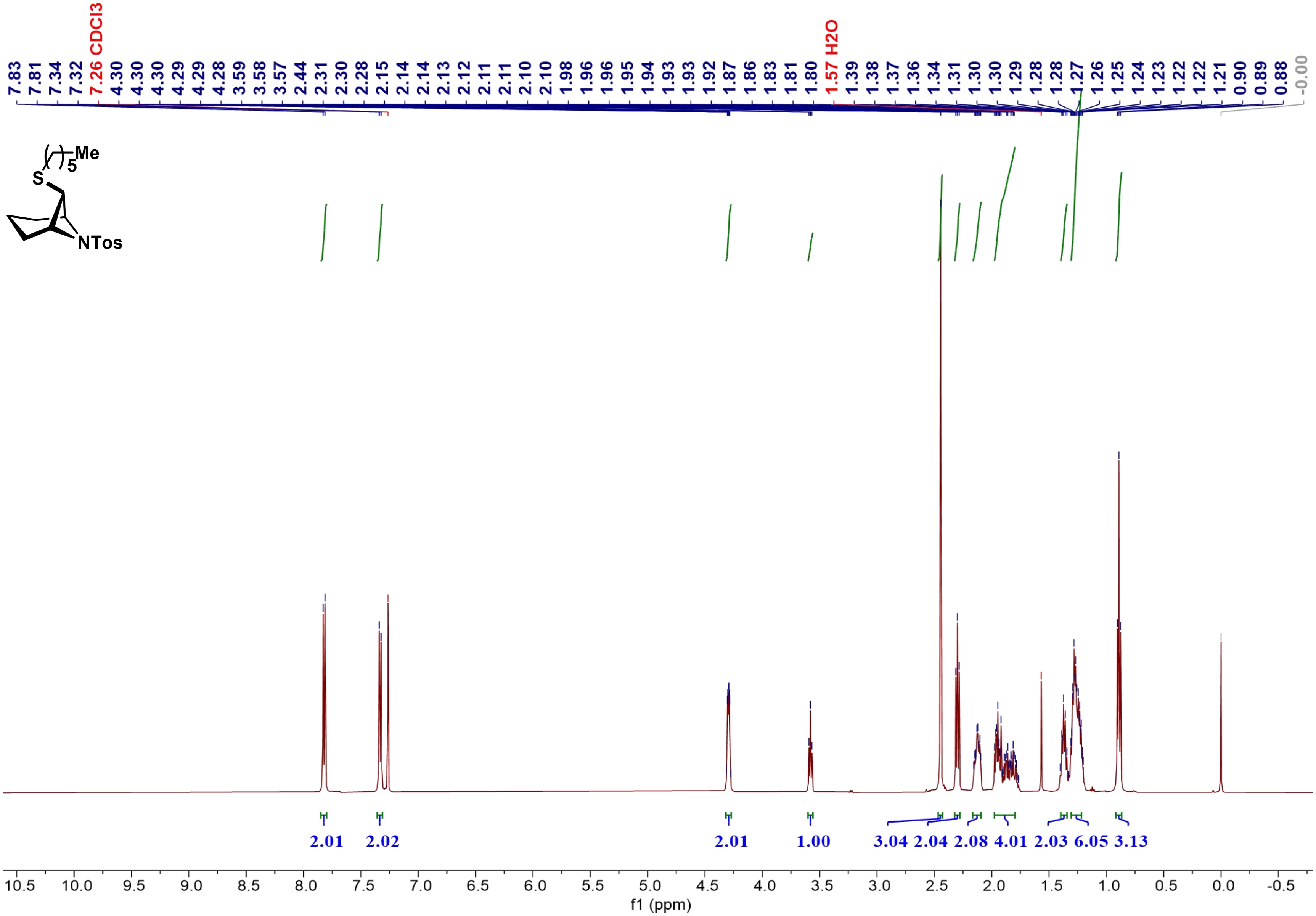
^1H NMR Spectrum of compound 42 (500 MHz, $CDCl_3$)



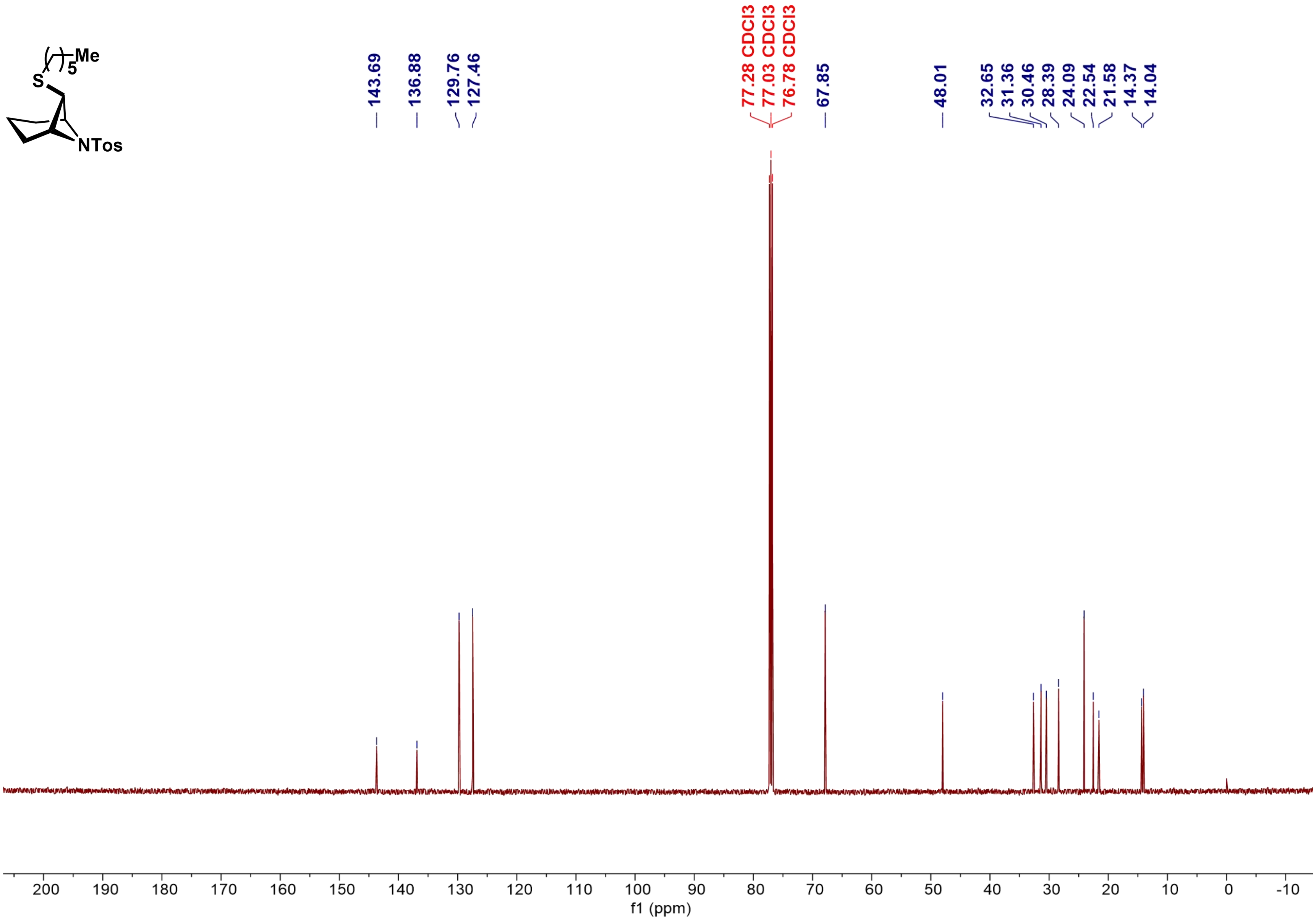
^{13}C NMR Spectrum of compound 42 (126 MHz, CDCl$_3$)



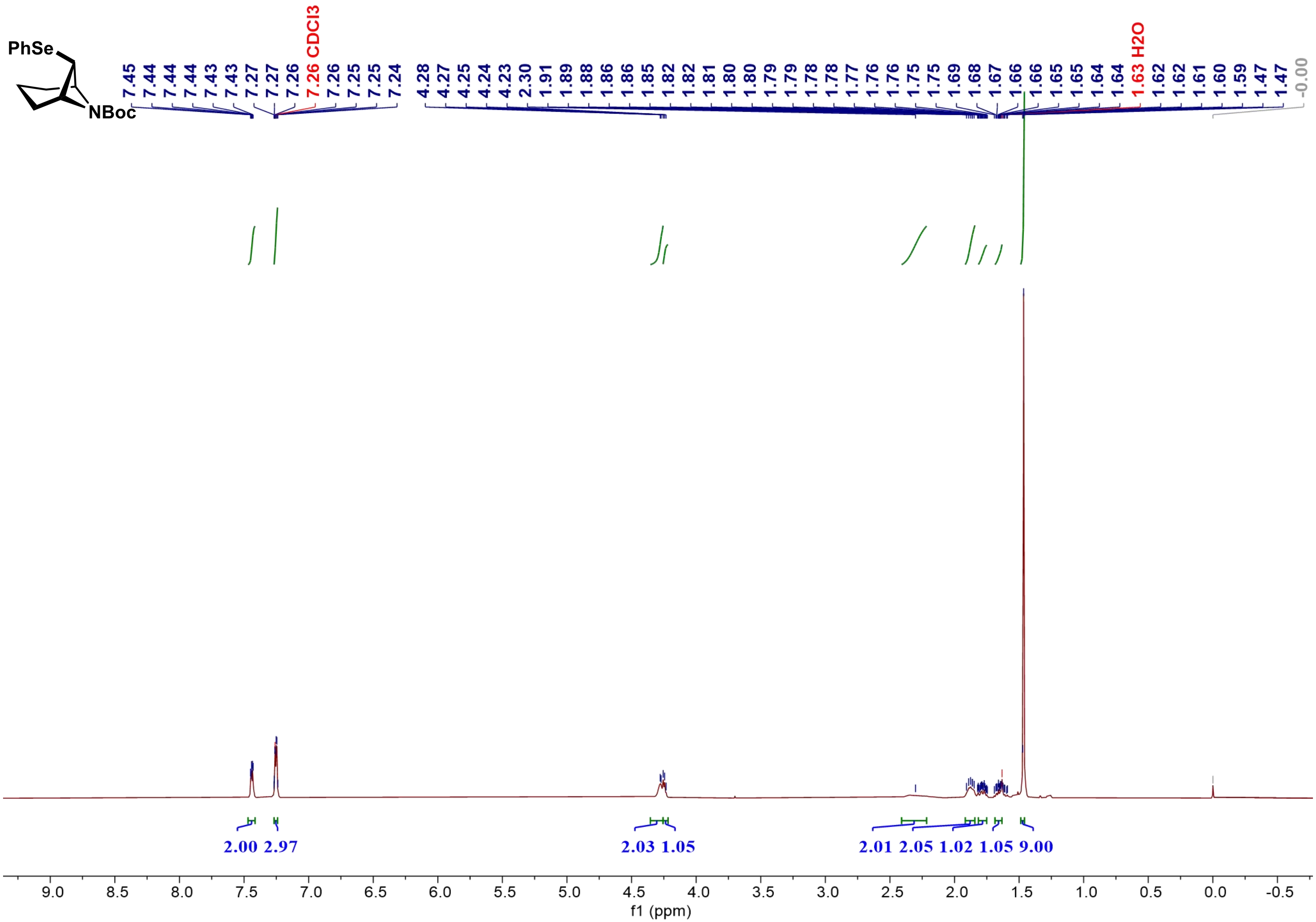
^{1}H NMR Spectrum of compound 43 (500 MHz, $CDCl_3$)



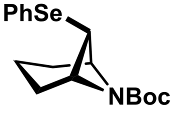
^{13}C NMR Spectrum of compound 43 (126 MHz, $CDCl_3$)

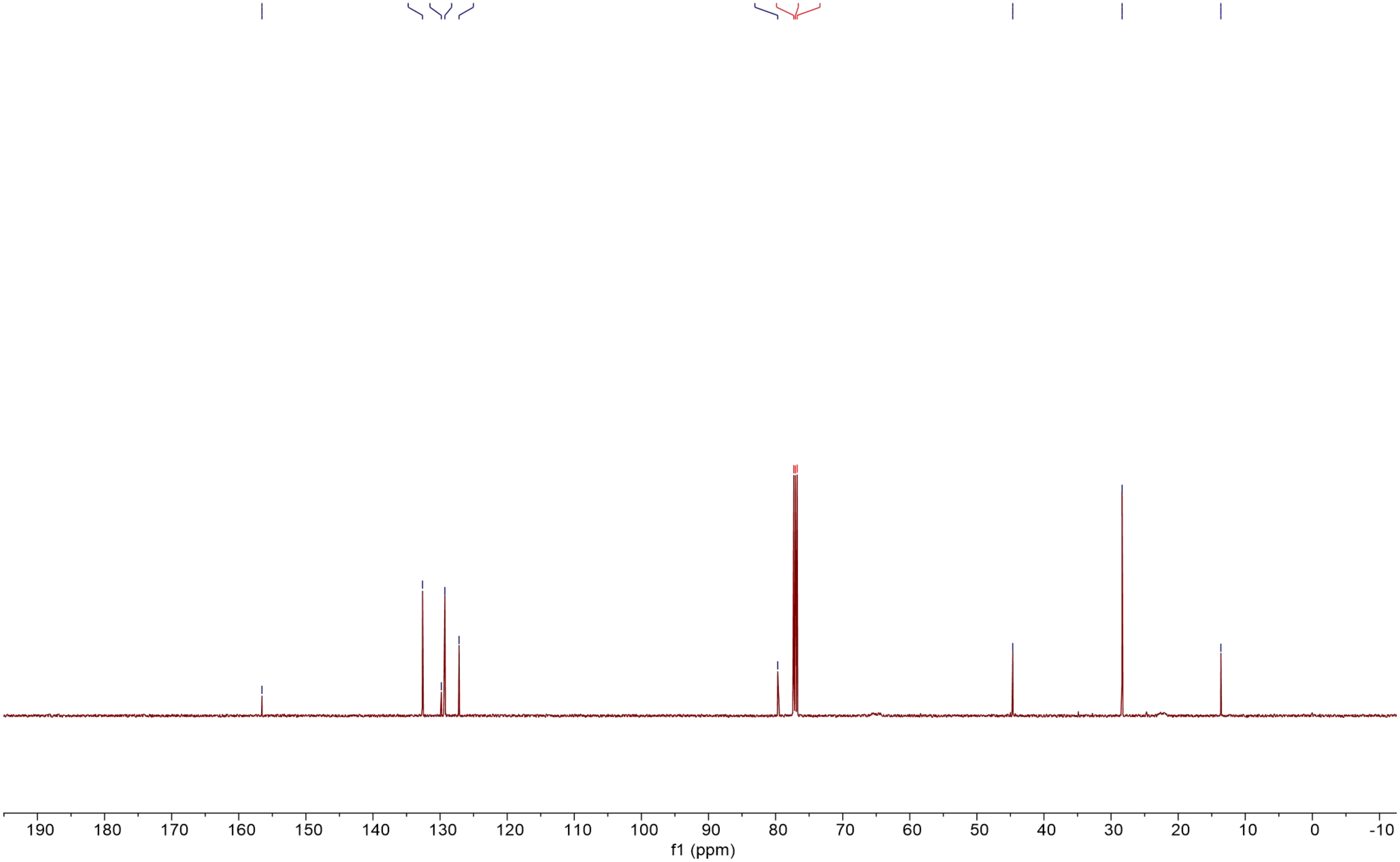


^{1}H NMR Spectrum of compound 44 (500 MHz, $CDCl_3$)

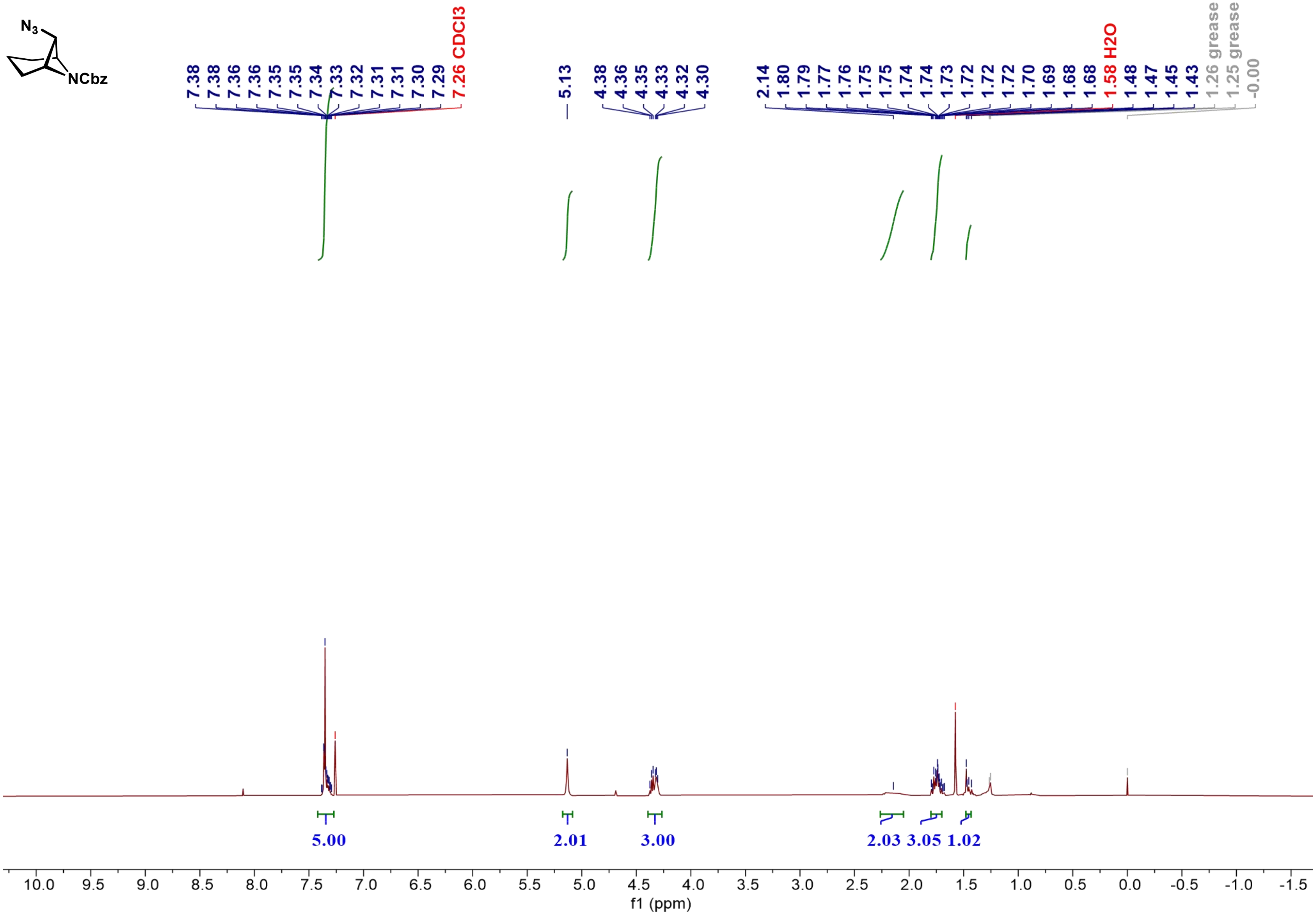


^{13}C NMR Spectrum of compound 44 (126 MHz, $CDCl_3$)

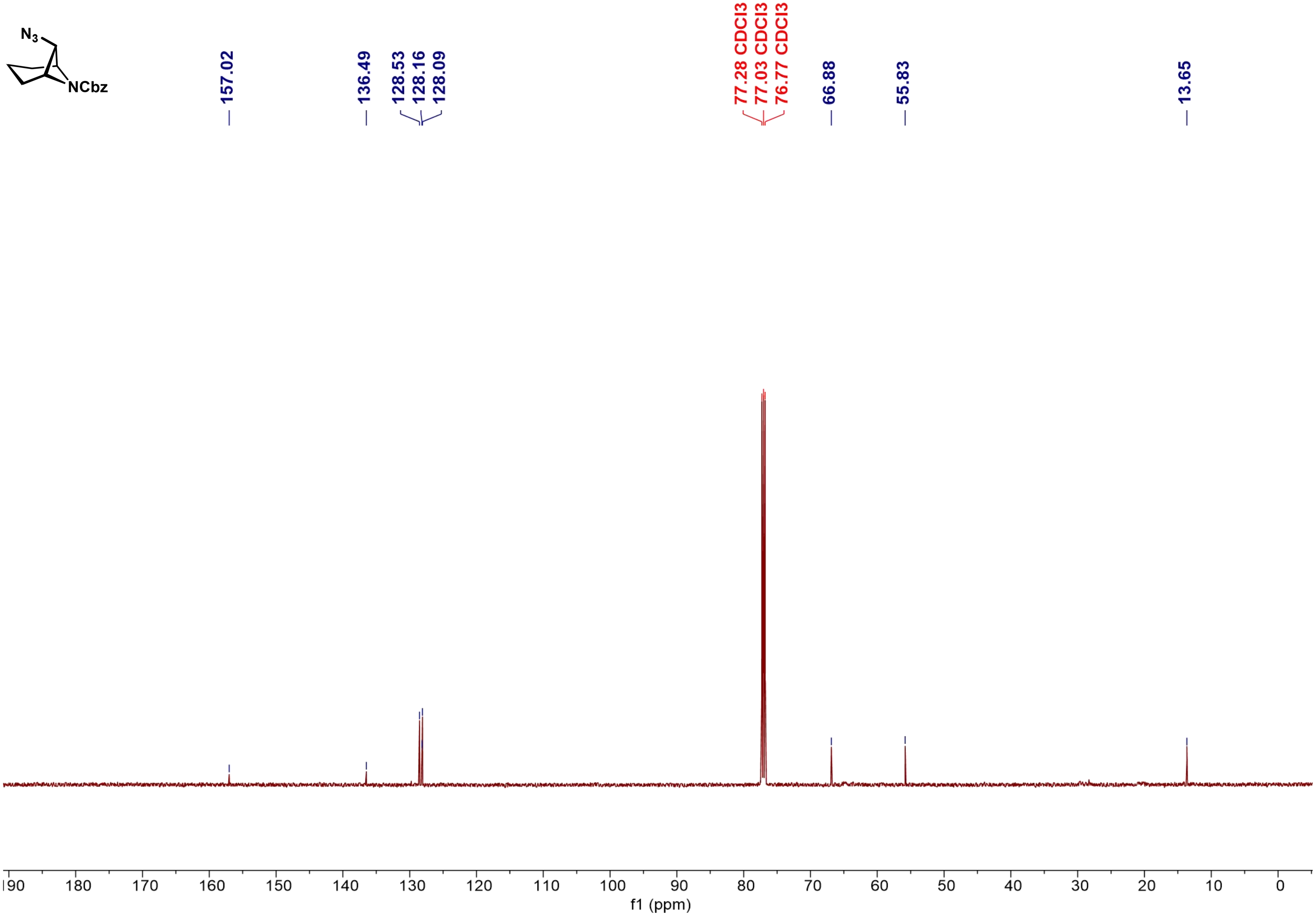




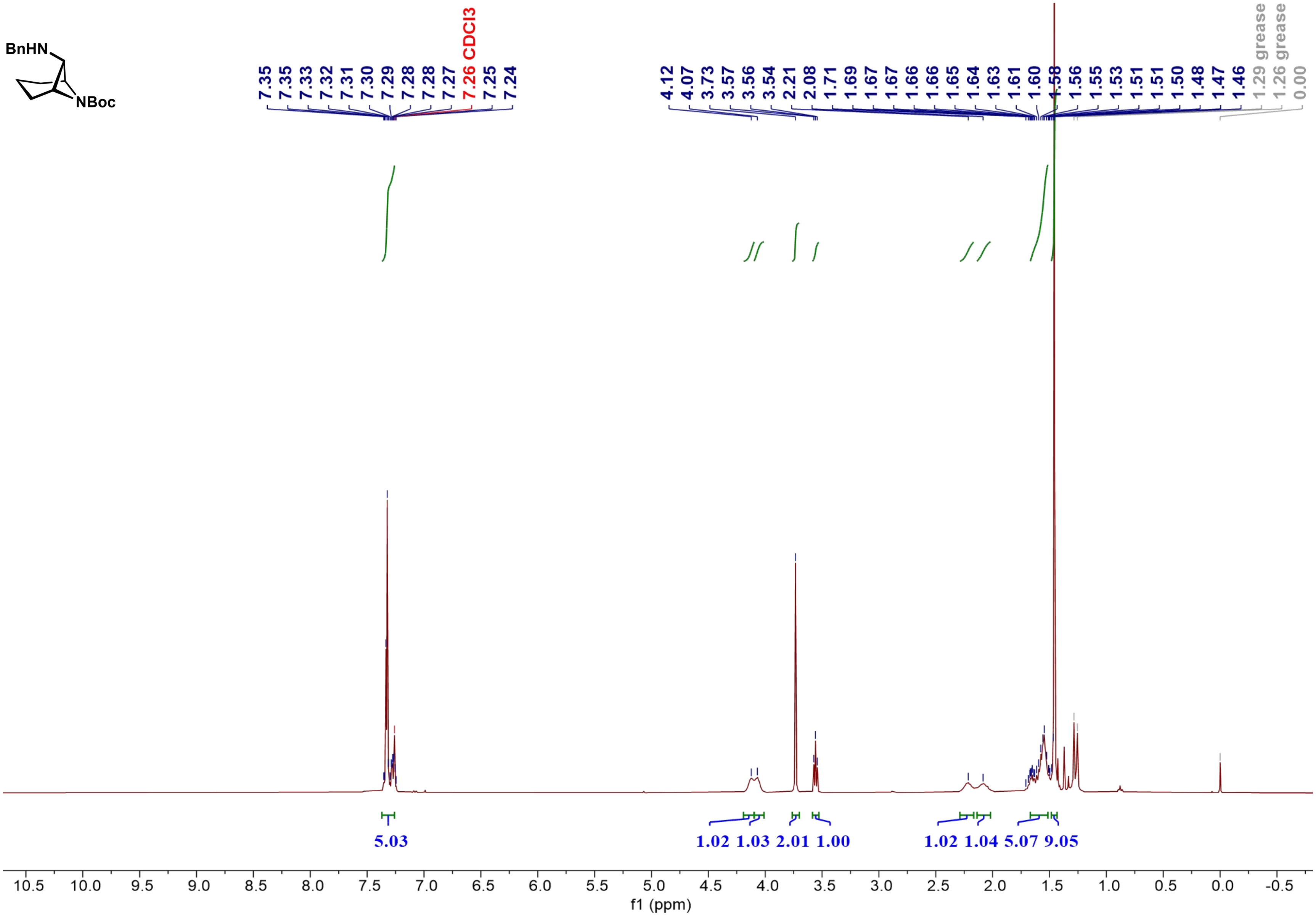
^{1}H NMR Spectrum of compound 45 (400 MHz, $CDCl_3$)



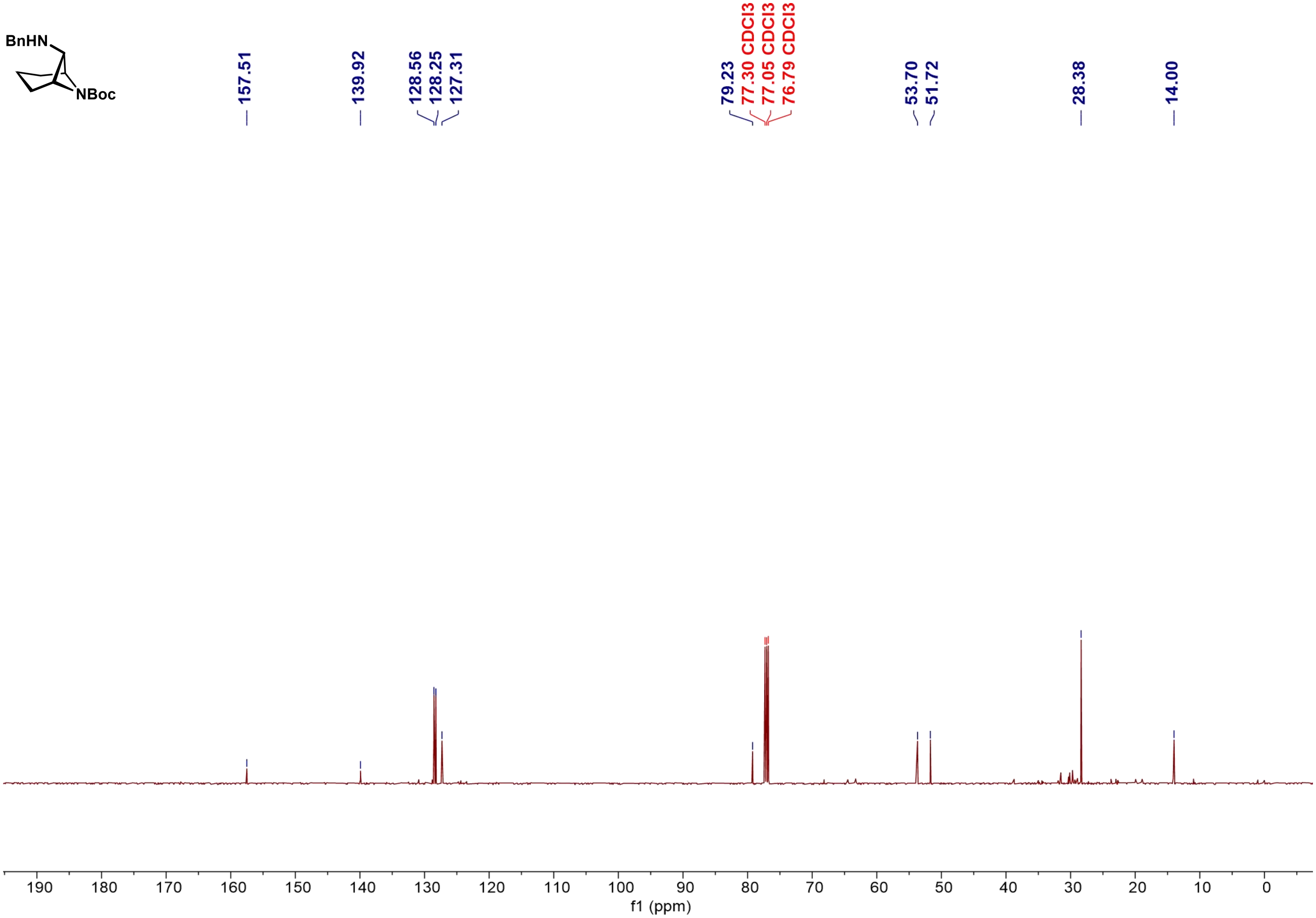
^{13}C NMR Spectrum of compound 45 (101 MHz, $CDCl_3$)



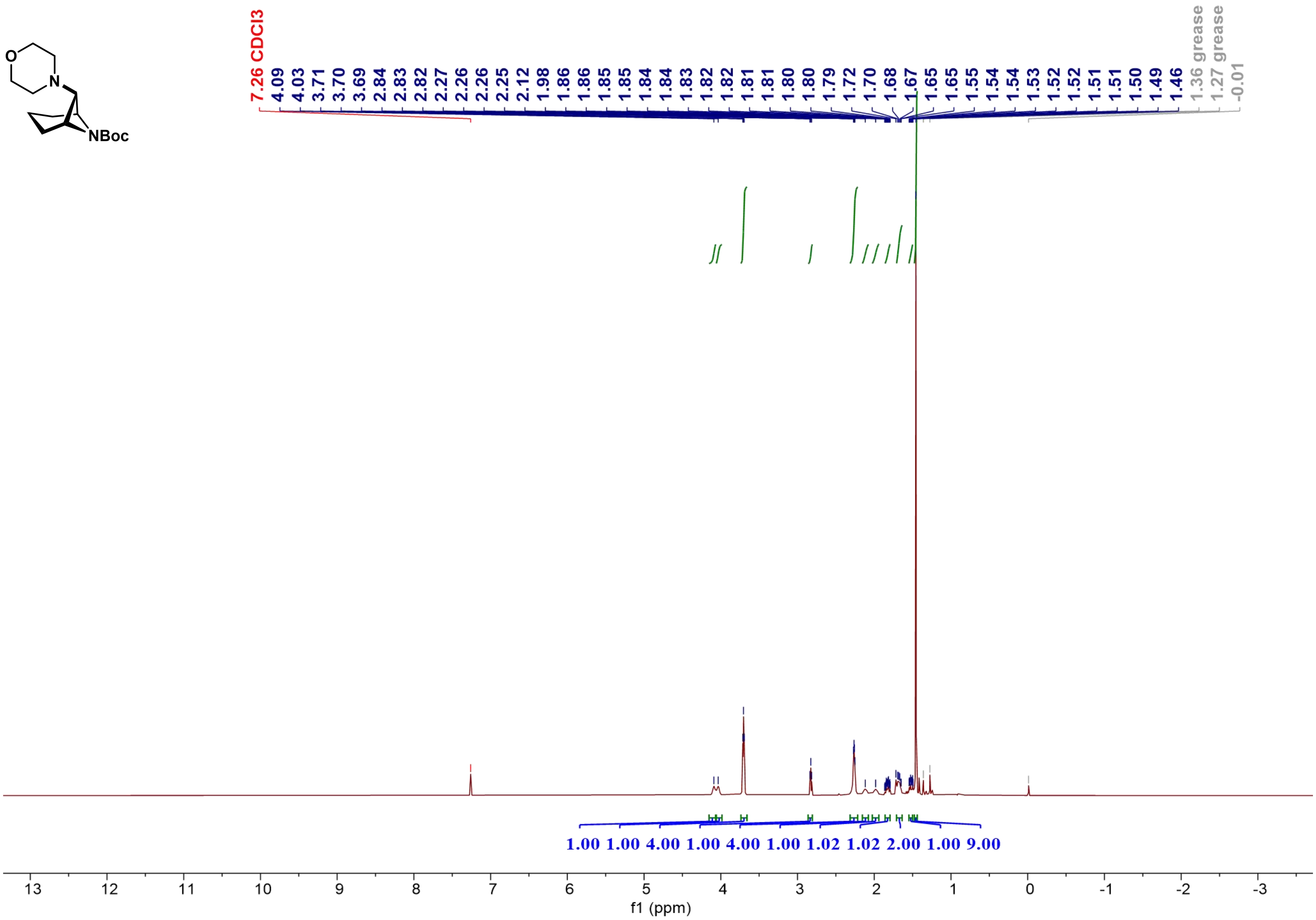
^{1}H NMR Spectrum of compound 46 (400 MHz, CDCl$_3$)



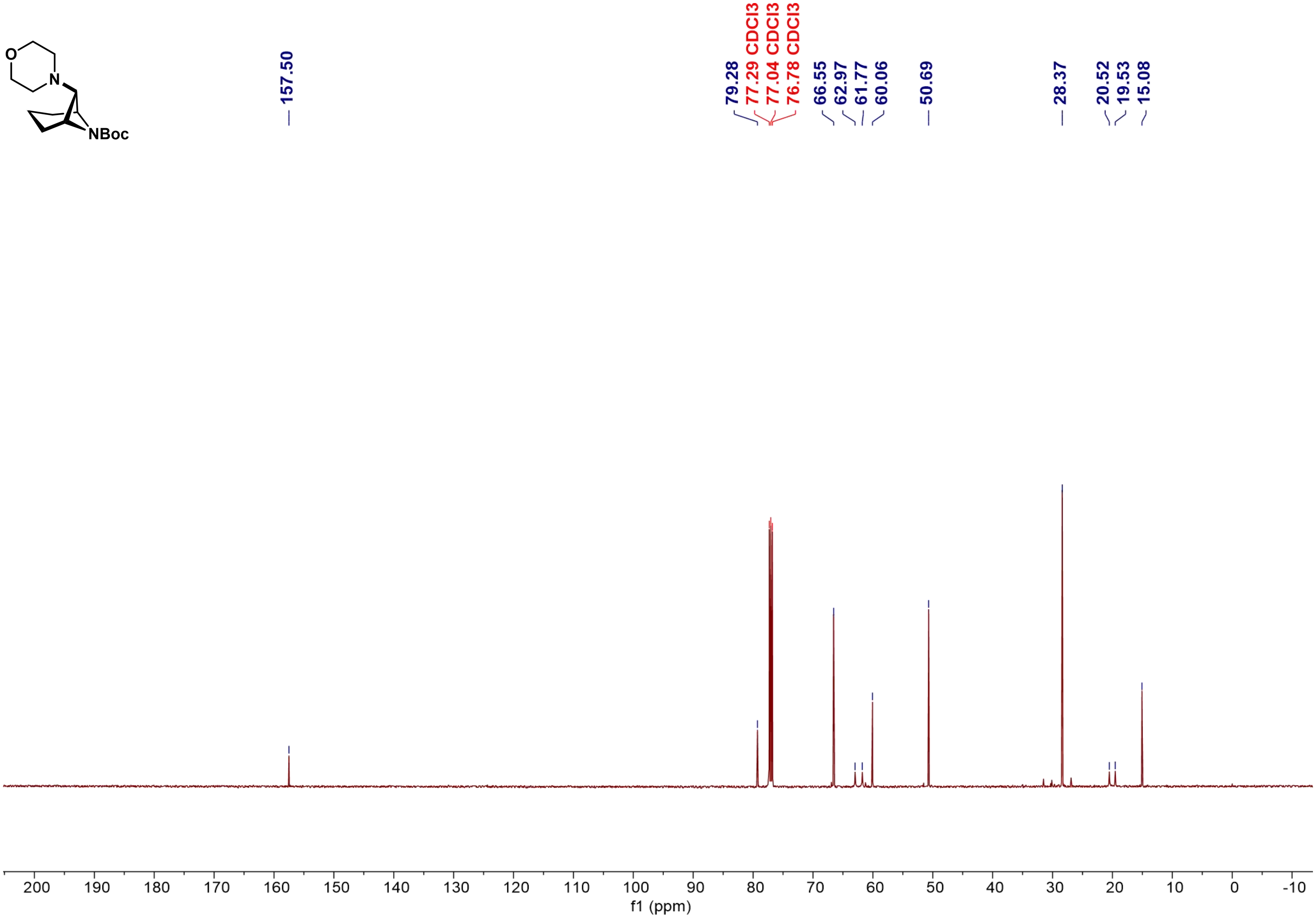
^{13}C NMR Spectrum of compound 46 (101 MHz, $CDCl_3$)



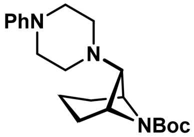
^{1}H NMR Spectrum of compound 47 (500 MHz, CDCl$_3$)

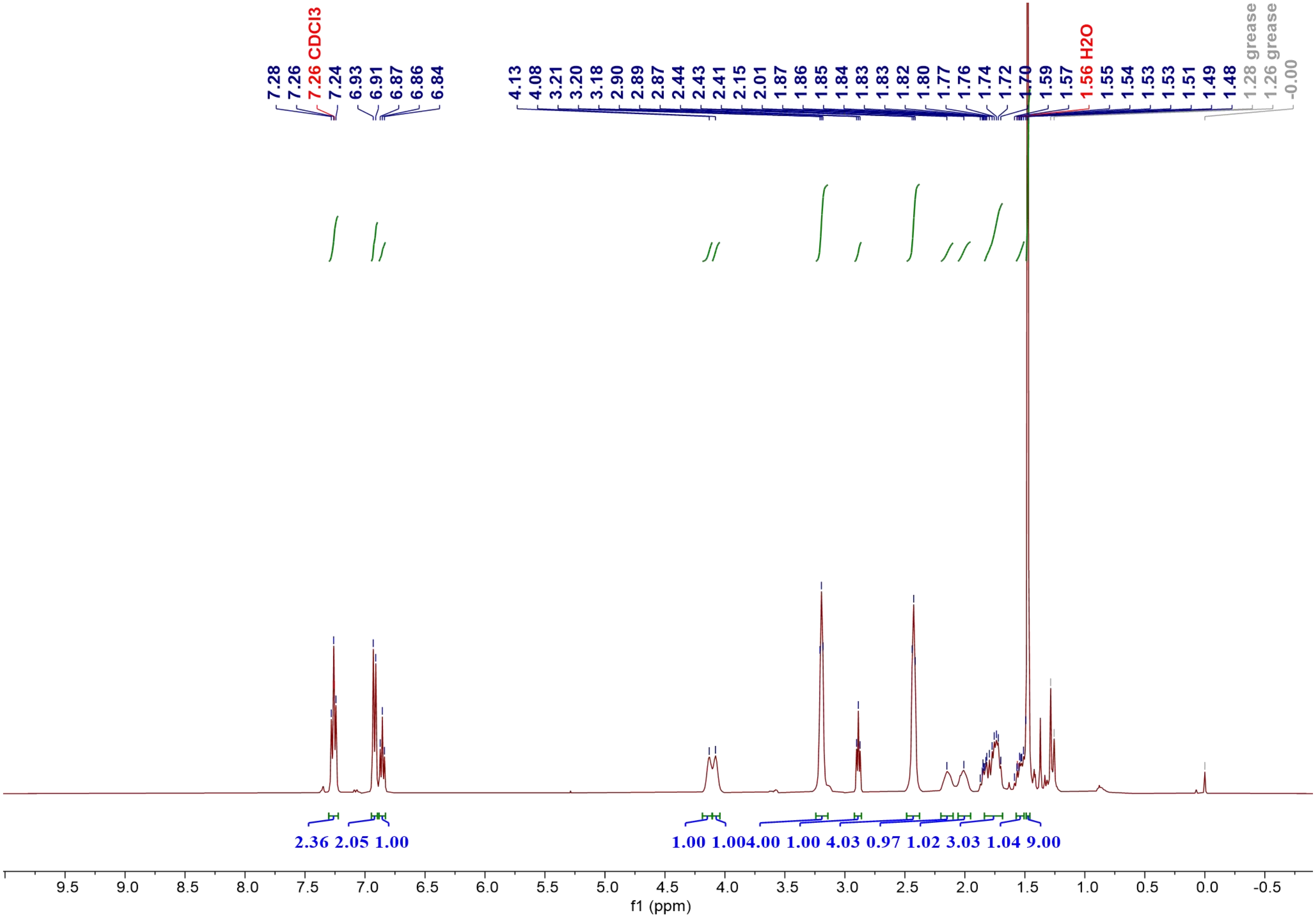


^{13}C NMR Spectrum of compound 47 (126 MHz, $CDCl_3$)

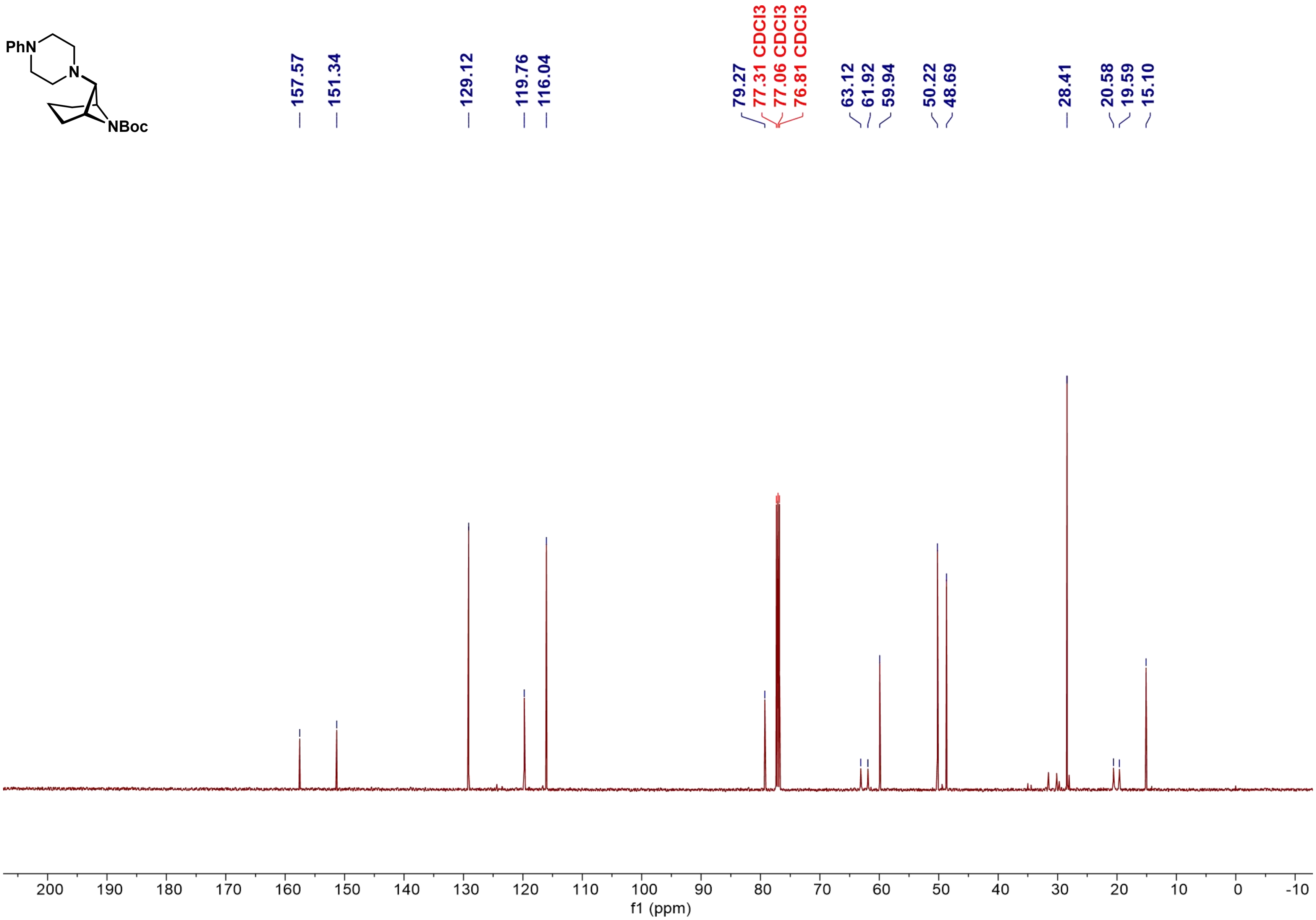


^{1}H NMR Spectrum of compound 48 (400 MHz, CDCl$_3$)

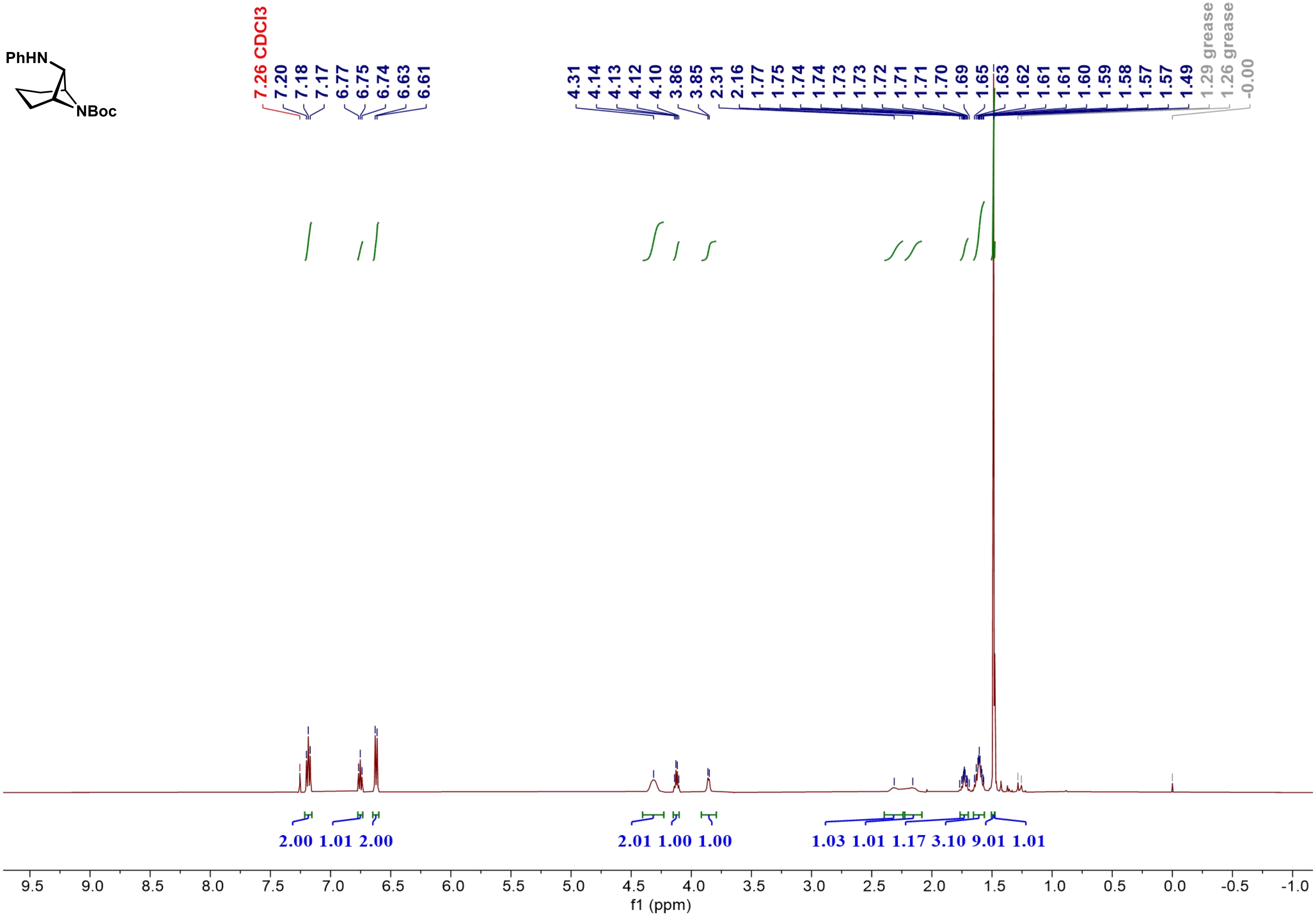



7.28
7.26
7.26 CDCl3
7.24
6.93
6.91
6.87
6.86
6.84
4.13
4.08
3.21
3.20
3.18
2.90
2.89
2.87
2.44
2.43
2.41
2.15
2.01
1.87
1.86
1.85
1.84
1.83
1.83
1.82
1.80
1.77
1.76
1.74
1.72
1.70
1.59
1.57
1.56 H2O
1.55
1.54
1.53
1.53
1.51
1.49
1.48
1.28 grease
1.26 grease
-0.00
2.36
2.05
1.00
1.00
1.00
4.00
1.00
4.03
0.97
1.02
3.03
1.04
9.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

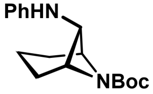
^{13}C NMR Spectrum of compound 48 (101 MHz, $CDCl_3$)

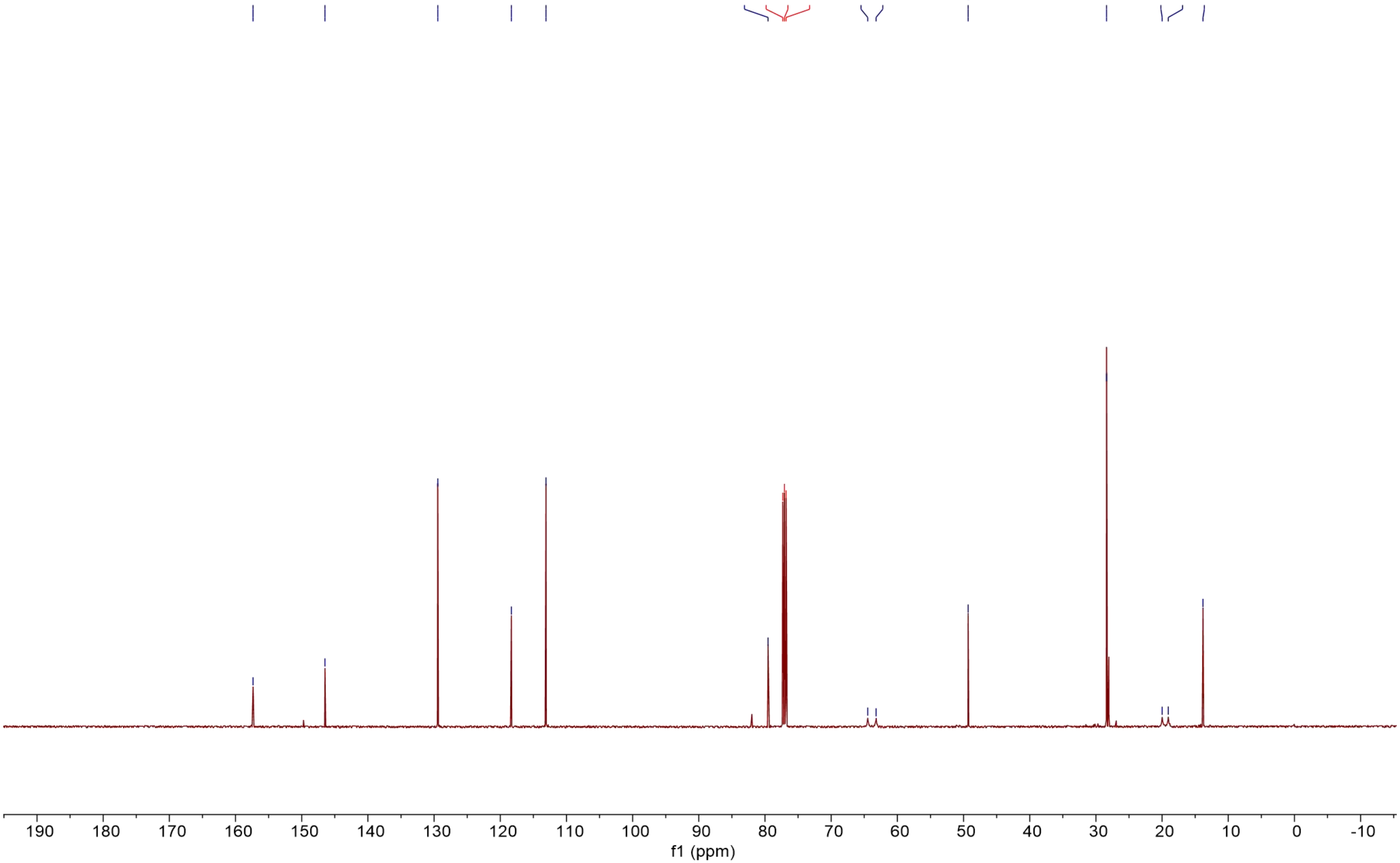


^{1}H NMR Spectrum of compound 49 (500 MHz, CDCl$_3$)

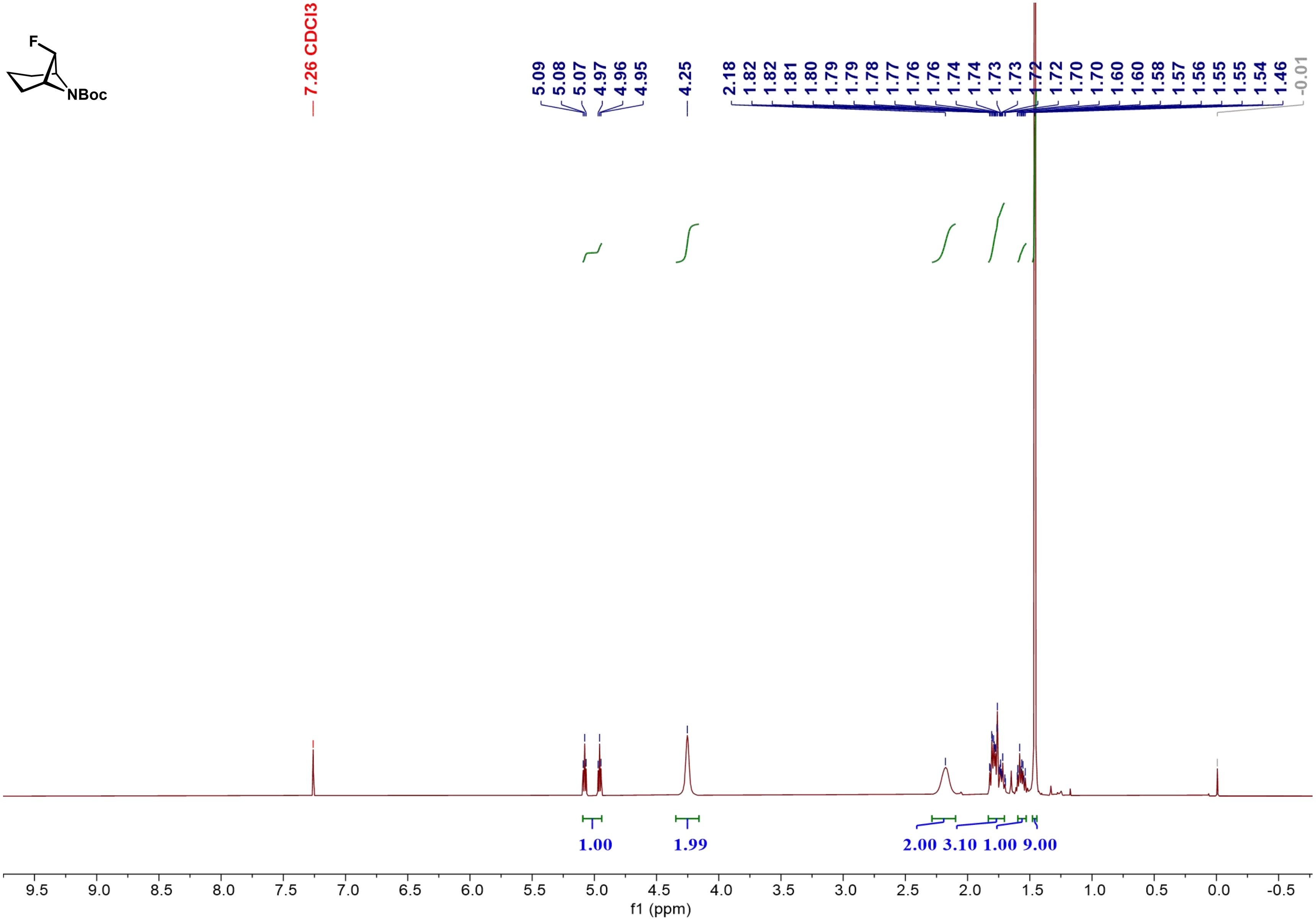


^{13}C NMR Spectrum of compound 49 (126 MHz, $CDCl_3$)

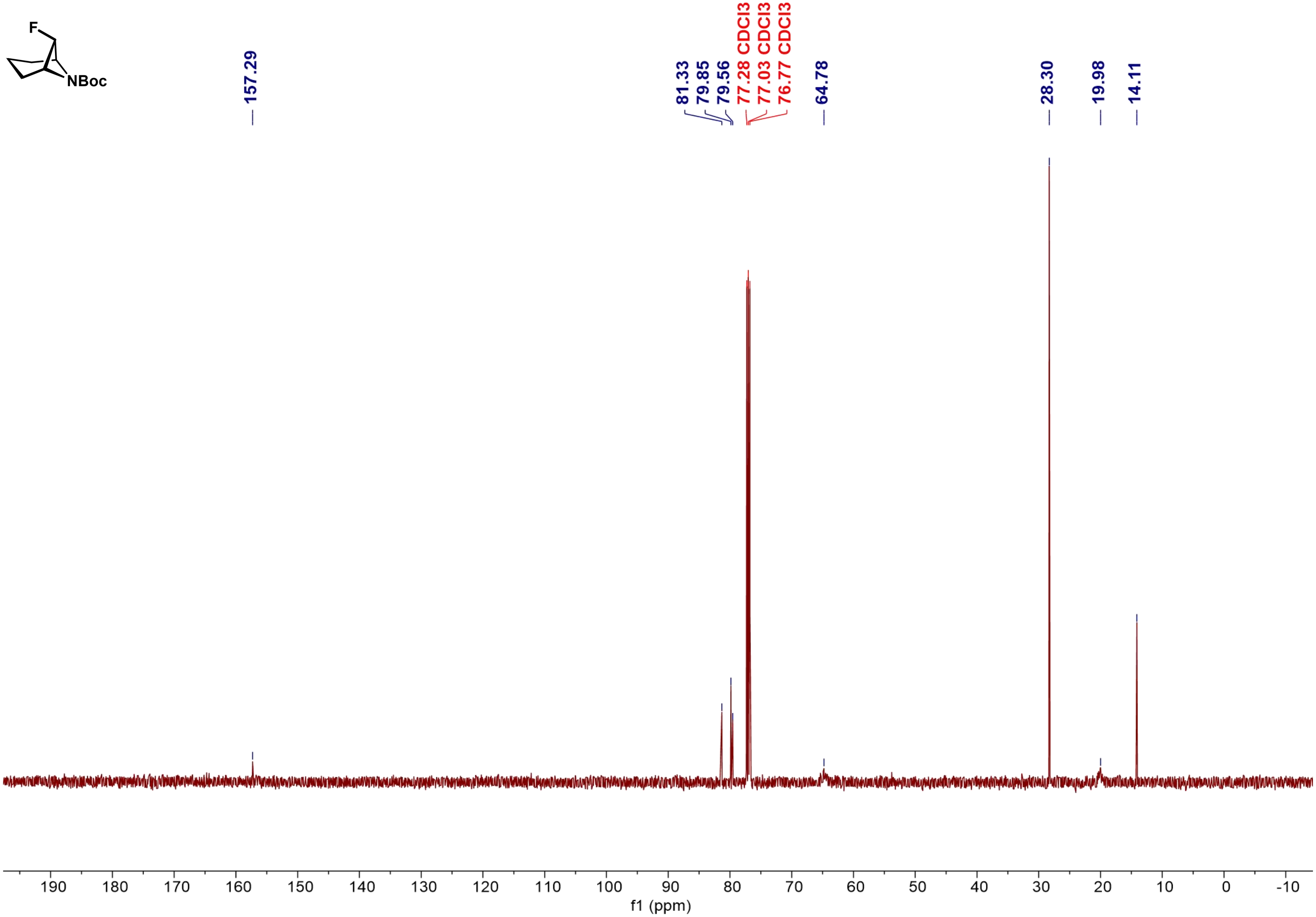




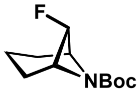
^{1}H NMR Spectrum of compound 50 (500 MHz, $CDCl_3$)

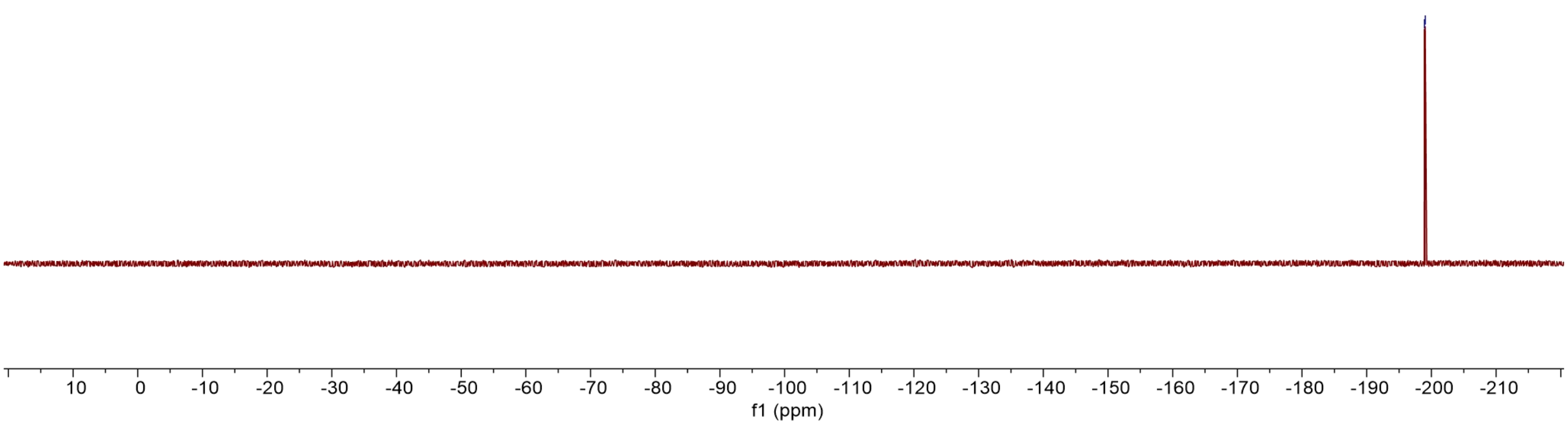


^{13}C NMR Spectrum of compound 50 (126 MHz, CDCl$_3$)

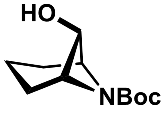


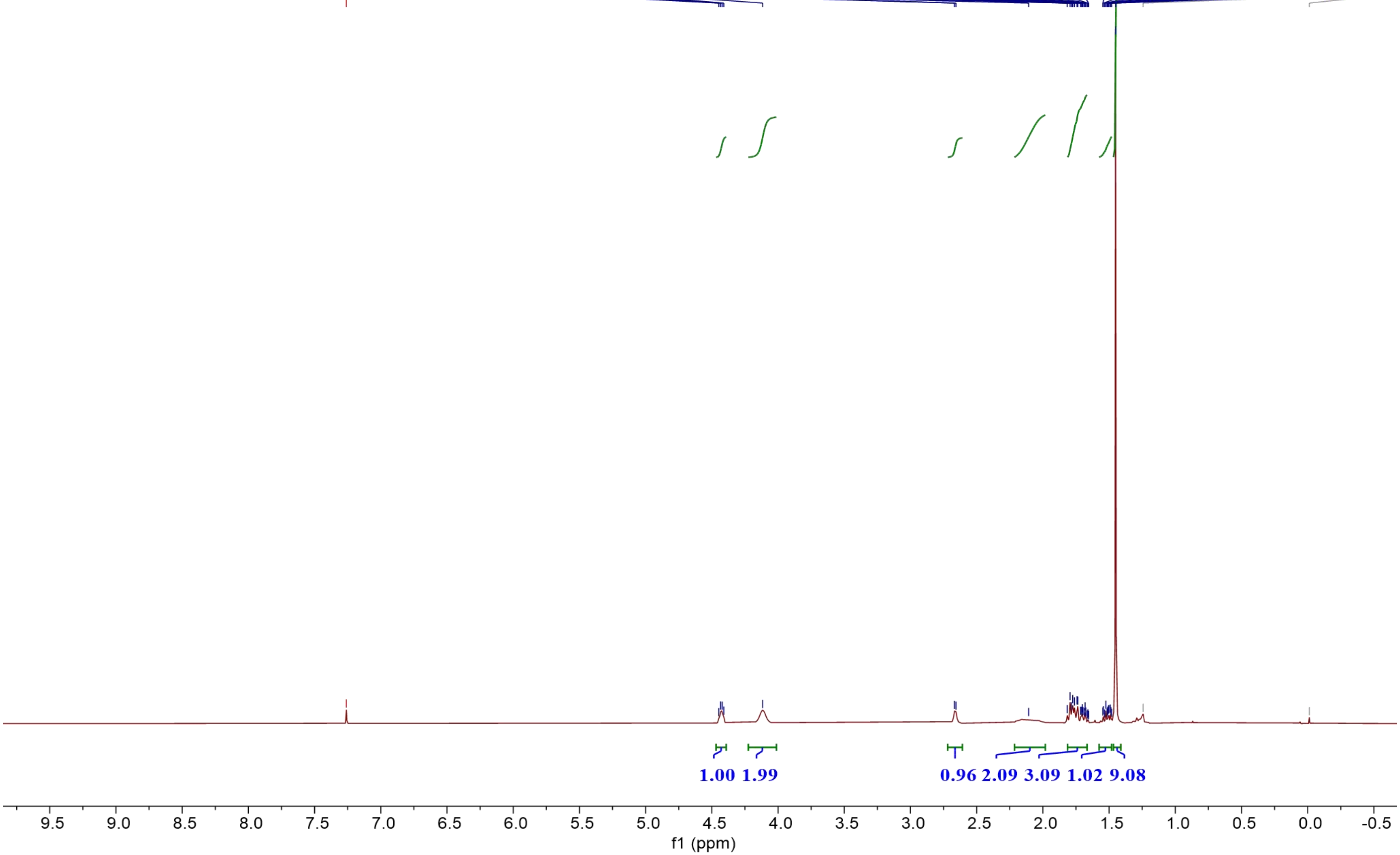
^{19}F NMR Spectrum of compound 50 (471 MHz, CDCl$_3$)



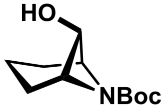


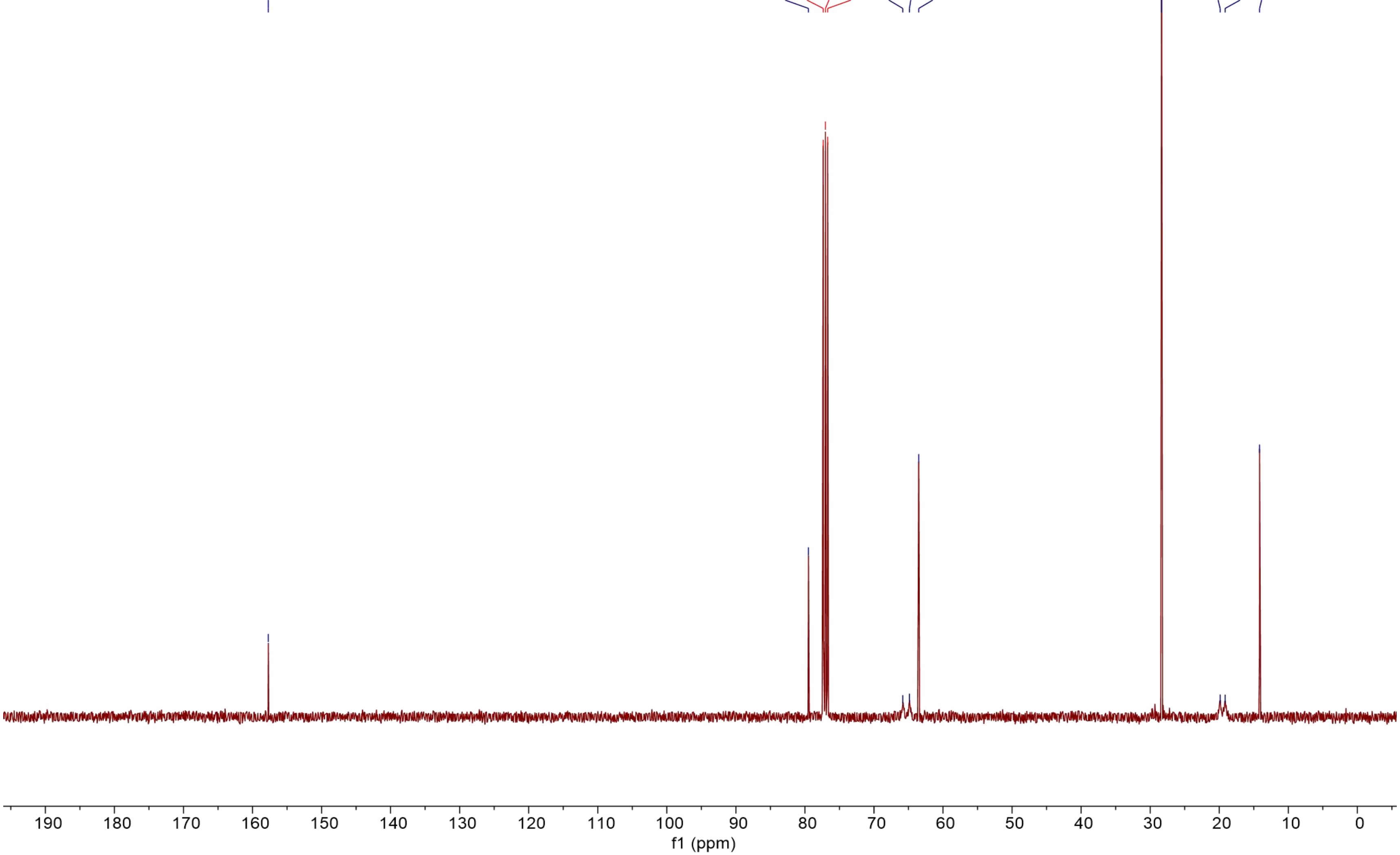
^{1}H NMR Spectrum of compound 51 (400 MHz, CDCl$_3$)



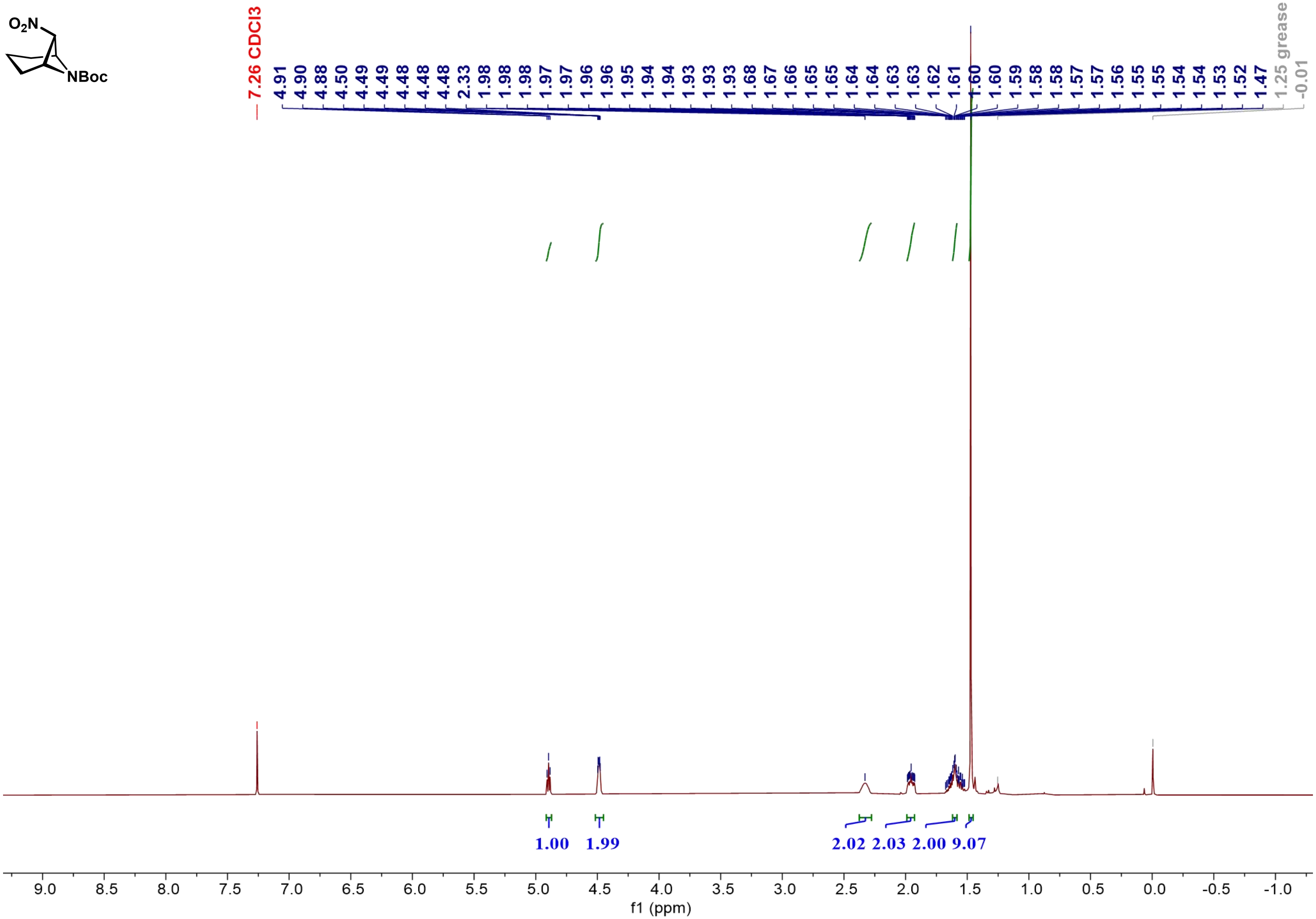


^{13}C NMR Spectrum of compound 51 (101 MHz, $CDCl_3$)

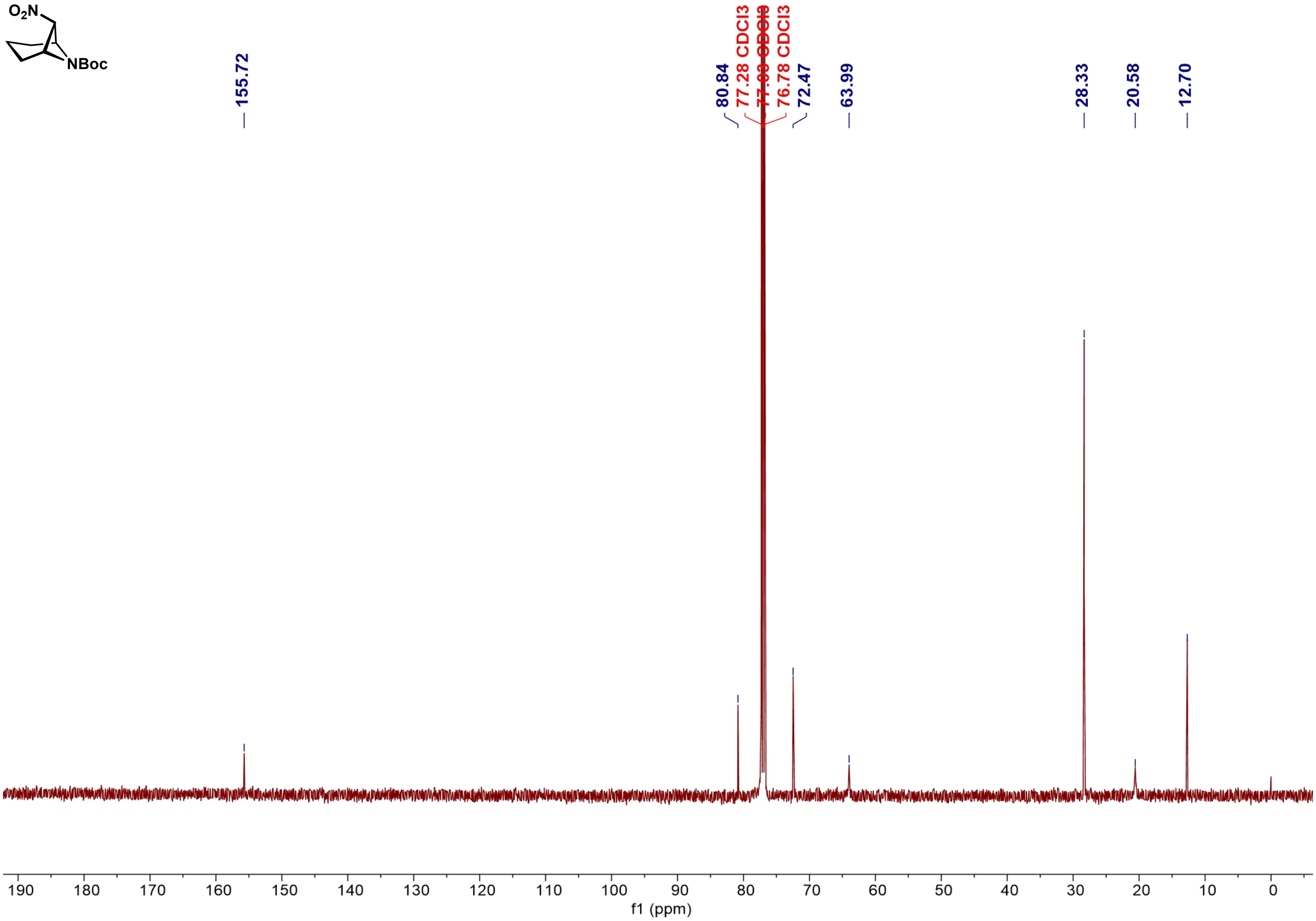




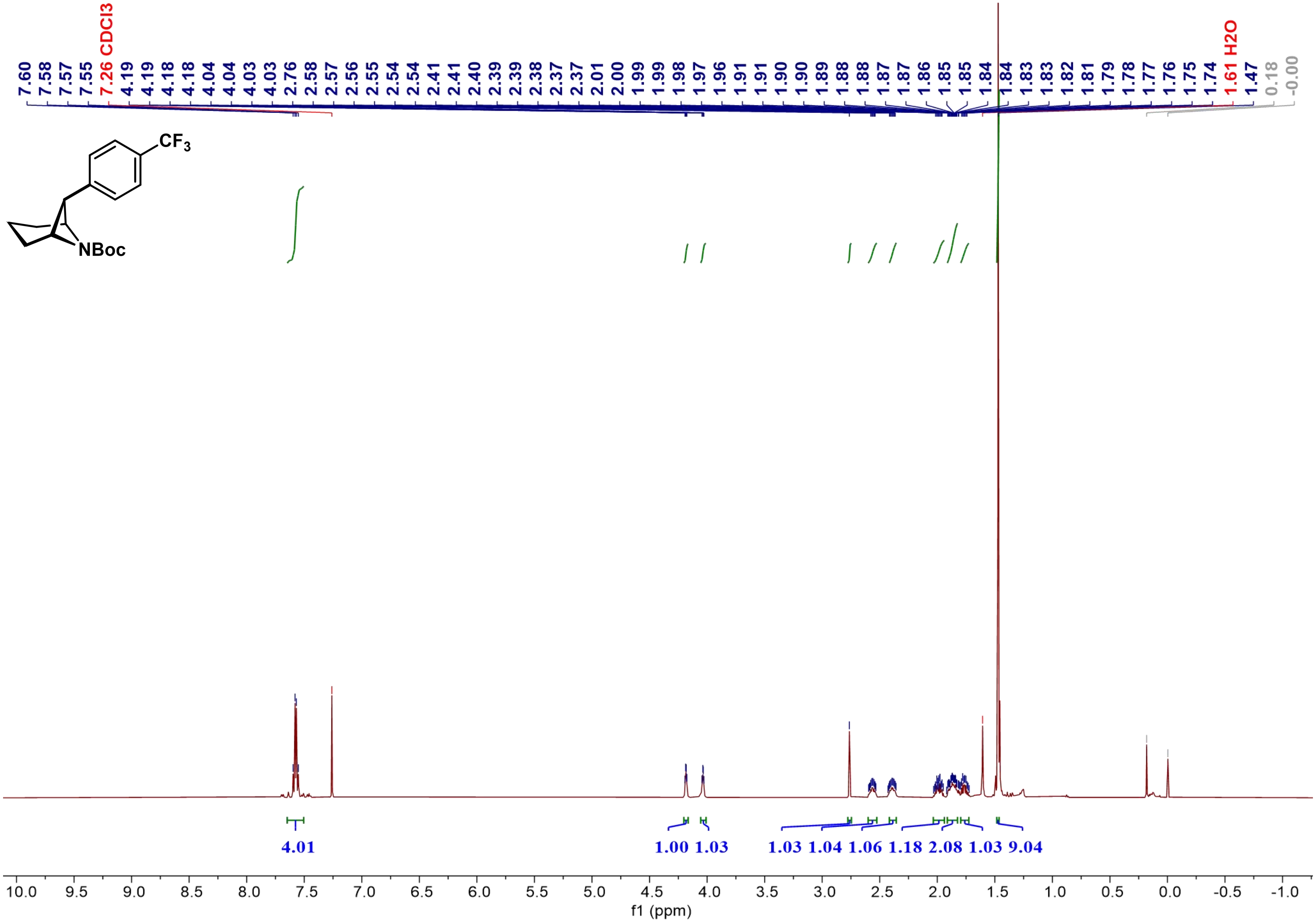
^{1}H NMR Spectrum of compound 52 (500 MHz, $CDCl_3$)



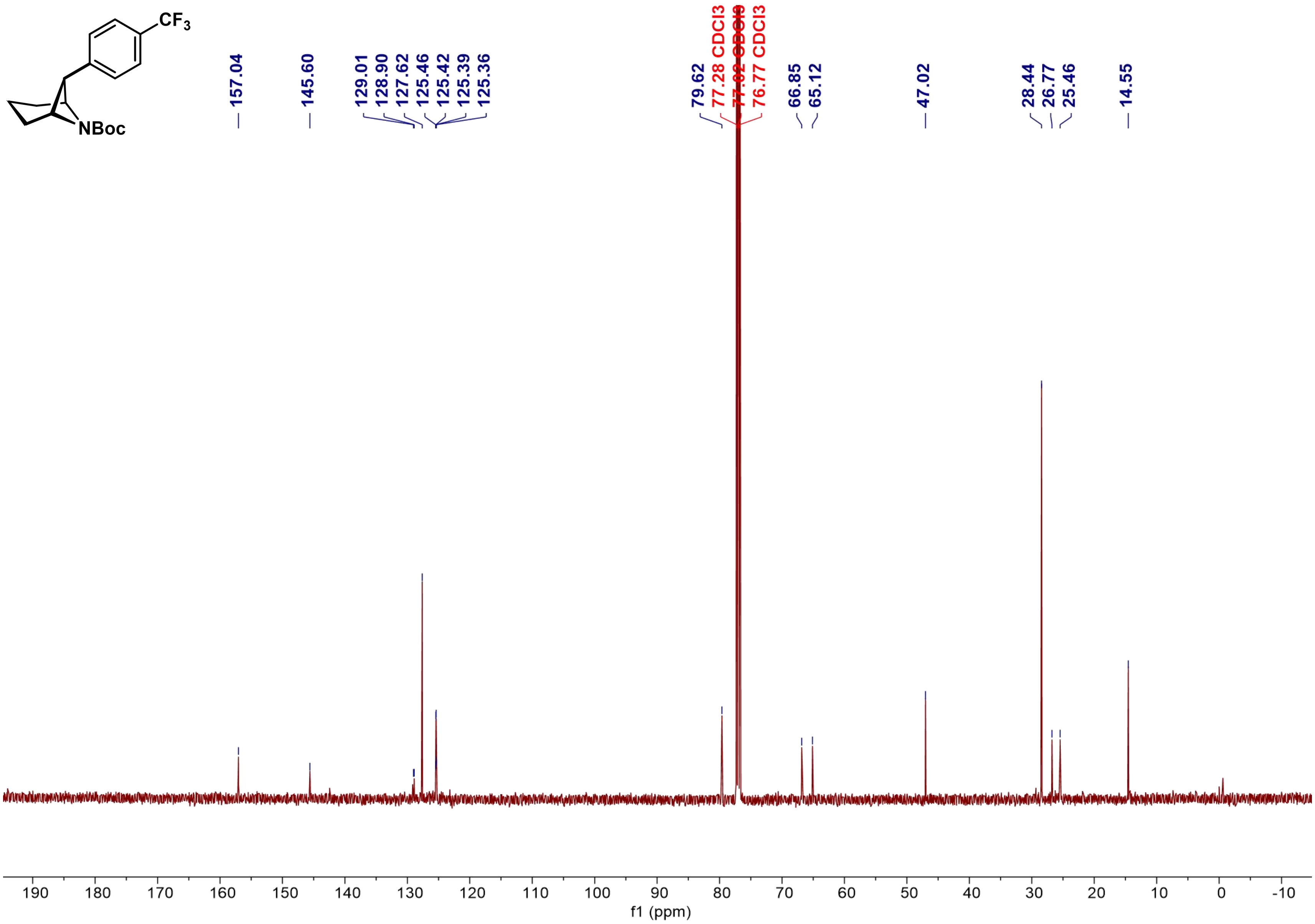
^{13}C NMR Spectrum of compound 52 (126 MHz, $CDCl_3$)



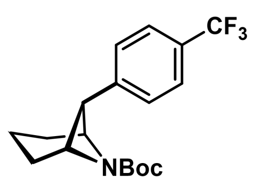
^{1}H NMR Spectrum of compound 53 (500 MHz, $CDCl_3$)

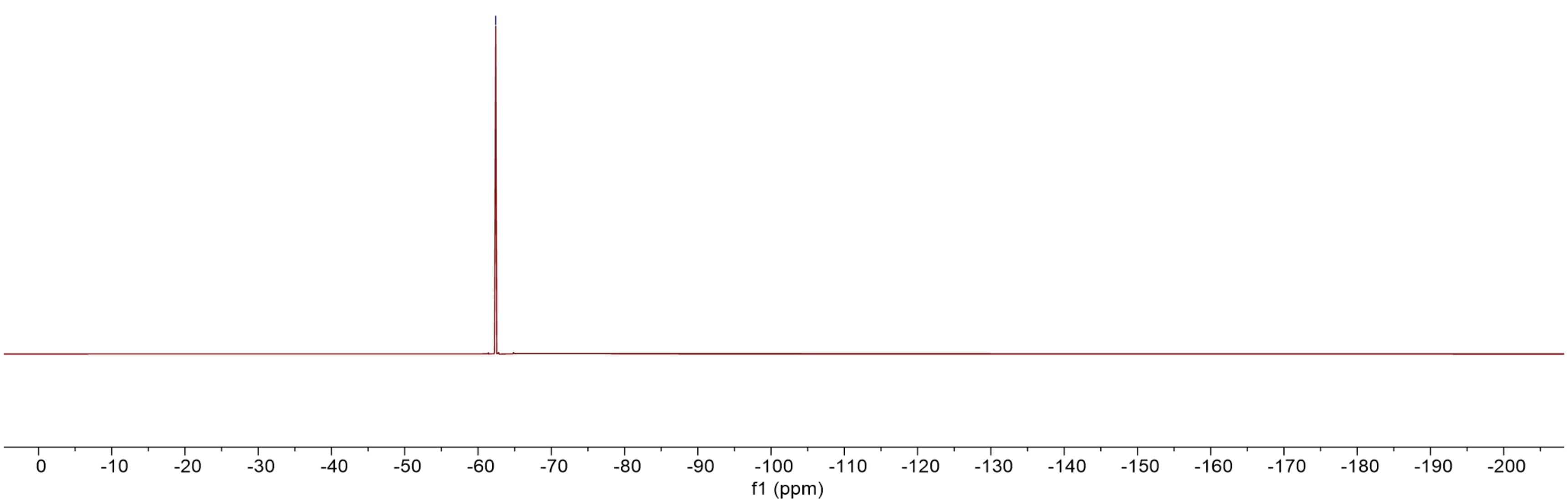


^{13}C NMR Spectrum of compound 53 (126 MHz, CDCl$_3$)

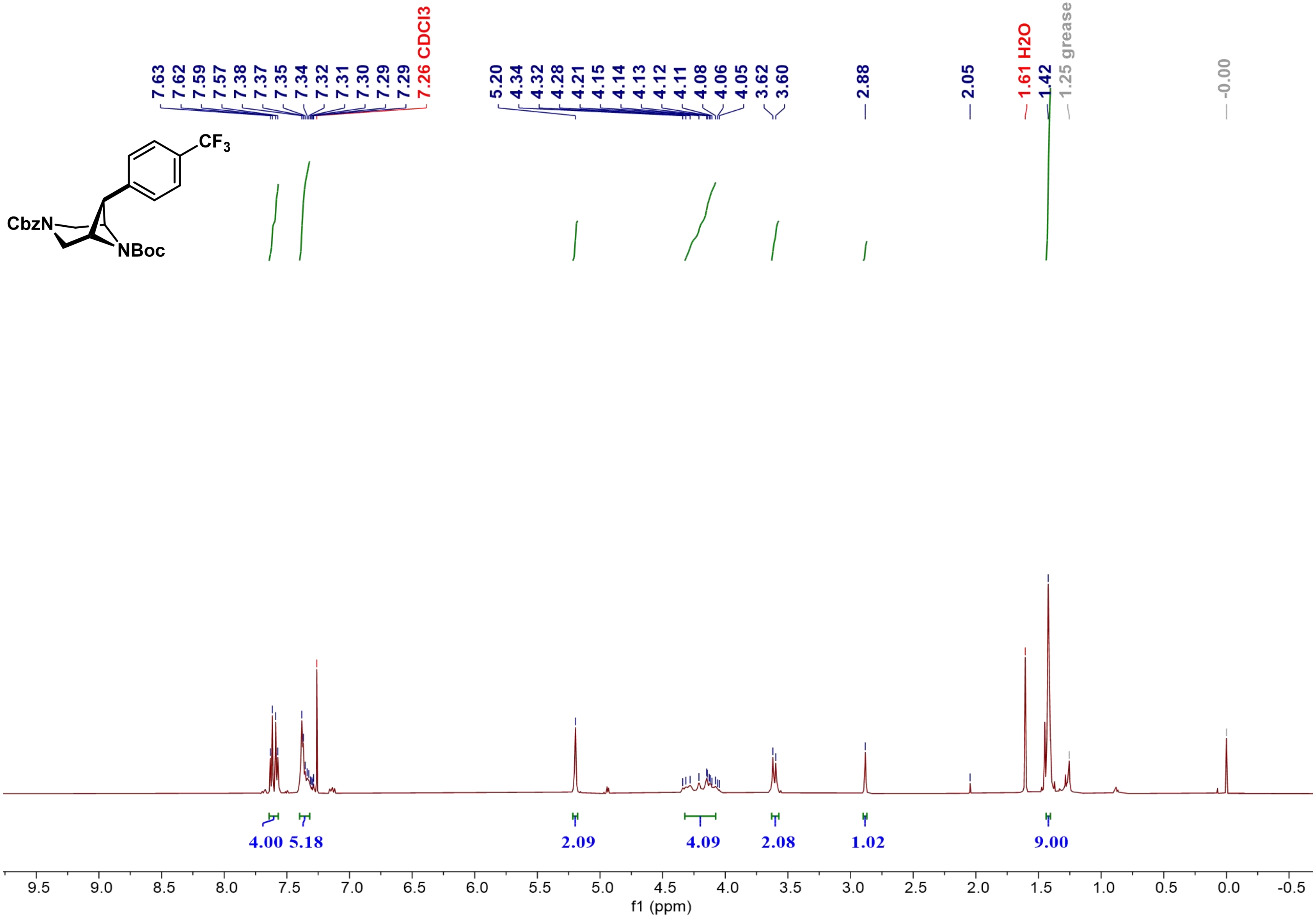


^{19}F NMR Spectrum of compound 53 (471 MHz, CDCl$_3$)

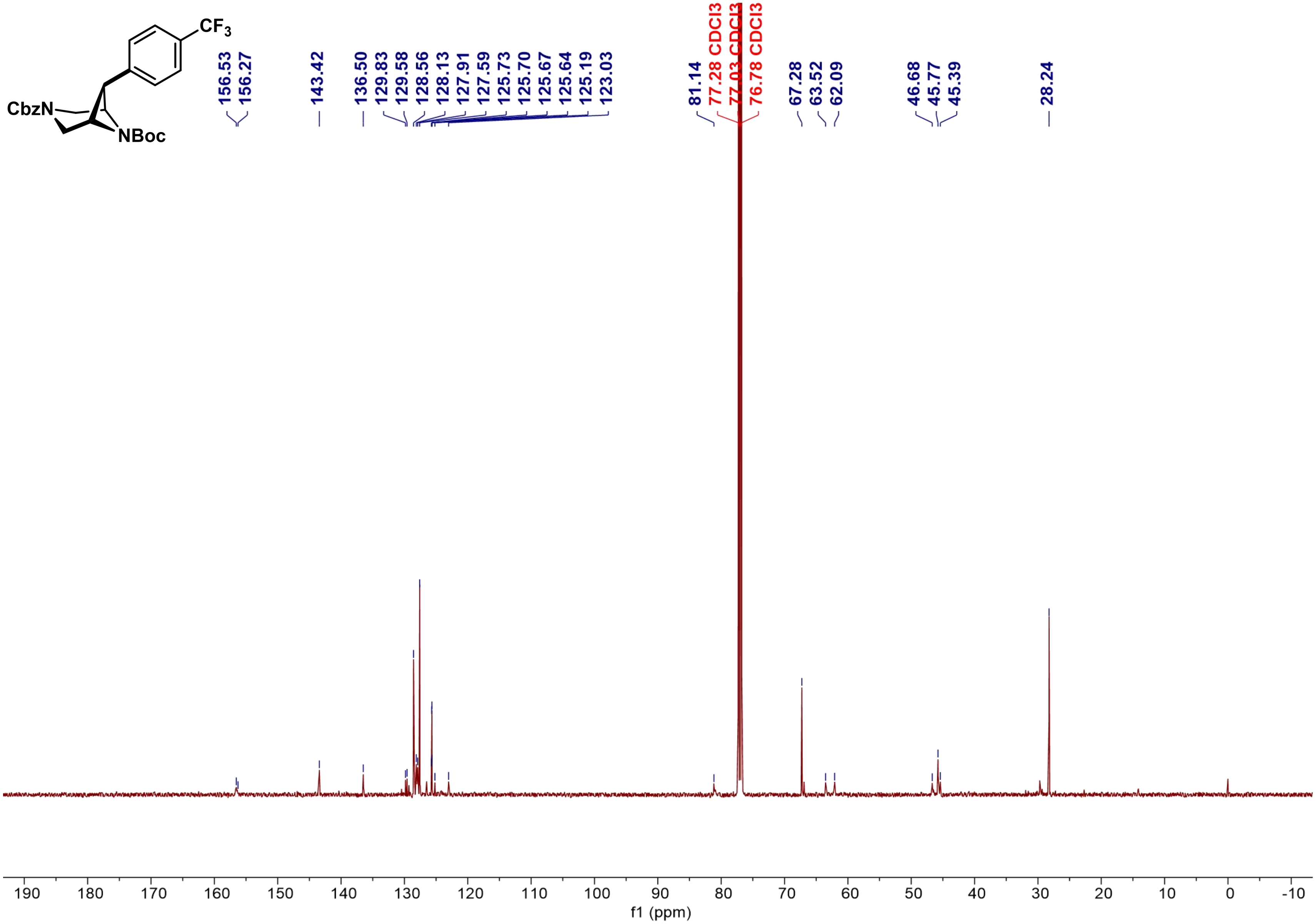




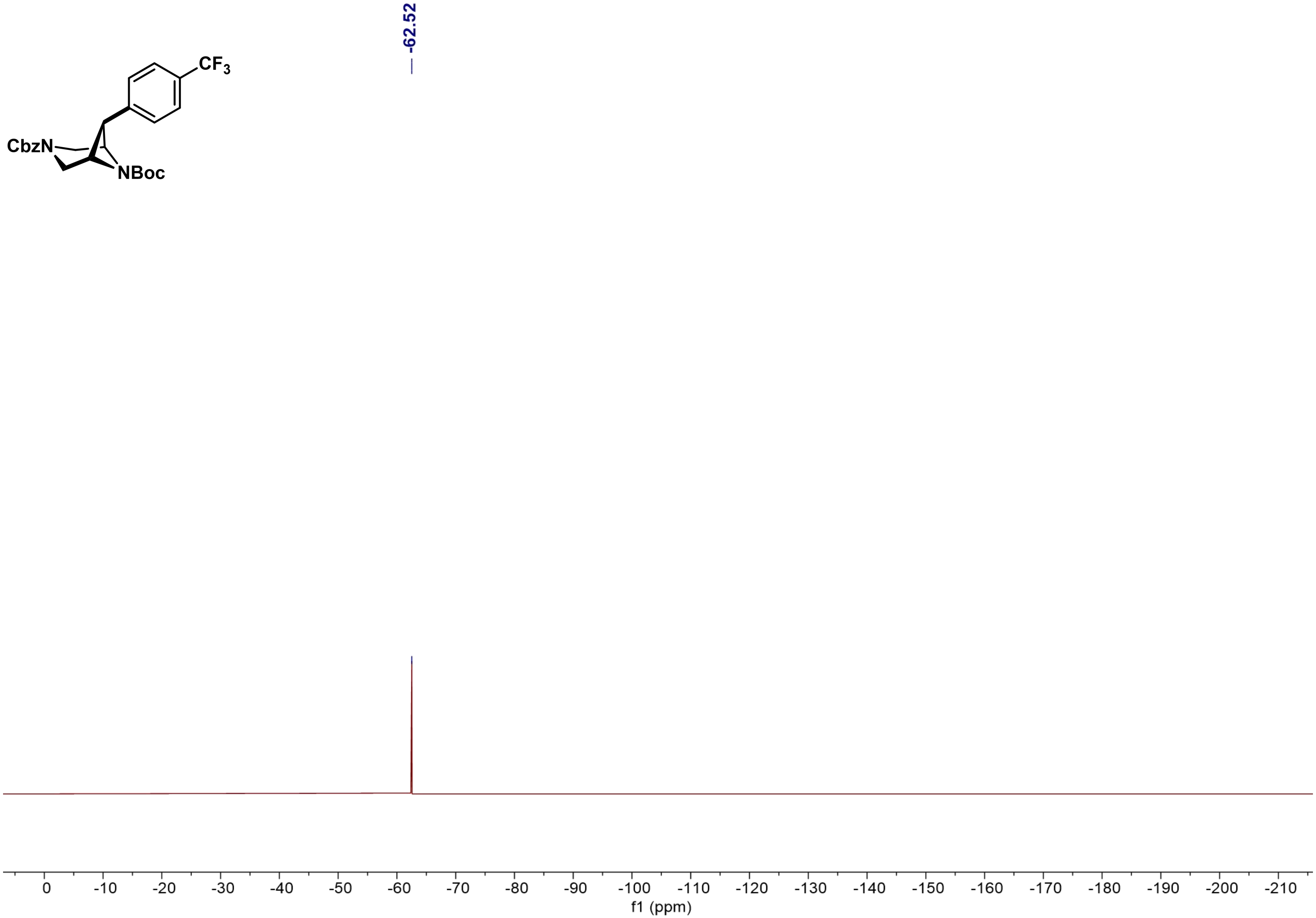
^{1}H NMR Spectrum of compound 54 (500 MHz, $CDCl_3$)



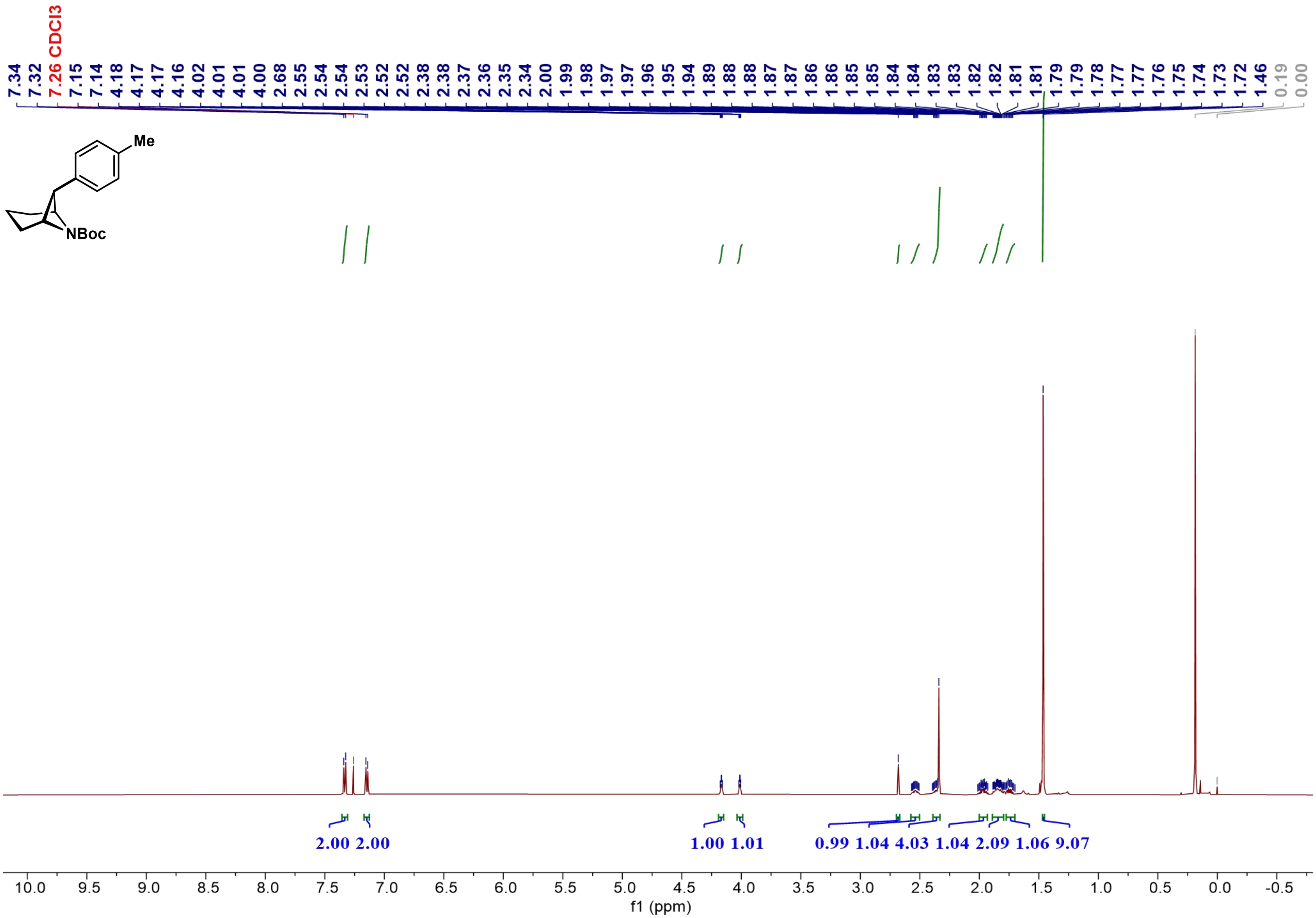
^{13}C NMR Spectrum of compound 54 (126 MHz, $CDCl_3$)



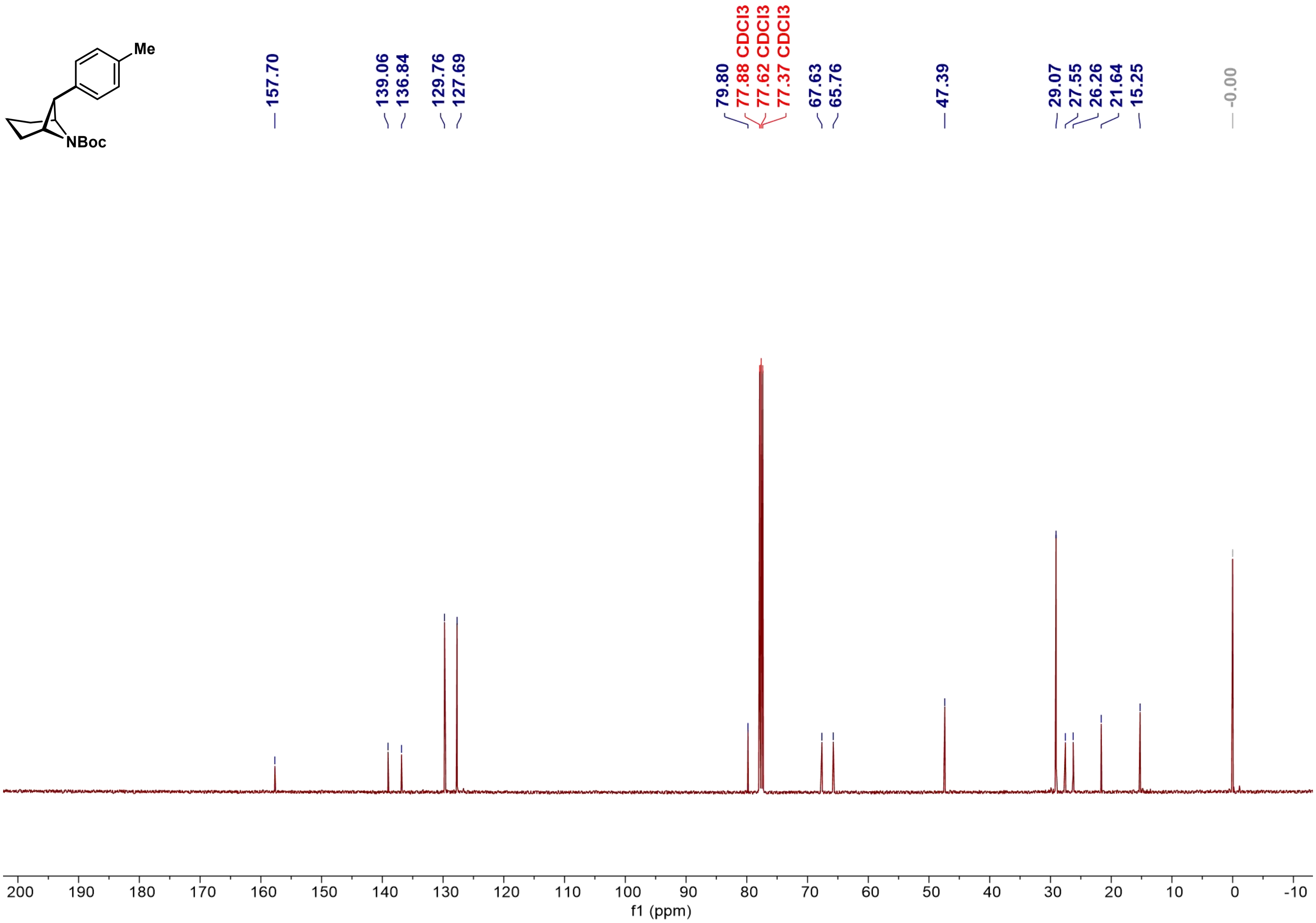
^{19}F NMR Spectrum of compound 54 (471 MHz, CDCl$_3$)



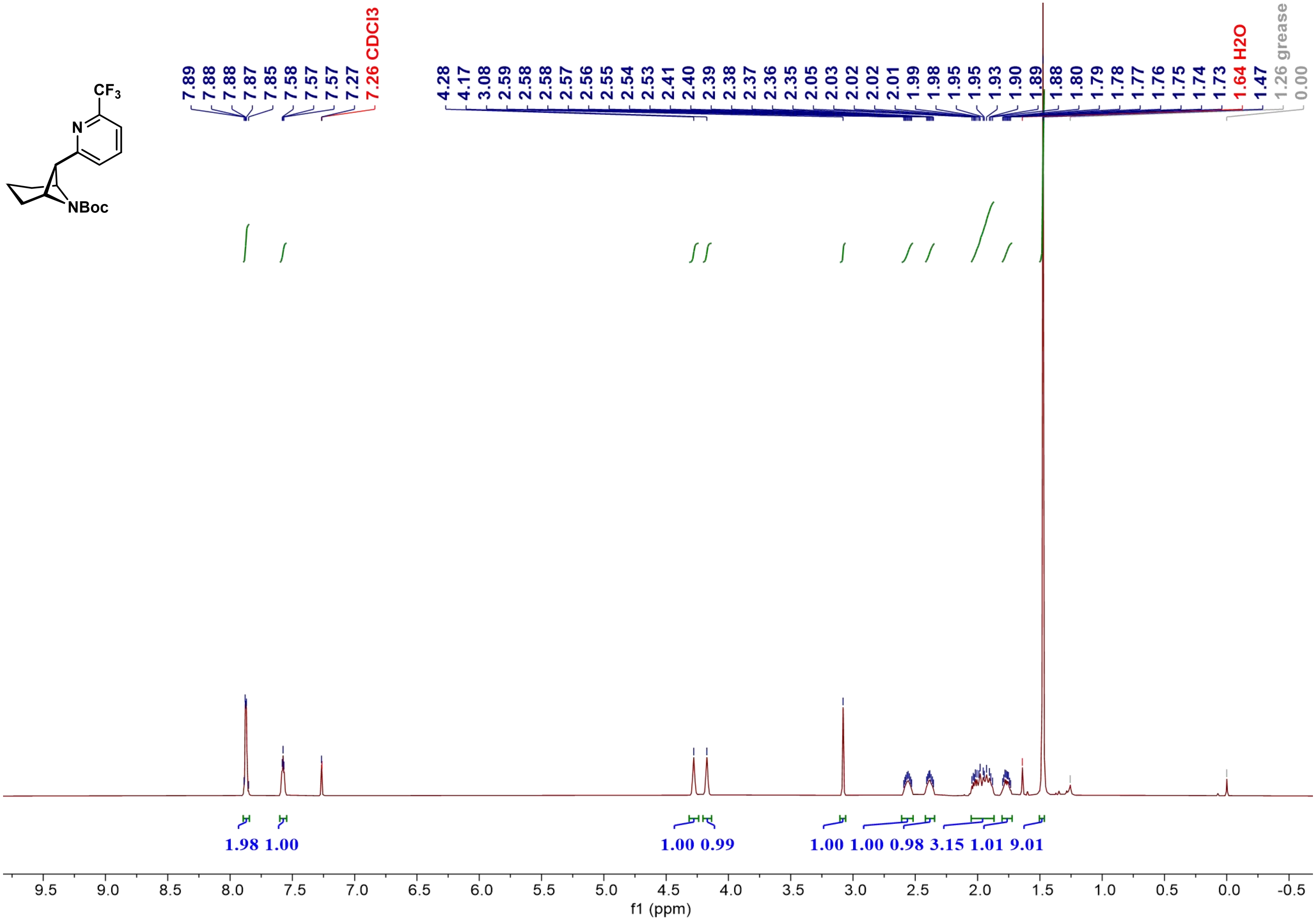
^{1}H NMR Spectrum of compound 55 (500 MHz, CDCl$_3$)



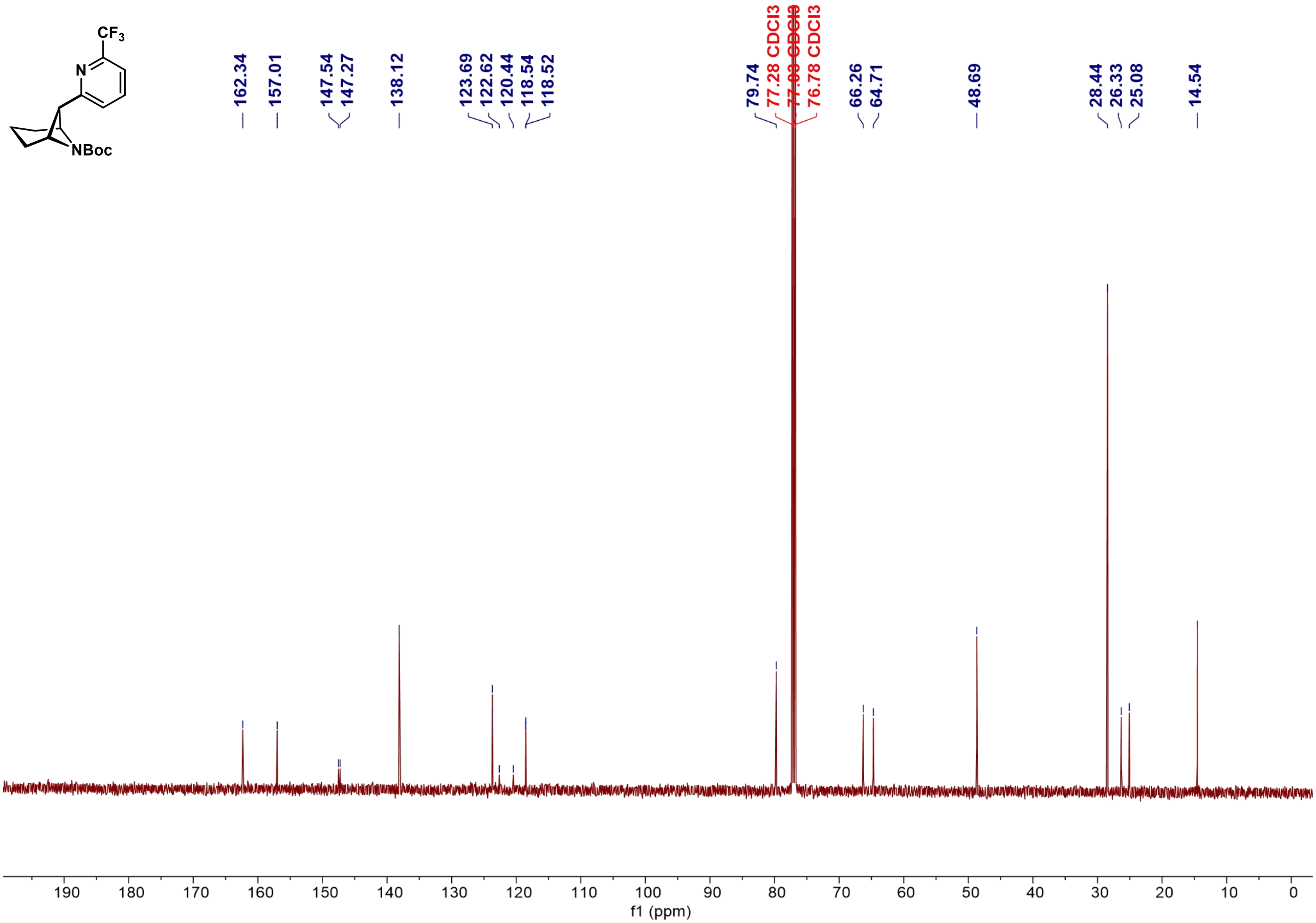
^{13}C NMR Spectrum of compound 55 (126 MHz, $CDCl_3$)



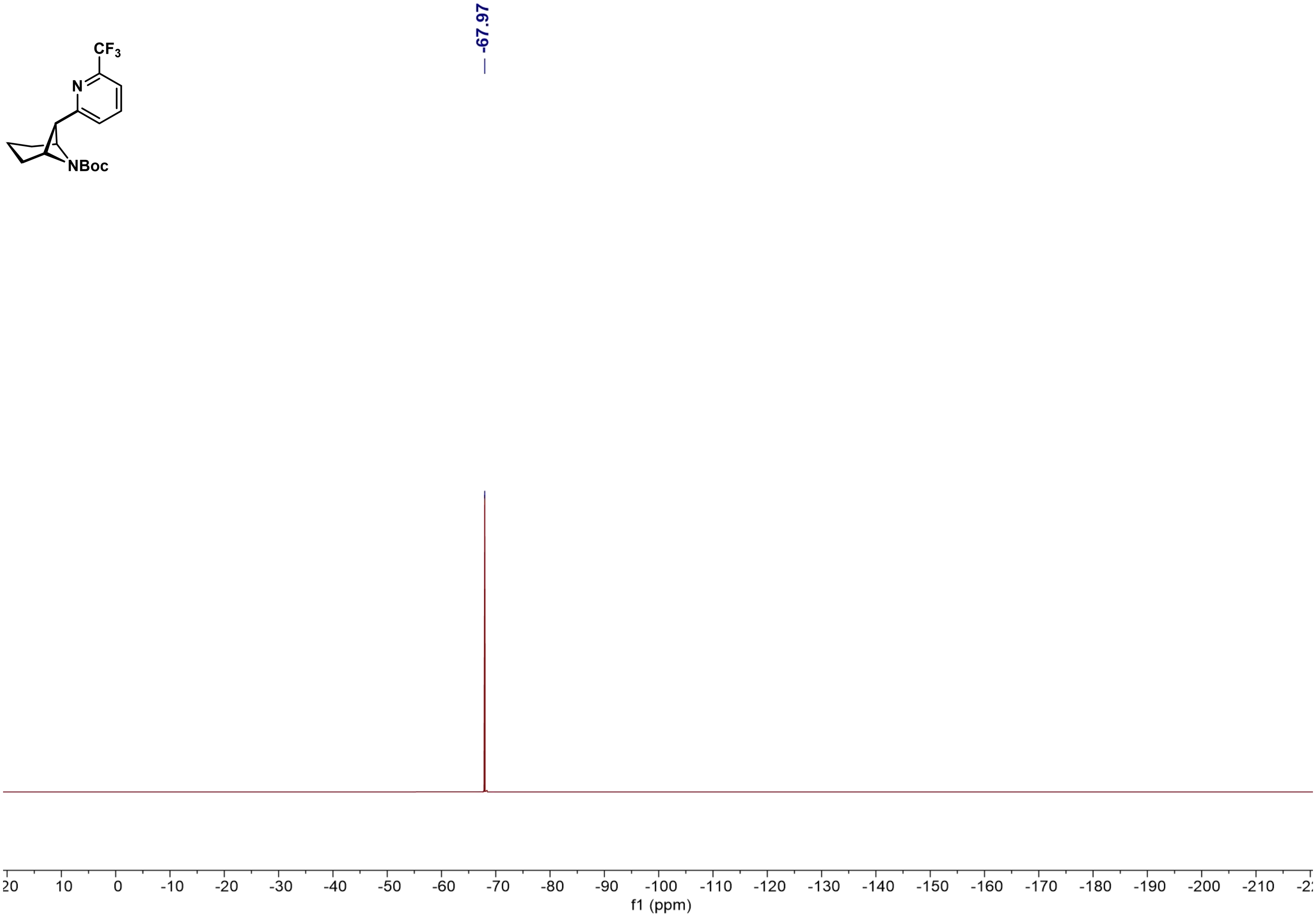
^{1}H NMR Spectrum of compound 56 (500 MHz, $CDCl_3$)



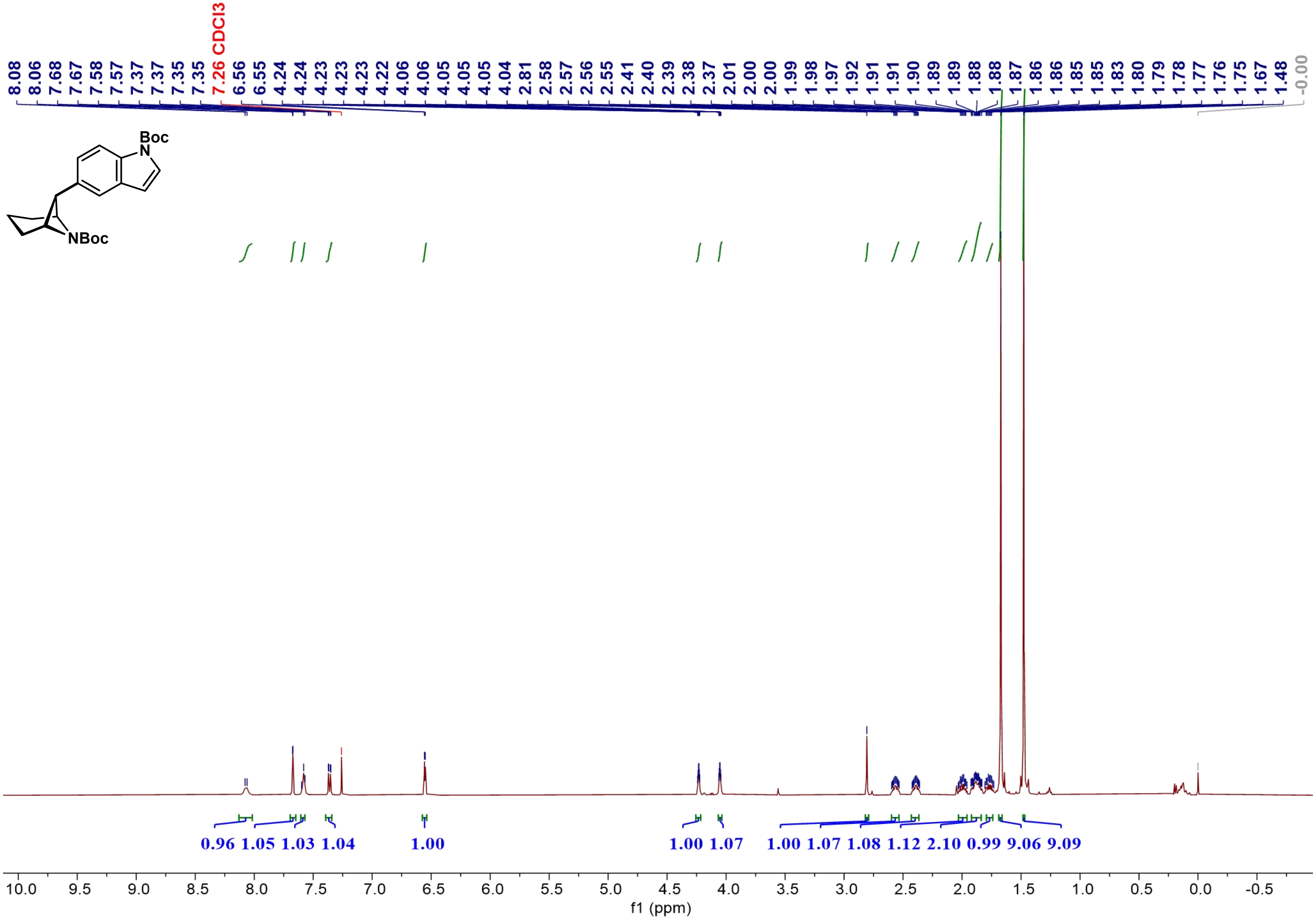
^{13}C NMR Spectrum of compound 56 (126 MHz, $CDCl_3$)



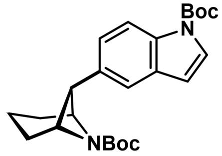
^{19}F NMR Spectrum of compound 56 (471 MHz, $CDCl_3$)

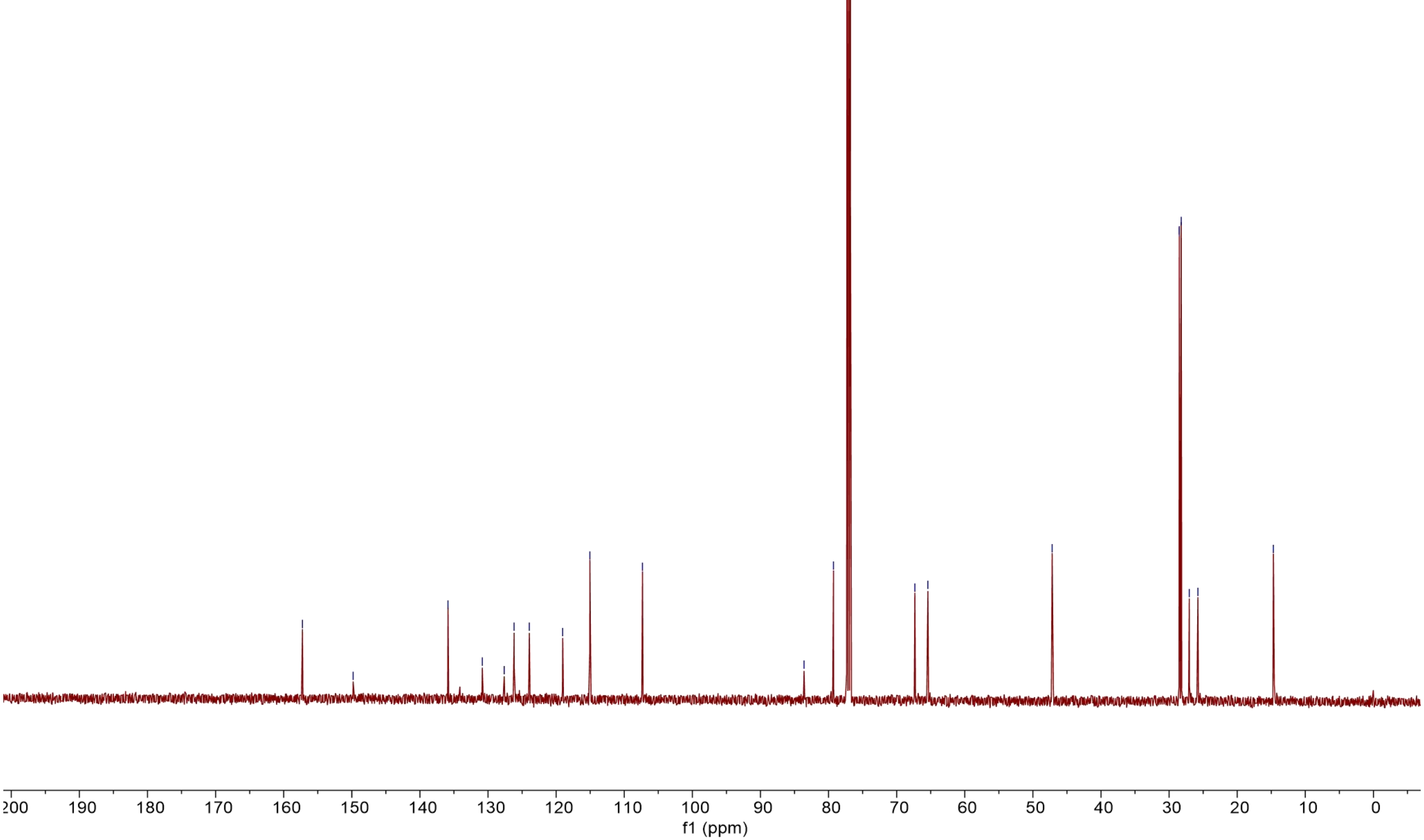


^{1}H NMR Spectrum of compound 57 (500 MHz, $CDCl_3$)

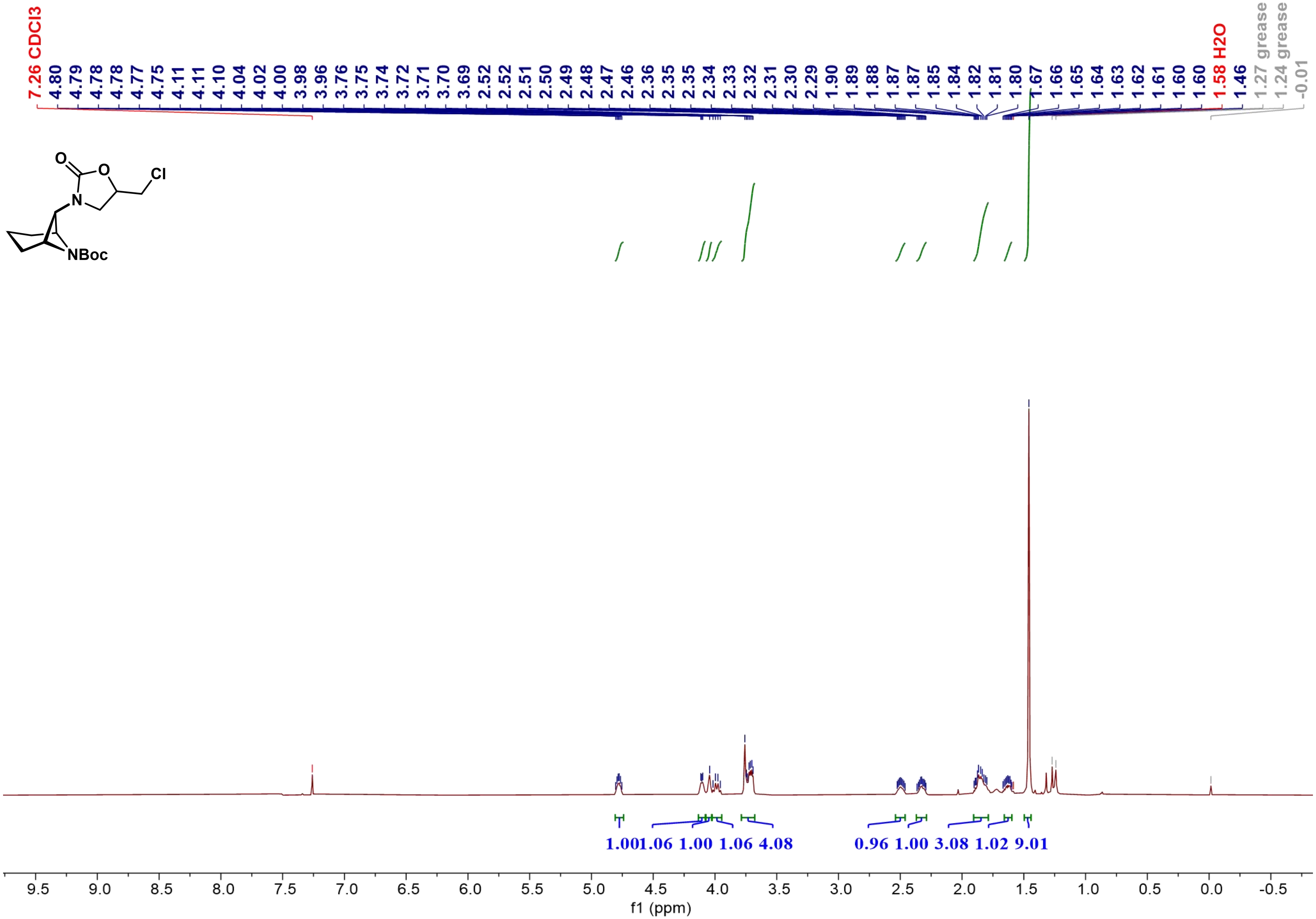


^{13}C NMR Spectrum of compound 57 (126 MHz, $CDCl_3$)

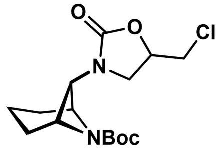


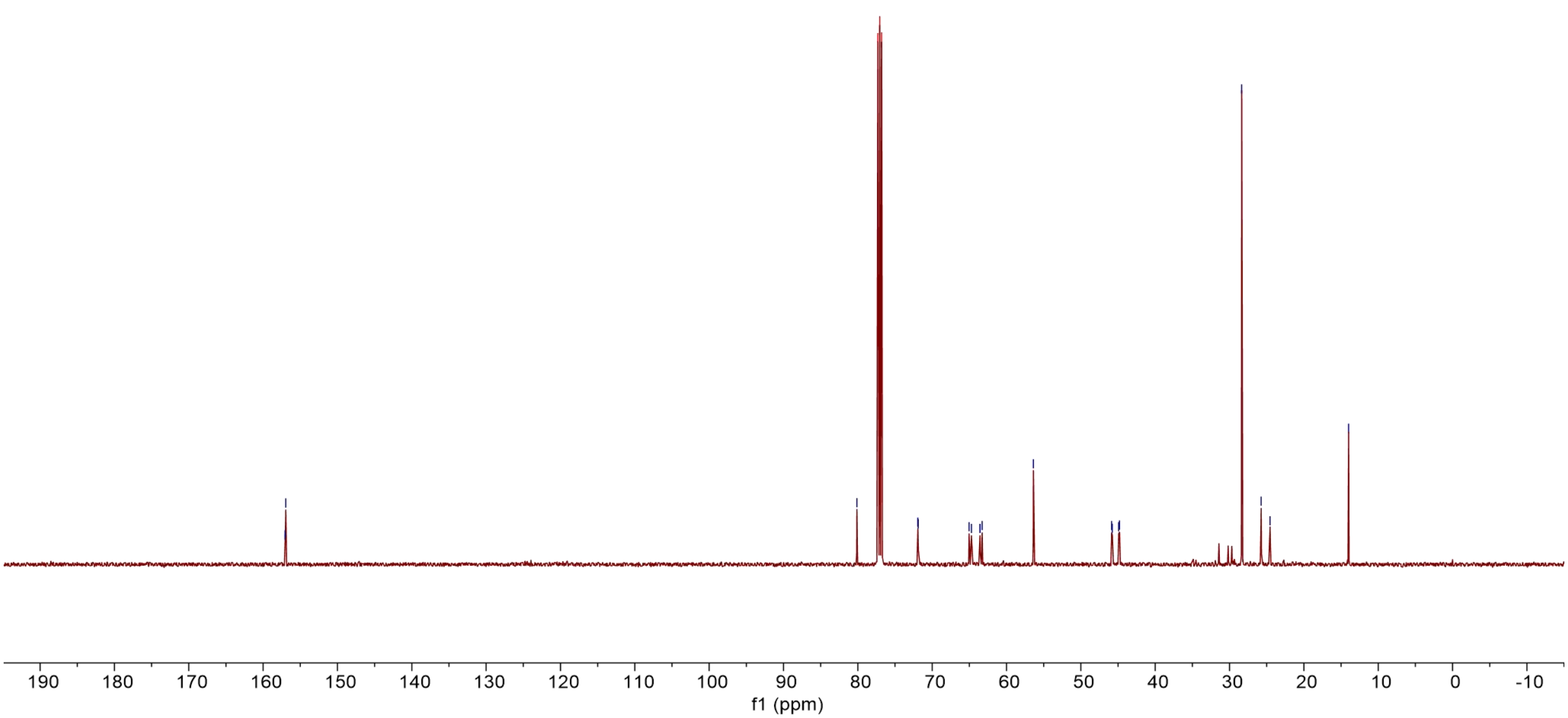


^{1}H NMR Spectrum of compound 58 (500 MHz, $CDCl_3$)

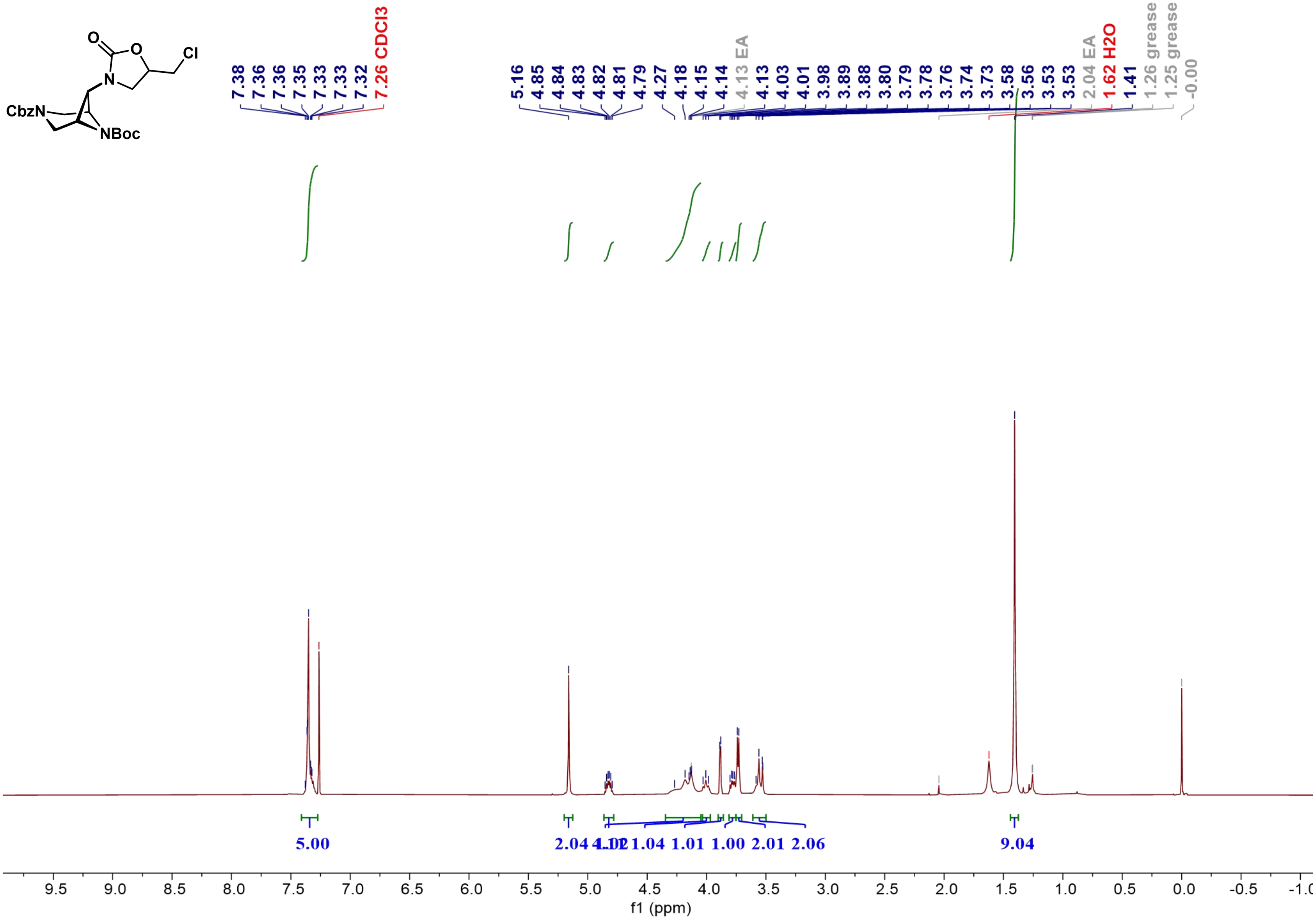


^{13}C NMR Spectrum of compound 58 (126 MHz, $CDCl_3$)

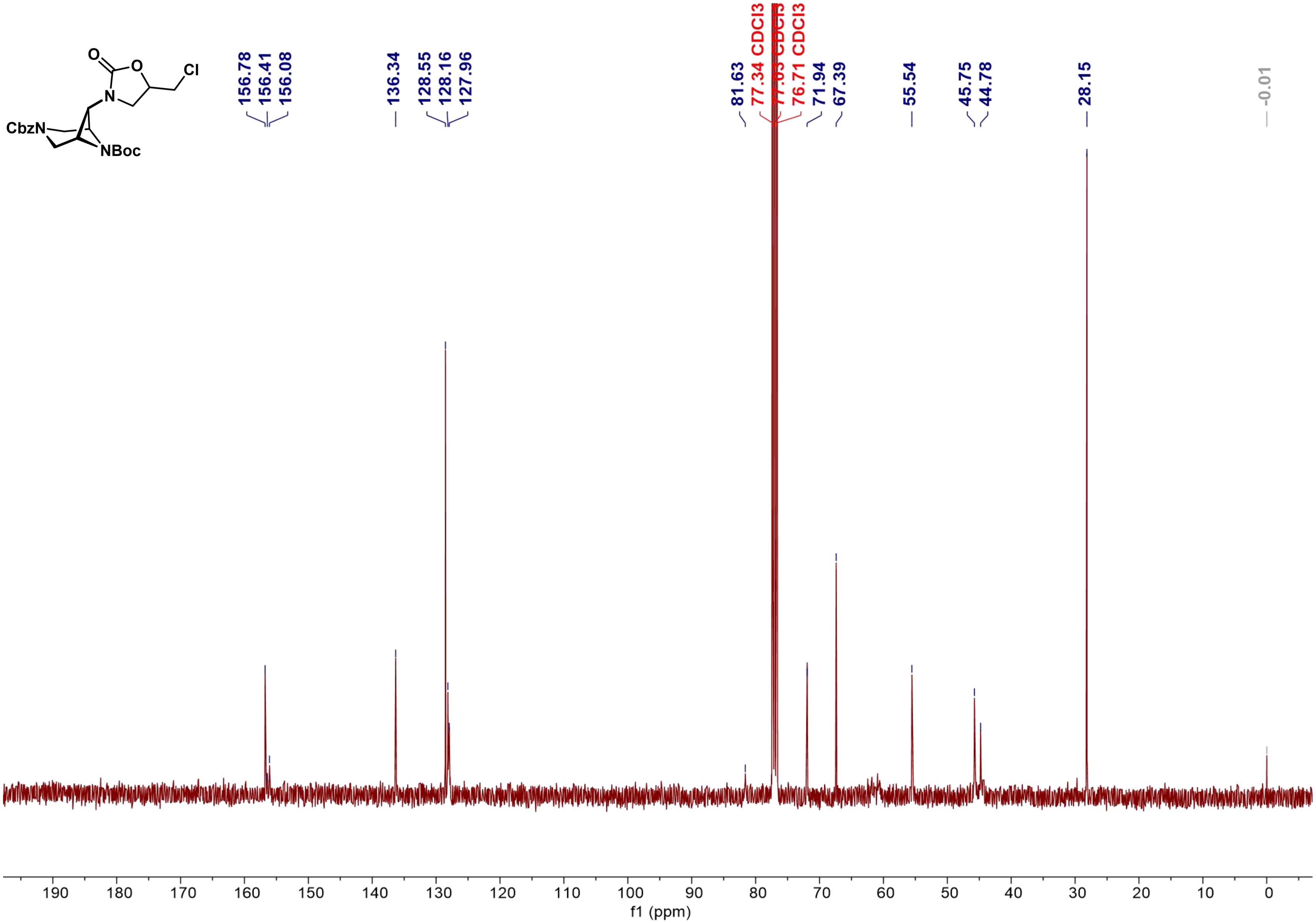




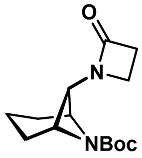
^{1}H NMR Spectrum of compound 59 (400 MHz, $CDCl_3$)

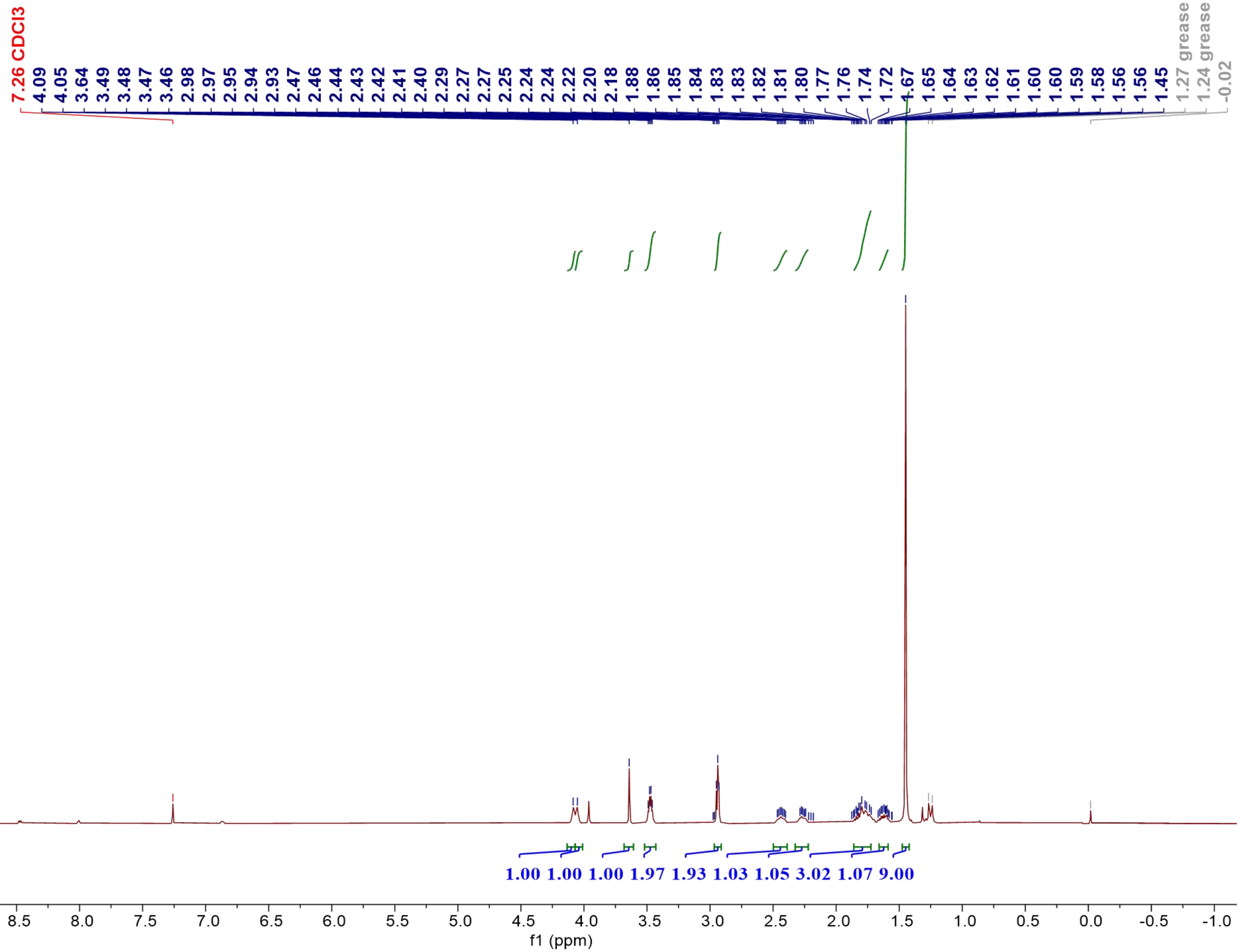


^{13}C NMR Spectrum of compound 59 (101 MHz, $CDCl_3$)

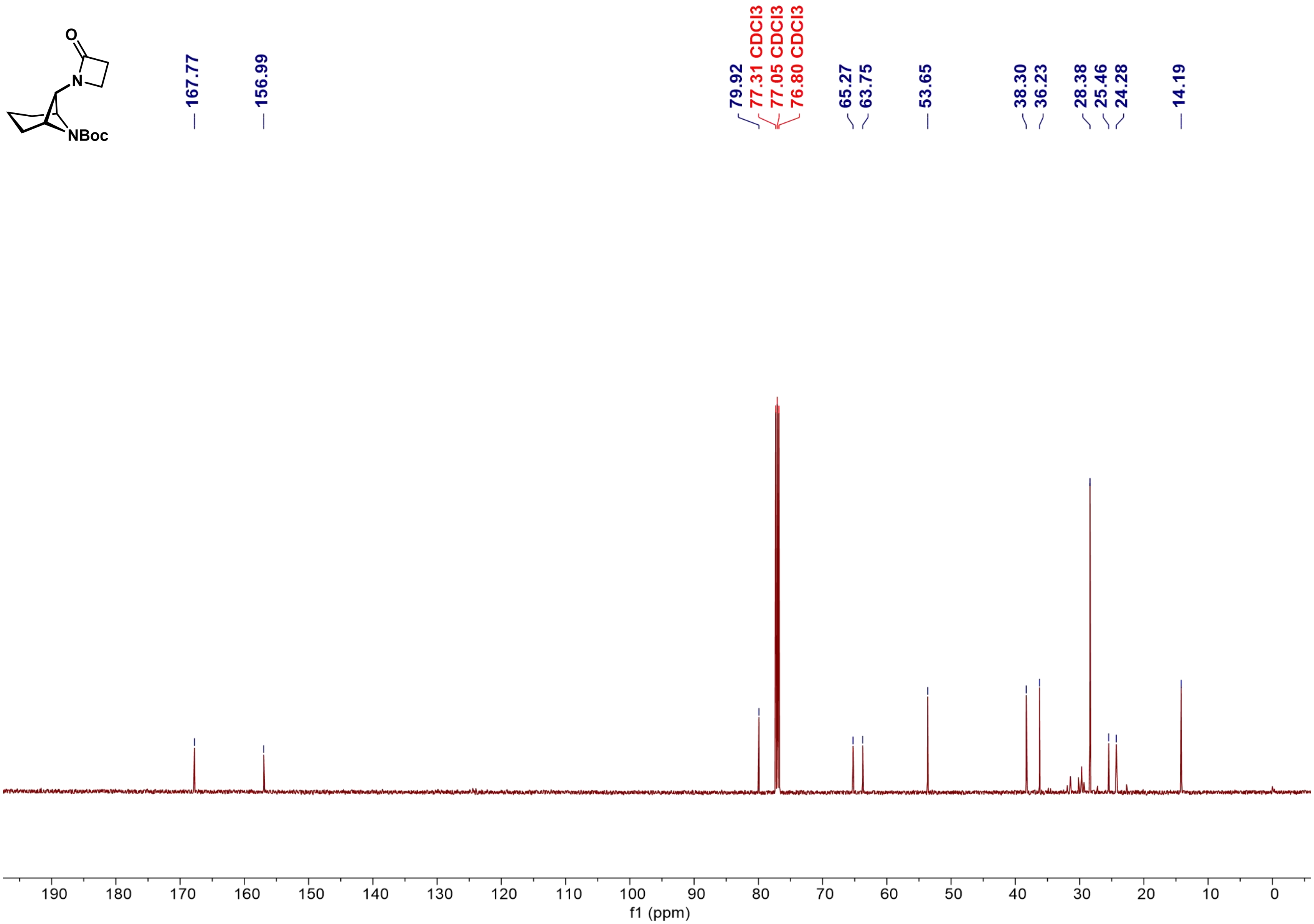


^{1}H NMR Spectrum of compound 60 (400 MHz, $CDCl_3$)

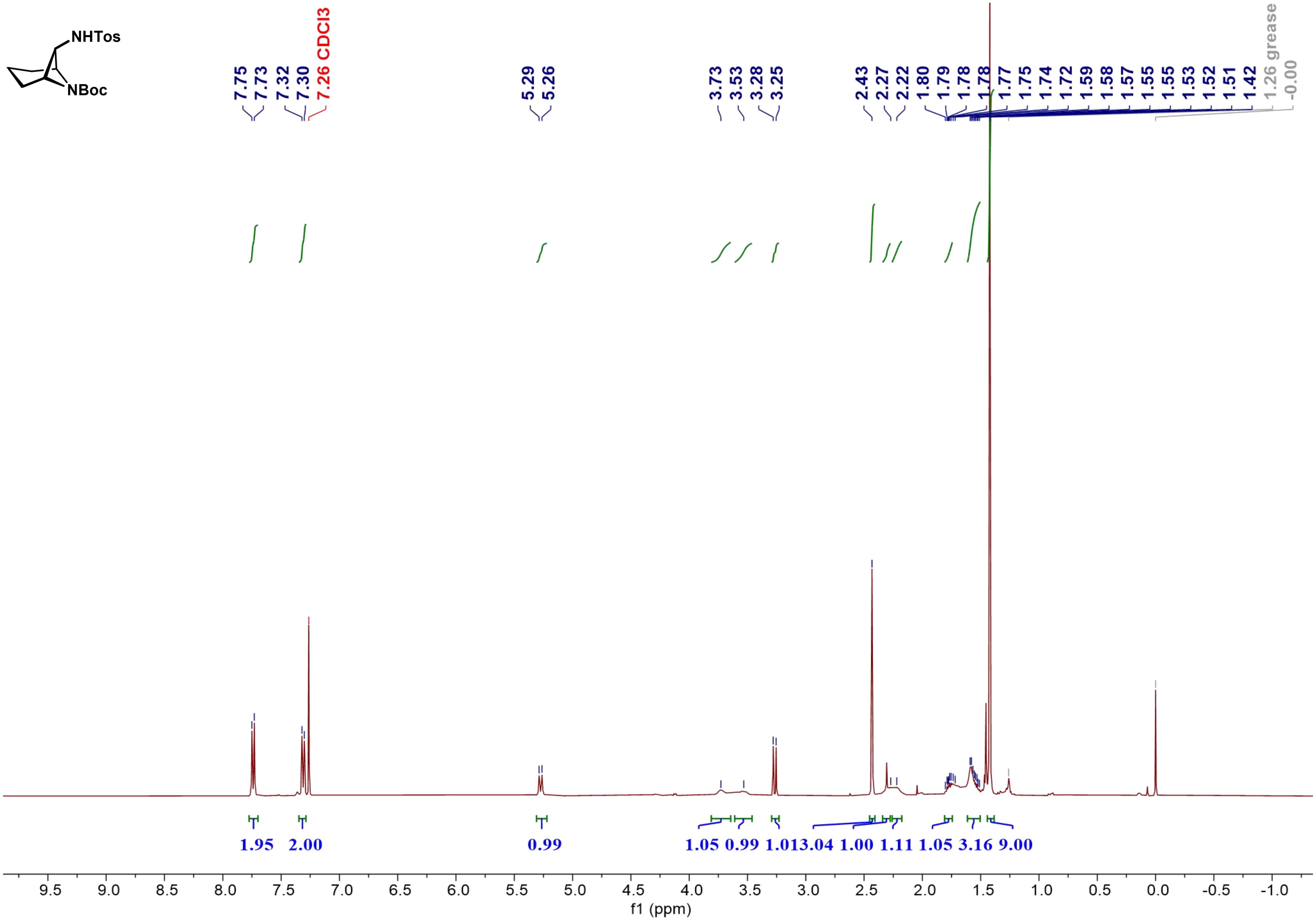




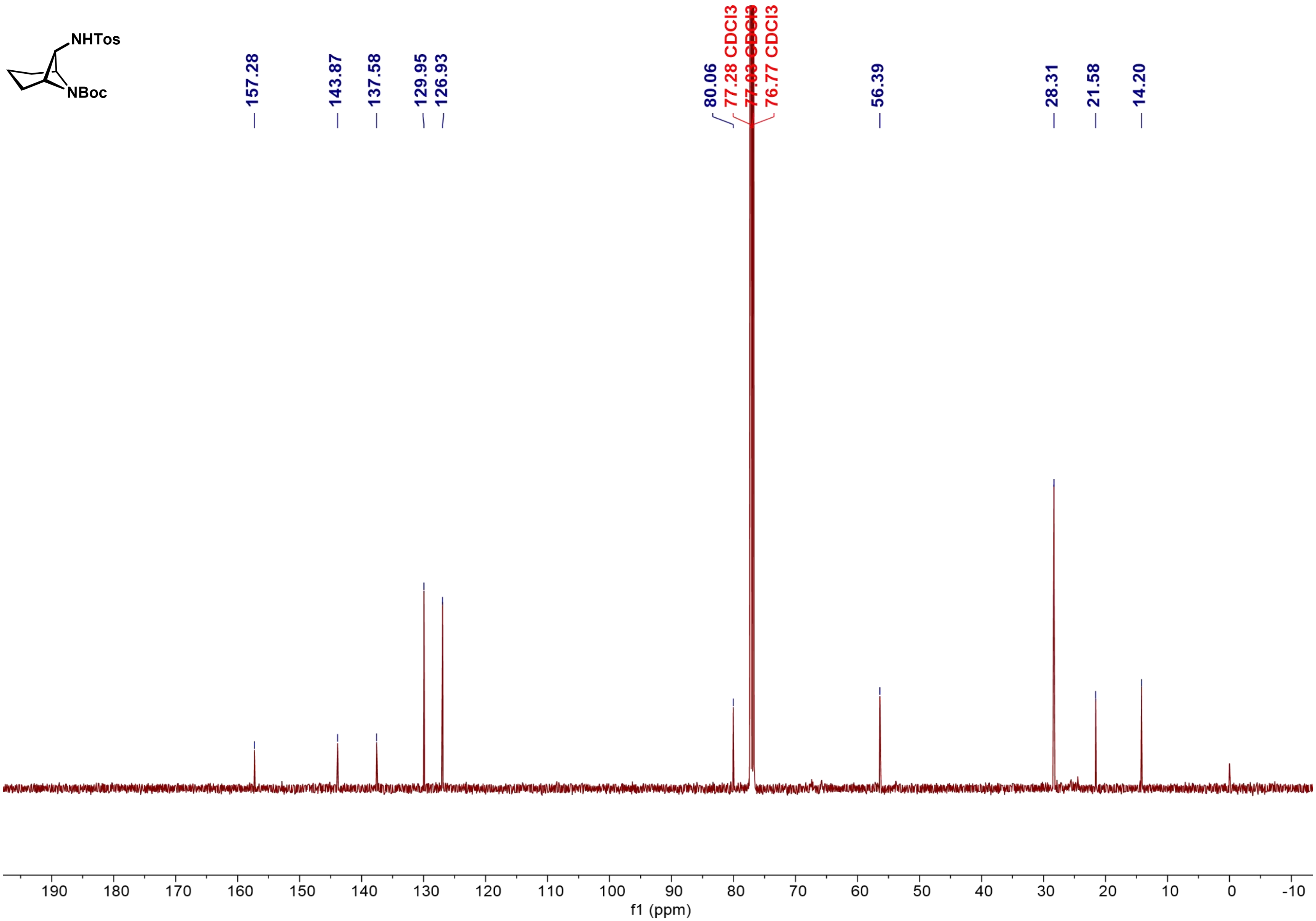
^{13}C NMR Spectrum of compound 60 (126 MHz, $CDCl_3$)



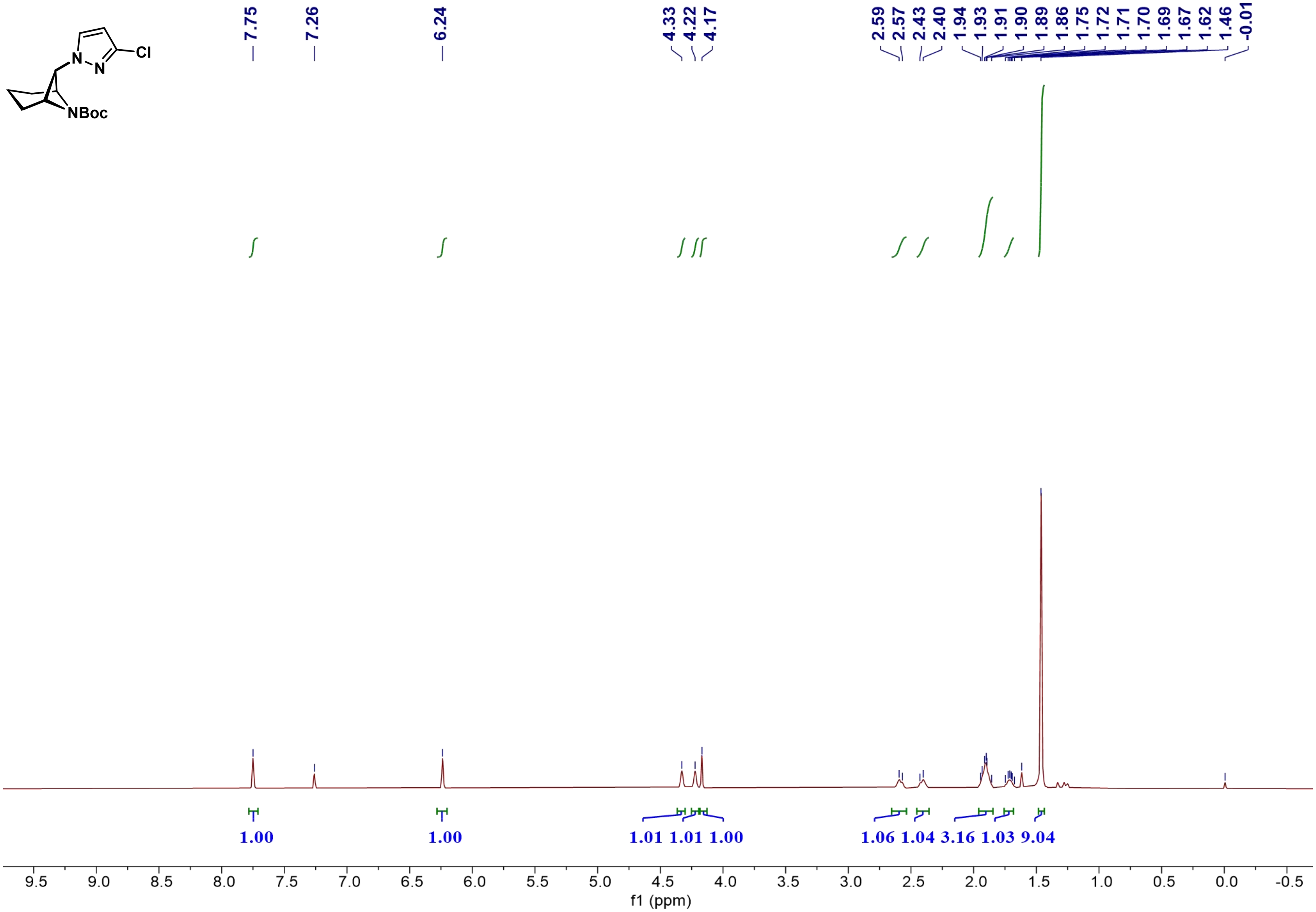
^{1}H NMR Spectrum of compound 61 (400 MHz, $CDCl_3$)



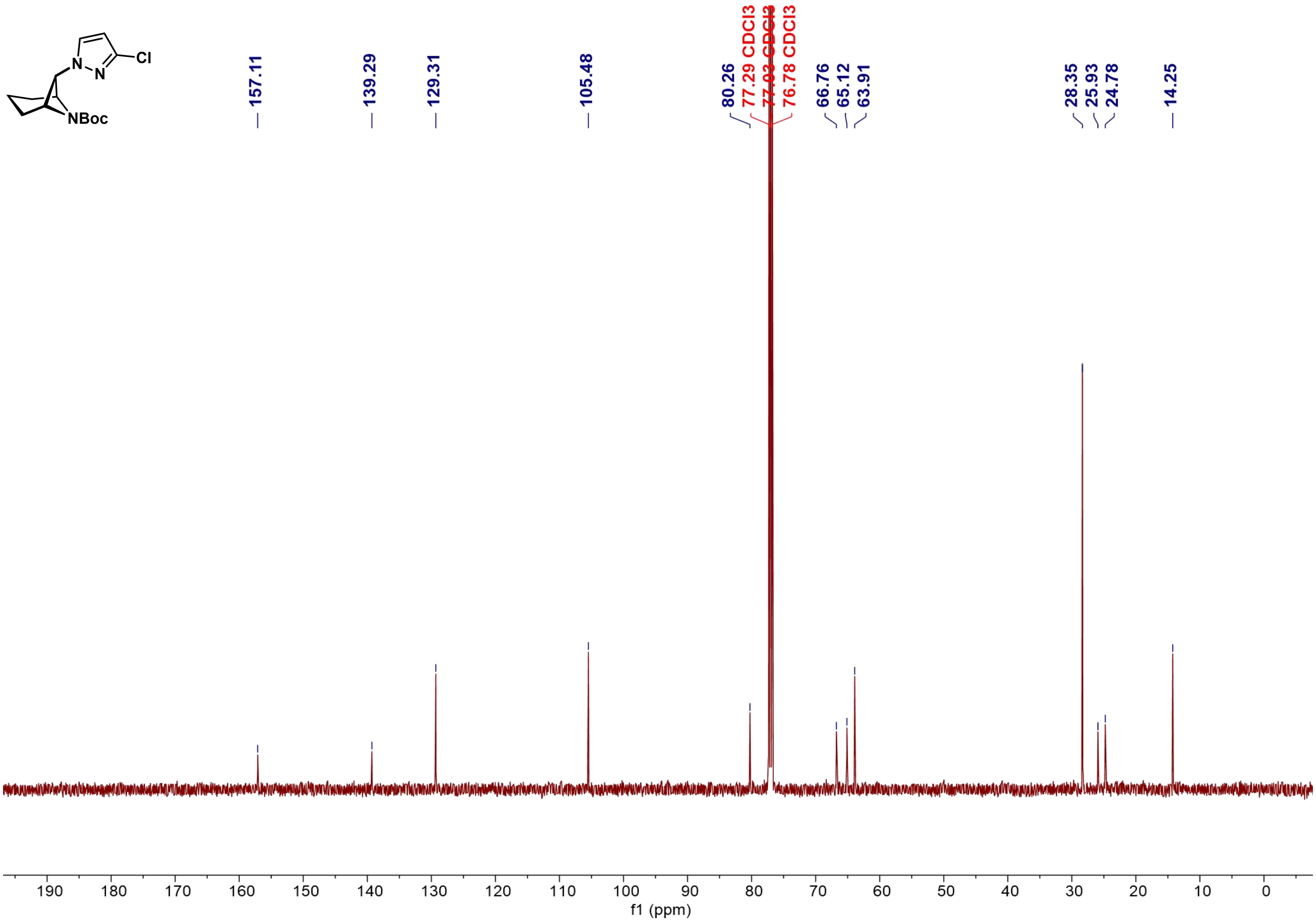
^{13}C NMR Spectrum of compound 61 (101 MHz, $CDCl_3$)



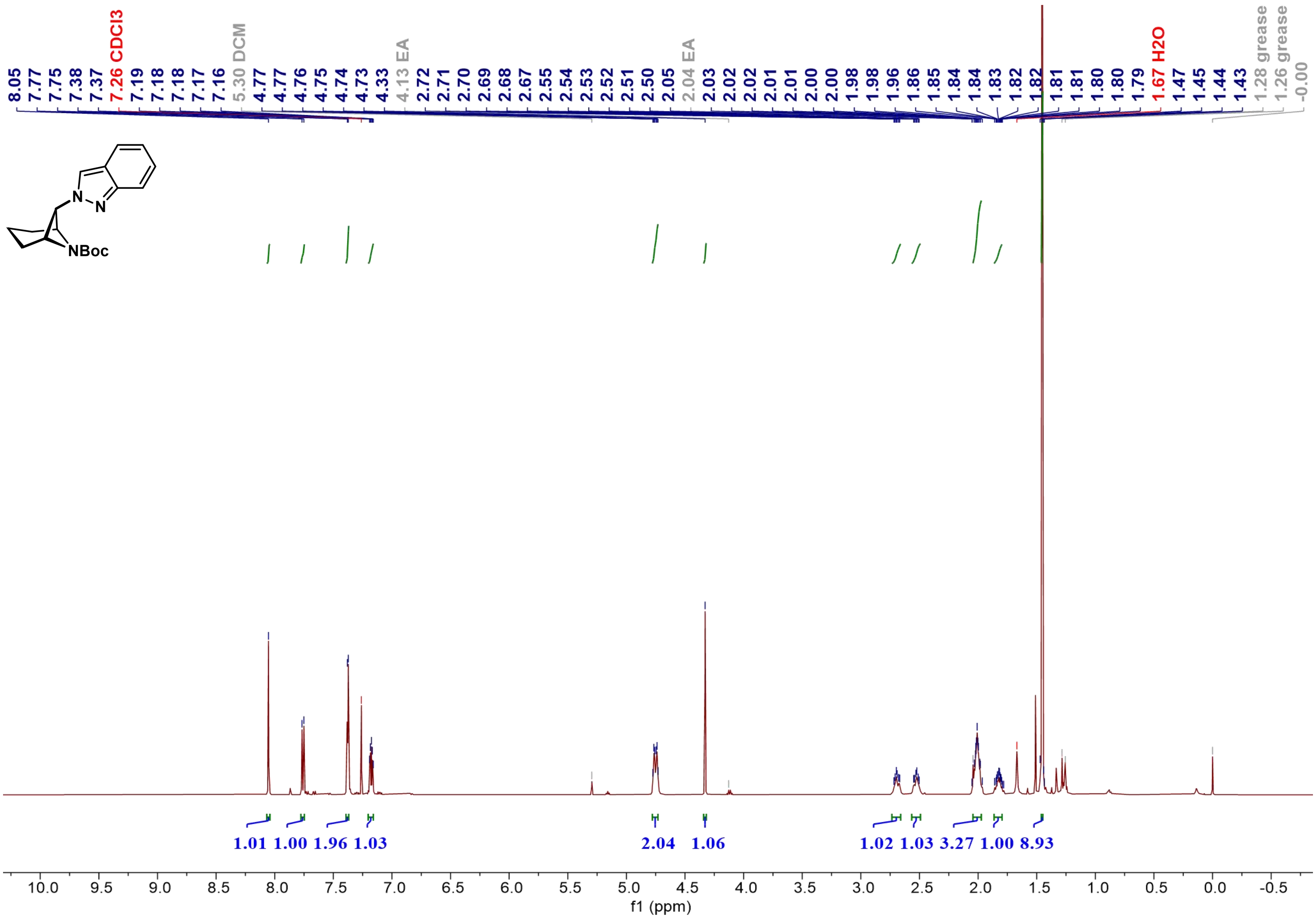
^{1}H NMR Spectrum of compound 62 (500 MHz, CDCl$_3$)



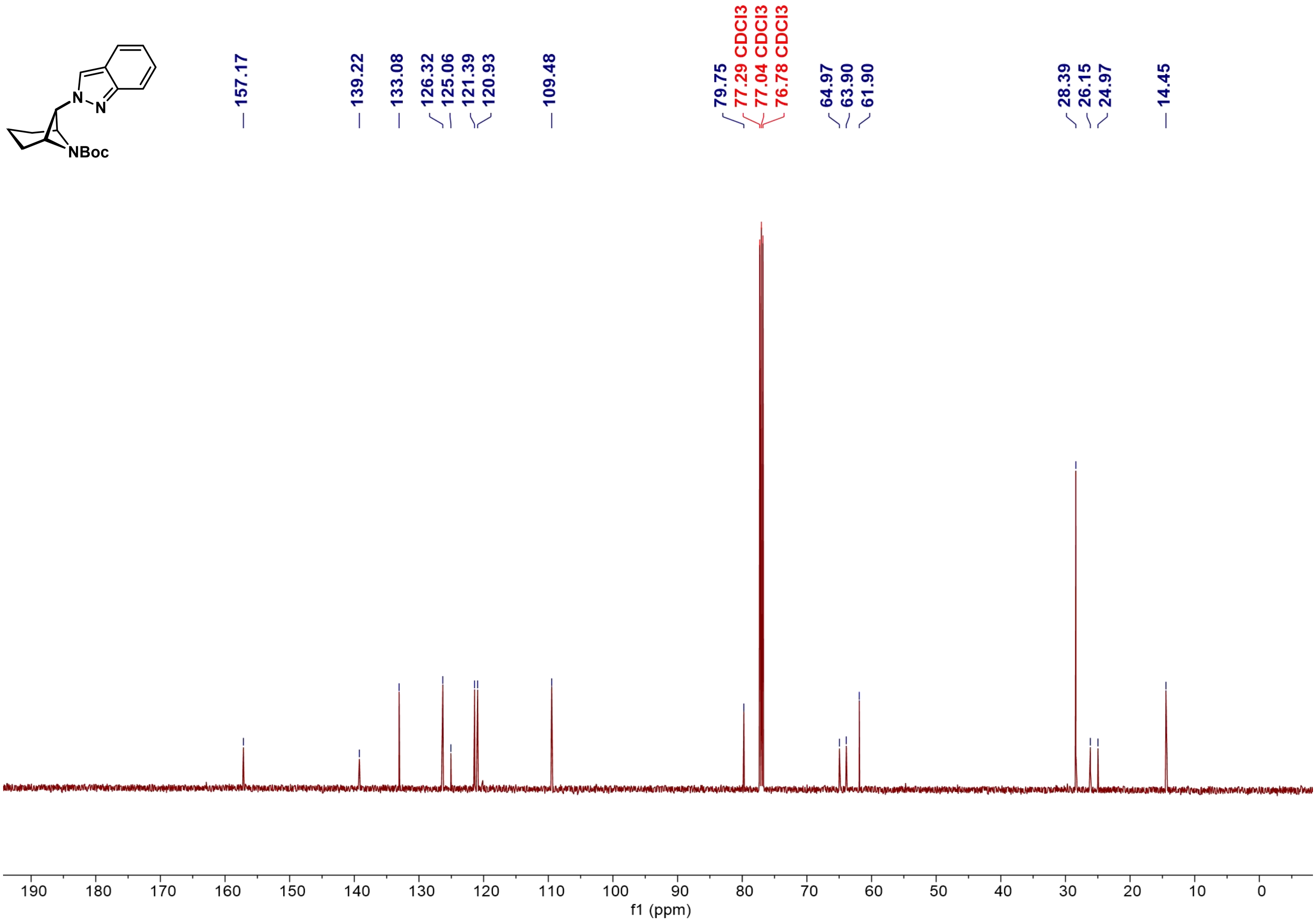
^{13}C NMR Spectrum of compound 62 (126 MHz, CDCl$_3$)



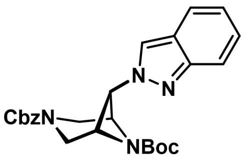
^{1}H NMR Spectrum of compound 63 (500 MHz, $CDCl_3$)

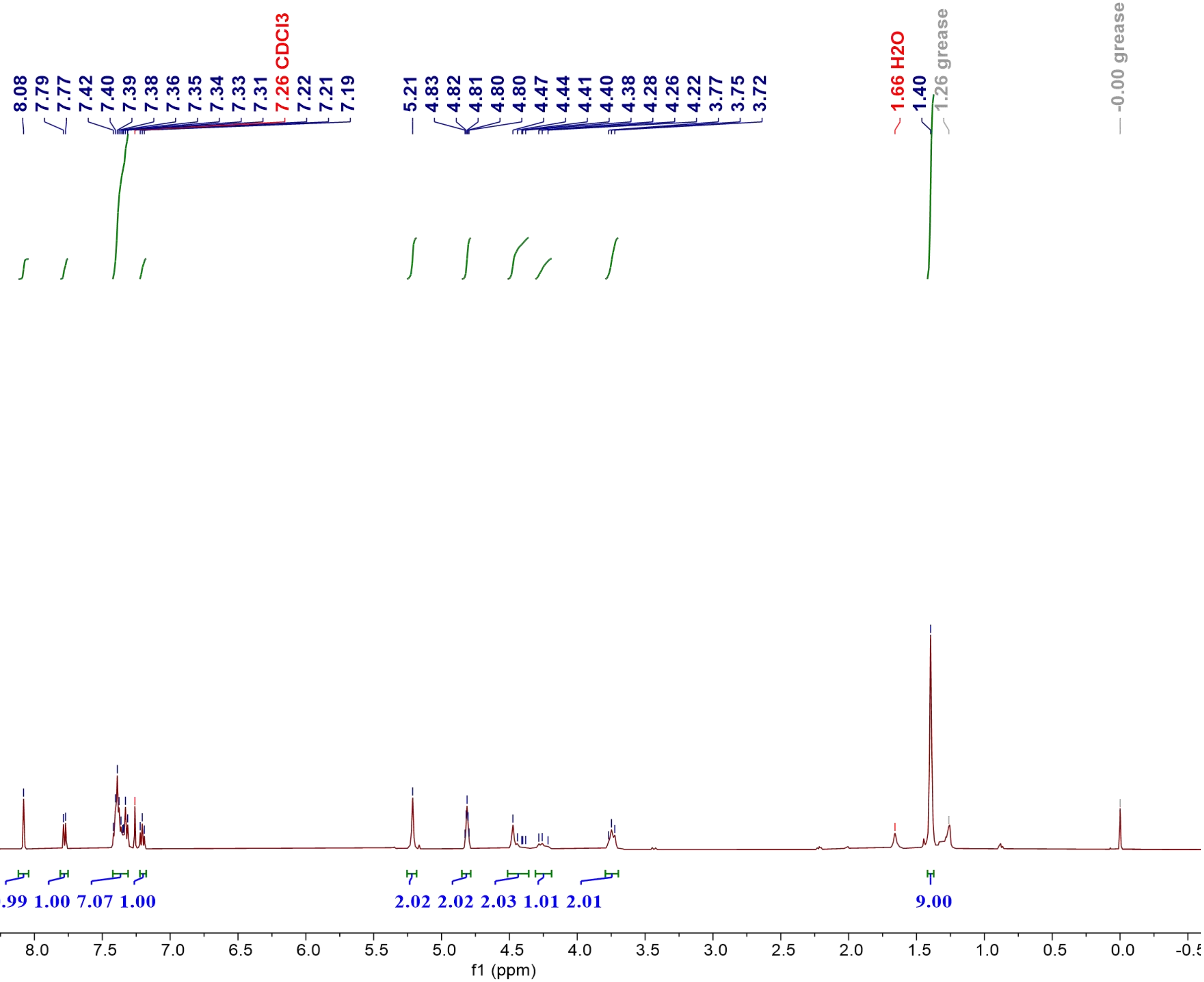


^{13}C NMR Spectrum of compound 63 (126 MHz, $CDCl_3$)

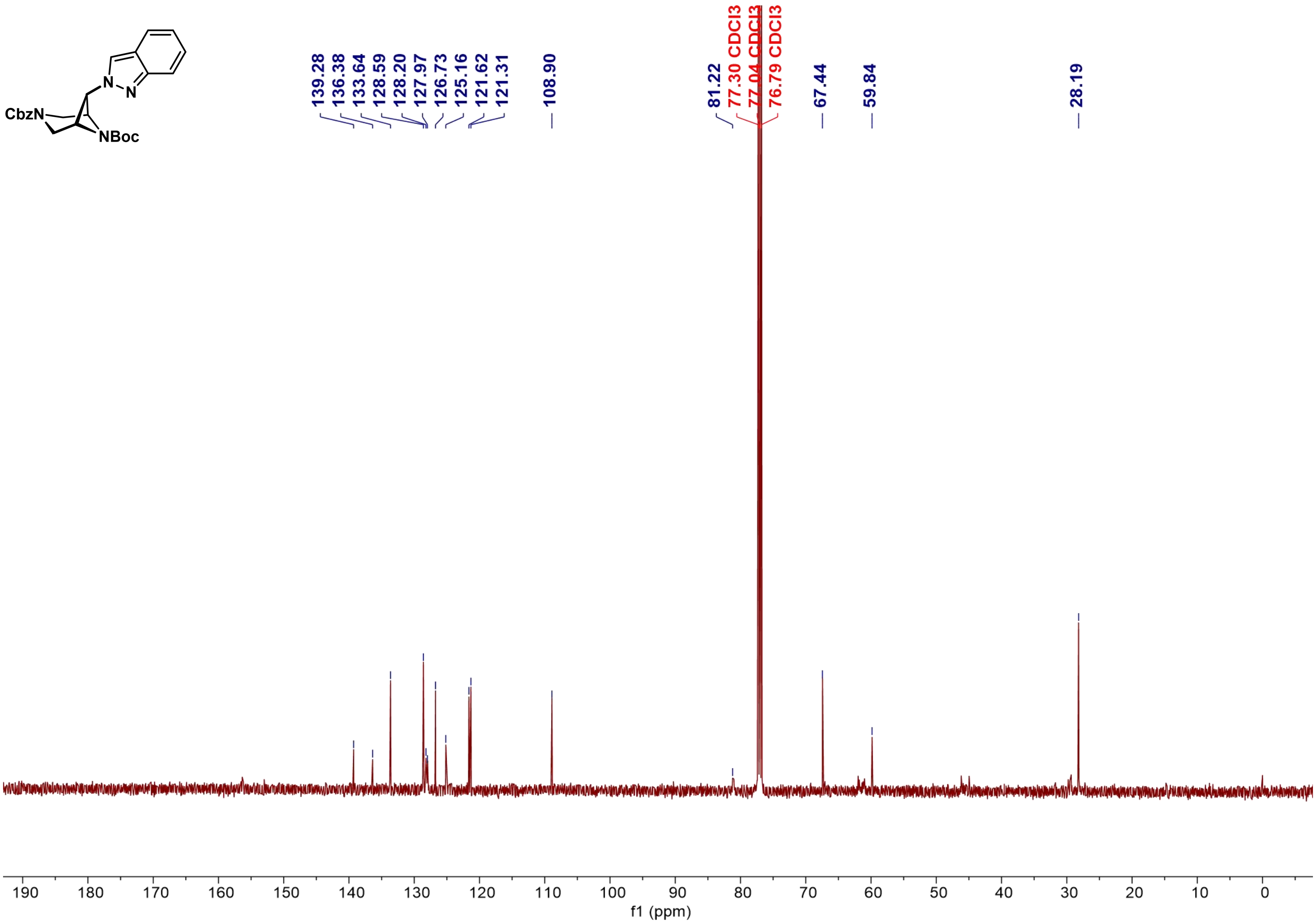


^{1}H NMR Spectrum of compound 64 (500 MHz, $CDCl_3$)

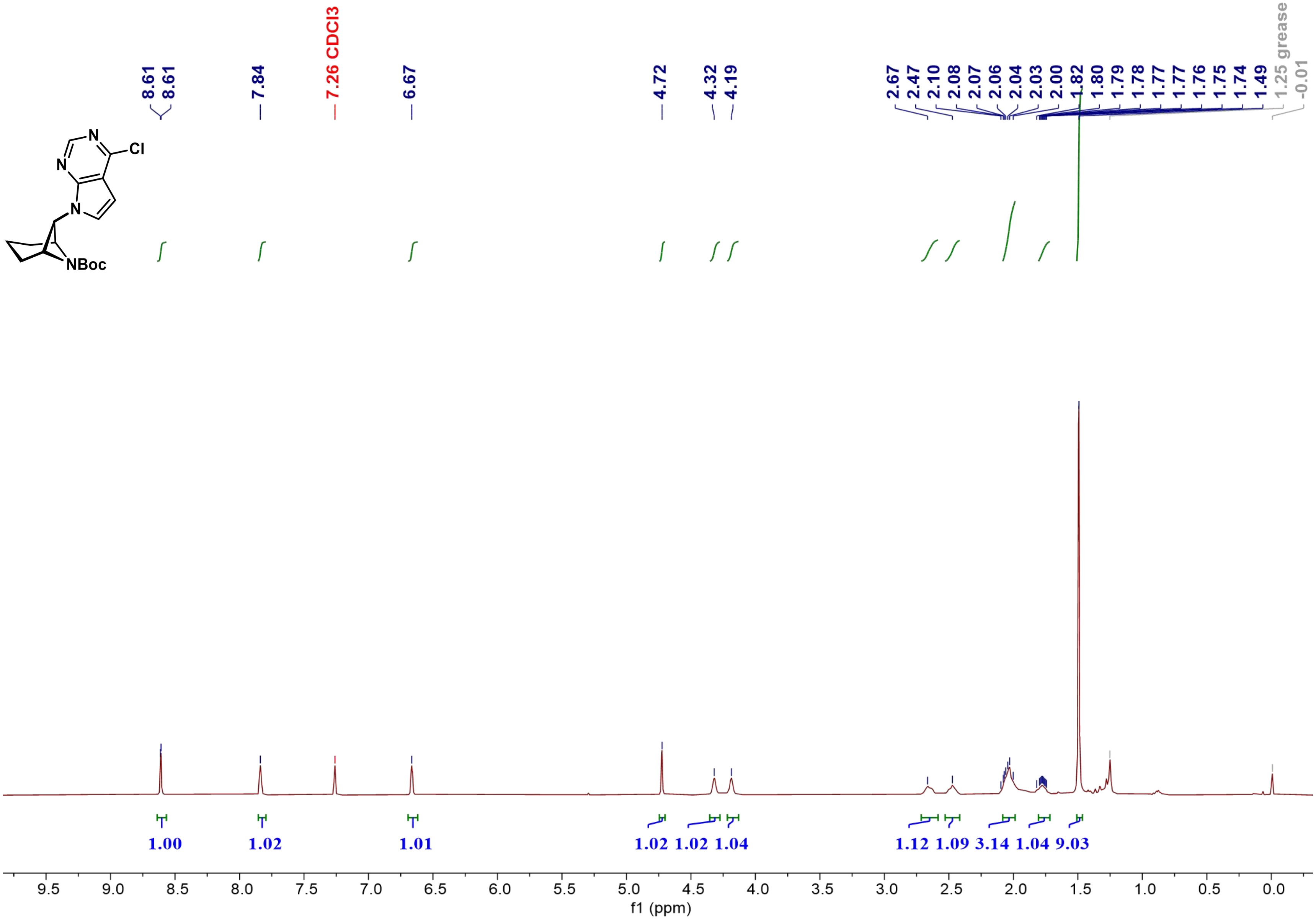




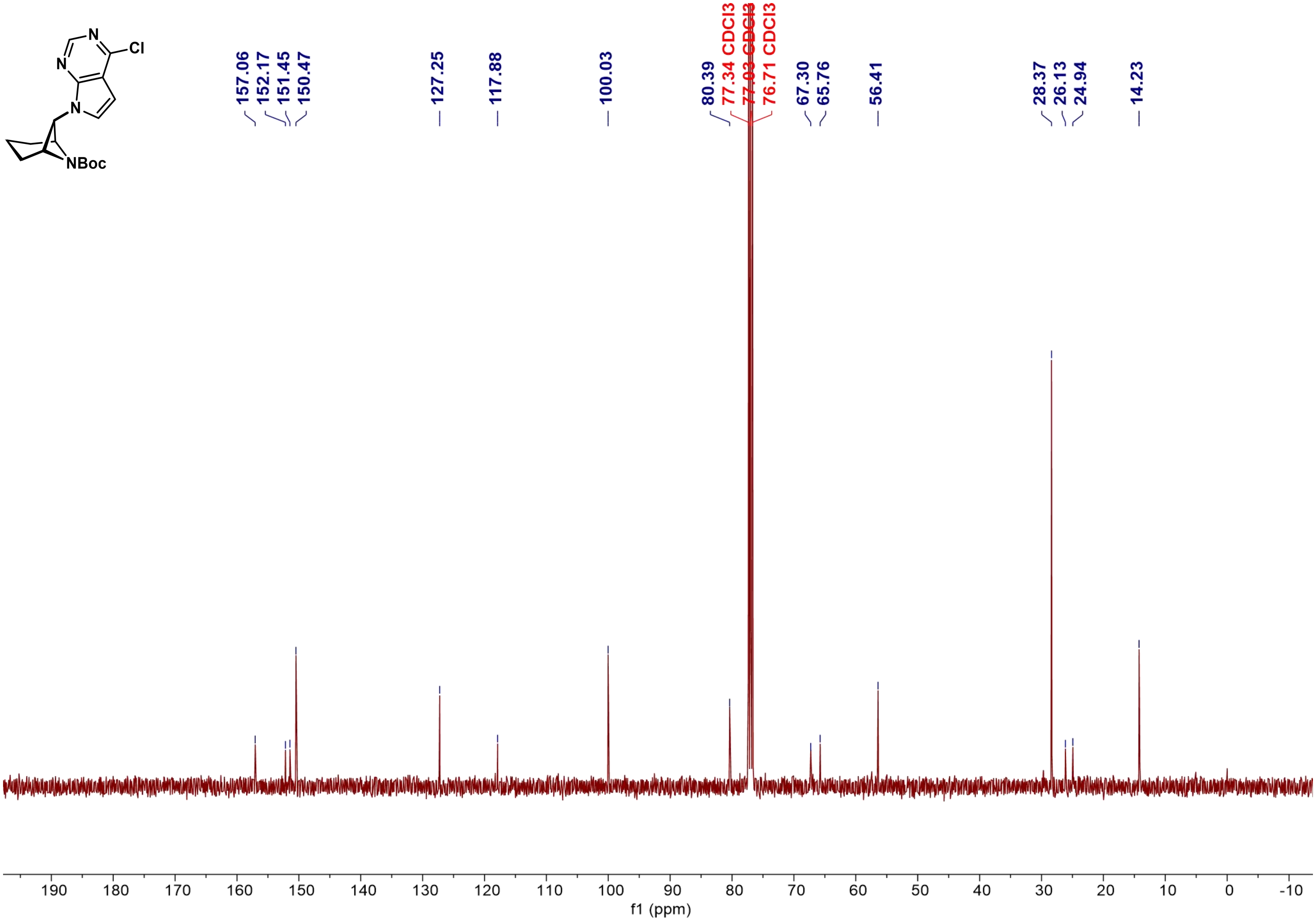
^{13}C NMR Spectrum of compound 64 (126 MHz, CDCl$_3$)



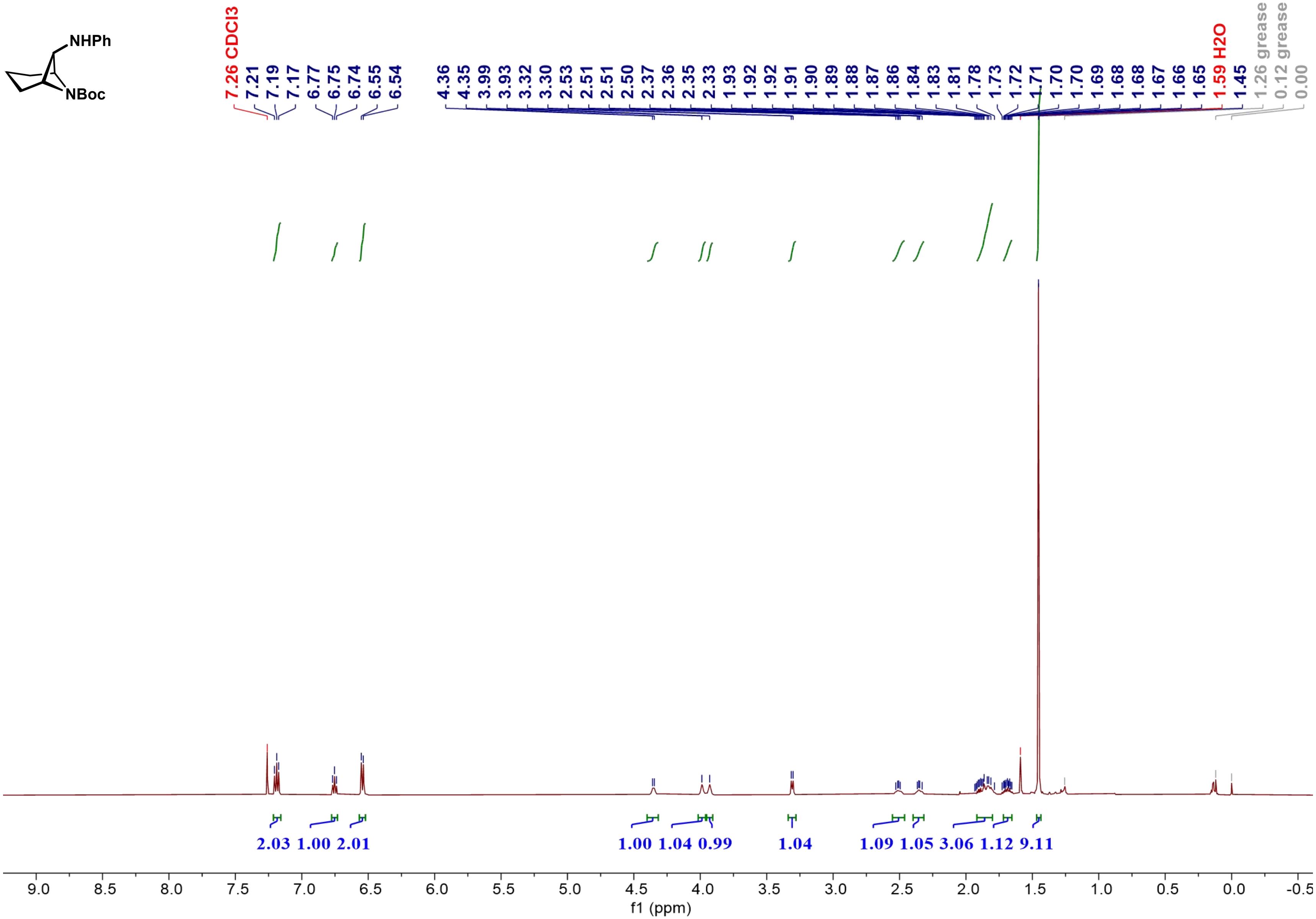
^{1}H NMR Spectrum of compound 65 (400 MHz, $CDCl_3$)



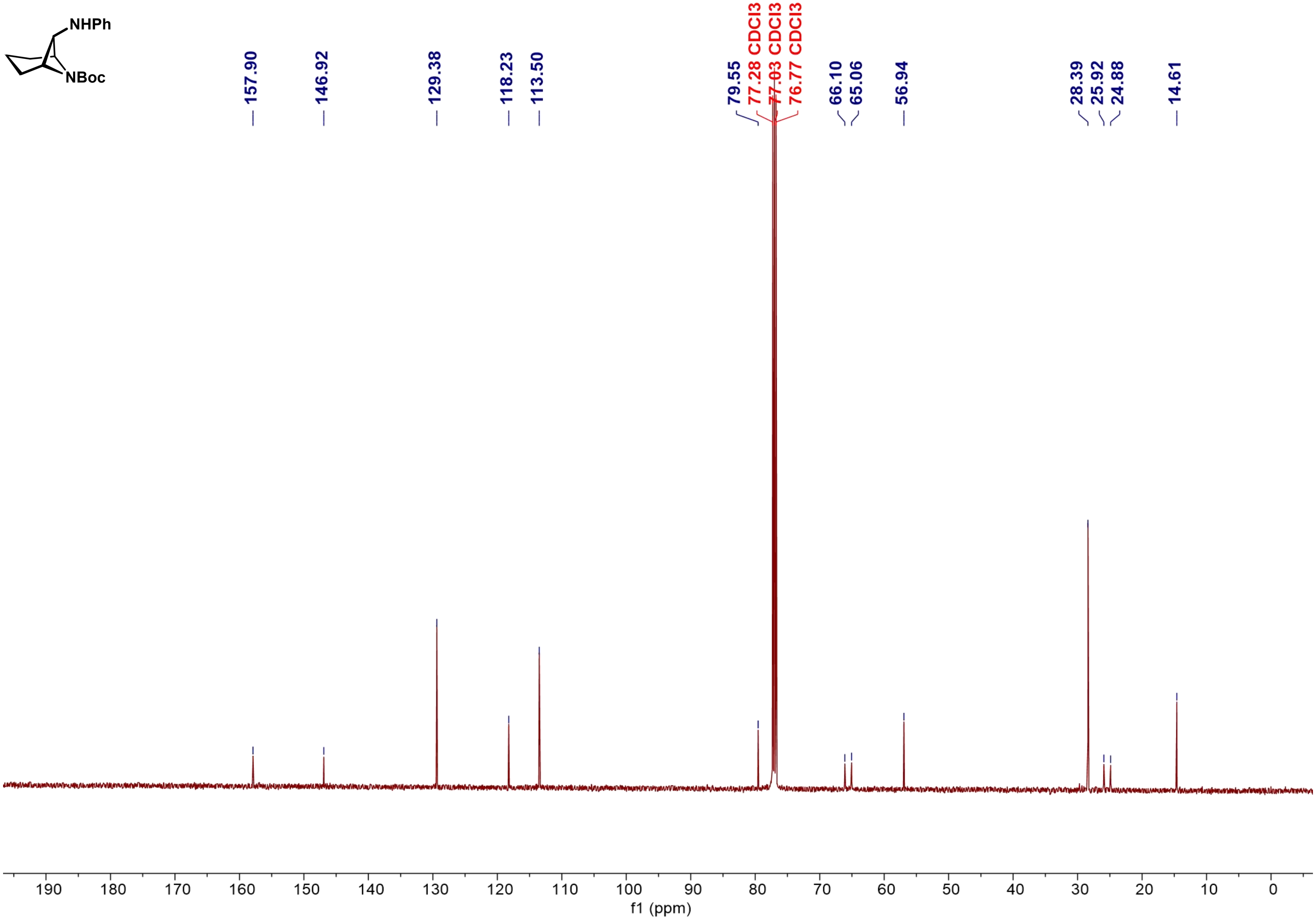
^{13}C NMR Spectrum of compound 65 (101 MHz, CDCl$_3$)



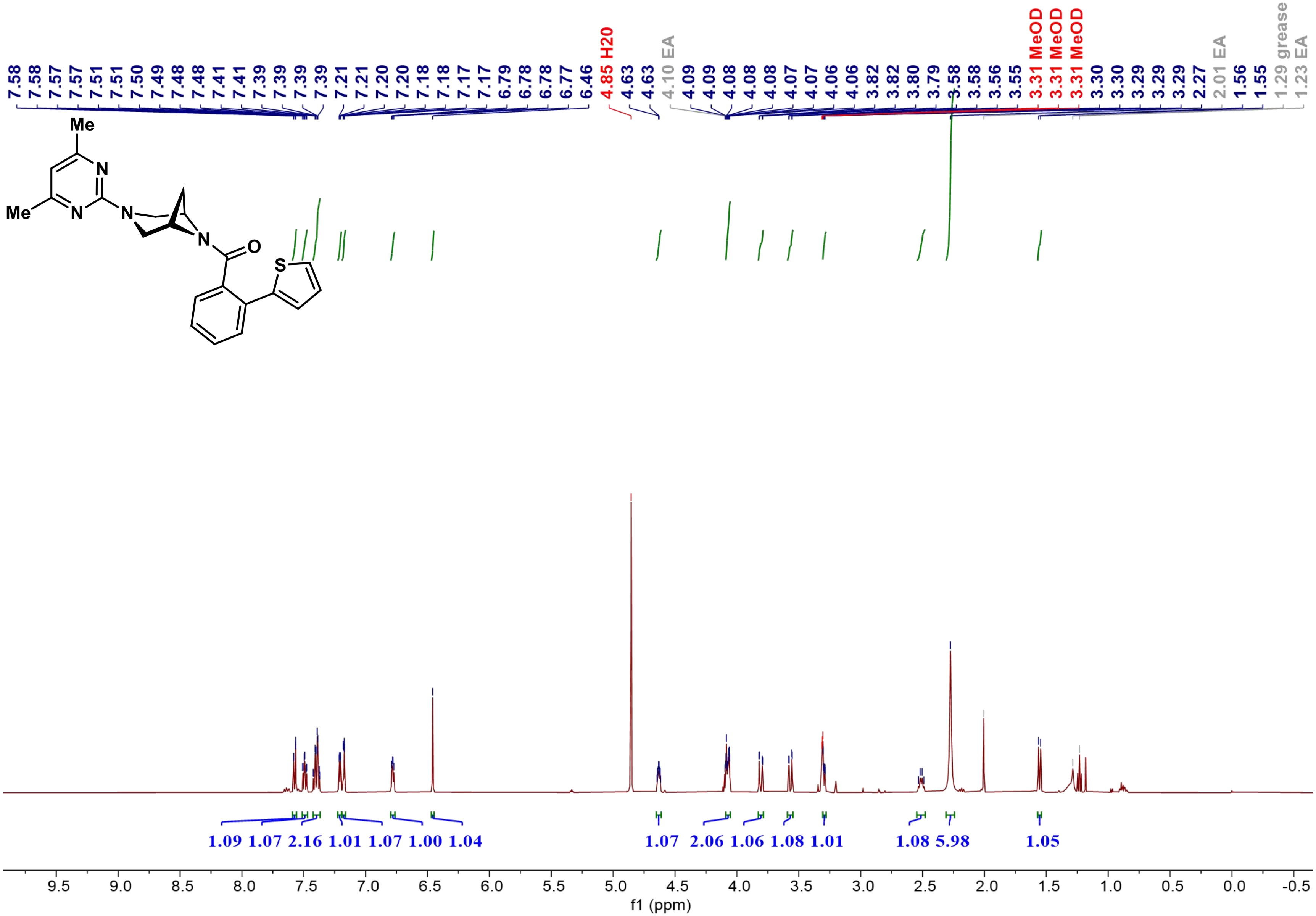
^{1}H NMR Spectrum of compound 66 (500 MHz, $CDCl_3$)



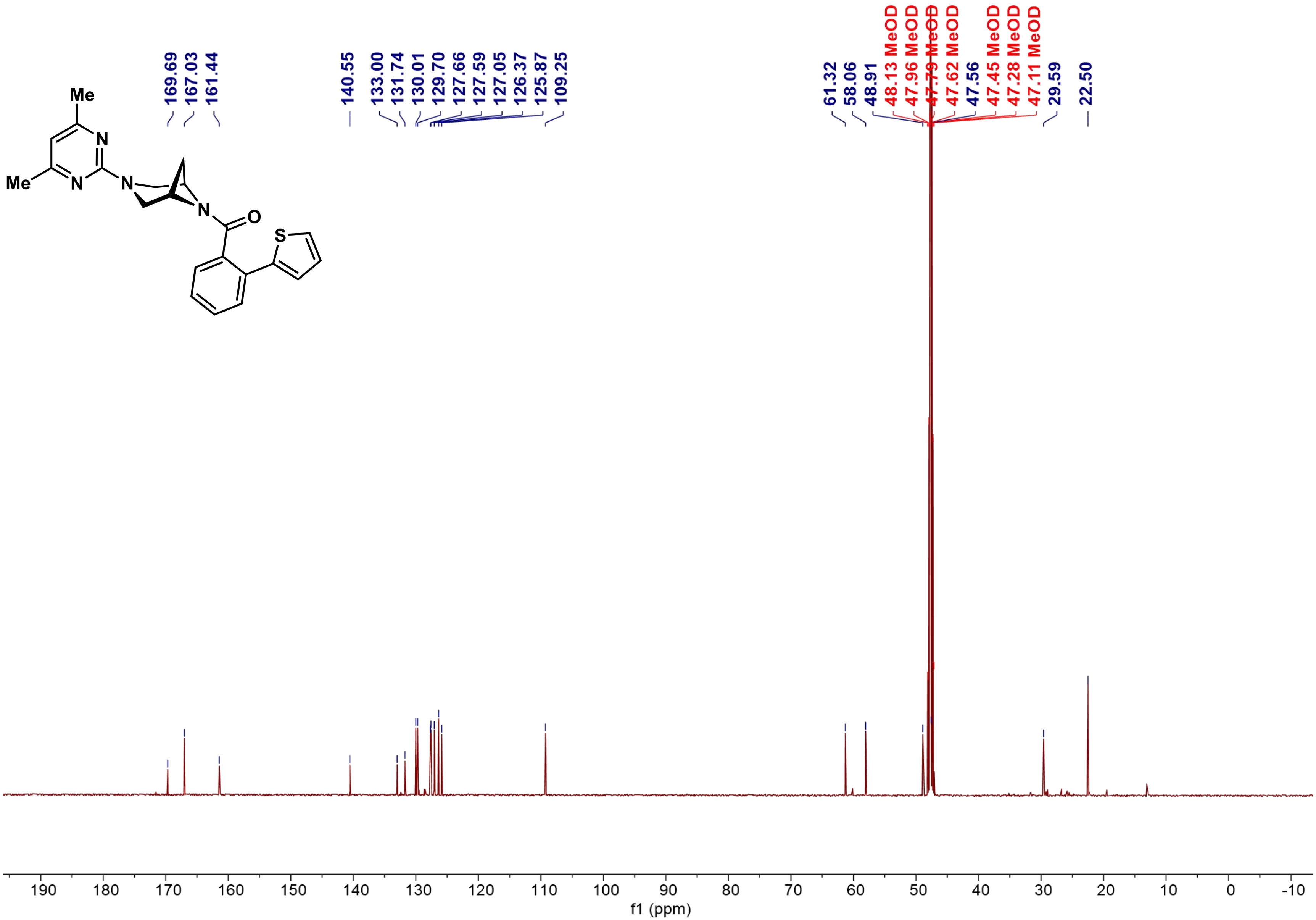
^{13}C NMR Spectrum of compound 66 (126 MHz, CDCl$_3$)



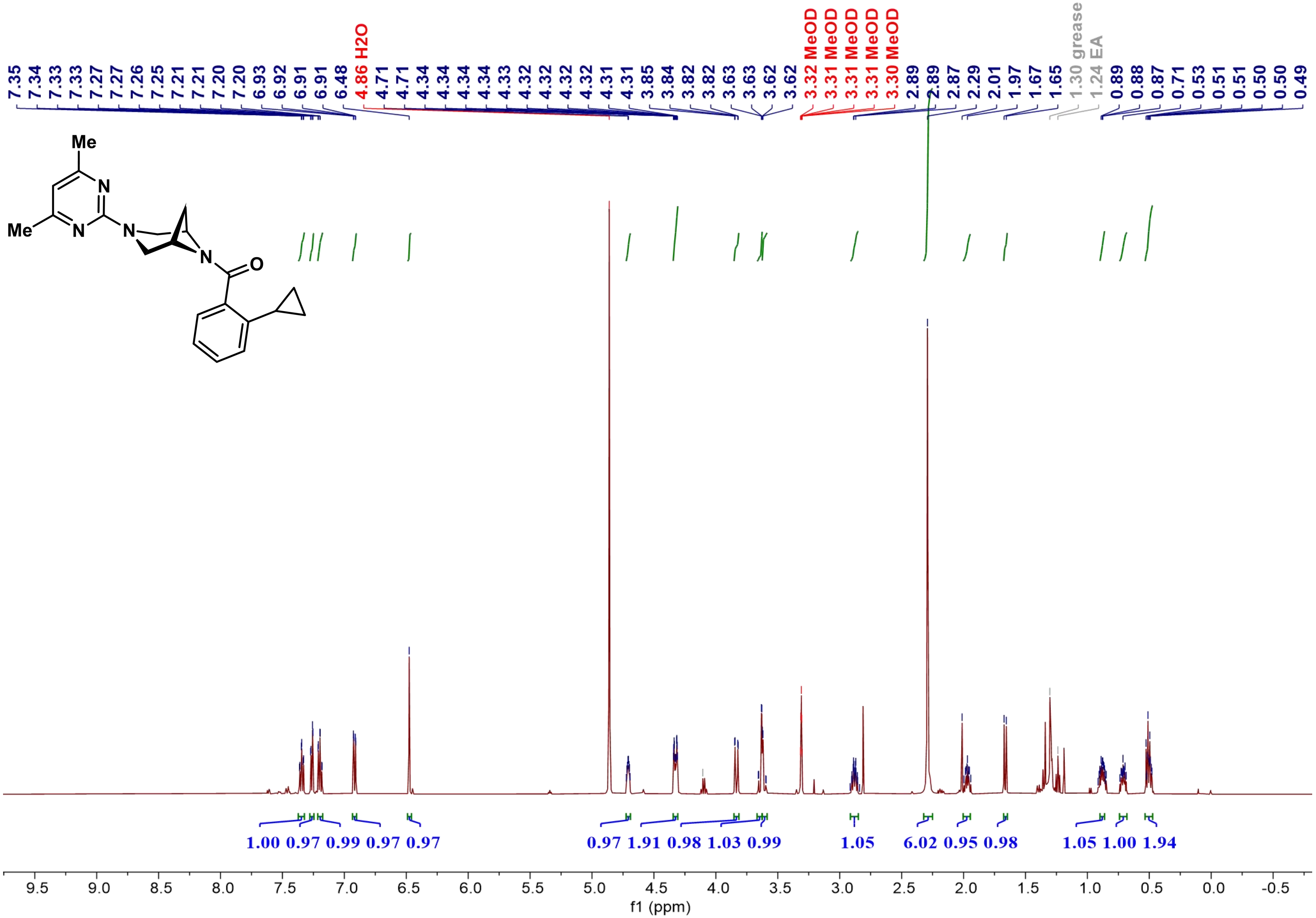
^{1}H NMR Spectrum of compound 67 (500 MHz, Methanol-d_4)



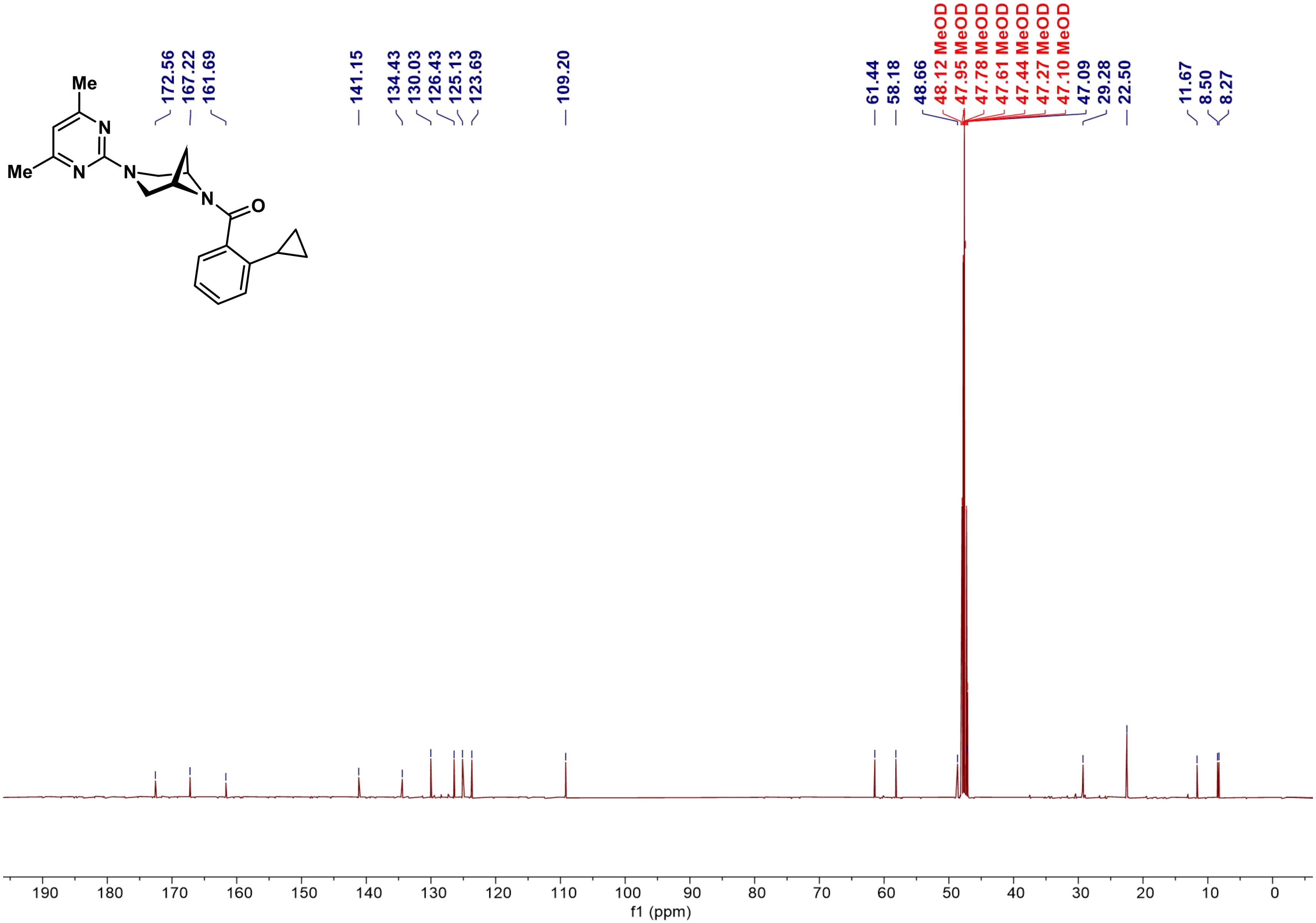
^{13}C NMR Spectrum of compound 67 (126 MHz, Methanol-*d*$_4$)



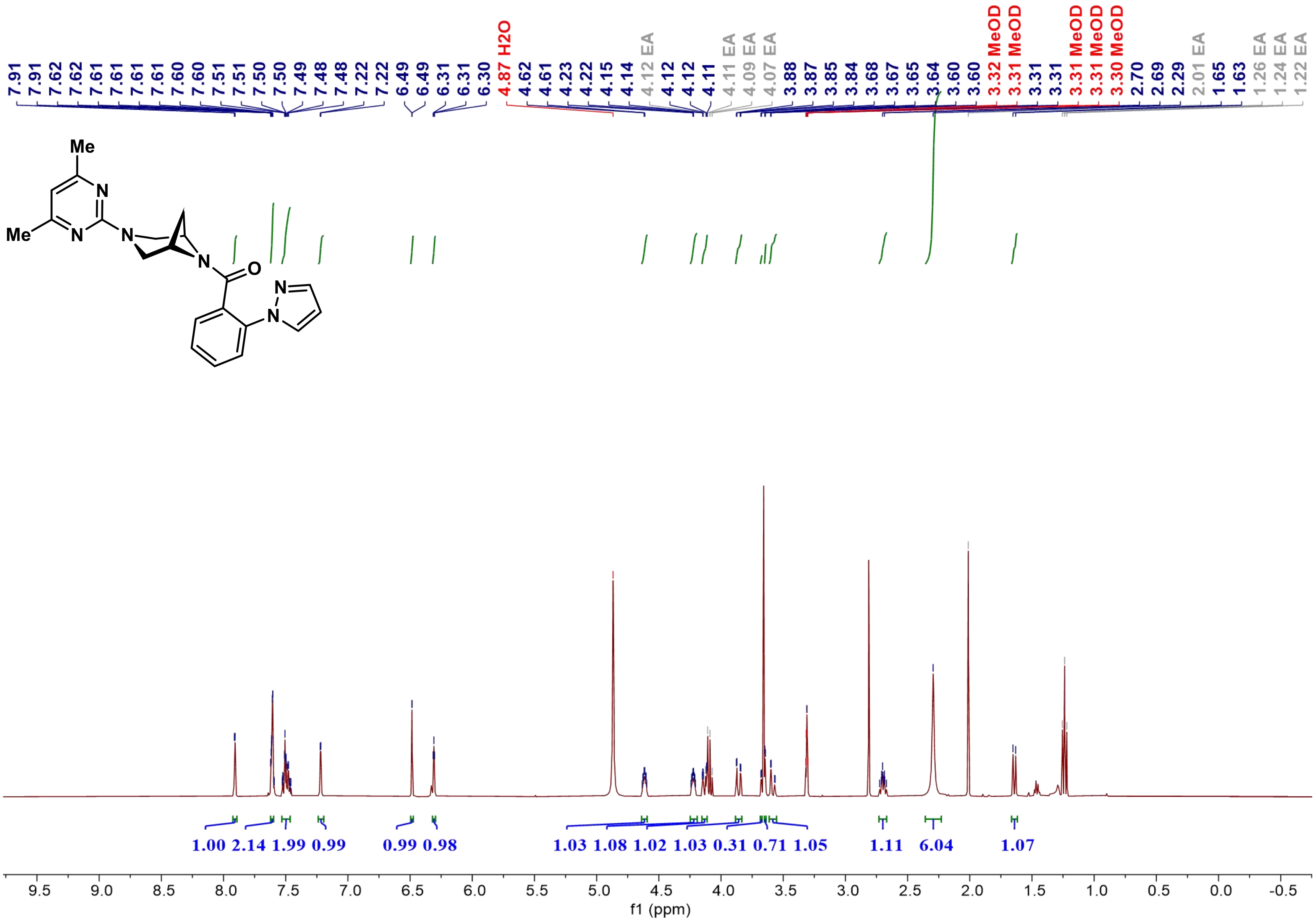
^{1}H NMR Spectrum of compound 68 (500 MHz, Methanol-d_4)



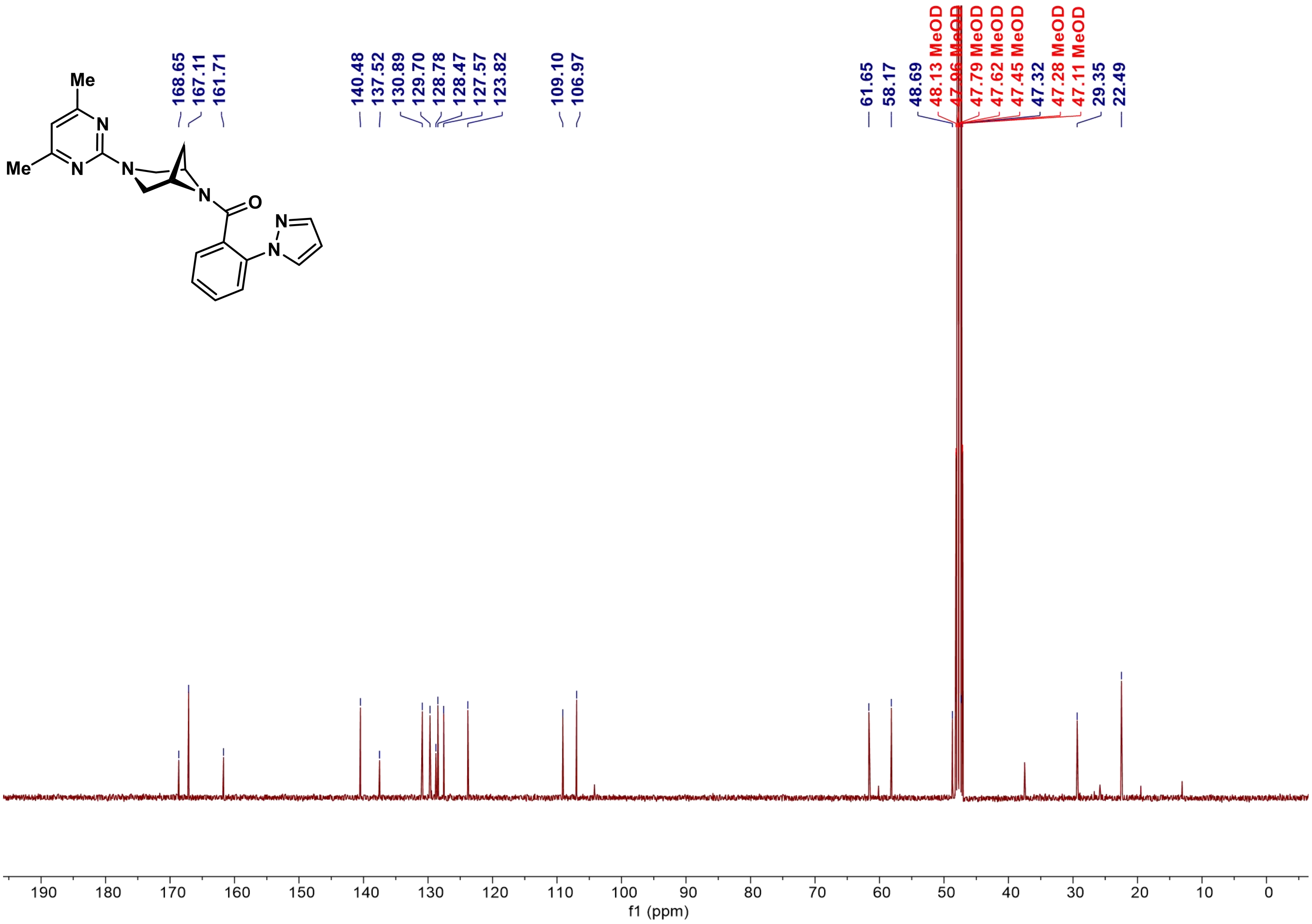
^{13}C NMR Spectrum of compound 68 (126 MHz, Methanol-d_4)



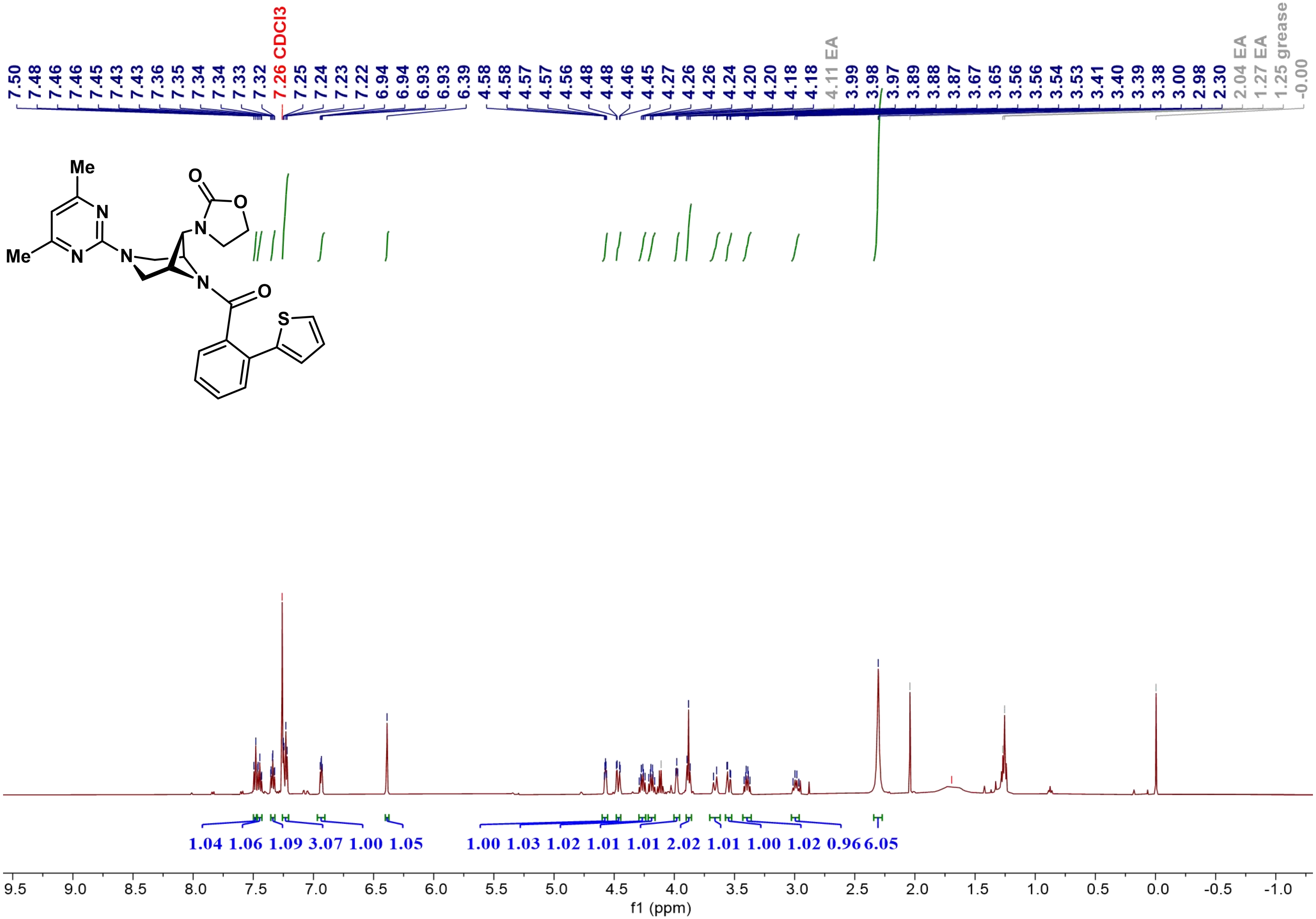
^{1}H NMR Spectrum of compound 69 (500 MHz, Methanol-d_4)



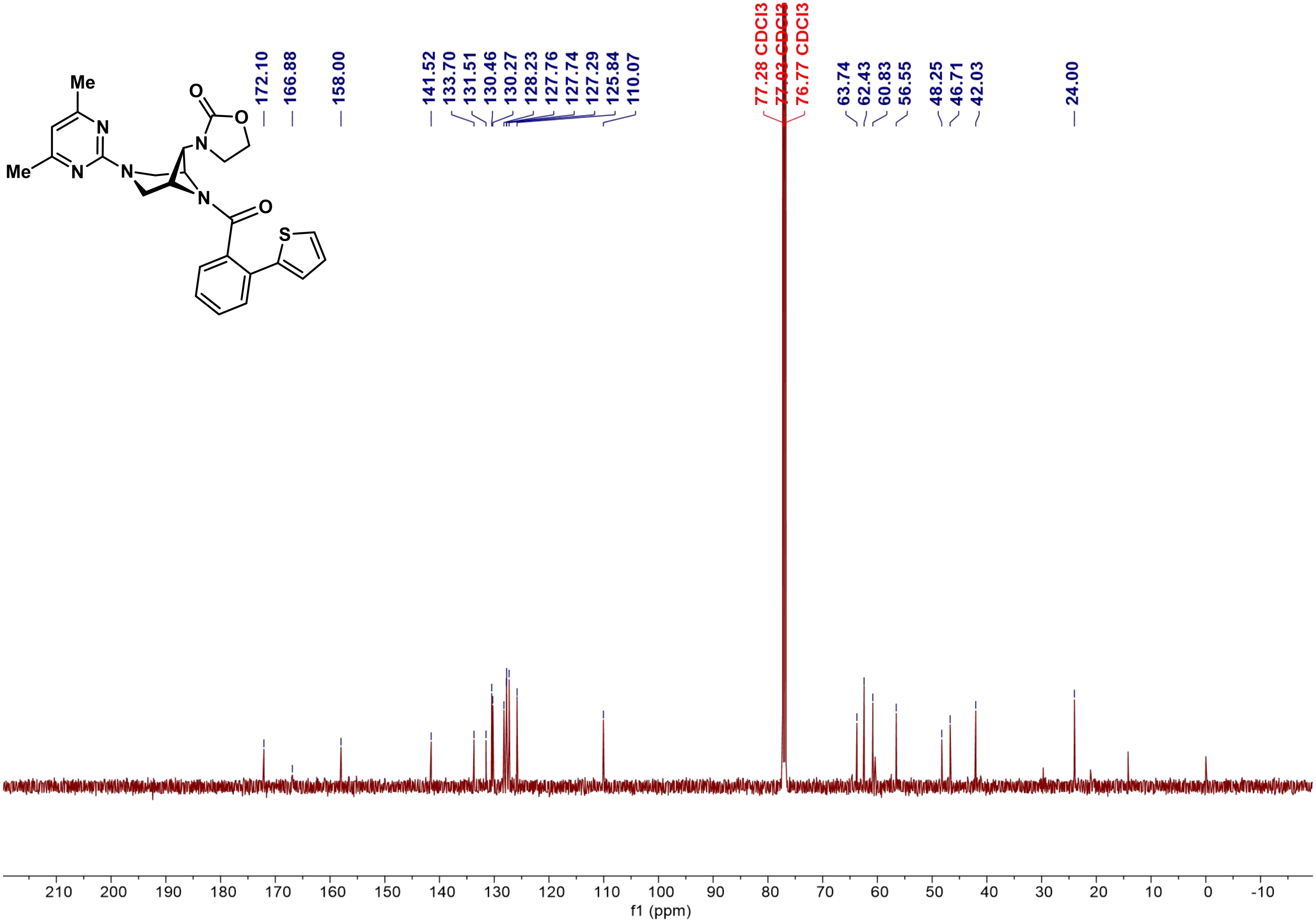
^{13}C NMR Spectrum of compound 69 (126 MHz, Methanol-d_4)



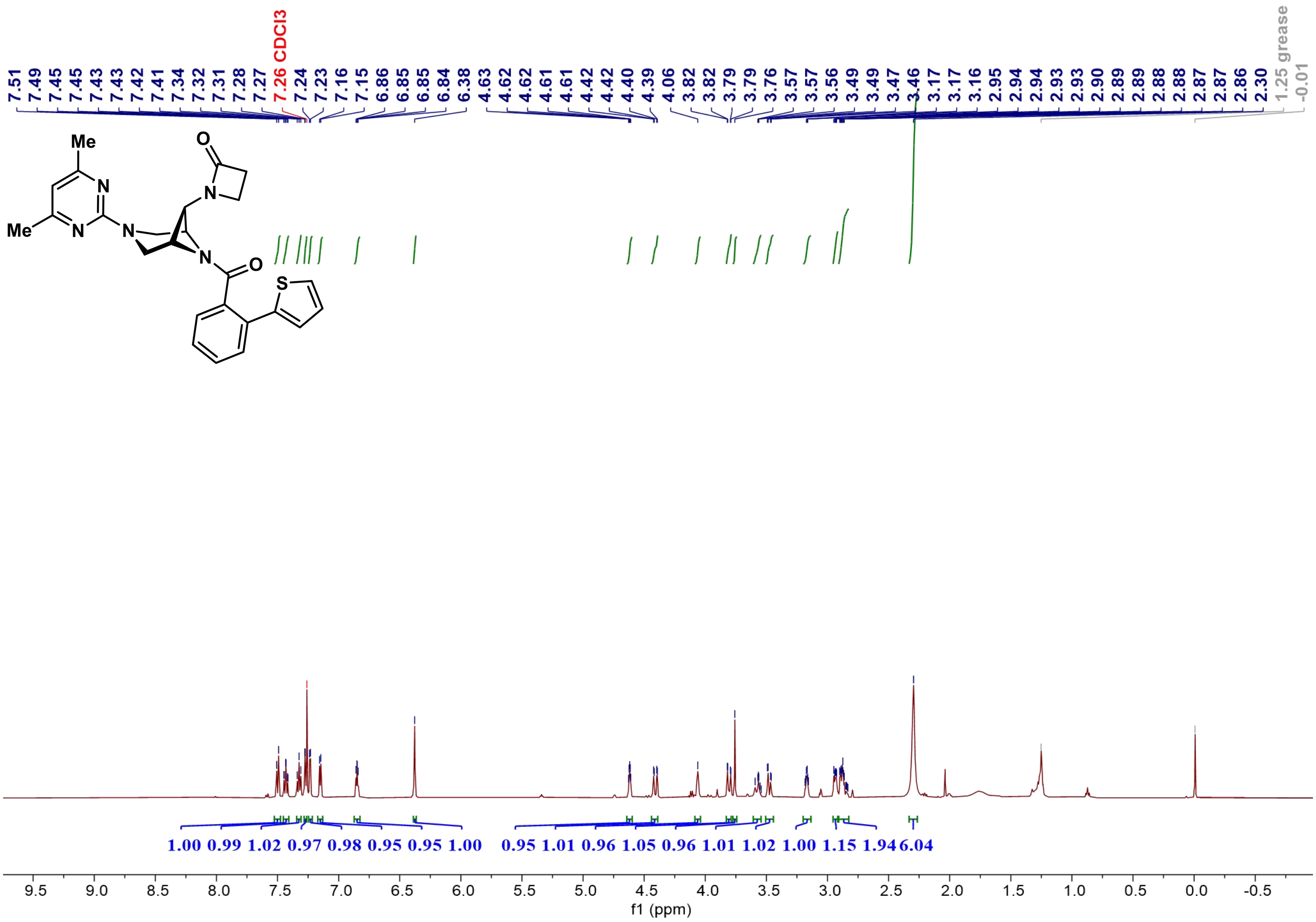
^{1}H NMR Spectrum of compound 70 (500 MHz, $CDCl_3$)



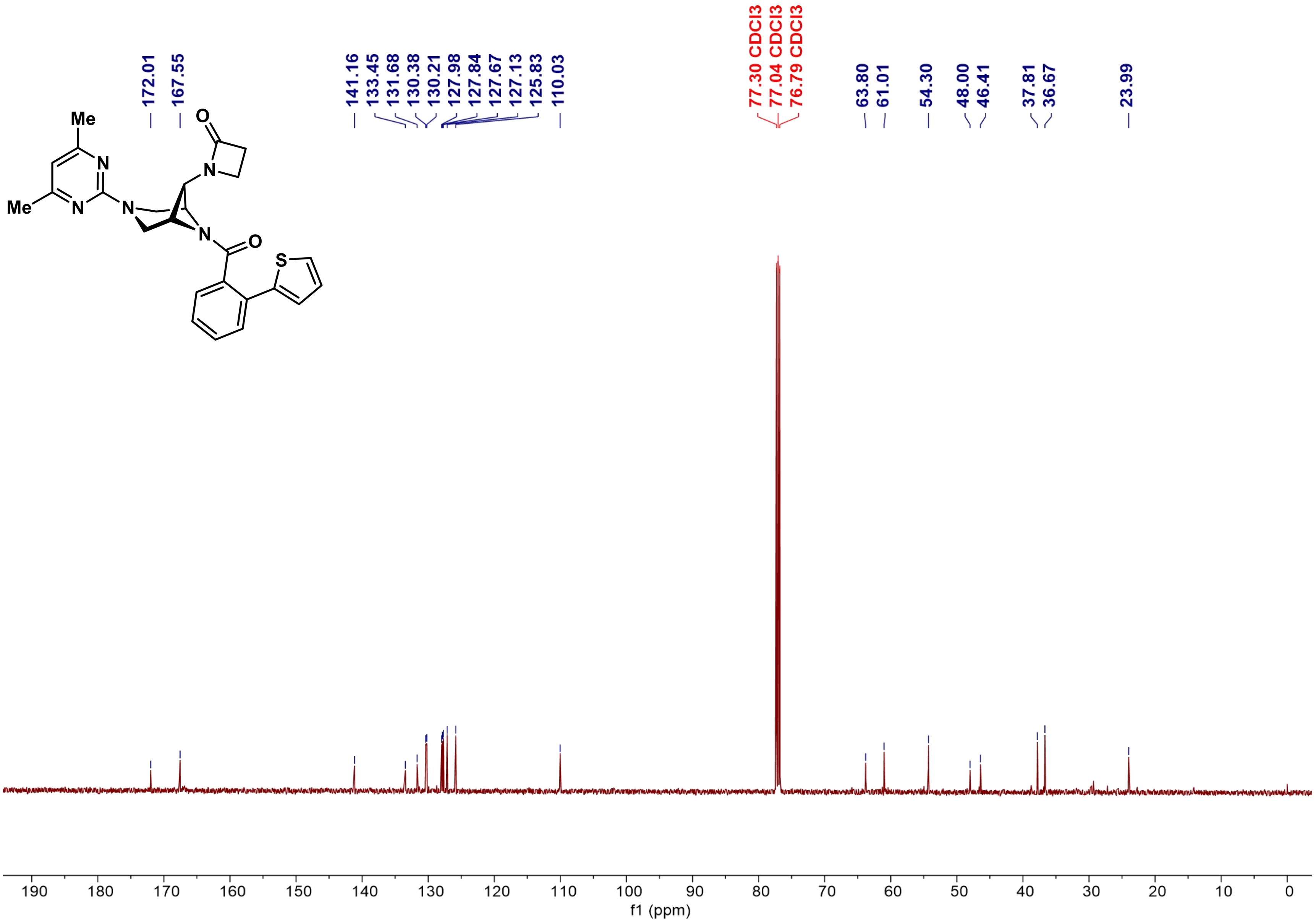
^{13}C NMR Spectrum of compound 70 (126 MHz, CDCl$_3$)



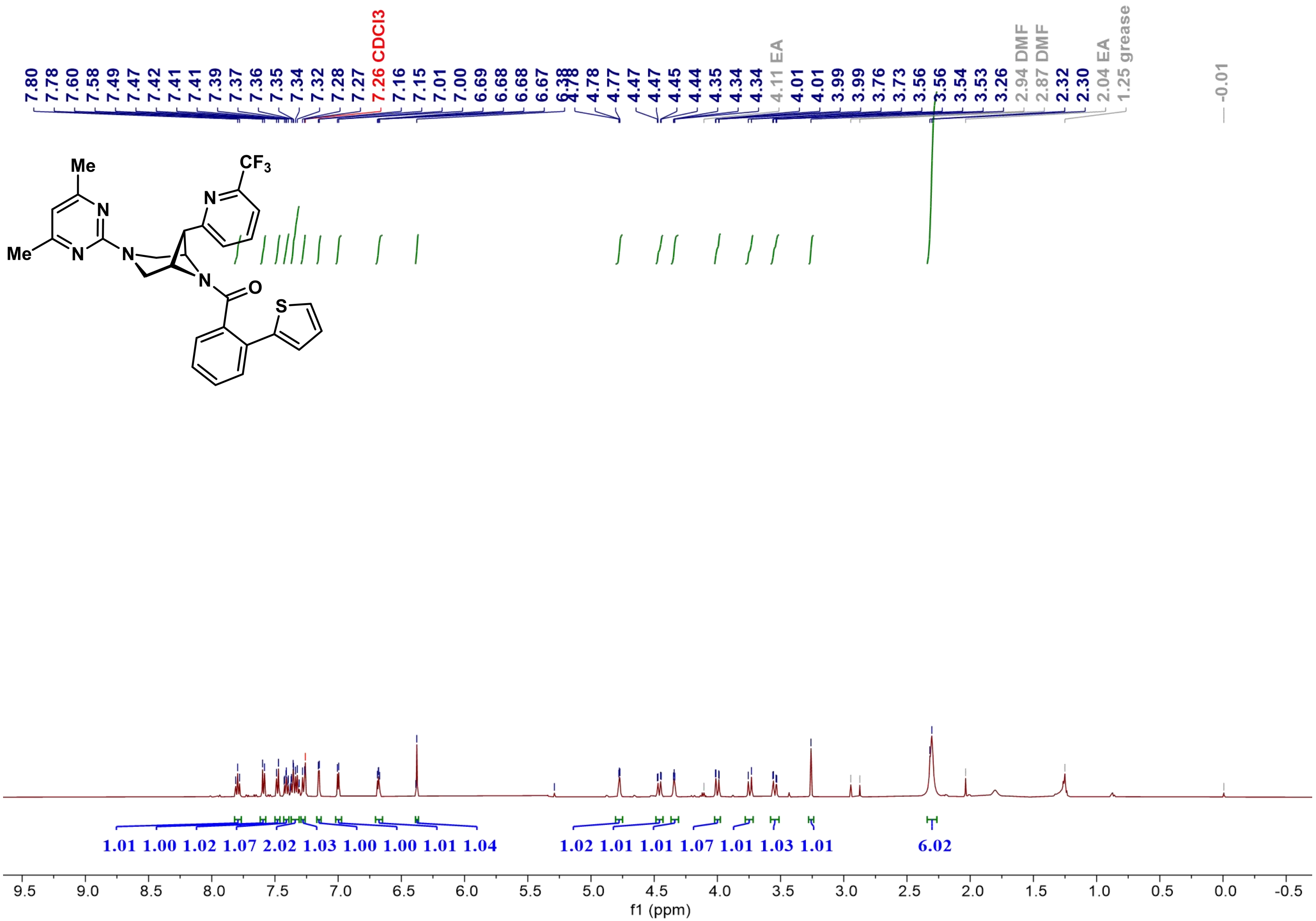
^1H NMR Spectrum of compound 71 (500 MHz, $CDCl_3$)



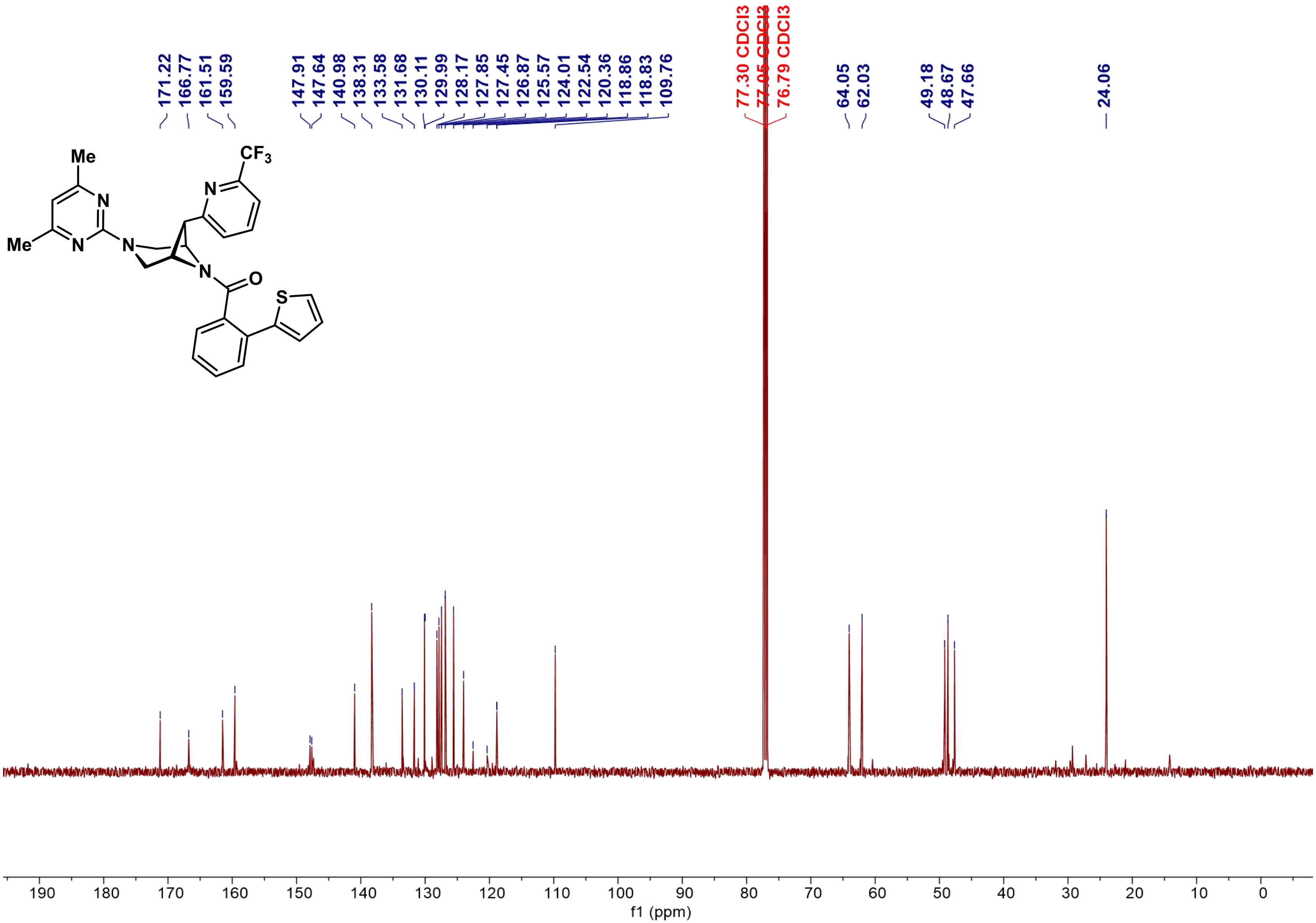
^{13}C NMR Spectrum of compound 71 (126 MHz, $CDCl_3$)



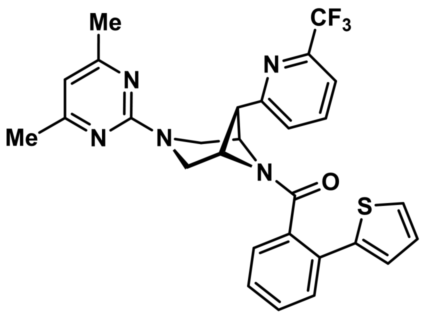
^{1}H NMR Spectrum of compound 72 (500 MHz, CDCl$_3$)

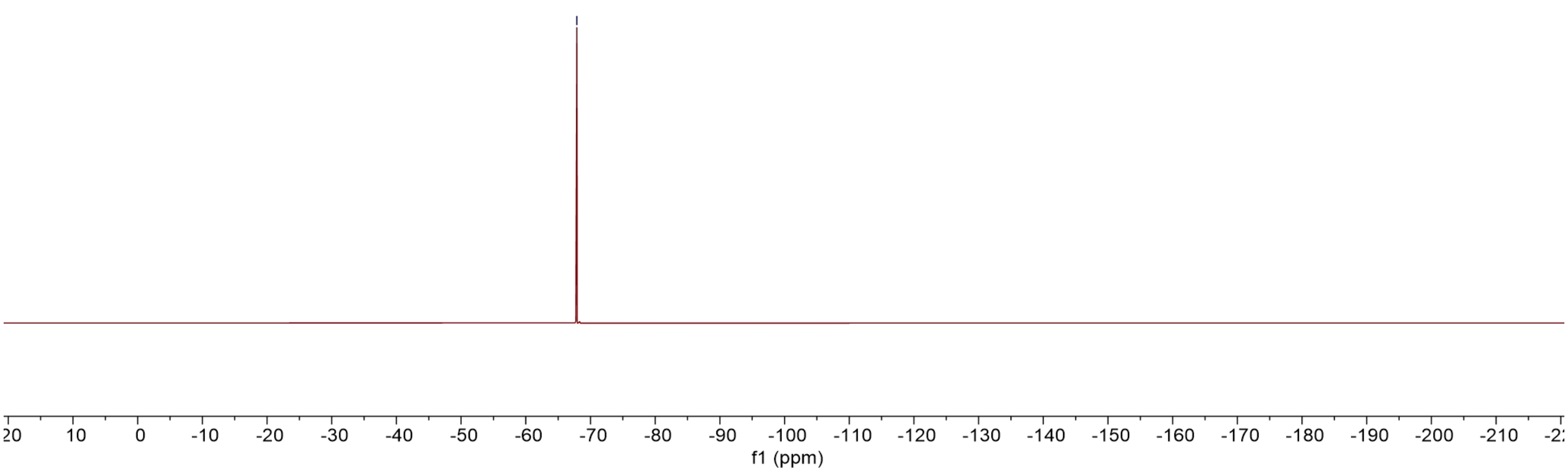


^{13}C NMR Spectrum of compound 72 (126 MHz, $CDCl_3$)

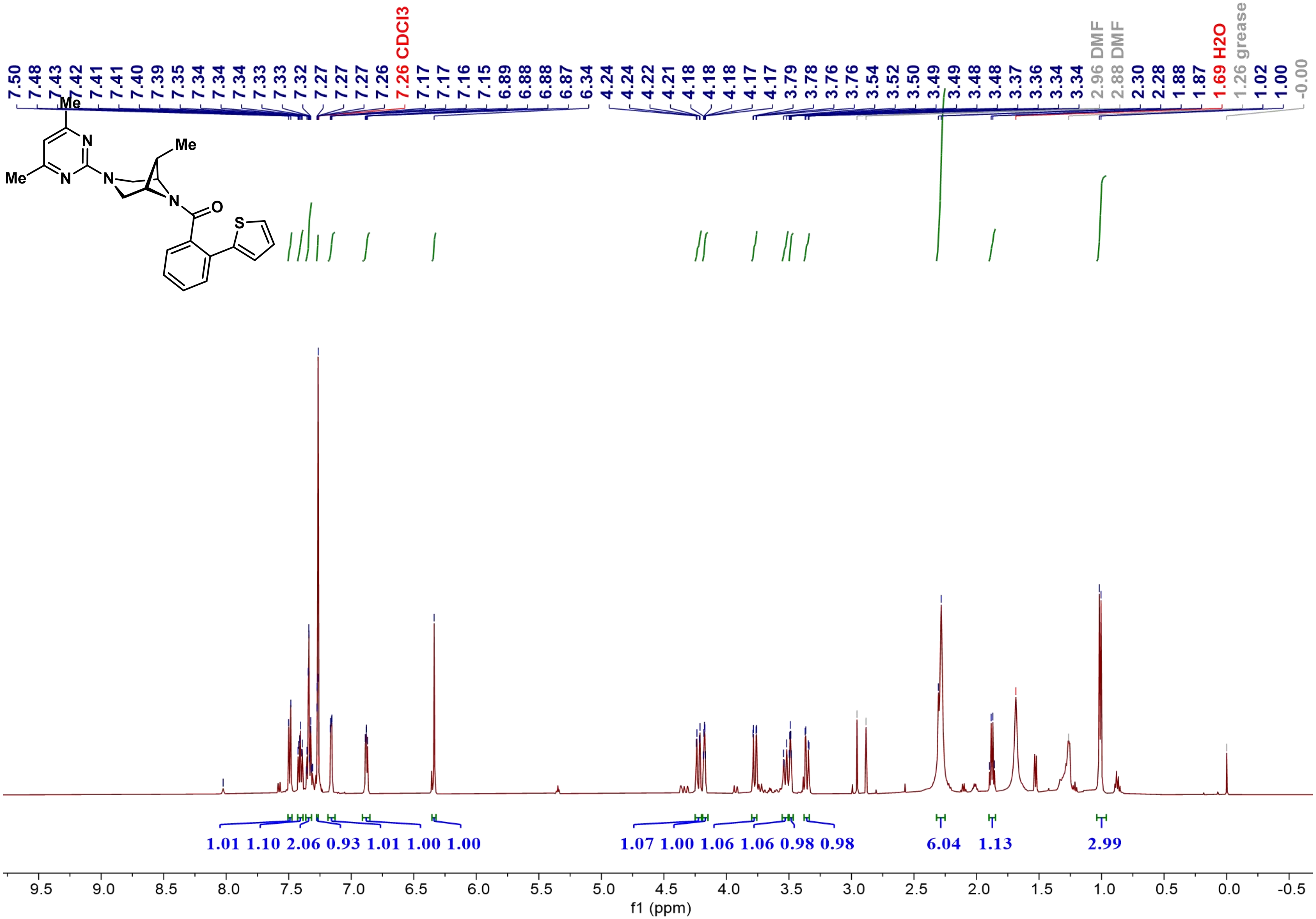


^{19}F NMR Spectrum of compound 72 (471 MHz, CDCl$_3$)

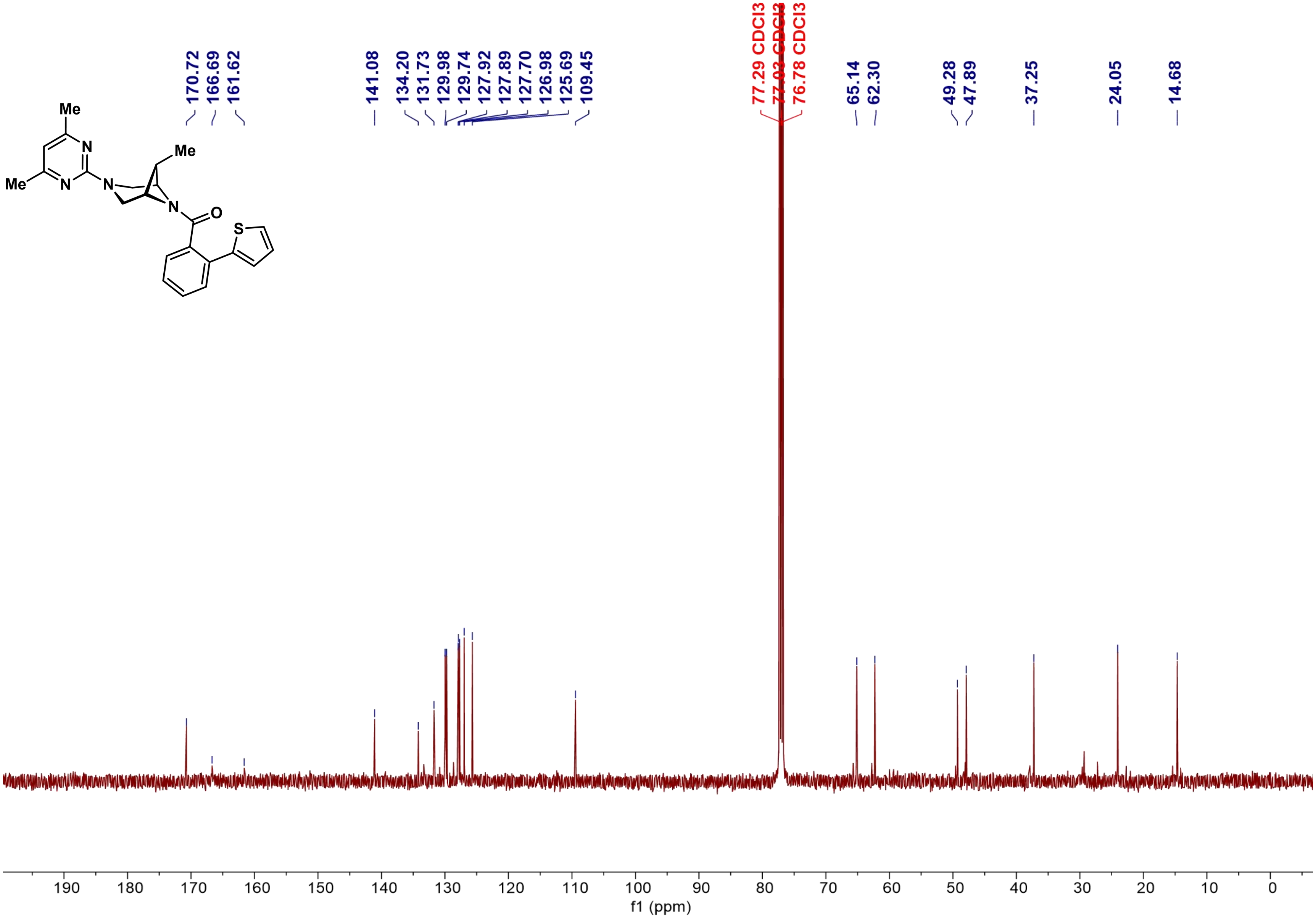




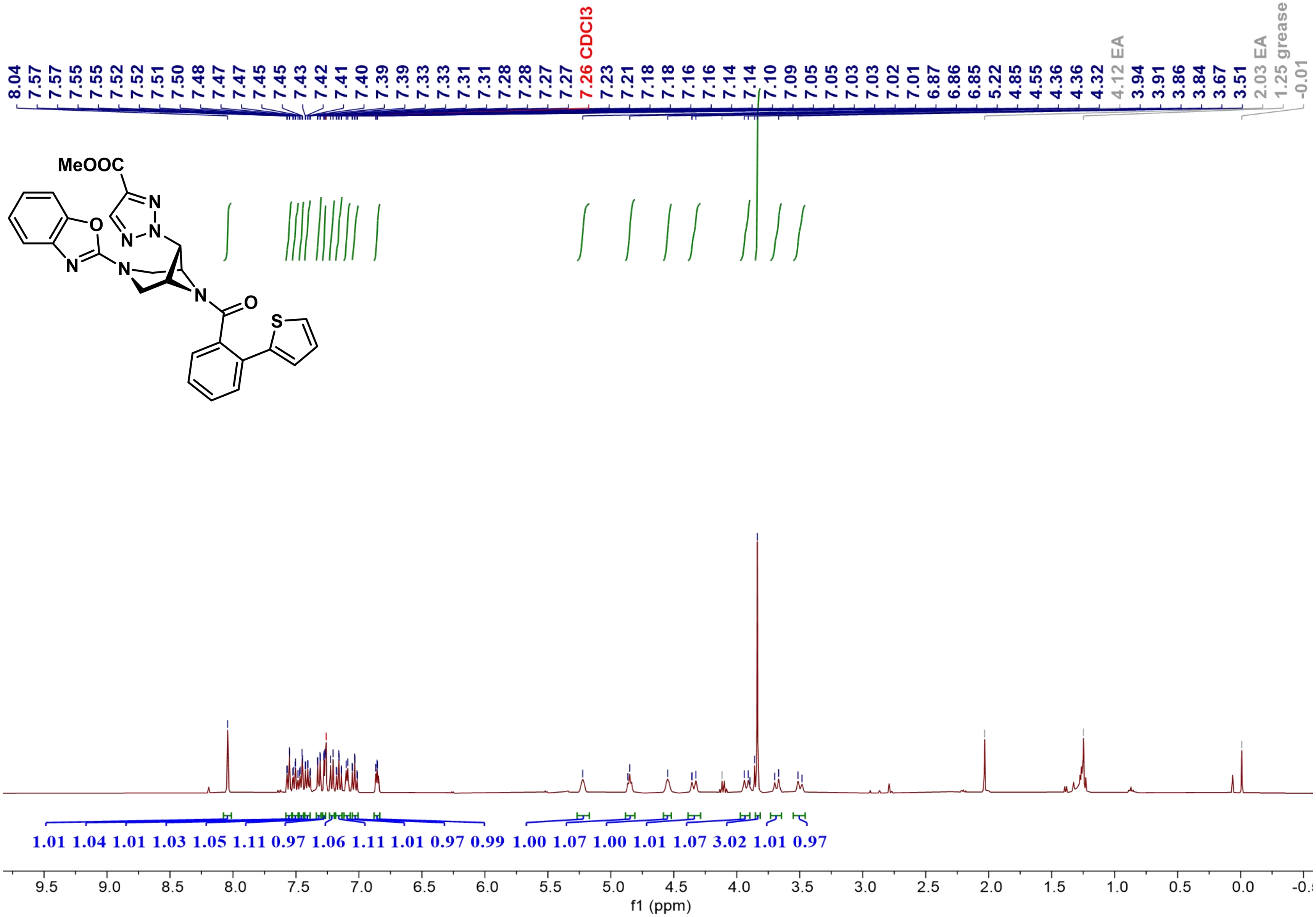
^{1}H NMR Spectrum of compound 73 (500 MHz, $CDCl_3$)



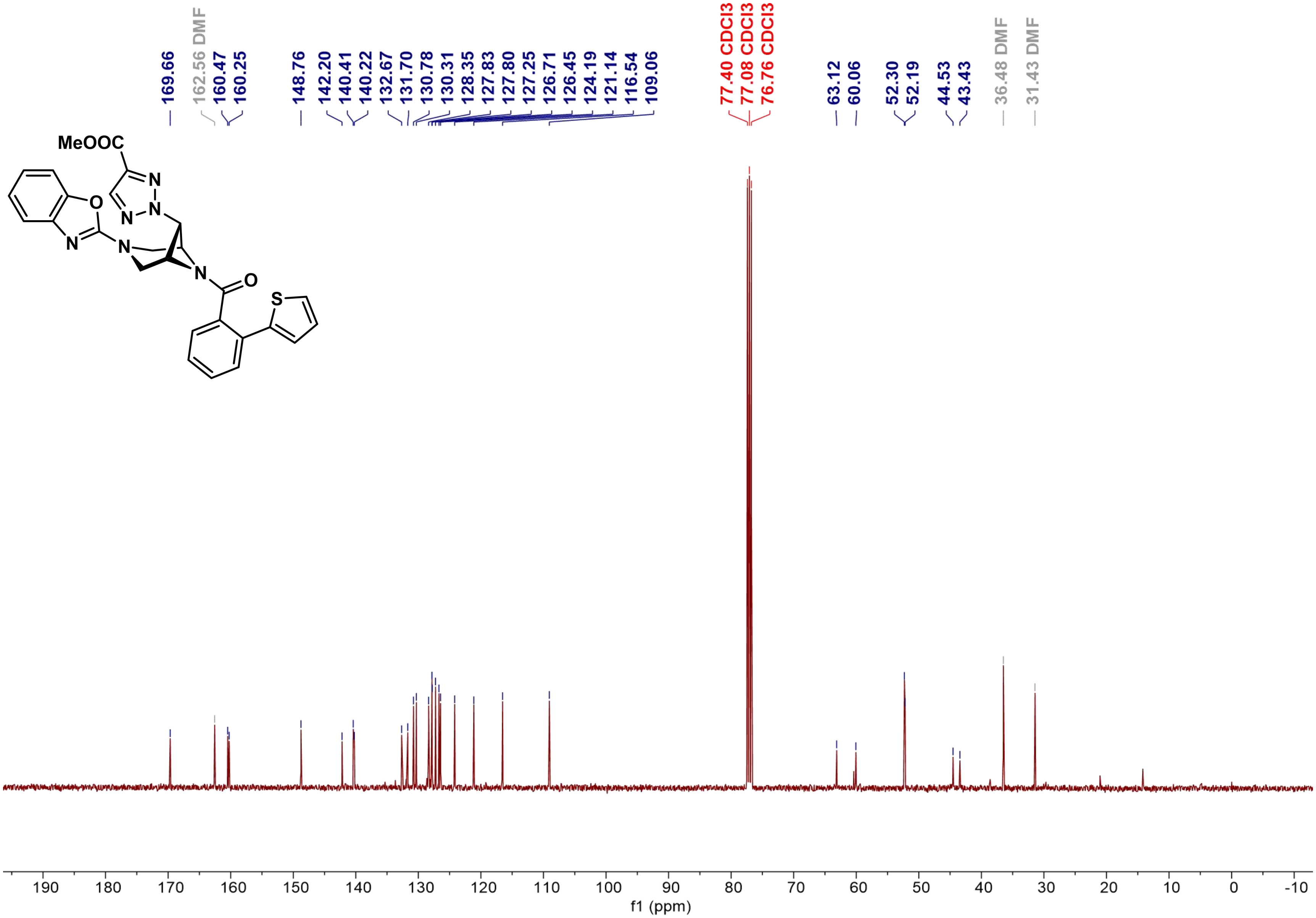
^{13}C NMR Spectrum of compound 73 (126 MHz, CDCl$_3$)



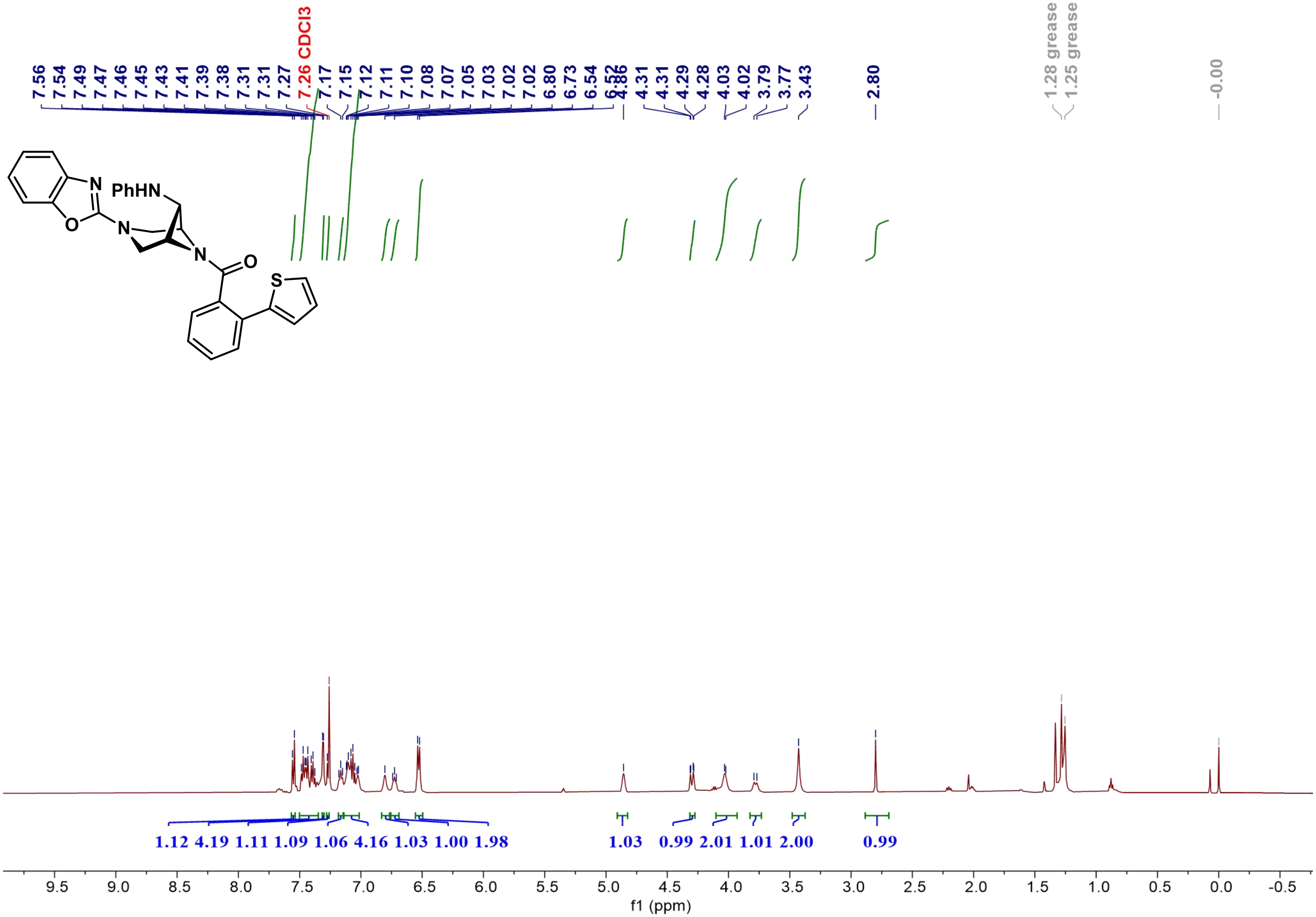
^{1}H NMR Spectrum of compound 74 (400 MHz, $CDCl_3$)



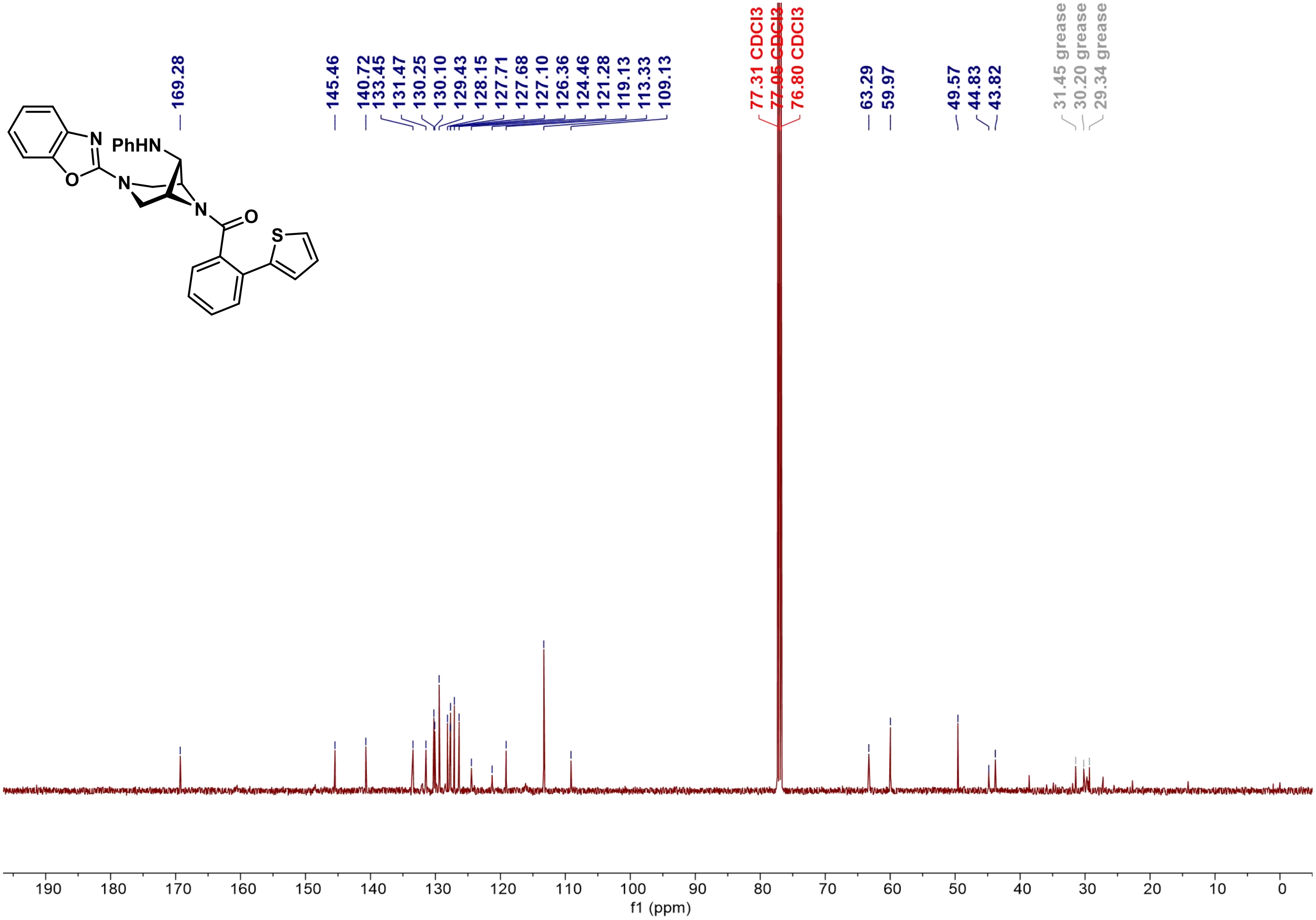
^{13}C NMR Spectrum of compound 74 (101 MHz, $CDCl_3$)



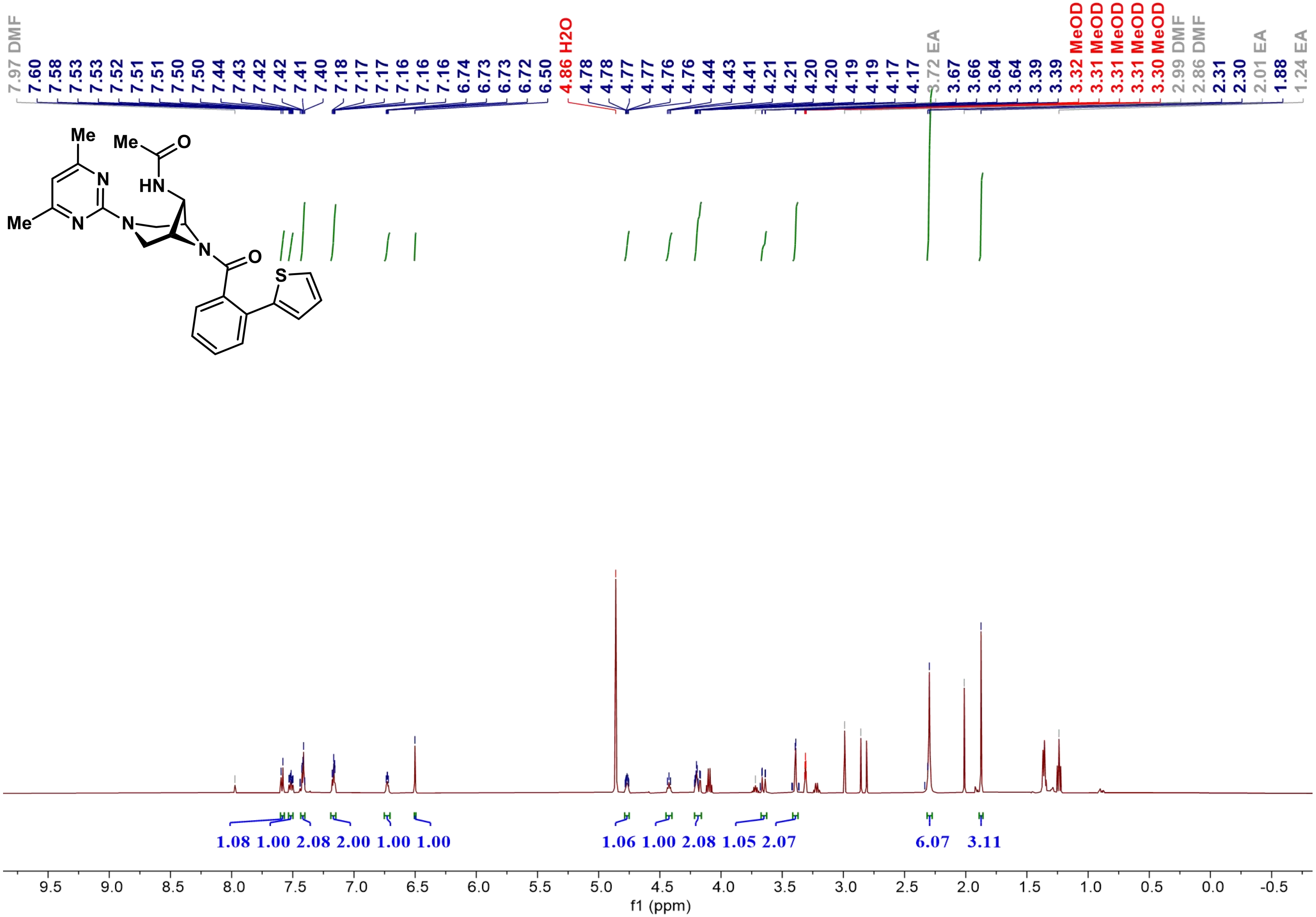
^{1}H NMR Spectrum of compound 75 (500 MHz, $CDCl_3$)



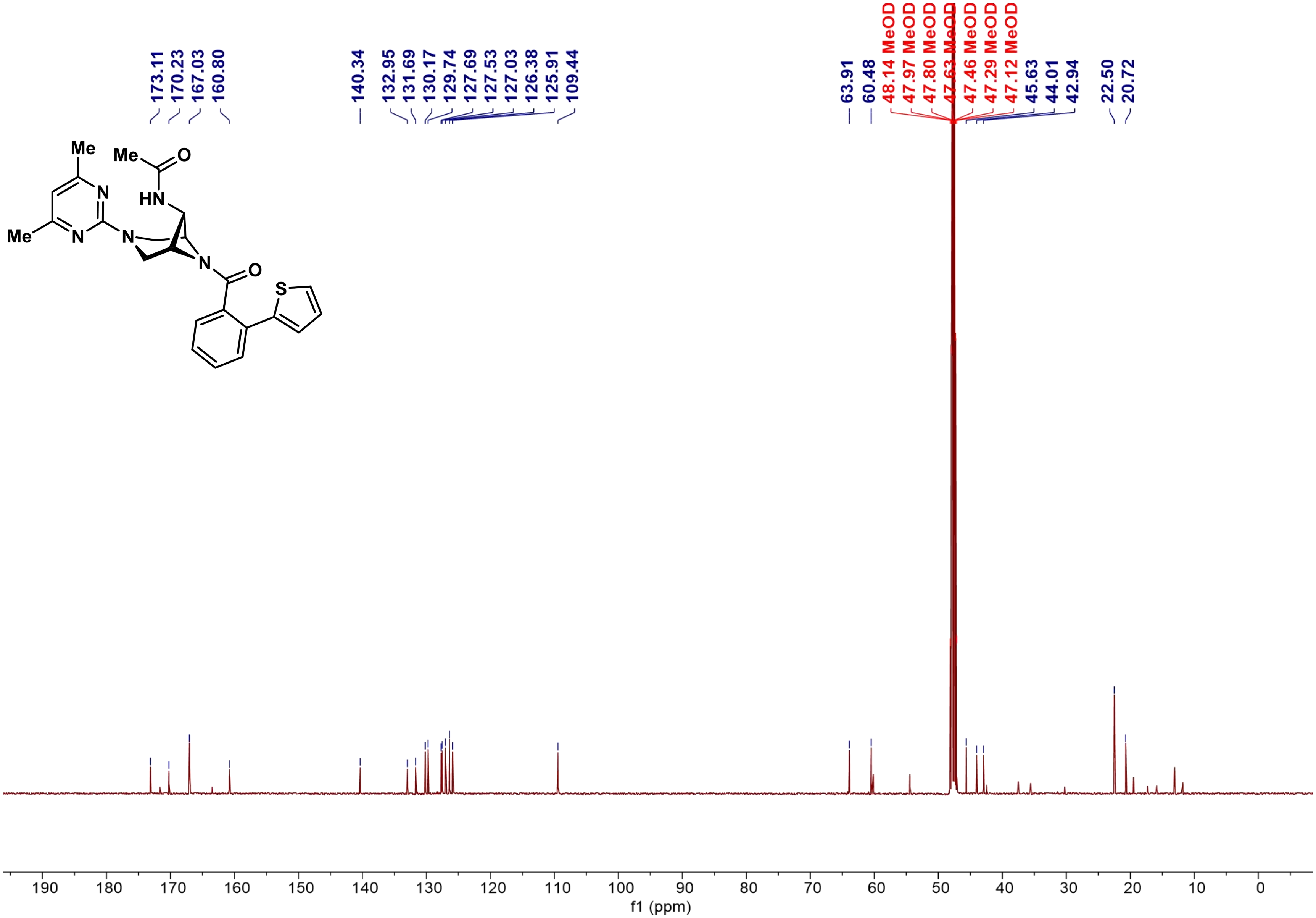
^{13}C NMR Spectrum of compound 75 (126 MHz, $CDCl_3$)



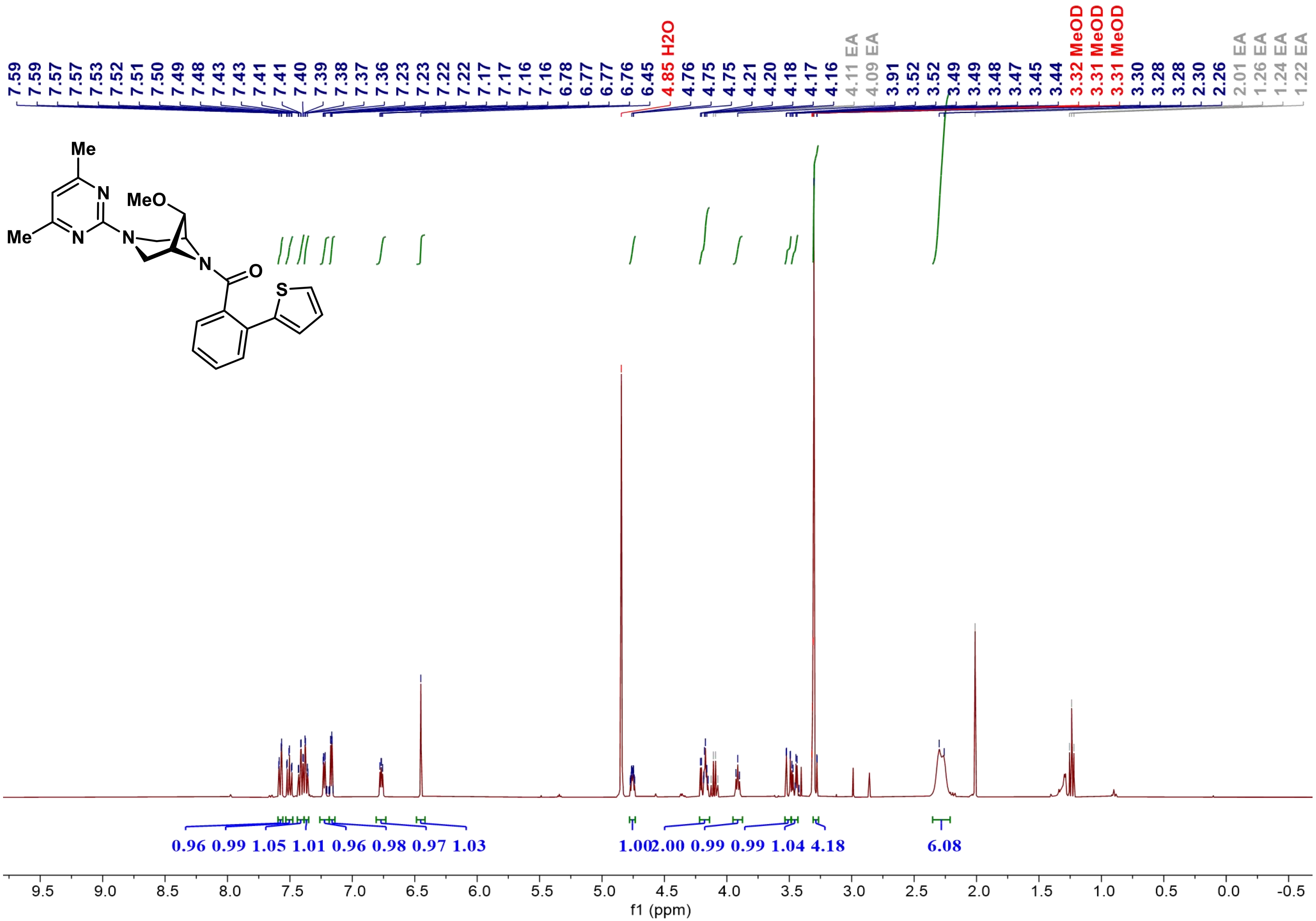
^{1}H NMR Spectrum of compound 76 (500 MHz, Methanol-*d*$_4$)



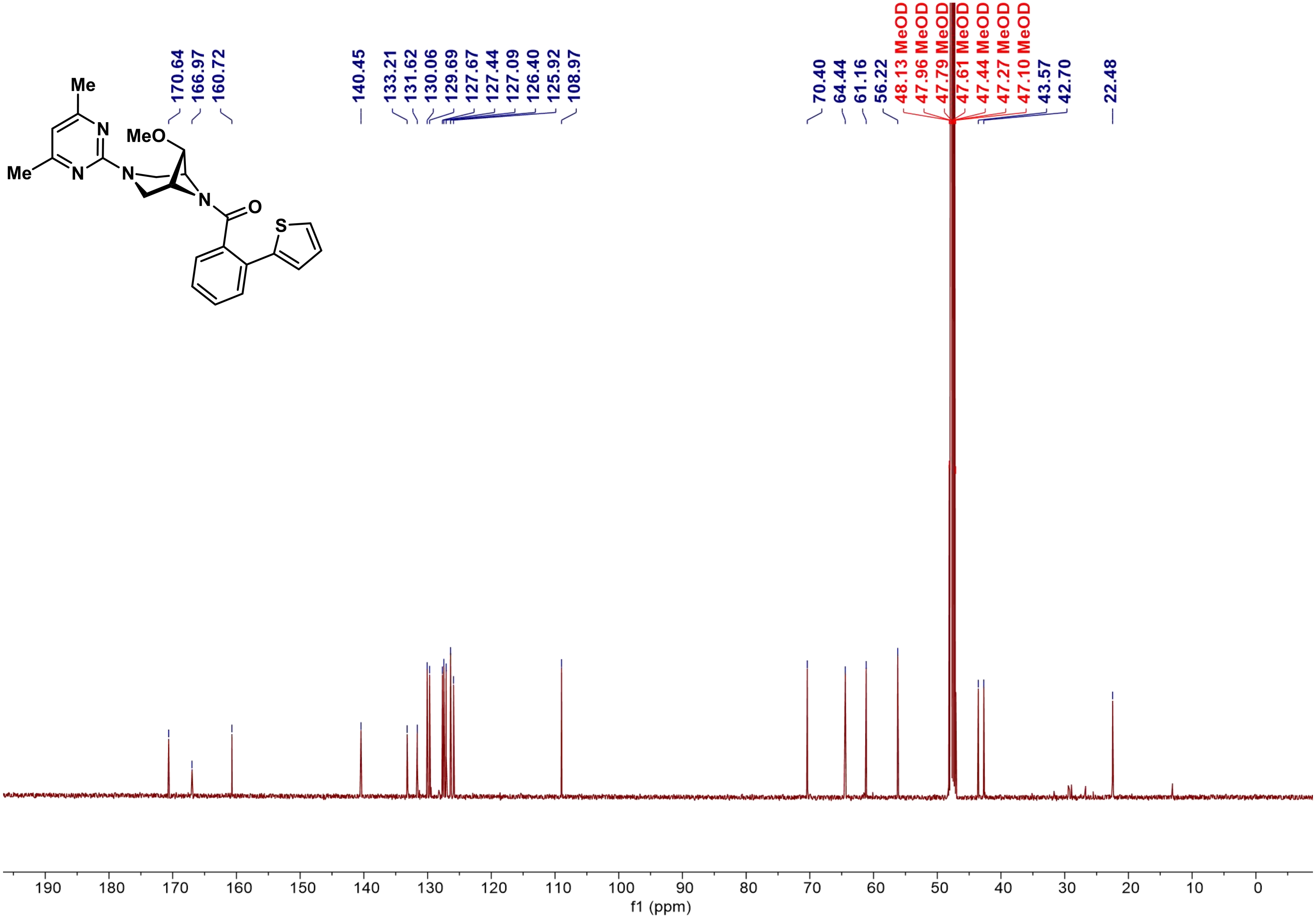
^{13}C NMR Spectrum of compound 76 (126 MHz, Methanol-d_4)



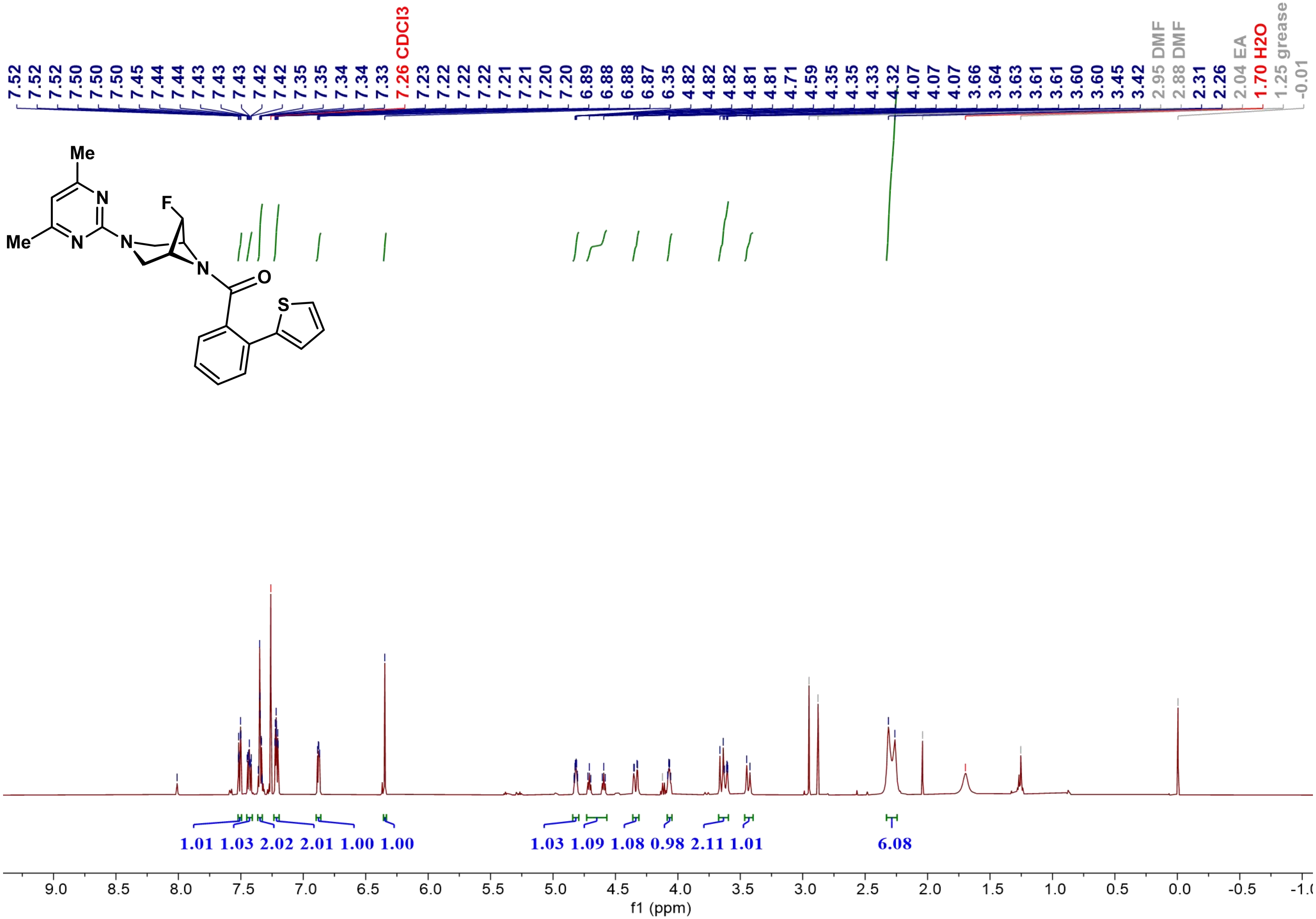
^{1}H NMR Spectrum of compound 77 (500 MHz, Methanol-d_4)



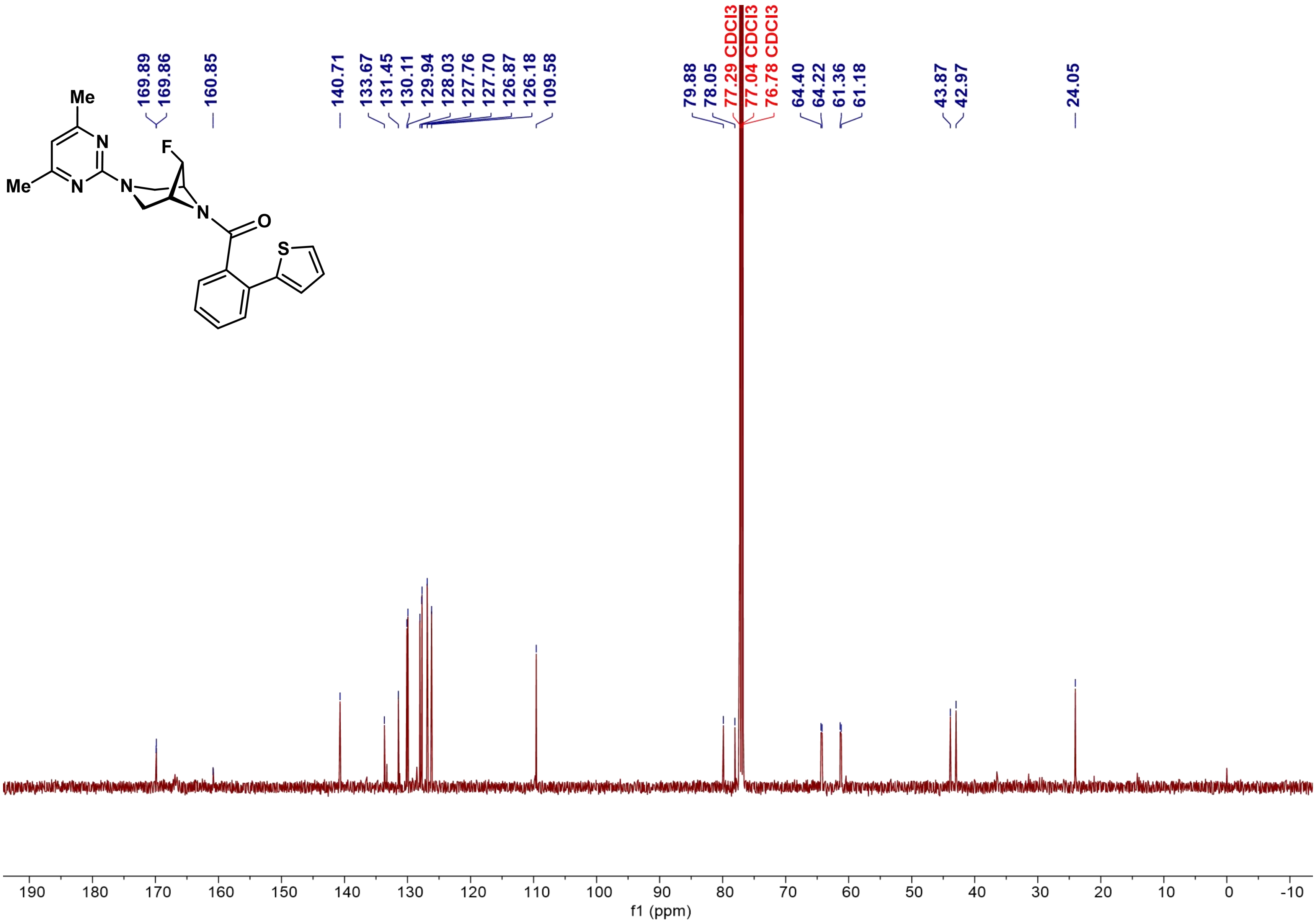
^{13}C NMR Spectrum of compound 77 (126 MHz, Methanol-*d*$_4$)



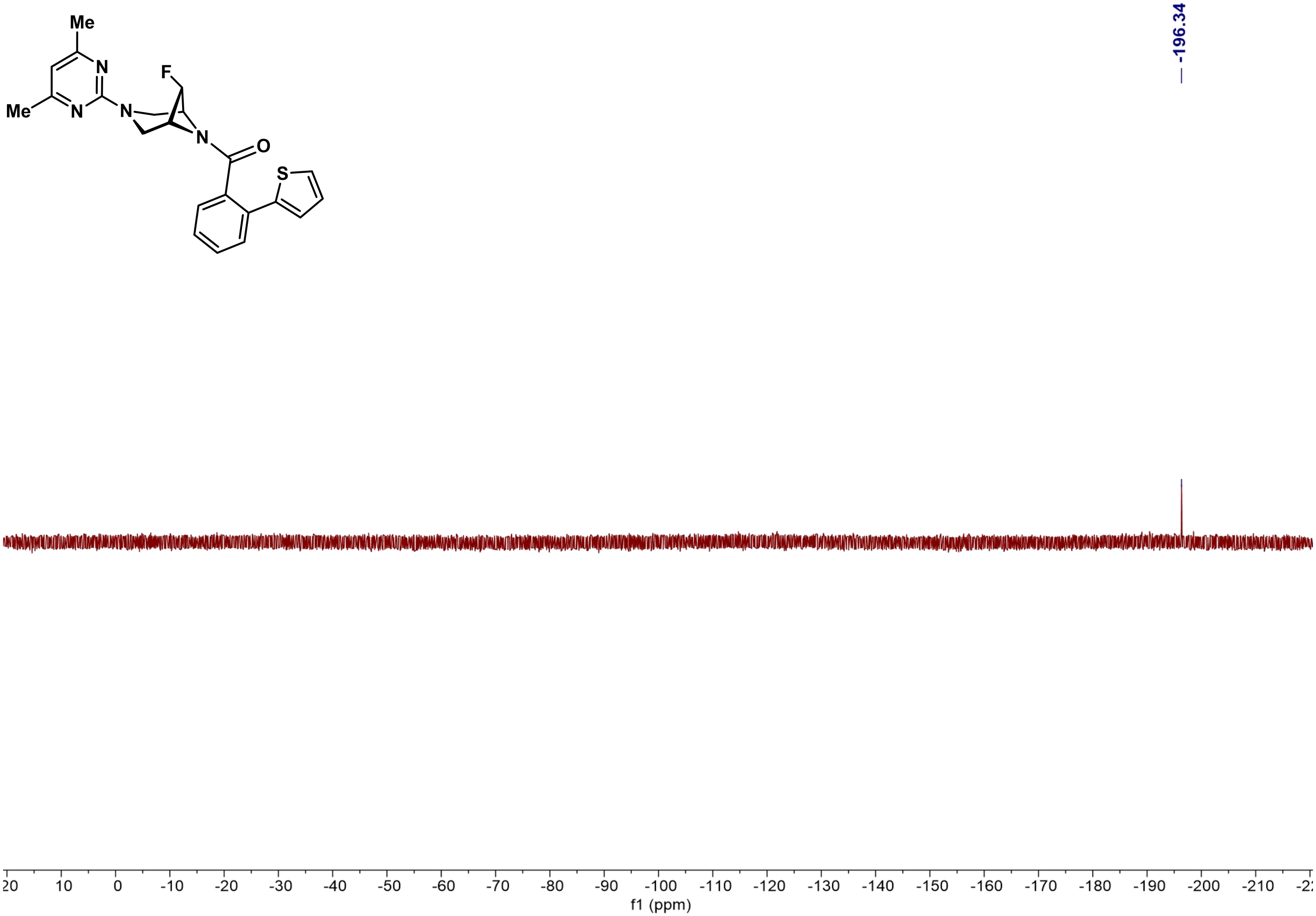
^{1}H NMR Spectrum of compound 78 (500 MHz, $CDCl_3$)



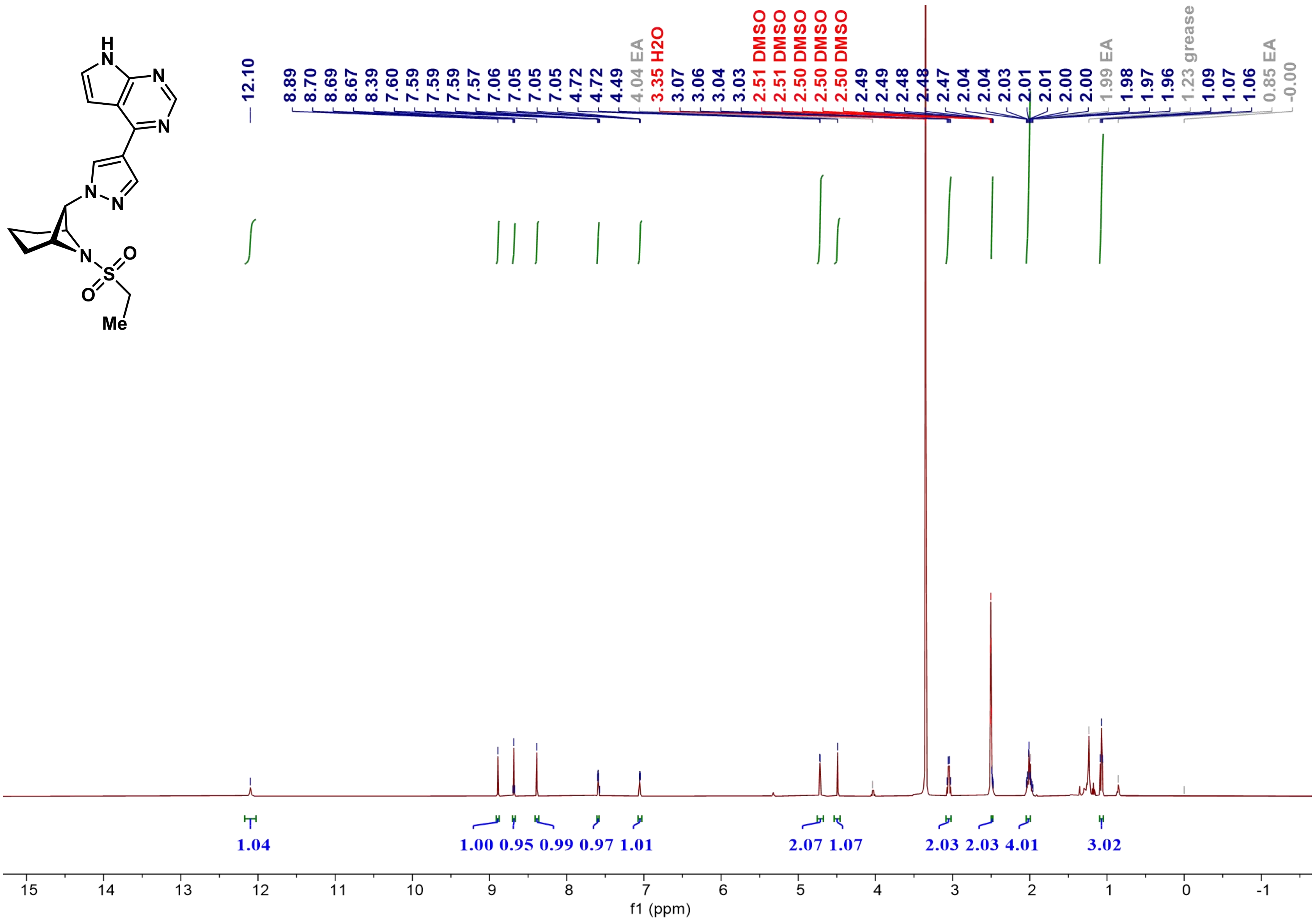
^{13}C NMR Spectrum of compound 78 (126 MHz, $CDCl_3$)



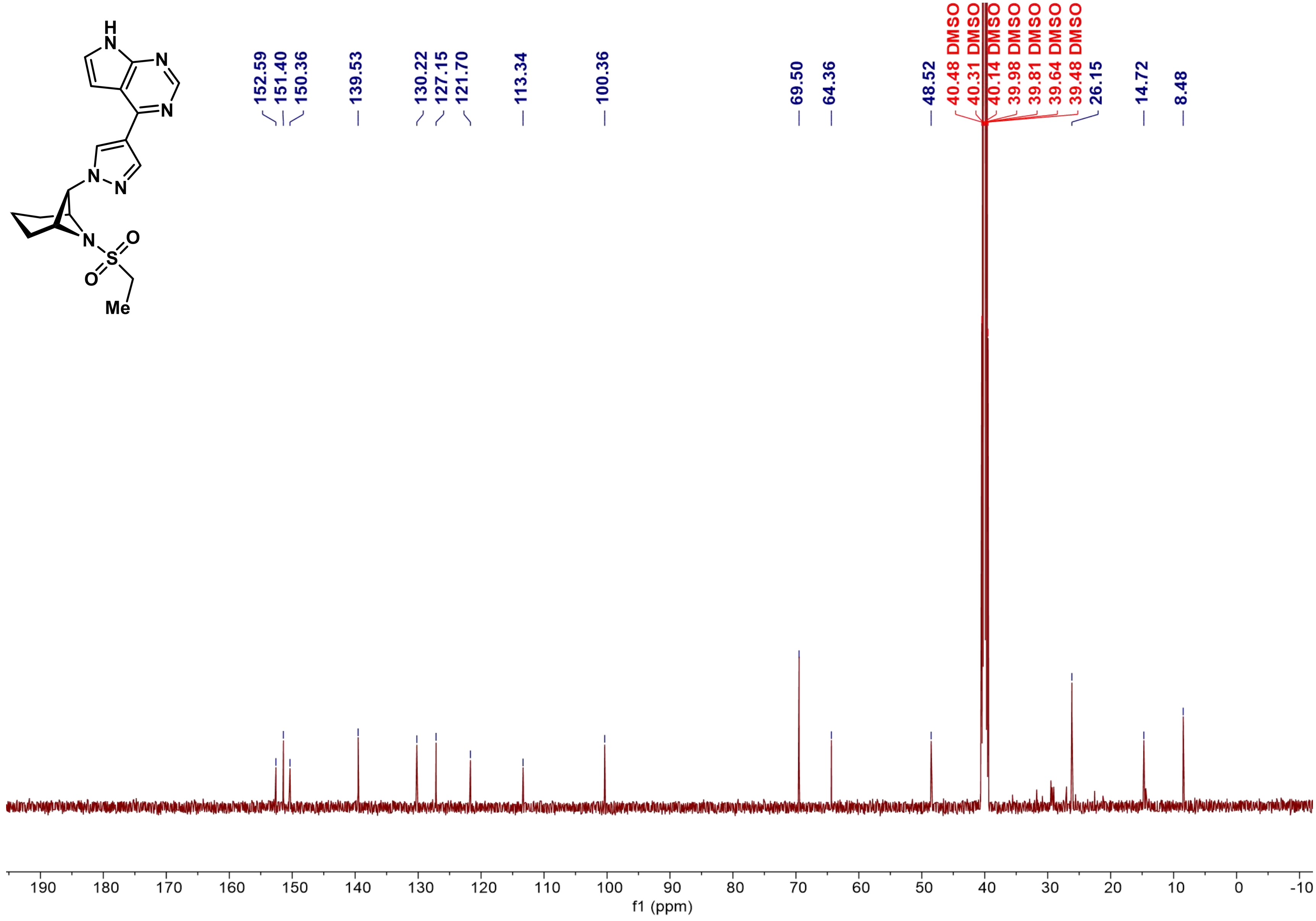
^{19}F NMR Spectrum of compound 78 (471 MHz, $CDCl_3$)



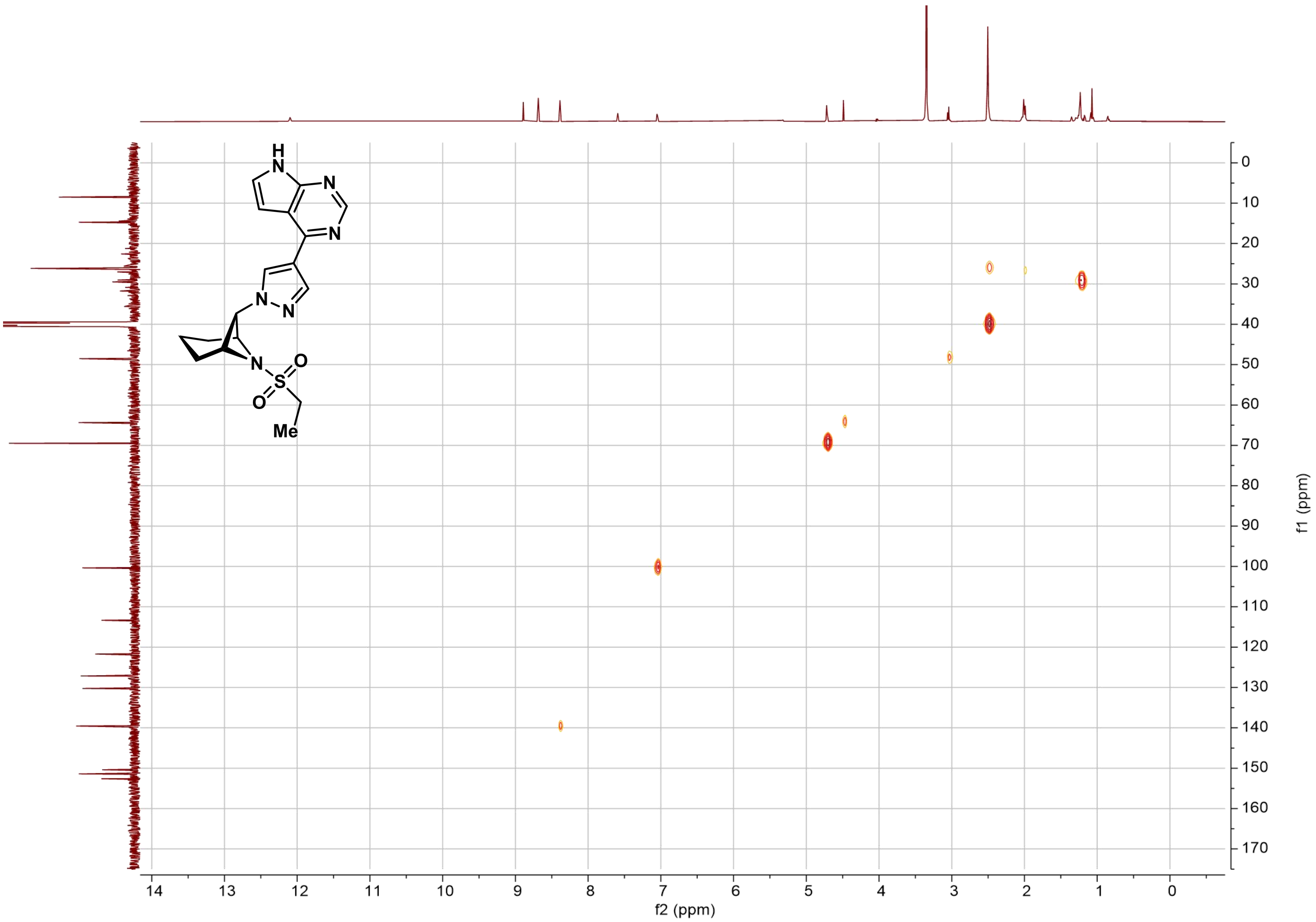
^{1}H NMR Spectrum of compound 79 (500 MHz, DMSO-d_6)



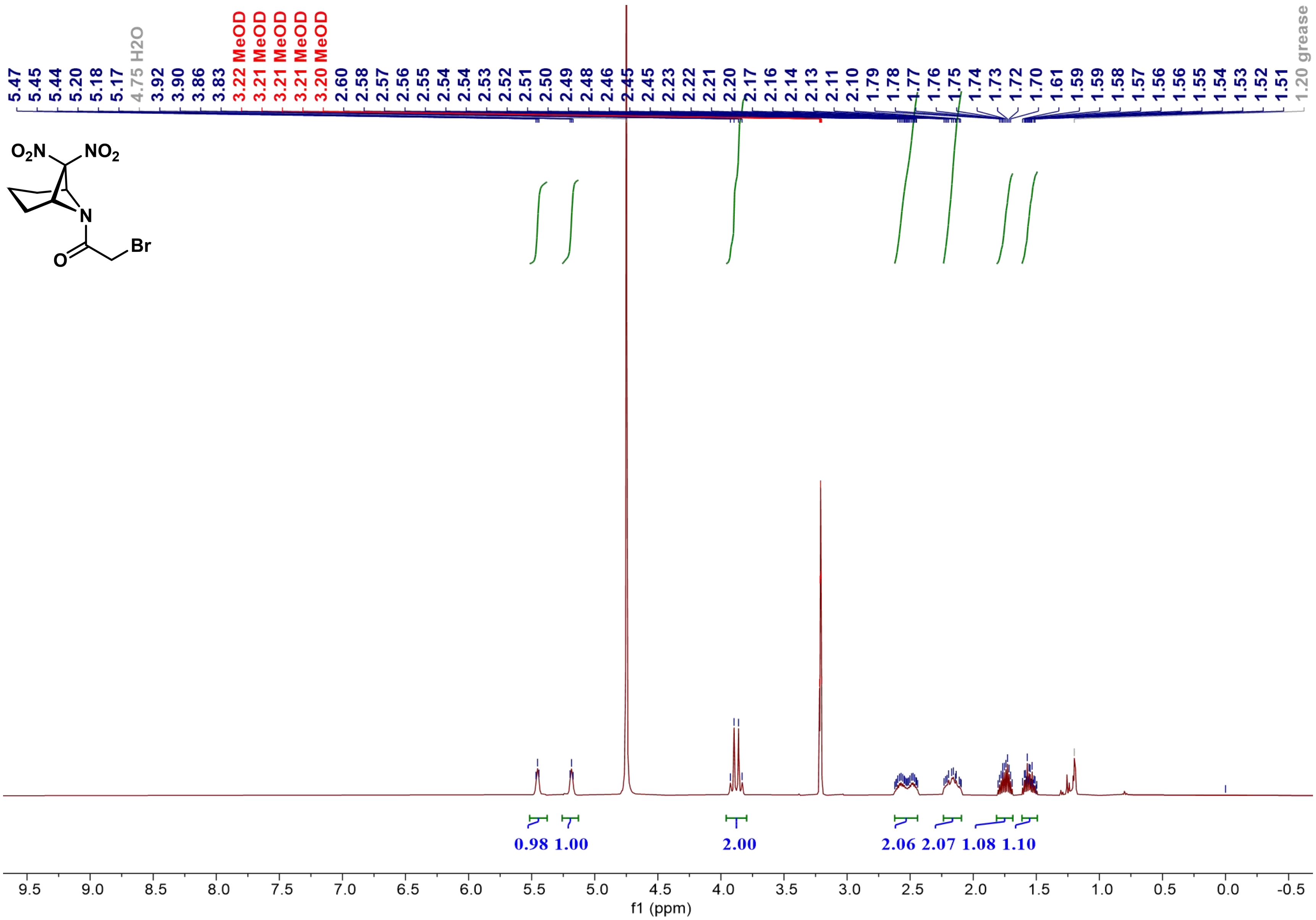
^{13}C NMR Spectrum of compound 79 (126 MHz, DMSO-d_6)



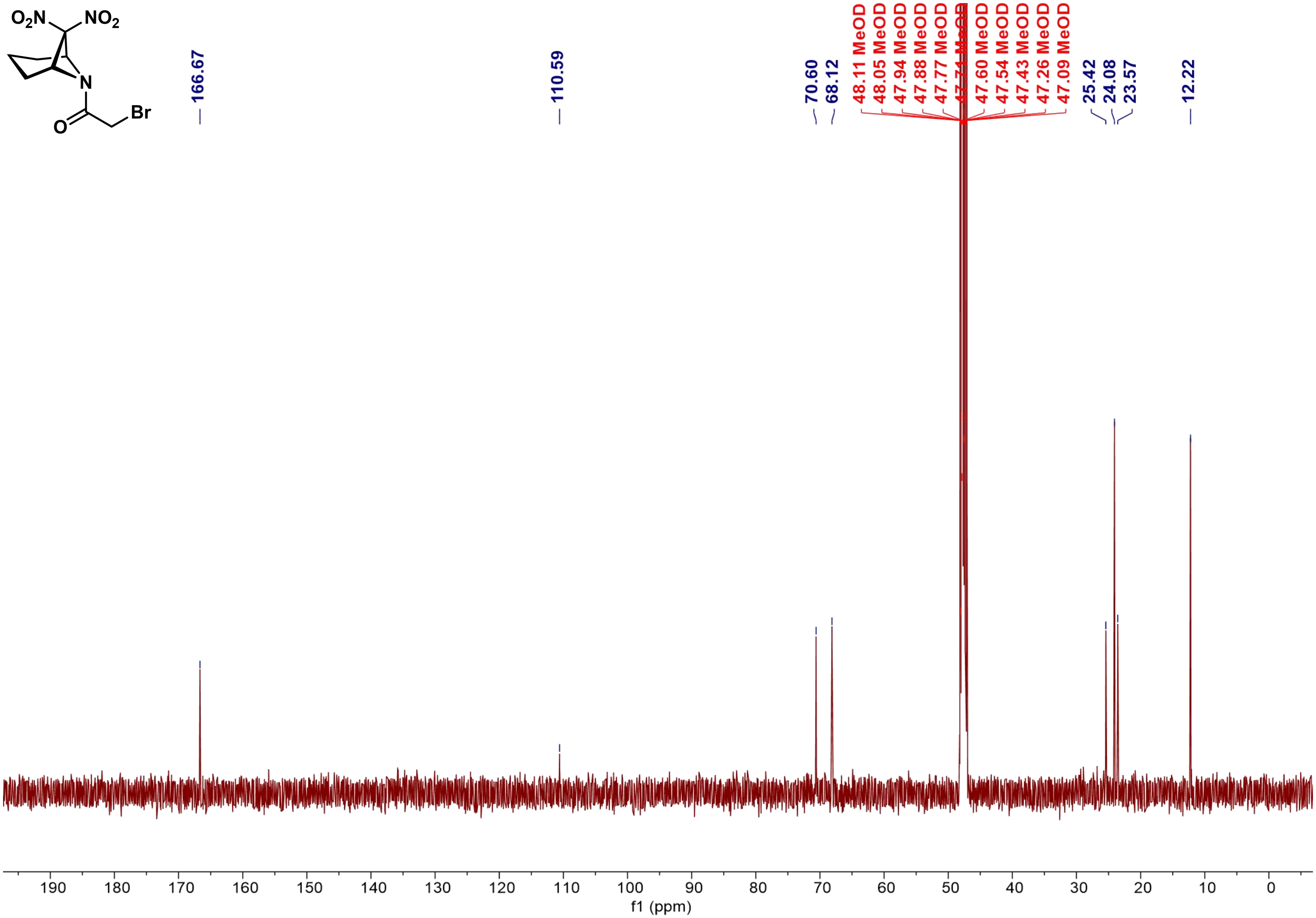
HSQC Spectrum of compound 79



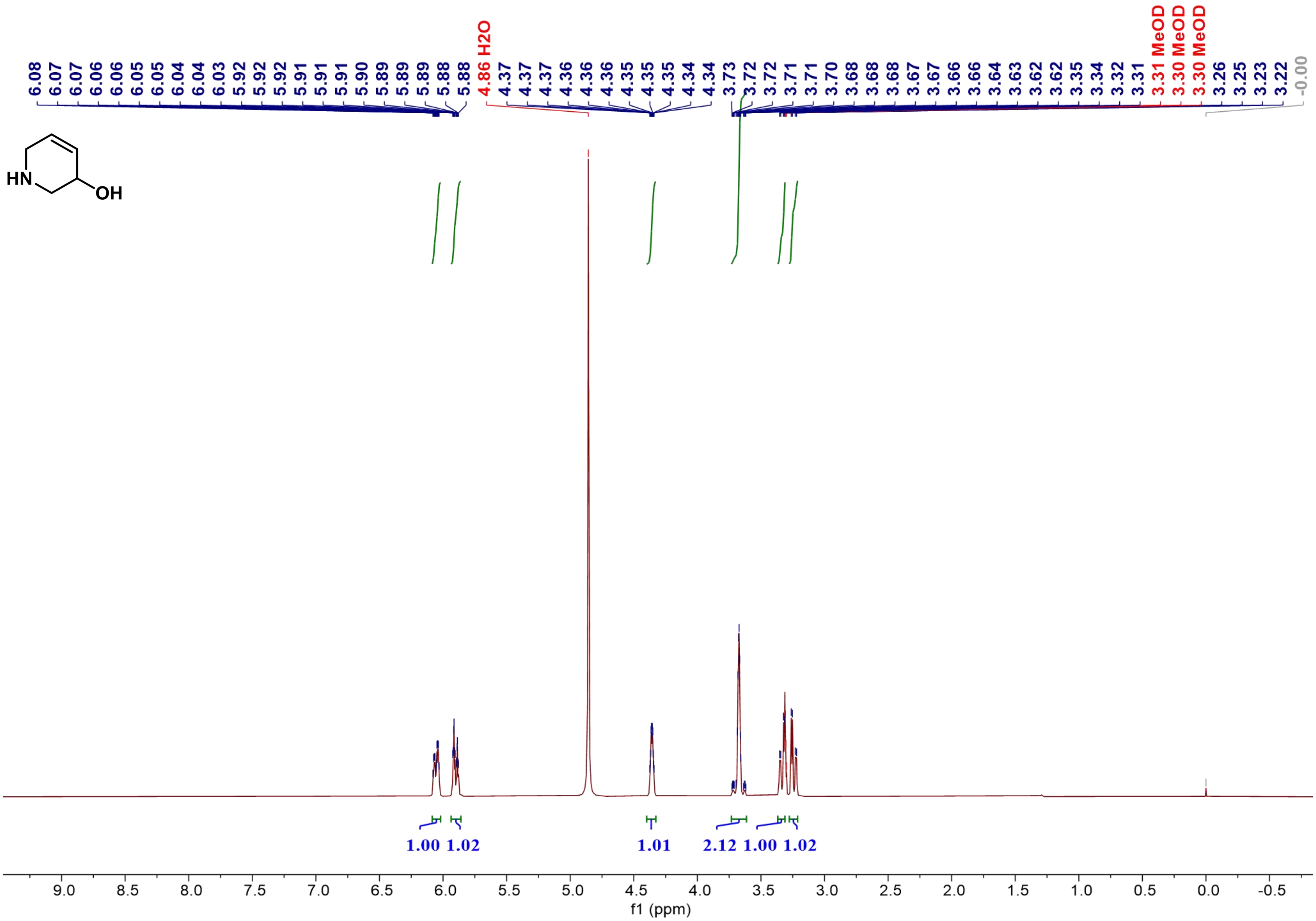
^{1}H NMR Spectrum of compound 80 (400 MHz, Methanol-d_4)



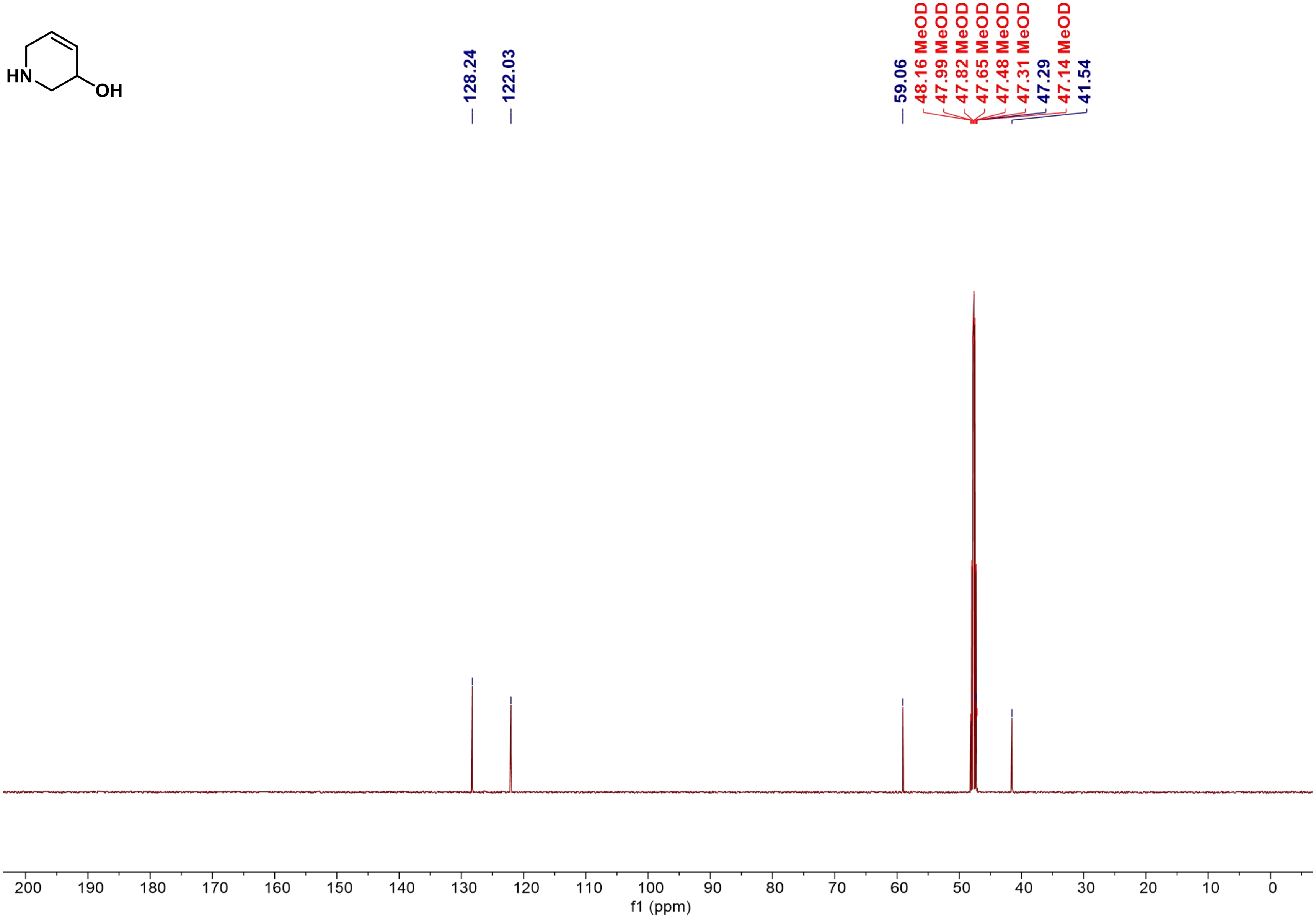
^{13}C NMR Spectrum of compound 80 (126 MHz, Methanol-*d*$_4$)



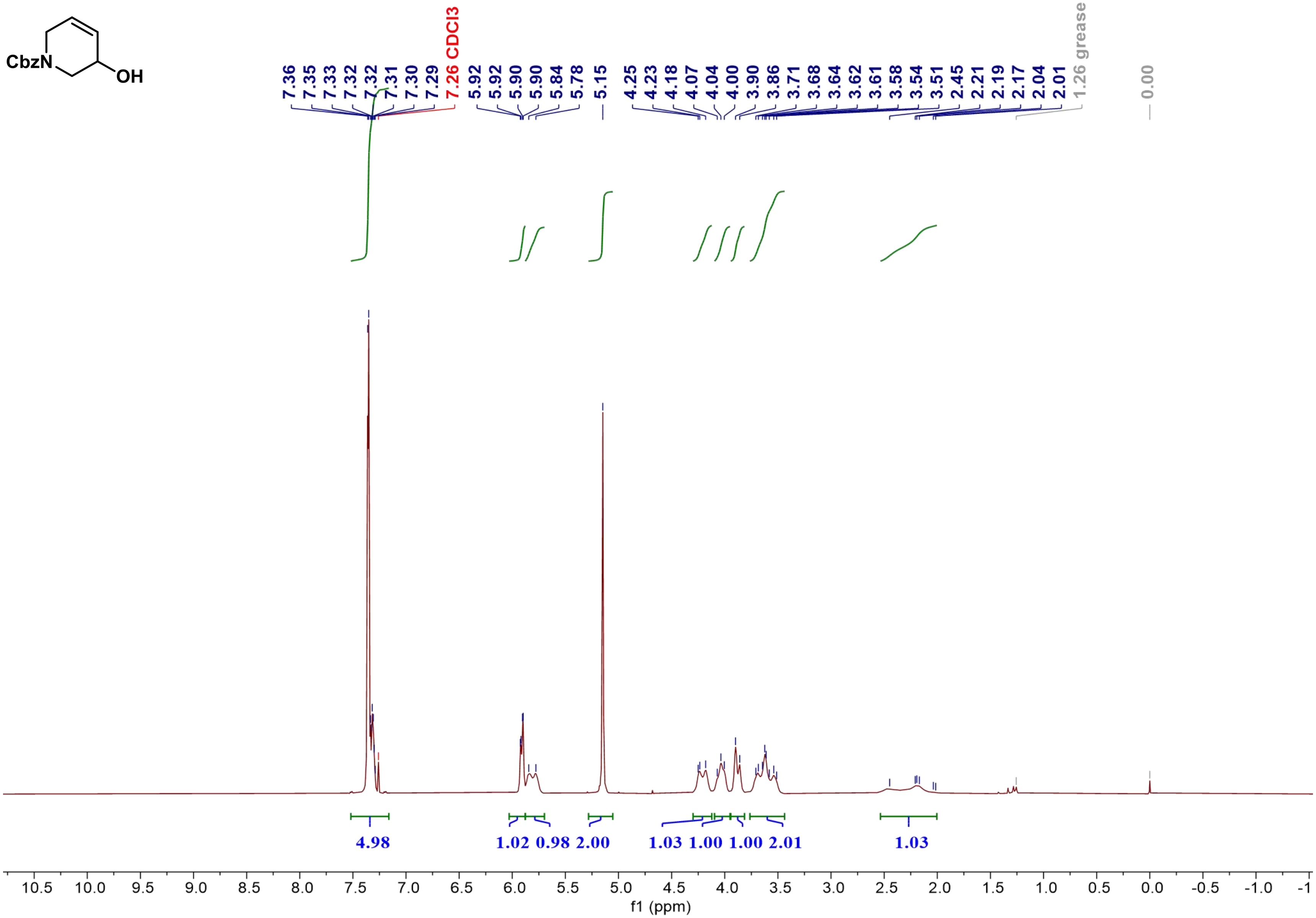
^{1}H NMR Spectrum of compound SI-1 (500 MHz, Methanol-d_4)



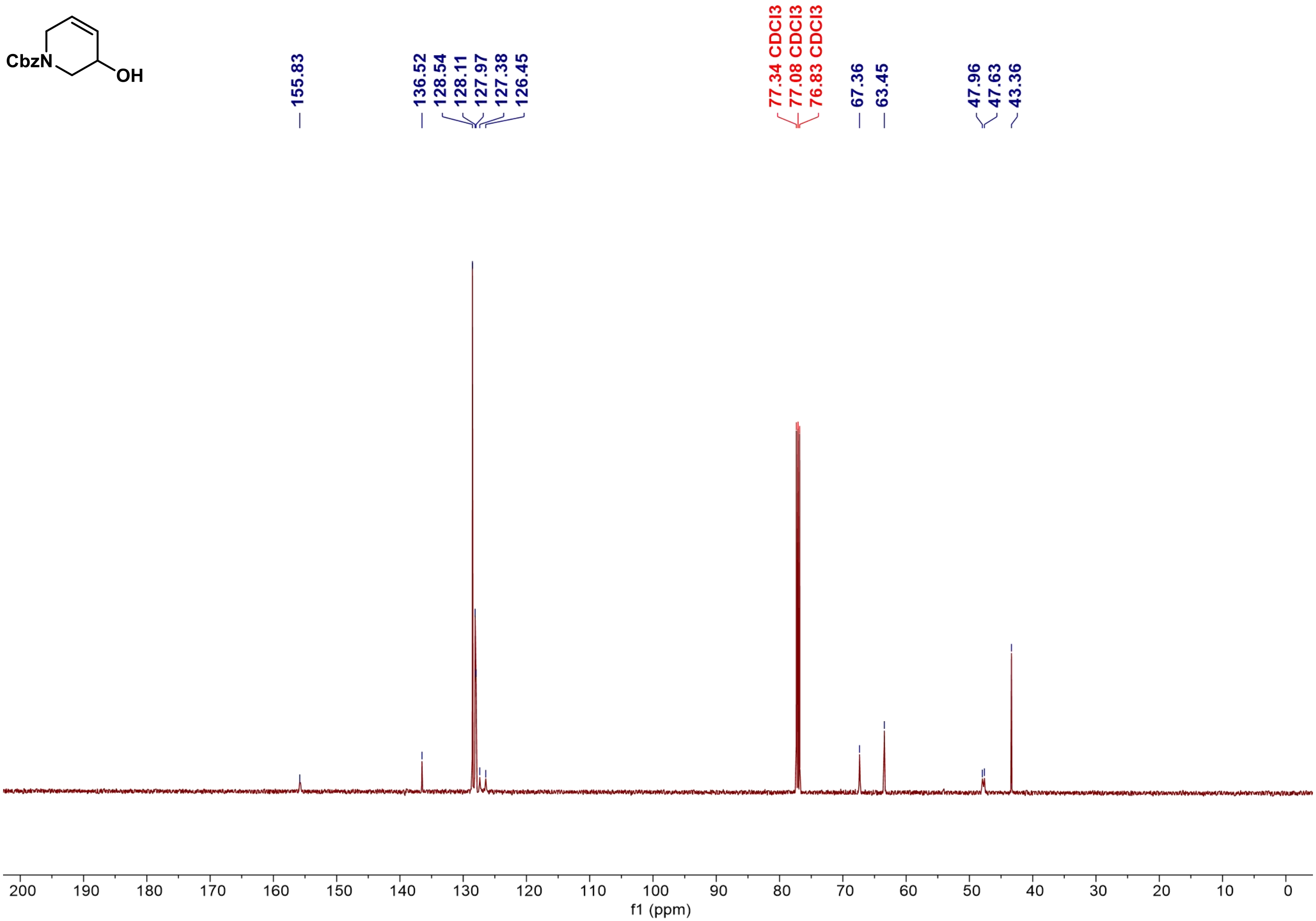
^{13}C NMR Spectrum of compound SI-1 (126 MHz, Methanol-d_4)



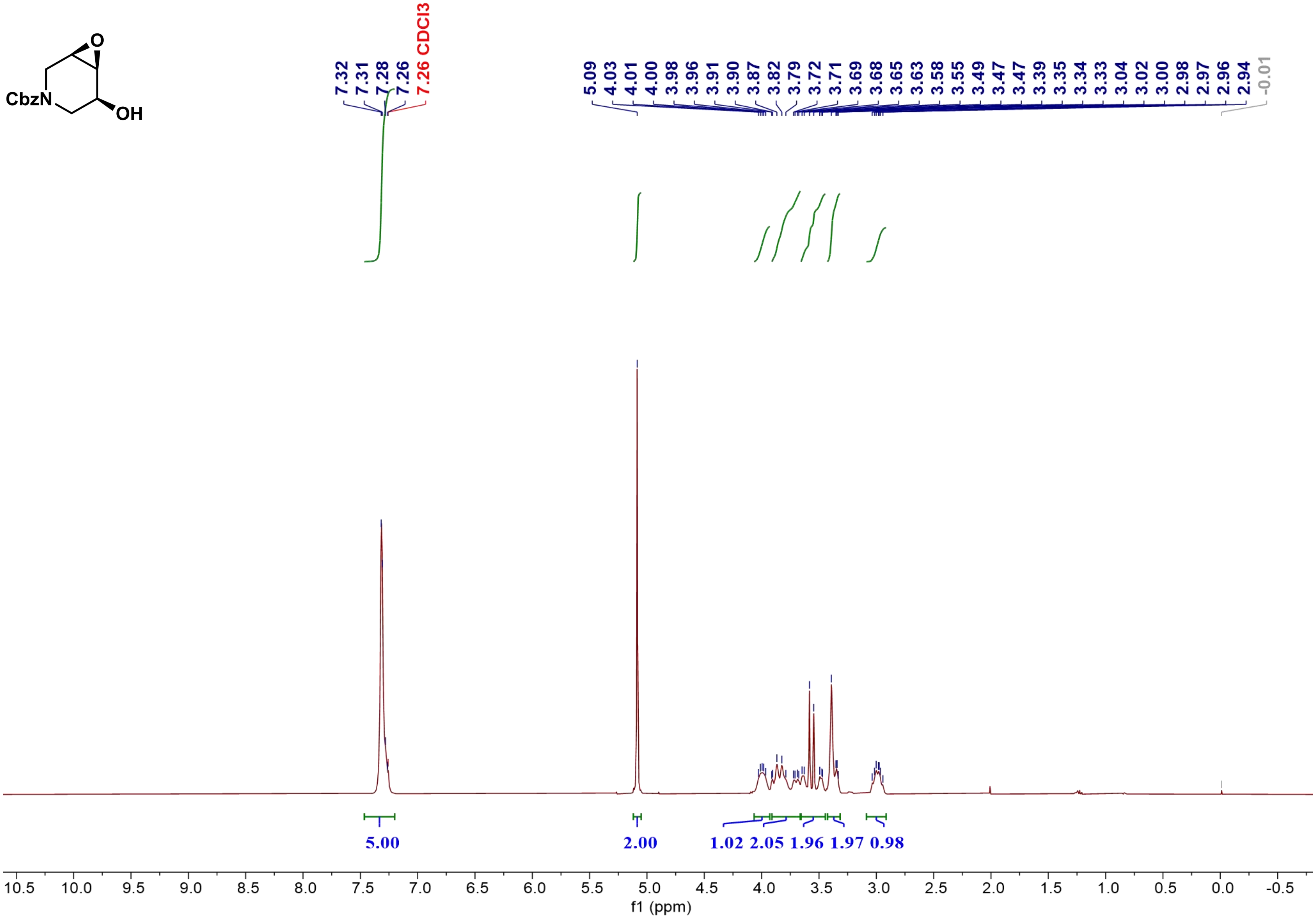
^{1}H NMR Spectrum of compound SI-2 (500 MHz, $CDCl_3$)



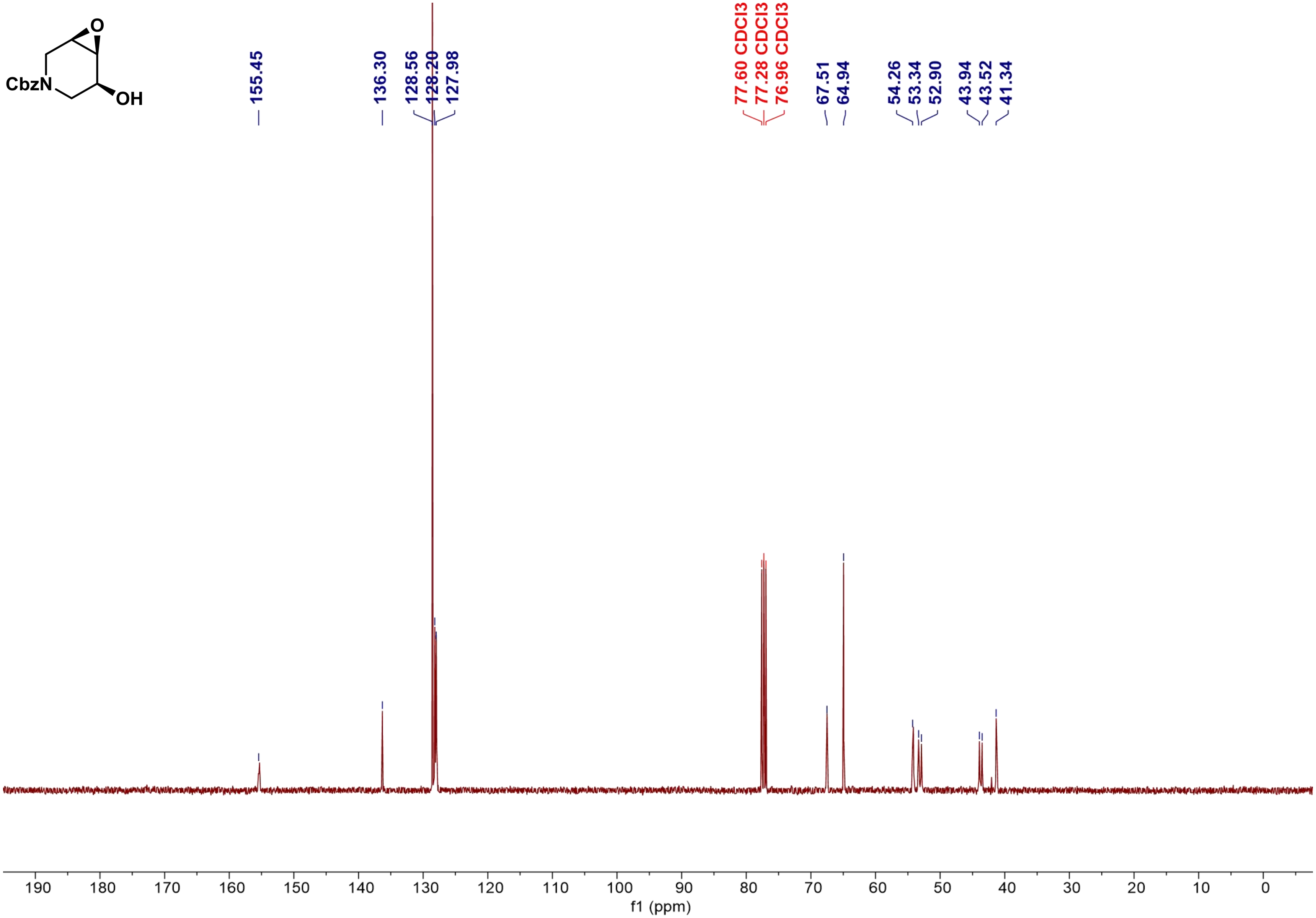
^{13}C NMR Spectrum of compound SI-2 (126 MHz, CDCl$_3$)



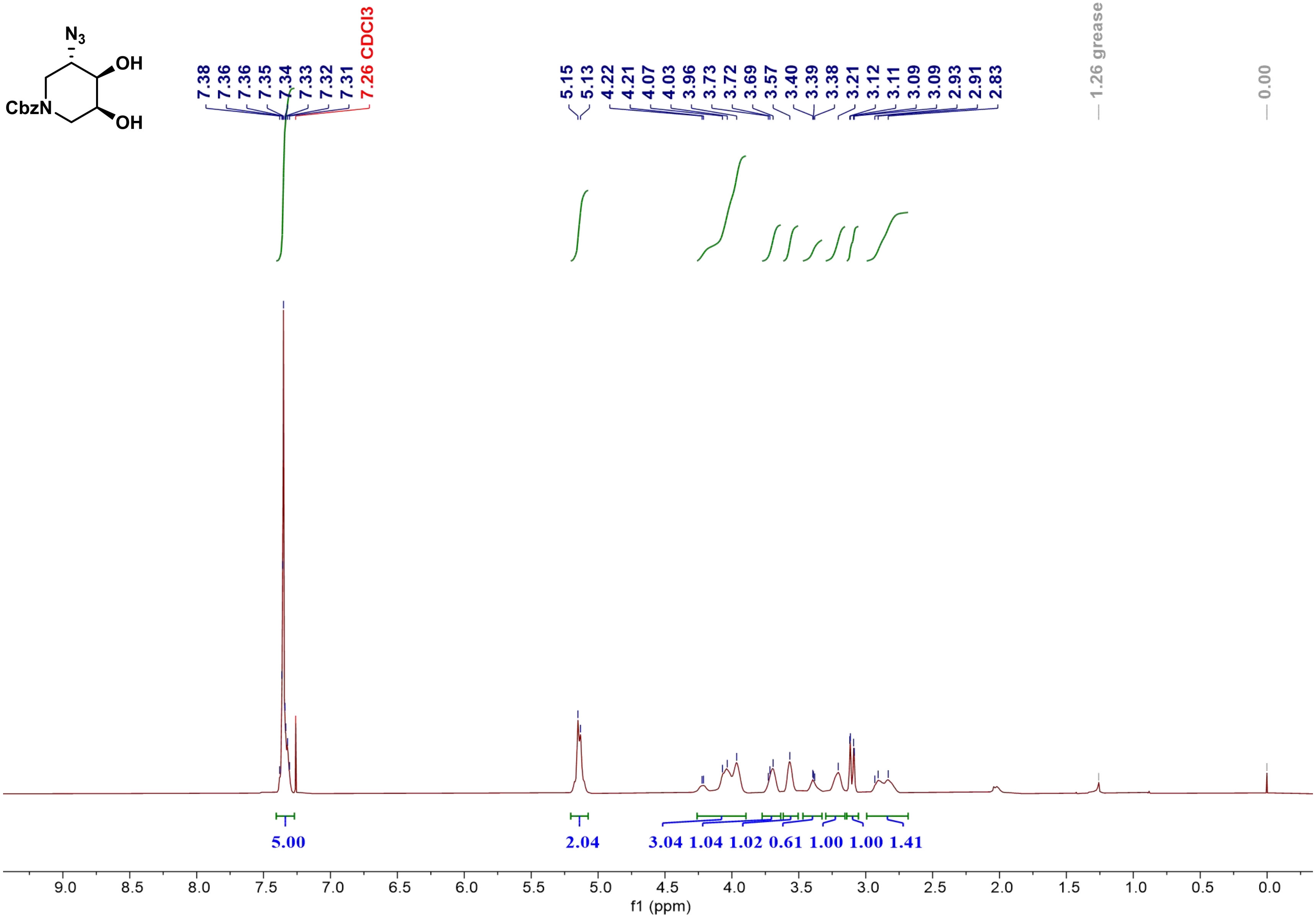
^{1}H NMR Spectrum of compound SI-3 (400 MHz, $CDCl_3$)



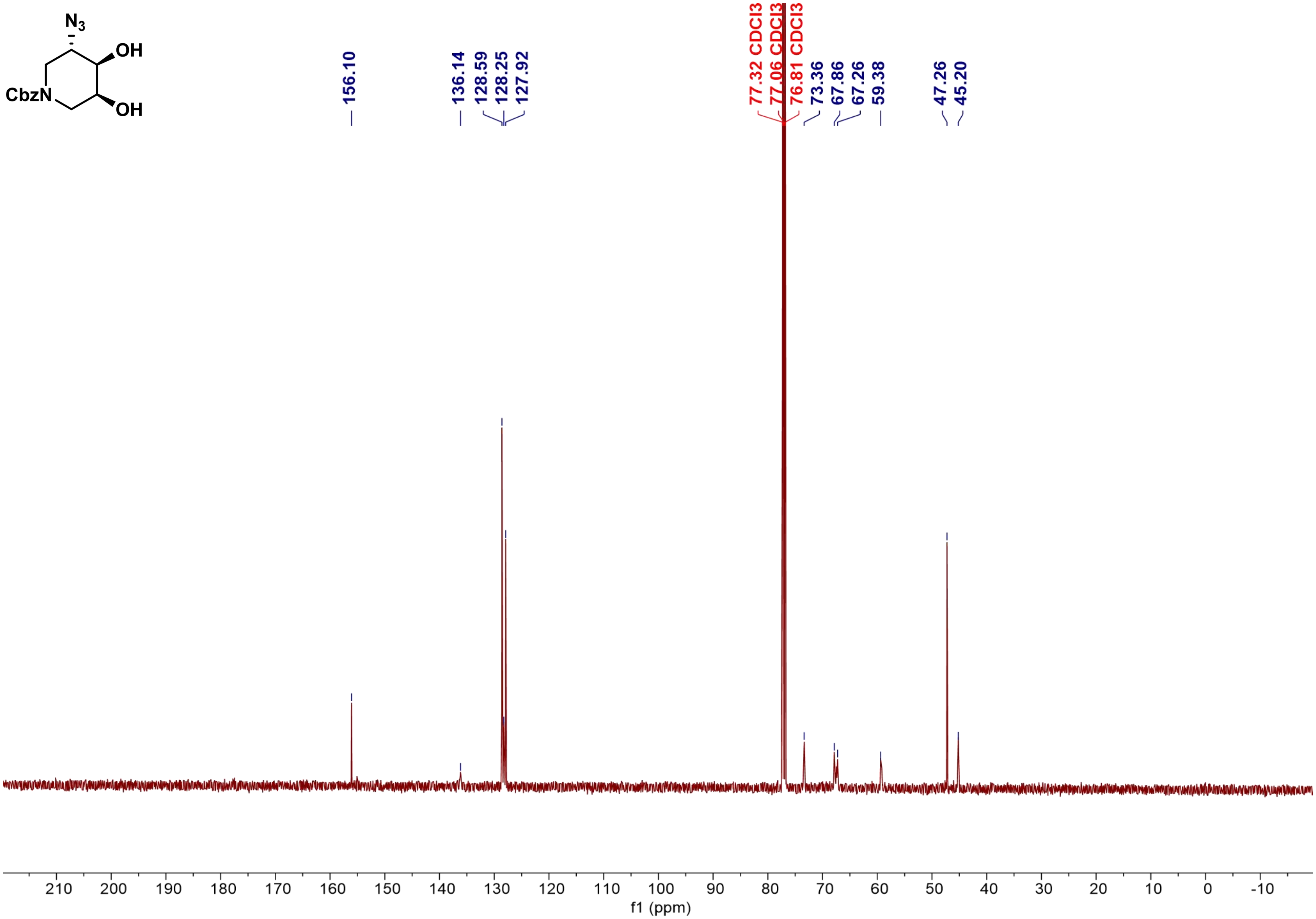
^{13}C NMR Spectrum of compound SI-3 (101 MHz, CDCl$_3$)



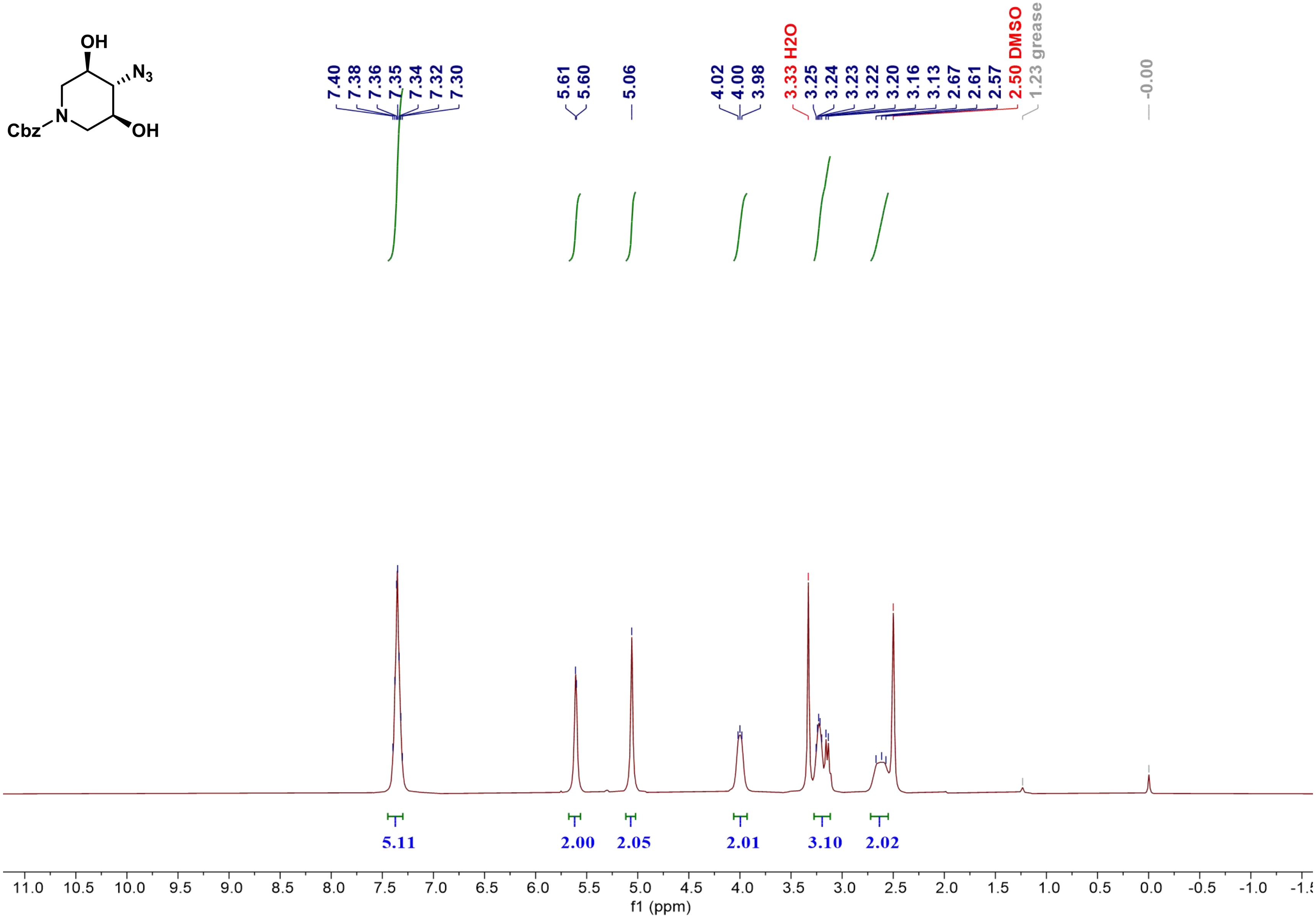
^{1}H NMR Spectrum of compound SI-4-1 (500 MHz, CDCl$_3$)



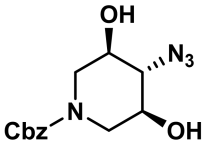
^{13}C NMR Spectrum of compound SI-4-1 (126 MHz, CDCl$_3$)

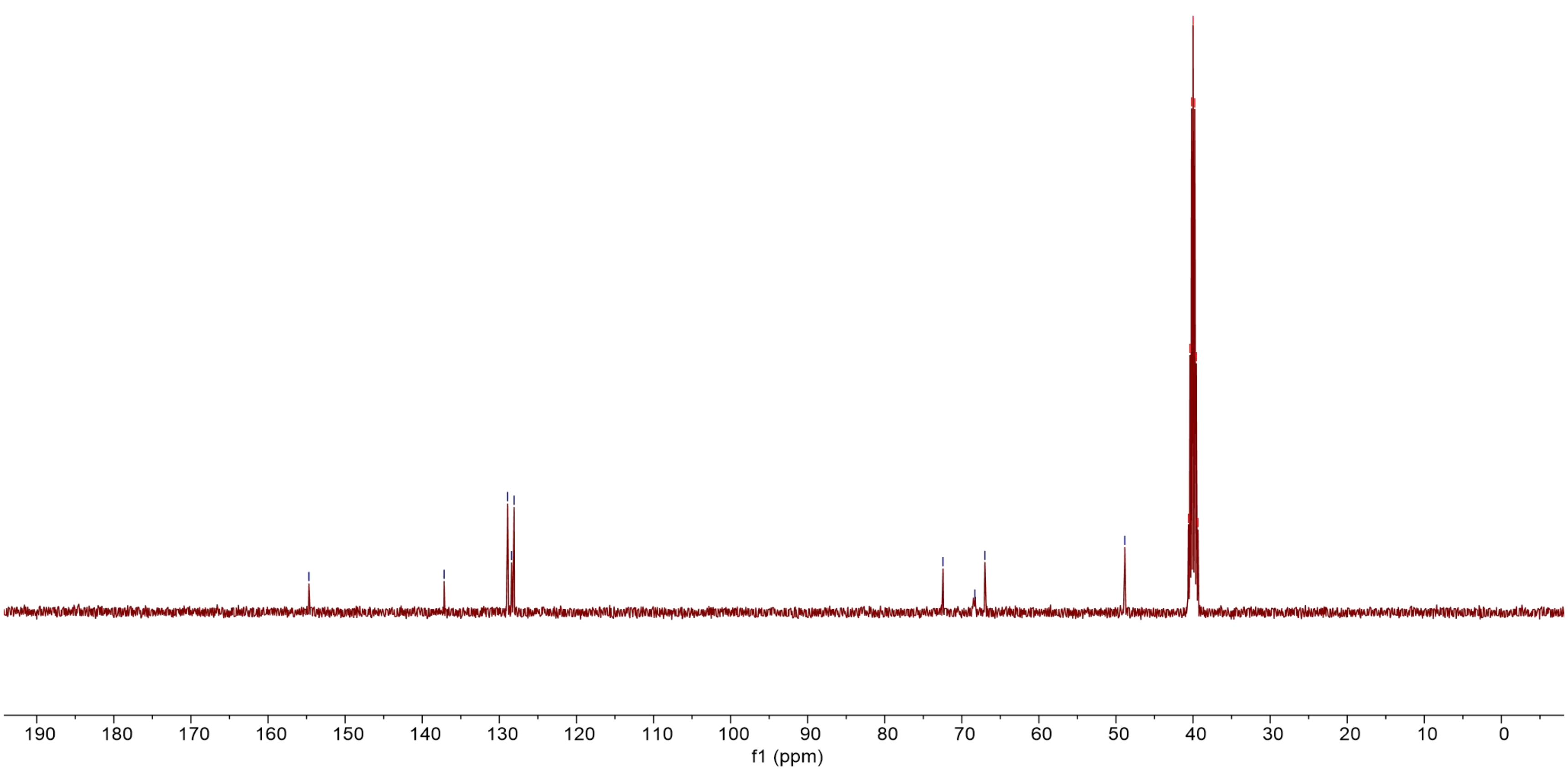


^{1}H NMR Spectrum of compound SI-4-2 (400 MHz, DMSO-d_6)

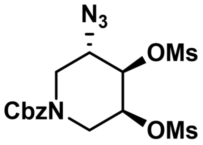


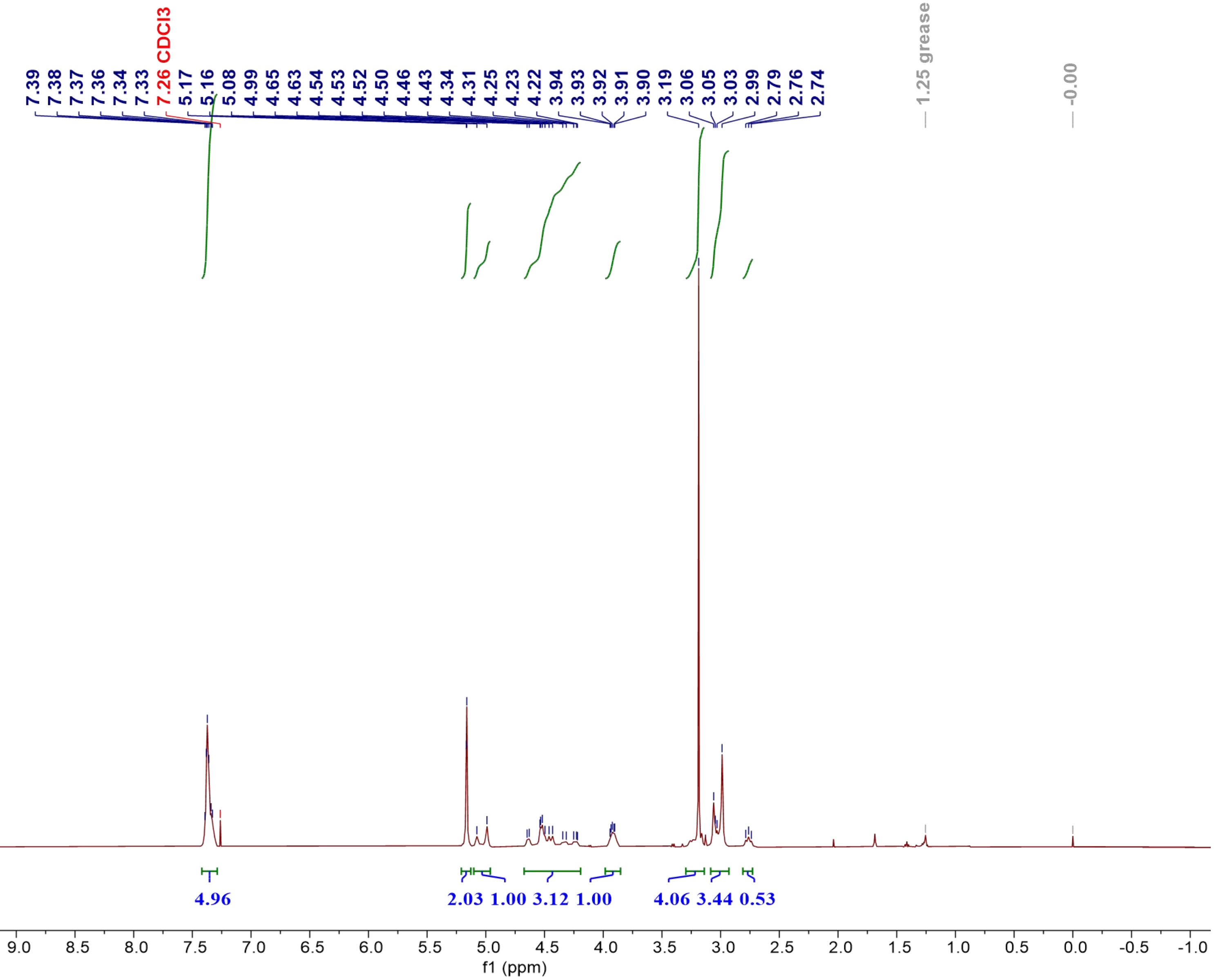
^{13}C NMR Spectrum of compound SI-4-2 (101 MHz, DMSO-d_6)



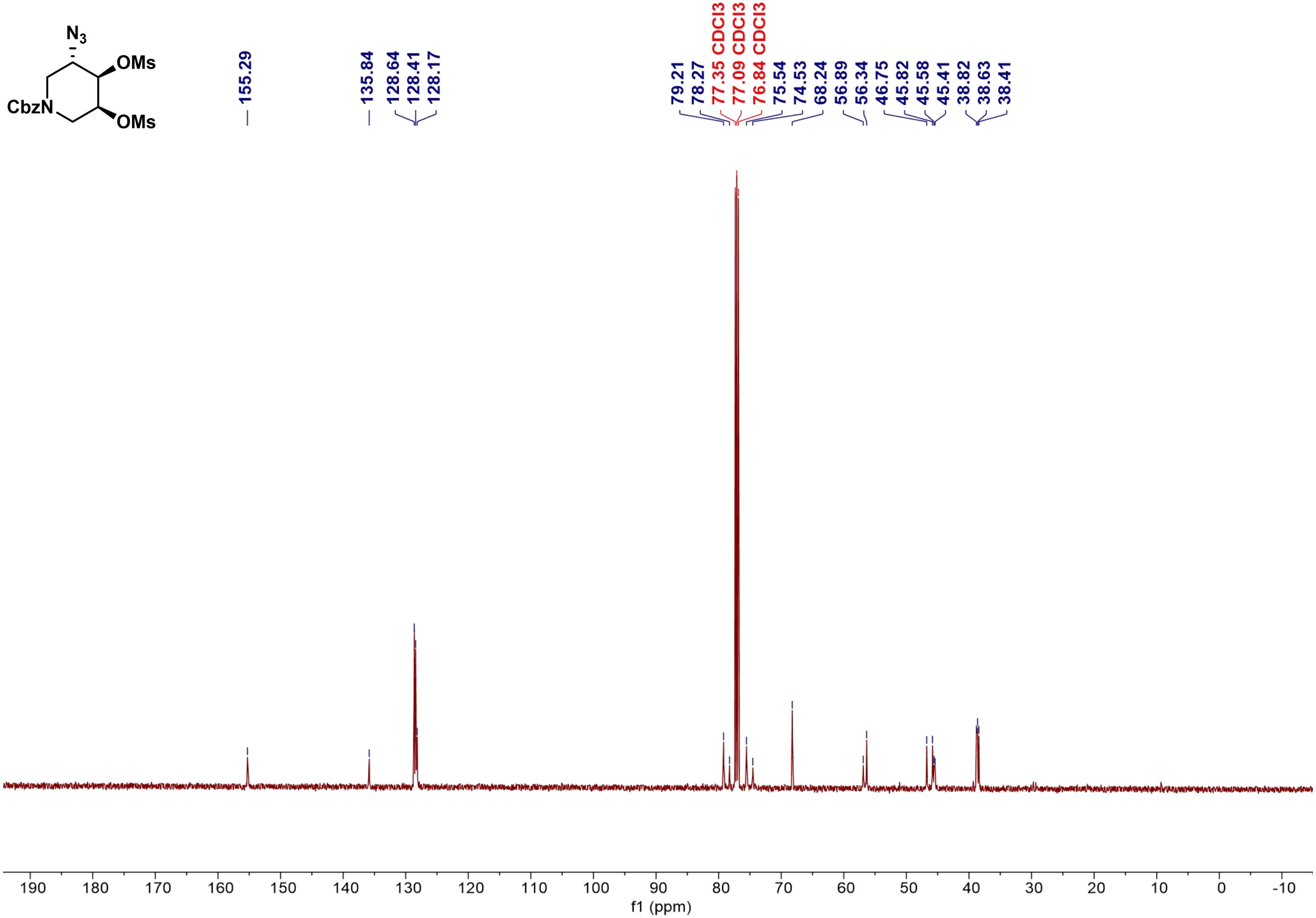


^{1}H NMR Spectrum of compound SI-5-1 (500 MHz, CDCl$_3$)

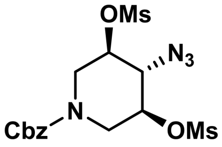


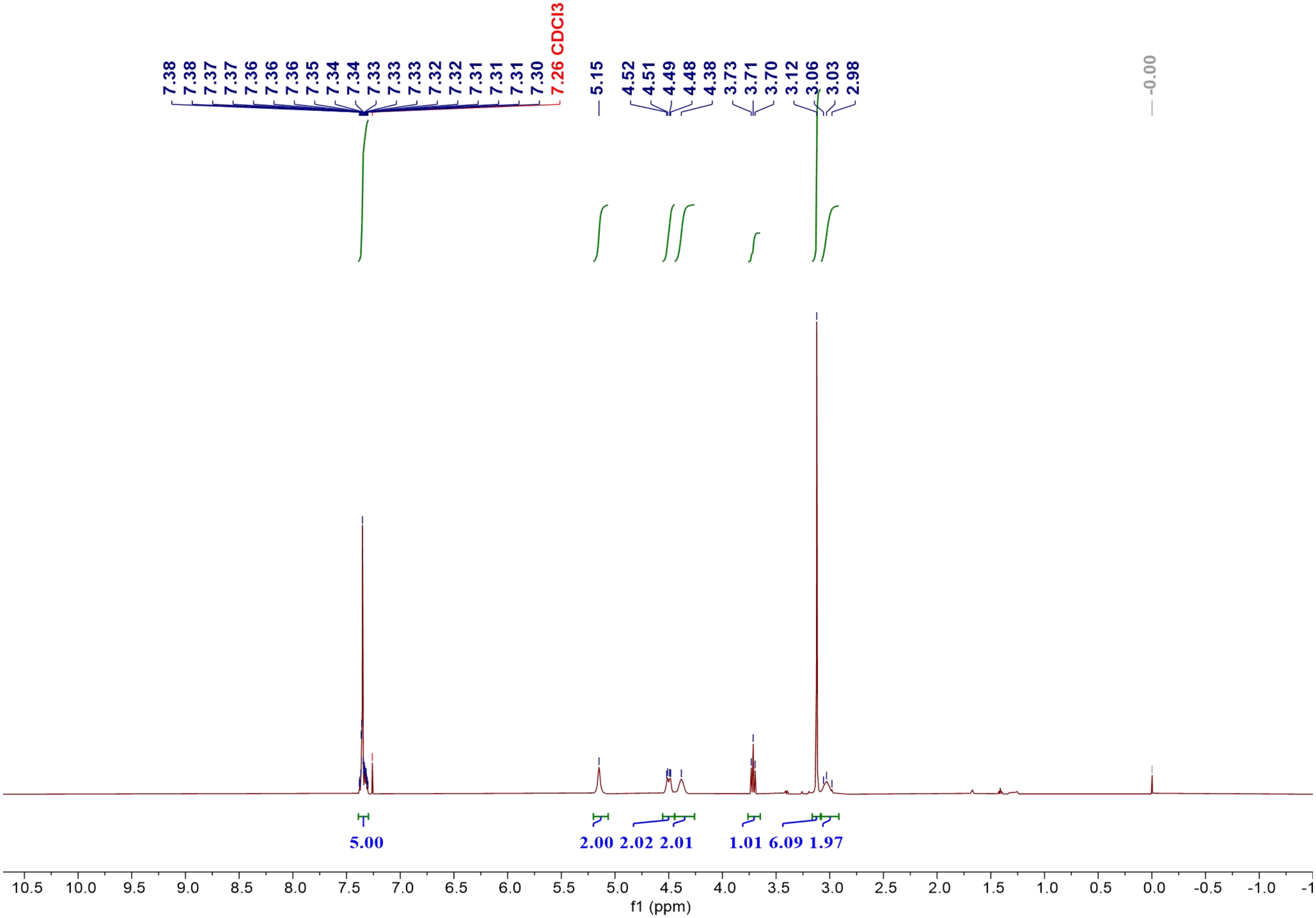


^{13}C NMR Spectrum of compound SI-5-1 (126 MHz, $CDCl_3$)



^{1}H NMR Spectrum of compound SI-5-2 (500 MHz, CDCl$_3$)

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2.01
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1.5
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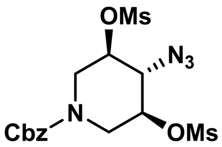
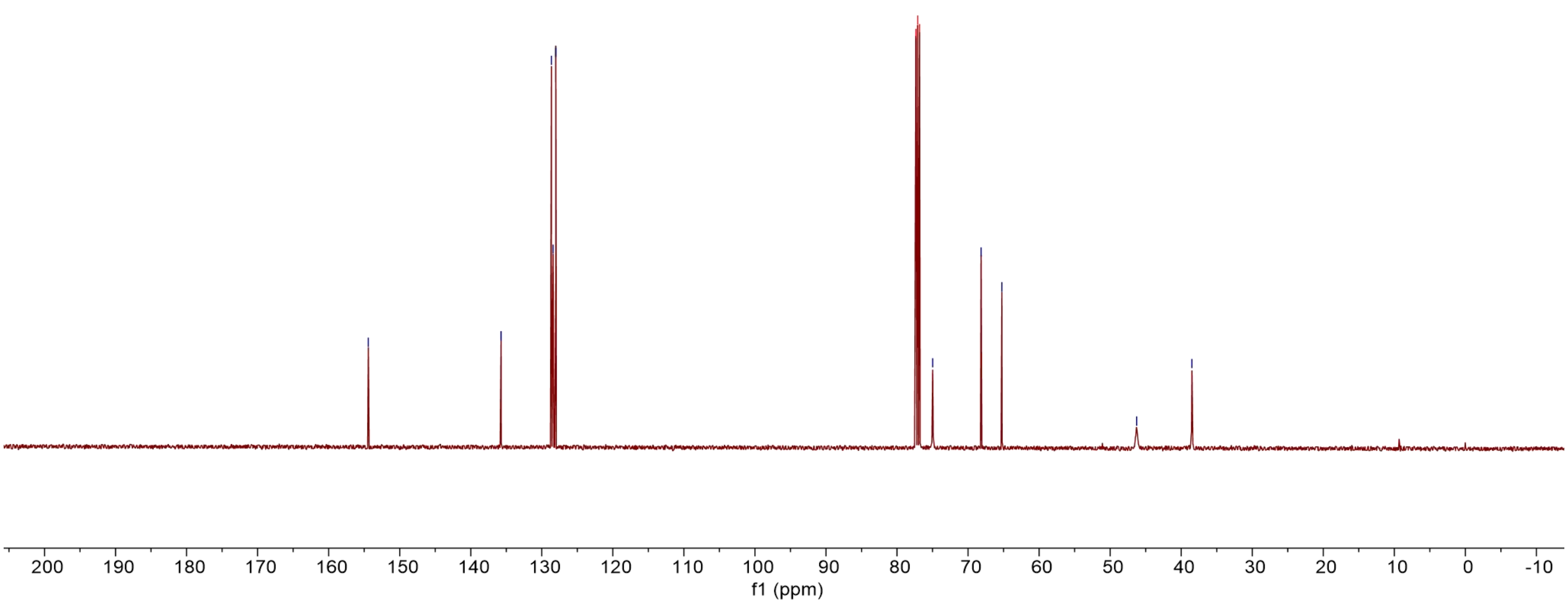
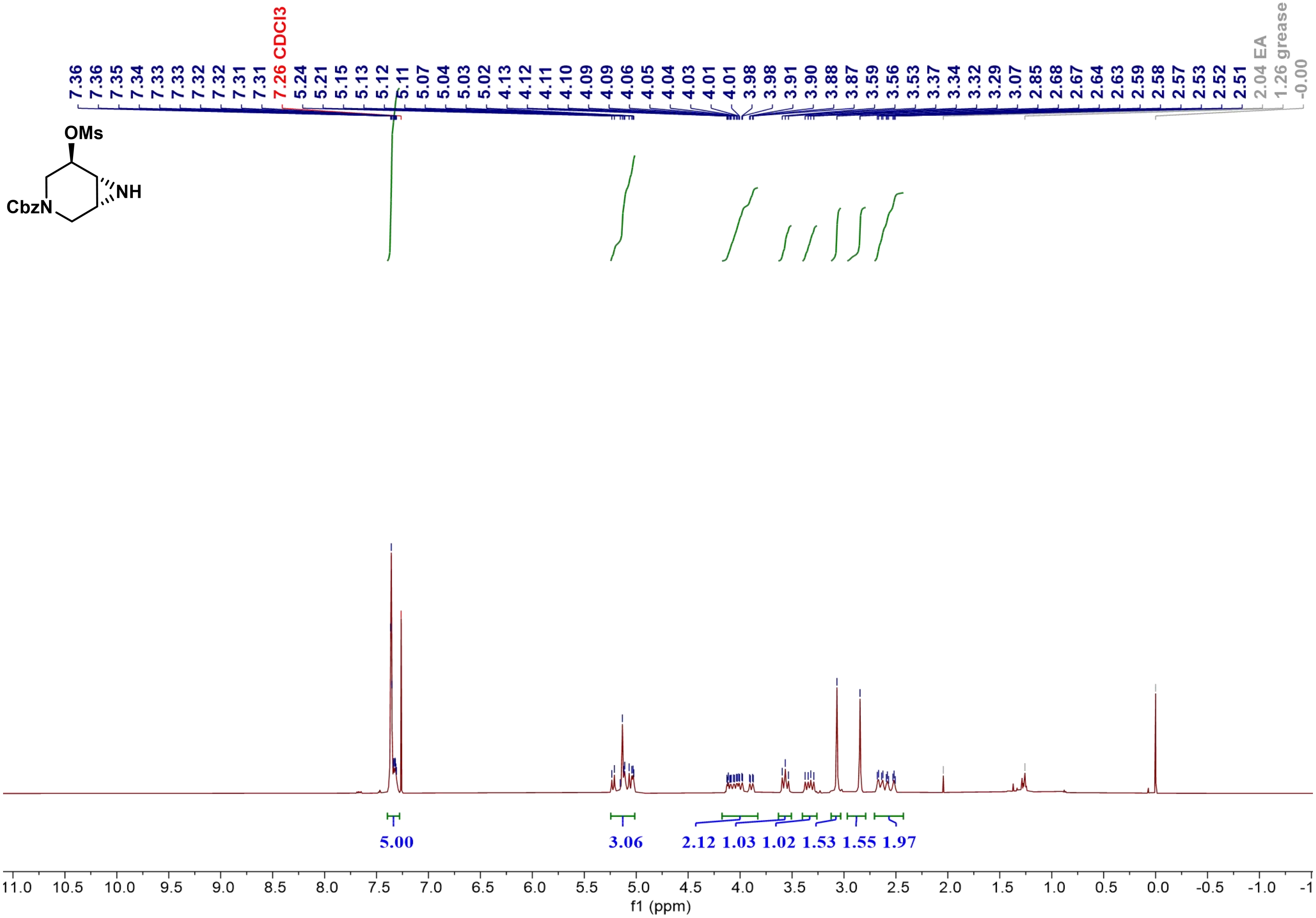
-0.5
-1.0
-1
f1 (ppm)

^{13}C NMR Spectrum of compound SI-5-2 (126 MHz, CDCl$_3$)

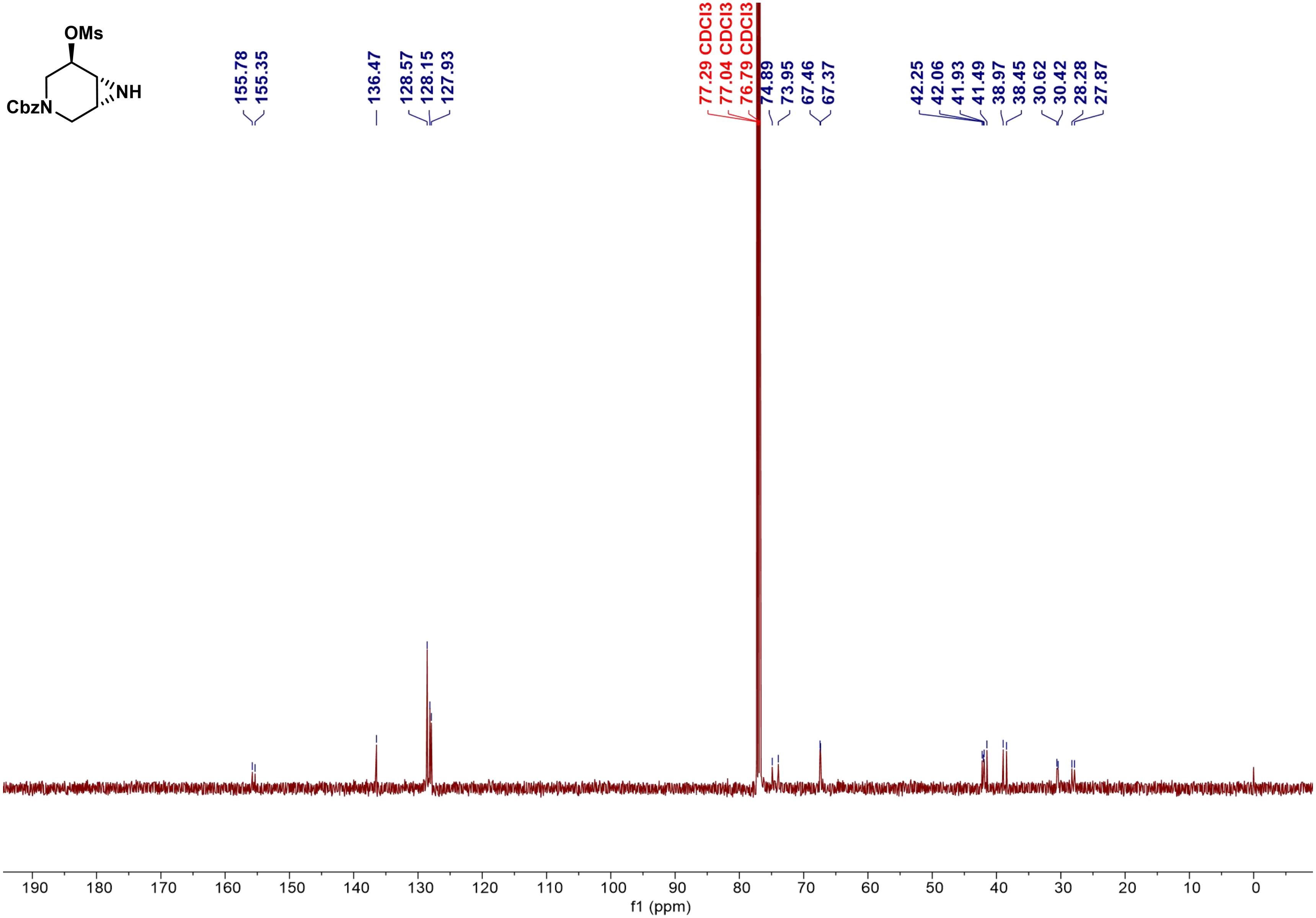




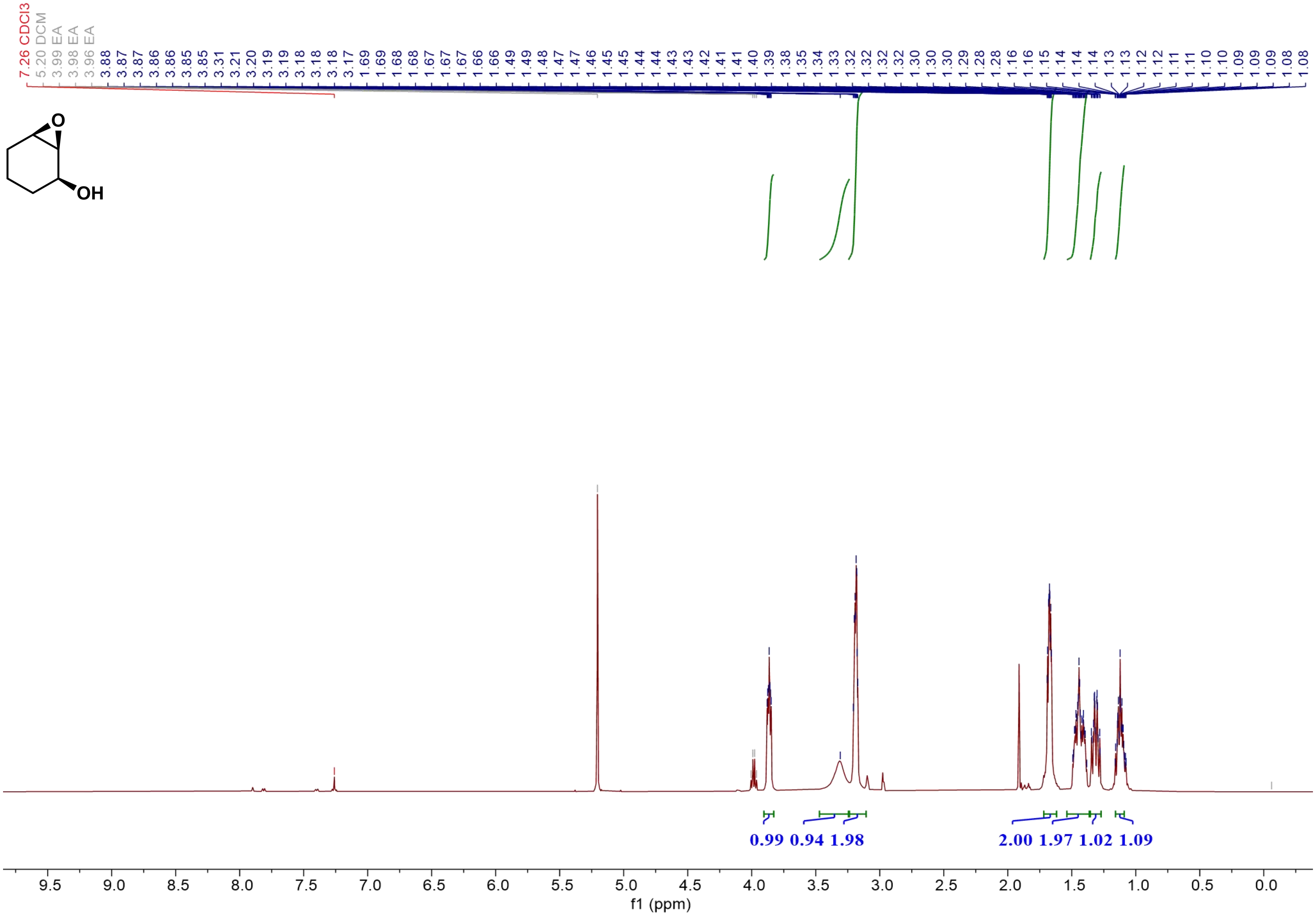
^{1}H NMR Spectrum of compound SI-7 (500 MHz, $CDCl_3$)



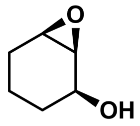
^{13}C NMR Spectrum of compound SI-7 (126 MHz, CDCl$_3$)

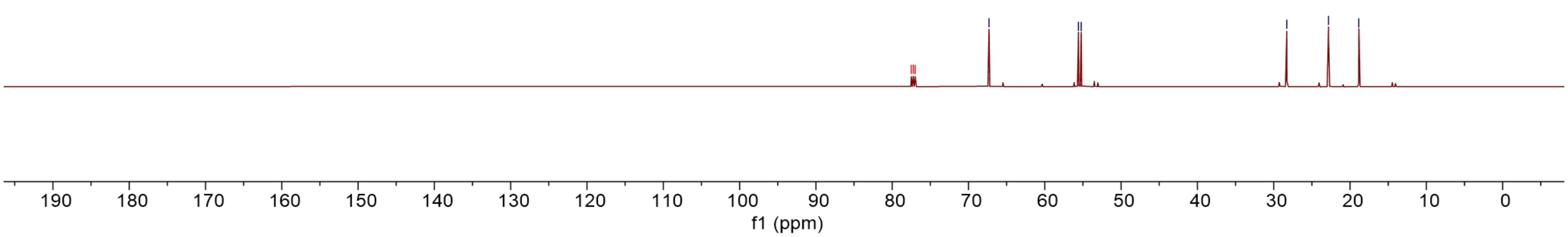


^{1}H NMR Spectrum of compound SI-8 (500 MHz, CDCl$_3$)

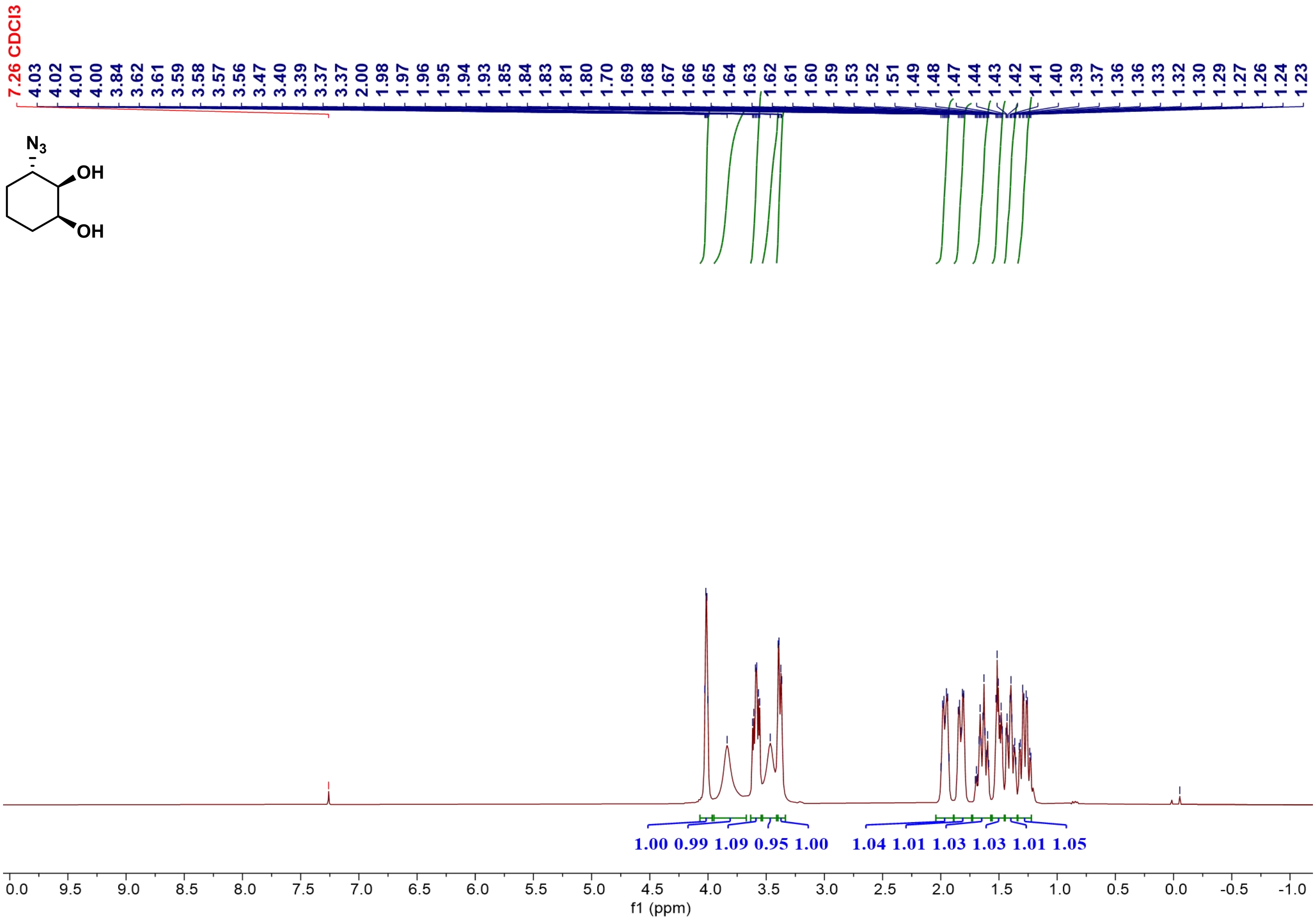


^{13}C NMR Spectrum of compound SI-8 (126 MHz, $CDCl_3$)

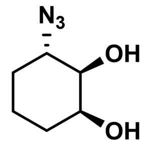


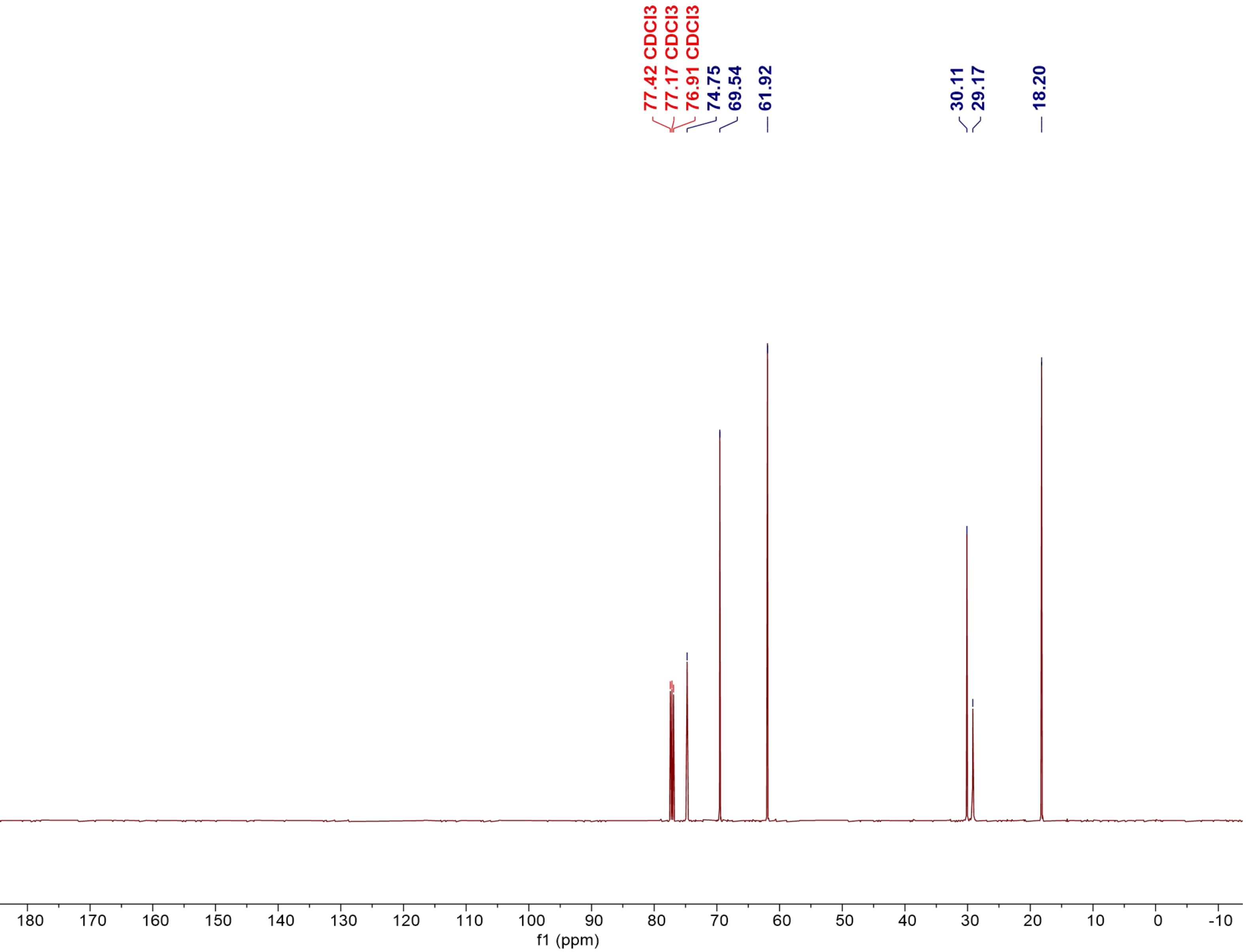


^{1}H NMR Spectrum of compound SI-9 (400 MHz, $CDCl_3$)

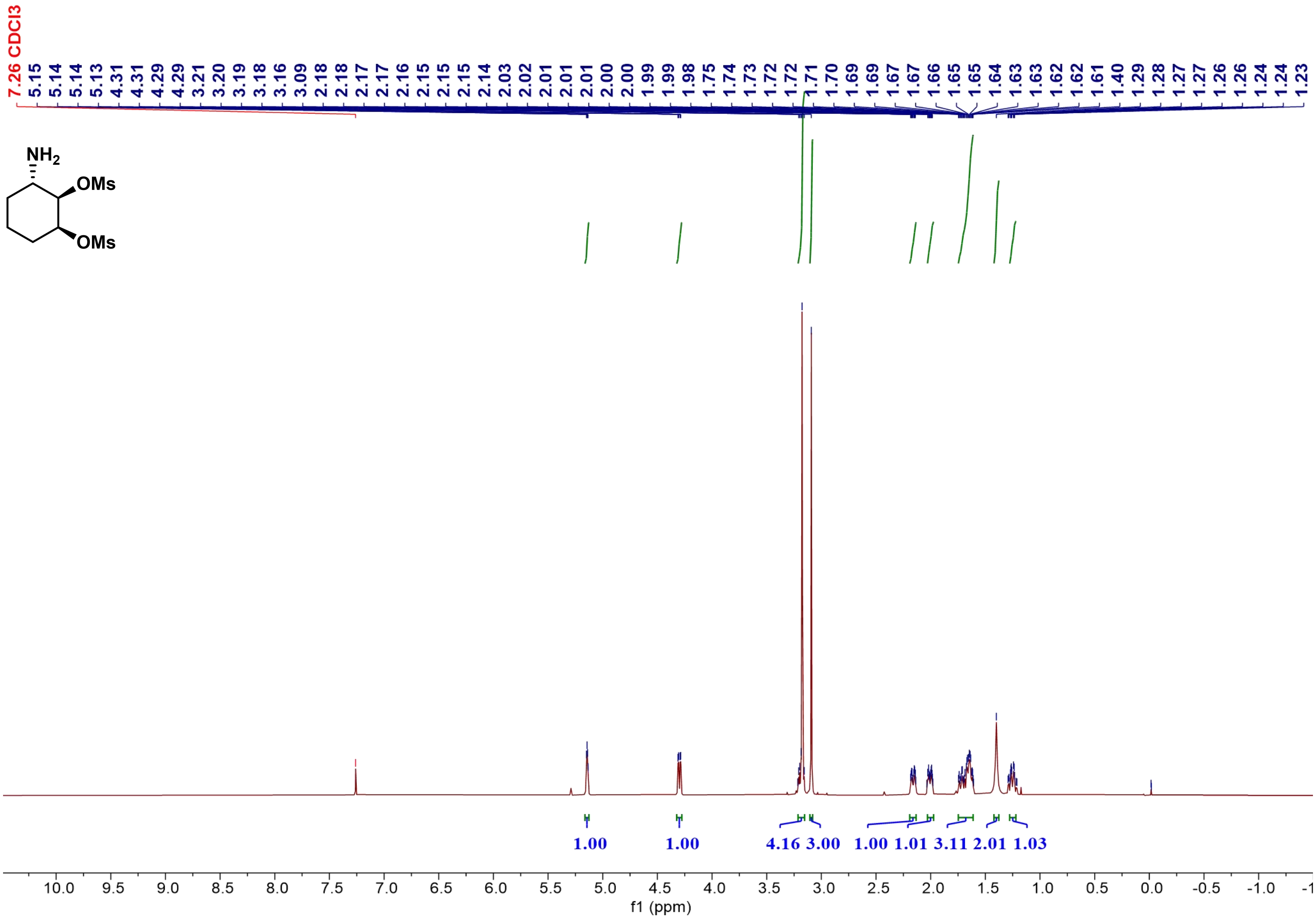


^{13}C NMR Spectrum of compound SI-9 (126 MHz, CDCl$_3$)

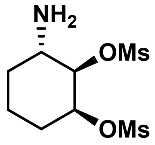


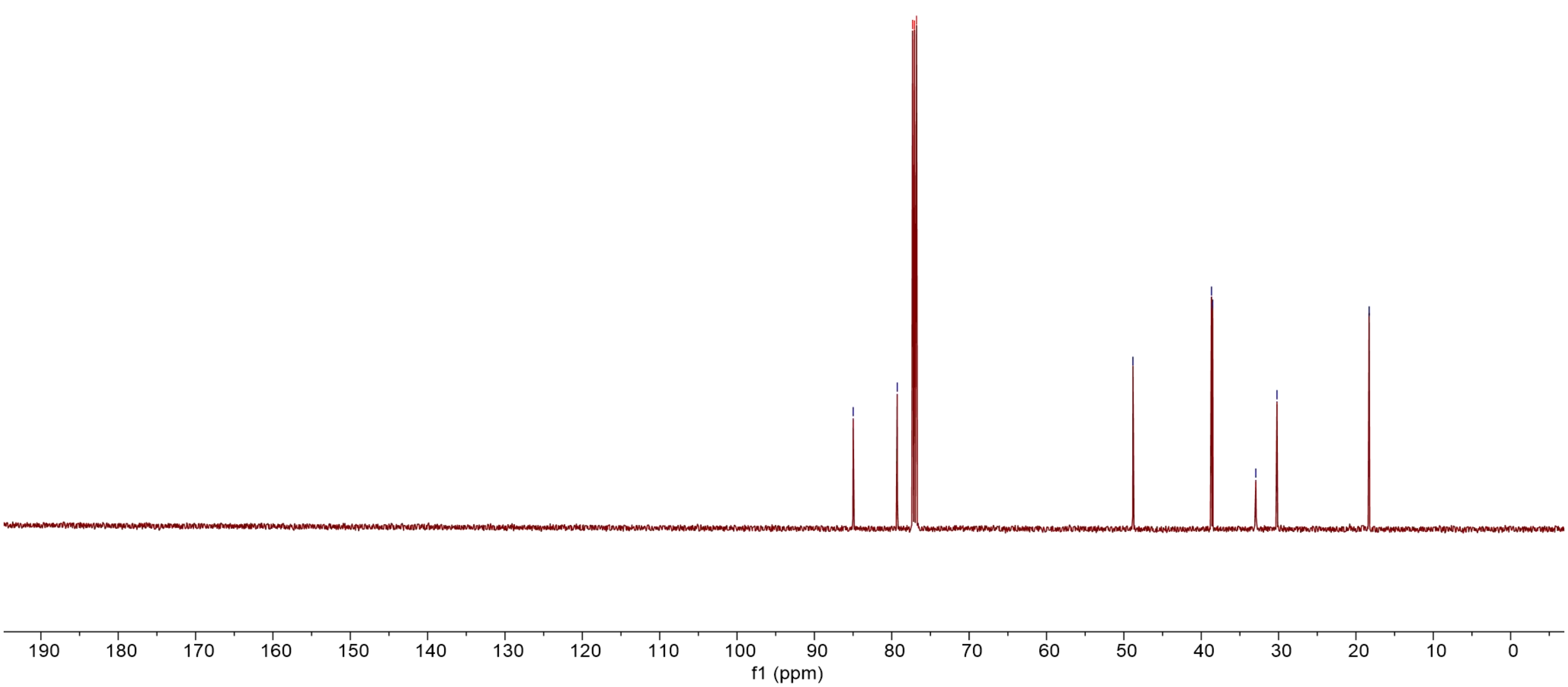


^{1}H NMR Spectrum of compound SI-10 (500 MHz, $CDCl_3$)

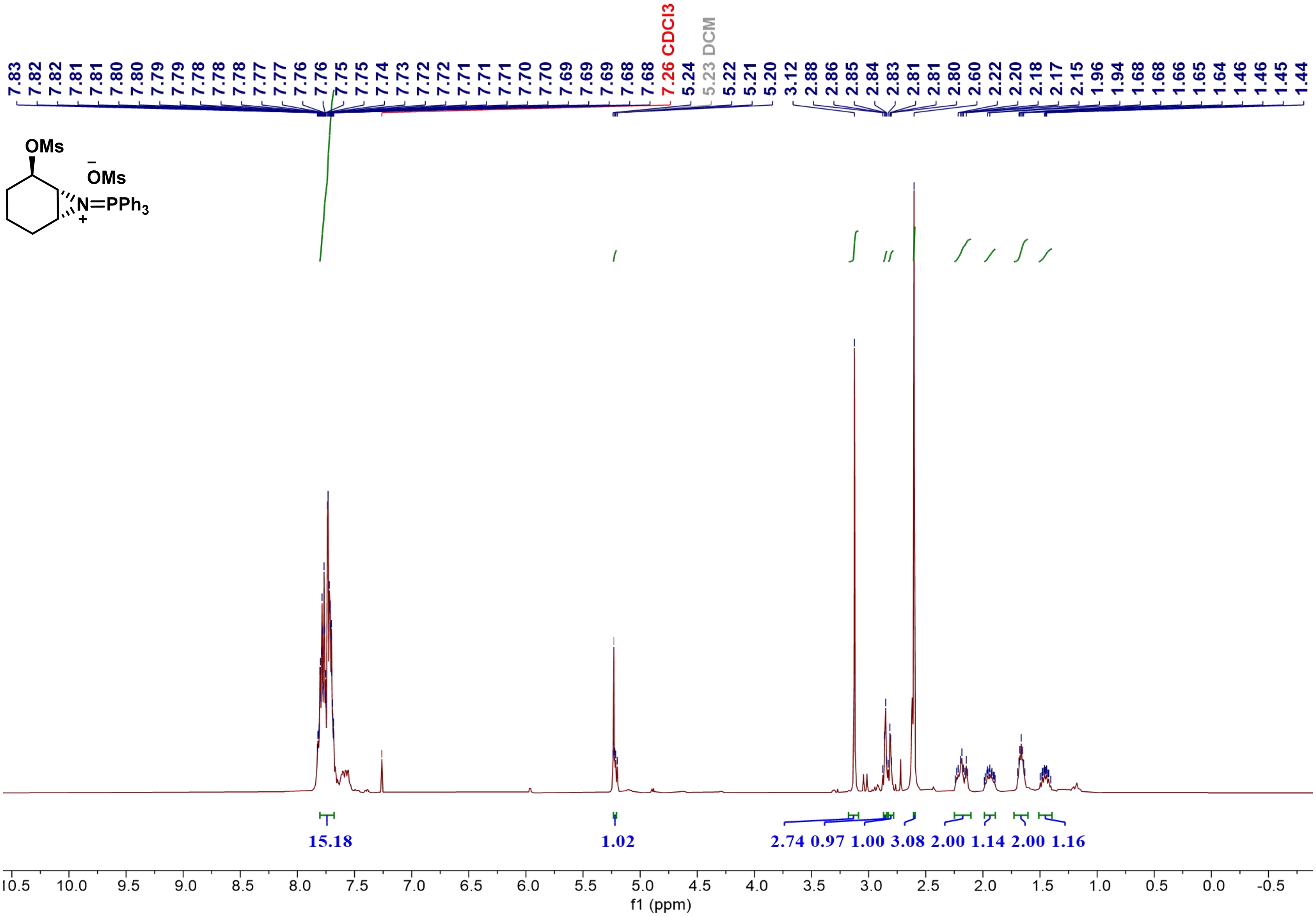


^{13}C NMR Spectrum of compound SI-10 (126 MHz, CDCl$_3$)

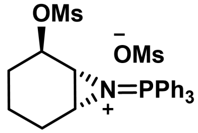


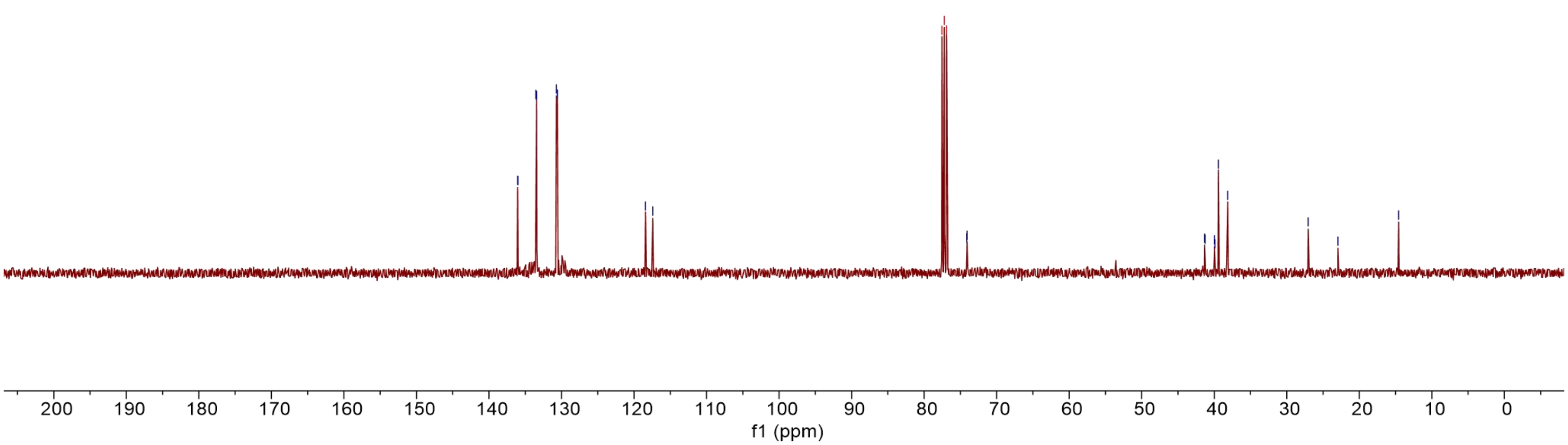


^{1}H NMR Spectrum of compound SI-11 (400 MHz, $CDCl_3$)

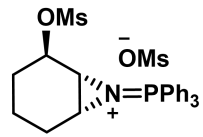


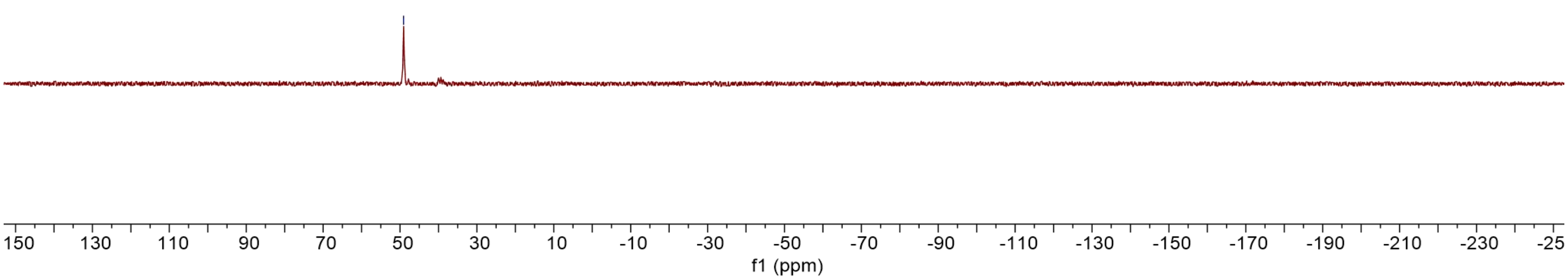
^{13}C NMR Spectrum of compound SI-11 (101 MHz, CDCl$_3$)



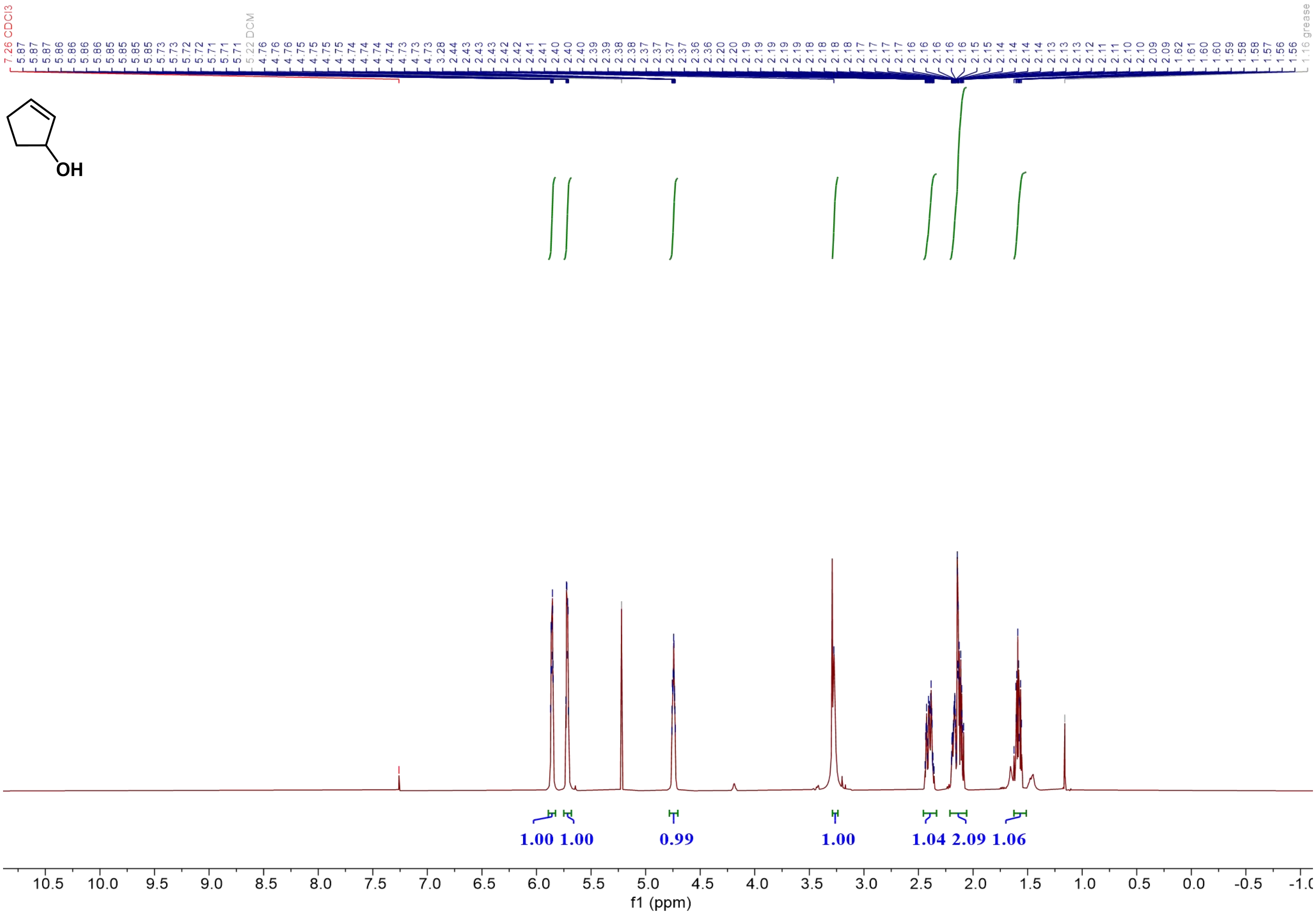


^{31}P NMR Spectrum of compound SI-11 (162 MHz, $CDCl_3$)

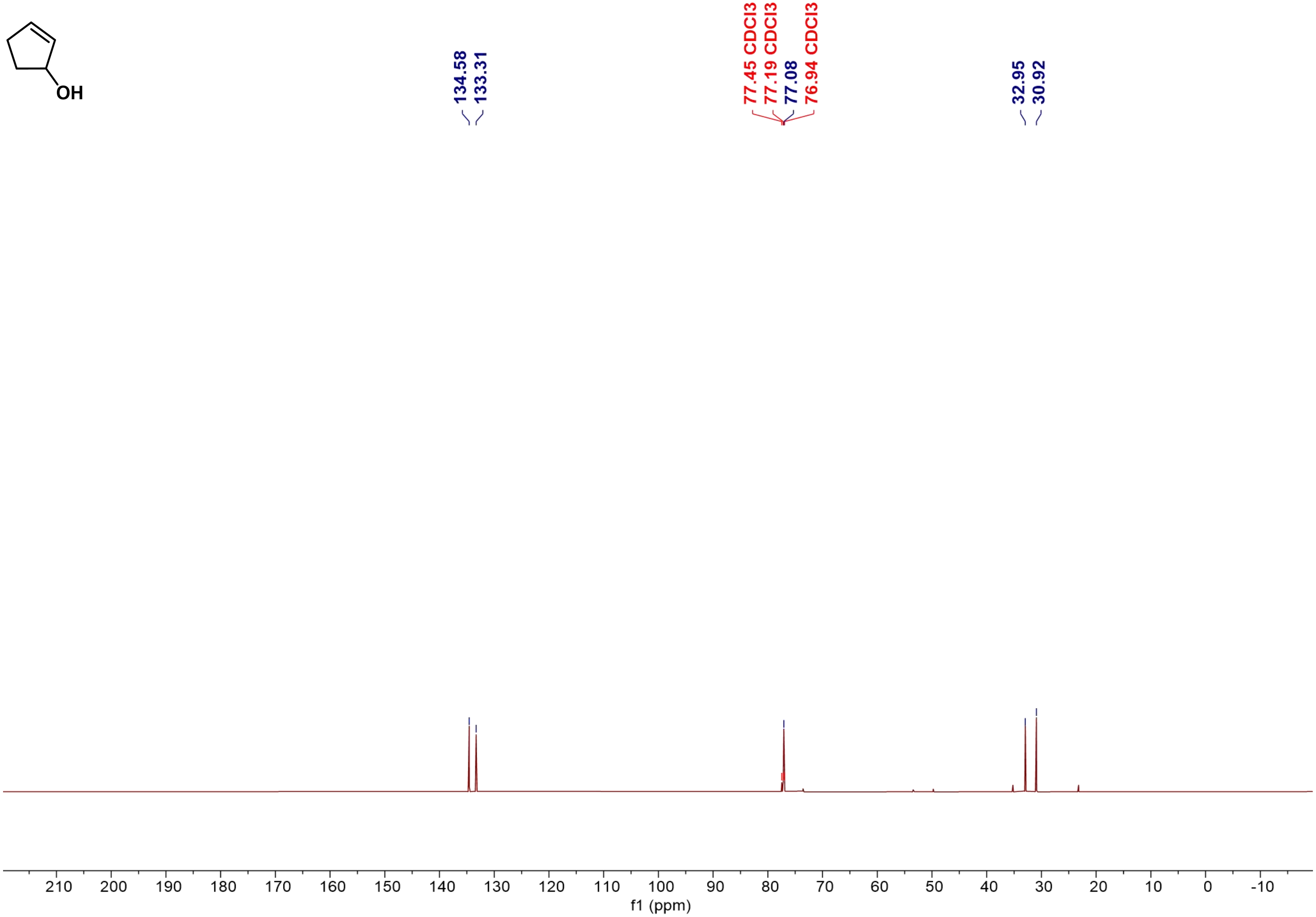




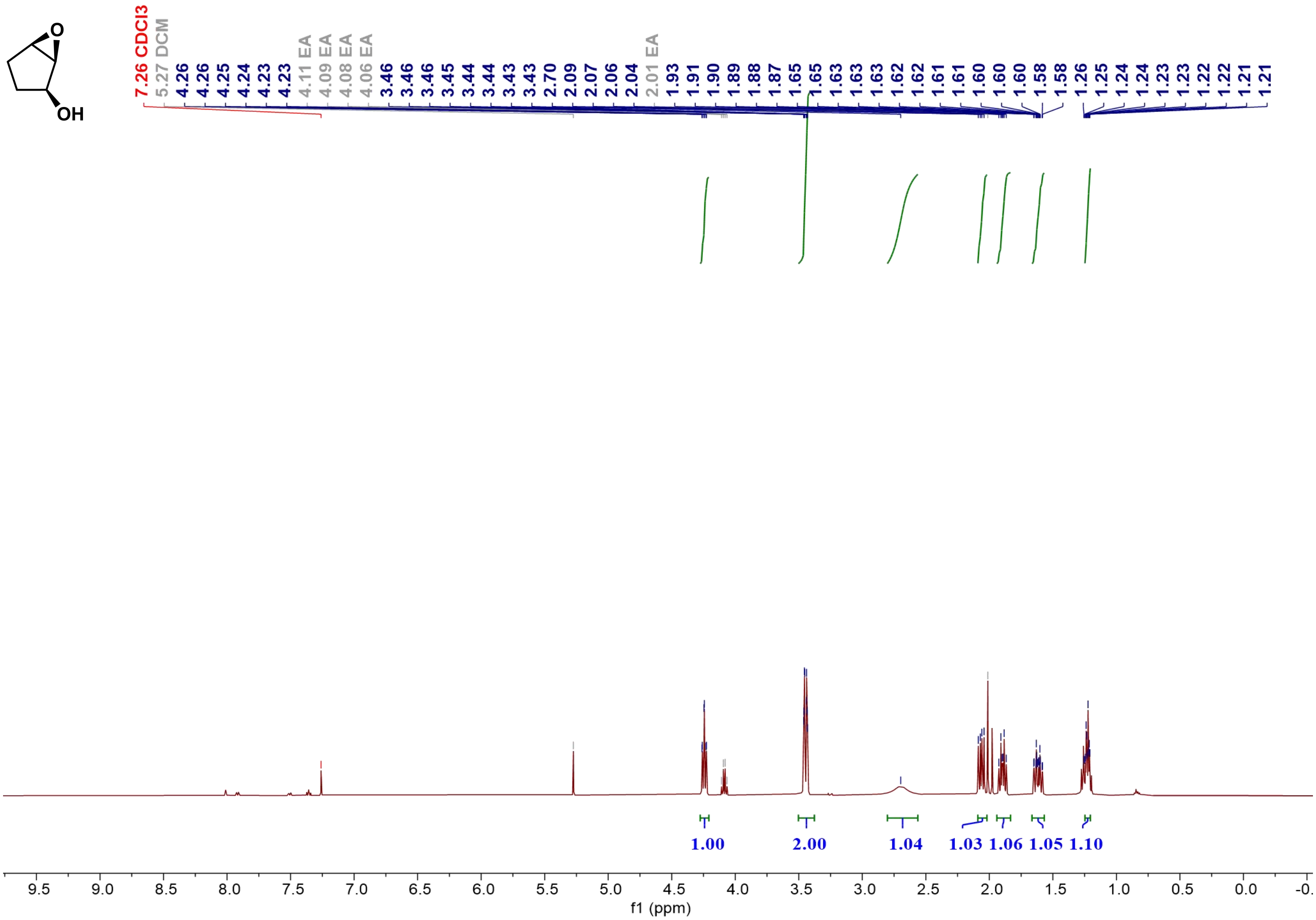
^{1}H NMR Spectrum of compound SI-12 (500 MHz, $CDCl_3$)



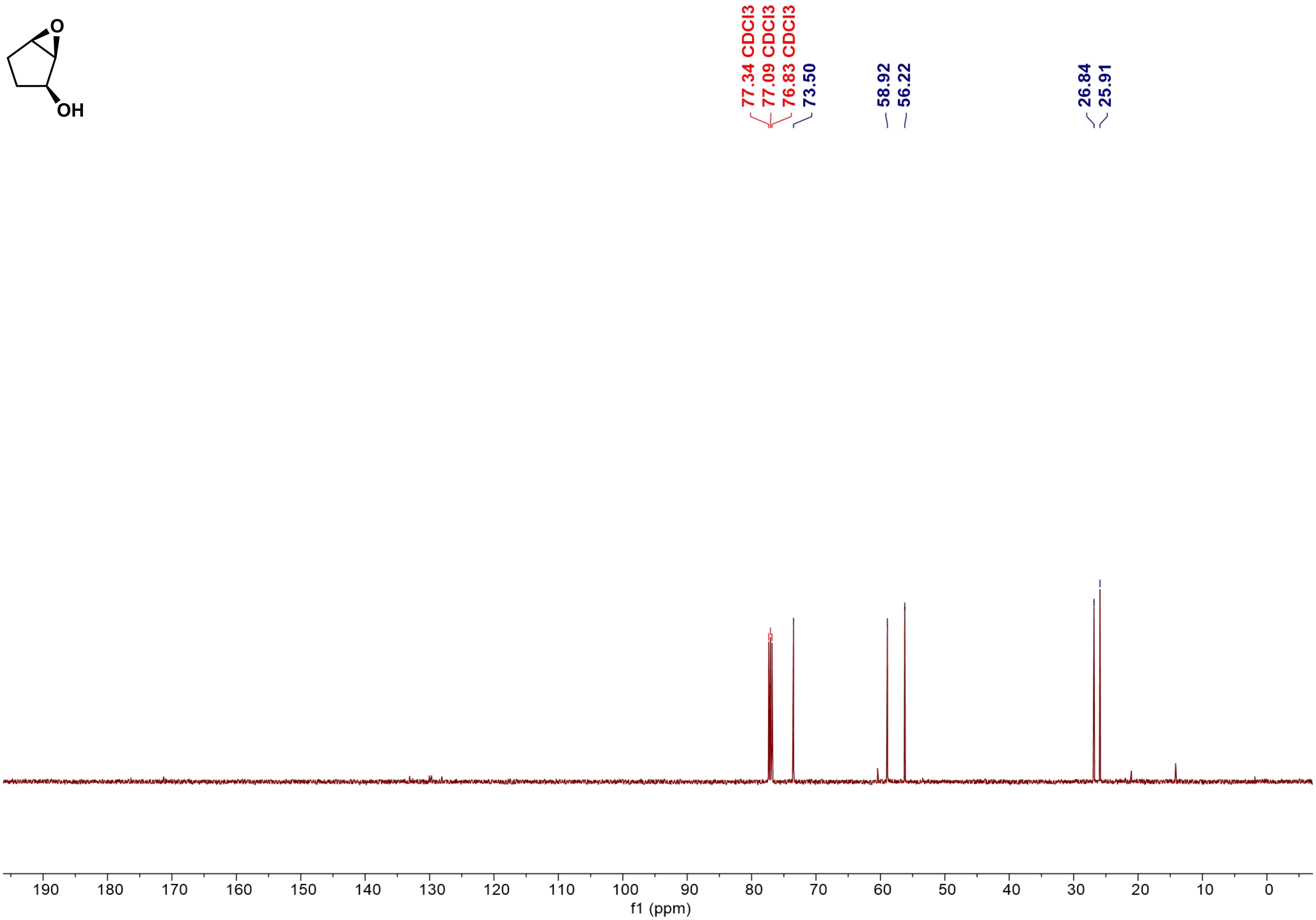
^{13}C NMR Spectrum of compound SI-12 (126 MHz, $CDCl_3$)



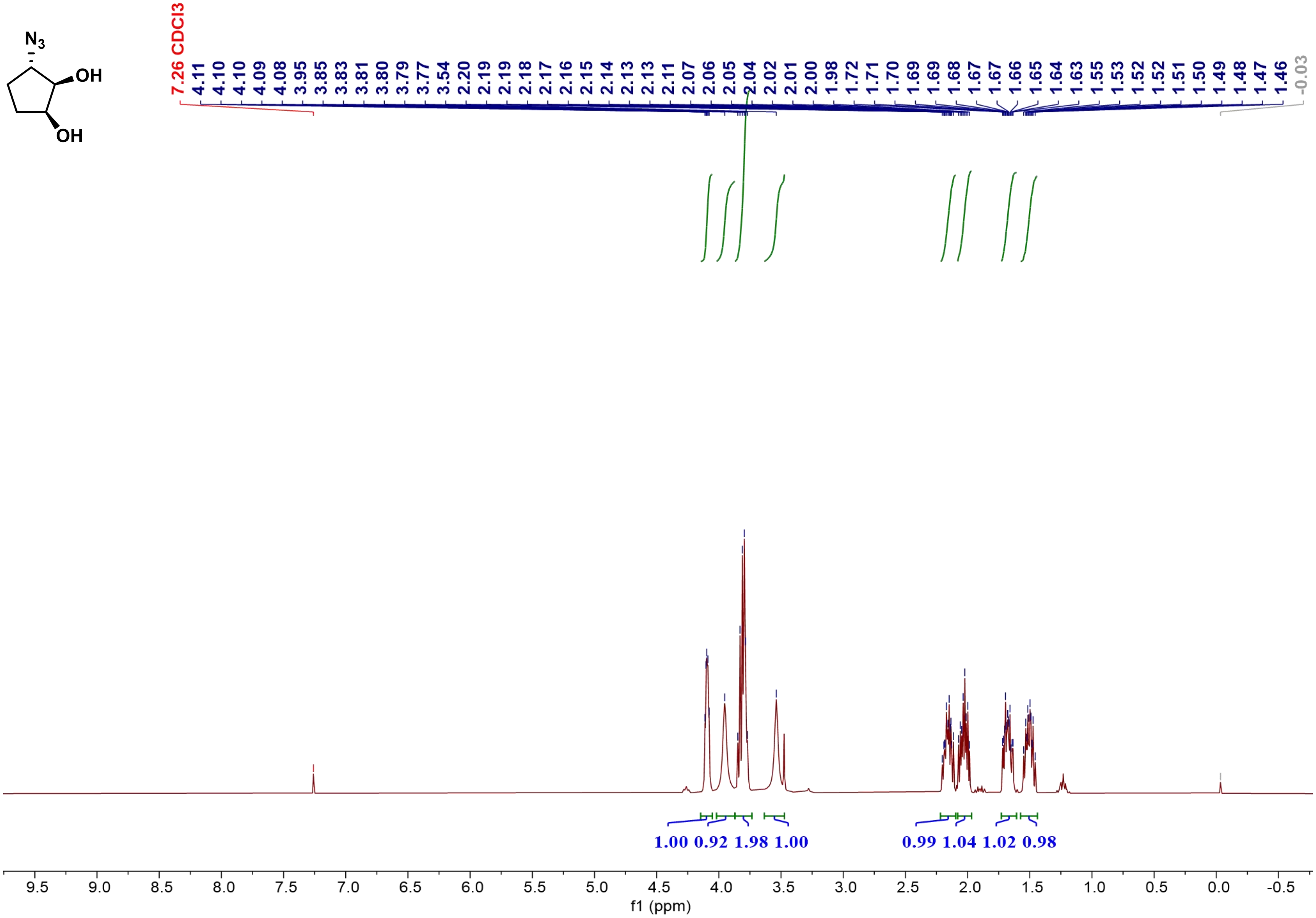
^{1}H NMR Spectrum of compound SI-13 (500 MHz, $CDCl_3$)



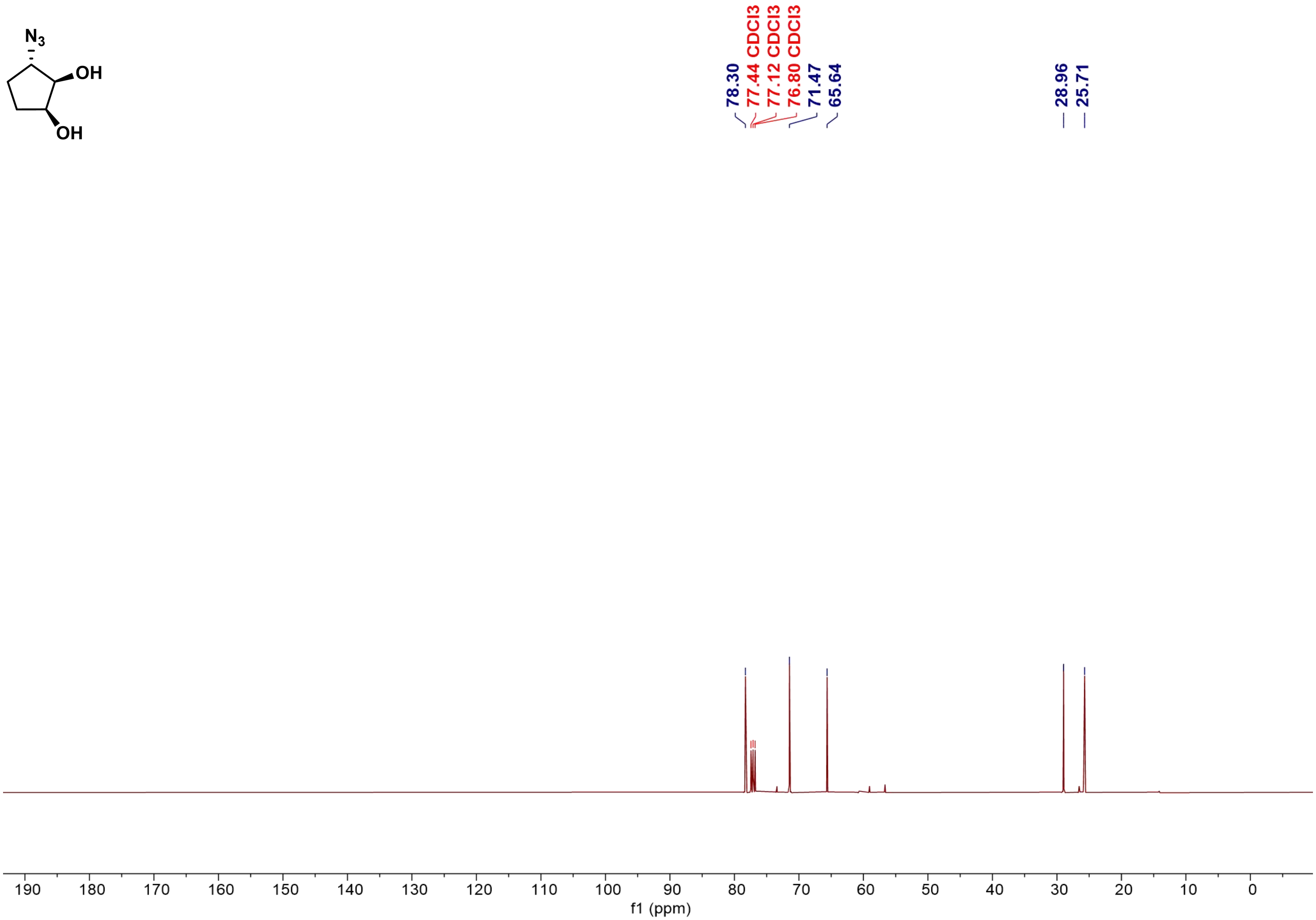
^{13}C NMR Spectrum of compound SI-13 (126 MHz, $CDCl_3$)



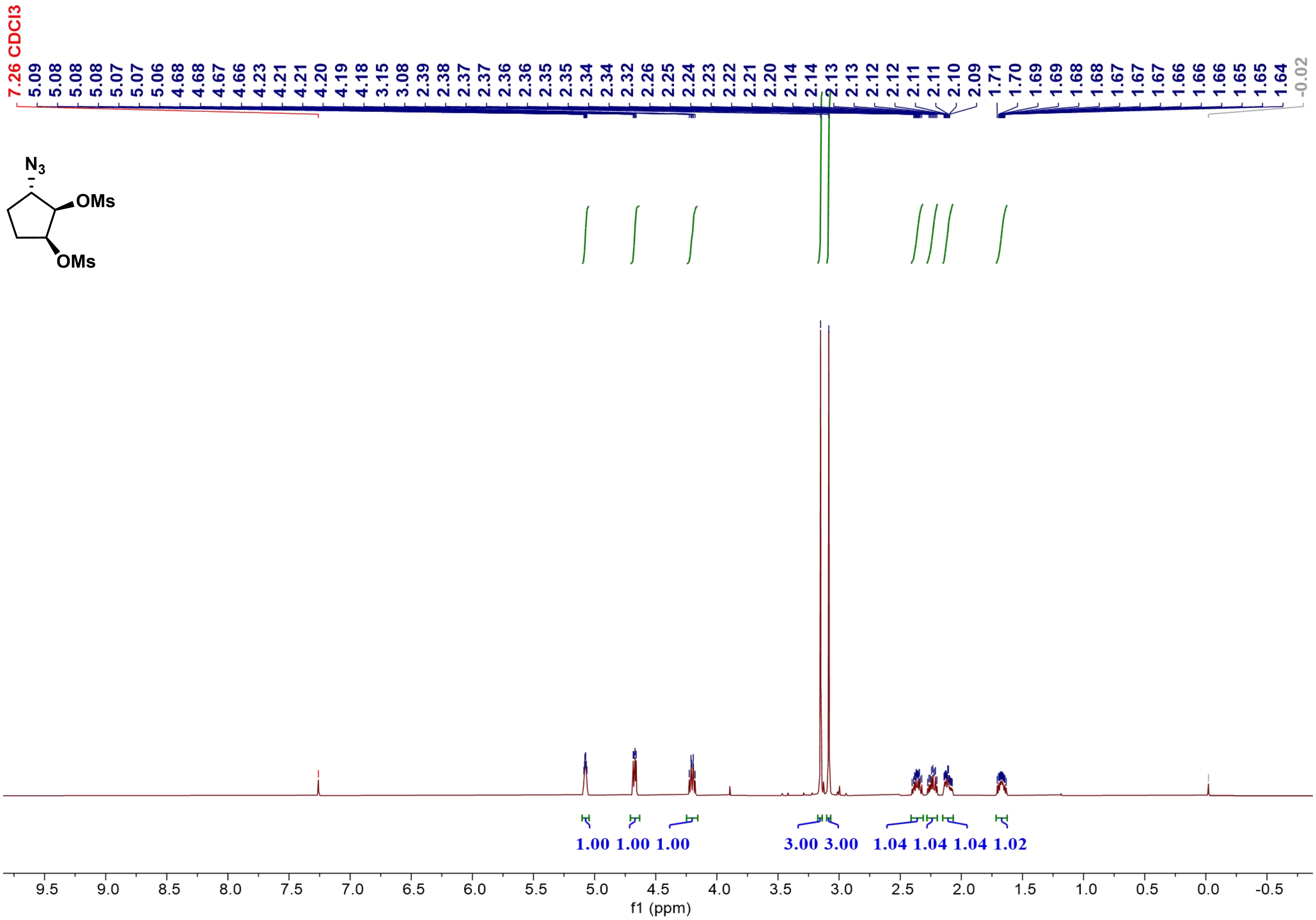
^{1}H NMR Spectrum of compound SI-14 (400 MHz, $CDCl_3$)



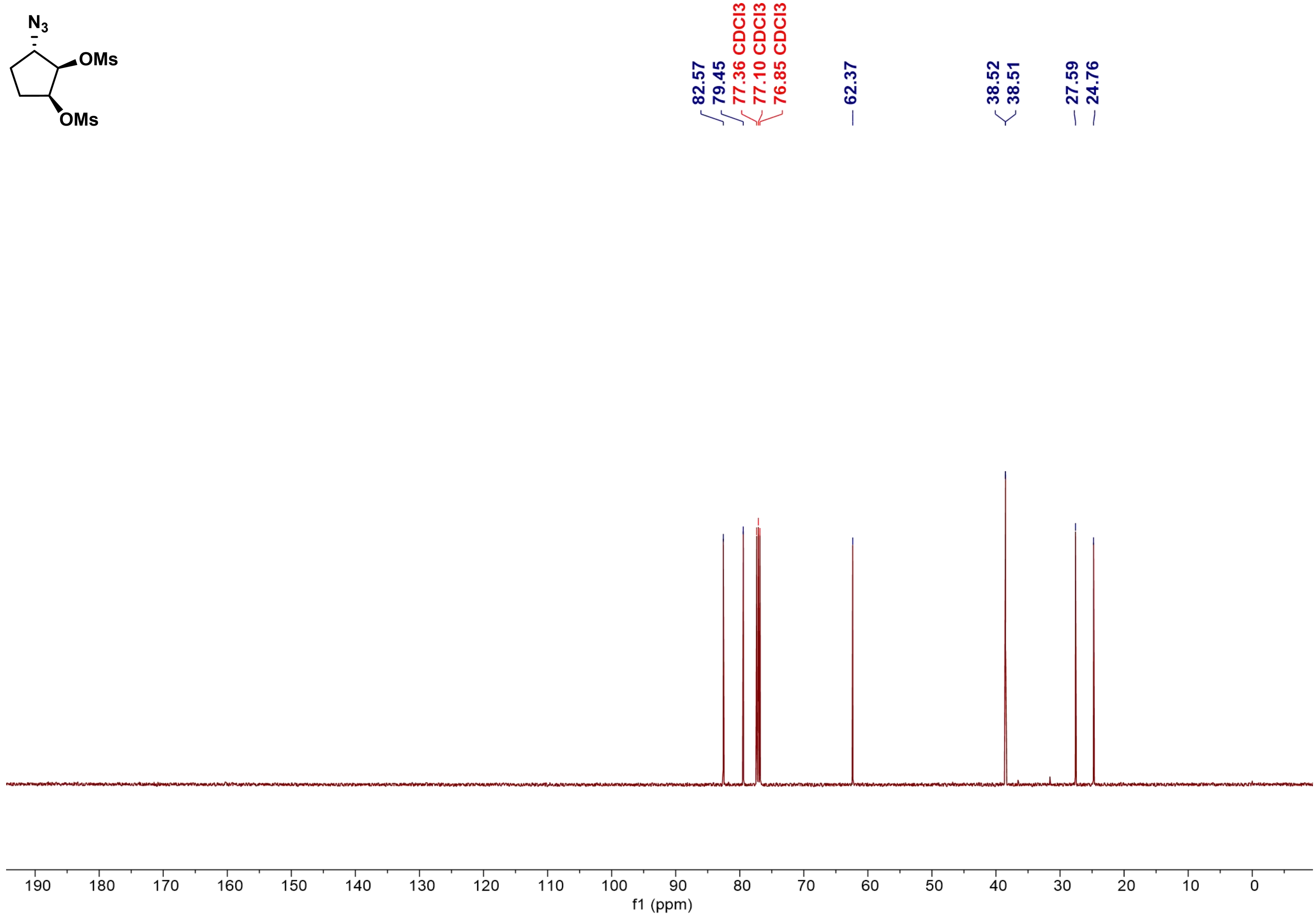
^{13}C NMR Spectrum of compound SI-14 (101 MHz, $CDCl_3$)



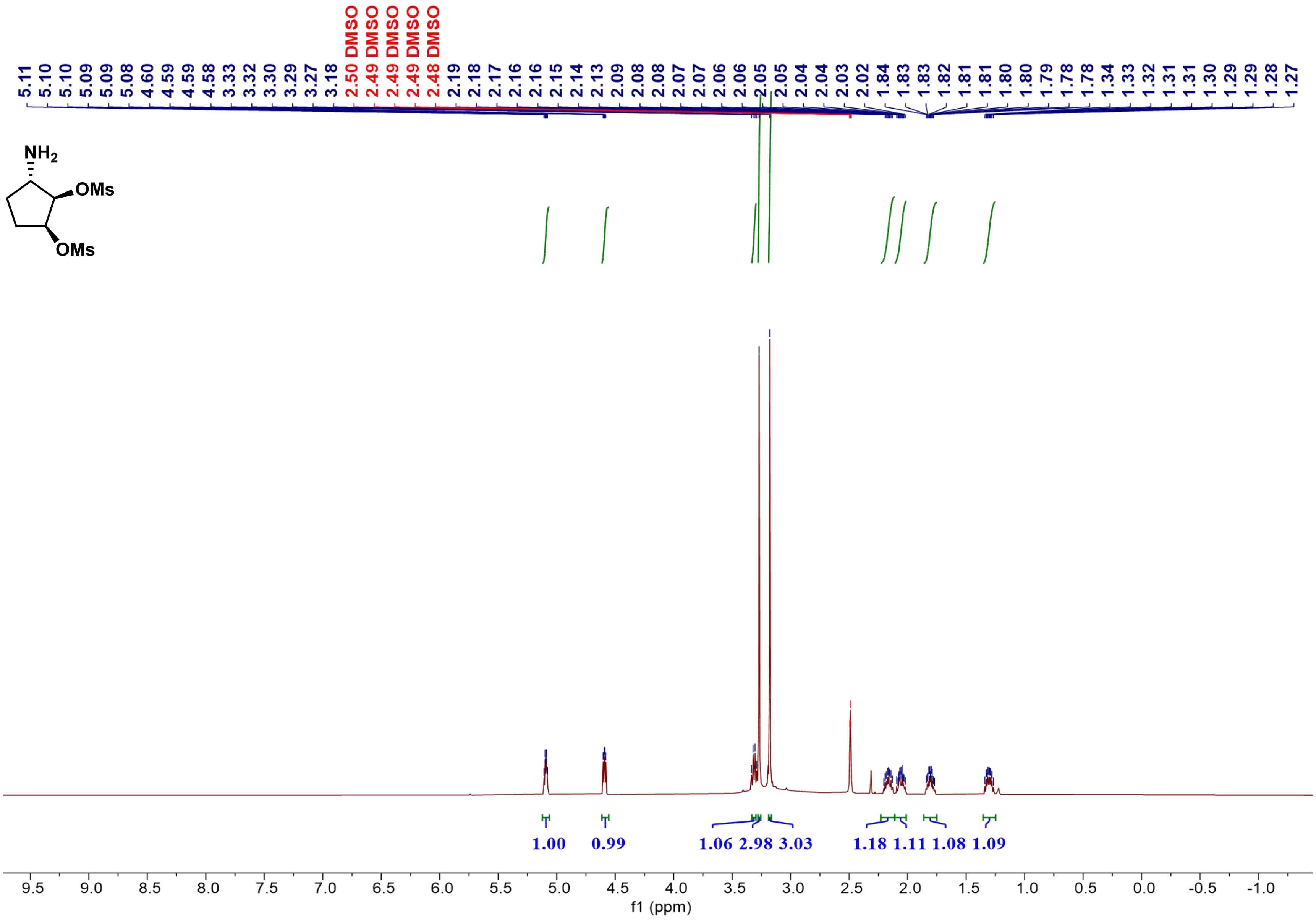
^{1}H NMR Spectrum of compound SI-15 (500 MHz, $CDCl_3$)



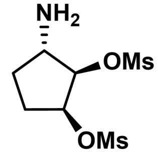
^{13}C NMR Spectrum of compound SI-15 (126 MHz, $CDCl_3$)

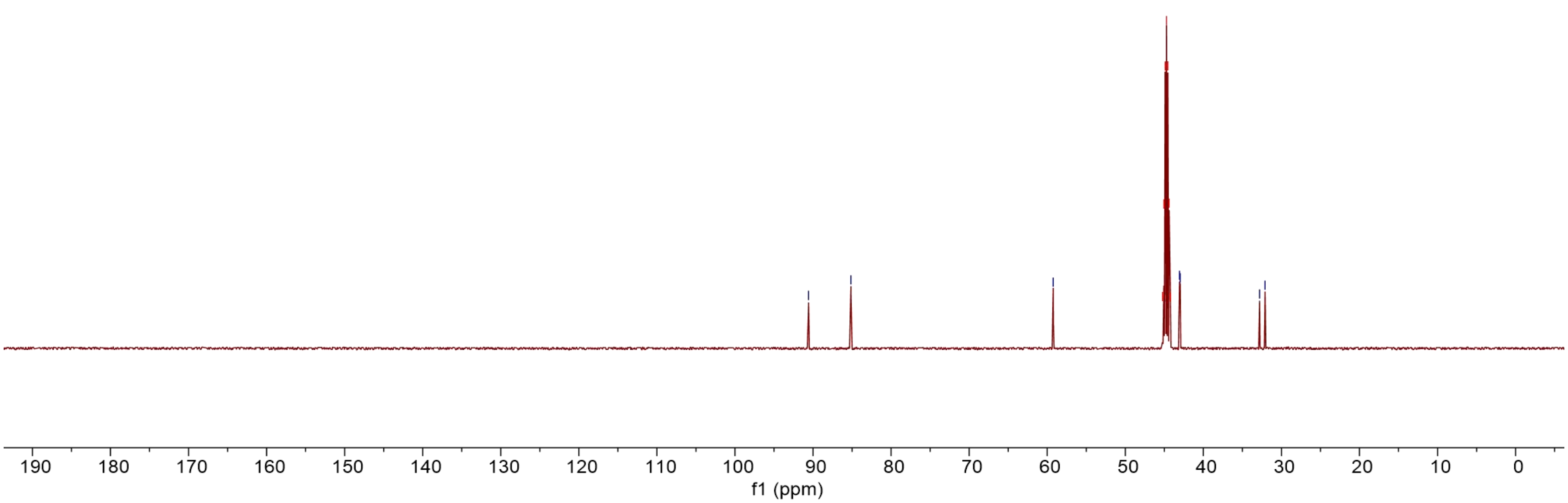


^{1}H NMR Spectrum of compound SI-16 (500 MHz, DMSO-d_6)

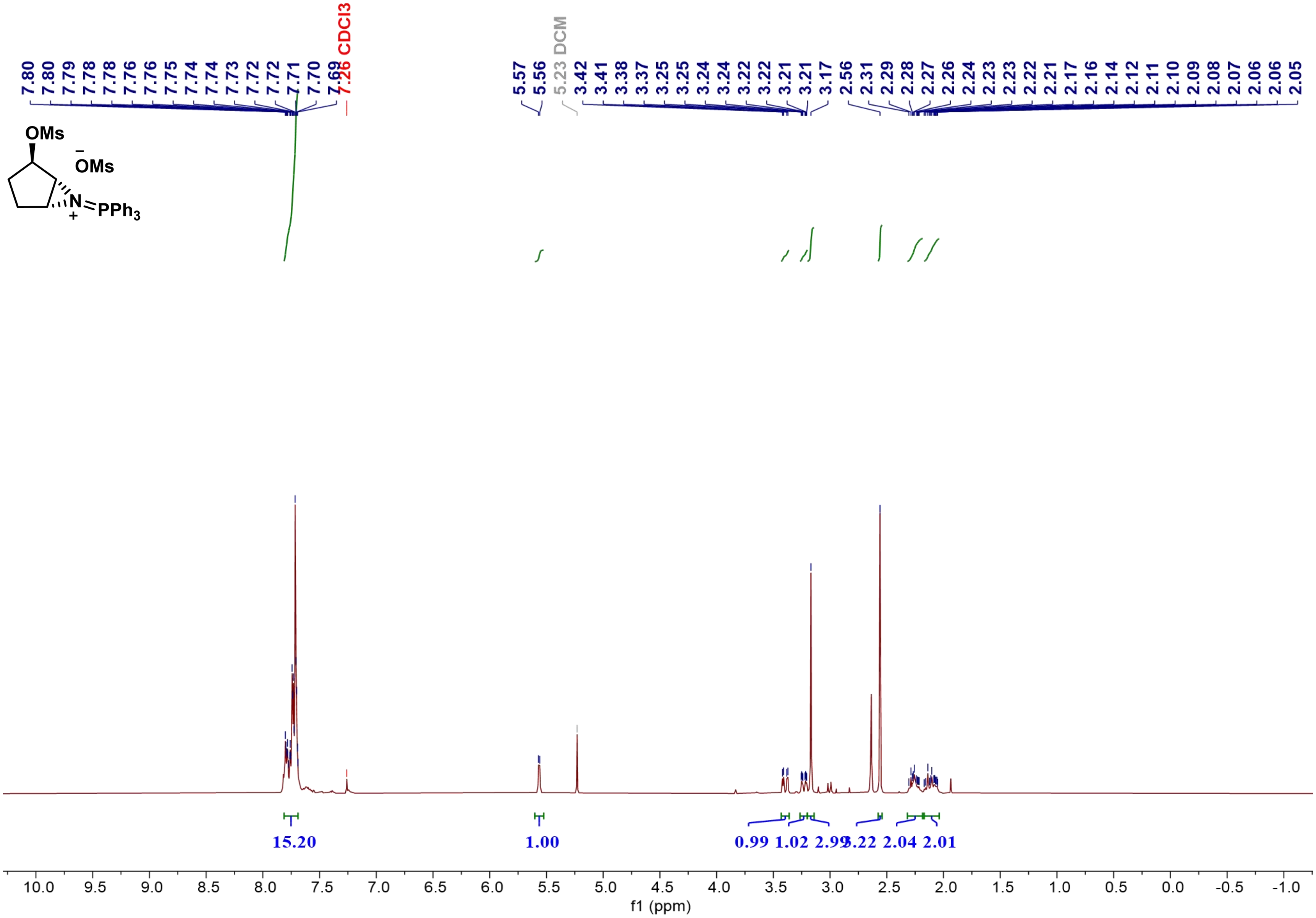


^{13}C NMR Spectrum of compound SI-16 (126 MHz, DMSO-d_6)

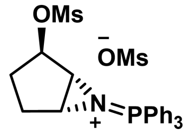


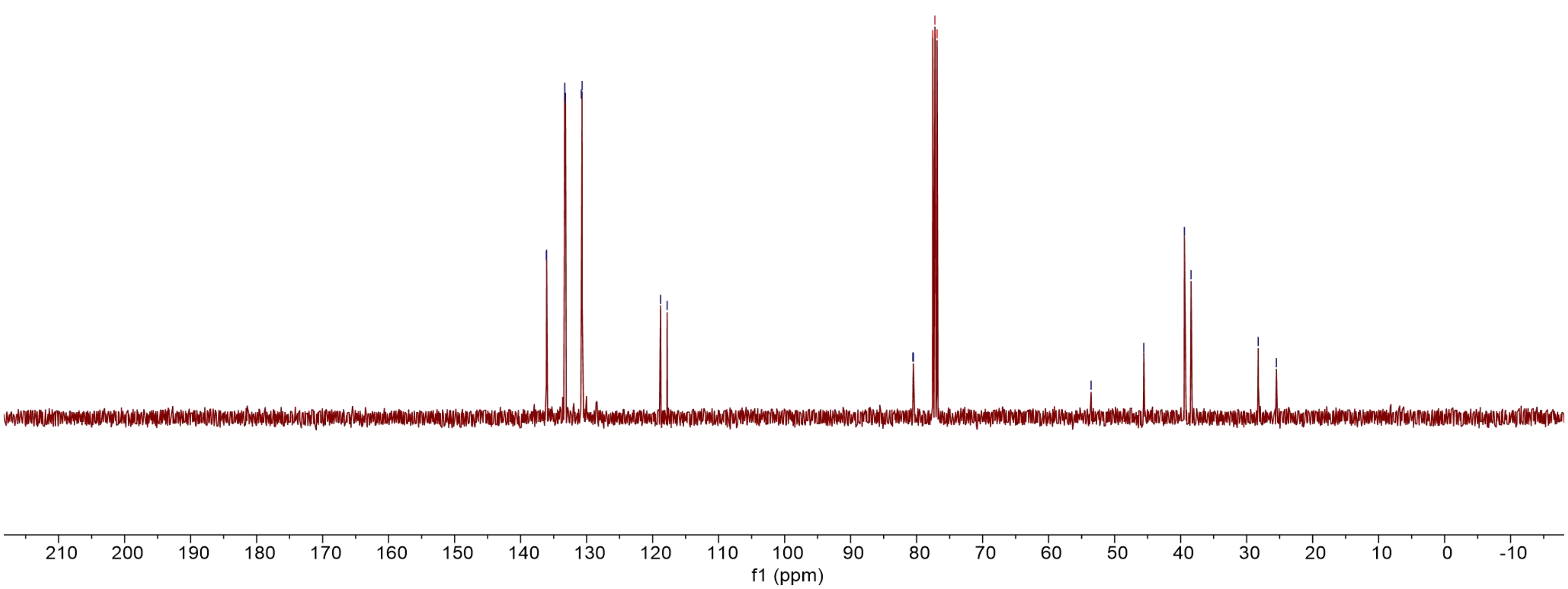


^{1}H NMR Spectrum of compound SI-17 (400 MHz, $CDCl_3$)

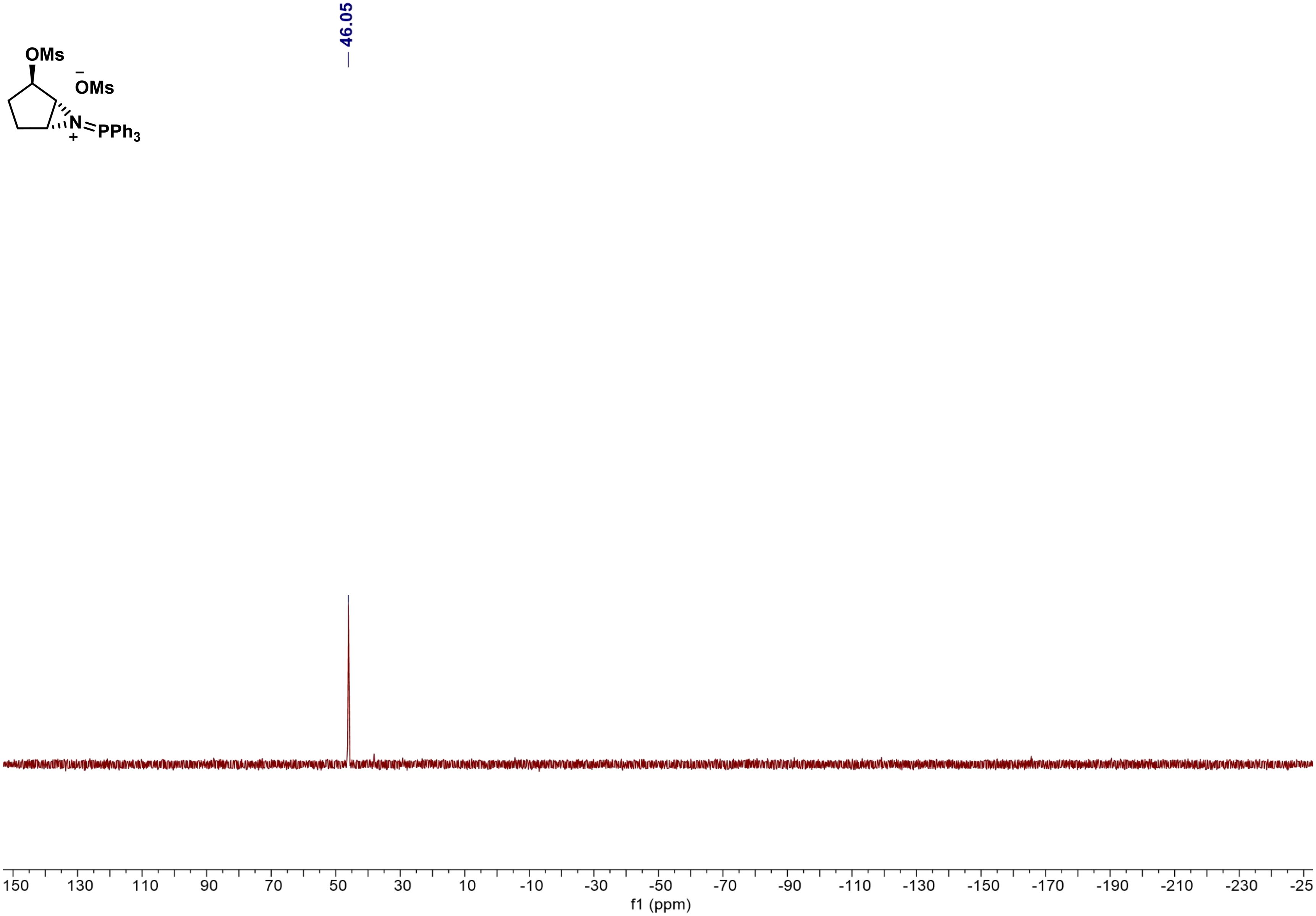


^{13}C NMR Spectrum of compound SI-17 (101 MHz, CDCl$_3$)

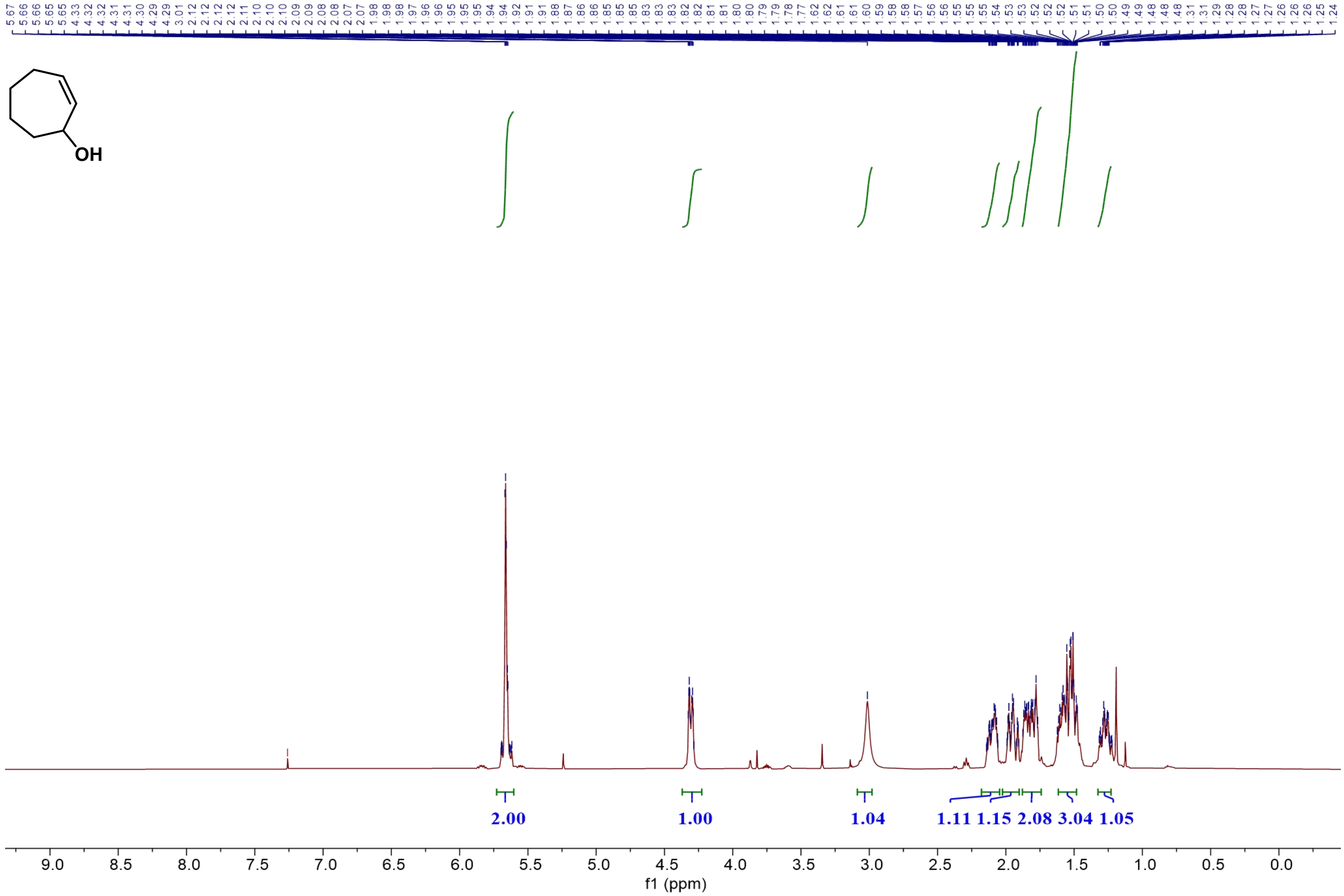




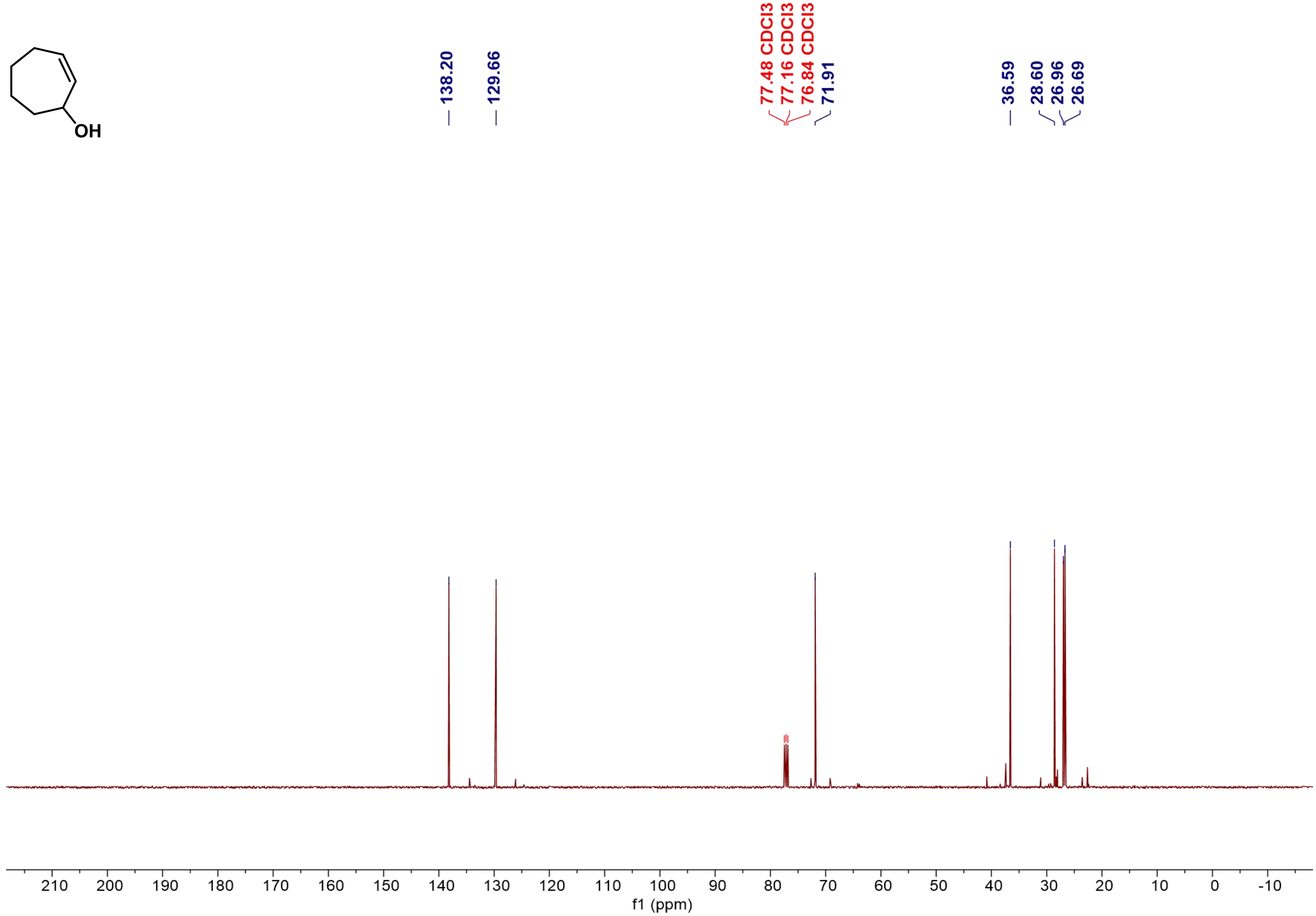
^{31}P NMR Spectrum of compound SI-17 (162 MHz, CDCl$_3$)



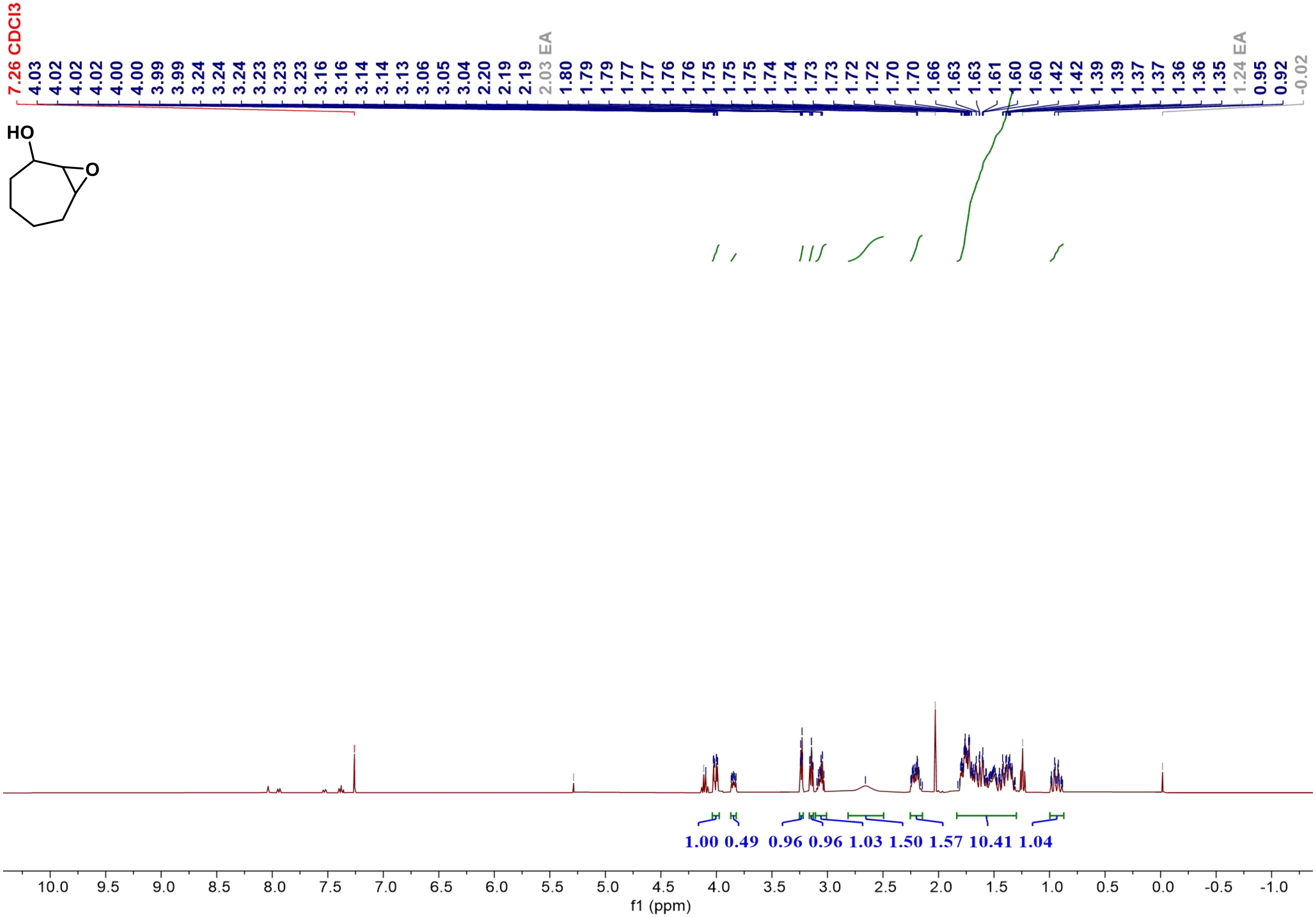
^{1}H NMR Spectrum of compound SI-18 (400 MHz, $CDCl_3$)



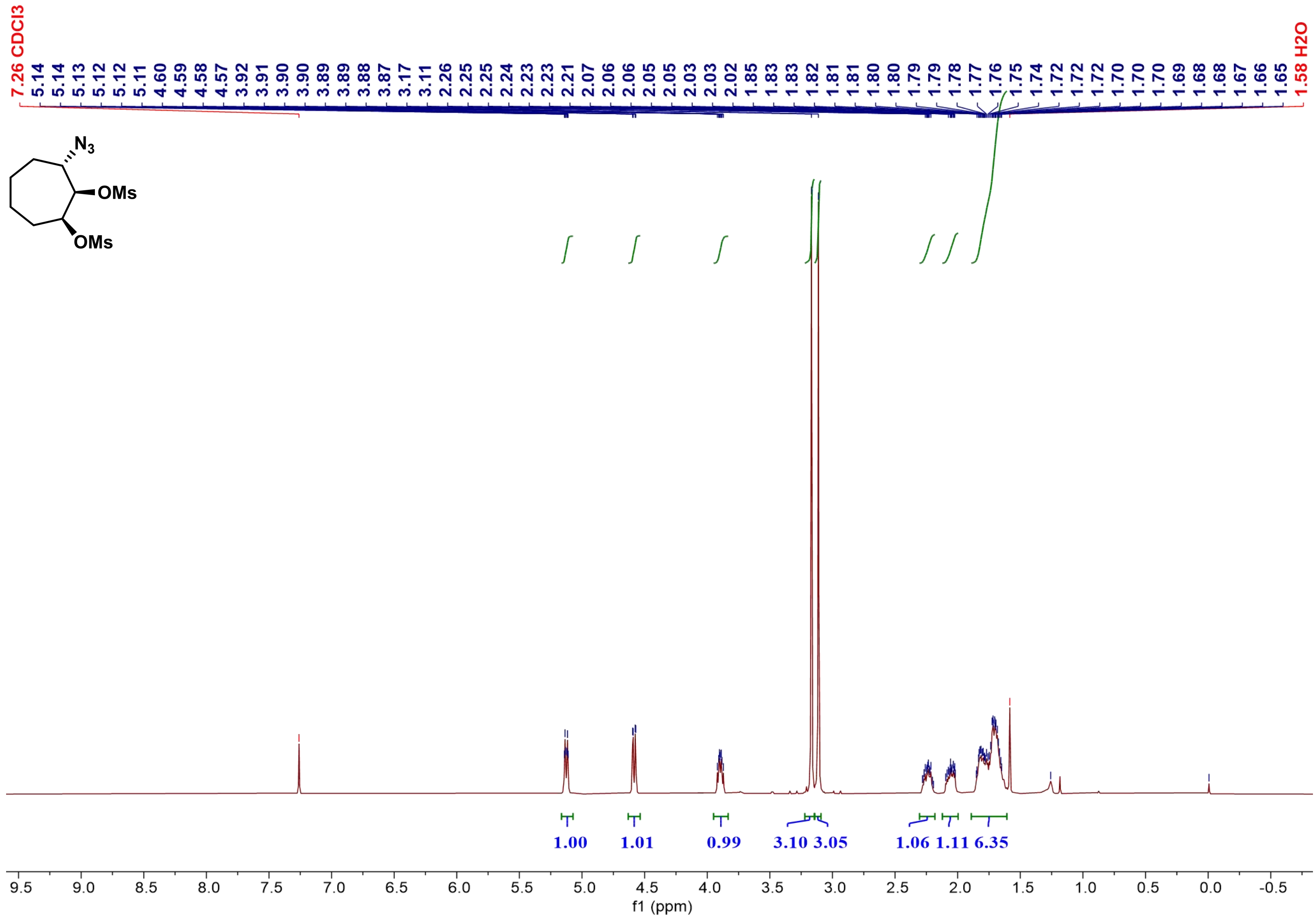
^{13}C NMR Spectrum of compound SI-18 (101 MHz, CDCl$_3$)



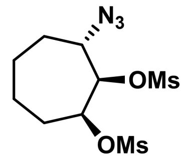
^{1}H NMR Spectrum of compound SI-19 (400 MHz, CDCl$_3$)

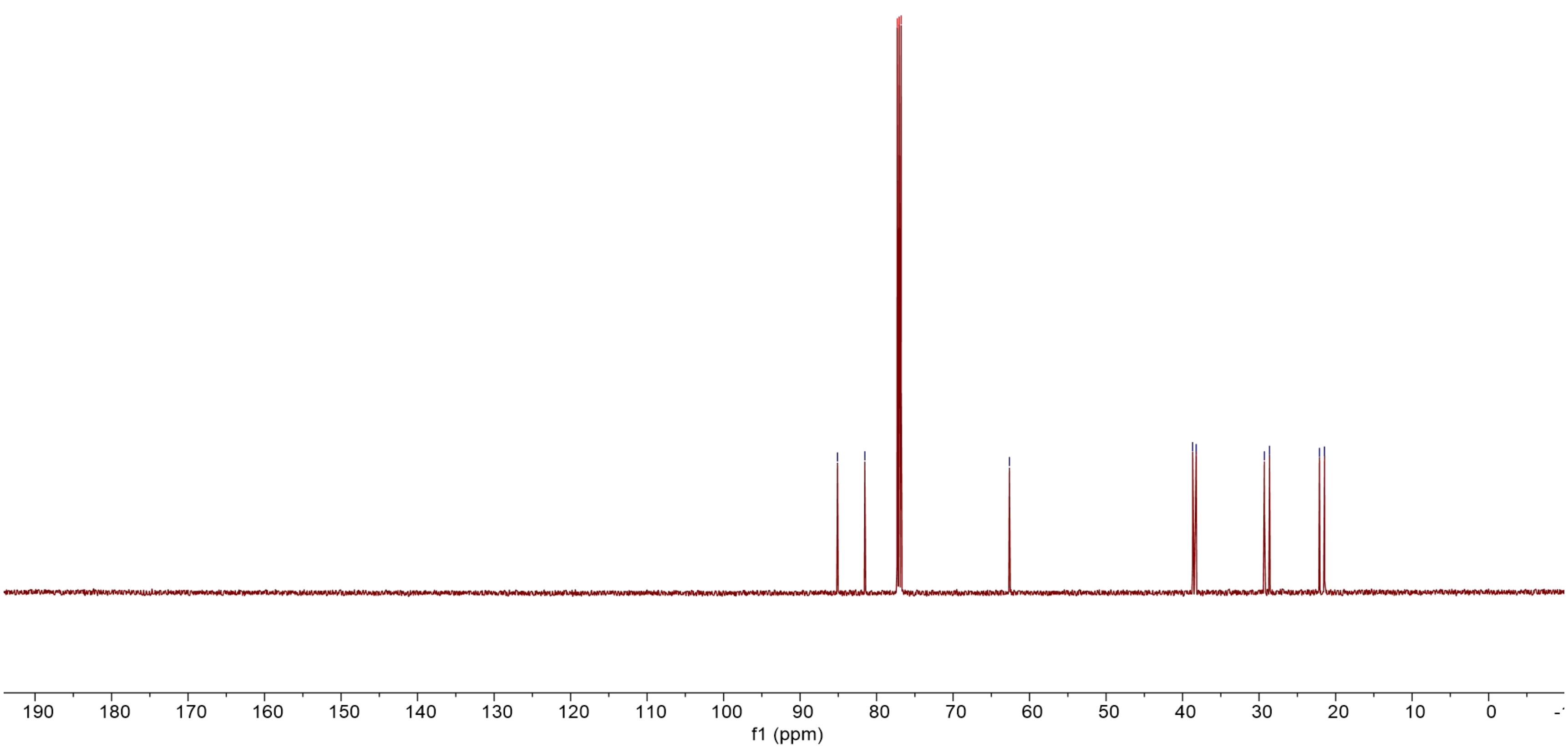


^{1}H NMR Spectrum of compound SI-21 (400 MHz, CDCl$_3$)

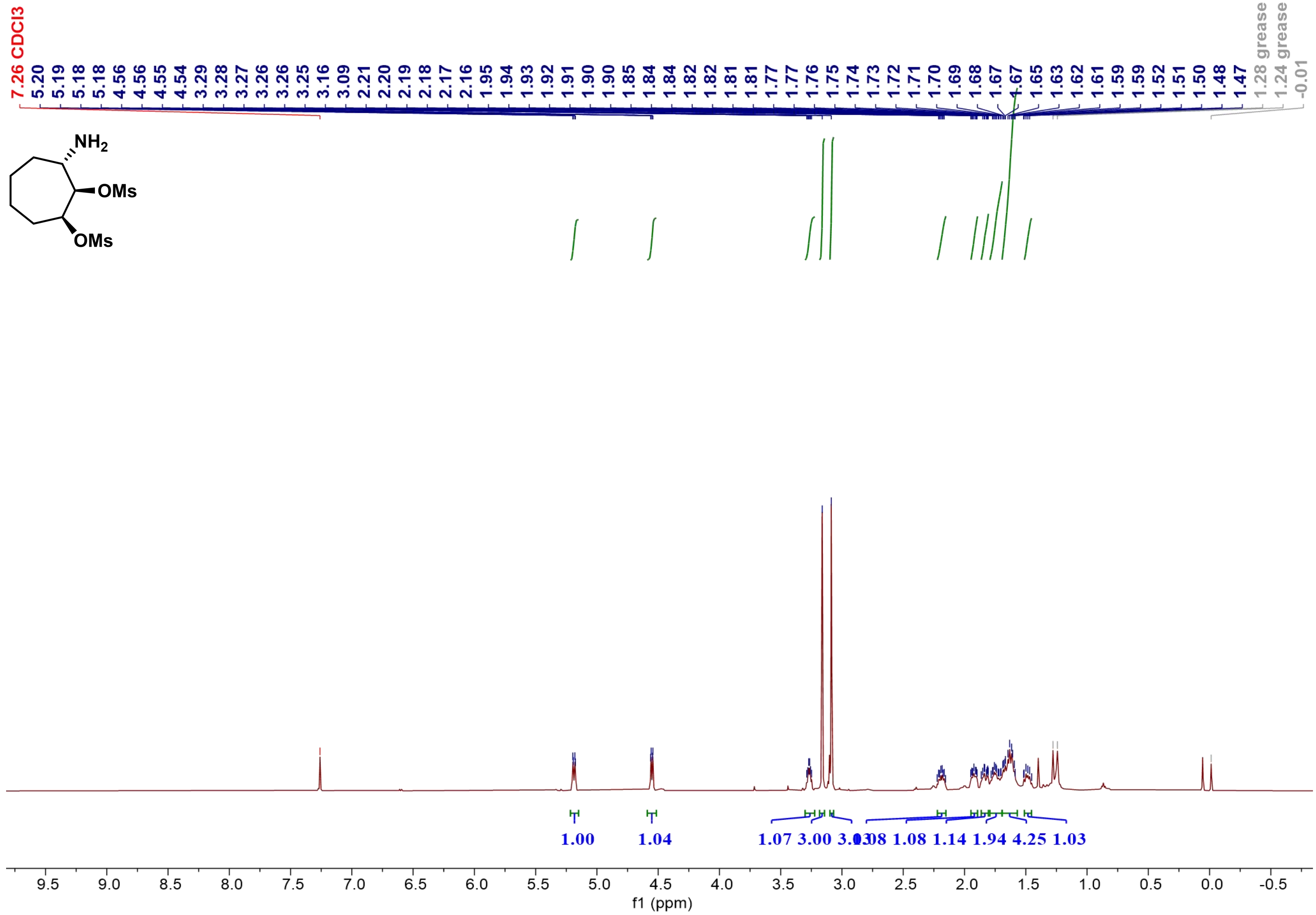


^{13}C NMR Spectrum of compound SI-21 (126 MHz, $CDCl_3$)

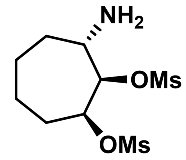


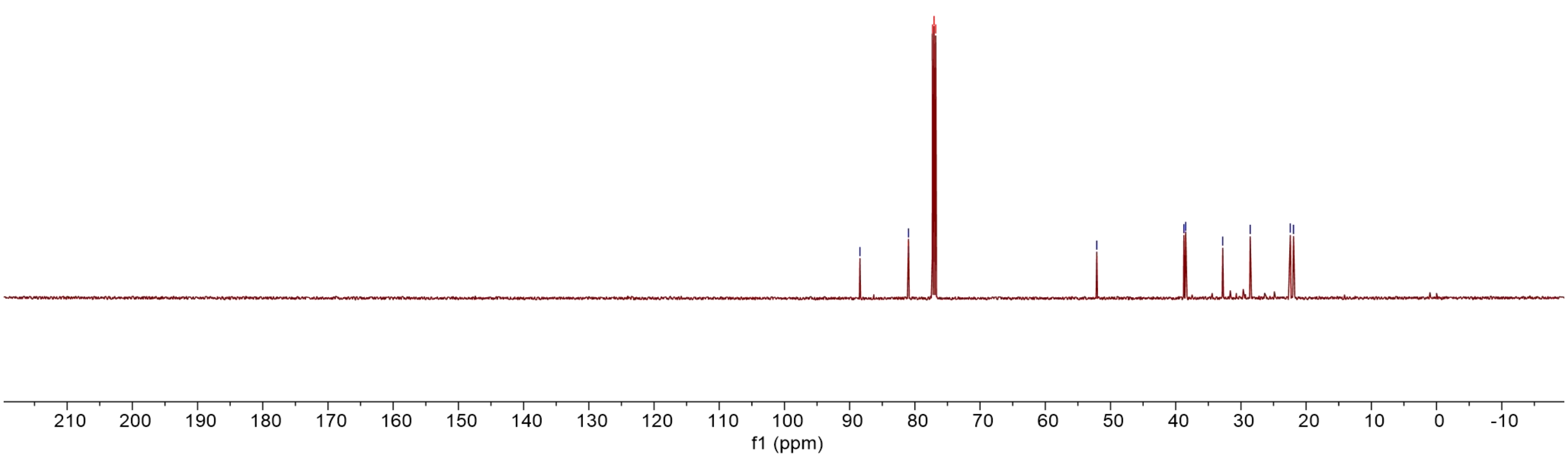


^{1}H NMR Spectrum of compound SI-22 (500 MHz, $CDCl_3$)

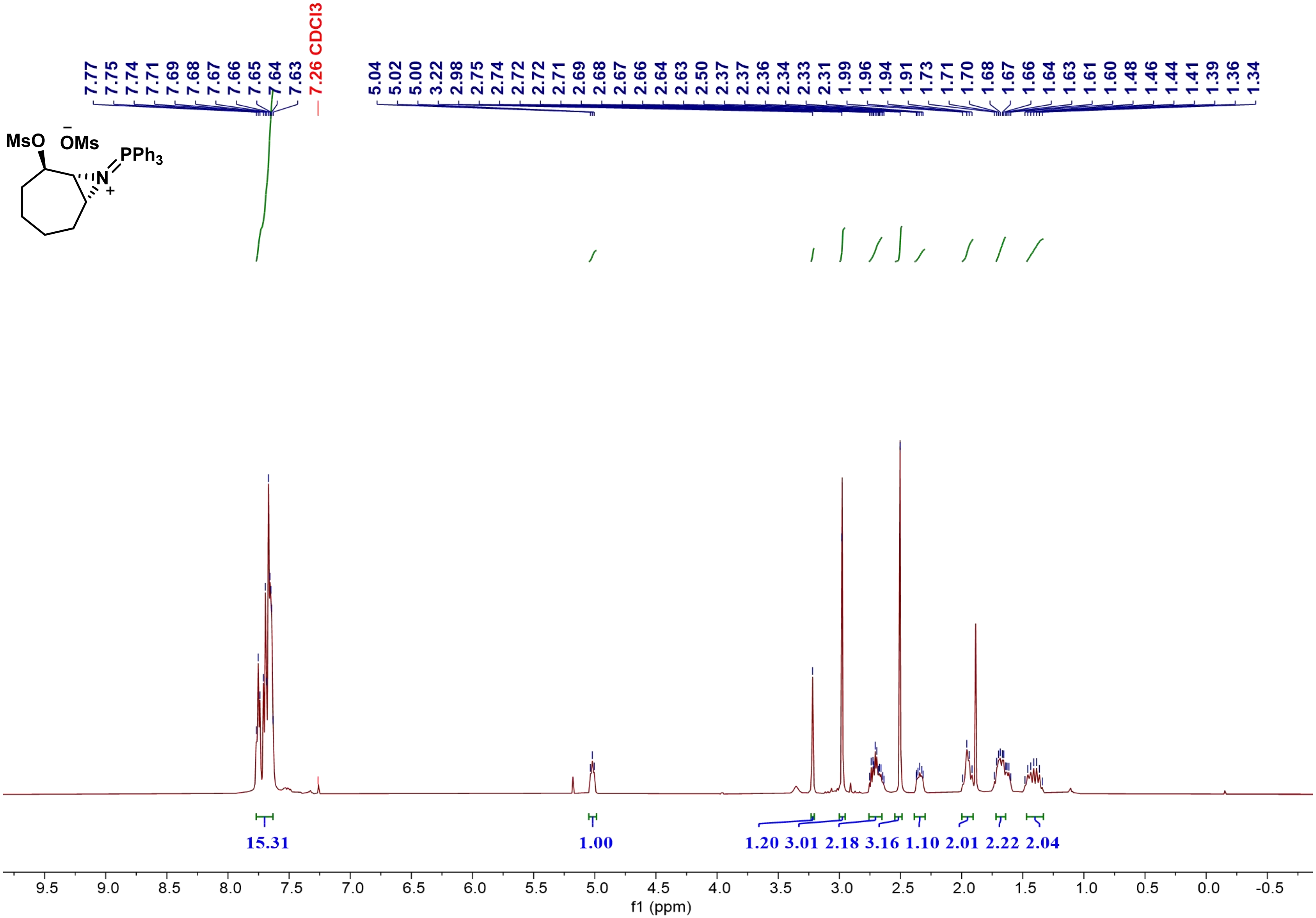


^{13}C NMR Spectrum of compound SI-22 (126 MHz, $CDCl_3$)

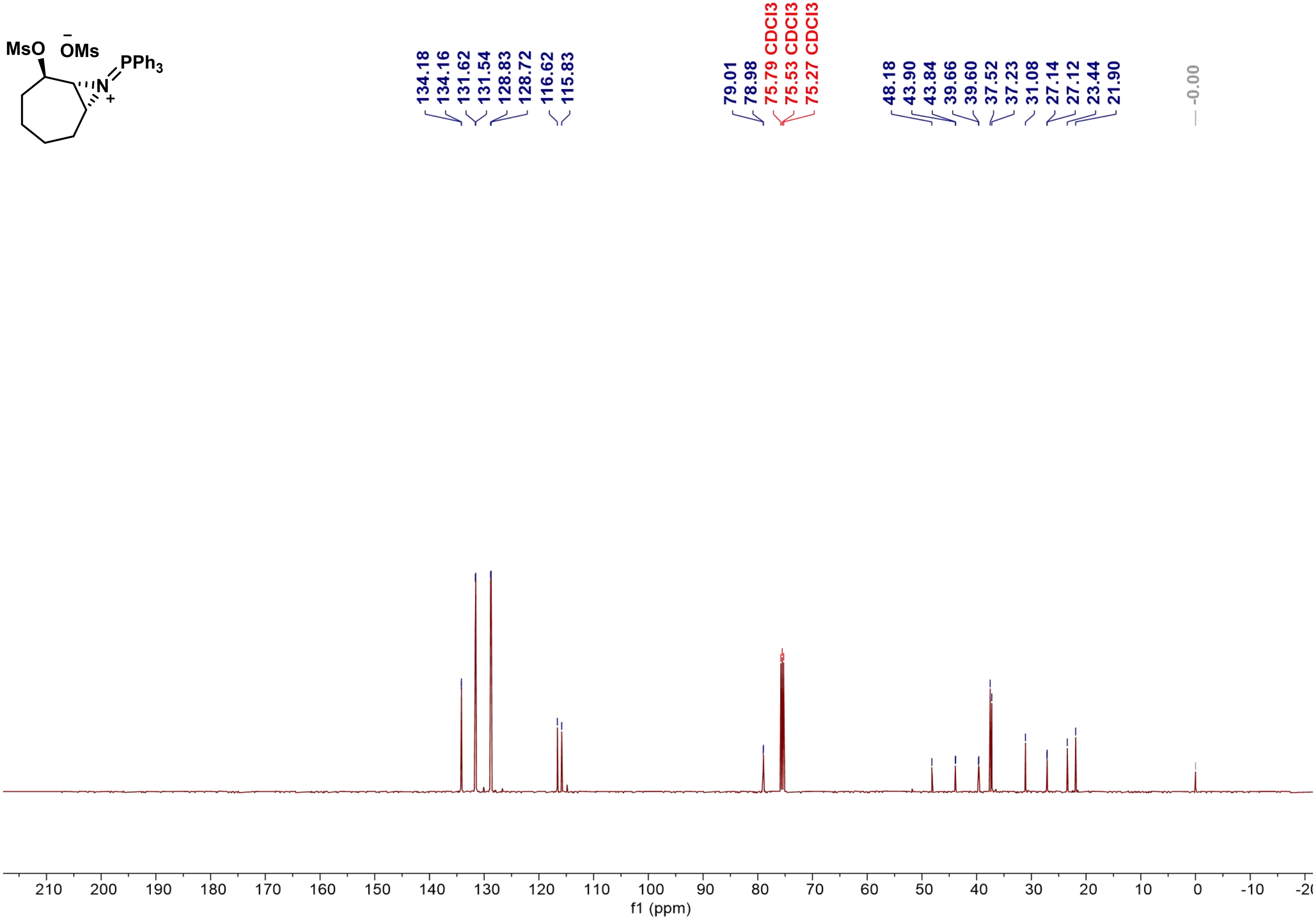




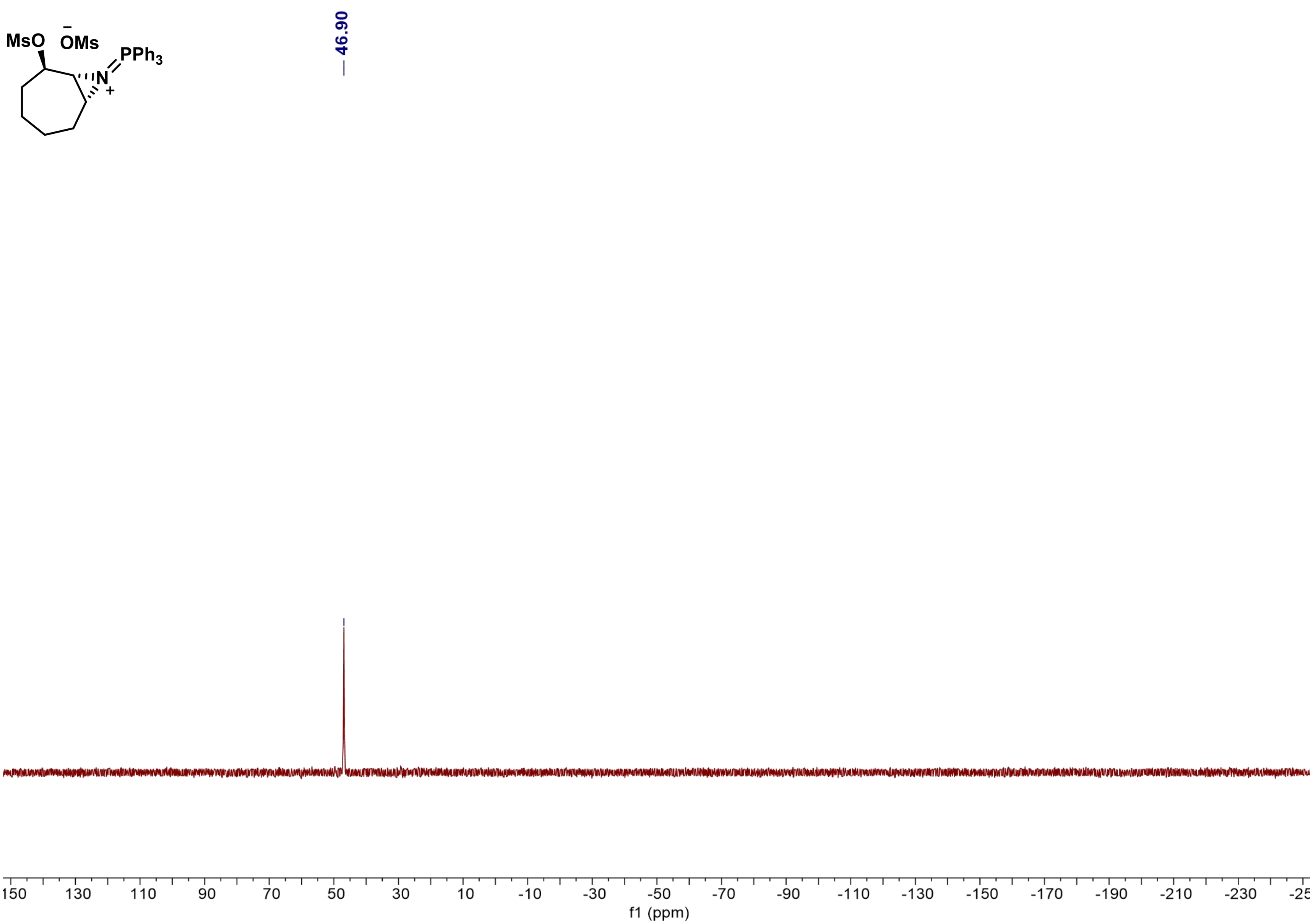
^{1}H NMR Spectrum of compound SI-23 (500 MHz, $CDCl_3$)



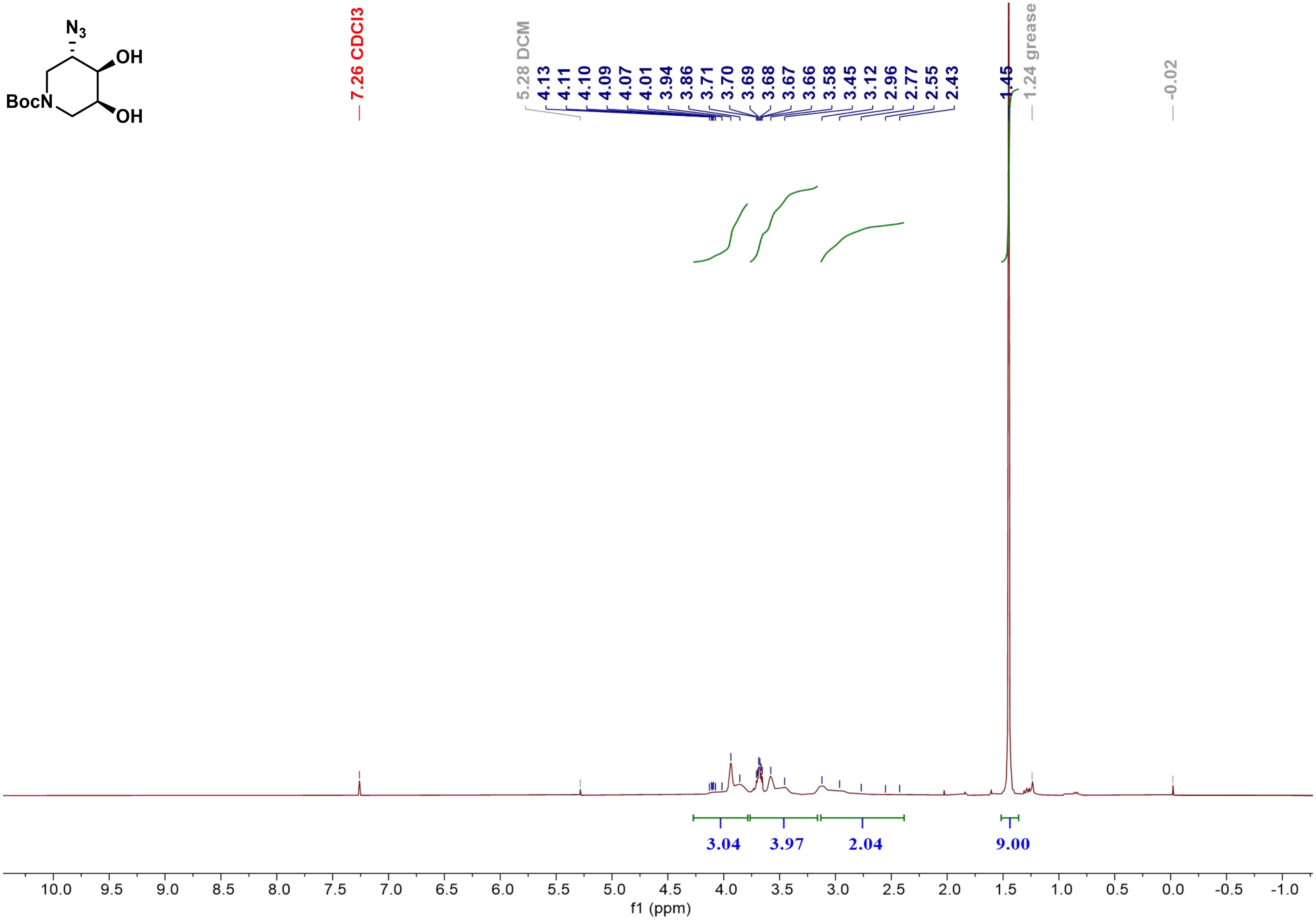
^{13}C NMR Spectrum of compound SI-23 (126 MHz, CDCl$_3$)



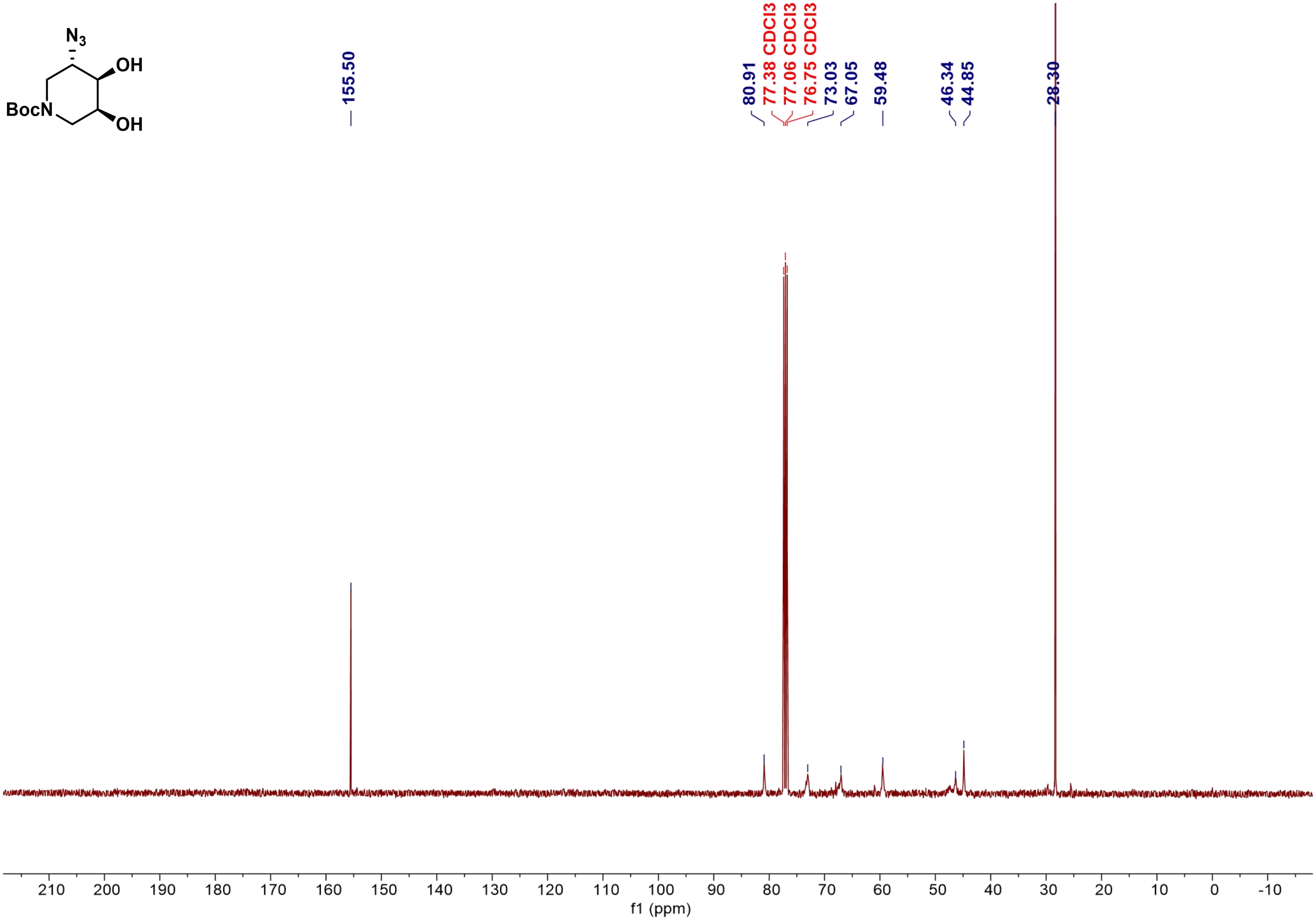
^{31}P NMR Spectrum of compound SI-23 (202 MHz, CDCl$_3$)



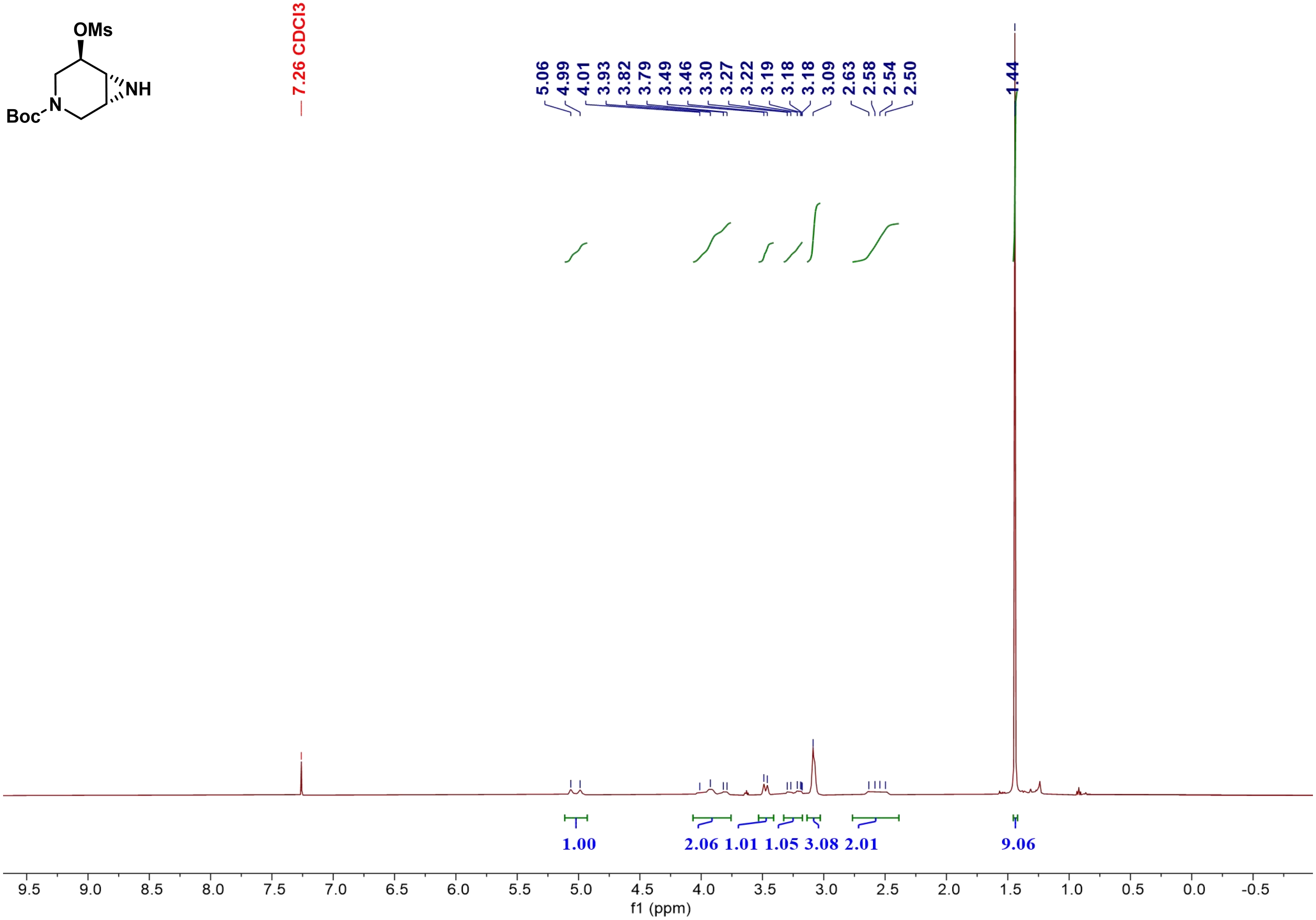
^{1}H NMR Spectrum of compound SI-24 (400 MHz, CDCl$_3$)



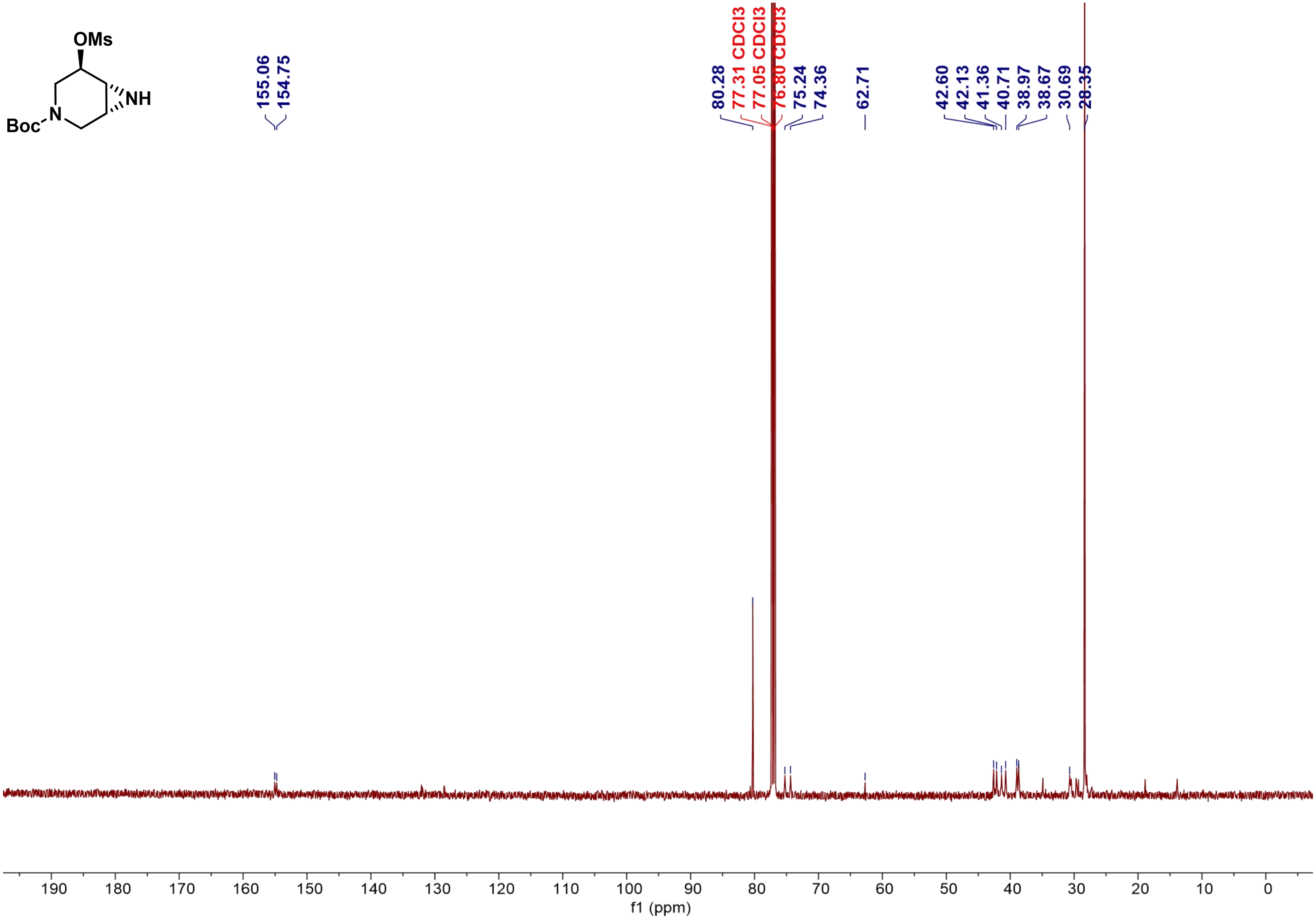
^{13}C NMR Spectrum of compound SI-24 (101 MHz, CDCl$_3$)



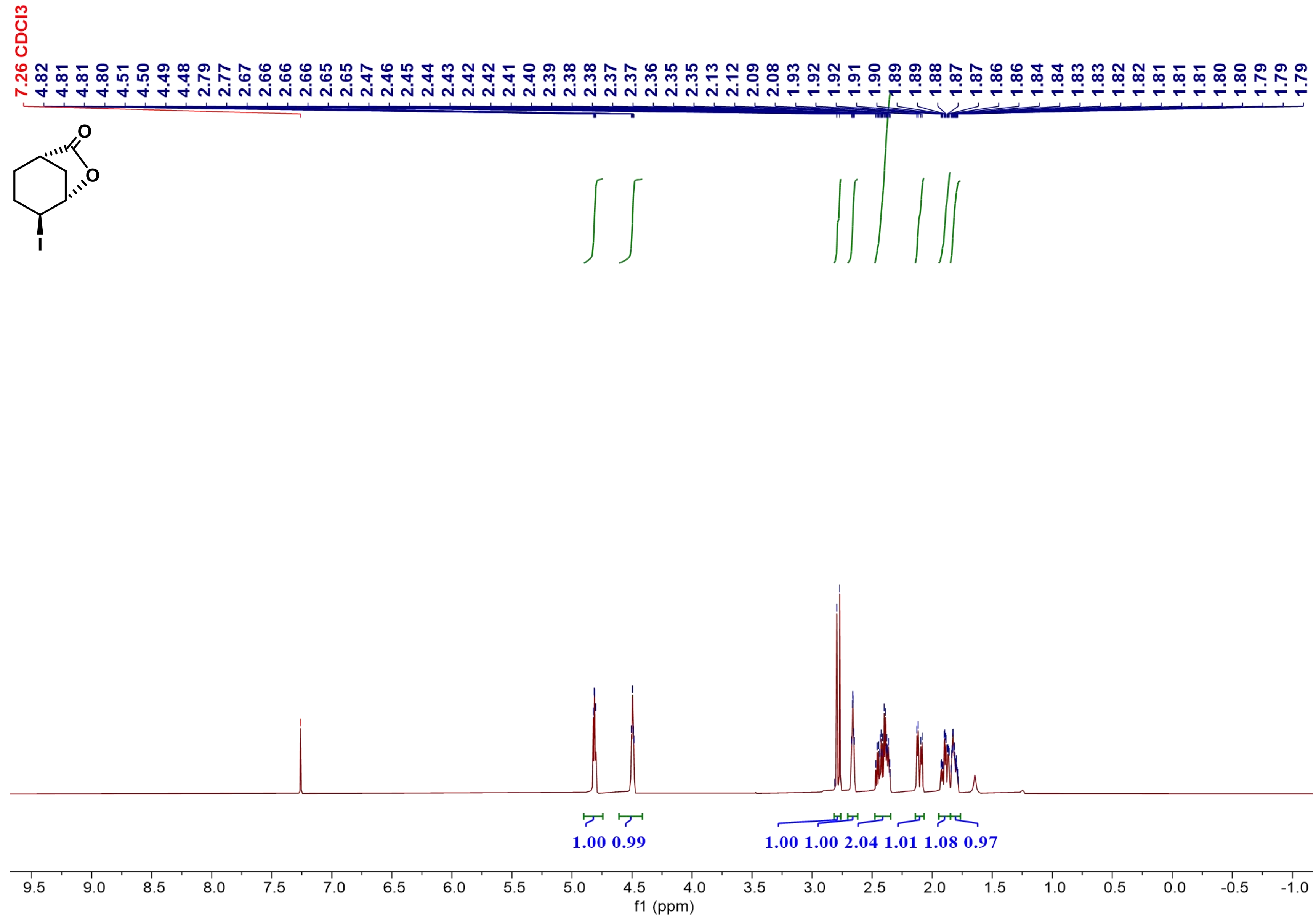
^{1}H NMR Spectrum of compound SI-25 (500 MHz, $CDCl_3$)



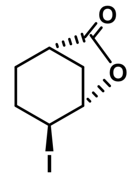
^{13}C NMR Spectrum of compound SI-25 (126 MHz, $CDCl_3$)

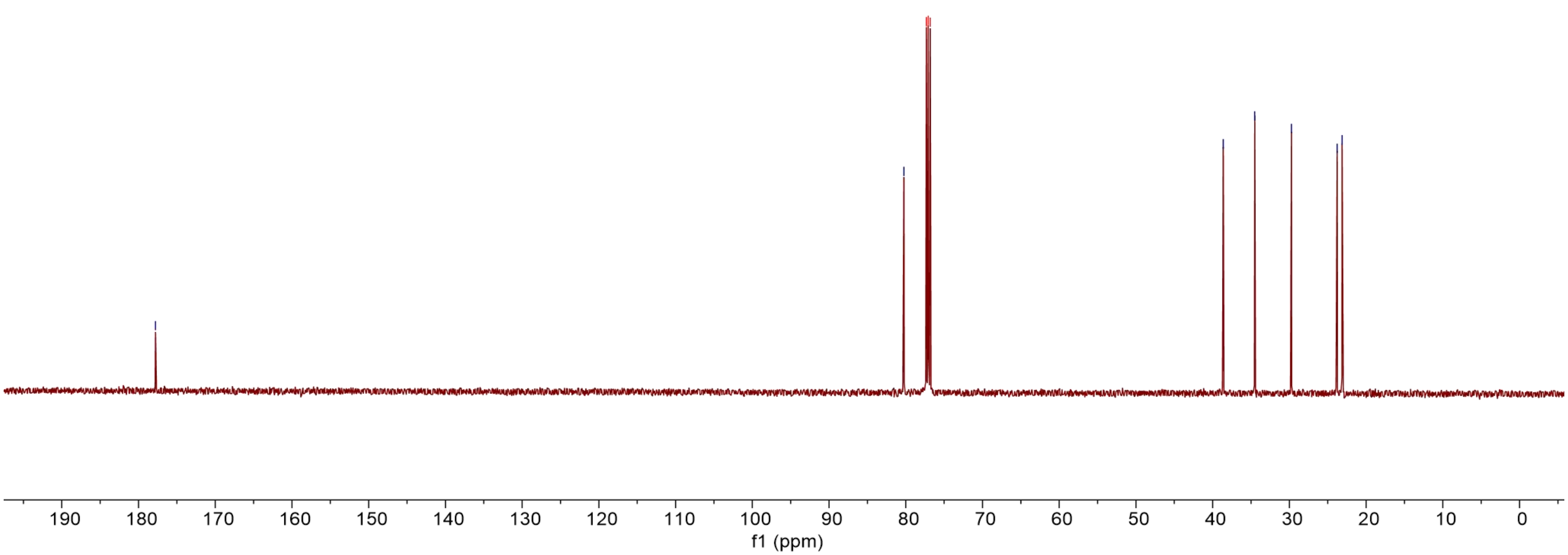


^{1}H NMR Spectrum of compound SI-26 (500 MHz, $CDCl_3$)

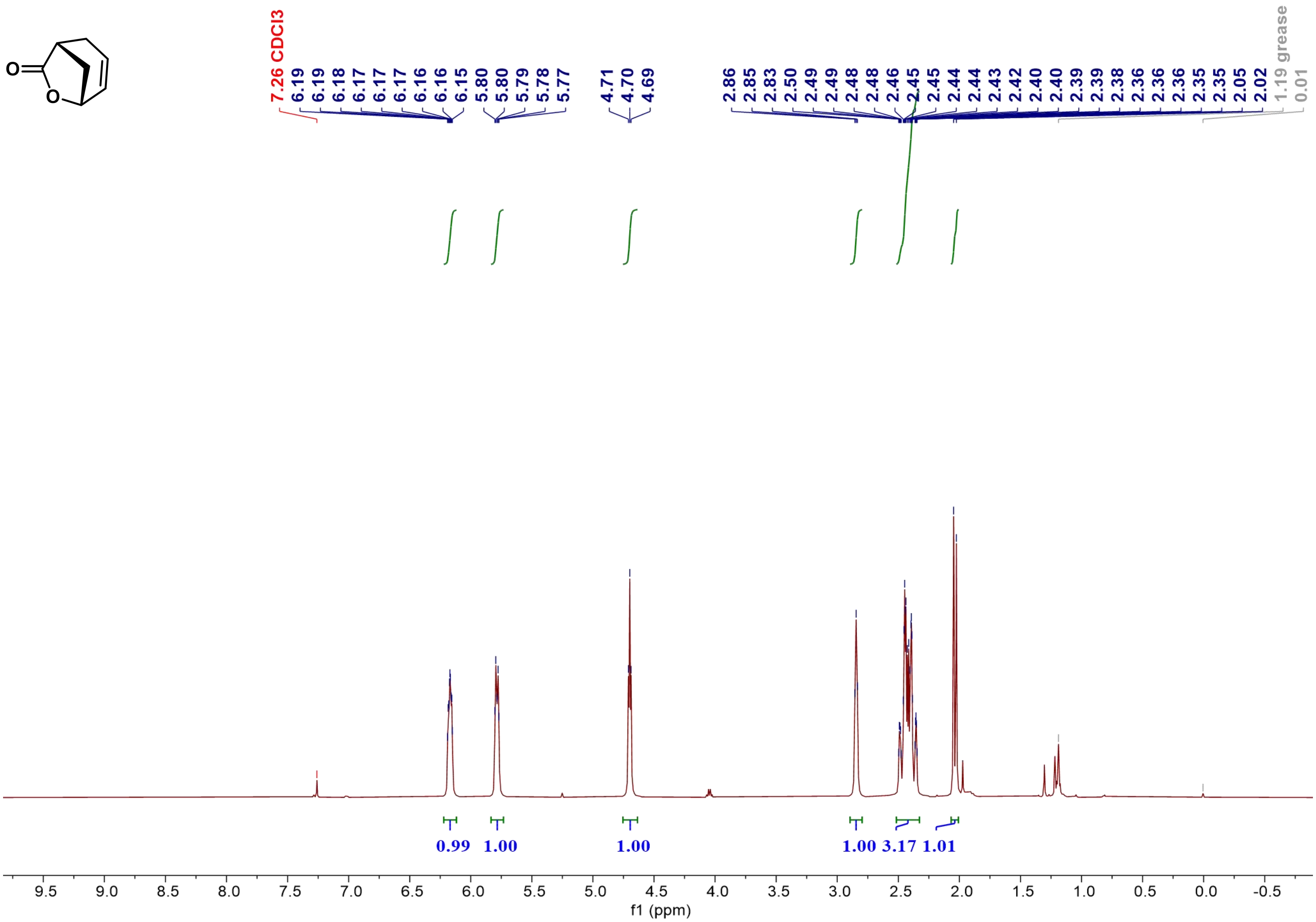


^{13}C NMR Spectrum of compound SI-26 (126 MHz, CDCl$_3$)

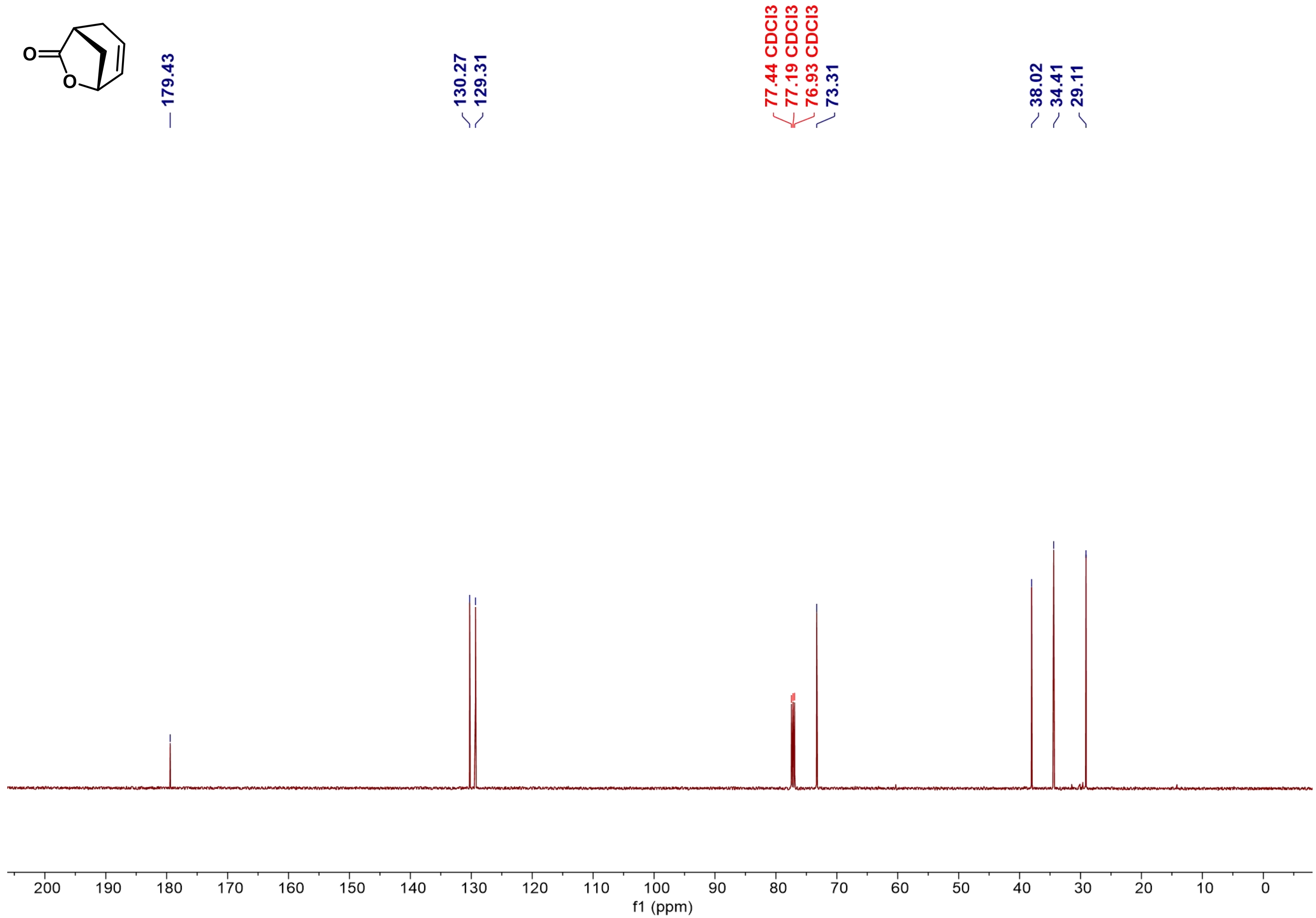




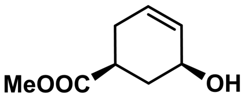
^{1}H NMR Spectrum of compound SI-27 (500 MHz, CDCl$_3$)

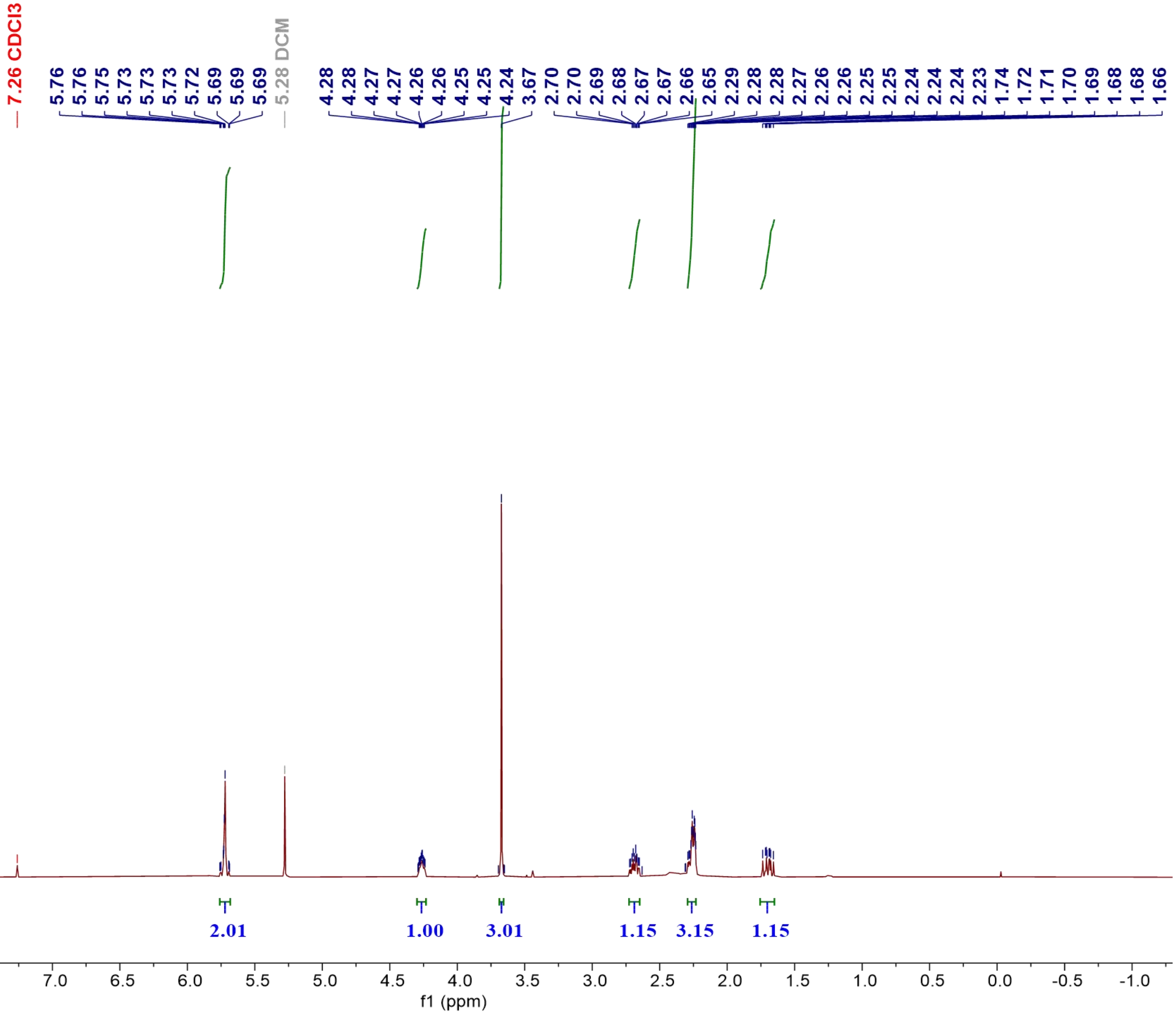


^{13}C NMR Spectrum of compound SI-27 (126 MHz, $CDCl_3$)

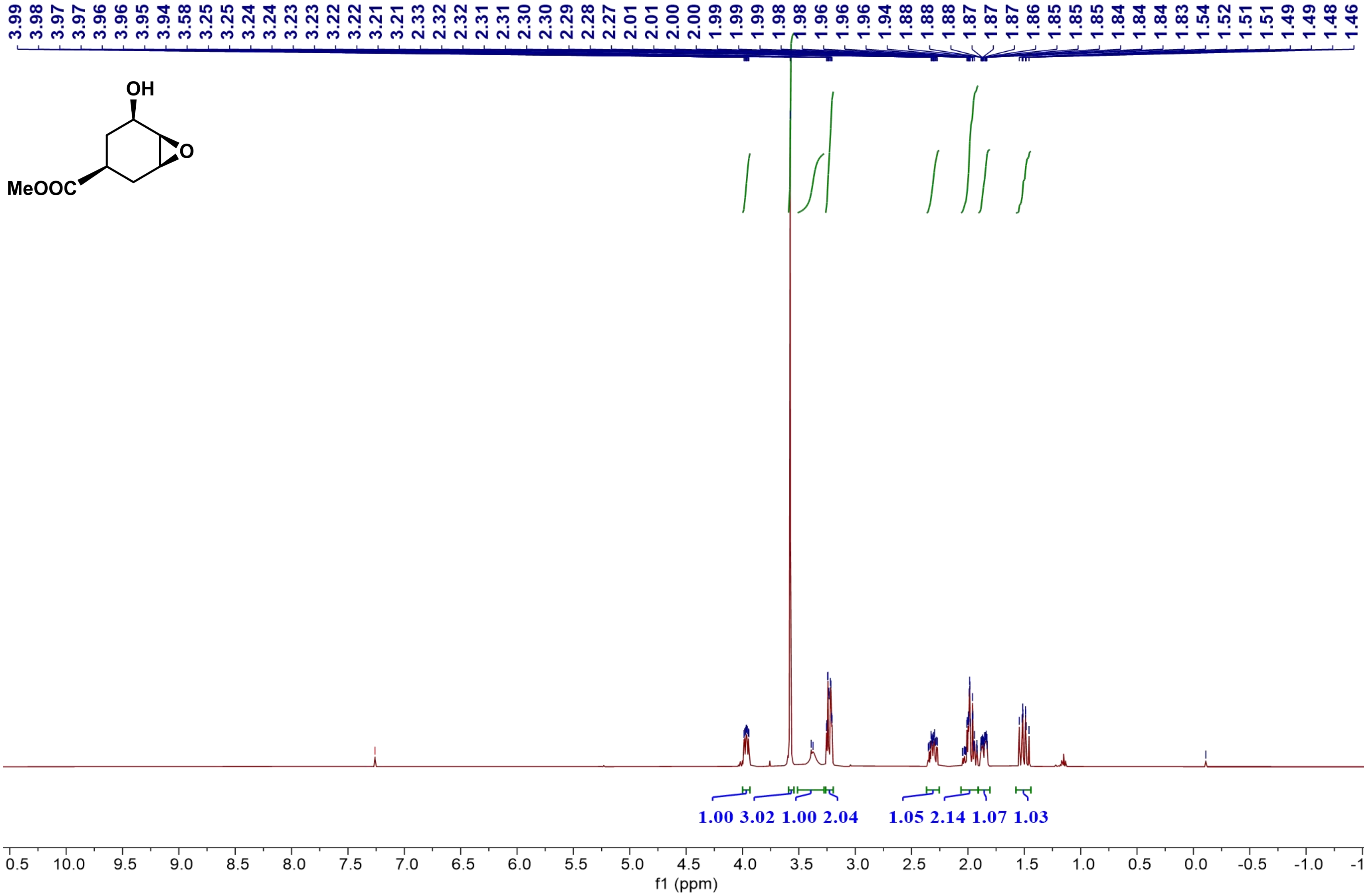


^{1}H NMR Spectrum of compound SI-28 (400 MHz, CDCl$_3$)

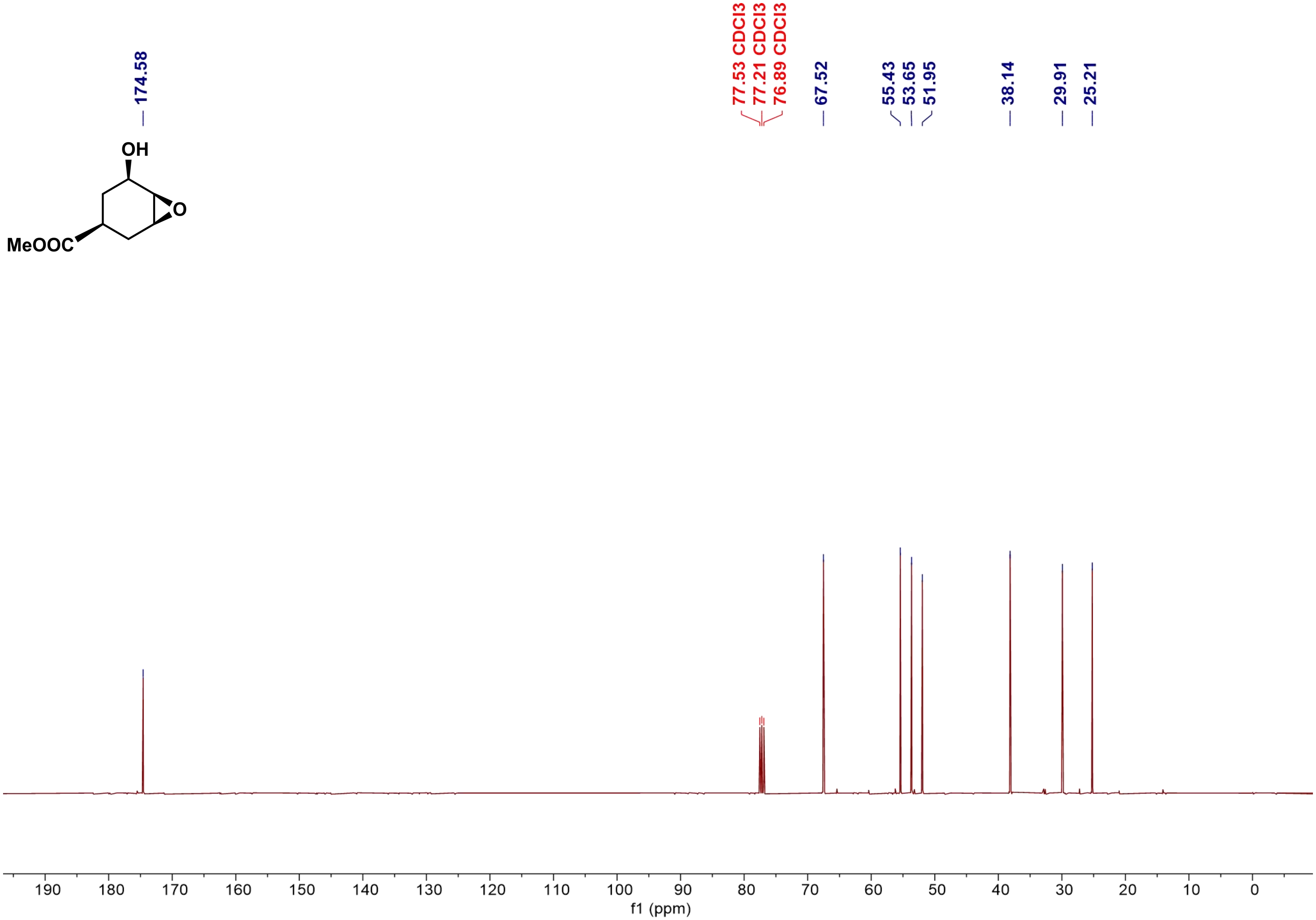




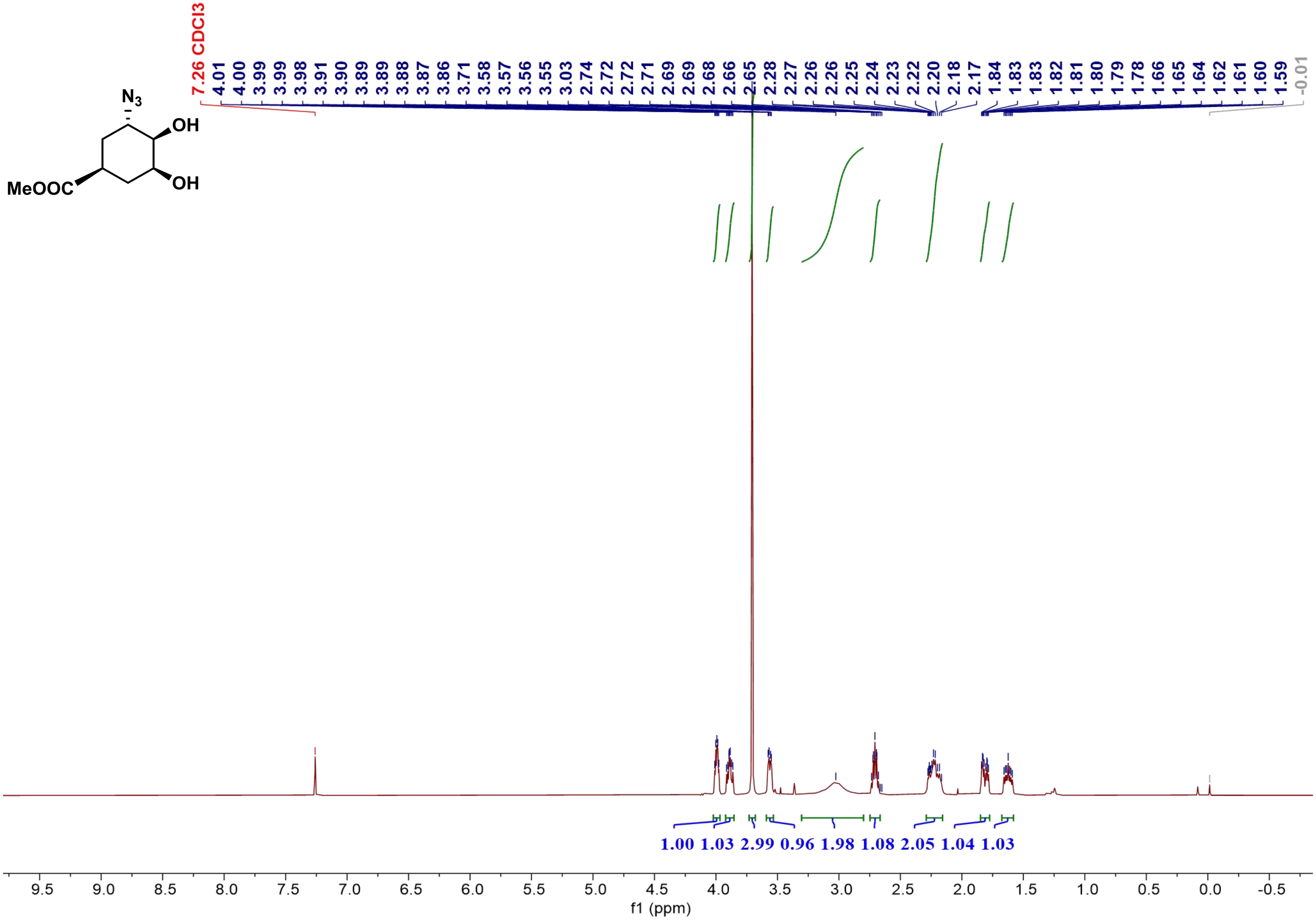
^{1}H NMR Spectrum of compound SI-29 (400 MHz, CDCl$_3$)



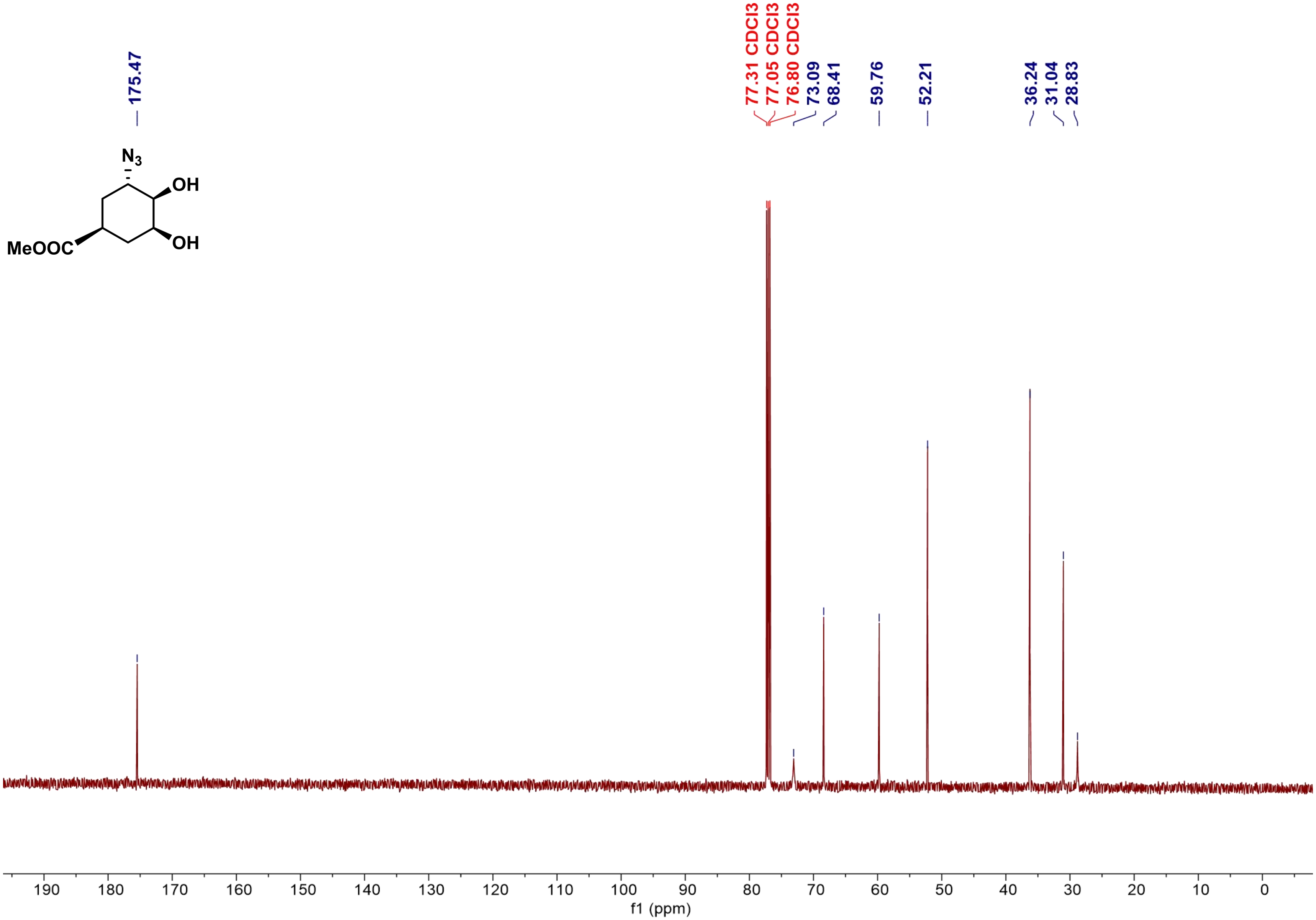
^{13}C NMR Spectrum of compound SI-29 (101 MHz, $CDCl_3$)



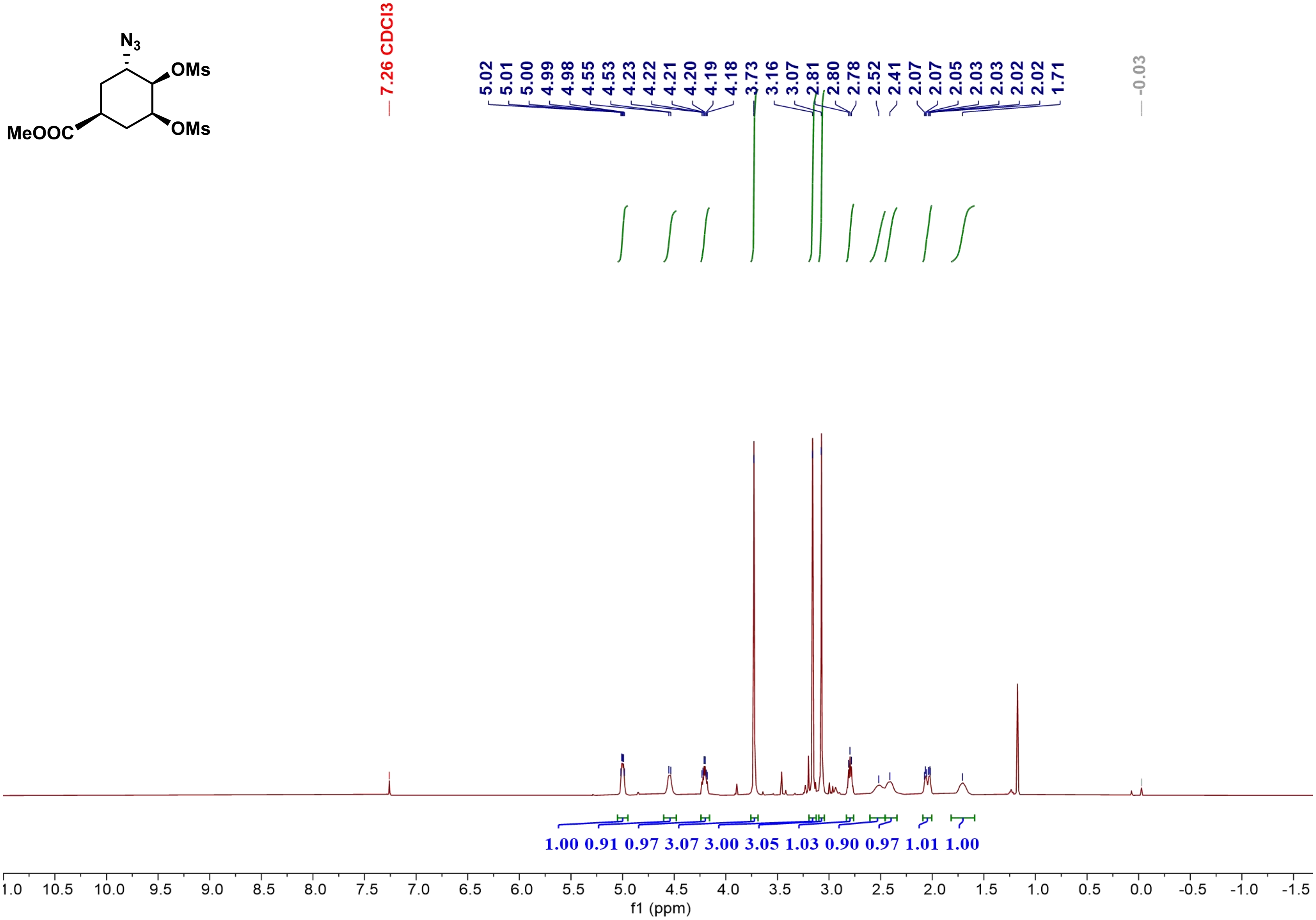
^{1}H NMR Spectrum of compound SI-30 (400 MHz, $CDCl_3$)



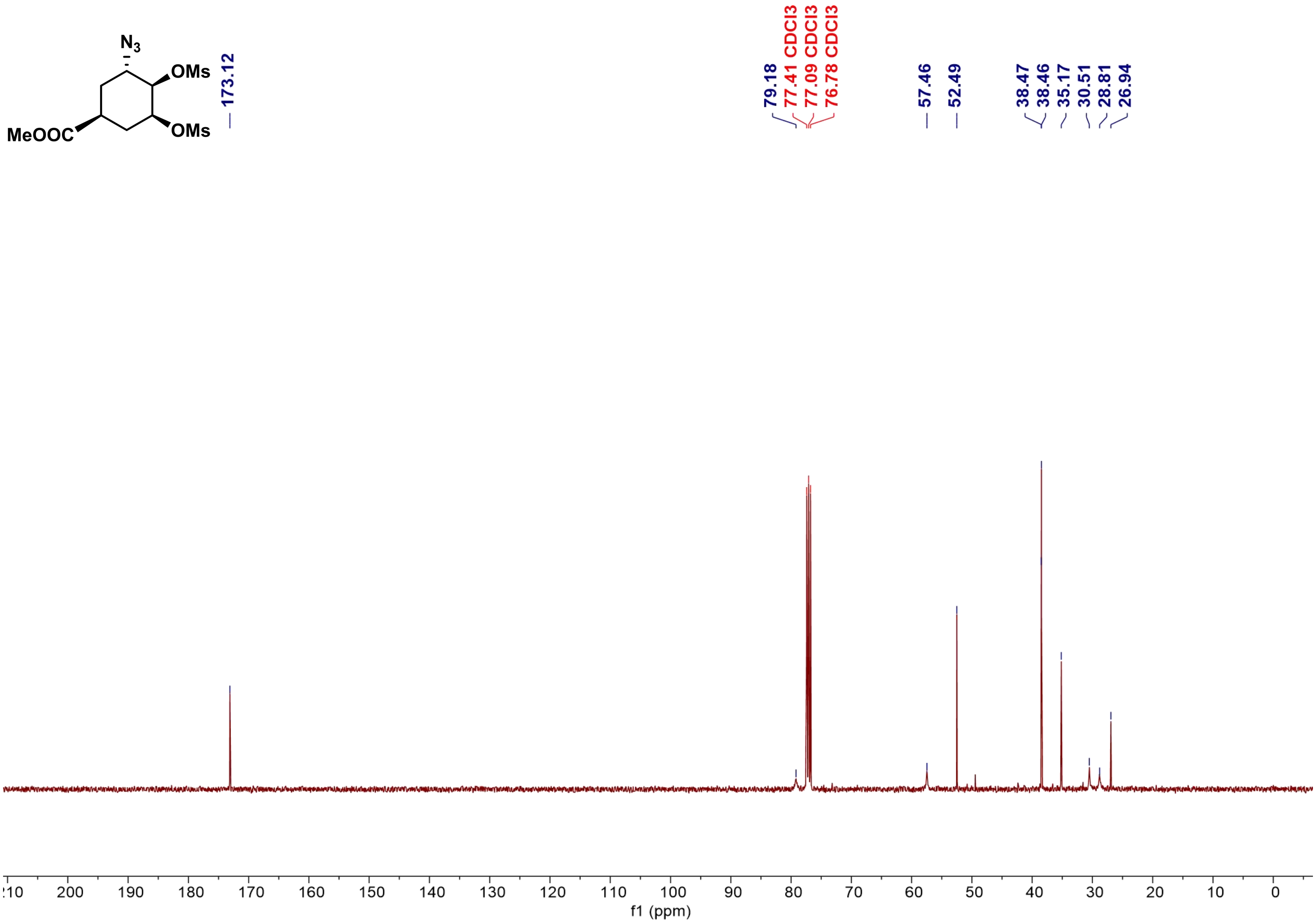
^{13}C NMR Spectrum of compound SI-30 (126 MHz, CDCl$_3$)



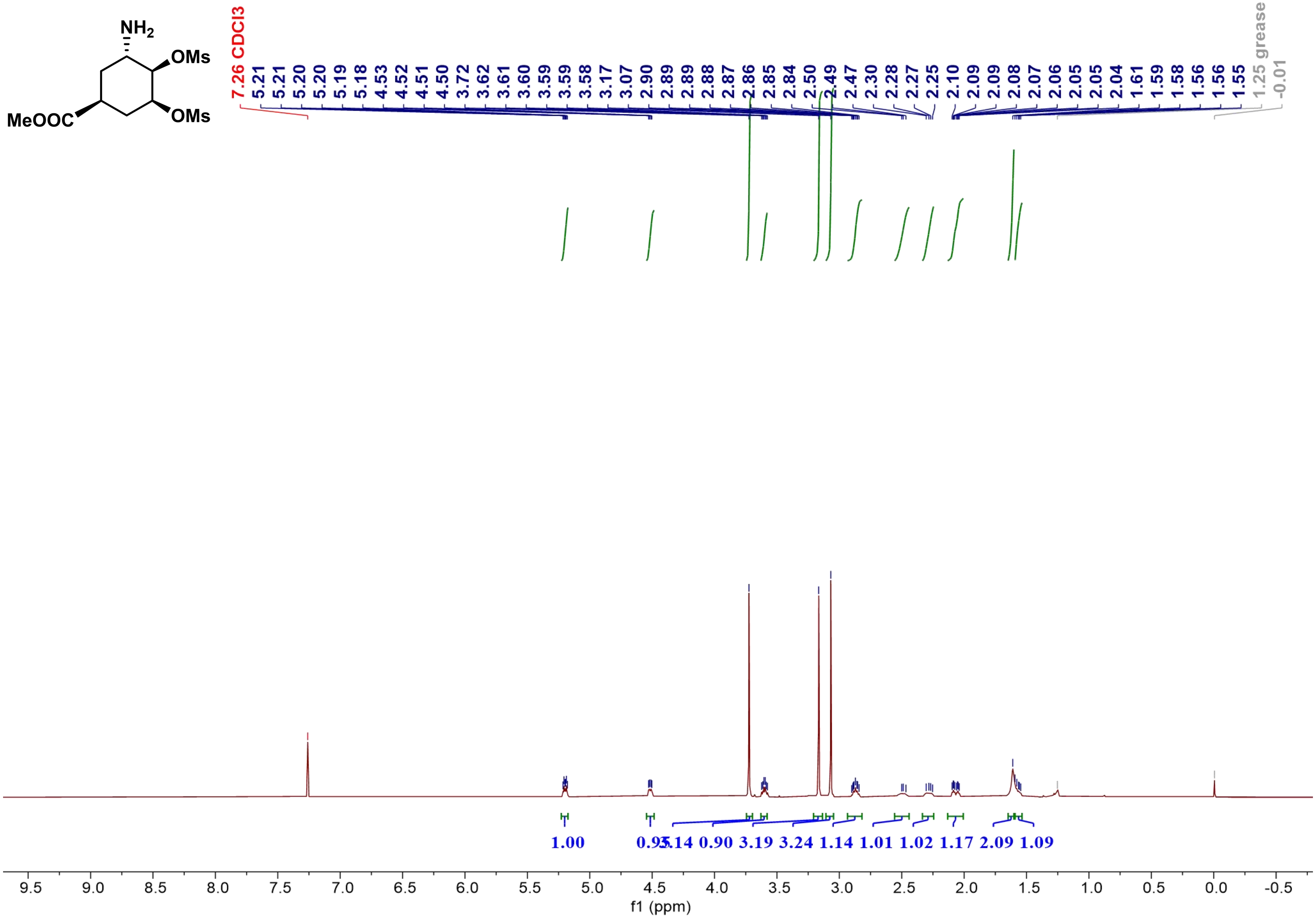
^{1}H NMR Spectrum of compound SI-31 (400 MHz, $CDCl_3$)



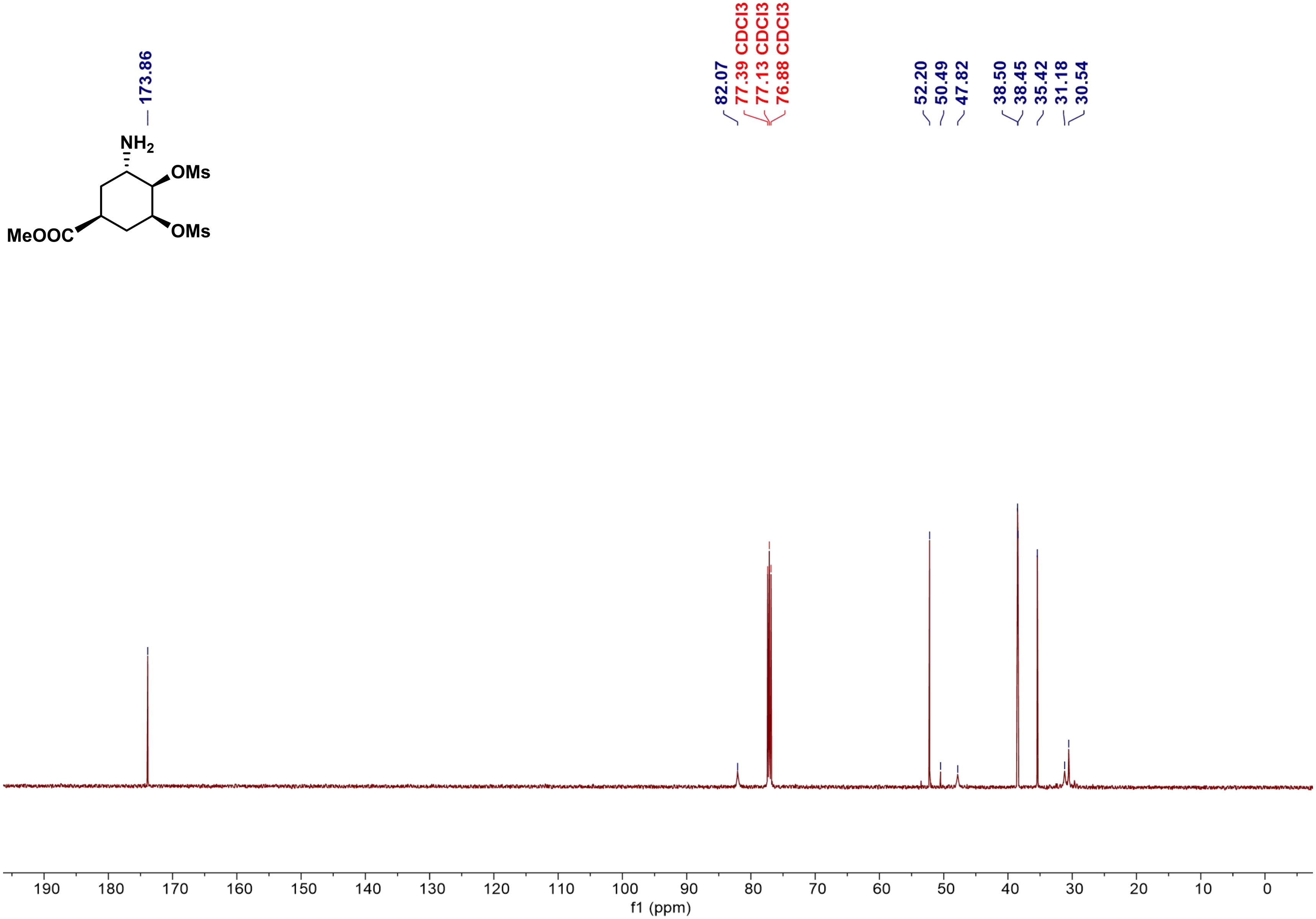
^{13}C NMR Spectrum of compound SI-31 (101 MHz, $CDCl_3$)



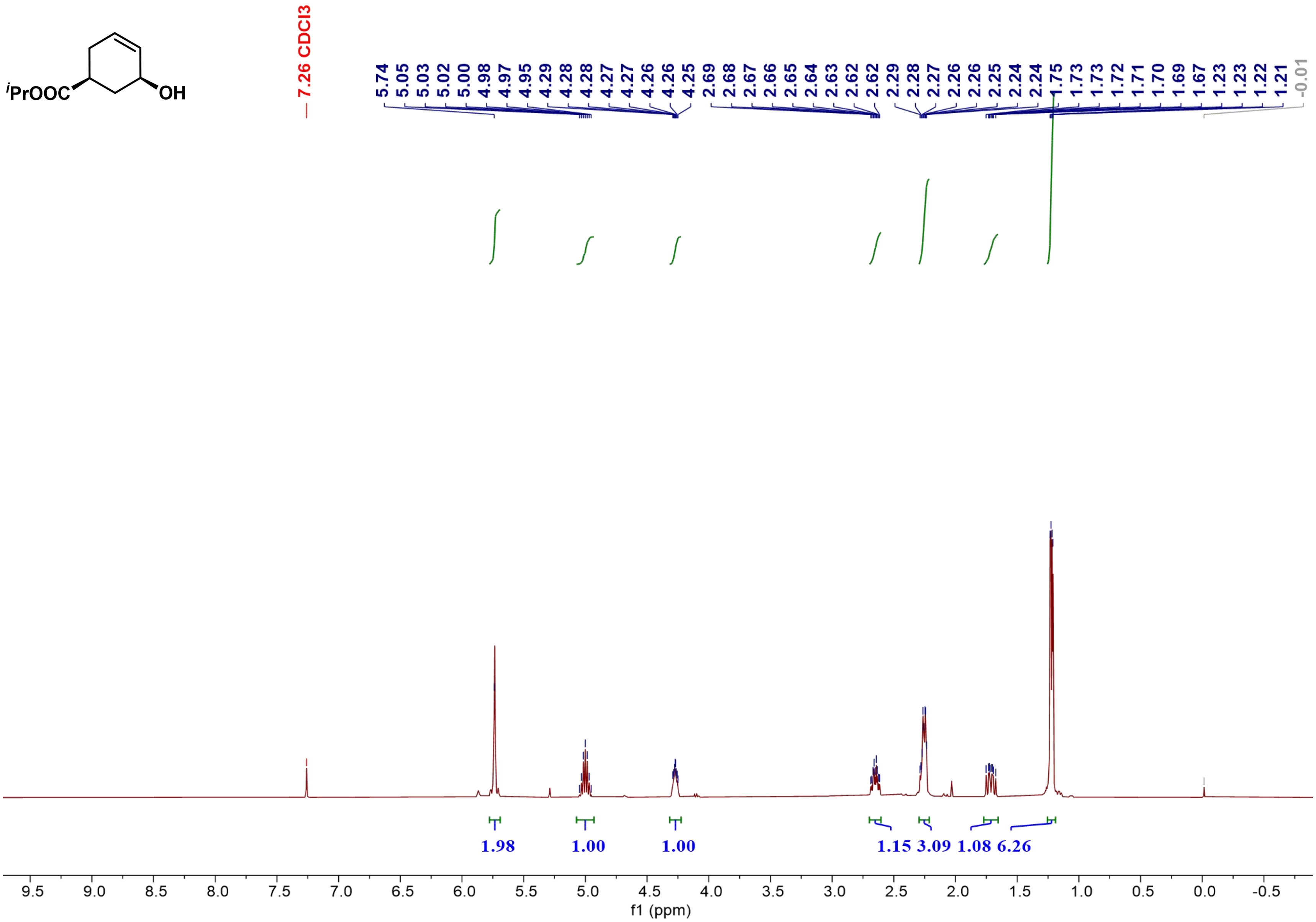
^{1}H NMR Spectrum of compound SI-32 (400 MHz, $CDCl_3$)



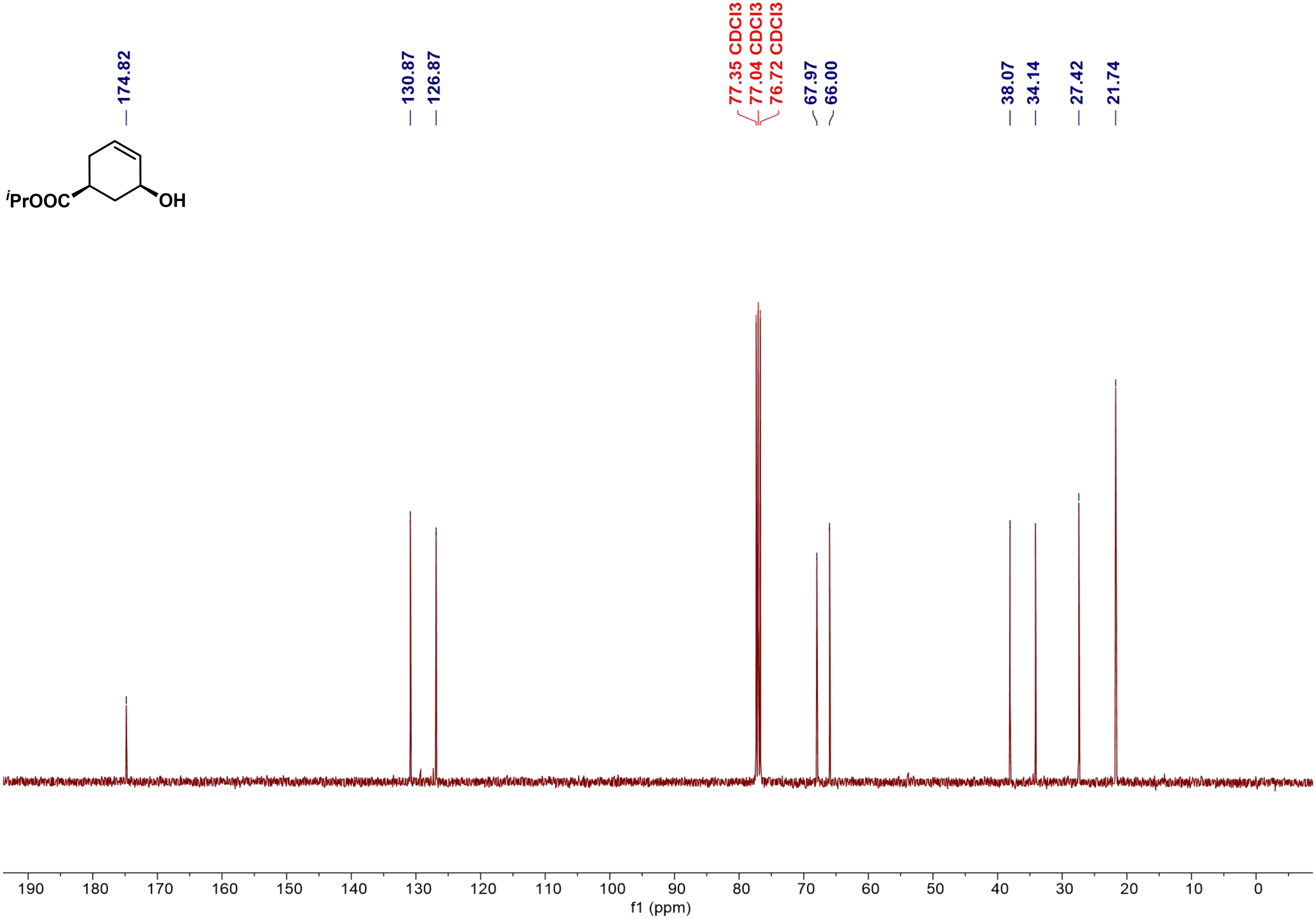
^{13}C NMR Spectrum of compound SI-32 (126 MHz, $CDCl_3$)



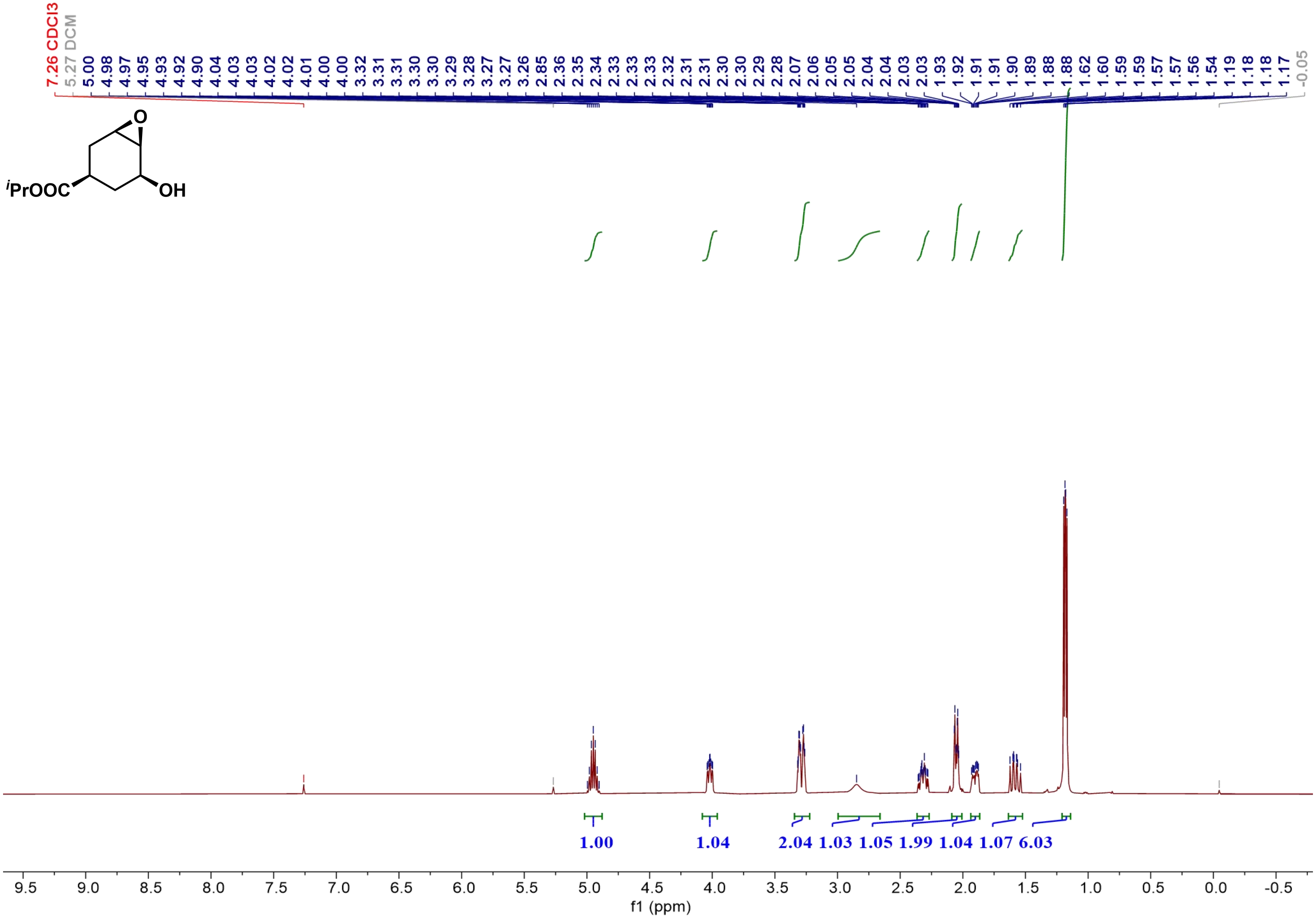
^{1}H NMR Spectrum of compound SI-33 (400 MHz, CDCl$_3$)



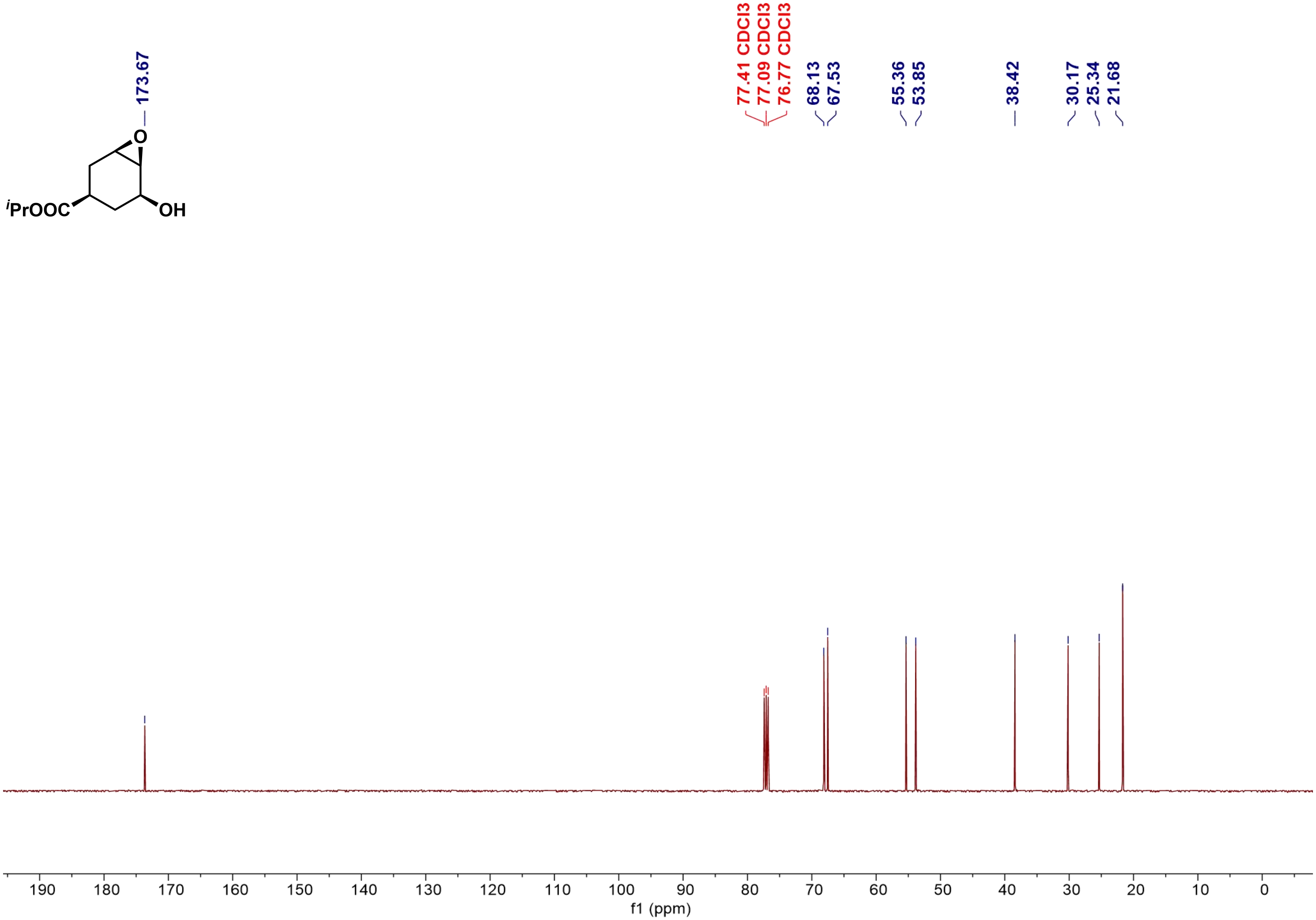
^{13}C NMR Spectrum of compound SI-33 (101 MHz, $CDCl_3$)



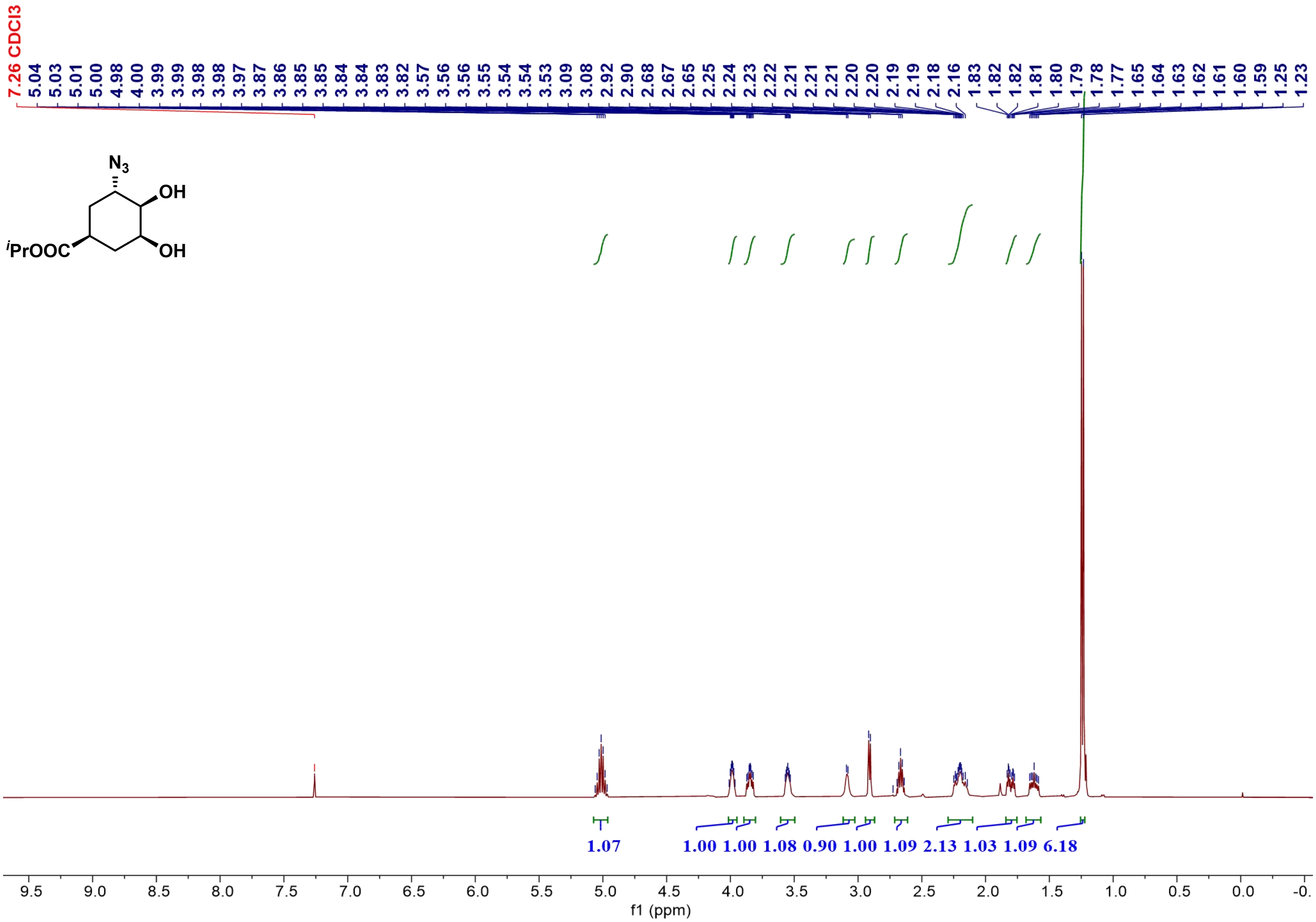
^{1}H NMR Spectrum of compound SI-34 (400 MHz, $CDCl_3$)



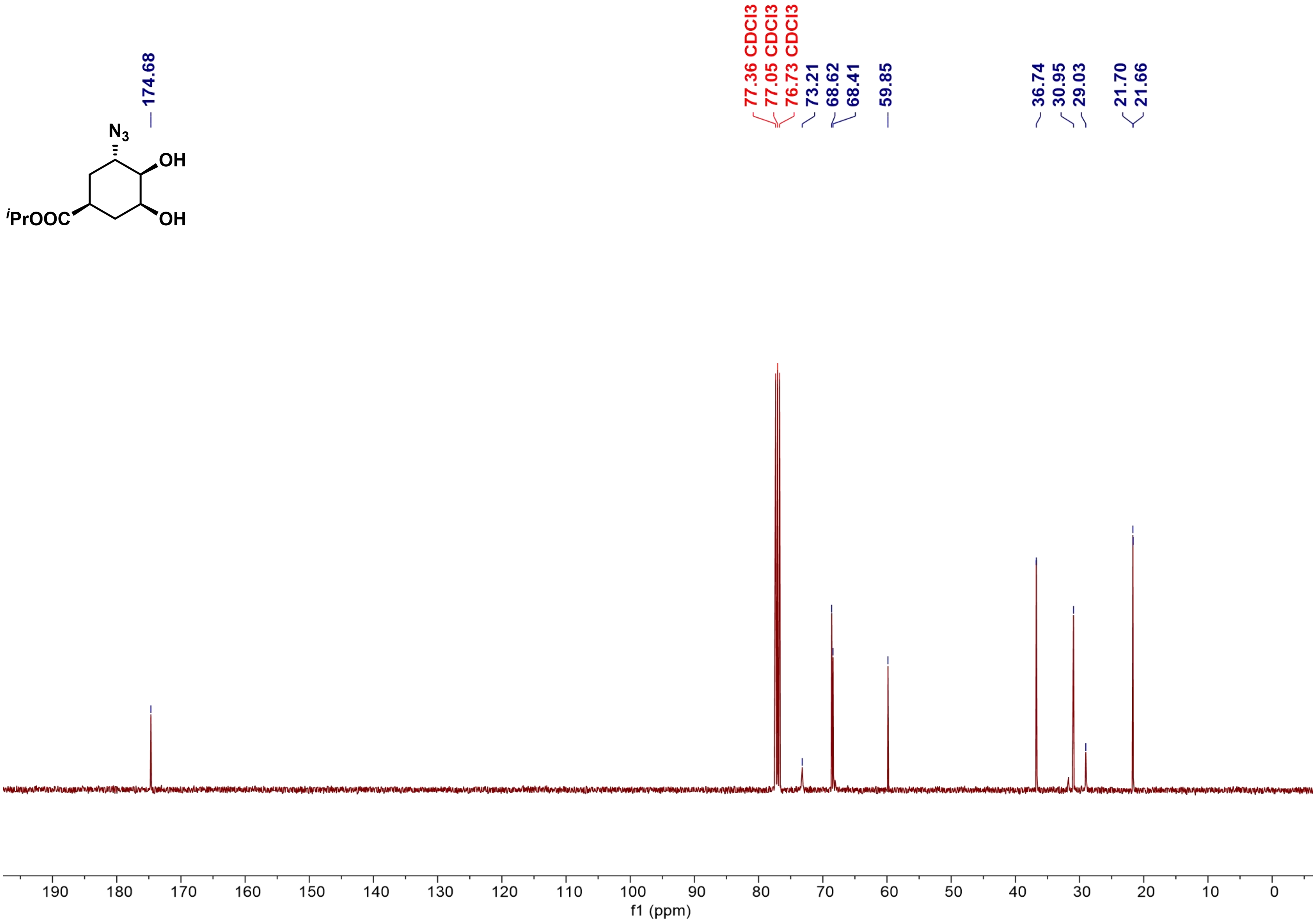
^{13}C NMR Spectrum of compound SI-34 (101 MHz, CDCl$_3$)



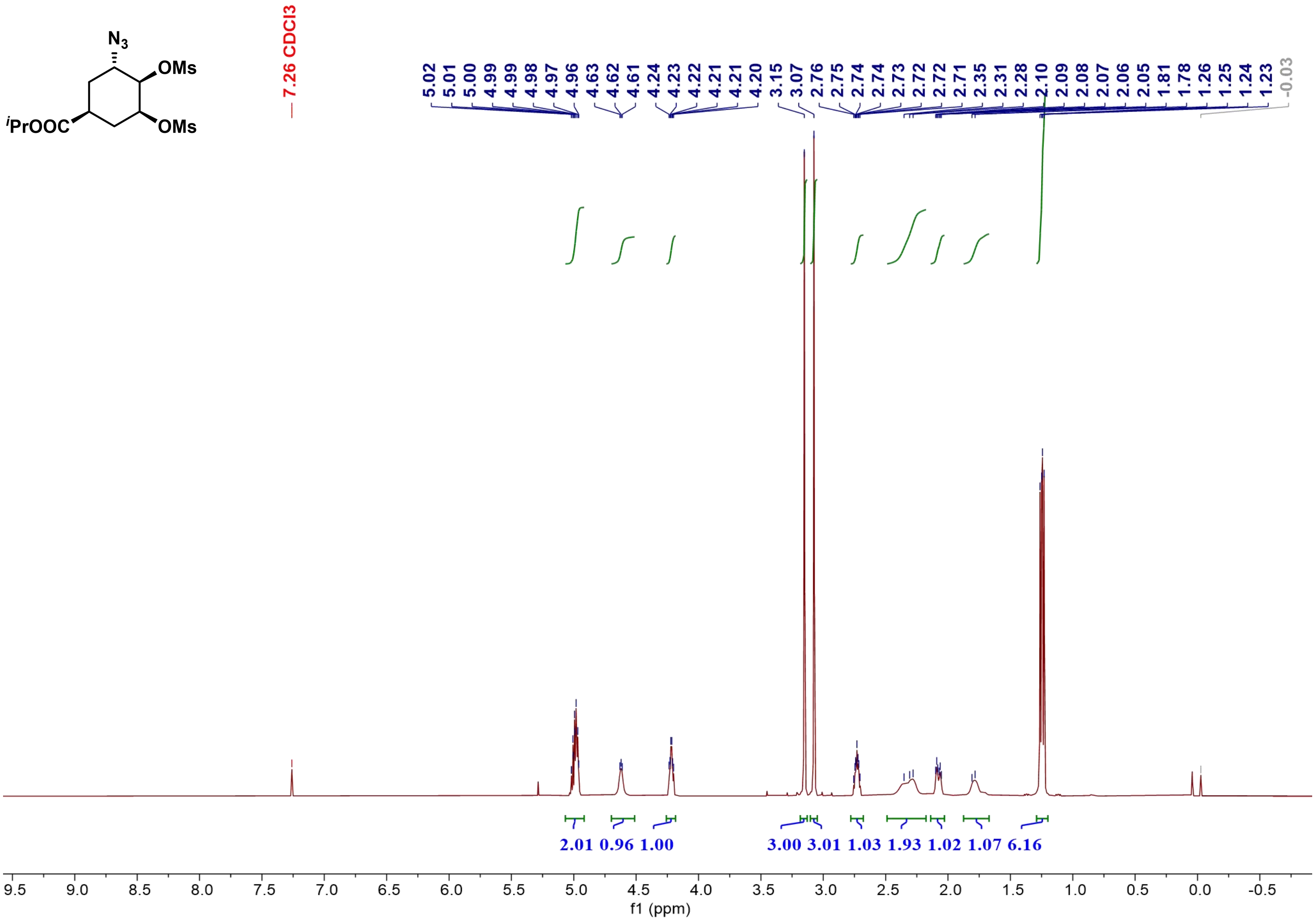
^{1}H NMR Spectrum of compound SI-35 (400 MHz, $CDCl_3$)



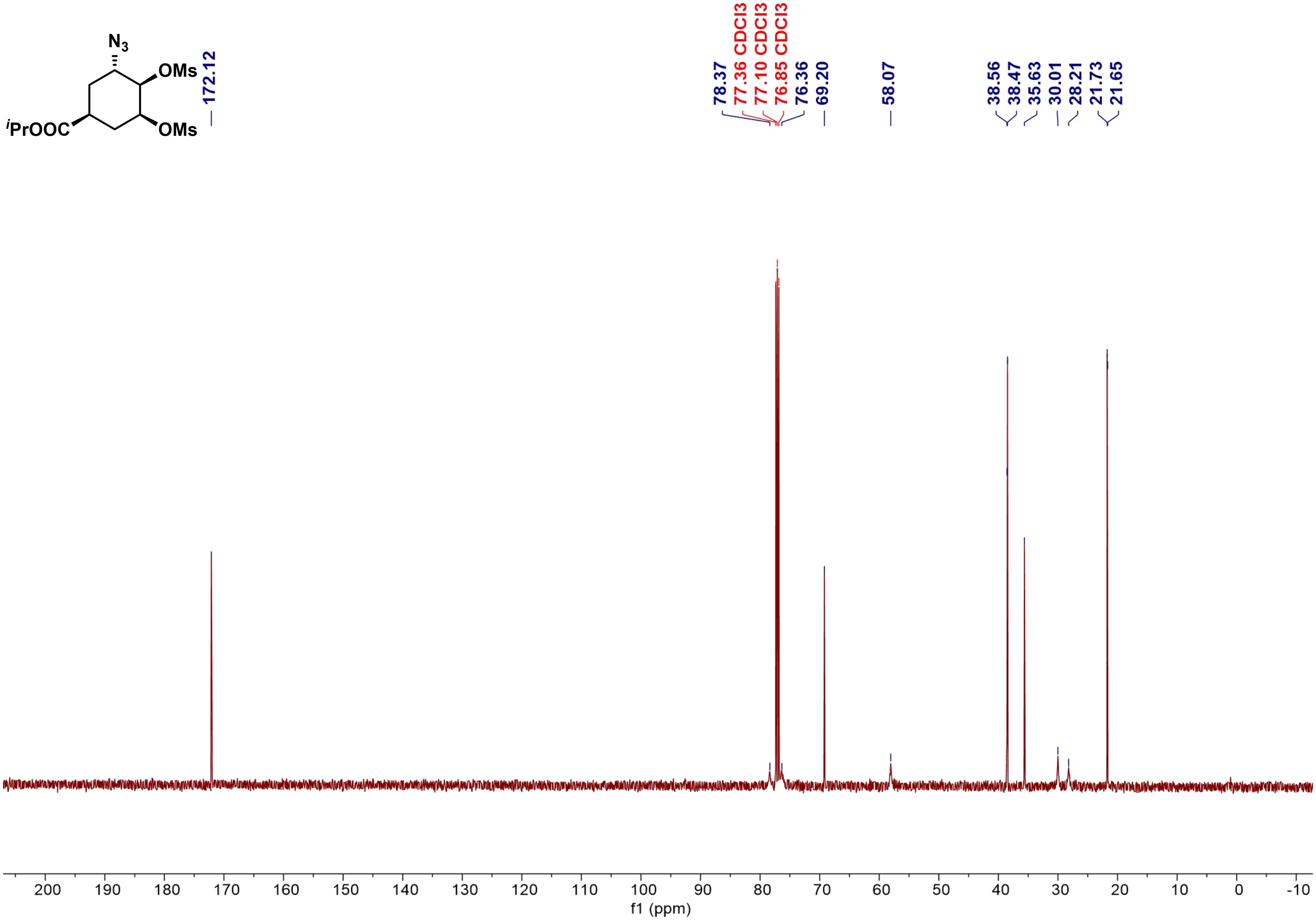
^{13}C NMR Spectrum of compound SI-35 (101 MHz, CDCl$_3$)



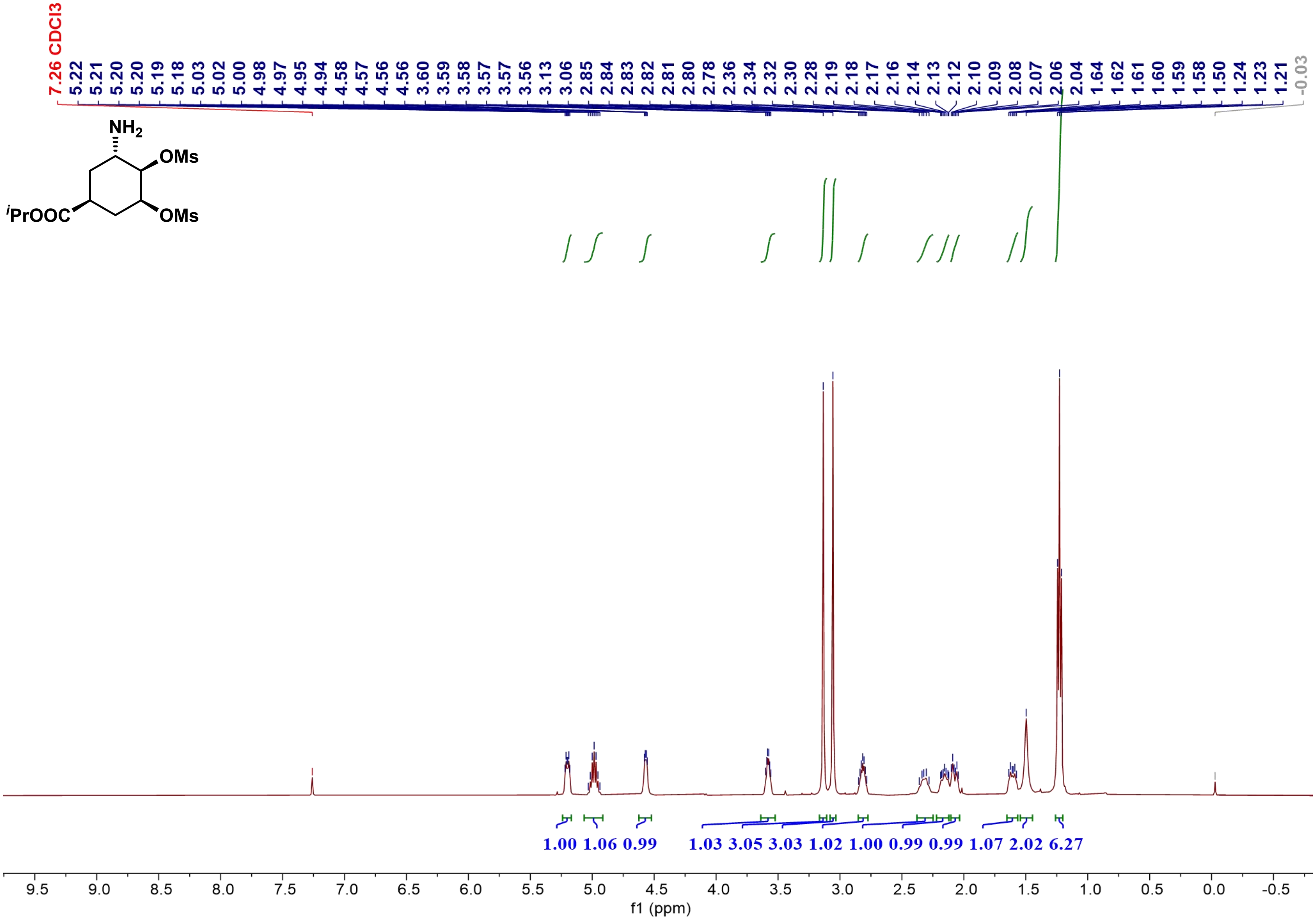
^{1}H NMR Spectrum of compound SI-36 (500 MHz, $CDCl_3$)



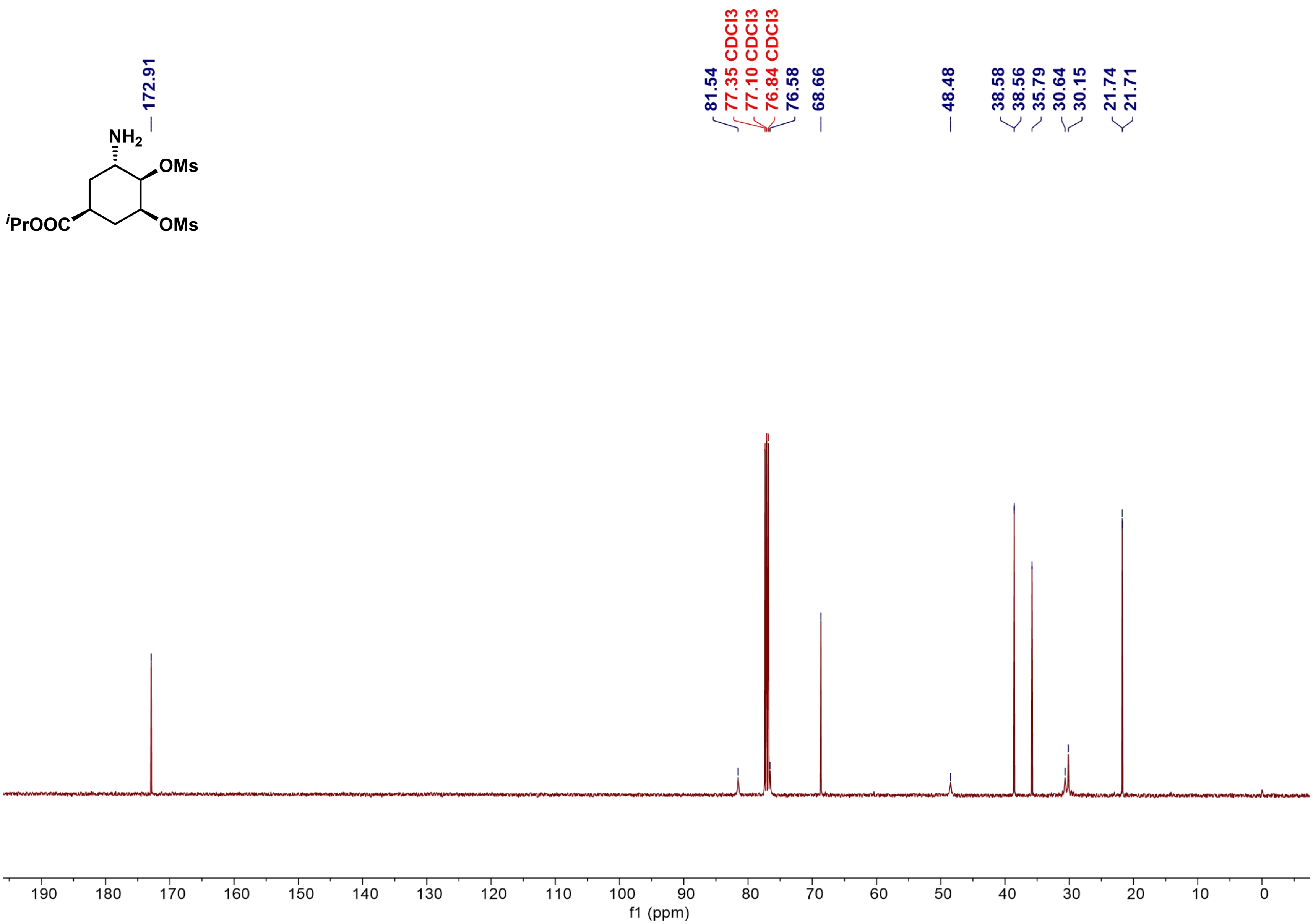
^{13}C NMR Spectrum of compound SI-36 (126 MHz, CDCl$_3$)



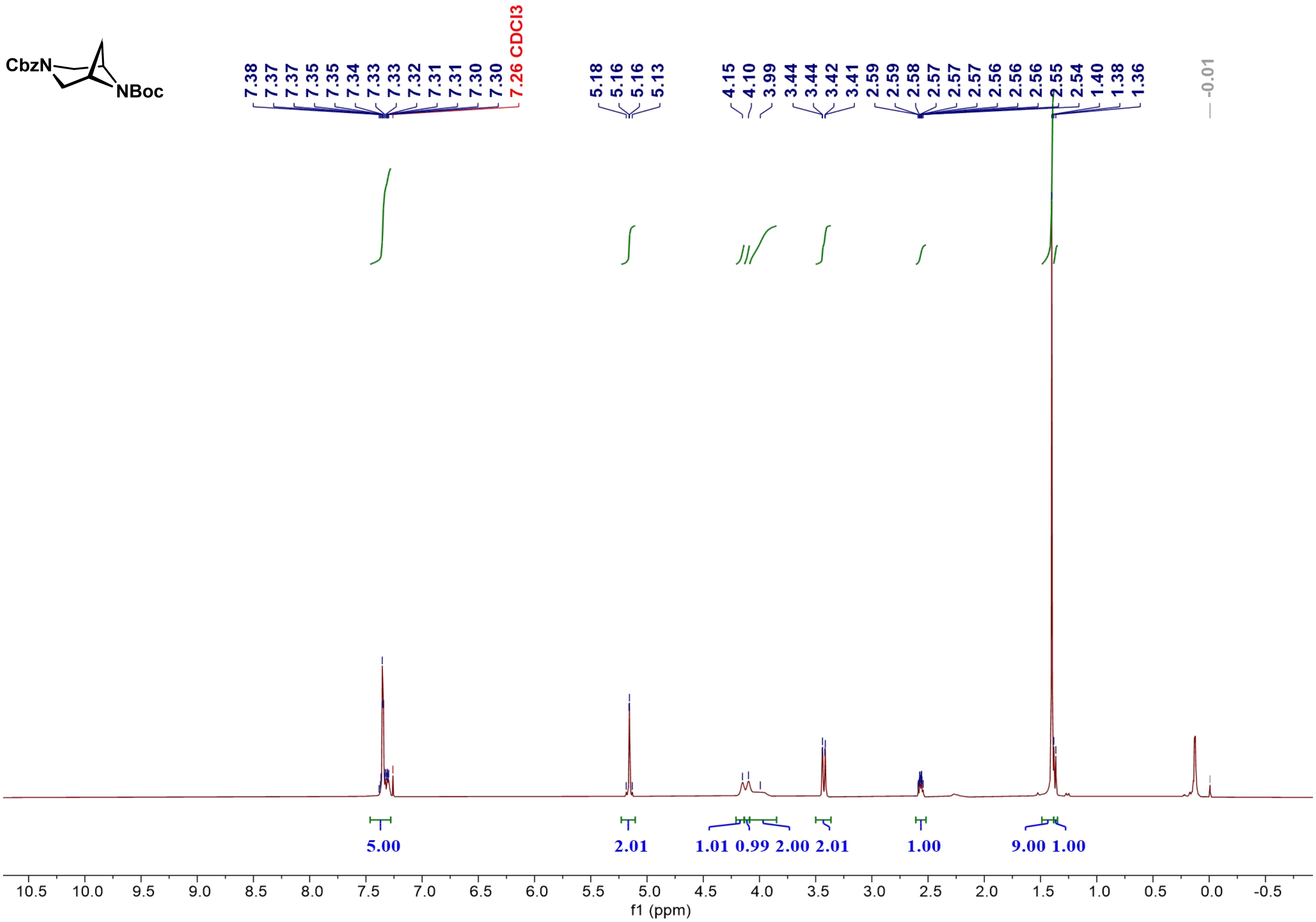
^{1}H NMR Spectrum of compound SI-37 (400 MHz, CDCl$_3$)



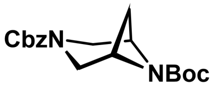
^{13}C NMR Spectrum of compound SI-37 (126 MHz, CDCl$_3$)

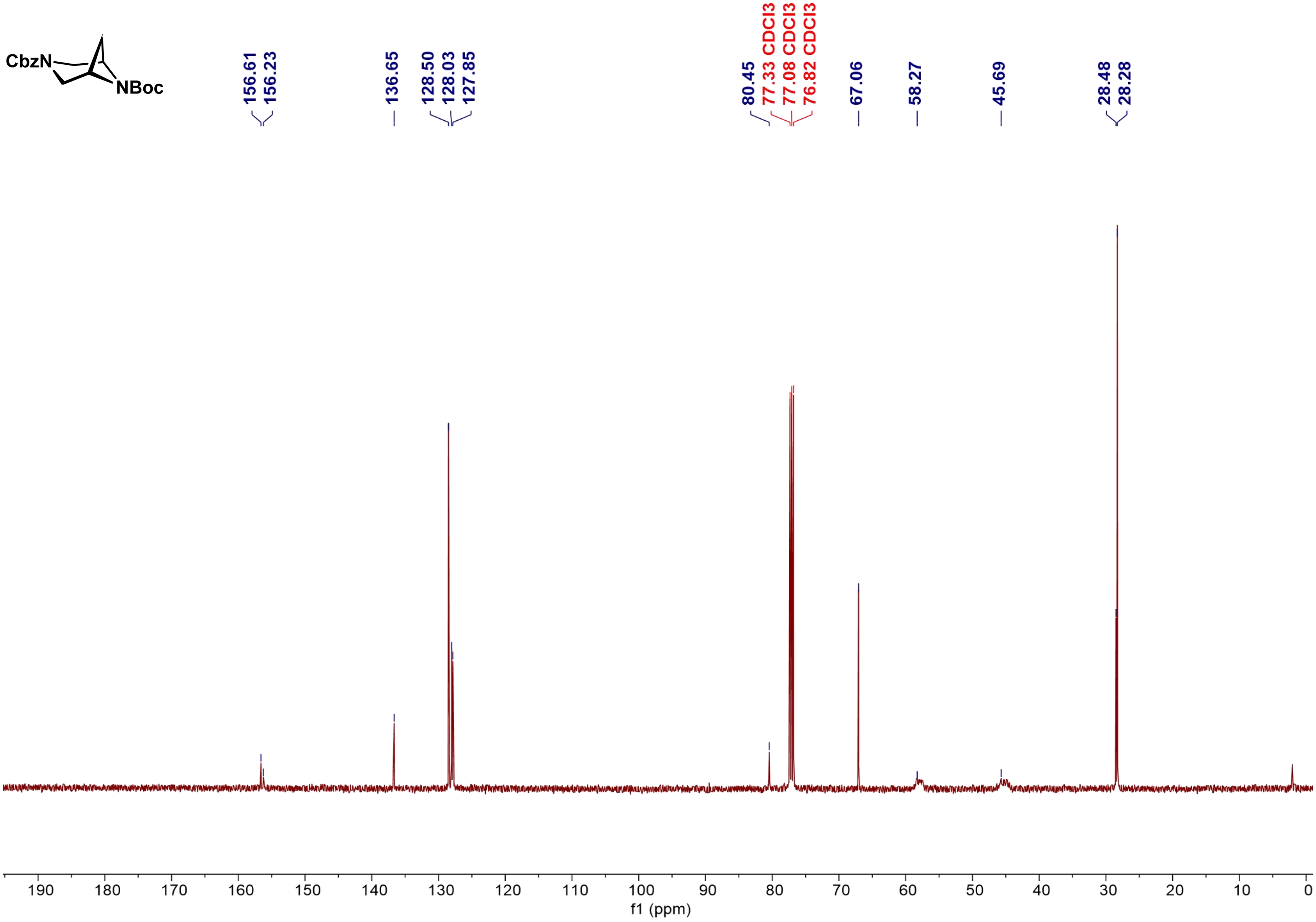


^{1}H NMR Spectrum of compound SI-38 (500 MHz, $CDCl_3$)

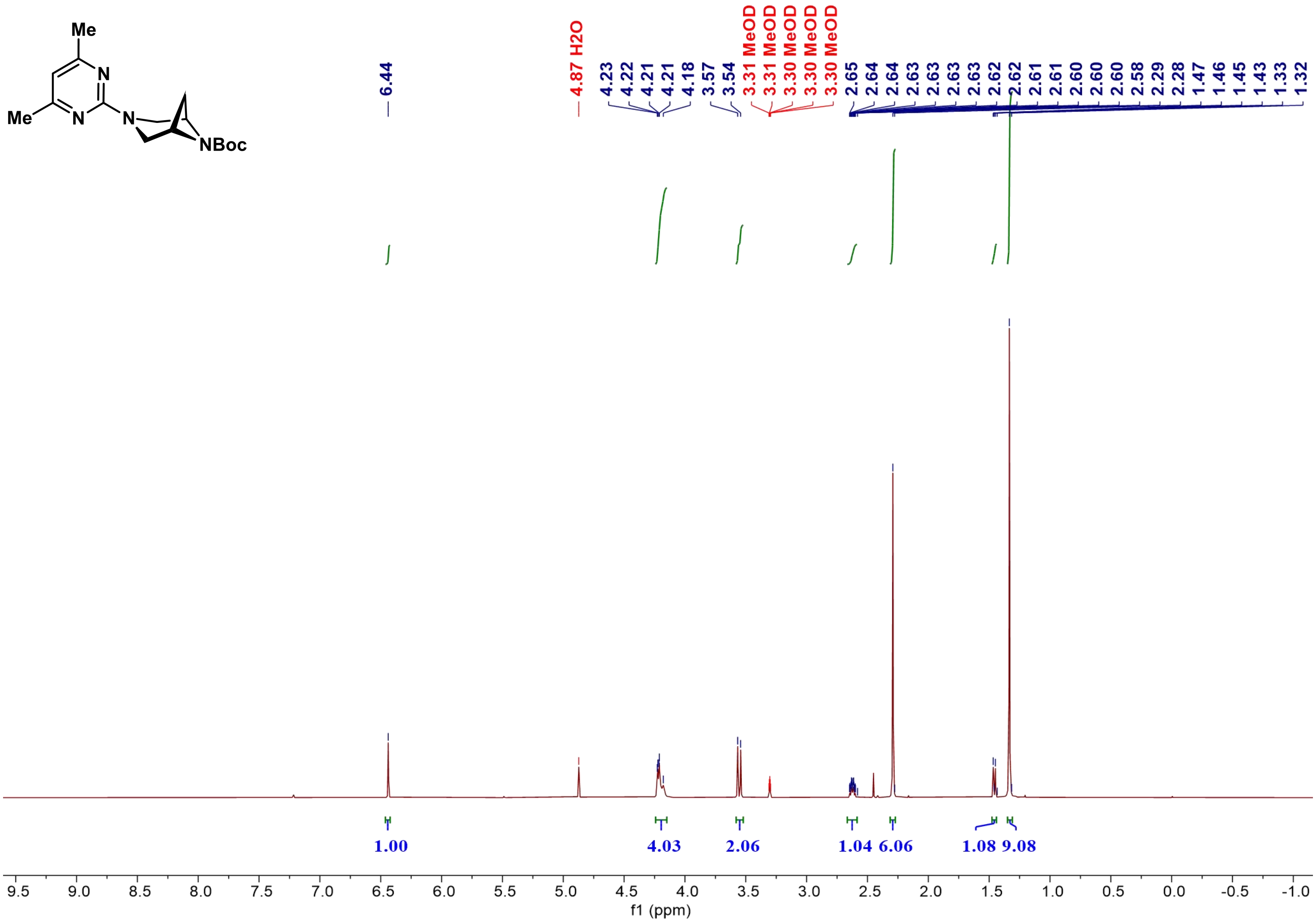


^{13}C NMR Spectrum of compound SI-38 (126 MHz, CDCl$_3$)

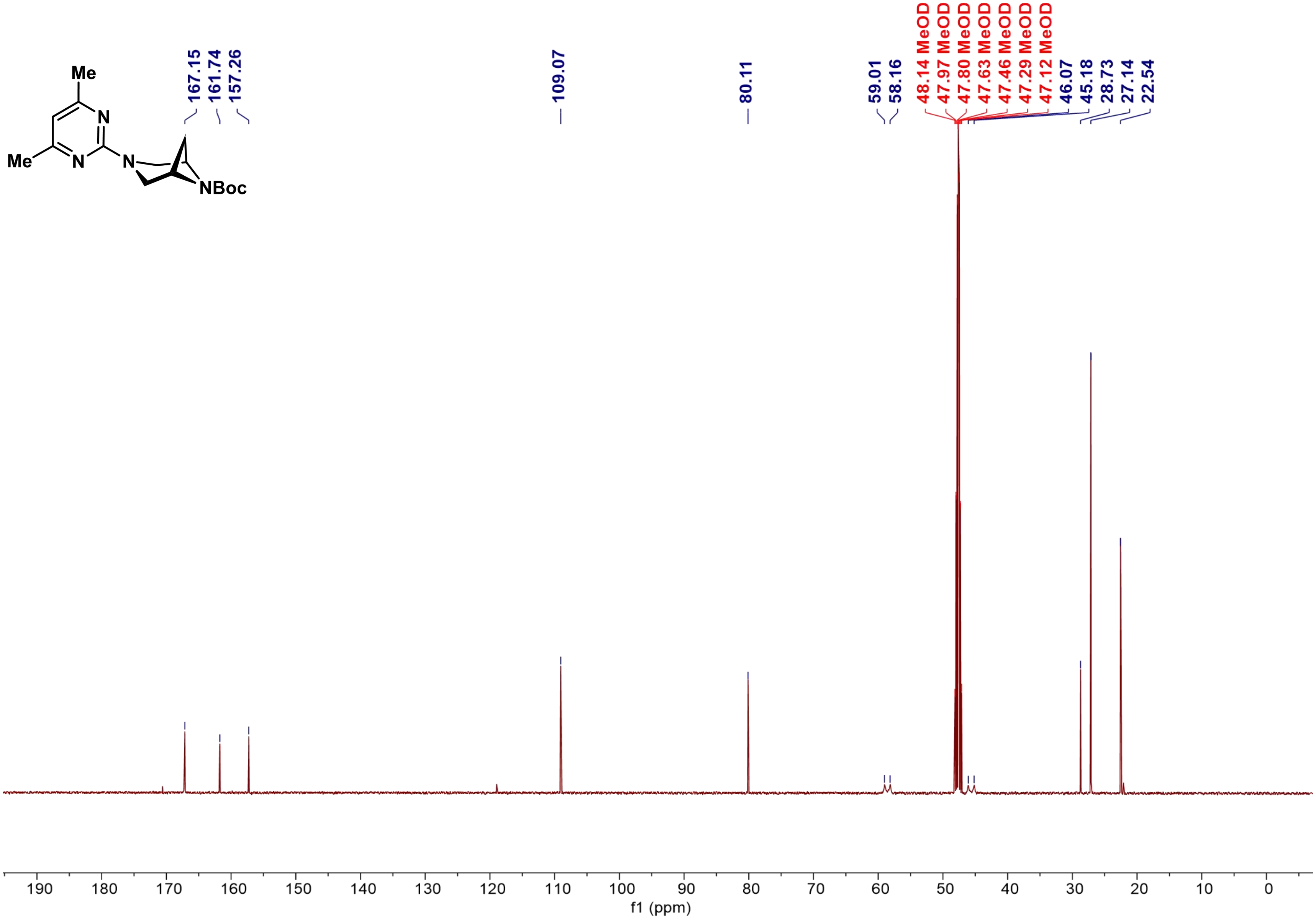




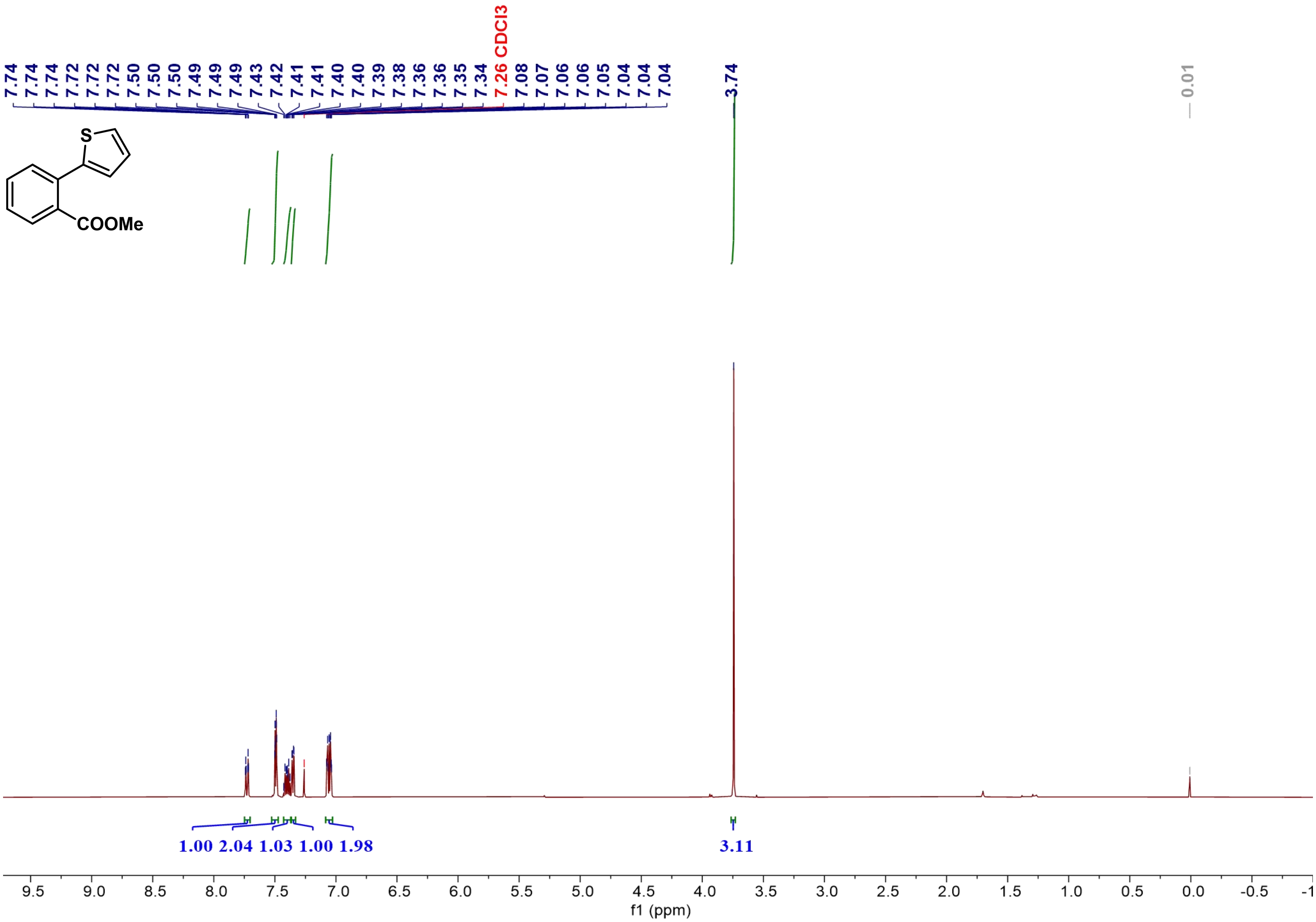
^{1}H NMR Spectrum of compound SI-39 (500 MHz, Methanol-*d*$_4$)



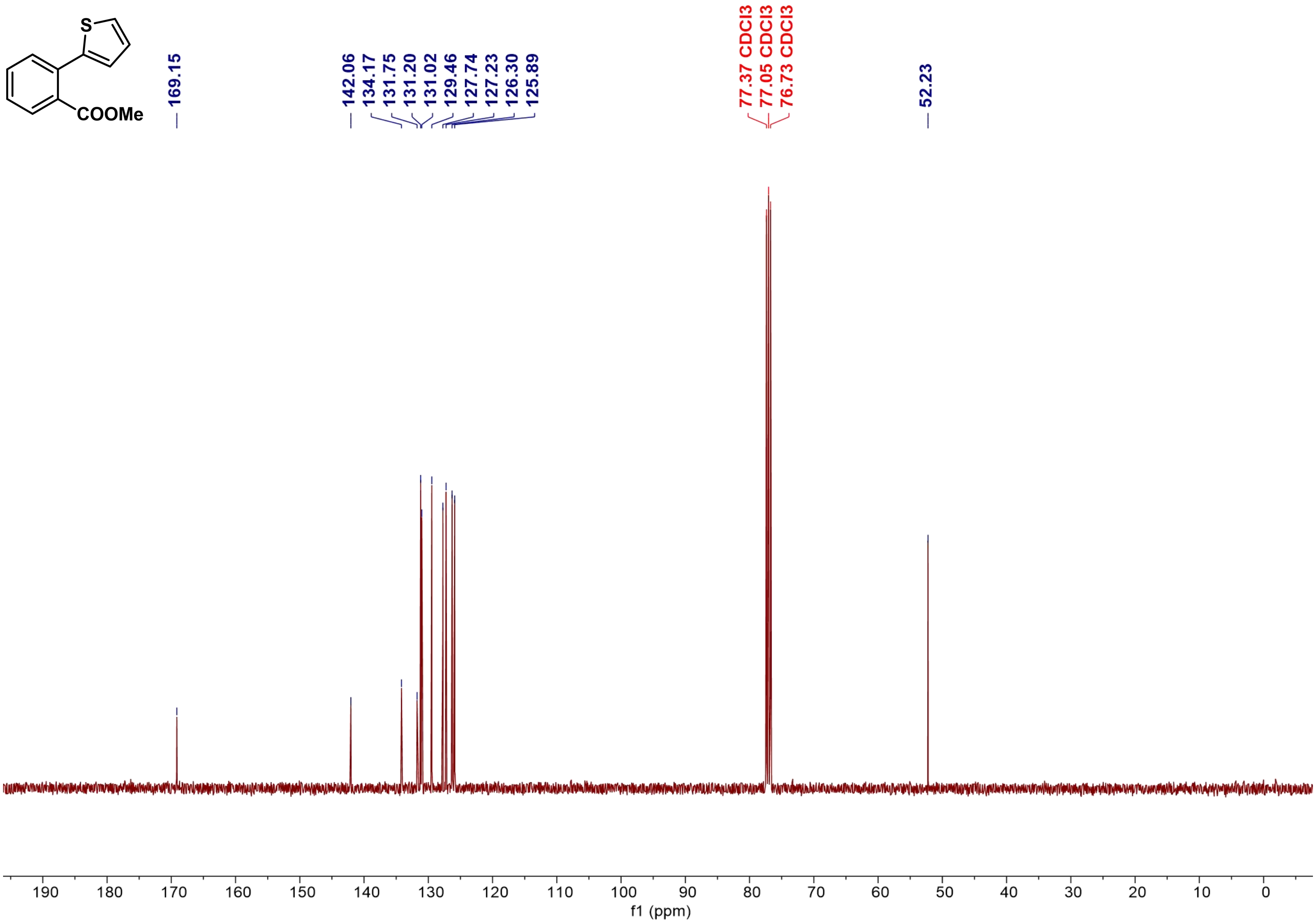
^{13}C NMR Spectrum of compound SI-39 (126 MHz, Methanol-d_4)



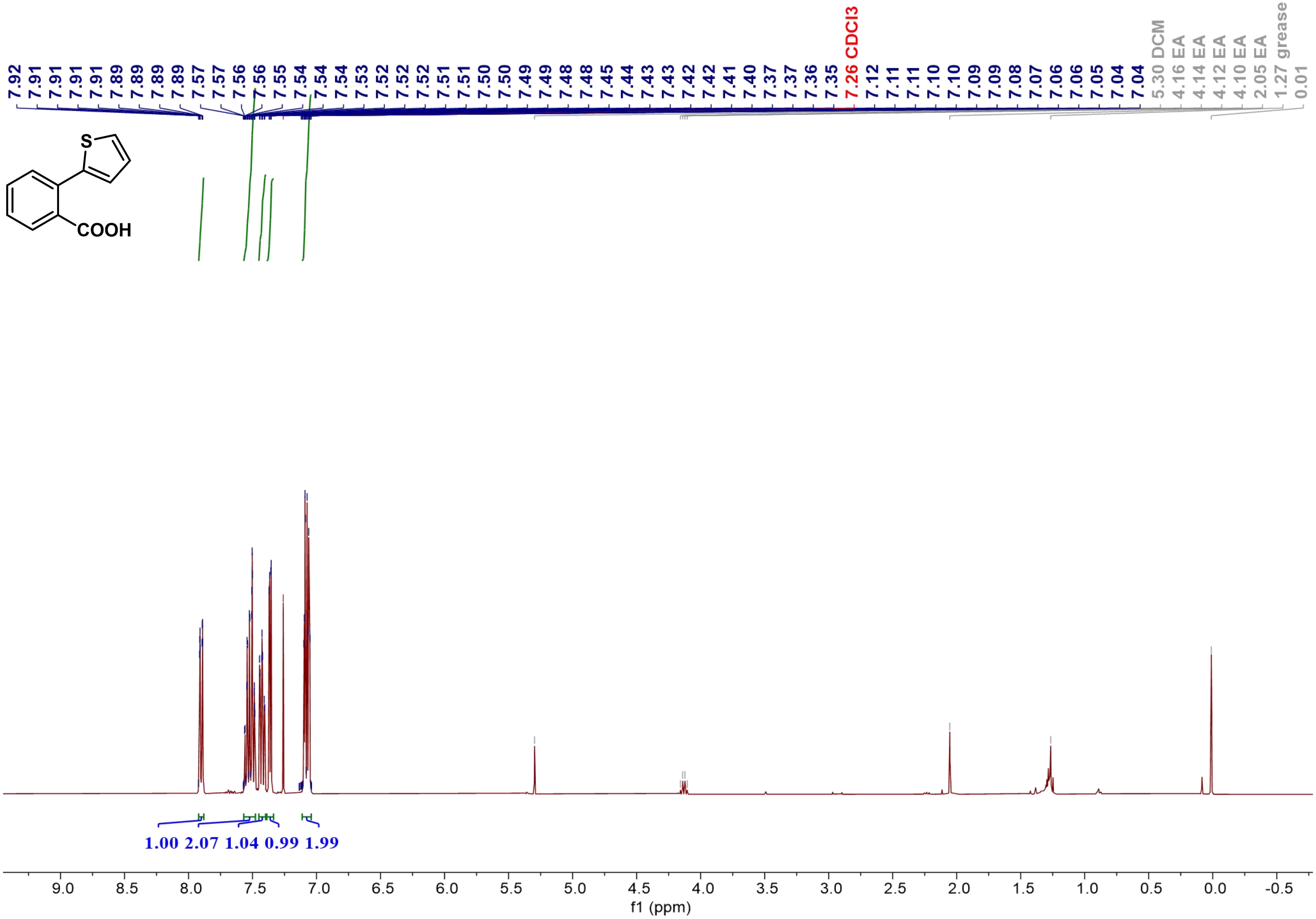
^{1}H NMR Spectrum of compound SI-40 (400 MHz, CDCl$_3$)



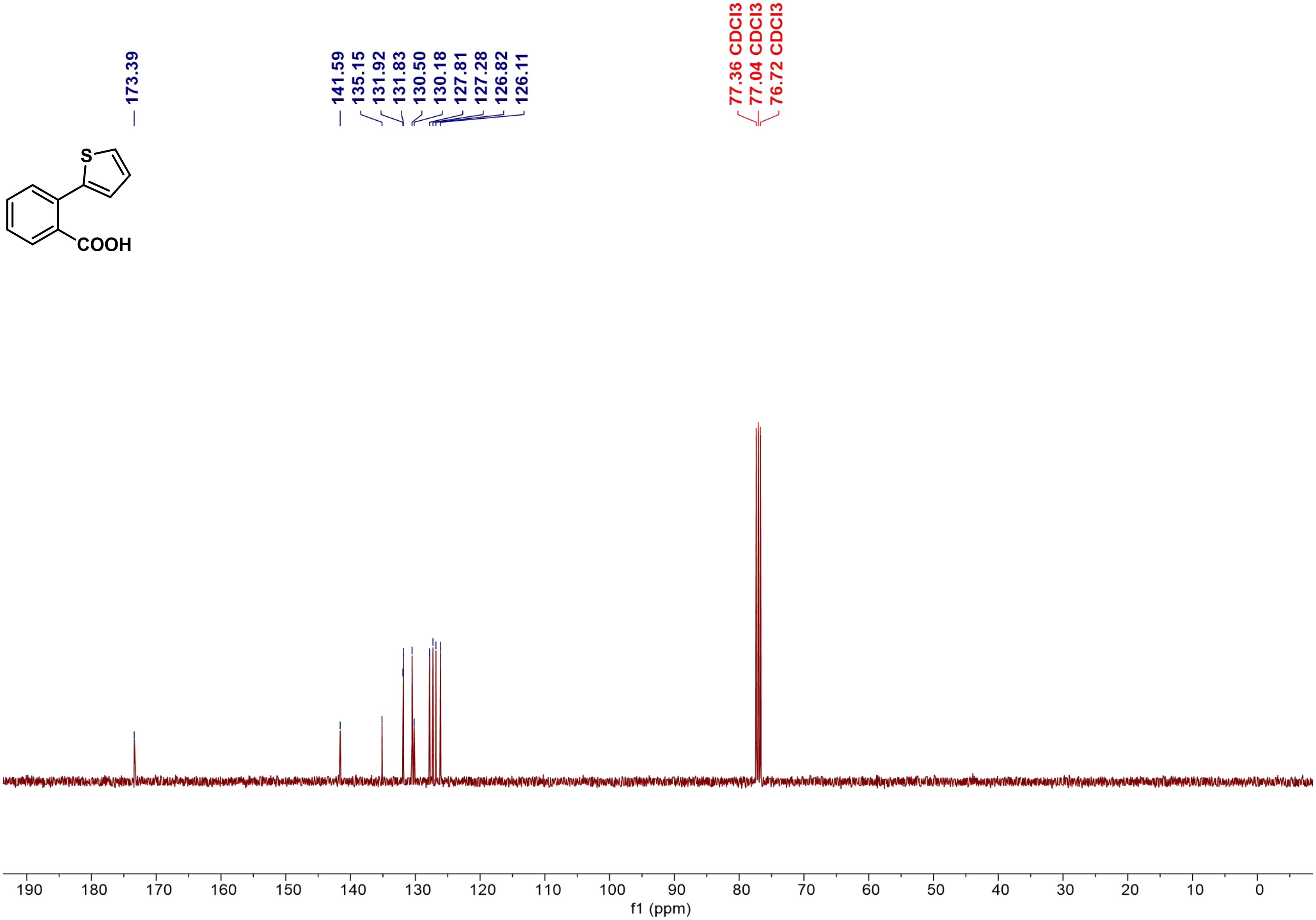
^{13}C NMR Spectrum of compound SI-40 (101 MHz, CDCl$_3$)



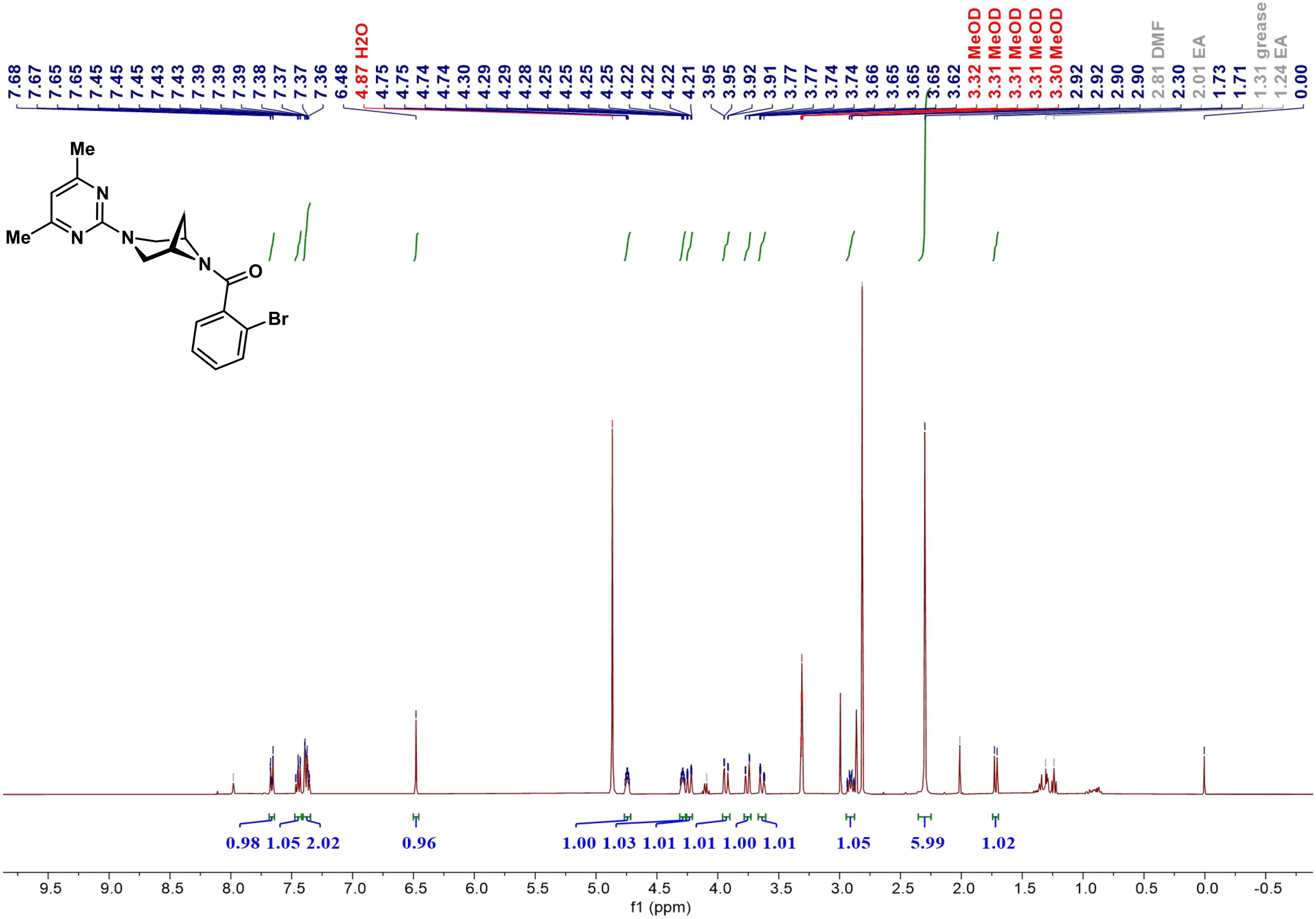
^{1}H NMR Spectrum of compound SI-41 (400 MHz, $CDCl_3$)



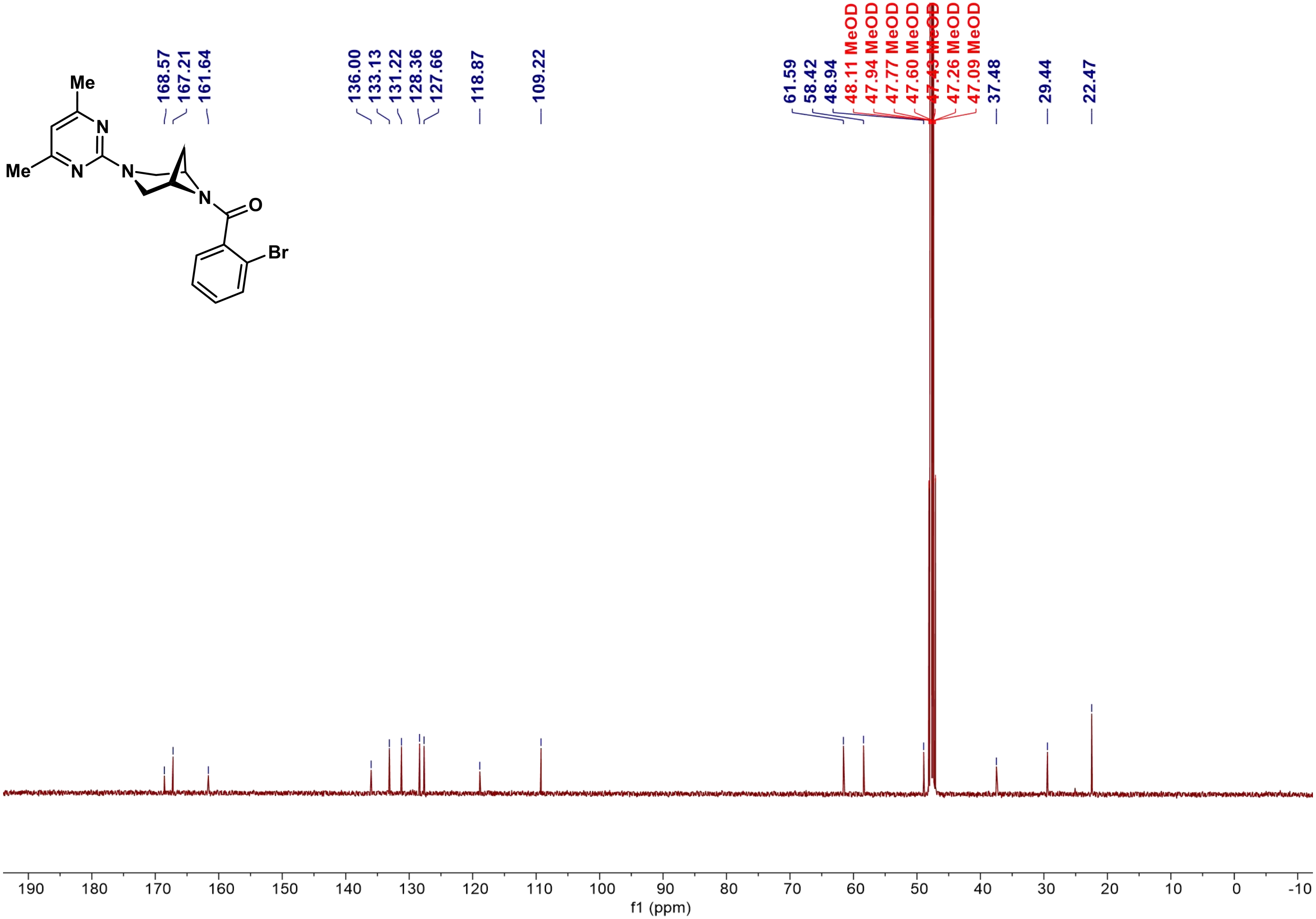
^{13}C NMR Spectrum of compound SI-41 (101 MHz, $CDCl_3$)



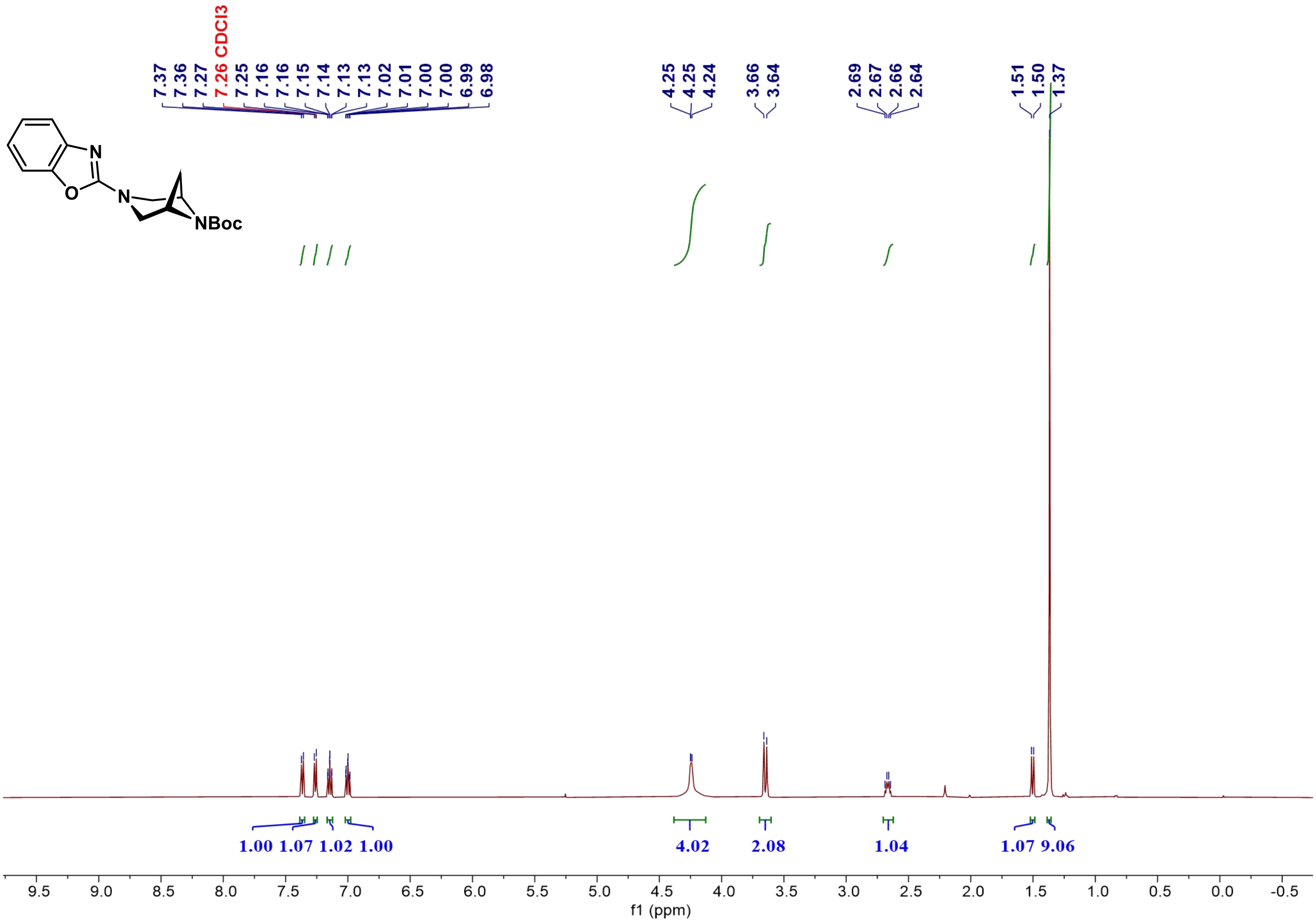
^{1}H NMR Spectrum of compound SI-42 (500 MHz, Methanol-d_4)



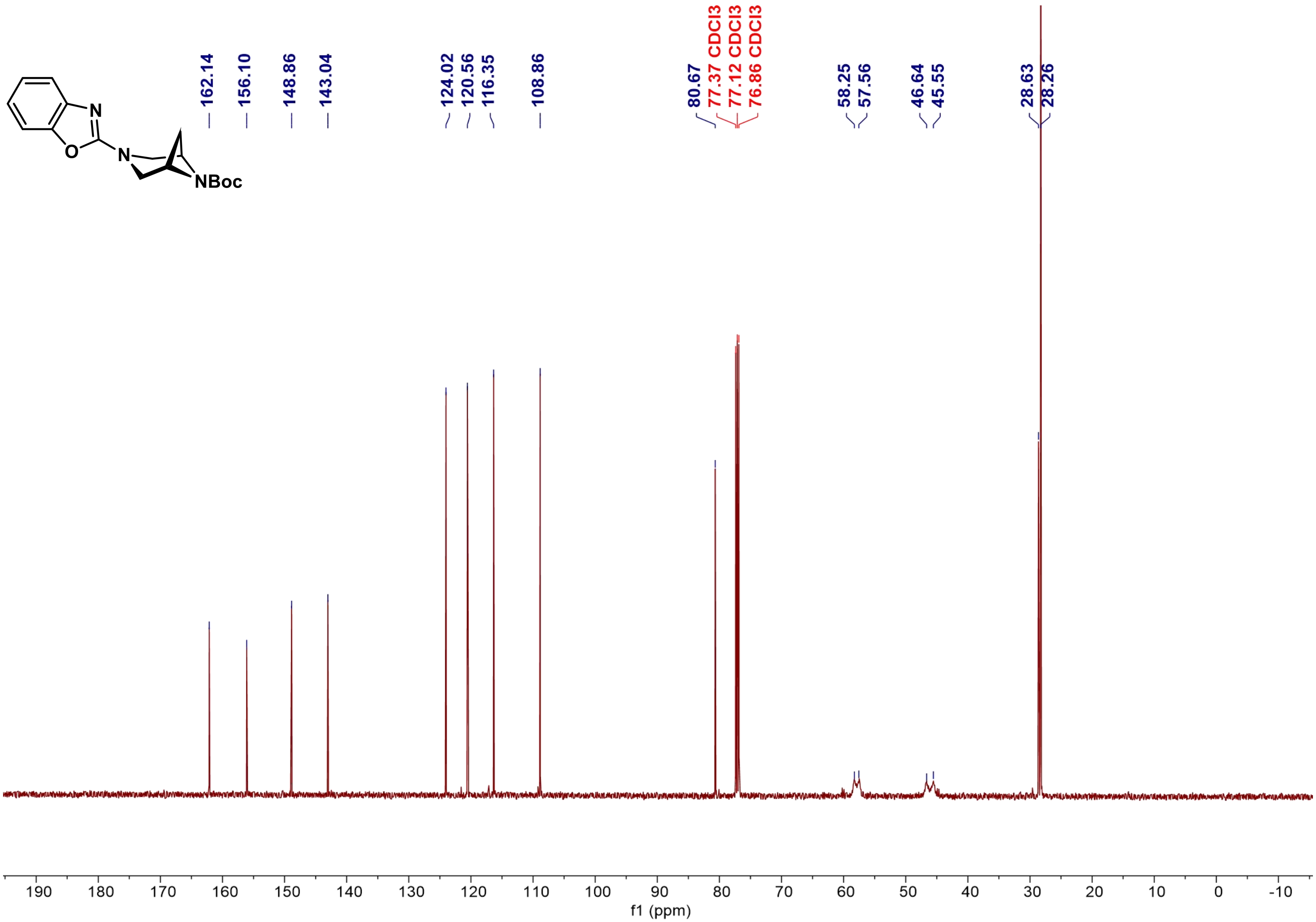
^{13}**C NMR Spectrum of compound SI-42 (126 MHz, Methanol-*d*$_4$)**



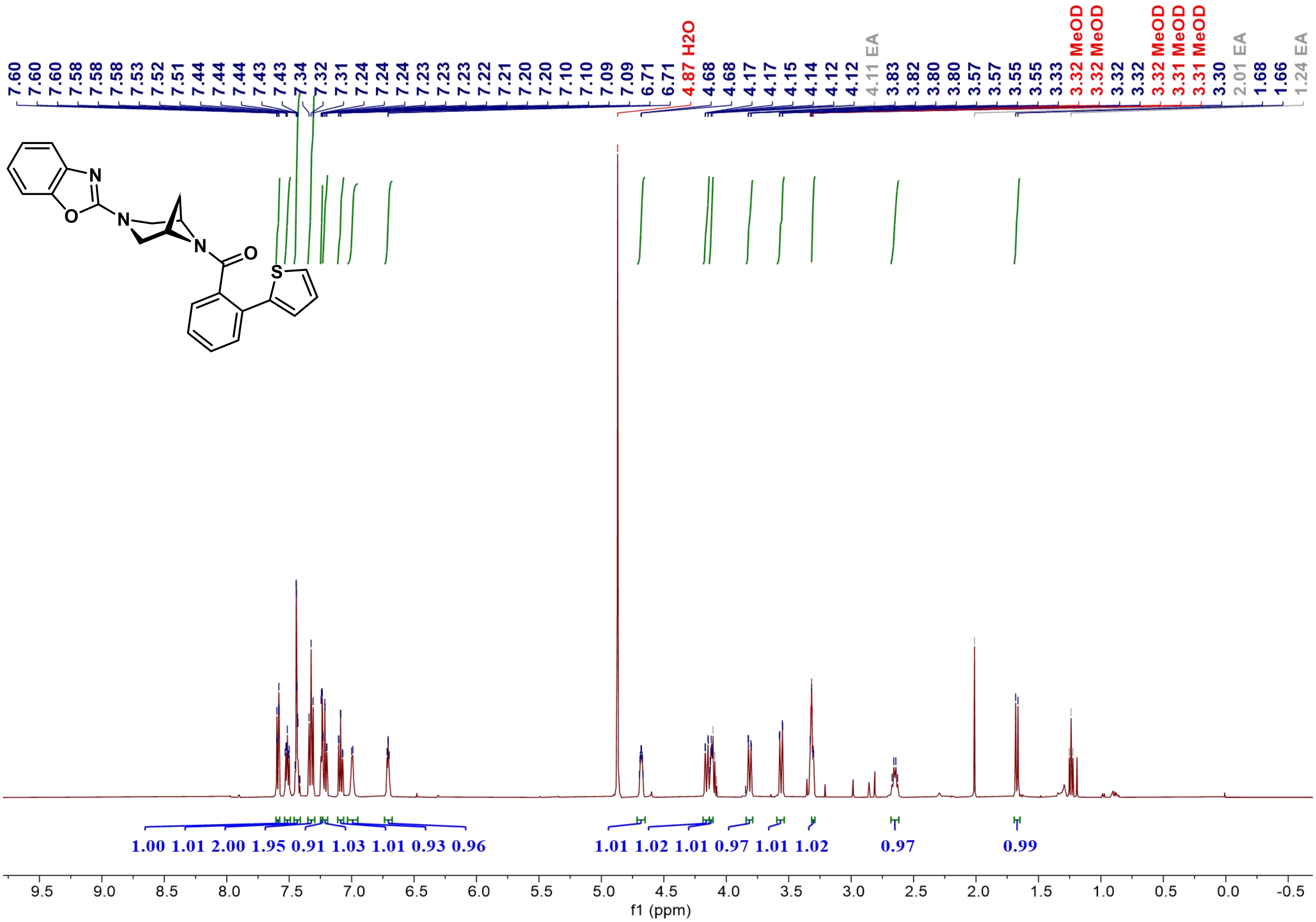
^{1}H NMR Spectrum of compound SI-43 (500 MHz, $CDCl_3$)



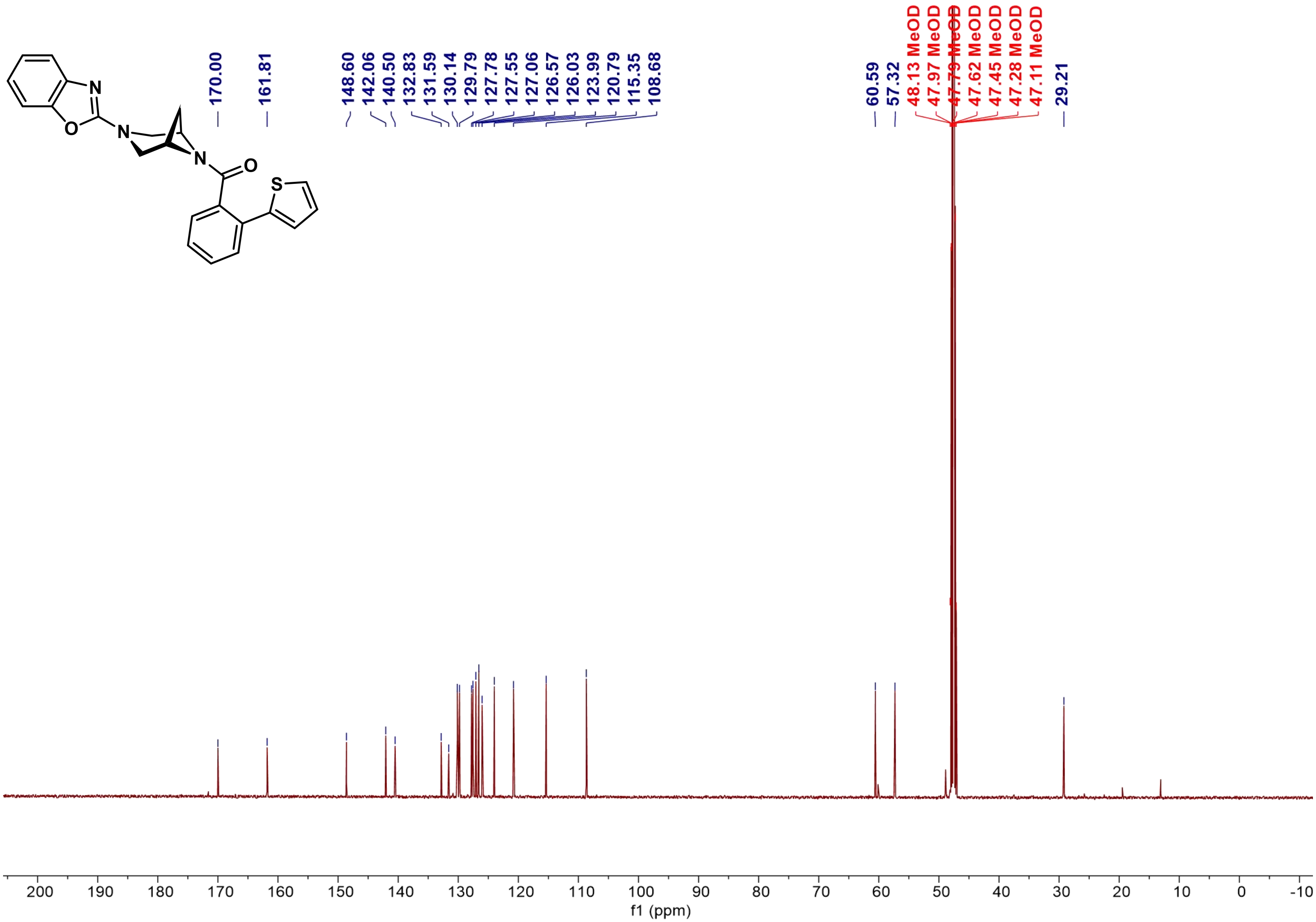
^{13}C NMR Spectrum of compound SI-43 (126 MHz, $CDCl_3$)



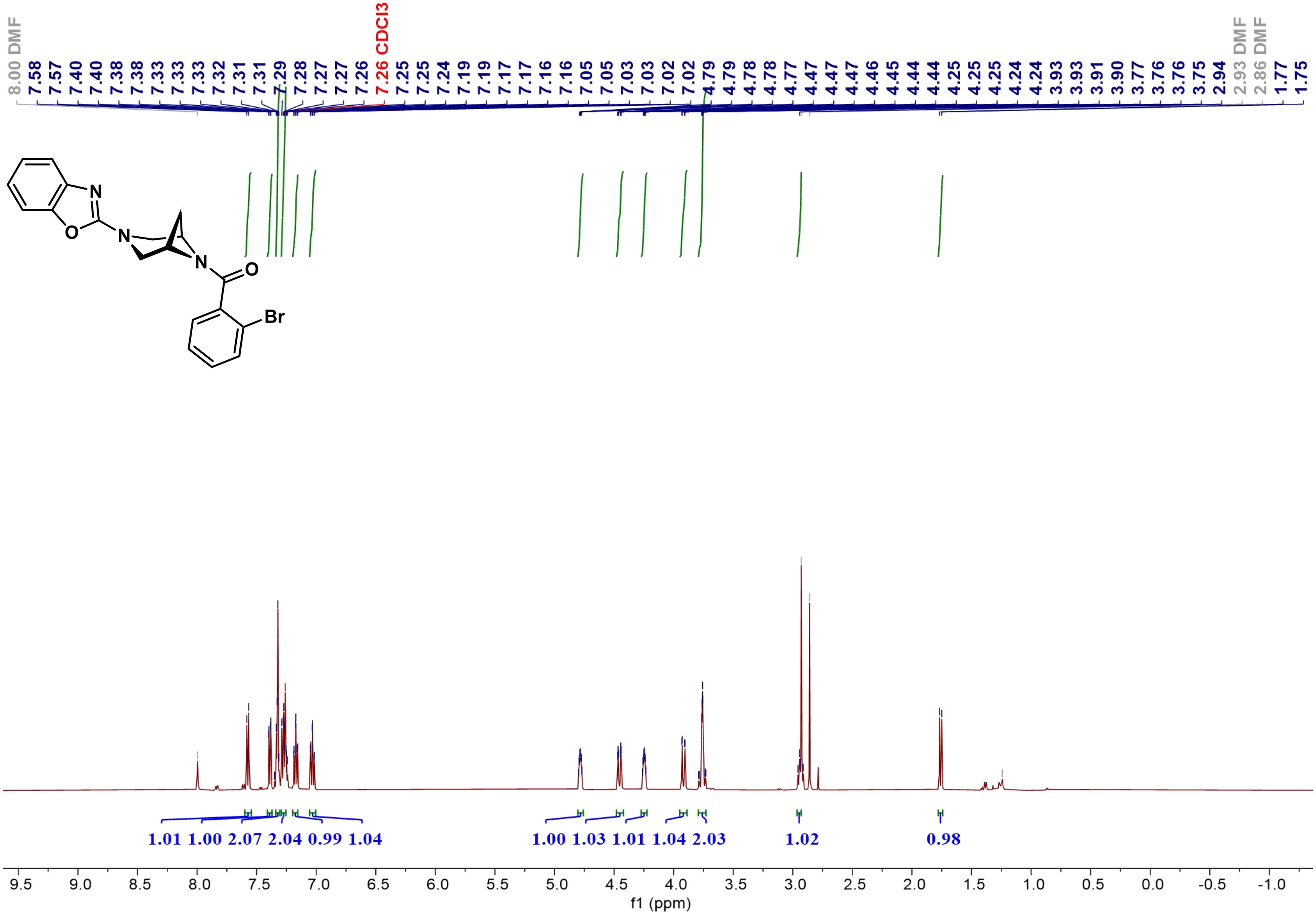
^{1}H NMR Spectrum of compound SI-44 (500 MHz, Methanol-d_4)



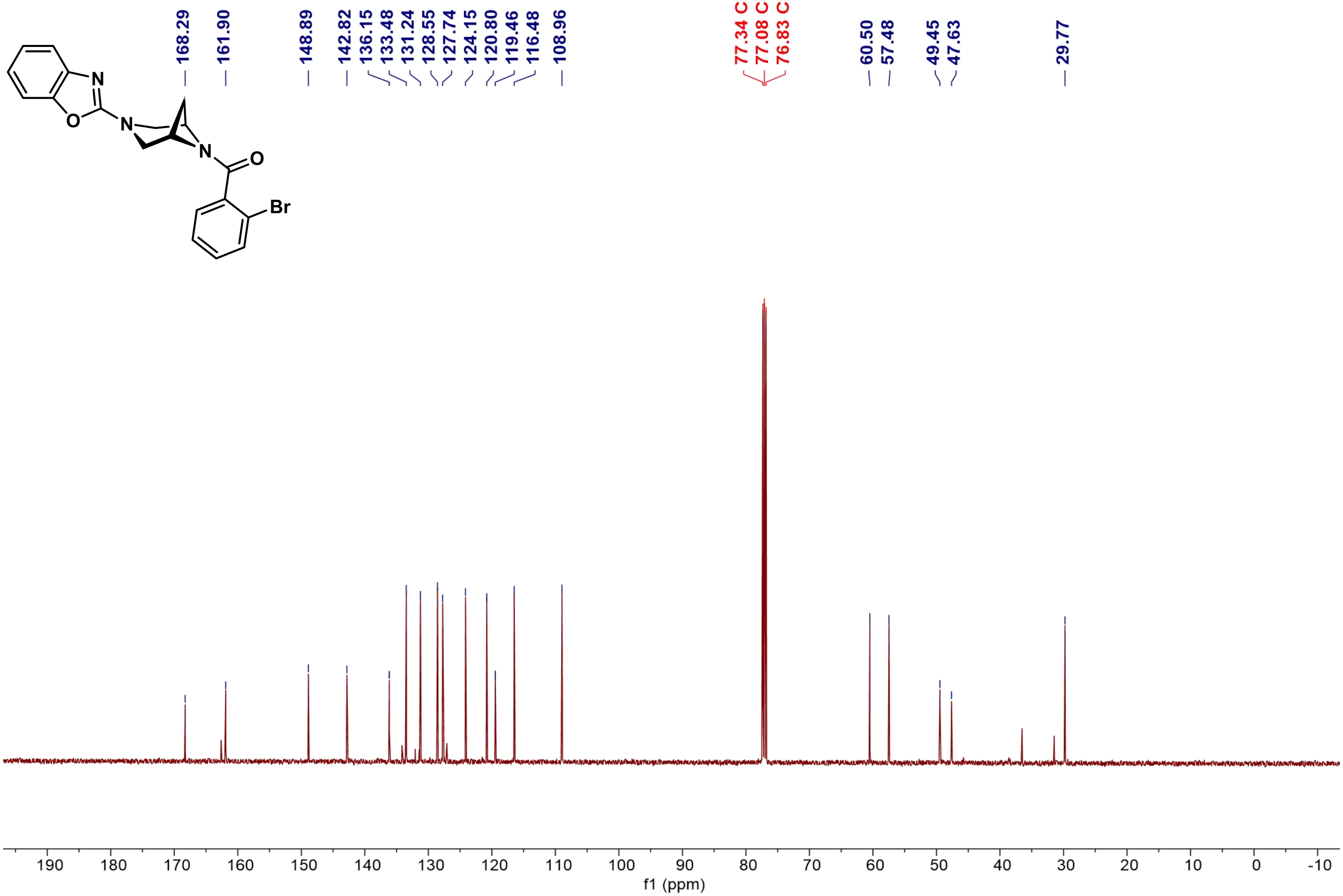
^{13}C NMR Spectrum of compound SI-44 (126 MHz, Methanol-d_4)



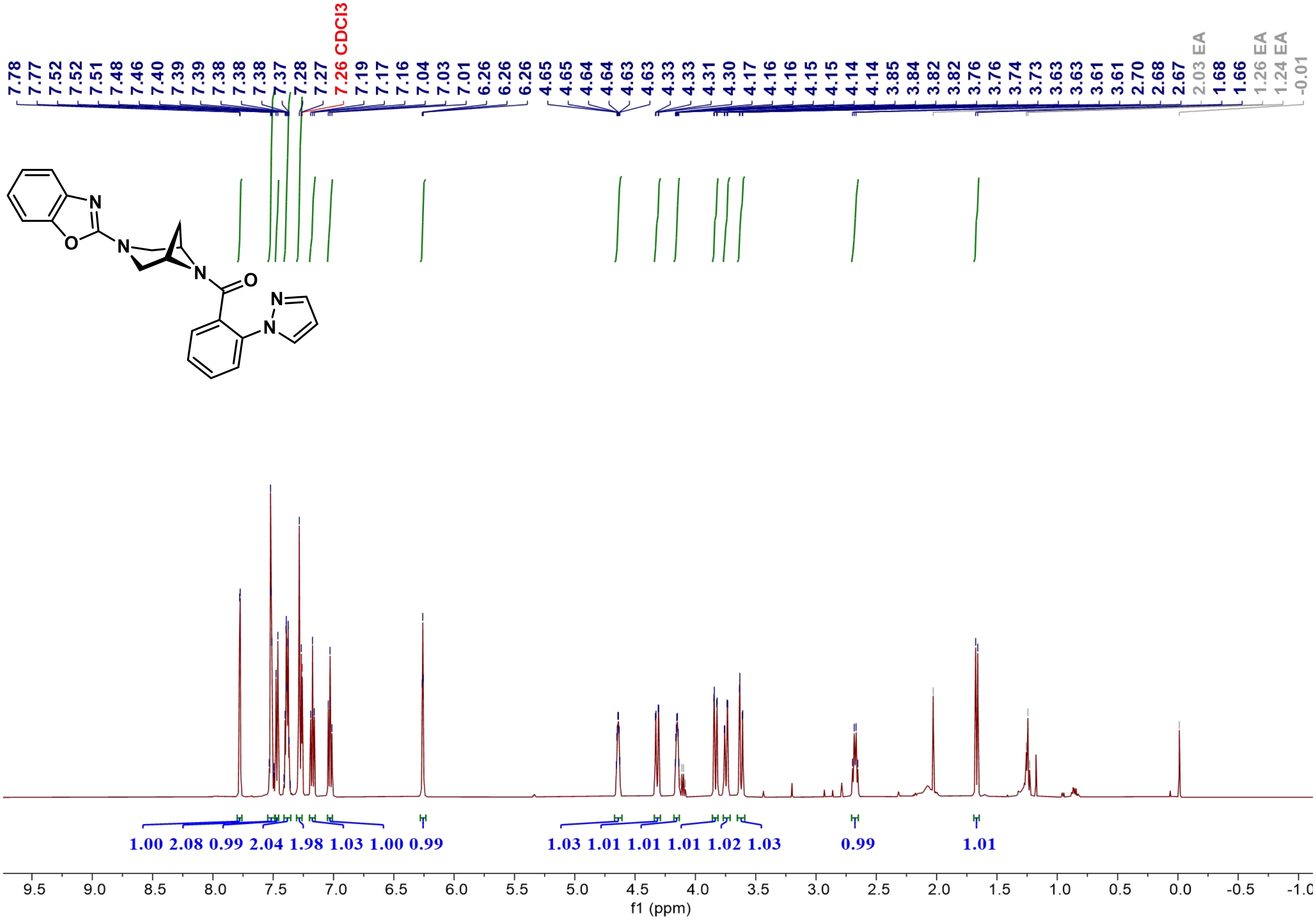
^{1}H NMR Spectrum of compound SI-45 (500 MHz, $CDCl_3$)



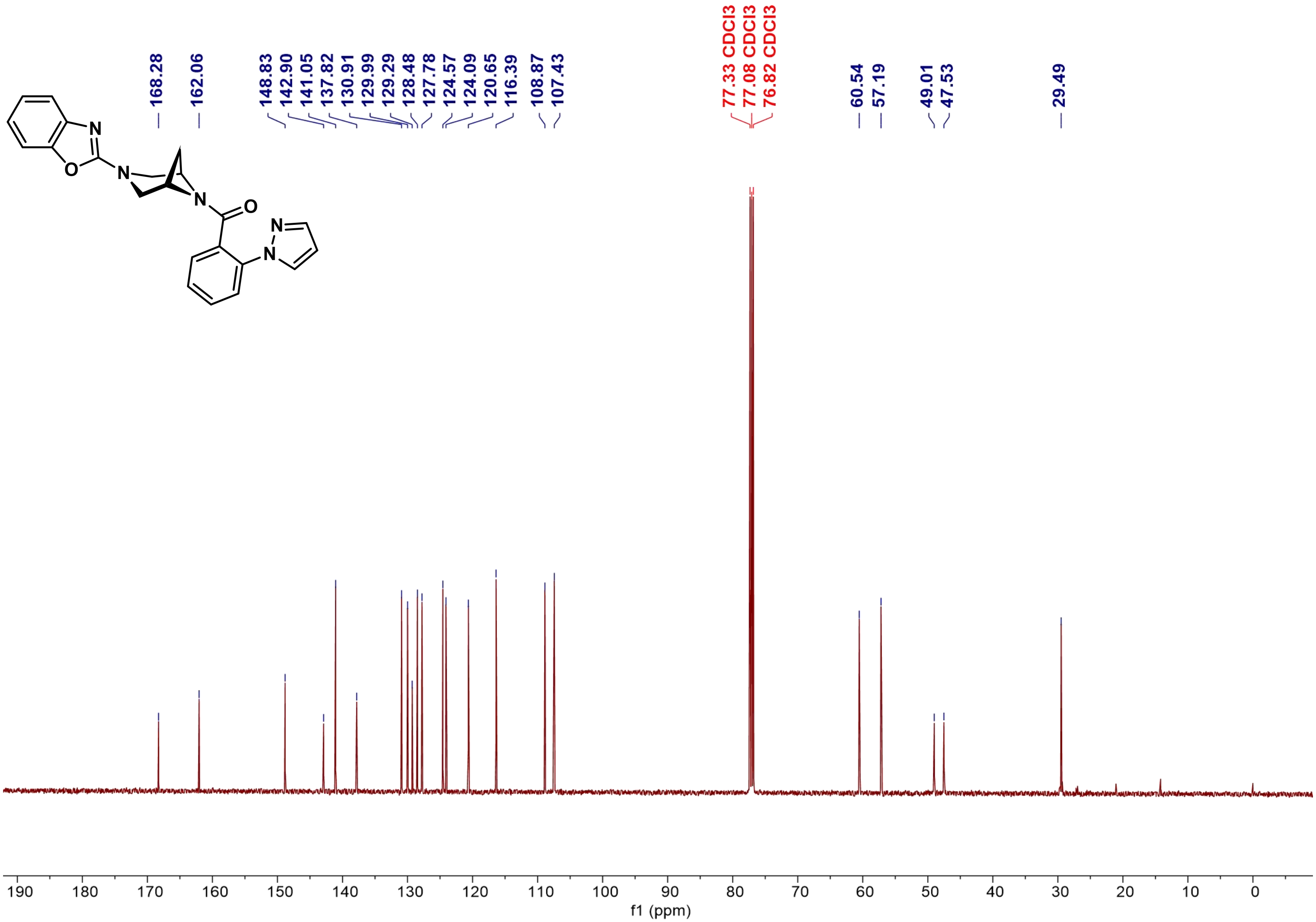
^{13}C NMR Spectrum of compound SI-45 (126 MHz, CDCl$_3$)



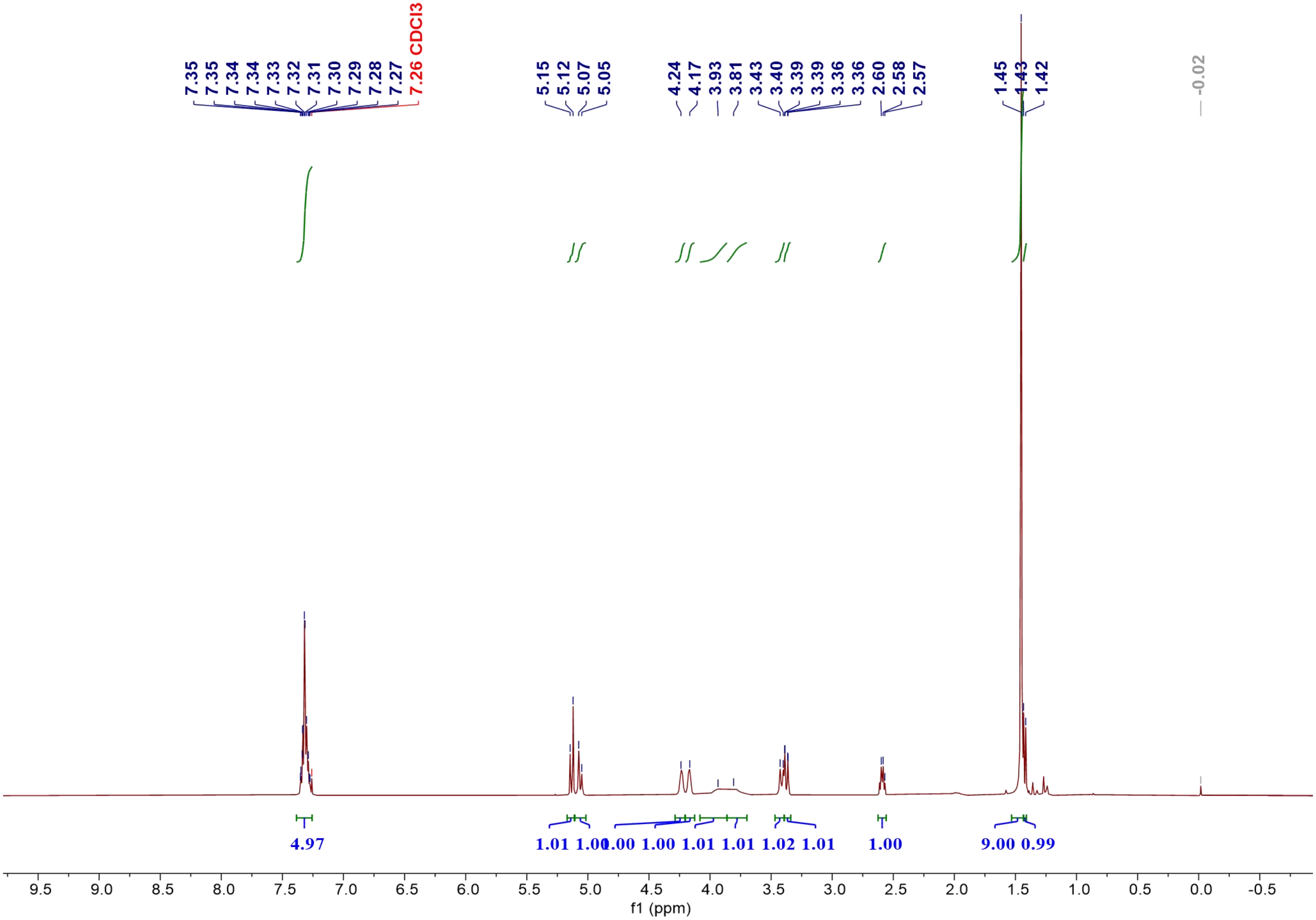
^{1}H NMR Spectrum of compound SI-46 (500 MHz, $CDCl_3$)



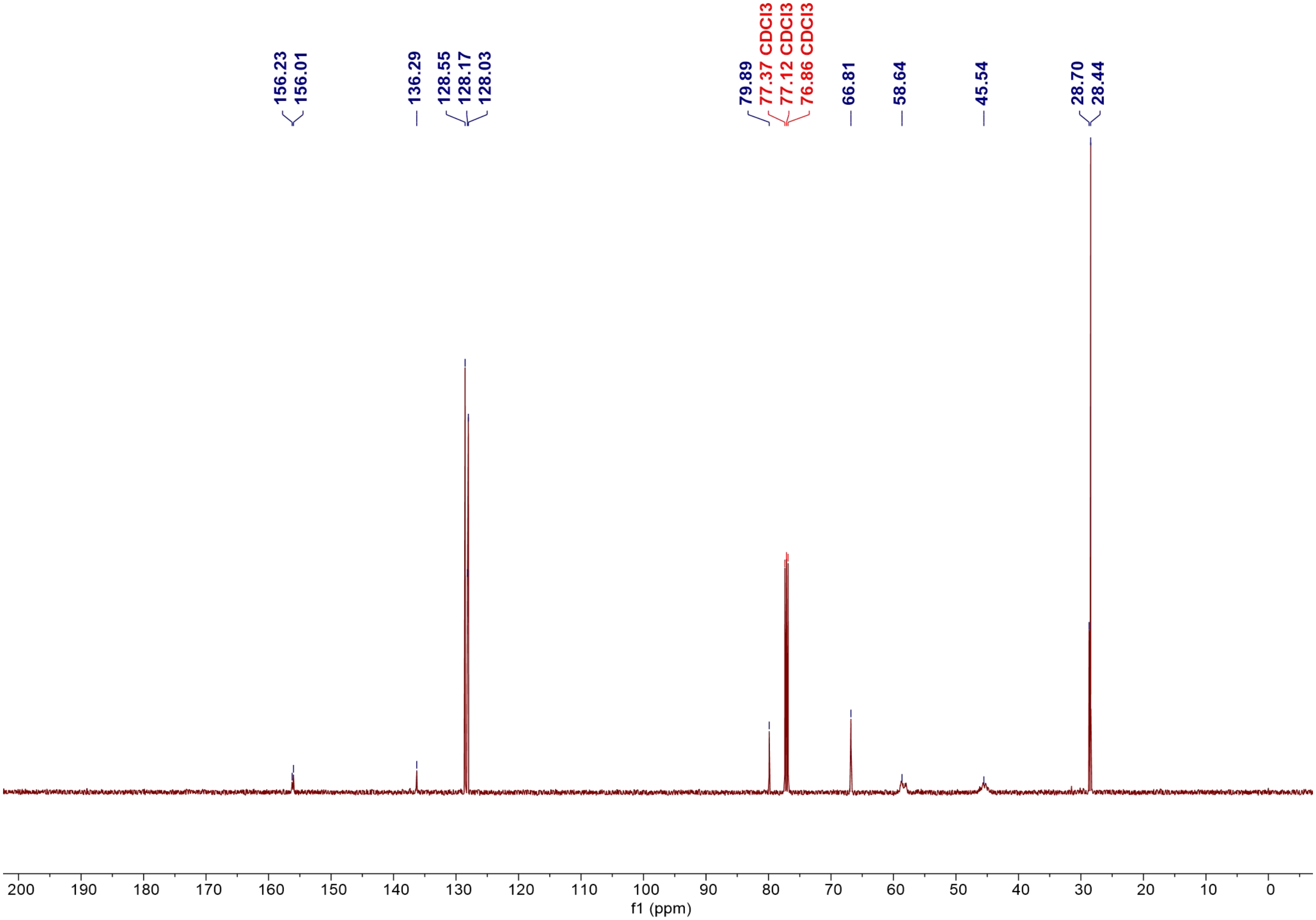
^{13}C NMR Spectrum of compound SI-46 (126 MHz, CDCl$_3$)



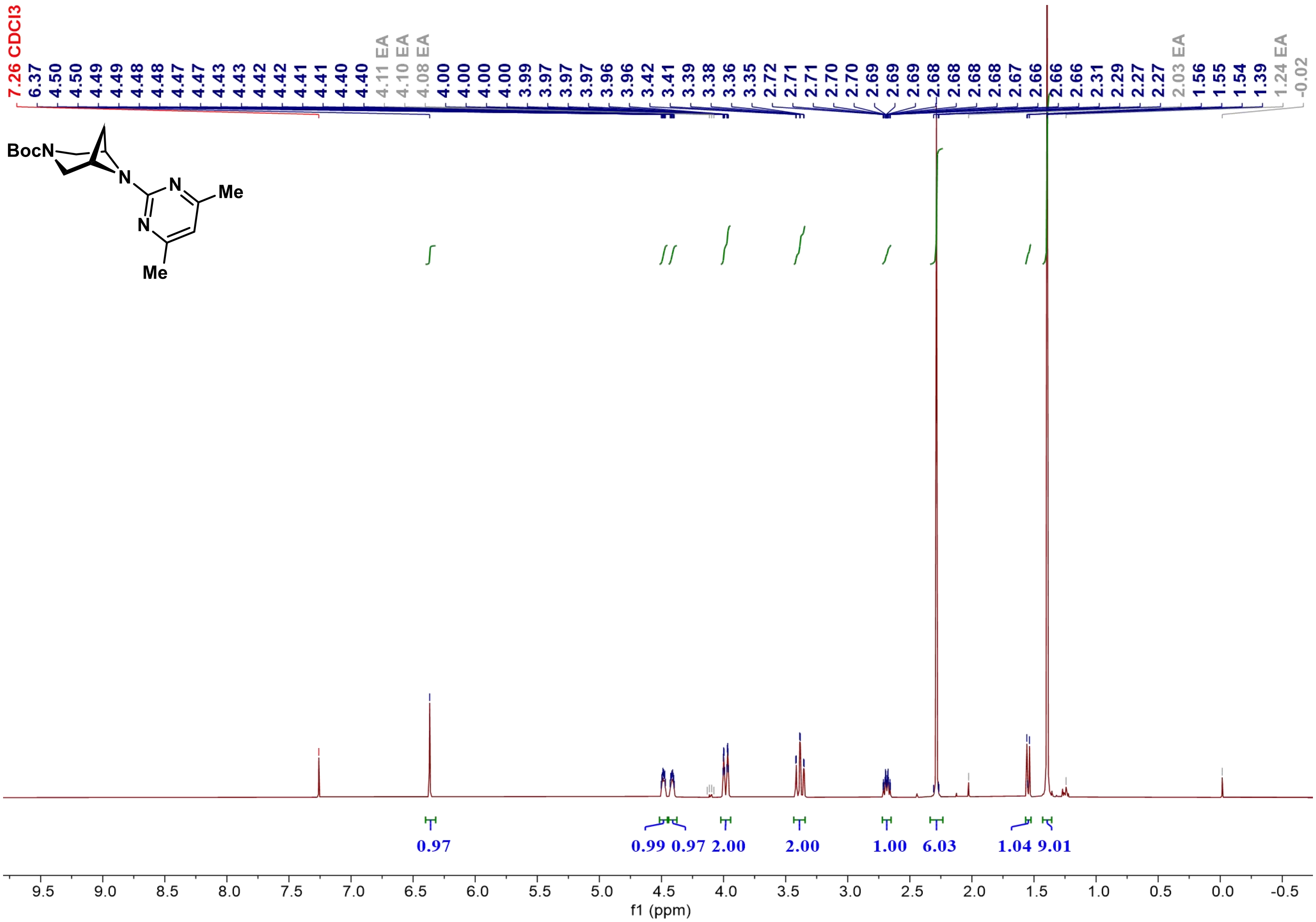
^{1}H NMR Spectrum of compound SI-47 (500 MHz, CDCl$_3$)



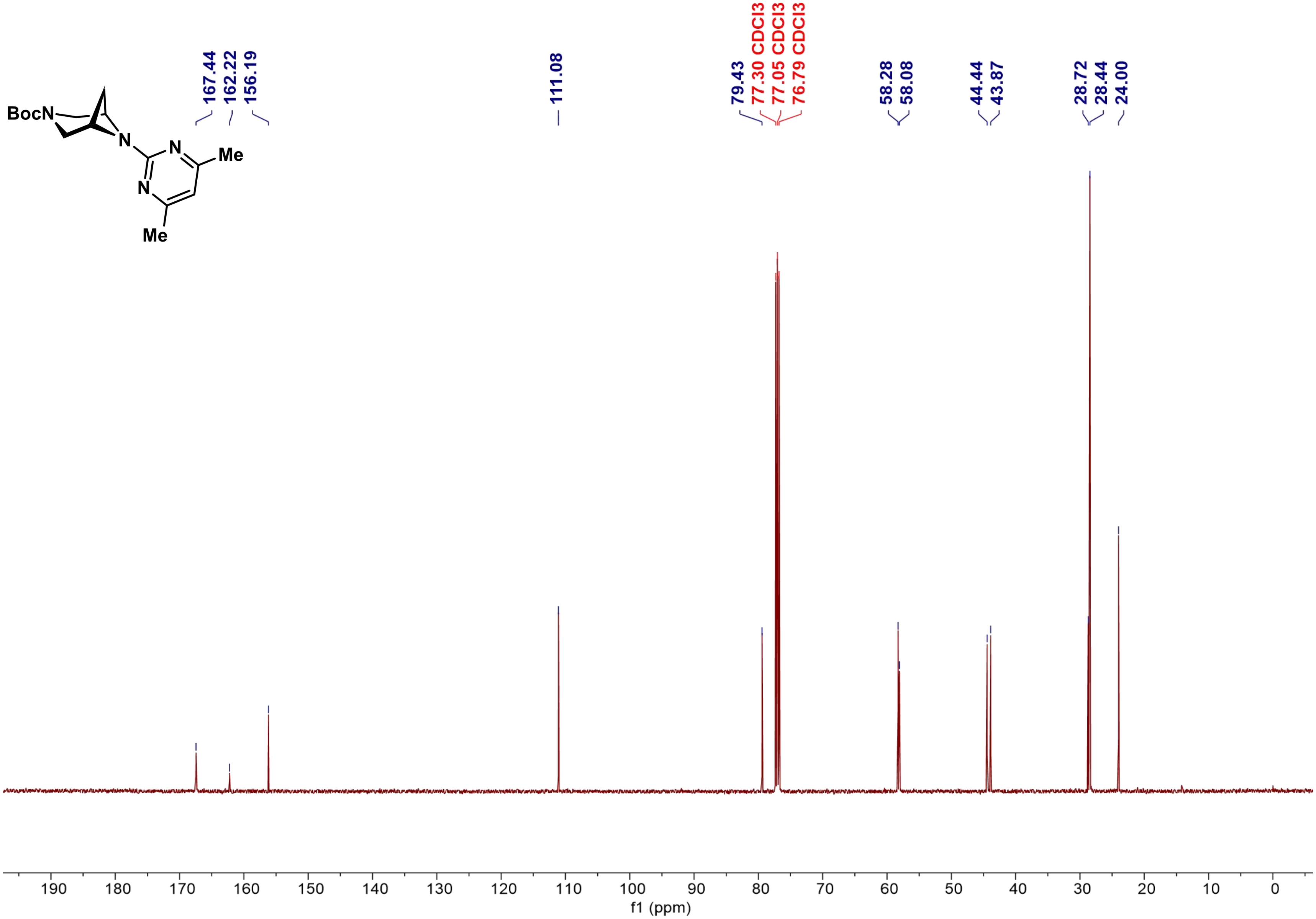
^{13}C NMR Spectrum of compound SI-47 (126 MHz, CDCl$_3$)



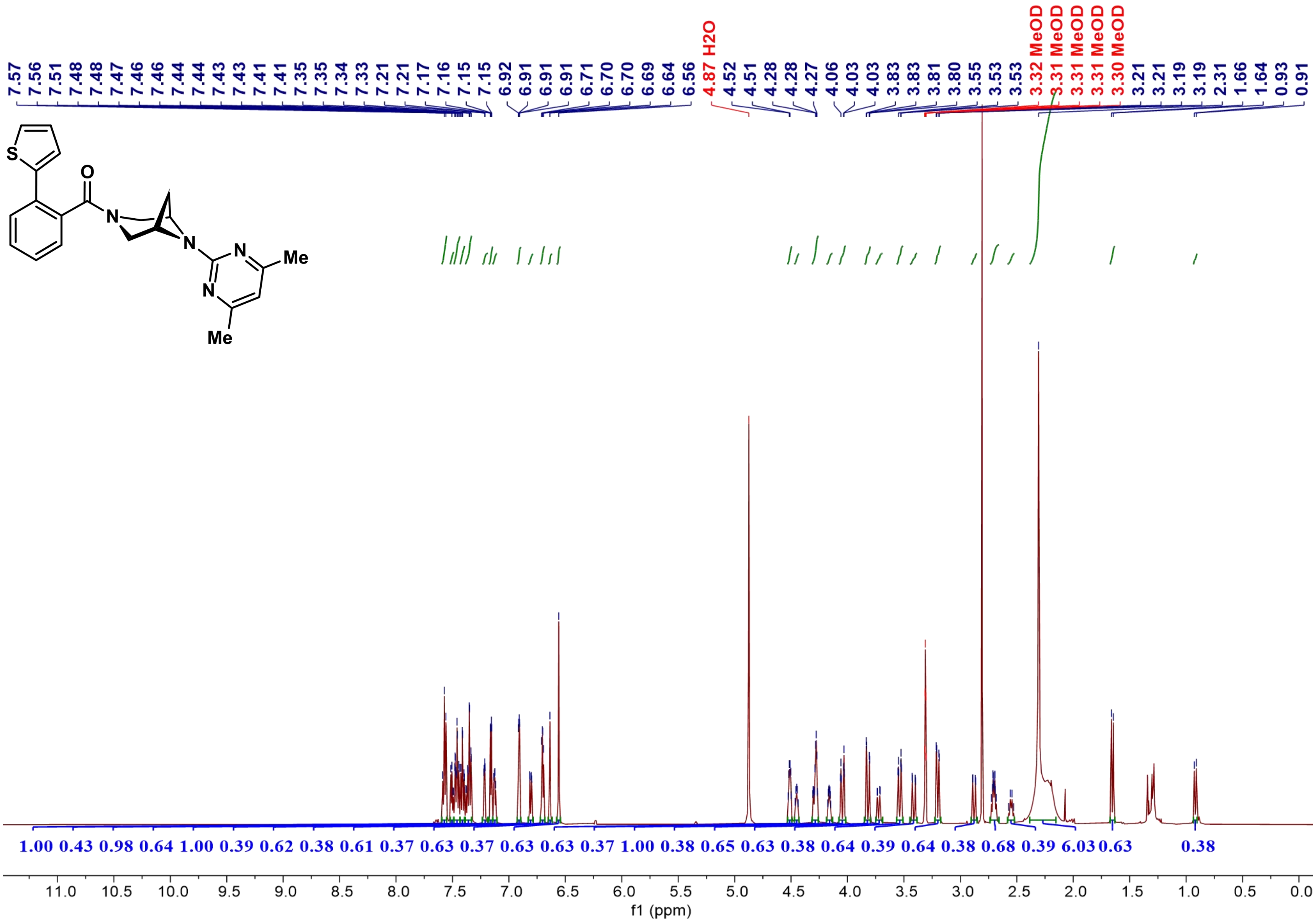
^{1}H NMR Spectrum of compound SI-48 (500 MHz, CDCl$_3$)



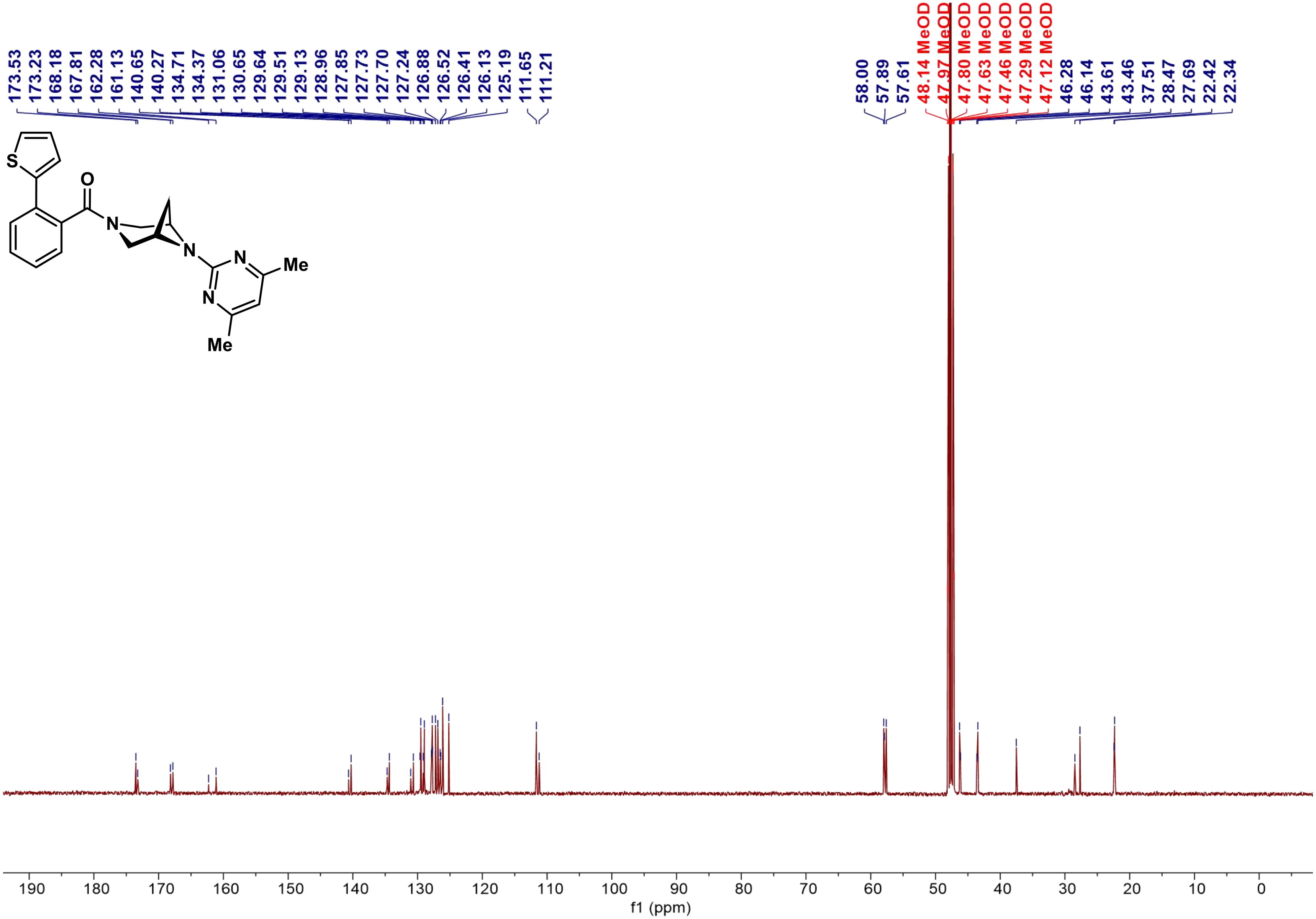
^{13}C NMR Spectrum of compound SI-48 (126 MHz, $CDCl_3$)



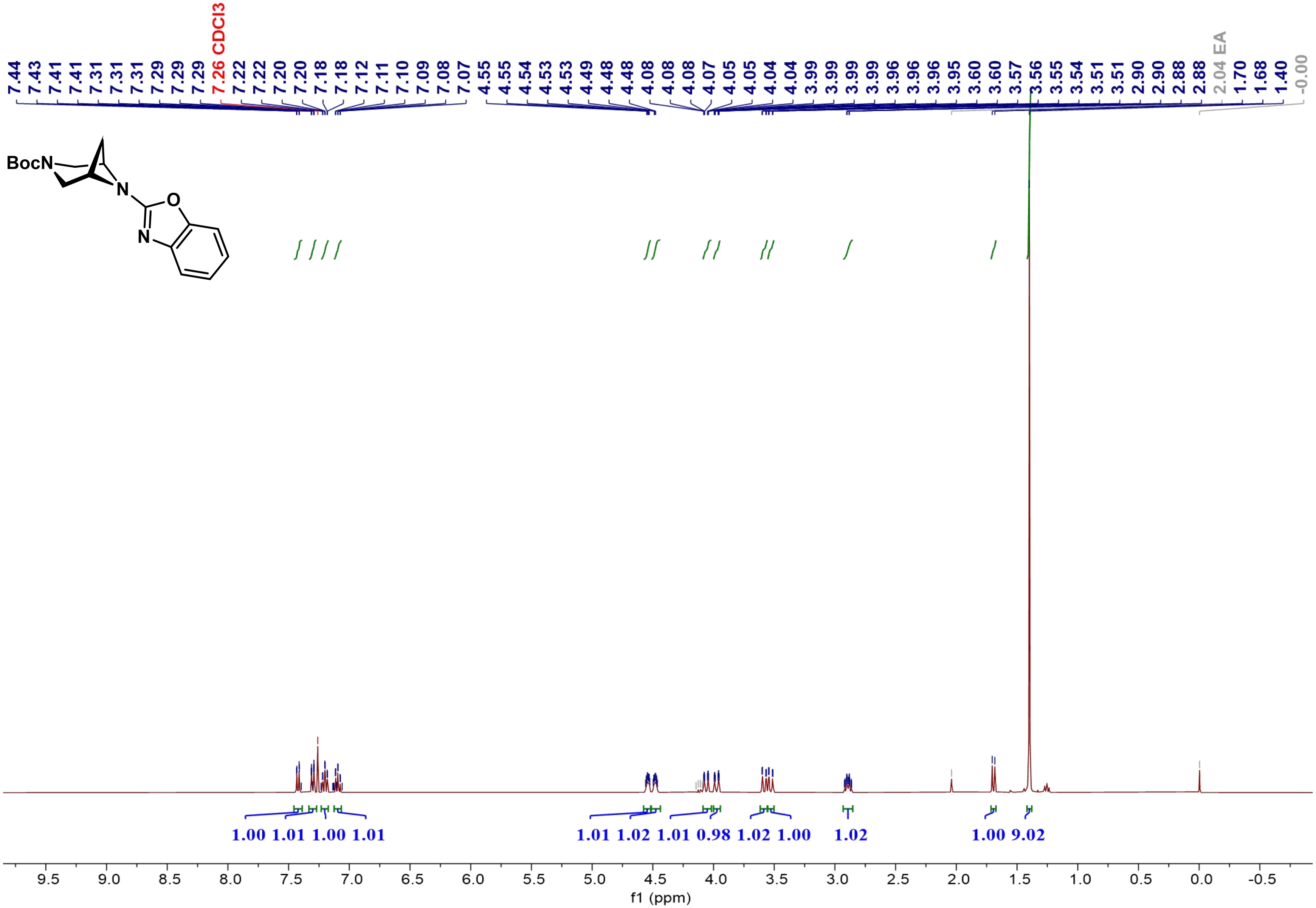
^{1}H NMR Spectrum of compound SI-49 (500 MHz, Methanol-d_4)



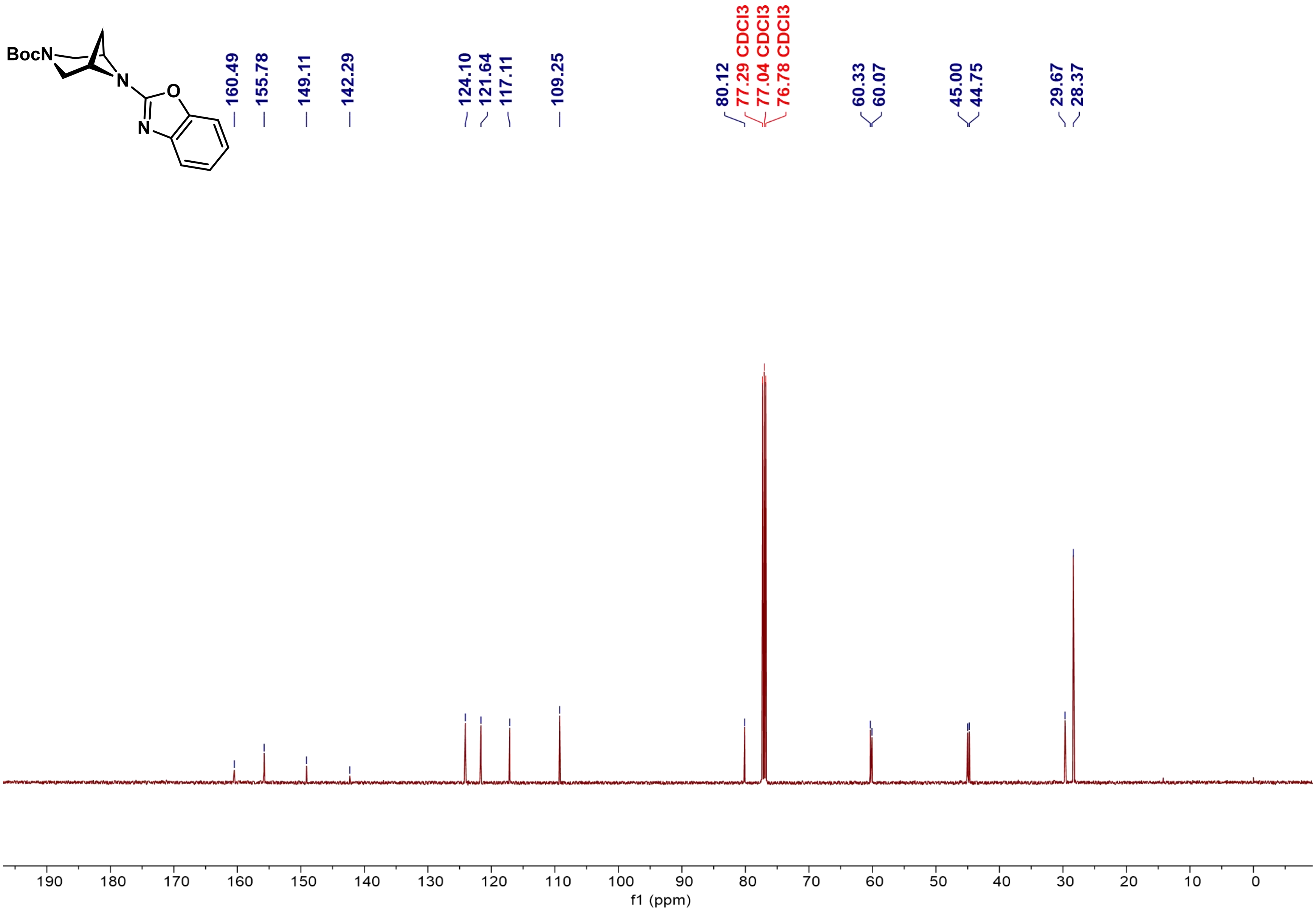
^{13}C NMR Spectrum of compound SI-49 (126 MHz, Methanol-*d*$_4$)



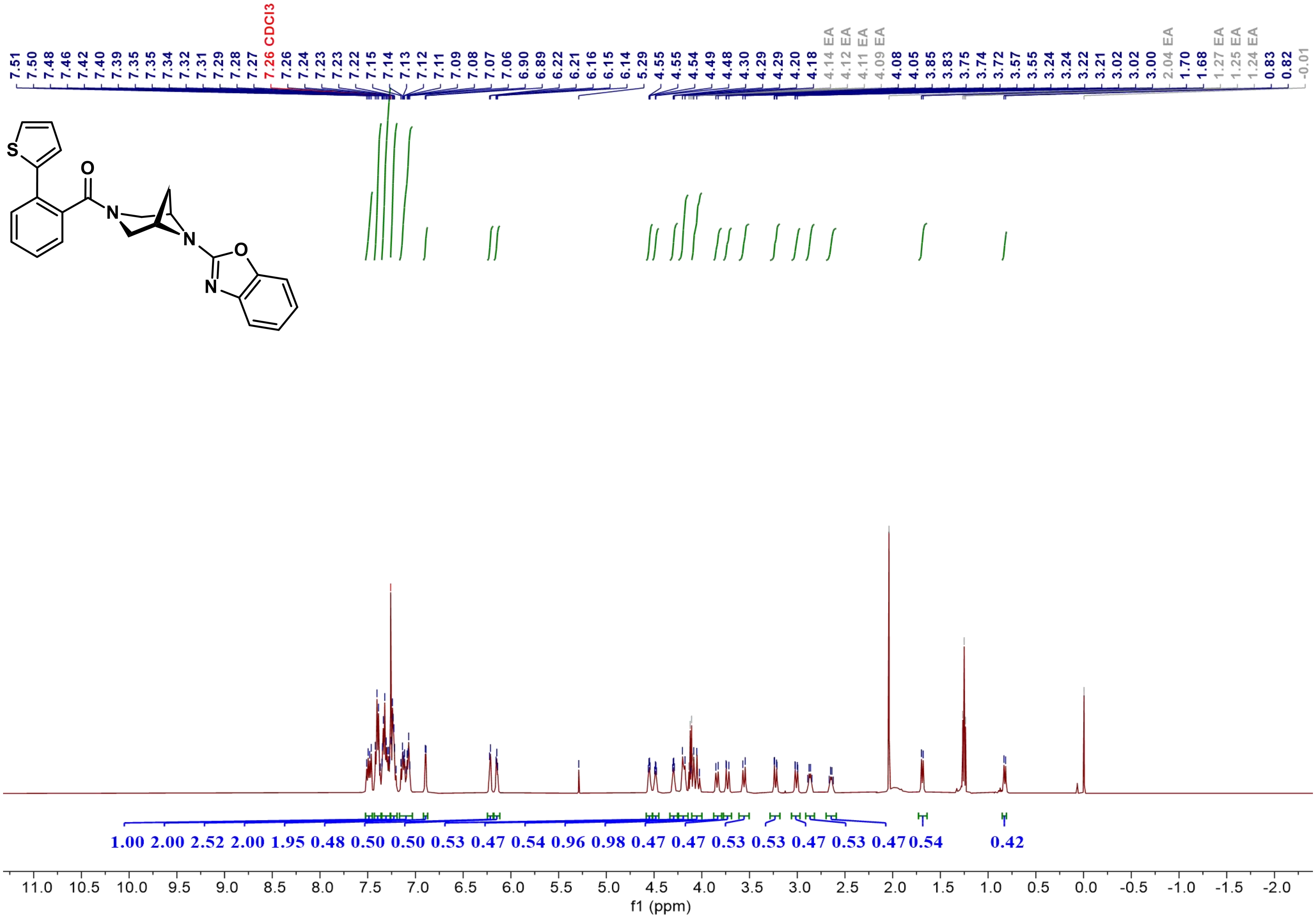
^{1}H NMR Spectrum of compound SI-50 (400 MHz, CDCl$_3$)



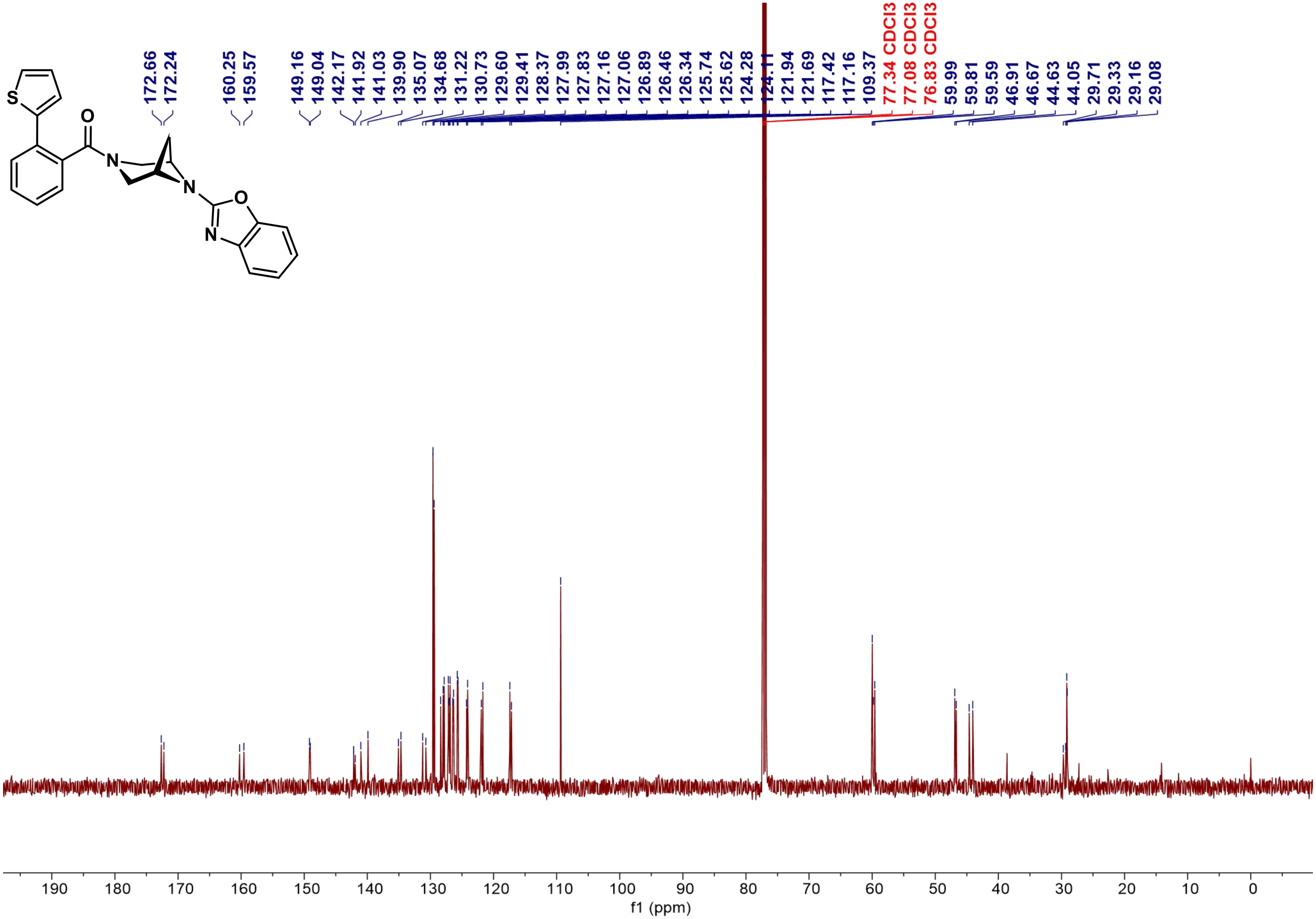
^{13}C NMR Spectrum of compound SI-50 (101 MHz, CDCl$_3$)



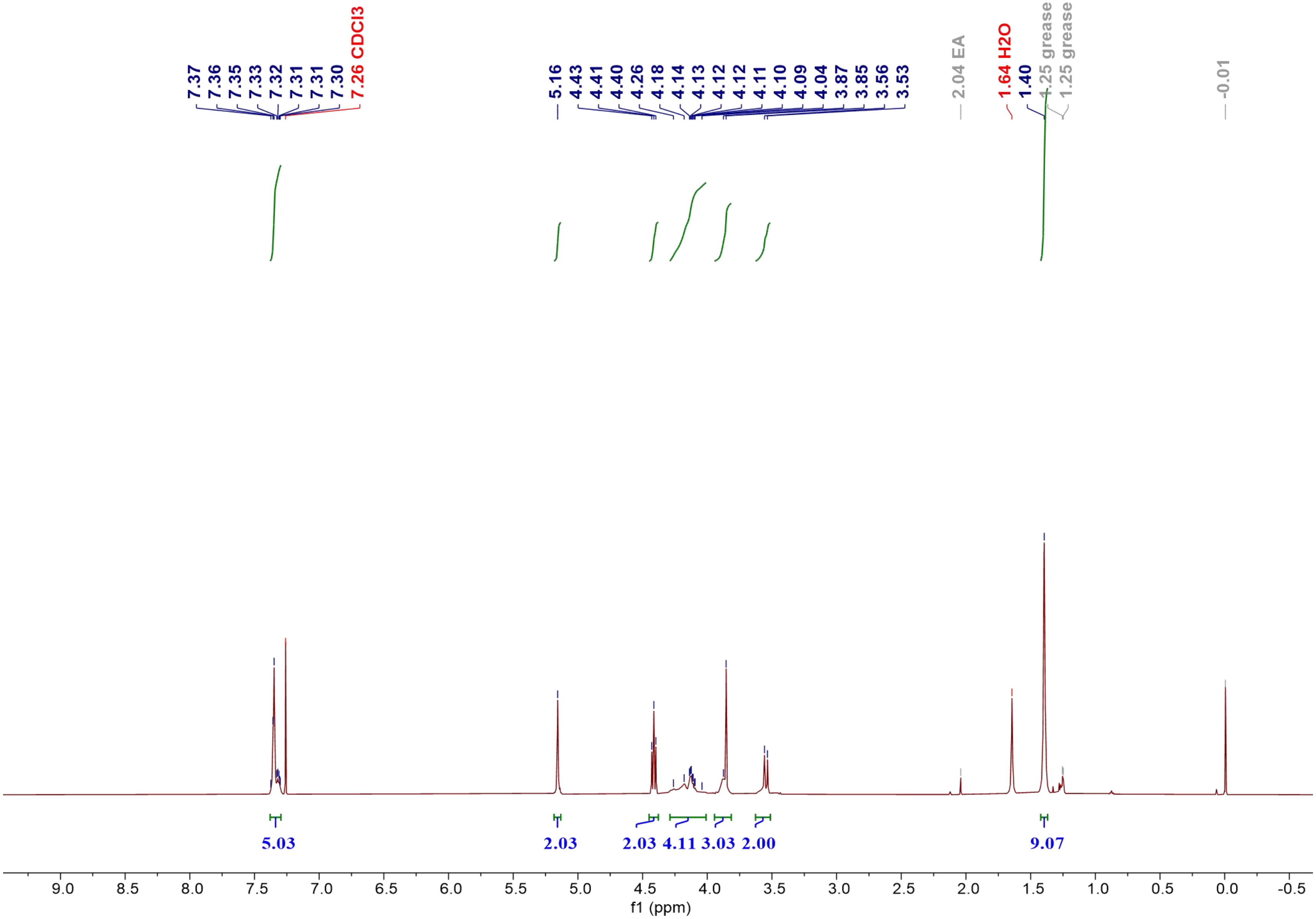
^{1}H NMR Spectrum of compound SI-51 (500 MHz, $CDCl_3$)



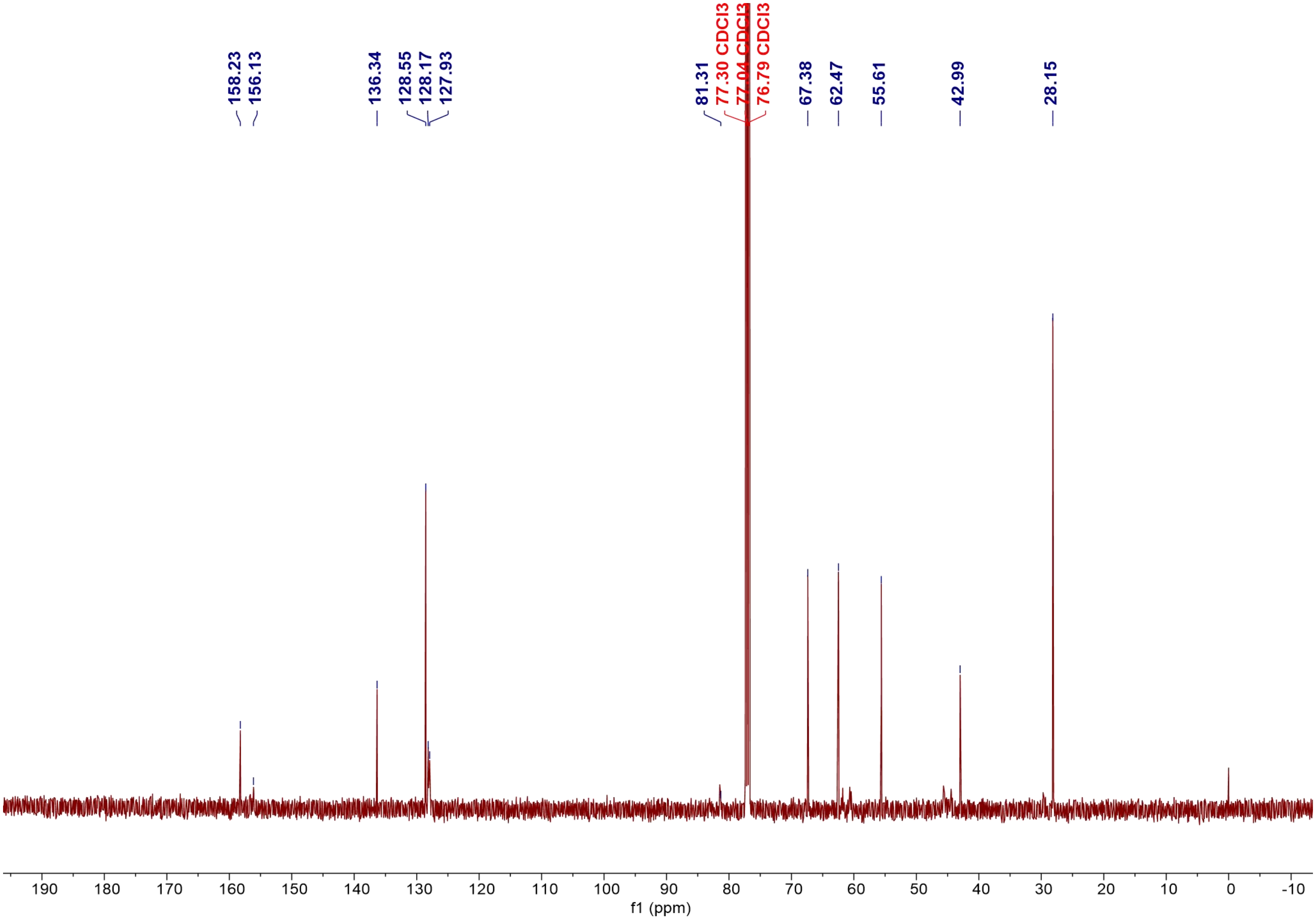
^{13}C NMR Spectrum of compound SI-51 (126 MHz, CDCl$_3$)



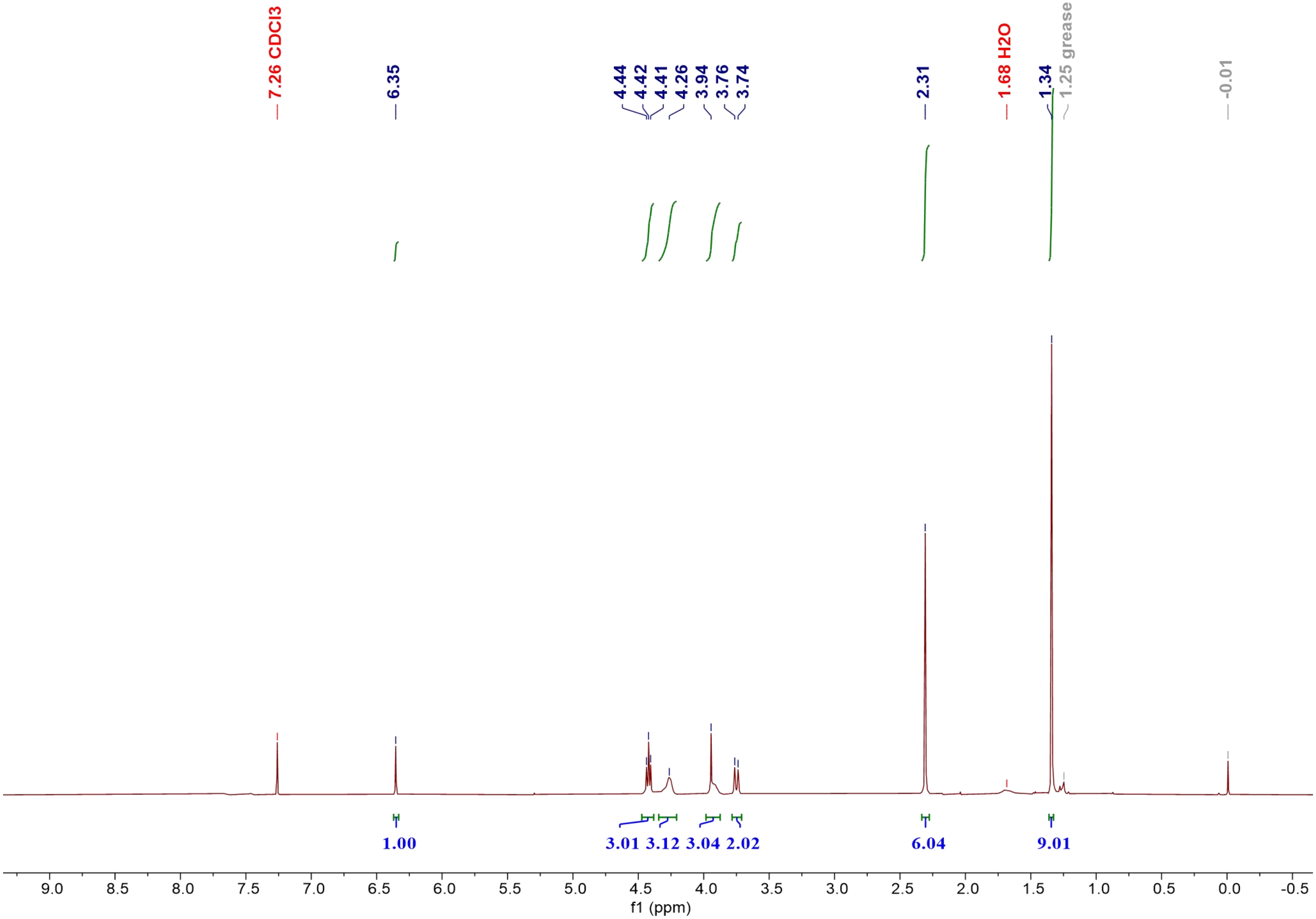
¹H NMR Spectrum of compound SI-52 (500 MHz, $CDCl_3$)



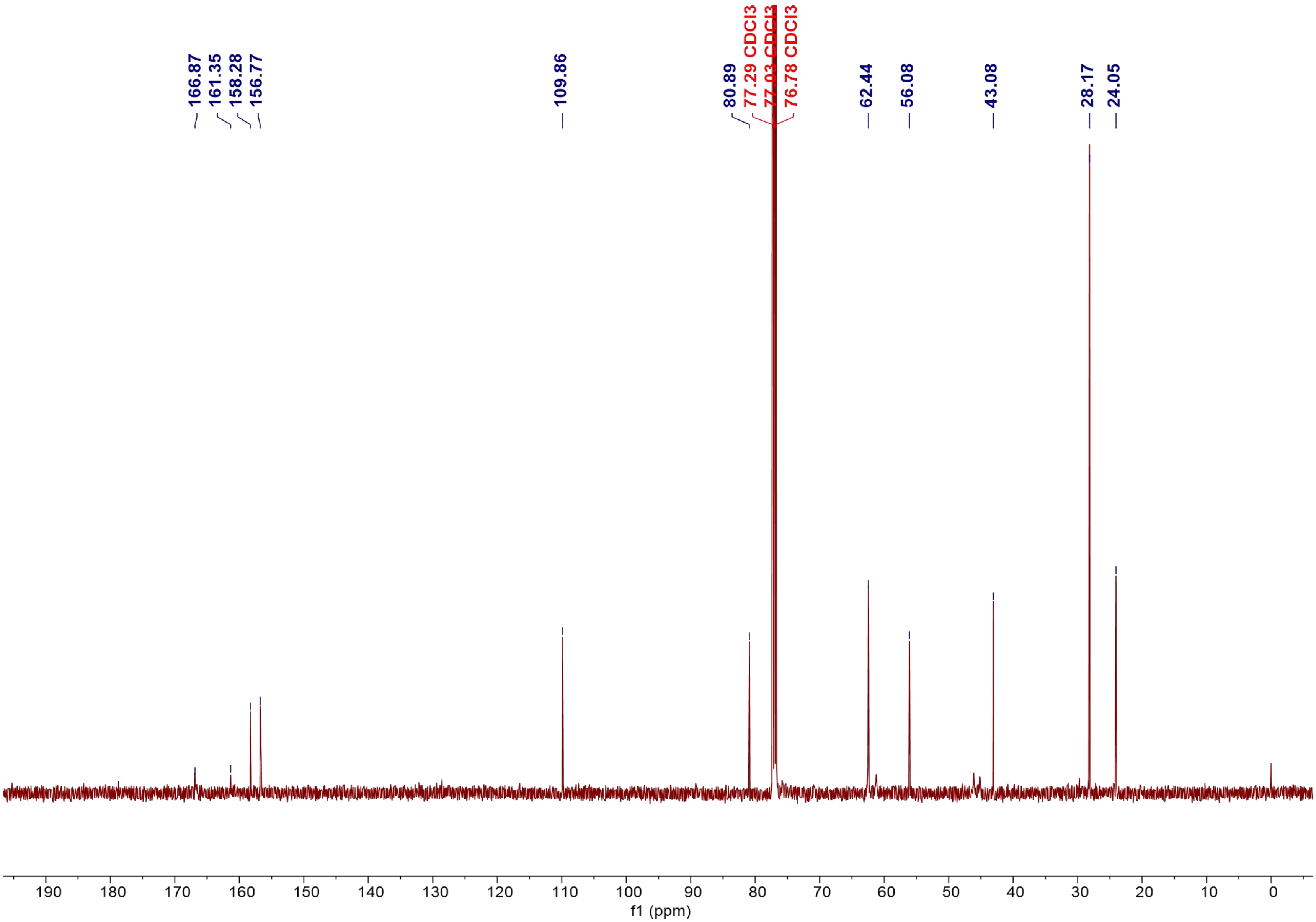
^{13}C NMR Spectrum of compound SI-52 (126 MHz, CDCl$_3$)



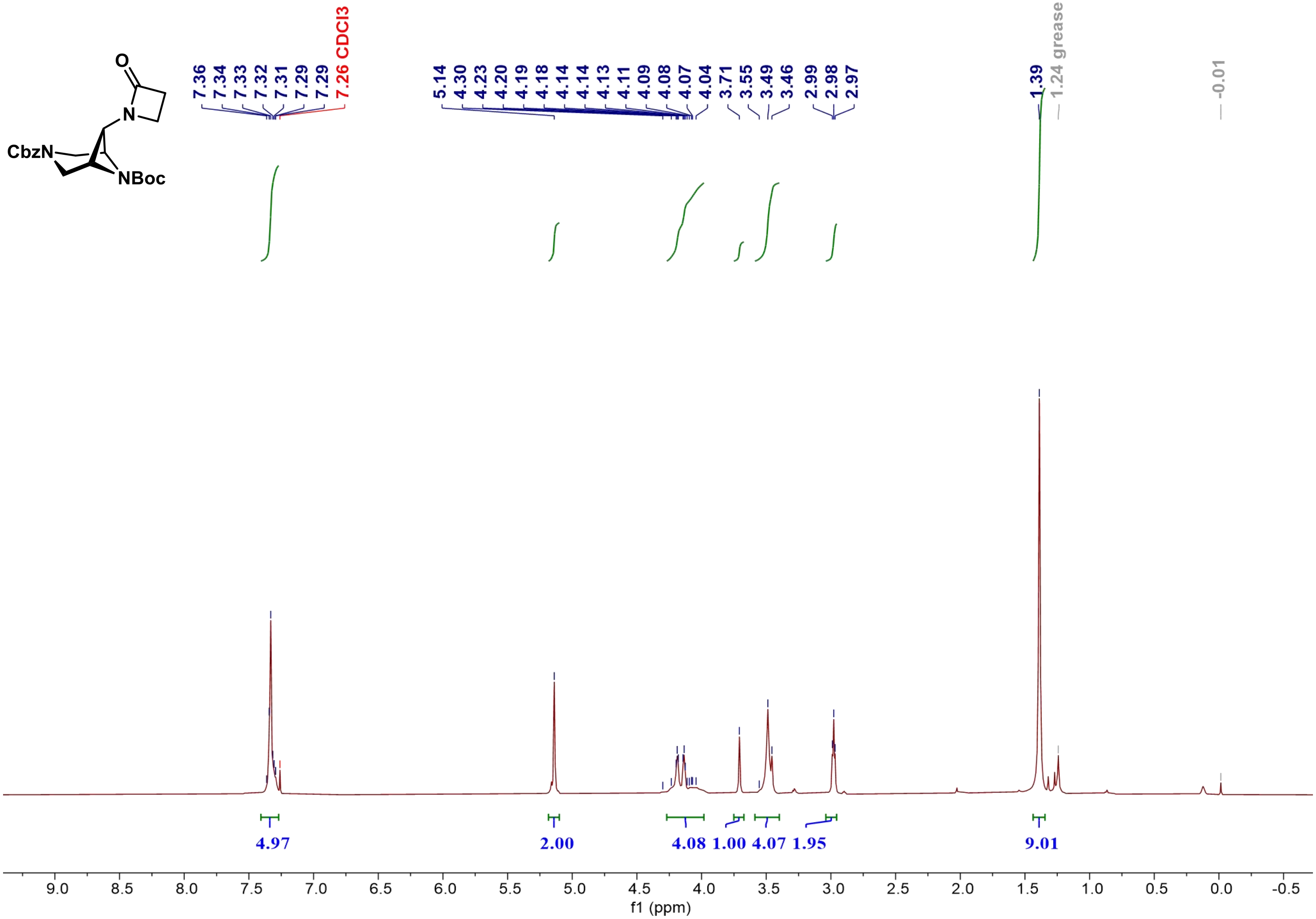
^{1}H NMR Spectrum of compound SI-53 (500 MHz, $CDCl_3$)



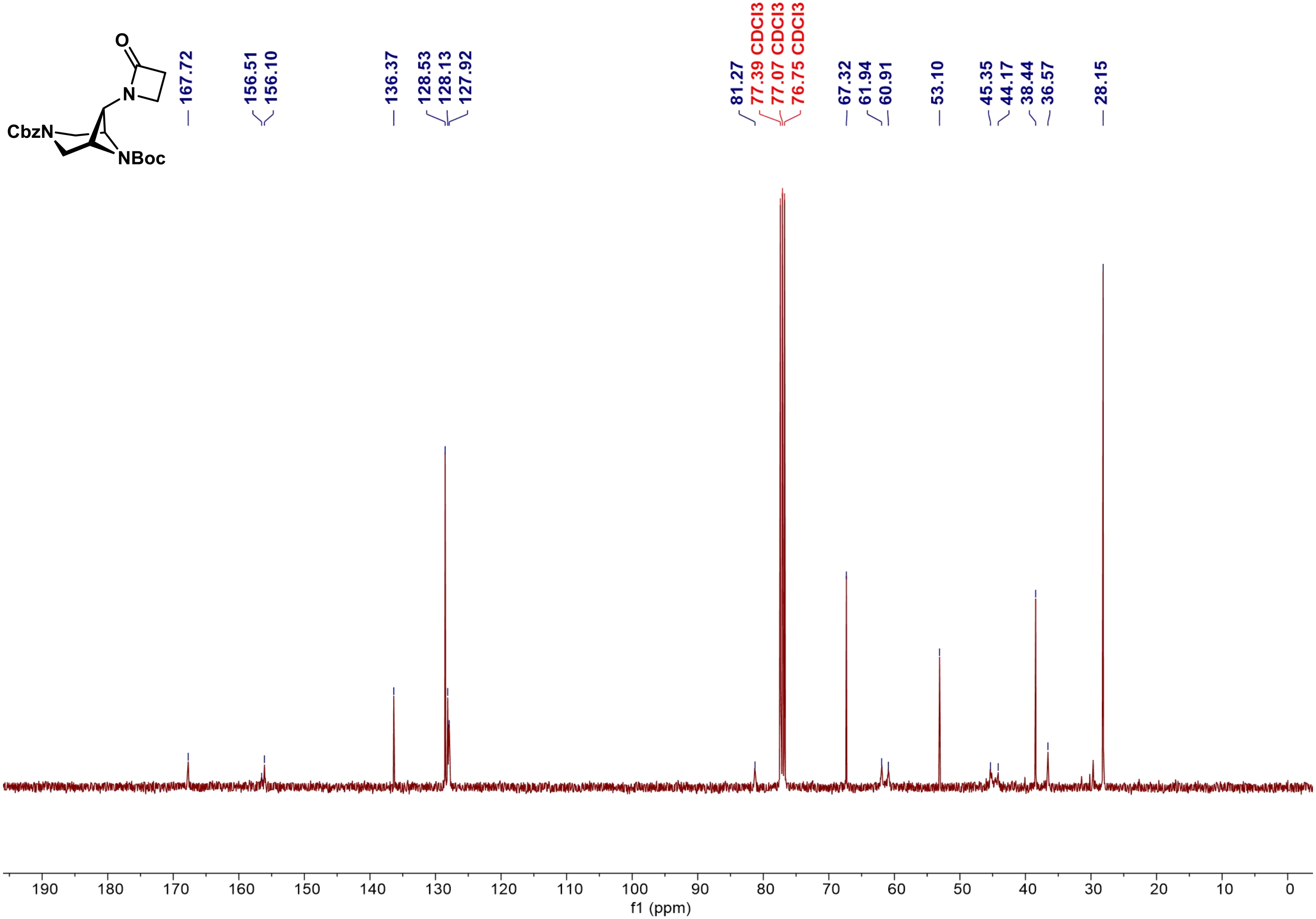
^{13}C NMR Spectrum of compound SI-53 (126 MHz, $CDCl_3$)



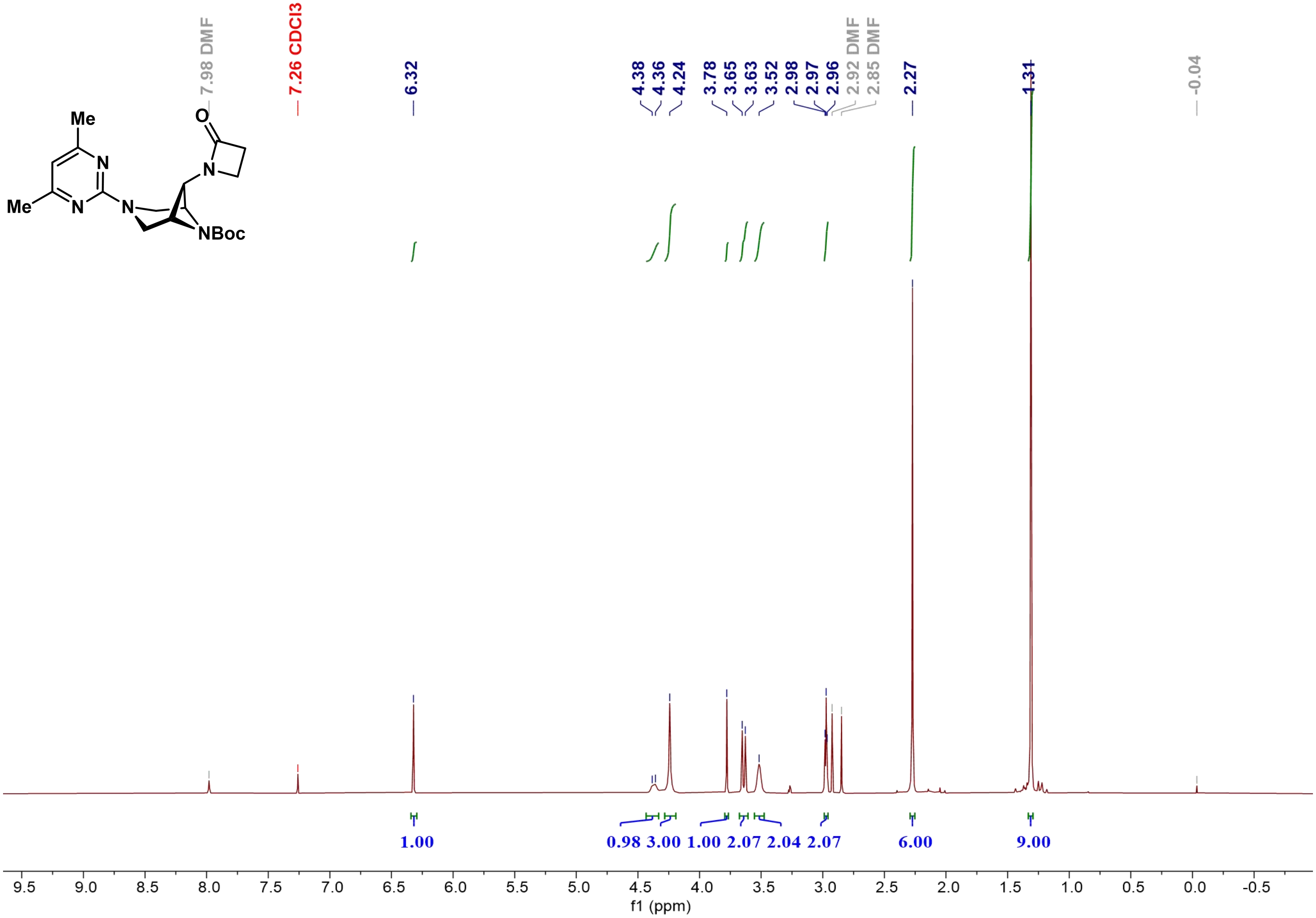
^{1}H NMR Spectrum of compound SI-54 (400 MHz, $CDCl_3$)



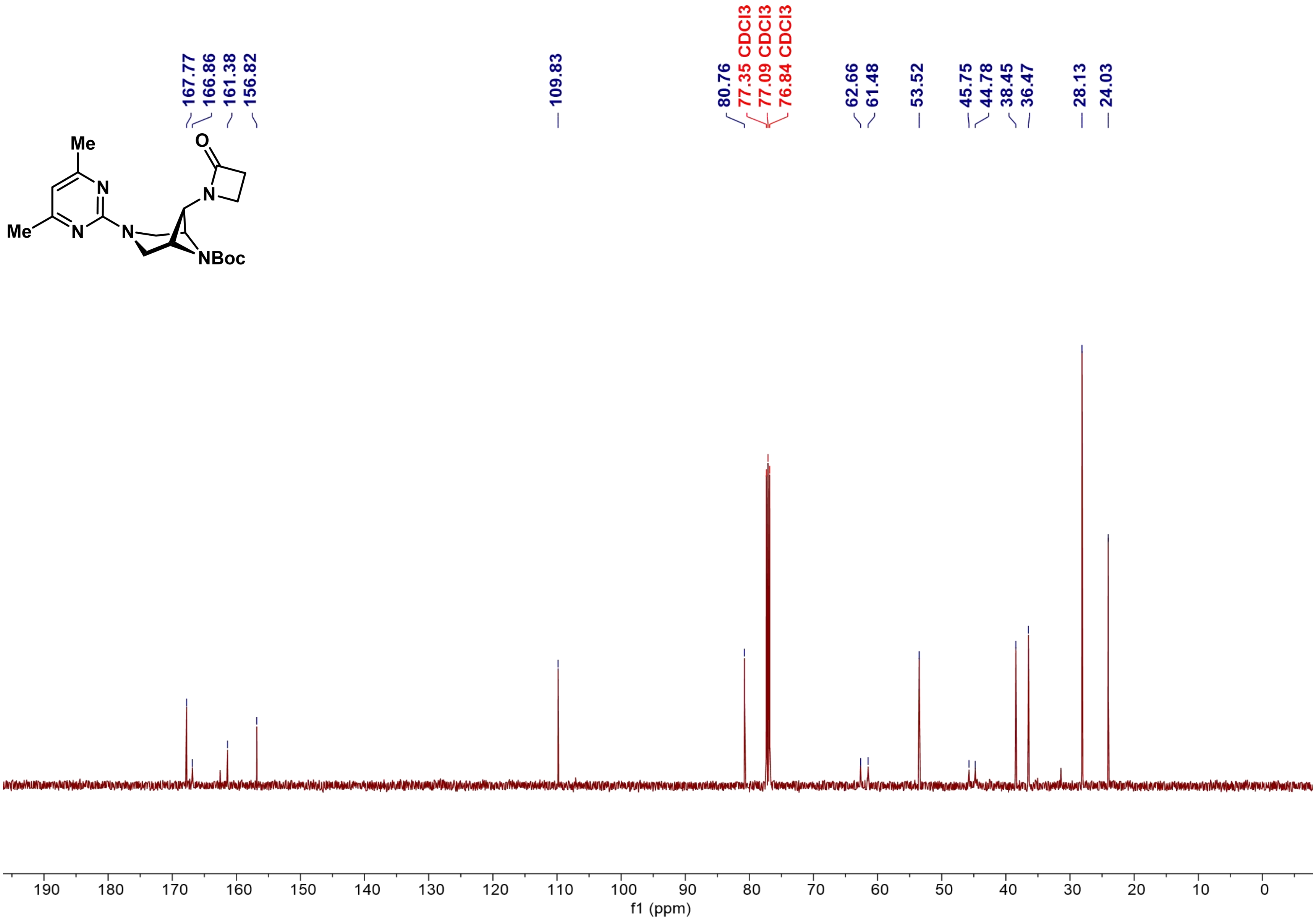
^{13}C NMR Spectrum of compound SI-54 (101 MHz, CDCl$_3$)



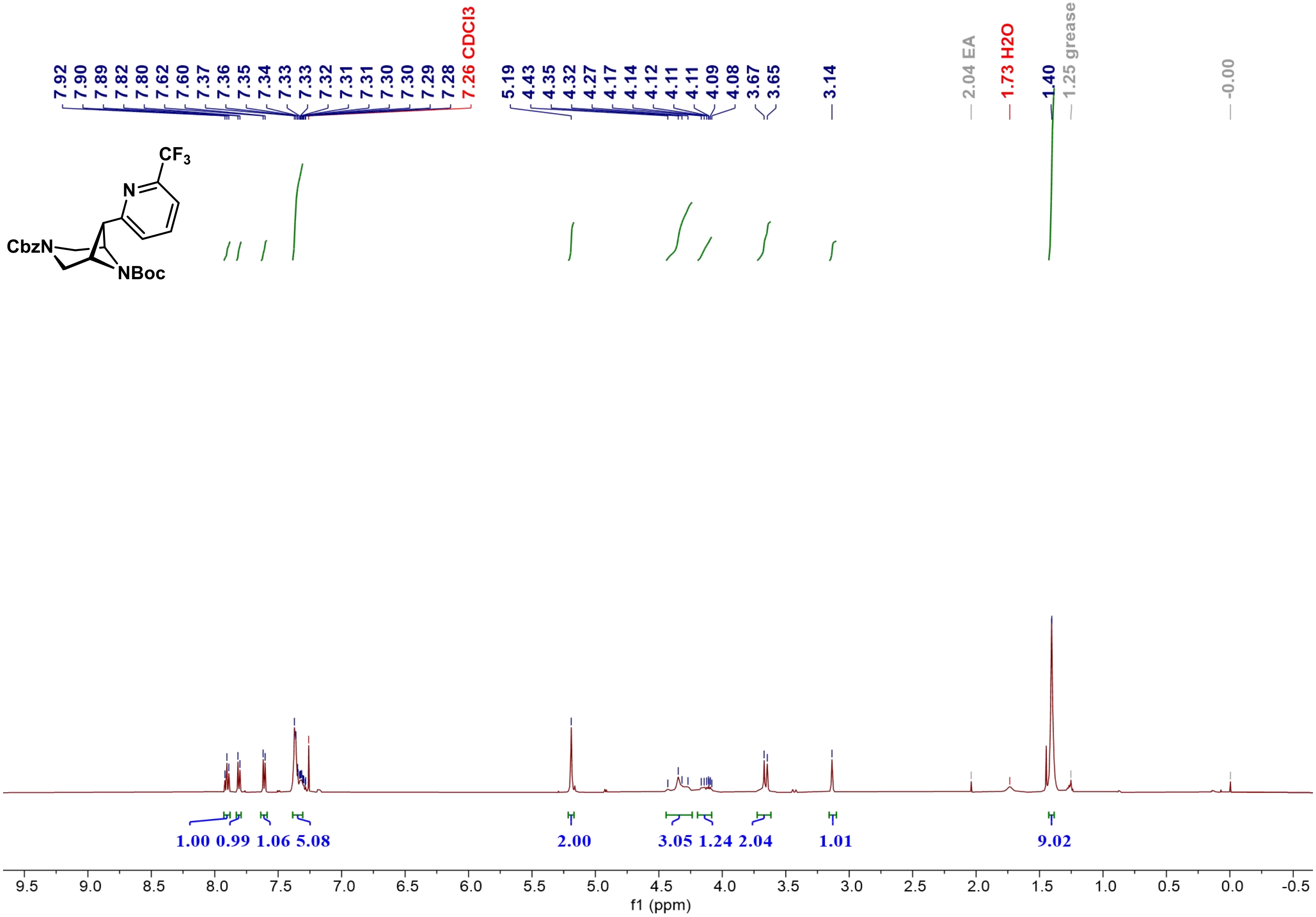
^{1}H NMR Spectrum of compound SI-55 (500 MHz, $CDCl_3$)



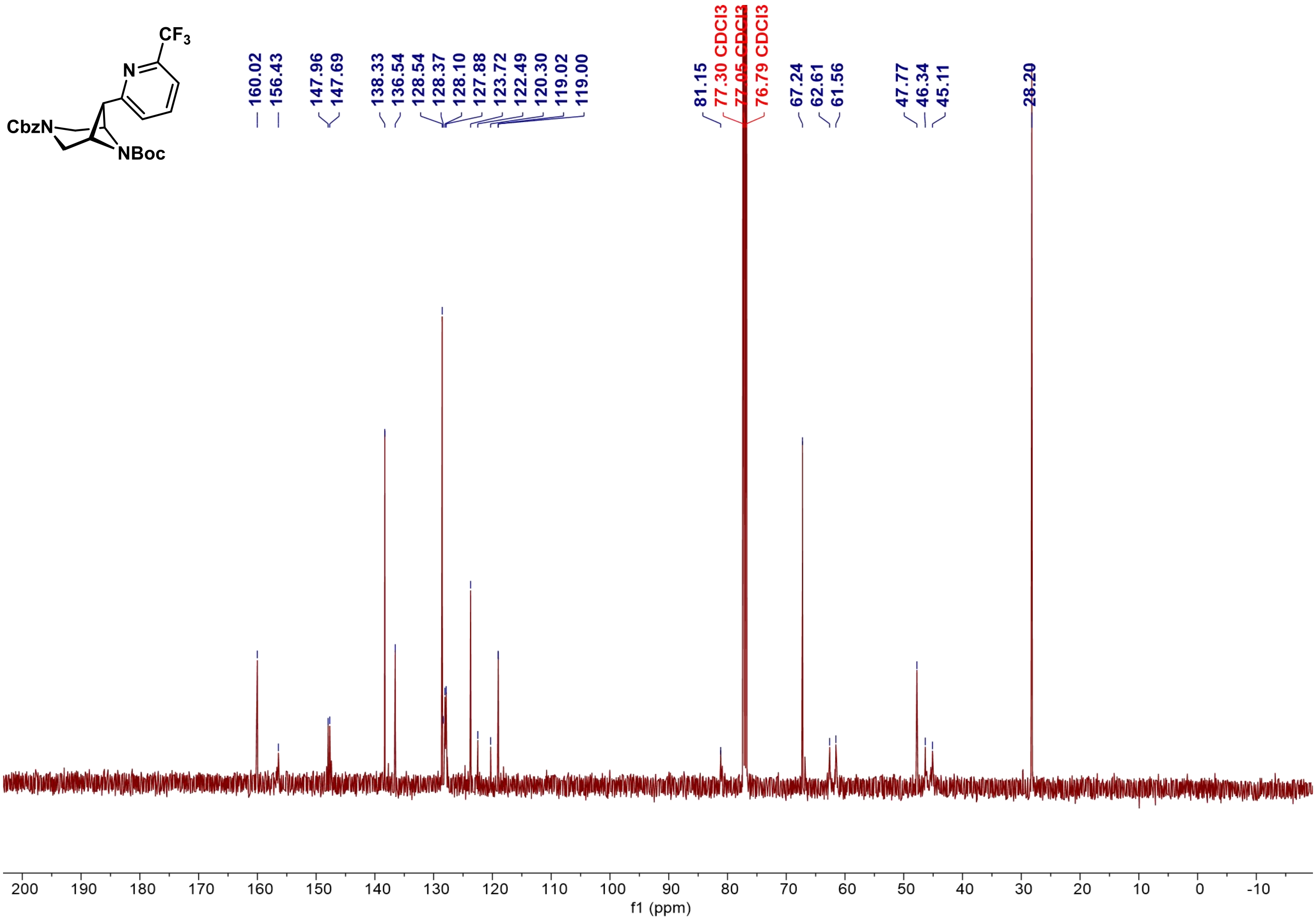
^{13}C NMR Spectrum of compound SI-55 (126 MHz, CDCl$_3$)



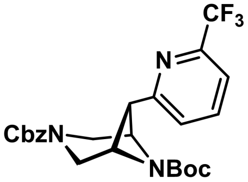
^{1}H NMR Spectrum of compound SI-56 (500 MHz, $CDCl_3$)

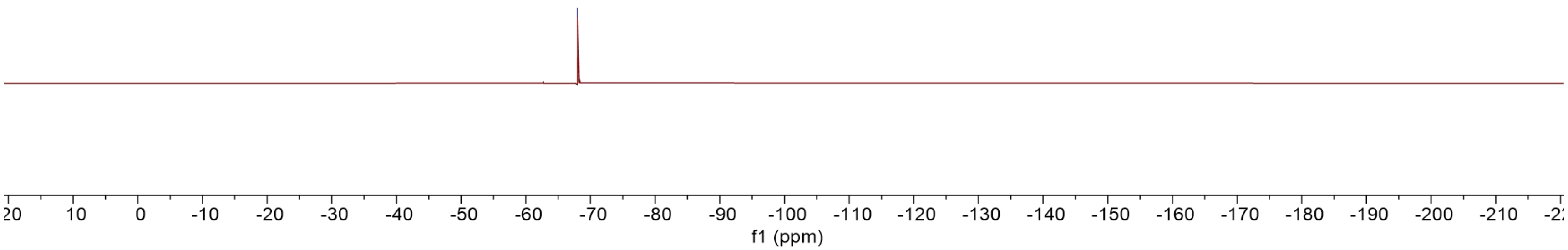


^{13}C NMR Spectrum of compound SI-56 (126 MHz, CDCl$_3$)

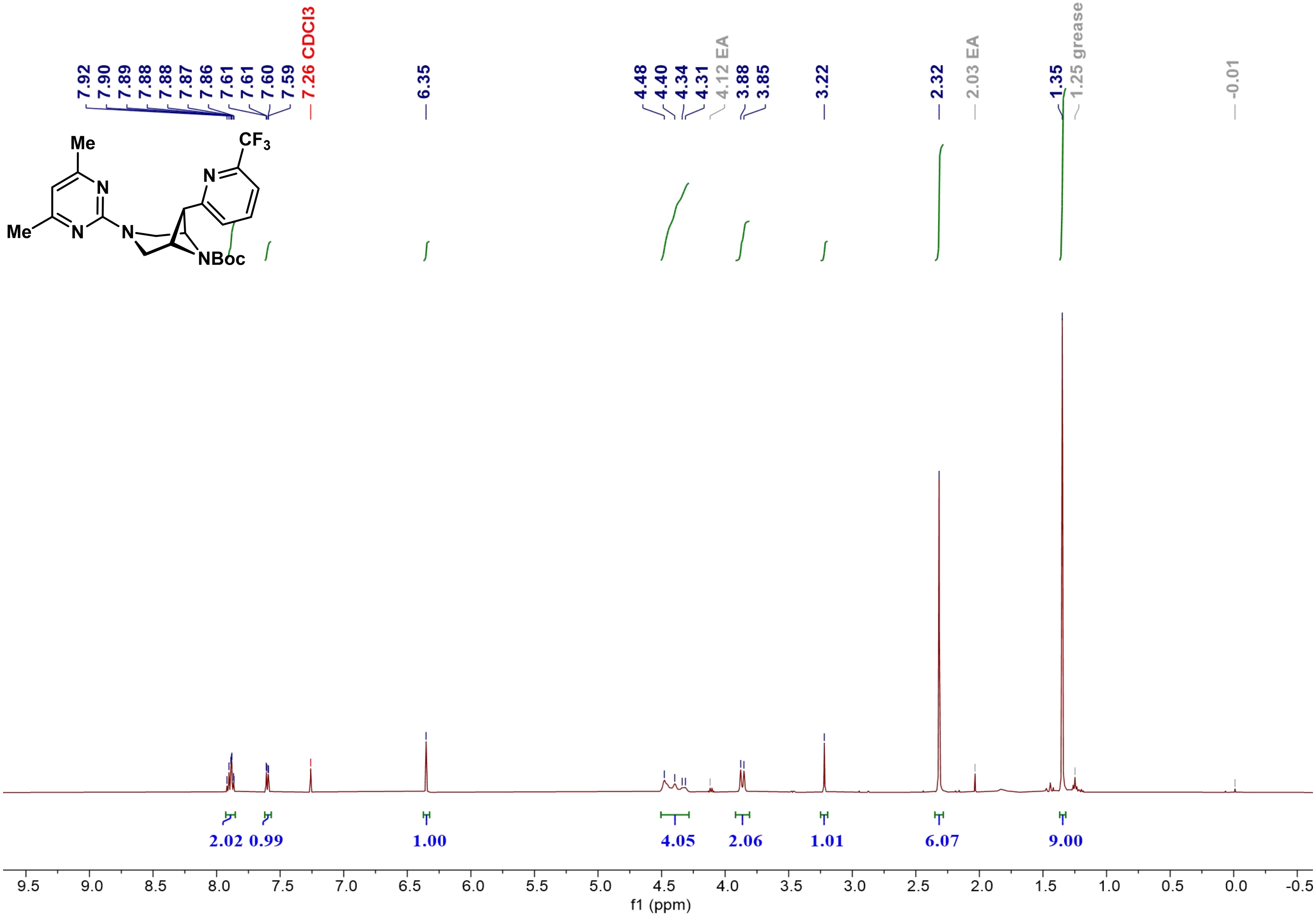


^{19}F NMR Spectrum of compound SI-56 (471 MHz, $CDCl_3$)

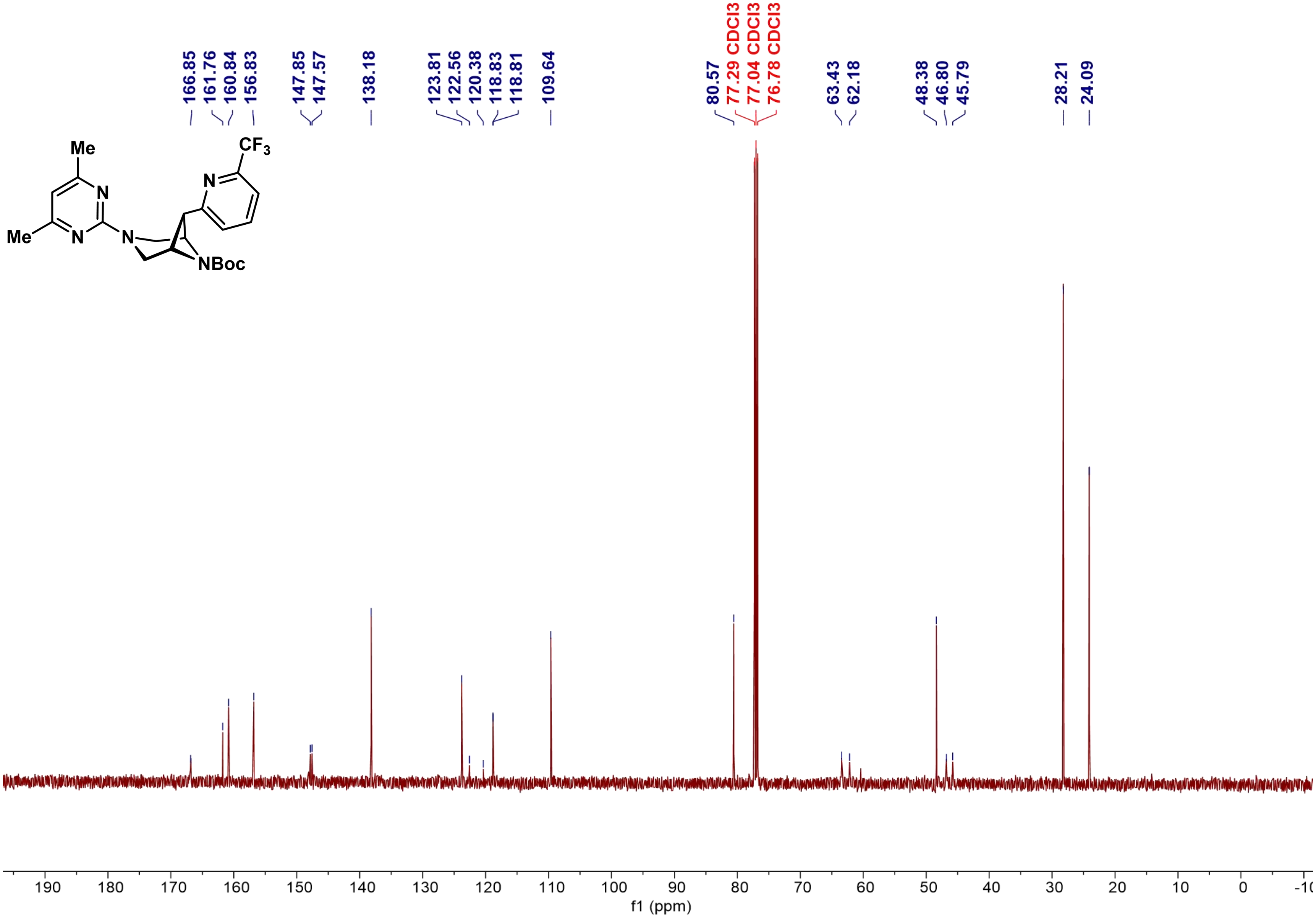




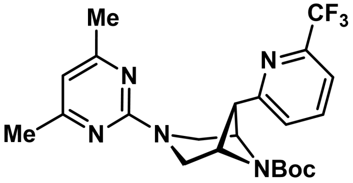
^{1}H NMR Spectrum of compound SI-57 (500 MHz, CDCl$_3$)

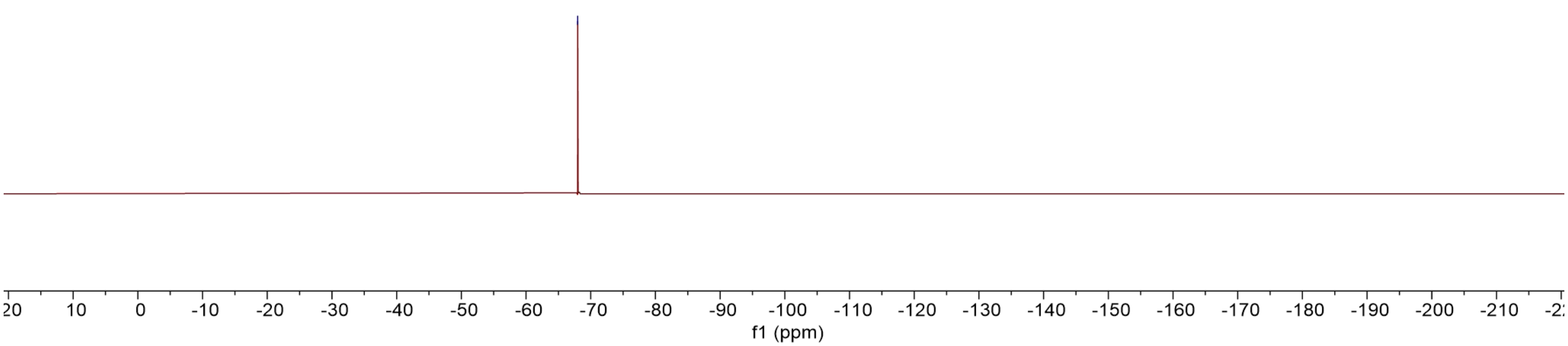


^{13}C NMR Spectrum of compound SI-57 (126 MHz, CDCl$_3$)

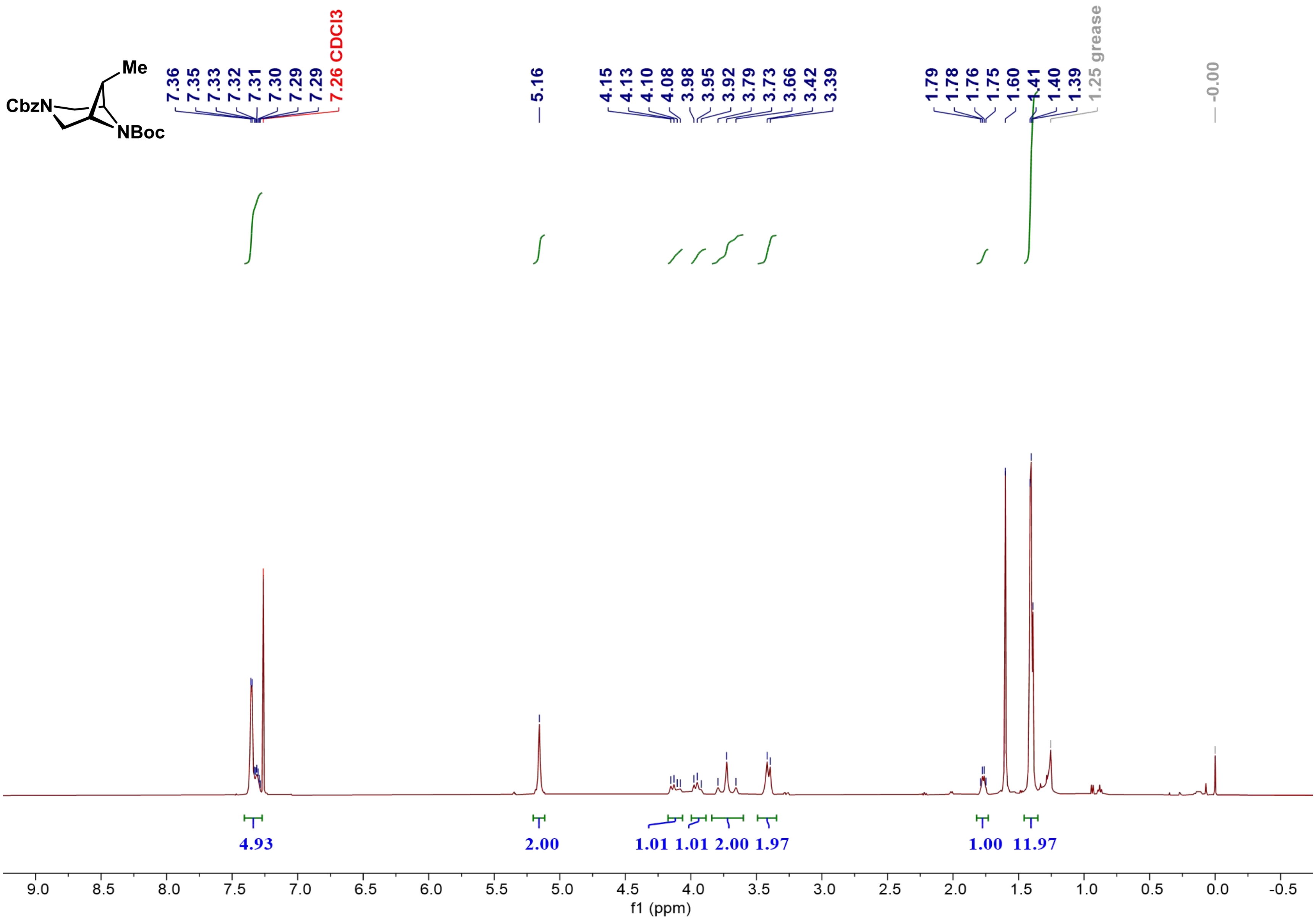


^{19}F NMR Spectrum of compound SI-57 (471 MHz, CDCl$_3$)

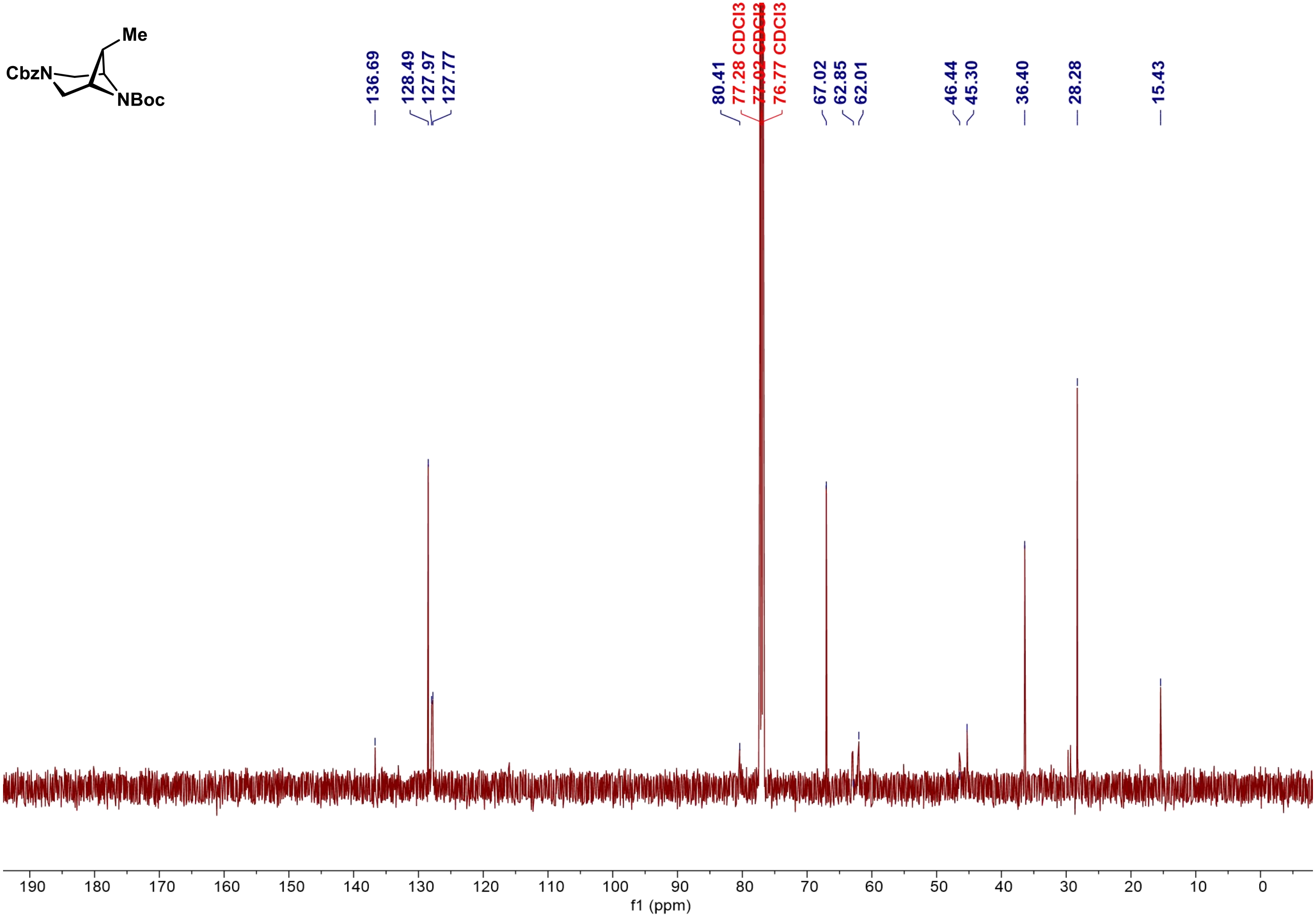




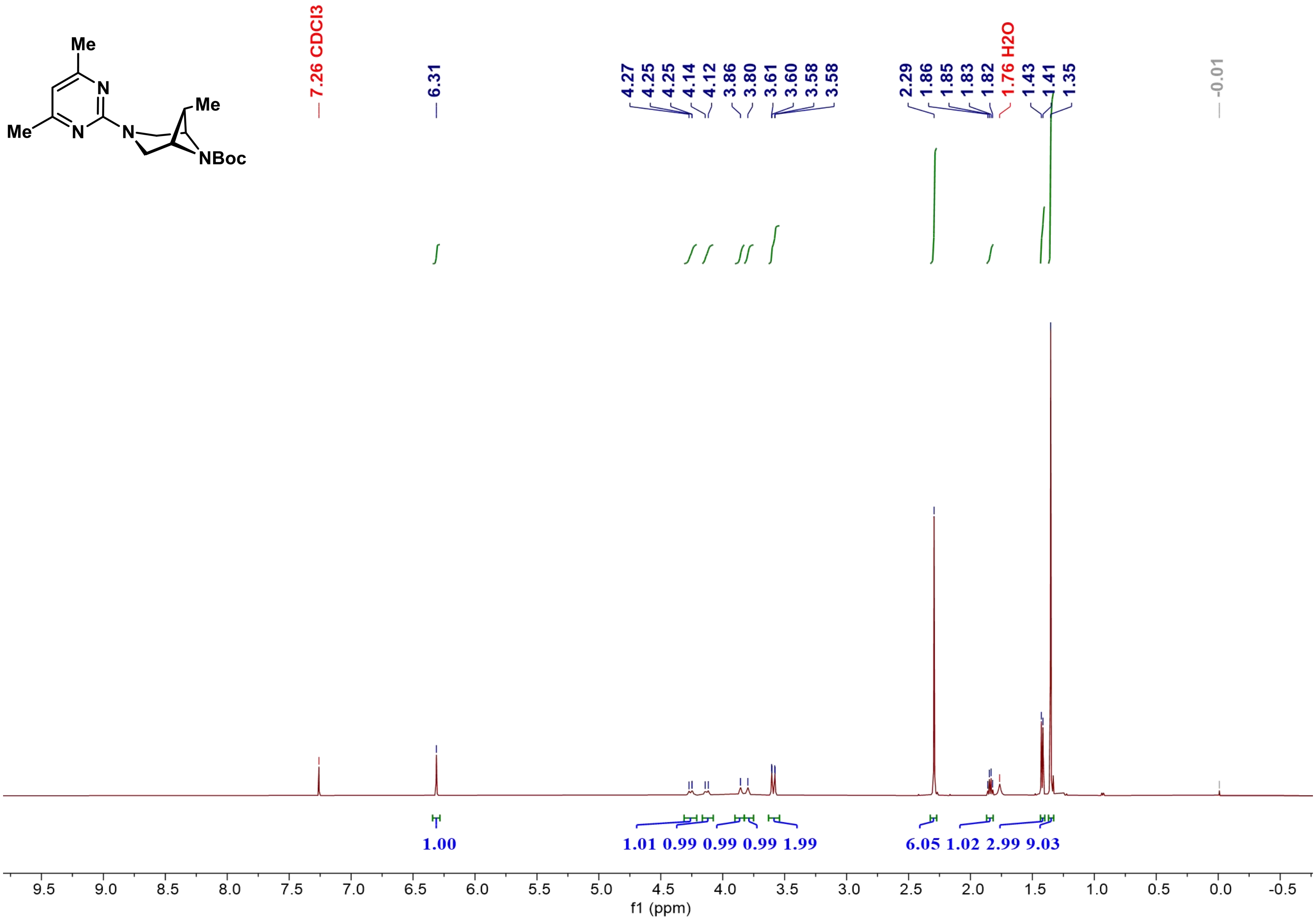
^{1}H NMR Spectrum of compound SI-58 (500 MHz, CDCl$_3$)



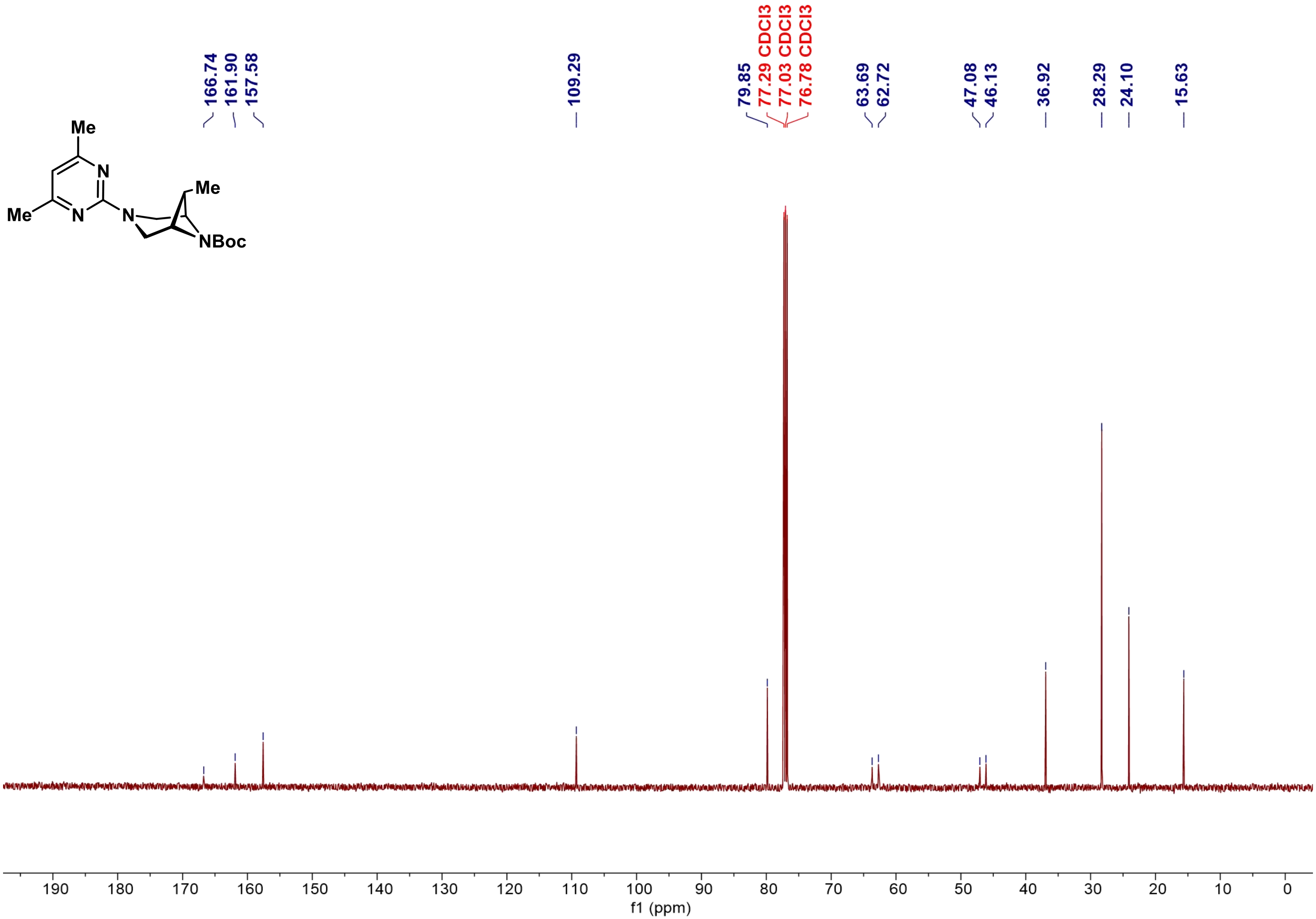
^{13}C NMR Spectrum of compound SI-58 (126 MHz, CDCl$_3$)



^{1}H NMR Spectrum of compound SI-59 (500 MHz, $CDCl_3$)

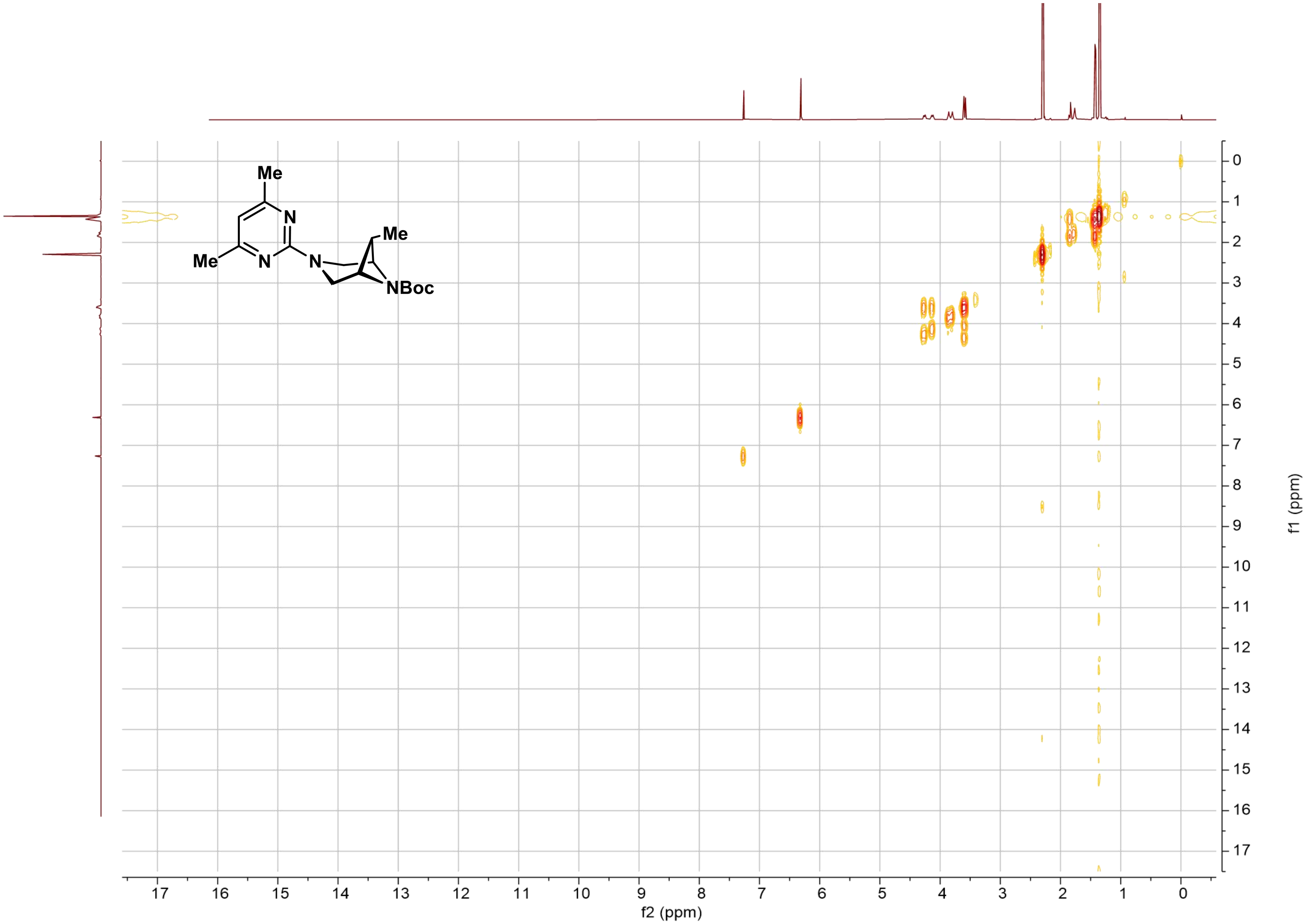


^{13}C NMR Spectrum of compound SI-59 (126 MHz, CDCl$_3$)

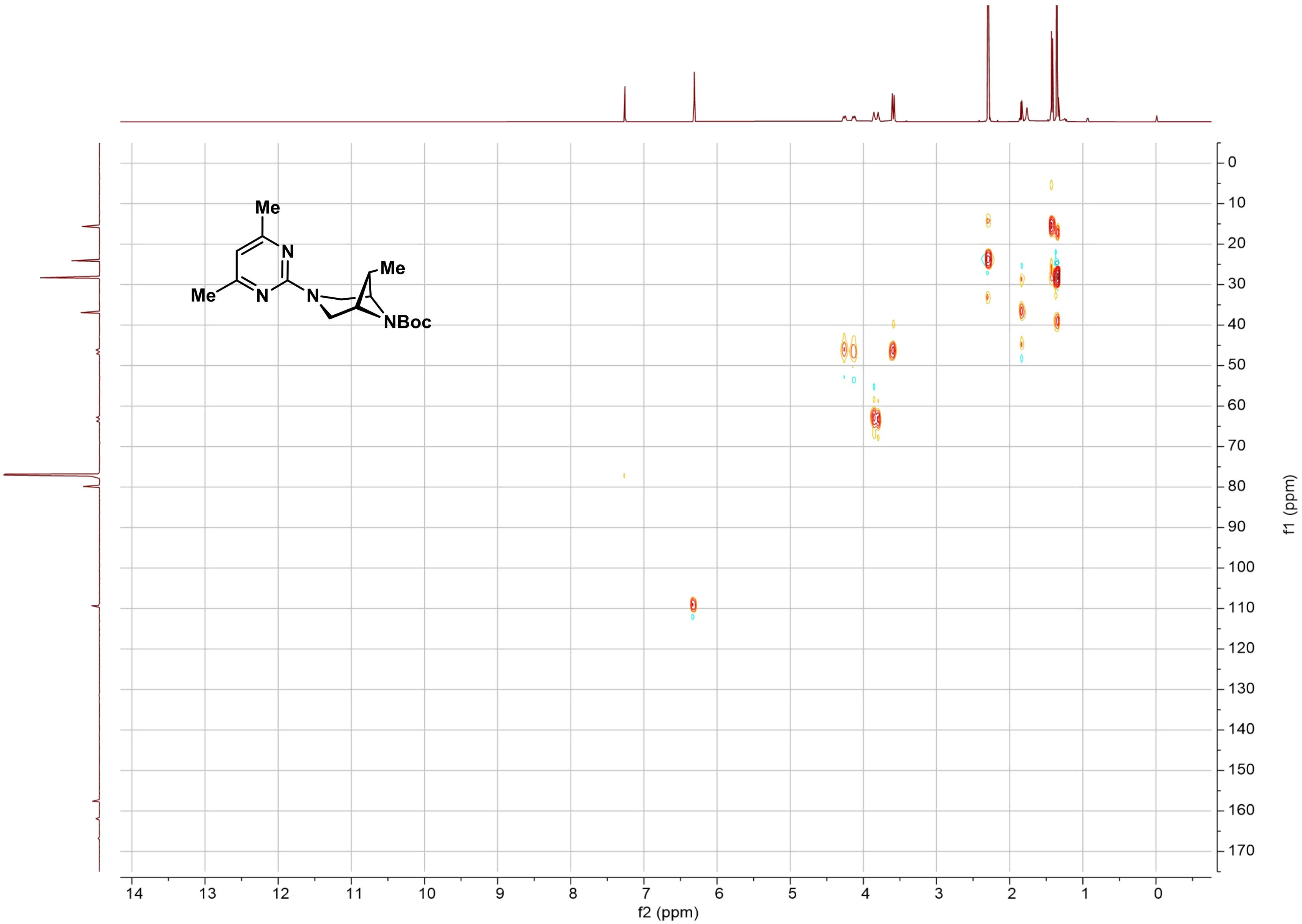


NOSY Spectrum of compound SI-59

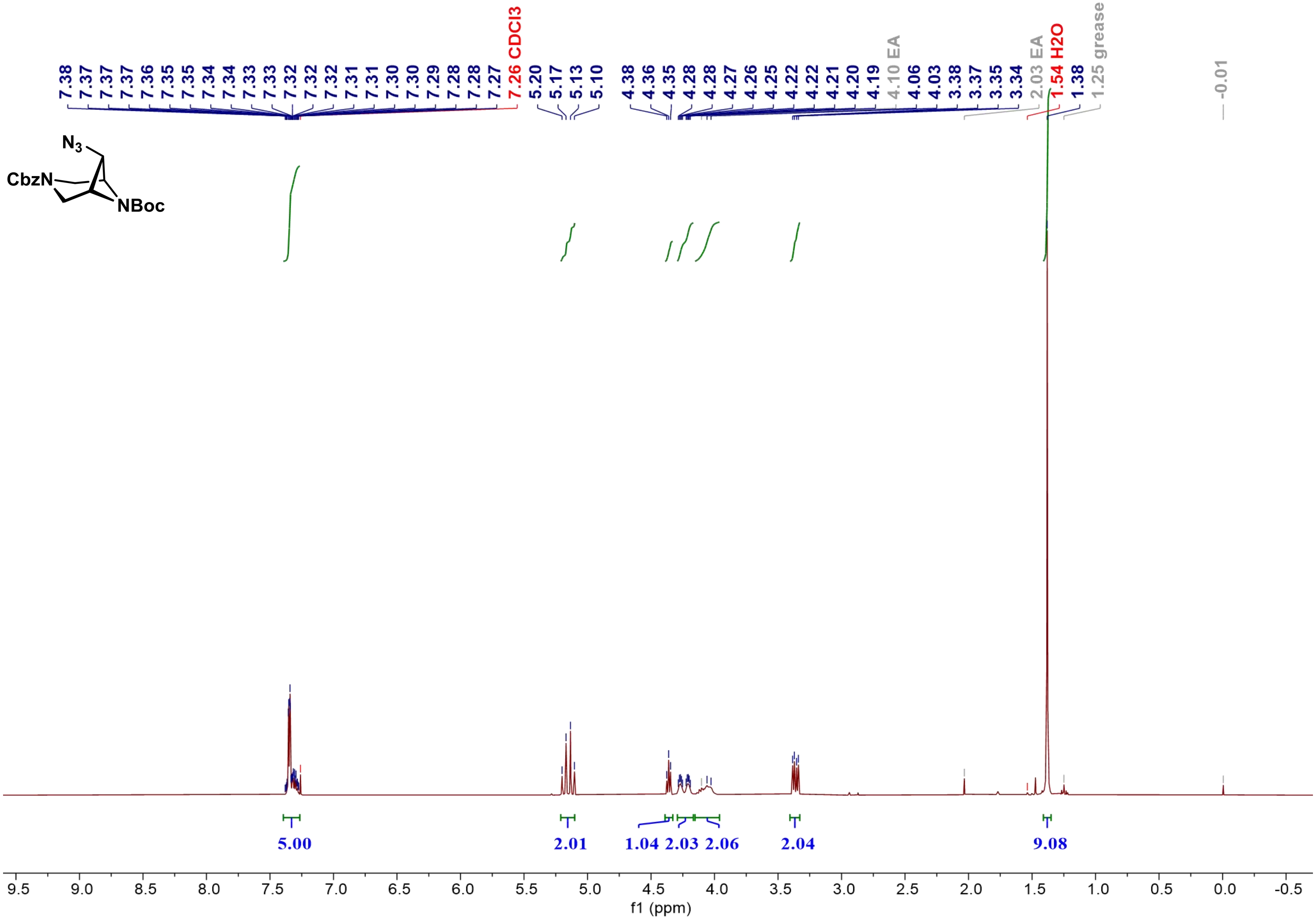
COSY Spectrum of compound SI-59



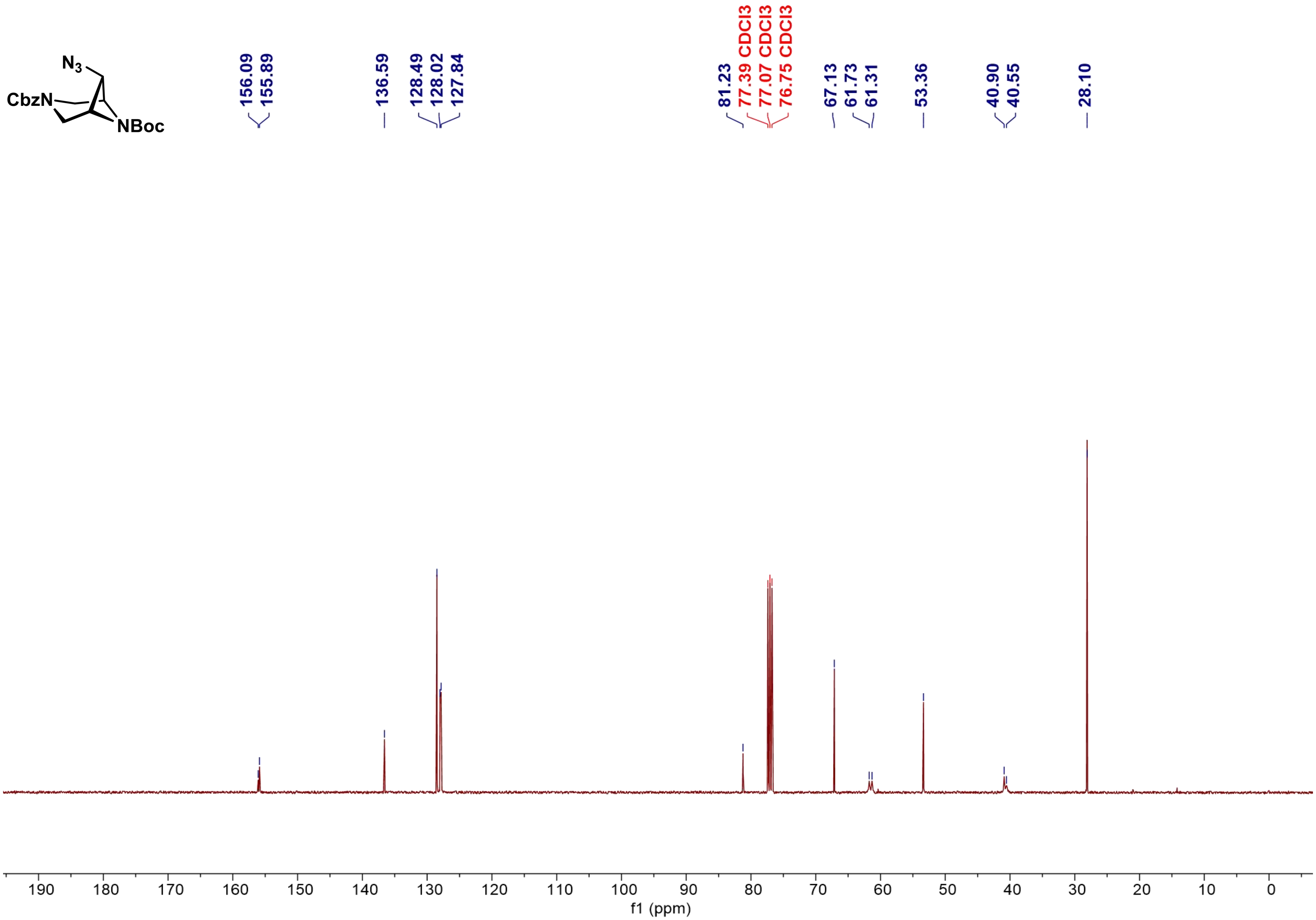
HSQC Spectrum of compound SI-59



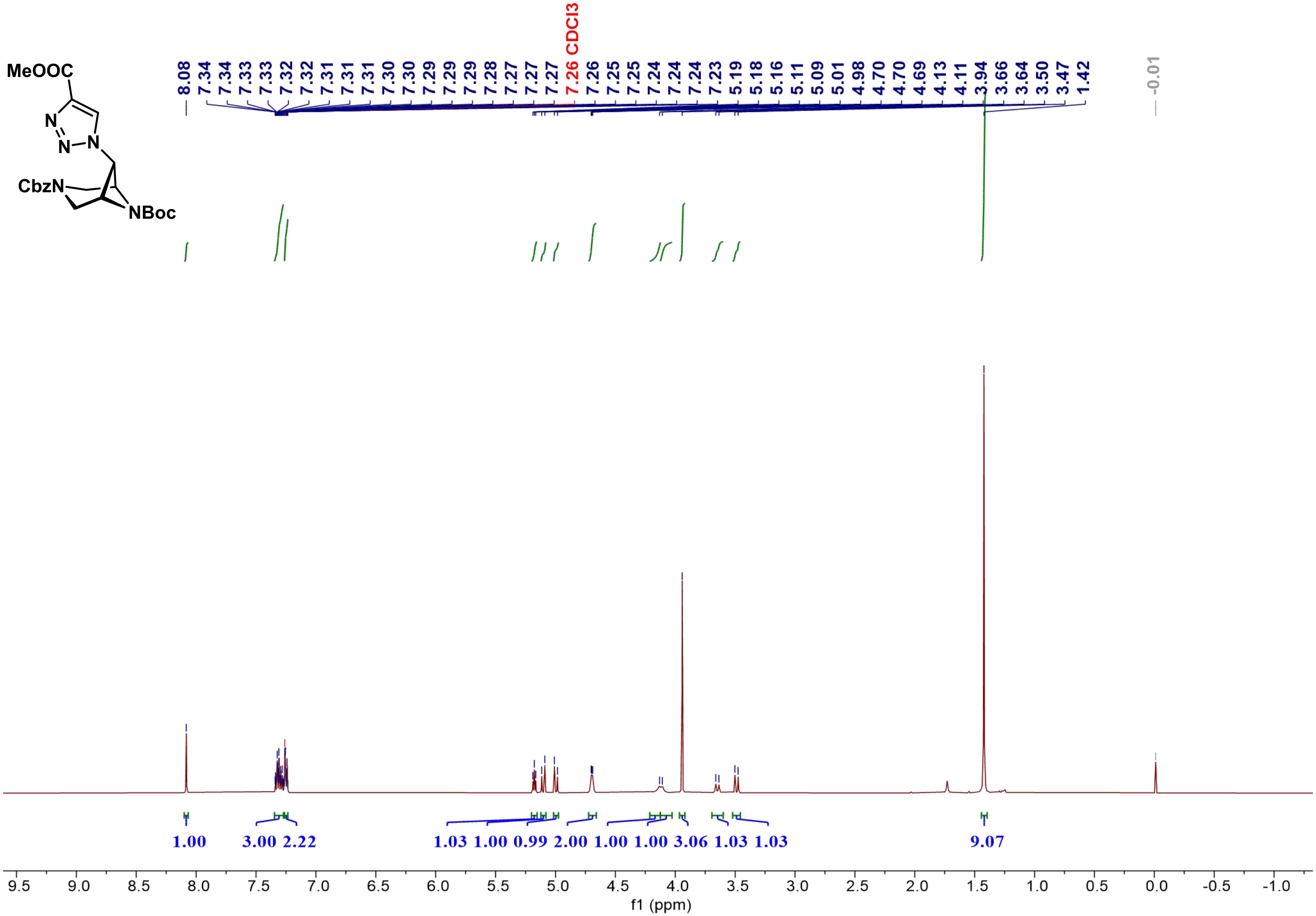
^{1}H NMR Spectrum of compound SI-60 (400 MHz, $CDCl_3$)



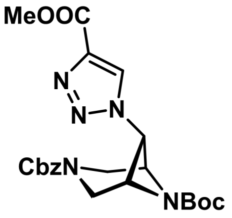
^{13}C NMR Spectrum of compound SI-60 (101 MHz, CDCl$_3$)

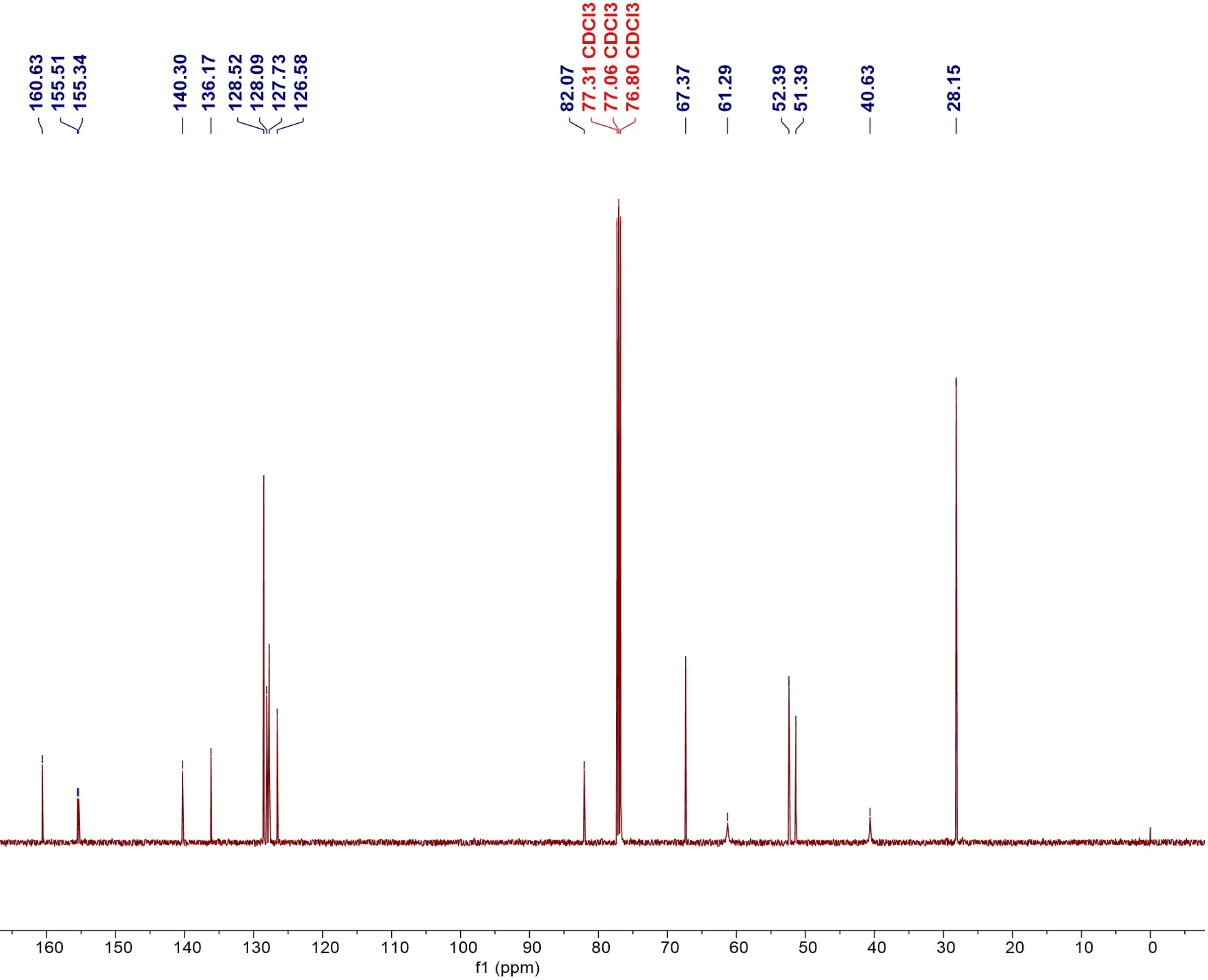


^{1}H NMR Spectrum of compound SI-61 (500 MHz, CDCl$_3$)

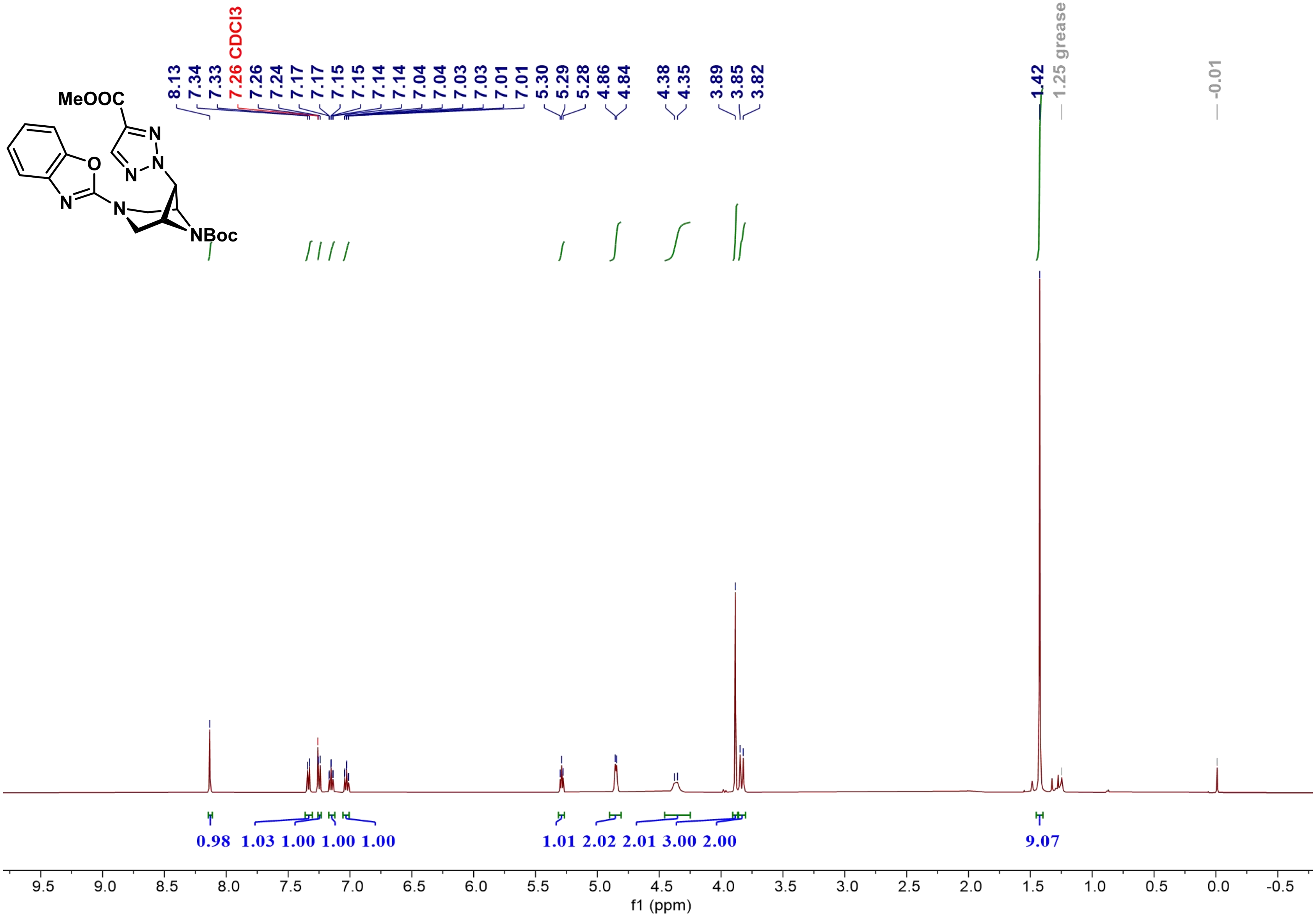


^{13}C NMR Spectrum of compound SI-61 (126 MHz, CDCl$_3$)

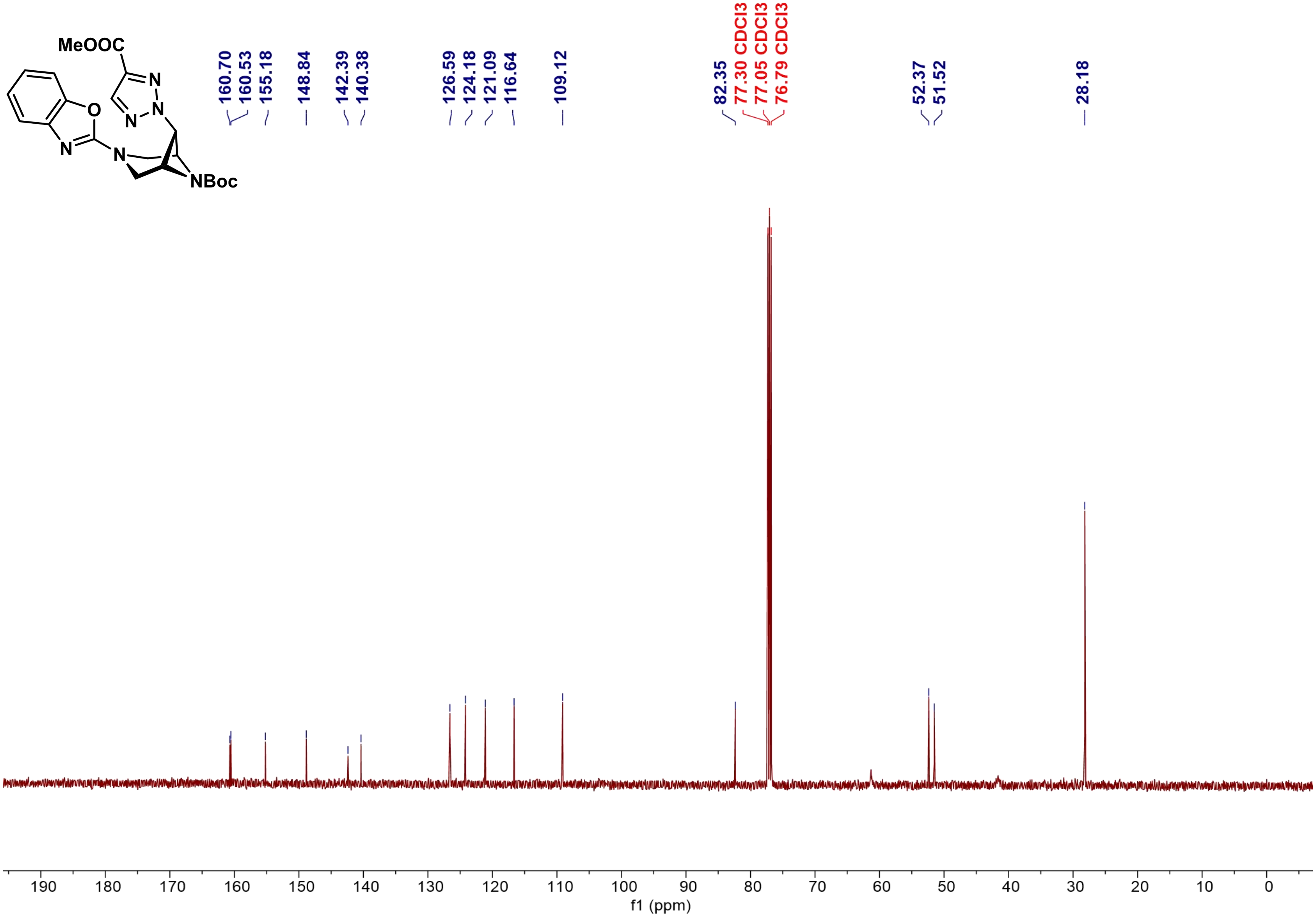




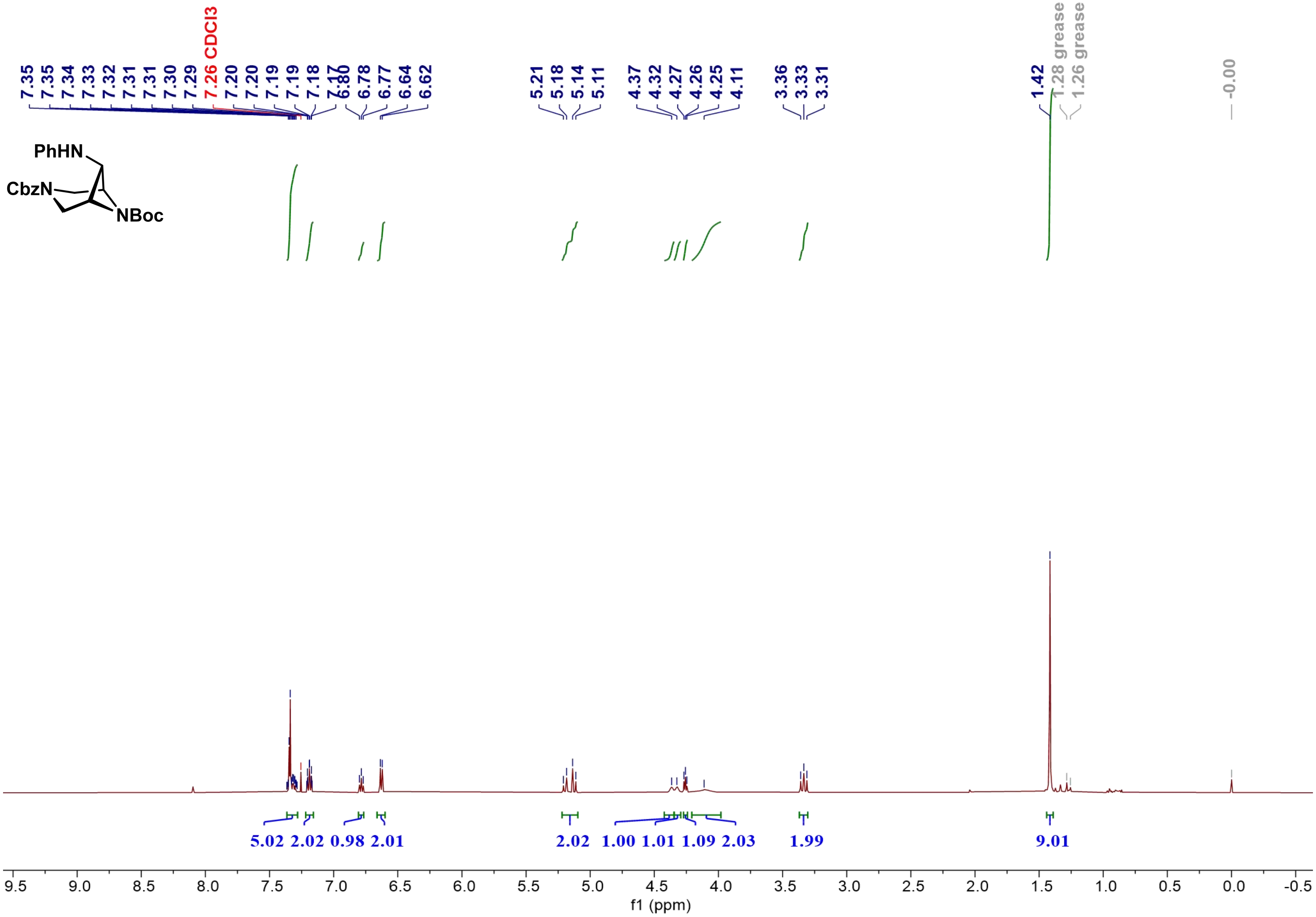
^1H NMR Spectrum of compound SI-62 (500 MHz, $CDCl_3$)



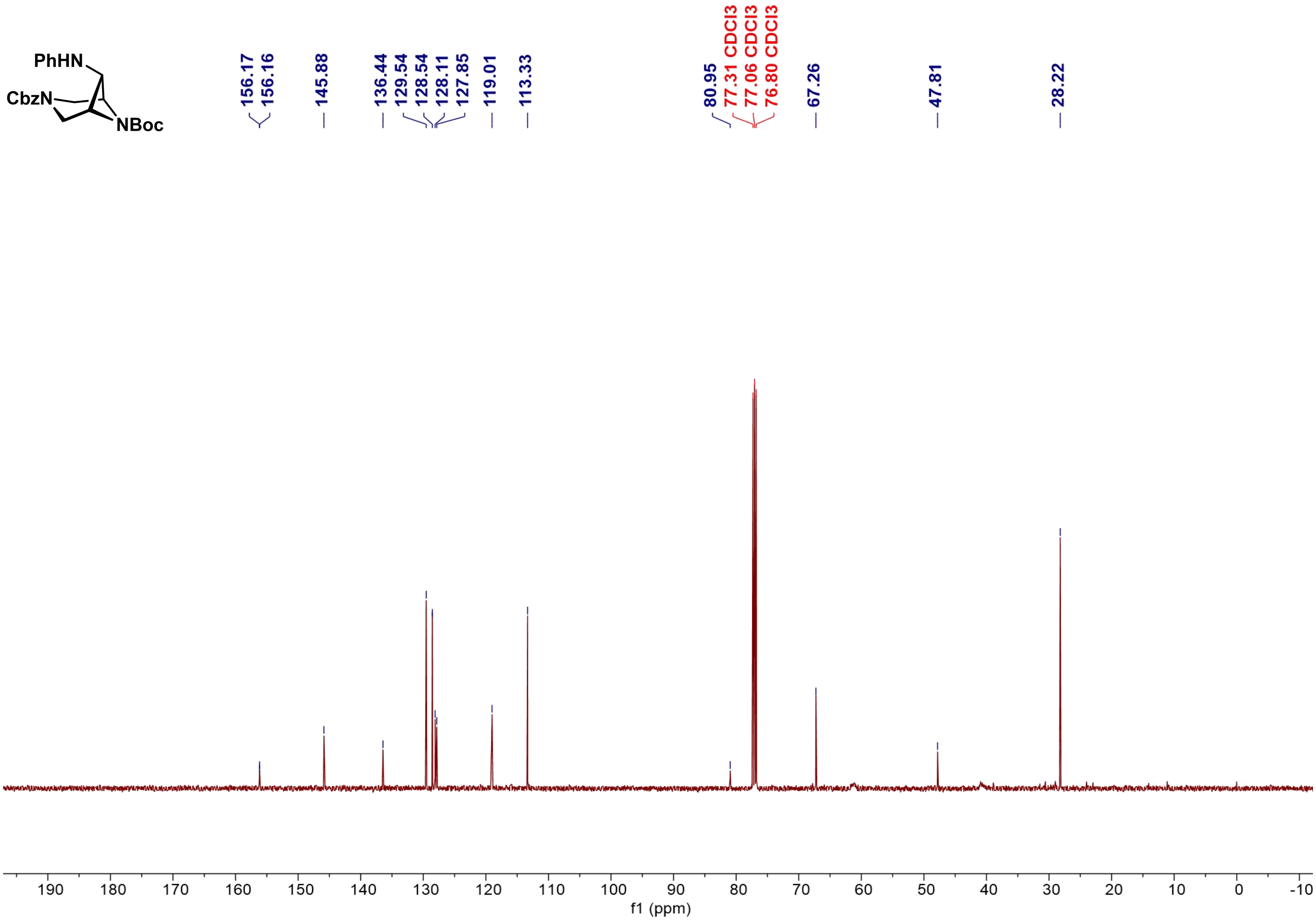
^{13}C NMR Spectrum of compound SI-62 (126 MHz, CDCl$_3$)



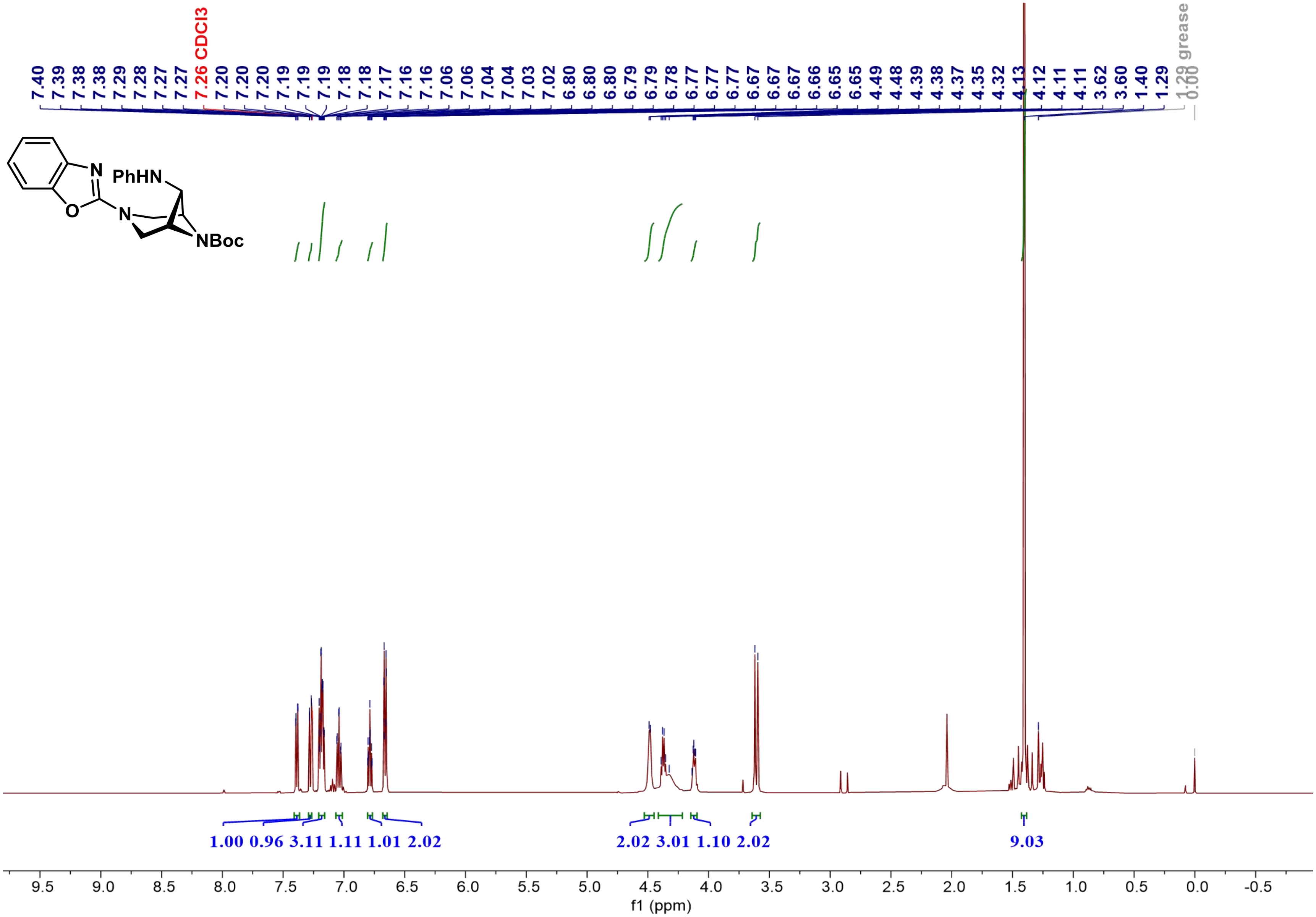
^{1}H NMR Spectrum of compound SI-63 (500 MHz, $CDCl_3$)



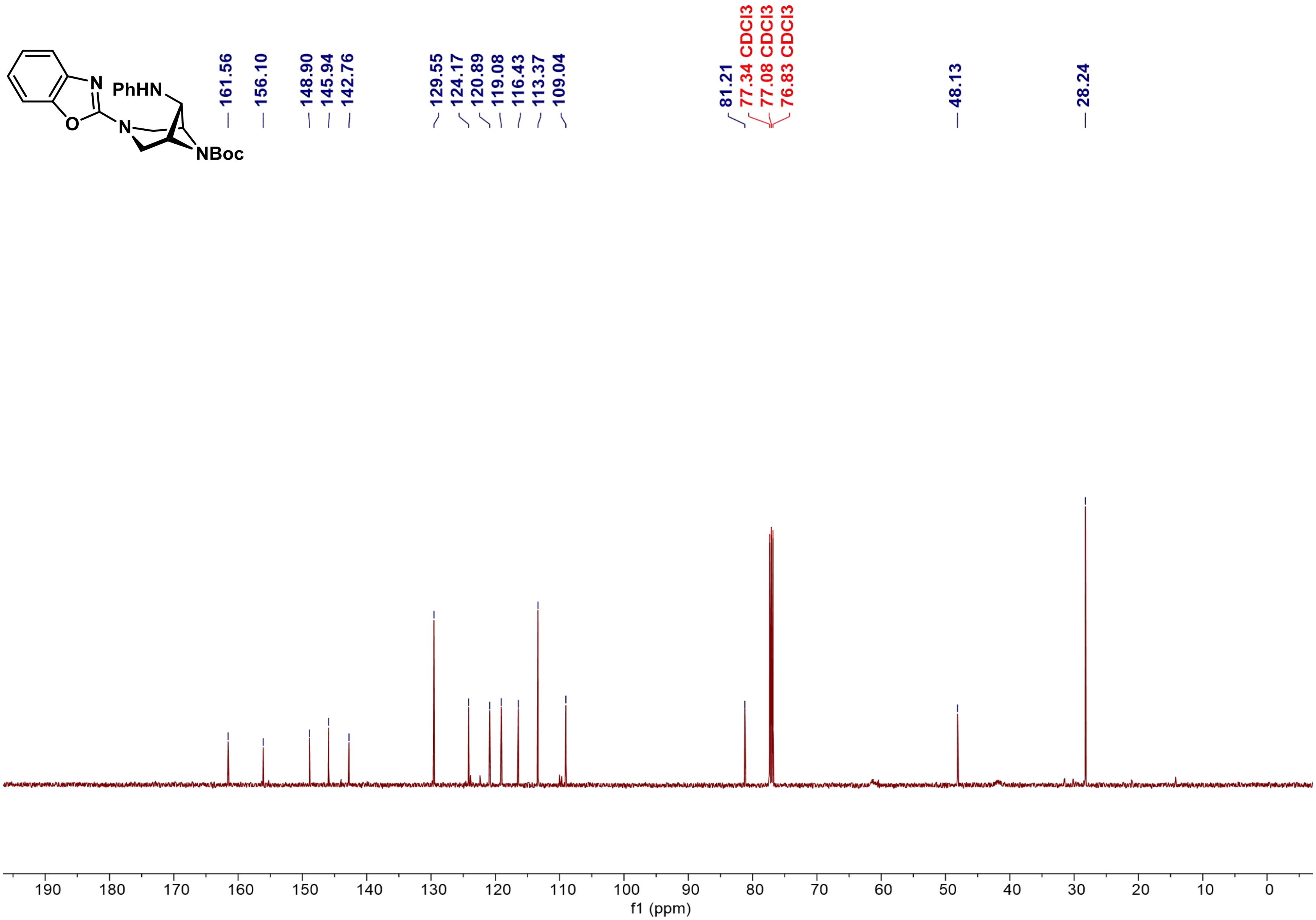
^{13}C NMR Spectrum of compound SI-63 (126 MHz, CDCl$_3$)



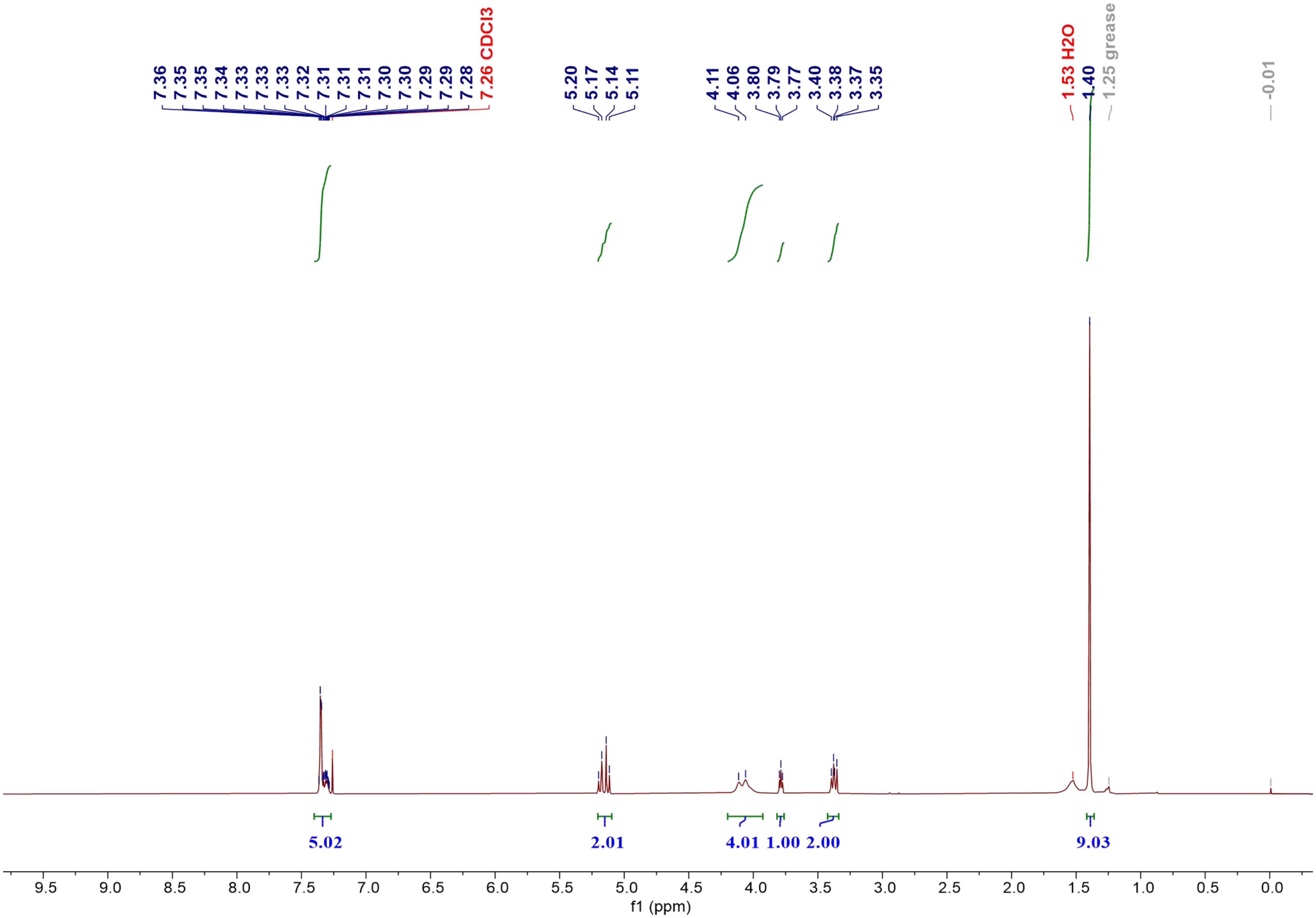
^{1}H NMR Spectrum of compound SI-64 (500 MHz, $CDCl_3$)



^{13}C NMR Spectrum of compound SI-64 (126 MHz, CDCl$_3$)



^{1}H NMR Spectrum of compound SI-66 (500 MHz, CDCl$_3$



7.36
7.35
7.35
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7.33
7.33
7.33
7.32
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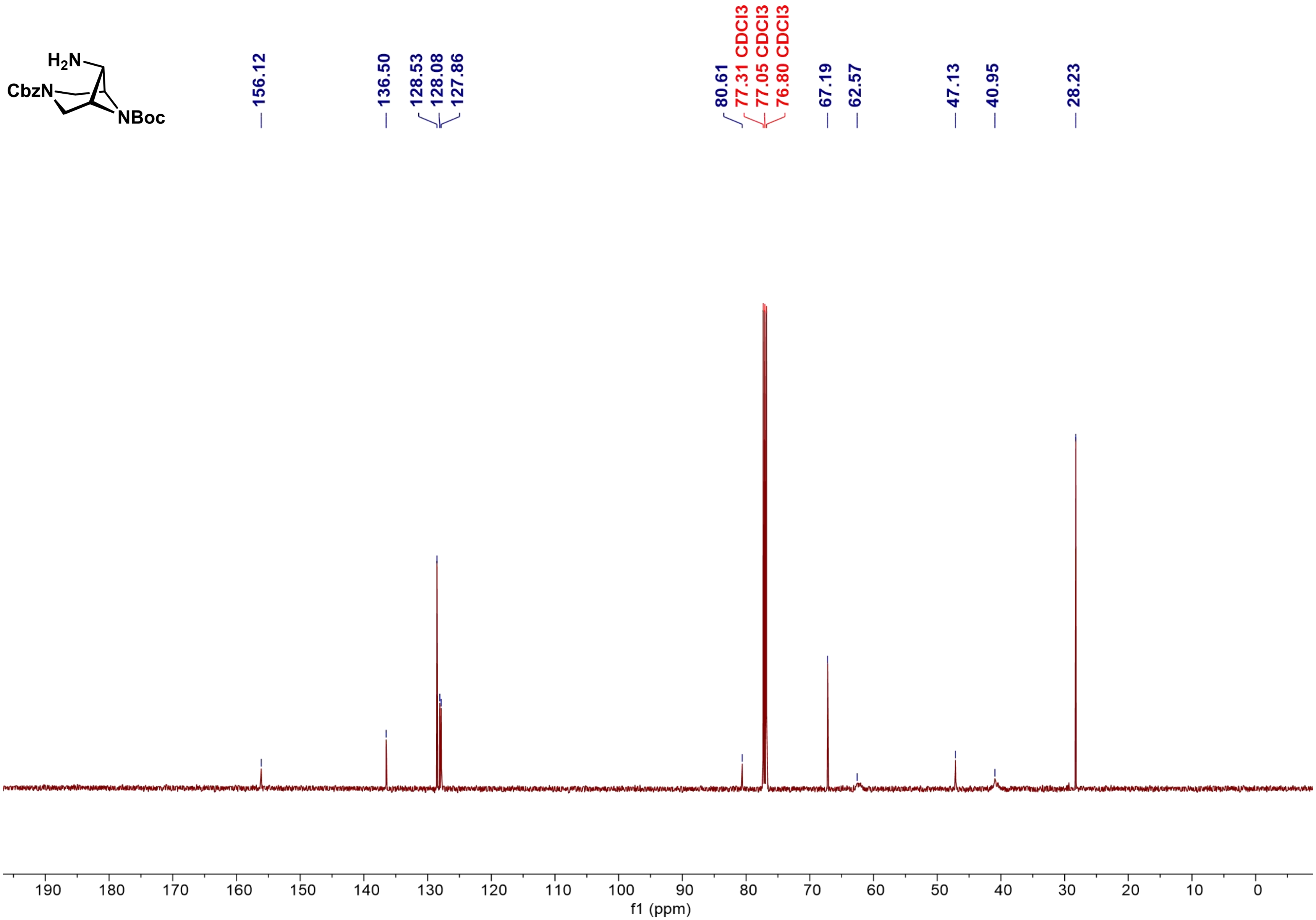
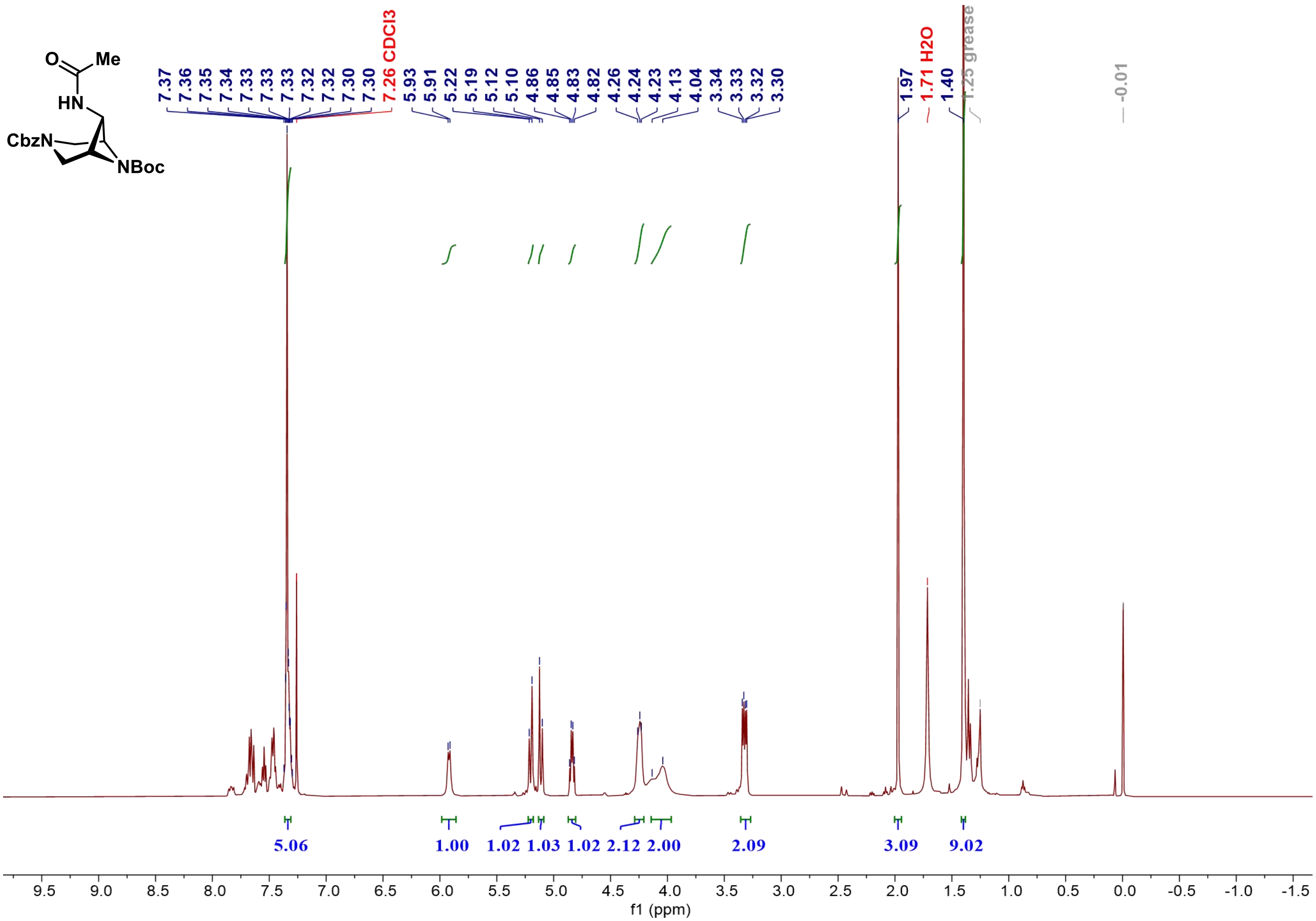
7.31
7.31
7.30
7.30
7.29
7.29
7.28
7.26 CDCl3
5.20
5.17
5.14
5.11
4.11
4.06
3.80
3.79
3.77
3.40
3.38
3.37
3.35
1.53 H2O
1.40
1.25 grease
-0.01
5.02
2.01
4.01
1.00
2.00
9.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

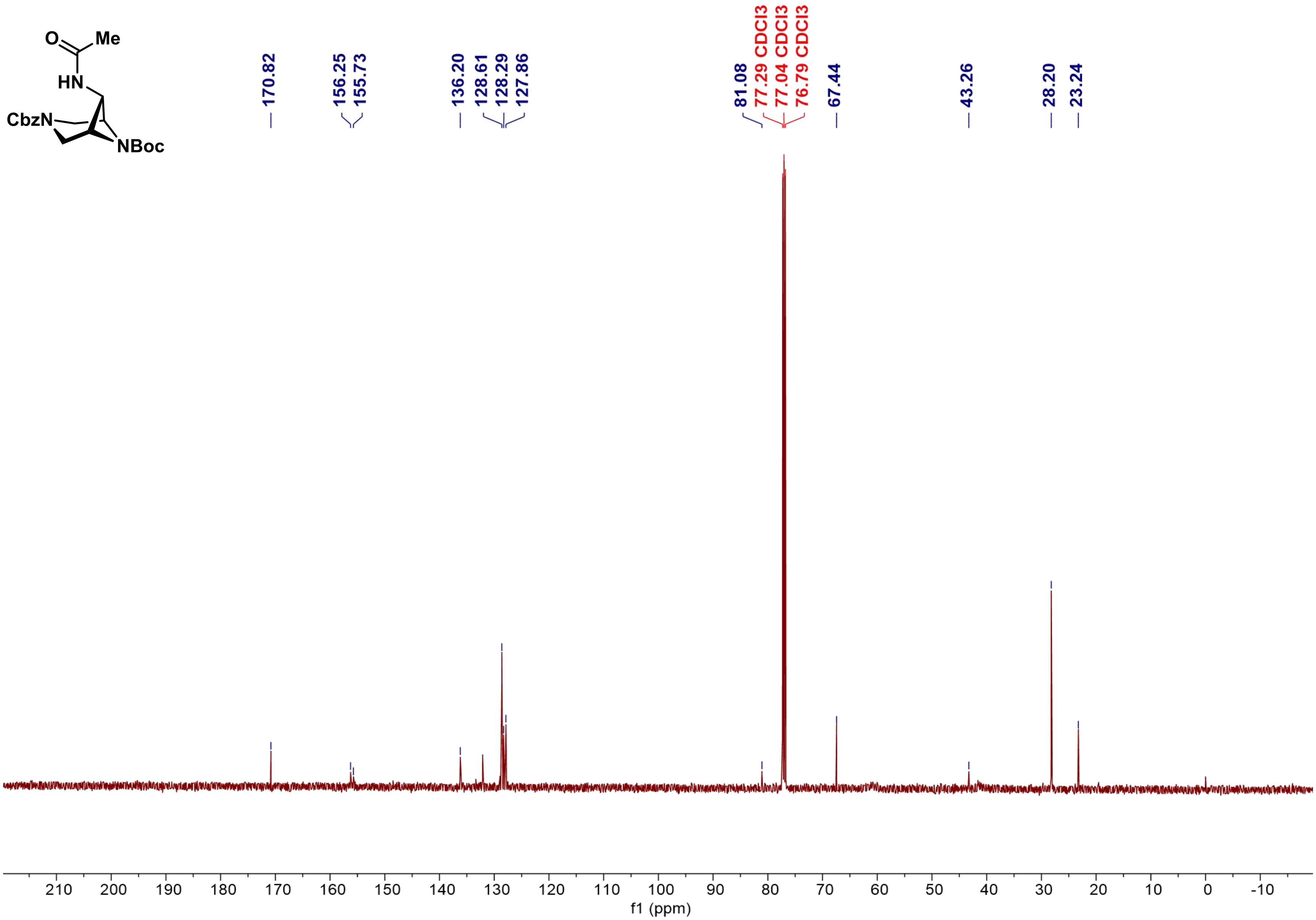
^{13}C NMR Spectrum of compound SI-66 (126 MHz, $CDCl_3$)



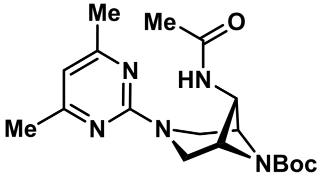
^{1}H NMR Spectrum of compound SI-67 (500 MHz, $CDCl_3$)

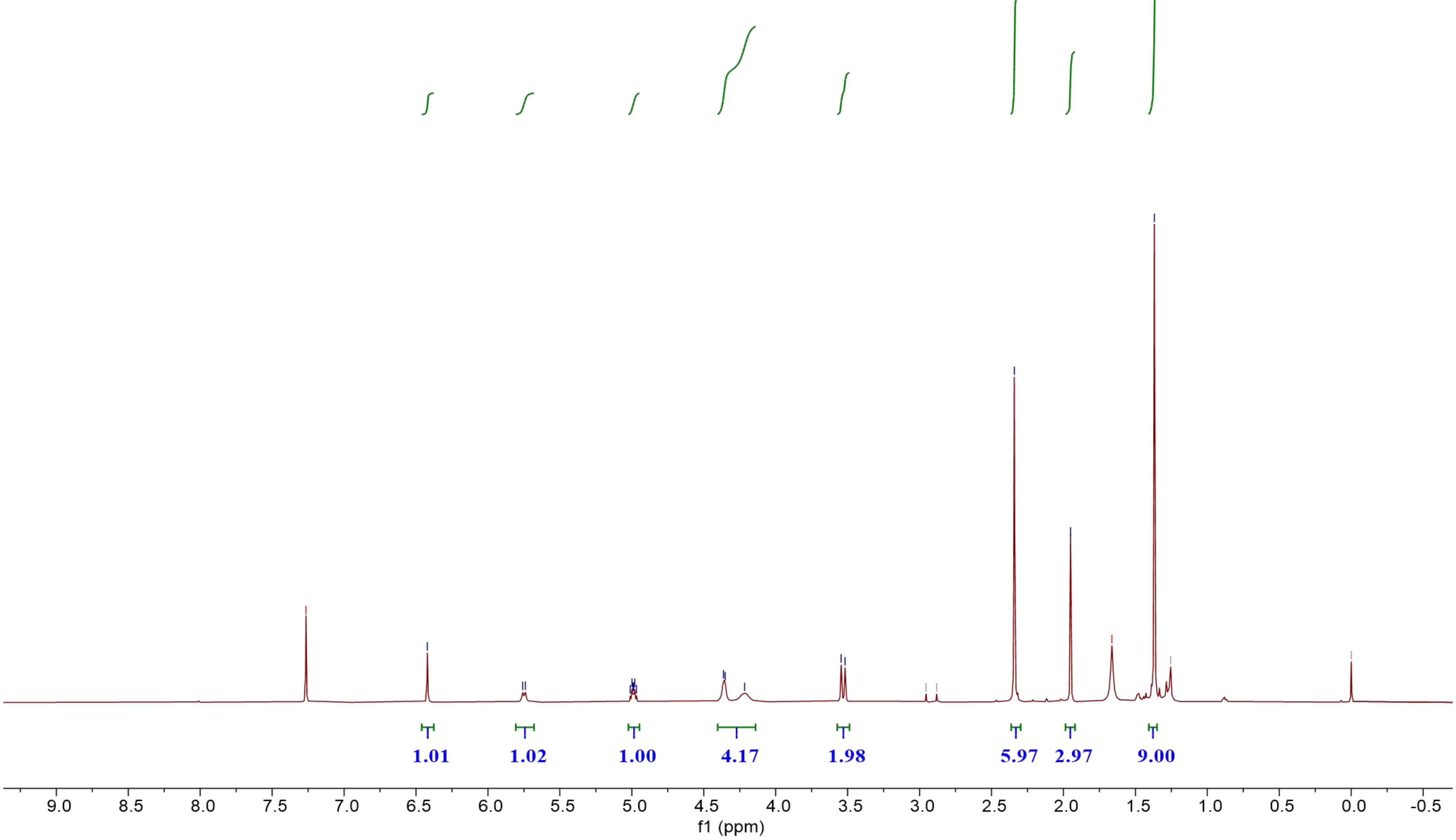


^{13}C NMR Spectrum of compound SI-67 (126 MHz, $CDCl_3$)

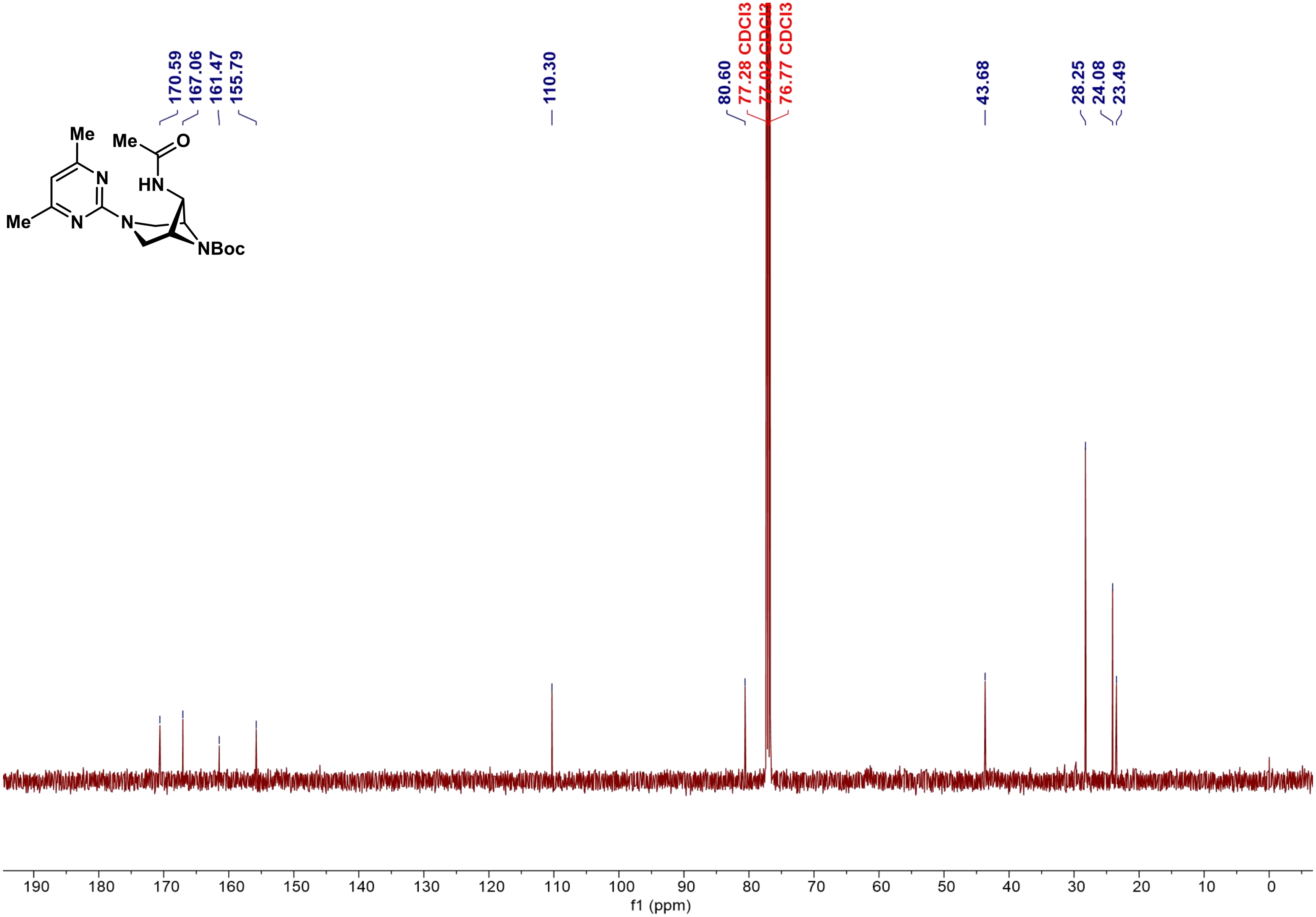


^{1}H NMR Spectrum of compound SI-68 (500 MHz, $CDCl_3$)

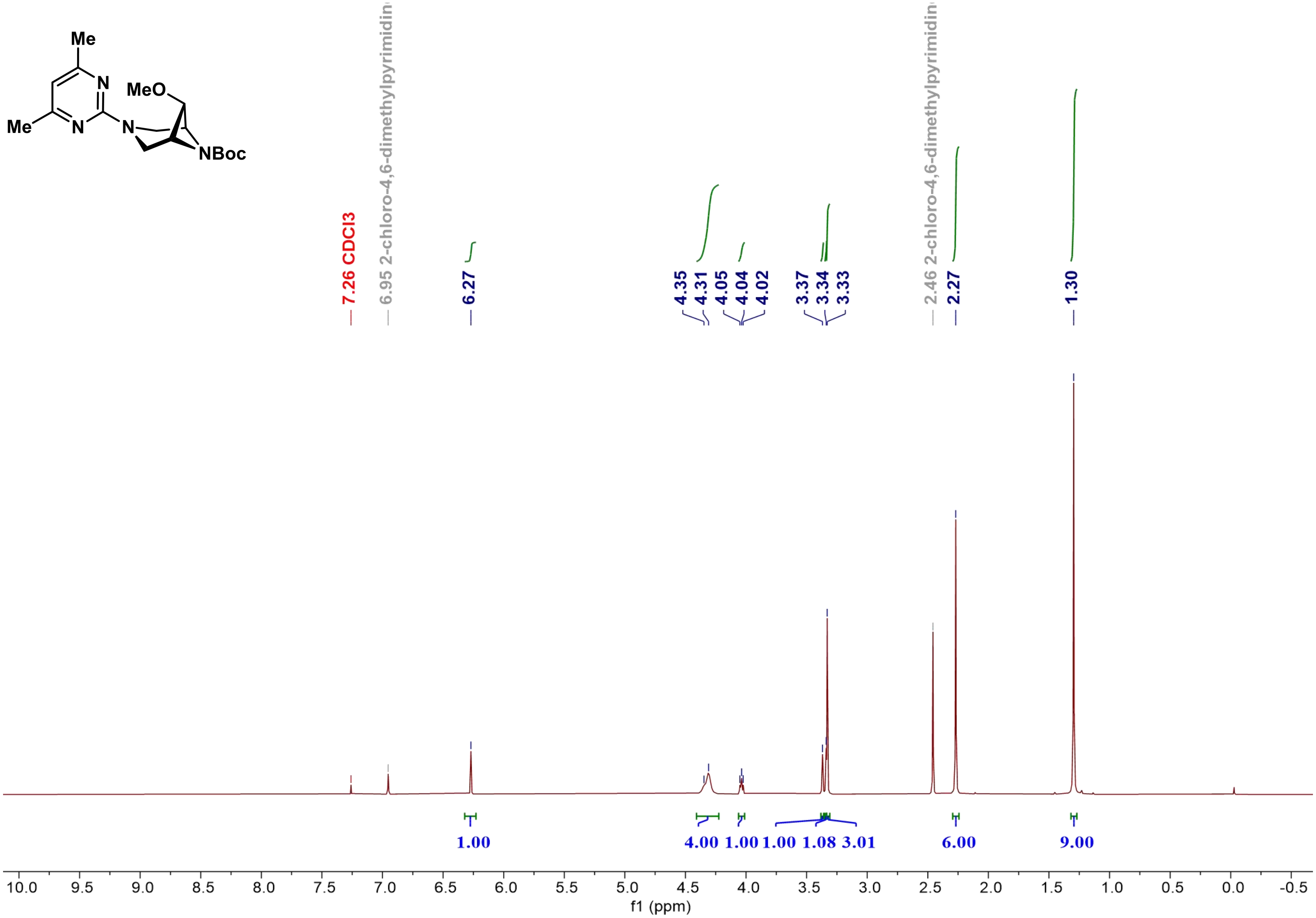




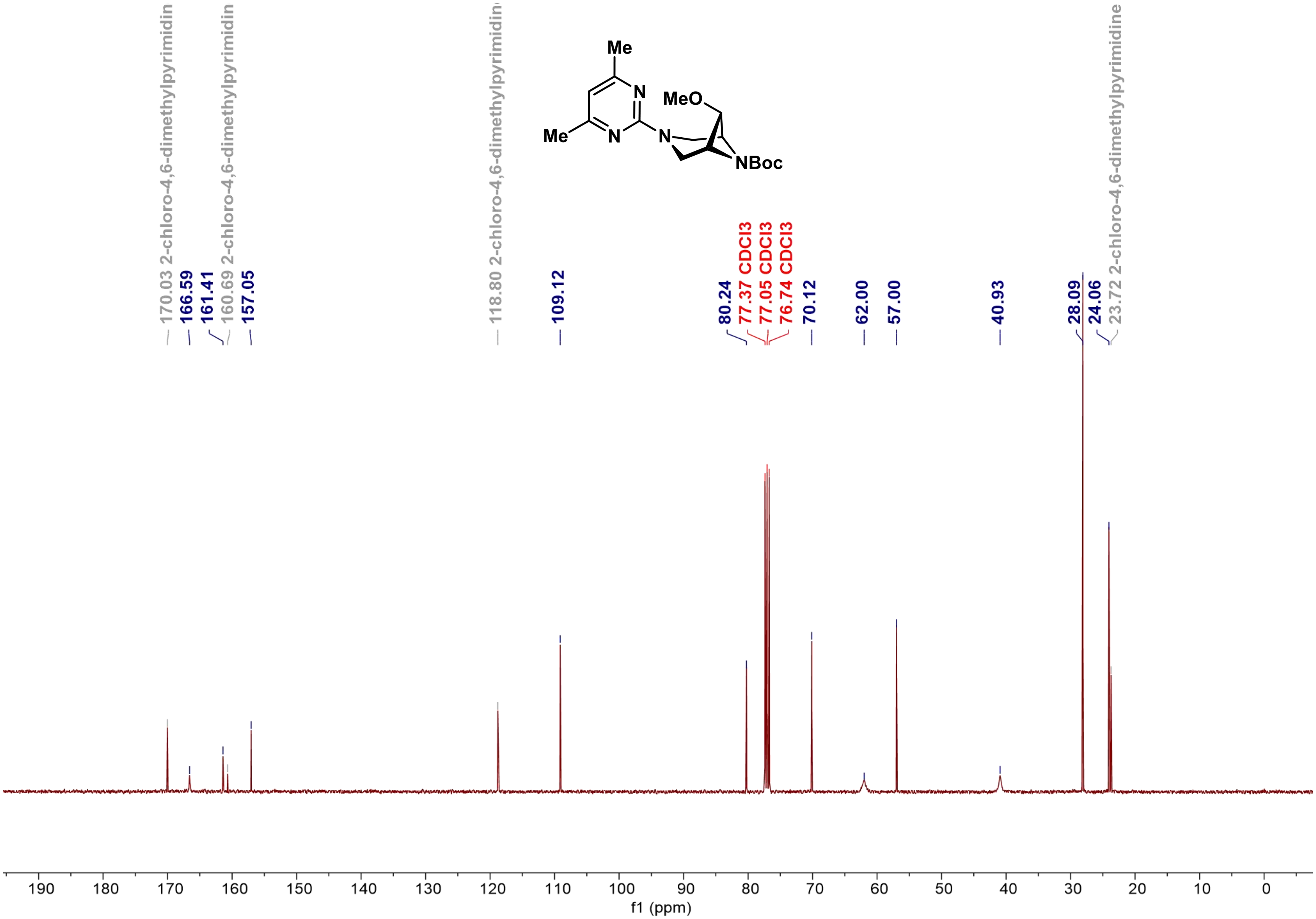
^{13}C NMR Spectrum of compound SI-68 (126 MHz, $CDCl_3$)



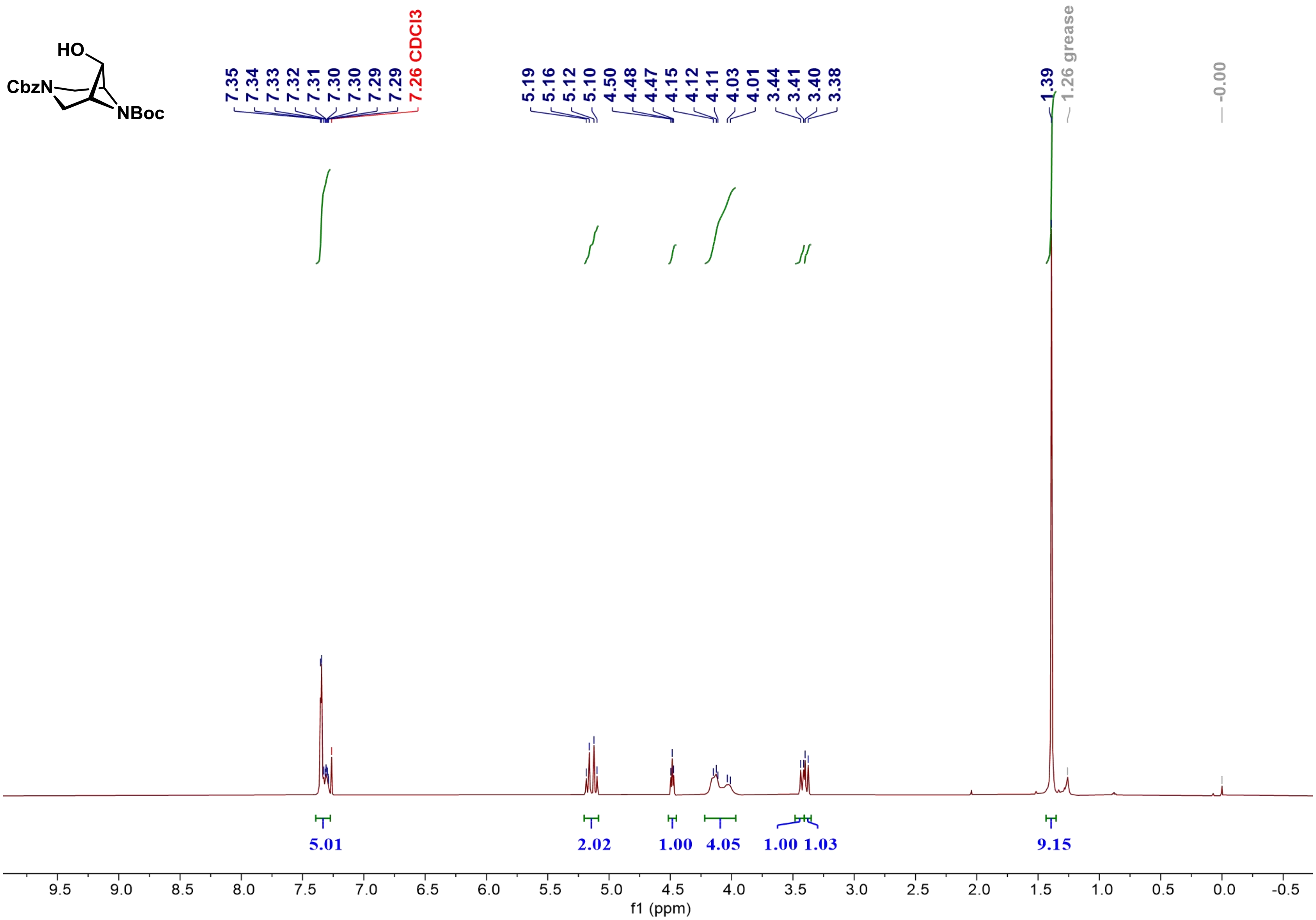
^{1}H NMR Spectrum of compound SI-69 (400 MHz, $CDCl_3$)



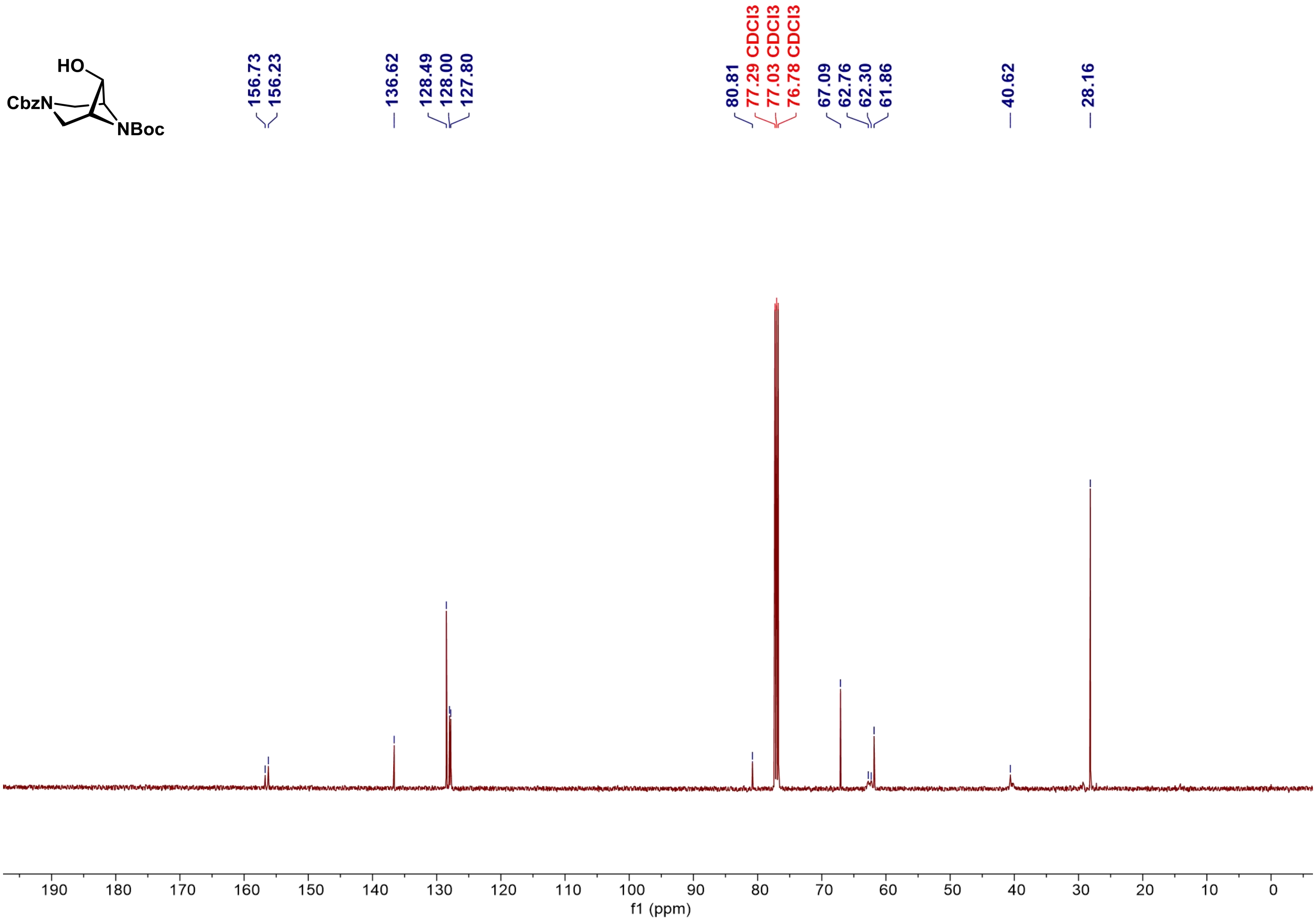
^{13}C NMR Spectrum of compound SI-69 (101 MHz, $CDCl_3$)



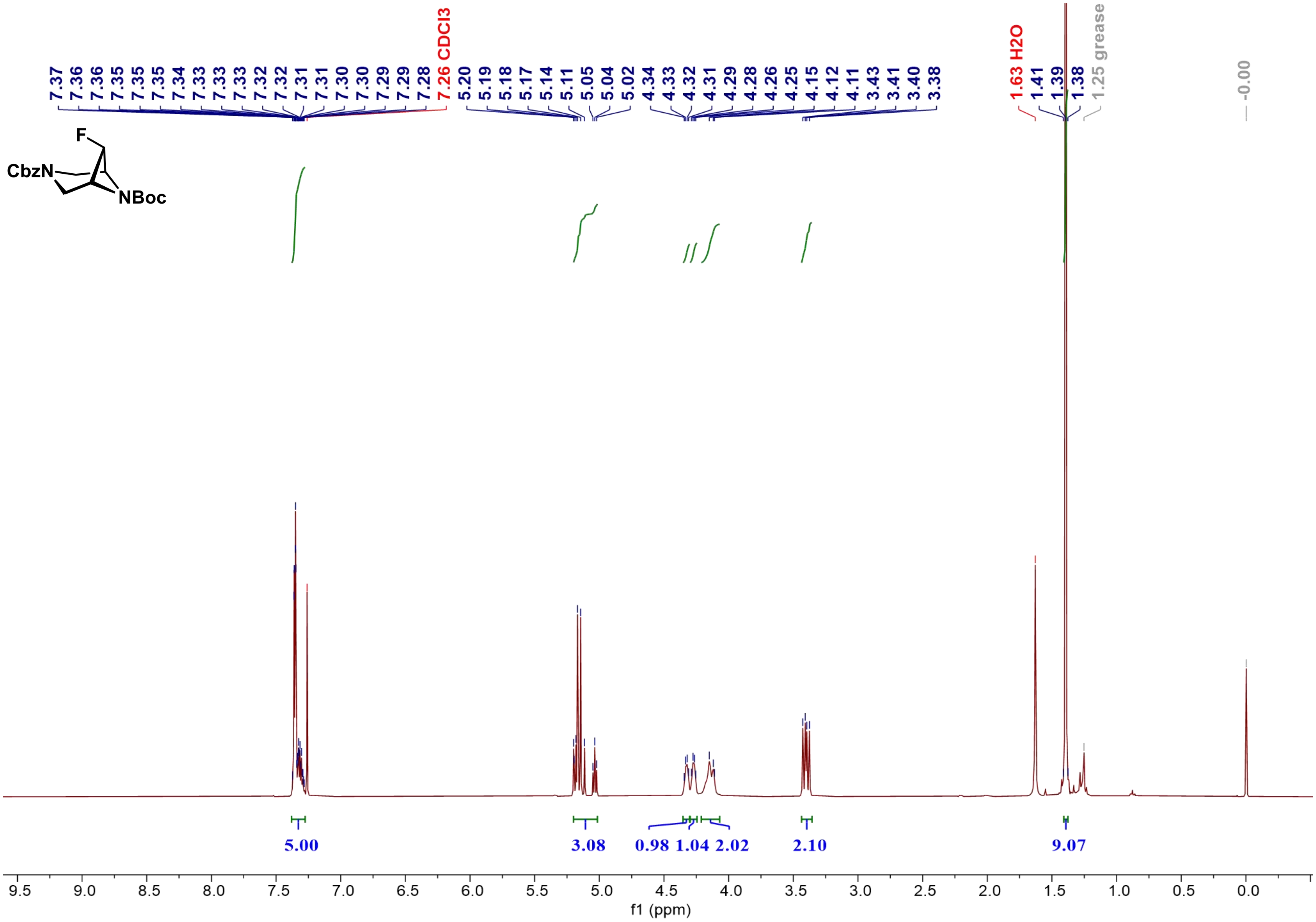
^{1}H NMR Spectrum of compound SI-70 (500 MHz, $CDCl_3$)



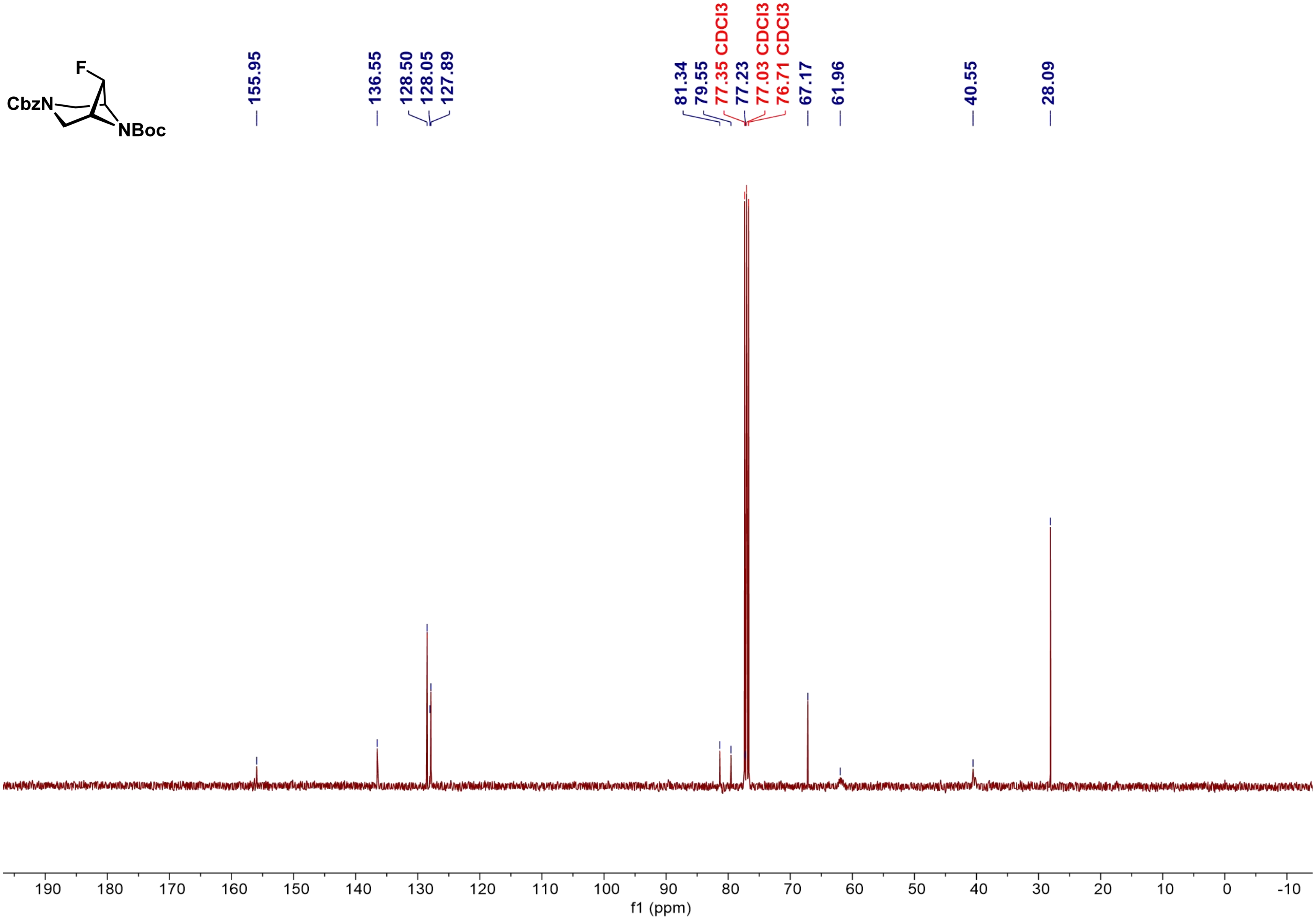
^{13}C NMR Spectrum of compound SI-70 (126 MHz, CDCl$_3$)



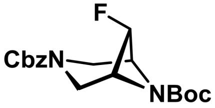
^{1}H NMR Spectrum of compound SI-71 (400 MHz, CDCl$_3$)

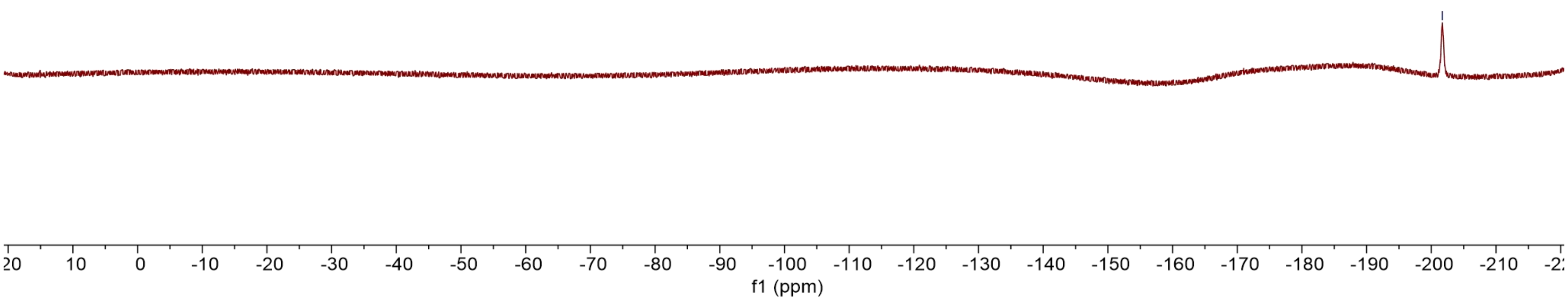


^{13}C NMR Spectrum of compound SI-71 (101 MHz, CDCl$_3$)

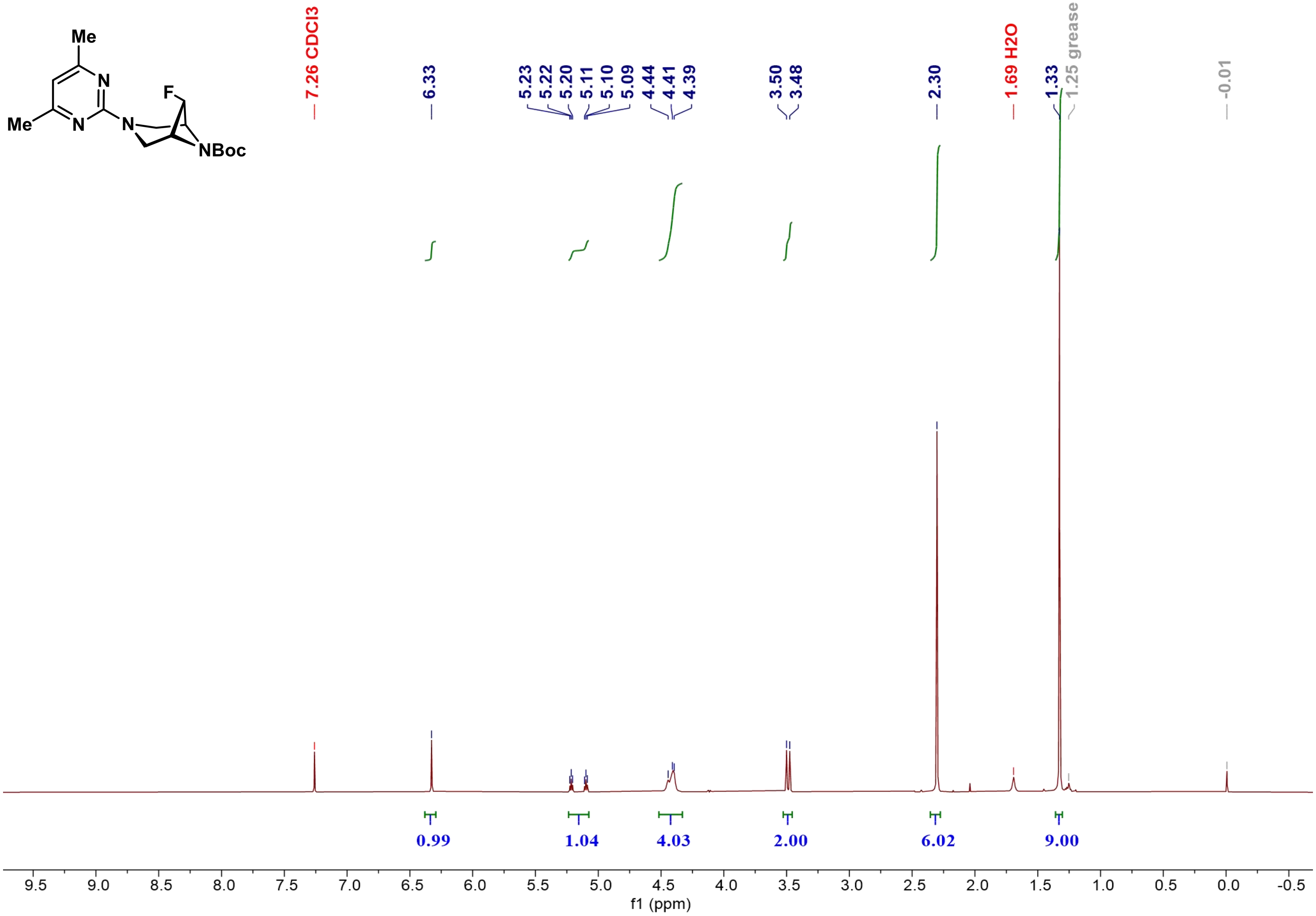


^{19}F NMR Spectrum of compound SI-71 (377 MHz, CDCl$_3$)

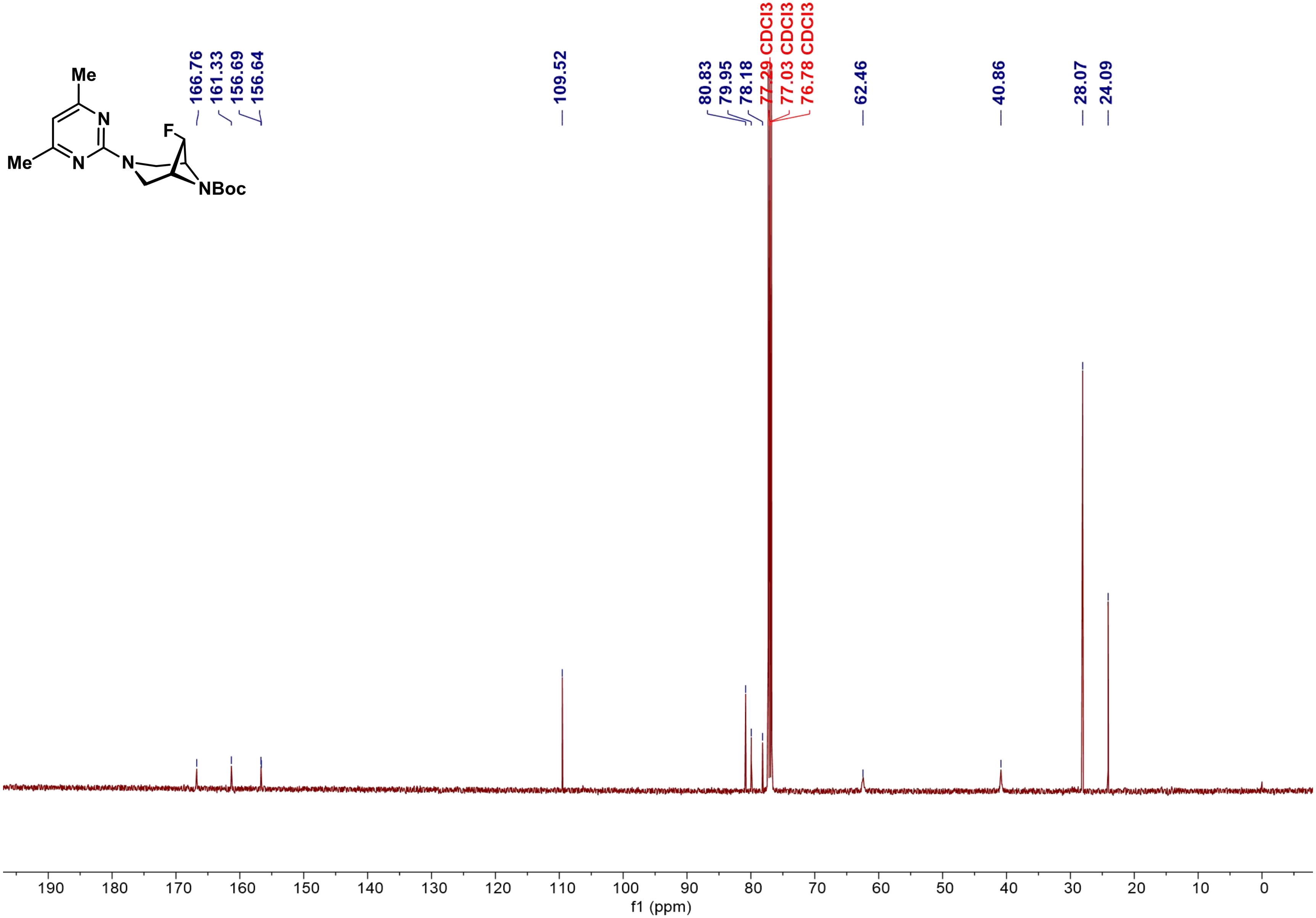




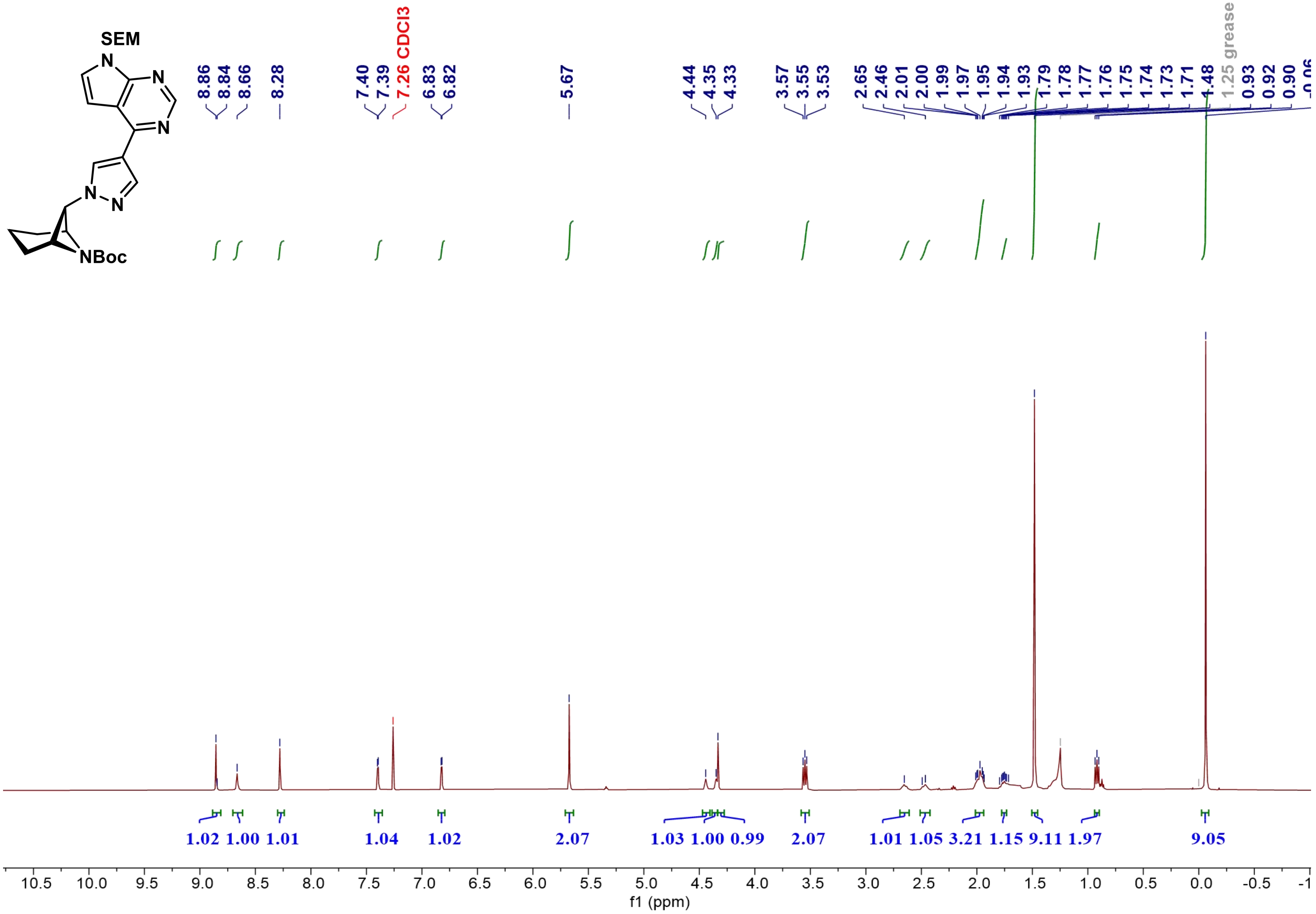
^{1}H NMR Spectrum of compound SI-72 (500 MHz, CDCl$_3$)



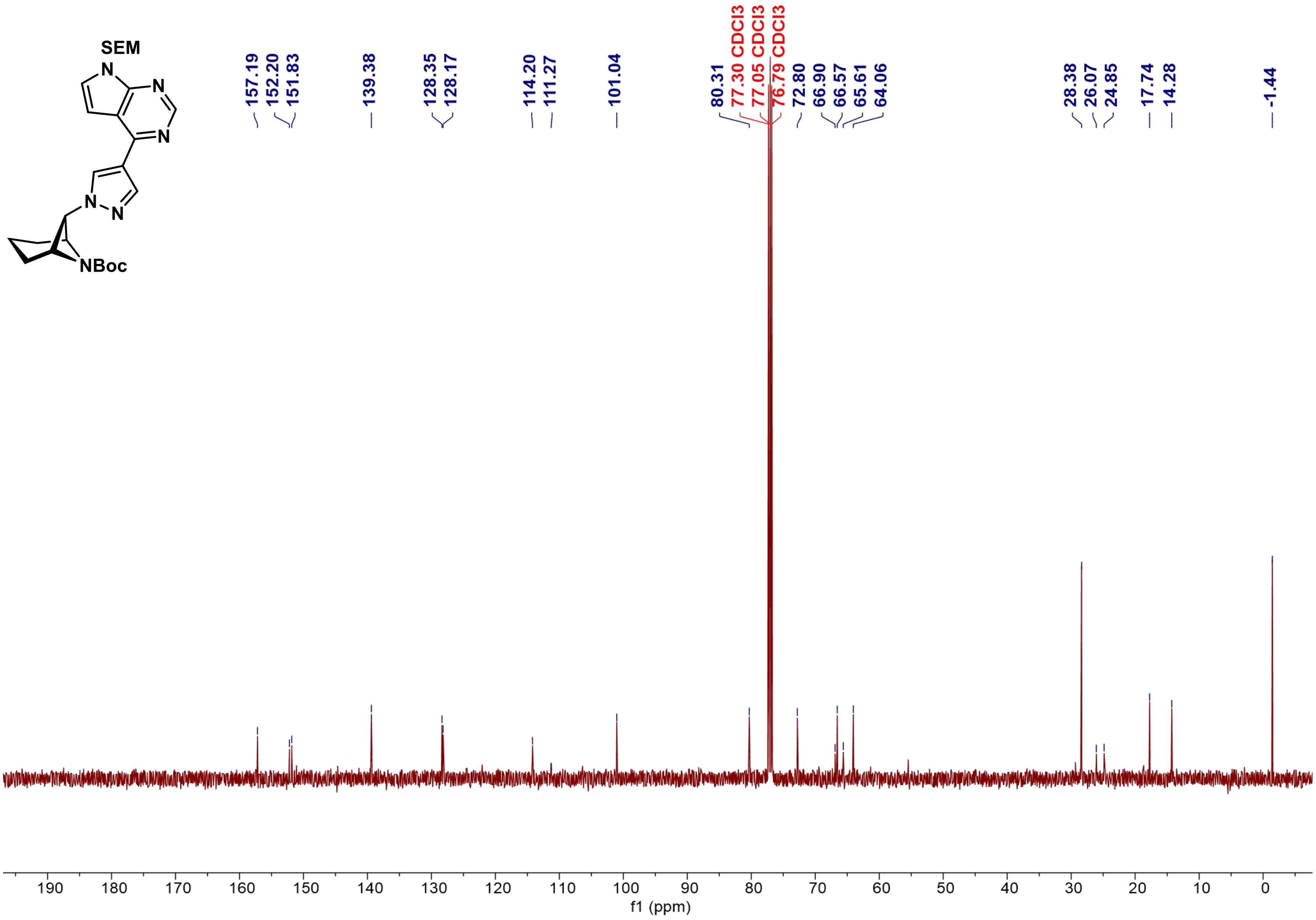
^{13}C NMR Spectrum of compound SI-72 (126 MHz, CDCl$_3$)



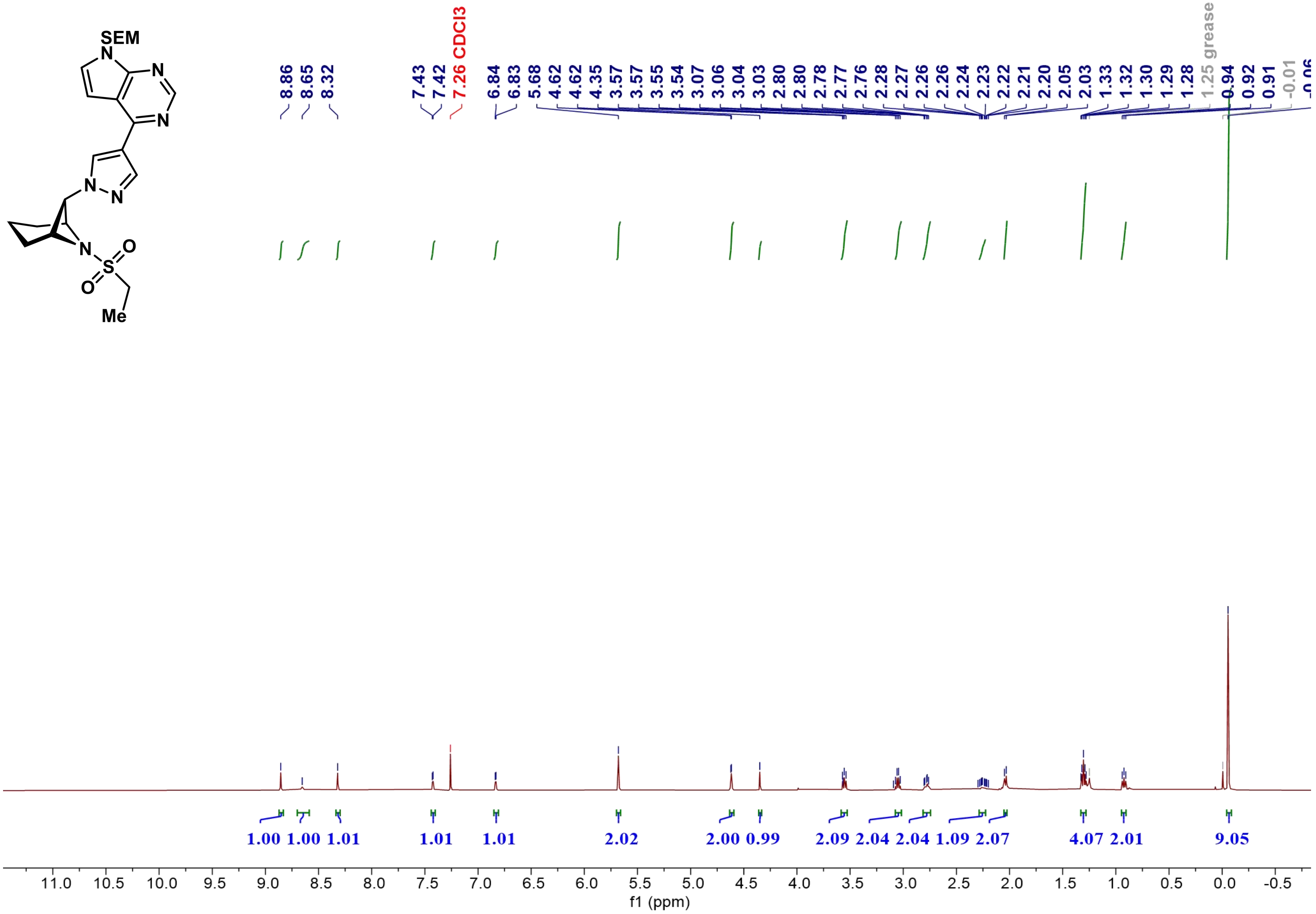
^{1}H NMR Spectrum of compound SI-73 (500 MHz, $CDCl_3$)



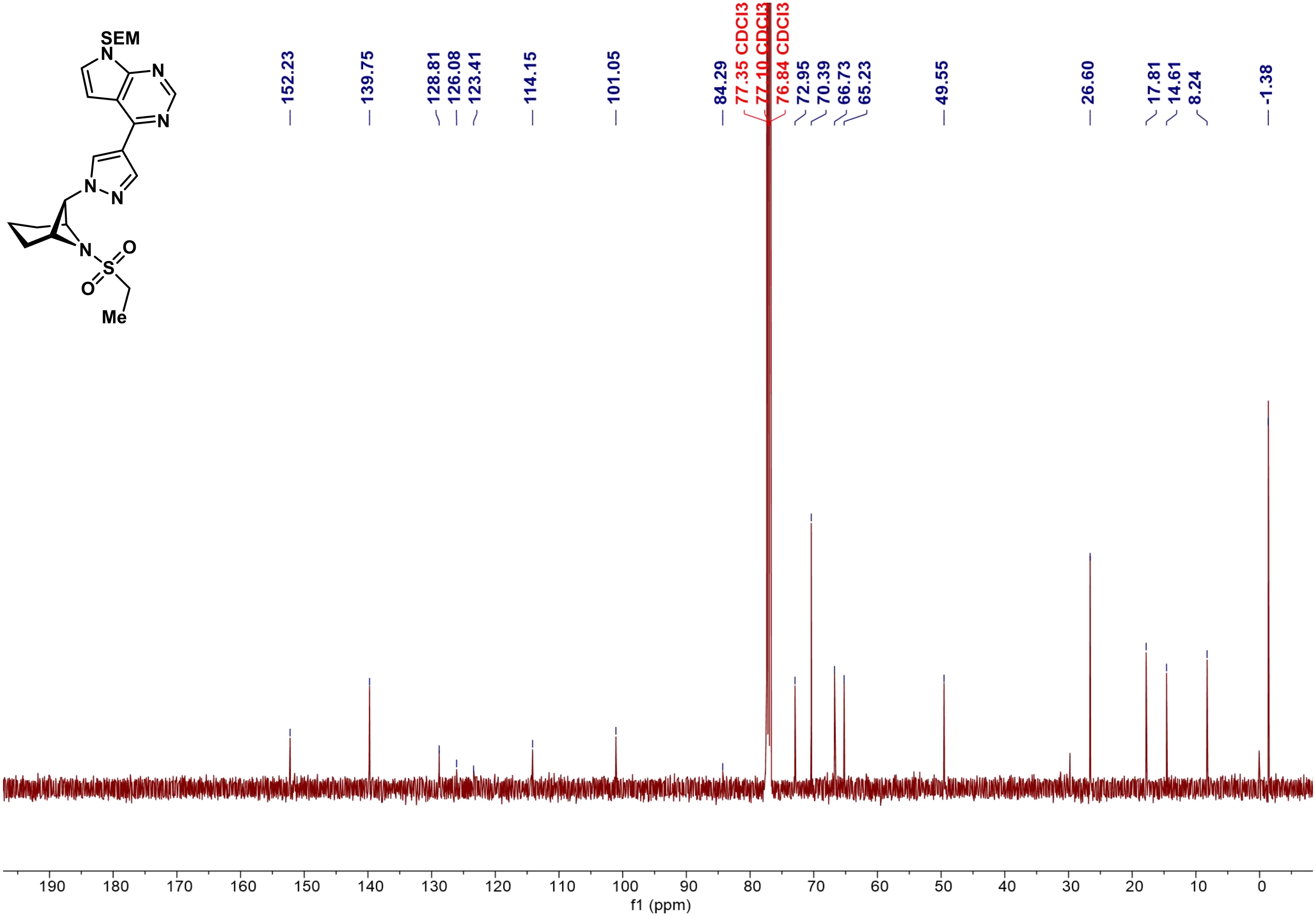
^{13}C NMR Spectrum of compound SI-73 (126 MHz, CDCl$_3$)



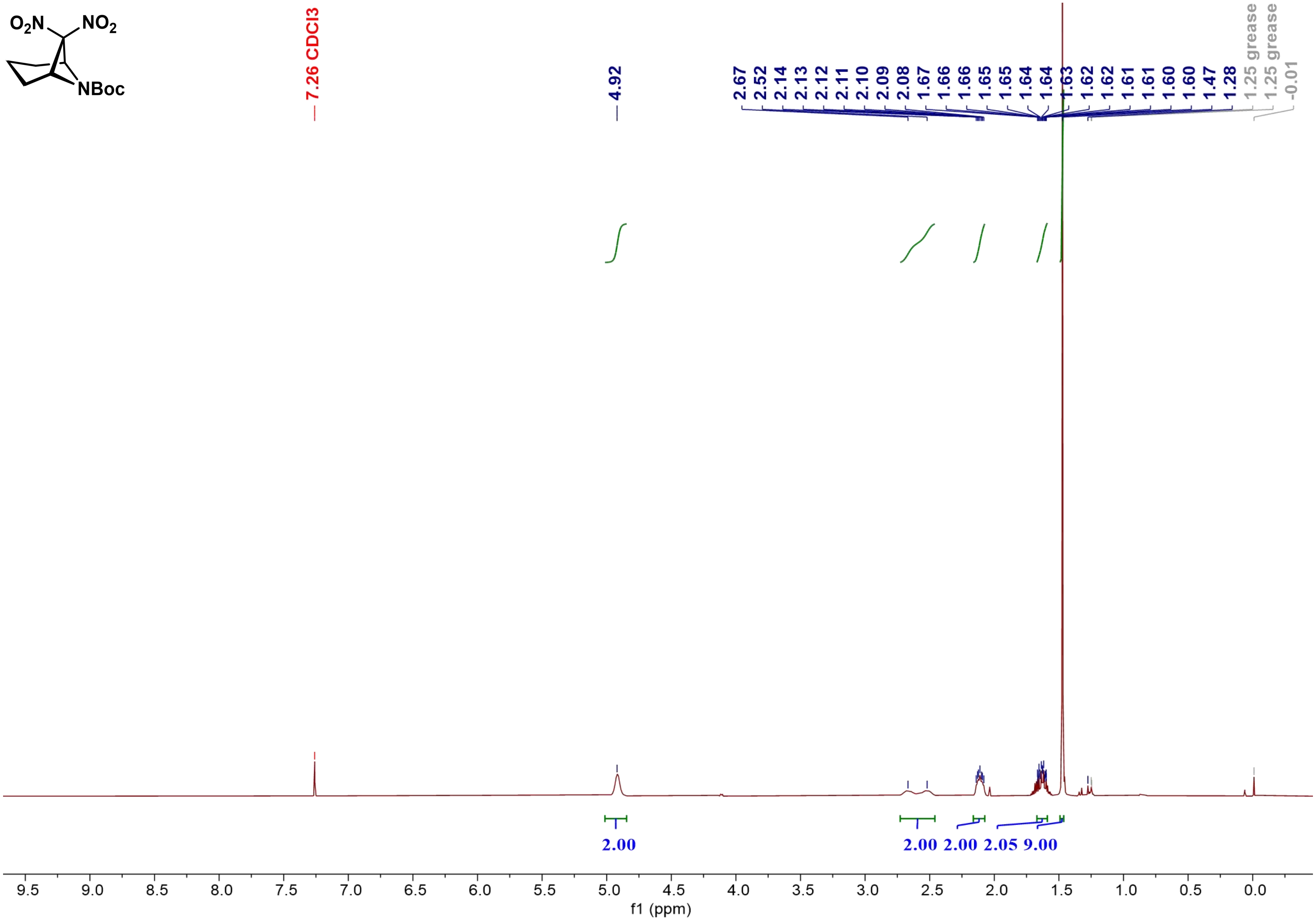
^{1}H NMR Spectrum of compound SI-74 (500 MHz, $CDCl_3$)



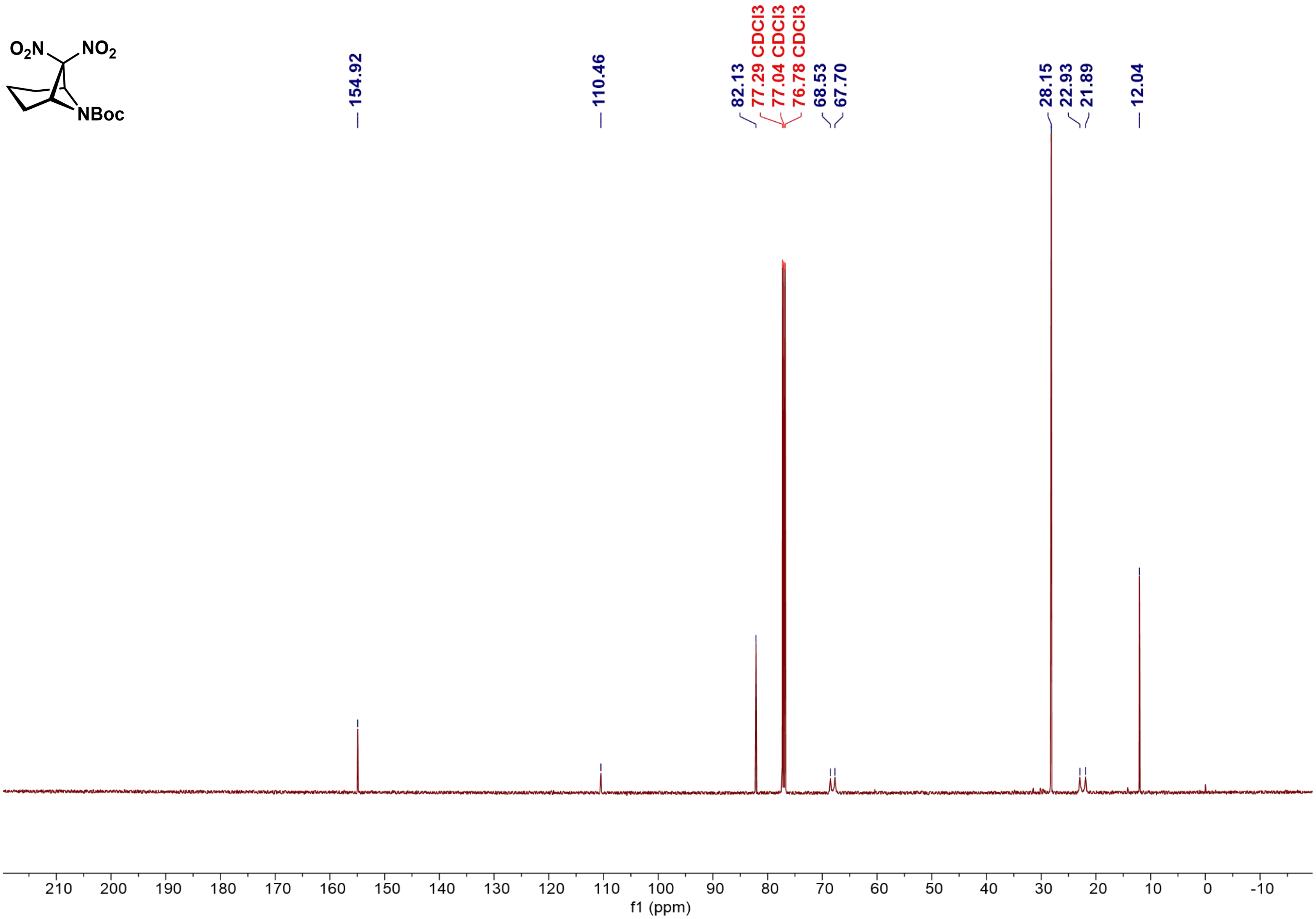
^{13}C NMR Spectrum of compound SI-74 (126 MHz, CDCl$_3$)



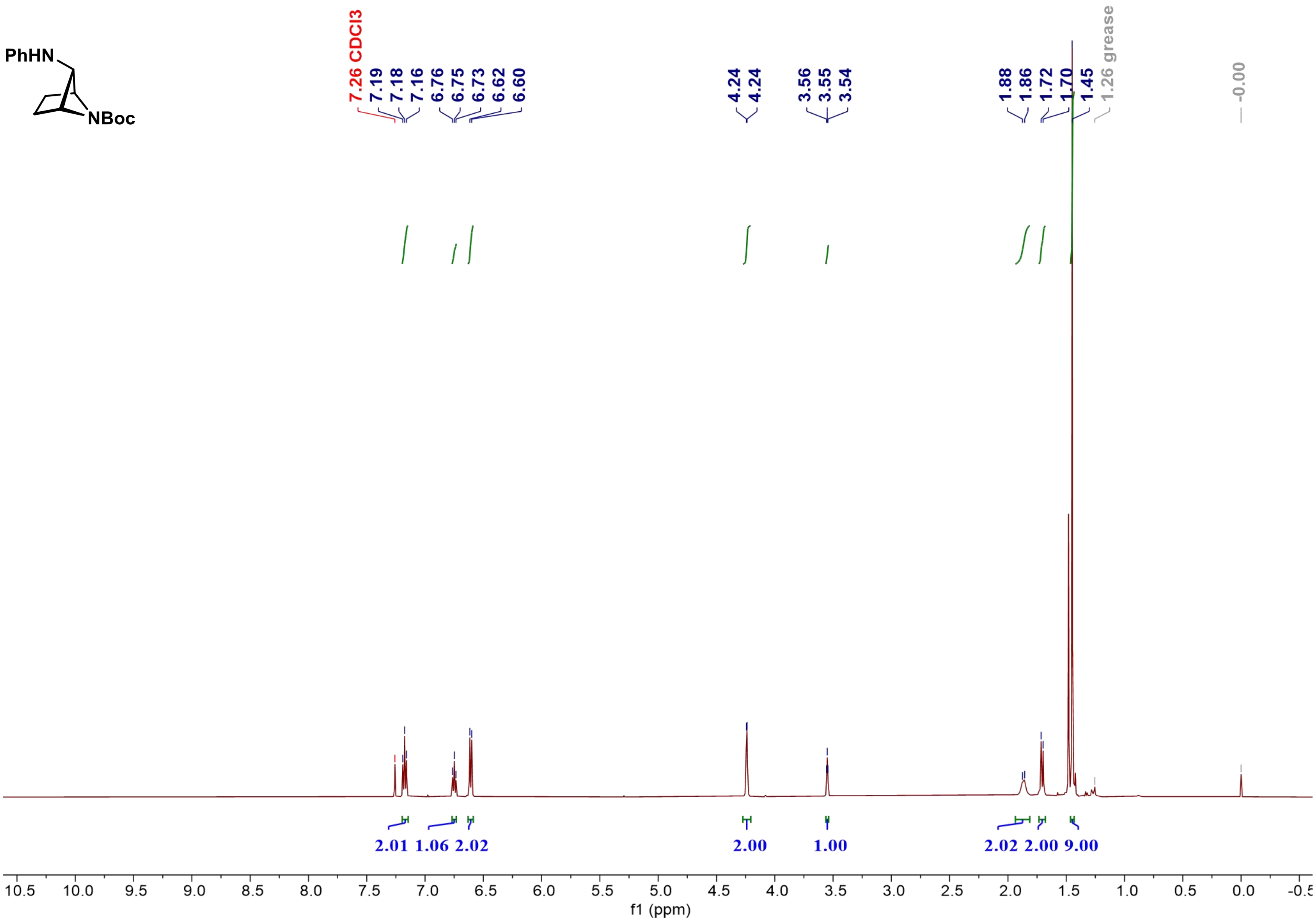
^{1}H NMR Spectrum of compound SI-75 (500 MHz, CDCl$_3$)



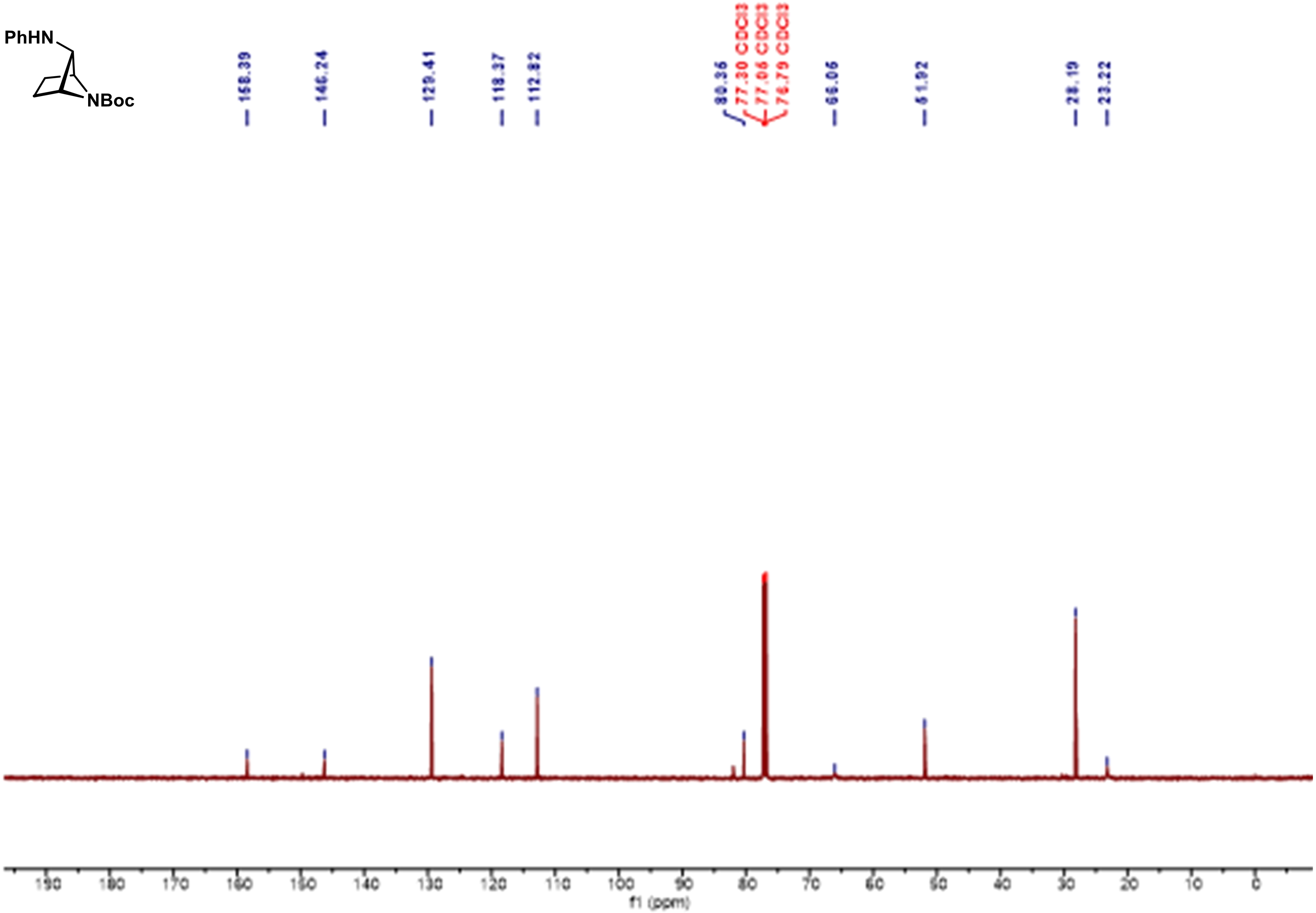
^{13}C NMR Spectrum of compound SI-75 (126 MHz, CDCl$_3$)



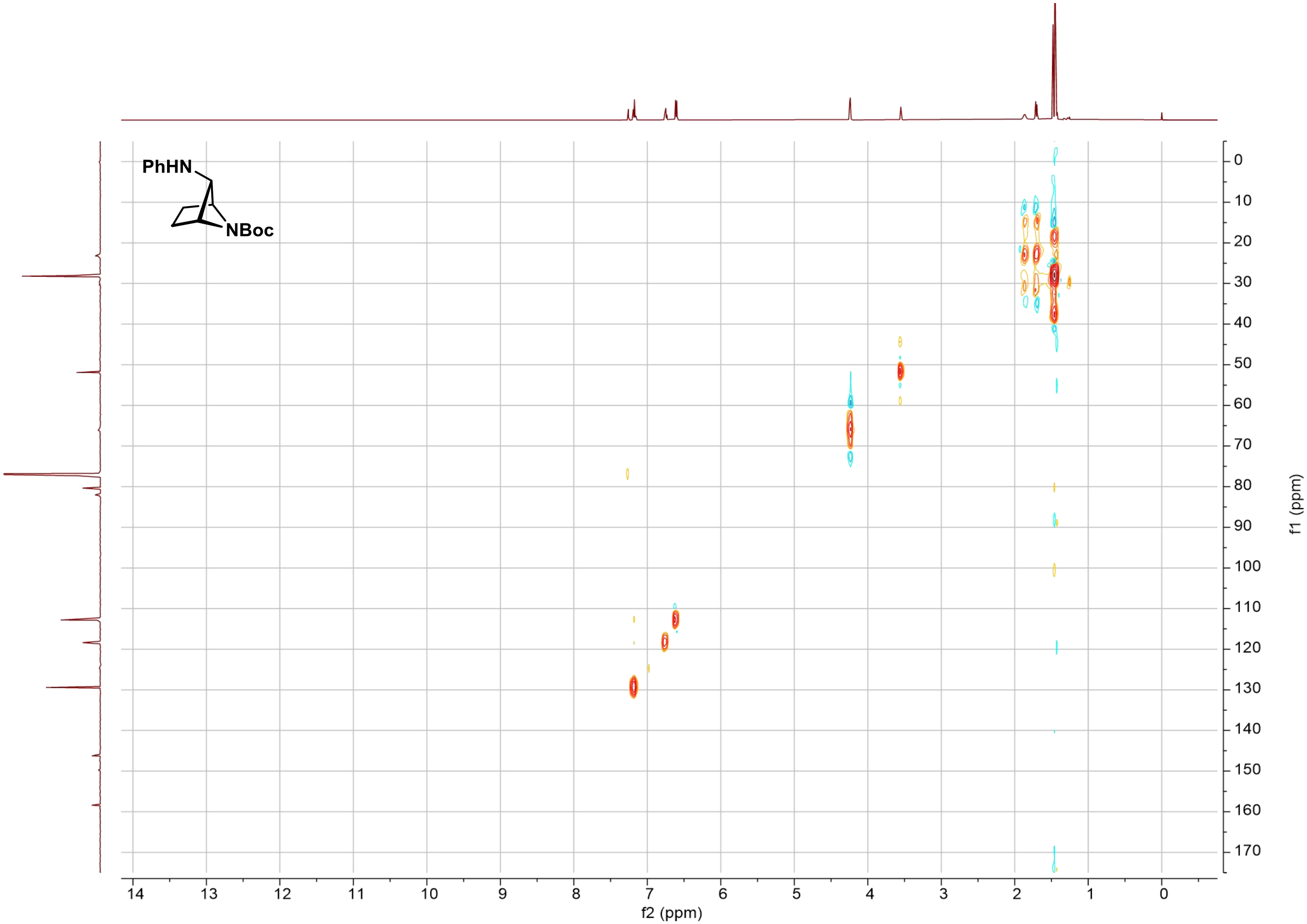
^{1}H NMR Spectrum of compound SI-76 (500 MHz, CDCl$_3$)



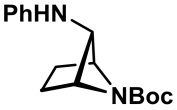
^{13}C NMR Spectrum of compound SI-76 (126 MHz, CDCl$_3$)

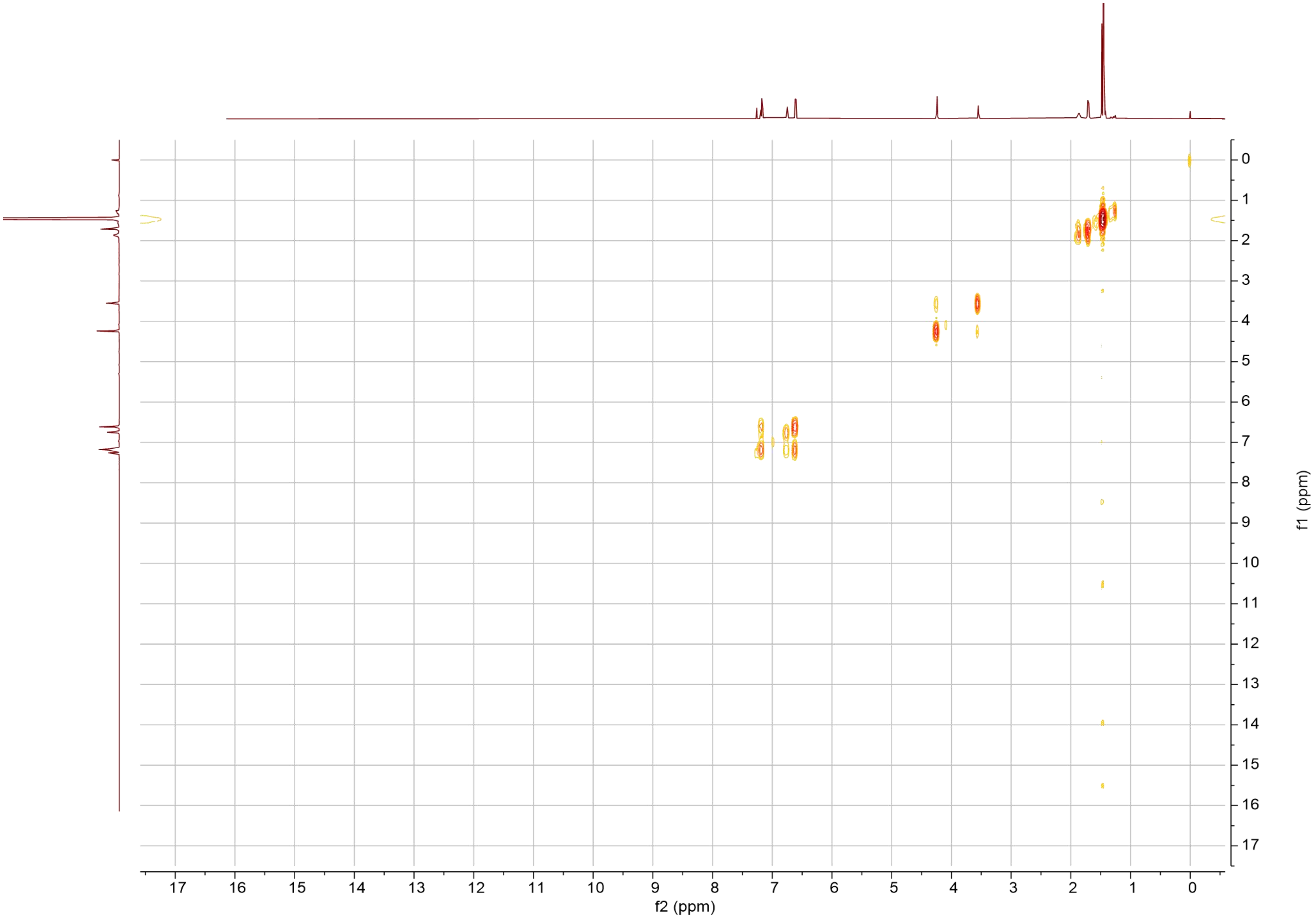


HSQC Spectrum of compound SI-76

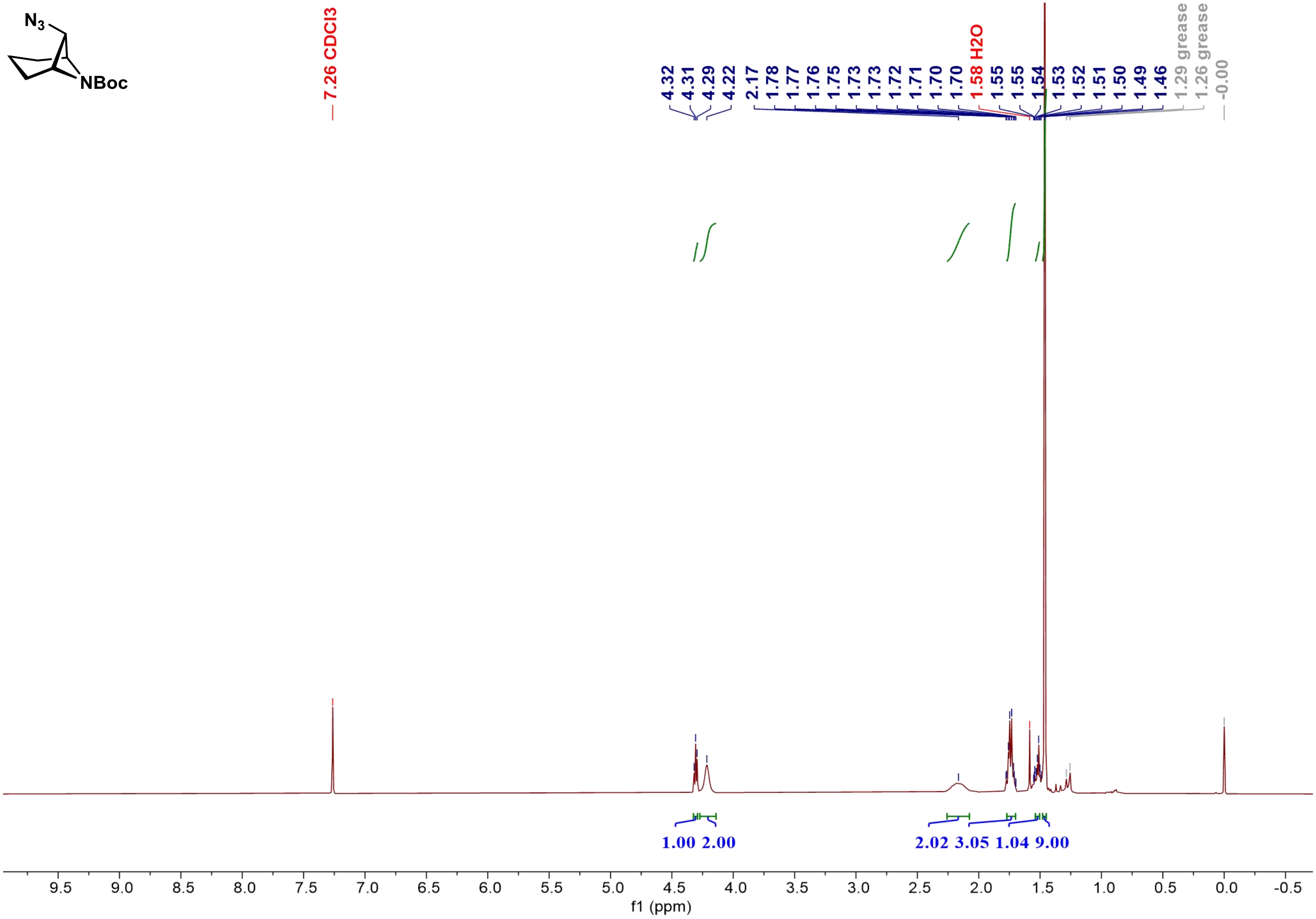


COSY Spectrum of compound SI-76

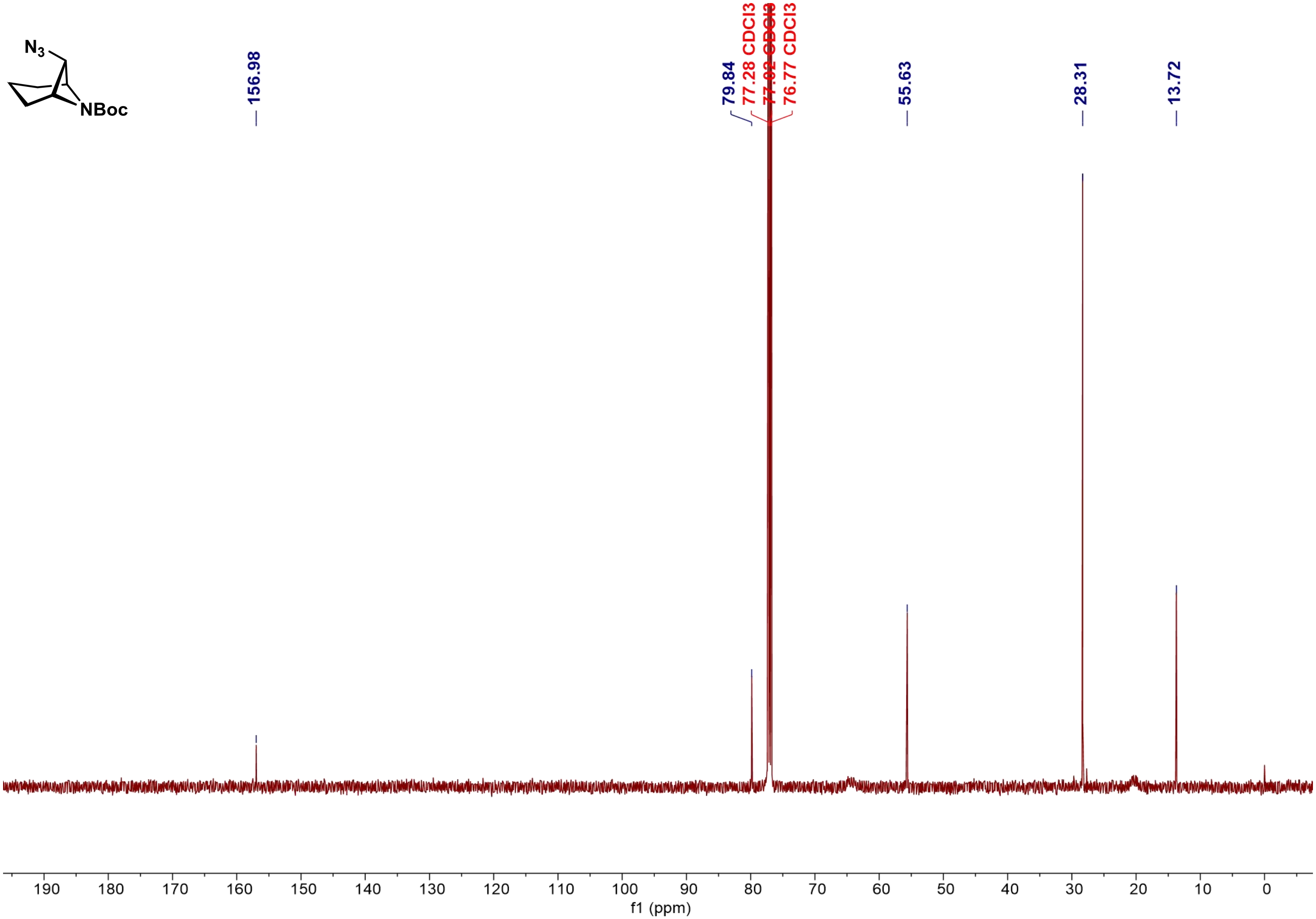



f2 (ppm)
f1 (ppm)
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0

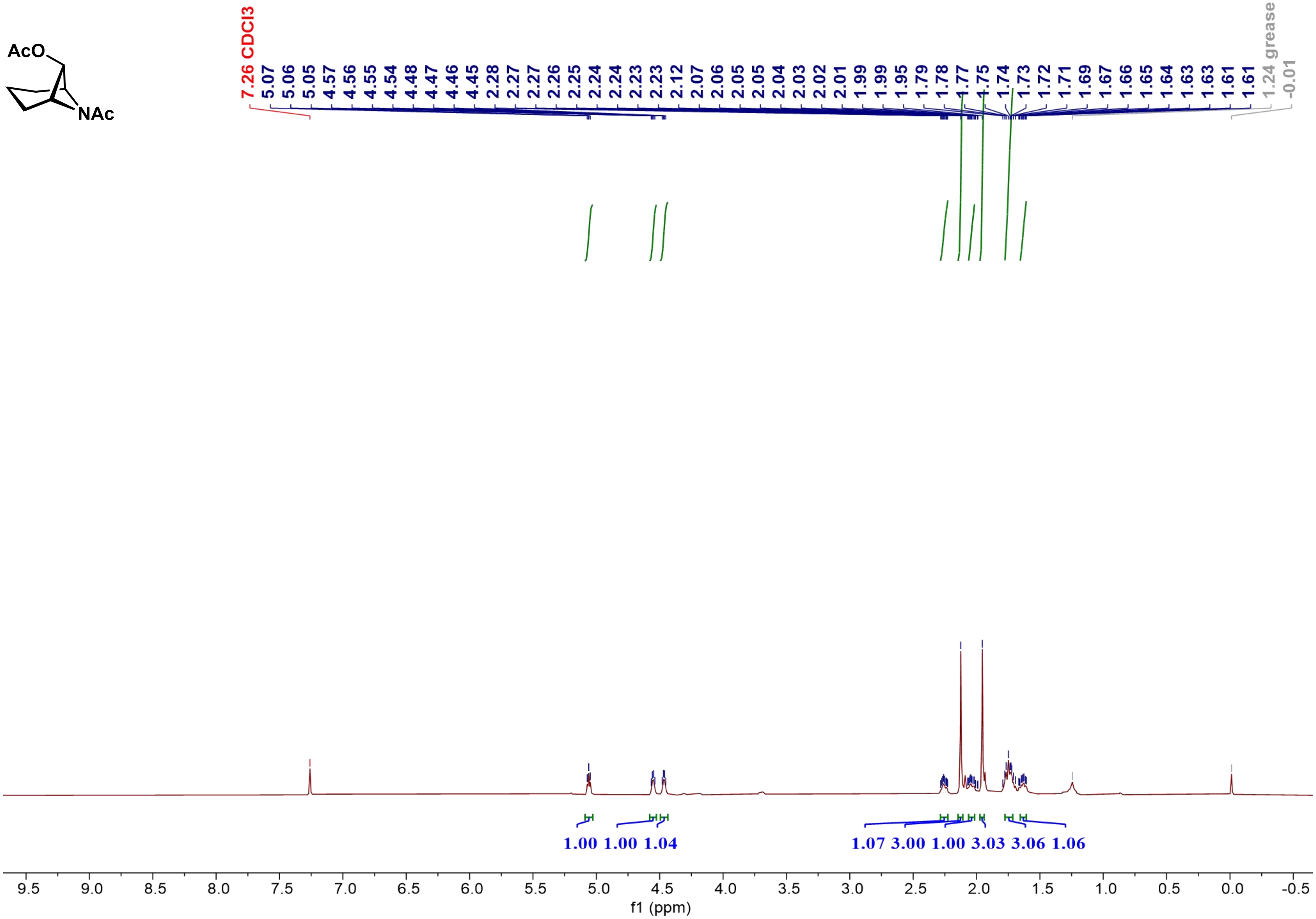
^{1}H NMR Spectrum of compound SI-77 (500 MHz, $CDCl_3$)



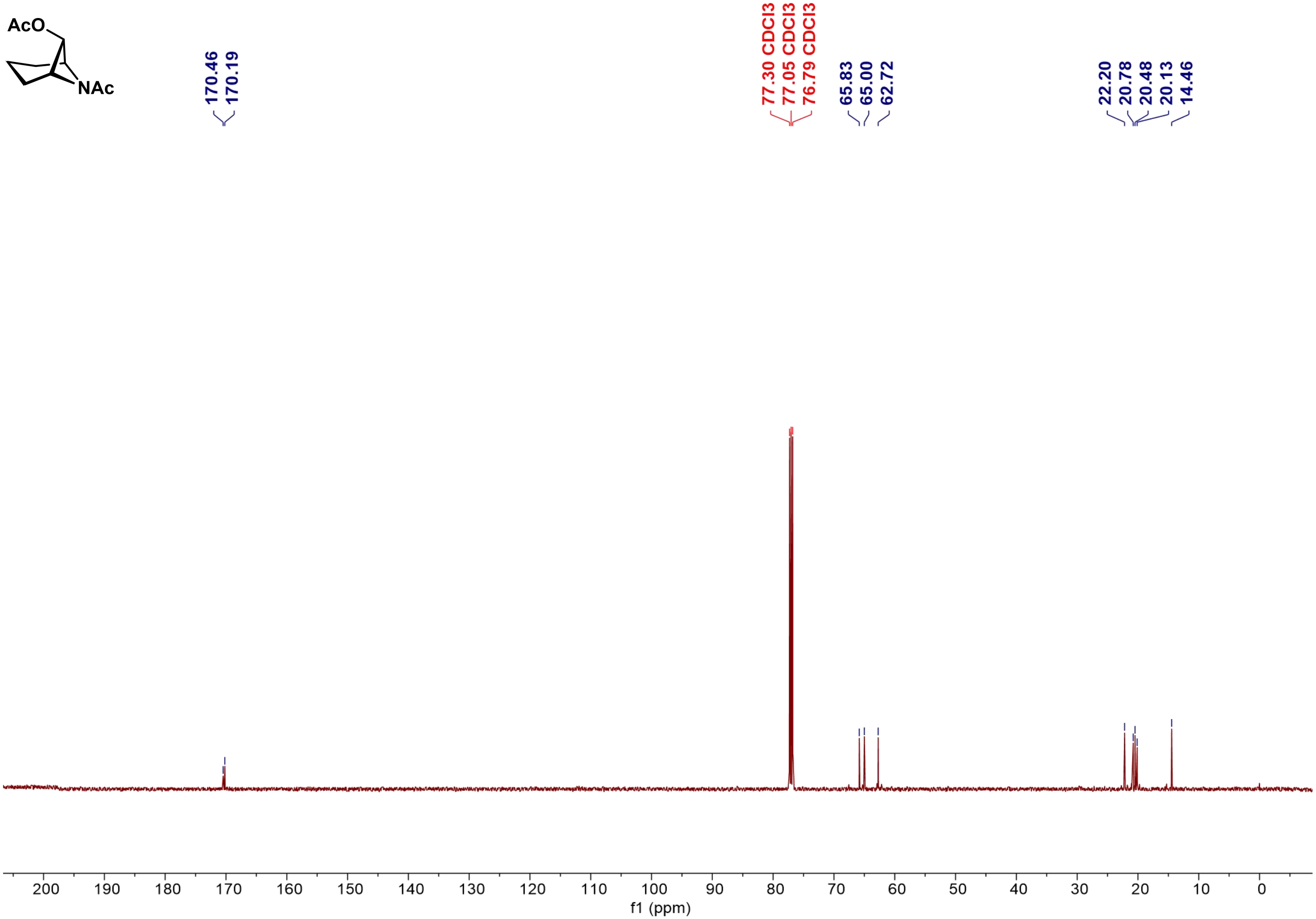
^{13}C NMR Spectrum of compound SI-77 (126 MHz, $CDCl_3$)



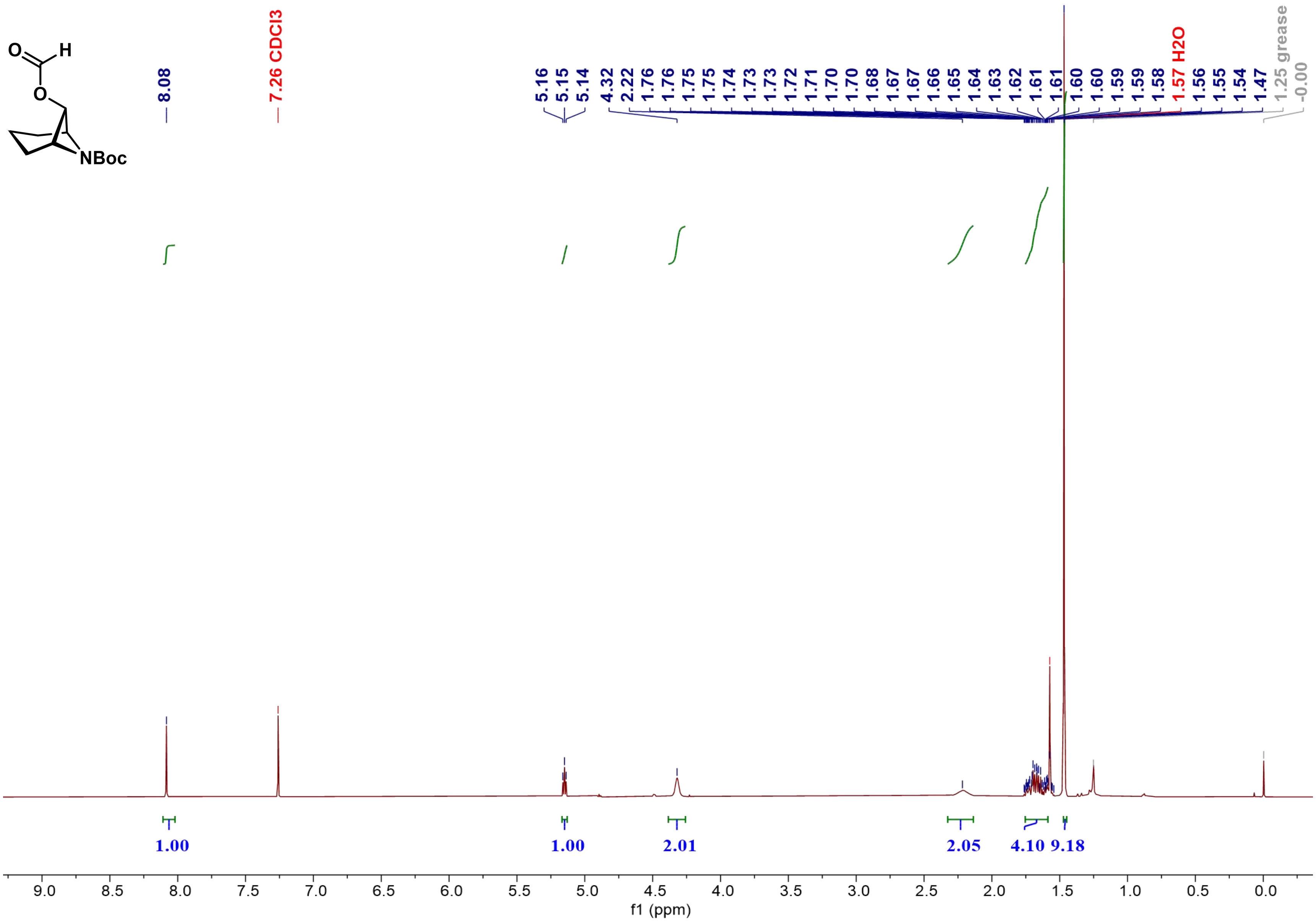
^{1}H NMR Spectrum of compound SI-78 (500 MHz, CDCl$_3$)



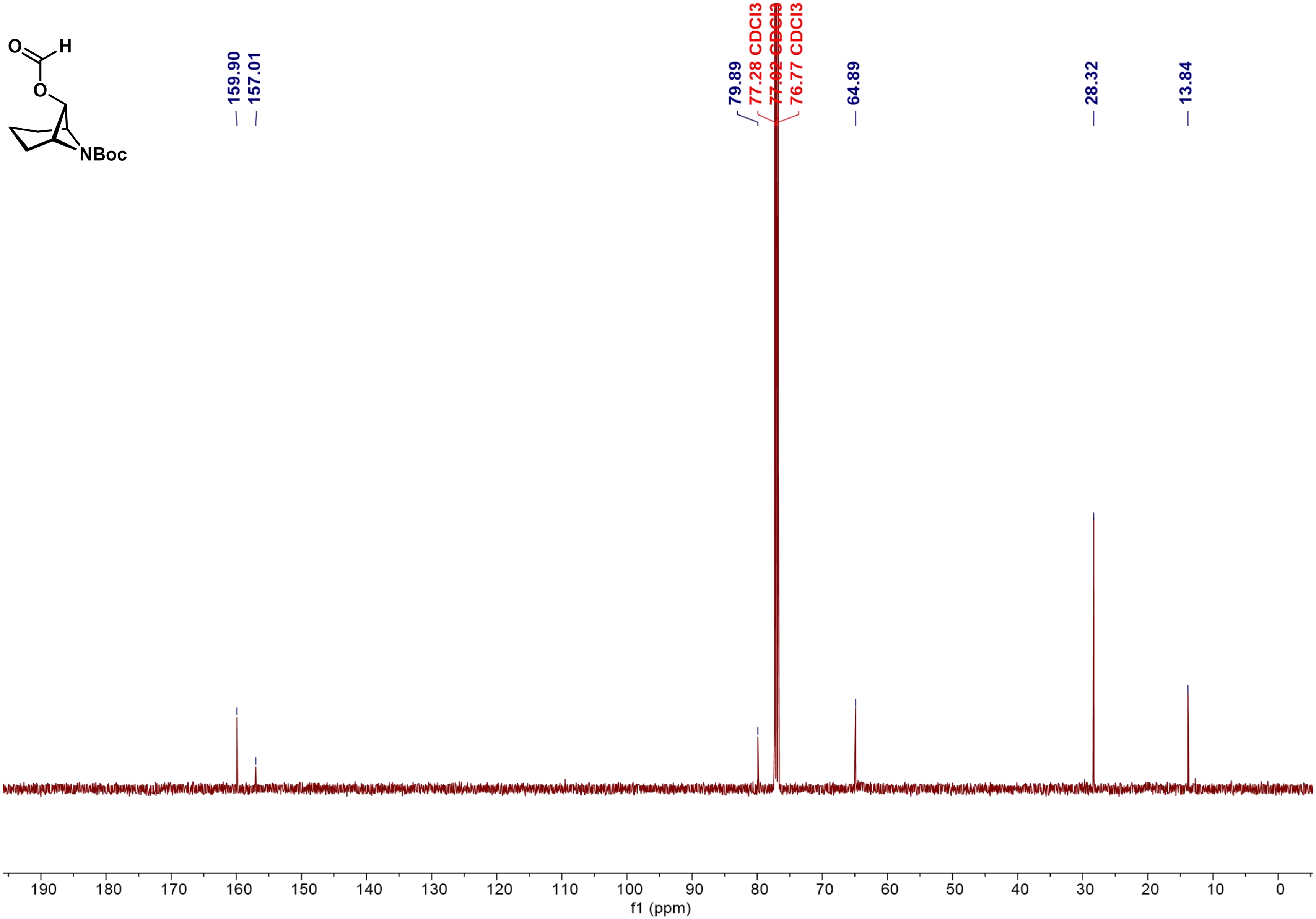
^{13}C NMR Spectrum of compound SI-78 (126 MHz, $CDCl_3$)



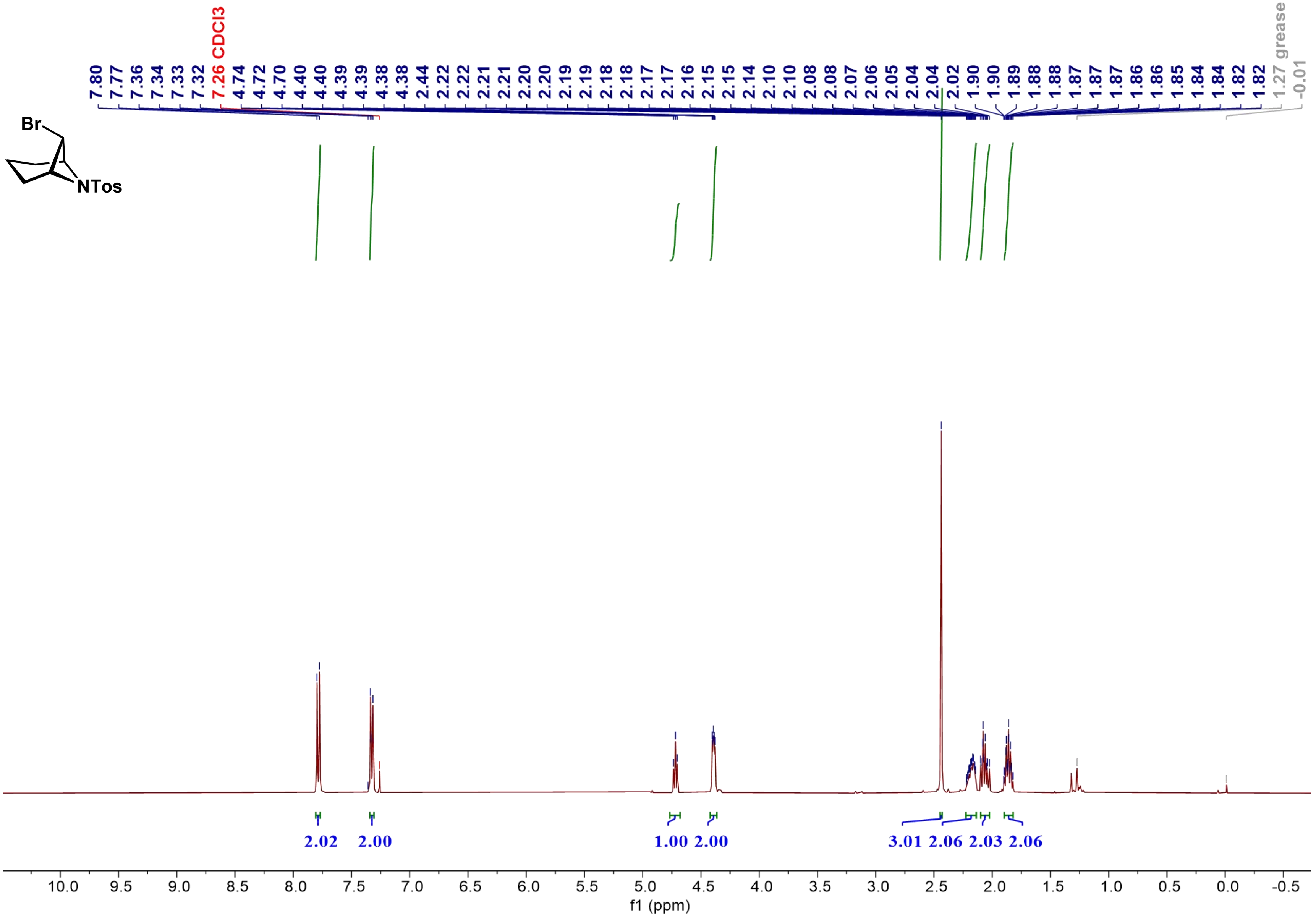
^{1}H NMR Spectrum of compound SI-79 (500 MHz, $CDCl_3$)



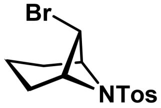
^{13}C NMR Spectrum of compound SI-79 (126 MHz, CDCl$_3$)

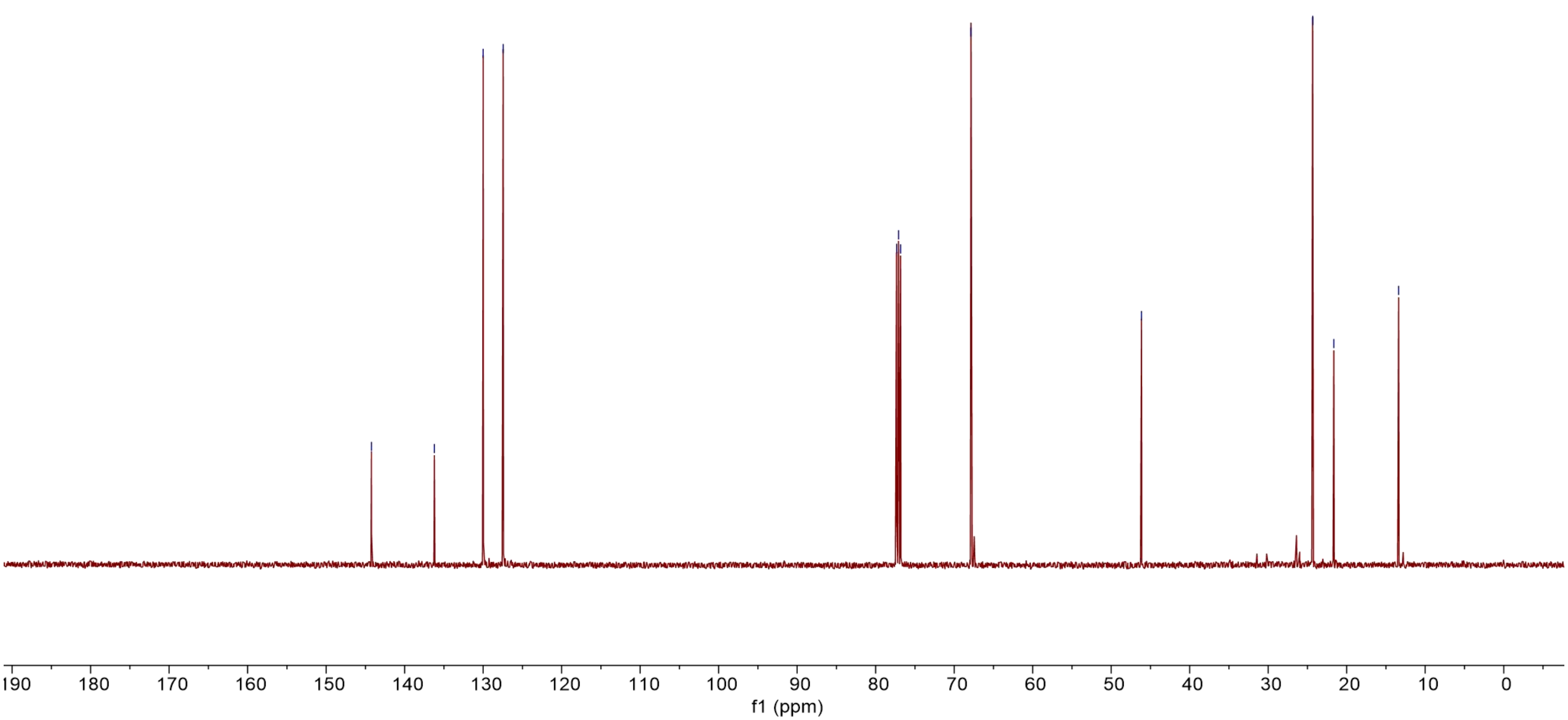


^{1}H NMR Spectrum of compound SI-80 (400 MHz, $CDCl_3$)

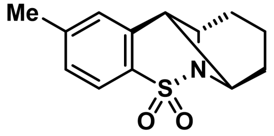


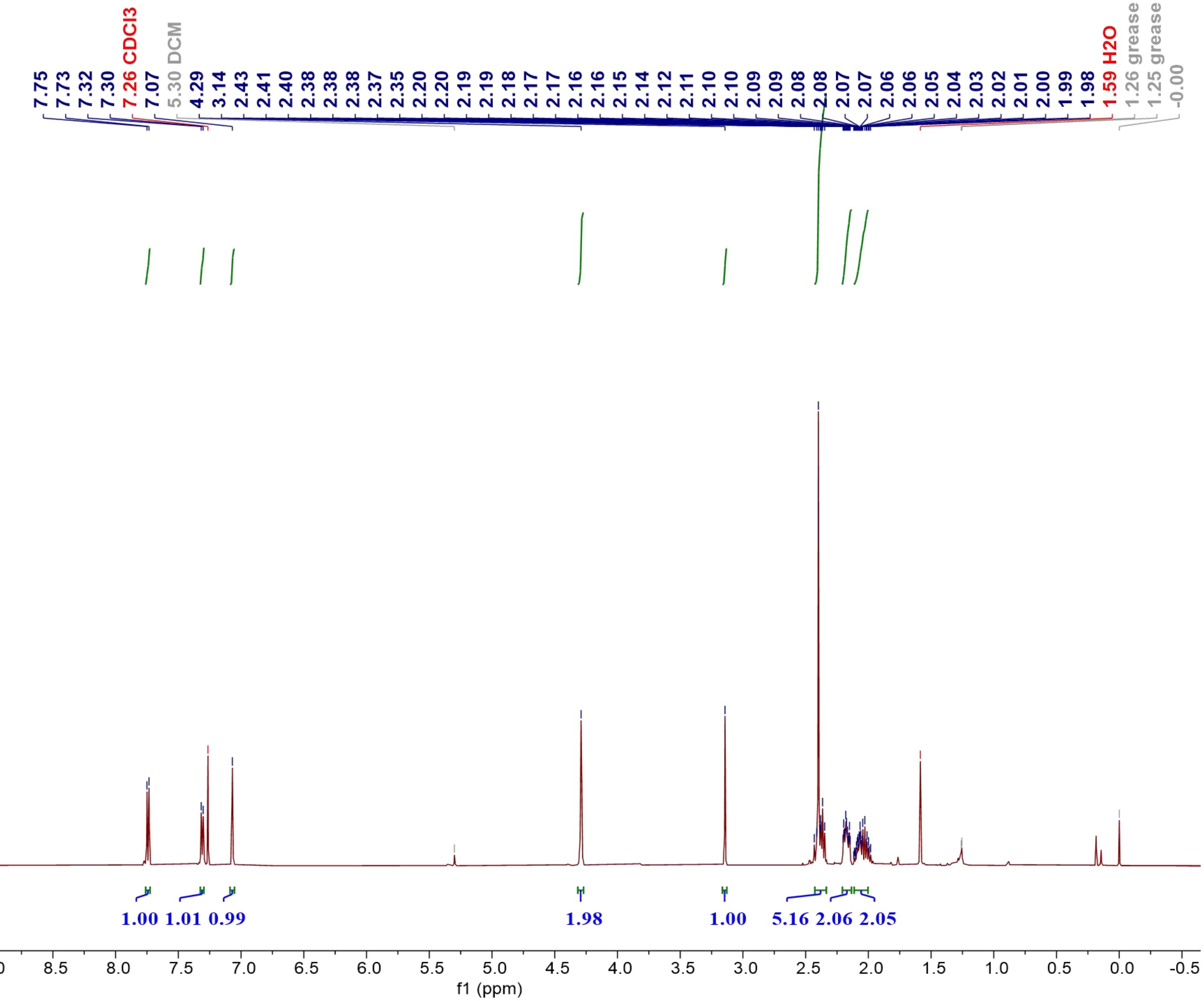
^{13}C NMR Spectrum of compound SI-80 (101 MHz, CDCl$_3$)



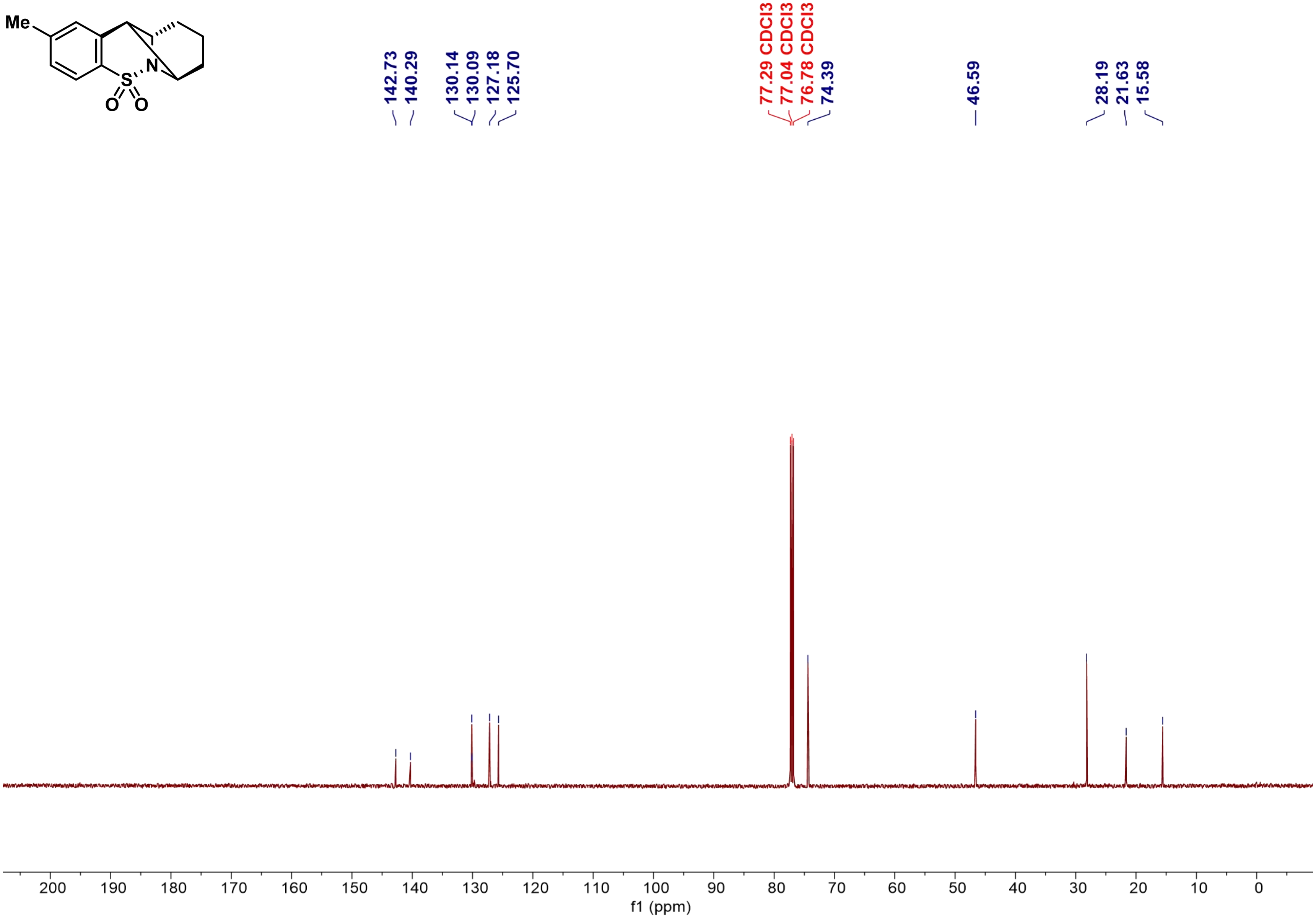


^{1}H NMR Spectrum of compound SI-81 (500 MHz, CDCl$_3$)

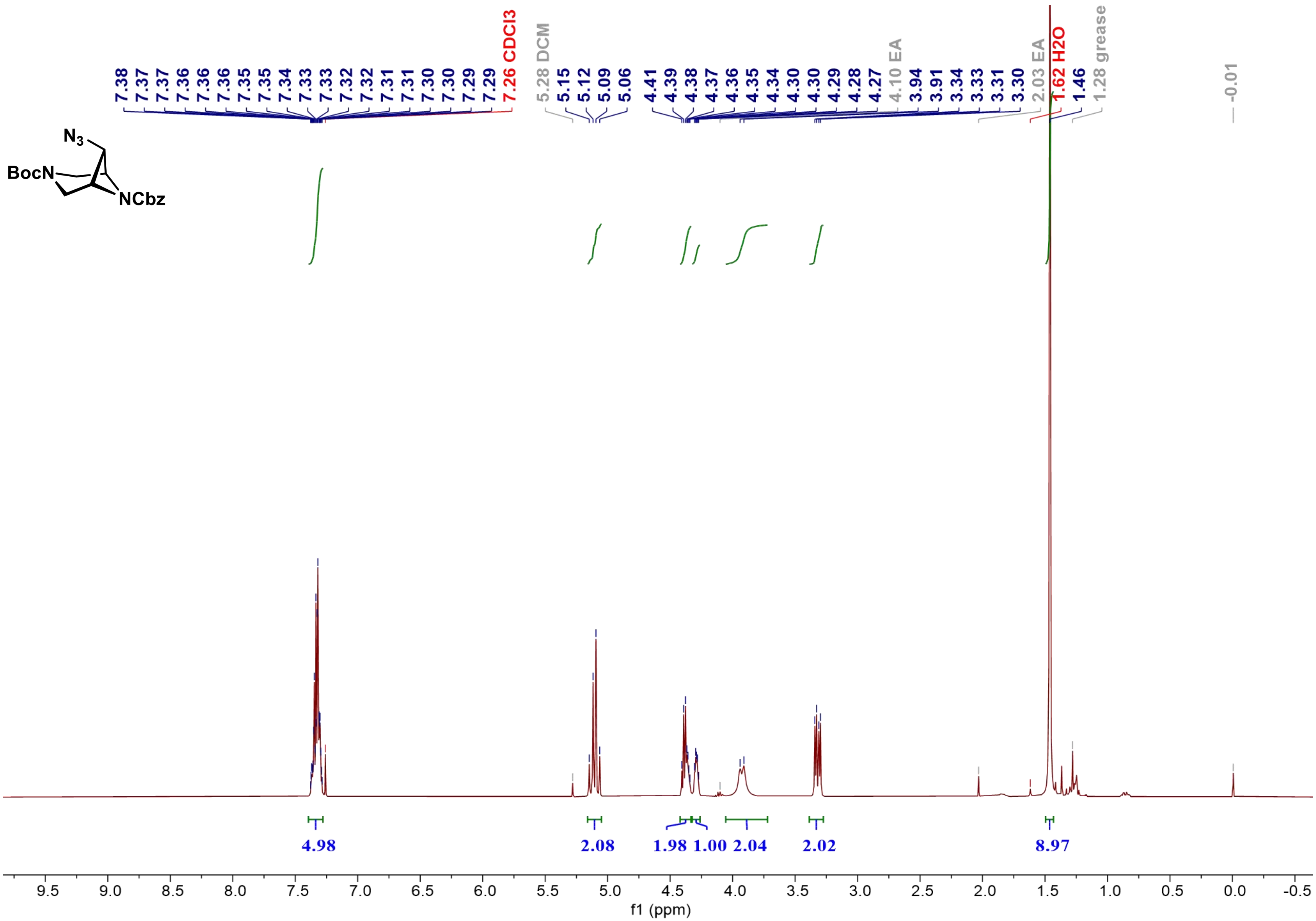




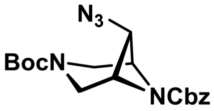
^{13}C NMR Spectrum of compound SI-81 (126 MHz, $CDCl_3$)

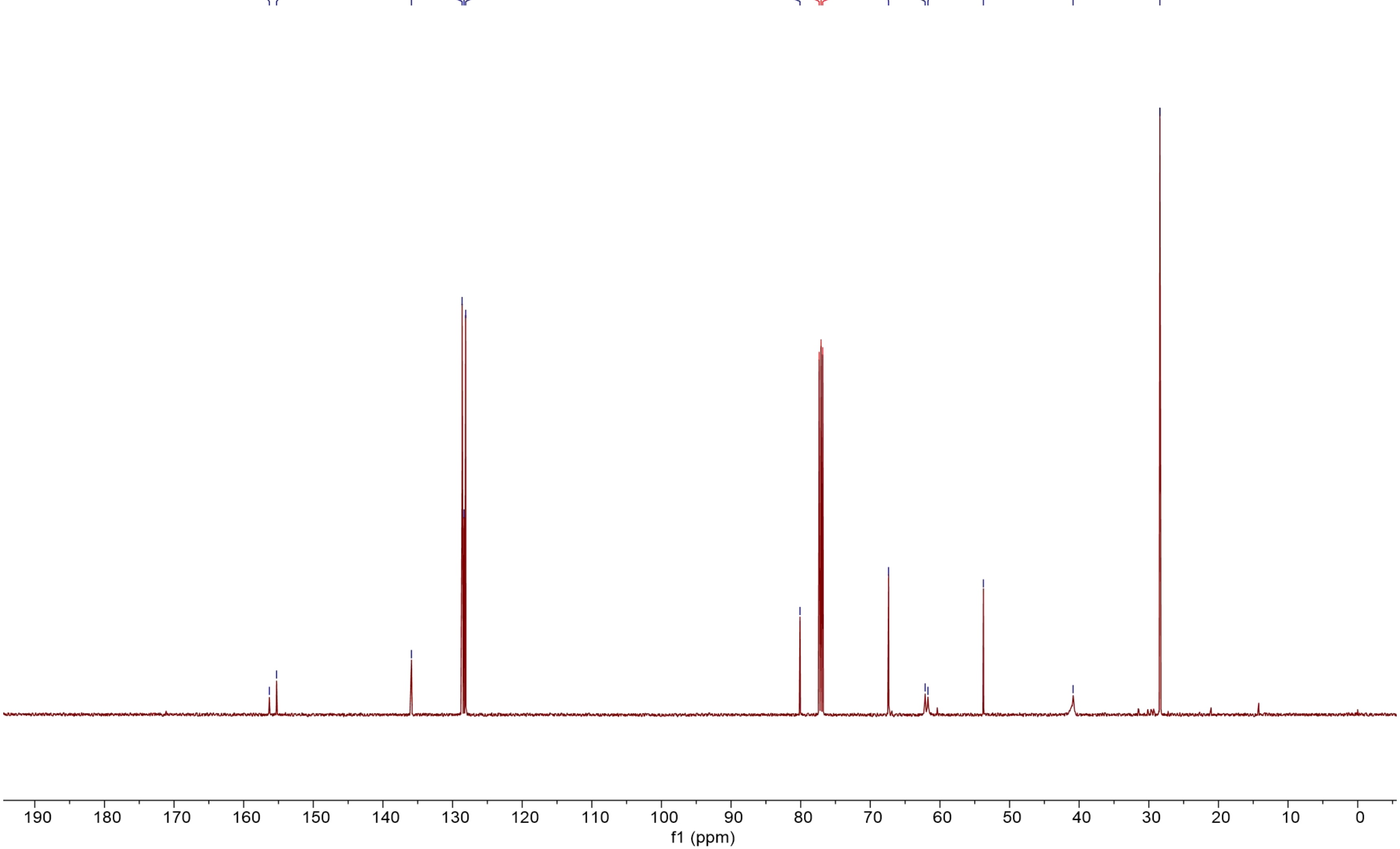


^{1}H NMR Spectrum of compound SI-82 (400 MHz, $CDCl_3$)

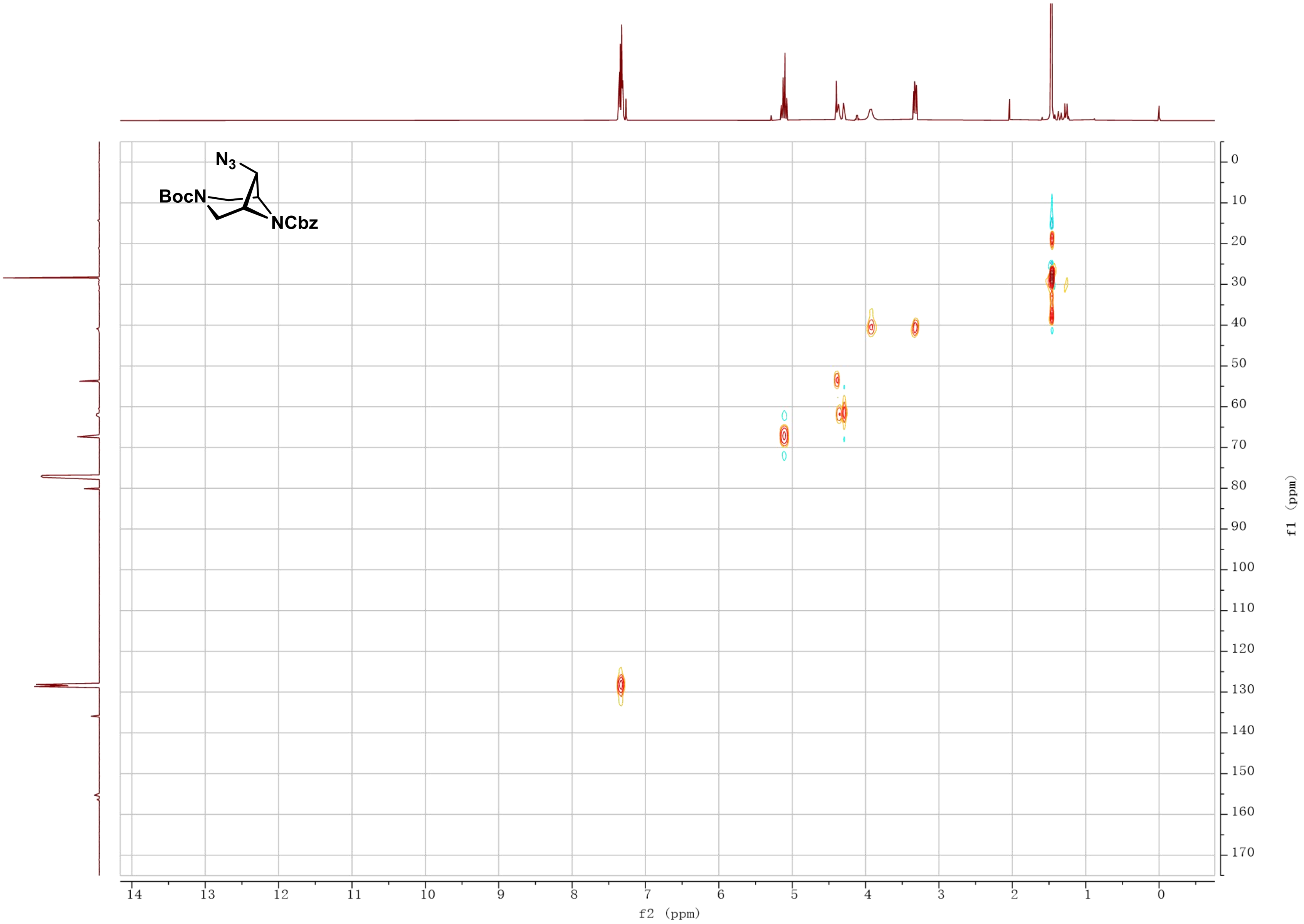


^{13}C NMR Spectrum of compound SI-82 (101 MHz, CDCl$_3$)

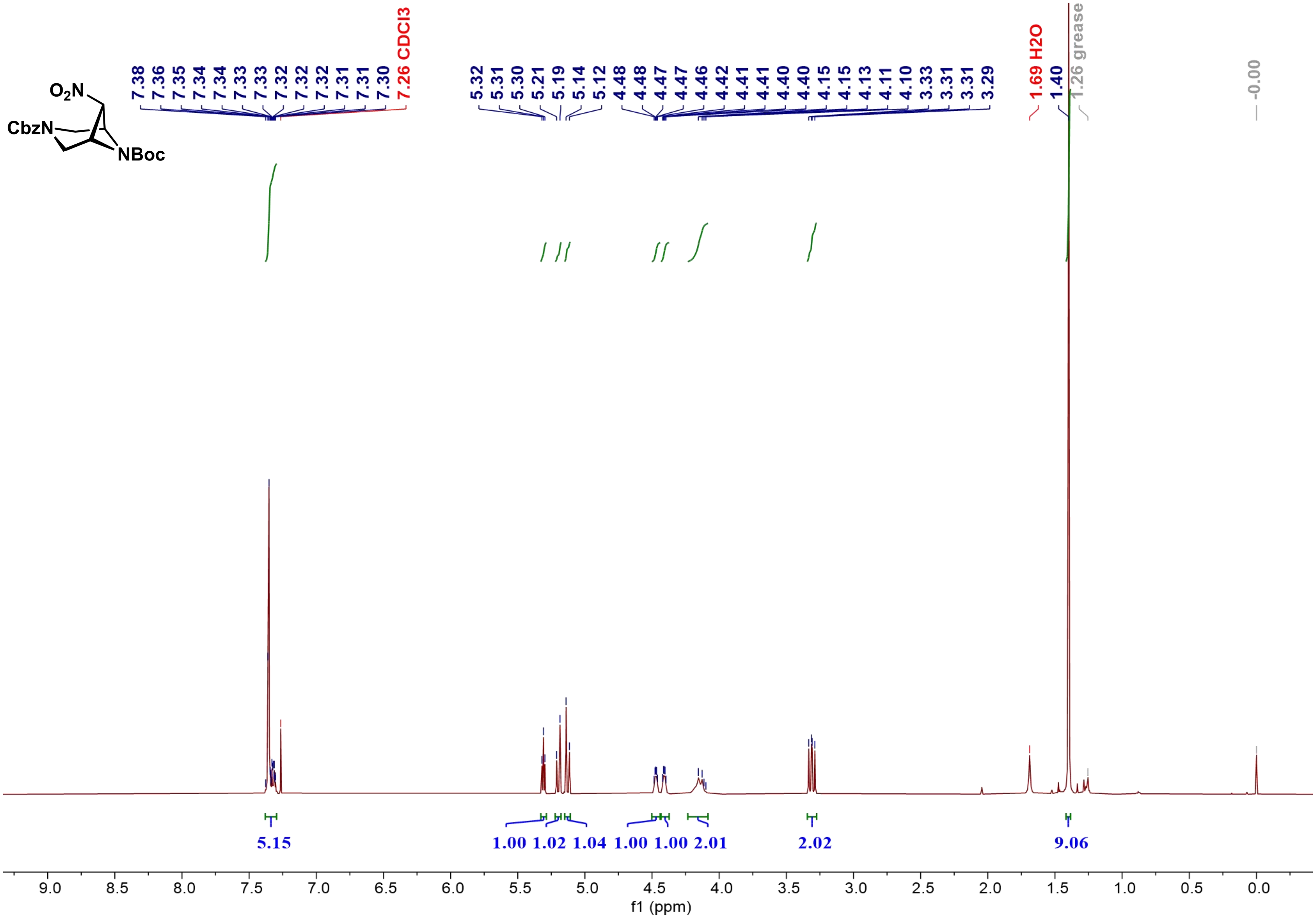




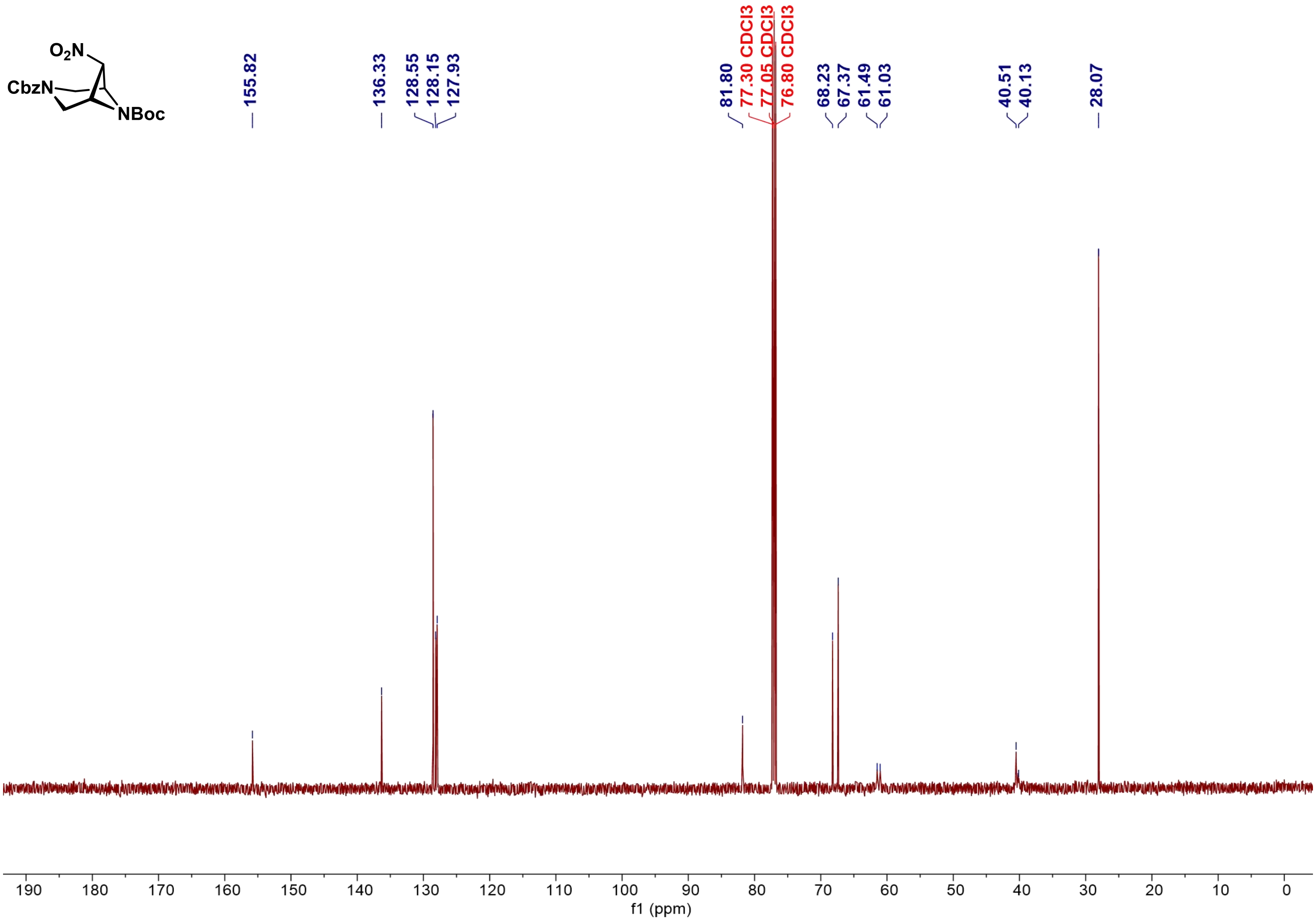
HSQC Spectrum of compound SI-82



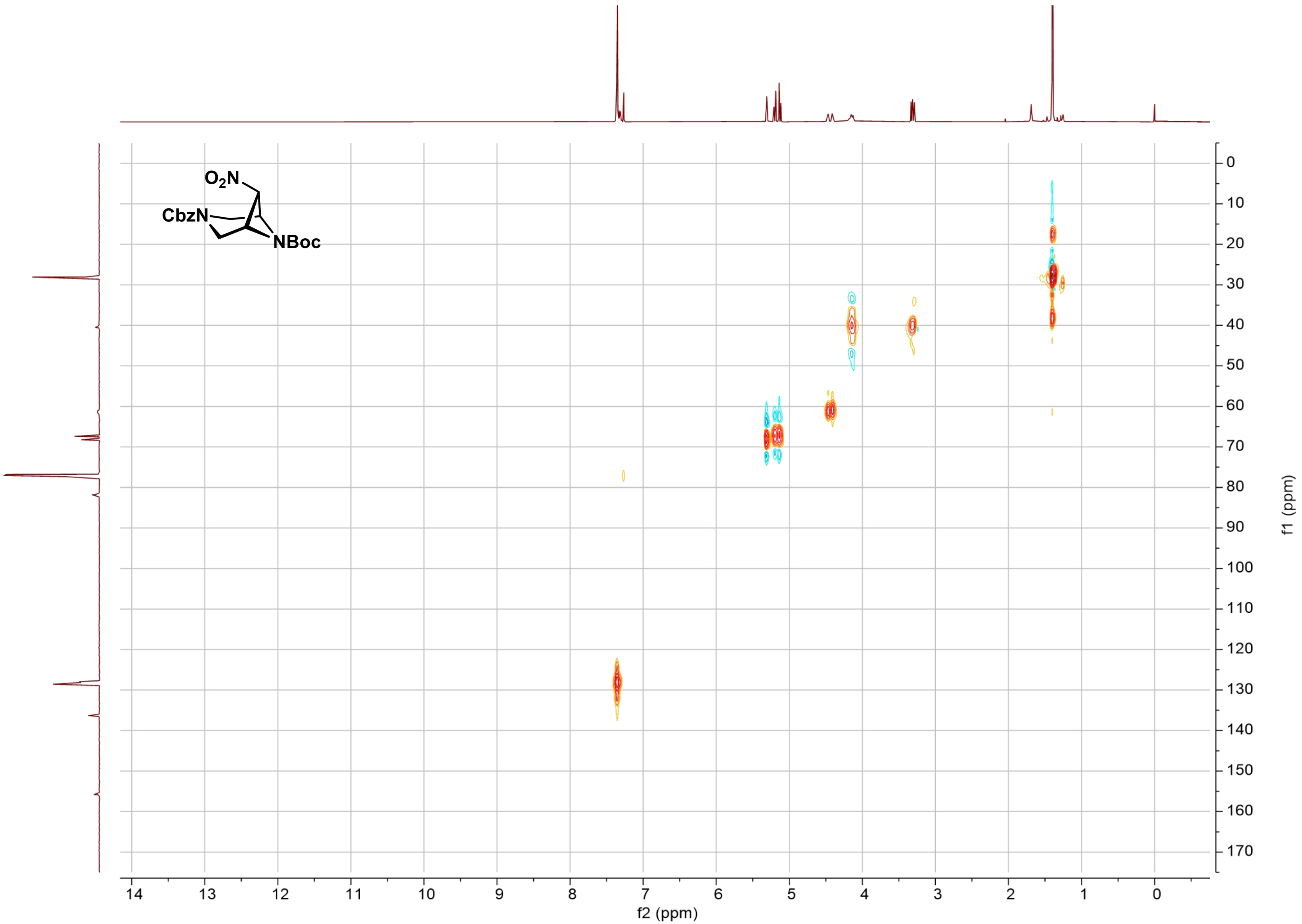
^{1}H NMR Spectrum of compound SI-83 (500 MHz, $CDCl_3$)



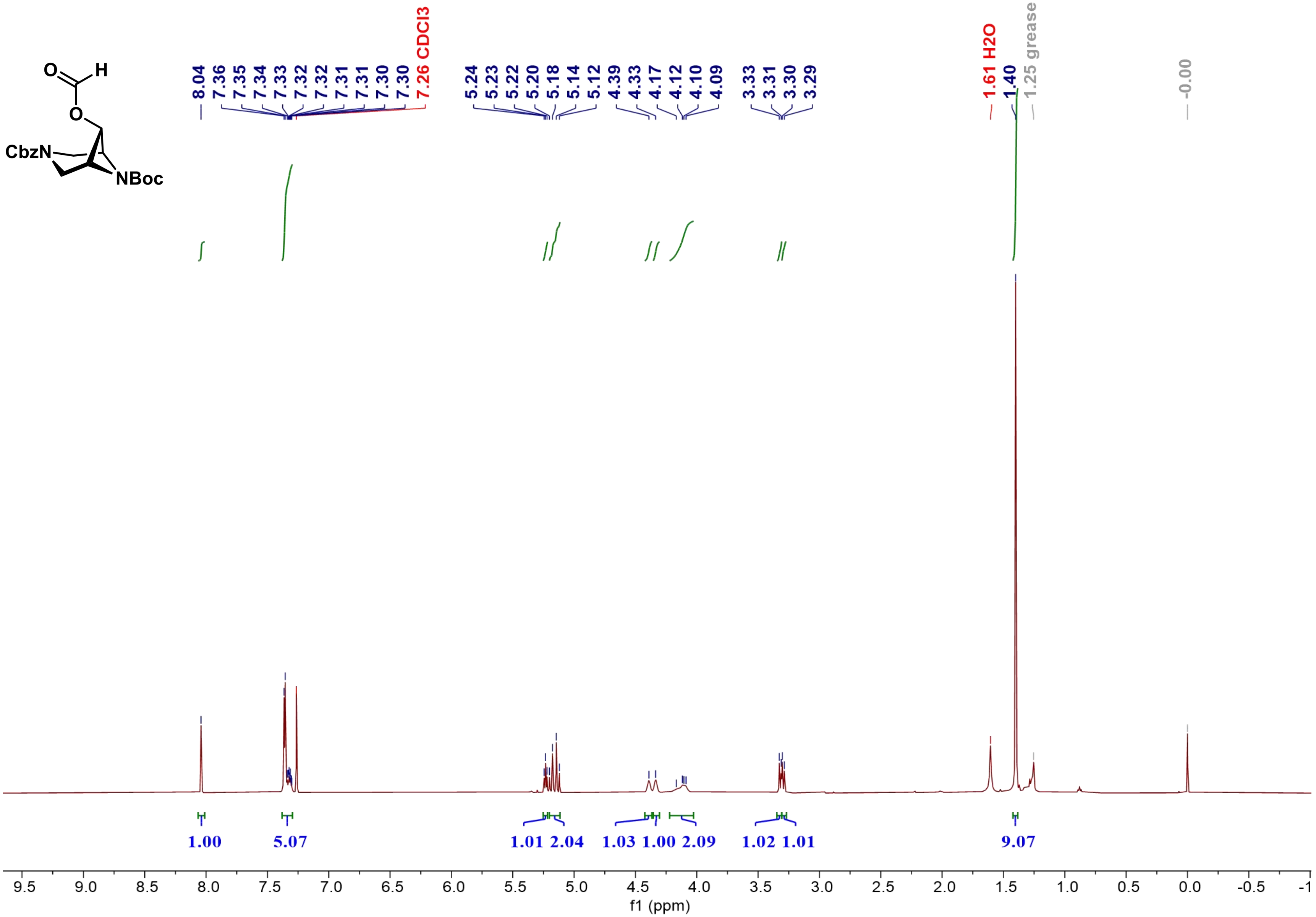
^{13}C NMR Spectrum of compound SI-83 (126 MHz, $CDCl_3$)



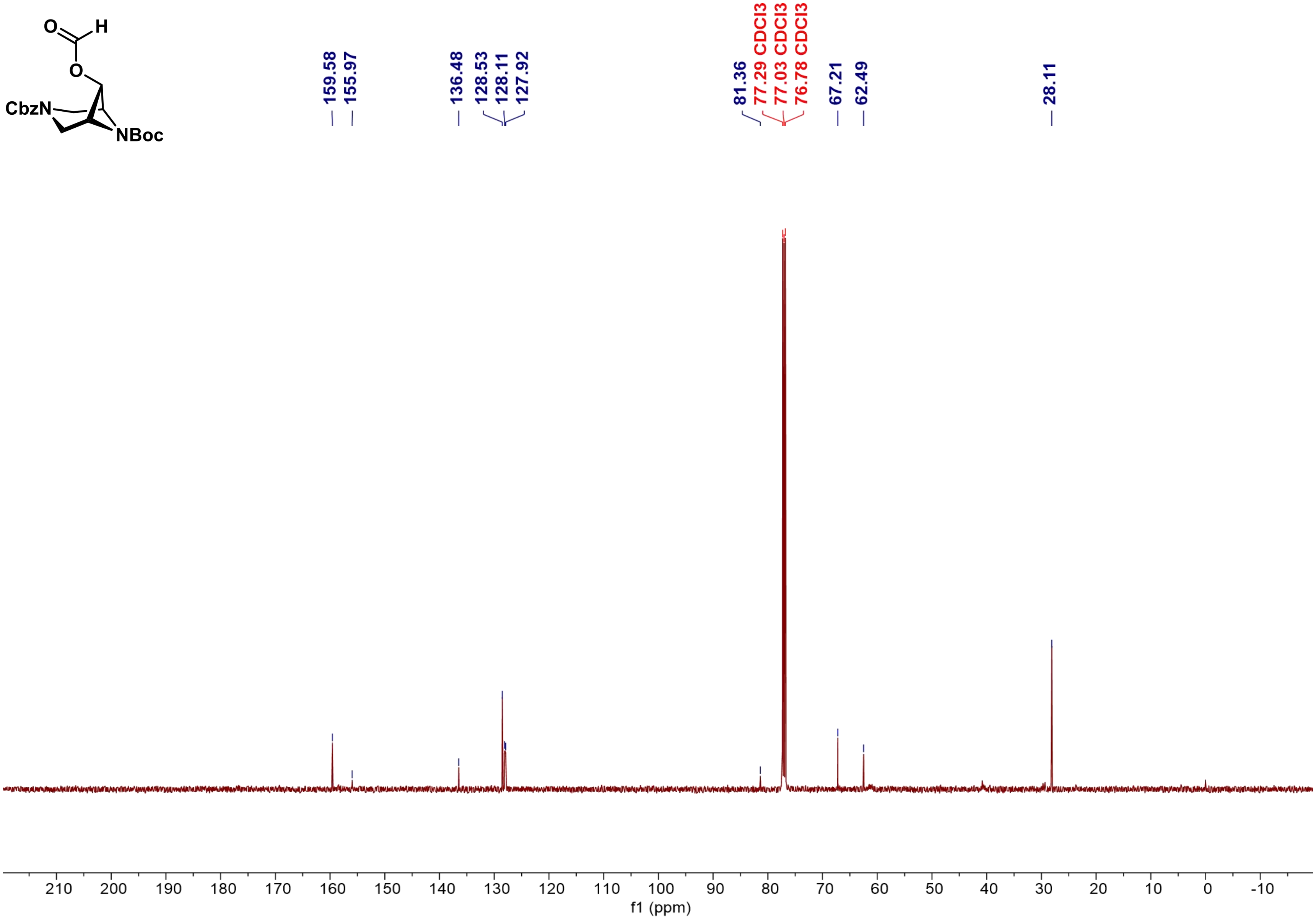
HSQC Spectrum of compound SI-83



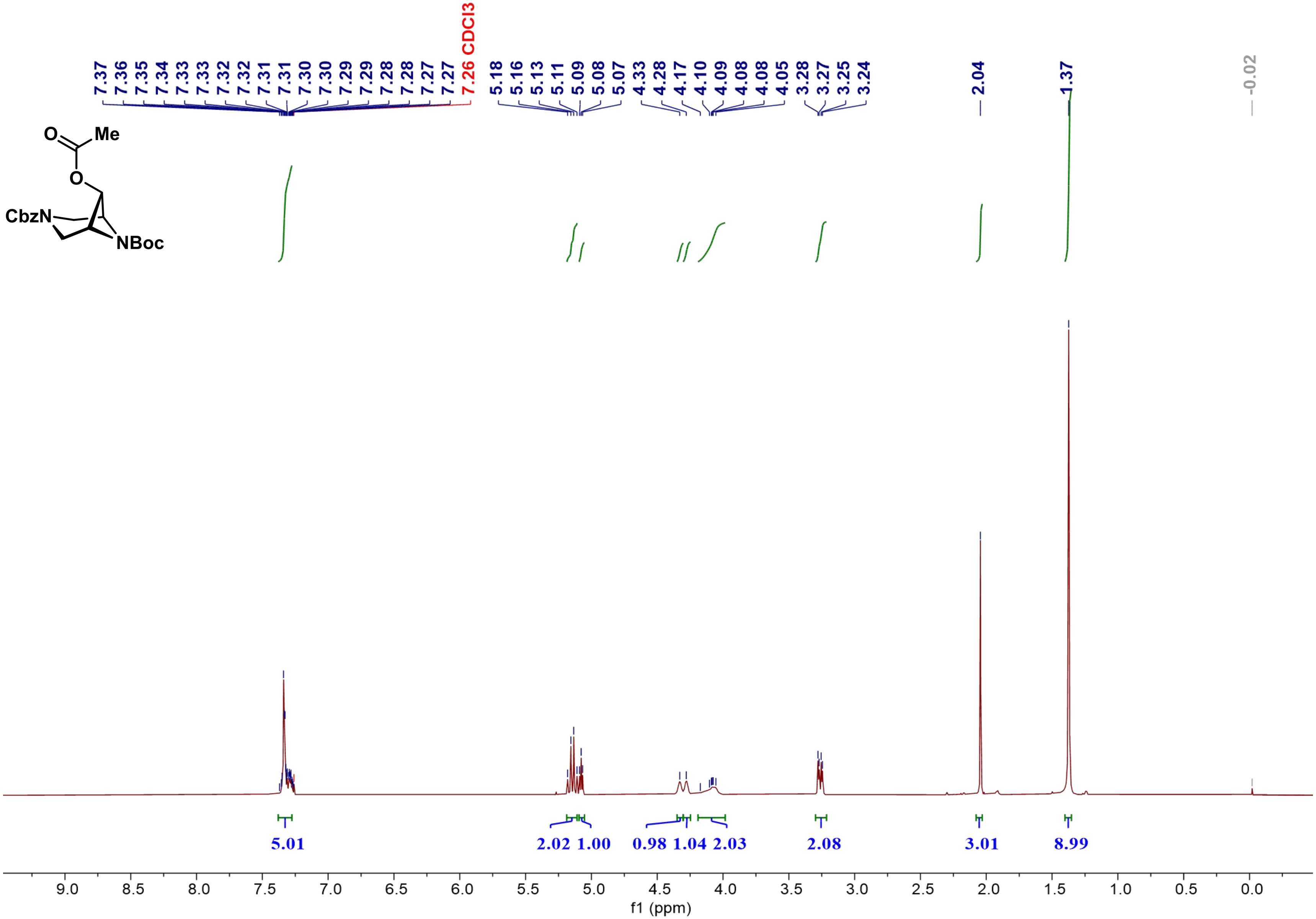
^{1}H NMR Spectrum of compound SI-84 (500 MHz, $CDCl_3$)



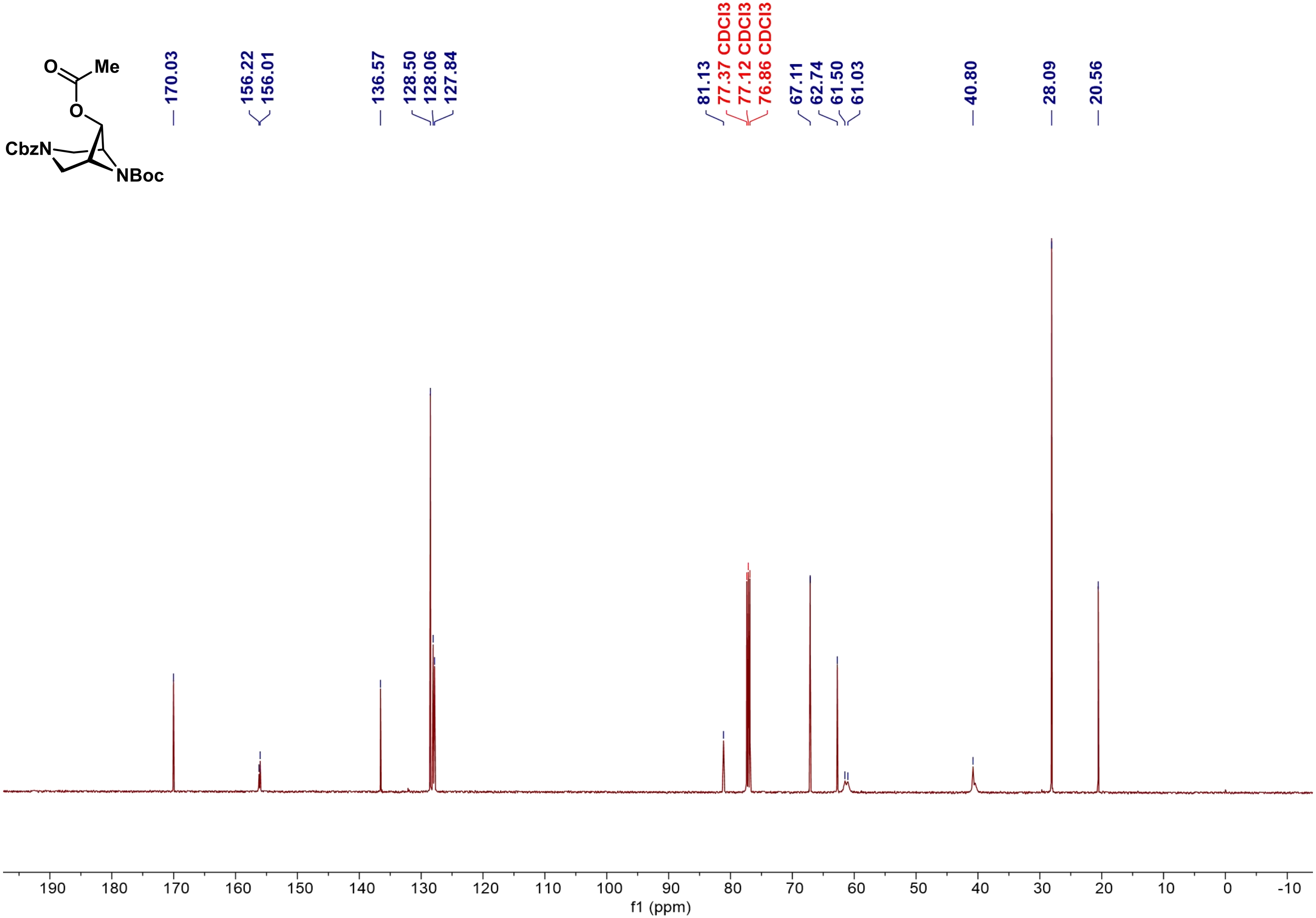
^{13}C NMR Spectrum of compound SI-84 (126 MHz, CDCl$_3$)



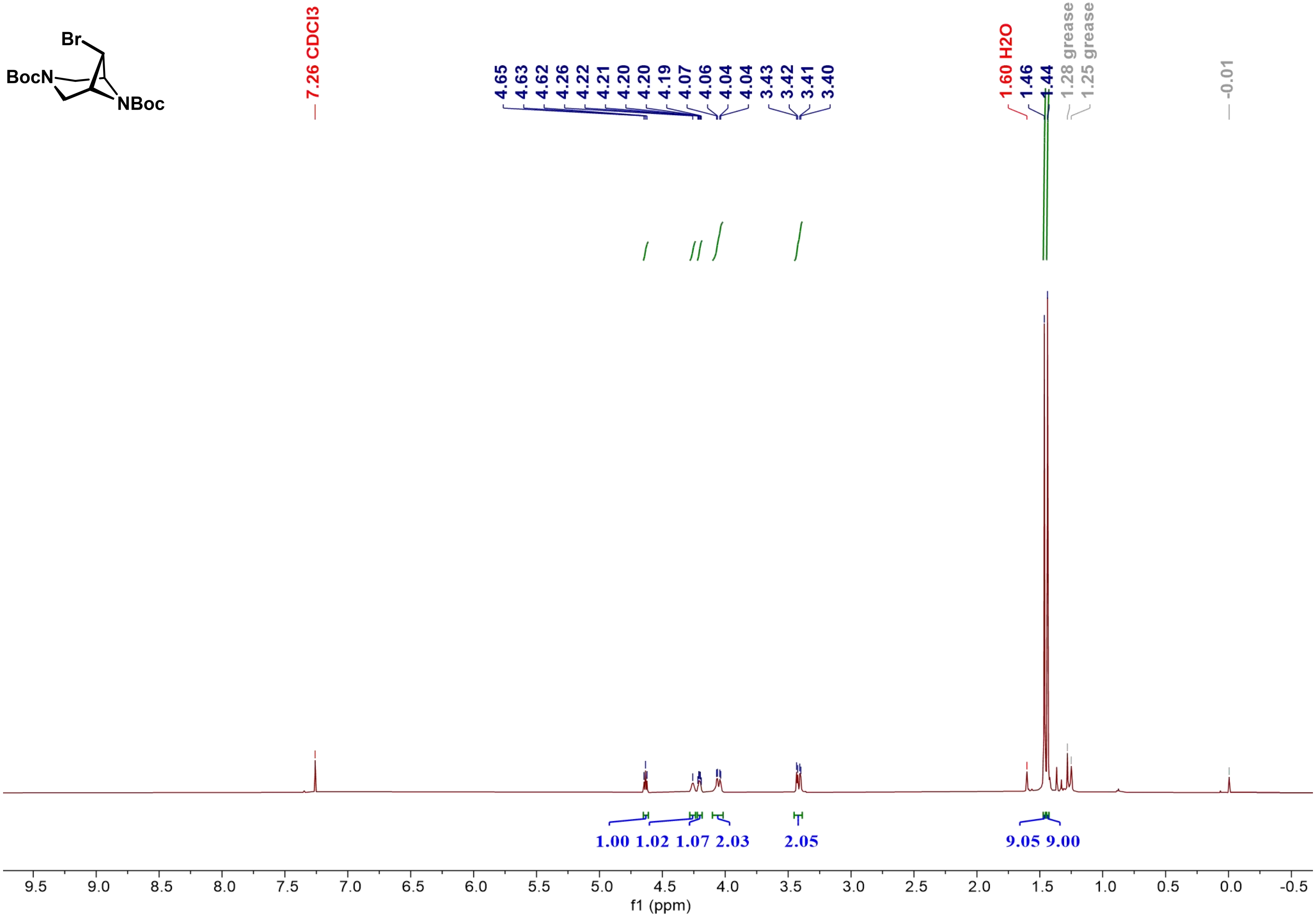
^{1}H NMR Spectrum of compound SI-85 (500 MHz, $CDCl_3$)



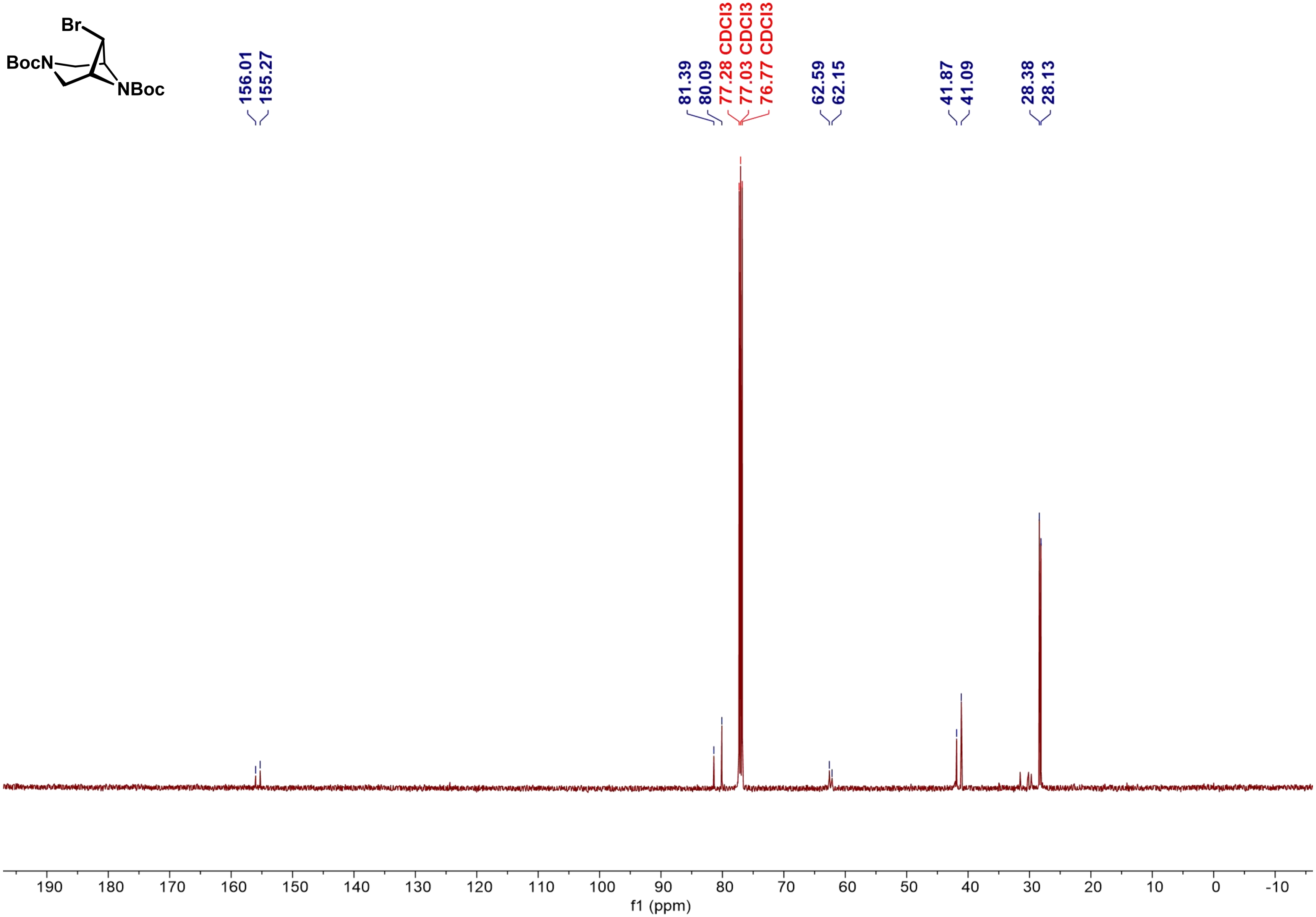
^{13}C NMR Spectrum of compound SI-85 (126 MHz, $CDCl_3$)



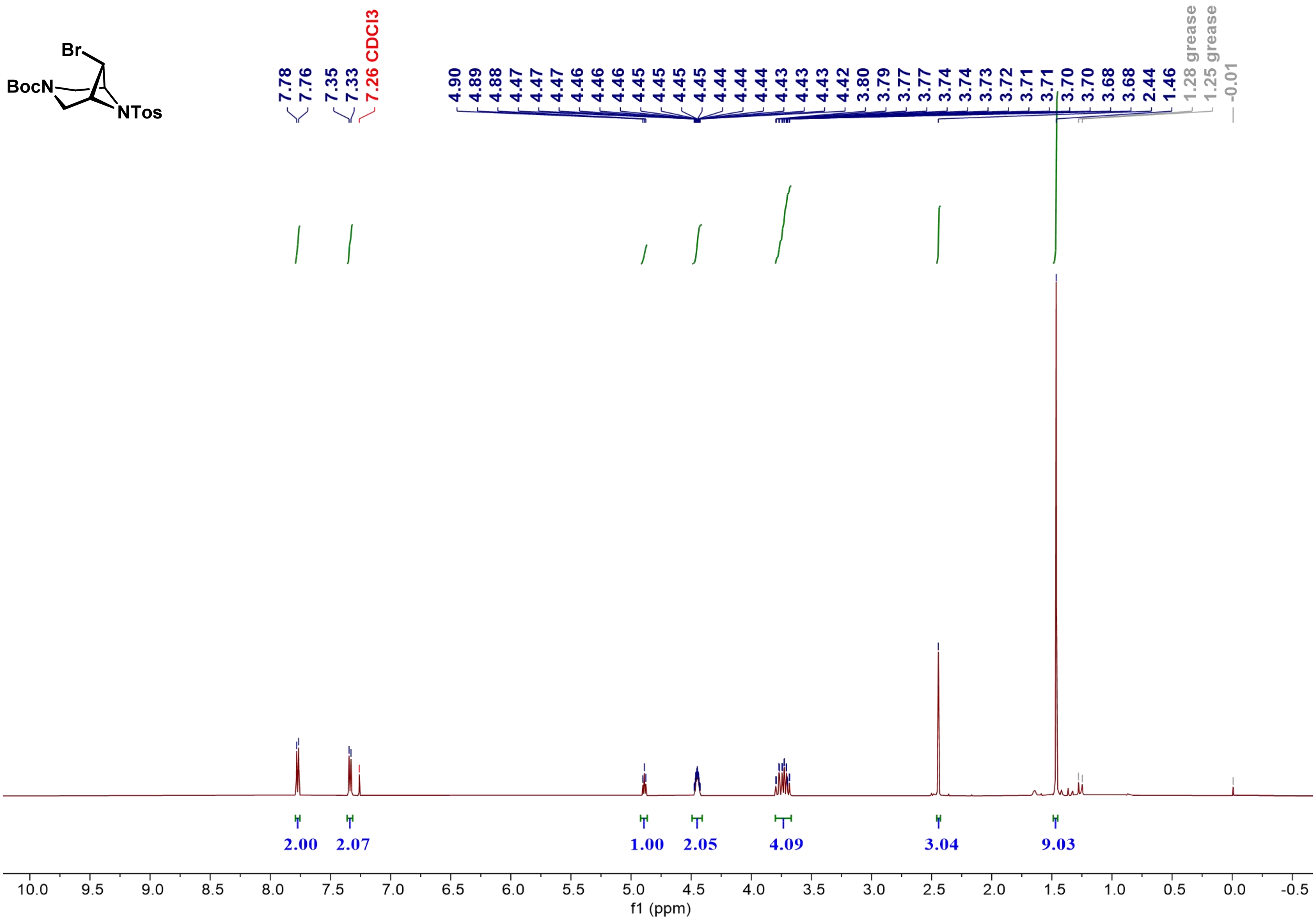
^{1}H NMR Spectrum of compound SI-86 (500 MHz, $CDCl_3$)



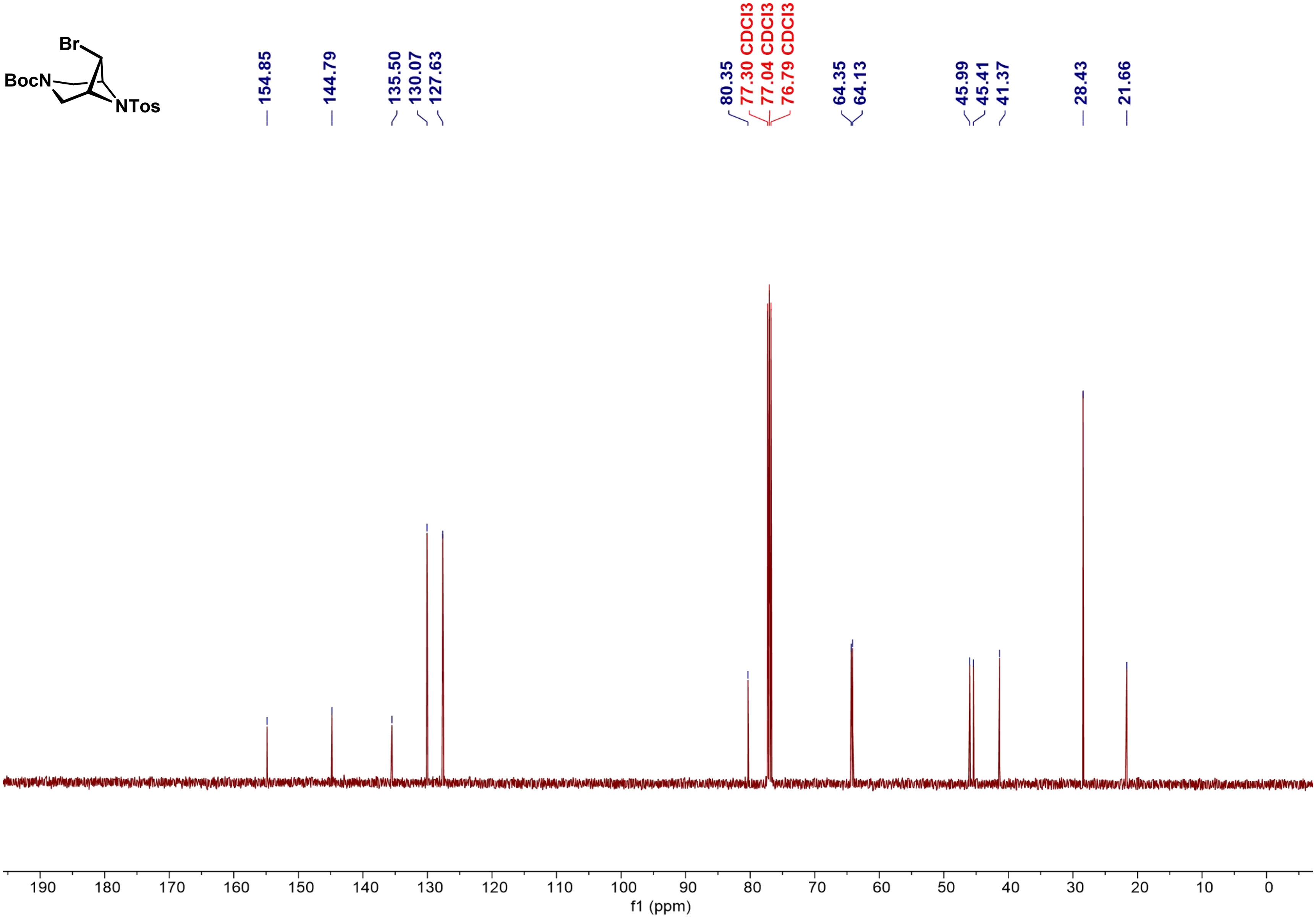
^{13}C NMR Spectrum of compound SI-86 (126 MHz, $CDCl_3$)



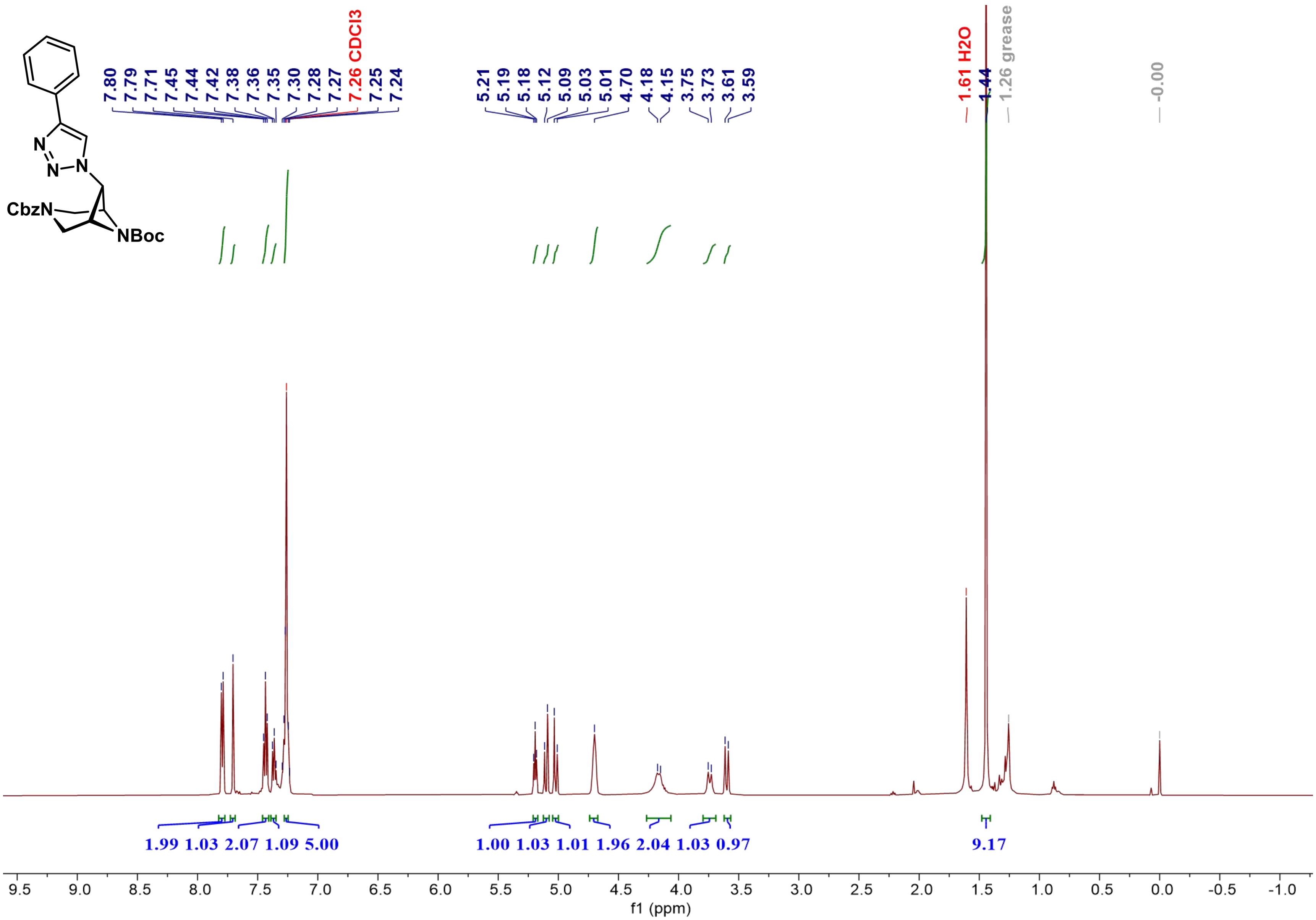
^{1}H NMR Spectrum of compound SI-87 (500 MHz, $CDCl_3$)



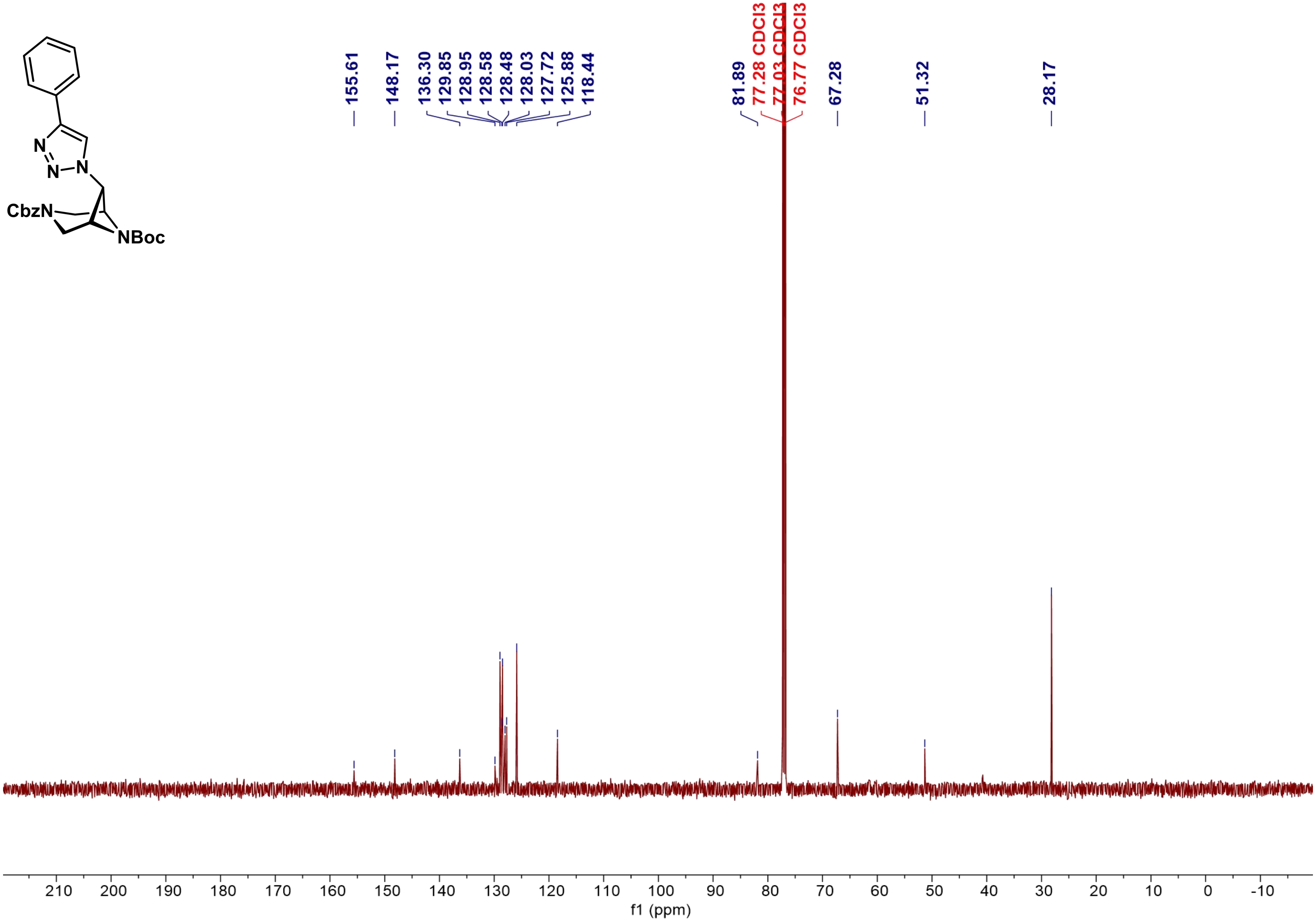
^{13}C NMR Spectrum of compound SI-87 (126 MHz, CDCl$_3$)



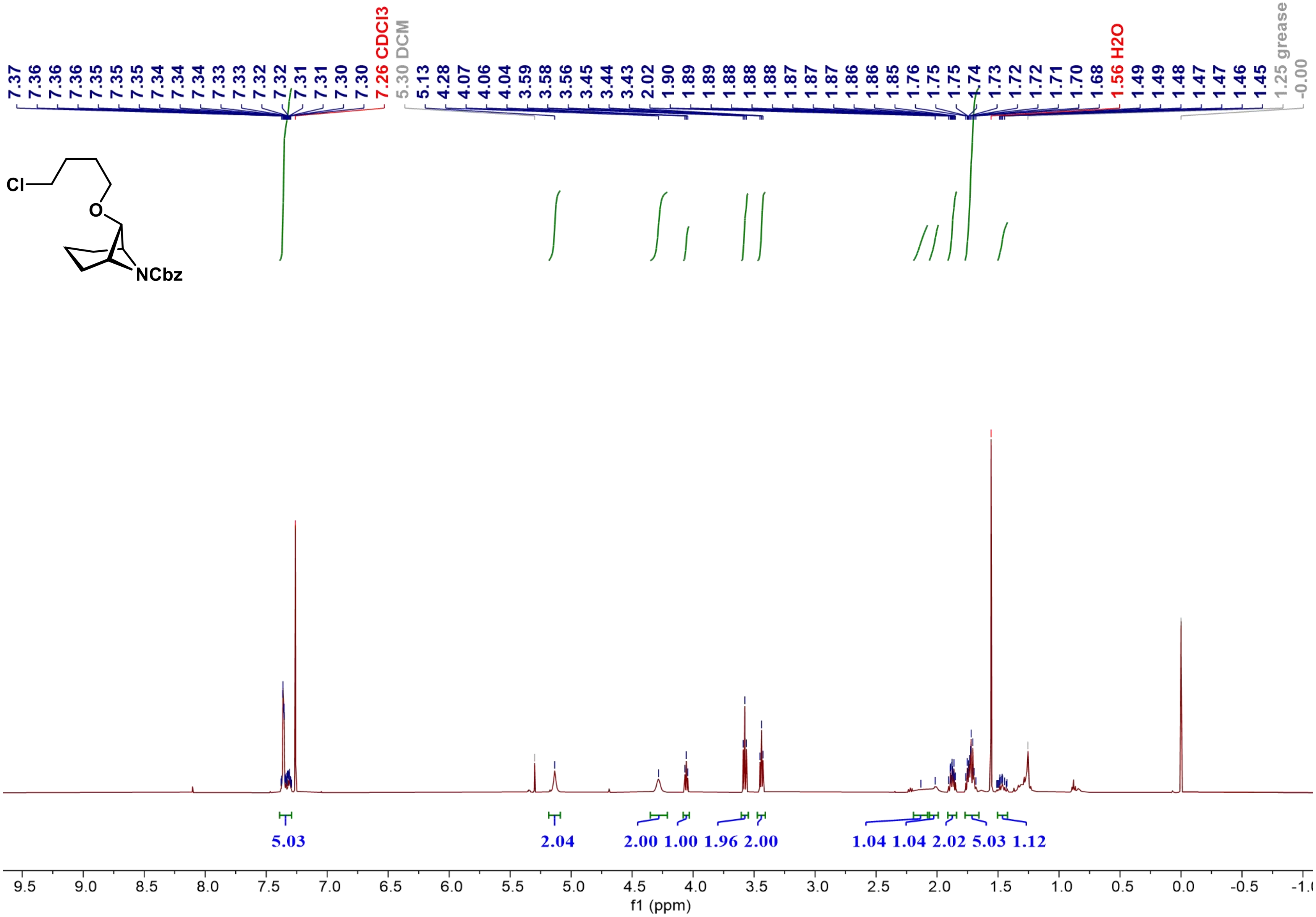
^{1}H NMR Spectrum of compound SI-88 (500 MHz, $CDCl_3$)



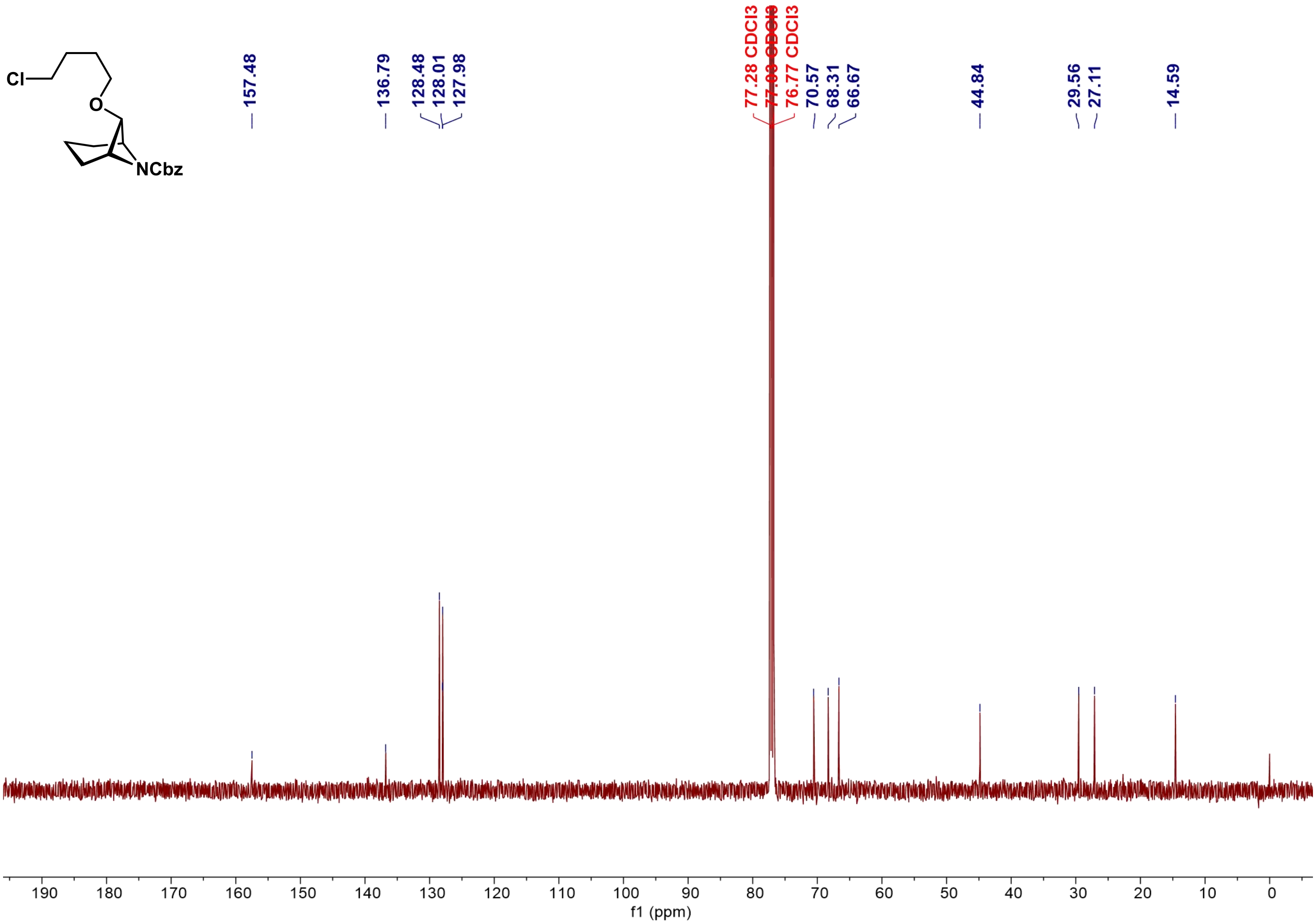
^{13}C NMR Spectrum of compound SI-88 (126 MHz, CDCl$_3$)



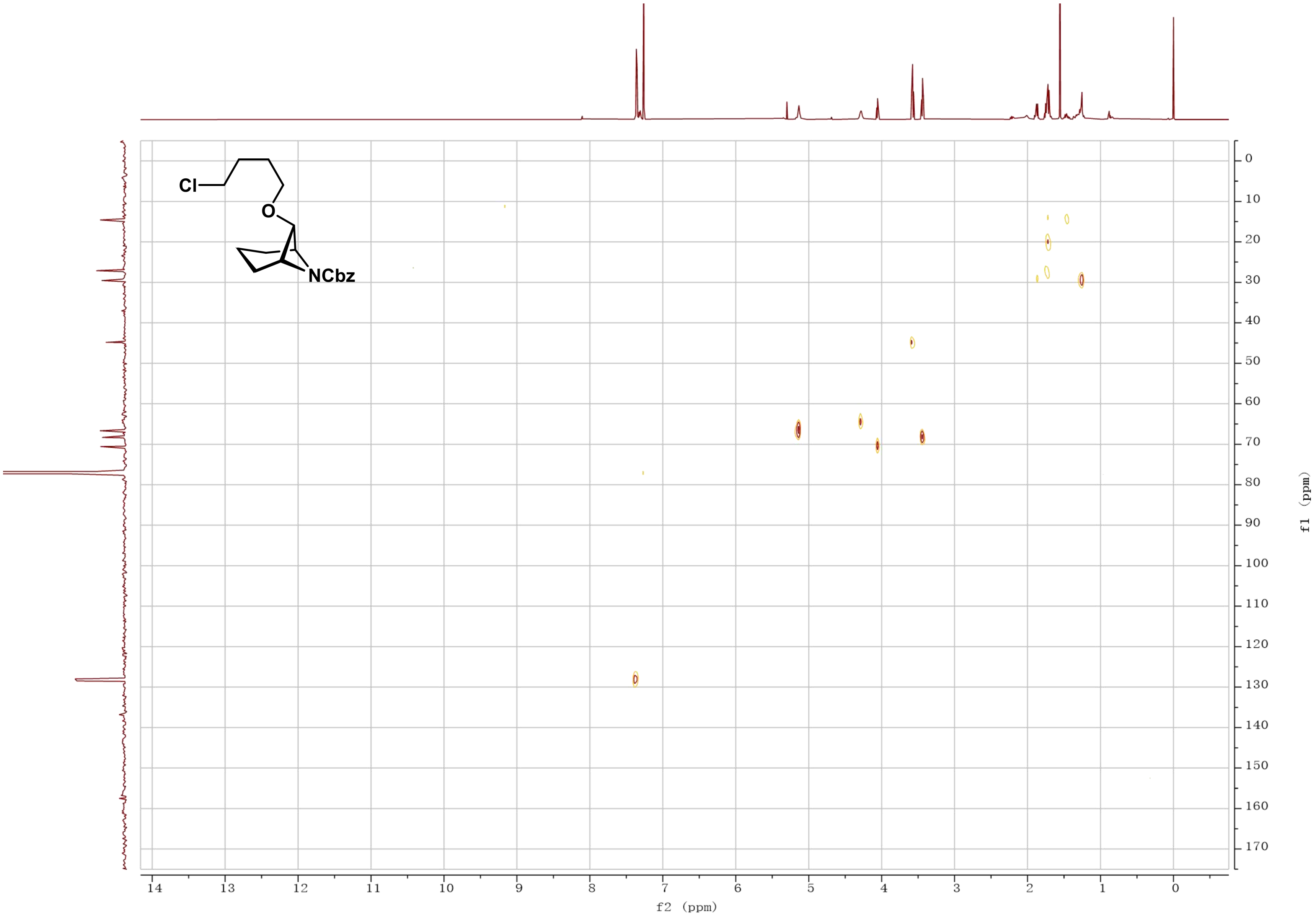
^{1}H NMR Spectrum of compound SI-89 (500 MHz, $CDCl_3$)



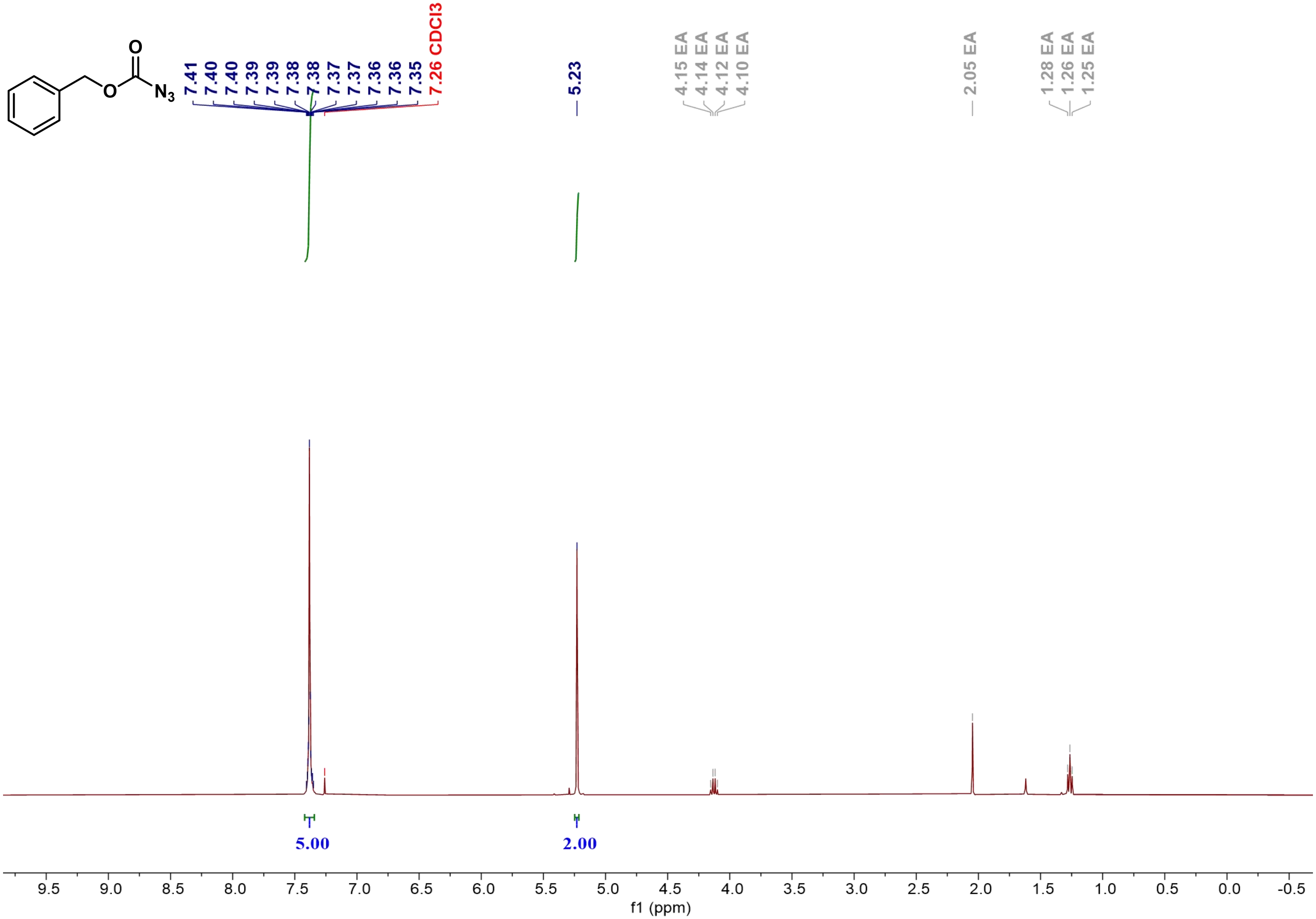
^{13}C NMR Spectrum of compound SI-89 (126 MHz, CDCl$_3$)



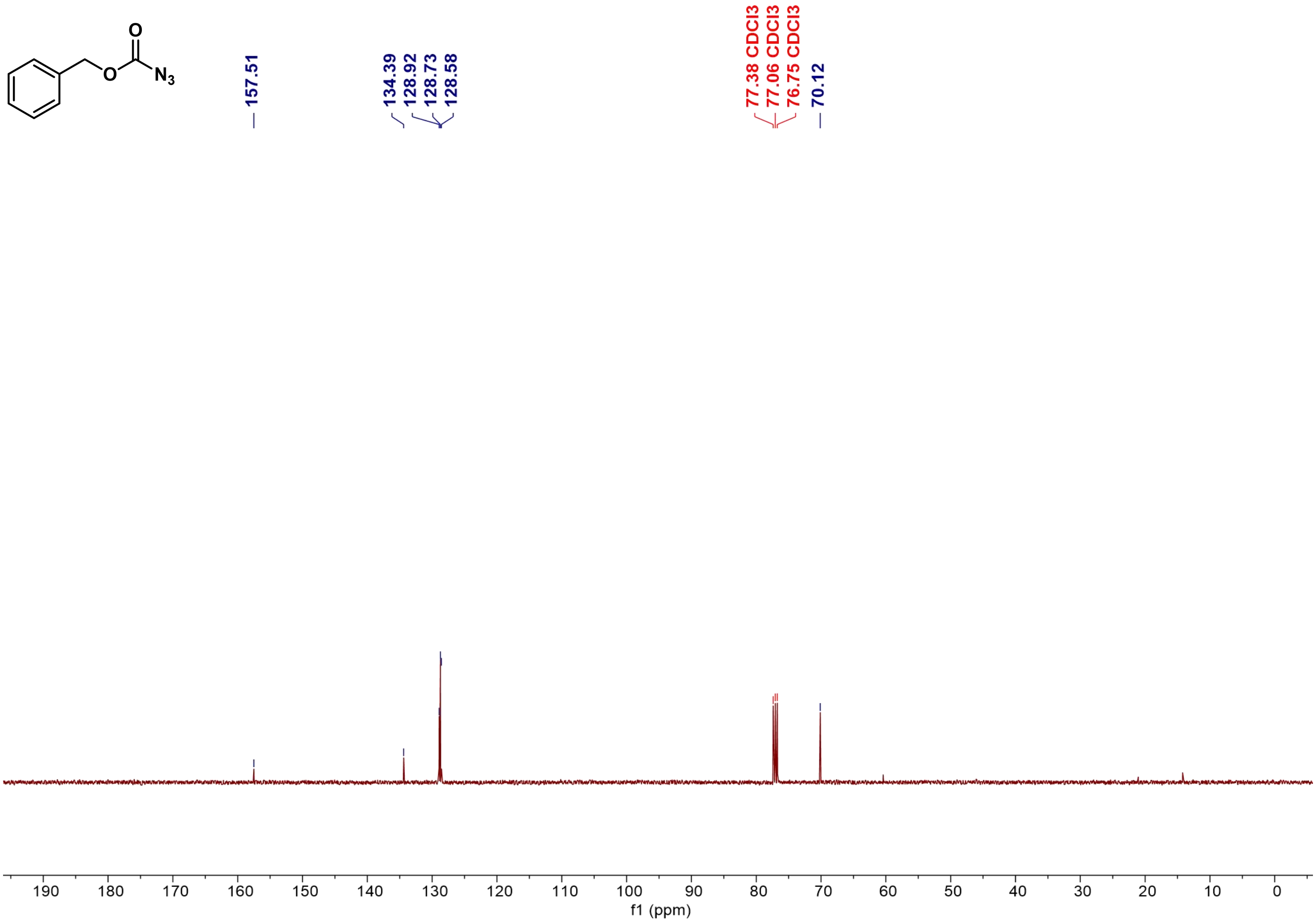
HSQC Spectrum of compound SI-89



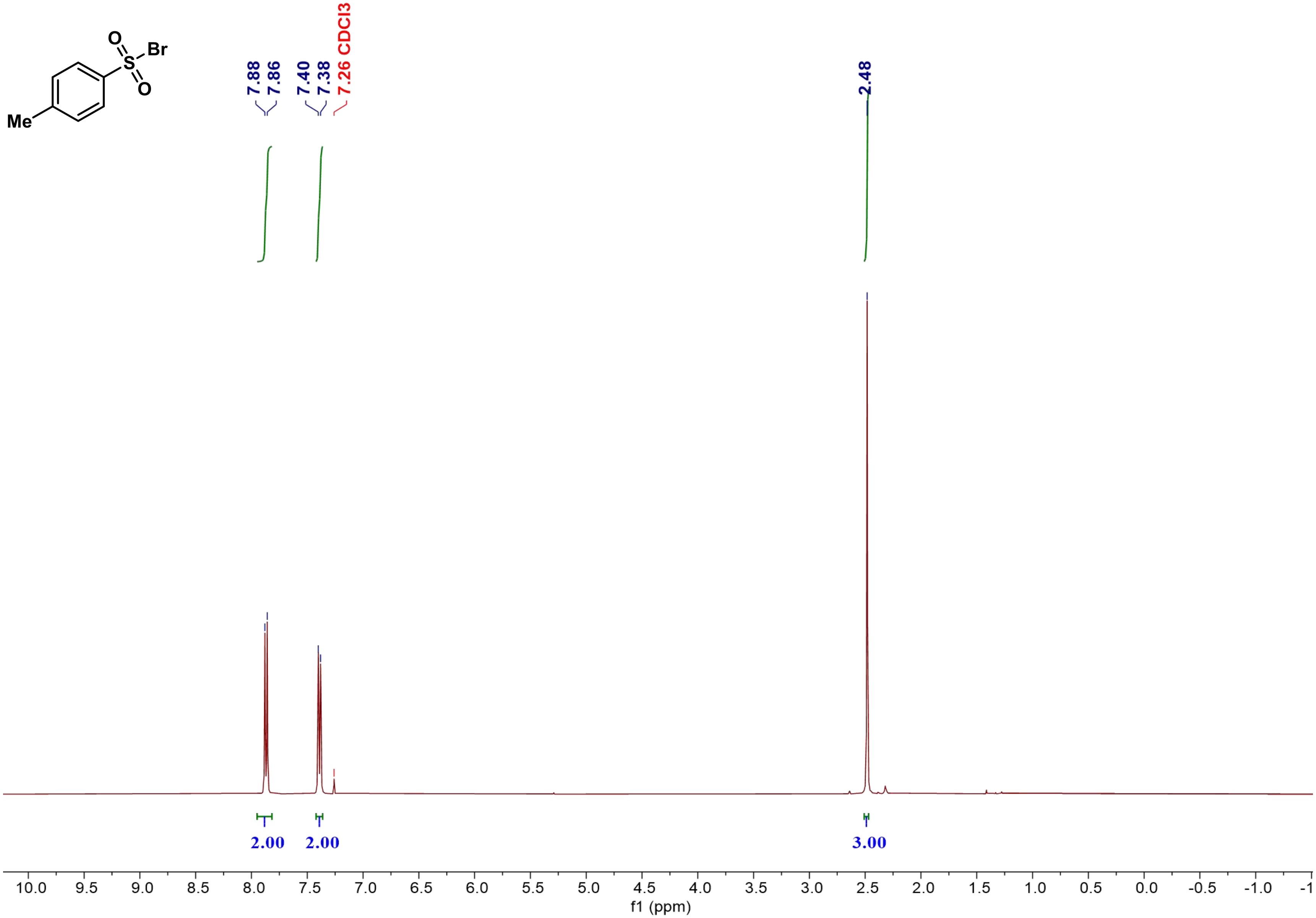
^{1}H NMR Spectrum of compound SI-90 (400 MHz, $CDCl_3$)



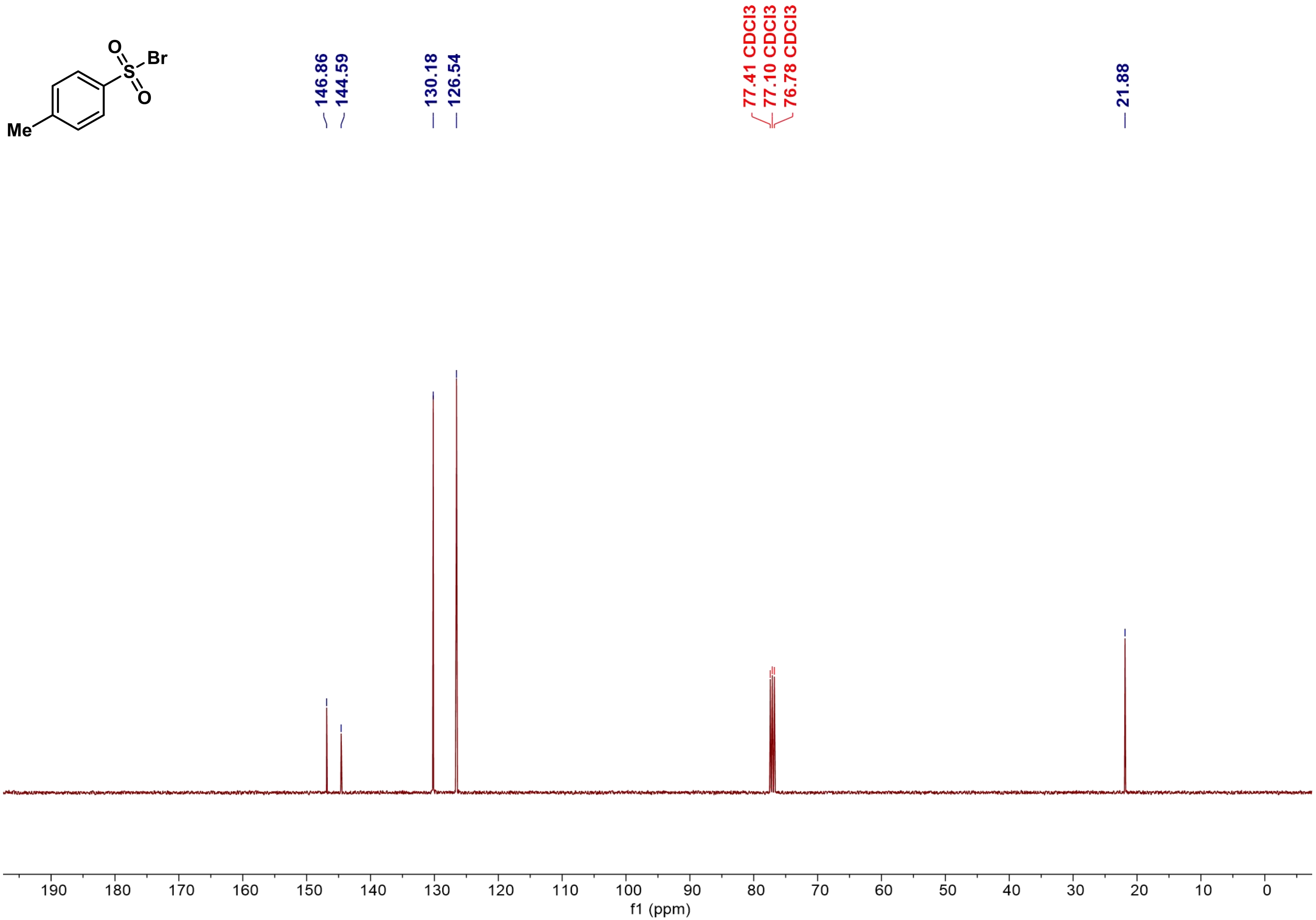
^{13}C NMR Spectrum of compound SI-90 (101 MHz, $CDCl_3$)



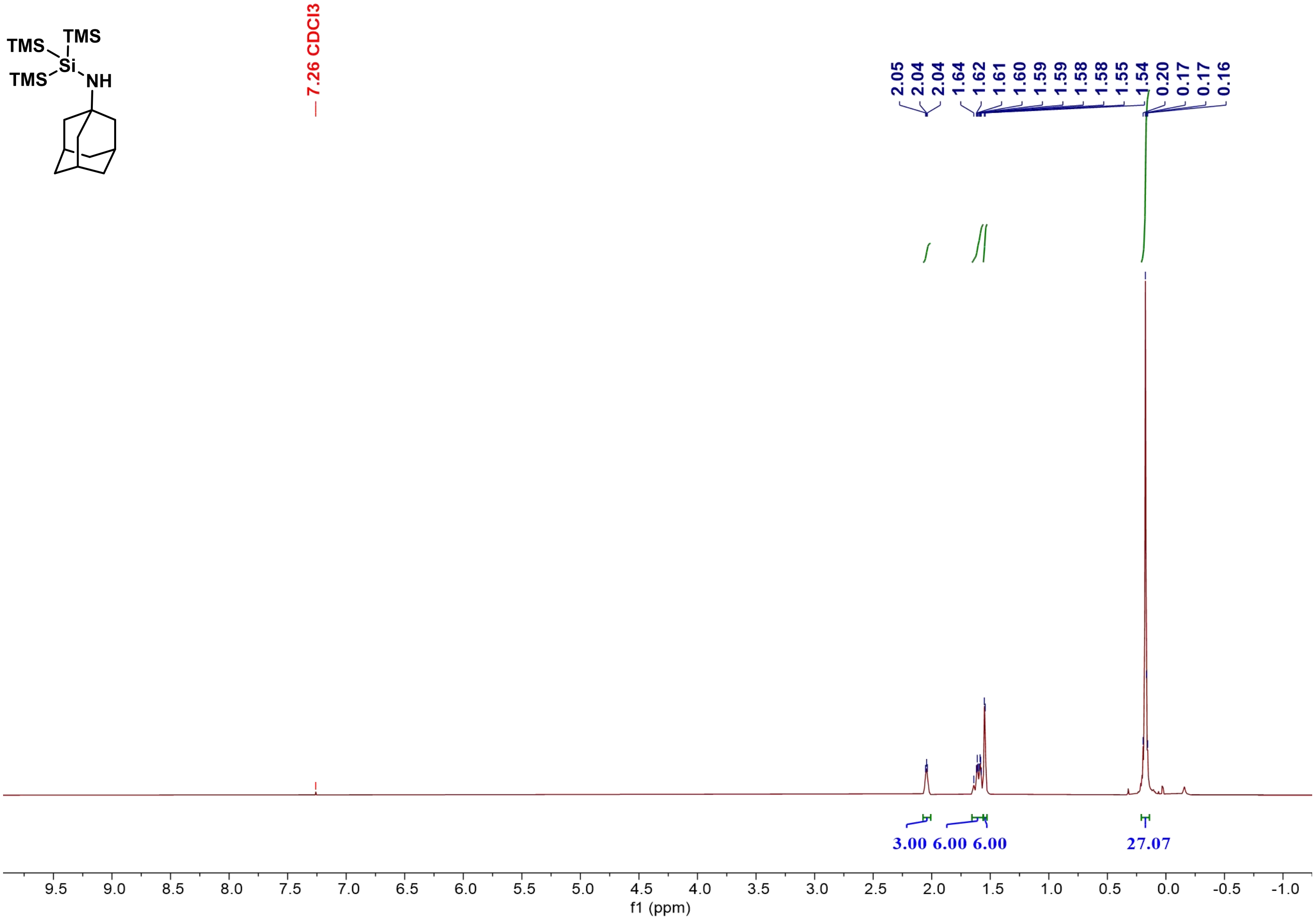
^{1}H NMR Spectrum of compound SI-91 (400 MHz, $CDCl_3$)



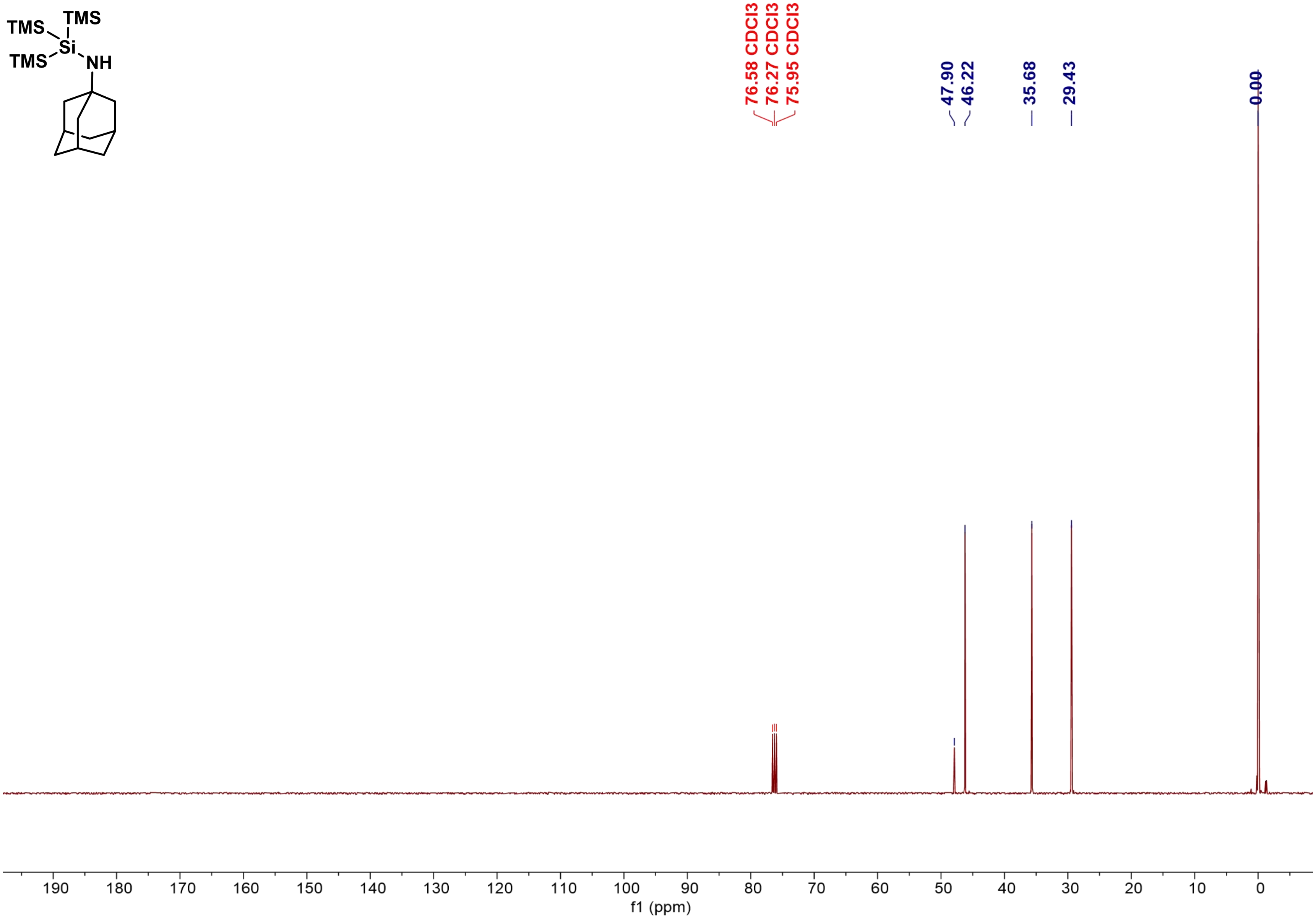
^{13}C NMR Spectrum of compound SI-91 (101 MHz, CDCl$_3$)



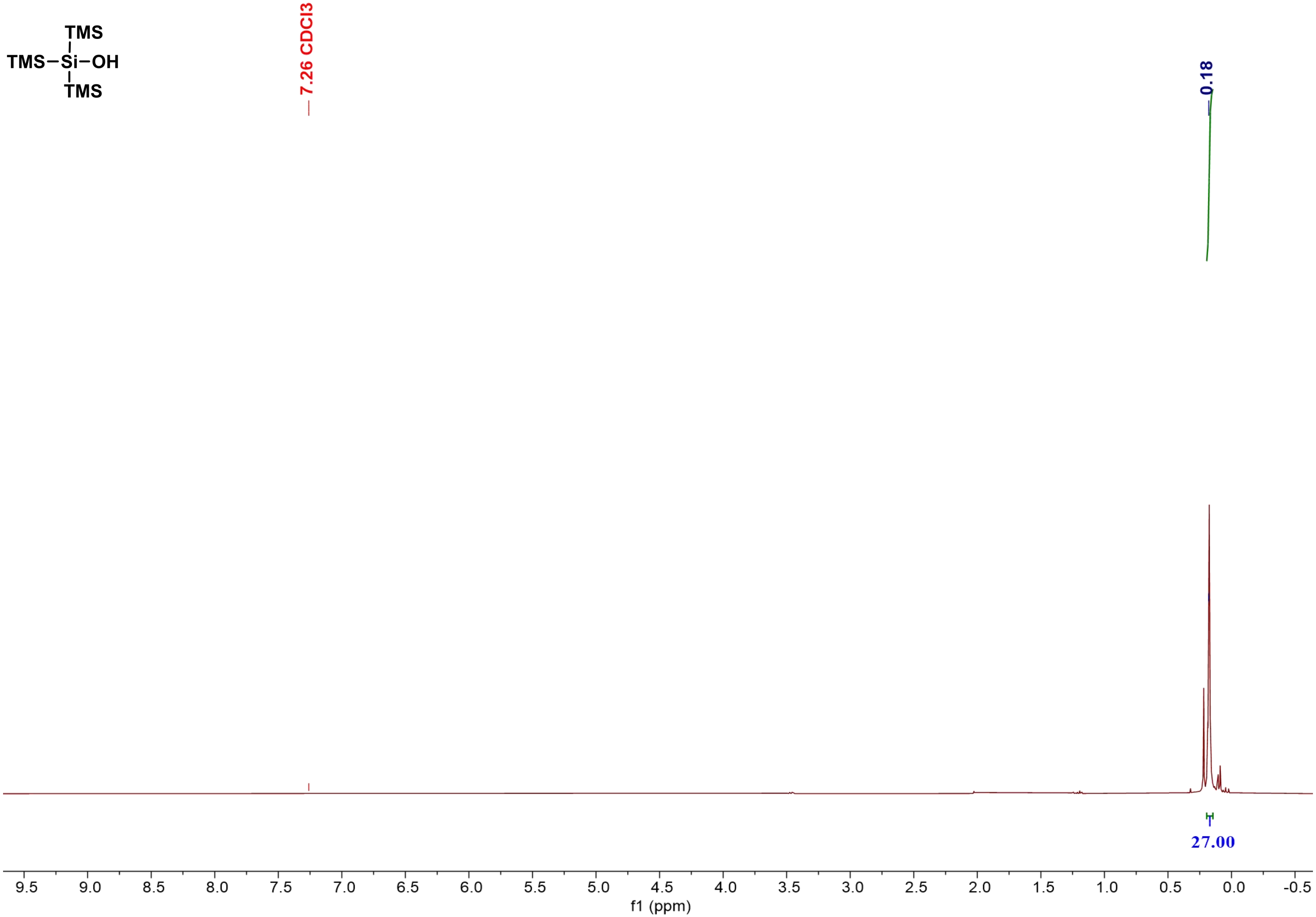
^{1}H NMR Spectrum of compound SI-92 (400 MHz, $CDCl_3$)



^{13}C NMR Spectrum of compound SI-92 (101 MHz, CDCl$_3$)



^{1}H NMR Spectrum of compound SI-93 (400 MHz, $CDCl_3$)



^{13}C NMR Spectrum of compound SI-93 (101 MHz, $CDCl_3$)