

Light-enabled scalable synthesis of bicyclo[1.1.1]pentane halides and their functionalizations

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Compound 14k	S658
Compound 16k	S660
Compound 35k	S662
Compound 21k	S664
Compound 22k	S667
Compound 24k	S670
Compound 25k	S673
Compound 26k	S676
Compound 27k	S679
Compound 34k	S682
Compound 38k	S684
Compound 39k	S686
Compound 41k	S688
Compound 48k	S690
Compound 50k	S692
Compound 51k	S694
Compound 52k	S696
Compound 53k	S698
Compound 54k	S700
Compound 55k	S702
Compound 56k	S704
Compound 57k	S706
Compound 58k	S708
Compound 59k	S710
Compound (O ₂ -59k)	S712
Compound 60k	S714
Compound 61k	S716

Compound 63k	S718
Compound 67k	S720
Compound 68k	S723
Compound 69k	S726
Compound 70k	S729
Compound 71k	S732
Compound 79k	S735
Compound 80k	S738
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Compound 7l	S752
Compound 14l	S756
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Compound 21l	S762
Compound 22l	S765
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Compound 26l	S774
Compound 27l	S777
Compound 34l	S780
Compound 41l	S782
Compound 48l	S784
Compound 50l	S786
Compound 52l	S788
Compound 53l	S790
Compound 54l	S792
Compound 55l	S794
Compound 56l	S796
Compound 57l	S798
Compound 59l	S800
Compound O ₂ -59l	S802

Compound 60l	S806
Compound 61l	S810
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Compound 67l	S816
Compound 68l	S819
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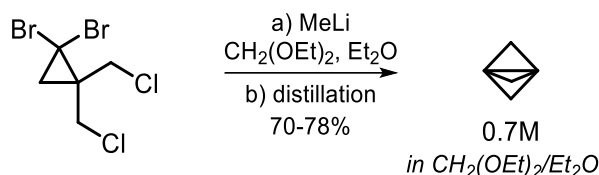
Experimental Section. Data description and procedures

General Considerations. All chemicals were provided by Enamine Ltd. (www.enamine.net). All solvents were treated according to standard methods. All reactions were monitored by thin-layer chromatography (TLC) and were visualized using UV light or TLC stains. Product purification was performed using silica gel column chromatography. TLC characterization was performed with pre-coated silica gel GF254 (0.2 mm), while column chromatography characterization was performed with silica gel (100-200 mesh). NMR spectra were recorded at Bruker Avance III 400 spectrometer equipped with 5 mm TXI probe, X channel $^{19}\text{F}/^{13}\text{C}/^{15}\text{N}$, Bruker Avance DRX 500 spectrometer equipped with 5 mm QNP probe tunable at ^{31}P , ^{13}C , and ^{15}N channels, Varian VNMRs 500 spectrometer equipped with 5 mm OneNMR probe, Agilent ProPulse 600 spectrometer equipped with 5 mm OneNMR probe. Samples were typically 20 mg dissolved in about 500 μL of the suitable deuterated solvent. The spectra were recorded at 500 and 600 MHz ^1H frequencies, 101, 126, and 151 MHz ^{13}C frequencies, and 376 MHz ^{19}F frequency. ^{31}P -NMR spectra were recorded at 202 MHz (Varian). ^1H -NMR chemical shifts are calibrated using residual undeuterated solvents CHCl_3 ($\delta = 7.26$ ppm), DMSO ($\delta = 2.50$ ppm), CH_3OH ($\delta = 3.31$ ppm), or H_2O ($\delta = 4.79$ ppm). ^{13}C -NMR chemical shifts for ^{13}C -NMR are reported relative to the central CDCl_3 ($\delta = 77.16$ ppm), CD_3OD ($\delta = 49.00$ ppm) or DMSO-d_6 ($\delta = 39.52$ ppm). Coupling constants are given in Hz. The high-resolution mass spectra (HRMS) were recorded using an electrospray ionization-time of flight (ESI-TOF) detection scheme. Liquid chromatography-mass spectrometry (LC-MS) was done with chemical ionization (CI).

List of abbreviations

Ar	argon
AIBN	azobisisobutyronitrile
BEt ₃	triethylborane
Bu ₃ SnH	tributyltin hydride
Cu(TMHD) ₂	copper <i>bis</i> (2,2,6,6-tetramethyl-3,5-heptanedionate)
DME	dimethoxyethane
<i>fac</i> -Ir(ppy) ₃	<i>fac-tris</i> (2-phenylpyridine)iridium(III)
Fe(acac) ₃	<i>tris</i> (acetylacetonato) iron(III)
GCMS	gas chromatography-mass spectrometry
HRMS	high-resolution mass spectrometry
HATU	1-[<i>bis</i> (dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxide hexafluorophosphate
LCMS	liquid chromatography-mass spectrometry
MeLi	methyllithium
NCS	<i>N</i> -chlorosuccinimide
(PhO) ₂ P(O)N ₃	diphenyl phosphoryl azide
py	pyridine
POCl ₃	phosphoryl chloride
rt	room temperature
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
<i>t</i> -BuLi	<i>tert</i> -butyllithium
<i>t</i> -BuCN	<i>tert</i> -butylnitrile
TIPS	triisopropyl silane
TFA	trifluoroacetic acid
TMEDA	tetramethylethylenediamine

Preparation of [1.1.1]propellane



According to a modified literature procedures.^{1,2} A flame-dried three-neck round-bottom flask (6 L) equipped with an overhead stirrer was charged with 1,1-bis(chloromethyl)-2,2-dibromocyclopropane (800.00 g, 2.70 mol, 1.00 equiv) in Et₂O (2 L) under Ar atmosphere. The mixture was cooled to -80 – -85 °C, and MeLi (3M in diethoxymethane, 2 L, 6.00 mol, 2.20 equiv) was added dropwise at the temperature range of -85 – -75 °C temperature under Ar (*large heat release was observed when 1/2 volume of MeLi was added*). The 1st liter of the solution of MeLi was added during ca. 50 min, and the 2^d liter – for an additional 20 min. The reaction mixture was allowed to warm up to -20 °C (ca. 20 min). *Caution: at this temperature, an additional exotherm was observed.* The internal reaction temperature was controlled not to exceed 0 °C. After ceasing the exotherm, the reaction mixture was additionally stirred at ~ 0 °C for 1 h. After that, the overhead stirrer was changed to a magnetic stirrer. The mixture was distilled to a 5 L flask (the flask was cooled with liquid nitrogen to ~ -100 °C) under reduced pressure (200 – 10 mmHg, gradually increasing the temperature to 20 – 25 °C in the reaction mixture). Distillation was continued until the temperature of vapors reached 20 – 25 °C to obtain the propellane solution in Et₂O (10 – 20% diethoxymethane, MeBr, and Et₂O). The solution was allowed to warm to -30 °C and was titrated with benzenethiol. Then the solution was transferred into 1 L bottles for storage (stored under Ar at -30 ± 10 °C) and yielded [1.1.1]propellane **1** (3000 mL, 2.10 mol, 0.7M in Et₂O, 78%).

Titration of propellane with thiophenol:

A solution of thiophenol (3.00 g) in Et₂O degassed with Ar was added to a solution of **1** (10 mL). The mixture was stirred for 15 min at room temperature, concentrated *in vacuo*, and subjected to ¹H NMR. The ratio of the obtained PhS-BCP-H and remaining PhSH was calculated based on the proton of the tertiary carbon in propellane **1** at 2.72 ppm (1H, s; CDCl₃) and the proton in PhSH at 3.44 ppm (1H, s; CDCl₃).

Note 1: Depending on a run, the concentration of propellane typically varies between 0.6-0.7M. Although a solution of propellane can be stored for weeks in closed bottles under Ar at -40 °C, its concentration slowly decreases over time (from 0.7M to 0.6M during ca. 1 month at -40 °C).

Note 2: Synthesis of propellane can also be performed in MeOtBu (2 L) instead of Et₂O (2 L) on the same scale. The obtained solution of propellane in MeOtBu has concentration of 0.6M (according to titration with thiophenol).

¹ Mondanaro, K. R.; Dailey, W. P., [1.1.1]Propellane, [Tricyclo[1.1.1.01,3]pentane]. *Org. Synth.* **1998**, 75, 98.

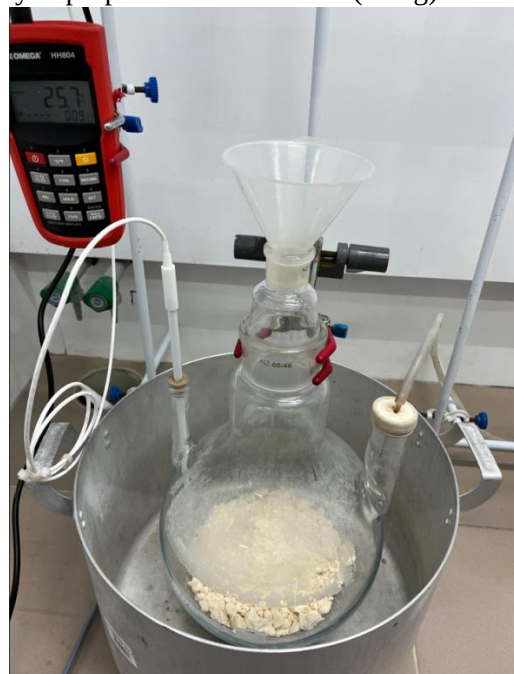
² Ripenko, V.; Vysochyn, D.; Klymov, I.; Zherish, S.; Mykhailiuk, P. K. Large-Scale Synthesis and Modifications of Bicyclo[1.1.1]pentane-1,3-dicarboxylic Acid (BCP). *J. Org. Chem.* **2021**, 86, 14061–14068.

Photos

I. Preparation for synthesis



Loading the 1,1-bis(chloromethyl)-2,2-dibromocyclopropane into the reactor (800 g)



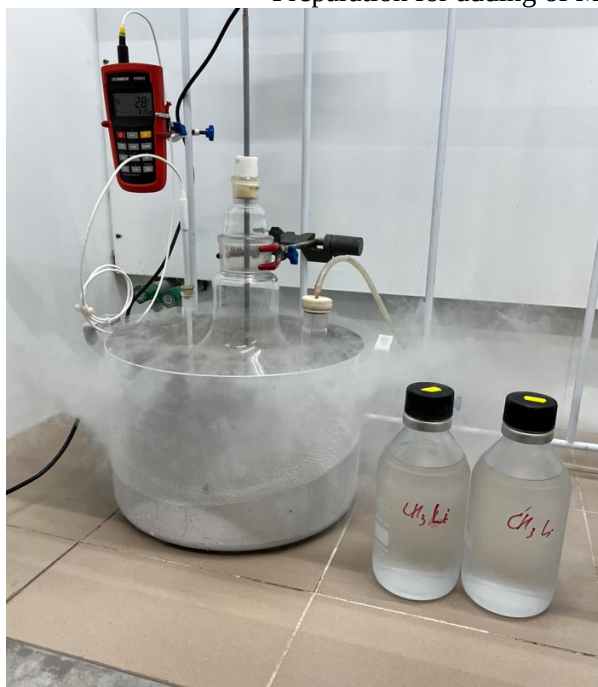
1,1-Bis(chloromethyl)-2,2-dibromocyclopropane is dissolved in diethyl ether (2 L)



Installation of mechanical stirring and the start of cooling of the reaction mixture



Preparation for adding of MeLi solution in $(\text{EtO})_2\text{CH}_2$ (2 L)



II. Lithiation

Cannulation of a solution of MeLi to the reactor



End addition of MeLi solution



III. Warming up the reaction mixture



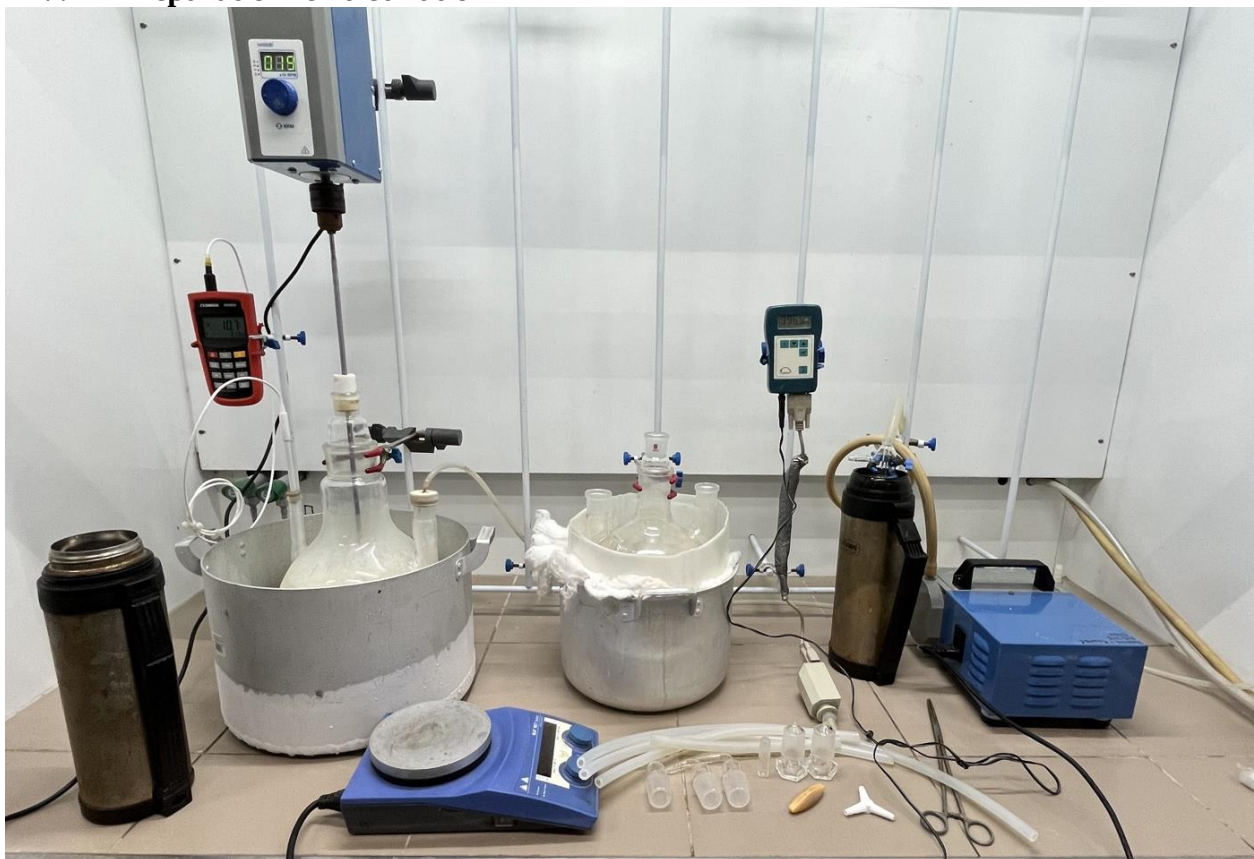
Adding two dewars of liquid nitrogen (1.8 L) at -25 and at -14 °C to control the exotherm of the BCP ring-closing



Final stirring of the reaction mixture at -5 – 0 °C for 1 h



IV. Preparation for distillation



Replacing the mechanical stirring of the reaction mixture with the anchor of a magnetic stirrer bar



Replacing the thermometer and connecting the traps to the reactor



Distillation system assembly



Cooling of the BCP trap (4 L three-necked reactor)



Cooling of the protection trap of the diaphragm pump



V. The beginning of the distillation



Entering the mode of stable distillation of BCP





Stable operating mode – $\sim -10\text{ }^{\circ}\text{C}$ temperature reaction mixture



Add warm water to the bath ($\sim 50\text{ }^{\circ}\text{C}$, $\sim 6\text{ L}$)



Stable operating mode – $\sim 20\text{ mbar}$ pressure of the system. Until the end of distillation keep the presence of liquid nitrogen in the BCP trap bath.



Stable operating mode after adding warm water to the bath – $\sim -10\text{ }^{\circ}\text{C}$ temperature reaction mixture. Until the end of distillation:

- the temperature of the reaction mass is gradually increased to $20\text{ }^{\circ}\text{C}$;
- the temperature of the water in the bath is kept in the range of $25 - 30\text{ }^{\circ}\text{C}$.



The pressure in the system is in the range of 10 to 20 mbar



VI. End of distillation



Disconnecting the trap of the membrane pump



Joining the argon ball to the distillation system



VII. Vacuum venting of BCP trap by an inert atmosphere of Ar



Preparation of bottle for storing BCP solution:

- washing
- drying by heat gun
- degassing with argon



**VIII. Cannulation of the BCP solution
from the trap reactor into the
storage jar**

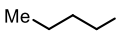
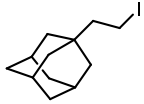
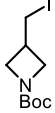
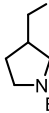
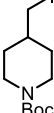
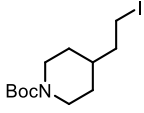
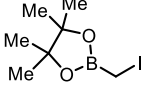
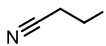
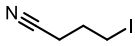
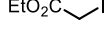
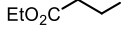
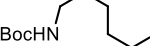
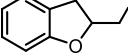
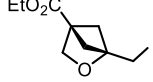
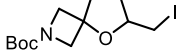
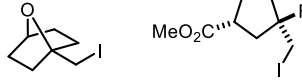
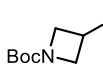
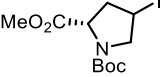
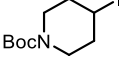
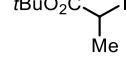
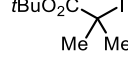
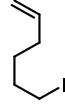


Final BCP solution (typ. 0.6 – 0.7M, 2.5 – 3 L)



List of starting materials

These compounds are commercially available at Enamine and were taken from stock:

					
EN300-125253	EN300-18902	EN300-19282	EN300-19286	EN300-19804	EN300-3070247
					
EN300-141727	EN300-182629	EN300-82529	EN300-1168640	EN300-137785	EN300-2938467
					
EN300-6729032	EN300-3625876	EN300-40046	EN300-7404931	EN300-244109	EN300-6733682
					
EN300-297917	EN300-316786	EN300-4254194	EN300-137701	EN300-91258	EN300-156159
					
EN300-207724	EN300-269331	EN300-216197	EN300-94771	EN300-96922	EN300-97498
					
EN300-101035	EN300-7374726	EN300-19919	EN300-221518	EN300-105013	EN300-4266718
					
EN300-98686	EN300-180814	EN300-2007991	EN300-2007889	EN300-298870	EN300-340718
					
EN300-19281	EN300-1265839	EN300-214303	EN300-761681	EN300-93401	EN300-19417
					
EN300-107095	EN300-211438	EN300-104914	EN300-2220397	EN300-7367576	EN300-83057
					
EN300-12471796	EN300-43010	EN300-187037	EN300-3992263	EN300-44822467	EN300-317202
					
EN300-26438	EN300-86075	EN300-49962	EN300-7596625	EN300-123491	EN300-85155
					
EN300-211428	EN300-141359	EN300-64594	EN300-1692836	EN300-88338	EN300-127380
					EN300-69951

Synthesis of 3-iodobicyclo[1.1.1]pentanes and 3-iodobicyclo[3.1.1]heptanes

General protocol A (manuscript: Table 1, entry 11)

This protocol was used for the synthesis of bicyclo[1.1.1]pentane iodides on a 5-10 g scale.

1) 210 mL coil (160 mL irradiated area).

Coil: inner diameter = 1/4 inch; outer diameter = 5/16 inch.

2) 365 nm LED diodes. 960 diodes (radiated power: 0.875W/diode at 0.5A). I = 0.5A.

Maximal radiated power (radiometric flux): $960 \times 0.875 = 840 \text{ W}$.

Maximal power consumption: $3.6\text{V} \times 0.5\text{A} \times 960 = \text{ca. } 1.7 \text{ kW}$.

For these experiments, we used 50% of the power: $0.5 \times 840 \text{ W} = 420 \text{ W}$ (radiated power).

3) 10 mL/min flow rate.

1-Methyl-3-iodobicyclo[1.1.1]pentane (**1**) as an example

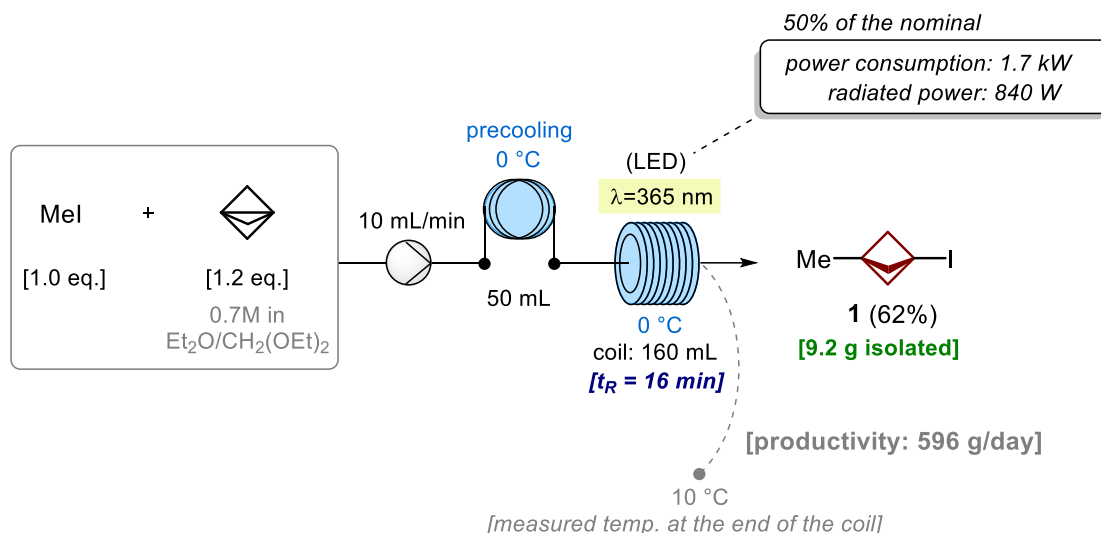
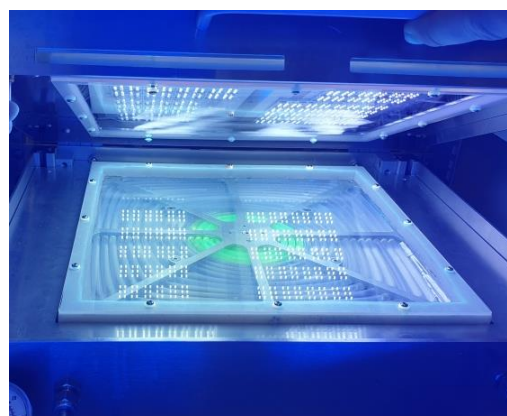


Photo of the photochemistry in flow



Irradiated coil

To a solution of MeI (10.00 g, 0.0704 mol, 1.00 equiv) in Et_2O (100 mL), was added propellane (120 mL, 0.0840 mol, 0.7M solution in Et_2O /diethoxymethane; 1.20 equiv) under Ar atmosphere.

The resulting mixture was passed through a photoreactor. Flow rate: 10 mL/min. Irradiated coil: 160 mL. Irradiation: 365 nm, LED, irradiated power: 420 W (50% of the maximal).

Before entering the irradiated area, the solution was precooled to 0 °C with Huber “Unistat 510” chiller. The irradiated coil was also cooled to 0 °C with Huber “Unistat 510” chiller. The temperature of the reaction mixture after the coil was ca. 10 °C.

After passing through the coil, after ca. 40 min. (residence time in the irradiated coil: 160/10 = ca. 16 min) the solution was evaporation under a reduced pressure (ca. 50 mm Hg, 20 °C in an external water-cooling bath), and the residue was purified by distillation under a reduced pressure (b.p. = 38-40 °C at 10 mmHg). After cooling down to room temperature, the product (9.21 g, 0.0438 mol, yield 62%) slowly solidified.

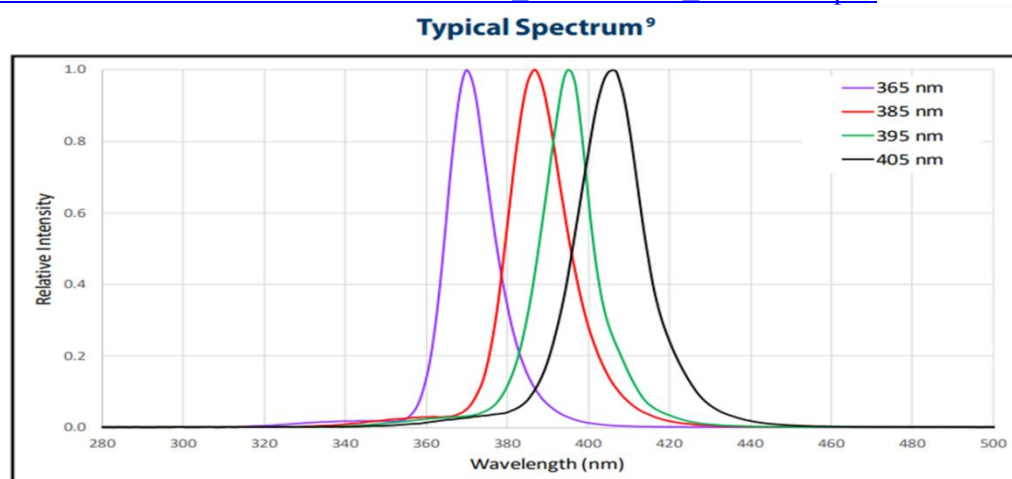
Alternatively, the crude residue (after evaporation of the reaction mixture after the irradiation) could be purified by adding pentane (ca. 50 mL) and cooling the formed suspension with an external dry ice bath to ca. -60 °C. The formed precipitate was quickly filtered off. The filtered solid was washed with the pre-cooled pentane (-60 °C, 50 mL) on the filter, and was dried under vacuum (20 mmHg) during 30 min at room temperature. Yield: 9.77 g, 0.0465 mol, 66%, white crystals, m.p. < 30 °C. ¹H NMR (400 MHz, CDCl₃): δ 2.20 (s, 6H), 1.21 (s, 3H) ppm. ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 62.3, 44.8, 18.4, 7.2 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.

Note 1: analogous reaction on the same scale with 2.00 equiv of methyl iodide (20.00 g, 0.1408 mol, 2.00 equiv) in Et₂O (100 mL) and propellane (120 mL, 0.0840 mol, 0.7M solution in Et₂O/diethoxymethane; 1.20 equiv)) gave the product **1** (10.69 g, 0.0514 mol) in 73% yield after distillation (manuscript: Table 1, entry 12).

Note 2: analogous reaction of methyl iodide (10.00 g, 0.0704 mol, 1.00 equiv) under identical conditions with a solution of propellane in MeOtBu (0.6M, 141 mL, 0.0845 mol, 1.20 equiv) provided pure product **1** in 7.49 g, 0.036 mol, 51% yield after distillation (manuscript: Table 1, entry 13).

For irradiation with 365 nm LED light, we used commercially available diodes SST-10-UV-B130-F365 (Luminus Devices Inc.)

https://download.luminus.com/datasheets/Luminus_SST-10-UV_Datasheet.pdf

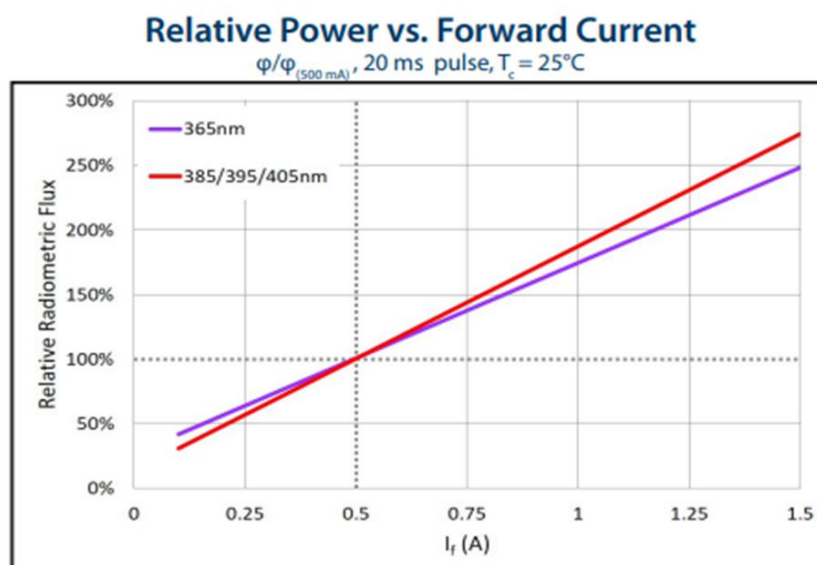


(365 nm version)

Optical & Electrical Characteristics ($T_{hs} = 25^{\circ}\text{C}$)

UV						
Parameter	Symbol	Values ⁵				Unit
Peak Wavelength Range	λ	365-375	380-390	390-400	400-410	nm
Test Current for binning ⁶	I	500	500	500	500	mA
Peak Wavelength Typ.	λ_p	370	385	395	405	nm
Forward Voltage	V_{Fmin}	3.0	3.0	3.0	3.0	V
	V_F	3.7	3.4	3.3	3.3	V
	V_{Fmax}	4.0	4.0	4.0	4.0	V
Radiometric Flux ⁷	Φ_{typ}	875	1015	1015	930	mW
FWHM at 50% of Φ	$\Delta\lambda_{1/2}$	10	10	10	10	nm
Viewing Angle	$2\Phi_{1/2}$	130	130	130	130	degrees

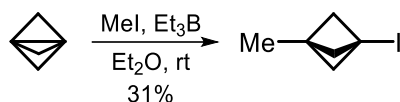
While SST-10-UV devices are tested at 500 mA, they can be driven at CW currents ranging from 200 mA to 1.5 A and at duty cycles ranging from 1% to 100%. Drive current and duty cycle should be adjusted as necessary to maintain the junction temperature desired to meet application lifetime requirements.



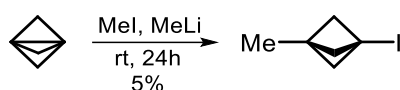
For the coil, we used commercially available tubes 200-0313-030-0C (inner diameter = 1/4 inch; outer diameter = 5/16 inch)

<https://www.altaflo.com/products/fep-altafluor-200/>

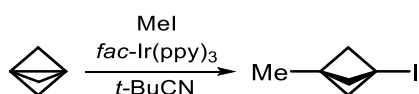
<https://www.altaflo.com/wp-content/uploads/2022/10/altaflo-maincatalog-v27-1.pdf>

General protocol B, [BEt₃] (manuscript: Table 1, entry 3)

To a solution of MeI (21.02 g, 0.148 mol, 1.00 equiv) in Et₂O (105 mL, 5 mL/g) was added propellane (259 mL, 0.18 mol, 0.7M in Et₂O, 1.20 equiv) under Ar atmosphere. Next, Et₃B (1.45 g, 0.0148 mol, 0.10 equiv) was added under Ar atmosphere. The reaction was stirred at room temperature under Ar atmosphere for 24 h. The next day, the reaction mixture was concentrated under reduced pressure. The residue was purified by distillation under reduced pressure (b.p. = 36-40 °C, 10 mmHg). Yield: 9.57 g, 0.046 mol, 31%, white solid, m.p. < 30 °C.

General protocol C, [MeLi] (manuscript: Table 1, entry 1)

MeI (9.89 g, 0.0696 mol, 1.00 equiv) was added to propellane (119 mL, 0.0836 mol, 1.20 equiv, 0.7M solution in Et₂O/diethoxymethane) under Ar. Next, MeLi (23 mL, 0.0697 mol, 3M in diethoxymethane, 1.00 equiv) was added dropwise at – 40 °C under Ar. The reaction mixture was allowed to warm to room temperature and was stirred for 24 h. The reaction mixture was cooled again to – 40 °C, and MeOH (60 mL) was added. The resulting solution was poured into an ice-cold mixture of H₂O (100 mL) and pentane (100 mL). After the separation of the layers, the organic phase was washed with H₂O (2 × 100 mL), dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by distillation under reduced pressure (b.p. = 36-40 °C, 10 mmHg). Yield: 0.760 g, 0.00365 mol, 5%, white solid, m.p. < 30 °C. ¹H NMR purity ca. 85%.

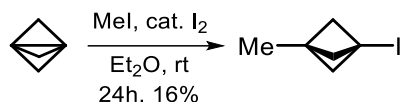
General protocol D, [Ir] (manuscript: Table 1, entry 5)

To a 500 mL glass flask were added MeI (10.50 g, 0.0739 mol, 1.00 equiv) and *fac*-Ir(ppy)₃ (1.21 g, 0.00185 mol, 0.025 equiv) dissolved in *t*-BuCN (50 mL). Then, propellane (126 mL, 0.0882 mol, 0.7M solution in Et₂O/diethoxymethane, 1.20 equiv) was added under Ar atmosphere. The glass bottle was placed in the photoreactor and irradiated with a wavelength of 450 nm for 15 h. The temperature limit of the reaction mixture was set at 18 °C, and the LED luminescence power decreased from 100% to 15% of the nominal. After that, the reaction mixture was concentrated under reduced pressure. Attempted purification of the residue by distillation at 10 mmHg gave only several mg of product **1** (yield < 0.5%).

The experiment with 2.00 equiv of propellane (210 mL, 0.1470 mol, 0.7M solution in Et₂O/diethoxymethane) gave after distillation at 10 mmHg the pure product **1** (2.17 g, 0.0103 mol) in 14% yield (manuscript: Table 1, entry 6).

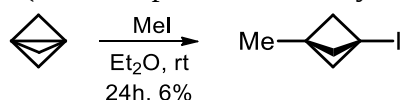
The experiment experiment with Et₂O (50 mL) instead of *t*-BuCN (50 mL) also gave only traces of the desired product **1** (manuscript: Table 1, entry 4).

Catalysis with I₂ (manuscript: Table 1, entry 2)



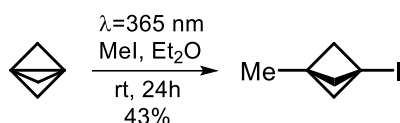
To a solution of MeI (10.43 g, 0.0735 mol, 1.00 equiv) in Et₂O (50 mL) were added propellane (126 mL, 0.0882 mol, 0.7M solution in Et₂O/diethoxymethane, 1.20 equiv) and I₂ (50 mg, 0.2 mmol, 0.0027 equiv) under Ar. The resulting mixture was stirred at rt for 24 h. The mixture was concentrated under reduced pressure. The residue was purified by distillation under reduced pressure (b.p. = 36-40 °C, 10 mmHg). Yield: 2.47 g, 0.0118 mol, 16%, white solid, m.p. < 30 °C.

Control experiment without light (manuscript: Table 1, entry 15)



MeI (9.87 g, 0.0695 mol, 1.00 equiv) was added to propellane (119 mL, 0.0836 mol, 1.20 equiv, 0.7M solution in Et₂O/diethoxymethane) under Ar. The reaction mixture was stirred at to room temperature for 24 h (no heating, no irradiation, no additional promotion). The resulting solution was concentrated under reduced pressure. The residue was purified by low-temperature crystallization from pentane. Yield: 0.82 g, 5.7%, white solid. ¹H NMR purity ca. 80%.

Photochemistry in batch (manuscript: Table 1, entry 10)



To a 100 mL glass bottle was added MeI (5.12 g, 0.036 mol, 1.00 equiv) and Et₂O (20 mL). Then propellane (72 mL, 0.0423 mol, 1.20 equiv, 0.6M solution in Et₂O/diethoxymethane) was added under Ar at room temperature. The glass bottle was placed in the photoreactor and irradiated with a wavelength of 365 nm for 24 h. The temperature limit of the reaction mixture was set at 18 °C, and the LED luminescence power of decreased from 100% (power consumption is 605 W; radiated power is 257 W) to 15% of the nominal. The reaction mixture was concentrated under reduced pressure and distilled at 10 mmHg. Yield: 3.22 g, 0.0155 mol, 43%, white solid, m.p. < 30 °C.

General protocol A-modified.

This protocol was used for the synthesis of bicyclo[1.1.1]pentane iodides on a 0.1-2 g scale.

1) 10.9 mL coil (7.6 mL irradiated area).

Coil: inner diameter = 1/8 inch; outer diameter = 3/16 inch.

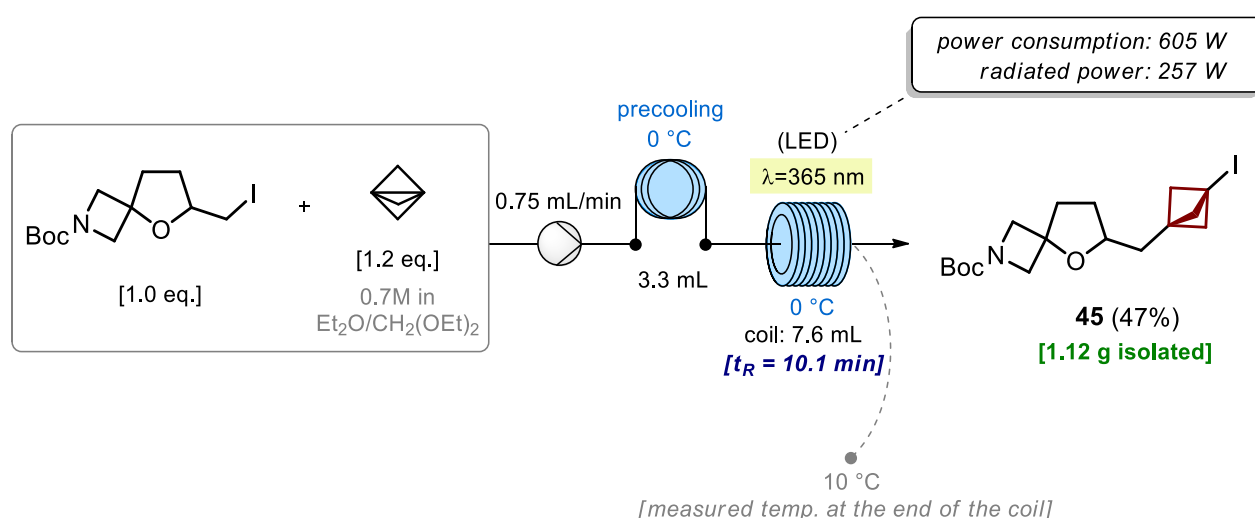
2) 365 nm LED diodes. 168 diodes (radiated power: 0.875W/diode at 0.5A). I = 1A.

Total radiated power (radiometric flux): $168 \times 0.875 \times 175\% = 257 \text{ W}$.

Total power consumption: $3.6\text{V} \times 1\text{A} \times 168 = 605 \text{ W}$.

3) 0.75 mL/min flow rate.

(±)-*Tert*-butyl 6-({3-iodobicyclo[1.1.1]pentan-1-yl}methyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (**45**) as an example



Coil



Coil and irradiation block



Cooling block

To a solution of (±)-*tert*-butyl 6-(iodomethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (2.00 g, 5.67 mmol, 1.00 equiv) in Et_2O (10 mL), was added propellane (9.7 mL, 6.79 mmol, 0.7M solution in Et_2O /diethoxymethane; 1.20 equiv) under Ar atmosphere. The resulting mixture was passed

through a photoreactor. Flow rate: 0.75 mL/min. Irradiated coil: 7.5 mL. Irradiation: 365 nm, LED. Power consumption is 605 W; radiated power is 257 W.

Before entering the irradiated area, the solution was precooled to 0 °C with Huber “Unistat 510” chiller. The irradiated coil was also cooled to 0 °C with Huber “Unistat 510” chiller. The temperature of the reaction mixture after the coil was ca. 10 °C.

After passing through the coil, ca. 40 min, (residence time in the irradiated coil: $7.6/0.75 = 10.1$ min) the solution was evaporation under reduced pressure. The residue was dissolved in pentane and cooled in liquid nitrogen. The resulting solution was passed through SiO₂ (10 mL) pre-wetted with cooled pentane. Yield: 1.12 g, 2.66 mmol, 47%, beige solid crystals, m.p. = 117-118 °C. ¹H NMR (400 MHz, CDCl₃): δ 3.97 – 3.80 (m, 5H), 2.24 (s, 6H), 2.12 – 1.96 (m, 3H), 1.78 – 1.60 (m, 2H), 1.50 – 1.35 (m, 1H), 1.43 (s, 9H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 156.5, 79.6, 77.9, 77.8, 62.5, 62.4, 61.4, 46.2, 38.5, 36.0, 31.3, 28.5, 7.5 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₇H₂₆INNaO₃, 442.0855; found 442.0842.

For the coil, we used commercially available tubes 200-0188-030-0C
(inner diameter = 1/8 inch; outer diameter = 3/16 inch)

<https://www.ataflo.com/products/fep-atafluor-200/>

<https://www.ataflo.com/wp-content/uploads/2022/10/ataflo-maincatalog-v27-1.pdf>



1-Iodo-3-(methyl-d₃)bicyclo[1.1.1]pentane (D₃-1)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C at 20-30 mmHg) and triturated in 60 mL of pentane at -40 °C. Yield: 10.04 g, 0.047 mol, 68%, white solid, m.p. = 30-31 °C. ¹H NMR (500 MHz, CDCl₃): δ 2.21 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 62.0, 44.5, 17.6 (p, *J* = 19.5 Hz), 6.9 ppm. GCMS (M)⁺: 211. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.

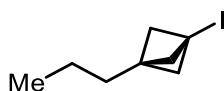


1-Ethyl-3-iodobicyclo[1.1.1]pentane (2)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C at 20-30 mmHg) and triturated in 60 mL of pentane at -40 °C. Yield: 9.95 g, 0.045 mol, 90%.

General protocol B, [BEt₃]. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 3.09 g, 0.014 mol, 28%.

Yellow solid, m.p. < 30 °C. ¹H NMR (400 MHz, CDCl₃): δ 2.17 (s, 6H), 1.52 (q, *J* = 7.5 Hz, 2H), 0.84 (t, *J* = 7.5 Hz, 3H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 60.1, 49.5, 25.4, 10.9, 8.3 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



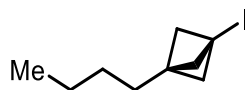
1-Iodo-3-propylbicyclo[1.1.1]pentane (3)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C at 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 10.62 g, 0.045 mol, 76%.

General protocol B, [BEt₃]. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 8.26 g, 0.035 mol, 63%.

General protocol C, [MeLi]. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 5.90 g, 0.025 mol, 42%.

Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 2.19 (s, 6H), 1.47 (dd, *J* = 9.2, 6.4 Hz, 2H), 1.32 – 1.20 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 60.8, 48.7, 34.4, 20.2, 14.2, 8.3 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



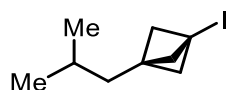
1-Butyl-3-iodobicyclo[1.1.1]pentane (4)

General protocol A. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 10.73 g, 0.0429 mol, 79%.

General protocol B, [BEt₃]. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 7.75 g, 0.031 mol, 57%.

General protocol C, [MeLi]. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 6.25 g, 0.025 mol, 46%.

Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 2.18 (s, 6H), 1.54 – 1.44 (m, 2H), 1.34 – 1.14 (m, 4H), 0.87 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 60.8, 48.7, 31.9, 29.1, 22.7, 14.1, 8.3 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



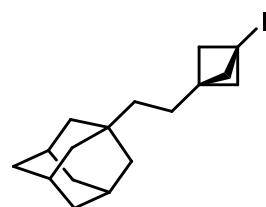
1-Iodo-3-isobutylbicyclo[1.1.1]pentane (5)

General protocol A. The final product was purified by trituration in 70 mL of pentane at -40 °C. Yield: 10.25 g, 0.041 mol, 75%.

General protocol B, [BEt₃]. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 6.00 g, 0.024 mol, 44%.

General protocol D, [Ir]. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 5.25 g, 0.021 mol, 39%.

Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 2.23 (s, 6H), 1.56 (sept, *J* = 6.6 Hz, 1H), 1.41 (d, *J* = 6.6 Hz, 2H), 0.87 (d, *J* = 6.6 Hz, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 61.6, 48.2, 41.3, 26.9, 23.2, 8.2 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.

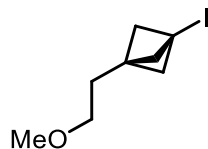


1-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)ethyl)adamantine (6)

General protocol A-mod. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and trituated in 10 mL of pentane at -40 °C. Yield: 0.10 g, 0.28 mmol, 61%.

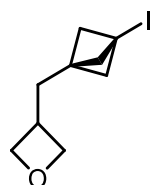
General protocol B, [BEt₃]. The final product was purified by trituration in 5 mL of pentane at -40 °C. Yield: 15 mg, 0.042 mmol, 15%.

White solid, m.p. < 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 2.16 (br s, 6H), 1.93 (s, 3H), 1.64 (dd, J = 38.3, 11.7 Hz, 6H), 1.50 – 1.36 (m, 8H), 1.02 – 0.91 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 60.5, 48.8, 42.5, 41.2, 37.3, 31.9, 28.8, 25.2, 8.5 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



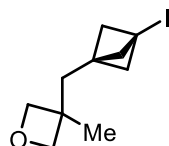
1-Iodo-3-(2-methoxyethyl)bicyclo[1.1.1]pentane (7)

General protocol A. The final product was purified by trituration in 60 mL of pentane at -40 °C. Yield: 7.06 g, 0.028 mol, 52%, colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 3.34 (t, J = 6.5 Hz, 2H), 3.30 (s, 3H), 2.23 (s, 6H), 1.78 (t, J = 6.5 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 70.5, 61.1, 58.7, 46.5, 32.0, 7.5 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{14}\text{IO}$, 253.0089; found 253.0080.



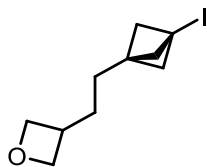
3-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)oxetane (8)

General protocol A. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 5.10 g, 0.0193 mol, 76%, white solid, m.p. < 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 4.77 (dd, J = 7.8, 6.2 Hz, 2H), 4.33 (t, J = 6.2 Hz, 2H), 3.05 – 2.90 (m, 1H), 2.15 (s, 6H), 1.92 (d, J = 7.8 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 77.5, 60.6, 46.8, 36.1, 33.4, 6.8 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{14}\text{IO}$, 265.0089; found 265.0085.



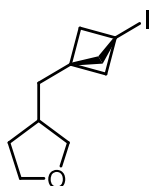
3-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)-3-methyloxetane (9)

General protocol A-mod. The final product was purified by trituration in 10 mL of pentane at -40 °C. Yield: 1.20 g, 0.0043 mol, 72%, yellow solid, m.p. < 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 4.40 (d, J = 5.6 Hz, 2H), 4.30 (d, J = 5.6 Hz, 2H), 2.26 (s, 6H), 1.93 (s, 2H), 1.33 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 83.0, 61.9, 46.4, 41.0, 39.3, 23.8, 6.6 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{16}\text{IO}$, 279.0246; found 279.0238.



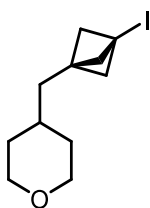
3-(2-(3-Iodobicyclo[1.1.1]pentan-1-yl)ethyl)oxetane (10)

General protocol A-mod. The final product was purified by trituration in 10 mL of pentane at -40 °C. Yield: 0.56 g, 0.002 mol, 86%, yellow solid, m.p. < 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 4.75 (dd, J = 7.6, 6.0 Hz, 2H), 4.32 (t, J = 6.0 Hz, 2H), 2.97 – 2.82 (m, 1H), 2.19 (s, 6H), 1.69 – 1.57 (m, 2H), 1.47 – 1.35 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 77.5, 60.5, 48.1, 35.0, 30.9, 29.4, 7.4 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{16}\text{IO}$, 279.0246; found 279.0239.



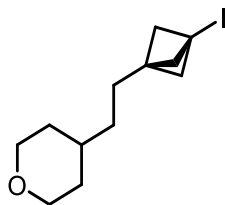
(±)-3-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)tetrahydrofuran (11)

General protocol A-mod. The final product was purified by trituration in 10 mL of pentane at -40 °C. Yield: 1.11 g, 0.004 mol, 85%, brown solid, m.p. < 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 3.88 (t, J = 7.8 Hz, 1H), 3.85 – 3.76 (m, 1H), 3.71 (q, J = 7.8 Hz, 1H), 3.25 (t, J = 7.8 Hz, 1H), 2.21 (s, 6H), 2.17 – 1.97 (m, 2H), 1.62 (d, J = 7.0 Hz, 2H), 1.51 – 1.37 (m, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 73.4, 67.9, 61.1, 48.0, 37.5, 36.1, 32.8, 7.4 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{16}\text{IO}$, 279.0246; found 279.0242.



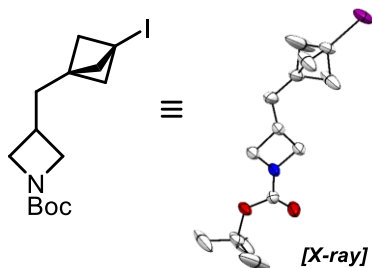
4-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)tetrahydro-2H-pyran (12)

General protocol A-mod. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and trituated in 10 mL of pentane at -40 °C. Yield: 1.06 g, 0.0036 mol, 82%, white solid, m.p. = 59-60 °C. ^1H NMR (400 MHz, CDCl_3): δ 3.91 (dd, J = 11.2, 4.0 Hz, 2H), 3.35 (td, J = 11.9, 1.7 Hz, 2H), 2.23 (s, 6H), 1.60 – 1.48 (m, 3H), 1.47 (br s, 2H), 1.34 – 1.17 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 68.0, 61.6, 47.6, 39.4, 33.7, 33.5, 7.5 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



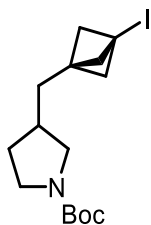
4-(2-(3-Iodobicyclo[1.1.1]pentan-1-yl)ethyl)tetrahydro-2H-pyran (13)

General protocol A-mod. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 10 mL of pentane at -40 °C. Yield: 0.53 g, 0.0017 mol, 83%, brown solid, m.p. < 30 °C. ¹H NMR (400 MHz, CDCl₃): δ 3.93 (dd, *J* = 11.7, 3.2 Hz, 2H), 3.33 (t, *J* = 11.7 Hz, 2H), 2.18 (s, 6H), 1.60 – 1.47 (m, 4H), 1.45 – 1.37 (m, 1H), 1.29 – 1.13 (m, 4H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 68.2, 60.5, 48.5, 35.0, 34.0, 33.2, 29.1, 8.0 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₂H₂₀IO, 307.0559; found 307.0557.



Tert-butyl 3-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)azetidine-1-carboxylate (14)

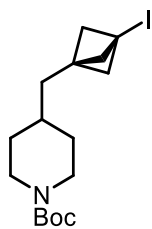
General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 60 mL of pentane at -40 °C. Yield: 11.25 g, 0.031 mol, 92%, white solid, m.p. = 96-97 °C. ¹H NMR (400 MHz, CDCl₃): δ 3.99 (t, *J* = 8.3 Hz, 2H), 3.50 (dd, *J* = 8.3, 5.7 Hz, 2H), 2.54 – 2.42 (m, 1H), 2.17 (s, 6H), 1.81 (d, *J* = 7.7 Hz, 2H), 1.42 (s, 9H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 156.4, 79.5, 60.6, 54.6, 46.9, 36.7, 28.5, 27.1, 6.9 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₄H₂₂INNaO₂, 386.0593; found 386.0591.



(±)-Tert-butyl 3-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)pyrrolidine-1-carboxylate (15)

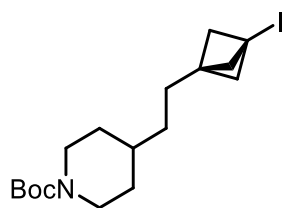
General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 70 mL of pentane at -40 °C. Yield: 9.43 g, 0.025 mol, 78%, white solid, m.p. = 53-54 °C. ¹H NMR (500 MHz, CDCl₃): δ 3.57 – 3.50 (m, 1H), 3.46 – 3.39 (m, 1H), 3.26 – 3.18 (m, 1H), 2.83 – 2.76 (m, 1H), 2.23 (s, 6H), 2.13 – 2.05 (m, 1H), 2.01 – 1.94 (m, 1H), 1.66 –

1.57 (m, 2H), 1.45 (s, 9H), 1.44 – 1.38 (m, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 154.6, 79.3, 61.1, 51.3 (br s), 47.8, 45.5 (br s), 37.4 (br s), 36.1, 32.4 (br s), 28.7, 7.2 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{24}\text{INNaO}_2$, 400.0749; found 400.0736.



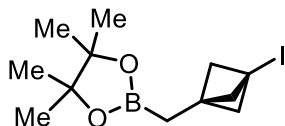
Tert-butyl 4-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)piperidine-1-carboxylate (16)

General protocol A-mod. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 10 mL of pentane at -40 °C. Yield: 0.90 g, 0.0023 mol, 77%, white solid, m.p. = 76-77 °C. ^1H NMR (400 MHz, CDCl_3): δ 4.03 (d, J = 13.2 Hz, 2H), 2.66 (t, J = 12.8 Hz, 2H), 2.23 (s, 6H), 1.61 (d, J = 12.8 Hz, 2H), 1.50 – 1.45 (m, 2H), 1.44 (s, 9H), 1.42 – 1.38 (m, 1H), 1.13 – 0.97 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 154.9, 79.4, 61.6, 47.6, 44.0, 39.0, 34.7, 32.6, 28.6, 7.5 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{26}\text{INNaO}_2$, 414.0906; found 414.0898.



Tert-butyl 4-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)ethyl)piperidine-1-carboxylate (17)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 4.25 g, 0.0105 mol, 71%, white solid, m.p. = 76-77 °C. ^1H NMR (400 MHz, CDCl_3): δ 4.05 (d, J = 13.0 Hz, 2H), 2.63 (t, J = 11.9 Hz, 2H), 2.17 (s, 6H), 1.59 (d, J = 13.5 Hz, 2H), 1.55 – 1.48 (m, 2H), 1.44 (s, 9H), 1.34 – 1.26 (m, 1H), 1.21 – 1.11 (m, 2H), 1.04 (ddd, J = 15.8, 12.6, 4.0 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 155.0, 79.4, 60.5, 48.5, 44.1, 36.0, 33.6, 32.2, 29.3, 28.6, 7.9 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{28}\text{INNaO}_2$, 428.1062; found 428.1057.

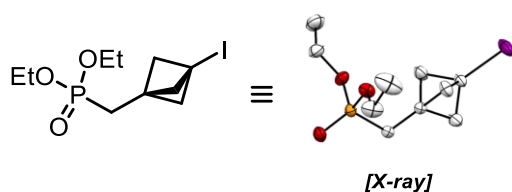


2-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 70 mL of pentane at -40 °C. Yield: 8.72 g, 0.0261 mol, 70%.

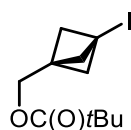
General protocol B, [BET₃]. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 4.34 g, 0.013 mol, 36%.

Yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 2.24 (s, 6H), 1.23 (s, 12H), 1.12 (s, 2H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 83.4, 62.6, 45.2, 25.0, 15.7 (br s), 7.7 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₂H₂₁BIO₂, 335.0679; found 335.0674.



Diethyl ((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)phosphonate (19)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 6.88 g, 0.02 mol, 55%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 4.14 – 3.99 (m, 4H), 2.35 (s, 6H), 2.04 (d, *J* = 18.6 Hz, 2H), 1.32 (t, *J* = 7.0 Hz, 6H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 61.9 (d, *J* = 7 Hz), 61.7 (d, *J* = 7 Hz), 41.8 (d, *J* = 8 Hz), 29.1 (d, *J* = 141 Hz), 16.6 (d, *J* = 6 Hz), 5.8 ppm. ³¹P{¹H} NMR (202 MHz, CDCl₃): δ 26.84 (s) ppm. LCMS (M + H)⁺: 345. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₀H₁₉IO₃P, 345.0116; found 345.0096.



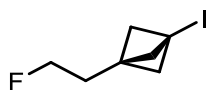
(3-Iodobicyclo[1.1.1]pentan-1-yl)methyl pivalate (20)

General protocol A-mod. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 10 mL of pentane at -40 °C. Yield: 1.00 g, 0.00325 mol, 80%, beige solid, m.p. < 30 °C. ¹H NMR (400 MHz, CDCl₃): δ 4.07 (s, 2H), 2.27 (s, 6H), 1.19 (s, 9H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 178.1, 63.0, 59.6, 46.1, 39.0, 27.4, 6.7 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₁H₁₈IO₂, 309.0351; found 309.0347.



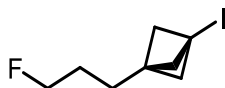
1-(Fluoromethyl)-3-iodobicyclo[1.1.1]pentane (21)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 10.40 g, 0.046 mol, 73%, white solid, m.p. < 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 4.33 (d, J = 47.3 Hz, 2H), 2.33 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 81.8 (d, J = 170 Hz), 59.1 (d, J = 4 Hz), 46.4 (d, J = 25 Hz), 6.9 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -220.9 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



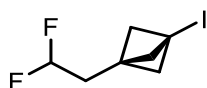
1-(2-Fluoroethyl)-3-iodobicyclo[1.1.1]pentane (22)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 80 mL of pentane at -40 °C. Yield: 11.04 g, 0.046 mol, 80%, white solid, m.p. < 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 4.43 (dt, J = 47.1, 5.8 Hz, 2H), 2.27 (s, 6H), 1.91 (dt, J = 26.9, 5.8 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 81.8 (d, J = 166.7 Hz), 61.0, 45.6, 32.8 (d, J = 20.1 Hz), 6.8 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -220.7 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



1-(3-Fluoropropyl)-3-iodobicyclo[1.1.1]pentane (23)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 60 mL of pentane at -40 °C. Yield: 10.67 g, 0.042 mol, 79%, colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 4.42 (dt, J = 47.4, 5.4 Hz, 2H), 2.21 (s, 6H), 1.84 – 1.56 (m, 4H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 83.6 (d, J = 165 Hz), 60.5, 48.0, 28.0 (d, J = 5 Hz), 27.9 (d, J = 20.0 Hz), 7.4 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -219.0 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



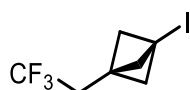
1-(2,2-Difluoroethyl)-3-iodobicyclo[1.1.1]pentane (24)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 100 mL of pentane at -40 °C. Yield: 12.36 g, 0.0479 mol, 92%.

General protocol B, [BEt₃]. The final product was purified by trituration in 60 mL of pentane at -40 °C. Yield: 9.03 g, 0.035 mol, 67%.

General protocol D, [Ir]. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 4.39 g, 0.017 mol, 34%.

Yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 5.77 (tt, *J* = 56.1, 4.4 Hz, 1H), 2.32 (s, 6H), 2.07 (td, *J* = 17.4, 4.4 Hz, 2H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 115.7 (t, *J* = 240 Hz), 61.2, 42.5 (t, *J* = 6 Hz), 36.4 (t, *J* = 22 Hz), 5.9 ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -116.7 (s) ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.

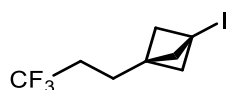


1-Iodo-3-(2,2,2-trifluoroethyl)bicyclo[1.1.1]pentane (25)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and trituated in 70 mL of pentane at -40 °C. Yield: 10.76 g, 0.039 mol, 82%.

General protocol B, [BEt₃]. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and trituated in 50 mL of pentane at -40 °C. Yield: 8.00 g, 0.029 mol, 62%.

Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 6H), 2.31 (q, *J* = 10.8 Hz, 2H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 125.8 (q, *J* = 277 Hz), 61.2, 41.5, 36.3 (q, *J* = 29 Hz), 4.9 ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -65.4 (s) ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.

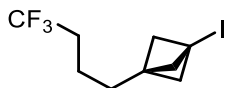


1-Iodo-3-(3,3,3-trifluoropropyl)bicyclo[1.1.1]pentane (26)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and trituated in 70 mL of pentane at -40 °C. Yield: 8.99 g, 0.031 mol, 69%.

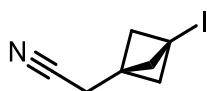
General protocol B, [BEt₃]. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and trituated in 60 mL of pentane at -40 °C. Yield: 7.54 g, 0.026 mol, 59%.

Yellow solid, m.p. = 40-41 °C. ¹H NMR (400 MHz, CDCl₃): δ 2.22 (s, 6H), 2.08 – 1.95 (m, 2H), 1.84 – 1.74 (m, 2H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 126.8 (q, *J* = 276 Hz), 60.1, 46.8, 31.3 (q, *J* = 29 Hz), 24.8, 6.0 ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -65.4 (s) ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



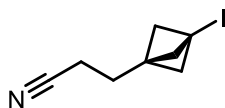
1-Iodo-3-(4,4,4-trifluorobutyl)bicyclo[1.1.1]pentane (27)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 8.12 g, 0.0267 mol, 89%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 2.21 (s, 6H), 2.14 – 1.98 (m, 2H), 1.64 – 1.47 (m, 4H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 127.1 (q, J = 276 Hz), 60.4, 47.9, 33.7 (q, J = 29 Hz), 31.3, 19.5 (q, J = 3 Hz), 7.1 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -66.9 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{13}\text{F}_3\text{I}$, 305.0014; found 304.9954.



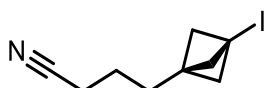
2-(3-Iodobicyclo[1.1.1]pentan-1-yl)acetonitrile (28)

General protocol A. The reaction mixture was concentrated and triturated in 50 mL of Et_2O . The filtrate was concentrated and triturated again in 50 mL of cold pentane at -40 °C. The precipitate was separated by filtration and dried *in vacuo*. Yield: 5.57 g, 0.0239 mol, 80%, yellow solid, m.p. < 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 2.62 (s, 3H), 2.35 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 116.4, 60.2, 42.0, 21.7, 3.5 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_7\text{H}_8\text{INNa}$, 255.9599; found 255.9602.



3-(3-Iodobicyclo[1.1.1]pentan-1-yl)propanenitrile (29)

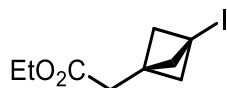
General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 5.12 g, 0.021 mol, 75%, yellow solid, m.p. < 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 2.31 (t, J = 7.2 Hz, 2H), 2.28 (s, 6H), 1.90 (t, J = 7.2 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 119.1, 60.1, 46.9, 27.9, 14.8, 5.5 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{11}\text{IN}$, 247.9936; found 247.9931.



4-(3-Iodobicyclo[1.1.1]pentan-1-yl)butanenitrile (30)

General protocol A. The reaction mixture was concentrated and triturated in 50 mL of Et_2O . Yield 5.10 g, 0.0195 mol, 76%, yellow solid, m.p. < 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 2.34 (t, J = 6.7 Hz, 2H), 2.21 (s, 6H), 1.74 – 1.54 (m, 4H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 119.3, 60.4,

47.5, 31.2, 22.9, 17.2, 6.6 ppm. HRMS (ESI-TOF) m/z : $[M + NH_4]^+$ calcd for $C_9H_{16}IN_2$, 279.0358; found 279.0354.

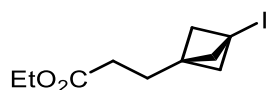


Ethyl 2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetate (31)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 60 mL of pentane at -40 °C. Yield: 8.40 g, 0.03 mol, 68%.

General protocol B, [BEt₃]. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 3.95 g, 0.0141 mol, 47%.

Olive oil. ¹H NMR (400 MHz, CDCl₃): δ 4.12 (q, J = 7.1 Hz, 2H), 2.53 (s, 2H), 2.31 (s, 6H), 1.25 (t, J = 7.1 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 170.4, 61.1, 60.7, 43.8, 37.6, 14.4, 6.1 ppm. HRMS (ESI-TOF) m/z : $[M + NH_4]^+$ calcd for $C_9H_{17}INO_2$, 298.0304; found 298.0298.

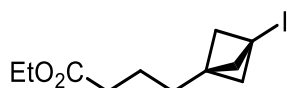


Ethyl 3-(3-iodobicyclo[1.1.1]pentan-1-yl)propanoate (32)

General protocol A-mod. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 20 mL of pentane at -40 °C. Yield: 1.47 g, 0.005 mol, 61%.

General protocol B, [BEt₃]. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 10 mL of pentane at -40 °C. Yield: 0.53 g, 0.0018 mol, 41%.

Brown oil. ¹H NMR (400 MHz, CDCl₃): δ 4.11 (q, J = 7.1 Hz, 2H), 2.25 (t, J = 7.5 Hz, 2H), 2.18 (s, 6H), 1.86 (t, J = 7.5 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 172.9, 60.6, 60.3, 47.7, 31.6, 27.4, 14.3, 6.9 ppm. HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{10}H_{16}IO_2$, 295.0195; found 295.0183.



Ethyl 4-(3-iodobicyclo[1.1.1]pentan-1-yl)butanoate (33)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 7.48 g, 0.0243 mol, 81%, yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 4.11 (q, J = 7.1 Hz, 2H), 2.26 (t, J = 6.7 Hz, 2H), 2.20 (s, 6H), 1.65 – 1.48 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 173.4, 60.6, 60.5, 48.2, 34.1, 31.7, 22.3, 14.4, 7.7 ppm. HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{11}H_{18}IO_2$, 309.0351; found 309.0343.



1-(Chloromethyl)-3-iodobicyclo[1.1.1]pentane (34)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 8.71 g, 0.036 mol, 90%.

General protocol B, [BEt₃]. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 5.30 g, 0.0219 mol, 73%.

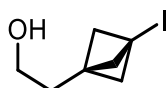
General protocol D, [Ir]. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 4.65 g, 0.0192 mol, 64%.

Green solid, m.p. = 47-48 °C. ¹H NMR (400 MHz, CDCl₃): δ 3.53 (s, 2H), 2.30 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 59.4, 47.3, 44.1, 6.1 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



1-(Bromomethyl)-3-iodobicyclo[1.1.1]pentane (35)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 5.26 g, 0.0184 mol, 81%, yellow solid, m.p. < 30 °C. ¹H NMR (500 MHz, CDCl₃): δ 3.40 (s, 2H), 2.29 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 59.7, 47.2, 32.2, 5.6 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.

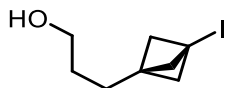


2-(3-Iodobicyclo[1.1.1]pentan-1-yl)ethan-1-ol (36)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 40 mL of pentane at -40 °C. Yield: 5.00 g, 0.021 mol, 70%.

General protocol B, [BEt₃]. The final product was purified by trituration in 30 mL of pentane at -40 °C. Yield: 3.00 g, 0.0126 mol, 42%.

White solid, m.p. < 30 °C. ¹H NMR (400 MHz, CDCl₃): δ 3.63 (t, *J* = 6.5 Hz, 2H), 2.25 (s, 6H), 1.78 (t, *J* = 6.5 Hz, 2H), 1.32 (br s, 1H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 61.1, 60.9, 46.3, 34.9, 7.3 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₇H₁₂IO, 238.9933; found 238.9915.

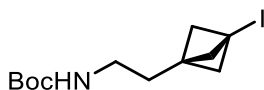


3-(3-Iodobicyclo[1.1.1]pentan-1-yl)propan-1-ol (37)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 70 mL of pentane at -40 °C. Yield: 9.45 g, 0.0375 mol, 75%.

General protocol B, [BEt₃]. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 5.70 g, 0.0226 mol, 39%.

Yellow solid, m.p. = 42-43 °C. ¹H NMR (400 MHz, CDCl₃): δ 3.61 (t, *J* = 6.3 Hz, 2H), 2.20 (s, 6H), 1.63 – 1.46 (m, 4H), 1.39 (s, 1H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 62.6, 60.6, 48.2, 30.0, 28.5, 7.7 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₈H₁₄IO, 253.0089; found 253.0073.

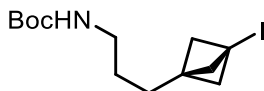


Tert-butyl (2-(3-iodobicyclo[1.1.1]pentan-1-yl)ethyl)carbamate (38)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 70 mL of pentane at -40 °C. Yield: 9.94 g, 0.0295 mol, 80%.

General protocol B, [BEt₃]. The final product was purified by trituration in 60 mL of pentane at -40 °C. Yield: 8.01 g, 0.024 mol, 65%.

White solid, m.p. = 87-88 °C. ¹H NMR (400 MHz, CDCl₃): δ 4.44 (br s, 1H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.23 (s, 6H), 1.70 (t, *J* = 7.2 Hz, 2H), 1.43 (s, 9H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 155.9, 79.5, 60.8, 46.6, 38.5, 32.4, 28.6, 7.0 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₂H₂₀INNaO₂, 360.0436; found 360.0418.

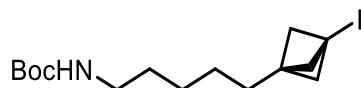


Tert-butyl (3-(3-iodobicyclo[1.1.1]pentan-1-yl)propyl)carbamate (39)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 70 mL of pentane at -40 °C. Yield: 9.97 g, 0.0284 mol, 81%.

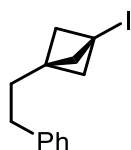
General protocol B, [BEt₃]. The final product was purified by trituration in 60 mL of pentane at -40 °C. Yield: 6.11 g, 0.0174 mol, 58%.

White solid, m.p. = 100-101 °C. ¹H NMR (400 MHz, CDCl₃): δ 4.50 (br s, 1H), 3.08 (t, *J* = 6.0 Hz, 2H), 2.18 (s, 6H), 1.57 – 1.46 (m, 2H), 1.43 (s, 9H), 1.46 – 1.34 (m, 2H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 156.0, 79.4, 60.5, 48.1, 40.4, 29.5, 28.6, 27.6, 7.6 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₃H₂₂INNaO₂, 374.0593; found 374.0581.



Tert-butyl (5-(3-iodobicyclo[1.1.1]pentan-1-yl)pentyl)carbamate (40)

General protocol A-mod. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 5 mL of pentane at -40 °C. Yield: 0.11 g, 0.00028 mol, 88%, yellow solid, m.p. = 62-63 °C. ^1H NMR (400 MHz, CDCl_3): δ 4.49 (br s, 1H), 3.13 – 3.01 (m, 2H), 2.17 (s, 6H), 1.51 – 1.40 (m, 4H), 1.43 (s, 9H), 1.30 – 1.21 (m, 4H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 156.1, 79.2, 60.7, 48.5, 40.6, 32.1, 30.1, 28.6, 26.8, 26.6, 8.1 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{26}\text{INNaO}_2$, 402.0906; found 402.0905.

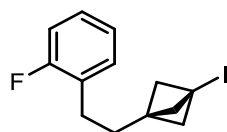


1-Iodo-3-phenethylbicyclo[1.1.1]pentane (41)

General protocol A-1. The reaction mixture was concentrated and triturated in 60 mL of pentane at -40 °C. Yield: 8.85 g, 0.0297 mol, 69%.

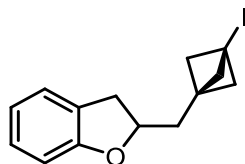
General protocol B, $[\text{BEt}_3]$. The final product was purified by trituration in 60 mL of pentane at -40 °C. Yield: 8.05 g, 0.027 mol, 63%.

Yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 7.33 – 7.12 (m, 5H), 2.60 (t, J = 7.9 Hz, 2H), 2.21 (s, 6H), 1.87 (t, J = 7.9 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 141.5, 128.5, 128.3, 126.1, 60.6, 48.4, 33.6, 33.2, 7.8 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{13}\text{H}_{19}\text{IN}$, 316.0562; found 316.0549.



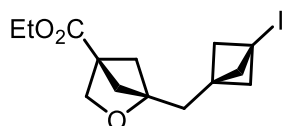
1-(2-Fluorophenethyl)-3-iodobicyclo[1.1.1]pentane (42)

General protocol A-mod. The reaction mixture was concentrated and triturated in 10 mL of pentane at -40 °C. Yield: 0.17 g, 0.000538 mol, 62%, yellow solid, m.p. = 40-41 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.22 – 7.11 (m, 2H), 7.08 – 6.95 (m, 2H), 2.64 – 2.54 (t, J = 7.8 Hz, 2H), 2.20 (s, 6H), 1.89 – 1.80 (t, J = 7.8 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 161.2 (d, J = 244.6 Hz), 130.5 (d, J = 5.0 Hz), 128.3 (d, J = 15.7 Hz), 127.9 (d, J = 8.1 Hz), 124.1 (d, J = 3.5 Hz), 115.4 (d, J = 22.2 Hz), 60.6, 48.3, 32.3, 26.4 (d, J = 2.3 Hz), 7.7 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -119.3 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{13}\text{H}_{18}\text{FIN}$, 334.0468; found 334.0476.



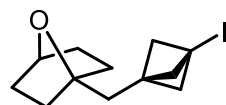
(±)-2-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)-2,3-dihydrobenzofuran (43)

General protocol A-mod. The reaction mixture was concentrated and triturated in 20 mL of pentane at -40 °C. Yield: 0.30 g, 0.00092 mol, 42%, brown solid, m.p. = 62-63 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.14 (d, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.82 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 4.78 – 4.67 (m, 1H), 3.28 (dd, *J* = 15.4, 9.1 Hz, 1H), 2.80 (dd, *J* = 15.4, 7.6 Hz, 1H), 2.32 (s, 6H), 2.07 (dd, *J* = 14.4, 7.4 Hz, 1H), 1.88 (dd, *J* = 14.4, 5.4 Hz, 1H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 159.4, 128.2, 126.5, 125.1, 120.5, 109.5, 81.2, 61.4, 45.8, 38.2, 35.8, 7.4 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₄H₁₆IO, 327.0246; found 327.0240.



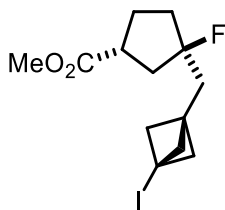
Ethyl 1-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)-2-oxabicyclo[2.1.1]hexane-4-carboxylate (44)

General protocol A-mod. The reaction mixture was concentrated and triturated in 20 mL of pentane at -40 °C. Yield: 0.38 g, 0.00105 mol, 63%, white solid, m.p. < 30 °C. ¹H NMR (400 MHz, CDCl₃): δ 4.18 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 2H), 2.29 (s, 6H), 2.00 (s, 2H), 1.99 – 1.94 (m, 2H), 1.82 (dd, *J* = 4.5, 1.4 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 170.2, 86.7, 69.9, 61.8, 60.9, 50.9, 45.6, 45.3, 34.4, 14.3, 7.1 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₄H₂₀IO₃, 363.0457; found 363.0461.



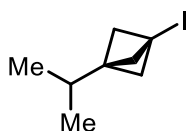
1-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)-7-oxabicyclo[2.2.1]heptane (46)

General protocol A-mod. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 20 mL of pentane at -40 °C. Yield: 0.72 g, 0.00235 mol, 56%, white solid, m.p. = 90-91 °C. ¹H NMR (400 MHz, CDCl₃): δ 4.45 (t, *J* = 5.2 Hz, 1H), 2.29 (s, 6H), 2.10 (s, 2H), 1.88 – 1.73 (m, 2H), 1.61 – 1.48 (m, 4H), 1.46 – 1.34 (m, 2H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 85.3, 75.8, 62.1, 46.1, 38.1, 34.6, 31.7, 7.3 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₂H₁₈IO₃, 305.0402; found 305.0392.



(±)-Methyl-3-fluoro-3-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)cyclopentane-1-carboxylate (47)

General protocol A-mod. The reaction mixture was concentrated and triturated in 10 mL of pentane at -40 °C, filtered, and dried. Yield: 0.50 g, 0.00143 mol, 41%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 3.67 (s, 3H), 3.06 (p, J = 7.4 Hz, 1H), 2.32 (d, J = 5.9 Hz, 6H), 2.28 – 2.06 (m, 3H), 2.03 (s, 1H), 1.97 (s, 1H), 1.92 – 1.69 (m, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 176.3, 105.6 (d, J = 175 Hz), 62.2, 52.0, 45.4 (d, J = 3 Hz), 42.0, 41.5 (d, J = 24 Hz), 40.1 (d, J = 24 Hz), 37.1 (d, J = 24 Hz), 28.0, 7.0 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -145.7 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{19}\text{FIO}_2$, 353.0414; found 353.0403.

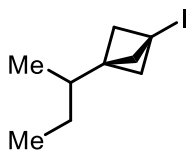


1-Iodo-3-isopropylbicyclo[1.1.1]pentane (48)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 70 mL of pentane at -40 °C. Yield: 11.56 g, 0.049 mol, 83%.

General protocol B, $[\text{BEt}_3]$. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 5.69 g, 0.0241 mol, 41%.

Yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 2.14 (s, 6H), 1.78 (sept, J = 6.8 Hz, 1H), 0.82 (d, J = 6.8 Hz, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 58.6, 53.4, 30.1, 19.3, 8.9 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



(±)-1-(sec-Butyl)-3-iodobicyclo[1.1.1]pentane (49)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 4.95 g, 0.0198 mol, 79%, yellow oil. ^1H NMR (500 MHz, CDCl_3): δ 2.17 (s, 6H), 1.56 – 1.47 (m, 1H), 1.42 – 1.33 (m, 1H), 1.07 – 0.93 (m, 1H), 0.86 (t, J = 7.4 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3):

δ 59.0, 53.1, 36.8, 26.7, 16.0, 12.1, 9.0 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



1-Cyclopropyl-3-iodobicyclo[1.1.1]pentane (50)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 60 mL of pentane at -40 °C. Yield: 10.31 g, 0.044 mol, 74%.

General protocol B, [BEt₃]. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 40 mL of pentane at -40 °C. Yield: 4.68 g, 0.02 mol, 34%.

White solid, m.p. < 30 °C. ¹H NMR (400 MHz, CDCl₃): δ 2.11 (s, 6H), 0.96 – 0.85 (m, 1H), 0.38 (q, J = 4.5 Hz, 2H), 0.11 (q, J = 4.5 Hz, 2H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 59.9, 49.8, 12.0, 7.9, 2.7 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.

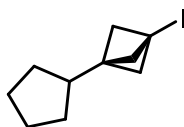


1-Cyclobutyl-3-iodobicyclo[1.1.1]pentane (51)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 40 mL of pentane at -40 °C. Yield: 5.46 g, 0.022 mol, 81%.

General protocol B, [BEt₃]. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 30 mL of pentane at -40 °C. Yield: 2.55 g, 0.01 mol, 58%.

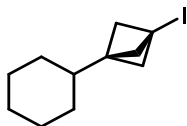
White solid, m.p. < 30 °C. ¹H NMR (500 MHz, CDCl₃): δ 2.48 – 2.37 (m, 1H), 2.18 (s, 6H), 1.99 – 1.90 (m, 2H), 1.88 – 1.77 (m, 1H), 1.76 – 1.61 (m, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 58.9, 51.4, 36.8, 25.0, 18.0, 9.3 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



1-Cyclopentyl-3-iodobicyclo[1.1.1]pentane (52)

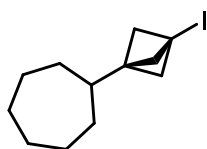
General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 8.69 g, 0.033 mol, 65%, colorless oil.

¹H NMR (400 MHz, CDCl₃): δ 2.15 (s, 6H), 2.04 – 1.94 (m, 1H), 1.66 – 1.44 (m, 6H), 1.27 – 1.12 (m, 2H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 59.4, 51.4, 41.3, 29.5, 25.6, 9.2 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



1-Cyclohexyl-3-iodobicyclo[1.1.1]pentane (53)

General protocol A. The reaction mixture was concentrated and triturated in 50 mL of Et₂O. The filtrate was concentrated and distilled under reduced pressure (b.p. = 80-81 °C, 1 mmHg). Yield: 5.80 g, 0.021 mol, 88%, olive oil. ¹H NMR (400 MHz, CDCl₃): δ 2.15 (s, 6H), 1.75 – 1.56 (m, 5H), 1.41 (tt, *J* = 11.7, 3.4 Hz, 1H), 1.24 – 1.03 (m, 3H), 0.84 (qd, *J* = 12.4, 2.9 Hz, 2H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 58.9, 52.6, 39.5, 29.8, 26.1, 26.0, 9.2 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.

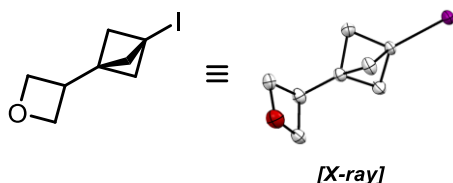


1-Cycloheptyl-3-iodobicyclo[1.1.1]pentane (54)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 60 mL of pentane at -40 °C. Yield: 10.73 g, 0.037 mol, 83%.

General protocol B, [BEt₃]. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 4.93 g, 0.017 mol, 76%.

Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 2.15 (s, 6H), 1.65 – 1.53 (m, 7H), 1.48 – 1.41 (m, 2H), 1.40 – 1.34 (m, 2H), 1.14 – 1.07 (m, 2H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 59.0, 53.2, 41.4, 31.3, 28.5, 26.3, 9.4 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



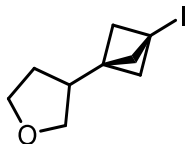
3-(3-Iodobicyclo[1.1.1]pentan-1-yl)oxetane (55)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 60 mL of pentane at -40 °C. Yield: 10.75 g, 0.043 mol, 80%.

General protocol B, [BEt₃]. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 60 mL of pentane at -30 °C. Yield: 12.50 g, 0.05 mol, 93%.

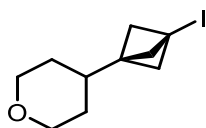
General protocol D, [Ir]. The final product was purified by trituration in 50 mL of pentane at -40 °C. Yield: 10.25 g, 0.041 mol, 76%.

White solid, m.p. < 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 4.70 (dd, J = 7.8, 6.1 Hz, 2H), 4.37 (t, J = 6.0 Hz, 2H), 3.15 – 3.06 (m, 1H), 2.29 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 74.1, 58.6, 48.5, 36.4, 7.3 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{12}\text{IO}$, 250.9933; found 250.9929.



(±)-3-(3-Iodobicyclo[1.1.1]pentan-1-yl)tetrahydrofuran (56)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 40 mL of pentane at -40 °C. Yield: 3.96 g, 0.015 mol, 30%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 3.86 – 3.65 (m, 3H), 3.48 (dd, J = 8.5, 6.0 Hz, 1H), 2.44 – 2.31 (m, 1H), 2.20 (s, 6H), 1.99 – 1.84 (m, 1H), 1.64 – 1.51 (m, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 70.4, 68.2, 59.2, 49.2, 40.7, 29.5, 7.6 ppm.

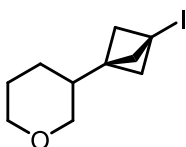


4-(3-Iodobicyclo[1.1.1]pentan-1-yl)tetrahydro-2H-pyran (57)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 70 mL of pentane at -40 °C. Yield: 11.68 g, 0.042 mol, 90%.

General protocol B, [BEt₃]. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 70 mL of pentane at -40 °C. Yield: 11.12 g, 0.04 mol, 85%.

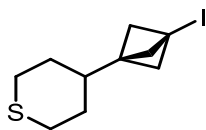
White solid, m.p. = 72-73 °C. ^1H NMR (400 MHz, CDCl_3): δ 3.95 (dd, J = 11.2, 3.9 Hz, 2H), 3.31 (t, J = 11.2 Hz, 2H), 2.17 (s, 6H), 1.72 – 1.62 (m, 1H), 1.46 (d, J = 12.5 Hz, 2H), 1.25 (qd, J = 12.5, 4.4 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 67.7, 58.4, 51.6, 36.8, 29.5, 8.1 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{16}\text{IO}$, 279.0246; found 279.0240.



(±)-3-(3-Iodobicyclo[1.1.1]pentan-1-yl)tetrahydro-2H-pyran (58)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 60 mL of pentane at -40 °C. Yield: 8.34 g, 0.03 mol, 65%, brown solid, m.p. > 30 °C. ^1H NMR (500 MHz, CDCl_3): δ 3.85 (d, J = 11.4 Hz, 1H), 3.82 – 3.74 (m, 1H), 3.30 –

3.22 (m, 1H), 3.01 (t, $J = 10.7$ Hz, 1H), 2.18 (s, 6H), 1.81 – 1.70 (m, 2H), 1.62 – 1.53 (m, 2H), 1.20 – 1.09 (m, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 70.4, 68.1, 59.1, 49.3, 37.6, 26.8, 25.5, 7.8 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{16}\text{IO}$, 279.0246; found 279.0235.

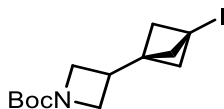


4-(3-Iodobicyclo[1.1.1]pentan-1-yl)tetrahydro-2H-thiopyran (59)

General protocol A. The reaction mixture was concentrated in *vacuo* and filtered from 100 mL of hexane. Yield: 10.88 g, 0.037 mol, 85%.

General protocol B, $[\text{BEt}_3]$. The reaction mixture was concentrated in *vacuo* and filtered from 100 mL of hexane. Yield: 9.41 g, 0.032 mol, 73%.

White solid, m.p. > 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 2.68 – 2.55 (m, 4H), 2.16 (s, 6H), 1.94 – 1.87 (m, 2H), 1.50 – 1.41 (m, 1H), 1.34 – 1.20 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 58.5, 52.2, 39.0, 30.7, 28.5, 7.9 ppm. GCMS (M^+): 294. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{16}\text{IS}$, 295.0017; found 295.0009.



Tert-butyl 3-(3-iodobicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (60)

General protocol A. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by column chromatography (SiO_2 , gradient, hexane/ MeOtBu – 100% to 80:20, $R_f = 0.65$, hexane/ MeOtBu , 3:2). Yield: 11.34 g, 0.0325 mol, 92%.

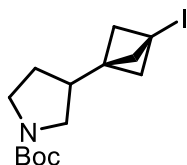
General protocol A (with a solution of propellane in MeOtBu , 0.6M, 71 mL, 0.0424 mol, 1.20 equiv). The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by column chromatography (SiO_2 , gradient, hexane/ MeOtBu – 100% to 80:20). Yield: 10.12 g, 0.029 mol, 83% yield.

General protocol B, $[\text{BEt}_3]$. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by column chromatography (SiO_2 , gradient, hexane/ MeOtBu – 100% to 80:20). Yield: 10.10 g, 0.0289 mol, 82%.

General protocol C, $[\text{MeLi}]$. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by column chromatography (SiO_2 , gradient, hexane/ MeOtBu – 100% to 80:20). Yield: 3.49 g, 0.01 mol, 30%.

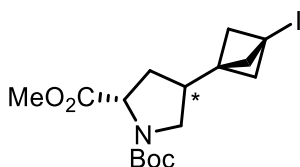
General protocol D, [Ir]. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by column chromatography (SiO₂, gradient, hexane/MeOtBu – 100% to 80:20). Yield: 10.47 g, 0.030 mol, 84%.

White solid, m.p. < 30 °C. ¹H NMR (400 MHz, CDCl₃): δ 3.90 (t, *J* = 8.5 Hz, 2H), 3.57 (dd, *J* = 8.5, 5.3 Hz, 2H), 2.70 – 2.55 (m, 1H), 2.24 (s, 6H), 1.42 (s, 9H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 156.5, 79.7, 58.4, 51.5, 49.1, 30.0, 28.5, 7.1 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₃H₂₀INNaO₂, 372.0436; found 372.0420.



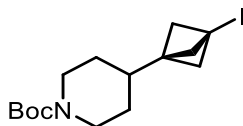
(±)-*Tert*-butyl 3-(3-iodobicyclo[1.1.1]pentan-1-yl)pyrrolidine-1-carboxylate (61)

General protocol A. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by column chromatography (SiO₂, gradient, hexane/MeOtBu – 100% to 80:20, *R_f* = 0.65, hexane/MeOtBu, 3:2). Yield: 9.80 g, 0.027 mol, 82%, white solid, m.p. < 30 °C. ¹H NMR (400 MHz, CDCl₃): δ 3.45 – 3.31 (m, 2H), 3.29 – 3.19 (m, 1H), 3.00 (dd, *J* = 10.4, 7.7 Hz, 1H), 2.38 – 2.24 (m, 1H), 2.20 (s, 6H), 1.92 – 1.78 (m, 1H), 1.63 – 1.56 (m, 1H), 1.45 (s, 9H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 154.6, 79.4, 59.2, 49.1, 48.5, 45.5, 40.0, 28.7, 6.9 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₄H₂₂INNaO₂, 386.0593; found 386.0581.



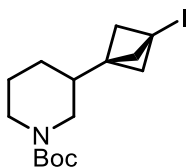
1-(*Tert*-butyl) 2-methyl-4-(3-iodobicyclo[1.1.1]pentan-1-yl)pyrrolidine-1,2-dicarboxylate (62)

General protocol A. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by column chromatography (SiO₂, gradient, hexane/MeOtBu – 100% to 80:20, *R_f* = 0.56, hexane/MeOtBu, 3:2). Yield: 9.47 g, 0.0225 mol, 80%, white solid, m.p. = 104-105 °C, d.r. = 3:2. ¹H NMR (500 MHz, CDCl₃): δ 4.25 (t, *J* = 8.3 Hz) and 4.19 (t, *J* = 7.6 Hz) 1H, 3.74 (s) and 3.73 (s) 3H, 3.67 (t, *J* = 8.0 Hz) and 3.57 (t, *J* = 8.0 Hz) 1H, 3.10 – 2.96 (m, 1H), 2.39 – 2.24 (m, 2H), 2.19 (s, 6H), 1.67 – 1.51 (m, 2H), 1.45 (s) and 1.39 (s) 9H ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 173.4, 173.2, 154.2, 153.6, 80.4, 59.5, 59.1, 52.4, 52.2, 49.4, 49.1, 47.99, 47.95, 40.1, 39.4, 34.4, 33.4, 28.5, 28.4, 6.5, 6.4 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₆H₂₄INNaO₄, 444.0648; found 444.0627.



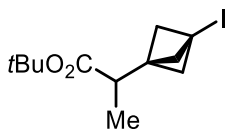
***Tert*-butyl 4-(3-iodobicyclo[1.1.1]pentan-1-yl)piperidine-1-carboxylate (63)**

General protocol A. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by column chromatography (SiO₂, gradient, hexane/MeOtBu – 100% to 80:20, R_f = 0.41, hexane/MeOtBu, 4:1). Yield: 10.56 g, 0.028 mol, 88%, white solid, m.p. < 30 °C. ¹H NMR (400 MHz, CDCl₃): δ 4.11 (d, *J* = 13.0 Hz, 2H), 2.60 (t, *J* = 13.0 Hz, 2H), 2.15 (s, 6H), 1.63 – 1.48 (m, 3H), 1.44 (s, 9H), 1.05 (qd, *J* = 12.4, 4.1 Hz, 2H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 154.9, 79.6, 58.6, 51.6, 43.6, 37.9, 28.8, 28.6, 7.9 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₅H₂₄INNaO₂, 400.0749; found 400.0743.



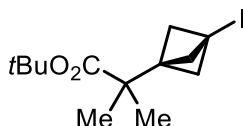
(±)-*Tert*-butyl 3-(3-iodobicyclo[1.1.1]pentan-1-yl)piperidine-1-carboxylate (64)

General protocol A. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by column chromatography (SiO₂, gradient, hexane/MeOtBu – 100% to 80:20, R_f = 0.45, hexane/MeOtBu, 4:1). Yield: 9.05 g, 0.024 mol, 74%, white solid, m.p. = 89-90 °C. ¹H NMR (500 MHz, CDCl₃): δ 3.91 (d, *J* = 13.0 Hz, 2H), 2.65 (td, *J* = 13.0, 2.8 Hz, 1H), 2.37 (br s, 1H), 2.19 (s, 2H), 1.72 – 1.58 (m, 3H), 1.44 (s, 9H), 1.40 – 1.32 (m, 1H), 1.11 – 1.00 (m, 1H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 154.9, 79.7, 59.0, 50.1, 46.7, 44.2, 37.3, 28.6, 27.8, 24.7, 7.4 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₅H₂₄INNaO₂, 400.0749; found 400.0736.



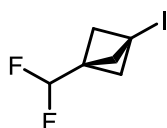
(±)-*Tert*-butyl 2-(3-iodobicyclo[1.1.1]pentan-1-yl)propanoate (65)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 40 mL of pentane at -40 °C. Yield: 3.16 g, 0.0098 mol, 25%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 2.53 (q, *J* = 7.0 Hz, 1H), 2.24 (s, 6H), 1.44 (s, 9H), 1.03 (d, *J* = 7.0 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 172.5, 80.8, 59.5, 48.8, 42.5, 28.3, 13.9, 6.6 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



Tert-butyl 2-(3-iodobicyclo[1.1.1]pentan-1-yl)-2-methylpropanoate (66)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 5.20 g, 0.0154 mol, 36%, brown oil. ^1H NMR (500 MHz, CDCl_3): δ 2.22 (s, 6H), 1.44 (s, 9H), 1.07 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 174.3, 80.7, 58.4, 56.5, 53.0, 44.3, 28.2, 22.4, 7.0 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.

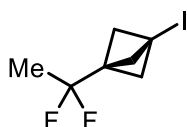


1-(Difluoromethyl)-3-iodobicyclo[1.1.1]pentane (67)

General protocol A. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and triturated in 100 mL of pentane at -40 °C. Yield: 12.20 g, 0.05 mol, 89%.

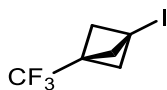
General protocol B, [BEt_3]. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and triturated in 100 mL of pentane at -40 °C. Yield: 9.52 g, 0.039 mol, 69%.

White solid, m.p. = 63-64 °C. ^1H NMR (400 MHz, CDCl_3): δ 5.65 (t, J = 56.2 Hz, 1H), 2.40 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 111.8 (t, J = 242 Hz), 57.6 (t, J = 3 Hz), 46.42 (t, J = 29 Hz), 5.3 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -121.2 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



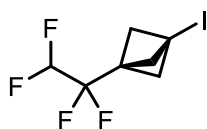
1-(1,1-Difluoroethyl)-3-iodobicyclo[1.1.1]pentane (68)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in 100 mL of pentane at -40 °C. Yield: 13.42 g, 0.052 mol, 80%, white solid, m.p. = 58-59 °C. ^1H NMR (400 MHz, CDCl_3): δ 2.37 (s, 6H), 1.52 (t, J = 18.0 Hz, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 119.5 (t, J = 240 Hz), 57.9 (t, J = 3.1 Hz), 49.1 (t, J = 35 Hz), 21.0 (t, J = 28 Hz), 4.9 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -96.8 (s) ppm. GCMS (M) $^+$: 258. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



1-Iodo-3-(trifluoromethyl)bicyclo[1.1.1]pentane (69)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg), dried from CH₂(OEt)₂ (20 °C, water bath, 10 mmHg), and triturated in 100 mL of pentane at -40 °C. Yield: 12.42 g, 0.0474 mol, 93%, white solid, m.p. < 30 °C. ¹H NMR (400 MHz, CDCl₃): δ 2.47 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 121.3 (q, *J* = 277 Hz), 57.7 (q, *J* = 2 Hz), 45.1 (q, *J* = 40 Hz), 2.9 (q, *J* = 2 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -72.2 (s) ppm. GCMS (M)⁺: 262. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.

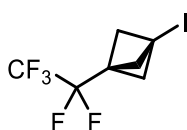


1-Iodo-3-(1,1,2,2-tetrafluoroethyl)bicyclo[1.1.1]pentane (70)

General protocol A. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and triturated in 70 mL of pentane at -40 °C. Yield: 10.29 g, 0.035 mol, 80%.

General protocol B, [BEt₃]. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and triturated in 70 mL of pentane at -40 °C. Yield: 8.53 g, 0.029 mol, 67%.

Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 5.85 – 5.59 (m, 1H), 2.50 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 122.0, 109.6 (tt, *J* = 250.2, 41.2 Hz), 58.3 (t, *J* = 2.8 Hz), 44.3 (t, *J* = 31.2 Hz), 3.9 ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -117.7, -134.4 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



1-Iodo-3-(perfluoroethyl)bicyclo[1.1.1]pentane (71)

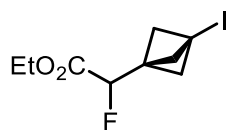
General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 100 mL of pentane at -40 °C. Yield: 11.42 g, 0.0366 mol, 90%.

General protocol B, [BEt₃]. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 6.24 g, 0.02 mol, 50%.

General protocol D, [Ir]. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 6.21 g, 0.02 mol, 49%.

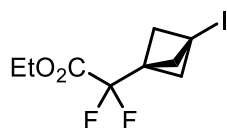
Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 2.50 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 119.0 (qt, *J* = 286.1, 36.5 Hz), 110.3 (tq, *J* = 253.5, 38.1 Hz), 58.1, 44.2 (t, *J* = 30.7 Hz), 2.7 ppm.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -83.3 (s), -119.5 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



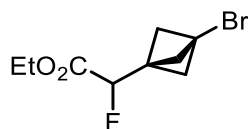
Ethyl 2-fluoro-2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetate (72)

General protocol A. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and triturated in 70 mL of pentane at -40 °C. Yield: 11.32 g, 0.038 mol, 88%, colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 4.81 (d, J = 49.0 Hz, 1H), 4.33 – 4.21 (m, 2H), 2.37 (s, 6H), 1.31 (t, J = 7.1 Hz, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 167.1 (d, J = 24.4 Hz), 86.5 (d, J = 188.0 Hz), 61.9, 58.9 (d, J = 3.6 Hz), 45.9 (d, J = 27.1 Hz), 14.4, 5.00 (d, J = 2.0 Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -191.9 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{13}\text{FIO}_2$, 298.9944; found 298.9937.



Ethyl 2,2-difluoro-2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetate (73)

General protocol A. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 5.75 g, 0.0182 mol, 91%, white solid, m.p. < 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 4.33 (q, J = 7.1 Hz, 2H), 2.43 (s, 6H), 1.35 (t, J = 7.1 Hz, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 162.6 (t, J = 32.8 Hz), 110.7 (t, J = 252.2 Hz), 63.2, 58.0 (t, J = 2.9 Hz), 46.4 (t, J = 32.7 Hz), 14.2, 3.8 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -109.6 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{12}\text{F}_2\text{IO}_2$, 316.9850; found 316.9832.



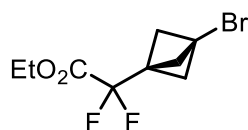
(±)-Ethyl 2-(3-bromobicyclo[1.1.1]pentan-1-yl)-2-fluoroacetate (74)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 5.42 g, 0.0216 mol, 40%.

General protocol B, $[\text{BEt}_3]$. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 4.34 g, 0.0173 mol, 32%.

Colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 4.88 (d, J = 49.0 Hz, 1H), 4.40 – 4.20 (m, 2H), 2.29 (s, 6H), 1.31 (t, J = 7.1 Hz, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 167.2 (d, J = 24.4 Hz),

86.4 (d, $J = 187.6$ Hz), 61.9, 57.3 (d, $J = 3.5$ Hz), 39.7 (d, $J = 27.1$ Hz), 36.0 (d, $J = 2.0$ Hz), 14.4 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -191.8 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{13}\text{BrFO}_2$, 251.0083; found 251.0064.



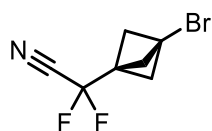
Ethyl 2-(3-bromobicyclo[1.1.1]pentan-1-yl)-2,2-difluoroacetate (75)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 100 mL of pentane at -40 °C. Yield: 10.60 g, 0.0394 mol, 80%.

General protocol B, $[\text{BEt}_3]$. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 100 mL of pentane at -40 °C. Yield: 9.15 g, 0.034 mol, 69%.

General protocol D, $[\text{Ir}]$. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 100 mL of pentane at -40 °C. Yield: 8.88 g, 0.033 mol, 68%.

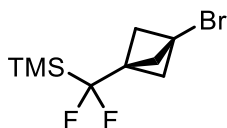
Beige solid, m.p. < 30 °C. ^1H NMR (400 MHz, CDCl_3): δ 4.34 (q, $J = 7.1$ Hz, 2H), 2.38 (s, 6H), 1.36 (t, $J = 7.1$ Hz, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 162.7 (t, $J = 32.8$ Hz), 111.4 (t, $J = 251.5$ Hz), 63.2, 56.6 (t, $J = 2.6$ Hz), 40.3 (t, $J = 32.8$ Hz), 35.5 (t, $J = 2.0$ Hz), 14.2 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -109.2 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



2-(3-Bromobicyclo[1.1.1]pentan-1-yl)-2,2-difluoroacetonitrile (76)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 5.68 g, 0.0526 mol, 82%, yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 2.45 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 110.9 (t, $J = 46.4$ Hz), 106.9 (t, $J = 245.5$ Hz), 56.0, 41.5 (t, $J = 32.1$ Hz), 34.8 (t, $J = 2.4$ Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -94.4 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_7\text{H}_{10}\text{BrF}_2\text{N}_2$, 238.9995; found 238.9979.

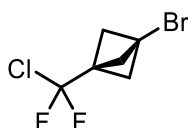


((3-Bromobicyclo[1.1.1]pentan-1-yl)difluoromethyl)trimethylsilane (77)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 60 mL of pentane at -40 °C. Yield: 5.92 g, 0.022 mol, 45%.

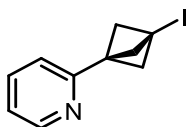
General protocol B, [BEt₃]. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 3.29 g, 0.0148 mol, 30%.

White solid, m.p. = 66-67 °C. ¹H NMR (400 MHz, CDCl₃): δ 2.33 (s, 6H), 0.18 (s, 9H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 125.1 (t, *J* = 259.8 Hz), 57.0 (t, *J* = 4.6 Hz), 42.5 (t, *J* = 29.2 Hz), 37.1 (t, *J* = 2.4 Hz), -3.9 ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -115.3 (s) ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



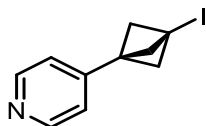
1-Bromo-3-(chlorodifluoromethyl)bicyclo[1.1.1]pentane (78)

General protocol A. The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and triturated in 50 mL of pentane at -40 °C. Yield: 3.00 g, 0.013 mol, 44%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 2.41 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 125.1 (t, *J* = 291.1 Hz), 56.7, 44.5 (t, *J* = 34.4 Hz), 35.2 ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -57.0 (s) ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



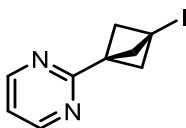
2-(3-Iodobicyclo[1.1.1]pentan-1-yl)pyridine (79)

General protocol A. Scale: 10.00 g, 0.049 mol, 1.00 equiv of 2-iodopyridine. The final product was purified by column chromatography (SiO₂, EtOAc/hexane, 1:4, *R_f* = 0.4). Yield: 12.00 g, 0.044 mol, 90%, yellow solid. ¹H NMR (500 MHz, CDCl₃): δ 8.53 (d, *J* = 4.7 Hz, 1H), 7.63 (td, *J* = 7.8, 1.6 Hz, 1H), 7.20 – 7.12 (m, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 2.68 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 157.1, 149.6, 136.6, 122.2, 120.8, 61.7, 51.2, 7.4 ppm. LCMS (M + H)⁺: 272. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₀H₁₁IN, 271.9936; found 271.9929.



4-(3-Iodobicyclo[1.1.1]pentan-1-yl)pyridine (80)

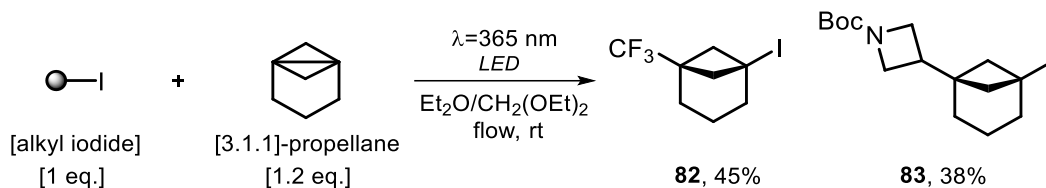
General protocol A. Scale: 10.00 g, 0.049 mol, 1.00 equiv of 4-iodopyridine. The final product was purified by column chromatography (SiO₂, EtOAc/hexane, 1:1, R_f = 0.45). Yield: 6.30 g, 0.023 mol, 47%, yellow solid. ¹H NMR (500 MHz, DMSO-d₆): δ 8.51 (d, *J* = 5.7 Hz, 2H), 7.20 (d, *J* = 5.7 Hz, 2H), 2.64 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 149.6, 146.2, 121.3, 60.9, 39.5 ppm. LCMS (M + H)⁺: 272. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₀H₁₁IN, 271.9936; found 271.9931.



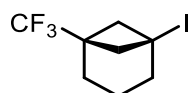
2-(3-Iodobicyclo[1.1.1]pentan-1-yl)pyrimidine (81)

General protocol A. Scale: 10.00 g, 0.0488 mol, 1.00 equiv of 2-iodopyrimidine, solvent (Et₂O) = 300 mL. The final product was recrystallized from a mixture of MeOtBu/hexane (1:1, ~ 300 mL). Yield: 11.30 g, 0.0415 mol, 85%, yellow solid, m.p. = 112-113 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.67 (d, *J* = 4.9 Hz, 2H), 7.17 (t, *J* = 4.9 Hz, 1H), 2.73 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 165.4, 157.3, 119.5, 61.6, 51.4, 7.4 ppm. LCMS (M + H)⁺: 273. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₉H₁₀IN₂, 272.9889; found 272.9885.

Bicyclo[3.1.1]heptanes

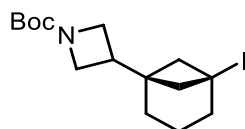


[3.1.1]Propellane was obtained using a modified procedure from N. Frank, J. Nugent, B. R. Shire, H. D. Pickford, P. Rabe, A. J. Sterling, T. Zarganes-Tzitzikas, T. Grimes, A. L. Thompson, R. C. Smith, C. J. Schofield, P. E. Brennan, F. Duarte, E. A. Anderson. Synthesis of *meta*-substituted arene bioisosteres from [3.1.1]propellane. *Nature* **2022**, 611, 721–726; Supplementary information, S13. We used MeLi (3M in diethoxymethane) instead of PhLi. The final product was titrated with thiophenol. The same procedure as for [1.1.1]propellane was applied. The concentration of the [3.1.1]propellane solution ranged between 0.10M and 0.14M, with yields of 50-60%.



1-Iodo-5-(trifluoromethyl)bicyclo[3.1.1]heptane (82)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 100 mL of pentane at -40 °C. Yield: 12.18 g, 0.042 mol, 45%, colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 2.88 – 2.80 (m, 2H), 2.56 (t, J = 6.8 Hz, 2H), 2.39 – 2.25 (m, 2H), 1.98 – 1.83 (m, 4H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 125.0 (q, J = 277.8 Hz), 47.7 (q, J = 31.1 Hz), 45.5 (q, J = 2.2 Hz), 42.7, 28.0, 24.8 (q, J = 2.0 Hz), 18.6 ppm. GCMS (M) $^+$: 290. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



Tert-butyl 3-(5-iodobicyclo[3.1.1]heptan-1-yl)azetidine-1-carboxylate (83)

General protocol A. The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg). The final product was purified by column chromatography (SiO_2 , hexane/MeOtBu, 6:4, R_f = 0.40). Yield: 7.31 g, 0.0194 mol, 38%, yellow solid. ^1H NMR (500 MHz, CDCl_3): δ 3.85 (t, J = 8.6 Hz, 2H), 3.64 (dd, J = 8.6, 5.7 Hz, 2H), 2.63 – 2.46 (m, 4H), 2.43 – 2.34 (m, 1H), 2.28 – 2.17 (m, 2H), 1.94 – 1.82 (m, 2H), 1.55 (t, J = 7.2 Hz, 2H), 1.44 (s, 9H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 156.4, 79.6, 50.2 (br s), 47.4, 47.3, 43.7, 35.1, 33.4, 29.9, 28.6, 19.6 ppm. HRMS (ESI-TOF) m/z : [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{15}\text{H}_{24}\text{INNaO}_2$, 400.0749; found 400.0740.

Multigram scale synthesis of 3-iodobicyclo[1.1.1]pentanes

This protocol was used for the synthesis of 3-iodo-bicyclo[1.1.1]pentanes on a 50-855 g scale.

1) 210 mL coil (160 mL irradiated area).

Coil: inner diameter = 1/4 inch; outer diameter = 5/16 inch.

2) 365 nm LED diodes. 960 diodes (radiated power: 0.875W/diode at 0.5A). $I = 0.5A$.

Total radiated power (radiometric flux): $960 \times 0.875 = 840 \text{ W}$.

Total power consumption: $3.6V \times 0.5A \times 960 = \text{ca. } 1.7 \text{ kW}$.

3) 20 mL/min flow rate.

1-Methyl-3-iodobicyclo[1.1.1]pentane (1) as an example

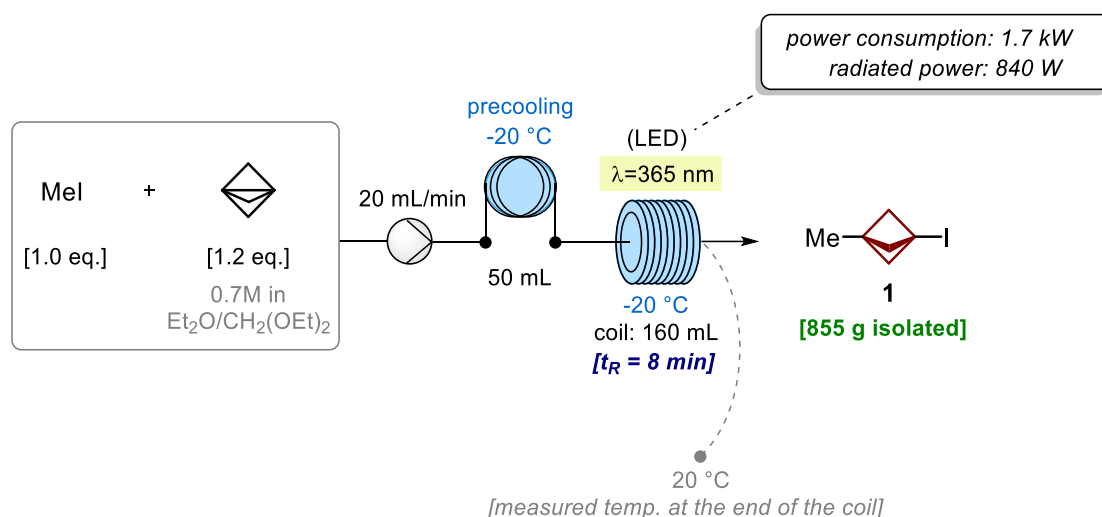


Photo of the set-up (photochemistry in flow)



Irradiated coil

To a solution of MeI (825.00 g, 5.84 mol, 1.00 equiv) in Et₂O (2500 mL, ~ 3 mL per 1 g), was added propellane (10 L, 7.00 mol, 0.7M in Et₂O, 1.20 equiv) under Ar atmosphere. The

resulting mixture was passed through a photoreactor. Flow rate: 20 mL/min. Irradiated coil: 160 mL. Irradiation: 365 nm, LED, irradiated power: 420 W (50% of the maximal).

Before entering the irradiated area, the solution was precooled to 0 °C with Huber “Unistat 510” chiller. The irradiated coil was also cooled to 0 °C with Huber “Unistat 510” chiller. The temperature of the reaction mixture after the coil was ca. 10 °C.

After passing through the coil, after ca. 40 min. (residence time in the irradiated coil: 160/10 = ca. 8 min), the reaction mixture was collected, and concentrated under vacuum (20 °C at 20-30 mmHg) to provide crude product **1**.

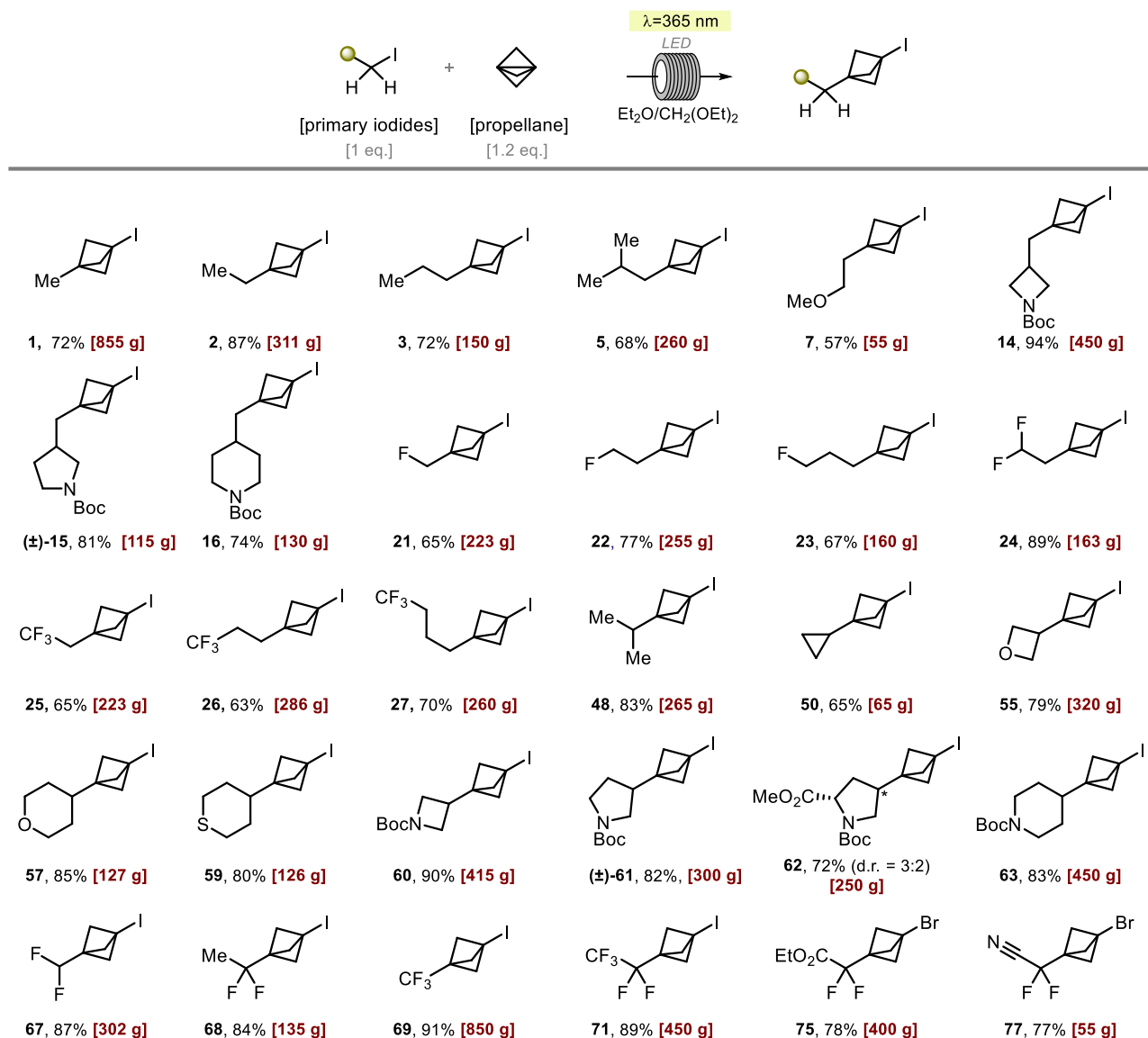
IMPORTANT. The obtained crude product **1** was sufficiently pure (ca. 90% purity by ¹H NMR containing the residual solvents) to be directly used in the next step: functionalization of the C-I bond. In fact, we often used this “crude” product (ca. 90% purity) in the subsequent C-I functionalization reactions. This is also true for all other Alk-[1.1.1]-I performed on scale.

For the preparation of the analytically pure material, the following additional steps were undertaken: the crude product was triturated in 1 L of pentane at -40 °C to afford 1-iodo-3-methylbicyclo[1.1.1]pentane (738 g) as light melting crystals. The liquid residue was concentrated under reduced pressure (20 °C at 20-30 mmHg) and the residue was purified by distillation (b.p. = 38-40 °C at 10 mmHg, the condenser was periodically slightly heated by a heat gun due to the crystallization of the product) to afford an additional portion of 1-iodo-3-methylbicyclo[1.1.1]pentane (117 g). Combined yield: 855 g of **1**, 4.19 mol, 72%, white crystals.

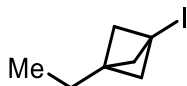
For the coil, we used commercially available tubes 200-0313-030-0C
(inner diameter = 1/4 inch; outer diameter = 5/16 inch)

<https://www.ataflo.com/products/fep-atafluor-200/>

<https://www.ataflo.com/wp-content/uploads/2022/10/ataflo-maincatalog-v27-1.pdf>

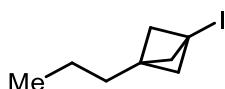


Important. In all examples, highlighted above, we obtained the desired iodides after purification in quantities indicated in burgundy. For subsequent modifications of the C-I bond, however, one can also use “crude” iodides (obtained by simple evaporation of the reaction mixture under reduced pressure after the photochemical irradiation). These products are typically of ca. 90% purity (by ^1H NMR) and only have residual solvents (Et_2O , MeOCH_2OMe) that are compatible with all reactions that we have tried.



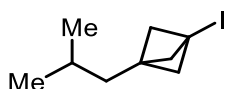
1-Ethyl-3-iodobicyclo[1.1.1]pentane (2)

The reaction mixture was concentrated under reduced pressure (20 °C at 20-30 mmHg) and triturated in ~ 500 mL of pentane at -40 °C to afford 1-ethyl-3-iodobicyclo[1.1.1]pentane (273 g). The liquid residue was concentrated and purified by distillation (b.p. = 25-27 °C, 1 mmHg) to afford an additional portion of the product (38 g). Combined yield: 311 g, 1.40 mol, 87%, yellow solid.



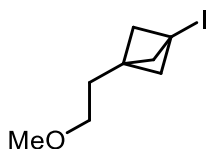
1-Iodo-3-propylbicyclo[1.1.1]pentane (3)

The reaction mixture was concentrated under reduced pressure (20 °C at 20-30 mmHg) and triturated in ~ 300 mL of pentane at -40 °C. Yield: 150.00 g, 0.64 mol, 72%, colorless oil.



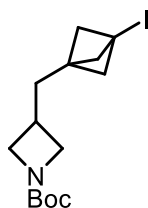
1-Iodo-3-isobutylbicyclo[1.1.1]pentane (5)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and purified by distillation (b.p. = 28-35 °C, at 1 mmHg). Yield: 259.75 g, 1.039 mol, 68%, colorless oil.



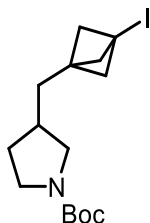
1-Iodo-3-(2-methoxyethyl)bicyclo[1.1.1]pentane (7)

The final product was purified by trituration in ~ 200 mL of pentane at -40 °C. Yield: 55.00 g, 0.754 mol, 57%, colorless oil.



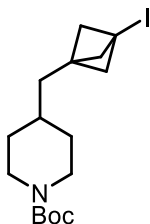
Tert-butyl 3-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)azetidine-1-carboxylate (14)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in ~ 500 mL of pentane at -40 °C. Yield: 450.00 g, 1.24 mol, 94%, white solid, m.p. = 96-97 °C.



(±)-tert-butyl 3-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)pyrrolidine-1-carboxylate (15)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in ~ 300 mL of pentane at -40 °C. Yield: 115.00 g, 0.305 mol, 81%, white solid, m.p. = 53-54 °C.



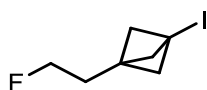
tert-butyl 4-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)piperidine-1-carboxylate (16)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in ~ 400 mL of pentane at -40 °C. Yield: 130.00 g, 0.33 mol, 74%, white solid, m.p. = 76-77 °C.



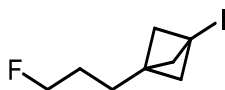
1-(Fluoromethyl)-3-iodobicyclo[1.1.1]pentane (21)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in ~ 400 mL of pentane at -40 °C. Yield: 223.14 g, 0.99 mol, 65%, white solid, m.p. < 30 °C.



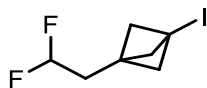
1-(2-Fluoroethyl)-3-iodobicyclo[1.1.1]pentane (22)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in ~ 400 mL of pentane at -40 °C. Yield: 255.00 g, 1.03 mol, 77%, white solid, m.p. < 30 °C.



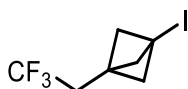
1-(3-Fluoropropyl)-3-iodobicyclo[1.1.1]pentane (23)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in pentane ~ 300 mL at -40 °C. Yield: 160.02 g, 0.63 mol, 67%, colorless oil.



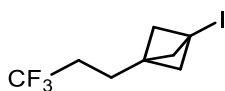
1-(2,2-Difluoroethyl)-3-iodobicyclo[1.1.1]pentane (24)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in ~ 300 mL of pentane at -40 °C. Yield: 163.00, 0.63 mol, 89%, yellow oil.



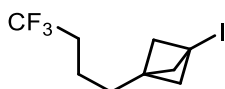
1-Iodo-3-(2,2,2-trifluoroethyl)bicyclo[1.1.1]pentane (25)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in ~ 400 mL of pentane at -40 °C. Yield: 223.10 g, 0.80 mol, 65%, colorless oil.



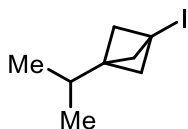
1-Iodo-3-(3,3,3-trifluoropropyl)bicyclo[1.1.1]pentane (26)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in ~ 400 mL of pentane at -40 °C. Yield: 285.56 g, 0.98 mol, 63%, yellow solid, m.p. = 40-41 °C.



1-Iodo-3-(4,4,4-trifluorobutyl)bicyclo[1.1.1]pentane (27)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in ~ 400 mL of pentane at -40 °C. Yield: 260.00 g, 0.855 mol, 70%, colorless oil.



1-Iodo-3-isopropylbicyclo[1.1.1]pentane (48)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in ~ 400 mL of pentane at -40 °C. Yield: 264.79 g, 1.122 mol, 83%, yellow oil.



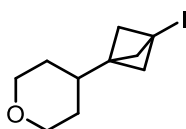
1-Cyclopropyl-3-iodobicyclo[1.1.1]pentane (50)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in ~ 200 mL of pentane at -40 °C. Yield: 65.05 g, 0.278 mol, 67%, white solid, m.p. < 30 °C.



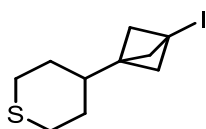
3-(3-Iodobicyclo[1.1.1]pentan-1-yl)oxetane (55)

The reaction mixture was concentrated under reduced pressure (20 °C, 20-30 mmHg) and triturated in ~ 500 mL of pentane at -40 °C. Yield: 319.50 g, 1.278 mol, 79%, white solid, m.p. < 30 °C.



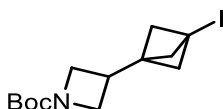
4-(3-Iodobicyclo[1.1.1]pentan-1-yl)tetrahydro-2H-pyran (57)

The reaction mixture was concentrated in *vacuo* and triturated in 400 mL of hexane. Yield: 127.00 g, 0.45 mol, 85%, white solid, m.p. = 72-73 °C.



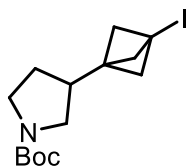
4-(3-Iodobicyclo[1.1.1]pentan-1-yl)tetrahydro-2H-thiopyran (59)

The reaction mixture was concentrated in *vacuo* and triturated in 500 mL of hexane. Yield: 126.00 g, 0.43 mol, 80%, white solid, m.p. > 30 °C.



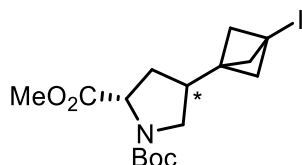
Tert-butyl 3-(3-iodobicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (60)

The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by flash column chromatography (SiO₂, gradient, hexane/MeOtBu – 100% to 80:20, R_f = 0.65, hexane/MeOtBu, 3:2). Yield: 414.61 g, 1.188 mol, 90%, white solid, m.p. < 30 °C.



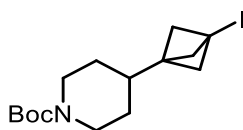
(±)-*Tert*-butyl 3-(3-iodobicyclo[1.1.1]pentan-1-yl)pyrrolidine-1-carboxylate (61)

The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by column chromatography (SiO₂, gradient, hexane/MeOtBu – 100% to 80:20, R_f = 0.65, hexane/MeOtBu, 3:2). Yield: 300.15 g, 0.827 mol, 82%, white solid, m.p. < 30 °C.



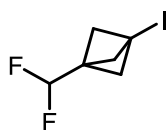
1-(*Tert*-butyl) 2-methyl-4-(3-iodobicyclo[1.1.1]pentan-1-yl)pyrrolidine-1,2-dicarboxylate (62)

The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by column chromatography (SiO₂, gradient, hexane/MeOtBu – 100% to 80:20, R_f = 0.56, hexane/MeOtBu, 3:2). Yield: 249.65 g, 0.593 mol, 72%, white solid, m.p. = 104-105 °C, d.r. = 3:2.



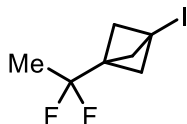
***Tert*-butyl 4-(3-iodobicyclo[1.1.1]pentan-1-yl)piperidine-1-carboxylate (63)**

The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by column chromatography (SiO₂, gradient, hexane/MeOtBu – 100% to 80:20, R_f = 0.41, hexane/MeOtBu, 4:1). Yield: 449.76 g, 1.193 mol, 83%, white solid, m.p. < 30 °C.



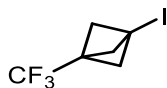
1-(Difluoromethyl)-3-iodobicyclo[1.1.1]pentane (67)

The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and triturated in ~ 500 mL of pentane at -40 °C. Yield: 302.00 g, 1.238 mol, 87%, white solid, m.p. = 63-64 °C.



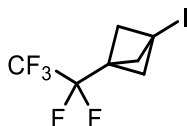
1-(1,1-Difluoroethyl)-3-iodobicyclo[1.1.1]pentane (68)

The reaction mixture was concentrated in *vacuo* and triturated in ~ 500 mL of pentane at -40 °C. Yield: 135.00 g, 0.525 mol, 84%, white solid, m.p. = 58-59 °C.



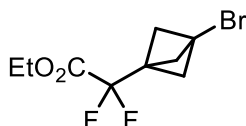
1-Iodo-3-(trifluoromethyl)bicyclo[1.1.1]pentane (69)

The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg), dried from DME (20 °C, water bath, 10 mmHg), and triturated in 1 L of pentane at -40 °C. Yield: 849.93 g, 3.244 mol, 91%, white solid, m.p. < 30 °C.



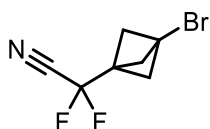
1-Iodo-3-(perfluoroethyl)bicyclo[1.1.1]pentane (71)

The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 500 mL of pentane at -40 °C. Yield: 449.90 g, 1.442 mol, 89%, colorless oil.



Ethyl 2-(3-bromobicyclo[1.1.1]pentan-1-yl)-2,2-difluoroacetate (75)

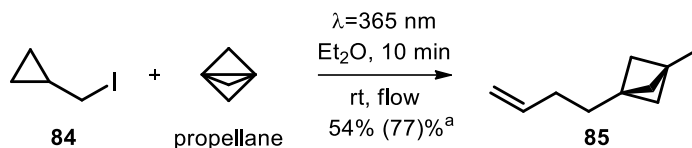
The reaction mixture was concentrated under reduced pressure (30 °C, 10 mmHg) and purified by column chromatography (SiO₂, gradient, hexane/MeOtBu – 100% to 80:20, R_f = 0.52, hexane/MeOtBu, 4:1). Yield: 400.00 g, 1.487 mol, 78%, beige solid, m.p. < 30 °C.



2-(3-Bromobicyclo[1.1.1]pentan-1-yl)-2,2-difluoroacetonitrile (77)

The reaction mixture was concentrated under reduced pressure (20 °C, 50 mmHg) and triturated in 150 mL of pentane at -40 °C. Yield: 55.06 g, 0.248 mol, 77%, yellow oil.

Radical clock experiments

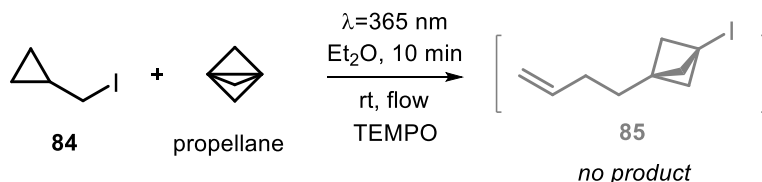


^aNMR yield using 1,3,5-trimethoxybenzene as an internal standard.

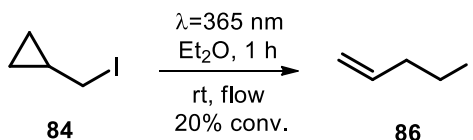
1-(But-3-en-1-yl)-3-iodobicyclo[1.1.1]pentane (**85**)

General protocol A-modified was used. Scale: (iodomethyl)cyclopropane (100 mg, 0.549 mmol). The mixture was concentrated under reduced pressure and 1,3,5-trimethoxybenzene (92 mg, 0.549 mmol, 1.00 equiv) and CDCl_3 were added. The NMR-yield of 77% was calculated from the ^1H NMR spectrum using 1,3,5-trimethoxybenzene as an internal standard.

The mixture was concentrated under reduced pressure at 30 °C (15 mmHg) and filtered through a syringe filter (CHROMAFIL PTFE-20/15 MS). Yield: 74 mg, 0.298 mmol, 54%, colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 5.80 – 5.68 (m, 1H), 4.98 (d, J = 17.1 Hz, 1H), 4.93 (d, J = 10.2 Hz, 1H), 2.18 (s, 6H), 2.03 – 1.95 (m, 2H), 1.60 (t, J = 7.7 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 138.0, 115.0, 60.6, 48.3, 31.3, 31.1, 7.8 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.

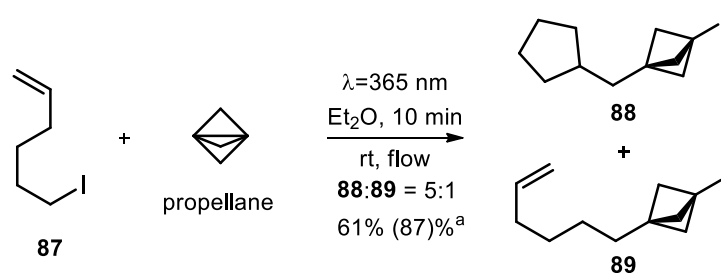


Analogous reaction under identical conditions in the presence of TEMPO (1.00 equiv) did not provide product **85**.



4-Iodobut-1-ene (**86**)

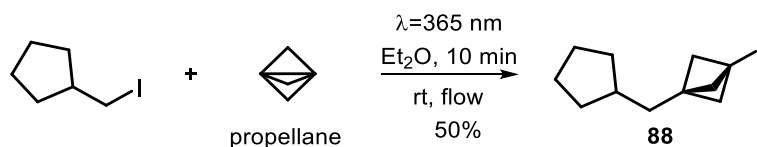
General protocol A-modified was used. The flow was reduced to 0.2 mL/min, so that the irradiation time in a coil was ca. 1 h. Scale: (iodomethyl)cyclopropane (100 mg, 0.549 mmol) in Et_2O (30 mL) at room temperature. After 1 h of irradiation, the reaction mixture was evaporated. Product **86** was formed. The reaction conversion was ca. 20%.



^aNMR yield using 1,3,5-trimethoxybenzene as an internal standard.

1-(Cyclopentylmethyl)-3-iodobicyclo[1.1.1]pentane (88) and 1-(hex-5-en-1-yl)-3-iodobicyclo[1.1.1]pentane (89)

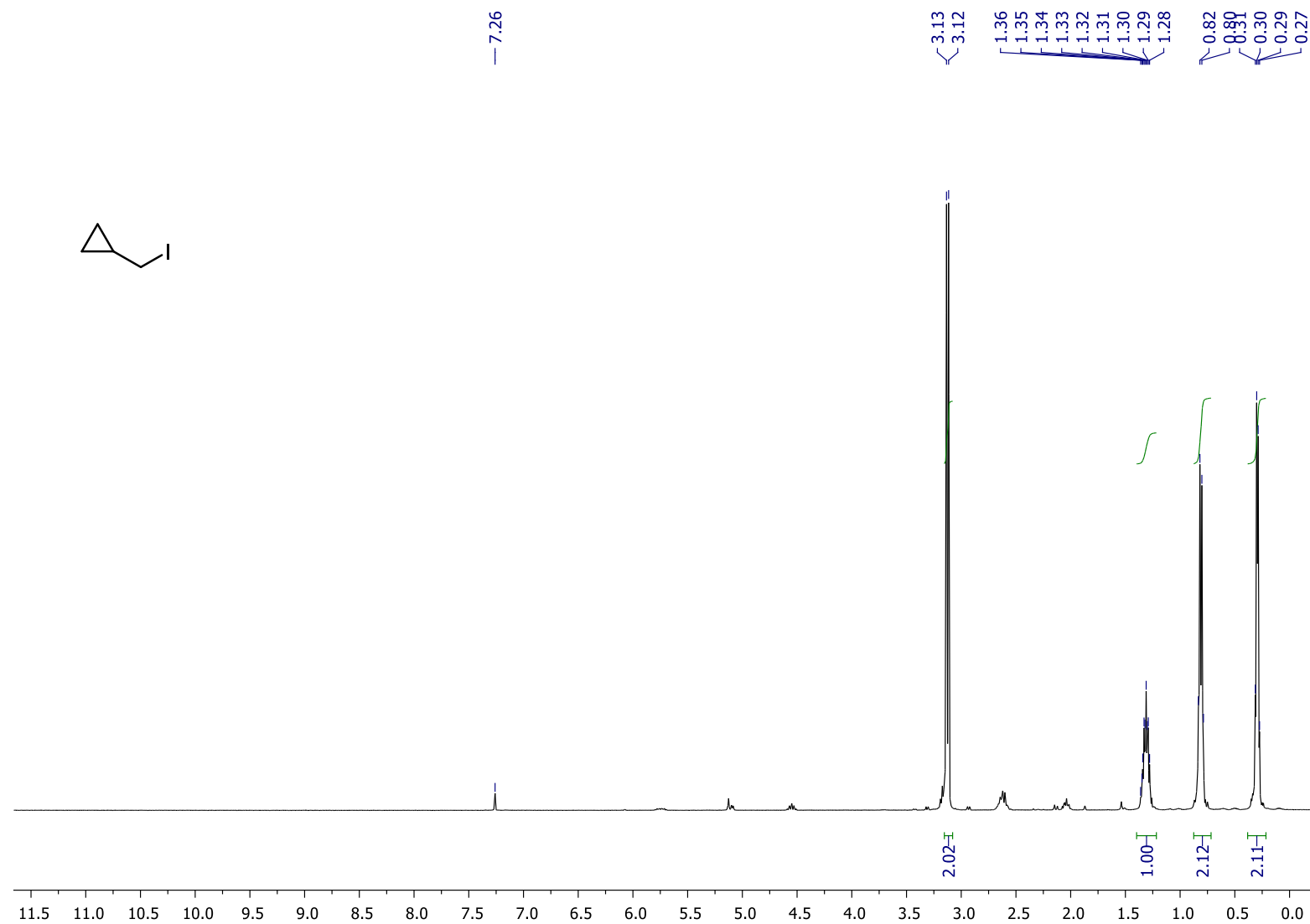
General protocol A-modified was used. Scale: 6-iodohex-1-ene (100 mg, 0.476 mmol). The mixture was concentrated under reduced pressure and 1,3,5-trimethoxybenzene (80 mg, 0.476 mmol, 1.00 equiv) and CDCl_3 were added. The combined NMR-yield of 87% was calculated from the ^1H NMR spectrum using 1,3,5-trimethoxybenzene as an internal standard. The mixture was concentrated under reduced pressure at 30 °C (15 mmHg) and filtered through a syringe filter (CHROMAFIL PTFE-20/15 MS). The combined NMR-yield of 61%. Major compound **88**: ^1H NMR (500 MHz, CDCl_3): δ 2.12 (s, 6H), 1.71 – 1.62 (m, 3H), 1.49 – 1.38 (m, 6H), 0.98 – 0.91 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): 61.3, 48.5, 38.8, 38.1, 33.1, 25.4, 8.2 ppm. Minor compound **89**: ^1H NMR (500 MHz, CDCl_3): δ 5.93 – 5.43 (m, 1H), 4.87 (dd, $J = 23.5, 13.5$ Hz, 2H), 2.09 (s, 6H), 1.99 – 1.86 (m, 2H), 1.48 (m, 4H), 1.32 – 1.23 (m, 2H) ppm.



General protocol A-modified. Scale of iodomethyl)cyclopentane: 500 mg, 2.38 mmol, 1.00 equiv. The mixture was concentrated under reduced pressure at 30 °C (15 mmHg) and filtered through a syringe filter (CHROMAFIL PTFE-20/15 MS). Yield: 330 mg, 1.196 mmol, 50%, yellow oil. ^1H NMR (500 MHz, CDCl_3): δ 2.17 (s, 6H), 1.76 – 1.65 (m, 3H), 1.56 – 1.43 (m, 6H), 1.04 – 0.95 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 61.3, 48.5, 38.8, 38.1, 33.1, 25.3, 8.2 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.

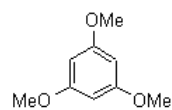
(Iodomethyl)cyclopropane (84) from stock

^1H NMR (400 MHz, CDCl_3)



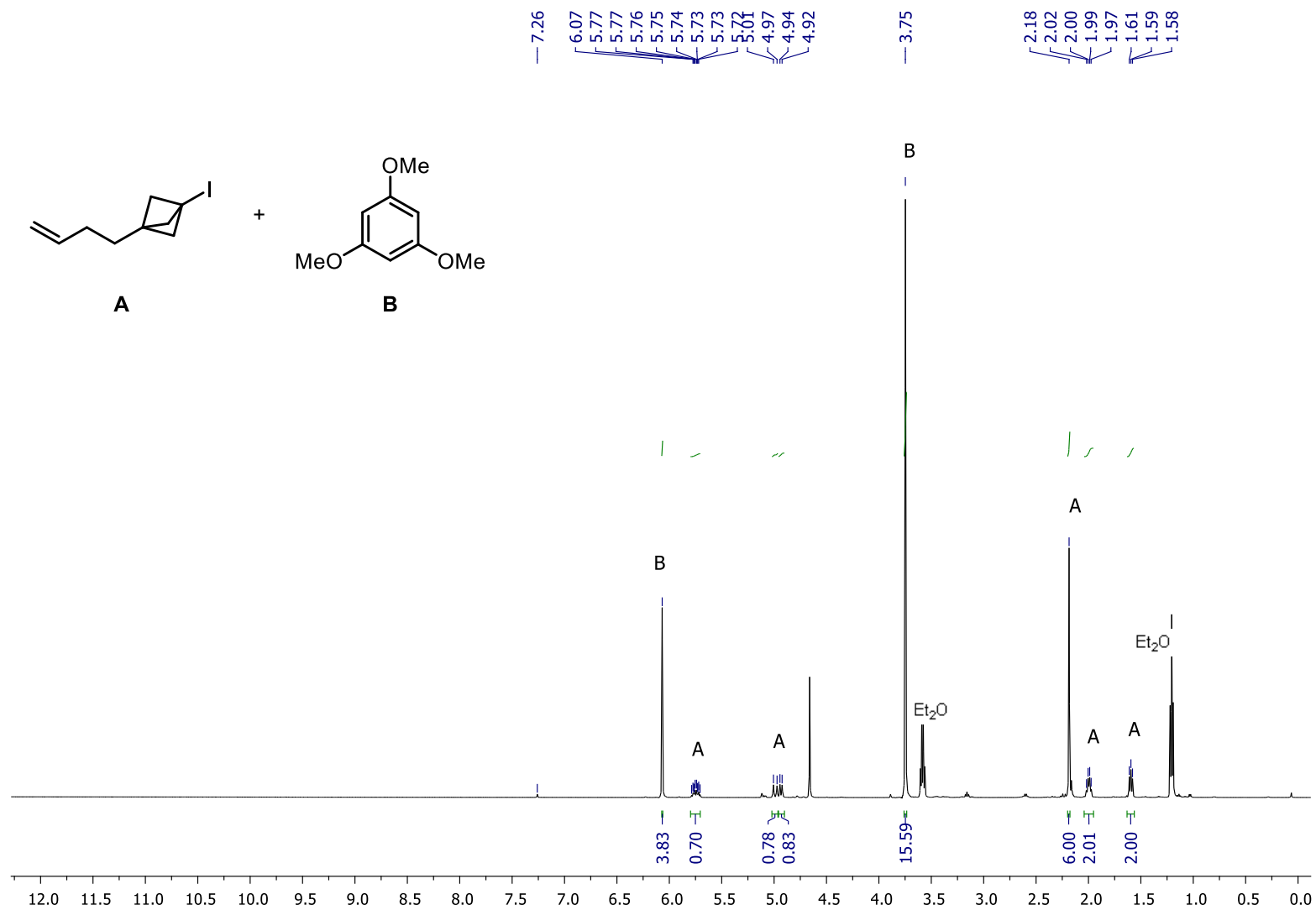
1,3,5-Trimethoxybenzene from stock

^1H NMR (400 MHz, CDCl_3)



A crude reaction mixture of 1-(but-3-en-1-yl)-3-iodobicyclo[1.1.1]pentane (85) and 1,3,5-trimethoxybenzene

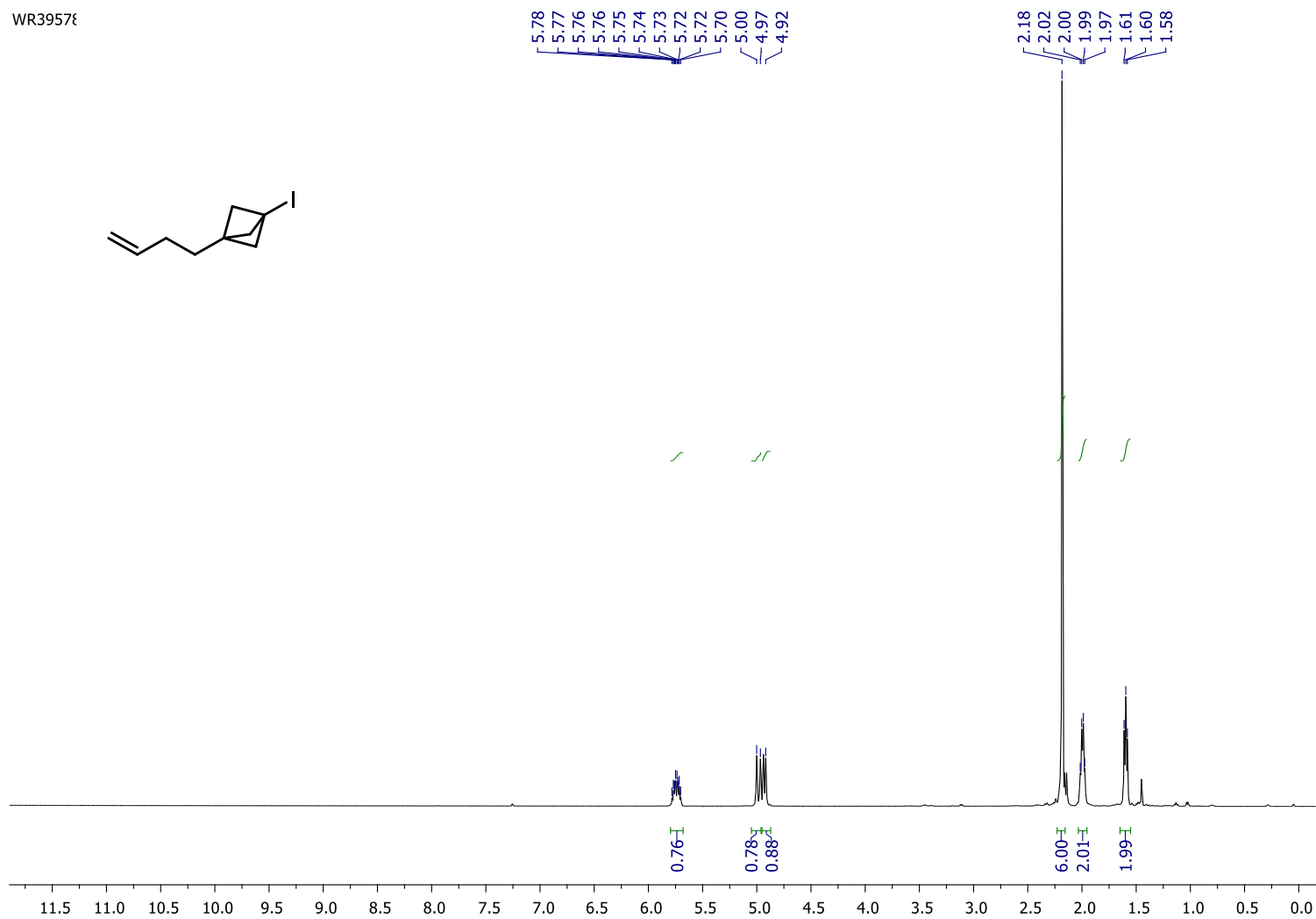
^1H NMR (500 MHz, CDCl_3)

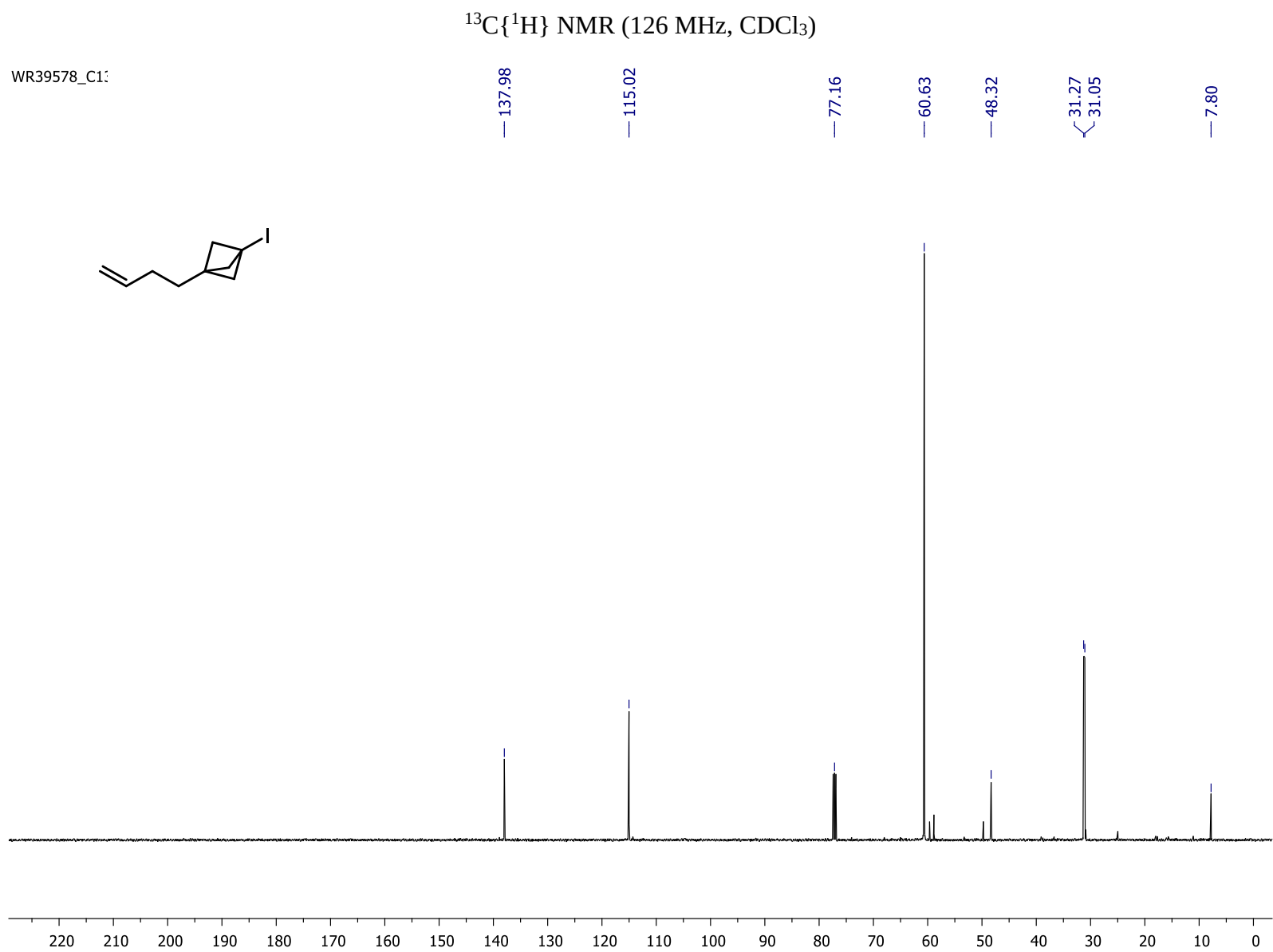


1-(But-3-en-1-yl)-3-iodobicyclo[1.1.1]pentane (85) after purification

^1H NMR (500 MHz, CDCl_3)

WR39578

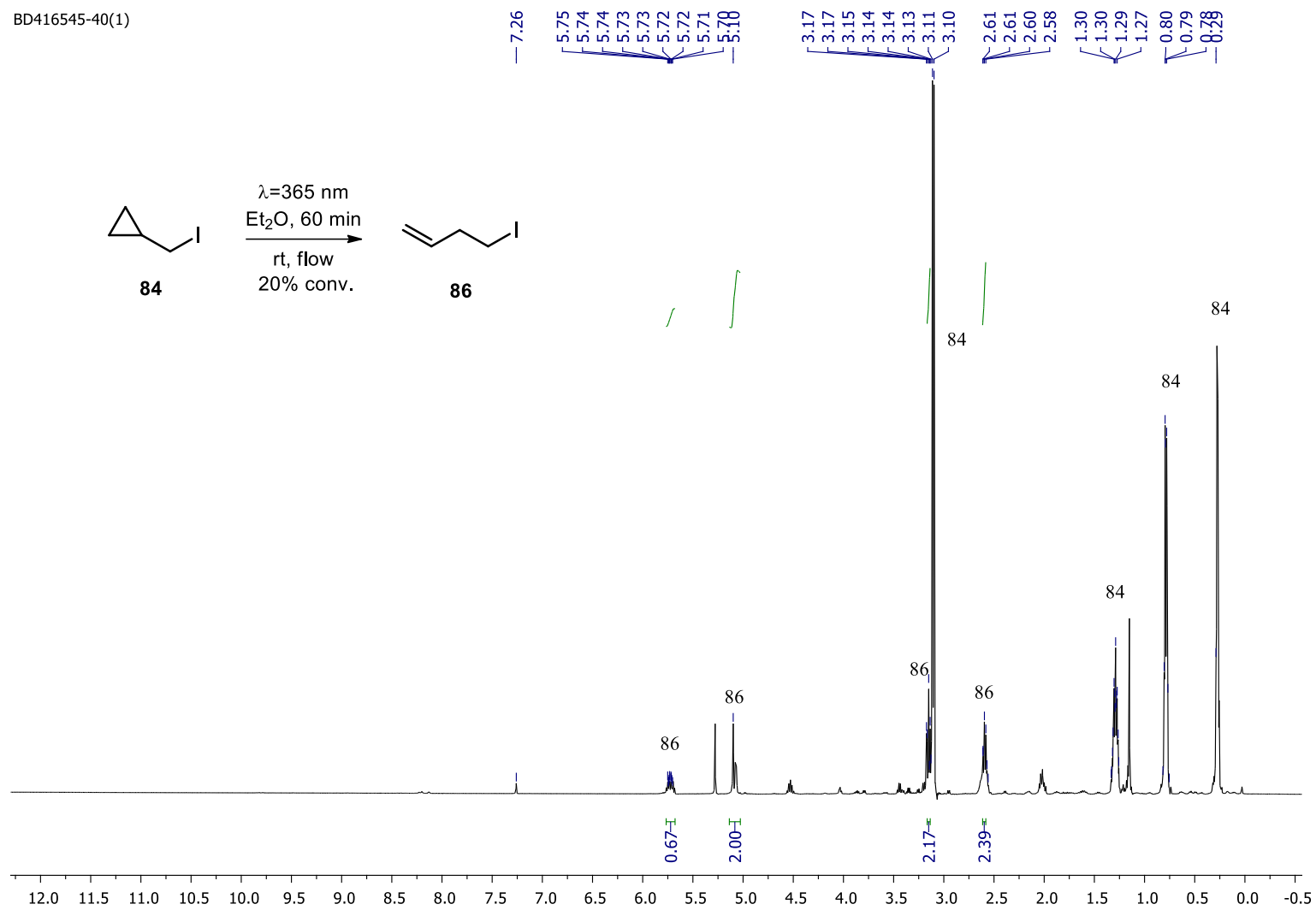
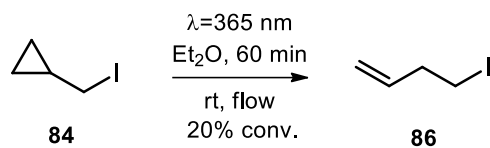




A reaction mixture after irradiation of compound 84 in flow (formation of 86 is observed)

¹H NMR (500 MHz, CDCl₃)

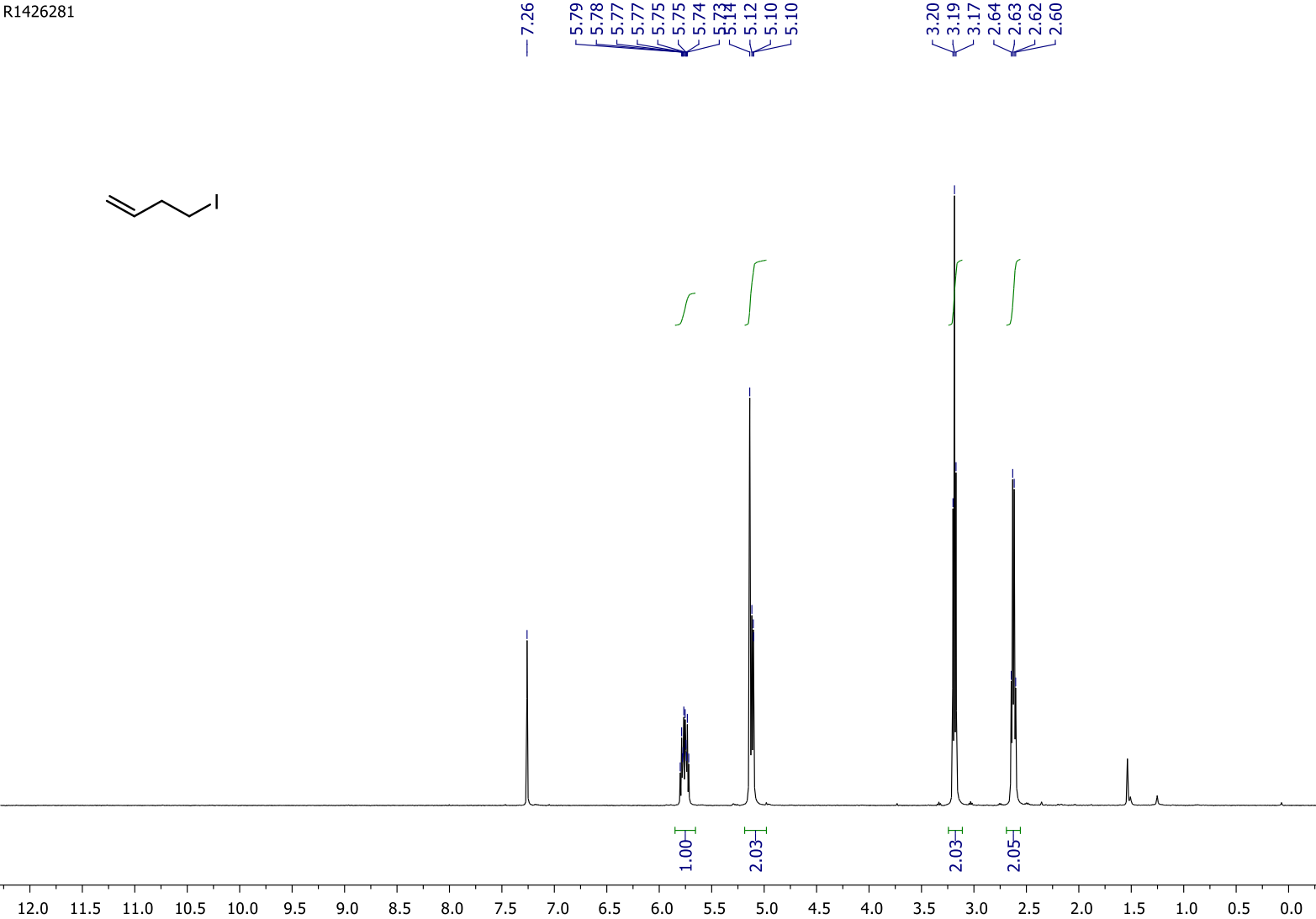
BD416545-40(1)



4-Iodobut-1-ene 86 (from stock)

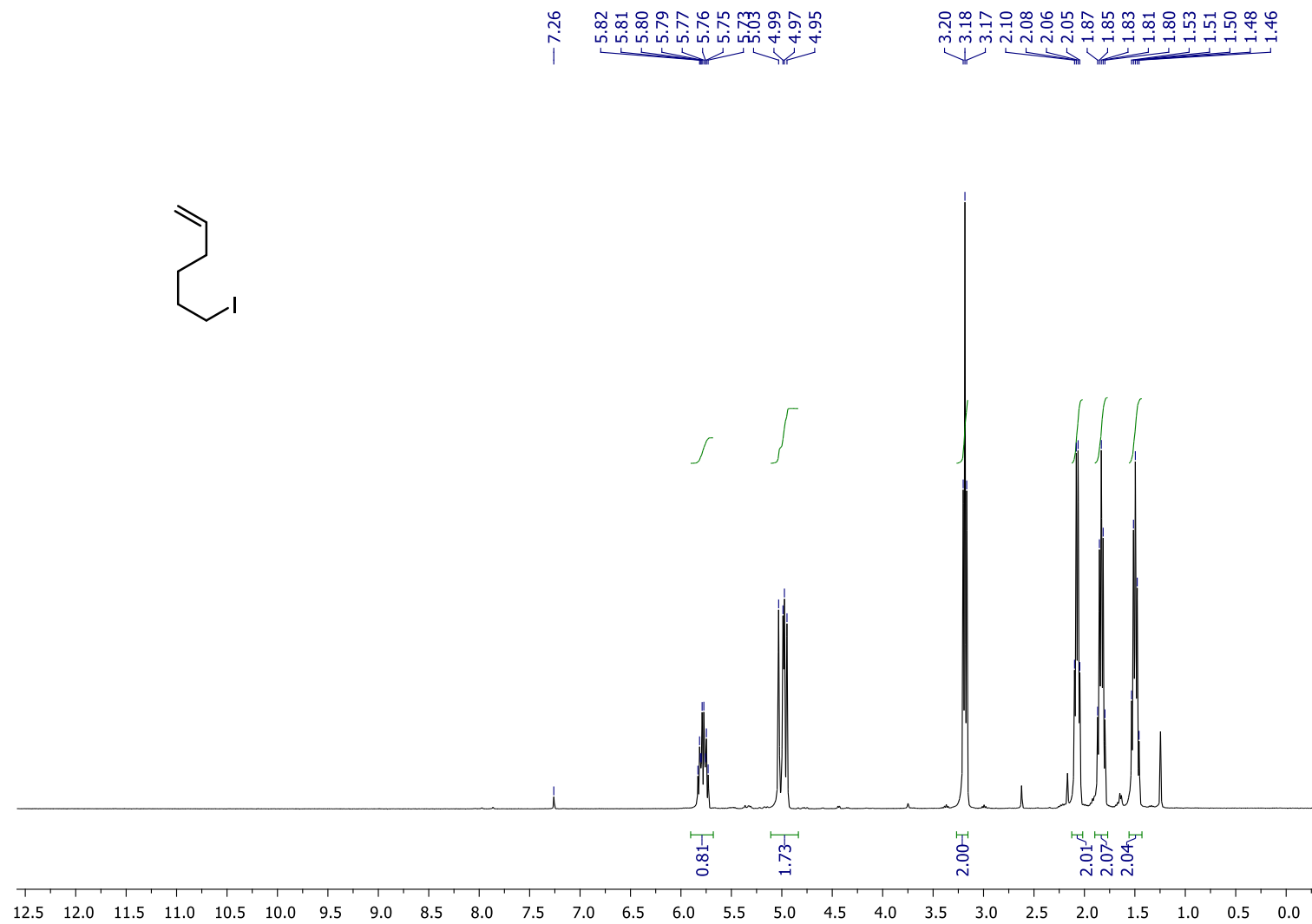
R1426281

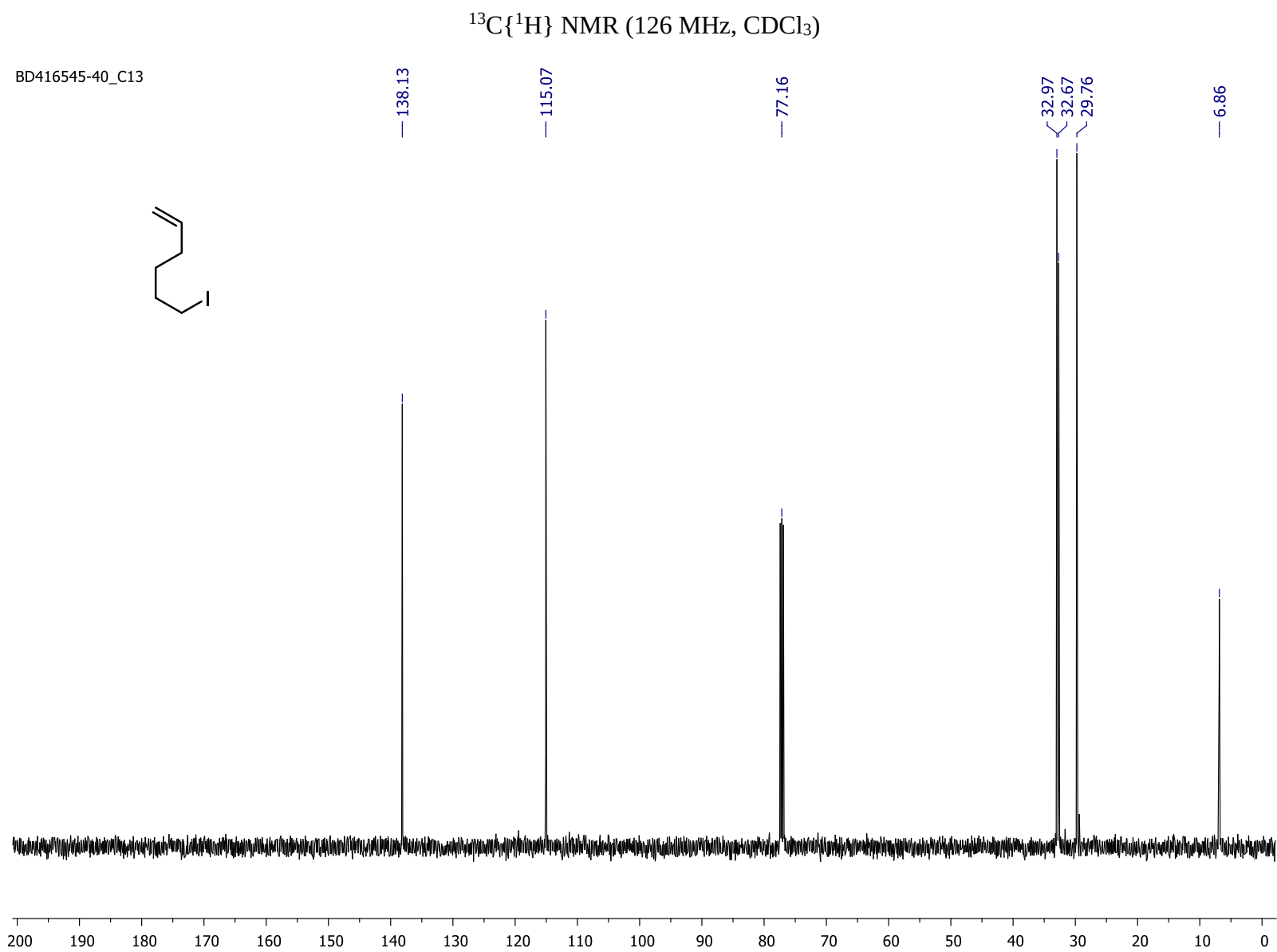
¹H NMR (500 MHz, CDCl₃)



6-Iodohex-1-ene 87 (from stock)

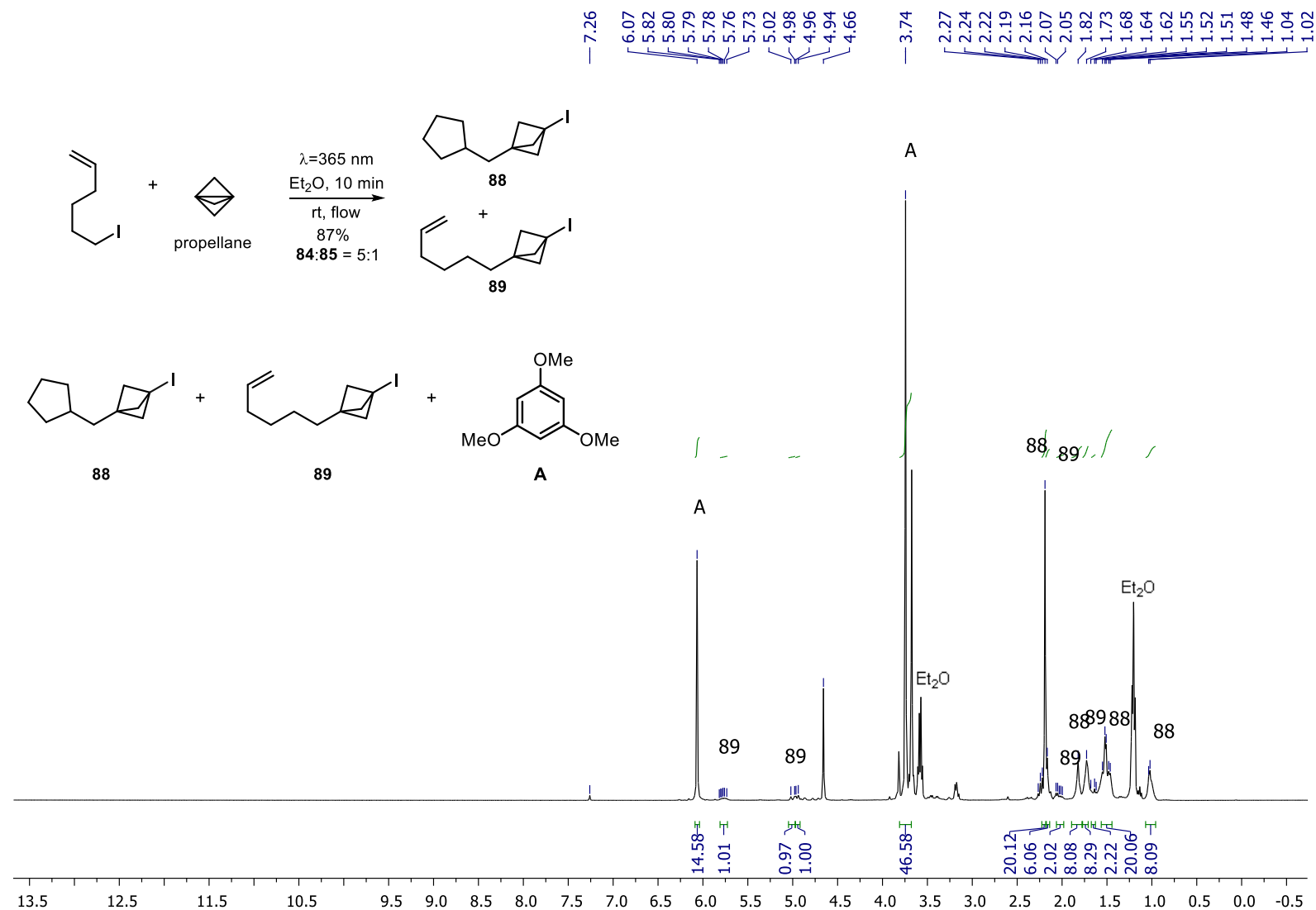
^1H NMR (400 MHz, CDCl_3)





A mixture of **1-(cyclopentylmethyl)-3-iodobicyclo[1.1.1]pentane (88)**, **1-(hex-5-en-1-yl)-3-iodobicyclo[1.1.1]pentane (89)**, and **1,3,5-trimethoxybenzene**

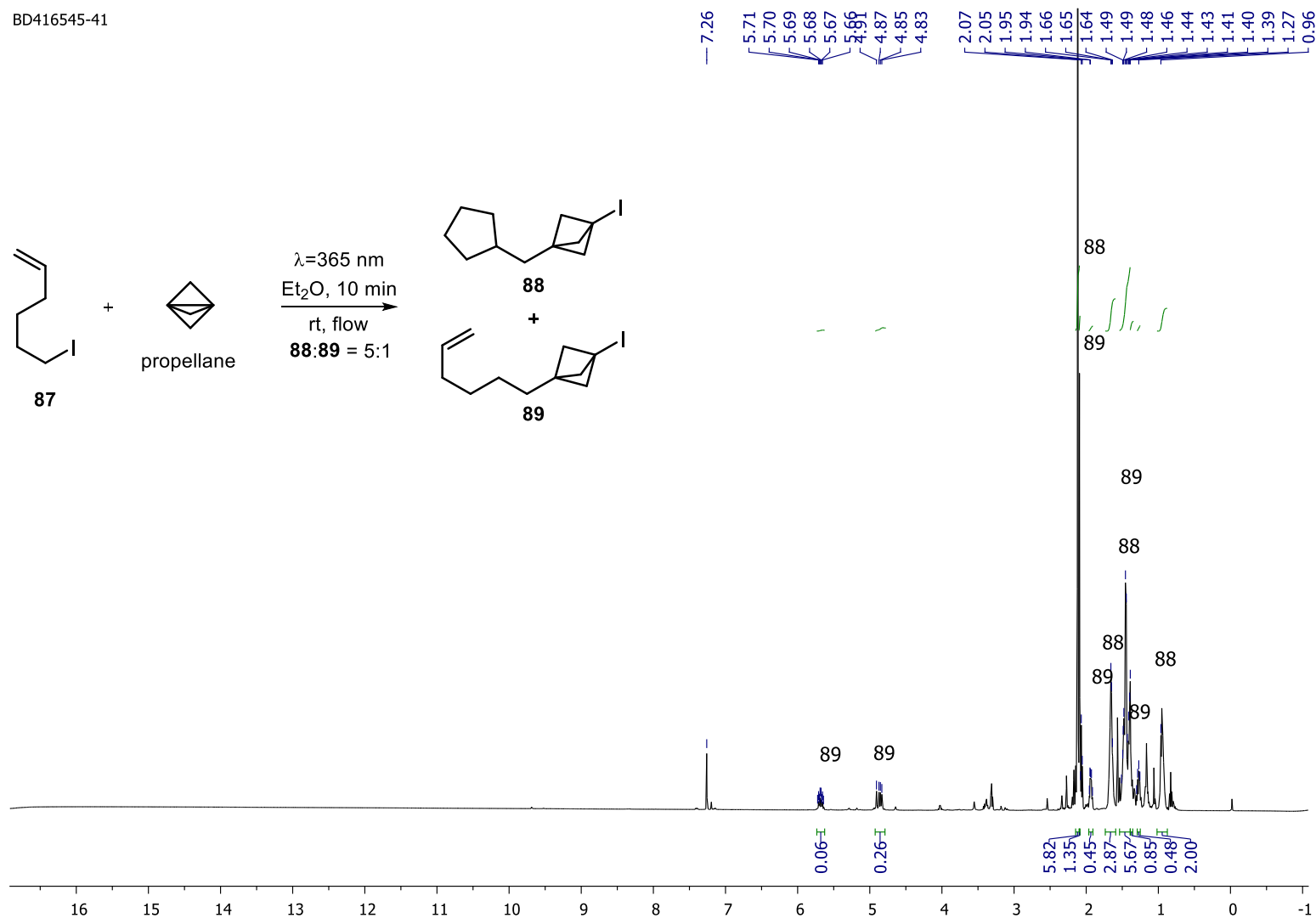
^1H NMR (400 MHz, CDCl_3)

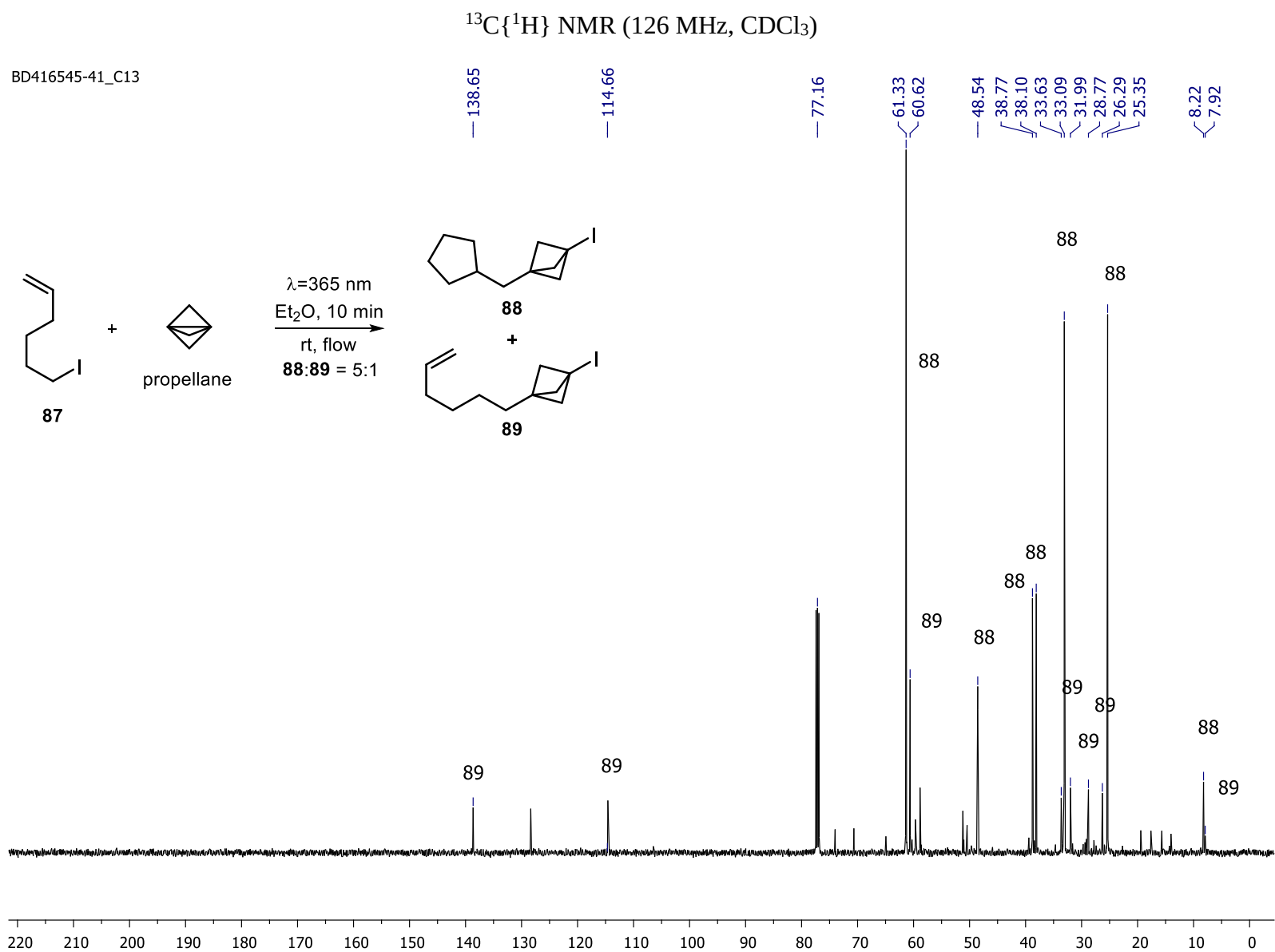


Purified mixture of 1-(cyclopentylmethyl)-3-iodobicyclo[1.1.1]pentane (88), 1-(hex-5-en-1-yl)-3-iodobicyclo[1.1.1]pentane (89)

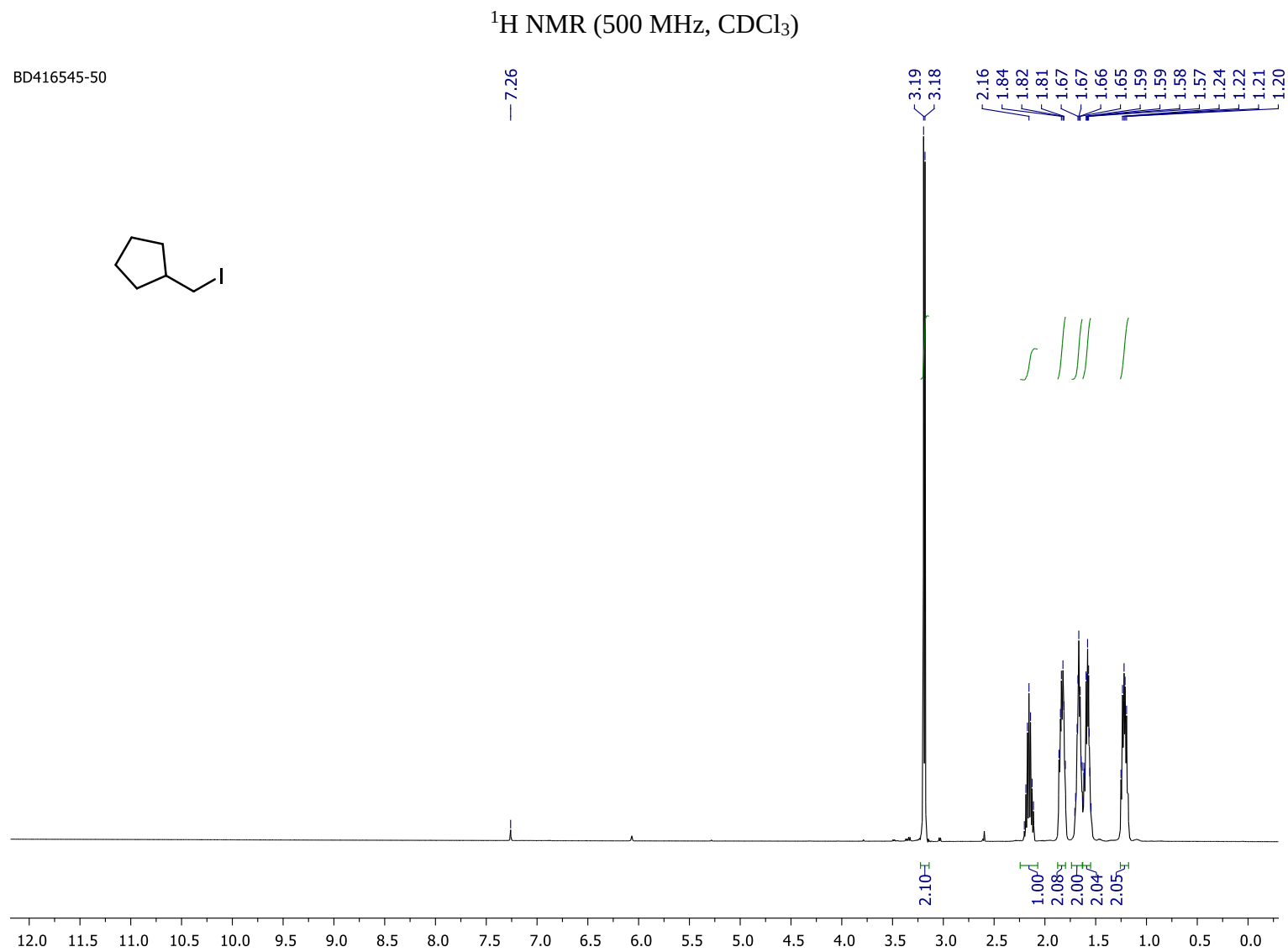
^1H NMR (500 MHz, CDCl_3)

BD416545-41





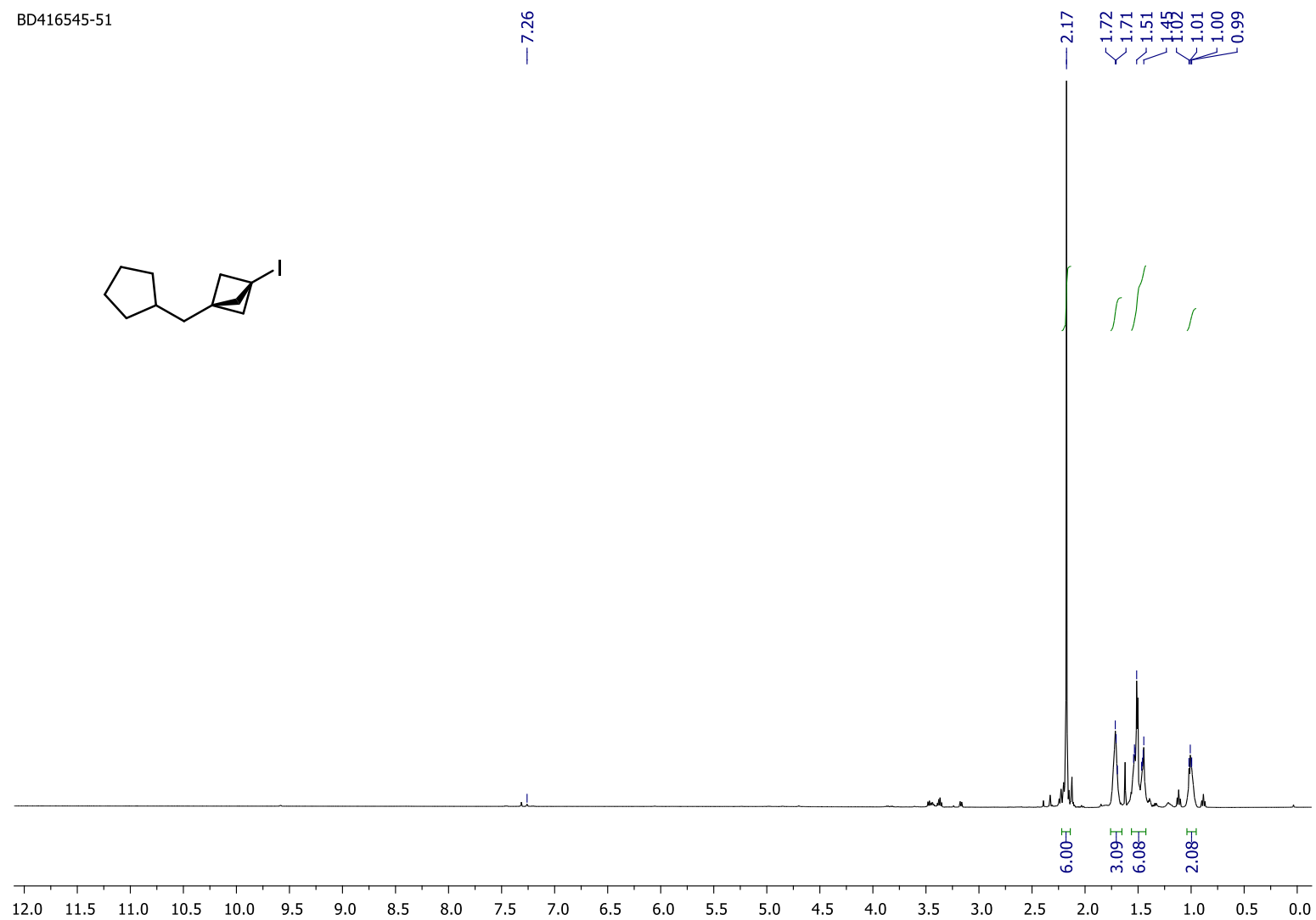
(Iodomethyl)cyclopentane (from stock)



1-(Cyclopentylmethyl)-3-iodobicyclo[1.1.1]pentane (88)

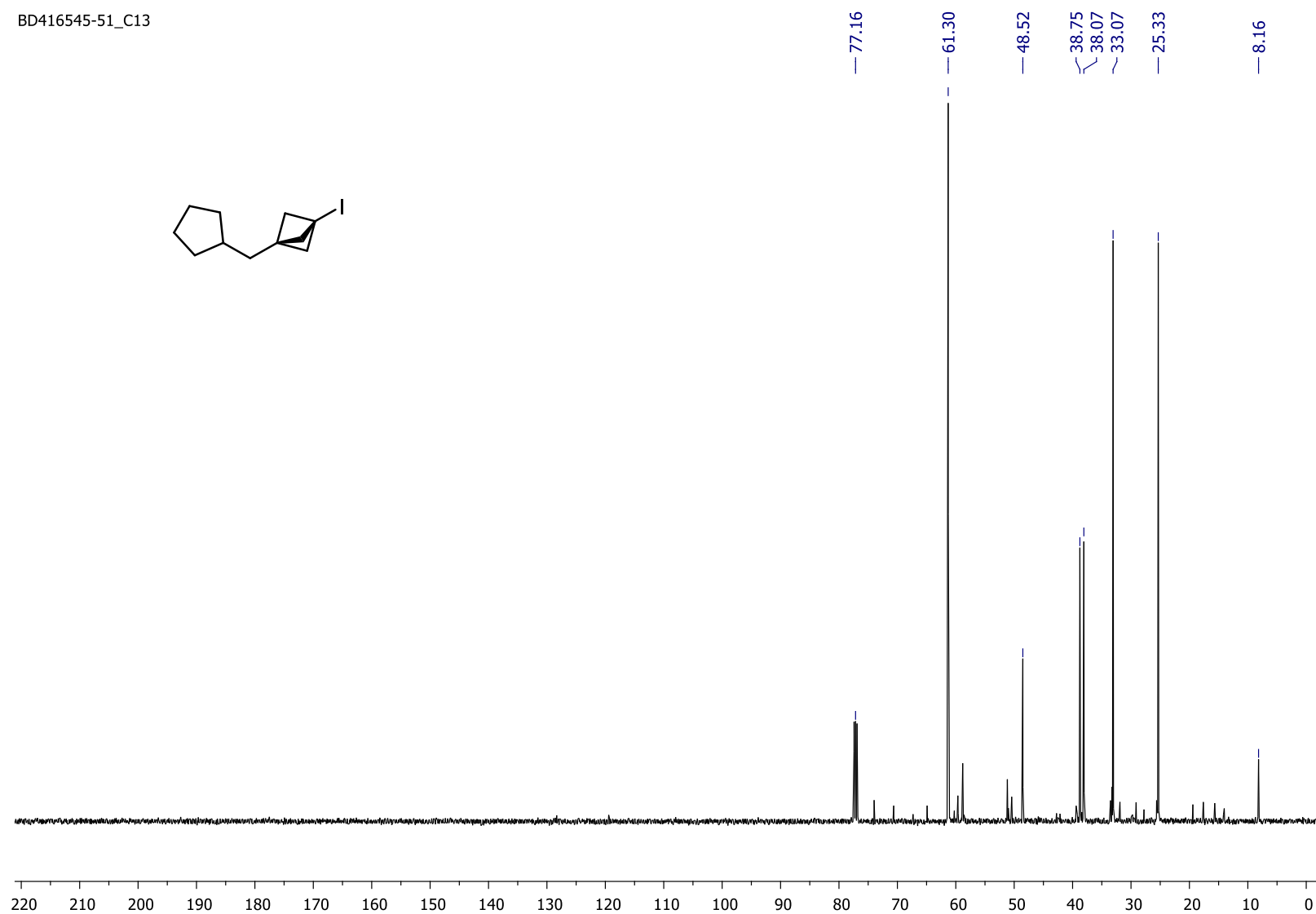
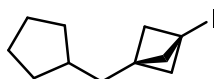
BD416545-51

^1H NMR (500 MHz, CDCl_3)



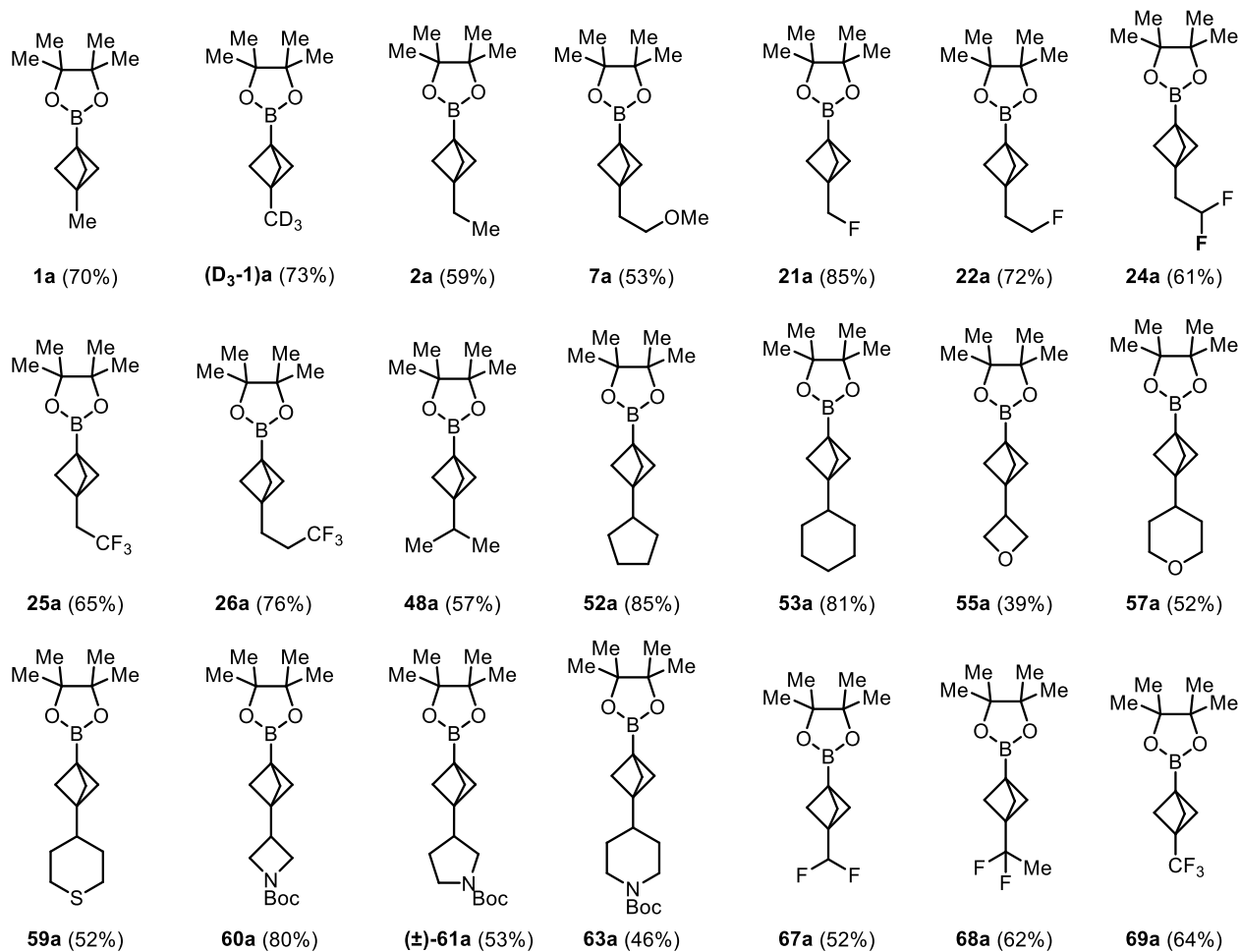
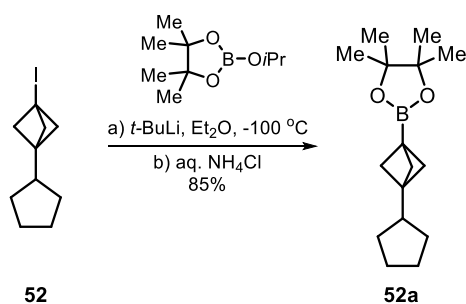
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

BD416545-51_C13

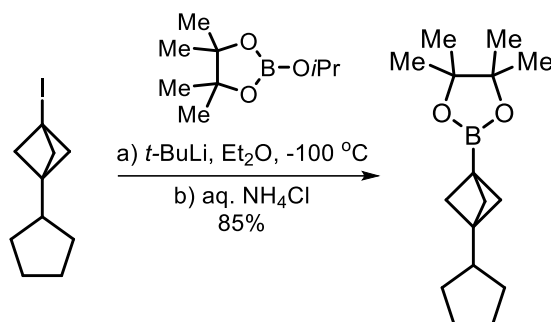


Modifications of bicyclo[1.1.1]pentane iodides

1. Boron pinacolates

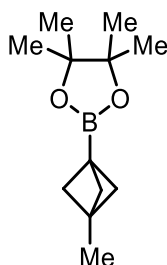


General procedure A (52a as an example)



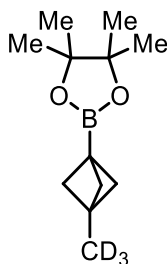
2-(3-Cyclopentylbicyclo[1.1.1]pentan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (52a)

A solution of **52** (67.90 g, 0.259 mol, 1.00 equiv) and 4,4,5,5-tetramethyl-2-(propan-2-yloxy)-1,3,2-dioxaborolane (53.00 g, 0.284 mol, 1.10 equiv) in dry Et₂O (1400 mL) was cooled to -100 °C under Ar. *t*-BuLi (300 mL, 0.57 mol, 2.20 equiv, 1.9M solution in pentane) was added by cannula over 20 min. The reaction mixture was warmed to room temperature and stirred overnight. The solution was quenched with a sat. solution of ammonium chloride (200 mL), washed with water (2 × 500 mL), dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by distillation (b.p. = 110-111 °C, 1 mmHg). Yield: 57.70 g, 0.22 mol, 85%, white solid, m.p. = 47-48 °C. ¹H NMR (500 MHz, CDCl₃): δ 1.82 – 1.74 (m, 1H), 1.67 (s, 6H), 1.27 – 1.23 (m, 2H), 1.22 (s, 12H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 83.3, 49.8, 48.9, 41.7, 28.6, 25.9, 24.9 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



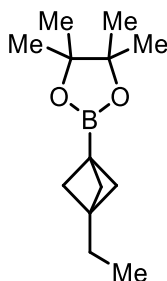
4,4,5,5-Tetramethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)-1,3,2-dioxaborolane (1a)

General procedure A. The resulting residue was purified by distillation from 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (40-50 °C, 1 mmHg) to afford the crude product which was triturated in 100 mL of pentane at -40 °C. Yield: 33.10 g, 0.159 mol, 70%, white solid, m.p. = 63-64 °C. ¹H NMR (500 MHz, CDCl₃): δ 1.75 (s, 6H), 1.22 (s, 12H), 1.05 (s, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 83.3, 53.4, 42.8, 24.9, 20.1 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



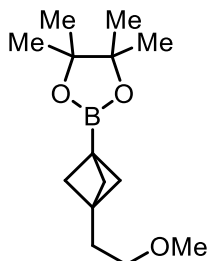
4,4,5,5-Tetramethyl-2-(3-(methyl-d₃)bicyclo[1.1.1]pentan-1-yl)-1,3,2-dioxaborolane (D₃-1)a

General procedure A. The resulting residue was purified by distillation from 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (40-50 °C, 1 mmHg) to afford the crude product which was triturated in 50 mL of pentane at -40 °C. Yield: 3.70 g, 0.0175 mol, 73%, white solid, m.p. = 74-75 °C. ¹H NMR (500 MHz, CDCl₃): δ 1.75 (s, 6H), 1.22 (s, 12H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 83.3, 53.3, 42.6, 24.9 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₂H₁₉D₃BO₂, 212.1901; found 212.1894.



2-(3-Ethylbicyclo[1.1.1]pentan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2a)

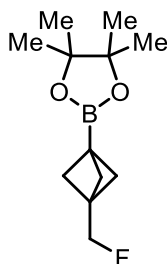
General procedure A. The resulting residue was purified by distillation (b.p. = 63-64 °C, 1 mmHg). Yield: 29.97 g, 0.135 mol, 59%, colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 1.70 (s, 6H), 1.32 (q, *J* = 7.5 Hz, 2H), 1.23 (s, 12H), 0.79 (t, *J* = 7.5 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 83.3, 50.9, 47.2, 26.2, 24.9, 10.1 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



2-(3-(2-Methoxyethyl)bicyclo[1.1.1]pentan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7a)

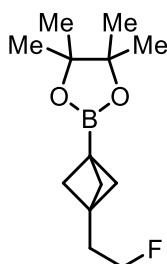
General procedure A. The resulting residue was purified by distillation (b.p. = 87-89 °C, 1 mmHg). Yield: 30.00 g, 0.119 mol, 53%, colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 3.33 (t, *J* = 7.0 Hz, 2H), 3.29 (s, 3H), 1.77 (s, 6H), 1.61 (t, *J* = 7.0 Hz, 2H), 1.22 (s, 12H) ppm. ¹³C{¹H} NMR

(151 MHz, CDCl₃): δ 83.3, 70.7, 58.6, 52.0, 44.0, 33.1, 24.9 ppm. HRMS (ESI-TOF) m/z : [M + H]⁺ calcd for C₁₄H₂₆BO₃, 253.1975; found 253.1963.



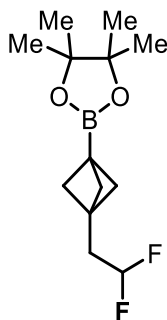
2-(3-(Fluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (21a)

General procedure A. The resulting residue was purified by distillation (b.p. = 62-63 °C, 1 mmHg) to afford the crude product which was triturated in 500 mL of pentane at -40 °C. Yield: 232.10 g, 1.027 mol, 85%, white solid, m.p. = 87-88 °C. ¹H NMR (500 MHz, CDCl₃): δ 4.19 (d, J = 47.8 Hz, 2H), 1.88 (s, 6H), 1.23 (s, 12H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 157.9, 83.6 (d, J = 165.3 Hz), 83.6, 50.3 (d, J = 5.3 Hz), 43.6 (d, J = 22.2 Hz), 24.9 ppm. HRMS (ESI-TOF) m/z : [M + H]⁺ calcd for C₁₂H₂₁BFO₂, 227.1619; found 227.1613.



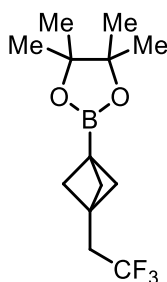
2-(3-(2-Fluoroethyl)bicyclo[1.1.1]pentan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (22a)

General procedure A. The resulting residue was purified by distillation (b.p. = 75-77 °C, 1 mmHg). Yield: 23.52 g, 0.098 mol, 72%, white oil. ¹H NMR (400 MHz, CDCl₃): δ 4.49 (t, J = 6.3 Hz, 1H), 4.38 (t, J = 6.3 Hz, 1H), 1.82 (s, 6H), 1.78 (t, J = 6.3 Hz, 1H), 1.72 (t, J = 6.2 Hz, 1H), 1.23 (s, 12H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 83.4, 82.4 (d, J = 165.1 Hz), 52.1, 43.1 (d, J = 5.4 Hz), 33.9 (d, J = 19.4 Hz), 24.9 ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -220.5 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



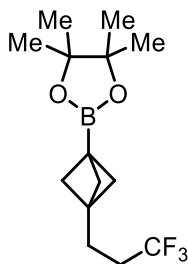
2-(3-(2,2-Difluoroethyl)bicyclo[1.1.1]pentan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (24a)

General procedure A. The resulting residue was purified by distillation (b.p. = 74-75 °C, 1 mmHg). Yield: 35.35 g, 0.137 mol, 61%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 5.75 (tt, J = 56.6, 4.8 Hz, 1H), 1.93 (dt, J = 17.7, 4.7 Hz, 2H), 1.88 (s, 6H), 1.23 (s, 12H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 116.8 (t, J = 239.4 Hz), 83.5, 52.6, 40.4, 37.7 (t, J = 20.0 Hz), 24.9 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -115.6 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{22}\text{BF}_2\text{O}_2$, 259.1681; found 259.1667.



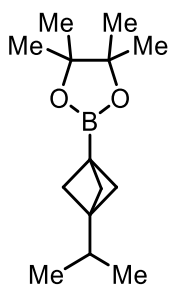
4,4,5,5-Tetramethyl-2-(3-(2,2,2-trifluoroethyl)bicyclo[1.1.1]pentan-1-yl)-1,3,2-dioxaborolane (25a)

General procedure A. The resulting residue was purified by distillation (b.p. = 63-64 °C, 1 mmHg). Yield: 40.57 g, 0.147 mol, 65%, colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 2.17 (q, J = 11.3 Hz, 2H), 1.93 (s, 6H), 1.23 (s, 12H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 126.5 (q, J = 277 Hz), 83.6, 52.7, 39.2, 37.3 (q, J = 27 Hz), 24.9 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -64.6 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{21}\text{BF}_3\text{O}_2$, 277.1587; found 277.1569.



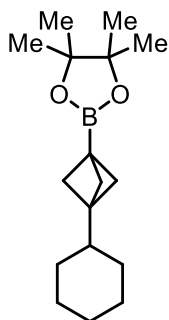
4,4,5,5-Tetramethyl-2-(3-(3,3,3-trifluoropropyl)bicyclo[1.1.1]pentan-1-yl)-1,3,2-dioxaborolane (26a)

General procedure A. The resulting residue was purified by distillation (b.p. = 78-79 °C, 1 mmHg). Yield: 29.87 g, 0.103 mol, 76%, white solid, m.p. < 30 °C. ^1H NMR (500 MHz, CDCl_3): δ 2.03 – 1.92 (m, 2H), 1.76 (s, 6H), 1.62 – 1.56 (m, 2H), 1.23 (s, 12H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 127.5 (q, J = 276 Hz), 83.5, 51.1, 44.3, 30.8 (q, J = 29 Hz), 25.6, 24.9 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -67.0 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{23}\text{BF}_3\text{O}_2$, 291.1743; found 291.1729.



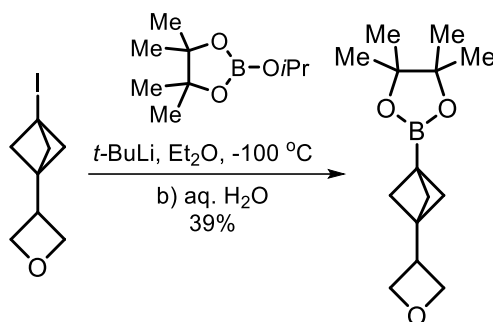
2-(3-Isopropylbicyclo[1.1.1]pentan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (48a)

General procedure A. The resulting residue was purified by distillation (b.p. = 73-74 °C, 1 mmHg). Yield: 30.21 g, 0.128 mol, 57%, white solid, m.p. = 51-52 °C. ^1H NMR (500 MHz, CDCl_3): δ 1.66 (s, 6H), 1.49 (sept, J = 6.8 Hz, 1H), 1.23 (s, 12H), 0.76 (d, J = 6.8 Hz, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 83.3, 50.8, 48.9, 29.7, 24.9, 18.4 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



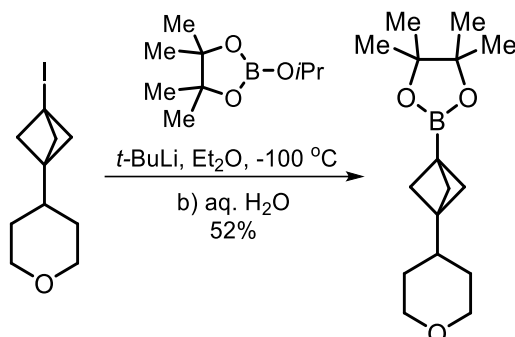
2-(3-Cyclohexylbicyclo[1.1.1]pentan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (53a)

General procedure A. The final product was purified by distillation (b.p. = 124-125 °C, 1 mmHg). Yield: 57.96 g, 0.21 mol, 81%, yellow oil. ^1H NMR (500 MHz, CDCl_3): δ 1.73 – 1.69 (m, 1H), 1.68 (s, 6H), 1.65 – 1.56 (m, 4H), 1.34 – 1.25 (m, 2H), 1.22 (s, 12H), 1.17 – 1.11 (m, 2H), 0.86 – 0.75 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 83.3, 77.2, 49.3, 39.4, 28.9, 28.1, 27.3, 26.2, 24.9 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



4,4,5,5-Tetramethyl-2-(3-(oxetan-3-yl)bicyclo[1.1.1]pentan-1-yl)-1,3,2-dioxaborolane (55a)

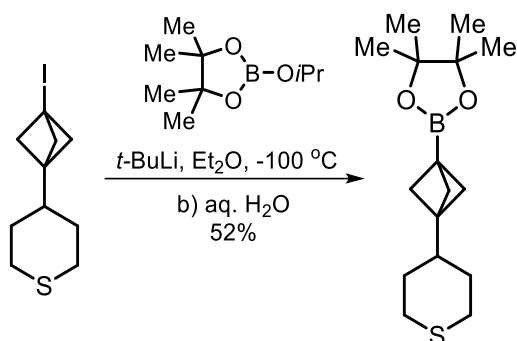
To a solution of 3-{3-iodobicyclo[1.1.1]pentan-1-yl}oxetane (41.30 g, 0.165 mol, 1.00 equiv) in a mixture of anhydrous THF (400 mL) and Et_2O (400 mL) was added 4,4,5,5-tetramethyl-2-(propan-2-yloxy)-1,3,2-dioxaborolane (33.30 g, 0.18 mol, 1.10 equiv). The resulting mixture was cooled to -100 °C under Ar and a solution of $t\text{-BuLi}$ (1.9 M in pentane, 200 mL, 0.38 mol, 2.30 equiv) was added slowly during 1 h, and the solution was stirred at -100 °C for 1 h under Ar. Then the solution was allowed to warm to room temperature overnight. The mixture was washed with H_2O (3×200 mL), dried over Na_2SO_4 , concentrated under reduced pressure, and filtered from 150 mL of hexane. Yield: 16.40 g, 0.065 mol, 39%, white solid, m.p. < 30 °C. ^1H NMR (500 MHz, CDCl_3): δ 4.66 (dd, $J = 8.0, 5.9$ Hz, 2H), 4.43 (t, $J = 6.0$ Hz, 2H), 3.02 – 2.87 (m, 1H), 1.82 (s, 6H), 1.23 (s, 12H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 83.5, 74.0, 49.4, 45.8, 36.7, 24.9 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{14}\text{H}_{27}\text{BNO}_3$, 268.2084; found 268.2068.



4,4,5,5-Tetramethyl-2-(3-(tetrahydro-2H-pyran-4-yl)bicyclo[1.1.1]pentan-1-yl)-1,3,2-dioxaborolane (57a)

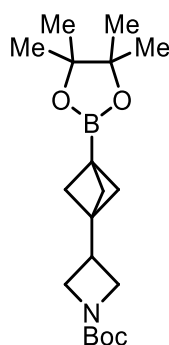
To a solution of 4-{3-iodobicyclo[1.1.1]pentan-1-yl}oxane (46.00 g, 0.165 mol, 1.00 equiv) in anhydrous Et_2O (800 mL) was added 4,4,5,5-tetramethyl-2-(propan-2-yloxy)-1,3,2-dioxaborolane

(33.30 g, 0.18 mol, 1.10 equiv) and cooled to -100 °C under Ar. A solution of *t*-BuLi (1.9 M in pentane, 0.38 mol, 200 mL, 2.30 equiv) was added slowly during 1 h under Ar, and the solution was stirred at -100 °C for 1 h. Then the mixture was allowed to warm to room temperature overnight. The mixture was washed with H₂O (3 × 200 mL), dried over Na₂SO₄, filtered, concentrated under reduced pressure, and filtered from 200 mL of hexane. Yield: 24.00 g, 0.086 mol, 52%, yellow solid, m.p. = 137-138 °C. ¹H NMR (500 MHz, CDCl₃): δ 3.94 (dd, *J* = 11.2, 4.2 Hz, 2H), 3.31 (t, *J* = 12.1 Hz, 2H), 1.69 (s, 6H), 1.49 – 1.38 (m, 3H), 1.28 – 1.24 (m, 2H), 1.22 (s, 12H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 83.4, 68.0, 49.0, 36.7, 28.7, 24.9 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



4,4,5,5-Tetramethyl-2-(3-(tetrahydro-2*H*-thiopyran-4-yl)bicyclo[1.1.1]pentan-1-yl)-1,3,2-dioxaborolane (59a)

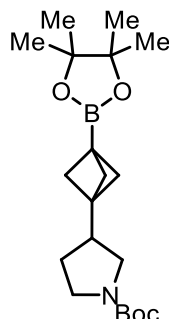
The same procedure as for **57a** was used. The final product was triturated in 200 mL of hexane. Yield: 25.20 g, 0.085 mol, 52%, white solid, m.p. = 154-155 °C. ¹H NMR (500 MHz, CDCl₃): δ 2.66 – 2.52 (m, 4H), 1.93 – 1.84 (m, 2H), 1.68 (s, 6H), 1.62 (br s, 1H), 1.28 – 1.22 (m, 2H), 1.22 (s, 12H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 83.4, 49.1, 38.9, 29.8, 28.7, 24.9 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



***Tert*-butyl 3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (60a)**

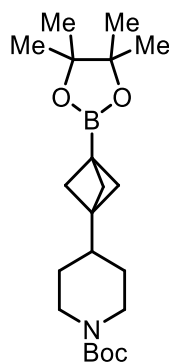
General procedure A. The final product was purified by column chromatography (SiO₂, hexane/EtOAc, 9:1, *R_f* = 0.50). Yield: 70.00 g, 0.20 mol, 80%, yellow solid, m.p. = 68-69 °C. ¹H

NMR (500 MHz, CDCl₃): δ 3.84 (t, J = 8.4 Hz, 2H), 3.60 (dd, J = 8.4, 5.5 Hz, 2H), 2.50 – 2.38 (m, 1H), 1.77 (s, 6H), 1.42 (s, 9H), 1.23 (s, 12H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 156.7, 83.5, 79.3, 51.0, 49.1, 46.2, 30.3, 28.6, 24.9 ppm. HRMS (ESI-TOF) m/z : [M + NH₄]⁺ calcd for C₁₉H₃₆BN₂O₄, 367.2768; found 367.2795.



(±)-*Tert*-butyl 3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[1.1.1]pentan-1-yl)pyrrolidine-1-carboxylate (**61a**)

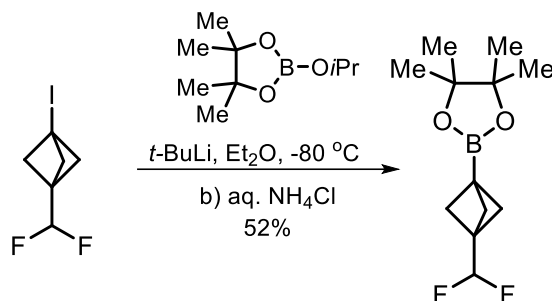
General procedure A. The resulting residue was purified by distillation from 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (40-50 °C, 1 mmHg). The crude product was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 95-5%, R_f = 0.50, hexane/MeOtBu, 9:1). Yield: 43.20 g, 0.119 mol, 53%, white solid, m.p. = 126-127 °C. ¹H NMR (500 MHz, CDCl₃): δ 3.40 – 3.27 (m, 2H), 3.25 – 3.17 (m, 1H), 3.01 (dd, J = 10.6, 7.6 Hz, 1H), 2.12 – 2.05 (m, 1H), 1.82 – 1.68 (m, 1H), 1.73 (s, 6H), 1.62 – 1.55 (m, 1H), 1.44 (s, 9H), 1.22 (s, 12H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 154.8, 83.4, 79.0, 50.0, 48.1, 46.5, 45.8, 40.4, 28.7, 28.0, 24.9 ppm. HRMS (ESI-TOF) m/z : [M + Na]⁺ calcd for C₂₀H₃₄BNNaO₄, 386.2479; found 386.2457.



Tert-butyl 4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-1-carboxylate (**63a**)

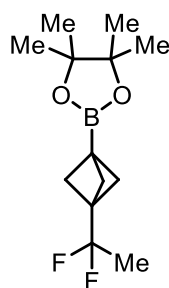
General procedure A. The resulting residue was purified by distillation from 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (40-50 °C, 1 mmHg). The crude product was purified by column chromatography (SiO₂, hexane/MeOtBu, 95-5%, R_f = 0.37, hexane/MeOtBu, 9:1). Yield: 38.45 g, 0.102 mol, 46%, white solid, m.p. = 105-106 °C. ¹H NMR (500 MHz, CDCl₃): δ 4.09 (d, J

= 12.9 Hz, 2H), 2.59 (td, J = 12.8, 1.8 Hz, 2H), 1.68 (s, 6H), 1.50 (d, J = 12.5 Hz, 2H), 1.44 (s, 9H), 1.35 – 1.28 (m, 1H), 1.22 (s, 12H), 1.07 – 0.97 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 155.1, 83.4, 79.3, 49.2, 48.8, 43.9, 37.8, 28.6, 28.0, 24.9 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



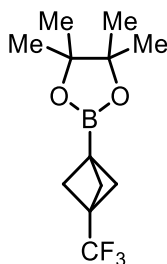
2-(3-(Difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (67a)

To a solution of 1-(difluoromethyl)-3-iodobicyclo[1.1.1]pentane (42.65 g, 0.175 mol, 1.00 equiv) in dry Et_2O (500 mL) was added a 1.9M $t\text{-BuLi}$ solution in pentane (193 mL, 0.367 mol, 2.10 equiv) dropwise by cannula at -80 to -75 °C (a dry ice/acetone bath) under Ar atmosphere. The reaction mixture was allowed to stir at this temperature for 30 min. A solution of 4,4,5,5-tetramethyl-2-(propan-2-yloxy)-1,3,2-dioxaborolane (35.77 g, 0.192 mol 1.10 equiv) in dry Et_2O (150 mL) was added to the reaction mixture at -80 to -75 °C under Ar. Then after 1 h, the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was quenched with a sat. aq. solution of ammonium chloride (200 mL). The organic layer was separated, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was recrystallized from 100 mL of hexane. Yield: 22.30 g, 0.091 mol, 52%, white solid, m.p. = 106-107 °C. ^1H NMR (400 MHz, CDCl_3): δ 5.49 (t, J = 56.6 Hz, 1H), 1.95 (s, 6H), 1.24 (s, 12H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 112.7 (t, J = 239.5 Hz), 83.8, 48.9 (t, J = 4.1 Hz), 43.2 (t, J = 27.1 Hz), 24.9 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -124.8 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



2-(3-(1,1-Difluoroethyl)bicyclo[1.1.1]pentan-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (68a)

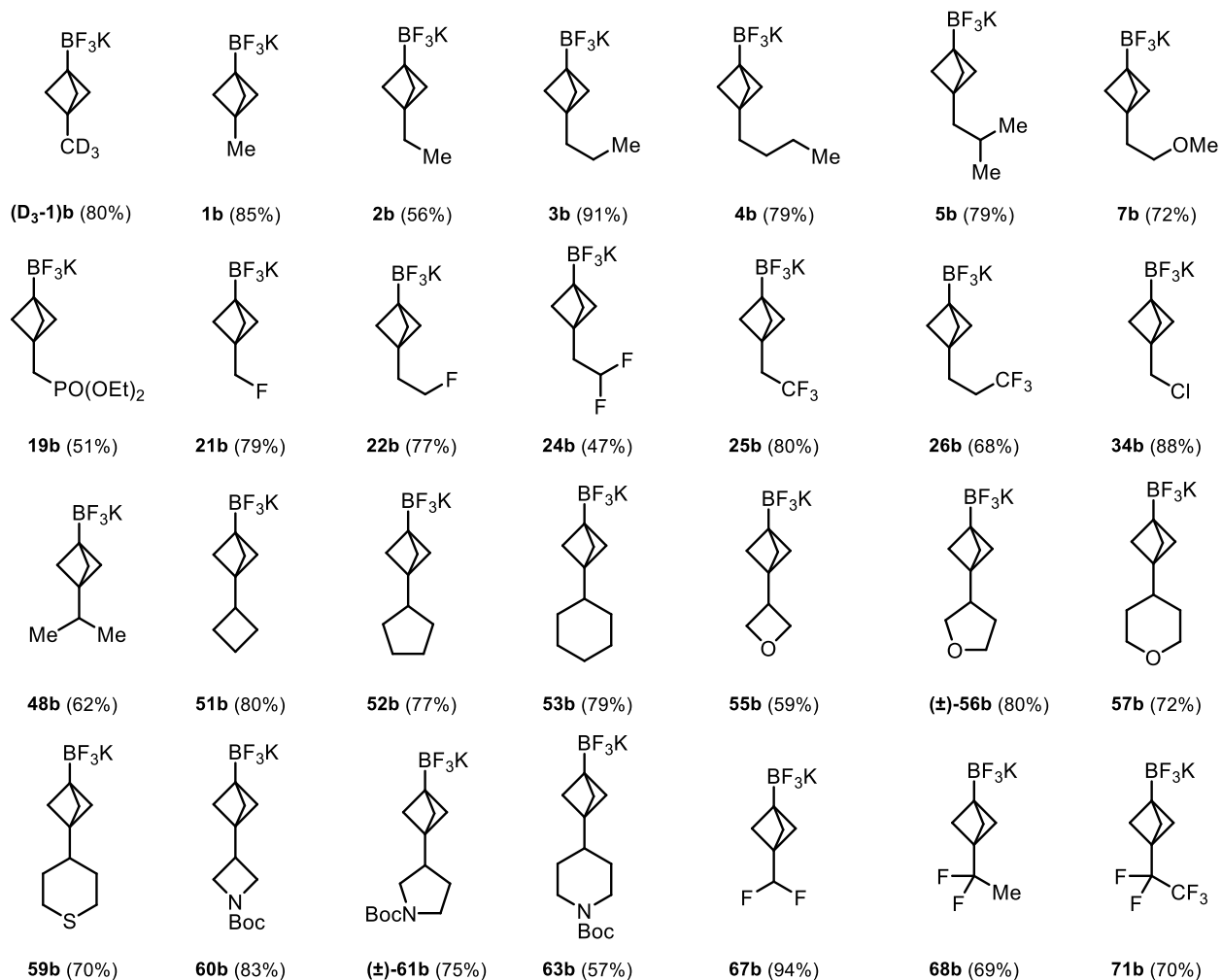
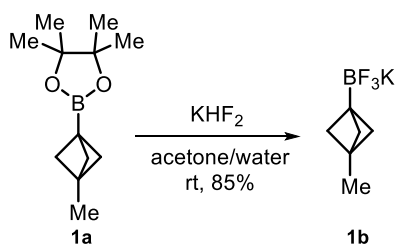
General procedure A. The final product was triturated in 200 mL of hexane. Yield: 25.80 g, 0.10 mol, 62%, white solid, m.p. = 69-70 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.93 (s, 6H), 1.48 (t, J = 18.2 Hz, 3H), 1.24 (s, 12H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 119.9 (t, J = 237.7 Hz), 83.7, 49.1 (t, J = 3.8 Hz), 45.9 (t, J = 32.9 Hz), 27.0, 24.9, 20.2 (t, J = 27.9 Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -100.9 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



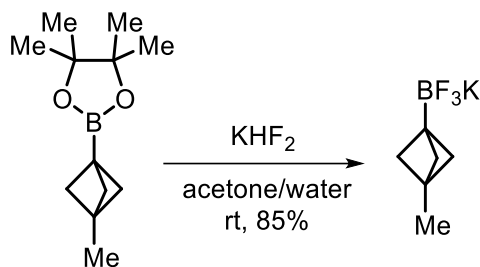
4,4,5,5-Tetramethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)-1,3,2-dioxaborolane (69a)

General procedure A. The final product was triturated in 100 mL of hexane. Yield: 16.77 g, 0.064 mol, 64%, white solid, m.p. = 124-125 °C. ^1H NMR (500 MHz, CDCl_3): δ 2.04 (s, 6H), 1.24 (s, 12H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 121.6 (q, J = 277.5 Hz), 83.9, 49.4 (d, J = 1.9 Hz), 41.8 (q, J = 36.5 Hz), 24.9 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -75.8 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.

2. Trifluoroborates



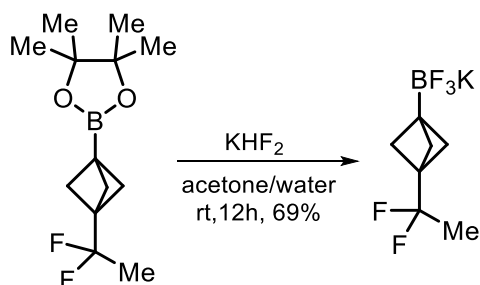
General procedure B-1 (1b as an example)



Potassium trifluoro({3-methylbicyclo[1.1.1]pentan-1-yl})boranuide (1b)

To a solution of 4,4,5,5-tetramethyl-2-{3-methylbicyclo[1.1.1]pentan-1-yl}-1,3,2-dioxaborolane (15.70 g, 0.075 mol, 1.00 equiv) in a mixture of acetone (300 mL) and water (100 mL) was added KHF_2 (23.60 g, 0.302 mol, 4.02 equiv). The mixture was stirred for 4 h at room temperature and concentrated under reduced pressure. The residue was recrystallized from 50 mL of acetonitrile. Yield: 12.00 g, 0.064 mol, 85%, white solid, m.p. = 231-232 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 1.26 (s, 6H), 0.95 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO-d_6): δ 51.4, 38.5, 20.8 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO-d_6): δ -142.5 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.

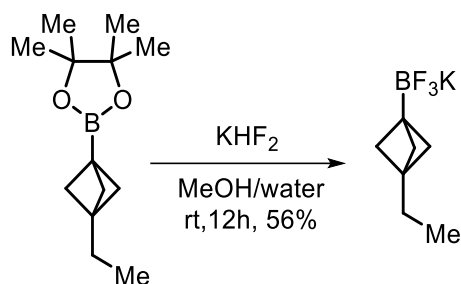
General procedure B-2 (68b as an example)



Potassium [3-(1,1-difluoroethyl)bicyclo[1.1.1]pentan-1-yl]trifluoroboranuide (68b)

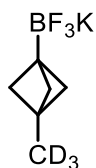
To a stirred solution of **68a** (45.00 g, 0.174 mol, 1.00 equiv) in MeOH (500 mL) was added a solution of KHF_2 (35.00 g, 0.44 mol, 2.50 equiv) in H_2O (500 mL). The resulting mixture was stirred for 12 h at room temperature. The reaction mixture was then concentrated in *vacuo* and washed with hot acetone (3×100 mL). The combined fractions were filtered and concentrated in *vacuo*. The residue was dissolved in MeOtBu (500 mL), and a white precipitate was collected by filtration and dried. Yield: 28.70 g, 0.12 mol, 69%, white solid, m.p. = 270-271 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 1.44 (t, J = 18.5 Hz, 3H), 1.39 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO-d_6): δ 120.9 (t, J = 237.8 Hz), 46.6, 42.7 (t, J = 31.8 Hz), 20.1 (t, J = 27.8 Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO-d_6): δ -98.2 (s), -143.3 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.

Modified general procedure B-2 (2b as an example)



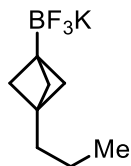
Potassium {3-ethylbicyclo[1.1.1]pentan-1-yl}trifluoroboranuide (2b)

To a stirred solution of **2a** (45.00 g, 0.174 mol, 1.00 equiv) in MeOH (500 mL) was added a solution of KHF₂ (35.00 g, 0.44 mol, 2.50 equiv) in H₂O (500 mL). The resulting mixture was stirred for 12 h at room temperature. After that, the mixture was concentrated under reduced pressure (30 – 15 mmHg, 40-50 °C). The product was dried in *vacuo* (0.1 – 2.0 mmHg, at 60 °C) under P₂O₅ until the amount of water was less than 0.1 – 0.2 mol%. At this stage, the crude product was crushed and shaken. The obtained solid was washed with dry MeOtBu (3 × 100 mL) to get rid of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. After that, the precipitate was washed with dry hot acetone (40 – 50 °C, 5 × 100 mL) and concentrated in *vacuo* (10 mmHg, 40 °C) to afford potassium {3-ethylbicyclo[1.1.1]pentan-1-yl}trifluoroboranuide. Yield: 15.32 g, 0.076 mol, 56%, white solid, m.p. = 284-285 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 1.22 (q, *J* = 7.5 Hz, 2H), 1.19 (s, 6H), 0.73 (t, *J* = 7.5 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 48.6, 43.0, 26.5, 10.3 ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -142.6 (s) ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



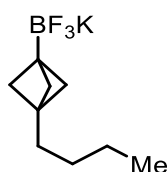
Trifluoro(3-(methyl-d₃)bicyclo[1.1.1]pentan-1-yl)-λ⁴-borane, potassium salt ((D₃-1)b)

Modified general procedure B-2. Yield: 1.15 g, 0.006 mol, 80%, white solid, m.p. = 268-270 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 1.26 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 51.4, 38.4 ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -142.5 (s) ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



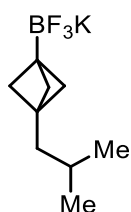
Potassium trifluoro(3-propylbicyclo[1.1.1]pentan-1-yl)boranuide (3b)

General procedure B-1. Yield: 46.15 g, 0.195 mol, 91%, white solid, m.p. = 271-273 °C. ^1H NMR (500 MHz, DMSO- d_6): δ 1.22 (s, 6H), 1.18 (br s, 4H), 0.84 (br s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 49.5, 42.3, 36.1, 19.4, 14.4 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -142.6 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



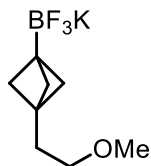
Potassium {3-butylbicyclo[1.1.1]pentan-1-yl}trifluoroboranuide (4b)

General procedure B-1. Yield: 21.10 g, 0.116 mol, 79%, white solid, m.p. = 284-285 °C. ^1H NMR (400 MHz, DMSO- d_6): δ 1.21 (s, 6H), 1.27 – 1.12 (m, 6H), 0.83 (t, J = 7.1 Hz, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6): δ 49.4, 42.3, 33.5, 28.4, 22.5, 14.1 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -142.6 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



Potassium trifluoro[3-(2-methylpropyl)bicyclo[1.1.1]pentan-1-yl]boranuide (5b)

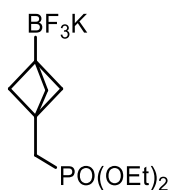
Modified general procedure B-2. Yield: 34.45 g, 0.15 mol, 95%, white solid, m.p. = 298-299 °C. ^1H NMR (500 MHz, DMSO- d_6): δ 1.58 – 1.47 (m, 1H), 1.27 (s, 6H), 1.12 (d, J = 6.4 Hz, 2H), 0.83 (d, J = 6.6 Hz, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 50.6, 43.2, 42.0, 26.1, 23.4 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -142.6 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



Potassium trifluoro[3-(2-methoxyethyl)bicyclo[1.1.1]pentan-1-yl]boranuide (7b)

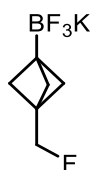
Modified general procedure B-2. Yield: 4.95 g, 0.021 mol, 72%, white solid, m.p. = 217-218 °C.

^1H NMR (500 MHz, DMSO- d_6): δ 3.23 (t, J = 7.4 Hz, 2H), 3.17 (s, 3H), 1.45 (t, J = 7.4 Hz, 2H), 1.25 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 70.4, 57.7, 50.9, 33.5 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -142.7 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



Potassium {3-[(diethoxyphosphoryl)methyl]bicyclo[1.1.1]pentan-1-yl}trifluoroboranuide (19b)

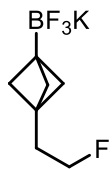
General procedure B-2. Yield: 9.90 g, 0.030 mol, 51%, white solid, m.p. = 139-140 °C. ^1H NMR (400 MHz, DMSO- d_6): δ 3.99 – 3.82 (m, 4H), 1.77 (d, J = 18.4 Hz, 2H), 1.38 (s, 6H), 1.20 (t, J = 7.0 Hz, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 60.3 (d, J = 6.2 Hz), 51.5 (d, J = 6.9 Hz), 35.9 (d, J = 5.4 Hz), 29.9 (d, J = 133.4 Hz), 16.3 (d, J = 5.3 Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -142.7 (s) ppm. $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, DMSO- d_6): δ 29.1 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



Potassium trifluoro[3-(fluoromethyl)bicyclo[1.1.1]pentan-1-yl]boranuide (21b)

Modified general procedure B-2. Yield: 27.74 g, 0.136 mol, 79%, white solid, m.p. = 235-236 °C.

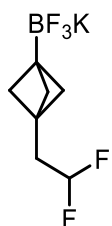
^1H NMR (400 MHz, DMSO- d_6): δ 4.10 (d, J = 48.3 Hz, 2H), 1.33 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 84.1 (d, J = 163.4 Hz), 48.0 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -143.2 (s), -220.3 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



Potassium trifluoro[3-(2-fluoroethyl)bicyclo[1.1.1]pentan-1-yl]boranuide (22b)

Modified general procedure B-2. Yield: 16.50 g, 0.075 mol, 77%, white solid, m.p. = 220-221 °C.

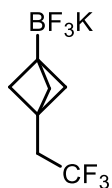
^1H NMR (500 MHz, DMSO- d_6): δ 4.37 (dt, J = 47.6, 6.5 Hz, 2H), 1.61 (dt, J = 24.6, 6.5 Hz, 2H), 1.29 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 82.5 (d, J = 162.9 Hz), 50.0, 34.2 (d, J = 19.0 Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -142.7, -217.9 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



Potassium [3-(2,2-difluoroethyl)bicyclo[1.1.1]pentan-1-yl]trifluoroboranuide (24b)

Modified general procedure B-2. Yield: 15.35 g, 0.065 mol, 47%, white solid, m.p. = 257-258 °C.

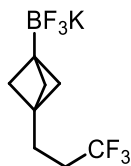
^1H NMR (500 MHz, DMSO- d_6): δ 5.90 (t, J = 56.7 Hz, 1H), 1.78 (td, J = 18.4, 4.2 Hz, 2H), 1.35 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 117.6 (t, J = 237.9 Hz), 50.5, 37.9 (t, J = 18.7 Hz), 36.7 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -114.0 (s), -143.1 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



Potassium trifluoro[3-(2,2,2-trifluoroethyl)bicyclo[1.1.1]pentan-1-yl]boranuide (25b)

Modified general procedure B-2. Yield: 29.97 g, 0.117 mol, 80%, white solid, m.p. = 255-256 °C.

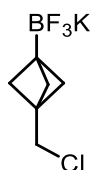
^1H NMR (500 MHz, DMSO- d_6): δ 2.19 (q, J = 12.1 Hz, 2H), 1.41 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 128.2 (q, J = 276.7 Hz), 50.6, 36.8 (q, J = 25.1 Hz), 35.6 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -62.9 (s), -143.0 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



Potassium trifluoro[3-(3,3,3-trifluoropropyl)bicyclo[1.1.1]pentan-1-yl]boranuide (26b)

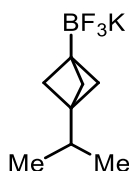
Modified general procedure B-2. Yield: 9.50 g, 0.035 mol, 68%, white solid, m.p. = 250-251 °C.

^1H NMR (500 MHz, DMSO- d_6): δ 2.07 – 1.97 (m, 2H), 1.43 (dd, J = 10.0, 6.8 Hz, 2H), 1.25 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 127.9 (q, J = 276.1 Hz), 48.8, 30.7, 30.1 (q, J = 27.5 Hz), 25.8 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -65.4 (s), -142.8 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



Potassium [3-(chloromethyl)bicyclo[1.1.1]pentan-1-yl]trifluoroboranuide (34b)

Modified general procedure B-2. Yield: 32.75 g, 0.147 mol, 88%, white solid, m.p. > 400 °C. ^1H NMR (400 MHz, DMSO- d_6): δ 3.40 (s, 2H), 1.31 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 48.3, 47.1, 41.3 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -143.0 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



Potassium trifluoro[3-(propan-2-yl)bicyclo[1.1.1]pentan-1-yl]boranuide (48b)

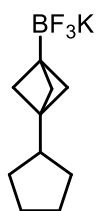
Modified general procedure B-2. Yield: 17.11 g, 0.078 mol, 62%, white solid, m.p. = 297-298 °C.

^1H NMR (500 MHz, DMSO- d_6): δ 1.36 (p, J = 6.8 Hz, 1H), 1.14 (s, 6H), 0.71 (d, J = 6.8 Hz, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 46.5, 29.5, 18.6 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -142.6 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



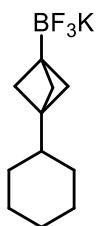
Potassium {3-cyclobutylbicyclo[1.1.1]pentan-1-yl}trifluoroborane (51b)

General procedure B-2. Yield: 25.13 g, 0.1102 mol, 80%, yellow solid, m.p. > 400 °C. ^1H NMR (500 MHz, DMSO- d_6): δ 2.15 – 2.06 (m, 1H), 1.83 – 1.59 (m, 6H), 1.19 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 46.9, 44.7, 37.2, 23.6, 17.6 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -61.8 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



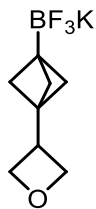
Potassium {3-cyclopentylbicyclo[1.1.1]pentan-1-yl}trifluoroborane (52b)

General procedure B-2. Yield: 23.80 g, 0.0983 mol, 77%, white solid, m.p. = 253-254 °C. ^1H NMR (500 MHz, DMSO- d_6): δ 1.74 – 1.62 (m, 1H), 1.52 – 1.37 (m, 6H), 1.26 – 1.11 (m, 2H), 1.16 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 47.5, 44.8, 41.5, 28.3, 25.4 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -142.6 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



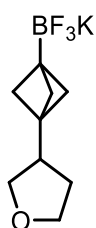
Potassium {3-cyclohexylbicyclo[1.1.1]pentan-1-yl}trifluoroborane (53b)

General procedure B-2. Yield: 12.50 g, 0.0488 mol, 79%, white solid, m.p. = 257-258 °C. ^1H NMR (500 MHz, DMSO- d_6): δ 1.68 – 1.49 (m, 5H), 1.15 (s, 6H), 1.20 – 0.93 (m, 5H), 0.74 (q, J = 12.5 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 46.9, 45.8, 28.8, 26.0, 25.7 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -142.6 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



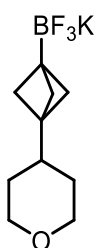
Potassium trifluoro[3-(oxetan-3-yl)bicyclo[1.1.1]pentan-1-yl]boranuide (55b)

Modified general procedure B-2. Yield: 13.61 g, 0.059 mol, 59%, white solid, m.p. > 400 °C. ^1H NMR (400 MHz, DMSO- d_6): δ 4.48 (dd, J = 8.0, 5.5 Hz, 2H), 4.25 (t, J = 5.8 Hz, 2H), 2.83 – 2.71 (m, 1H), 1.28 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 72.8, 46.9, 42.1, 36.3 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -143.0 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



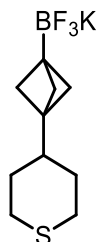
(±)-Potassium trifluoro[3-(oxolan-3-yl)bicyclo[1.1.1]pentan-1-yl]boranuide (56b)

General procedure B-2. Yield: 17.60 g, 0.0721 mol, 80%, white solid, m.p. = 212-213 °C. ^1H NMR (500 MHz, DMSO- d_6): δ 3.61 – 3.49 (m, 3H), 3.33 – 3.30 (m, 1H), 2.06 – 1.94 (m, 1H), 1.75 – 1.65 (m, 1H), 1.55 – 1.44 (m, 1H), 1.19 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 69.4, 67.4, 47.6, 42.7, 41.0, 28.8 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -142.8 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



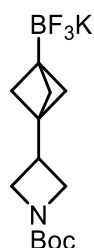
Potassium trifluoro[3-(oxan-4-yl)bicyclo[1.1.1]pentan-1-yl]boranuide (57b)

General procedure B-2. Yield: 29.90 g, 0.116 mol, 72%, white solid, m.p. = 260-261 °C. ^1H NMR (400 MHz, DMSO- d_6): δ 3.81 (dd, J = 10.9, 3.8 Hz, 2H), 3.19 (t, J = 10.9 Hz, 2H), 1.37 – 1.20 (m, 3H), 1.15 (s, 6H), 1.11 – 0.99 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 67.0, 46.6, 45.1, 36.6, 28.7 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -142.7 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



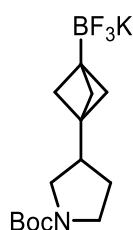
Potassium trifluoro[3-(thian-4-yl)bicyclo[1.1.1]pentan-1-yl]boranuide (59b)

General procedure B-2. Yield: 26.10 g, 0.095 mol, 70%, white solid, m.p. = 268-269 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 2.57 – 2.51 (m, 4H), 1.84 – 1.77 (m, 2H), 1.16 (s, 6H), 1.11 – 1.01 (m, 3H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 46.6, 45.7, 38.7, 29.8, 27.8 ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -142.7 (s) ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



Potassium (3-{1-[(*tert*-butoxy)carbonyl]azetidin-3-yl}bicyclo[1.1.1]pentan-1-yl)trifluoroboranuide (60b)

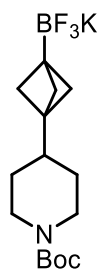
General procedure B-2. Yield: 15.40 g, 0.0468 mol, 83%, white solid, m.p. > 400 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 3.72 (br s, 2H), 3.45 (br s, 2H), 3.32 (s, 12H), 2.36 – 2.29 (m, 1H), 1.36 (s, 9H), 1.24 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 155.8, 78.2, 51.4, 50.3, 46.5, 42.4, 30.1, 28.1 ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -143.0 (s) ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



(±)-Potassium (3-{1-[(*tert*-butoxy)carbonyl]pyrrolidin-3-yl}bicyclo[1.1.1]pentan-1-yl)trifluoroboranuide (61b)

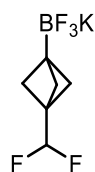
Modified general procedure B-2. Yield: 30.68 g, 0.089 mol, 75%, white solid, m.p. = 226-228 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 3.28 – 3.20 (m, 1H), 3.18 – 3.05 (m, 2H), 2.92, 2.90 (2×d, *J* = 7.0 Hz, 1H), 2.00 – 1.91 (m, 2H), 1.70 (br s, 1H), 1.55 – 1.44 (m, 1H), 1.382, 1.377 (2×s, 9H), 1.21, 1.20 (2×s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 153.6, 77.9, 48.1, 47.9, 47.6, 45.6,

45.3, 42.72, 42.67, 40.6, 40.1, 28.2, 28.1, 27.2 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -142.9 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



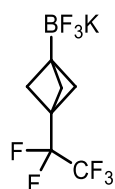
Potassium (3-{1-[(*tert*-butoxy)carbonyl]piperidin-4-yl}bicyclo[1.1.1]pentan-1-yl)trifluoroborane (63b)

Modified general procedure B-2. Yield: 20.83 g, 0.058 mol, 57%, white solid, m.p. > 400 °C. ^1H NMR (400 MHz, DMSO- d_6): δ 3.99 – 3.85 (m, 2H), 2.70 – 2.52 (m, 2H), 1.46 – 1.39 (m, 2H), 1.37 (s, 9H), 1.23 – 1.17 (m, 1H), 1.15 (s, 6H), 0.89 – 0.74 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 153.8, 78.3, 46.8, 44.9, 43.2 (br s), 37.5, 28.1, 27.9 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -142.8 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



Potassium [3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl]trifluoroborane (67b)

General procedure B-1. Yield: 15.55 g, 0.064 mol, 94%, white solid, m.p. = 256-258 °C. ^1H NMR (500 MHz, DMSO- d_6): δ 5.64 (t, J = 57.1 Hz, 1H), 1.40 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 113.6 (t, J = 237.8 Hz), 46.5 (d, J = 1.5 Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -123.0 (s), -143.6 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.

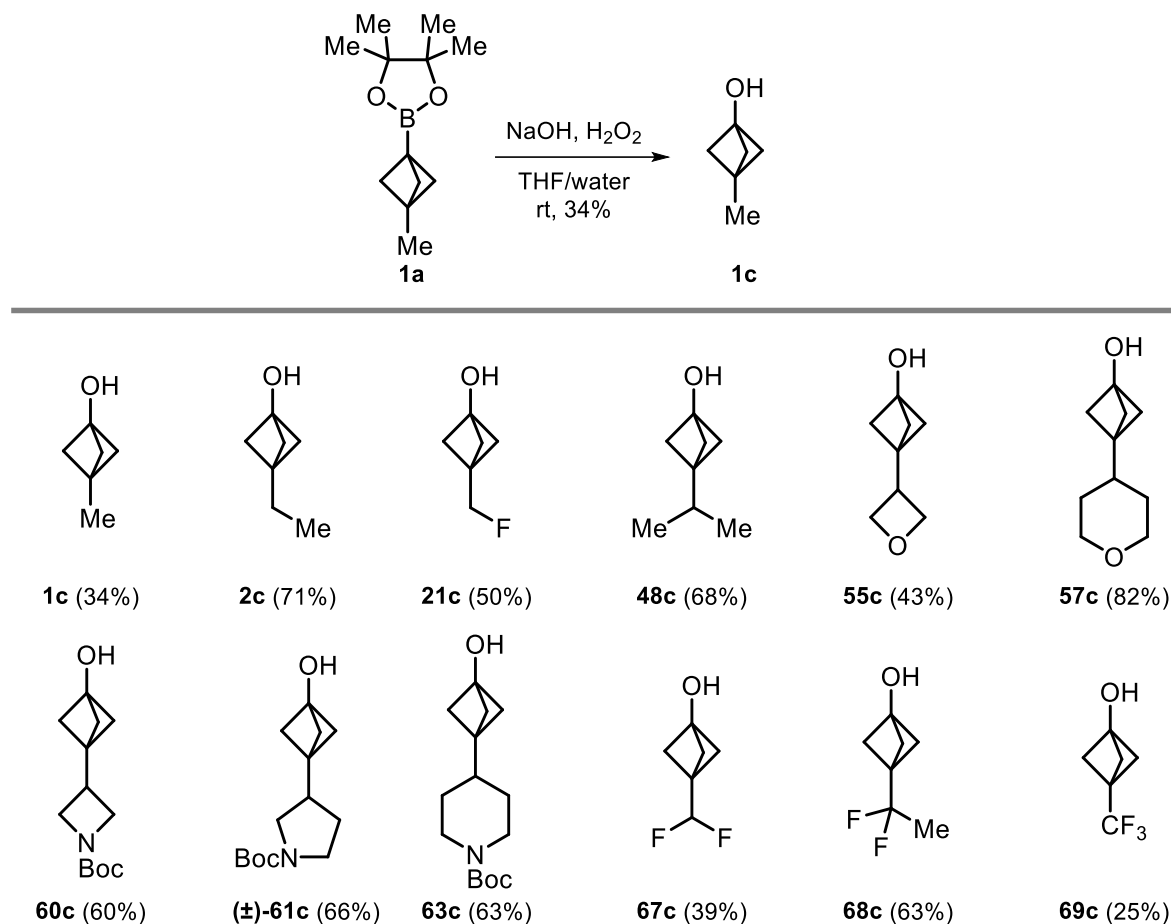


Potassium trifluoro[3-(1,1,2,2,2-pentafluoroethyl)bicyclo[1.1.1]pentan-1-yl]borane (71b)

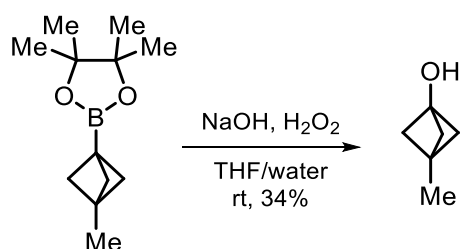
General procedure B-2 was used: cyclohexane (absolute) was used instead of acetone. Yield: 13.00 g, 0.0445 mol, 70%, white solid, m.p. = 247-249 °C. ^1H NMR (500 MHz, DMSO- d_6): δ 1.57 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 119.1 (qt, J = 286.8, 37.6 Hz), 110.4 (tq, J =

250.4, 35.9 Hz), 47.3, 37.7 (t, $J = 27.6$ Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -82.2 (s), -121.2 (s), -144.1 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.

3. Alcohols



General procedure C-1 (1c as an example)

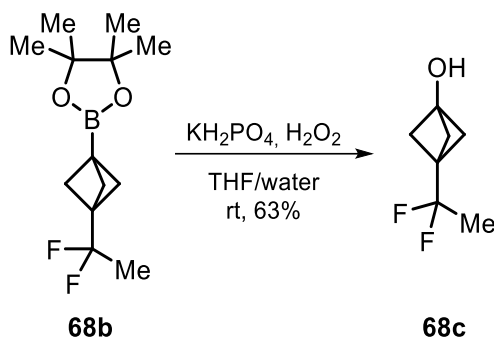


3-Methylbicyclo[1.1.1]pentan-1-ol (1c)

To a solution of 4,4,5,5-tetramethyl-2-{3-methylbicyclo[1.1.1]pentan-1-yl}-1,3,2-dioxaborolane (60.00 g, 0.288 mol, 1.00 equiv) in THF (300 mL) was added a solution of NaOH (13.85 g 0.346 mol 1.20 equiv) and hydrogen peroxide (36.00 g, 0.317 mol, 1.10 equiv) in water (100 mL). The reaction mixture was stirred overnight, and then extracted with MeOtBu (3 × 200 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO₂, MeOtBu/hexane, 4:1, R_f = 0.48). Yield: 9.50 g, 0.097 mol, 34%, white solid, m.p. = 53-54 °C. ¹H NMR (400 MHz,

CDCl₃): δ 2.74 (s, 1H), 1.76 (s, 6H), 1.22 (s, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 62.1, 55.5, 27.2, 15.5 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.

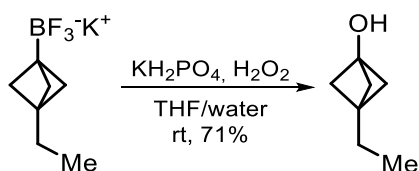
General procedure C-2 (68c as an example)



3-(1,1-Difluoroethyl)bicyclo[1.1.1]pentan-1-ol (68c)

To a solution of KH₂PO₄ (49.00 g, 0.36 mol, 3.00 equiv) and **68b** (28.70 g, 0.12 mol, 1.00 equiv) in a mixture of H₂O (300 mL) and THF (300 mL) was added H₂O₂ (30%, 136.00 g, 1.20 mol, 10.00 equiv) dropwise at 0 °C. The resulting mixture was stirred at room temperature overnight. The solution was diluted with water (500 mL) and extracted with MeOtBu (2 × 300 mL). The combined organic layers were washed with water (1 × 500 mL) and a sat. aq. solution of NaHSO₃ (1 × 500 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was dissolved in a mixture of hexane/MeOtBu (1:1, 150 mL), filtered through SiO₂, and concentrated under reduced pressure. Yield: 11.30 g, 0.076 mol, 63%, white solid, m.p. = 51-52 °C. ¹H NMR (400 MHz, CDCl₃): δ 2.34 (br s, 1H), 2.01 (s, 6H), 1.58 (t, *J* = 18.0 Hz, 3H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 121.4 (t, *J* = 236.7 Hz), 62.4, 52.4 (t, *J* = 2.8 Hz), 33.4 (t, *J* = 34.4 Hz), 21.5 (t, *J* = 28.1 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -96.0 (s) ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.

General procedure C-3 (2c as an example)



3-Ethylbicyclo[1.1.1]pentan-1-ol (2c)

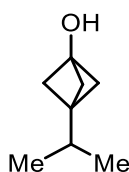
To a solution of KH₂PO₄ (91.70 g, 0.674 mol, 3.00 equiv) and **2b** (45.50 g, 0.225 mol, 1.00 equiv) in a mixture of H₂O (900 mL) and THF (1400 mL) was added H₂O₂ (30%, 260 mL, 2.25 mol, 10.00 equiv) dropwise at 0 °C. The resulting mixture was stirred at room temperature overnight. The

solution was diluted with water (1 L) and extracted with CHCl₃ (3 × 500 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by distillation (b.p. = 54-55 °C, 10 mmHg). Yield: 17.80 g, 0.159 mol, 71%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 2.24 (br s, 1H), 1.73 (s, 6H), 1.55 (q, *J* = 7.4 Hz, 2H), 0.86 (t, *J* = 7.4 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 62.6, 53.1, 31.8, 22.3, 11.5 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



3-(Fluoromethyl)bicyclo[1.1.1]pentan-1-ol (21c)

General procedure C-2. Yield: 20.00 g, 0.172 mol, 50%, colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 4.52 (d, *J* = 47.6 Hz, 2H), 2.23 (br s, 1H), 1.94 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 82.0 (d, *J* = 166.2 Hz), 63.3, 53.1 (d, *J* = 3.7 Hz), 29.7 (d, *J* = 23.6 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -220.3 (s) ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₆H₁₀FO, 117.0716; found 117.0710.



3-Isopropylbicyclo[1.1.1]pentan-1-ol (48c)

General procedure C-3. The residue was purified by distillation (b.p. = 68-69 °C at 10 mmHg). Yield: 20.00 g, 0.158 mol, 68%, brown oil. ¹H NMR (500 MHz, CDCl₃): δ 2.43 (br s, 1H), 1.79 (sept, *J* = 6.8 Hz, 1H), 1.68 (s, 6H), 0.83 (d, *J* = 6.8 Hz, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 119.5, 62.5, 51.4, 35.7, 26.8, 19.7 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



3-(Oxetan-3-yl)bicyclo[1.1.1]pentan-1-ol (55c)

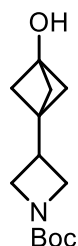
General procedure C-2. Yield: 7.30 g, 0.052 mol, 43%, yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 4.73 (dd, *J* = 7.9, 6.0 Hz, 2H), 4.37 (t, *J* = 6.0 Hz, 2H), 3.22 – 3.15 (m, 1H), 1.84 (s, 6H) ppm.

$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 74.9, 63.2, 52.1, 34.0, 31.5 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



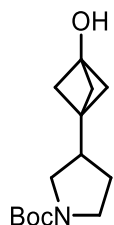
3-(Tetrahydro-2H-pyran-4-yl)bicyclo[1.1.1]pentan-1-ol (57c)

General procedure C-2. Yield: 16.60 g, 0.098 mol, 82%, olive solid, m.p. = 76-77 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 5.99 (br s, 1H), 3.82 (dd, J = 11.1, 4.0 Hz, 2H), 3.24 (t, J = 11.0 Hz, 2H), 1.66 – 1.60 (m, 1H), 1.56 (s, 9H), 1.41 (d, J = 13.0 Hz, 2H), 1.08 (qd, J = 12.5, 4.4 Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO-d_6): δ 66.8, 61.8, 51.1, 34.6, 33.2, 29.7 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{17}\text{O}_2$, 169.1229; found 169.1222.



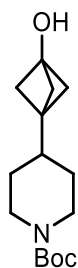
Tert-butyl 3-(3-hydroxybicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (60c)

To a solution of KH_2PO_4 (73.10 g, 0.538 mol, 2.50 equiv) and **60b** (70.76 g, 0.215 mol, 1.00 equiv) in a mixture of H_2O (510 mL) and THF (950 mL) was added H_2O_2 (30%, 510 mL, 4.50 mol, 8.36 equiv) dropwise at 0 °C. The resulting mixture was stirred at room temperature overnight. The solution was diluted with water (1000 mL) and extracted with CHCl_3 (3 $\times$ 250 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Yield: 30.82 g, 0.129 mol, 60%, colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 3.93 (t, J = 8.4 Hz, 2H), 3.56 (dd, J = 8.6, 5.4 Hz, 2H), 2.73 – 2.67 (m, 1H), 1.81 (s, 6H), 1.42 (s, 9H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 156.7, 79.7, 63.2, 52.1, 52.0, 32.2, 28.5, 27.8 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



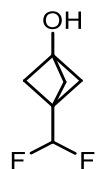
(±)-tert-butyl 3-(3-hydroxybicyclo[1.1.1]pentan-1-yl)pyrrolidine-1-carboxylate (61c)

General procedure C-3. The residue was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 9:1 to 7:3, R_f = 0.30, EtOAc/hexane, 7:3). Yield: 15.10 g, 0.059 mol, 66%, yellow solid, m.p. = 86-87 °C. ¹H NMR (400 MHz, CDCl₃): δ 3.46 – 3.35 (m, 2H), 3.30 – 3.21 (m, 1H), 3.01 – 2.93 (m, 1H), 2.40 – 2.30 (m, 2H), 1.92 – 1.83 (m, 1H), 1.77 (s, 6H), 1.61 – 1.51 (m, 1H), 1.45 (s, 9H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 154.8, 79.3, 62.6, 52.6, 49.2, 45.8, 37.3, 31.9, 29.3, 28.7 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



tert-butyl 4-(3-hydroxybicyclo[1.1.1]pentan-1-yl)piperidine-1-carboxylate (63c)

General procedure C-3. The residue was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 9:1 to 7:3, R_f = 0.44, EtOAc/hexane, 7:3). Yield: 15.60 g, 0.058 mol, 63%, white solid, m.p. = 76-77 °C. ¹H NMR (500 MHz, CDCl₃): δ 4.10 (d, *J* = 13.2 Hz, 2H), 2.63 (td, *J* = 12.9, 2.1 Hz, 3H), 1.70 (s, 6H), 1.64 – 1.52 (m, 3H), 1.44 (s, 9H), 1.09 – 0.98 (m, 2H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 155.0, 79.5, 62.6, 51.7, 43.9, 34.7, 34.1, 29.3, 28.6 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₅H₂₅NNaO₃, 290.1732; found 290.1715.



3-(Difluoromethyl)bicyclo[1.1.1]pentan-1-ol (67c)

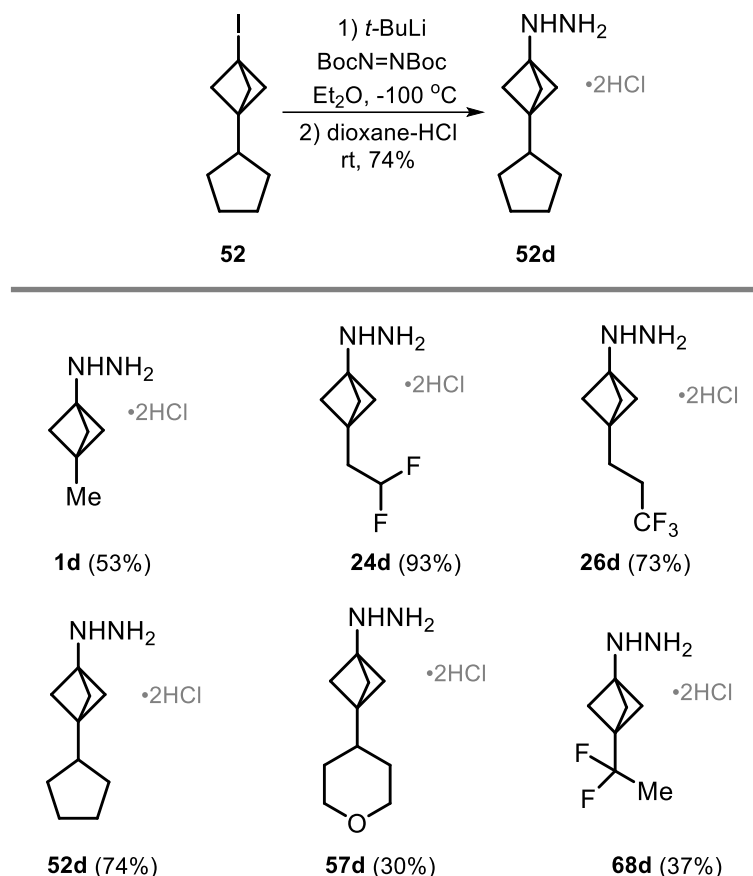
General procedure C-1. Yield: 3.40 g, 0.025 mol, 39%, colorless solid, m.p. = 42-44 °C. ¹H NMR (400 MHz, CDCl₃): δ 5.88 (t, *J* = 56.6 Hz, 1H), 2.74 (br s, 1H), 2.02 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 113.9(t, *J* = 238.5 Hz), 63.2, 52.2 (t, *J* = 3.4 Hz), 30.5 (t, *J* = 28.7 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -120.1 (s) ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₆H₉F₂O, 135.0621; found 135.0615.



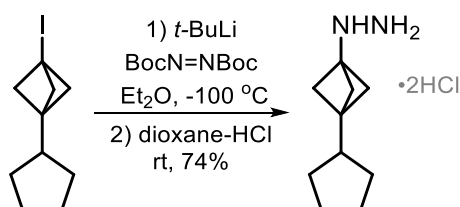
3-(Trifluoromethyl)bicyclo[1.1.1]pentan-1-ol (69c)

General procedure C-1. Yield: 5.17 g, 0.034 mol, 25%, white solid, m.p. = 77-78 °C. ^1H NMR (400 MHz, CDCl_3): δ 2.49 (br s, 1H), 2.15 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 124.4 (q, $J = 273.3$ Hz), 62.5 (q, $J = 2.4$ Hz), 52.9, 30.3 (q, $J = 39.8$ Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -70.5 (s) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.

4. Hydrazines



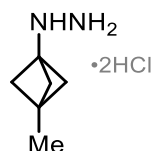
General procedure D (52d as an example)



(3-Cyclopentylbicyclo[1.1.1]pentan-1-yl)hydrazine dihydrochloride (**52d**)

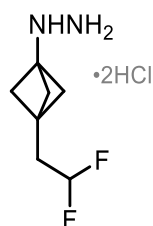
A solution of **52** (67.90 g, 0.259 mol, 1.00 equiv) in Et₂O (1400 mL), was cooled to -100 °C in a stream of argon, and *t*-BuLi (300 mL, 0.57 mol, 2.20 equiv, 1.9M solution in pentane) was added via cannula over 20 min. After 2 min, *di-tert*-butyl diazene-1,2-dicarboxylate (62.60 g, 0.272 mol, 1.10 equiv) was added in portions over 15 min. The reaction mixture was stirred overnight at room temperature, and then washed with water (2 × 500 mL), dried over Na₂SO₄, filtered, and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO₂, gradient, hexane/EtOAc, 10-15% of EtOAc, R_f = 0.30, EtOAc/hexane, 1:9). The product was dissolved in CH₂Cl₂ (500 mL) and 5M HCl in dioxane (300 mL) was added in one portion. The mixture was stirred overnight at room temperature. The solution was concentrated, triturated with MeOtBu (200

mL), and filtered off. The residue was dried under reduced pressure (~ 20 mmHg) to give the desired product. Yield over 2 steps: 45.90 g, 0.193 mol, 74%, yellow solid, m.p. = 137-138 °C. ^1H NMR (500 MHz, D_2O): δ 2.10 (p, J = 7.7 Hz, 1H), 1.79 (s, 6H), 1.66 – 1.59 (m, 2H), 1.57 – 1.46 (m, 4H), 1.31 – 1.22 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, D_2O): δ 50.7, 47.9, 38.0, 38.0, 28.7, 25.2 ppm. LCMS ($\text{M}+\text{H}$) $^+$: 167. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{19}\text{N}_2$, 167.1548; found 167.1540.



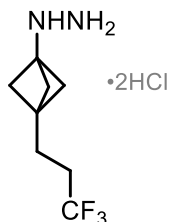
(3-Methylbicyclo[1.1.1]pentan-1-yl)hydrazine dihydrochloride (1d)

General procedure D. The final product was washed with a mixture of Et_2O /hexane, (100 mL, 1:9). Yield over 2 steps: 33.50 g, 0.181 mol, 53%, yellow solid, m.p. = 146-147 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 5.53 (br s, 5H), 1.69 (s, 6H), 1.19 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, $\text{DMSO}-d_6$): δ 52.0, 51.2, 31.6, 16.5 ppm. LCMS ($\text{M}+\text{H}$) $^+$: 113. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_6\text{H}_{13}\text{N}_2$, 113.1079; found 113.1074.



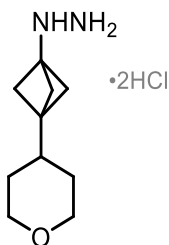
(3-(2,2-Difluoroethyl)bicyclo[1.1.1]pentan-1-yl)hydrazine dihydrochloride (24d)

General procedure D. Deprotection: 2M HCl in Et_2O (100 mL). Yield over 2 steps: 4.52 g, 0.0192 mol, 93% yellow solid, m.p. = 152-153 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.37 (br s, 5H), 6.05 (tt, J = 56.2, 4.5 Hz, 1H), 2.10 (td, J = 18.2, 4.4 Hz, 2H), 1.79 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, $\text{DMSO}-d_6$): δ 117.1 (t, J = 238 Hz), 52.19, 52.15 (t, J = 180 Hz), 51.6, 34.0 (t, J = 21 Hz). $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, $\text{DMSO}-d_6$): δ -115.5 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



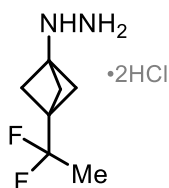
(3-(3,3,3-Trifluoropropyl)bicyclo[1.1.1]pentan-1-yl)hydrazine dihydrochloride (26d)

General procedure D. Deprotection: 2M HCl in Et₂O (100 mL). Yield over 2 steps: 6.20 g, 0.0232 mol, 73%, white solid, m.p. = 136-137 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 9.24 (br s, 2H), 2.29 – 2.06 (m, 2H), 1.79 – 1.70 (m, 2H), 1.70 (s, 9H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 127.5 (q, *J* = 276 Hz), 51.4, 50.1, 34.0, 30.3 (q, *J* = 28 Hz), 22.3 ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -65.4 ppm. LCMS (M + H)⁺: 195. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₈H₁₄F₃N₂, 195.1109; found 195.1100.



(3-(Tetrahydro-2H-pyran-4-yl)bicyclo[1.1.1]pentan-1-yl)hydrazine dihydrochloride (57d)

General procedure D. Yield over 2 steps: 2.10 g, 0.0082 mol, 30%, yellow solid, m.p. = 190-191 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 7.70 (br s, 5H), 3.81 (dd, *J* = 11.0, 3.9 Hz, 2H), 3.22 (t, *J* = 11.7 Hz, 2H), 1.60 (s, 6H), 1.59 – 1.54 (m, 1H), 1.39 (d, 2H), 1.06 (qd, *J* = 12.5, 4.4 Hz, 2H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 66.7, 51.3, 48.1, 38.5, 33.7, 29.2 ppm. LCMS (M + H)⁺: 183. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₀H₁₉N₂O, 183.1497; found 183.1487.

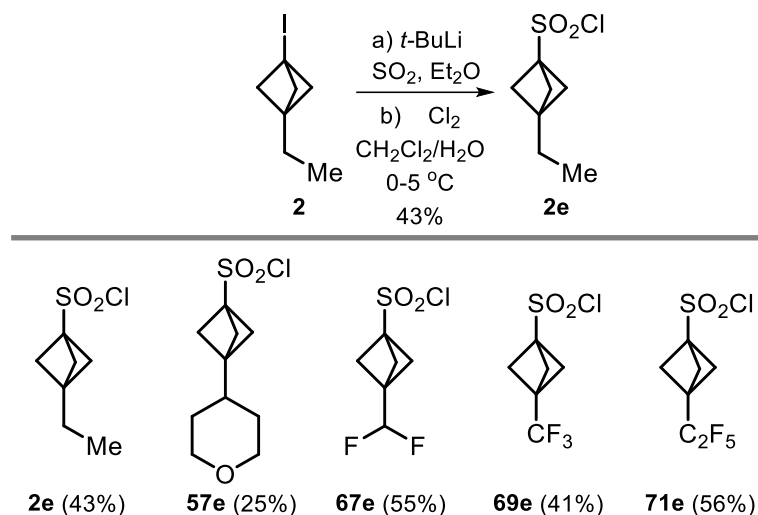


(3-(1,1-Difluoroethyl)bicyclo[1.1.1]pentan-1-yl)hydrazine dihydrochloride (68d)

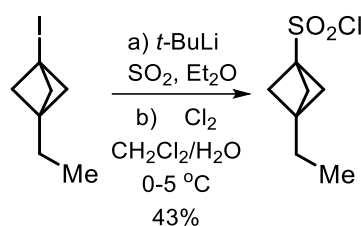
Compound **68** (42.00 g, 0.162 mol, 1.00 equiv) was dissolved in dry Et₂O (800 mL) and cooled to -100 °C. A solution of *t*-BuLi (1.9 M in pentane, 0.38 mol, 200 mL, 2.30 equiv) was added slowly during 45 min. The resulting mixture was stirred at -100 °C for 30 min. Then *di-tert*-butyl diazene-1,2-dicarboxylate (41.00 g, 0.178 mol, 1.10 equiv) was added, and the solution was stirred at -100 °C for 1 h. The mixture was warmed to room temperature and stirred overnight. The solution was diluted with saturated aq. NH₄Cl and extracted with EtOAc (3 × 100 mL). The combined organic

extracts were dried over Na₂SO₄, filtered, concentrated, and purified by column chromatography (SiO₂, EtOAc/hexane, 2:3, R_f = 0.45). The product was dissolved in dry Et₂O (100 mL), and a solution of Et₂O (200 mL) saturated by dry gas HCl (~ 15%) was added. The resulting solution was stirred at room temperature for 15 h. The precipitate was filtered and dried. Yield over 2 steps: 14.00 g, 0.06 mol, 37%, white solid, m.p. = 154-155 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 9.34 (br s, 2H), 6.43 (br s, 3H), 1.89 (s, 6H), 1.58 (t, *J* = 18.6 Hz, 3H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 121.5 (t, *J* = 236 Hz), 51.1, 49.0, 36.9 (t, *J* = 34 Hz), 20.8 (t, *J* = 27 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -95.3 (s) ppm. LCMS (M + H)⁺: 163. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₇H₁₃F₂N₂, 163.1047; found 163.1037.

5. Sulfonyl chlorides



General procedure E (2e as an example)

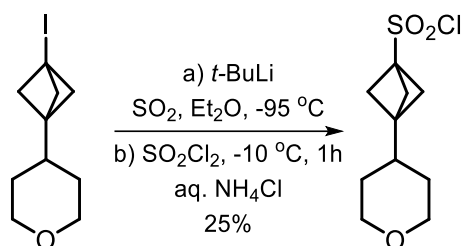


3-Ethylbicyclo[1.1.1]pentane-1-sulfonyl chloride (2e)

a). *Lithium 3-ethylbicyclo[1.1.1]pentane-1-sulfinate*. A solution of 1-ethyl-3-iodobicyclo[1.1.1]pentane (40.20 g, 0.181 mol 1.00 equiv) in dry Et₂O (400 mL) was cooled to -95-100 °C under Ar. *t*-BuLi (200 mL, 0.382 mol, 2.11 equiv, 1.9M solution in pentane) was added dropwise over ~20 min. The mixture was stirred at -95-100 °C for 15 min. The solution was bubbled with SO₂ for 20 min and warmed to room temperature. The mixture was diluted with 500 mL of pentane. The formed precipitate was filtered, Et₂O (250 mL), anhydrous pentane (250 mL) and dried under reduced pressure. The obtained crude product was taken for the next step without further purification.

b). *3-Ethylbicyclo[1.1.1]pentane-1-sulfonyl chloride*. Chlorine gas was bubbled through a stirred solution of lithium 3-ethylbicyclo[1.1.1]pentane-1-sulfinate (24.60 g, 0.126 mol, 1.00 equiv) in CH₂Cl₂ (360 mL) and H₂O (40 mL) for 10 min at 0-5 °C. The reaction mixture was stirred for 1 h at room temperature and diluted with 200 mL of H₂O. The organic layer was separated and dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 100% to 7:3, R_f = 0.77, hexane/MeOtBu, 7:3). Yield over 2 steps: 13.20 g, 0.079 mol, 43%, beige solid, m.p. = 47-48 °C. ¹H NMR (500

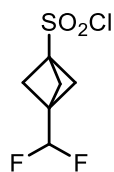
MHz, CDCl₃): δ 2.23 (s, 6H), 1.66 (q, J = 7.5 Hz, 2H), 0.92 (t, J = 7.5 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 59.4, 52.5, 39.5, 23.4, 10.4 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



3-(Tetrahydro-2H-pyran-4-yl)bicyclo[1.1.1]pentane-1-sulfonyl chloride (57e)

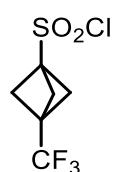
a). *Lithium 3-(tetrahydro-2H-pyran-4-yl)bicyclo[1.1.1]pentane-1-sulfinate*. A solution of 4-(3-iodobicyclo[1.1.1]pentan-1-yl)tetrahydro-2H-pyran (55.00 g, 0.198 mol 1.00 equiv) in dry Et₂O (500 mL) was cooled to -95-100 °C under Ar. *t*-BuLi (220 mL, 0.418 mol, 2.11 equiv, 1.9M solution in pentane) was added dropwise over ~ 30 min. The mixture was stirred at -95-100 °C for 15 min. The solution was bubbled with SO₂ for 20 min and warmed to room temperature. The mixture was diluted with 500 mL of pentane. The formed precipitate was filtered, washed with Et₂O (250 mL), anhydrous pentane (250 mL), and dried under reduced pressure. The obtained crude product was taken for the next step without further purification.

b). *3-(Tetrahydro-2H-pyran-4-yl)bicyclo[1.1.1]pentane-1-sulfonyl*. A solution of lithium 3-(tetrahydro-2H-pyran-4-yl)bicyclo[1.1.1]pentane-1-sulfinate (43.96 g, 0.198 mol, 1.00 equiv) in hexane (500 mL) was cooled to -10 °C and SO₂Cl₂ (32.13 g, 0.238 mol, 1.20 equiv) was added dropwise over 20 min. The mixture was stirred for 1 h and quenched with aq. sat. NH₄Cl (200 mL). The mixture was concentrated under reduced pressure. The aqueous residue was extracted with MeOtBu (3 × 200 mL). The combined organic layers were washed with brine (1 × 200 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 100% to 7:3, R_f = 0.40). Yield over 2 steps: 12.60 g, 0.05 mol, 25%, brown solid, m.p. = 109-110 °C. ¹H NMR (500 MHz, CDCl₃): δ 4.01 (dd, J = 11.2, 3.8 Hz, 2H), 3.37 (t, J = 11.4 Hz, 2H), 2.23 (s, 6H), 1.87 – 1.75 (m, 1H), 1.52 (d, J = 11.6 Hz, 2H), 1.38 – 1.23 (m, 2H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 67.5, 59.4, 50.9, 41.5, 34.5, 29.0 ppm. HRMS (ESI-TOF) m/z : [M + H]⁺ calcd for C₁₀H₁₆ClO₃S, 251.0509; found 251.0499.



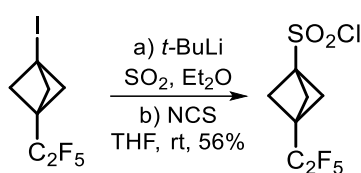
3-(Difluoromethyl)bicyclo[1.1.1]pentane-1-sulfonyl chloride (67e)

General procedure E. The final product was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 100% to 7:3, R_f = 0.80, hexane/MeOtBu, 7:3). Yield over 2 steps: 22.08 g, 0.102 mol, 55%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 5.88 (t, *J* = 55.5 Hz, 1H), 2.51 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 111.6 (t, *J* = 241.4 Hz), 59.1, 51.3 (t, *J* = 3.9 Hz), 36.5 (t, *J* = 30.1 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -122.9 (s) ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



3-(Trifluoromethyl)bicyclo[1.1.1]pentane-1-sulfonyl chloride (69e)

General procedure E. The final product was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 100% to 7:3, R_f = 0.77, hexane/MeOtBu, 7:3). Yield over 2 steps: 17.68 g, 0.0754 mol, 41%, beige solid, m.p. = 86-87 °C. ¹H NMR (400 MHz, CDCl₃): δ 2.62 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 121.9 (q, *J* = 275.9 Hz), 58.0, 51.8 (d, *J* = 1.9 Hz), 35.7 (t, *J* = 41.6 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -72.5 (s) ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.

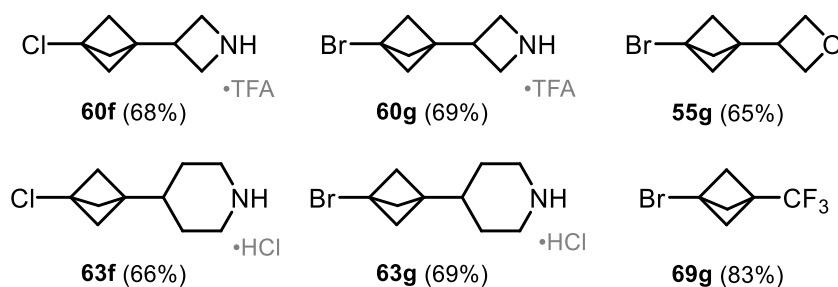


3-(Perfluoroethyl)bicyclo[1.1.1]pentane-1-sulfonyl chloride (71e)

a). *Lithium 3-(perfluoroethyl)bicyclo[1.1.1]pentane-1-sulfinate*. A solution of 1-iodo-3-(perfluoroethyl)bicyclo[1.1.1]pentane (23.84 g, 0.0764 mol, 1.00 equiv) in dry Et₂O (410 mL) was cooled to -100 °C under Ar. *t*-BuLi (88 mL, 0.168 mol, 2.20 equiv, 1.9M solution in pentane) was added dropwise over 20 min. The resulting mixture was bubbled with SO₂ for 20 min and warmed to room temperature. The mixture was diluted with 500 mL of pentane. The formed precipitate was filtered, washed with pentane (250 mL), and dried under reduced pressure. The obtained crude product was taken for the next step without further purification.

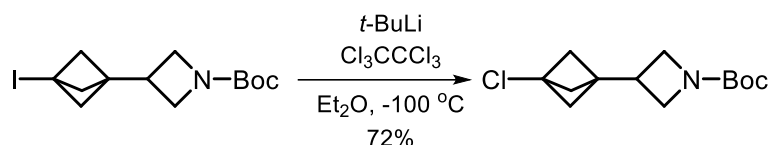
b). *3-(Perfluoroethyl)bicyclo[1.1.1]pentane-1-sulfonyl chloride*. To a suspension of 3-(perfluoroethyl)bicyclo[1.1.1]pentane-1-lithium sulfinat (15.66 g, 0.0611 mol, 1.00 equiv) in dry THF (160 mL) was added NCS (8.57 g, 0.064 mol, 1.05 equiv) in one portion at 0 °C in a stream of argon. The reaction mixture was warmed and stirred at room temperature for 16 h. The volatiles were evaporated under reduced pressure. The resulting residue was triturated in Et₂O (150 mL) and filtered. The organic layer was washed with water (3 × 50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the title product. Yield over 2 steps: 12.18 g, 0.043 mol, 56%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 2.64 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 118.7 (qt, *J* = 286.2, 35.8 Hz), 109.9 (tq, *J* = 253.7, 38.6 Hz), 58.1, 52.1, 35.1 (t, *J* = 31.6 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -83.2 (s), -120.8 (s) ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.

Halides



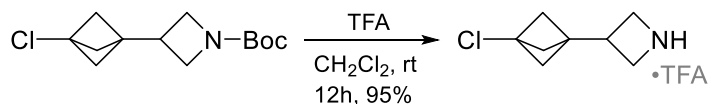
6. Chlorides

General procedure for F (60f-Boc as an example)



Tert-butyl 3-(3-chlorobicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (60f-Boc)

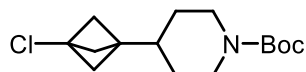
A solution of *tert*-butyl 3-(3-iodobicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (88.00 g, 0.252 mol, 1.00 equiv) in 1500 mL of Et_2O was cooled to -100°C under Ar. *t*-BuLi (279 mL, 0.529 mol, 2.10 equiv, 1.9M solution in pentane) was added dropwise over 20 min. The mixture was stirred for 15 min at the same temperature, and a solution of hexachloroethane (71.59 g, 0.302 mol, 1.20 equiv) in 100 mL of Et_2O was added dropwise. The mixture was stirred for 1 h at -90°C and then warmed to room temperature. The mixture was quenched with an aqueous saturated solution of NH_4Cl (~ 100 g in 1 L of water). The organic layer was separated and washed with water (1 $\times$ 200 mL), and brine (1 $\times$ 200 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , hexane/ MeOtBu , 9:1, $R_f = 0.30$). Yield: 46.61 g, 0.181 mol, 72%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 3.94 (t, $J = 8.4$ Hz, 2H), 3.57 (dd, $J = 8.6, 5.3$ Hz, 2H), 2.75 – 2.64 (m, 1H), 2.07 (s, 6H), 1.43 (s, 9H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 156.5, 79.7, 55.3, 51.8, 49.0, 38.9, 28.5, 28.4 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{20}\text{ClNNaO}_2$, 280.1080; found 280.1074.



3-(3-Chlorobicyclo[1.1.1]pentan-1-yl)azetidine trifluoroacetic acid (60f)

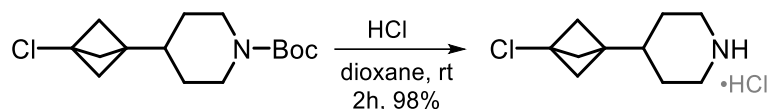
To a solution of *tert*-butyl 3-(3-chlorobicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (46.61 g, 0.181 mol, 1.00 equiv) in CH_2Cl_2 (200 mL) was added TFA (51.64 g, 34.66 mL, 0.453 mol, 2.50 equiv) in one portion at room temperature. The resulting mixture was stirred overnight at the same

temperature, and then concentrated under reduced pressure. The residue was triturated in MeOtBu (~ 200 mL), filtered, and dried. Yield: 46.70 g, 0.172 mol, 95%, white solid, m.p. = 166-167 °C. ^1H NMR (400 MHz, DMSO- d_6): δ 8.92 (br s, 2H), 3.96 (t, J = 9.4 Hz, 2H), 3.70 (br s, 2H), 3.10 – 2.97 (m, 1H), 2.13 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 54.9, 49.0, 47.9 (br s), 37.7, 30.6 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -74.1 (s) ppm. LCMS ($M + H$) $^+$: 158. HRMS (ESI-TOF) m/z : [$M + H$] $^+$ calcd for $\text{C}_8\text{H}_{13}\text{ClN}$, 158.0737; found 158.0734.



***Tert*-butyl 4-(3-chlorobicyclo[1.1.1]pentan-1-yl)piperidine-1-carboxylate (63f-Boc)**

General procedure for F. The residue was purified by column chromatography (SiO_2 , hexane/MeOtBu, 9:1, R_f = 0.48). Yield: 43.00 g, 0.151 mol, 67%, white solid, m.p. = 77-78 °C. ^1H NMR (500 MHz, CDCl_3): δ 4.13 (br s, 2H), 2.62 (br s, 2H), 1.97 (s, 6H), 1.65 – 1.58 (m, 1H), 1.55 (d, J = 12.9 Hz, 2H), 1.44 (s, 9H), 1.13 – 1.03 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 154.9, 79.6, 55.2, 48.8, 43.7, 41.0, 35.8, 29.0, 28.6 ppm. HRMS (ESI-TOF) m/z : [$M + H$] $^+$ calcd for $\text{C}_{15}\text{H}_{24}\text{ClNNaO}_2$, 308.1393; found 308.1387.

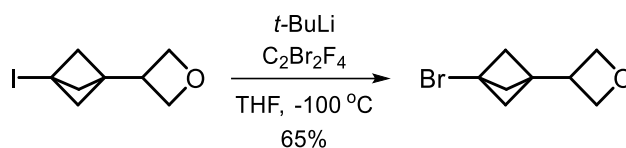


4-(3-Chlorobicyclo[1.1.1]pentan-1-yl)piperidine hydrochloride (63f)

Tert-butyl 4-(3-chlorobicyclo[1.1.1]pentan-1-yl)piperidine-1-carboxylate (43.00 g, 0.151 mol) was dissolved in 5M HCl (300 mL) in dioxane at room temperature. The mixture was stirred for 2 h and concentrated under reduced pressure. The residue was triturated in MeOtBu (150 mL), filtered, and dried. Yield: 32.86 g, 0.148 mol, 98%, white solid, m.p. = 182-183 °C. ^1H NMR (500 MHz, DMSO- d_6): δ 9.28 (br s, 1H), 8.84 (br s, 1H), 3.20 (d, J = 12.5 Hz, 2H), 2.82 – 2.73 (m, 2H), 2.00 (s, 6H), 1.81 – 1.75 (m, 1H), 1.65 (d, J = 13.4 Hz, 2H), 1.36 – 1.26 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 54.7, 48.6, 42.5, 40.4, 32.4, 25.4 ppm. LCMS ($M + H$) $^+$: 186. HRMS (ESI-TOF) m/z : [$M + H$] $^+$ calcd for $\text{C}_{10}\text{H}_{17}\text{ClN}$, 186.1050; found 186.1040.

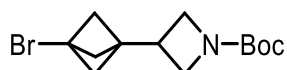
7. Bromides

General procedure G (compound 55g as an example)



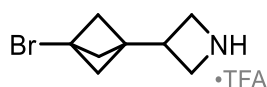
3-(3-Bromobicyclo[1.1.1]pentan-1-yl)oxetane (55g)

A solution of 3-(3-iodobicyclo[1.1.1]pentan-1-yl)oxetane (66.25 g, 0.265 mol, 1.00 equiv) in 1500 mL of THF was cooled to $-100\text{ }^\circ\text{C}$ under Ar. $t\text{-BuLi}$ (293 mL, 0.557 mol, 2.10 equiv, 1.9M solution in pentane) was added dropwise over 20 min. The mixture was stirred for 15 min at the same temperature, and a solution of 1,2-dibromotetrafluoroethane (151.58 g, 0.583 mol, 2.20 equiv) in 150 mL of THF was added dropwise. The mixture was stirred for 1 h at $-90\text{ }^\circ\text{C}$ and then warmed to room temperature. The mixture was quenched with an aqueous saturated solution of NH_4Cl (~ 100 g in 1 L of water). The organic layer was separated; the aqueous layer was additionally extracted with MeOtBu ($2 \times 400\text{ mL}$). The combined organic layers were washed with water ($1 \times 300\text{ mL}$), and brine ($1 \times 300\text{ mL}$), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , hexane/ MeOtBu , 9:1, $R_f = 0.37$). Yield: 34.92 g, 0.172 mol, 65%, yellow solid, m.p. = $84\text{--}85\text{ }^\circ\text{C}$. ^1H NMR (500 MHz, CDCl_3): δ 4.73 (t, $J = 6.9\text{ Hz}$, 2H), 4.37 (t, $J = 6.0\text{ Hz}$, 2H), 3.16 (p, $J = 6.9\text{ Hz}$, 1H), 2.20 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 74.2, 56.8, 41.8, 37.2, 35.5 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{12}\text{BrO}$, 203.0072; found 203.0063.



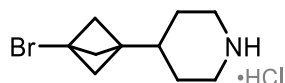
Tert-butyl 3-(3-bromobicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (60g-Boc)

General procedure G, solvent – Et_2O . The final product was purified by column chromatography (SiO_2 , hexane/ MeOtBu , 9:1, $R_f = 0.3$). Yield: 60.01 g, 0.199 mol, 70%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 3.93 (t, $J = 8.5\text{ Hz}$, 2H), 3.57 (dd, $J = 8.5, 5.3\text{ Hz}$, 2H), 2.72 – 2.62 (m, 1H), 2.15 (s, 6H), 1.42 (s, 9H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 156.5, 79.7, 56.6, 51.7, 42.4, 37.2, 29.2, 28.5 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{20}\text{BrNNaO}_2$, 324.0575; found 324.0565.



3-(3-Bromobicyclo[1.1.1]pentan-1-yl)azetidine trifluoroacetic acid (60g)

The same procedure as for **60f** was applied. Yield: 32.86 g, 0.104 mol, 98%, white solid, m.p. = 147-149 °C. ^1H NMR (400 MHz, DMSO- d_6): δ 8.89 (br s, 2H), 3.95 (br s, 2H), 3.71 (br s, 2H), 3.10 – 2.96 (m, 1H), 2.22 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 56.3, 47.8, 41.2, 37.9, 31.3 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -74.1 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{13}\text{BrN}$, 202.0231; found 202.0227.



4-(3-Bromobicyclo[1.1.1]pentan-1-yl)piperidine hydrochloride (**63g**)

The same procedure as for **63f** was applied. Yield: 42.64 g, 0.16 mol, 98%, white solid, m.p. = 156-158 °C. ^1H NMR (500 MHz, DMSO- d_6): δ 9.25 (br s, 1H), 8.80 (br s, 1H), 3.18 (d, J = 12.4 Hz, 2H), 2.76 (q, J = 12.1 Hz, 2H), 2.08 (s, 6H), 1.80 – 1.72 (m, 1H), 1.63 (d, J = 13.4 Hz, 2H), 1.34 – 1.24 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 56.1, 43.9, 42.5, 37.8, 33.4, 25.3 ppm. LCMS ($\text{M} + \text{H}$) $^+$: 232. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{17}\text{BrN}$, 230.0544; found 230.0529.



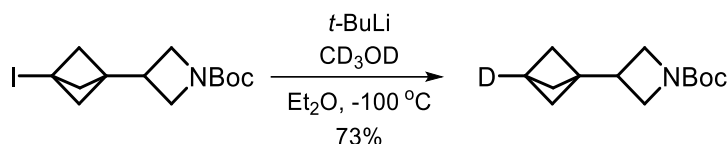
1-Bromo-3-(trifluoromethyl)bicyclo[1.1.1]pentane (**69g**)

Modified general procedure G: solvent – Et_2O . The final product was purified by column chromatography (SiO_2 , hexane/ MeOtBu , 9:1, R_f = 0.37). Yield: 29.89 g, 0.139 mol, 83%, yellow solid, m.p. = 65-66 °C. ^1H NMR (500 MHz, CDCl_3): δ 2.42 (s, 6H) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -71.4 (s) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 122.3 (q, J = 275 Hz), 56.4 (q, J = 2 Hz), 39.1 (q, J = 40 Hz), 35.0 (q, J = 2 Hz) ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.

8. ²D-compounds

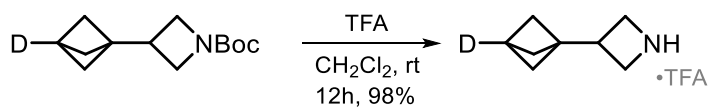


General procedure H (60h as an example)



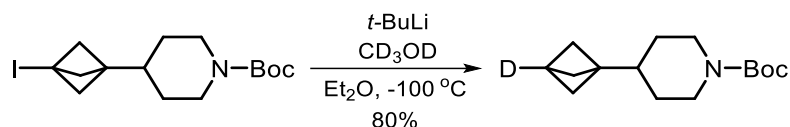
Tert-butyl 3-(bicyclo[1.1.1]pentan-1-yl-3-d)azetidine-1-carboxylate (60h-Boc)

A solution of *tert*-butyl 3-(3-iodobicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (0.325 g, 0.00093 mol, 1.00 equiv) in 20 mL of Et₂O was cooled to -100 °C under Ar. *t*-BuLi (1 mL, 0.00195 mol, 2.10 equiv, 1.9M solution in pentane) was added dropwise over 5 min. The mixture was stirred for 15 min at the same temperature, and CD₃OD (0.10 g, 0.11 mL, 0.00279 mol, 3.00 equiv) was added dropwise. The mixture was stirred for 1 h at -90 °C and then warmed to room temperature. The mixture was quenched with an aqueous saturated solution of NH₄Cl (20 mL). The organic layer was separated; the aqueous layer was additionally extracted with MeOtBu (2 × 5 mL). The combined organic layers were washed with water (1 × 10 mL), and brine (1 × 10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was triturated in MeOtBu (~10 mL), filtered and dried. Yield: 0.15 g, 0.00068 mol, 73%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 3.86 (t, *J* = 8.4 Hz, 2H), 3.61 (dd, *J* = 8.4, 5.4 Hz, 2H), 2.55 – 2.49 (m, 1H), 1.68 (s, 6H), 1.42 (s, 9H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 156.7, 79.3, 51.4, 48.2, 48.1, 45.9, 30.0, 28.6 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₃H₂₀DNNaO₂, 247.1533; found 247.1525.



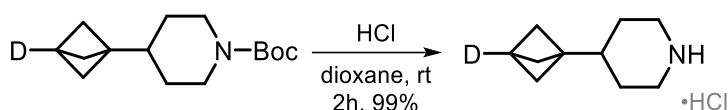
3-(Bicyclo[1.1.1]pentan-1-yl-3-d)azetidine trifluoroacetic acid (60h)

The same procedure as for **60f** was used. Yield: 0.16 g, 0.00067 mol, 98%, beige solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.94 (br s, 1H), 8.79 (br s, 1H), 3.92 (br s, 2H), 3.68 (br s, 2H), 2.86 (p, *J* = 8.1 Hz, 1H), 1.70 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-*d*₆): δ 158.5 (q, *J* = 31.7 Hz), 117.1 (q, *J* = 299.0 Hz), 47.7, 47.5, 44.5, 32.2 ppm. LCMS (M + H)⁺: 125. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₈H₁₃DN, 125.1189; found 125.1181.



***Tert*-butyl 4-(bicyclo[1.1.1]pentan-1-yl-3-d)piperidine-1-carboxylate (63h-Boc)**

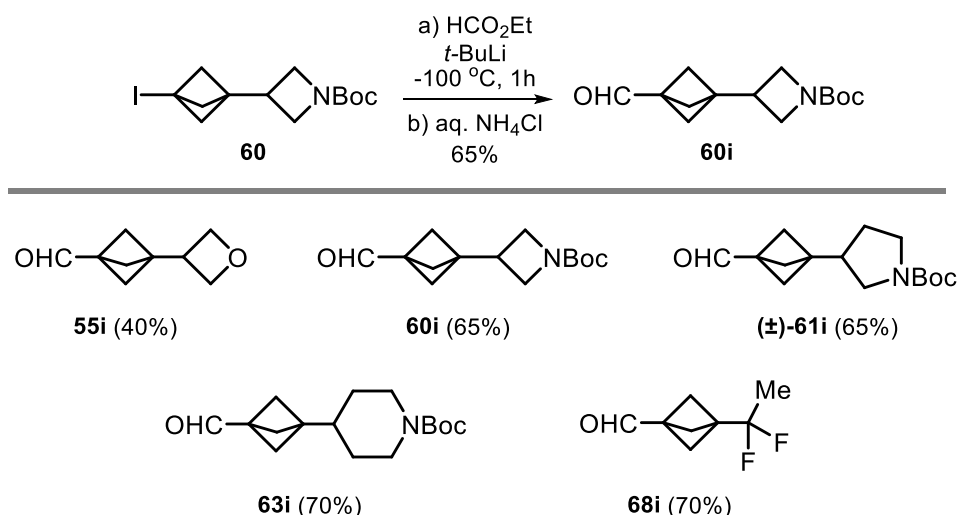
General procedure H. The final product was triturated in MeOtBu (~ 10 mL), filtered, and dried. Yield: 0.18 g, 0.000697 mol, 80%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 4.10 (d, J = 13.1 Hz, 2H), 2.61 (td, J = 12.9, 2.1 Hz, 2H), 1.58 (s, 6H), 1.52 (d, J = 13.8 Hz, 2H), 1.44 (s, 9H), 1.41 – 1.33 (m, 1H), 1.12 – 0.95 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 155.0, 79.3, 48.5, 48.2, 48.0, 43.9, 37.4, 28.6, 28.5 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{24}\text{DNNaO}_2$, 275.1846; found 275.1839.



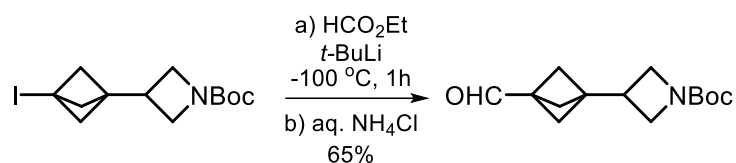
4-(Bicyclo[1.1.1]pentan-1-yl-3-d)piperidine hydrochloride (63h)

The same procedure as for **63f** was used. Yield: 0.13 g, 0.00069 mol, 99%, white solid, m.p. = 208–209 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 9.24 (br s, 1H), 8.82 (br s, 1H), 3.19 (d, J = 12.1 Hz, 2H), 2.83 – 2.68 (m, 2H), 1.58 (s, 6H), 1.69 – 1.45 (m, 3H), 1.36 – 1.21 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO-d_6): δ 47.6, 47.5, 47.3, 42.7, 34.1, 24.8 ppm. LCMS ($\text{M} + \text{H}$) $^+$: 153. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{17}\text{DN}$, 153.1502; found 153.1494.

9. Aldehydes



General procedure I (60i as an example)



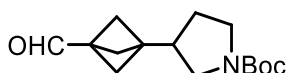
***Tert*-butyl 3-(3-formylbicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (60i)**

A solution of *tert*-butyl 3-(3-iodobicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (76.78 g, 0.22 mol, 1.00 equiv) in 1000 mL of Et₂O was cooled to -100 °C under Ar. *t*-BuLi (243 mL, 0.462 mol, 2.10 equiv, 1.9M solution in pentane) was added dropwise over 20 min. The mixture was stirred for 15 min at the same temperature, and a solution of ethyl formate (24.42 g, 0.33 mol, 1.50 equiv) in 150 mL of Et₂O was added dropwise. The mixture was stirred for 1 h at -90 °C and then warmed to room temperature. The mixture was quenched with an aqueous saturated solution of NH₄Cl (~ 100 g in 1 L of water). The organic layer was separated; the aqueous layer was additionally extracted with MeOtBu (2 × 200 mL). The combined organic layers were washed with water (1 × 300 mL), and brine (1 × 300 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 9:1 to 7:3, EtOAc/hexane, 3:7, R_f = 0.44). Yield: 35.90 g, 0.143 mol, 65%, yellow solid, m.p. = 48-49 °C. ¹H NMR (500 MHz, CDCl₃): δ 9.58 (s, 1H), 3.92 (t, *J* = 8.5 Hz, 2H), 3.61 (dd, *J* = 8.6, 5.3 Hz, 2H), 2.65 – 2.57 (m, 1H), 1.94 (s, 6H), 1.42 (s, 9H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 198.8, 156.6, 79.6, 51.1 (br s), 48.4, 44.2, 41.7, 29.3, 28.5 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.



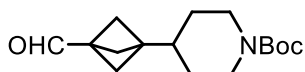
3-(Oxetan-3-yl)bicyclo[1.1.1]pentane-1-carbaldehyde (55i)

Modified general procedure I: solvent – Et₂O. The final product was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 9:1 to 7:3, EtOAc/hexane, 3:7, R_f = 0.5). Yield: 9.18 g, 0.06 mol, 40%, yellow oil. ¹H NMR (500 MHz, C₆D₆): δ 9.18 (s, 1H), 4.30 (dd, *J* = 7.8, 6.0 Hz, 2H), 4.04 (t, *J* = 5.9 Hz, 2H), 2.40 – 2.33 (m, 1H), 1.42 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, C₆D₆): δ 197.2, 73.0, 48.1, 44.1, 40.8, 35.7 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₉H₁₃O₂, 153.0916; found 153.0908.



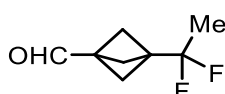
(±)-Tert-butyl 3-(3-formylbicyclo[1.1.1]pentan-1-yl)pyrrolidine-1-carboxylate (61i)

General procedure I. The final product was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 9:1 to 7:3, EtOAc/hexane, 3:7, R_f = 0.44). Yield: 25.03 g, 0.094 mol, 65%, yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 9.57 (s, 1H), 3.45 – 3.34 (m, 2H), 3.32 – 3.23 (m, 1H), 3.08 – 3.01 (m, 1H), 2.33 – 2.22 (m, 1H), 1.91 (s, 6H), 1.90 – 1.83 (m, 2H), 1.71 – 1.54 (m, 2H), 1.46 (s, 9H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 198.9, 154.7, 79.4, 49.2, 48.2, 45.7, 43.9, 41.8, 28.7 ppm. GCMS (M)⁺: 265. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₅H₂₃NNaO₃, 288.1576; found 288.1569.



Tert-butyl 4-(3-formylbicyclo[1.1.1]pentan-1-yl)piperidine-1-carboxylate (63i)

General procedure I. The final product was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 9:1 to 7:3, MeOtBu/hexane, 3:7, R_f = 0.35). Yield: 29.13 g, 0.104 mol, 70%, yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 9.57 (s, 1H), 4.13 (d, *J* = 12.4 Hz, 2H), 2.63 (t, *J* = 12.5 Hz, 2H), 1.84 (s, 6H), 1.55 (d, *J* = 15.2 Hz, 2H), 1.52 – 1.47 (m, 1H), 1.44 (s, 9H), 1.13 – 1.01 (m, 2H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 199.4, 155.0, 79.5, 48.3, 44.1, 43.7, 43.5, 36.5, 28.6, 28.2 ppm. GCMS (M)⁺: 279. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₆H₂₅NNaO₃, 302.1732; found 302.1724.



3-(1,1-Difluoroethyl)bicyclo[1.1.1]pentane-1-carbaldehyde (68i)

General procedure I. The final product was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 9:1 to 7:3, EtOAc/hexane, 3:7, R_f = 0.37). Yield: 21.43 g, 0.134 mol, 70%, colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 9.62 (s, 1H), 2.12 (s, 6H), 1.57 (t, *J* = 18.2 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 198.2, 120.2 (t, *J* = 238 Hz), 48.6 (t, *J* = 4 Hz), 42.7, 41.7 (t, *J* = 34 Hz), 20.5 (t, *J* = 28 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -99.7 (s) ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₈H₁₀F₂NaO, 183.0597; found 183.0607.

10. Reduced derivatives

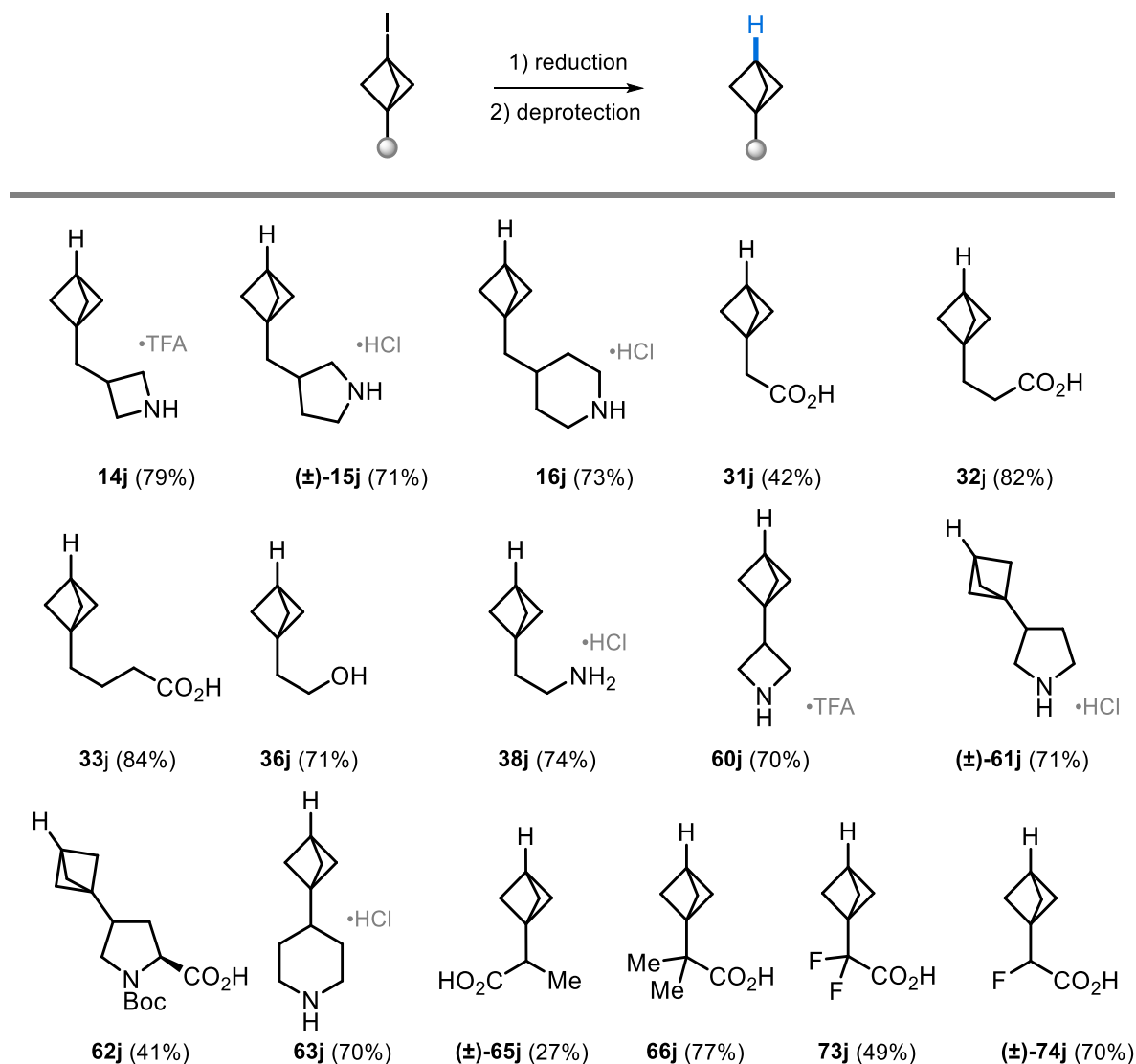
For the C-I reduction step, we used four complementary methods depending on the structure of the starting material:

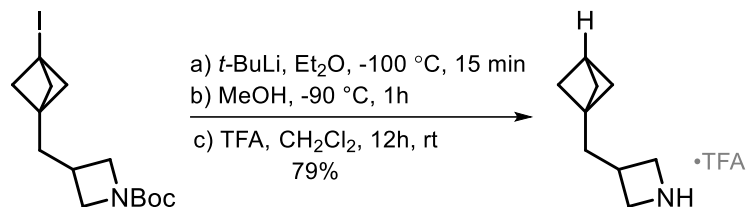
1 method: (i) *t*-BuLi, Et₂O, -100 °C. (ii) MeOH.

2 method: Raney-Ni, EtOH, H₂NCH₂CH₂NH₂, rt.

3 method: Bu₃SnH, AIBN, CCl₄, t.

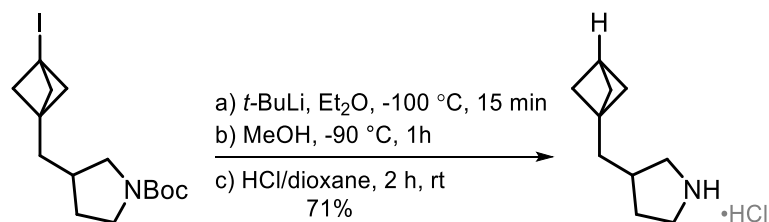
4 method: Pd/C, H₂, NEt₃, MeOH, rt.





3-(Bicyclo[1.1.1]pentan-1-ylmethyl)azetidine trifluoroacetic acid (14j)

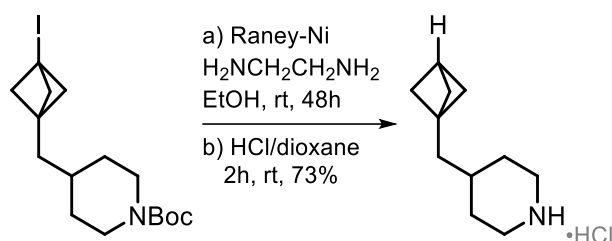
To a solution of *tert*-butyl 3-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)azetidine-1-carboxylate (67.16 g, 0.185 mol, 1.00 equiv) in dry Et₂O (1000 mL) was added dropwise a 1.9M *t*-BuLi solution in pentane (205 mL, 0.389 mol, 2.10 equiv) at -85 to -100 °C ~ over 30 min under Ar. The mixture was stirred for 15 min at the same temperature, and MeOH (23.68 g, 0.74 mol, 4.00 equiv) was added dropwise. The mixture was stirred for 1 h at -90 °C and then warmed to room temperature. The mixture was quenched with an aqueous saturated solution of NH₄Cl (1000 mL). The organic layer was separated. The organic layer was washed with water (1 × 200 mL), and brine (1 × 200 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, gradient, hexane/MeOTBu, 9:1 to 7:3, R_f = 0.75, hexane/MeOTBu, 7:3). The crude product (34.60 g, 0.146 mol) was dissolved in CH₂Cl₂ (200 mL) and TFA (35.04 g, 0.365 mol, 2.50 equiv) was added in one portion at room temperature. The resulting mixture was stirred overnight at the same temperature, and then concentrated under reduced pressure. The residue was triturated in MeOTBu (~ 100 mL), filtered and dried. Yield: 34.02 g, 0.146 mol, 79%, brown oil. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.85 (br s, 1H), 8.69 (br s, 1H), 4.05 – 3.96 (m, 2H), 3.66 – 3.53 (m, 2H), 2.81 – 2.68 (m, 1H), 2.44 (s, 1H), 1.71 (d, *J* = 7.8 Hz, 2H), 1.61 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-*d*₆): δ 158.4 (q, *J* = 35 Hz), 116.1 (q, *J* = 293 Hz), 51.1, 50.0, 43.2, 35.5, 29.9, 27.6 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₉H₁₆N, 138.1283; found 138.1274.



(±)-3-(Bicyclo[1.1.1]pentan-1-ylmethyl)pyrrolidine hydrochloride (15j)

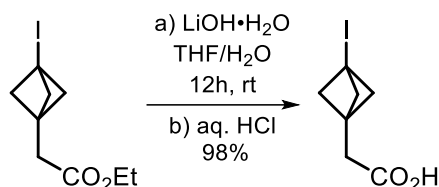
To a solution of (±)-*tert*-butyl 3-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)pyrrolidine-1-carboxylate (113.57 g, 0.337 mol, 1.00 equiv) in dry Et₂O (1500 mL) was added dropwise a 1.9M *t*-BuLi solution in pentane (369 mL, 0.701 mol, 2.10 equiv) at -85 to -100 °C ~ over 30 min under Ar. The mixture was stirred for 15 min at the same temperature, and MeOH (43.14 g, 1.348 mol, 4.00 equiv) was added dropwise. The mixture was stirred for 1 h at -90 °C and then warmed to room temperature. The mixture was quenched with an aqueous saturated solution of NH₄Cl (1000

mL). The organic layer was separated. The organic layer was washed with water (1 × 300 mL), and brine (1 × 300 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 9:1 to 7:3, R_f = 0.75, hexane/MeOtBu, 7:3). The product (60.00 g, 0.239 mol) was dissolved in 5M HCl (400 mL) in dioxane at room temperature. The mixture was stirred for 2 h and concentrated under reduced pressure. The residue was triturated in MeOtBu (~ 200 mL), filtered, and dried. Yield: 44.81 g, 0.239 mol, 71%, white solid, m.p. = 99-101 °C. ¹H NMR (500 MHz, CD₃OD): δ 3.45 (dd, *J* = 11.2, 7.7 Hz, 1H), 3.39 – 3.32 (m, 1H), 3.21 (dd, *J* = 18.1, 9.9 Hz, 1H), 2.76 (t, *J* = 10.2 Hz, 1H), 2.47 (s, 1H), 2.35 – 2.17 (m, 2H), 1.74 (s, 6H), 1.66 – 1.48 (m, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CD₃OD): δ 51.8, 51.5, 46.2, 45.6, 37.5, 36.8, 31.8, 28.7 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₀H₁₈N, 152.1439; found 152.1431.



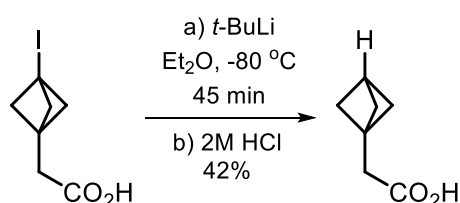
4-(Bicyclo[1.1.1]pentan-1-ylmethyl)piperidine hydrochloride (16j)

To a stirred solution of *tert*-butyl 4-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)piperidine-1-carboxylate (62.77 g, 0.160 mol, 1.00 equiv) in EtOH (800 mL), 2 teaspoons of Raney-Ni (freshly prepared) were added followed by ethane-1,2-diamine (38.40 g, 0.64 mol, 4.00 equiv) in one portion. This suspension was stirred for 48 h in a sealed reactor at room temperature. The solvent was decanted under an argon stream (*to prevent ignition*). The residue was washed with MeOtBu (2 × 200 mL). The combined liquids were concentrated under reduced pressure and dissolved in MeOtBu (400 mL), washed with water (1 × 200 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 9:1 to 7:3, R_f = 0.8, hexane/MeOtBu, 7:3). The product (31.01 g, 0.117 mol) was dissolved in 5M HCl (200 mL) in dioxane at room temperature. The mixture was stirred for 2 h and concentrated under reduced pressure. The residue was triturated in 100 mL of MeOtBu, filtered, and dried. Yield: 23.58 g, 0.117 mol, 73%, white solid, m.p. = 249-251 °C. ¹H NMR (500 MHz, DMSO-*d*₆): δ 9.10 (br s, 1H), 8.91 (br s, 1H), 3.16 (d, *J* = 12.5 Hz, 2H), 2.85 – 2.73 (m, 2H), 2.44 (s, 1H), 1.76 (d, *J* = 13.3 Hz, 2H), 1.68 (s, 6H), 1.58 – 1.52 (m, 1H), 1.38 – 1.28 (m, 4H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-*d*₆): δ 50.9, 44.1, 42.9, 38.4, 31.7, 28.7, 27.4 ppm. LCMS (M + H)⁺: 166. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₁H₂₀N, 166.1596; found 166.1583.



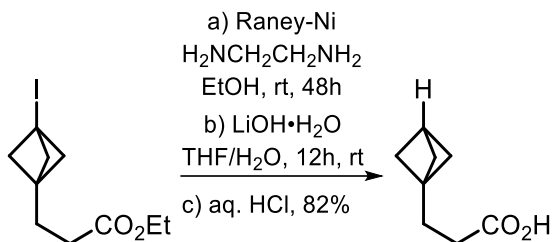
2-(3-Iodobicyclo[1.1.1]pentan-1-yl)acetic acid

Ethyl 2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetate (48.44 g, 0.173 mol, 1.00 equiv) was dissolved in THF (200 mL) and water (400 mL). The solution was cooled to 0 °C (ice-methanol bath) and LiOH·H₂O (9.79 g, 0.233 mol, 1.35 equiv) was added in one portion. The mixture was stirred at room temperature overnight. THF was removed under reduced pressure. The residue was washed with MeOtBu (1 × 200 mL). The aqueous layer was acidified to pH ~ 2 with HCl solution (35%) and extracted with MeOtBu (1 × 200 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Yield: 43.22 g, 0.172 mol, 98%, grey solid. ¹H NMR (400 MHz, CDCl₃): δ 10.80 (br s, 1H), 2.60 (s, 2H), 2.34 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 176.9, 61.0, 43.2, 37.2, 5.8 ppm. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₇H₈IO₂, 250.9569; found 250.9566.



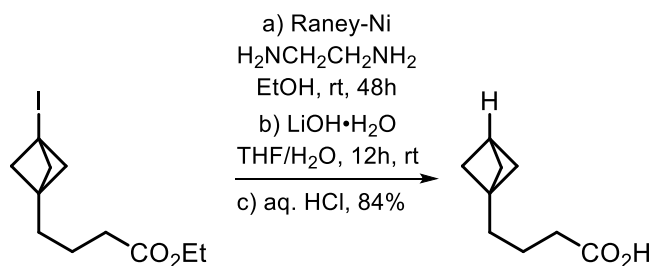
2-(Bicyclo[1.1.1]pentan-1-yl)acetic acid (31j)

To a solution of 2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetic acid (19.85 g, 0.079 mol, 1.00 equiv) in dry Et₂O (700 mL) was added dropwise a 1.9M *t*-BuLi solution in pentane (128 mL, 0.244 mol, 3.10 equiv) at -80 to -75 °C under Ar. After that, the reaction mixture was allowed to stir at this temperature for 45 min. Then the reaction mixture was quenched with 2M HCl to pH = 2. The aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The final product was recrystallized from ~ 40 mL of hexane. Yield: 4.15 g, 0.0329 mol, 42%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 11.57 (br s, 1H), 2.50 (s, 2H), 2.49 (s, 1H), 1.82 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 178.4, 51.4, 40.7, 38.3, 28.2 ppm. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₇H₉O₂, 125.0603; found 125.0604.



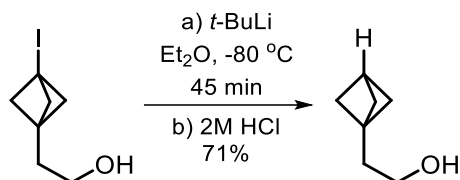
3-(Bicyclo[1.1.1]pentan-1-yl)propanoic acid (32j)

To a stirred solution of ethyl 3-(3-iodobicyclo[1.1.1]pentan-1-yl)propanoate (90.00 g, 0.306 mol, 1.00 equiv) in EtOH (1000 mL) 3 teaspoons of Raney-Ni (freshly prepared) were added followed by ethane-1,2-diamine (73.55 g, 1.224 mol, 4.00 equiv) in one portion. This suspension was stirred for 48 h in a sealed reactor at room temperature. The solvent was decanted under an argon stream (*to prevent ignition*). The residue was washed with MeOtBu (2×300 mL). The combined liquids were concentrated under reduced pressure and dissolved in MeOtBu (500 mL), washed with water (1×400 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The obtained product (42.72 g, 0.254 mol) was dissolved in a mixture of THF (200 mL) and water (400 mL). The solution was cooled to 0 °C (ice-methanol bath) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (14.40 g, 0.34 mol, 1.35 equiv) was added in one portion. The mixture was stirred at room temperature overnight, and then THF was distilled off using a rotary evaporator. The residue was washed with MeOtBu (1×100 mL). The aqueous layer was acidified to pH 2 with HCl solution (35%) and extracted with MeOtBu (3×100 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Yield: 35.20 g, 0.251 mol, 82%, yellow solid, m.p. = 52-53 °C. ^1H NMR (500 MHz, CDCl_3): δ 10.90 (br s, 1H), 2.46 (s, 1H), 2.31 (t, $J = 7.7$ Hz, 2H), 1.76 (t, $J = 7.7$ Hz, 2H), 1.66 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 180.3, 50.2, 44.8, 31.4, 27.6, 27.5 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_8\text{H}_{11}\text{O}_2$, 139.0759; found 139.0764.



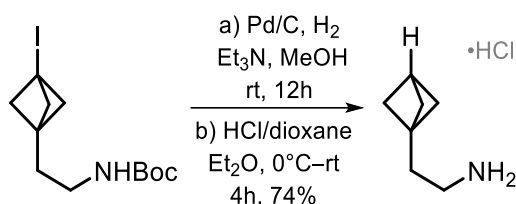
4-(Bicyclo[1.1.1]pentan-1-yl)butanoic acid (33j)

The same procedure as for **32j** was used. Yield: 6.34 g, 0.041 mol, 84%, white oil. ^1H NMR (500 MHz, CDCl_3): δ 11.50 (br s, 1H), 2.45 (s, 1H), 2.34 (t, $J = 7.5$ Hz, 2H), 1.65 (s, 6H), 1.63 – 1.56 (m, 2H), 1.44 (dd, $J = 9.6, 6.3$ Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 180.4, 50.4, 45.3, 34.3, 32.0, 27.6, 22.0 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_9\text{H}_{13}\text{O}_2$, 153.0916; found 153.0919.



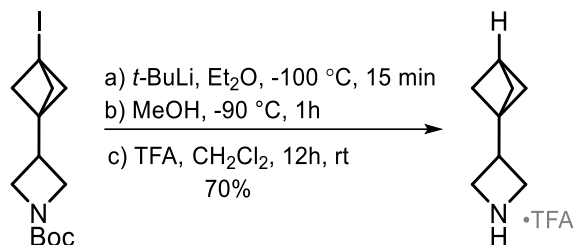
2-(Bicyclo[1.1.1]pentan-1-yl)ethan-1-ol (36j)

The same procedure as for **31j** was used. The final product was recrystallized from ~ 100 mL of hexane. Yield: 40.32 g, 71%, 0.36 mol, brown oil. ^1H NMR (500 MHz, CDCl_3): δ 3.64 (t, J = 6.8 Hz, 2H), 2.46 (s, 1H), 1.71 (s, 6H), 1.68 (t, J = 6.8 Hz, 2H), 1.42 (s, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 61.4, 51.1, 43.4, 35.6, 28.2 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_{13}\text{O}$, 113.0966; found 113.0962.



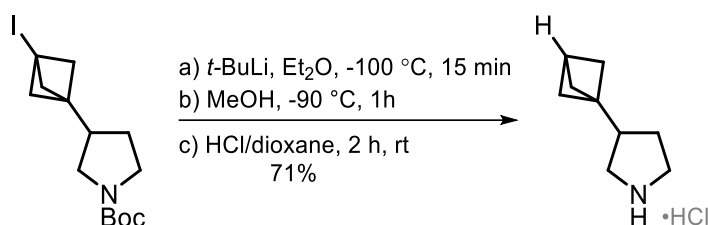
2-(Bicyclo[1.1.1]pentan-1-yl)ethan-1-amine hydrochloride (38j)

To a solution of *tert*-butyl (2-(3-iodobicyclo[1.1.1]pentan-1-yl)ethyl)carbamate (120.60 g, 0.358 mol, 1.00 equiv) in dry MeOH (1200 mL) were added Et_3N (55 mL, 0.393 mol, 1.10 equiv) and 10% Pd/C (19.00 g, 0.018 mmol, 0.05 equiv). The reaction mixture was placed under a 50 atm hydrogen atmosphere. The reaction was monitored by ^1H NMR. After ~ 12 h, the reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (300 mL) and washed with water (3×100 mL). The crude product was purified by column chromatography (SiO_2 , MeOtBu /hexane, 9:1). The product (56.50 g, 0.269 mol) was dissolved in Et_2O (300 mL) and 5M HCl in dioxane (150 mL) was added under cold conditions (ice-water bath). The reaction mixture was stirred for 4 h until a precipitate was formed. The product was filtered and washed with a mixture of Et_2O /hexane (100 mL, 1:9). Yield: 38.94 g, 0.264 mol, 74%, yellow solid, m.p. = 232–234 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 8.12 (br s, 3H), 2.67 (s, 2H), 2.45 (s, 1H), 1.76 – 1.69 (m, 2H), 1.67 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO-d_6): δ 49.8, 42.4, 36.6, 29.8, 27.2 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_{14}\text{N}$, 112.1126; found 112.1120.



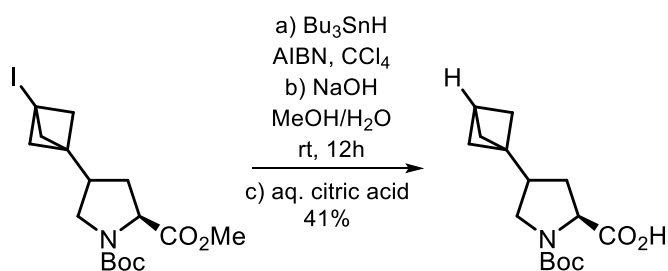
3-(Bicyclo[1.1.1]pentan-1-yl)azetidine trifluoroacetic acid (60j)

The same procedure as for **14j** was used. Yield: 29.07 g, 0.133 mol, 70%, yellow oil. ^1H NMR (500 MHz, DMSO- d_6): δ 8.84 (br s, 1H), 8.68 (br s, 1H), 3.98 – 3.83 (m, 2H), 3.73 – 3.60 (m, 2H), 2.86 (p, J = 8.1 Hz, 1H), 2.53 (s, 1H), 1.71 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 158.5 (q, J = 34.9 Hz), 115.0 (q, J = 293.4 Hz), 47.7, 47.6, 44.6, 32.2, 27.1 ppm. LCMS ($M + H$) $^+$: 124. HRMS (ESI-TOF) m/z : [$M + H$] $^+$ calcd for $\text{C}_8\text{H}_{14}\text{N}$, 124.1126; found 124.1121. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



(±)-3-(Bicyclo[1.1.1]pentan-1-yl)pyrrolidine hydrochloride (61j)

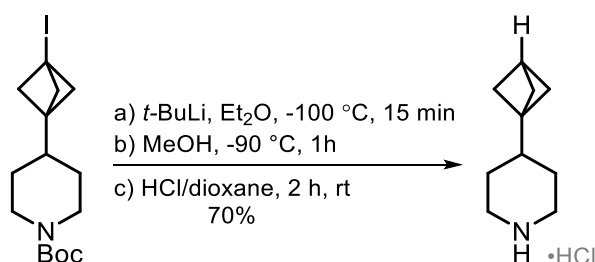
The same procedure as for **15j** was used. Yield: 12.40 g, 0.0905 mol, 71%, yellow solid, m.p. = 80–81 °C. ^1H NMR (500 MHz, DMSO- d_6): 9.43 (br s, 2H), 3.21 – 3.13 (m, 1H), 3.12 – 3.03 (m, 2H), 2.75 – 2.64 (m, 1H), 2.49 (s, 1H), 2.28 (p, J = 8.1 Hz, 1H), 1.93 – 1.82 (m, 1H), 1.66 (q, J = 9.5 Hz, 6H), 1.59 – 1.51 (m, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 48.3, 46.3, 44.7, 44.4, 38.8, 27.3, 26.9 ppm. HRMS (ESI-TOF) m/z : [$M + H$] $^+$ calcd for $\text{C}_9\text{H}_{16}\text{N}$, 138.1283; found 138.1278.



(±)-4-(Bicyclo[1.1.1]pentan-1-yl)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (62j)

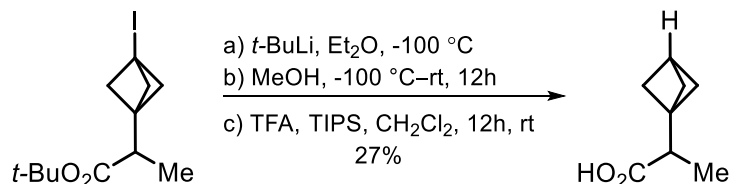
To a solution of (±)-1-(tert-butyl) 2-methyl 4-(3-iodobicyclo[1.1.1]pentan-1-yl)pyrrolidine-1,2-dicarboxylate (55.15 g, 0.131 mol, 1.00 equiv) in dry toluene (1.2 L) were added Bu_3SnH (114.36 g, 0.393 mol, 3.00 equiv) in one portion followed by azobisisobutyronitrile (AIBN) (2.20 g, 0.0131 mol, 10% mol) under Ar at room temperature. The resulting mixture was heated at 115 °C (in an oil bath with a thermocouple) for 15 h under Ar. The mixture was cooled to room temperature and

CCl₄ (182.00 g, 1.18 mol, 9.00 equiv) was added. The solution was heated under reflux (in an oil bath with a thermocouple) for 15 h under Ar. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, gradient, hexane/MeOtBu, 9:1 to 1:1). The product (22.42 g, 0.076 mol) was dissolved in MeOH (200 mL), and a solution of NaOH (9.12 g, 0.228 mol, 3.00 equiv) in 200 mL of water was added in one portion. The mixture was stirred at room temperature overnight, and then concentrated under reduced pressure. The residue was diluted with water (500 mL) and washed with MeOtBu (1 × 200 mL) and filtered. The aqueous layer was acidified with citric acid to pH = 5-6 and extracted with EtOAc (3 × 200 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Yield: 15.09 g, 0.0537 mol, 41%, yellow solid, m.p. = 131-132 °C, d.r. = 3:2. A mixture of *N*-Boc rotamers. ¹H NMR (500 MHz, DMSO-d₆): δ 12.49 (br s, 1H), 4.13 – 4.00 (m, 1H), 3.48 – 3.33 (m, 1H), 3.09 – 2.84 (m, 1H), 2.47 (s, 1H), 2.27 – 2.20 (m, 1H), 2.02 – 1.89 (m, 1H), 1.88 – 1.75 (m, 1H), 1.62 (s, 6H), 1.39, 1.38, 1.33, 1.33 (s, 9H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 174.3, 174.1, 173.8, 173.7, 153.4, 153.3, 153.0, 152.8, 78.8, 78.6, 59.1, 58.9, 58.7, 58.4, 49.0, 48.8, 48.6, 48.4, 48.3, 48.2, 45.4, 45.3, 44.7, 44.7, 38.4, 38.2, 37.3, 33.5, 33.0, 32.7, 32.2, 28.1, 27.92, 27.87, 26.5 ppm. LCMS (M - H)⁻: 280. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₅H₂₃NNaO₄, 304.1525; found 304.1519.



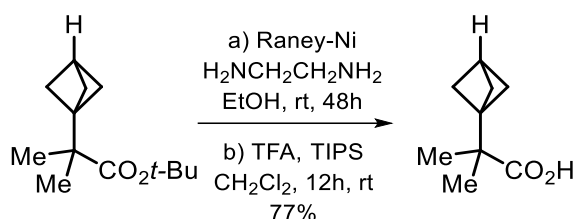
4-(Bicyclo[1.1.1]pentan-1-yl)piperidine hydrochloride (63j)

The same procedure as for **15j** was used. Yield: 11.00 g, 0.0587 mol, 70%, white solid, m.p. = 225-227 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 9.02 (br s, 1H), 8.57 (br s, 1H), 3.21 (d, *J* = 12.0 Hz, 2H), 2.85 – 2.69 (m, 2H), 2.48 (br s, 1H), 1.70 – 1.44 (m, 3H), 1.60 (s, 6H), 1.35 – 1.17 (m, 2H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 47.7, 47.5, 42.7, 34.0, 26.0, 24.8 ppm. LCMS (M + H)⁺: 152. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₀H₁₈N, 152.1439; found 152.1502.



(±)-2-(Bicyclo[1.1.1]pentan-1-yl)propanoic acid (65j)

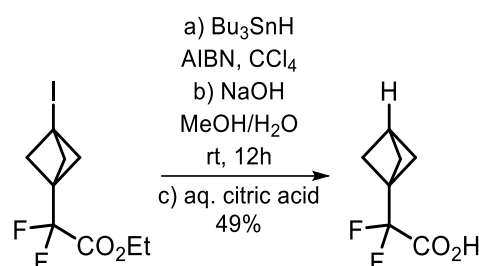
A solution of (±)-*tert*-butyl 2-(3-iodobicyclo[1.1.1]pentan-1-yl)propanoate (100.00 g, 0.31 mol, 1.00 equiv) in Et₂O (1500 mL) was cooled to -100 °C in a stream of argon with the help of liquid nitrogen. *t*-BuLi (359 mL, 0.682 mol, 2.20 equiv, 1.9M solution in pentane) was added into the reactor over 20 min. 3 min after the addition, MeOH (39.80 g, 1.24 mol, 4.00 equiv) was added dropwise at the same temperature, and the mixture was left overnight. The resulting solution was washed with distilled water (2 × 300 mL), dried over Na₂SO₄, filtered, and concentrated. The resulting mixture was purified by column chromatography (SiO₂, hexane/EtOAc, 9:1, R_f = 0.9). The product (17.00 g, 0.087 mol) was dissolved in CH₂Cl₂ (200 mL). TIPS (27.49 g, 0.174 mol, 2.00 equiv) was added, followed by addition of TFA (50 mL) in one portion. The solution was stirred overnight, and concentrated. The residue was dissolved in a sat. aq. Na₂CO₃ solution (100 mL) and washed with MeOtBu (1 × 100 mL). The aqueous layer was acidified to pH ~ 2 with con. HCl and extracted with MeOtBu (2 × 100 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to obtain the desired product. Yield: 11.57 g, 0.0826 mol, 27%, yellow solid, m.p. = 42-43 °C. ¹H NMR (500 MHz, CDCl₃): δ 11.23 (br s, 1H), 2.57 (q, *J* = 7.0 Hz, 1H), 2.50 (s, 1H), 1.74 (s, 6H), 1.10 (d, *J* = 7.0 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 180.9, 49.3, 45.4, 41.6, 26.7, 13.3 ppm. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₈H₁₁O₂, 139.0759; found 139.0761.



2-(Bicyclo[1.1.1]pentan-1-yl)-2-methylpropanoic acid (66j)

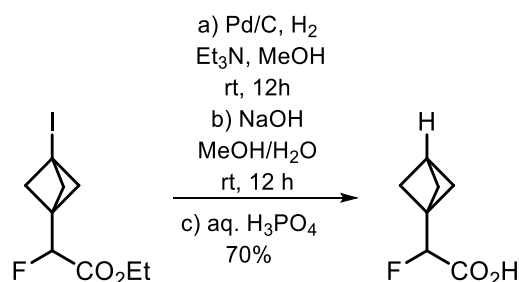
To a stirred solution of *tert*-butyl 2-(bicyclo[1.1.1]pentan-1-yl)-2-methylpropanoate **66** (39.50 g, 0.118 mol, 1.00 equiv) in EtOH (500 mL) 1 teaspoon of Raney-Ni (freshly prepared) was added followed by ethane-1,2-diamine (28.20 g, 0.47 mol, 4.00 equiv) in one portion. This suspension was stirred for 48 h in a sealed reactor at room temperature. The solvent was decanted under an argon stream. The residue was washed with MeOtBu (2 × 200 mL). The combined liquids were concentrated under reduced pressure and dissolved in MeOtBu (300 mL), washed with water (1 × 200 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product (19.50

g, 0.093 mol) was dissolved in CH₂Cl₂ (200 mL). TIPS (29.39 g, 0.186 mol, 2.00 equiv) was added, followed by addition of TFA (50 mL) in one portion. The solution was stirred at room temperature overnight, concentrated, and redissolved in a sat. aq. Na₂CO₃ solution (100 mL) and washed with MeOtBu (1 × 100 mL). The aqueous layer was acidified to pH ~ 2 with con. HCl and extracted with MeOtBu (2 × 100 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Yield: 14.00 g, 0.091 mol, 77%, brown oil. ¹H NMR (500 MHz, DMSO-d₆): δ 12.00 (br s, 1H), 2.45 (s, 1H), 1.62 (s, 6H), 1.01 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 176.7, 49.6, 47.2, 41.7, 24.5, 21.6 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₉H₁₅O₂, 155.1072; found 155.1063.



2-(Bicyclo[1.1.1]pentan-1-yl)-2,2-difluoroacetic acid (73j)

The same procedure as for **62j** was used. Yield: 40.57 g, 0.25 mol, 49%, white solid, m.p. = 97-98 °C. ¹H NMR (400 MHz, CDCl₃): δ 11.52 (s, 1H), 2.59 (s, 1H), 2.00 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 168.2 (t, *J* = 34 Hz), 111.4 (t, *J* = 250 Hz), 48.7 (t, *J* = 3 Hz), 42.6 (t, *J* = 31 Hz), 27.5 ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -112.8 (s) ppm. LCMS (*M* - H)⁻: 161. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₇H₉F₂O₂, 163.0571; found 163.0565.

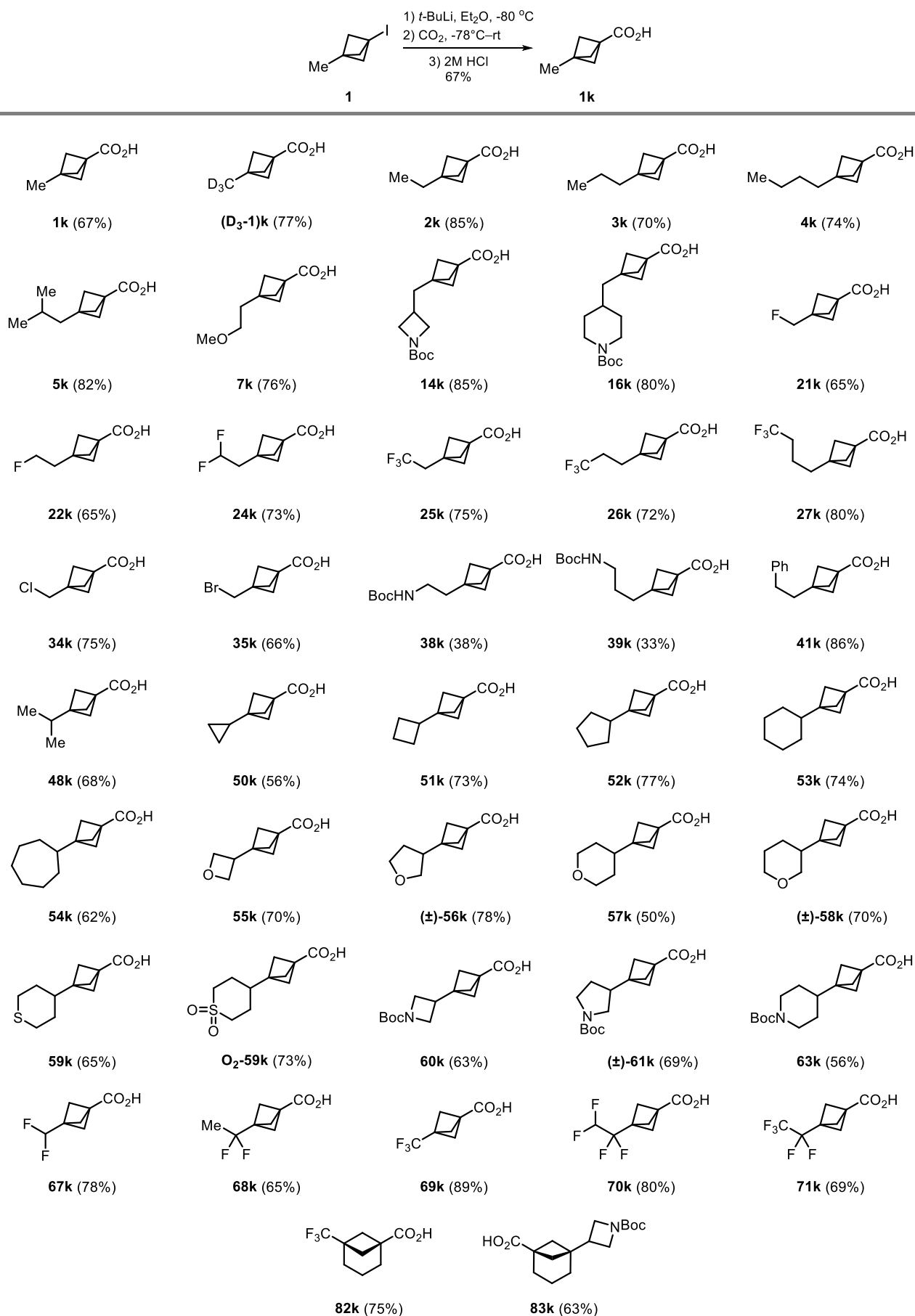


(±)-2-(Bicyclo[1.1.1]pentan-1-yl)-2-fluoroacetic acid (74j)

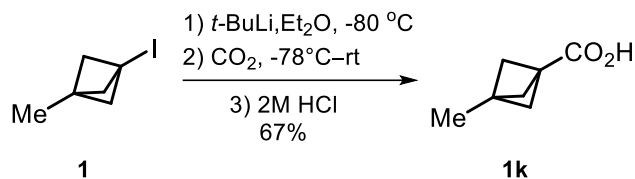
To a solution of iodide (±)-**74** (120.60 g, 0.358 mol, 1.00 equiv) in dry MeOH (1.2 L) was added Et₃N (55 mL, 0.393 mol, 1.10 equiv.) and 10% Pd/C (19.00 g, 0.018 mmol, 0.05 equiv). The reaction mixture was placed under a 50 atm hydrogen atmosphere. The competition of reaction was monitored by ¹H NMR (ca. 12 h). After that, the reaction mixture was filtered and concentrated. The residue was dissolved in CH₂Cl₂ (500 mL) and washed with water (3 × 100 mL). The organic layer was concentrated under reduced pressure. The crude product was used for the next step without purification. To a solution of ethyl 2-(bicyclo[1.1.1]pentan-1-yl)-2-fluoroacetate (52.60 g,

0.305 mol, 1.00 equiv) in EtOH (300 mL) was added NaOH (18.35 g, 0.458 mol, 1.50 equiv) in water (200 mL). The reaction mixture was stirred at room temperature overnight. The mixture was concentrated and extracted with CH₂Cl₂ (3 × 250 mL). The water layer was acidified with aq. H₃PO₄ to pH = 4 and extracted with CH₂Cl₂ (3 × 250 mL). The combined organic layers were dried over Na₂SO₄, filtered, and evaporated to afford the crude product, which was recrystallized from hexane. Yield: 36.50 g, 0.253 mol, 70%, white solid, m.p. = 62-63 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 13.22 (br s, 1H), 4.87 (d, *J* = 49.4 Hz, 1H), 2.52 (s, 1H), 1.78 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 169.0 (d, *J* = 24 Hz), 87.0 (d, *J* = 180 Hz), 48.8 (d, *J* = 4 Hz), 42.6 (d, *J* = 25 Hz), 27.2 ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -191.9 (s) ppm. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₇H₈FO₂, 143.0508; found 143.0507.

11. Carboxylic acids and amino acids

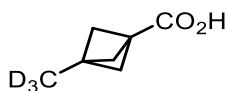


General procedure K (1k as an example)



3-Methylbicyclo[1.1.1]pentane-1-carboxylic acid (**1k**)

To a solution of **1** (68.70 g, 0.33 mol, 1.00 equiv) in dry Et₂O (1000 mL) was added a 1.9M *t*-BuLi solution in pentane (348 mL, 0.66 mol, 2.10 equiv) dropwise at -80 – -85 °C under Ar atmosphere. After that, the reaction mixture was stirred at this temperature for 10 min and poured on freshly crushed dry ice (290.40 g, 6.60 mol, 20.00 equiv). The reaction mixture was warmed to room temperature and diluted with distilled water (400 mL). The layers were separated. The aqueous layer was washed with MeOtBu (2 × 200 mL), acidified with 2M HCl to pH ~ 2, and extracted with MeOtBu (3 × 200 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was recrystallized from 100 mL of hexane. Yield: 27.80 g, 0.22 mol, 67%, white solid, m.p. = 122-123 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.16 (br s, 1H), 1.82 (s, 6H), 1.14 (s, 3H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-*d*₆): δ 171.0, 52.5, 37.5, 35.8, 17.7 ppm. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₇H₉O₂, 125.0603; found 125.0602.



3-(Methyl-*d*₃)bicyclo[1.1.1]pentane-1-carboxylic acid ((*D*₃-**1**)**k**)

General procedure K. The crude product was recrystallized from 50 mL of hexane. Yield: 7.58 g, 0.059 mol, 77%, yellow solid, m.p. = 120-121 °C. ¹H NMR (500 MHz, CDCl₃): δ 11.27 (s, 1H), 1.94 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 176.5, 53.3, 37.7, 36.7, 17.0 (p, *J* = 19.2 Hz) ppm. GCMS (M)⁺: 129. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₇H₆D₃O₂, 128.0791; found 128.0793.



3-Ethylbicyclo[1.1.1]pentane-1-carboxylic acid (**2k**)

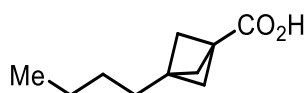
General procedure K. The final product was purified by sublimation under a reduced pressure (100 °C, 1 mmHg) and washed with hexane (~ 100 mL). Yield: 70.00 g, 0.50 mol, 85%, white solid, m.p. = 87-88 °C. ¹H NMR (500 MHz, CDCl₃): δ 1.90 (s, 6H), 1.47 (q, *J* = 7.5 Hz, 2H), 0.85

(t, $J = 7.5$ Hz, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 176.8, 51.1, 41.3, 37.5, 24.3, 10.4 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_8\text{H}_{11}\text{O}_2$, 139.0759; found 139.0761.



3-Propylbicyclo[1.1.1]pentane-1-carboxylic acid (3k)

General procedure K. The final product was purified by sublimation under a reduced pressure (100 °C, 1 mmHg) and washed with hexane (~ 100 mL). Yield: 24.79 g, 0.161 mol, 70%, yellow solid, m.p. = 78-79 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.20 (br s, 1H), 1.79 (s, 6H), 1.39 (dd, $J = 9.2, 6.1$ Hz, 2H), 1.30 – 1.18 (m, 2H), 0.87 (t, $J = 7.3$ Hz, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, $\text{DMSO}-d_6$): δ 171.1, 50.9, 37.4, 33.0, 19.2, 14.0 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_9\text{H}_{13}\text{O}_2$, 153.0916; found 153.0915.



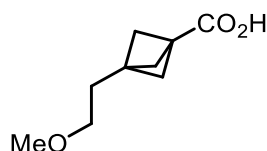
3-Butylbicyclo[1.1.1]pentane-1-carboxylic acid (4k)

General procedure K. The final product was purified by sublimation under a reduced pressure (100 °C, 1 mmHg) and washed with hexane (~ 100 mL). Yield: 29.90 g, 0.178 mol, 74%, yellow solid, m.p. = 91-92 °C. ^1H NMR (400 MHz, CDCl_3): δ 11.43 (br s, 1H), 1.91 (s, 6H), 1.52 – 1.37 (m, 2H), 1.34 – 1.12 (m, 4H), 0.88 (t, $J = 7.1$ Hz, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 176.7, 51.7, 40.5, 37.7, 31.1, 28.6, 22.9, 14.2 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{10}\text{H}_{15}\text{O}_2$, 167.1072; found 167.1074.



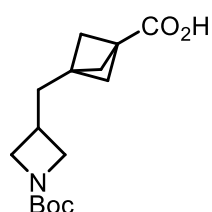
3-Isobutylbicyclo[1.1.1]pentane-1-carboxylic acid (5k)

General procedure K. The final product was purified by sublimation under a reduced pressure (100 °C, 1 mmHg) and washed with hexane (~ 500 mL). Yield: 97.44 g, 0.58 mol, white solid, m.p. = 81-82 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 12.18 (br s, 1H), 1.84 (s, 6H), 1.62 – 1.52 (m, 1H), 1.33 (d, $J = 6.5$ Hz, 2H), 0.86 (d, $J = 6.5$ Hz, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, $\text{DMSO}-d_6$): δ 171.0, 51.8, 47.3, 37.9, 26.1, 23.2 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{10}\text{H}_{15}\text{O}_2$, 167.1072; found 167.1072.



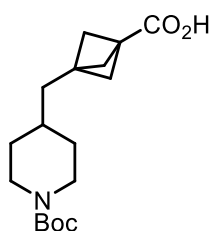
3-(2-Methoxyethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (7k)

General procedure K. The final product was purified by sublimation under a reduced pressure (100 °C, 1 mmHg) and washed with hexane (~ 300 mL). Yield: 59.50 g, 0.35 mol, 76%, colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 10.26 (br s, 1H), 3.38 (t, J = 6.7 Hz, 2H), 3.31 (s, 3H), 1.96 (s, 6H), 1.74 (t, J = 6.7 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 175.9, 70.5, 58.6, 52.2, 38.3, 38.0, 31.0 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_9\text{H}_{13}\text{O}_3$, 169.0865; found 169.0866.



3-((1-(Tert-butoxycarbonyl)azetidin-3-yl)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid (14k)

General procedure K. The mixture was carefully acidified with citric acid to pH ~ 5-6. The final product was triturated in a mixture of hexane/MeOtBu (200 mL, ~ 9:1). Yield: 61.90 g, 0.22 mol, 85%, yellow solid, m.p. = 119-120 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 12.21 (br s, 1H), 3.91 (br s, 2H), 3.42 (br s, 2H), 2.49 – 2.44 (m, 1H), 1.78 (s, 6H), 1.70 (d, J = 7.7 Hz, 2H), 1.36 (s, 9H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO-d_6): δ 170.9, 155.5, 78.3, 55.0 (br s), 53.9 (br s), 51.0, 38.0, 38.0, 35.2, 28.1, 26.3 ppm. LCMS (M-H) $^-$: 280. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{23}\text{NNaO}_4$, 304.1525; found 304.1516.



3-((1-(Tert-butoxycarbonyl)piperidin-4-yl)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid (16k)

General procedure K. The mixture was carefully acidified with citric acid to pH ~ 5-6. The final product was triturated in a mixture of hexane/MeOtBu (300 mL, ~ 9:1). Yield: 64.00 g, 0.207 mol, 80%, yellow solid, m.p. = 134-135 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 12.18 (br s, 1H), 3.87 (d, J = 11.6 Hz, 2H), 2.68 (br s, 2H), 1.84 (s, 6H), 1.62 (d, J = 12.7 Hz, 2H), 1.47 – 1.39 (m, 1H), 1.38 (s, 9H), 1.36 – 1.33 (m, 2H), 1.01 – 0.91 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO-d_6): δ

170.9, 153.8, 78.3, 51.8, 44.0 (br s), 43.2 (br s), 38.5, 37.9, 37.7, 33.6, 32.2, 28.1 ppm. LCMS (M-H)⁻: 308. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₁₇H₂₆NO₄, 308.1862; found 308.1866.



3-(Fluoromethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (21k)

General procedure K. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg), washed with hexane (~ 300 mL), and dried. Yield: 73.44 g, 0.51 mol, 65%, yellow solid, m.p. = 102-103 °C. ¹H NMR (500 MHz, CDCl₃): δ 10.72 (br s, 1H), 4.38 (d, *J* = 47.4 Hz, 2H), 2.10 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 175.8, 82.4 (d, *J* = 166.7 Hz), 50.7 (d, *J* = 5.1 Hz), 38.5, 38.1 (d, *J* = 23.5 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -224.5 (s) ppm. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₇H₈FO₂, 143.0508; found 143.0509.



3-(2-Fluoroethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (22k)

General procedure K. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg), washed with hexane (~ 400 mL), and dried. Yield: 93.22 g, 0.59 mol, 65%, yellow solid, m.p. = 90-91 °C. ¹H NMR (500 MHz, CDCl₃): δ 10.44 (br s, 1H), 4.52 (t, *J* = 5.9 Hz, 1H), 4.42 (t, *J* = 5.9 Hz, 1H), 2.03 (s, 6H), 1.91 (t, *J* = 5.8 Hz, 1H), 1.85 (t, *J* = 5.9 Hz, 1H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 176.1, 82.0 (d, *J* = 166.1 Hz), 52.3, 38.2, 37.6 (d, *J* = 4.8 Hz), 32.0 (d, *J* = 19.9 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -220.8 (s) ppm. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₈H₁₀FO₂, 157.0665; found 157.0664.



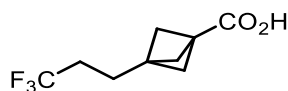
3-(2,2-Difluoroethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (24k)

General procedure K. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg), washed with hexane (~ 500 mL), and dried. Yield: 139.92 g, 0.795 mol, 73%, white solid, m.p. = 96-97 °C. ¹H NMR (500 MHz, CDCl₃): δ 10.67 (br s, 1H), 5.80 (tt, *J* = 56.2, 4.5 Hz, 1H), 2.09 (s, 6H), 2.04 (dt, *J* = 17.6, 4.5 Hz, 2H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 175.6, 116.2 (t, *J* = 239.9 Hz), 52.8, 38.9, 35.8 (t, *J* = 21.1 Hz), 34.8 (t, *J* = 6.0 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -116.2 (s) ppm. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₈H₉F₂O₂, 175.0571; found 175.0571.



3-(2,2,2-Trifluoroethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (25k)

General procedure K. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg), washed with hexane (~ 500 mL), and dried. Yield: 139.68 g, 0.72 mol, 75%, white solid, m.p. = 108-109 °C. ^1H NMR (500 MHz, CDCl_3): δ 10.49 (br s, 1H), 2.32 (q, J = 11.0 Hz, 2H), 2.13 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 175.4, 126.2 (q, J = 277.2 Hz), 52.9, 38.5, 35.7 (q, J = 28.5 Hz), 33.9 (q, J = 2.8 Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -64.9 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_8\text{H}_8\text{F}_3\text{O}_2$, 193.0476; found 193.0473.



3-(3,3,3-Trifluoropropyl)bicyclo[1.1.1]pentane-1-carboxylic acid (26k)

General procedure K. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg), washed with hexane (~ 400 mL), and dried. Yield: 120.02 g, 0.577 mol, 72%, yellow solid, m.p. = 132-133 °C. ^1H NMR (500 MHz, CDCl_3): δ 10.60 (br s, 1H), 2.08 – 2.00 (m, 2H), 1.97 (s, 6H), 1.81 – 1.72 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 176.0, 127.1 (q, J = 276.1 Hz), 51.4, 38.9, 37.7, 31.1 (q, J = 29.1 Hz), 23.9 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -67.0 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_9\text{H}_{10}\text{F}_3\text{O}_2$, 207.0633; found 207.0634



3-(4,4,4-Trifluorobutyl)bicyclo[1.1.1]pentane-1-carboxylic acid (27k)

General procedure K. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg), washed with hexane (~ 300 mL), and dried. Yield: 79.92 g, 0.36 mol, 80%, yellow solid, m.p. = 89-90 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 12.22 (br s, 1H), 2.30 – 2.15 (m, 2H), 1.82 (s, 6H), 1.56 – 1.47 (m, 2H), 1.47 – 1.36 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, $\text{DMSO}-d_6$): δ 171.0, 127.6 (q, J = 276.6 Hz), 50.7, 37.4, 32.3 (q, J = 27.3 Hz), 29.6, 18.6 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, $\text{DMSO}-d_6$): δ -65.3 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{10}\text{H}_{12}\text{F}_3\text{O}_2$, 221.0789; found 221.0791.



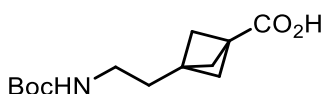
3-(Chloromethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (34k)

General procedure K. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg), washed with hexane (~ 400 mL), and dried. Yield: 110.40 g, 0.69 mol, 75%, white solid, m.p. = 96-97 °C. ¹H NMR (500 MHz, CDCl₃): δ 10.82 (br s, 1H), 3.56 (s, 2H), 2.07 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 175.9, 51.1, 44.3, 39.6, 37.7 ppm. LCMS (M-H)⁻: 159. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₇H₈ClO₂, 159.0213; found 159.0210.



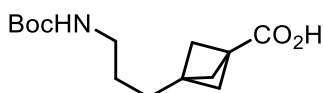
3-(Bromomethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (35k)

General procedure K. The final product was purified by sublimation under a reduced pressure (100 °C, 1 mmHg), washed with ~ 300 mL of hexane, and dried. Yield: 69.70 g, 0.34 mol, 66%, yellow solid, m.p. = 88-89 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.64 (br s, 1H), 3.44 (s, 2H), 2.06 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 175.7, 51.5, 39.6, 37.2, 32.9 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₇H₁₀BrO₂, 204.9864; found 204.9851.



3-(2-((*Tert*-butoxycarbonyl)amino)ethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (38k)

General procedure K. The mixture was carefully acidified with citric acid to pH ~ 5-6. The final product was recrystallized from a mixture of MeOtBu/hexane (100 mL, ~ 9:1). Yield: 23.45 g, 0.092 mol, 38%, yellow solid, m.p. = 106-107 °C. ¹H NMR (400 MHz, CDCl₃): δ 11.15 (br s, 1H), 4.49 (br s, 2H), 3.11 (s, 2H), 1.98 (s, 6H), 1.66 (t, *J* = 7.2 Hz, 2H), 1.43 (s, 9H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 175.3, 156.0, 79.5, 52.0, 38.4, 38.1, 31.5, 28.6 ppm. LCMS (M-H)⁻: 254. HRMS (ESI-TOF) *m/z*: [2M + H]⁺ calcd for C₂₆H₄₃N₂O₈, 511.302; found 511.2917.



3-(3-((*Tert*-butoxycarbonyl)amino)propyl)bicyclo[1.1.1]pentane-1-carboxylic acid (39k)

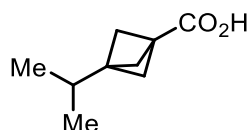
General procedure K. The mixture was carefully acidified with citric acid to pH ~ 5-6. The final product was triturated in a mixture of hexane/MeOtBu (50 mL, ~ 9:1). Yield: 7.80 g, 0.029 mol, 33%, white solid, m.p. = 88-89 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 12.20 (br s, 1H), 6.78 (t, *J* = 5.1 Hz, 1H), 2.92 – 2.82 (m, 2H), 1.78 (s, 6H), 1.36 (s, 9H), 1.36 – 1.24 (m, 4H) ppm. ¹³C{¹H} NMR (101 MHz, DMSO-d₆): δ 175.3, 156.0, 79.5, 52.0, 38.4, 38.1, 31.5, 28.6 ppm.

NMR (126 MHz, DMSO- d_6): δ 171.1, 155.6, 77.3, 50.8, 37.4, 28.3, 28.1, 26.6 ppm. LCMS (M-H) $^-$: 268. HRMS (ESI-TOF) m/z : [M - H] $^-$ calcd for $C_{14}H_{22}NO_4$, 268.1549; found 268.1549.



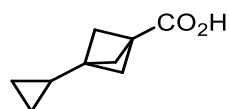
3-Phenethylbicyclo[1.1.1]pentane-1-carboxylic acid (41k)

General procedure K. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg), triturated in hexane (~ 400 mL), and dried. Yield: 101.52 g, 0.47 mol, 86%, white solid, m.p. = 138-139 °C. 1H NMR (500 MHz, DMSO- d_6): δ 12.20 (s, 1H), 7.26 (t, J = 7.5 Hz, 2H), 7.19 (d, J = 7.1 Hz, 2H), 7.16 (t, J = 7.2 Hz, 1H), 2.54 (dd, J = 9.0, 7.1 Hz, 2H), 1.79 (s, 6H), 1.77 – 1.72 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO- d_6): δ 171.1, 141.7, 128.2, 128.2, 125.7, 50.9, 37.5, 32.4, 32.1 ppm. HRMS (ESI-TOF) m/z : [M - H] $^-$ calcd for $C_{14}H_{15}O_2$, 215.1072; found 215.1071.



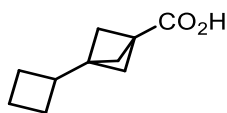
3-Isopropylbicyclo[1.1.1]pentane-1-carboxylic acid (48k)

General procedure K. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg), triturated in 500 mL of hexane, and dried. Yield: 90.09 g, 0.585 mol, 68%, white solid, m.p. = 127-128 °C. 1H NMR (500 MHz, DMSO- d_6): δ 12.20 (br s, 1H), 1.73 (s, 6H), 1.67 – 1.61 (sept, J = 6.8 Hz, 1H), 0.79 (d, J = 6.8 Hz, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO- d_6): δ 171.4, 48.4, 44.0, 36.4, 27.6, 18.5 ppm. HRMS (ESI-TOF) m/z : [M - H] $^-$ calcd for $C_9H_{13}O_2$, 153.0916; found 153.0917.



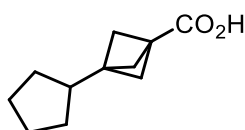
3-Cyclopropylbicyclo[1.1.1]pentane-1-carboxylic acid (50k)

General procedure K. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg), triturated in 100 mL of hexane, and dried. Yield: 18.85 g, 0.124 mol, 56%, yellow solid, m.p. = 140-141 °C. 1H NMR (500 MHz, $CDCl_3$): δ 1.84 (s, 6H), 0.90 – 0.82 (m, 1H), 0.41 – 0.35 (m, 2H), 0.16 – 0.09 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 176.8, 51.0, 41.6, 37.0, 11.1, 2.4 ppm. HRMS (ESI-TOF) m/z : [M + H] $^+$ calcd for $C_9H_{13}O_2$, 153.0916; found 153.0907.



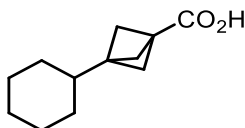
3-Cyclobutylbicyclo[1.1.1]pentane-1-carboxylic acid (51k)

General procedure K. The final product was triturated in 200 mL of hexane and dried. Yield: 36.52 g, 0.22 mol, 73%, olive solid, m.p. = 111-112 °C. ^1H NMR (500 MHz, CDCl_3): δ 10.69 (br s, 1H), 2.46 – 2.32 (m, 1H), 1.98 – 1.92 (m, 2H), 1.90 (s, 6H), 1.89 – 1.79 (m, 1H), 1.80 – 1.62 (m, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 176.9, 49.8, 42.9, 37.4, 35.8, 24.3, 18.2 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{10}\text{H}_{13}\text{O}_2$, 165.0916; found 165.0917.



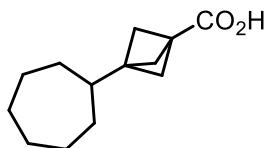
3-Cyclopentylbicyclo[1.1.1]pentane-1-carboxylic acid (52k)

General procedure K. The combined aqueous layers were acidified with sodium hydrogen sulfate to pH ~ 2. The final product was triturated in 200 mL of hexane and dried. Yield: 36.00 g, 0.20 mol, 77%, beige solid, m.p. = 130-131 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 12.18 (s, 1H), 1.97 – 1.86 (m, 1H), 1.74 (s, 6H), 1.61 – 1.40 (m, 6H), 1.28 – 1.13 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, $\text{DMSO}-d_6$): δ 171.3, 49.8, 49.2, 42.1, 37.3, 28.5, 25.3 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{11}\text{H}_{15}\text{O}_2$, 179.1072; found 179.1074.



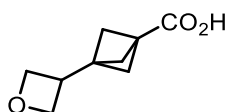
3-Cyclohexylbicyclo[1.1.1]pentane-1-carboxylic acid (53k)

General procedure K. The final product was triturated in 100 mL of hexane and dried. Yield: 29.14 g, 0.15 mol, 74%, yellow solid, m.p. = 166-167 °C. ^1H NMR (500 MHz, CDCl_3): δ 9.86 (br s, 1H), 1.86 (s, 6H), 1.72 (d, J = 13.0 Hz, 2H), 1.68 – 1.57 (m, 3H), 1.37 – 1.27 (m, 1H), 1.22 – 1.14 (m, 2H), 1.13 – 1.01 (m, 1H), 0.84 (qd, J = 12.5, 2.9 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 176.9, 49.6, 44.1, 37.8, 37.0, 29.2, 26.3, 26.1 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{12}\text{H}_{17}\text{O}_2$, 193.1229; found 193.1230.



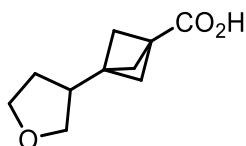
3-Cycloheptylbicyclo[1.1.1]pentane-1-carboxylic acid (54k)

General procedure K. The final product was triturated in 300 mL of hexane and dried. Yield: 74.88 g, 0.36 mol, 62%, white solid, m.p. = 192-193 °C. ^1H NMR (400 MHz, CDCl_3): δ 11.03 (br s, 1H), 1.87 (s, 6H), 1.72 – 1.30 (m, 11H), 1.17 – 1.03 (m, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 177.0, 49.7, 44.8, 39.6, 37.1, 30.7, 28.6, 26.5 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{13}\text{H}_{19}\text{O}_2$, 207.1385; found 207.1388.



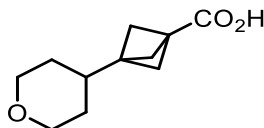
3-(Oxetan-3-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (55k)

Modified general procedure K was used: solvent THF. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg), triturated in 500 mL of hexane, and dried. Yield: 159.94 g, 0.952 mol, 70%, white solid, m.p. = 202-203 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 12.30 (br s, 1H), 4.58 (dd, J = 7.9, 5.9 Hz, 2H), 4.28 (t, J = 5.9 Hz, 2H), 3.10 – 2.98 (m, 1H), 1.90 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO-d_6): δ 171.1, 72.5, 48.9, 37.8, 34.5 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{13}\text{O}_3$, 169.0865; found 169.0854.



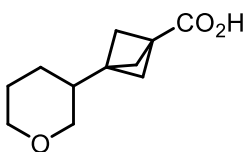
(±)-3-(Tetrahydrofuran-3-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (56k)

General procedure K. The crude product was recrystallized from 200 mL of hexane. Yield: 37.00 g, 0.209 mol, 78%, yellow solid, m.p. = 59-60 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 12.25 (br s, 1H), 3.68 – 3.55 (m, 3H), 3.41 (dd, J = 8.3, 5.9 Hz, 1H), 2.26 (p, J = 7.4 Hz, 1H), 1.87 – 1.82 (m, 1H), 1.79 (s, 6H), 1.62 – 1.54 (m, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO-d_6): δ 171.1, 69.3, 67.3, 49.4, 40.3, 38.8, 37.6, 28.6 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{10}\text{H}_{13}\text{O}_3$, 181.0865; found 181.0863.



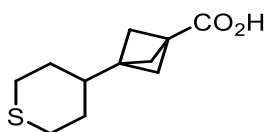
3-(Tetrahydro-2H-pyran-4-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (57k)

General procedure K. The crude product was recrystallized from 100 mL of hexane. Yield: 23.30 g, 0.083 mol, 50%, white solid, m.p. = 207-208 °C. ^1H NMR (500 MHz, CDCl_3): δ 10.44 (br s, 1H), 3.99 (dd, J = 11.1, 4.0 Hz, 2H), 3.35 (t, J = 11.0 Hz, 2H), 1.89 (s, 6H), 1.60 (tt, J = 11.8, 3.7 Hz, 1H), 1.51 – 1.44 (m, 2H), 1.27 (qd, J = 12.6, 4.5 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 176.0, 67.7, 49.4, 43.2, 37.1, 35.1, 28.9 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{11}\text{H}_{15}\text{O}_3$, 195.1021; found 195.1023.



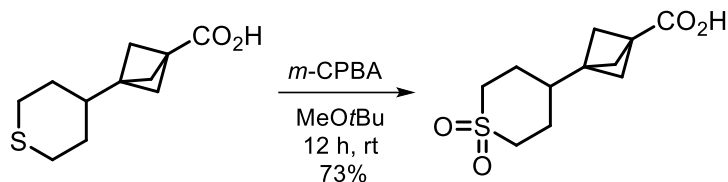
(±)-3-(Tetrahydro-2H-pyran-3-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (58k)

General procedure K. The final product was purified by sublimation under a reduced pressure (100 °C, 1 mmHg), and triturated in 150 mL of hexane. Yield: 27.48 g, 0.14 mol, 70%, yellow solid, m.p. = 143-145 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 12.25 (br s, 1H), 3.72 (t, J = 13.6 Hz, 1H), 3.17 (td, J = 11.3, 2.2 Hz, 1H), 2.95 (t, J = 10.8 Hz, 1H), 1.78 (s, 6H), 1.66 (d, J = 12.8 Hz, 1H), 1.60 – 1.42 (m, 3H), 1.15 – 1.06 (m, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO-d_6): δ 171.1, 69.5, 67.1, 49.2, 37.1, 35.5, 25.8, 25.0 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{11}\text{H}_{15}\text{O}_3$, 195.1021; found 195.1025.



3-(Tetrahydro-2H-thiopyran-4-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (59k)

General procedure K. The final product was triturated in 250 mL of hexane. Yield: 50.94 g, 0.24 mol, 65%, yellow solid, m.p. = 209-210 °C. ^1H NMR (500 MHz, CDCl_3): δ 10.87 (br s, 1H), 2.78 – 2.44 (m, 4H), 1.98 – 1.77 (m, 2H), 1.89 (s, 6H), 1.41 – 1.20 (m, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 176.4, 49.4, 43.8, 37.3, 37.0, 30.2, 28.5 ppm. GCMS (M^+): 212. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{11}\text{H}_{15}\text{O}_2\text{S}$, 211.0793; found 211.0792.



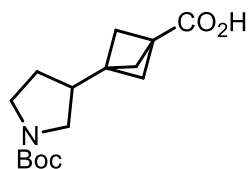
3-(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (O₂-59k)

To a solution of **59k** (20.00 g, 0.0943 mol, 1.00 equiv) in MeOtBu (~ 20 mL per 1 g, 400 mL) was added *m*-CPBA (50.54 g, 0.293 mol, 3.00 equiv) in portions at 0 °C (~ 30 min). The mixture was stirred at room temperature for 12 h. The precipitate was filtered, triturated in 150 mL of MeOtBu, filtered, and dried. Yield: 16.84 g, 0.069 mol, 73%, white solid, m.p. = 250-251 °C. ¹H NMR (500 MHz, DMSO-*d*₆): δ 12.29 (br s, 1H), 3.13 (t, *J* = 13.2 Hz, 2H), 2.99 (d, *J* = 12.7 Hz, 2H), 1.88 (t, *J* = 19.2 Hz, 2H), 1.80 (s, 6H), 1.70 (t, *J* = 12.0 Hz, 1H), 1.57 – 1.44 (m, 2H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-*d*₆): δ 171.1, 49.7, 48.9, 41.8, 36.5, 34.1, 26.6 ppm. LCMS (M-H)⁻: 243. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₁₁H₁₅O₄S, 243.0691; found 243.0687.



3-(1-(*Tert*-butoxycarbonyl)azetidin-3-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (60k)

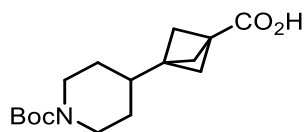
General procedure K. The mixture was carefully acidified with citric acid to pH ~ 5-6. The final product was triturated in a mixture of hexane/MeOtBu (400 mL, ~ 9:1). Yield: 153.00 g, 0.573 mol, 63%, yellow solid, m.p. = 149-150 °C. ¹H NMR (500 MHz, CDCl₃): δ 9.74 (br s, 1H), 3.92 (t, *J* = 8.5 Hz, 2H), 3.61 (dd, *J* = 8.5, 5.4 Hz, 2H), 2.64 – 2.54 (m, 1H), 1.98 (s, 6H), 1.42 (s, 9H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 175.1, 156.7, 79.8, 51.2, 49.7, 40.8, 37.9, 29.0, 28.5 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₄H₂₂NO₄, 268.1549; found 268.1526.



(±)-3-(1-(*Tert*-butoxycarbonyl)pyrrolidin-3-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (61k)

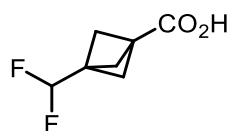
General procedure K. The mixture was carefully acidified with citric acid to pH ~ 5-6. The final product was triturated in a mixture of hexane/MeOtBu (300 mL, ~ 9:1), filtered, and dried. Yield: 80.09 g, 0.285 mol, 69%, yellow solid, m.p. = 130-132 °C. ¹H NMR (500 MHz, DMSO-*d*₆): δ 12.25 (br s, 1H), 3.29 – 3.20 (m, 2H), 3.19 – 3.11 (m, 1H), 2.99 – 2.91 (m, 1H), 2.25 – 2.17 (m, 1H), 1.80 (s, 6H), 1.60 – 1.49 (m, 1H), 1.39 (s, 9H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-*d*₆): δ 171.0,

153.5, 78.2, 49.5, 48.0, 47.8, 45.4, 45.2, 37.1, 28.2, 27.2 ppm. HRMS (ESI-TOF) m/z : $[M - H]^-$ calcd for $C_{15}H_{22}NO_4$, 280.1549; found 280.1547.



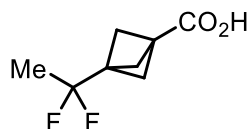
3-(1-(*Tert*-butoxycarbonyl)piperidin-4-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (63k)

General procedure K. The mixture was carefully acidified with citric acid to pH ~ 5-6. The final product was triturated in a mixture of hexane/MeOtBu (500 mL, ~ 9:1), filtered, and dried. Yield: 147.50 g, 0.50 mol, 56%, yellow solid, m.p. = 128-129 °C. 1H NMR (500 MHz, $CDCl_3$): δ 9.86 (br s, 1H), 4.12 (d, J = 8.3 Hz, 2H), 2.62 (t, J = 12.5 Hz, 2H), 1.88 (s, 6H), 1.61 – 1.47 (m, 3H), 1.44 (s, 9H), 1.06 (qd, J = 12.5, 4.2 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 175.8, 155.0, 79.6, 49.6, 43.8 (br s), 43.2, 37.1, 36.3, 28.6, 28.3 ppm. HRMS (ESI-TOF) m/z : $[M - H]^-$ calcd for $C_{16}H_{24}NO_4$, 294.1705; found 294.1711.



3-(Difluoromethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (67k)

General procedure K. The final product was triturated in 100 mL of hexane. Yield: 8.91 g, 0.055 mol, 78%, yellow solid, m.p. = 116-117 °C. 1H NMR (400 MHz, $DMSO-d_6$): δ 12.59 (s, 1H), 6.05 (t, J = 56.1 Hz, 1H), 2.02 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, $DMSO-d_6$): δ 170.3, 113.3 (t, J = 237.2 Hz), 48.7 (t, J = 4.5 Hz), 37.9, 37.2 (t, J = 27.9 Hz) ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $DMSO-d_6$): δ -123.2 (s) ppm. HRMS (ESI-TOF) m/z : $[M - H]^-$ calcd for $C_7H_7F_2O_2$, 161.0414; found 161.0414.



3-(1,1-Difluoroethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (68k)

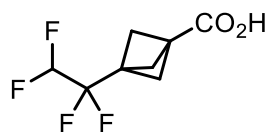
Compound **68** (42.00 g, 0.162 mol, 1.00 equiv) was dissolved in dry Et_2O (800 mL) and cooled to -100 °C. A solution of *t*-BuLi (1.9 M in pentane, 0.38 mol, 200 mL, 2.30 equiv) was added slowly during 45 min, and the solution was stirred at -100 °C for an additional 30 min. Then the solution was added to 2 kg of dry ice and warmed to room temperature overnight. The resulting mixture was extracted with H_2O (3 $\times$ 200 mL). The combined aqueous layers were acidified with 2M HCl to pH = 2, then extracted with EtOAc (3 $\times$ 300 mL). The combined organic layers were dried over

Na₂SO₄, concentrated under reduced pressure, and filtered from 200 mL of hexane. Yield: 18.60 g, 0.10 mol, 65%, yellow solid, m.p. = 144-145 °C. ¹H NMR (500 MHz, CDCl₃): δ 10.64 (br s, 1H), 2.15 (s, 6H), 1.55 (t, *J* = 18.1 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 175.6, 120.1 (t, *J* = 237.5 Hz), 49.8 (t, *J* = 3.5 Hz), 41.0 (t, *J* = 34.4 Hz), 36.6, 20.6 (t, *J* = 27.4 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -99.4 (s) ppm. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₈H₉F₂O₂, 175.0571; found 175.0569.



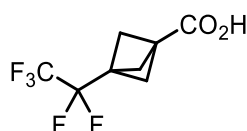
3-(Trifluoromethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (69k)

General procedure K. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg), triturated in 500 mL of hexane, filtered, and dried. Yield: 144.00 g, 0.80 mol, 89%, white solid, m.p. = 160-161 °C. ¹H NMR (500 MHz, CDCl₃): δ 10.62 (br s, 1H), 2.28 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 174.8, 122.4 (q, *J* = 275.4 Hz), 50.2 (d, *J* = 1.9 Hz), 37.3 (q, *J* = 39.5 Hz), 37.1 ppm. ¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -73.8 (s) ppm. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₇H₆F₃O₂, 179.0320; found 179.0317.



3-(1,1,2,2-Tetrafluoroethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (70k)

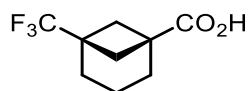
General procedure K. The crude product was recrystallized from 200 mL of hexane. Yield: 42.57 g, 0.20 mol, 80%, white solid, m.p. = 104-105 °C. ¹H NMR (500 MHz, DMSO-*d*₆): δ 12.68 (br s, 1H), 6.53 (tt, *J* = 52.0, 4.4 Hz, 1H), 2.15 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-*d*₆): δ 169.7, 114.0 (tt, *J* = 246.0, 27.4 Hz), 109.2 (tt, *J* = 248.0, 36.6 Hz), 49.5, 37.9, 35.8 (t, *J* = 30.1 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-*d*₆): δ -121.5 (t, *J* = 6.1 Hz), -137.1 (t, *J* = 6.1 Hz) ppm. HRMS (ESI-TOF) *m/z*: [M - H]⁻ calcd for C₈H₇F₄O₂, 211.0382; found 211.0384.



3-(Perfluoroethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (71k)

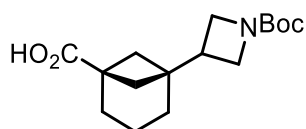
General procedure K. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg) triturated in 200 mL of hexane, filtered, and dried. Yield: 57.96 g, 0.252 mol, 69%, yellow solid, m.p. = 105-106 °C. ¹H NMR (500 MHz, CDCl₃): δ 10.14 (br s, 1H), 2.31 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 174.3, 119.1 (qt, *J* = 285.9, 36.3 Hz), 112.1 (tq, *J* = 251.7,

37.9 Hz), 50.6 (t, $J = 3.8$ Hz), 37.6, 36.5 (t, $J = 30.2$ Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -82.7 (s), -120.3 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_8\text{H}_6\text{F}_5\text{O}_2$, 229.0288; found 229.0291.



5-(Trifluoromethyl)bicyclo[3.1.1]heptane-1-carboxylic acid (82k)

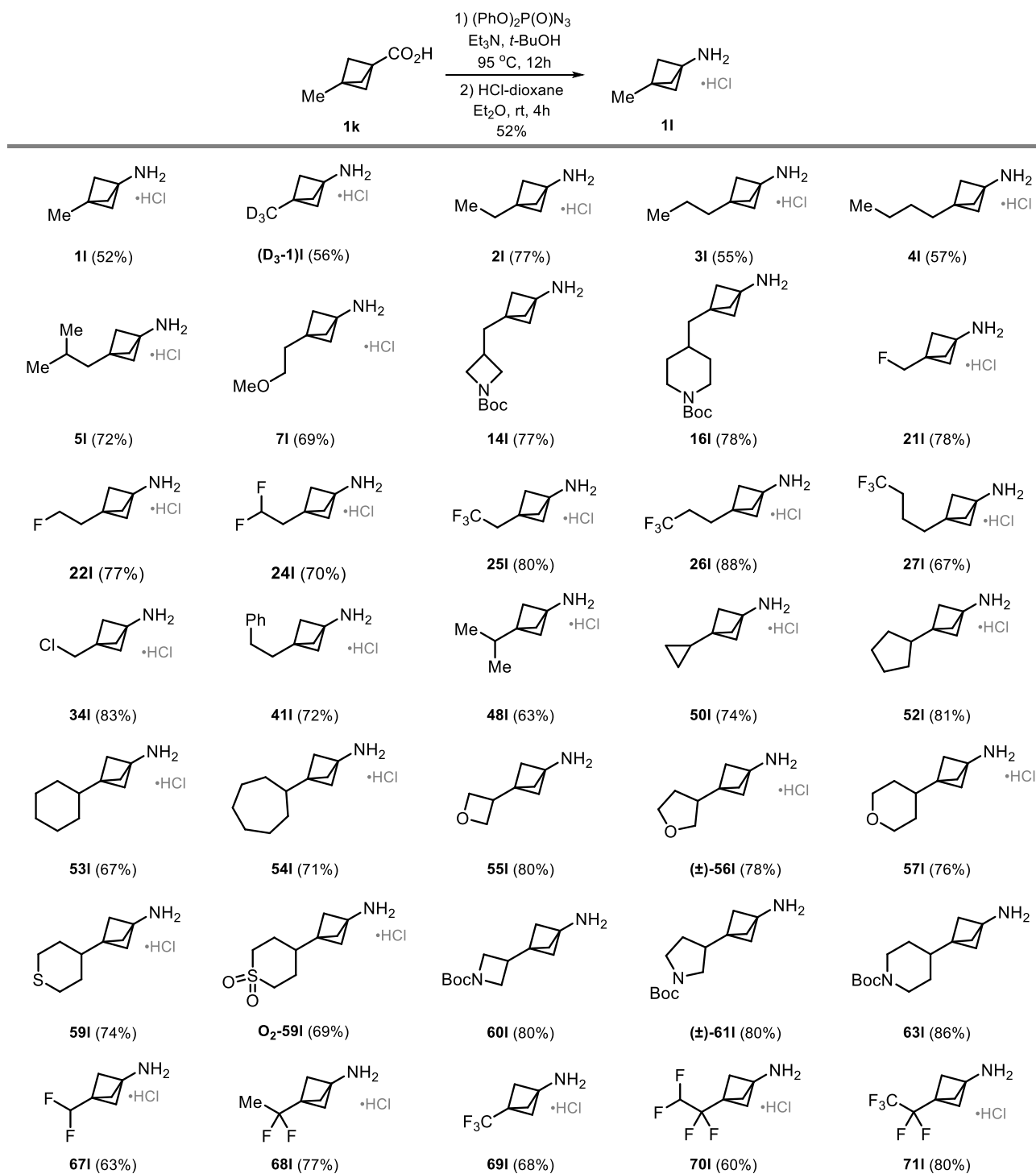
General procedure K. The final product was purified by sublimation under reduced pressure (100 °C, 1 mmHg), triturated in 50 mL of hexane, filtered, and dried. Yield: 5.82 g, 0.028 mol, 75%, brown solid, m.p. = 64-65 °C. ^1H NMR (500 MHz, CDCl_3): δ 11.03 (br s, 1H), 2.44 (d, $J = 7.6$ Hz, 2H), 2.10 – 2.00 (m, 2H), 2.00 – 1.87 (m, 4H), 1.78 – 1.68 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 181.1, 126.5 (q, $J = 277.0$ Hz), 41.9, 41.2 (q, $J = 30.9$ Hz), 34.4 (q, $J = 2.3$ Hz), 29.3, 26.1, 15.7 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -78.9 (s) ppm. GCMS (M) $^+$: 208. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_9\text{H}_{10}\text{F}_3\text{O}_2$, 207.0633; found 207.0631.



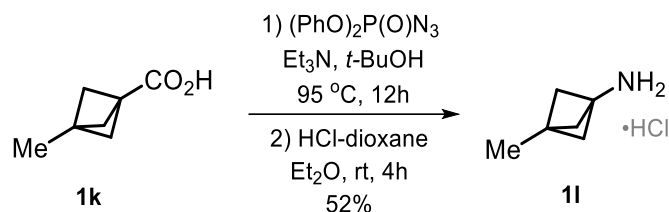
5-(1-(Tert-butoxycarbonyl)azetidin-3-yl)bicyclo[3.1.1]heptane-1-carboxylic acid (83k)

General procedure K. The mixture was carefully acidified with citric acid to pH ~ 5-6. The final product was triturated in a mixture of hexane/MeOtBu (60 mL, ~ 9:1), filtered, and dried. Yield: 8.00 g, 0.0271 mol, 63%, yellow solid, m.p. = 133-134 °C. ^1H NMR (500 MHz, CDCl_3): δ 9.88 (br s, 1H), 3.85 (t, $J = 8.6$ Hz, 2H), 3.73 – 3.62 (m, 2H), 2.48 – 2.34 (m, 1H), 2.10 (d, $J = 6.5$ Hz, 2H), 2.01 (t, $J = 6.9$ Hz, 2H), 1.92 – 1.82 (m, 2H), 1.63 – 1.51 (m, 4H), 1.43 (s, 9H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 181.4, 159.2, 156.6, 79.6, 49.9, 42.3, 39.6, 35.2, 35.1, 31.4, 30.1, 28.6, 16.4 ppm. HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_4$, 294.1705; found 294.1699.

12. Amines



General procedure L-1 (1l as an example)



3-Methylbicyclo[1.1.1]pentan-1-amine hydrochloride (**1l**)

$(\text{PhO})_2\text{P}(\text{O})\text{N}_3$ (75 mL, 0.35 mol, 1.20 equiv) was gradually added to a solution of **1k** (36.75 g, 0.29 mol, 1.00 equiv) and Et_3N (124 mL, 0.89 mol, 3.05 equiv) in $t\text{-BuOH}$ (300 mL) at room temperature. The reaction mixture was carefully warmed to 95°C (in an oil bath with a thermocouple) and stirred overnight. The mixture was concentrated under reduced pressure and quenched with aqueous K_2CO_3 (1×200 mL) and MeOtBu (300 mL). A precipitate was filtered off. The organic layer was washed with water (1×100 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2 , MeOtBu /hexane, 9:1). The product (32.40 g, 0.164 mol) was dissolved in Et_2O (200 mL) and 7M HCl in dioxane (150 mL) was added under cold conditions (ice-water bath). The reaction mixture was stirred for 4 h until a precipitate was formed. The product was filtered and triturated in a mixture of Et_2O /hexane (~ 100 mL, 9:1). Yield over two steps: 19.85 g, 0.149 mol, 52%, white solid, m.p. = $198\text{--}199^\circ\text{C}$. ^1H NMR (500 MHz, DMSO-d_6): δ 8.92 (br s, 3H), 1.83 (s, 6H), 1.21 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO-d_6): δ 52.8, 42.7, 33.1, 15.9 ppm. HRMS (ESI-TOF) m/z : $[\text{2M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{23}\text{N}_2$, 195.1861; found 195.1852.



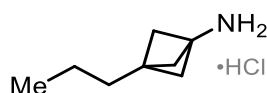
3-(Methyl-d₃)bicyclo[1.1.1]pentan-1-amine hydrochloride ((**D₃-1**)l)

General procedure L-1. The product was filtered and triturated in a mixture of Et_2O /hexane (~ 20 mL, 9:1). Yield over two steps: 1.53 g, 0.0112 mol, 56%, yellow solid, m.p. = $216\text{--}217^\circ\text{C}$. ^1H NMR (500 MHz, DMSO-d_6): δ 8.91 (s, 3H), 1.83 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO-d_6): δ 52.7, 42.7, 33.0, 15.1 (p, $J = 19.4$ Hz) ppm. HRMS (ESI-TOF) m/z : $[\text{2M} + \text{H}]^+$ calcd for $\text{C}_6\text{H}_8\text{D}_3\text{NNa}$, 123.0977; found 123.0967.



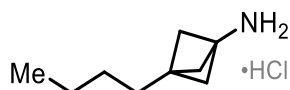
3-Ethylbicyclo[1.1.1]pentan-1-amine hydrochloride (2l)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 200 mL, 9:1). Yield over two steps: 39.83 g, 0.27 mol, 77%, white solid, m.p. = 215-216 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 8.94 (br s, 3H), 1.79 (s, 6H), 1.51 (q, *J* = 7.5 Hz, 2H), 0.82 (t, *J* = 7.5 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 50.5, 43.0, 37.7, 22.2, 10.7 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₇H₁₄N, 112.1126; found 112.1121.



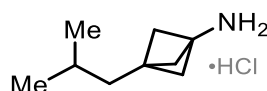
3-Propylbicyclo[1.1.1]pentan-1-amine hydrochloride (3l)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 50 mL, 9:1). Yield over 2 steps: 9.04 g, 0.056 mol, 55%, beige solid, m.p. = 131-132 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 8.92 (br s, 3H), 1.81 (s, 6H), 1.47 (dd, *J* = 9.0, 6.5 Hz, 2H), 1.29 – 1.19 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 51.2, 43.0, 36.8, 31.3, 19.6, 14.0 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₈H₁₆N, 126.1283; found 126.1284.



3-Butylbicyclo[1.1.1]pentan-1-amine hydrochloride (4l)

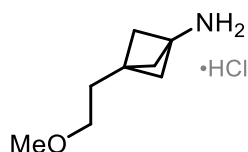
General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 50 mL, 9:1). Yield over 2 steps: 11.69 g, 0.066 mol, 57%, beige solid, m.p. = 191-192 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 8.74 (br s, 3H), 1.81 (s, 6H), 1.56 – 1.45 (m, 2H), 1.35 – 1.13 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 51.2, 43.0, 36.7, 28.8, 28.5, 22.1, 13.9 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₉H₁₈N, 140.1439; found 140.1444.



3-Isobutylbicyclo[1.1.1]pentan-1-amine hydrochloride (5l)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 300 mL, 9:1). Yield over two steps: 66.92 g, 0.377 mol, 72%, white solid, m.p. = 181-182 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 8.93 (br s, 3H), 1.86 (s, 6H), 1.60 – 1.51 (m, 1H), 1.41 (d, *J* = 6.5 Hz, 2H),

0.86 (d, $J = 6.5$ Hz, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 52.1, 43.1, 38.3, 36.3, 26.3, 23.0 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{18}\text{N}$, 140.1439; found 140.1454.



3-(2-Methoxyethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (7l)

General procedure L-1. The product was filtered and triturated in a mixture of Et_2O /hexane (~ 300 mL, 9:1). Yield over two steps: 69.94 g, 0.394 mol, 69%, white solid, m.p. = 151-152 $^\circ\text{C}$. ^1H NMR (500 MHz, DMSO- d_6): δ 8.92 (br s, 3H), 3.30 (t, $J = 6.5$ Hz, 2H), 3.20 (s, 3H), 1.84 (s, 6H), 1.74 (t, $J = 6.5$ Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 69.8, 57.8, 51.7, 43.0, 34.9, 28.8 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{16}\text{NO}$, 142.1232; found 142.1223.



3-(Fluoromethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (21l)

General procedure L-1. The product was filtered and triturated in a mixture of Et_2O /hexane (~ 100 mL, 9:1). Yield over two steps: 21.06 g, 0.139 mol, 78%, yellow solid, m.p. = 191-192 $^\circ\text{C}$. ^1H NMR (400 MHz, DMSO- d_6): δ 8.97 (br s, 3H), 4.51 (d, $J = 47.4$ Hz, 2H), 1.97 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 81.1 (d, $J = 163.3$ Hz), 50.4 (d, $J = 4.7$ Hz), 43.9 (d, $J = 2.0$ Hz), 35.0 (d, $J = 23.5$ Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -221.4 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_6\text{H}_{11}\text{FN}$, 116.0876; found 116.0870.



3-(2-Fluoroethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (22l)

General procedure L-1. The product was filtered and triturated in a mixture of Et_2O /hexane (~ 200 mL, 9:1). Yield over two steps: 39.89 g, 0.241 mol, 77%, yellow solid, m.p. = 191-192 $^\circ\text{C}$. ^1H NMR (500 MHz, DMSO- d_6): δ 8.95 (br s, 3H), 4.50 (t, $J = 5.8$ Hz, 1H), 4.41 (t, $J = 5.8$ Hz, 1H), 1.93 (t, $J = 5.8$ Hz, 1H), 1.89 (s, 6H), 1.87 (t, $J = 5.9$ Hz, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 82.0 (d, $J = 163.0$ Hz), 51.8, 43.1, 34.2 (d, $J = 5.1$ Hz), 29.8 (d, $J = 19.6$ Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -219.3 (s) ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_{13}\text{FN}$, 130.1032; found 130.1024.



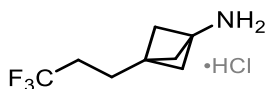
3-(2,2-Difluoroethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (24I)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 400 mL, 9:1). Yield over two steps: 77.99 g, 0.425 mol, 70%, yellow solid, m.p. = 192-193 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 8.98 (br s, 3H), 6.08 (tt, *J* = 56.1, 4.4 Hz, 1H), 2.13 (dt, *J* = 18.2, 4.4 Hz, 2H), 1.95 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 116.8 (t, *J* = 237.7 Hz), 52.3, 43.5, 33.3 (t, *J* = 21.1 Hz), 31.5 (t, *J* = 6.6 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -115.9 (s) ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₇H₁₂F₂N, 148.0938; found 148.0927.



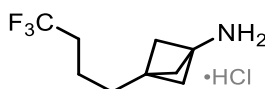
3-(2,2,2-Trifluoroethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (25I)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 400 mL, 9:1). Yield over two steps: 82.62 g, 0.41 mol, 80%, white solid, m.p. = 210-211 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 9.04 (br s, 3H), 2.64 (q, *J* = 11.6 Hz, 2H), 1.99 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 126.6 (q, *J* = 277.1 Hz), 52.3, 43.3, 32.8 (q, *J* = 28.0 Hz), 30.8 (q, *J* = 3.3 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -63.7 (s) ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₇H₁₁F₃N, 166.0844; found 166.0834.



3-(3,3,3-Trifluoropropyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (26I)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 400 mL, 9:1). Yield over two steps: 82.97 g, 0.385 mol, 88%, yellow solid, m.p. = 224-225 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 8.95 (br s, 3H), 2.29 – 2.16 (m, 2H), 1.86 (s, 6H), 1.79 – 1.71 (m, 2H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 127.5 (q, *J* = 276.4 Hz), 51.0, 42.9, 35.5, 30.1 (q, *J* = 27.9 Hz), 21.8 (q, *J* = 2.4 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -65.4 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₈H₁₃F₃N, 180.1000; found 180.0990.



3-(4,4,4-Trifluorobutyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (27I)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 300 mL, 9:1). Yield over two steps: 48.88 g, 0.213 mol, 67%, yellow solid, m.p. = 215-226 °C. ¹H NMR

(500 MHz, DMSO- d_6): δ 8.93 (br s, 3H), 2.29 – 2.17 (m, 2H), 1.84 (s, 6H), 1.62 – 1.56 (m, 2H), 1.47 – 1.39 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 127.6 (q, J = 276.5 Hz), 51.1, 43.0, 36.4, 32.3 (q, J = 27.5 Hz), 28.0, 19.0 (q, J = 2.7 Hz) ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6): δ -65.3 (s) ppm. LCMS ($M + \text{H}$) $^+$: 194. HRMS (ESI-TOF) m/z : [$M + \text{H}$] $^+$ calcd for $\text{C}_9\text{H}_{15}\text{F}_3\text{N}$, 194.1157; found 194.1146.



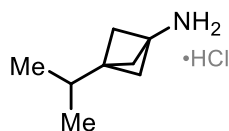
3-(Chloromethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (34l)

General procedure L-1. The product was filtered and triturated in a mixture of Et_2O /hexane (~ 100 mL, 9:1). Yield over two steps: 31.99 g, 0.191 mol, 83%, yellow solid, m.p. = 191-192 °C. ^1H NMR (500 MHz, DMSO- d_6): δ 9.06 (br s, 3H), 3.80 (s, 2H), 1.94 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6): δ 50.6, 43.5, 43.3, 36.8 ppm. LCMS ($M + \text{H}$) $^+$: 132. HRMS (ESI-TOF) m/z : [$M + \text{H}$] $^+$ calcd for $\text{C}_6\text{H}_{11}\text{ClN}$, 132.0580; found 132.0574.



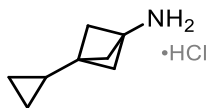
3-Phenethylbicyclo[1.1.1]pentan-1-amine hydrochloride (41l)

General procedure L-1. The product was filtered and triturated in a mixture of Et_2O /hexane (~ 200 mL, 9:1). Yield over 2 steps: 27.71 g, 0.124 mol, 72%, yellow solid, m.p. = 201-202 °C. ^1H NMR (400 MHz, DMSO- d_6): δ 8.89 (br s, 3H), 7.32 – 7.11 (m, 5H), 2.56 (t, J = 8.0 Hz, 2H), 1.85 (t, J = 8.4 Hz, 2H), 1.80 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 141.5, 128.3, 128.2, 125.8, 51.2, 43.0, 36.7, 32.4, 30.5 ppm. HRMS (ESI-TOF) m/z : [$M + \text{H}$] $^+$ calcd for $\text{C}_{13}\text{H}_{18}\text{N}$, 188.1439; found 188.1448.



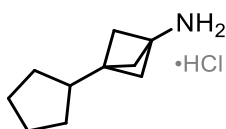
3-Isopropylbicyclo[1.1.1]pentan-1-amine hydrochloride (48l)

General procedure L-1. The product was filtered and triturated in a mixture of Et_2O /hexane (~ 100 mL, 9:1). Yield over two steps: 16.47 g, 0.102 mol, 63%, yellow solid, m.p. = 169-170 °C. ^1H NMR (500 MHz, DMSO- d_6): δ 8.94 (br s, 3H), 1.79 (sept, J = 6.8 Hz, 1H), 1.75 (s, 6H), 0.81 (d, J = 6.8 Hz, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 48.8, 42.8, 41.6, 26.6, 18.9 ppm. HRMS (ESI-TOF) m/z : [$M + \text{H}$] $^+$ calcd for $\text{C}_8\text{H}_{16}\text{N}$, 126.1283; found 126.1289.



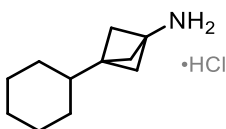
3-Cyclopropylbicyclo[1.1.1]pentan-1-amine hydrochloride (50l)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 50 mL, 9:1). Yield over 2 steps: 5.07 g, 0.0318 mol, 74%, white solid, m.p. = 223-224 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 8.94 (br s, 3H), 1.74 (s, 6H), 0.97 – 0.91 (m, 1H), 0.42 – 0.36 (m, 2H), 0.15 – 0.10 (m, 2H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 50.5, 42.9, 38.4, 9.5, 2.7 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₈H₁₄N, 124.1126; found 124.1120.



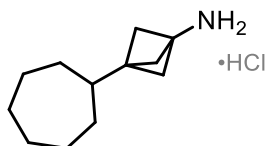
3-Cyclopentylbicyclo[1.1.1]pentan-1-amine hydrochloride (52l)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 150 mL, 9:1). Yield over 2 steps: 31.50 g, 0.168 mol, 81%, beige solid, m.p. = 177-179 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 8.92 (br s, 3H), 2.01 (p, *J* = 7.7 Hz, 1H), 1.77 (s, 6H), 1.63 – 1.42 (m, 6H), 1.24 – 1.15 (m, 2H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 49.7, 43.3, 38.1, 28.9, 25.1 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₀H₁₈N, 152.1439; found 152.1459.



3-Cyclohexylbicyclo[1.1.1]pentan-1-amine hydrochloride (53l)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 150 mL, 9:1). Yield over 2 steps: 28.21 g, 0.14 mol, 67%, white solid, m.p. = 229-230 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 8.91 (br s, 3H), 1.75 (s, 6H), 1.71 – 1.64 (m, 2H), 1.63 – 1.53 (m, 3H), 1.43 – 1.35 (m, 1H), 1.22 – 1.12 (m, 2H), 1.10 – 1.00 (m, 1H), 0.87 – 0.76 (m, 2H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 49.1, 42.8, 40.6, 35.9, 29.1, 25.6, 25.3 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₁H₂₀N, 166.1596; found 166.1588.



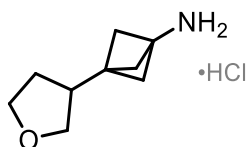
3-Cycloheptylbicyclo[1.1.1]pentan-1-amine hydrochloride (54l)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 150 mL, 9:1). Yield over 2 steps: 18.10 g, 0.084 mol, 71%, white solid, m.p. = 204-205 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 8.89 (br s, 3H), 1.76 (s, 6H), 1.68 – 1.28 (m, 11H), 1.15 – 1.03 (m, 2H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 49.2, 43.1, 41.26 (s), 37.7, 30.5, 28.0, 25.6 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₂H₂₂N, 180.1752; found 180.1739.



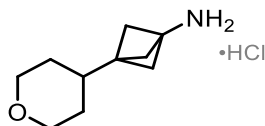
3-(Oxetan-3-yl)bicyclo[1.1.1]pentan-1-amine (55l)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 50 mL, 9:1). Yield over two steps: 1.71 g, 0.0123 mol, 80%, yellow oil. ¹H NMR (500 MHz, DMSO-d₆): δ 4.56 (dd, *J* = 7.8, 5.9 Hz, 2H), 4.23 (t, *J* = 5.9 Hz, 2H), 3.09 – 2.98 (m, 1H), 2.14 (br s, 2H), 1.59 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 74.7, 51.7, 49.6, 34.7 ppm. LCMS (M + H)⁺: 140. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₈H₁₄NO, 140.1075; found 140.1071.



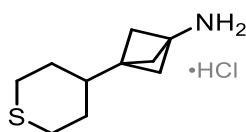
(±)-3-(Tetrahydrofuran-3-yl)bicyclo[1.1.1]pentan-1-amine hydrochloride (56l)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 200 mL, 9:1). Yield over two steps: 25.96 g, 0.137 mol, 78%, yellow solid, m.p. = 206-207 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 8.96 (br s, 3H), 3.68 – 3.57 (m, 3H), 3.38 (dd, *J* = 8.4, 5.8 Hz, 1H), 2.36 (p, *J* = 7.5 Hz, 1H), 1.90 – 1.84 (m, 1H), 1.82 (s, 5H), 1.61 – 1.53 (m, 1H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 69.5, 67.2, 49.9, 43.4, 37.9, 37.5, 29.0 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₉H₁₆NO, 154.1232; found 154.1223.



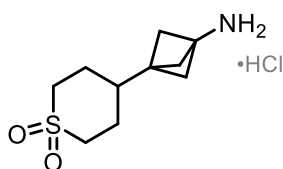
3-(Tetrahydro-2H-pyran-4-yl)bicyclo[1.1.1]pentan-1-amine hydrochloride (57l)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 200 mL, 9:1). Yield over two steps: 32.56 g, 0.16 mol, 76%, white solid, m.p. = 230-231 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 8.95 (br s, 3H), 3.83 (dd, *J* = 11.0, 3.7 Hz, 2H), 3.24 (t, *J* = 11.2 Hz, 2H), 1.77 (s, 6H), 1.71 – 1.59 (m, 1H), 1.43 (d, *J* = 12.8 Hz, 2H), 1.10 (dq, *J* = 12.5, 4.4 Hz, 2H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 66.6, 49.0, 43.0, 33.3, 29.0 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₀H₁₈NO, 168.1388; found 168.1383.



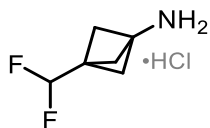
3-(Tetrahydro-2H-thiopyran-4-yl)bicyclo[1.1.1]pentan-1-amine hydrochloride (59l)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 200 mL, 9:1). Yield over two steps: 34.46 g, 0.157 mol, 74%, white solid, m.p. = 239-241 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 8.93 (br s, 3H), 2.64 – 2.51 (m, 4H), 1.86 (dd, *J* = 13.2, 2.7 Hz, 2H), 1.77 (s, 6H), 1.47 (tt, *J* = 11.6, 2.7 Hz, 1H), 1.14 (ddd, *J* = 16.2, 12.3, 4.4 Hz, 2H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 49.0, 42.9, 40.5, 35.3, 30.1, 27.4 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₀H₁₈NS, 184.1160; found 184.1151.



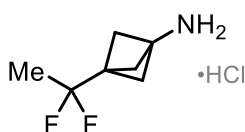
4-(3-Aminobicyclo[1.1.1]pentan-1-yl)tetrahydro-2H-thiopyran 1,1-dioxide hydrochloride (O₂-59l)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 50 mL, 9:1). Yield over two steps: 5.79 g, 0.023 mol, 69%, beige solid, m.p. = 240-242 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 8.95 (br s, 3H), 3.15 (td, *J* = 13.7, 2.8 Hz, 2H), 2.99 (d, *J* = 12.1 Hz, 2H), 1.91 (d, *J* = 13.6 Hz, 2H), 1.87 – 1.83 (m, 1H), 1.82 (s, 6H), 1.53 (q, *J* = 12.6 Hz, 2H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 49.6, 49.5, 42.7, 32.9, 27.0 ppm. LCMS (M + H)⁺: 216. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₀H₁₈NO₂S, 216.1058; found 216.1049.



3-(Difluoromethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (67l)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 300 mL, 9:1). Yield over two steps: 70.00 g, 0.413 g, 63%, white solid, m.p. = 221-222 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 9.10 (br s, 3H), 6.21 (t, *J* = 56.1 Hz, 1H), 2.07 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 112.9 (t, *J* = 236.9 Hz), 49.5, 43.8, 35.3 (t, *J* = 28.5 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -121.7 (s) ppm. LCMS (M + H)⁺: 134. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₆H₁₀F₂N, 134.0781; found 134.0774.



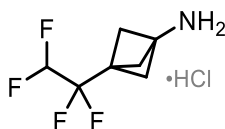
3-(1,1-Difluoroethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (68l)

3-(1,1-Difluoroethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (**68k**) (38.00 g, 0.21 mol, 1.00 equiv) was dissolved in *t*-BuOH (500 mL), followed by dropwise addition of Et₃N (50.00 g, 0.49 mol, 2.30 equiv), Boc₂O (94.00 g, 0.43 mol, 2.00 equiv), and then (PhO)₂P(O)N₃ (69.30 g, 0.25 mol, 1.20 equiv) was slowly added dropwise. The reaction mixture was stirred for 1 h at room temperature, and then heated to reflux for 16 h (in an oil bath with a thermocouple). After completion of the reaction, the solution was concentrated under reduced pressure, dissolved in MeOtBu (600 mL), and washed with saturated Na₂CO₃ (1 × 200 mL). The aqueous layer was extracted with MeOtBu (2 × 100 mL). The combined organic phases were washed with water (1 × 200 mL), and brine (1 × 200 mL), dried over Na₂SO₄, filtered, concentrated, and purified by column chromatography (SiO₂, EtOAc/hexane, 4:1). The obtained product (41.00 g, 0.16 mol) was dissolved in dry Et₂O (100 mL) and a solution of Et₂O saturated by dry HCl gas (300 mL, 15%) was added in one portion. The reaction mixture was stirred at room temperature for 15 h. A precipitate was filtered and washed with Et₂O (~ 100 mL). Yield over two steps: 25.69 g, 0.14 mol, 70%, white solid, m.p. = 207-208 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 9.18 (br s, 3H), 2.06 (s, 6H), 1.60 (t, *J* = 18.7 Hz, 3H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 120.7 (t, *J* = 236.5 Hz), 49.7, 42.8, 38.1 (t, *J* = 34.5 Hz), 20.7 (t, *J* = 26.5 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -95.1 (s) ppm. LCMS (M + H)⁺: 148. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₇H₁₂F₂N, 148.0938; found 148.0927.



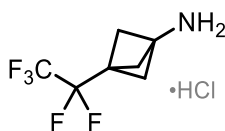
3-(Trifluoromethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (69I)

General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 300 mL, 9:1). Yield over 2 steps: 81.00 g, 0.432 mol, 68%, white solid, m.p. = 219-220 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 9.18 (br s, 3H), 2.25 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 122.8 (q, *J* = 274.8 Hz), 50.2, 43.2, 34.3 (q, *J* = 39.4 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -70.2 (s) ppm. LCMS (M + H)⁺: 152. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₆H₉F₃N, 152.0687; found 152.0677.



3-(1,1,2,2-Tetrafluoroethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (70I)

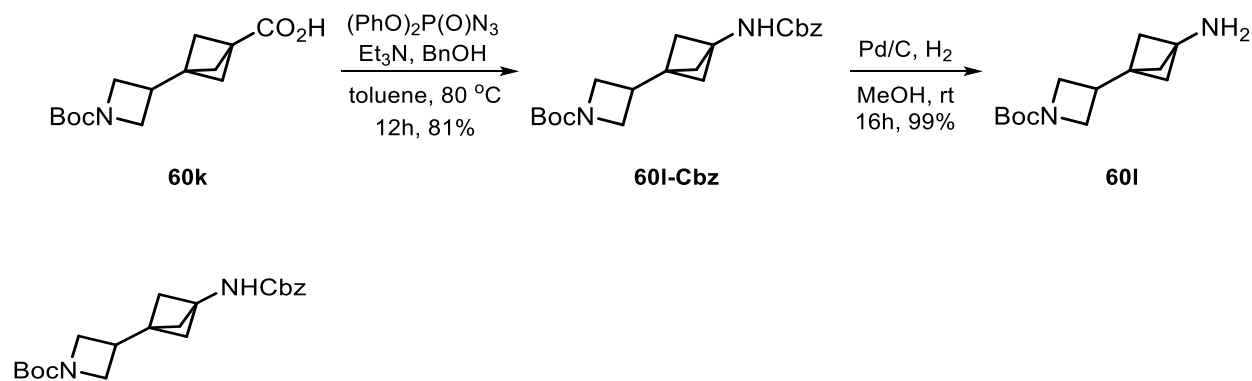
General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 60 mL, 9:1). Yield over 2 steps: 4.08 g, 0.0186 mol, 60%, white solid, m.p. = 224-225 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 9.24 (br s, 3H), 6.60 (tt, *J* = 51.9, 4.4 Hz, 1H), 2.20 (s, 6H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 114.3 (tt, *J* = 54.7, 27.9 Hz), 109.1 (tt, *J* = 247.8, 36.2 Hz), 50.4, 43.6, 33.9 (t, *J* = 30.6 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -119.9 (t, *J* = 6.3 Hz), -137.0 (t, *J* = 6.3 Hz) ppm. LCMS (M + H)⁺: 184. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₇H₁₀F₄N, 184.0749; found 184.0737.



3-(Perfluoroethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (71I)

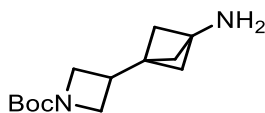
General procedure L-1. The product was filtered and triturated in a mixture of Et₂O/hexane (~ 100 mL, 9:1). Yield over 2 steps: 24.00 g, 0.101 mol, 80%, beige solid, m.p. = 201-202 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 9.33 (br s, 3H), 2.28 (s, 6H) ppm. ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 118.5 (qt, *J* = 286.2, 36.6 Hz), 111.4 (tq, *J* = 250.8, 37.9 Hz), 50.6, 43.2, 33.3 (t, *J* = 29.8 Hz) ppm. ¹⁹F{¹H} NMR (376 MHz, DMSO-d₆): δ -82.8, -118.6 ppm. LCMS (M + H)⁺: 202. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₇H₉F₅N, 202.0655; found 202.0642.

General procedure L-2 (60l as an example)



***Tert*-butyl 3-(3-(((benzyloxy)carbonyl)amino)bicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (60l-Cbz)**

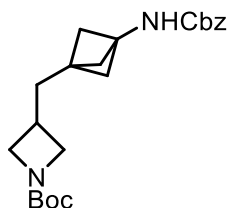
Et_3N (12.32 g, 0.122 mol, 2.00 equiv) and molecular sieves ($3\text{ \AA}$, 80.00 g) were added to a solution of **60k** (16.20 g, 0.061 mol, 1.00 equiv) in toluene (400 mL). Then it was heated to $60\text{ }^\circ\text{C}$ (in an oil bath with a thermocouple) and $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$ (17.60 g, 0.064 mol, 1.05 equiv) was added dropwise over 30 min. The mixture was stirred until gas evolution stopped (approximately 1.5 h), then the temperature was raised to $80\text{ }^\circ\text{C}$, and benzyl alcohol (distilled over CaH_2 , 7.25 g, 0.067 mol, 1.10 equiv) was added dropwise during 30 min. The mixture was stirred overnight at the same temperature. The mixture was cooled, filtered through Na_2SO_4 , and washed with a sat. aq. Na_2CO_3 ($1 \times 300\text{ mL}$), water ($1 \times 300\text{ mL}$), then dried over Na_2SO_4 , filtered and concentrated. The resulting mixture was purified by column chromatography (SiO_2 , hexane/ EtOAc , 9:1, $R_f = 0.5$). Yield: 18.26 g, 0.049 mol, 81%, yellow oil. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 7.95 (br s, 1H), 7.42 – 7.21 (m, 5H), 4.98 (s, 2H), 3.84 (br s, 2H), 3.48 (br s, 2H), 2.68 – 2.64 (m, 1H), 1.81 (s, 6H), 1.36 (s, 9H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 156.6, 136.5, 128.7, 128.3, 119.5, 79.5, 66.6, 51.8, 50.8, 46.3, 37.8, 28.5, 28.3 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{NaO}_4$, 395.1947; found 395.1943.



***Tert*-butyl 3-(3-aminobicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (60l)**

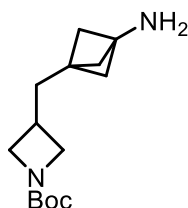
To a solution of *tert*-butyl 3-(3-aminobicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate (18.26 g, 0.049 mol) in MeOH (150 mL), 5% Pd/C (2 g) was added in one portion. The solution was stirred for 16 h under the balloon of H_2 ($\sim 1.5\text{ atm}$). The mixture was filtered and concentrated to obtain the desired product. Yield: 11.57 g, 0.048 mol, 99%, yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 3.81 (br s, 2H), 3.44 (br s, 2H), 2.64 – 2.54 (m, 1H), 1.55 (s, 6H), 1.36 (s, 9H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR

(126 MHz, DMSO- d_6): δ 156.6, 79.4, 51.5, 49.5, 35.4, 28.5, 28.4 ppm. HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{13}H_{23}N_2O_2$, 239.1760; found 239.1742.



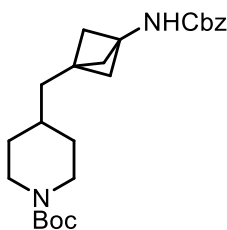
Tert-butyl 3-((3-(((benzyloxy)carbonyl)amino)bicyclo[1.1.1]pentan-1-yl)methyl)azetidine-1-carboxylate (14l-Cbz)

General procedure L-2 (Cbz). The final product was purified by column chromatography (SiO_2 , hexane/EtOAc, 9:1, R_f = 0.65). Yield: 118.5 g, 0.307 mol, 78%, yellow oil. 1H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 5H), 5.18 (br s, 1H), 5.06 (br s, 2H), 3.99 (t, J = 8.3 Hz, 2H), 3.51 (dd, J = 8.1, 5.9 Hz, 2H), 2.54 – 2.44 (m, 1H), 1.87 (s, 6H), 1.82 (d, J = 7.6 Hz, 2H), 1.43 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 156.5, 136.6, 128.7, 128.3, 79.4, 66.6, 54.8, 52.9, 46.0, 34.8, 28.6, 27.4 ppm. HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{22}H_{31}N_2O_4$, 387.2284; found 387.2282.



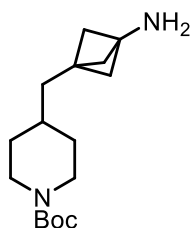
Tert-butyl 3-((3-aminobicyclo[1.1.1]pentan-1-yl)methyl)azetidine-1-carboxylate (14l)

General procedure L-2 (cleavage of Cbz). Yield: 76.60 g, 0.304 mol, 99%, yellow oil. 1H NMR (500 MHz, DMSO- d_6): δ 3.89 (br s, 2H), 3.40 (br s, 2H), 2.46 – 2.36 (m, 1H), 2.00 (s, 2H), 1.69 (d, J = 7.7 Hz, 2H), 1.49 (s, 6H), 1.36 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (151 MHz, DMSO- d_6): δ 155.4, 78.2, 55.1, 53.9, 53.2, 49.7, 34.6, 32.8, 28.1, 26.9 ppm. HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{14}H_{25}N_2O_2$, 253.1916; found 253.1904.



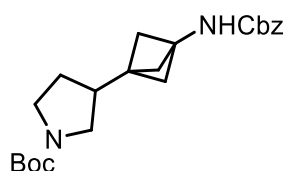
Tert-butyl 4-((3-(((benzyloxy)carbonyl)amino)bicyclo[1.1.1]pentan-1-yl)methyl)piperidine-1-carboxylate (16l-Cbz)

General procedure L-2 (Cbz). The final product was purified by column chromatography (SiO₂, hexane/EtOAc, 9:1, R_f = 0.62). Yield: 115.42 g, 0.279 mol, 79%, yellow solid, m.p. = 106-107 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.38 – 7.30 (m, 5H), 5.18 (br s, 1H), 5.07 (br s, 2H), 4.03 (d, *J* = 13.2 Hz, 2H), 2.67 (td, *J* = 13.1, 2.1 Hz, 2H), 1.92 (s, 3H), 1.64 (d, *J* = 12.5 Hz, 2H), 1.49 – 1.38 (m, 3H), 1.44 (s, 9H), 1.11 – 1.02 (m, 2H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 155.0, 136.6, 128.6, 128.2, 79.3, 66.5, 53.7, 45.9, 44.0, 37.0, 34.9, 32.7, 28.6 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₄H₃₄N₂NaO₄, 437.2416; found 437.2411.



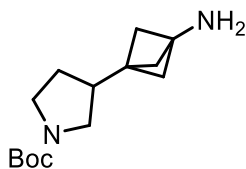
Tert-butyl 4-((3-aminobicyclo[1.1.1]pentan-1-yl)methyl)piperidine-1-carboxylate (16l)

General procedure L-2 (cleavage of Cbz). Yield: 77.30 g, 0.276 mol, 99%, yellow solid, m.p. = 51-52 °C. ¹H NMR (500 MHz, DMSO-d₆): δ 3.86 (d, *J* = 11.5 Hz, 2H), 2.67 (br s, 2H), 1.99 (br s, 2H), 1.61 (d, *J* = 12.9 Hz, 2H), 1.55 (s, 6H), 1.38 (s, 9H), 1.37 (br s, 3H), 0.97 – 0.87 (m, 2H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 153.8, 78.3, 54.1, 49.6, 43.4 (br s), 36.9, 34.3, 33.3, 32.2, 28.1 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₆H₂₉N₂O₂, 281.2229; found 281.2213.



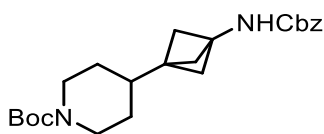
(±)-Tert-butyl 3-(3-(((benzyloxy)carbonyl)amino)bicyclo[1.1.1]pentan-1-yl)pyrrolidine-1-carboxylate (61l-Cbz)

General procedure L-2 (Cbz). The final product was purified by column chromatography (SiO₂, hexane/EtOAc, 9:1, R_f = 0.6). Yield: 6.95 g, 0.018 mol, 82%, yellow solid, m.p. = 50-52 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.39 – 7.28 (m, 5H), 5.22 (br s, 1H), 5.07 (br s, 2H), 3.44 – 3.35 (m, 2H), 3.31 – 3.20 (m, 1H), 3.00 (t, *J* = 8.6 Hz, 1H), 2.37 – 2.27 (m, 1H), 1.89 (br s, 7H), 1.62 – 1.53 (m, 1H), 1.45 (s, 9H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 154.7, 136.6, 128.6, 128.2, 79.2, 66.6, 51.4, 48.8, 45.7, 37.7, 28.7 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₂H₃₀N₂NaO₄, 409.2103; found 409.2098.



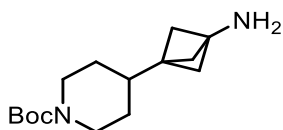
(±)-tert-butyl 3-(3-aminobicyclo[1.1.1]pentan-1-yl)pyrrolidine-1-carboxylate (61l)

General procedure L-2 (cleavage of Cbz). Yield: 4.60 g, 0.018 mol, 98%, colorless oil. A mixture of *N*-Boc rotamers. ^1H NMR (500 MHz, CDCl_3): δ 3.43 – 3.19 (m, 3H), 3.00 (dd, J = 10.2, 8.1 Hz), 2.93 (dd, J = 10.2, 8.1 Hz) 1H, 2.31 – 2.22 (m, 1H), 1.95 (s, 2H), 1.87 – 1.81 (m, 1H), 1.63 (2×s, 6H), 1.59 – 1.50 (m, 1H), 1.44 (s), 1.43 (s) 9H ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 154.7, 79.1, 52.1, 49.0, 48.8, 48.7, 46.0, 45.6, 38.6, 37.7, 35.23, 35.16, 29.3, 29.2, 28.7, 28.6 ppm. HRMS (ESI-TOF) m/z : not detected under the experimental conditions.



tert-butyl 4-(3-(((benzyloxy)carbonyl)amino)bicyclo[1.1.1]pentan-1-yl)piperidine-1-carboxylate (63l-Cbz)

General procedure L-2 (Cbz). The final product was purified by column chromatography (SiO_2 , hexane/EtOAc, 9:1, R_f = 0.62). Yield: 4.60 g, 0.018 mol, 88%, colorless oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.90 (br s, 1H), 7.40 – 7.24 (m, 5H), 4.97 (s, 2H), 3.93 (br s, 2H), 3.34 (s, 1H), 2.74 – 2.54 (m, 1H), 1.71 (s, 6H), 1.60 – 1.45 (m, 3H), 1.38 (s, 9H), 0.95 – 0.82 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, $\text{DMSO}-d_6$): δ 154.9, 153.8, 137.1, 128.3, 127.8, 127.7, 78.4, 64.9, 49.8, 45.0, 42.9, 34.5, 28.4, 28.1 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{32}\text{N}_2\text{NaO}_4$, 423.2260; found 423.2253.



tert-butyl 4-(3-aminobicyclo[1.1.1]pentan-1-yl)piperidine-1-carboxylate (63l)

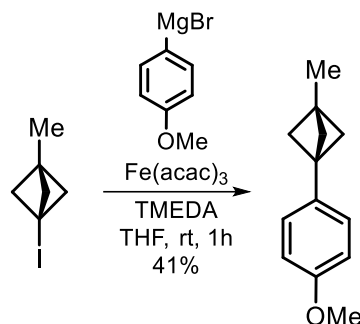
General procedure L-2 (cleavage of Cbz). Yield: 19.50 g, 0.073 mol, 98%, yellow solid, m.p. = 50–52 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 3.94 (d, J = 9.8 Hz, 2H), 2.63 (br s, 2H), 1.50 (br s, 3H), 1.47 (s, 6H), 1.38 (s, 9H), 0.88 (dq, J = 12.8, 4.0 Hz, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, $\text{DMSO}-d_6$): δ 153.8, 78.4, 50.7, 48.6, 43.1 (br s), 37.4, 34.7, 28.6, 28.1 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{27}\text{N}_2\text{O}_2$, 267.2073; found 267.2054.

Radical modifications of bicyclo[1.1.1]pentane iodides

[Fe]-catalyzed reaction with ArMgBr

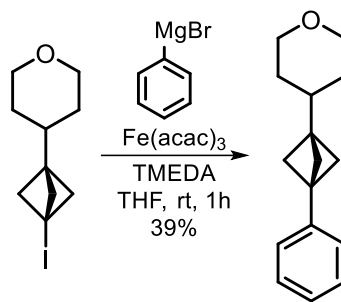
(according to J. Nugent, B. R. Shire, D. F. J. Caputo, H. D. Pickford, F. Nightingale, I. T. T. Houlsby, J. J. Mousseau, E. A. Anderson. *Angew. Chem. Int. Ed.* **2020**, 59, 11866-11870).

General procedure M



1-(4-Methoxyphenyl)-3-methylbicyclo[1.1.1]pentane (**1m**)

In a three-neck reactor equipped with a thermometer and a dropping funnel were dissolved 1-iodo-3-methylbicyclo[1.1.1]pentane (0.75 g, 3.60 mmol, 1.00 equiv) and Fe(acac)₃ (0.127 g, 0.36 mmol, 0.10 equiv) in 20 mL of dry THF. The resulting mixture was purged with argon 3 times and TMEDA (0.22 mL, 1.40 mmol, 0.40 equiv) was added at room temperature. The solution was stirred for 5 min and then bromo(4-methoxyphenyl)magnesium (a 1M solution in THF, 5.7 mL, 5.70 mmol, 1.60 equiv) was added dropwise, keeping the temperature within 20-25 °C for 5 min. The reaction was stirred for 1 h at room temperature and then quenched with a saturated solution of ammonium chloride (30 mL). The mixture was concentrated in *vacuo* and the aqueous layer was extracted with MeOtBu (3 × 40 mL). The combined organic layers were dried over sodium sulfate, filtered, and evaporated in *vacuo*. The final product was purified by flash chromatography (SiO₂, hexane/MeOtBu, 95:5, R_f = 0.9) and additionally recrystallized from hexane. Yield: 0.28 g, 1.49 mmol, 41%, yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 1.89 (s, 6H), 1.24 (s, 3H) ppm. ¹³C{¹H} NMR (151 MHz, CDCl₃): δ 158.2, 134.1, 127.2, 113.7, 55.5, 54.1, 41.2, 35.3, 18.4 ppm. HRMS (ESI-TOF) *m/z*: not detected under the experimental conditions.

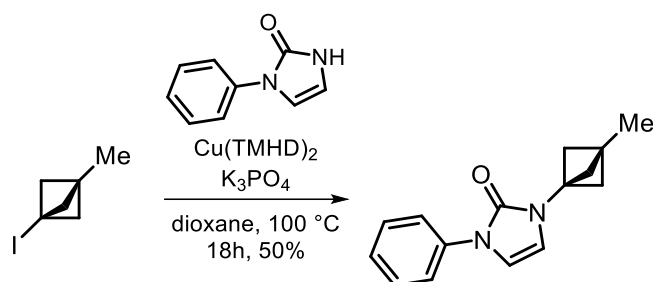


4-(3-Phenylbicyclo[1.1.1]pentan-1-yl)tetrahydro-2H-pyran (2m)

General procedure M. Scale: 1.00 g, 3.60 mmol, 1.00 equiv of 4-(3-iodobicyclo[1.1.1]pentan-1-yl)tetrahydro-2H-pyran. The final product was purified by flash chromatography (SiO₂, hexane/MeOtBu, 95:5, R_f = 0.85) and additionally recrystallized from hexane. Yield: 0.32 g, 1.40 mmol, 39%, white solid. ¹H NMR (500 MHz, DMSO-d₆): δ 7.28 (m, 5H), 3.87 (d, *J* = 8.1 Hz, 2H), 3.28 (t, *J* = 11.2 Hz, 2H), 1.81 (s, 6H), 1.61 (t, *J* = 11.2 Hz, 1H), 1.48 (d, *J* = 12.5 Hz, 2H), 1.17 (dd, *J* = 20.5, 11.2 Hz, 2H) ppm. ¹³C{¹H} NMR (126 MHz, DMSO-d₆): δ 141.0, 128.1, 126.3, 125.8, 66.8, 49.2, 41.5, 40.5, 34.7, 28.9 ppm. LCMS (M + H)⁺: 229. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₆H₂₁O, 229.1592; found 229.1586.

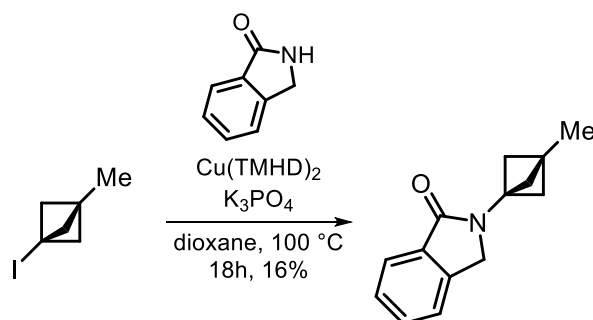
[Cu]-catalyzed coupling with *N*-azoles

(according to M. Alonso, S. Cañellas, F. Delgado, M. Serrano, A. Diéguez-Vázquez, J. E. Gómez. *Org. Lett.* **2023**, 25, 771–776).



1-(3-Methylbicyclo[1.1.1]pentan-1-yl)-3-phenyl-1,3-dihydro-2H-imidazol-2-one (**1n**)

1-Phenyl-1,3-dihydro-2H-imidazol-2-one (200 mg, 1.25 mmol, 1.00 equiv), 1-iodo-3-methylbicyclo[1.1.1]pentane (1.04 g, 5.00 mmol, 4.00 equiv), Cu(TMHD)_2 (268.8 mg, 0.625 mmol, 50 mol%) and K_3PO_4 (795 mg, 3.75 mmol, 3.00 equiv) were weighed into an 30 mL vial and dissolved in 1,4-dioxane (13 mL, 0.1M) at room temperature under Ar. The reaction was sealed and stirred at 100 °C for 18 h (in an oil bath with a thermocouple). After the reaction was completed, the mixture was allowed to cool down to room temperature. The mixture was concentrated under reduced pressure. The residue was mashed in EtOAc (~ 10 mL) and filtered. The filtrate was concentrated under reduced pressure. The final product was purified by column chromatography (SiO_2 , hexane/EtOAc, 7:3, R_f = 0.58). Yield: 150 mg, 0.625 mmol, 50%, white solid. ^1H NMR (500 MHz, CDCl_3): δ 7.58 (d, J = 7.8 Hz, 2H), 7.39 (t, J = 7.3 Hz, 2H), 7.20 (t, J = 7.0 Hz, 1H), 6.51 (s, 1H), 6.27 (s, 1H), 2.14 (s, 6H), 1.30 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 151.6, 137.4, 129.2, 125.7, 121.7, 110.1, 109.1, 54.2, 47.2, 33.5, 16.4 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}$, 241.1341; found 241.1335.

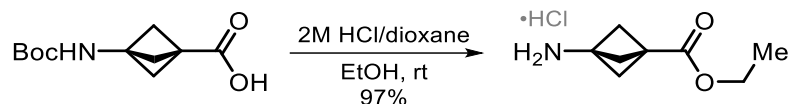


2-(3-Methylbicyclo[1.1.1]pentan-1-yl)isoindolin-1-one (**2n**)

Isoindolin-1-one (200 mg, 1.50 mmol, 1.00 equiv), 1-iodo-3-methylbicyclo[1.1.1]pentane (624 mg, 3.00 mmol, 2.00 equiv), Cu(TMHD)_2 (322.5 mg, 0.75 mmol, 50 mol%) and K_3PO_4 (954 mg, 4.5 mmol, 3.00 equiv) were weighed into a 30 mL vial and dissolved in 1,4-dioxane (15 mL, 0.1M) at room temperature under Ar. The reaction was sealed and stirred at 100 °C for 18 h (in an oil bath

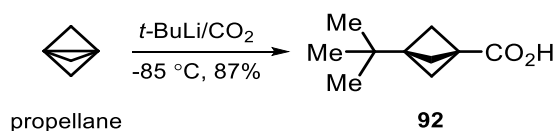
with a thermocouple). After the reaction was completed, the mixture was allowed to cool down to room temperature. The mixture was concentrated under reduced pressure. The residue was mashed in EtOAc (~ 10 mL) and filtered. The filtrate was concentrated under reduced pressure. The final product was purified by column chromatography (SiO₂, hexane/EtOAc, 7:3, R_f = 0.53). Yield: 50 mg, 0.23 mmol, 16%, white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.71 (d, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 7.3 Hz, 1H), 4.25 (s, 2H), 2.07 (s, 6H), 1.23 (s, 3H) ppm. ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 168.4, 140.8, 133.5, 131.2, 127.9, 123.4, 122.6, 54.3, 48.6, 47.2, 34.0, 16.5 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₄H₁₆NO, 214.1232; found 214.1224.

Synthesis of BCP bioactive derivatives



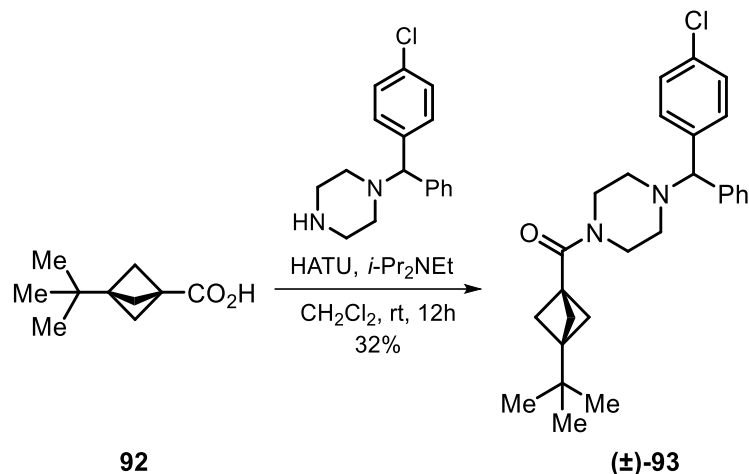
Ethyl 3-aminobicyclo[1.1.1]pentane-1-carboxylate hydrochloride (91)

To a solution of 4-((*tert*-butoxycarbonyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid (5.83 g, 0.0257 mol) in EtOH (100 mL) was added 2M HCl in dioxane (60 mL) at room temperature. The resulting mixture was stirred overnight and then concentrated under reduced pressure. The residue was dried under reduced pressure ($\sim 20\text{ }^{\circ}\text{C}$, 0.1 torr). Yield: 4.76 g, 0.0249 mol, 97%, beige solid, m.p. = 201-202 $^{\circ}\text{C}$. ^1H NMR (500 MHz, DMSO- d_6): δ 9.14 (br s, 3H), 4.07 (t, $J = 7.1$ Hz, 2H), 2.23 (s, 6H), 1.18 (t, $J = 7.1$ Hz, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 167.6, 60.6, 52.7, 43.2, 34.9, 14.0 ppm. LCMS ($M + H$) $^+$: 156. HRMS (ESI-TOF) m/z : [$M + H$] $^+$ calcd for $\text{C}_8\text{H}_{14}\text{NO}_2$, 156.1025; found 156.1016.



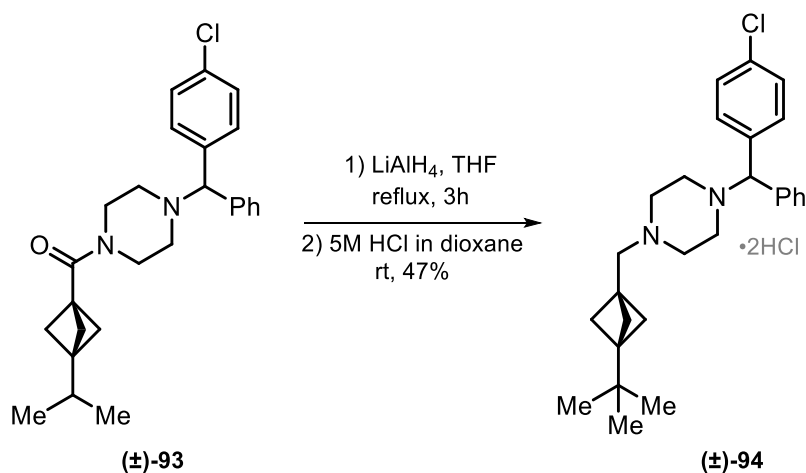
3-(*Tert*-butyl)bicyclo[1.1.1]pentane-1-carboxylic acid (92)

A solution of $t\text{-BuLi}$ (250 mL, 0.45 mol, 1.10 equiv, 1.9 M in pentane) was added to a solution of propellane (400 mL, 0.43 mol, 1.00 equiv, ~ 1.1 M in Et_2O) dropwise at $-85\text{ }^{\circ}\text{C}$ under Ar. The resulting mixture was stirred at $-85\text{ }^{\circ}\text{C}$ for 30 min. After 30 min, the solution was poured on dry CO_2 (~ 1000 g), and the reaction was allowed to warm to room temperature. H_2O (1000 mL) was added, and the mixture was extracted with MeOtBu (3×500 mL). The aqueous layer was acidified with 1M HCl to pH ~ 2 , and then extracted with MeOtBu (5×300 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure ($\sim 30\text{-}15$ mmHg, $35\text{-}50\text{ }^{\circ}\text{C}$). The residue was dried from pivalic acid under reduced pressure (0.1 - 2 mmHg, at $80\text{ }^{\circ}\text{C}$ for 10 h) to obtain the product which was triturated in hexane. Yield: 63.00 g, 0.37 mol, 87%, beige solid, m.p. = 185-186 $^{\circ}\text{C}$. ^1H NMR (500 MHz, CDCl_3): δ 10.88 (br s, 1H), 1.86 (s, 6H), 0.84 (s, 9H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 177.3, 48.3, 48.2, 35.5, 29.5, 25.9 ppm. HRMS (ESI-TOF) m/z : [$M - H$] $^-$ calcd for $\text{C}_{10}\text{H}_{15}\text{O}_2$, 167.1072; found 167.1071.



(±)-(3-(*Tert*-butyl)bicyclo[1.1.1]pentan-1-yl)(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)methanone (93)

To a solution of 3-(*tert*-butyl)bicyclo[1.1.1]pentane-1-carboxylic acid **92** (3.00 g, 0.0179 mol, 1.00 equiv) and 1-((4-chlorophenyl)(phenyl)methyl)piperazine (5.13 g, 0.0179 mol, 1.00 equiv) in CH_2Cl_2 (100 mL) was added *i*-Pr₂NEt (3.47 g, 0.0269 mol, 1.50 equiv) at room temperature. The resulting solution was stirred for 10 min and then HATU (10.22 g, 0.0269 mol, 1.50 equiv) was added in one portion at 0 °C under Ar. The resulting mixture was stirred at room temperature overnight. The residue was diluted with aq. 5M NH_4Cl (200 mL). The organic layer was separated, and the aqueous layer was additionally extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with aq. sat. NaHCO_3 (2 × 100 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The final product was purified by column chromatography (SiO_2 , MeOtBu/hexane, 7:3, R_f = 0.7). Yield: 2.50 g, 0.00572 mol, 32%, white solid, m.p. = 58-59 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.41 – 7.19 (m, 9H), 4.21 (s, 1H), 3.72 – 3.54 (m, 4H), 2.37 (s, 4H), 1.88 (s, 6H), 0.83 (s, 9H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 168.9, 141.8, 141.0, 132.9, 129.2, 128.9, 128.9, 127.9, 127.5, 75.5, 52.2, 51.7, 49.4, 45.7, 42.2, 37.5, 29.5, 25.9 ppm. LCMS ($\text{M} + \text{H}$)⁺: 437. HRMS (ESI-TOF) m/z : [$\text{M} + \text{H}$]⁺ calcd for $\text{C}_{27}\text{H}_{34}\text{ClN}_2\text{O}$, 437.2360; found 437.2355.



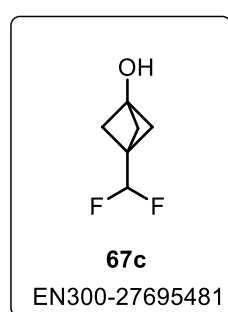
(±)-1-((3-(*Tert*-butyl)bicyclo[1.1.1]pentan-1-yl)methyl)-4-((4-chlorophenyl)(phenyl)methyl)piperazine dihydrochloride (94)

To a solution of (±)-(3-(*tert*-butyl)bicyclo[1.1.1]pentan-1-yl)(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)methanone (2.00 g, 0.00458 mol, 1.00 equiv) in THF (100 mL) was added LiAlH₄ (0.52 g, 0.0137 mol, 3.00 equiv) at 0 °C. The reaction mixture was heated under reflux (in an oil bath) for 3 h. The mixture was cooled to room temperature, and then carefully at 0 °C quenched with THF: H₂O 9:1 (50 mL), then an aqueous sat. solution of NaOH (1.83 g, 0.0458 mol, 10.00 equiv). The solution was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, CHCl₃/EtOAc, 95:5, R_f = 0.6). The final amine was dissolved in 5M HCl in dioxane (50 mL) and stirred at room temperature for 1 h. The mixture was diluted with 20 mL of distilled water and concentrated under reduced pressure. The residue was dissolved again in 20 mL of distilled water and concentrated under reduced pressure. The final product was dried at 50 °C over P₂O₅ for 24 h. Yield: 0.91 g, 0.00215 mol, 47%, white solid, m.p. = 229-230 °C. ¹H NMR (400 MHz, CD₃OD): δ 7.87 (t, *J* = 7.0 Hz, 4H), 7.62 – 7.36 (m, 5H), 5.67 (s, 1H), 3.84 (br s, 4H), 3.58 (br s, 4H), 3.44 (br s, 2H), 1.79 (s, 6H), 0.85 (s, 9H) ppm. ¹³C{¹H} NMR (126 MHz, MeOD): δ 136.6, 135.7, 134.9, 131.4, 130.8, 130.8, 129.6, 76.2, 58.5, 50.7, 50.1, 33.0, 30.4, 26.1 ppm. LCMS (M + H)⁺: 423. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₂₇H₃₆ClN₂, 423.2567; found 423.2560

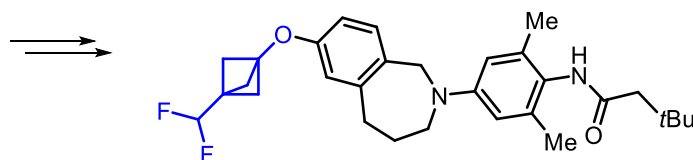
Application of bicyclo[1.1.1]pentanes from this work in medicinal chemistry by other academic and industrial groups

The project described herein started more than 5 years ago. The first compounds from this work have been synthesized and commercialized via Enamine (www.enamine.net) already several years ago. Many of these compounds have been subsequently purchased by various pharmaceutical companies, and used in medicinal chemistry projects, and the corresponding derivatives have been patented.

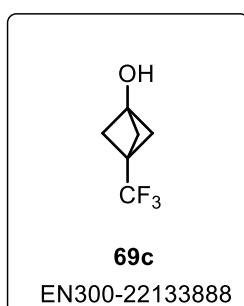
Below are shown some representative compounds from this work - **67c**, **69c**, **62j**, **55k**, **60k**, **69e**, **60i**, **60j**, **2k**, **21l**, **67l**, - synthesis of which has been still not reported anywhere. The application of these compounds in medicinal chemistry by pharmaceutical companies is shown:



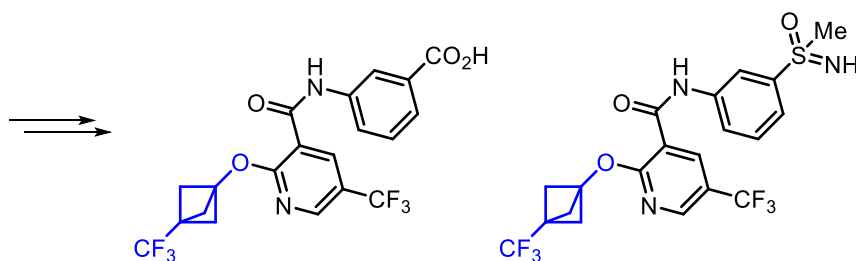
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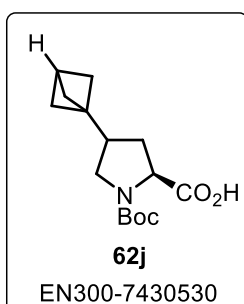
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Hangzhou Healzen Therapeutics



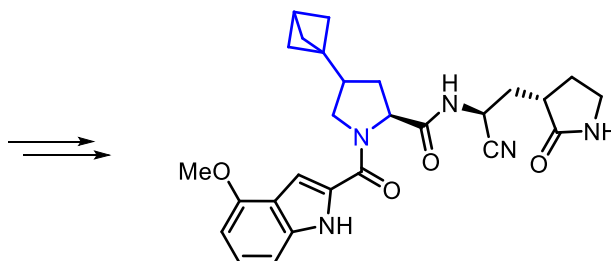
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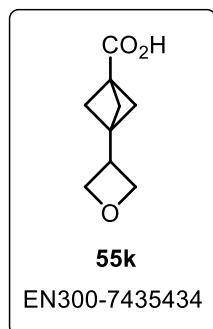
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Latigo Biotherapeutics



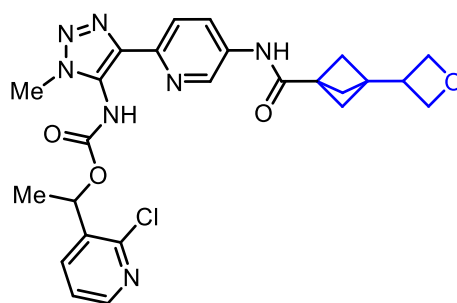
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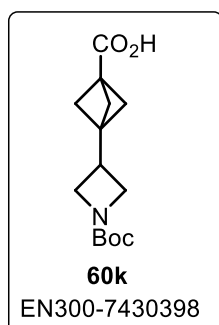


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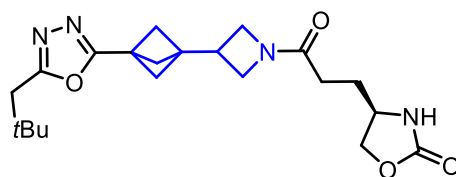
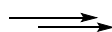


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Lysophosphatidic acid receptor 1 antagonist
WO2021247217
Gilead Sciences

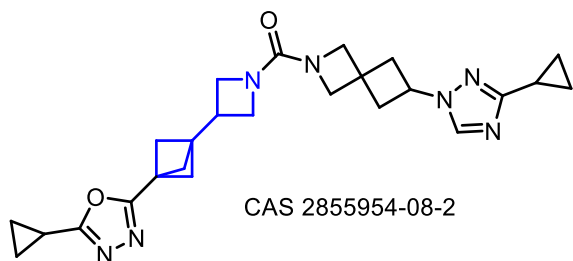


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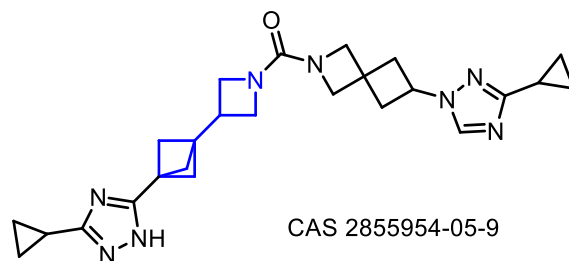


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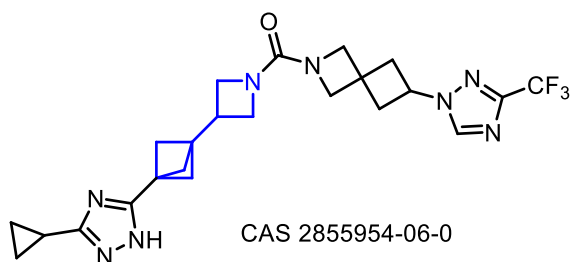
Monoacylglycerol lipase inhibitor
WO2022049134
Hoffmann-La Roche



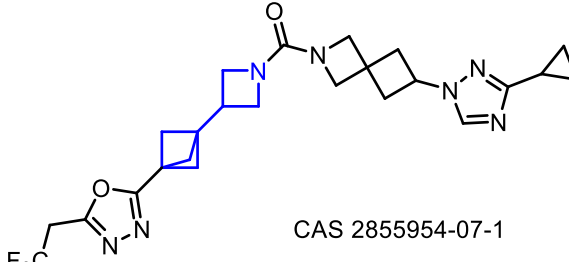
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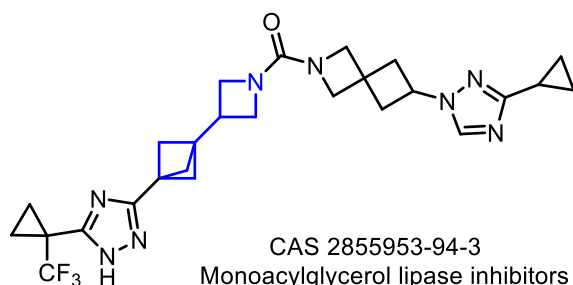
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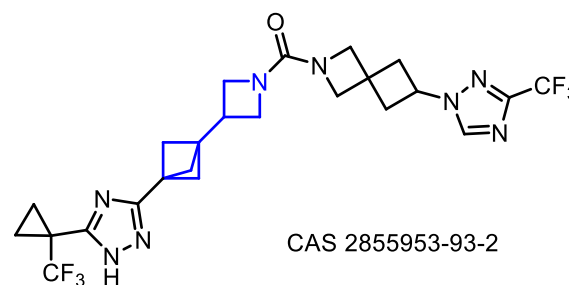
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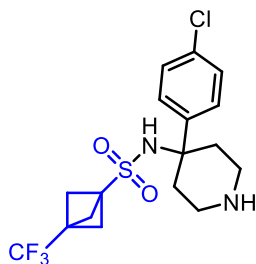
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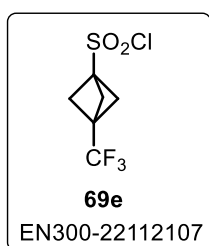
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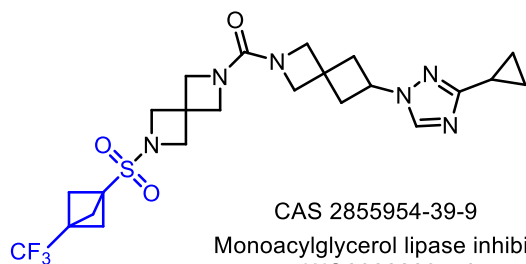
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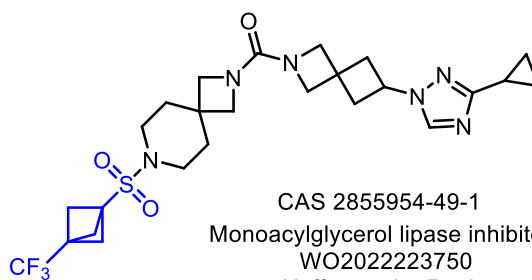
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Rappra Therapeutics



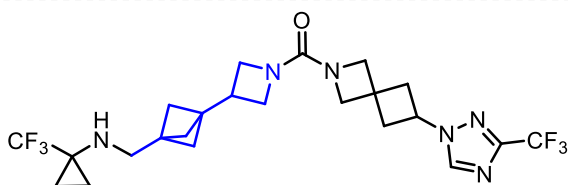
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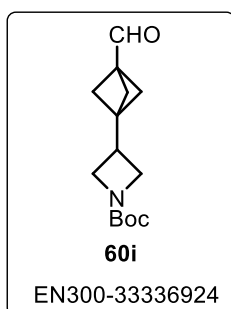
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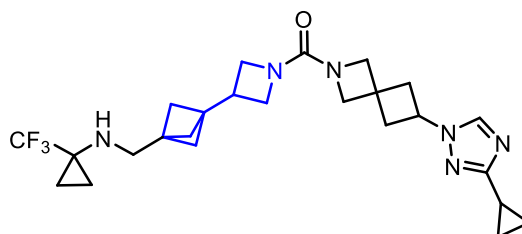
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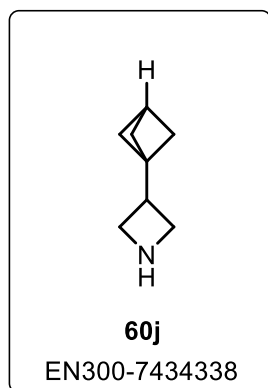
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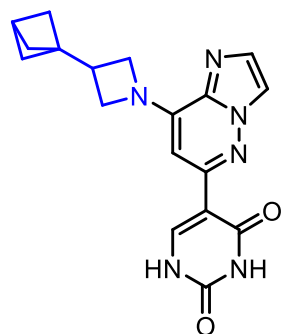
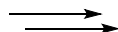
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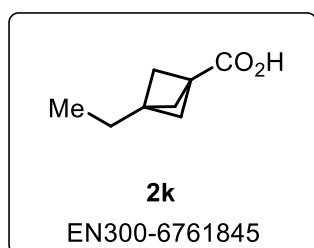
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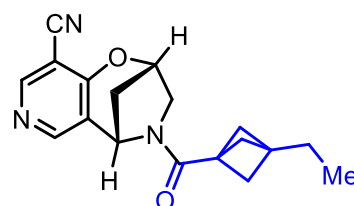
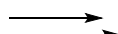
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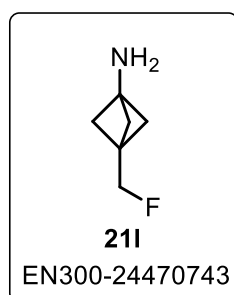
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WO 2021/222522
Gilead sciences



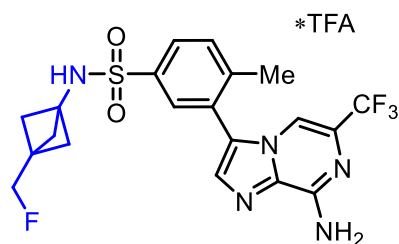
synthesis has not
been reported



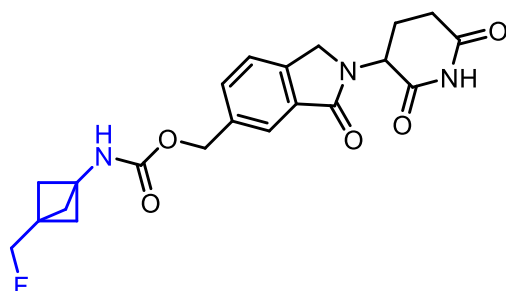
CAS 2857846-41-2
Receptor-interacting protein-1 kinase inhibitors
WO2022231928
Merck Sharp and Dohme



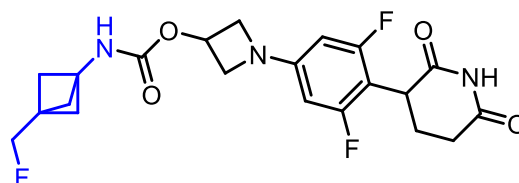
synthesis has not
been reported



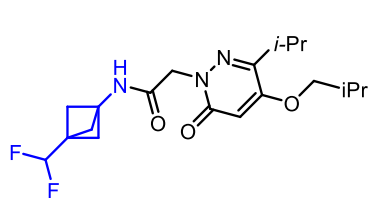
CAS 2170367-19-6
Phosphatidylinositol 3-kinase inhibitor
WO2017223414
Incyte Corporation



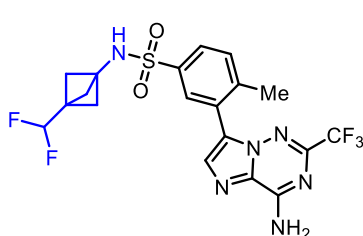
CAS 2803881-71-0
GSPT1 and cereblon modulator
WO2022152821 and WO2022152822
Monte Rosa



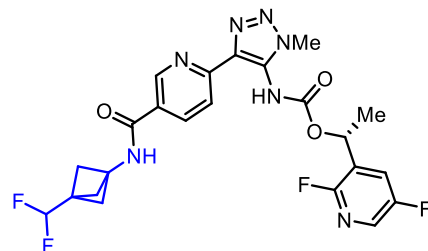
CAS 2924091-62-1
GSPT1 and cereblon modulators
WO 2023/069708
Monte Rosa



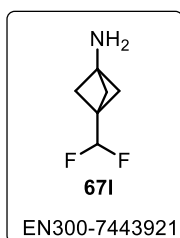
CAS 2830578-15-7
NLRP3 inflammasome production inhibitor
WO2022184842
Janssen Pharmaceutica



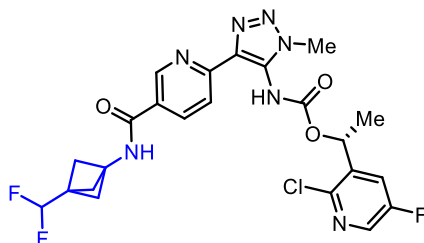
CAS 2170367-99-2
Phosphatidylinositol 3-kinase inhibitors
WO2017223414
Incyte Corporation



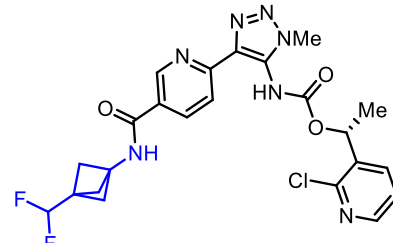
CAS 2866049-44-5



synthesis has not
been reported

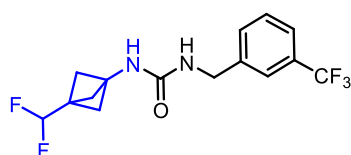


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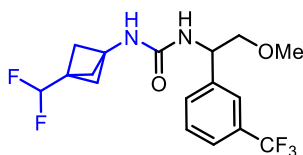


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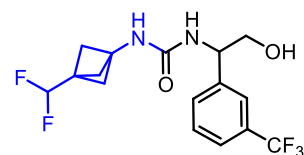
Lysophosphatidic acid receptor 1 inhibitors
WO2022241023
Gilead Sciences



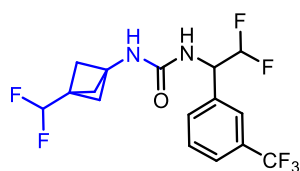
CAS 2756581-81-2
Kv7 potassium channel openers
WO2021260090
Idorsia



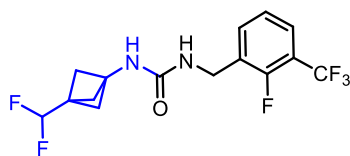
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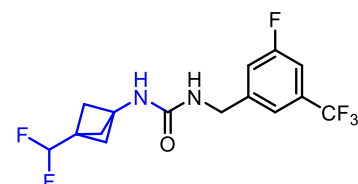
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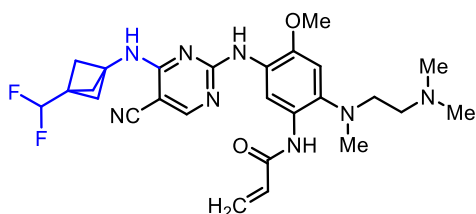
CAS 2756581-47-0



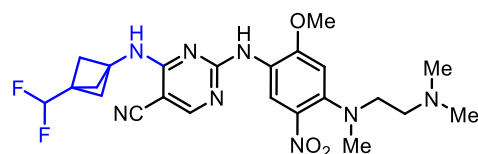
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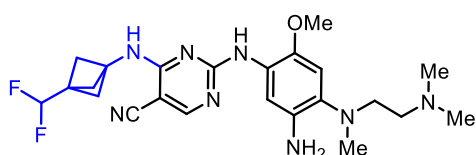
CAS 2756581-50-5



CAS 2663776-91-6



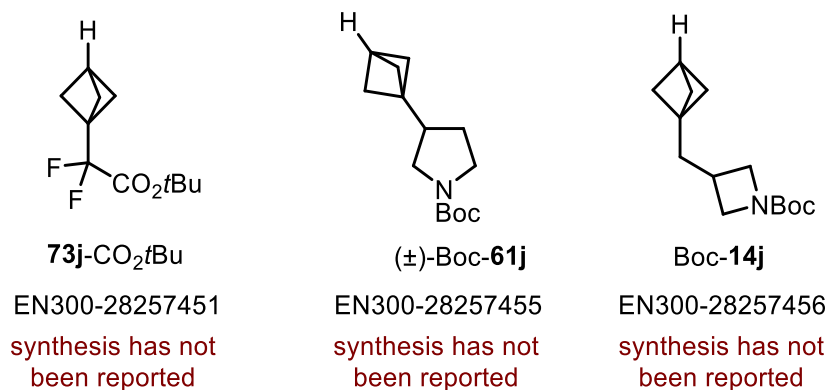
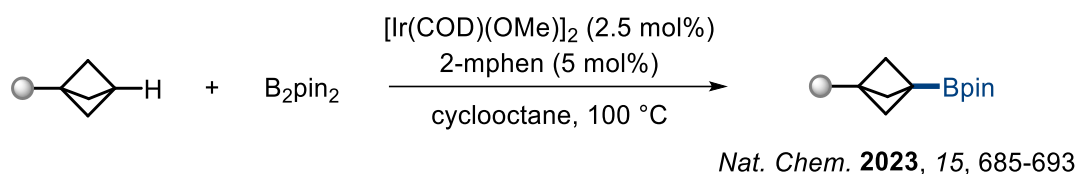
CAS 2663778-32-1
Epidermal growth factor-activated receptor inhibitor
WO2021141960
Dana-Farber cancer institute



CAS 2663778-34-3

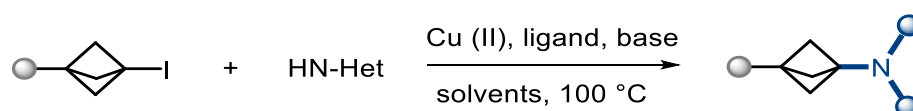
Compounds **73j**-CO₂tBu, Boc-**61j**, and Boc-**14j** (their synthesis has not been described before) from this study have been used by Prof. *J. Hartwig* and coworkers in the [Ir]-catalyzed borylation reaction:

<https://www.nature.com/articles/s41557-023-01159-4> (*Nat. Chem.* **2023**, *15*, 685–693)



Compounds **21**, **25**, **55**, **57**, **60**, **63**, **67**, and **69** from this work, have been already used by *Gomez* and coworkers in the [Cu]-catalyzed amination of BCP-iodides.

<https://pubs.acs.org/doi/10.1021/acs.orglett.2c04226> (*Org. Lett.* **2023**, *25*, 771–776)



Supporting Information, page 12:

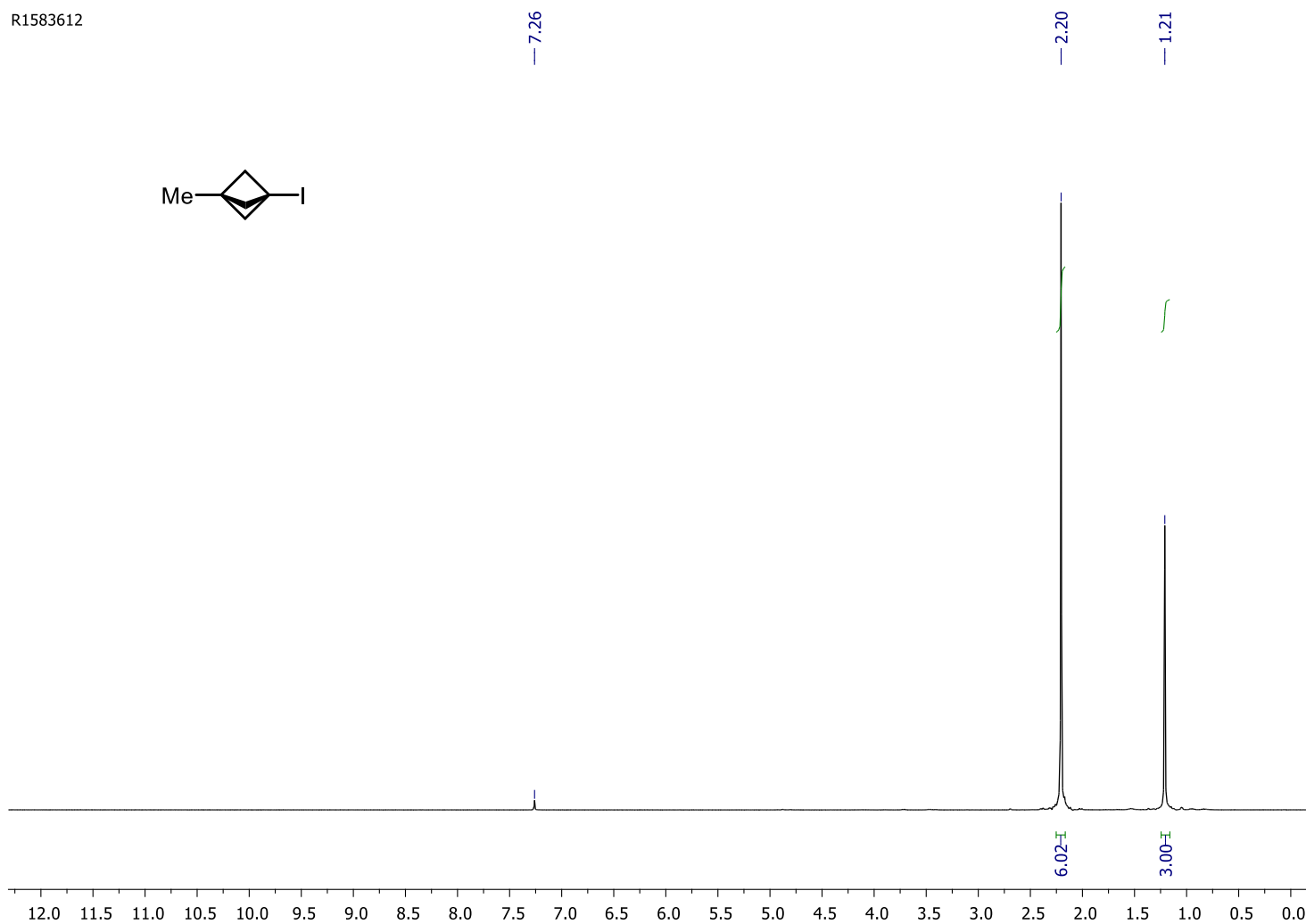
	Enamine	EN300-27028946; CAS: 2490375-54-5
	Enamine	EN300-27702136; CAS: 2580210-26-8
	Prepared according to a reported literature procedure	<i>ACS Catal.</i> 2019 , <i>9</i> , 9568-9574
	Enamine	EN300-27693959; CAS: 2363075-15-2
	Enamine	EN300-7443769; CAS: 2375271-09-1
	Enamine	EN300-28243632; CAS: 2680533-05-3
	Enamine	EN300-7443759; no CAS
	Enamine	EN300-27028946; CAS: 2375261-02-0
	Enamine	EN300-173147; CAS: 119934-12-2

Compound 1

Copies of ^1H , $^{13}\text{C}\{^1\text{H}\}$, $^{31}\text{P}\{^1\text{H}\}$ and $^{19}\text{F}\{^1\text{H}\}$ NMR spectra

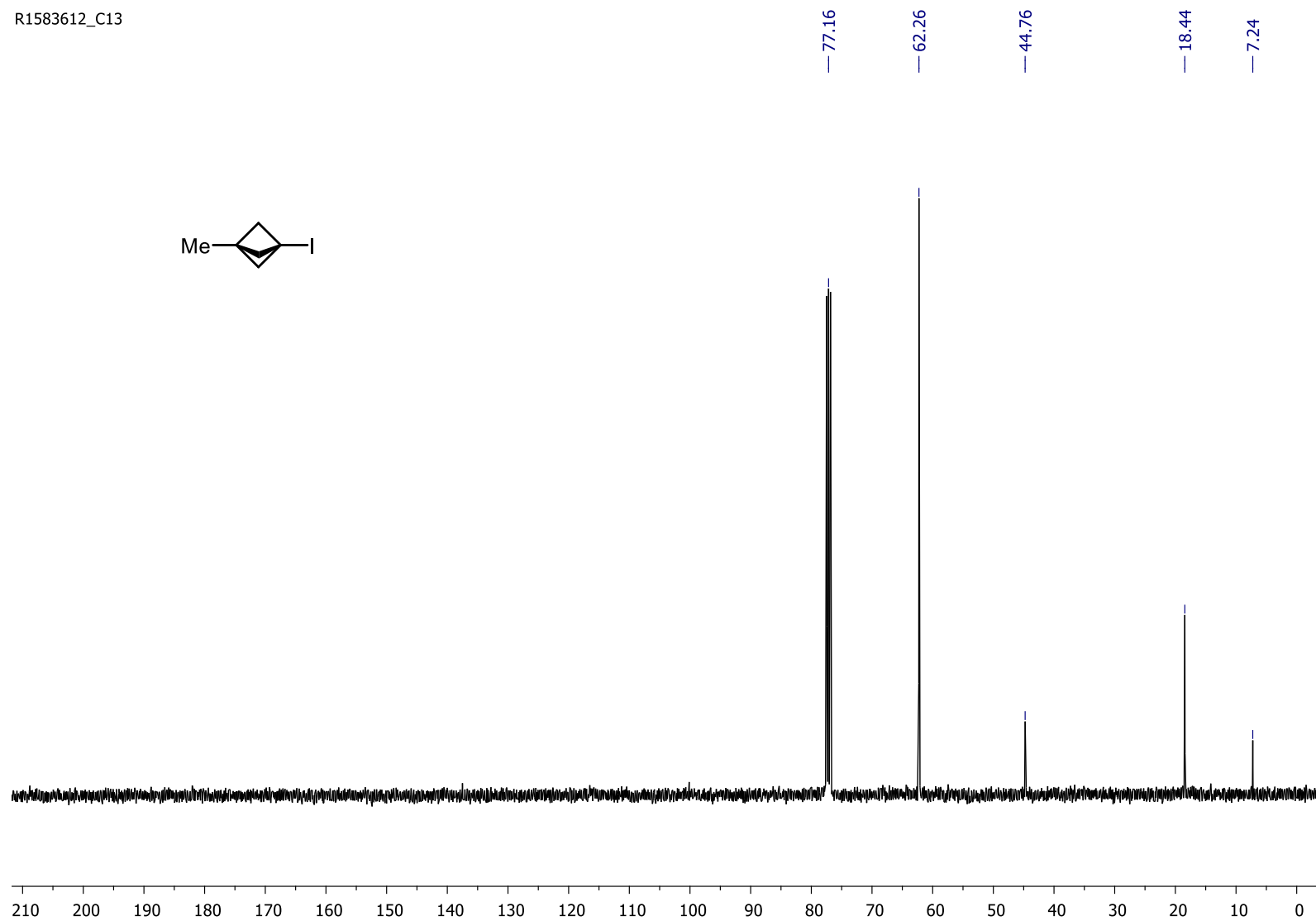
^1H NMR (400 MHz, CDCl_3)

R1583612



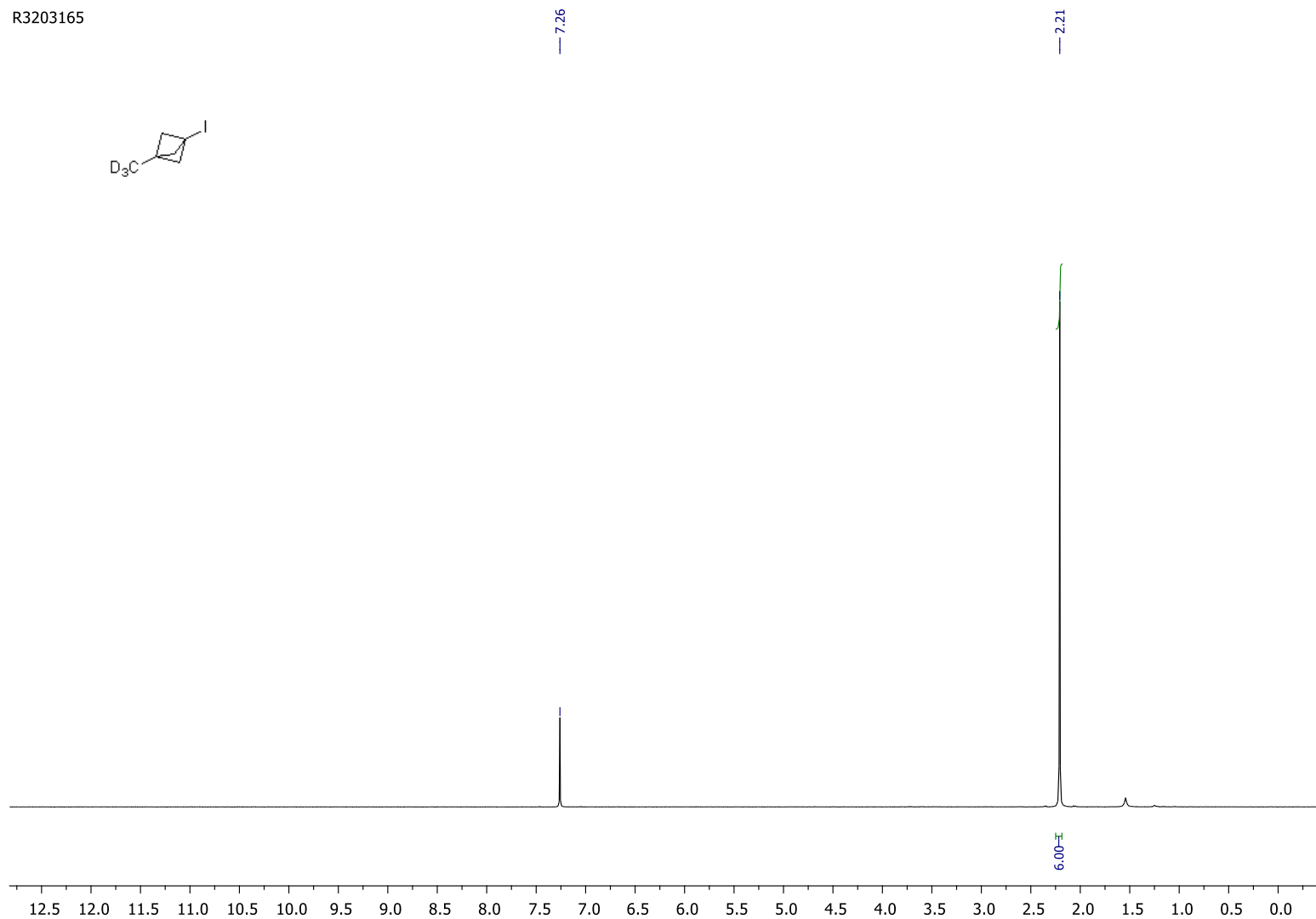
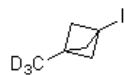
$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

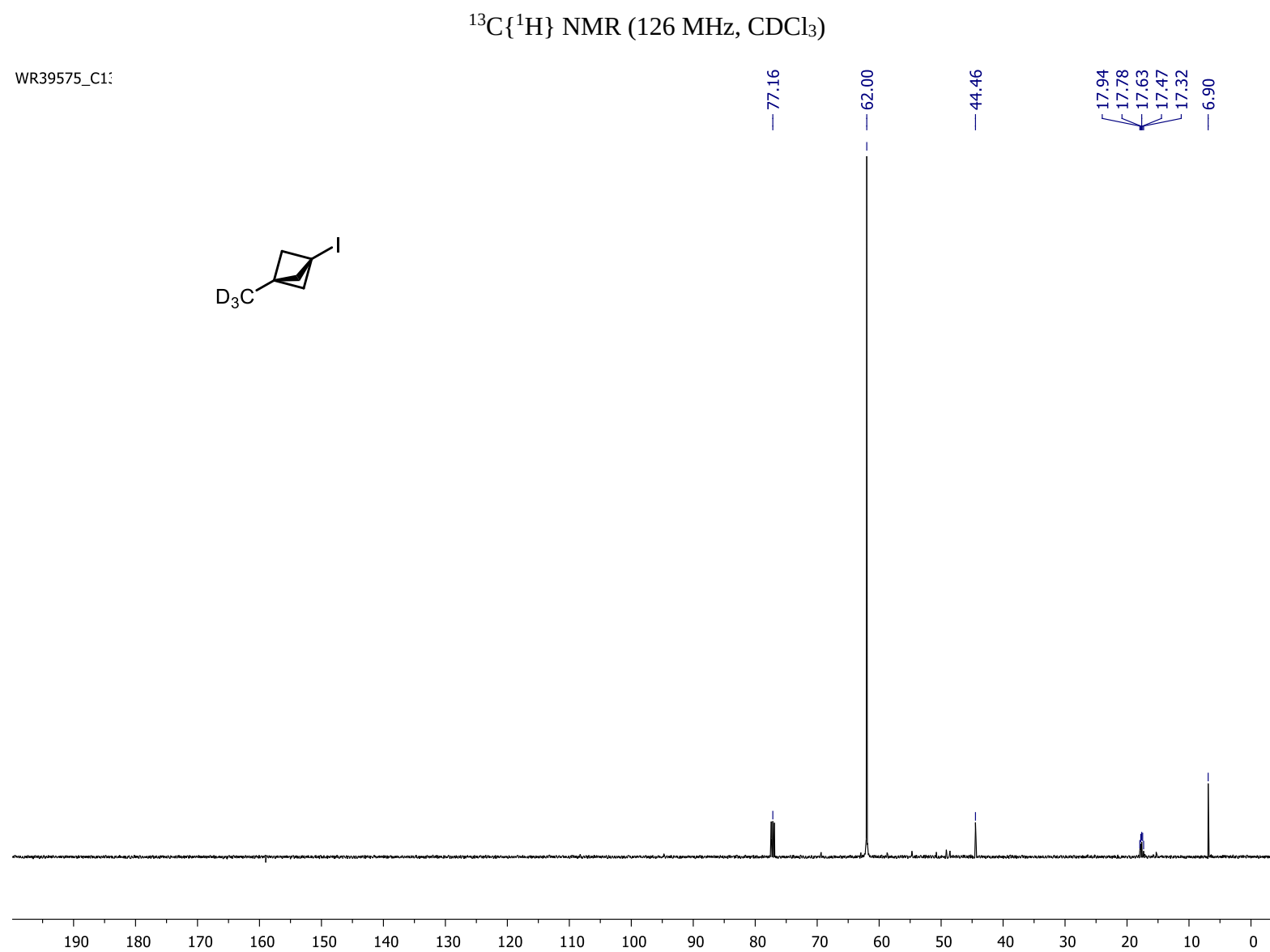
R1583612_C13



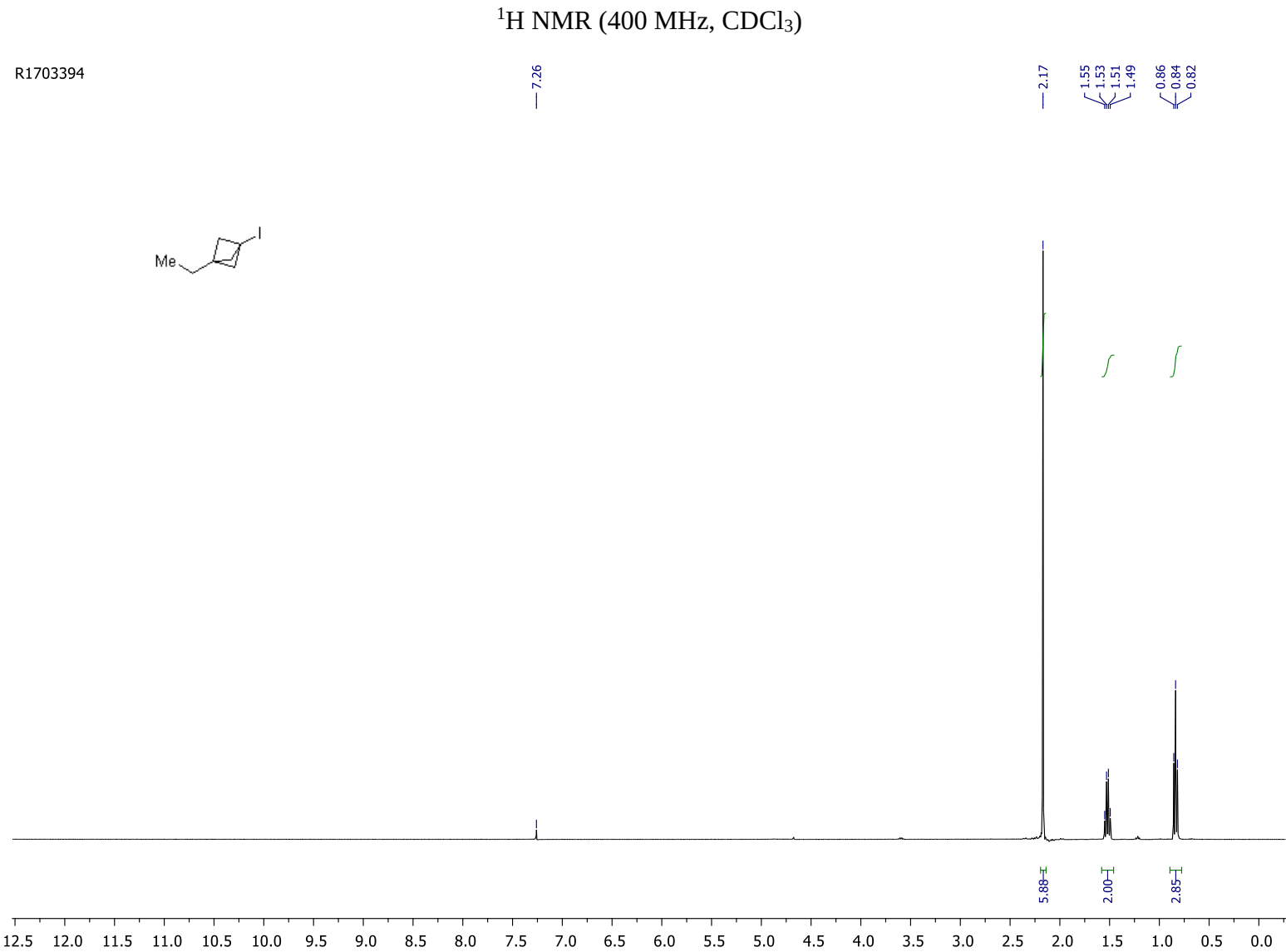
Compound D₃-1

R3203165

¹H NMR (500 MHz, CDCl₃)

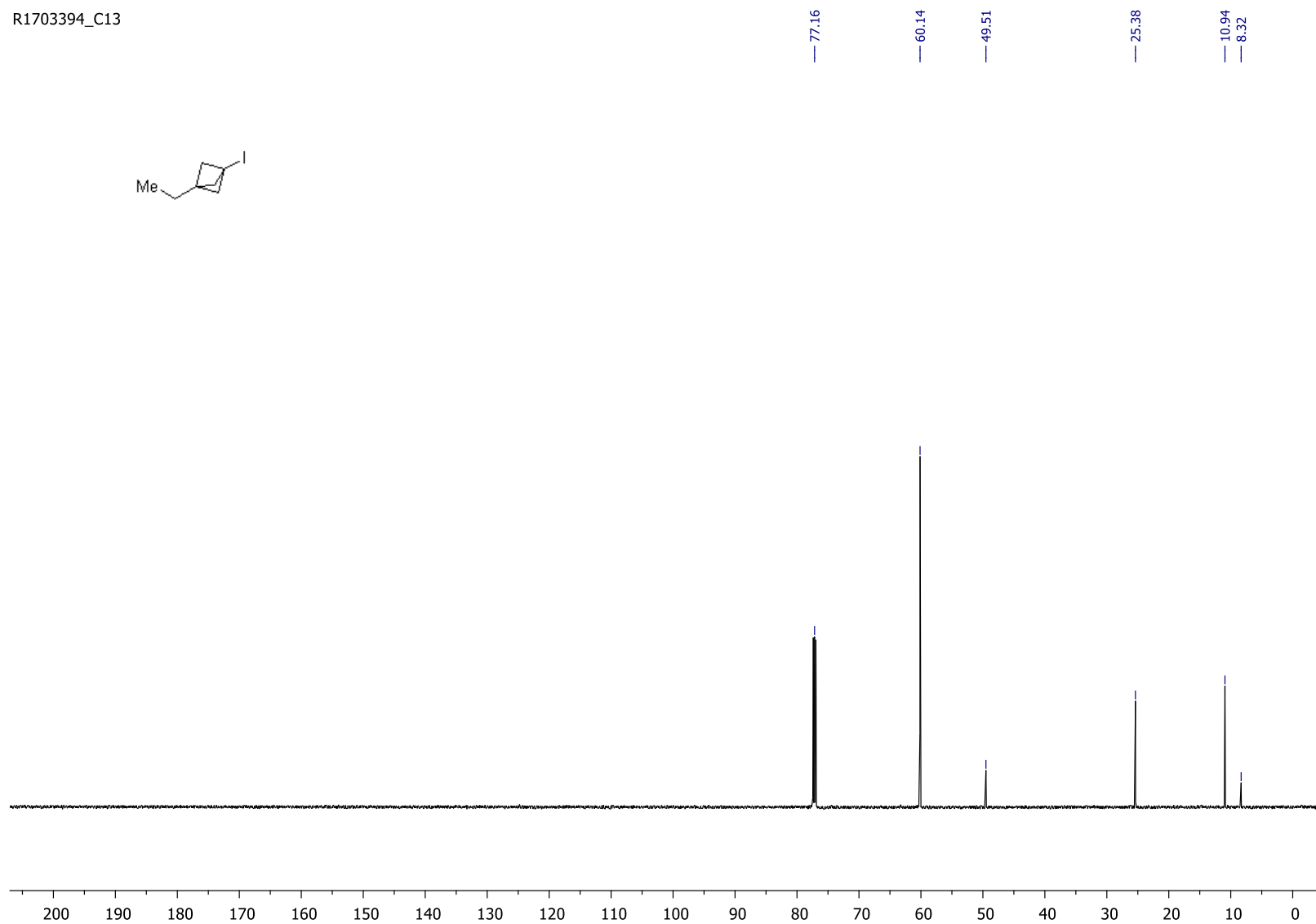


Compound 2



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

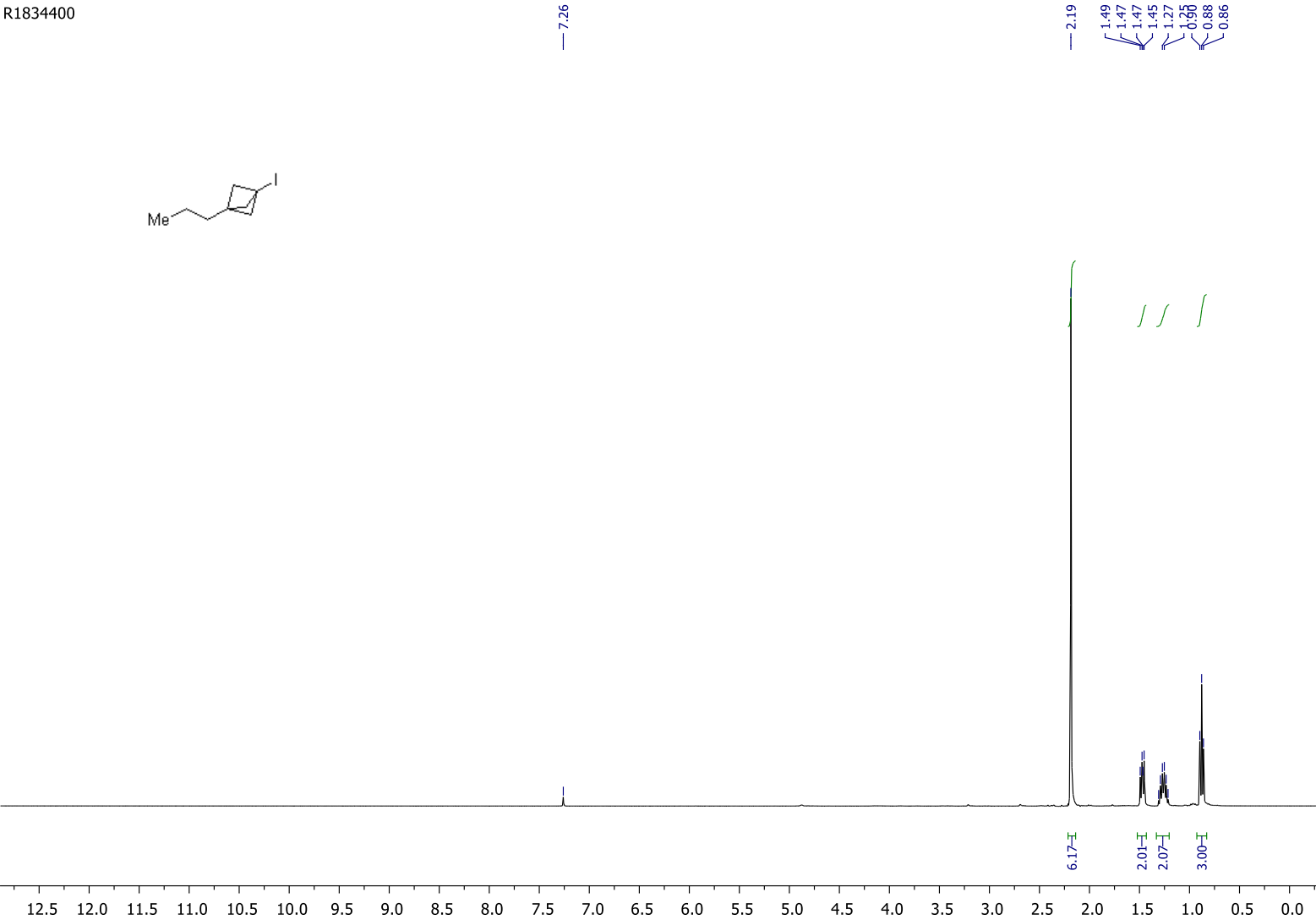
R1703394_C13

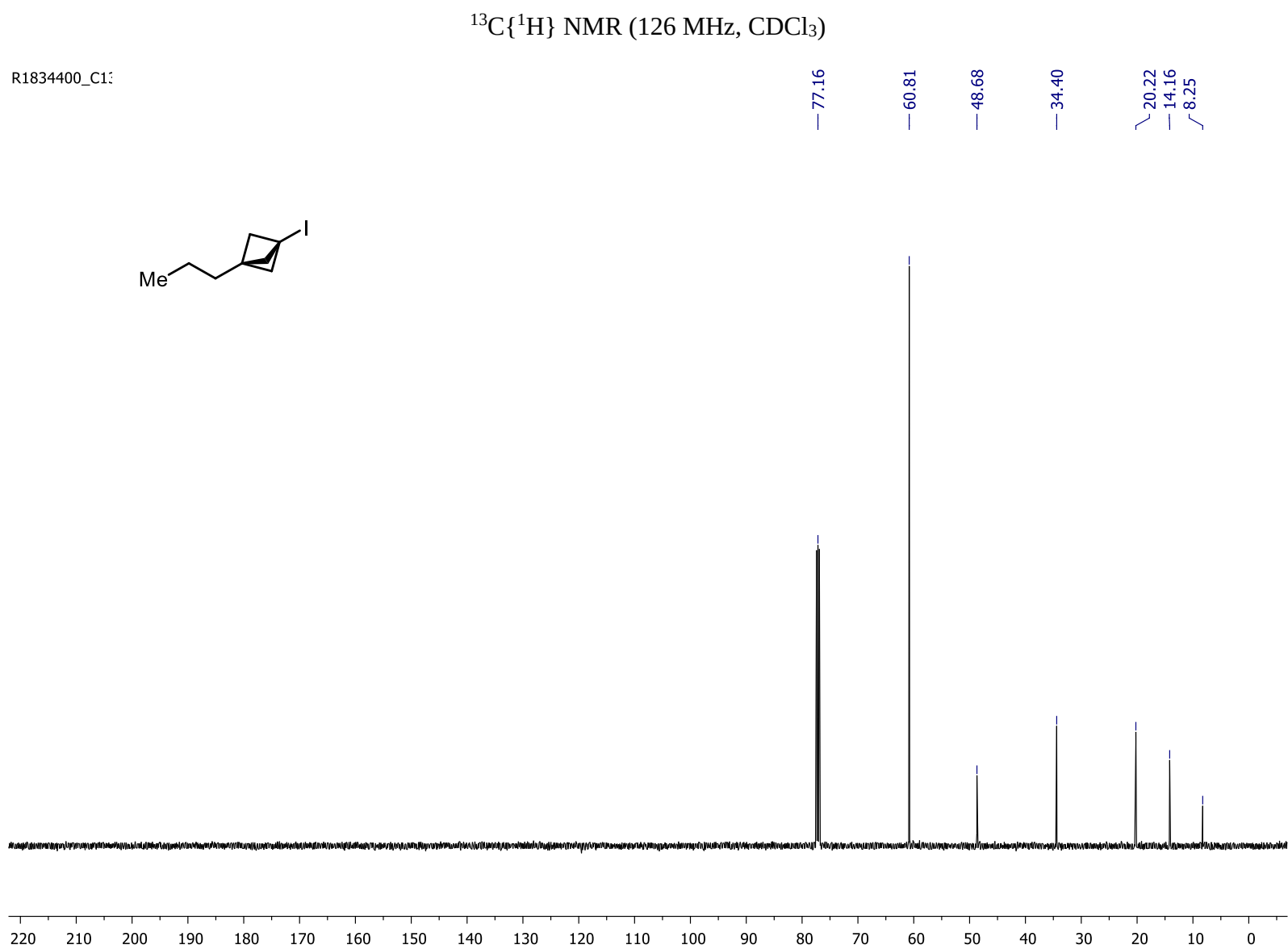


Compound 3

R1834400

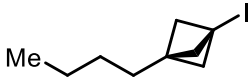
¹H NMR (400 MHz, CDCl₃)



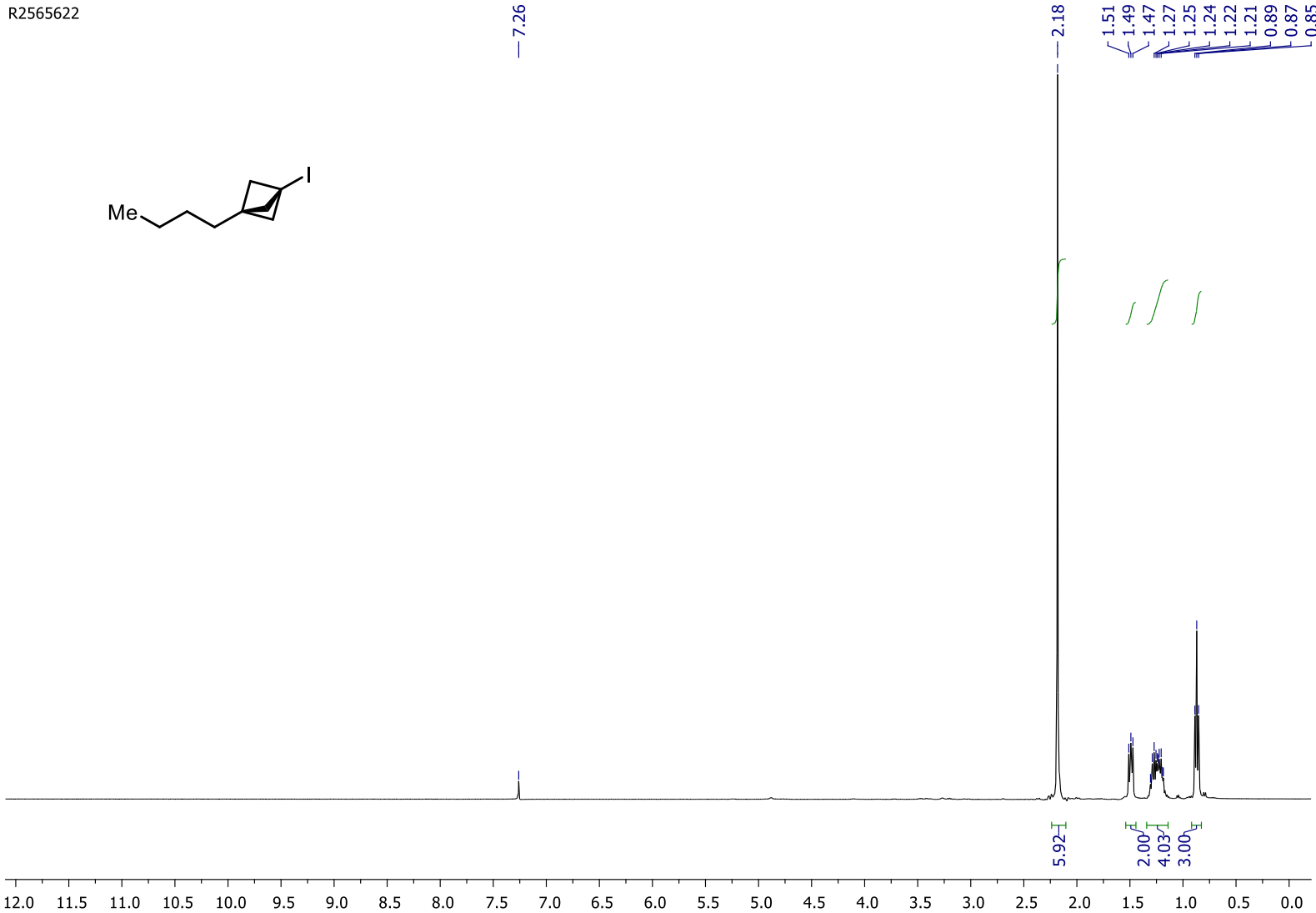


Compound 4

R2565622

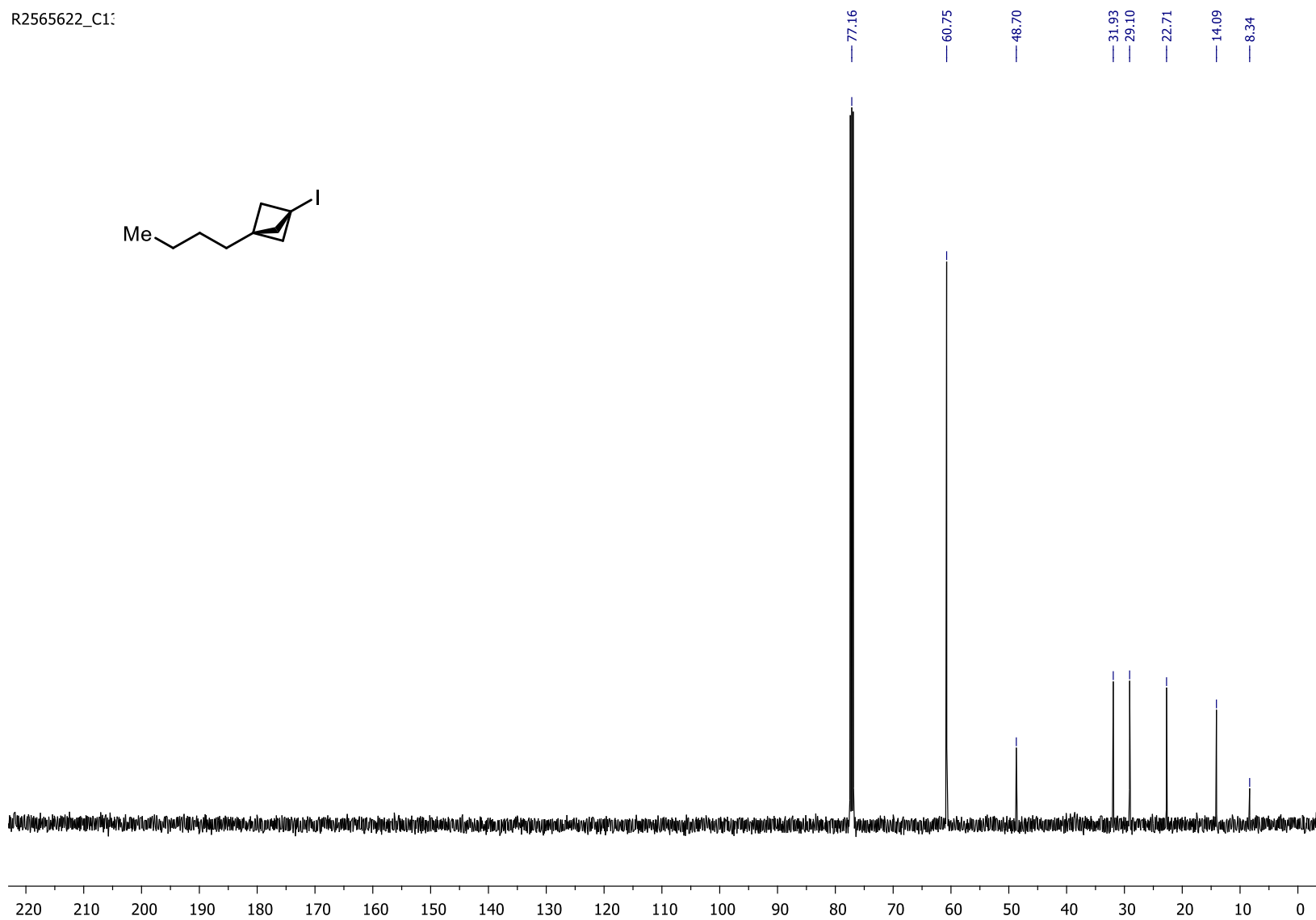


¹H NMR (400 MHz, CDCl₃)



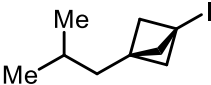
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2565622_C13

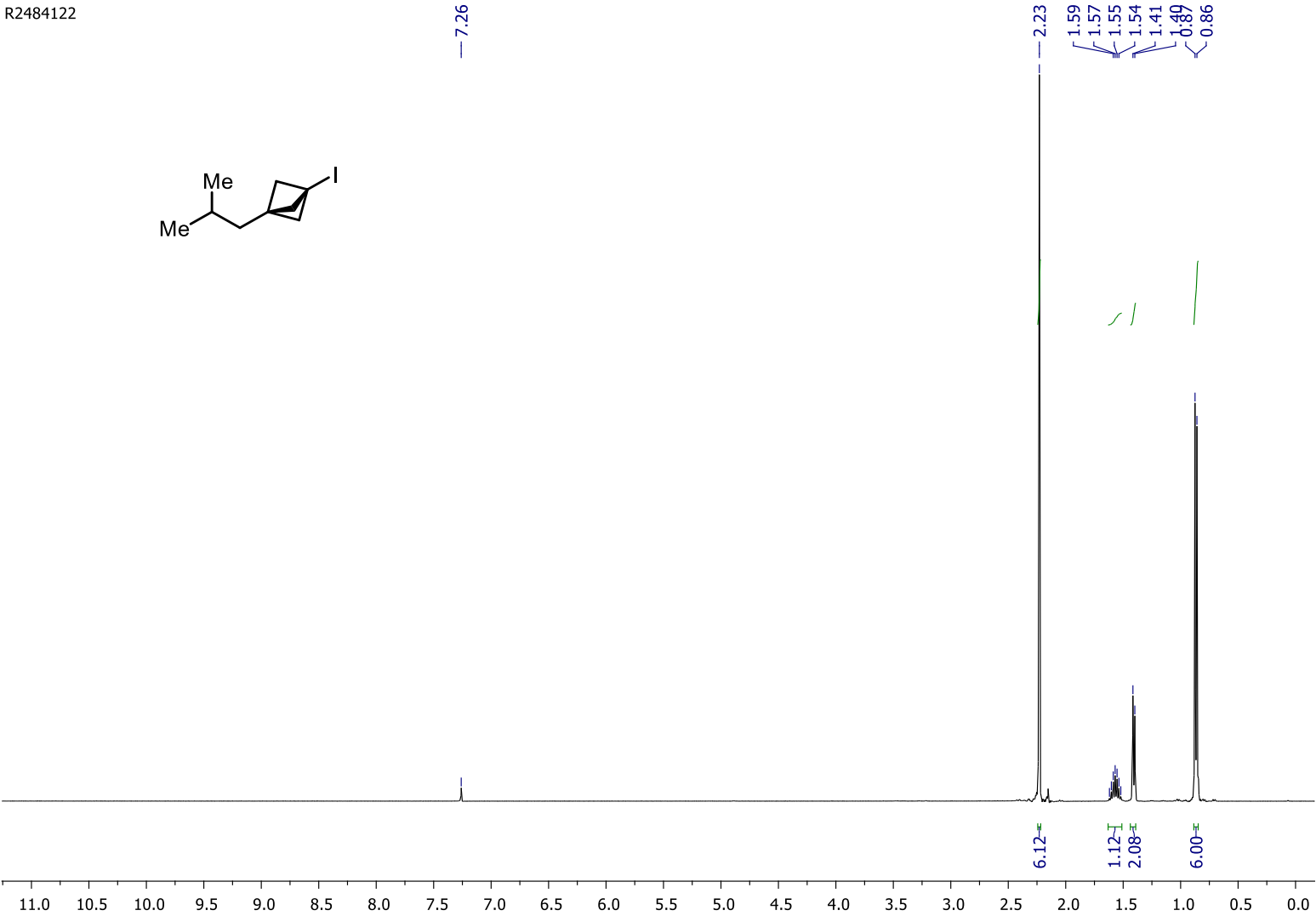


Compound 5

R2484122

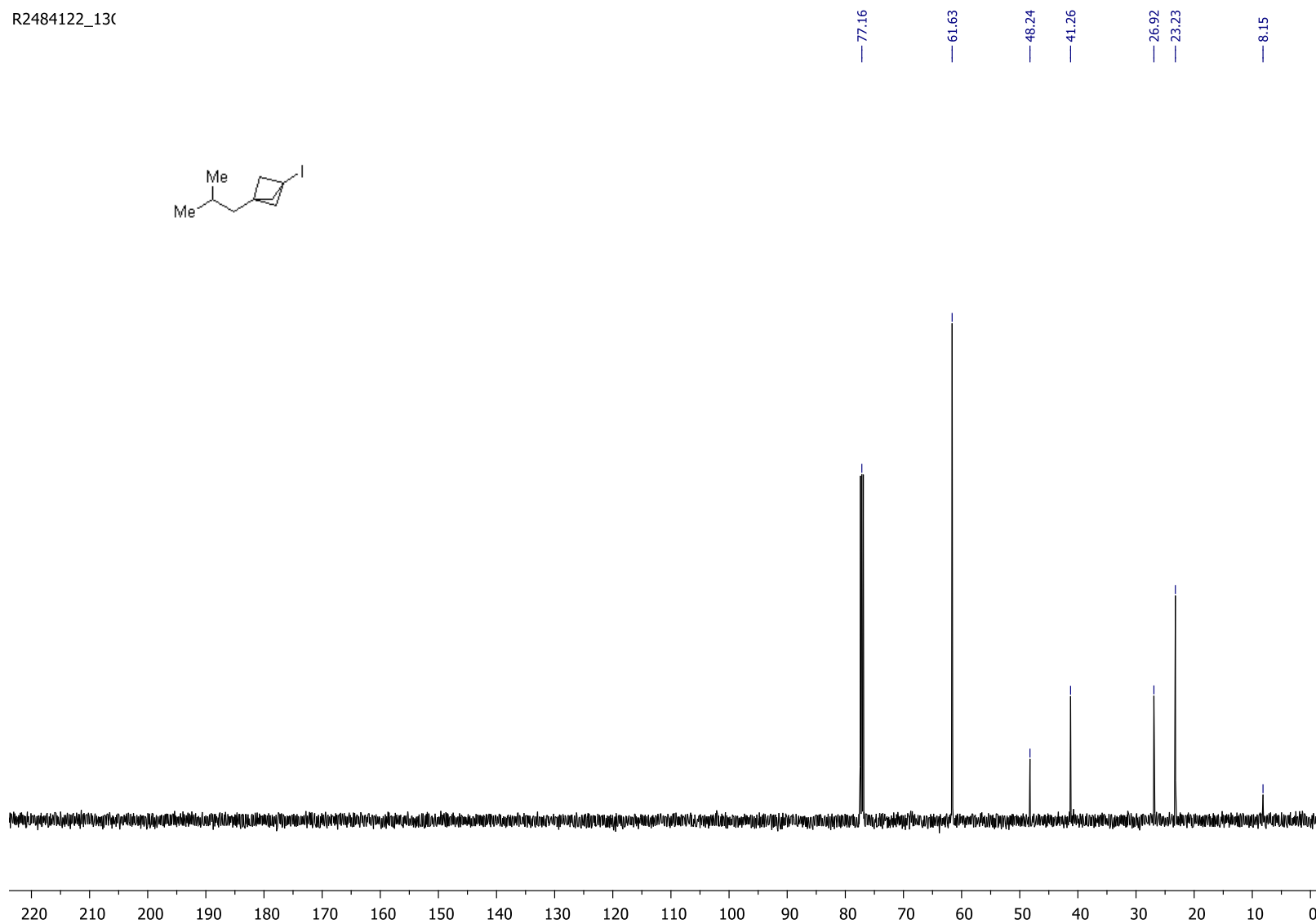
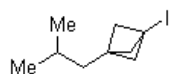


¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

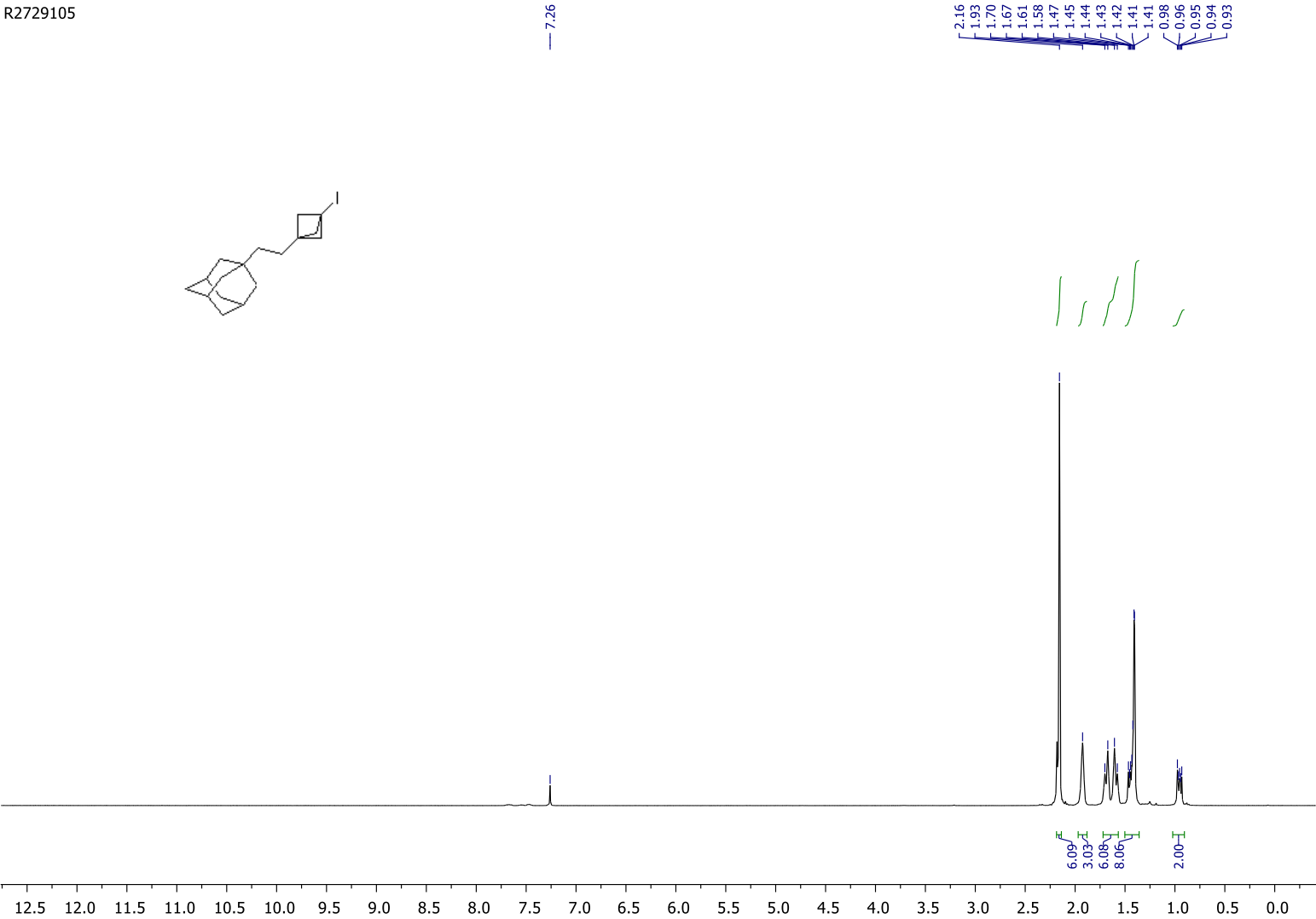
R2484122_13C



Compound 6

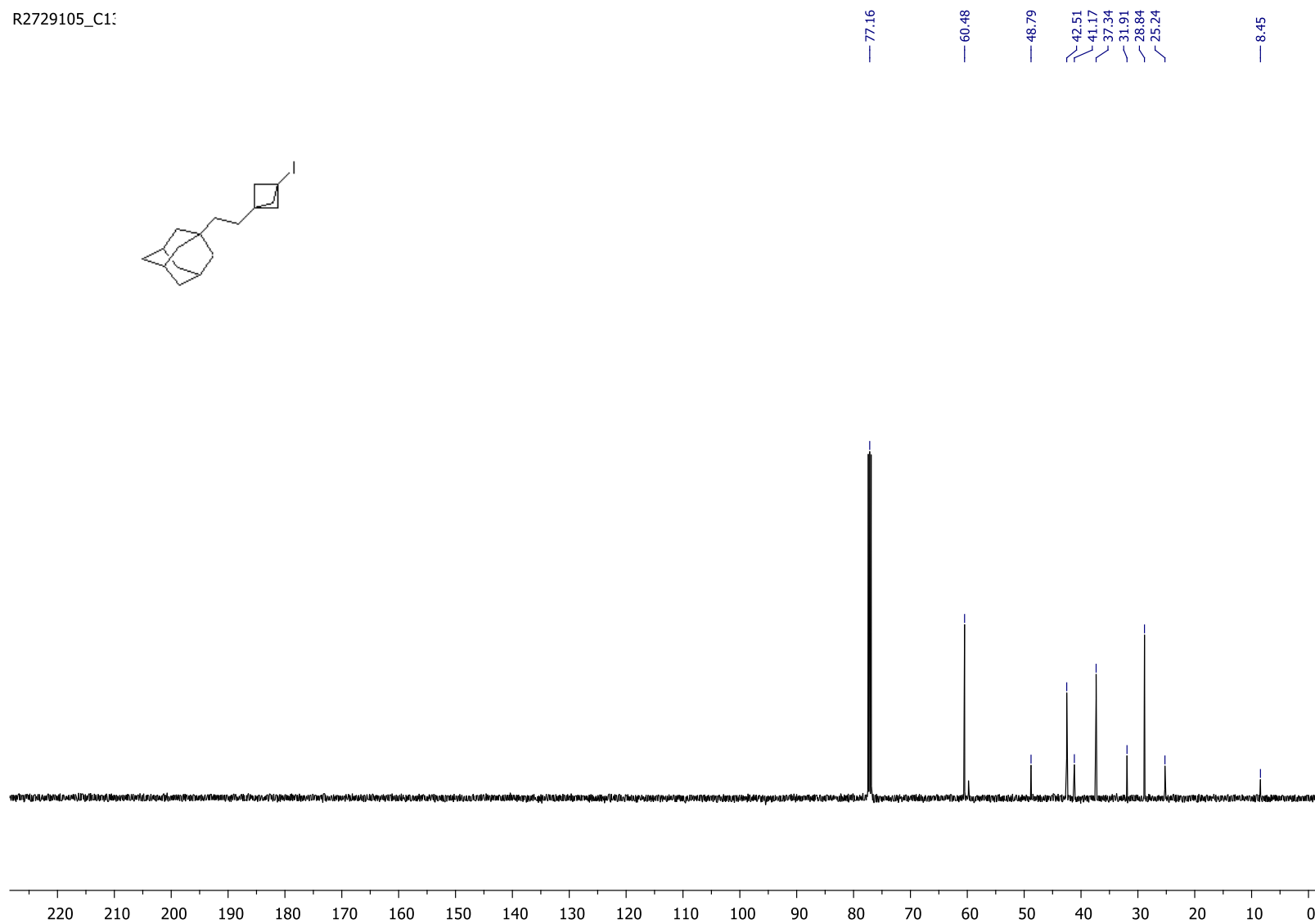
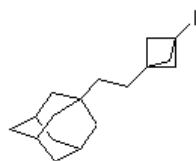
R2729105

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

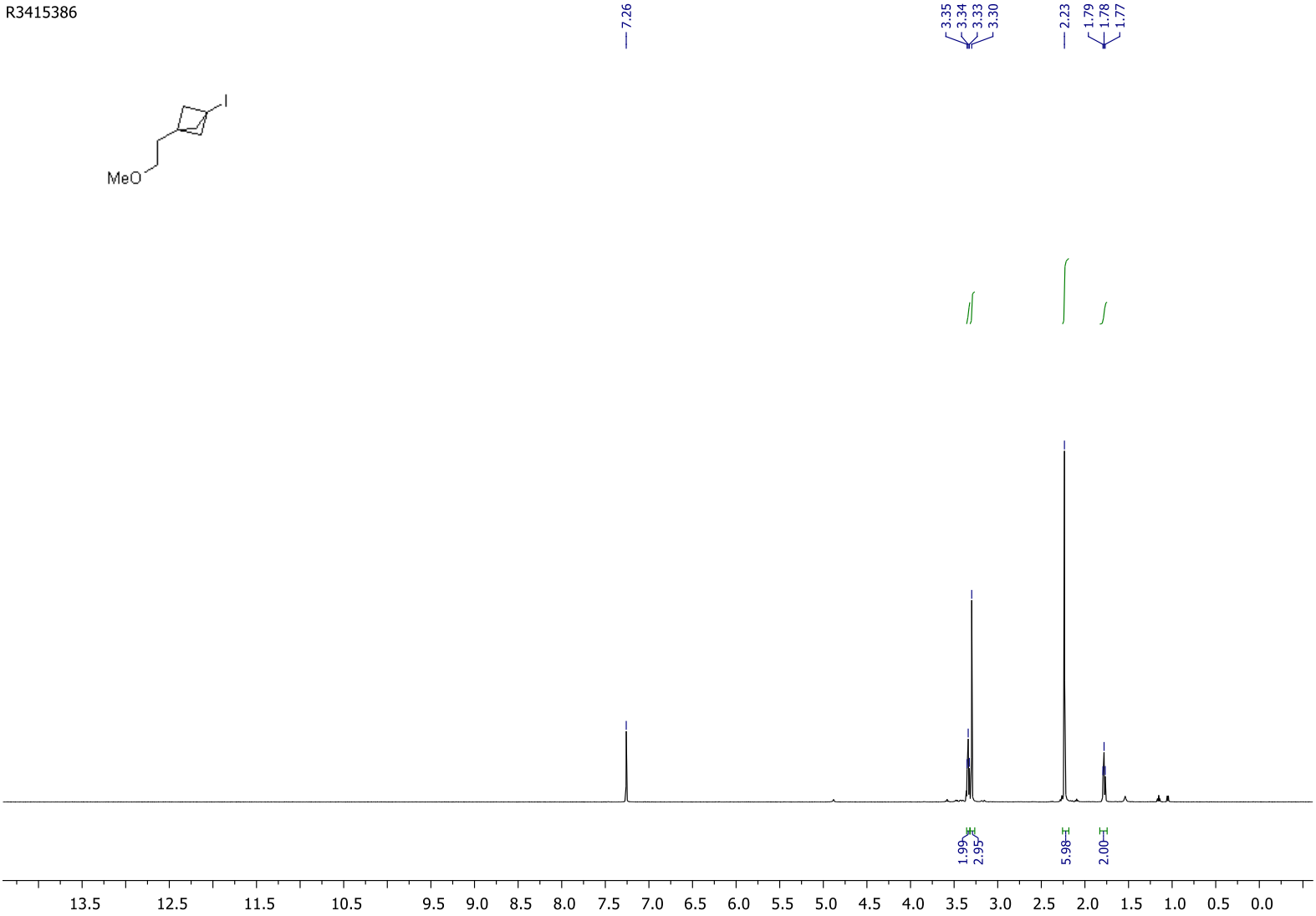
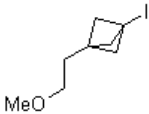
R2729105_C1:



Compound 7

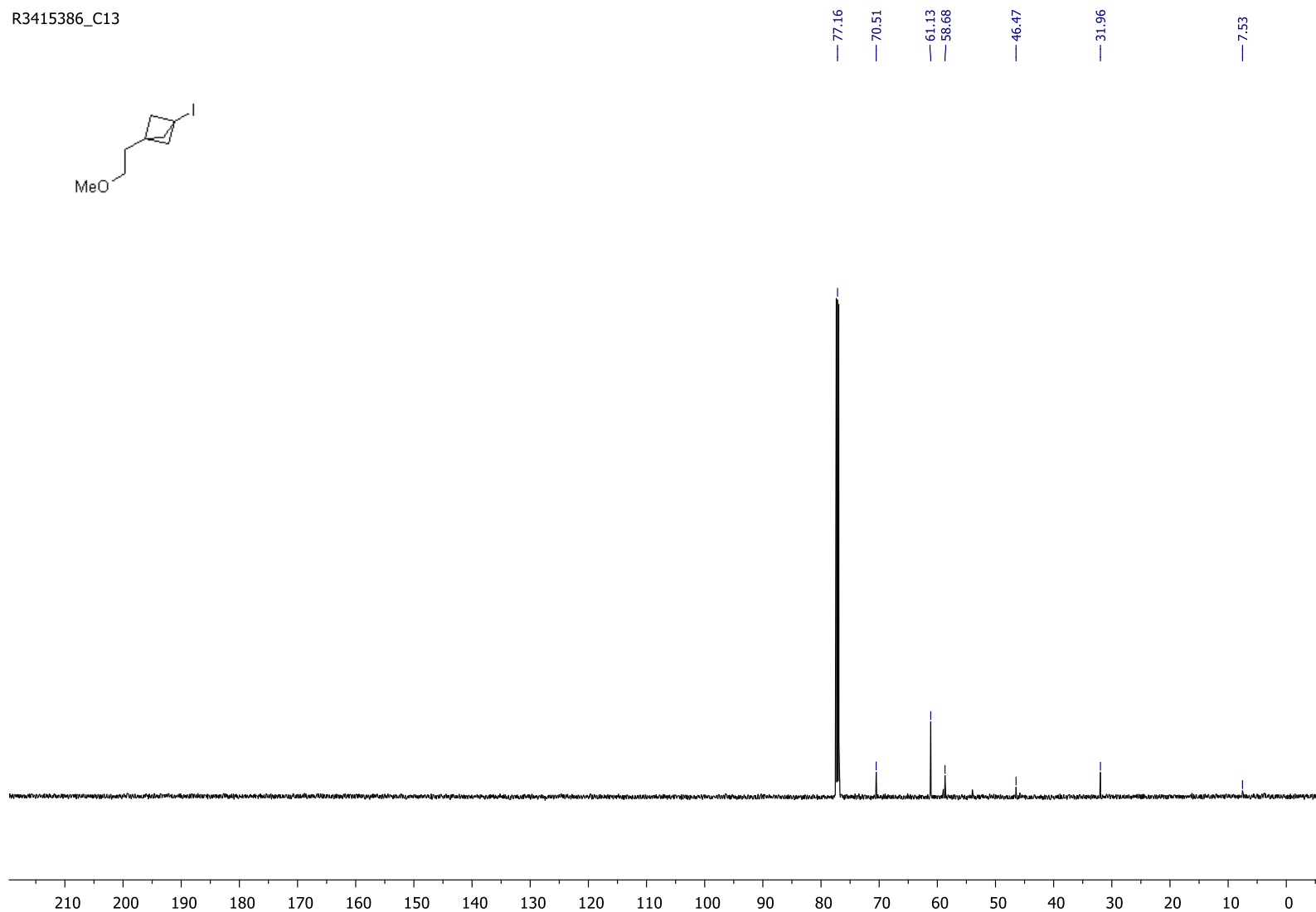
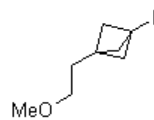
¹H NMR (500 MHz, CDCl₃)

R3415386



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

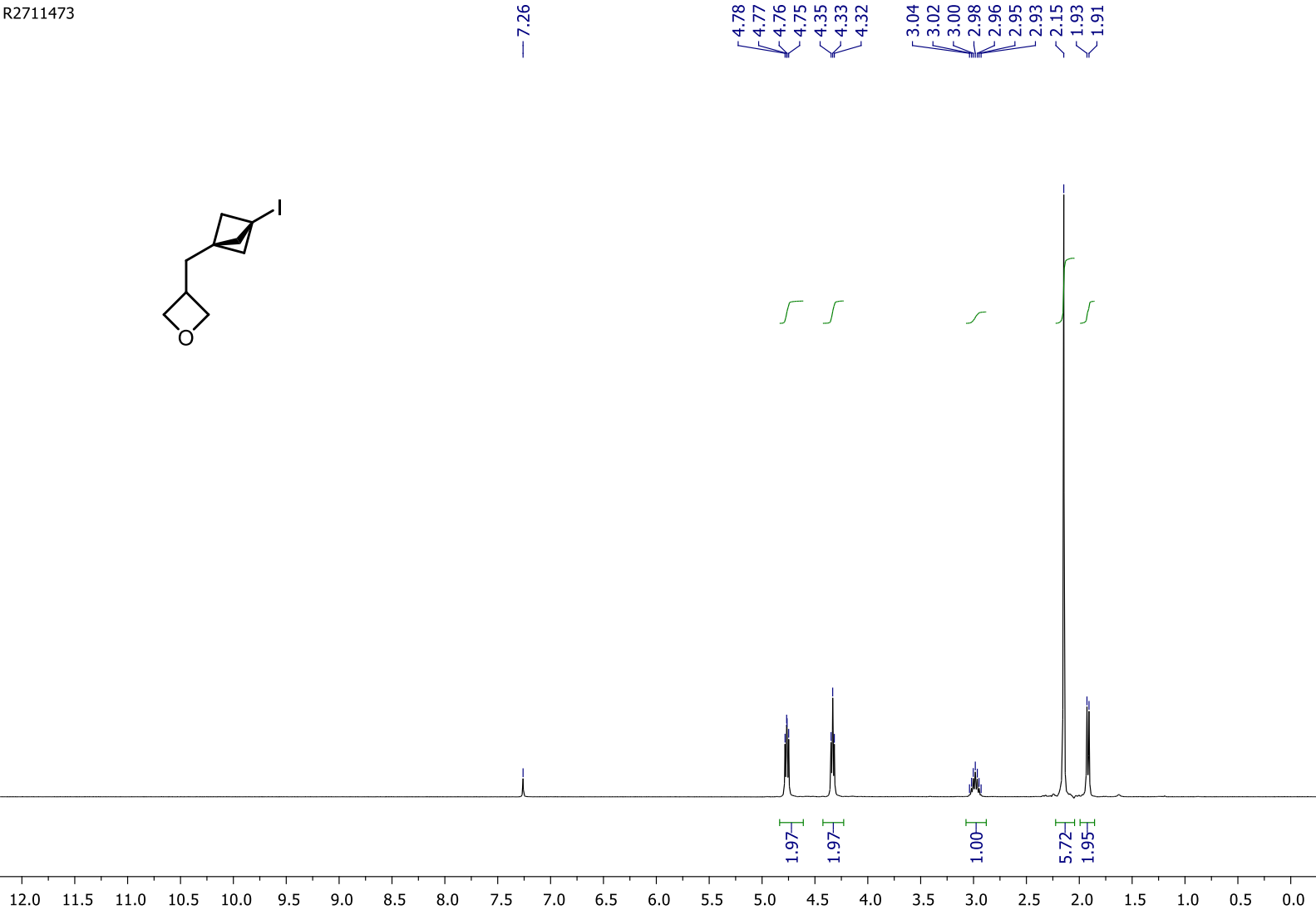
R3415386_C13



Compound 8

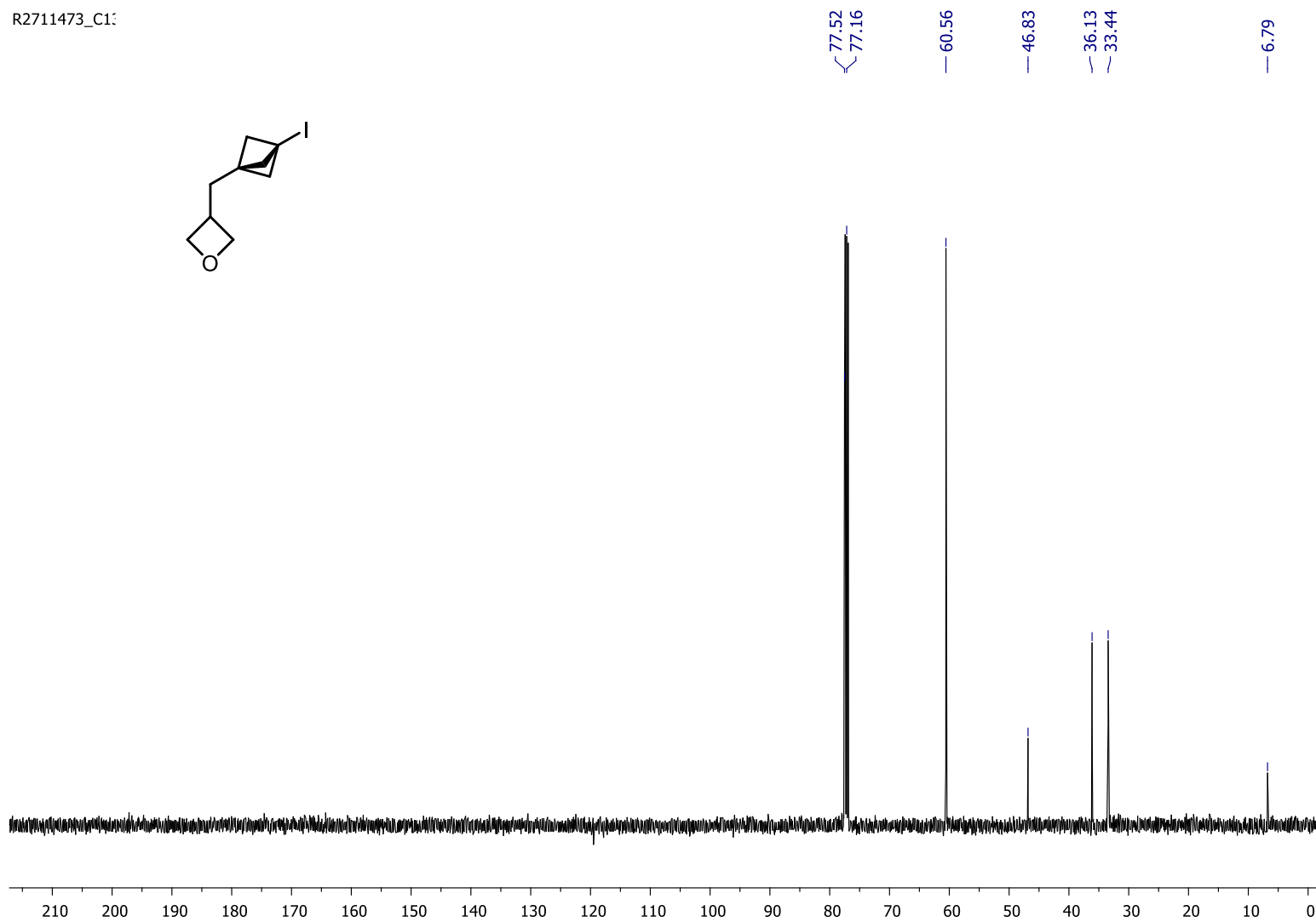
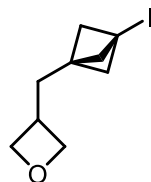
R2711473

¹H NMR (400 MHz, CDCl₃)

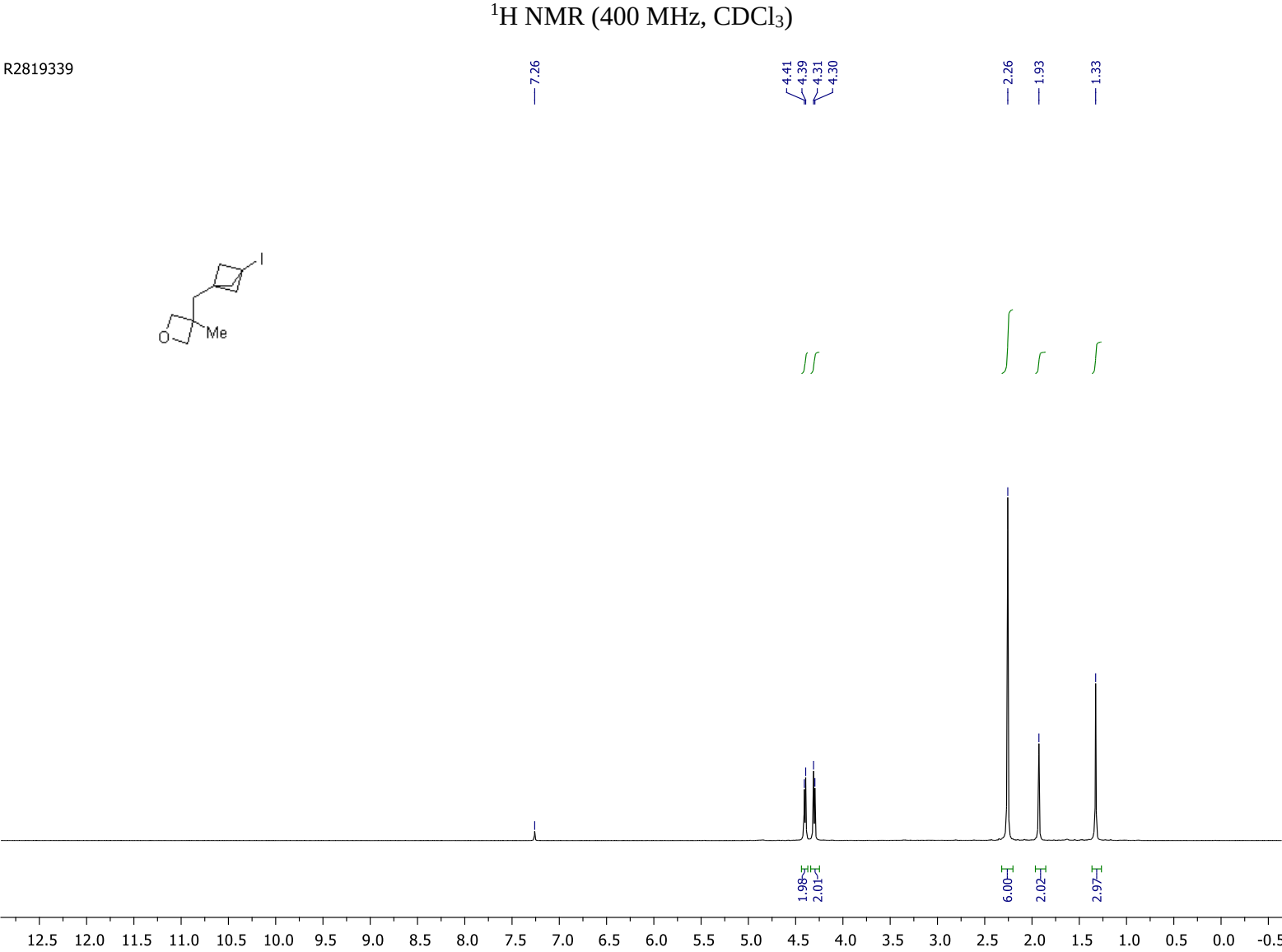


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2711473_C1:

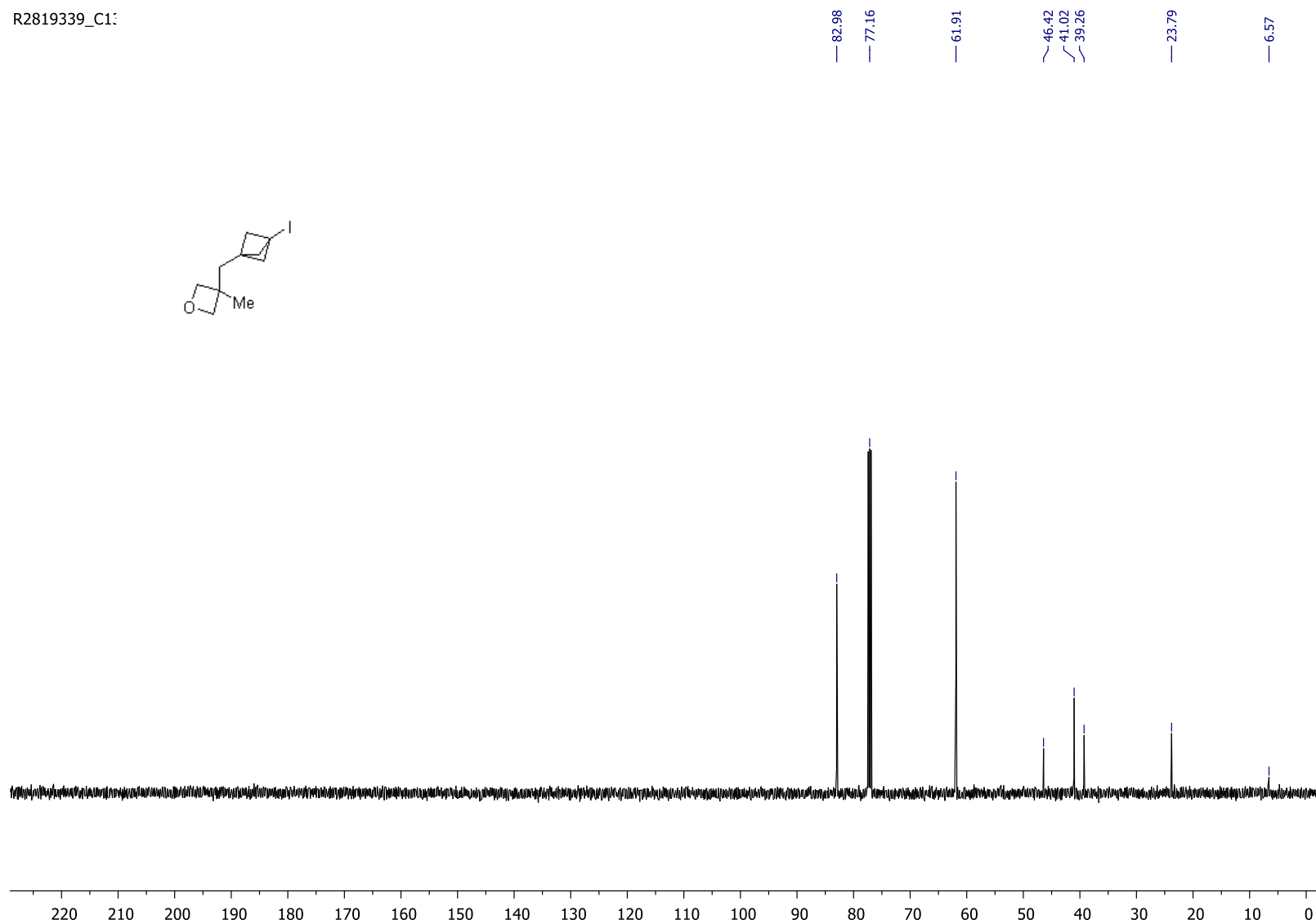
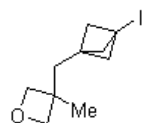


Compound 9



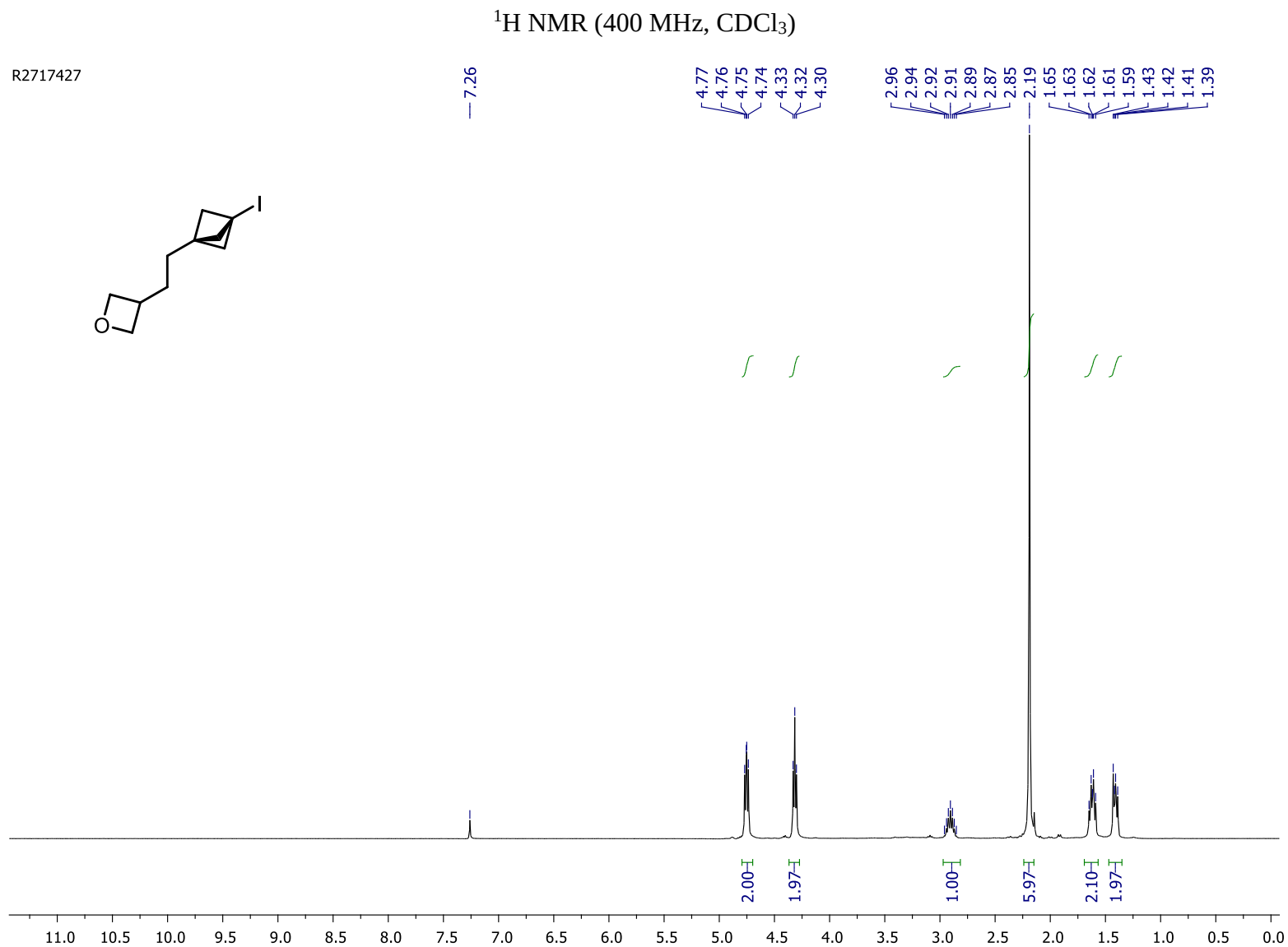
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2819339_C1:



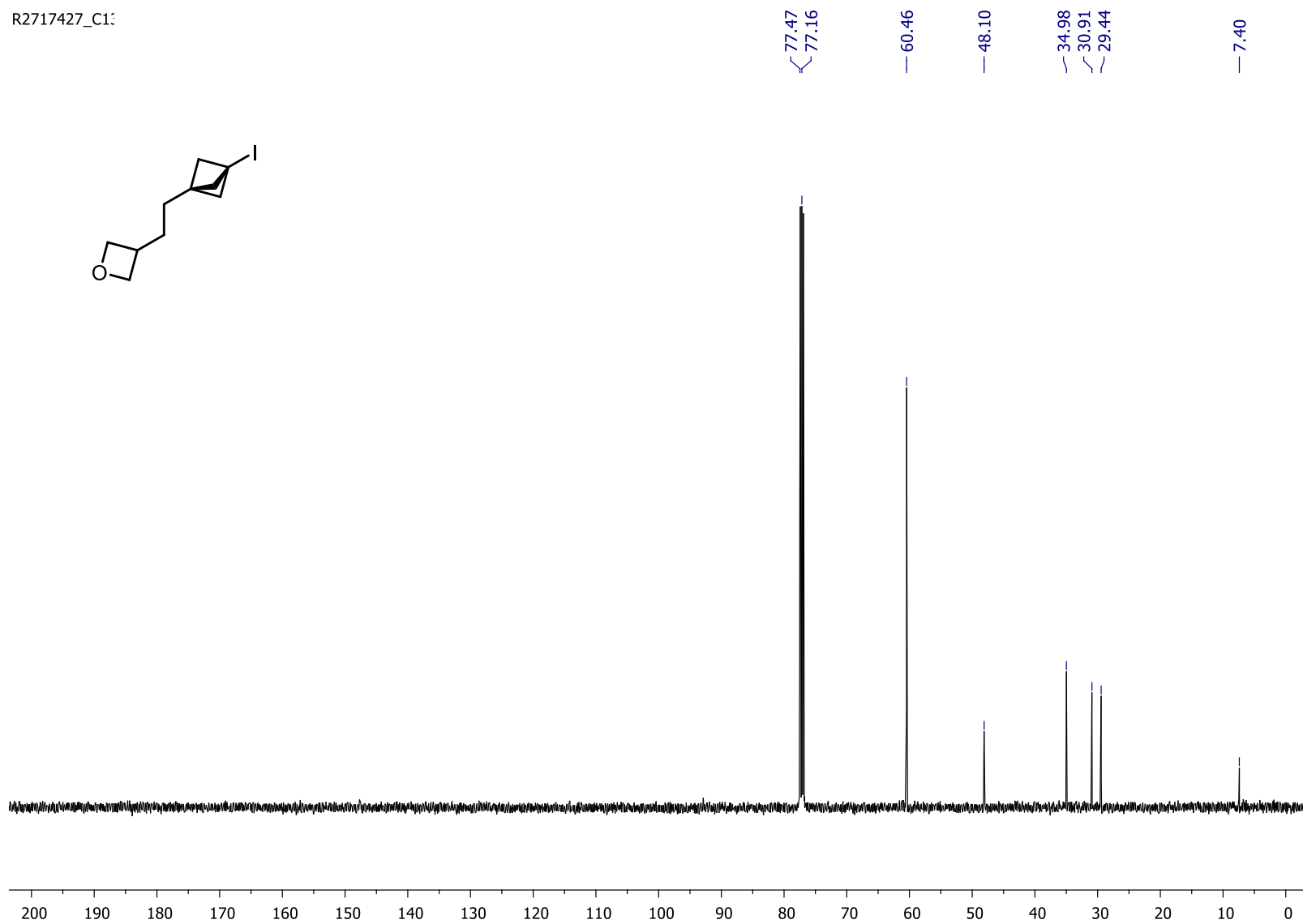
Compound 10

R2717427



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

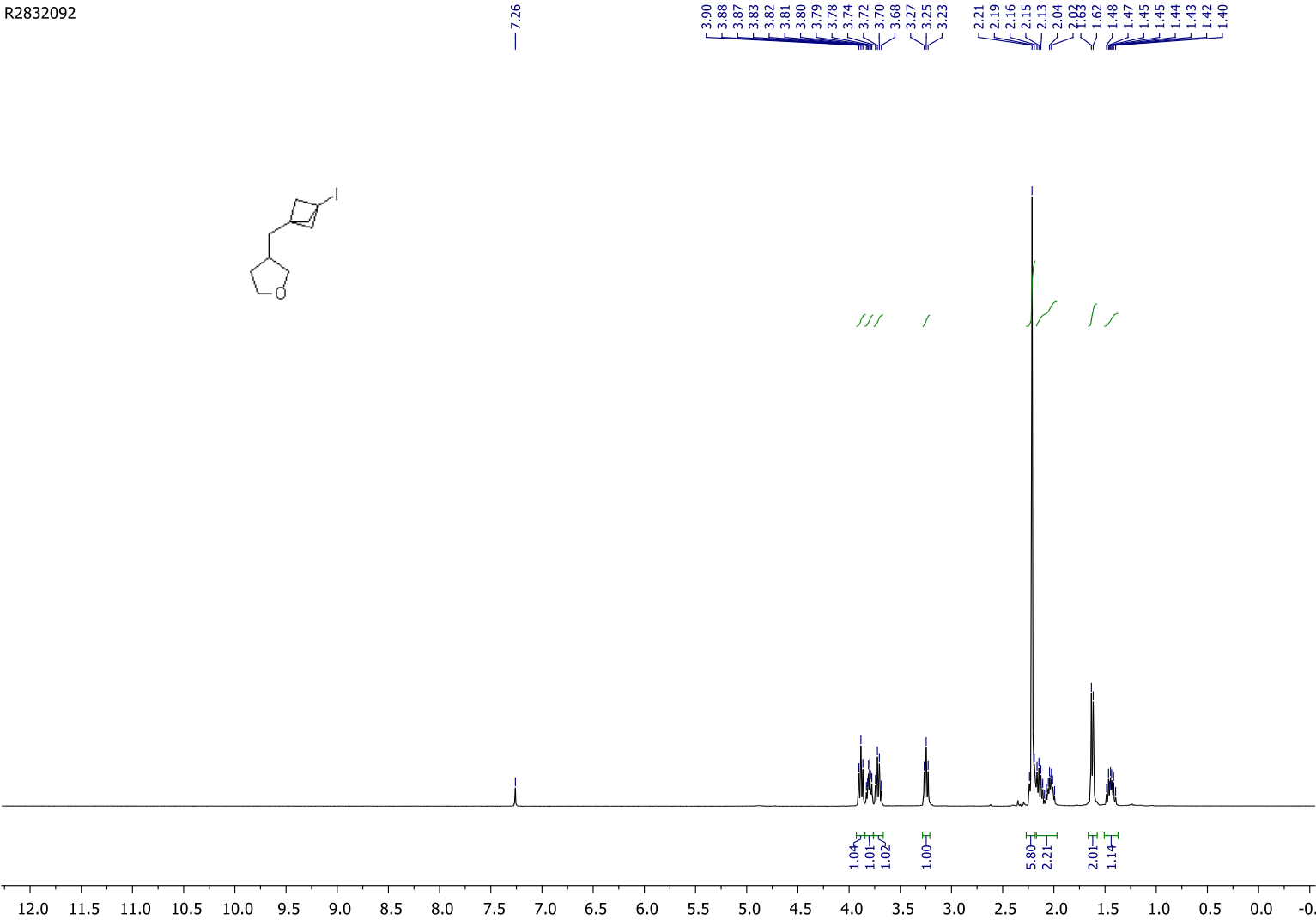
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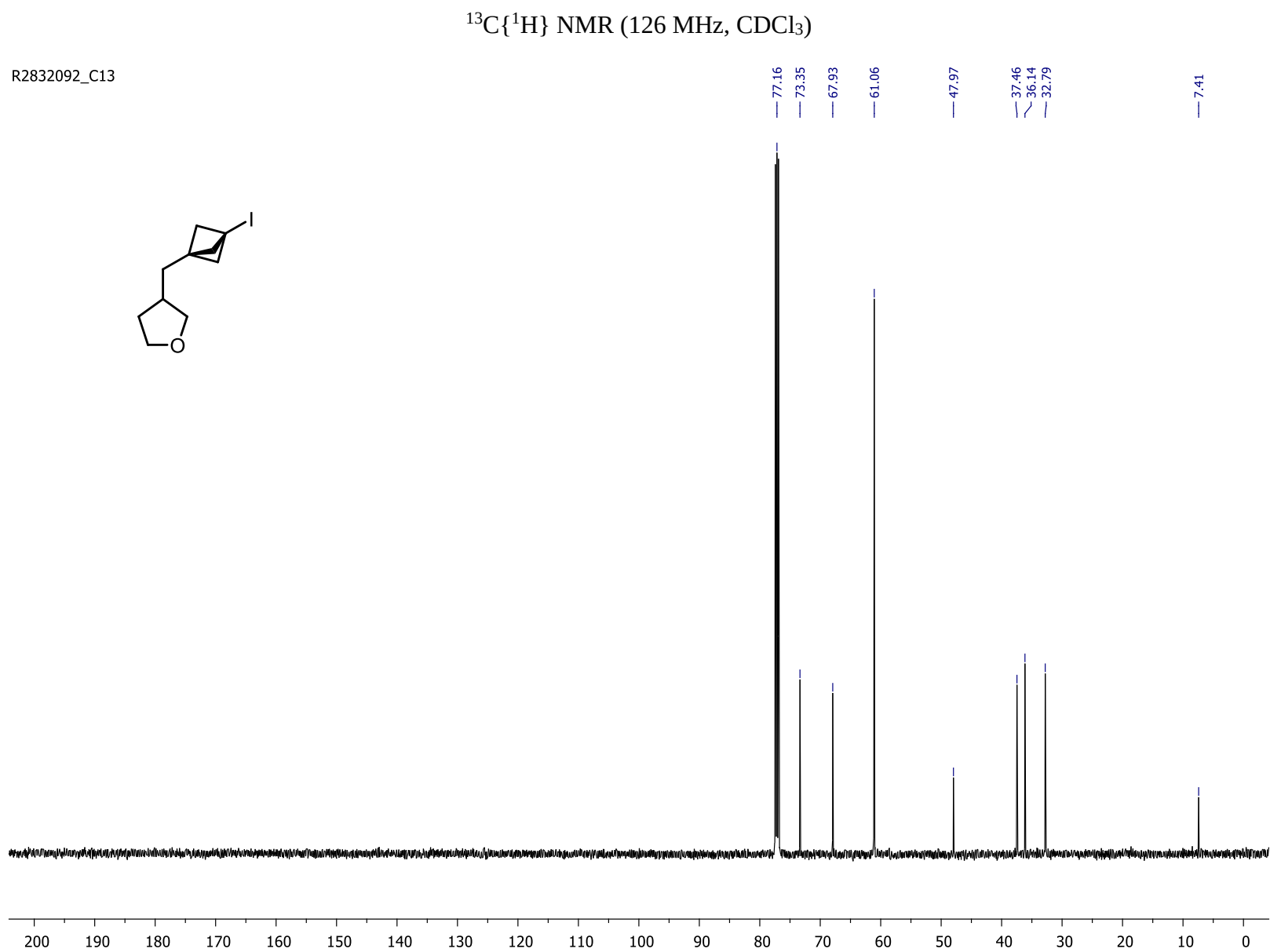


Compound 11

R2832092

¹H NMR (400 MHz, CDCl₃)

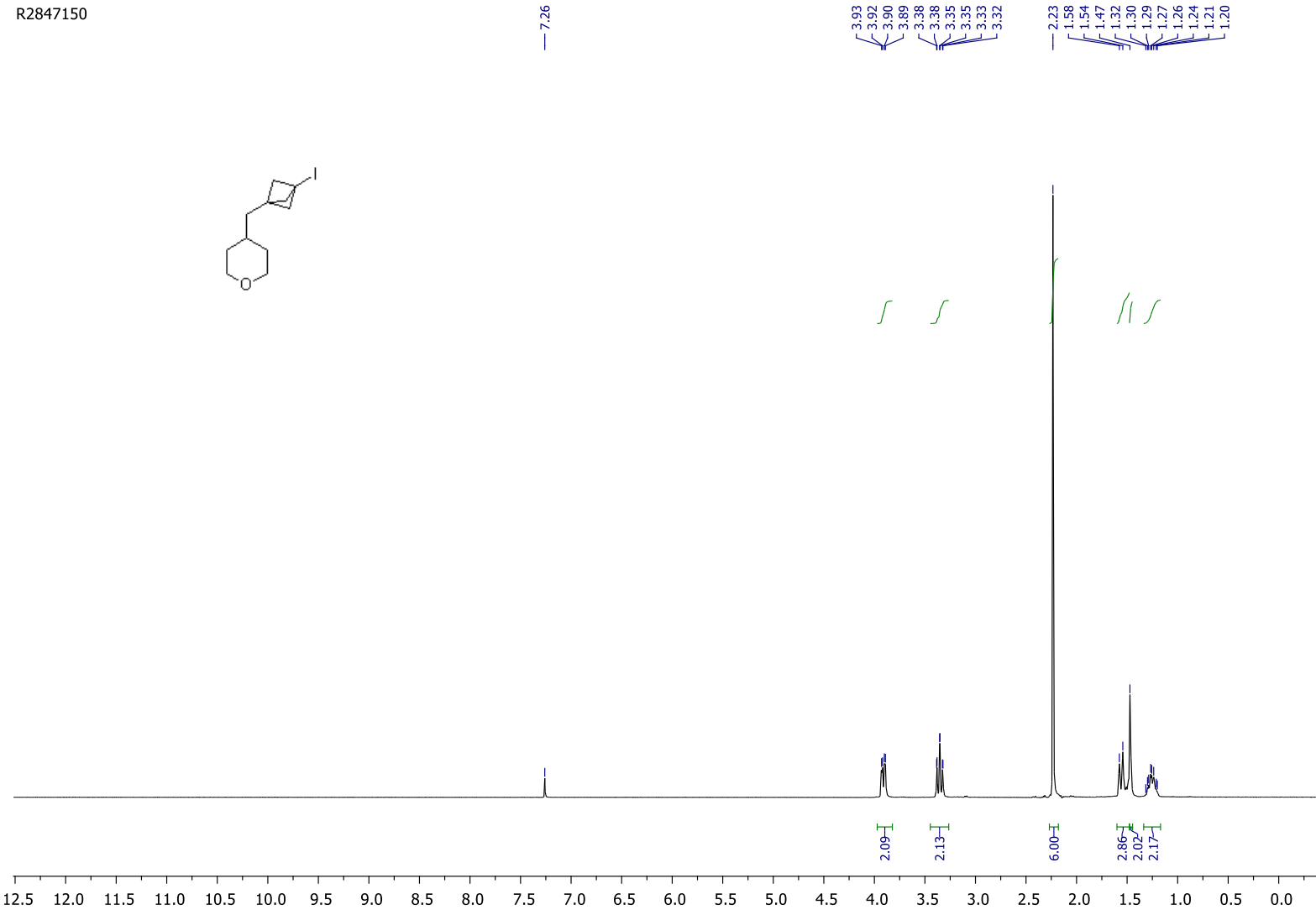


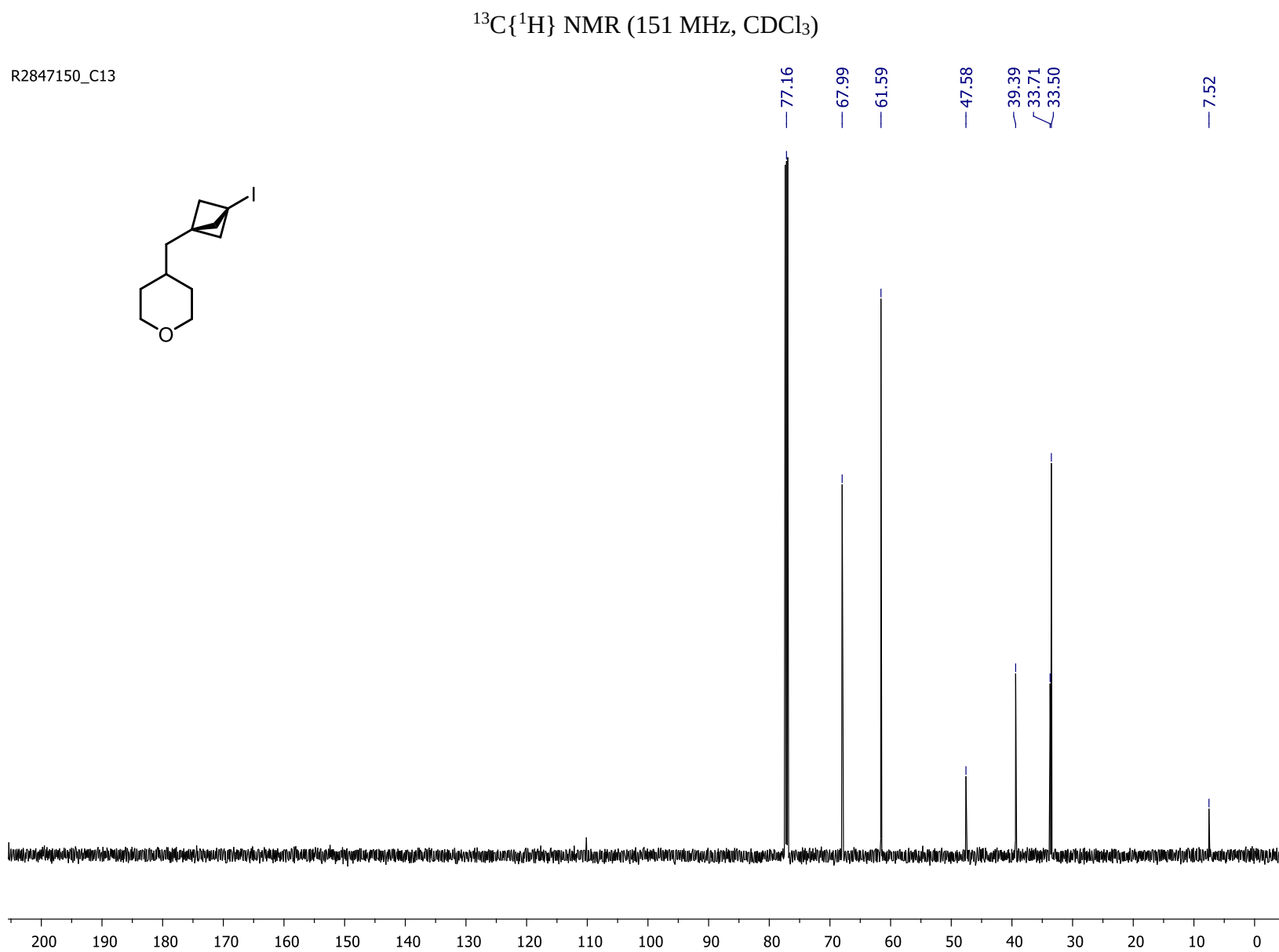


Compound 12

R2847150

¹H NMR (400 MHz, CDCl₃)

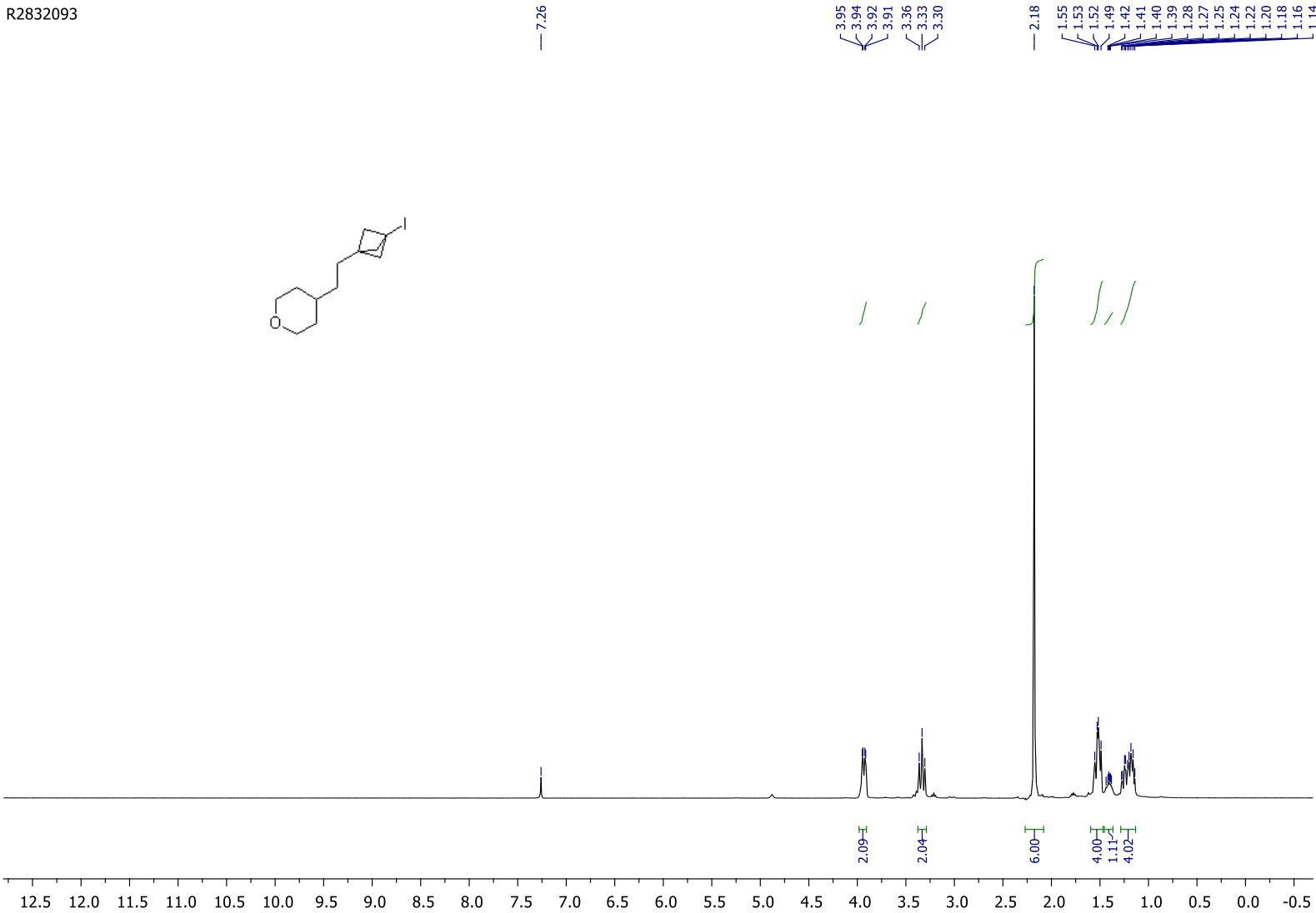


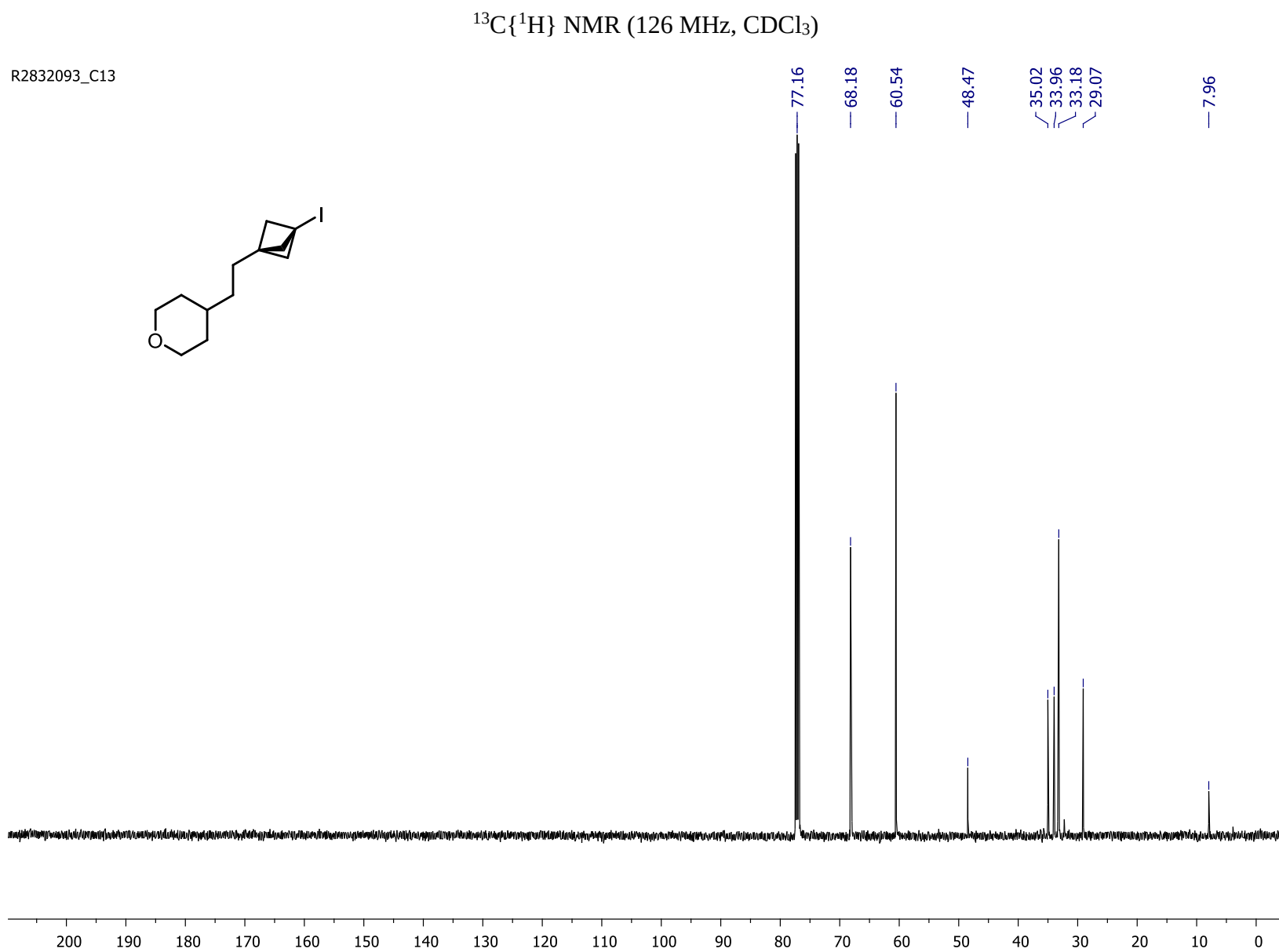


Compound 13

R2832093

¹H NMR (400 MHz, CDCl₃)

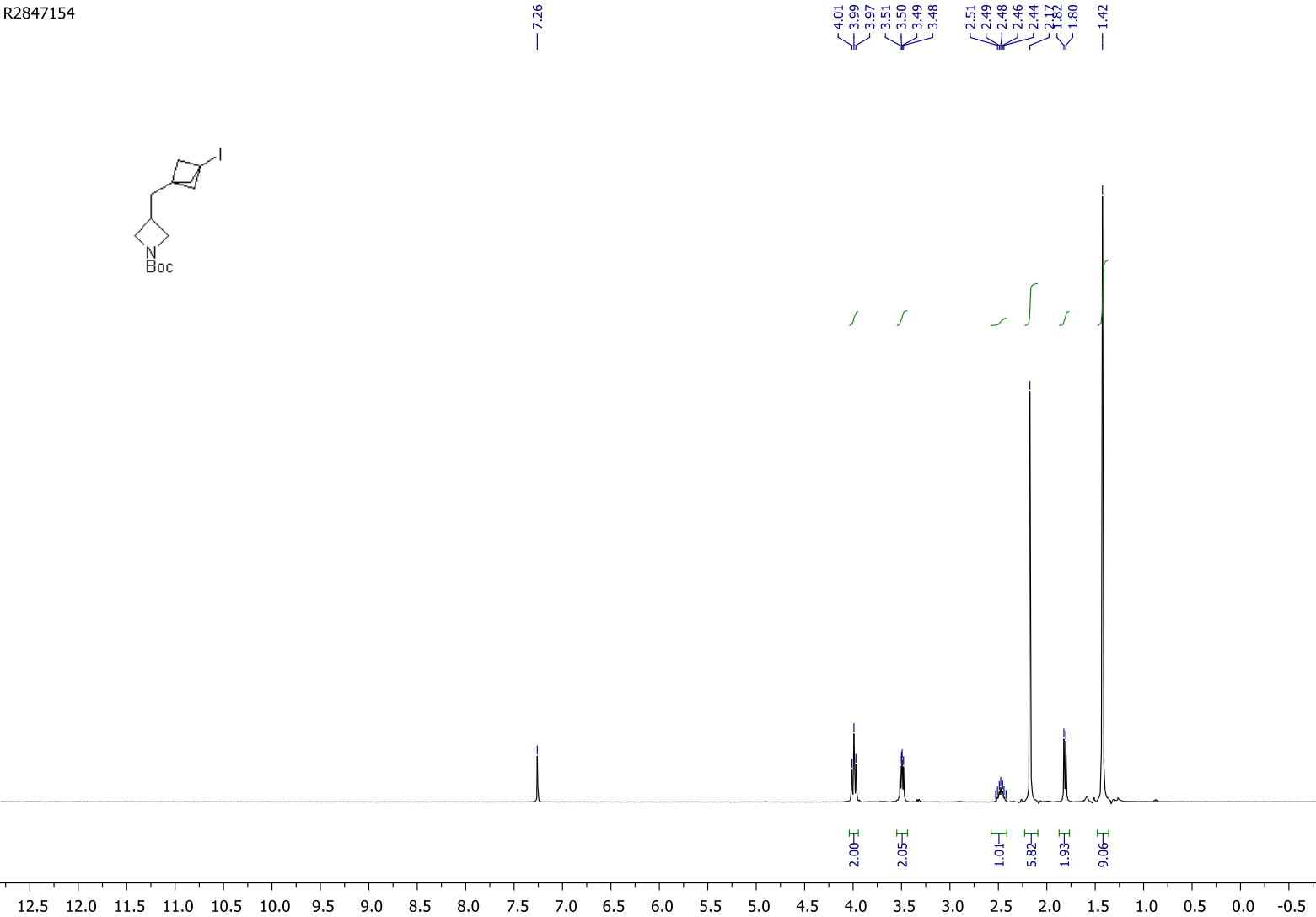


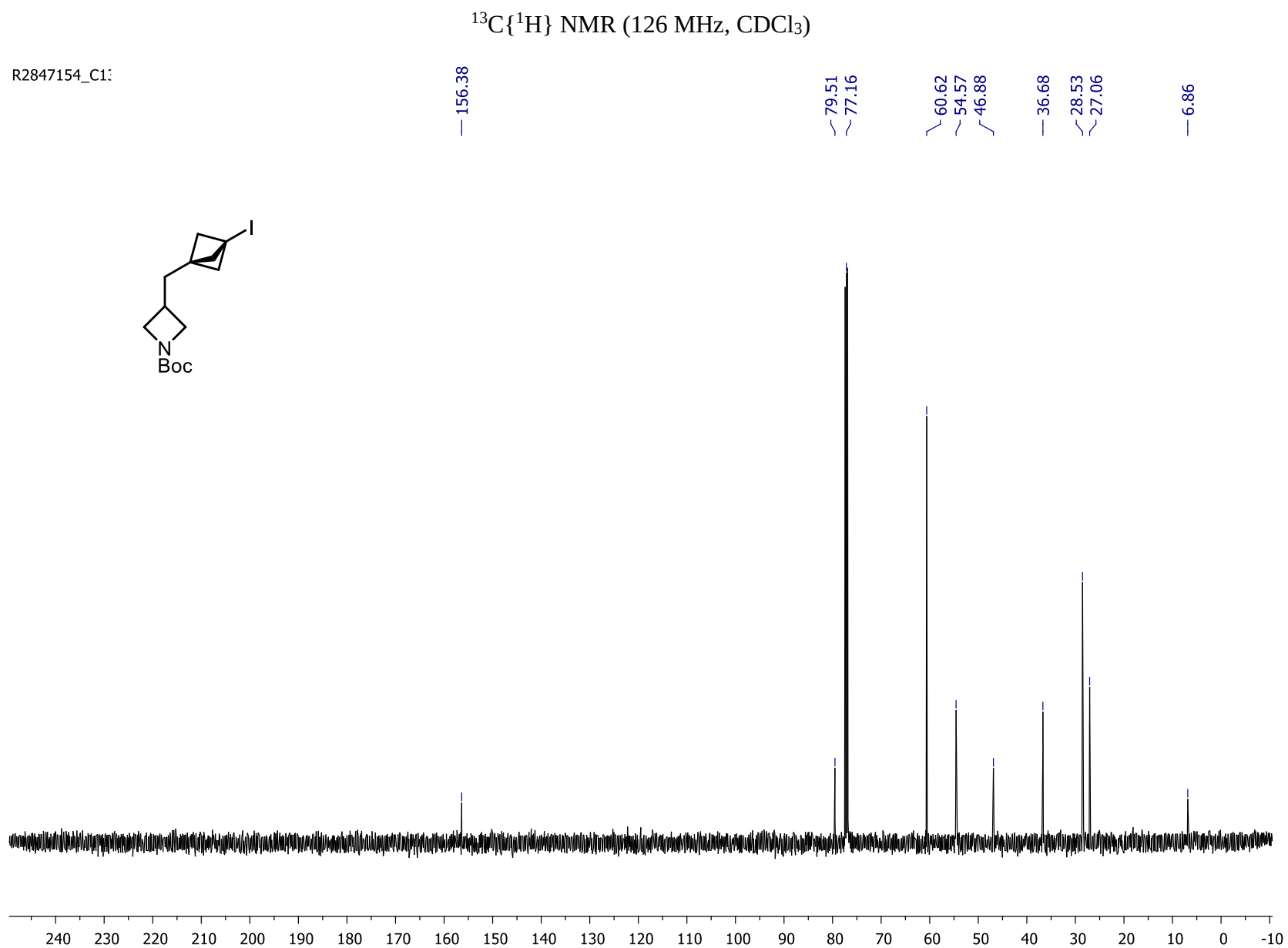


Compound 14

R2847154

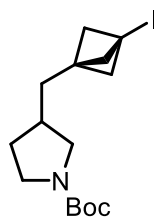
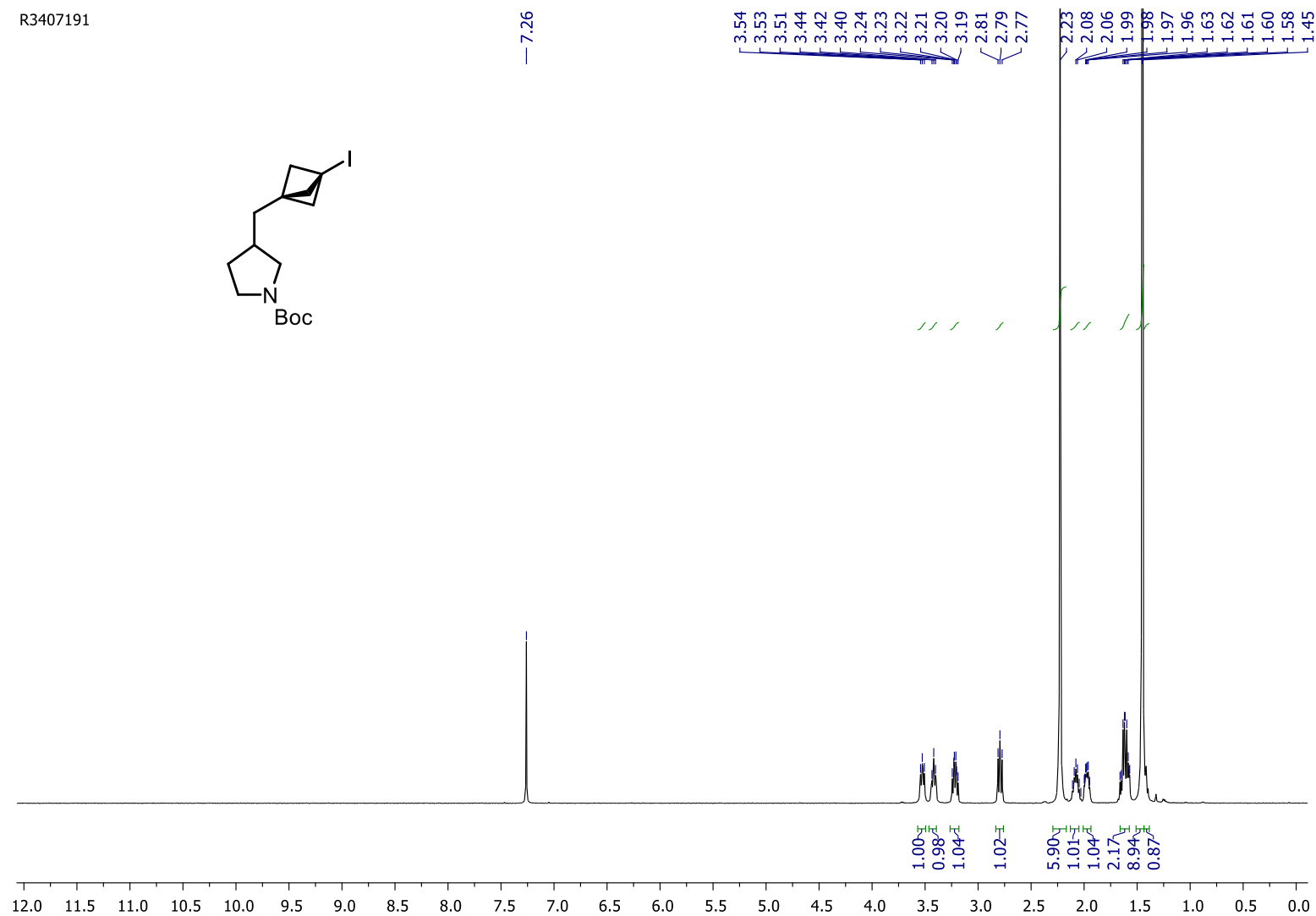
¹H NMR (400 MHz, CDCl₃)





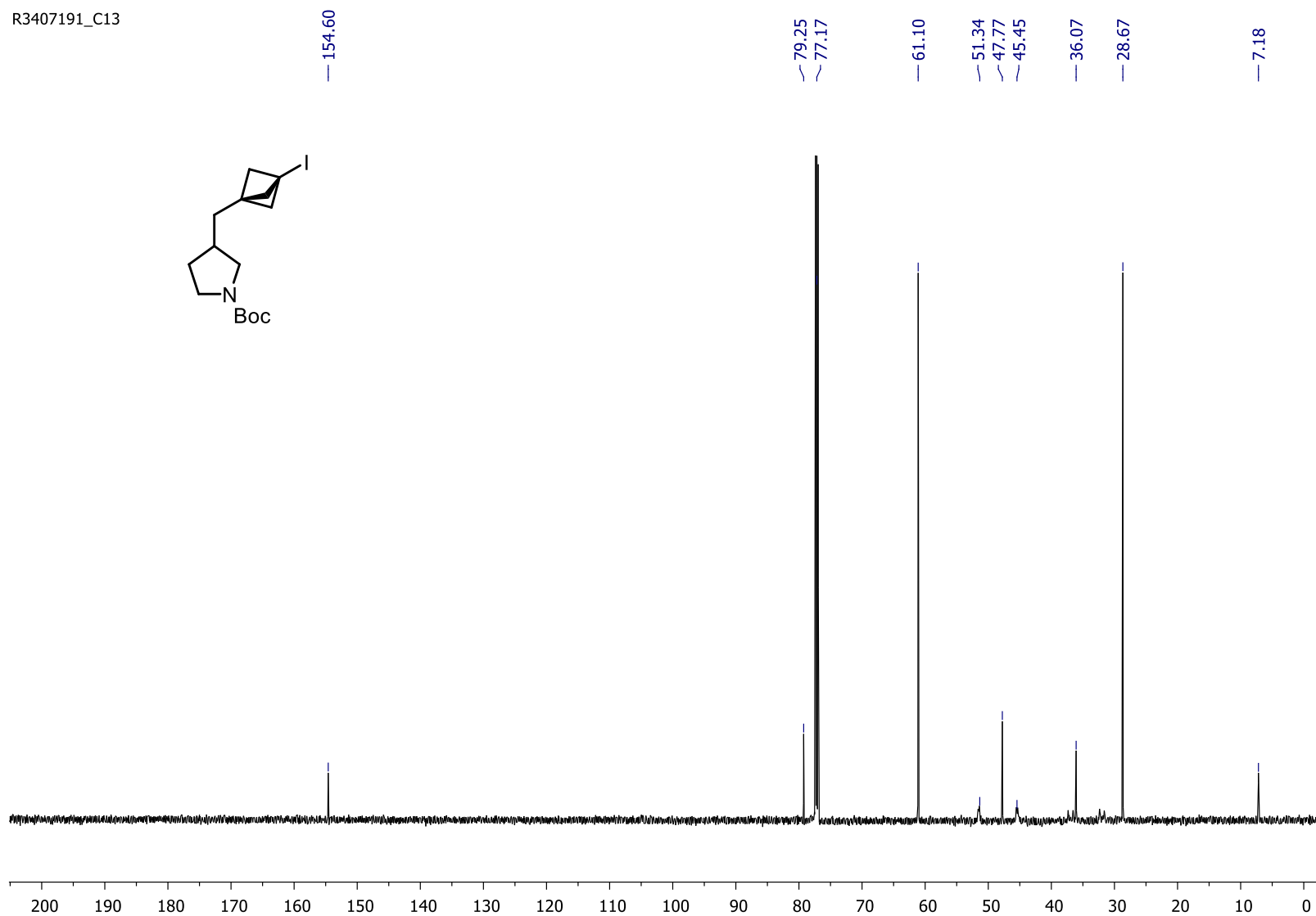
Compound 15

R3407191

¹H NMR (500 MHz, CDCl₃)

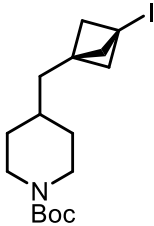
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

R3407191_C13

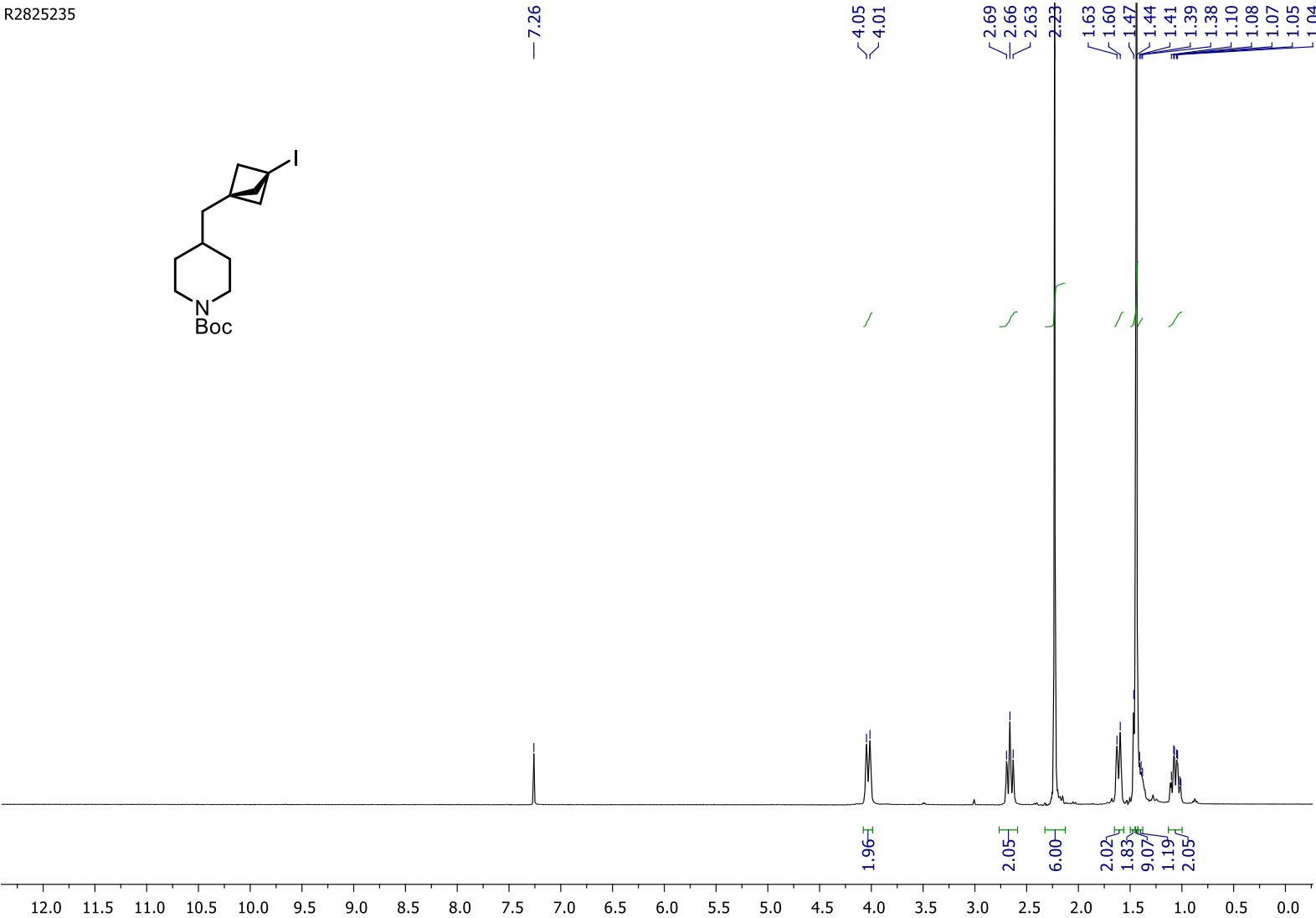


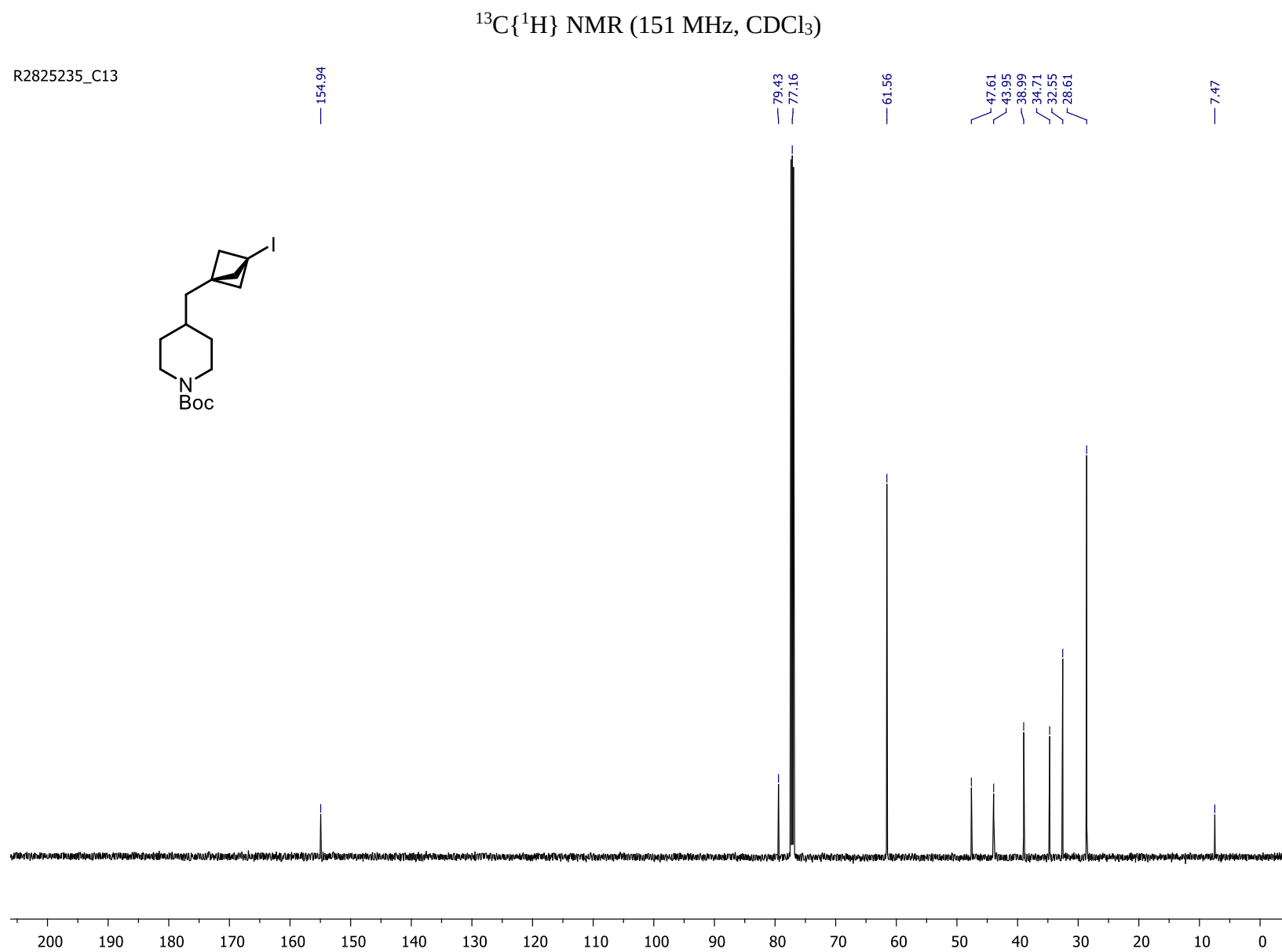
Compound 16

R2825235



¹H NMR (400 MHz, CDCl₃)

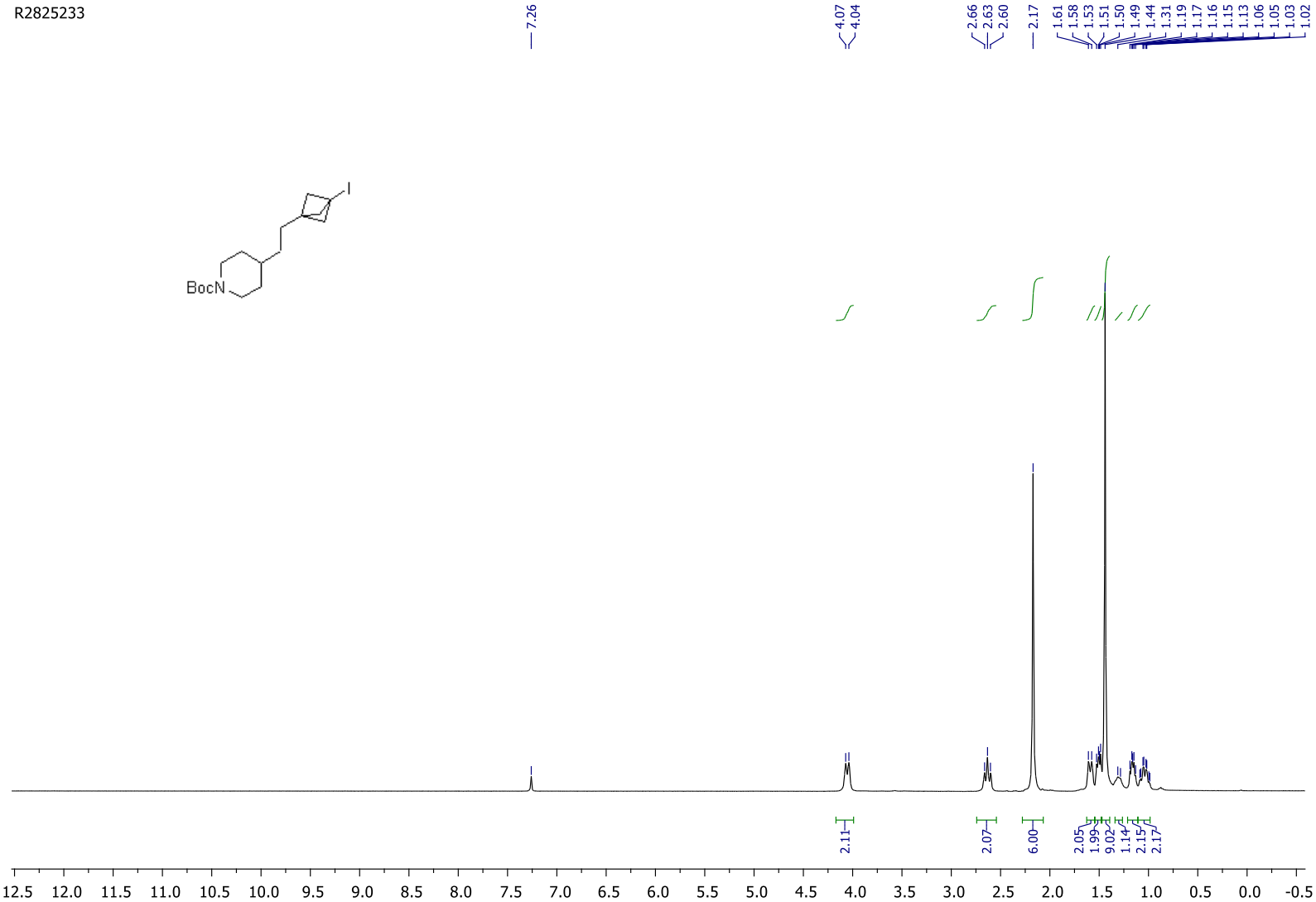


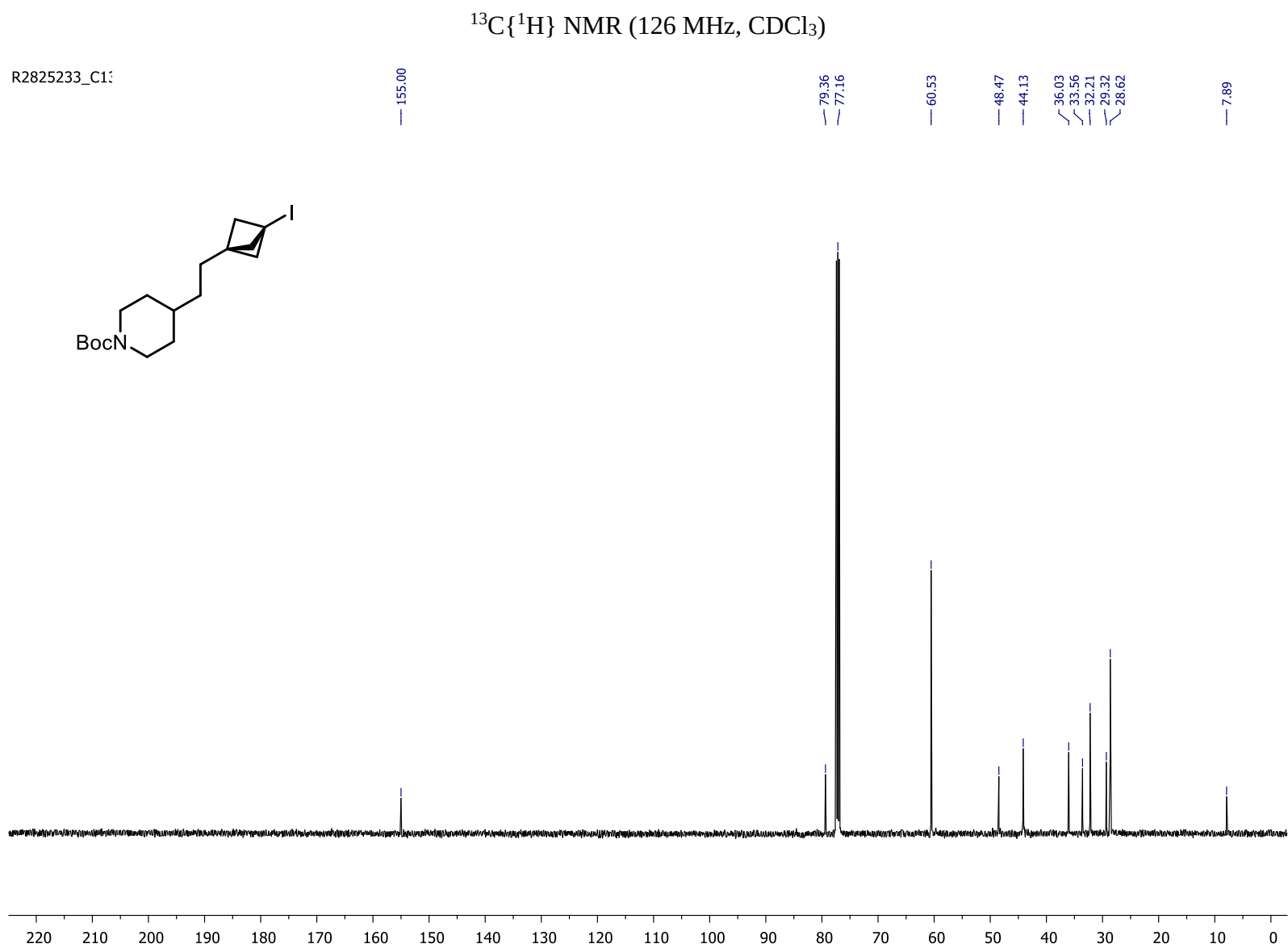


Compound 17

R2825233

¹H NMR (400 MHz, CDCl₃)

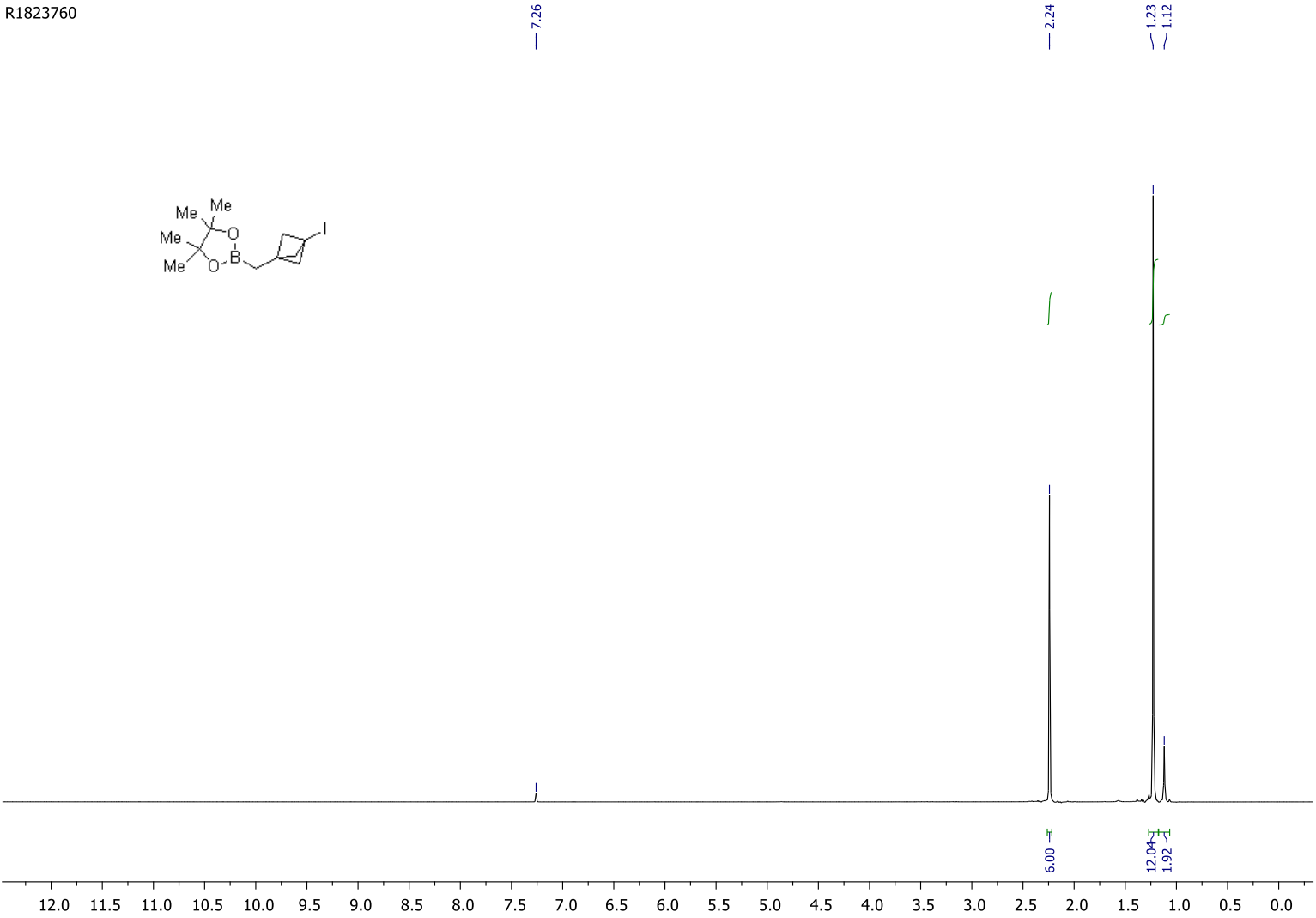




Compound 18

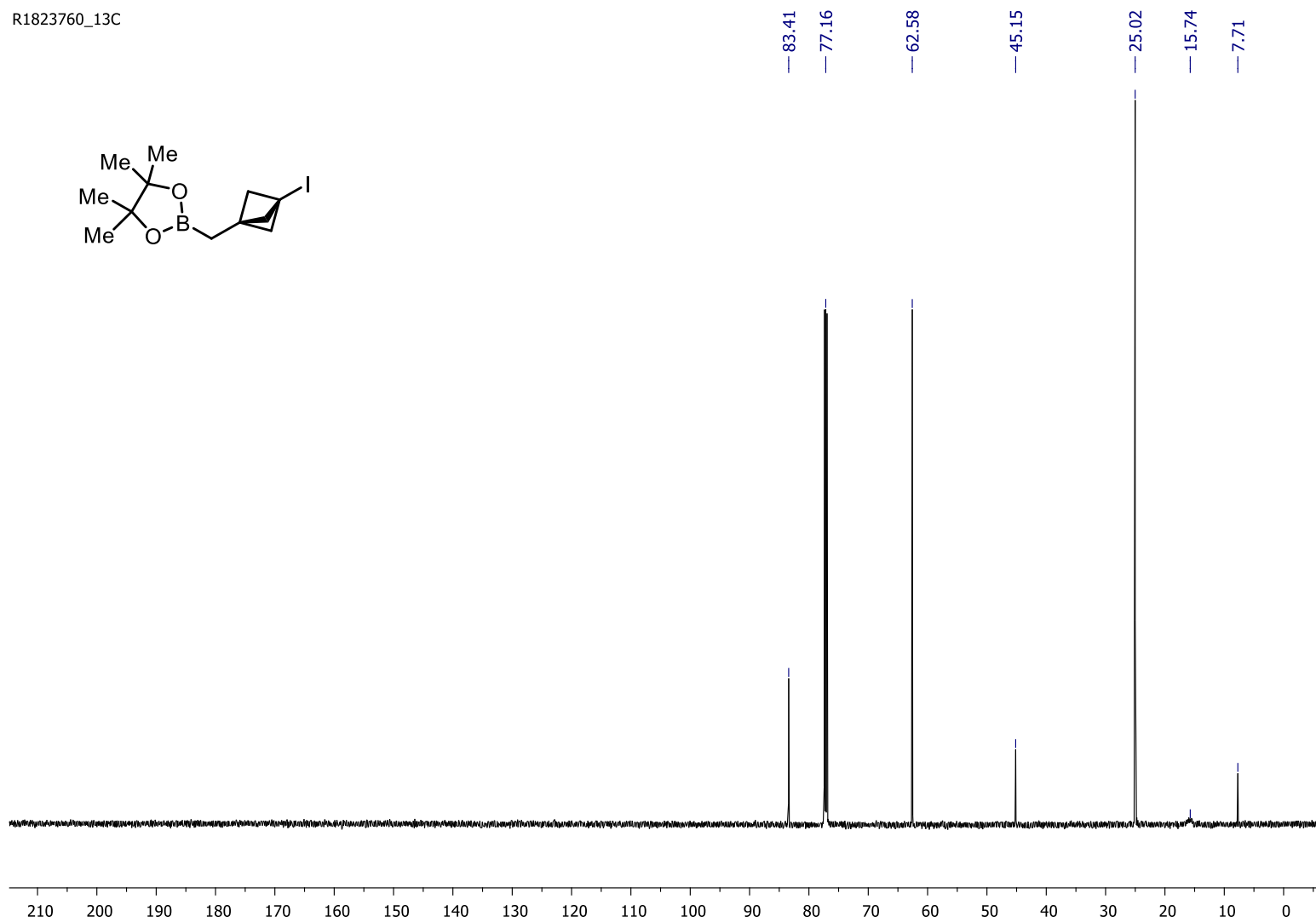
R1823760

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

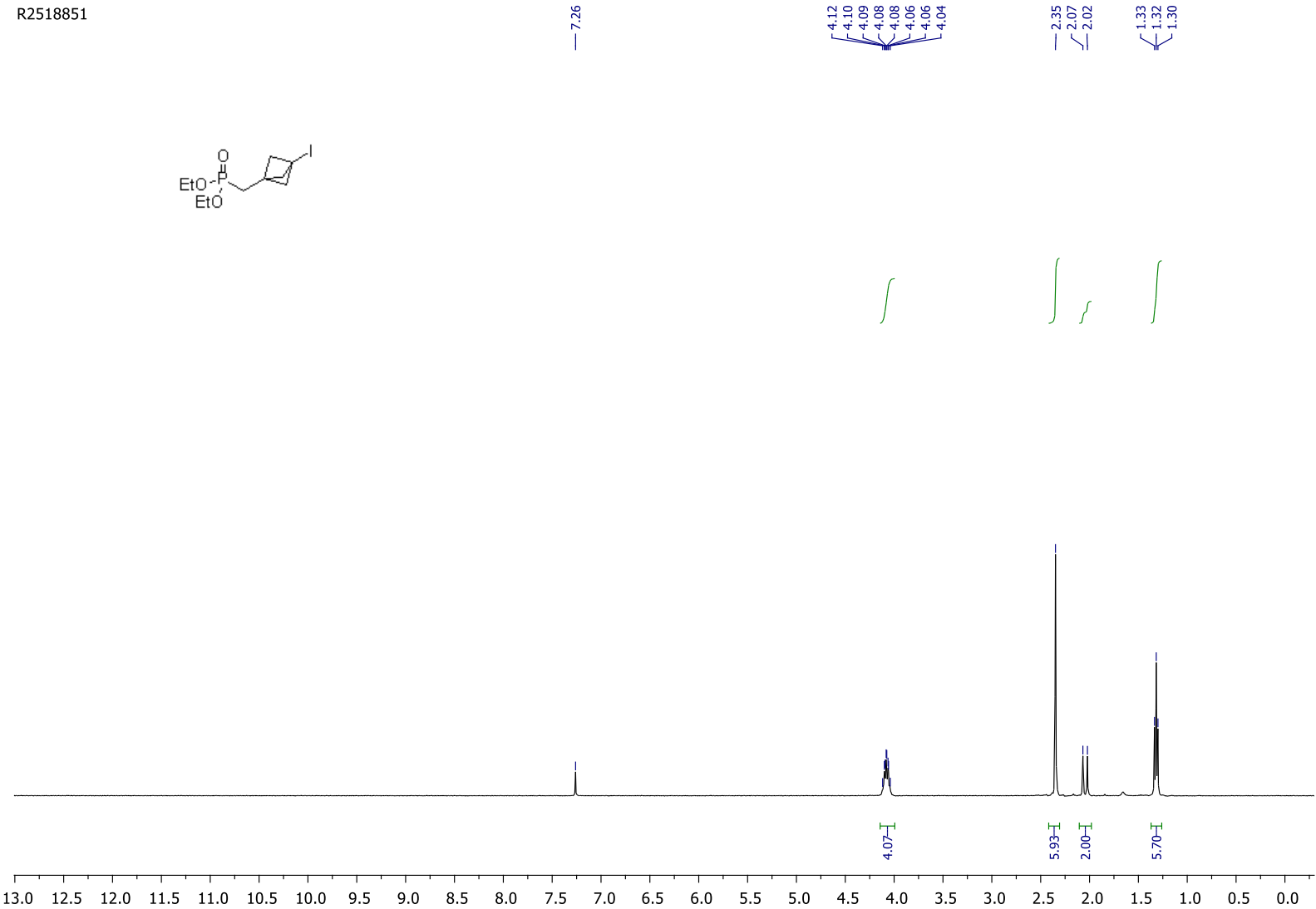
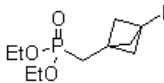
R1823760_13C



Compound 19

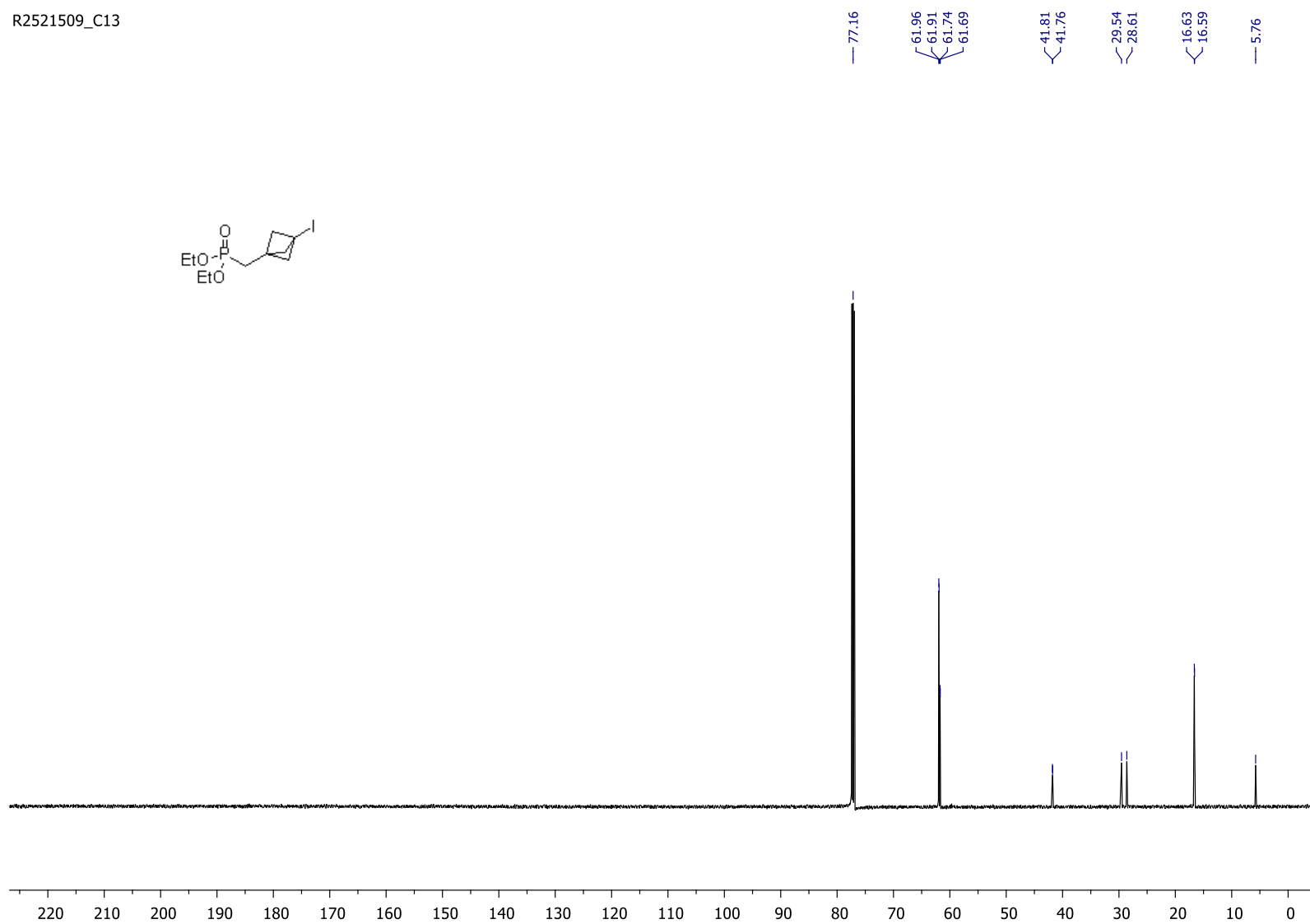
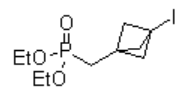
R2518851

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

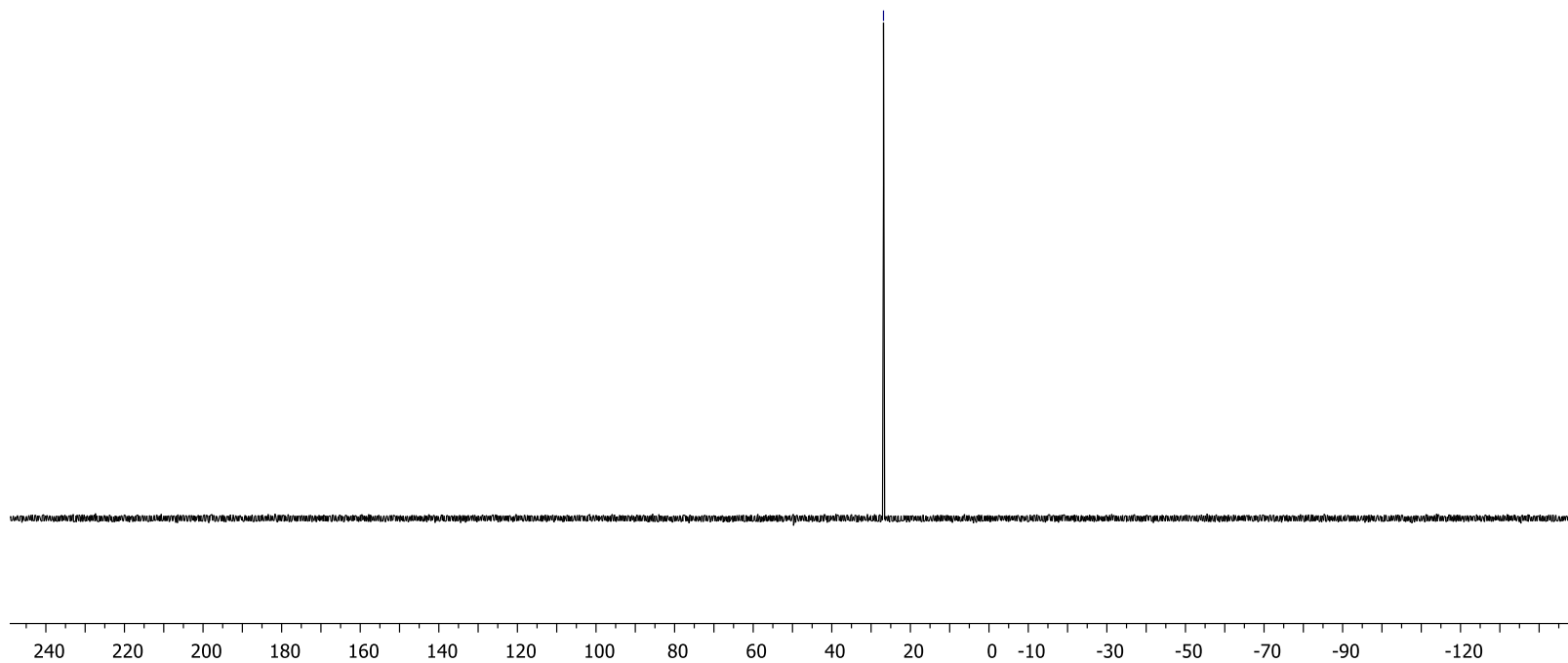
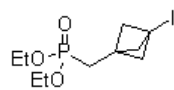
R2521509_C13



$^{31}\text{P}\{^1\text{H}\}$ NMR (202 MHz, CDCl_3)

R2518851_31P{H}

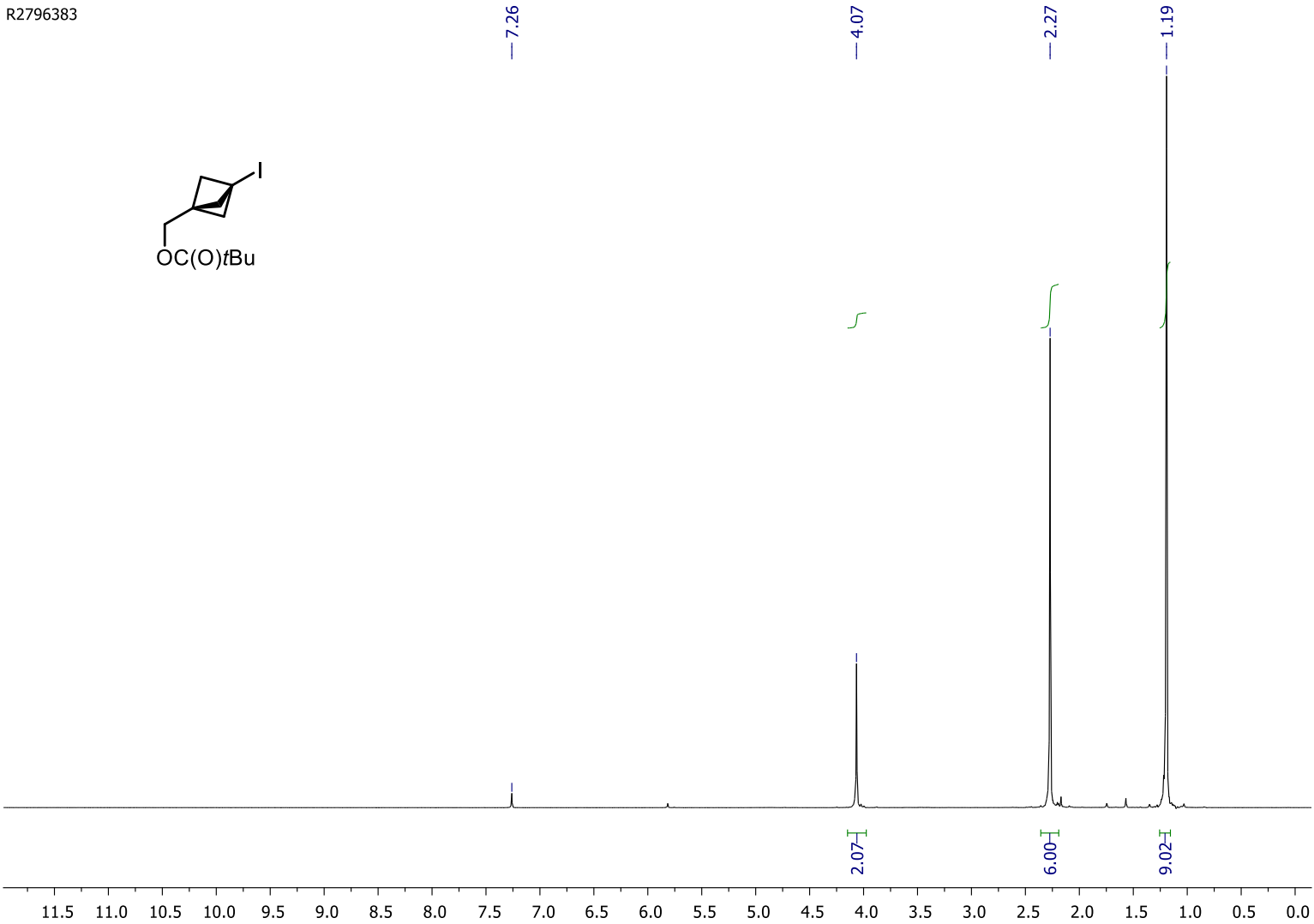
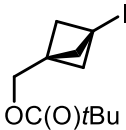
26.84

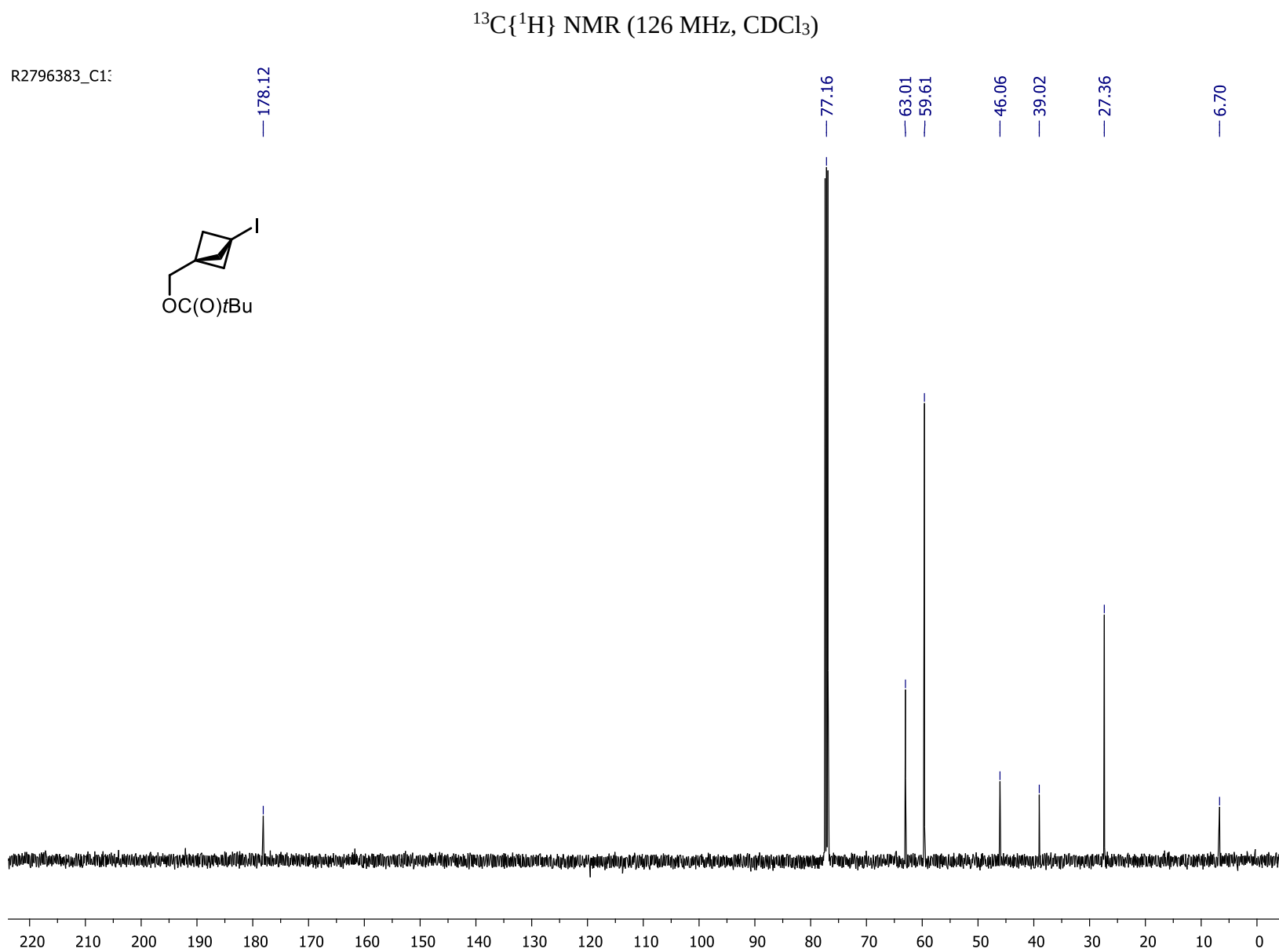


Compound 20

R2796383

¹H NMR (400 MHz, CDCl₃)

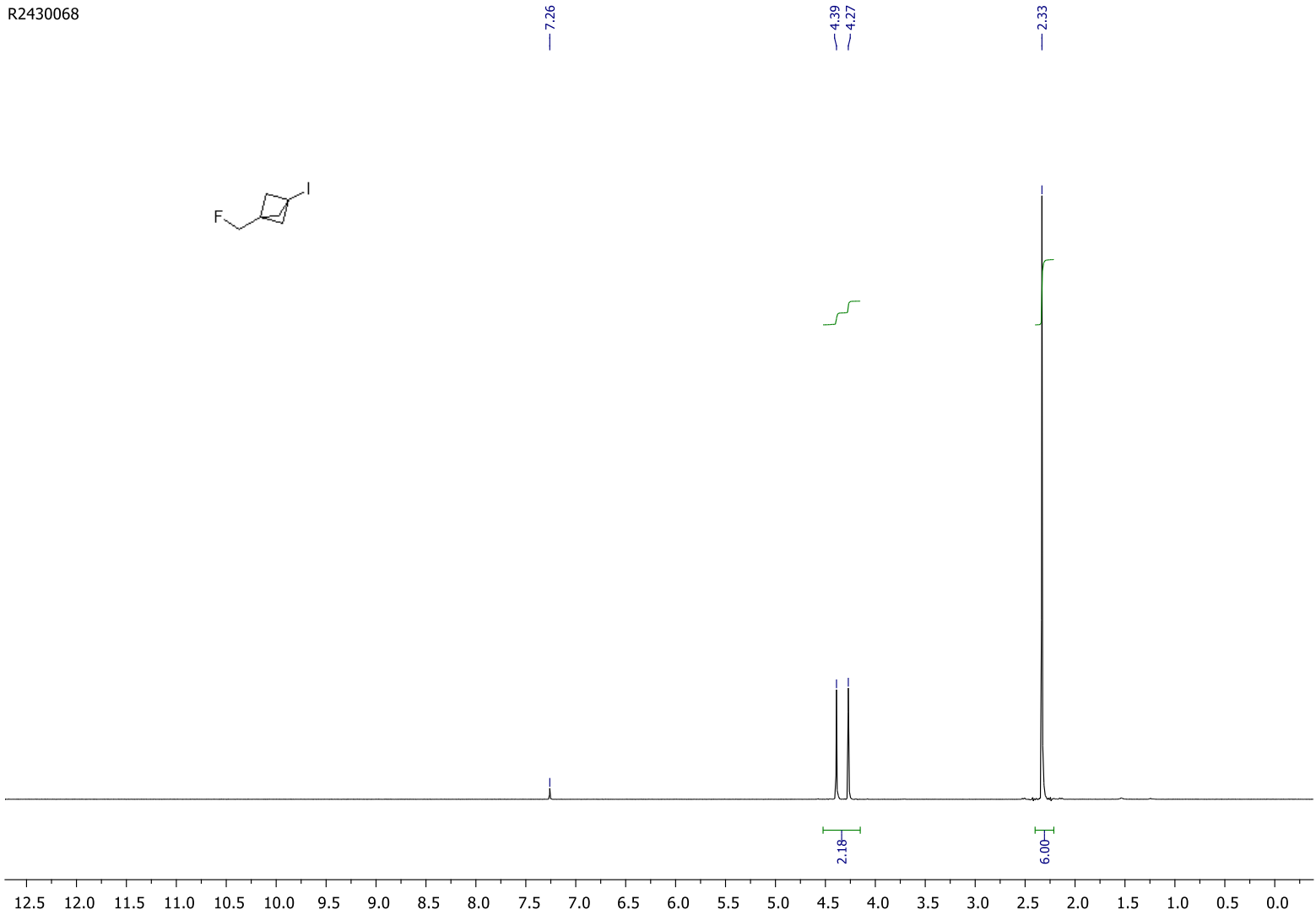




Compound 21

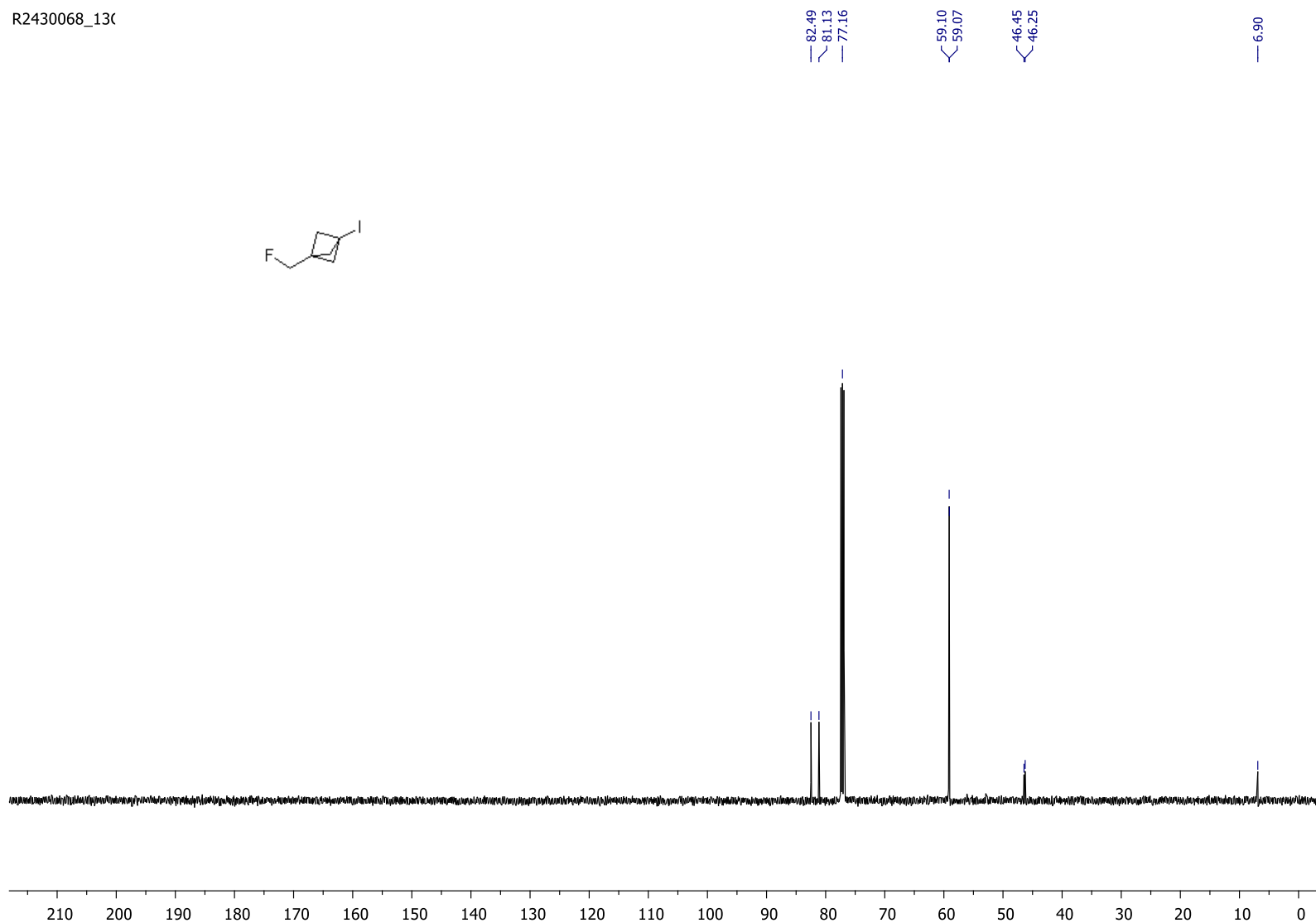
R2430068

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2430068_13C

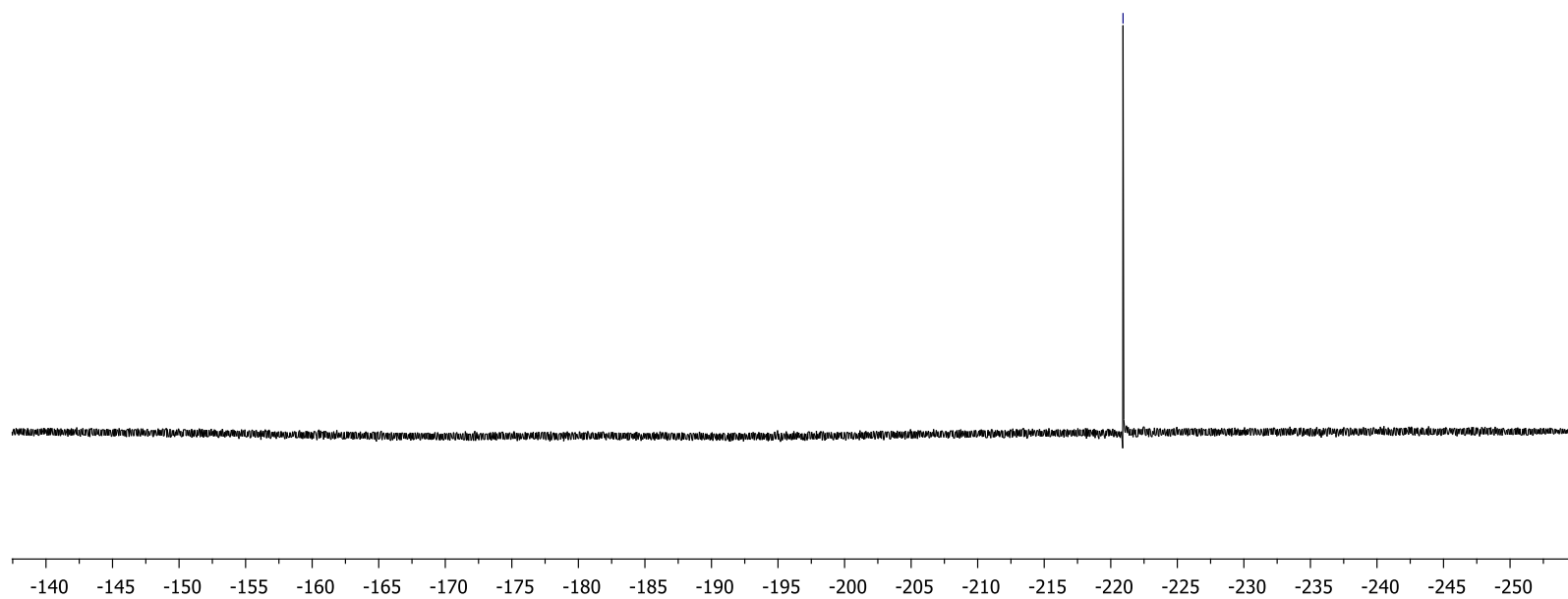


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

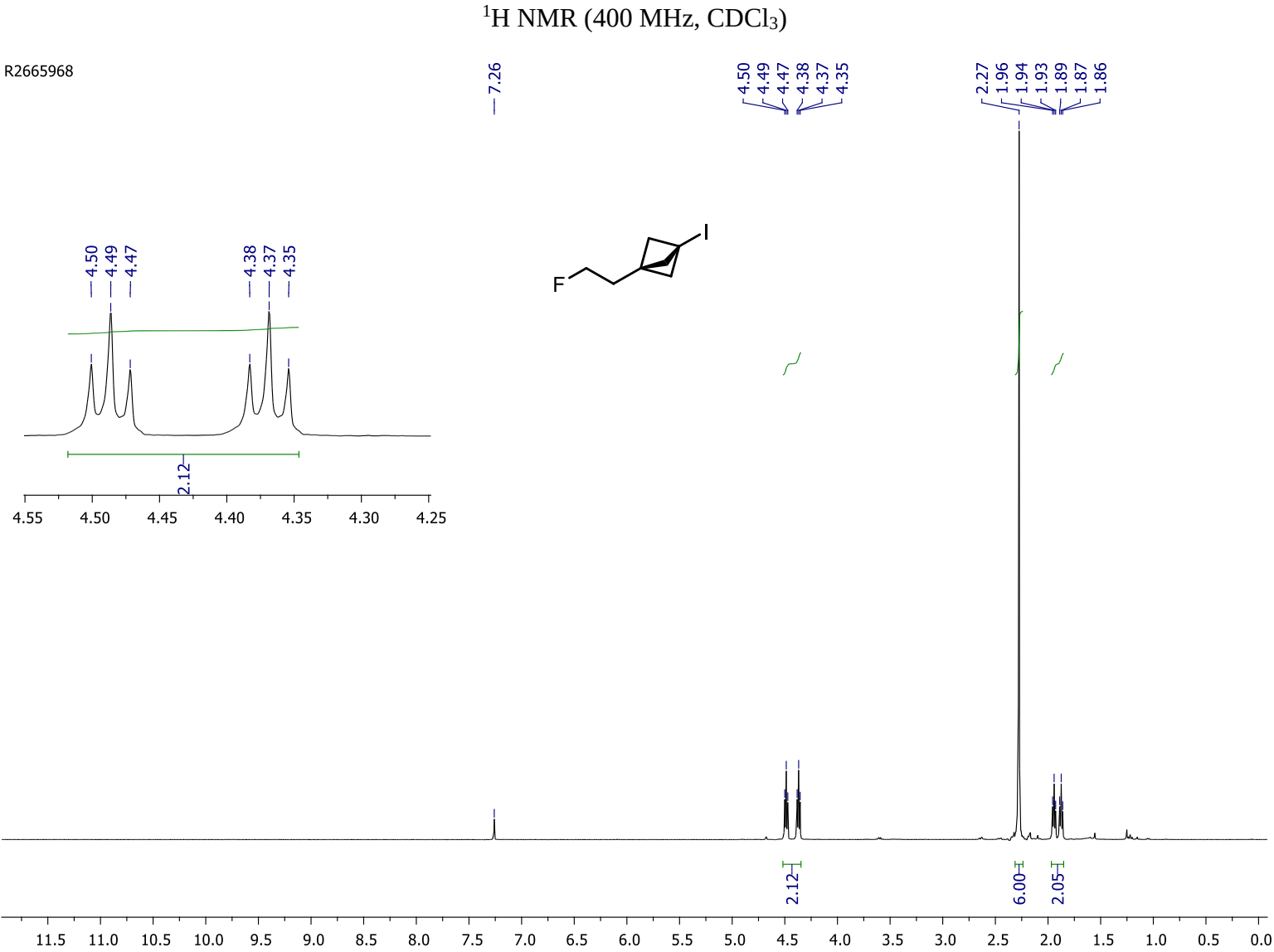
R2430068_F19{H}

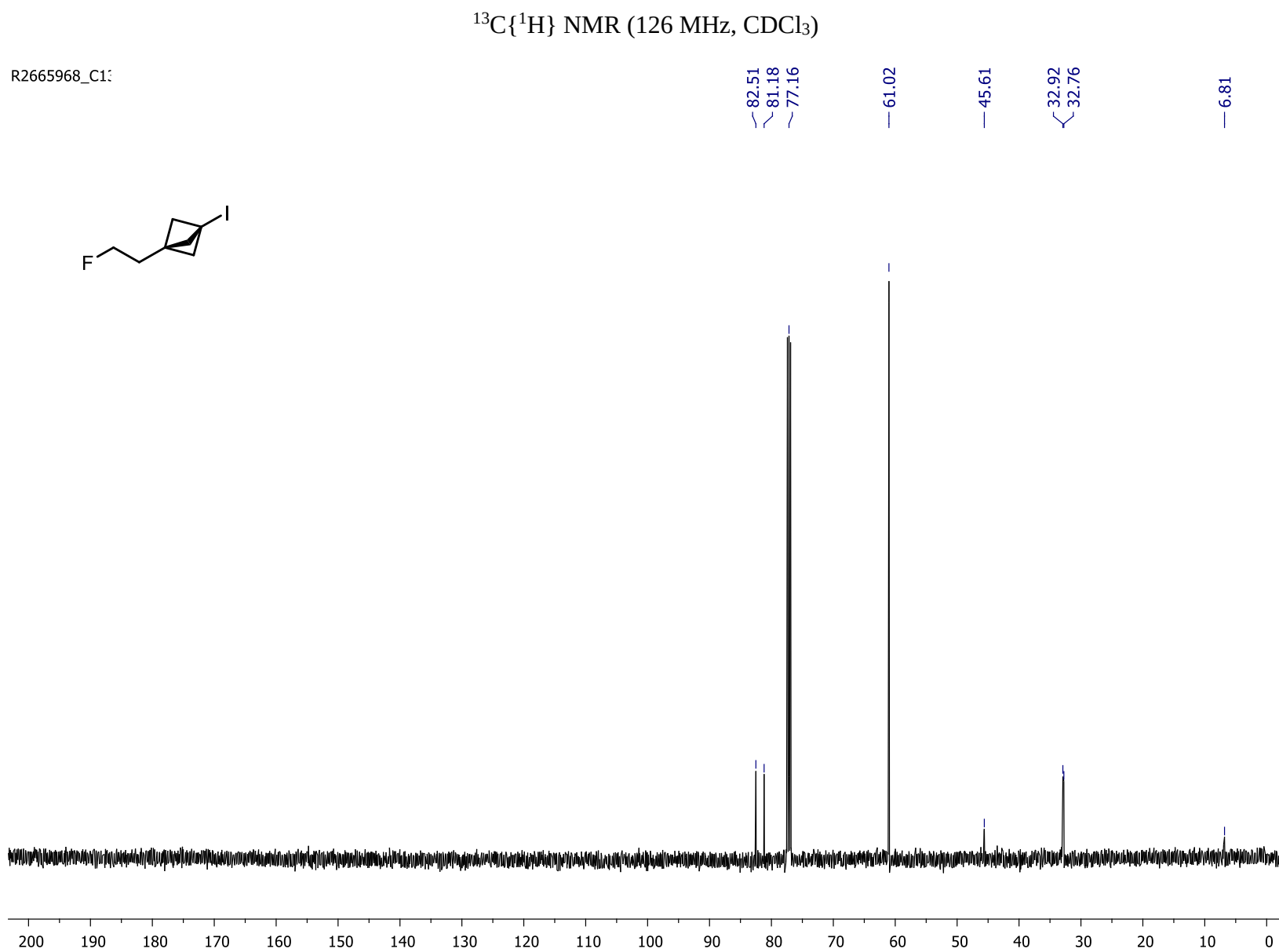


— -220.92



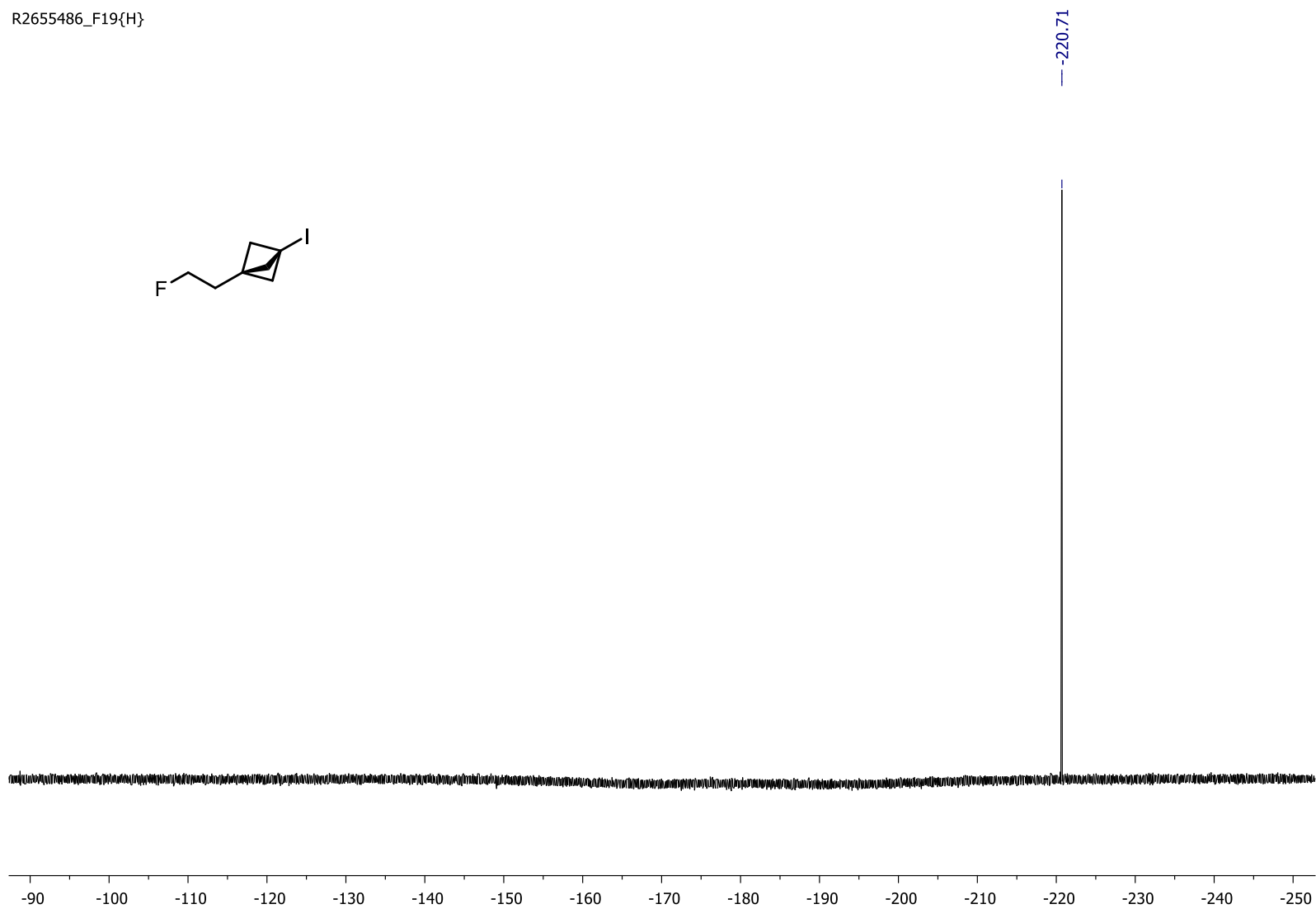
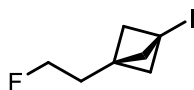
Compound 22





$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

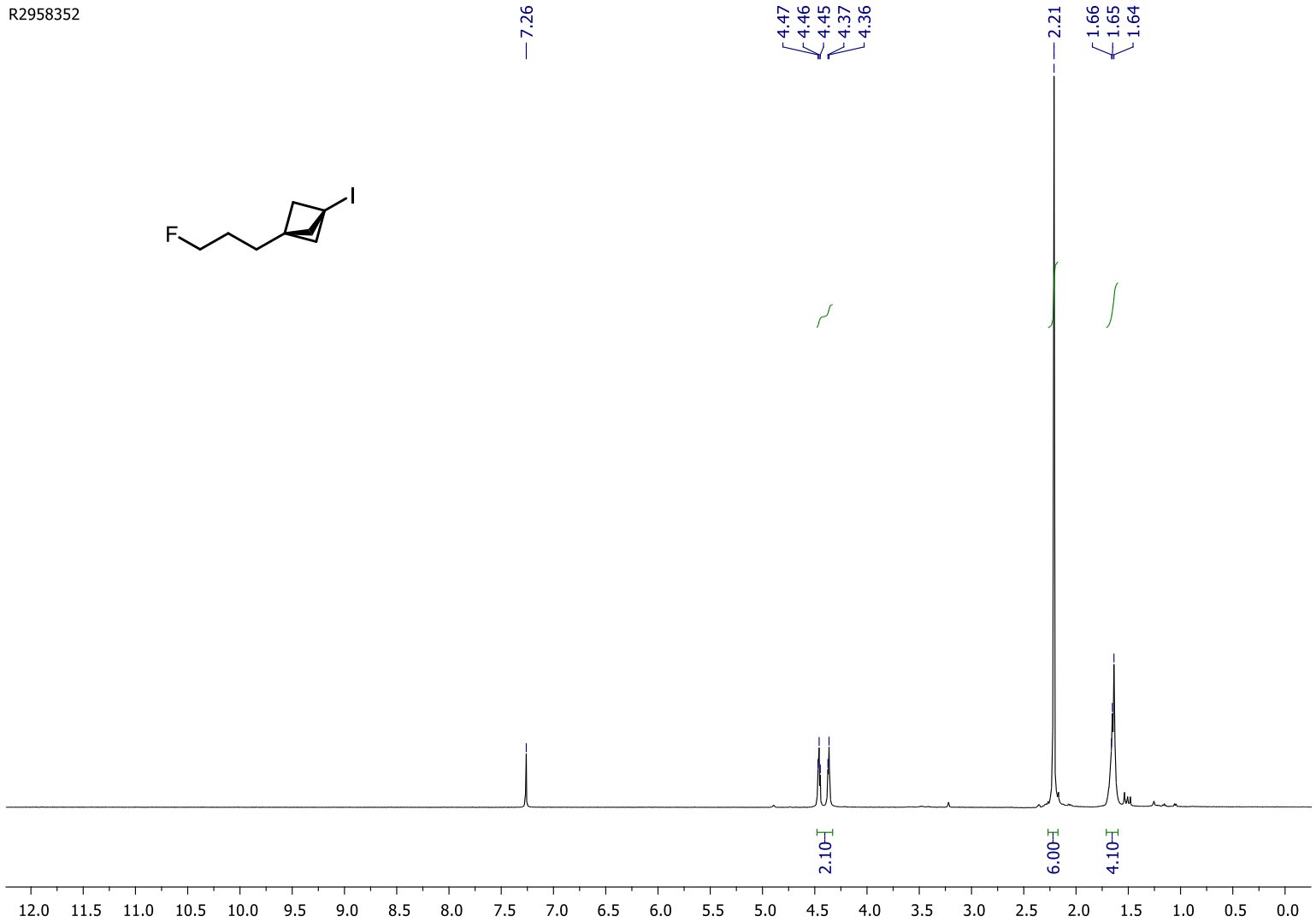
R2655486_F19{H}



Compound 23

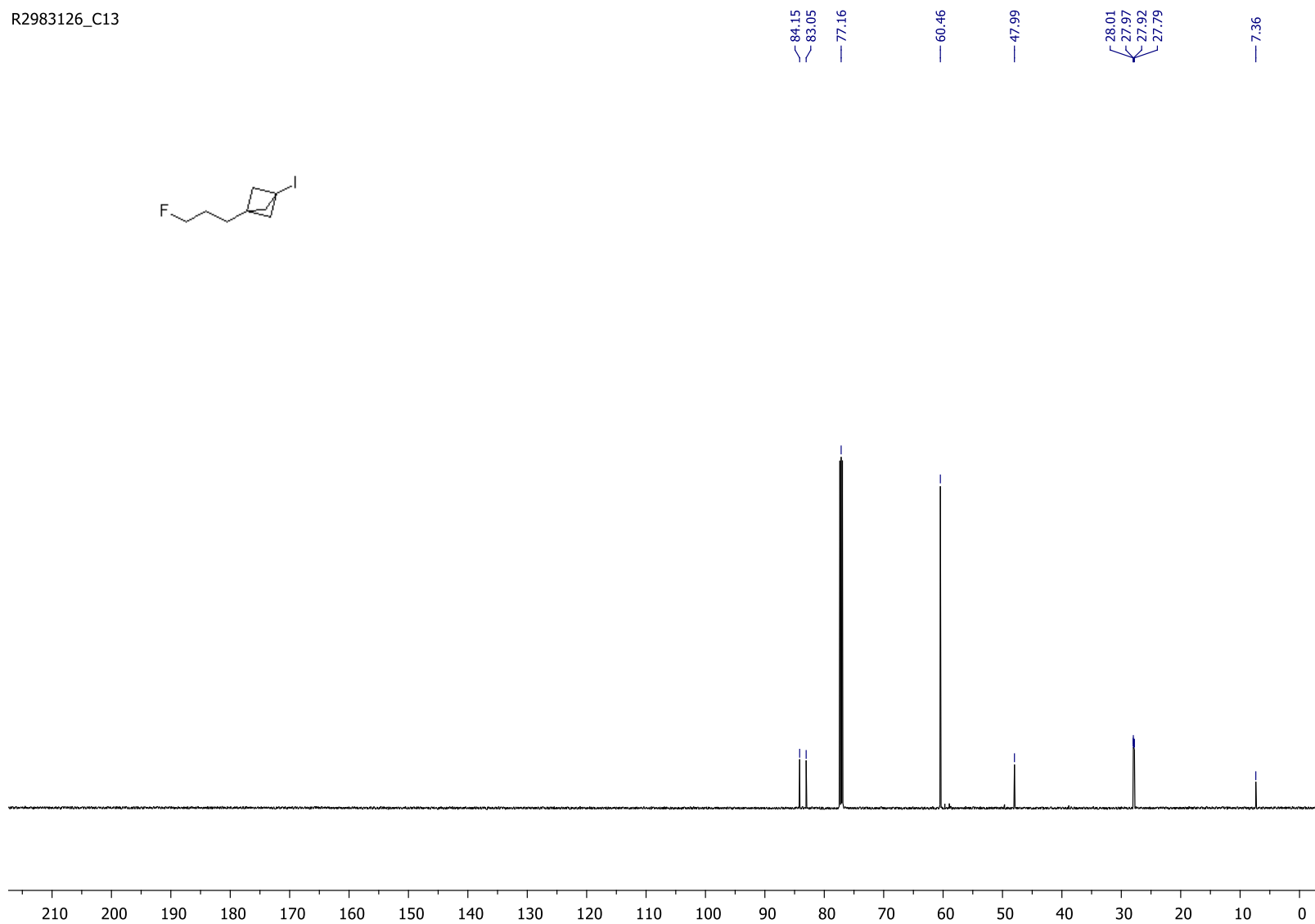
R2958352

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

R2983126_C13

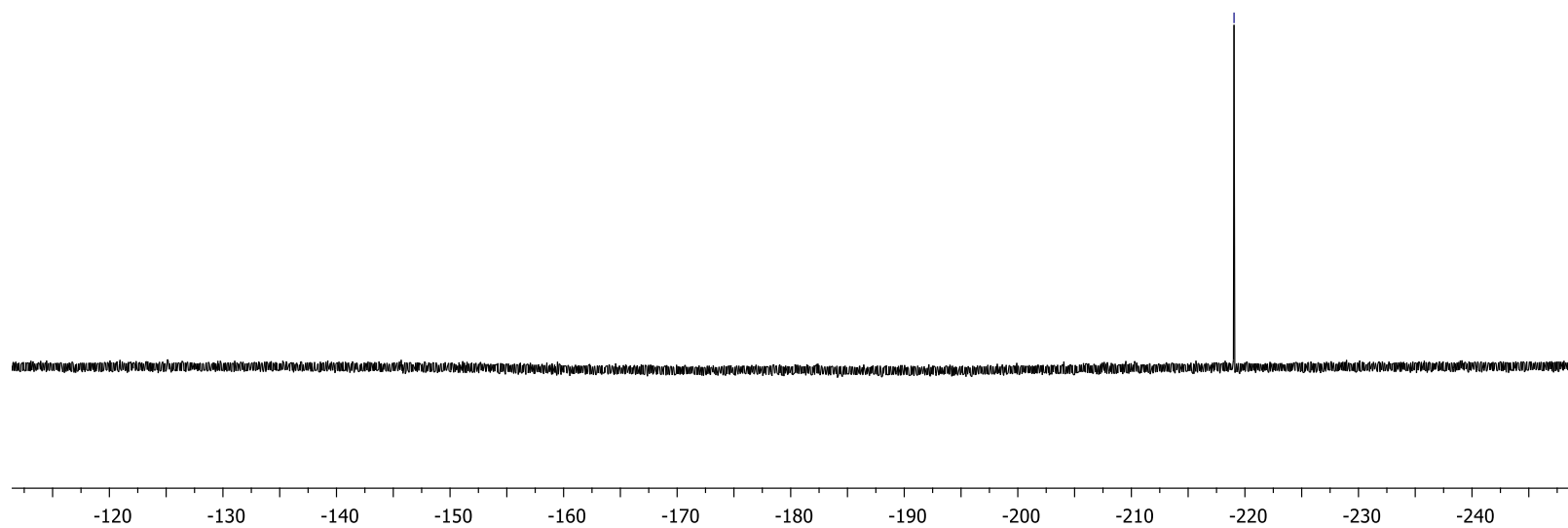


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2958352_F19{H}



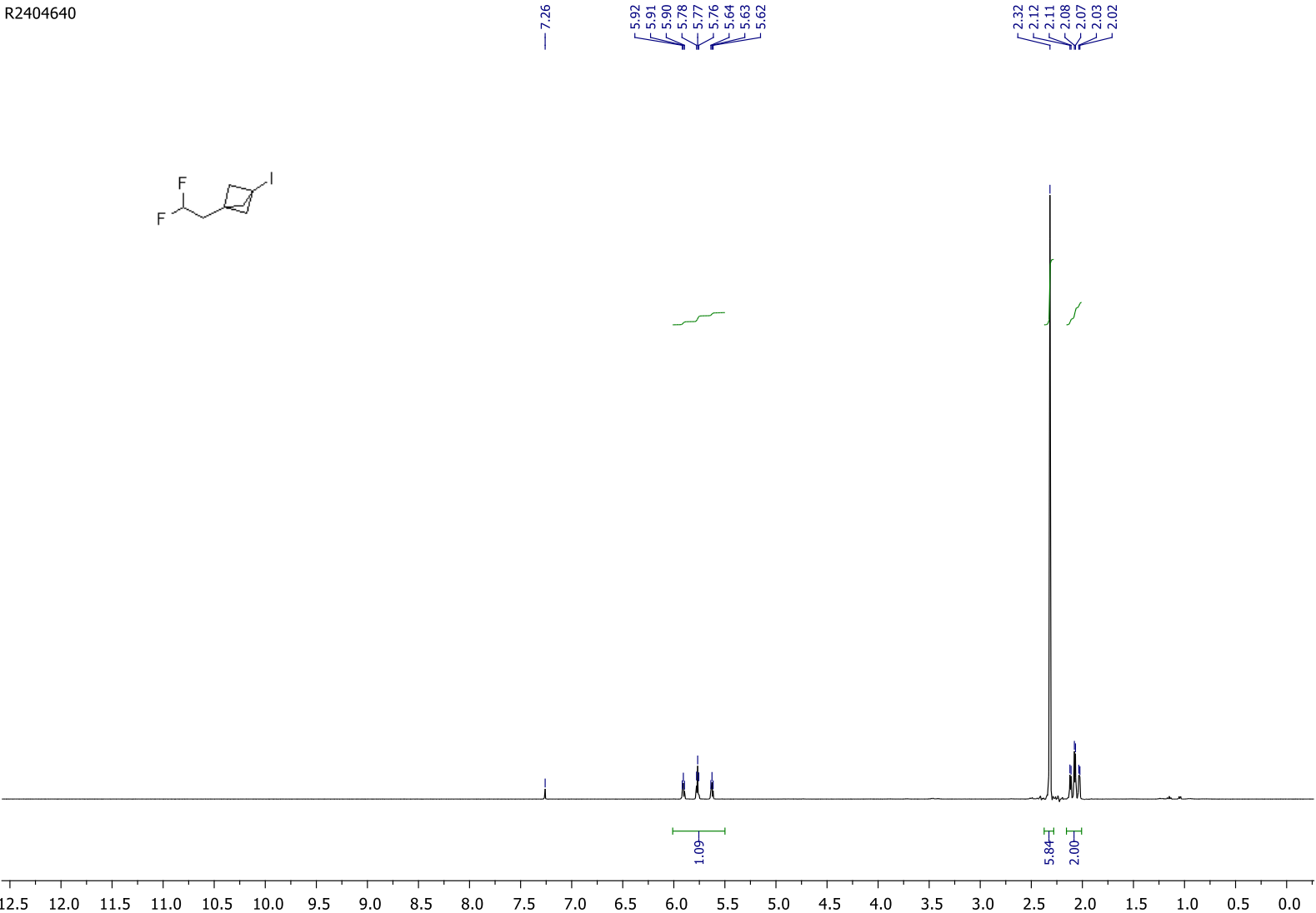
— -219.04



Compound 24

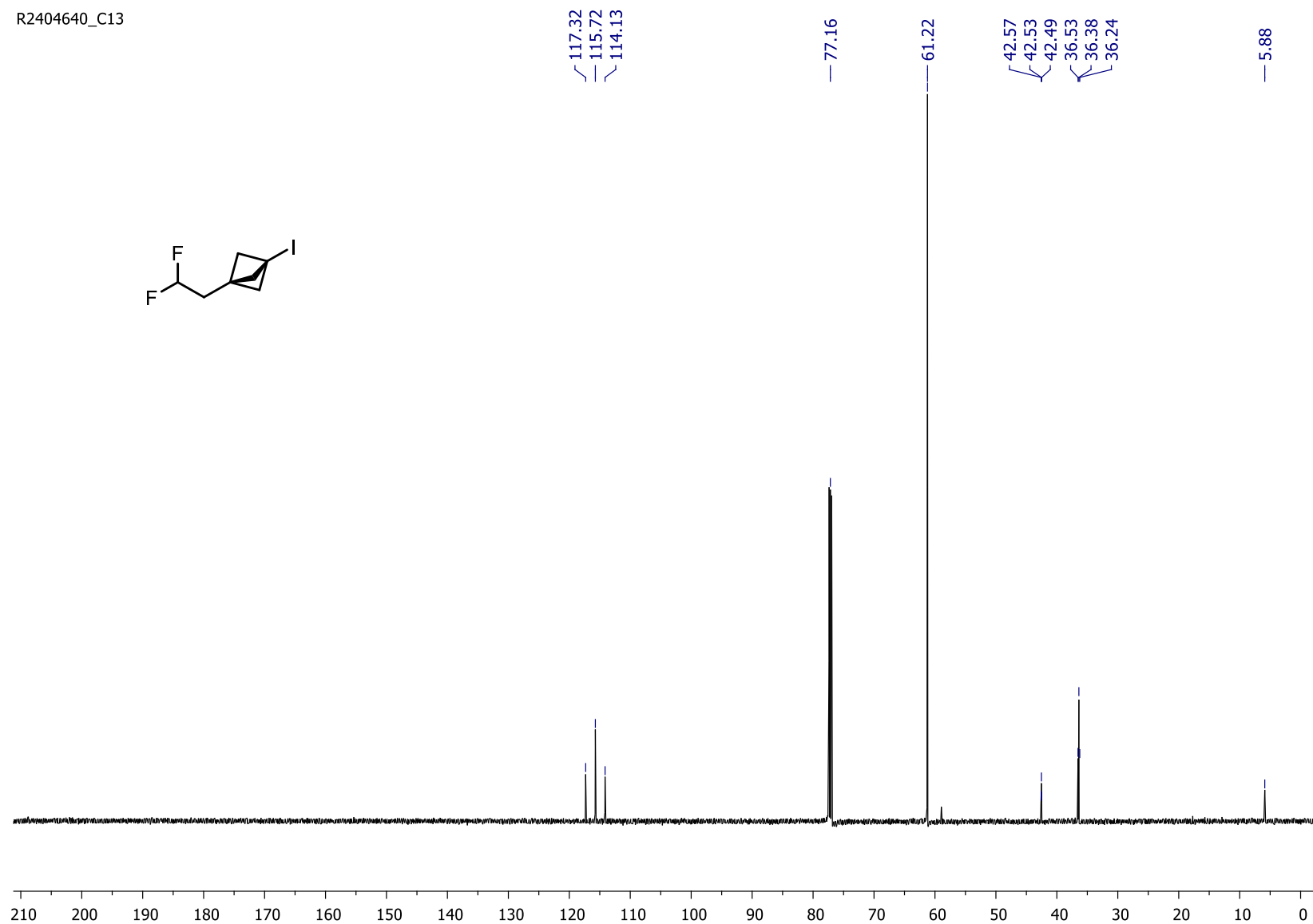
R2404640

¹H NMR (400 MHz, CDCl₃)



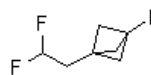
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

R2404640_C13

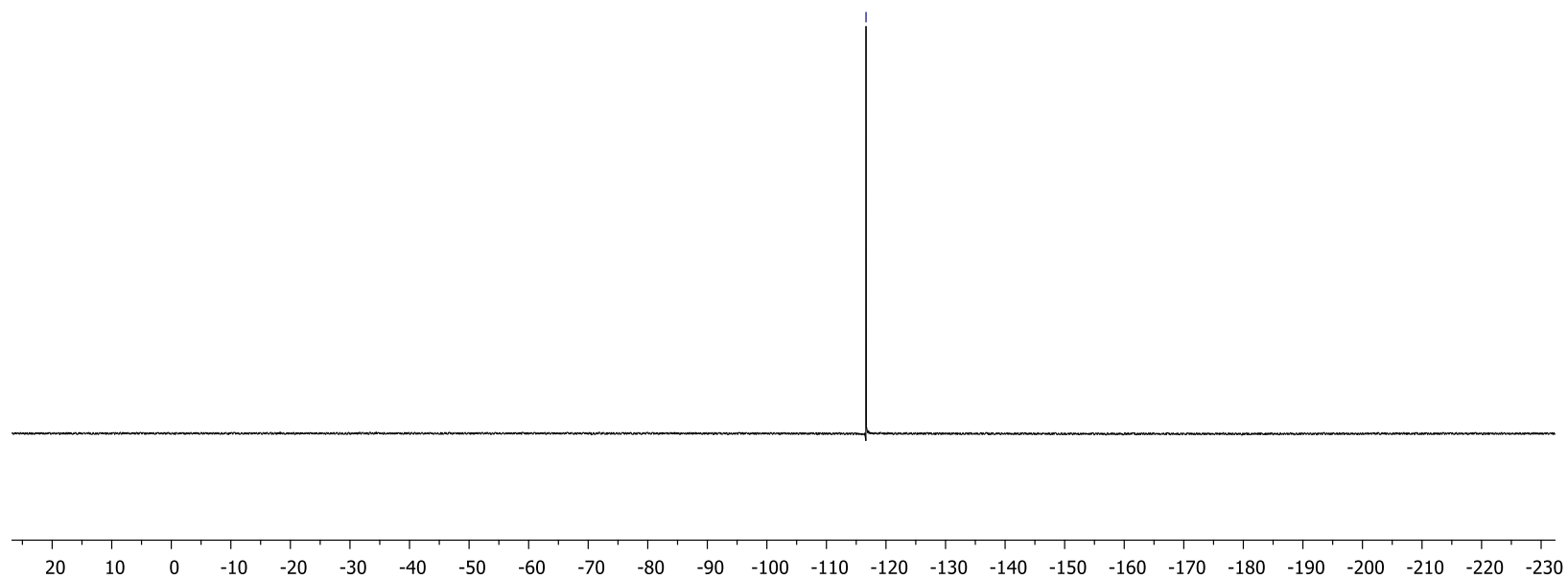


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R1826468_F19
 $^{19}\text{F}\{^1\text{H}\}$

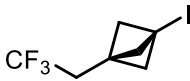


— -116.65

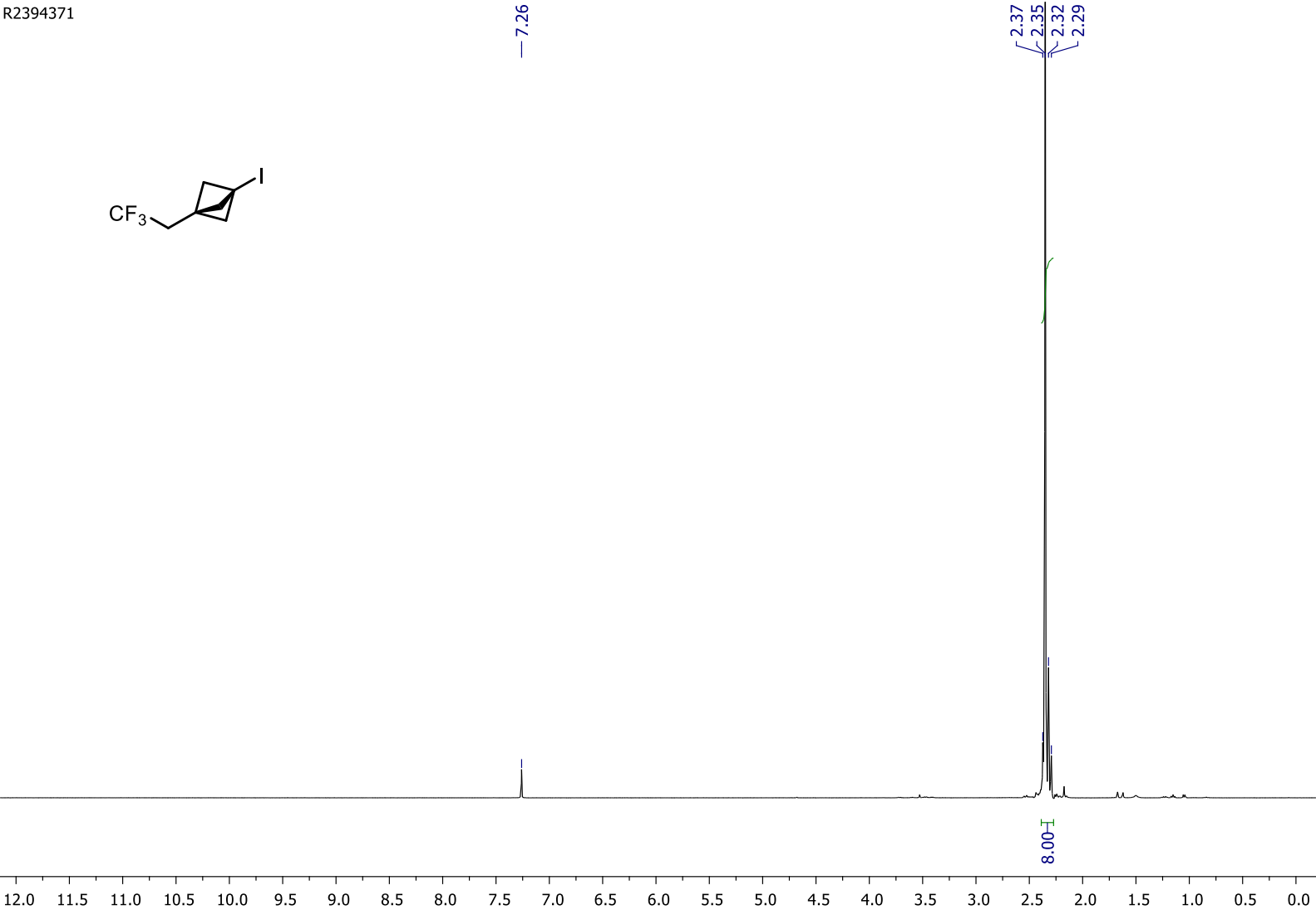


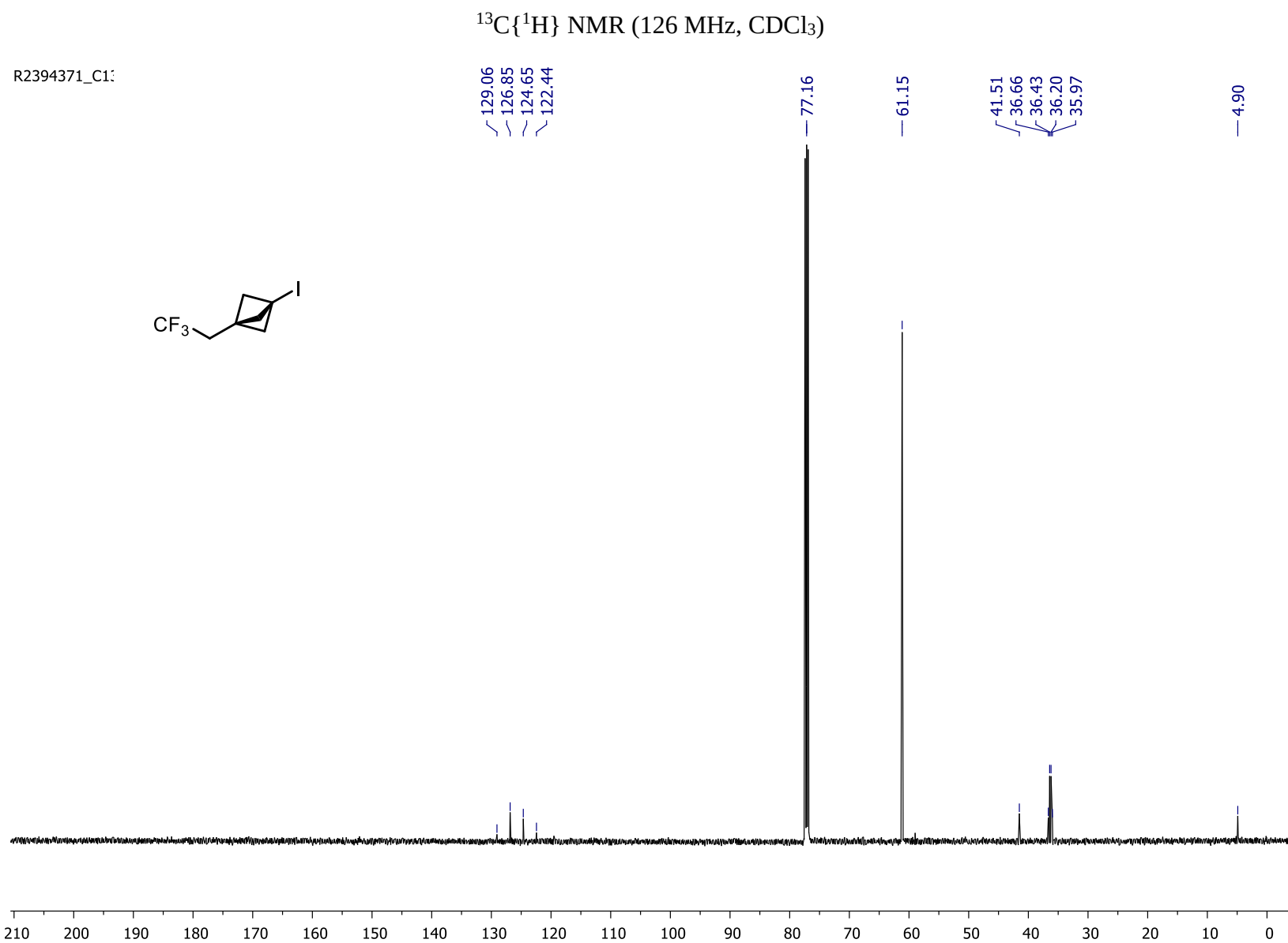
Compound 25

R2394371



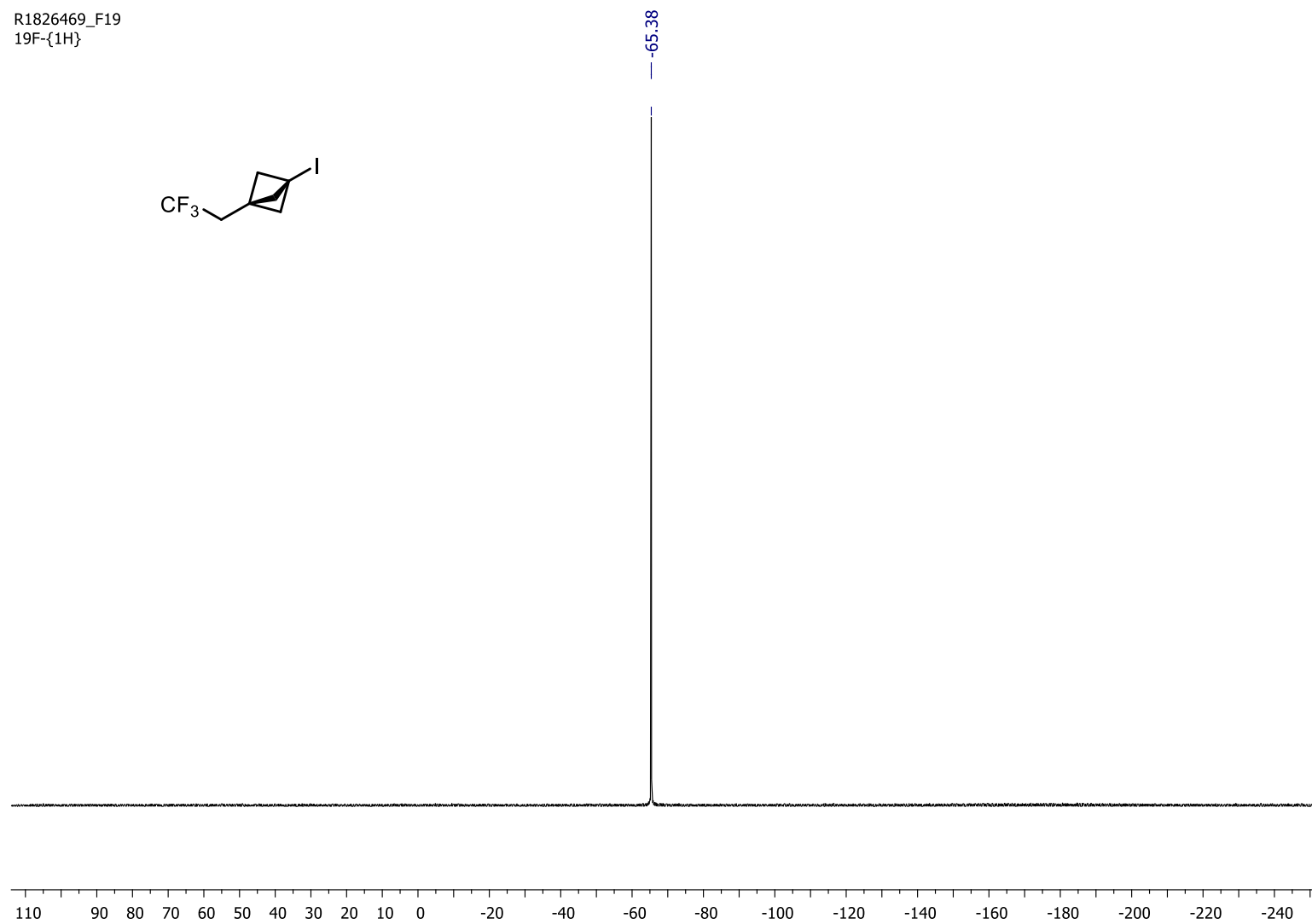
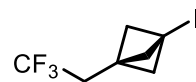
¹H NMR (400 MHz, CDCl₃)





$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

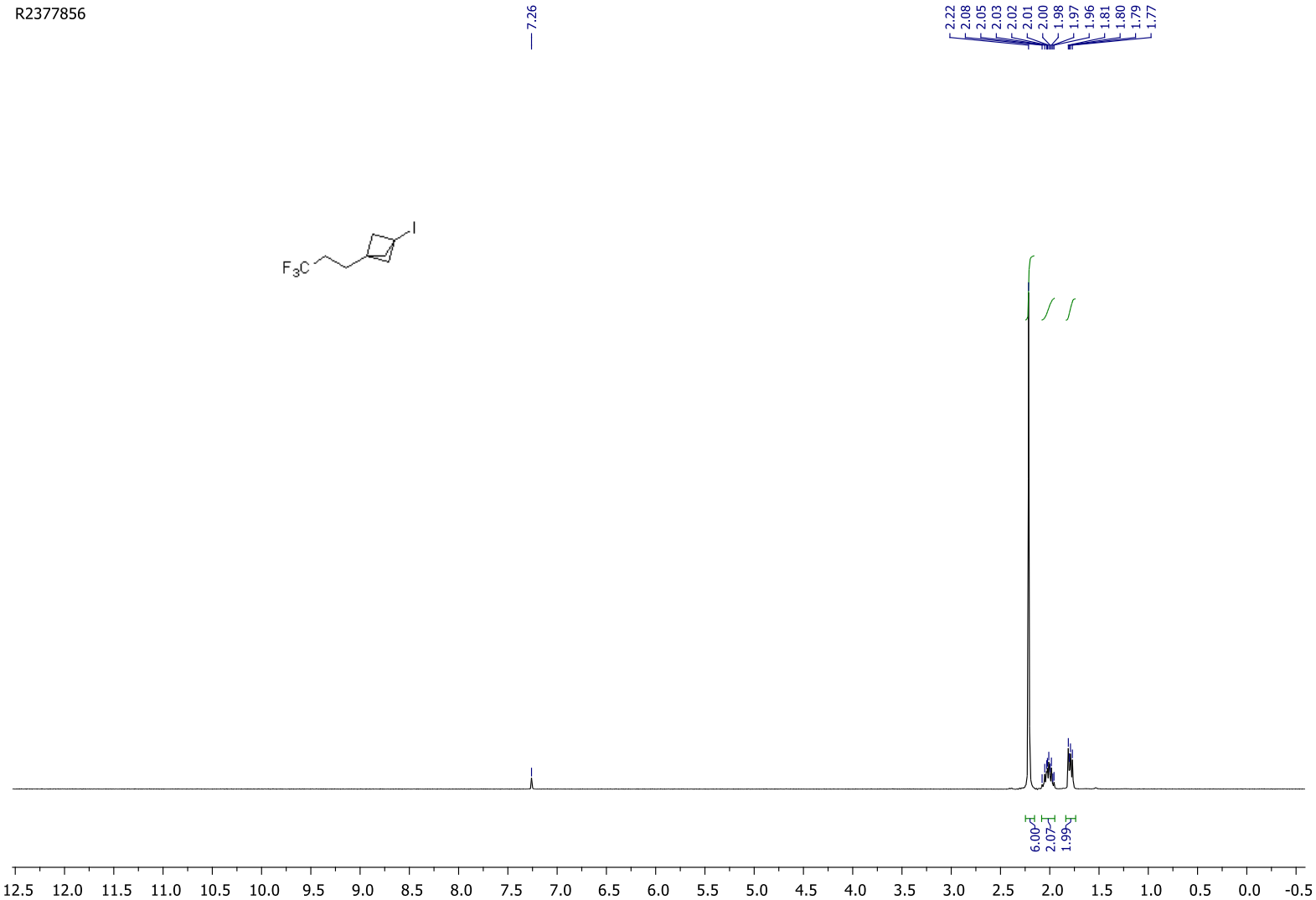
R1826469_F19
 $^{19}\text{F}\{^1\text{H}\}$



Compound 26

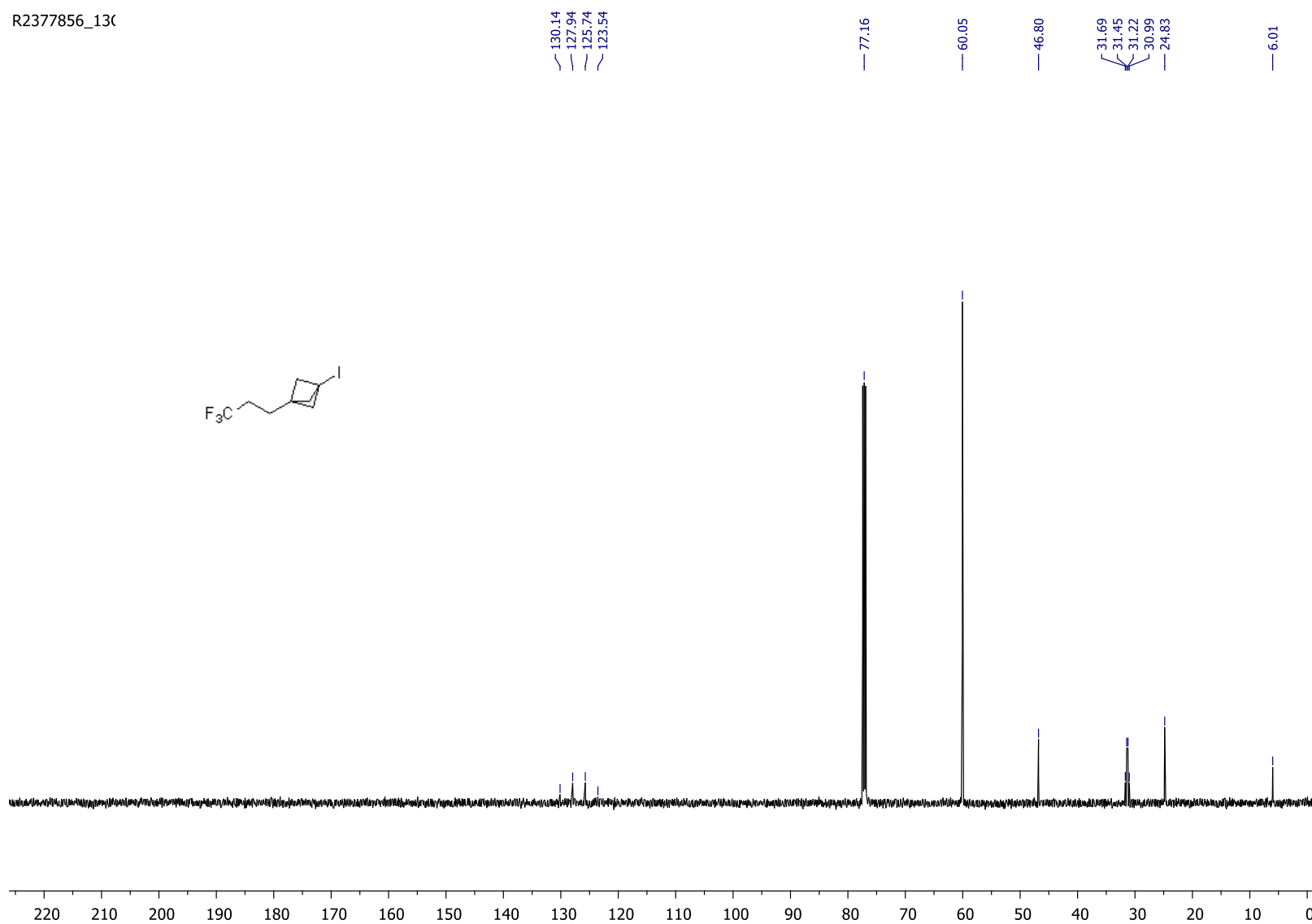
R2377856

¹H NMR (400 MHz, CDCl₃)



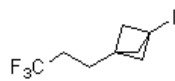
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2377856_13C

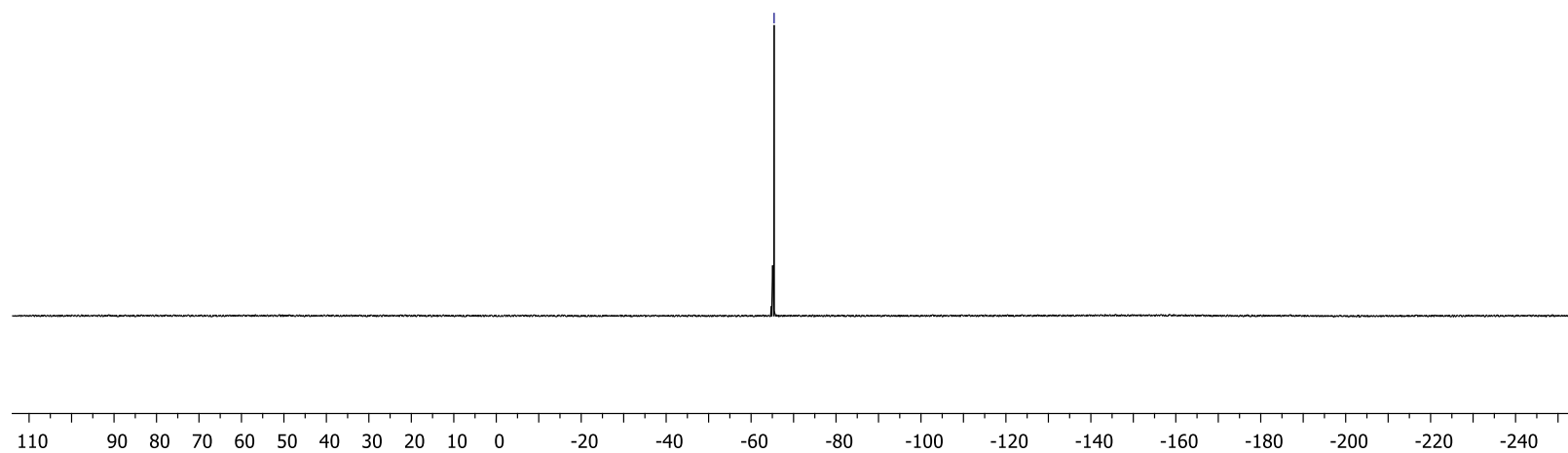


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2377856_F19{H}



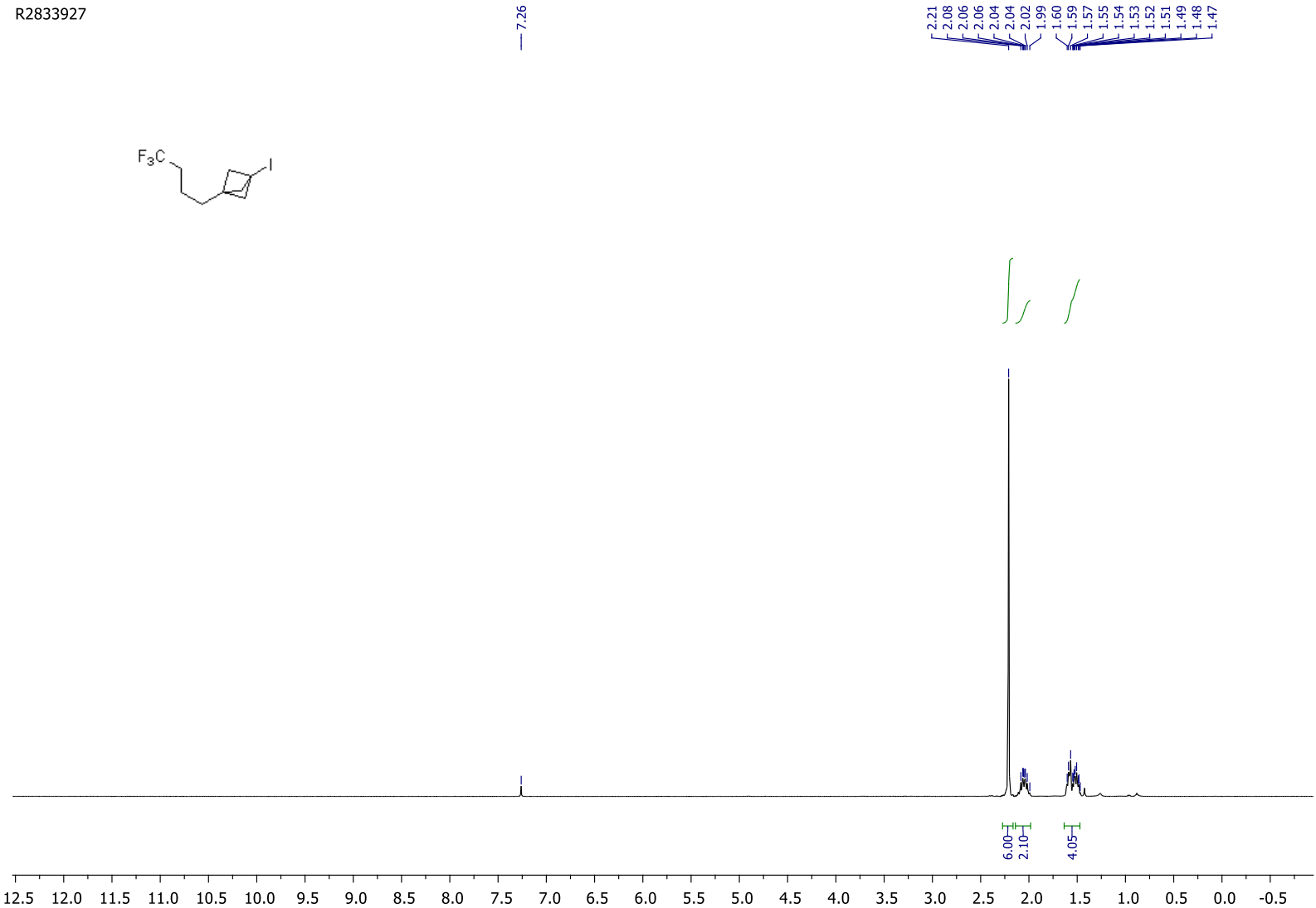
— -65.43



Compound 27

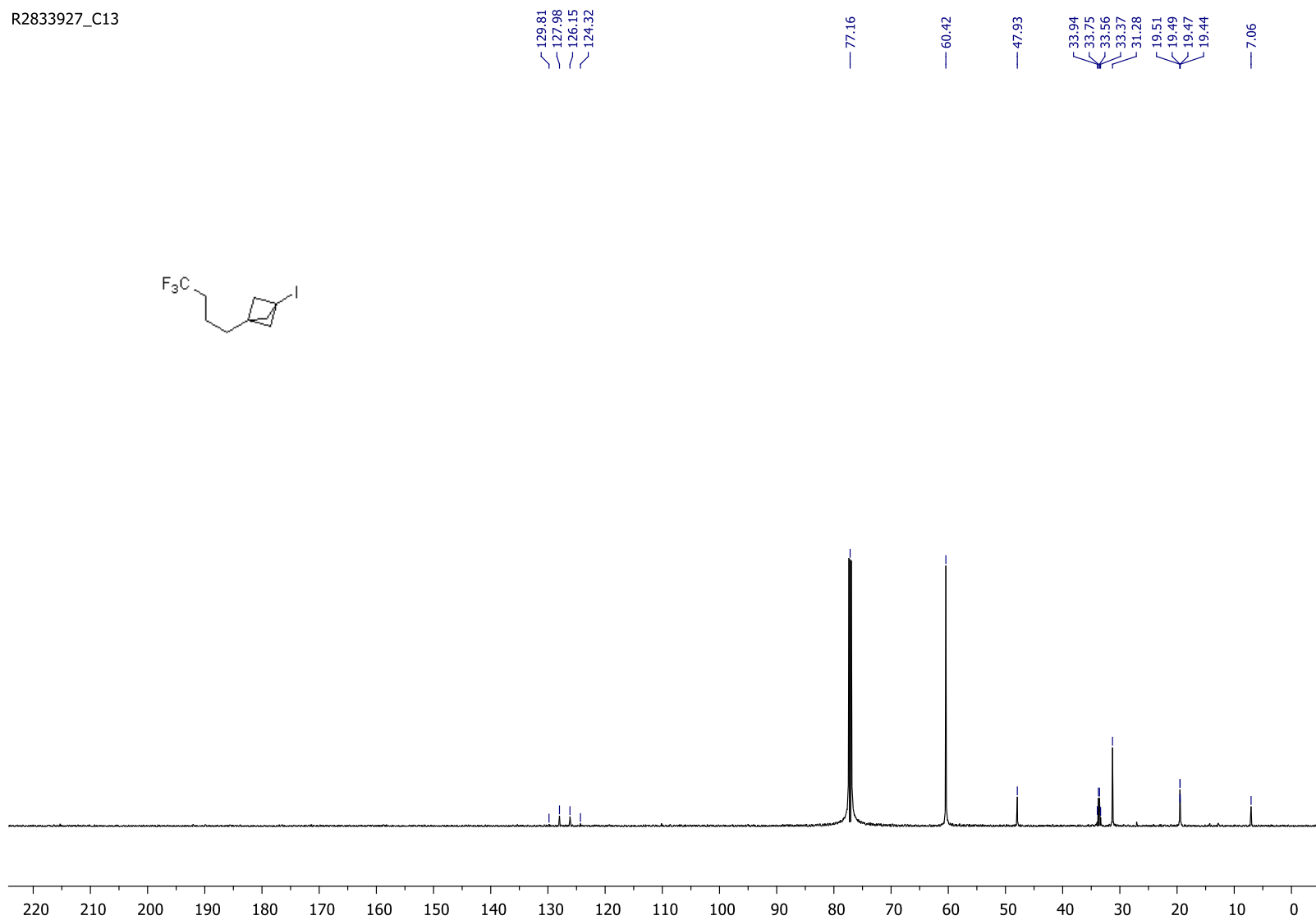
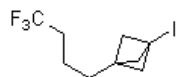
R2833927

¹H NMR (400 MHz, CDCl₃)



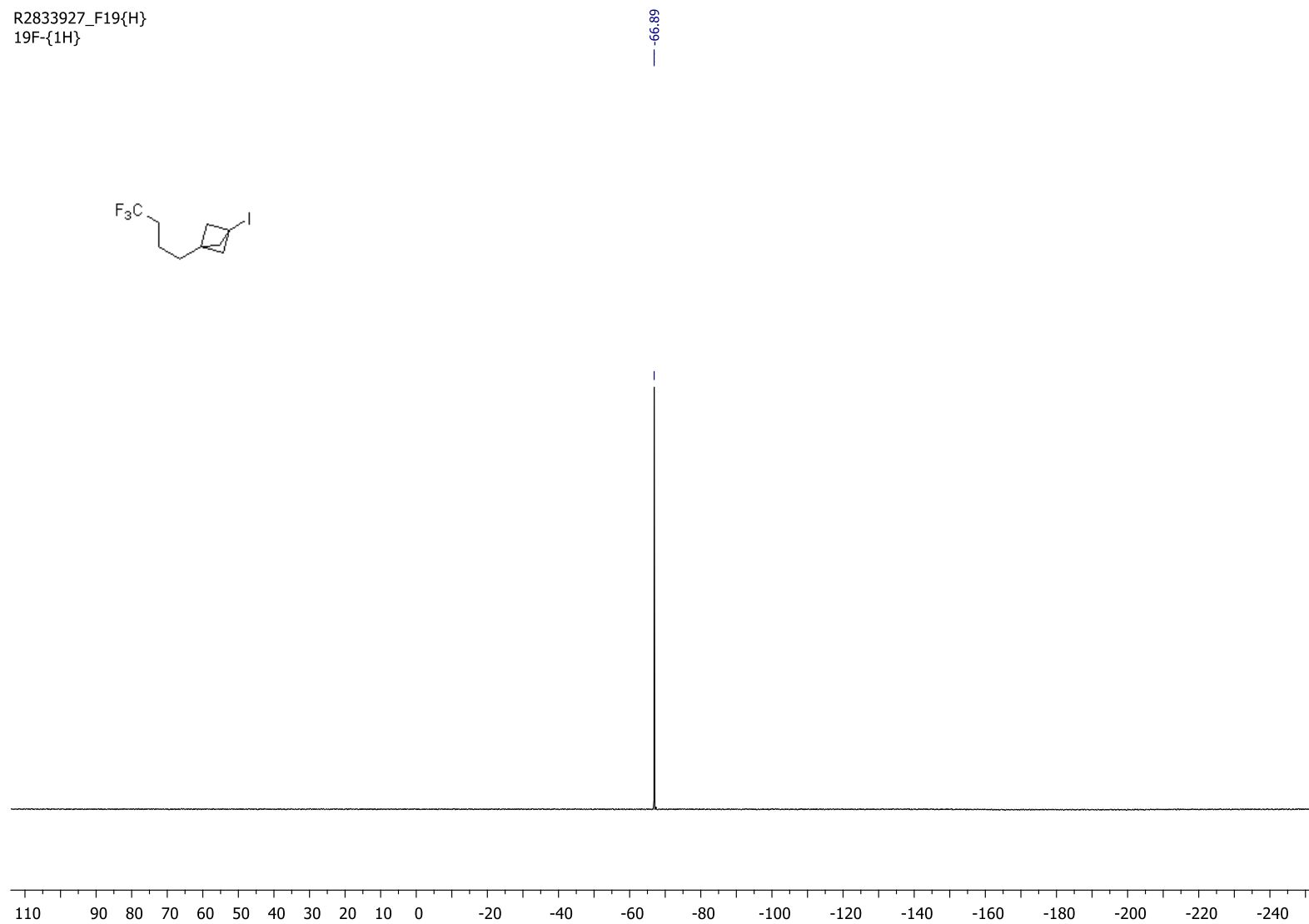
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

R2833927_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

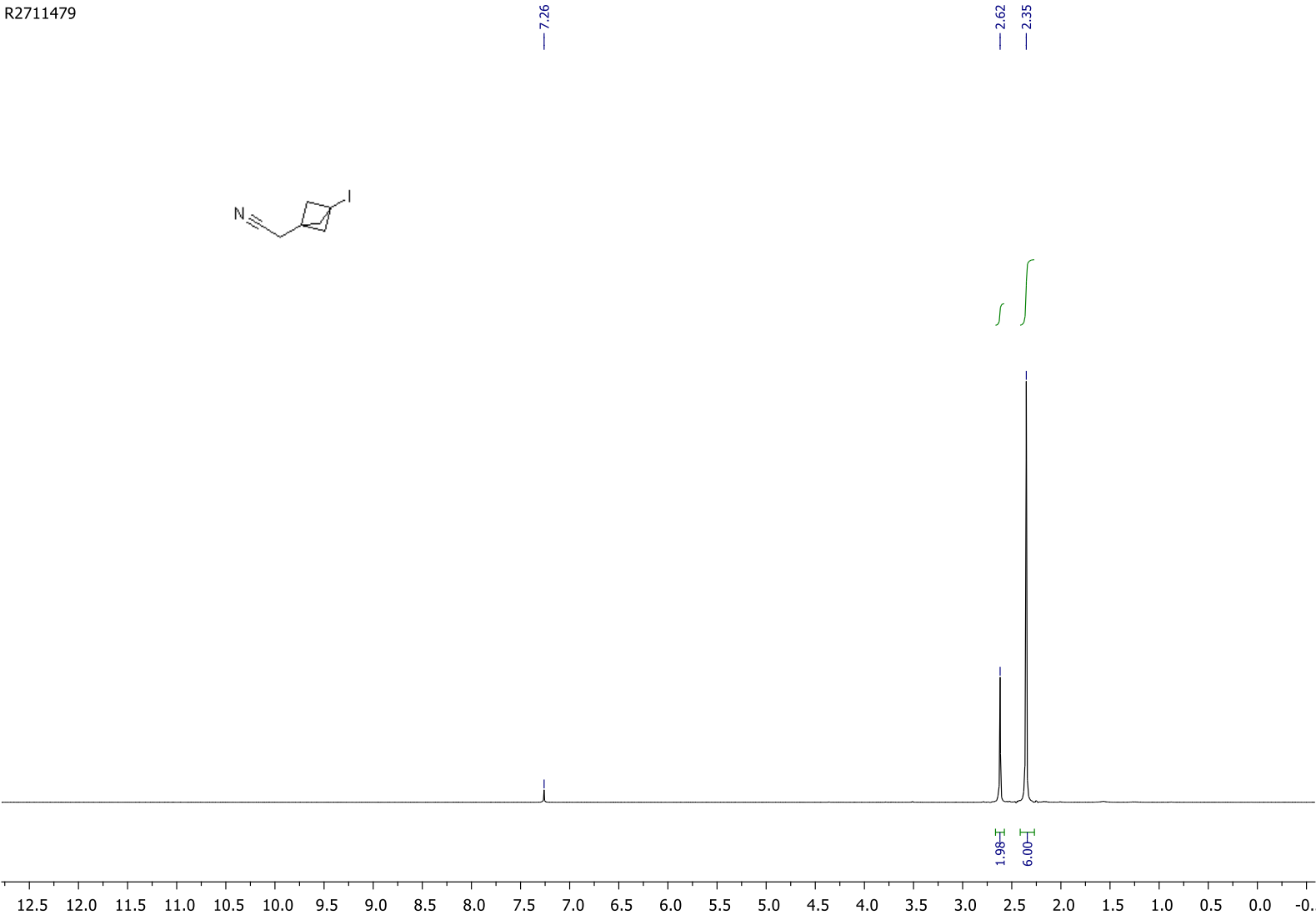
R2833927_F19{H}
19F-{1H}



Compound 28

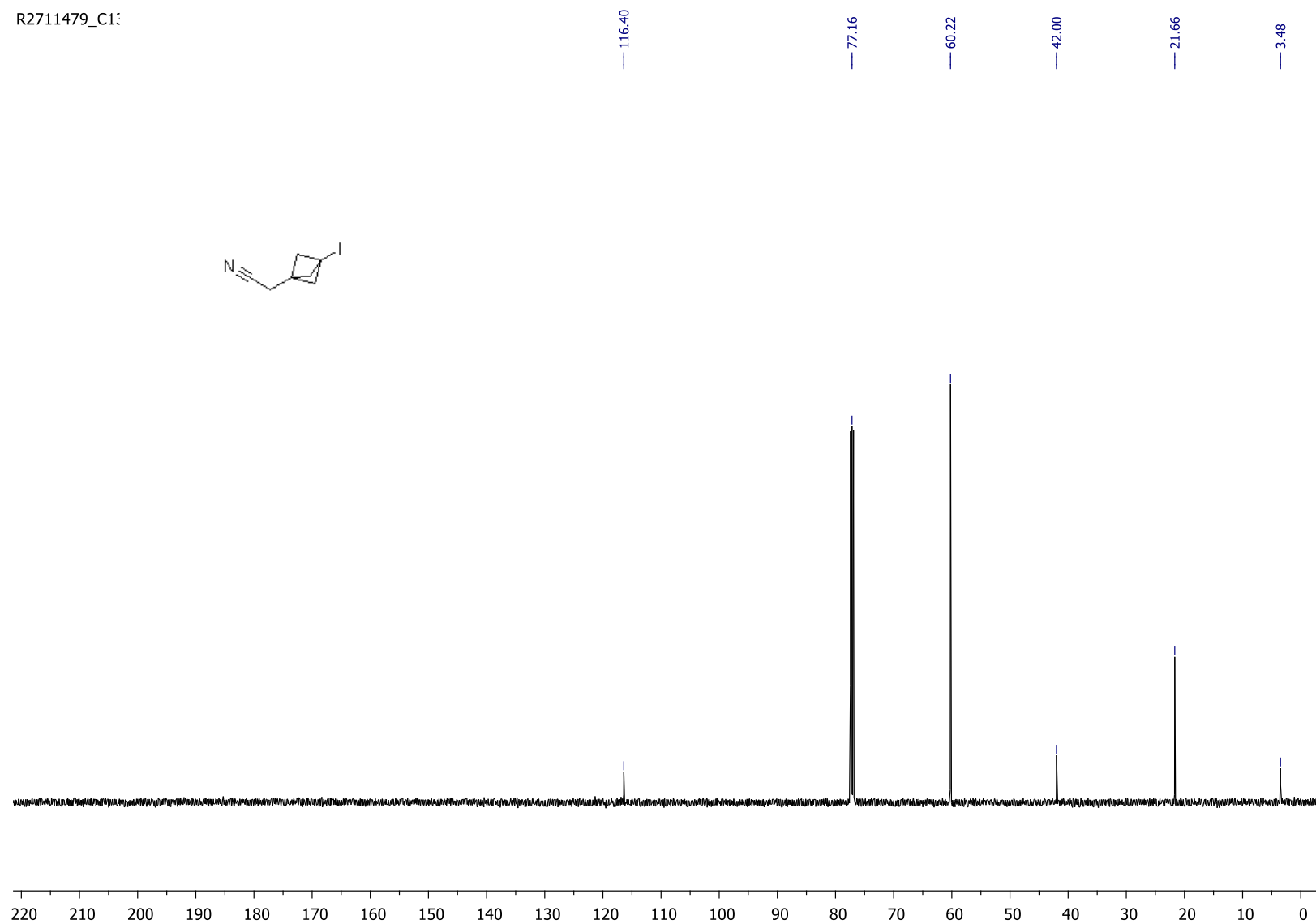
R2711479

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

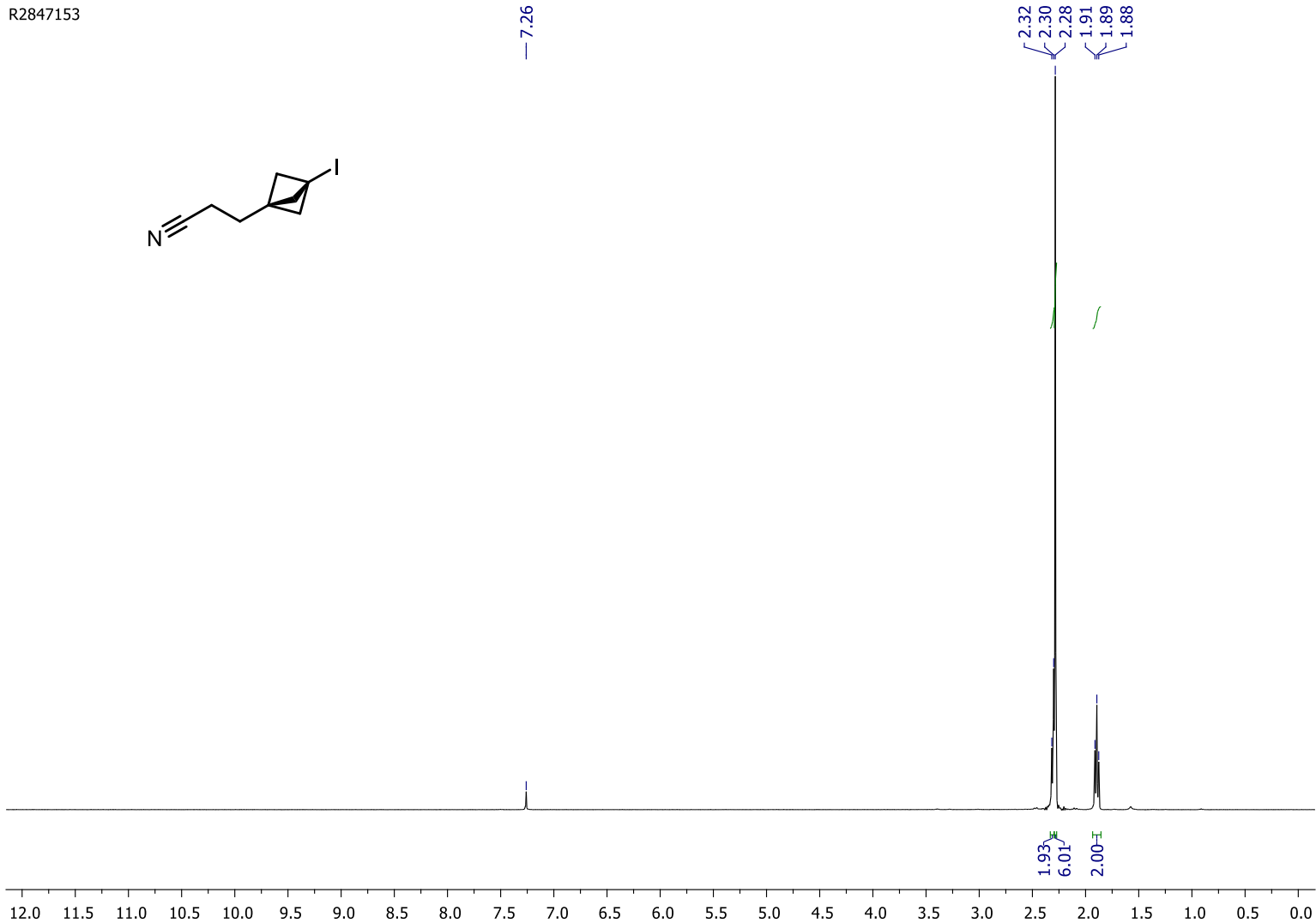
R2711479_C13

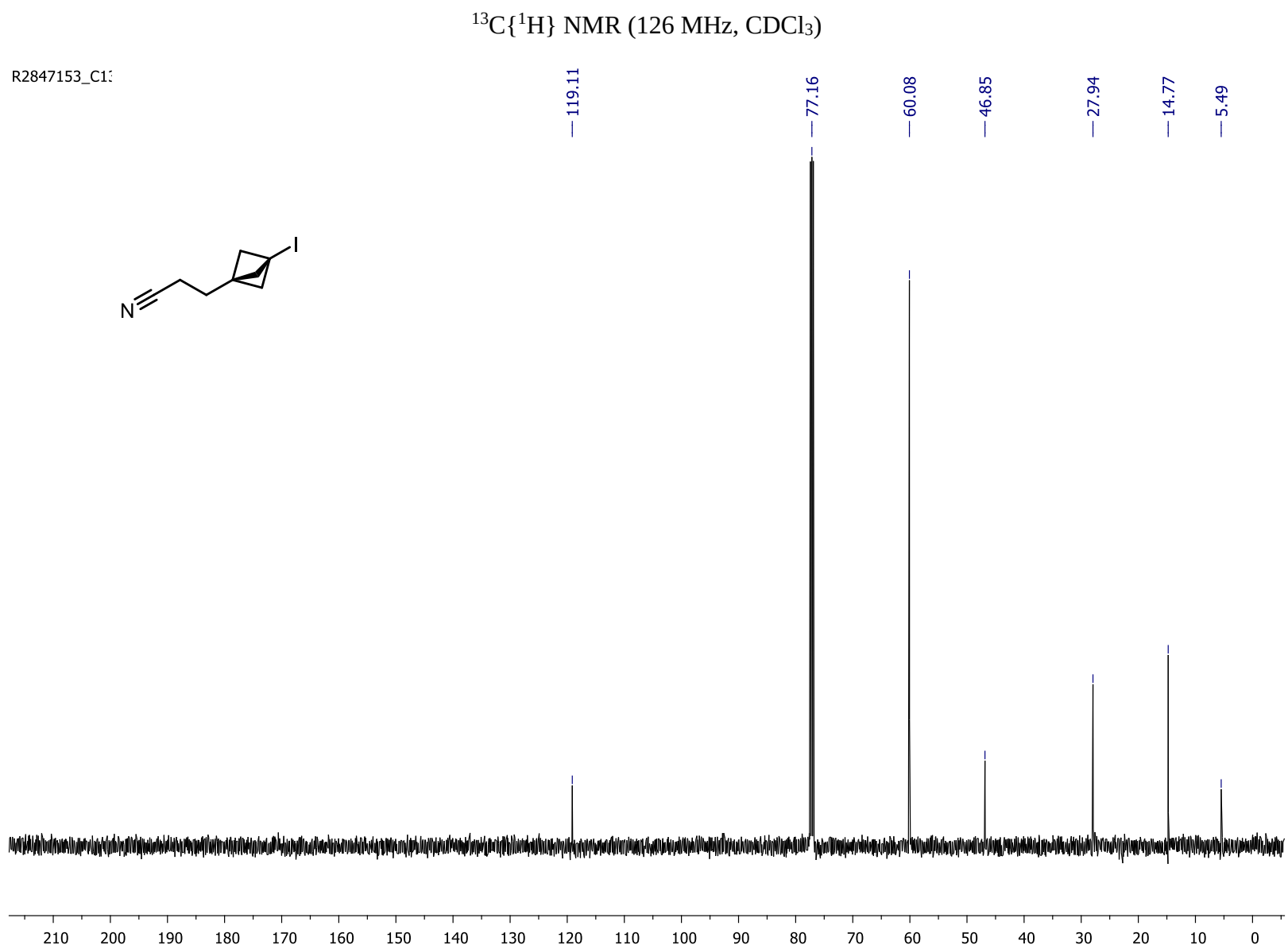


Compound 29

R2847153

¹H NMR (400 MHz, CDCl₃)

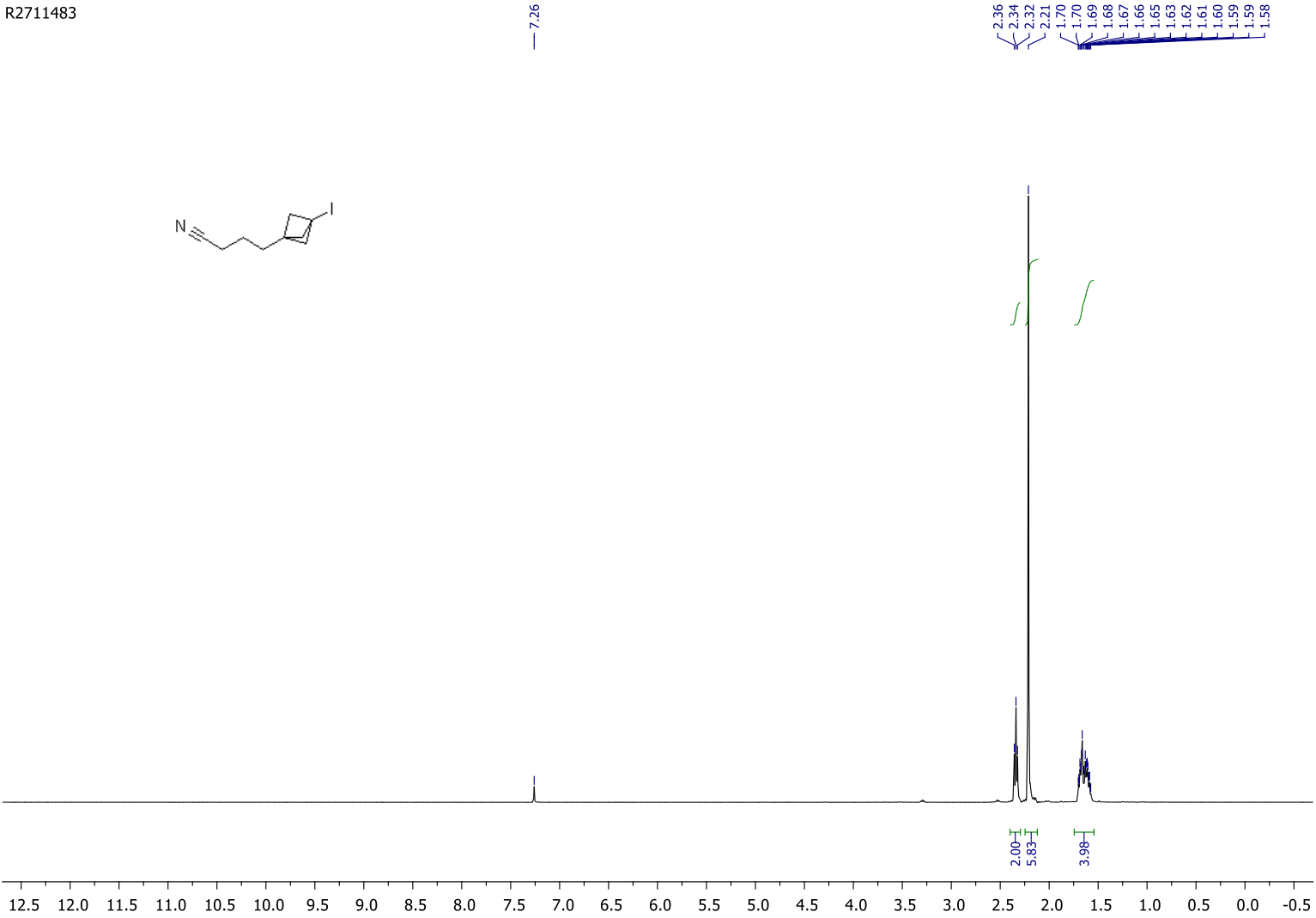


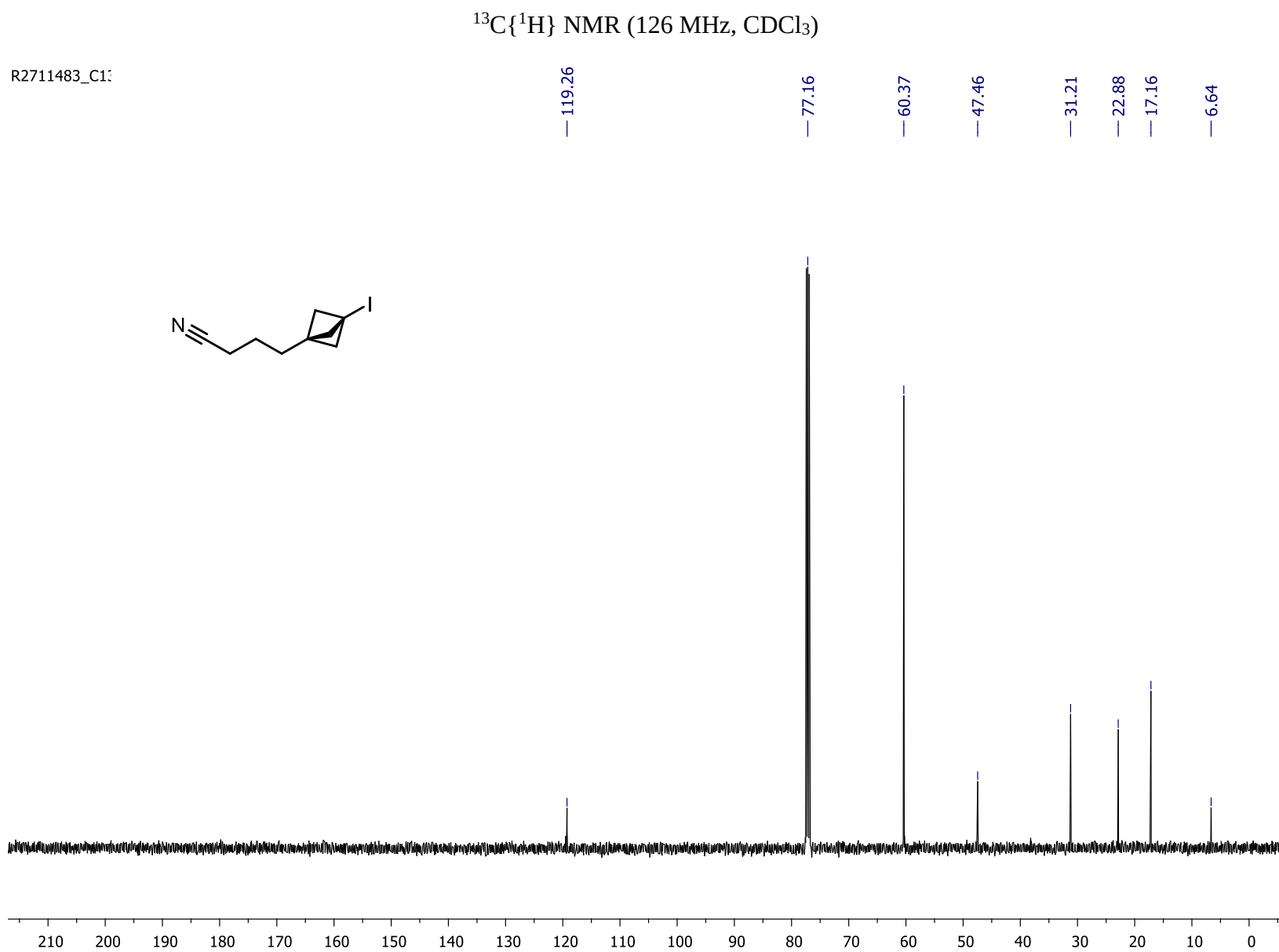


Compound 30

R2711483

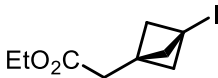
¹H NMR (400 MHz, CDCl₃)



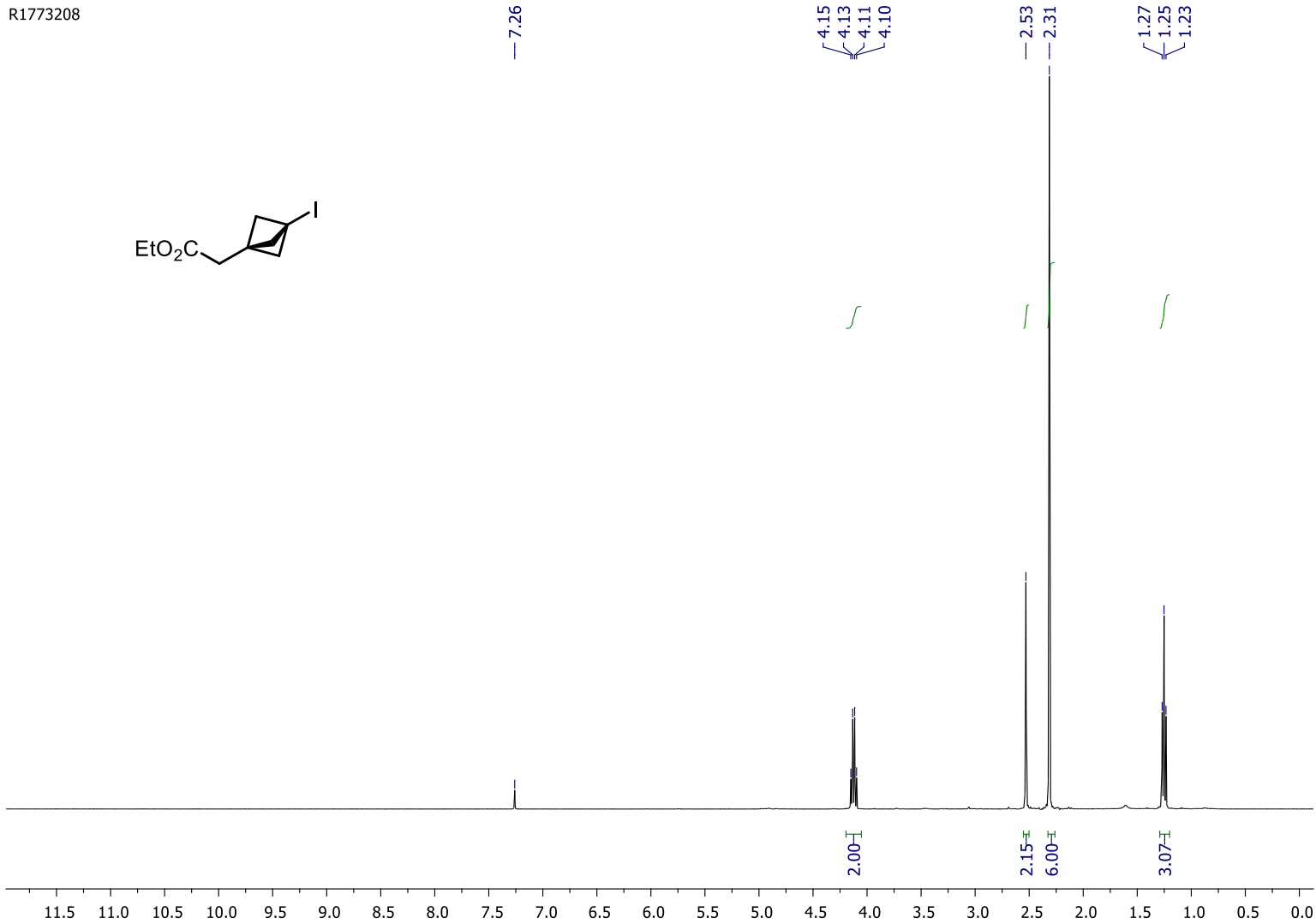


Compound 31

R1773208

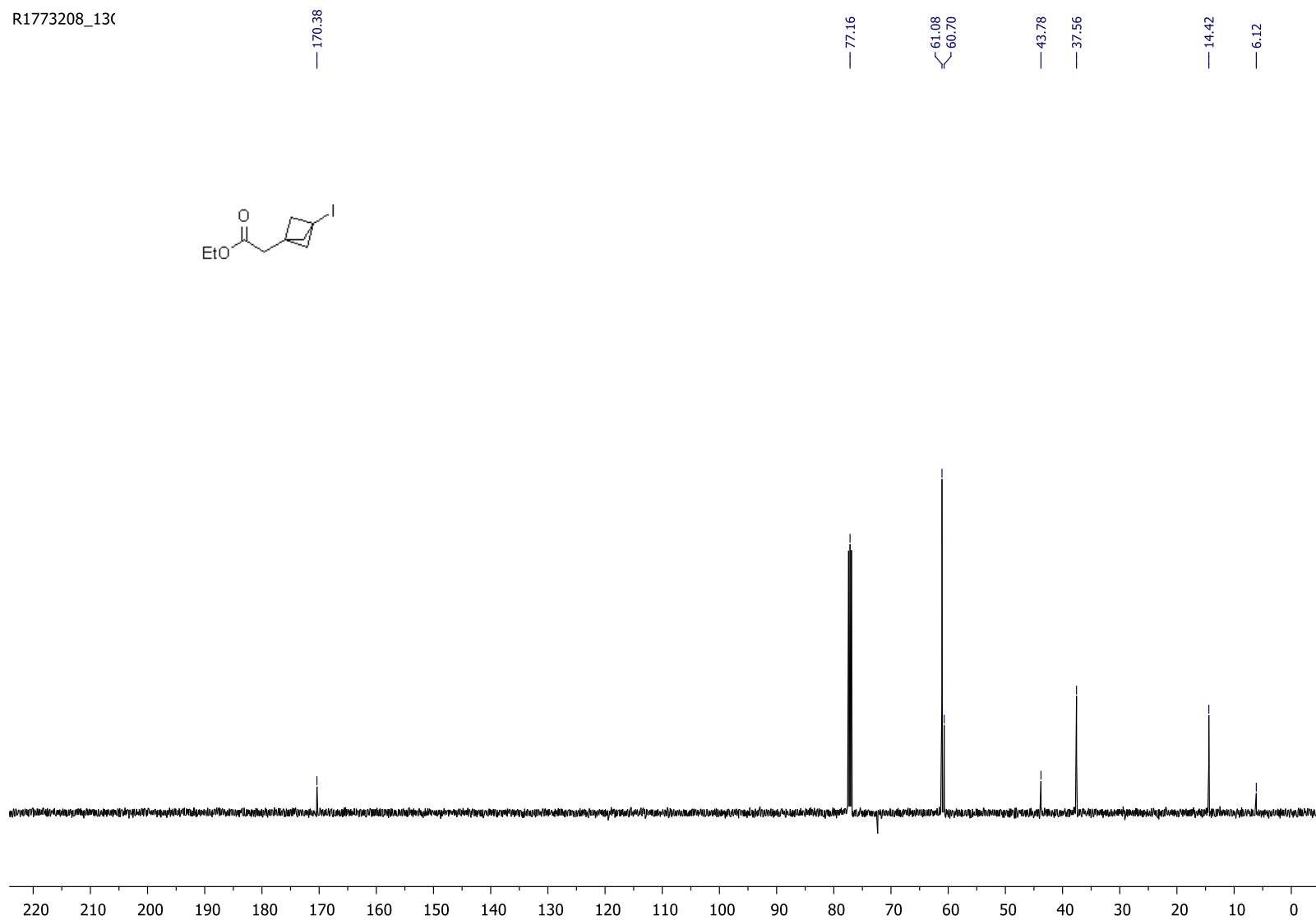
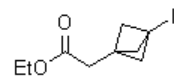


¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

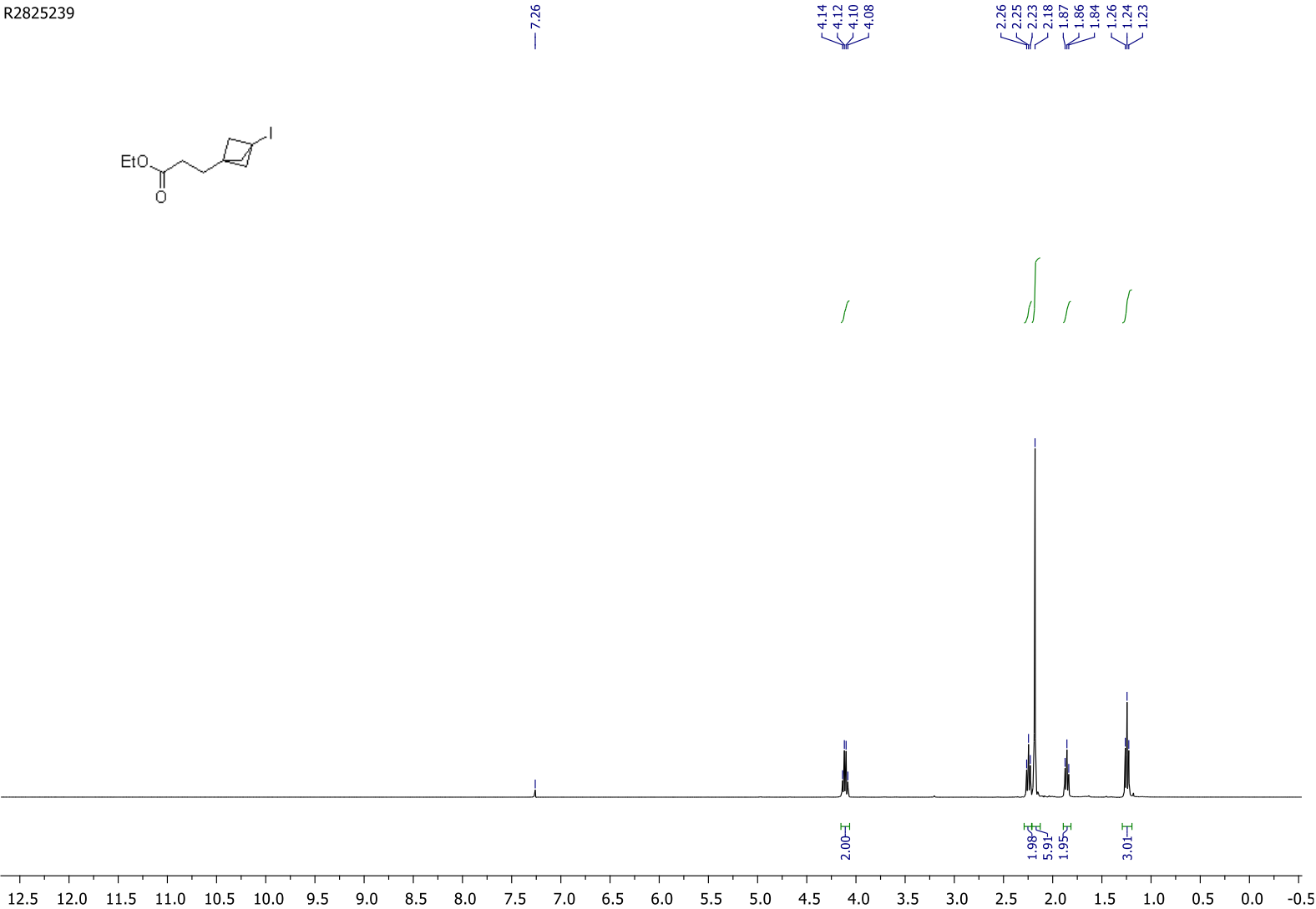
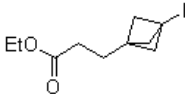
R1773208_13C



Compound 32

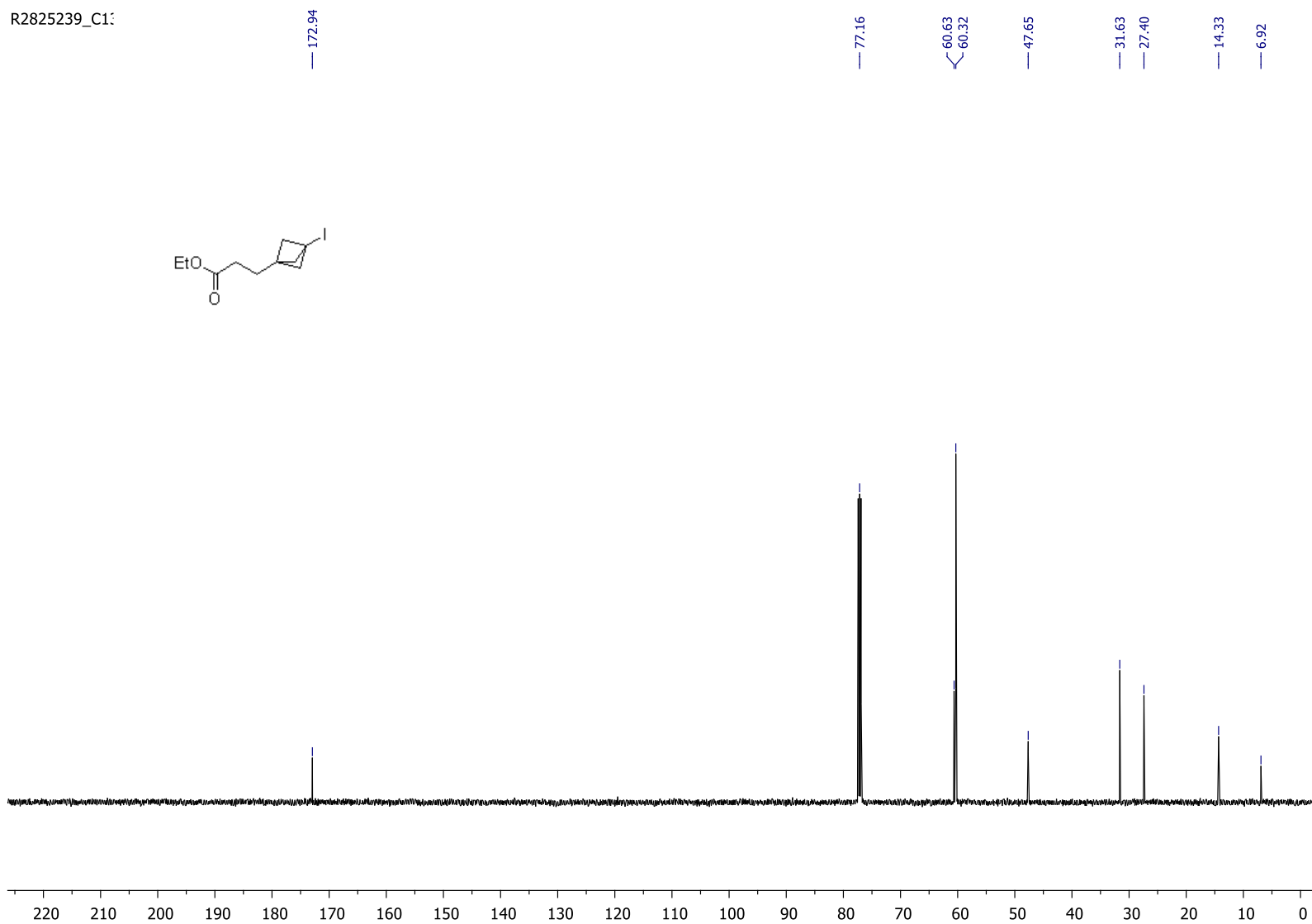
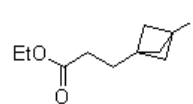
R2825239

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

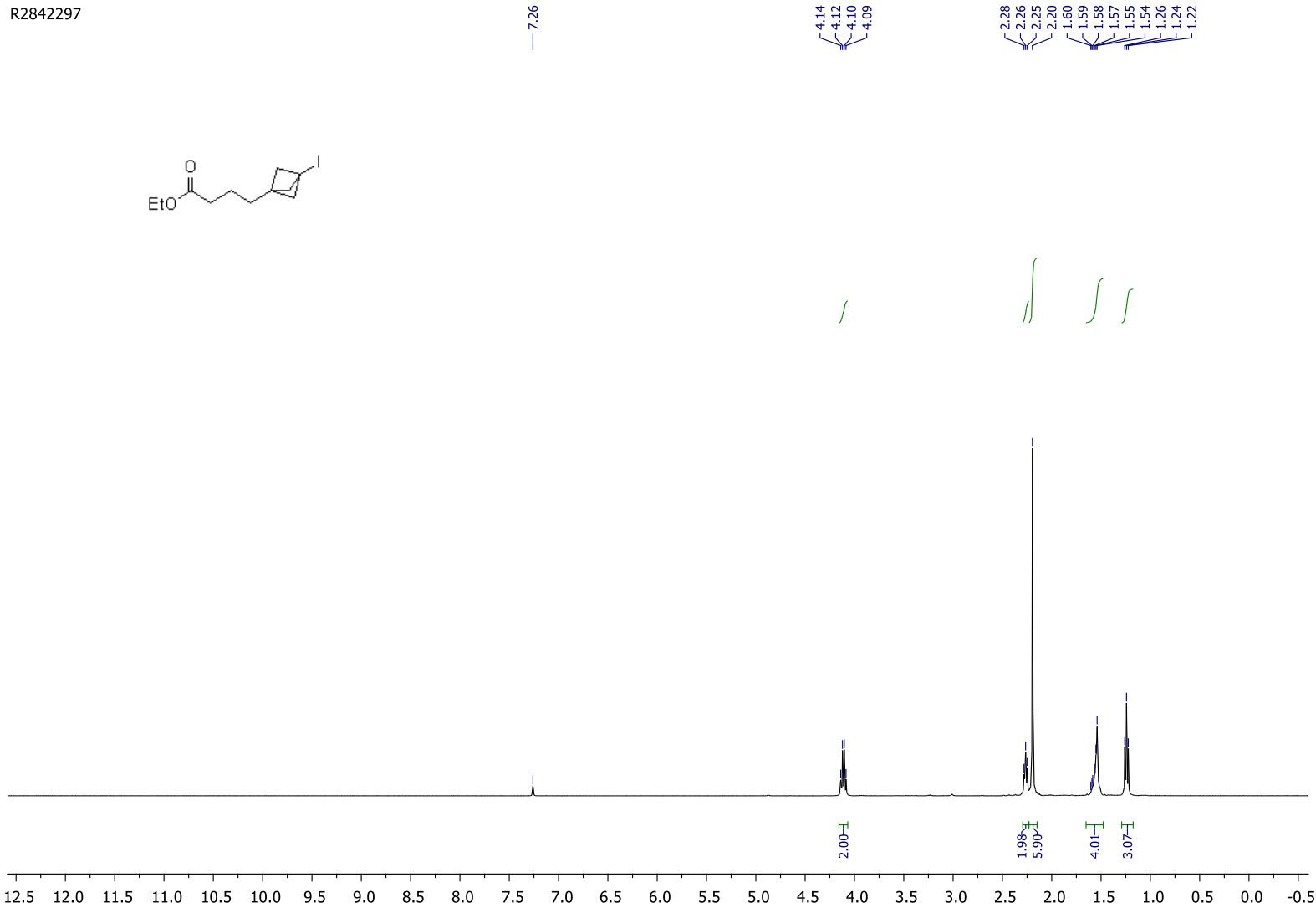
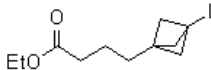
R2825239_C13



Compound 33

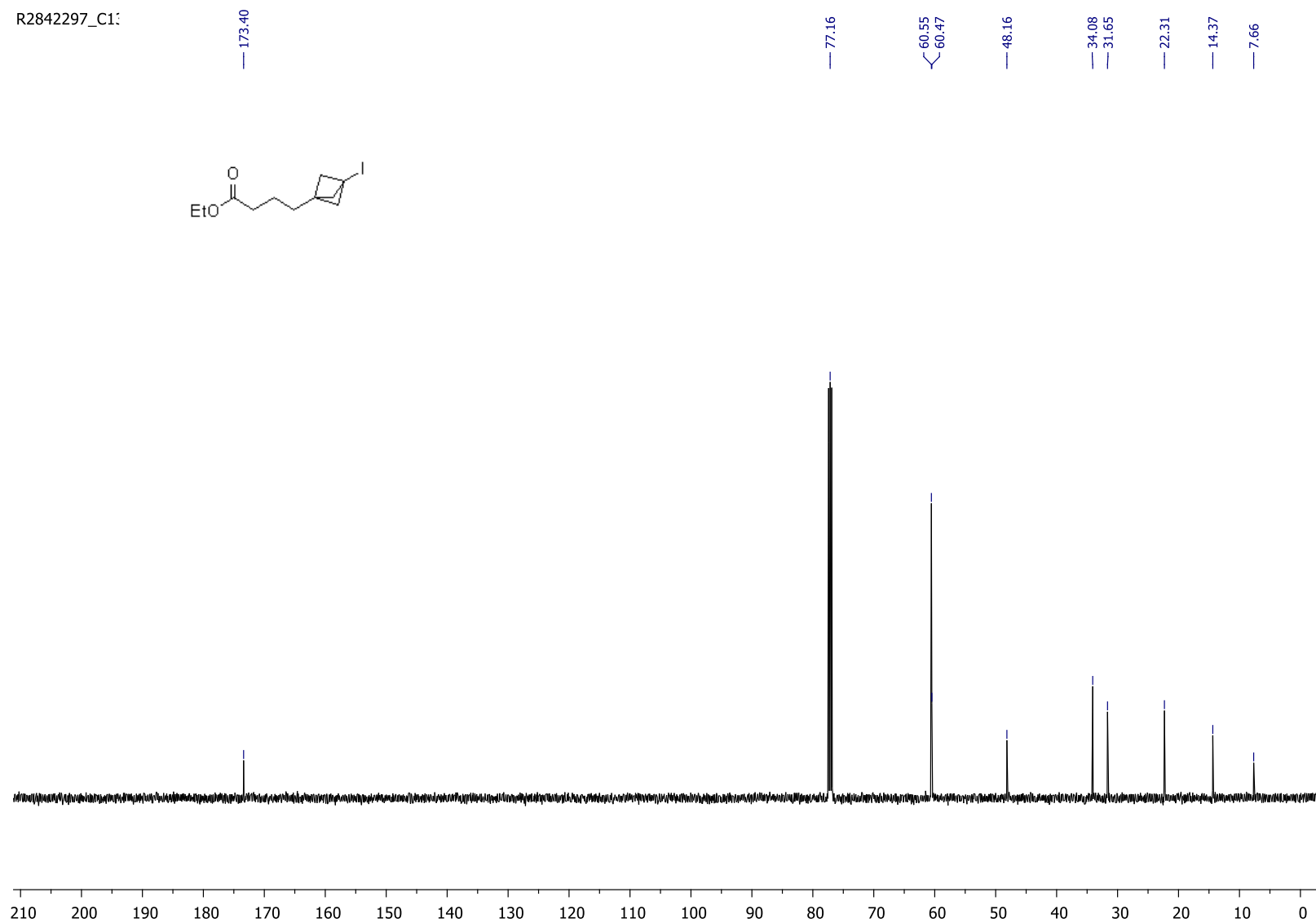
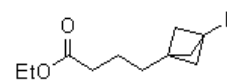
R2842297

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2842297_C1:

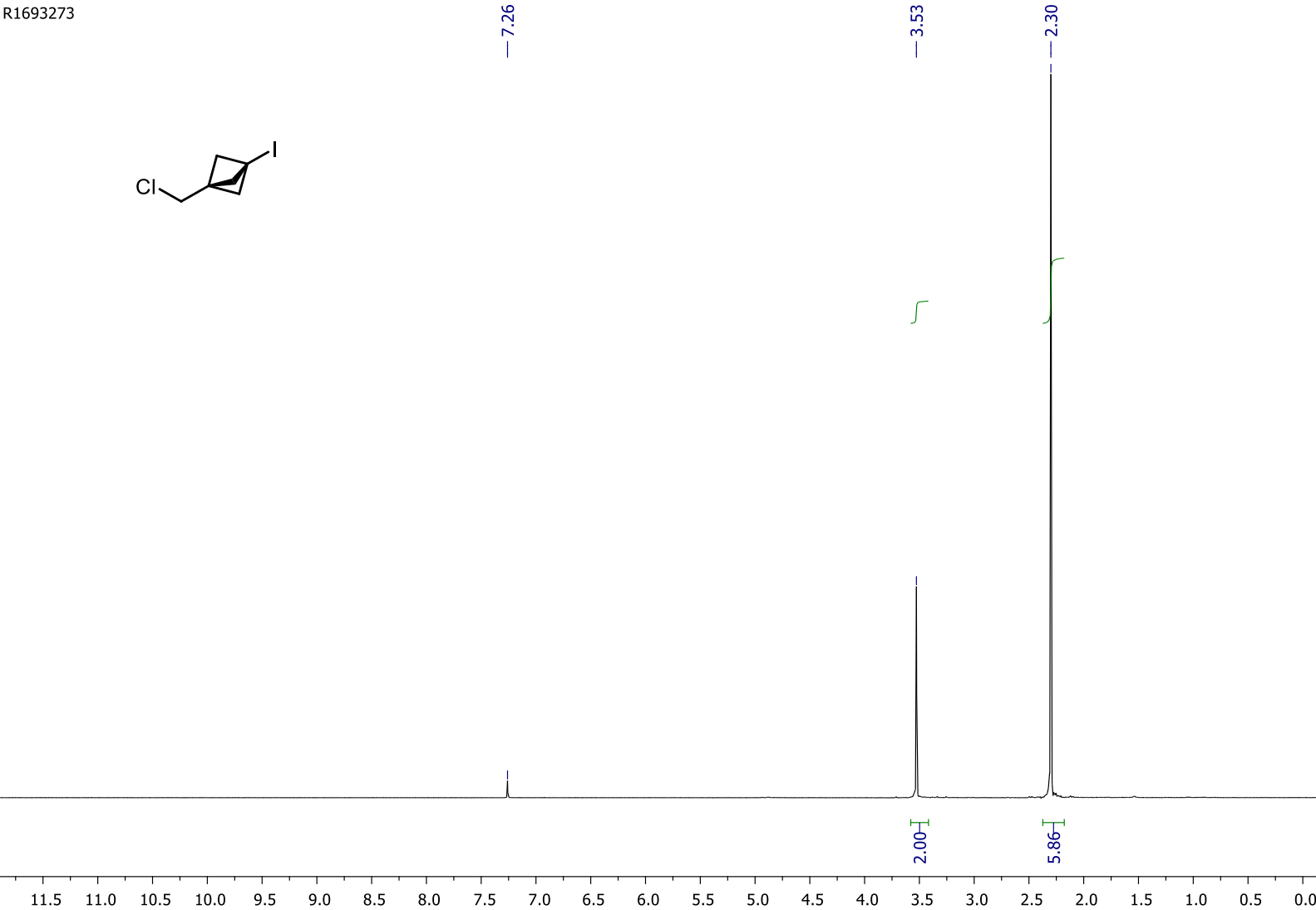


Compound 34

R1693273

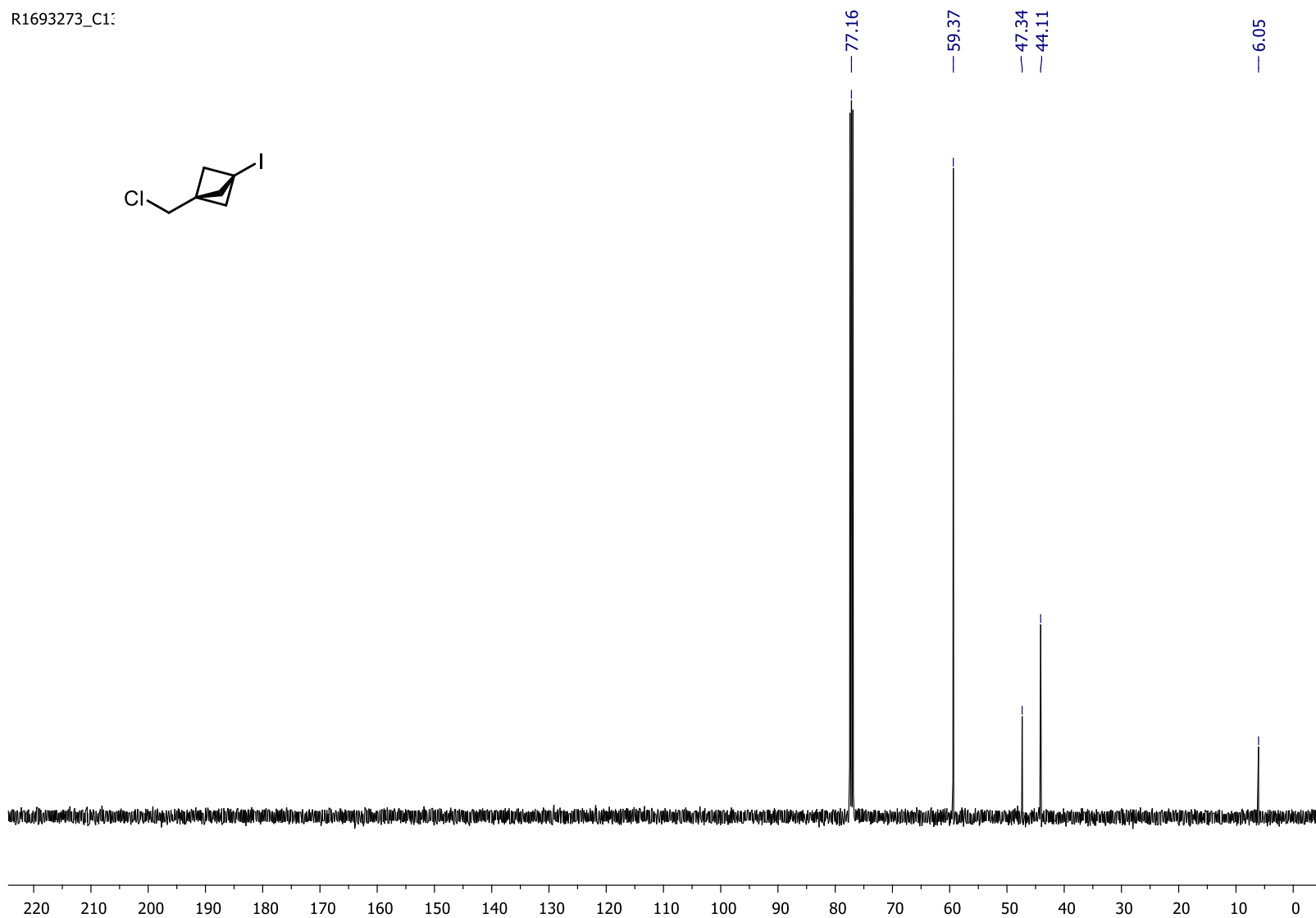


¹H NMR (400 MHz, CDCl₃)

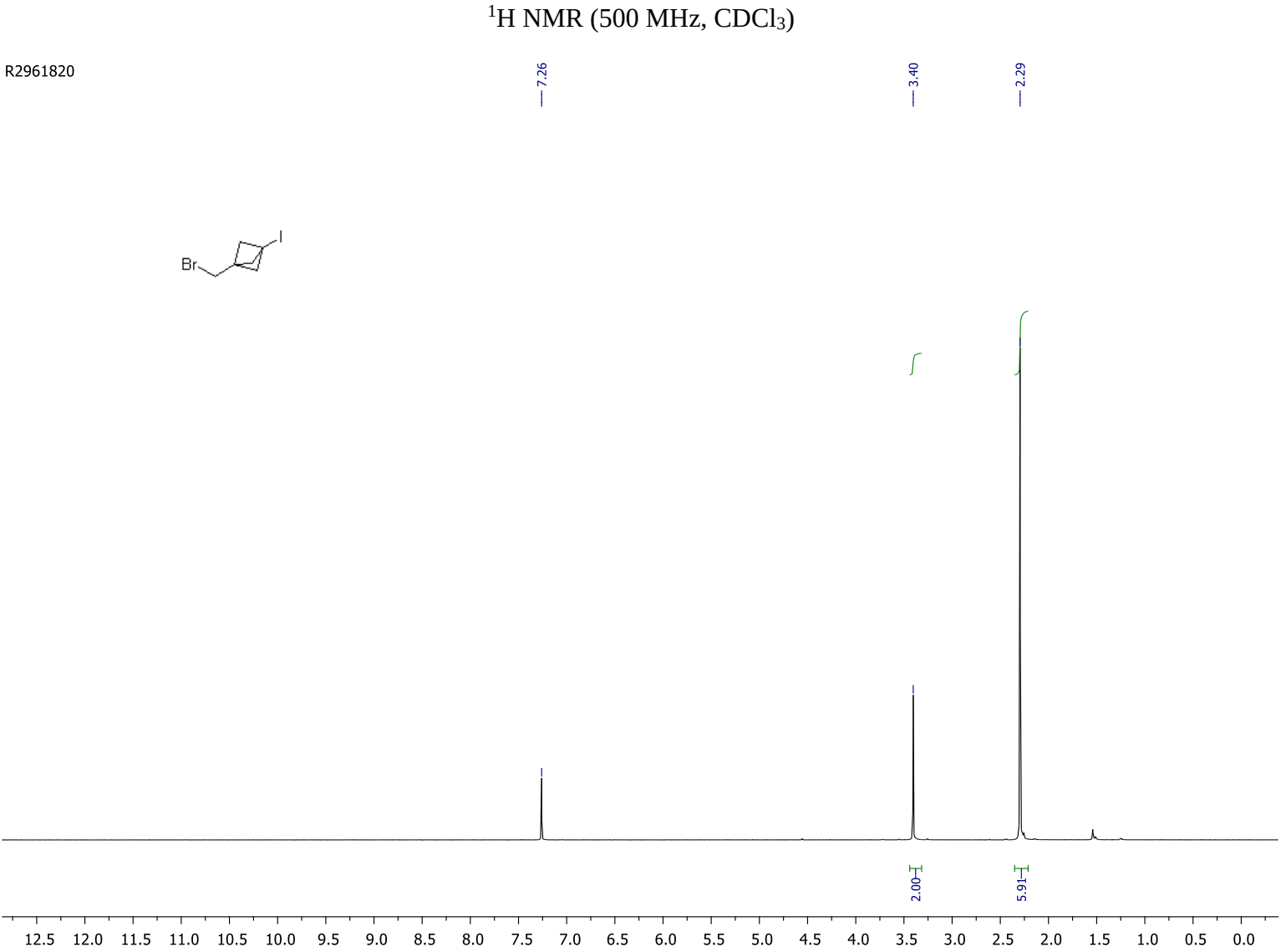


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R1693273_C1:

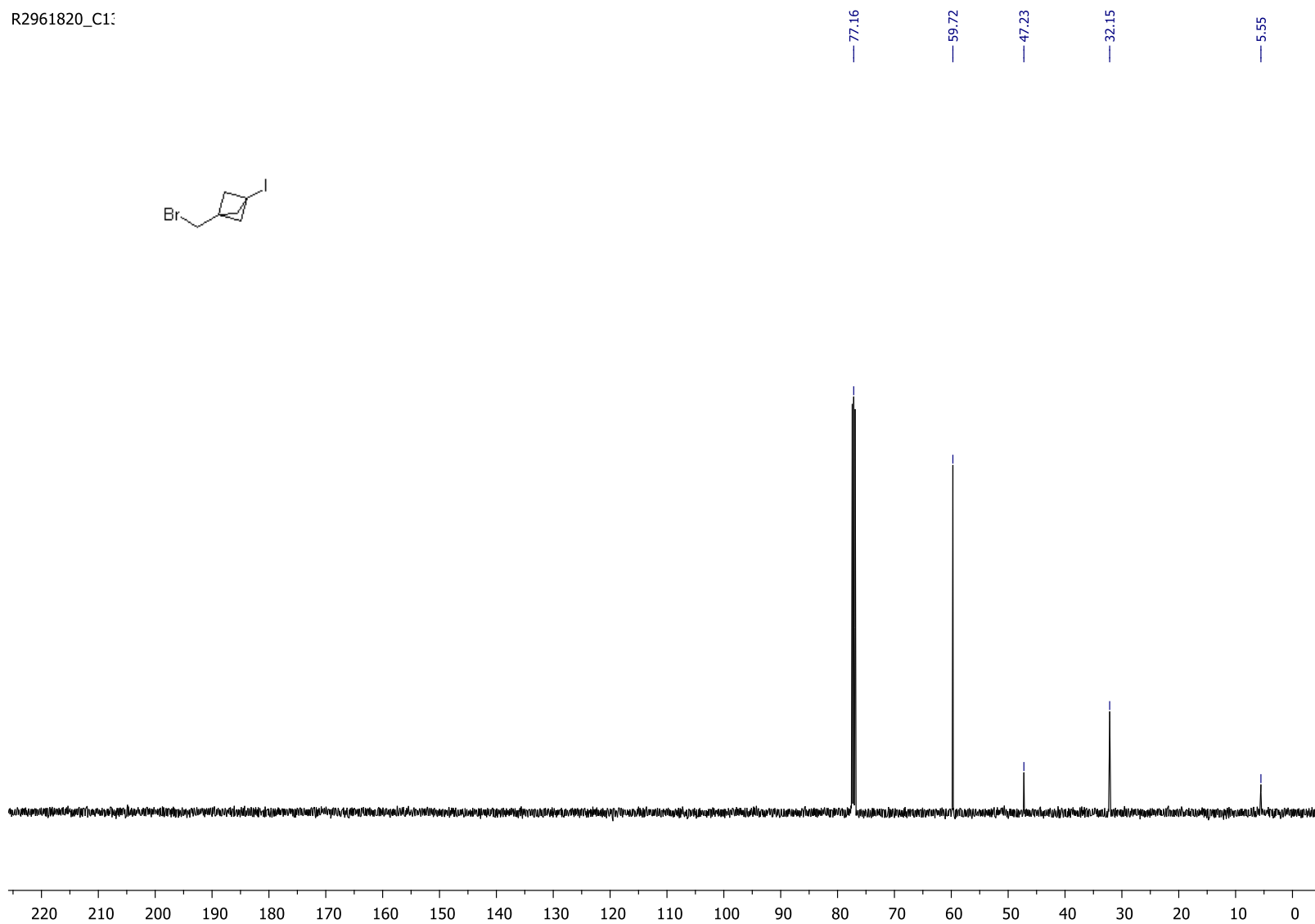


Compound 35

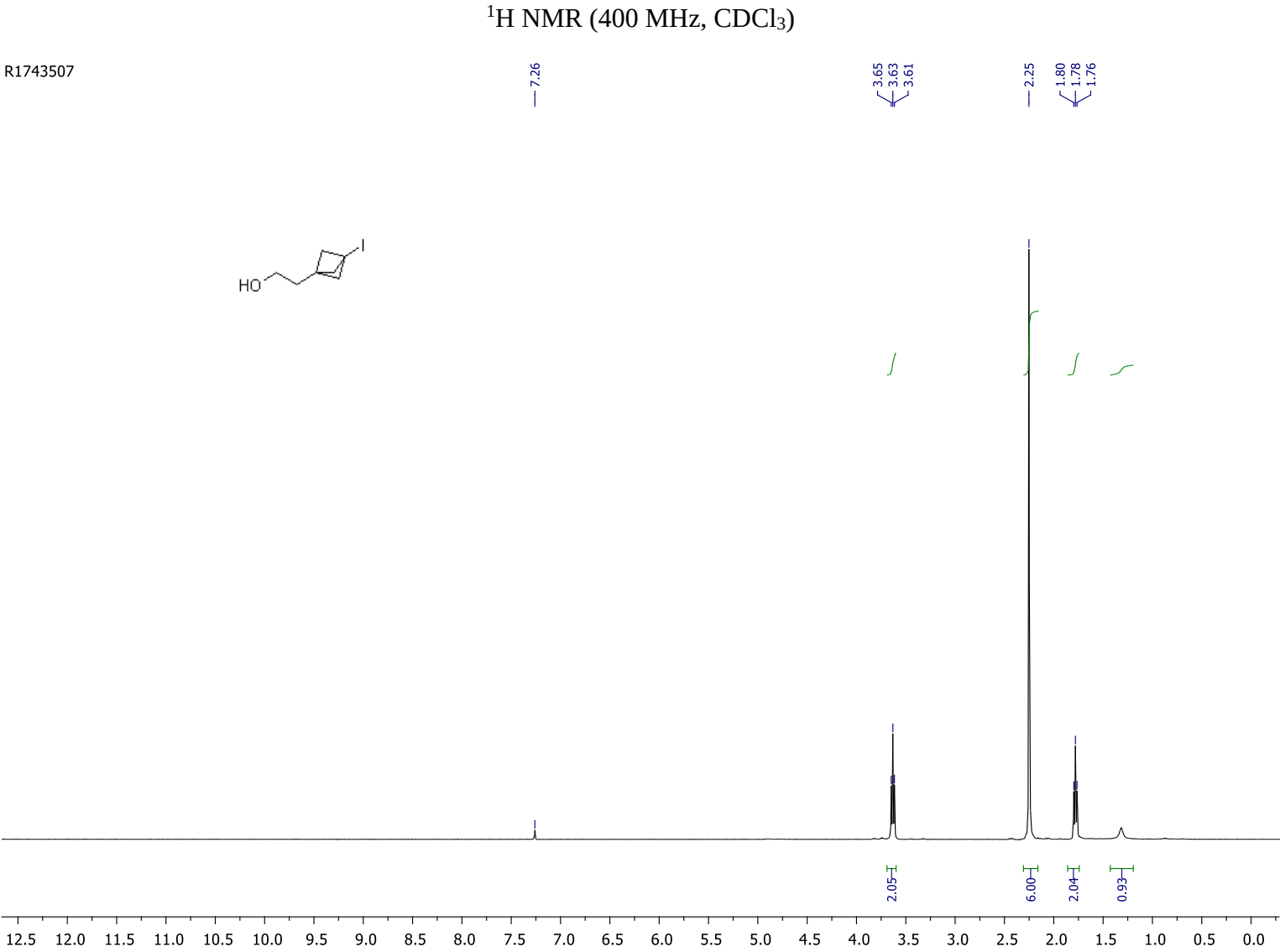


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2961820_C1:

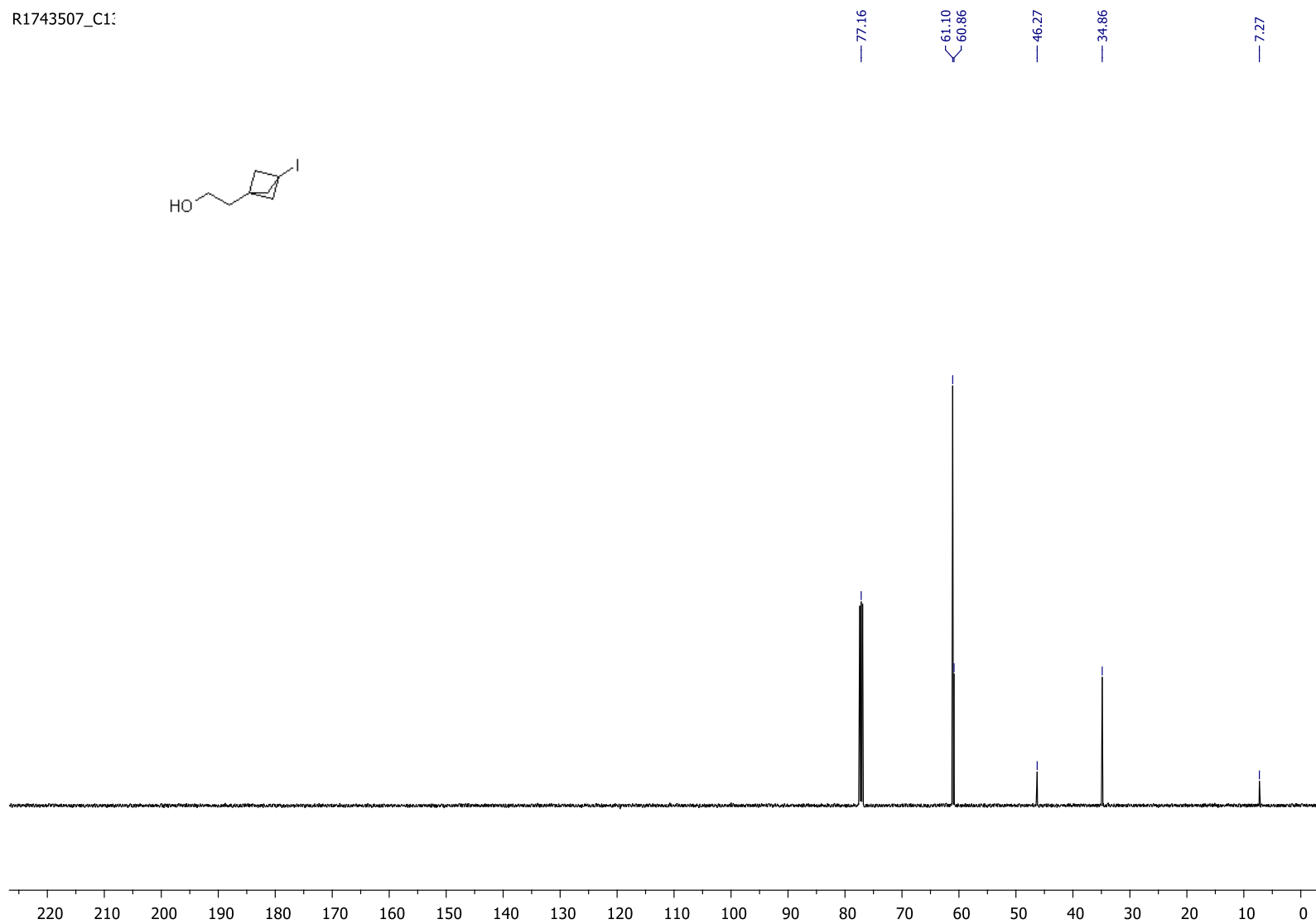


Compound 36



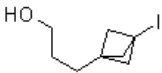
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R1743507_C1:

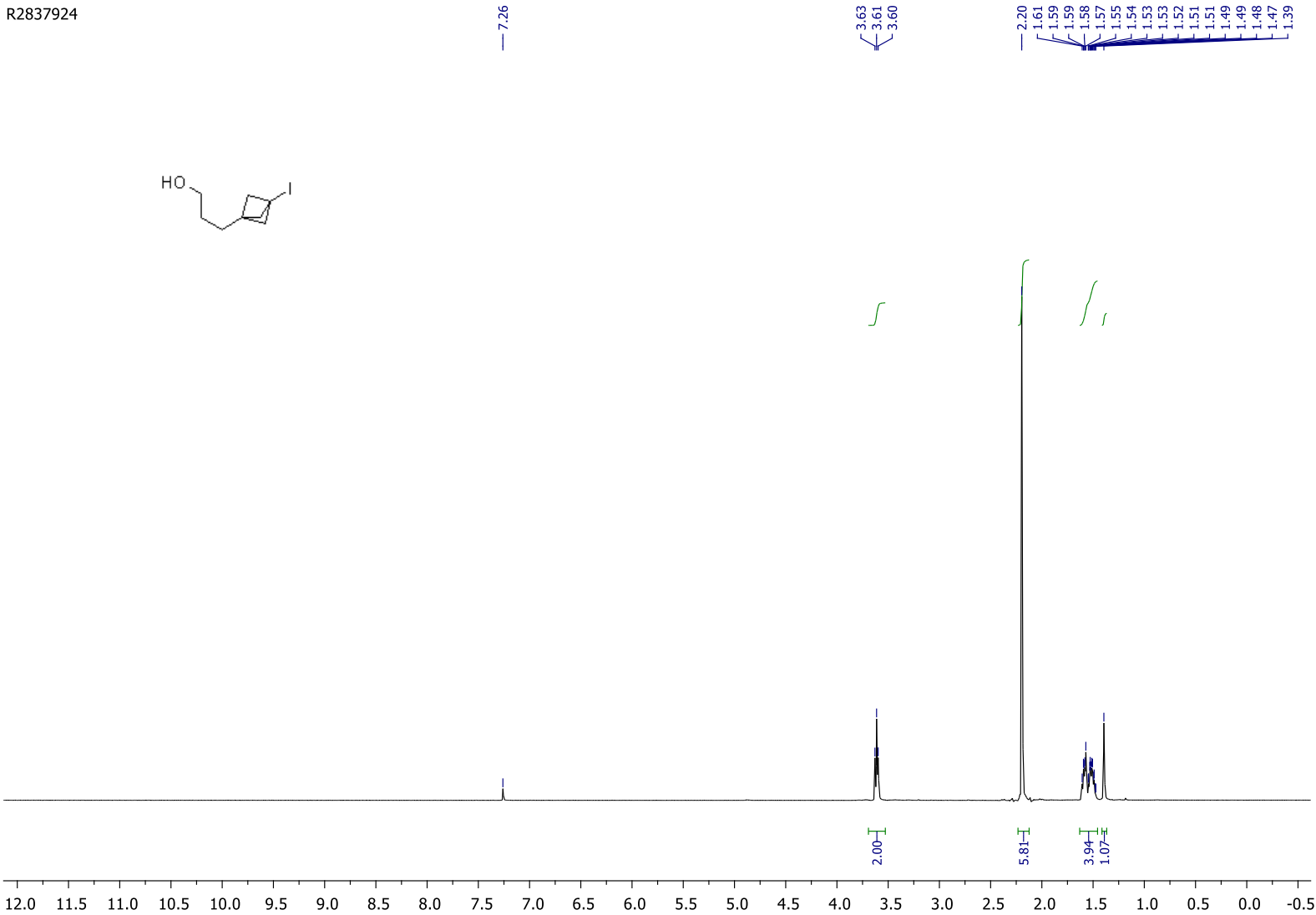


Compound 37

R2837924

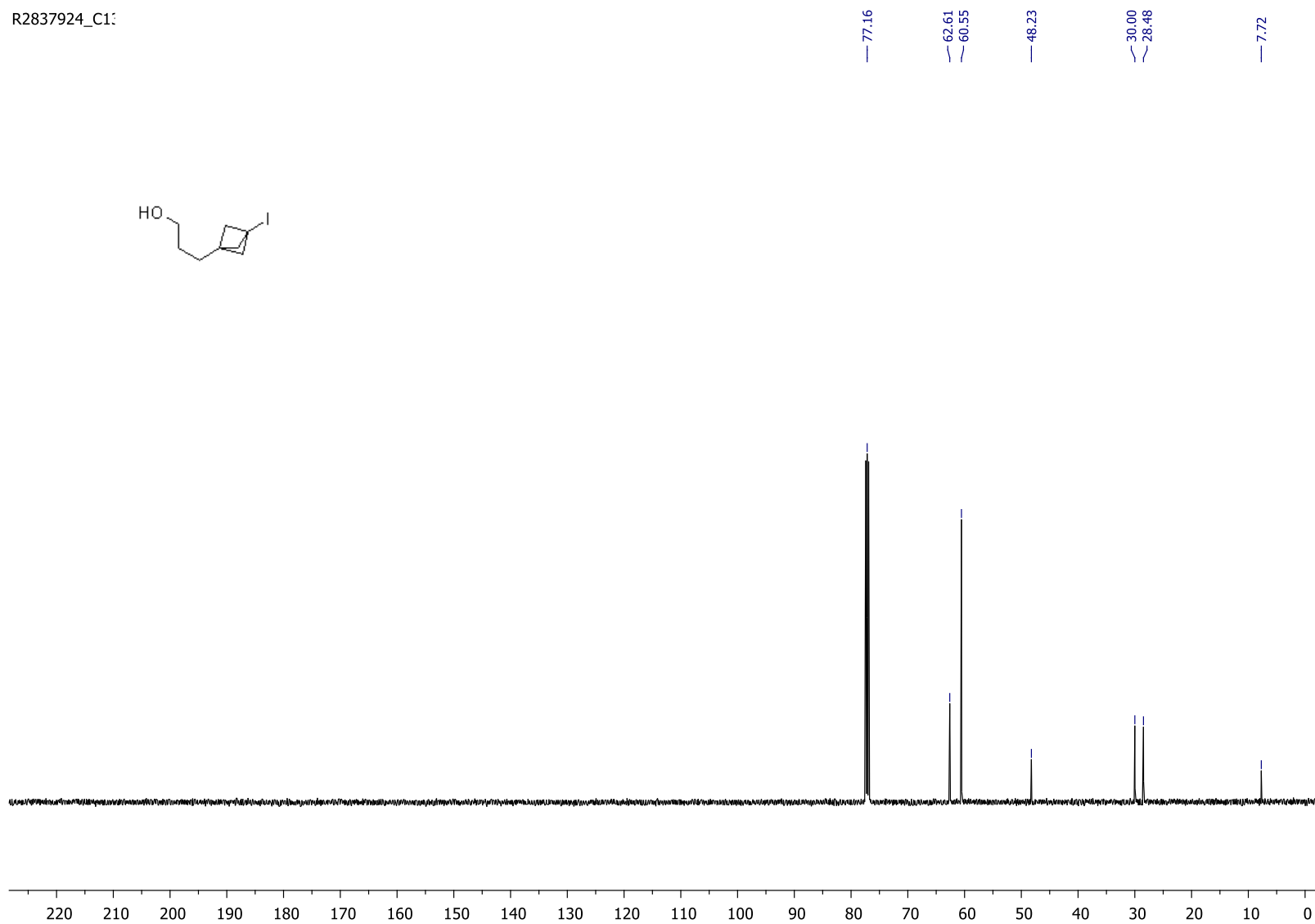


¹H NMR (400 MHz, CDCl₃)



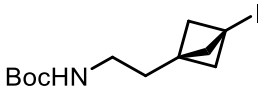
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2837924_C1:

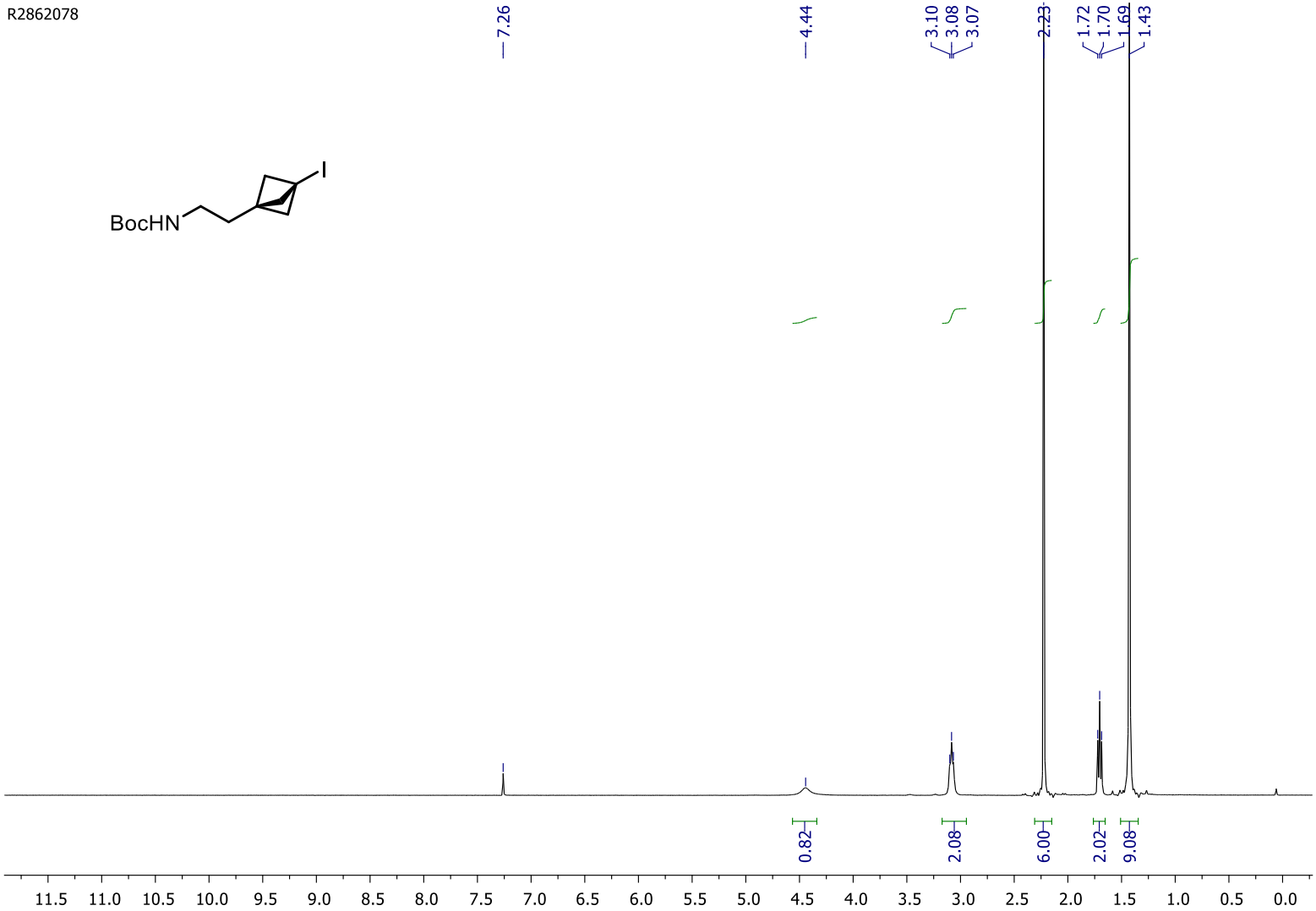


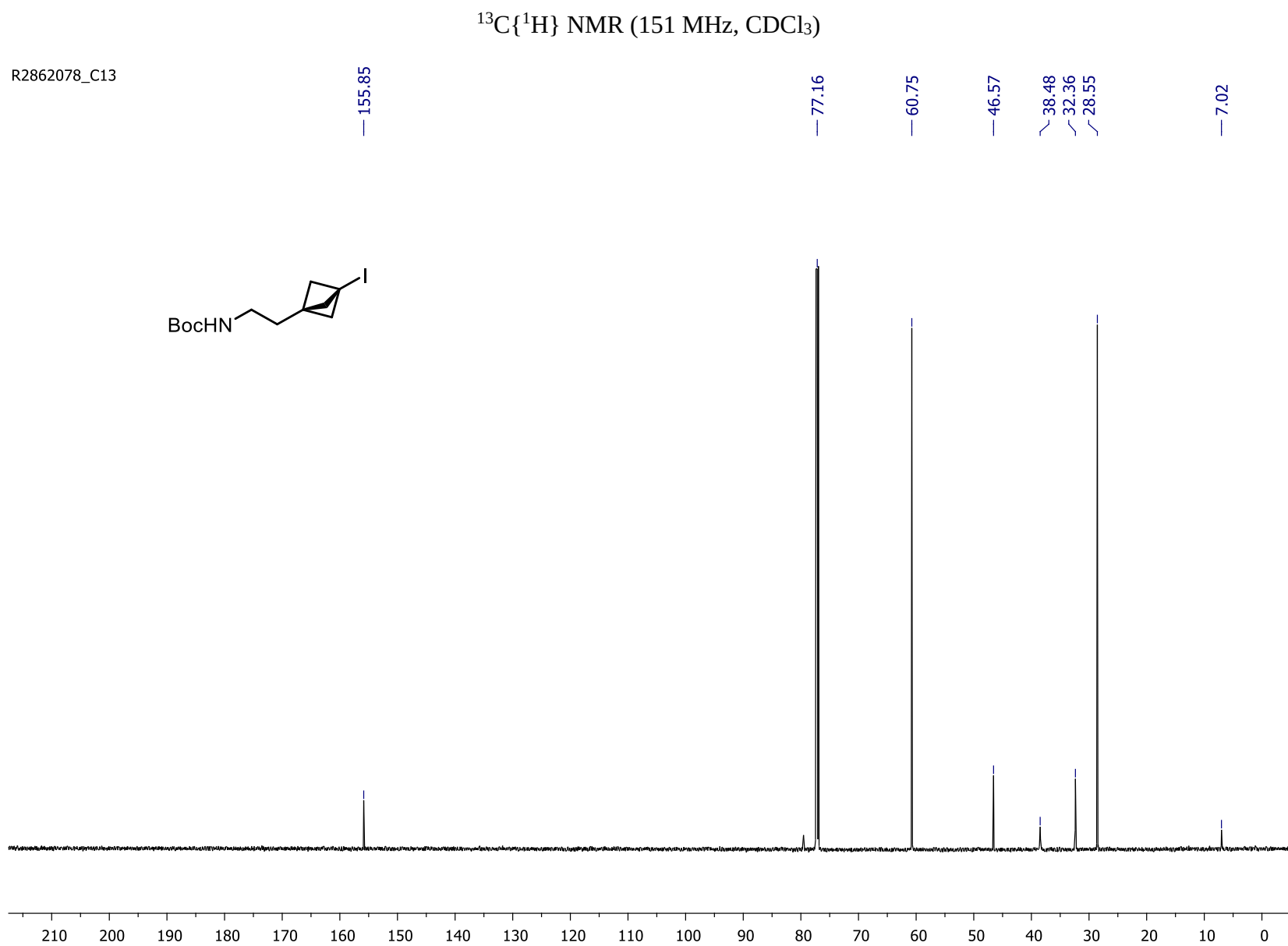
Compound 38

R2862078



¹H NMR (400 MHz, CDCl₃)

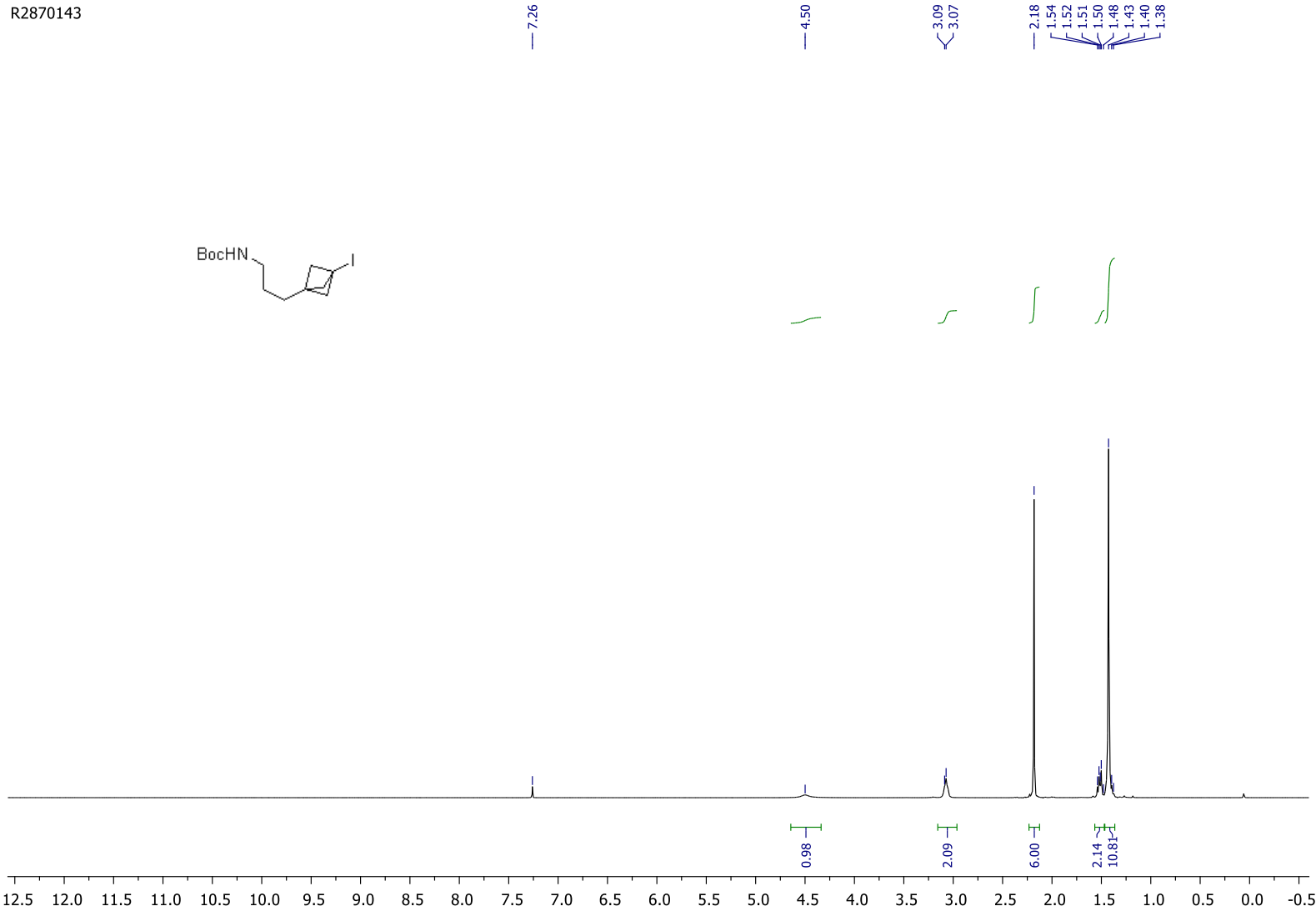




Compound 39

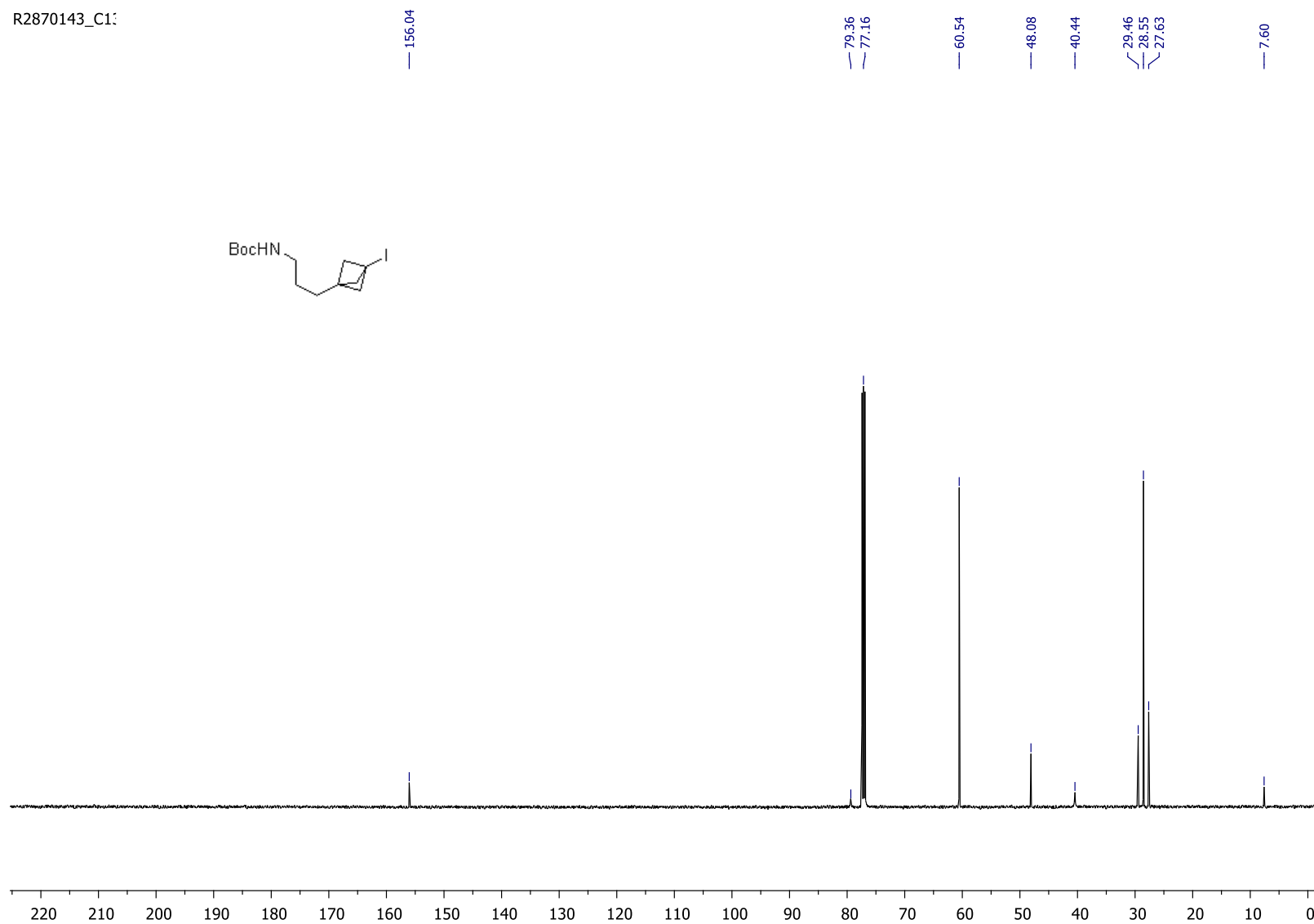
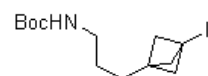
R2870143

¹H NMR (400 MHz, CDCl₃)



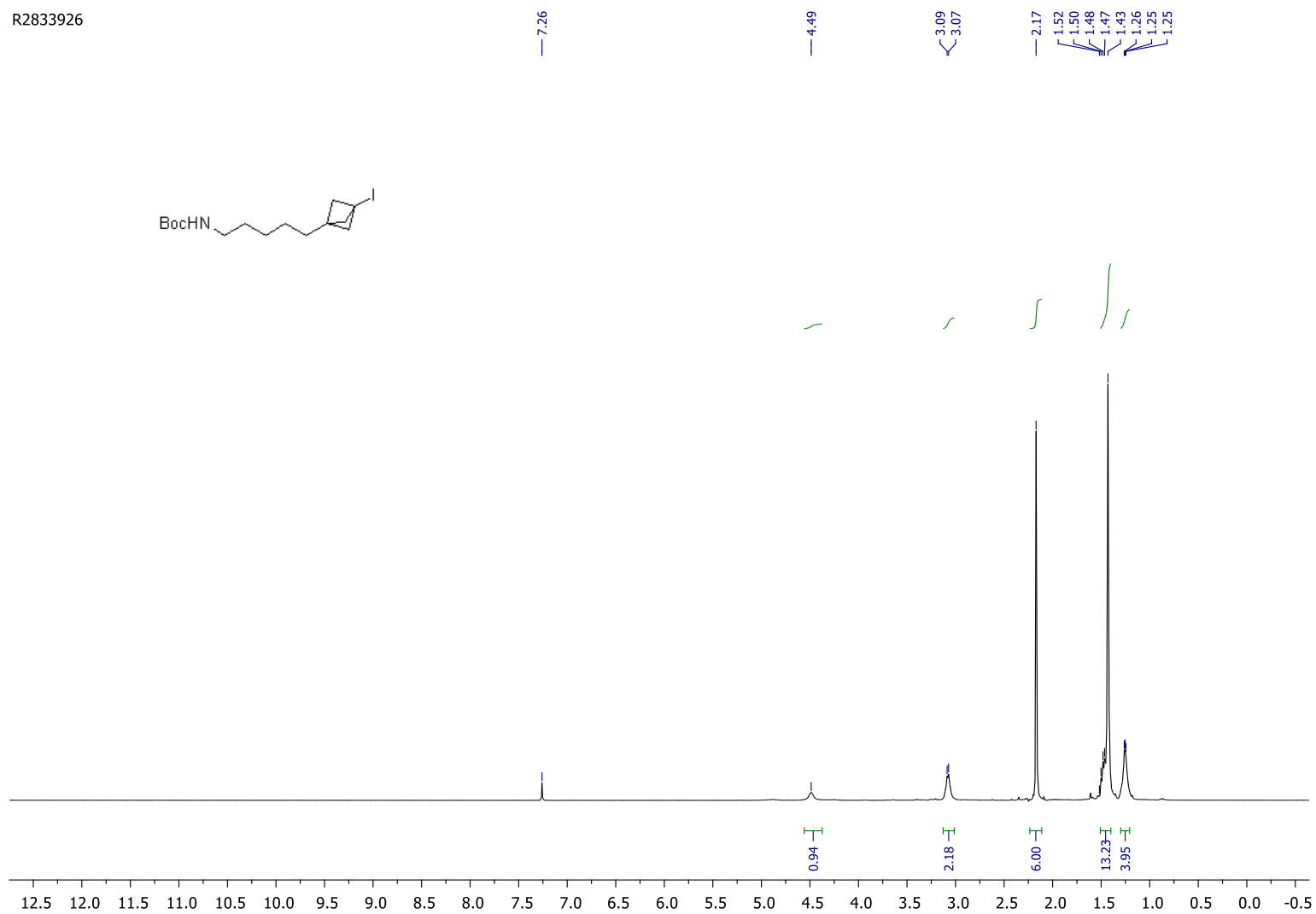
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2870143_C1:



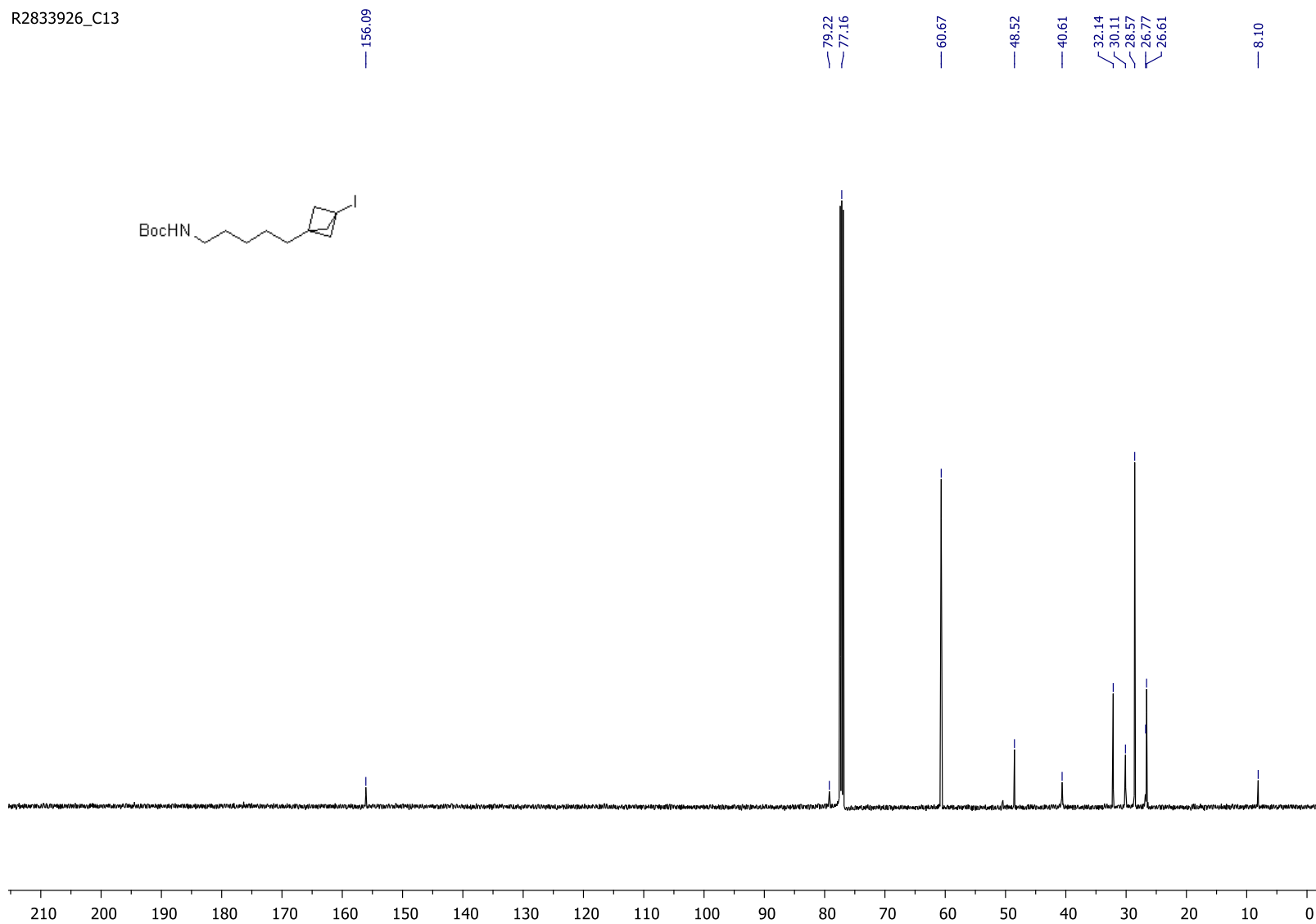
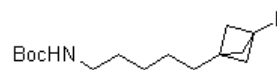
Compound 40

R2833926

¹H NMR (400 MHz, CDCl₃)

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

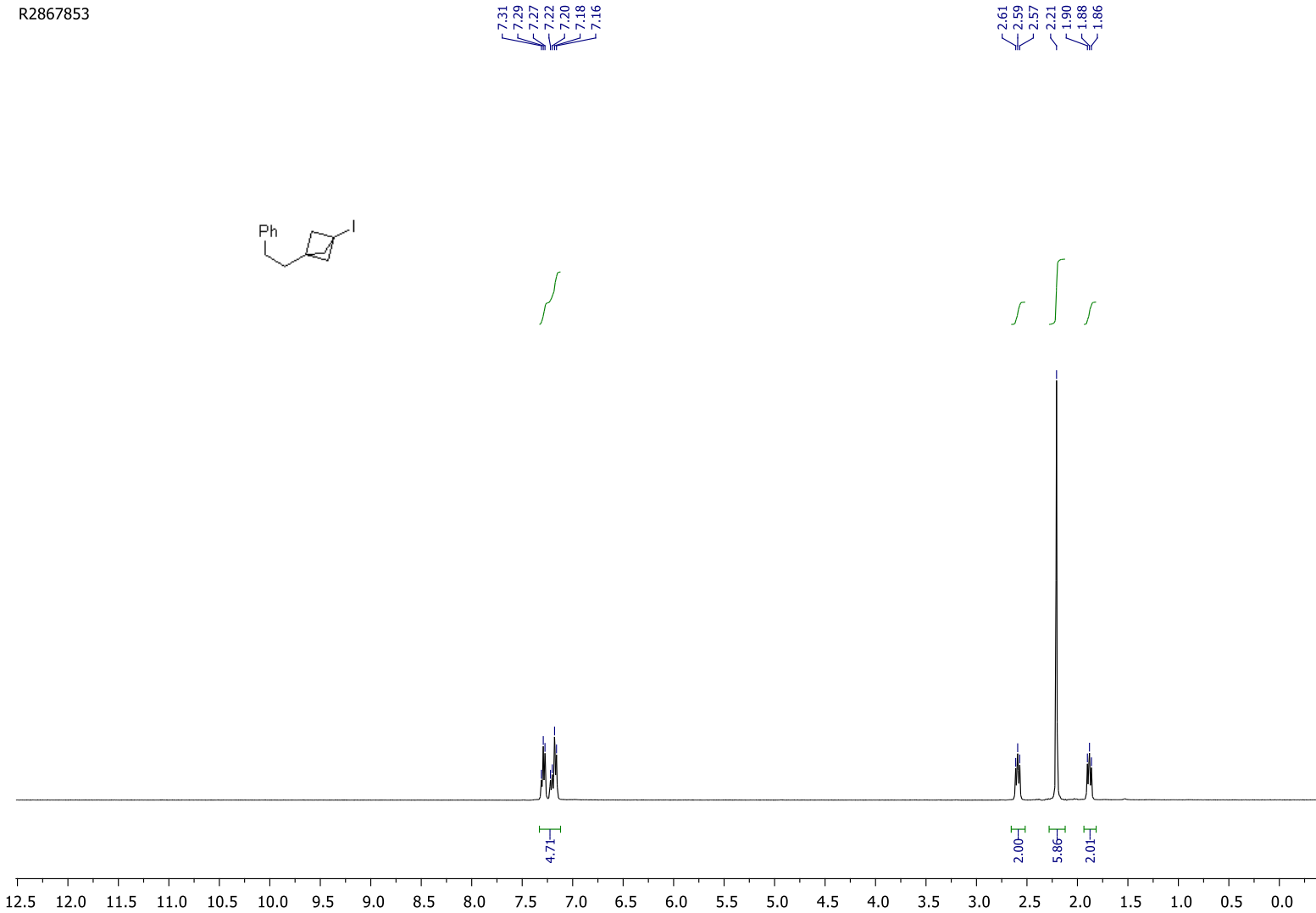
R2833926_C13



Compound 41

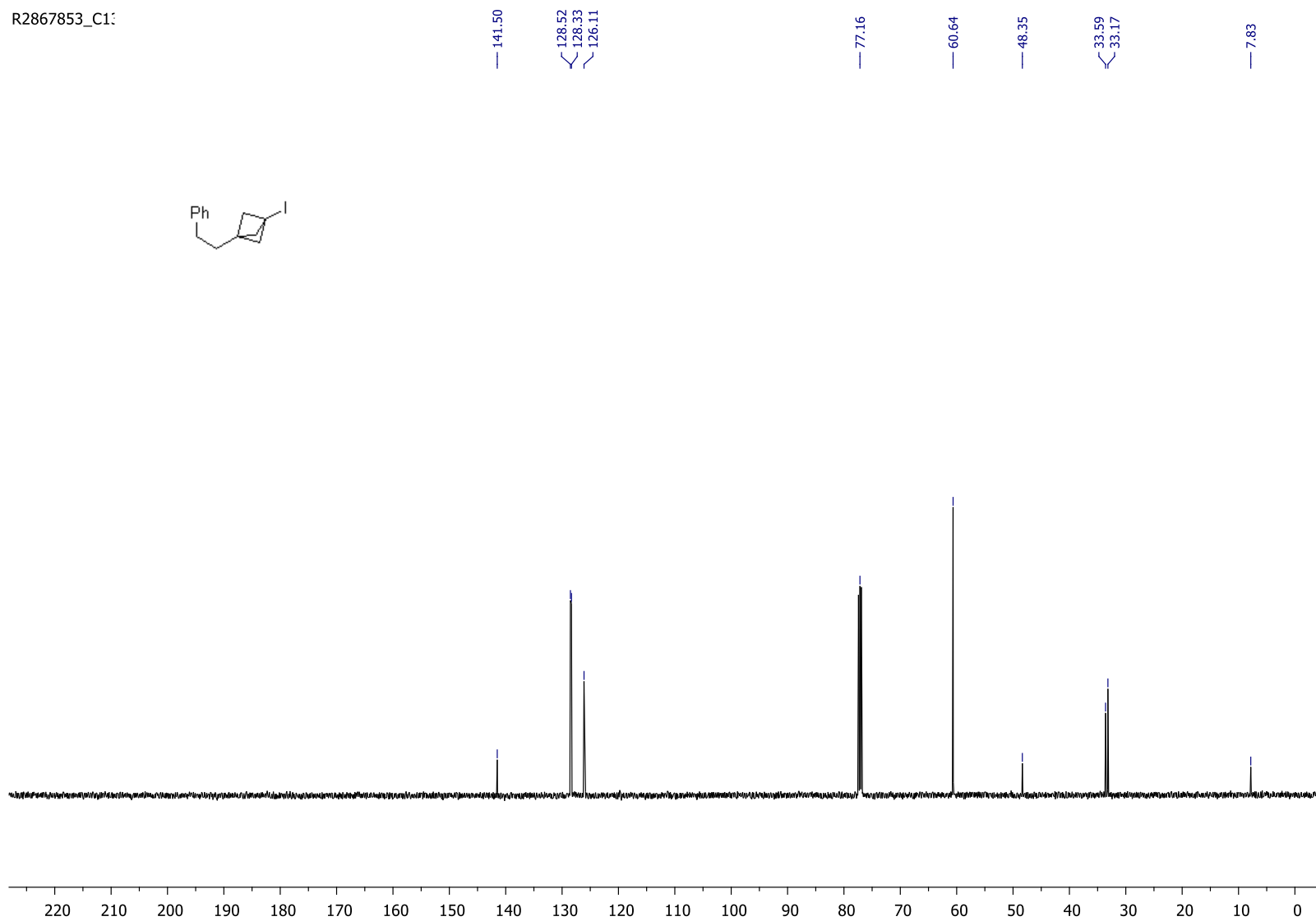
R2867853

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

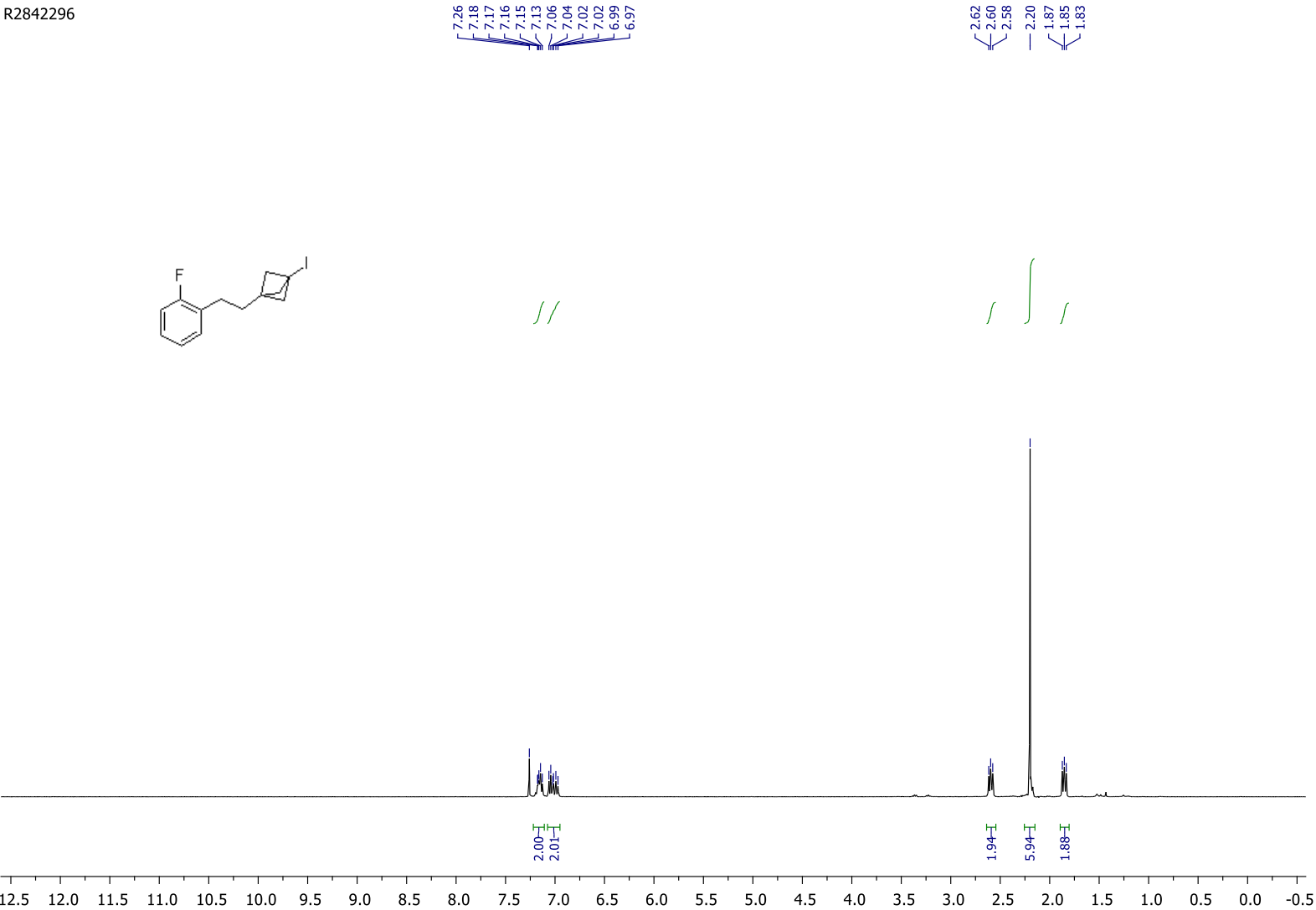
R2867853_C13



Compound 42

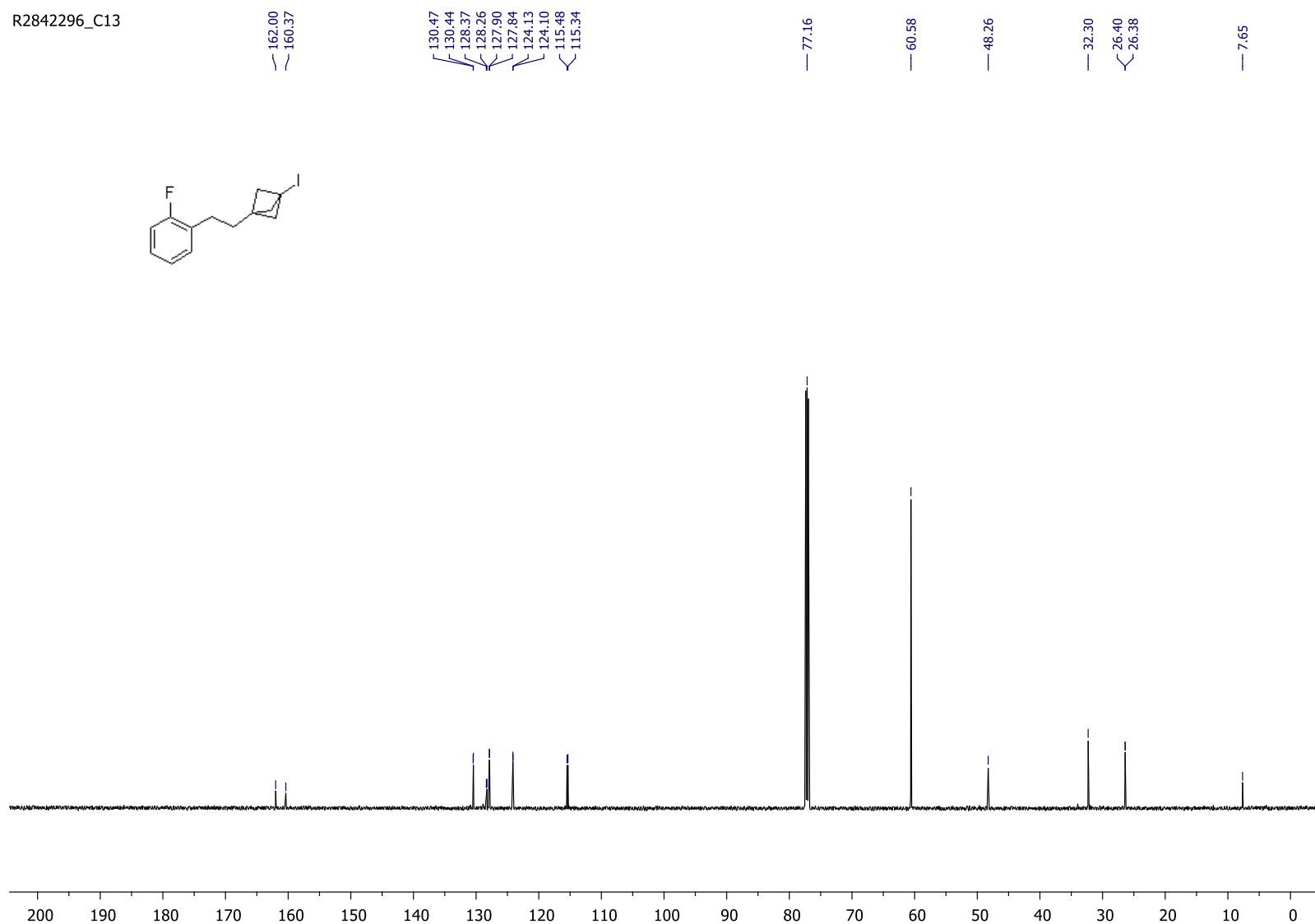
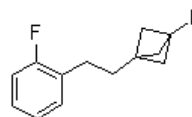
R2842296

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

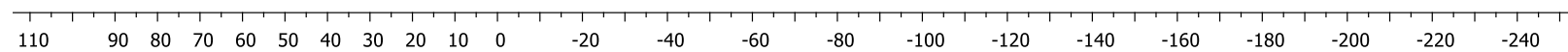
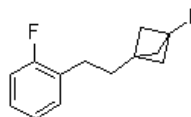
R2842296_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2842296_F19{H}
19F-{1H}

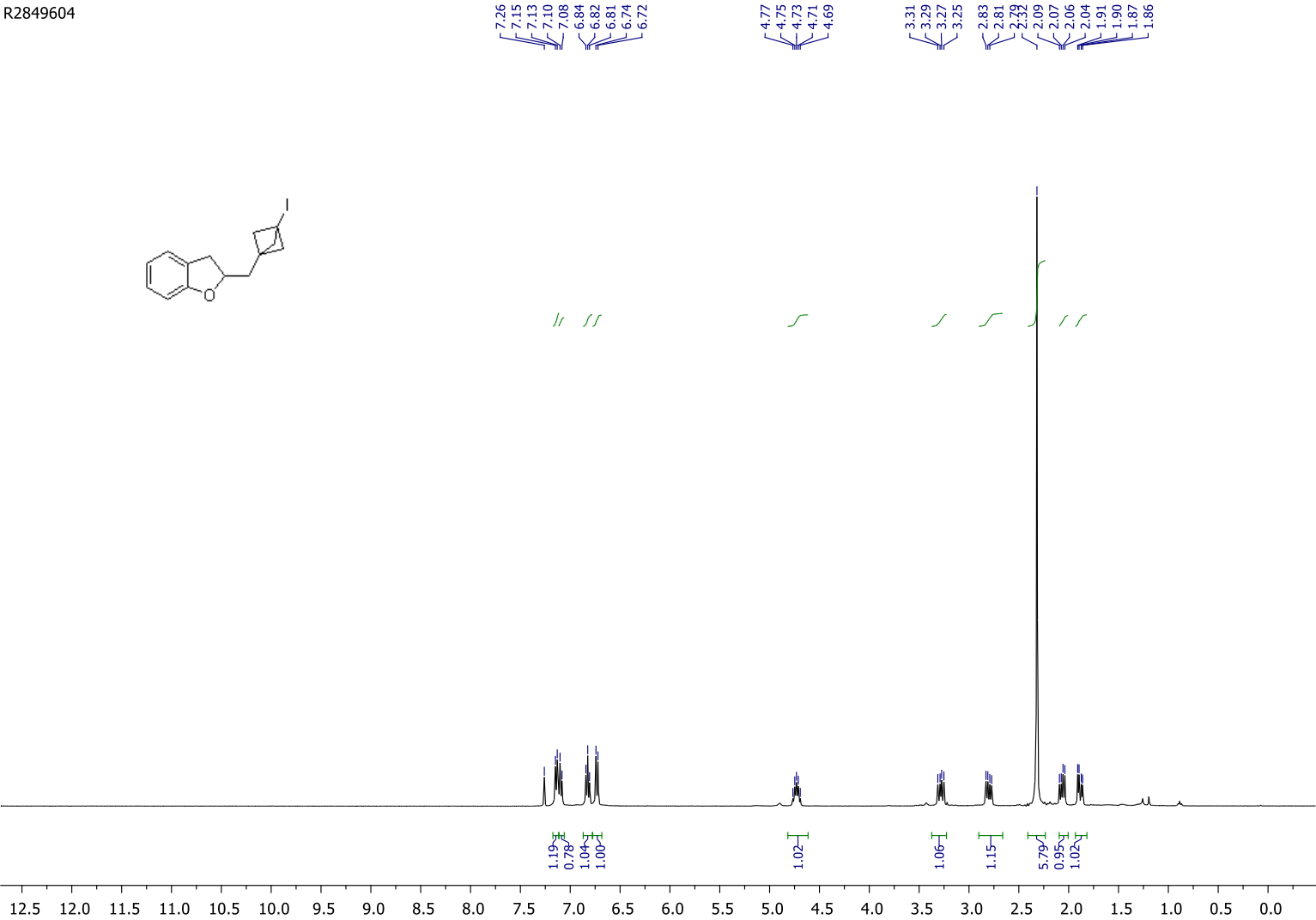
— -119.25



Compound 43

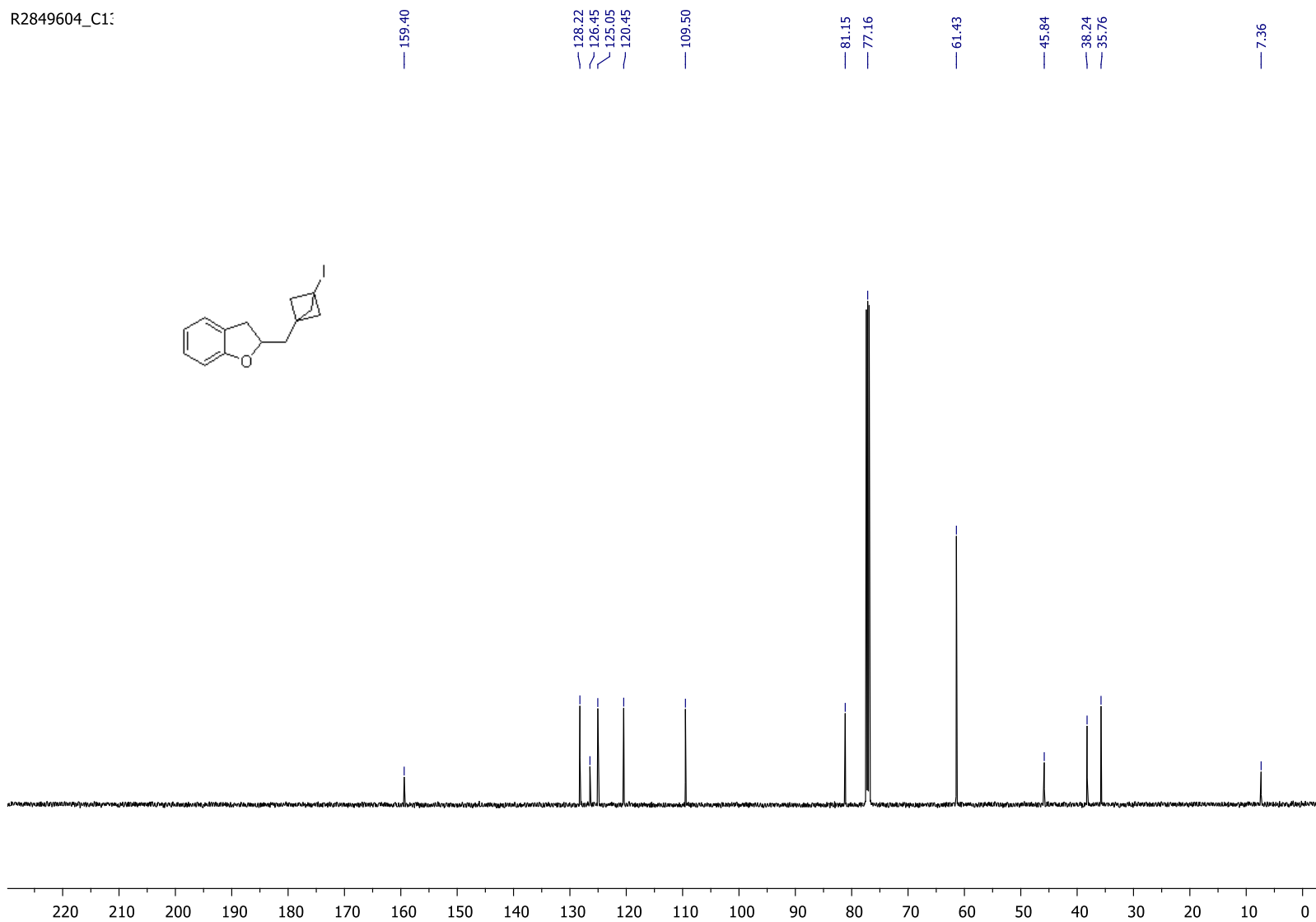
R2849604

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

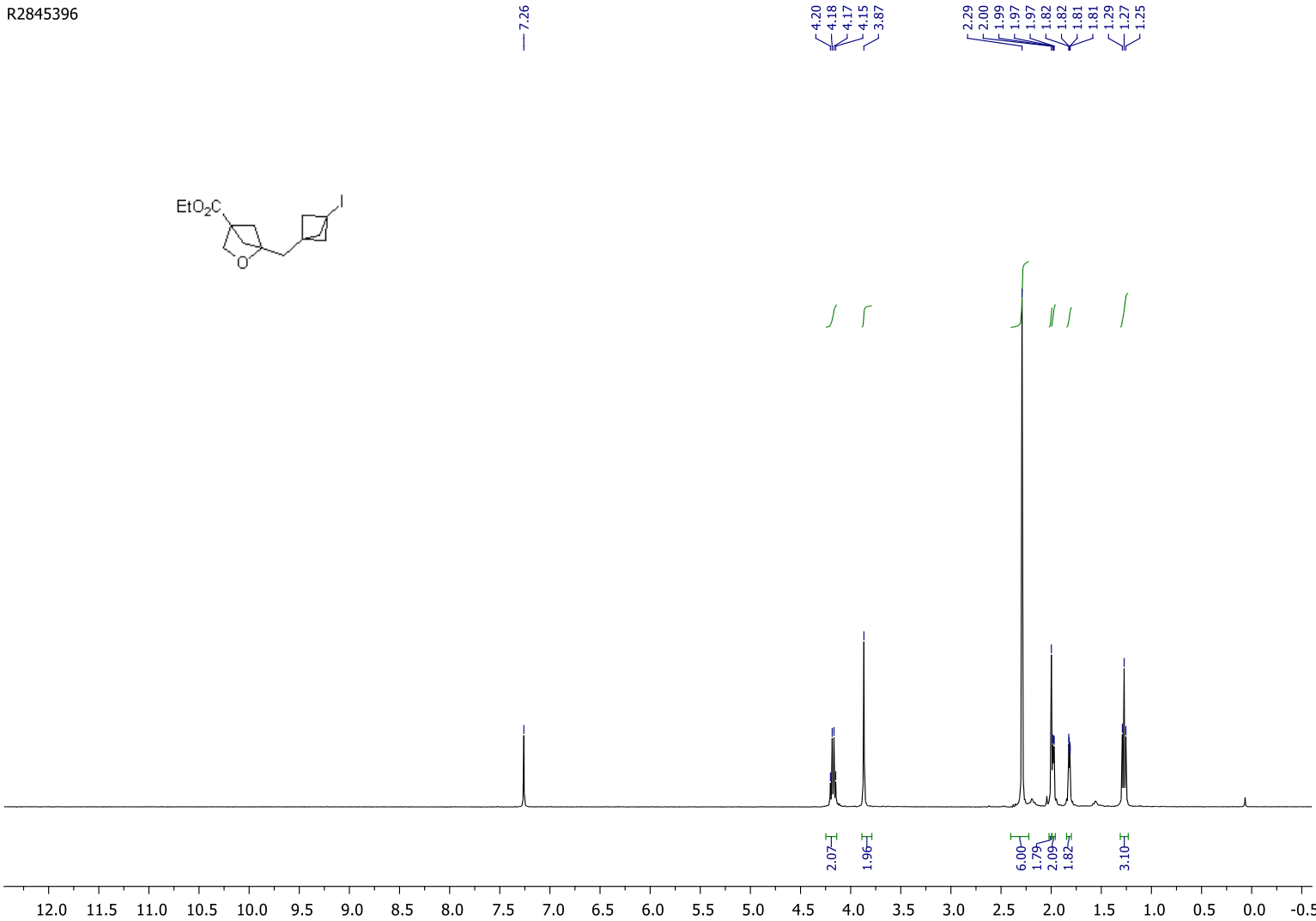
R2849604_C13



Compound 44

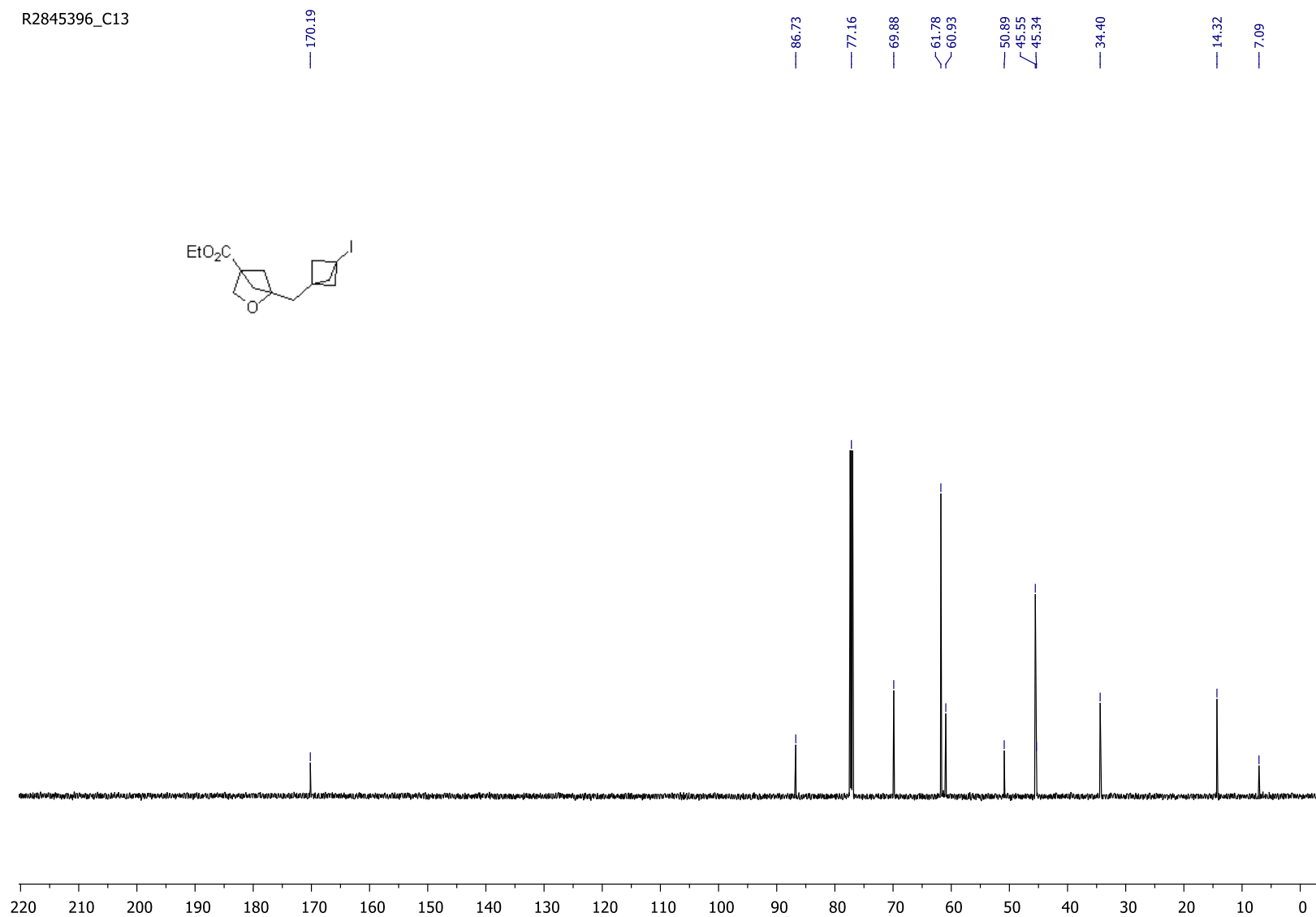
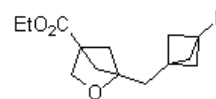
R2845396

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

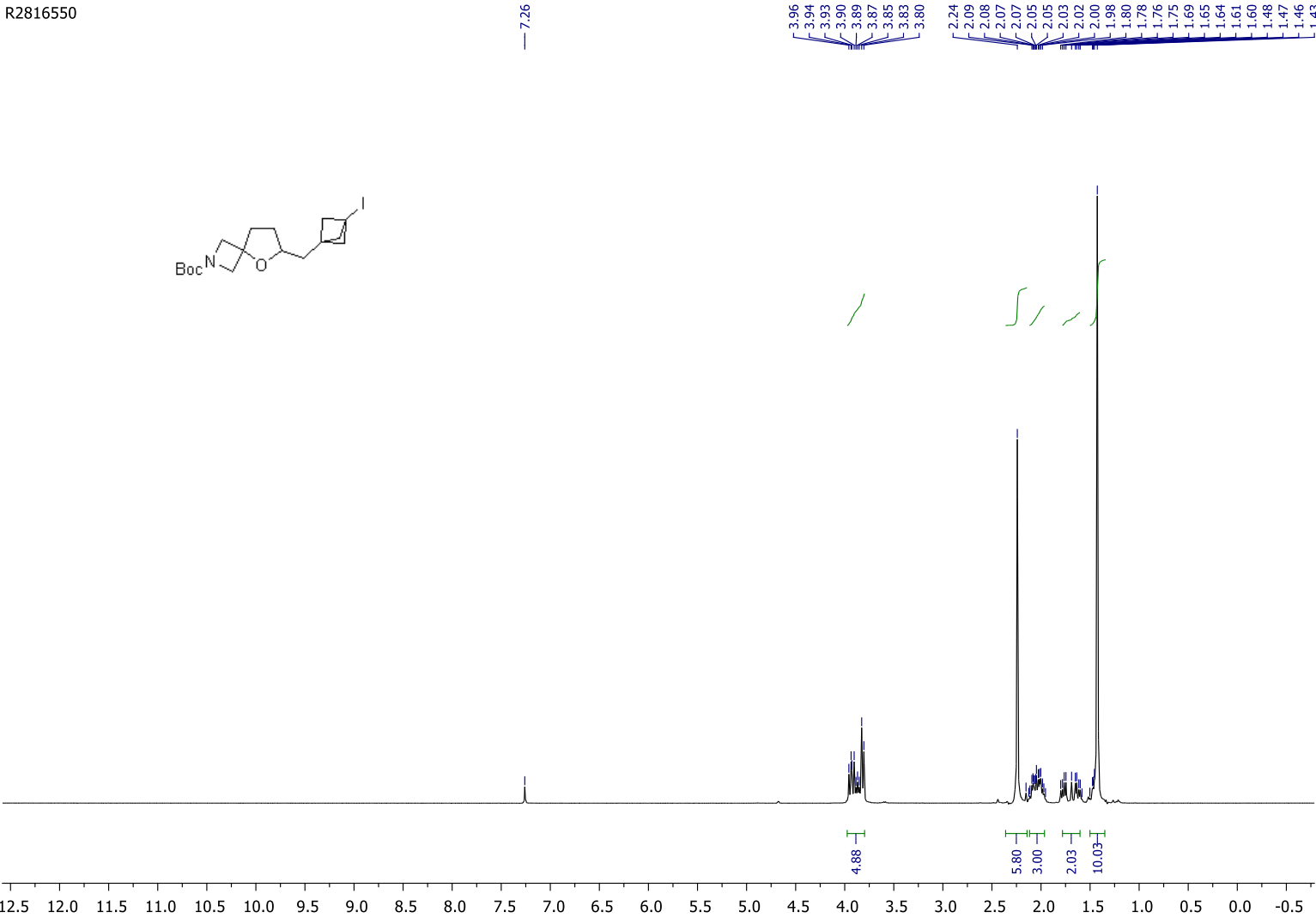
R2845396_C13



Compound 45

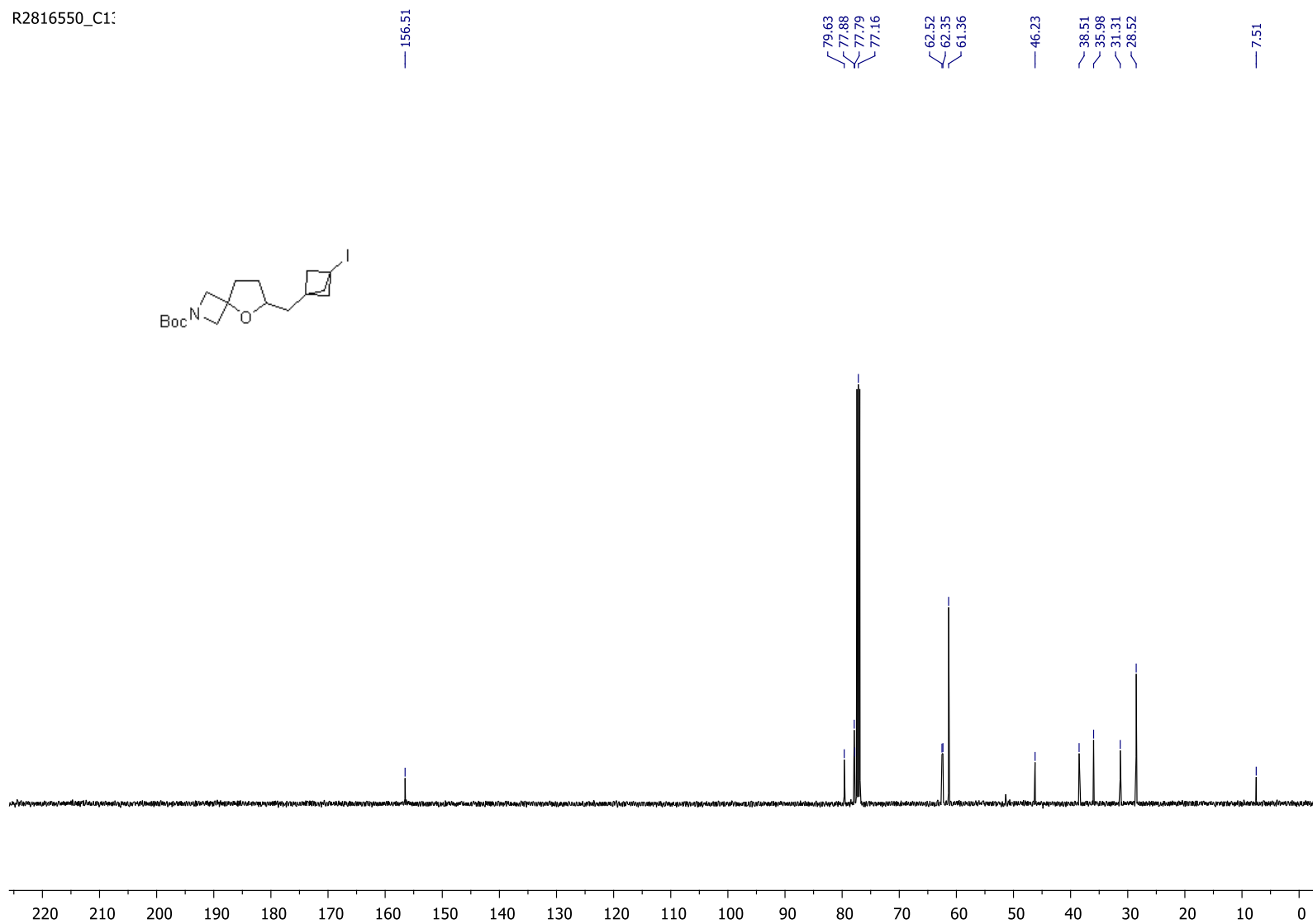
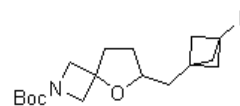
R2816550

¹H NMR (400 MHz, CDCl₃)



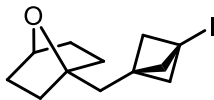
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2816550_C1:

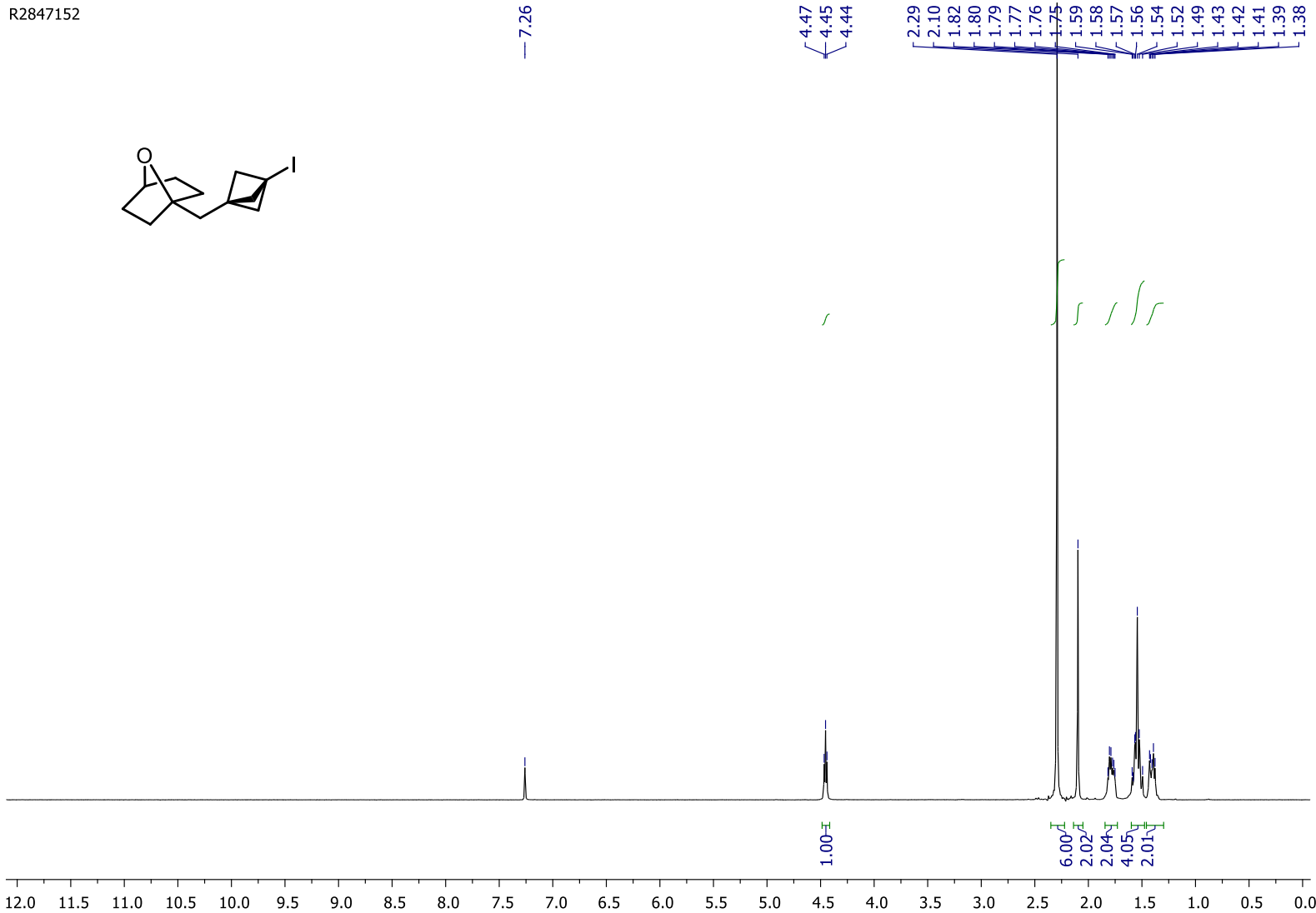


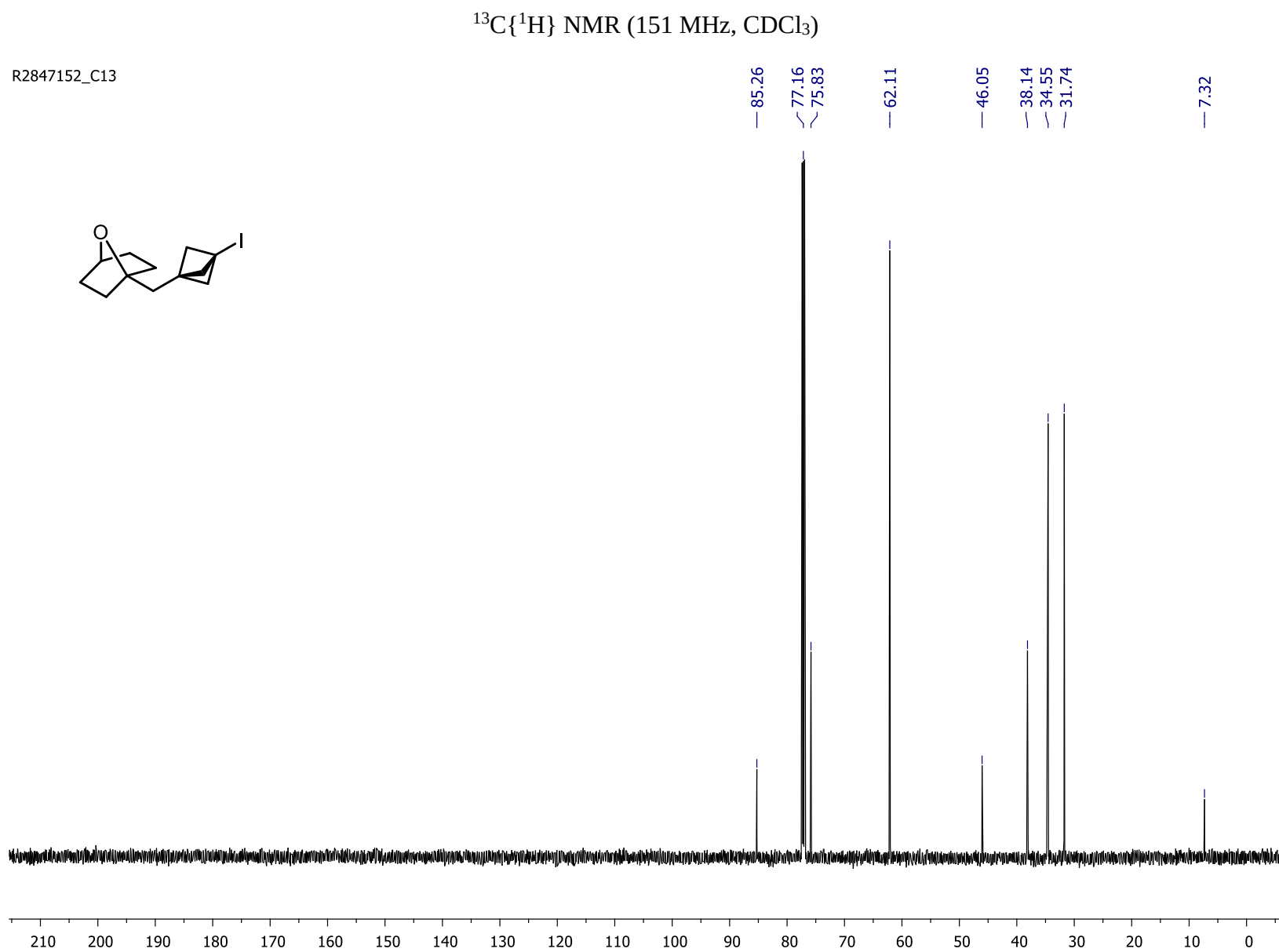
Compound 46

R2847152



¹H NMR (400 MHz, CDCl₃)

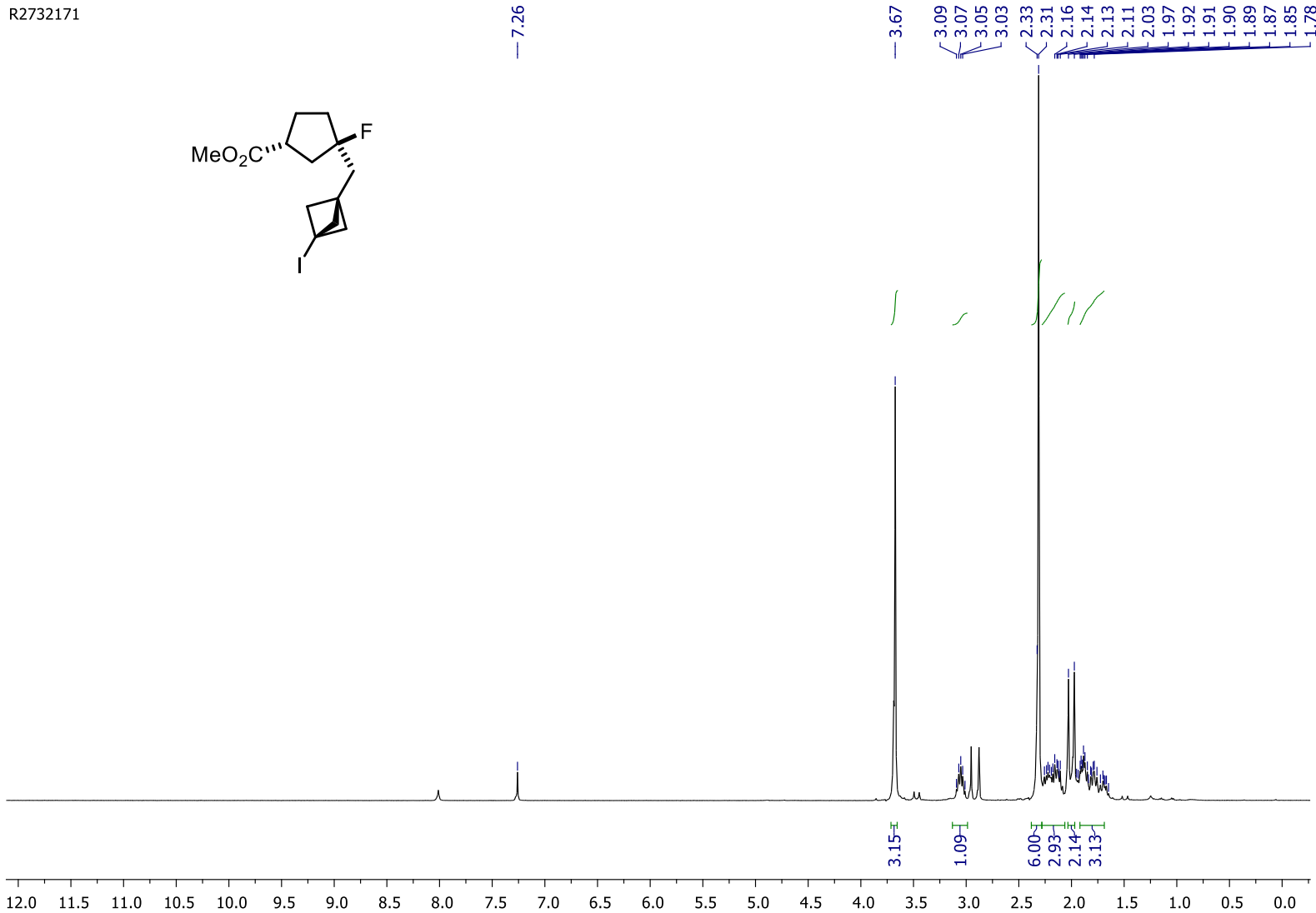
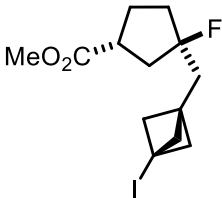


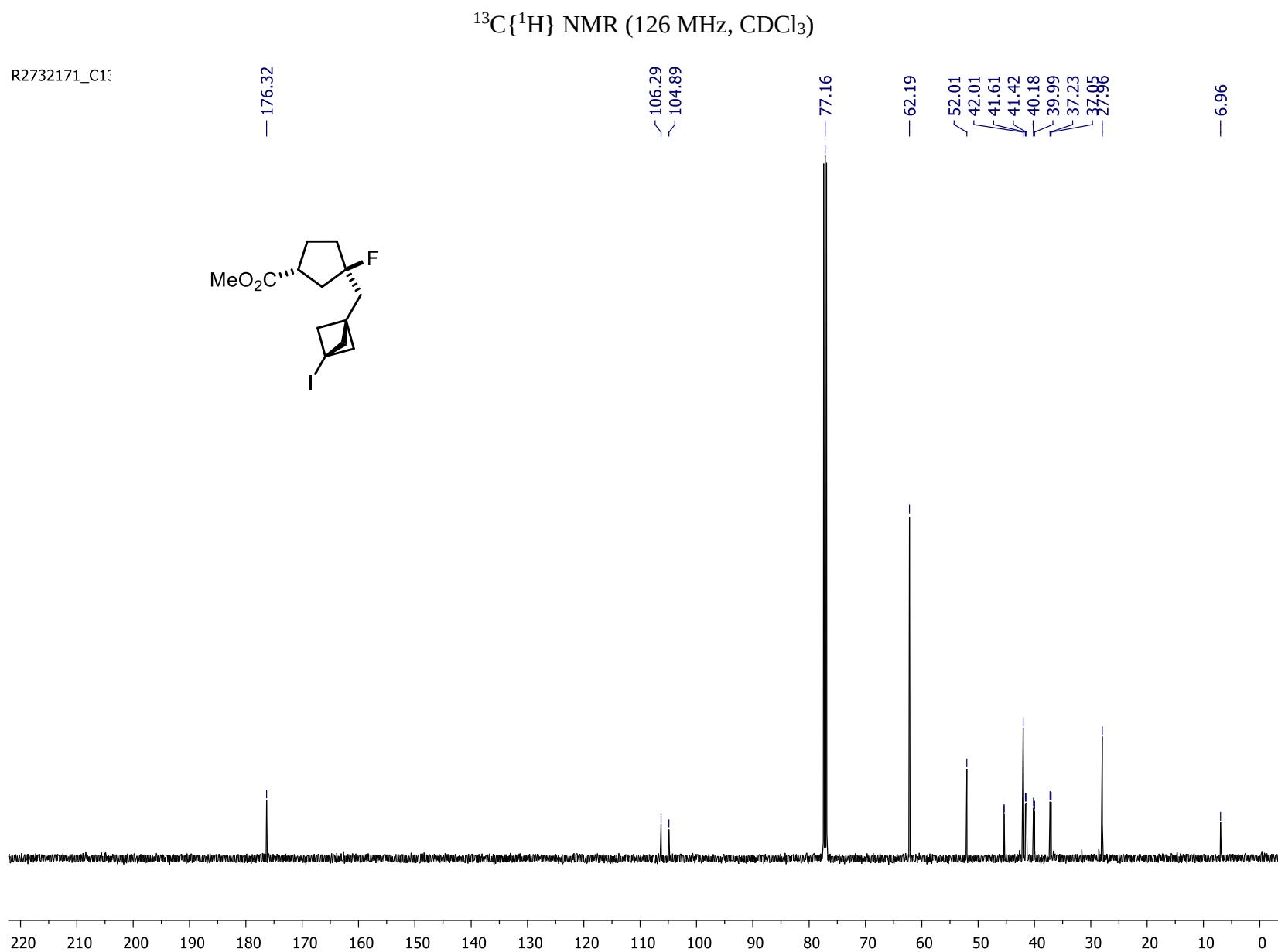


Compound 47

R2732171

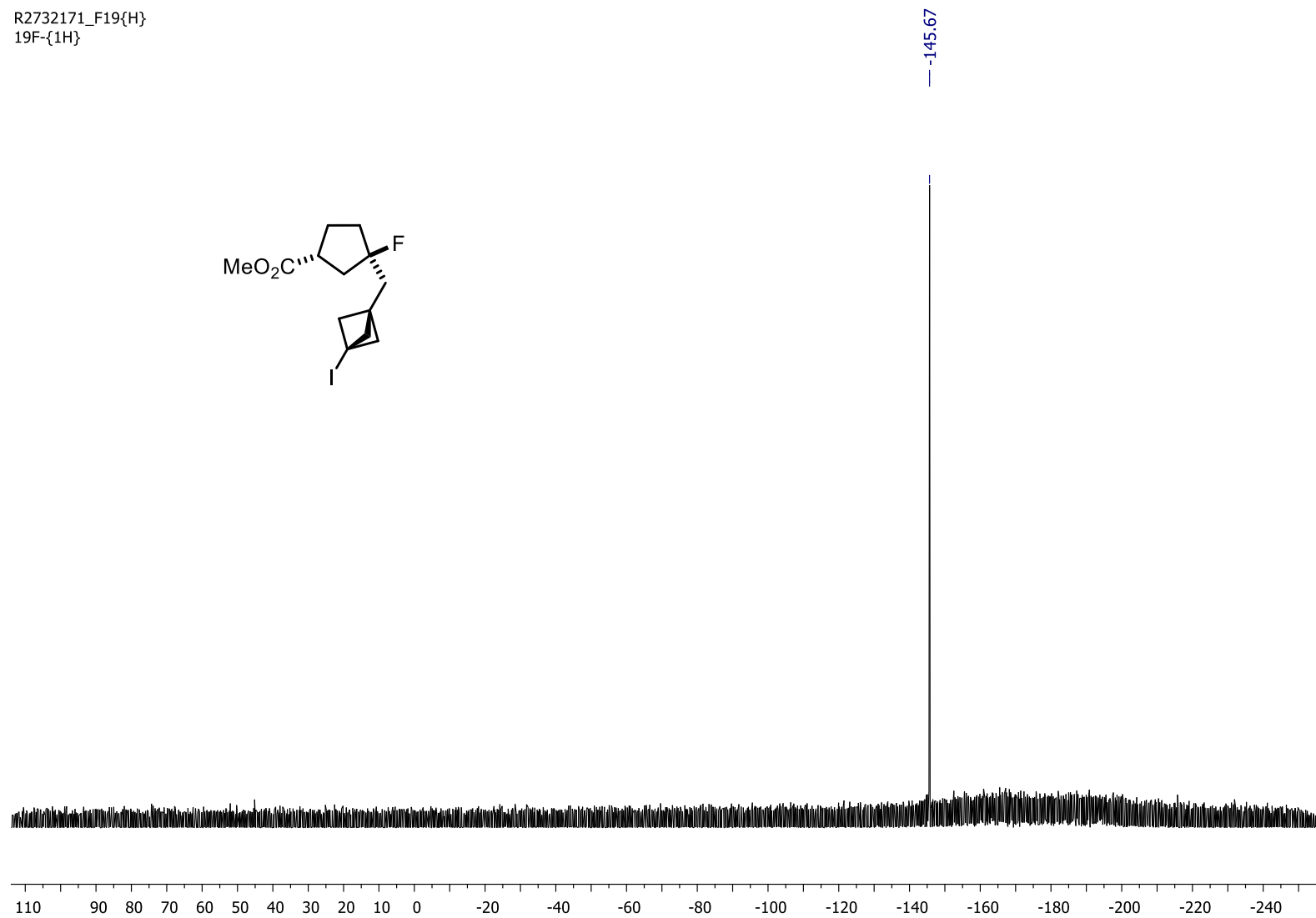
¹H NMR (400 MHz, CDCl₃)





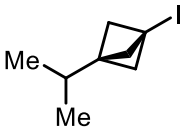
$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2732171_F19{H}
 $^{19}\text{F}\{^1\text{H}\}$

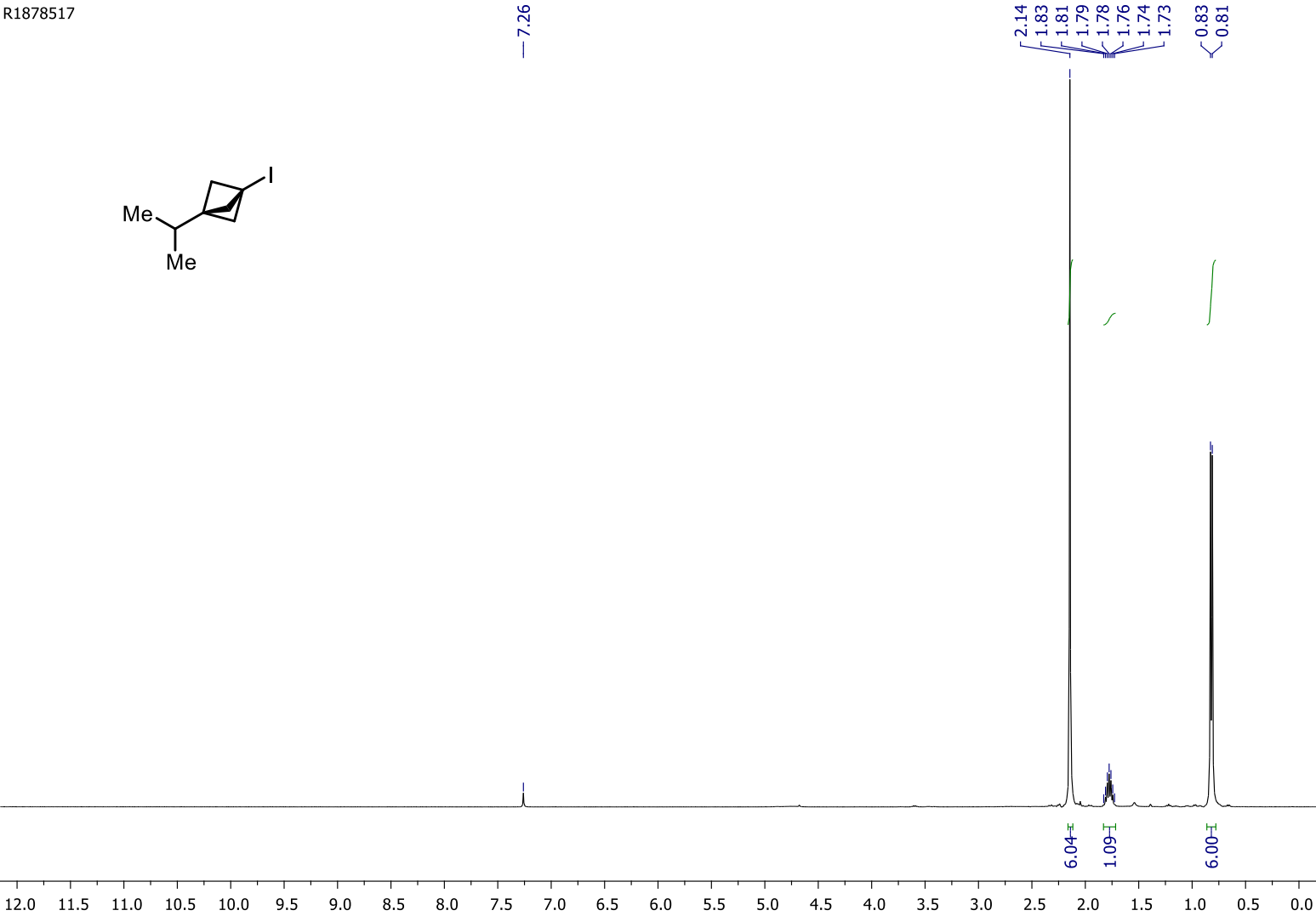


Compound 48

R1878517

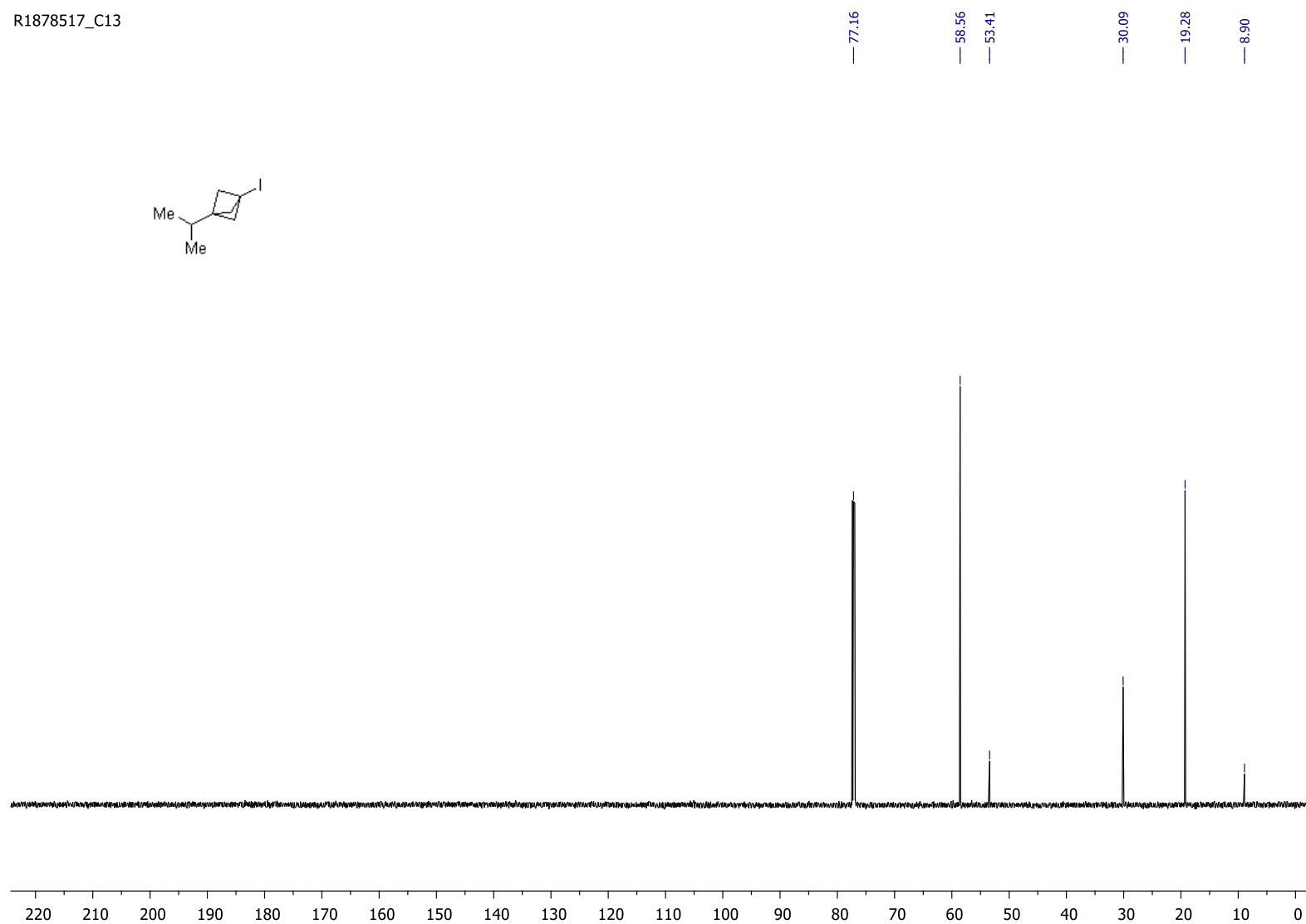
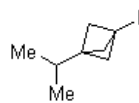


¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

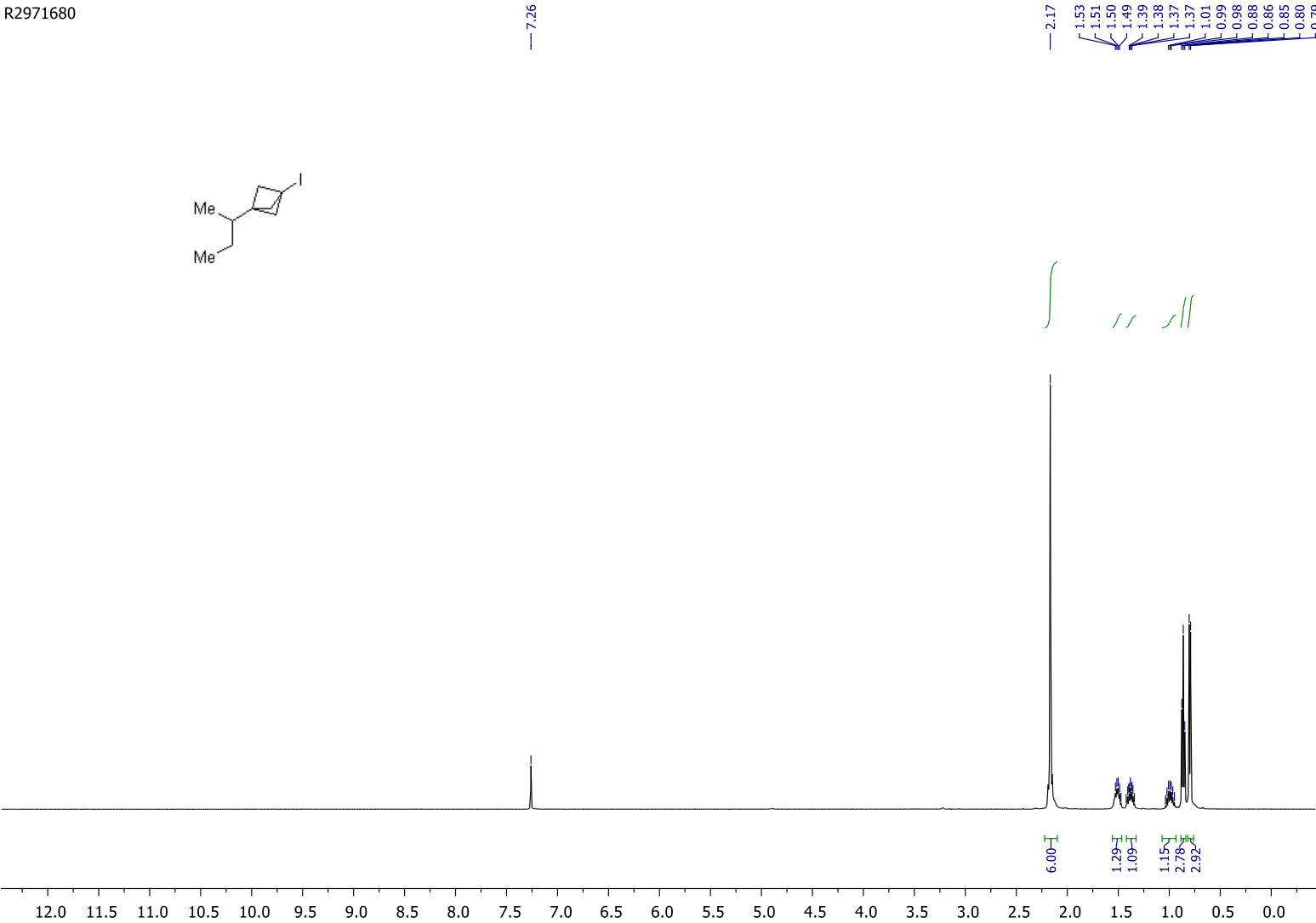
R1878517_C13



Compound 49

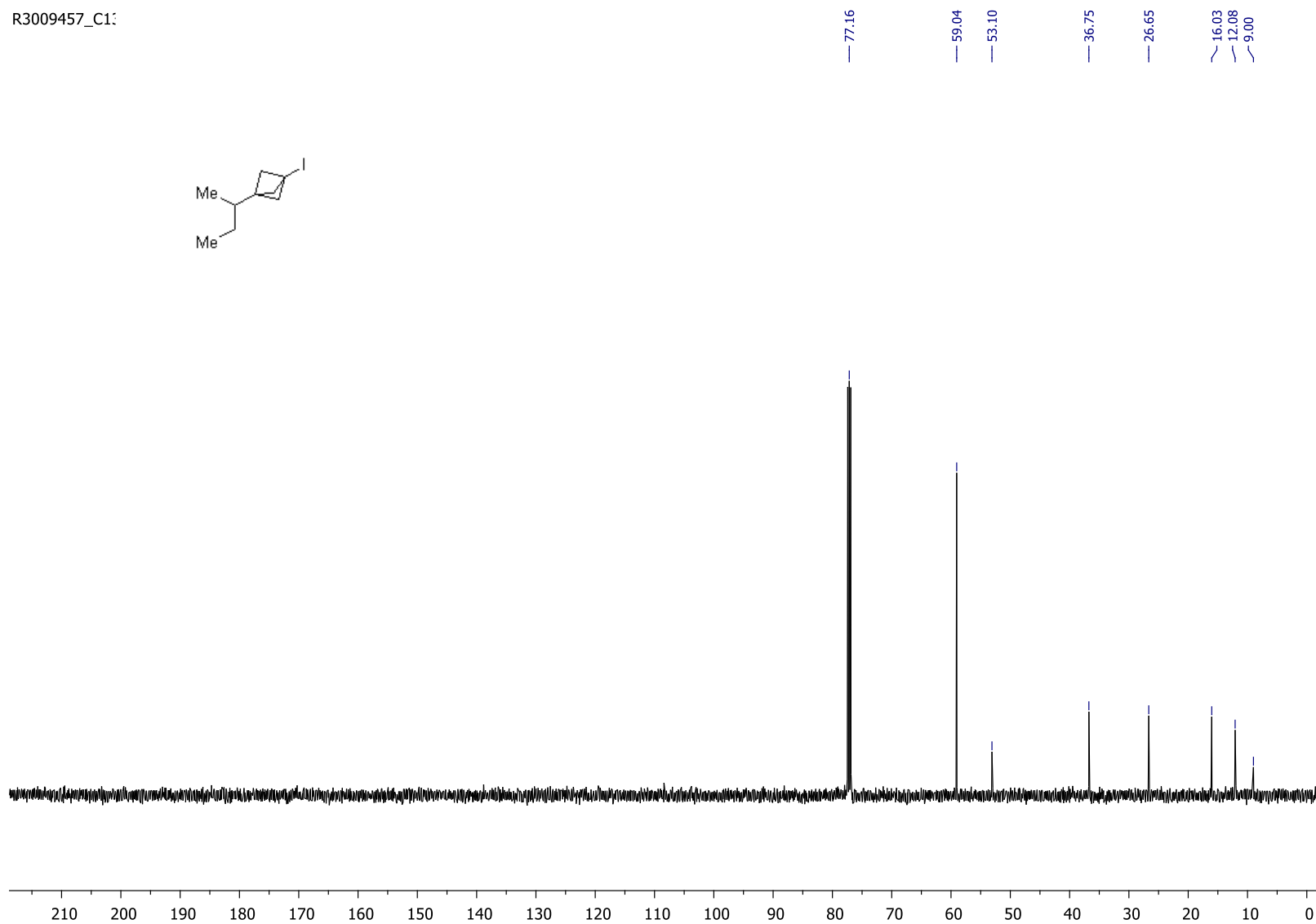
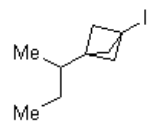
R2971680

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

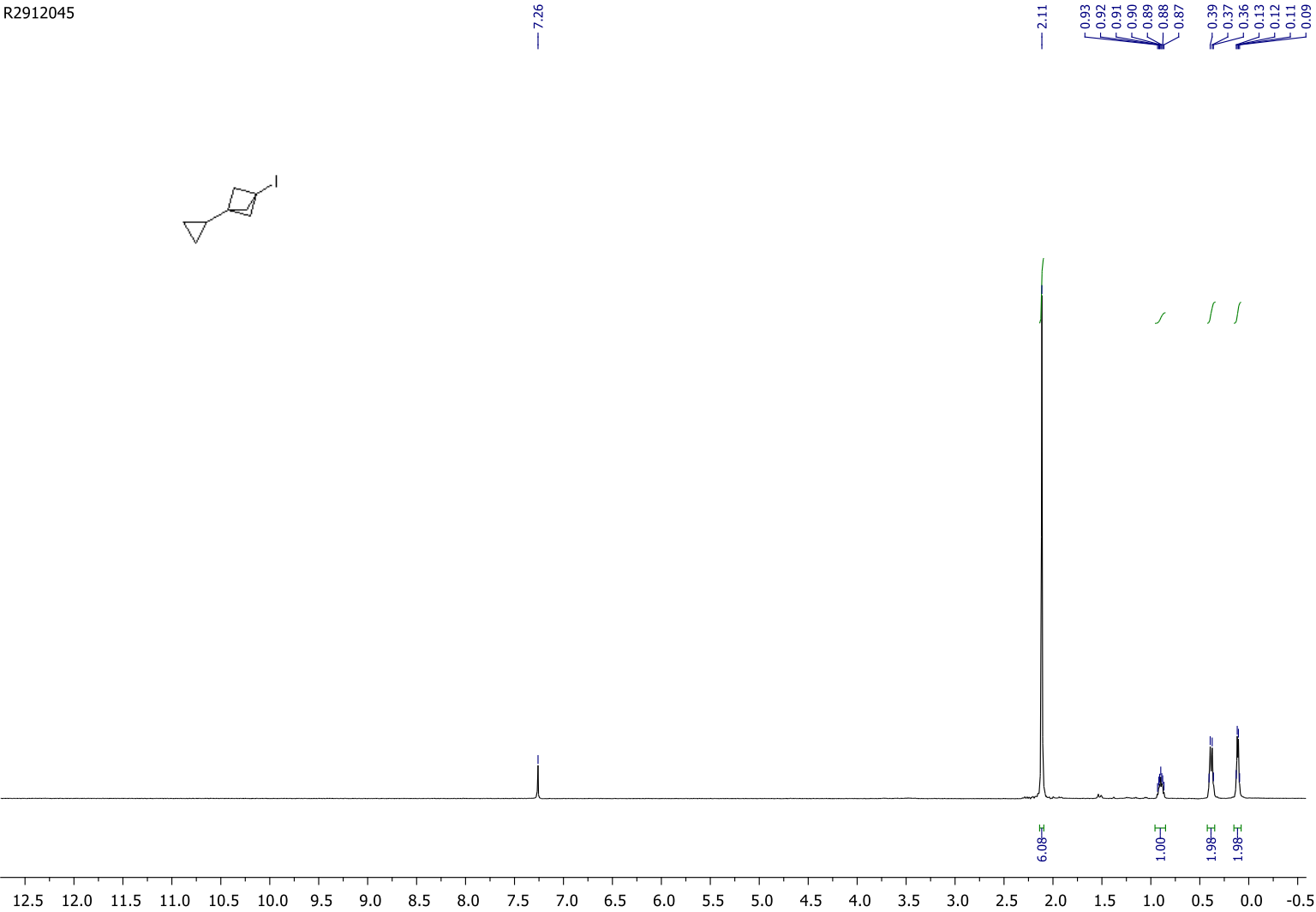
R3009457_C1:



Compound 50

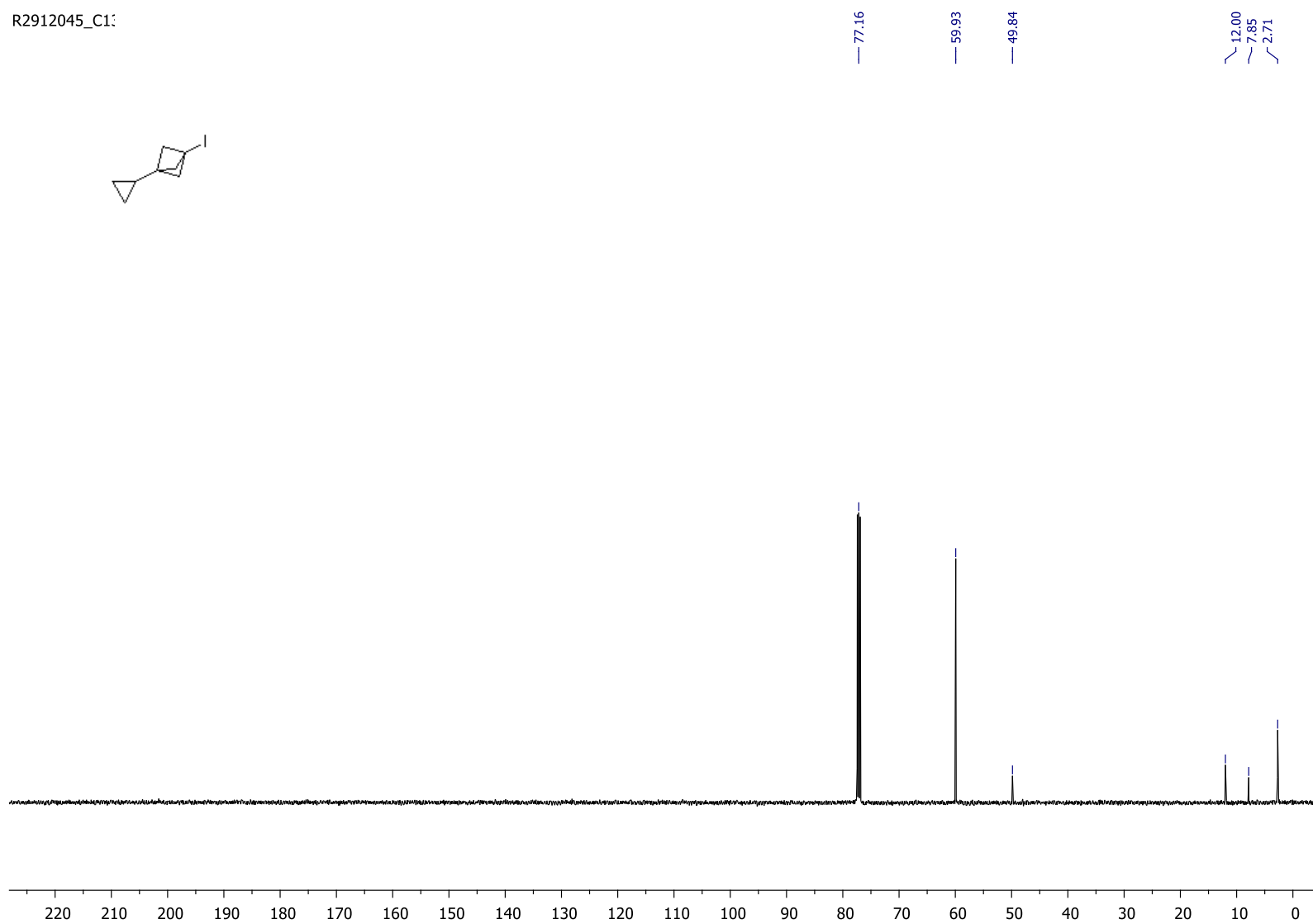
R2912045

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

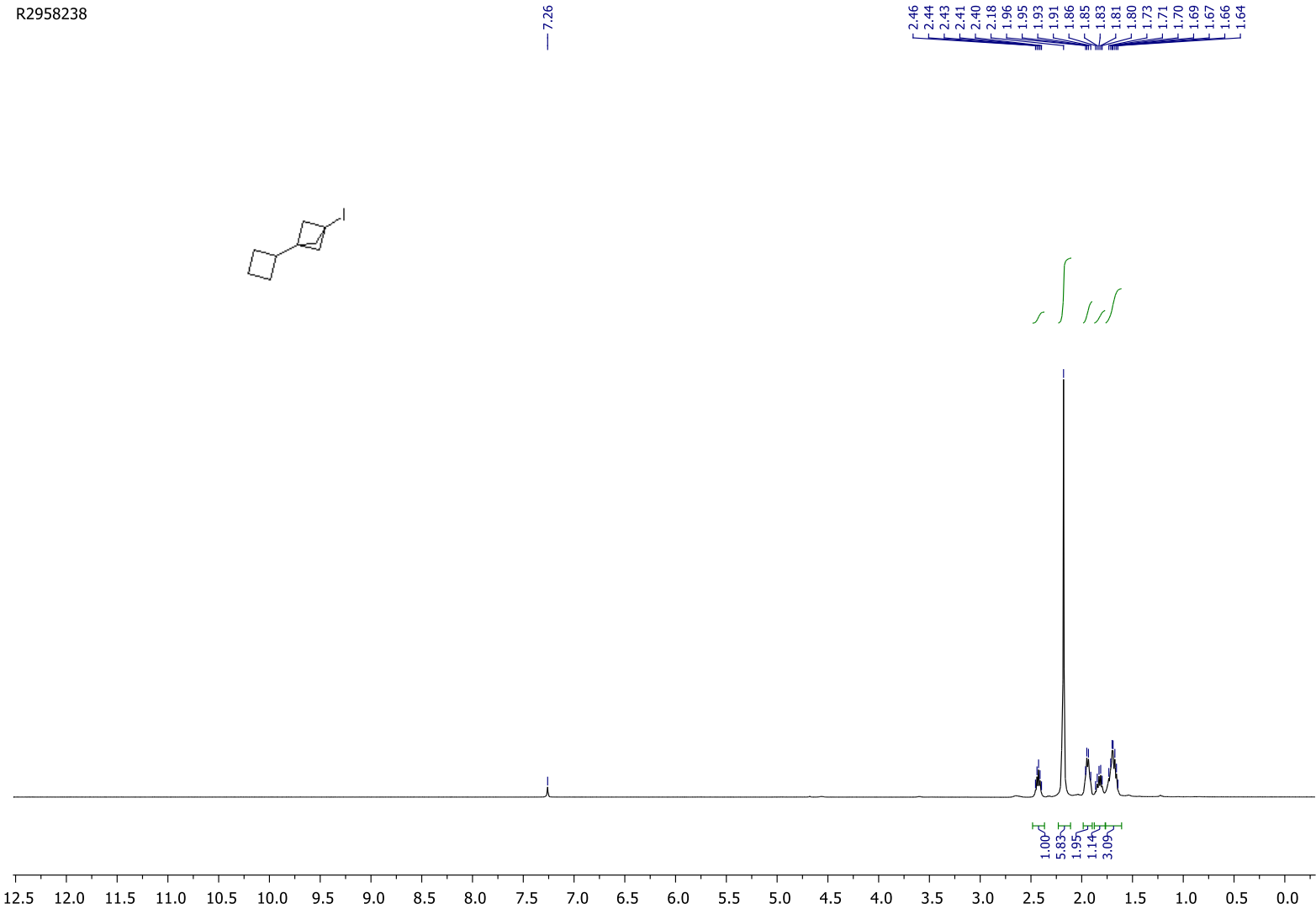
R2912045_C1:



Compound 51

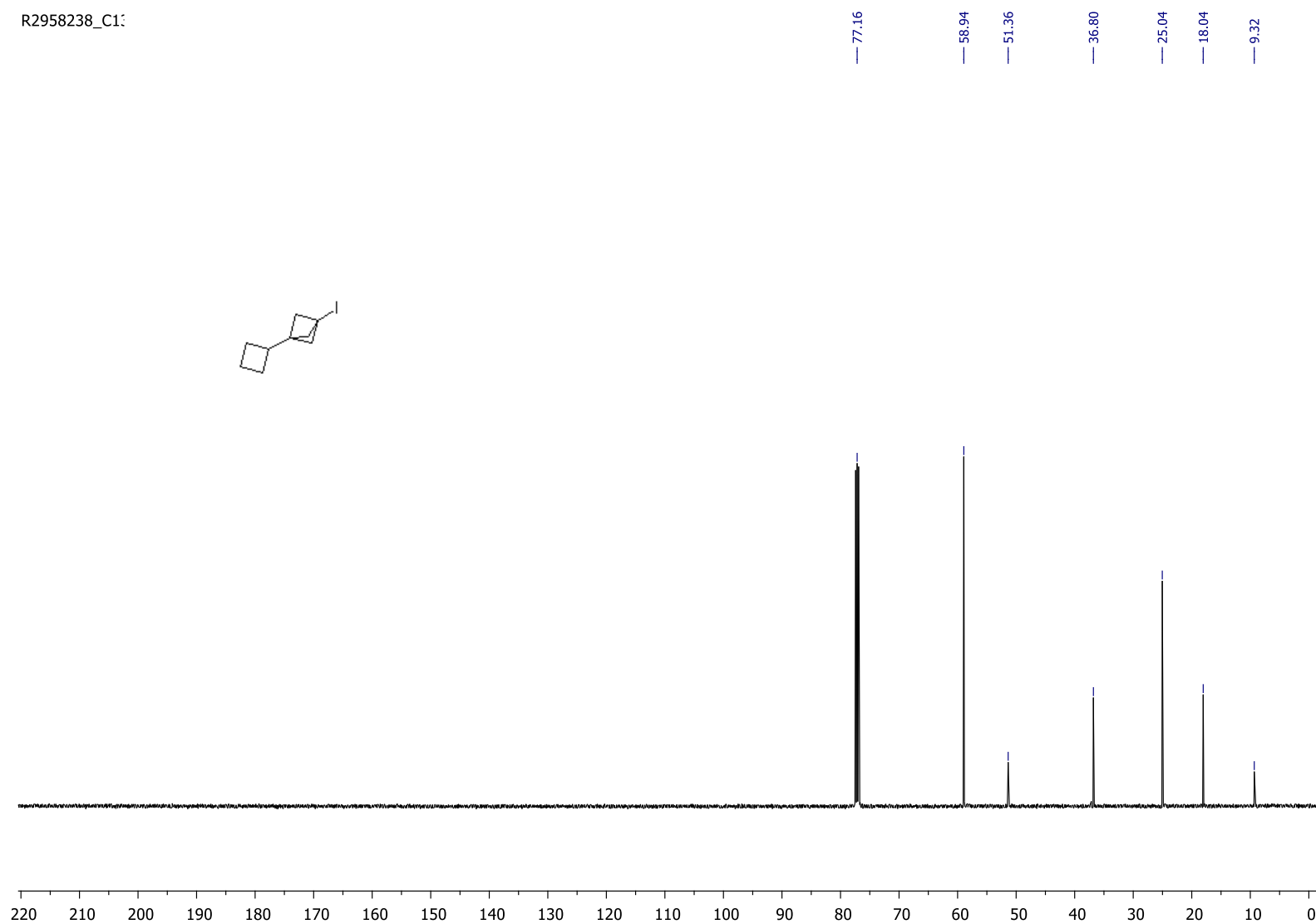
R2958238

¹H NMR (500 MHz, CDCl₃)



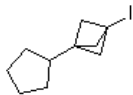
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2958238_C1:

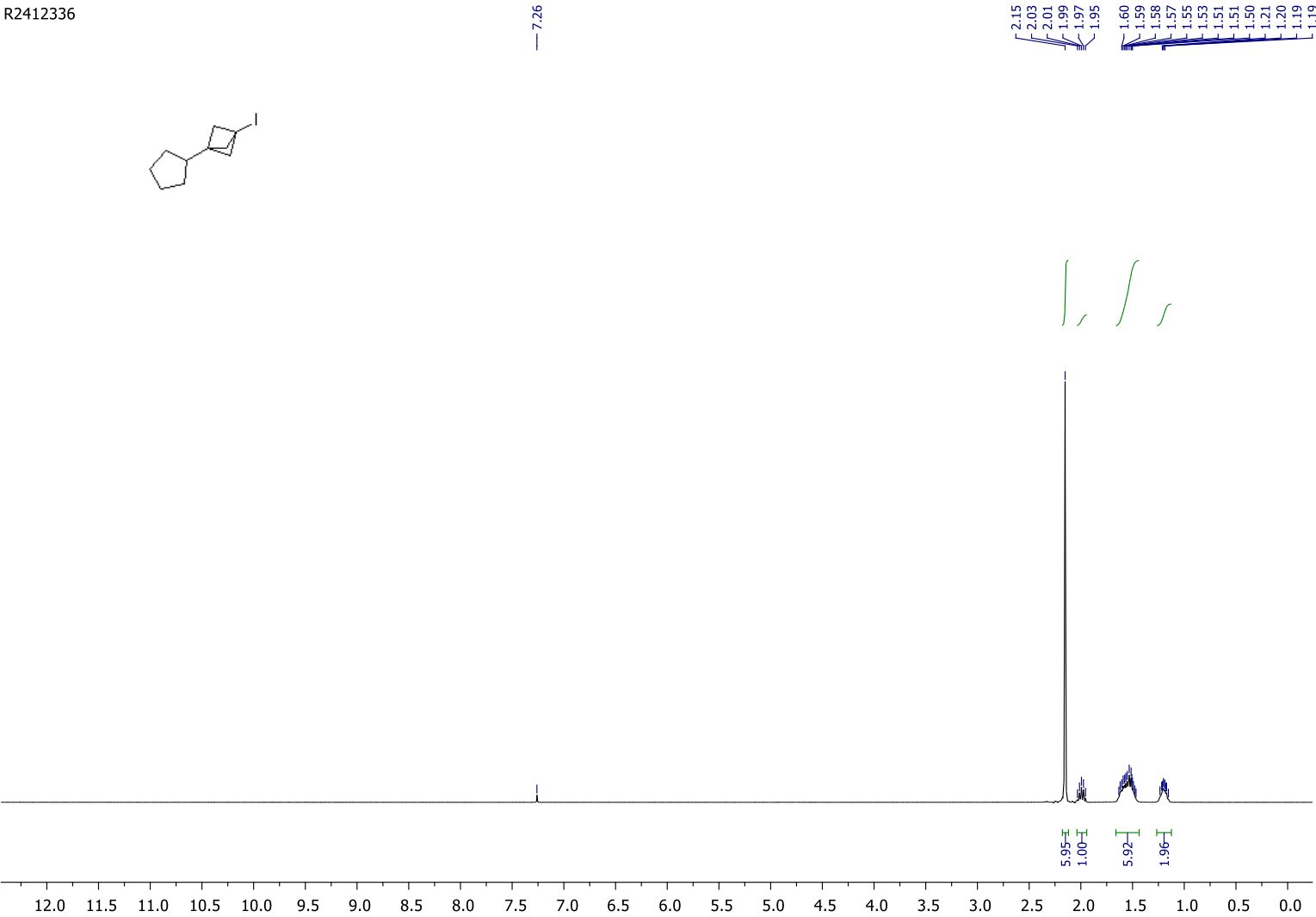


Compound 52

R2412336

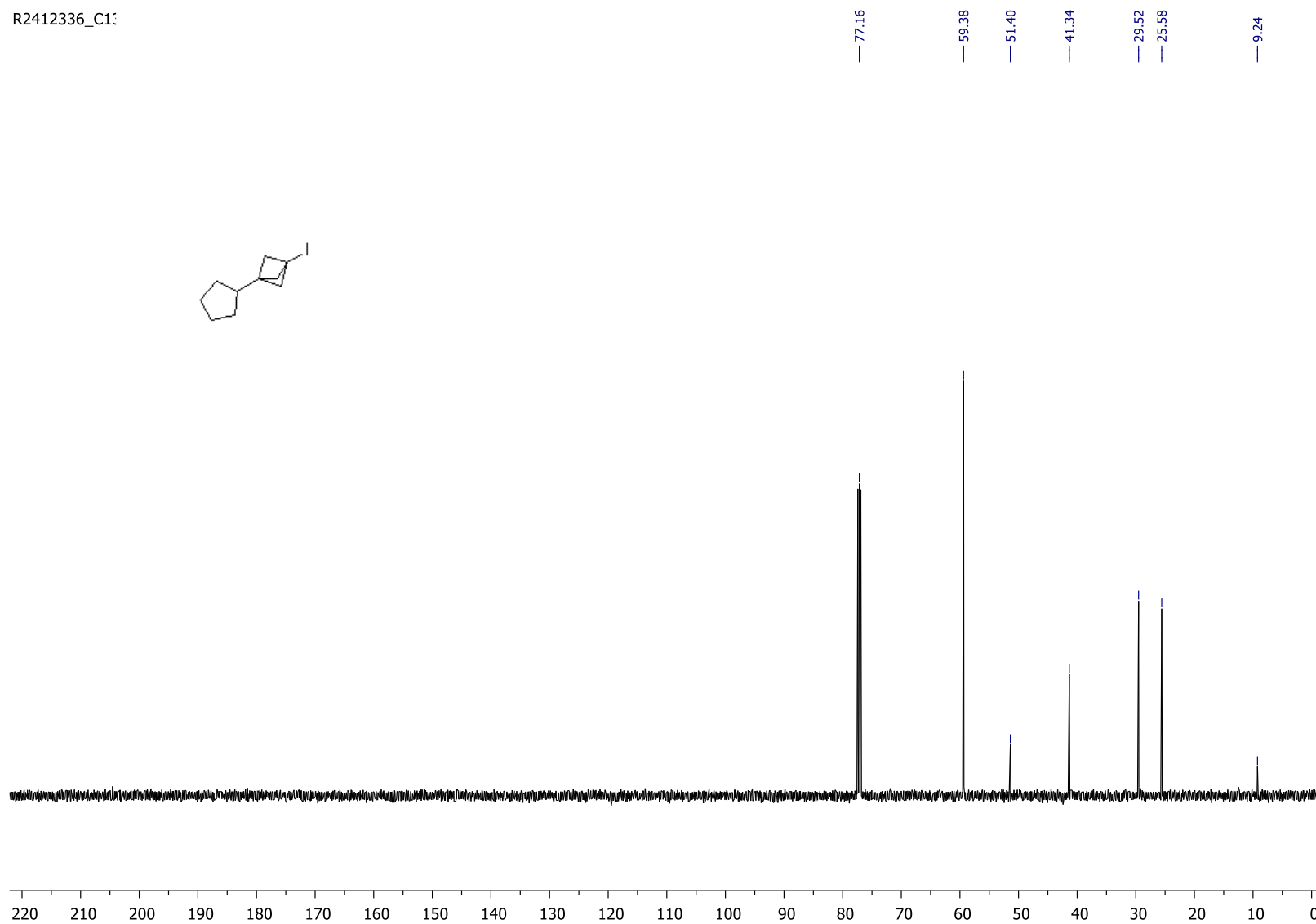
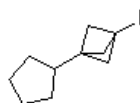


¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

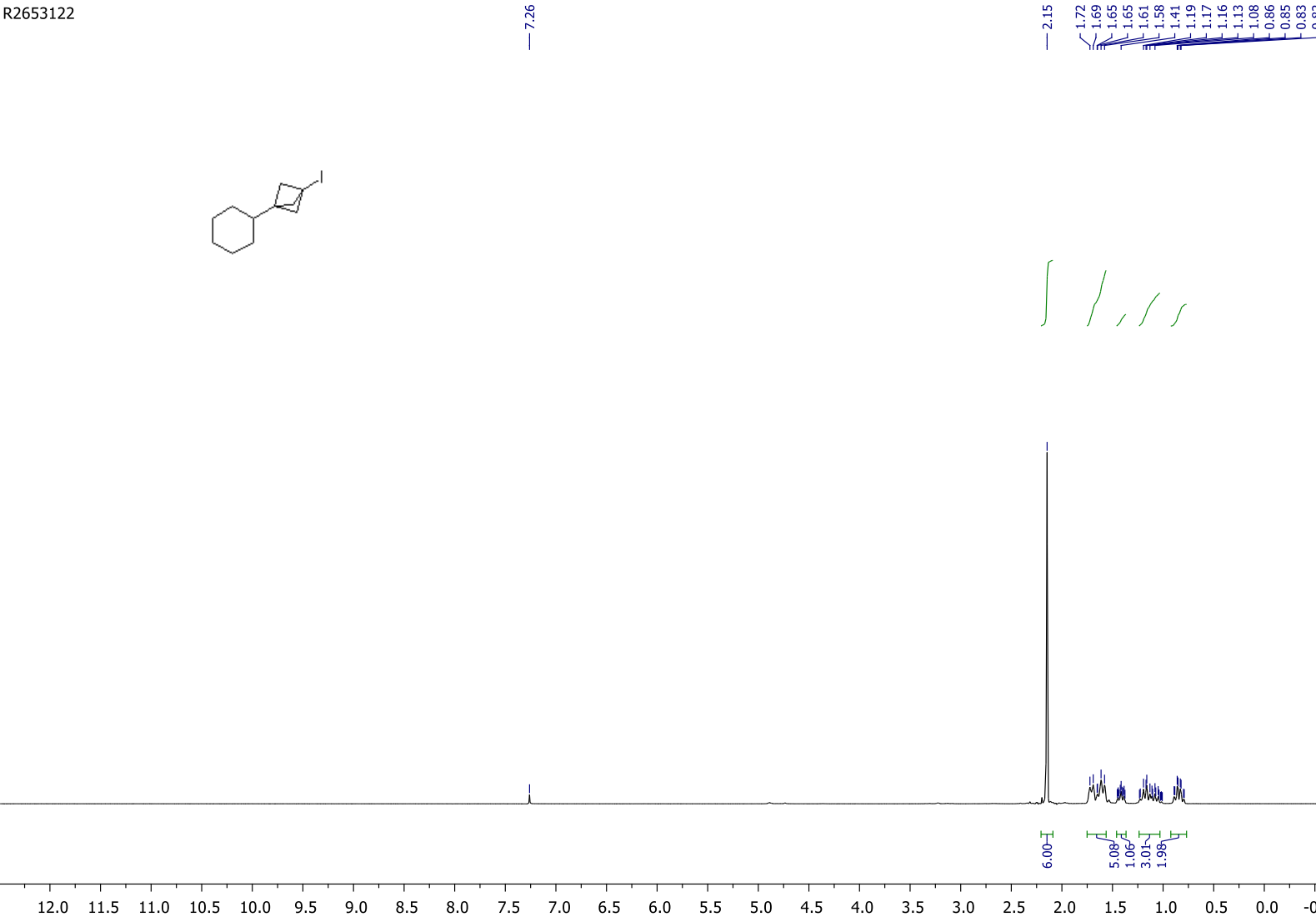
R2412336_C1:



Compound 53

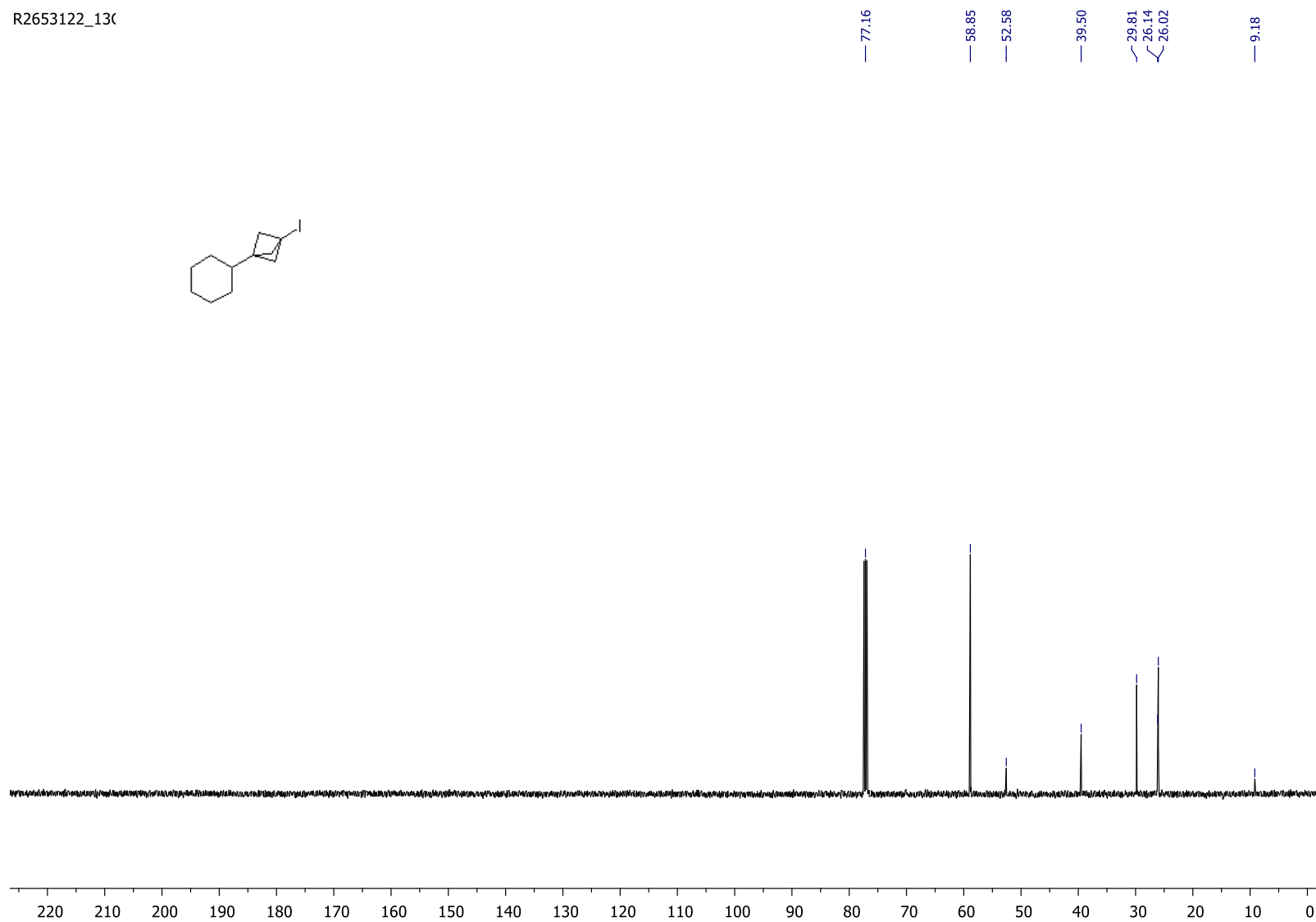
R2653122

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

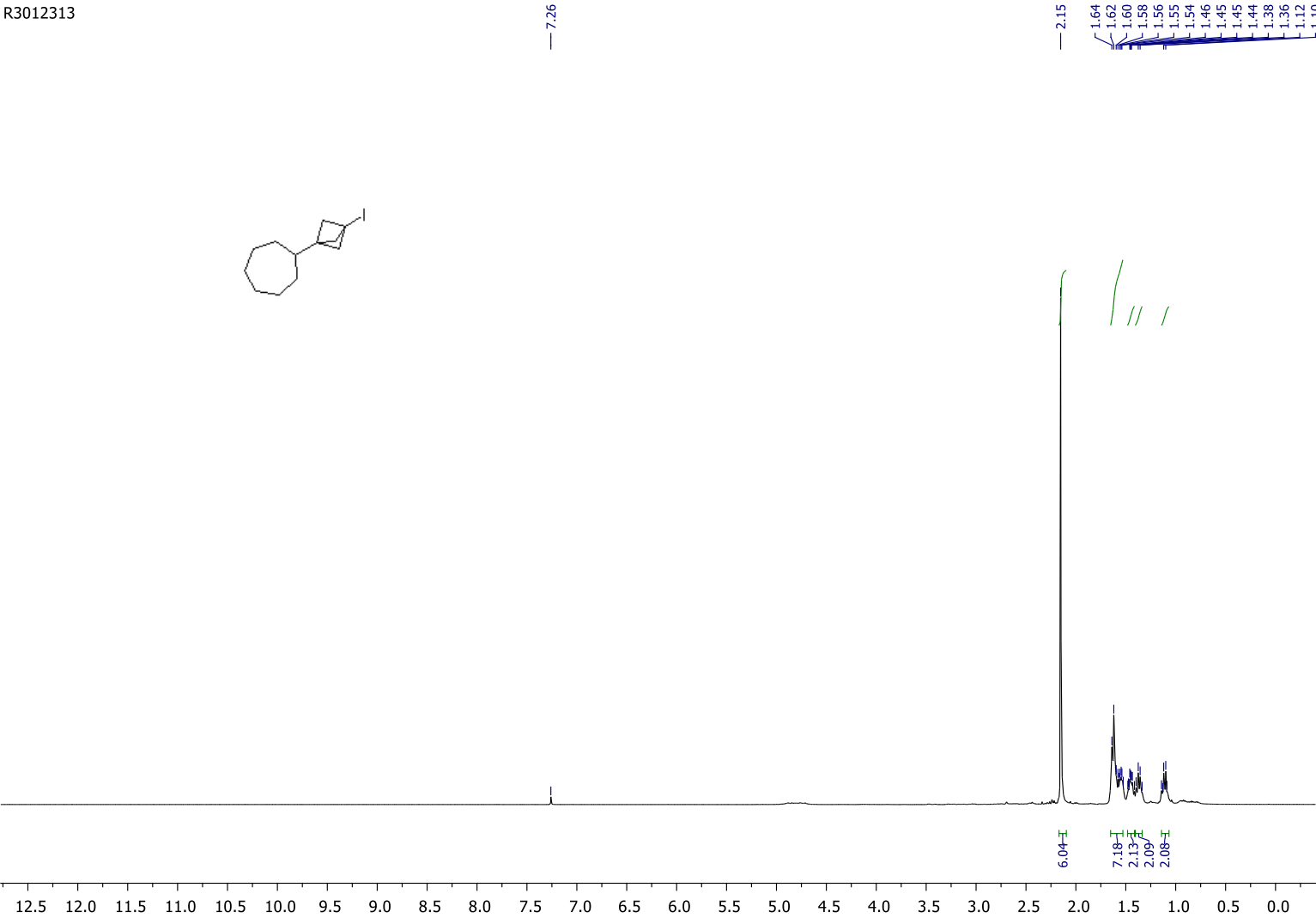
R2653122_13C



Compound 54

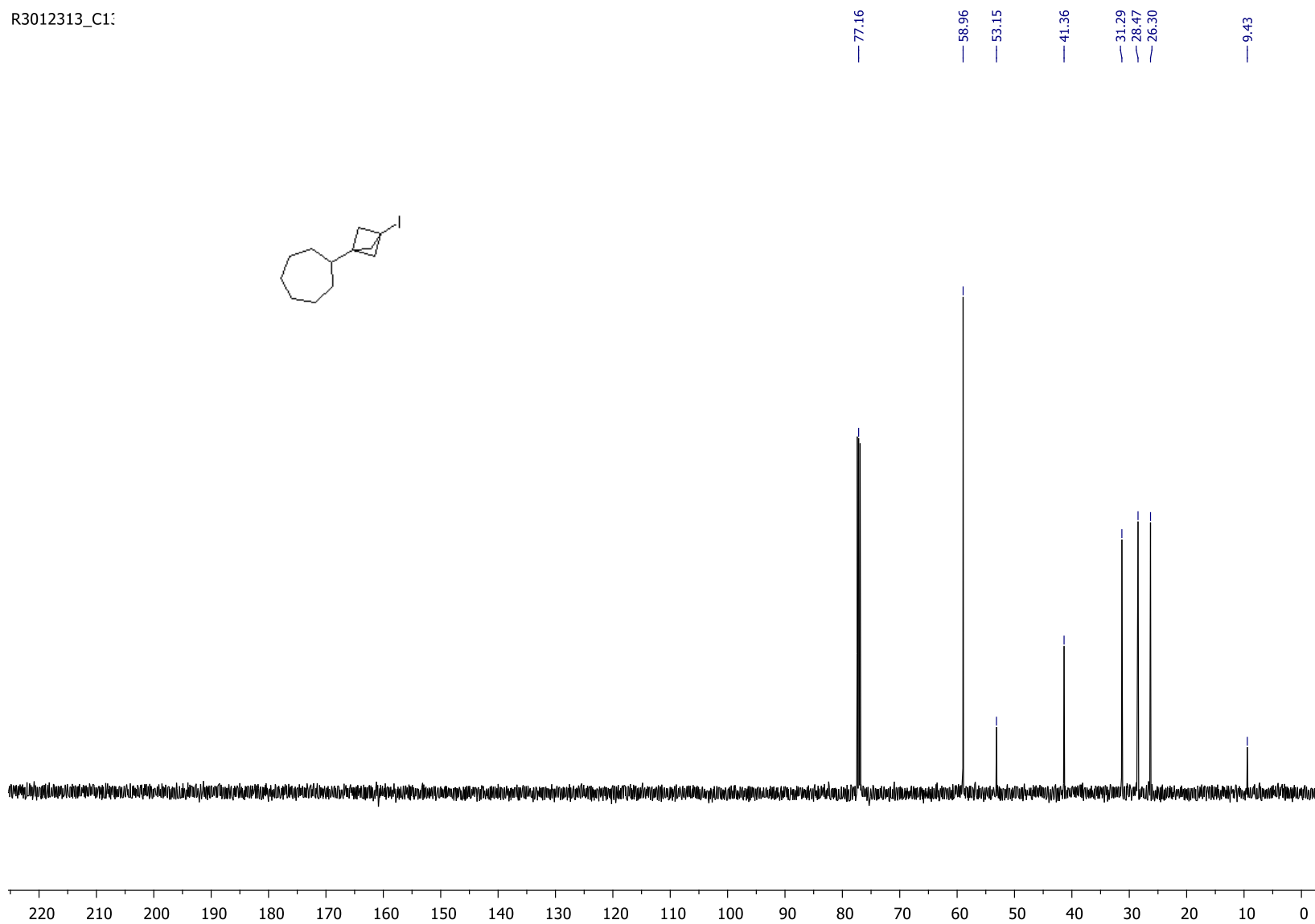
R3012313

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

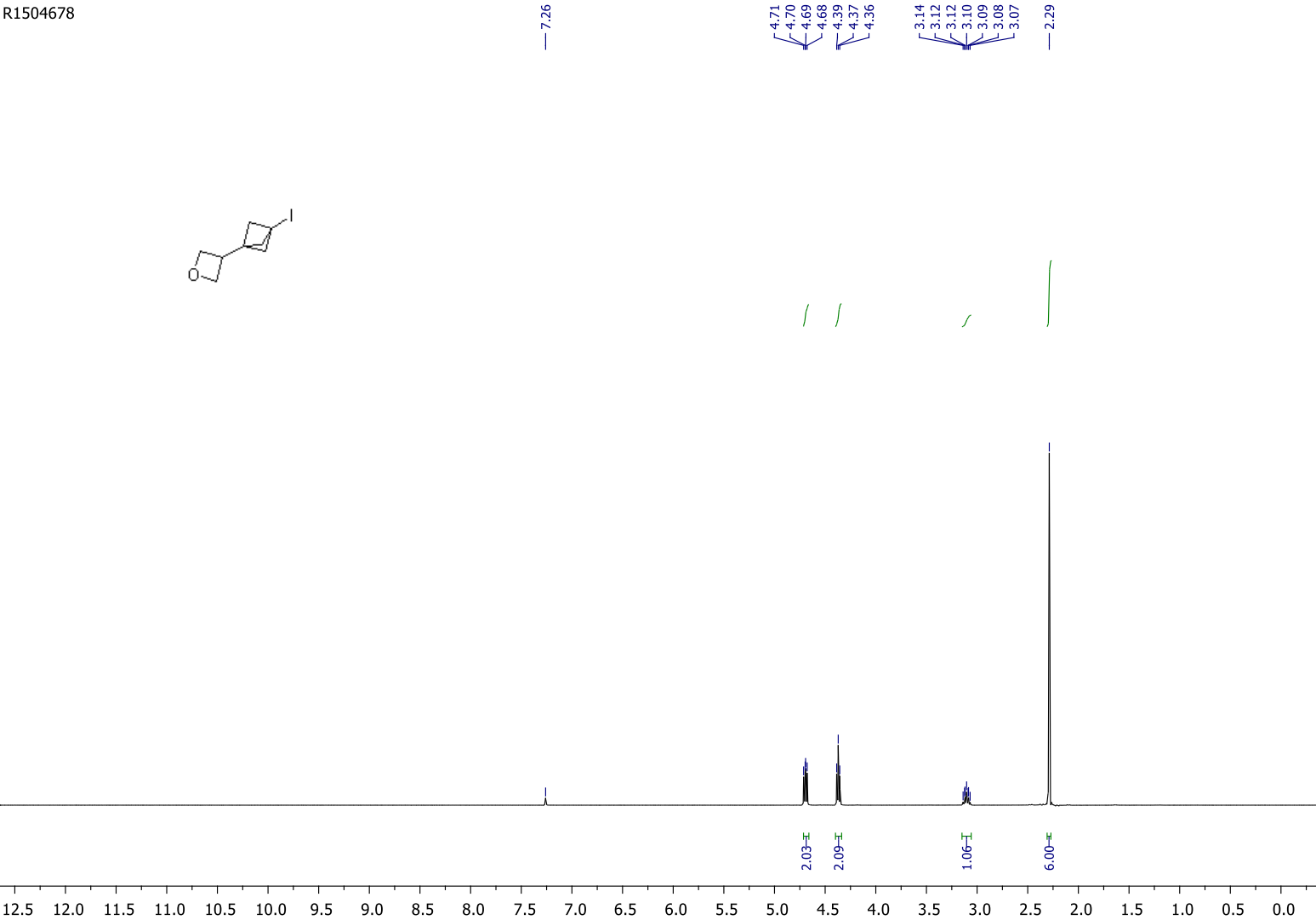
R3012313_C13



Compound 55

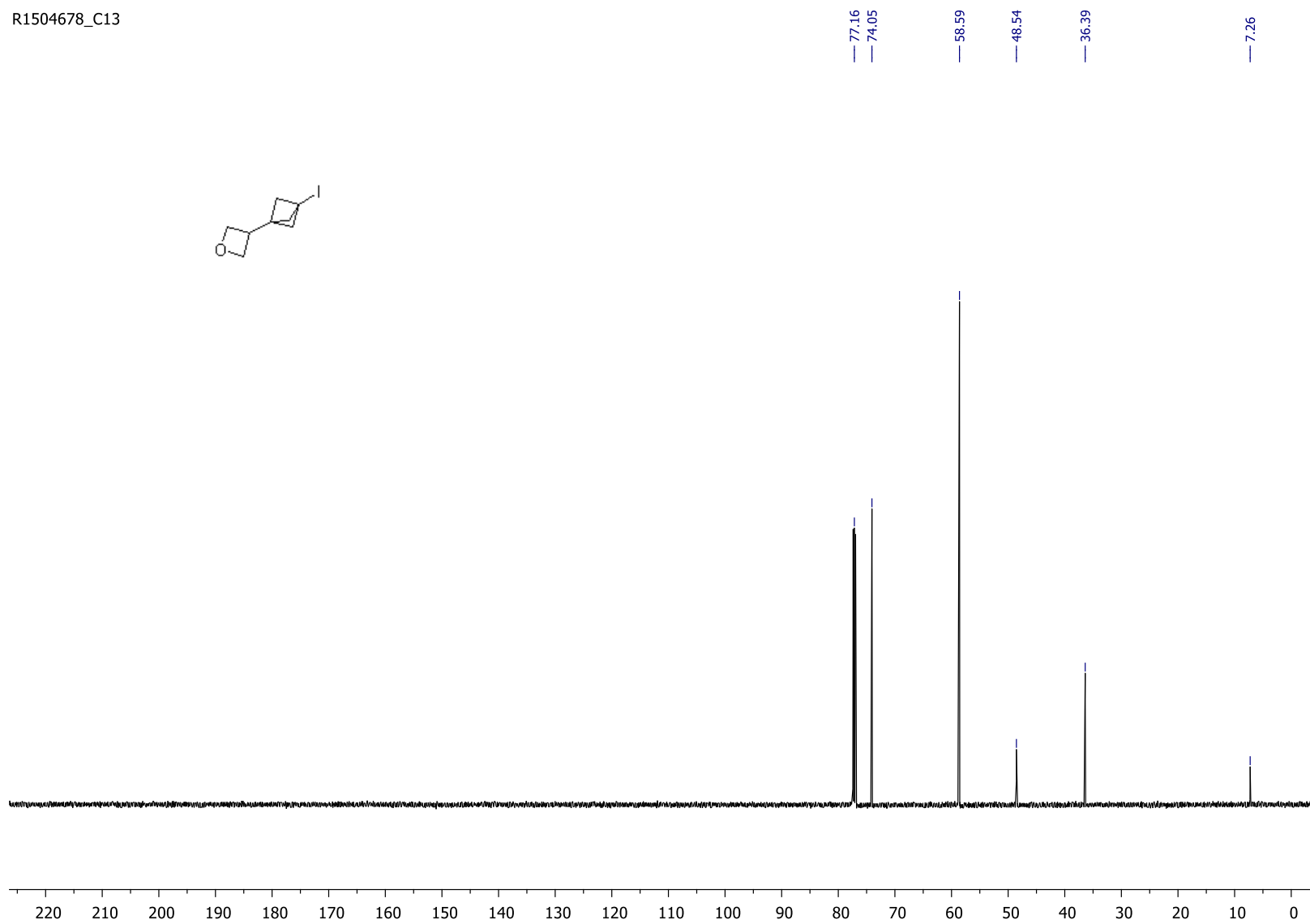
R1504678

¹H NMR (400 MHz, CDCl₃)



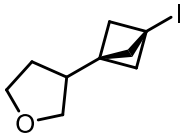
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

R1504678_C13

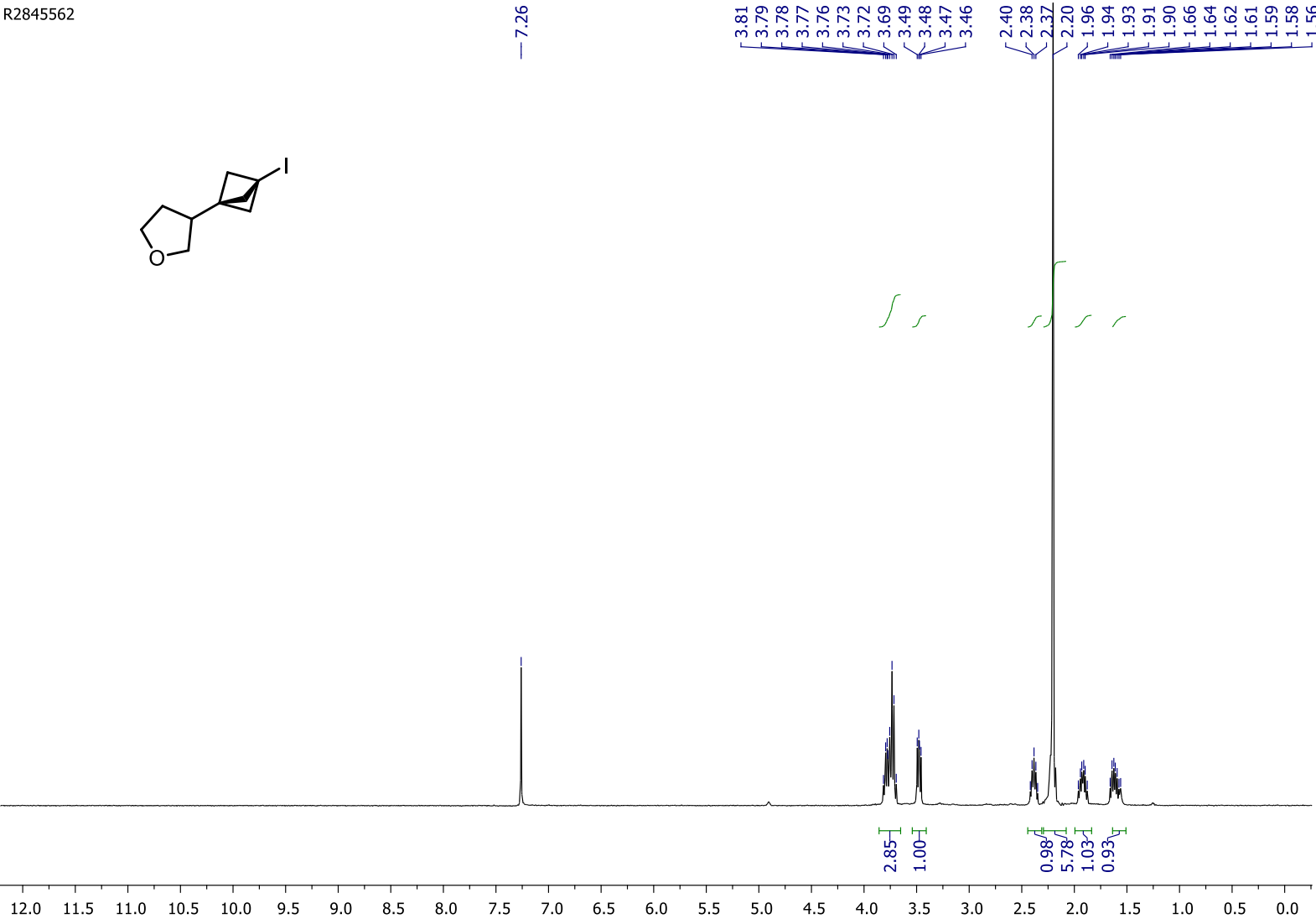


Compound 56

R2845562

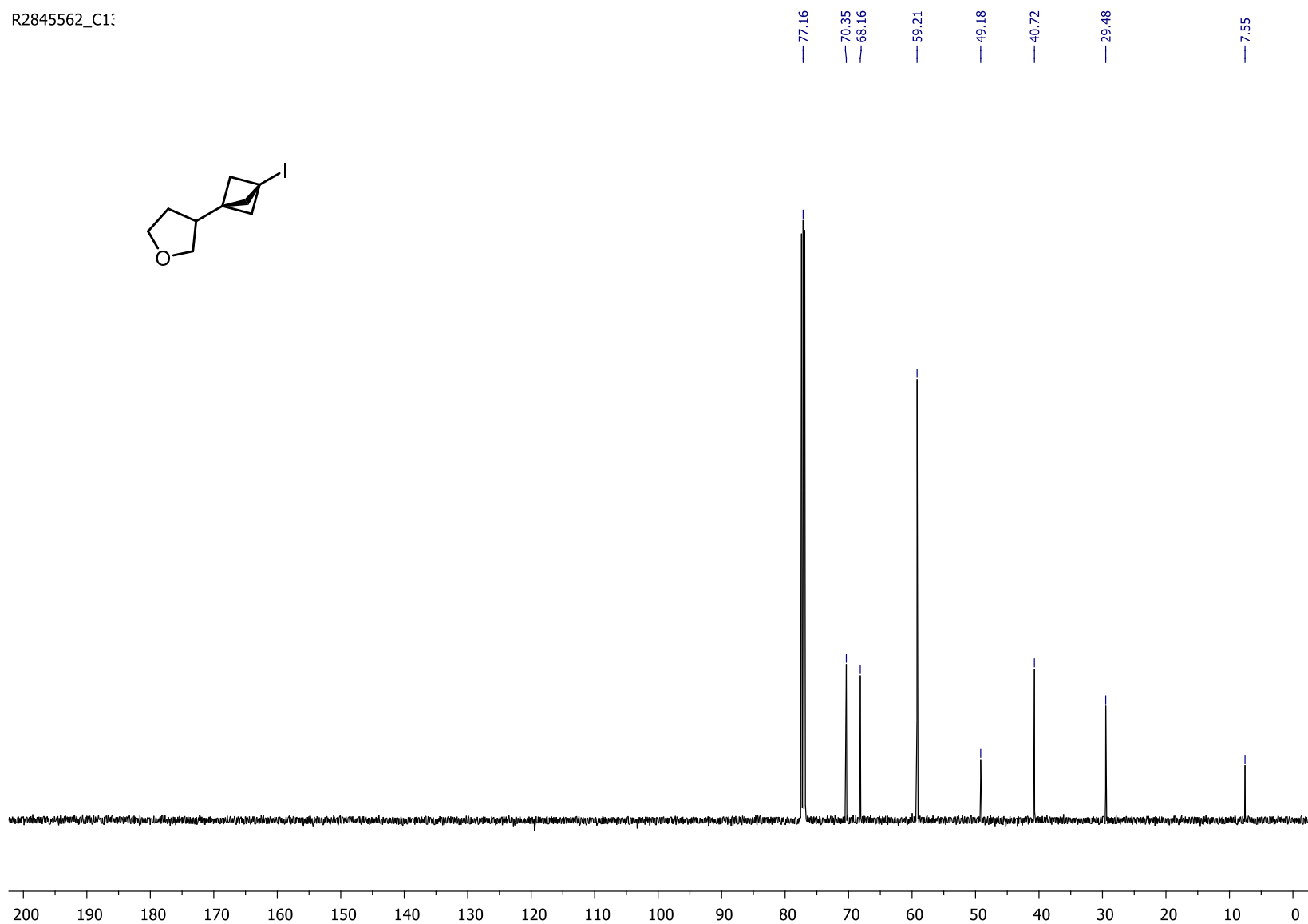


¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

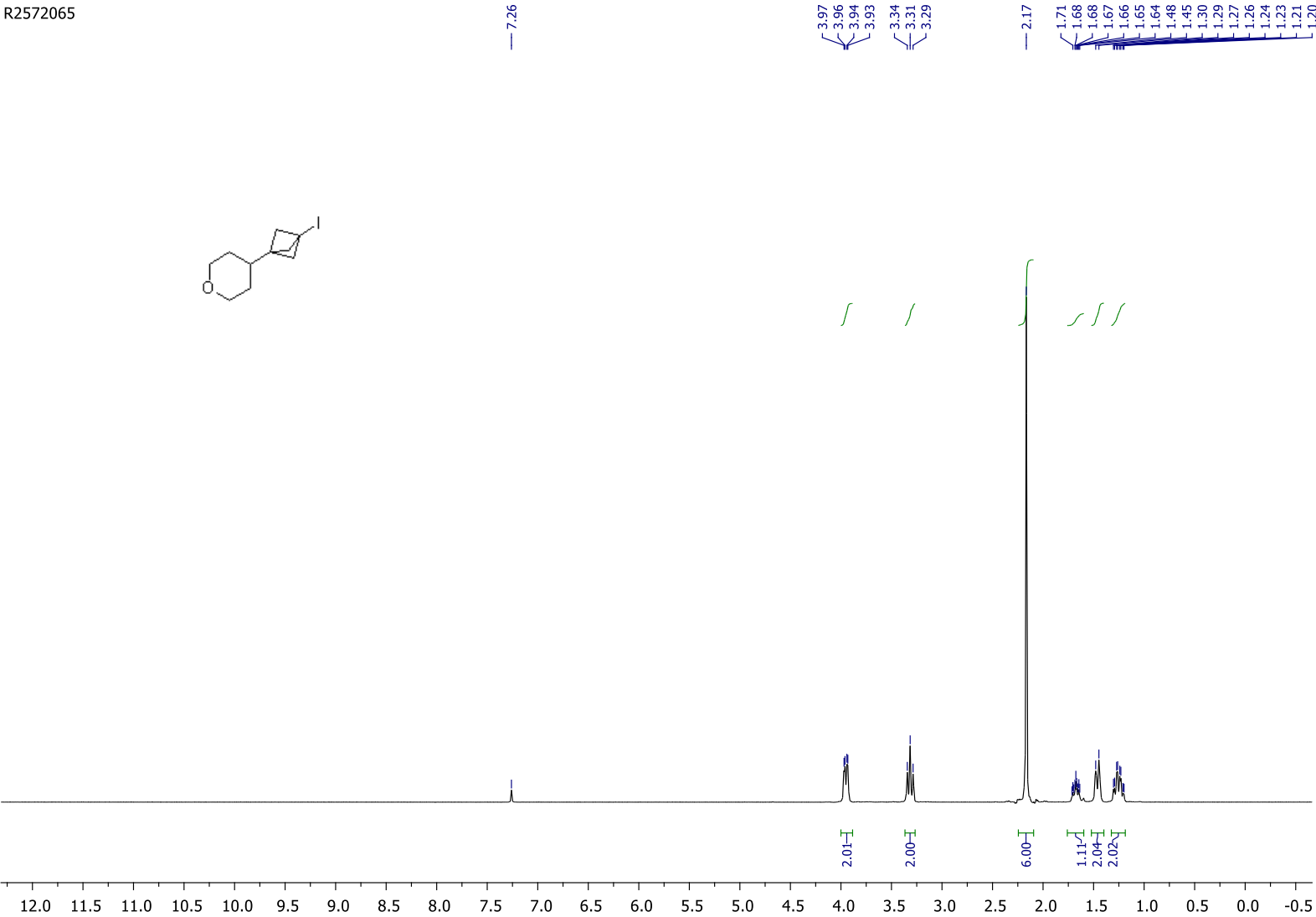
R2845562_C1:



Compound 57

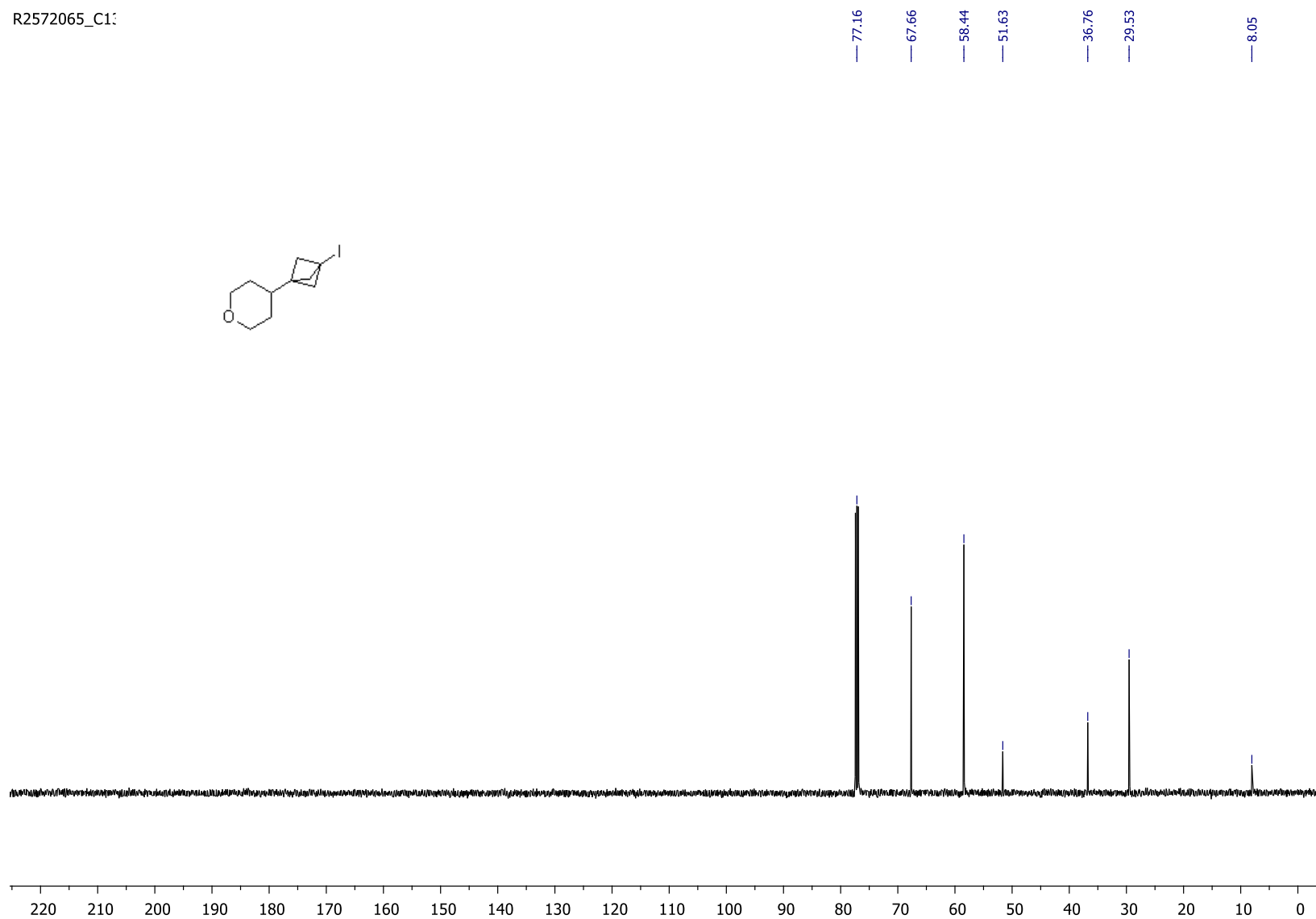
R2572065

¹H NMR (400 MHz, CDCl₃)



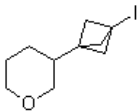
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2572065_C13

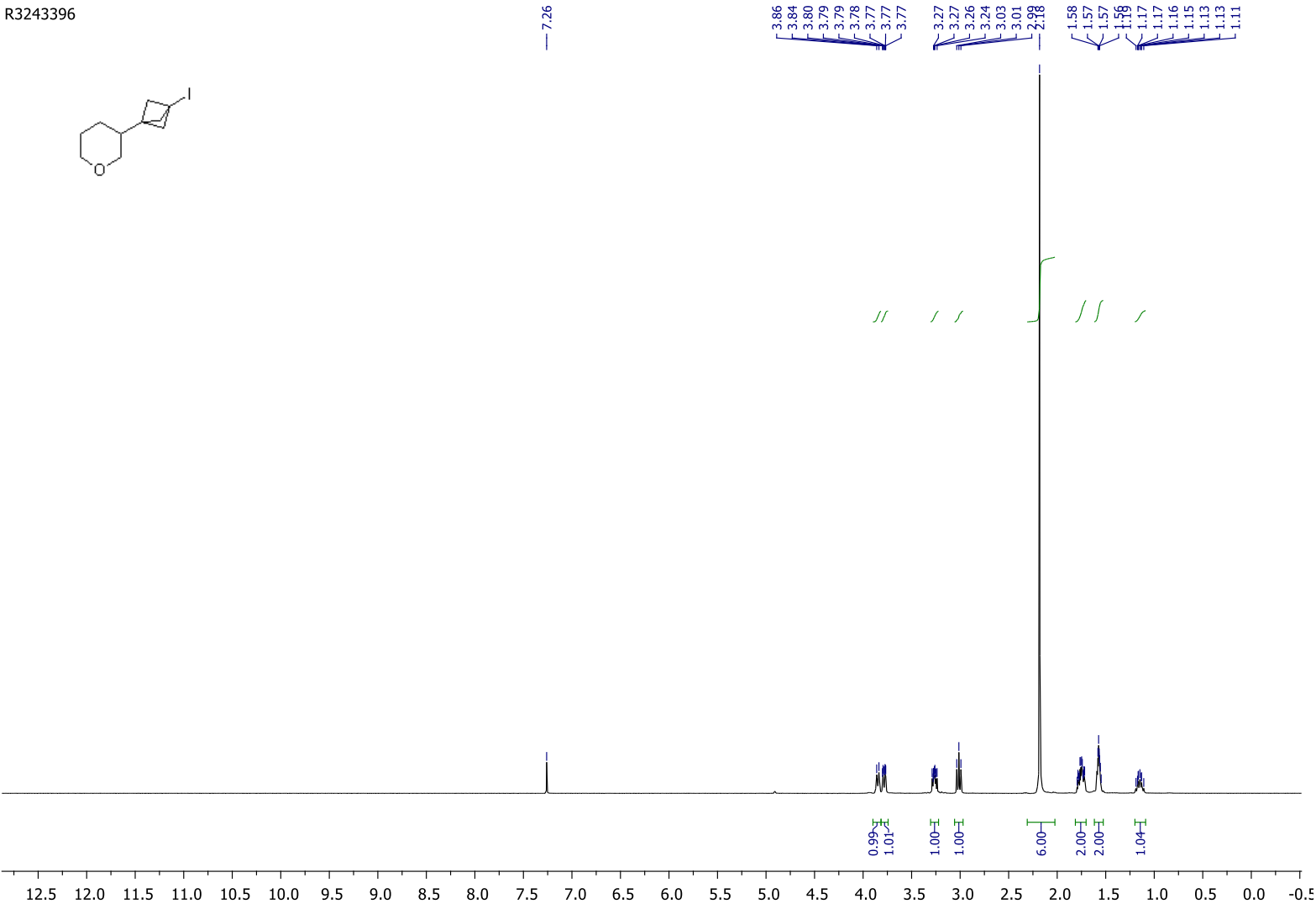


Compound 58

R3243396

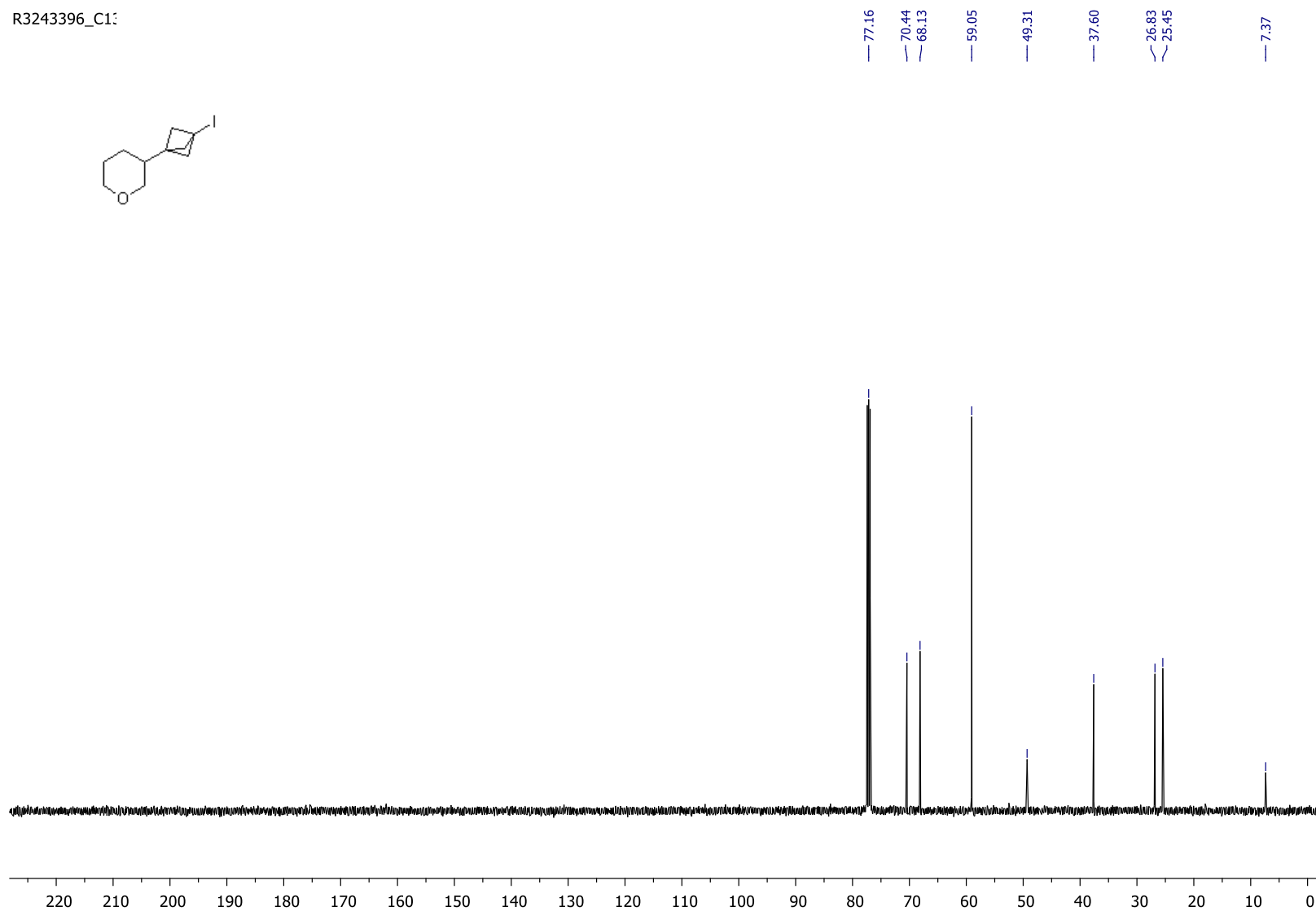
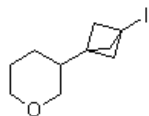


¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

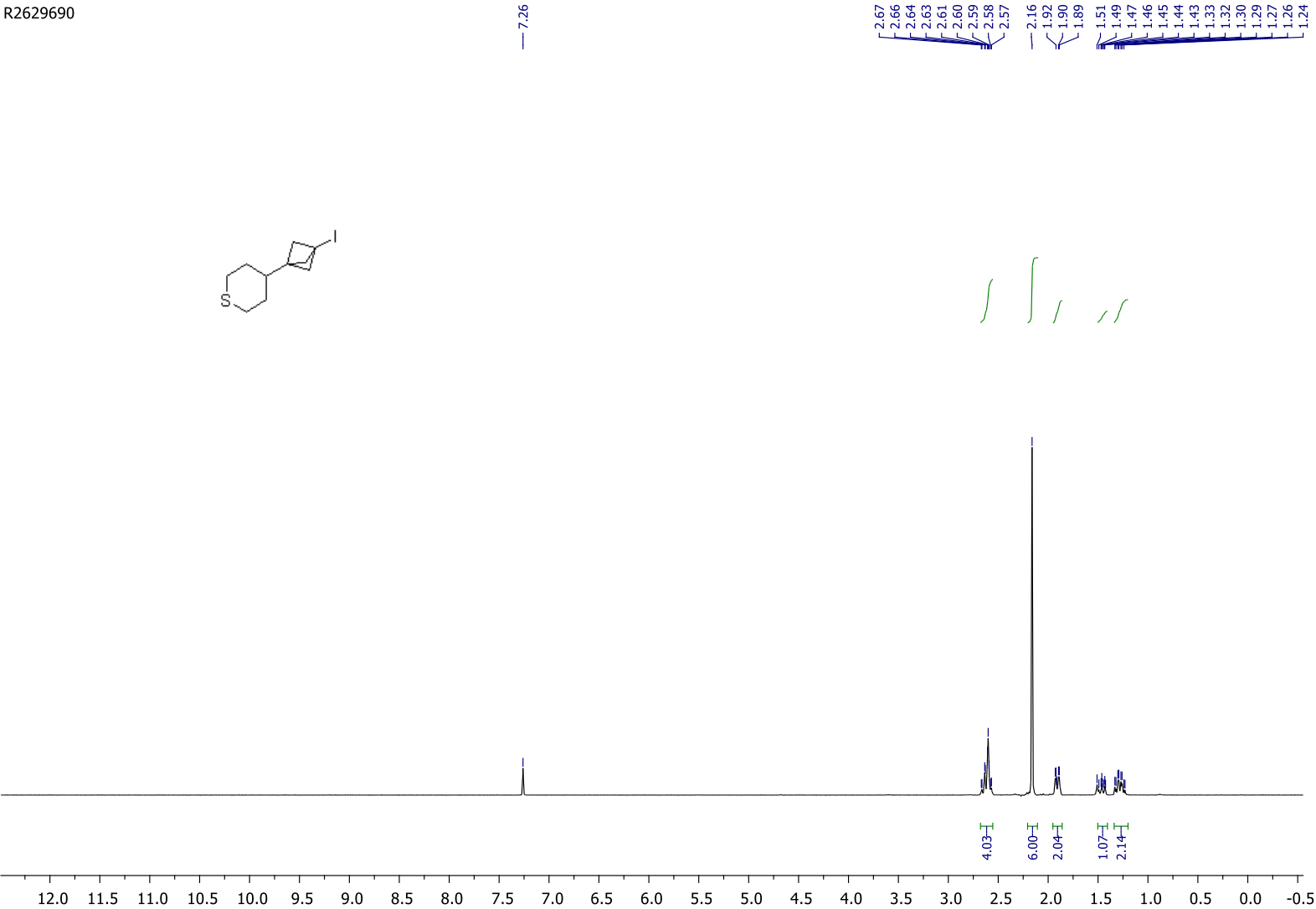
R3243396_C1:



Compound 59

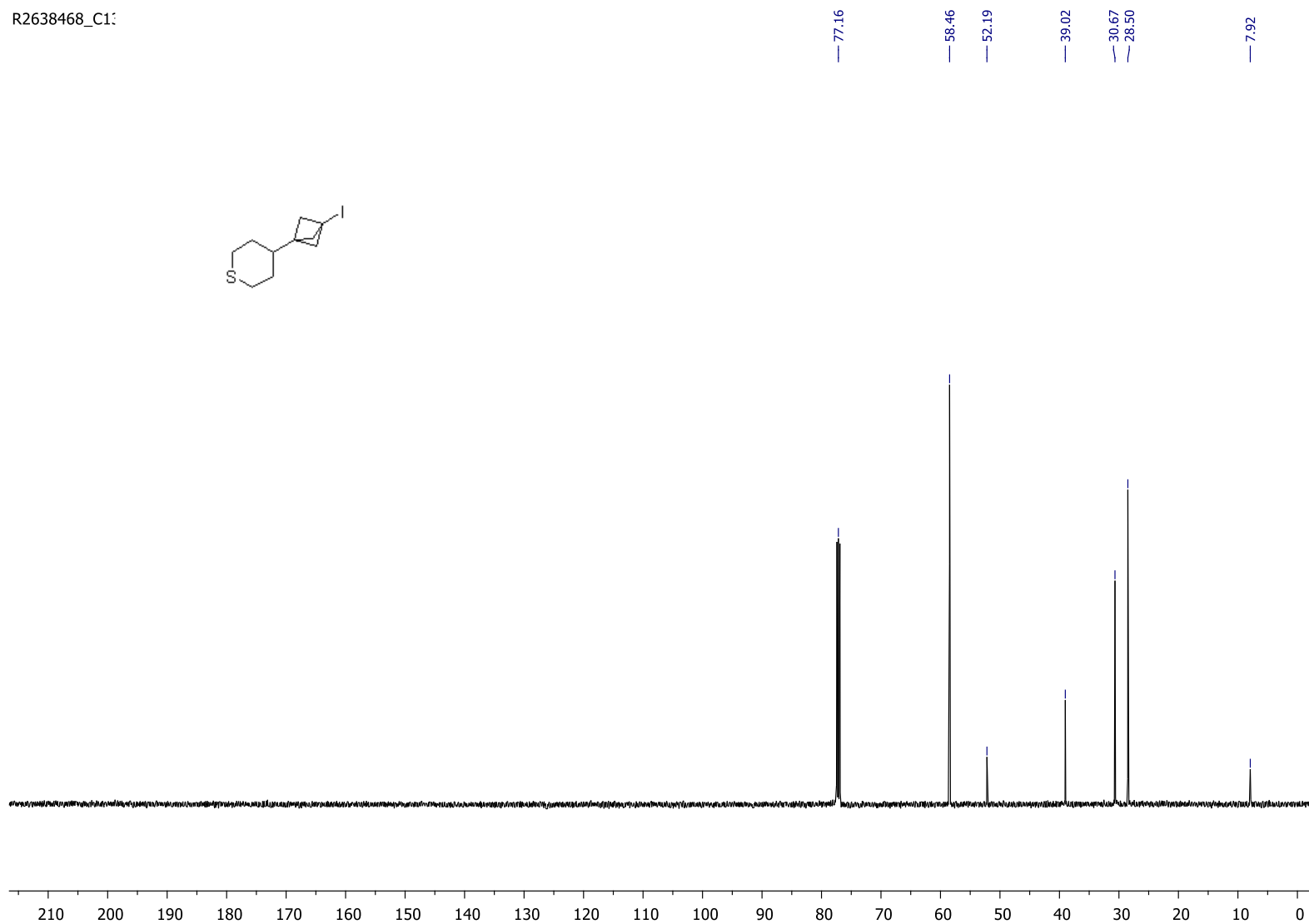
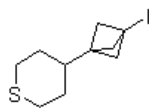
R2629690

¹H NMR (400 MHz, CDCl₃)



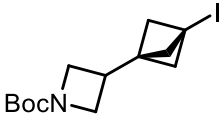
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2638468_C1:

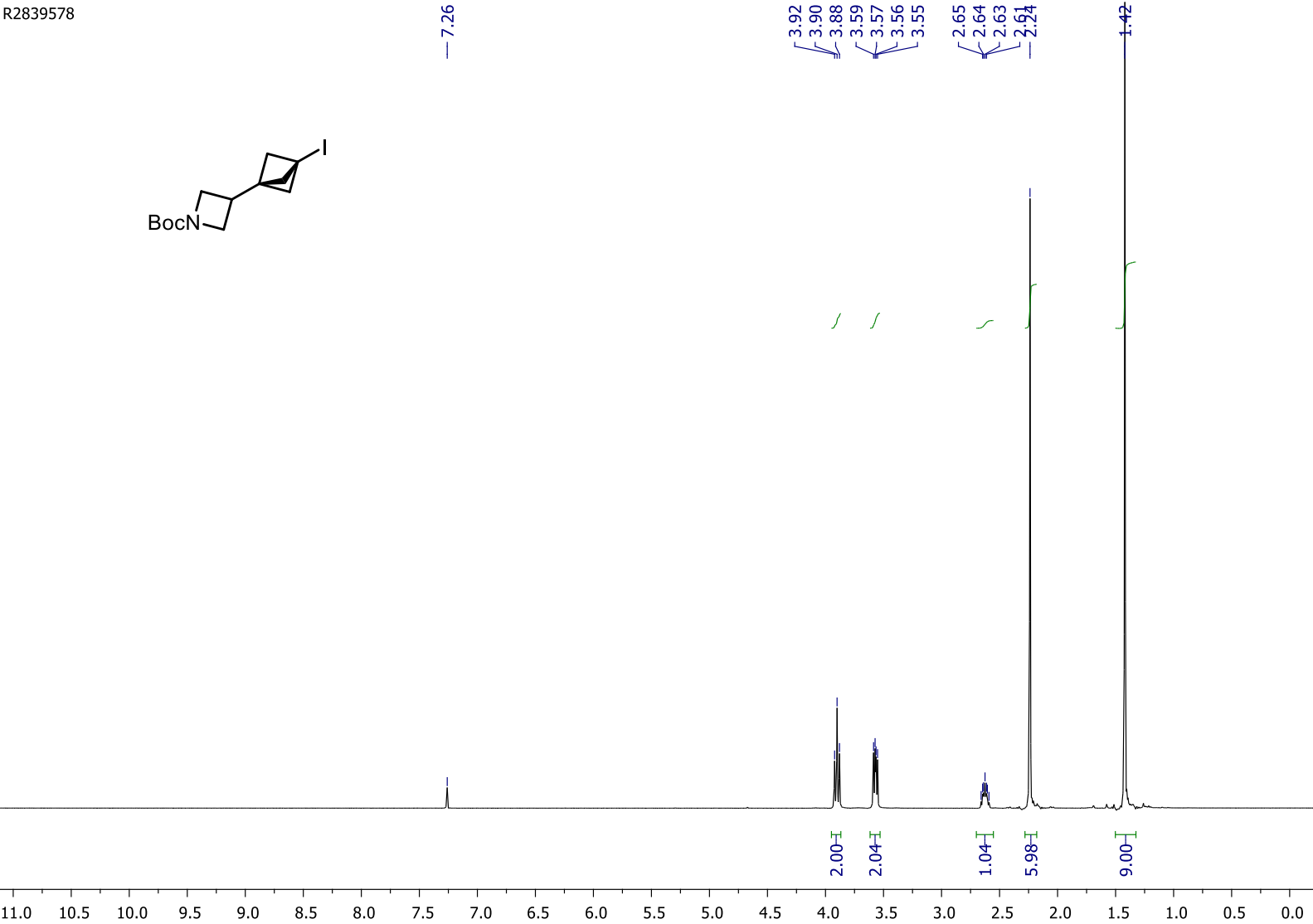


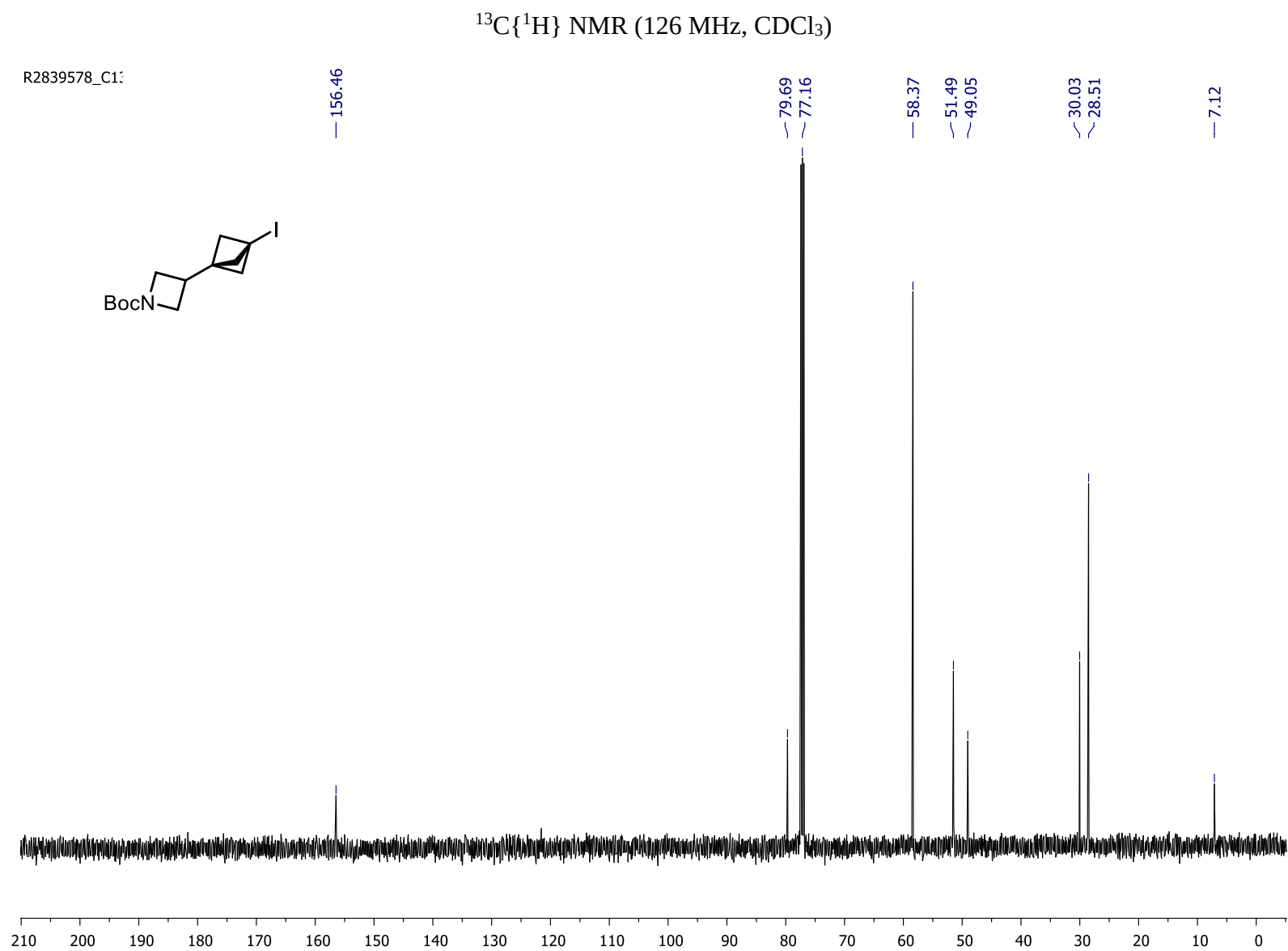
Compound 60

R2839578



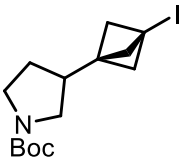
¹H NMR (400 MHz, CDCl₃)



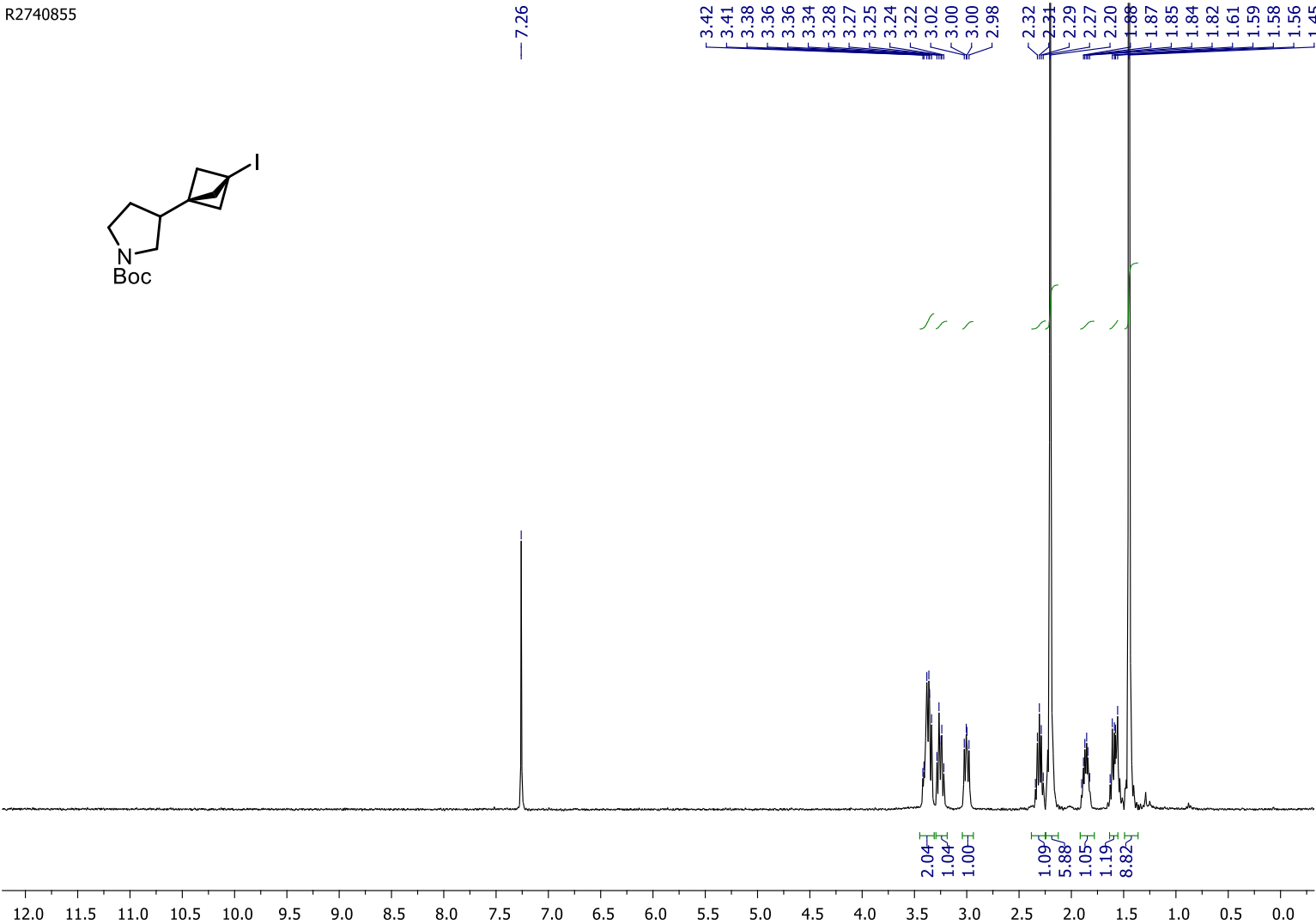


Compound 61

R2740855

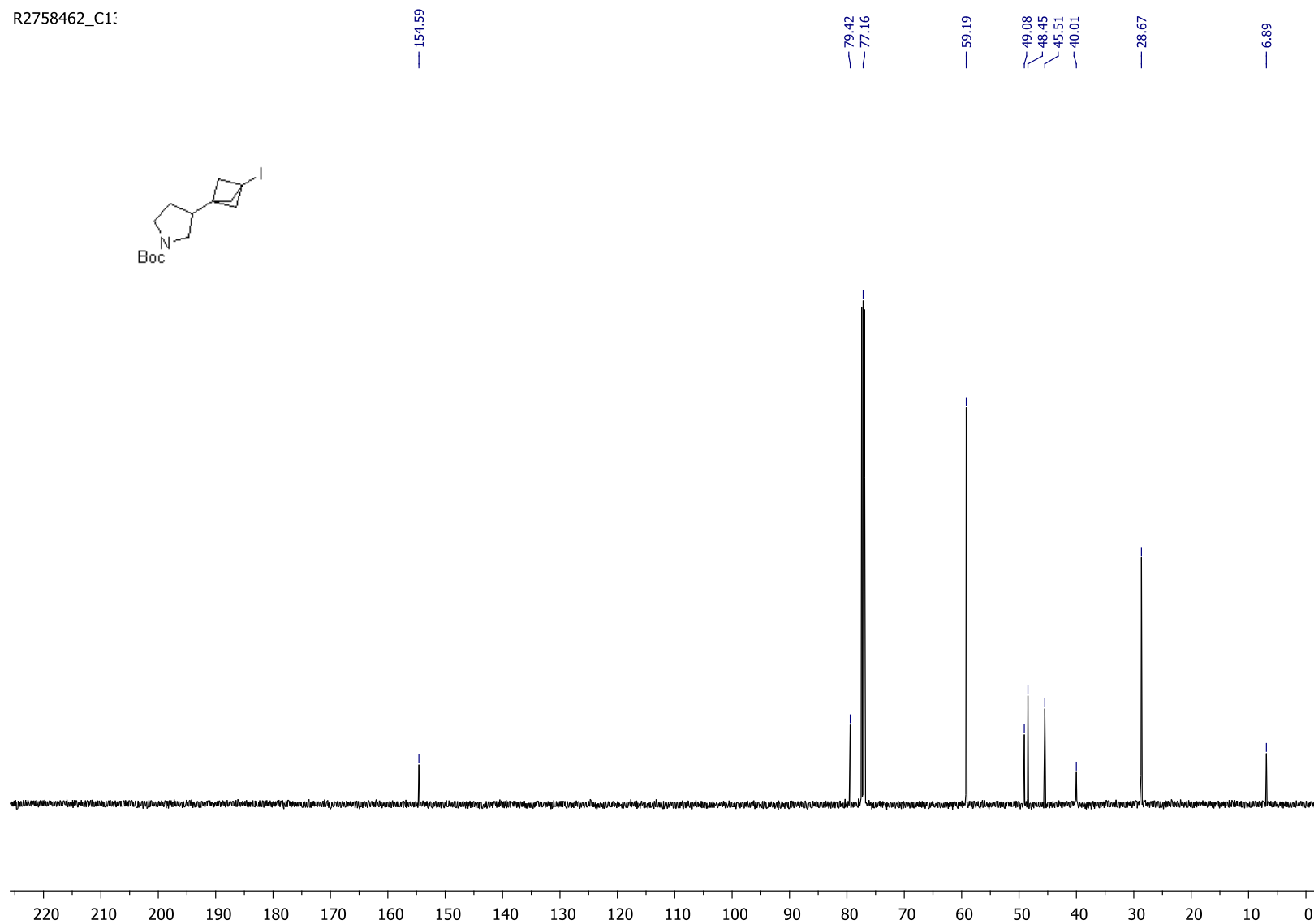
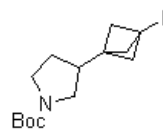


¹H NMR (400 MHz, CDCl₃)



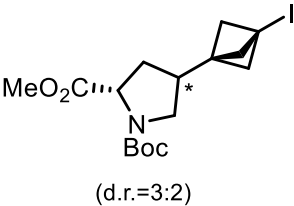
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2758462_C1:

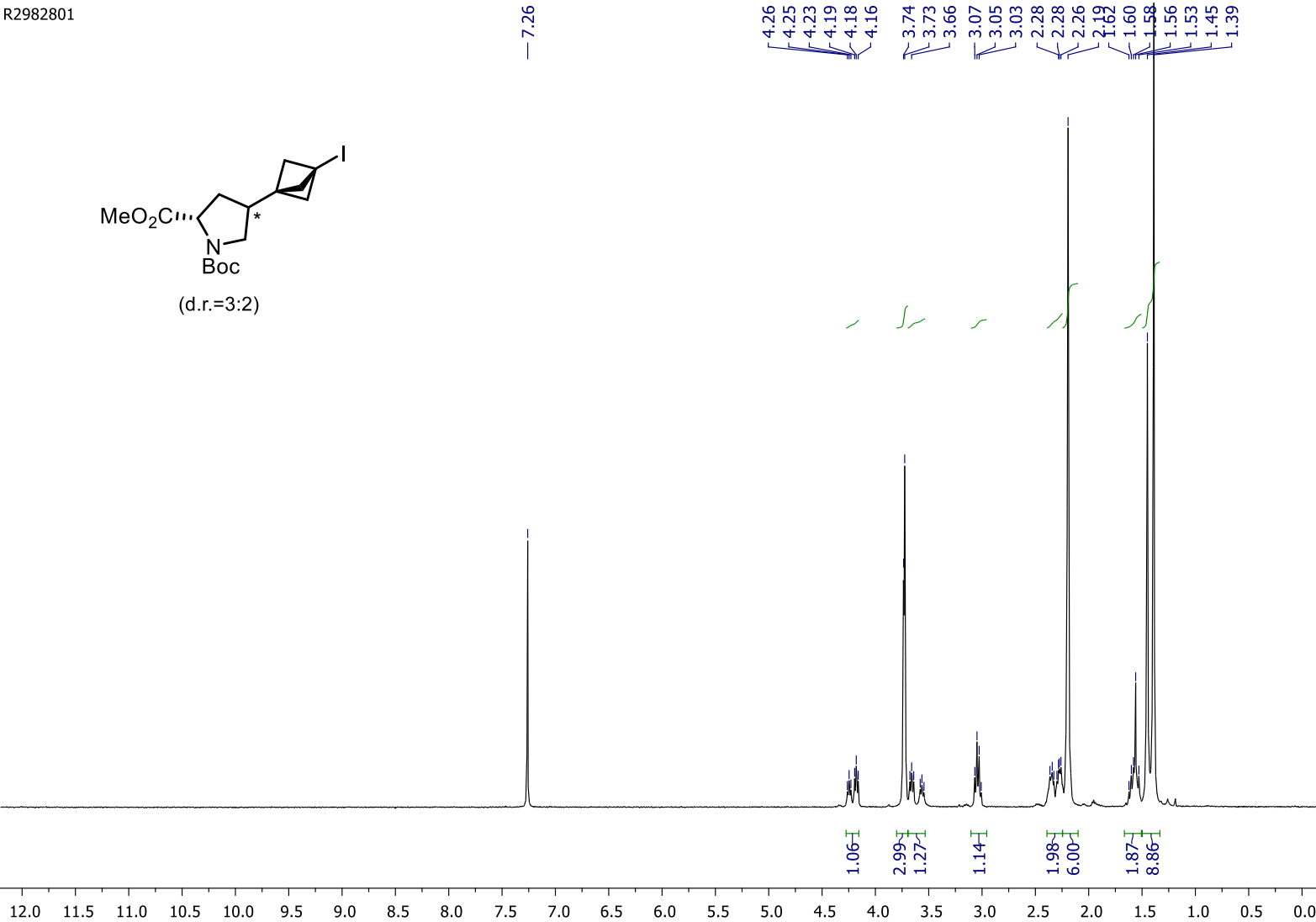


Compound 62

R2982801

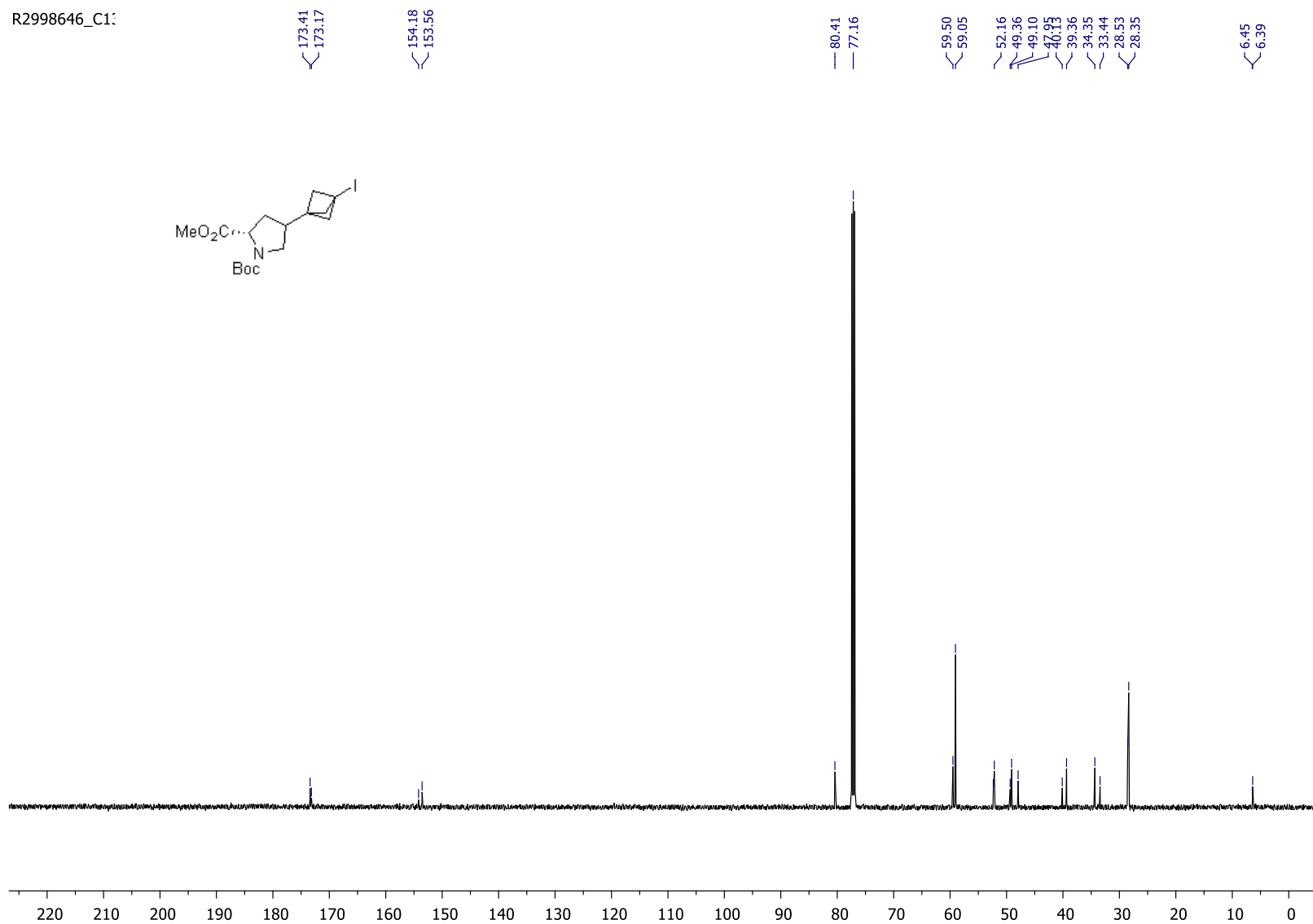
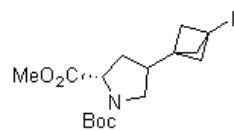


¹H NMR (500 MHz, CDCl₃)



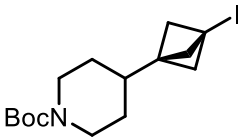
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2998646_C1:

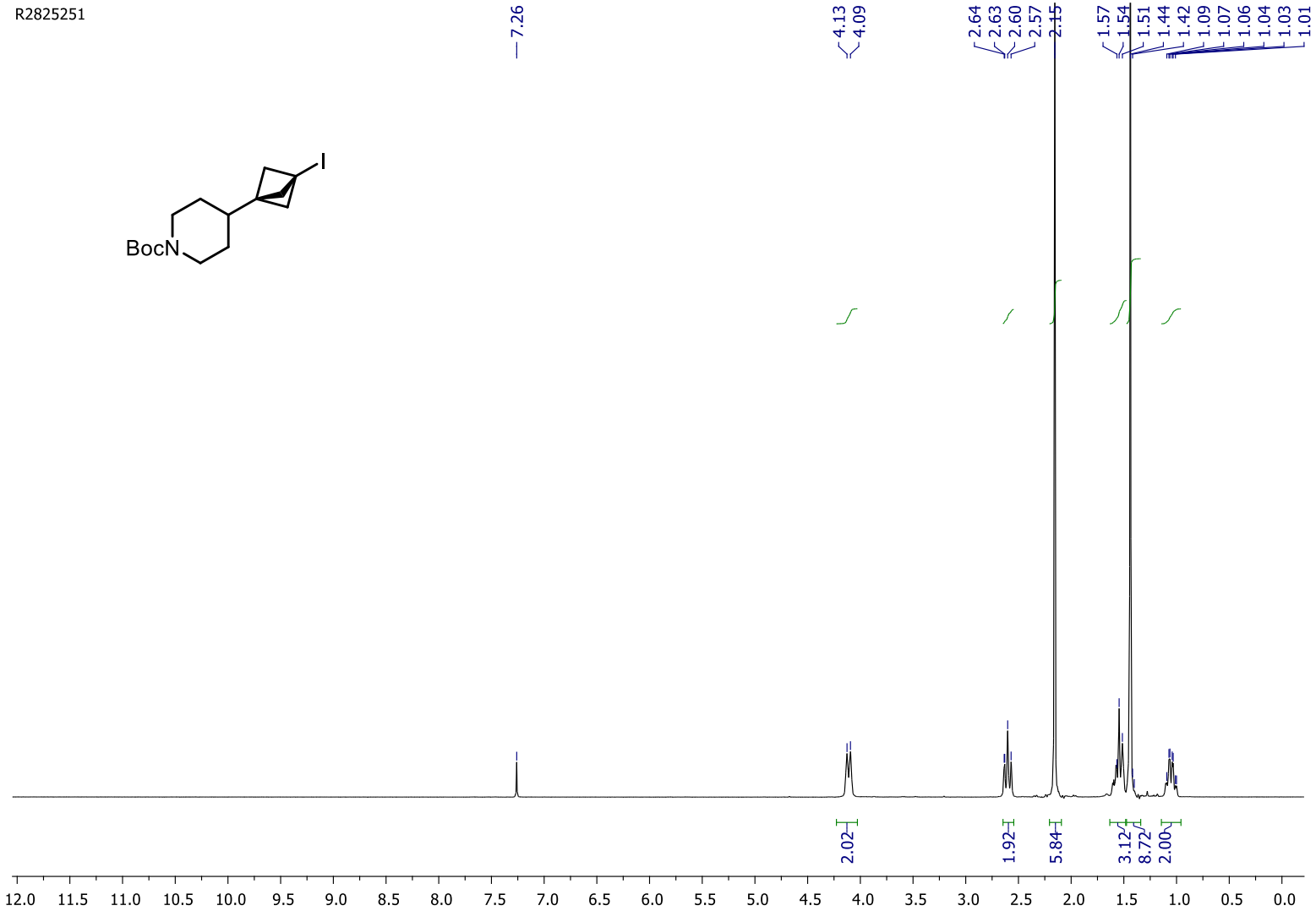


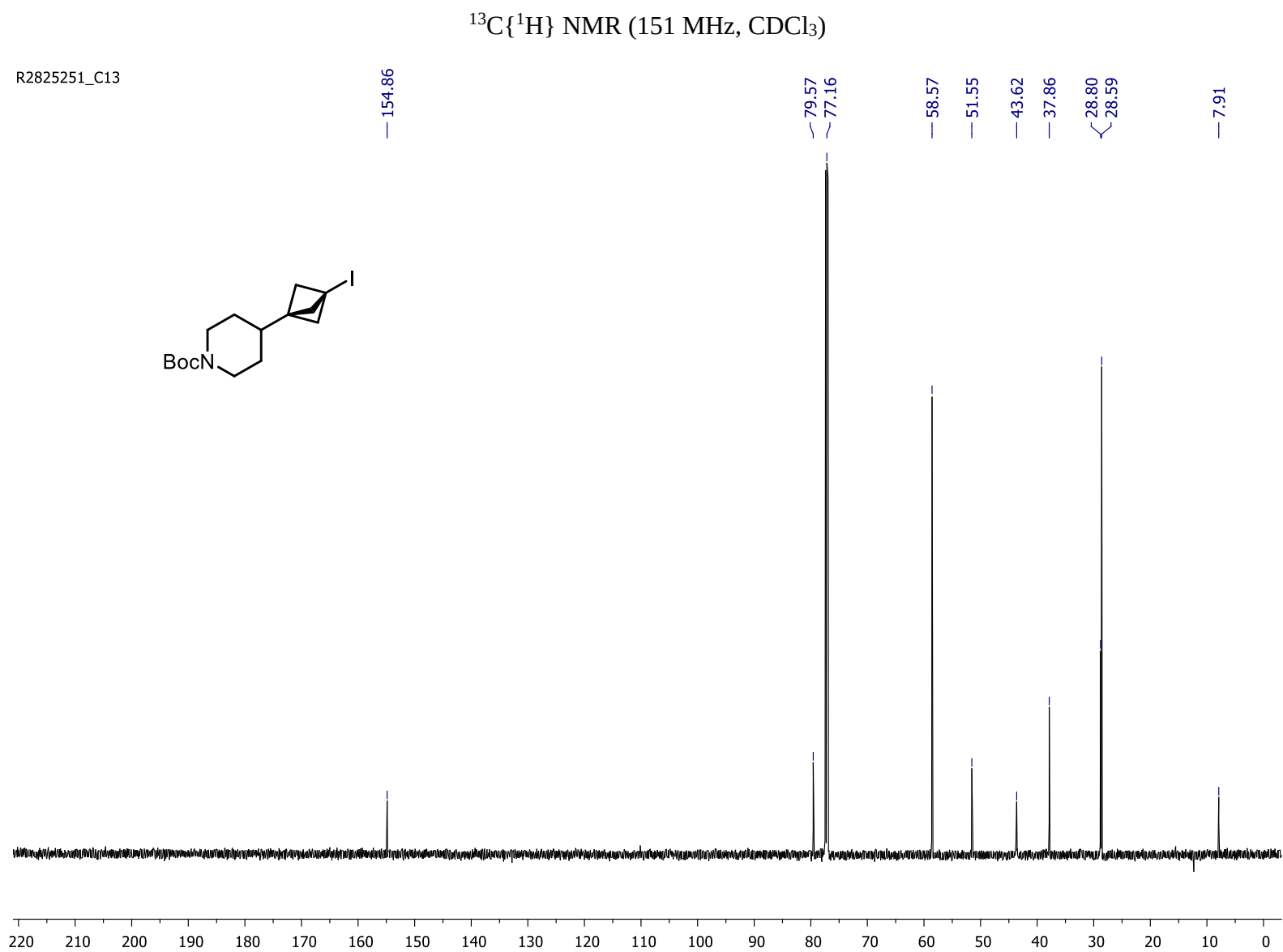
Compound 63

R2825251



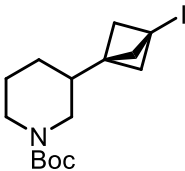
¹H NMR (400 MHz, CDCl₃)



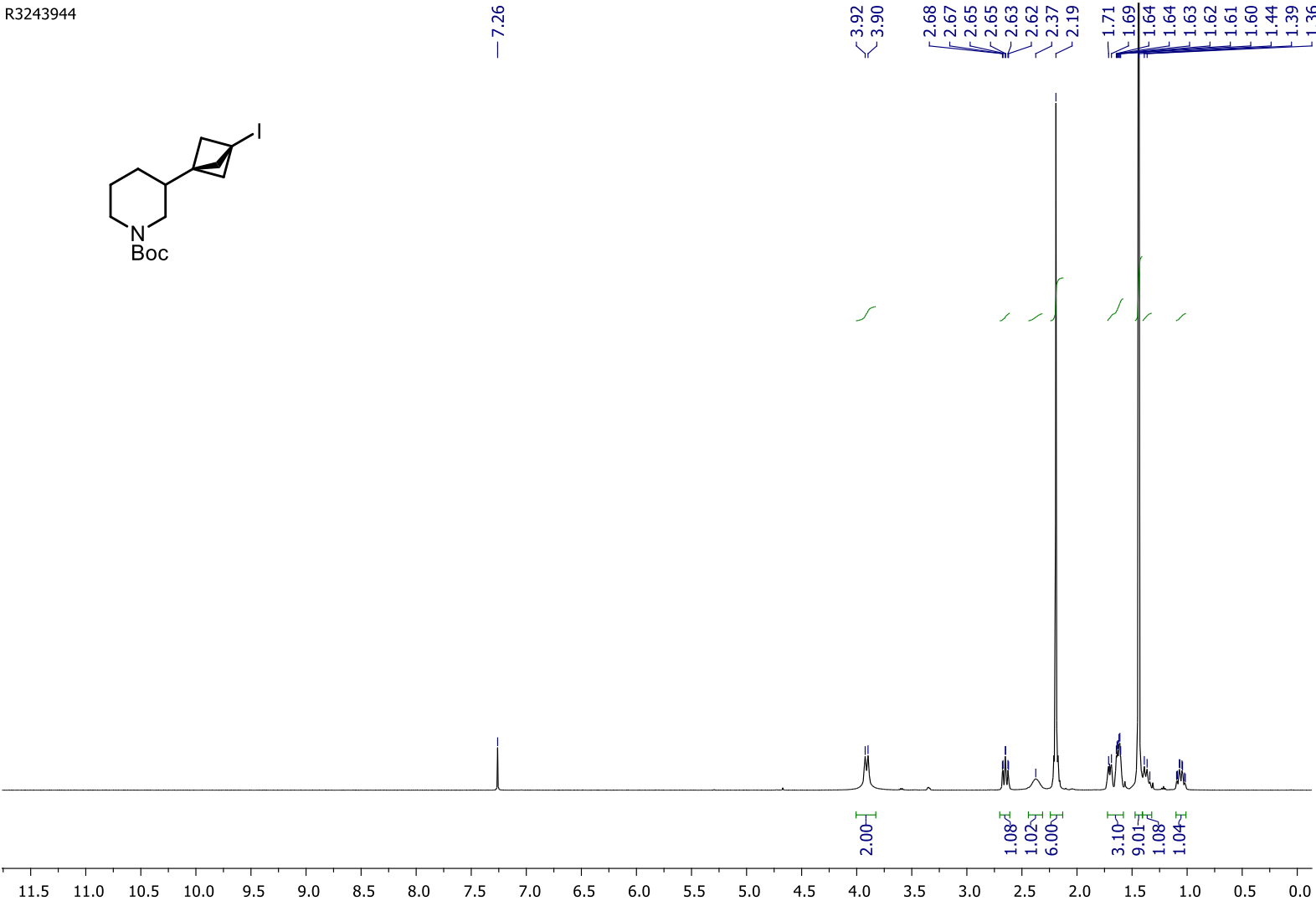


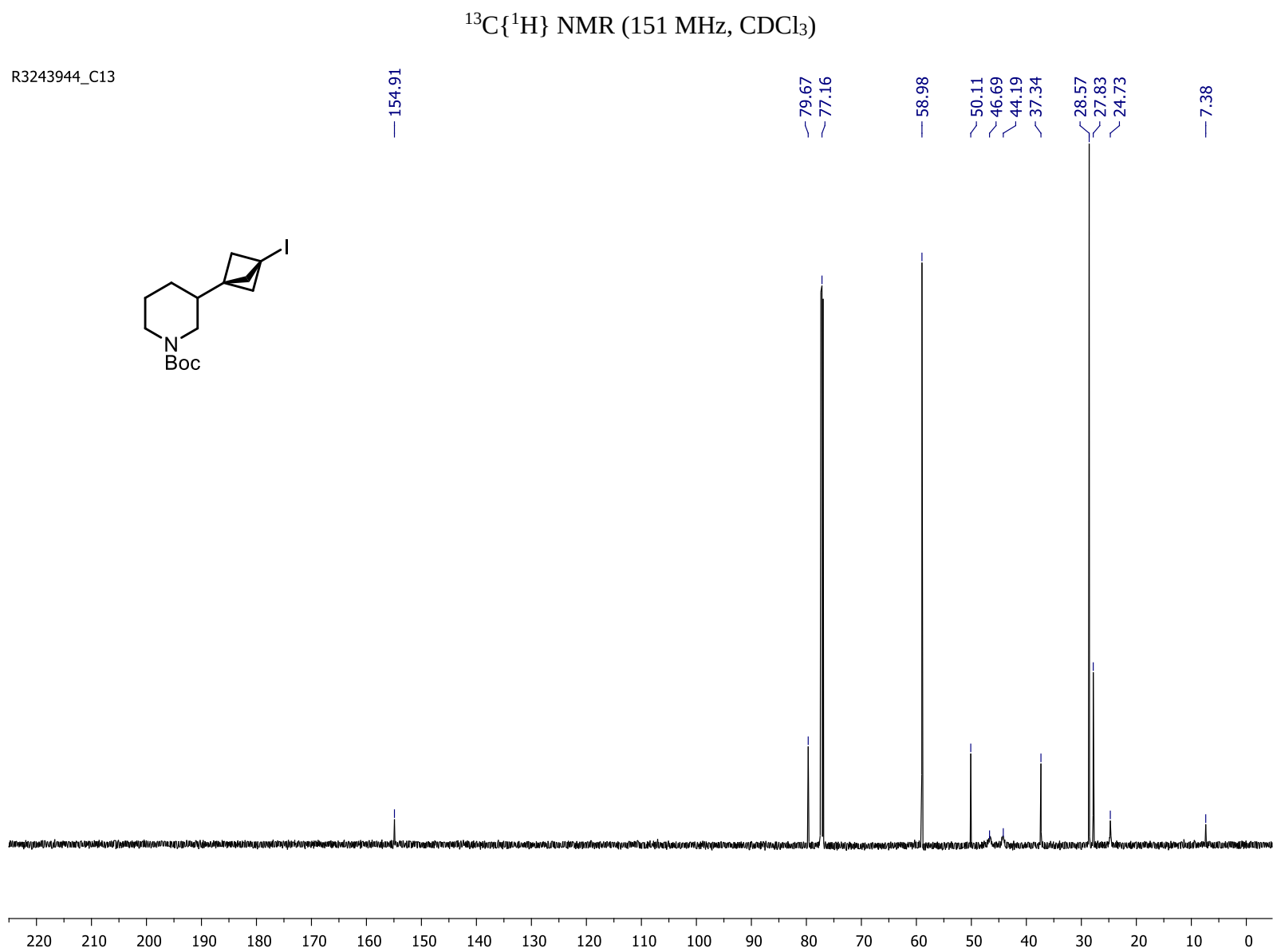
Compound 64

R3243944

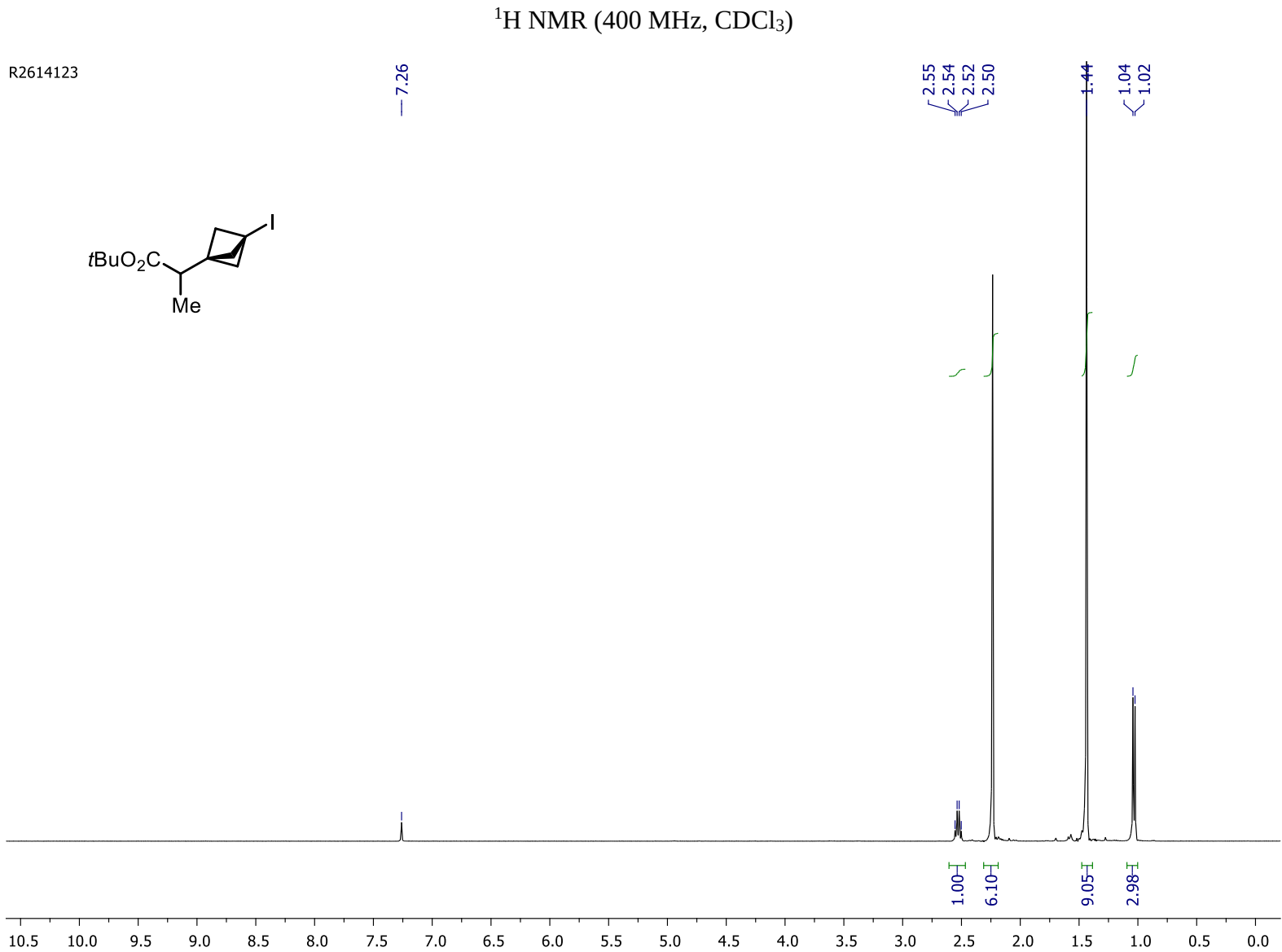


¹H NMR (500 MHz, CDCl₃)



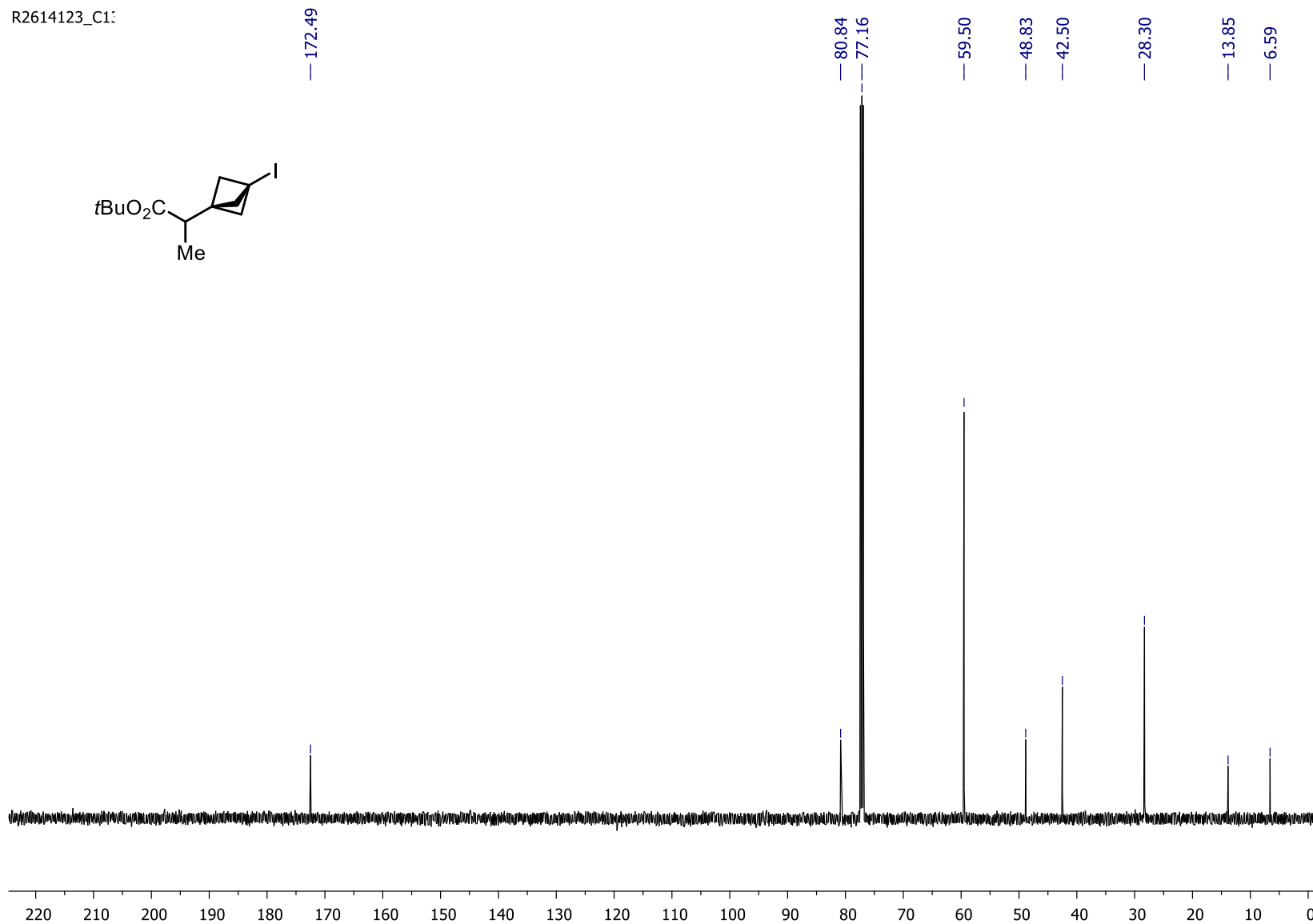
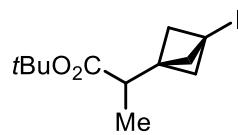


Compound 65



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

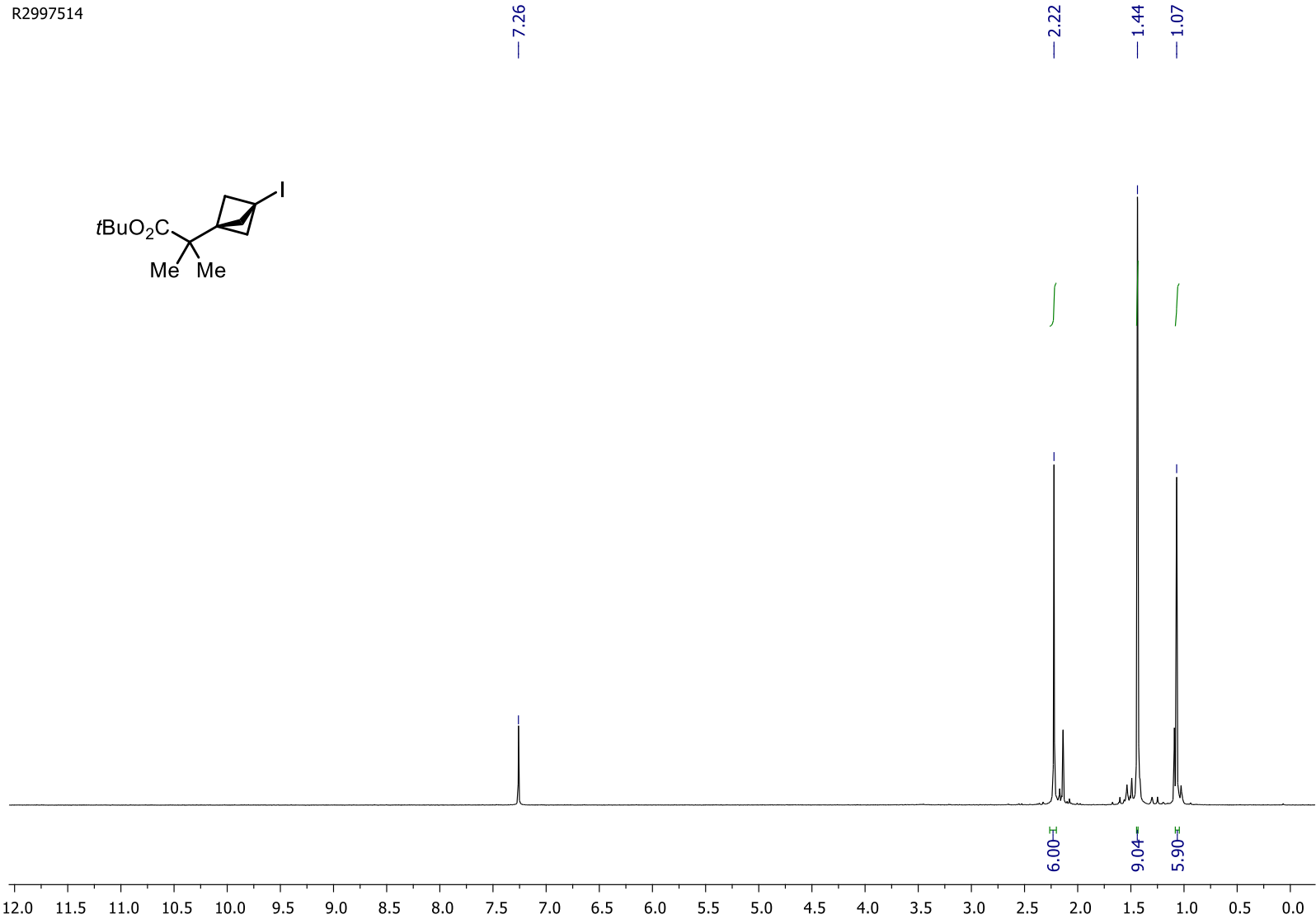
R2614123_C1:



Compound 66

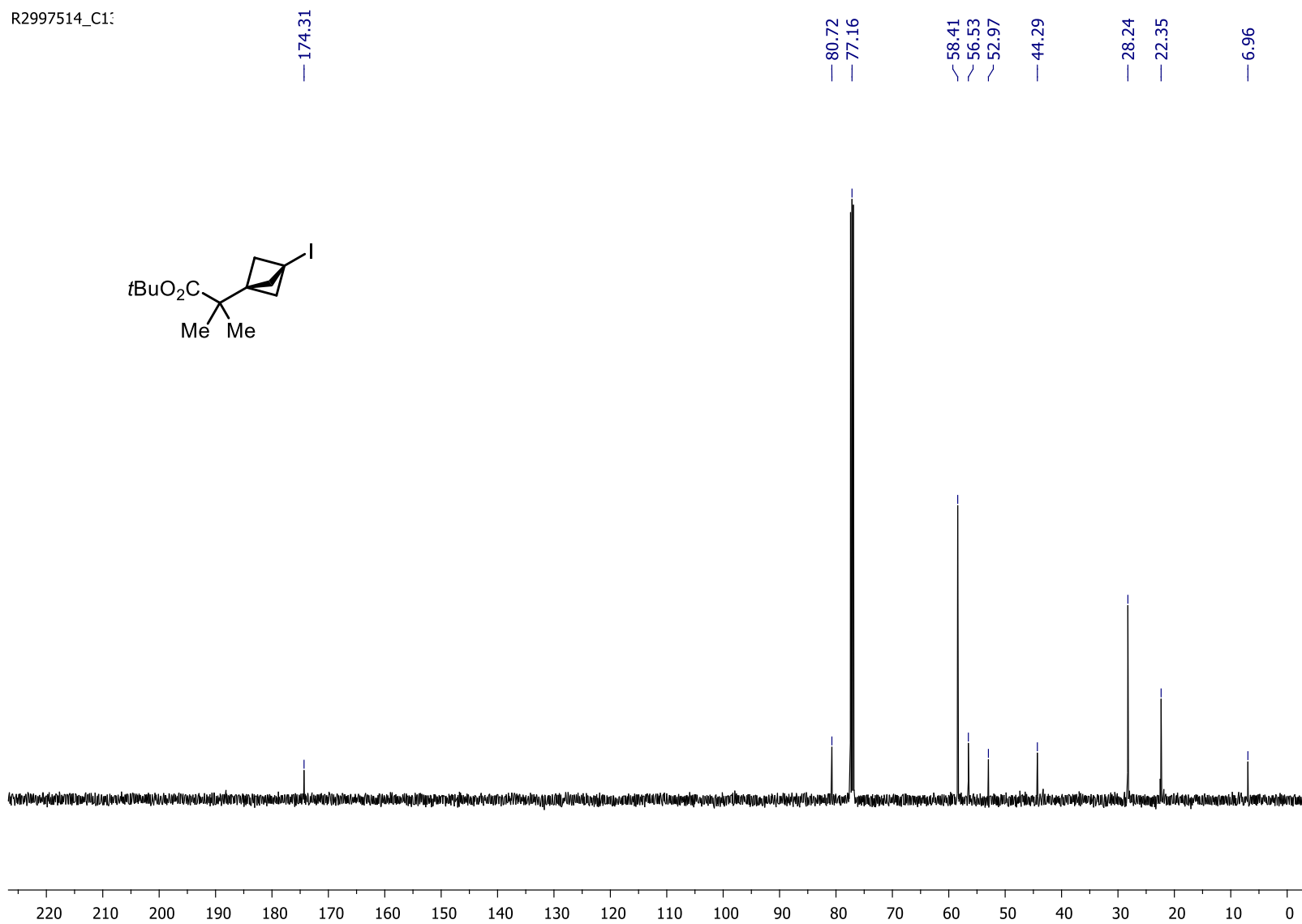
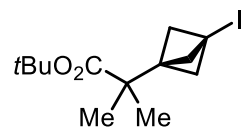
R2997514

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

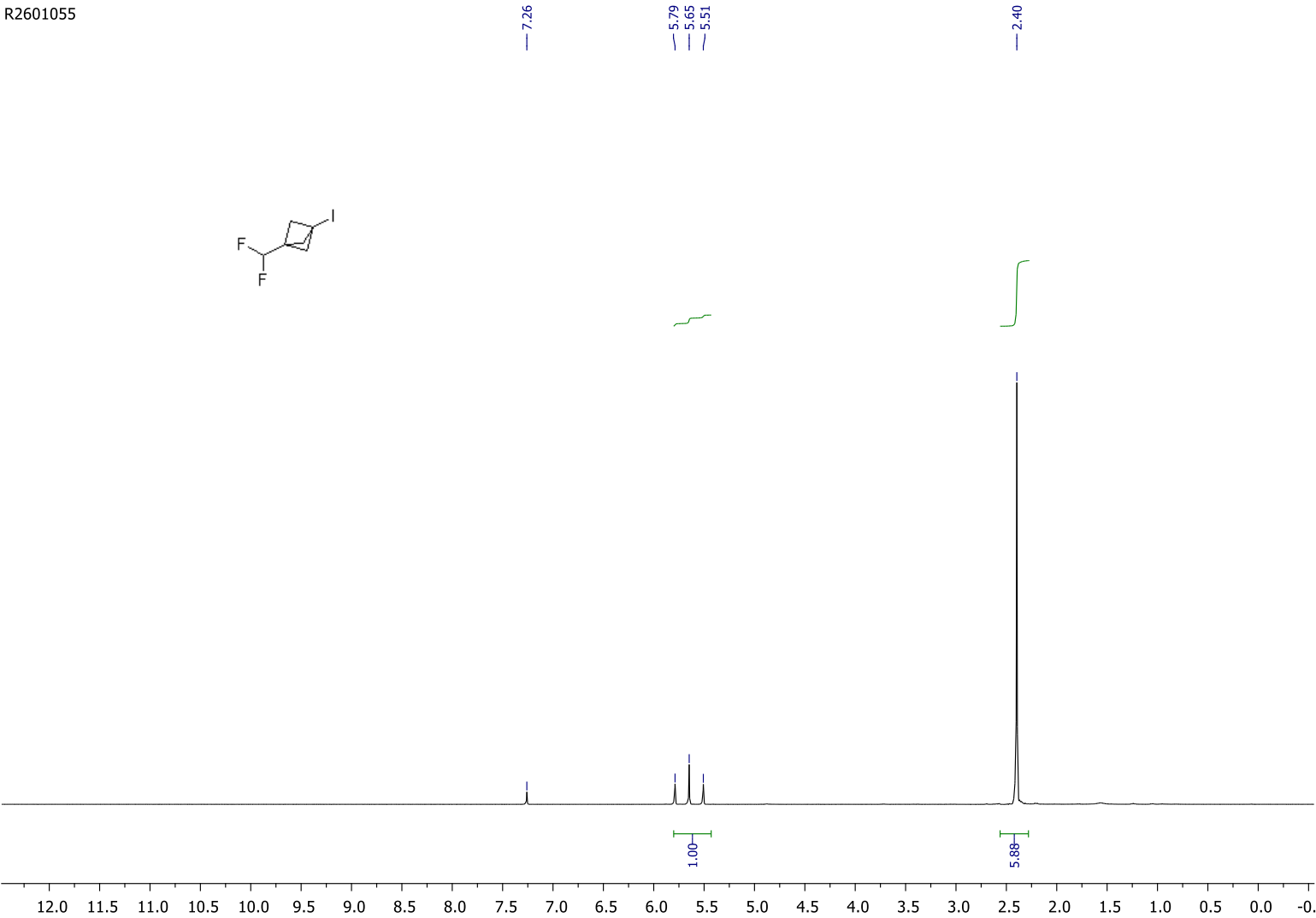
R2997514_C1:

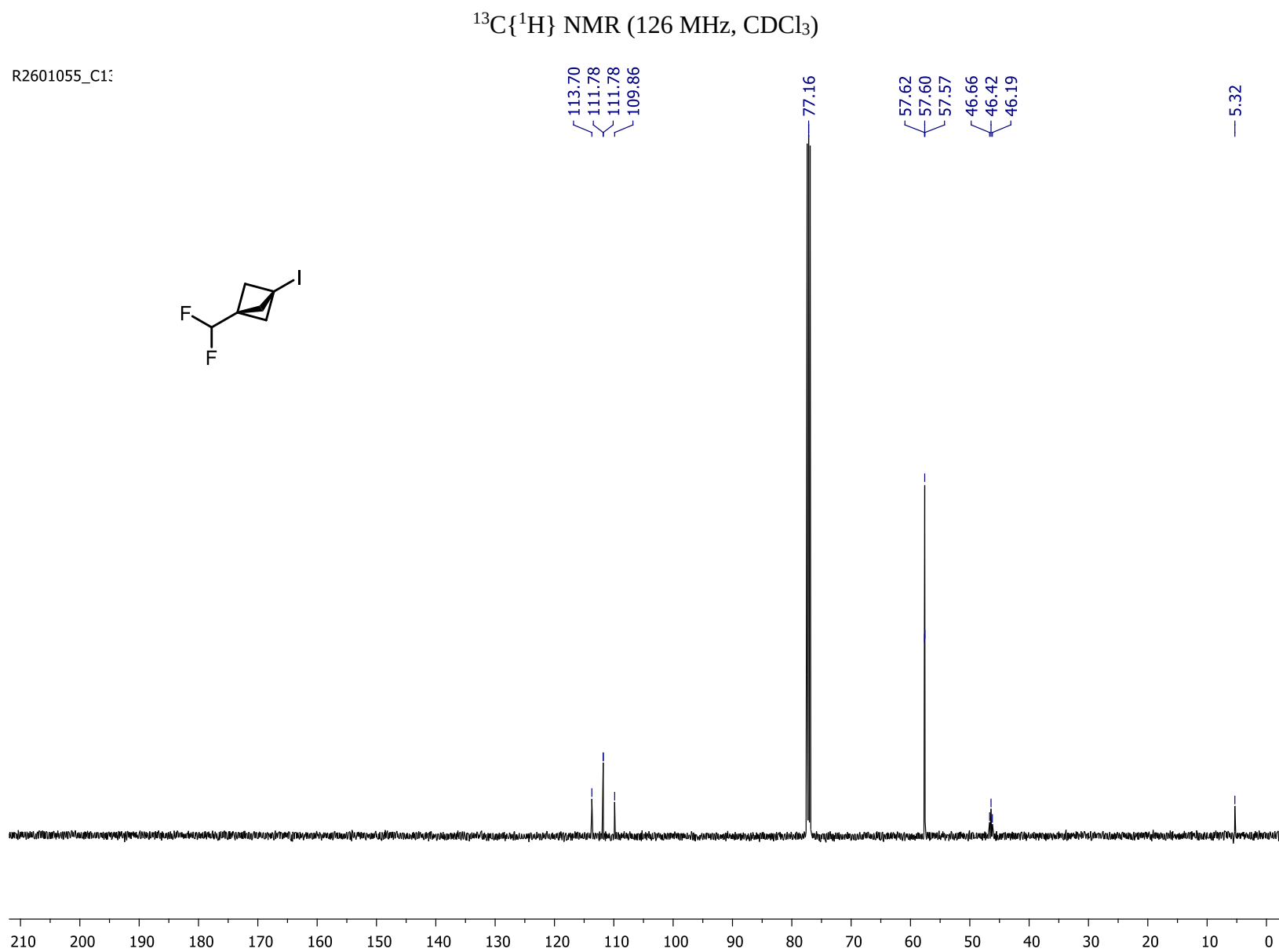


Compound 67

R2601055

¹H NMR (400 MHz, CDCl₃)

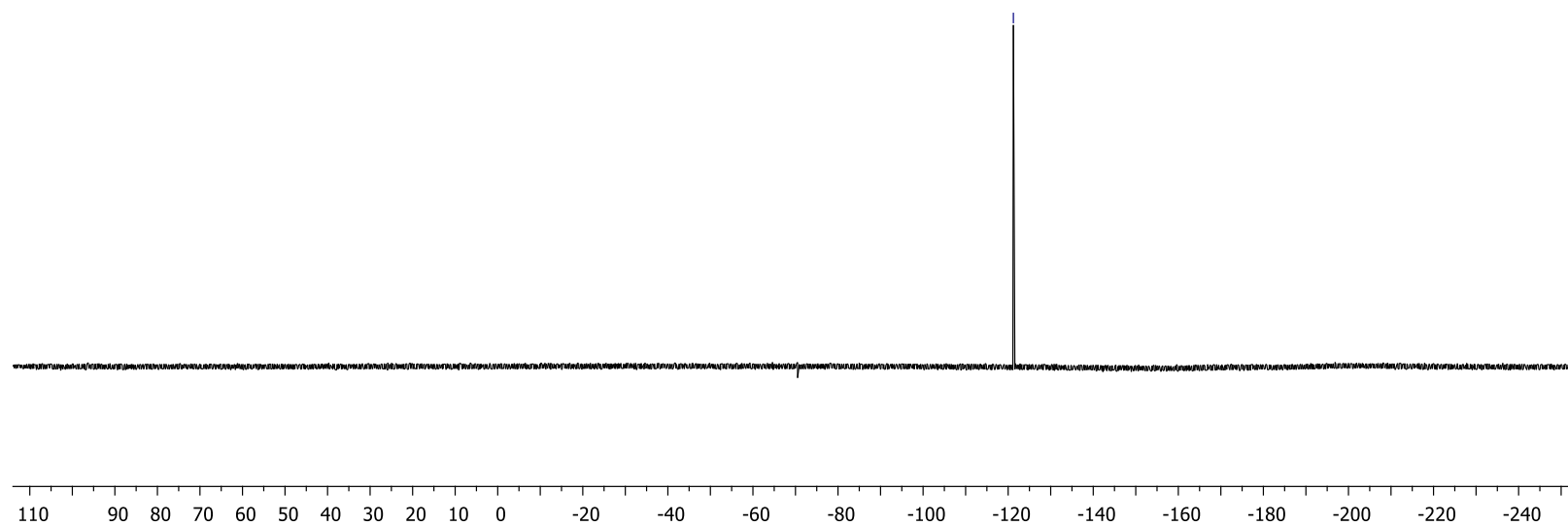
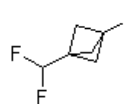




$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2597894_F19{H}

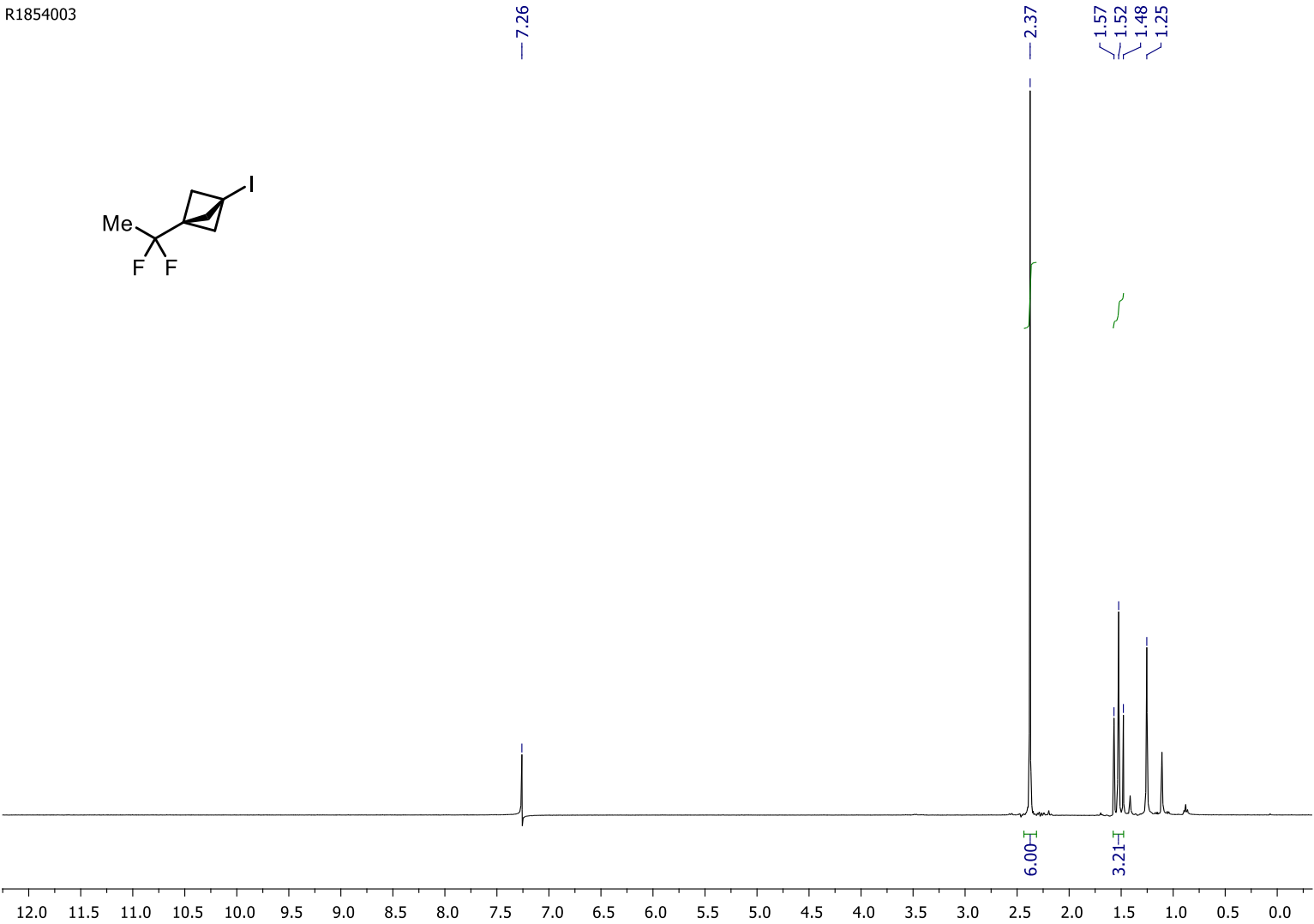
— -121.23

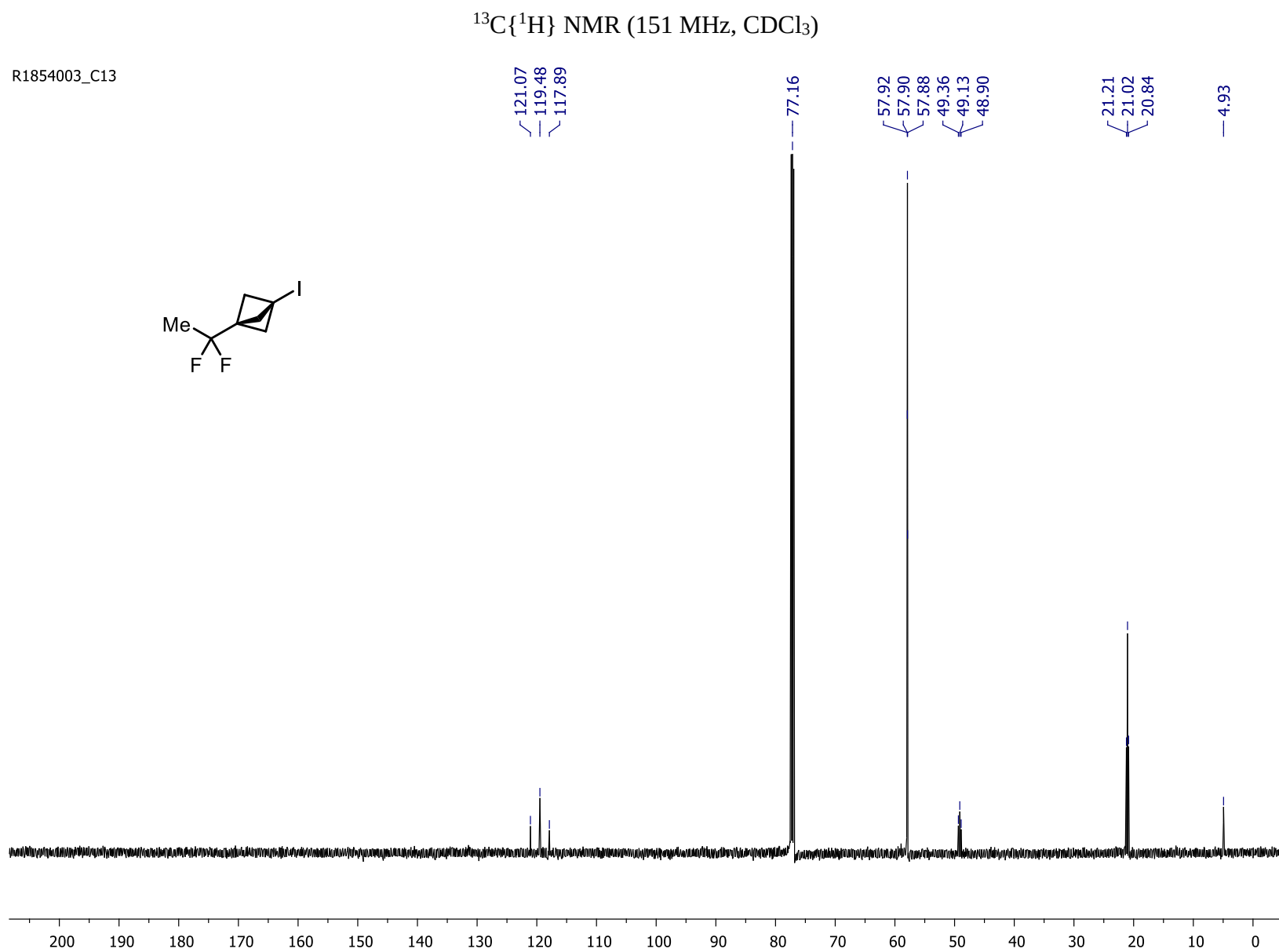


Compound 68

R1854003

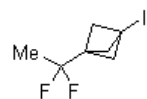
¹H NMR (400 MHz, CDCl₃)



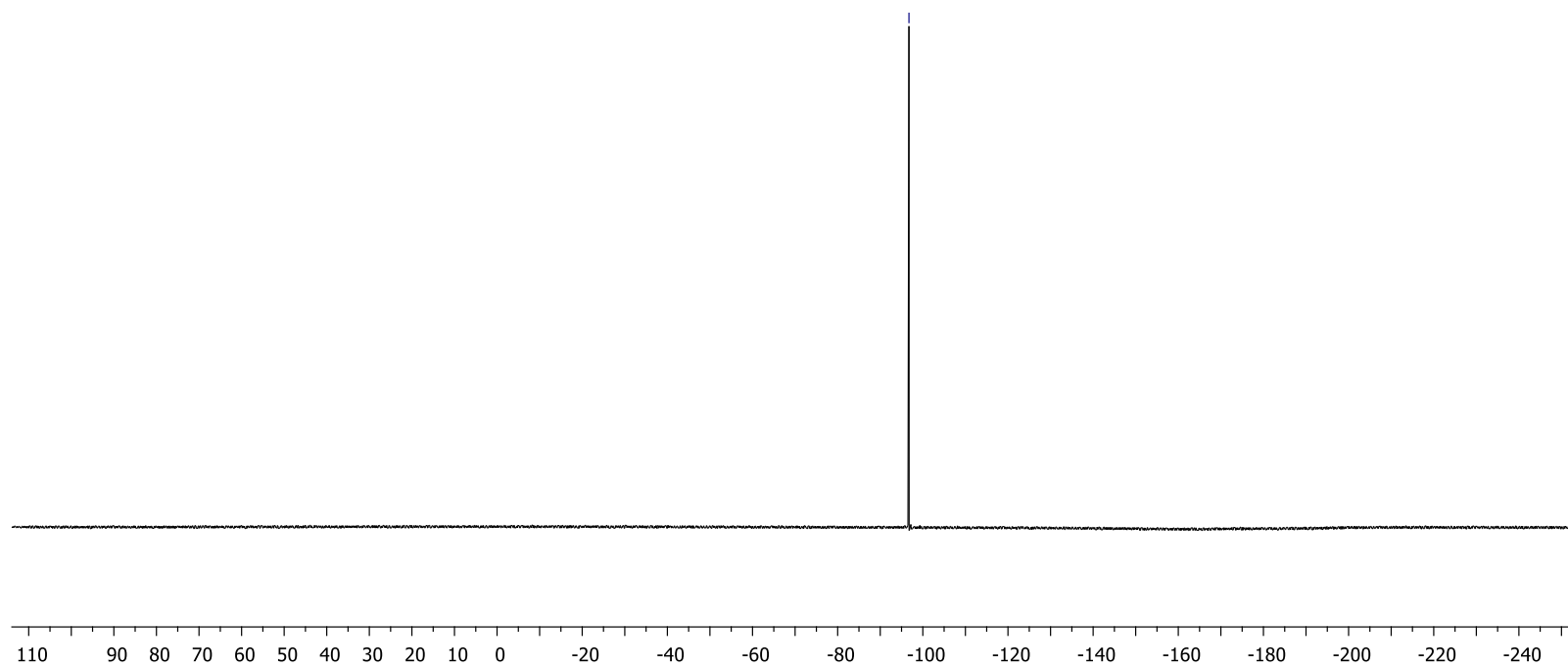


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R1854003_F19{H}
 $^{19}\text{F}\{^1\text{H}\}$

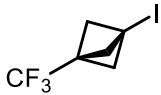


-96.75

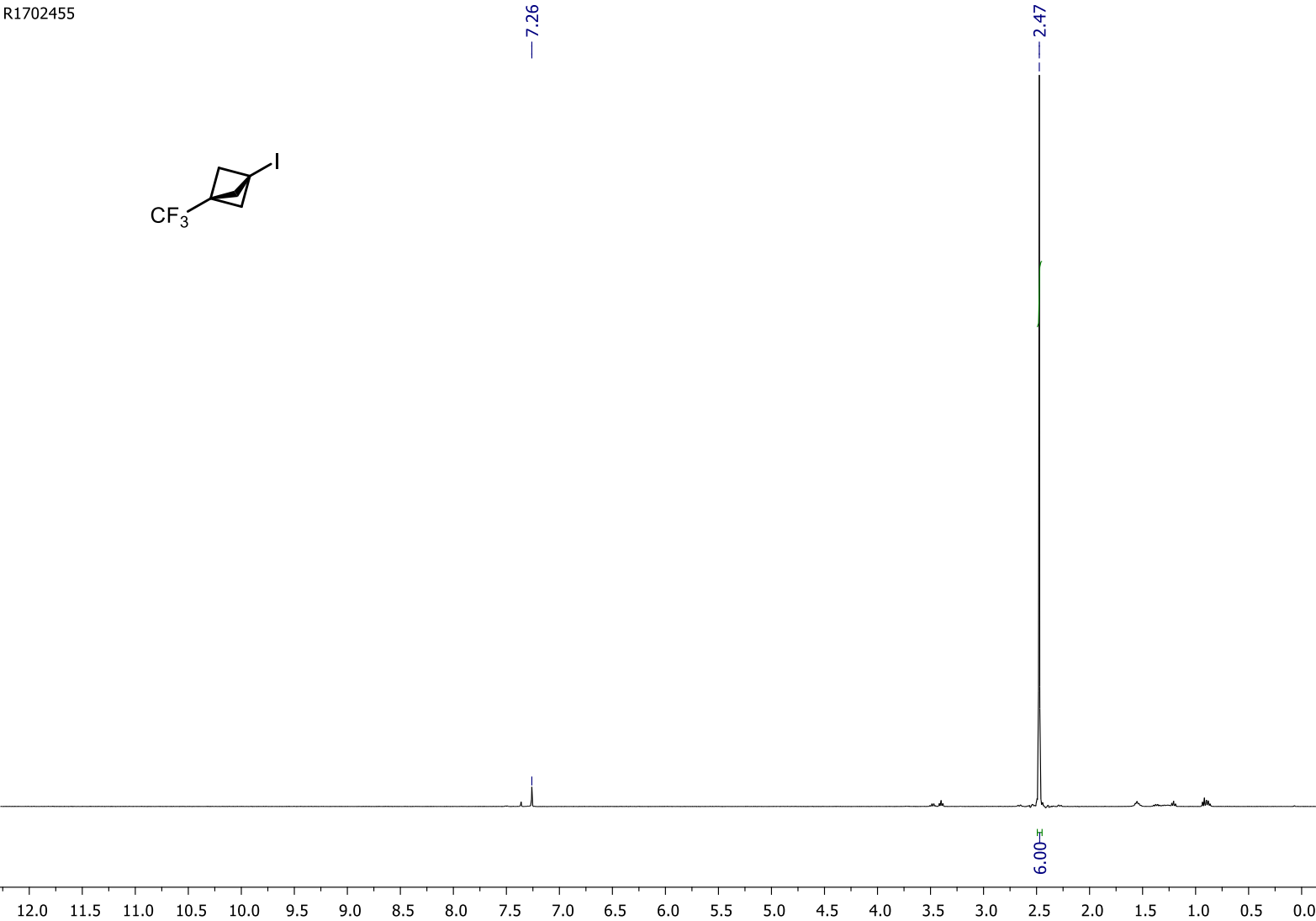


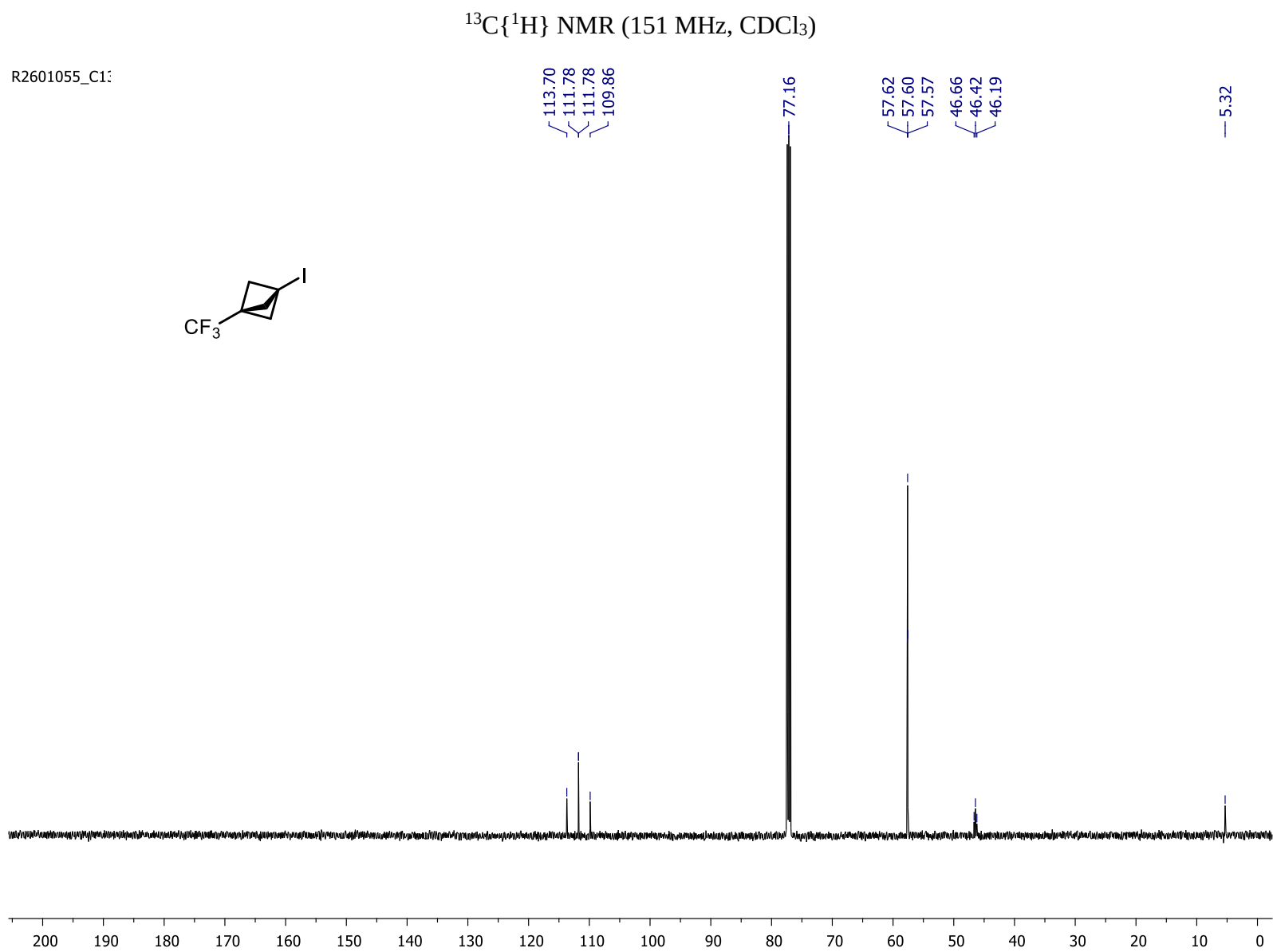
Compound 69

R1702455



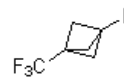
¹H NMR (400 MHz, CDCl₃)



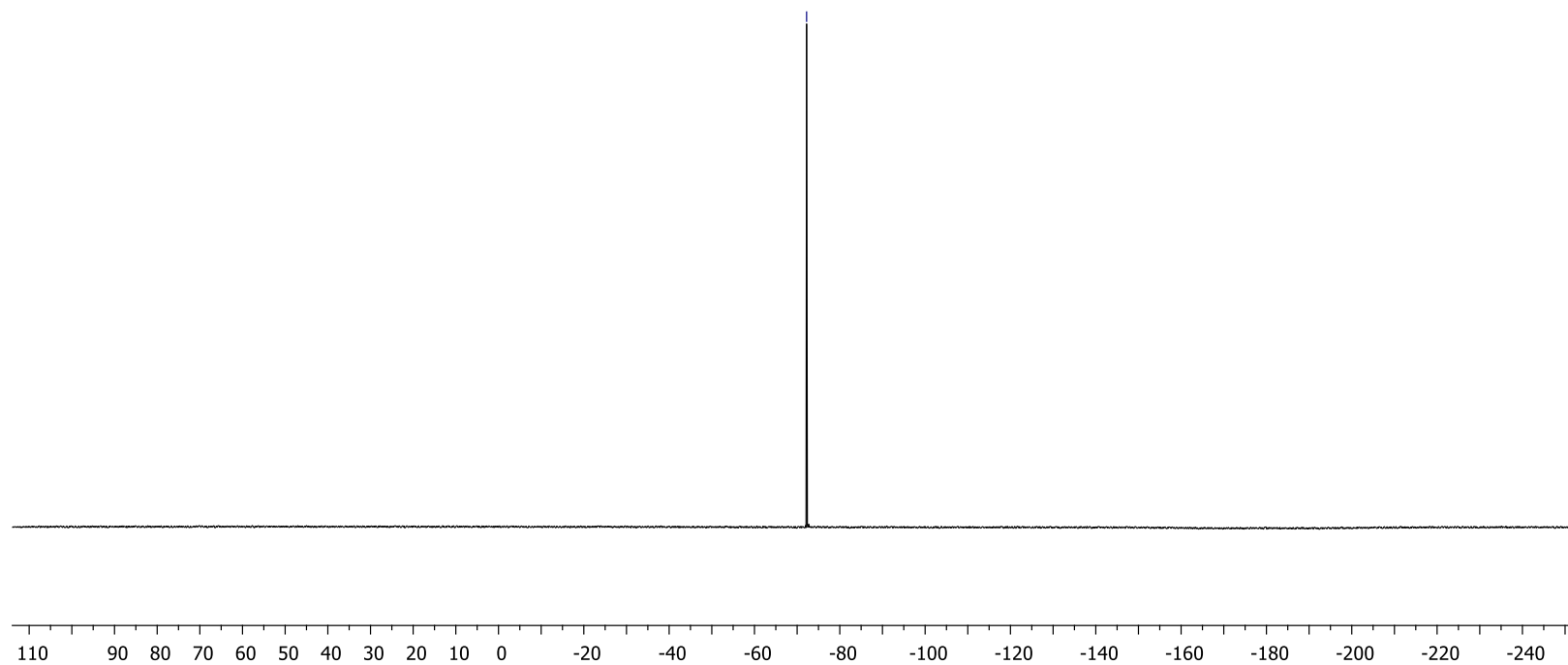


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R1702455_F19{H}
19F-{1H}



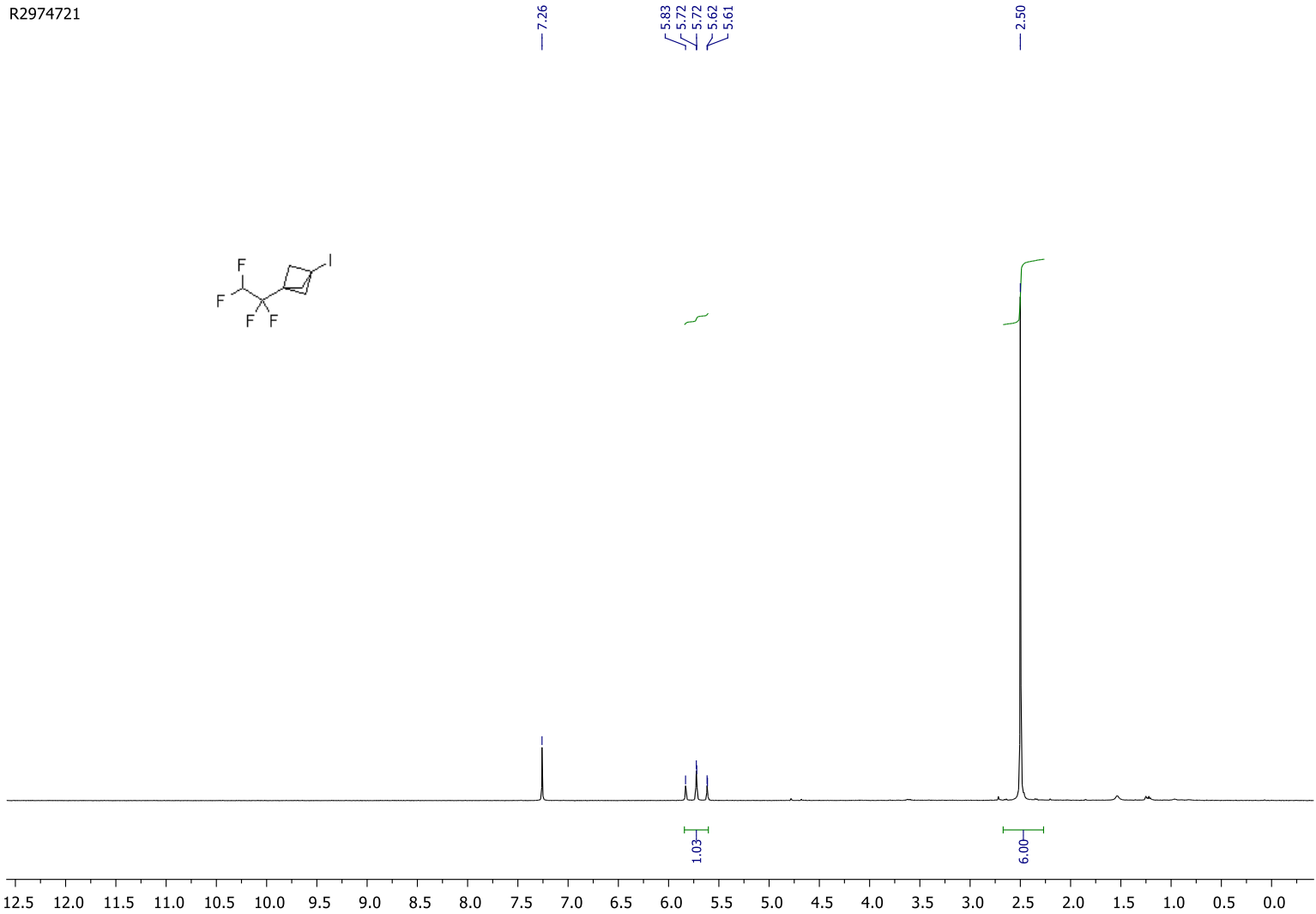
— -72.22



Compound 70

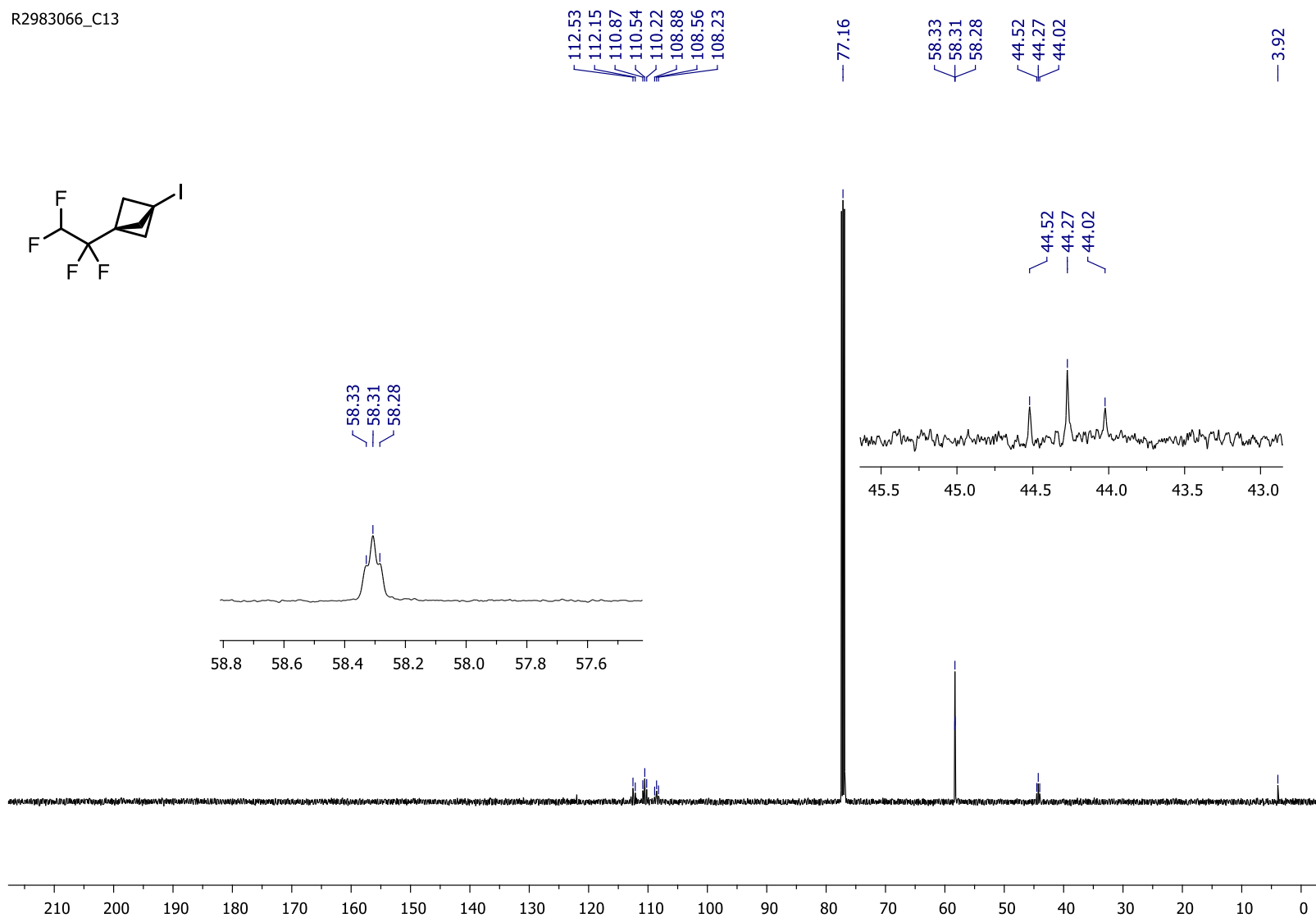
R2974721

¹H NMR (500 MHz, CDCl₃)



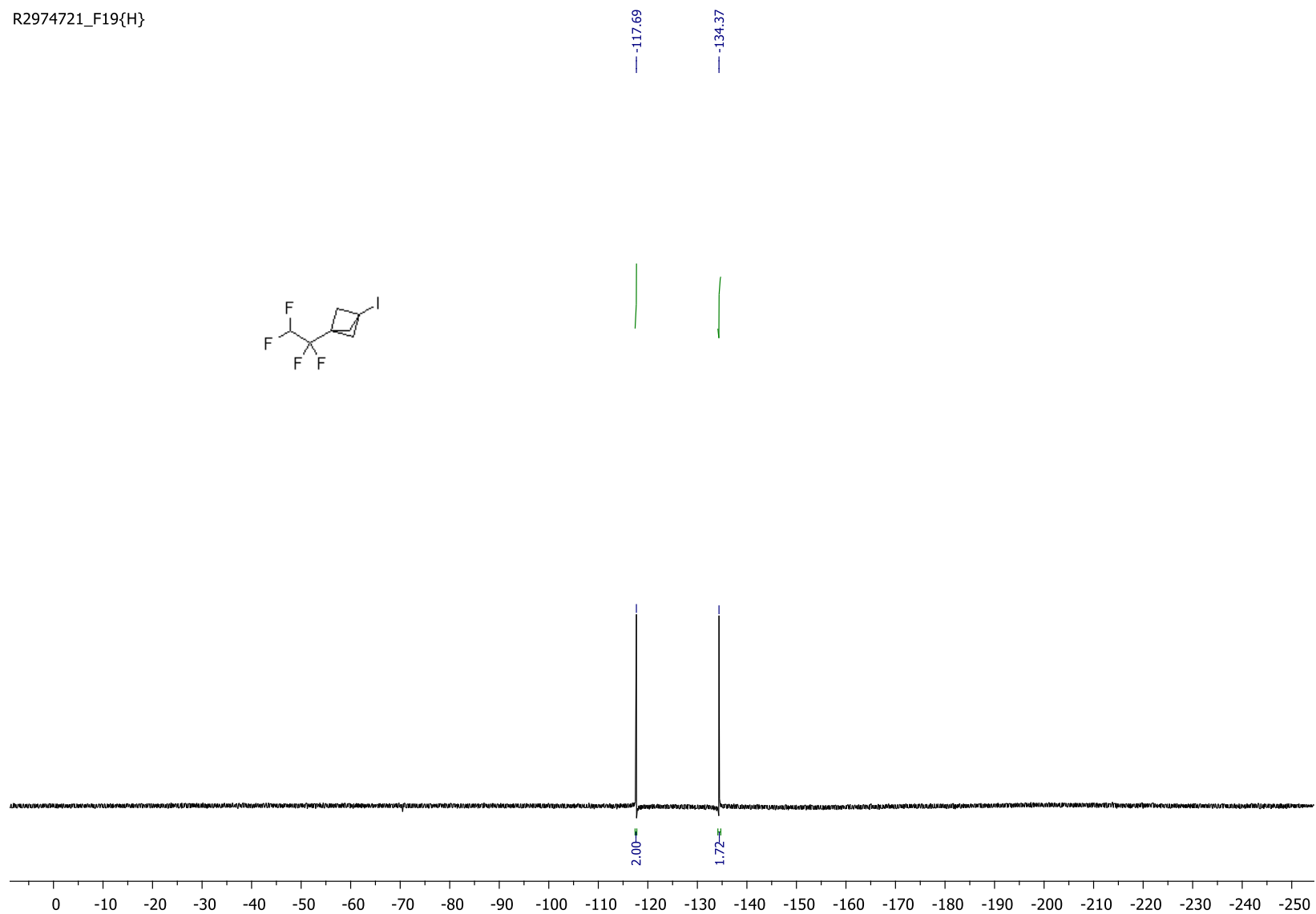
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2983066_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

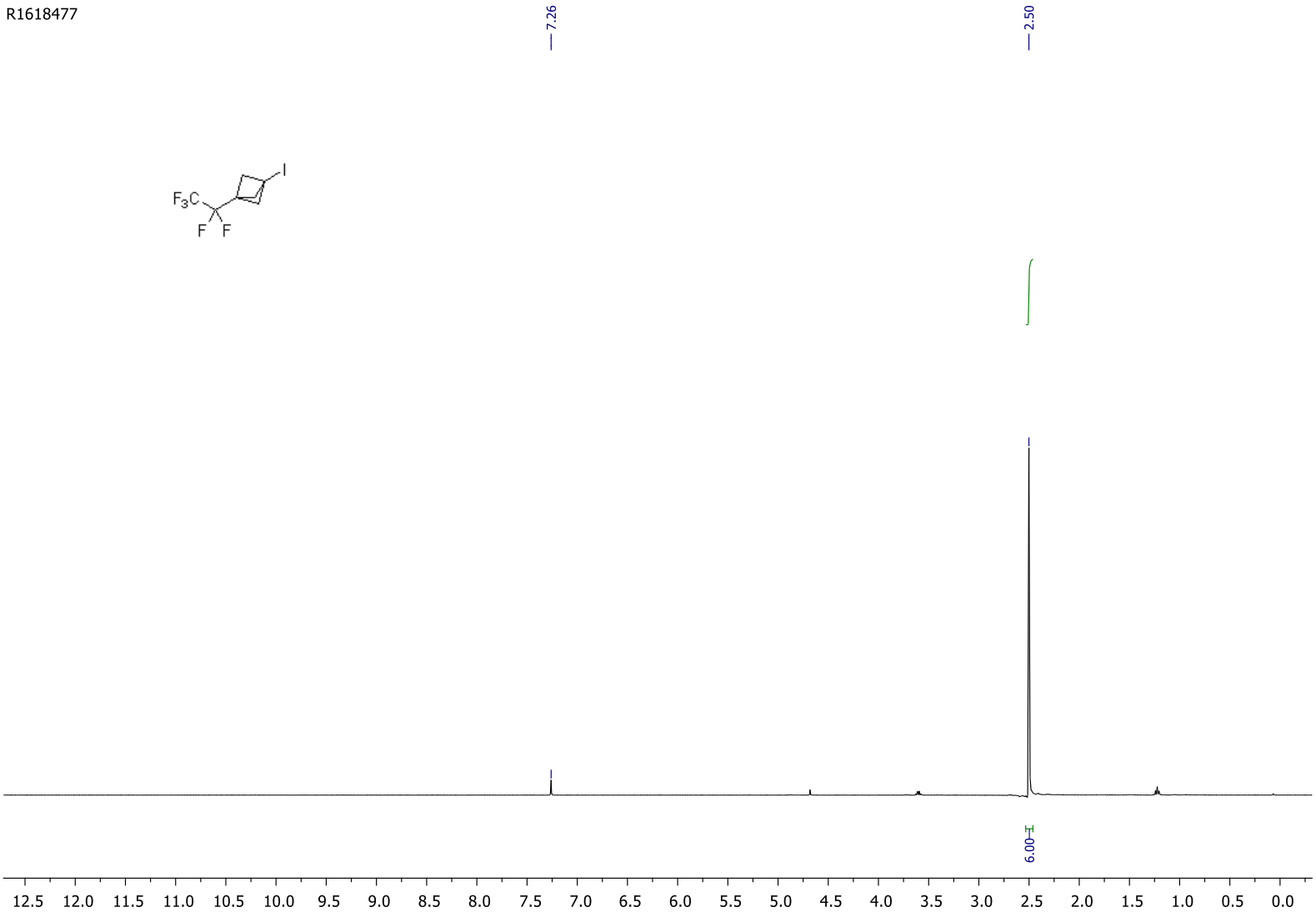
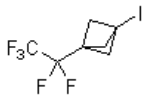
R2974721_F19{H}

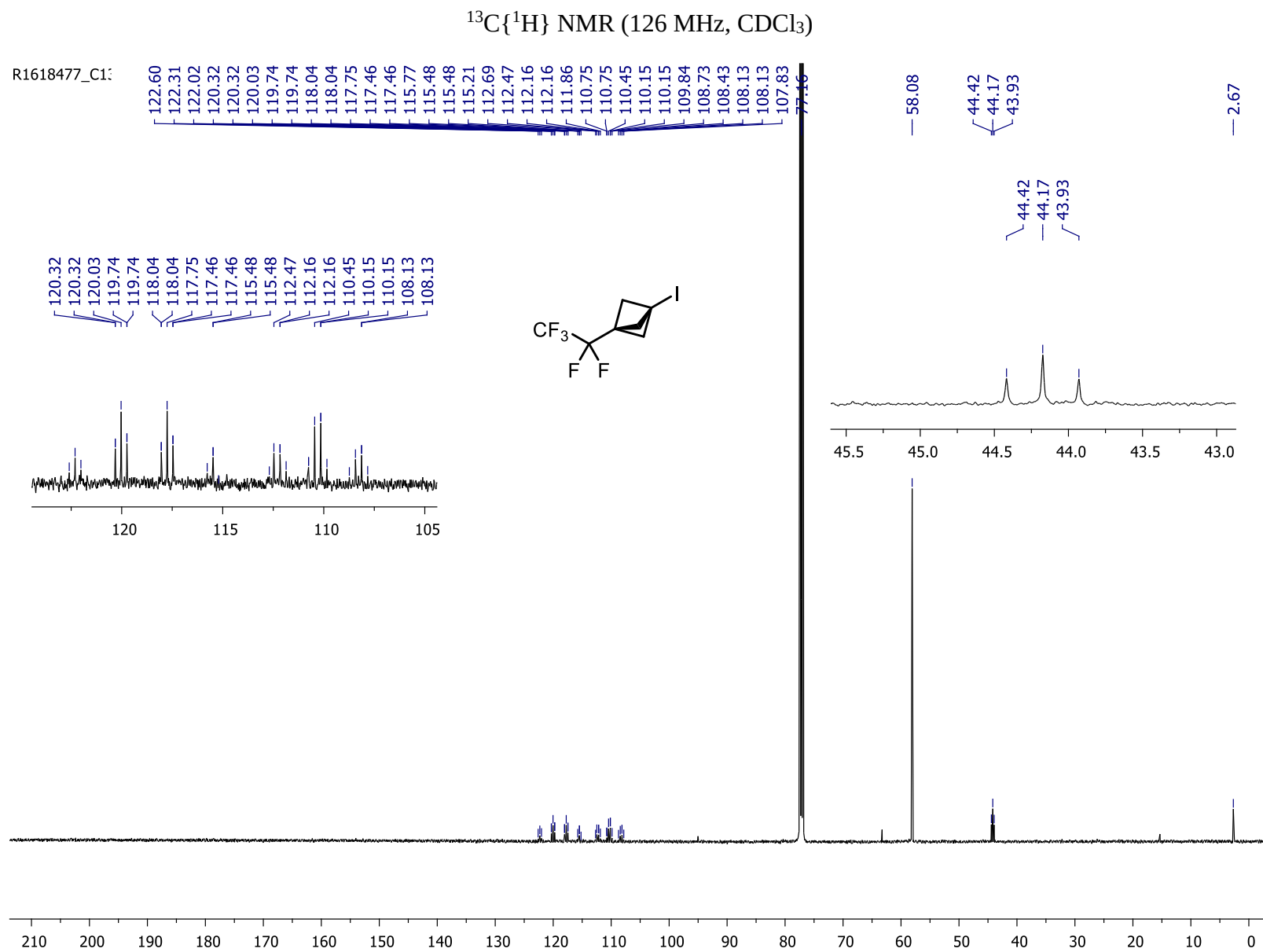


Compound 71

R1618477

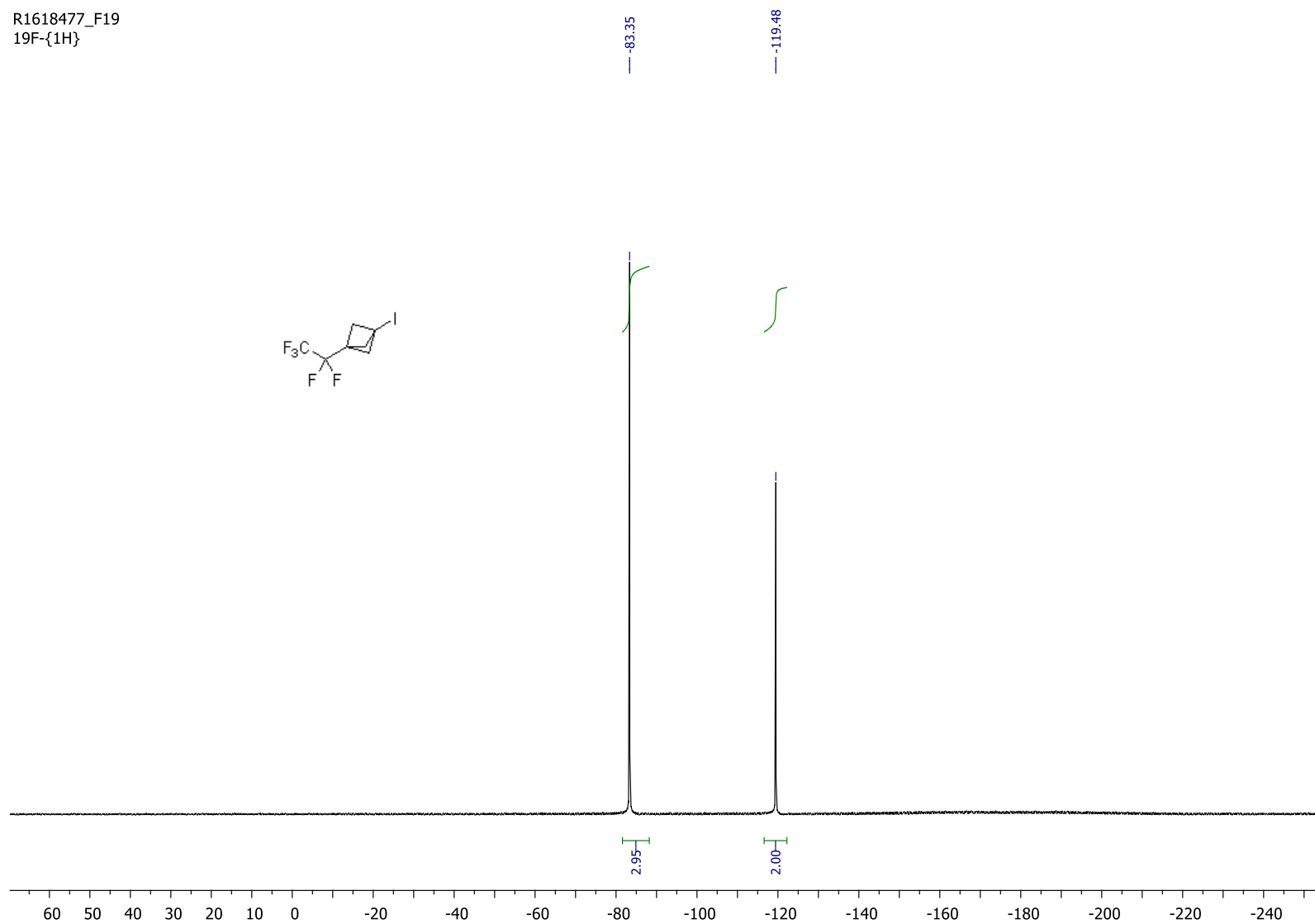
¹H NMR (400 MHz, CDCl₃)





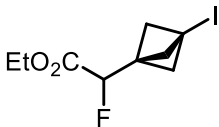
$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R1618477_F19
 $^{19}\text{F}\{^1\text{H}\}$

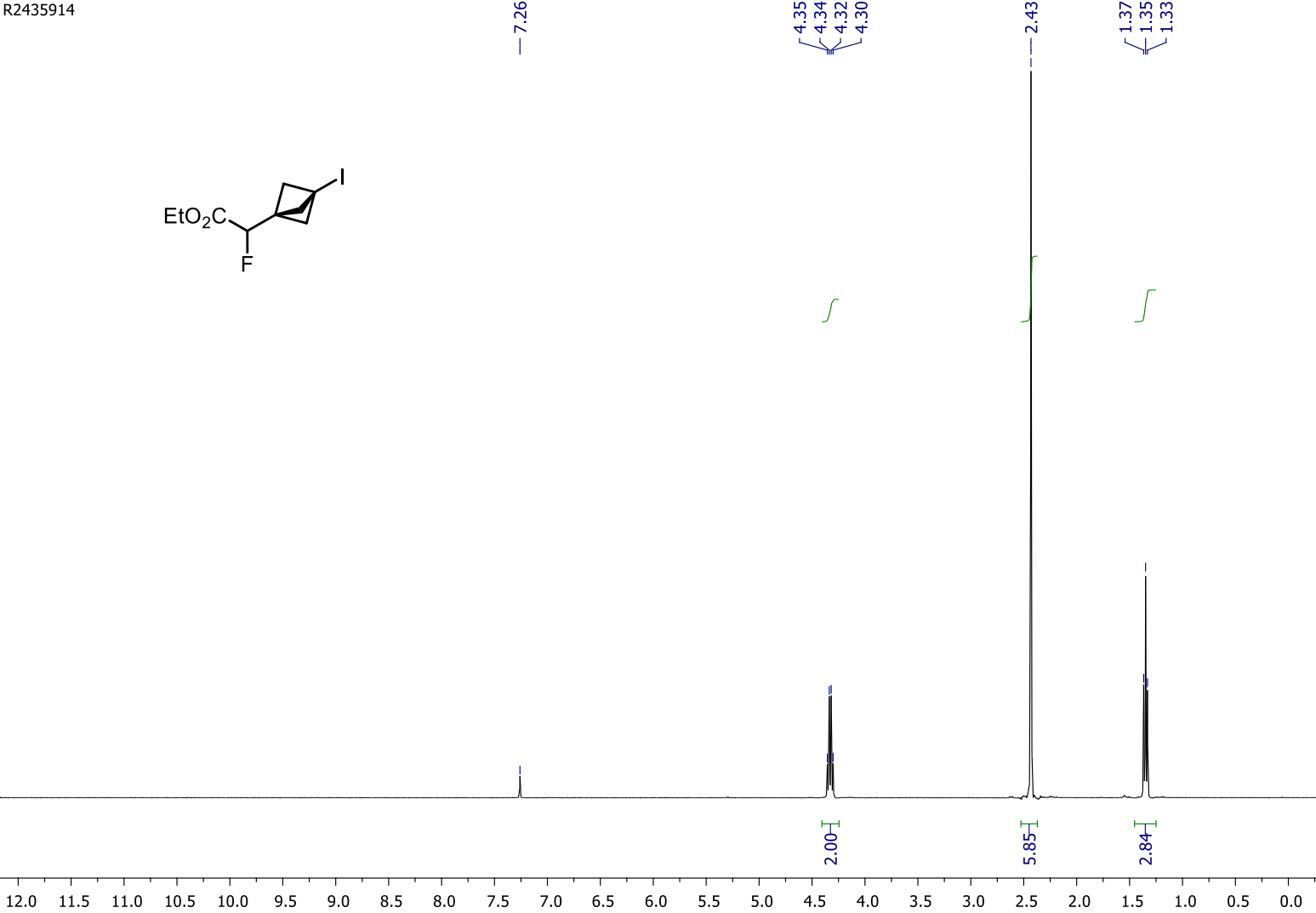


Compound 72

R2435914

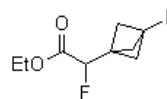


¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R3407188_C1:



167.17
166.98

87.28
85.78

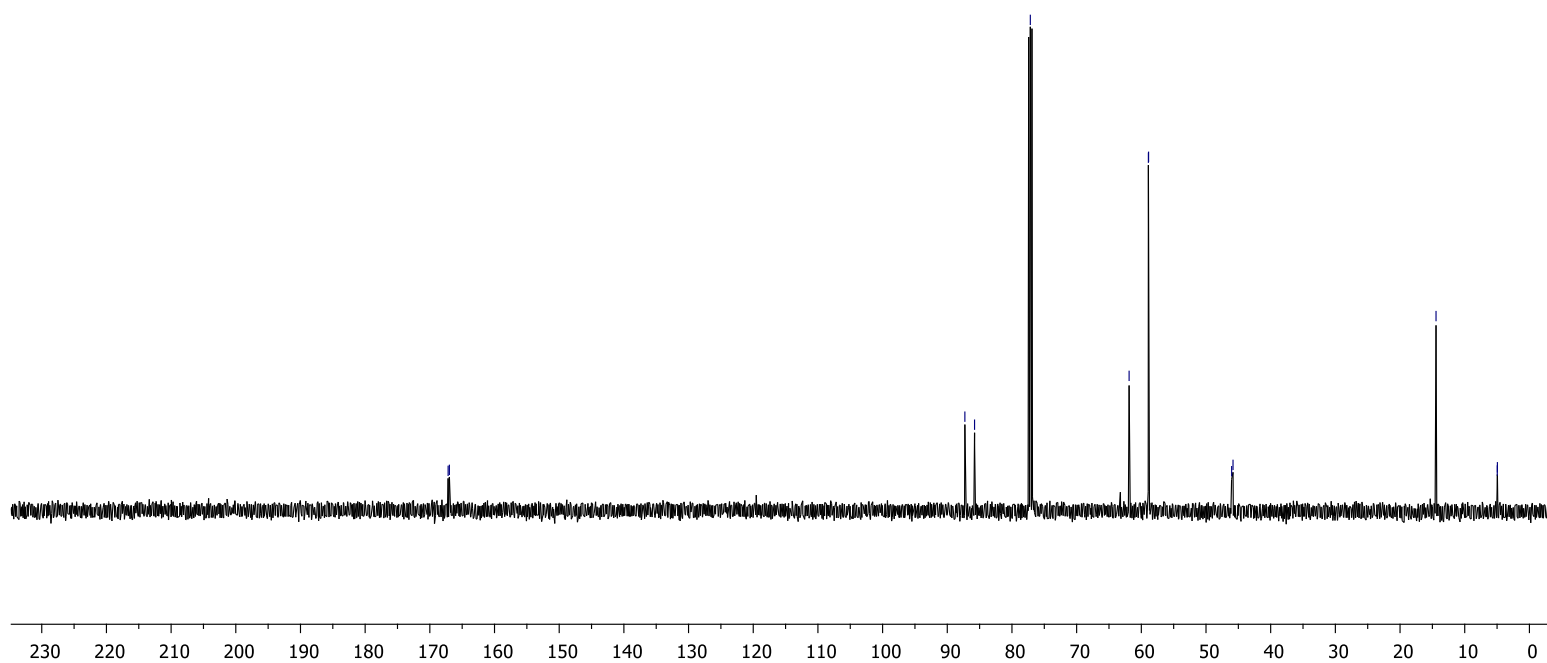
77.16

61.89
58.91
58.88

46.04
45.82

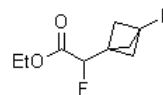
14.43

4.97
4.95

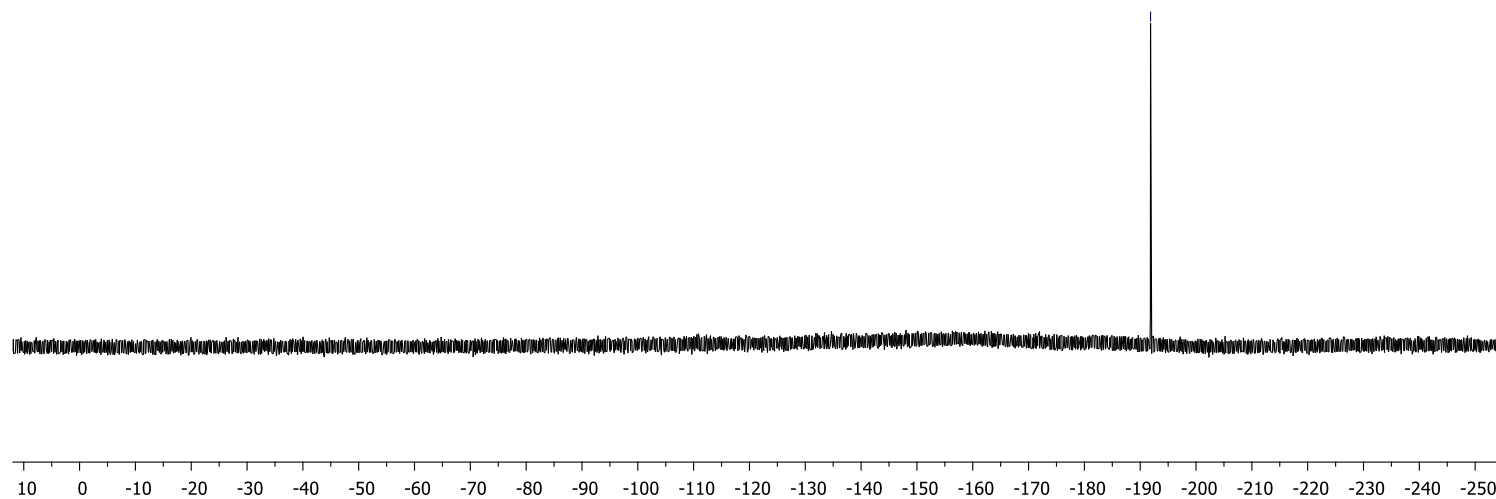


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R3407188_F19{H}
19F-{1H}



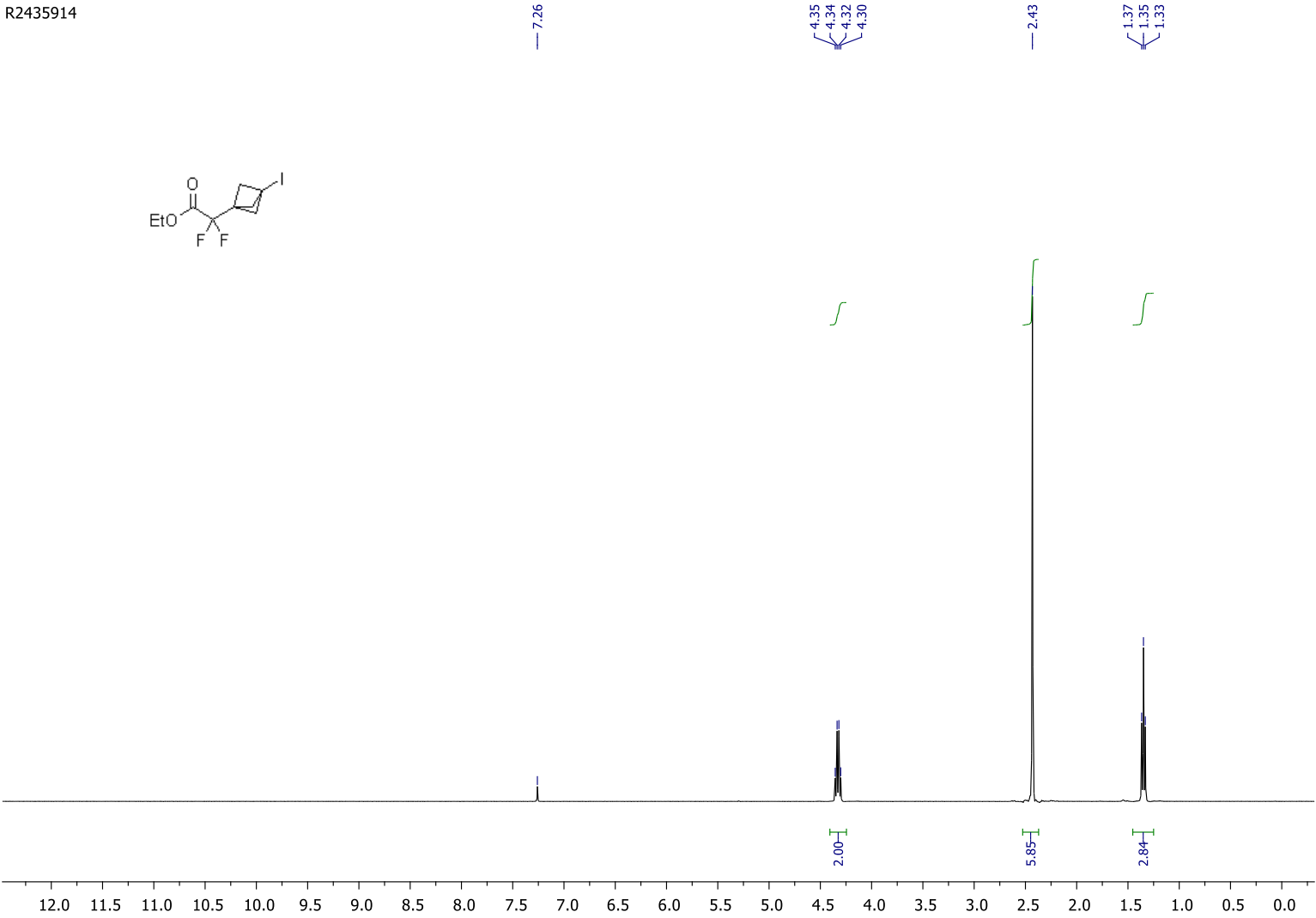
— -191.85



Compound 73

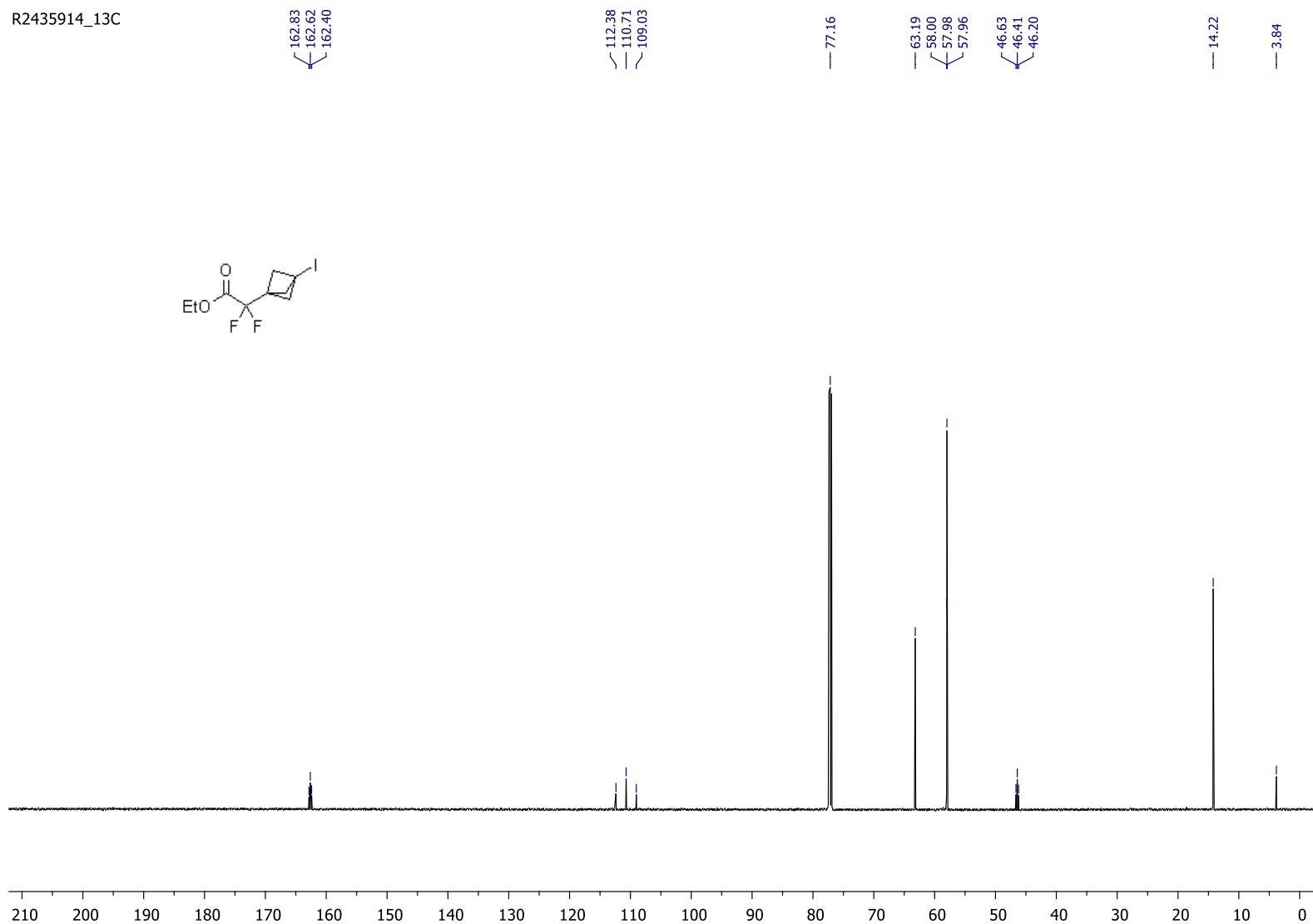
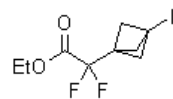
R2435914

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

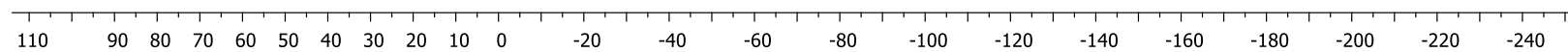
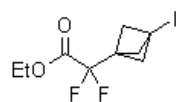
R2435914_13C



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2435914_F19{H}
19F-{1H}

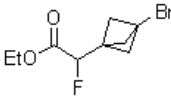
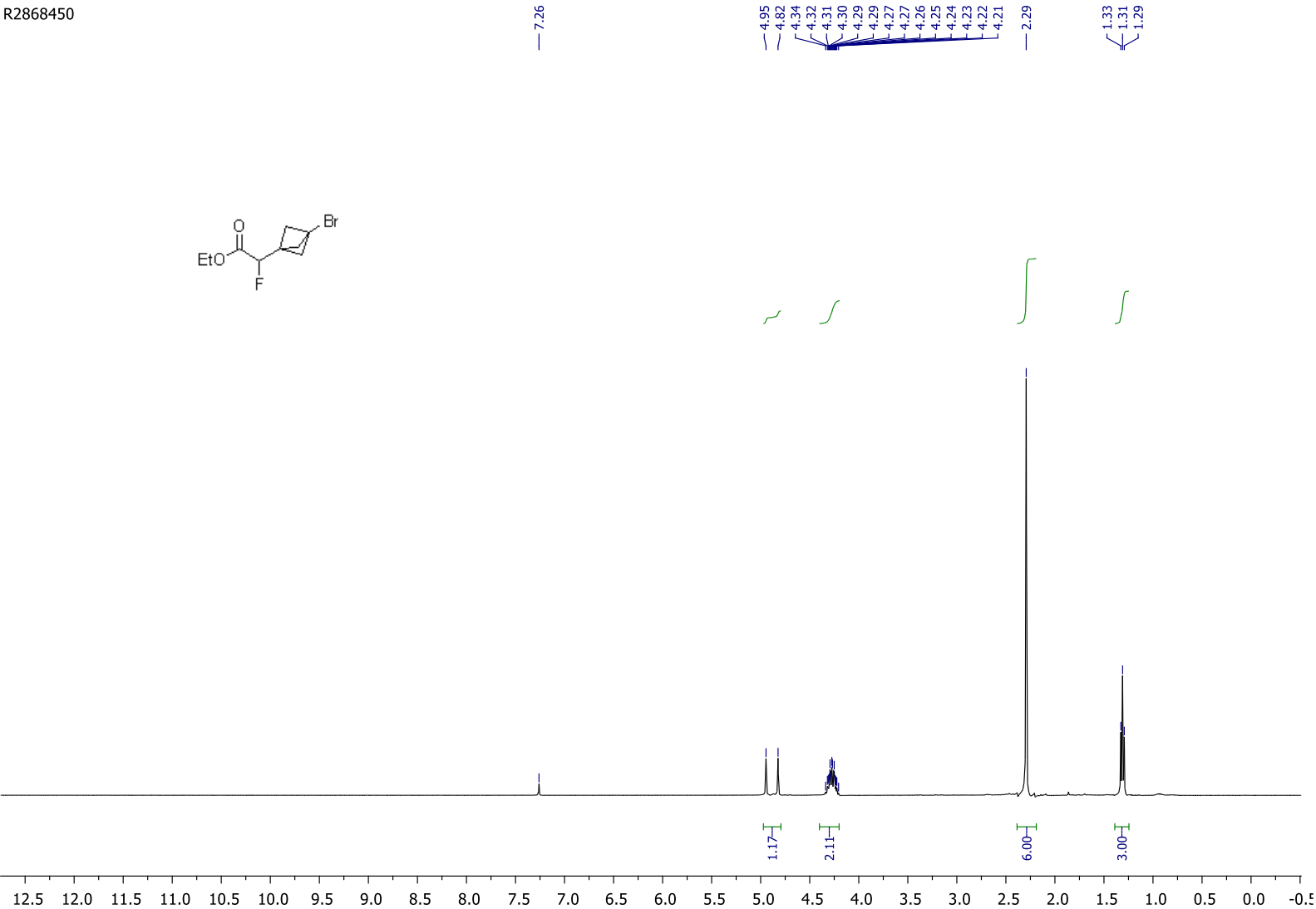
— -109.63



Compound 74

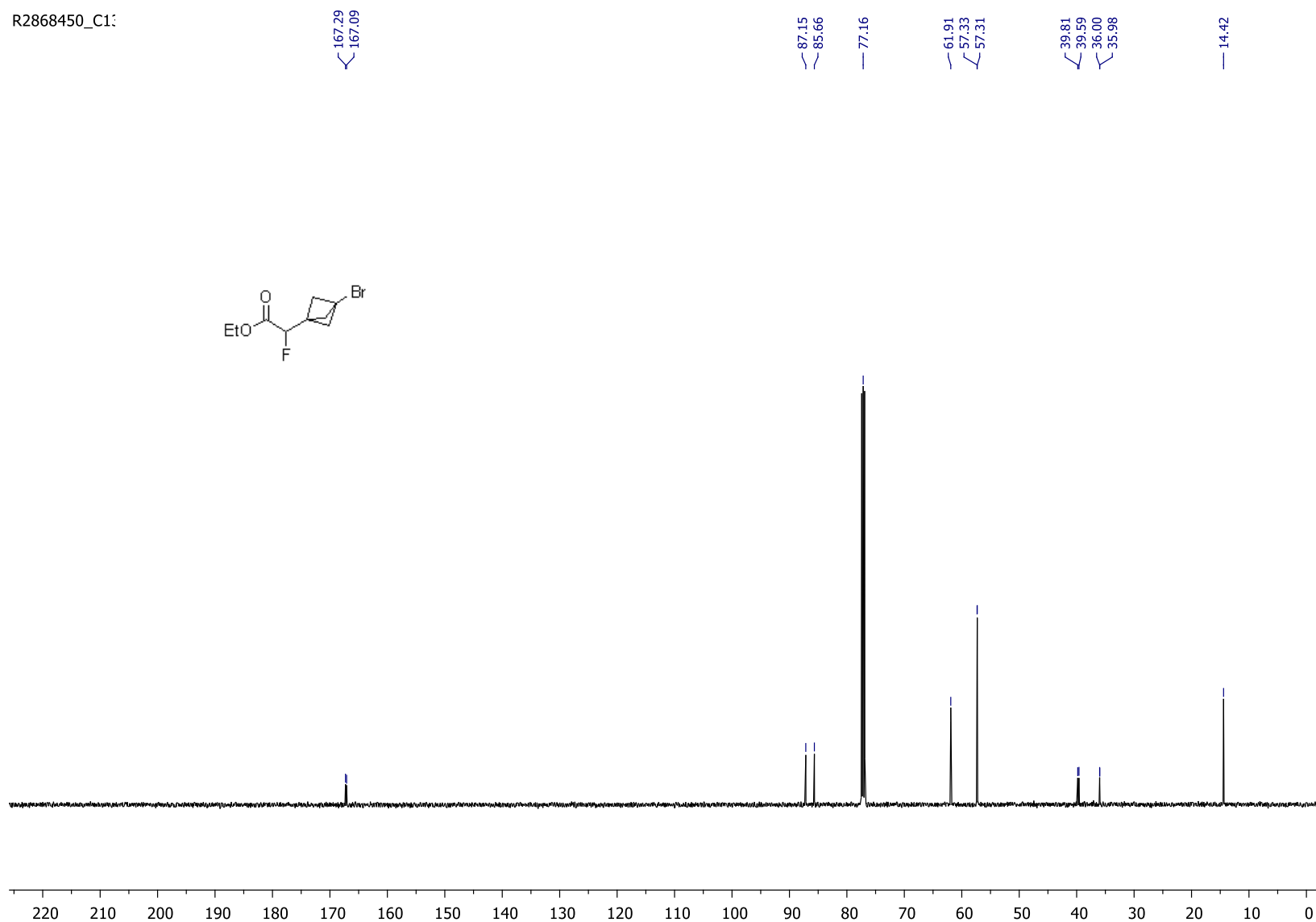
R2868450

¹H NMR (400 MHz, CDCl₃)



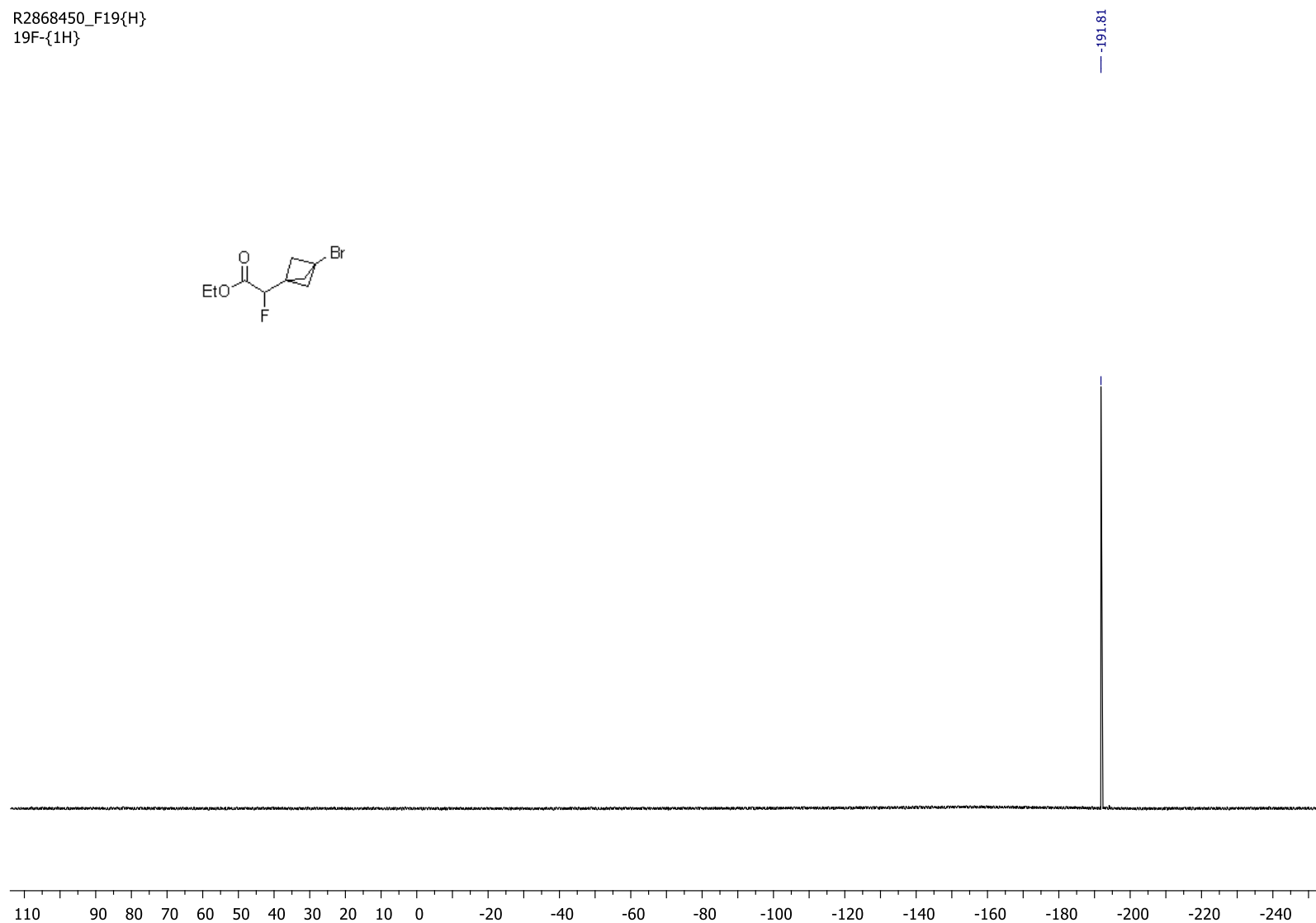
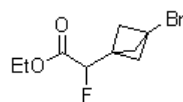
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2868450_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

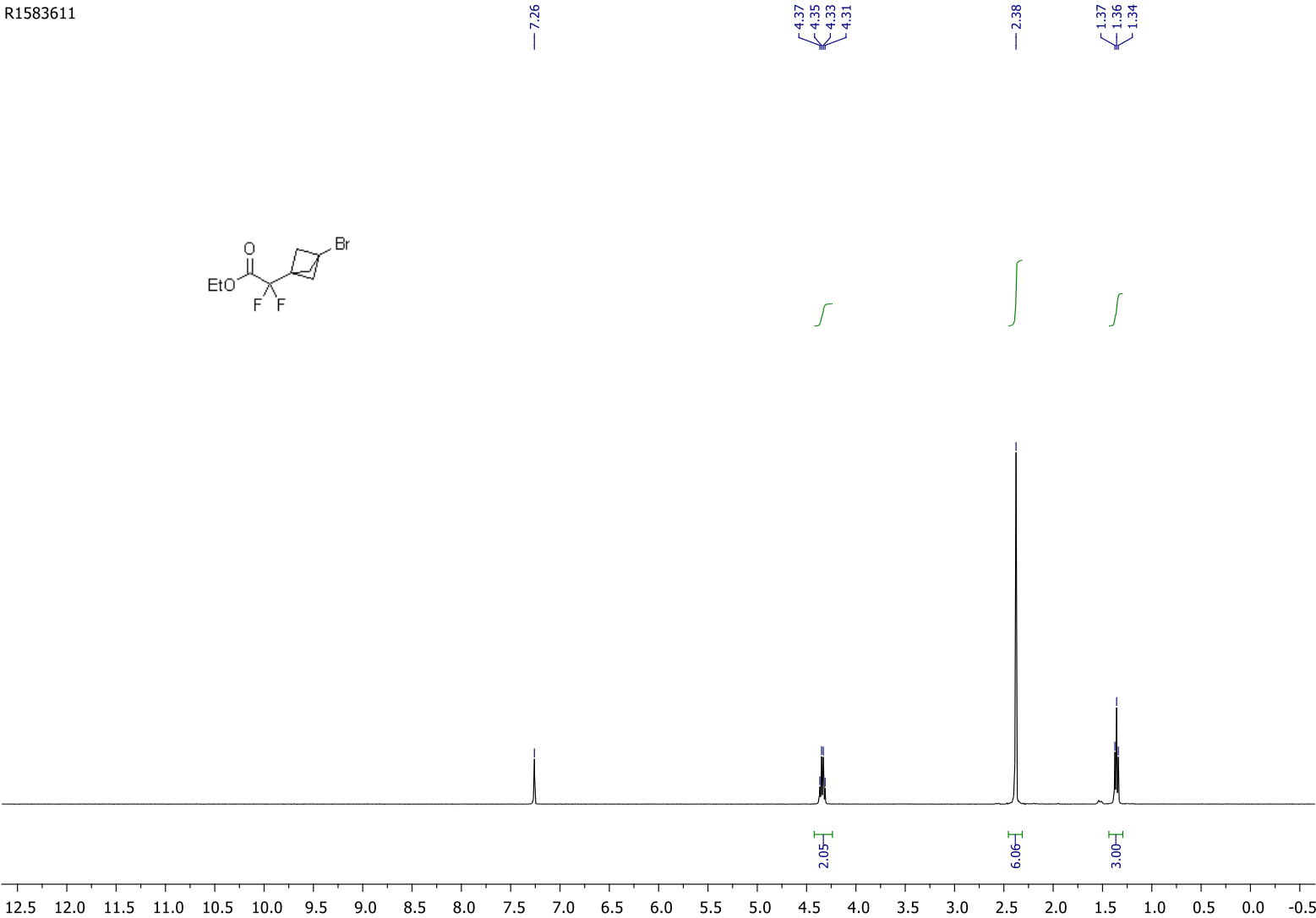
R2868450_F19{H}
19F-{1H}



Compound 75

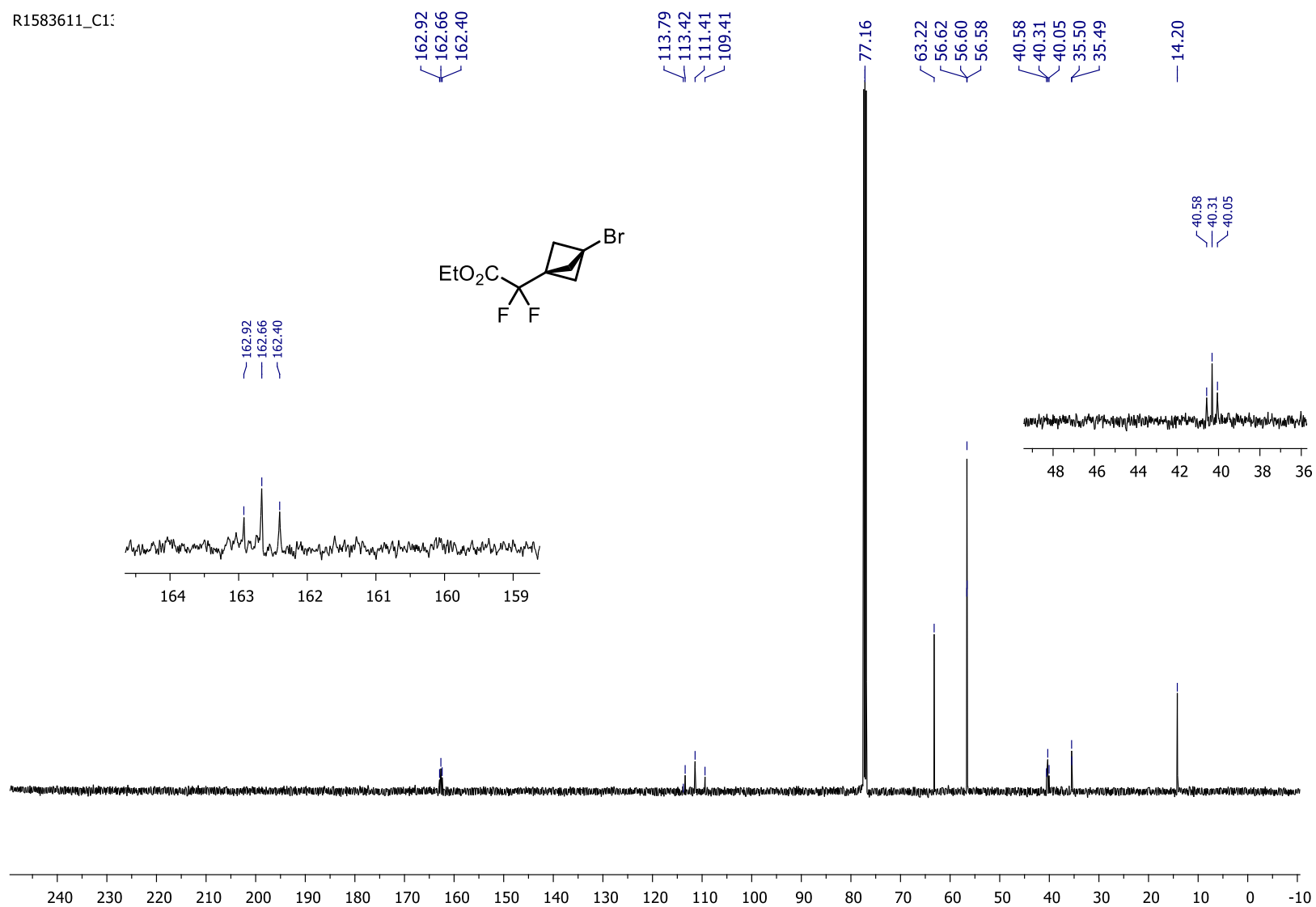
R1583611

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

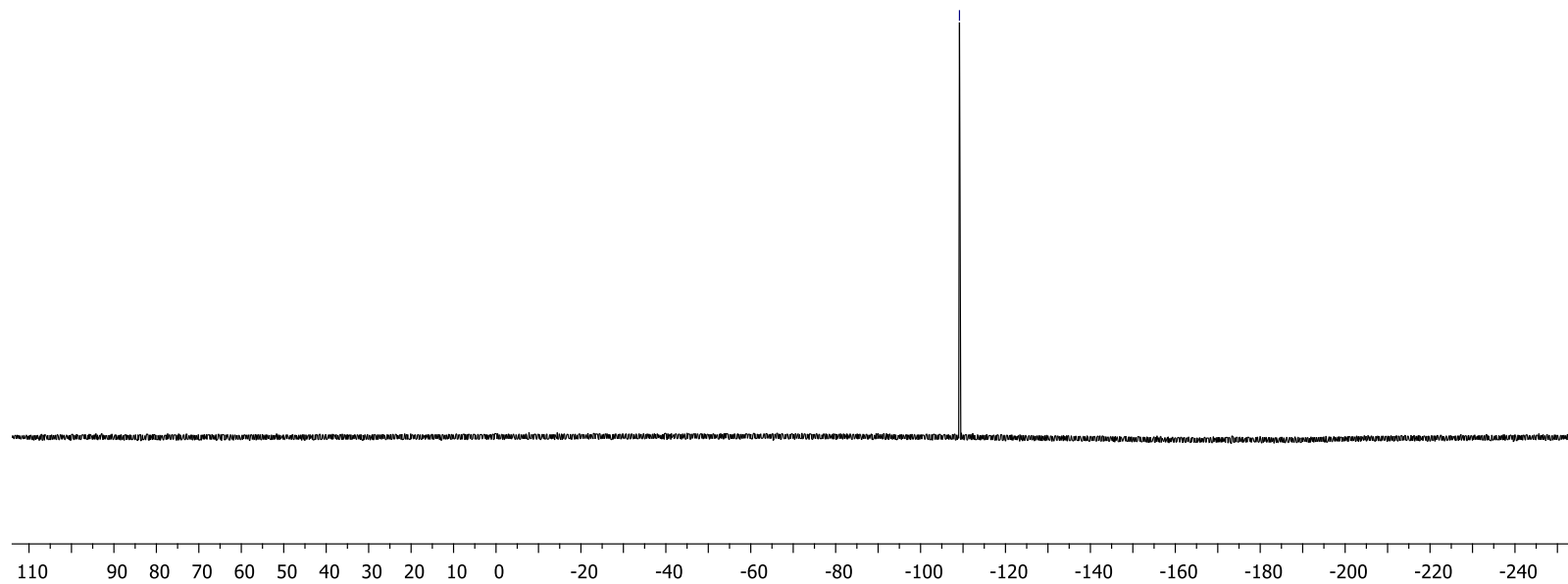
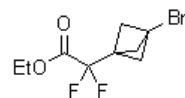
R1583611_C1:



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R1583611_F19{H}
 $^{19}\text{F}\{-^1\text{H}\}$

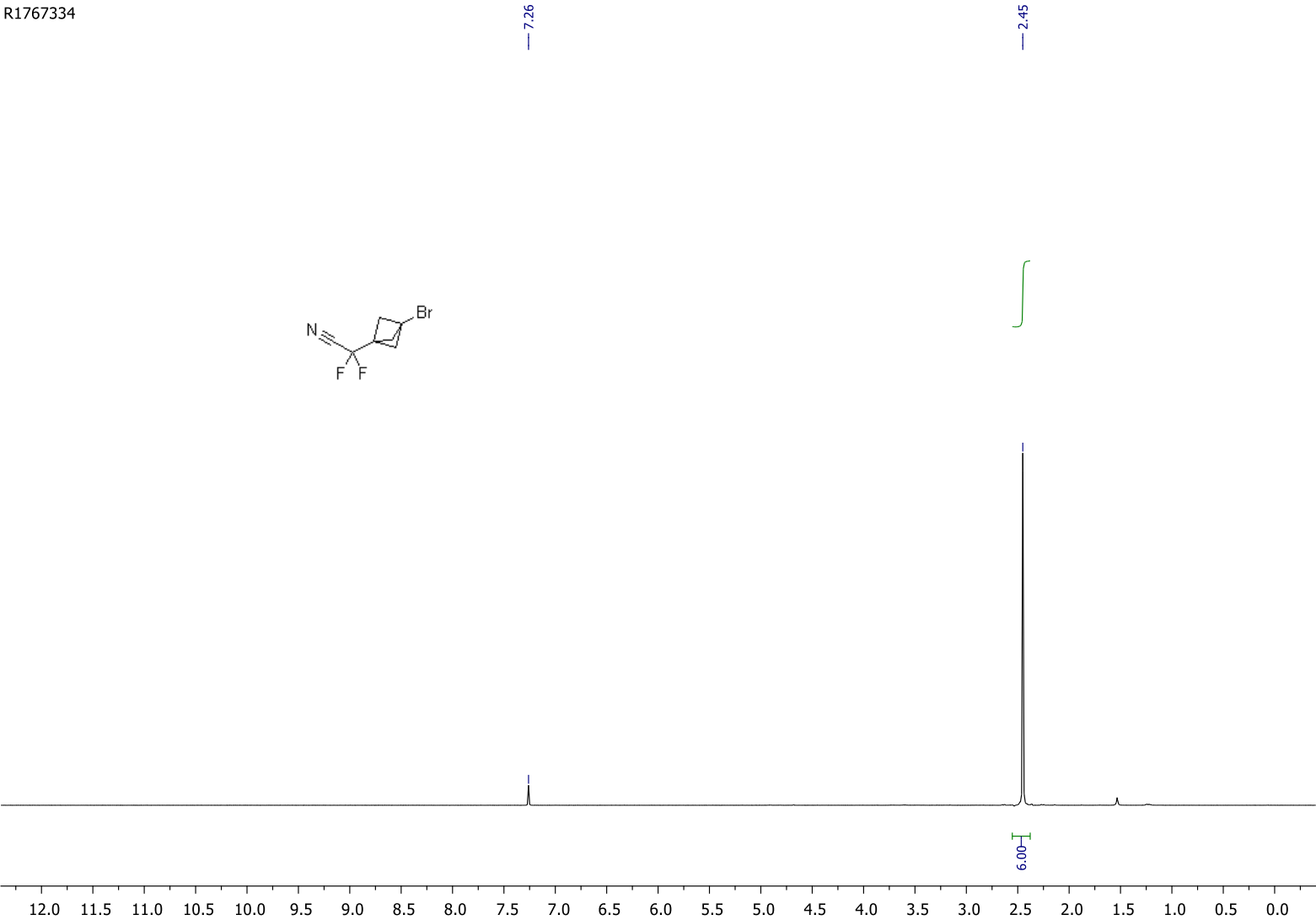
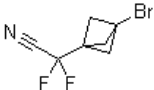
— -109.16



Compound 76

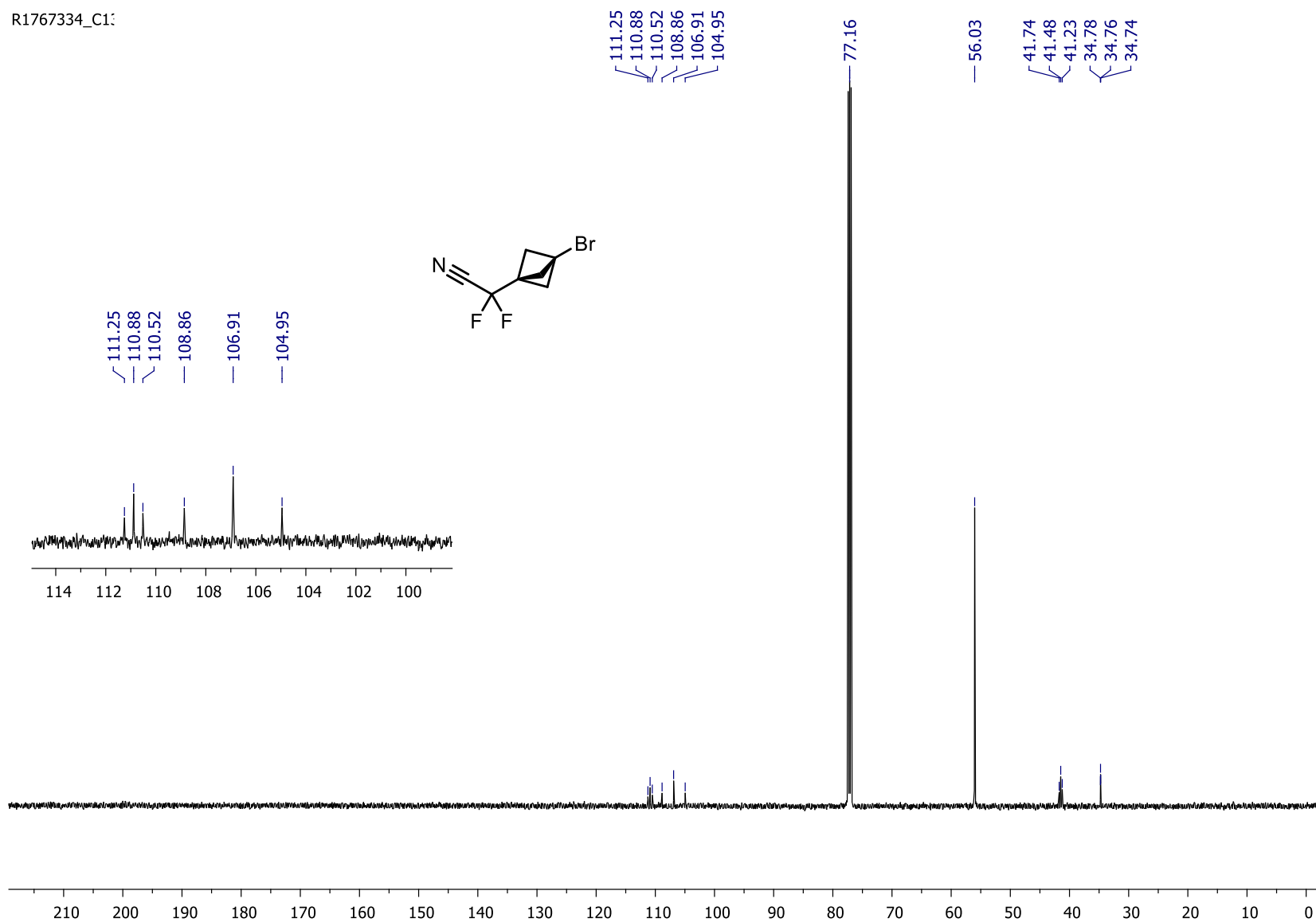
R1767334

¹H NMR (400 MHz, CDCl₃)



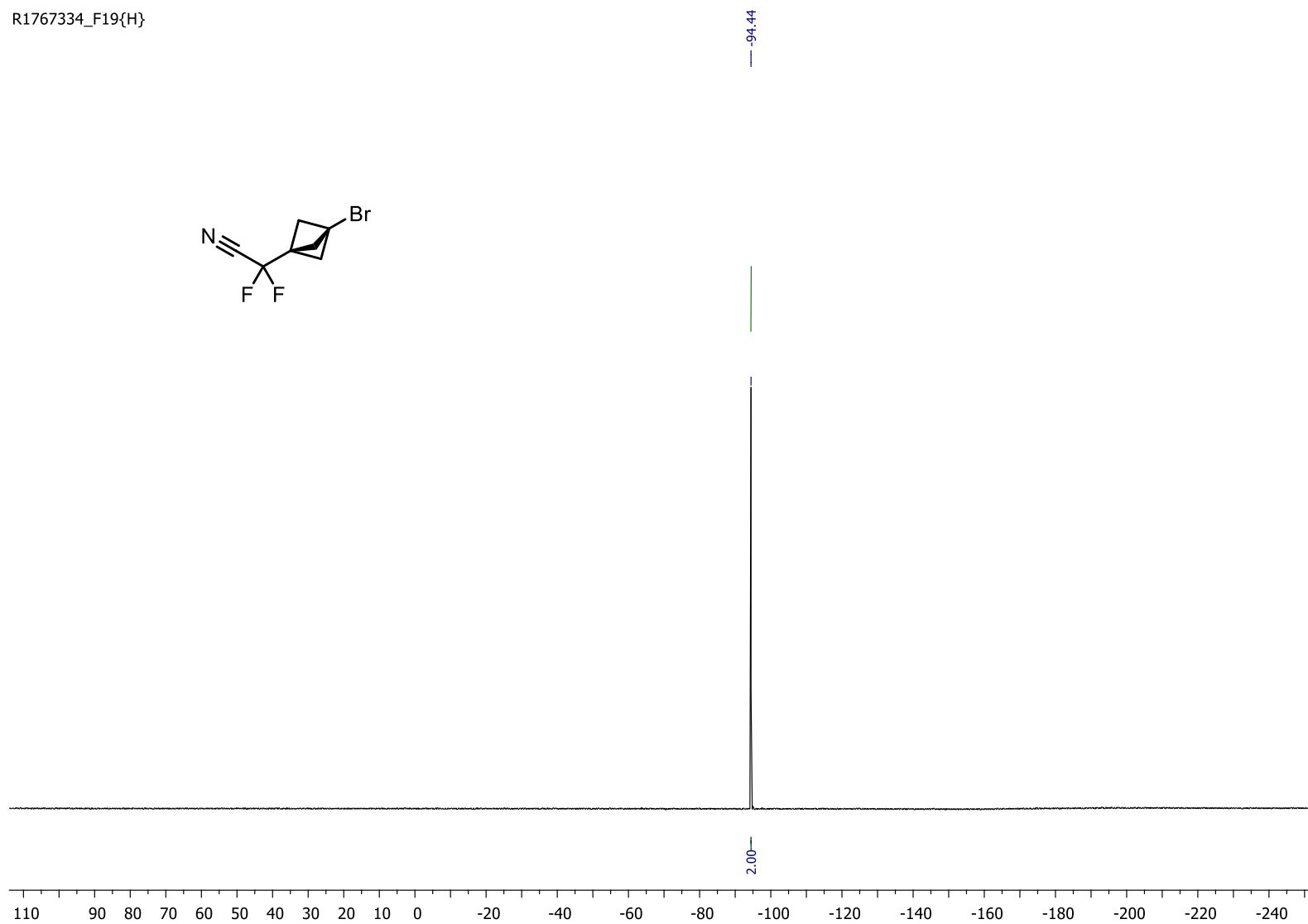
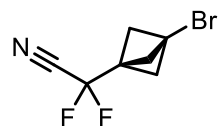
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R1767334_C1:



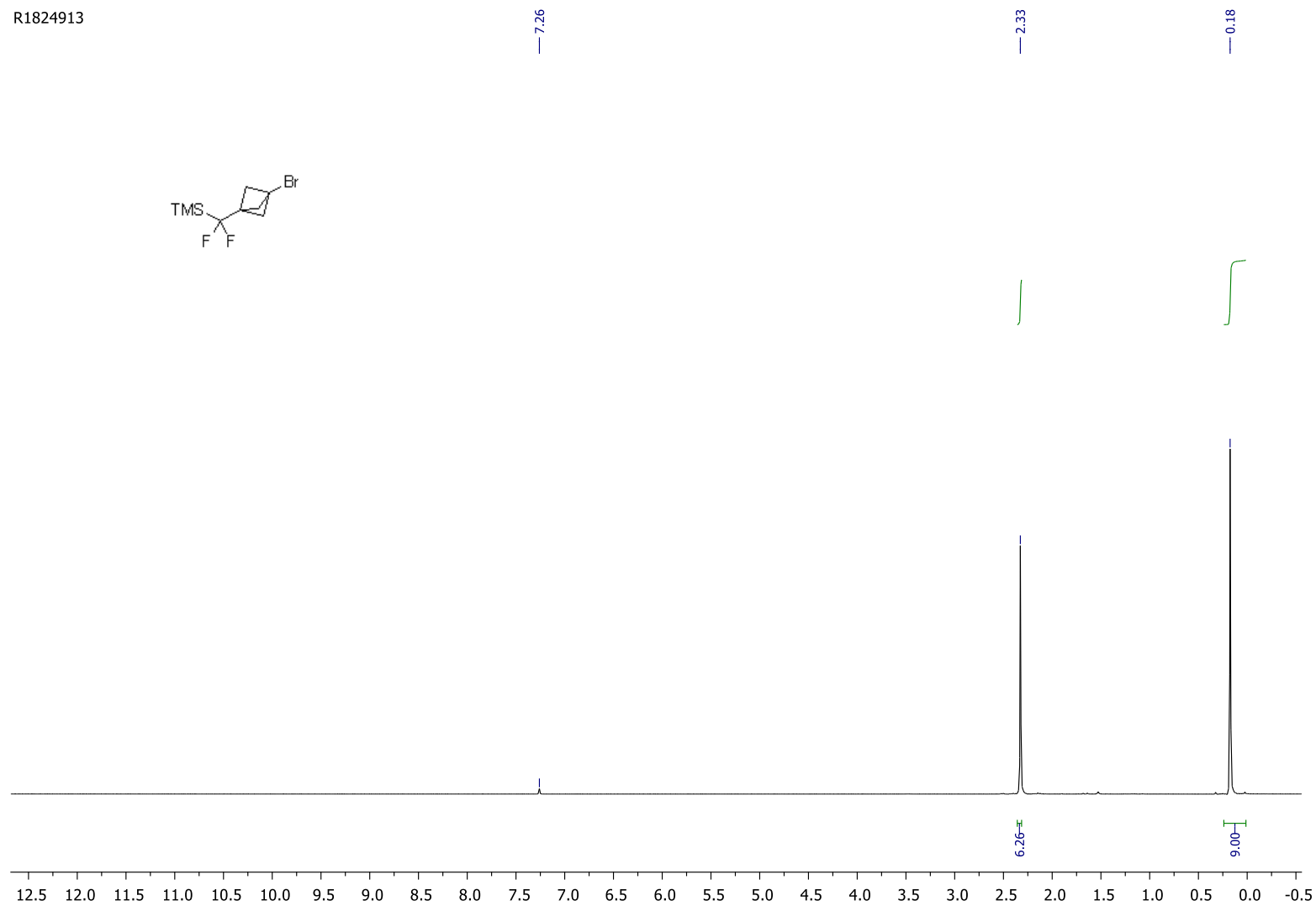
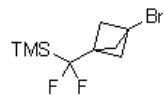
$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

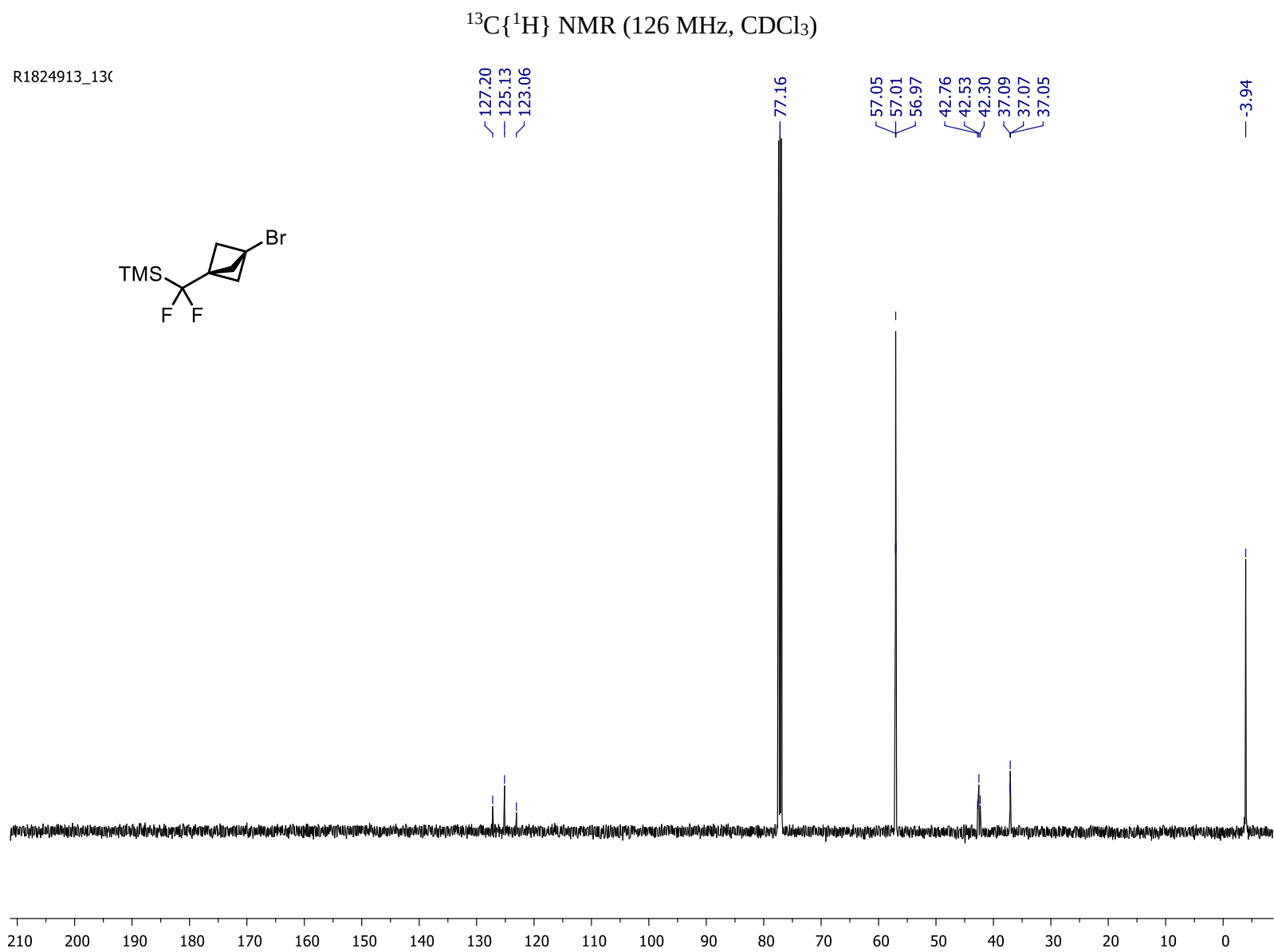
R1767334_F19{H}



Compound 77

R1824913

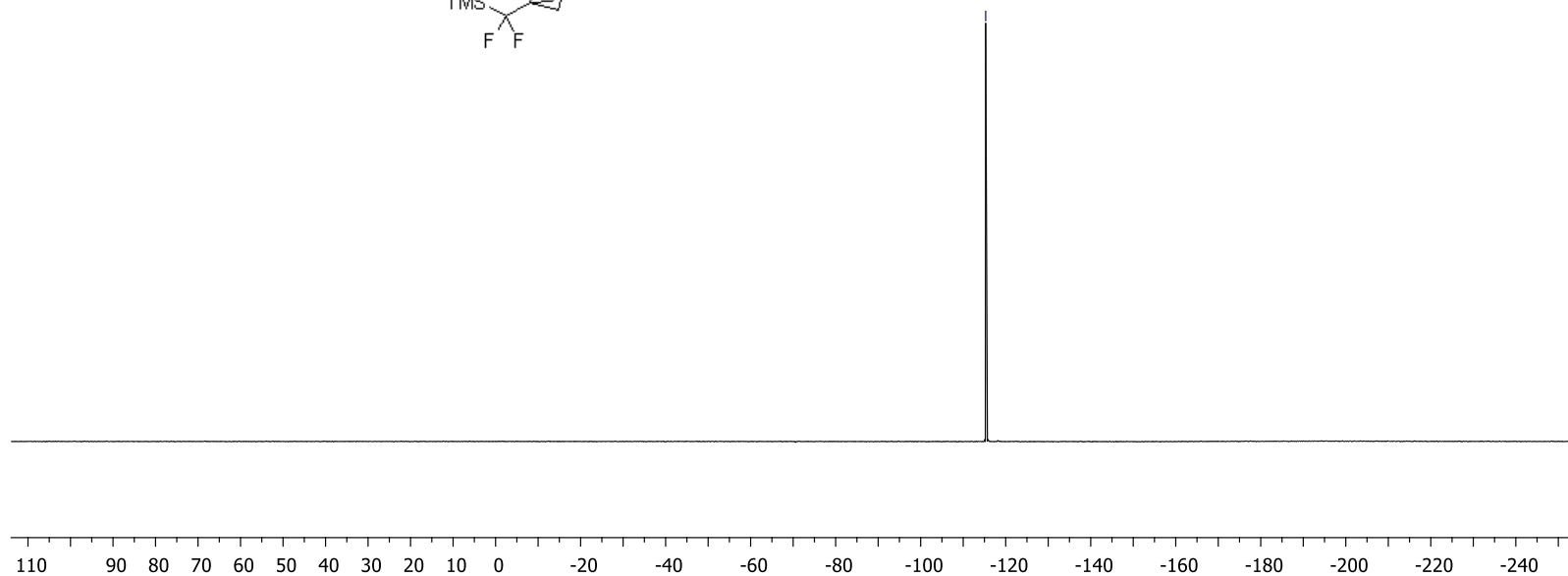
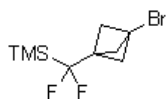
¹H NMR (400 MHz, CDCl₃)



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R1824913_F19{H}
 $^{19}\text{F}\{^1\text{H}\}$

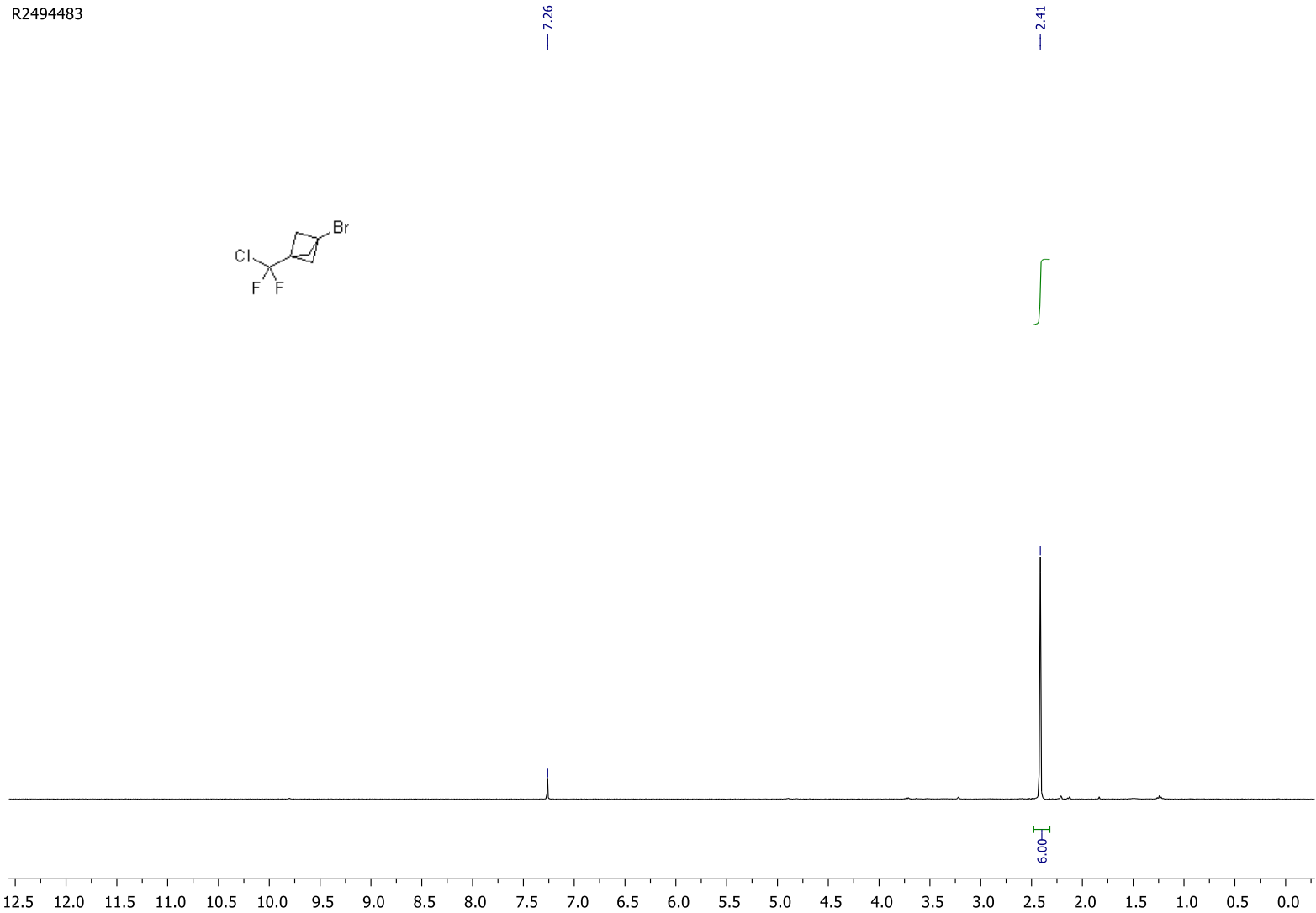
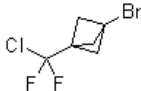
— -115.29



Compound 78

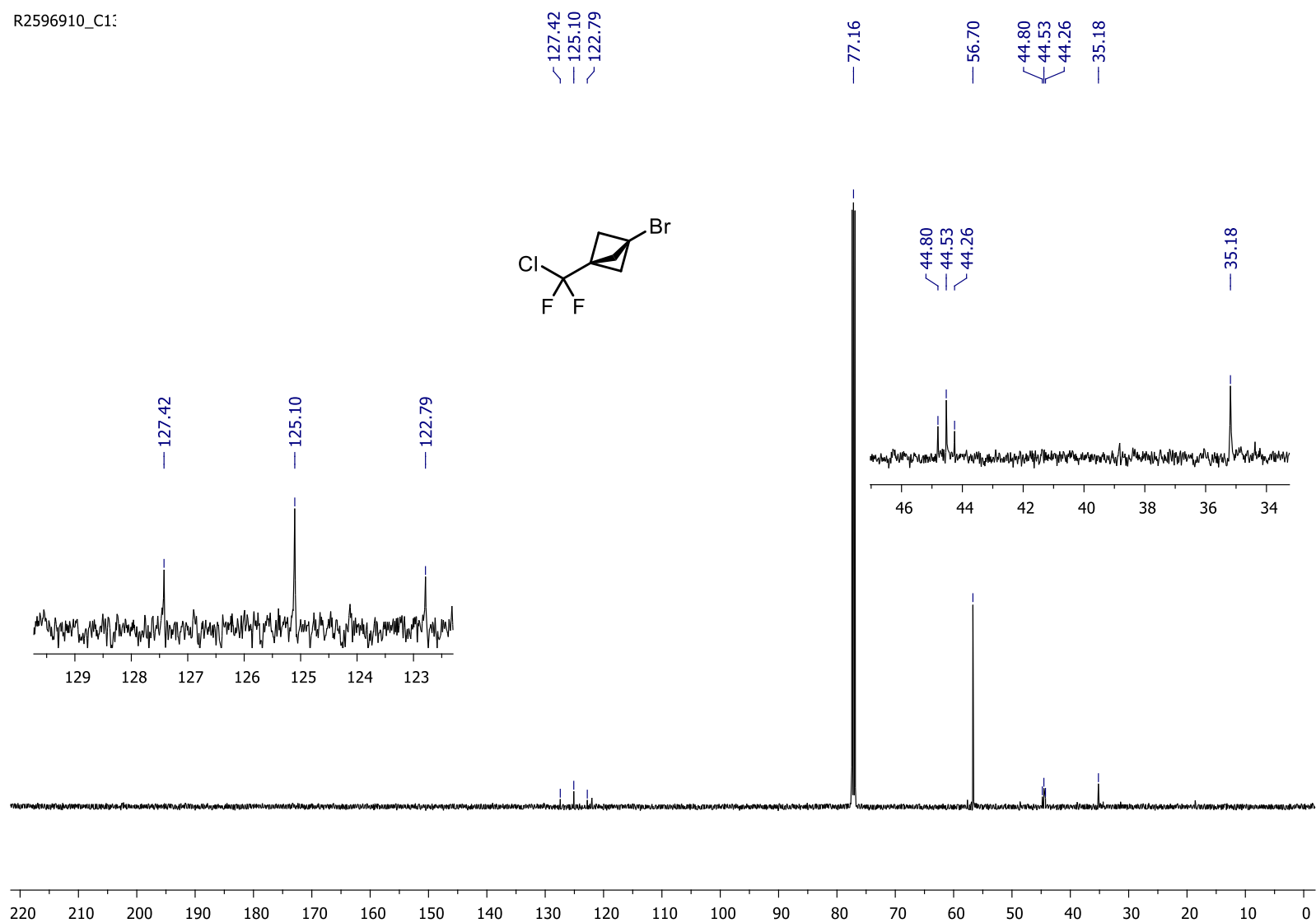
R2494483

¹H NMR (400 MHz, CDCl₃)



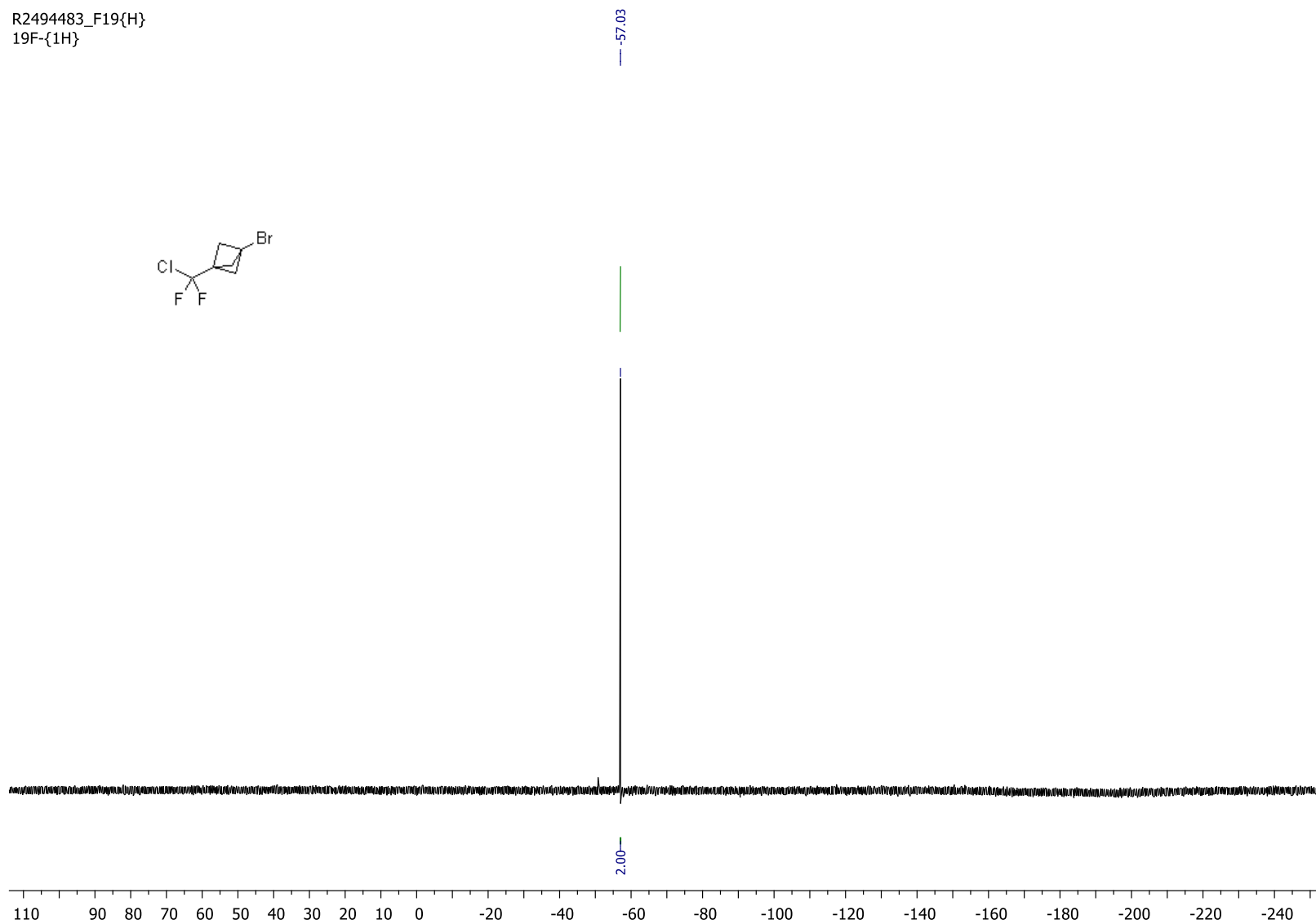
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2596910_C1:



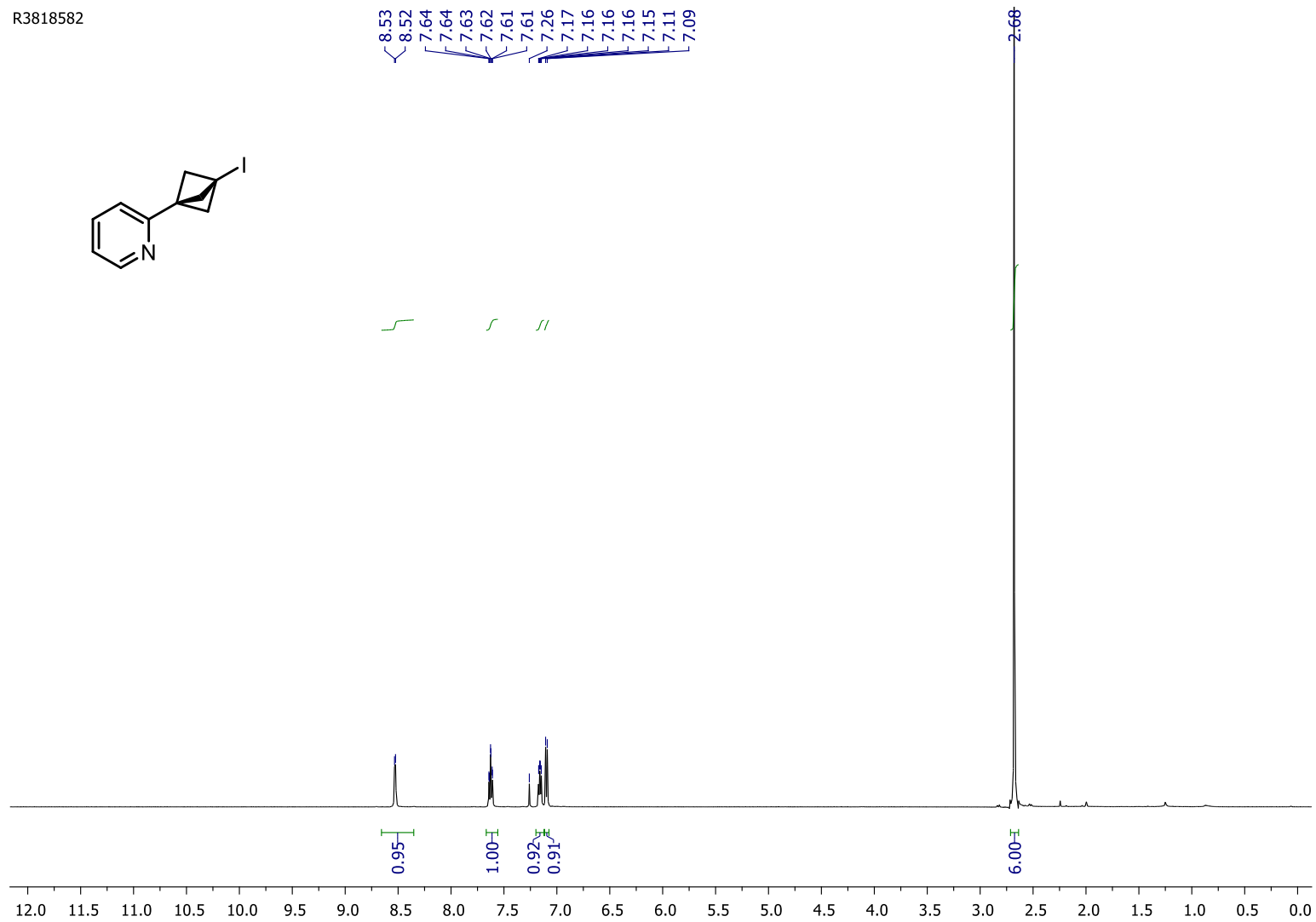
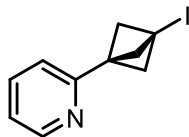
$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

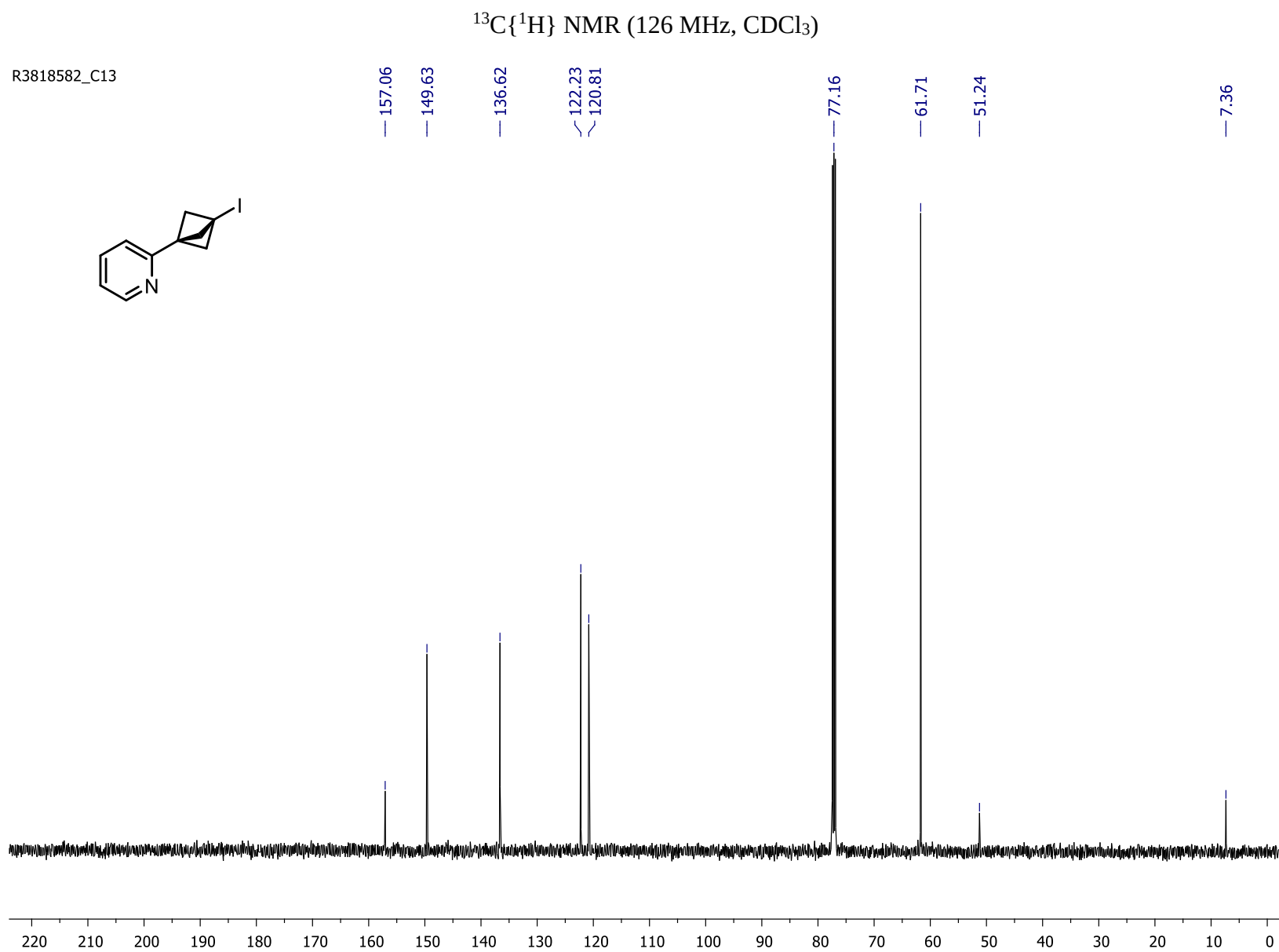
R2494483_F19{H}
19F-{1H}



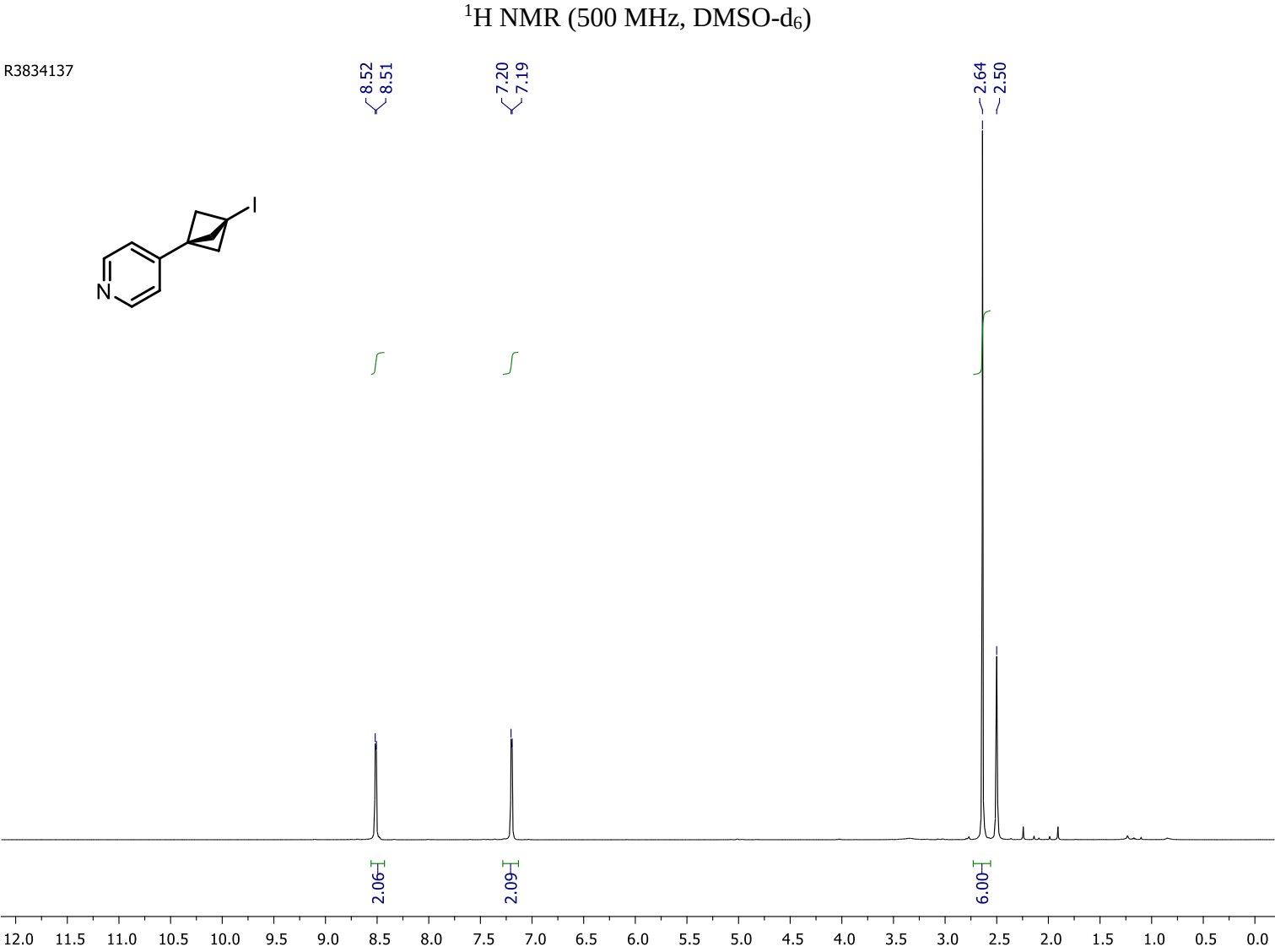
Compound 79

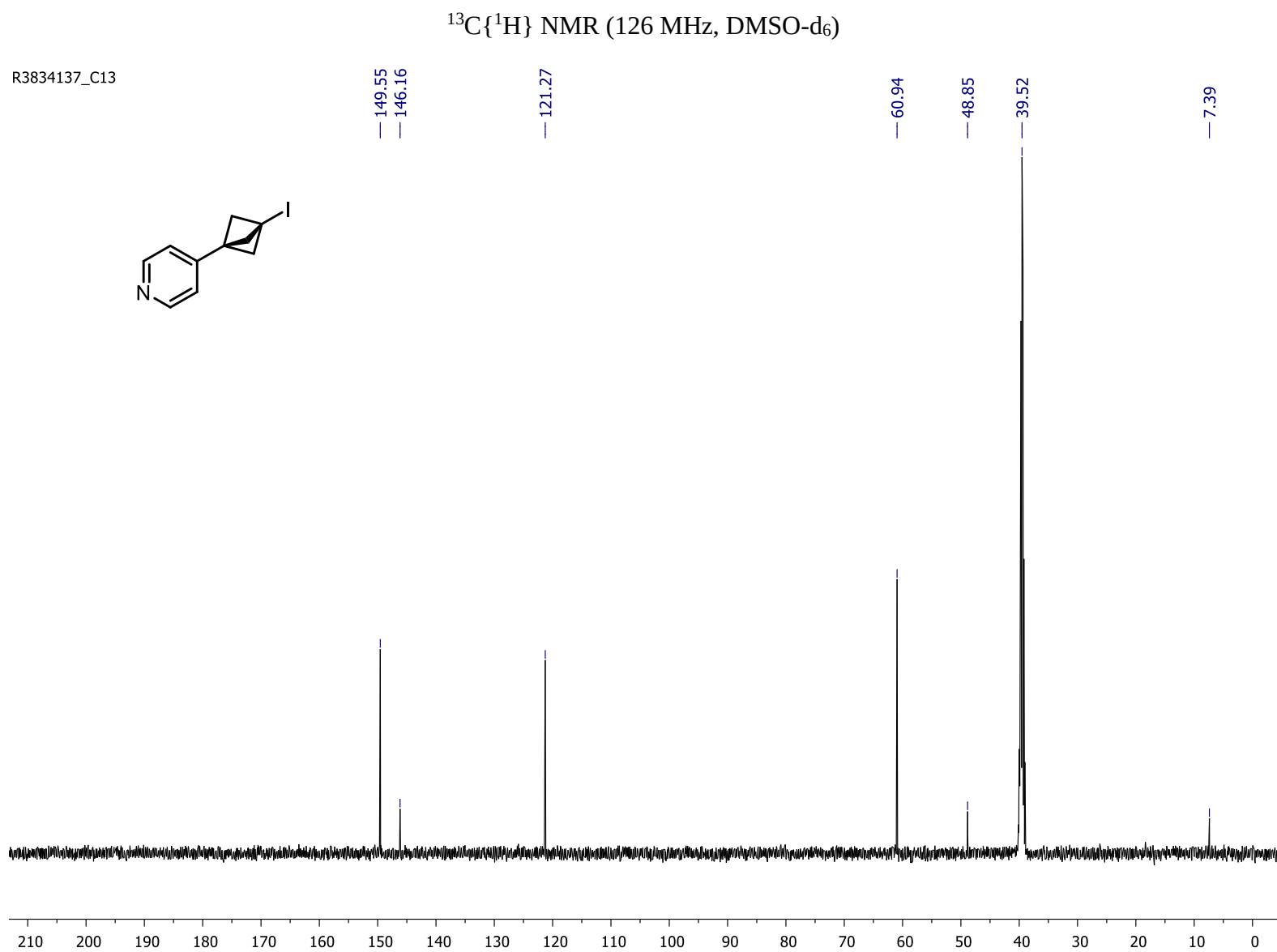
R3818582

¹H NMR (500 MHz, CDCl₃)

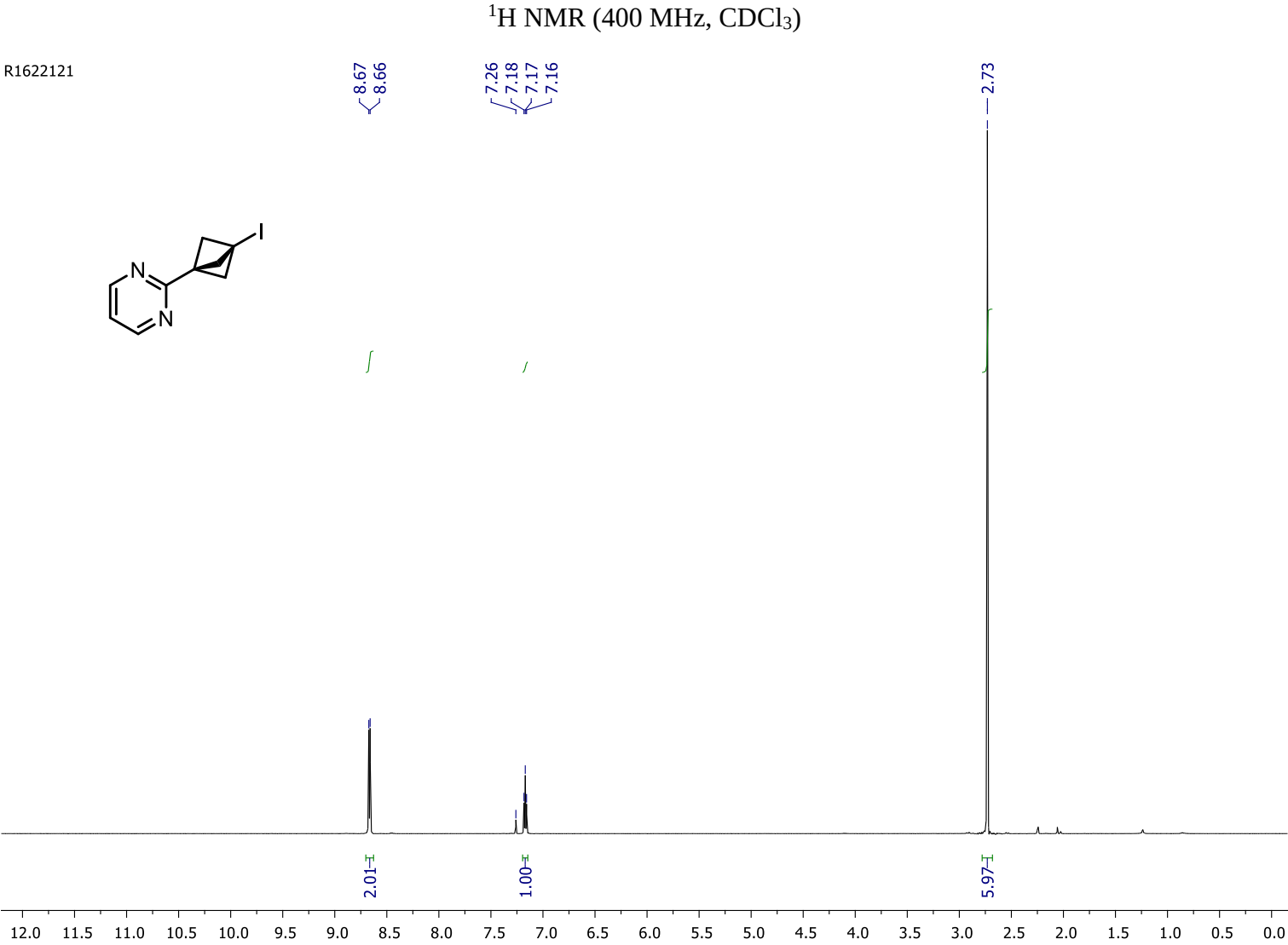


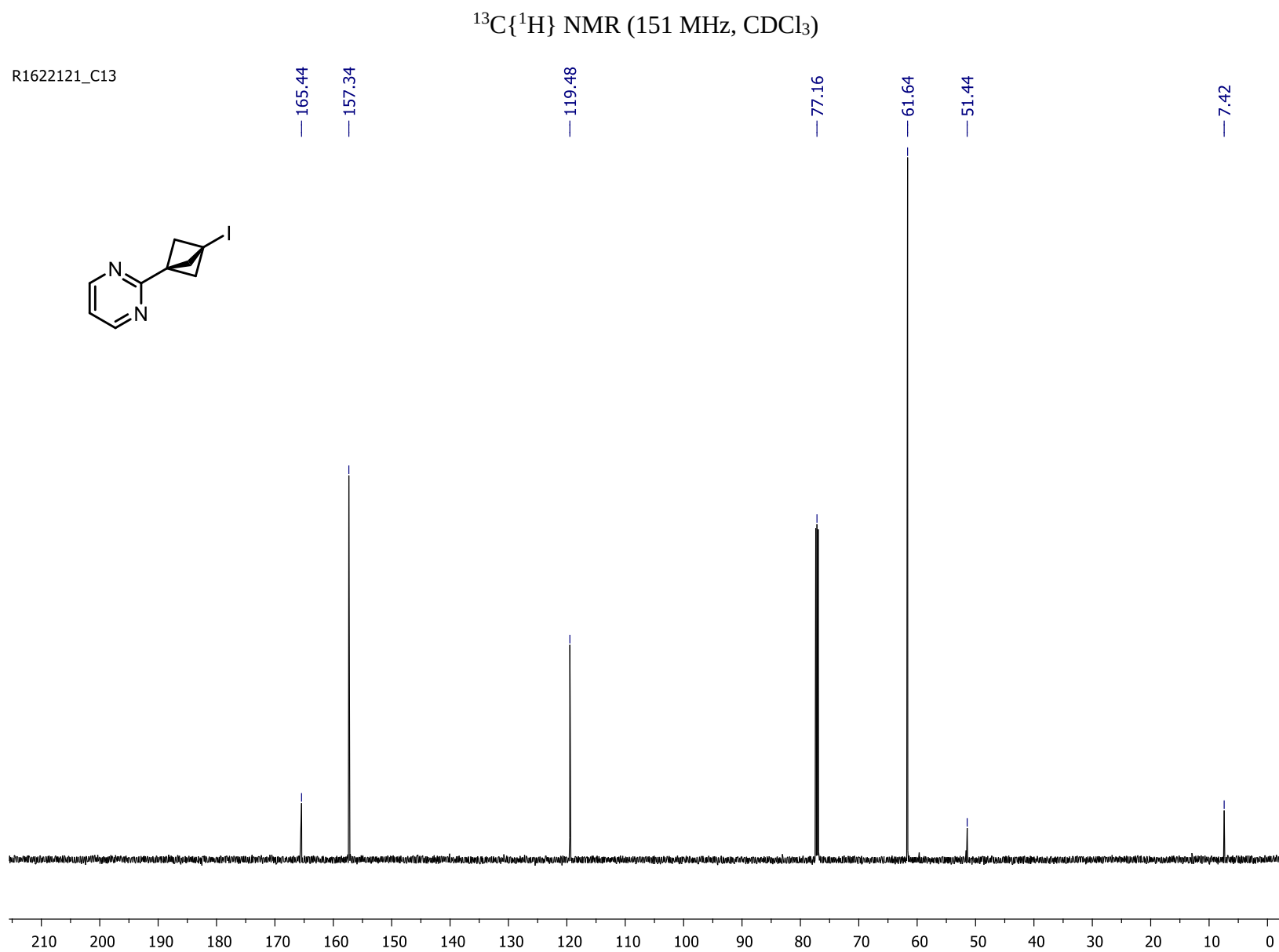
Compound 80





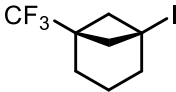
Compound 81



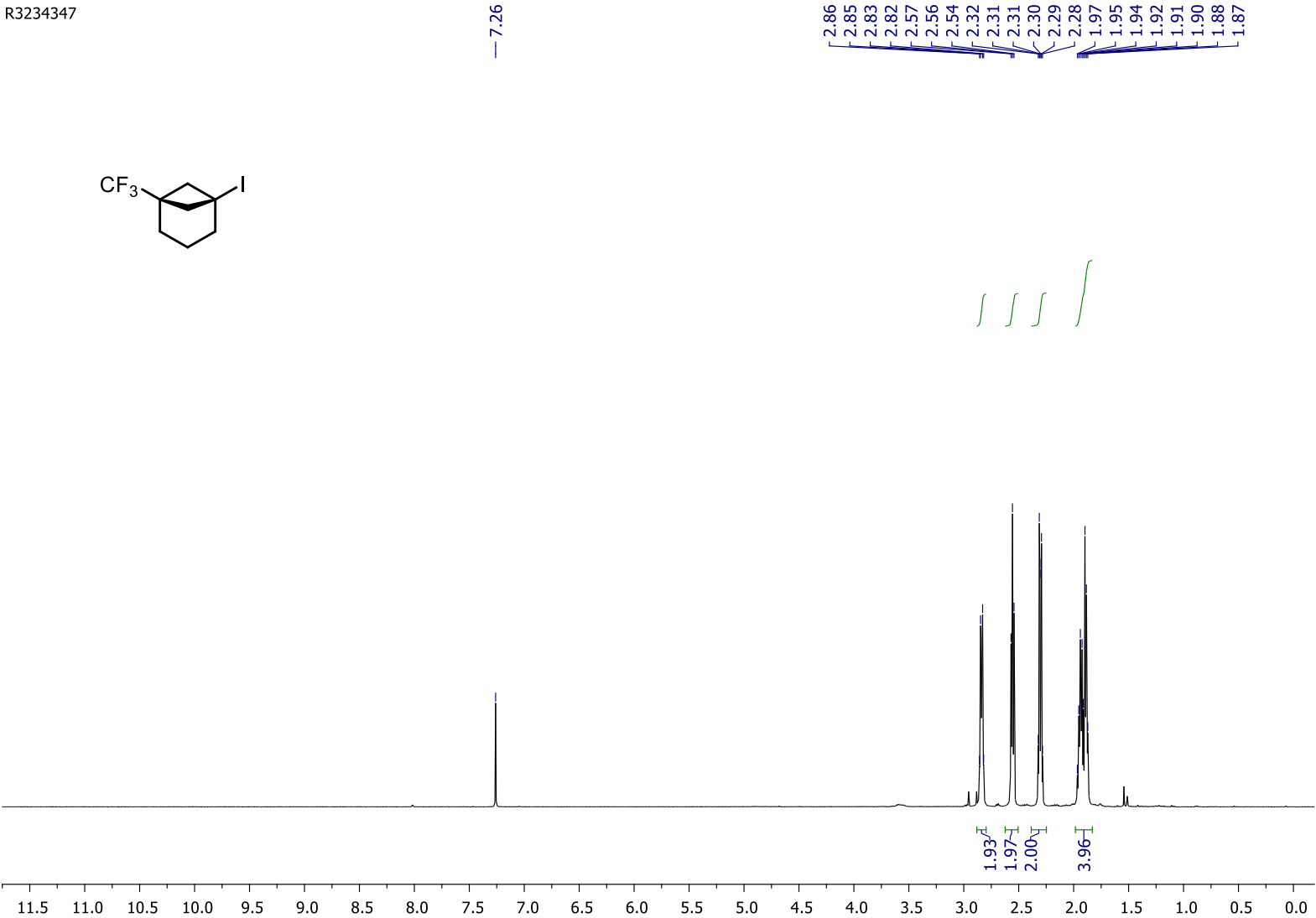


Compound 82

R3234347

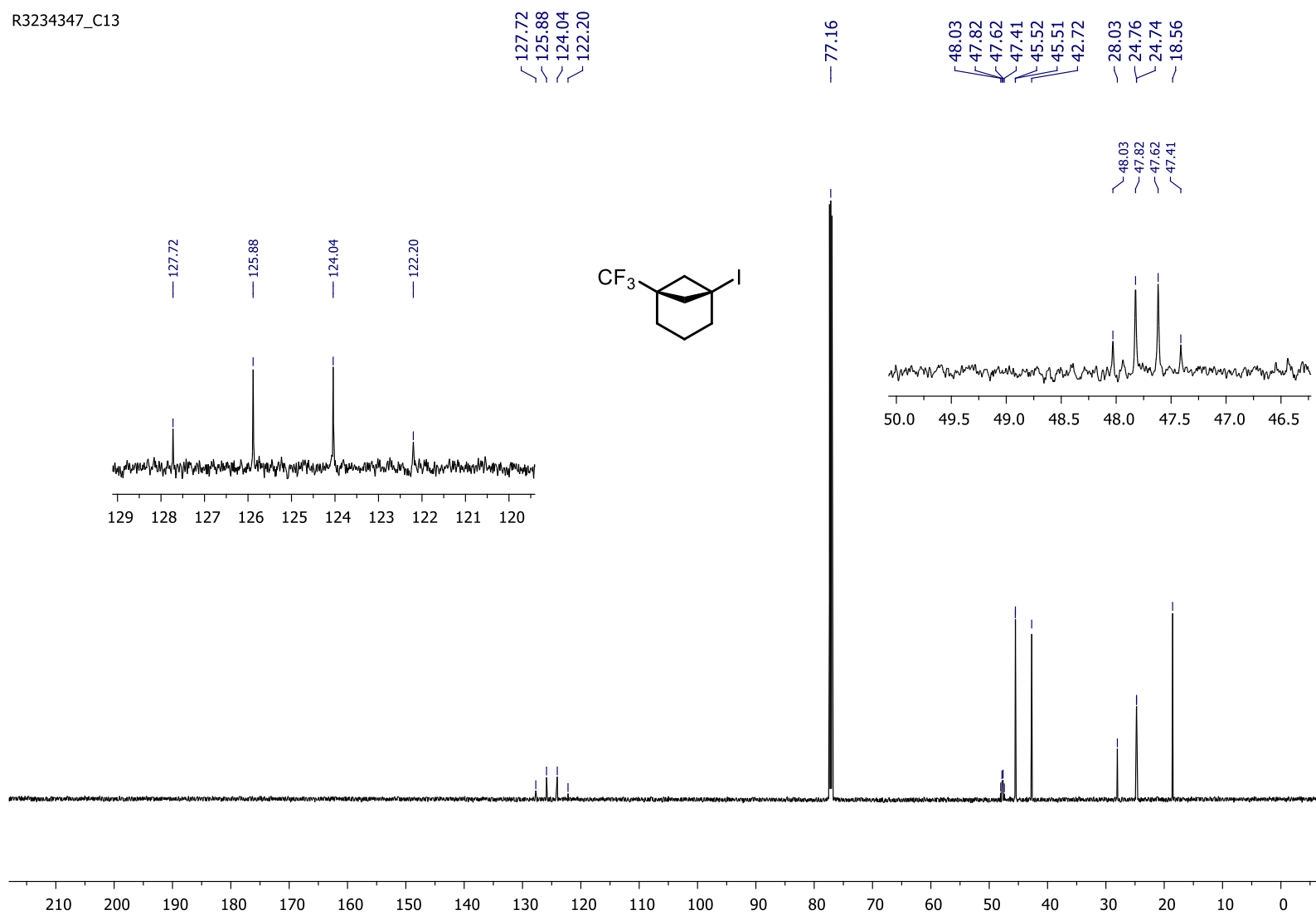


¹H NMR (500 MHz, CDCl₃)

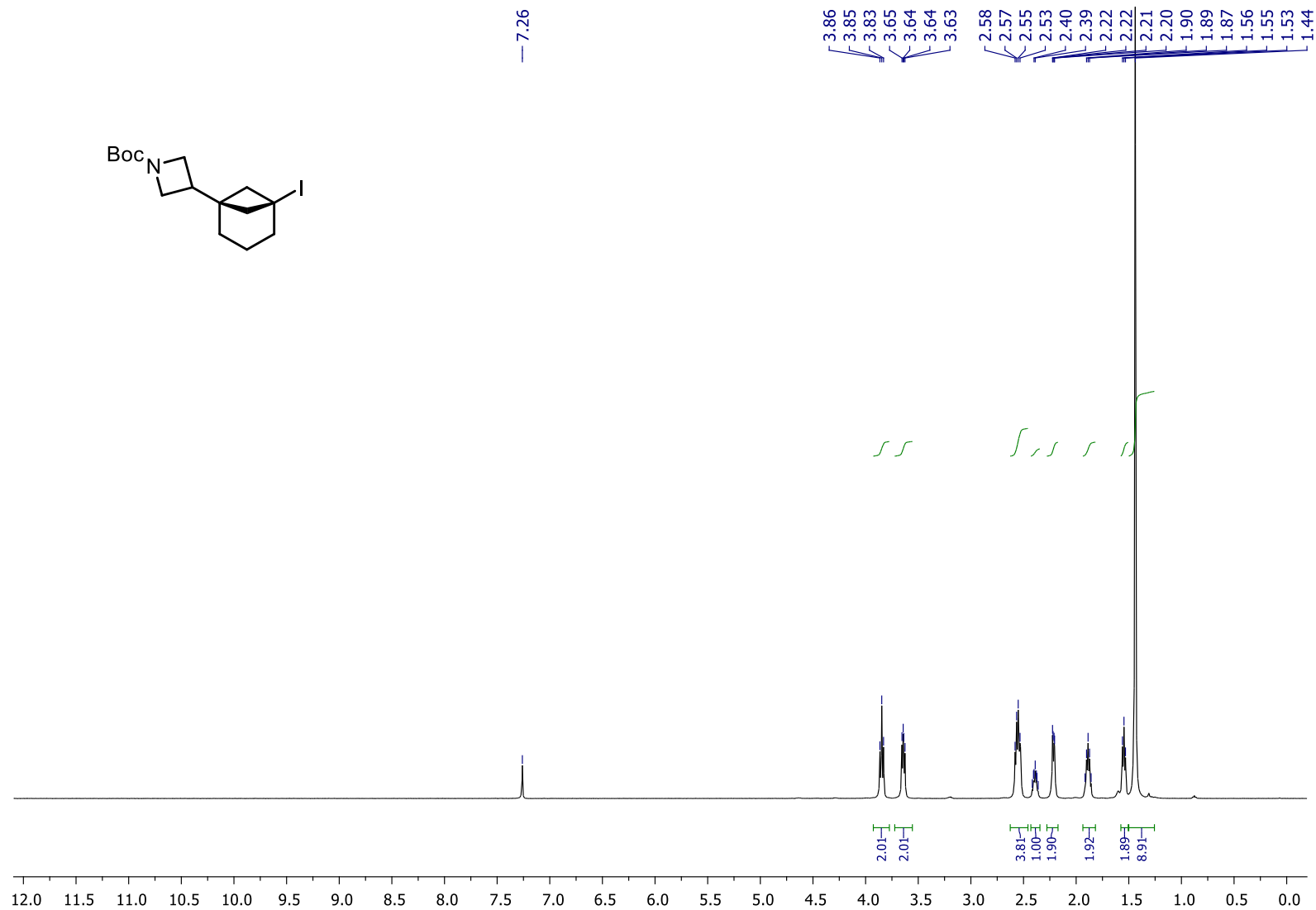
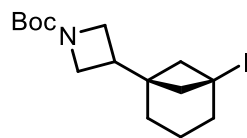


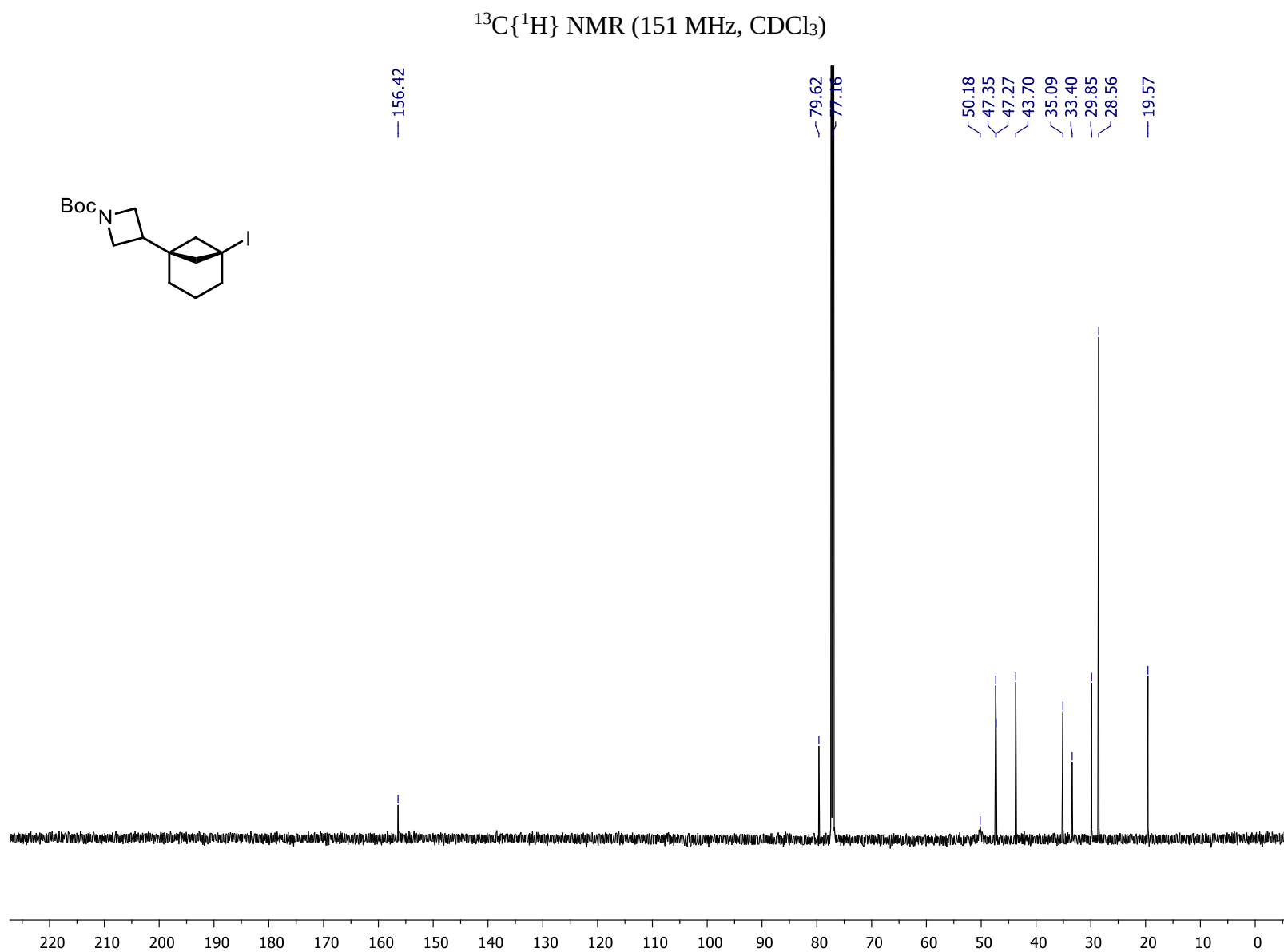
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

R3234347_C13



Compound 83

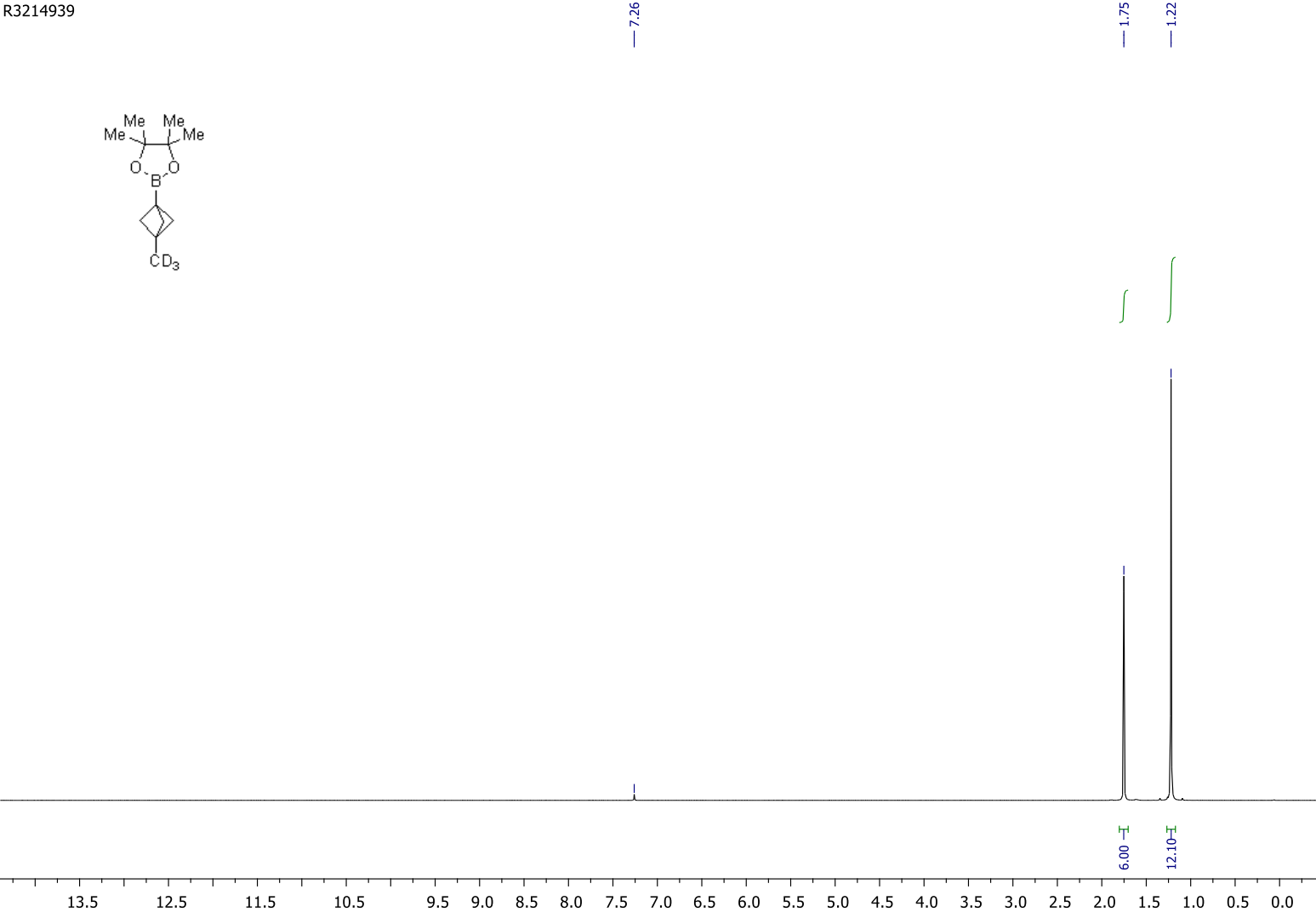
¹H NMR (500 MHz, CDCl₃)



Compound (D₃-1)a

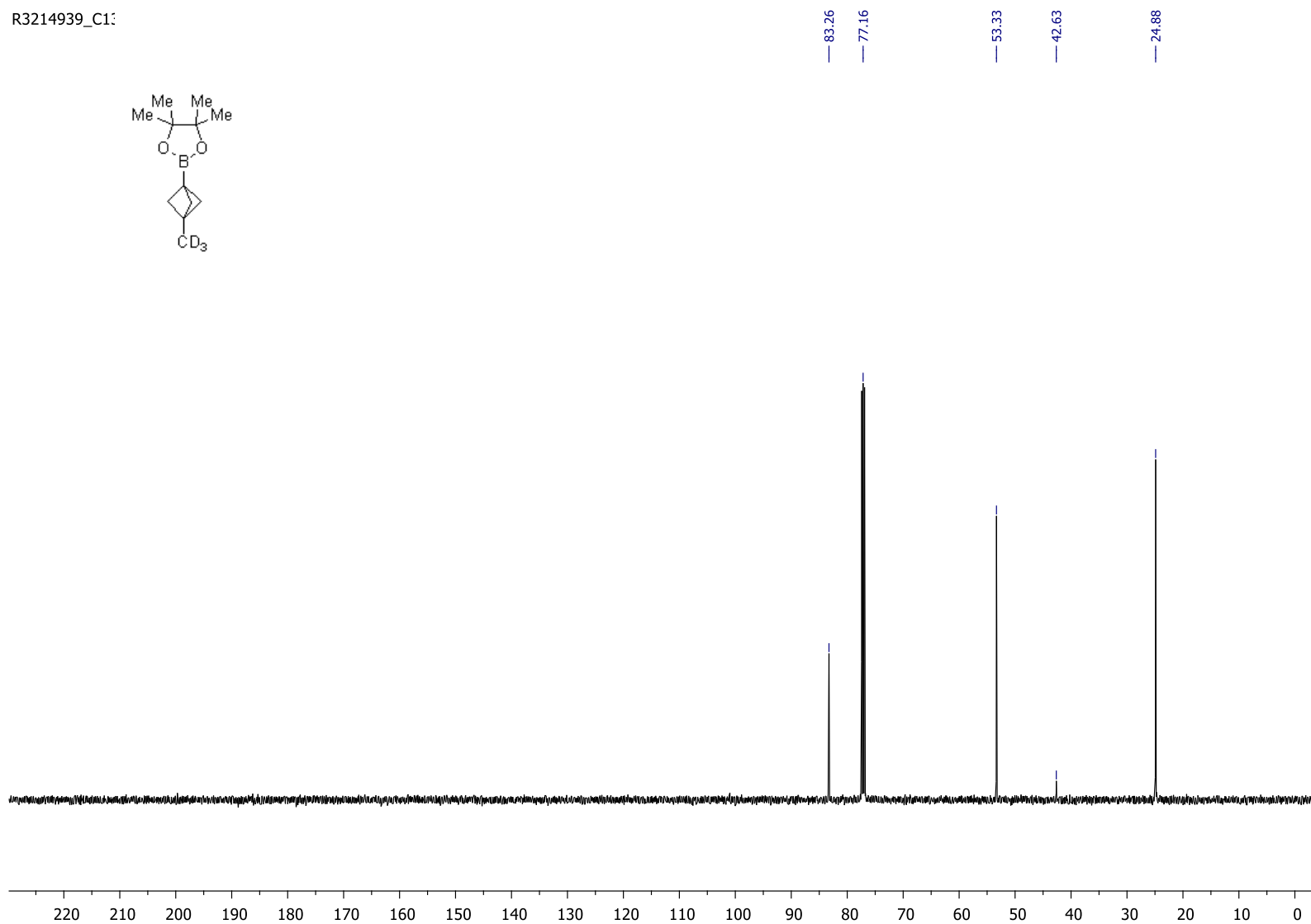
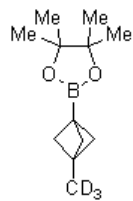
R3214939

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

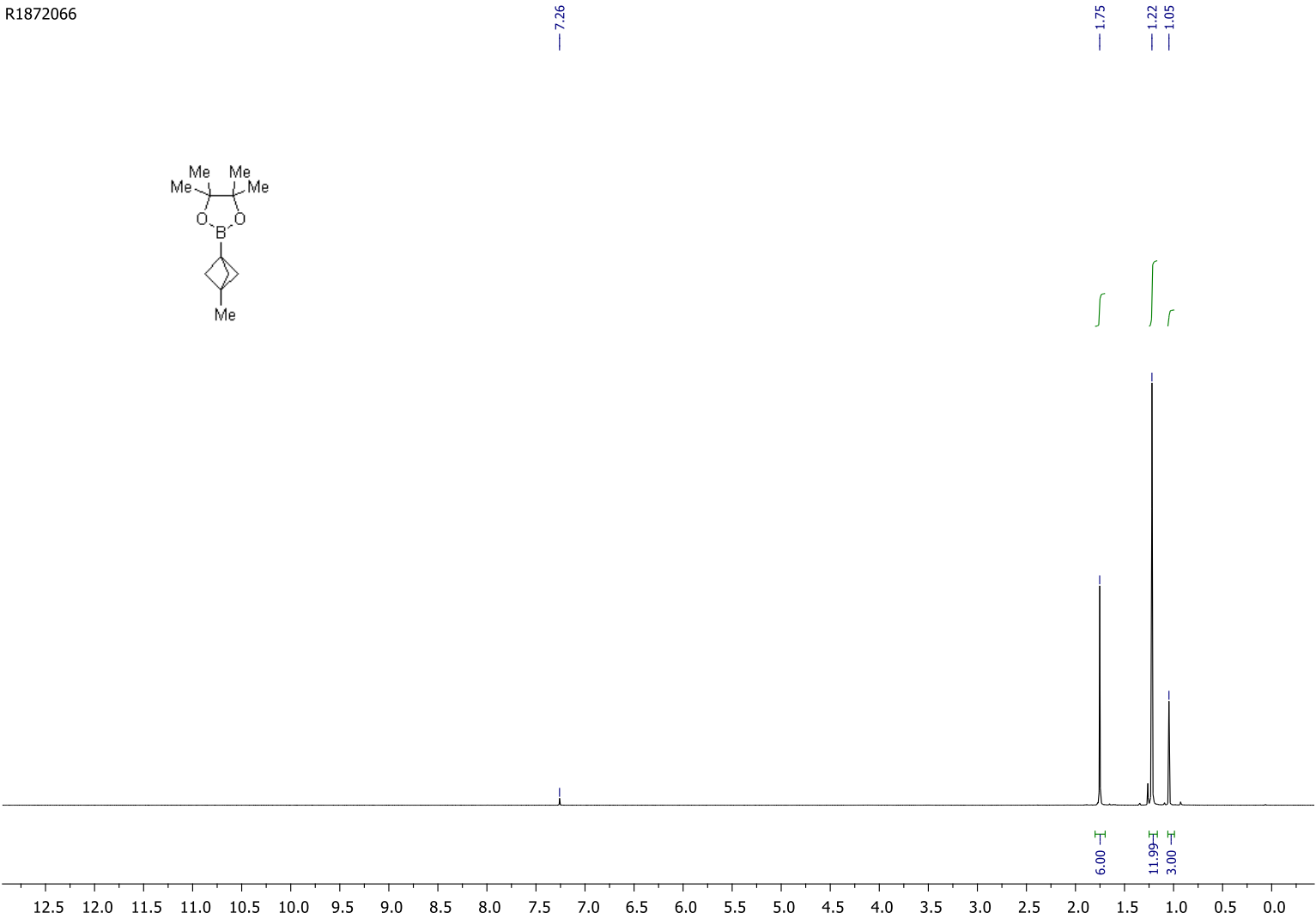
R3214939_C13



Compound 1a

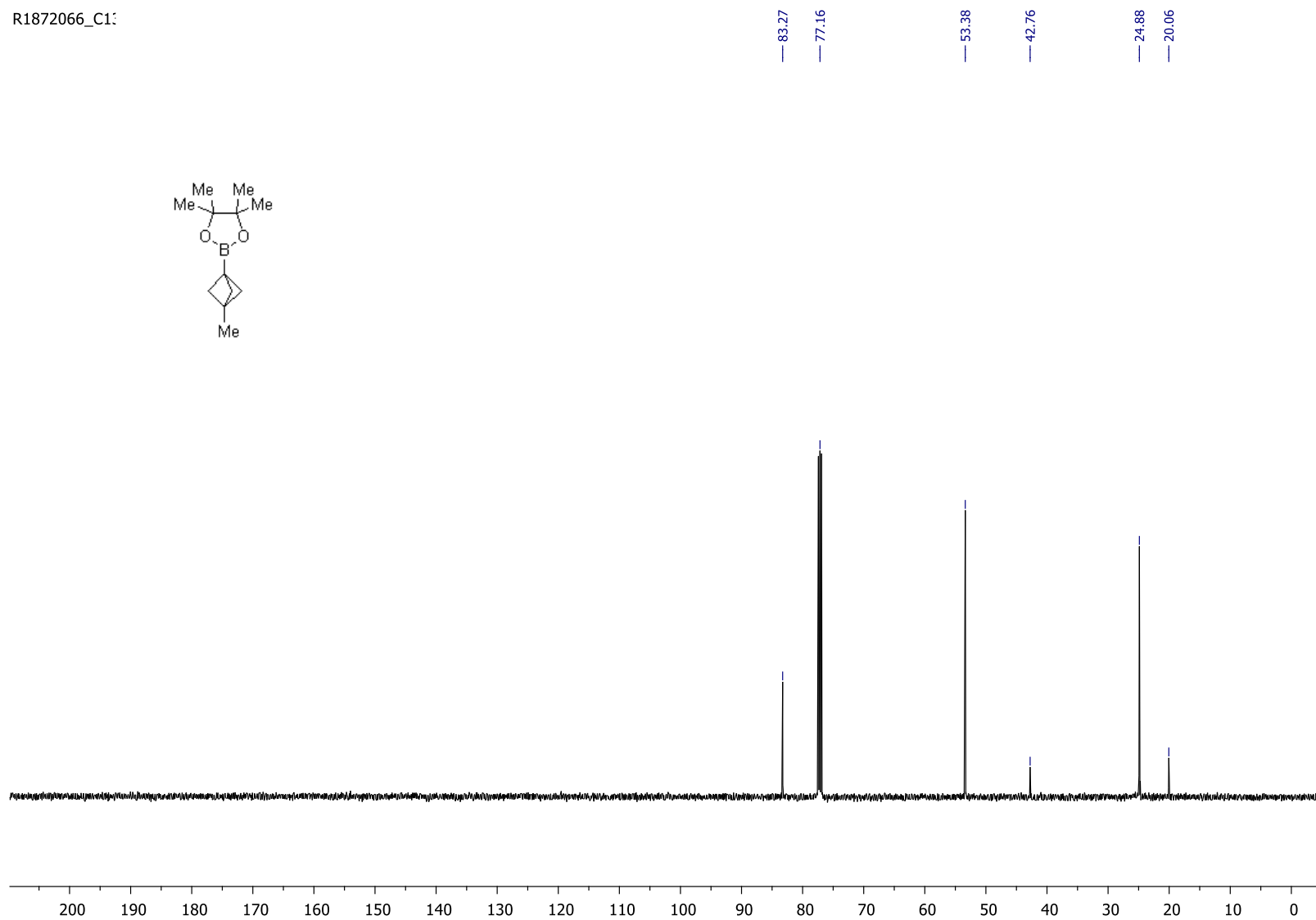
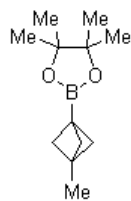
R1872066

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

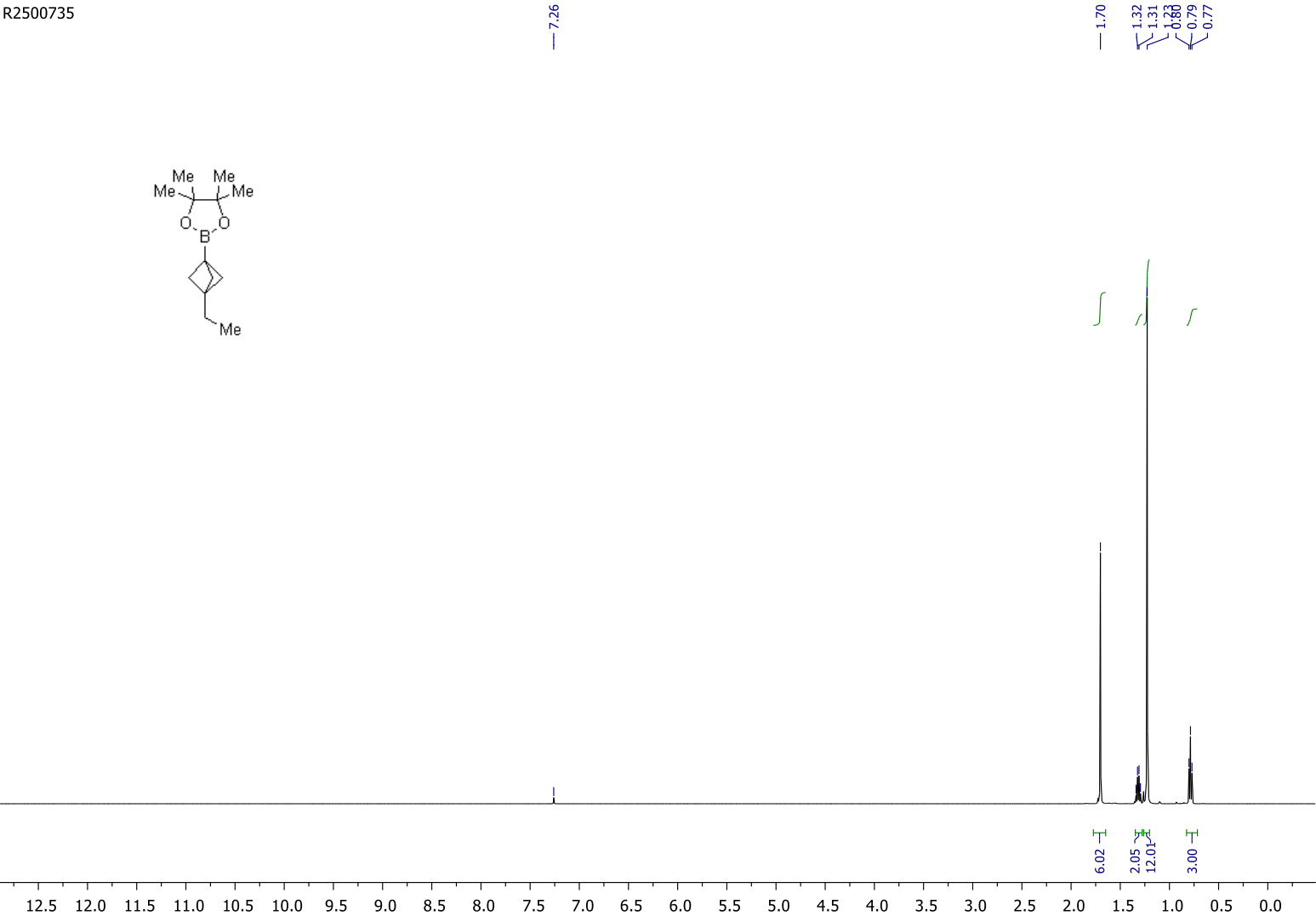
R1872066_C1:



Compound 2a

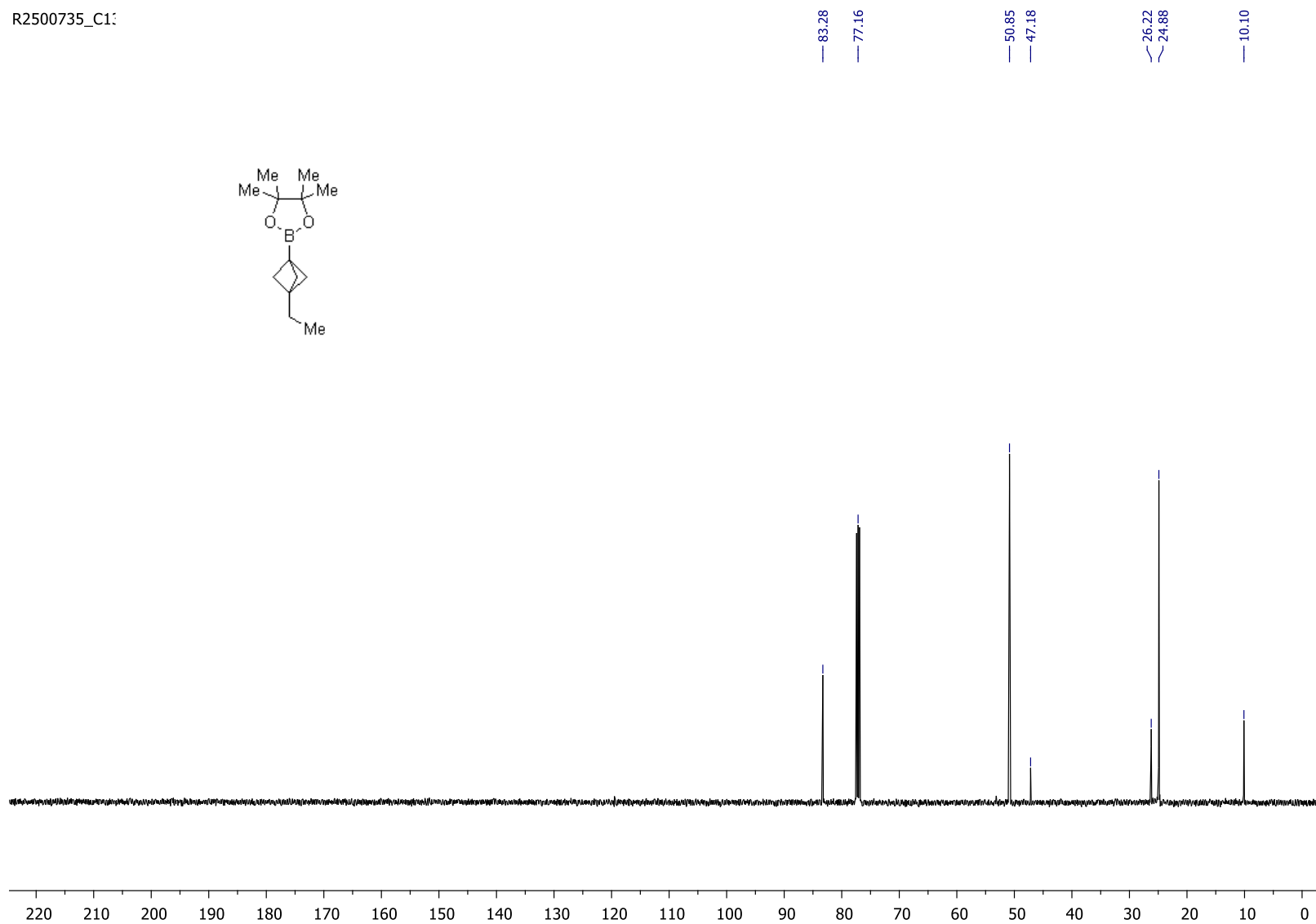
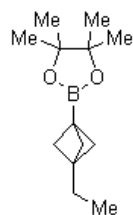
R2500735

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

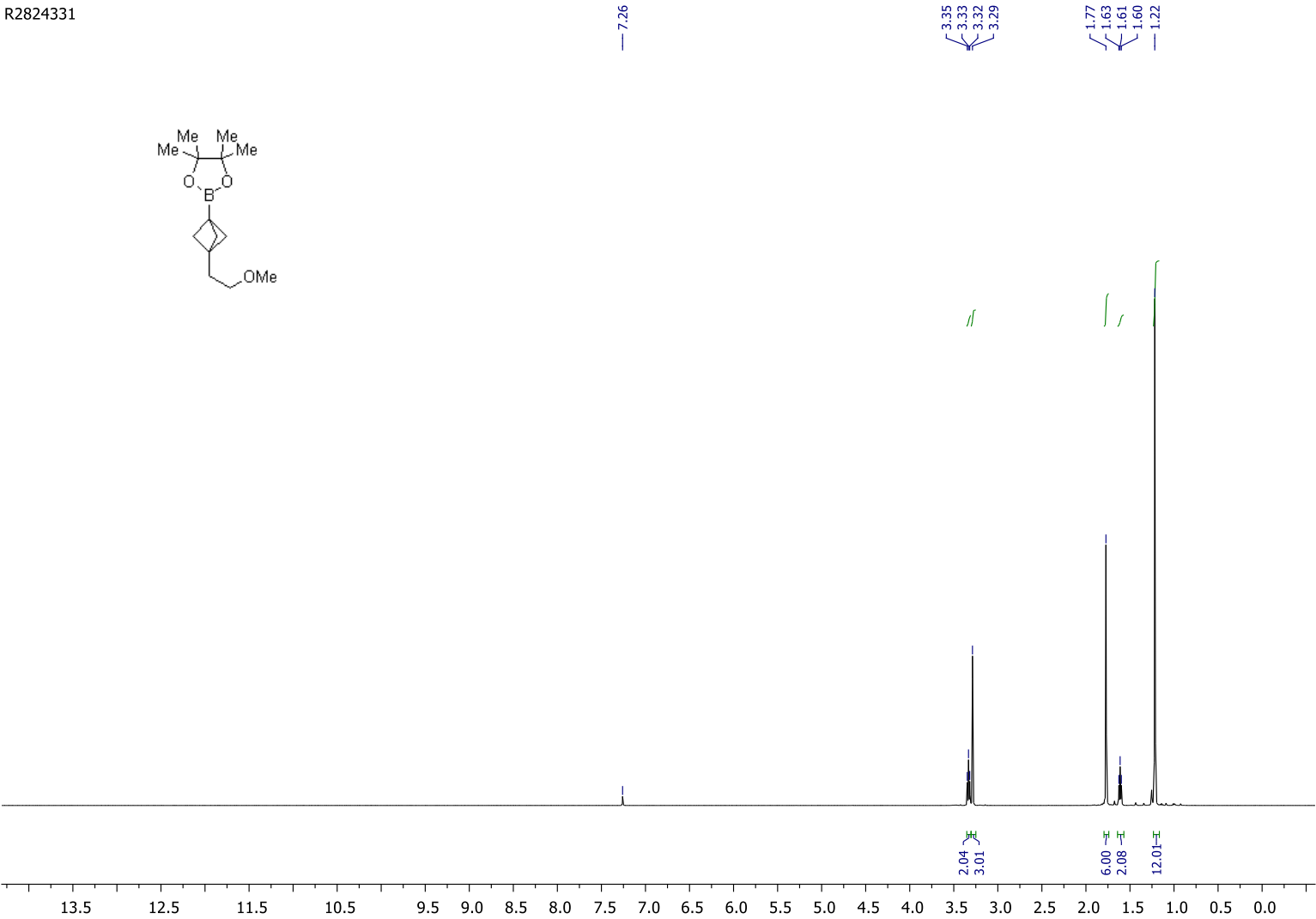
R2500735_C1:



Compound 7a

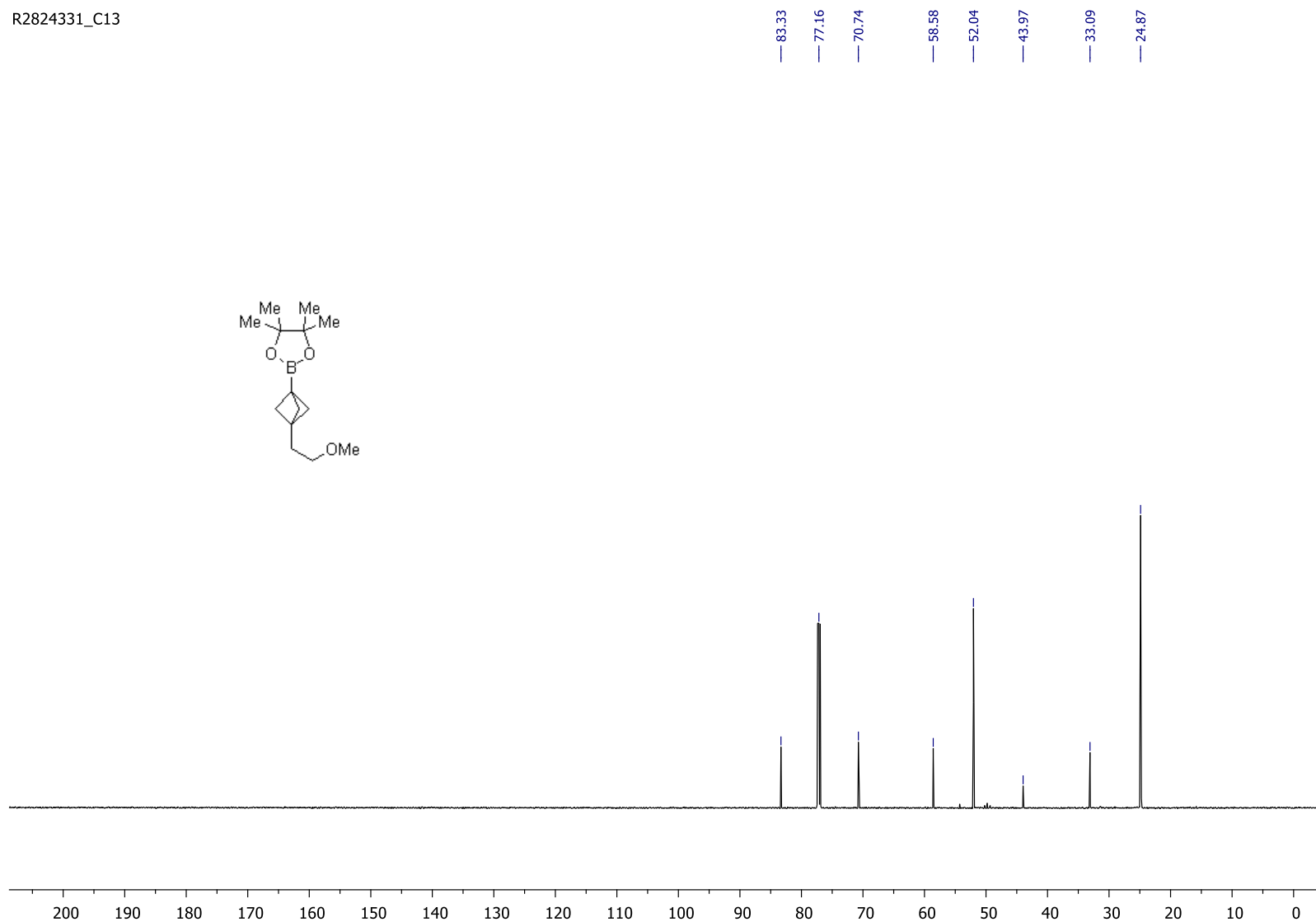
R2824331

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

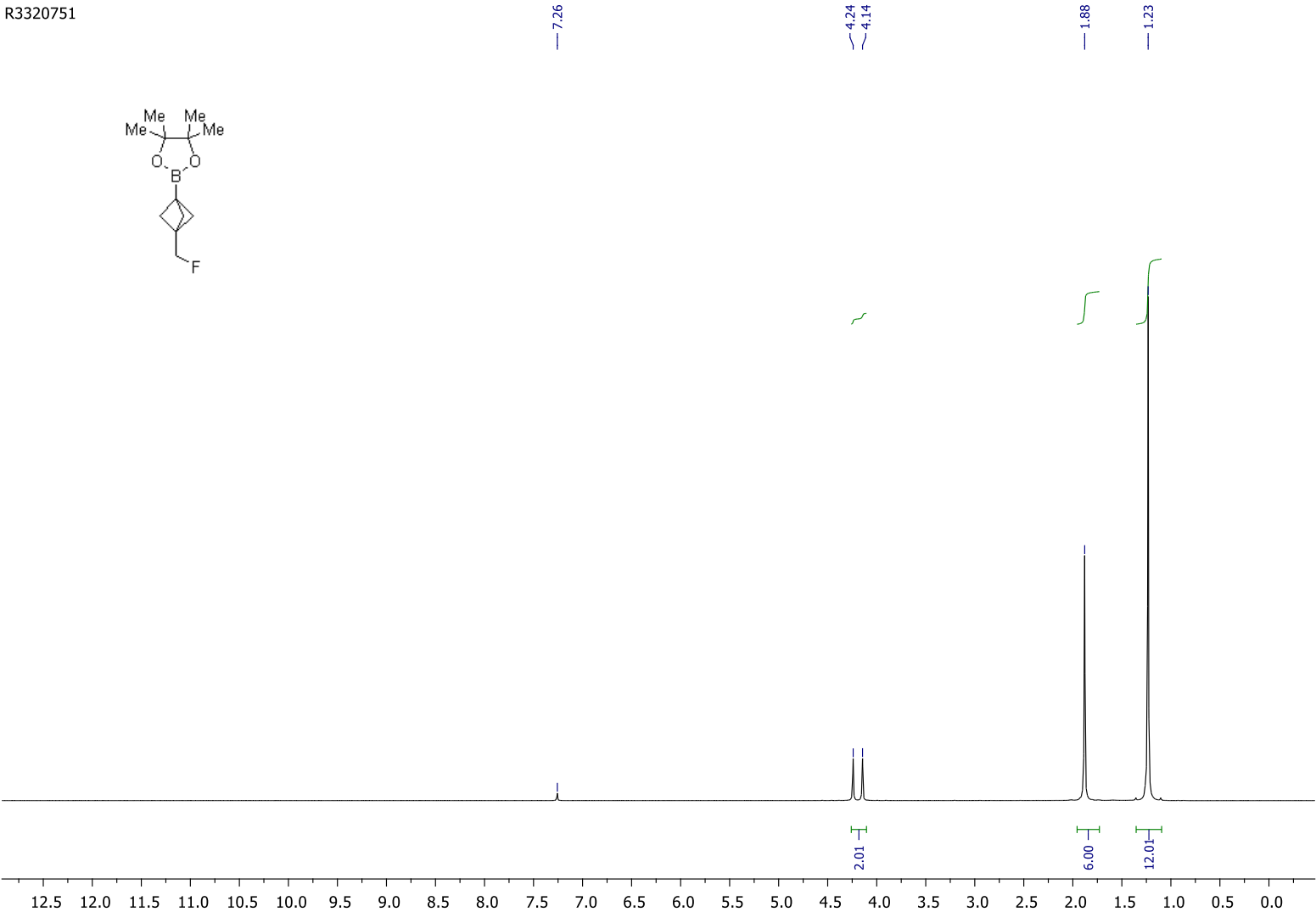
R2824331_C13



Compound 21a

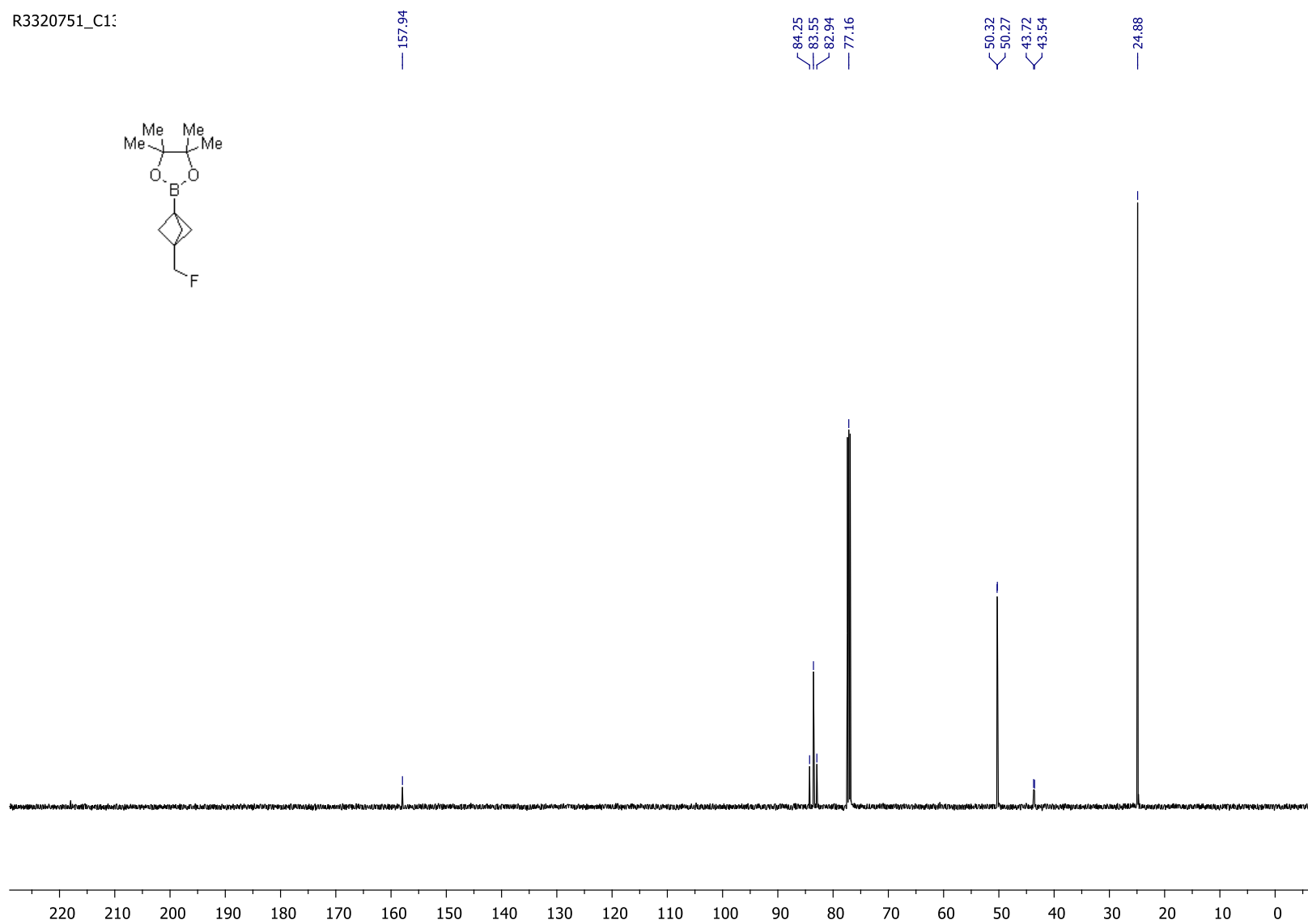
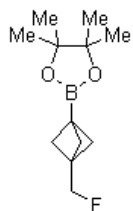
R3320751

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

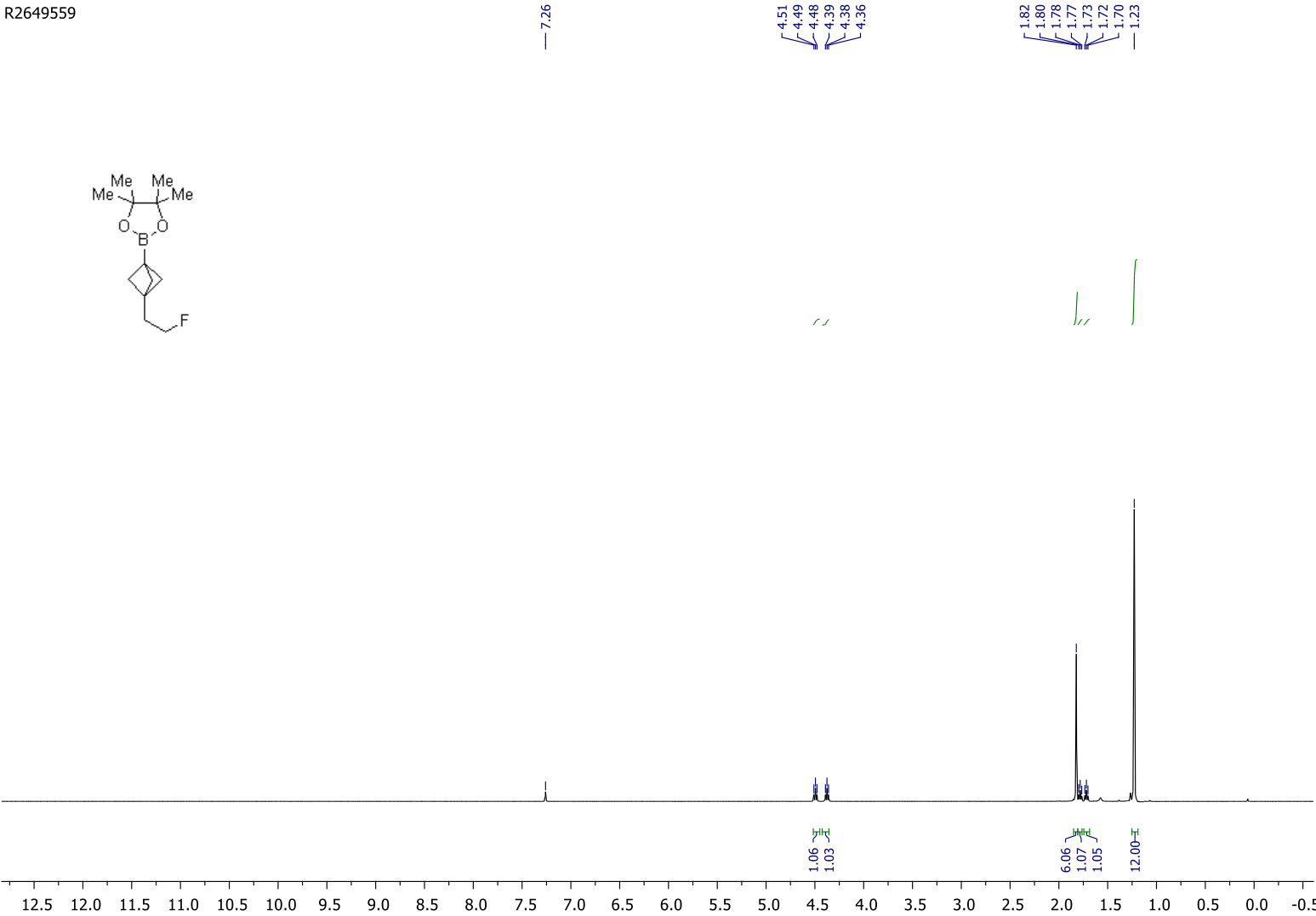
R3320751_C13



Compound 22a

R2649559

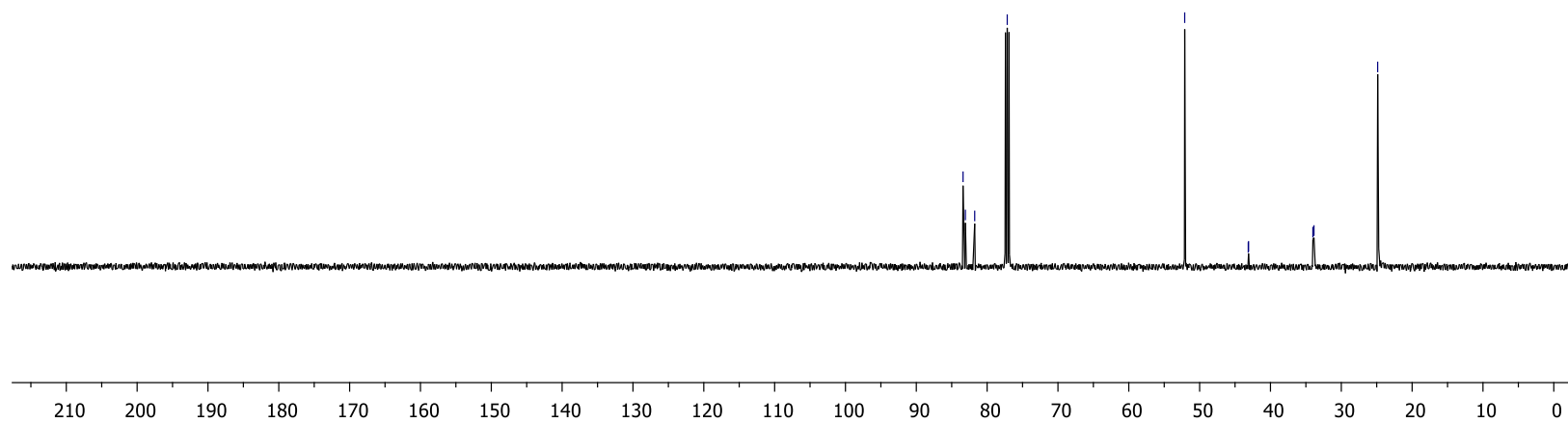
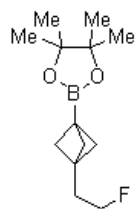
¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2661150_C13

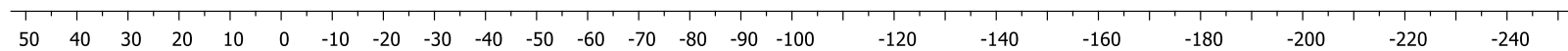
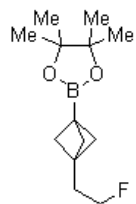
83.40
83.07
81.76
77.16
— 52.11
43.14
43.09
34.01
33.86
— 24.86



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2649559_F19{H}
 $^{19}\text{F}\{^1\text{H}\}$

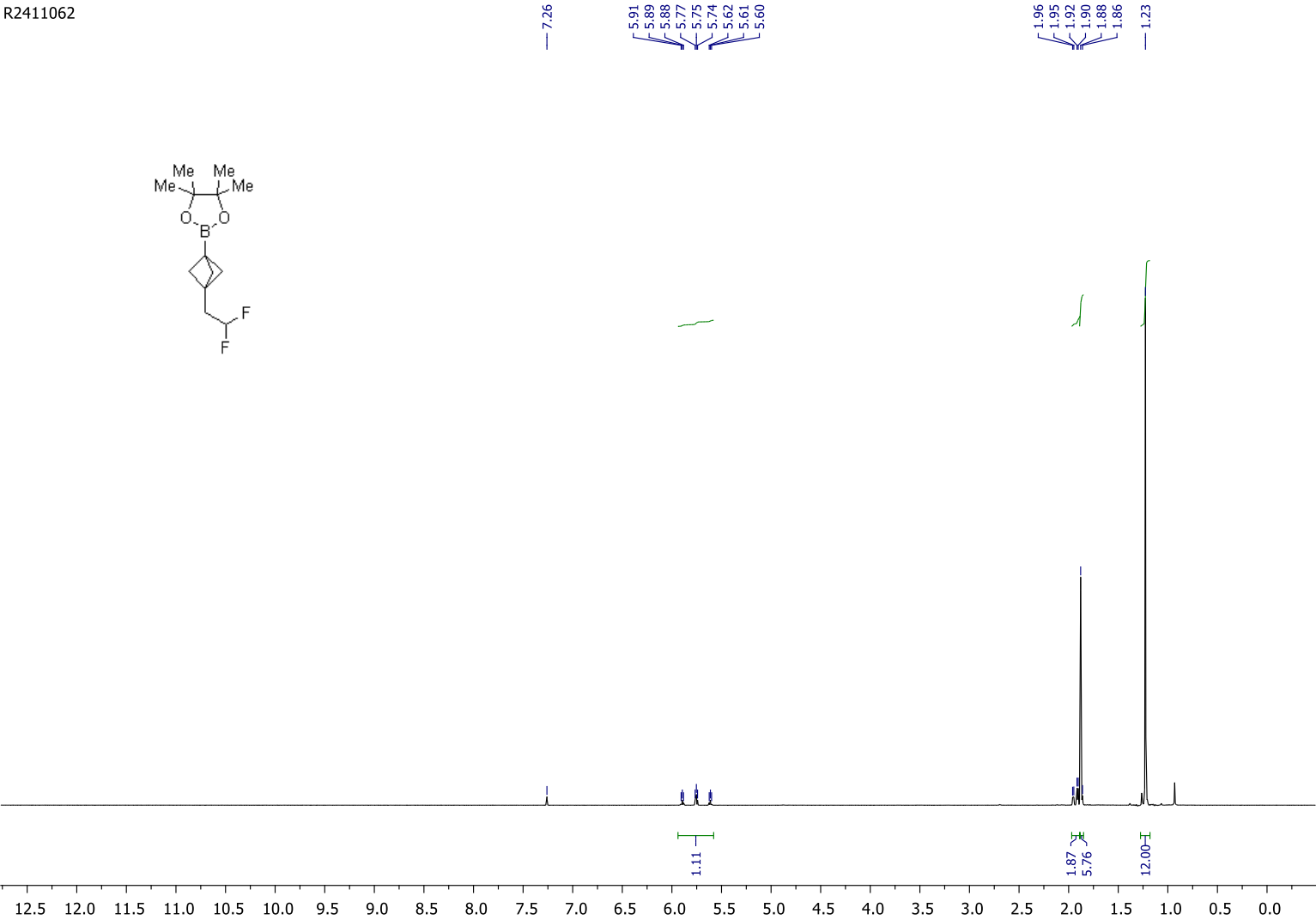
— -220.51



Compound 24a

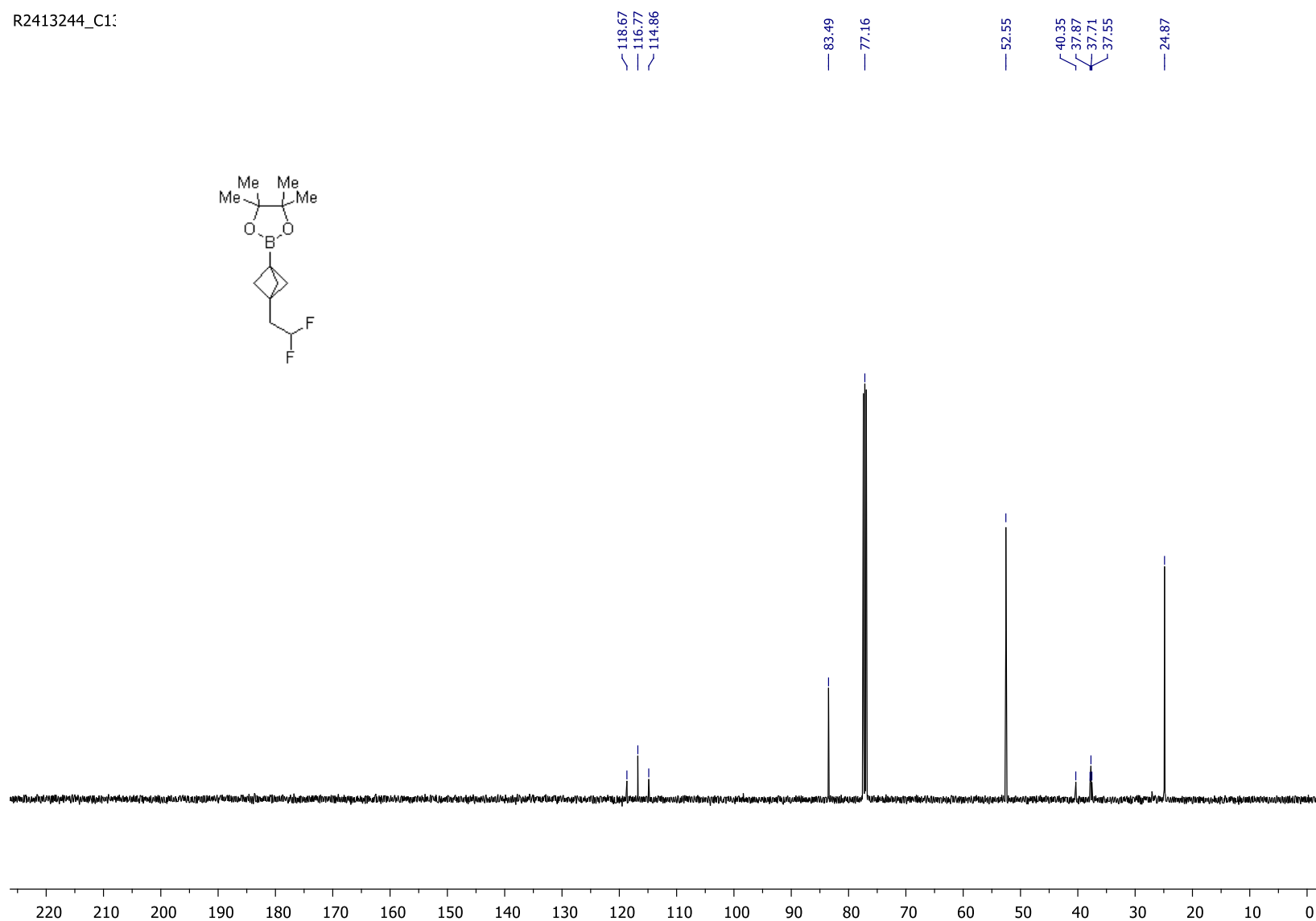
R2411062

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

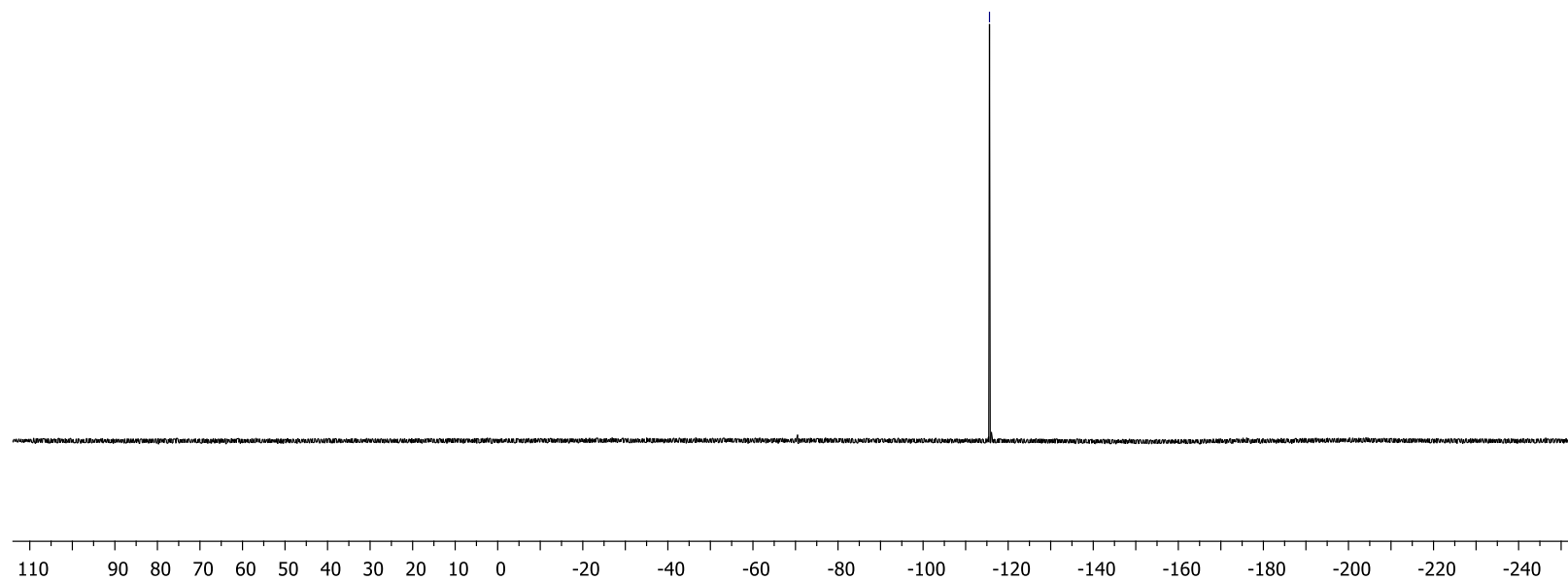
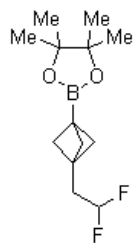
R2413244_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2411062_F19{H}
19F-{1H}

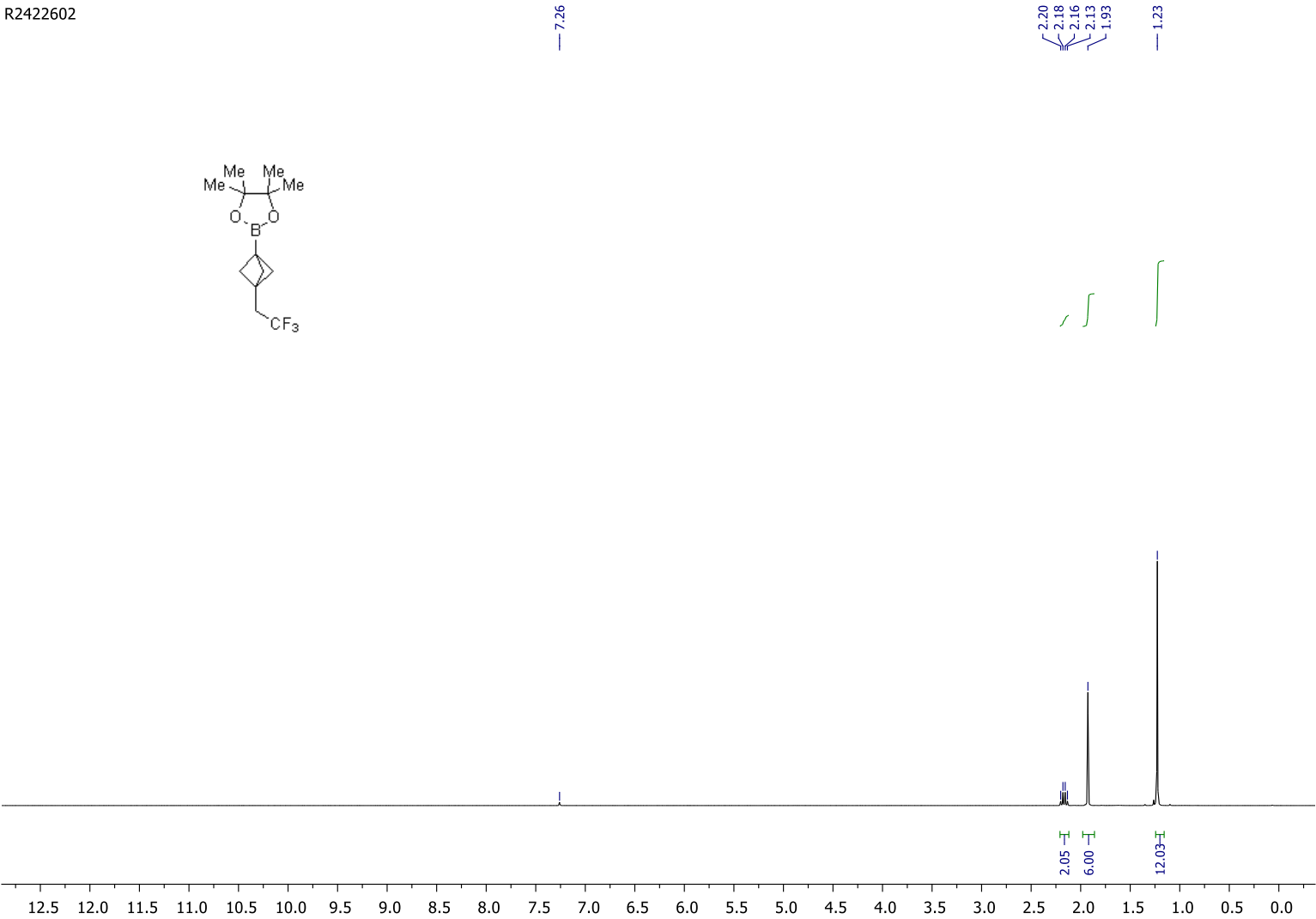
— -115.61



Compound 25a

R2422602

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2422602_C13

— 129.83
— 127.62
— 125.42
— 123.21

— 83.55

— 77.16

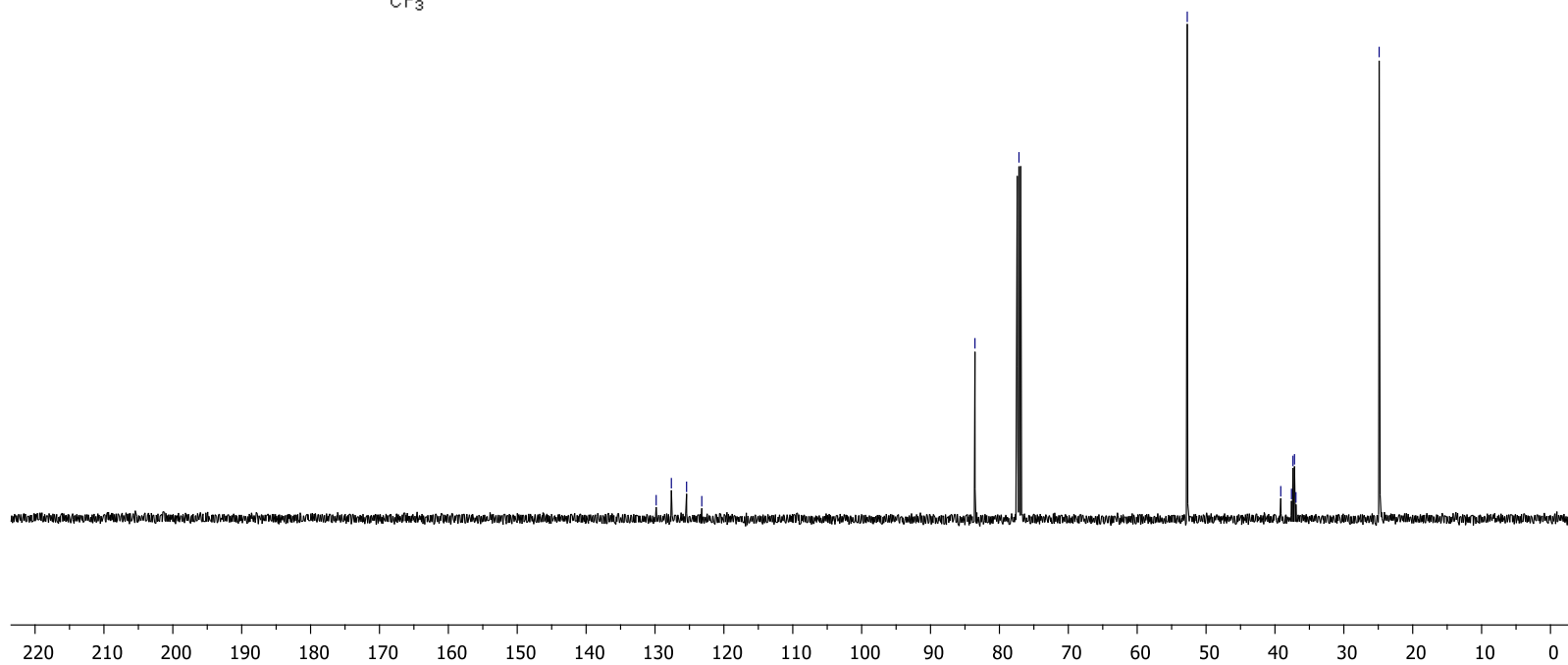
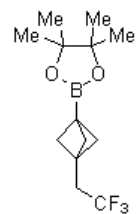
— 52.73

- 39.16

37.00
37.38

✓ 37.17
✓ 36.95

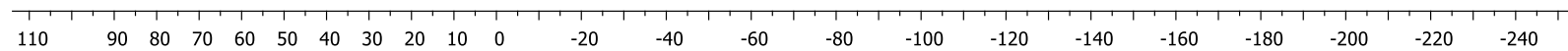
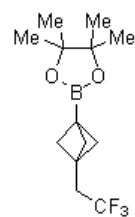
— 24.87



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2419346_F19{H}

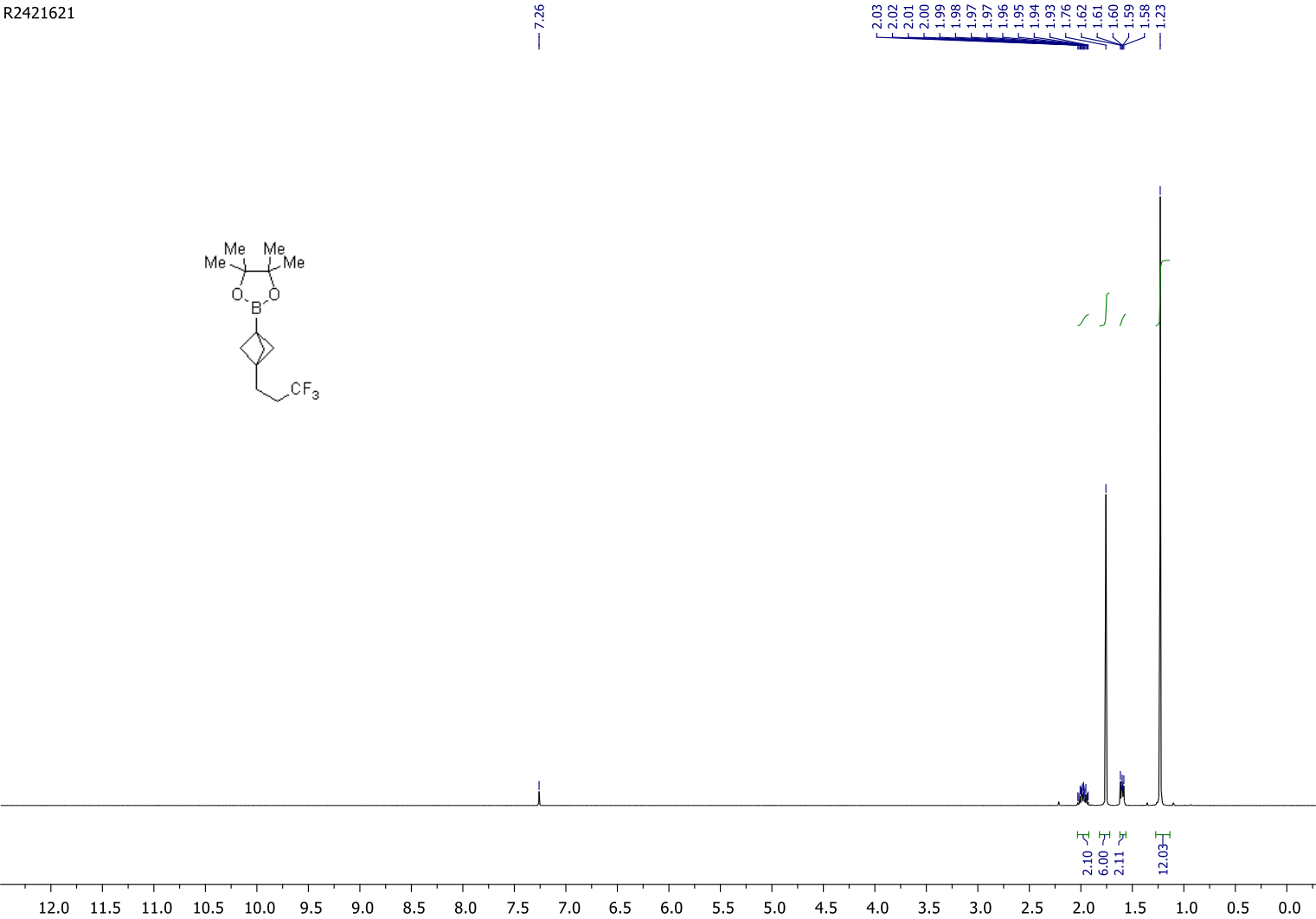
— -64.59



Compound 26a

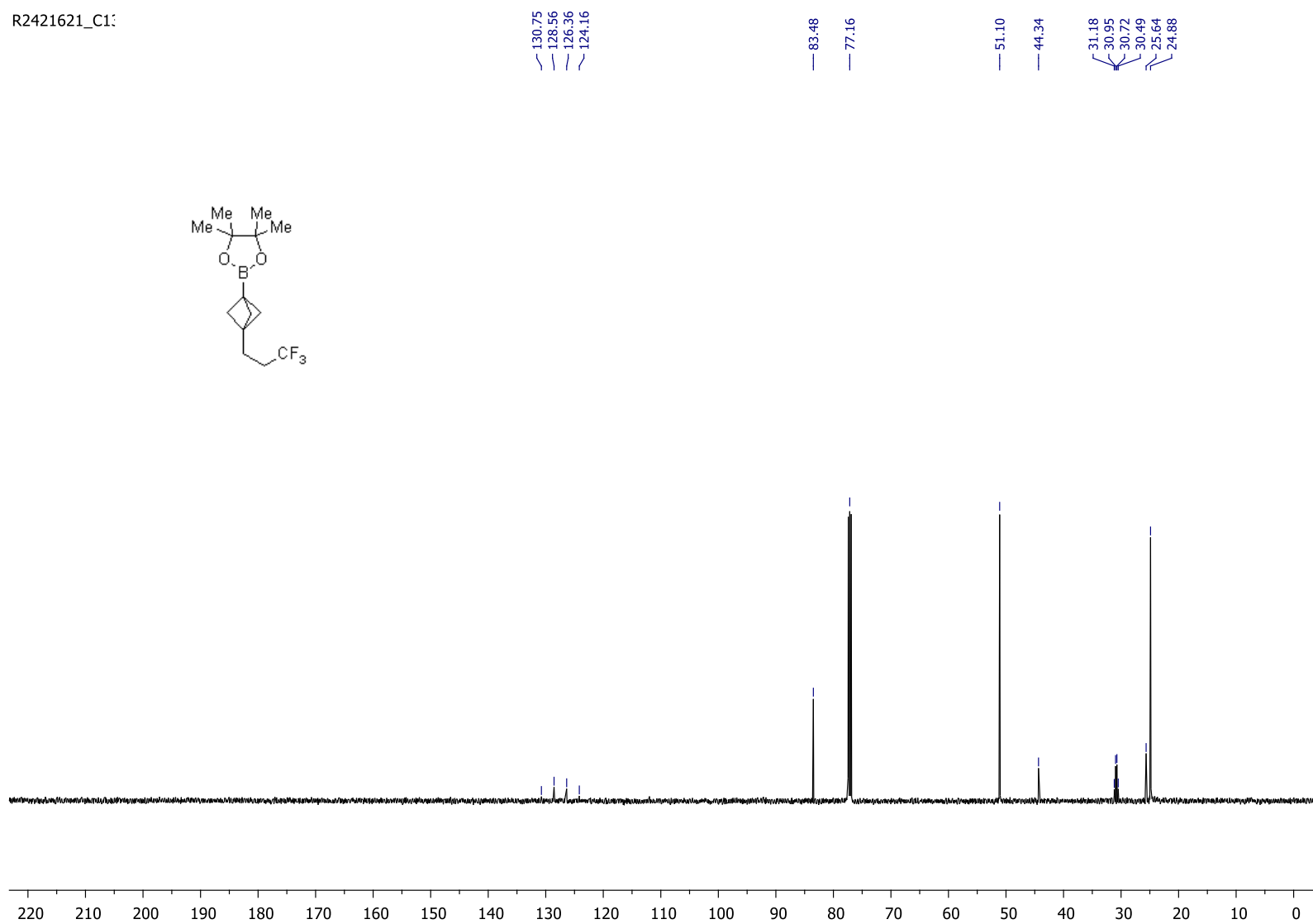
R2421621

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

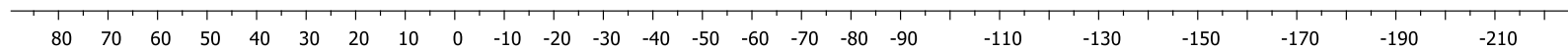
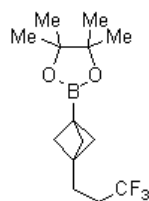
R2421621_C1:



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

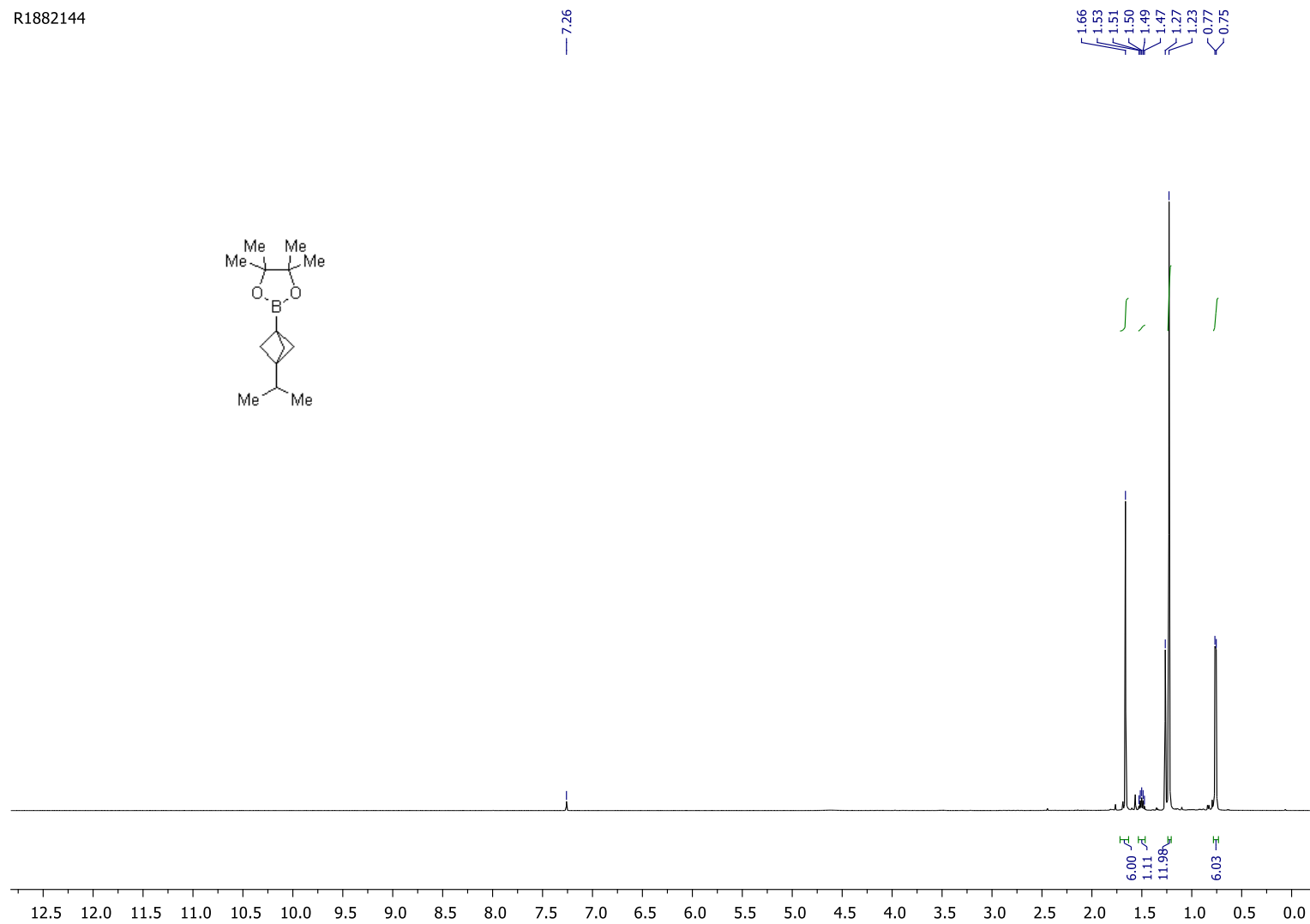
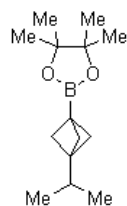
R2411038_F19{H}
19F-{1H}

— -67.02



Compound 48a

R1882144

¹H NMR (500 MHz, CDCl₃)

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

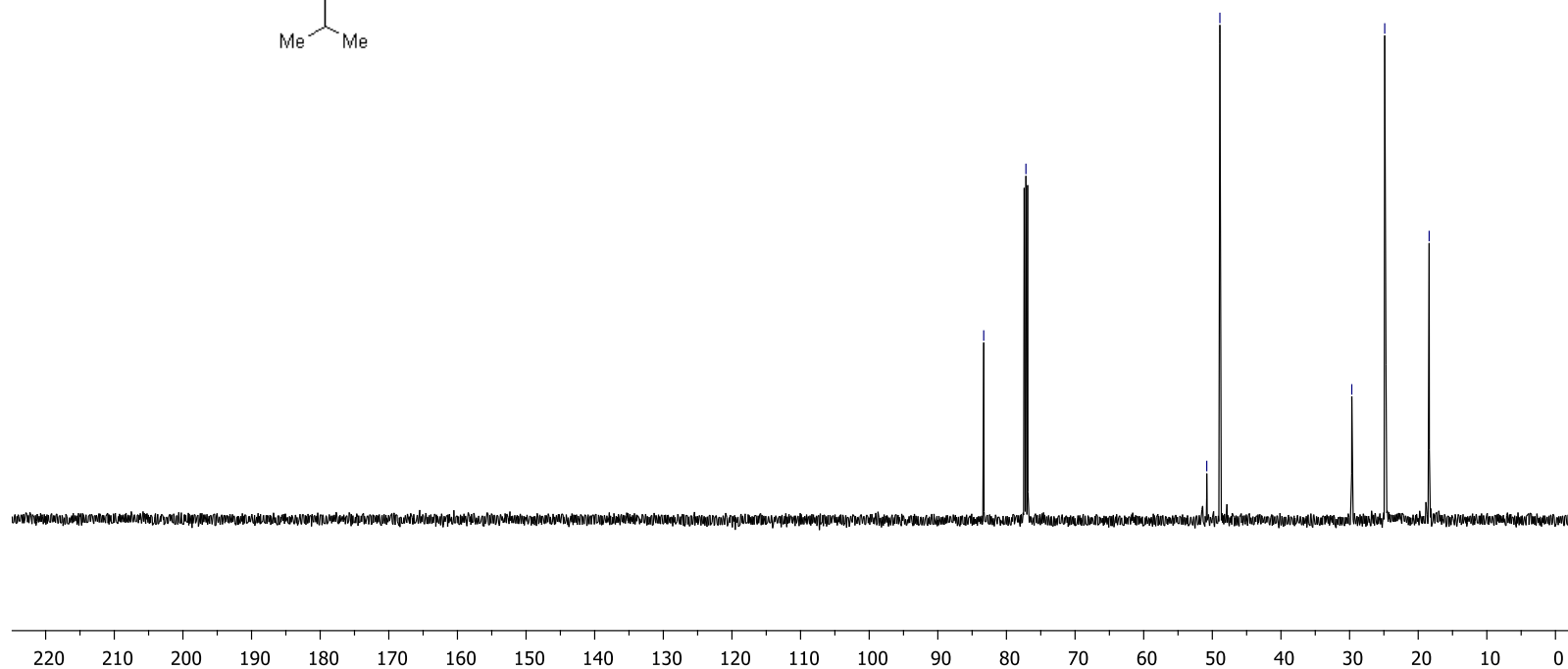
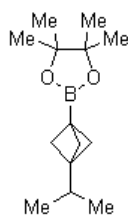
R1882144_C13

— 83.31

— 77.16

— 50.81
— 48.90

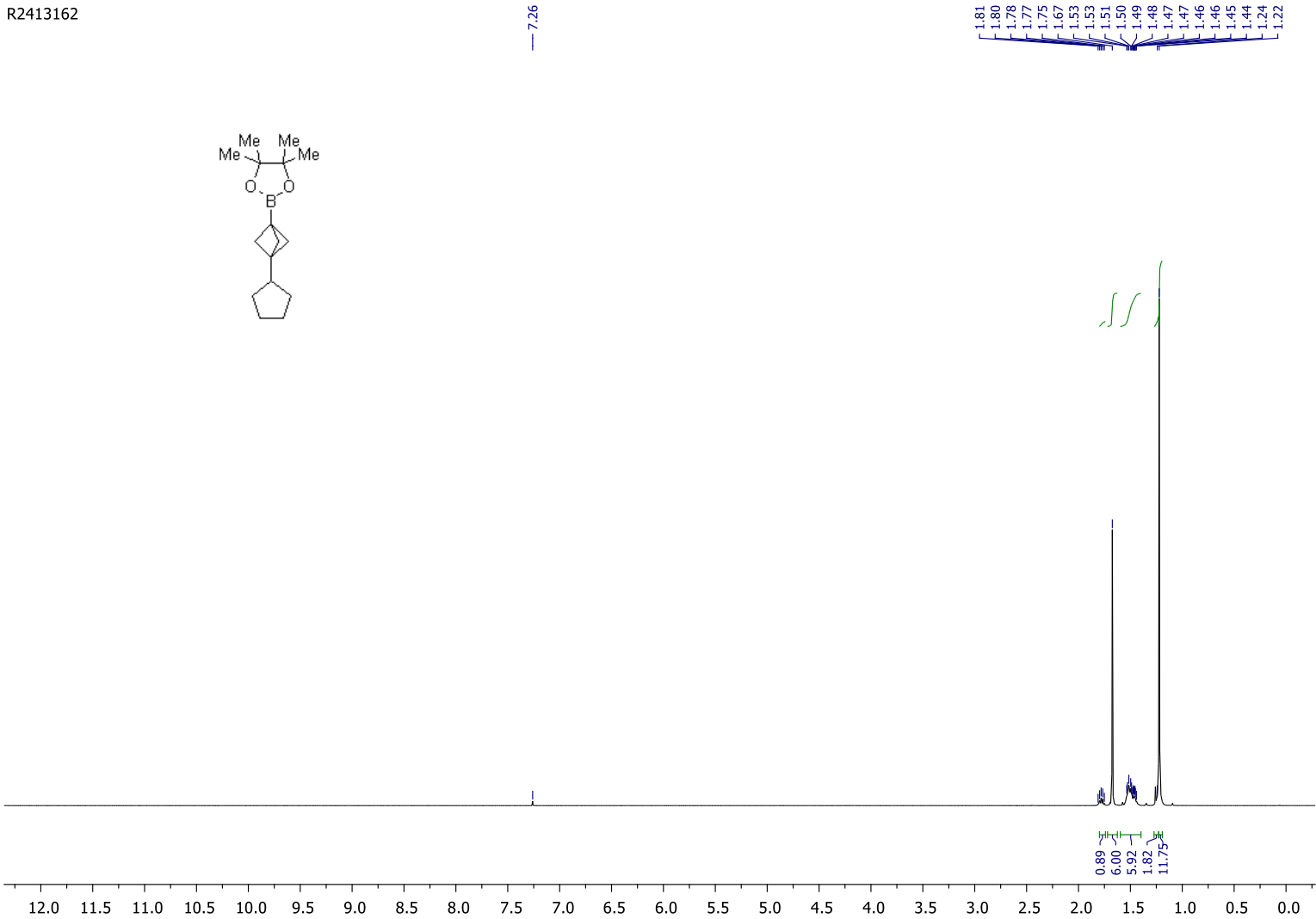
— 29.68
— 24.88
— 18.40



Compound 52a

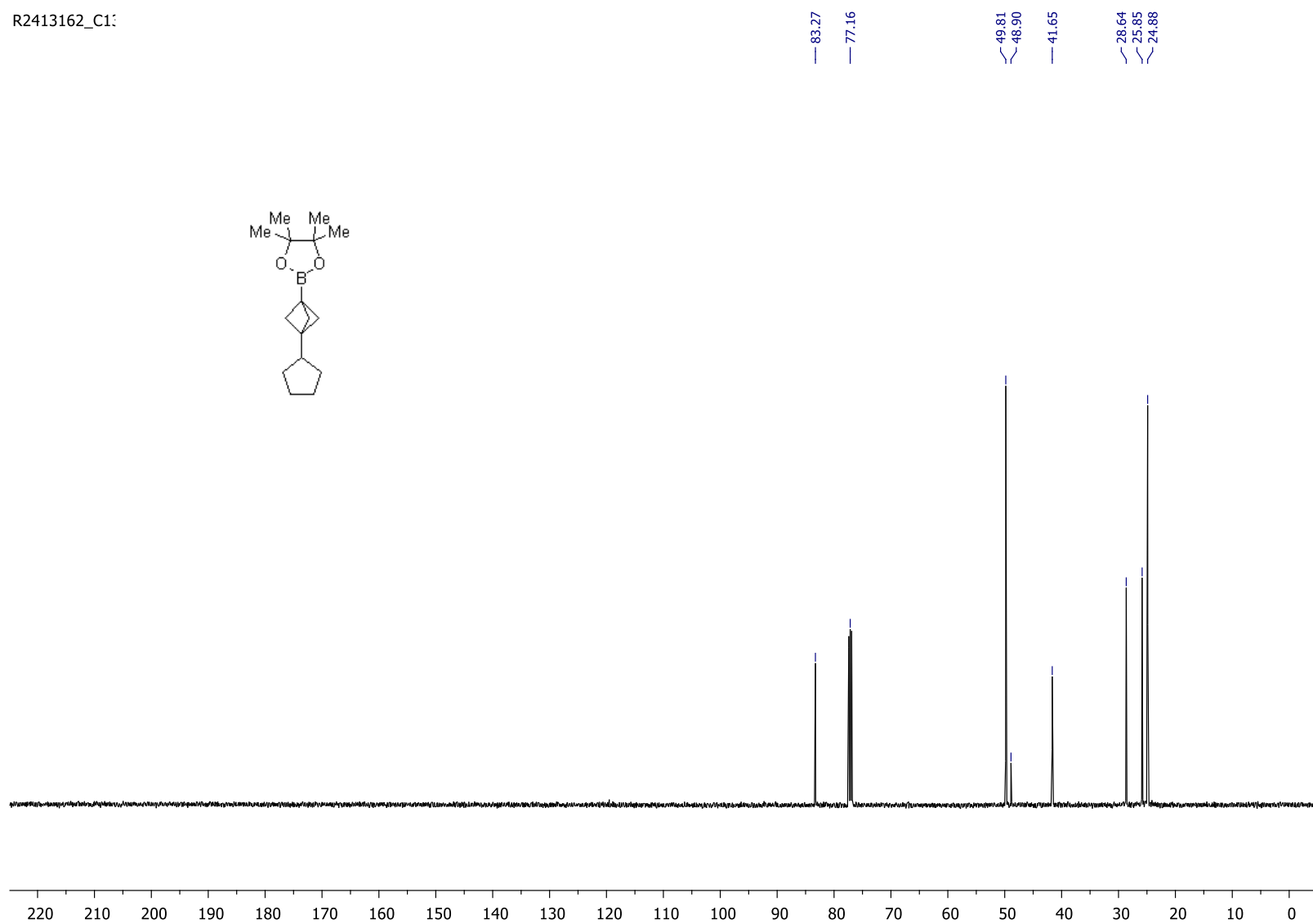
R2413162

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

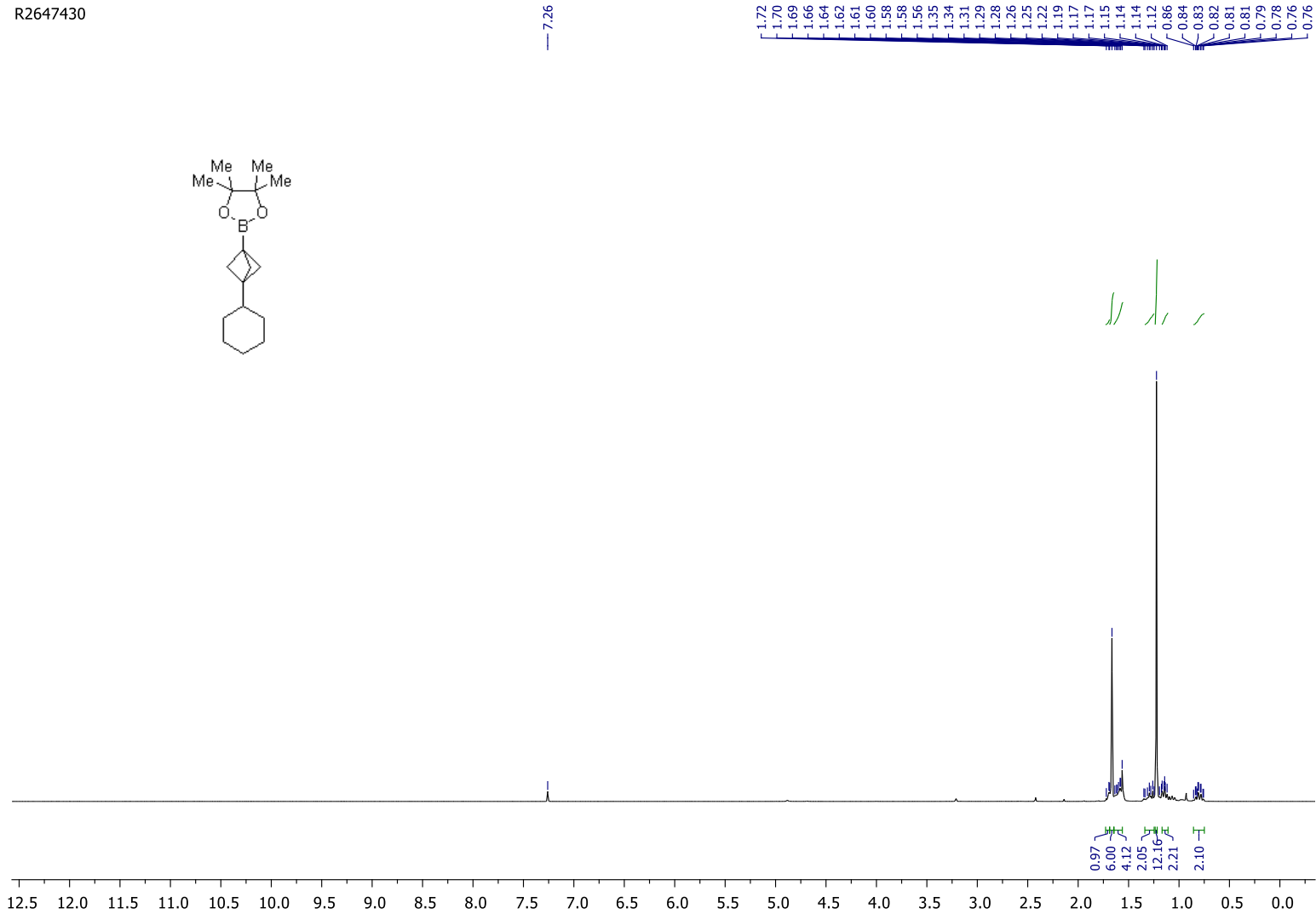
R2413162_C1:



Compound 53a

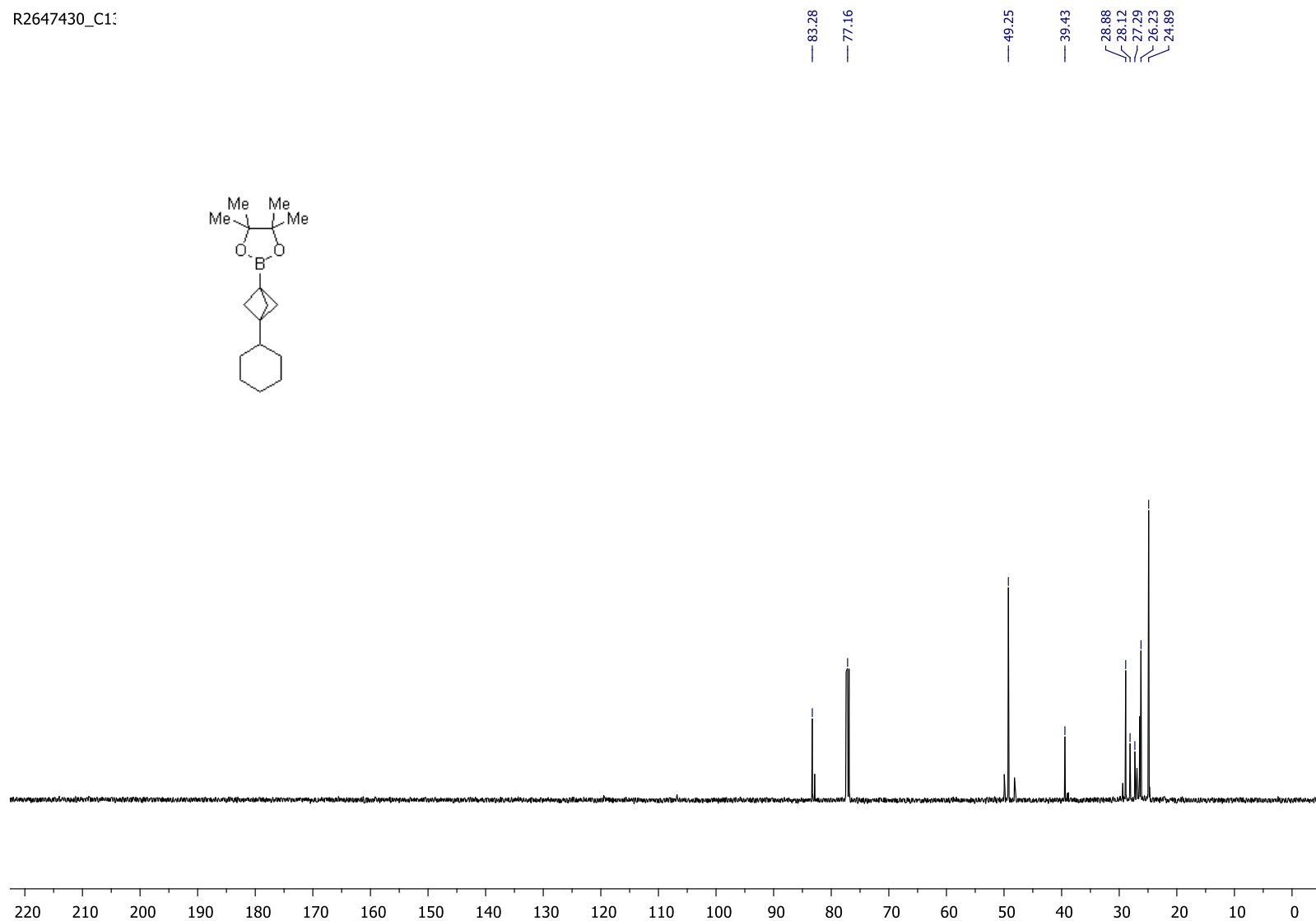
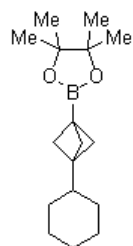
R2647430

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

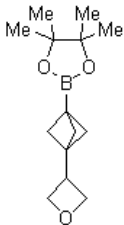
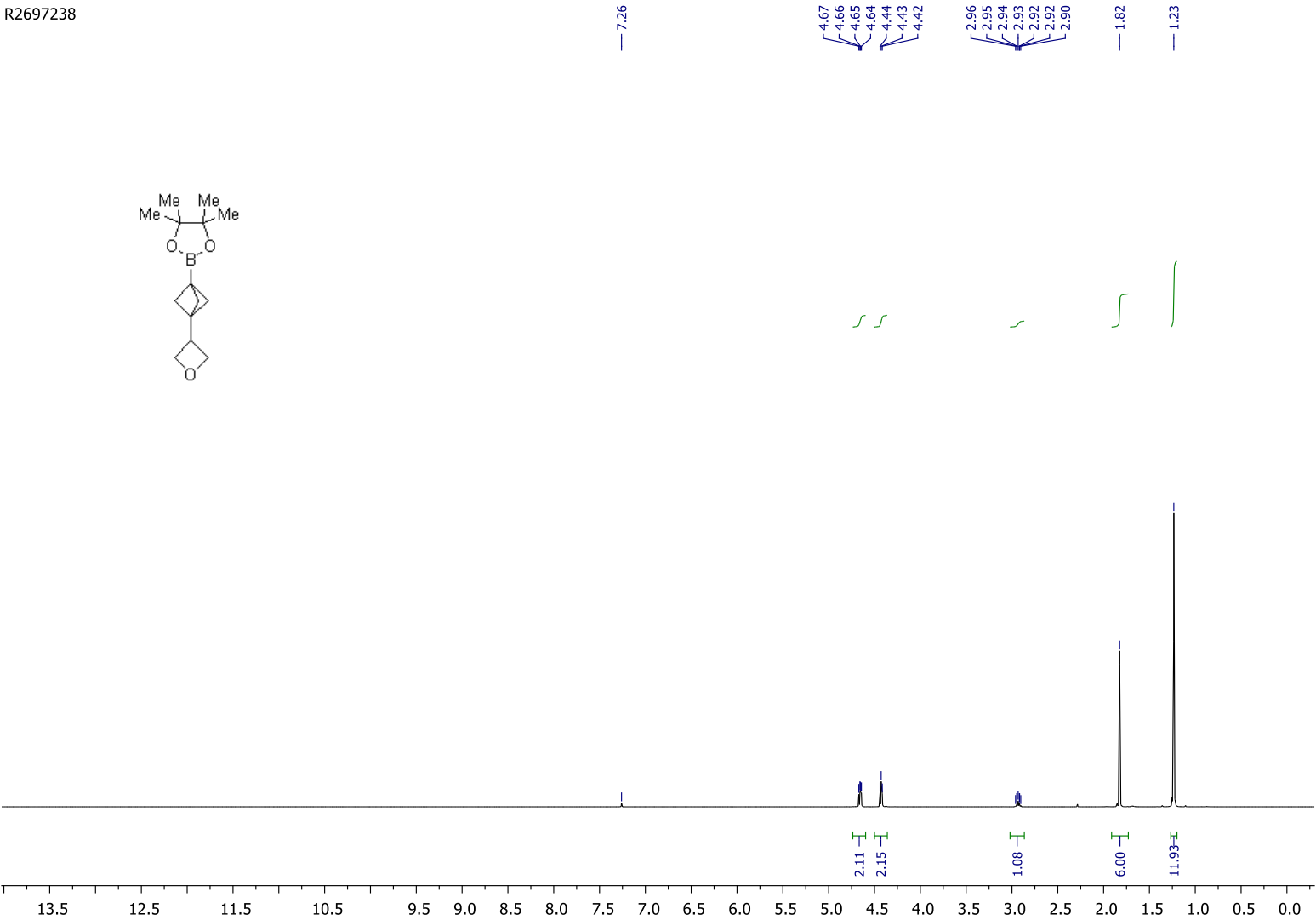
R2647430_C1:



Compound 55a

R2697238

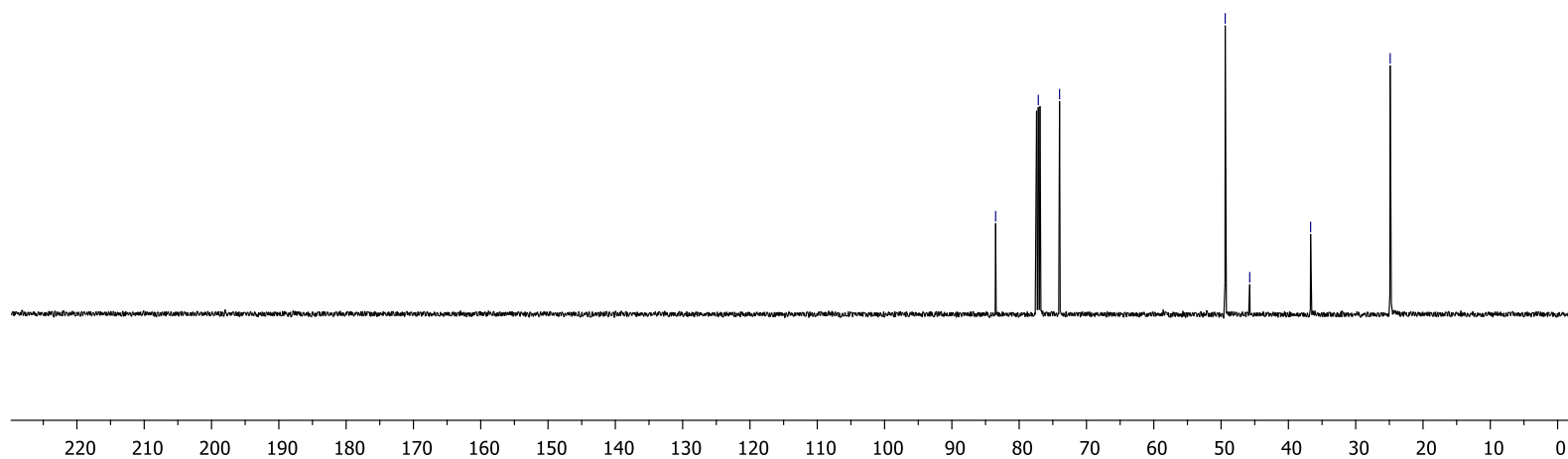
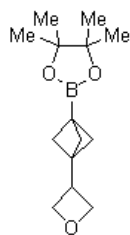
¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2697238_C1:

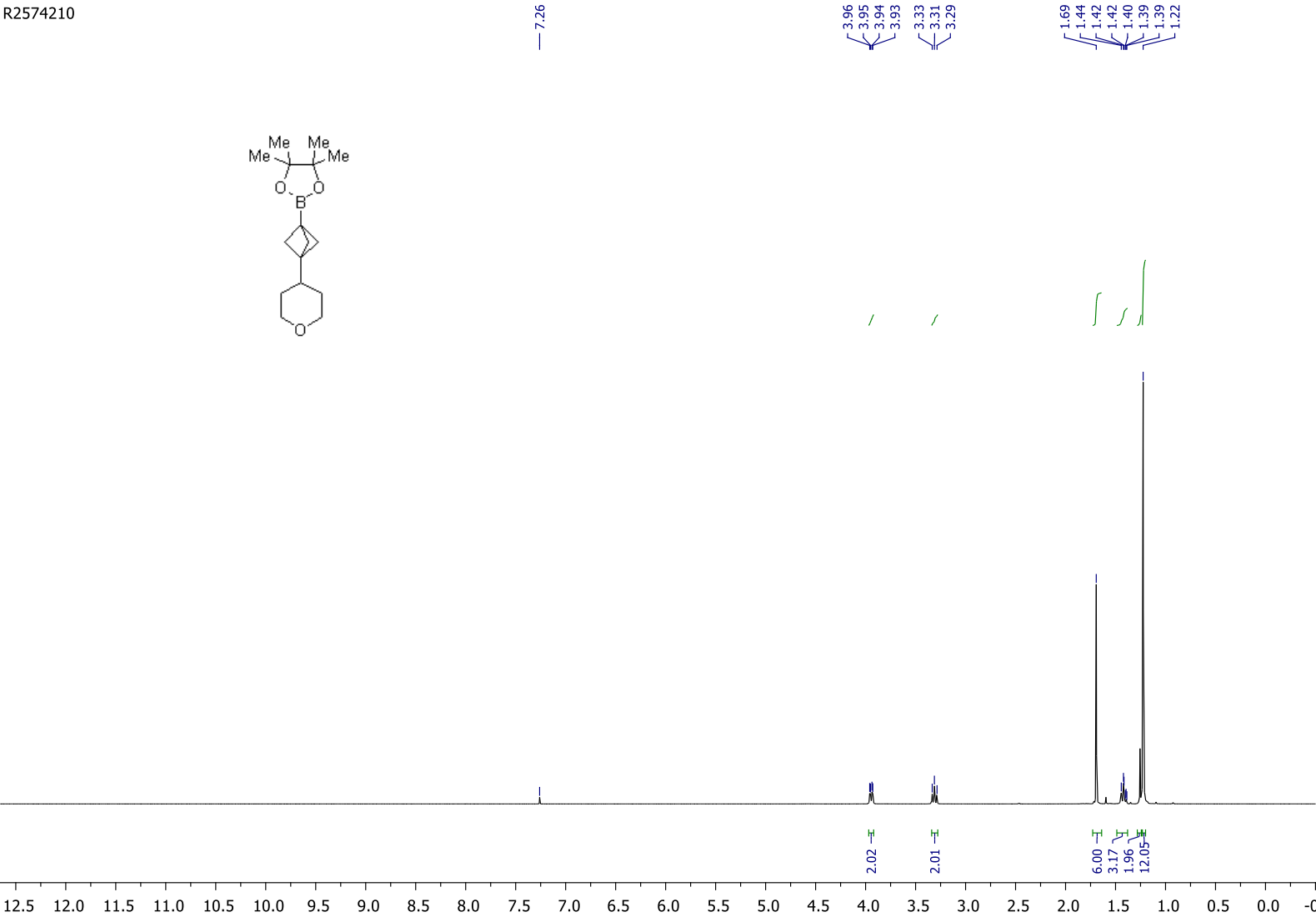
83.50
77.16
74.00
49.39
45.75
36.70
24.87



Compound 57a

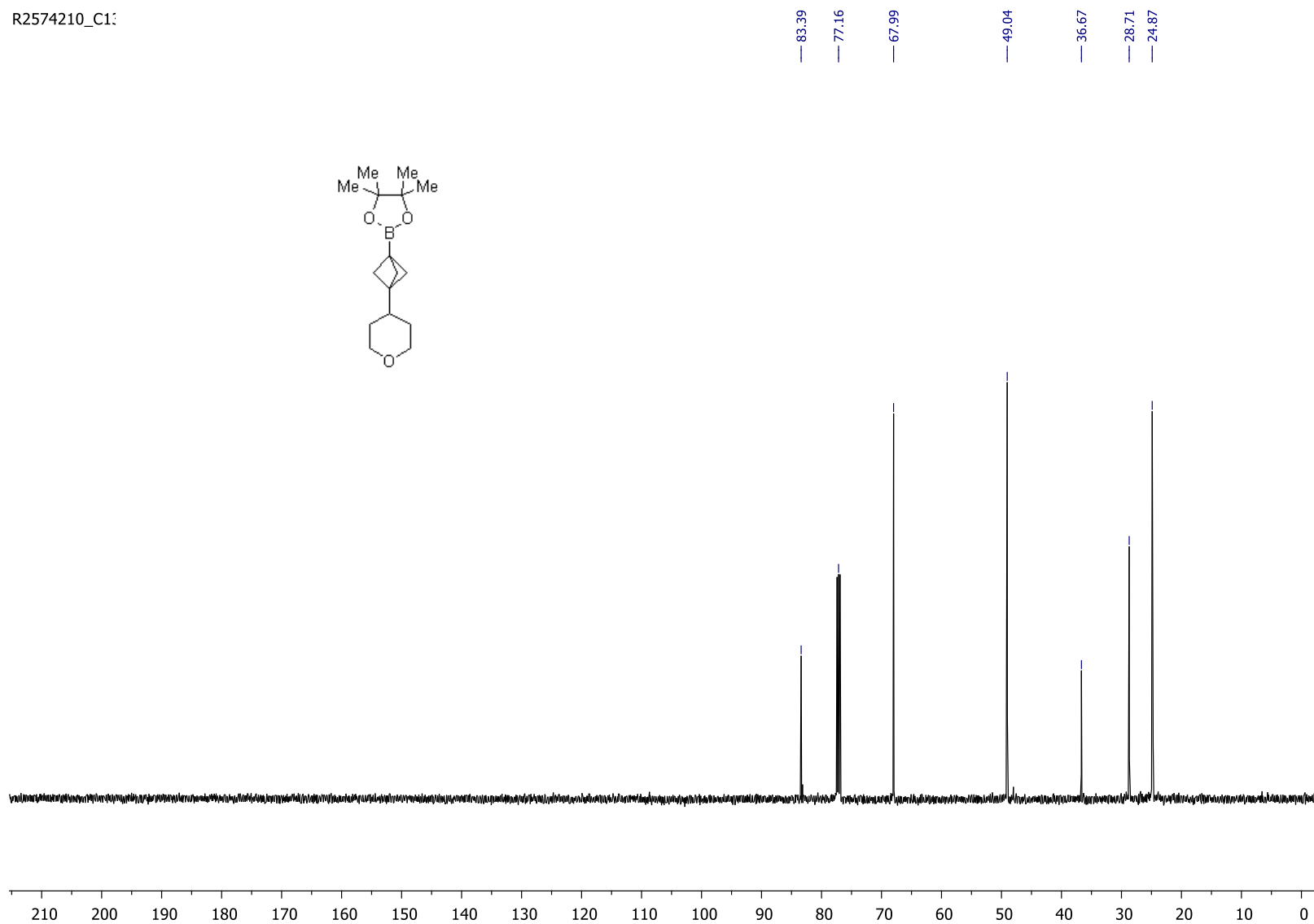
R2574210

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

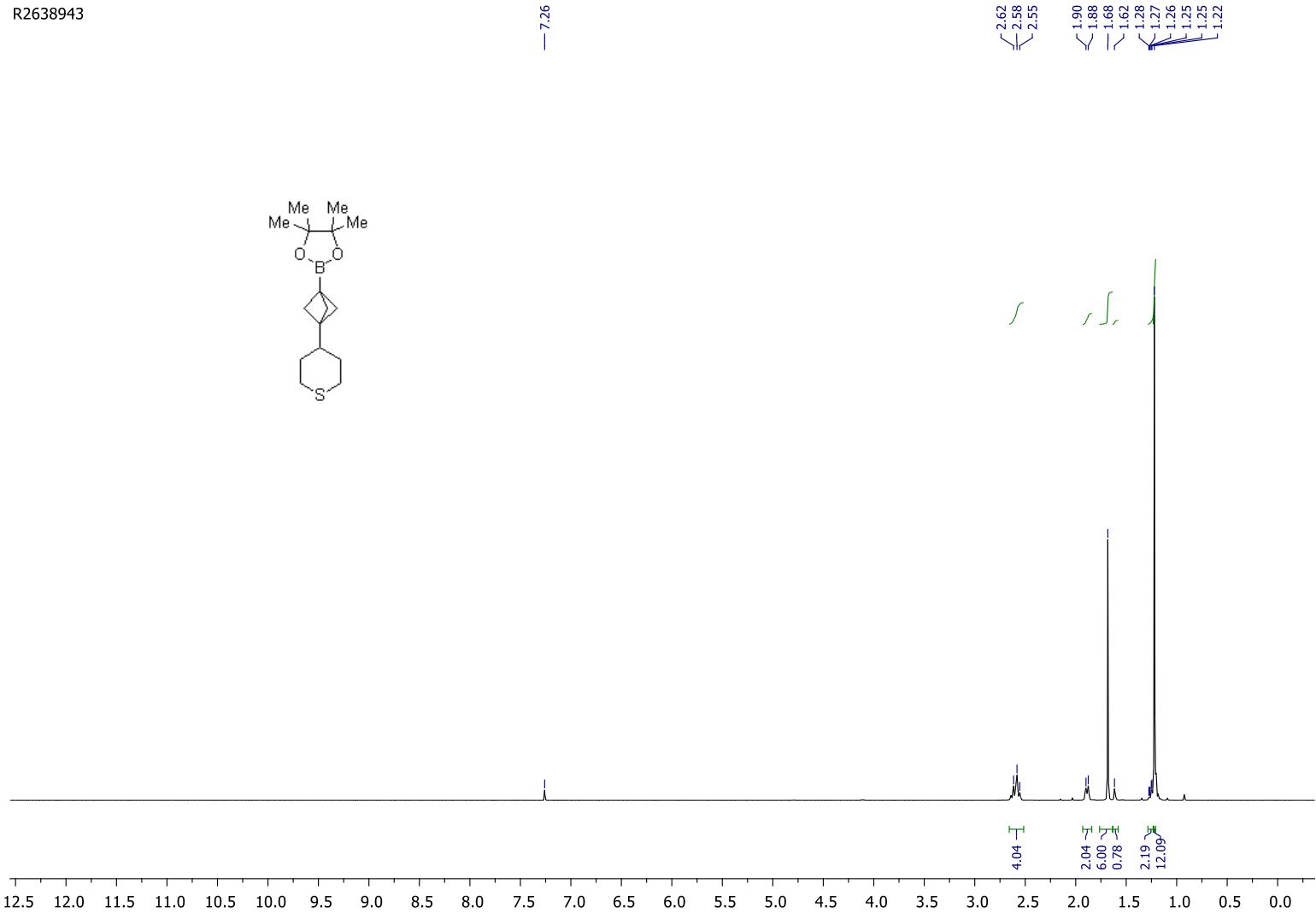
R2574210_C13



Compound 59a

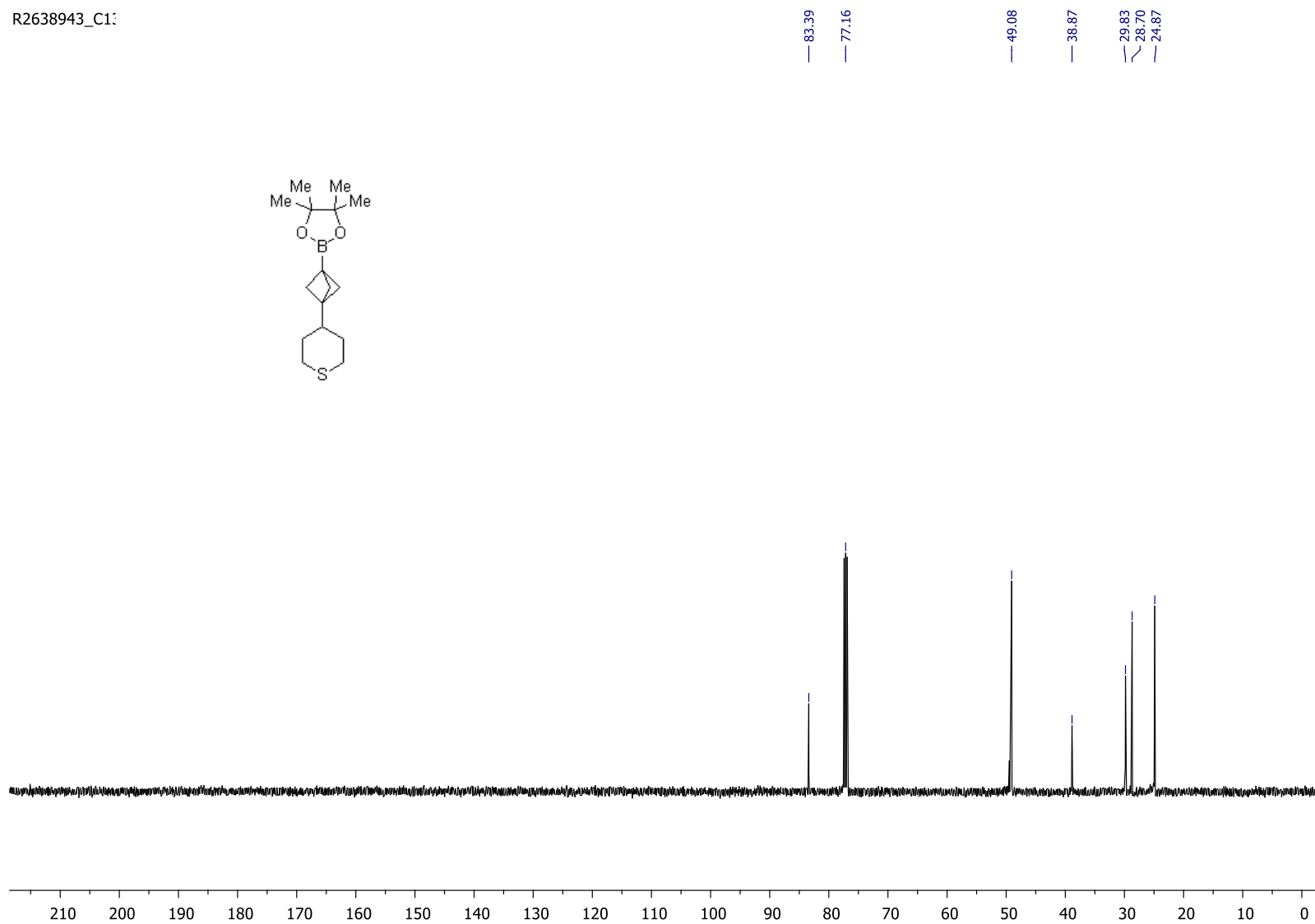
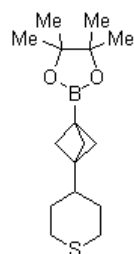
R2638943

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

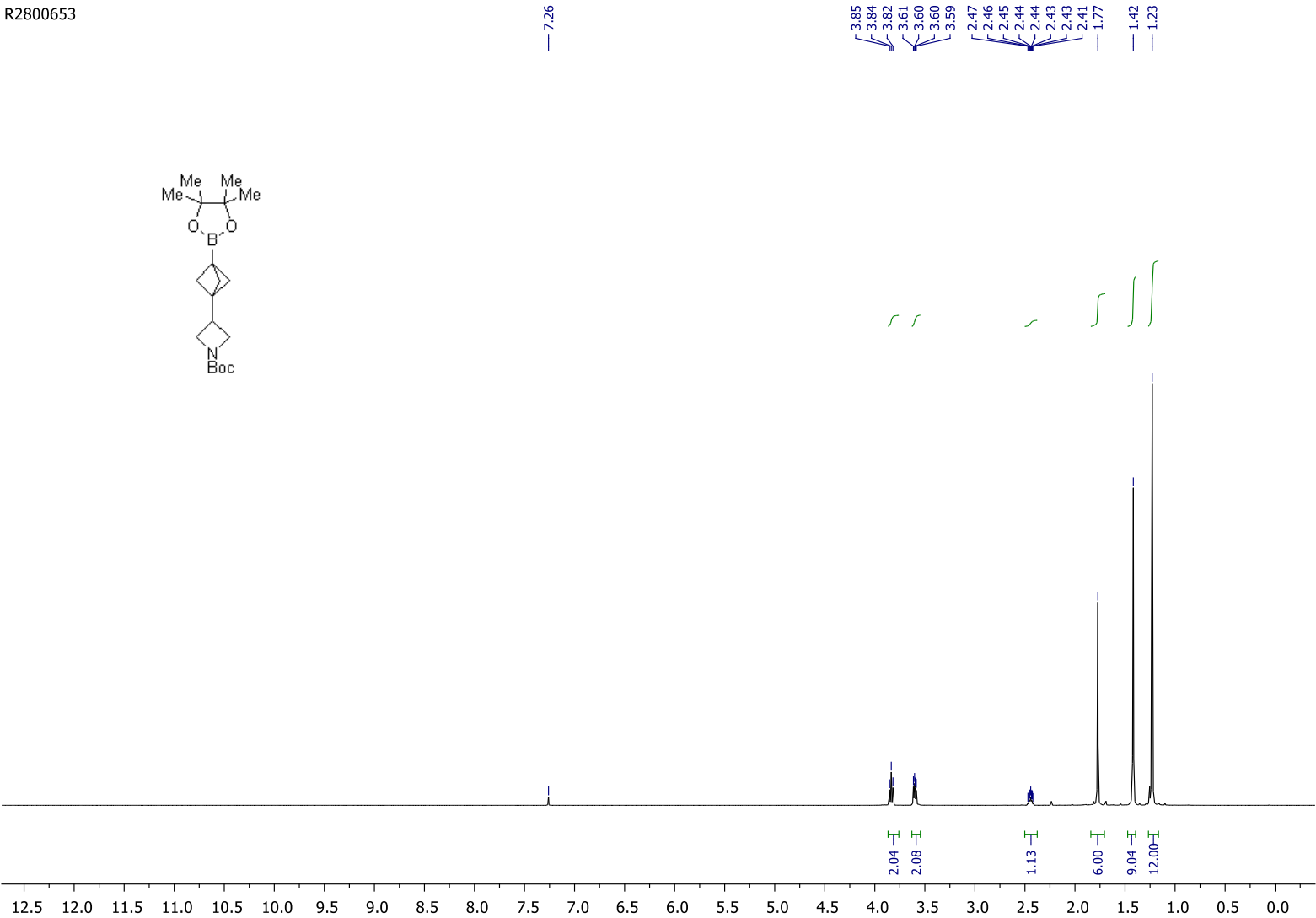
R2638943_C1:



Compound 60a

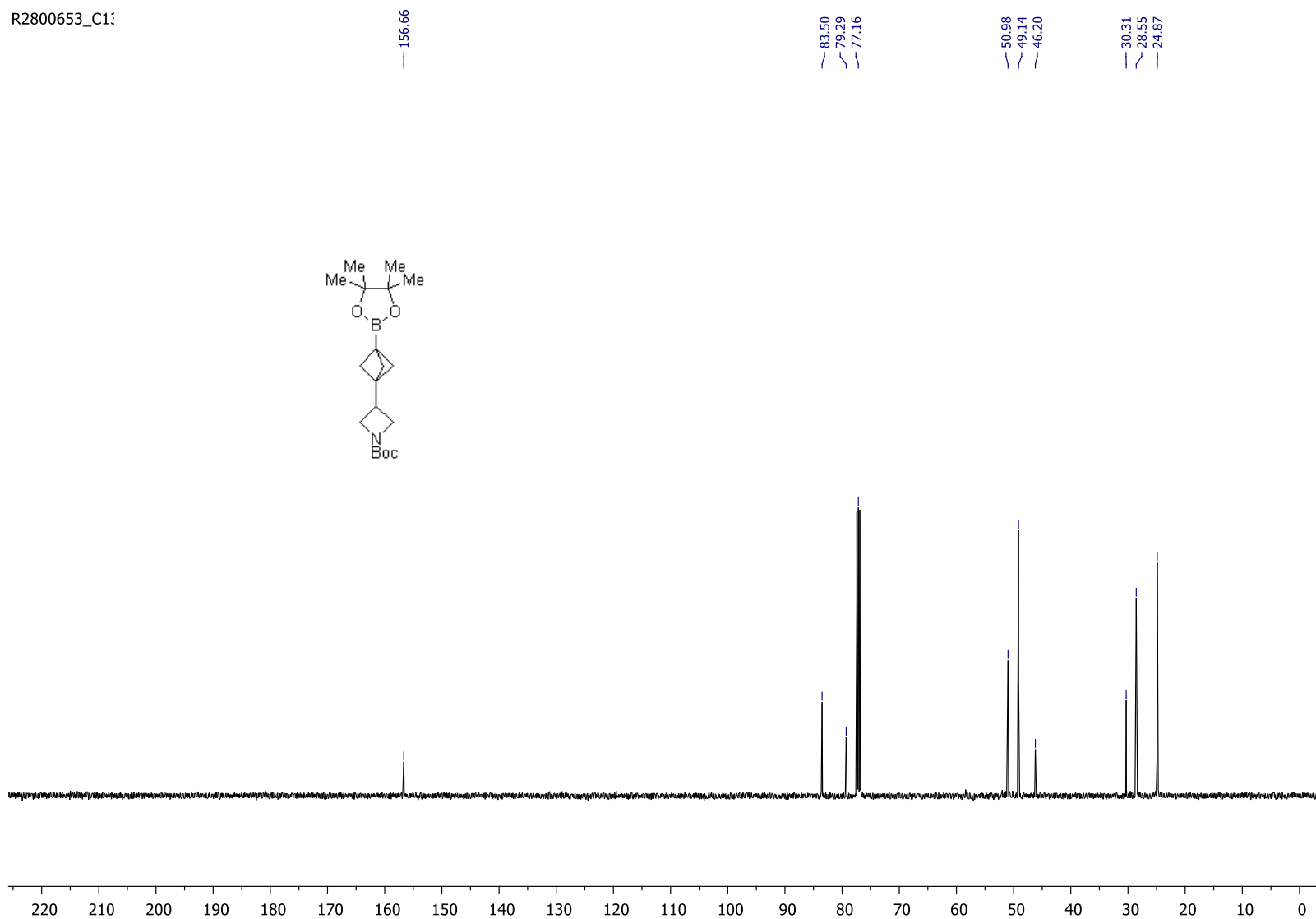
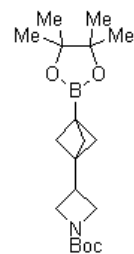
R2800653

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

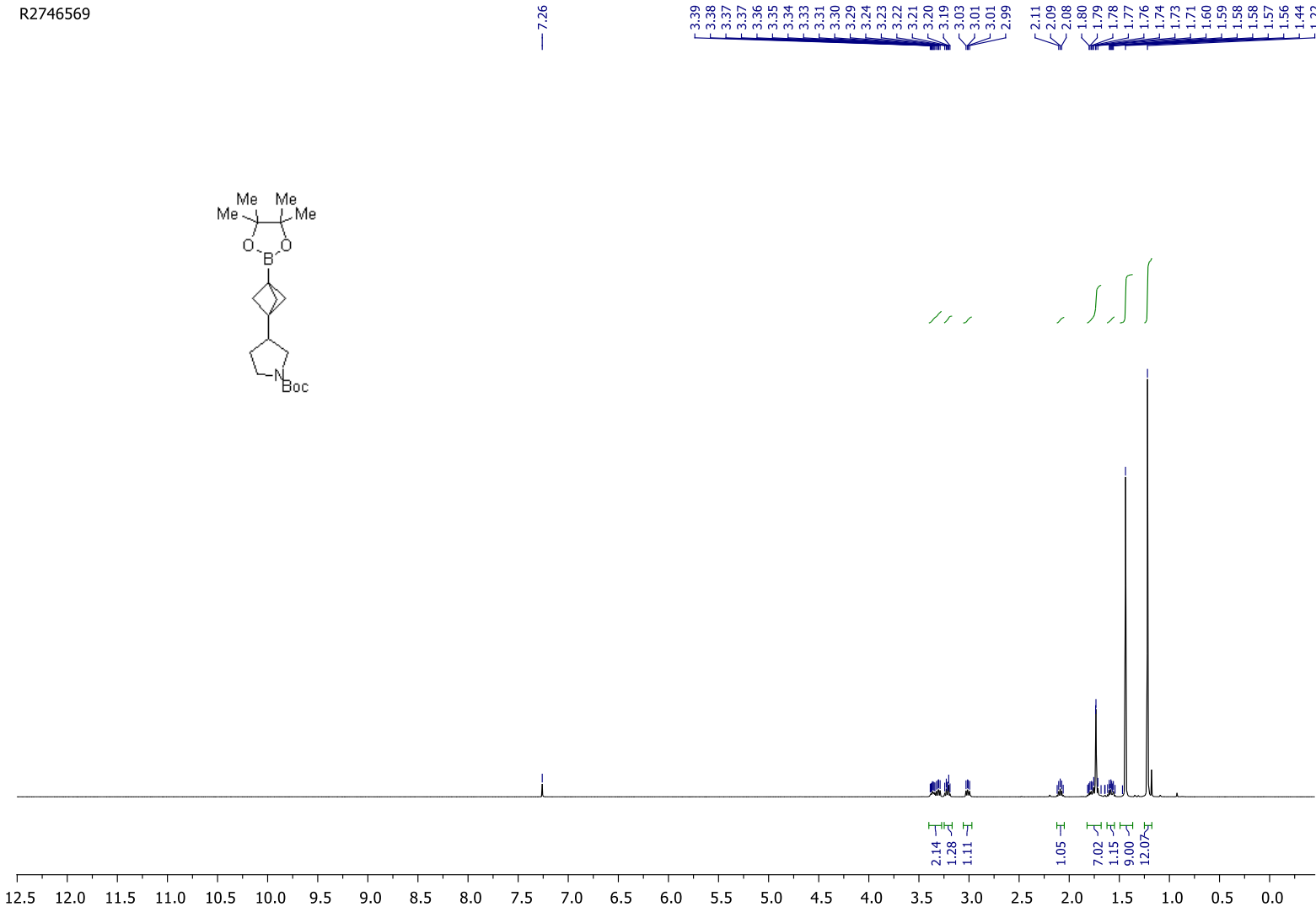
R2800653_C13



Compound 61a

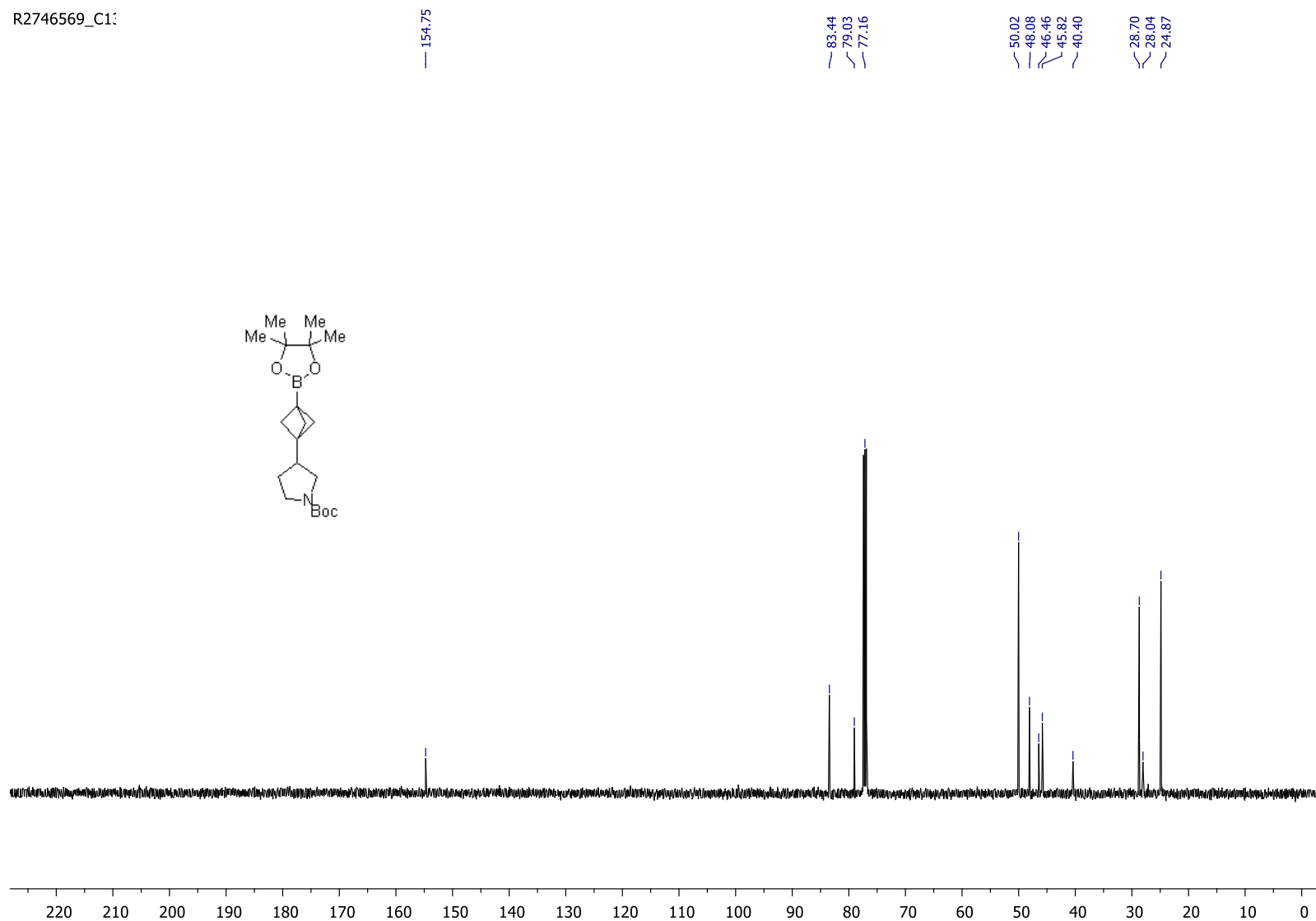
R2746569

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

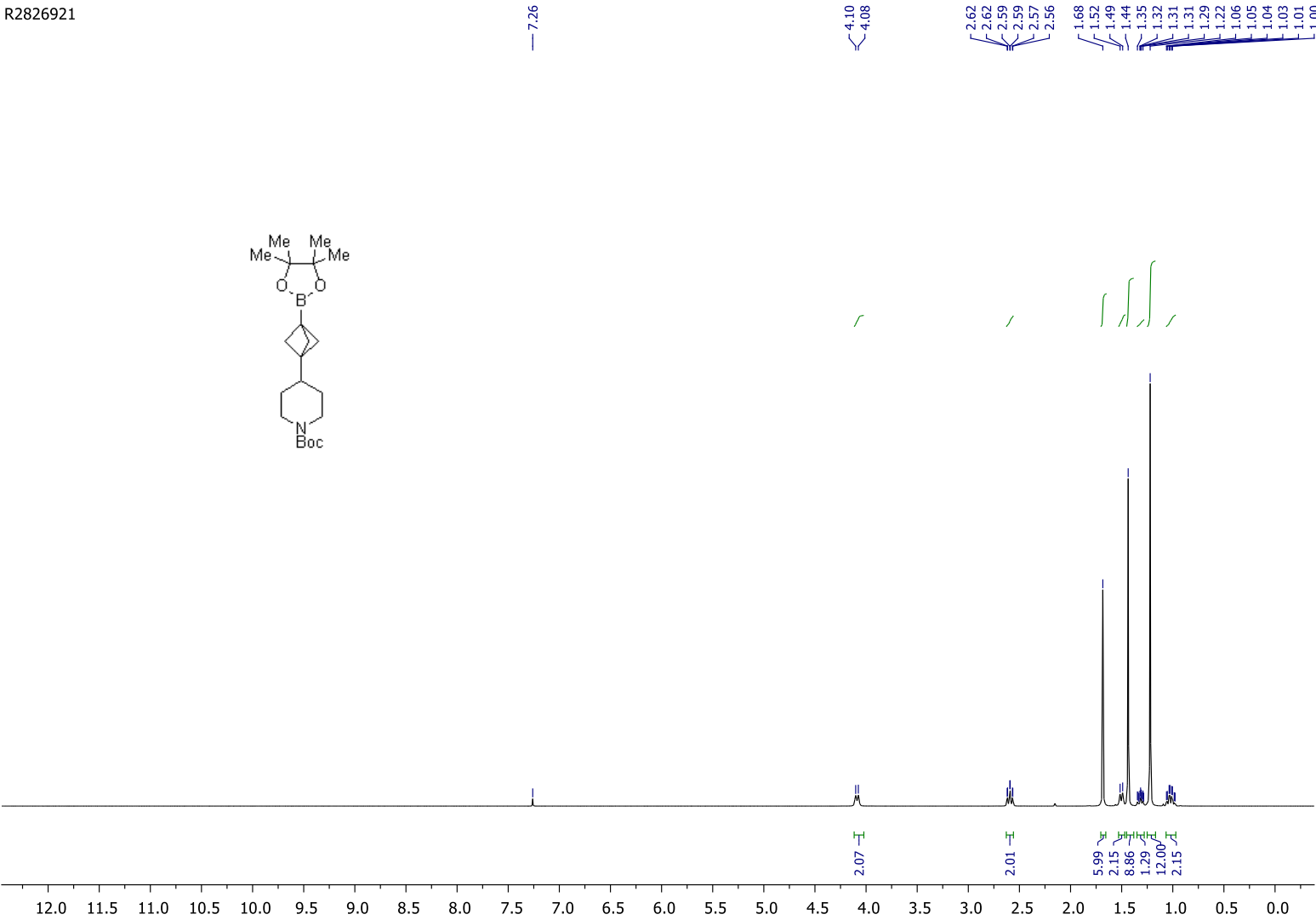
R2746569_C1:



Compound 63a

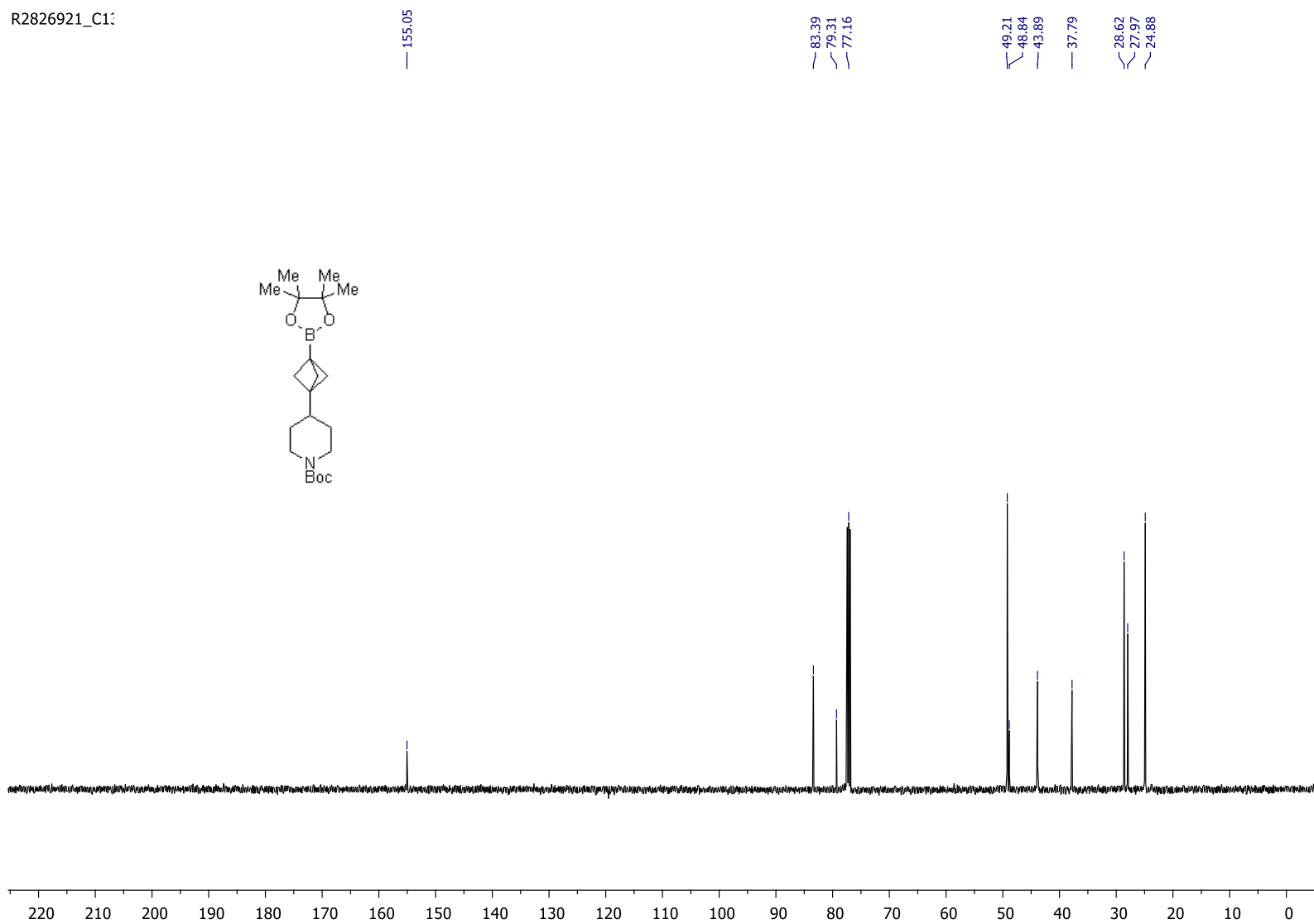
R2826921

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

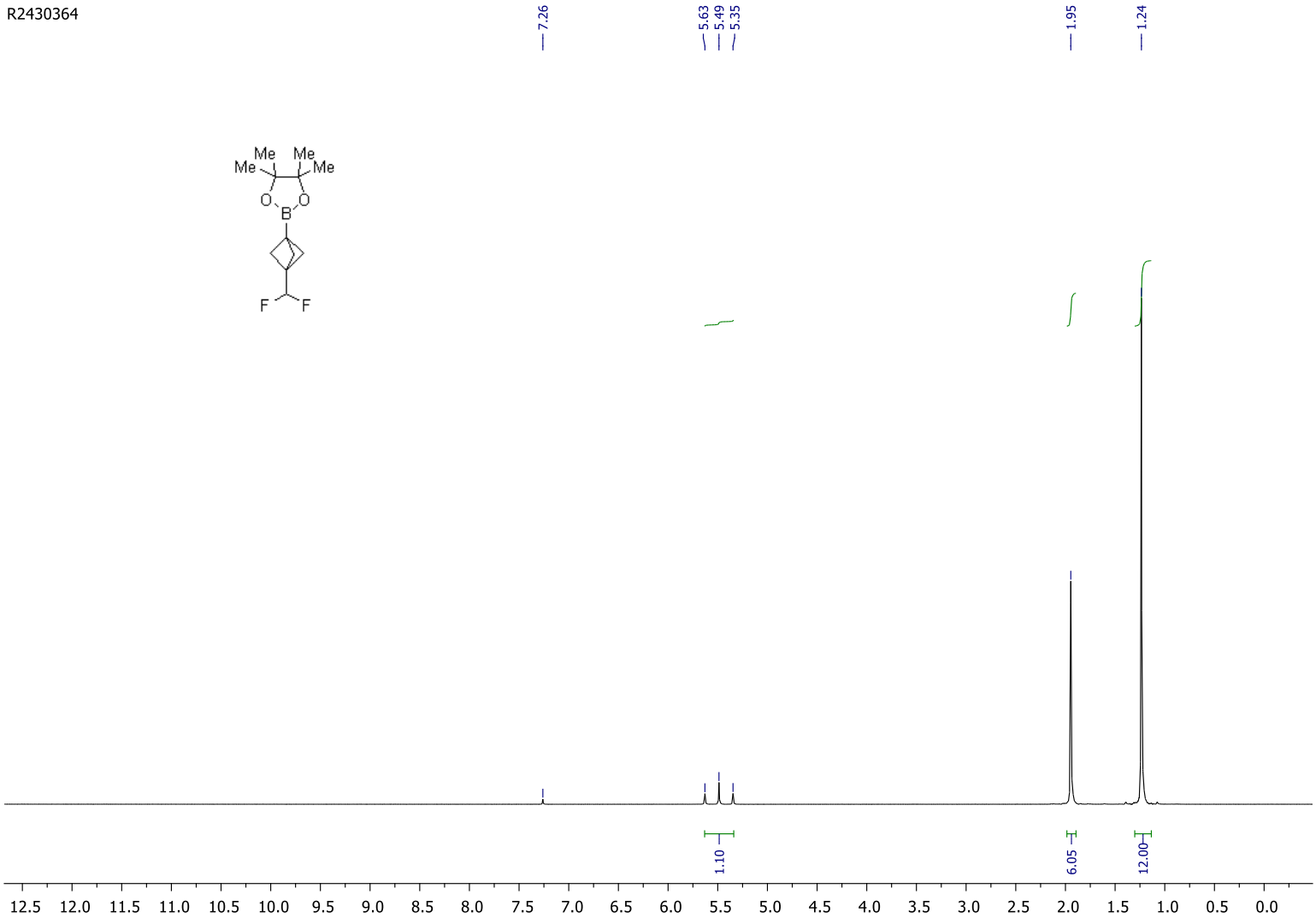
R2826921_C1:



Compound 67a

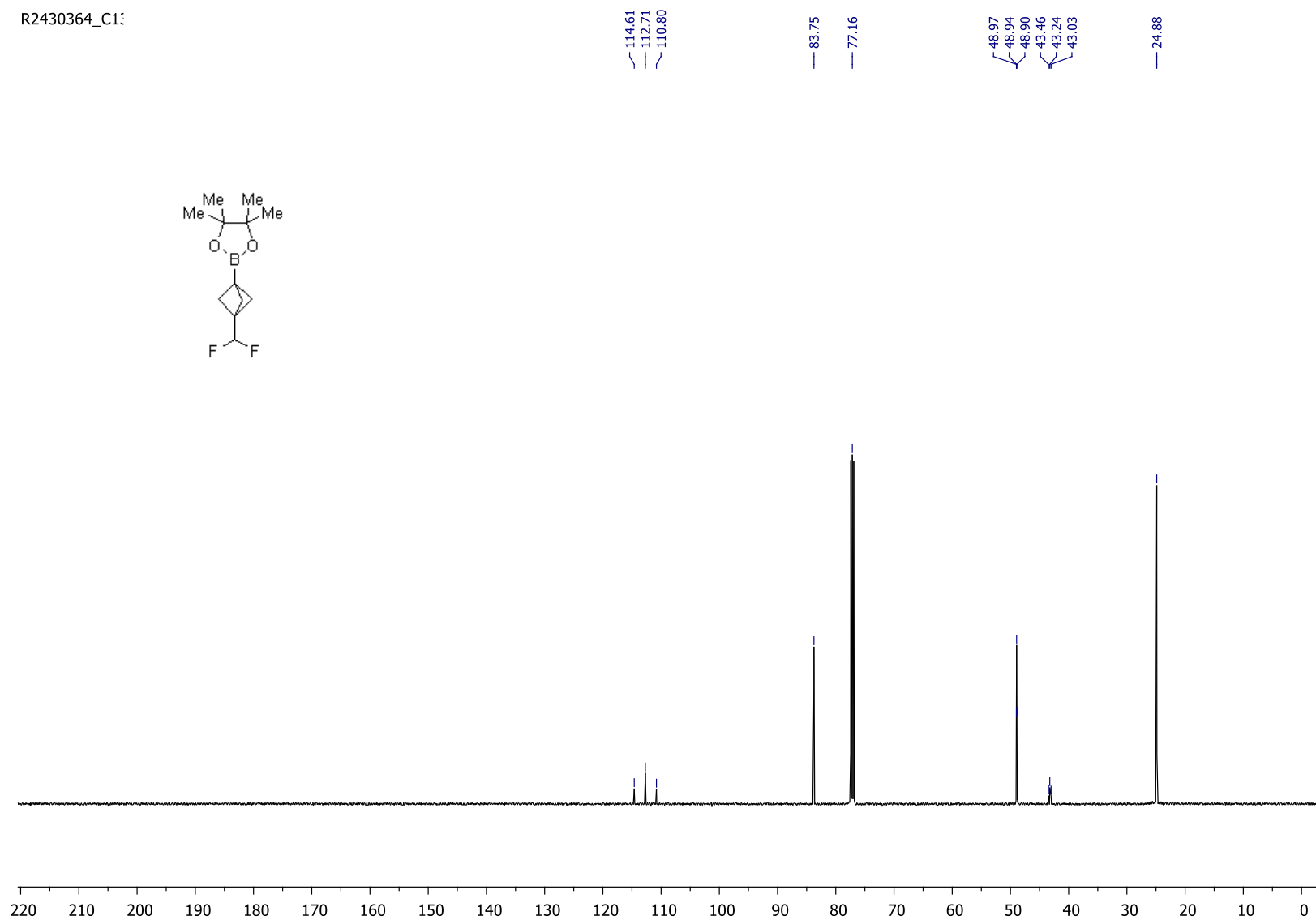
R2430364

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

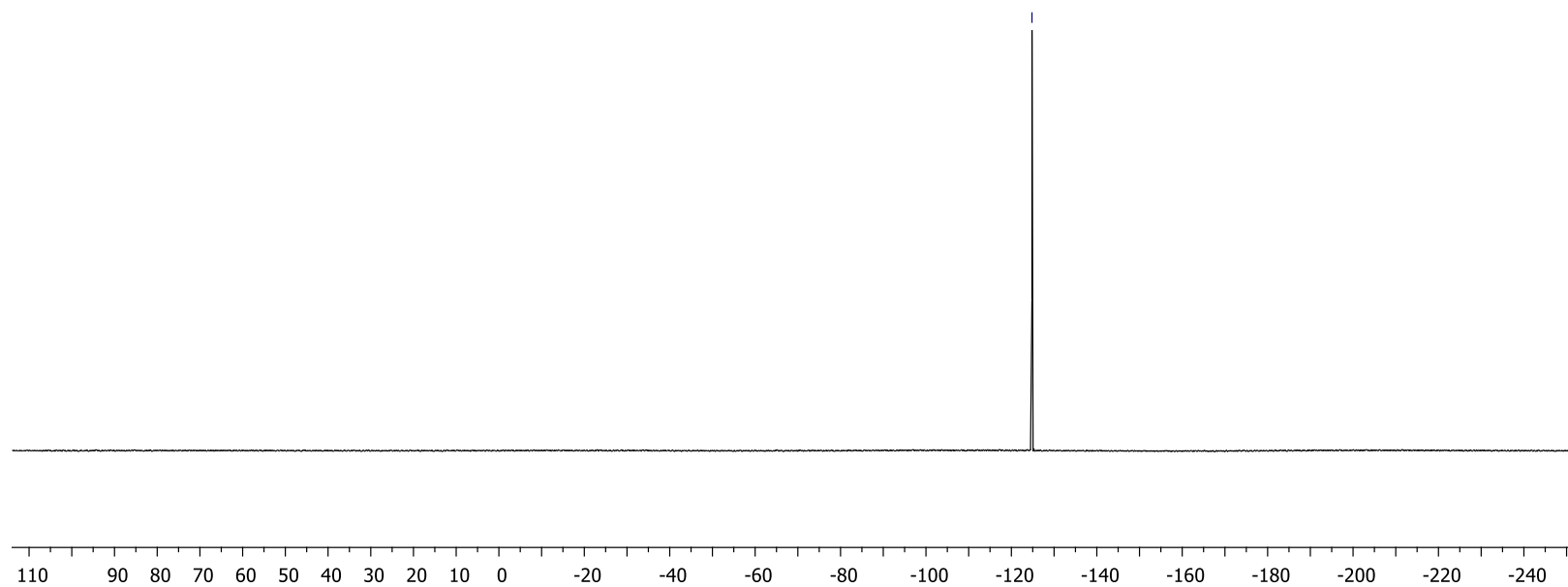
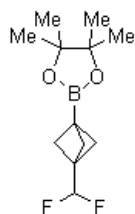
R2430364_C1:



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2430364_F19{H}
19F-{1H}

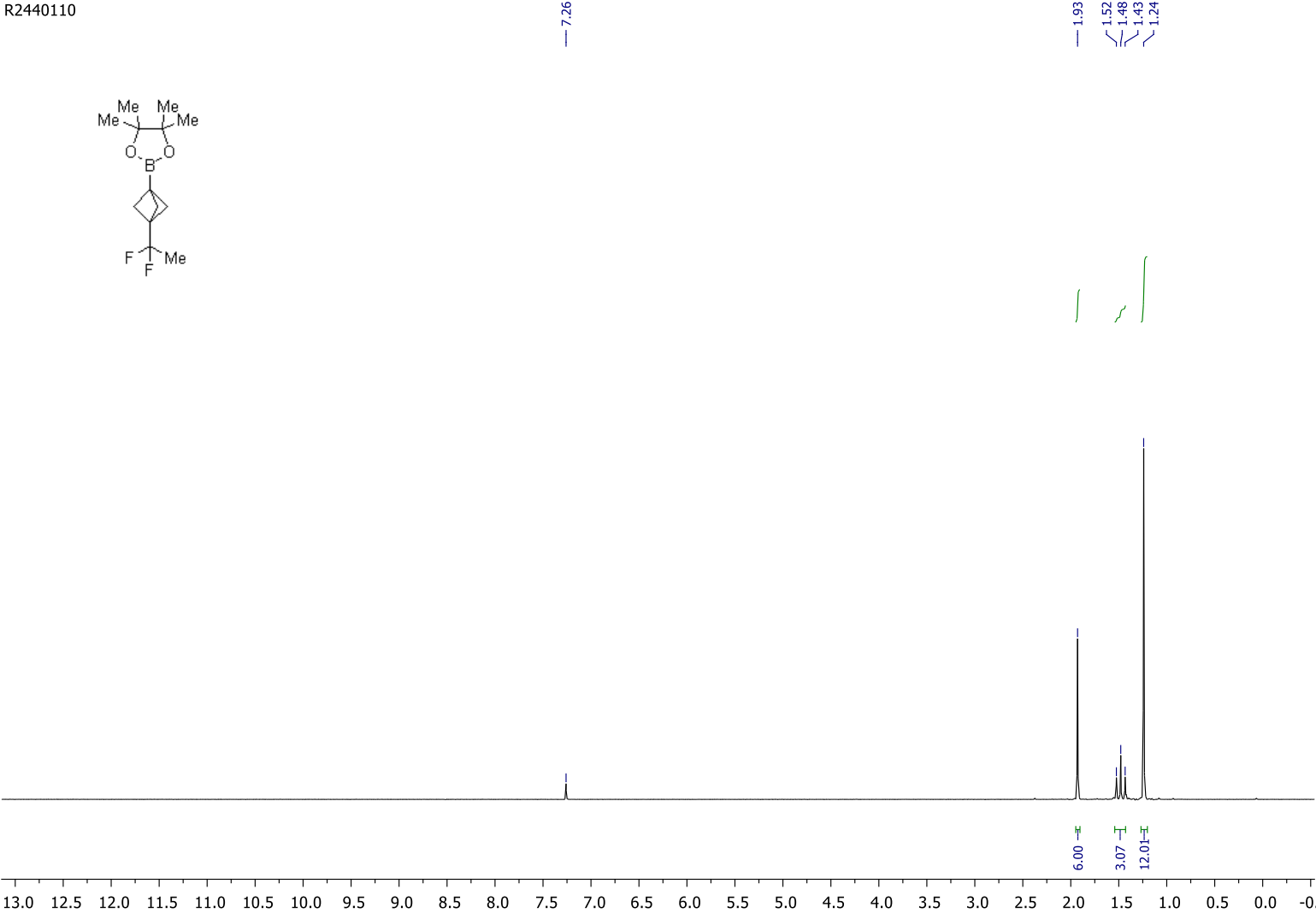
— -124.82



Compound 68a

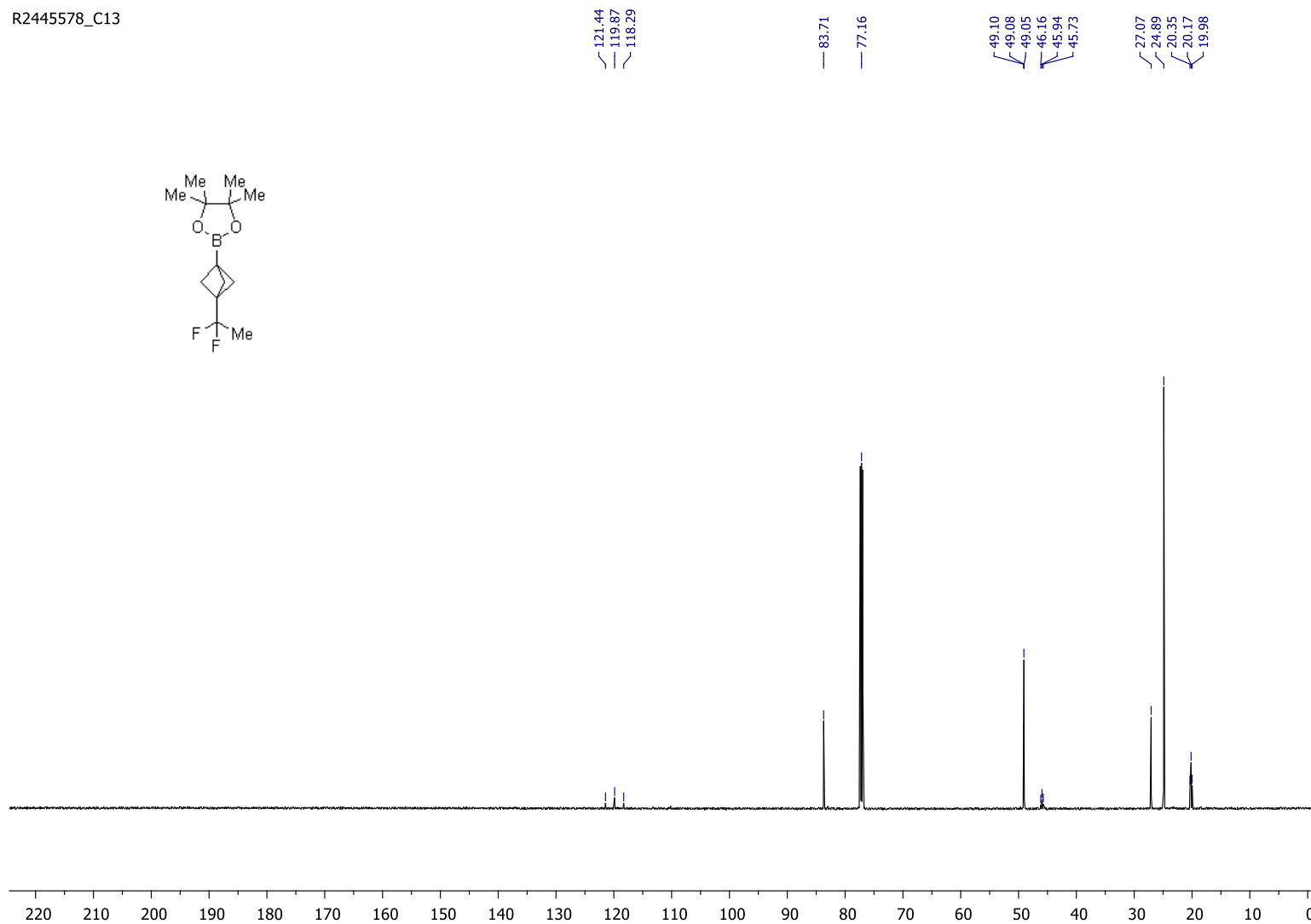
¹H NMR (400 MHz, CDCl₃)

R2440110



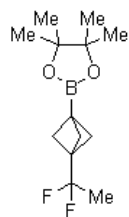
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

R2445578_C13

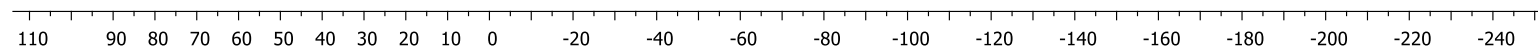


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2440110_F19{H}
19F-{1H}



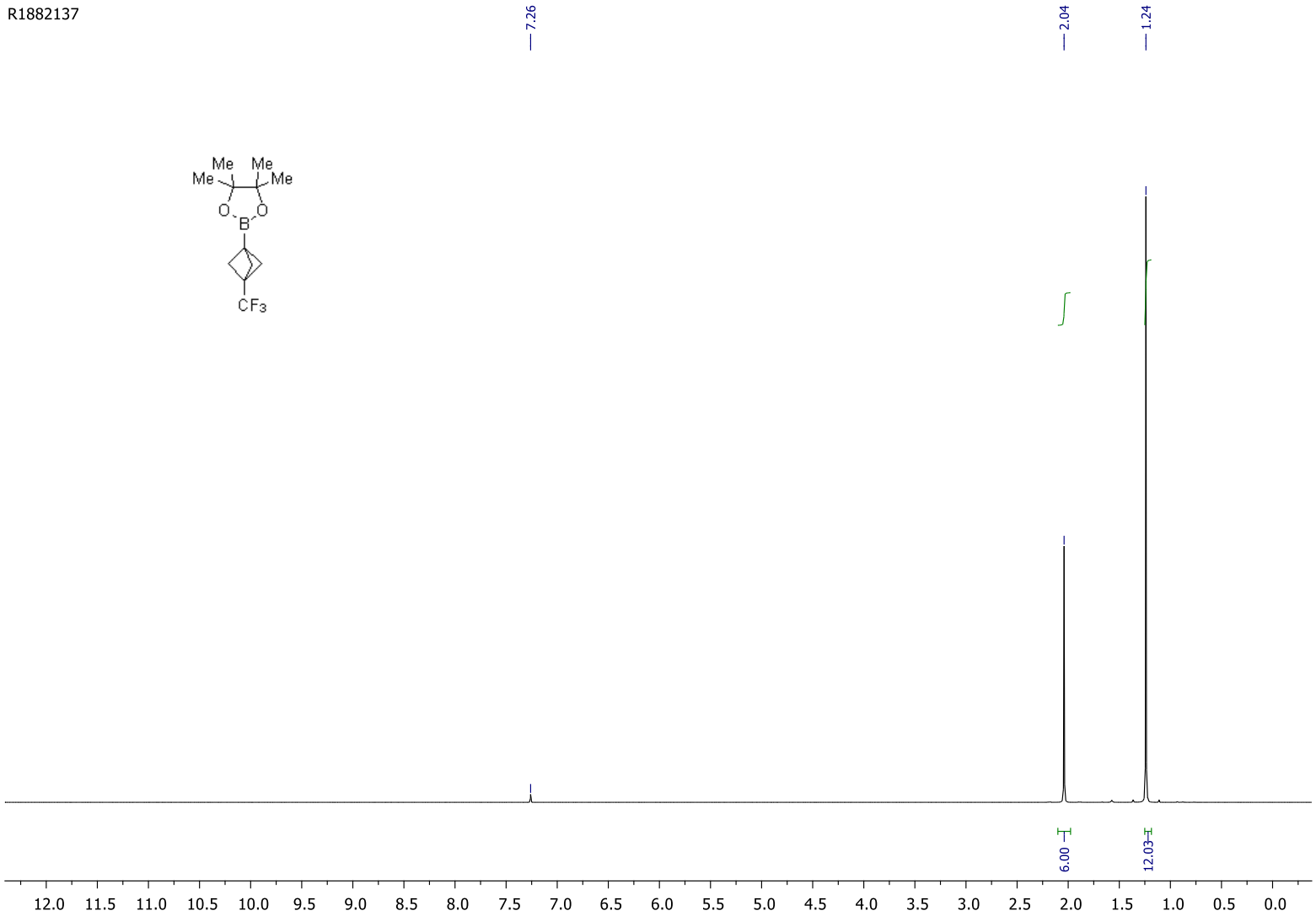
-100.94



Compound 69a

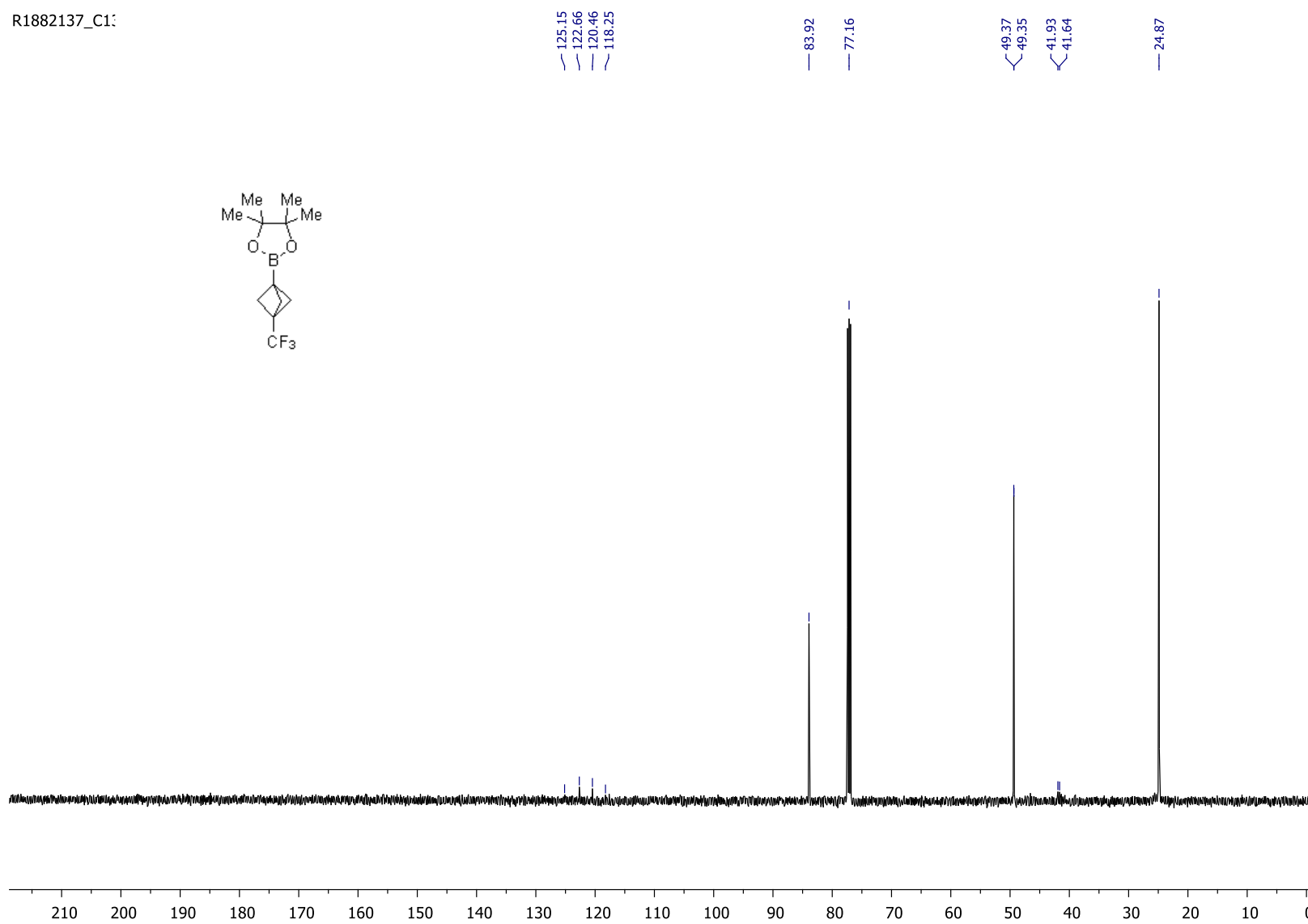
R1882137

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

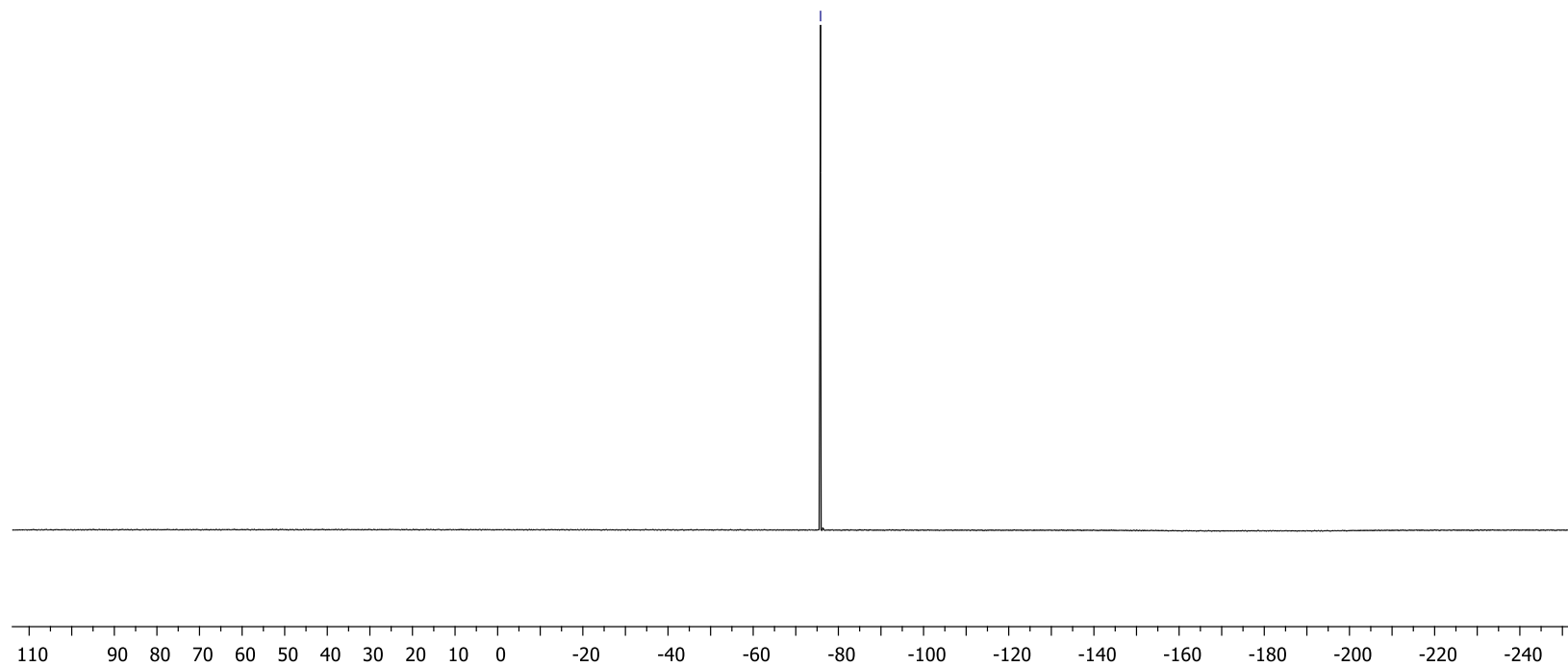
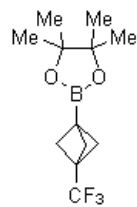
R1882137_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R1882137_F19{H}
 $^{19}\text{F}\{^1\text{H}\}$

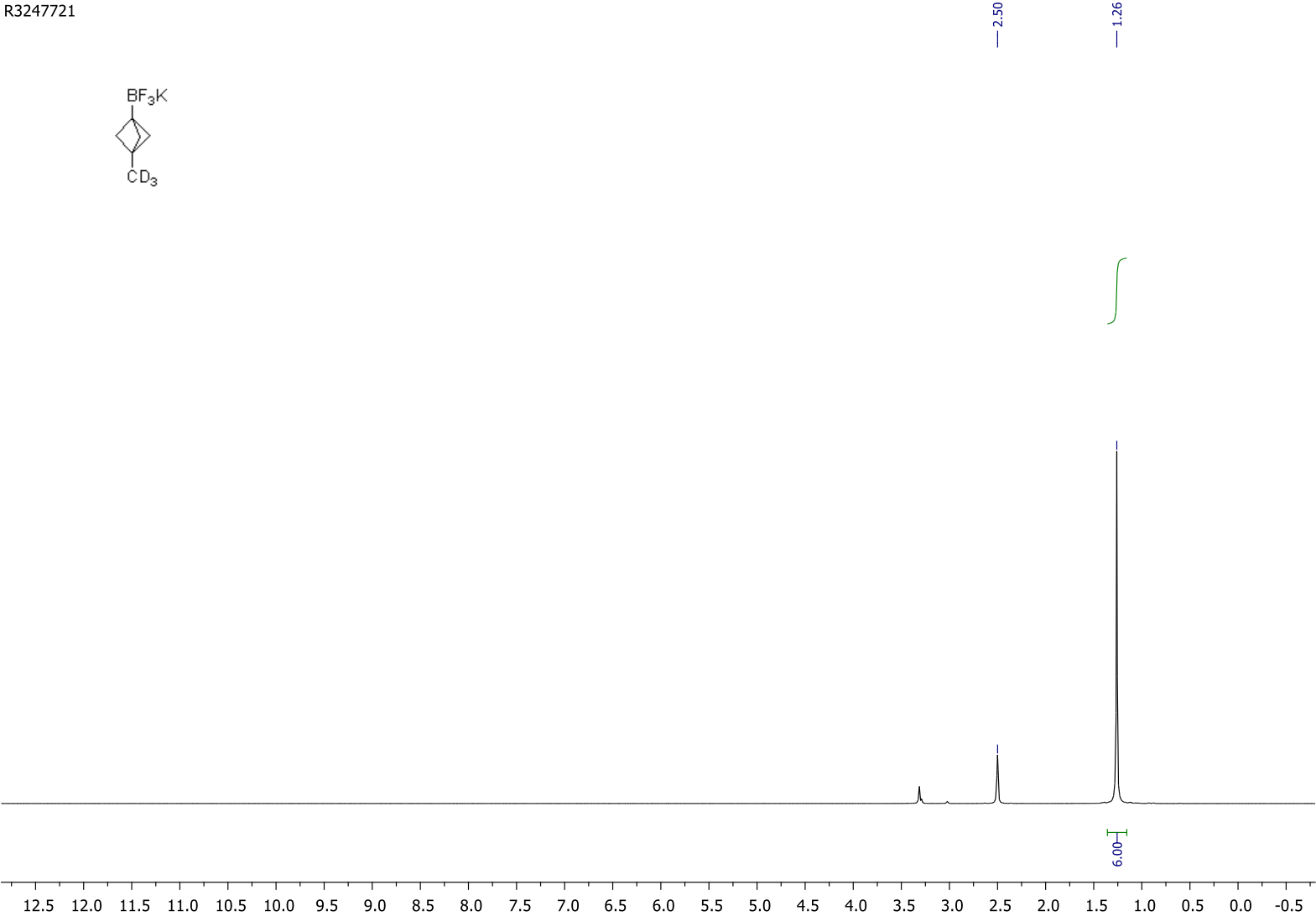
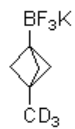
— -75.81



Compound (D₃-1)b

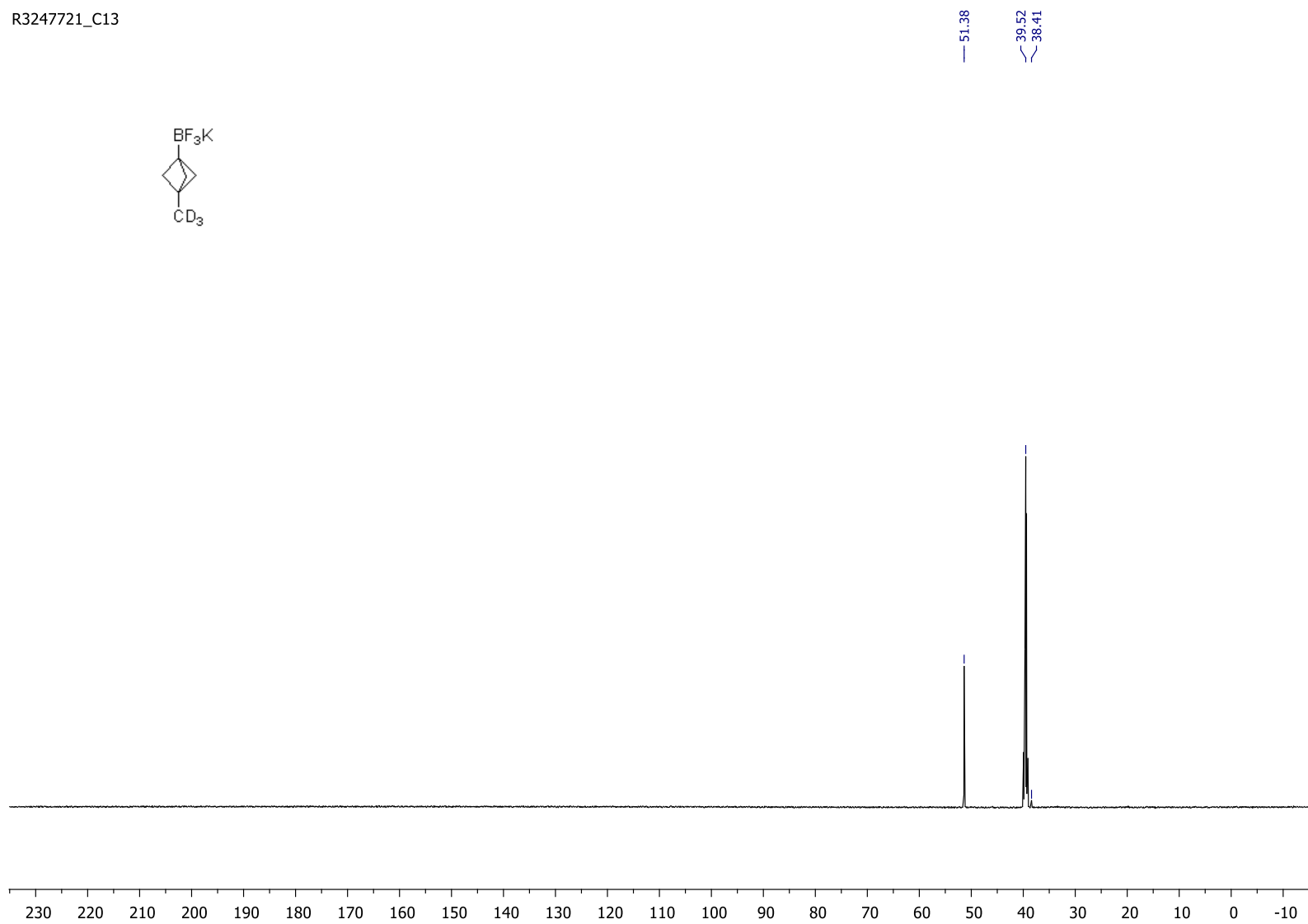
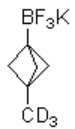
¹H NMR (500 MHz, DMSO-d₆)

R3247721



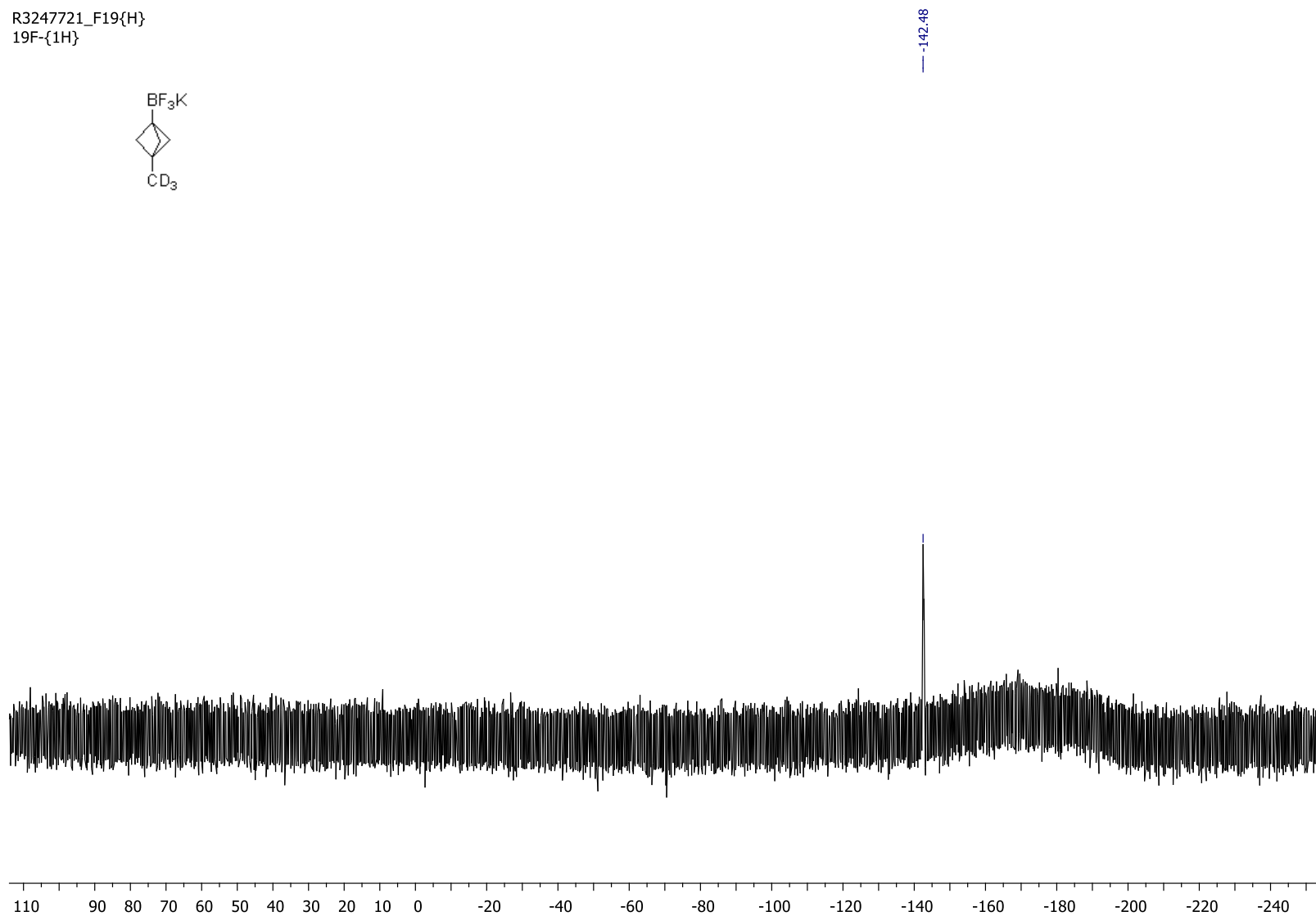
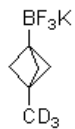
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R3247721_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

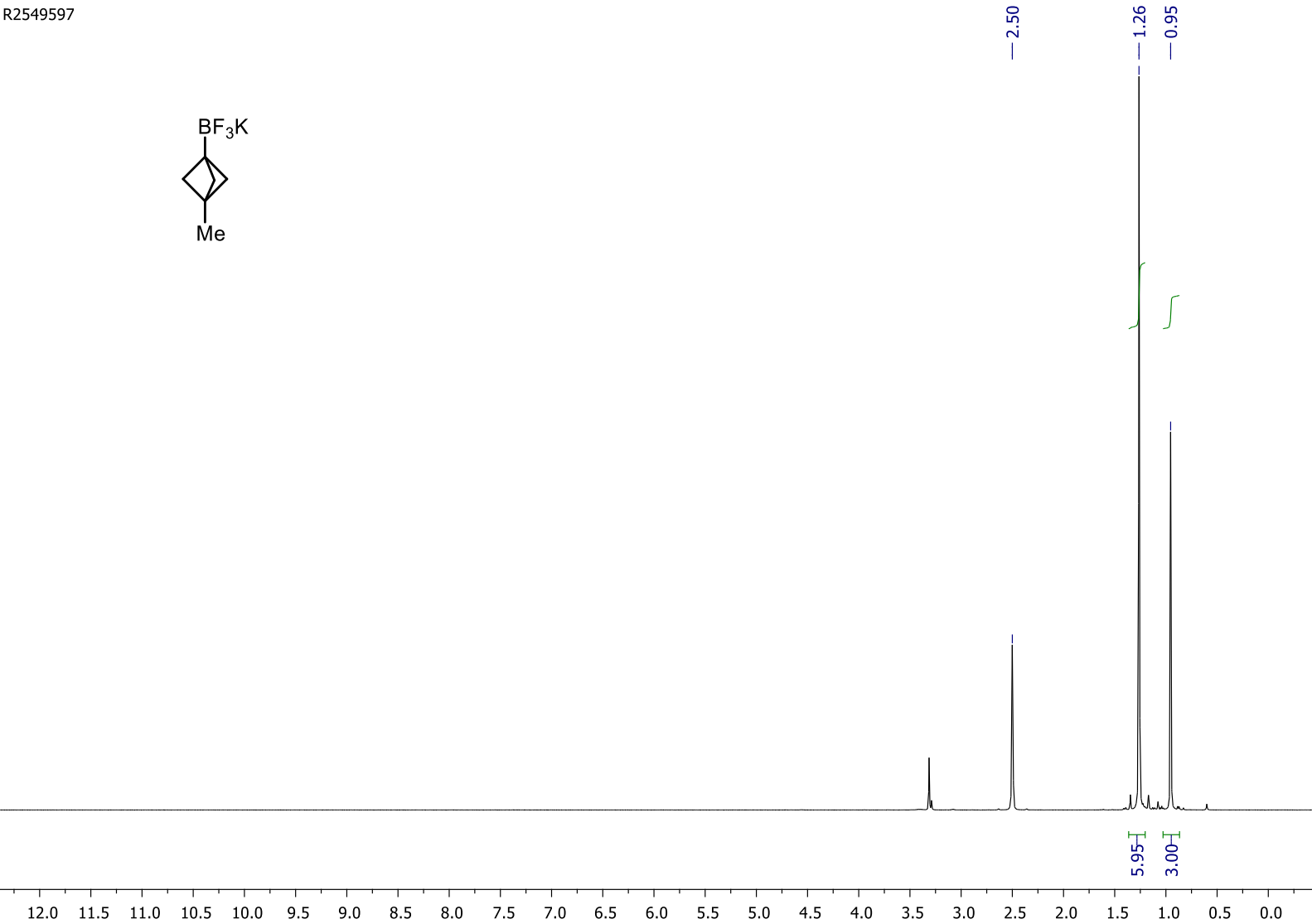
R3247721_F19{H}
19F-{1H}



Compound 1b

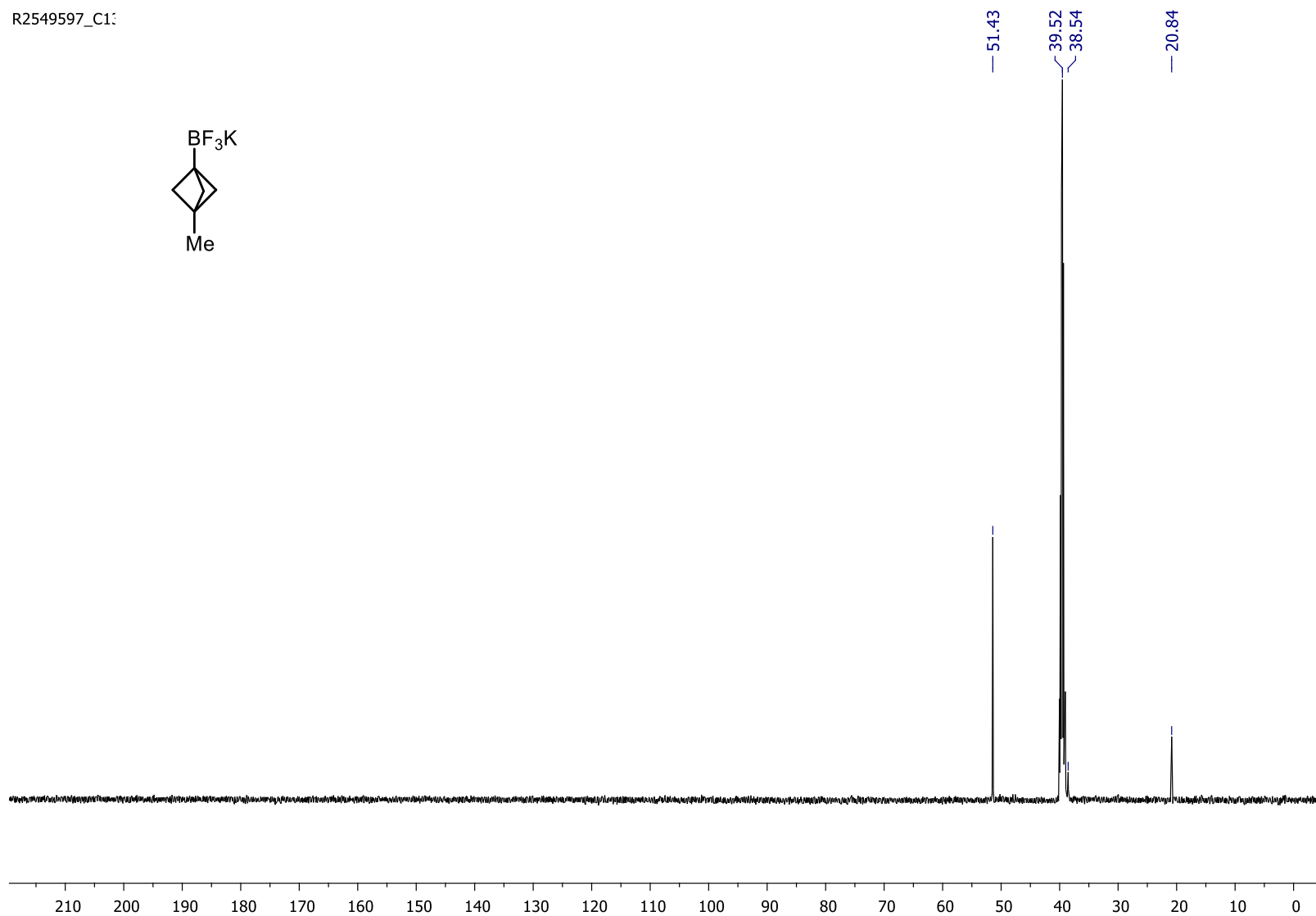
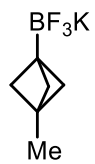
¹H NMR (500 MHz, DMSO-d₆)

R2549597



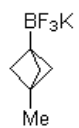
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2549597_C1:

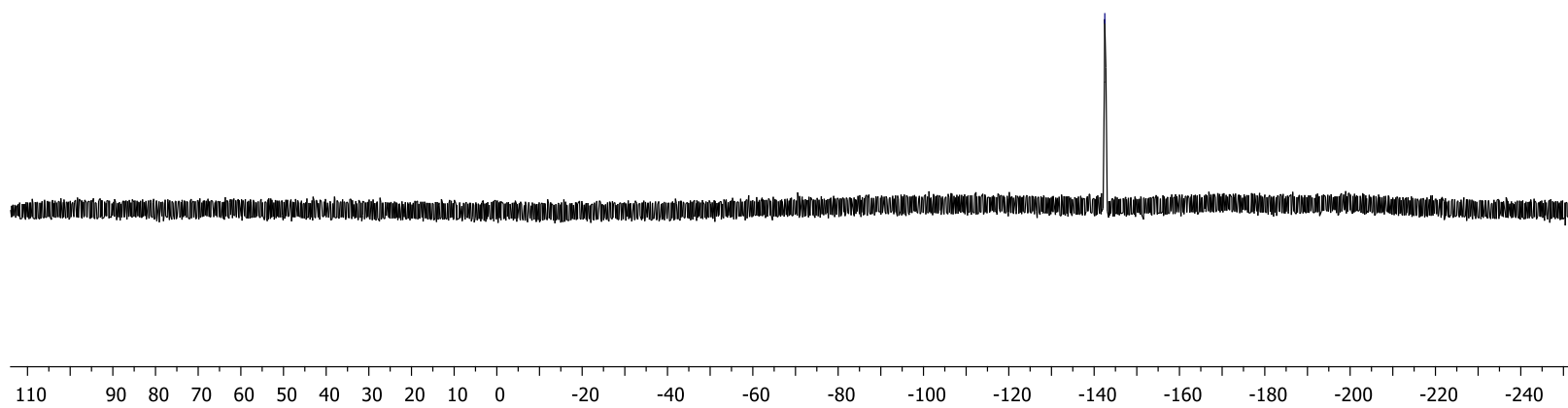


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2549597_F19{H}



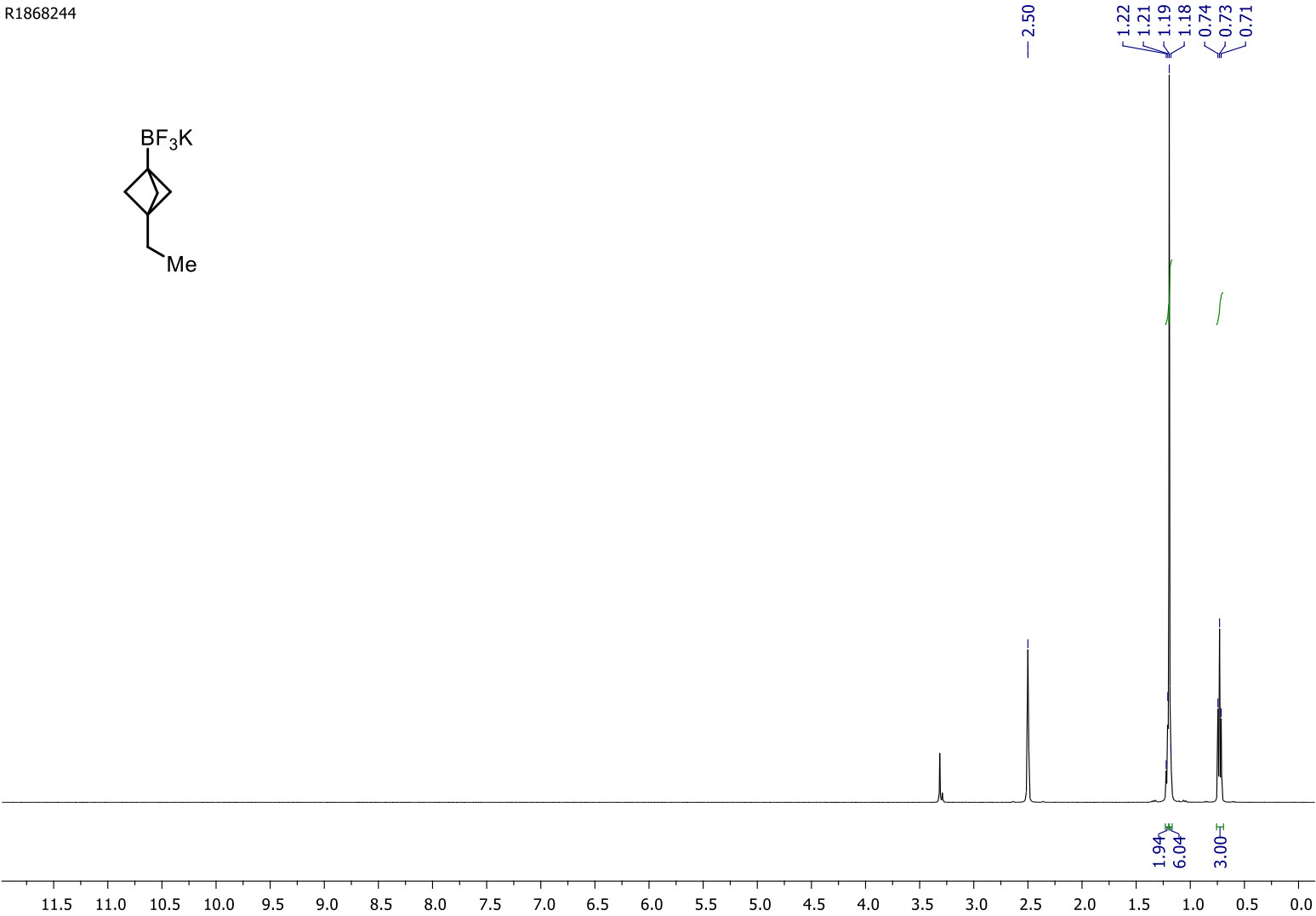
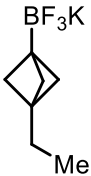
— -142.50



Compound 2b

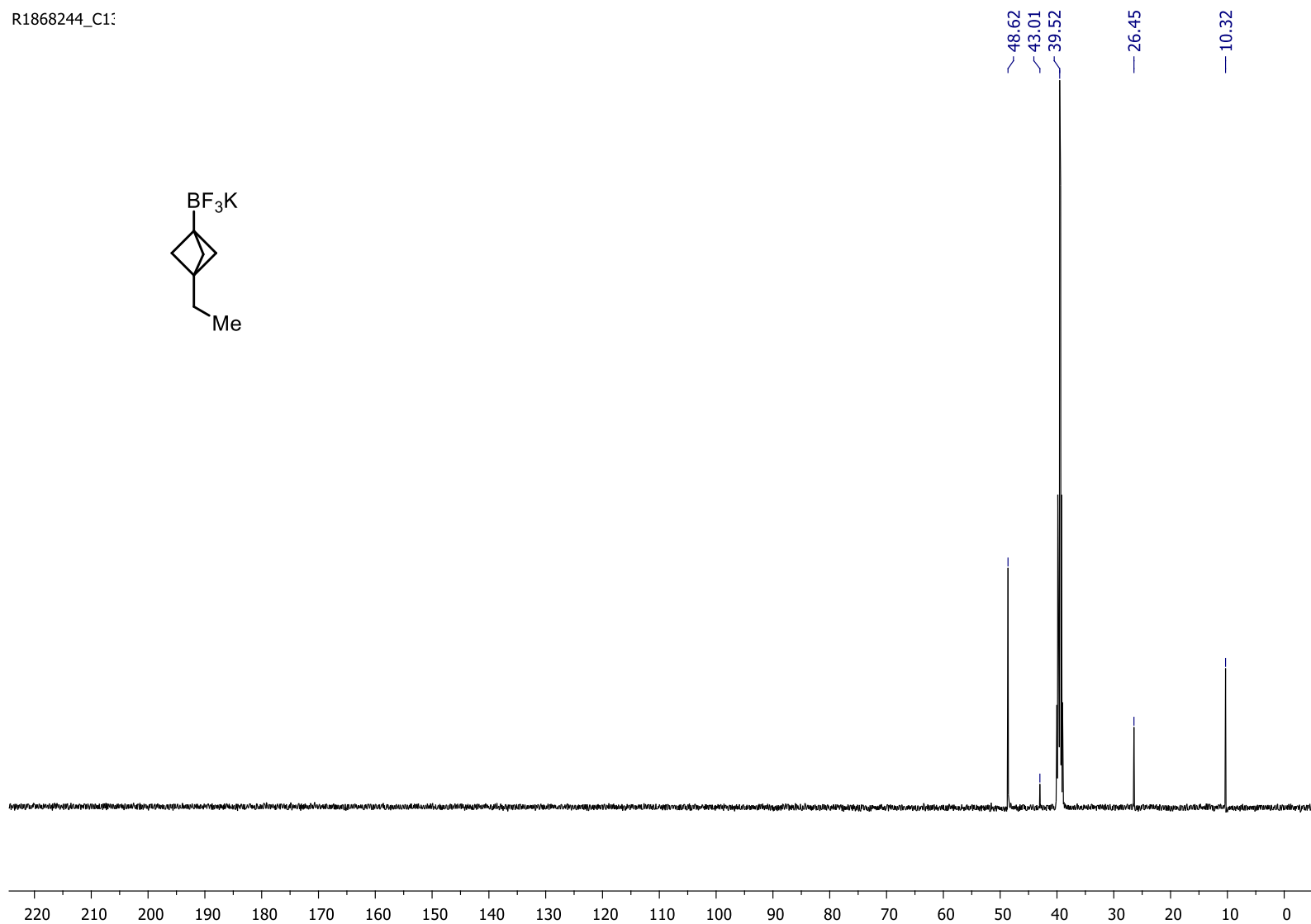
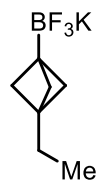
¹H NMR (500 MHz, DMSO-d₆)

R1868244



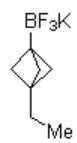
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R1868244_C13

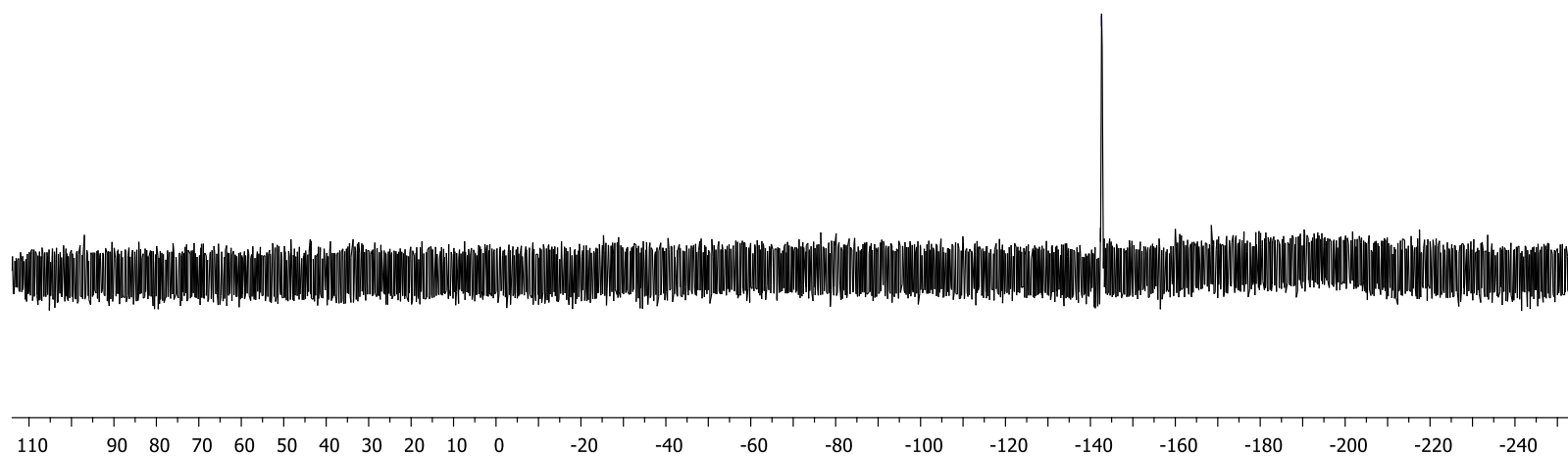


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R1868244_F19{H}
19F-{1H}



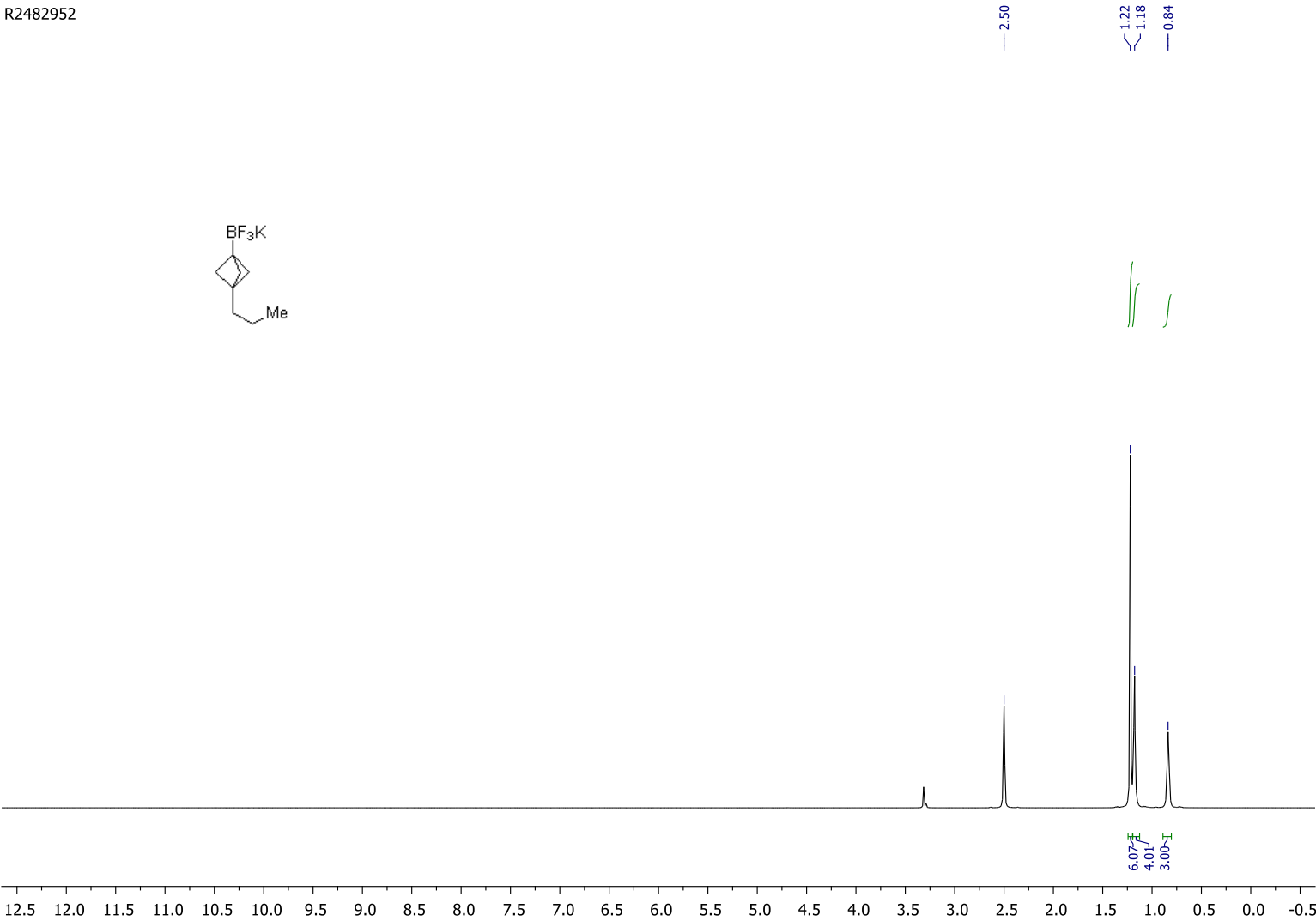
— -142.62



Compound 3b

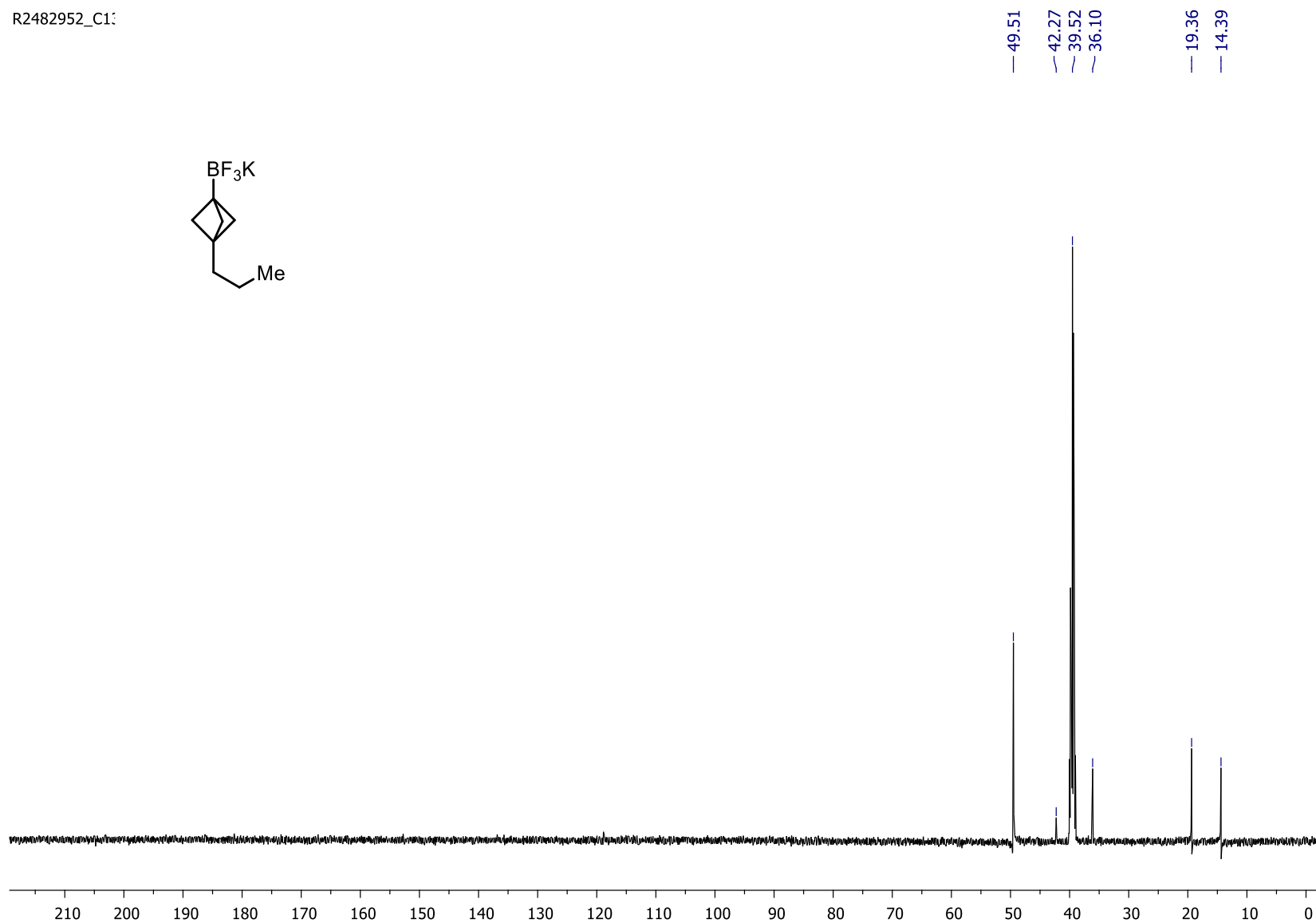
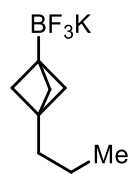
¹H NMR (500 MHz, DMSO-d₆)

R2482952



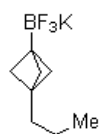
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2482952_C1:

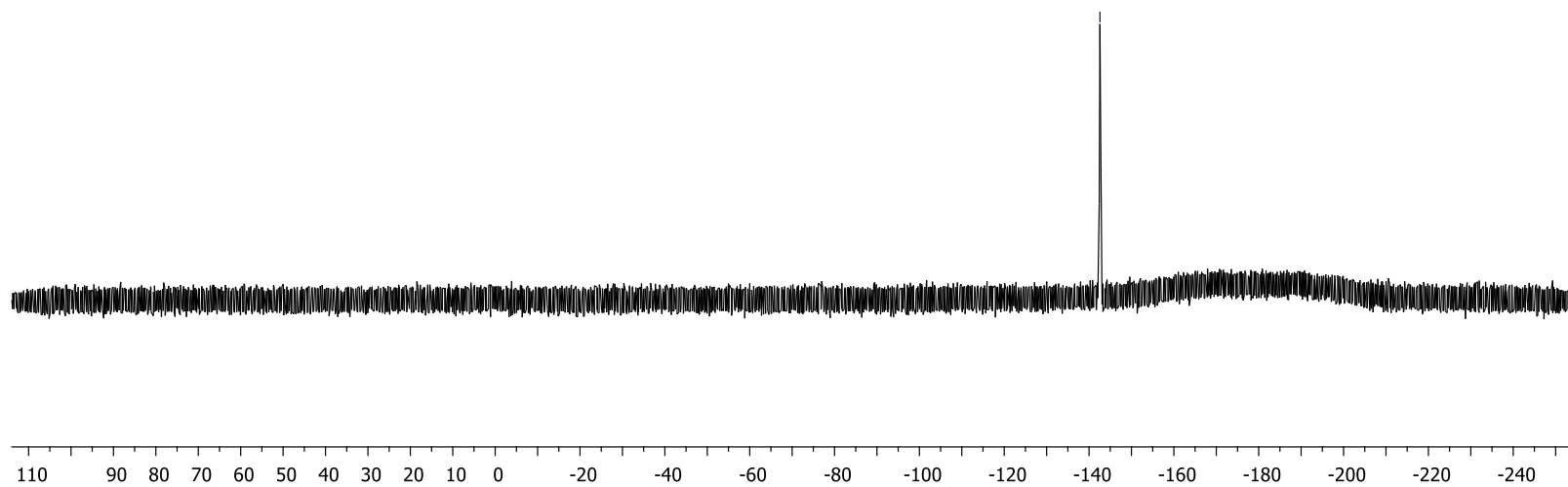


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2482952_F19
 $^{19}\text{F}\{^1\text{H}\}$



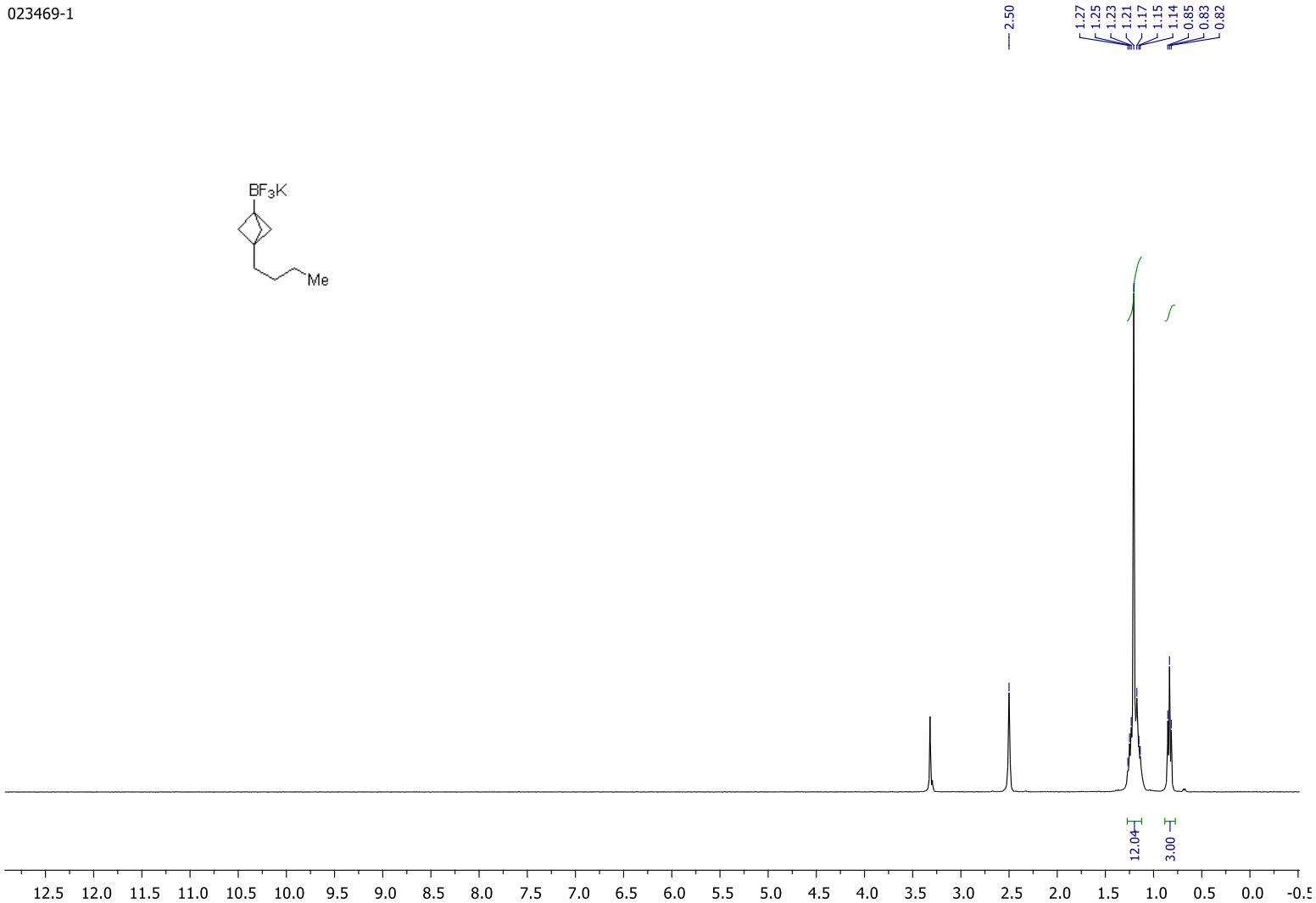
— -142.57



Compound 4b

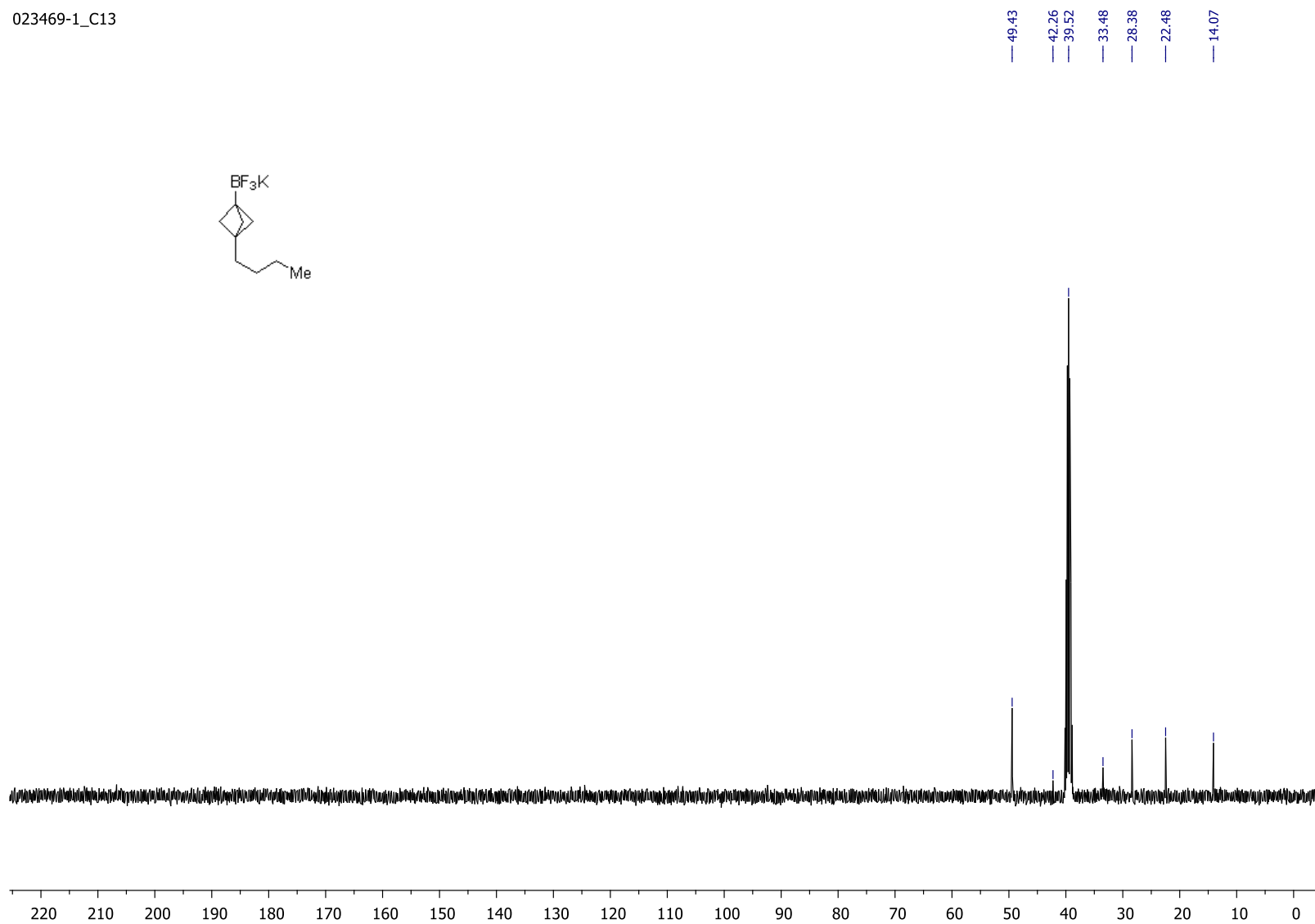
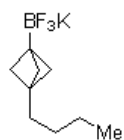
¹H NMR (400 MHz, DMSO-d₆)

023469-1



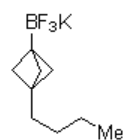
$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6)

023469-1_C13

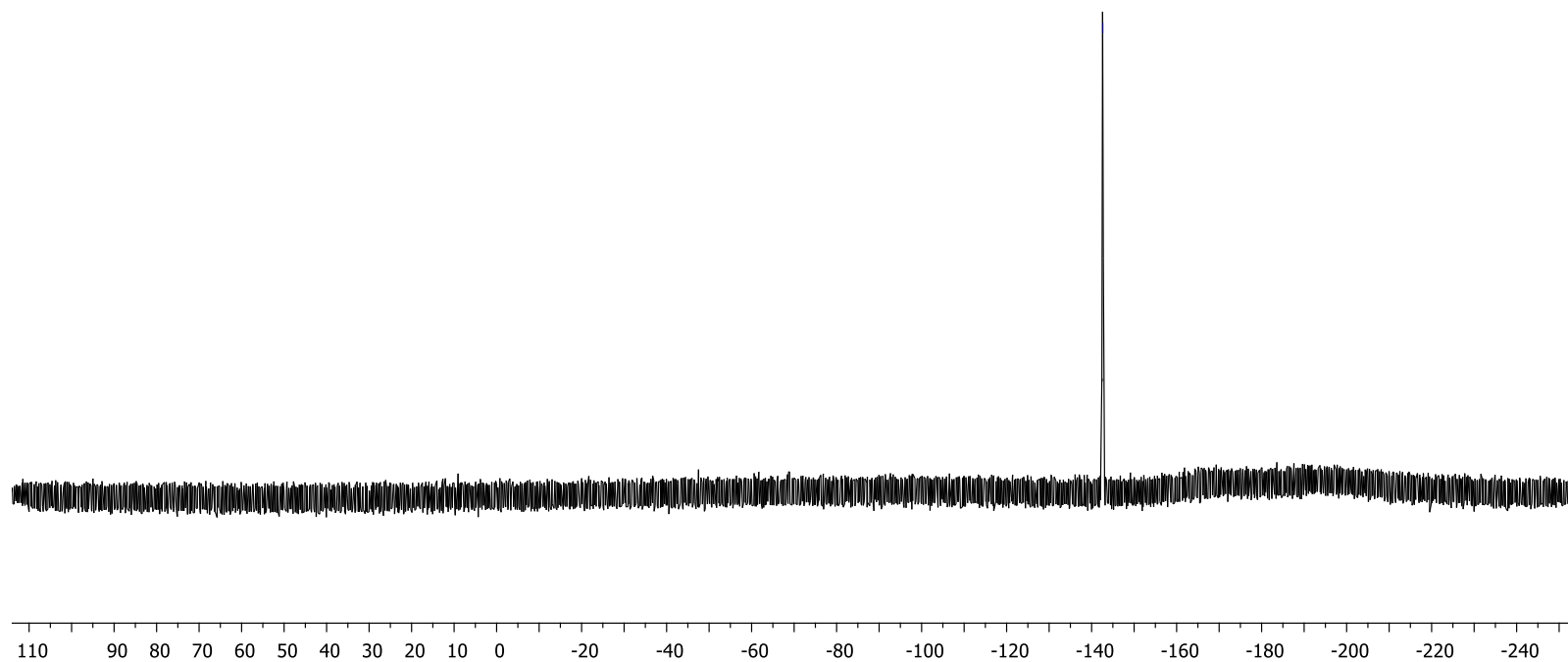


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

023469-1_F19{H}



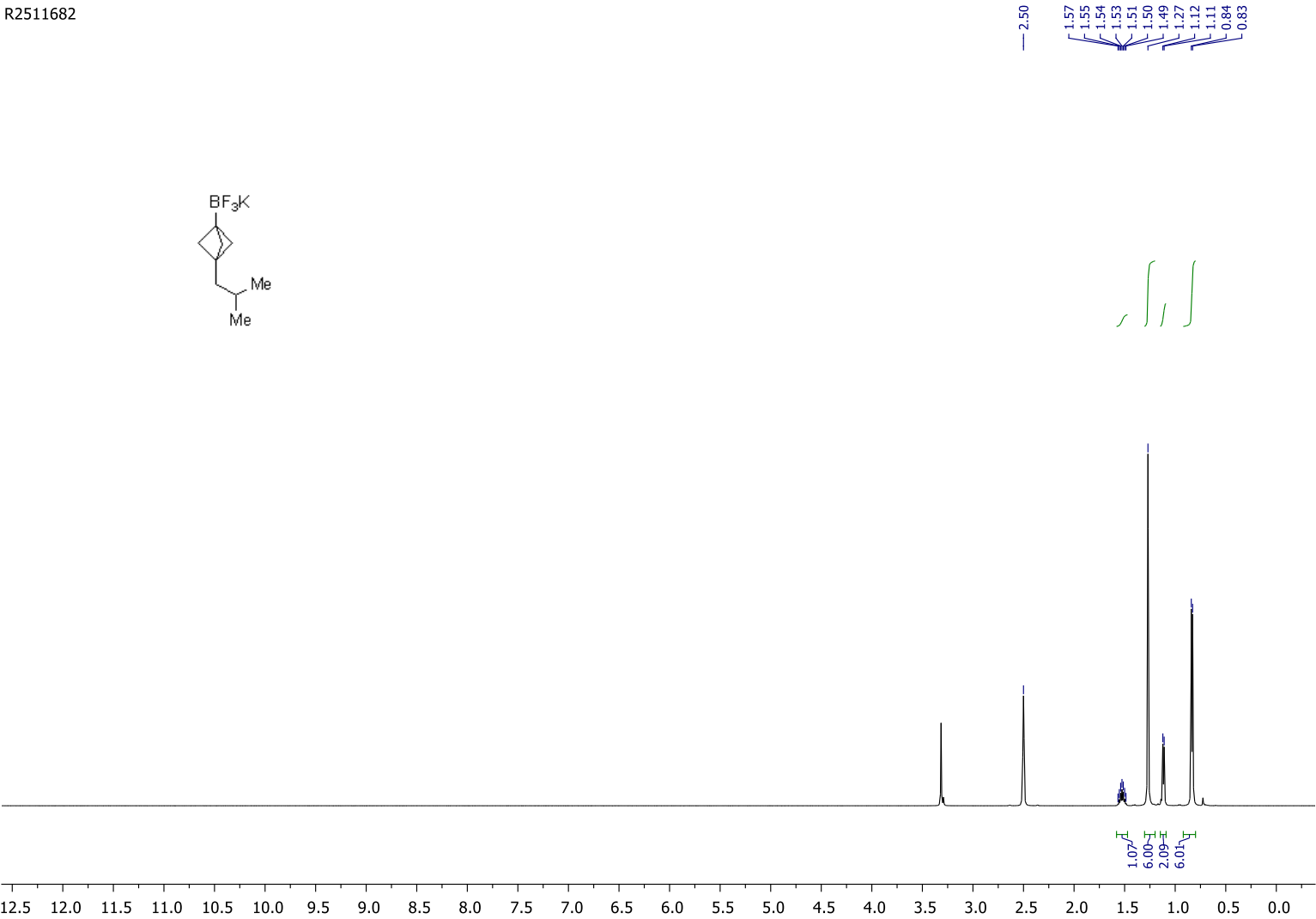
— -142.62



Compound 5b

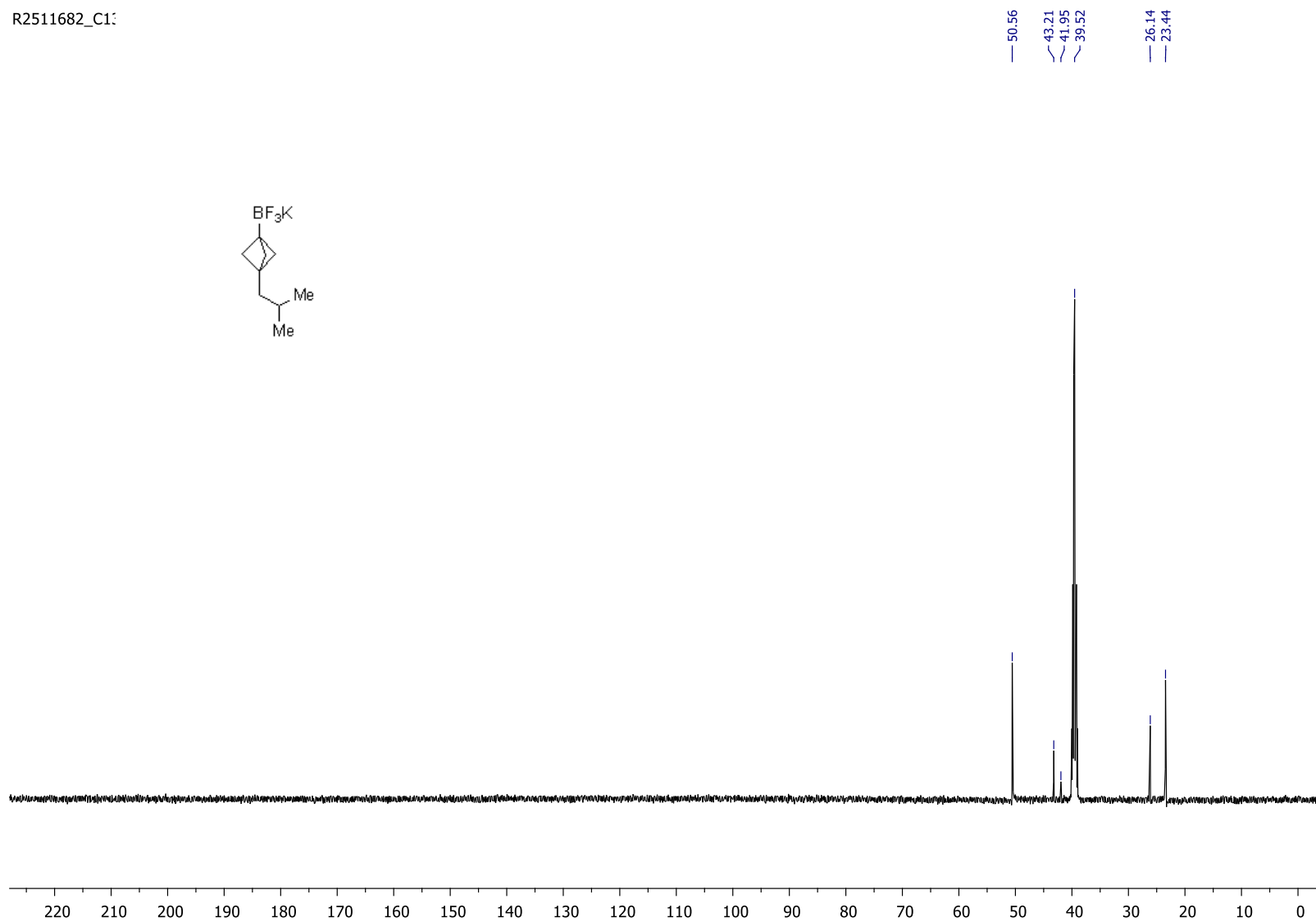
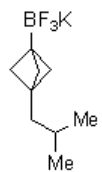
¹H NMR (500 MHz, DMSO-d₆)

R2511682



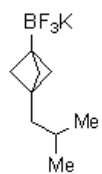
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2511682_C1:

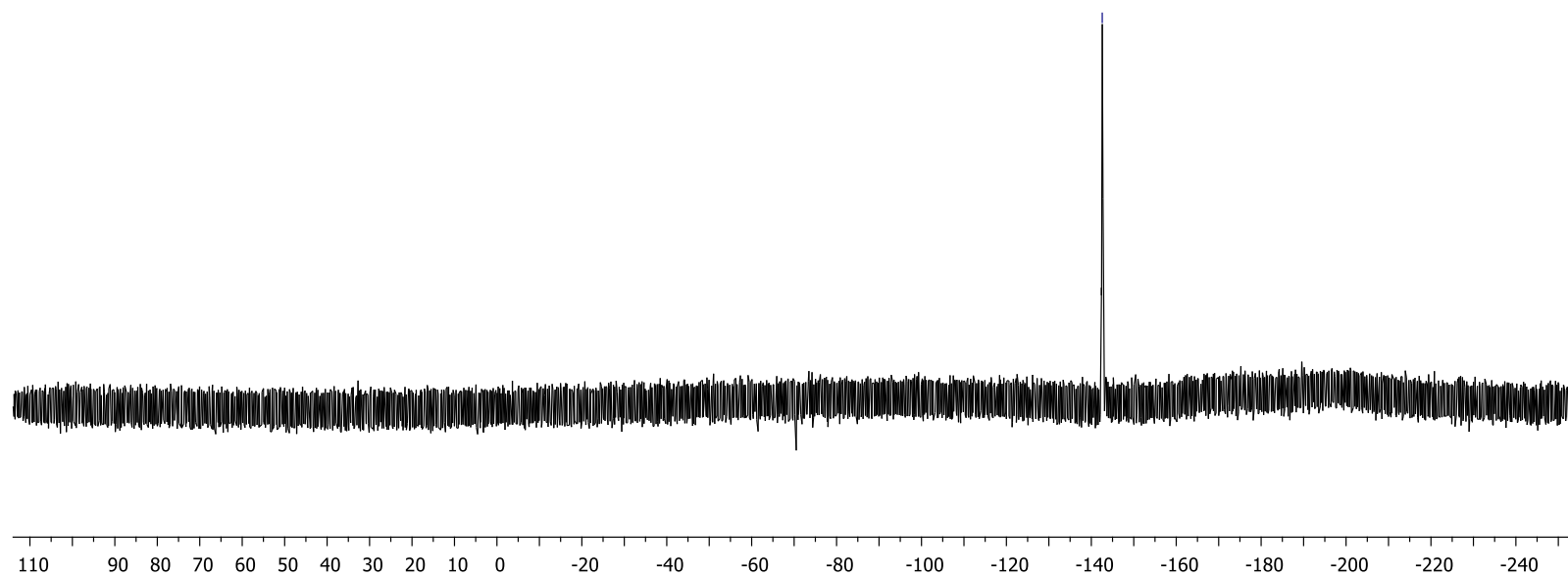


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2511682_F19{H}
19F-{1H}



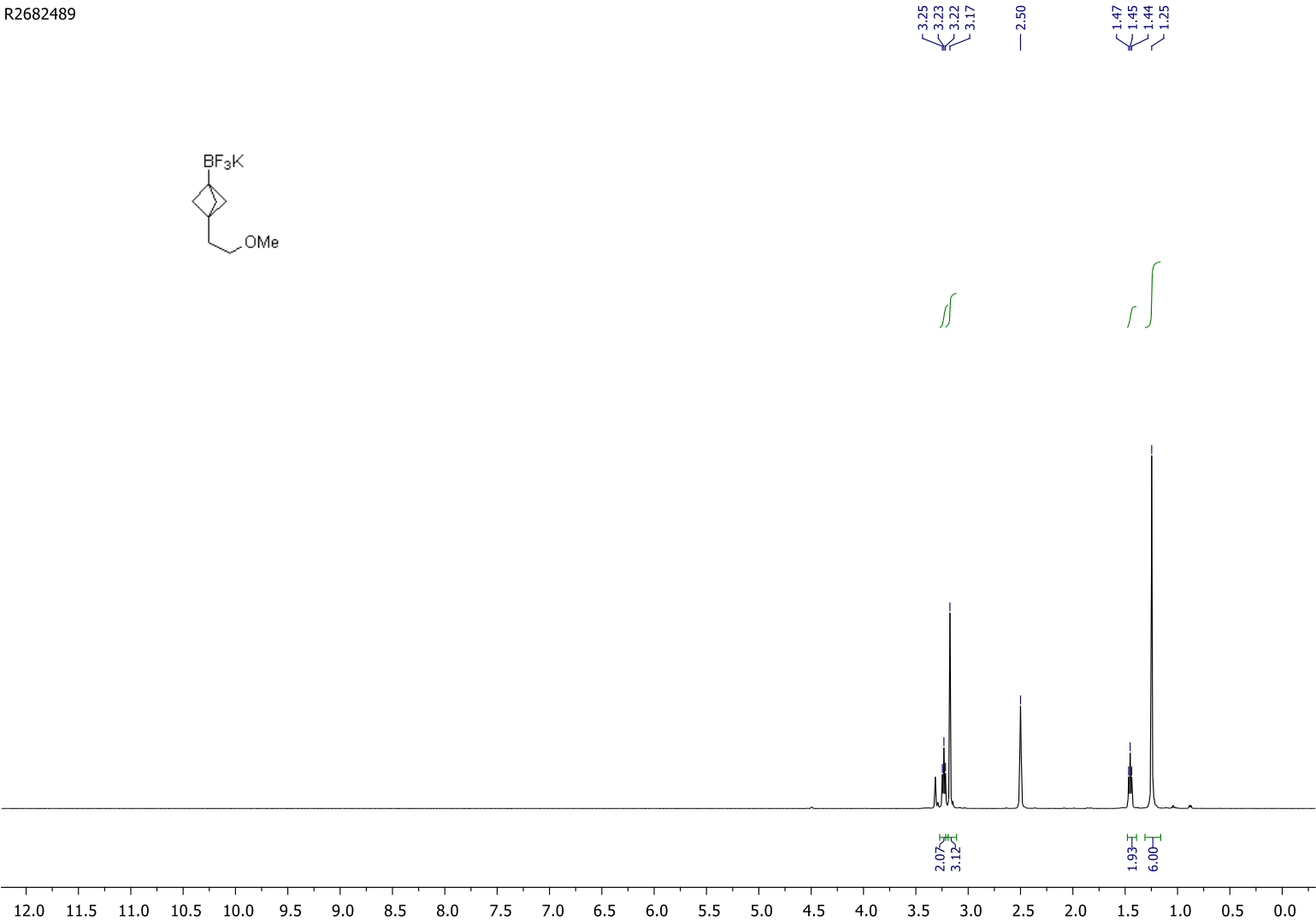
— -142.58



Compound 7b

¹H NMR (500 MHz, DMSO-d₆)

R2682489

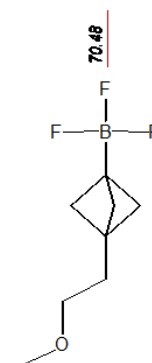


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

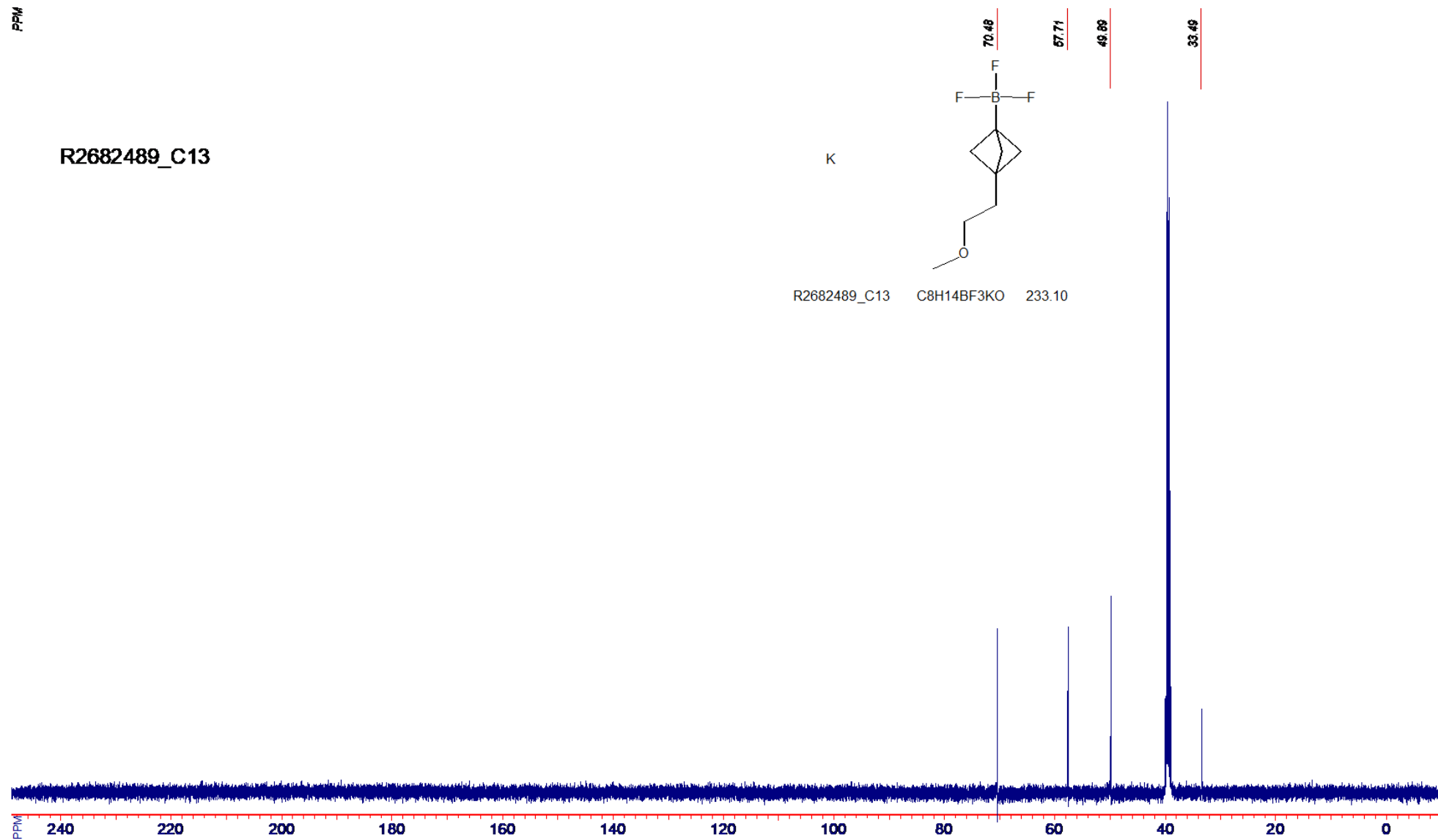
PPM

R2682489_C13

K

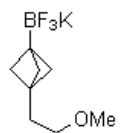


R2682489_C13 C₈H₁₄BF₃KO 233.10

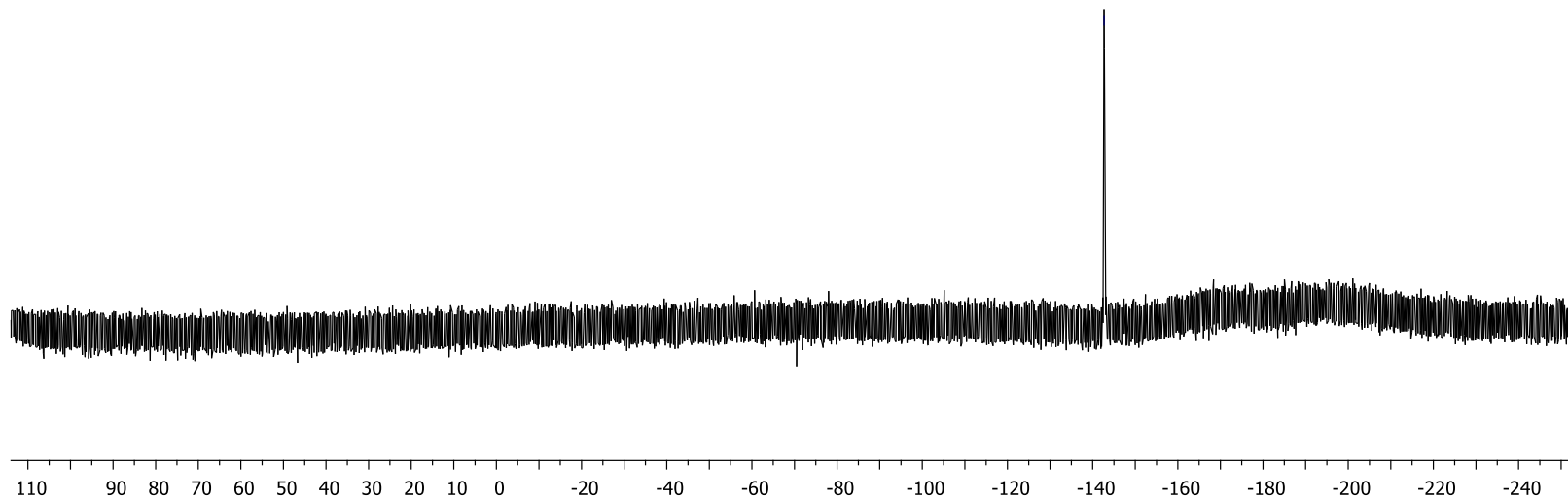


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2682489_F19{H}



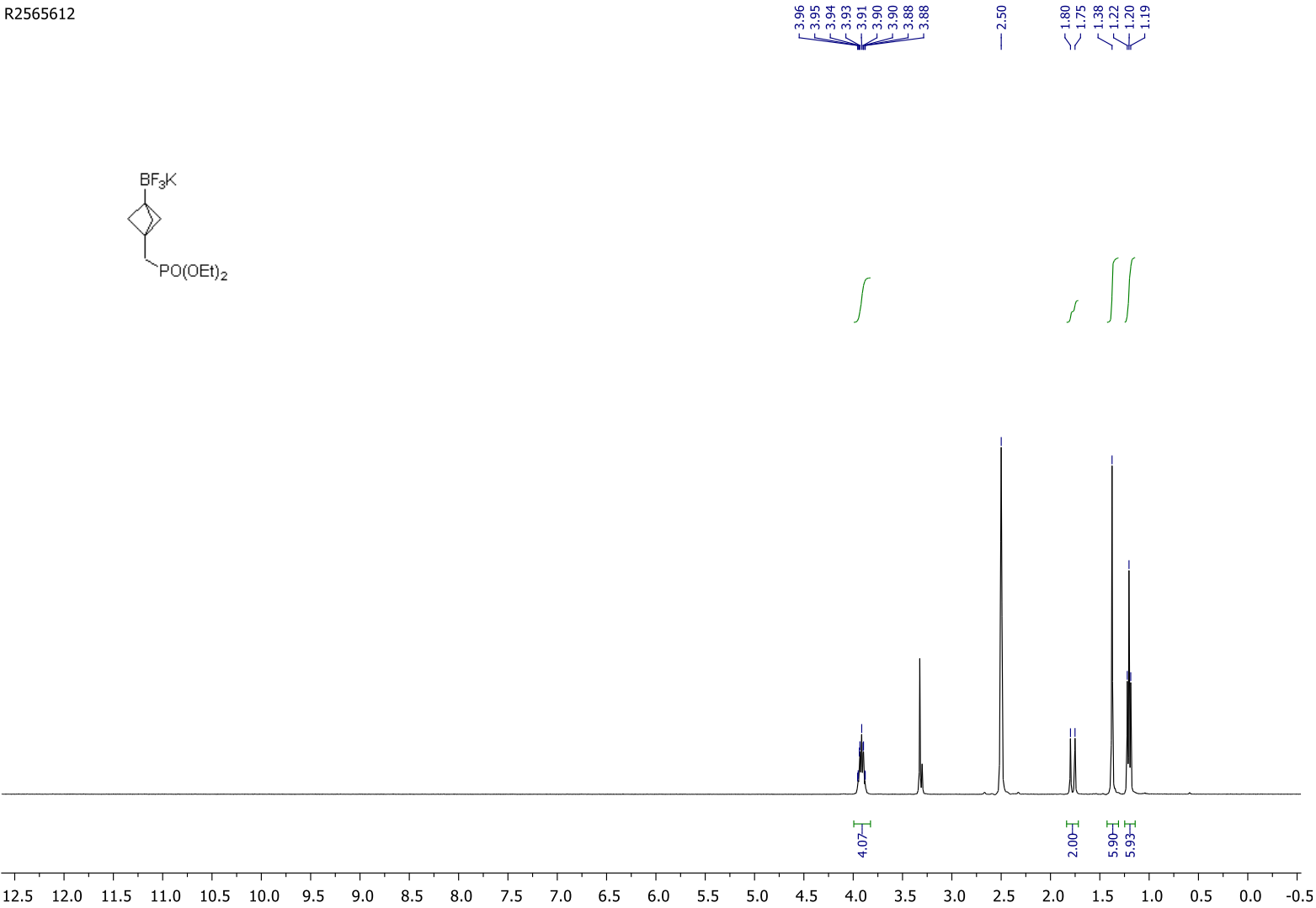
— -142.69



Compound 19b

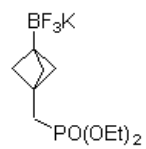
¹H NMR (400 MHz, DMSO-d₆)

R2565612

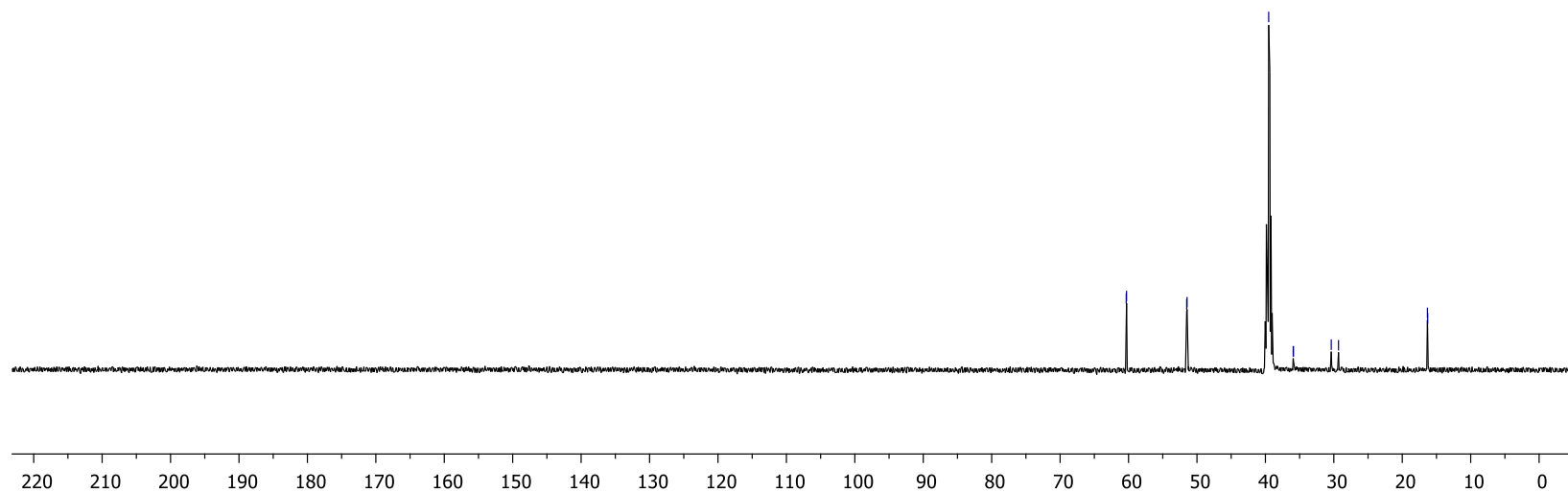


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2565612_C13

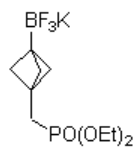


60.34
60.29
51.50
51.45
39.52
35.94
35.90
30.38
29.32
16.32
16.28

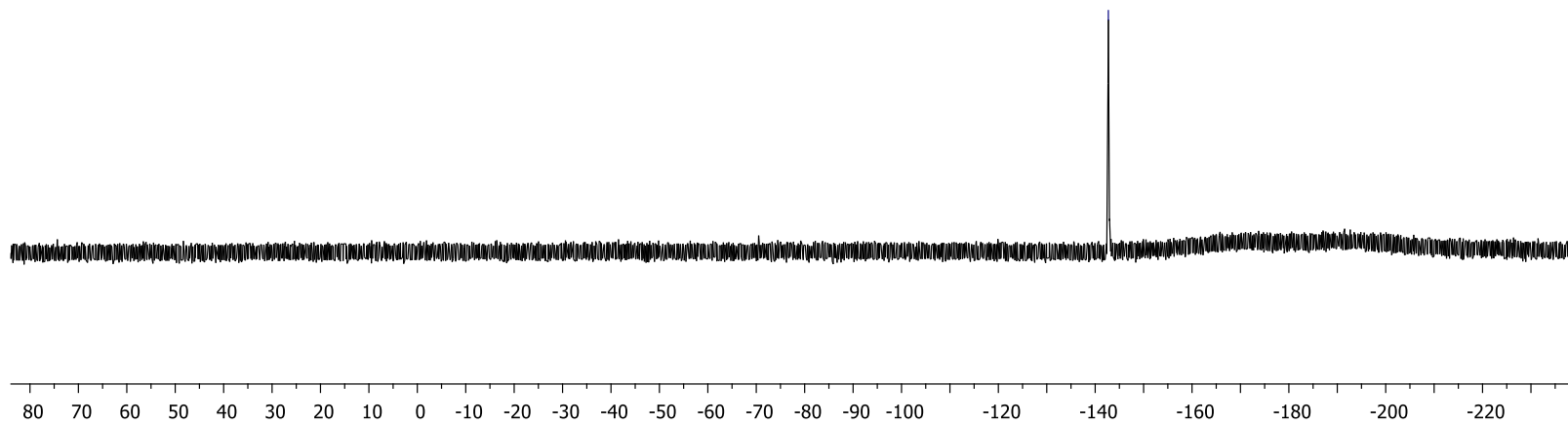


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2565612_F19{H}

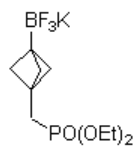


— -142.71

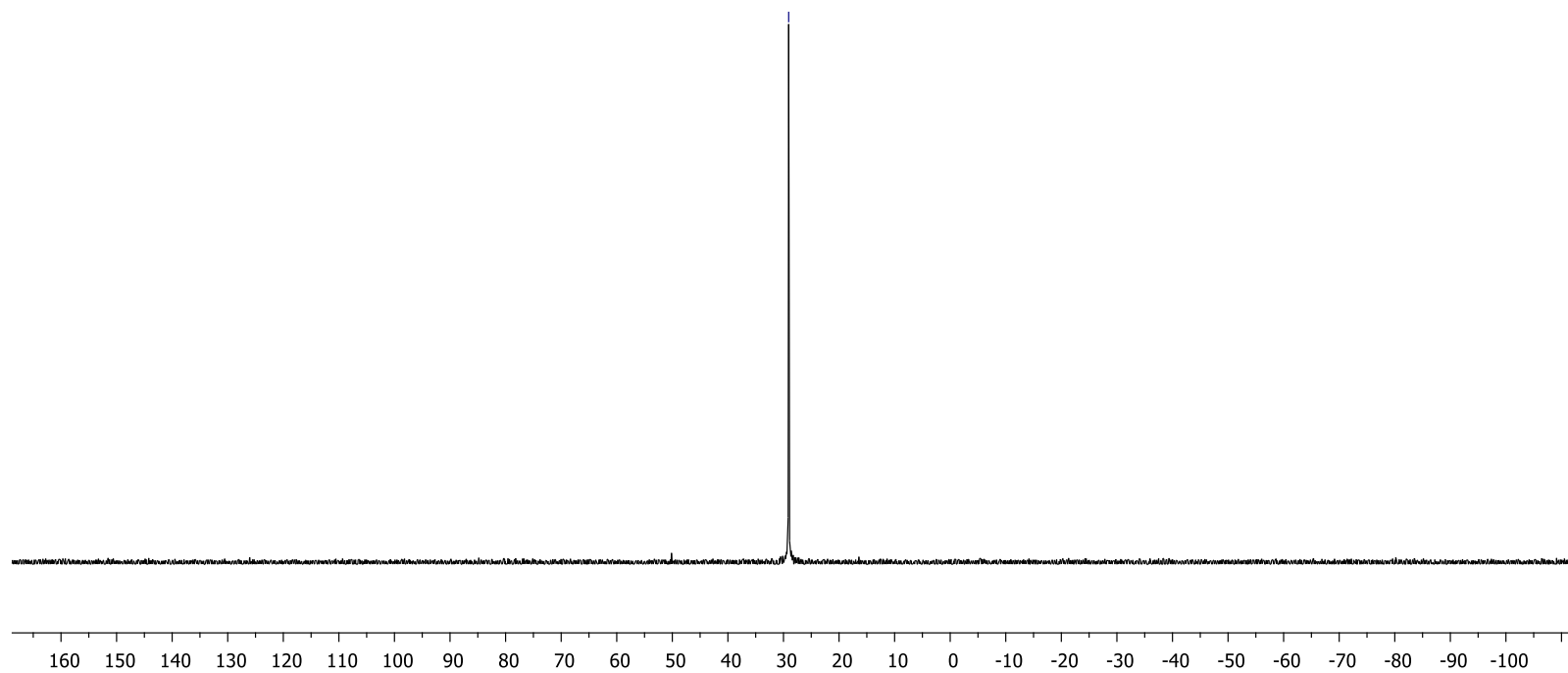


$^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, DMSO- d_6)

R2565612_P31_H1



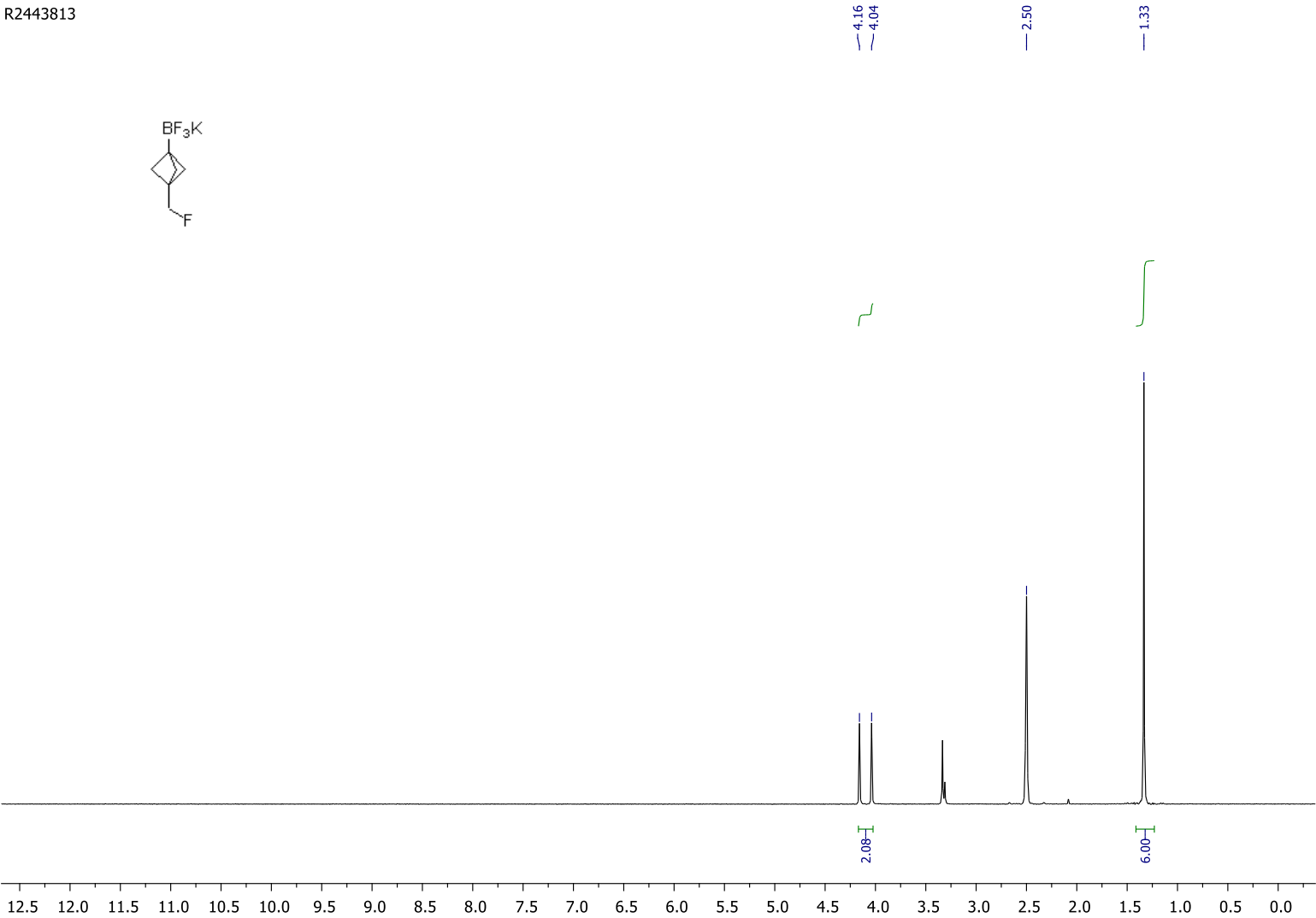
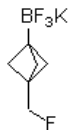
29.06



Compound 21b

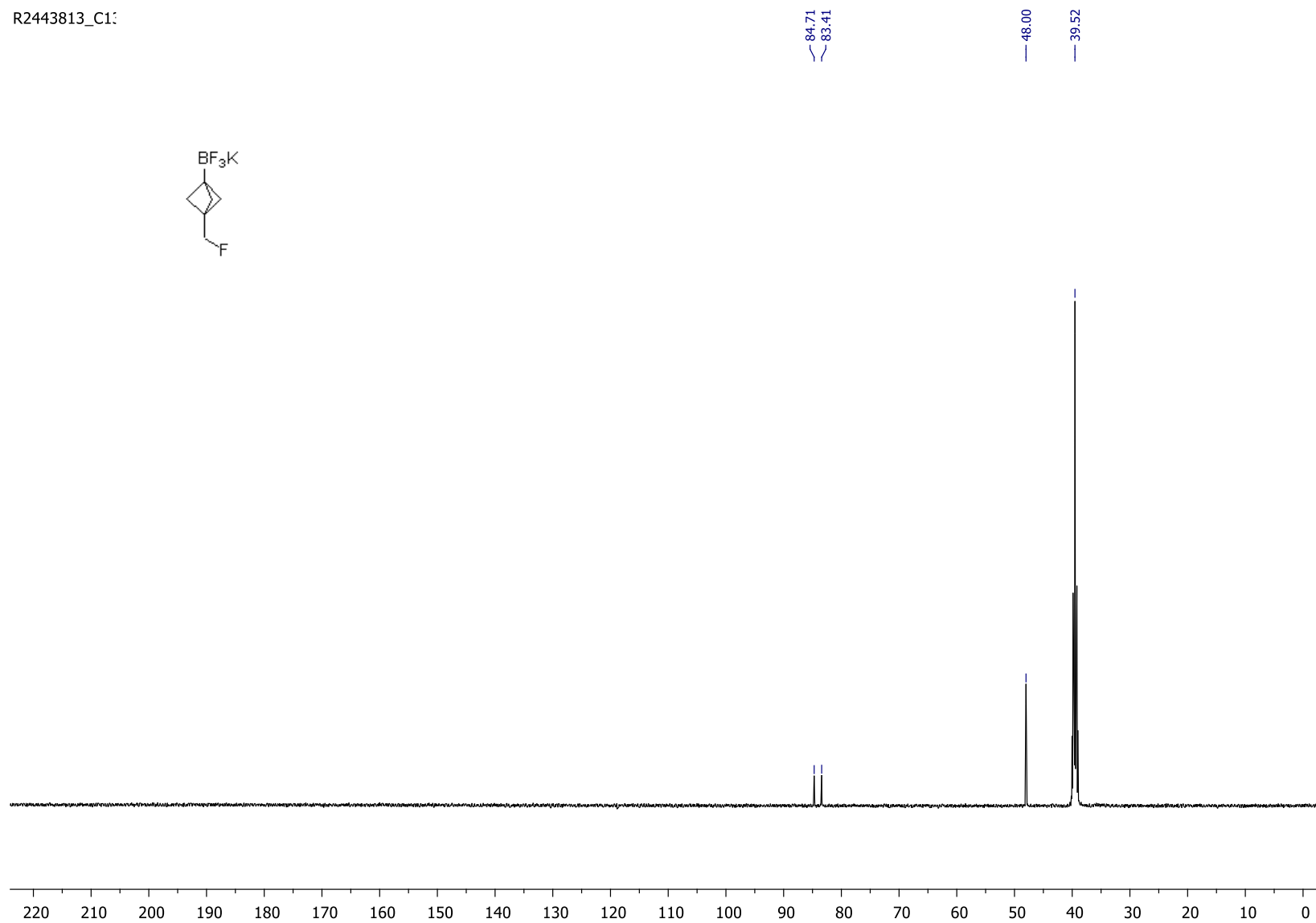
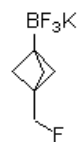
¹H NMR (400 MHz, DMSO-d₆)

R2443813



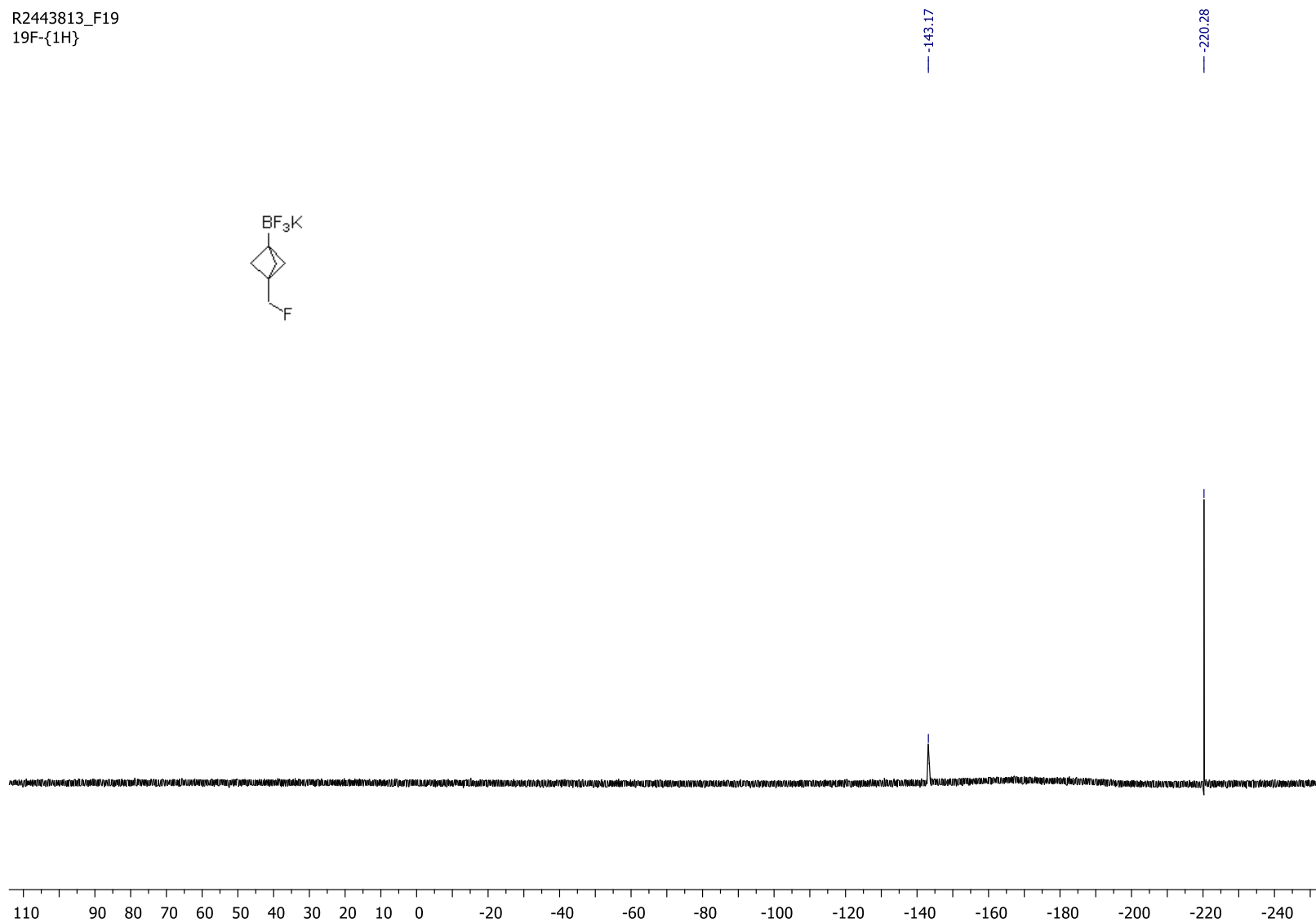
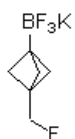
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2443813_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

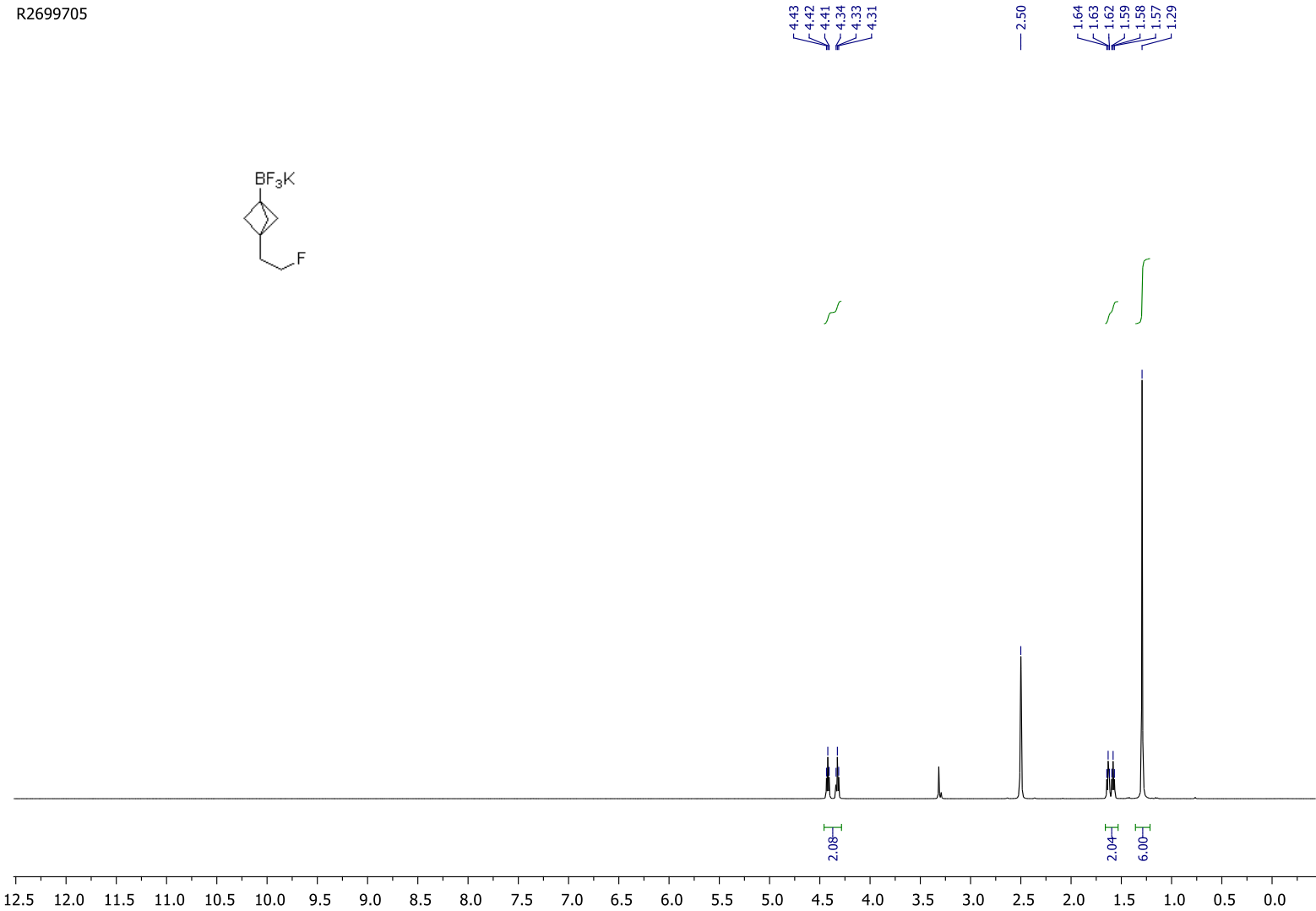
R2443813_F19
 $^{19}\text{F}\{^1\text{H}\}$



Compound 22b

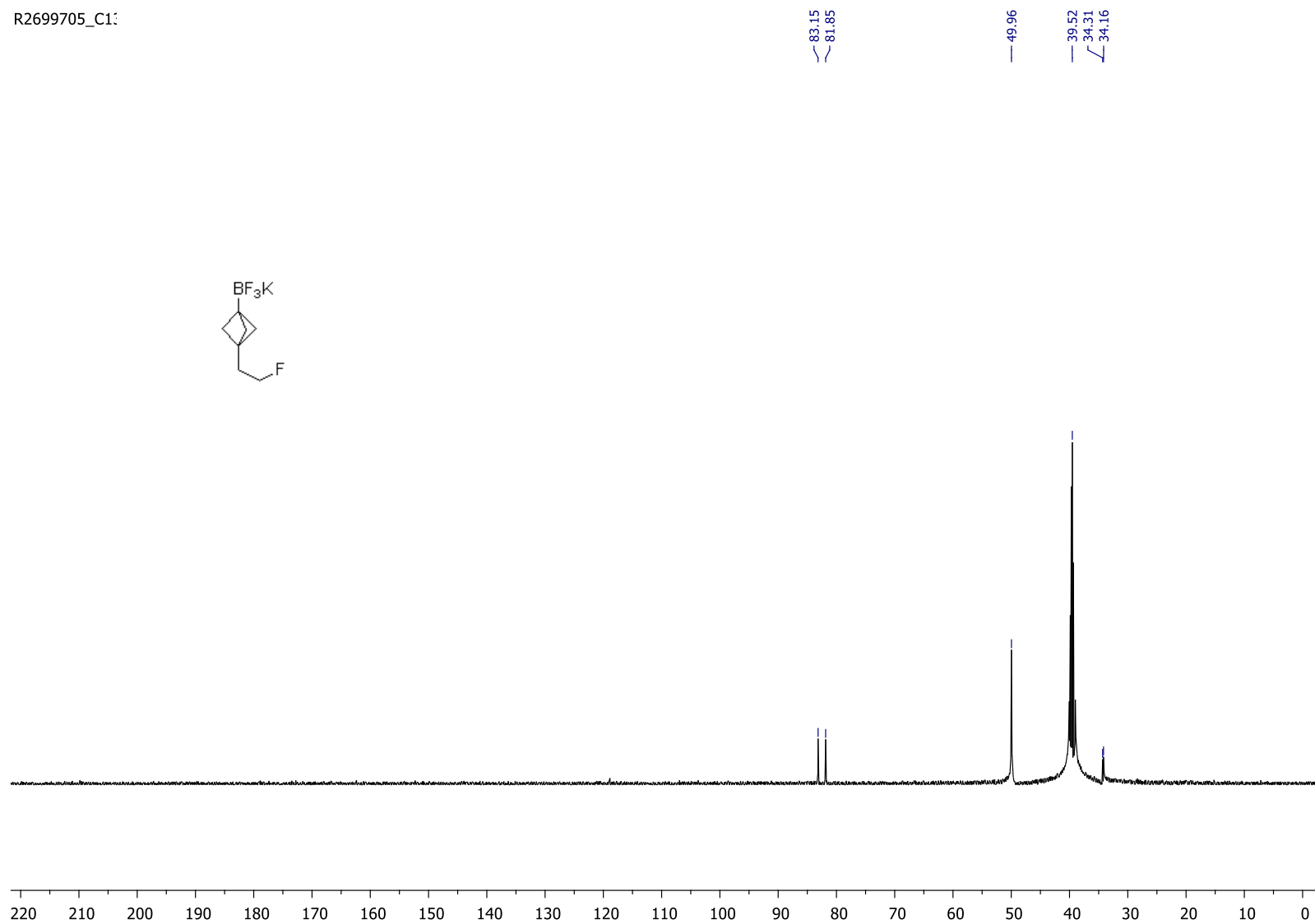
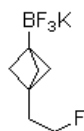
R2699705

¹H NMR (500 MHz, DMSO-d₆)



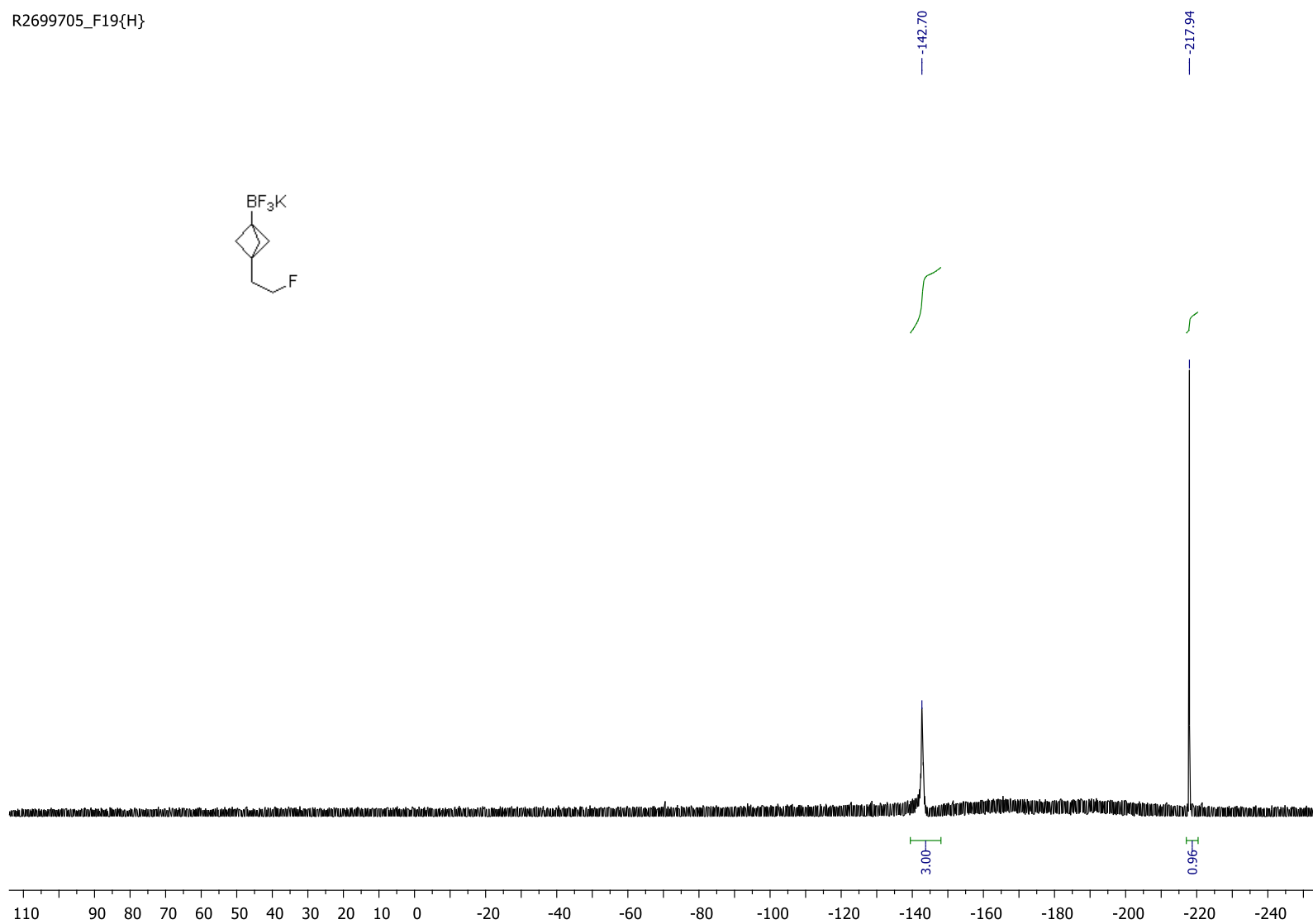
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2699705_C1:



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

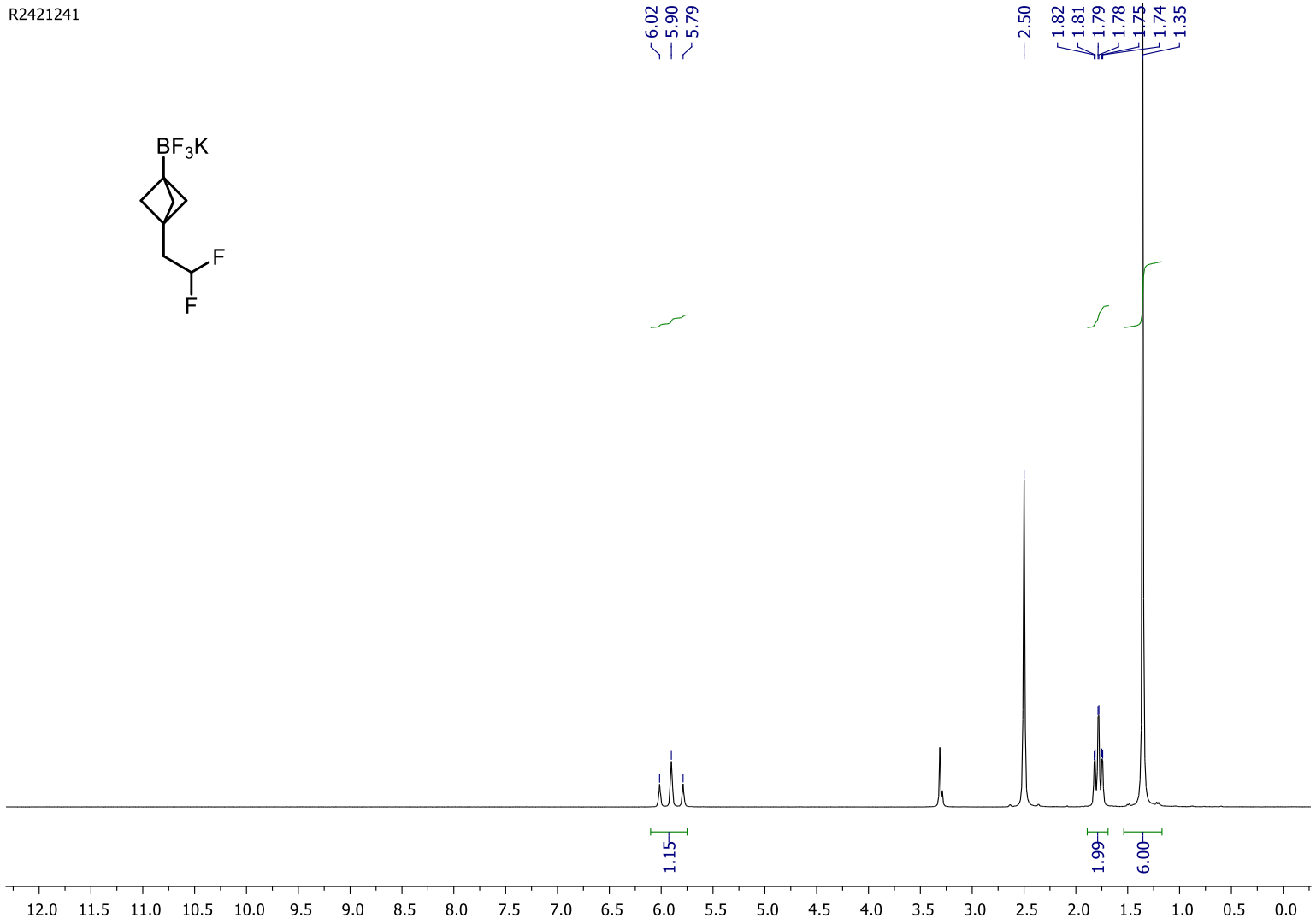
R2699705_F19{H}



Compound 24b

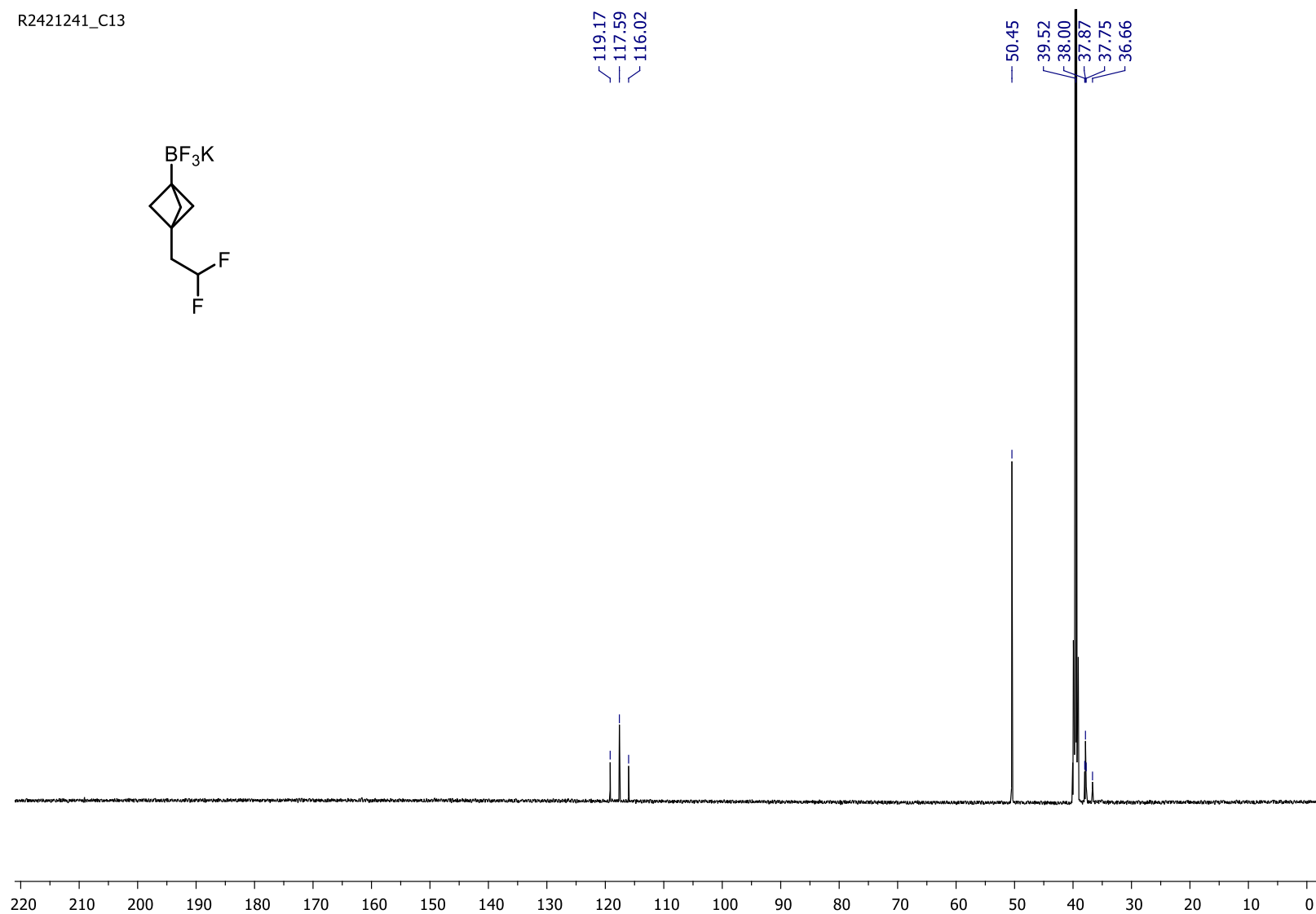
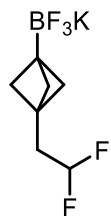
R2421241

¹H NMR (500 MHz, DMSO-d₆)



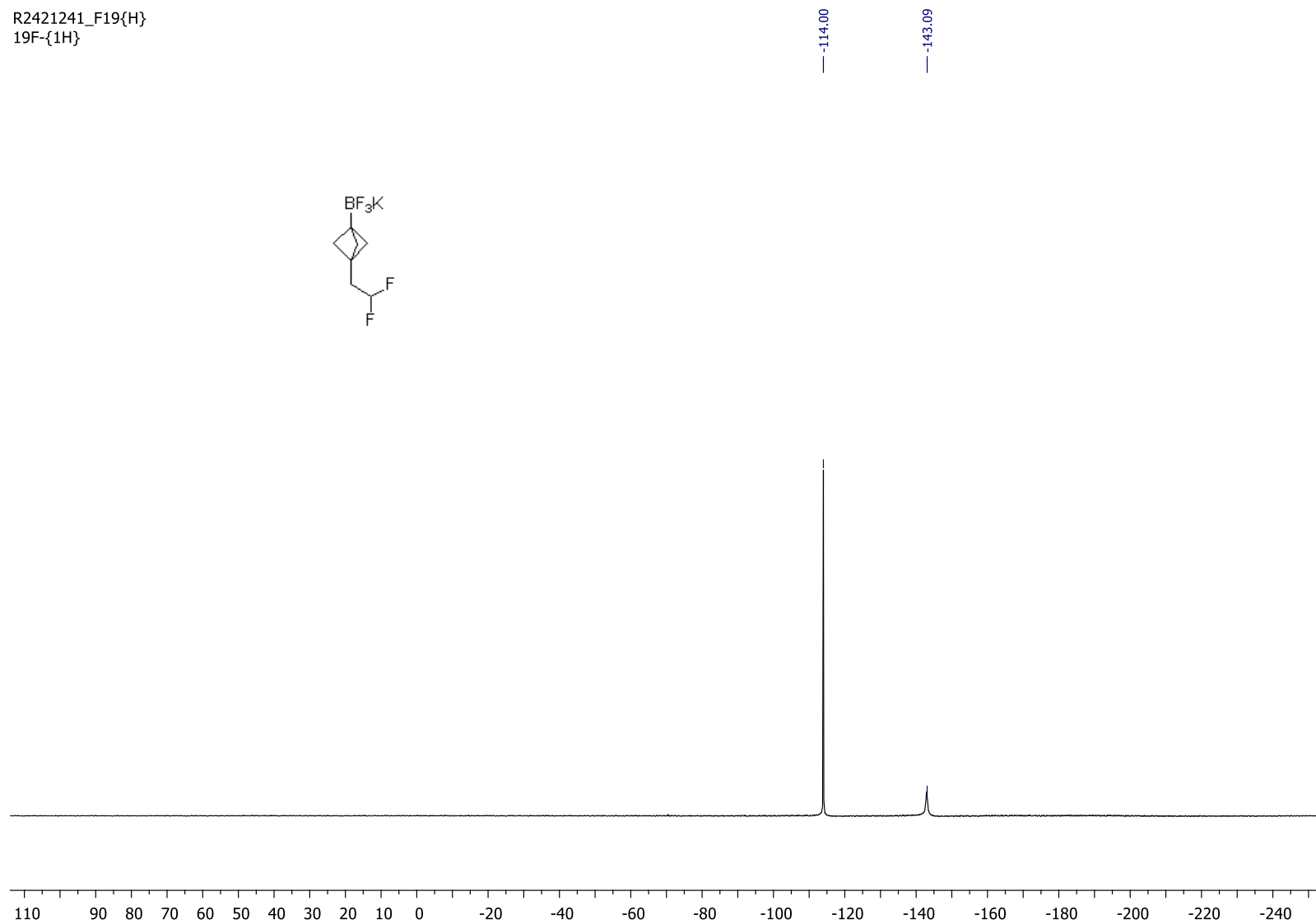
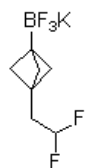
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2421241_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

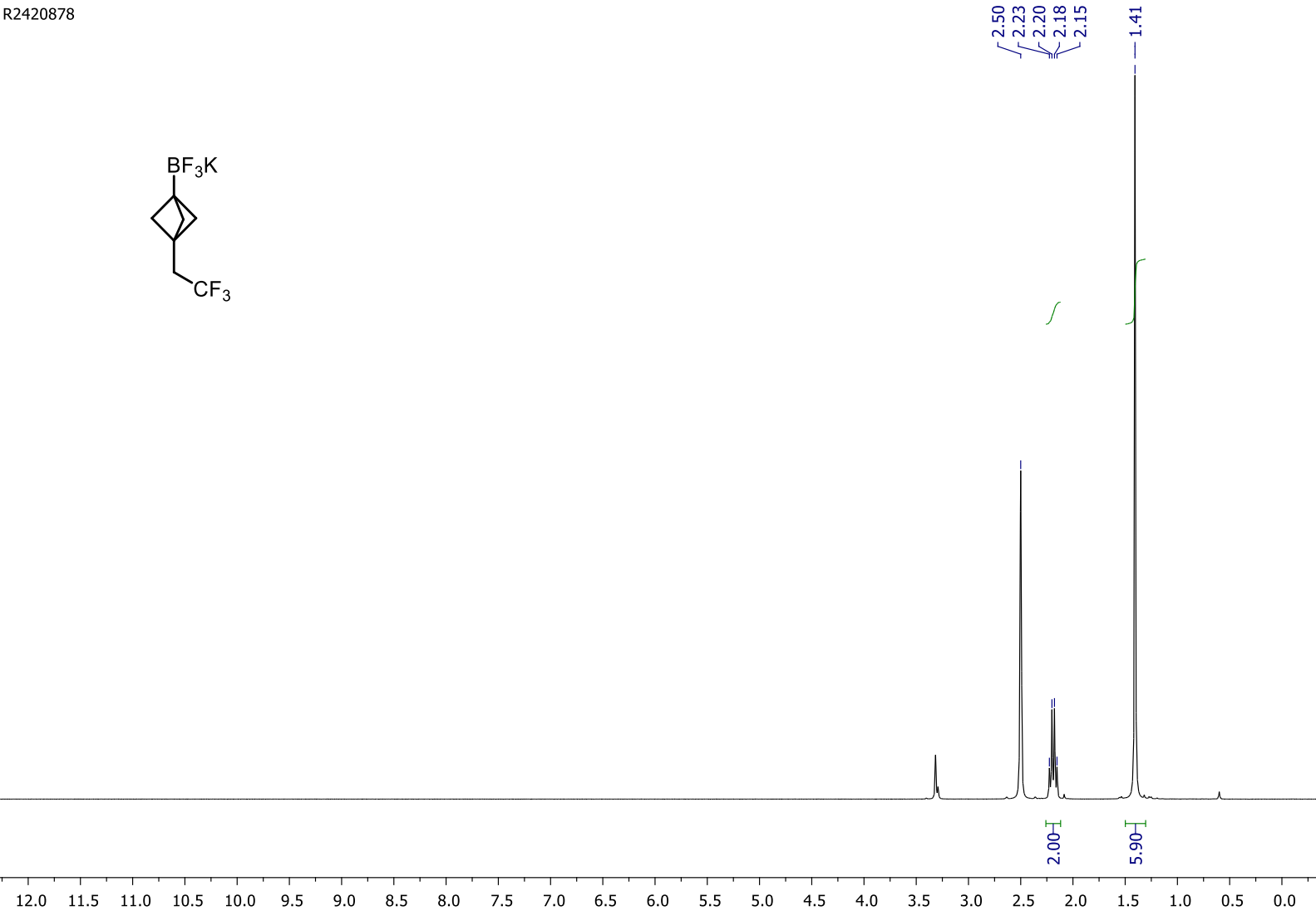
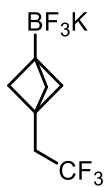
R2421241_F19{H}
19F-{1H}



Compound 25b

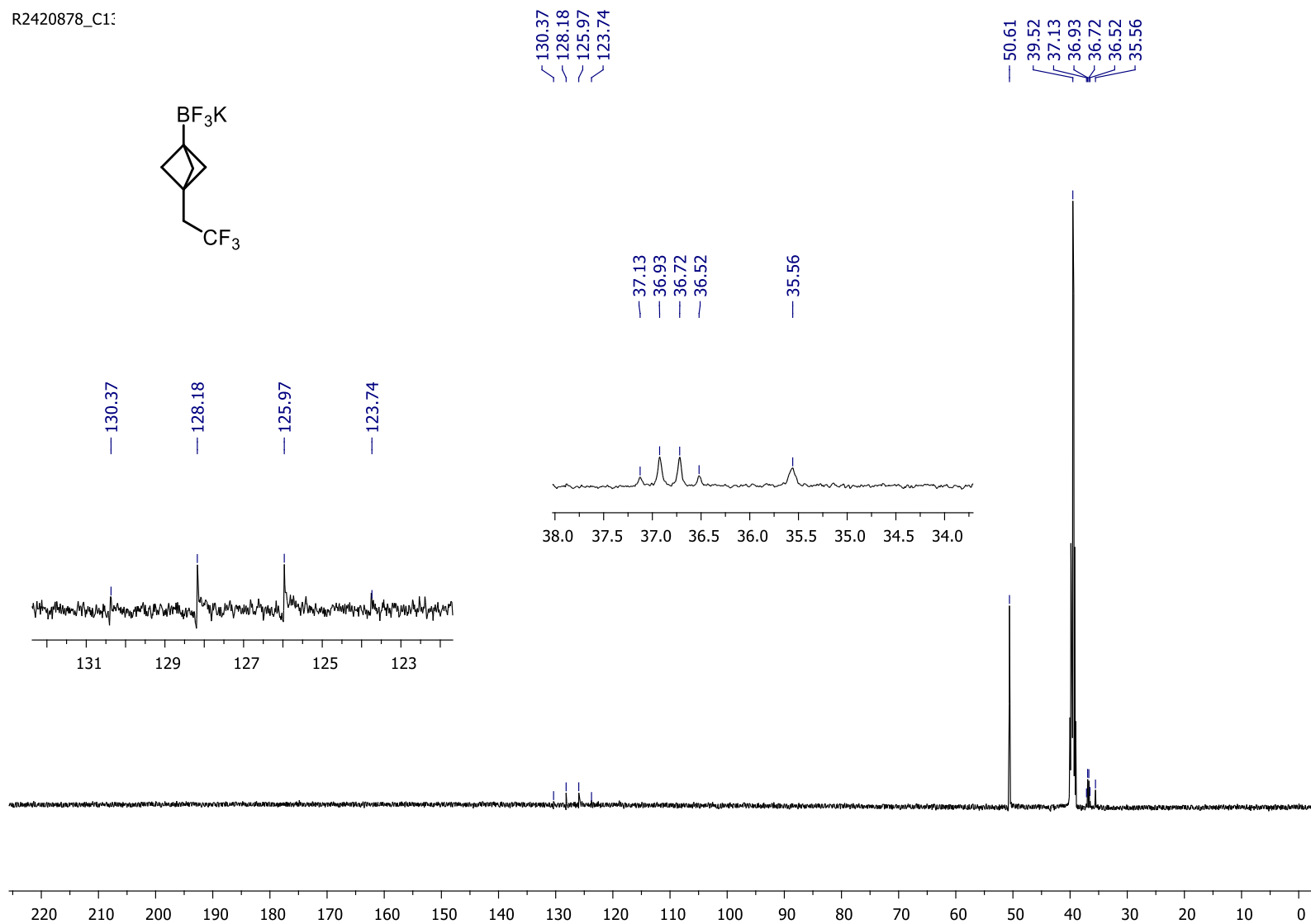
¹H NMR (500 MHz, DMSO-d₆)

R2420878



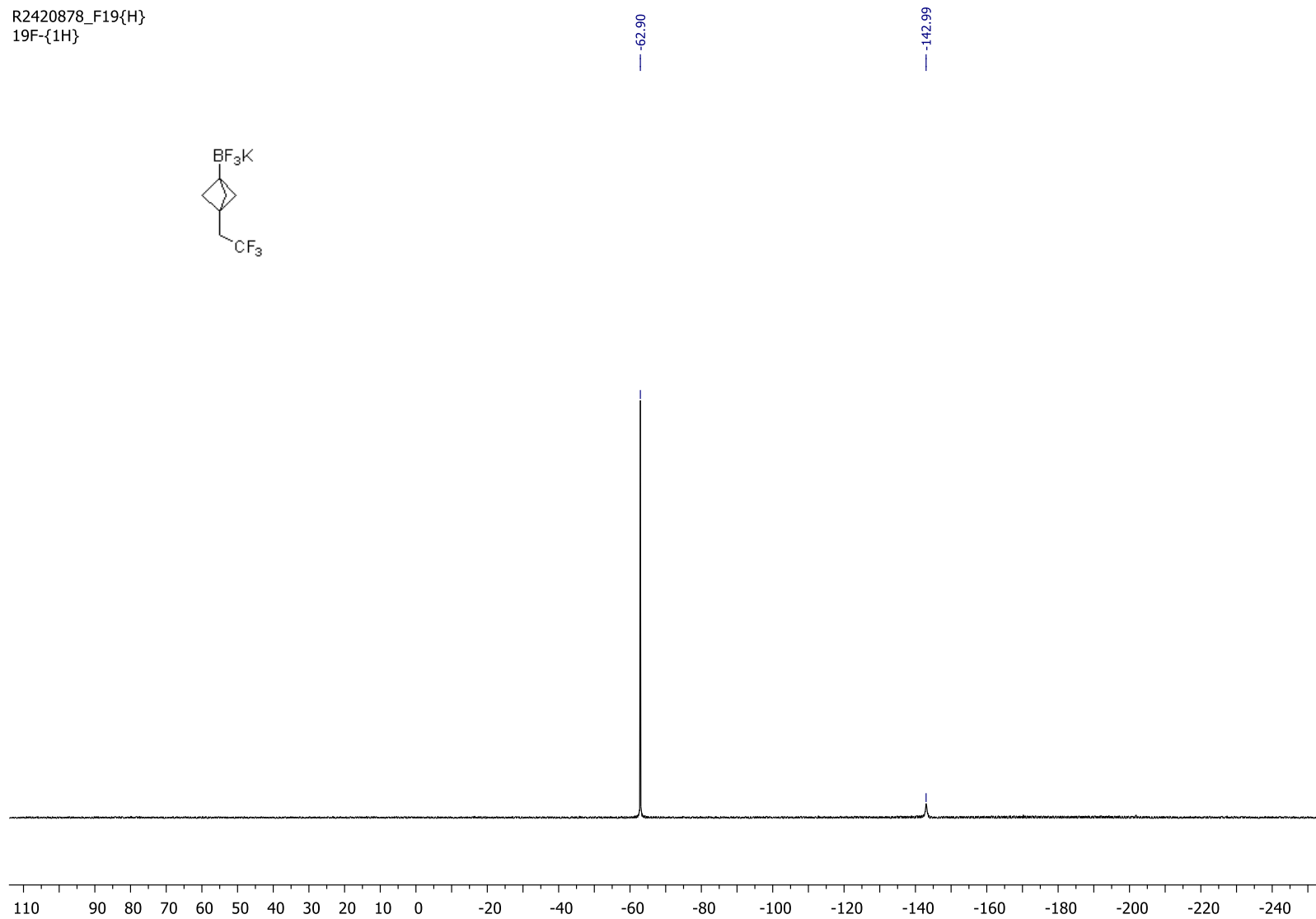
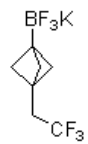
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2420878_C1:



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

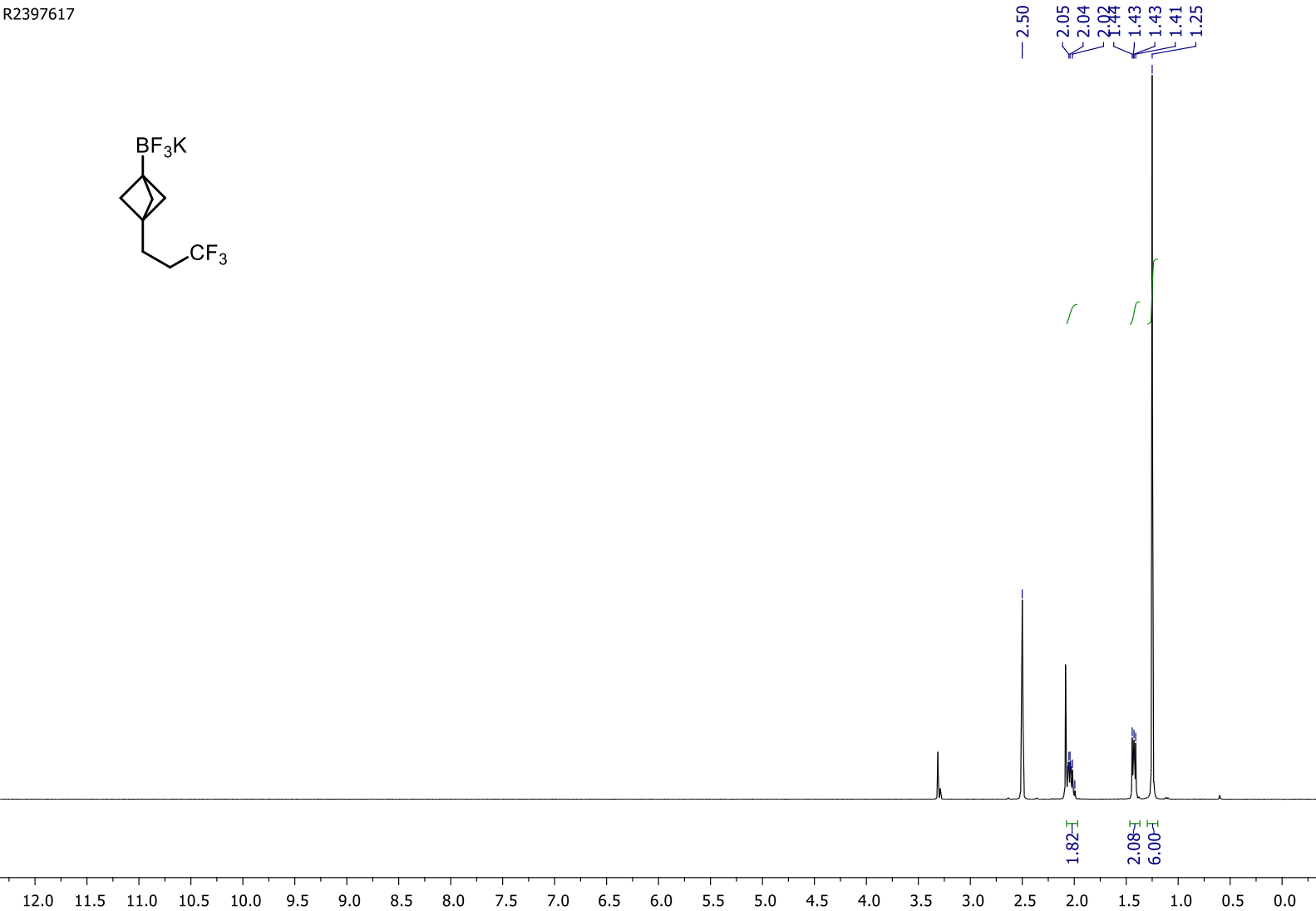
R2420878_F19{H}
 $^{19}\text{F}\{^1\text{H}\}$



Compound 26b

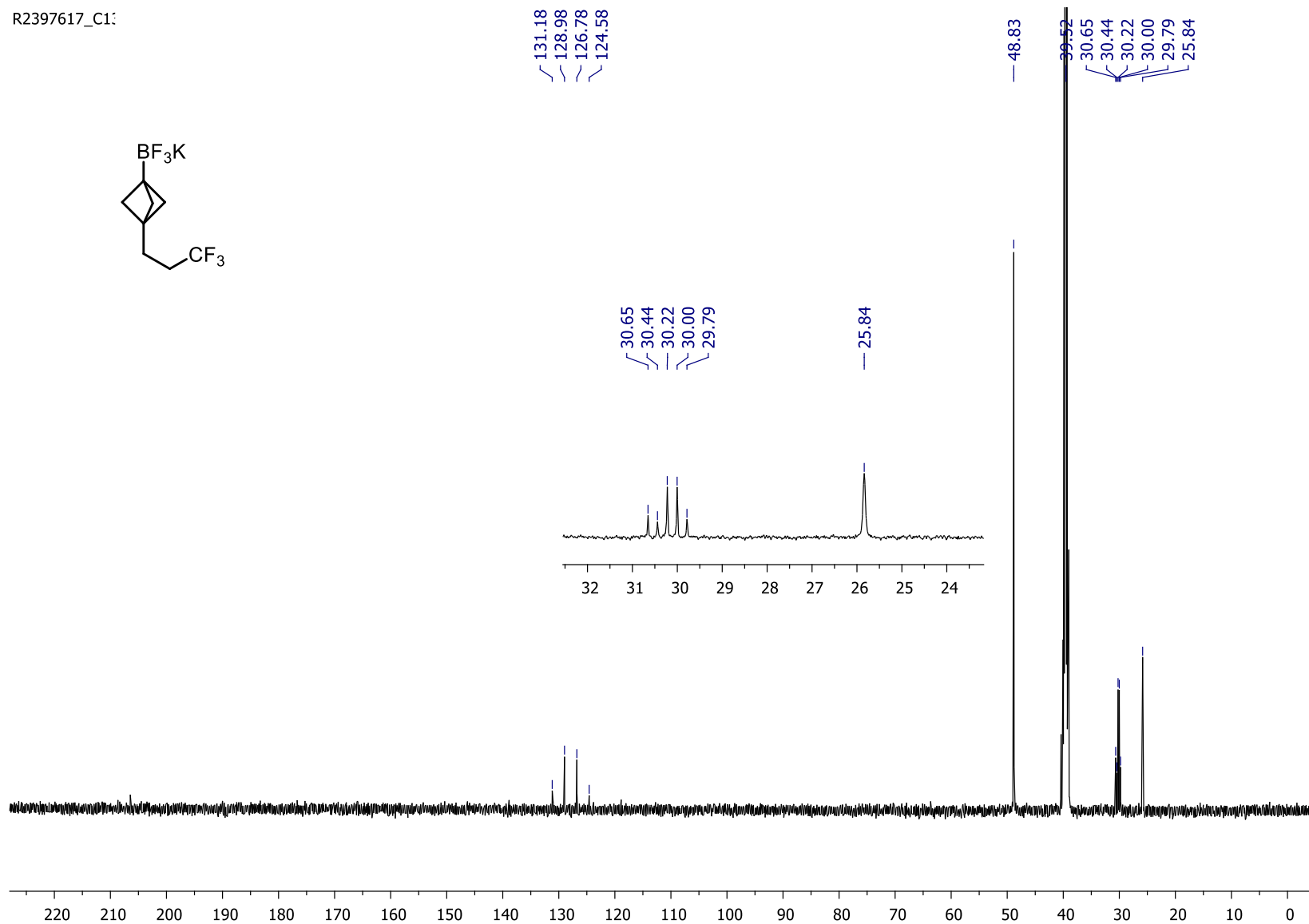
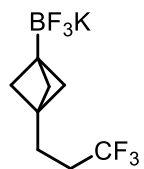
¹H NMR (500 MHz, DMSO-d₆)

R2397617



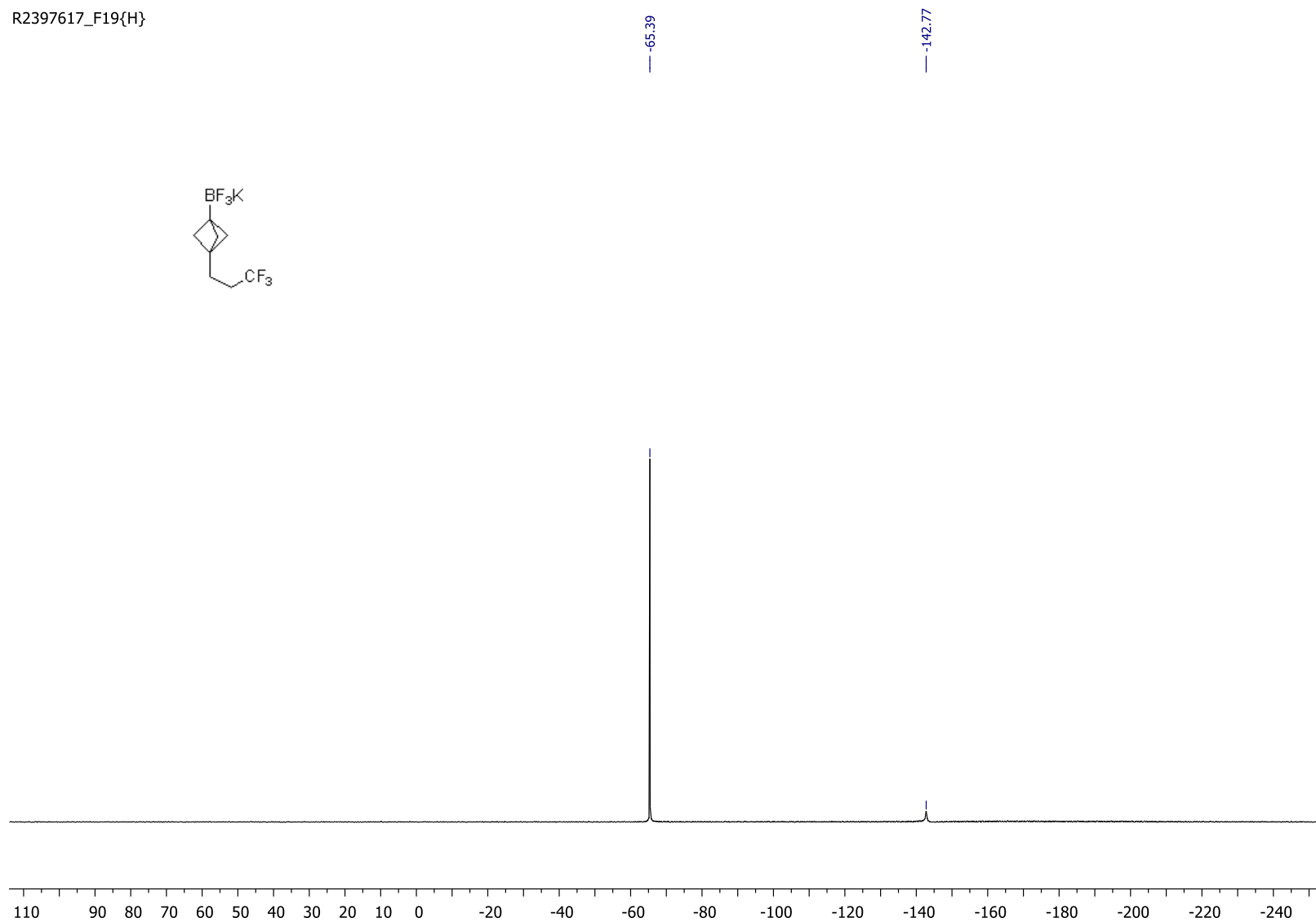
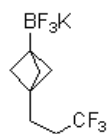
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2397617_C1:



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

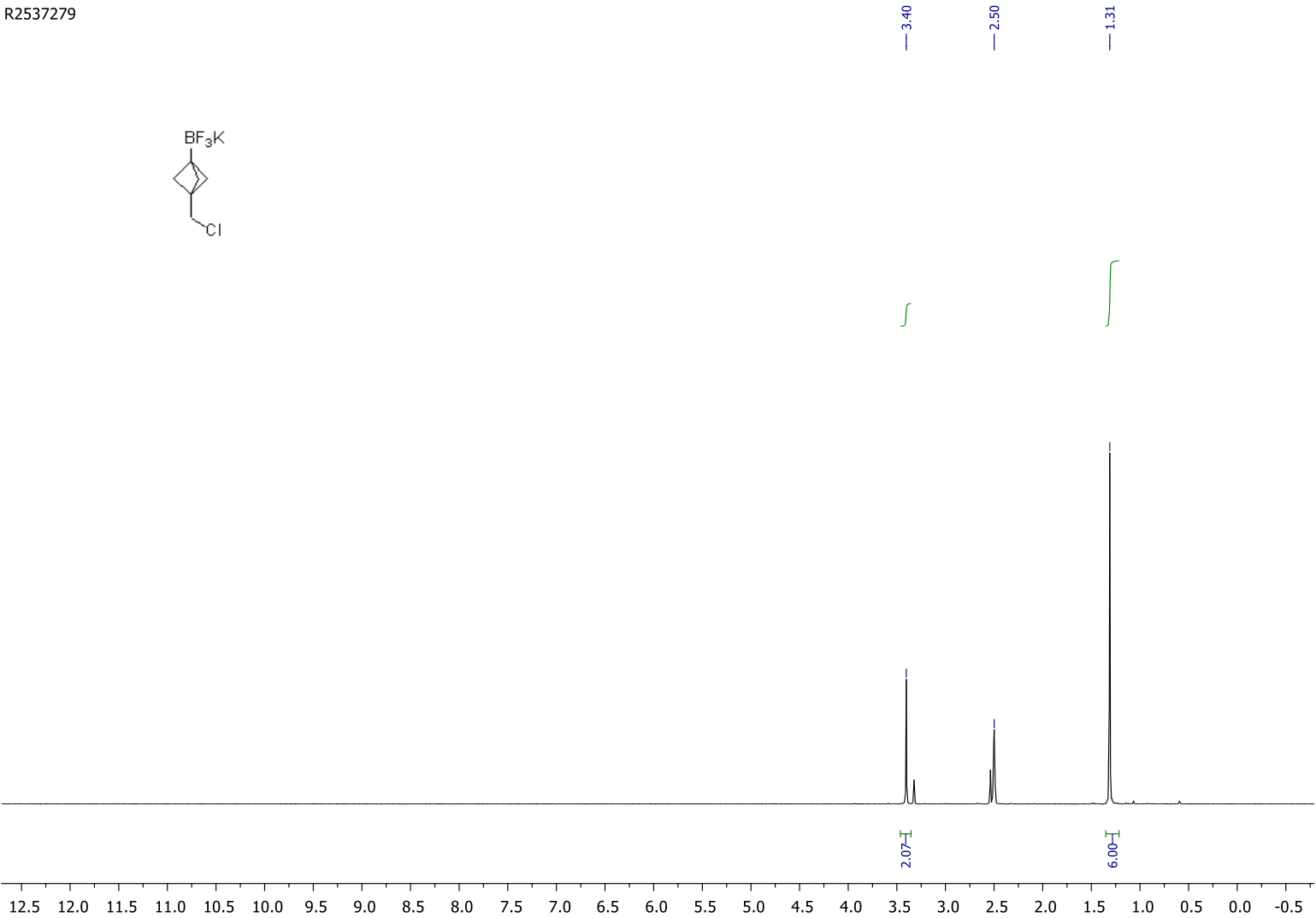
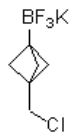
R2397617_F19{H}



Compound 34b

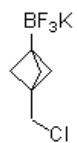
¹H NMR (400 MHz, DMSO-d₆)

R2537279

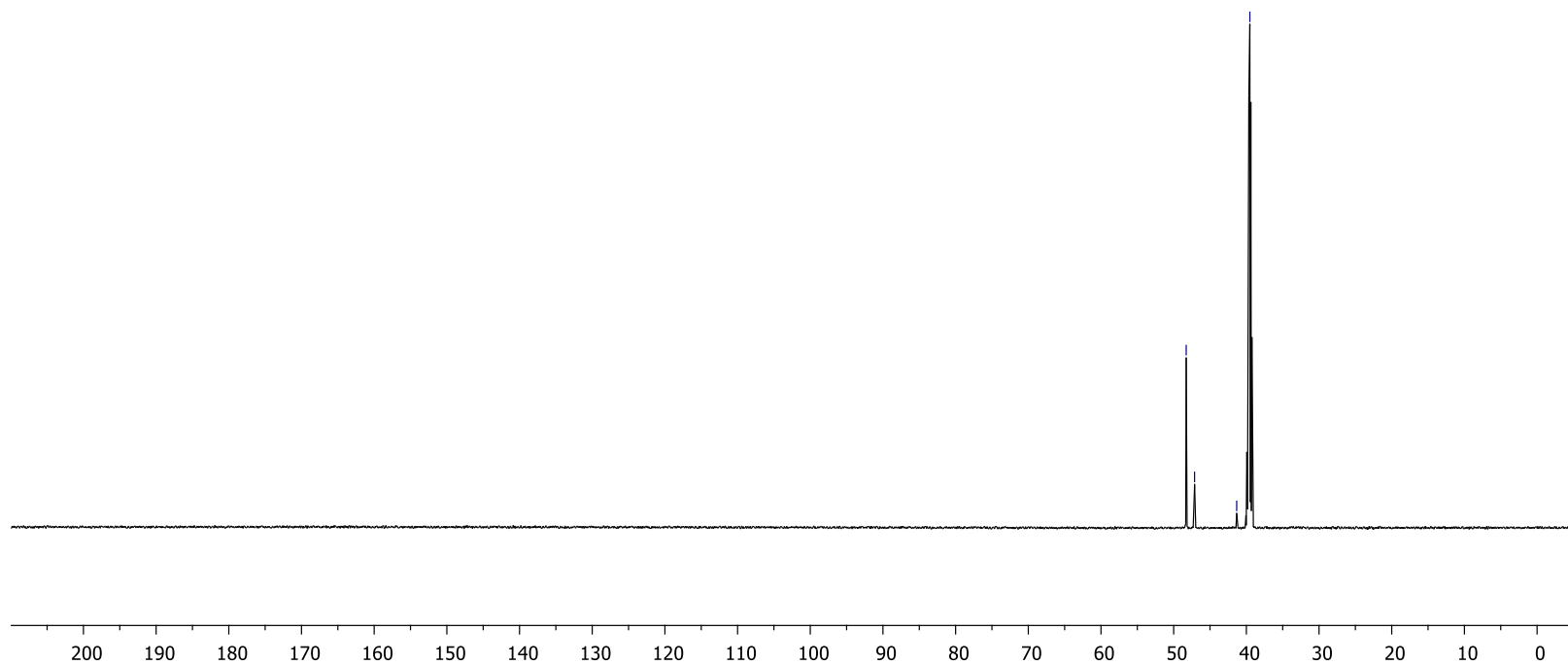


$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2537279_C13

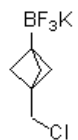


48.28
47.12
41.33
39.52

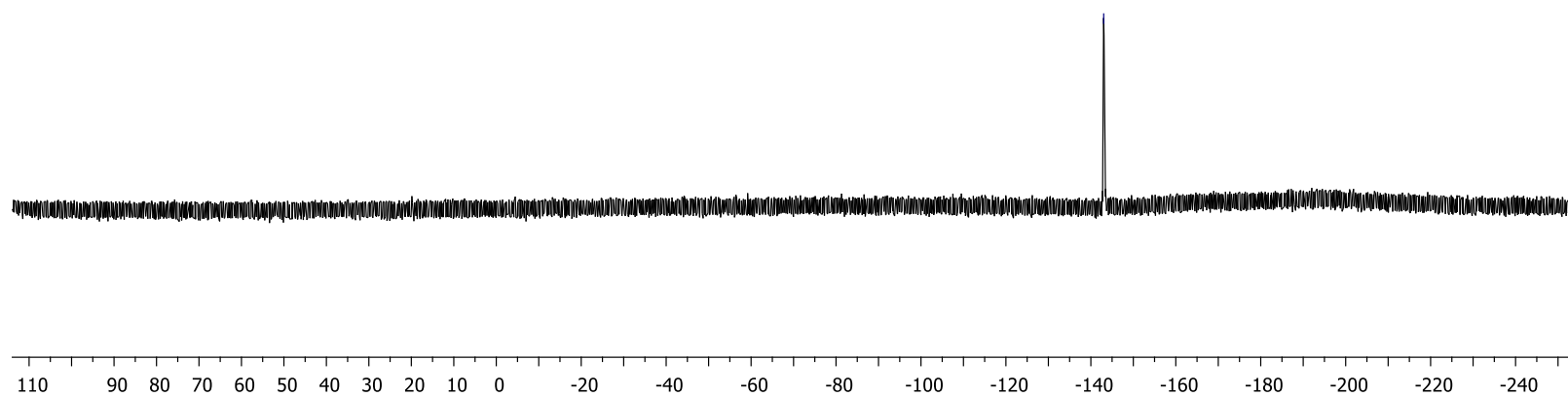


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2537279_F19{H}
19F-{1H}



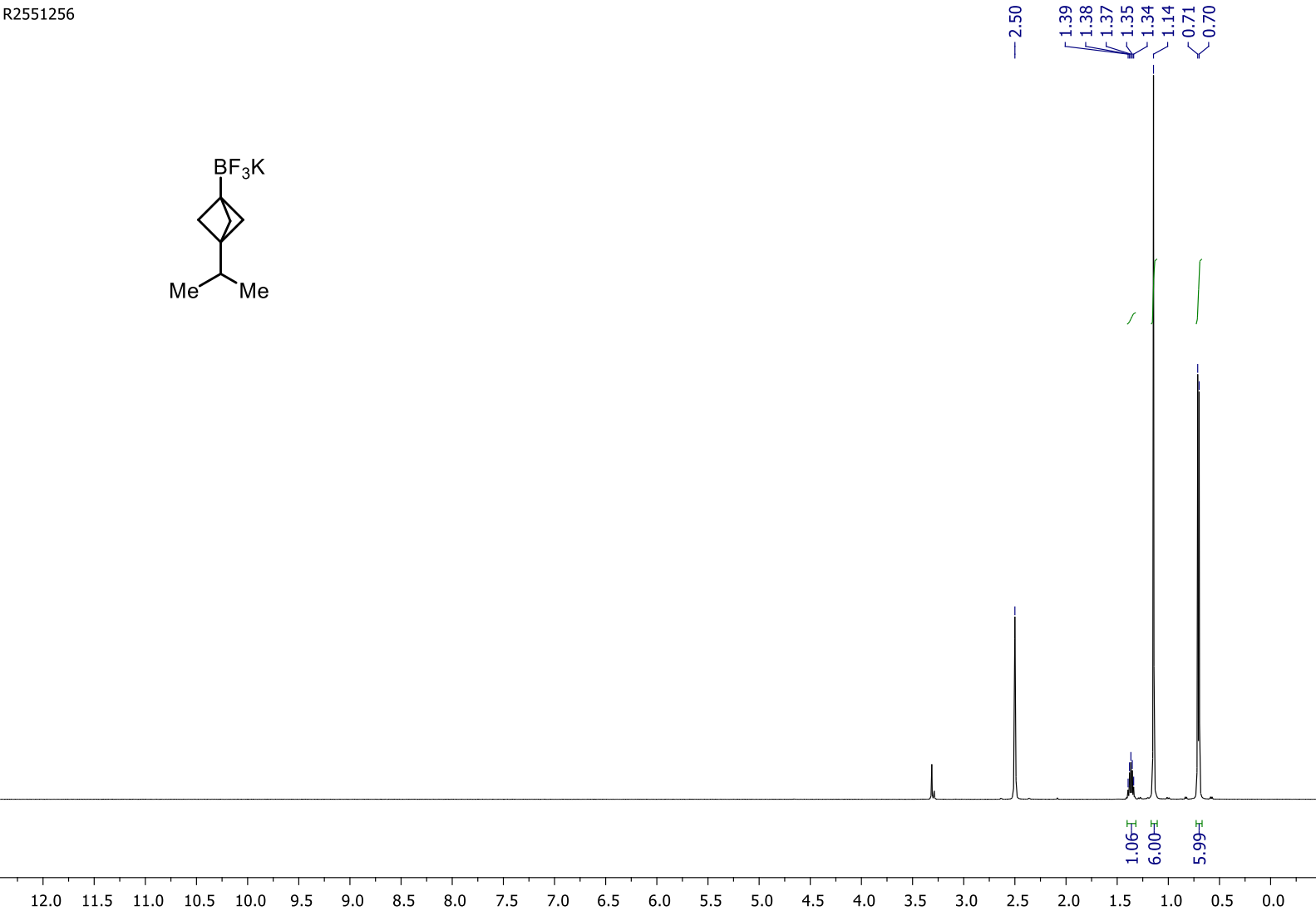
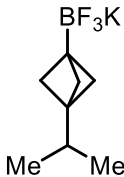
— -143.02



Compound 48b

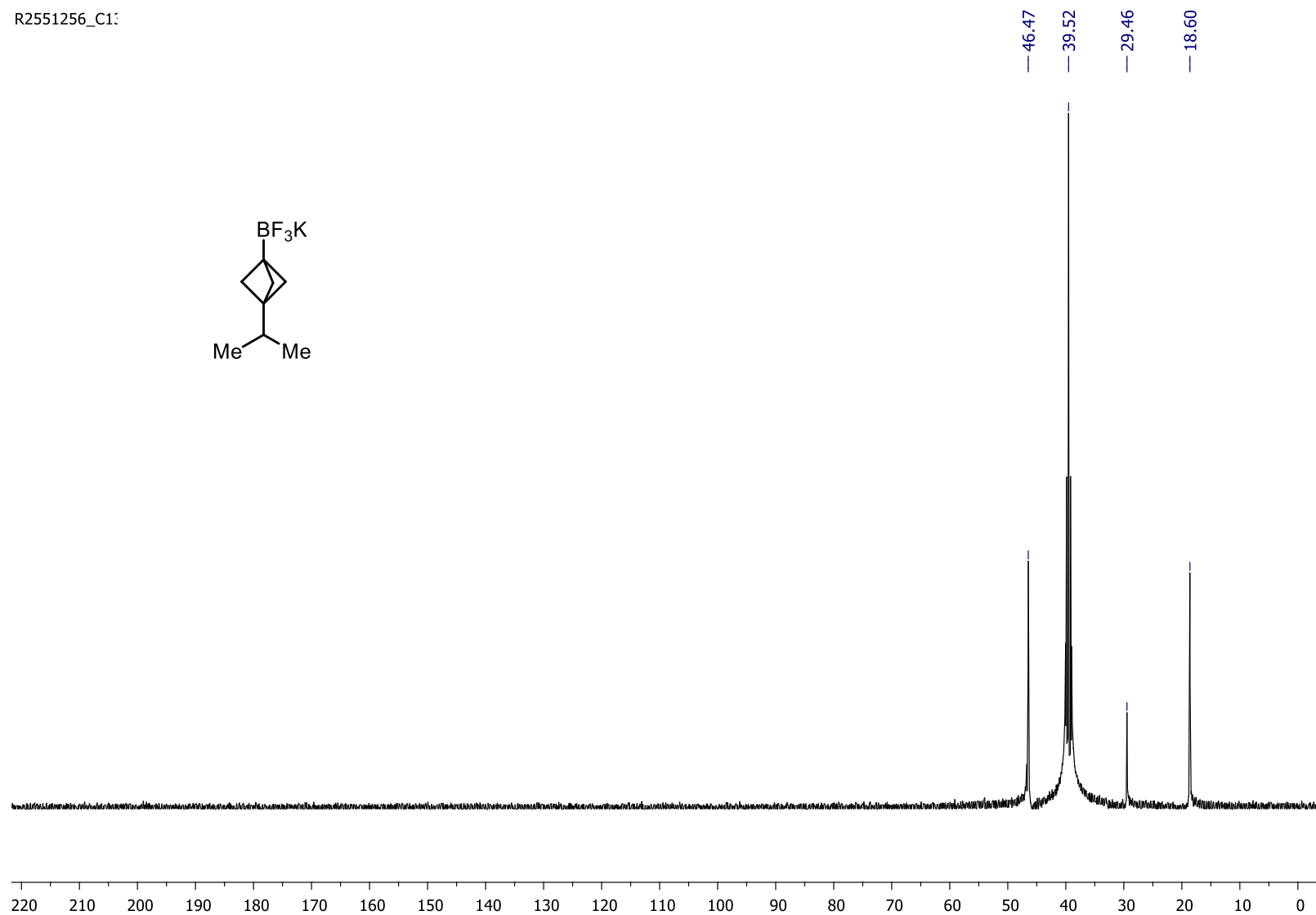
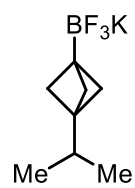
¹H NMR (500 MHz, DMSO-d₆)

R2551256



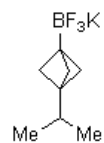
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2551256_C1:

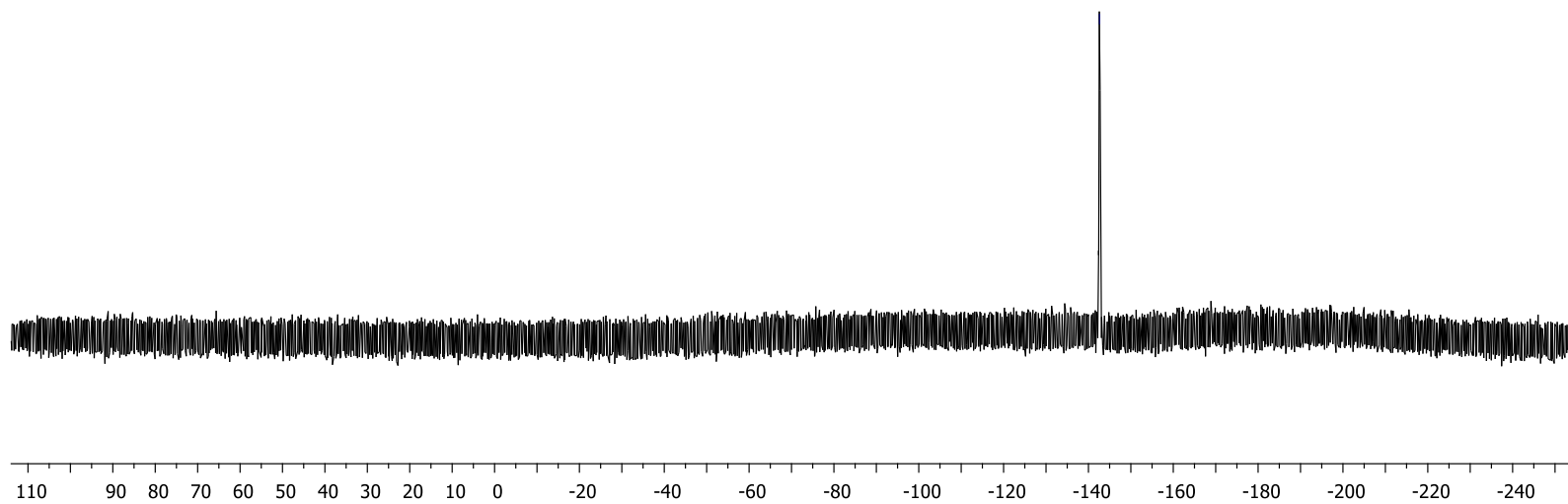


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2551256_F19
 $^{19}\text{F}\{^1\text{H}\}$



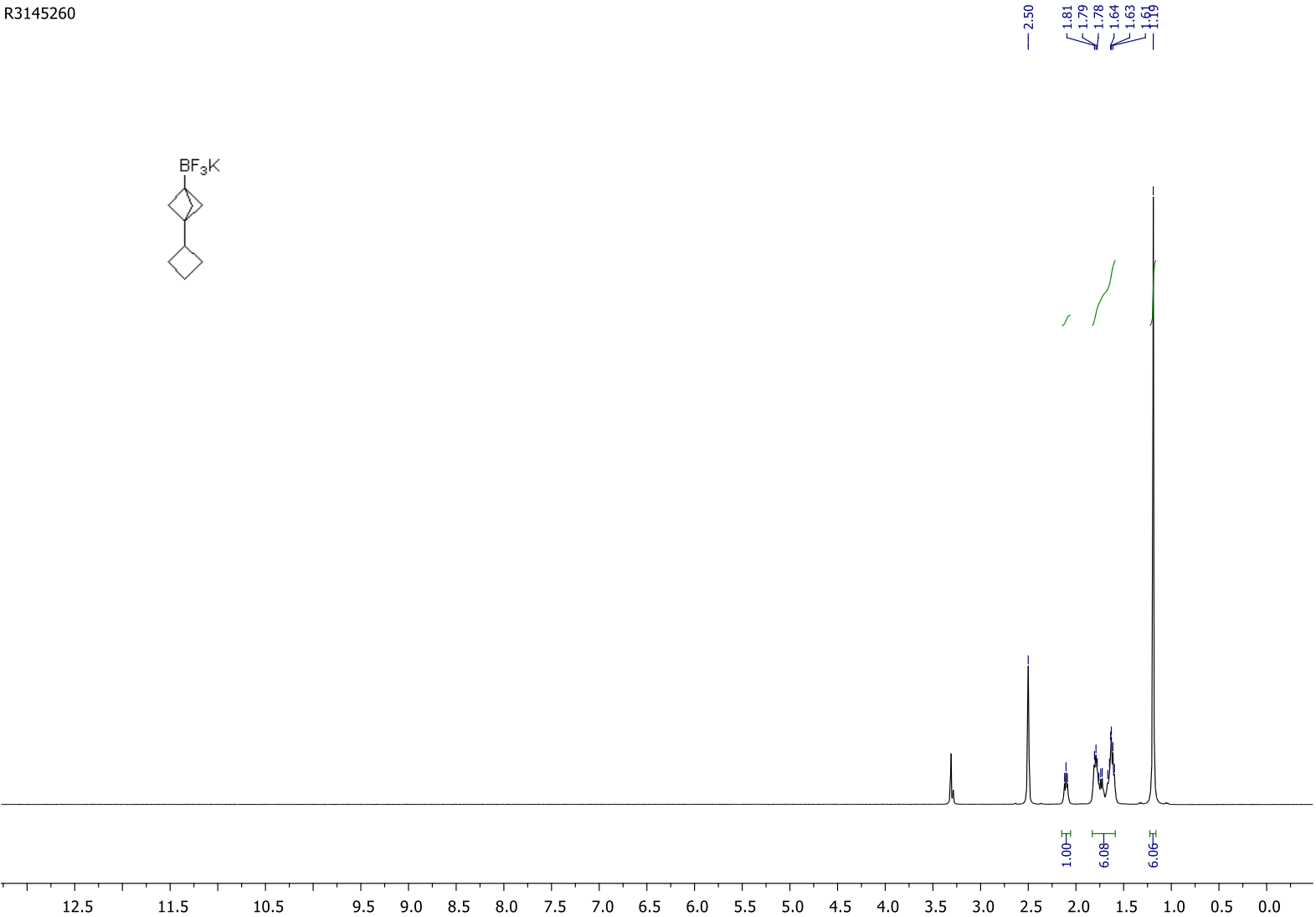
— -142.61



Compound 51b

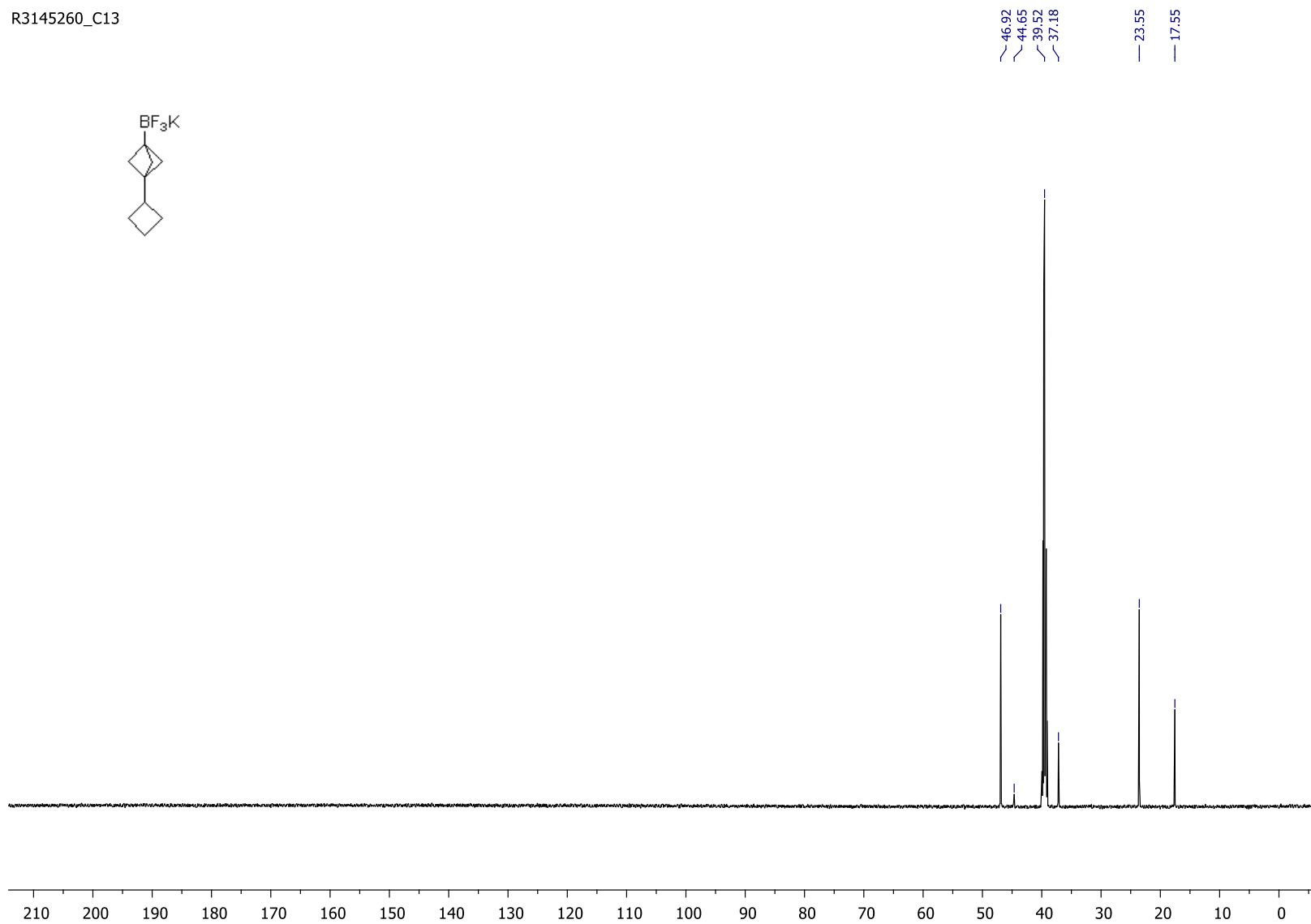
R3145260

¹H NMR (500 MHz, DMSO-d₆)



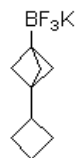
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R3145260_C13

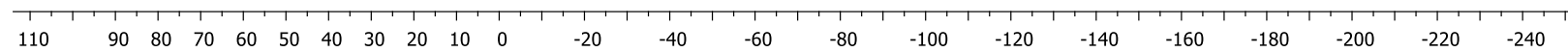


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R1548260_F19{H}



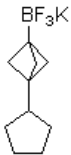
-61.80



Compound 52b

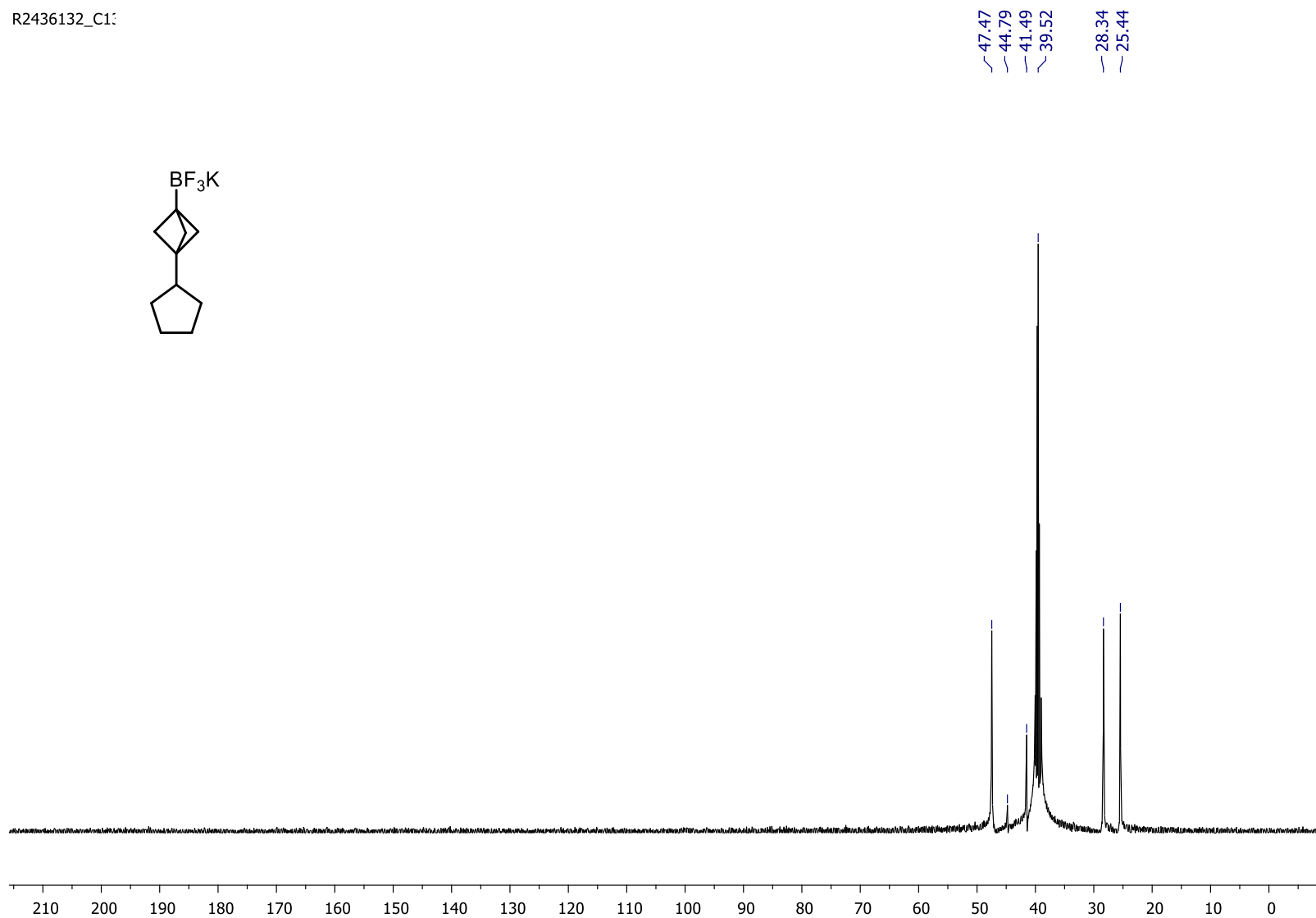
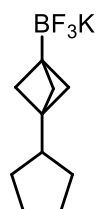
¹H NMR (500 MHz, DMSO-d₆)

R2436132



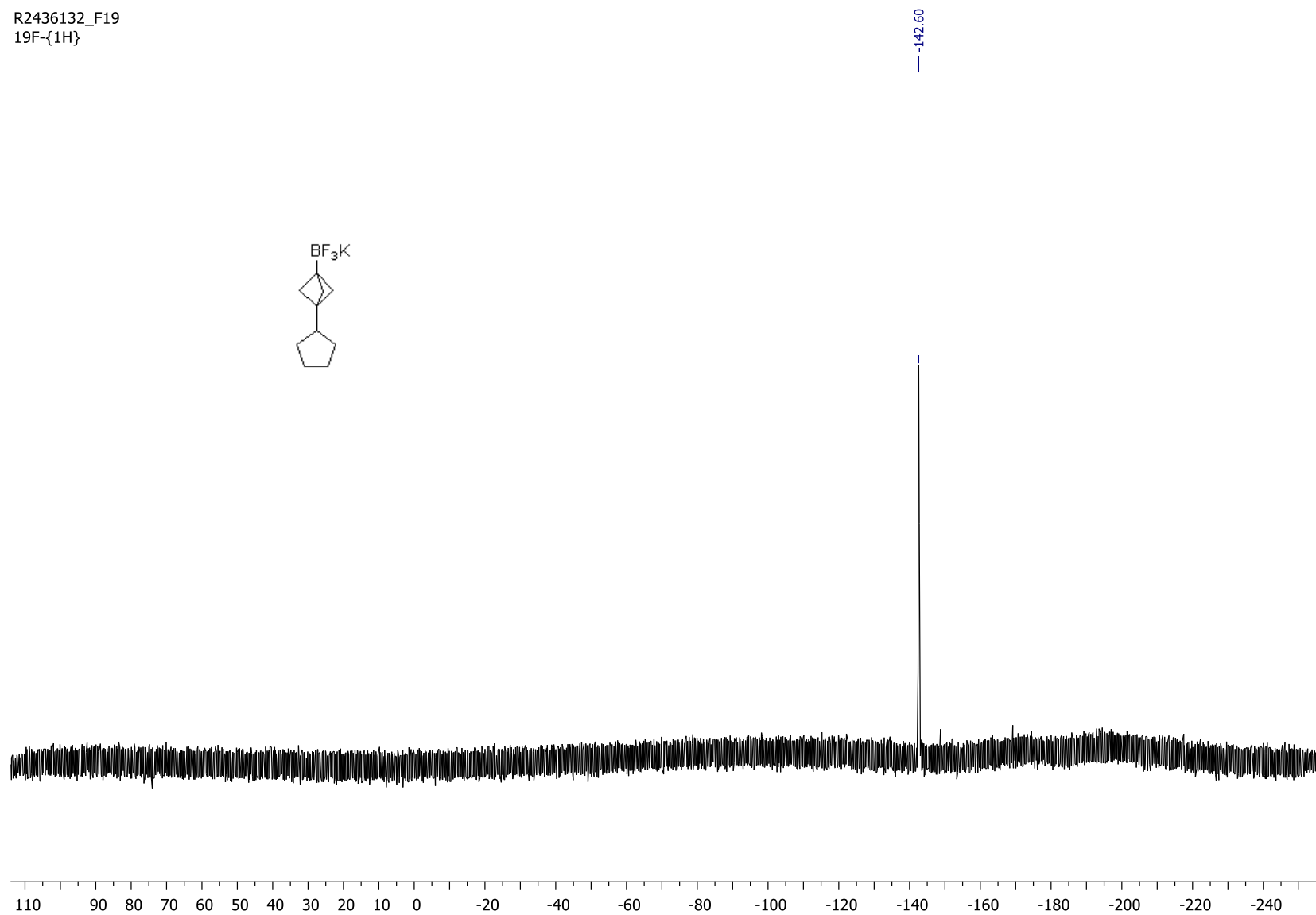
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2436132_C1:



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

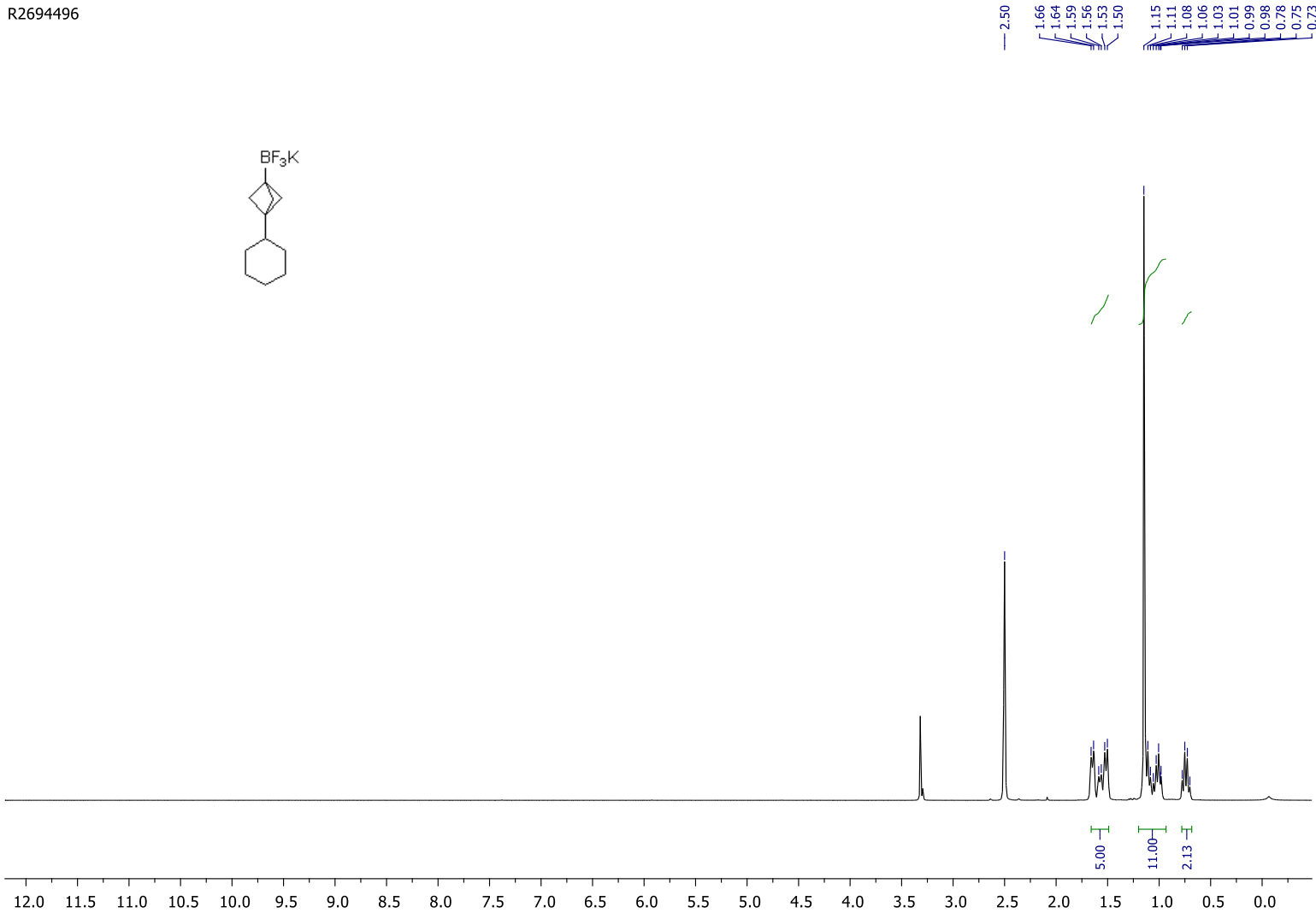
R2436132_F19
 $^{19}\text{F}\{^1\text{H}\}$



Compound 53b

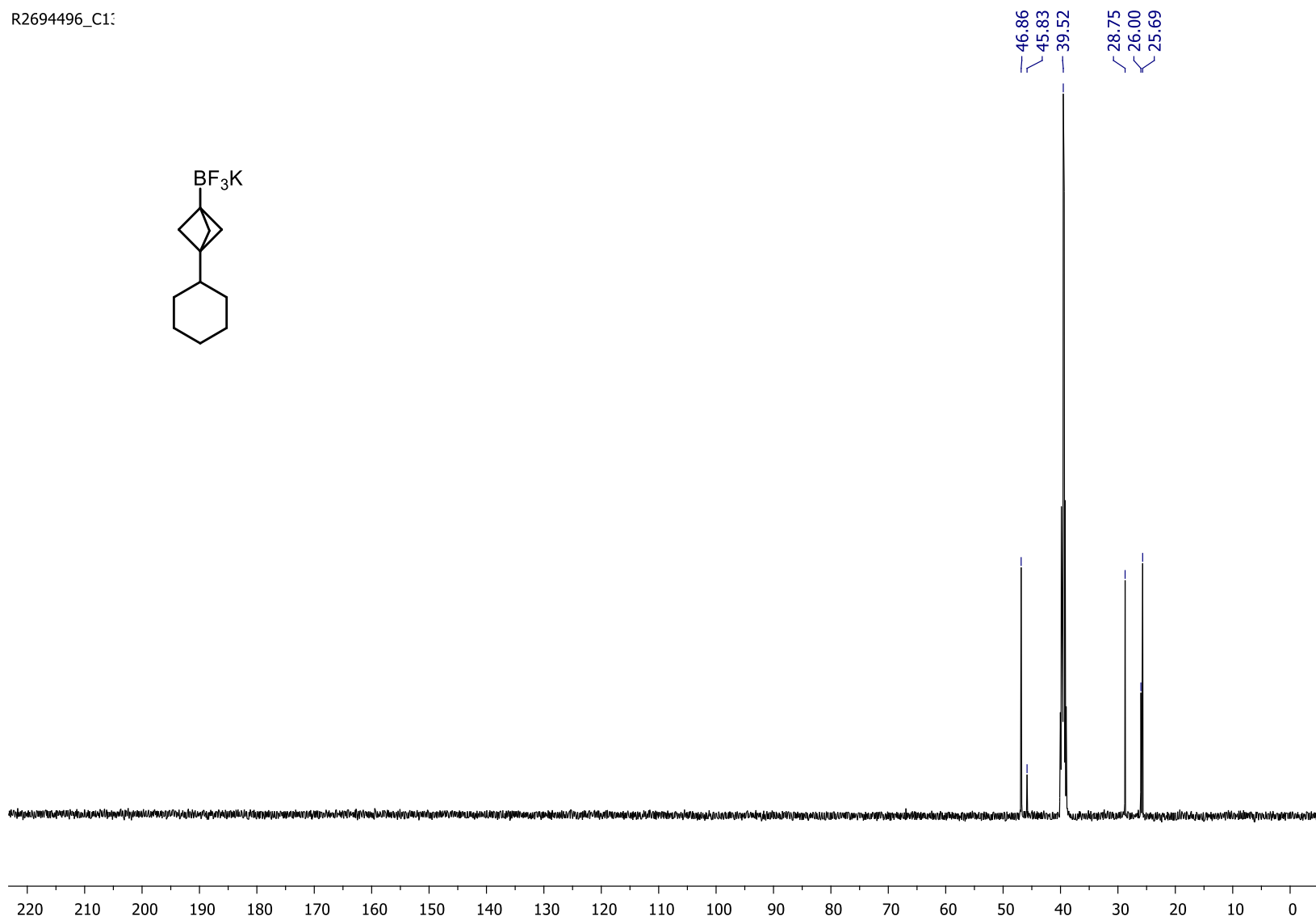
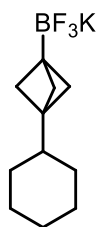
¹H NMR (500 MHz, DMSO-d₆)

R2694496



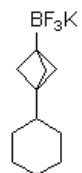
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2694496_C13

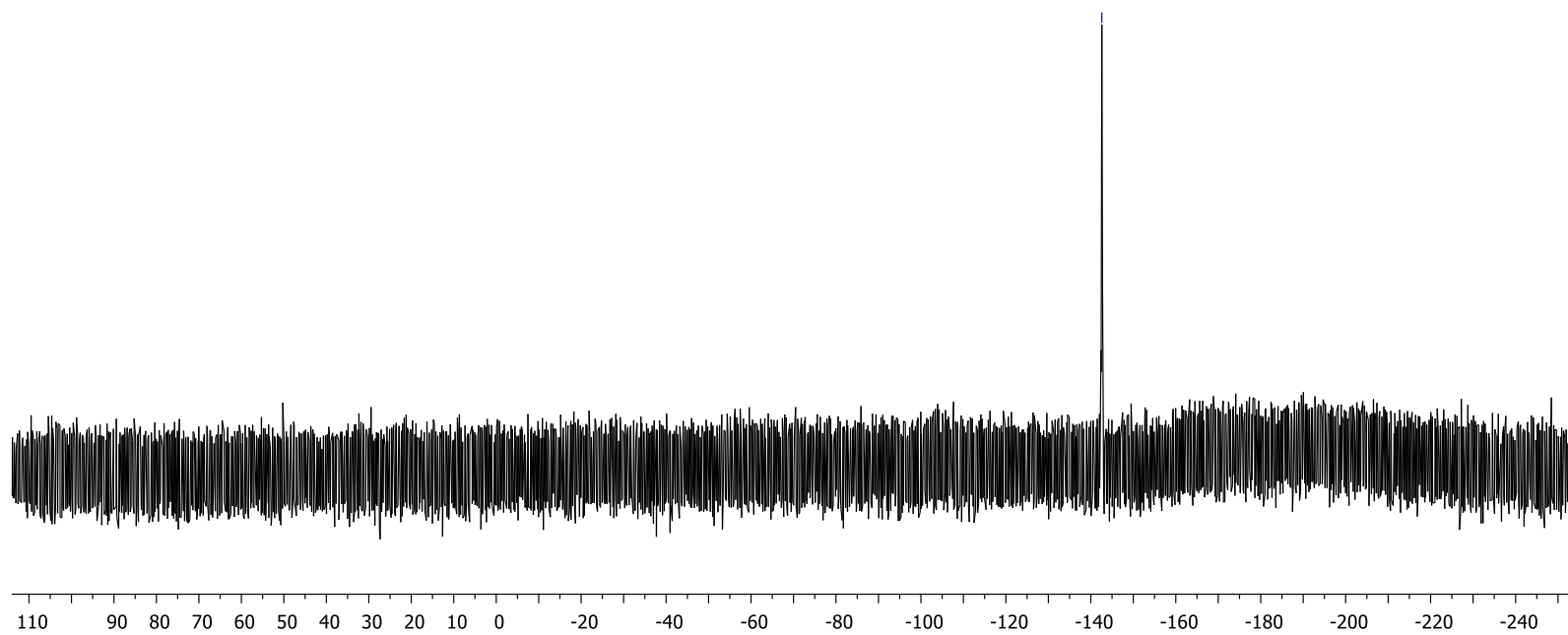


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2694496_F19{H}
19F-{1H}



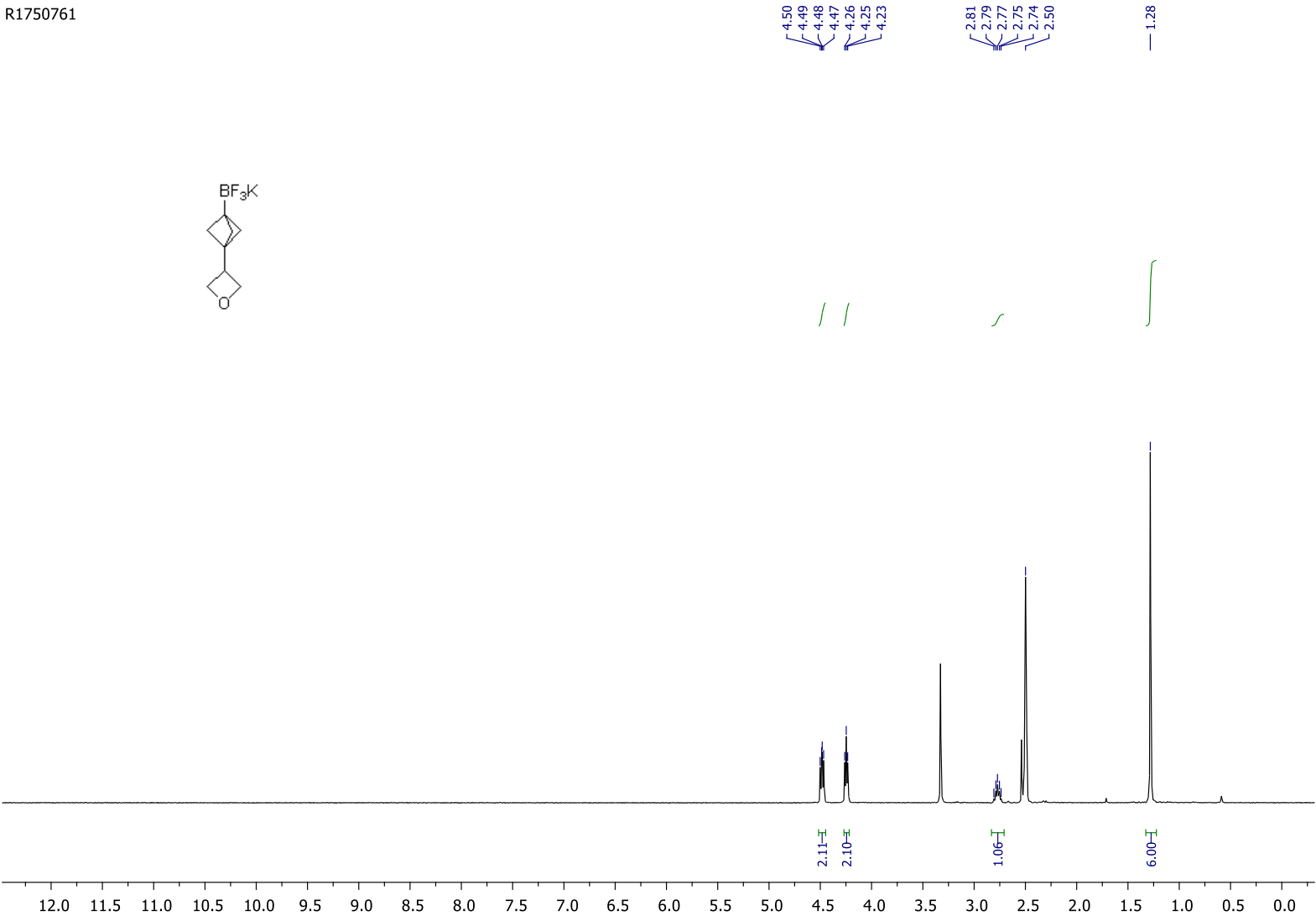
— -142.59



Compound 55b

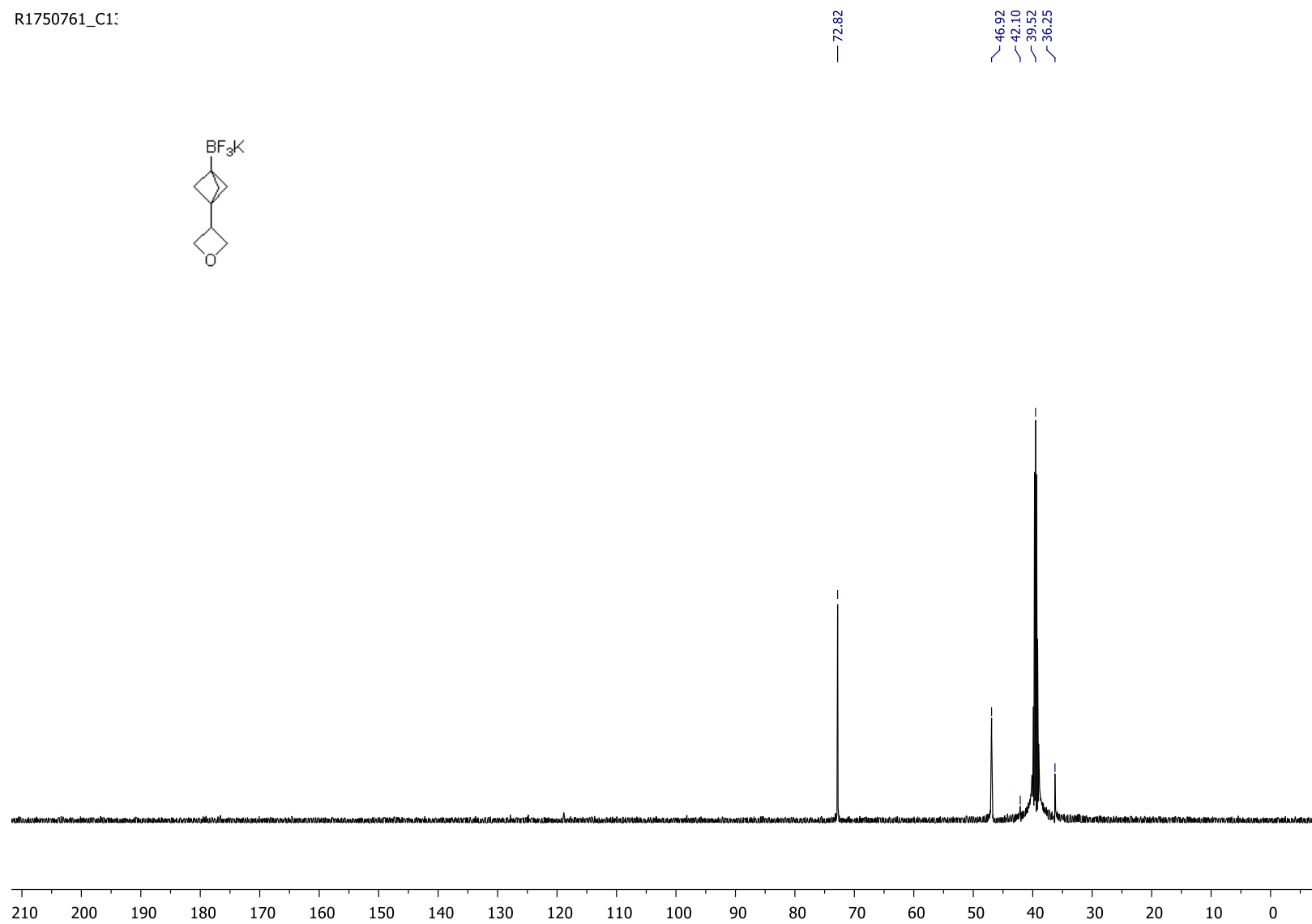
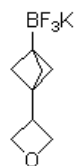
¹H NMR (400 MHz, DMSO-d₆)

R1750761



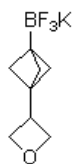
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R1750761_C13

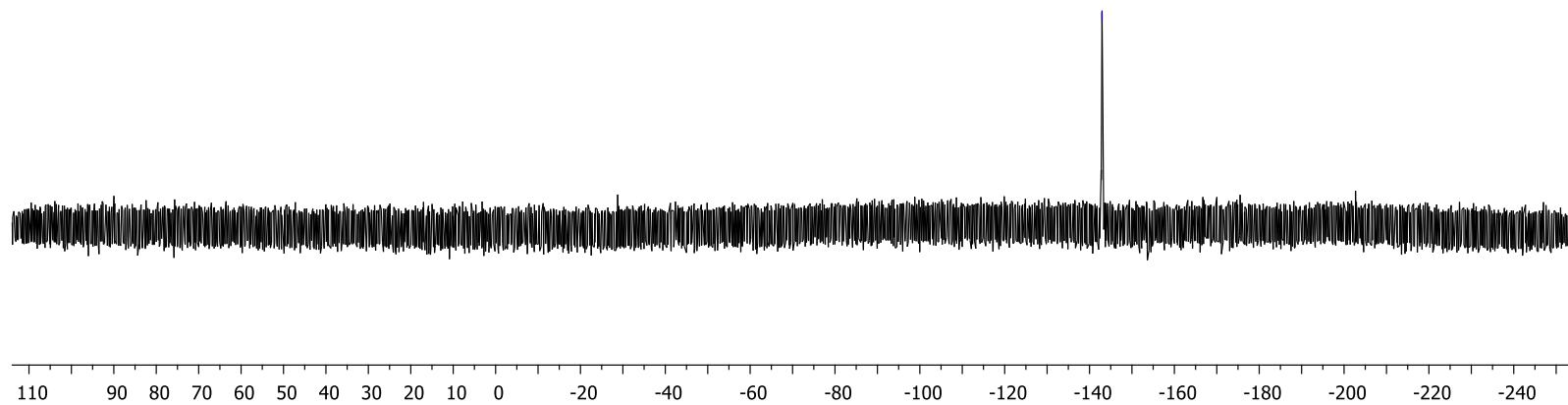


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R1750761_F19{H}

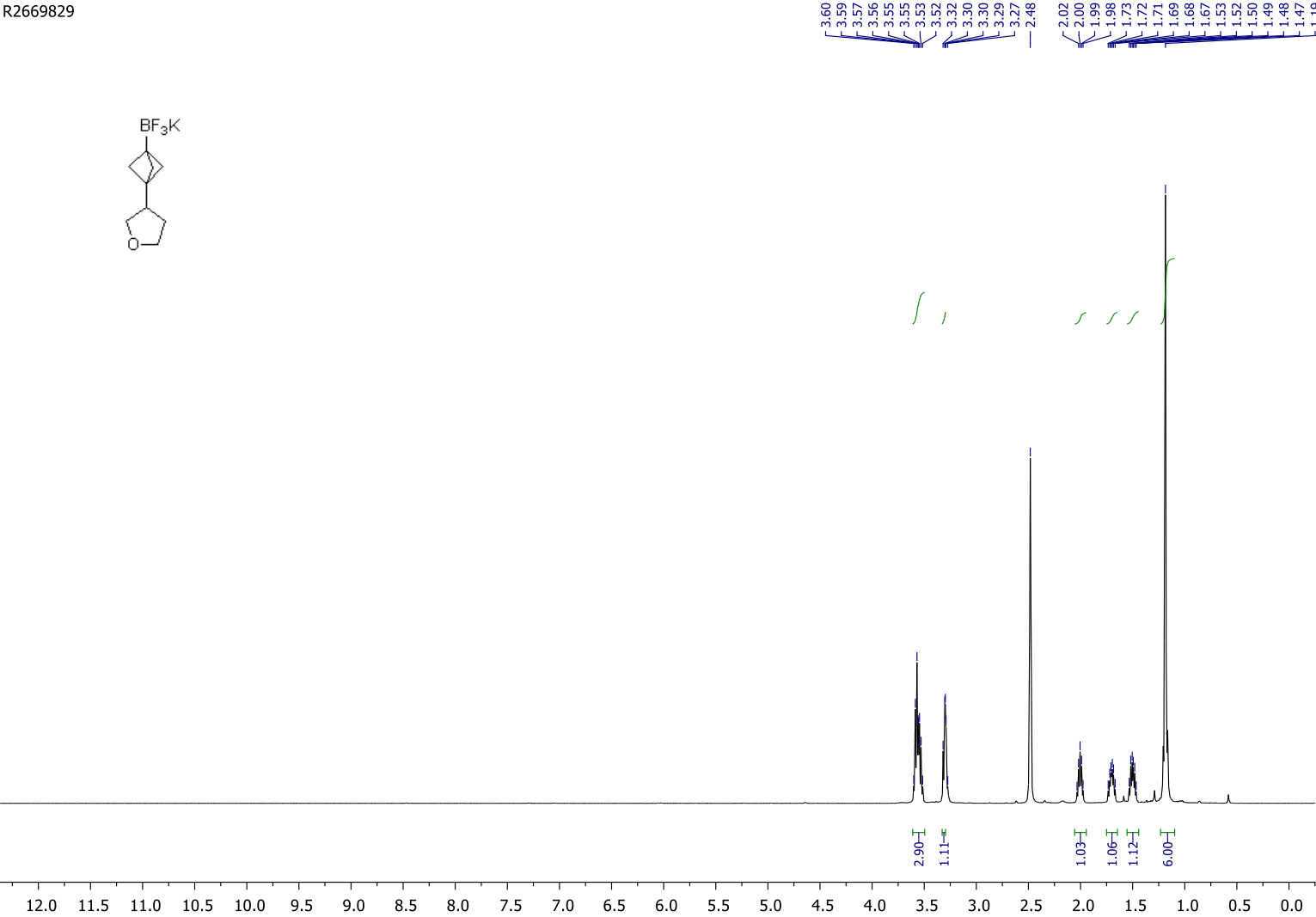


— -142.96



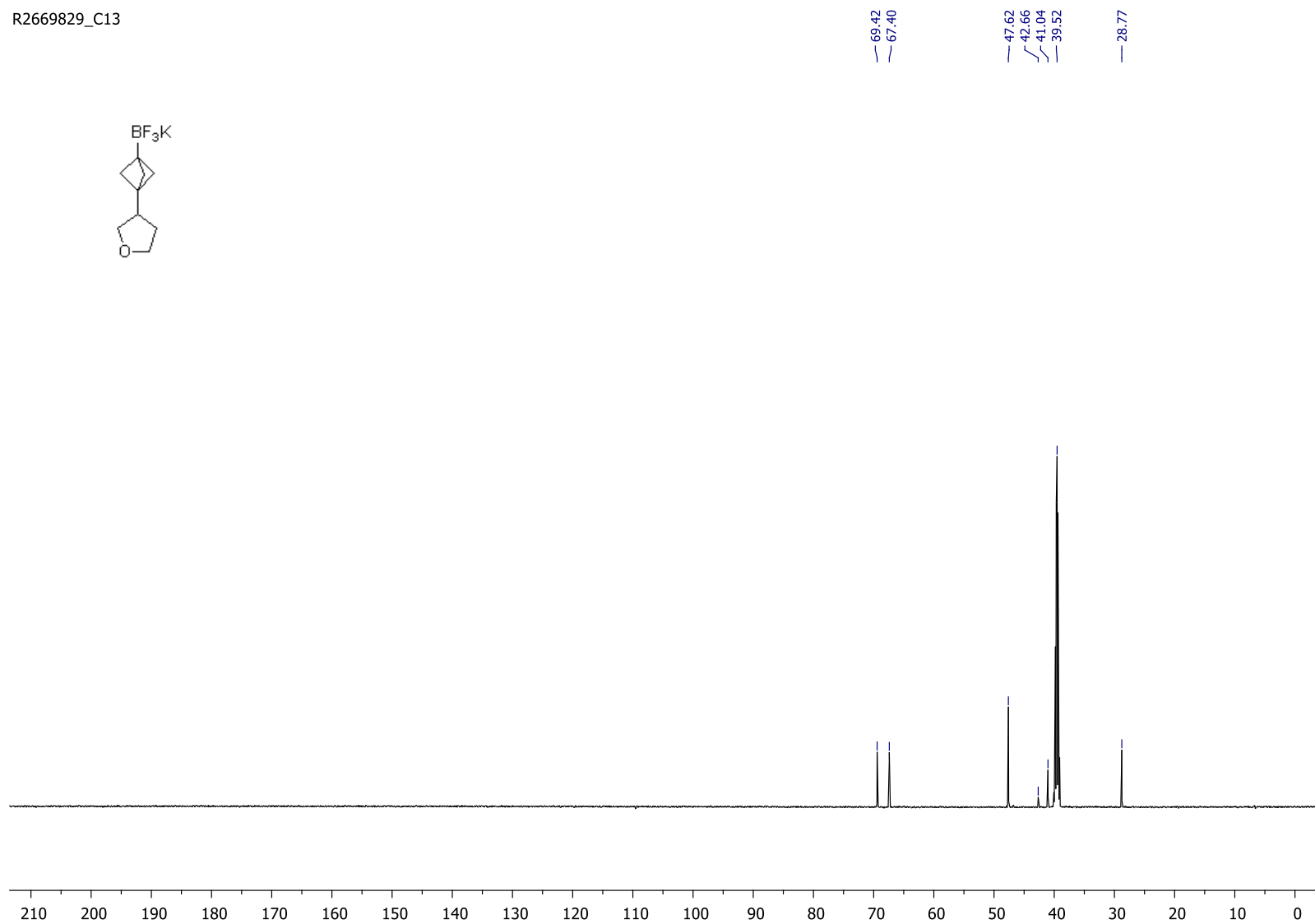
Compound 56b

¹H NMR (500 MHz, DMSO-d₆)



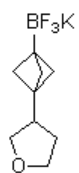
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2669829_C13

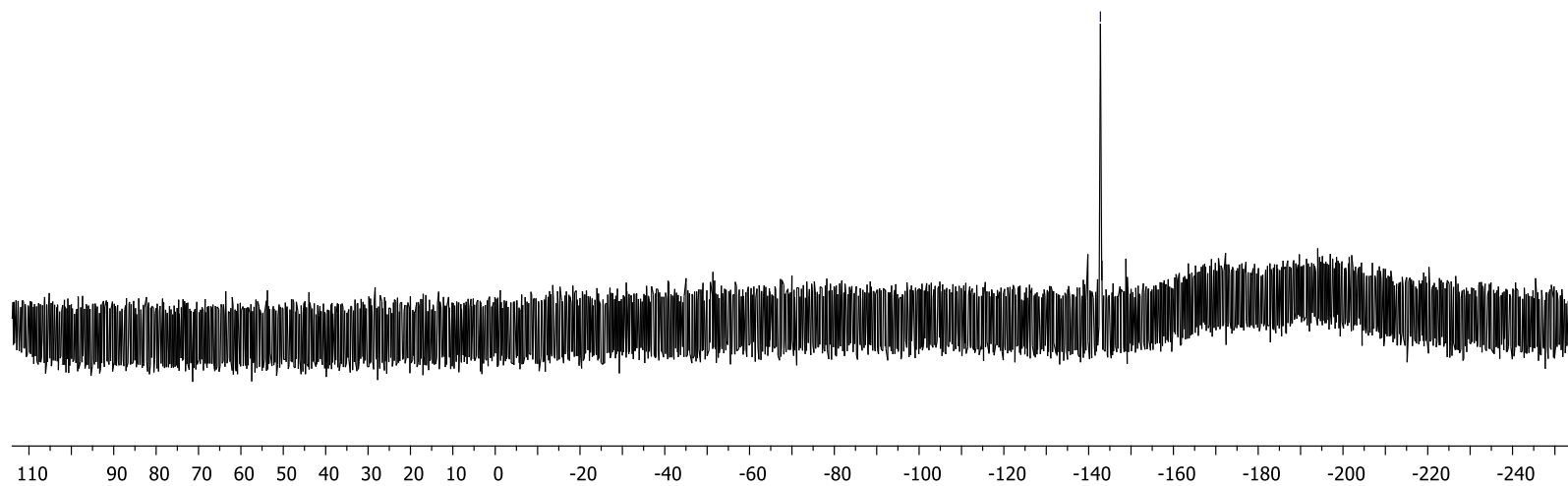


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2669829_F19{H}
19F-{1H}



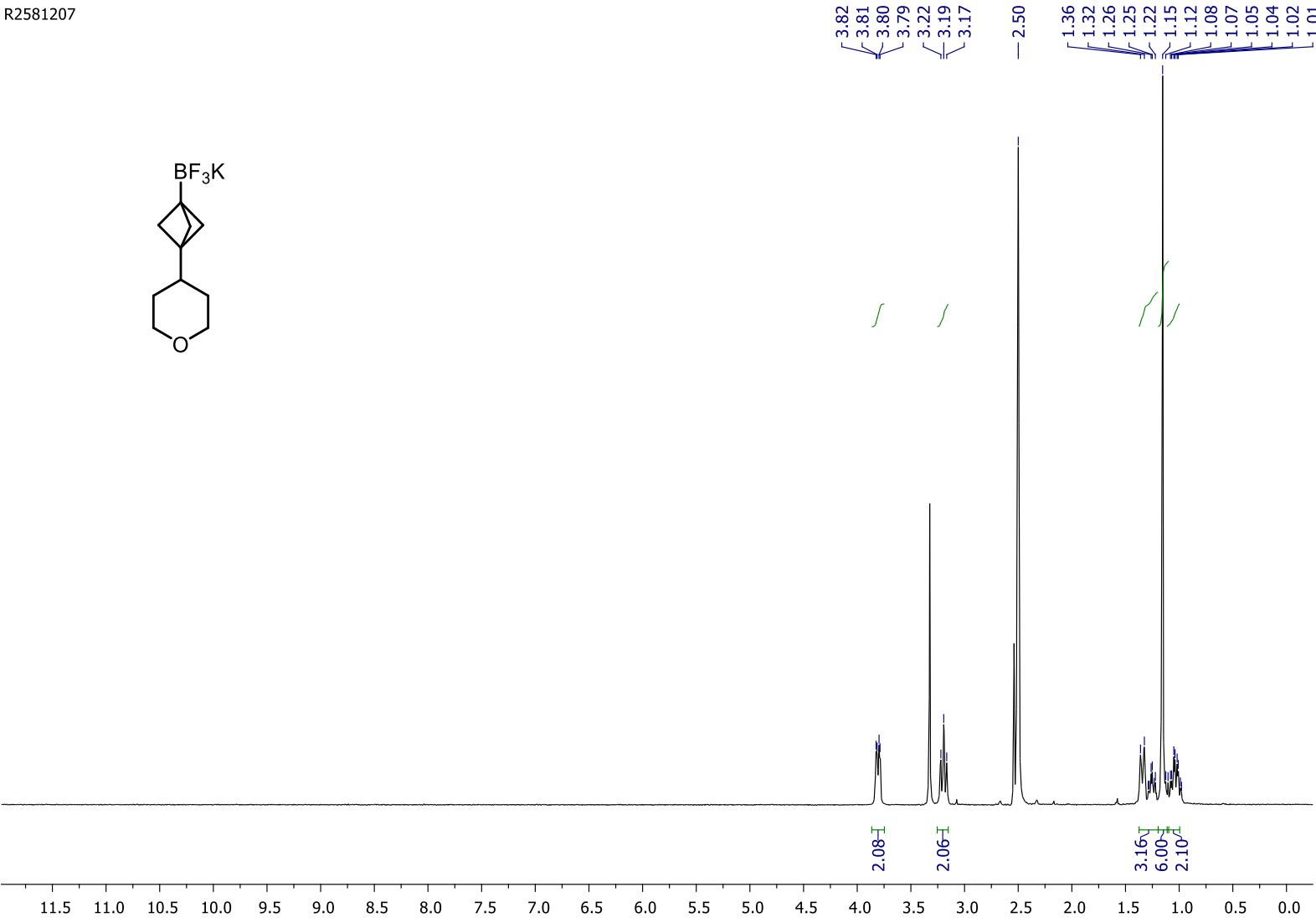
— -142.78



Compound 57b

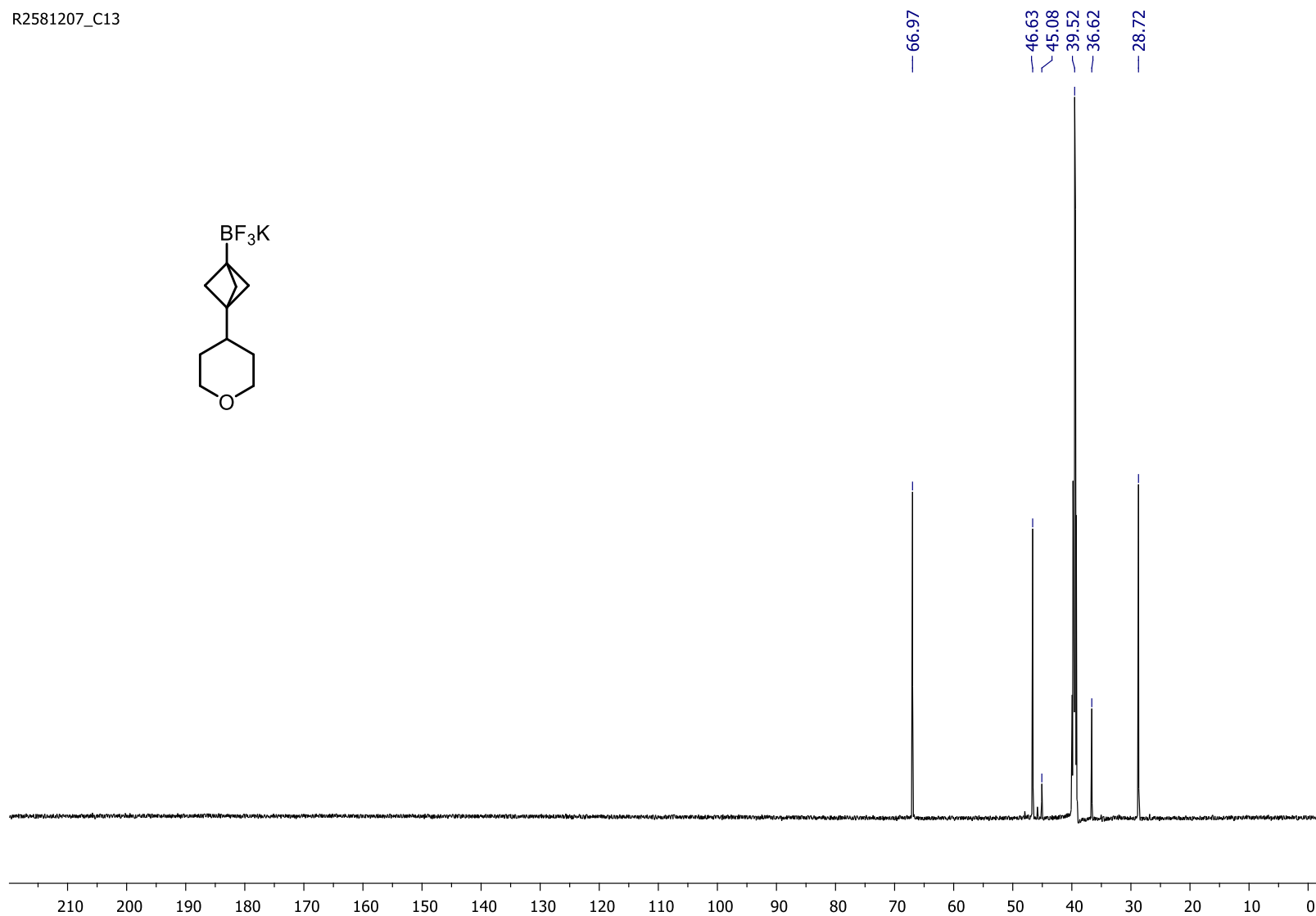
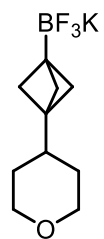
R2581207

¹H NMR (400 MHz, DMSO-d₆)



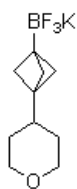
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2581207_C13

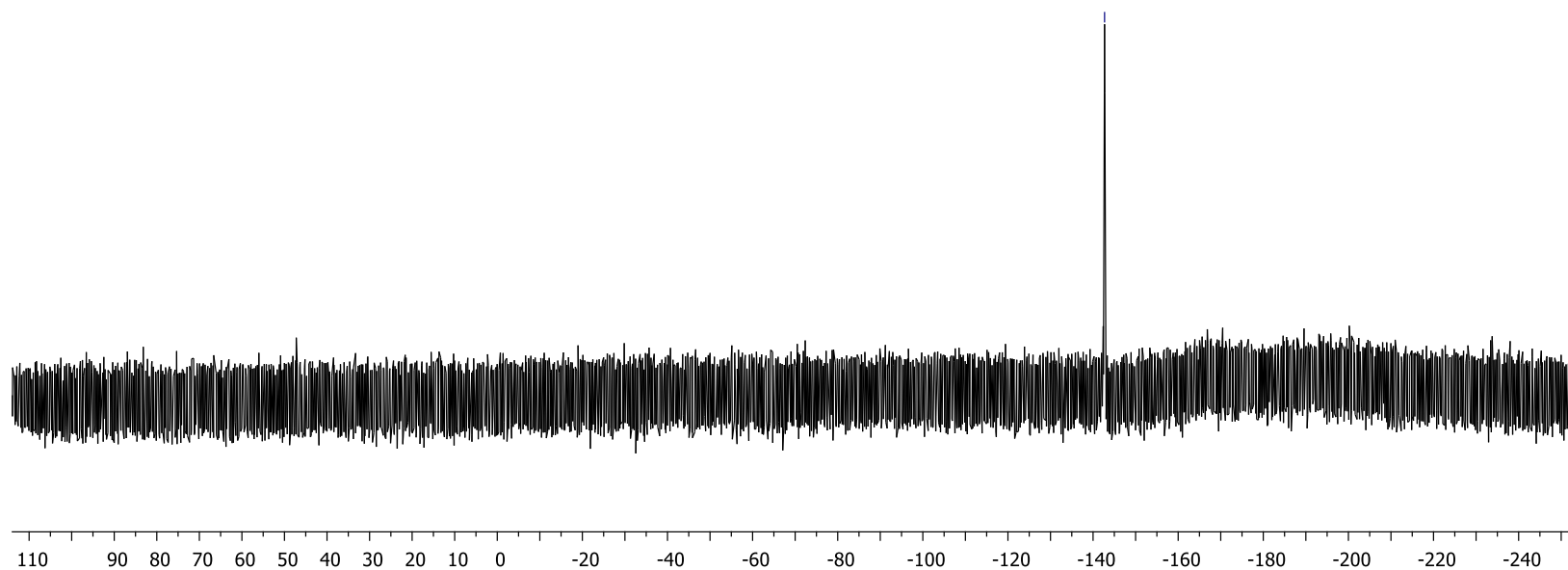


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2581207_F19{H}



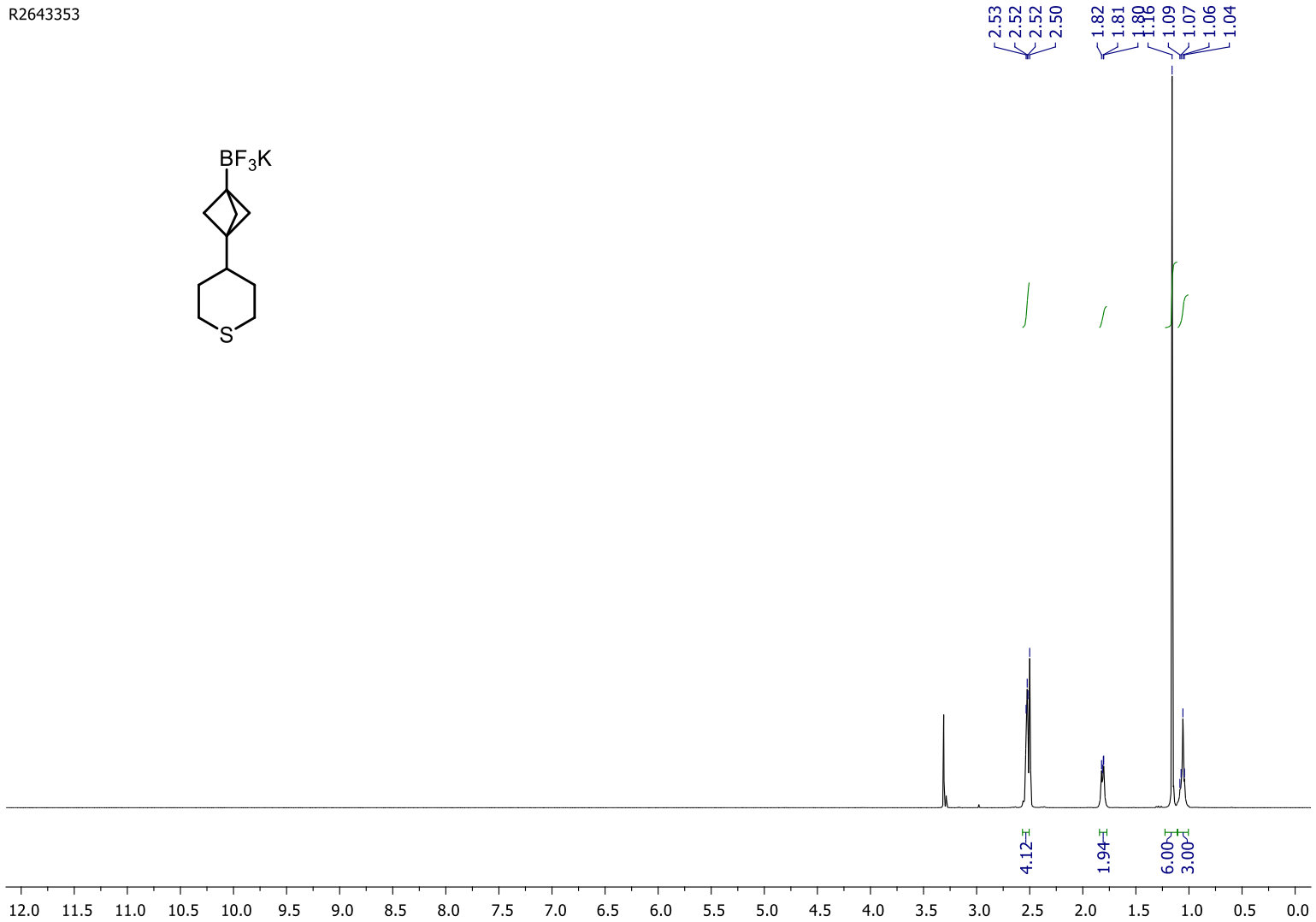
— -142.71



Compound 59b

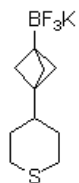
R2643353

¹H NMR (500 MHz, DMSO-d₆)

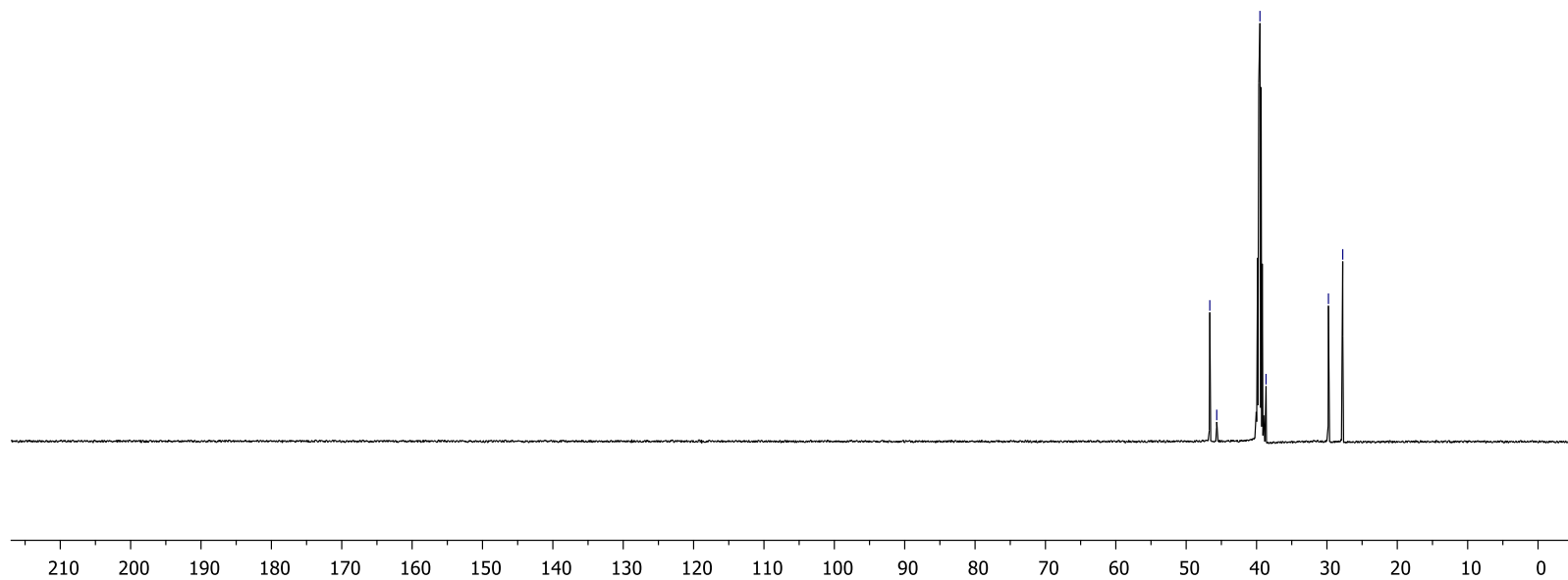


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2643353_C1:

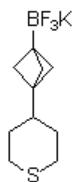


46.64
45.66
39.52
38.65
29.79
27.75

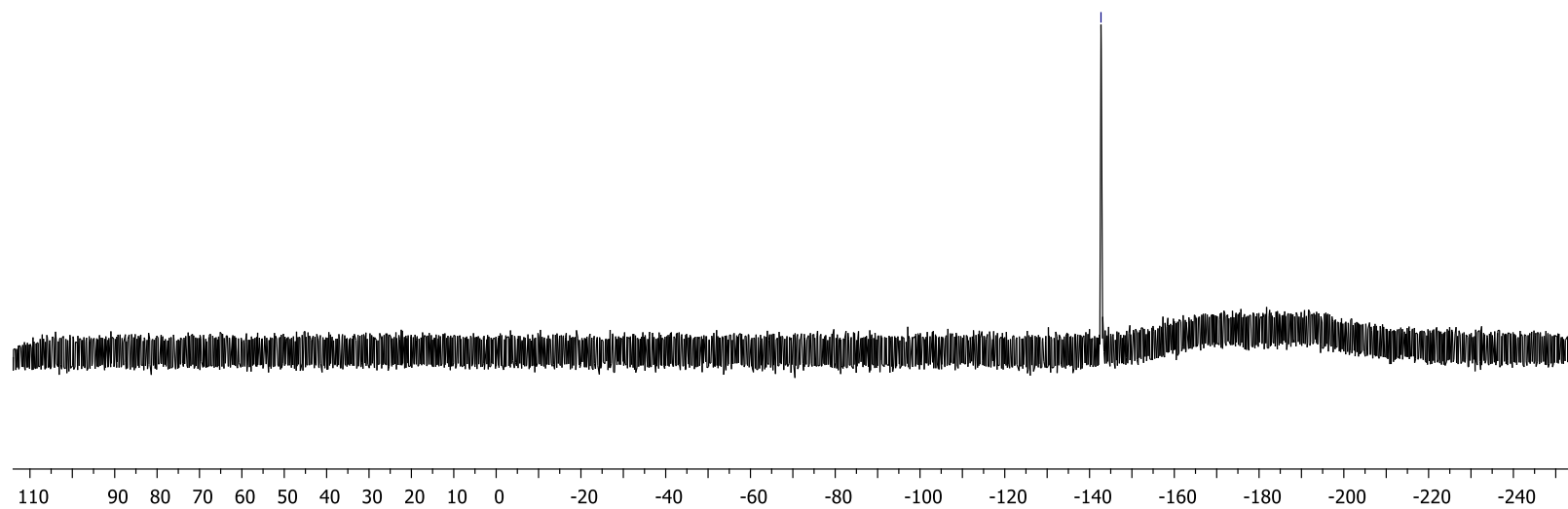


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2643353_F19{H}



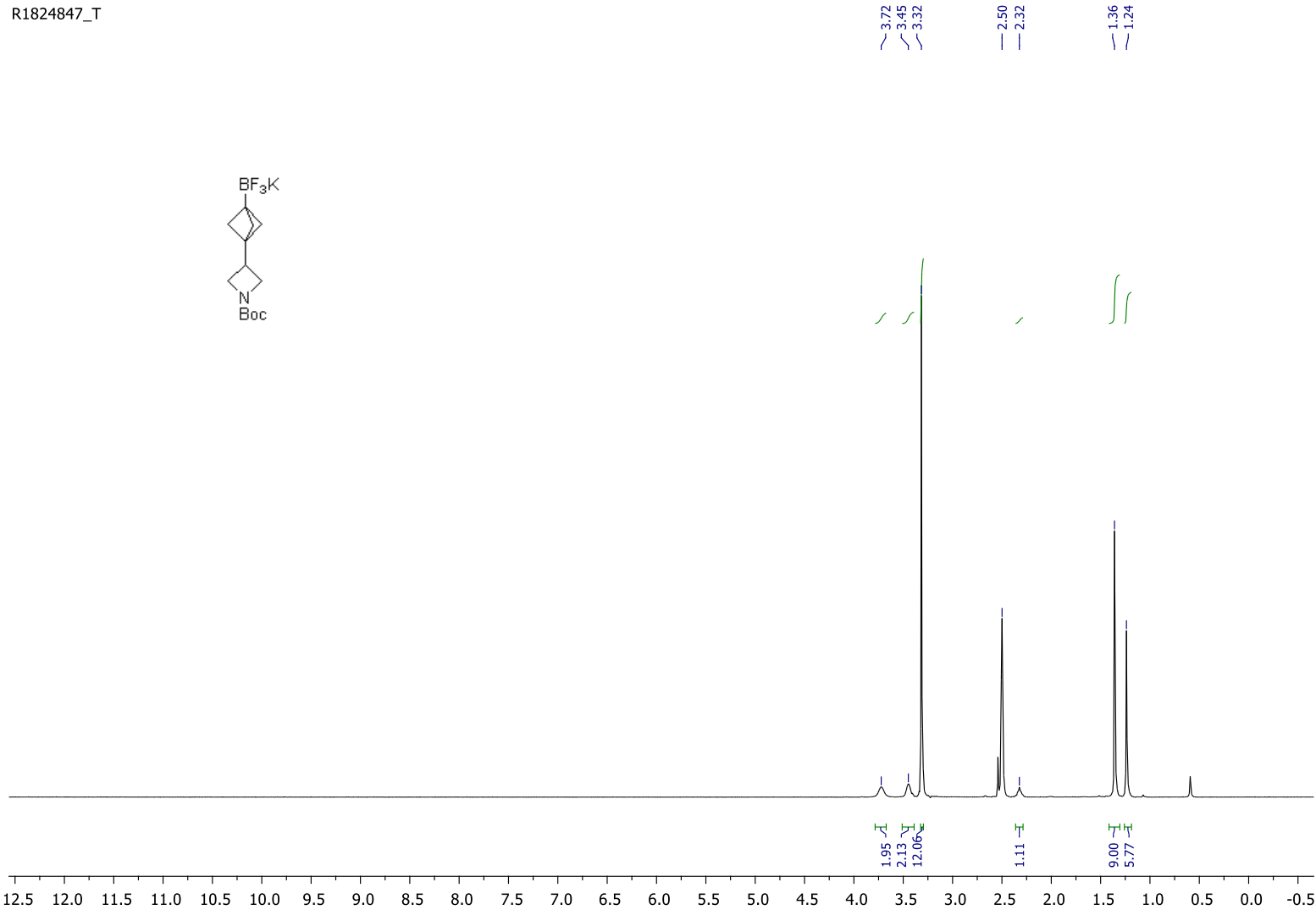
— -142.70



Compound 60b

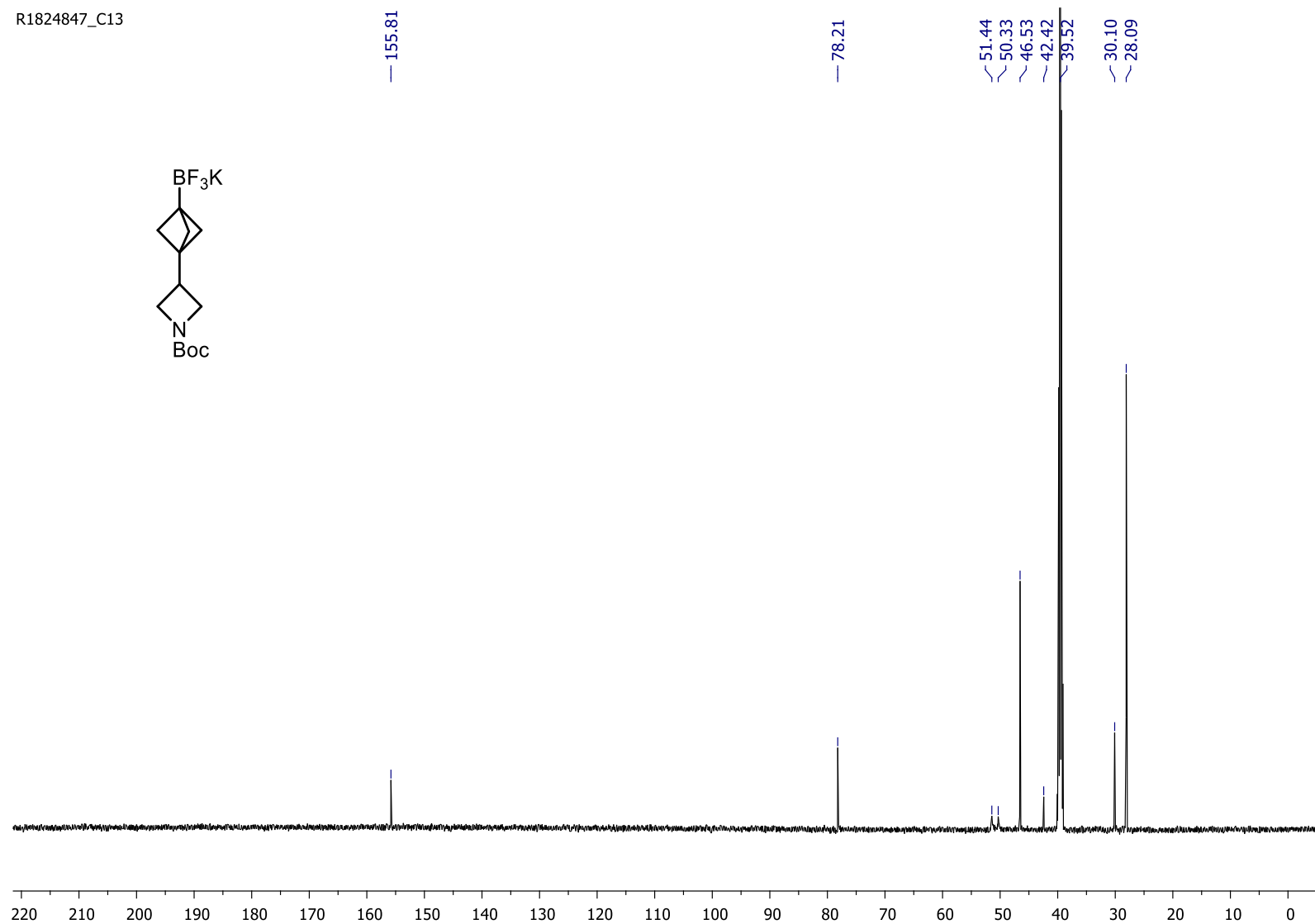
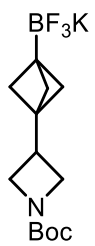
¹H NMR (400 MHz, DMSO-d₆)

R1824847_T



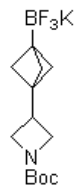
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R1824847_C13

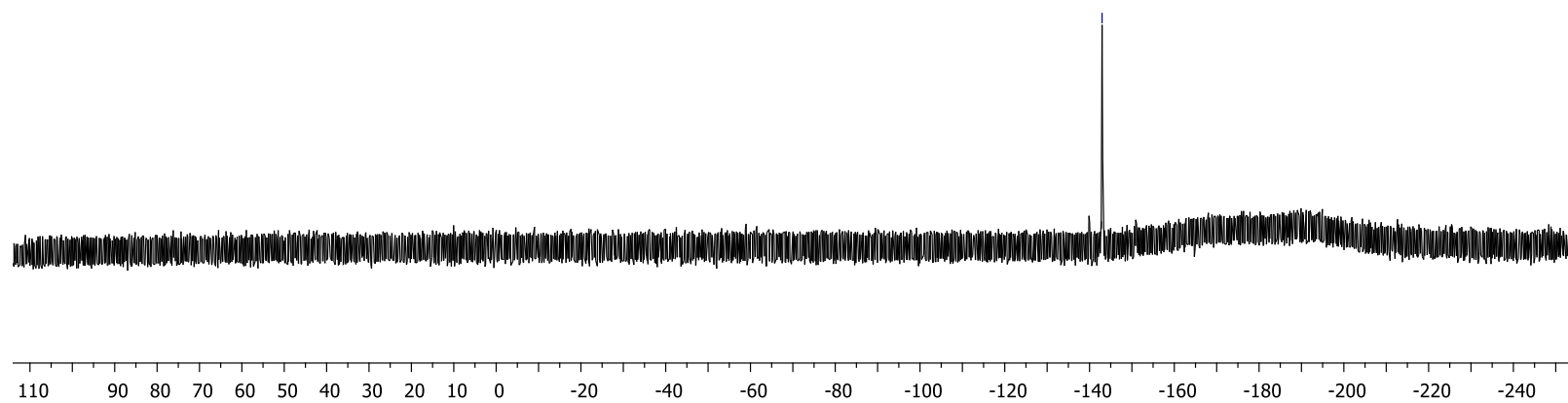


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R1824847_F19{H}
19F-{1H}

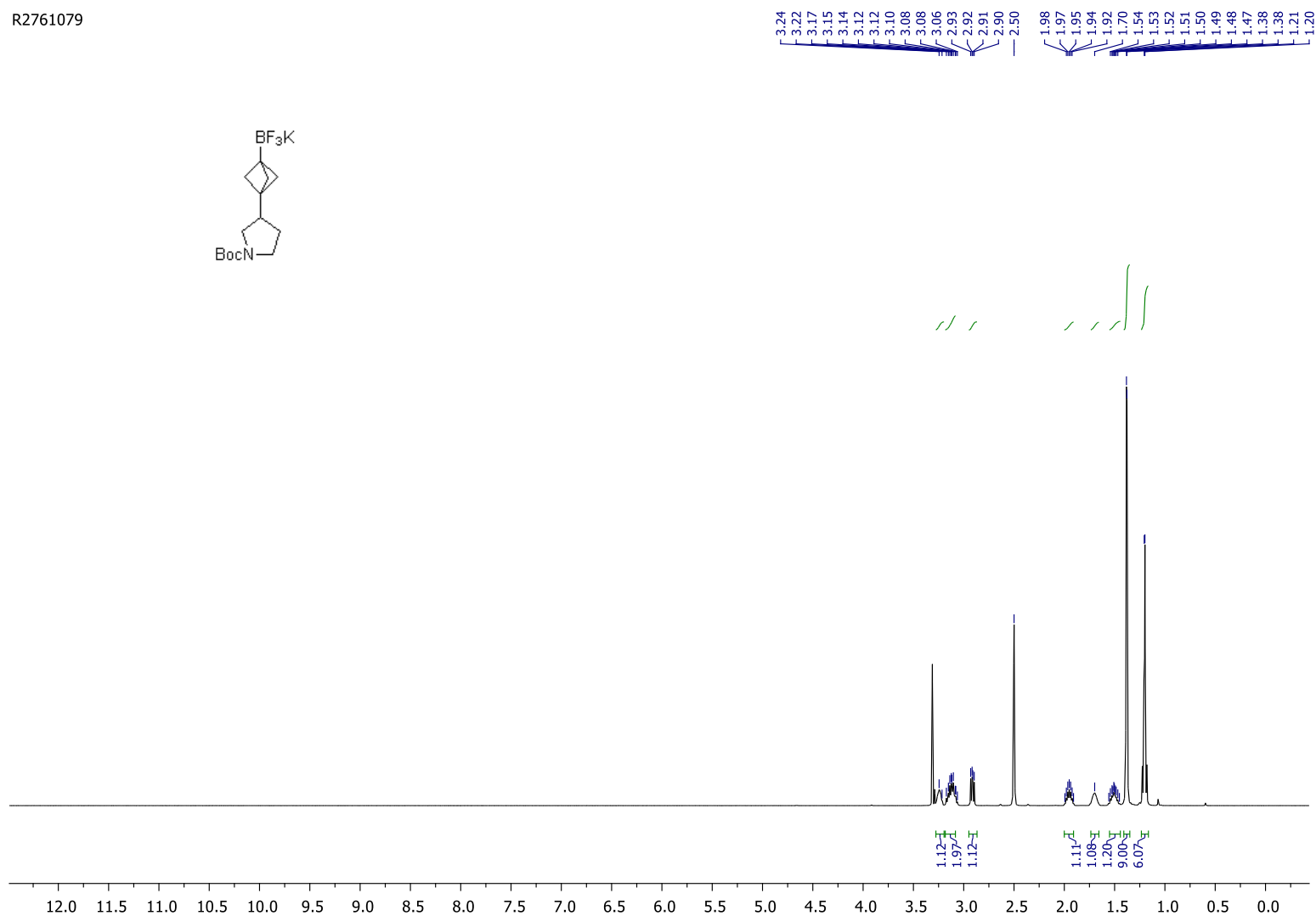
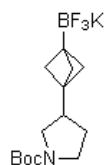


— -142.96



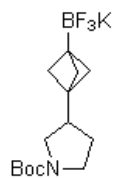
Compound 61b

R2761079

¹H NMR (500 MHz, DMSO-d₆)

$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2761079_C13



— 153.55

77.88
77.86

77.86

48.06

47.87

47.63
45.58

45.33

42.72

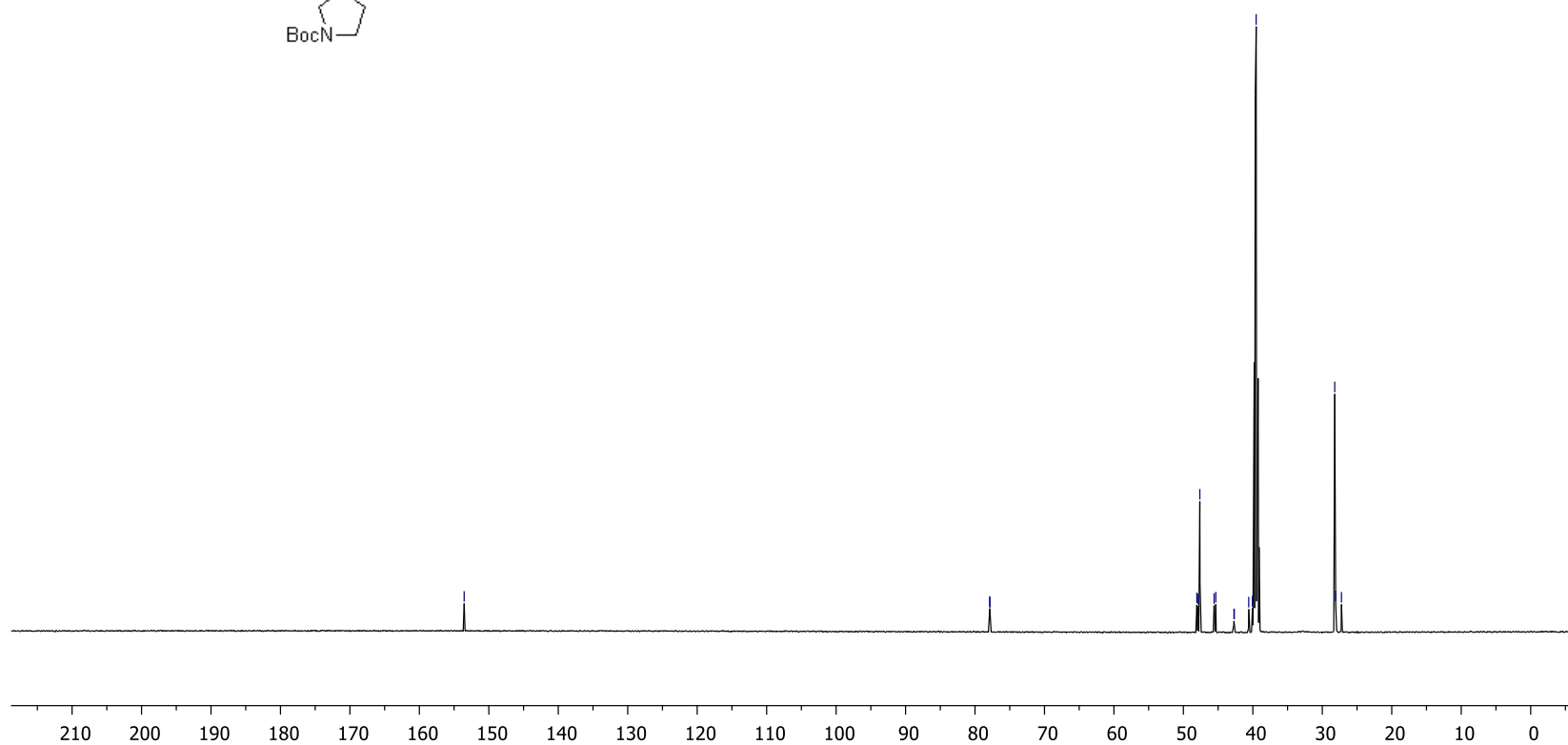
42.67
40.59

40.06

39.52
39.71

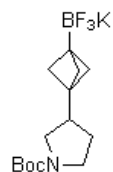
28.07
28.21

27.24

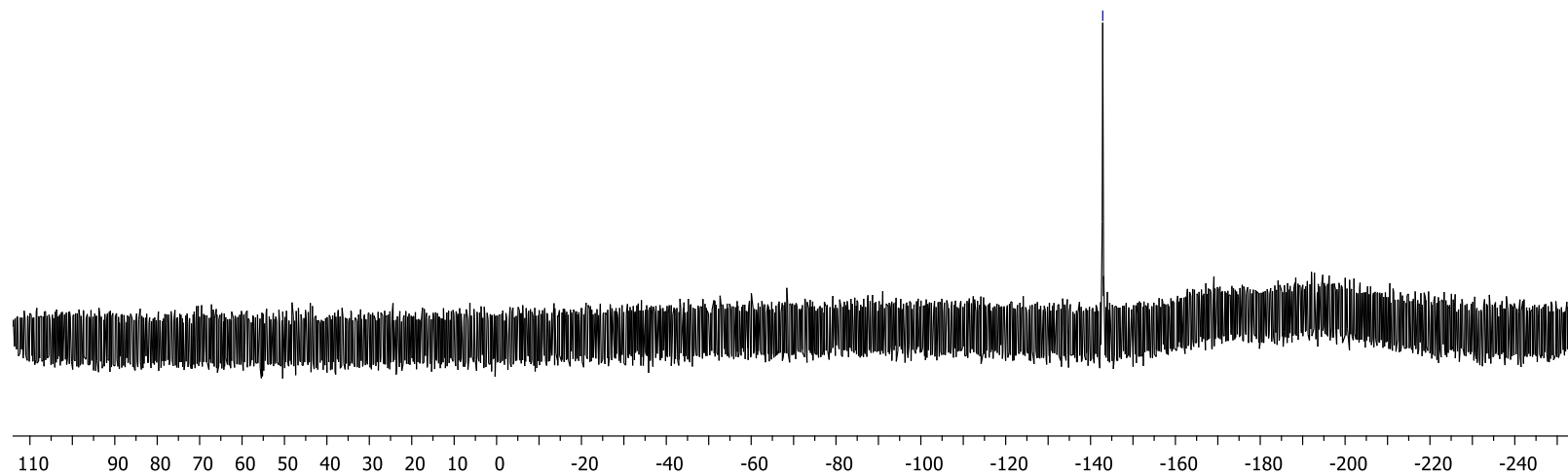


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2761079_F19
 $^{19}\text{F}\{^1\text{H}\}$



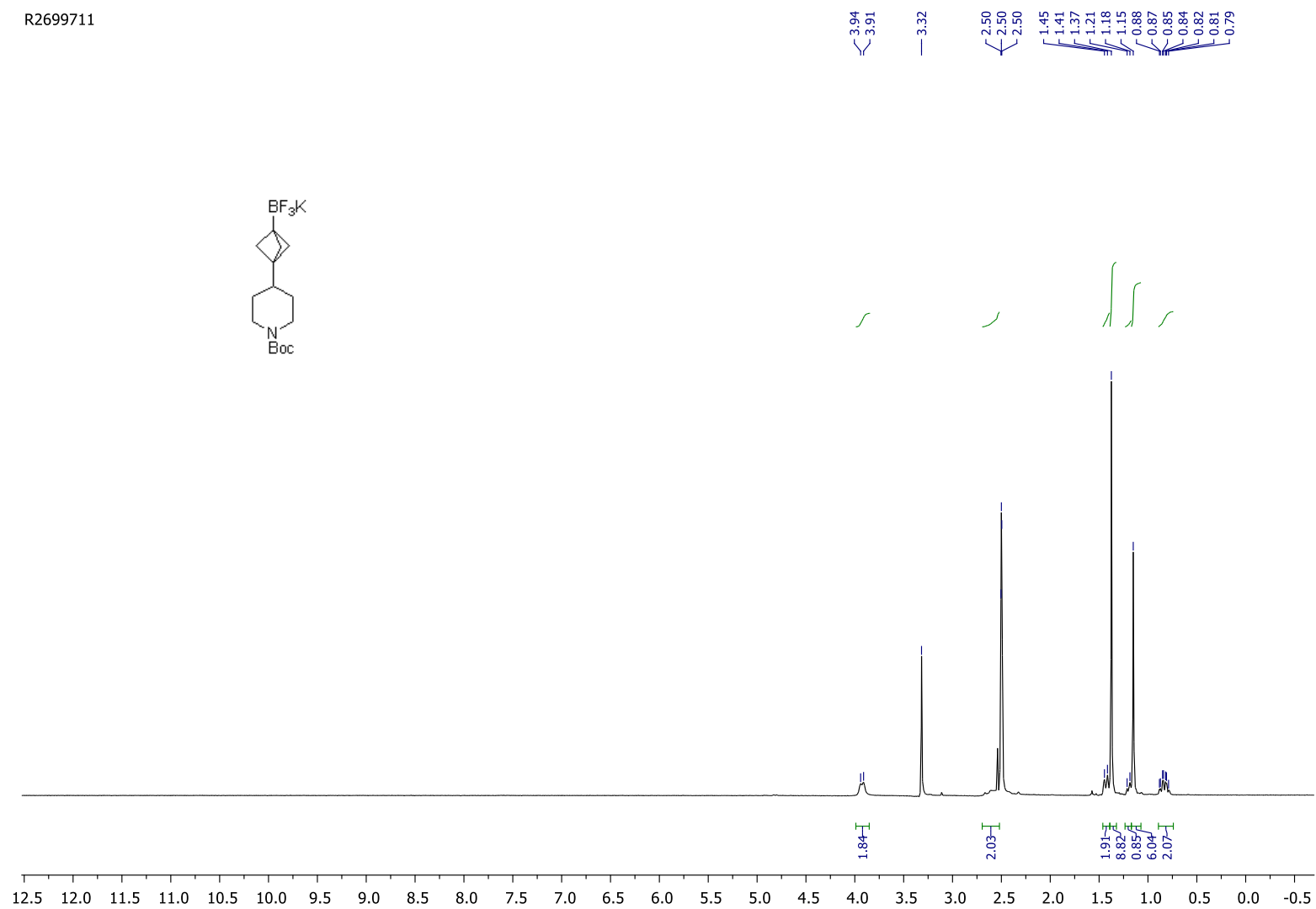
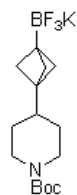
— -142.87



Compound 63b

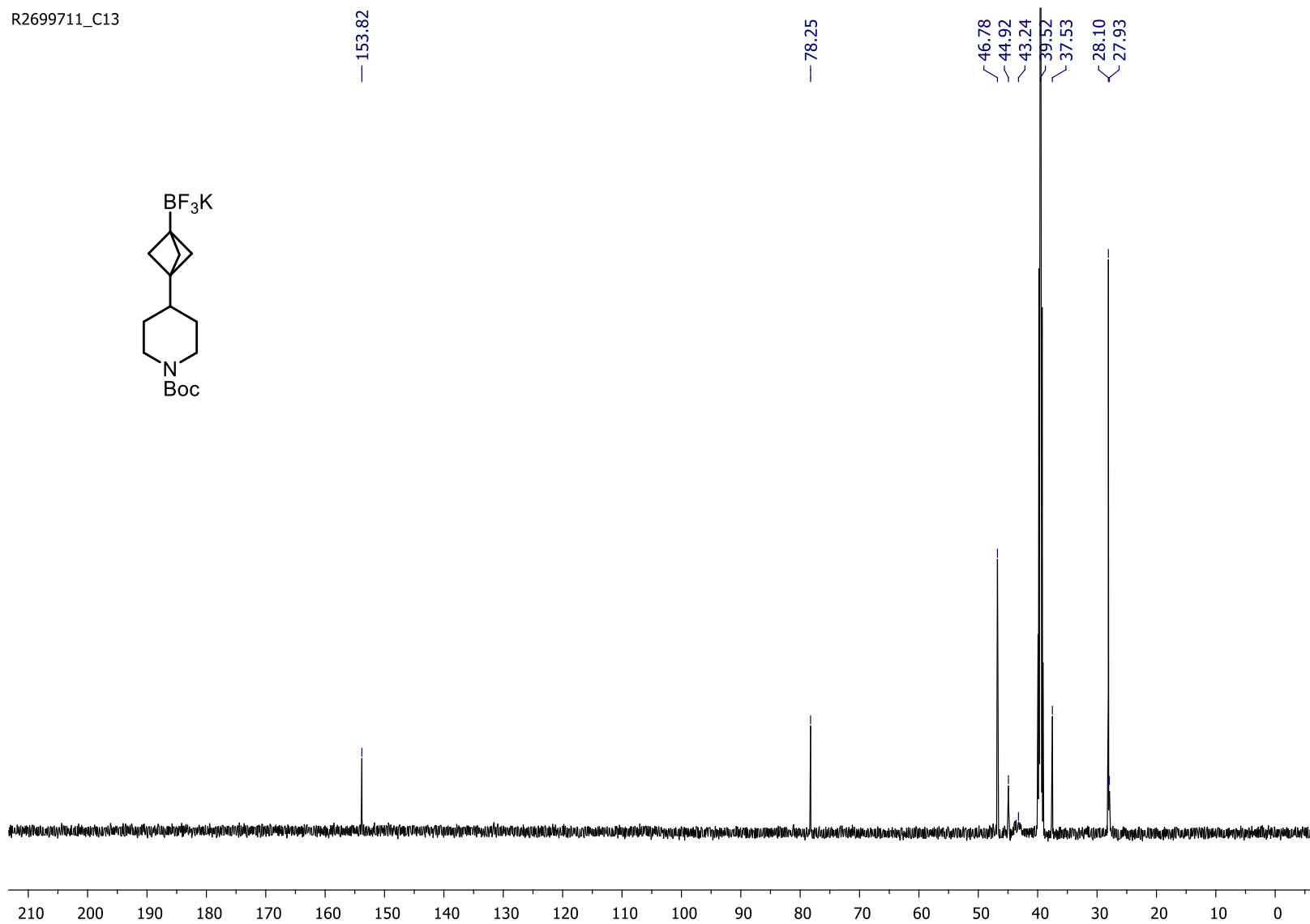
¹H NMR (400 MHz, DMSO-d₆)

R2699711



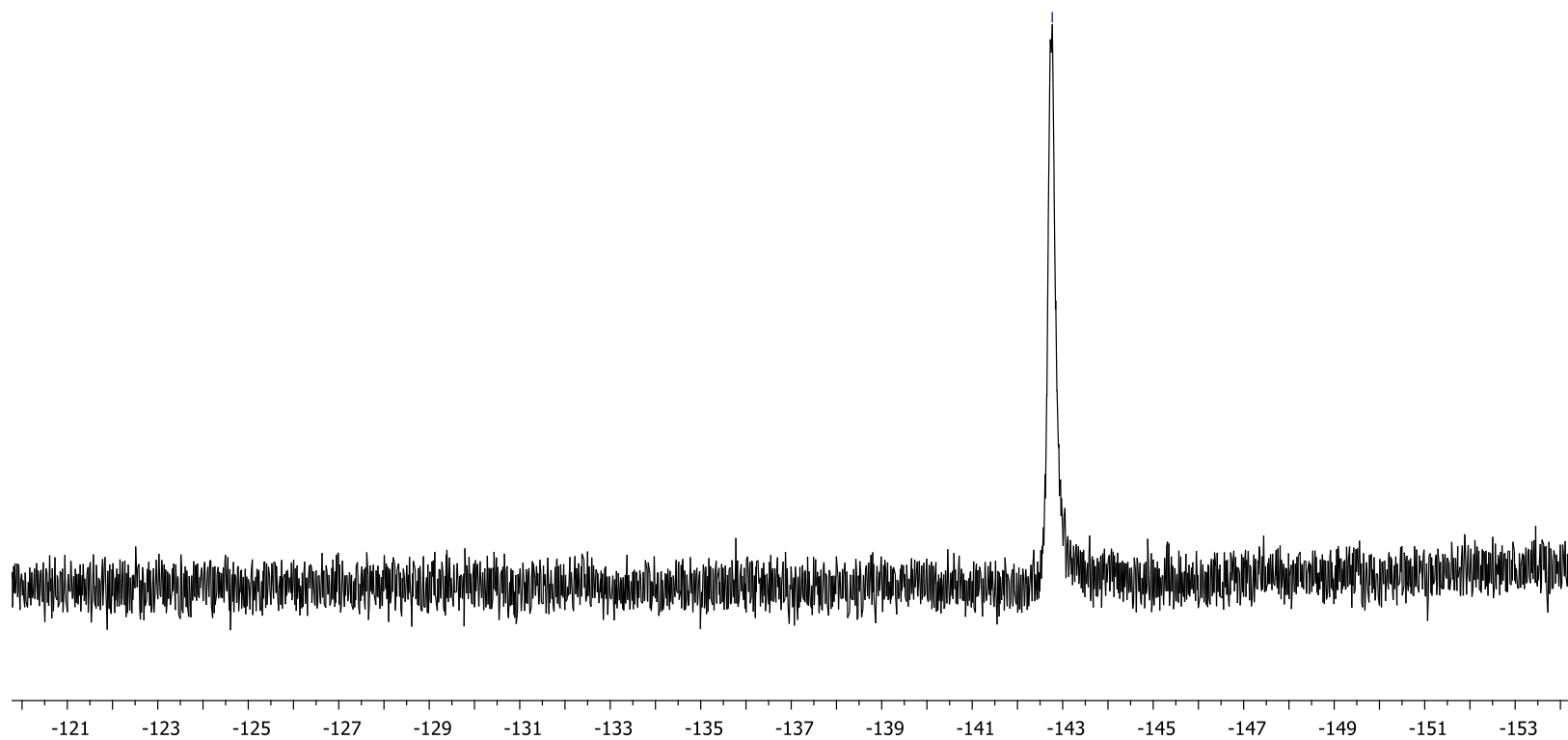
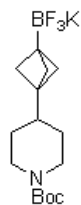
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2699711_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

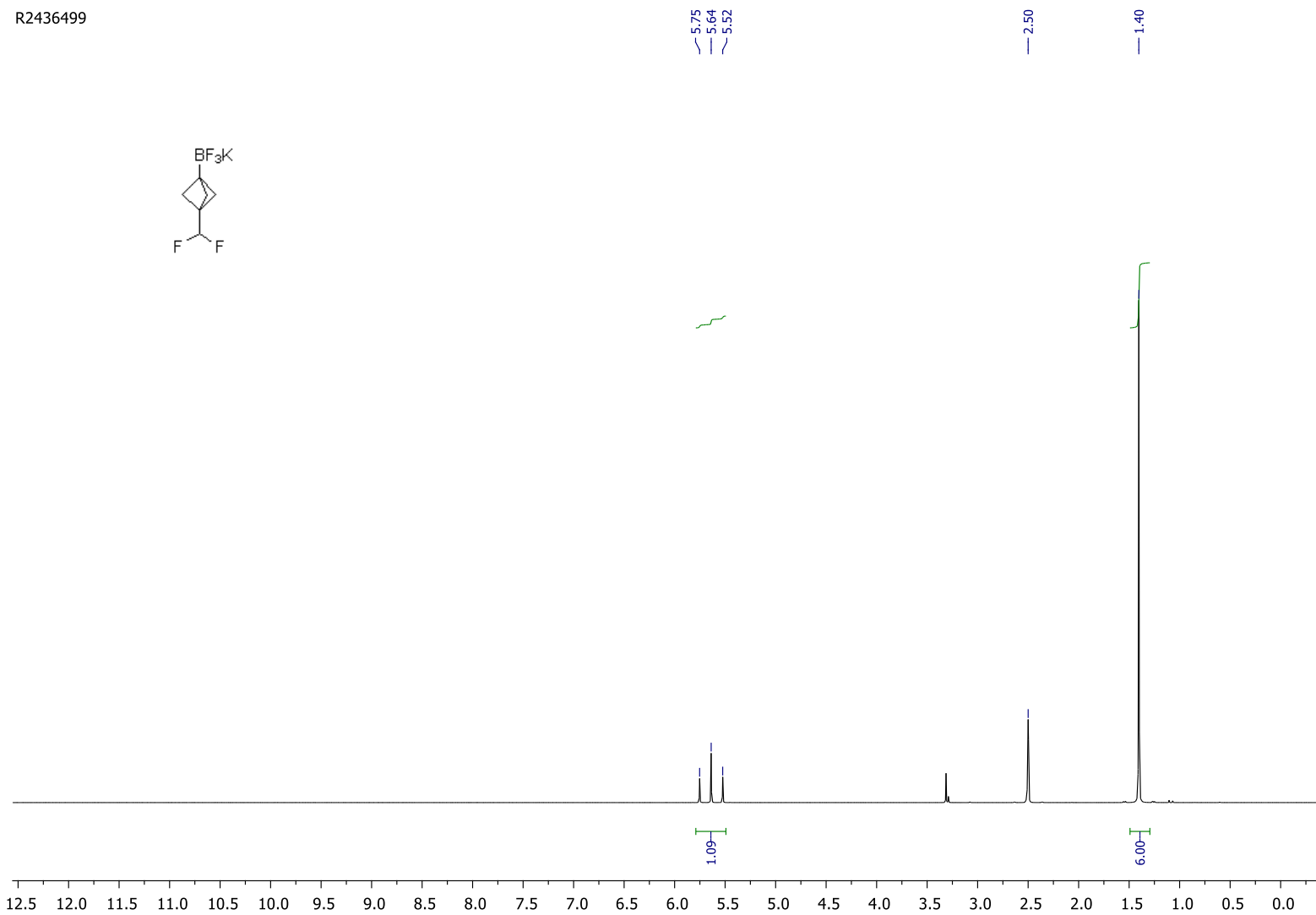
R2699711_F19{H}
19F-{1H}



Compound 67b

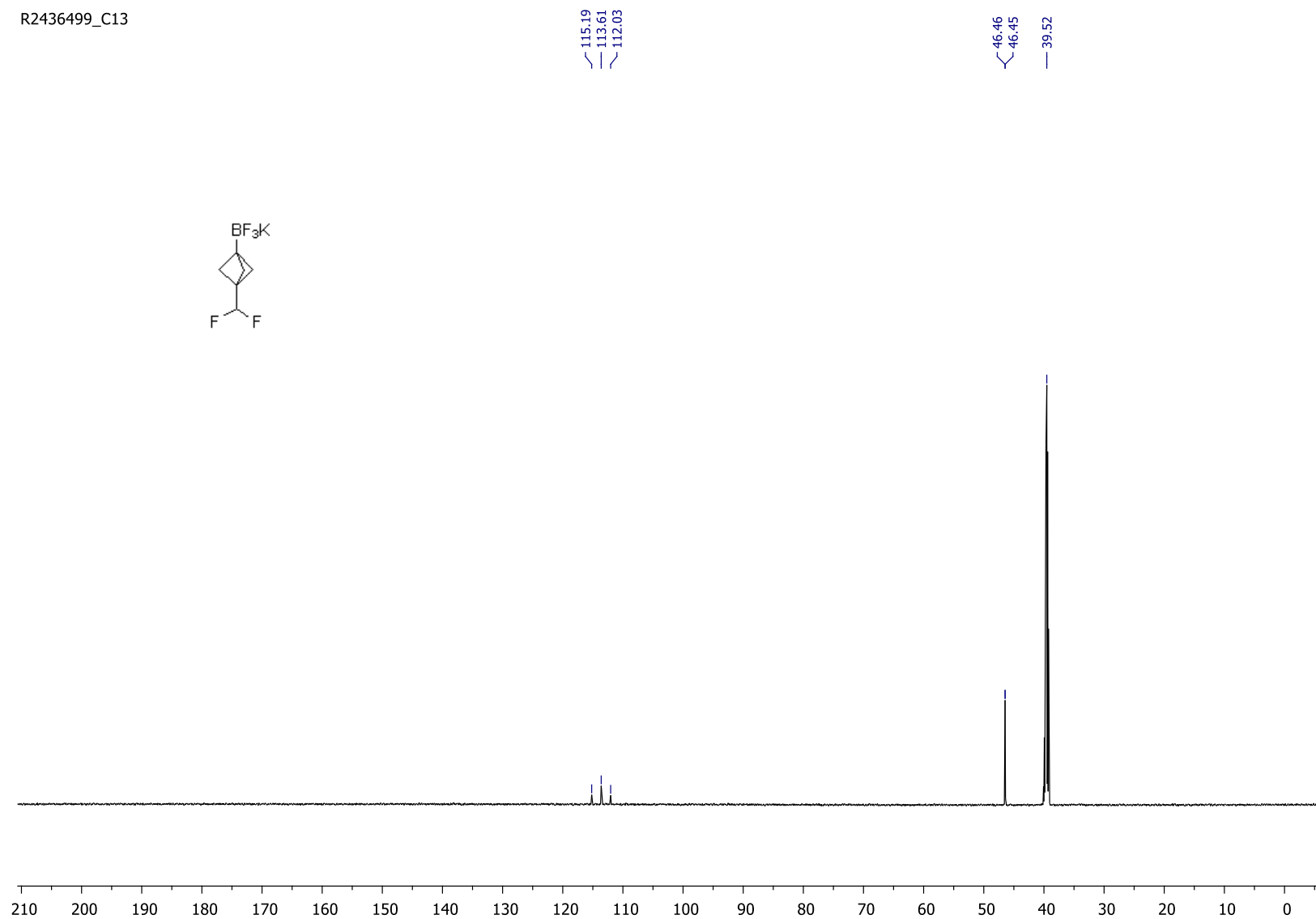
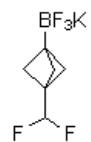
R2436499

¹H NMR (500 MHz, DMSO-d₆)



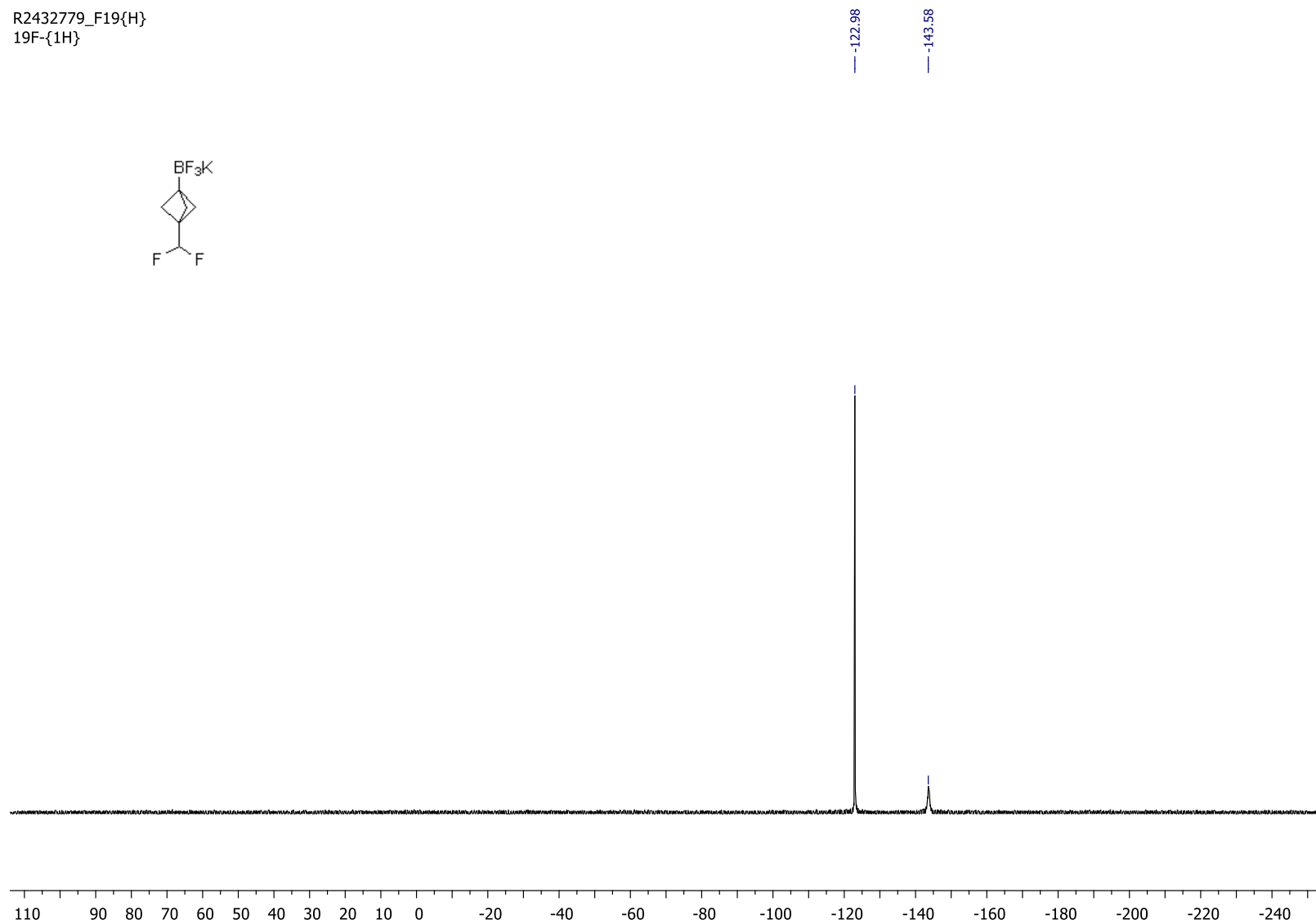
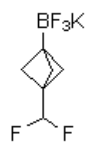
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2436499_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

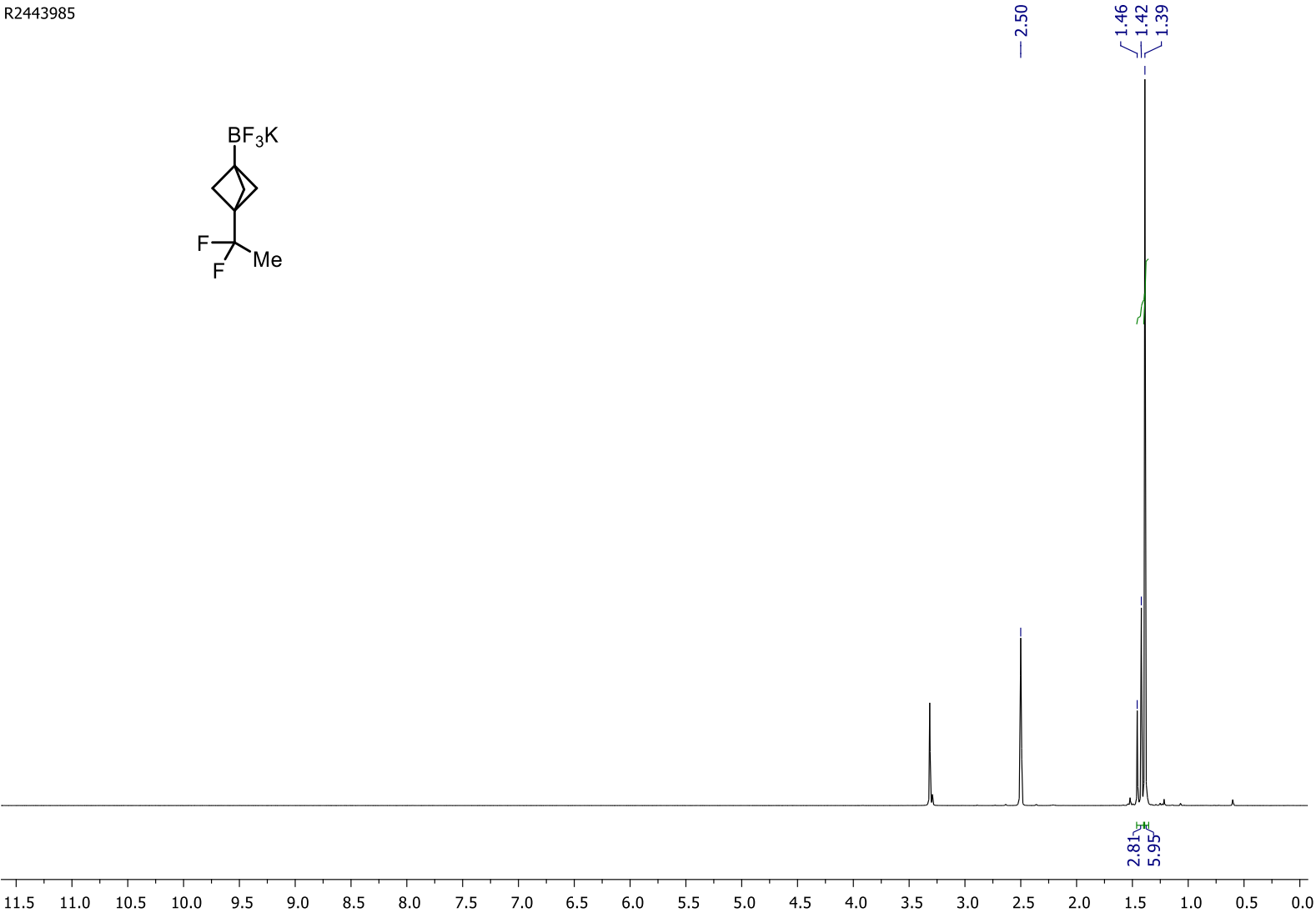
R2432779_F19{H}
 $^{19}\text{F}\{^1\text{H}\}$



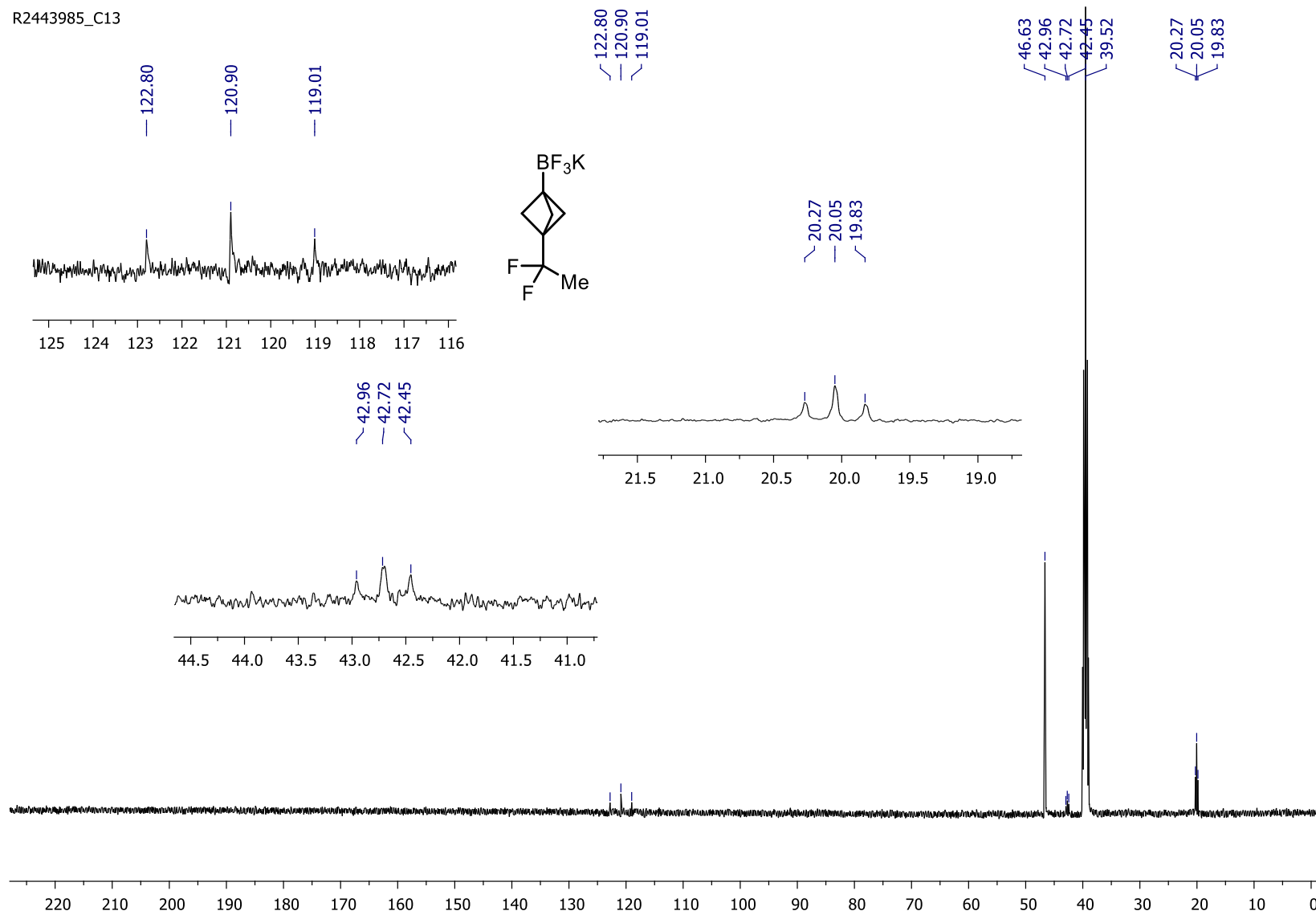
Compound 68b

R2443985

¹H NMR (500 MHz, DMSO-d₆)

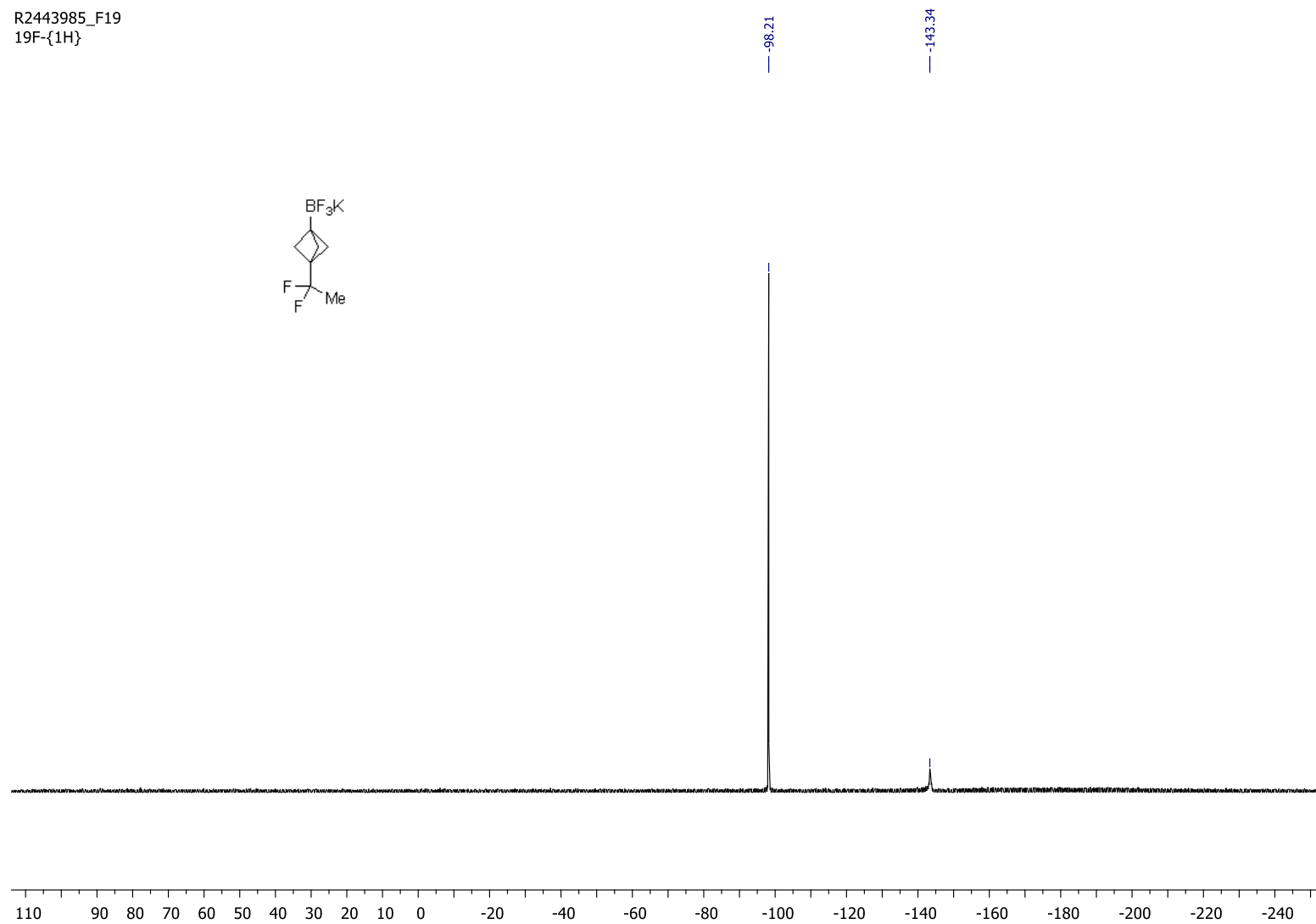


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

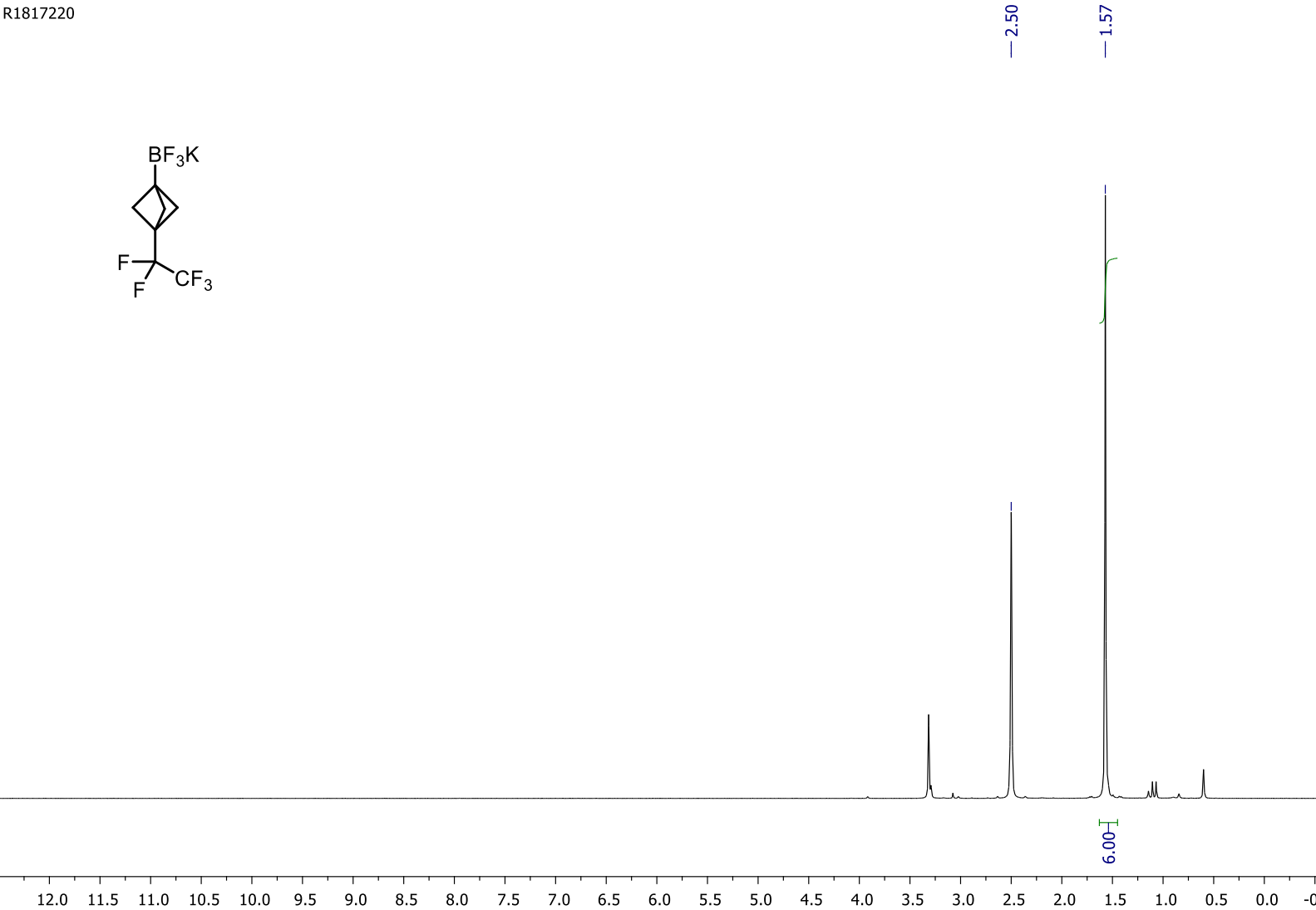
R2443985_F19
 $^{19}\text{F}\{^1\text{H}\}$



Compound 71b

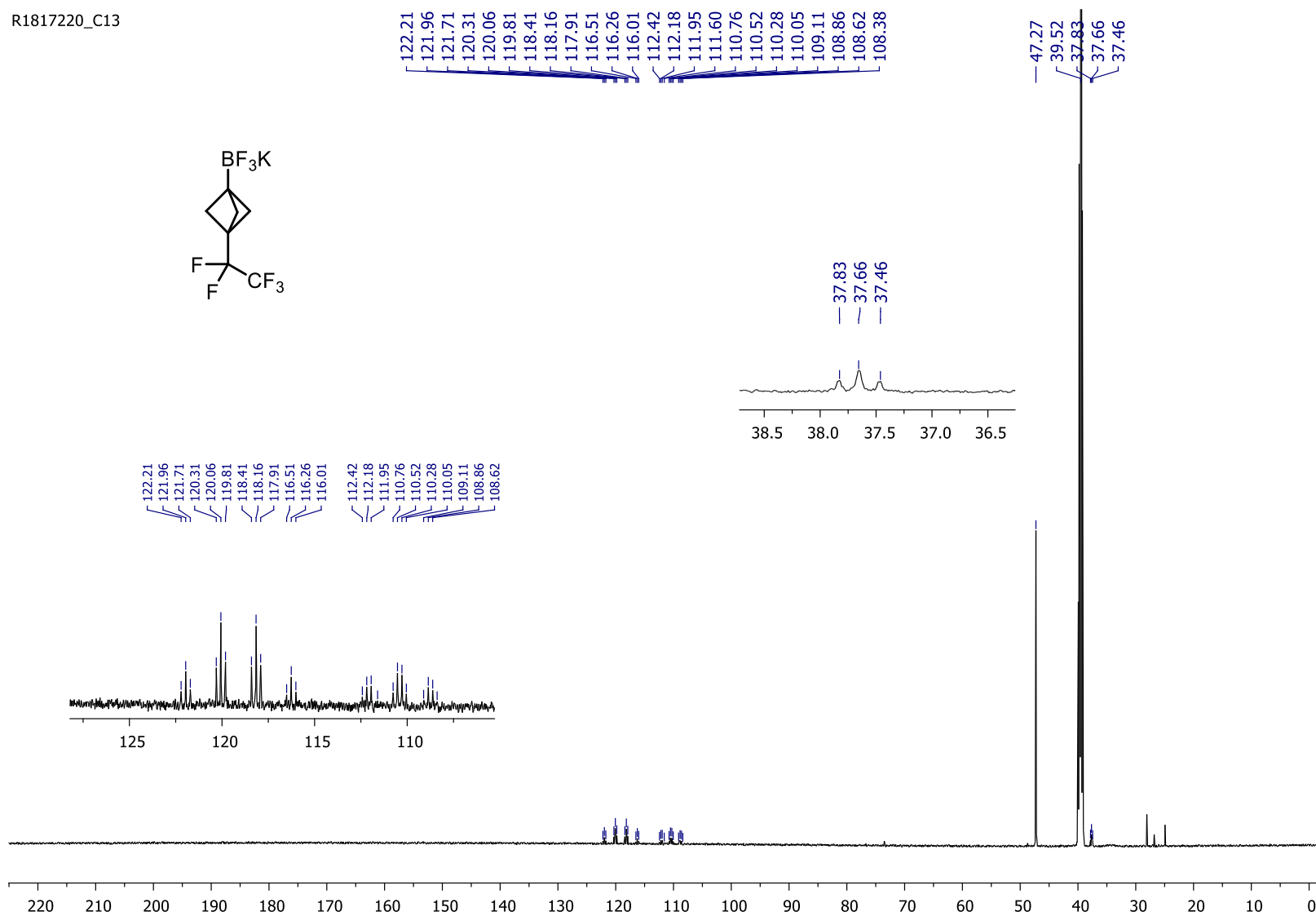
¹H NMR (500 MHz, DMSO-d₆)

R1817220



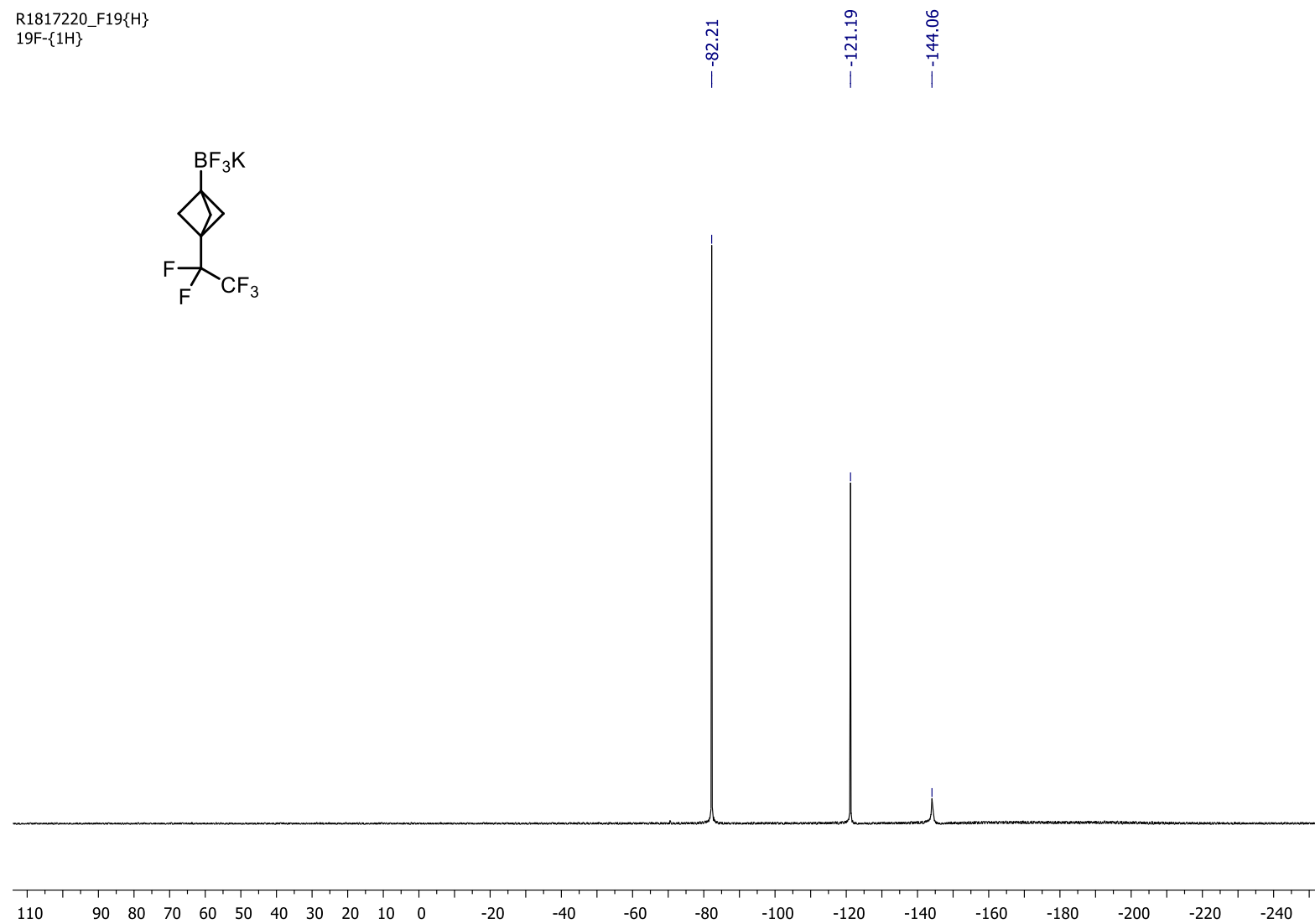
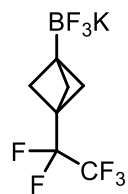
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R1817220_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

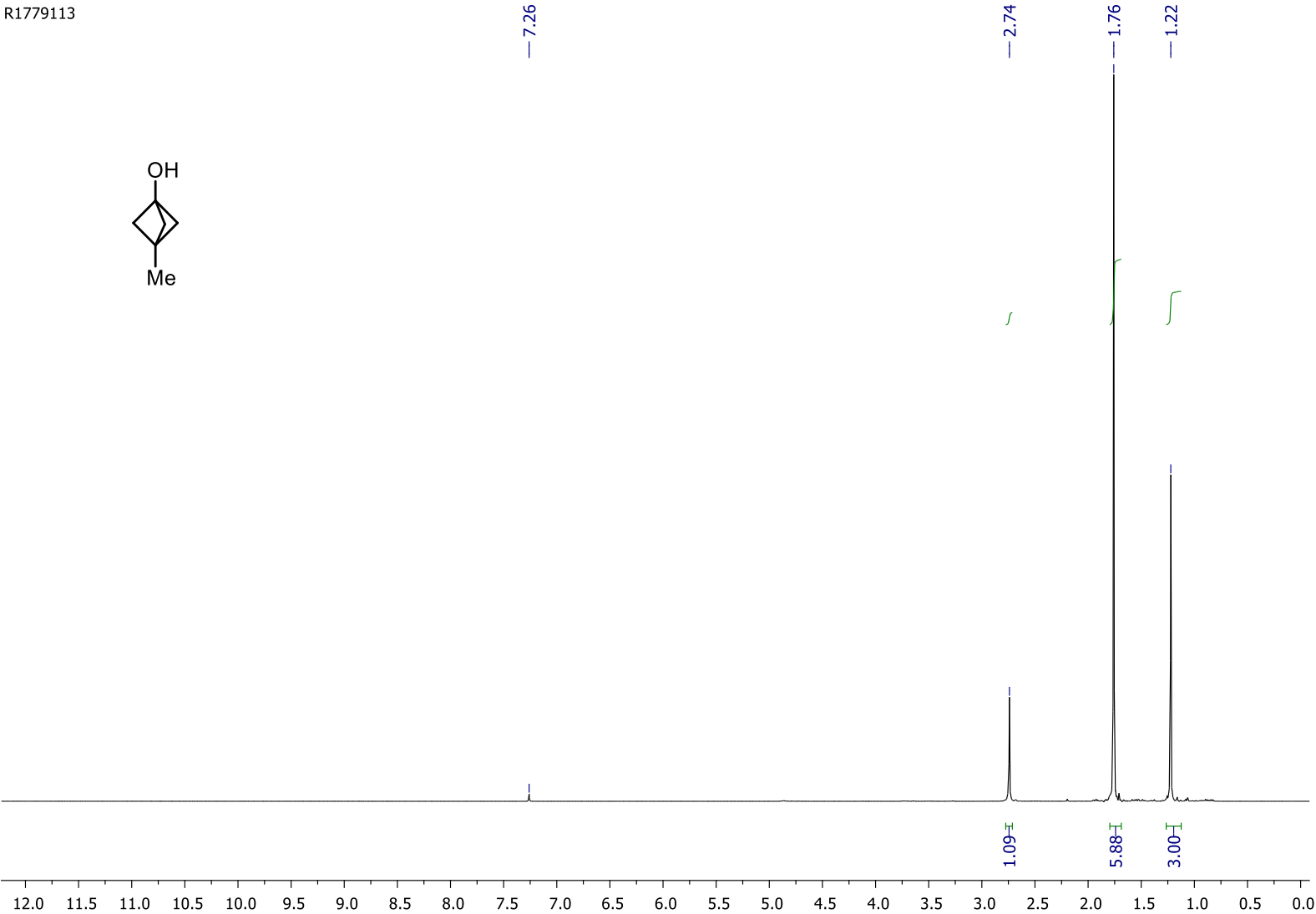
R1817220_F19{H}
19F-{1H}

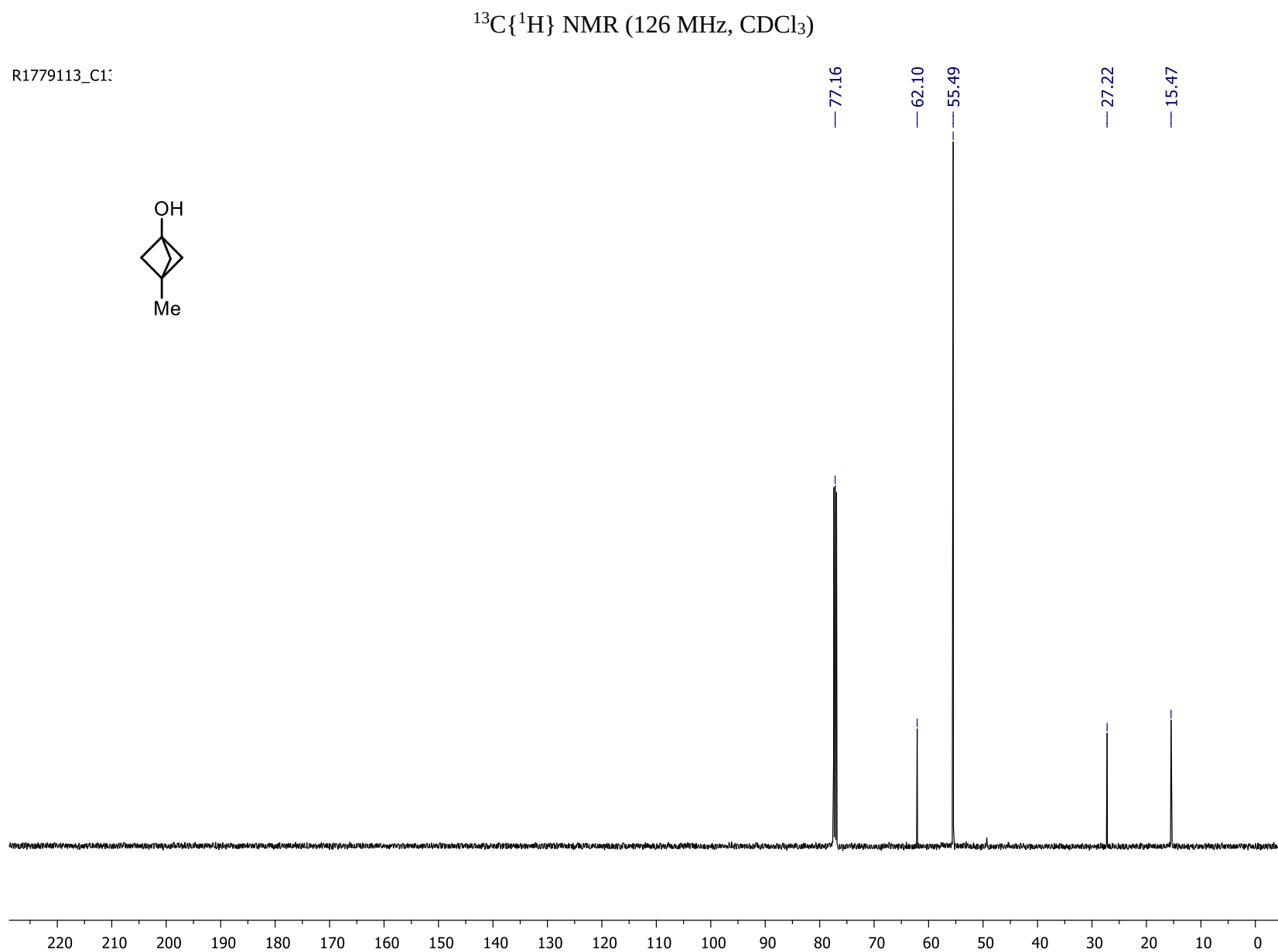


Compound 1c

R1779113

¹H NMR (400 MHz, CDCl₃)

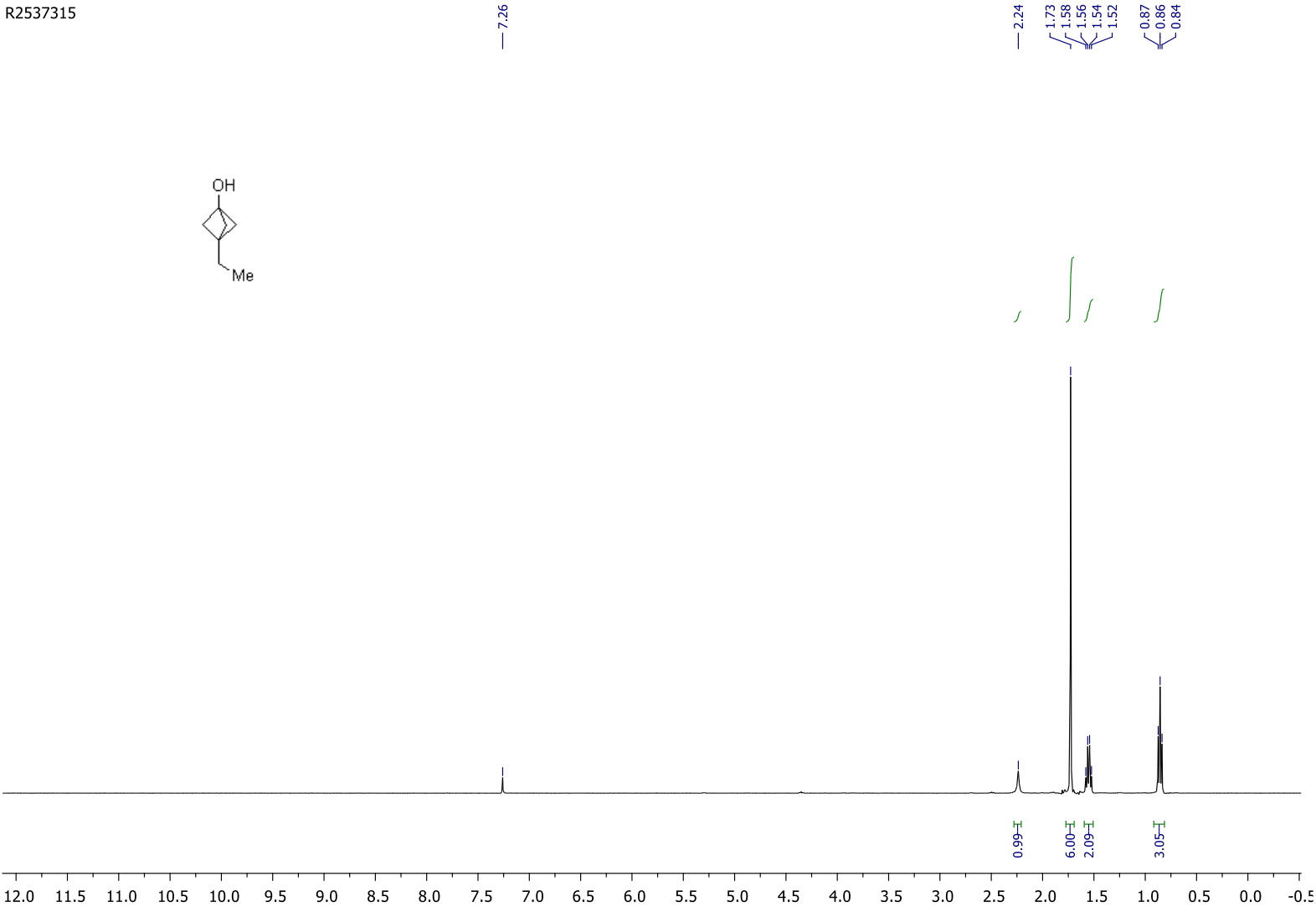




Compound 2c

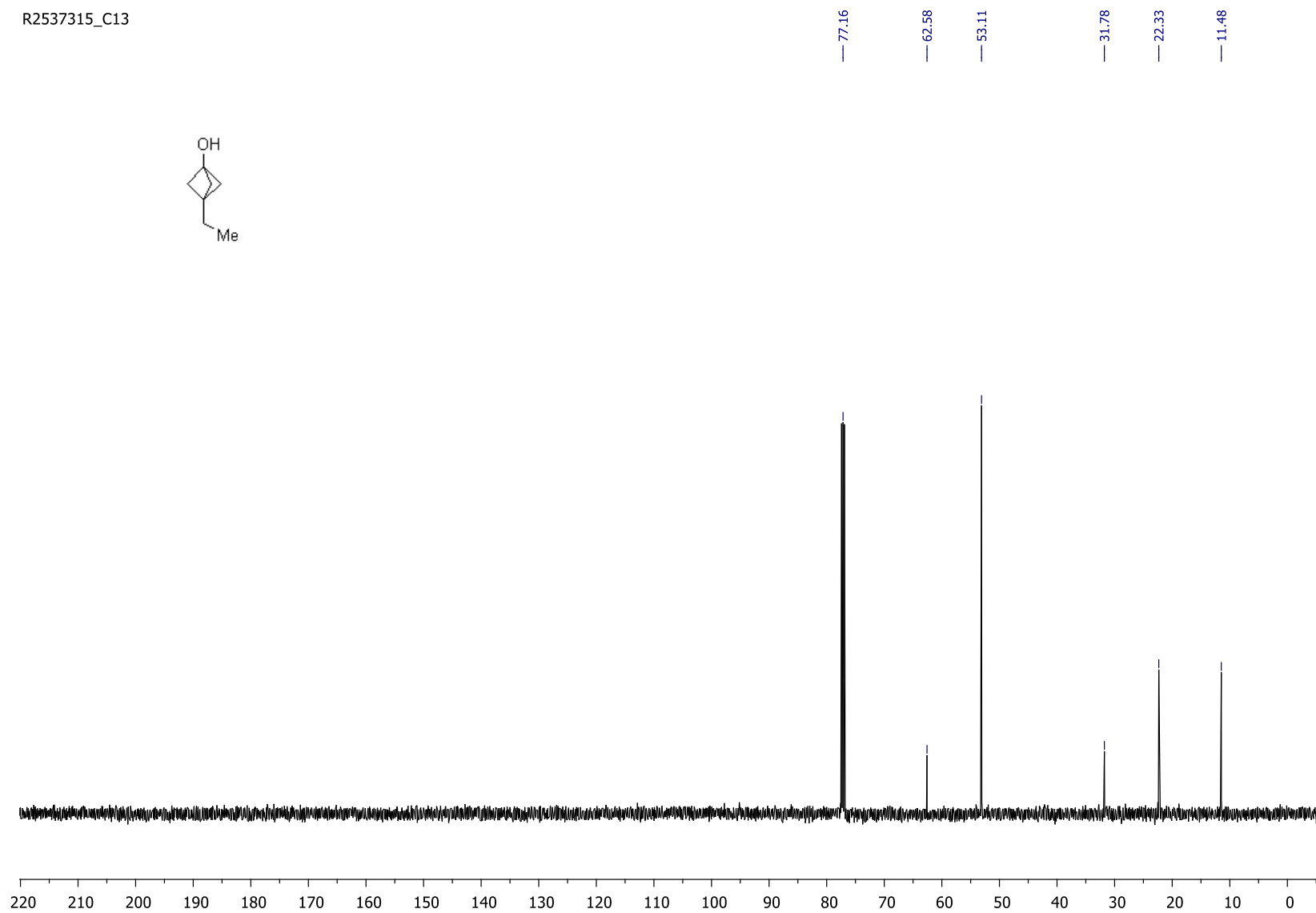
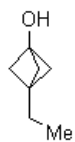
R2537315

¹H NMR (400 MHz, CDCl₃)

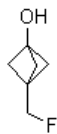


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

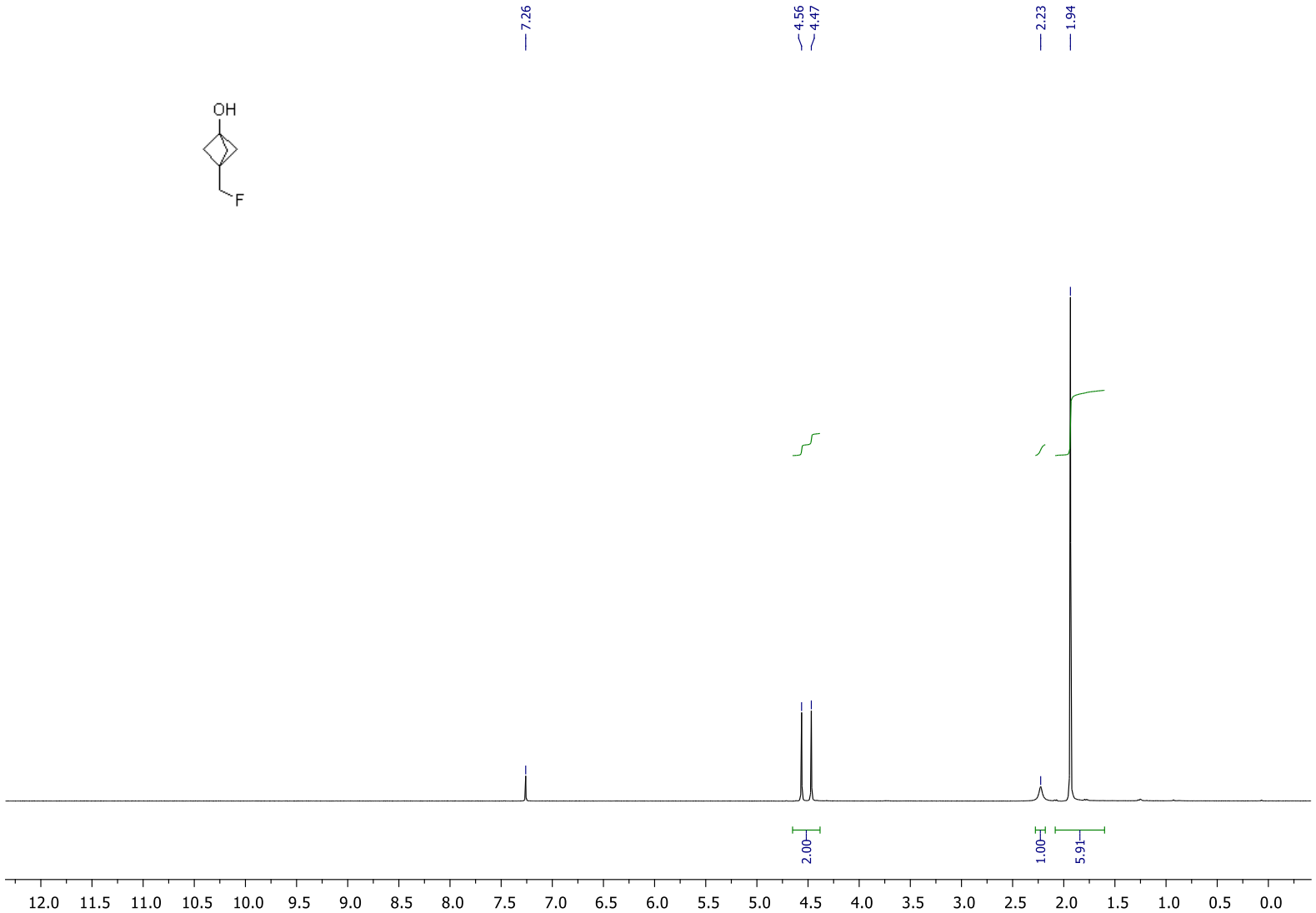
R2537315_C13



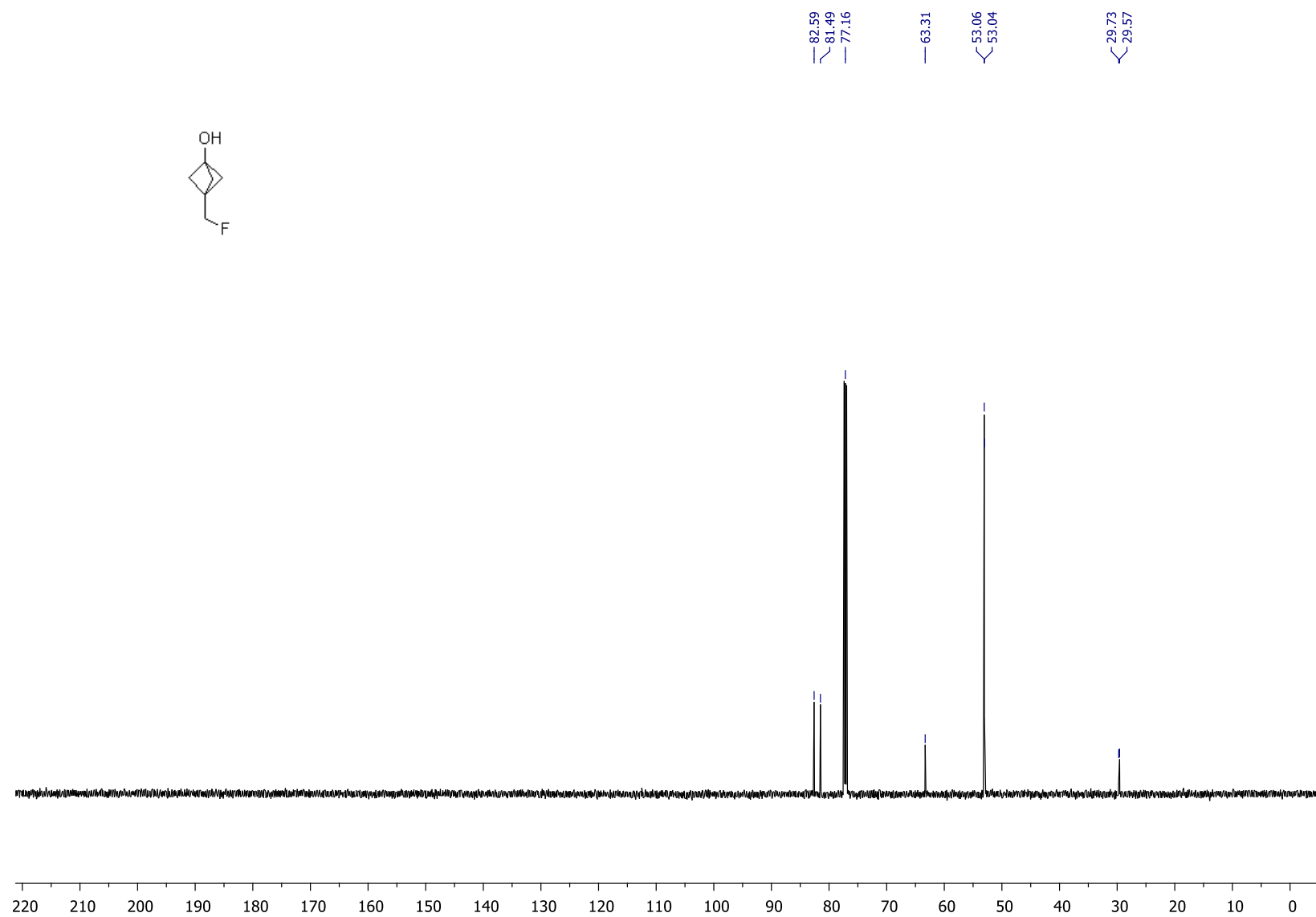
Compound 21c



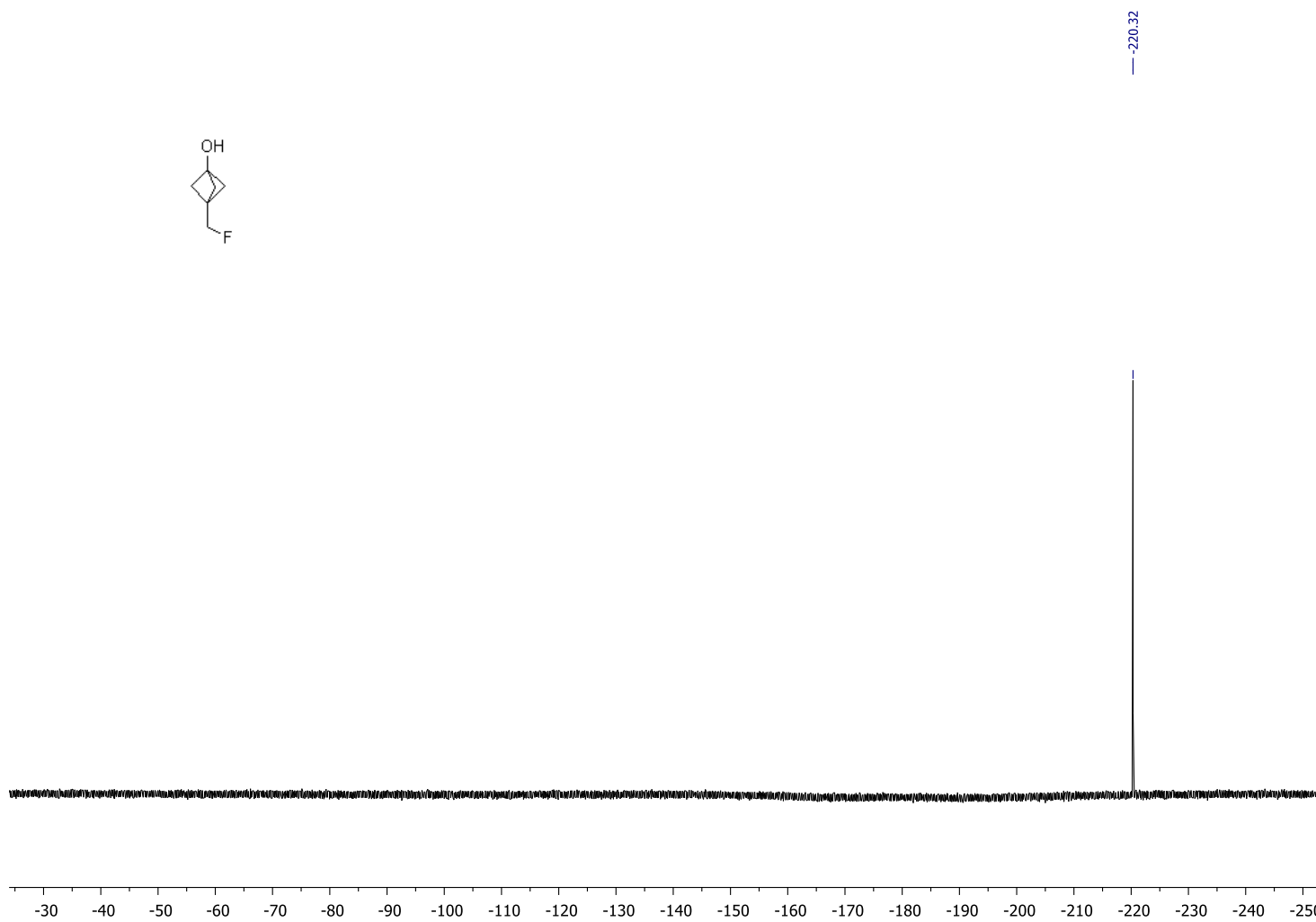
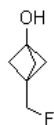
¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)



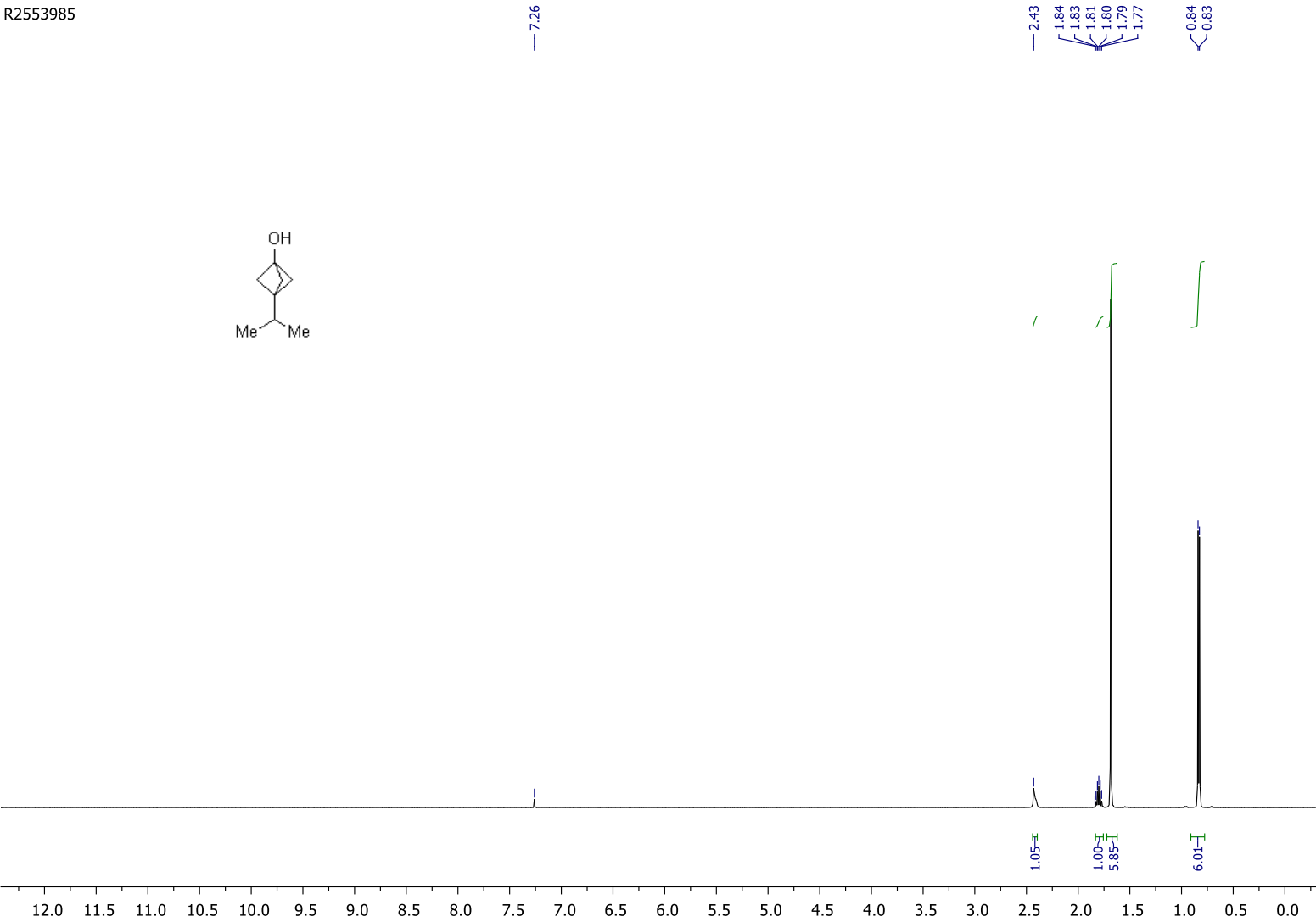
$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)



Compound 48c

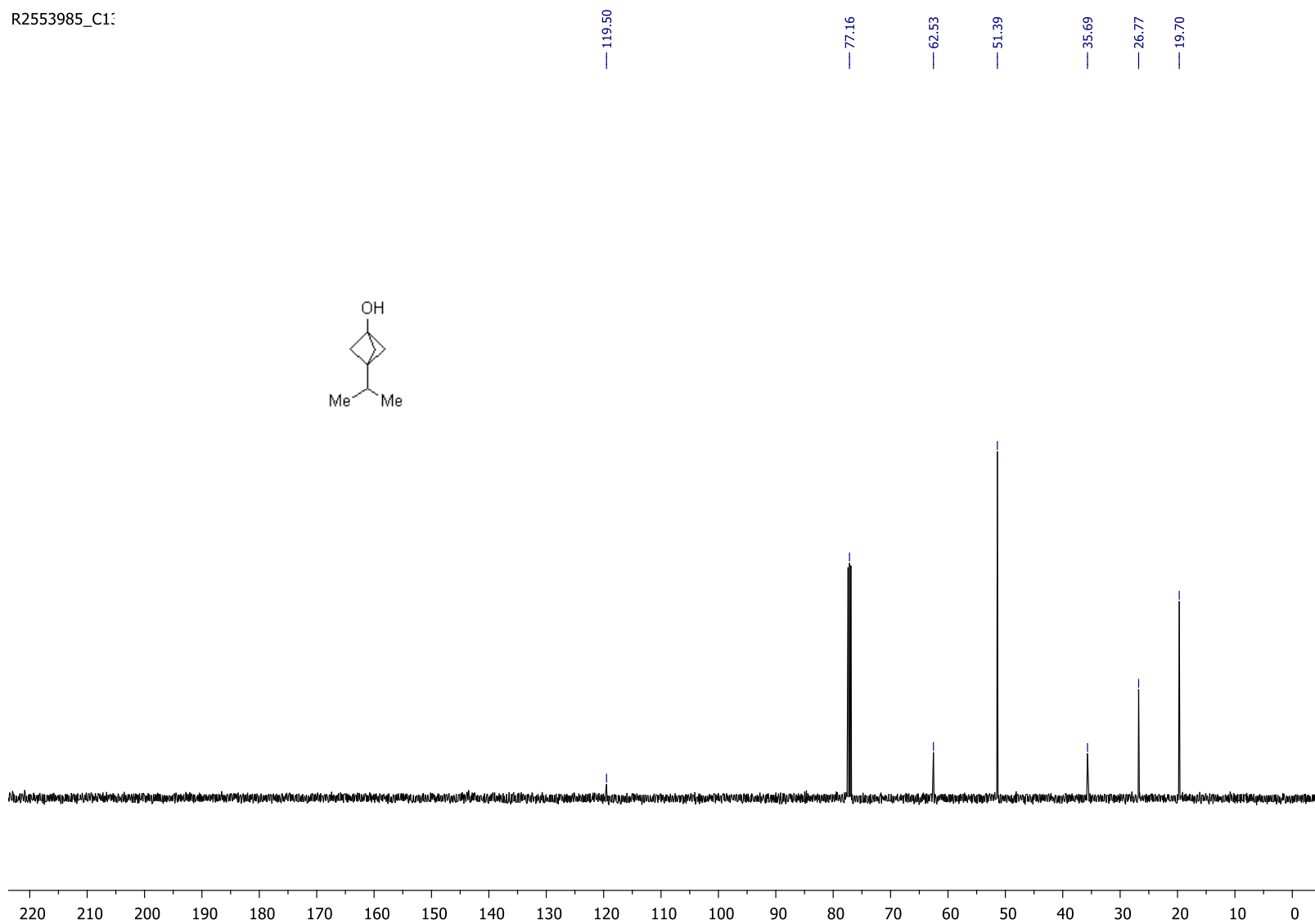
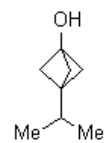
R2553985

¹H NMR (500 MHz, CDCl₃)



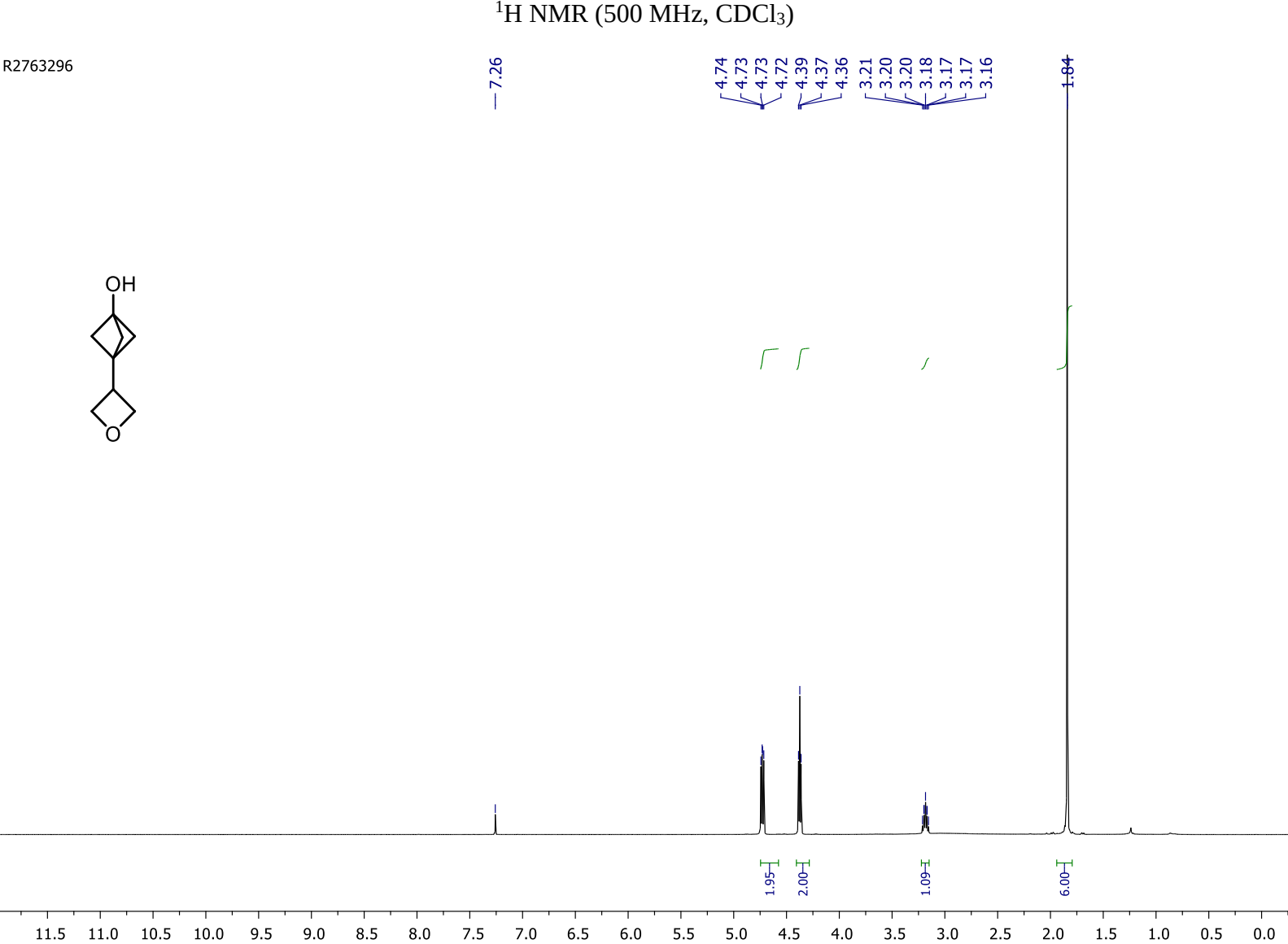
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2553985_C1:



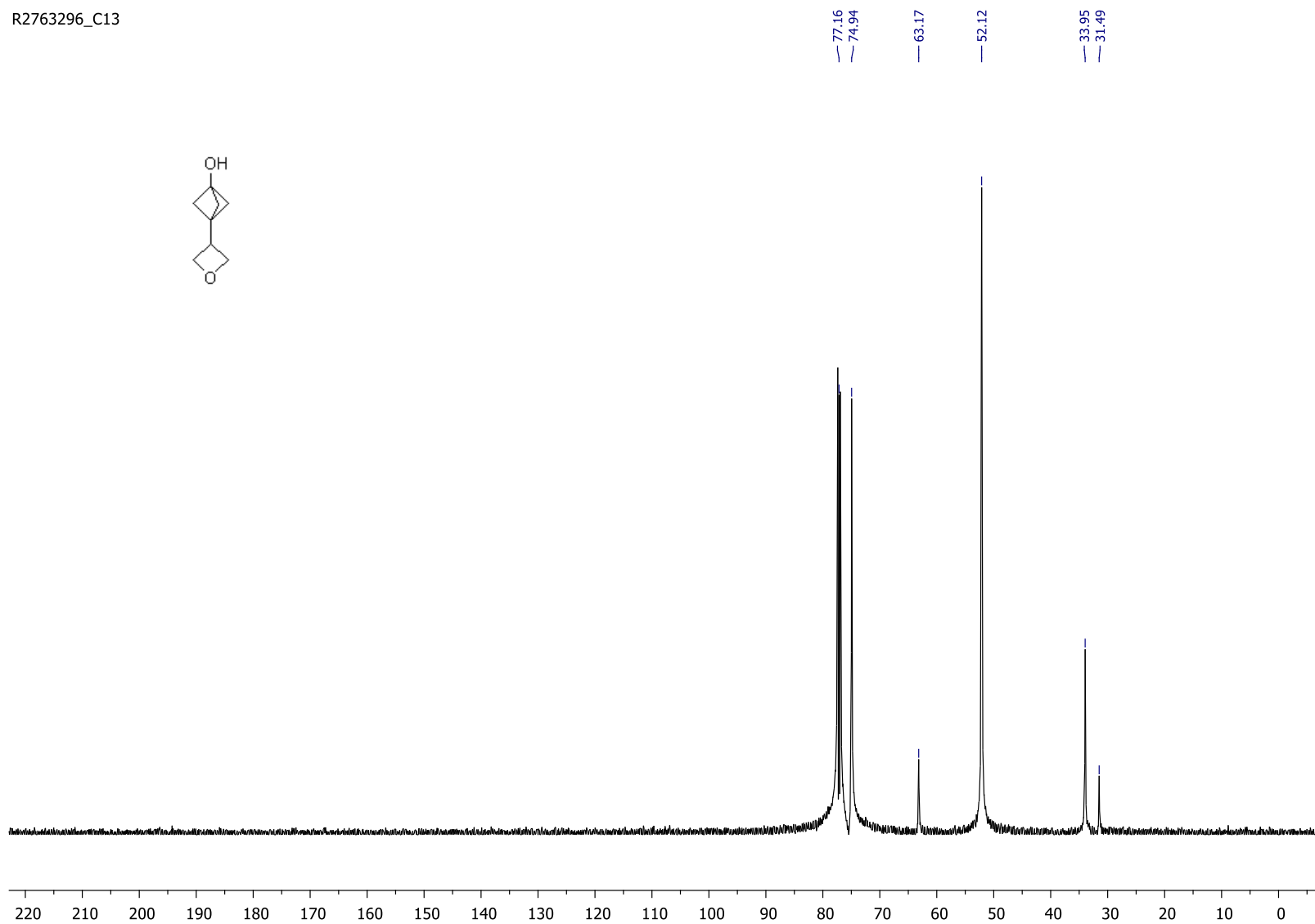
Compound 55c

R2763296



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

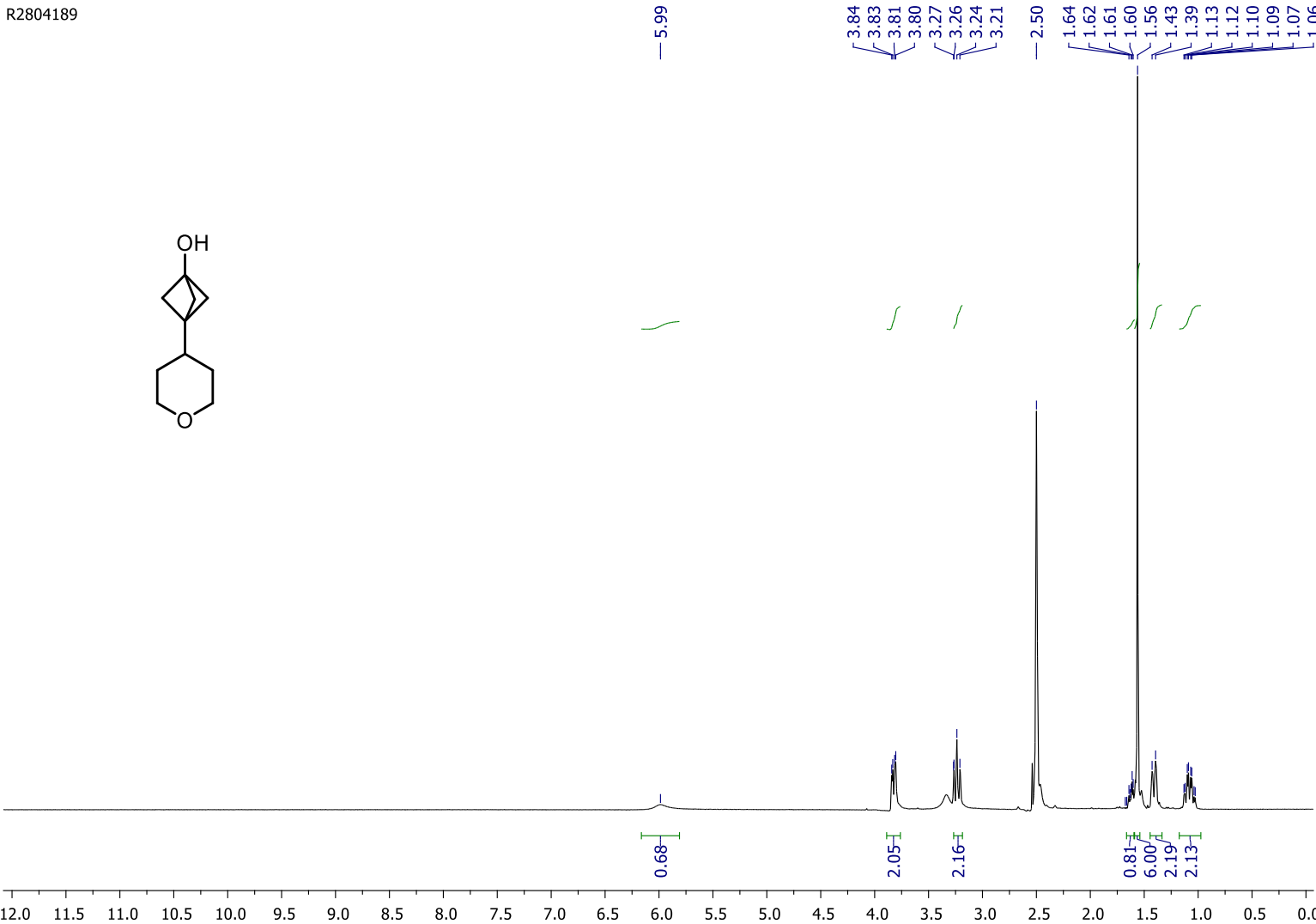
R2763296_C13



Compound 57c

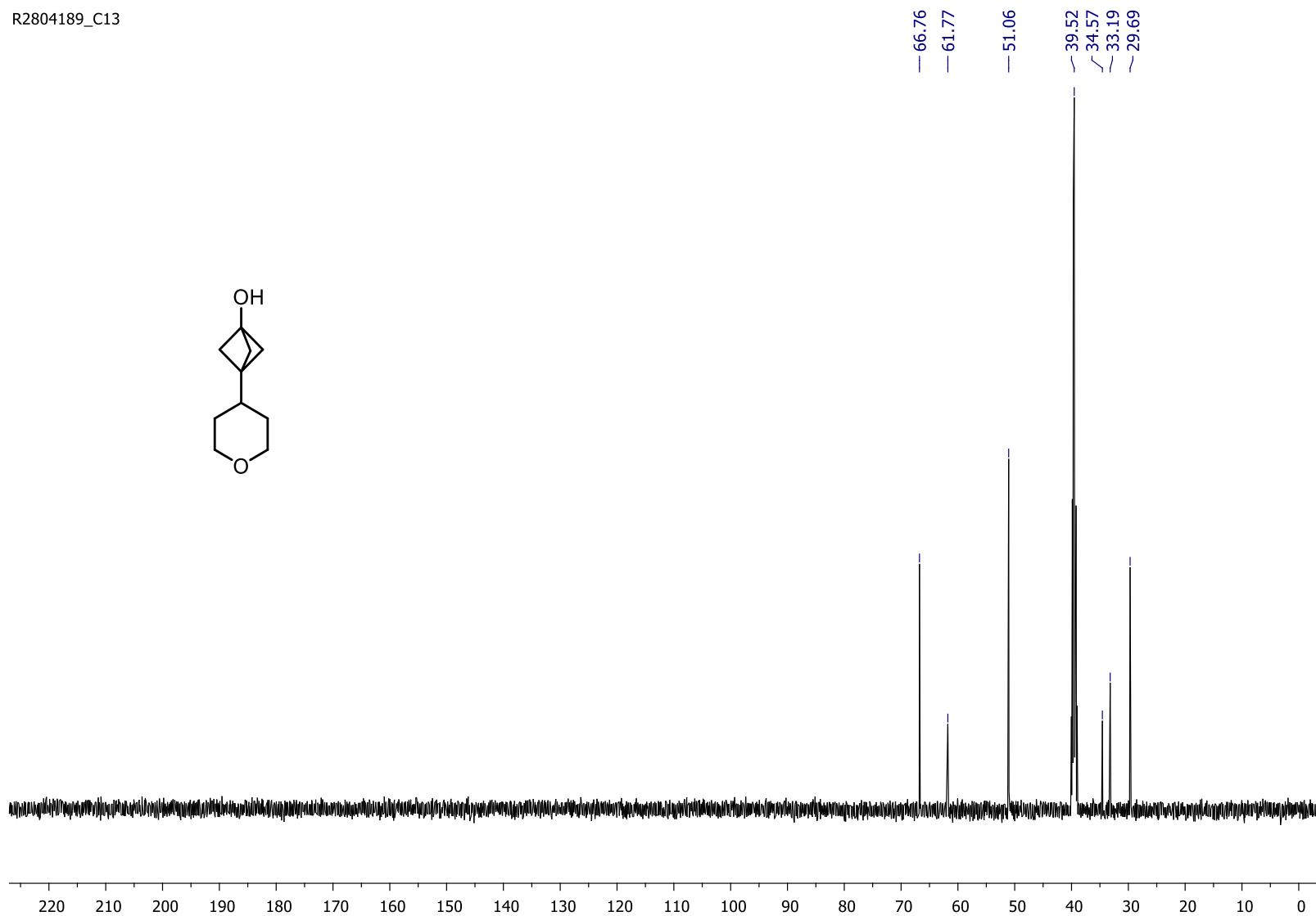
R2804189

¹H NMR (400 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

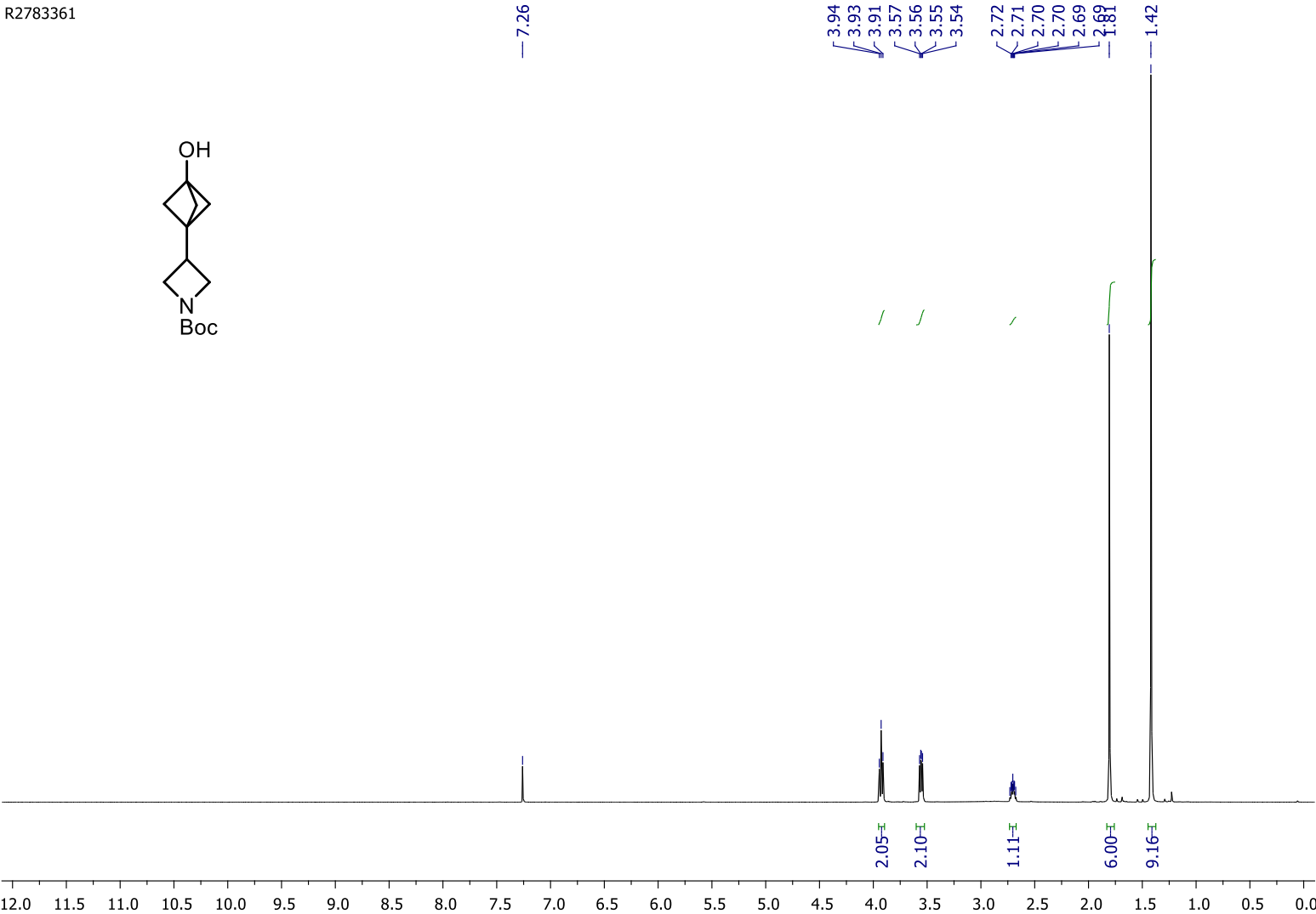
R2804189_C13

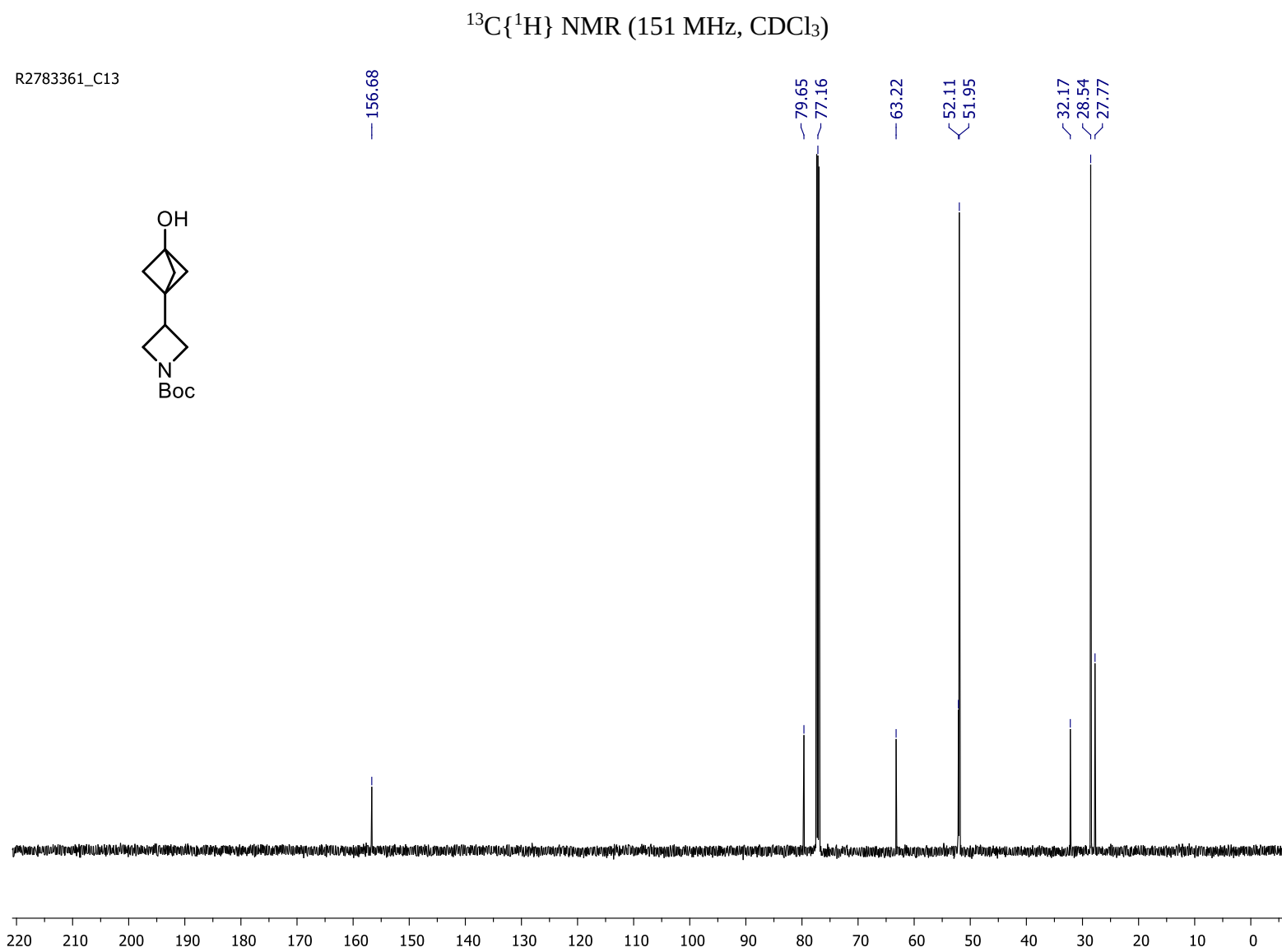


Compound 60c

R2783361

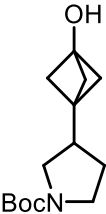
¹H NMR (500 MHz, CDCl₃)



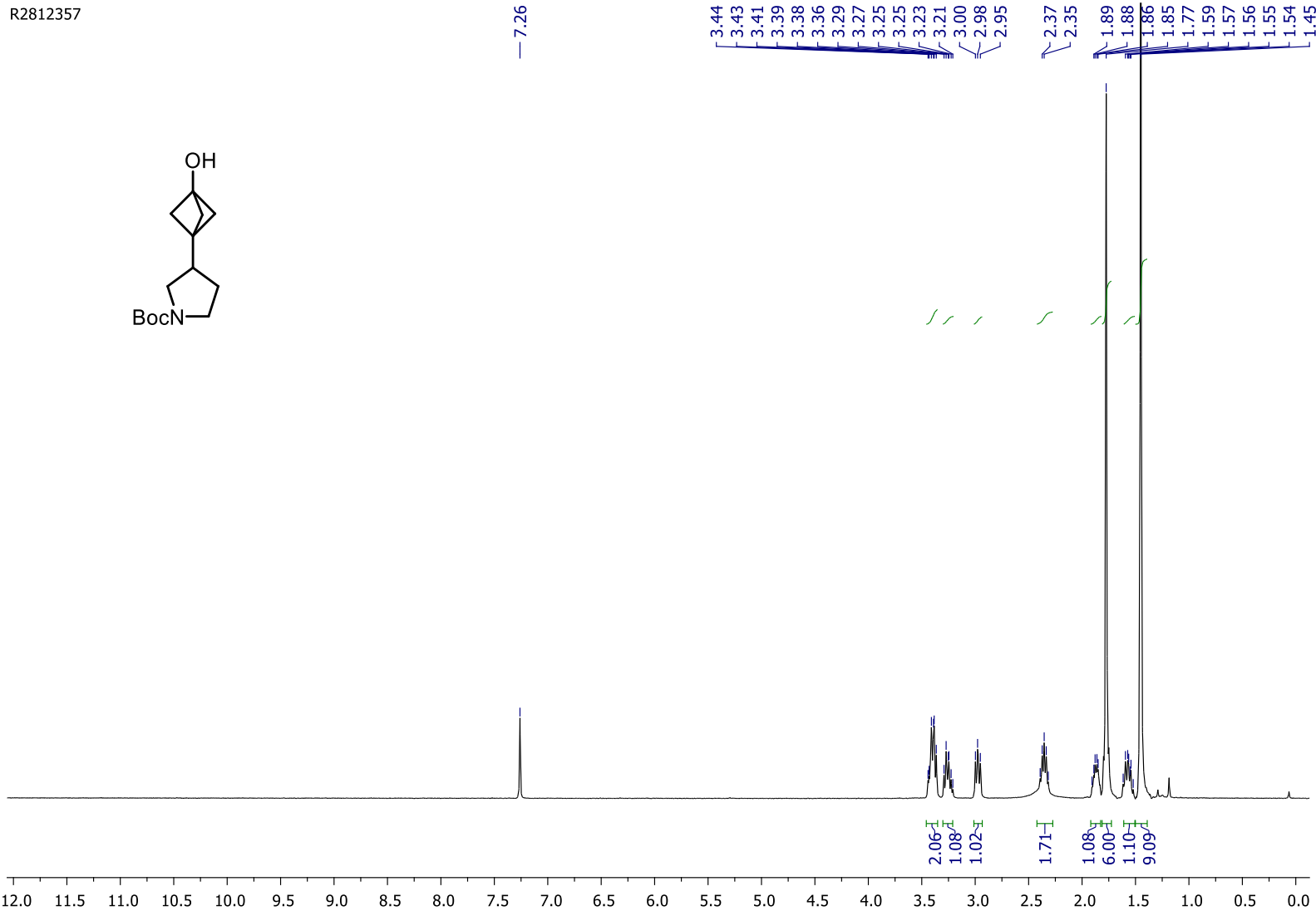


Compound 61c

R2812357

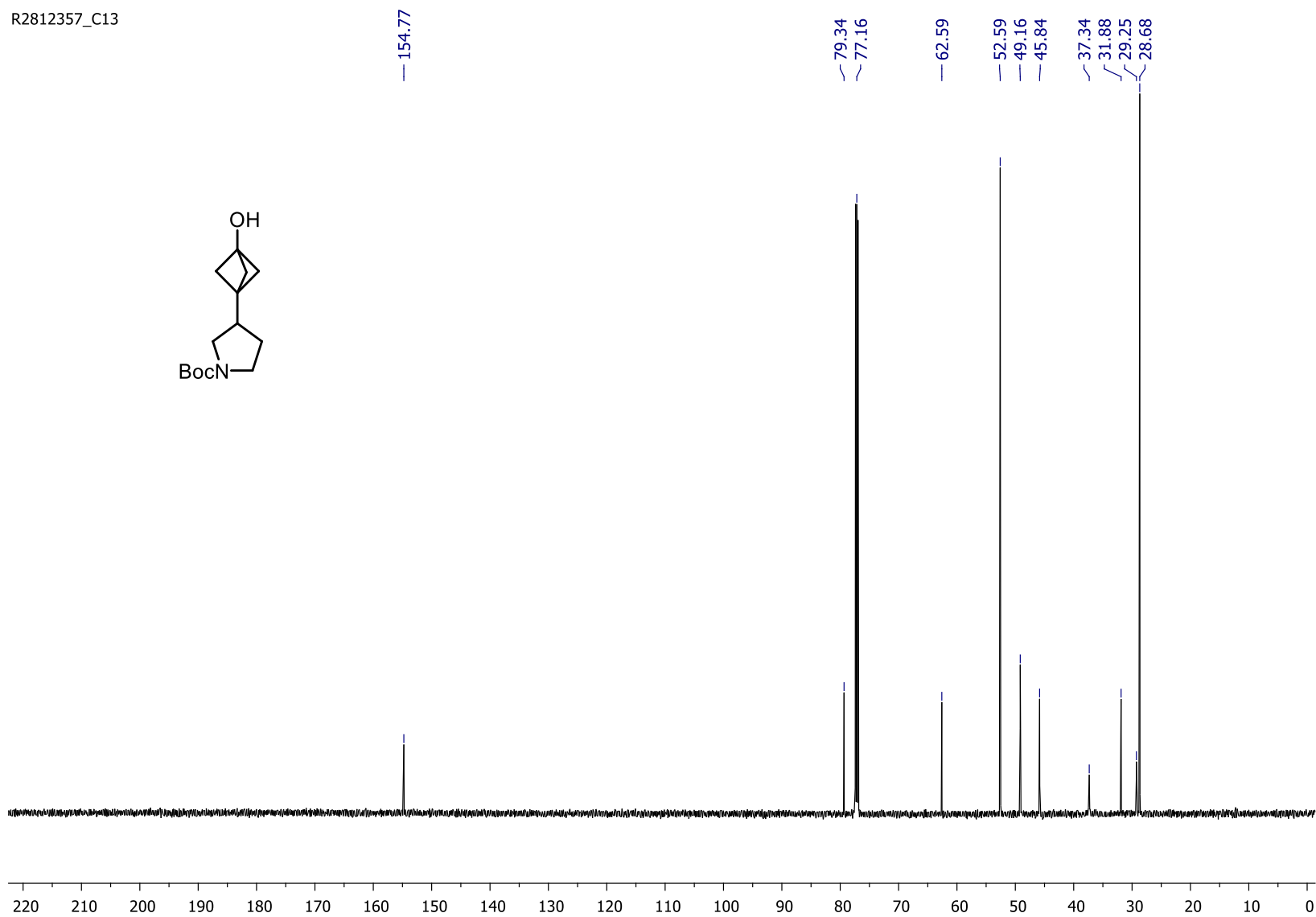
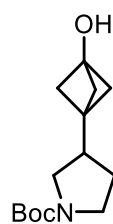


¹H NMR (400 MHz, CDCl₃)



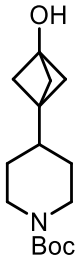
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

R2812357_C13

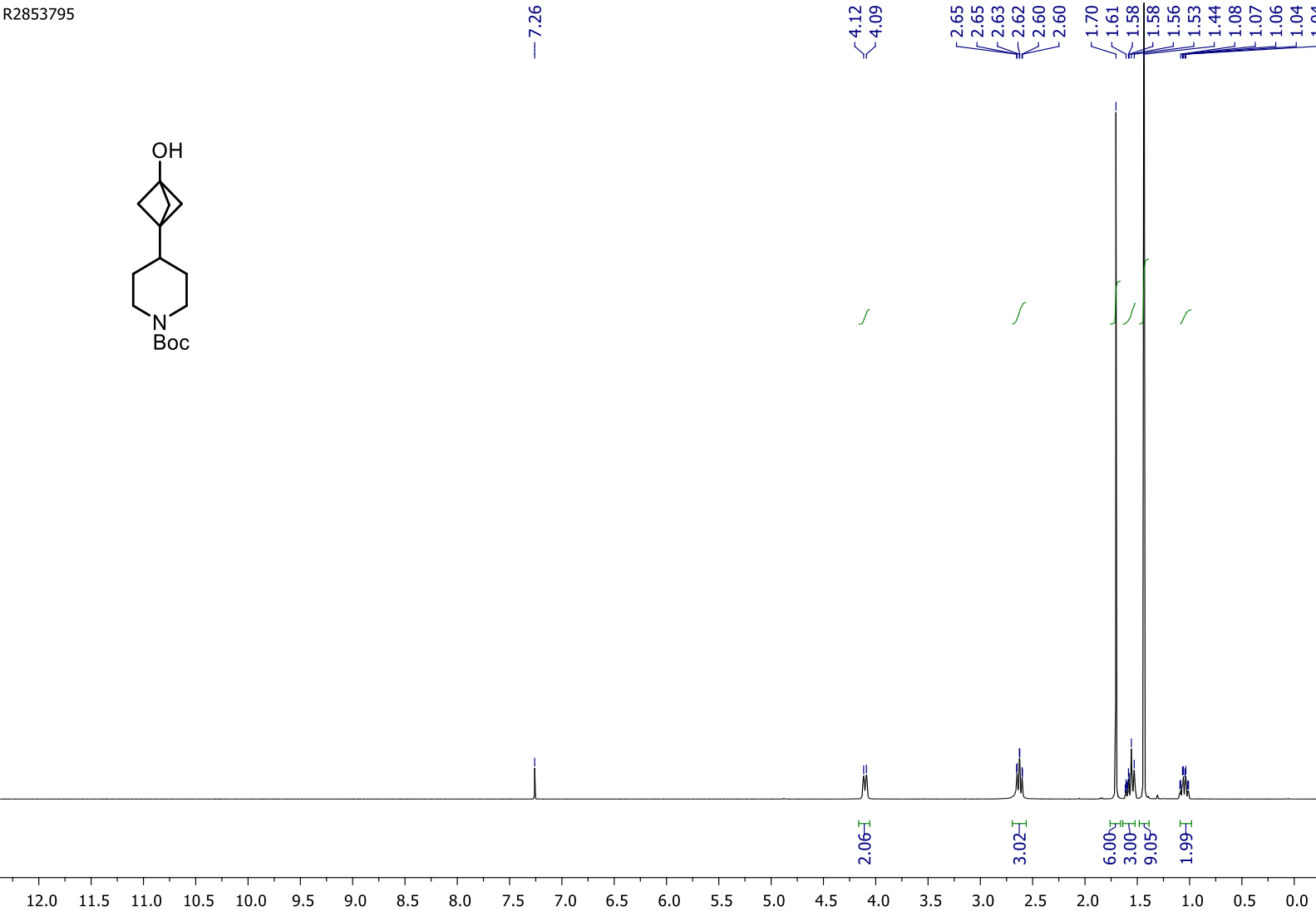


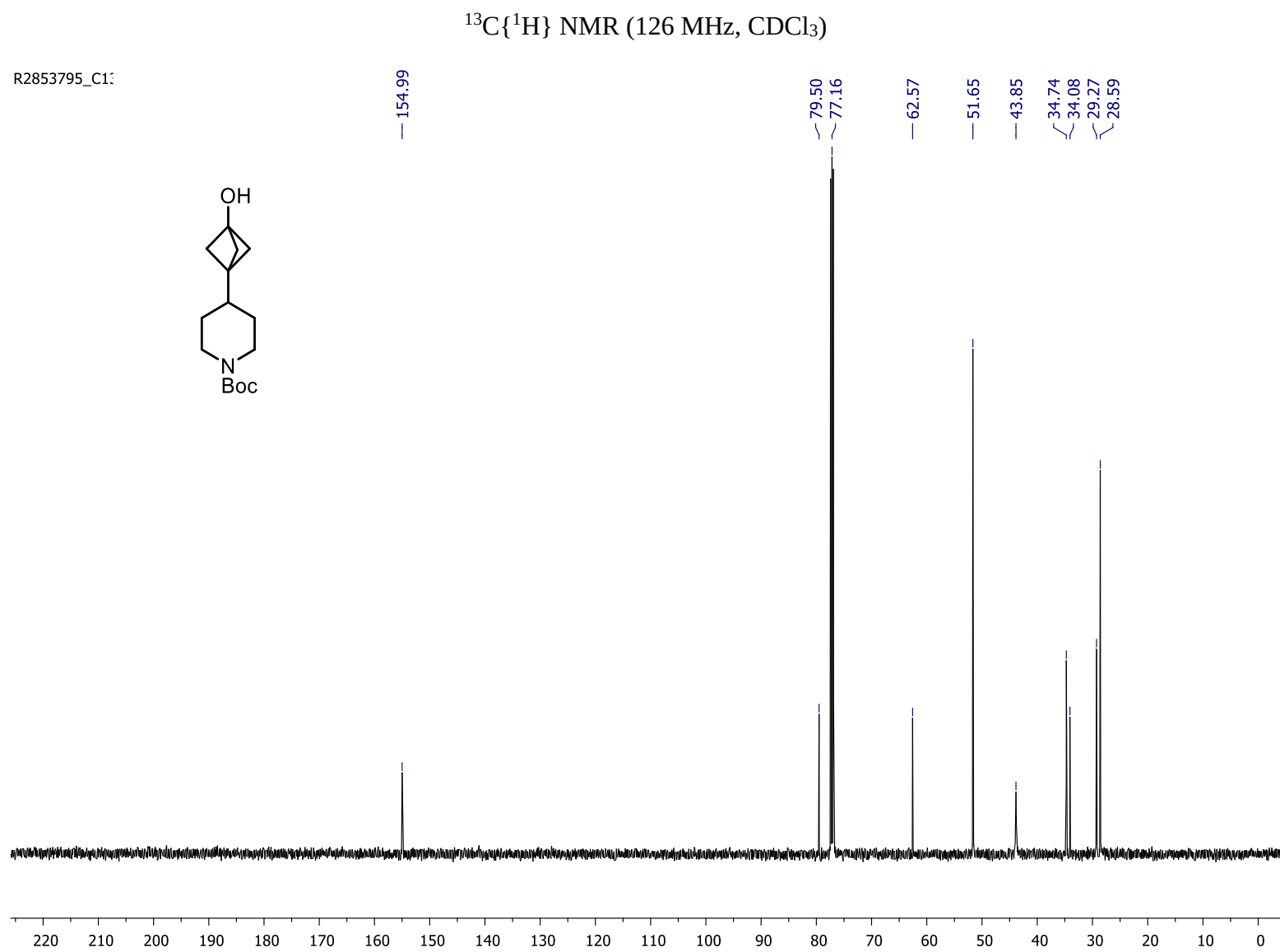
Compound 63c

R2853795



¹H NMR (500 MHz, CDCl₃)

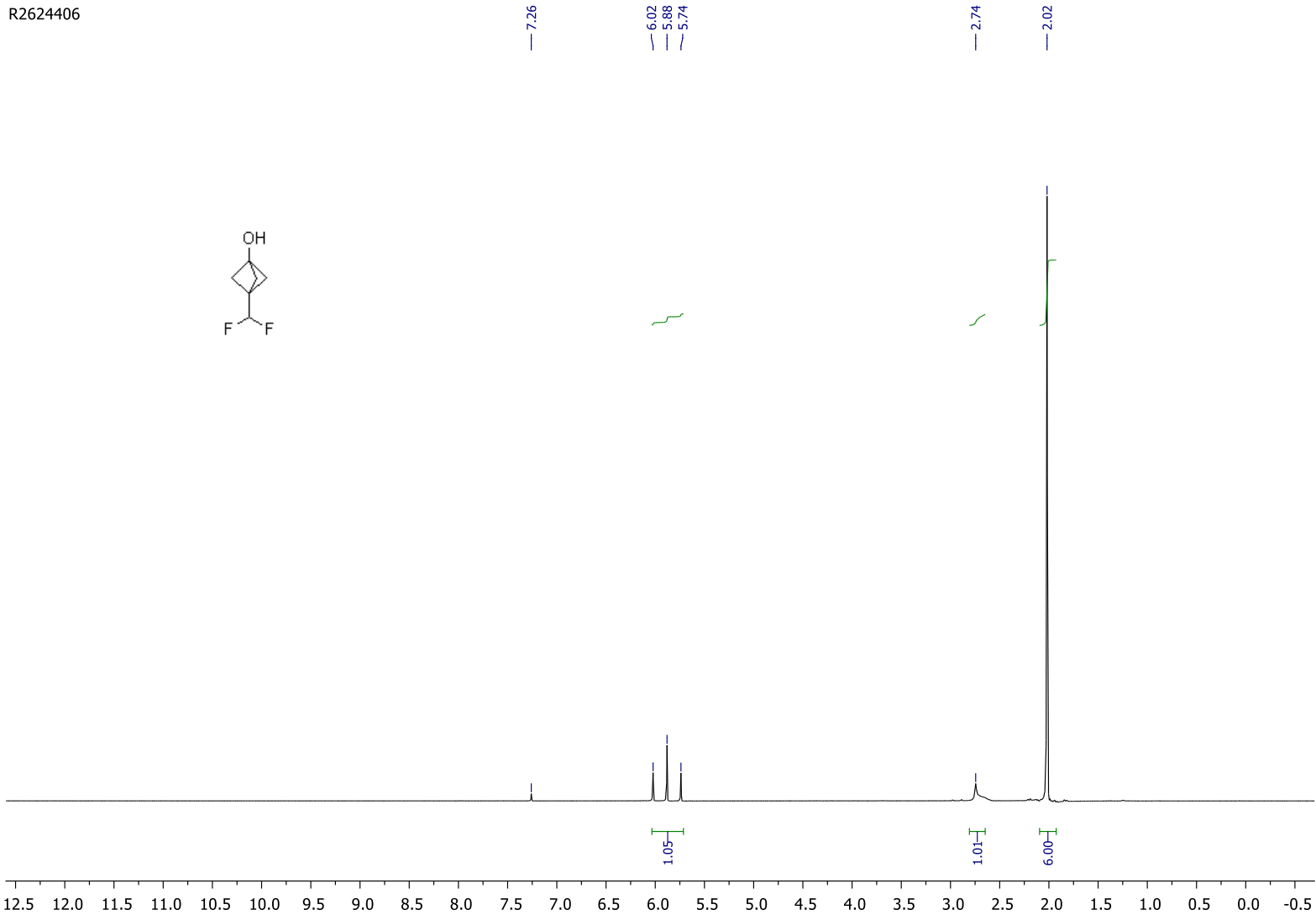




Compound 67c

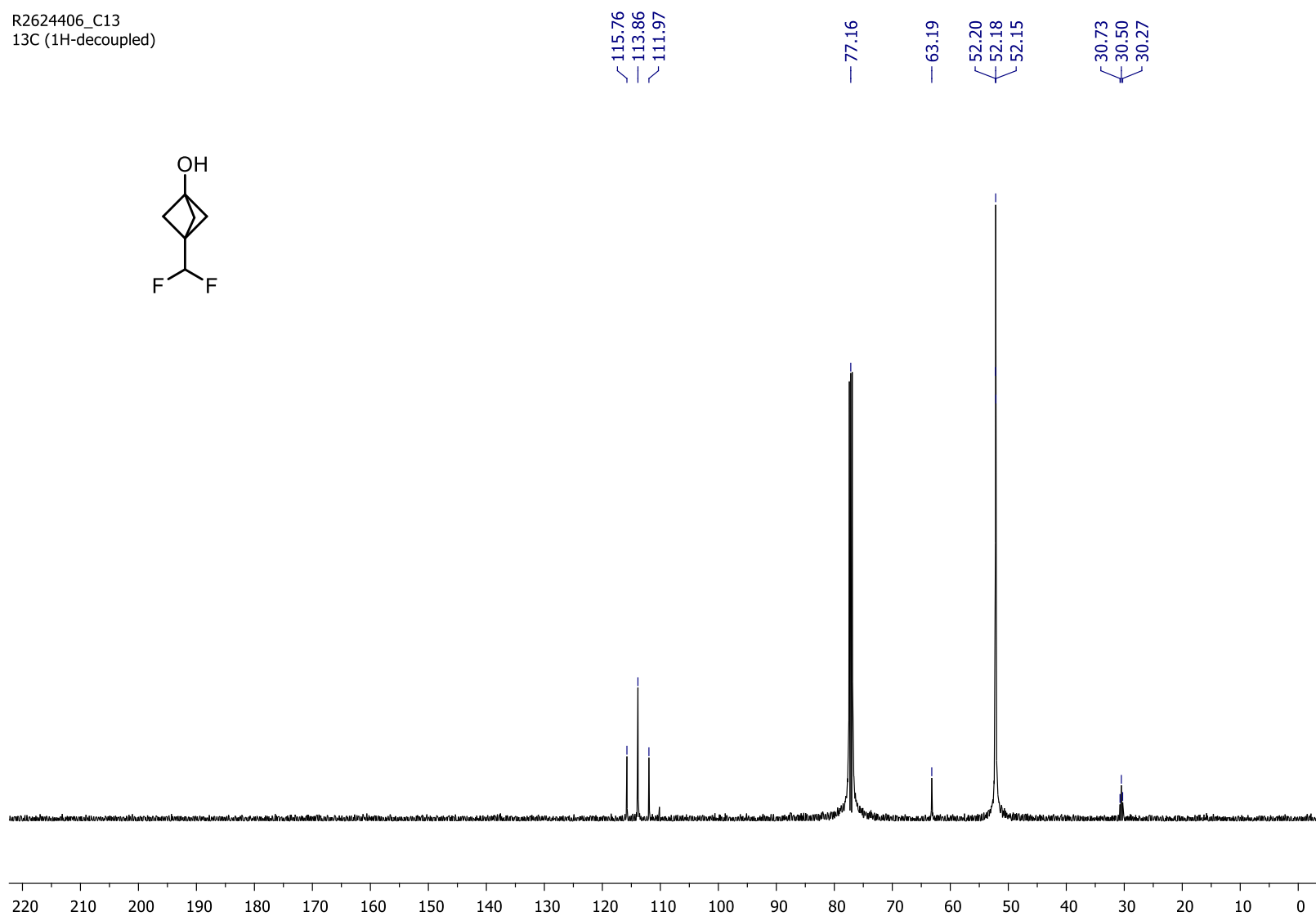
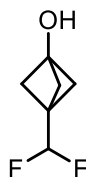
R2624406

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

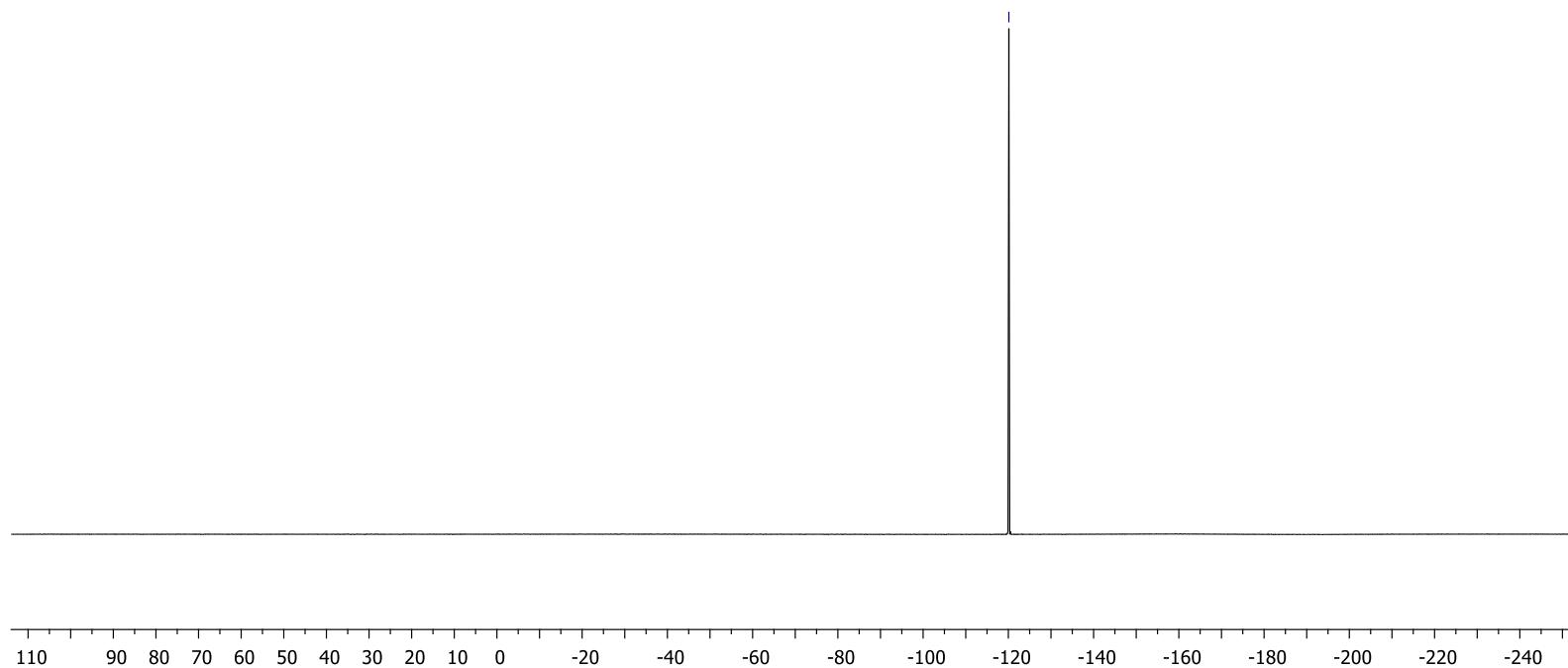
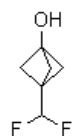
R2624406_C13
13C (1H-decoupled)



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2624406_F19{H}

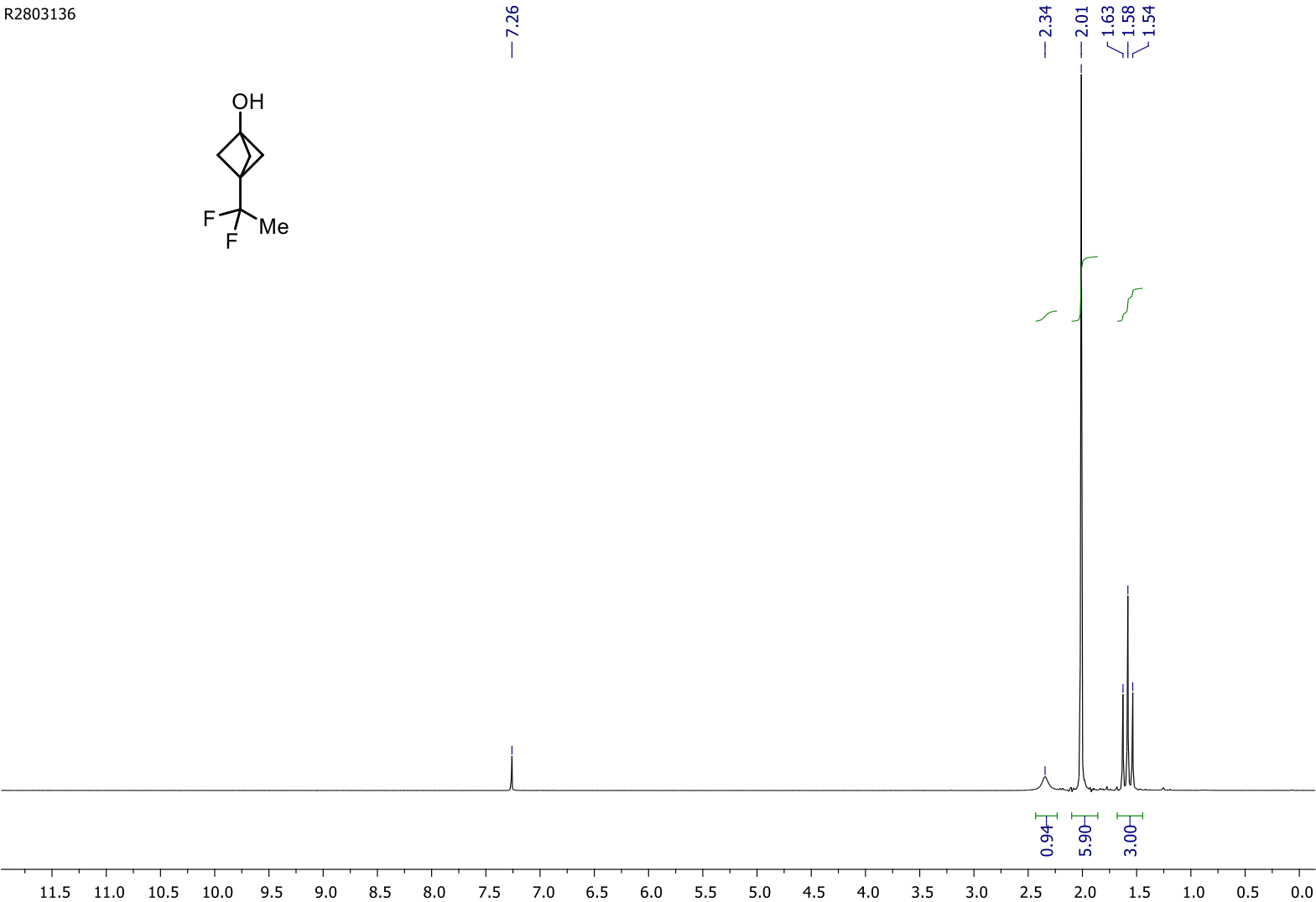
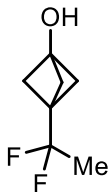
— -120.12



Compound 68c

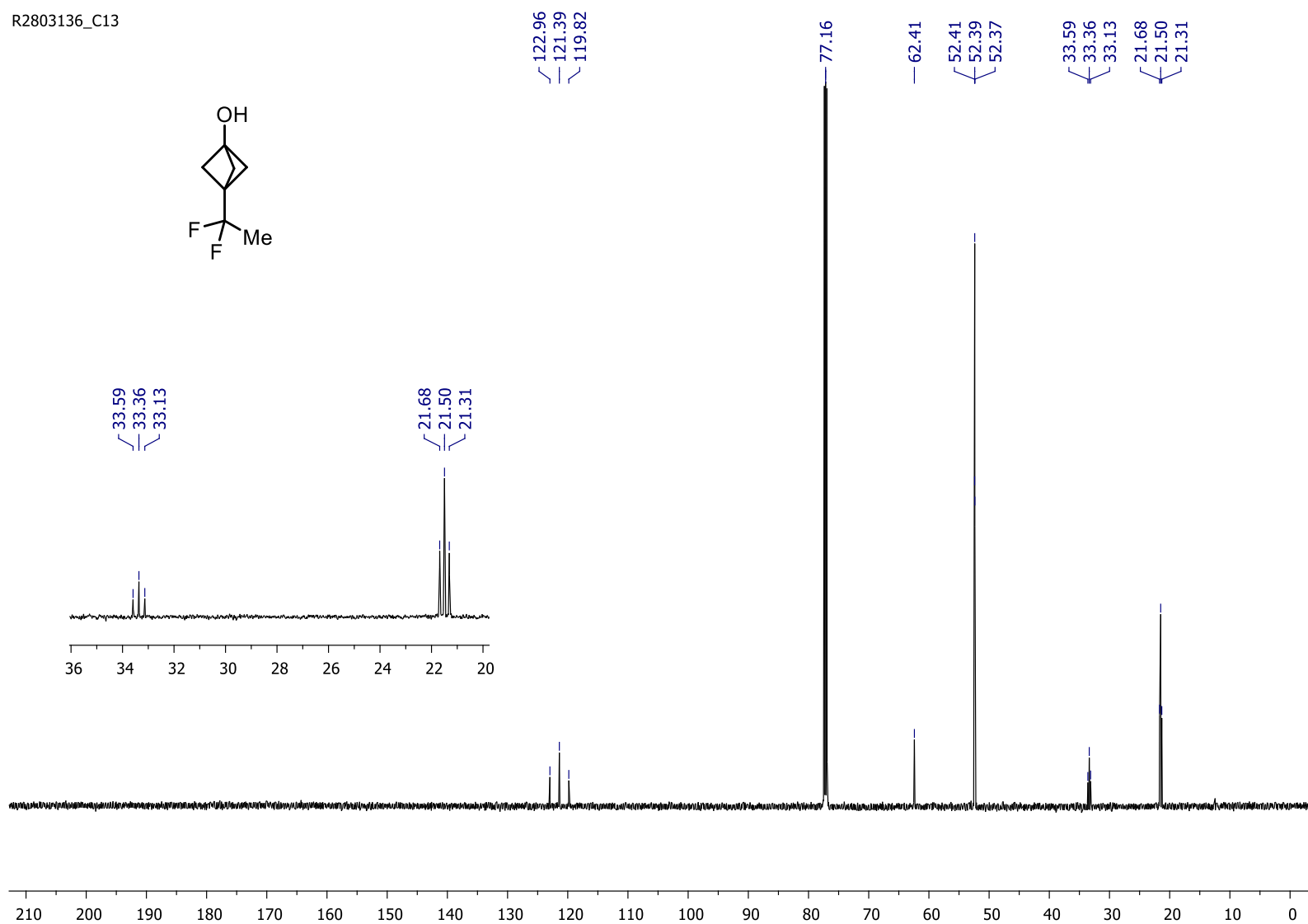
R2803136

¹H NMR (400 MHz, CDCl₃)



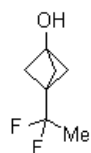
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

R2803136_C13

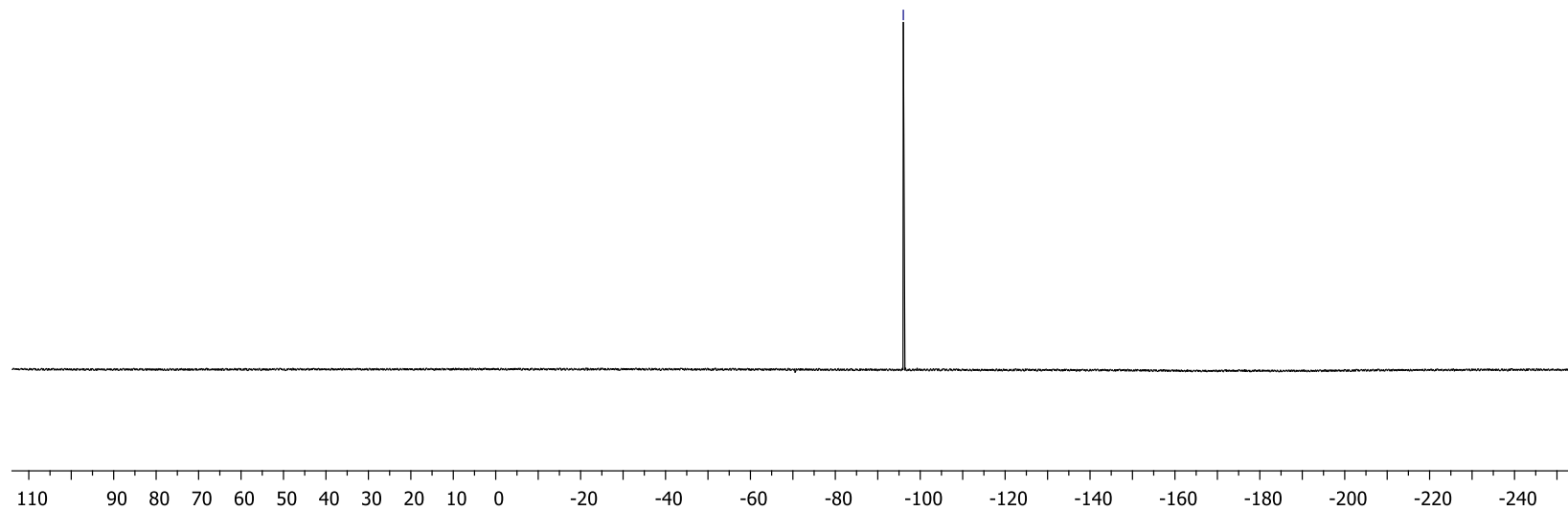


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2803136_F19{H}
 $^{19}\text{F}\{^1\text{H}\}$



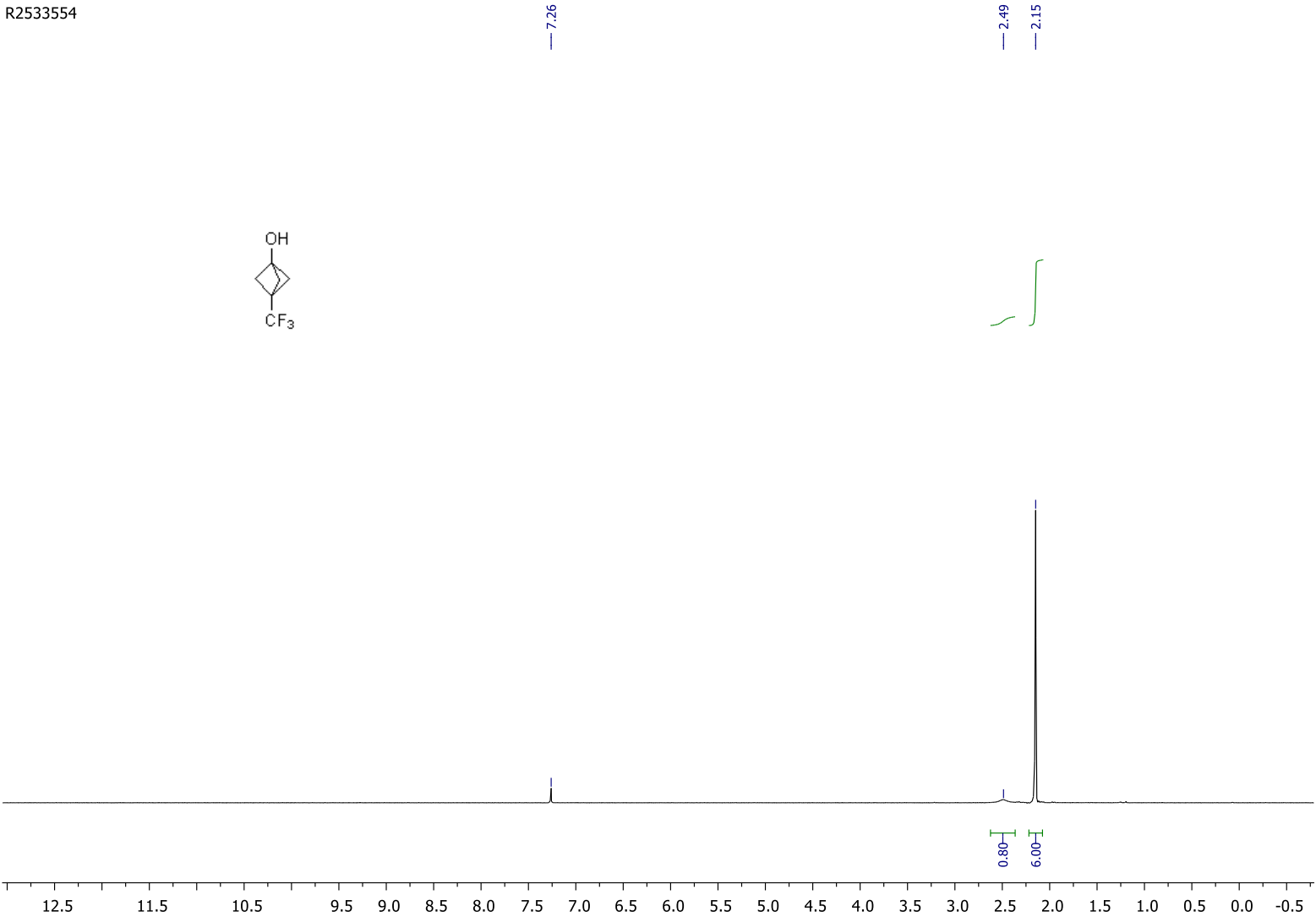
— -96.02

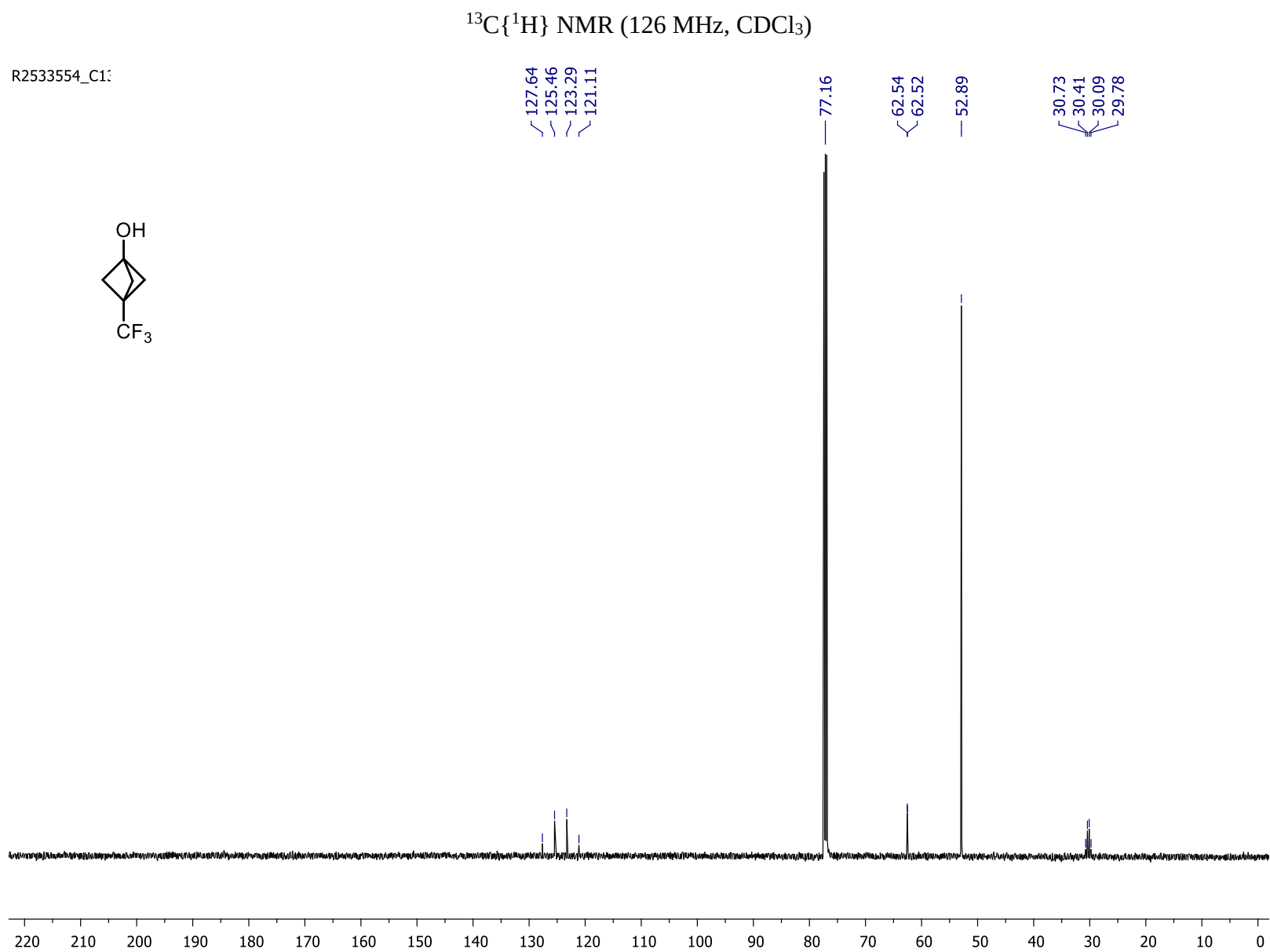


Compound 69c

R2533554

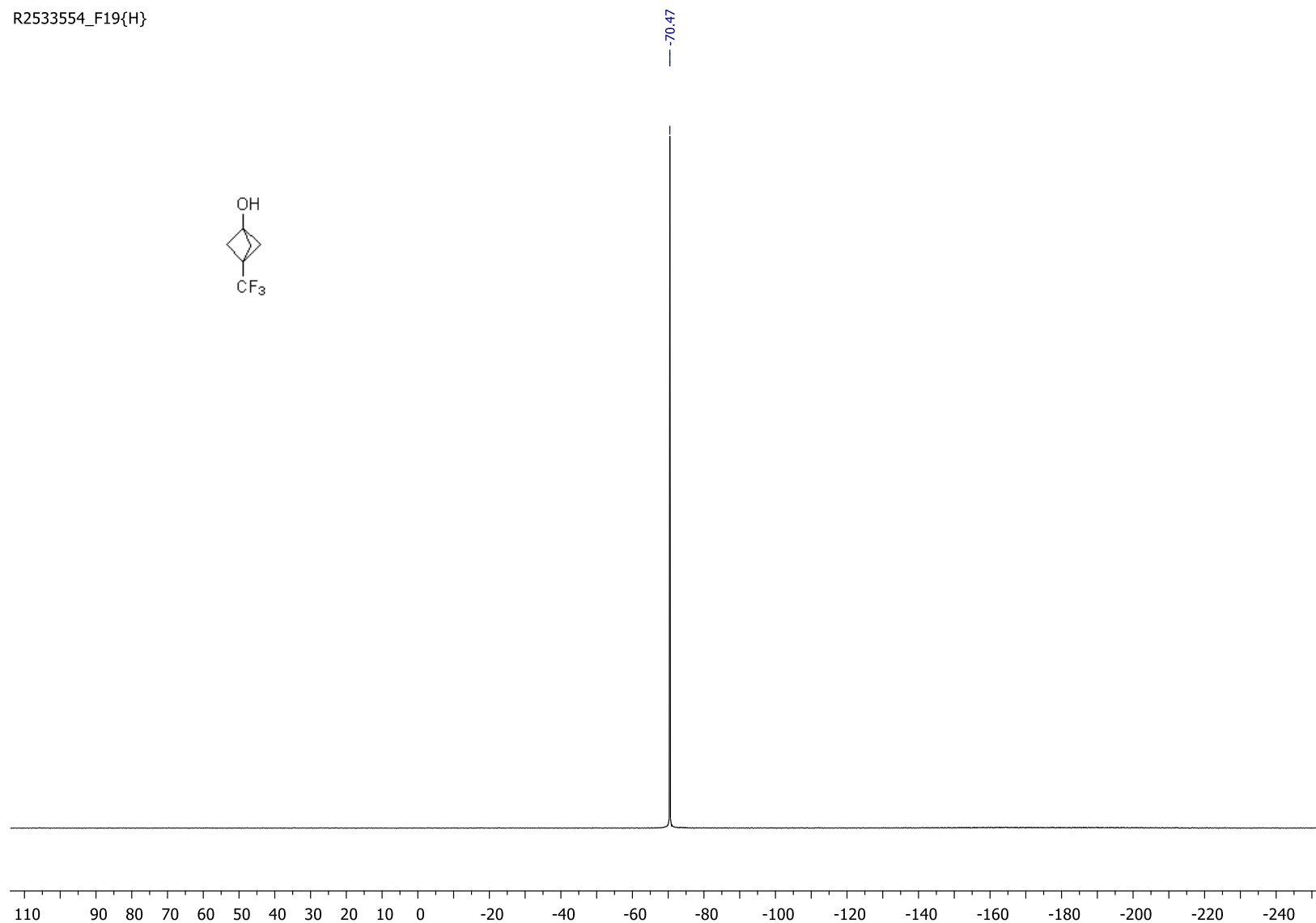
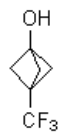
¹H NMR (400 MHz, CDCl₃)





$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

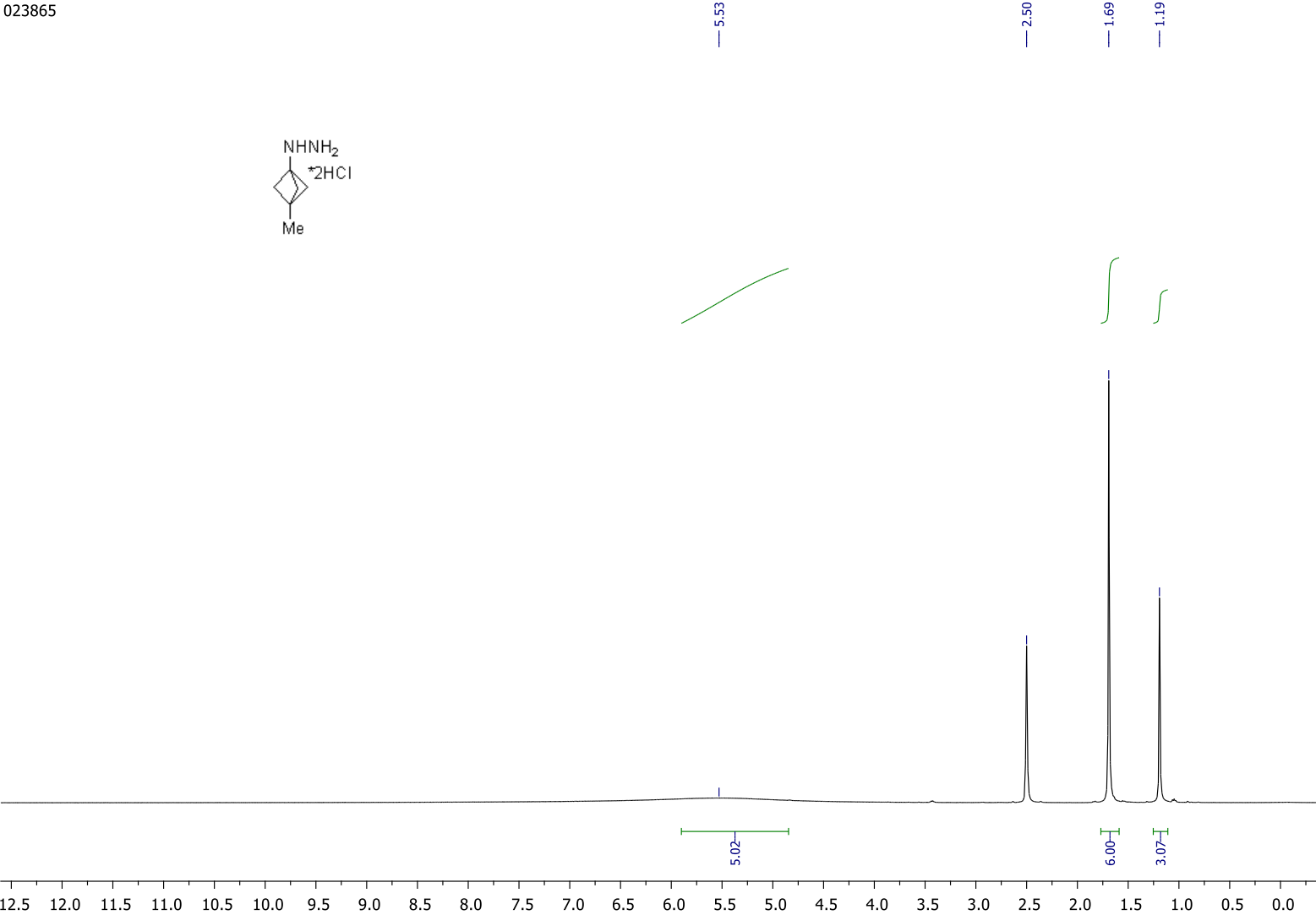
R2533554_F19{H}



Compound 1d

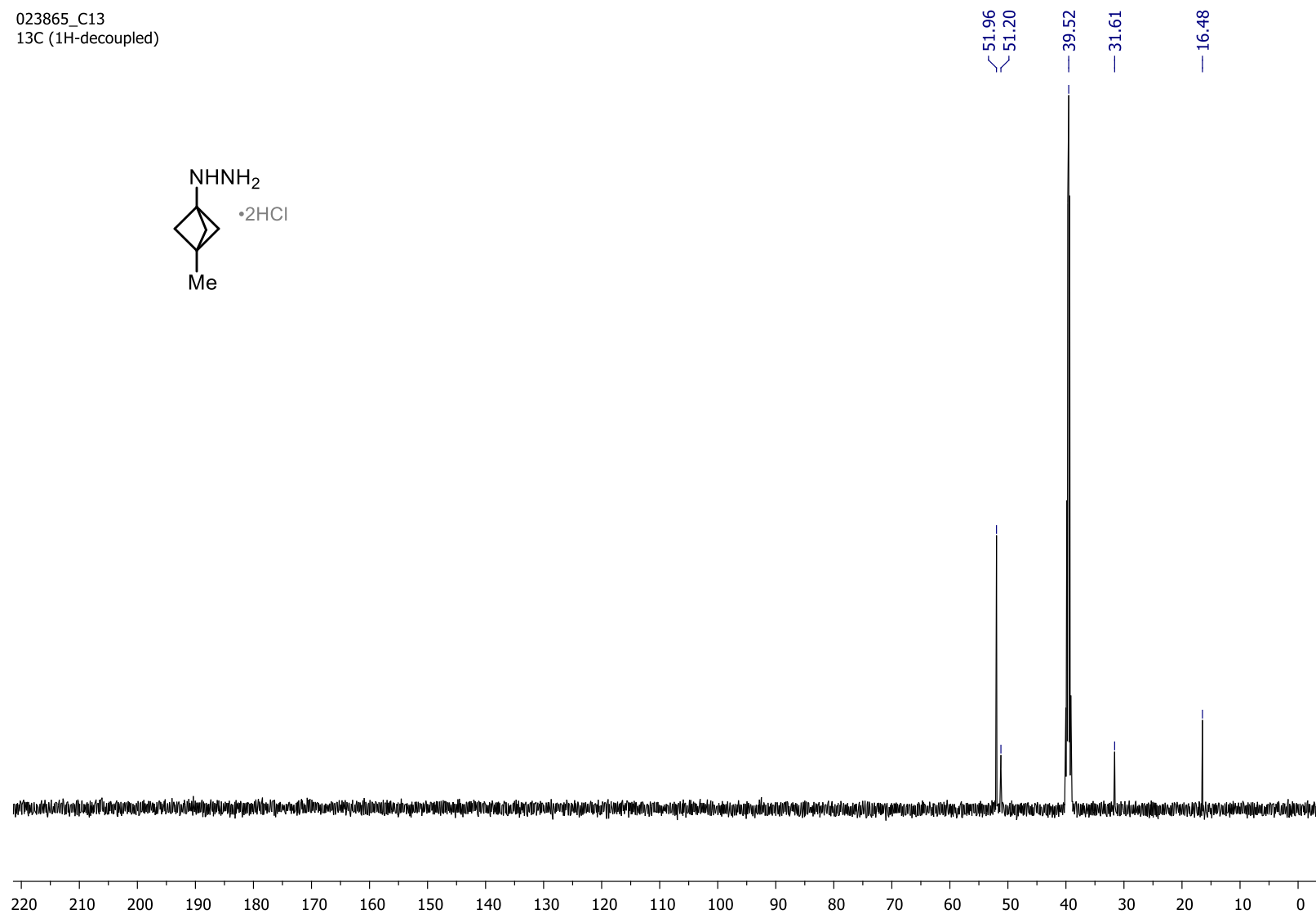
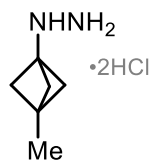
023865

¹H NMR (500 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

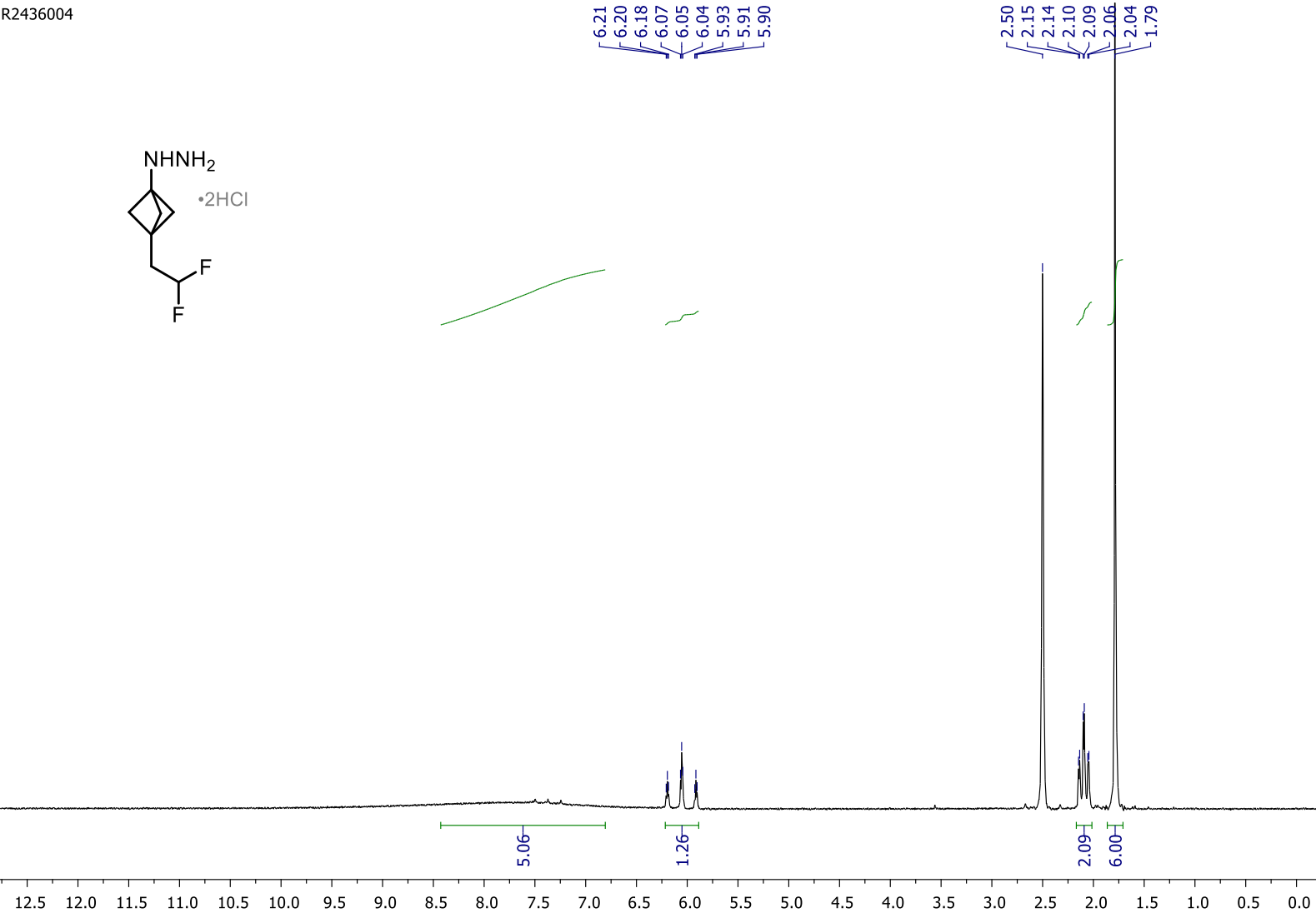
023865_C13
 ^{13}C (1H-decoupled)



Compound 24d

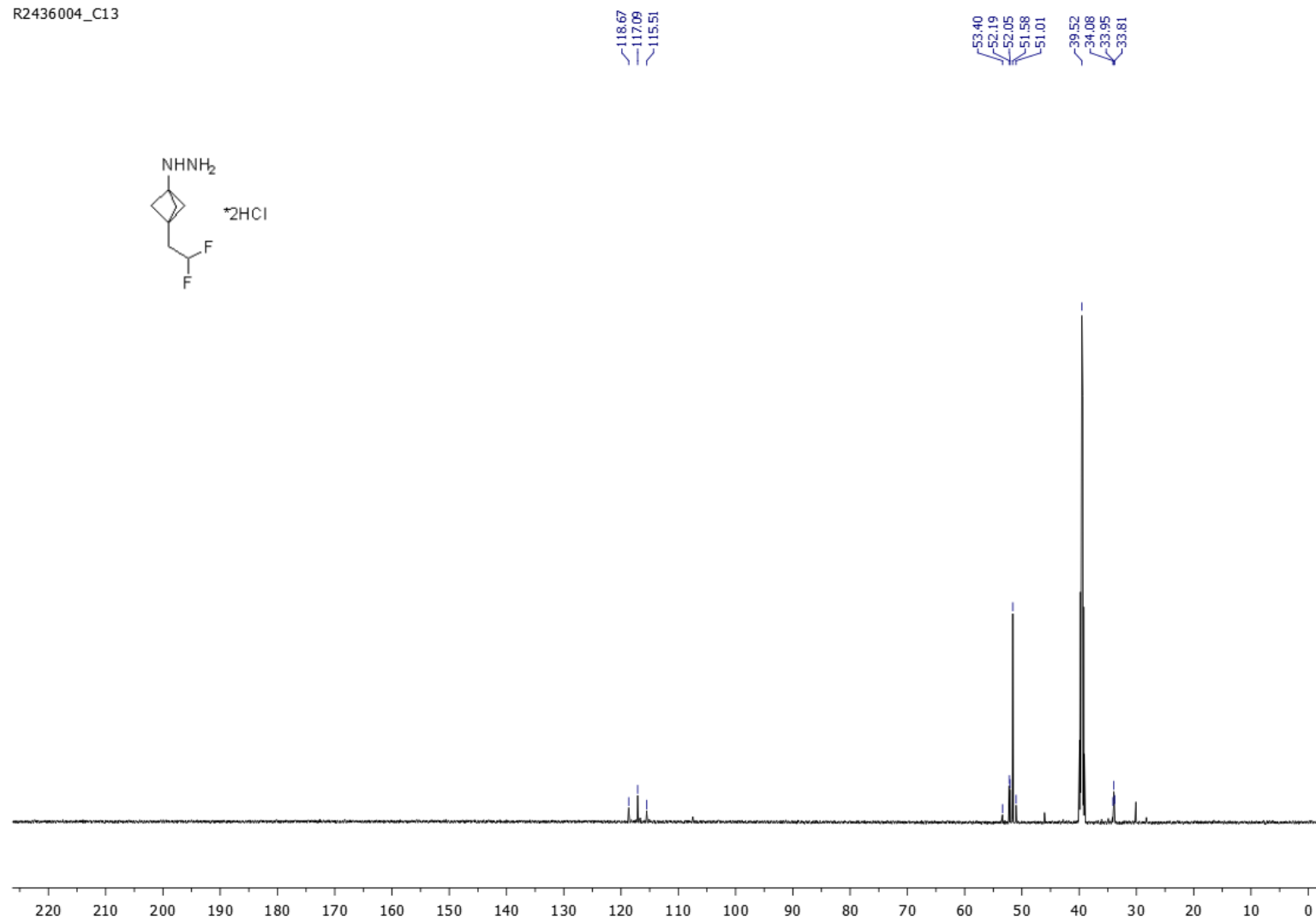
R2436004

¹H NMR (400 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

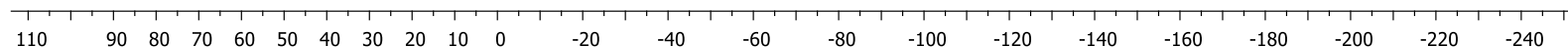
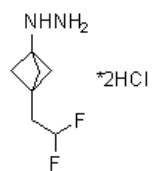
R2436004_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2436004_F19{H}

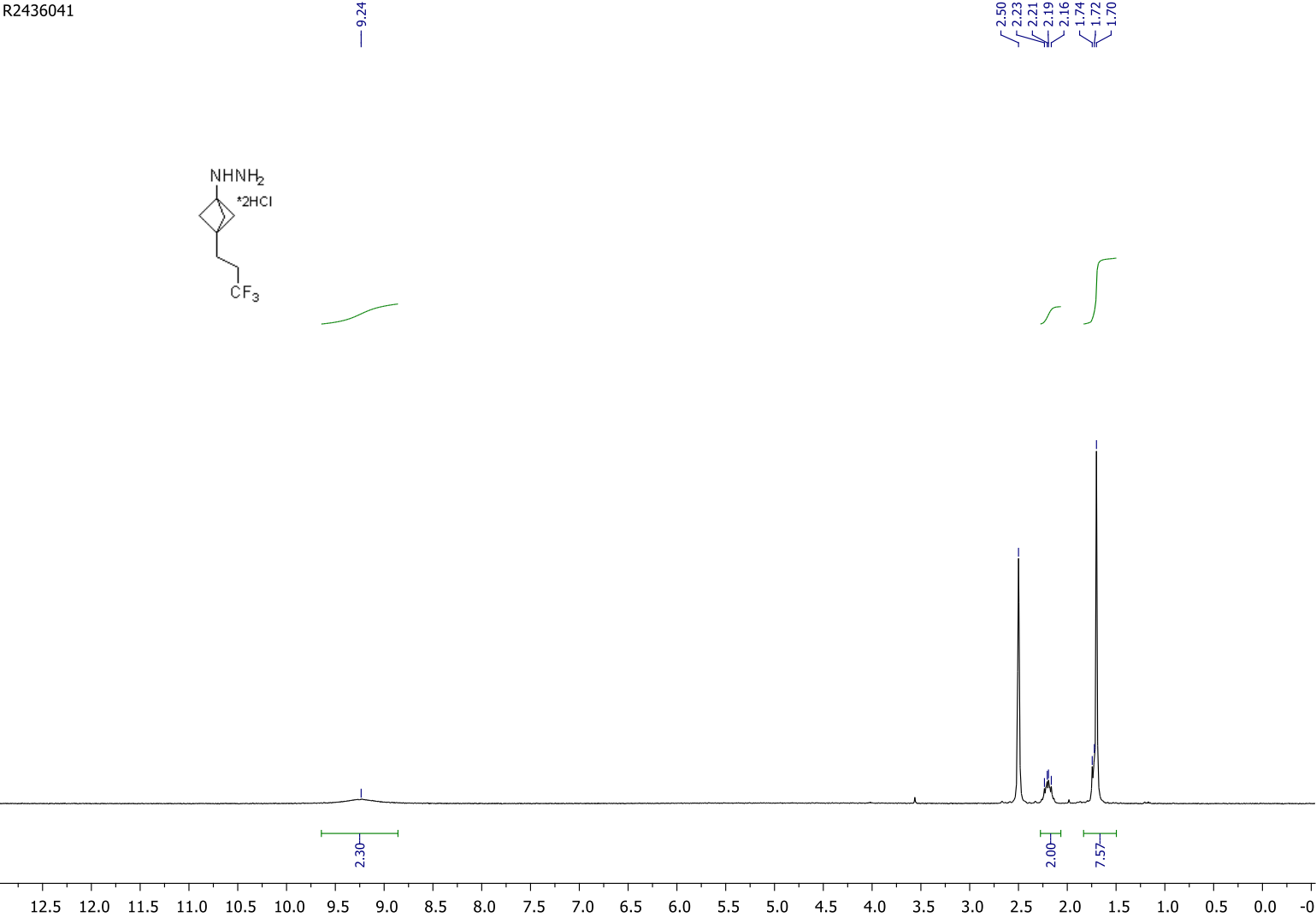
— -115.51



Compound 26d

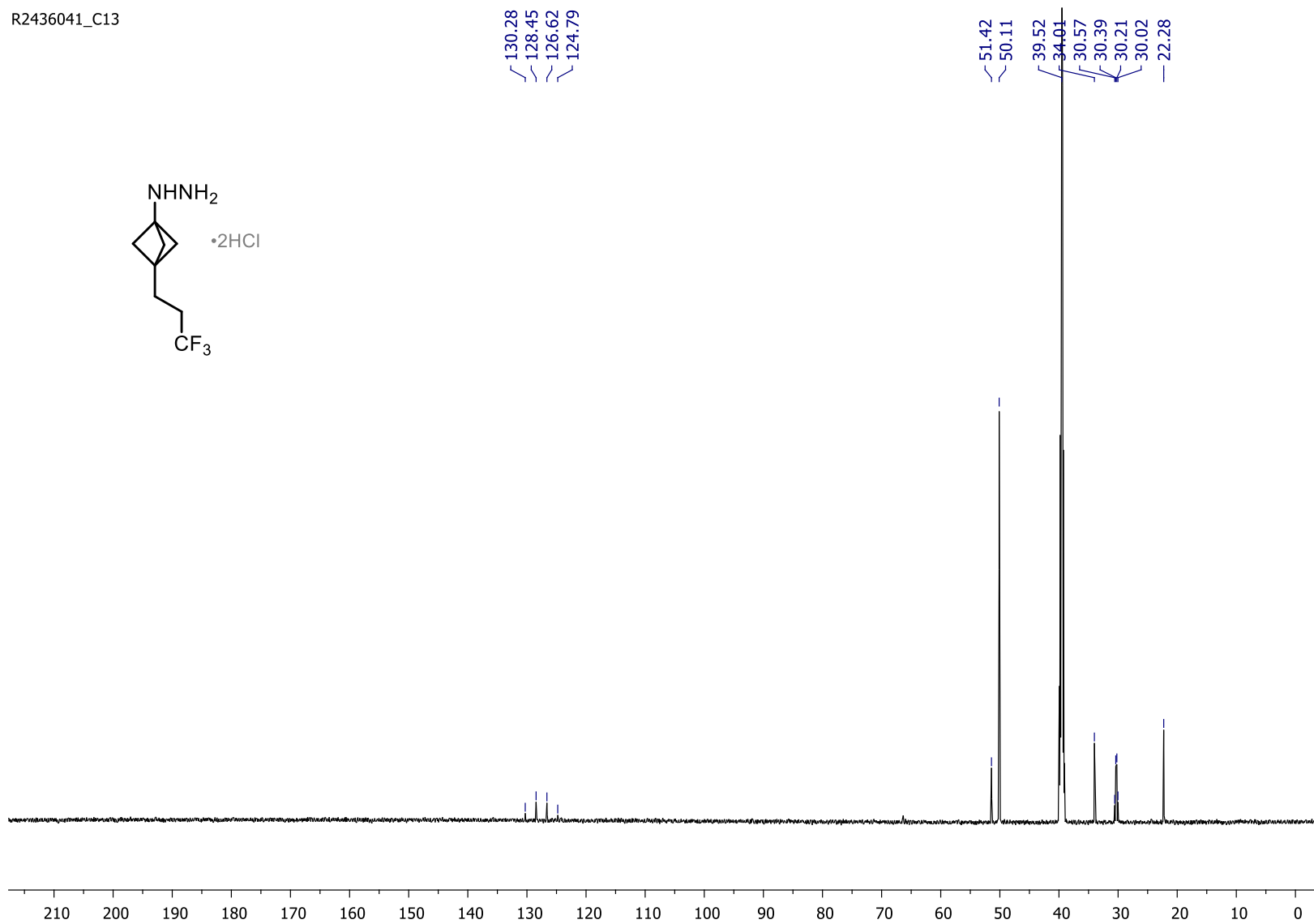
¹H NMR (400 MHz, DMSO-d₆)

R2436041



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

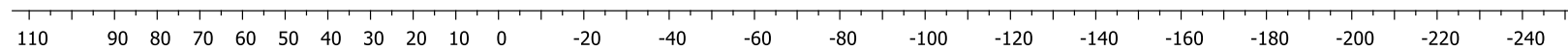
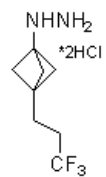
R2436041_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2436041_F19{H}

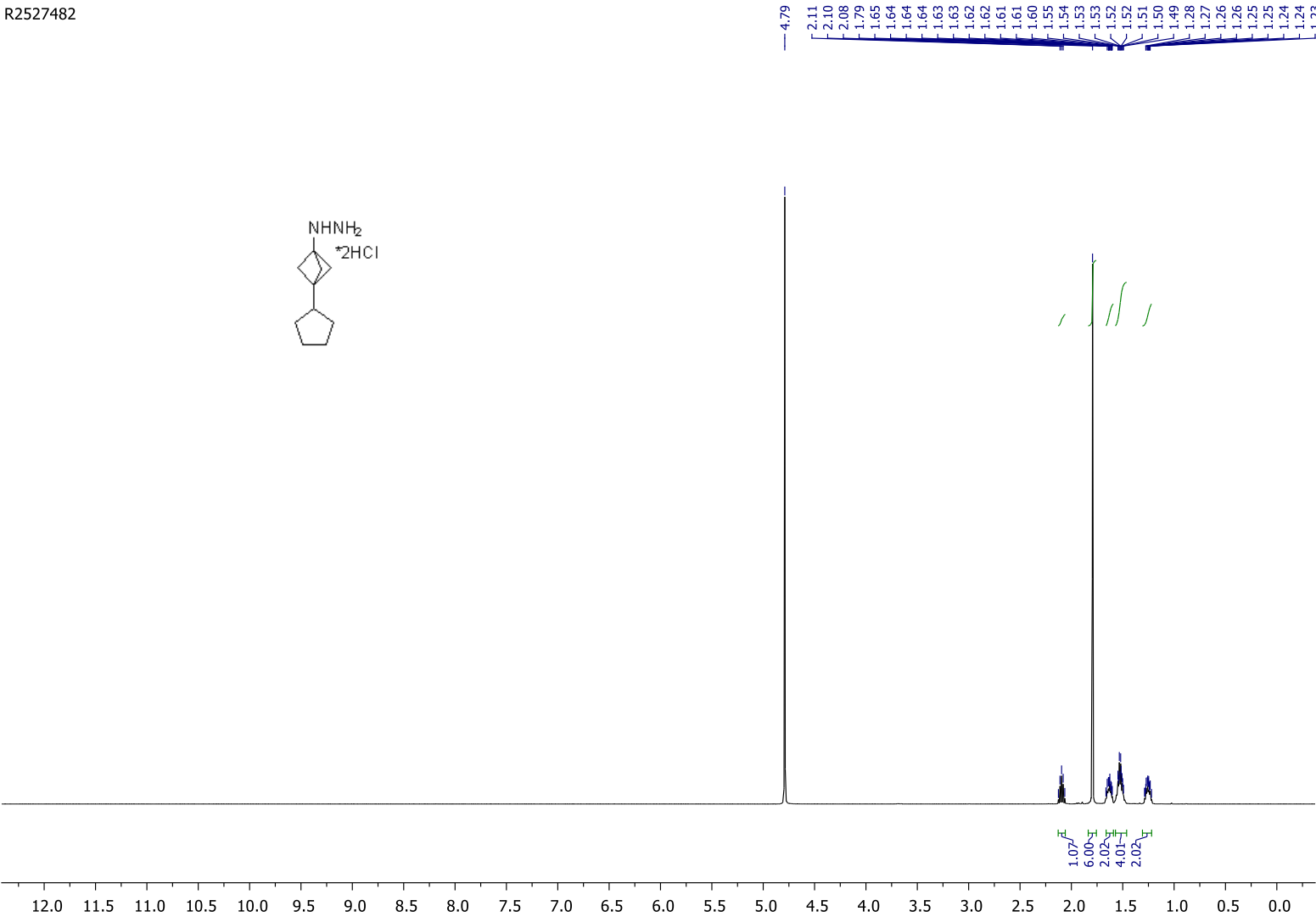
— -65.39



Compound 52d

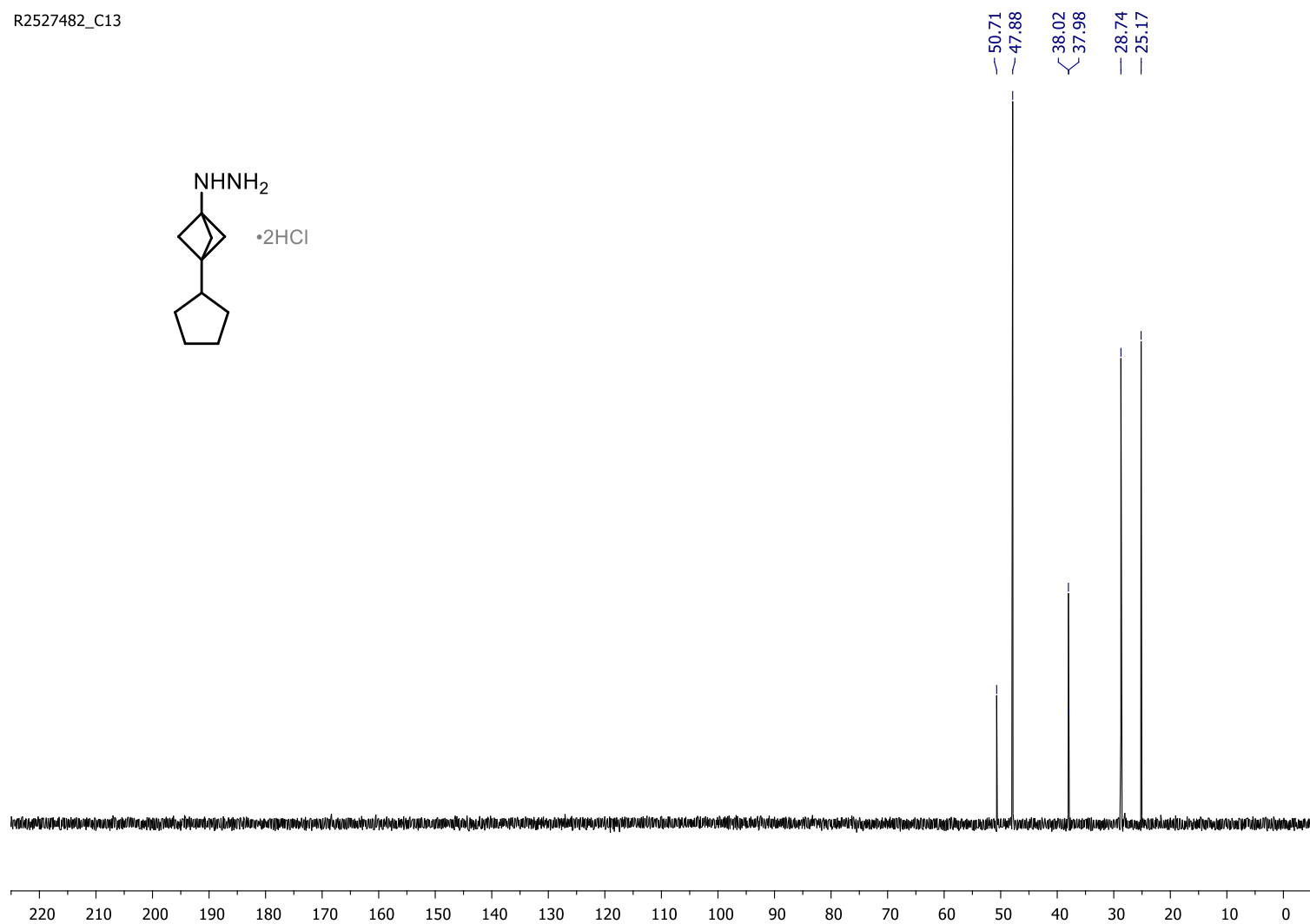
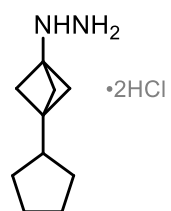
¹H NMR (500 MHz, D₂O)

R2527482



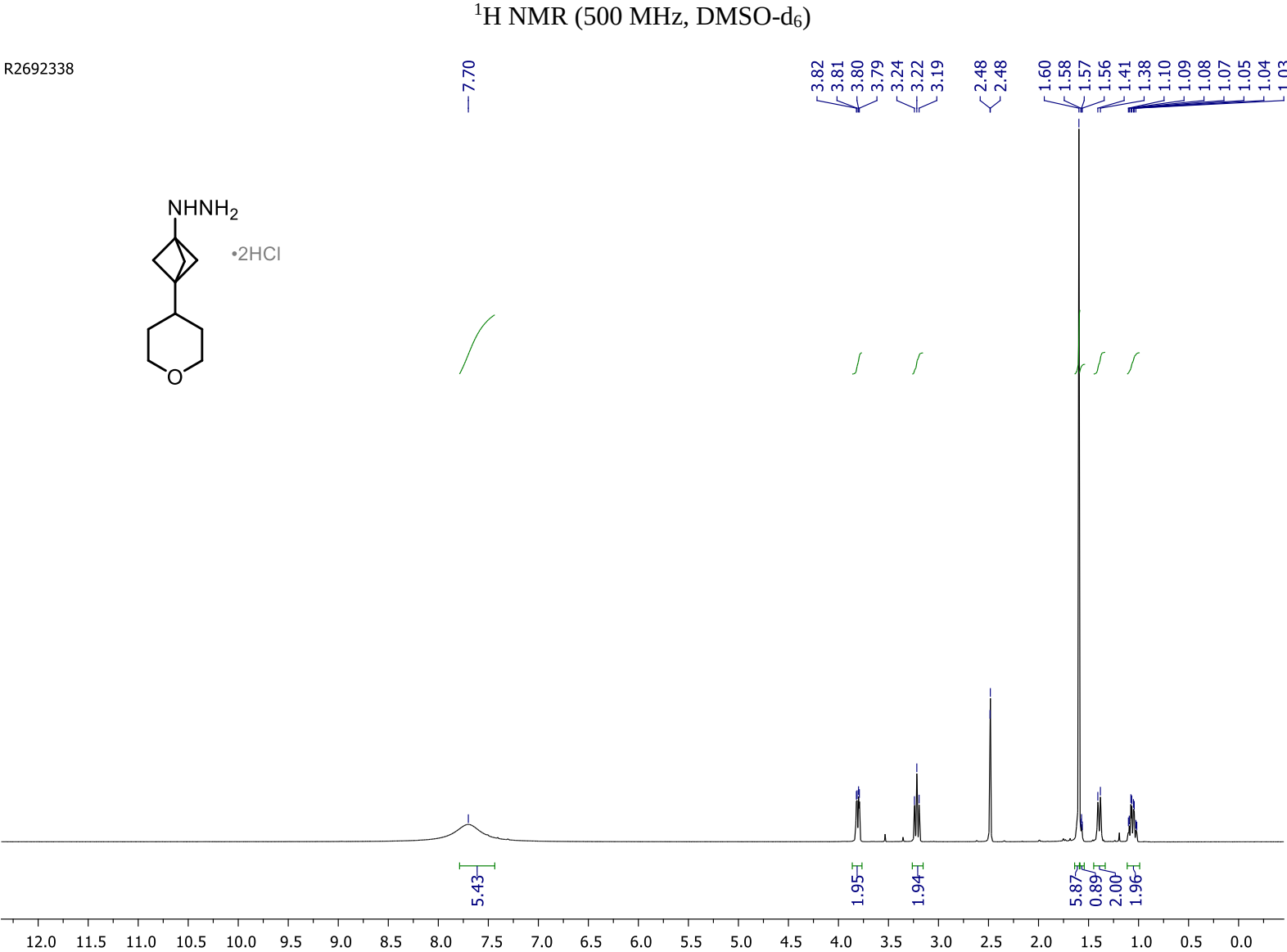
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, D_2O)

R2527482_C13



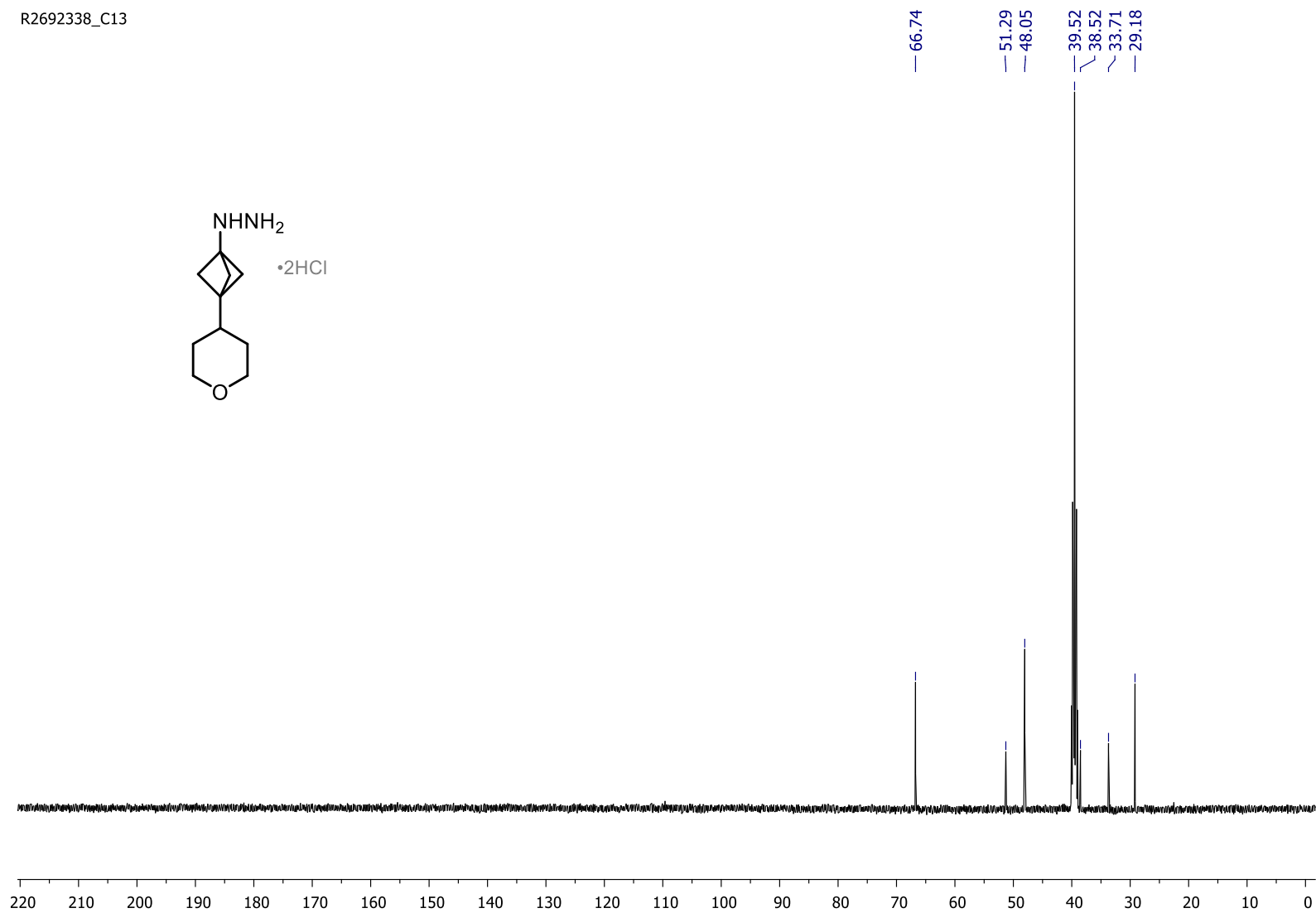
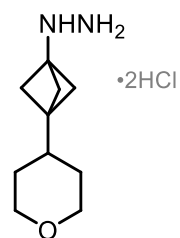
Compound 57d

R2692338



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

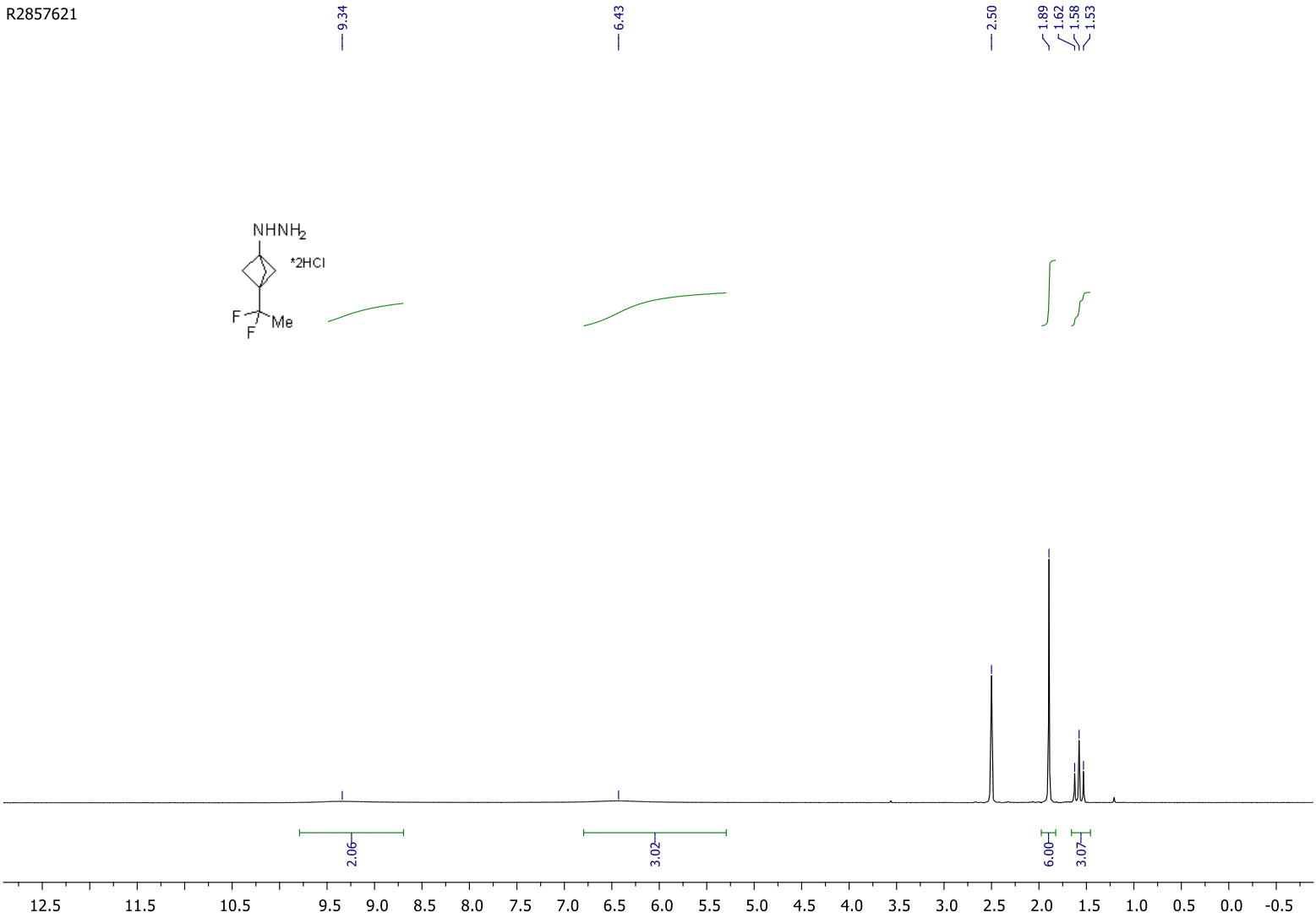
R2692338_C13



Compound 68d

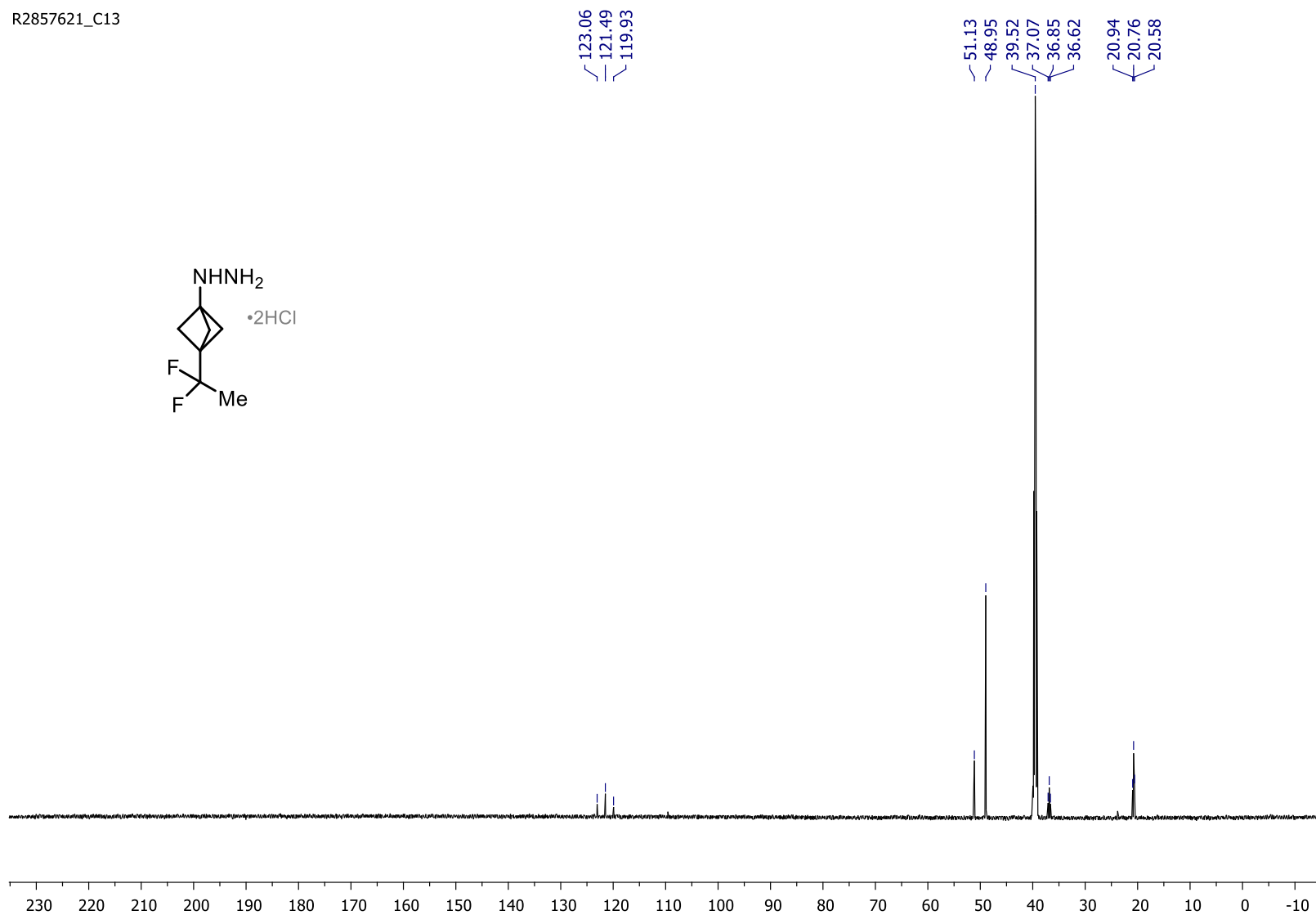
¹H NMR (400 MHz, DMSO-d₆)

R2857621



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

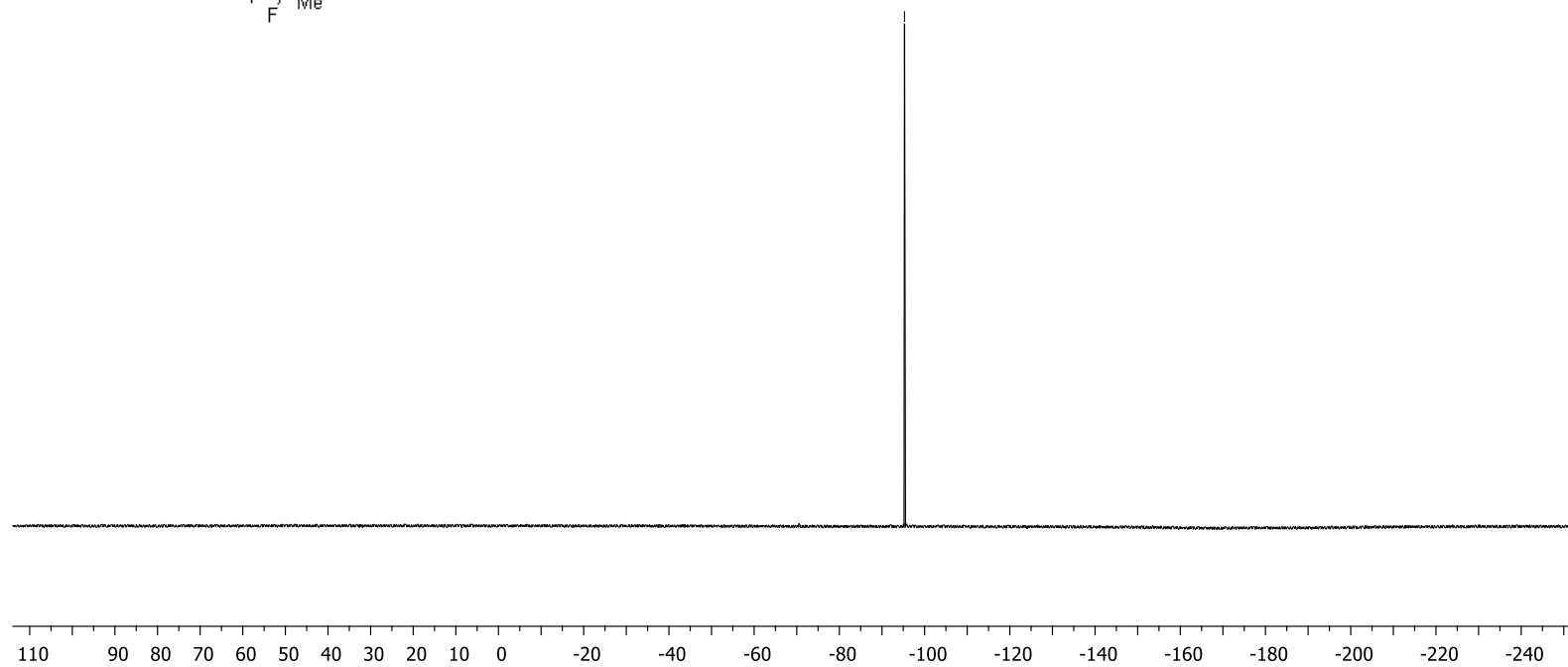
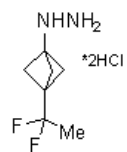
R2857621_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2857621_F19{H}

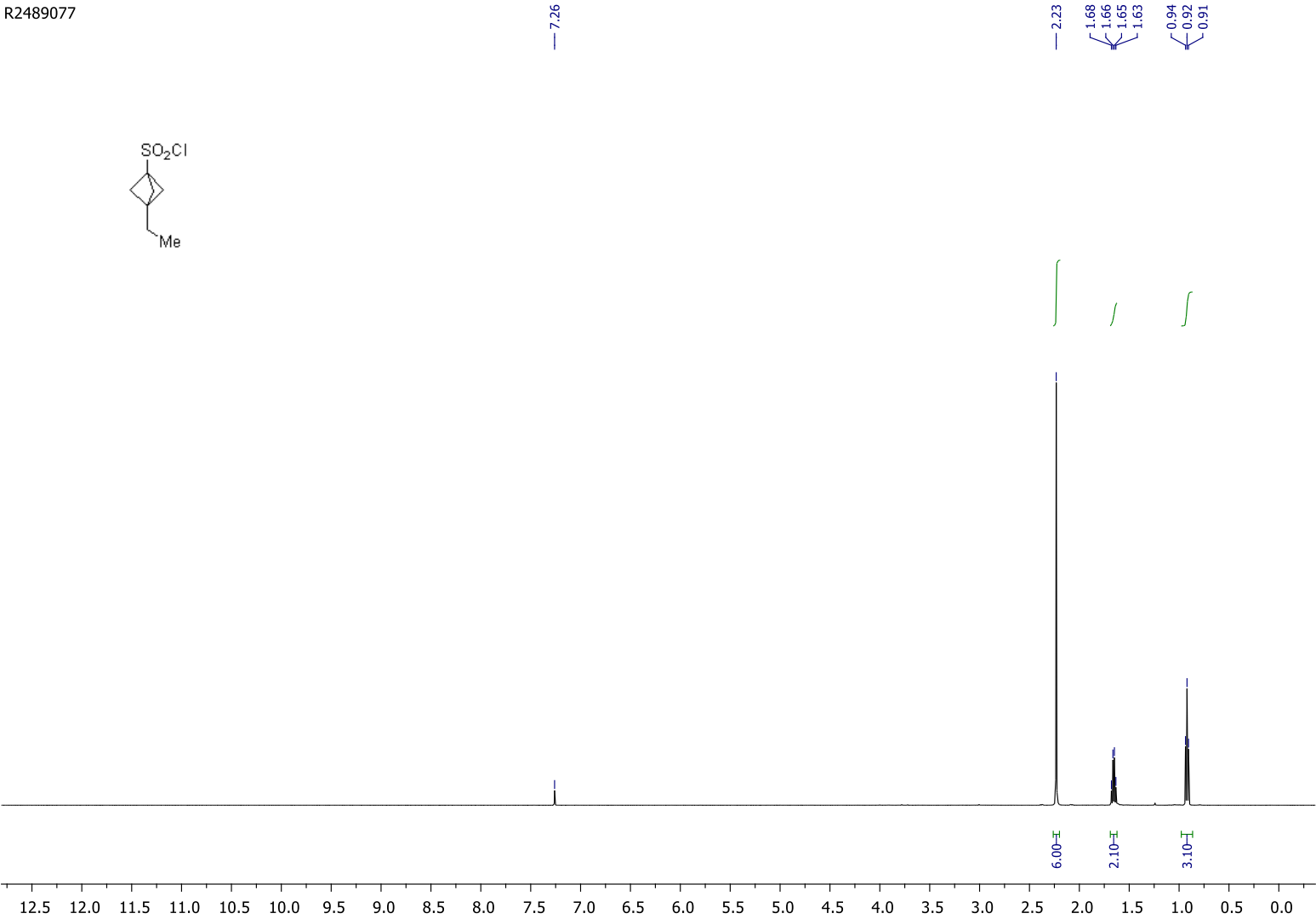
— -95.29



Compound 2e

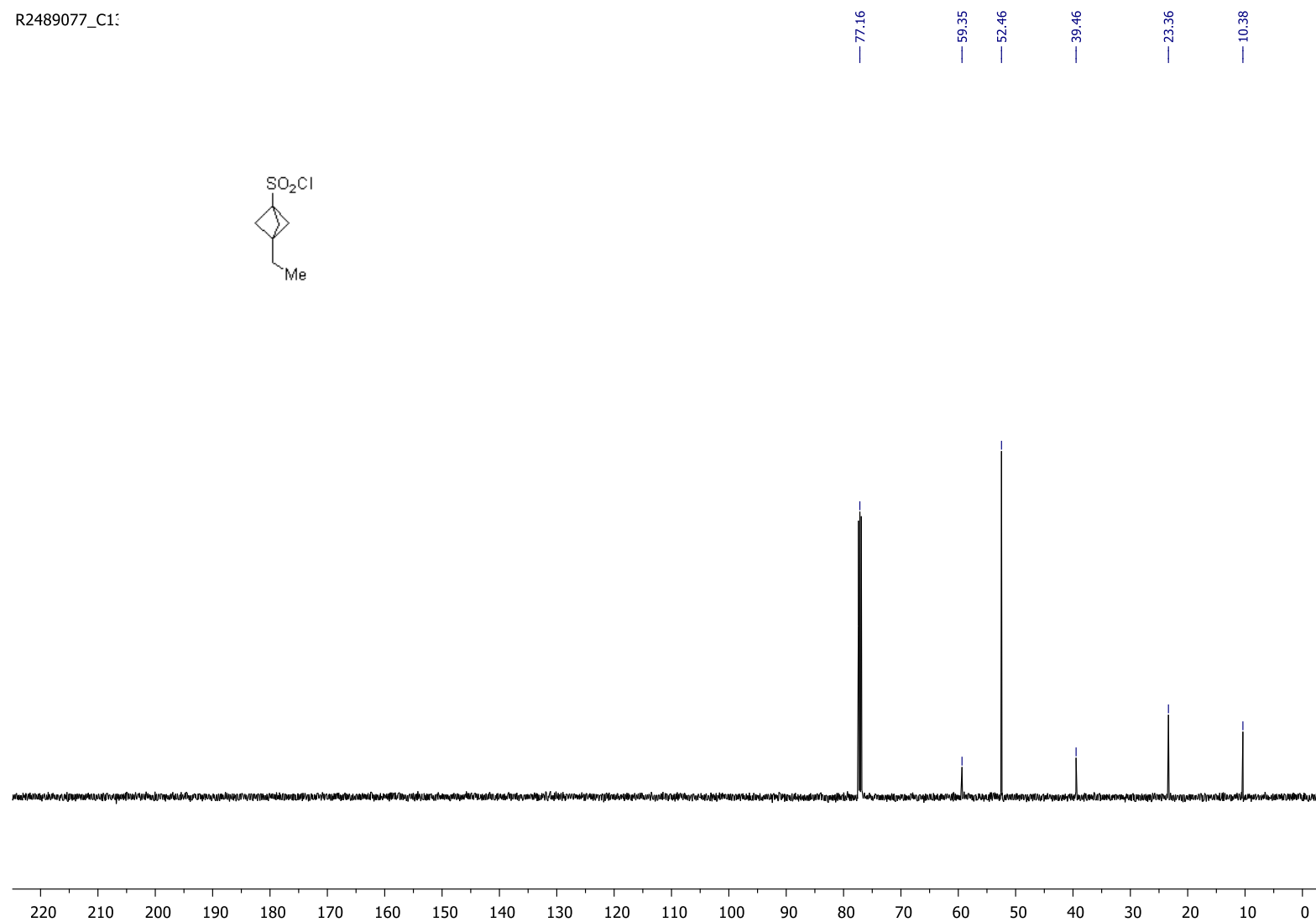
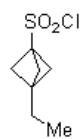
R2489077

¹H NMR (500 MHz, CDCl₃)



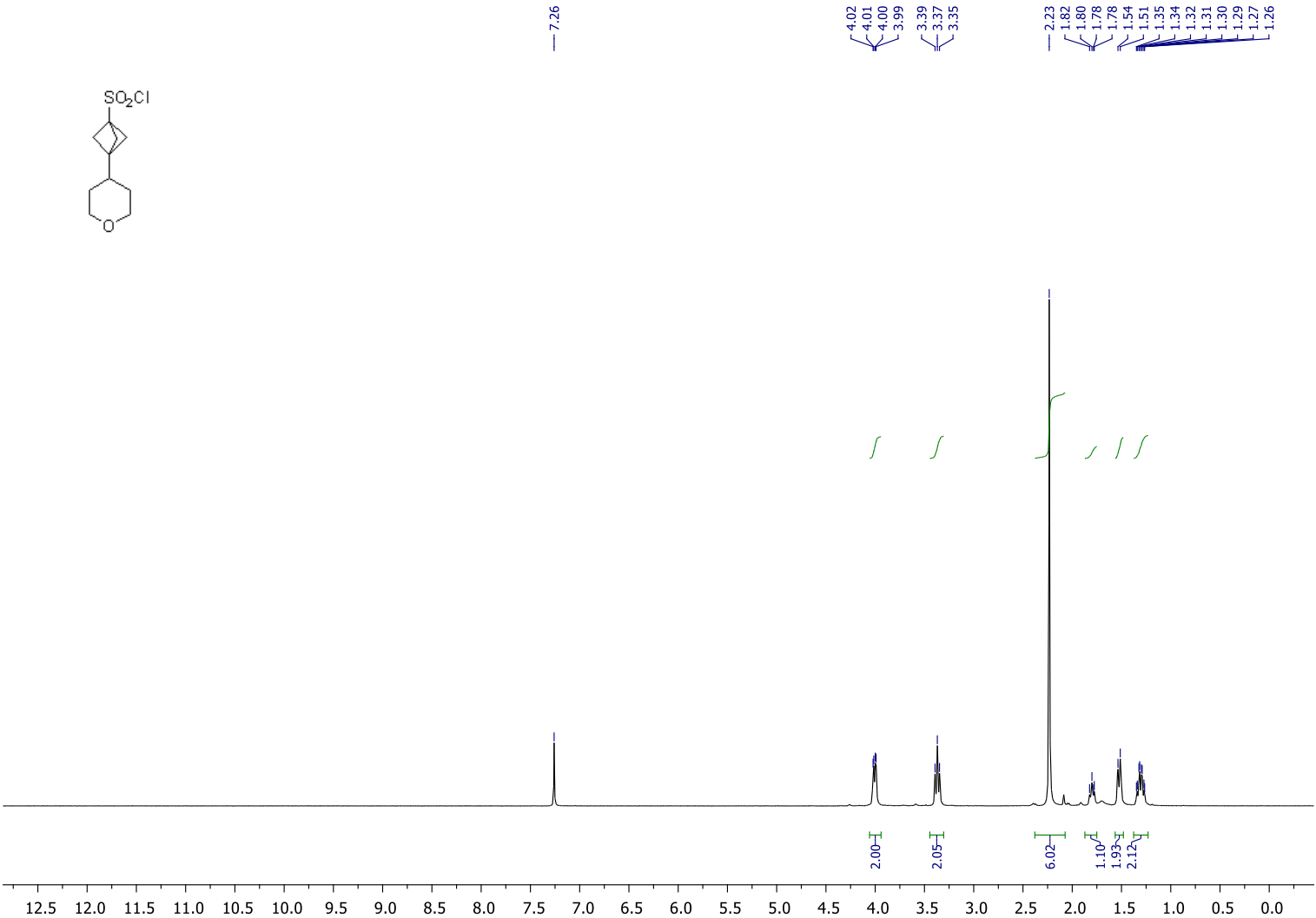
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2489077_C1:

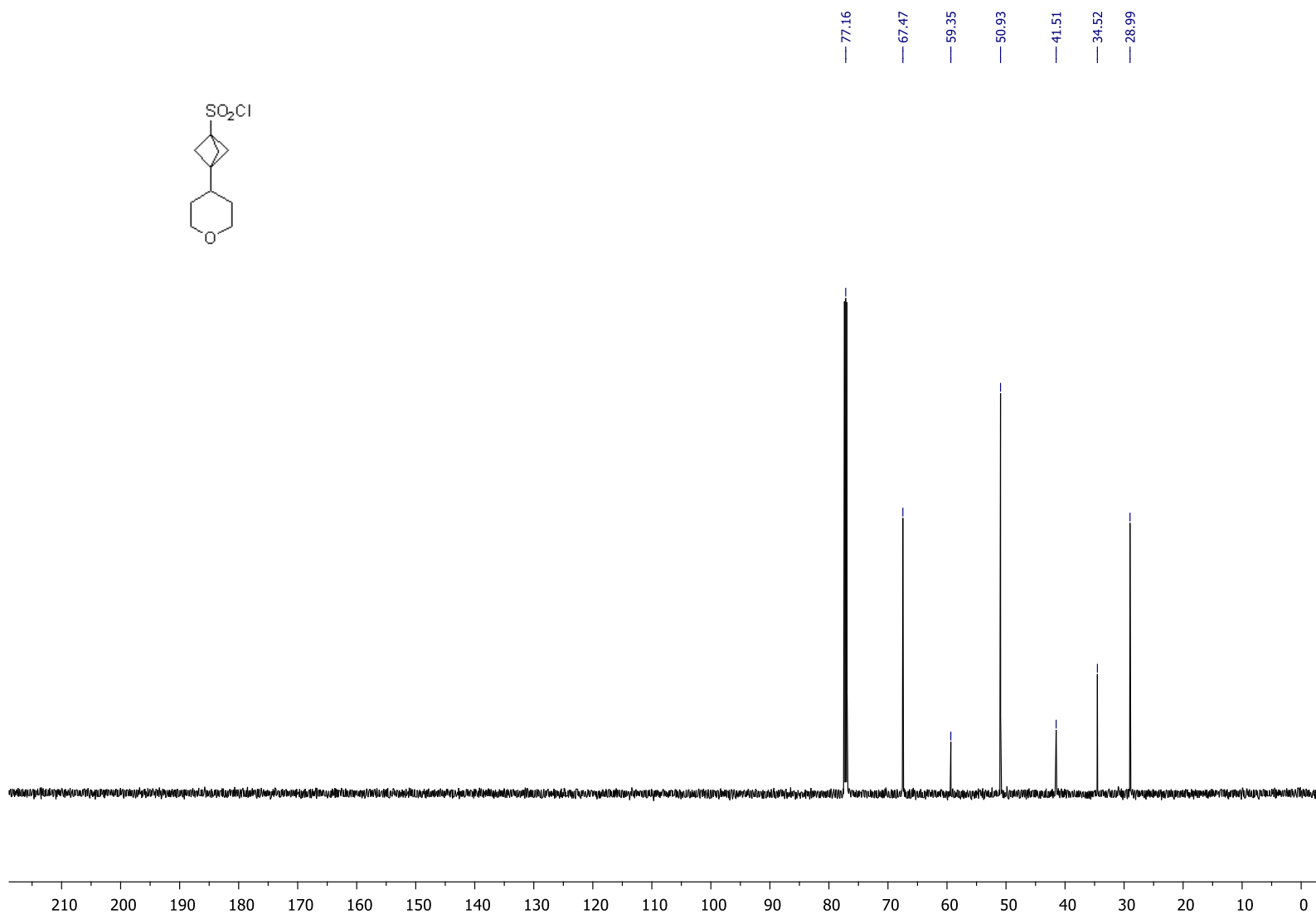


Compound 57e

¹H NMR (500 MHz, CDCl₃)



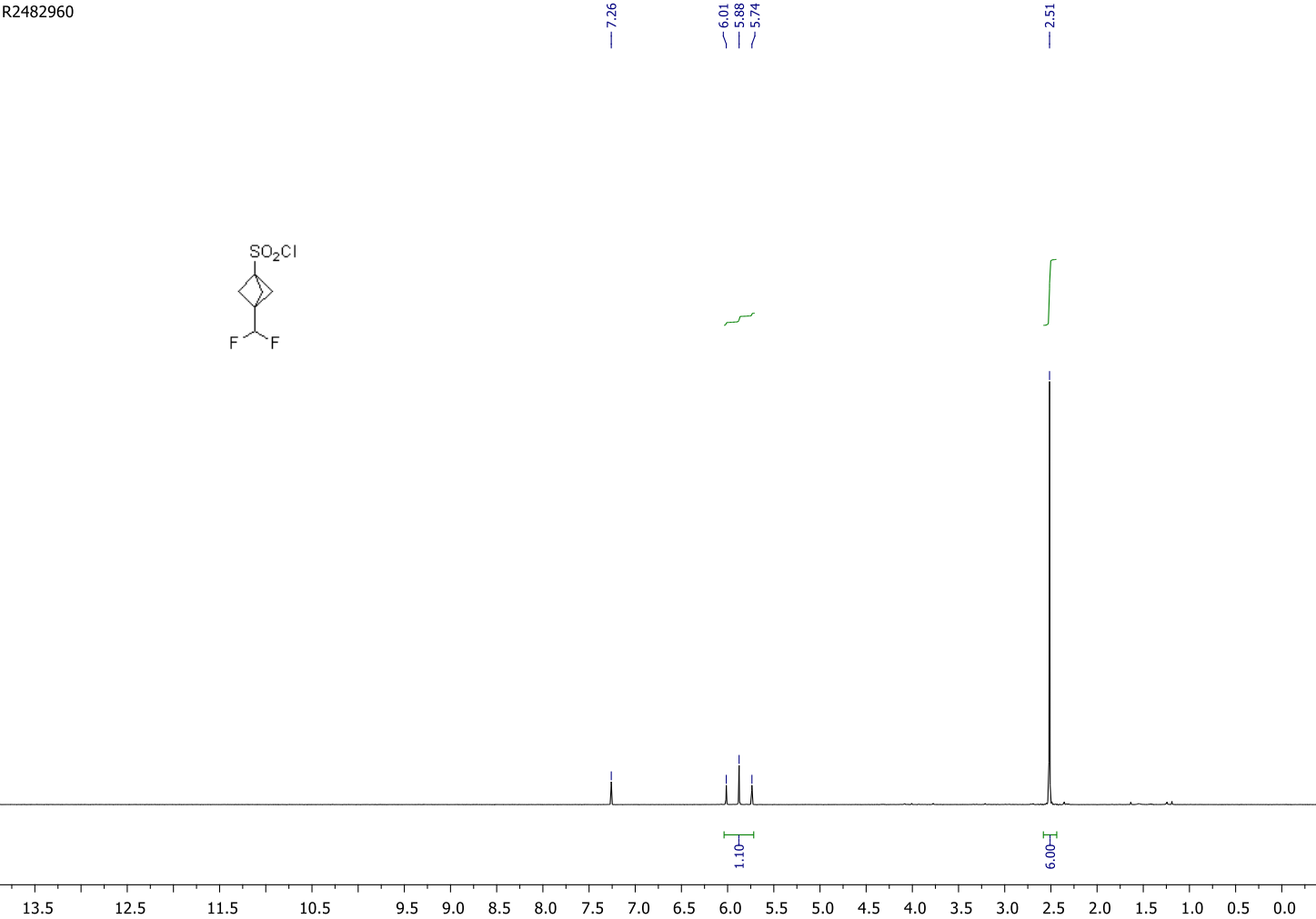
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)



Compound 67e

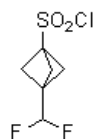
¹H NMR (400 MHz, CDCl₃)

R2482960



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2485905_C1:



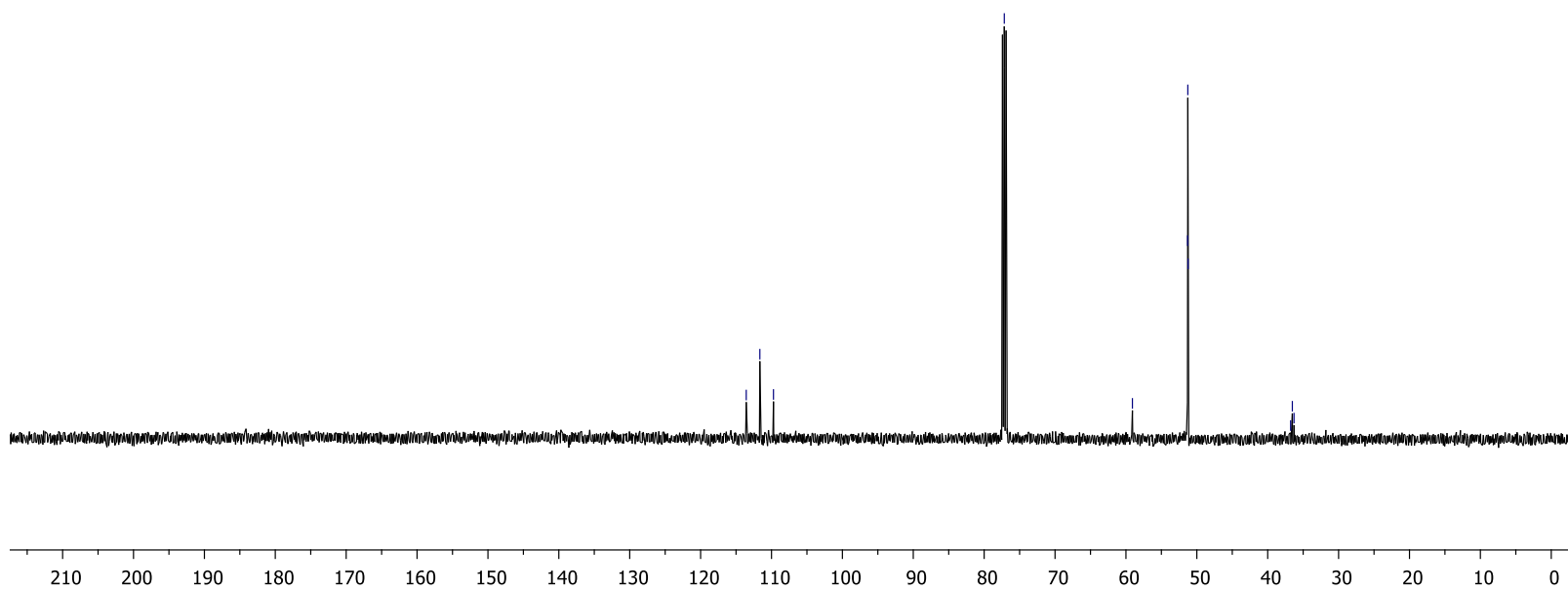
113.56
—
111.64
—
109.72

— 77.16

— 59.09

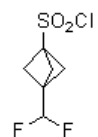
51.30
—
51.27
—
51.24

36.77
—
36.53
—
36.29

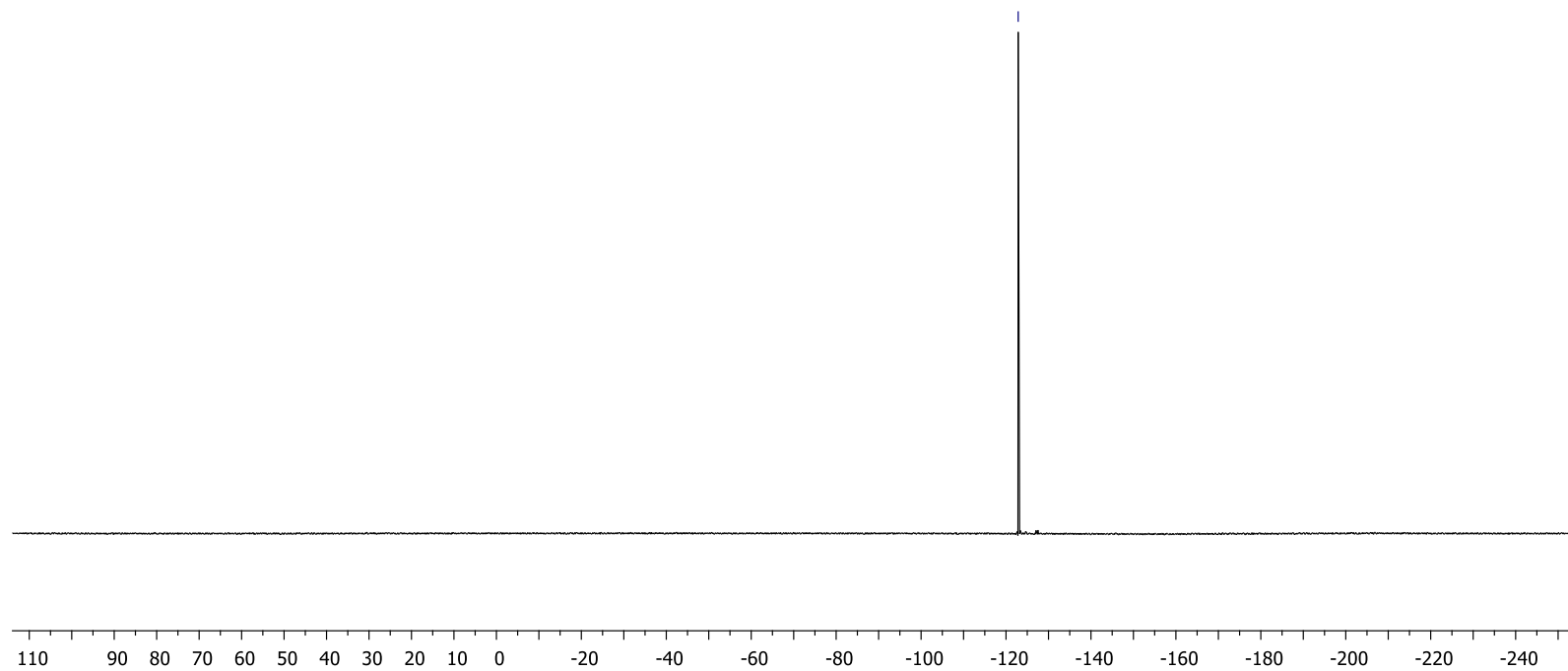


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2482960_F19{H}



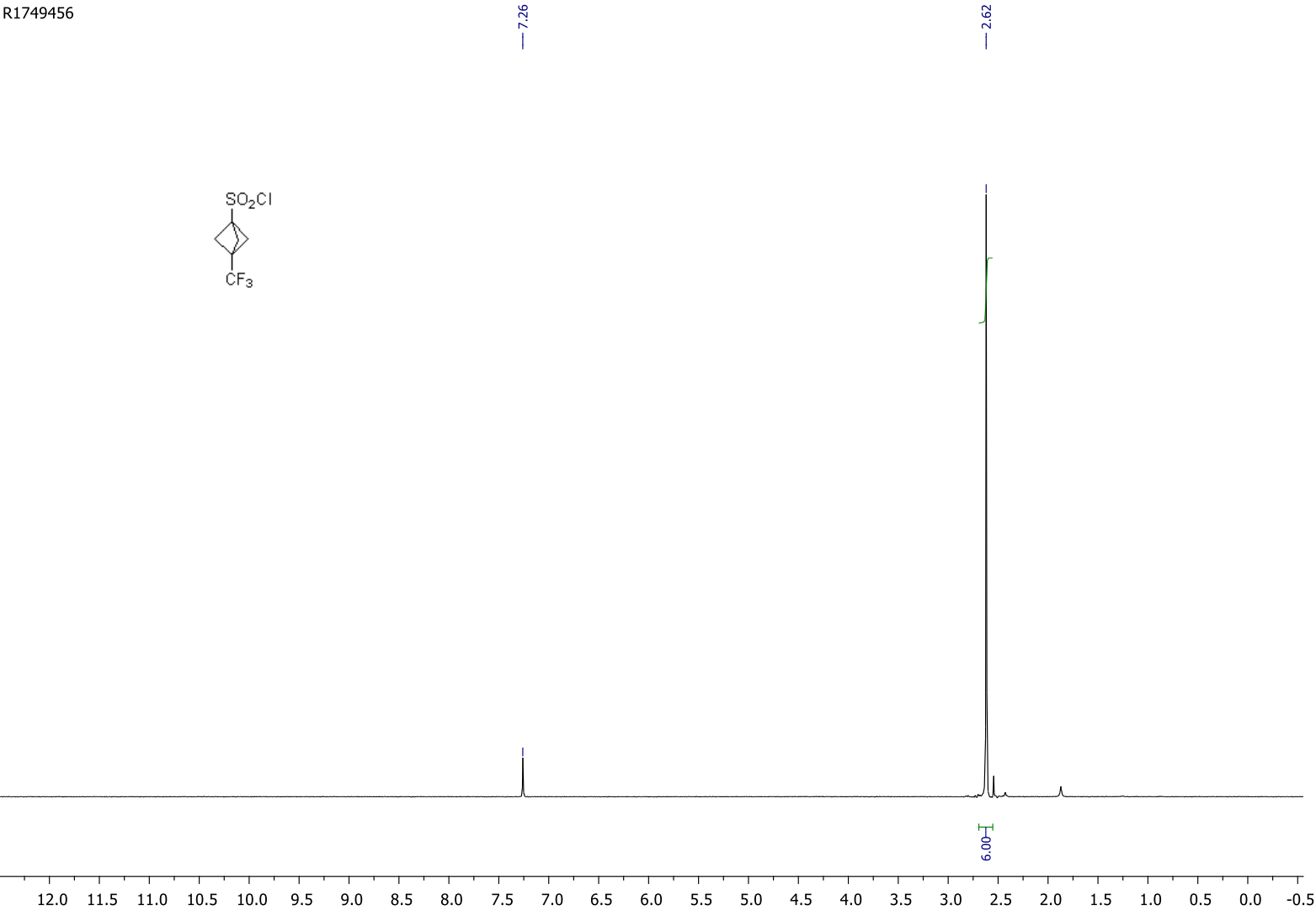
— -122.87



Compound 69e

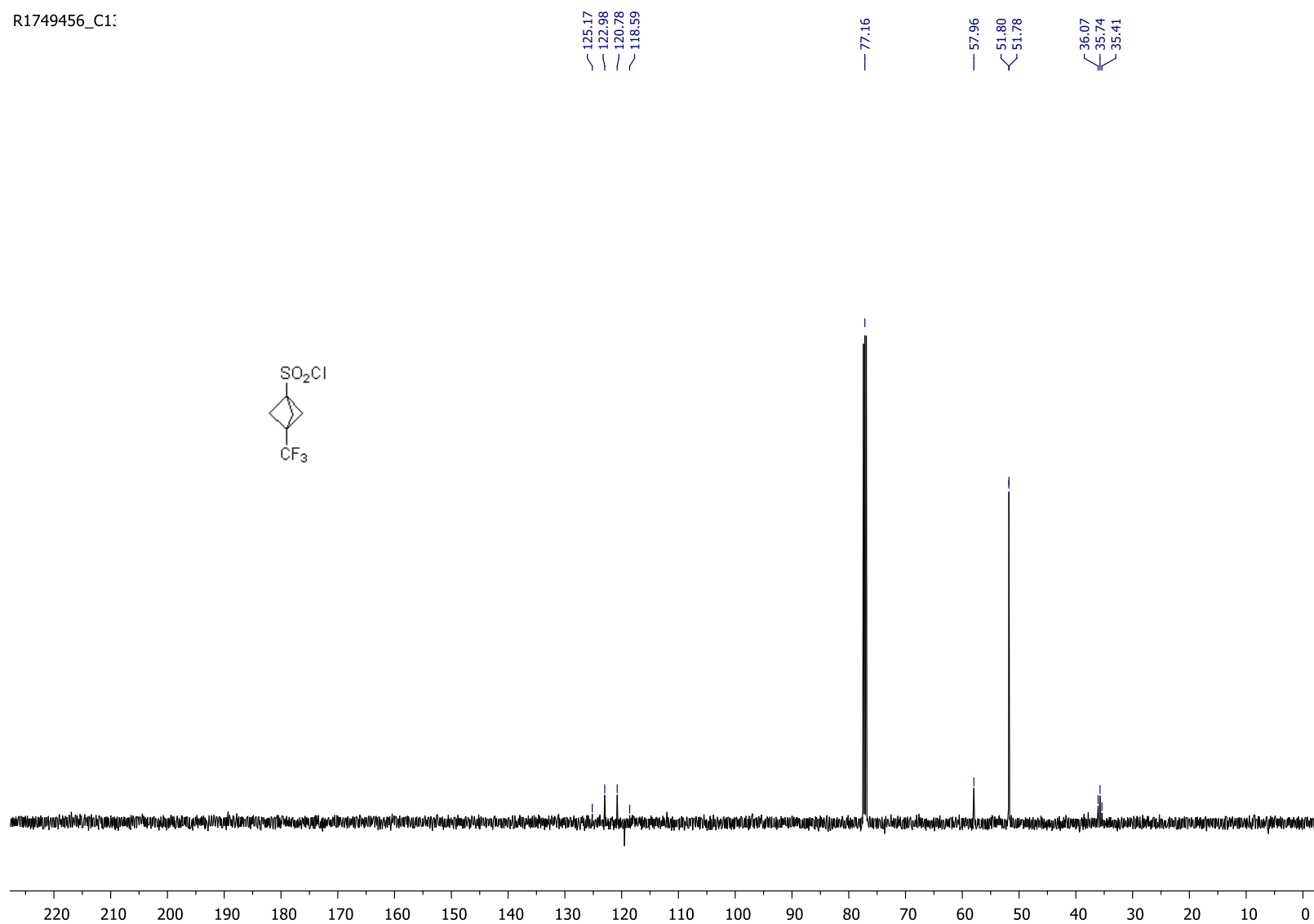
R1749456

¹H NMR (400 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

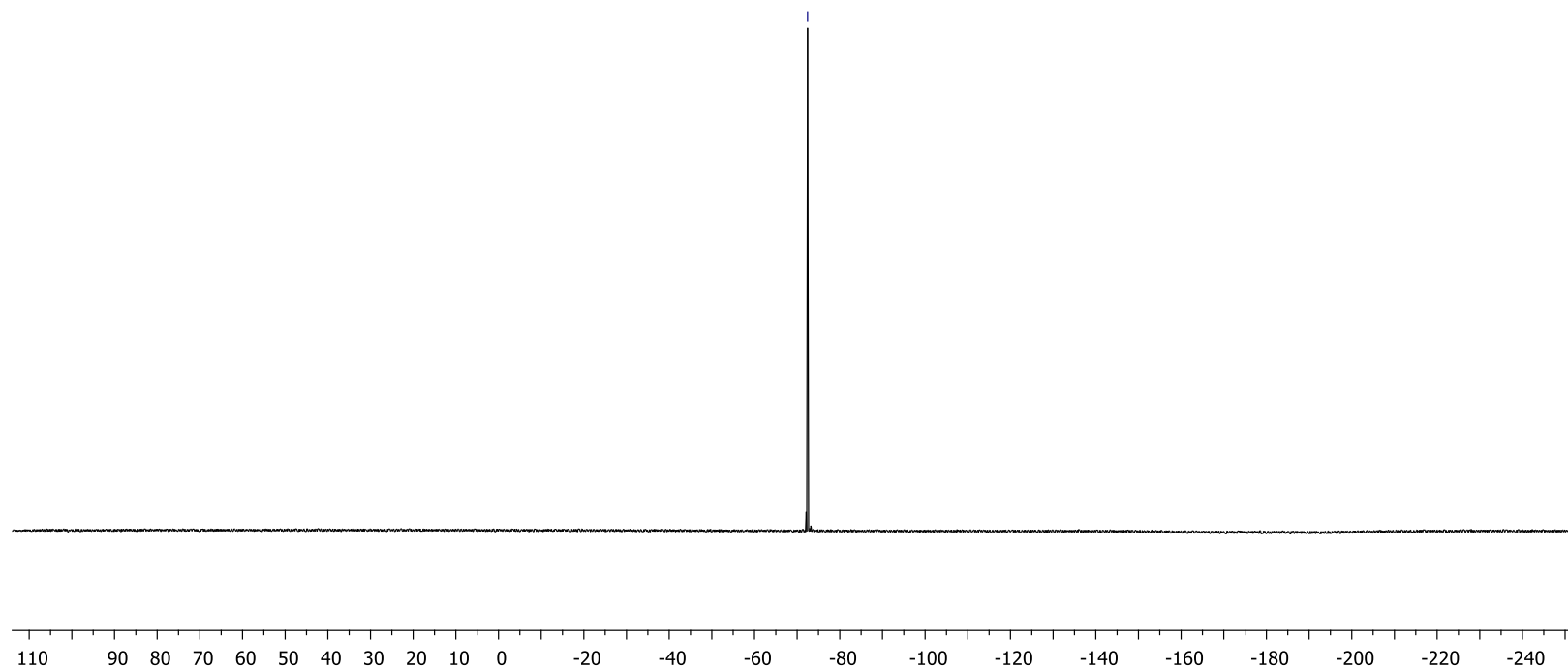
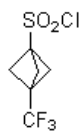
R1749456_C1:



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R1749456_F19{H}
19F-{1H}

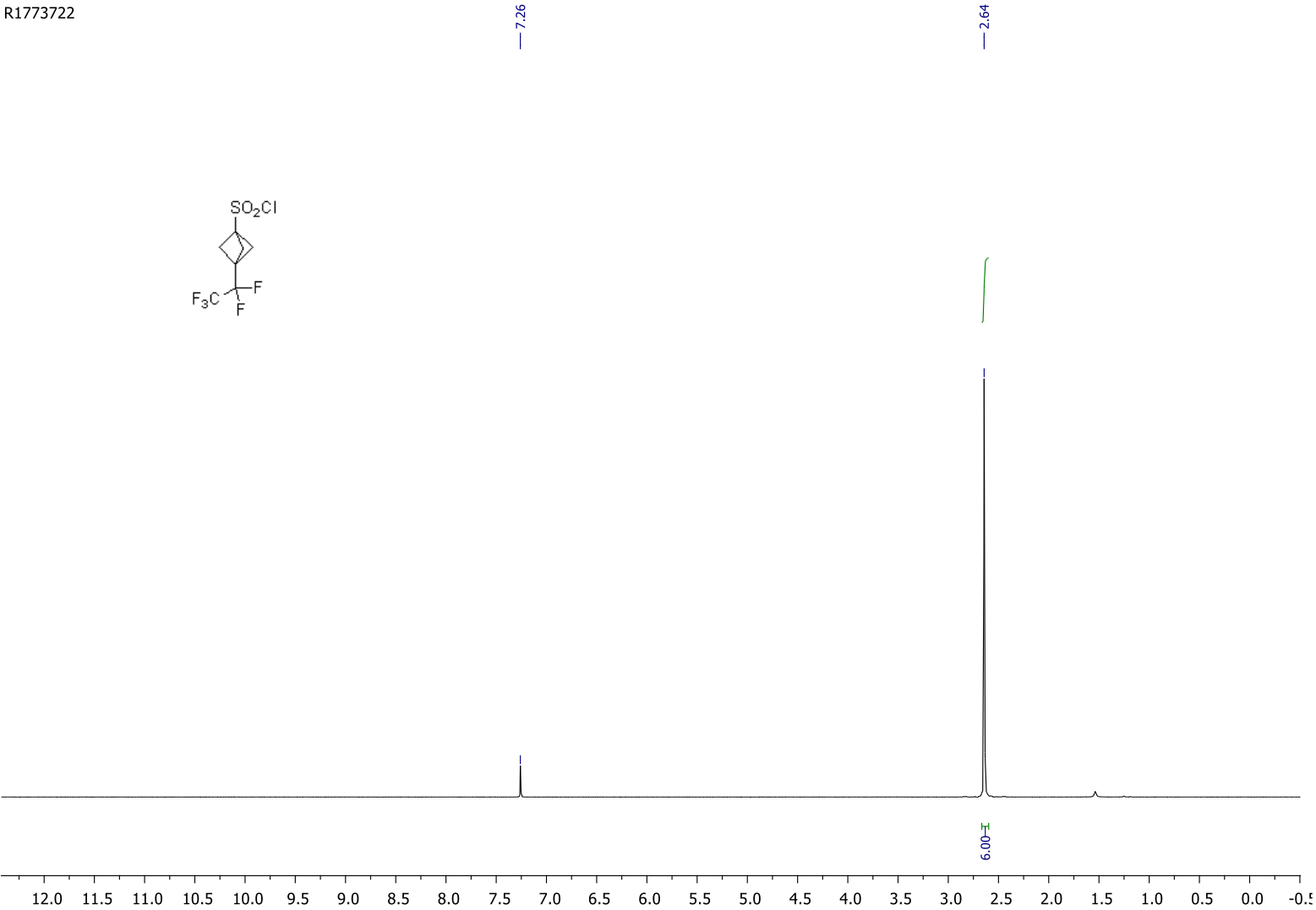
— -72.45

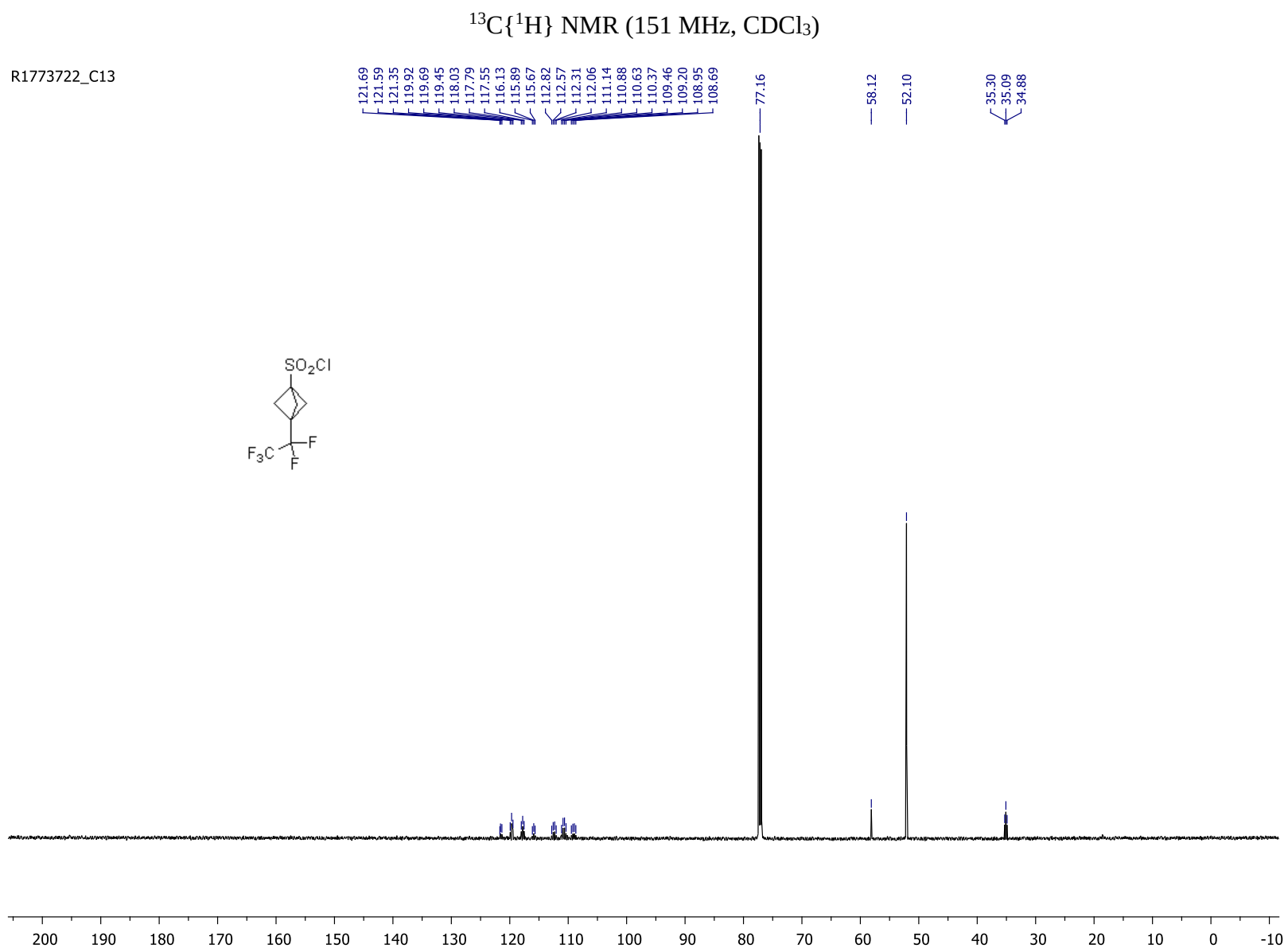


Compound 71e

R1773722

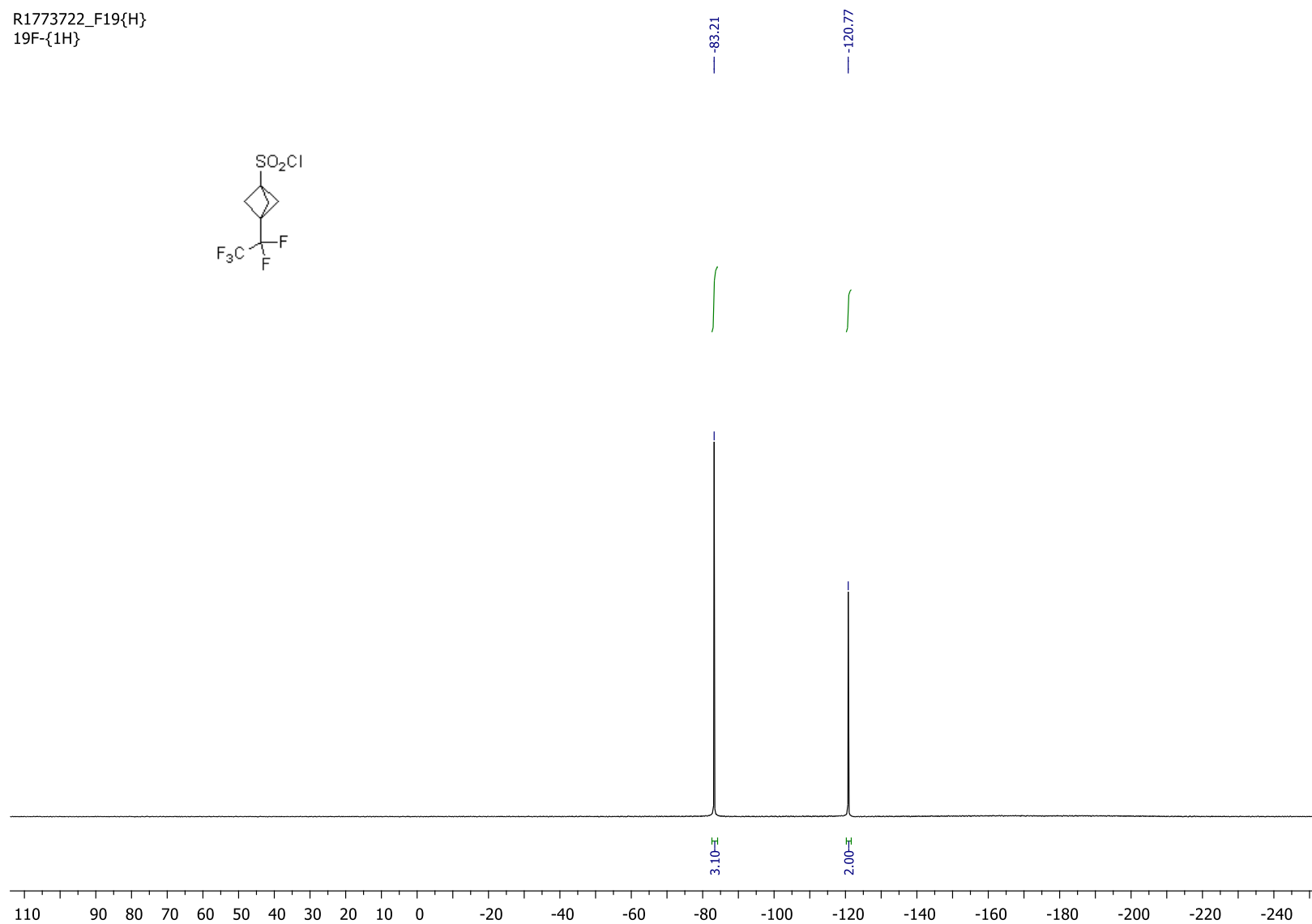
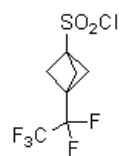
¹H NMR (400 MHz, CDCl₃)





$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

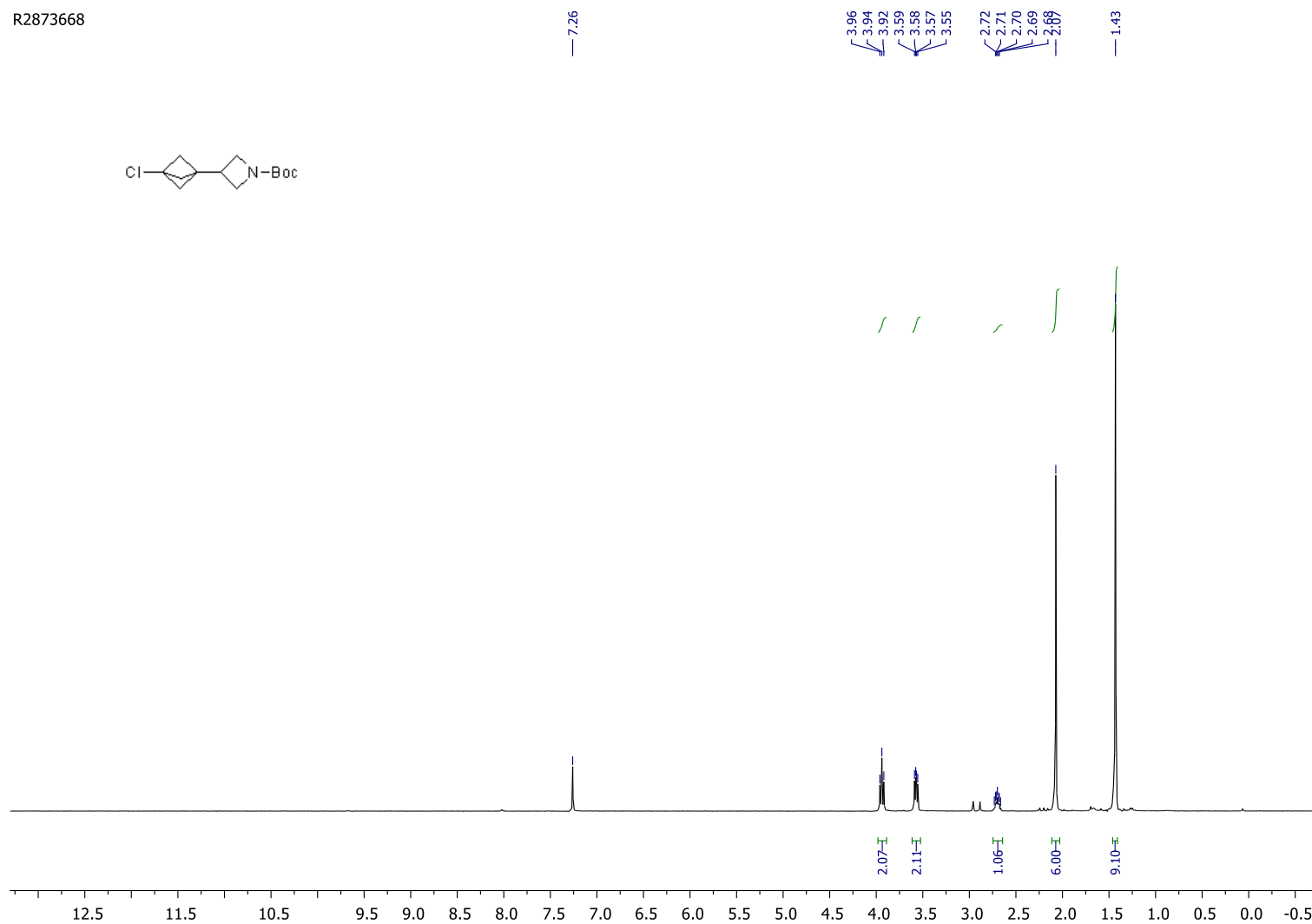
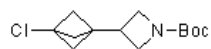
R1773722_F19{H}
19F-{1H}



***Tert*-butyl 3-(3-chlorobicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate**

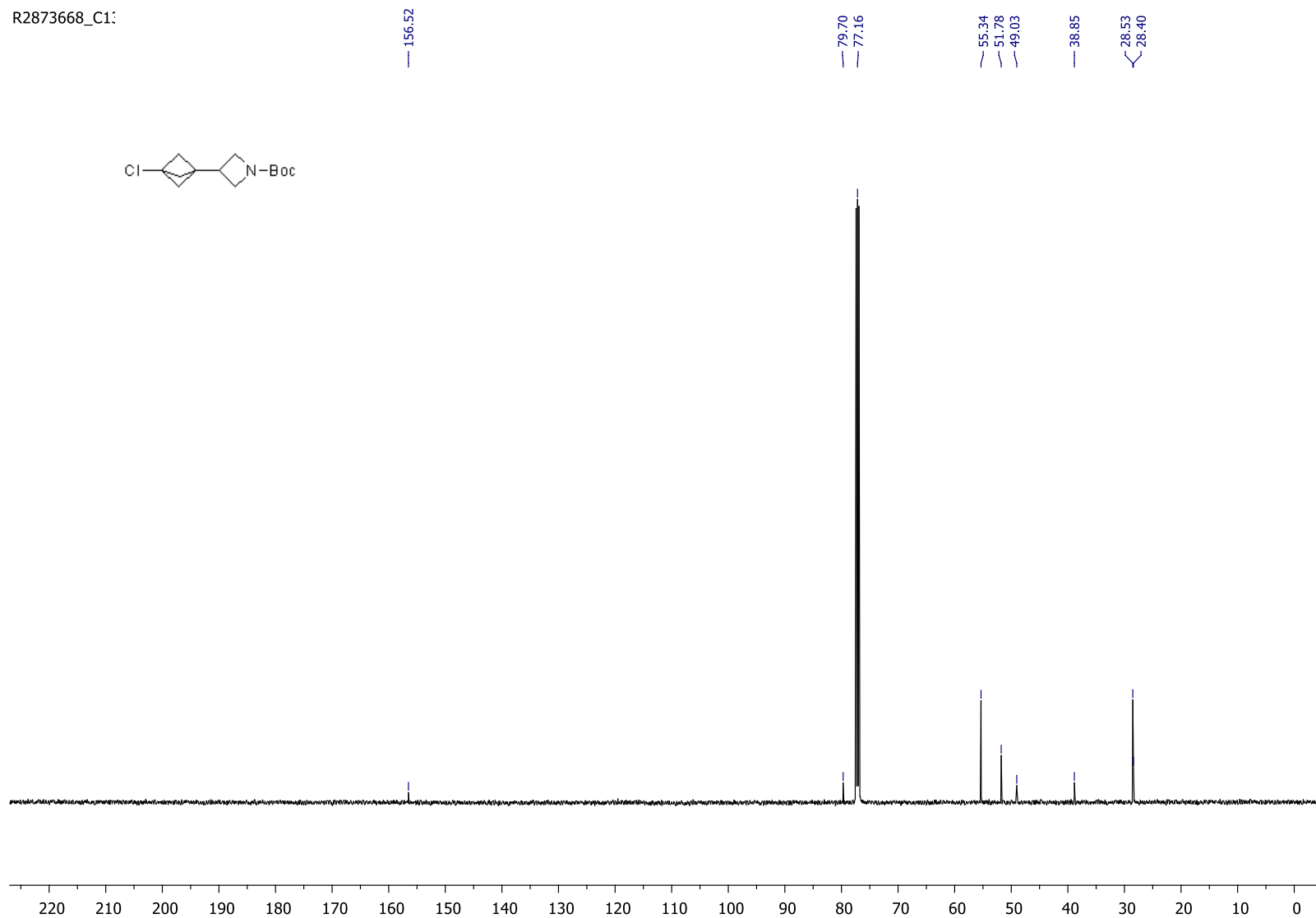
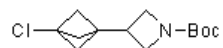
^1H NMR (400 MHz, CDCl_3)

R2873668



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

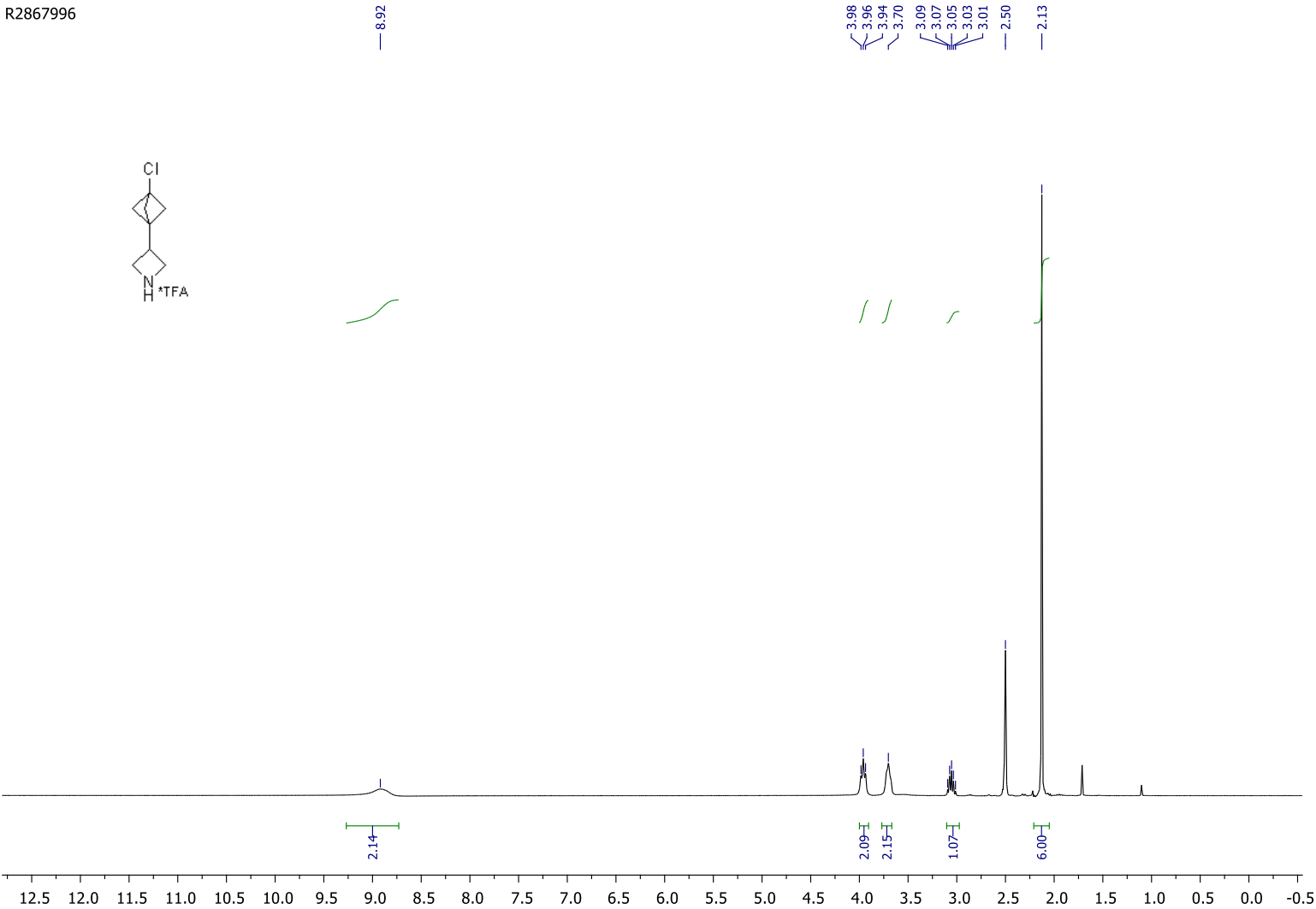
R2873668_C11



Compound 60f

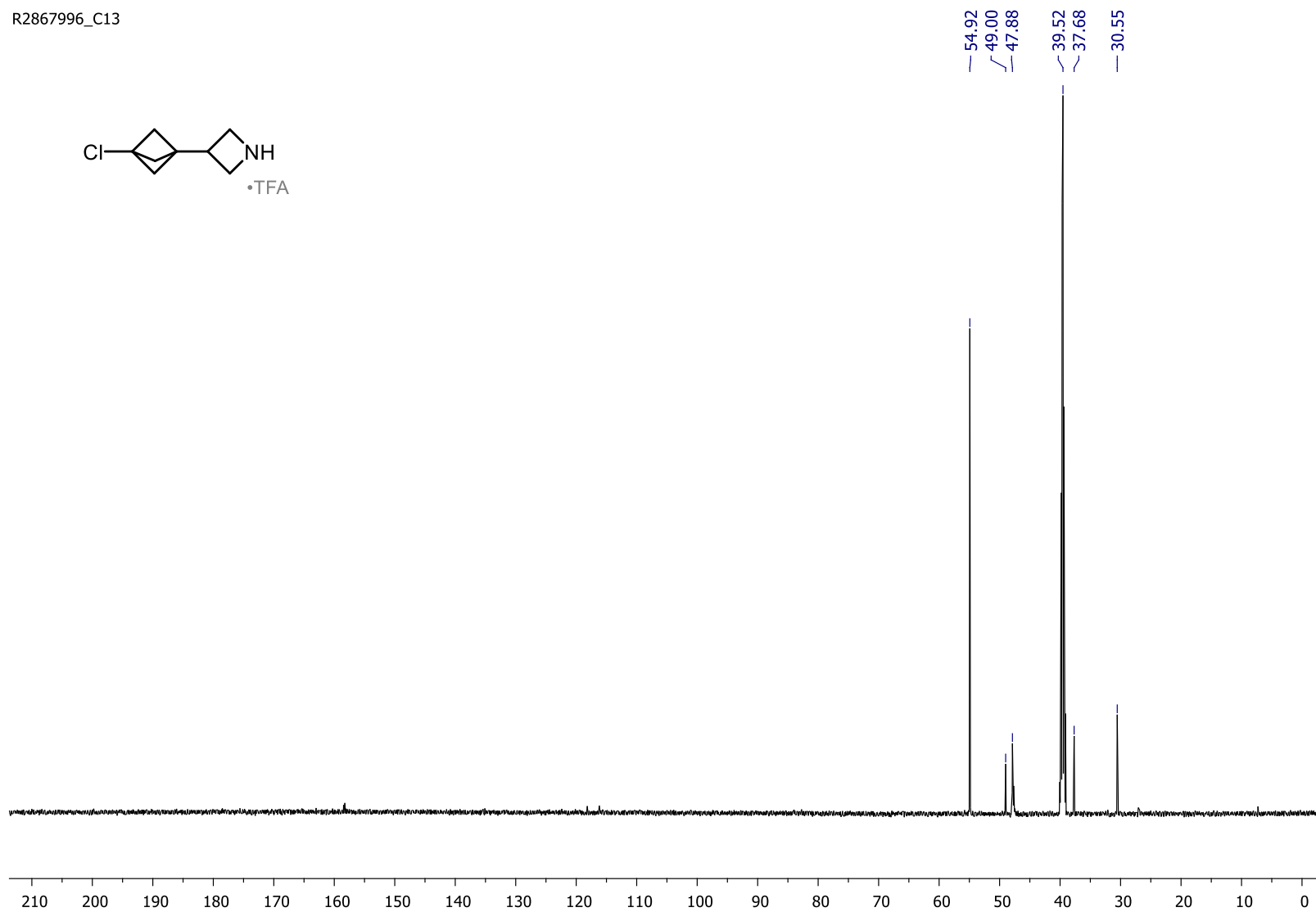
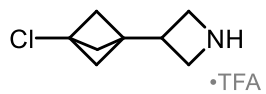
¹H NMR (400 MHz, DMSO-d₆)

R2867996



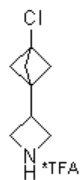
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2867996_C13

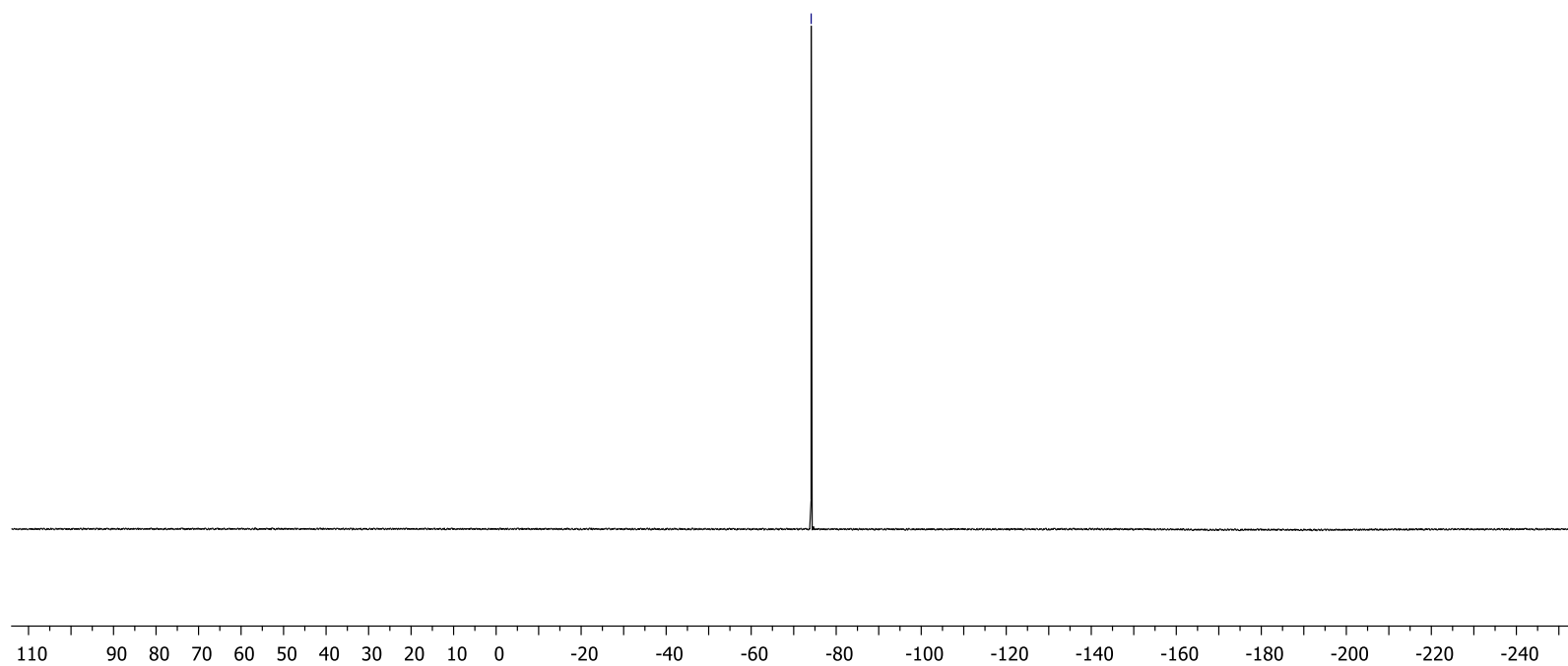


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2867996_F19
 $^{19}\text{F}\{^1\text{H}\}$



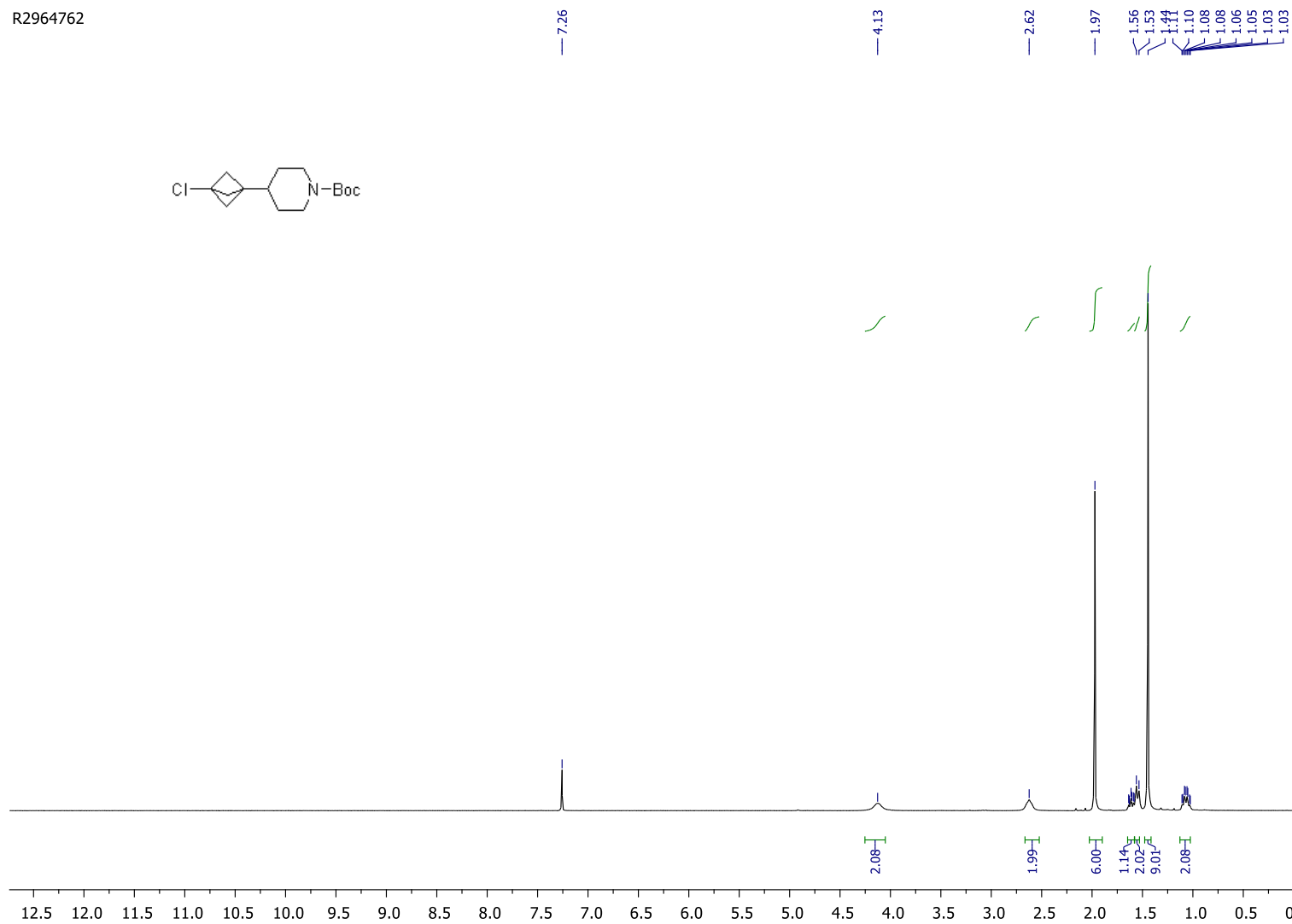
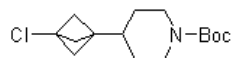
-74.12



***Tert*-butyl 4-(3-chlorobicyclo[1.1.1]pentan-1-yl)piperidine-1-carboxylate**

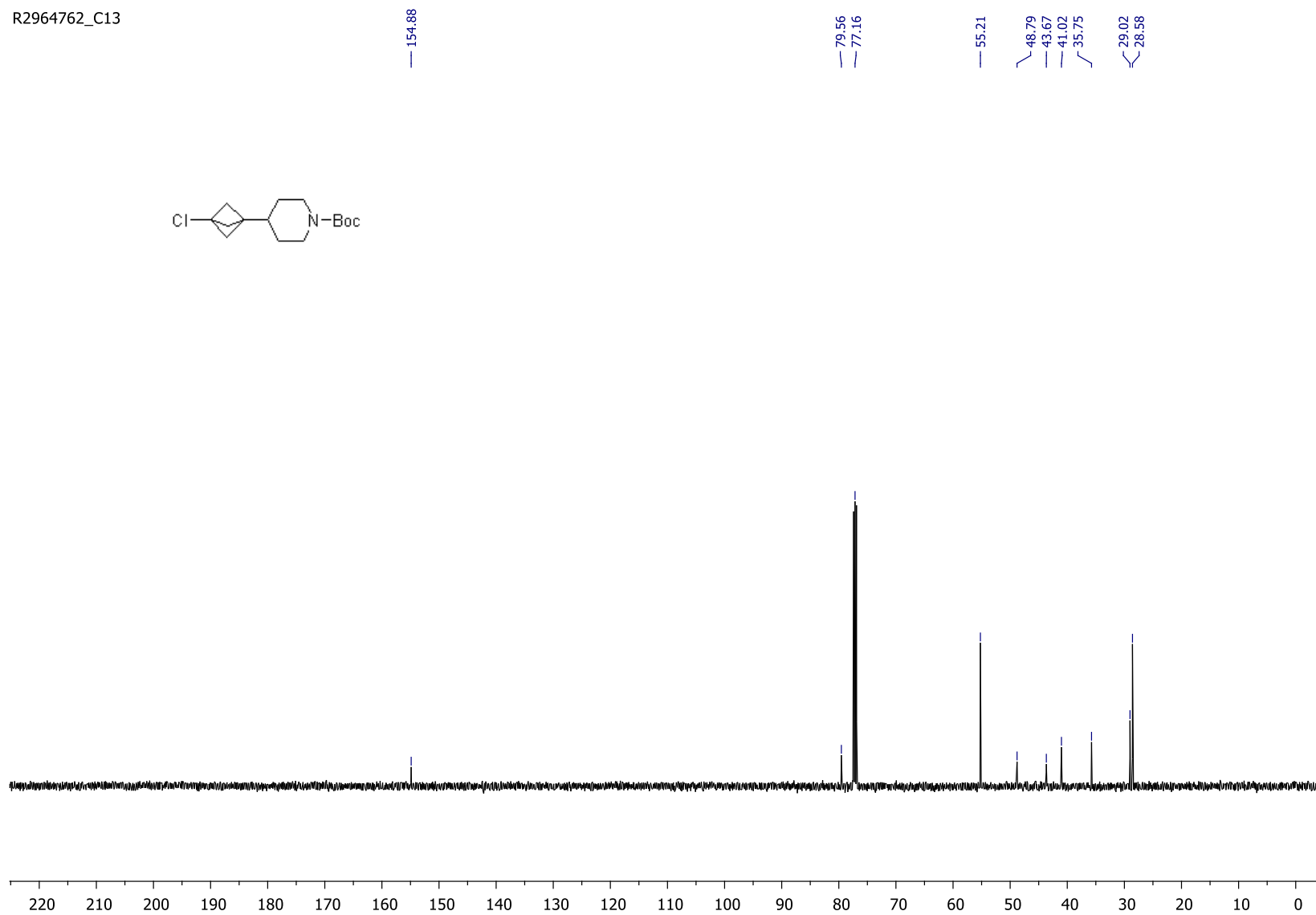
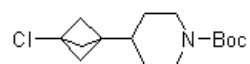
^1H NMR (500 MHz, CDCl_3)

R2964762

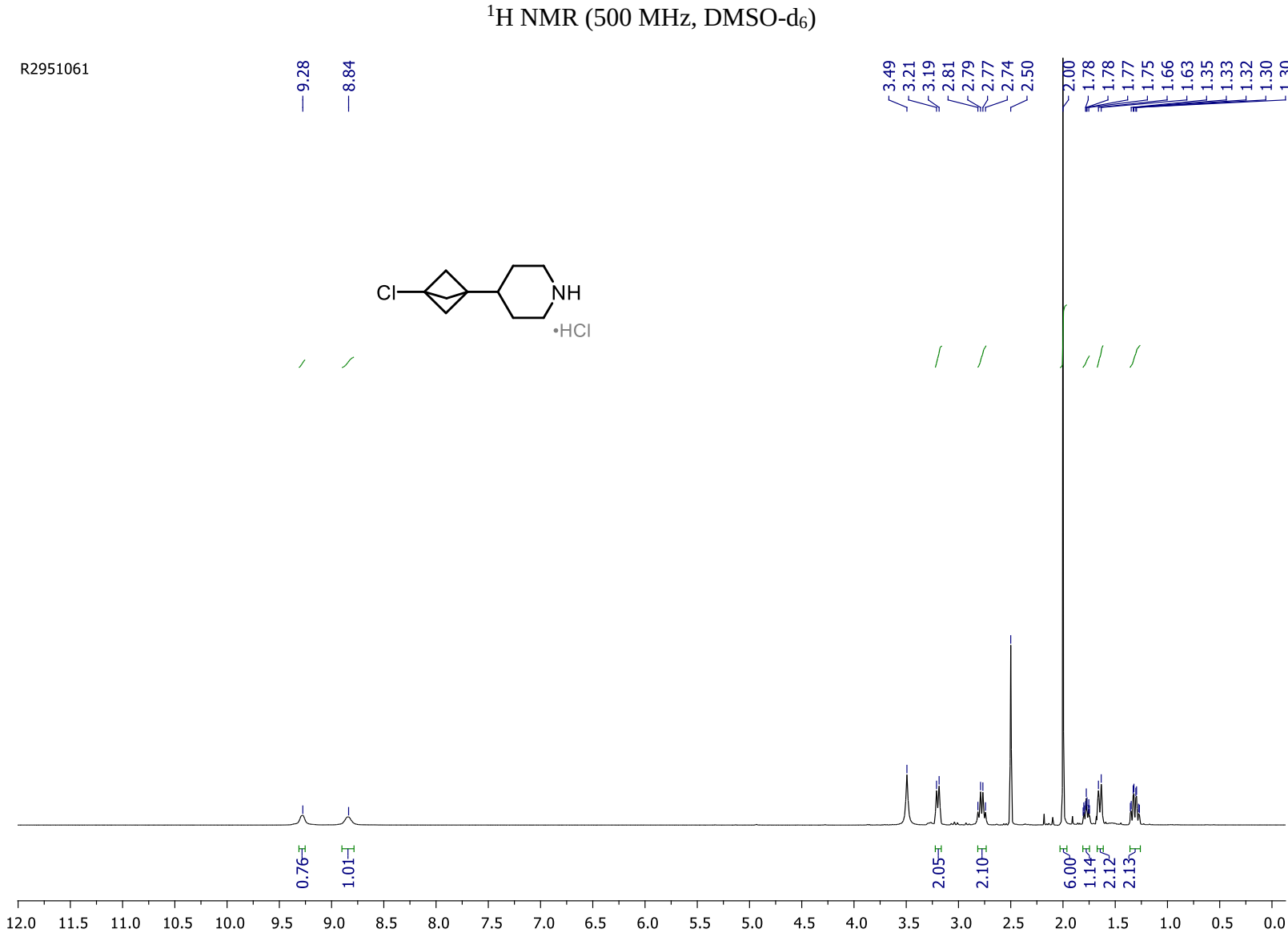


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2964762_C13

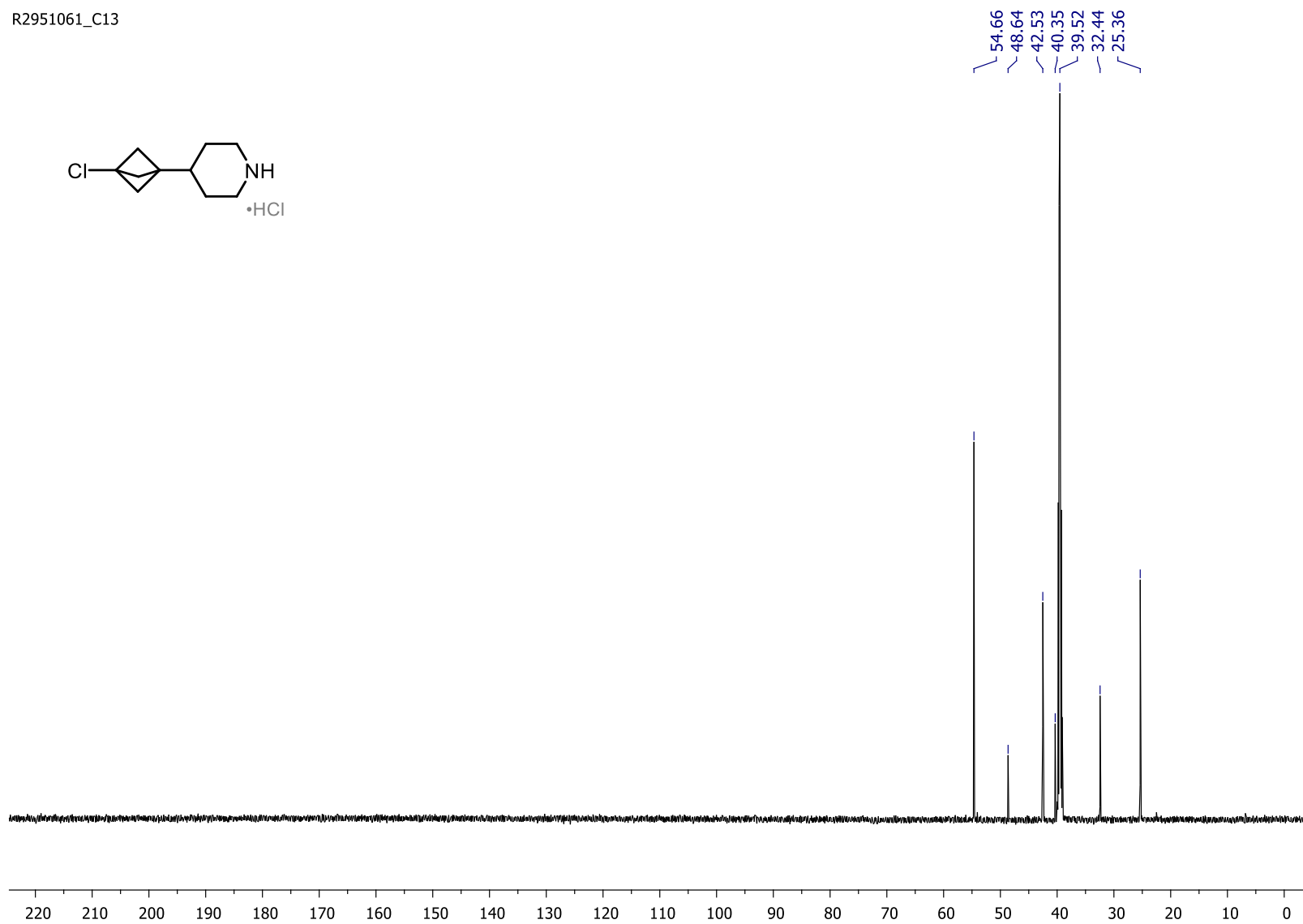
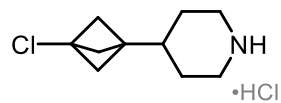


Compound 63f



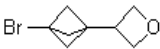
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2951061_C13

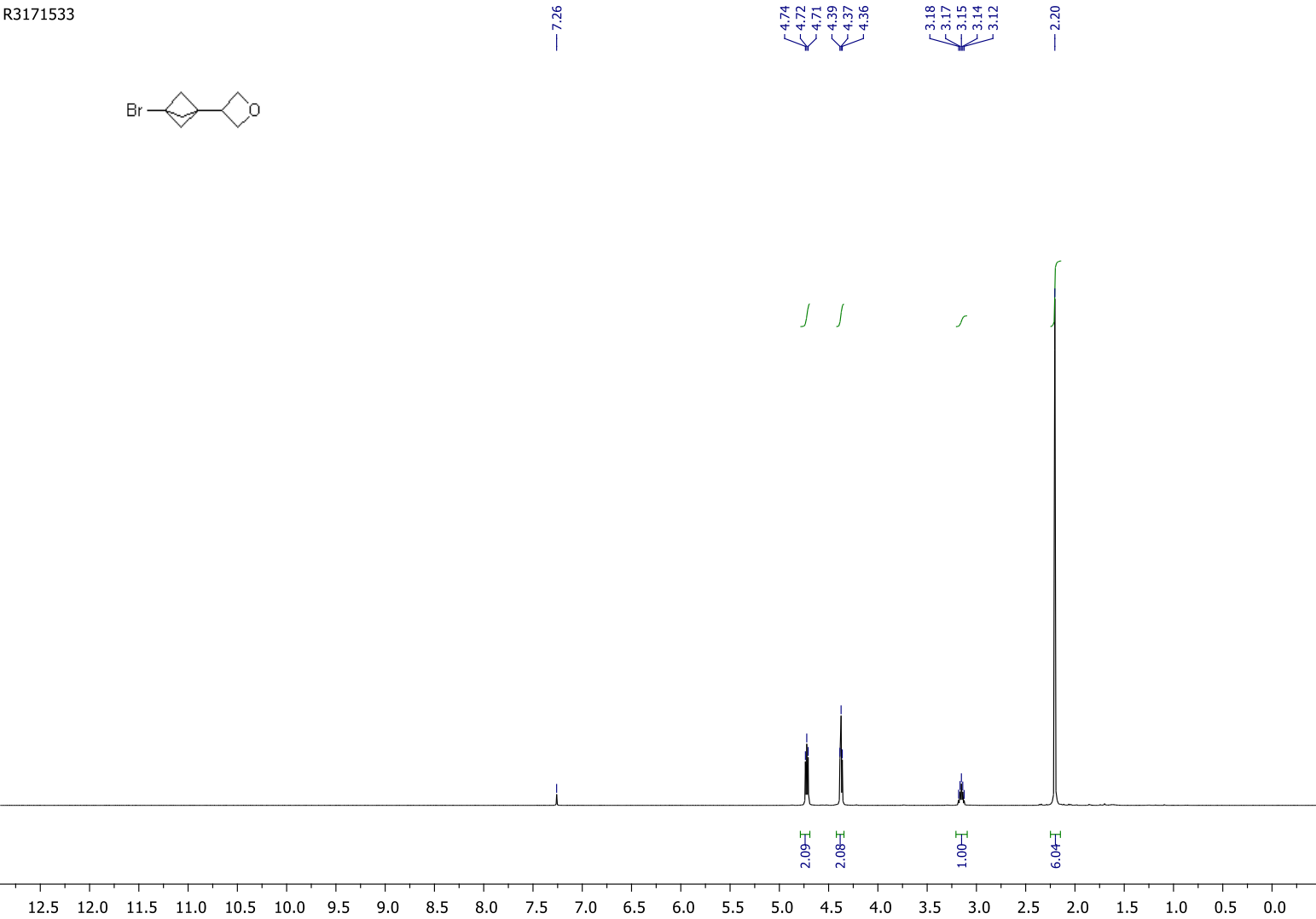


Compound 55g

R3171533

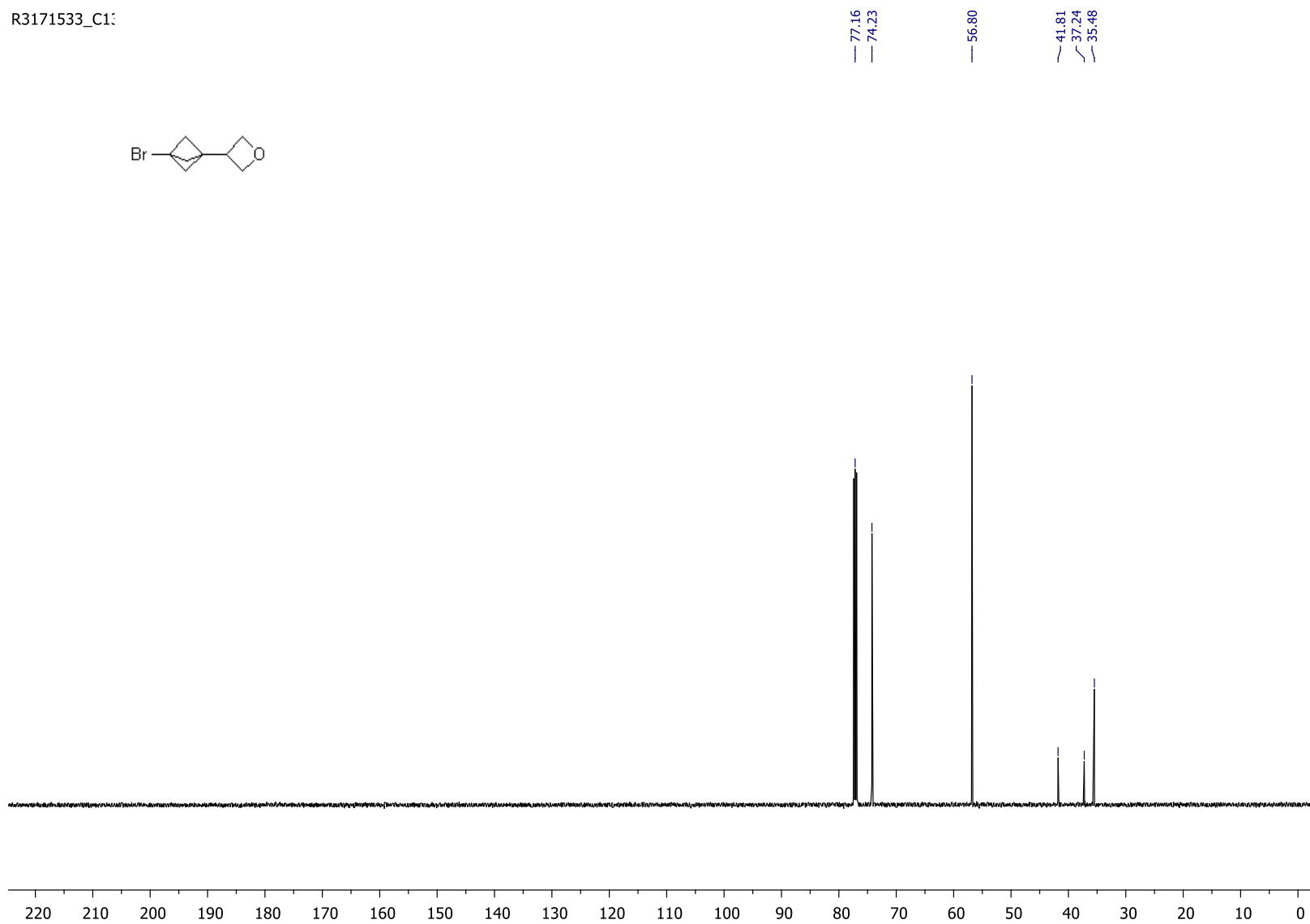
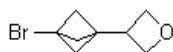


¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

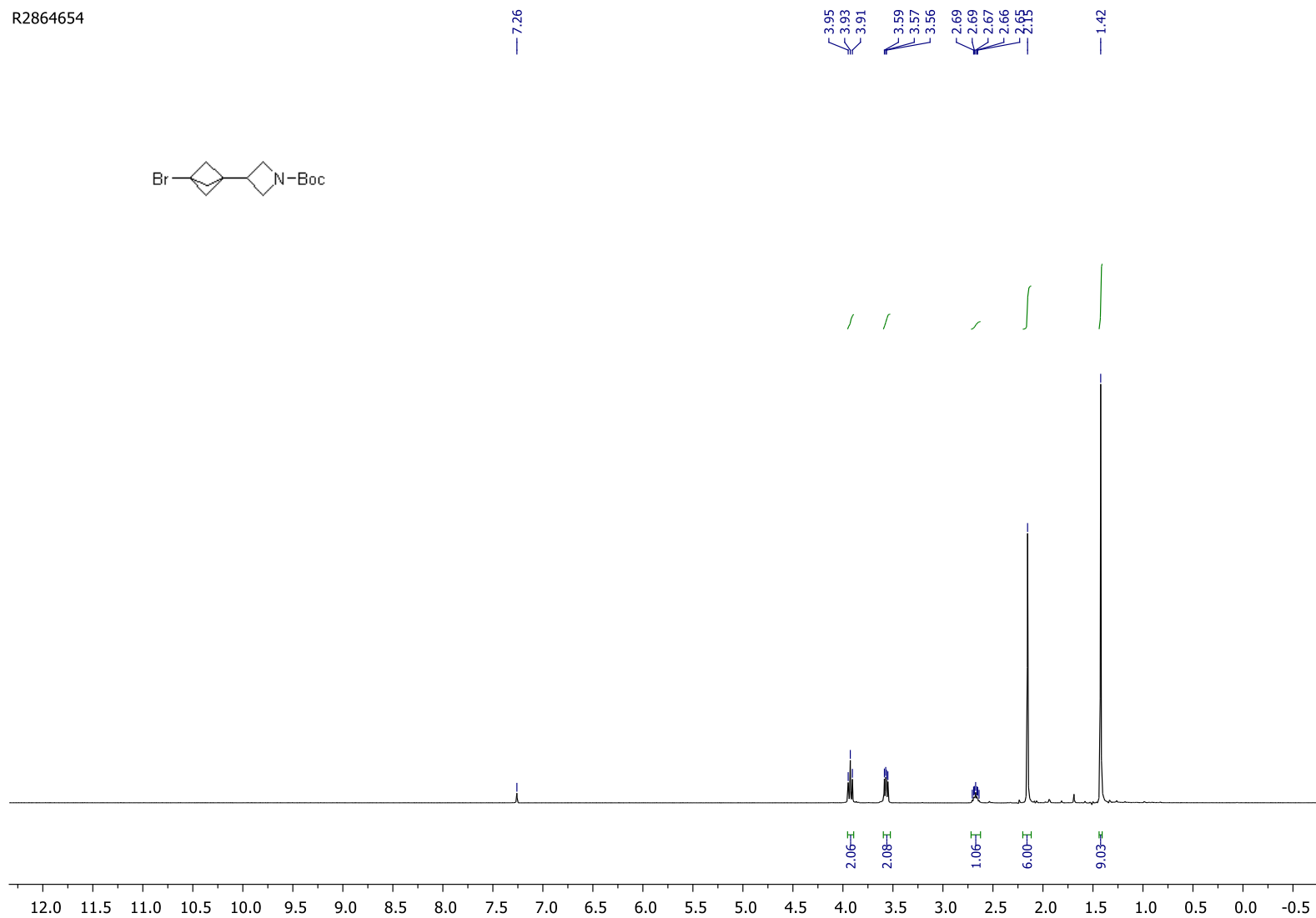
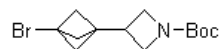
R3171533_C13



***Tert*-butyl 3-(3-bromobicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate**

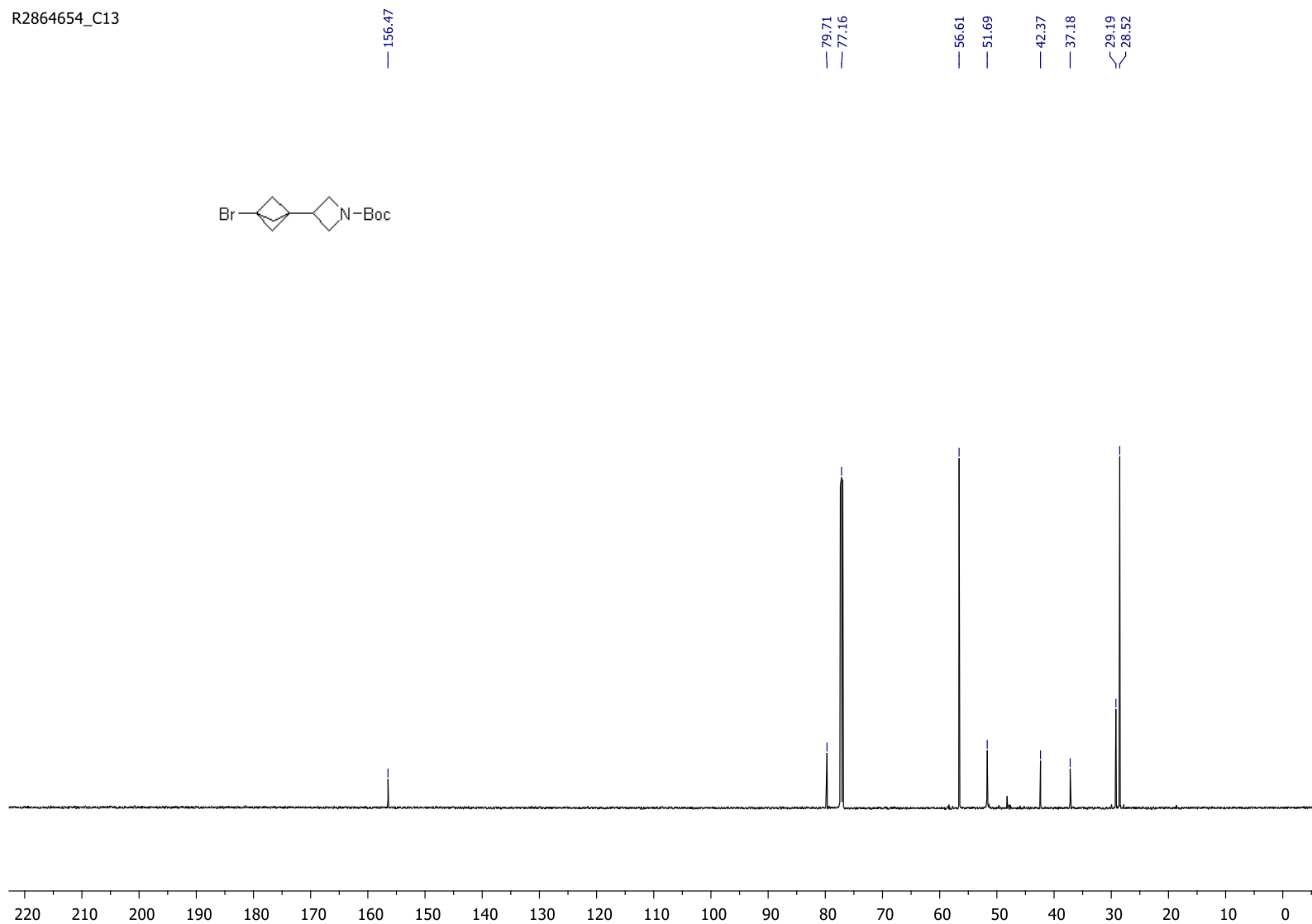
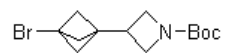
^1H NMR (400 MHz, CDCl_3)

R2864654



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

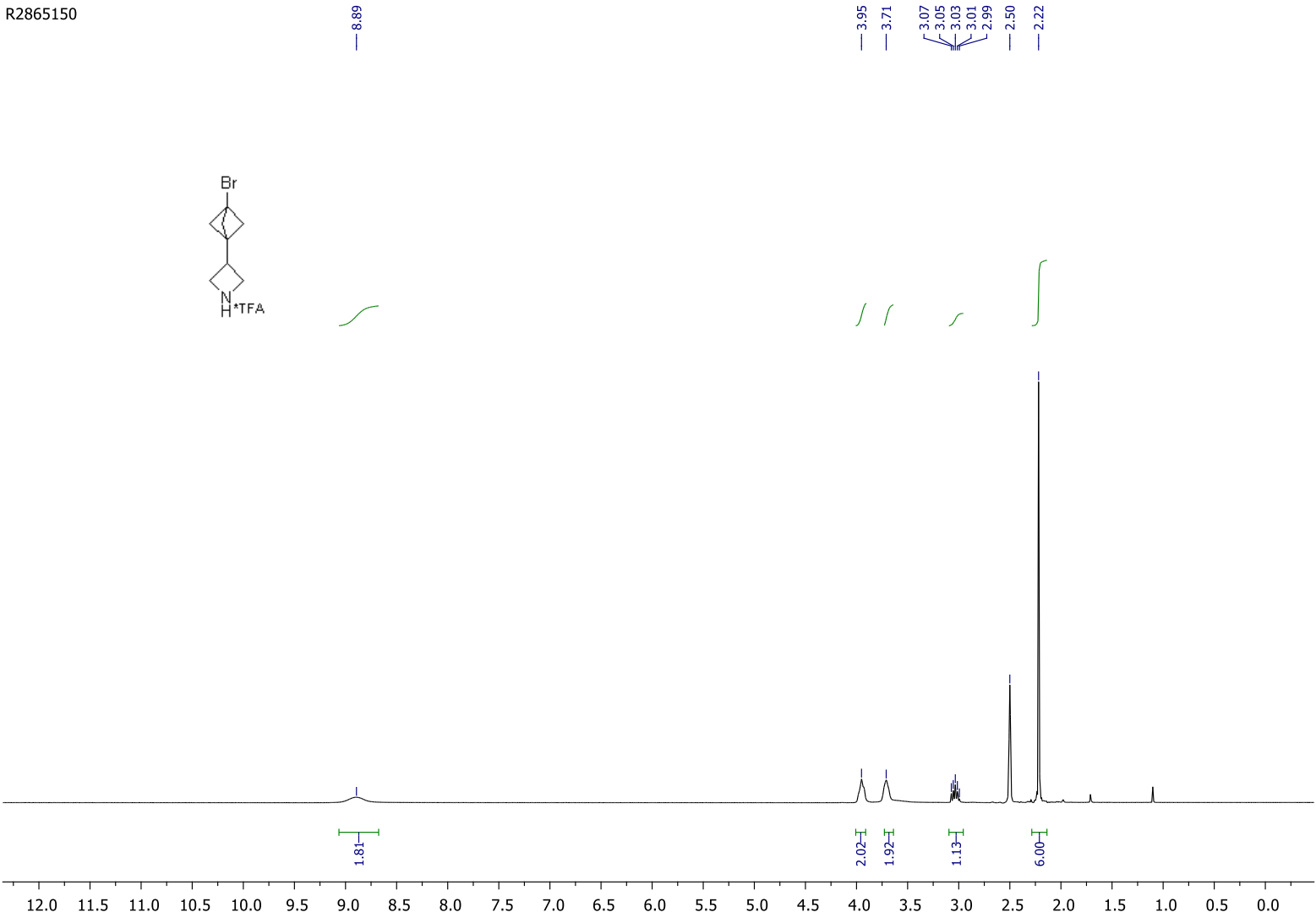
R2864654_C13



Compound 60g

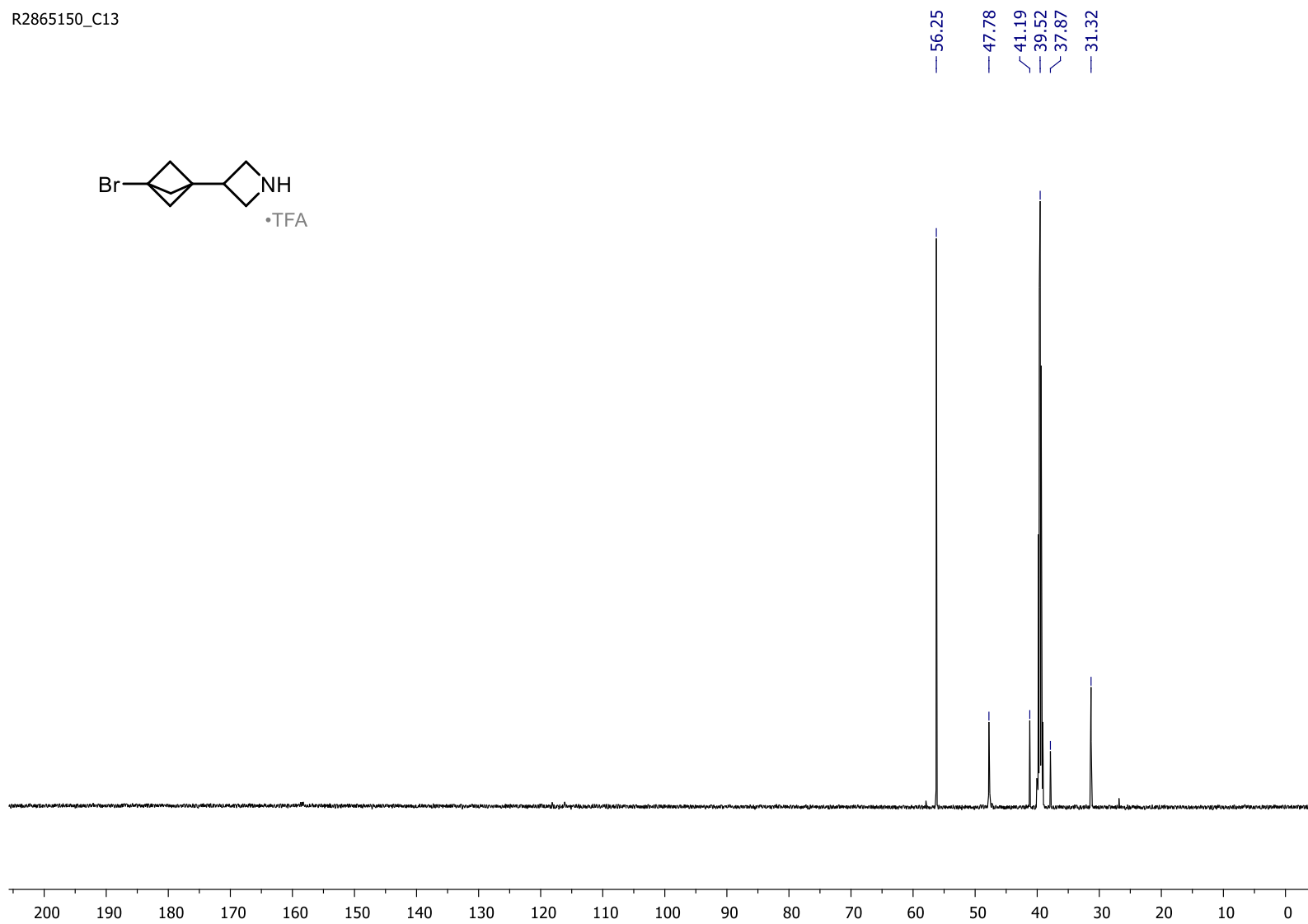
¹H NMR (400 MHz, DMSO-d₆)

R2865150



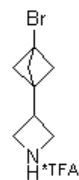
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2865150_C13

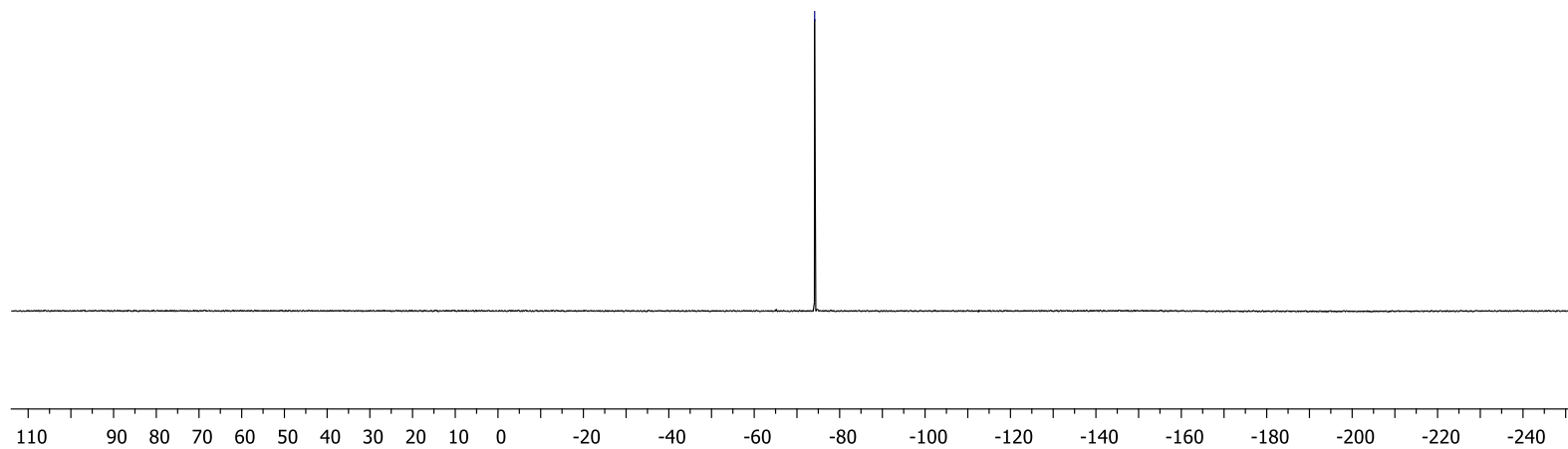


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2865150_F19{H}



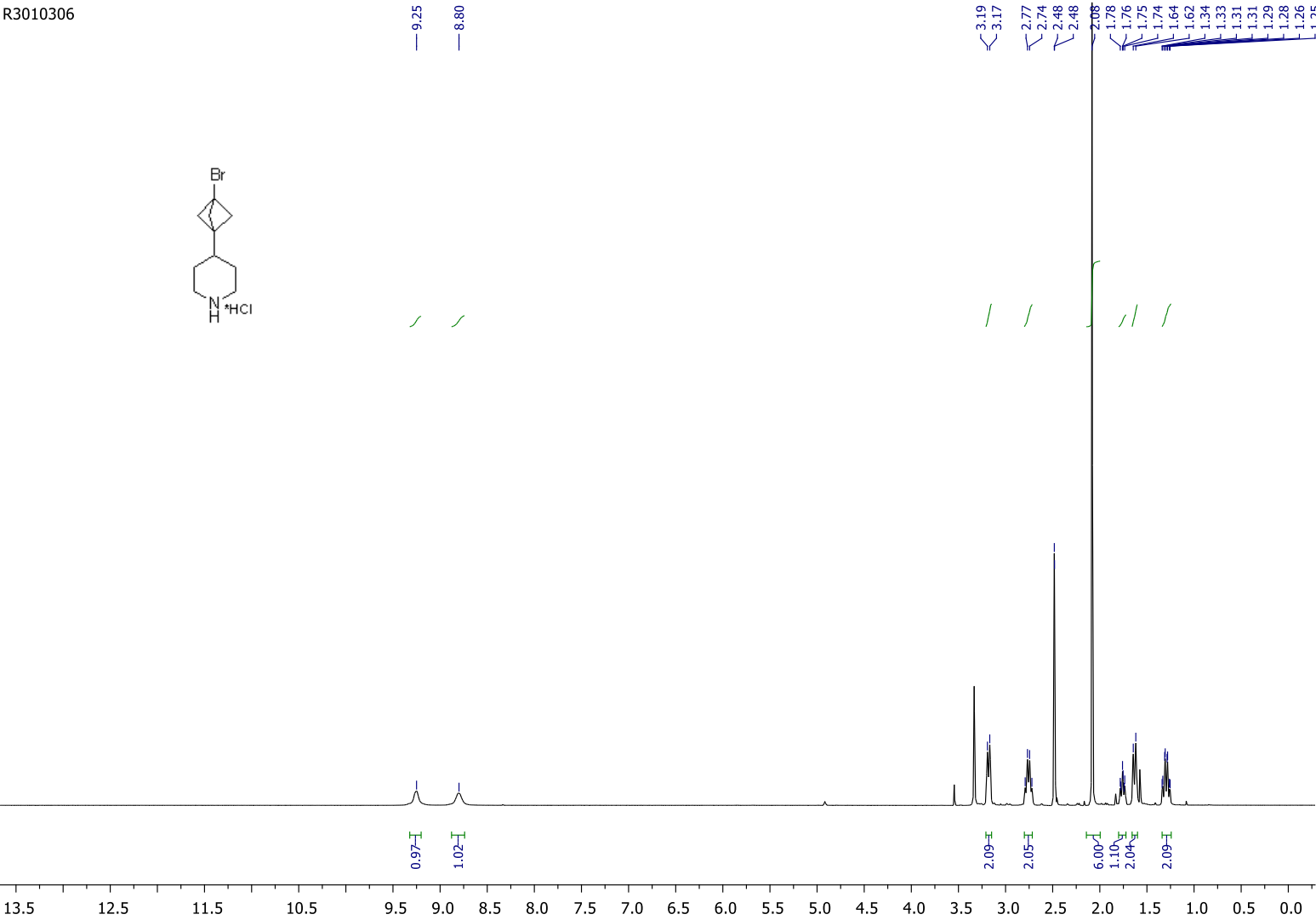
-74.14



Compound 63g

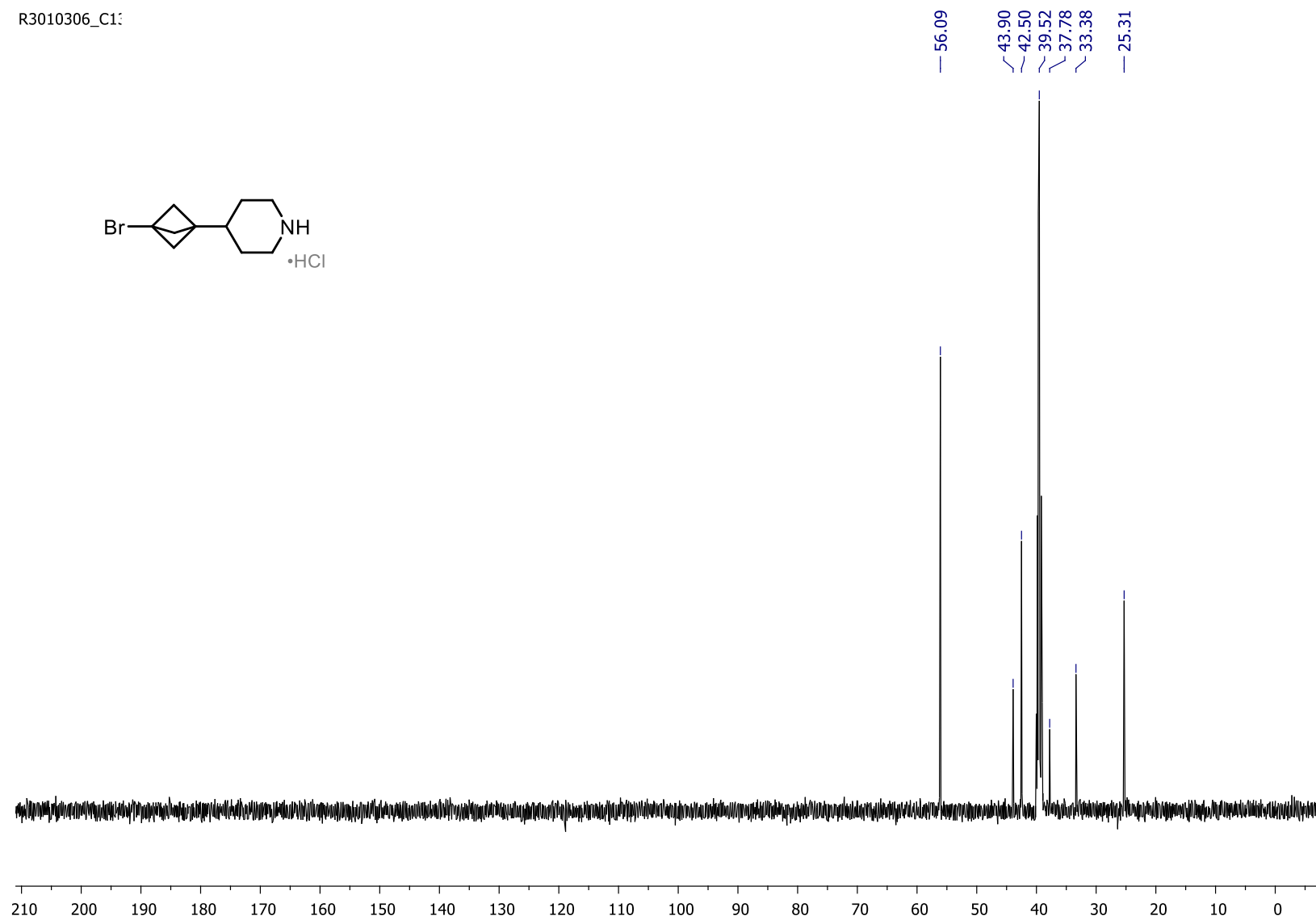
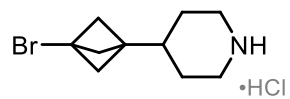
R3010306

¹H NMR (500 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

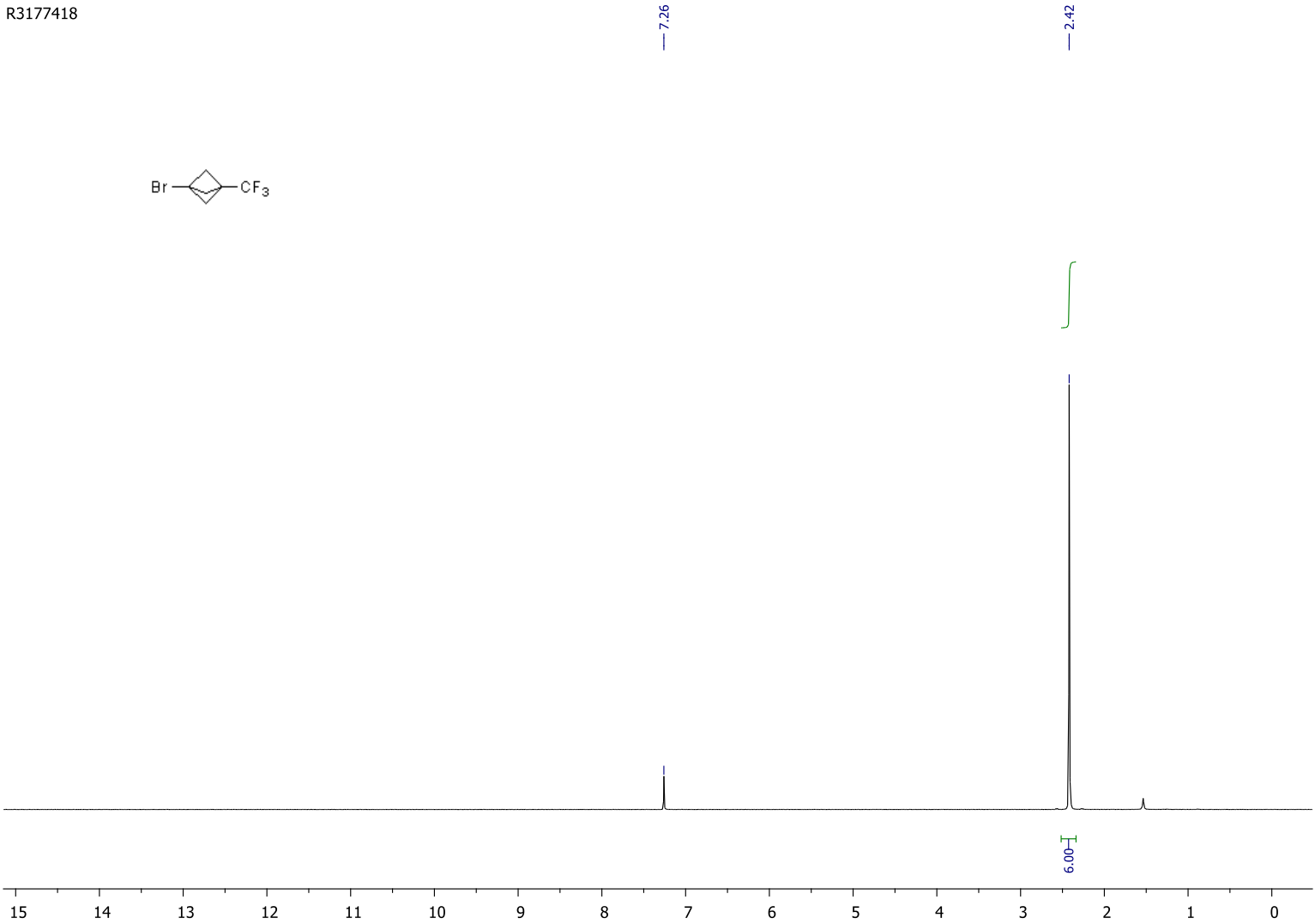
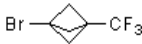
R3010306_C13



Compound 69g

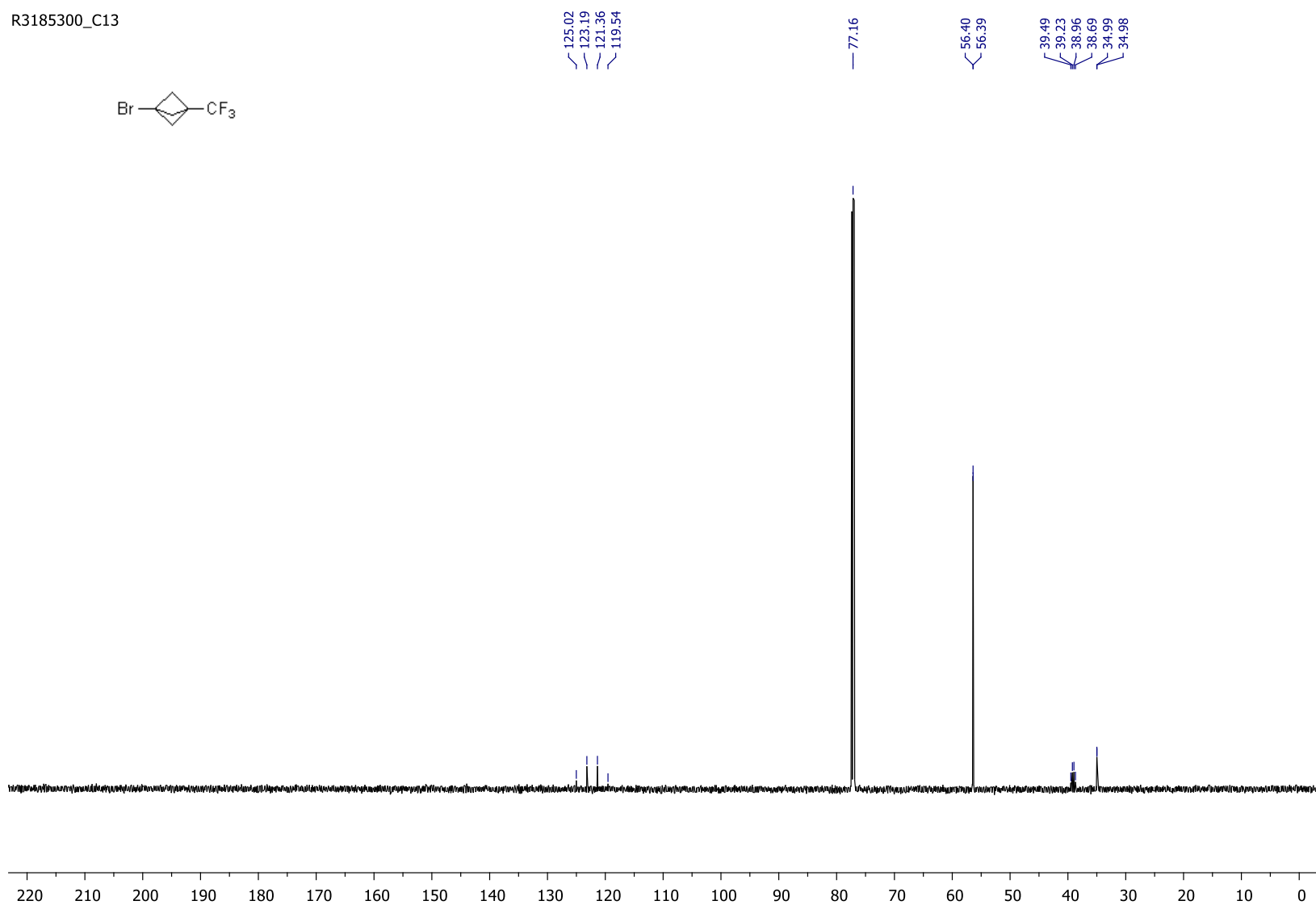
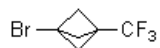
R3177418

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

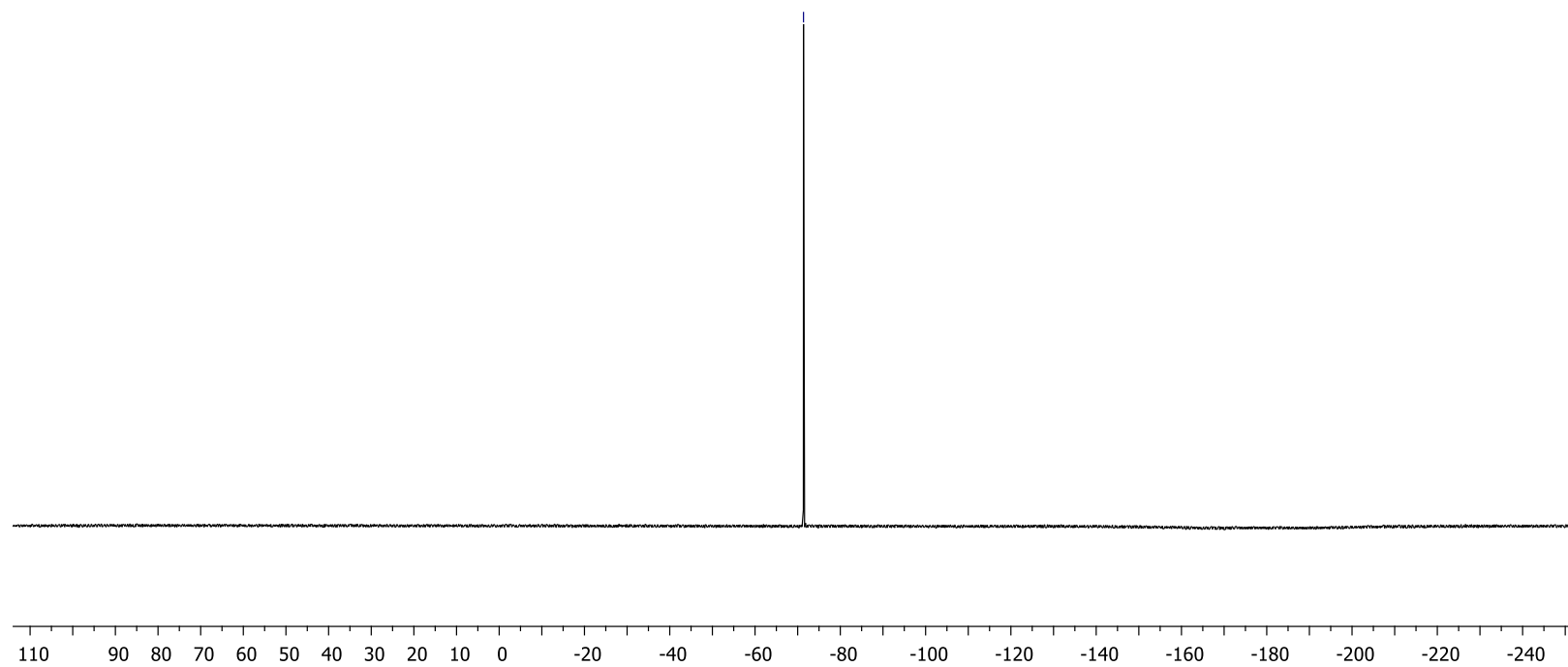
R3185300_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R3177418_F19{H}
19F-{1H}

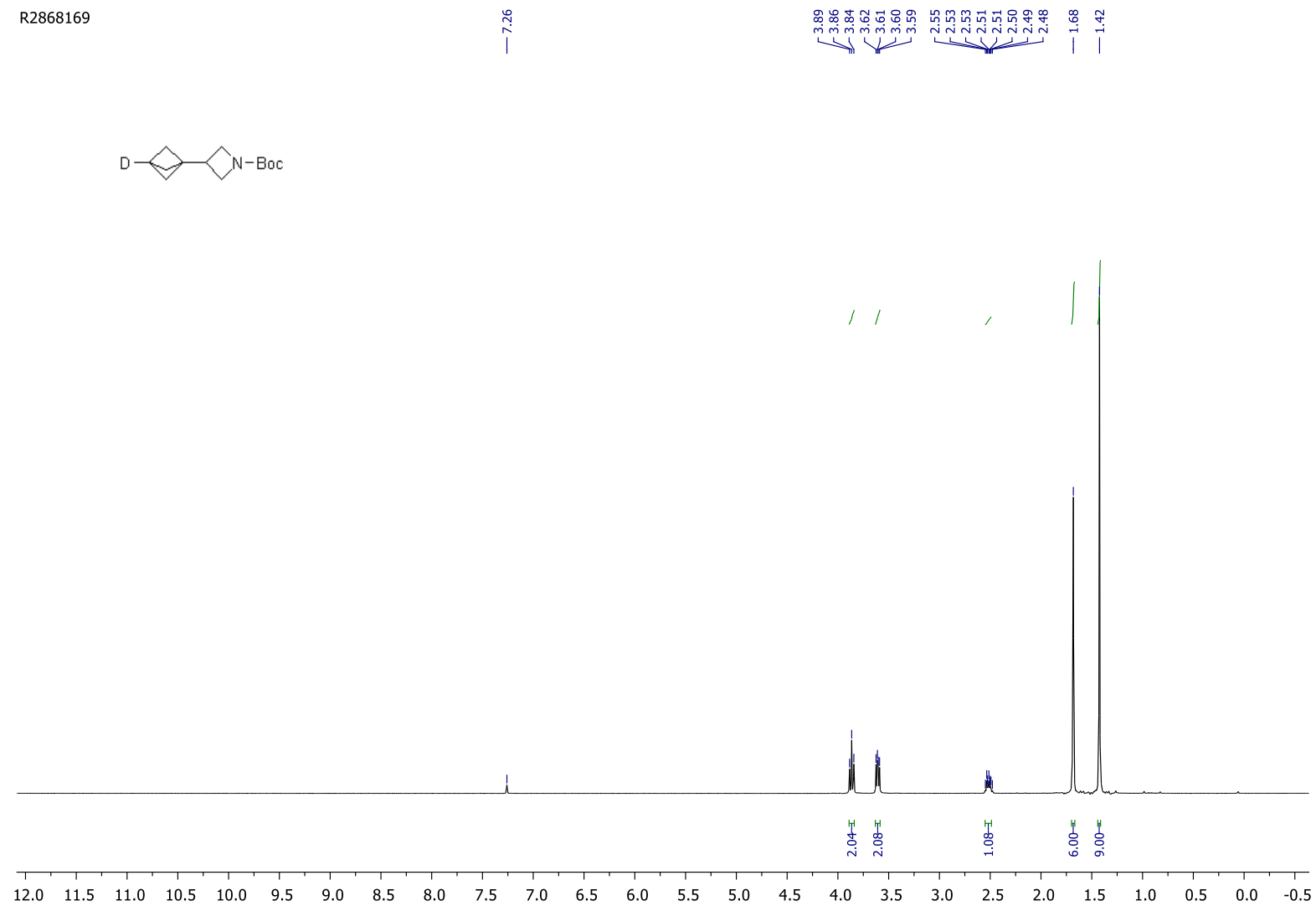
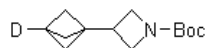
-71.37



***Tert*-butyl 3-(bicyclo[1.1.1]pentan-1-yl-3-d)azetidine-1-carboxylate**

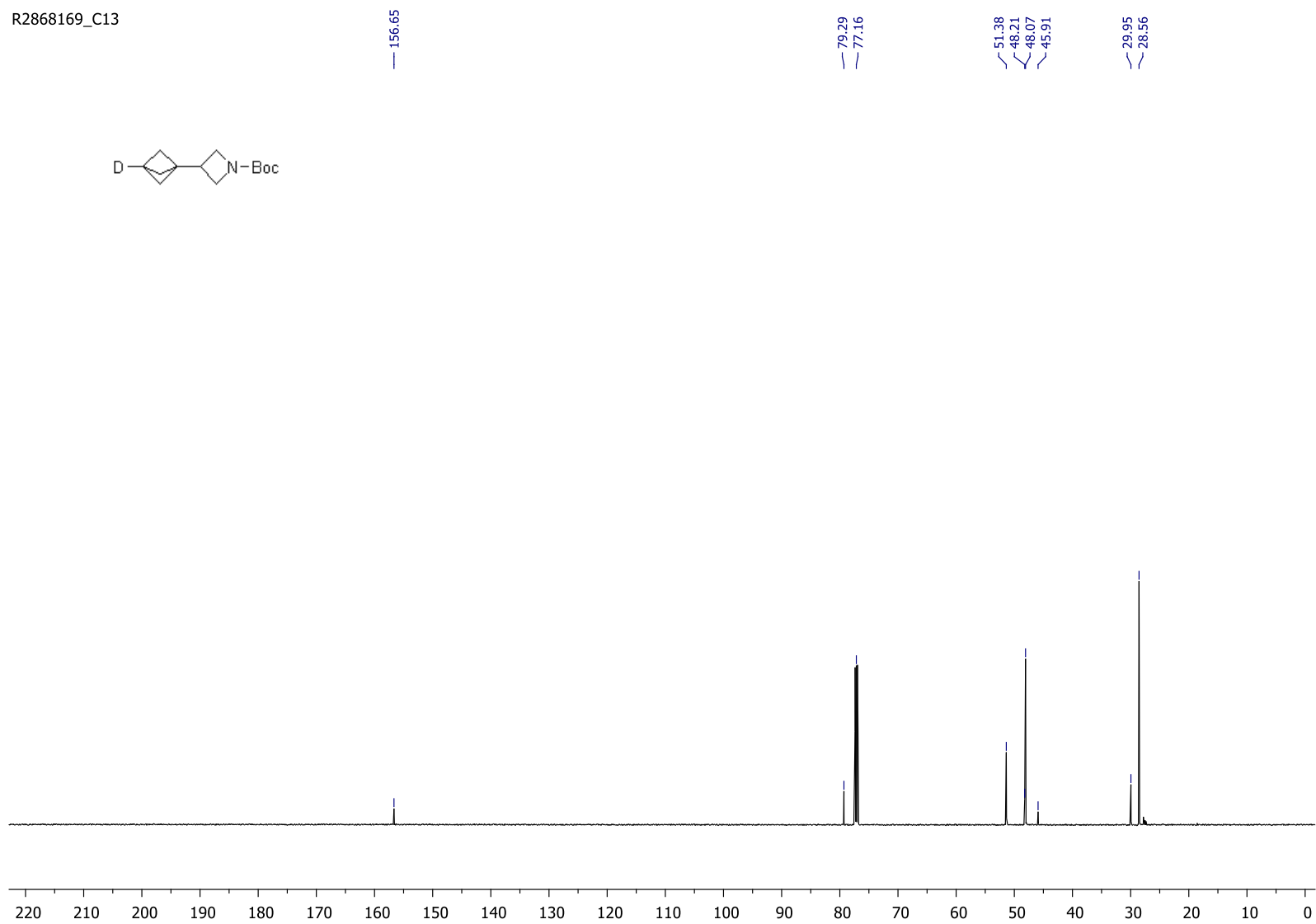
^1H NMR (400 MHz, CDCl_3)

R2868169



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

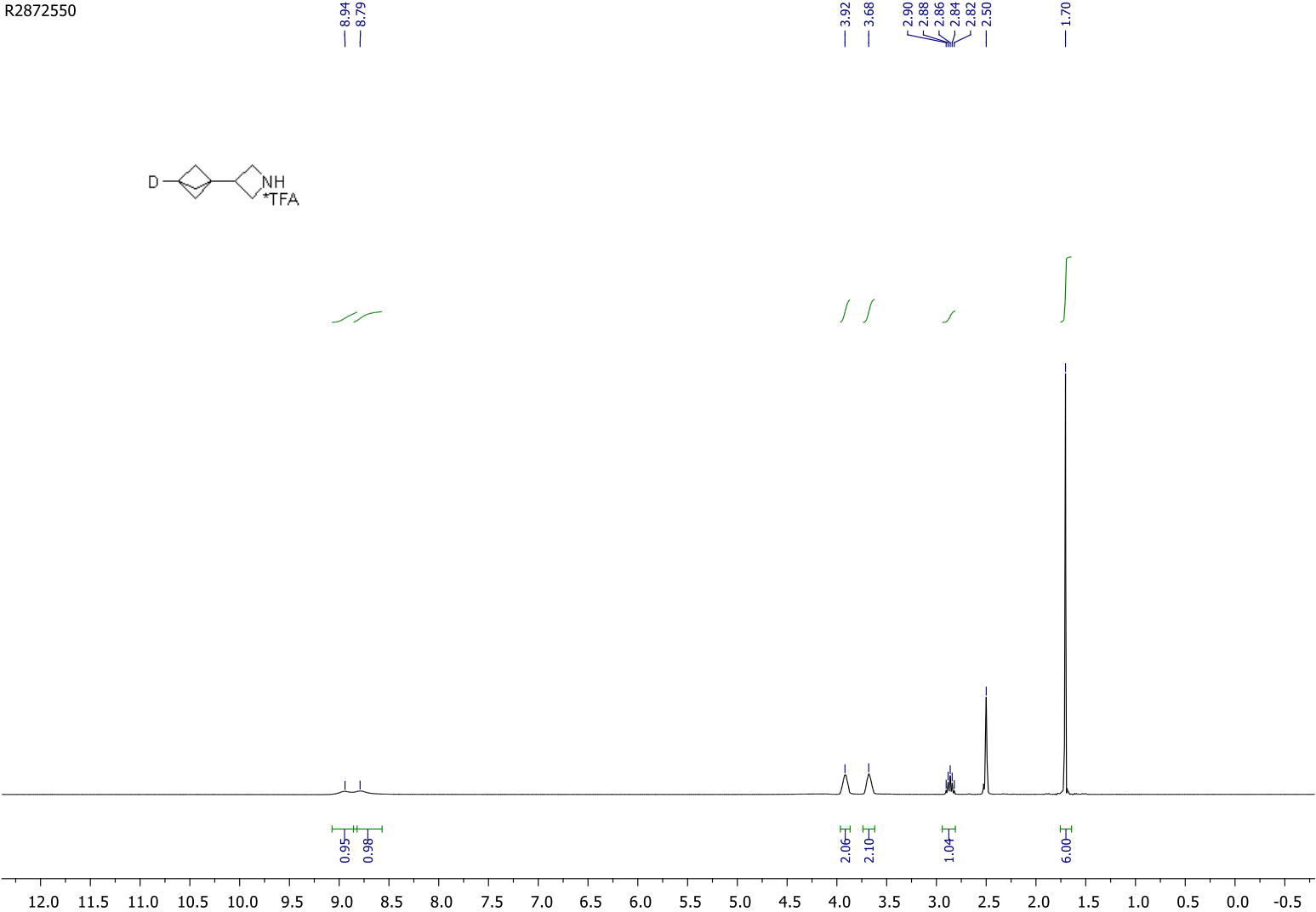
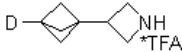
R2868169_C13



Compound 60h

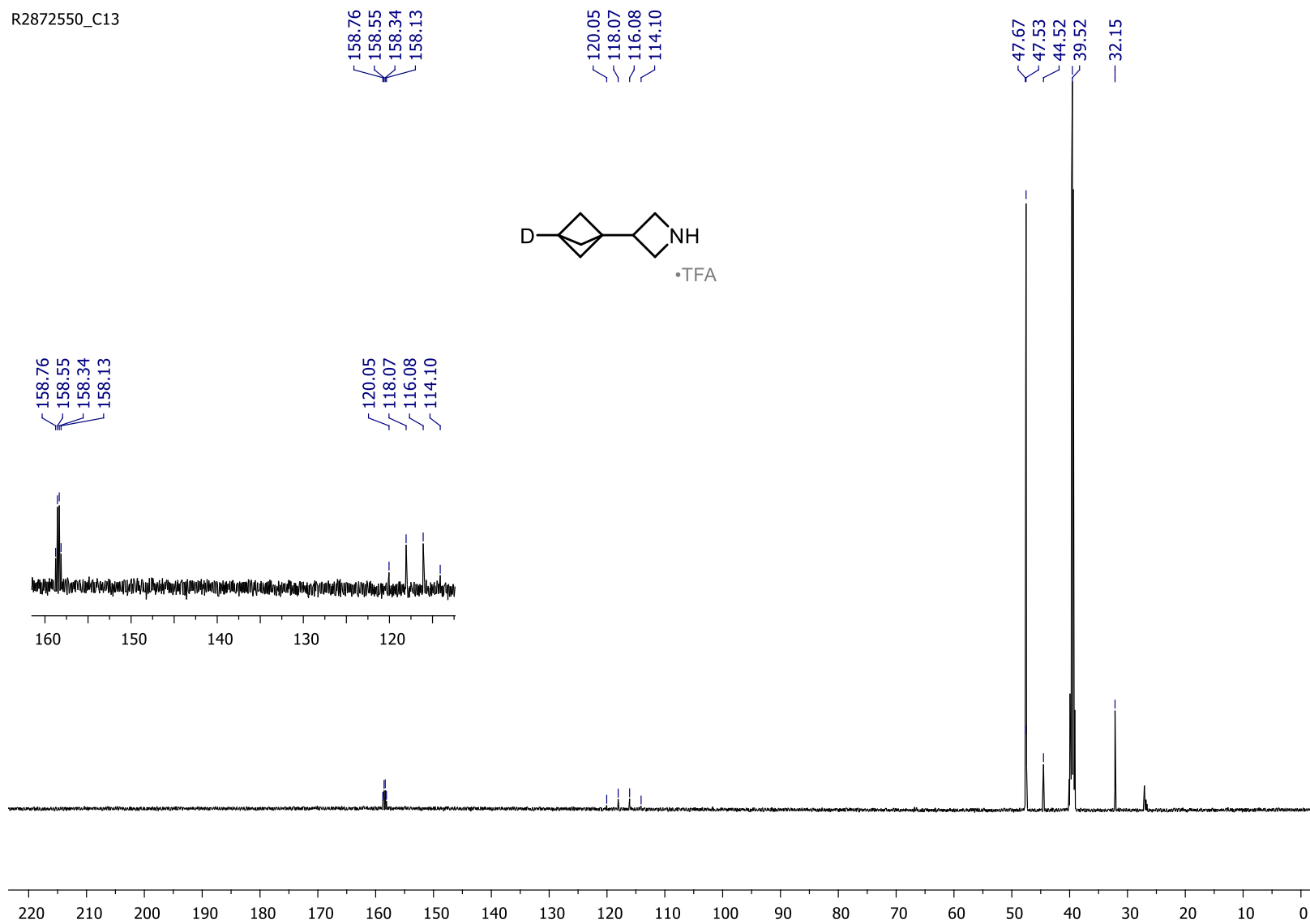
¹H NMR (400 MHz, DMSO-d₆)

R2872550



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

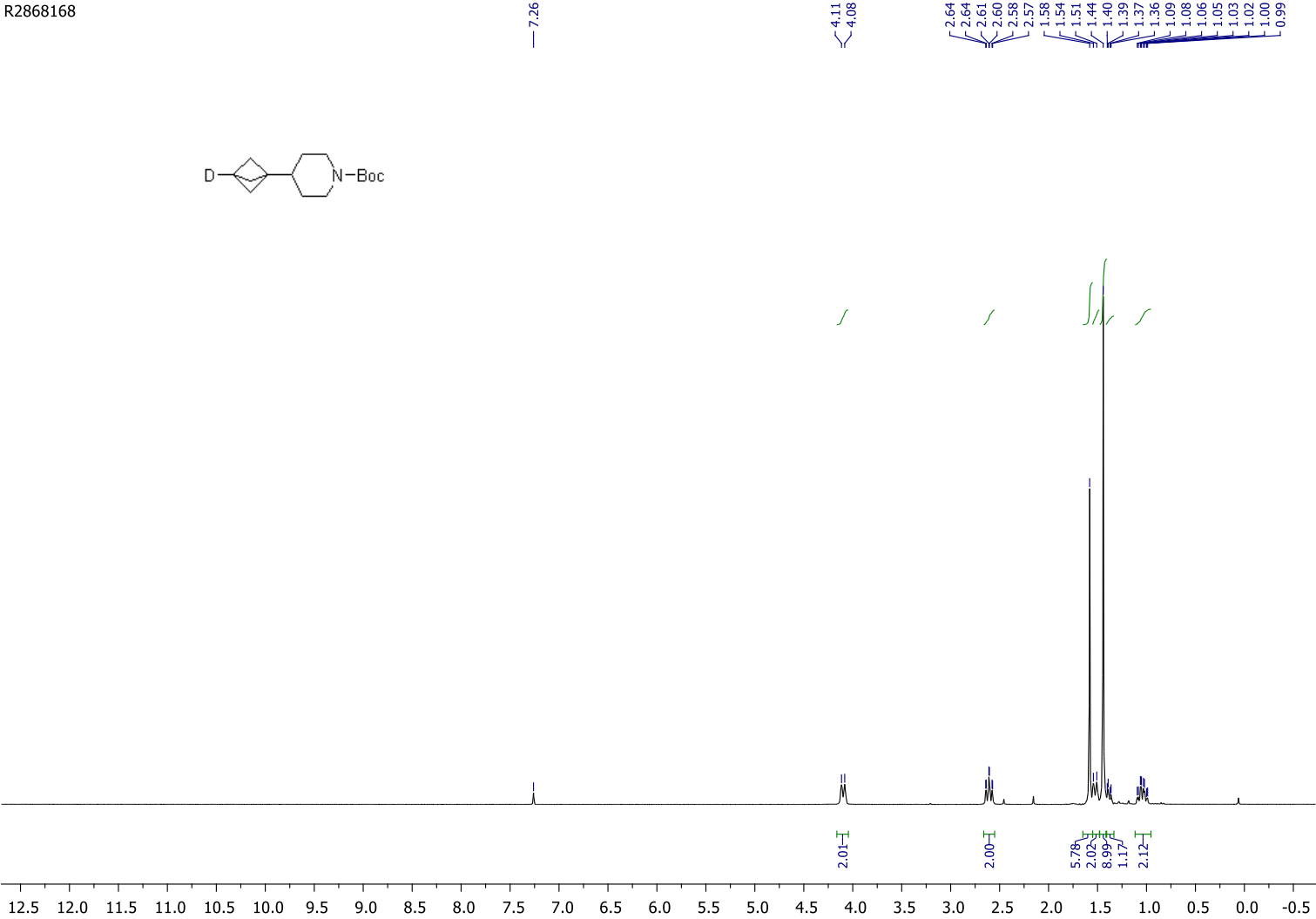
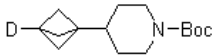
R2872550_C13



***Tert*-butyl 4-(bicyclo[1.1.1]pentan-1-yl-3-d)piperidine-1-carboxylate**

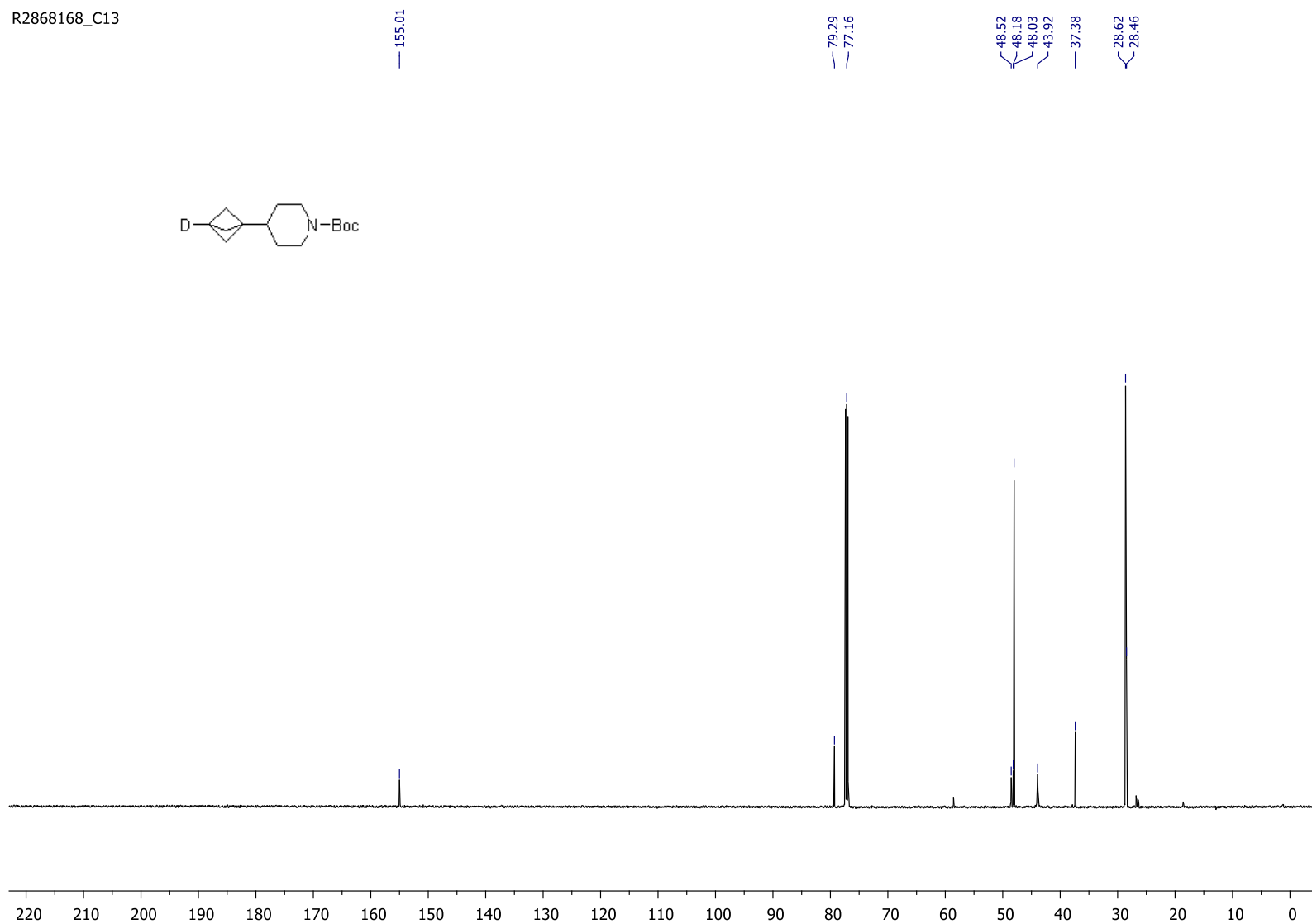
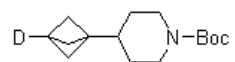
¹H NMR (400 MHz, CDCl₃)

R2868168



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

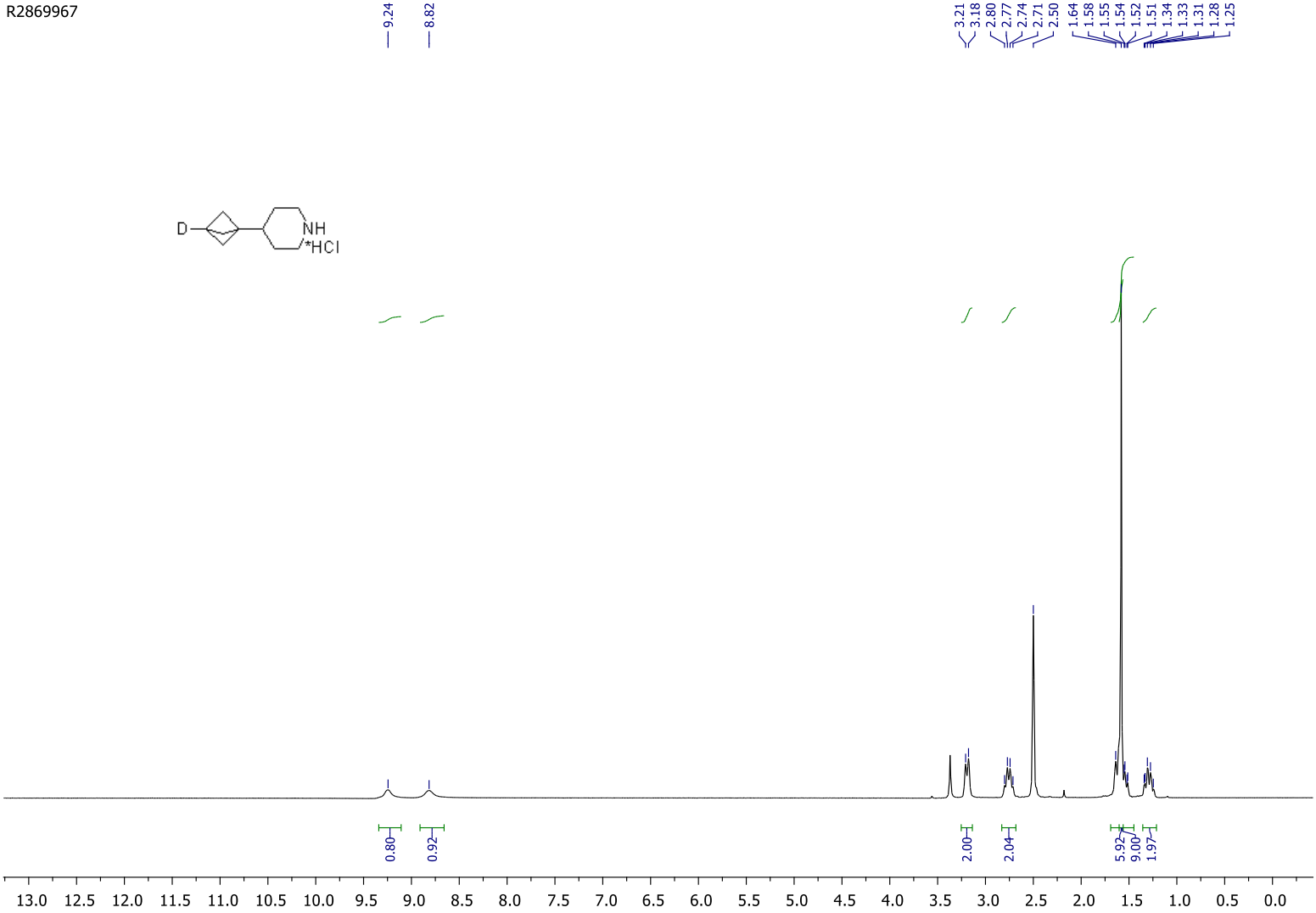
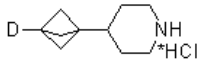
R2868168_C13



Compound 63h

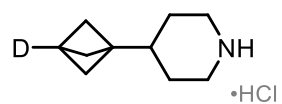
¹H NMR (400 MHz, DMSO-d₆)

R2869967

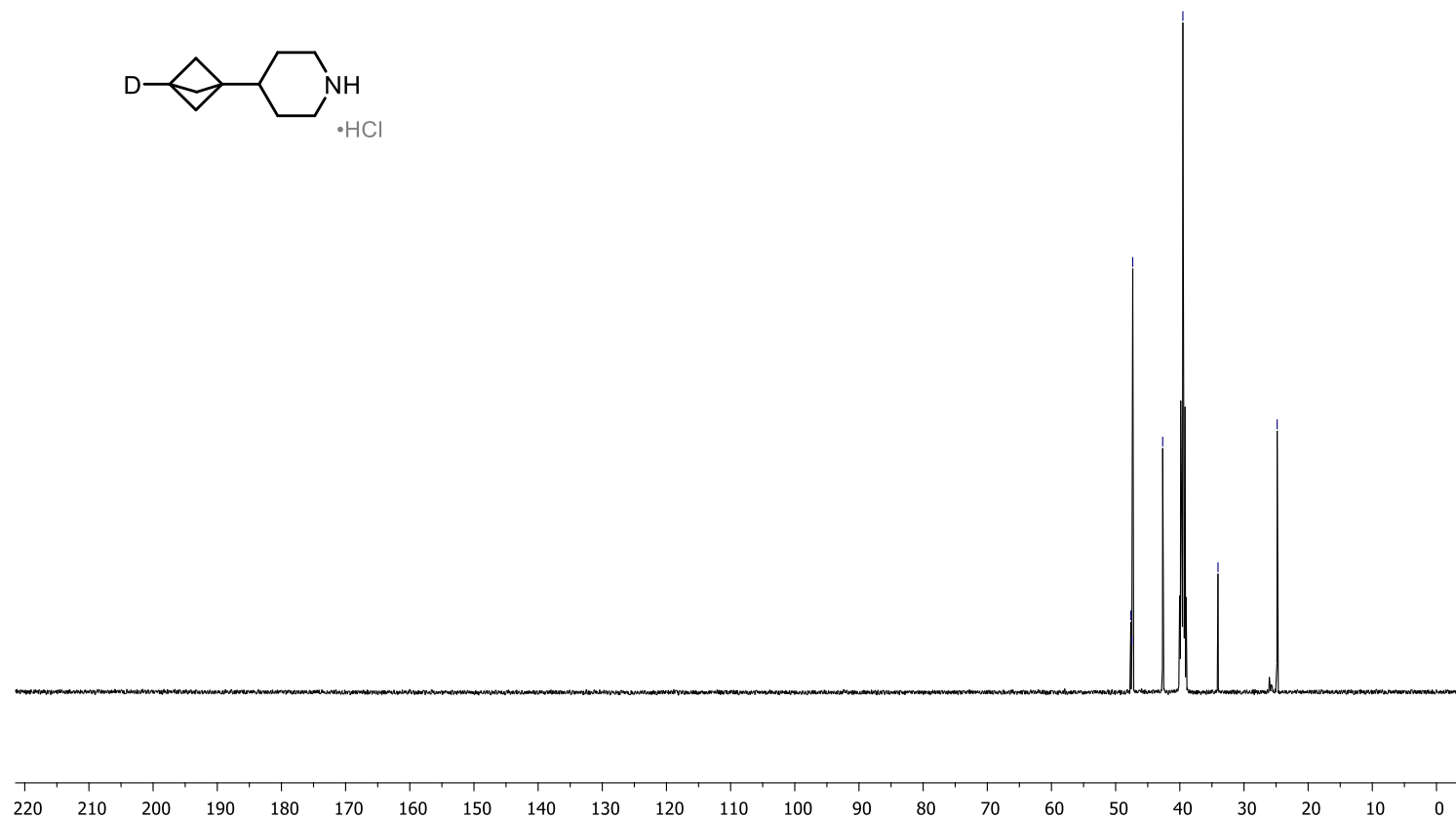


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

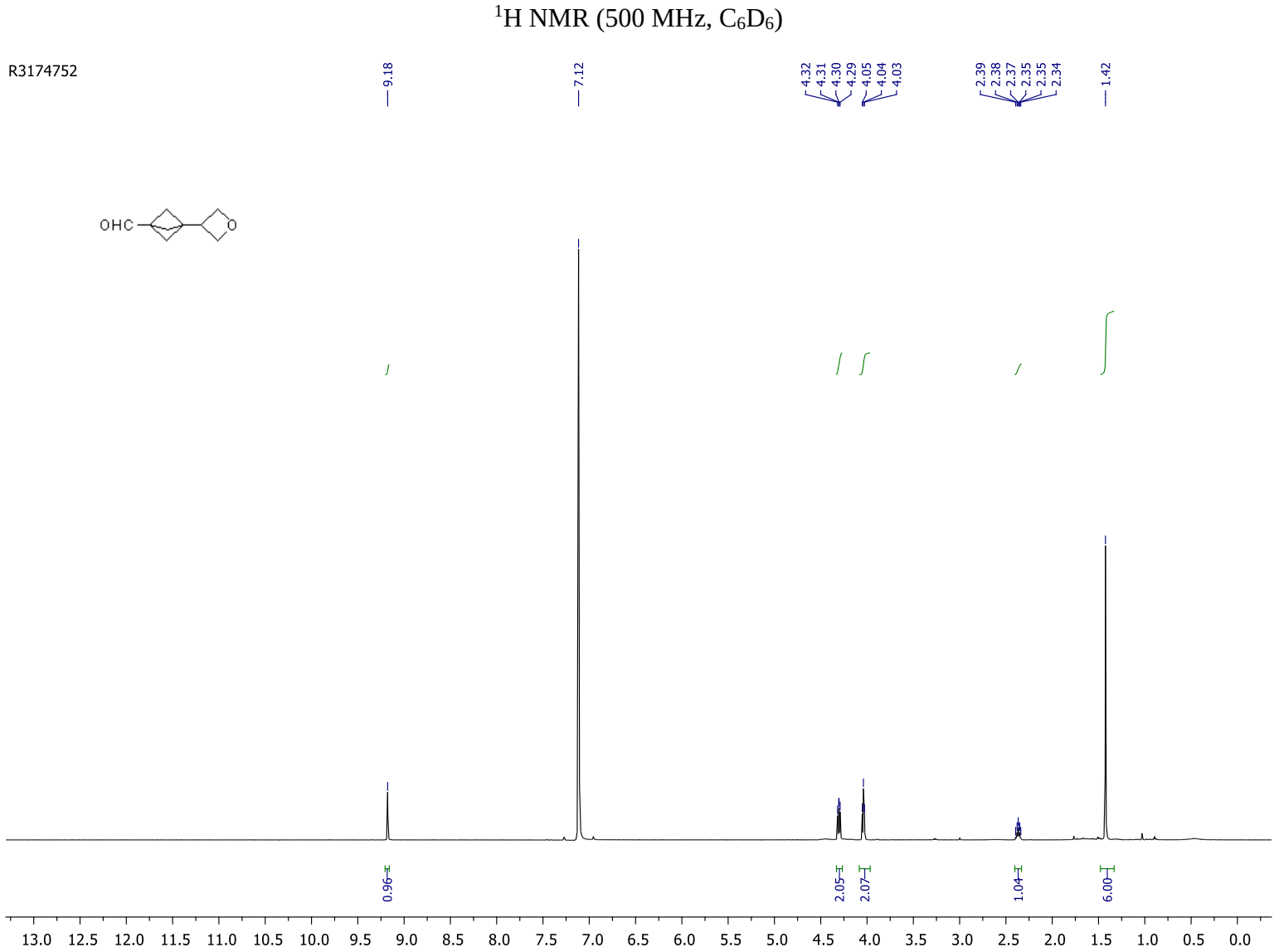
R2869967_C1:

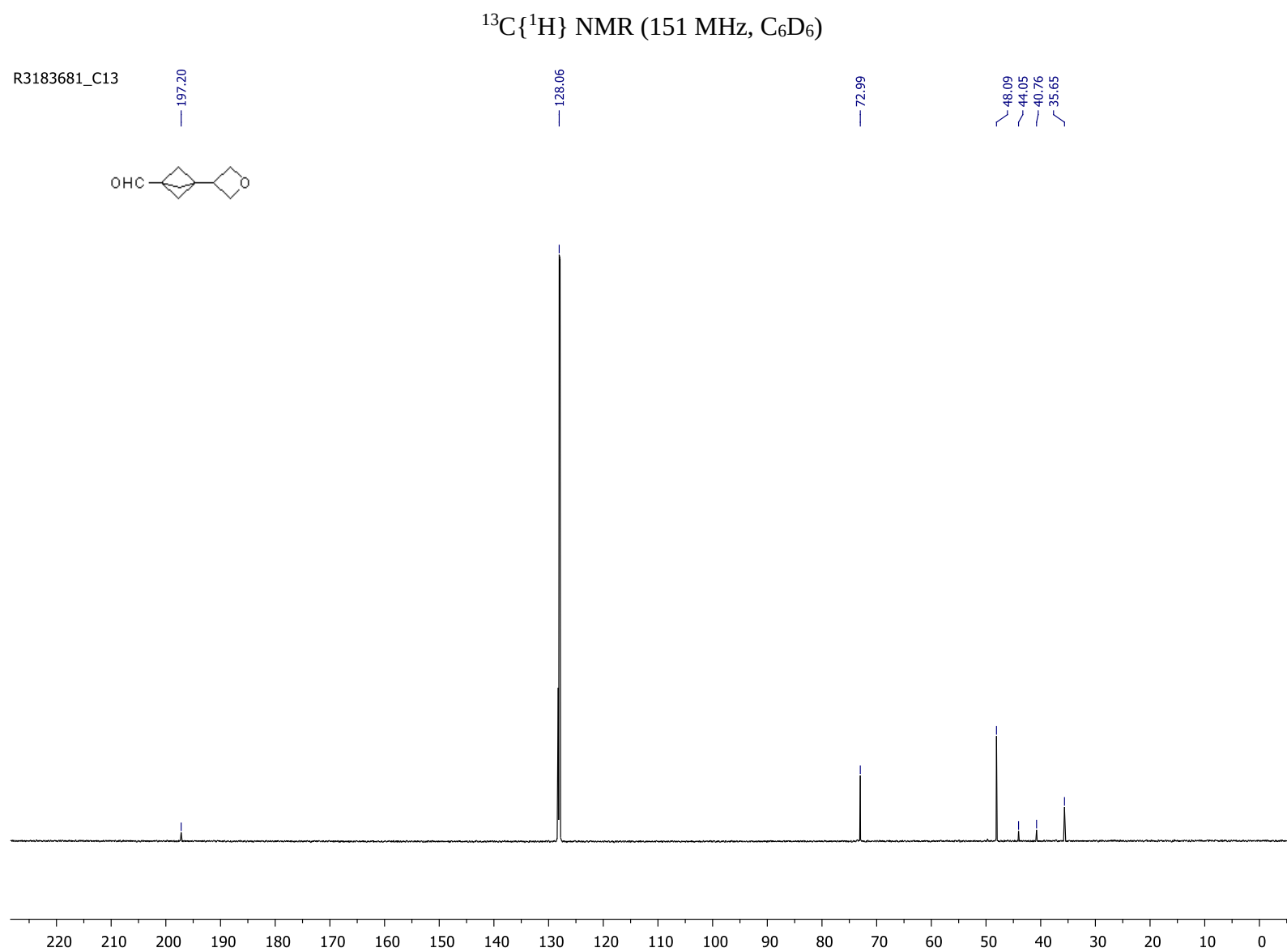


47.63
47.48
47.33
42.67
39.52
34.05
24.83

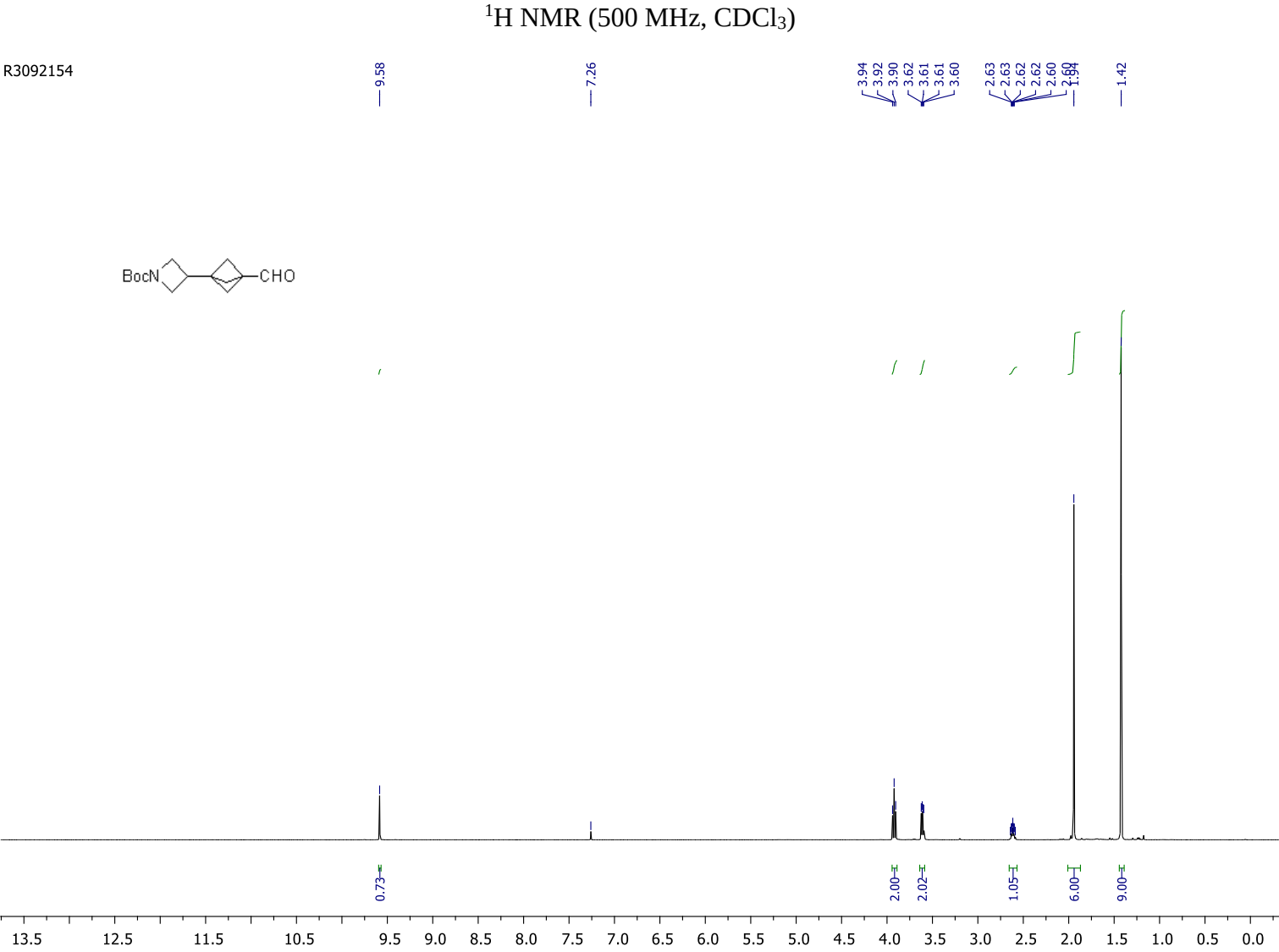


Compound 55i





Compound 60i



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R3092154_C13

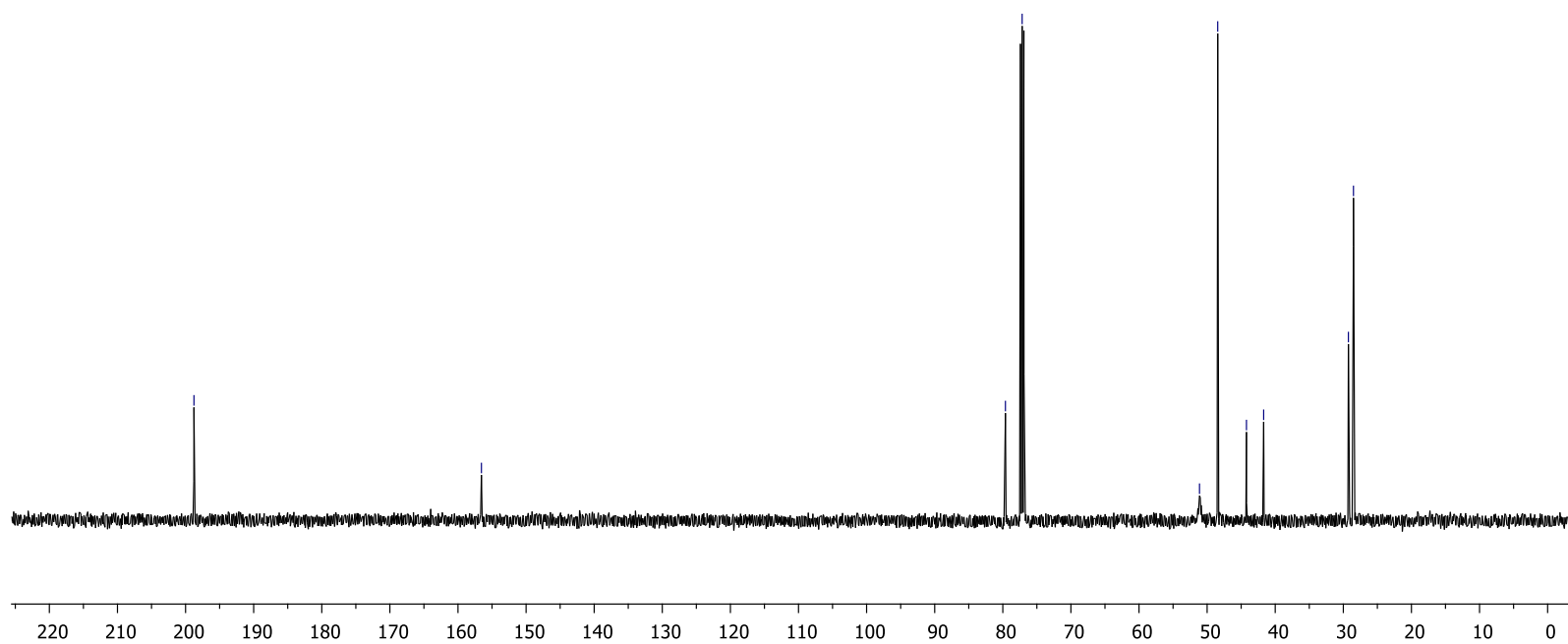
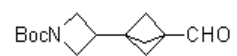
198.77

156.56

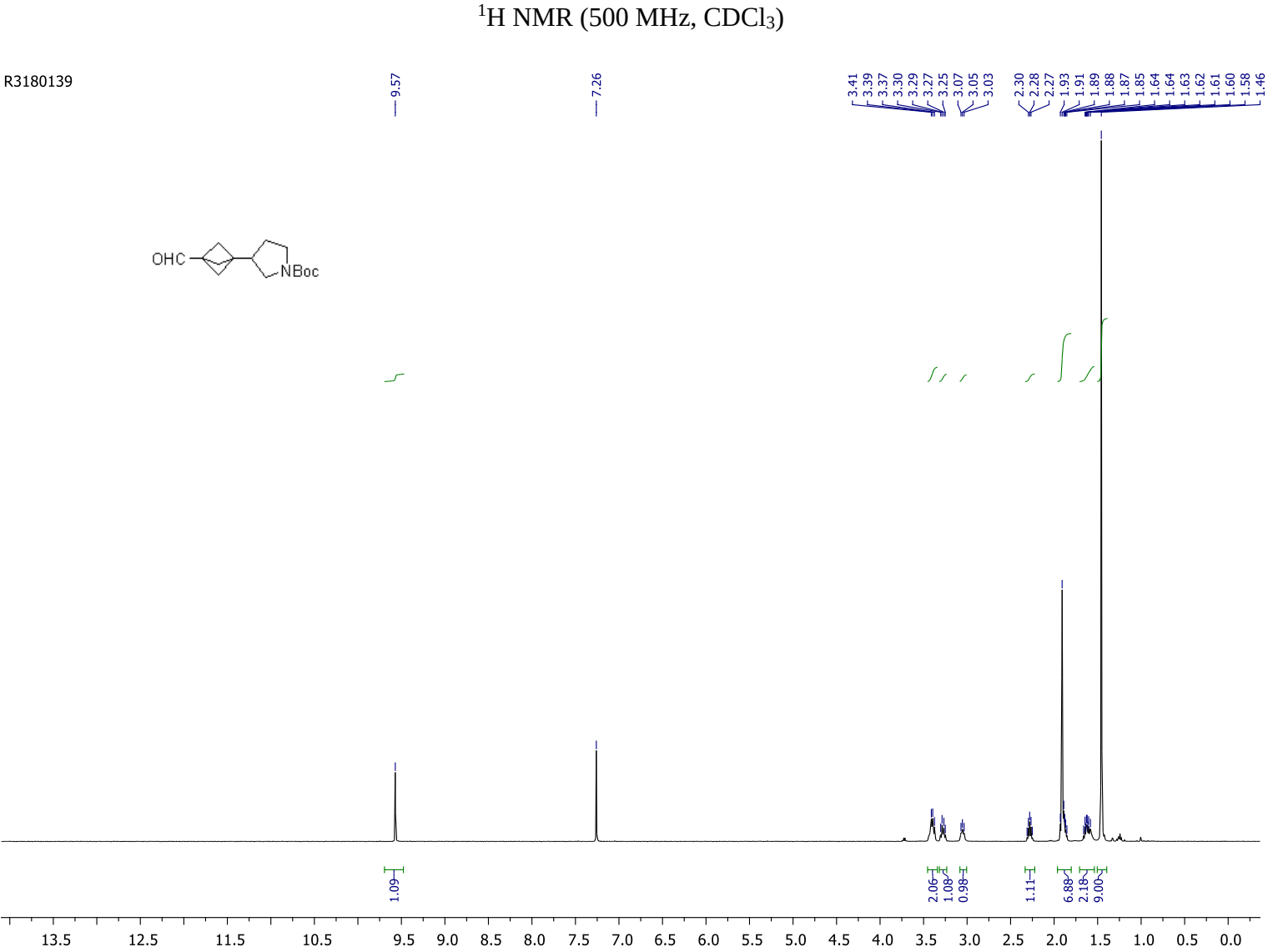
79.62
77.16

51.12
48.44
44.22
41.70

29.25
28.51



Compound 61i



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

R3183610_C13

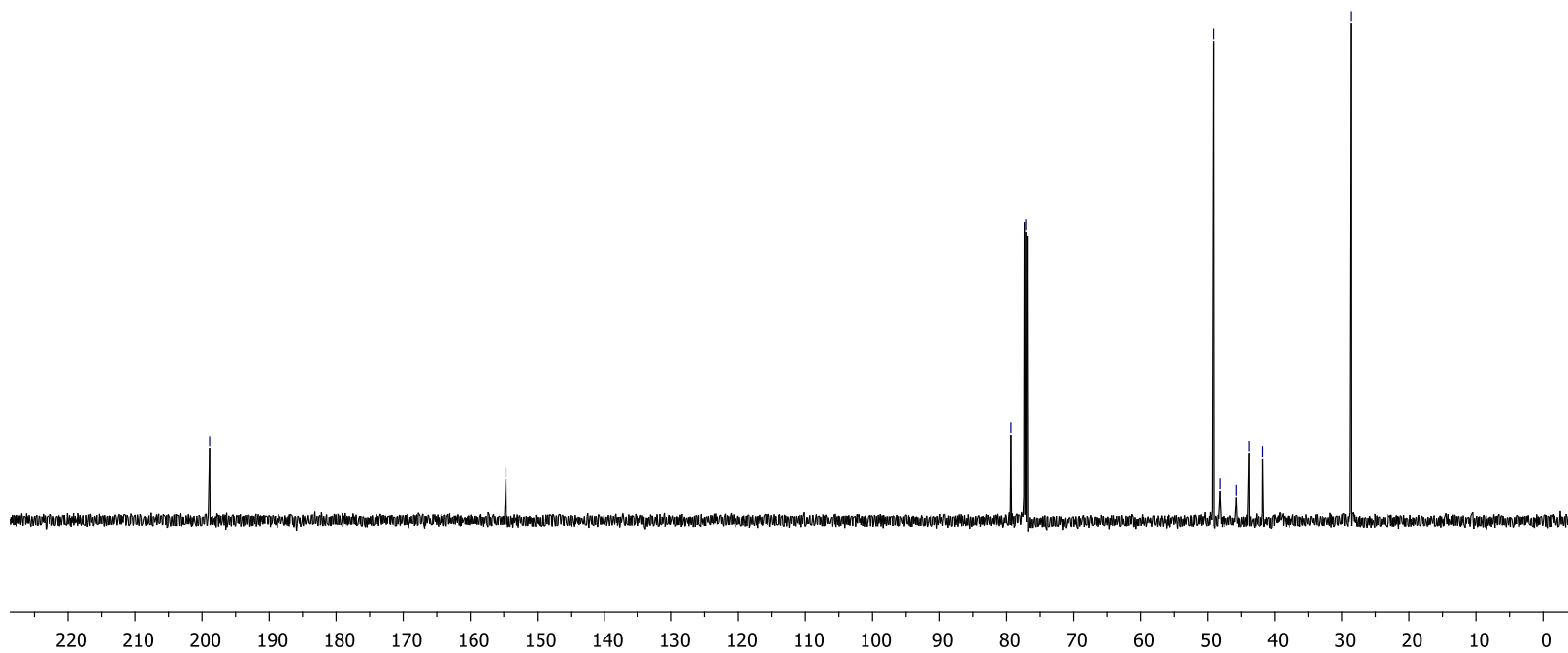
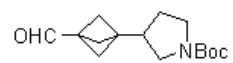
— 198.87

— 154.67

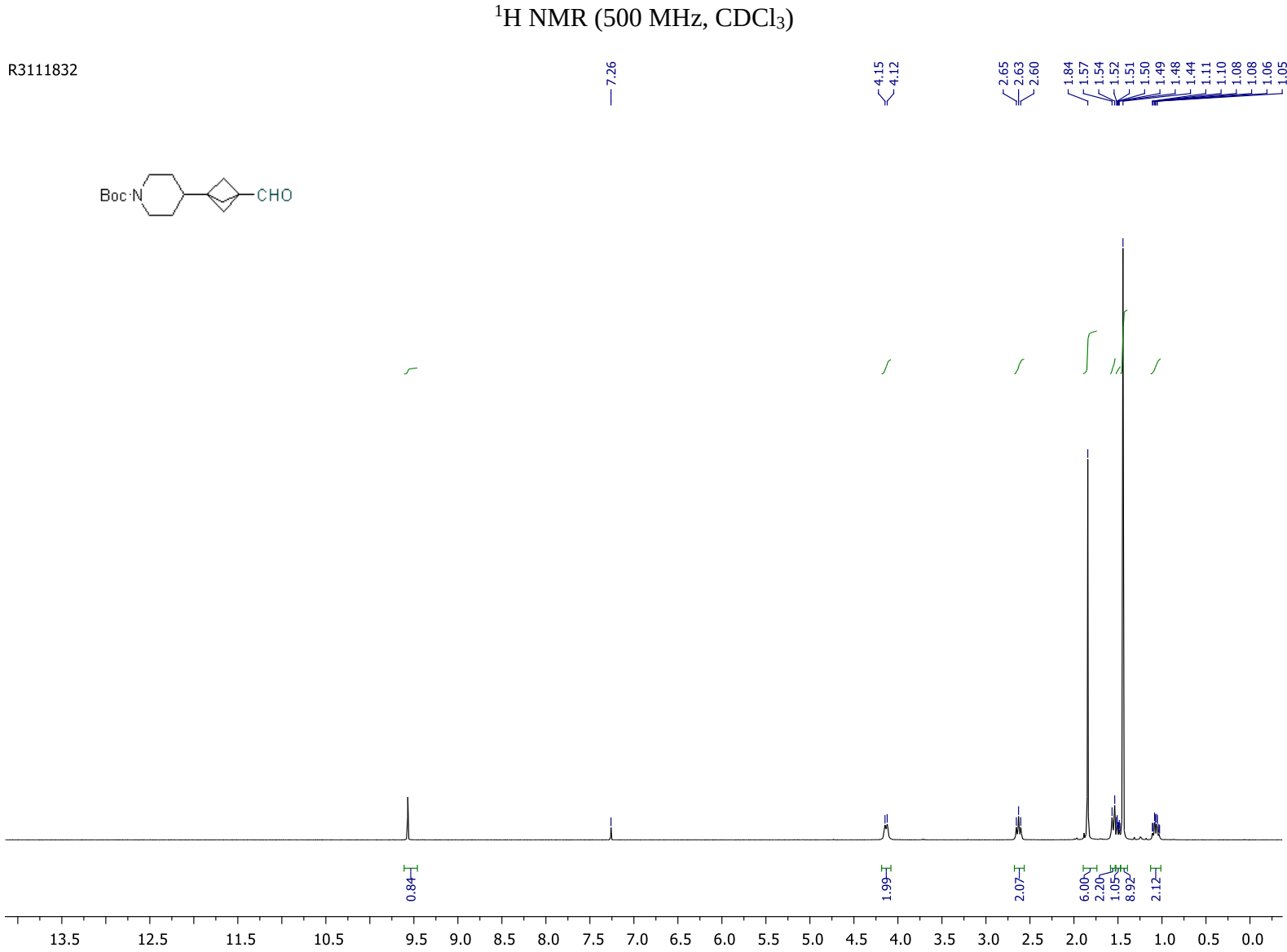
— 79.35
— 77.16

— 49.16
— 48.21
— 45.73
— 43.87
— 41.79

— 28.68

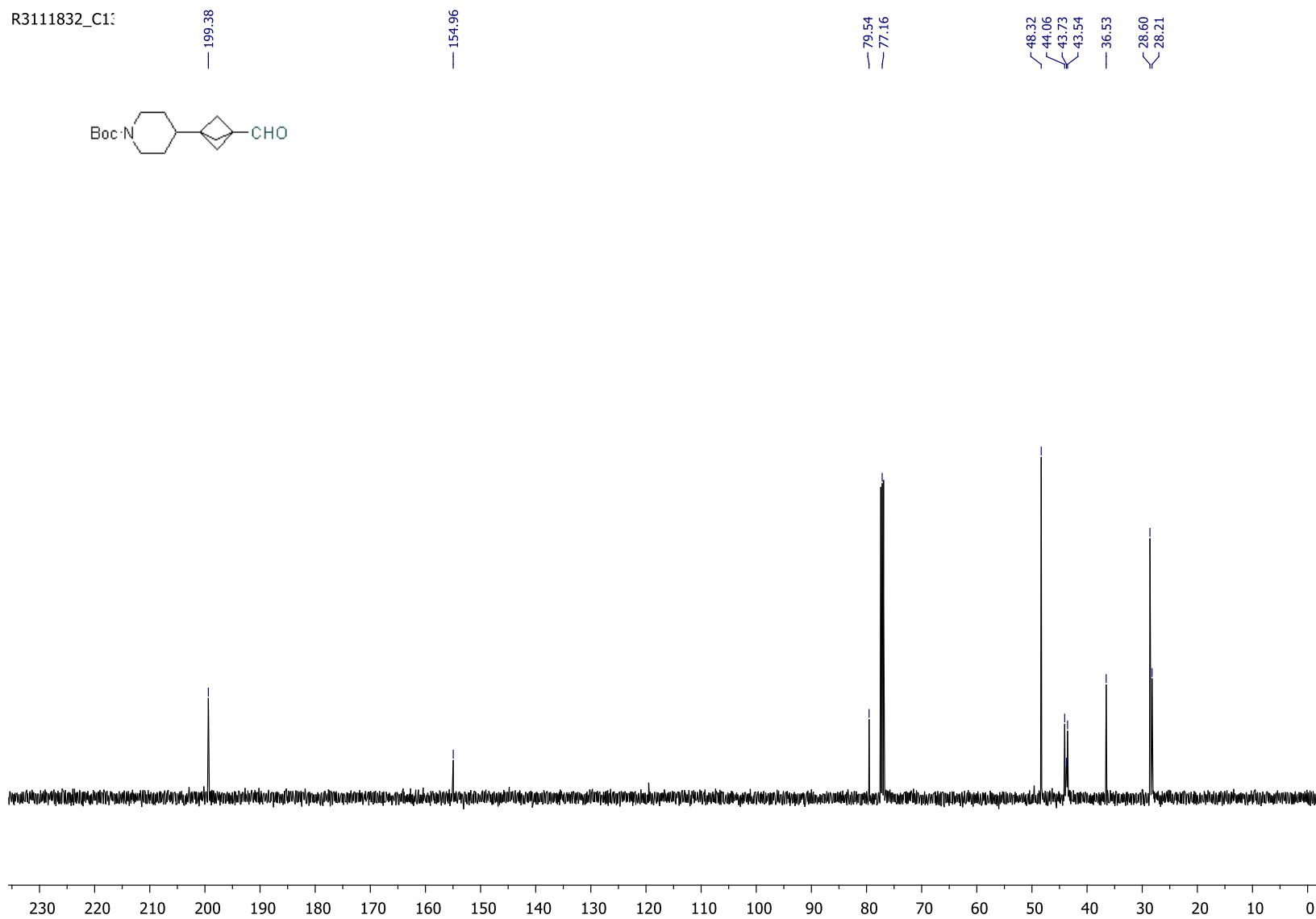
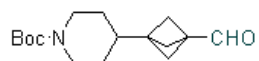


Compound 63i

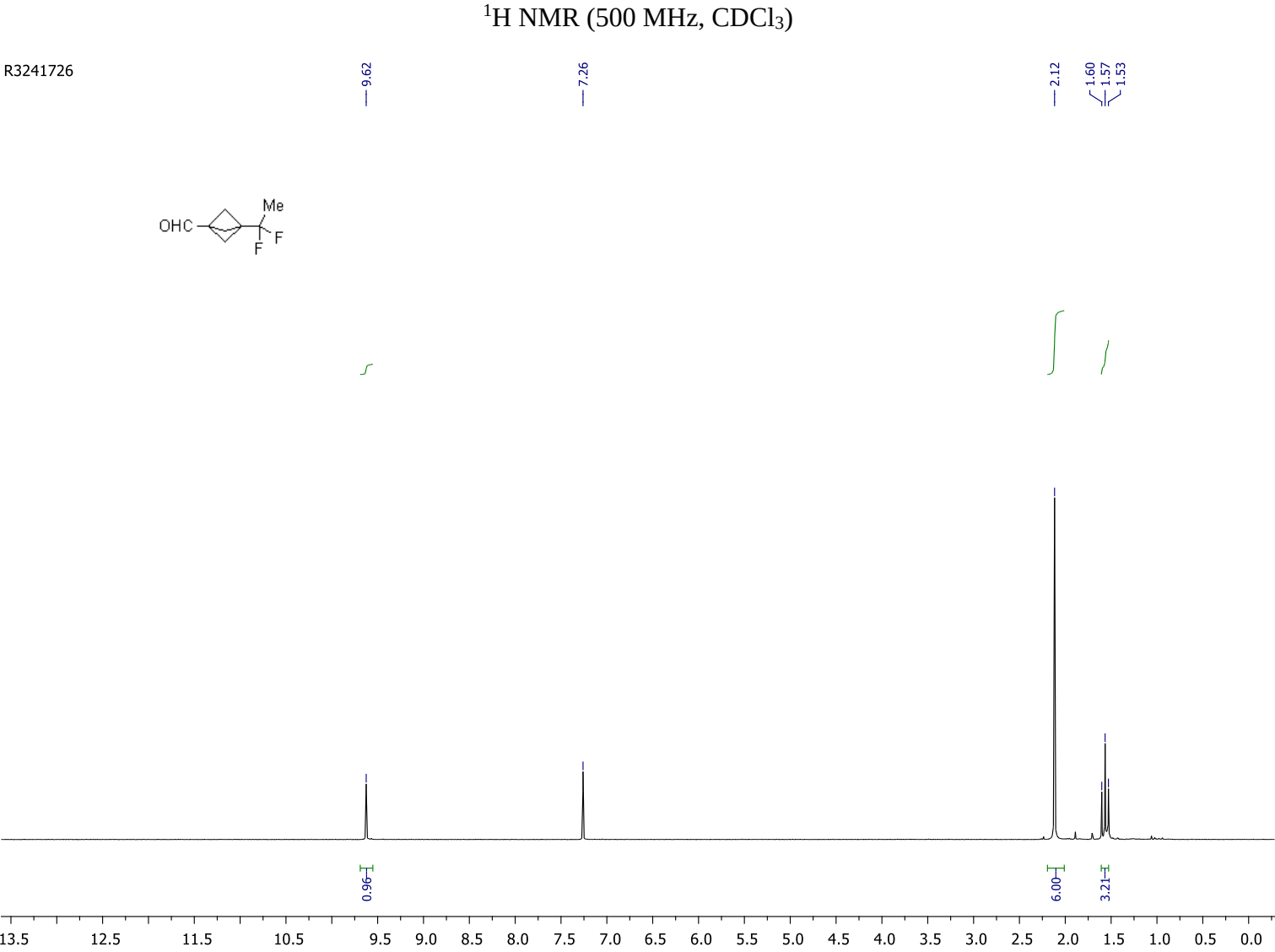


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R3111832_C13

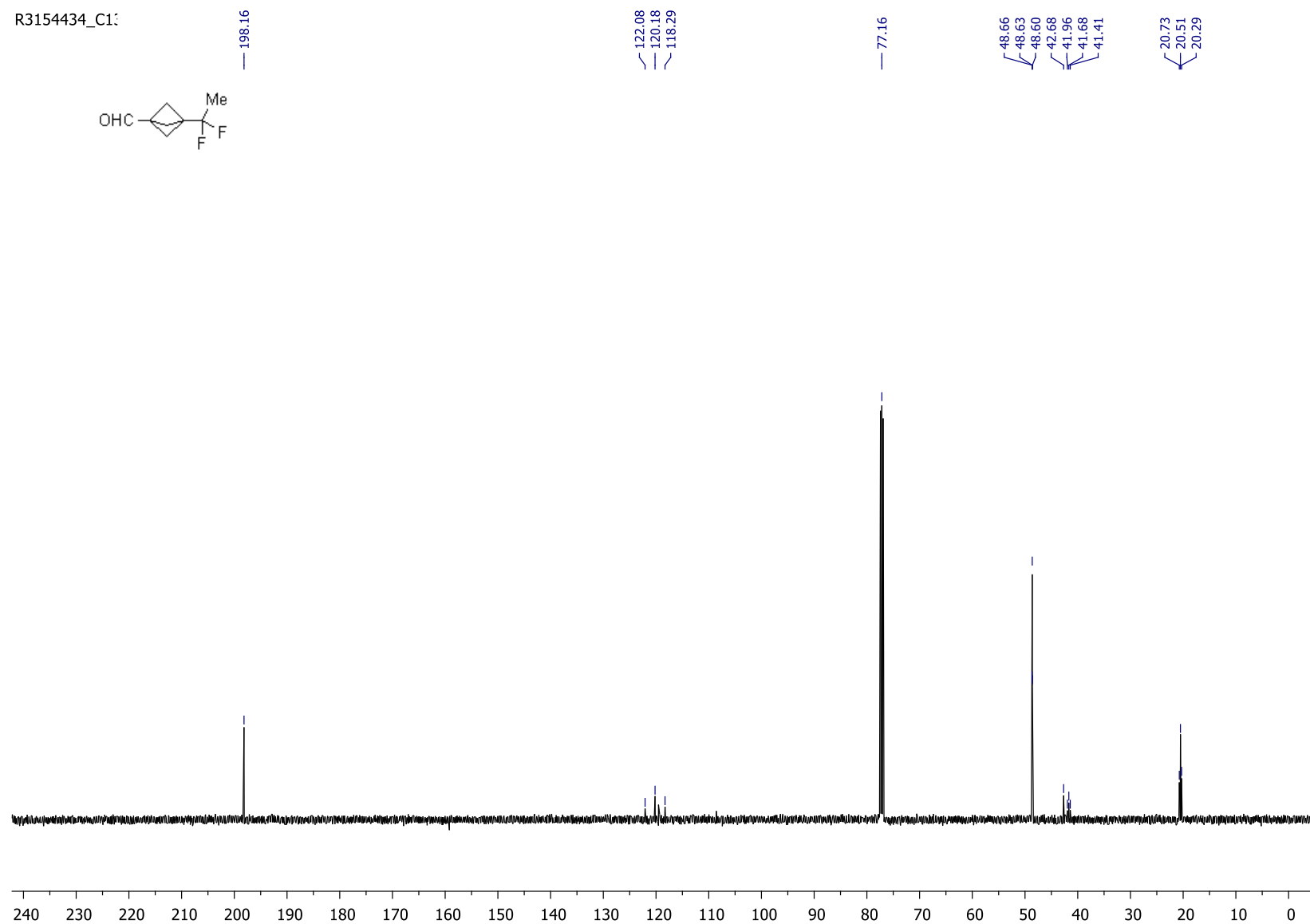
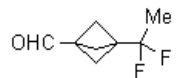


Compound 68i



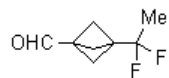
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R3154434_C1:

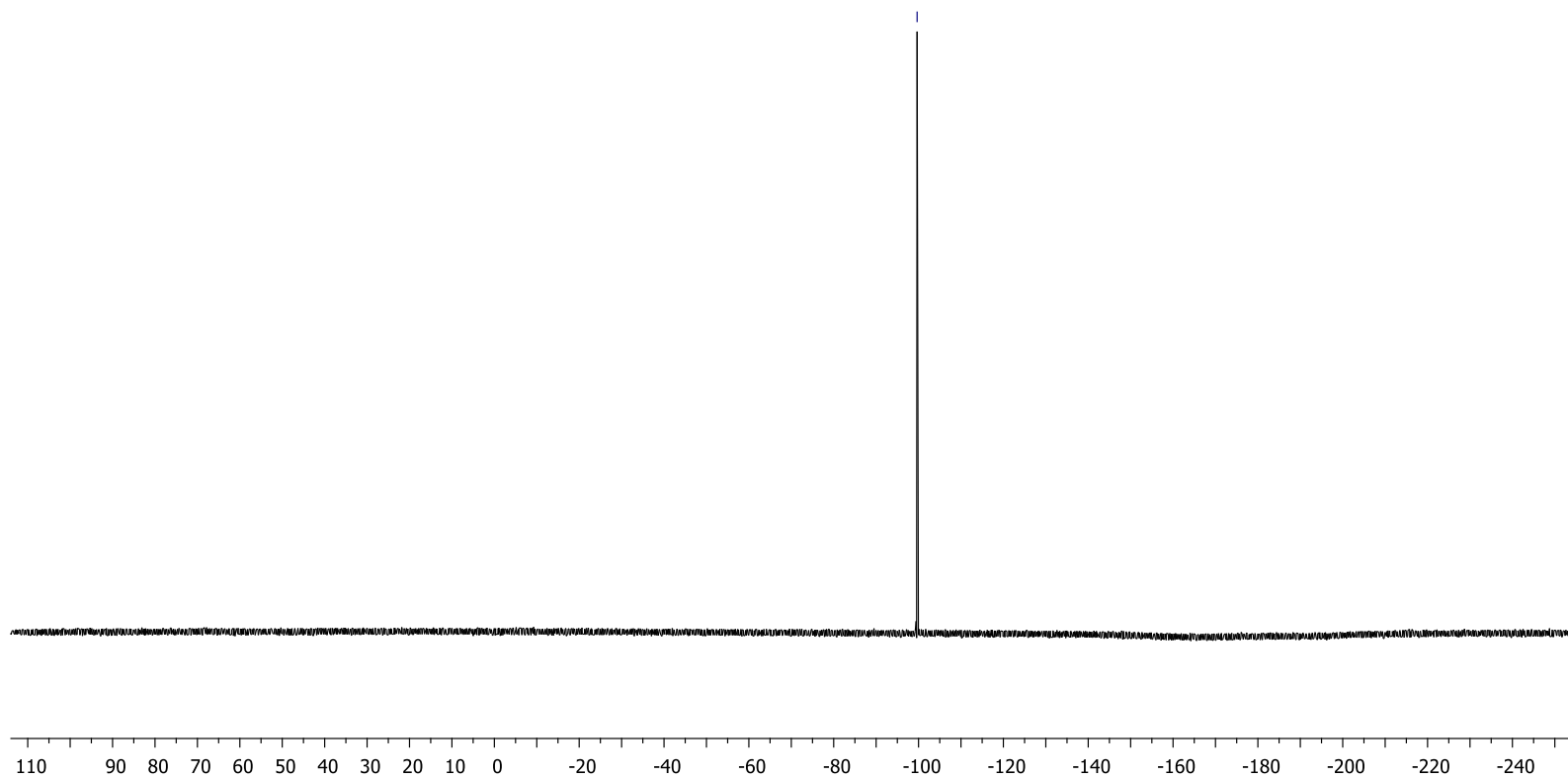


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R3241726_F19{H}



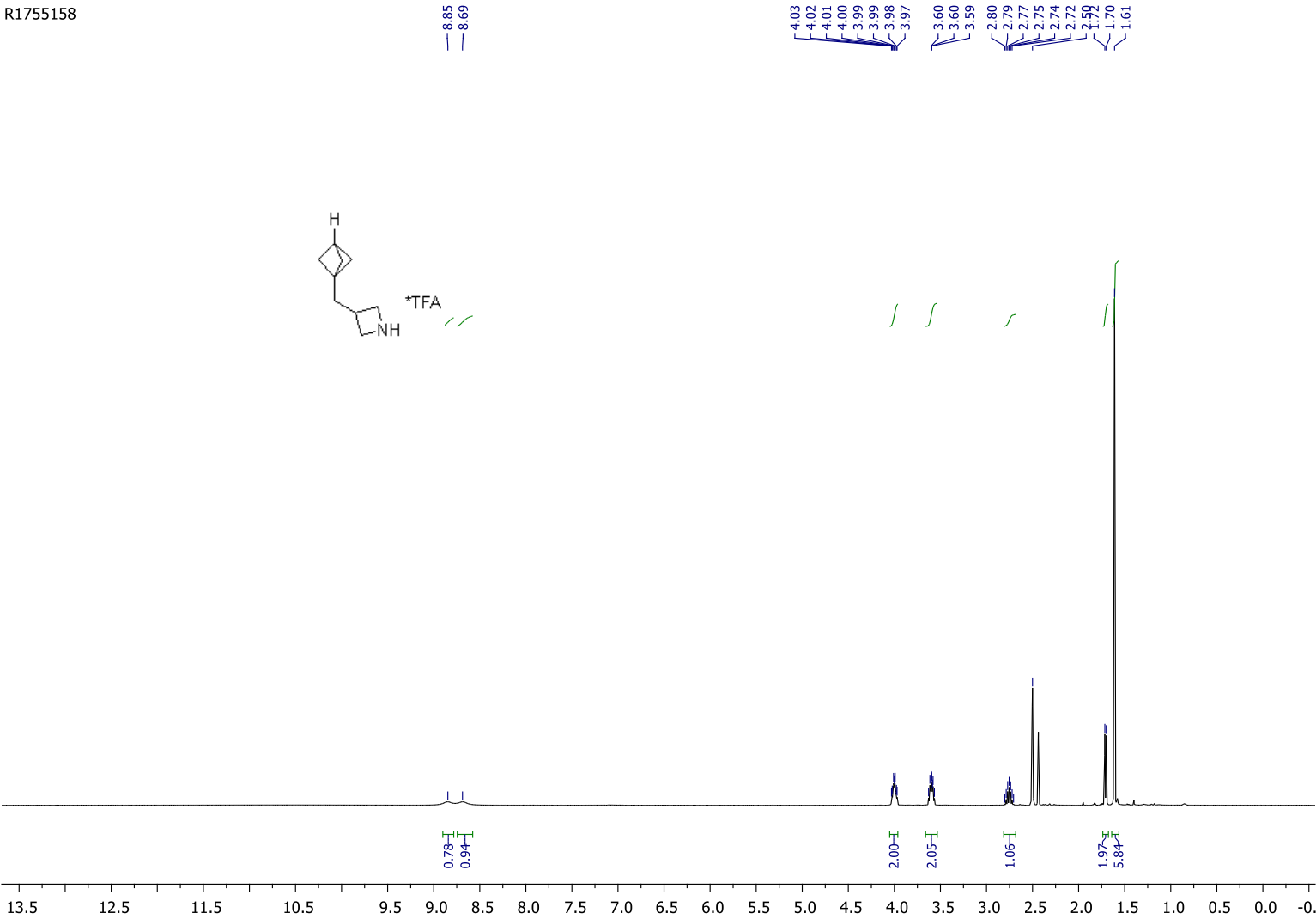
— -99.67



Compound 14j

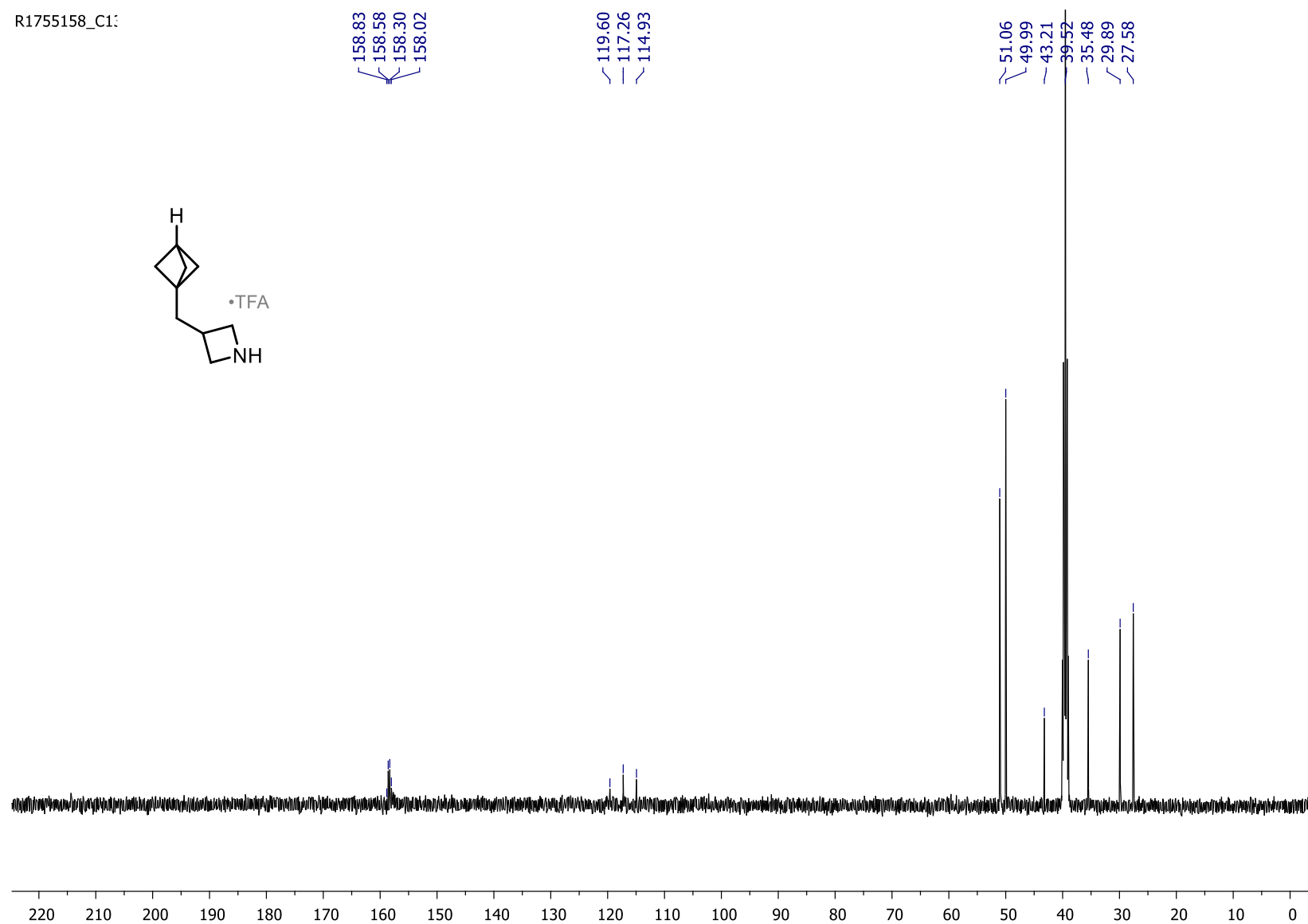
¹H NMR (500 MHz, DMSO-d₆)

R1755158



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

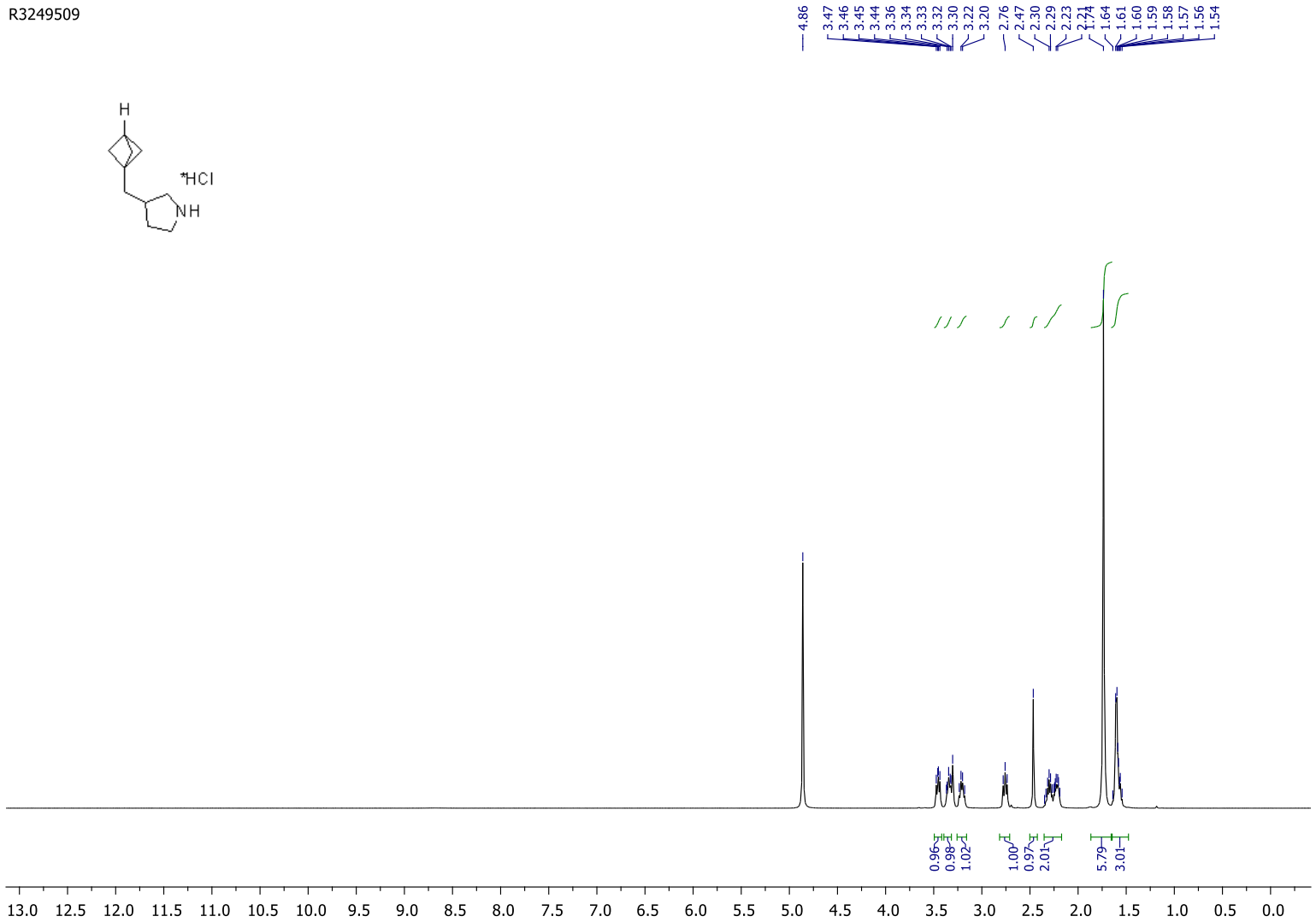
R1755158_C1:



Compound 15j

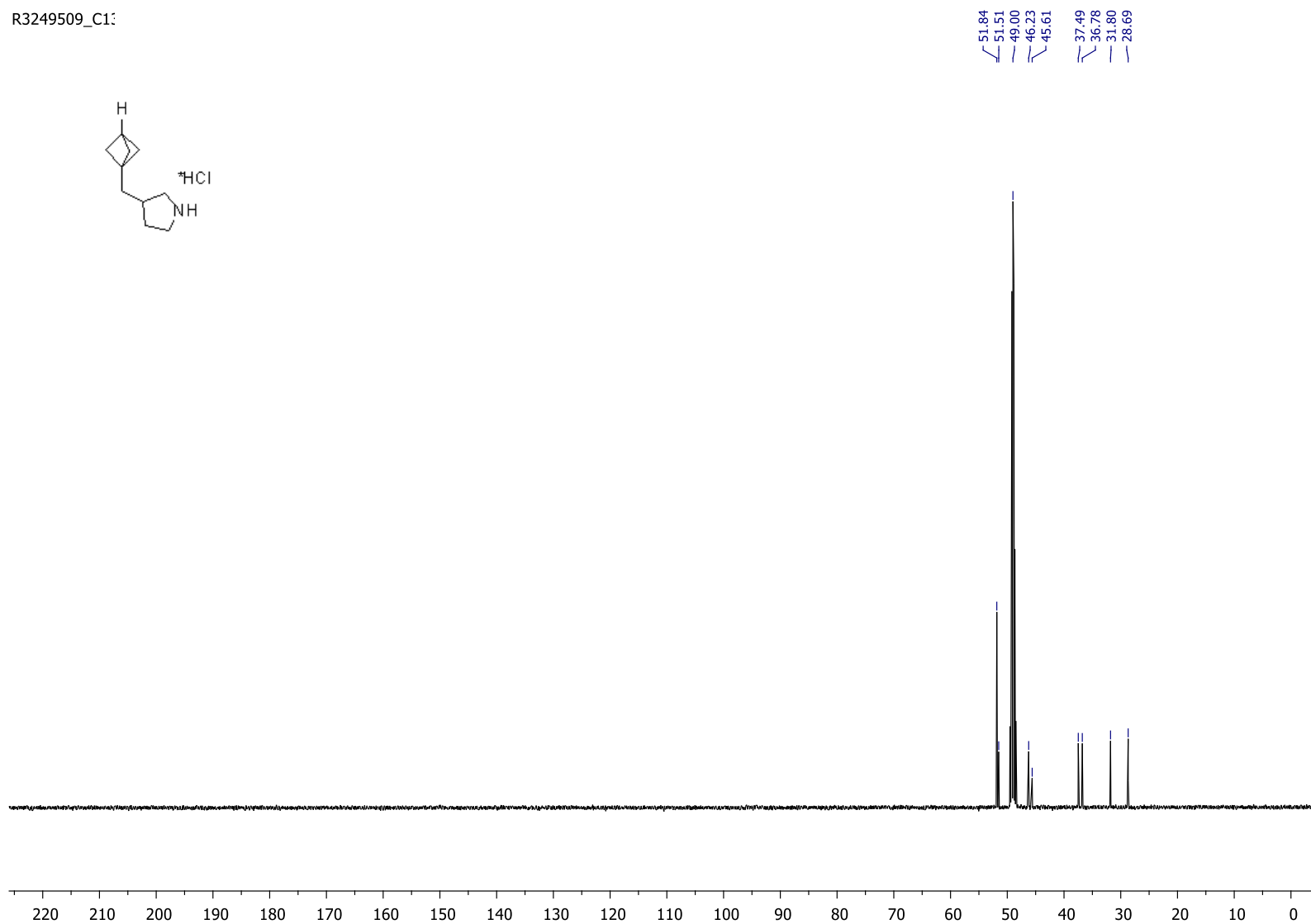
¹H NMR (500 MHz, CD₃OD)

R3249509



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CD_3OD)

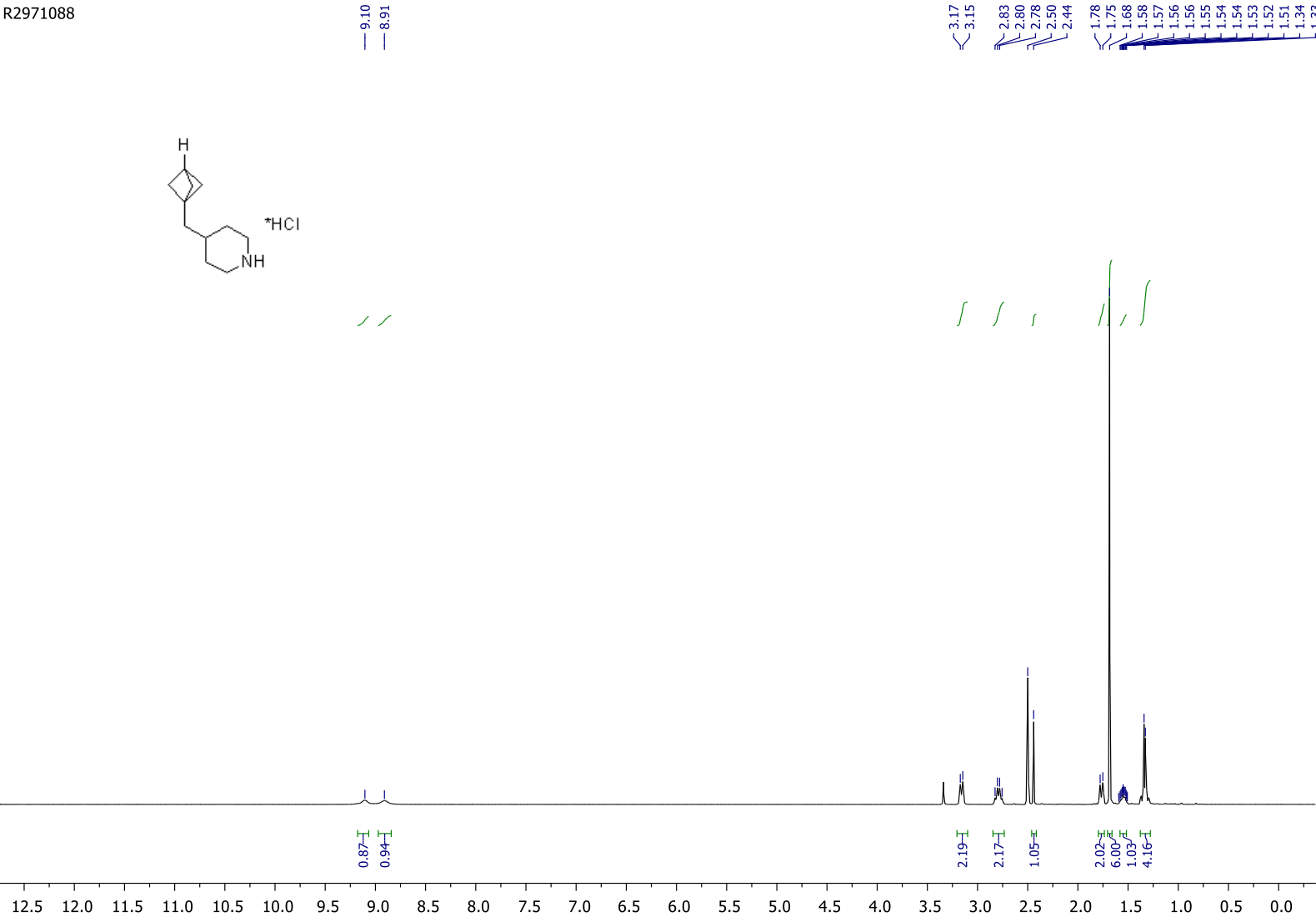
R3249509_C13



Compound 16j

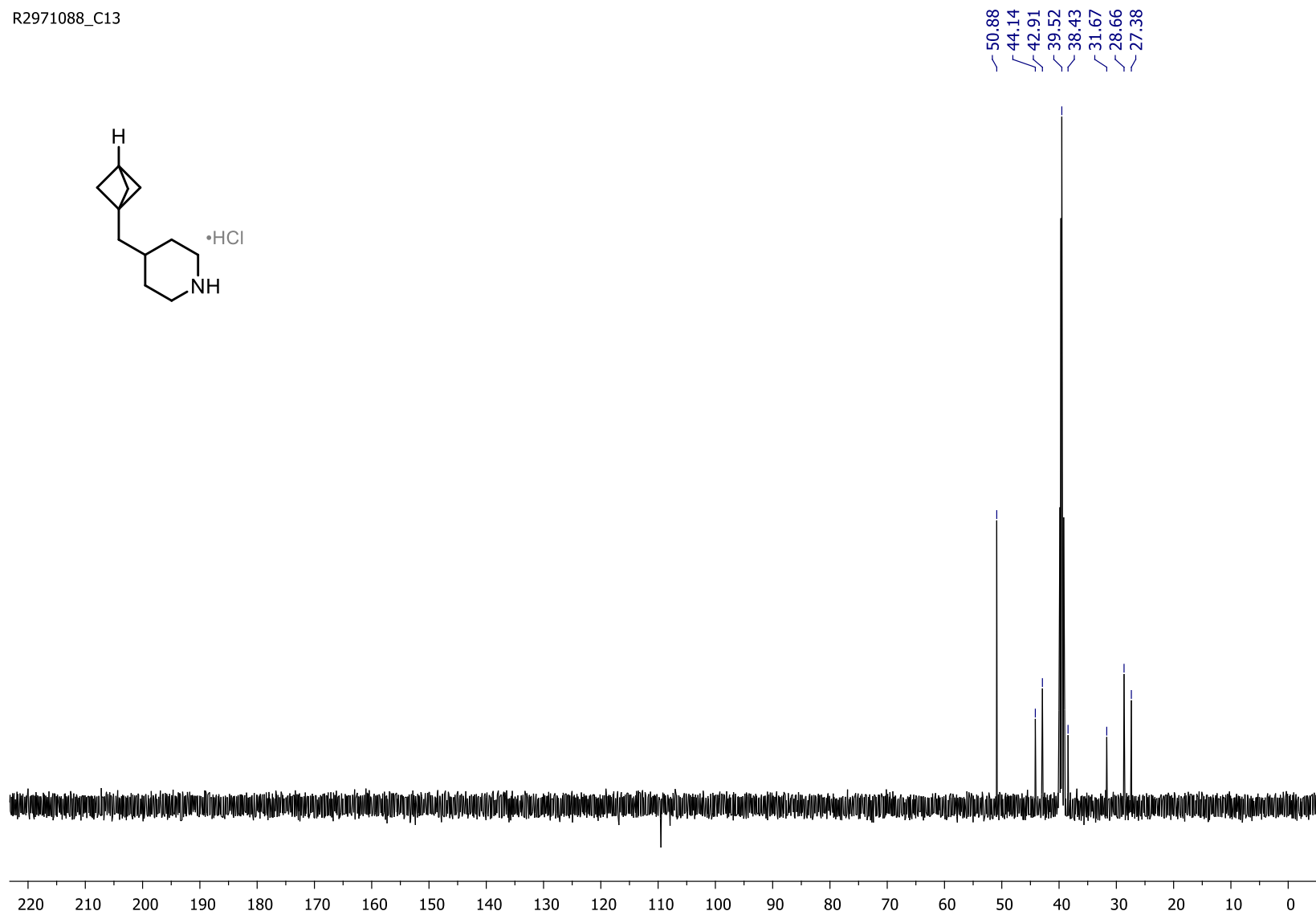
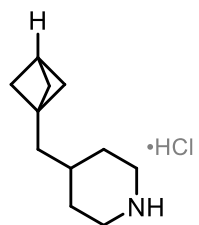
¹H NMR (500 MHz, DMSO-d₆)

R2971088



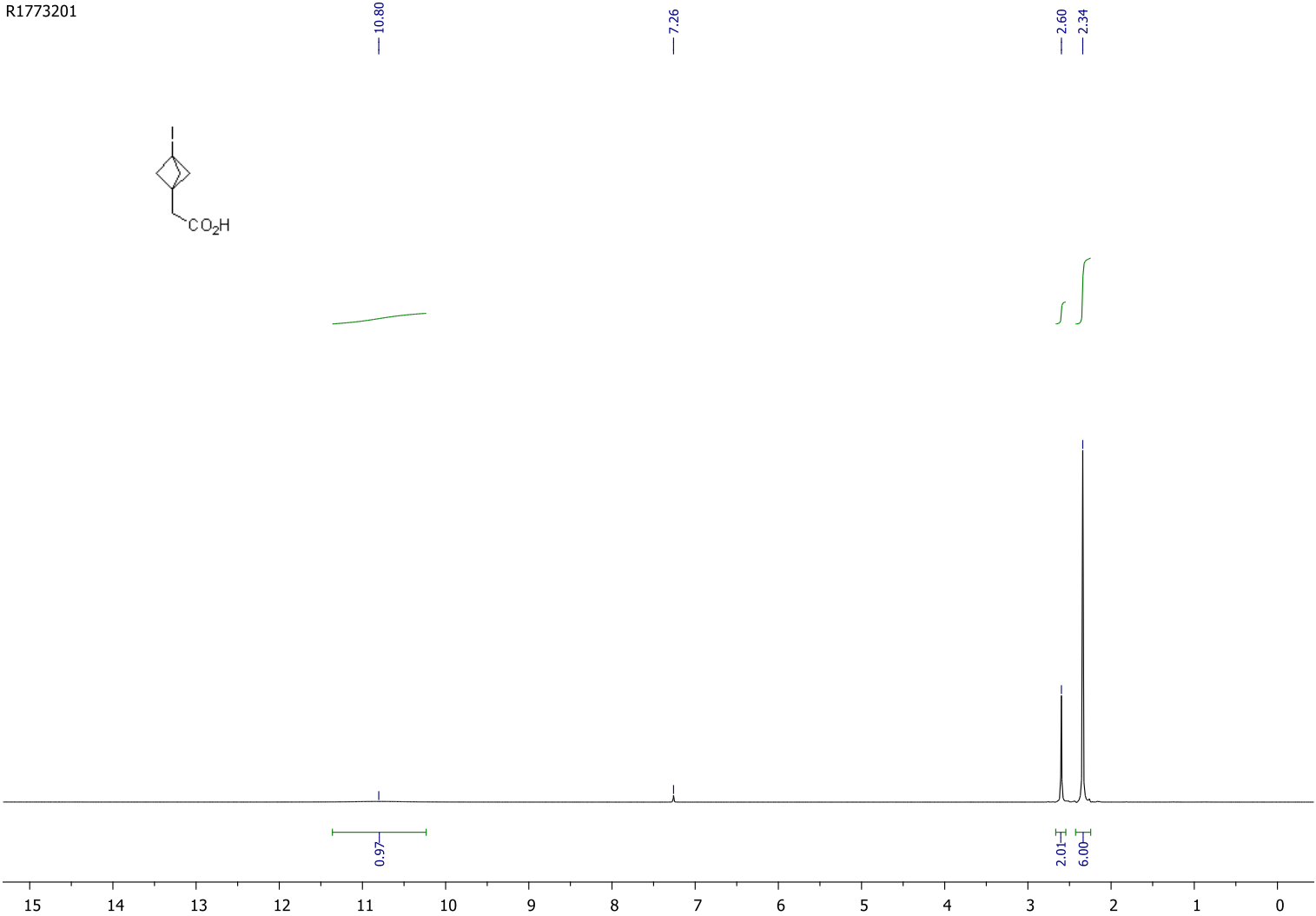
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

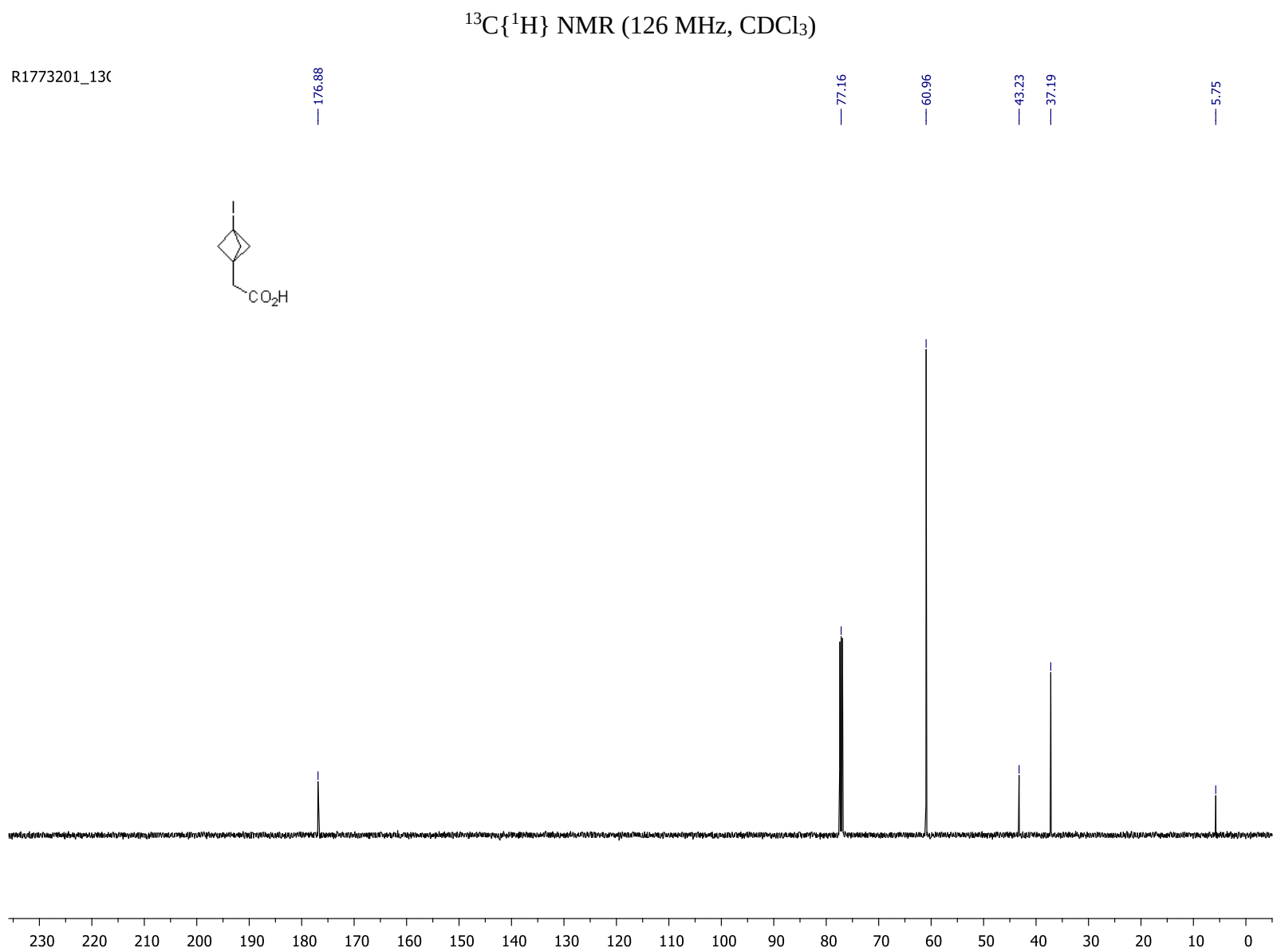
R2971088_C13



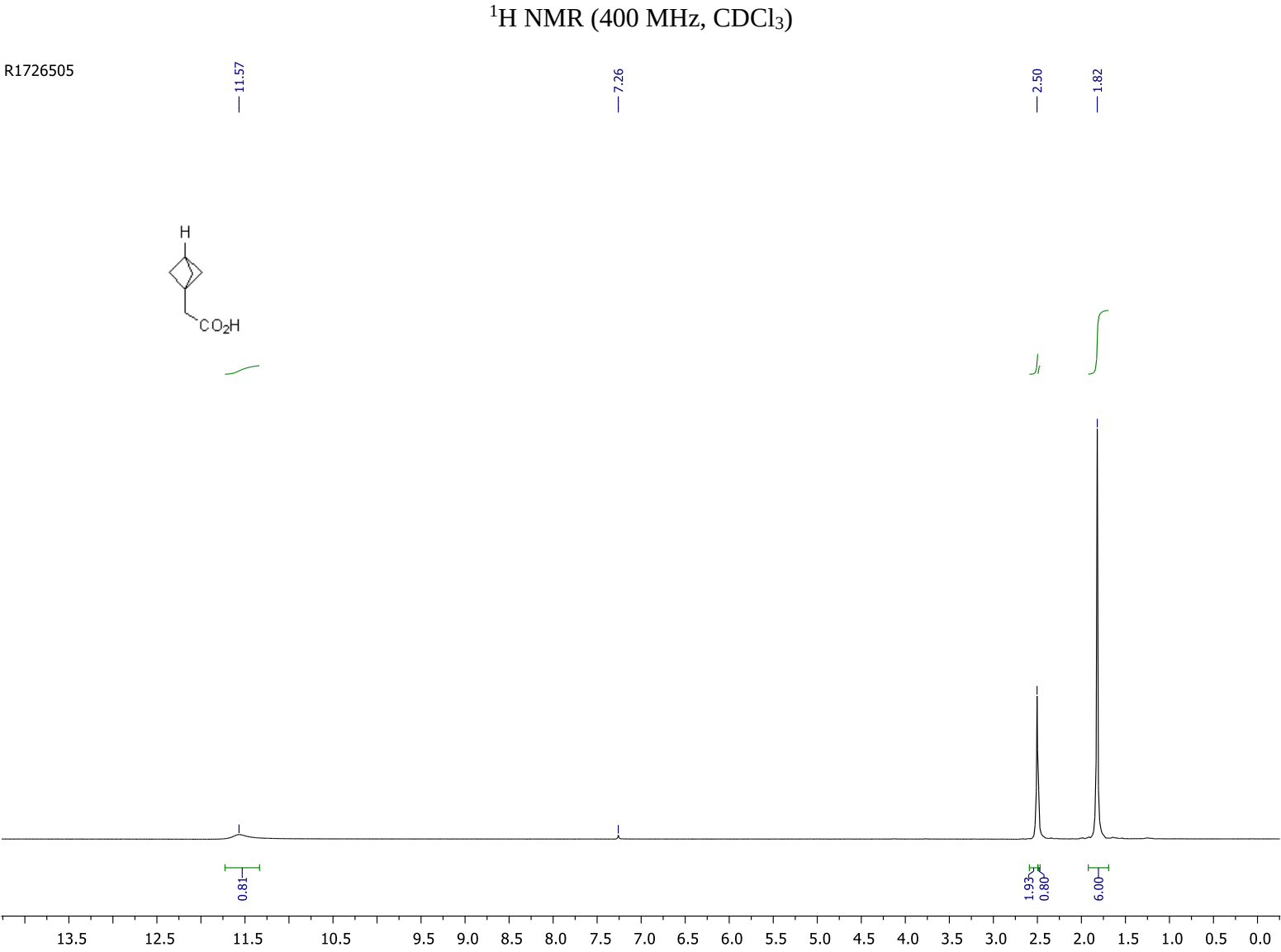
2-(3-Iodobicyclo[1.1.1]pentan-1-yl)acetic acid

¹H NMR (400 MHz, CDCl₃)



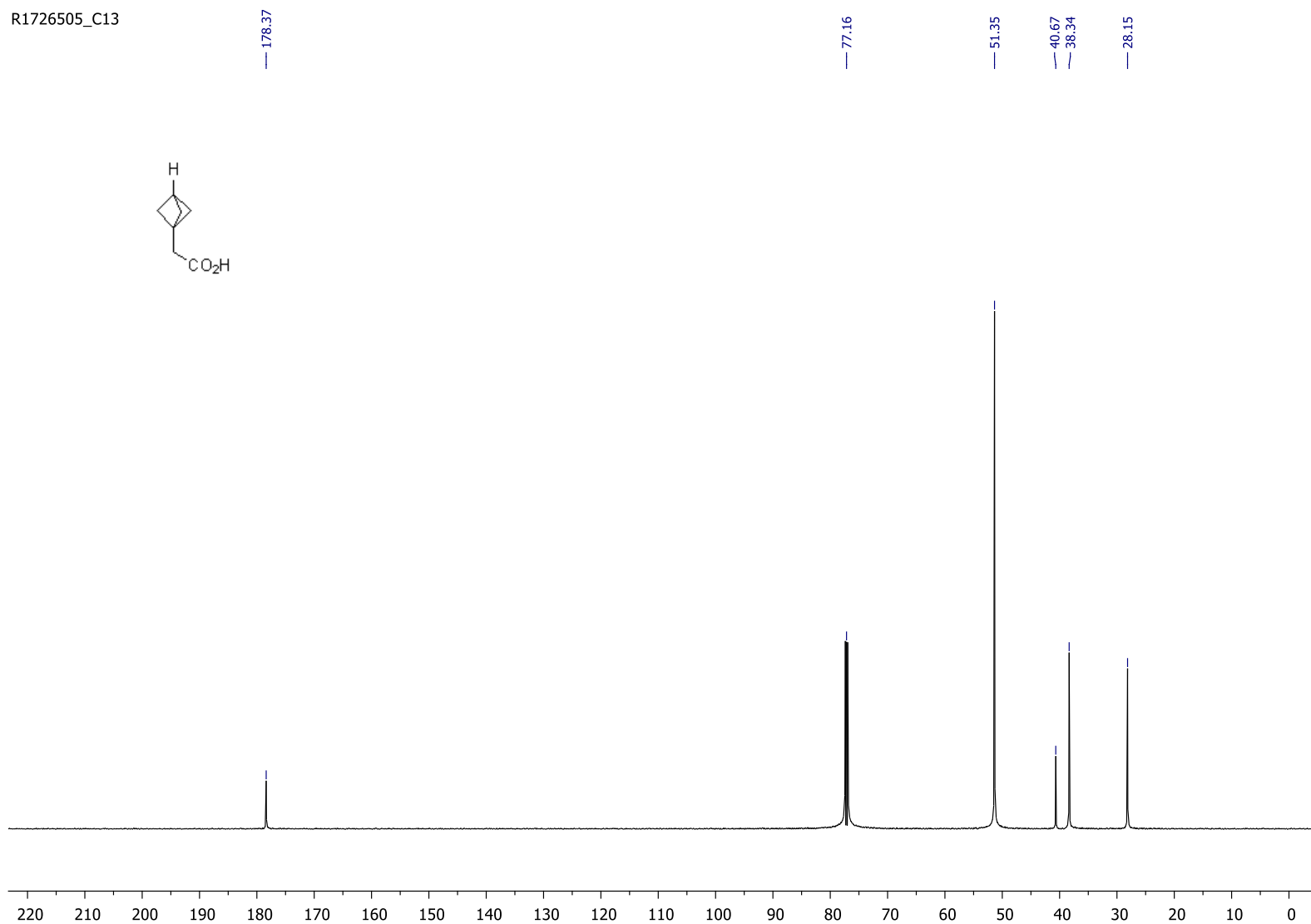


Compound 31j



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

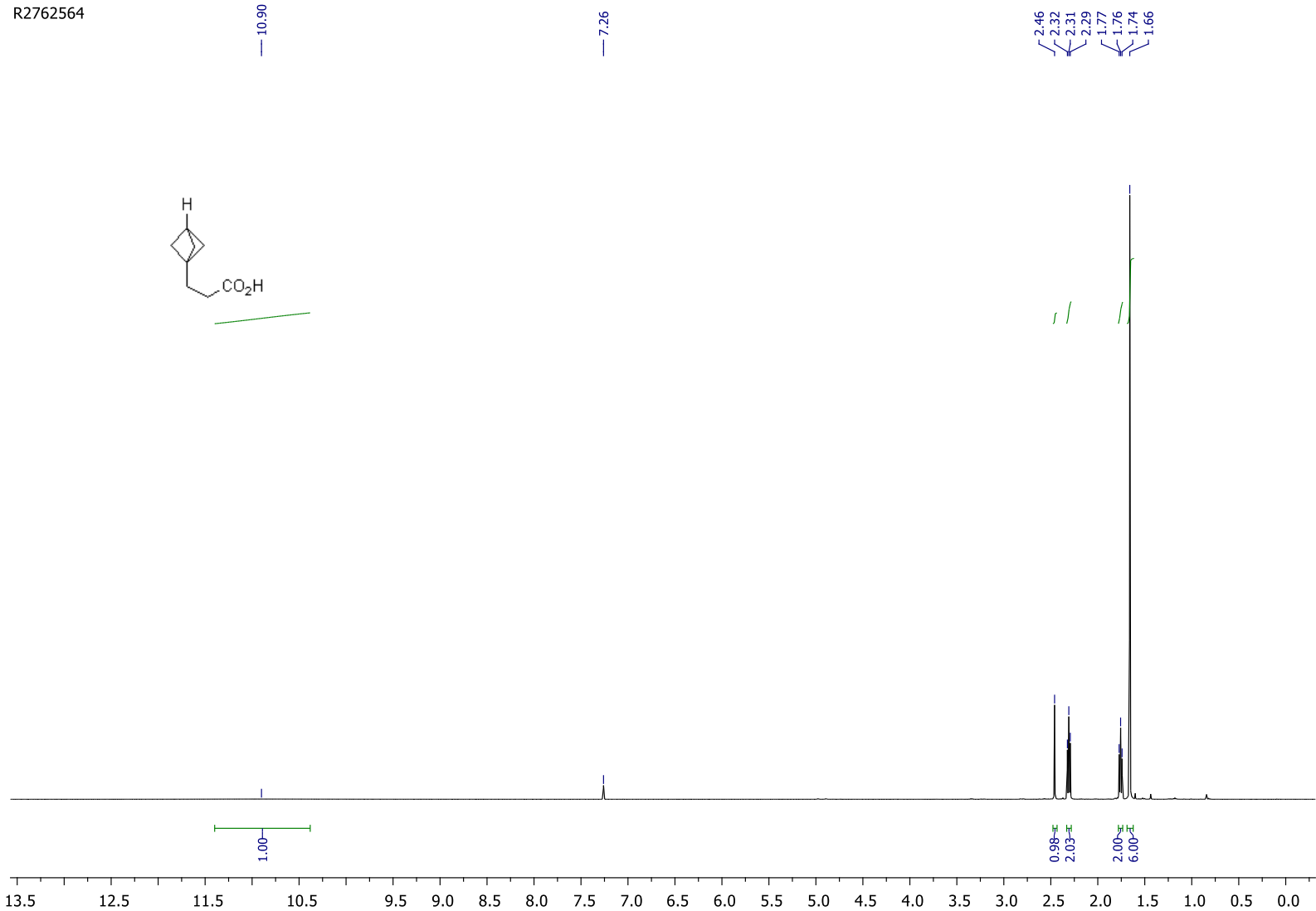
R1726505_C13



Compound 32j

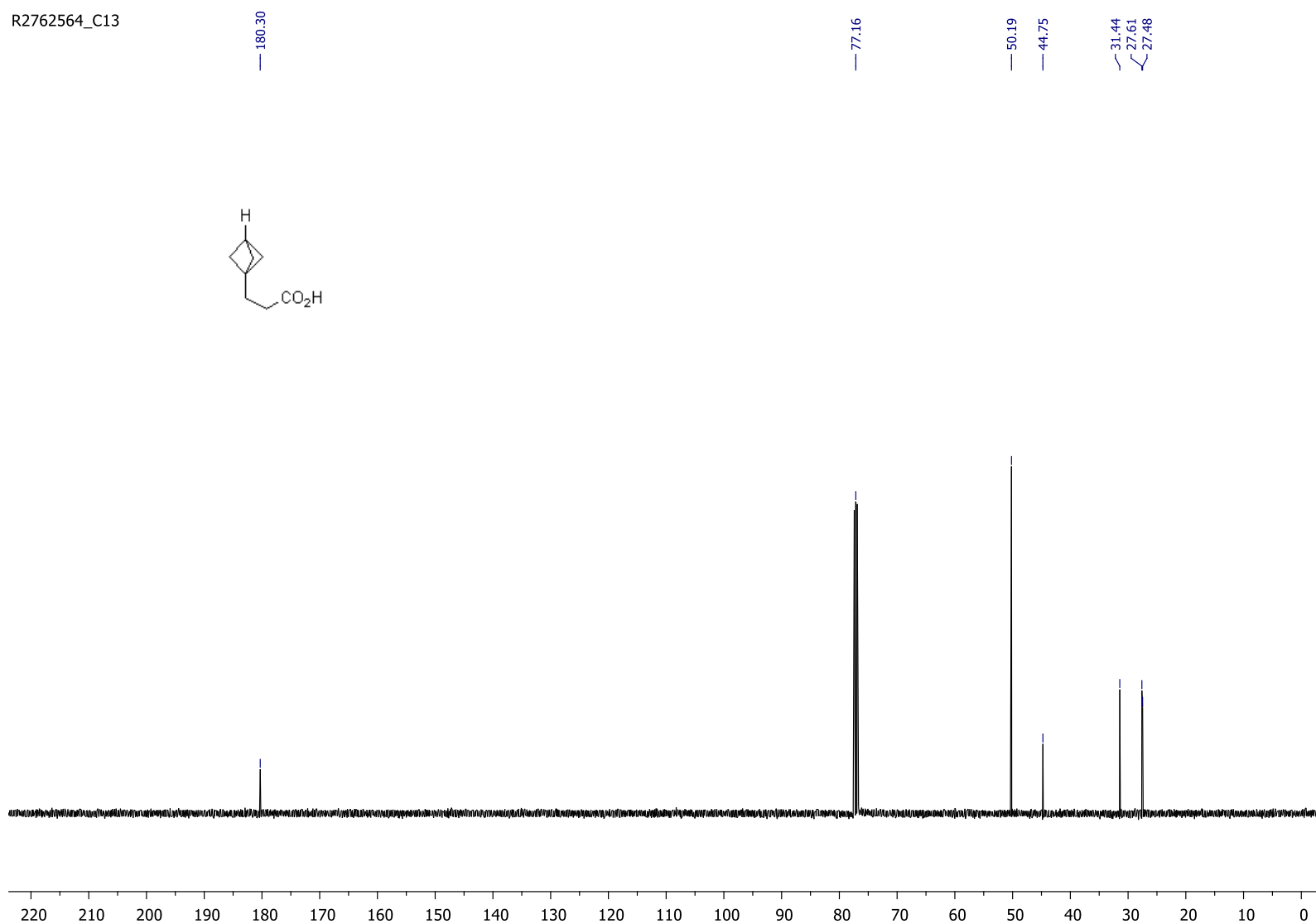
R2762564

¹H NMR (500 MHz, CDCl₃)

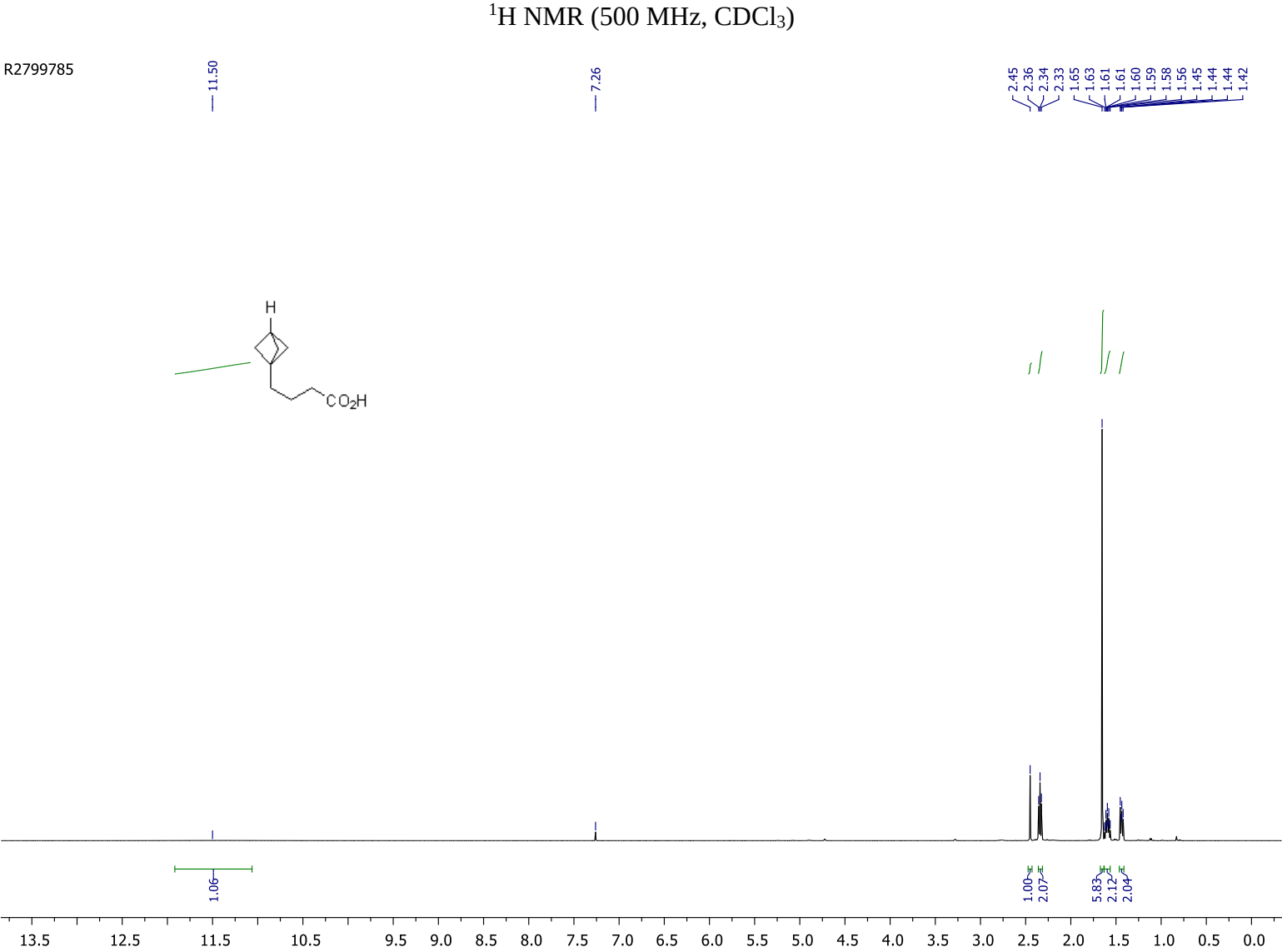


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2762564_C13

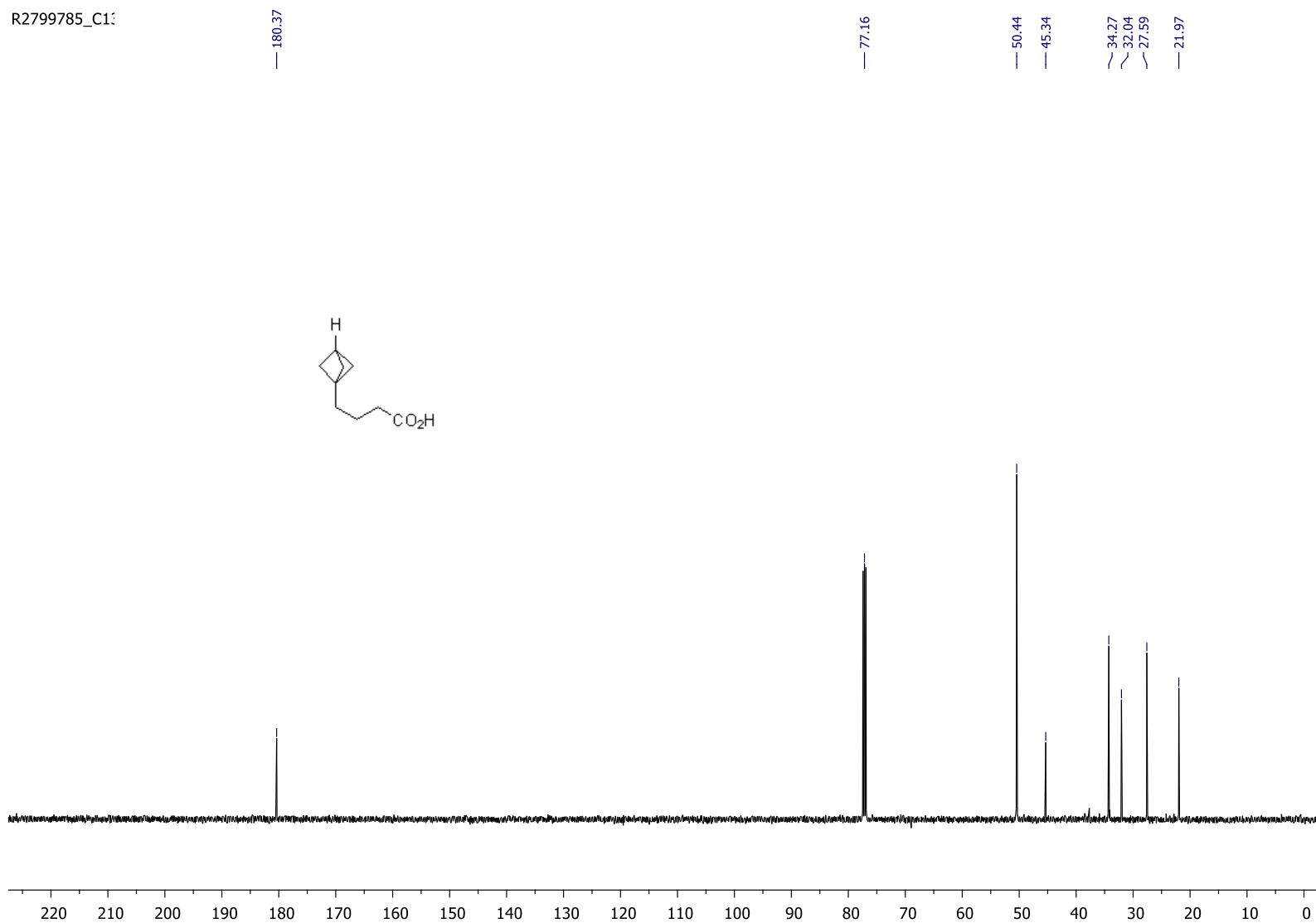


Compound 33j



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

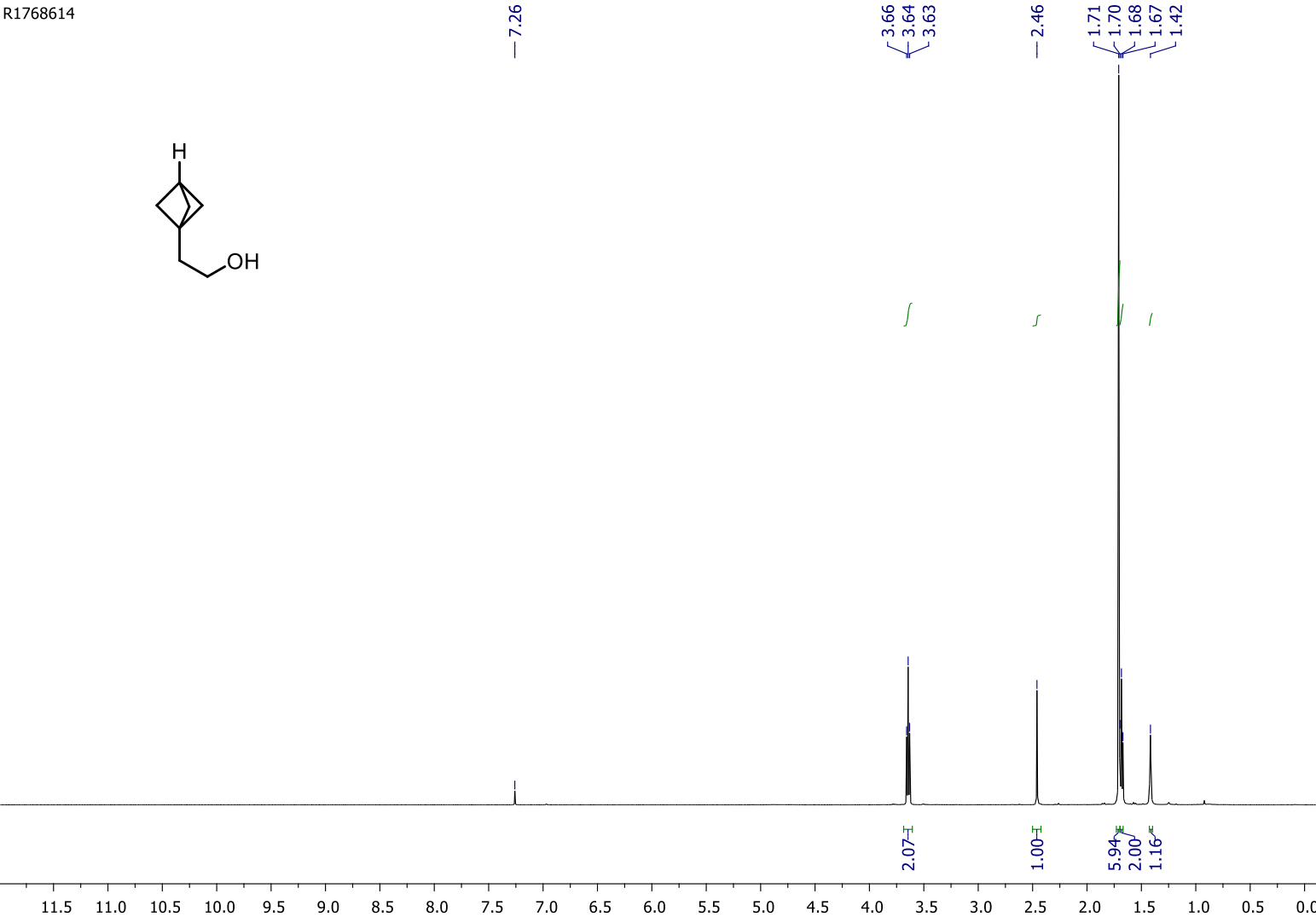
R2799785_C1:



Compound 36j

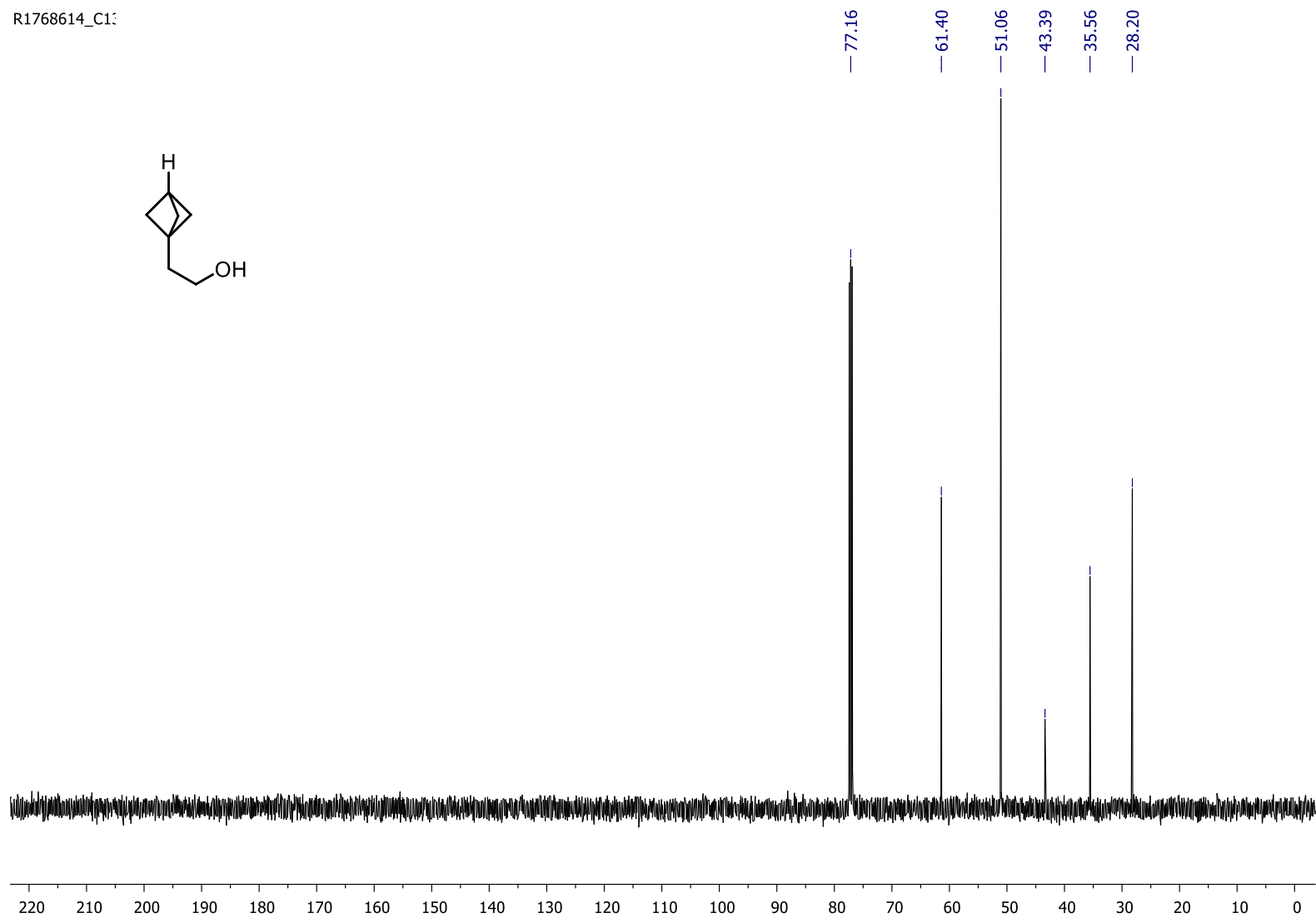
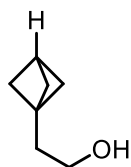
R1768614

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

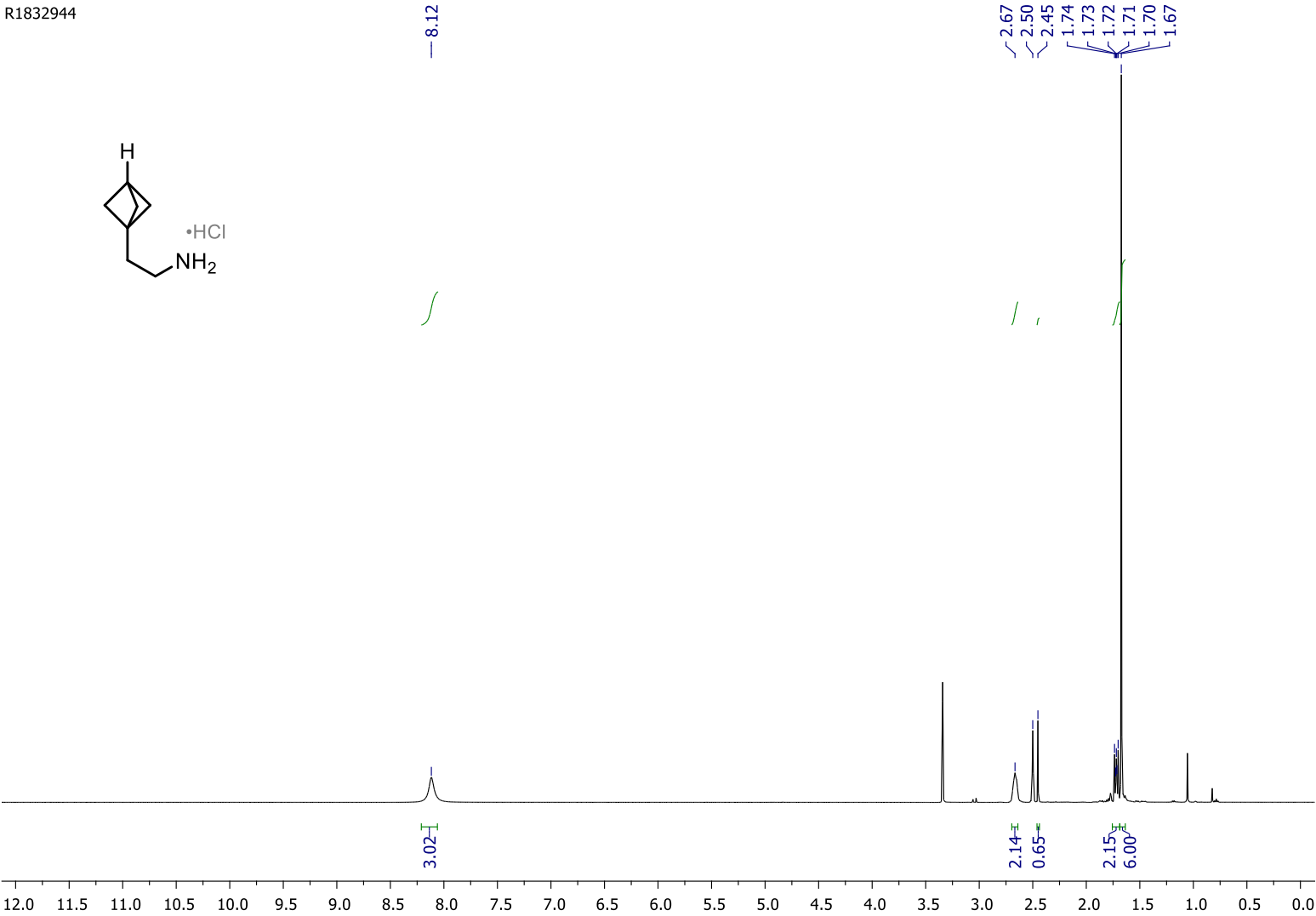
R1768614_C1:



Compound 38j

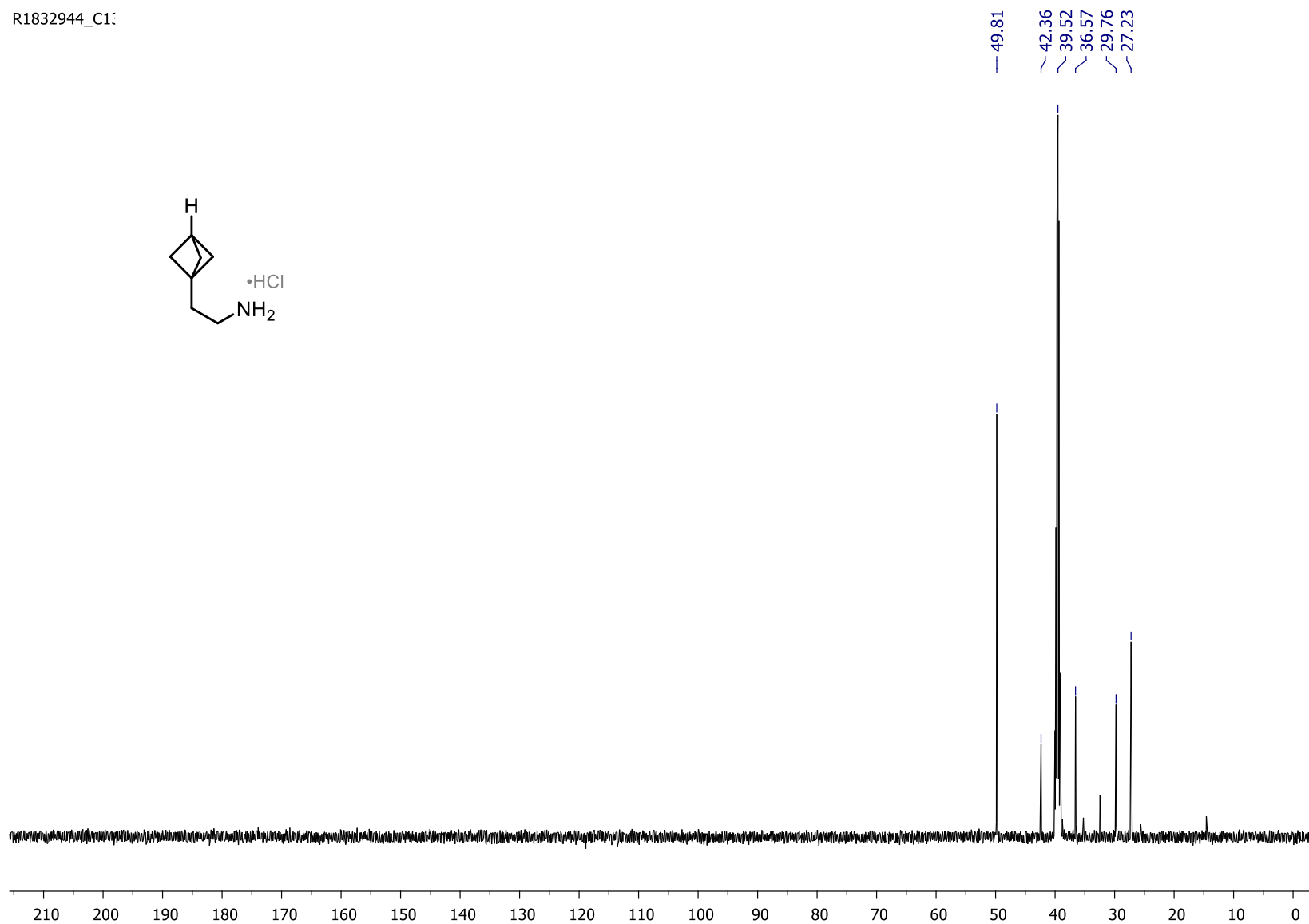
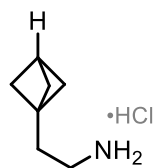
R1832944

¹H NMR (500 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

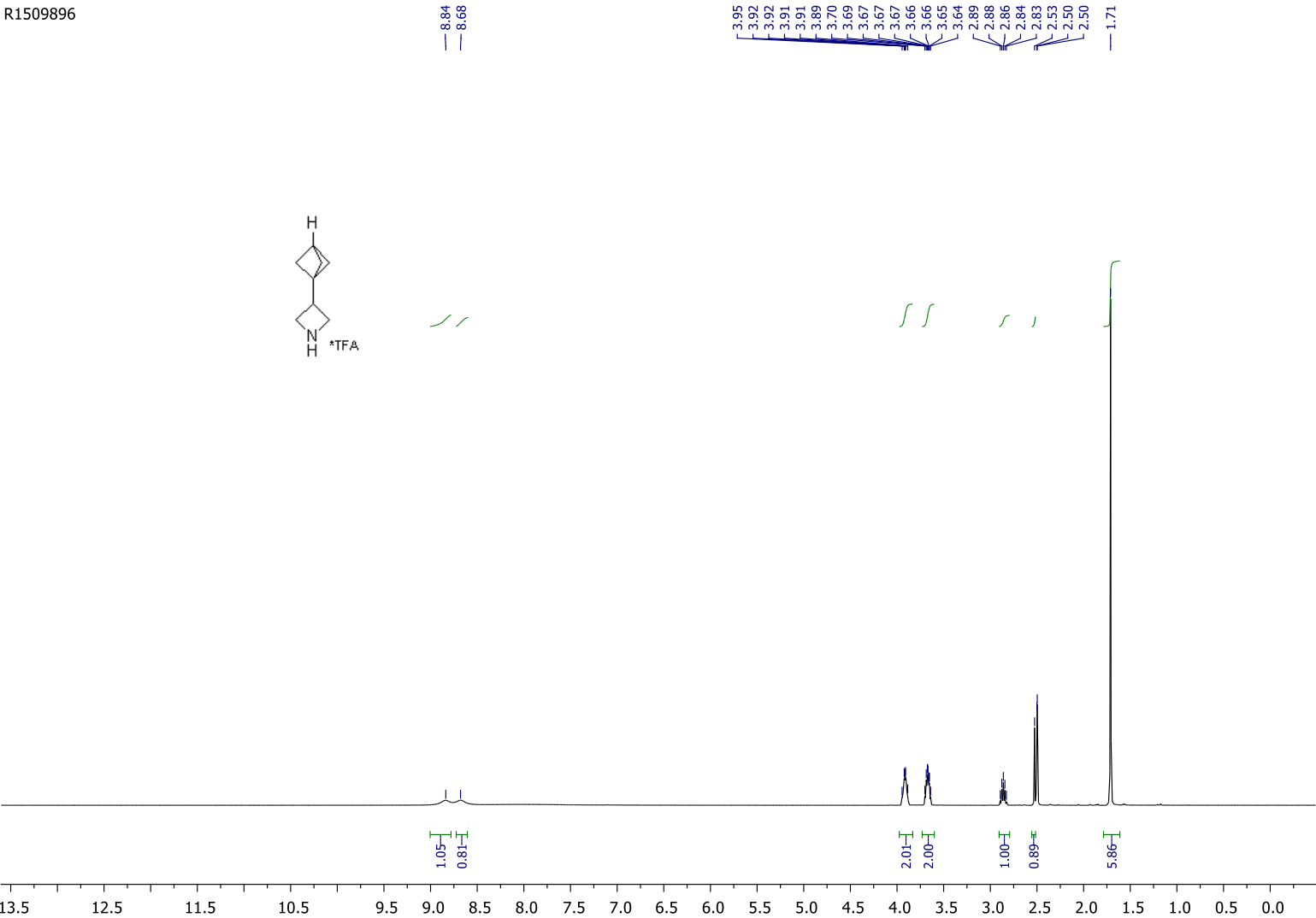
R1832944_C1:

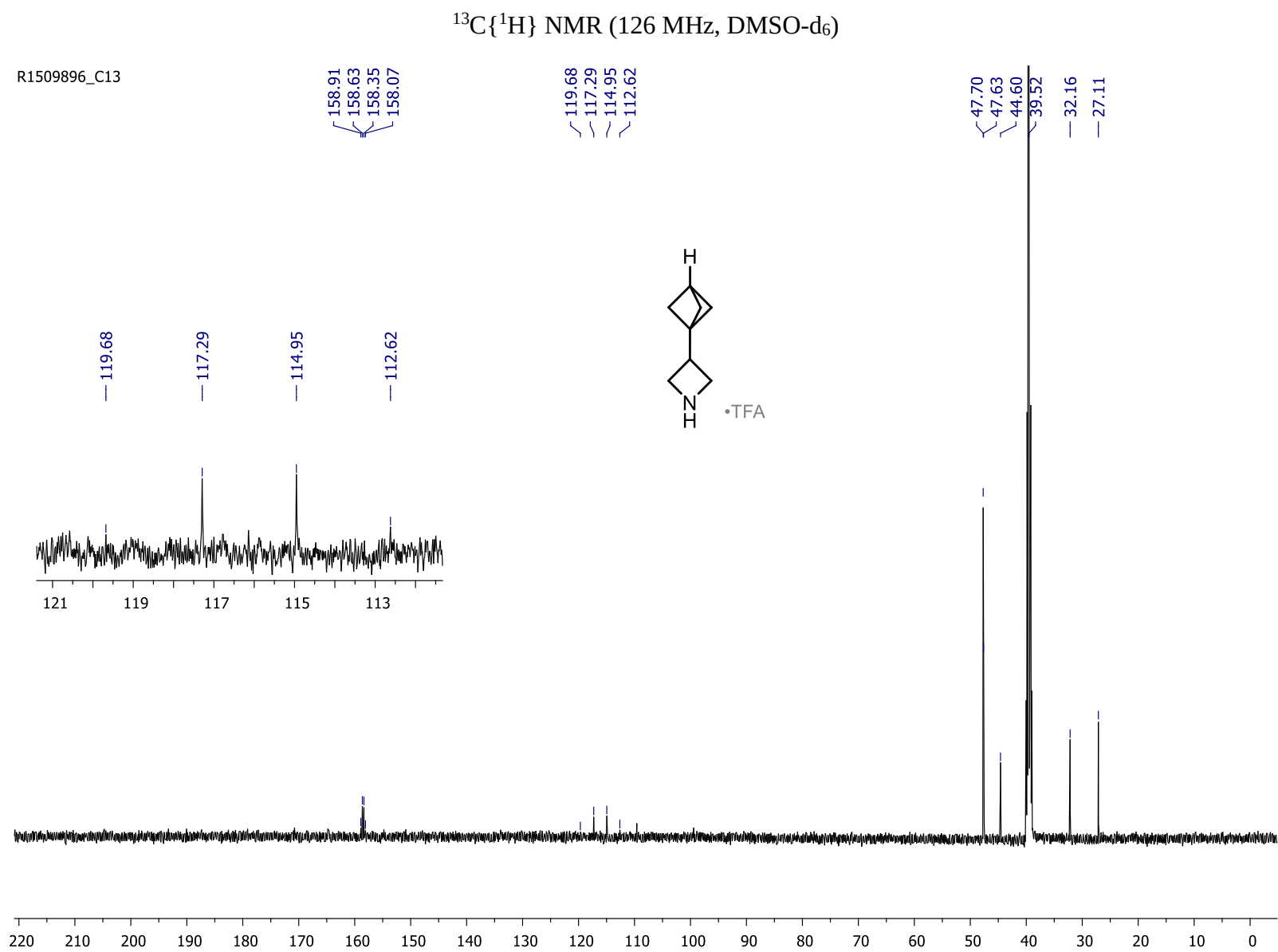


Compound 60j

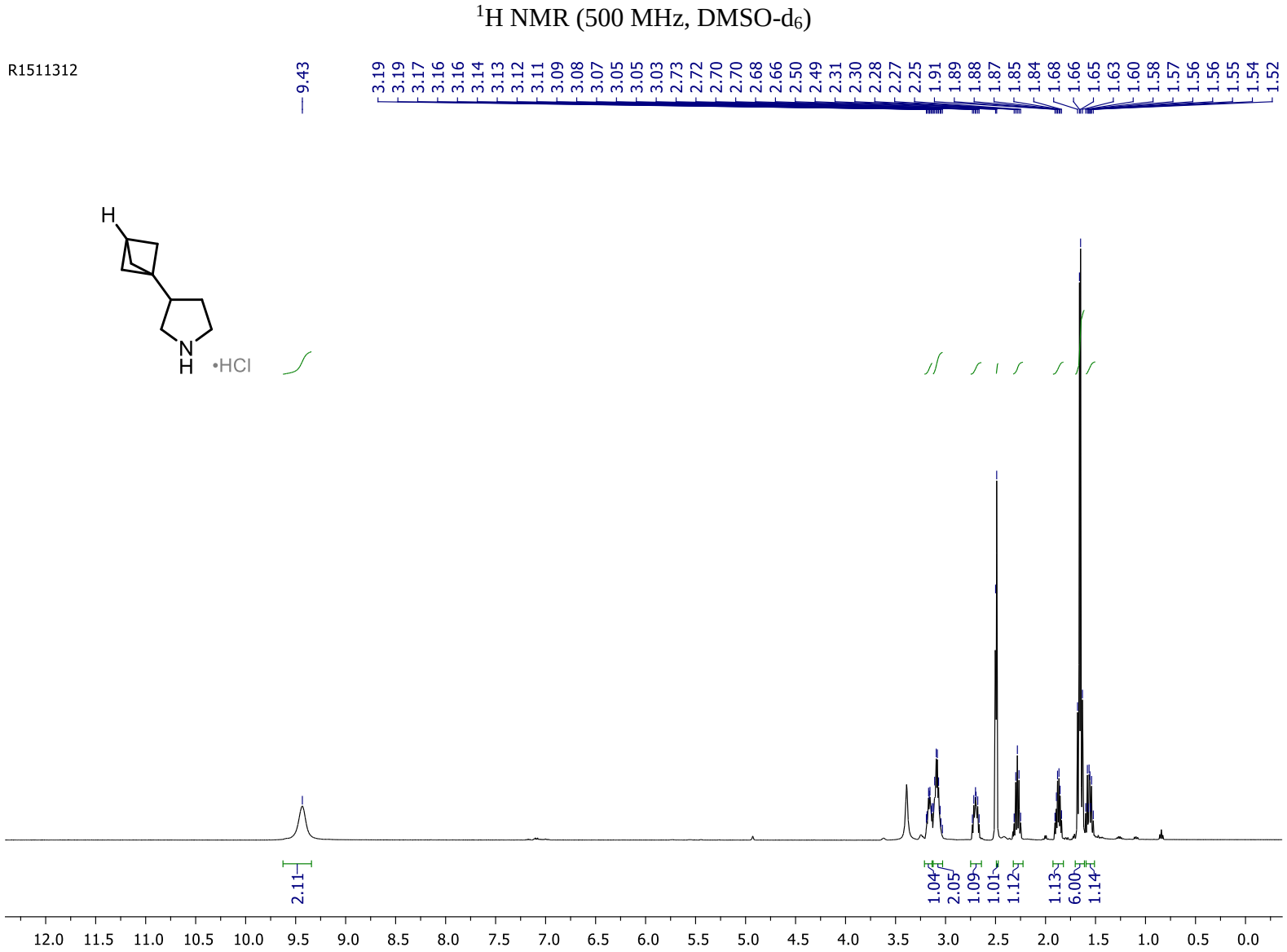
R1509896

¹H NMR (500 MHz, DMSO-d₆)



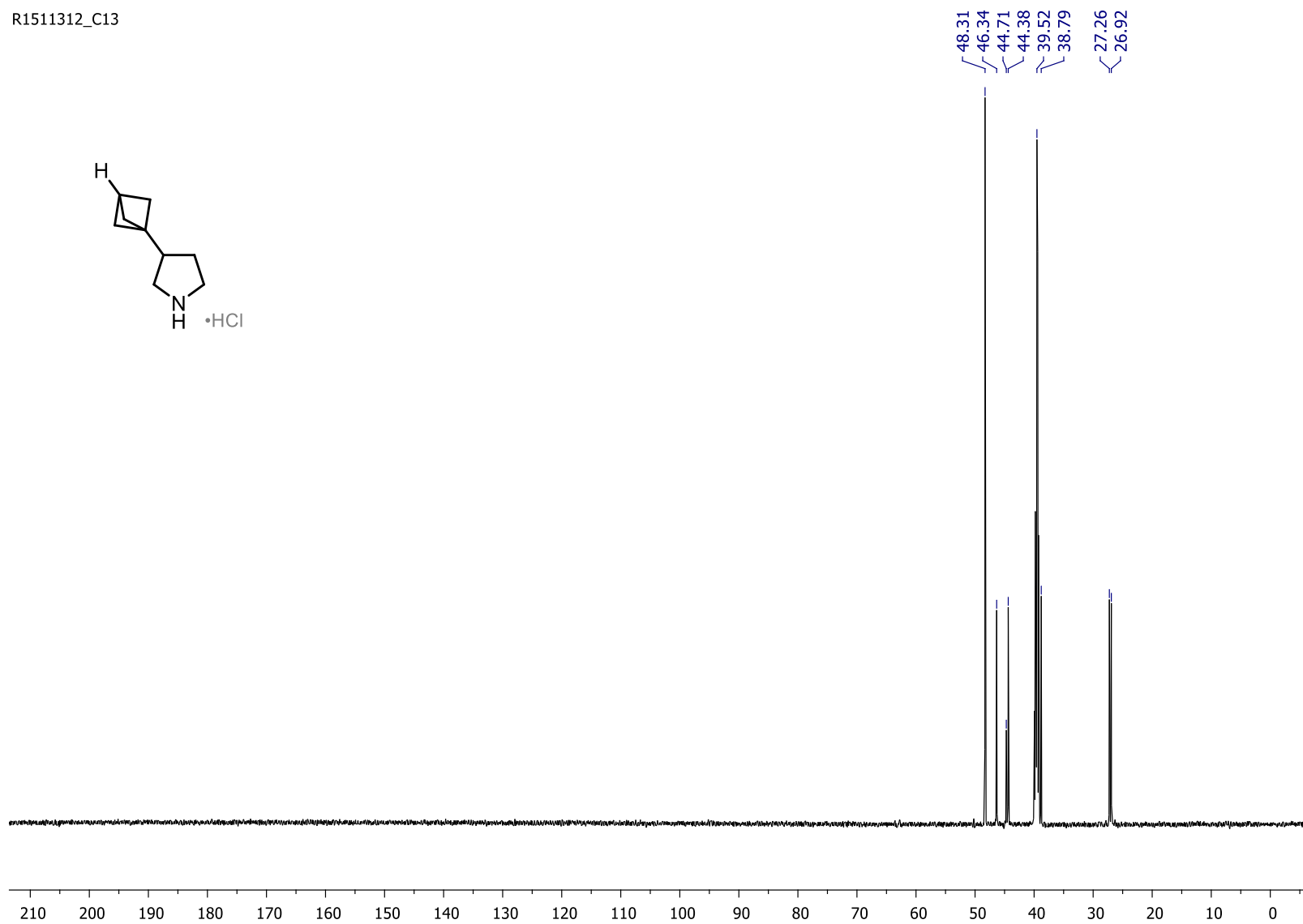
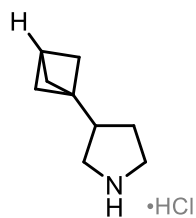


Compound 61j



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R1511312_C13

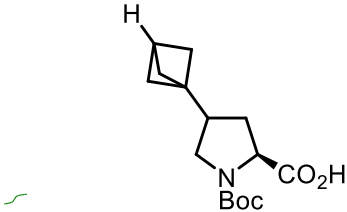


Compound 62j

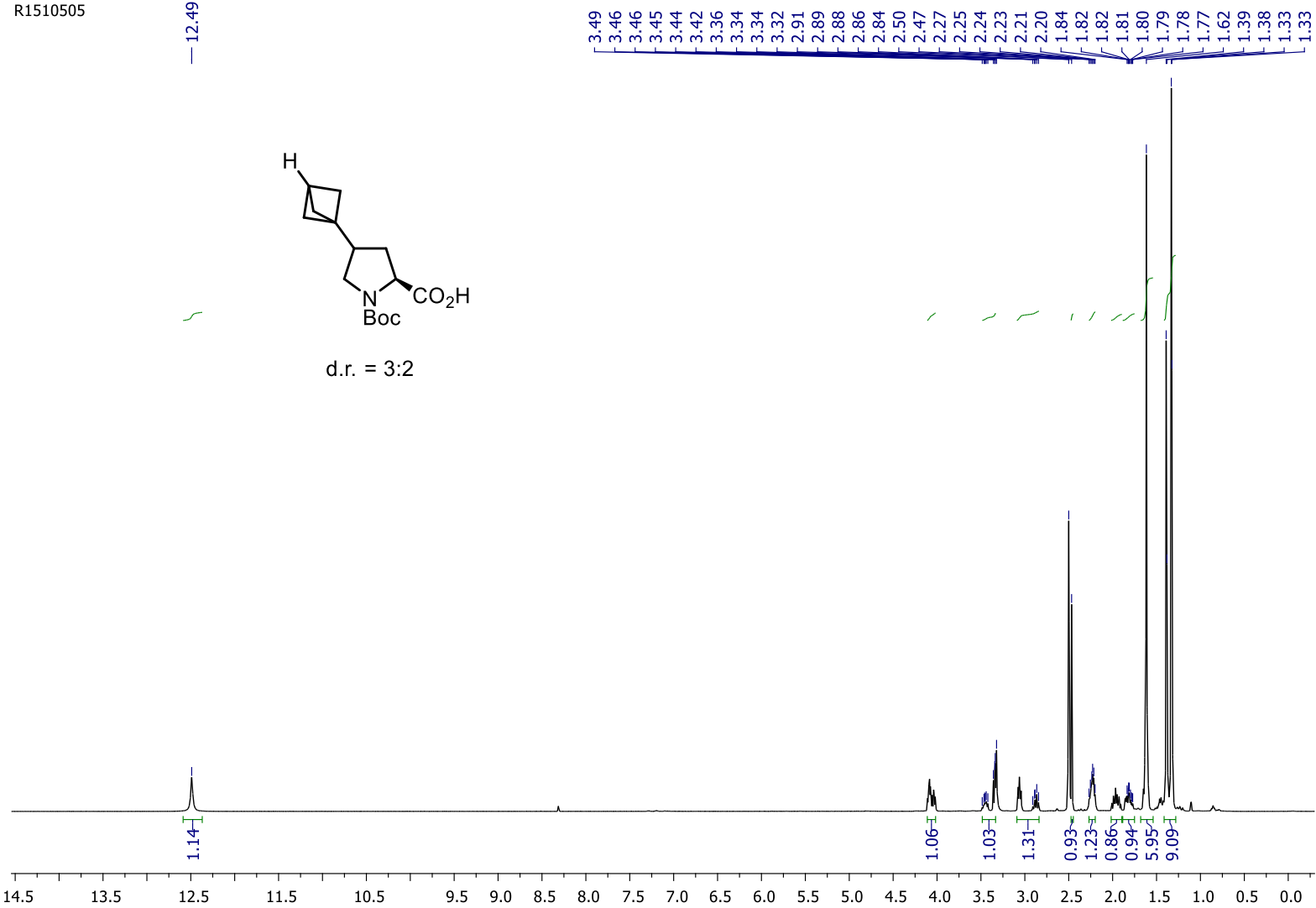
¹H NMR (500 MHz, DMSO-d₆)

R1510505

12.49

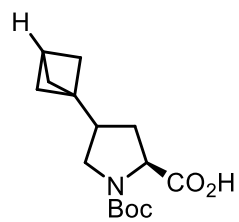


d.r. = 3:2

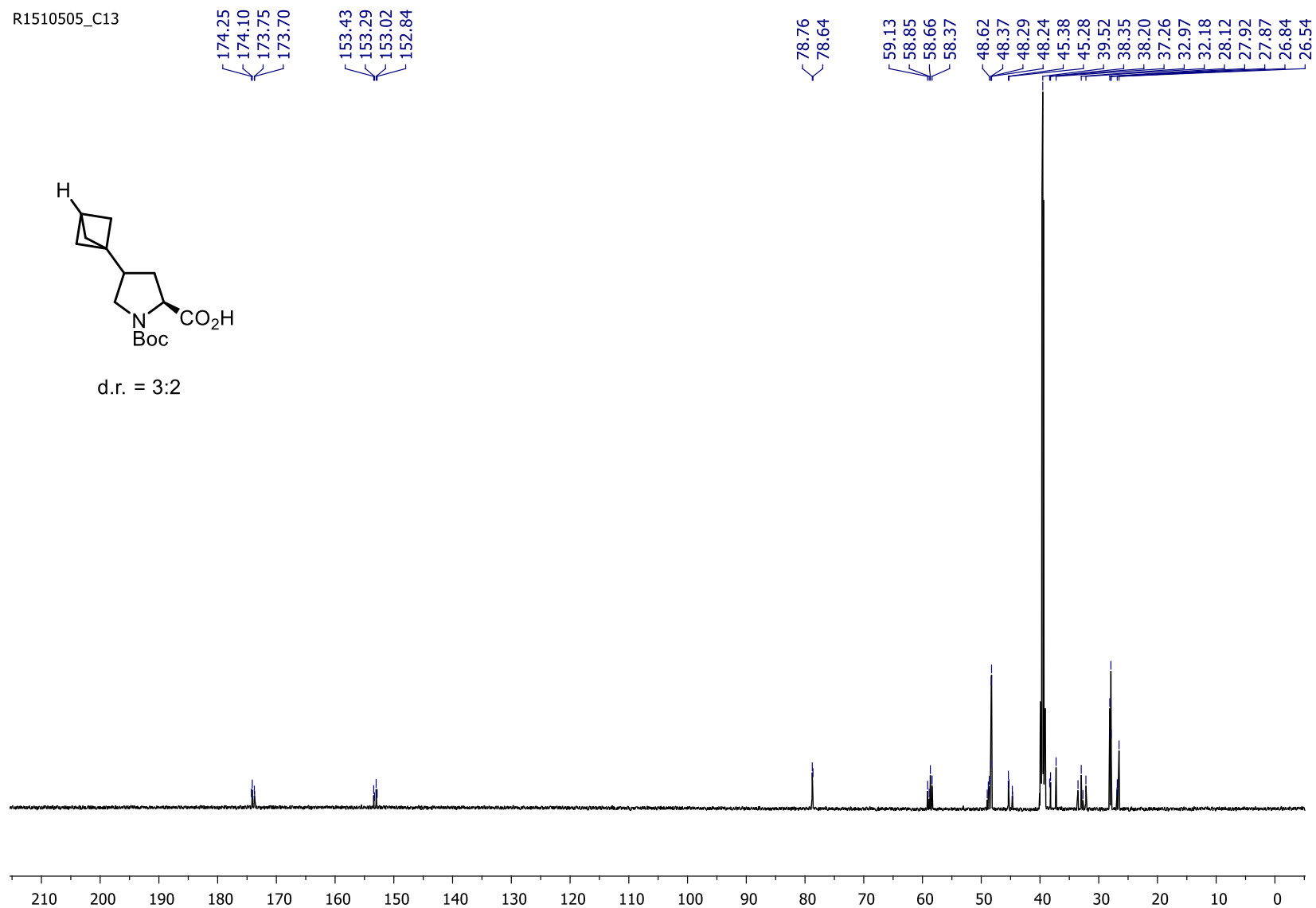


$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R1510505_C13



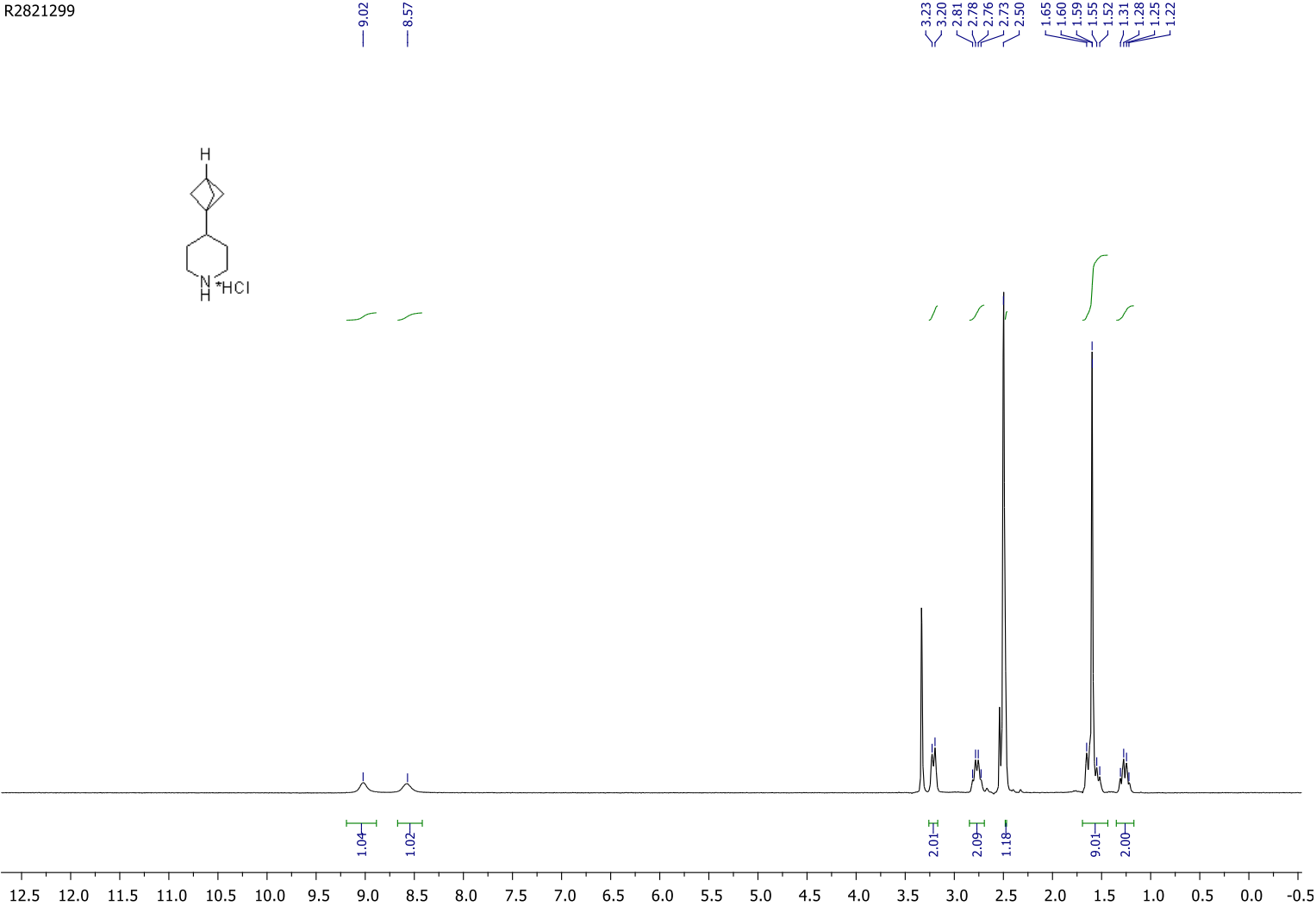
d.r. = 3:2



Compound 63j

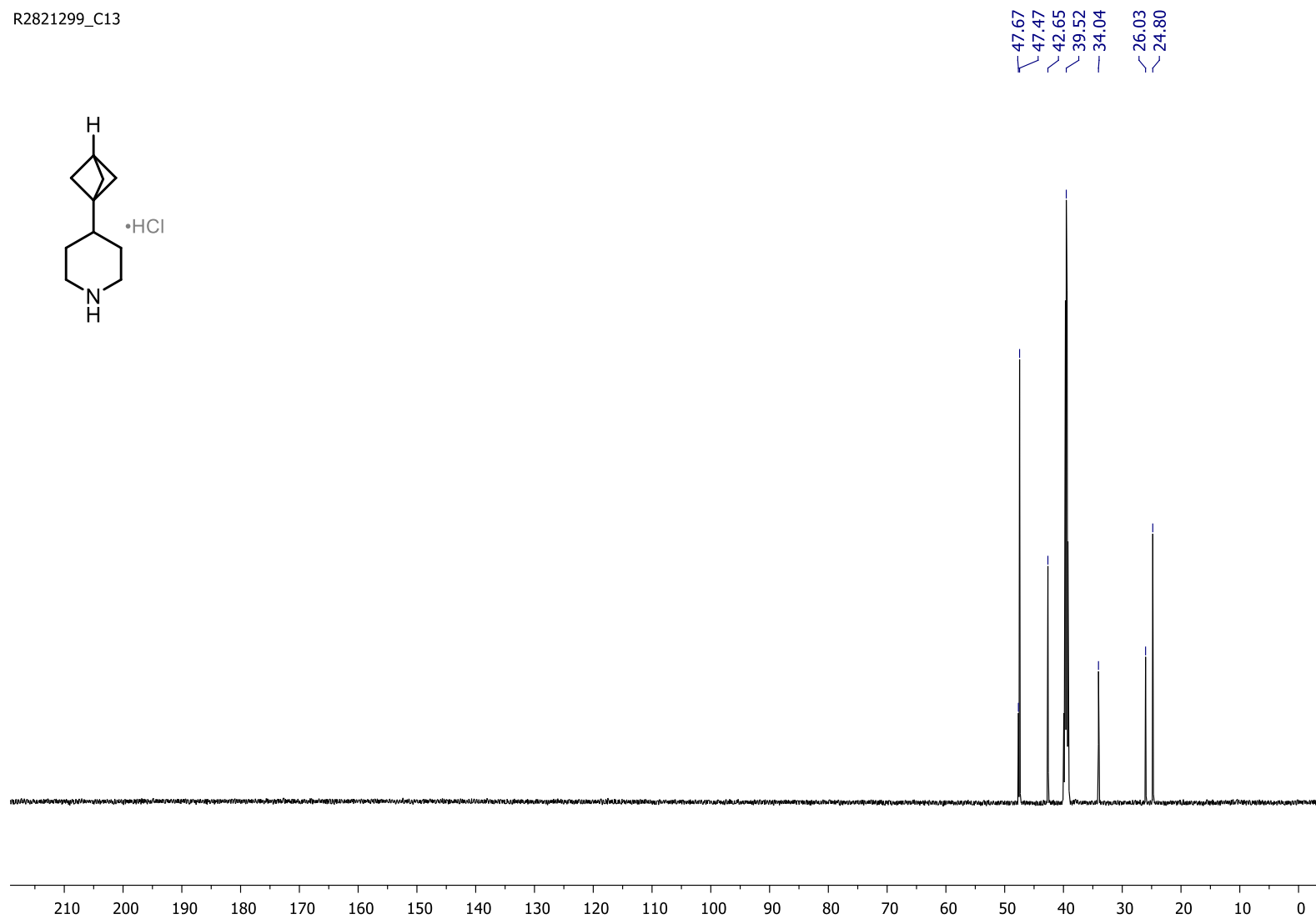
¹H NMR (400 MHz, DMSO-d₆)

R2821299

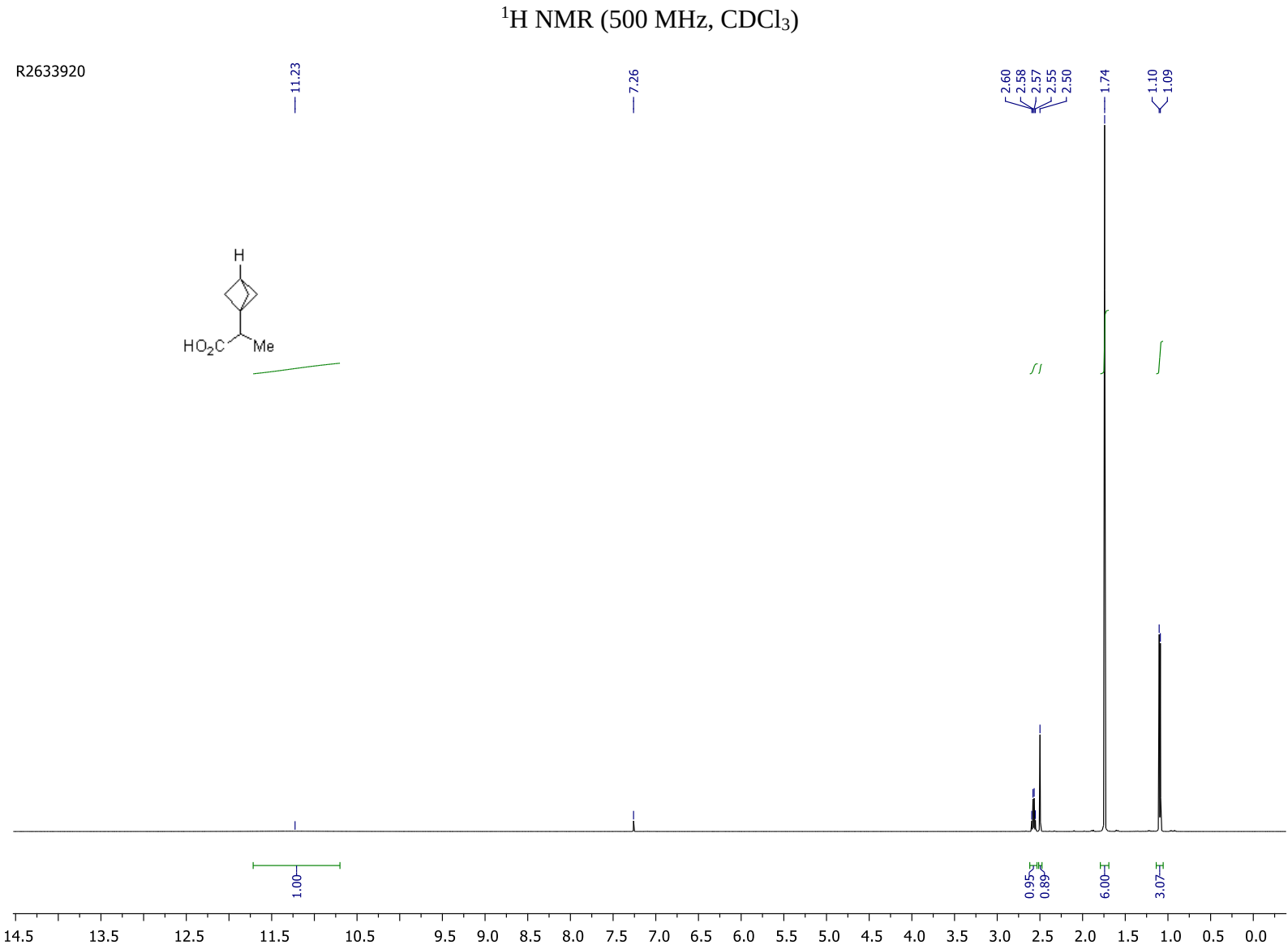


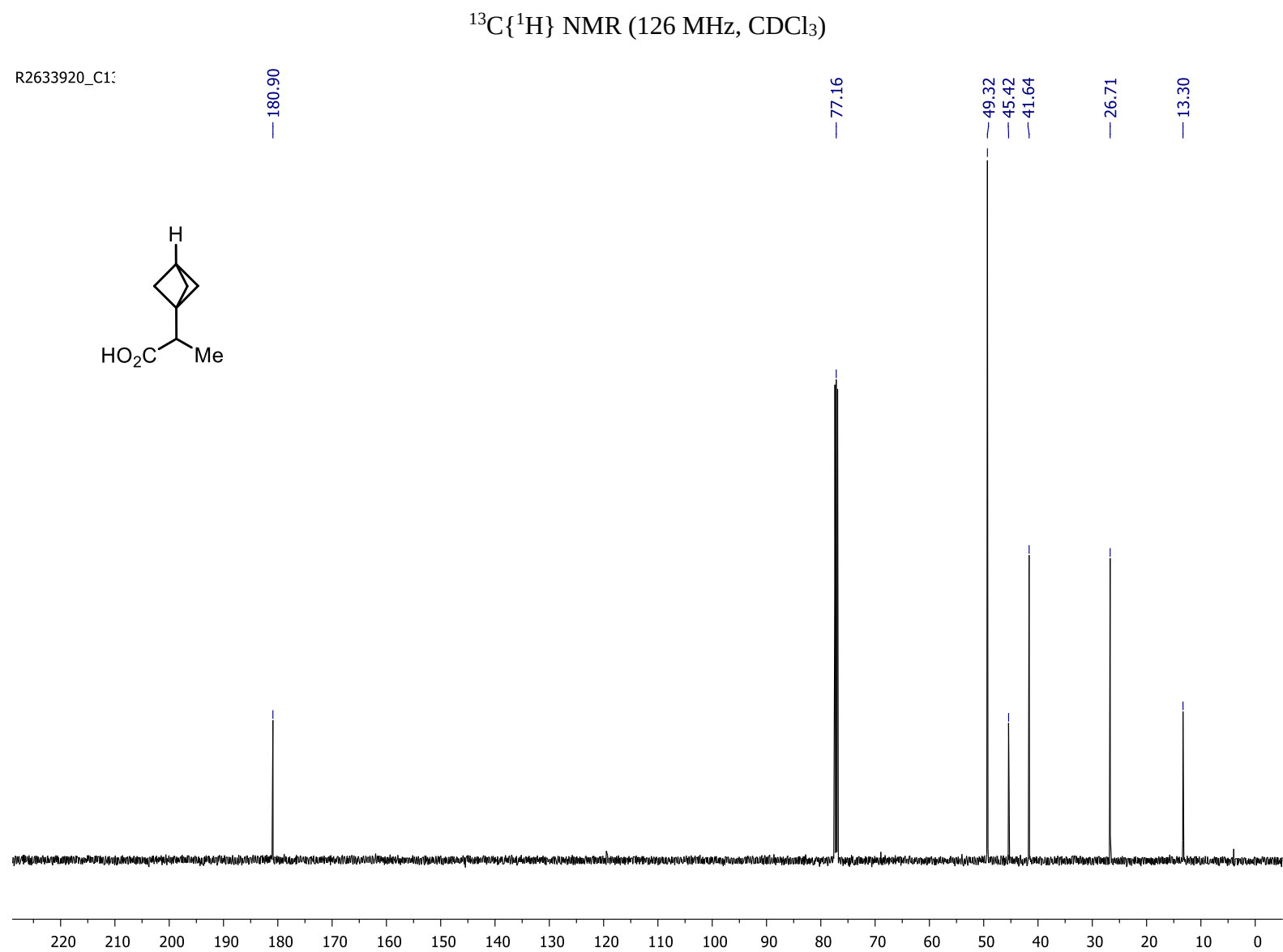
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2821299_C13



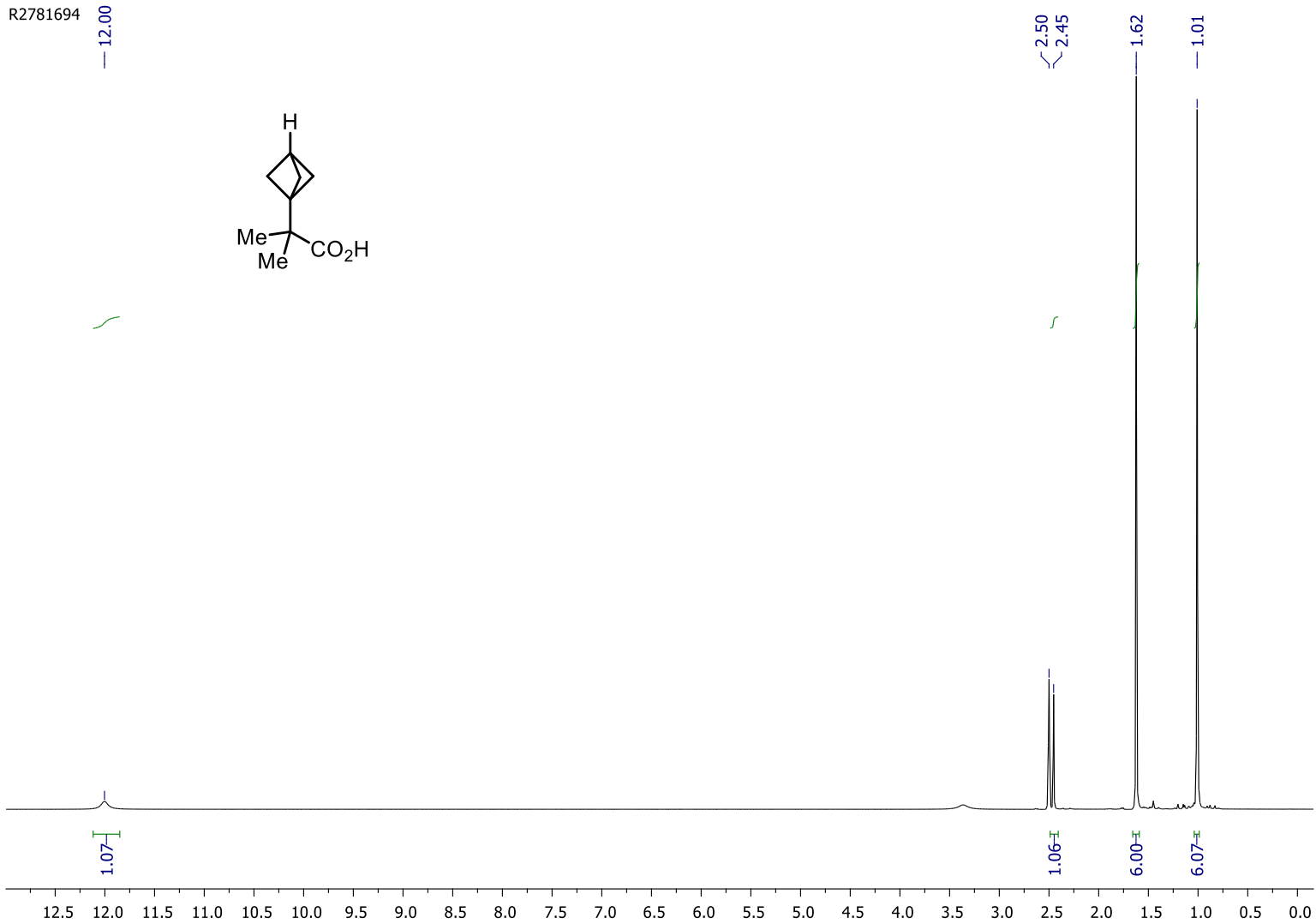
Compound 65j





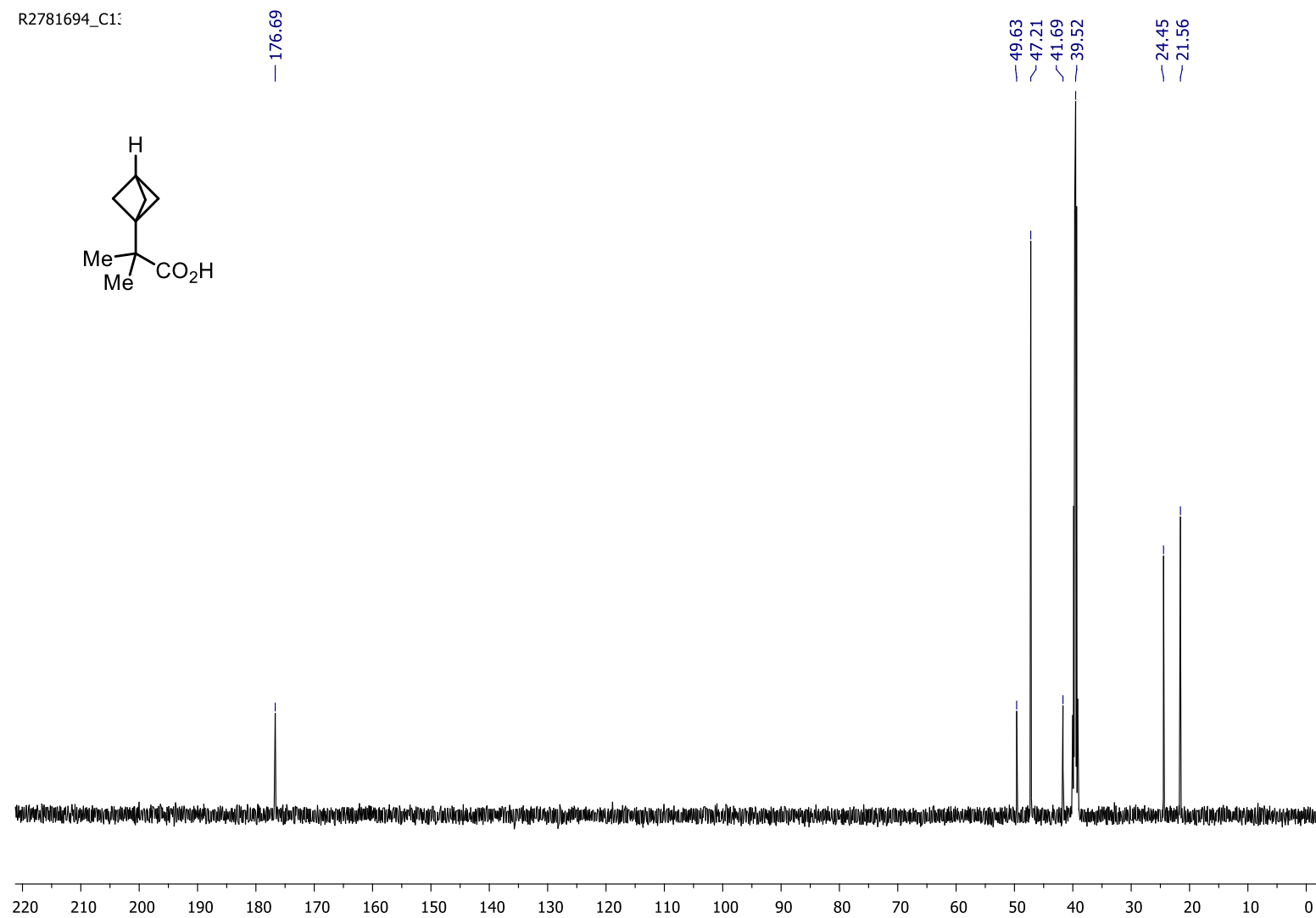
Compound 66j

¹H NMR (500 MHz, DMSO-d₆)



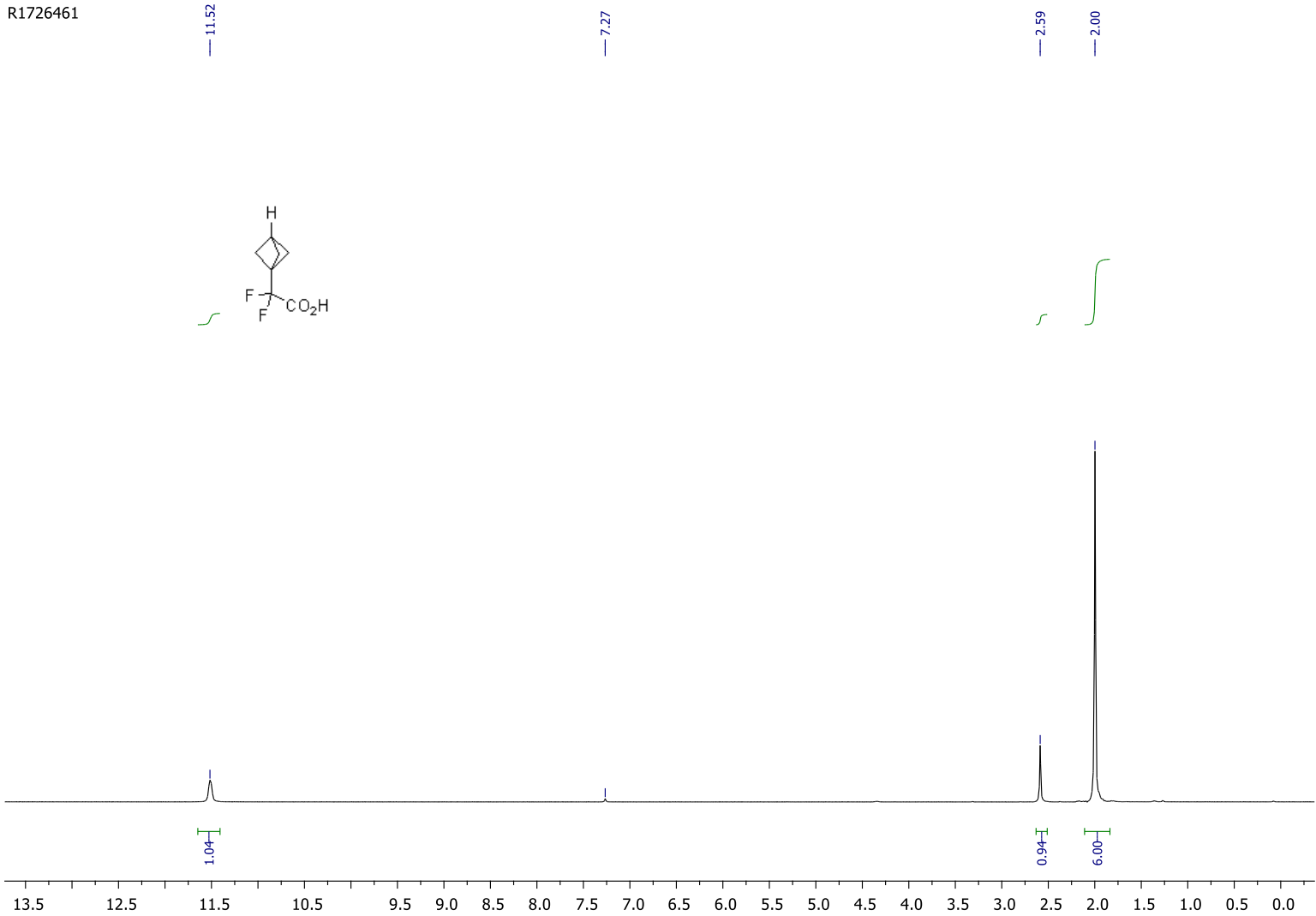
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

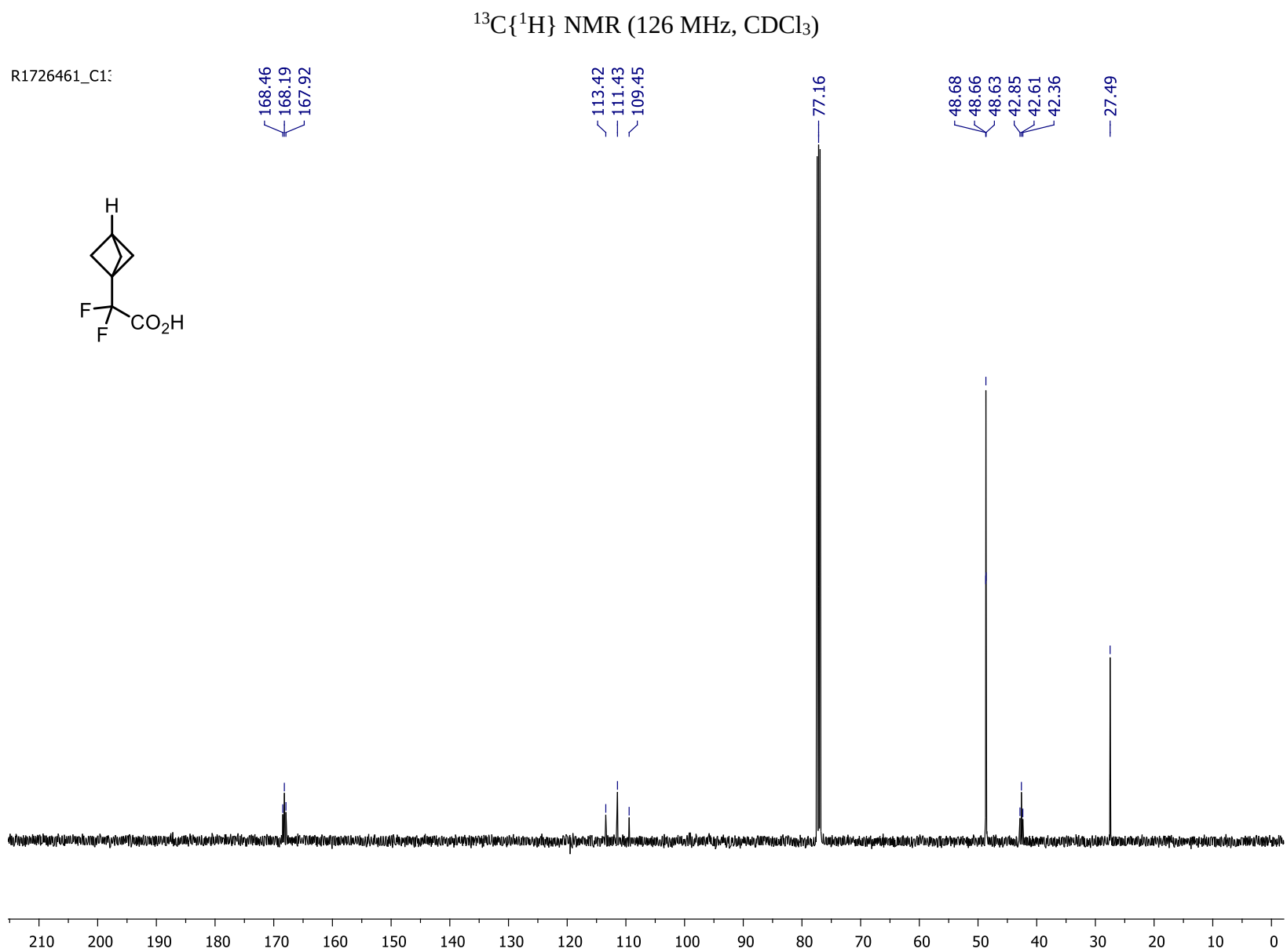
R2781694_C11



Compound 73j

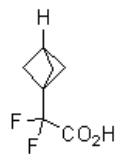
¹H NMR (400 MHz, CDCl₃)



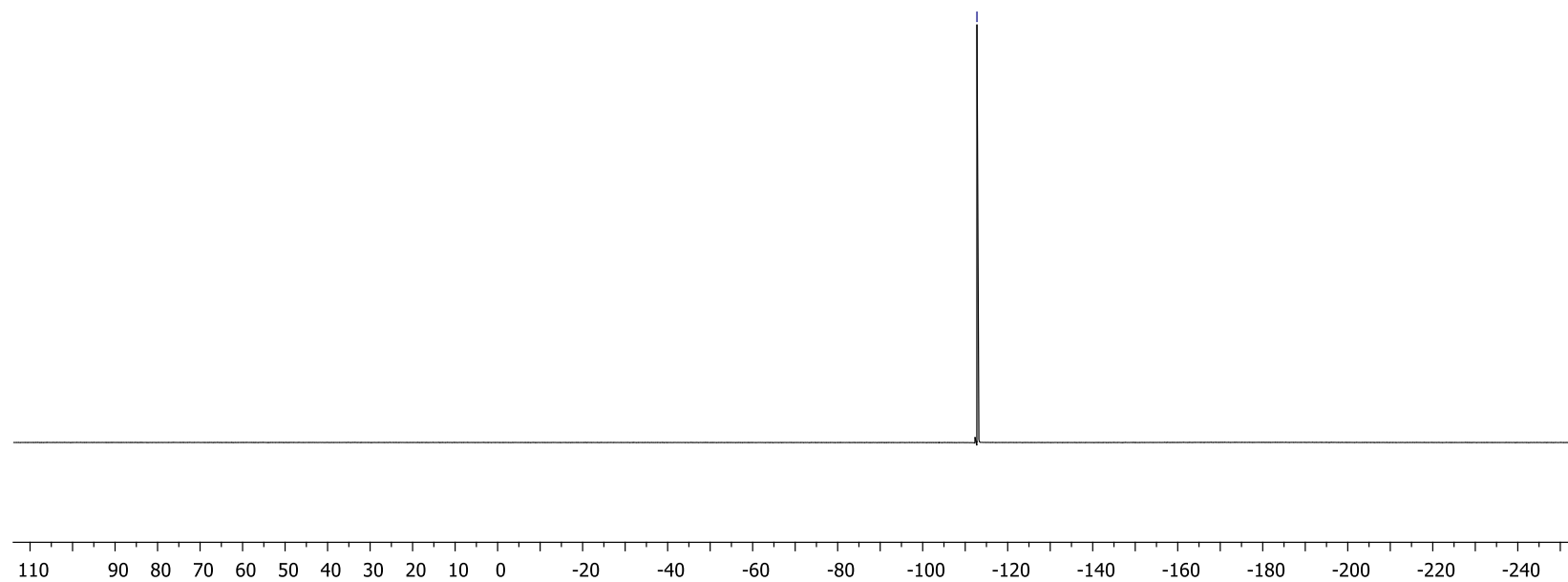


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R1726461_F19{H}

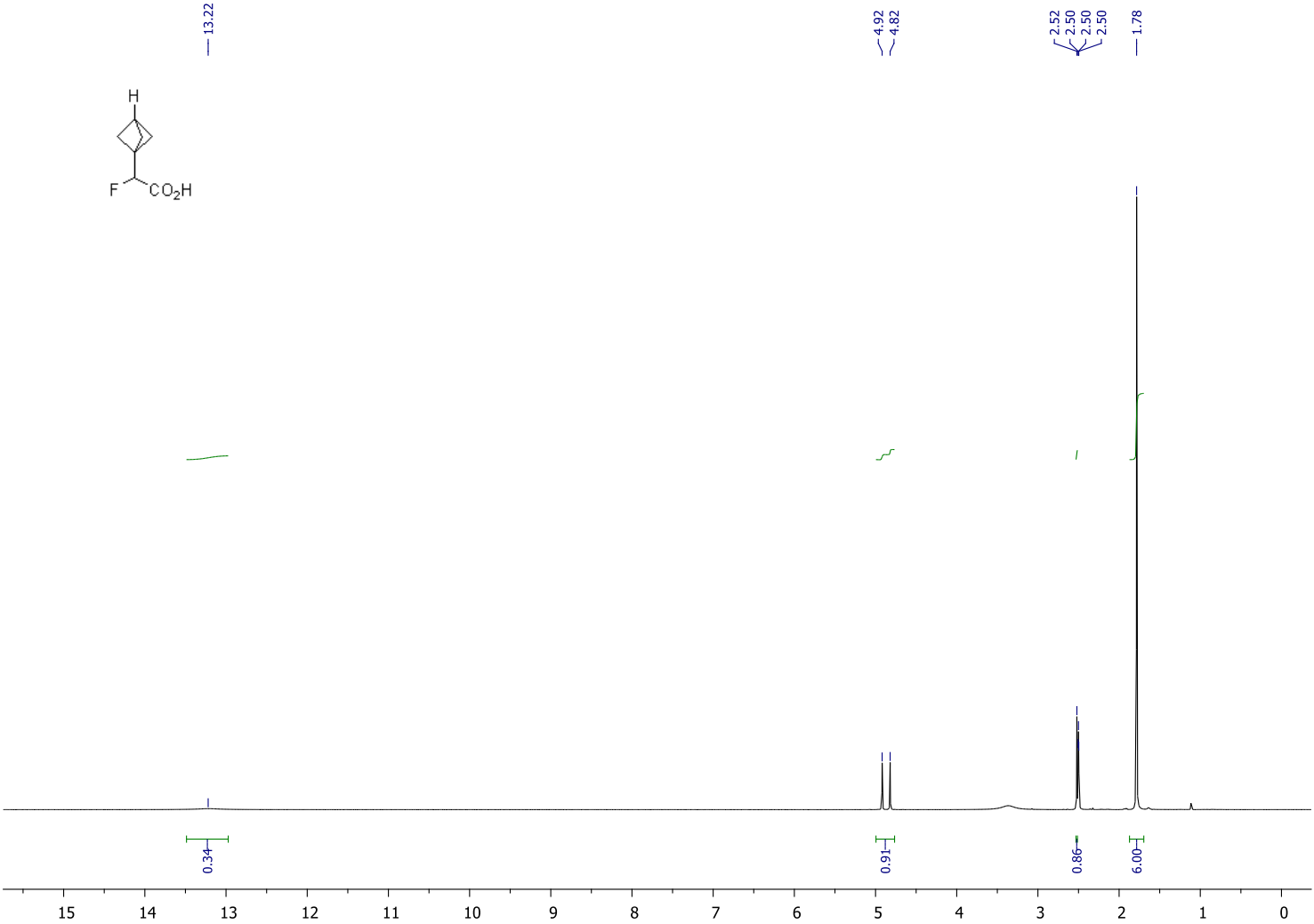


— -112.76

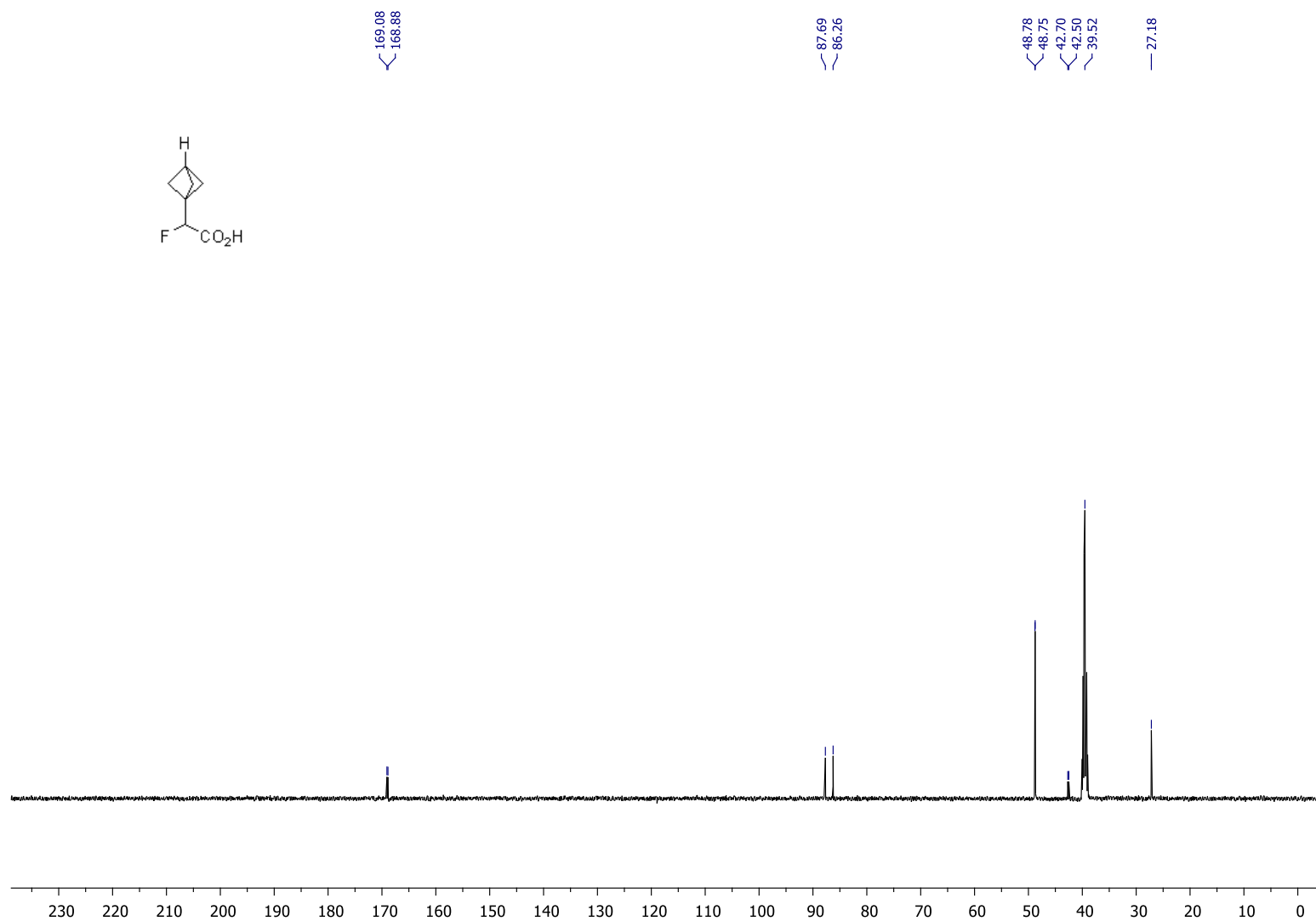
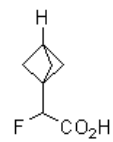


Compound 74j

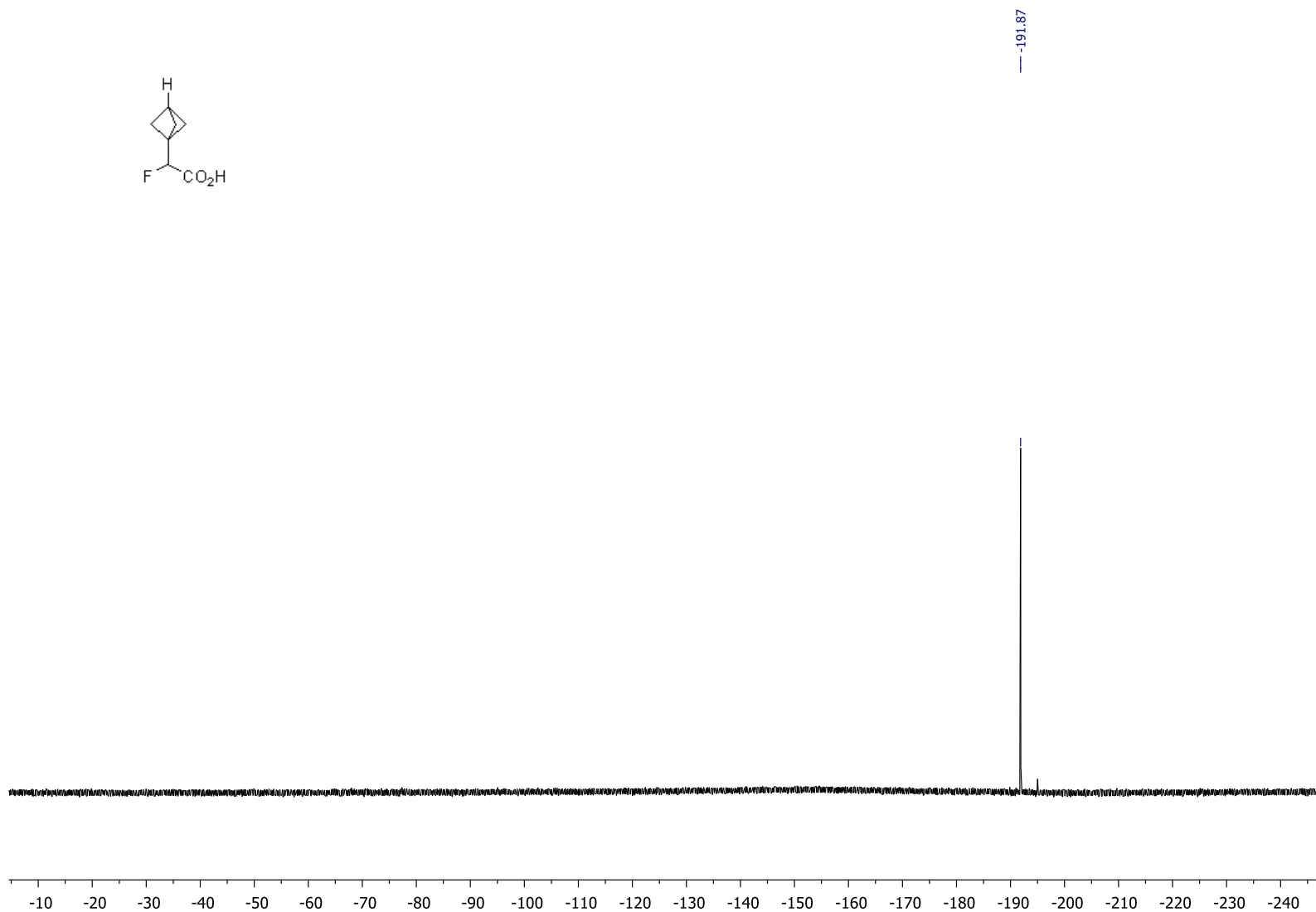
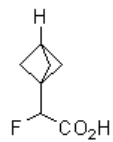
¹H NMR (500 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

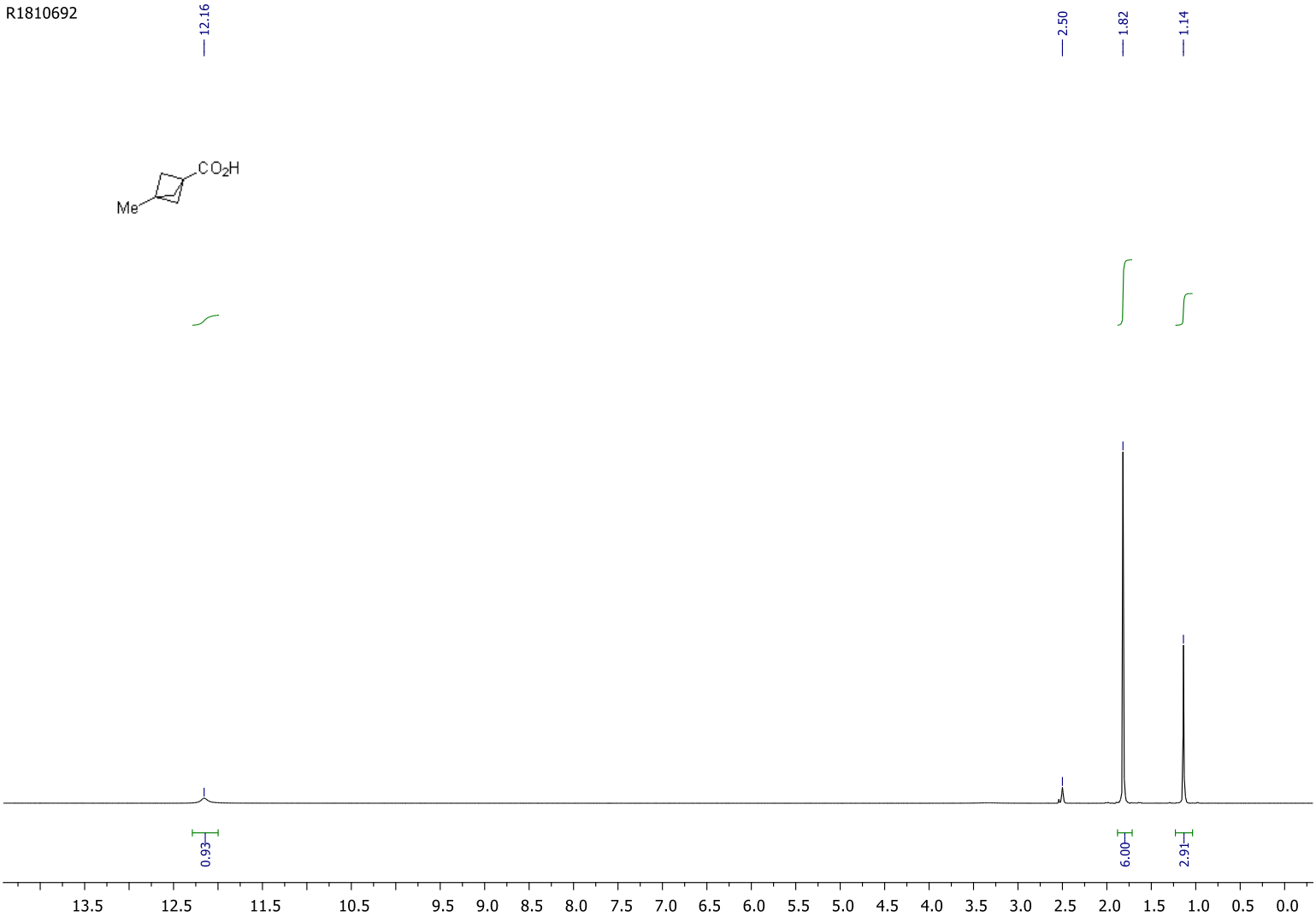


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)



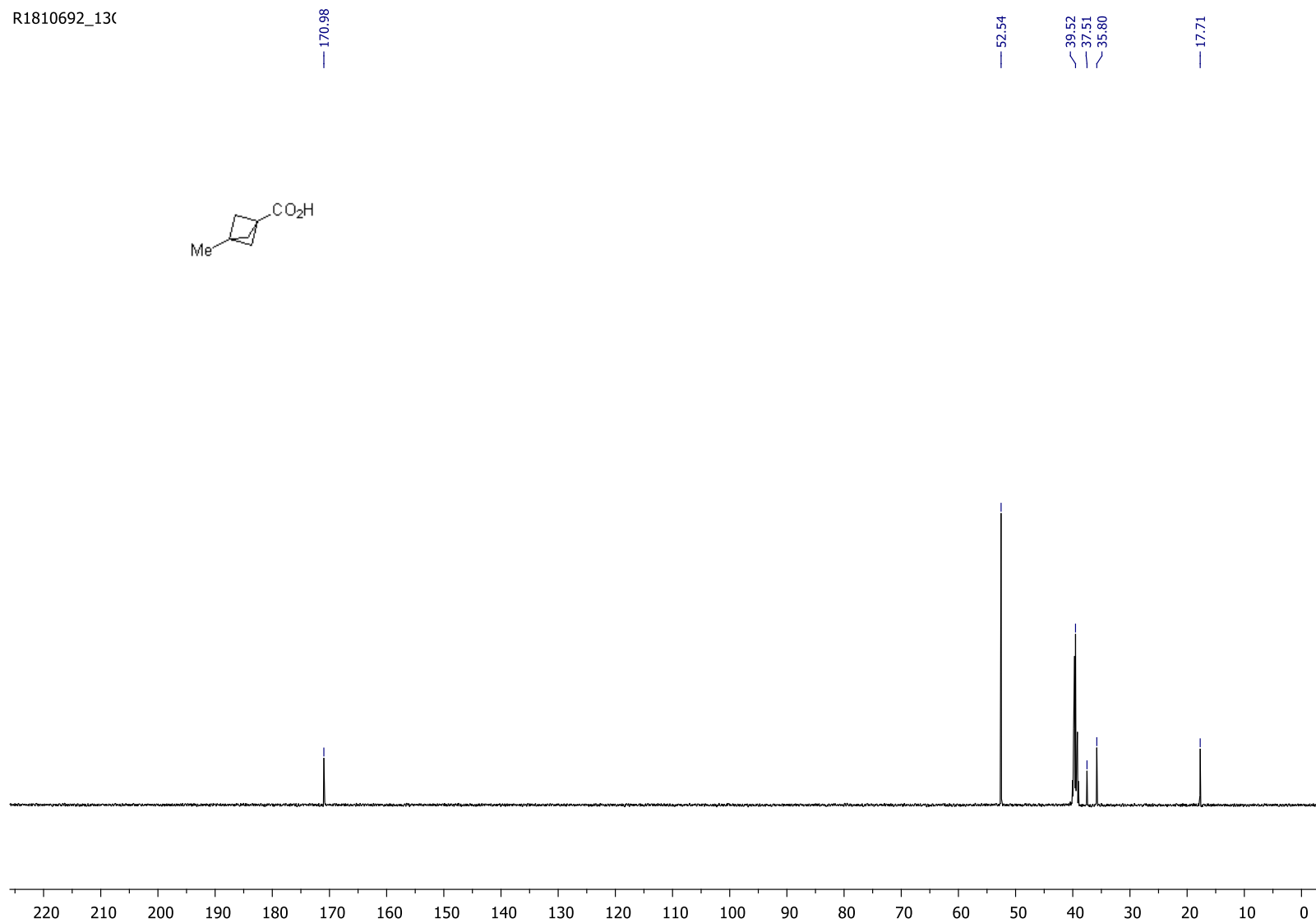
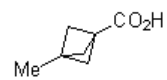
Compound 1k

¹H NMR (400 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

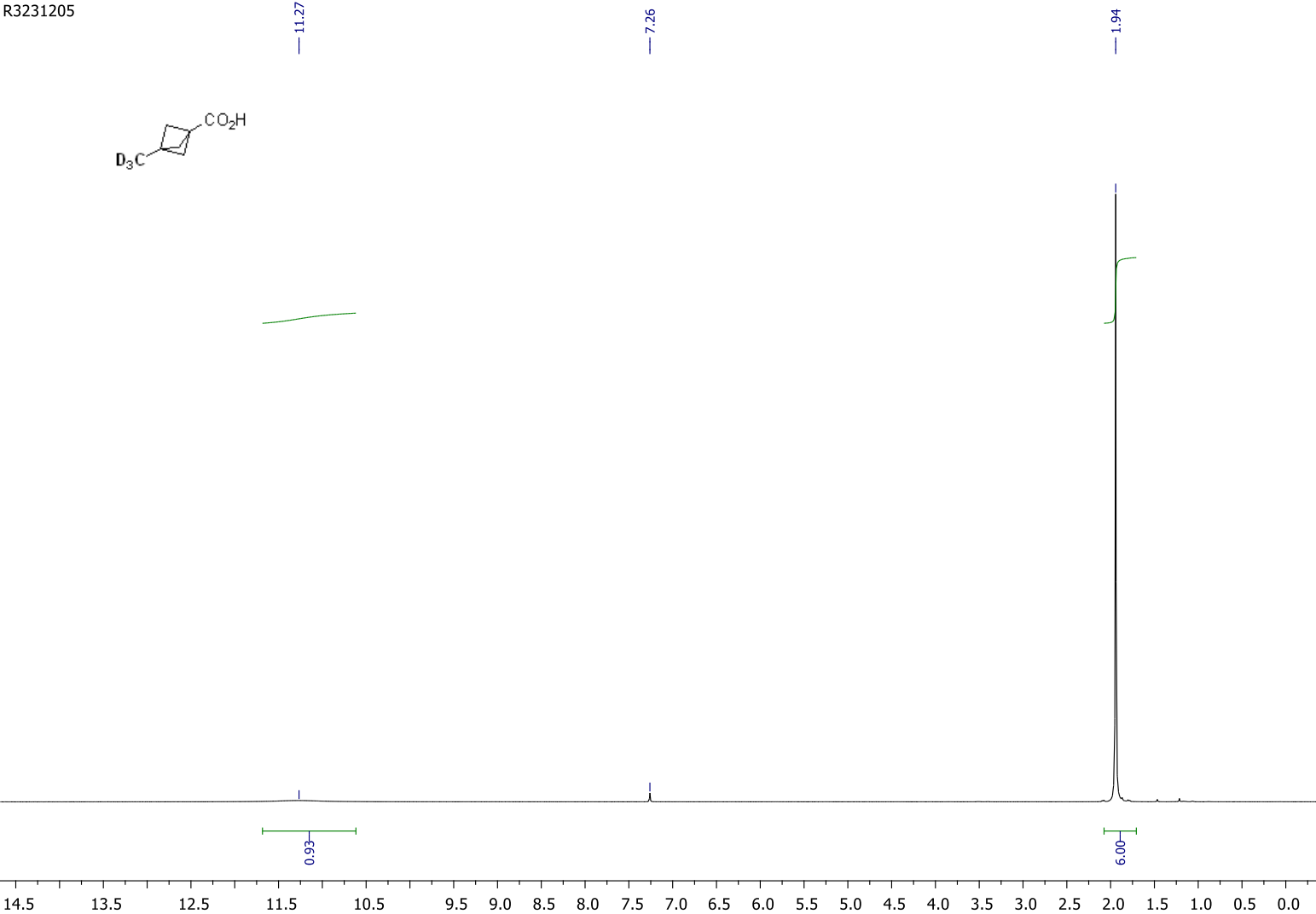
R1810692_13C

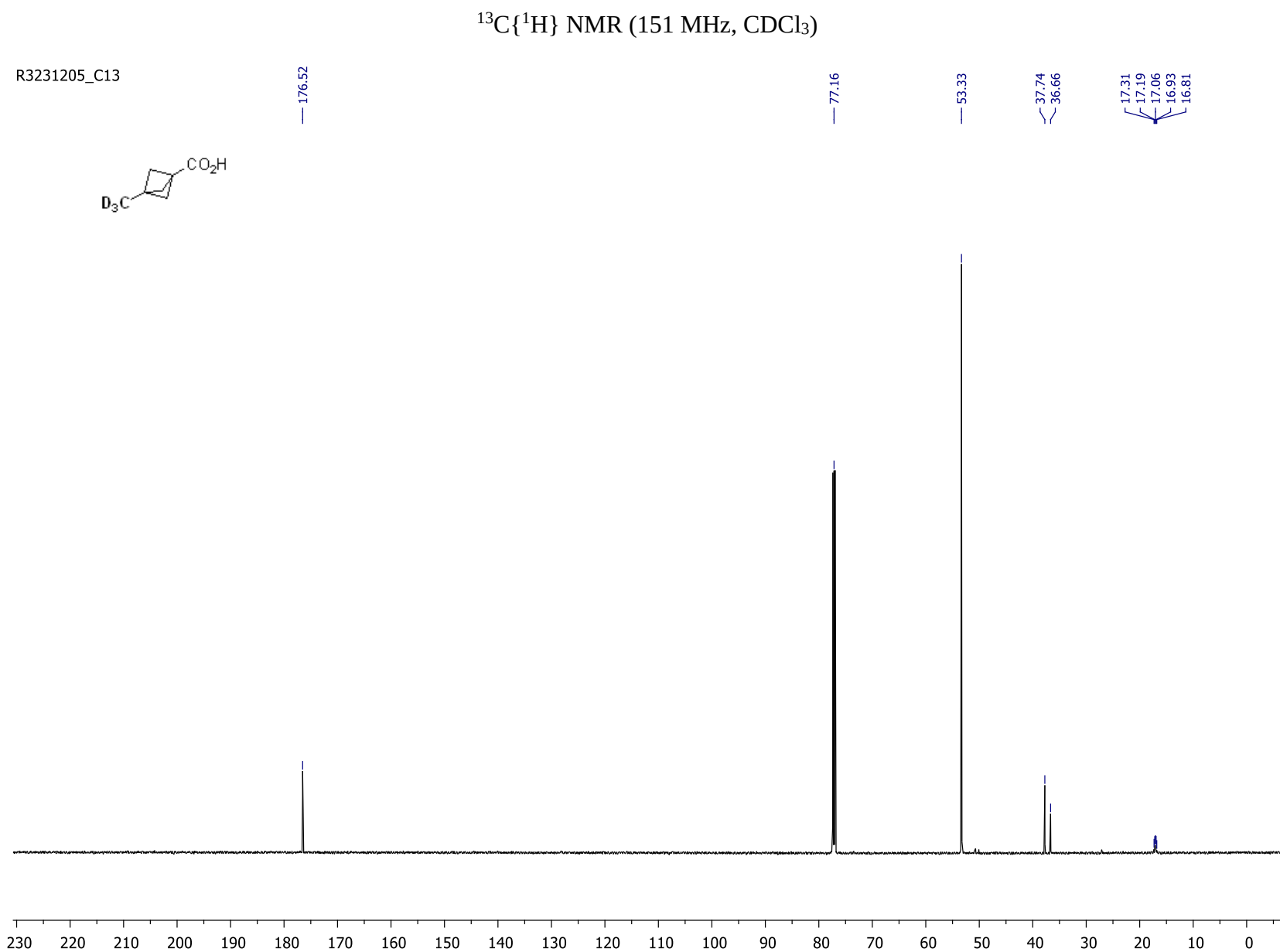


Compound (D₃-1)k

R3231205

¹H NMR (500 MHz, CDCl₃)

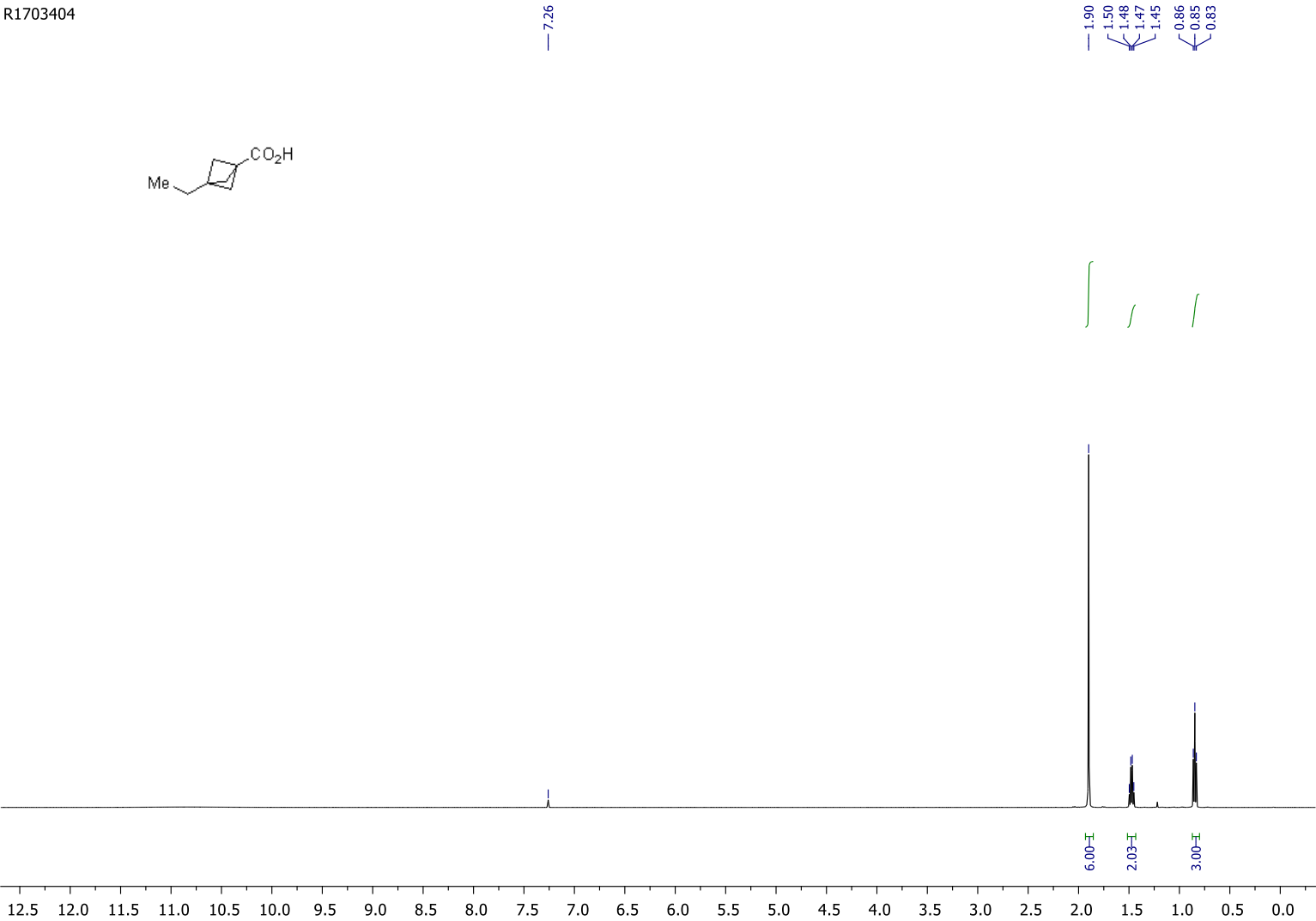




Compound 2k

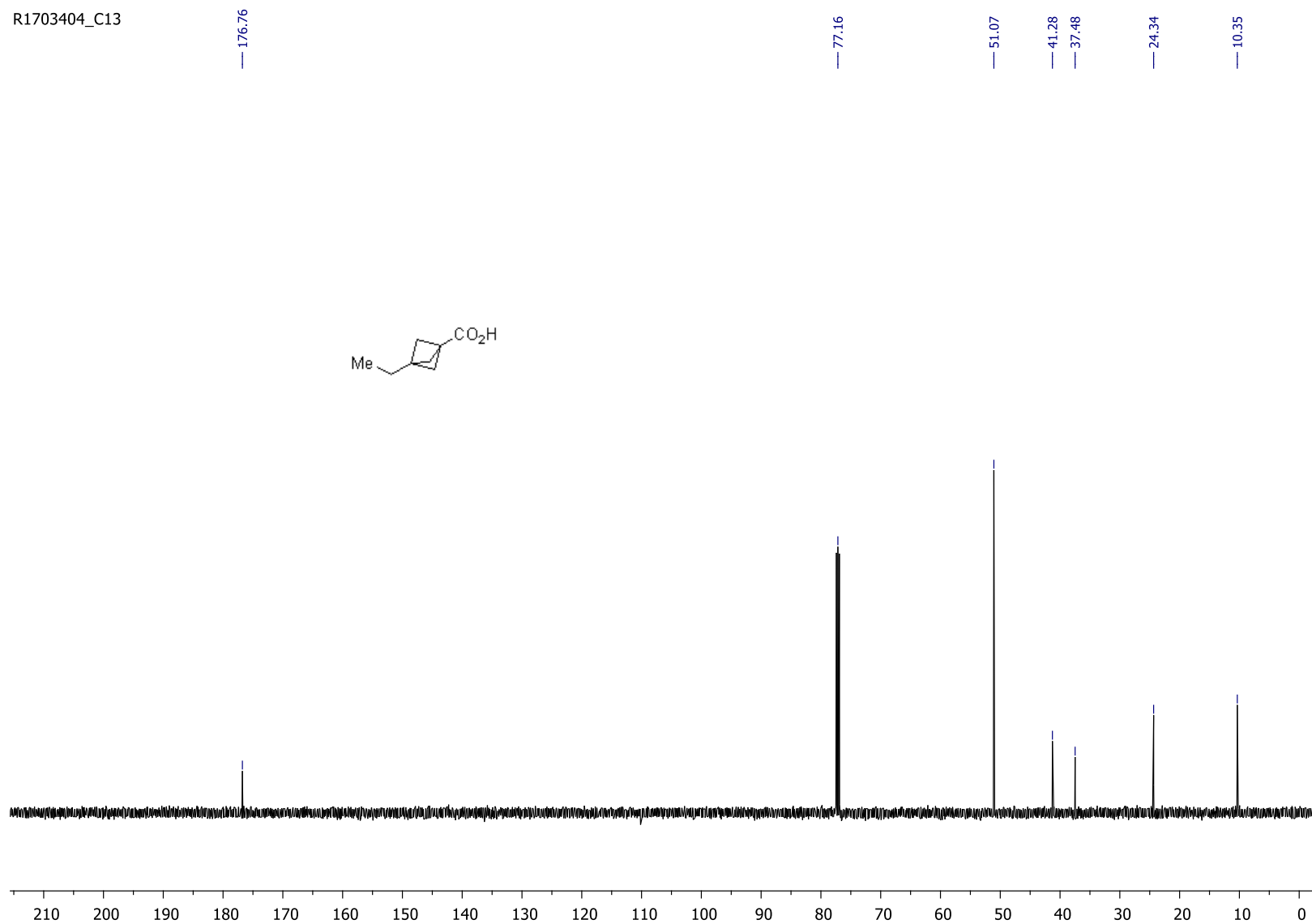
R1703404

¹H NMR (500 MHz, CDCl₃)



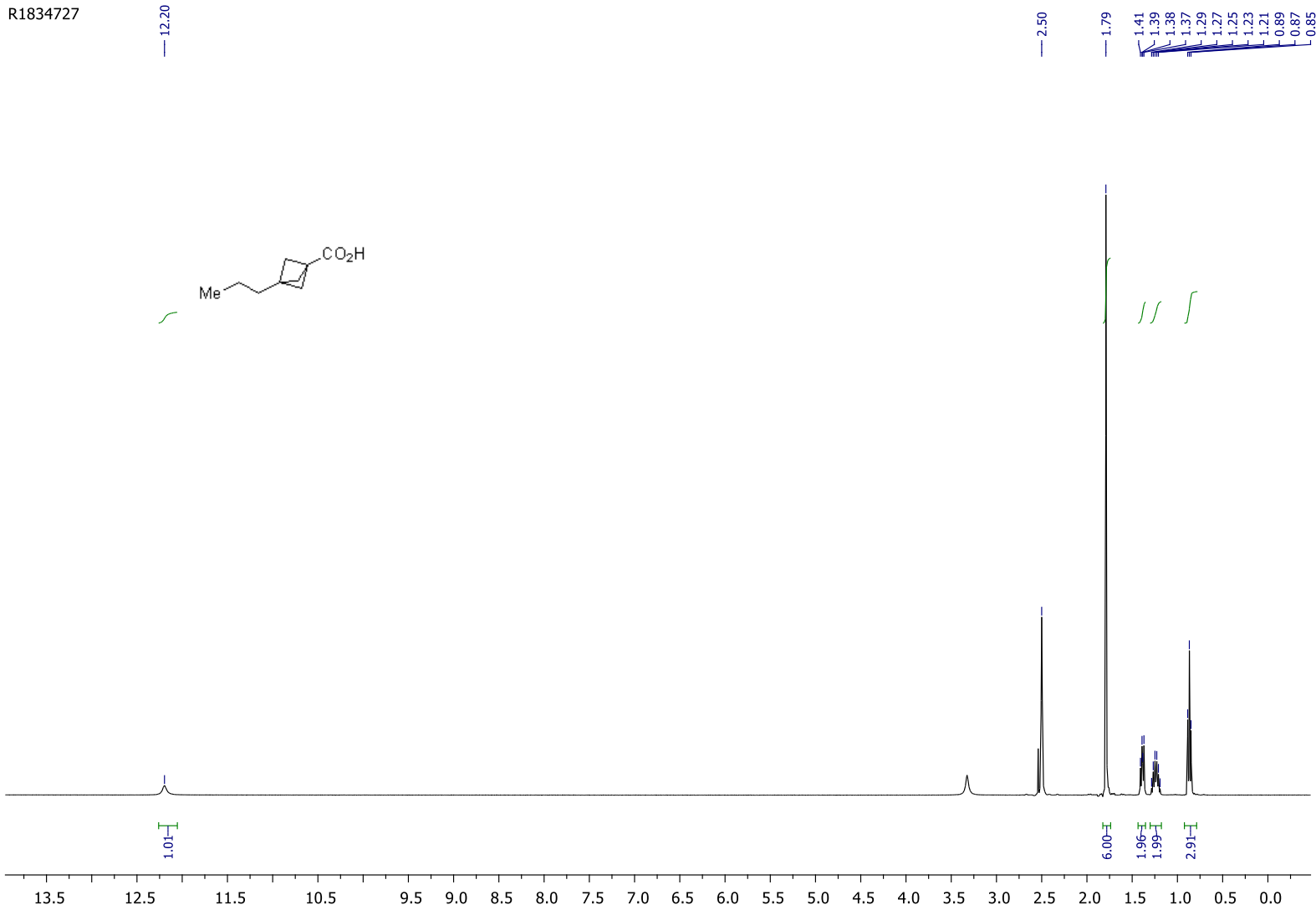
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R1703404_C13



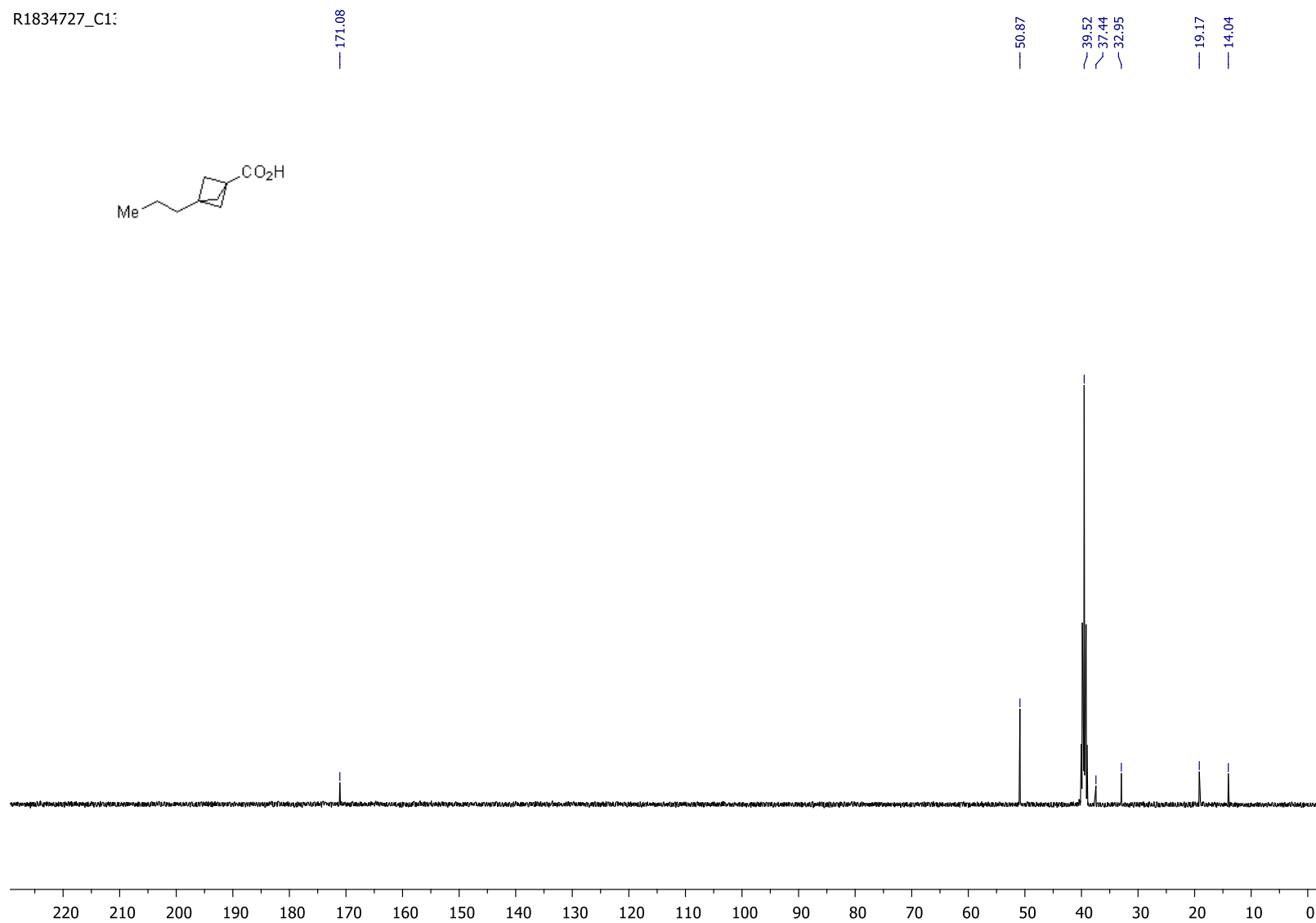
Compound 3k

¹H NMR (400 MHz, DMSO-d₆)

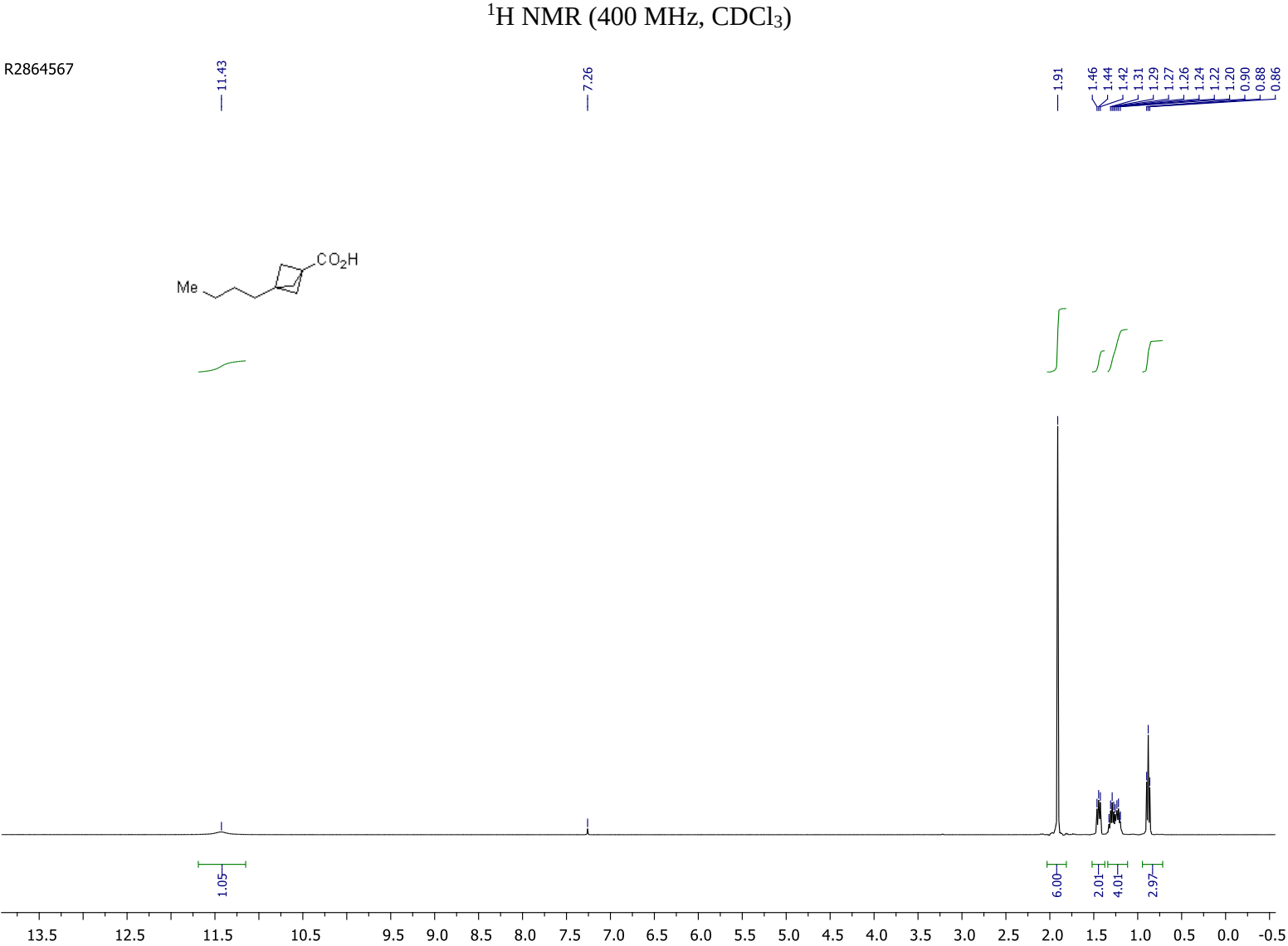


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R1834727_C1:

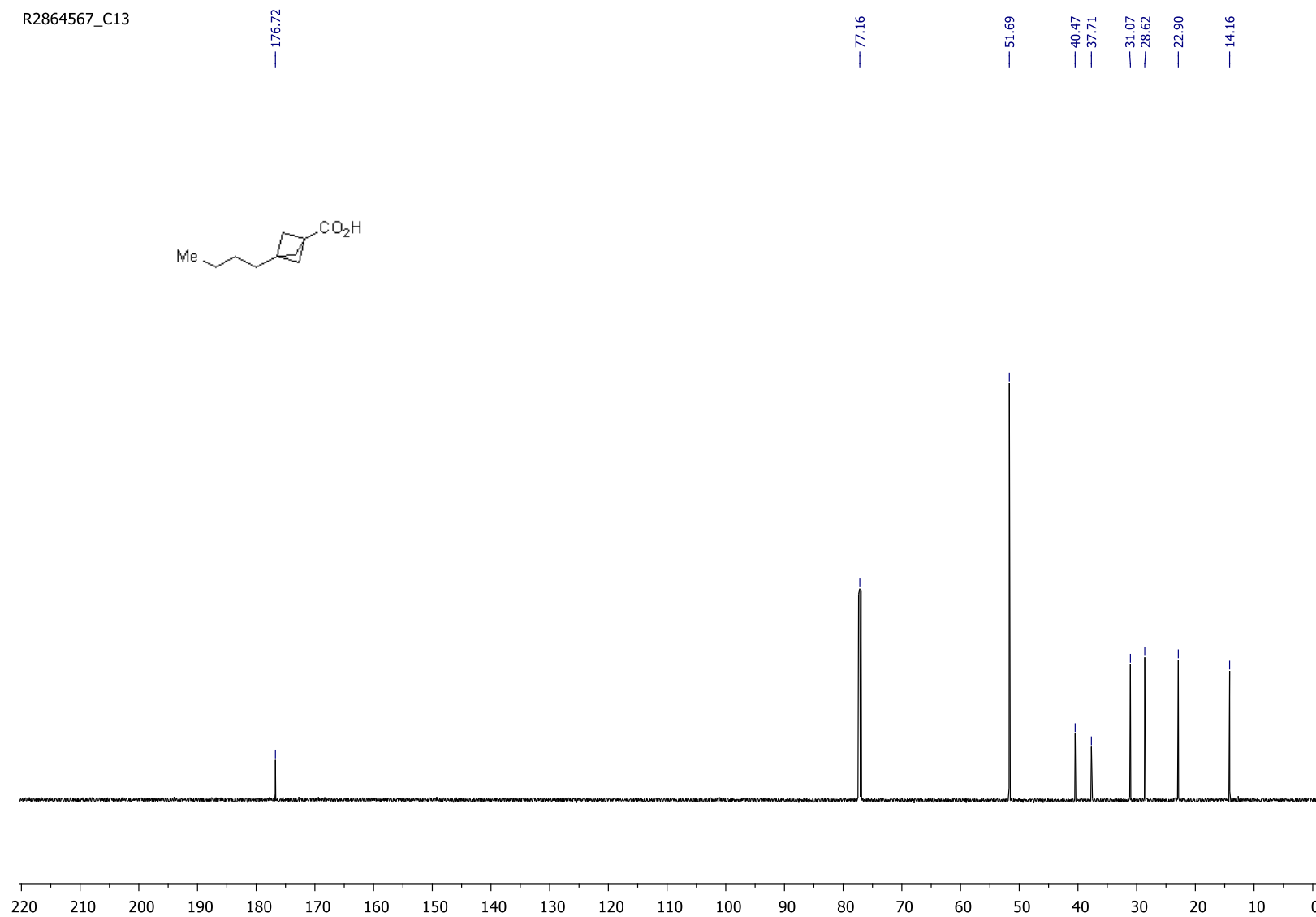


Compound 4k



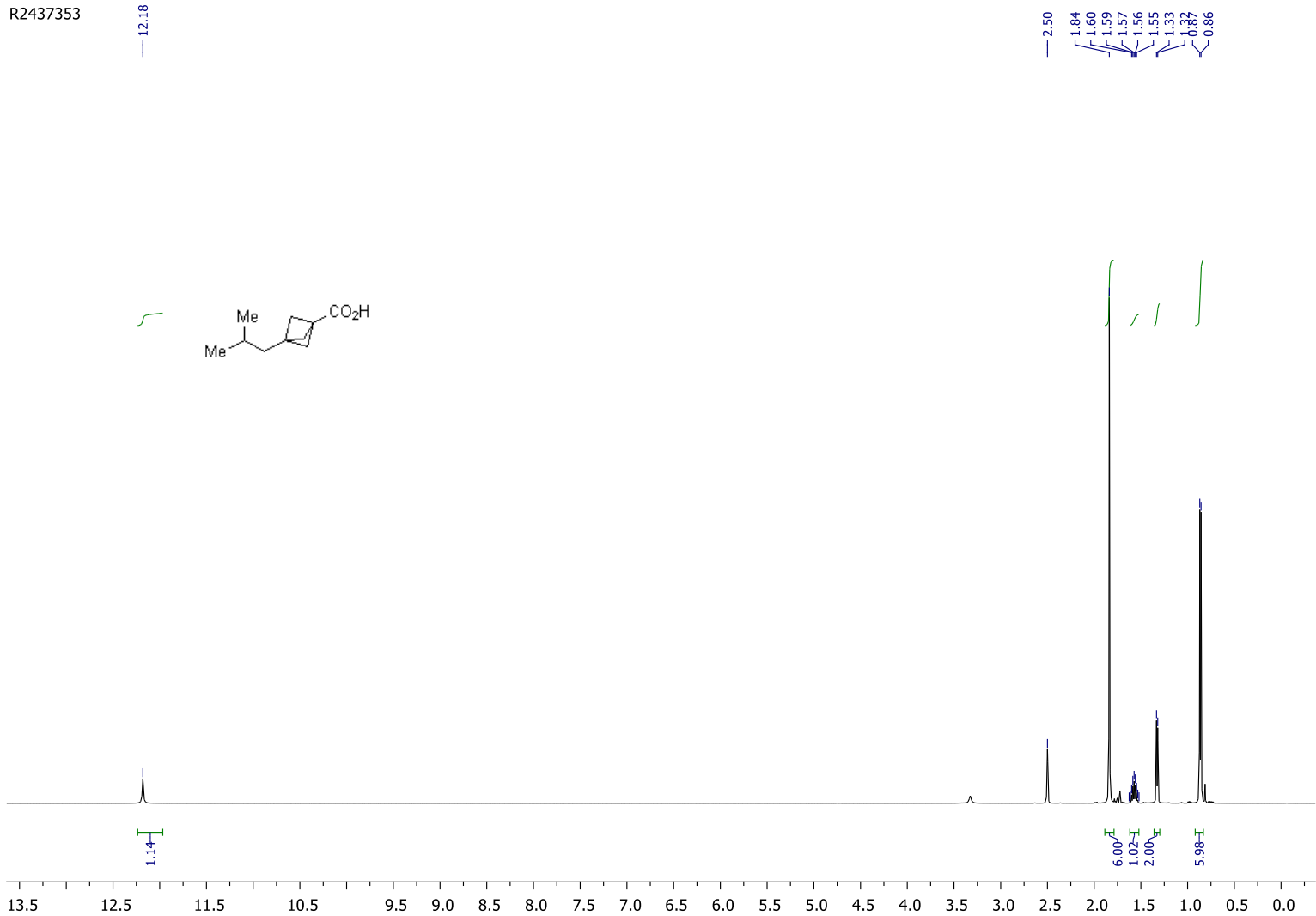
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

R2864567_C13



Compound 5k

¹H NMR (500 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2437353_C1:

— 171.01

— 51.78

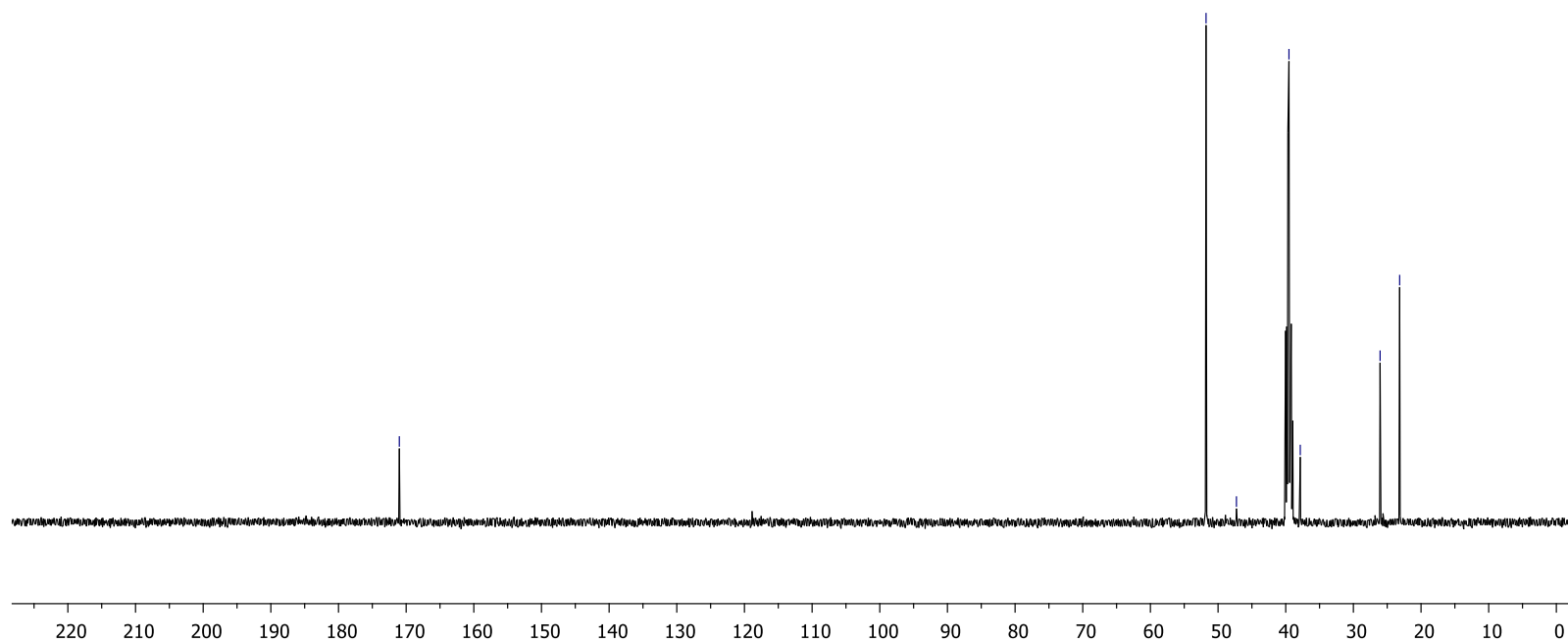
— 47.28

— 39.52

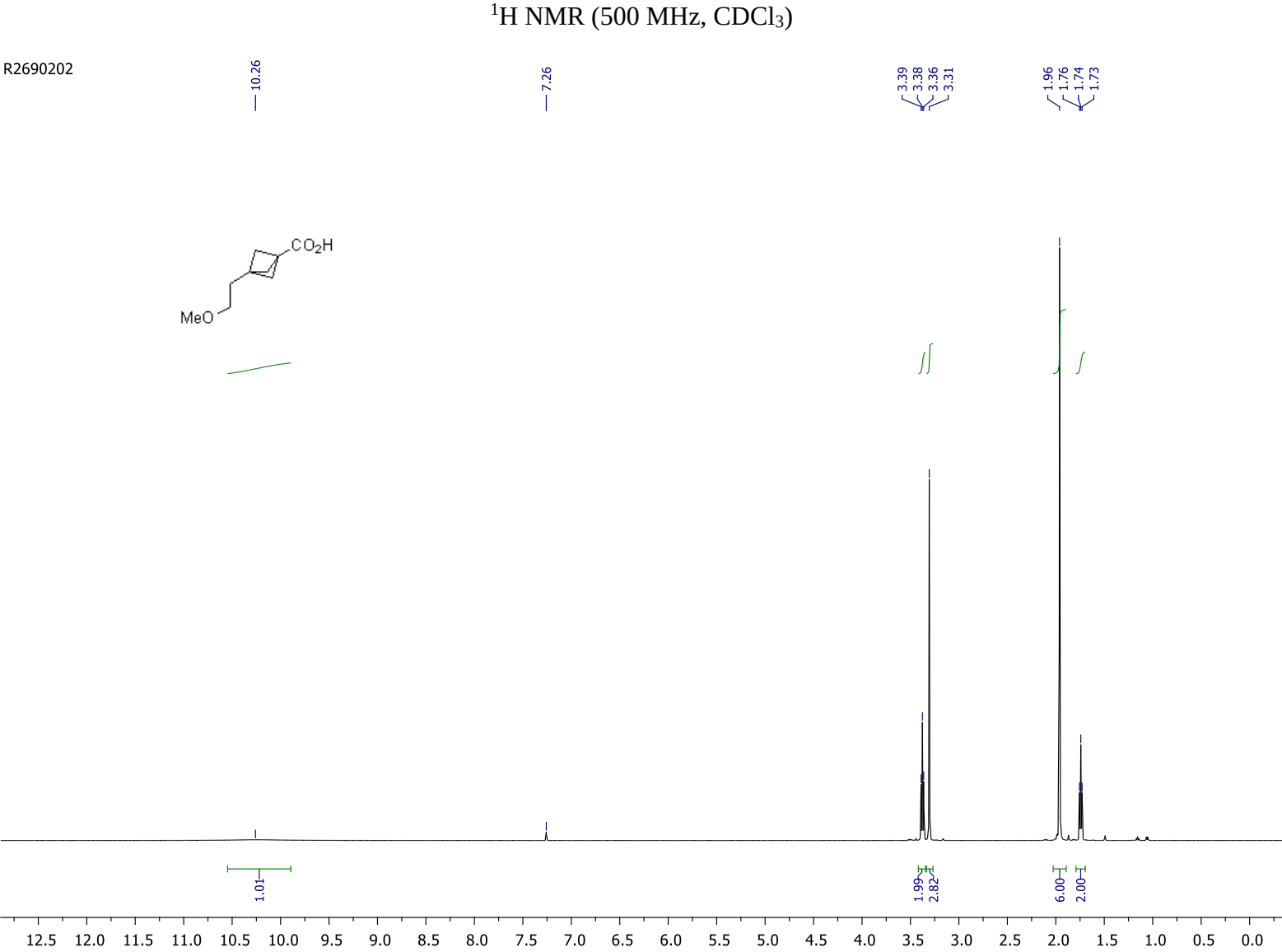
— 37.85

— 26.05

— 23.16

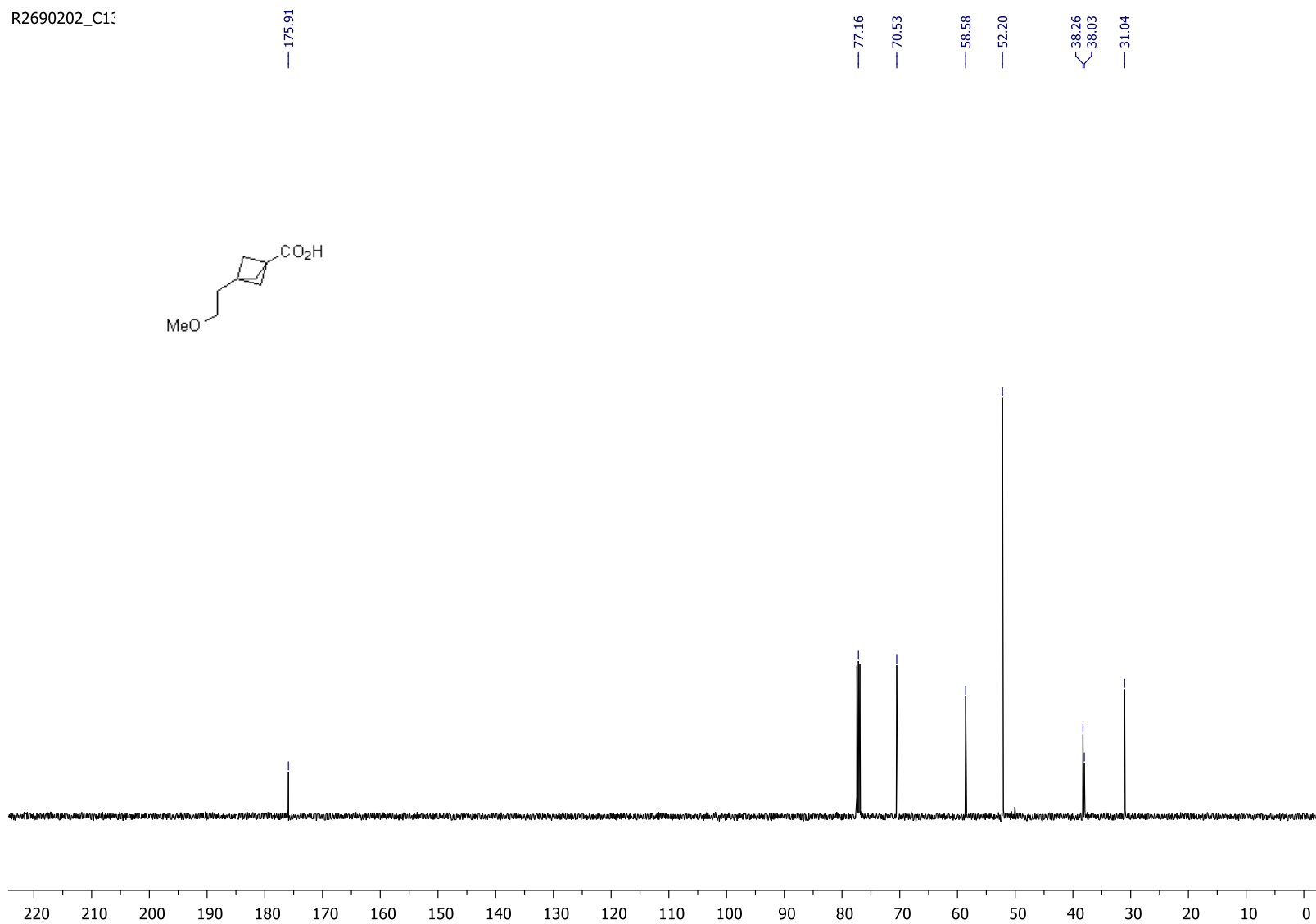
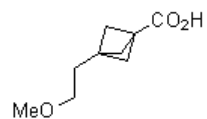


Compound 7k



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

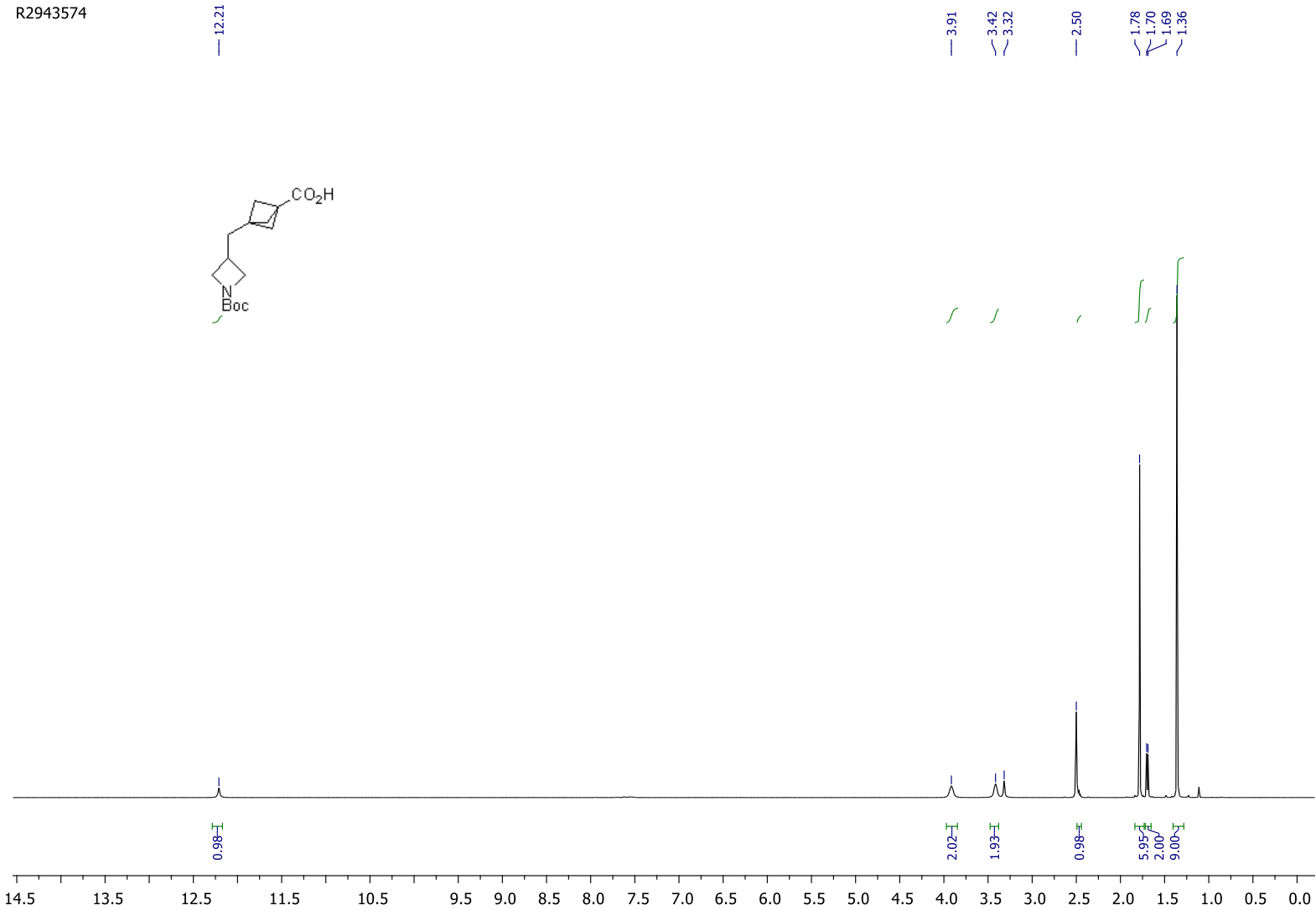
R2690202_C1:



Compound 14k

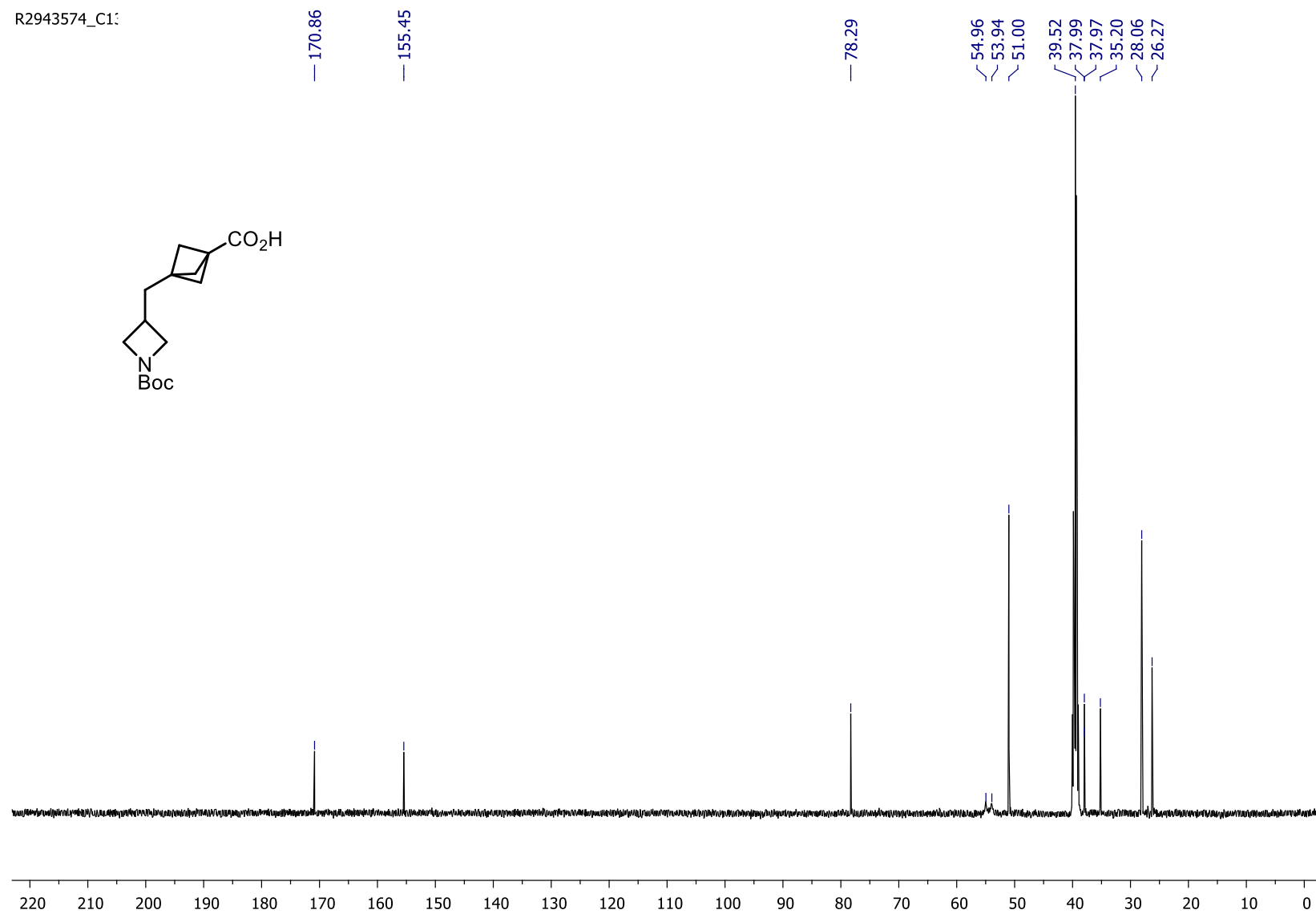
¹H NMR (500 MHz, DMSO-d₆)

R2943574



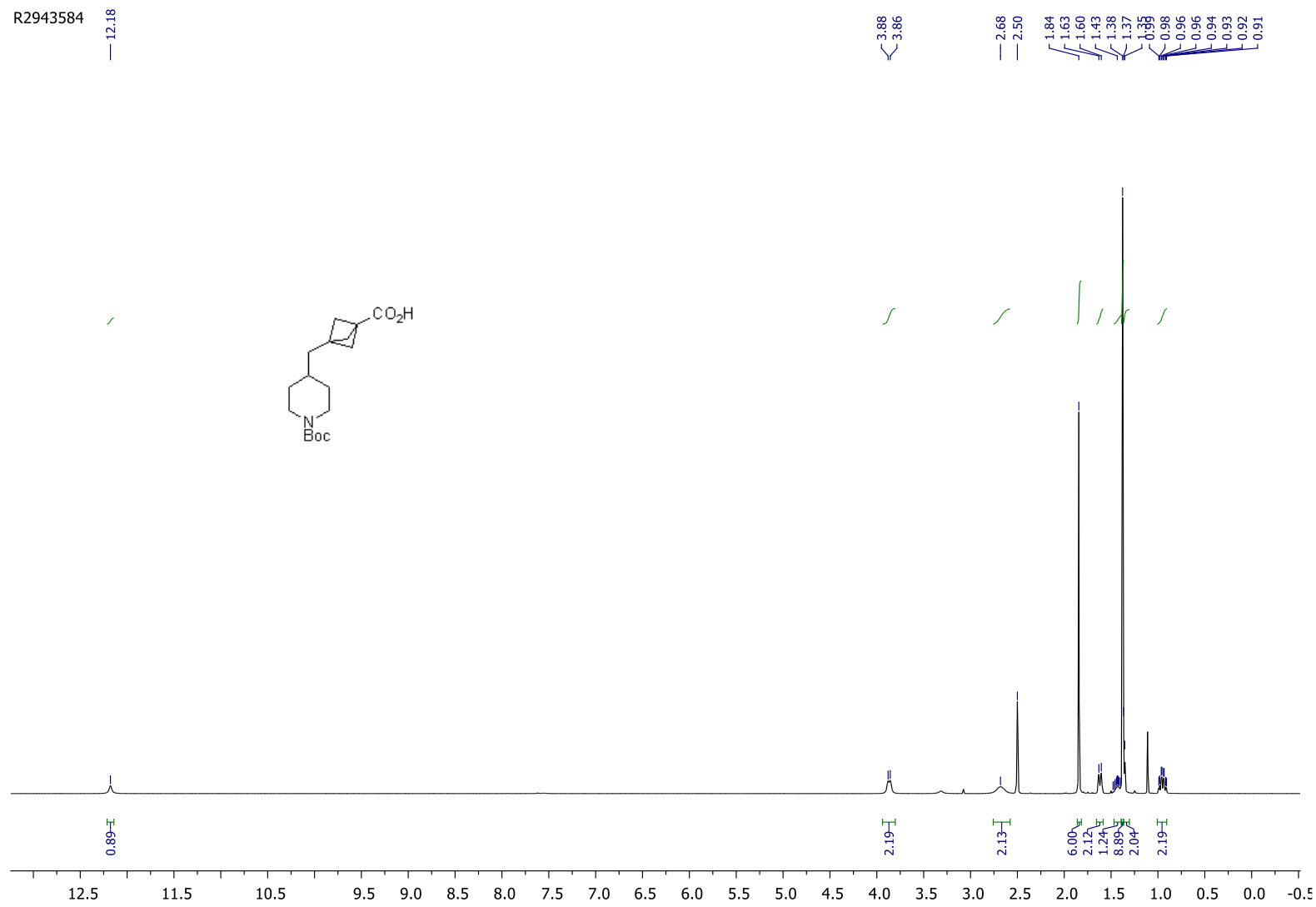
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

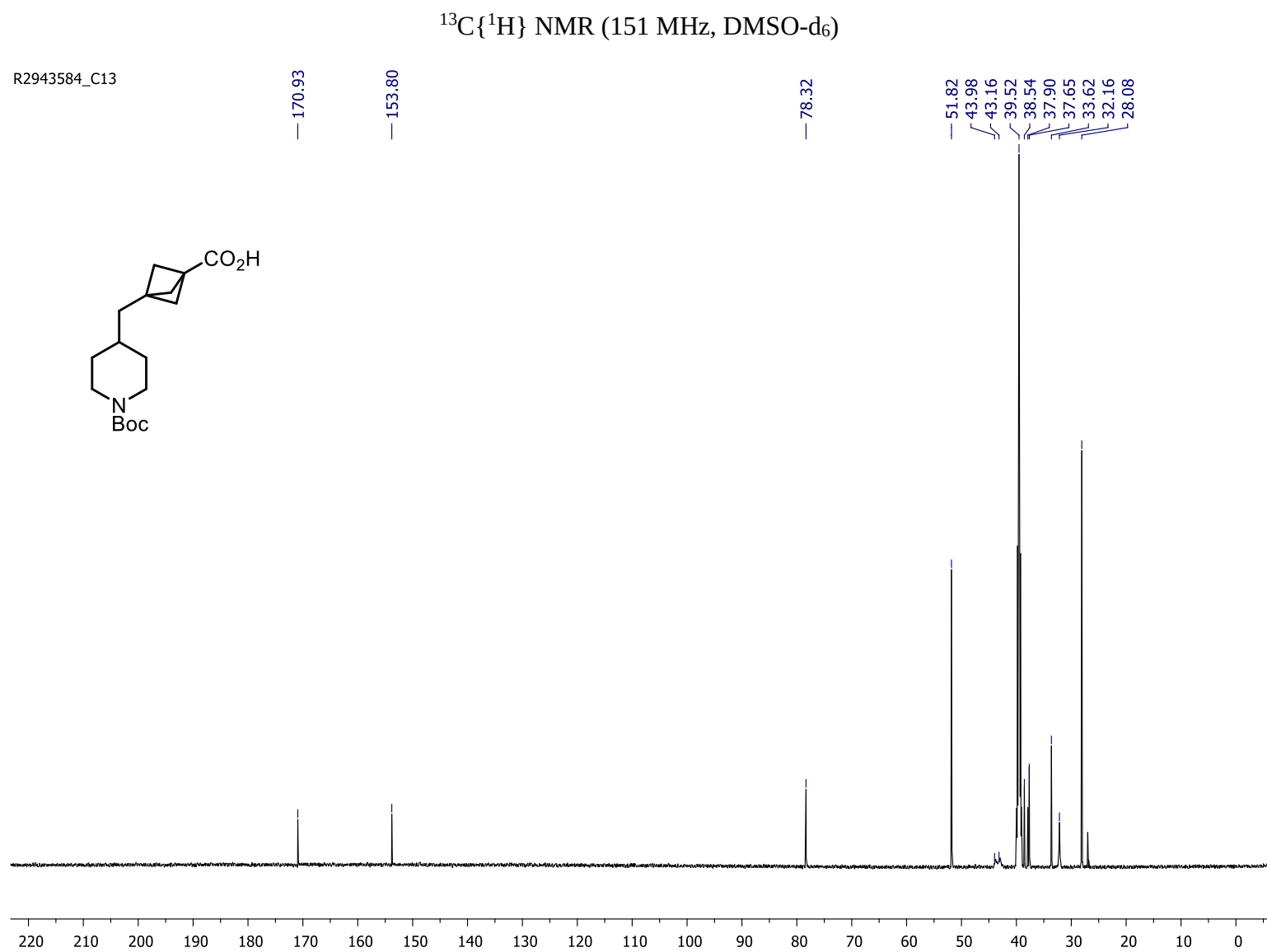
R2943574_C1:



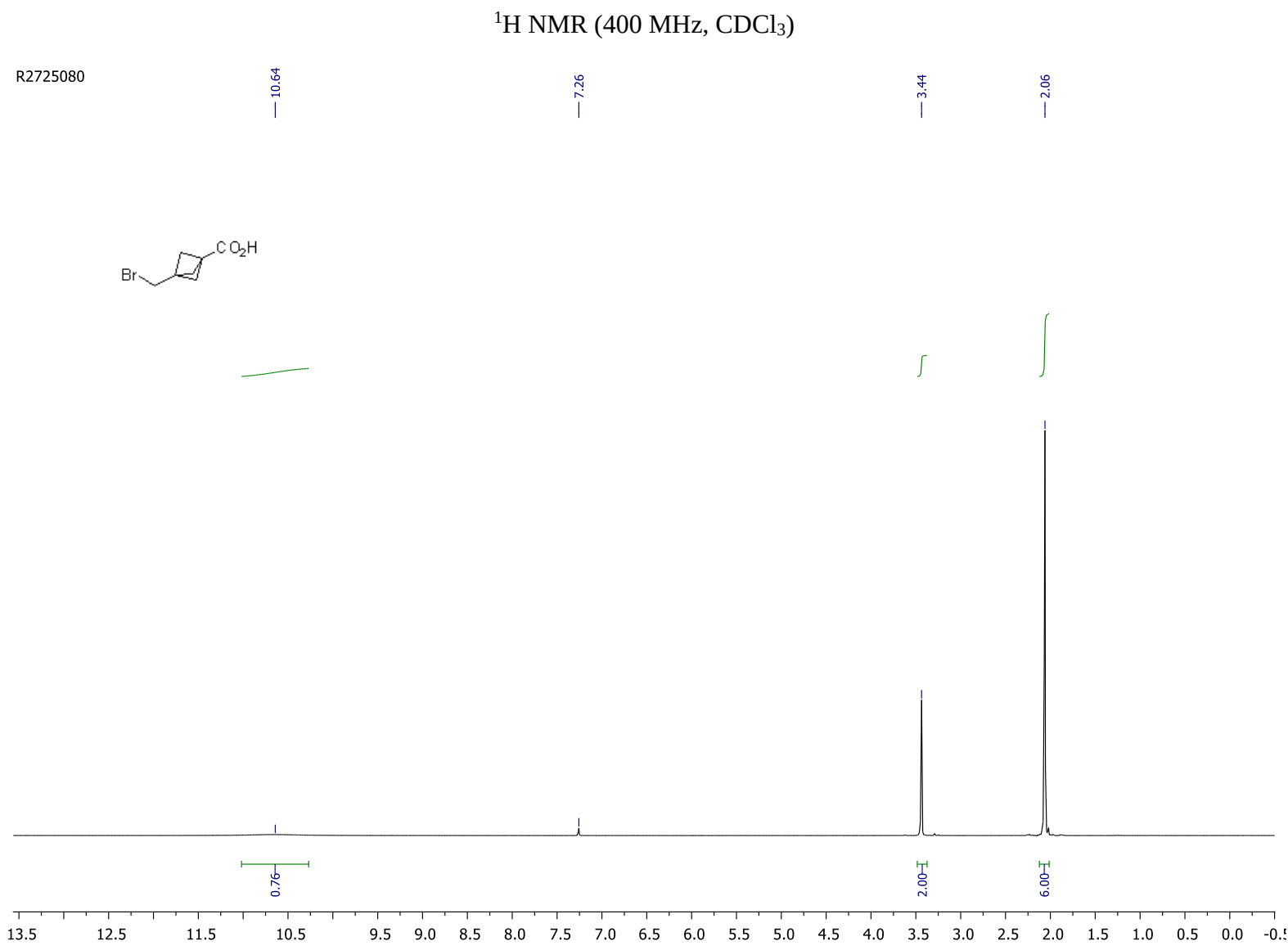
Compound 16k

¹H NMR (500 MHz, DMSO-d₆)



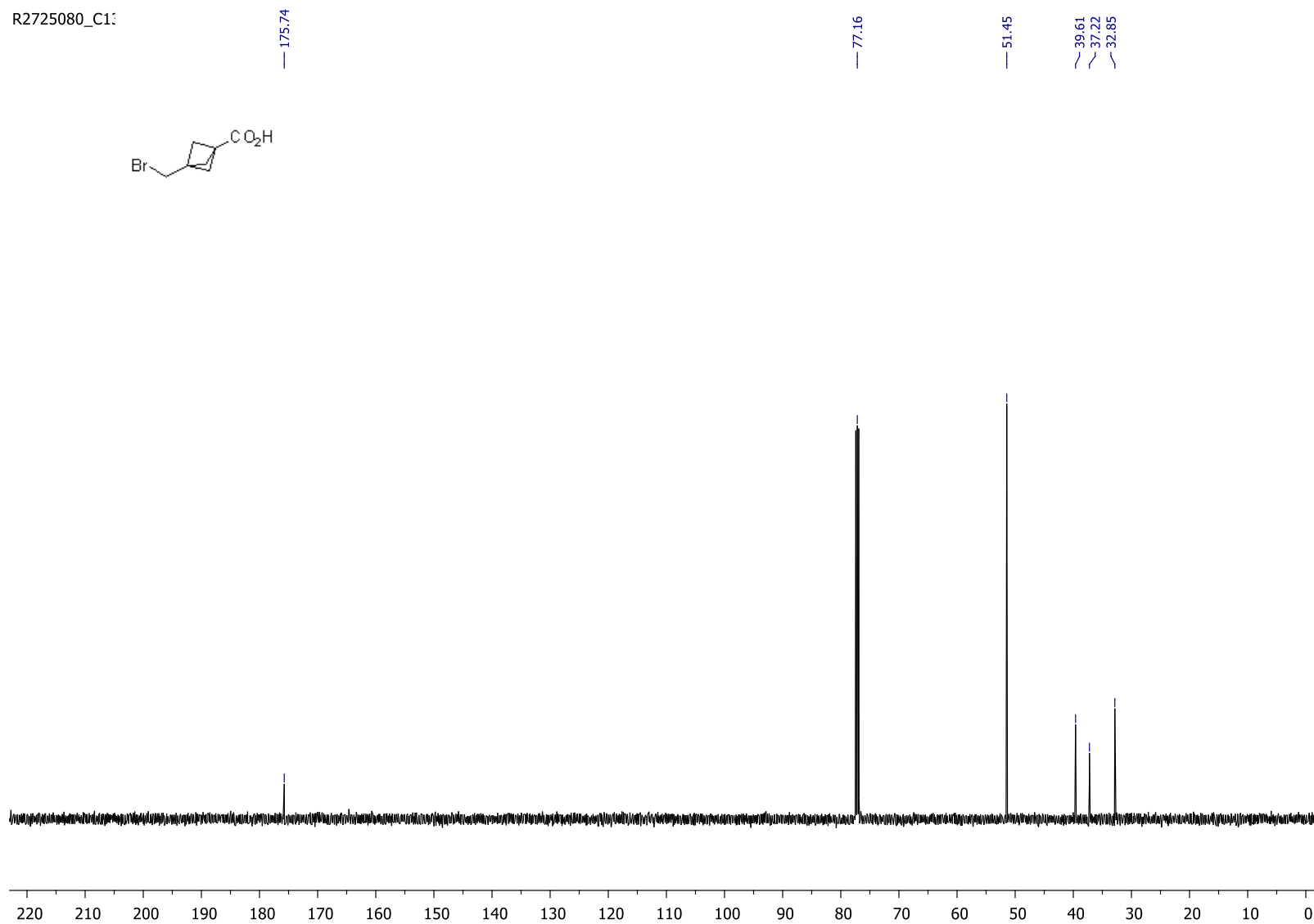


Compound 35k

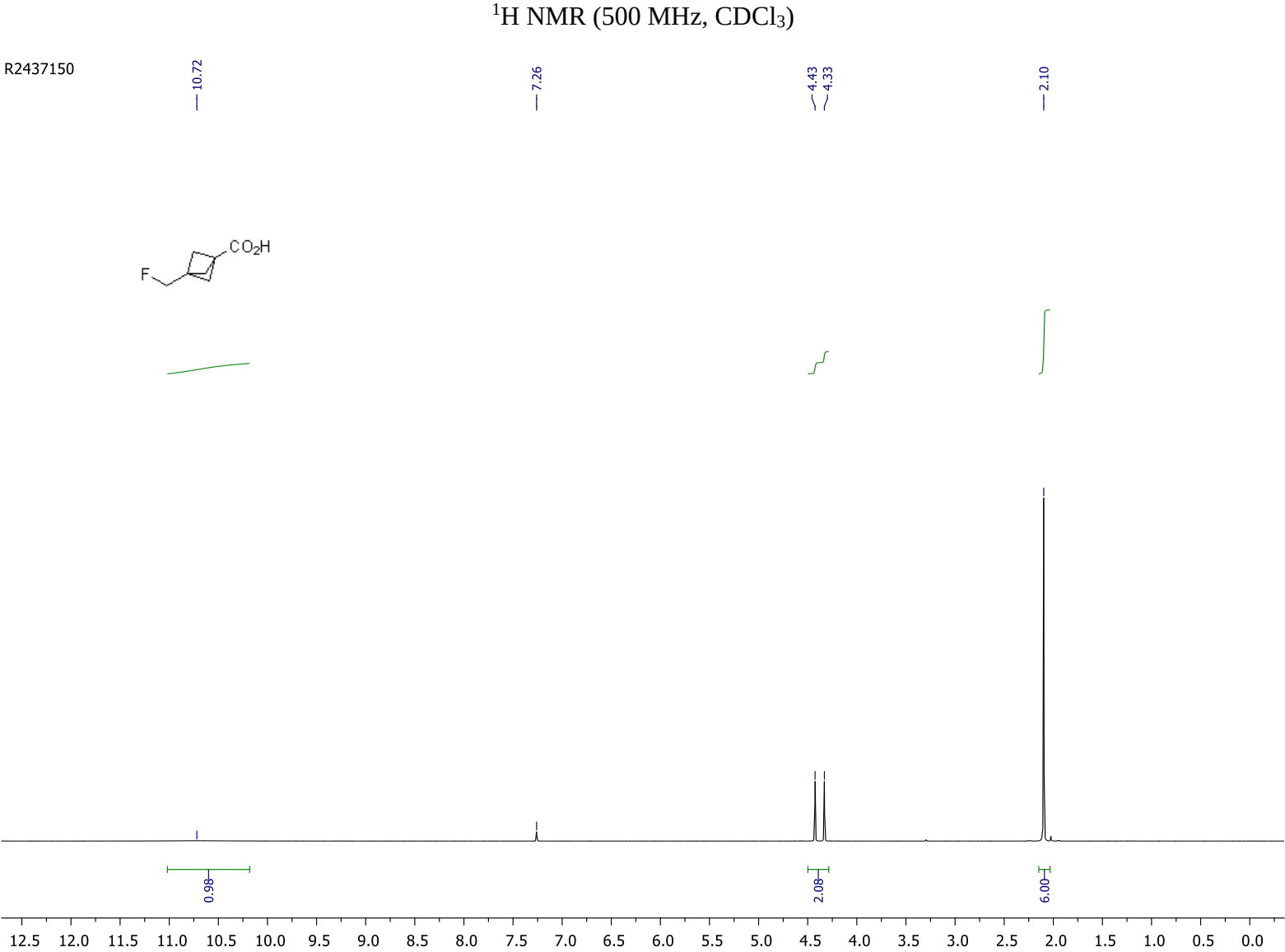


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2725080_C1:

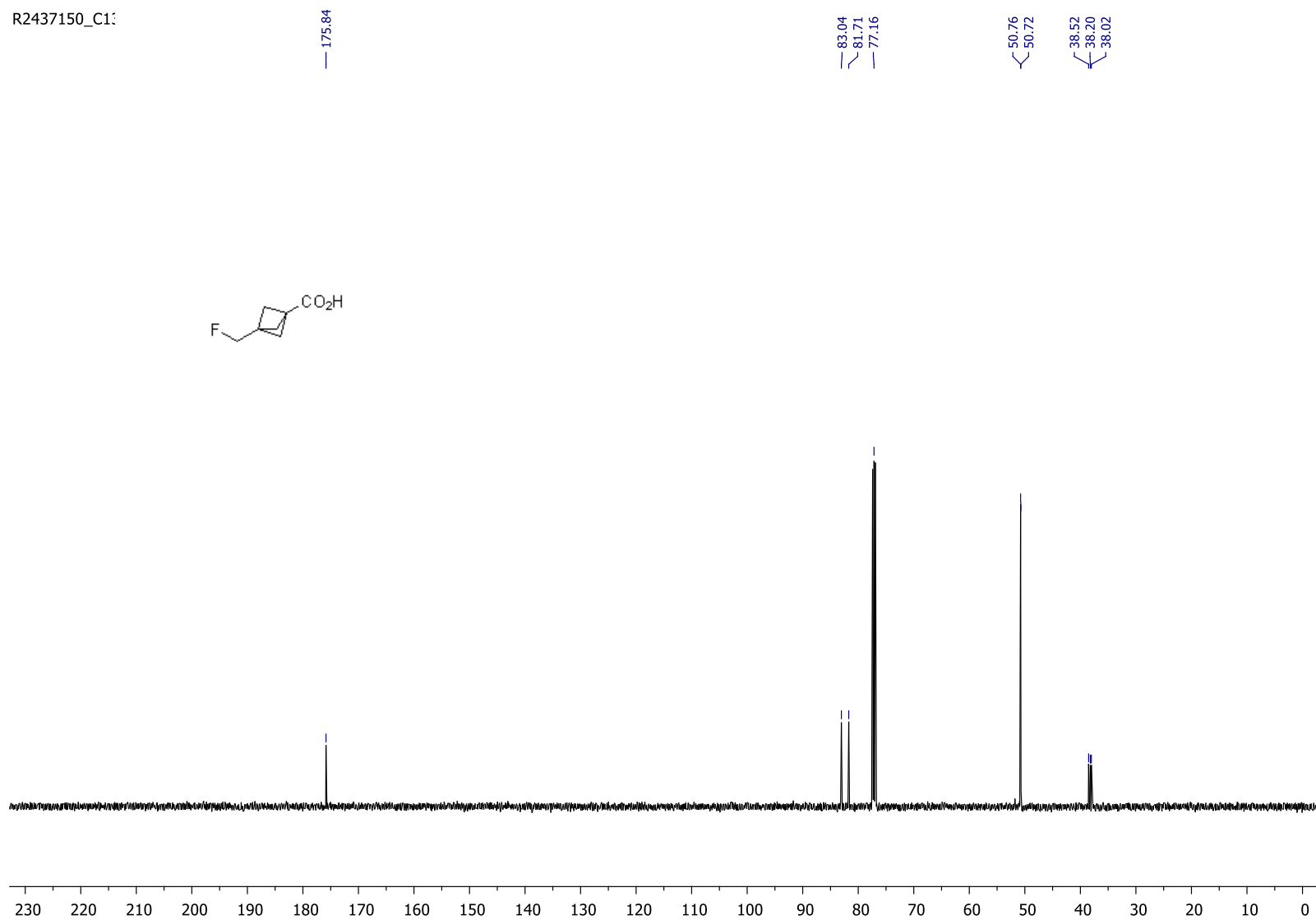


Compound 21k



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2437150_C13

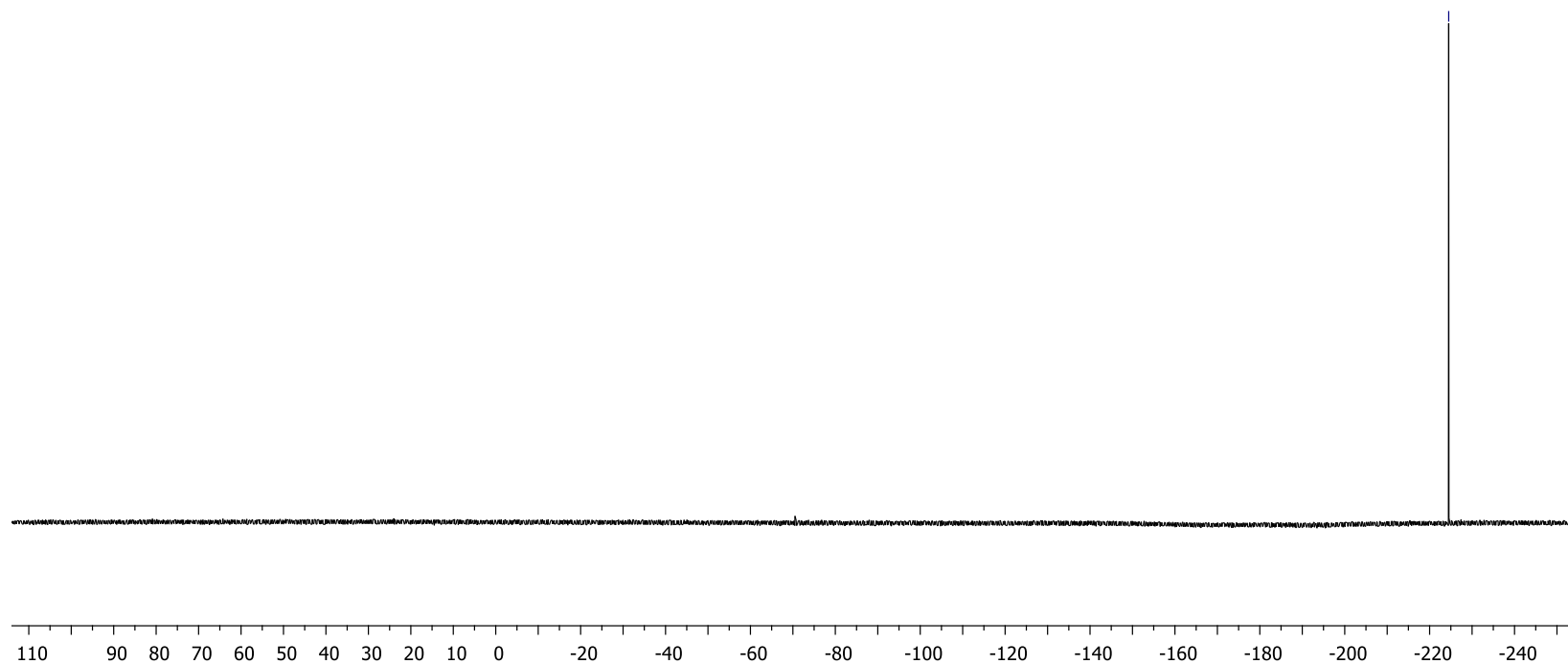


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

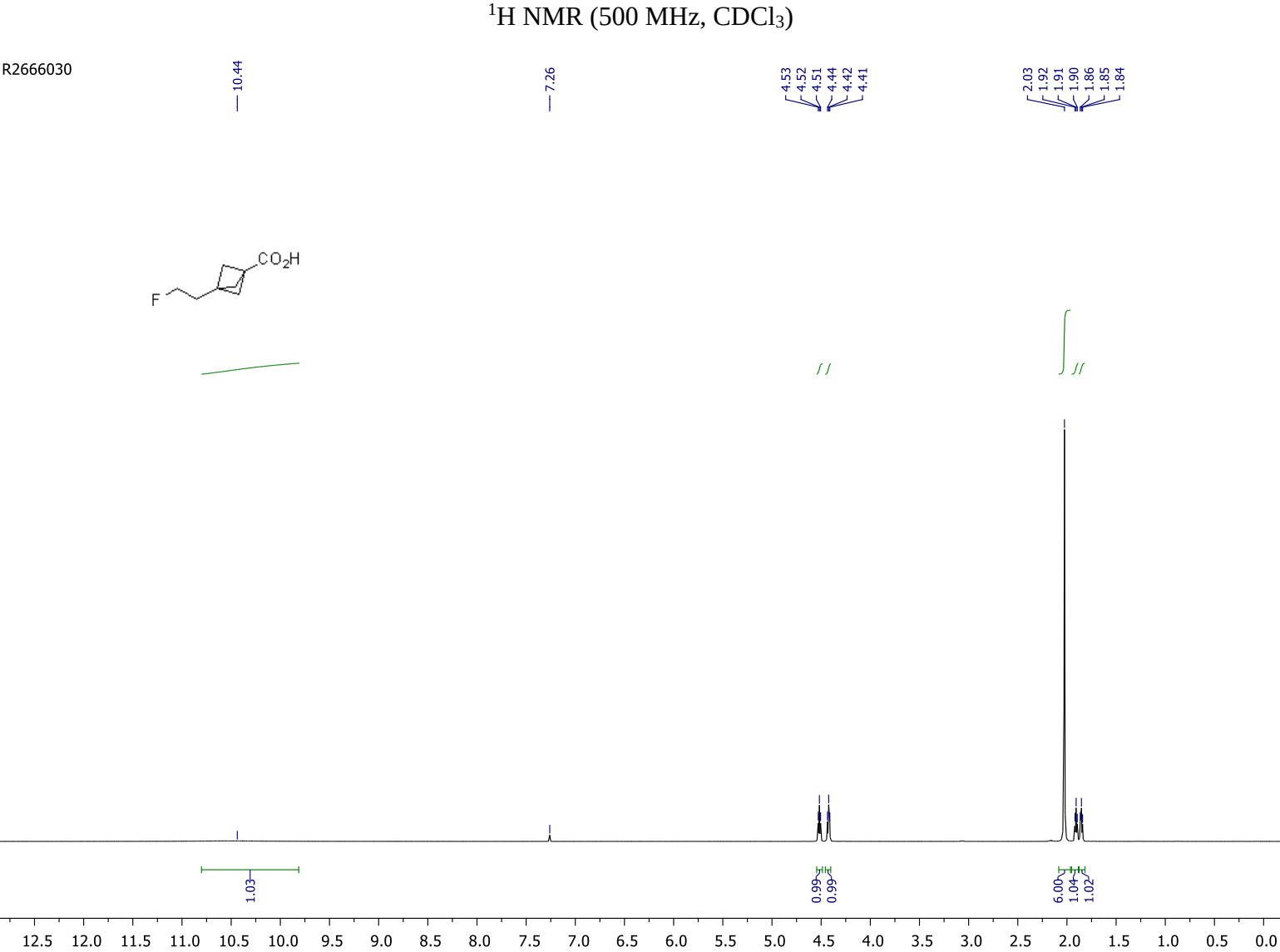
R2437150_F19{H}



— -224.50

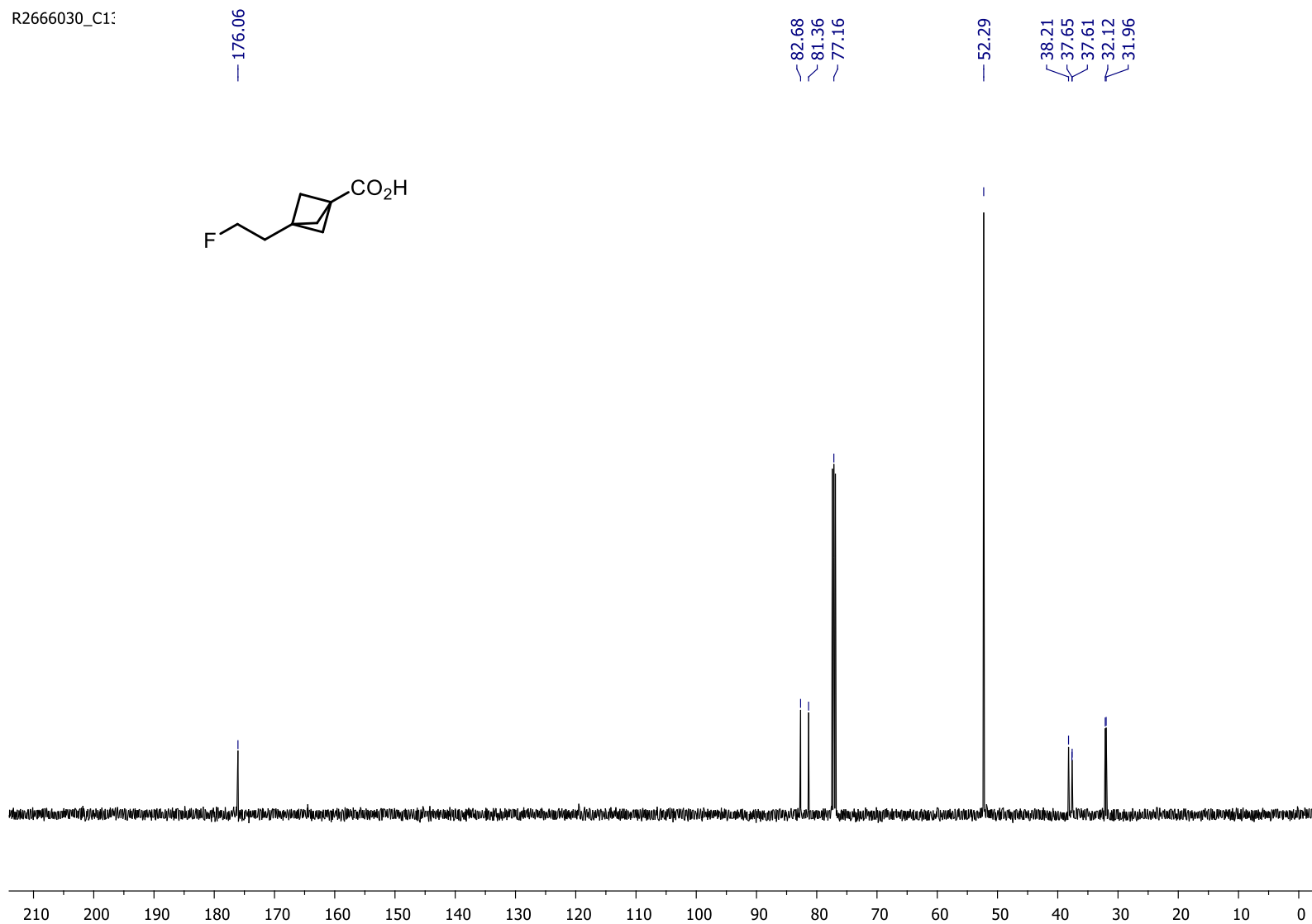


Compound 22k



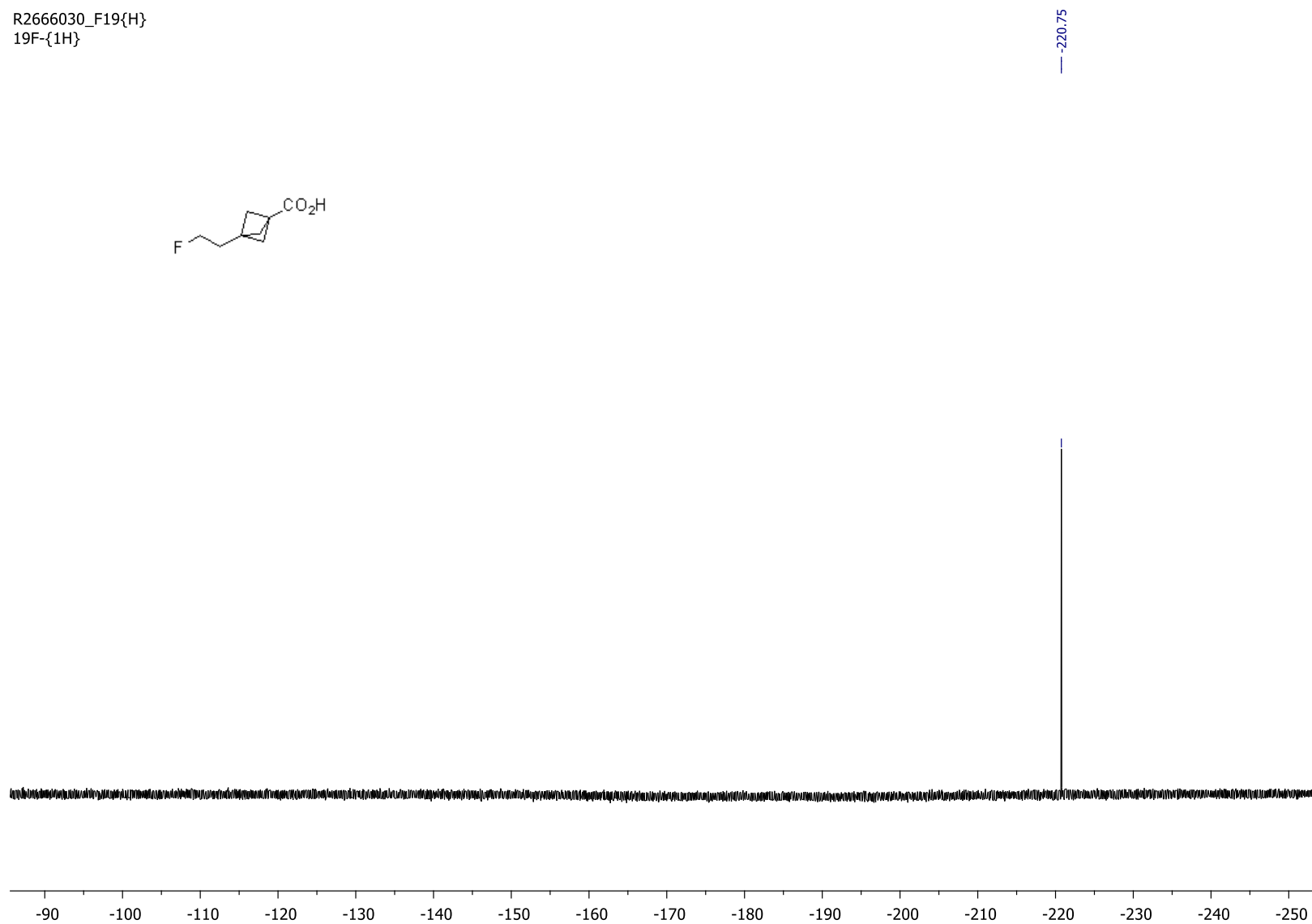
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2666030_C13

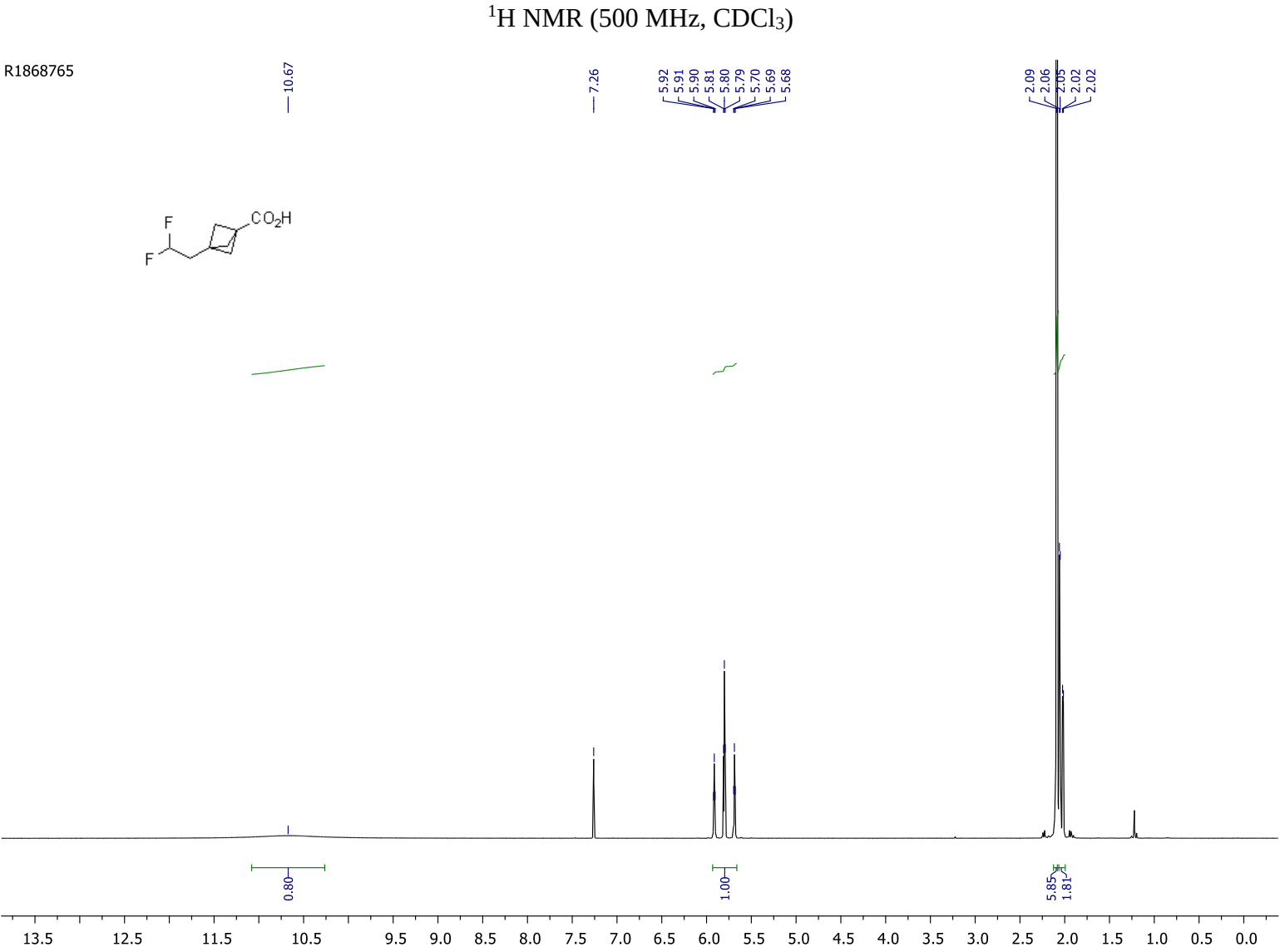


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2666030_F19{H}
19F-{1H}

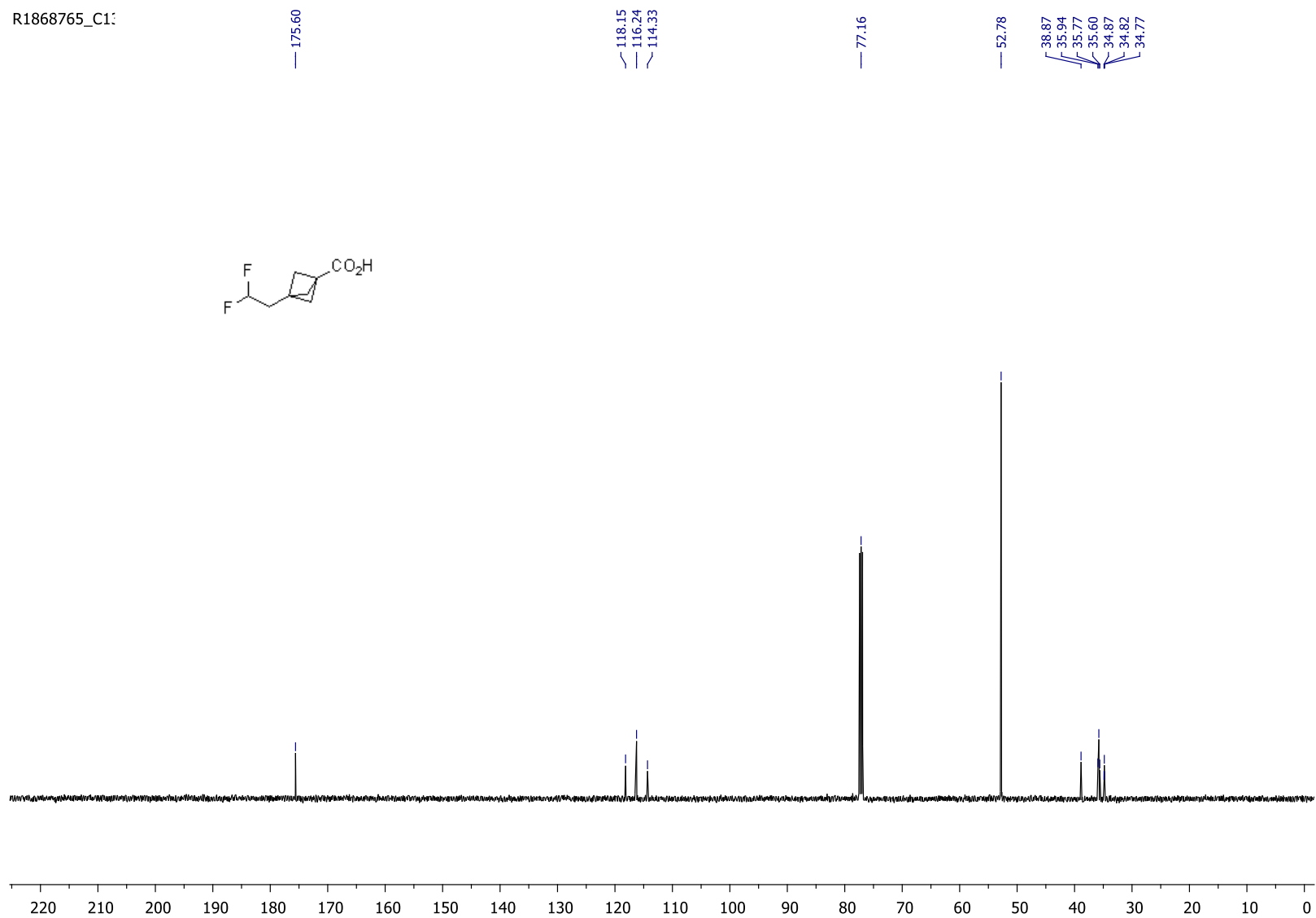


Compound 24k



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R1868765_C1:

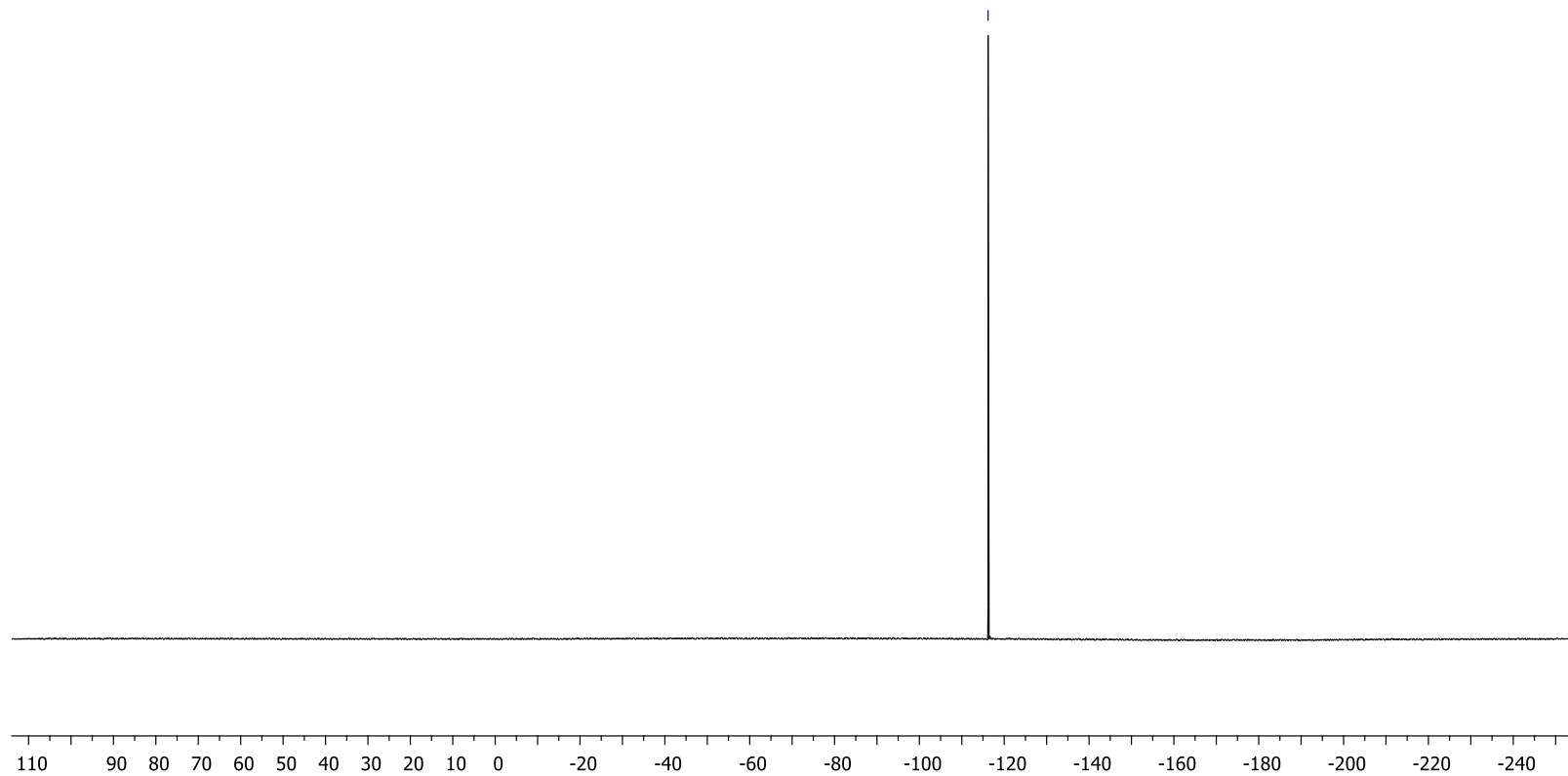


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

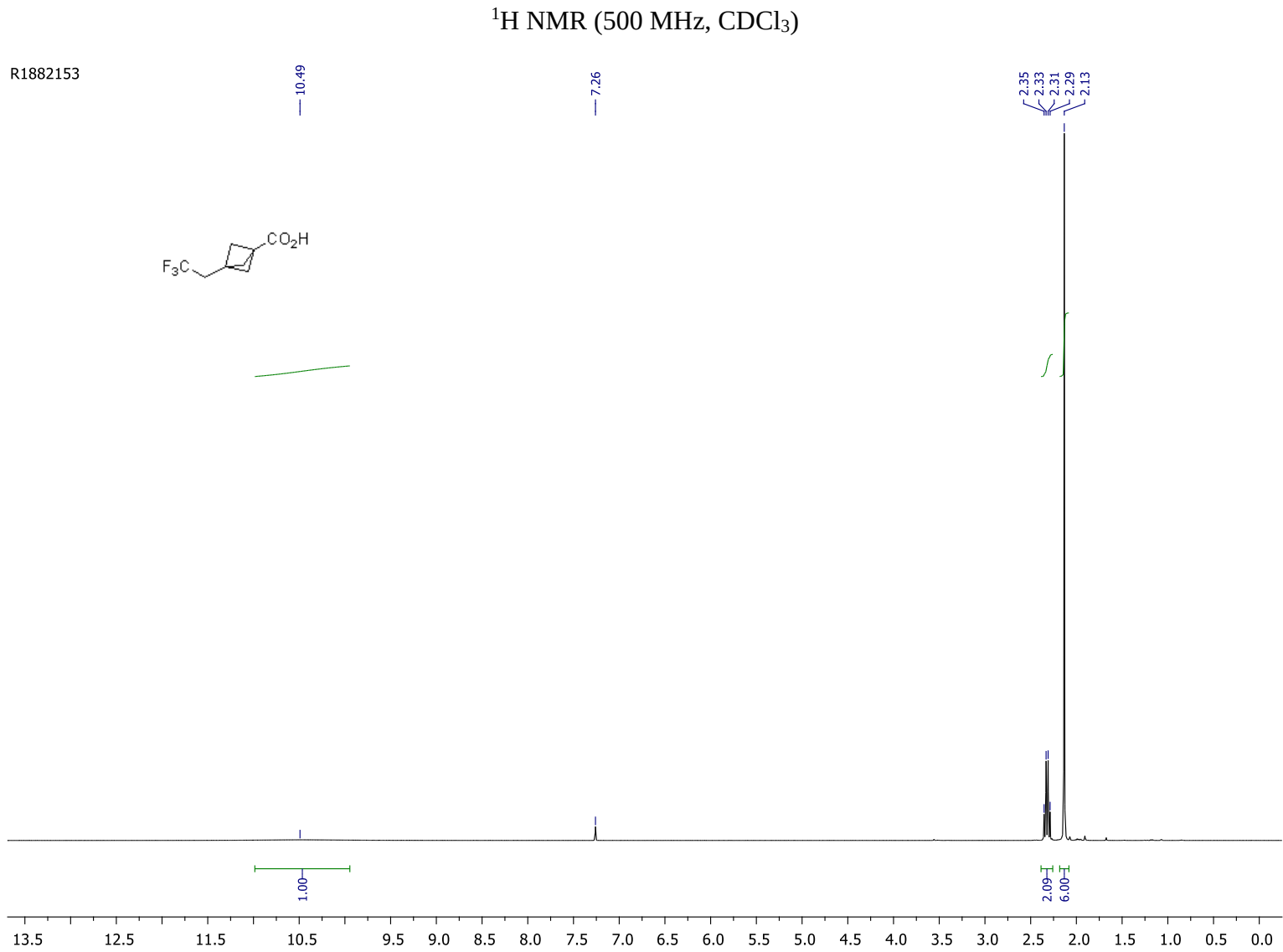
R1868765_F19{H}
19F-{1H}



— -116.20

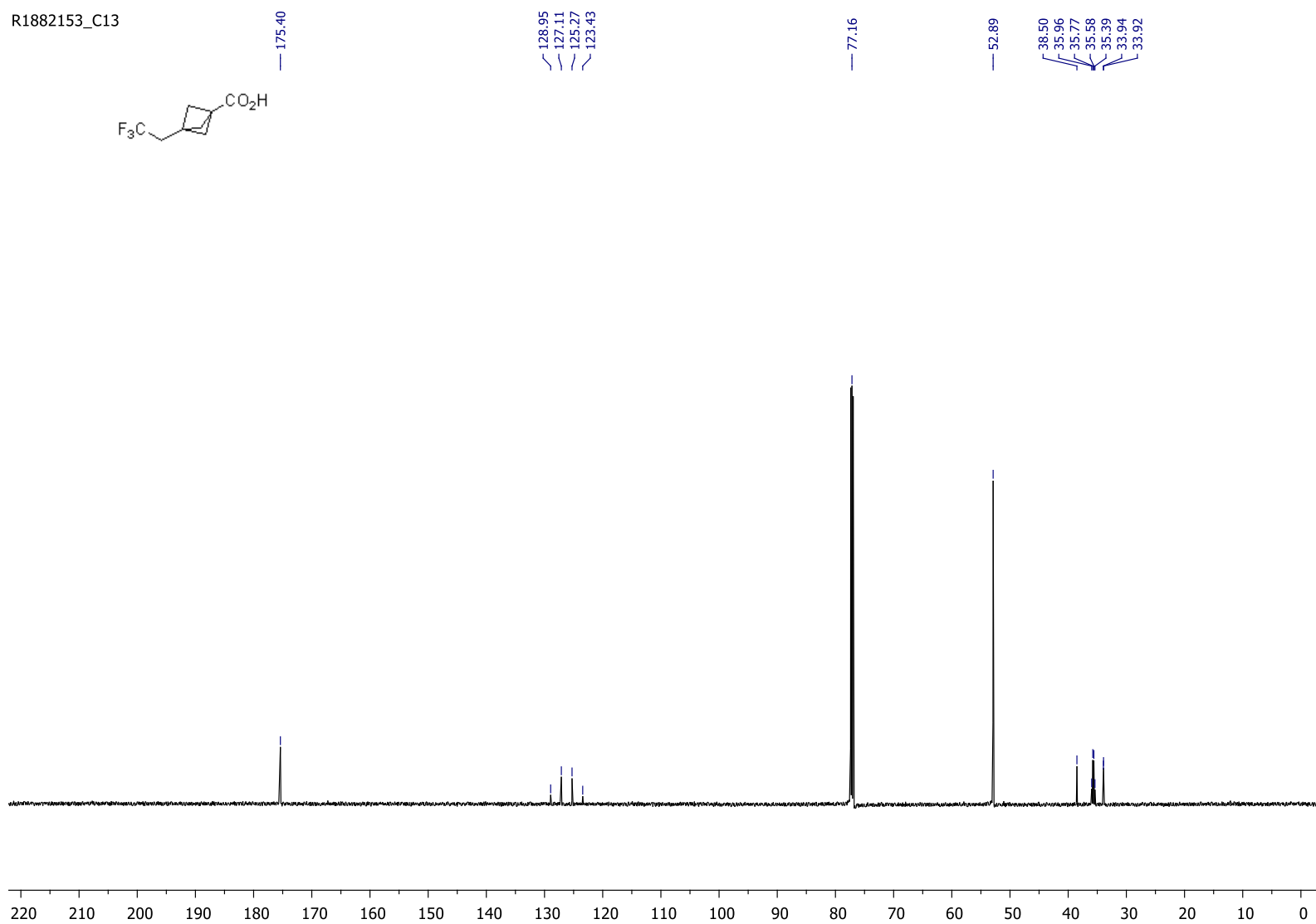


Compound 25k



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

R1882153_C13

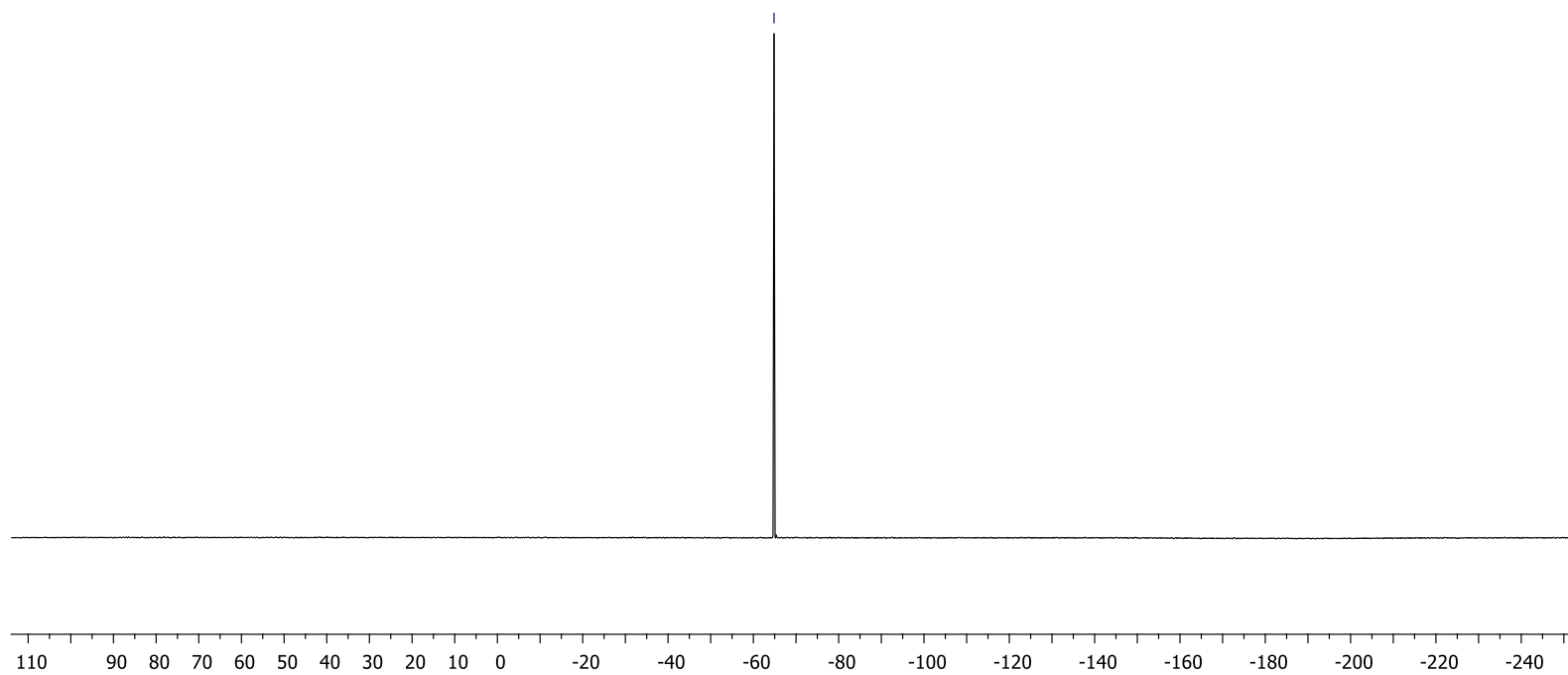


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R1882153_F19{H}
19F-{1H}

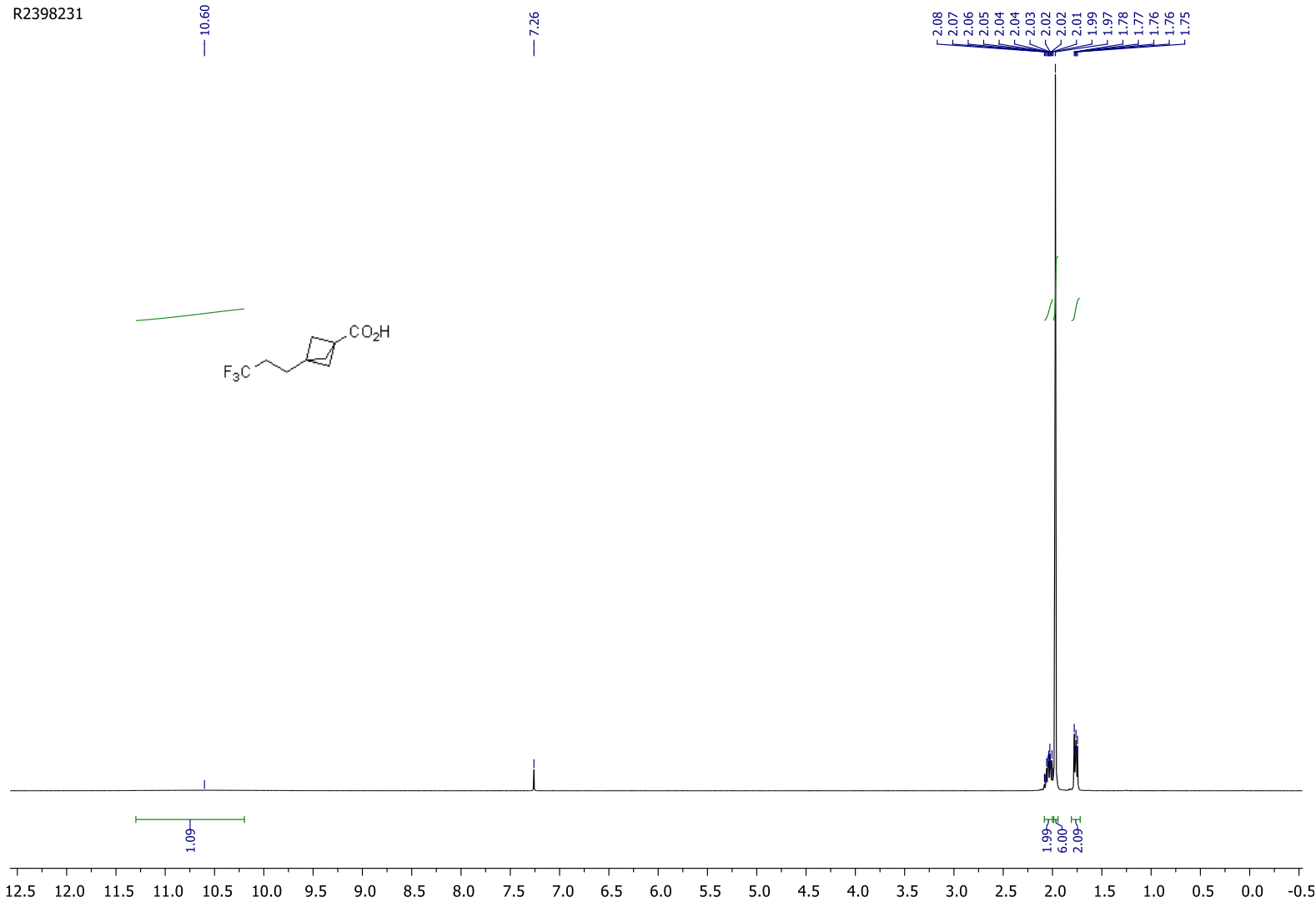


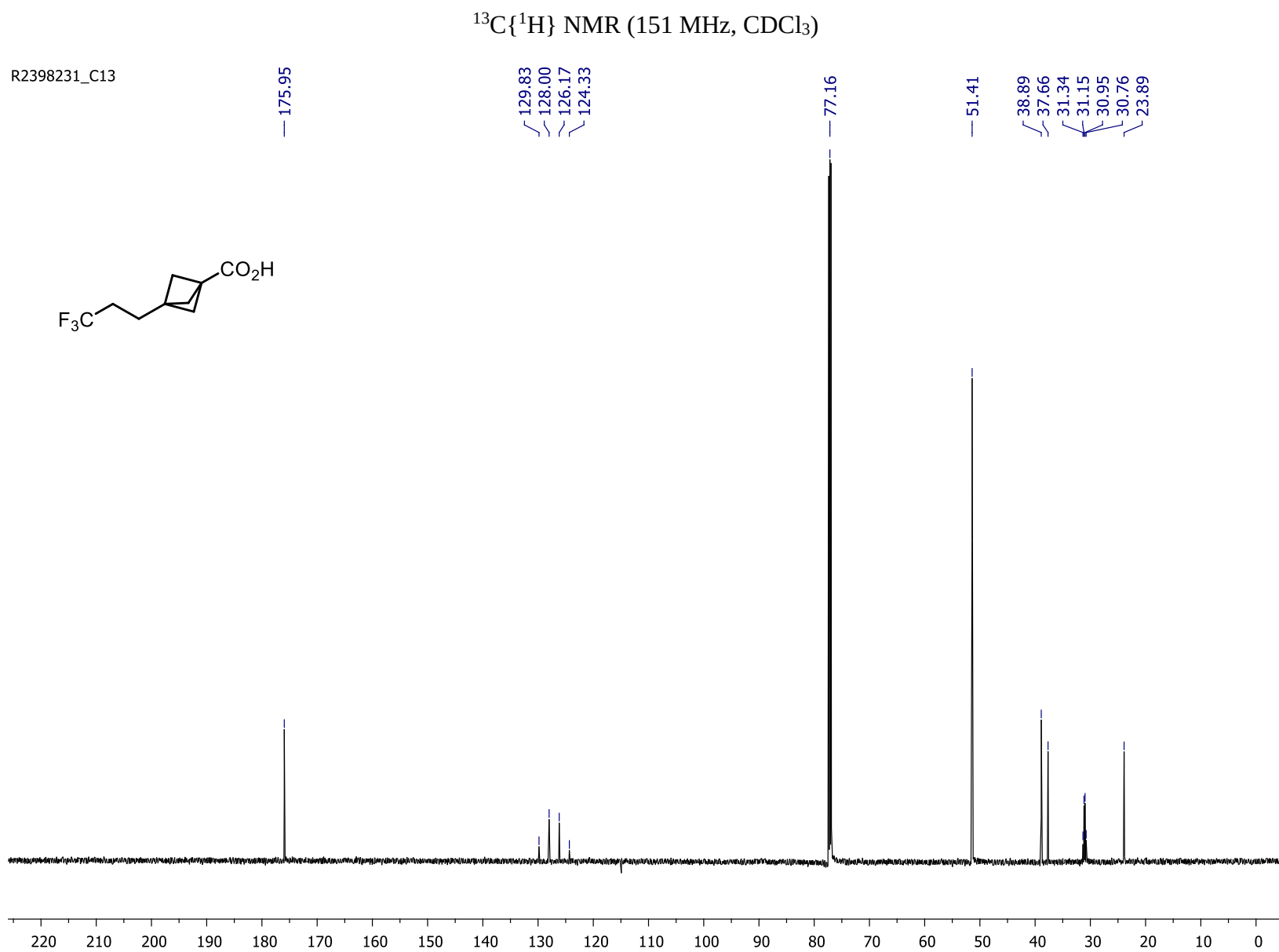
— -64.85



Compound 26k

¹H NMR (500 MHz, CDCl₃)



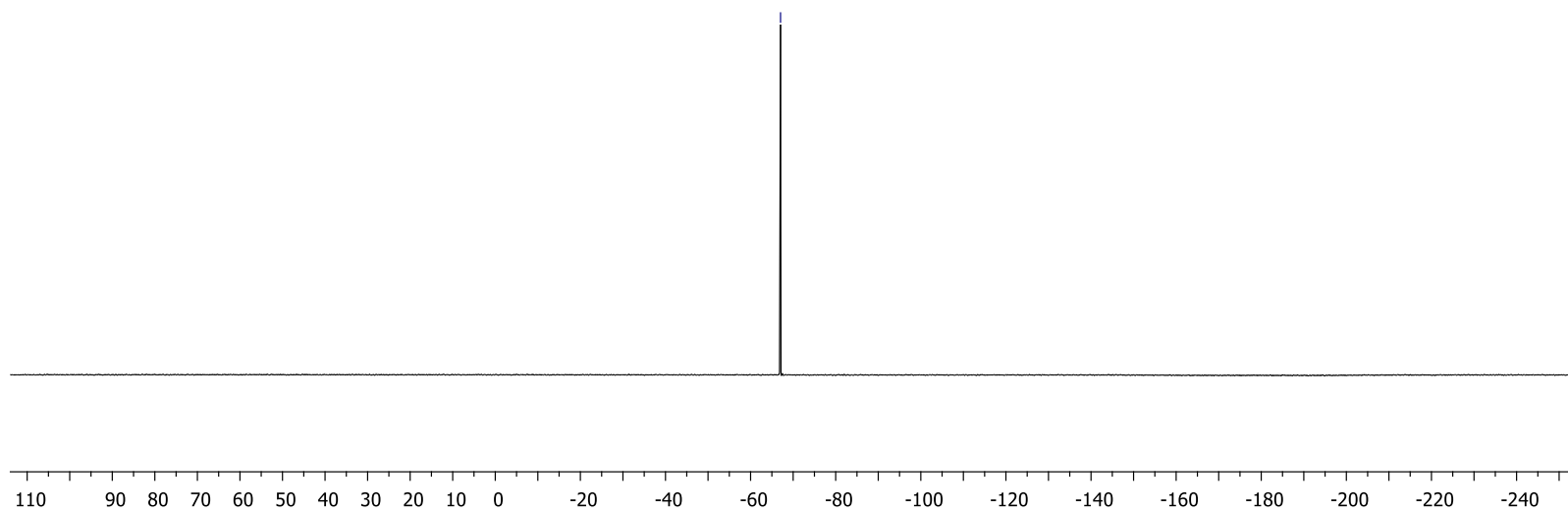


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R2398231_F19{H}
19F-{1H}



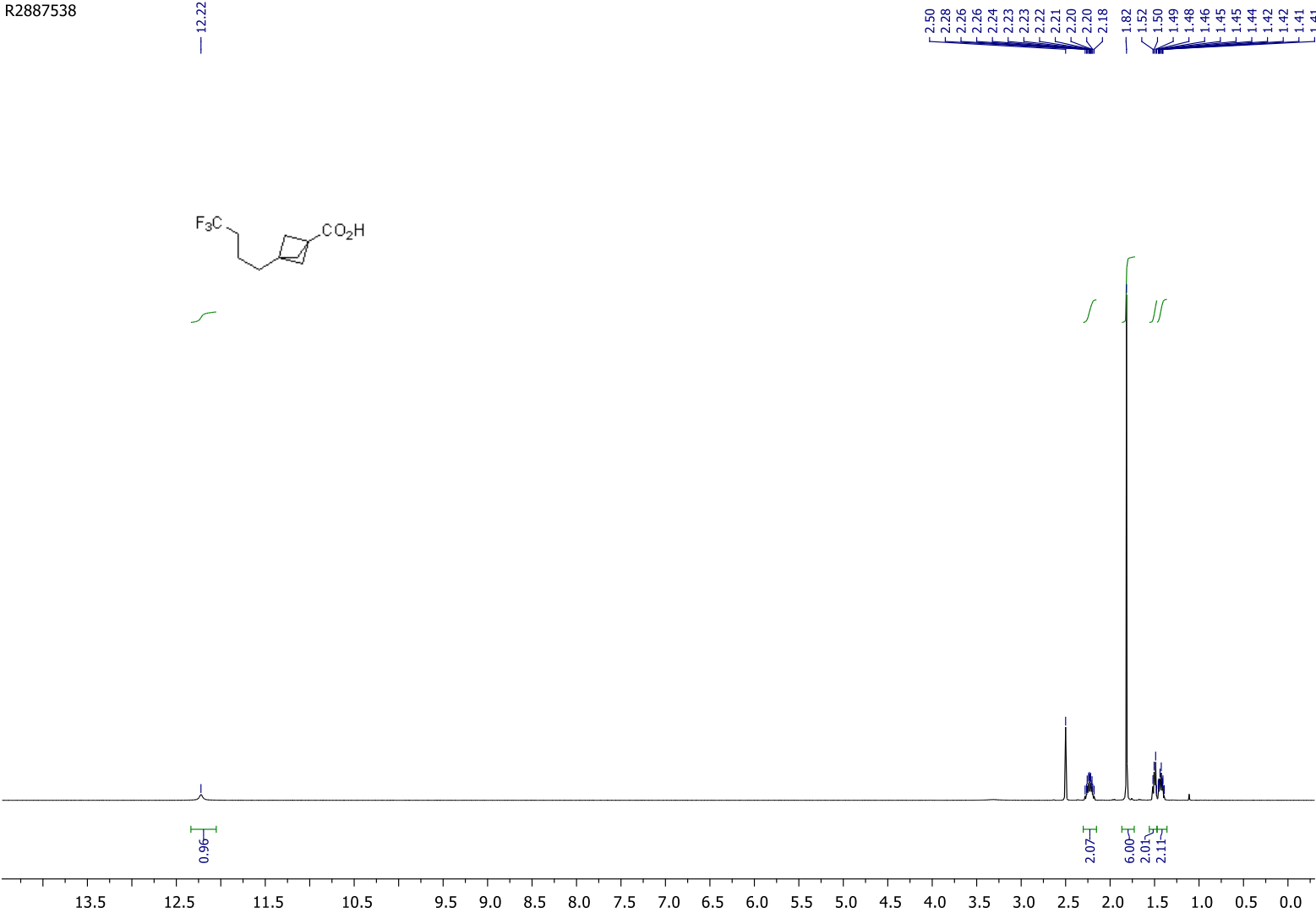
-67.04



Compound 27k

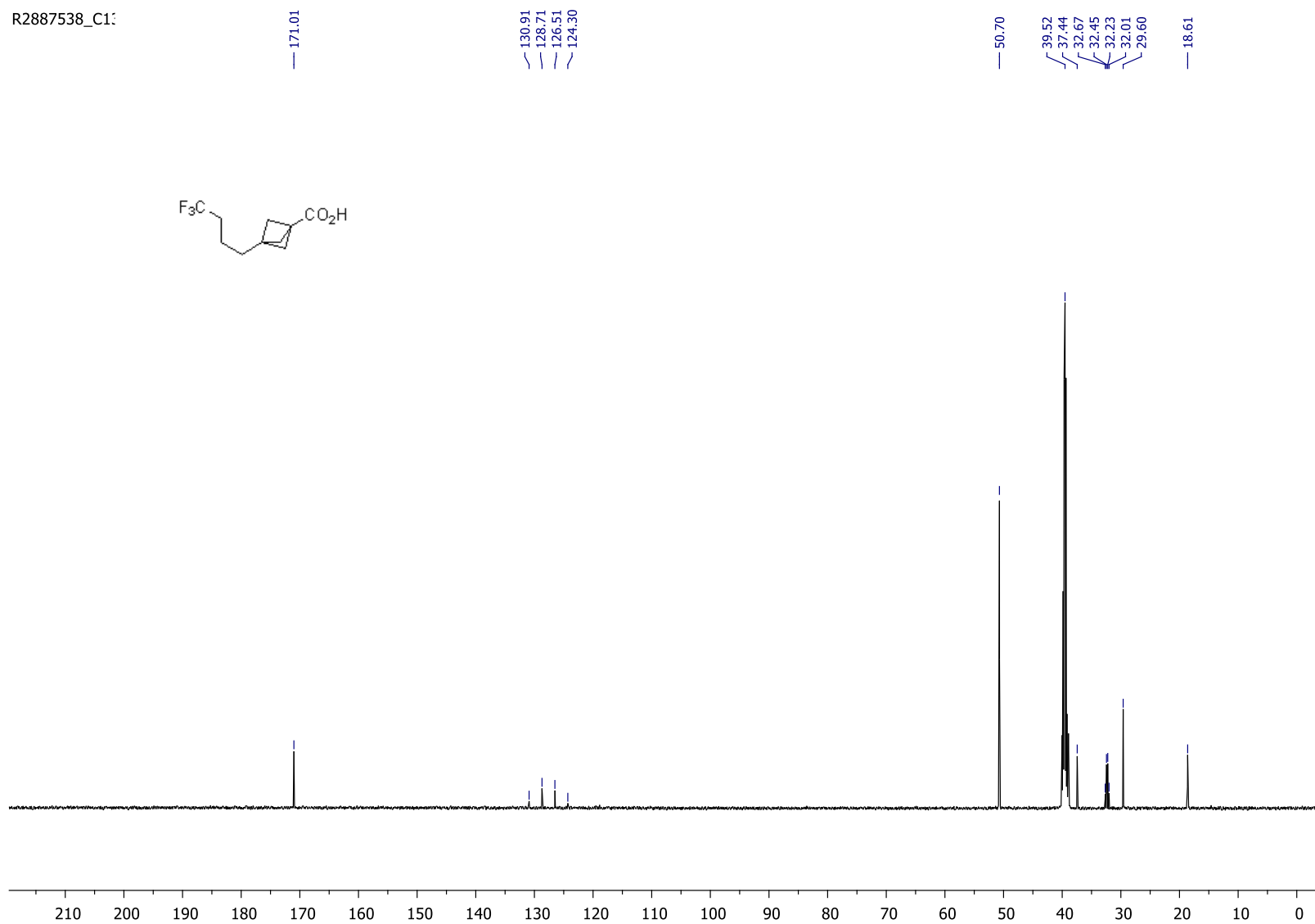
¹H NMR (500 MHz, DMSO-d₆)

R2887538



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

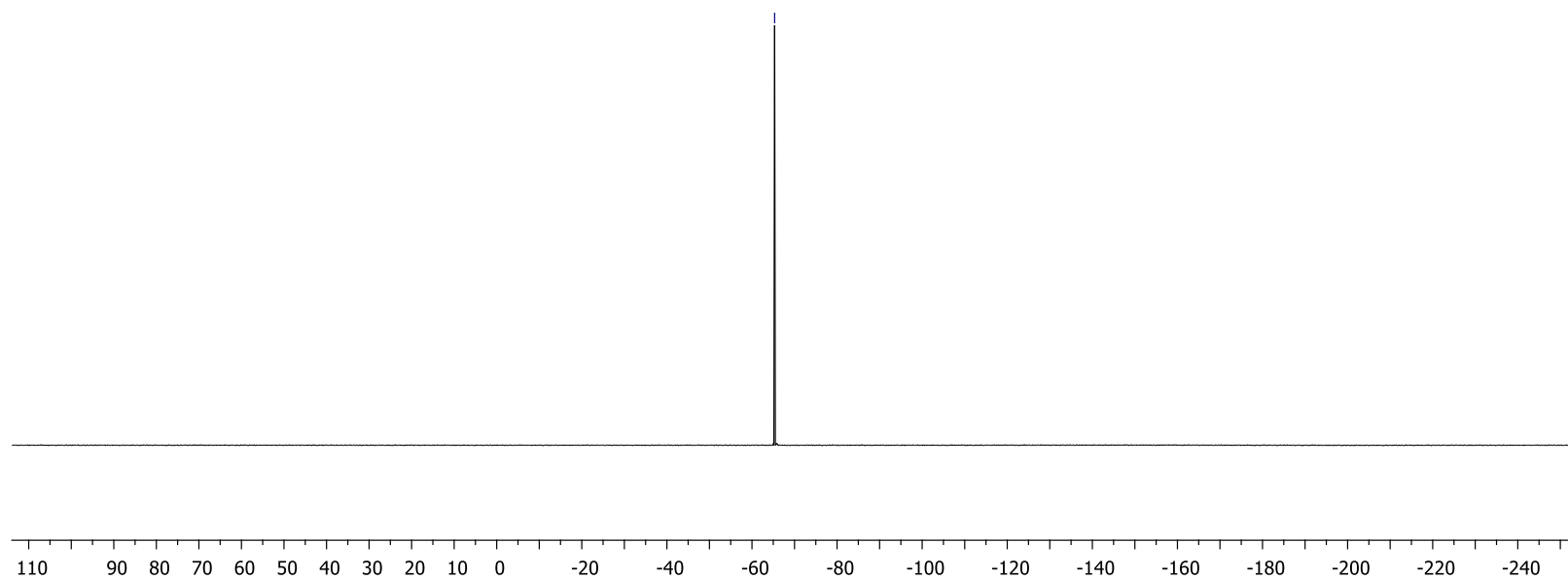
R2887538_C1:



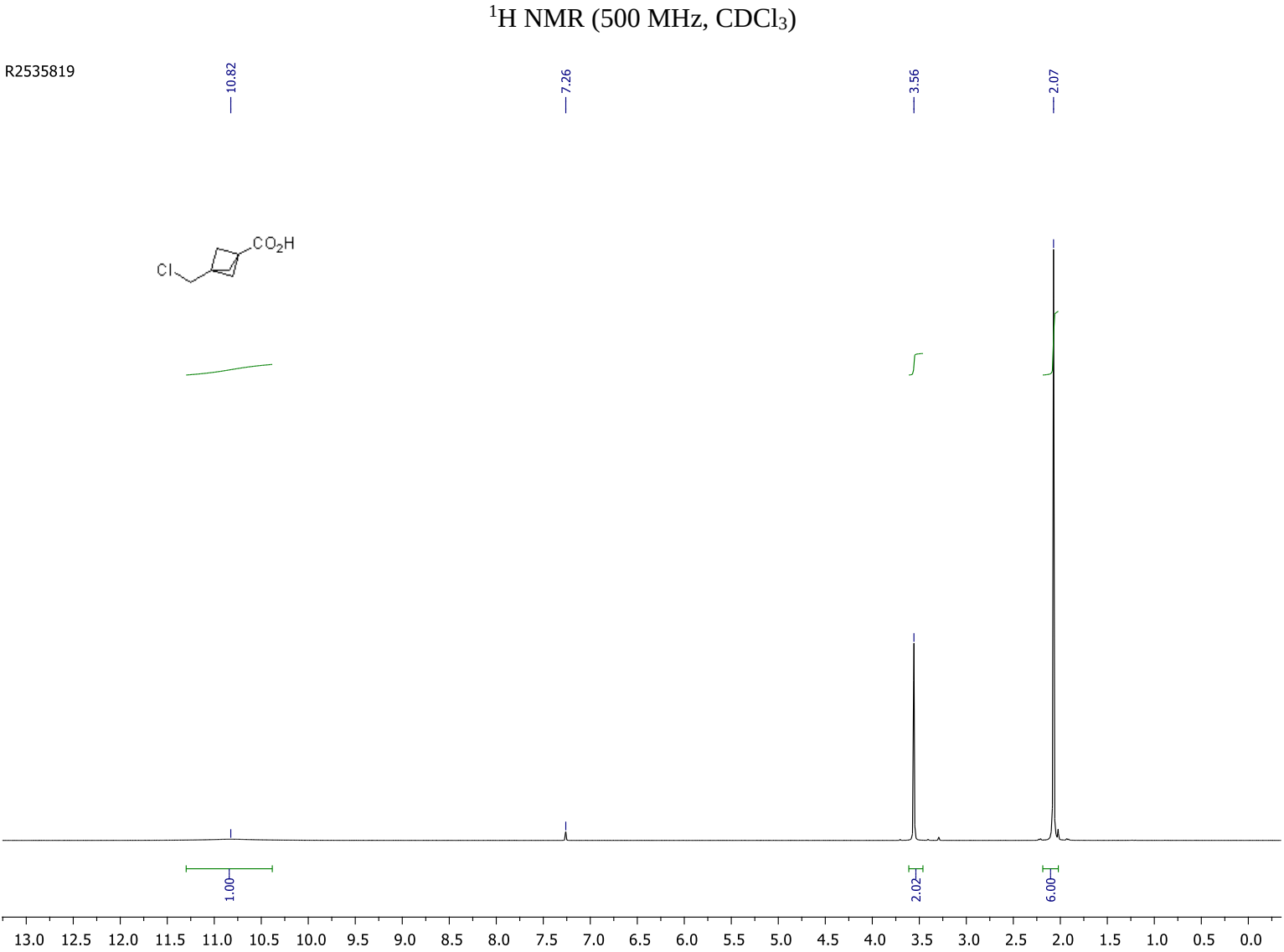
$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2887538_F19{H}

— -65.32



Compound 34k



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2535819_C13

— 175.89

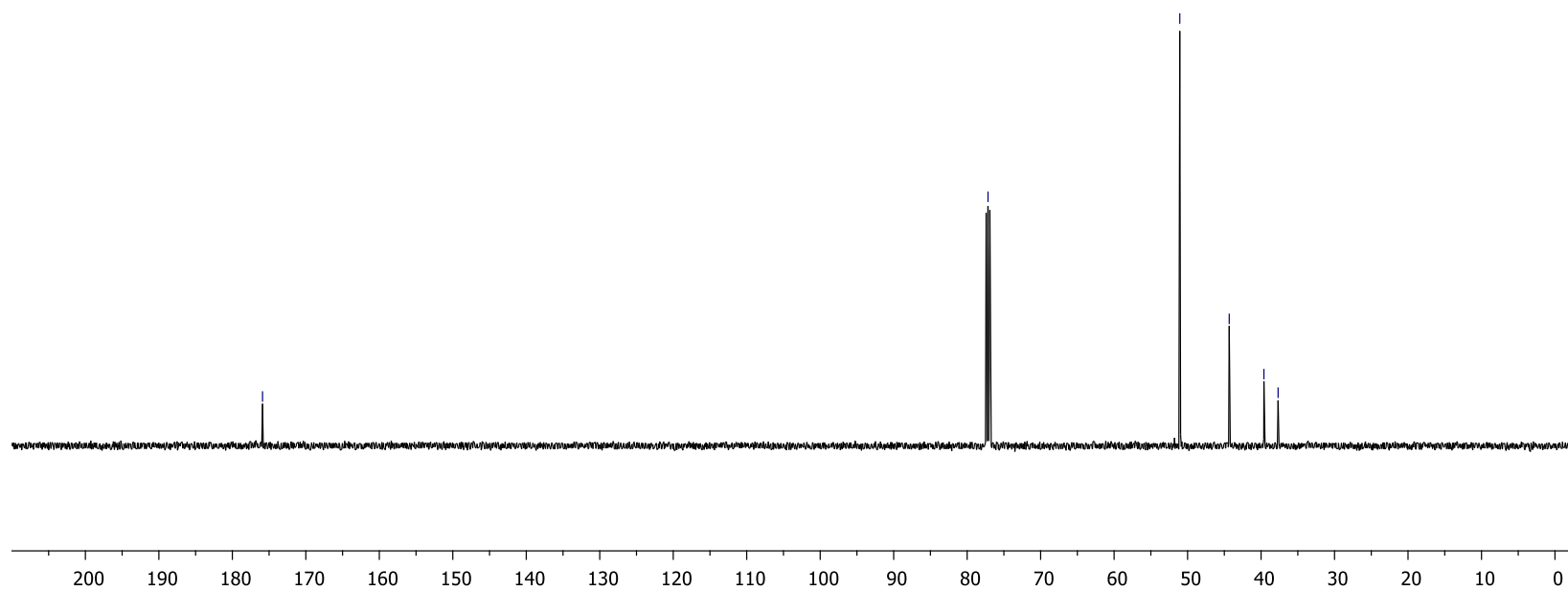
— 77.16

— 51.06

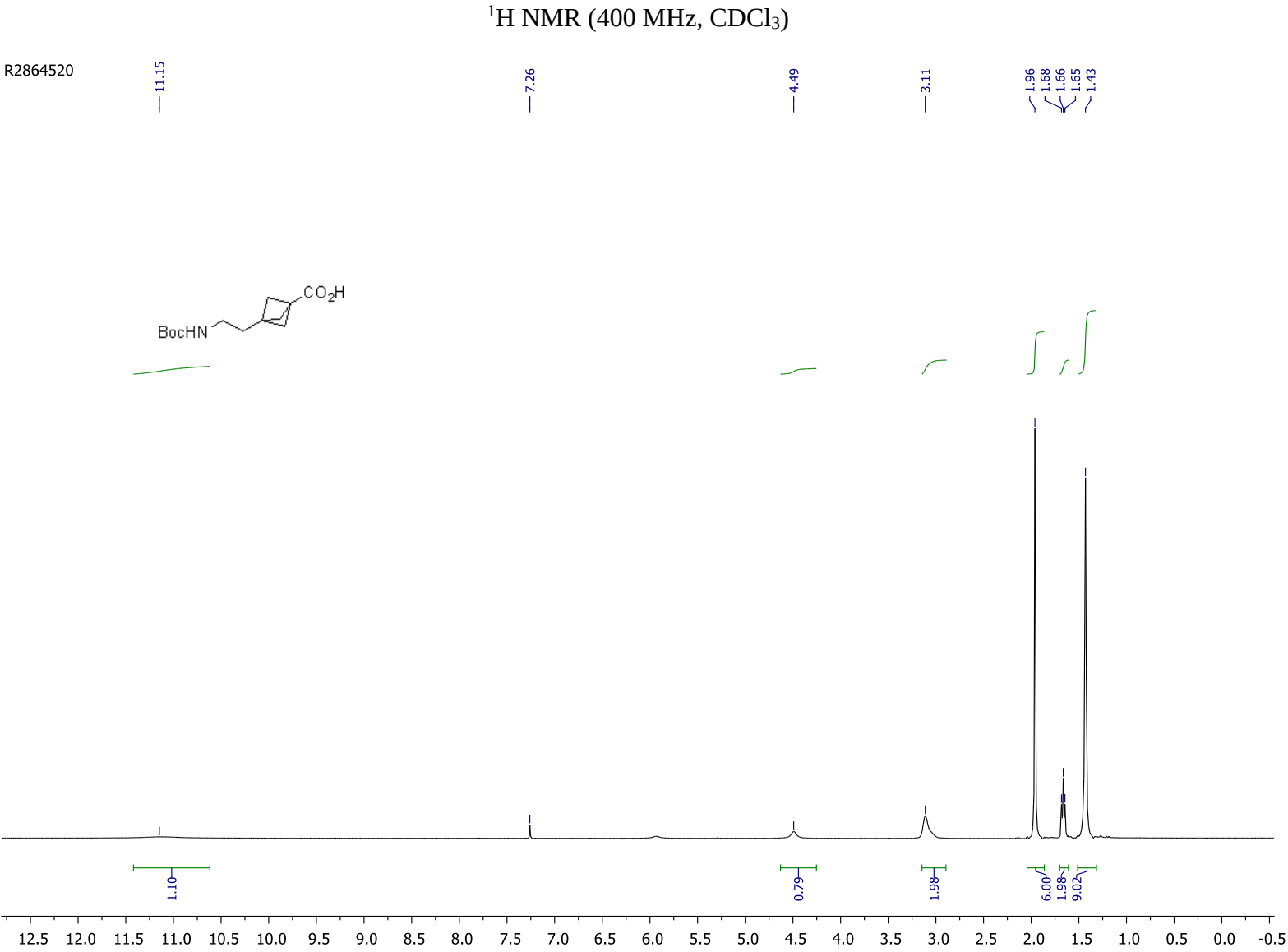
— 44.33

— 39.61

— 37.88

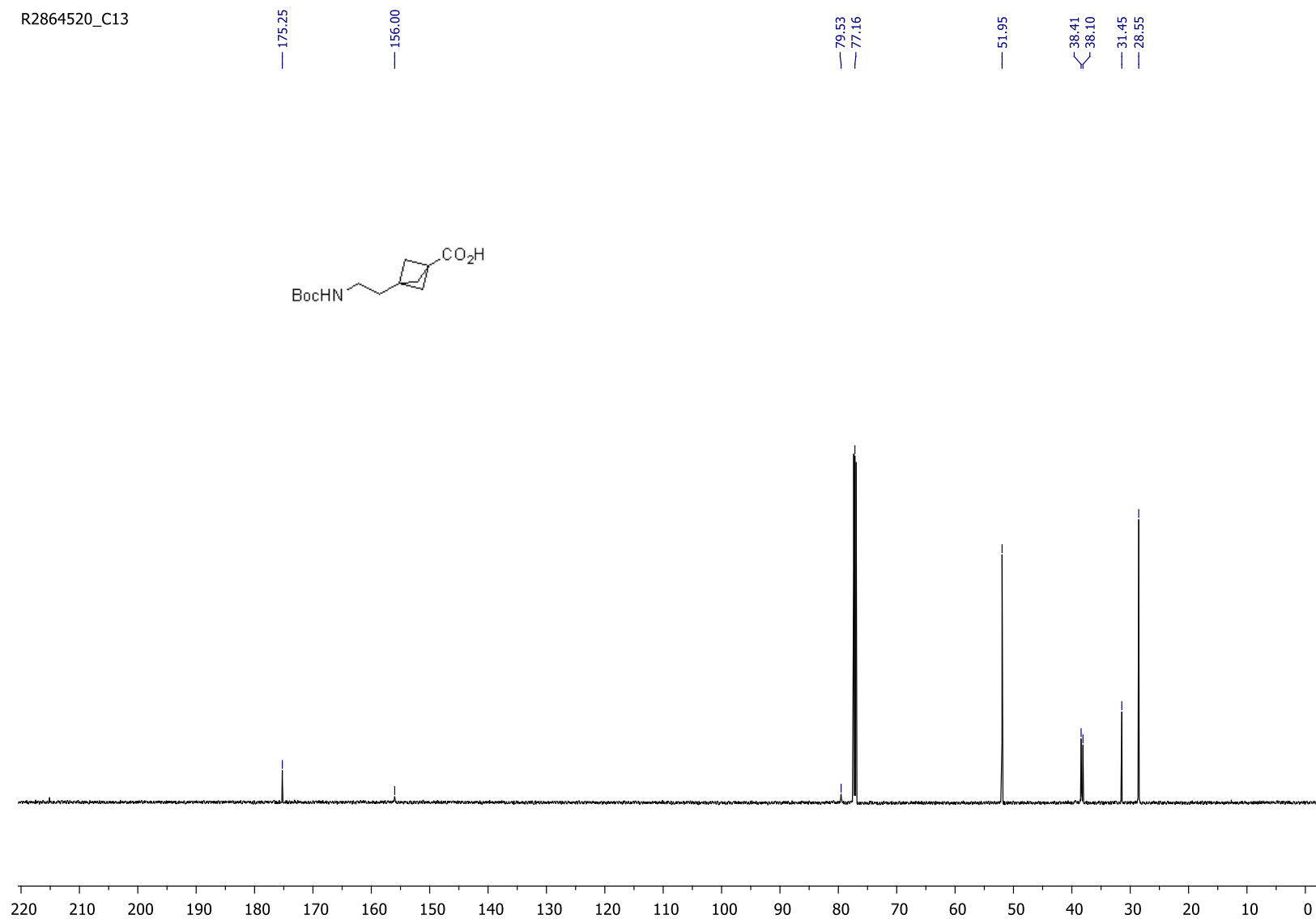


Compound 38k

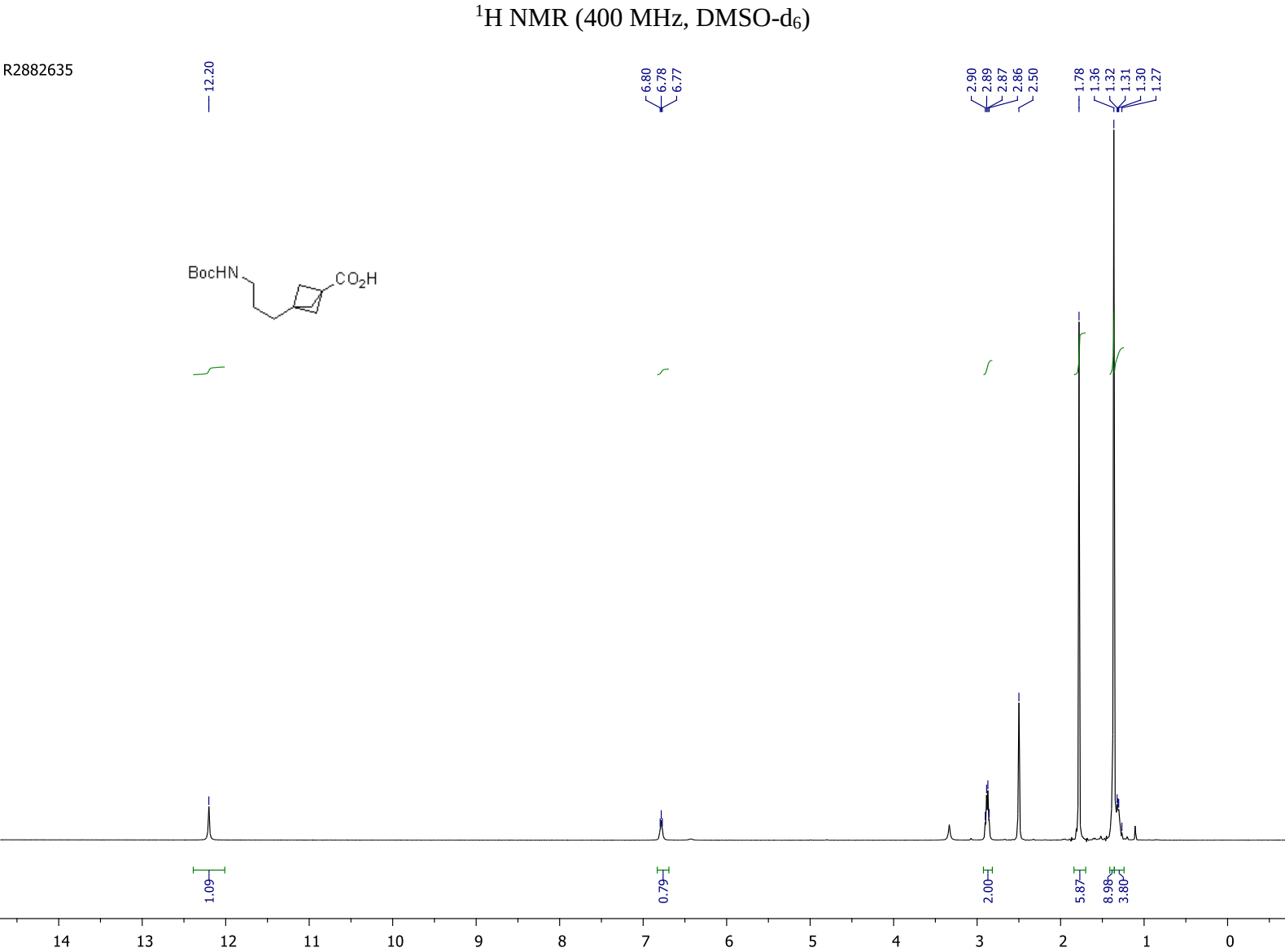


$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

R2864520_C13

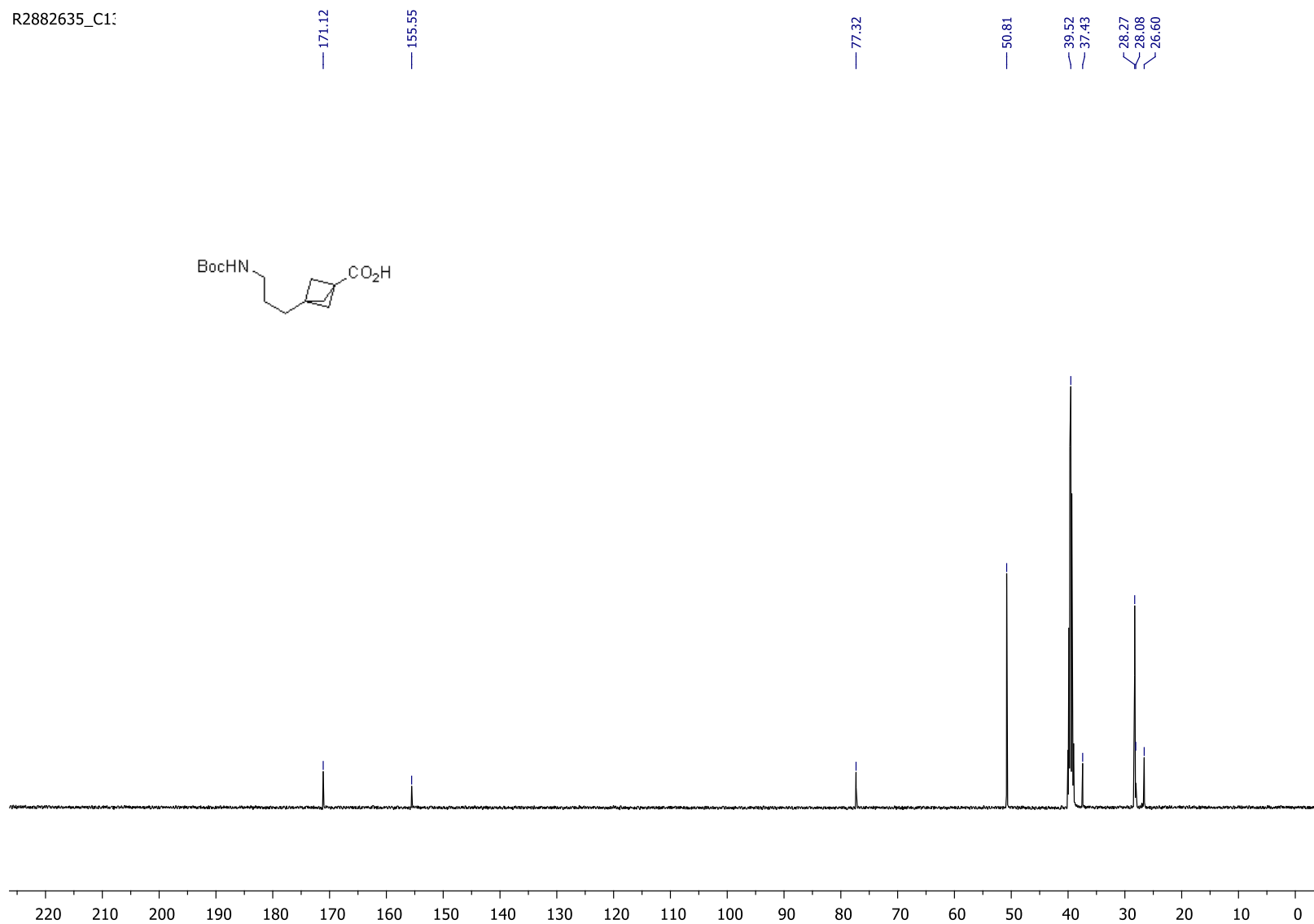


Compound 39k



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

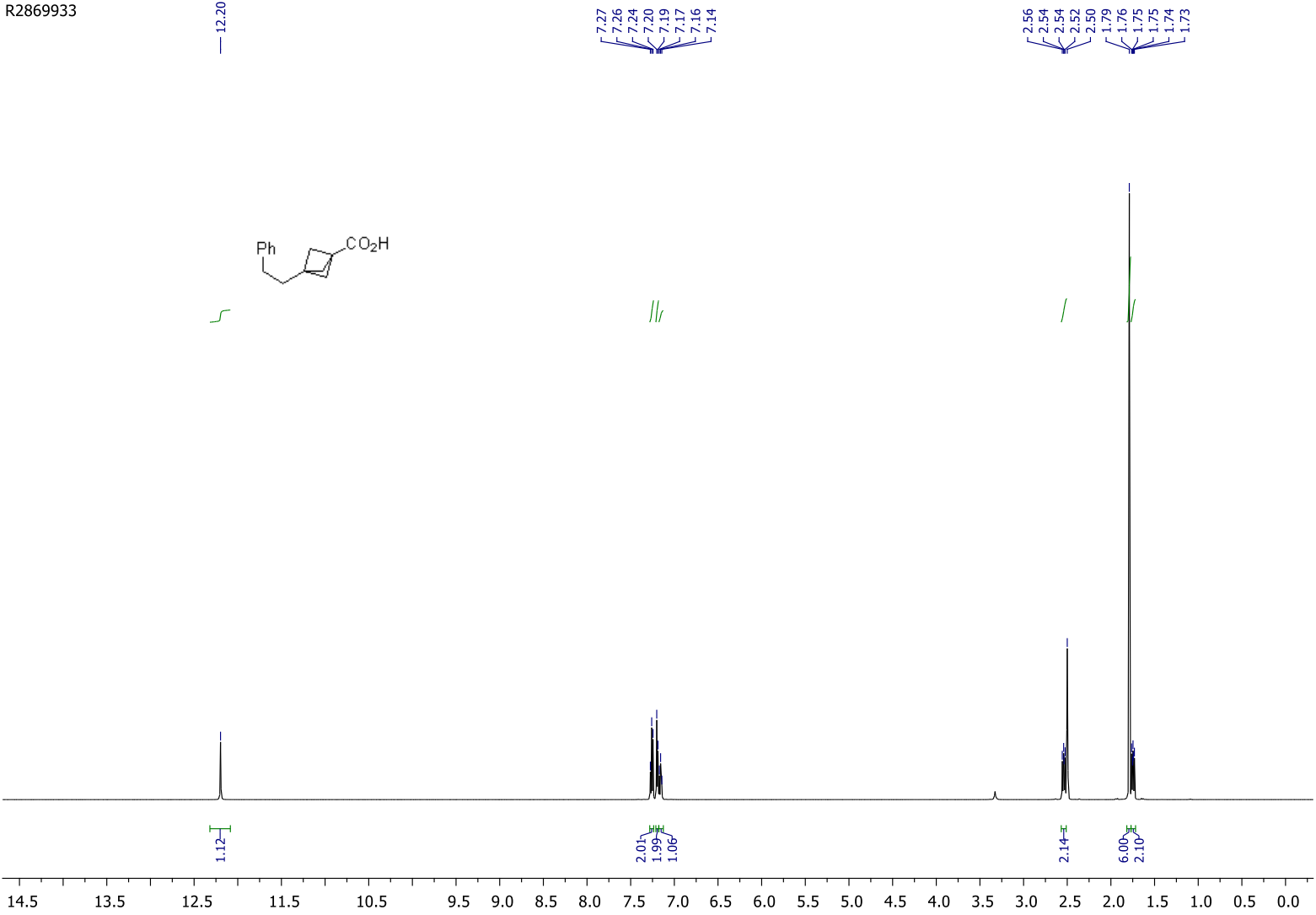
R2882635_C1:

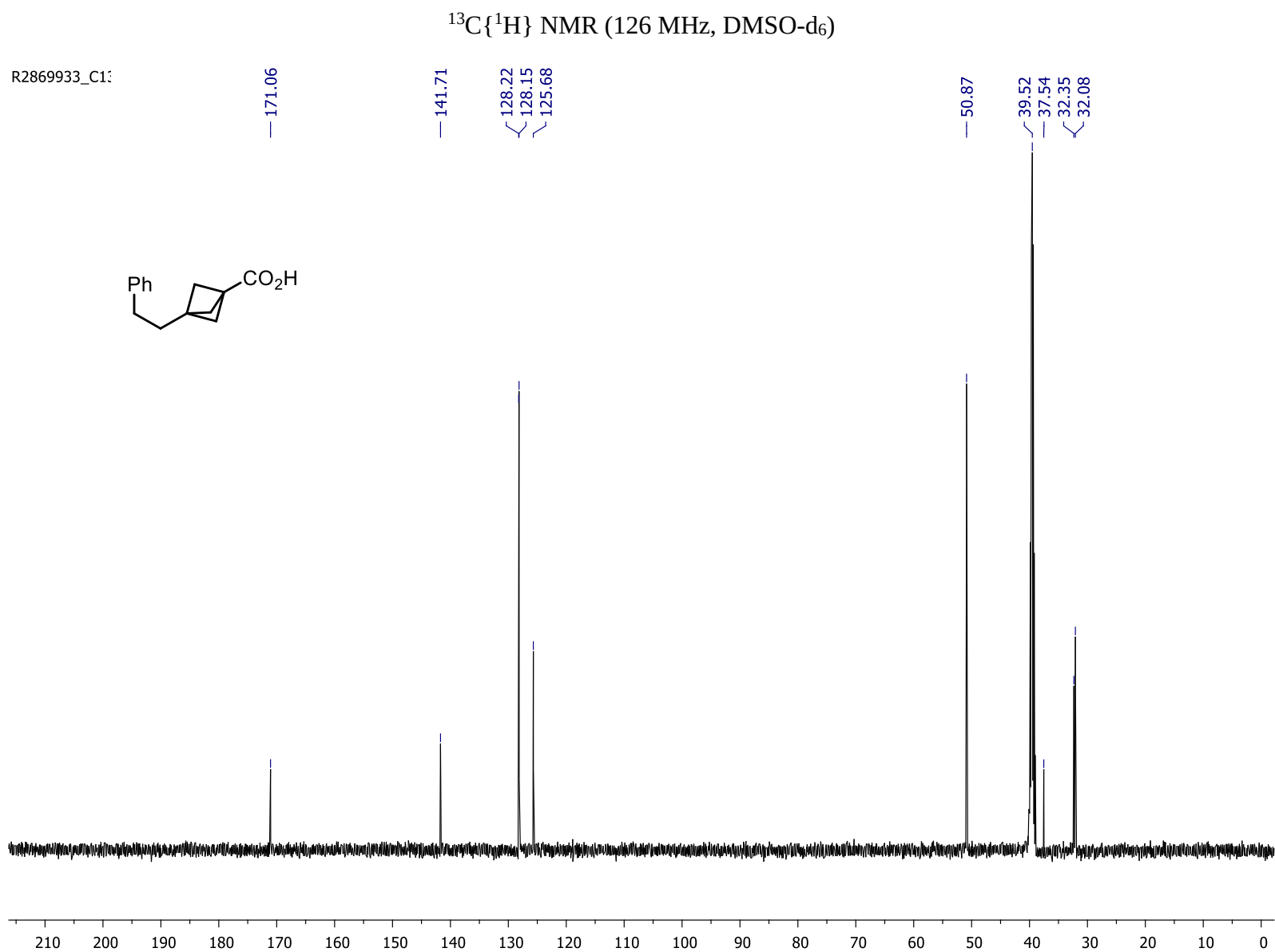


Compound 41k

¹H NMR (500 MHz, DMSO-d₆)

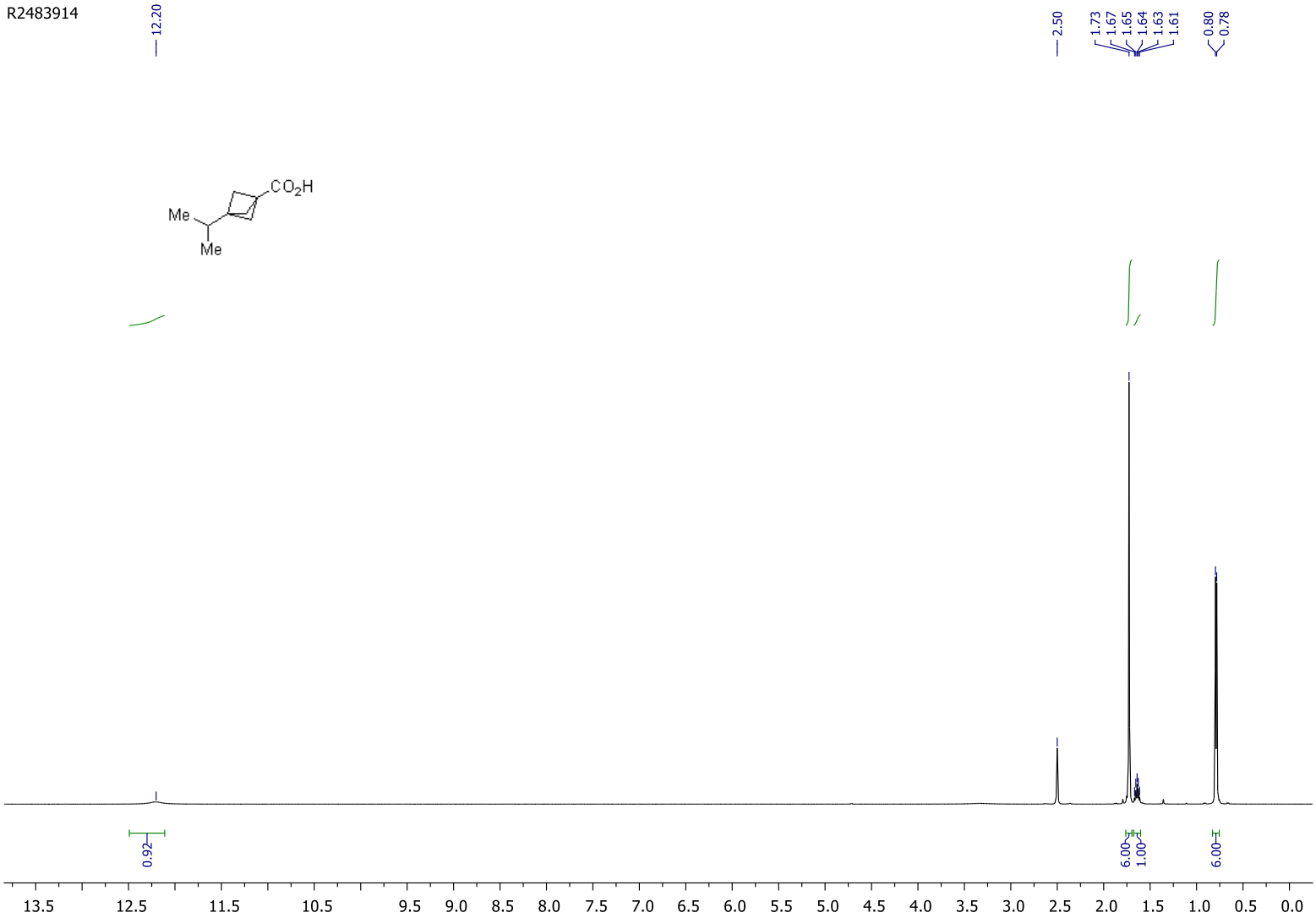
R2869933





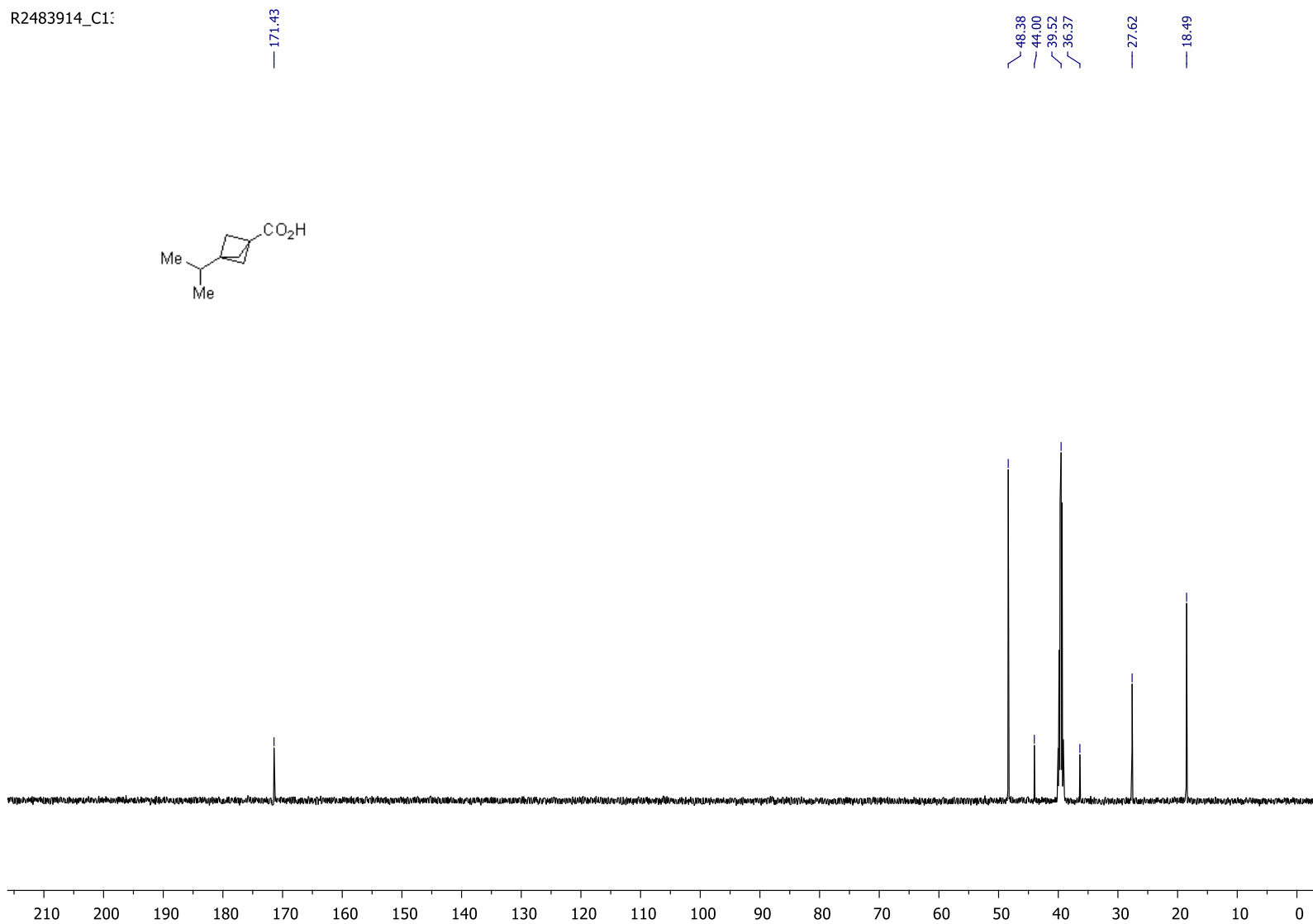
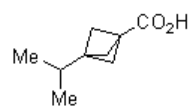
Compound 48k

¹H NMR (500 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

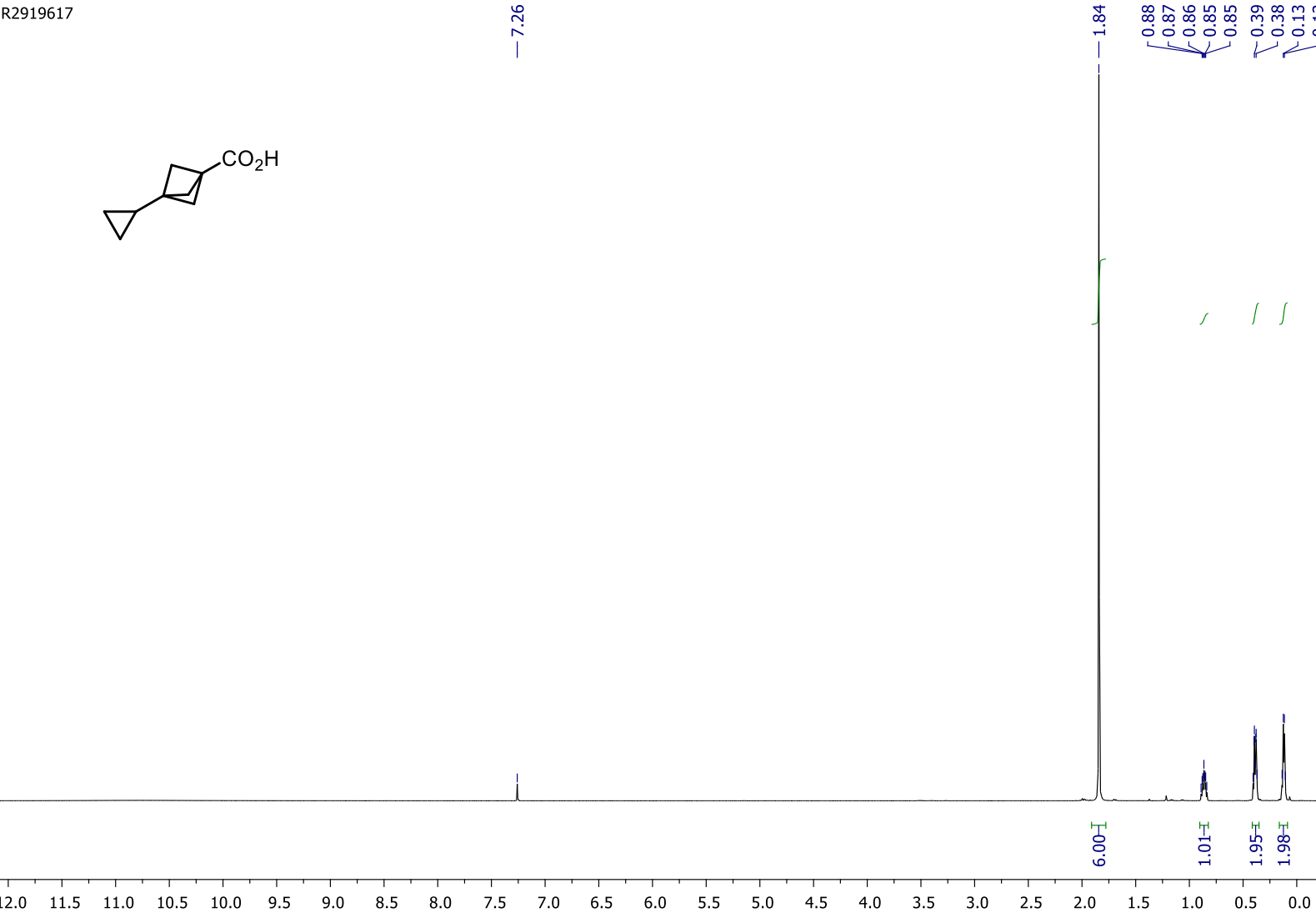
R2483914_C13



Compound 50k

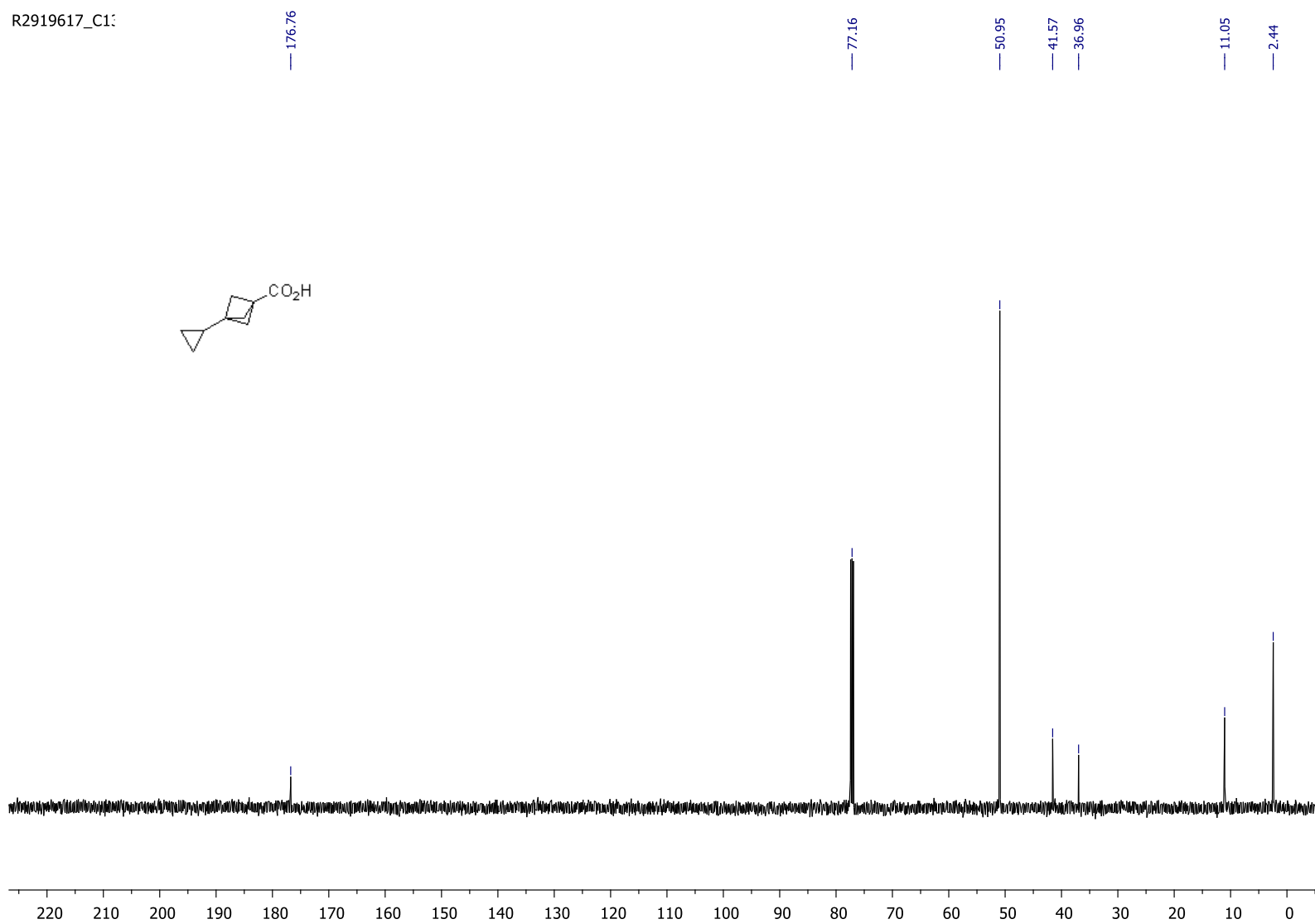
R2919617

¹H NMR (500 MHz, CDCl₃)



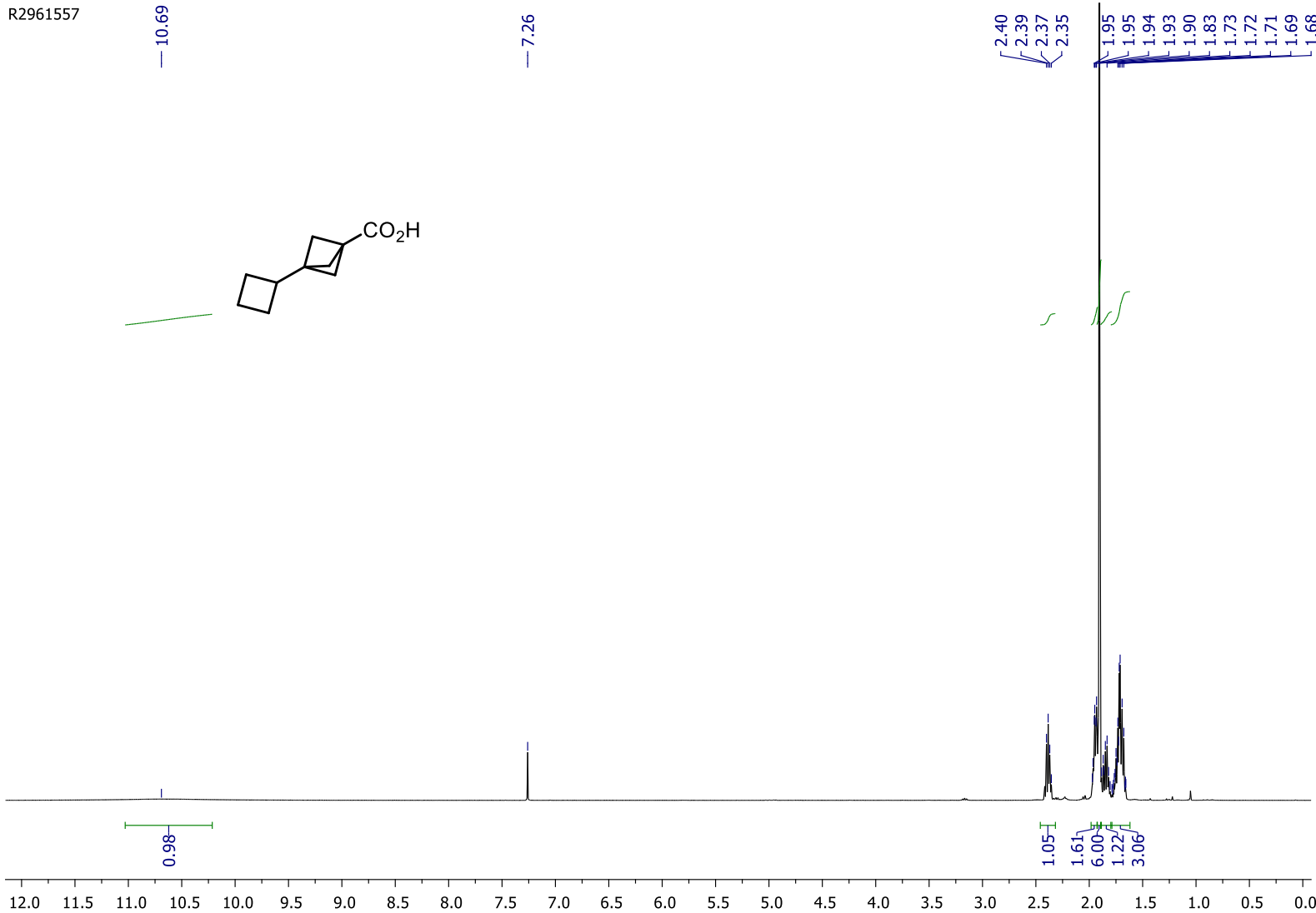
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2919617_C1:



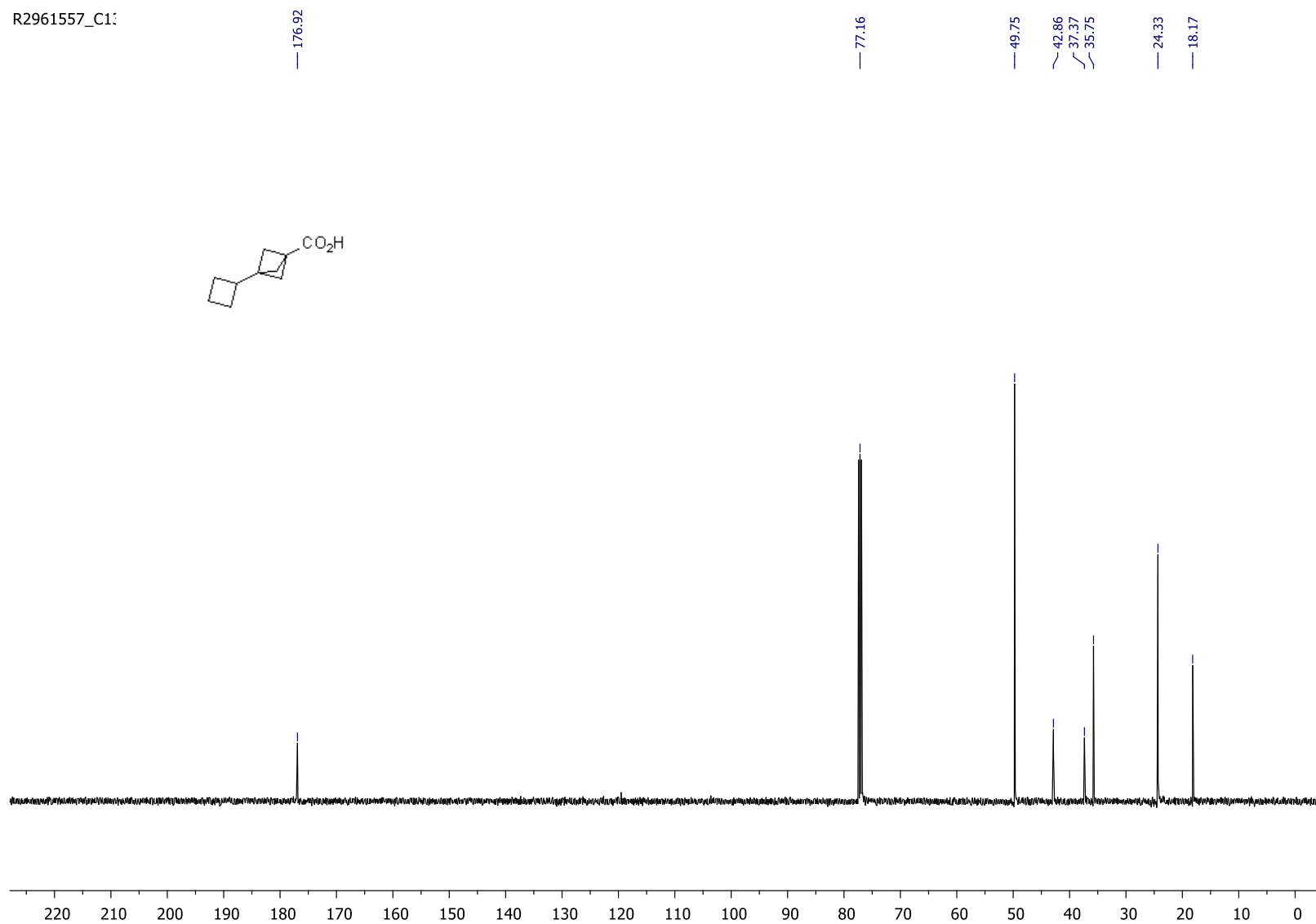
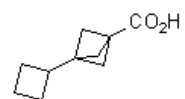
Compound 51k

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

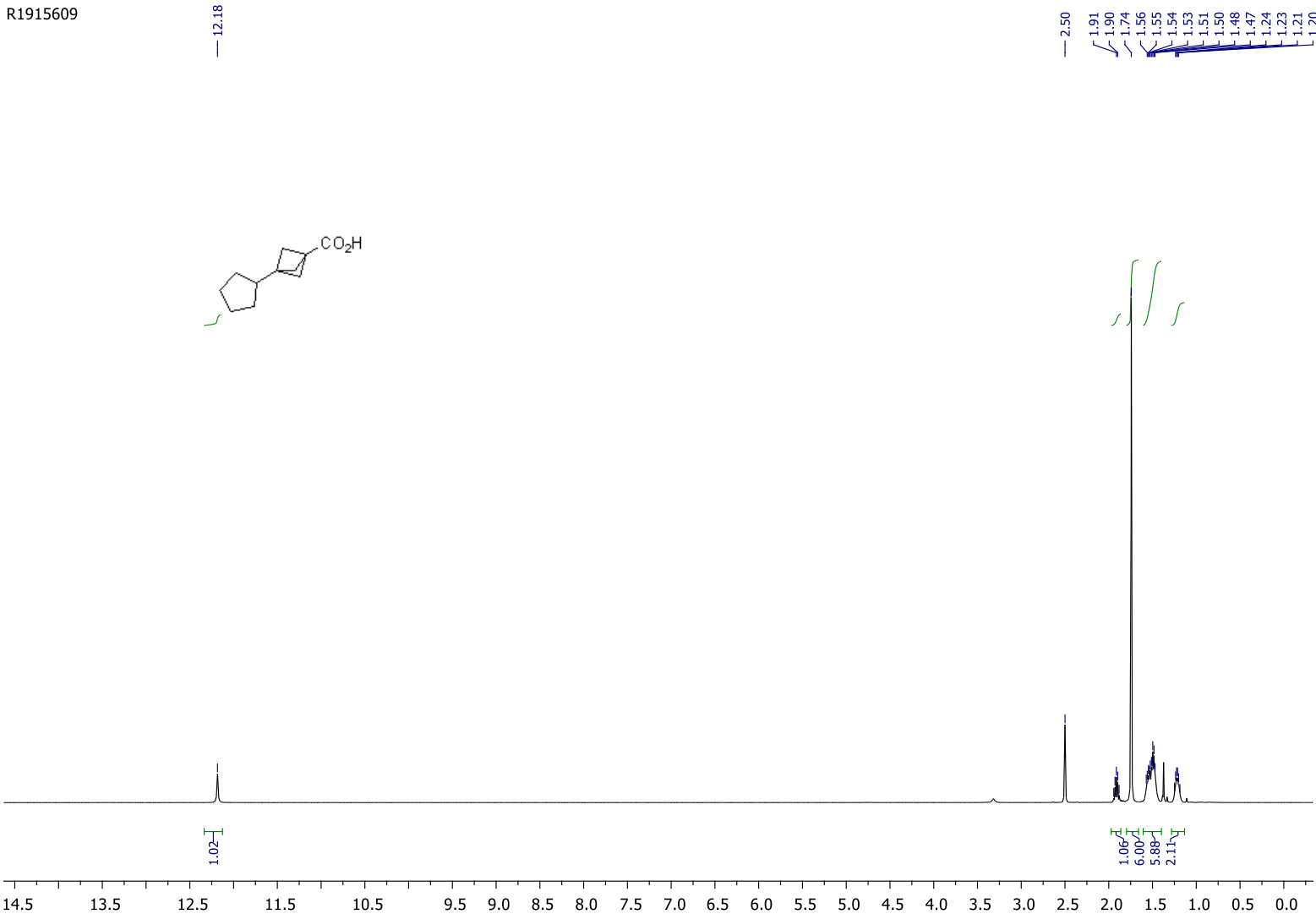
R2961557_C1:



Compound 52k

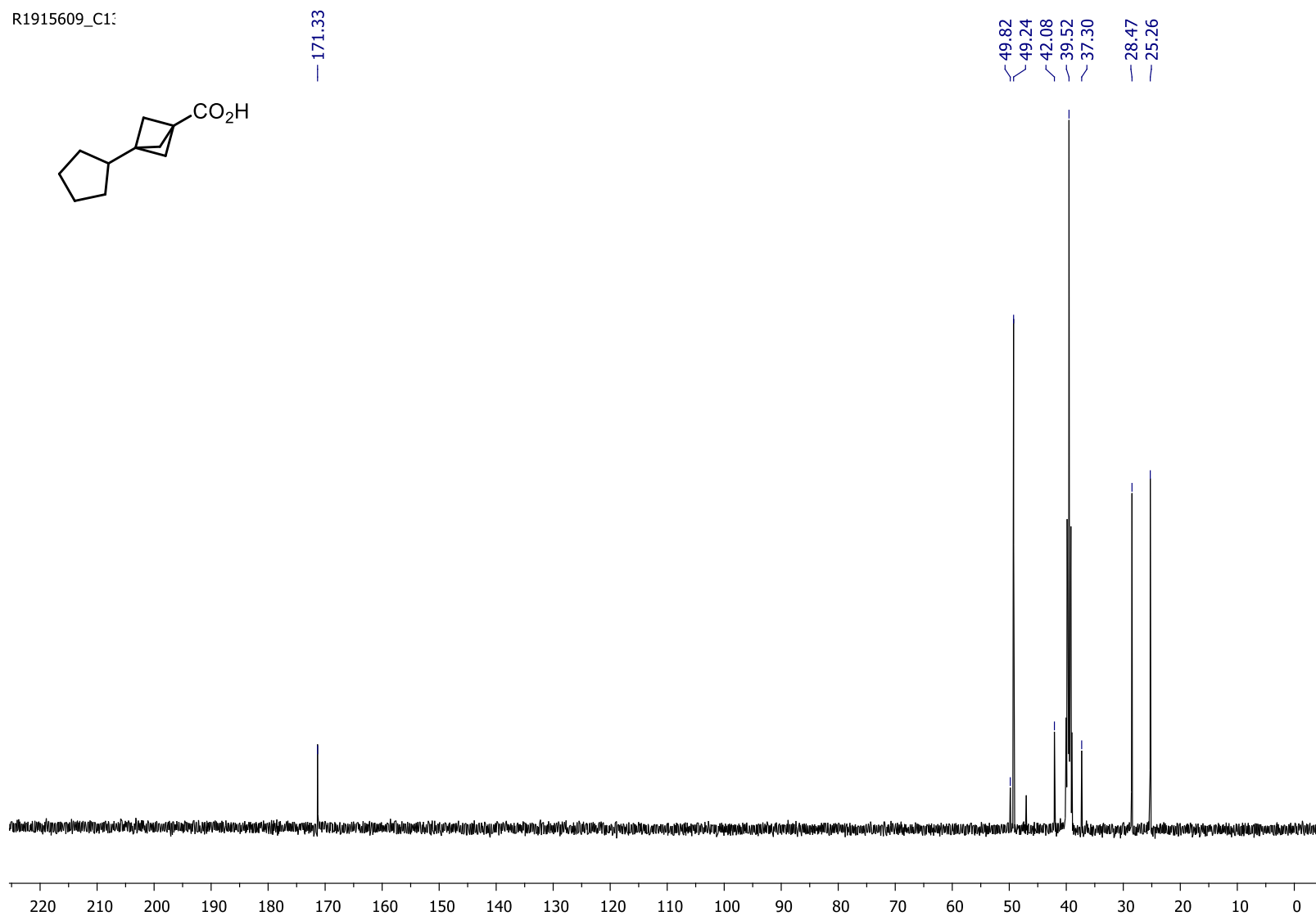
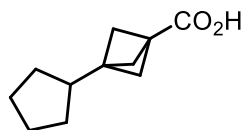
¹H NMR (500 MHz,DMSO-d₆)

R1915609

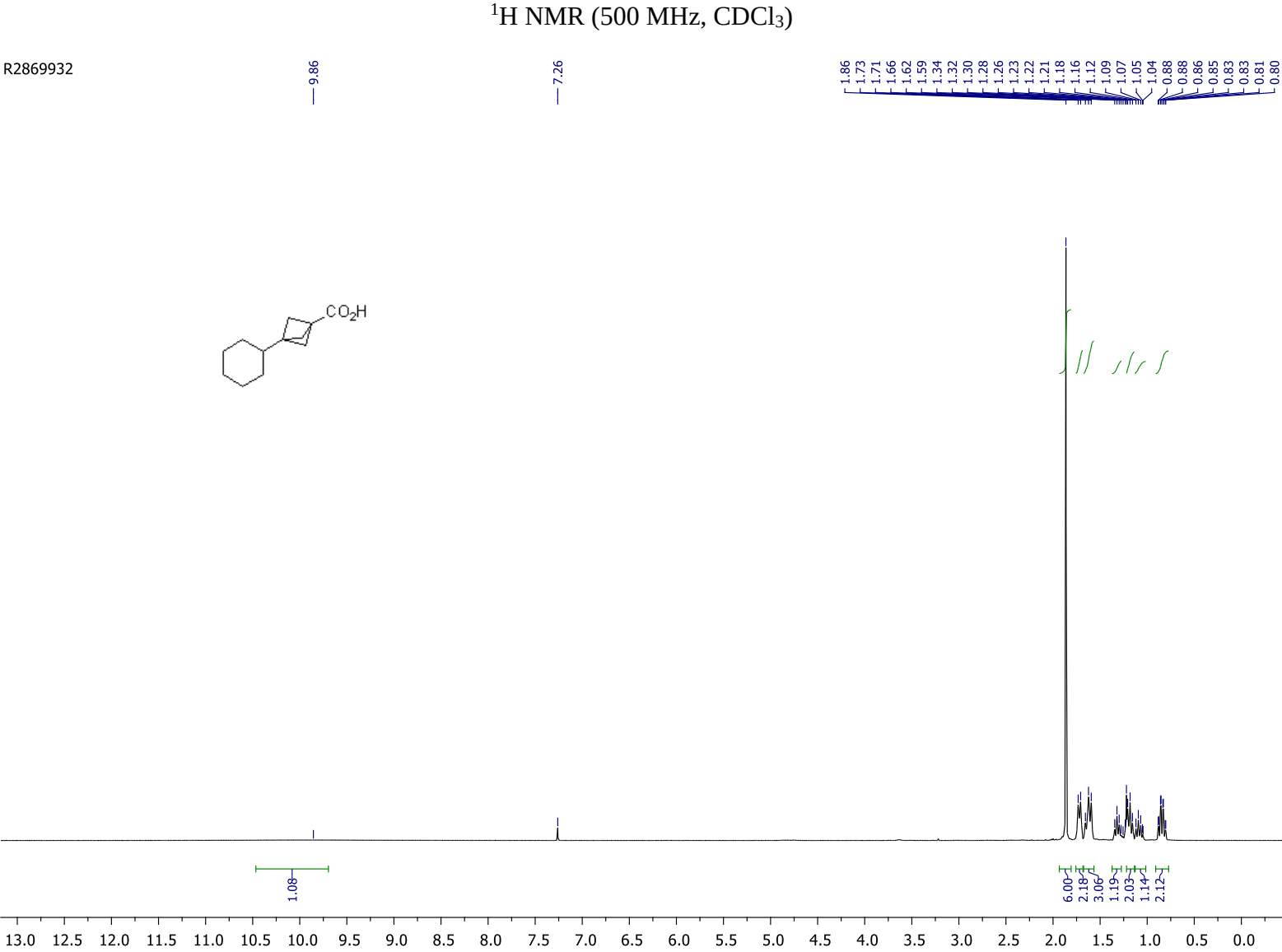


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R1915609_C1:

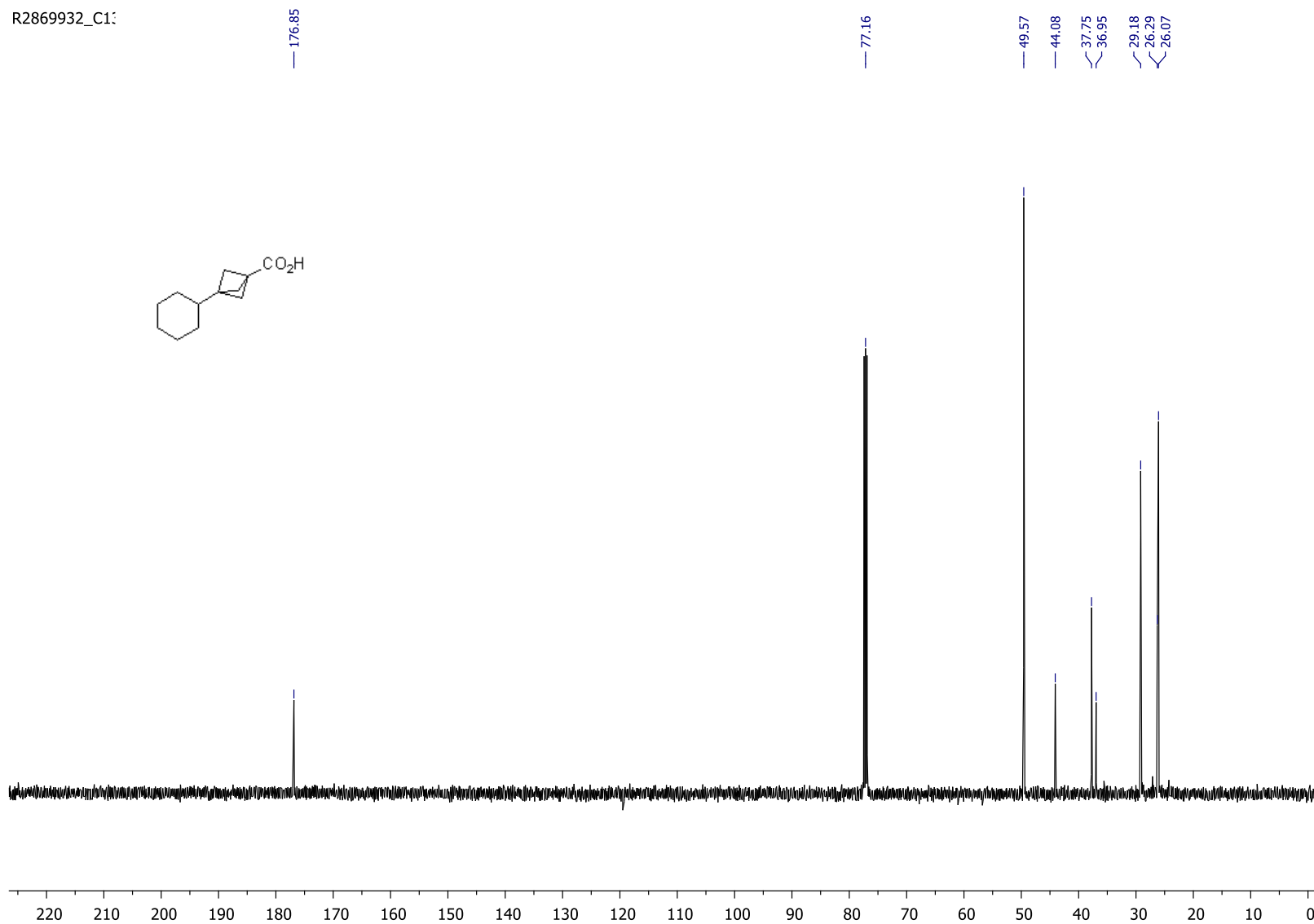
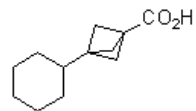


Compound 53k

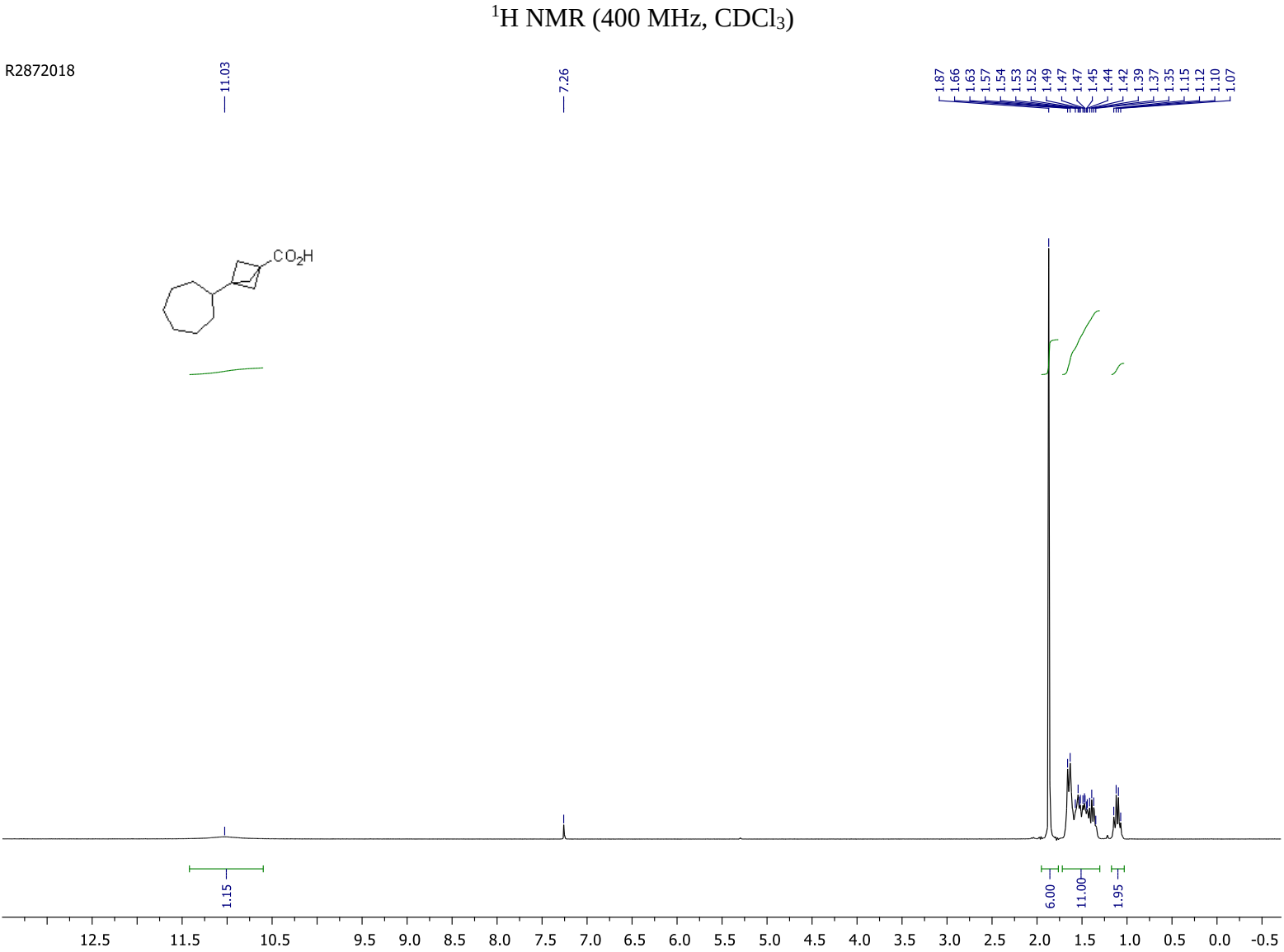


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2869932_C1:

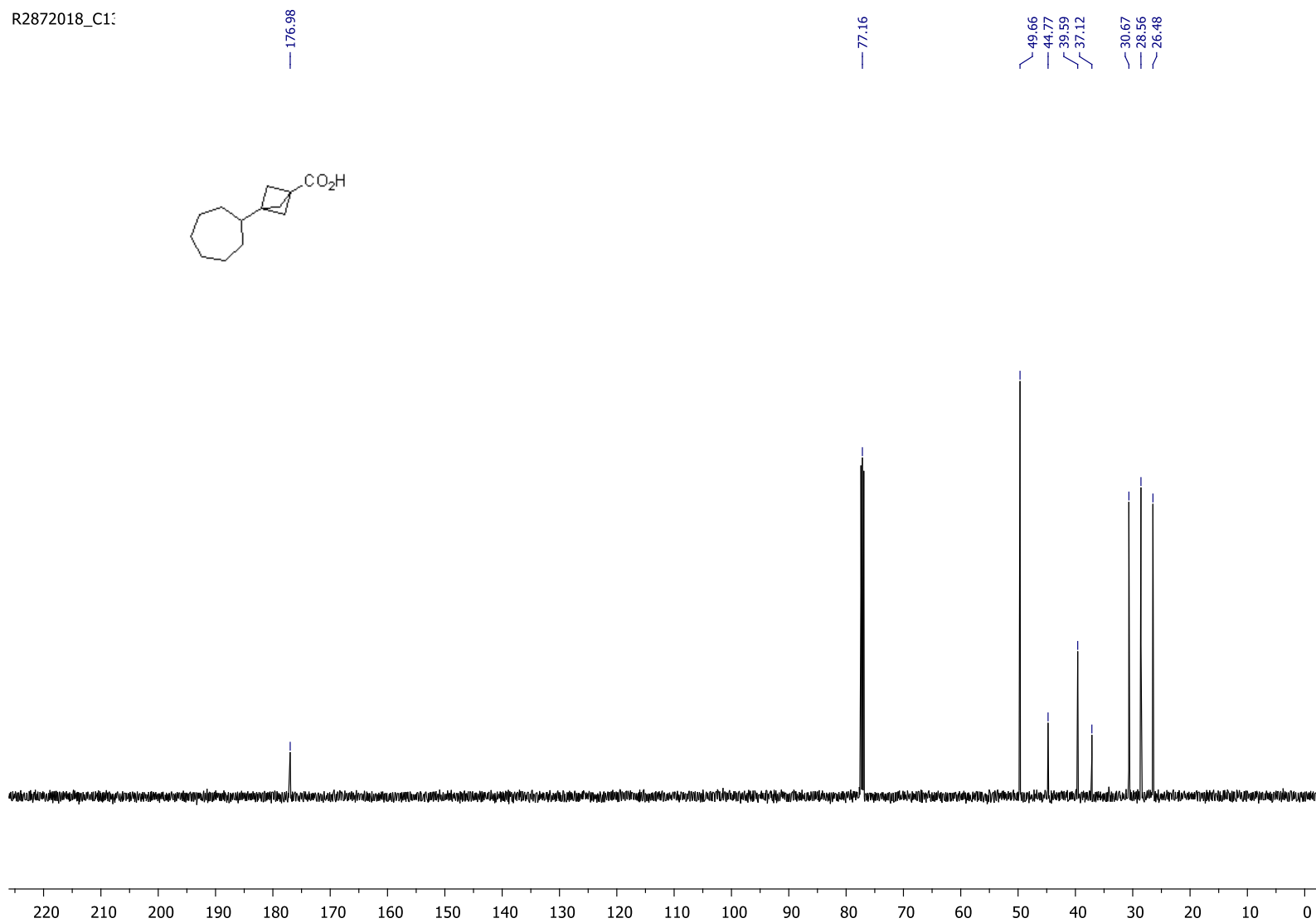


Compound 54k

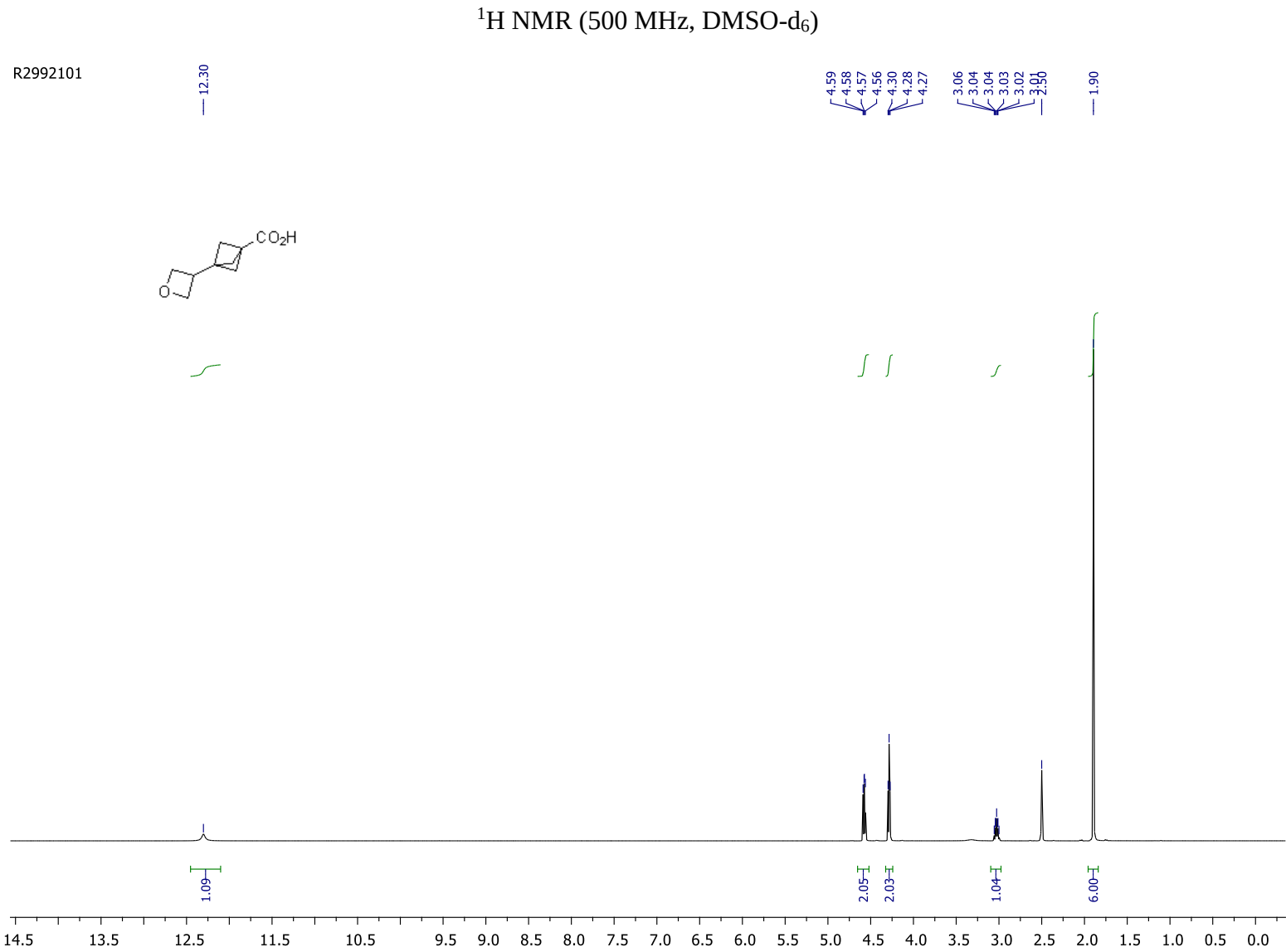


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2872018_C1:

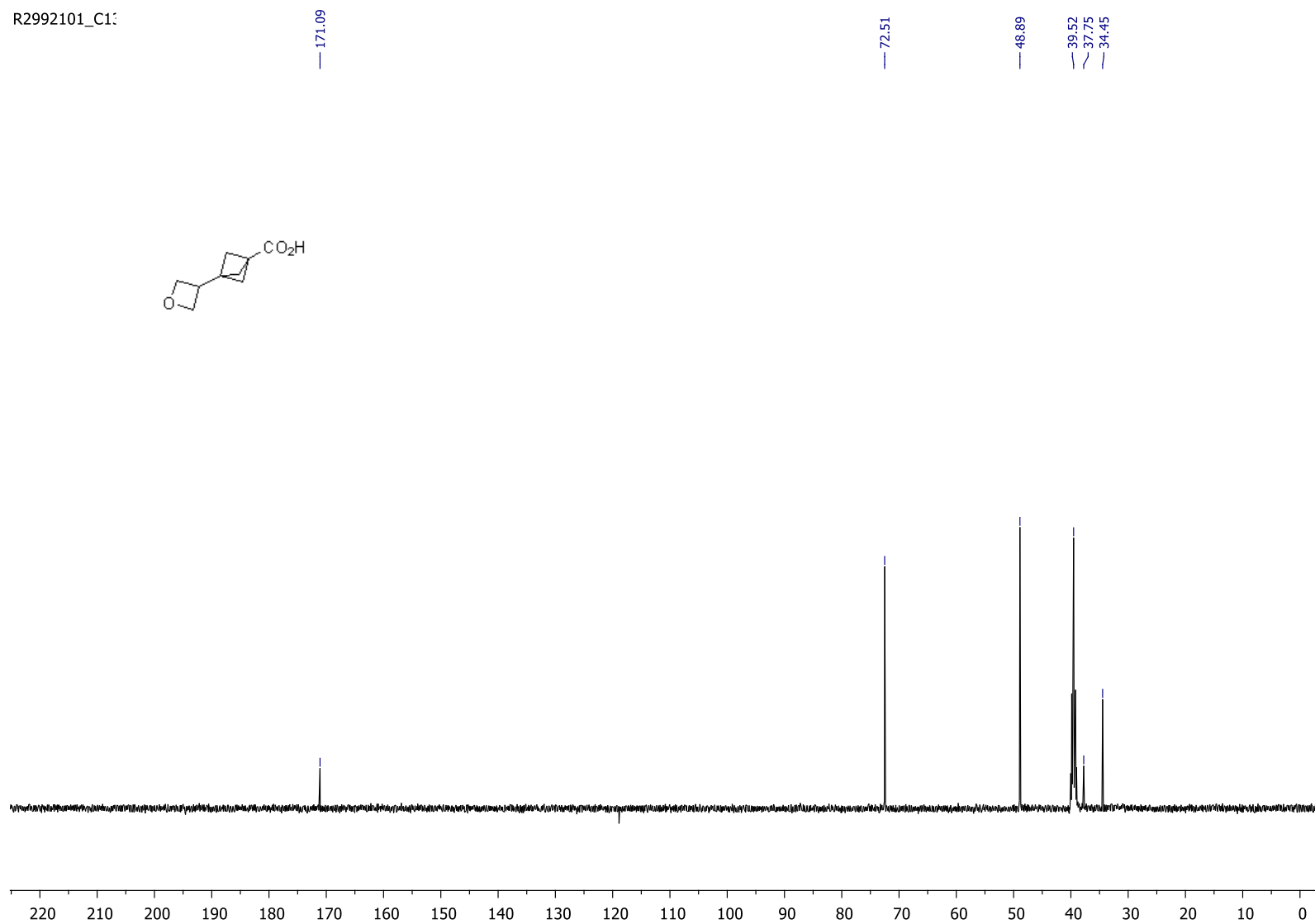


Compound 55k



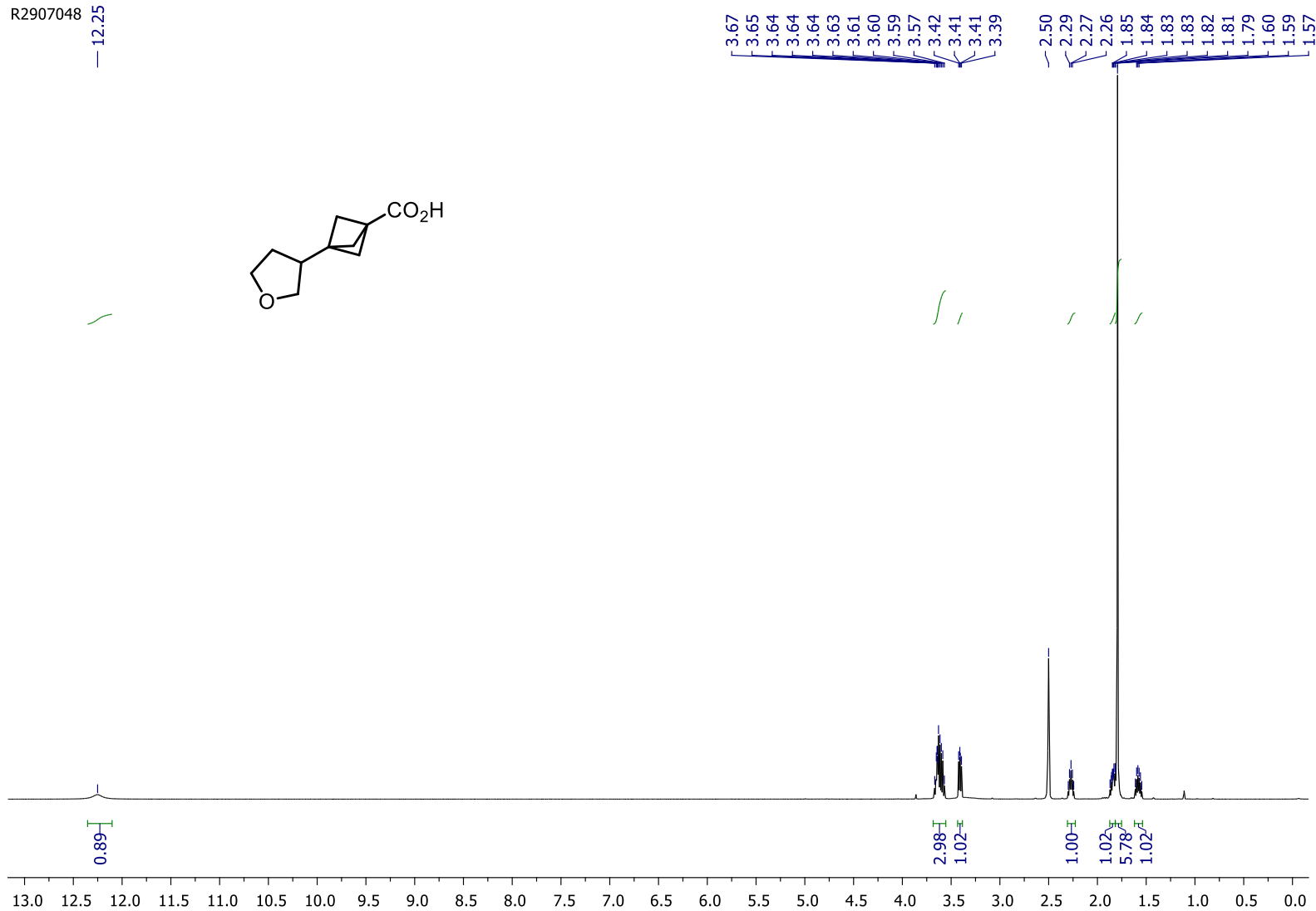
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

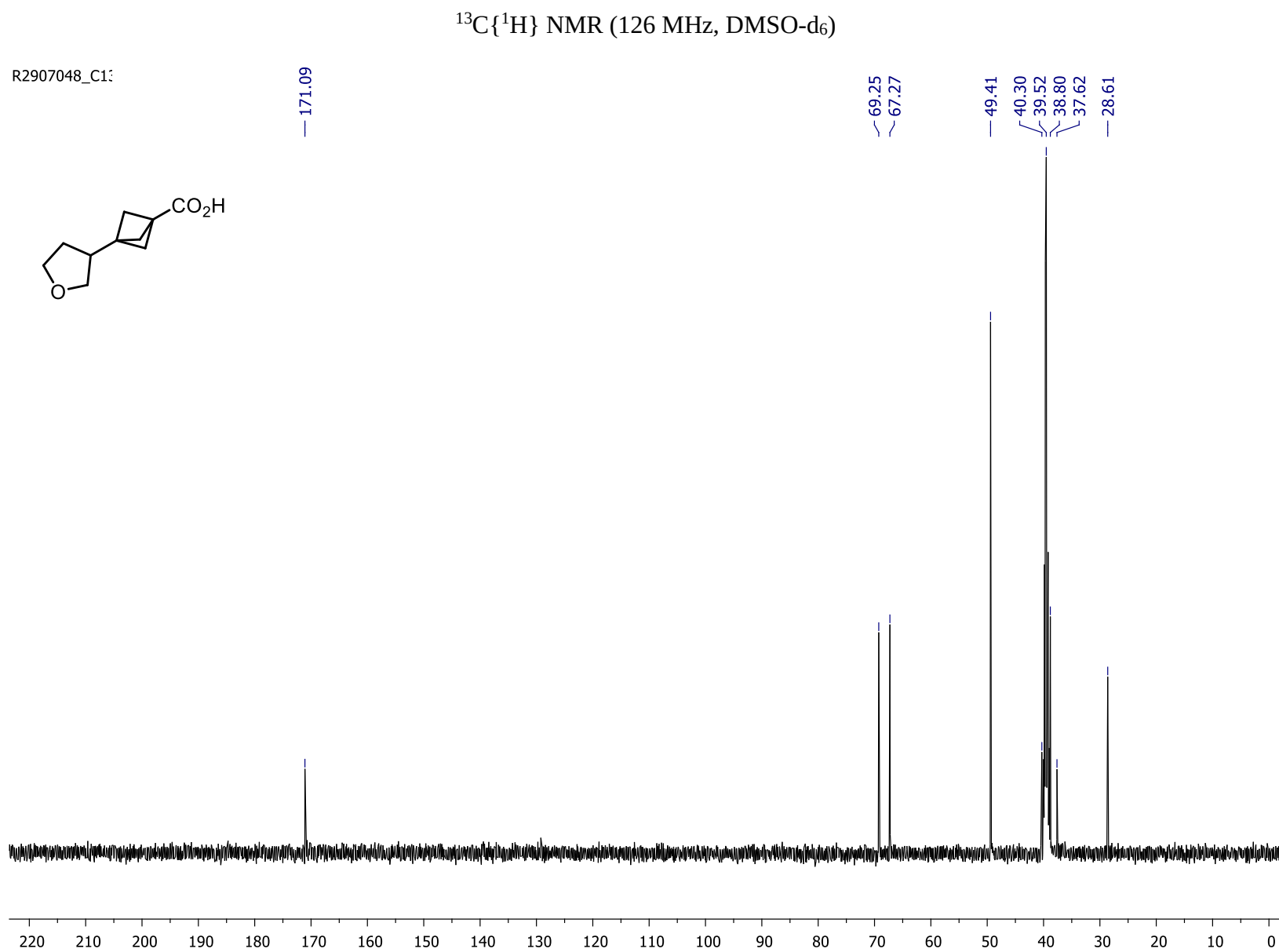
R2992101_C13



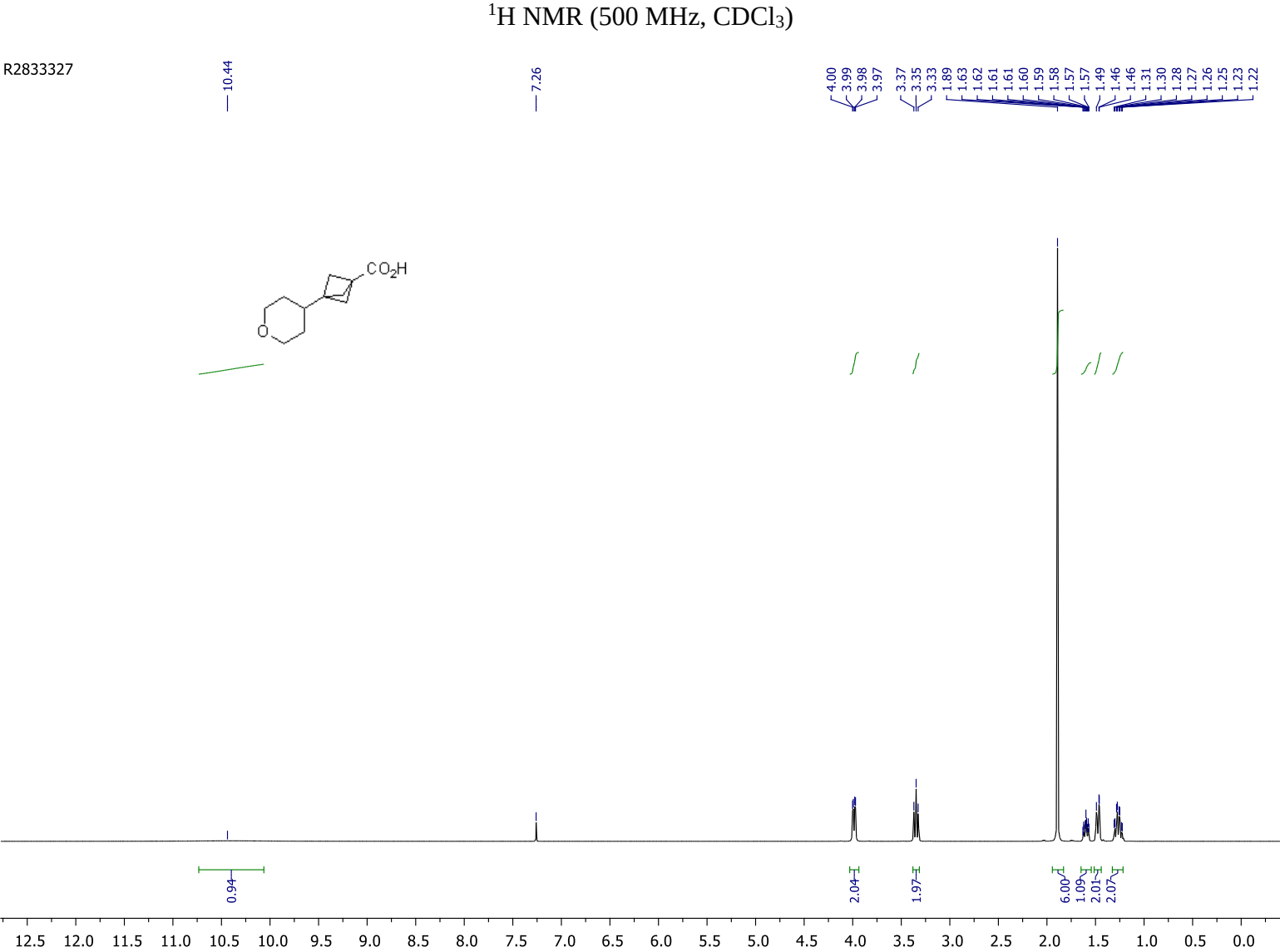
Compound 56k

¹H NMR (500 MHz, DMSO-d₆)





Compound 57k



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2833327_C13

— 175.98

— 77.16

— 67.74

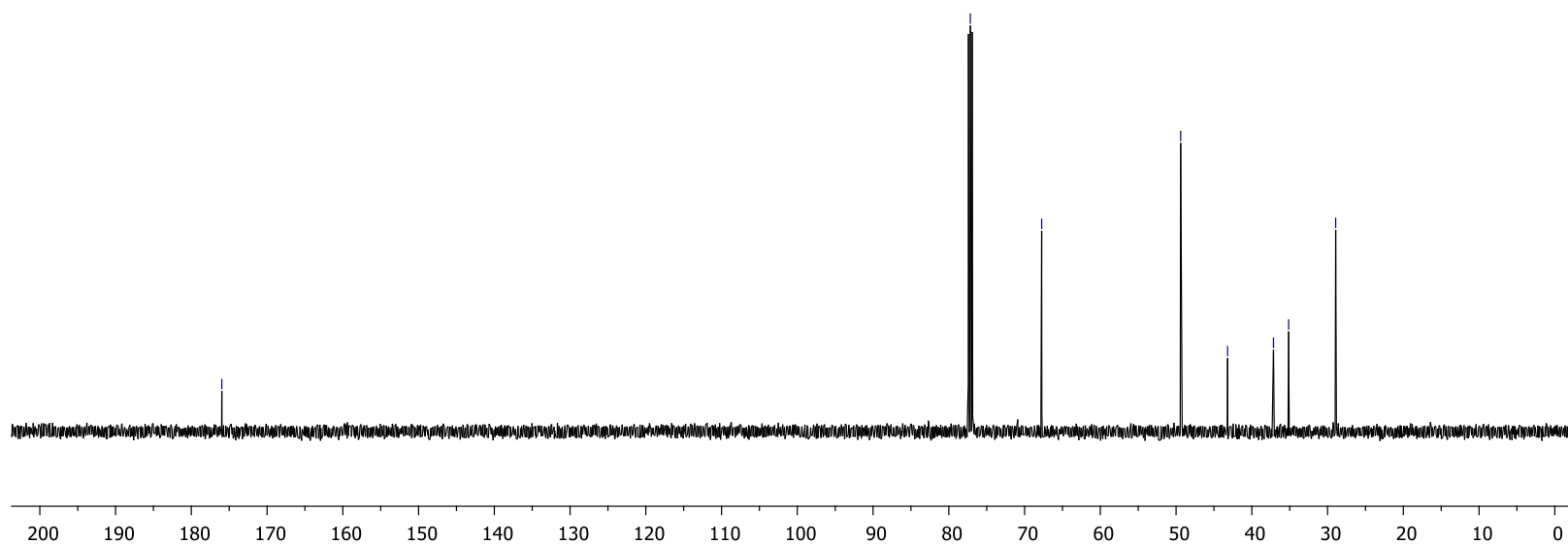
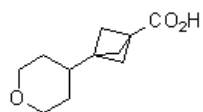
— 49.40

— 43.20

— 37.14

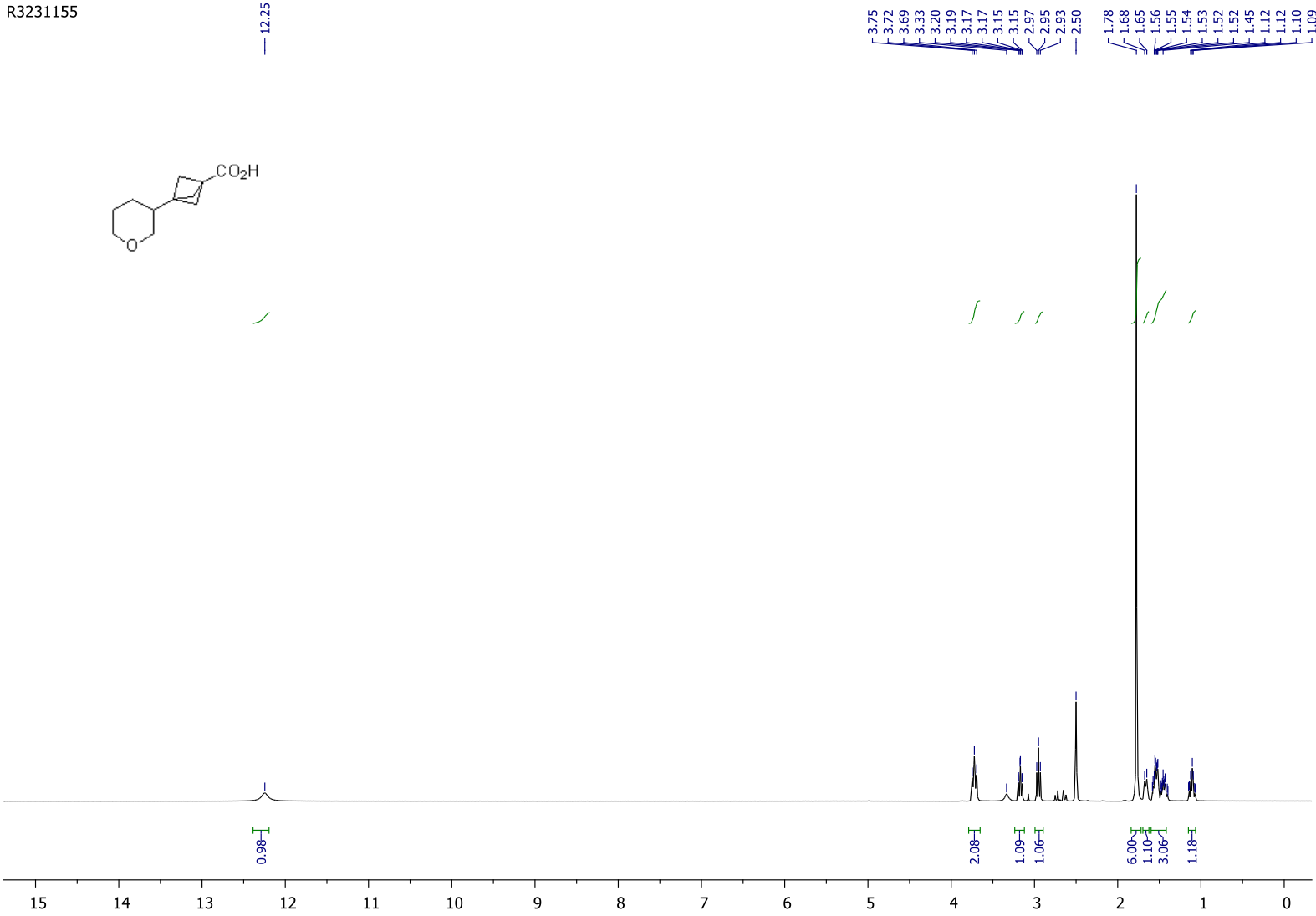
— 35.14

— 28.93



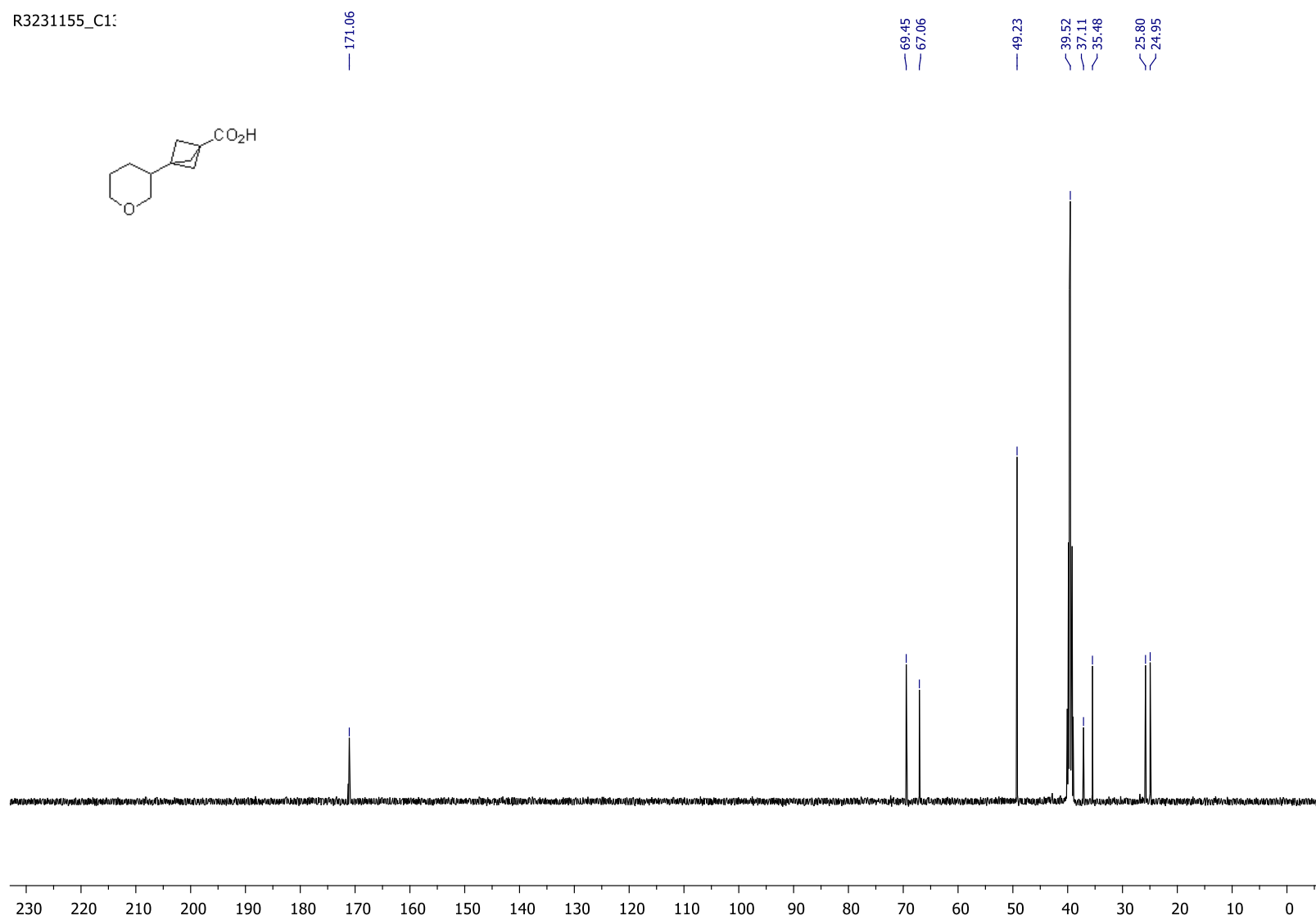
Compound 58k

¹H NMR (500 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

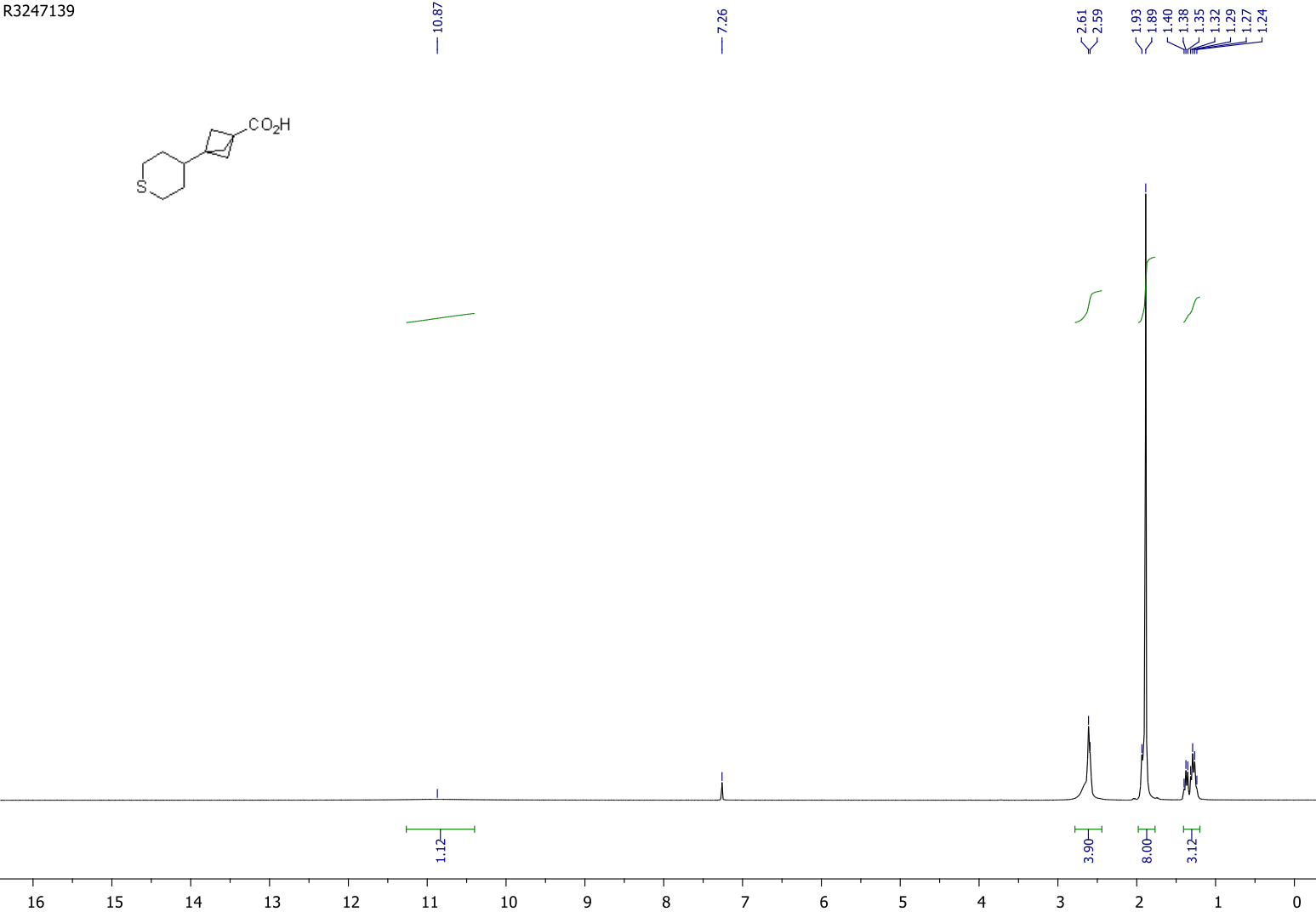
R3231155_C1:



Compound 59k

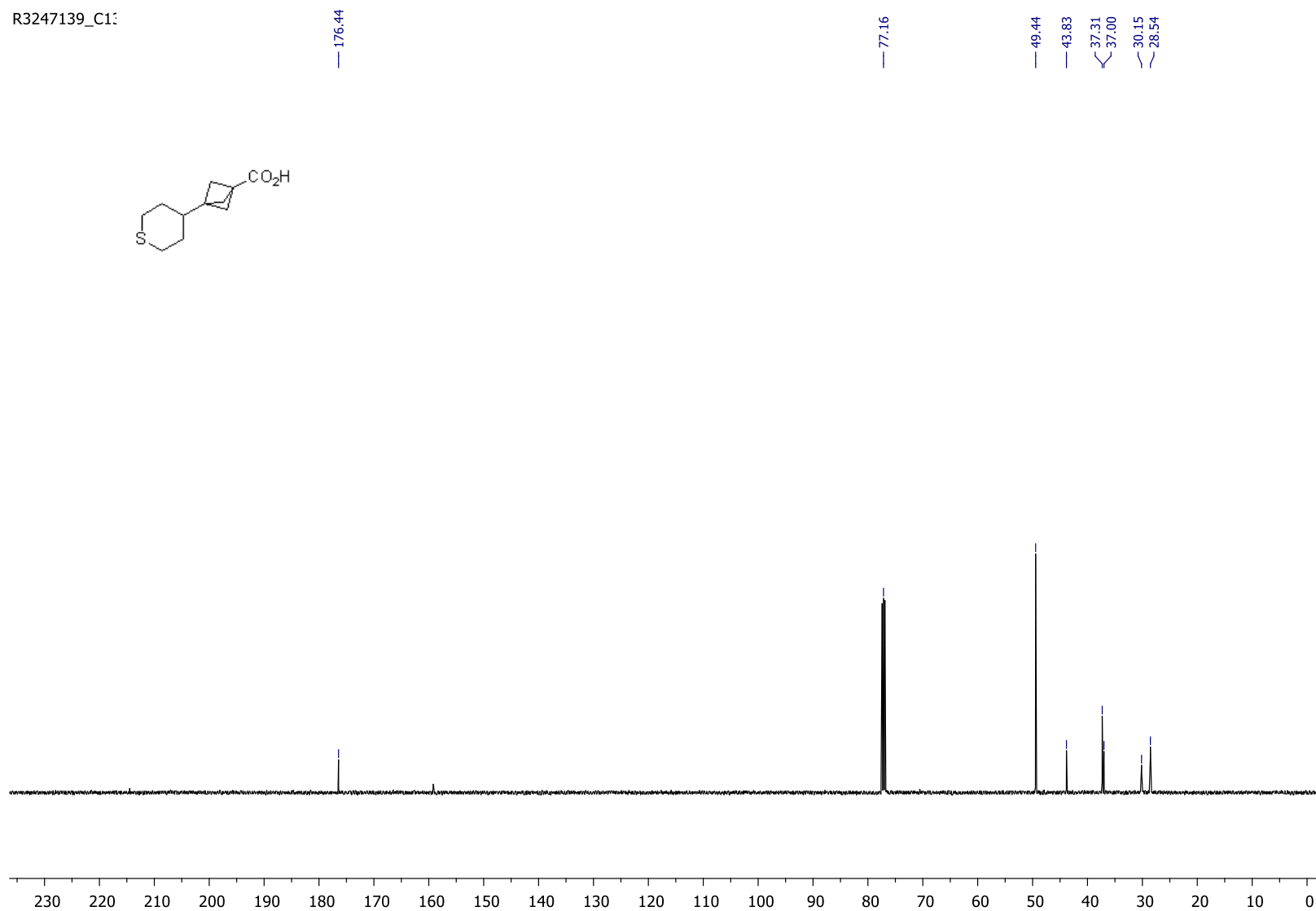
R3247139

¹H NMR (500 MHz, CDCl₃)



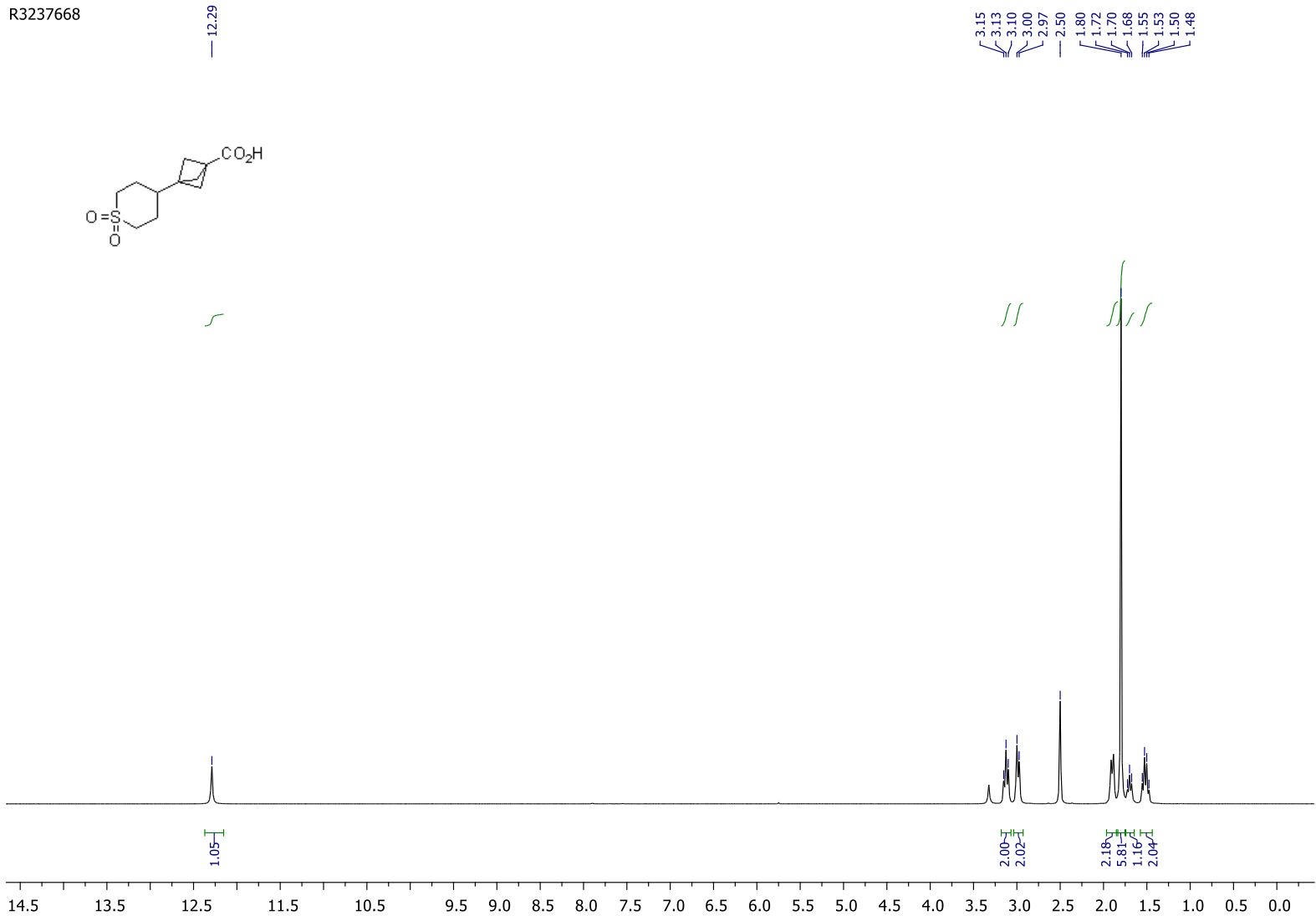
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R3247139_C13



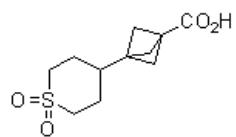
Compound (O2-59k)

¹H NMR (500 MHz, DMSO-d₆)



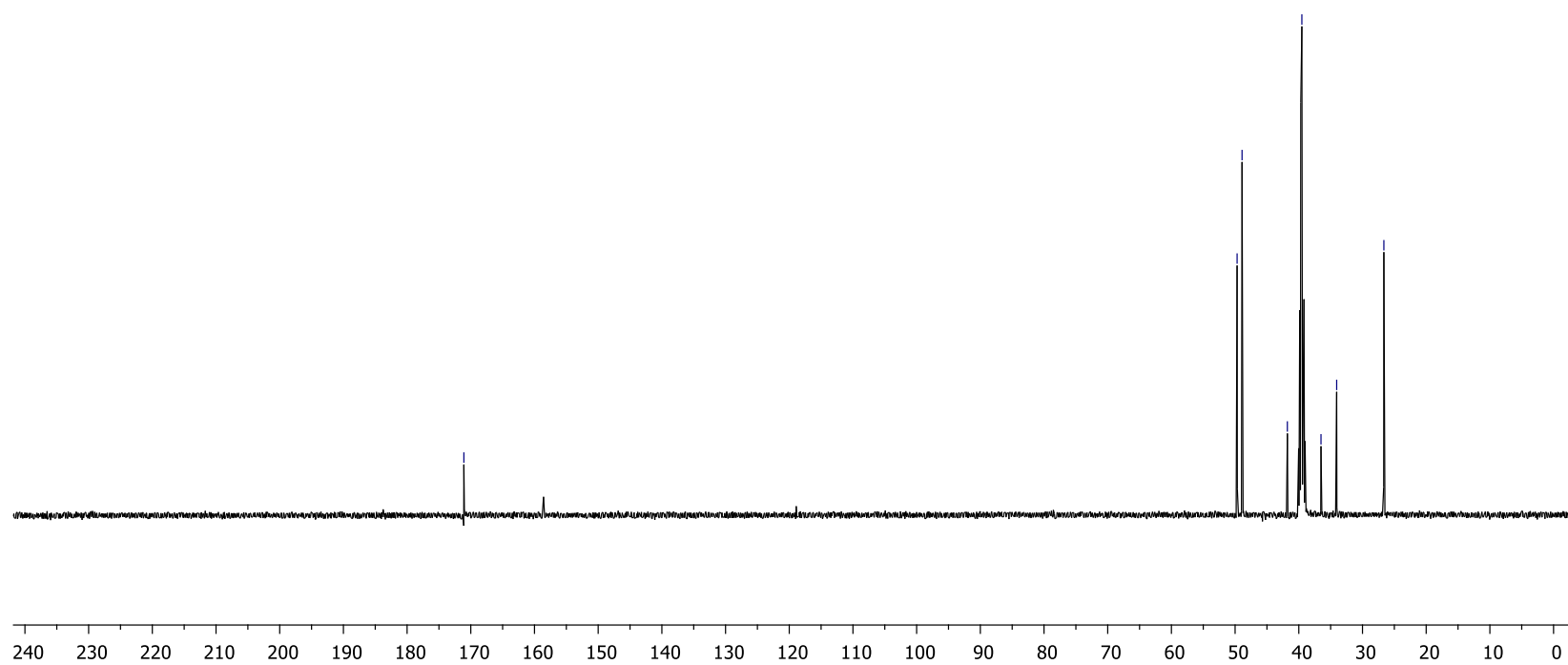
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R3237668_C1:

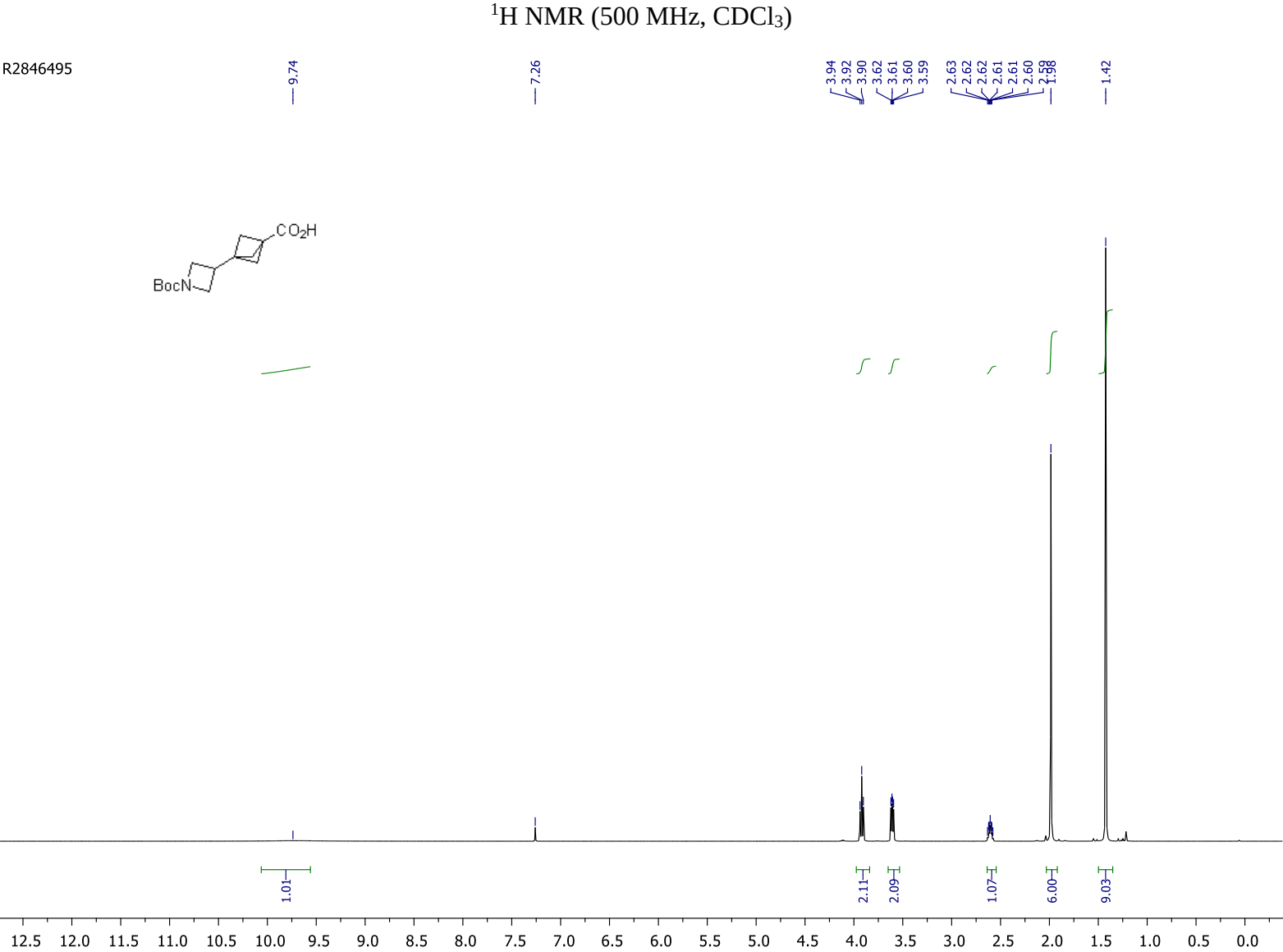


— 171.09

49.68
48.91
41.80
39.52
36.51
34.05
26.64

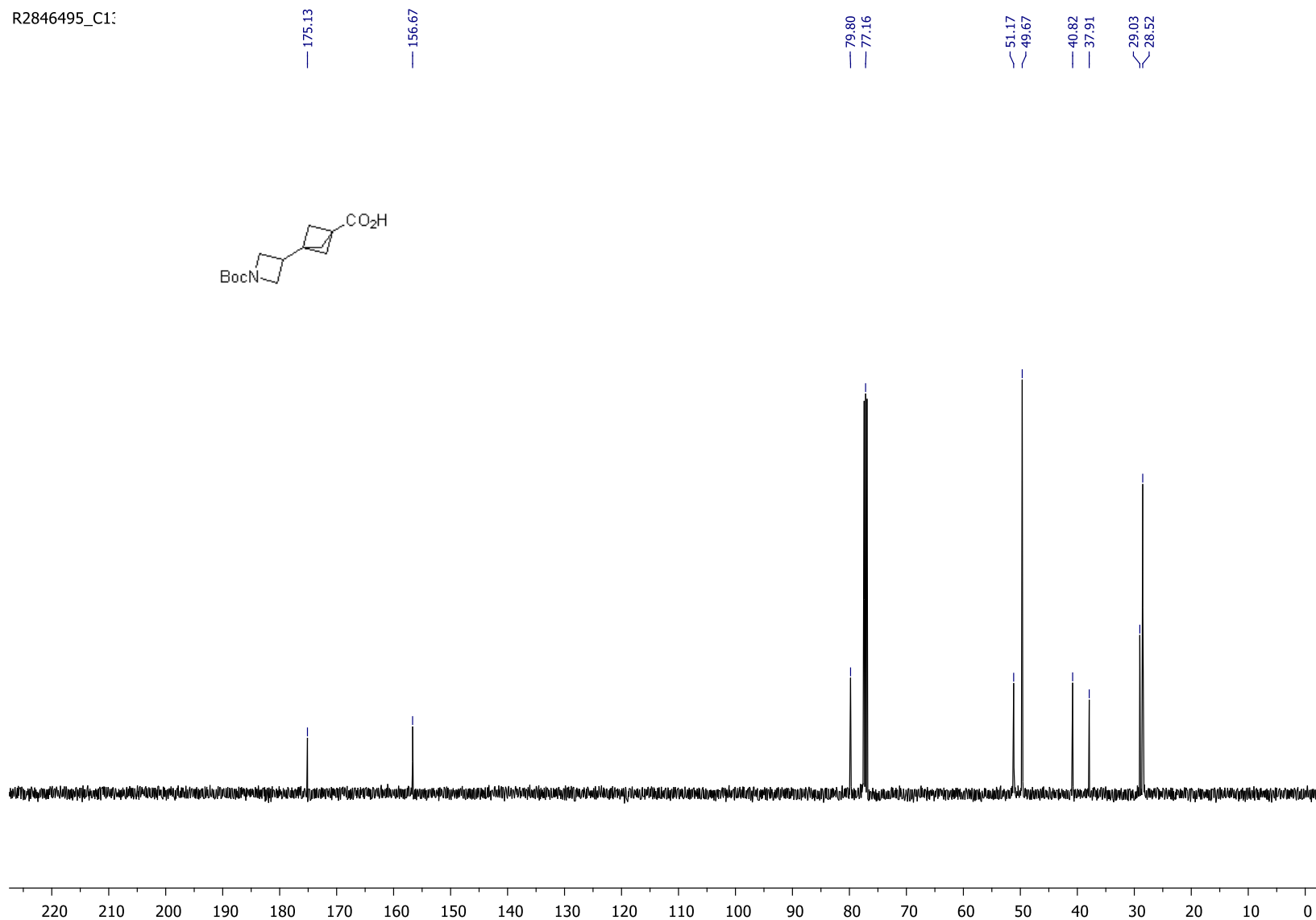


Compound 60k



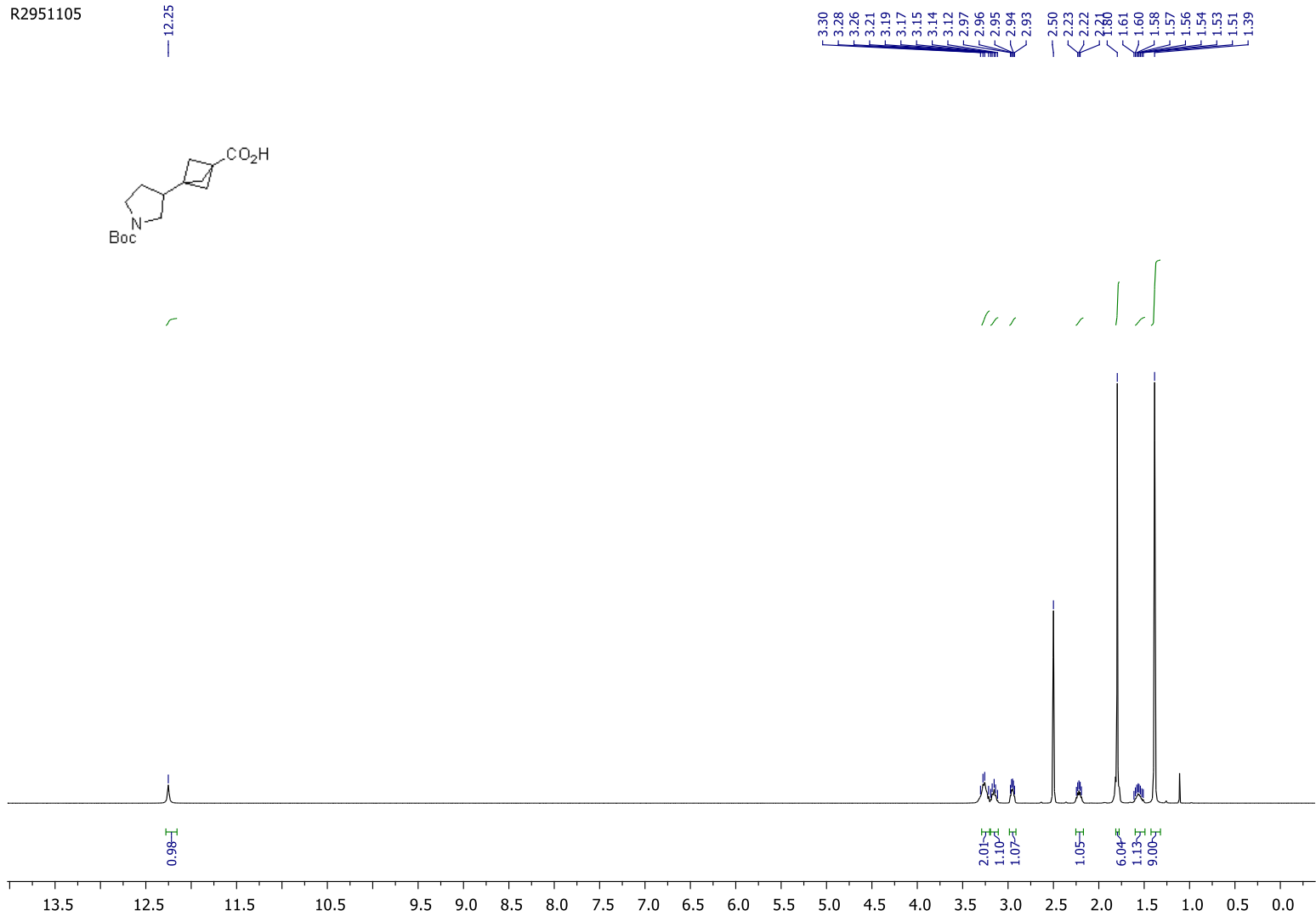
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

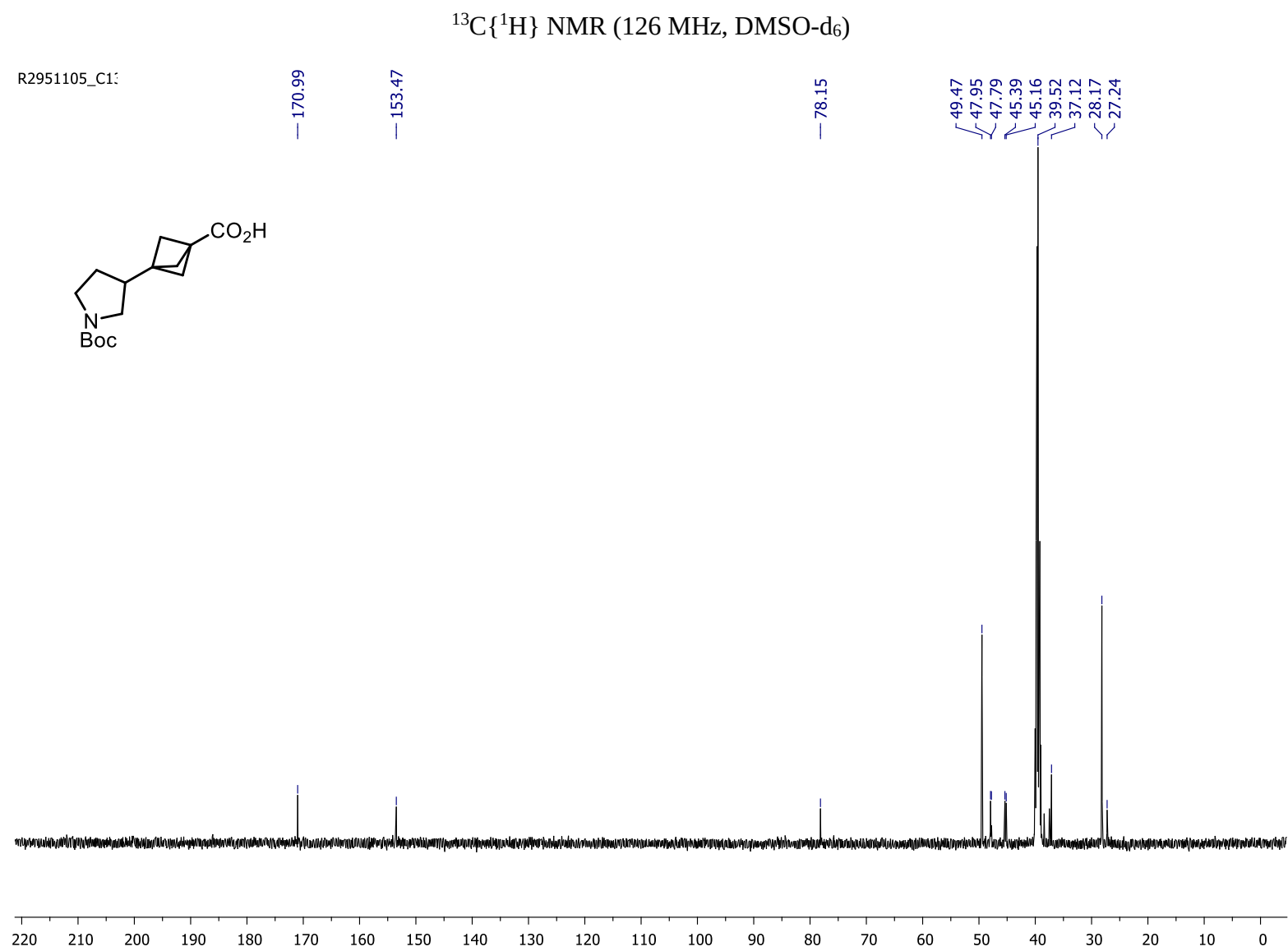
R2846495_C13



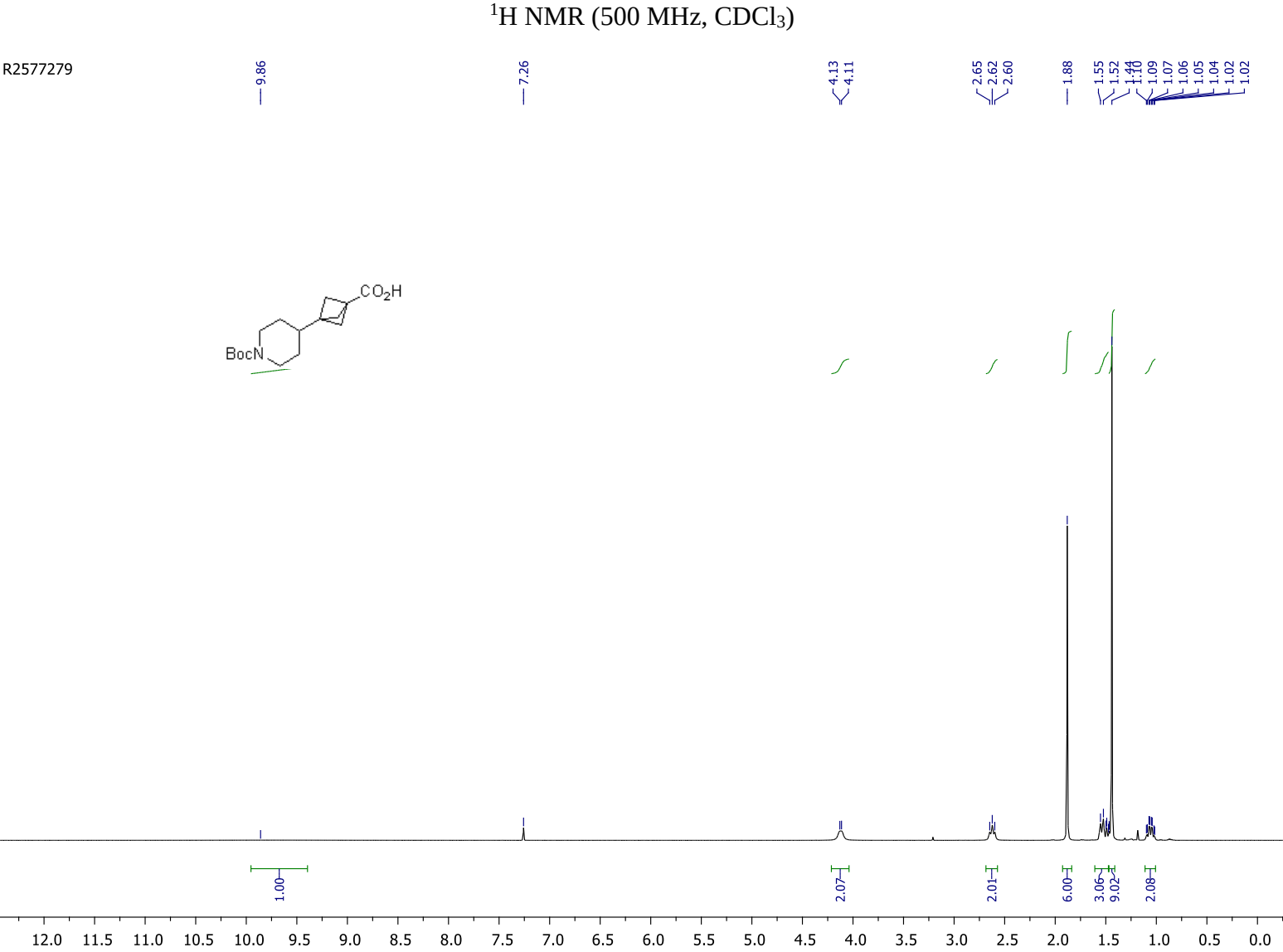
Compound 61k

¹H NMR (500 MHz, DMSO-d₆)





Compound 63k



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R2577279_C13

— 175.79

— 155.02

— 79.64

77.16

— 49.57

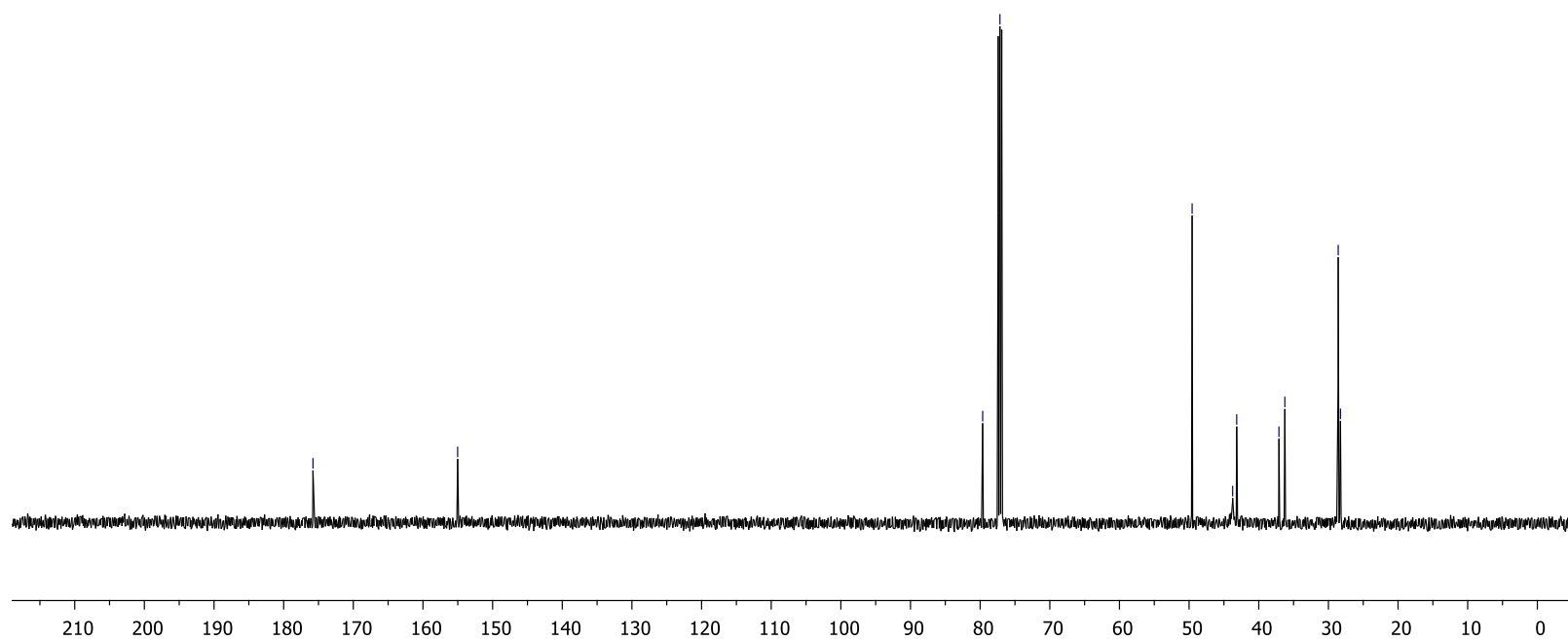
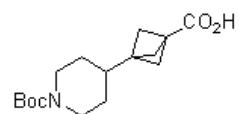
43.75

43.15
43.16

37.10
36.25

[illegible]

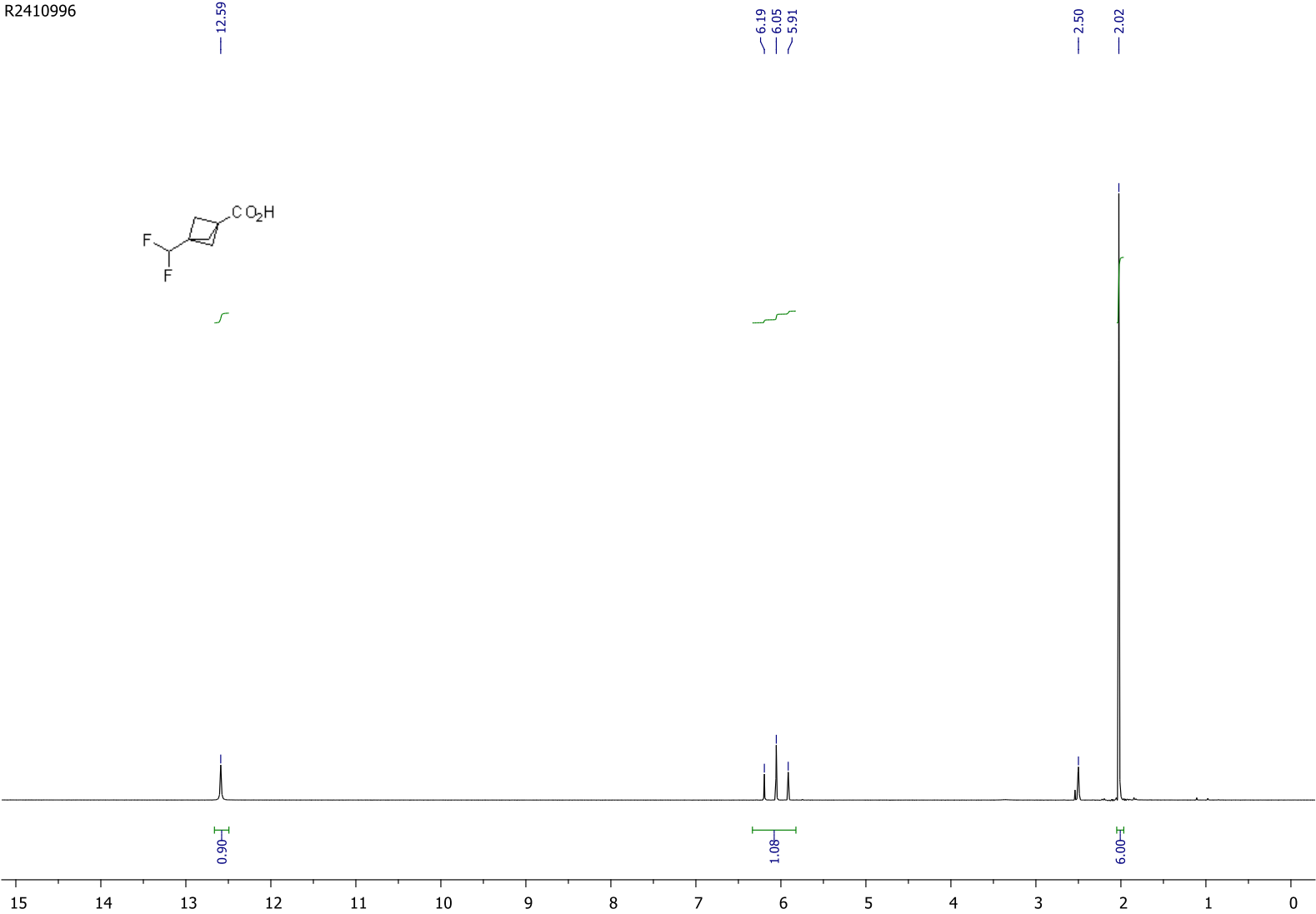
28.59

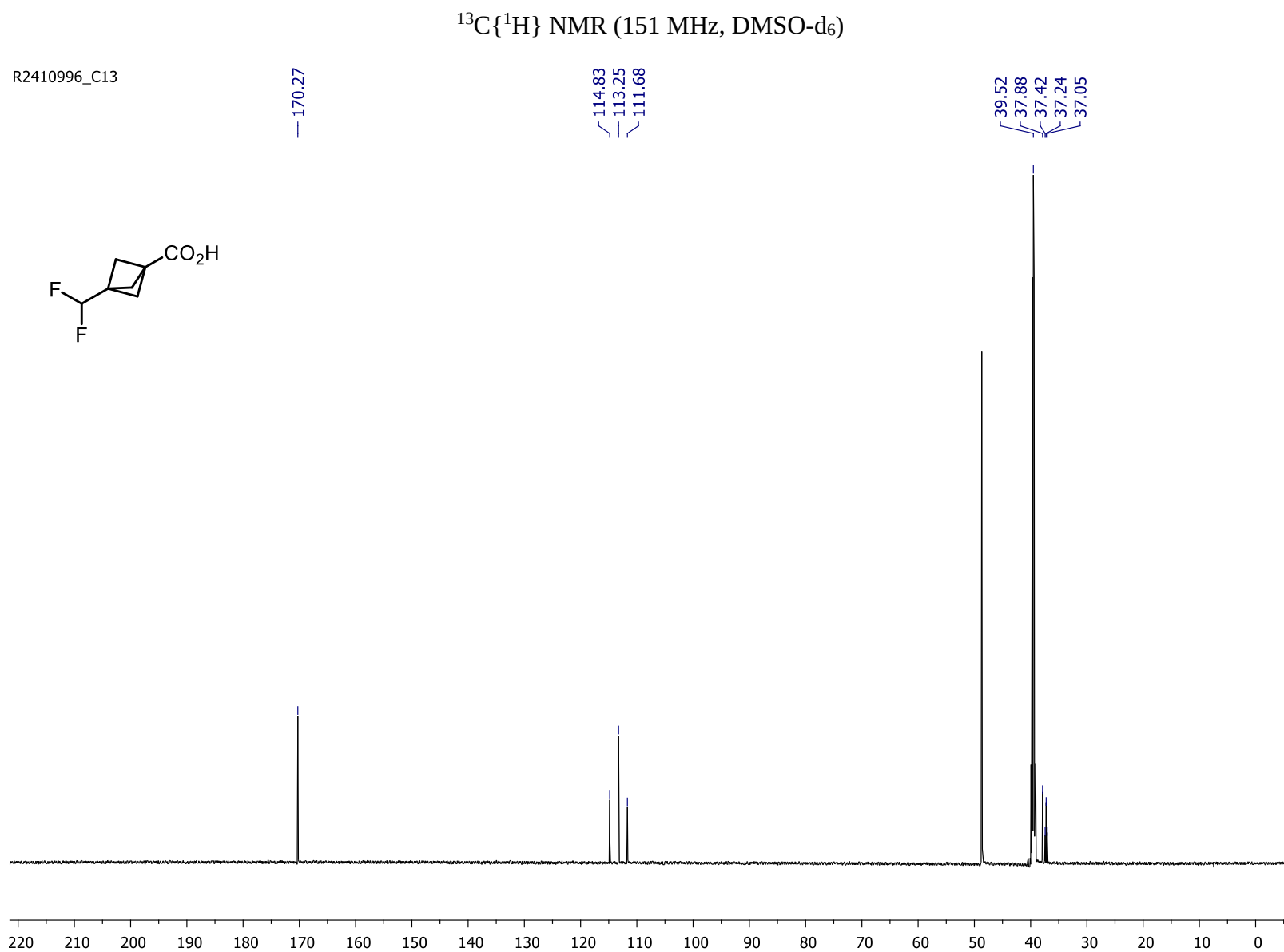


Compound 67k

¹H NMR (400 MHz, DMSO-d₆)

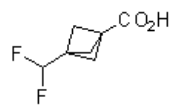
R2410996



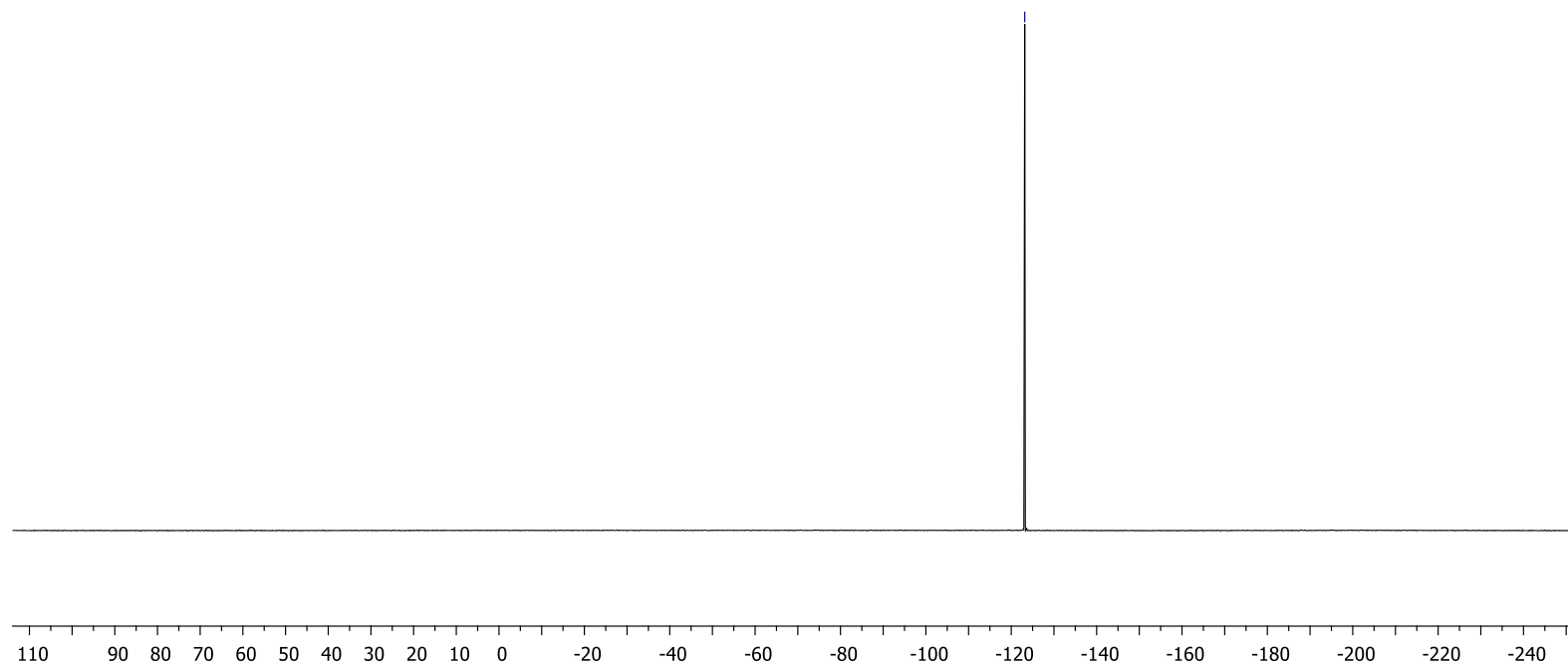


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

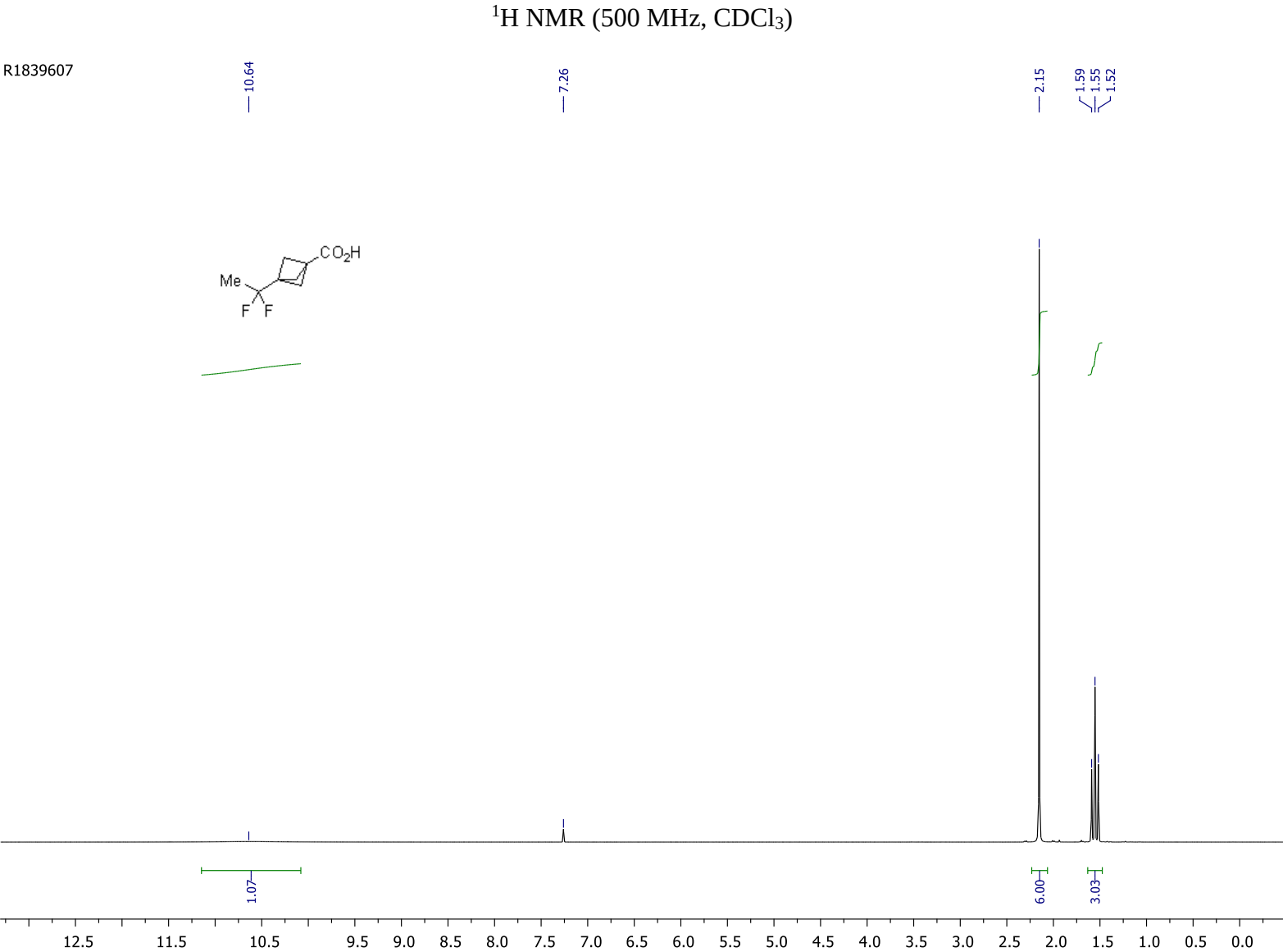
R2410996_F19{H}
19F-{1H}



— -123.16

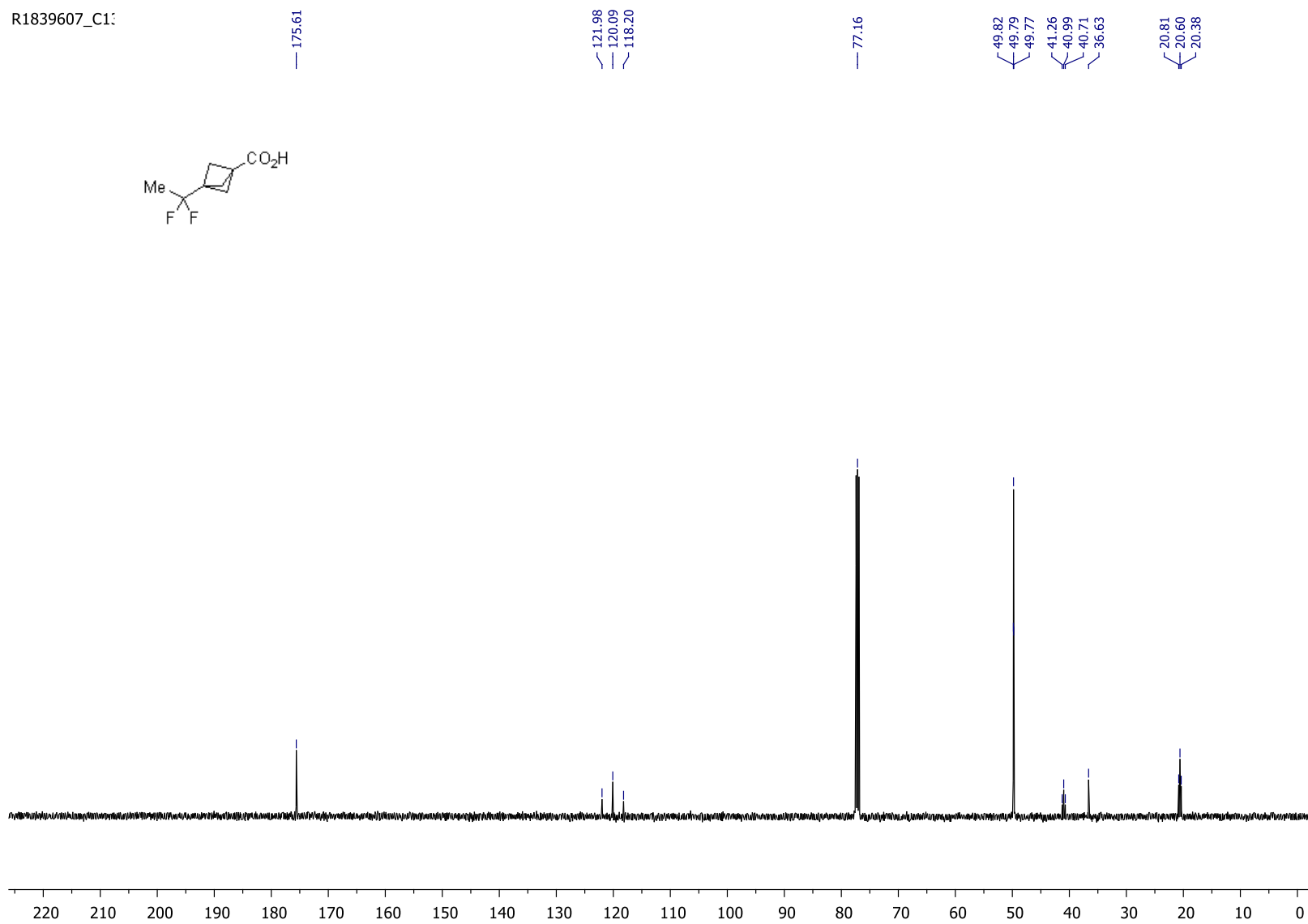
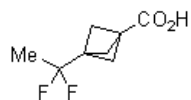


Compound 68k



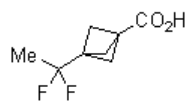
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R1839607_C1:

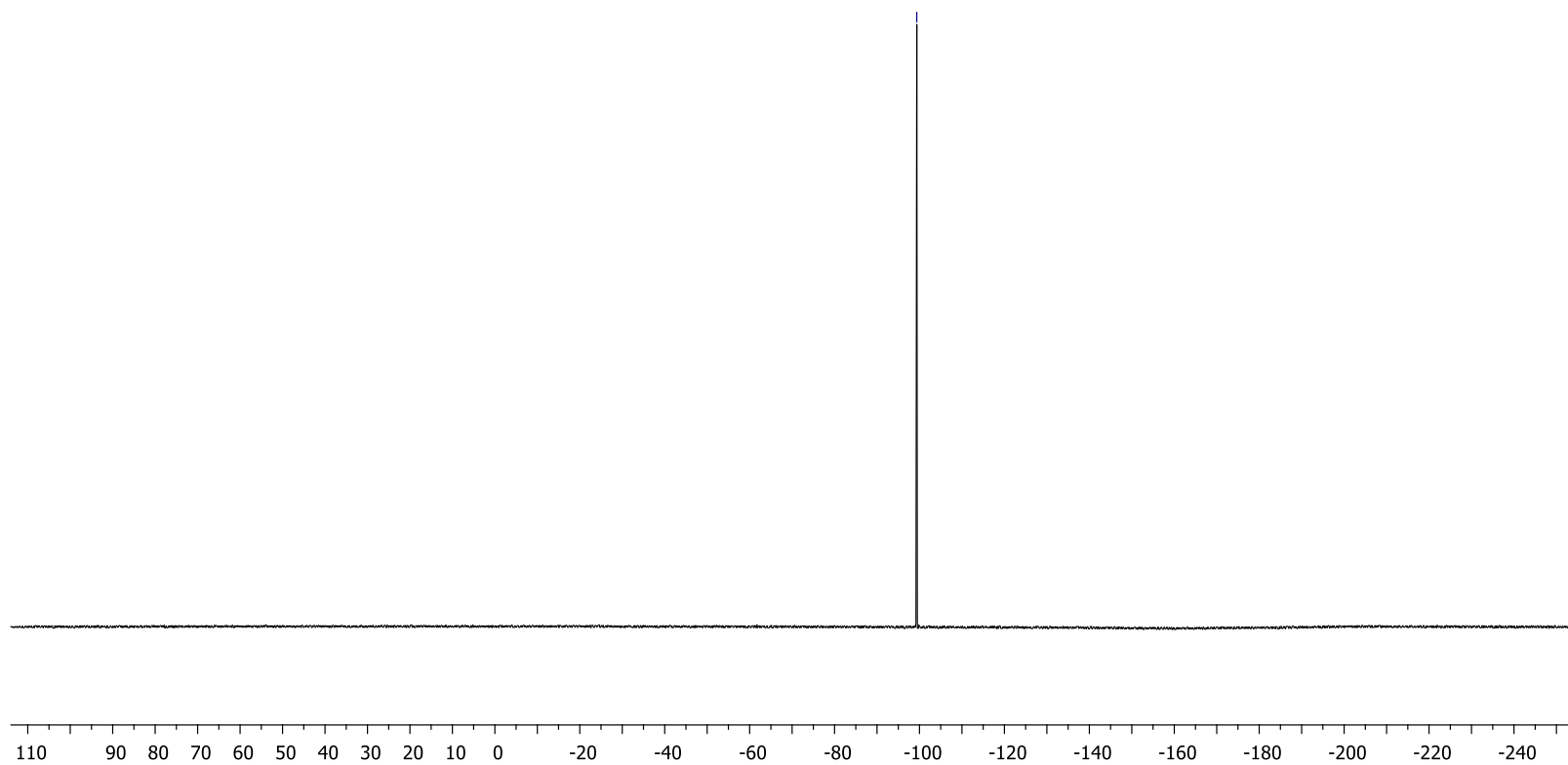


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

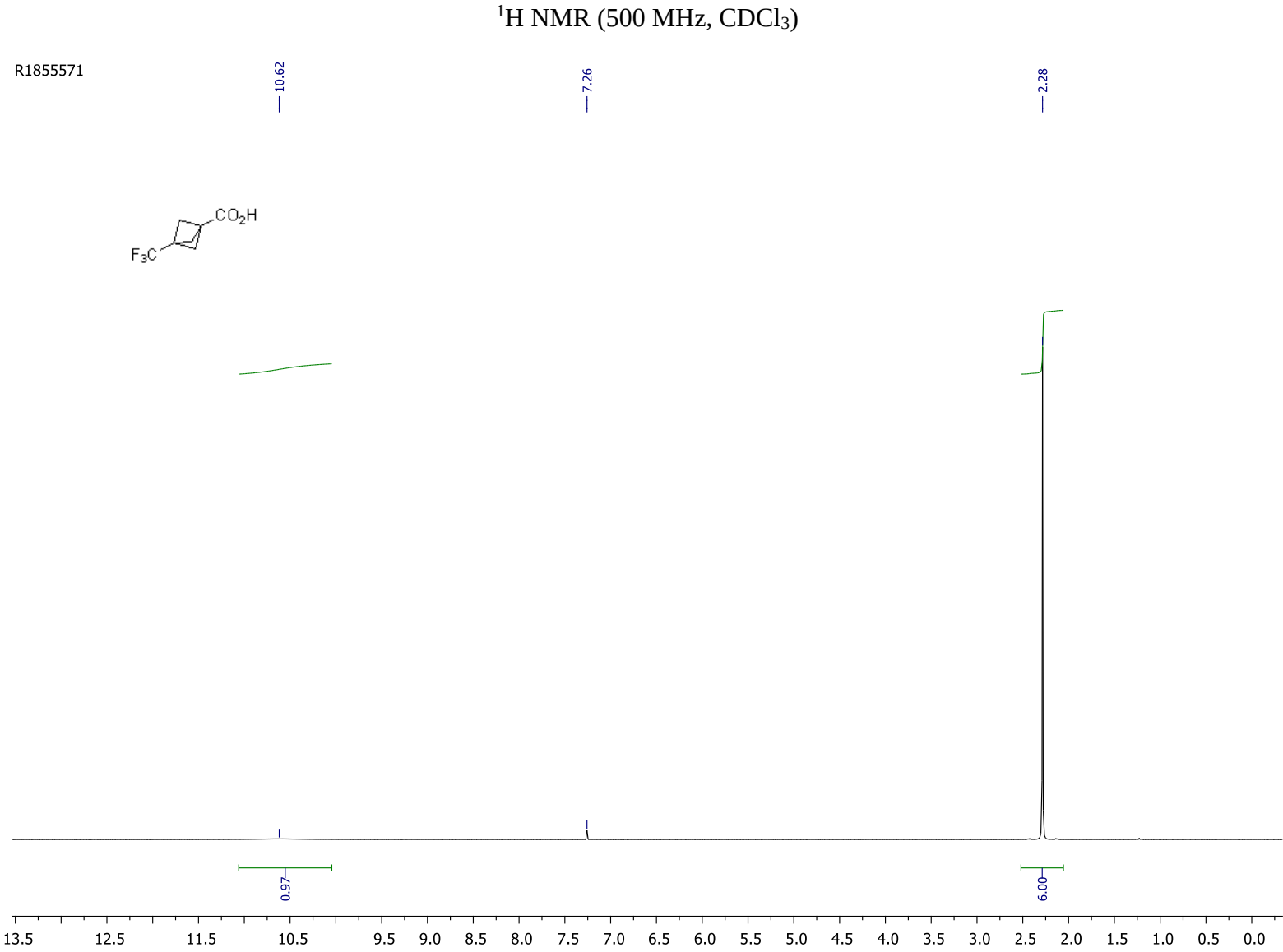
R1839607_F19{H}
19F-{1H}

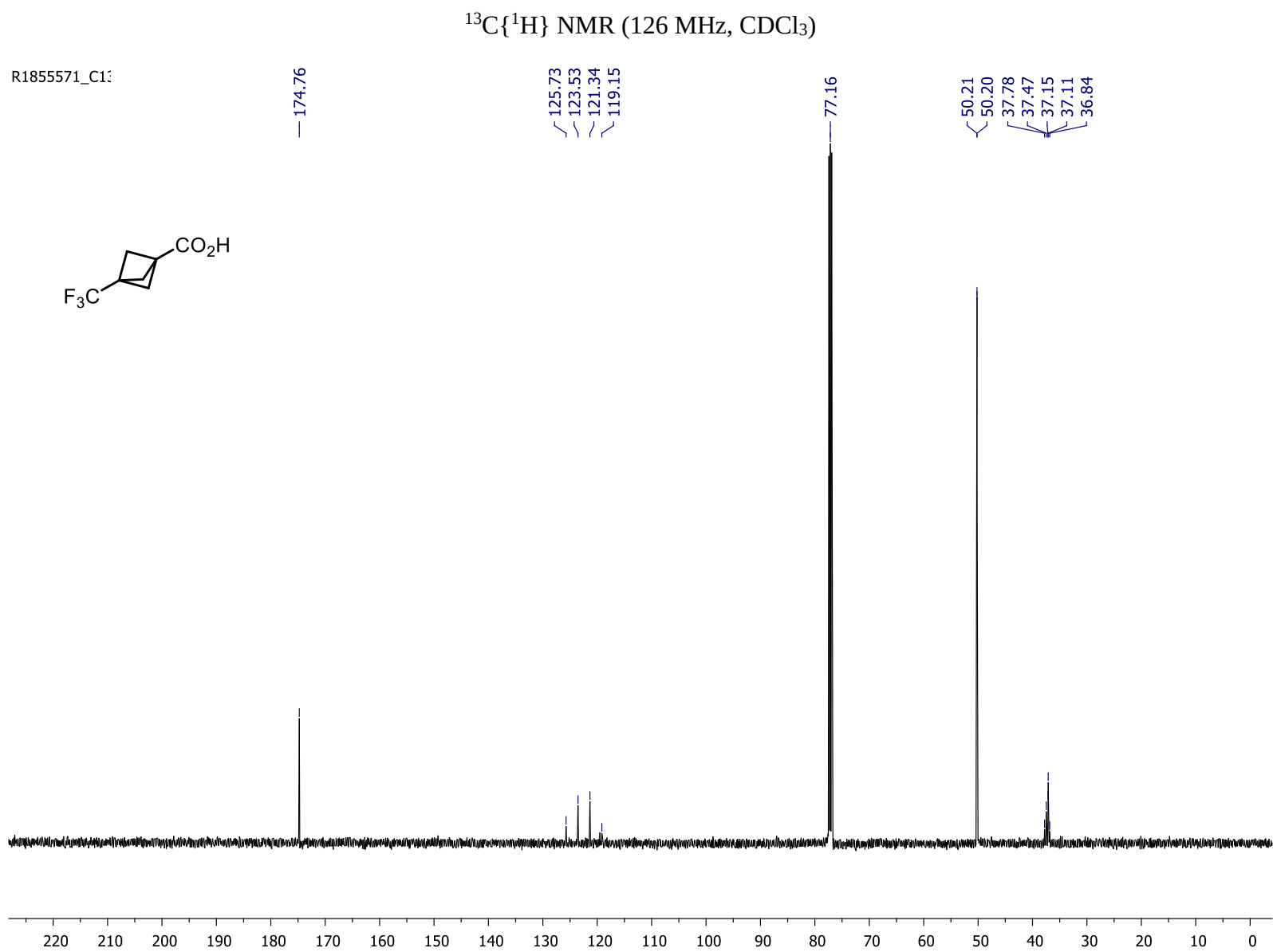


— -99.36



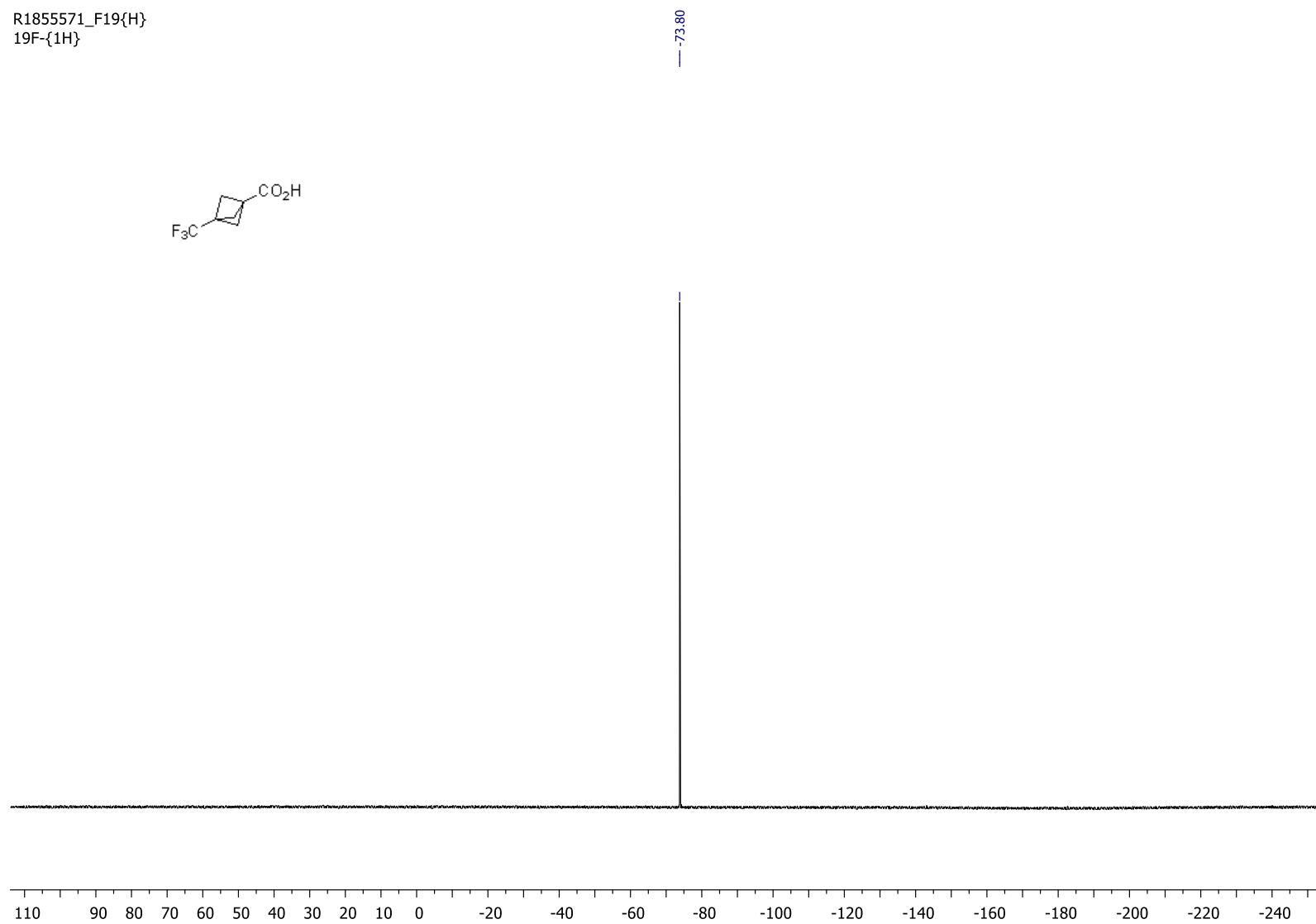
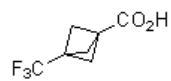
Compound 69k





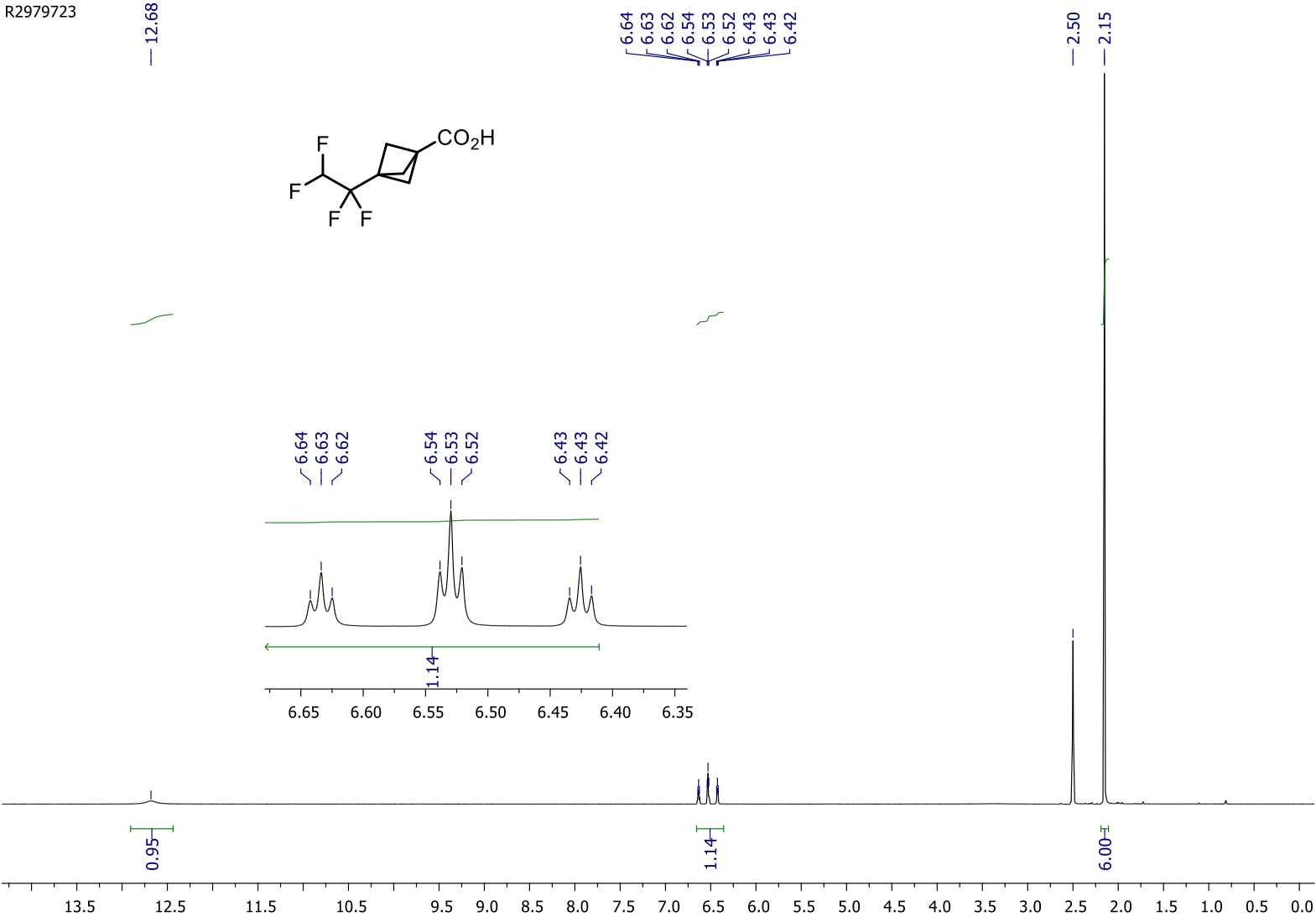
$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R1855571_F19{H}
19F-{1H}



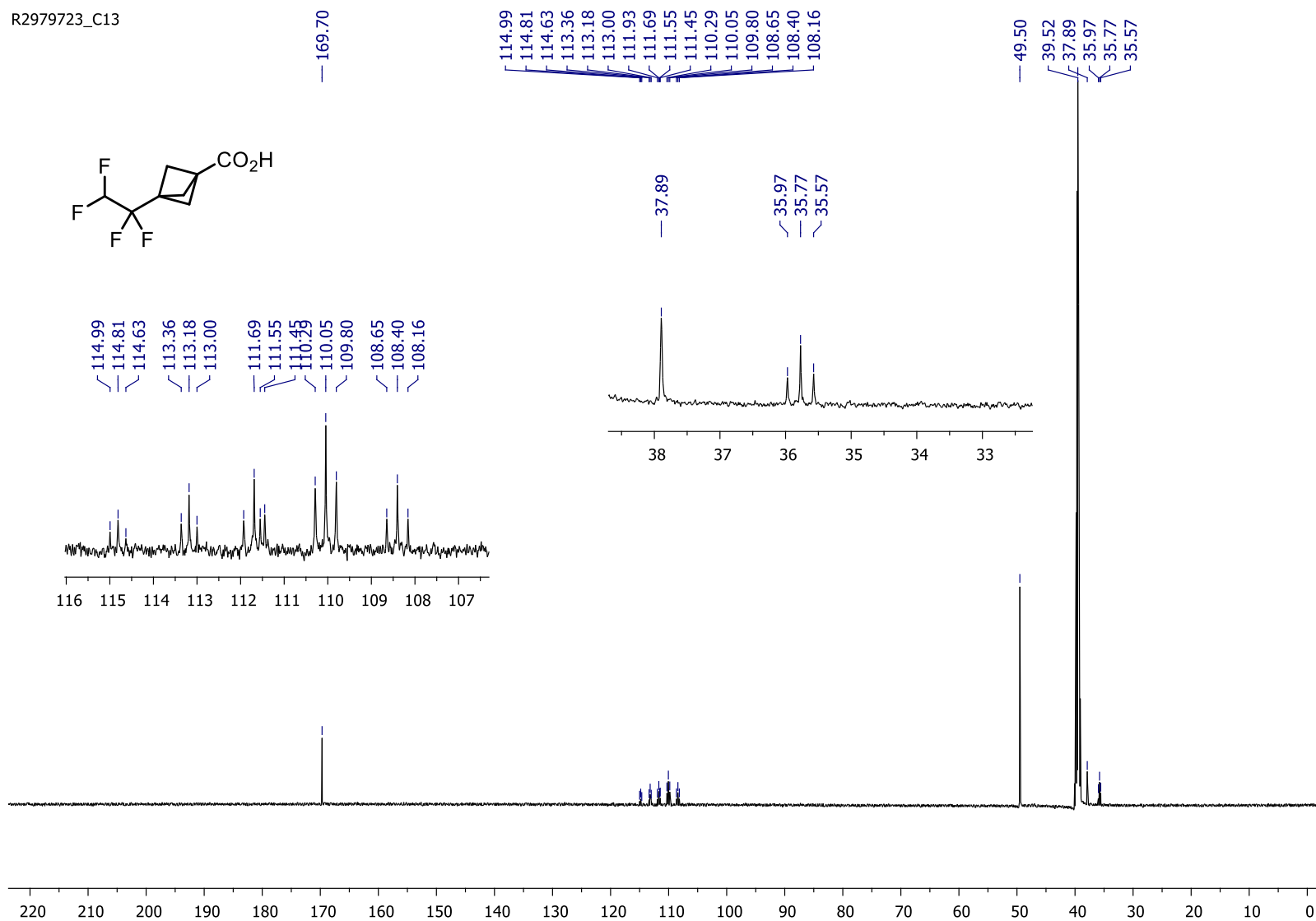
Compound 70k

¹H NMR (500 MHz, DMSO-d₆)



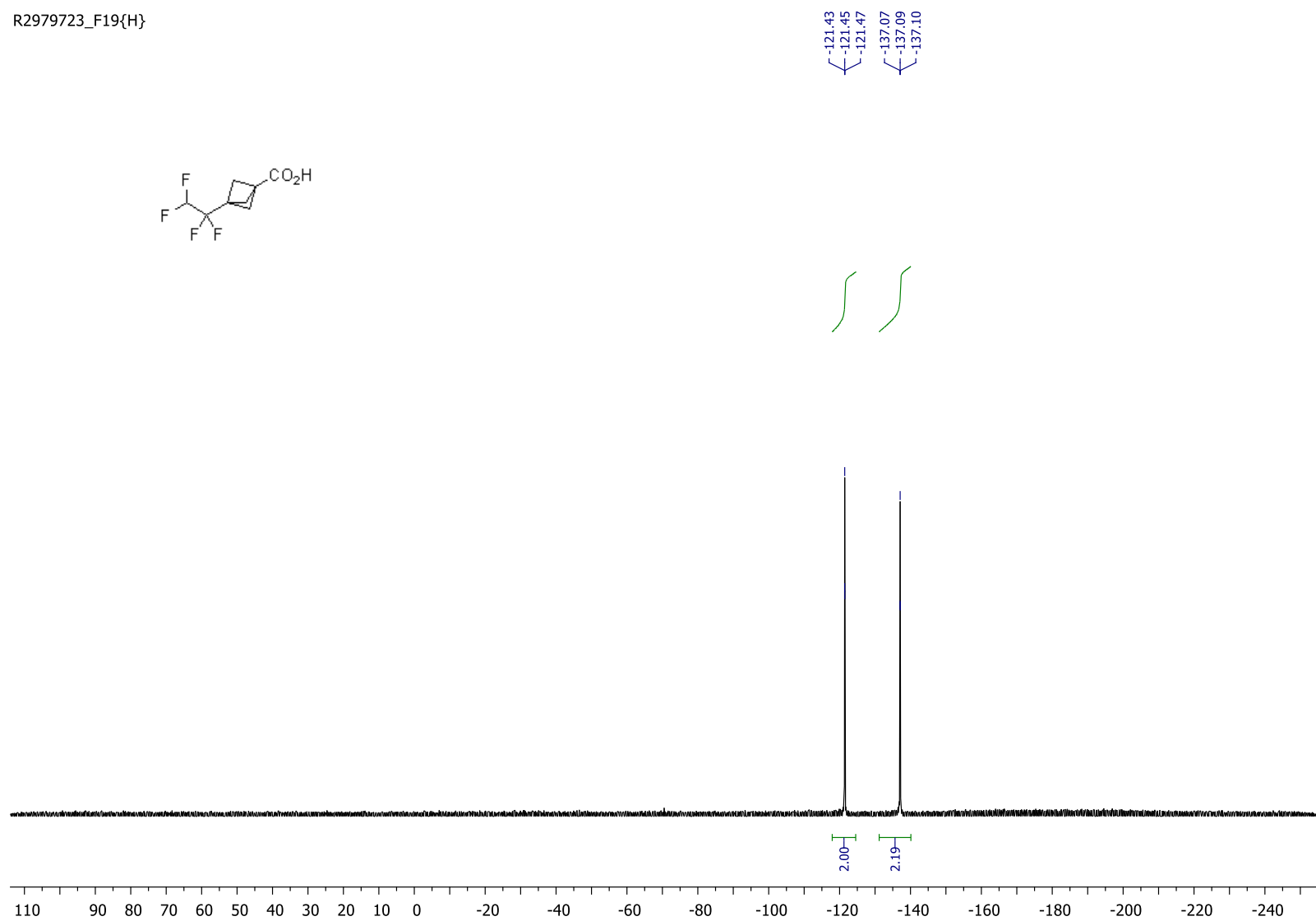
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2979723_C13

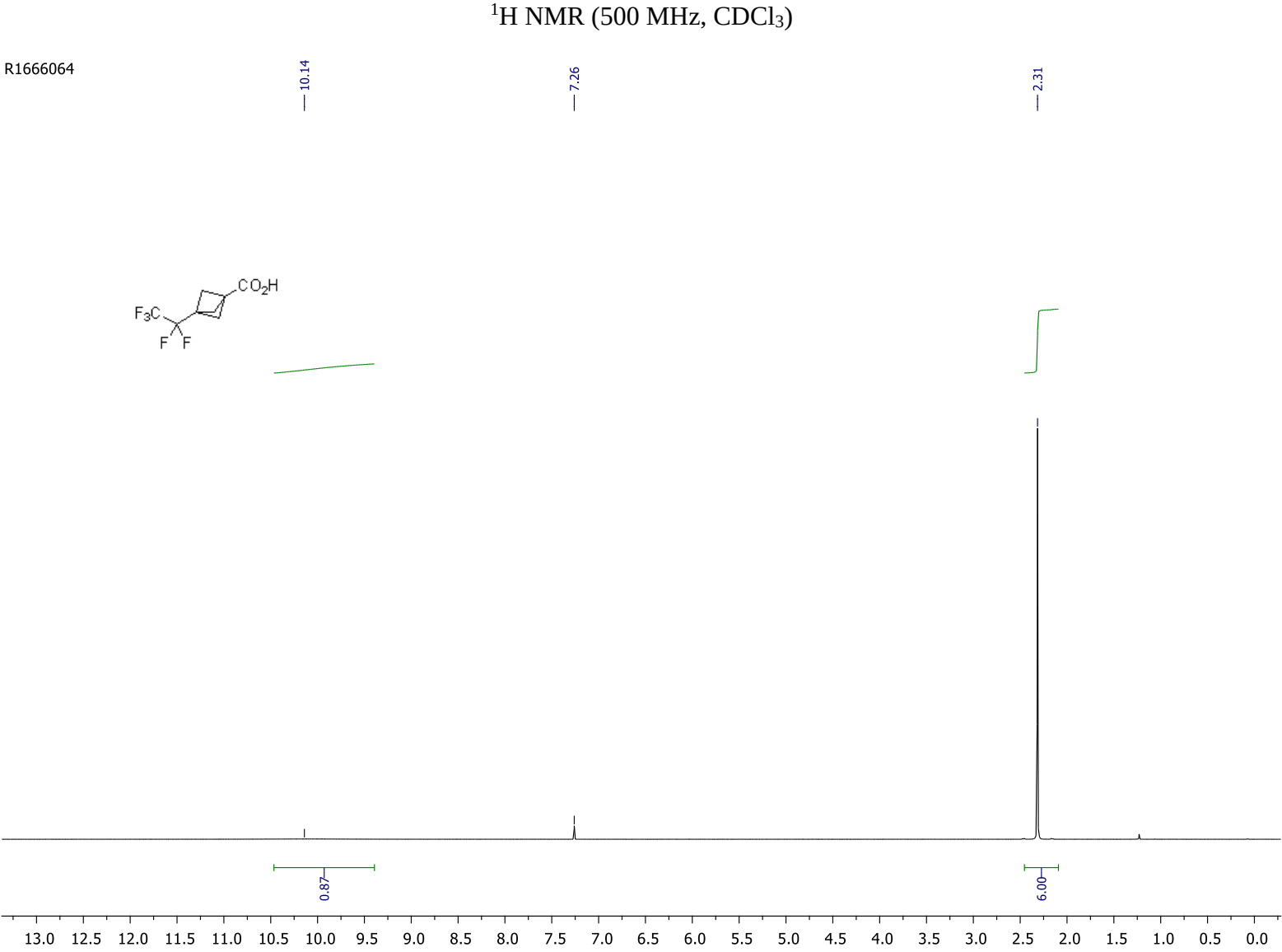


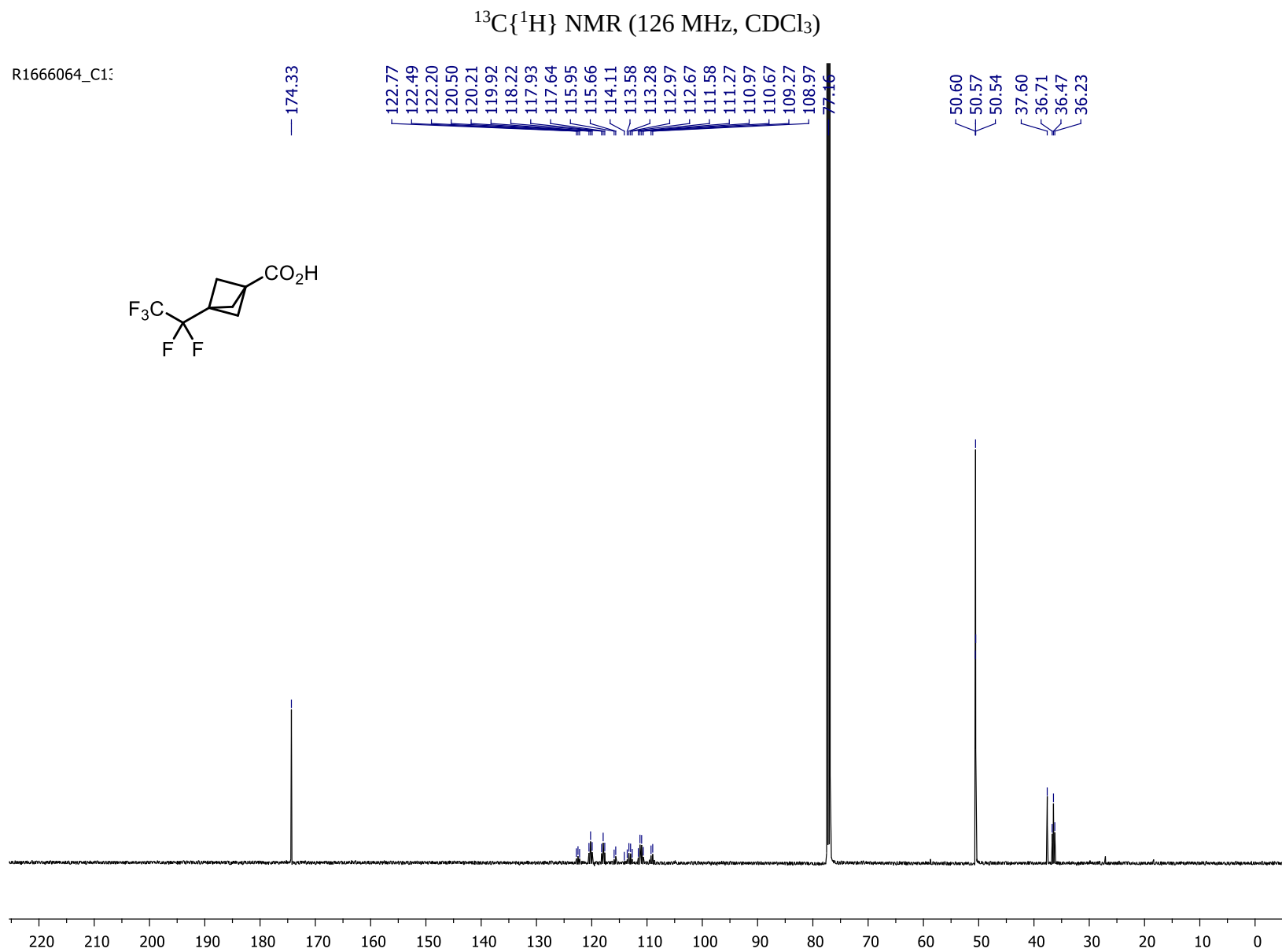
$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2979723_F19{H}



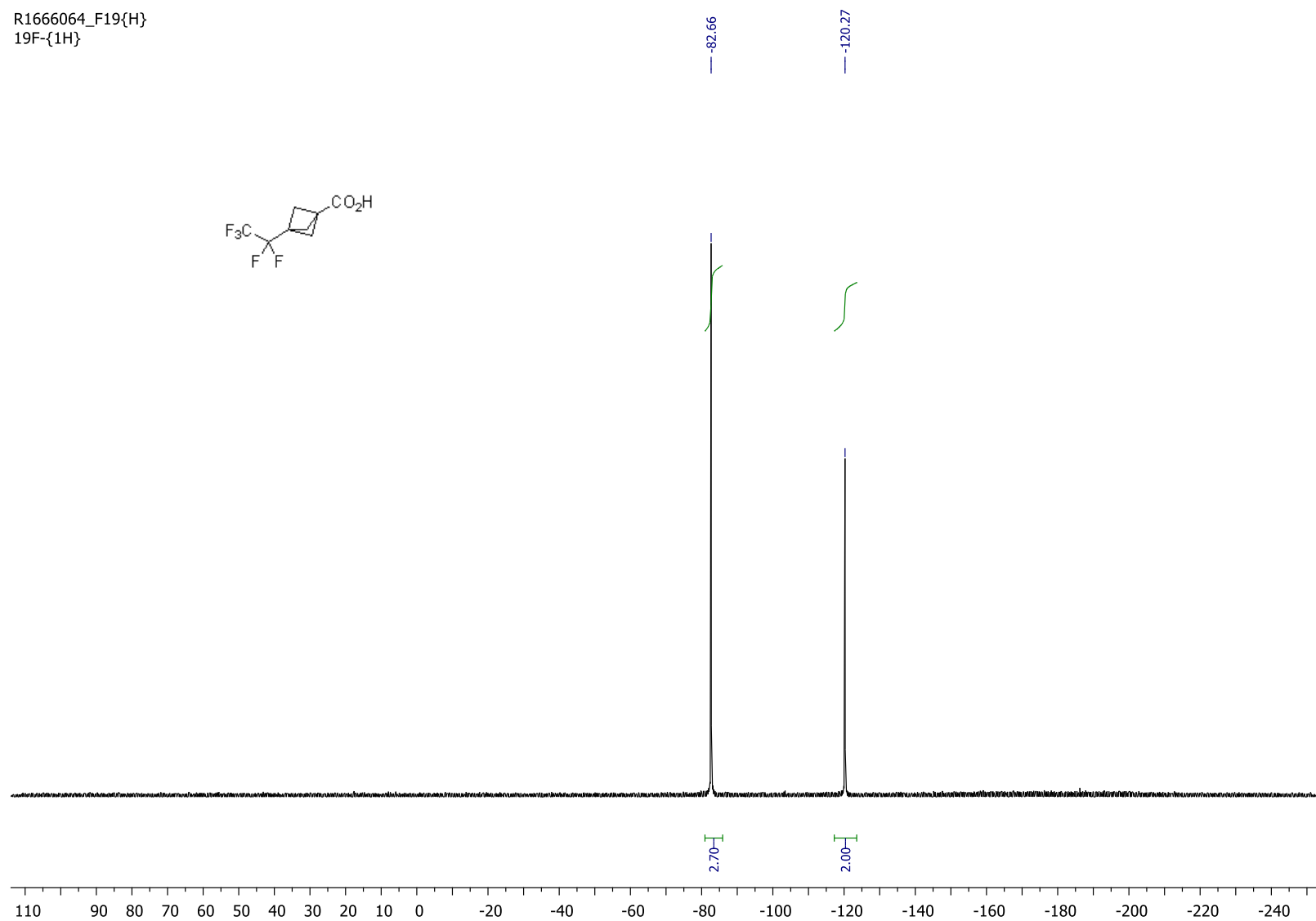
Compound 71k



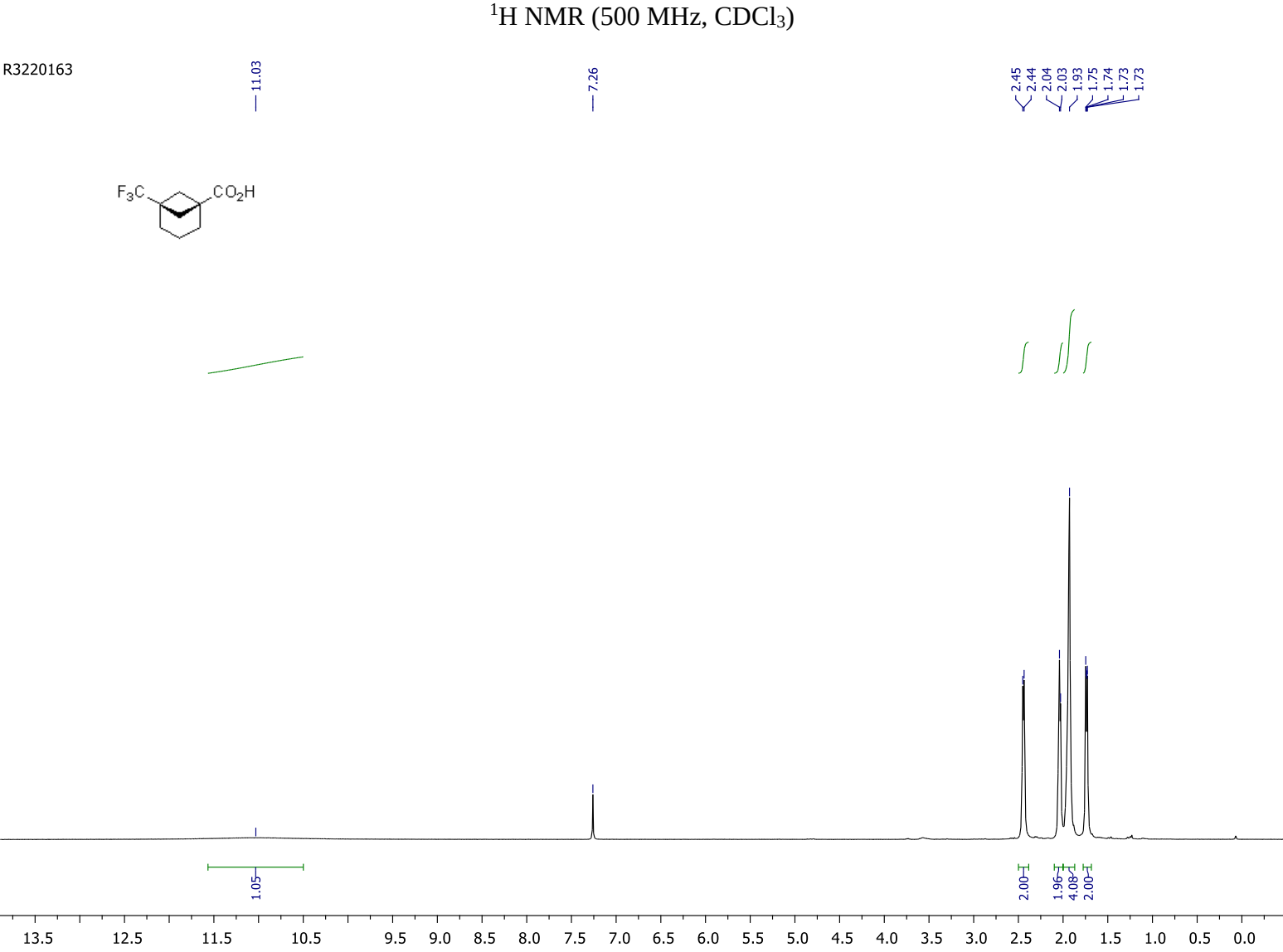


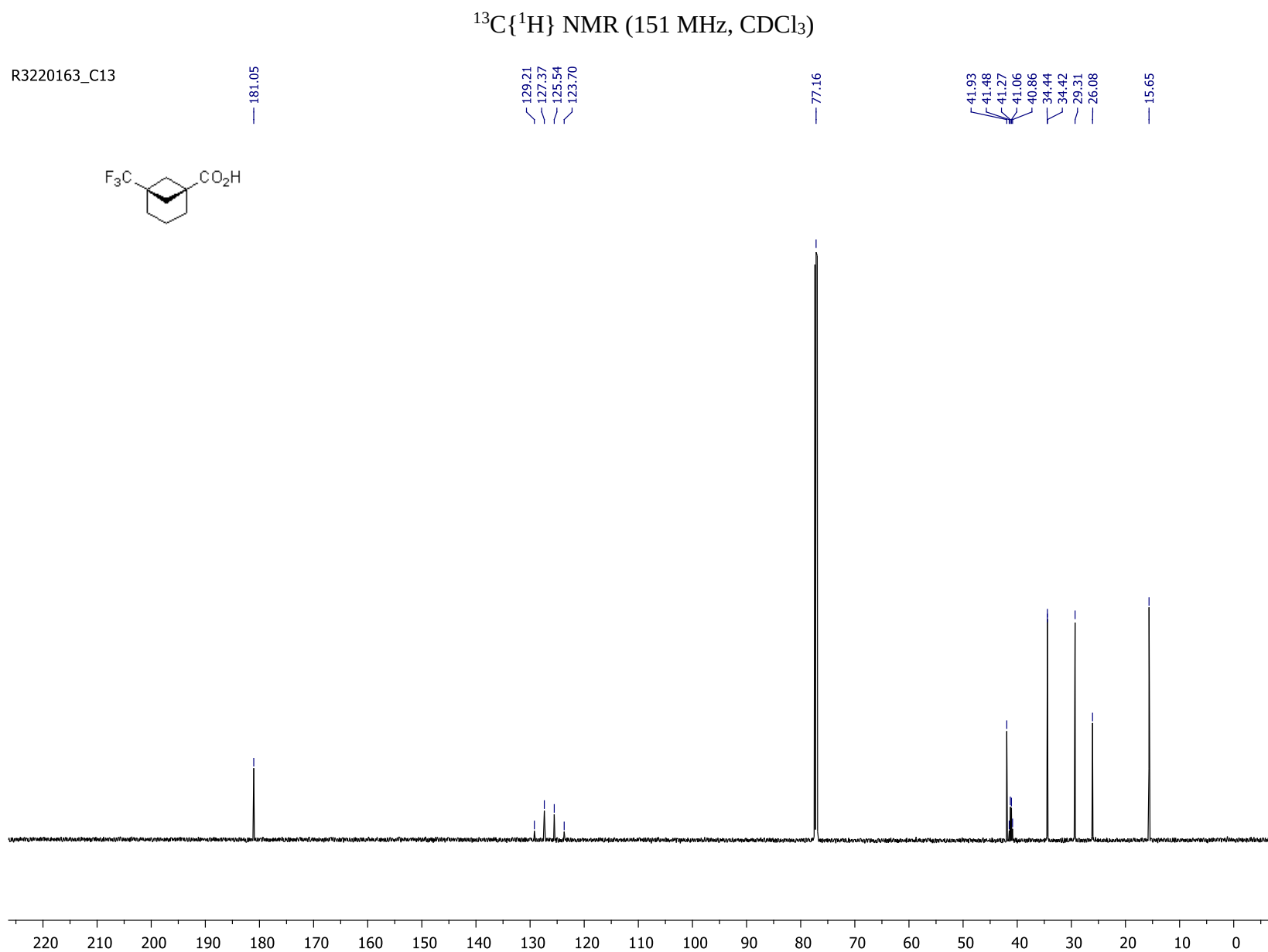
$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

R1666064_F19{H}
 $^{19}\text{F}\{^1\text{H}\}$



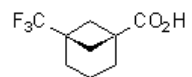
Compound 79k



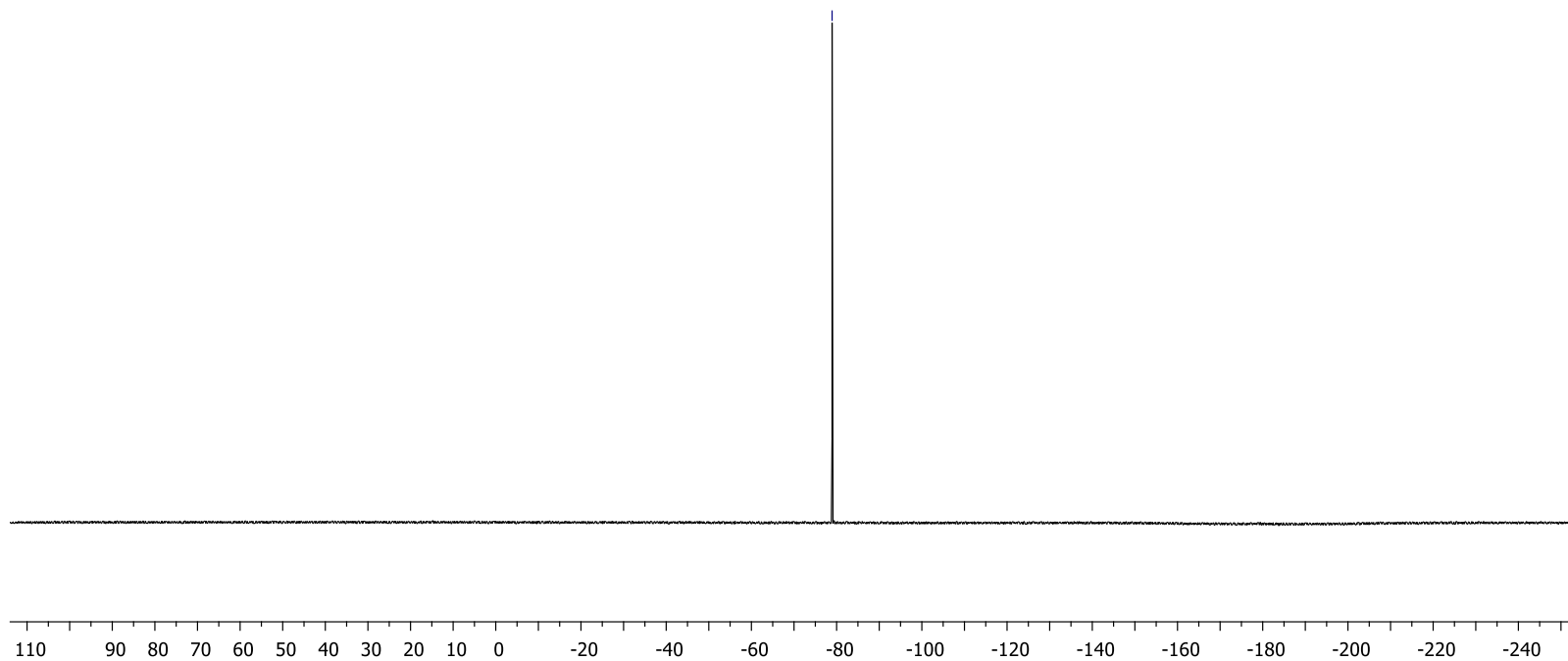


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3)

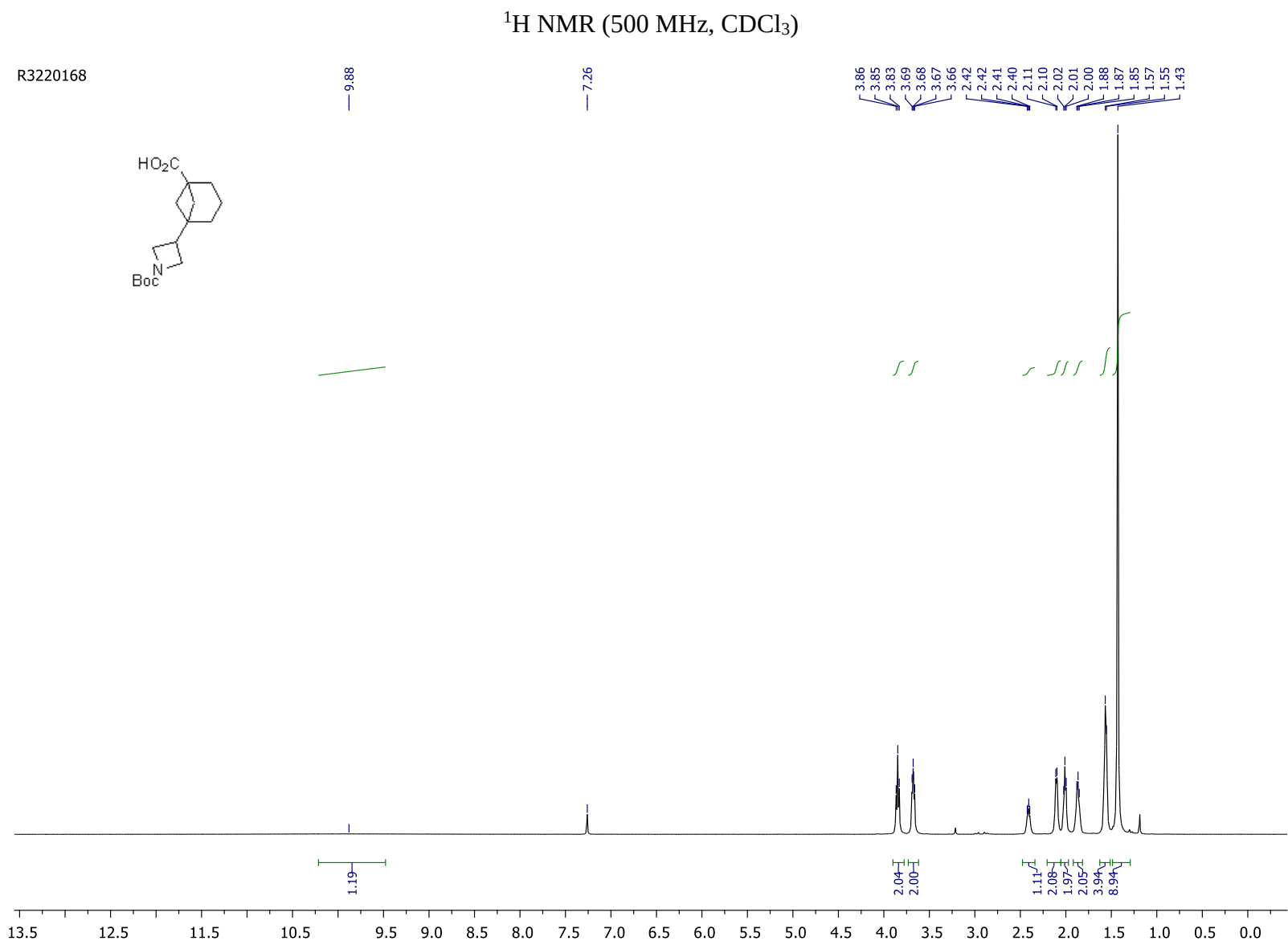
R3220163_F19{H}



— -78.94

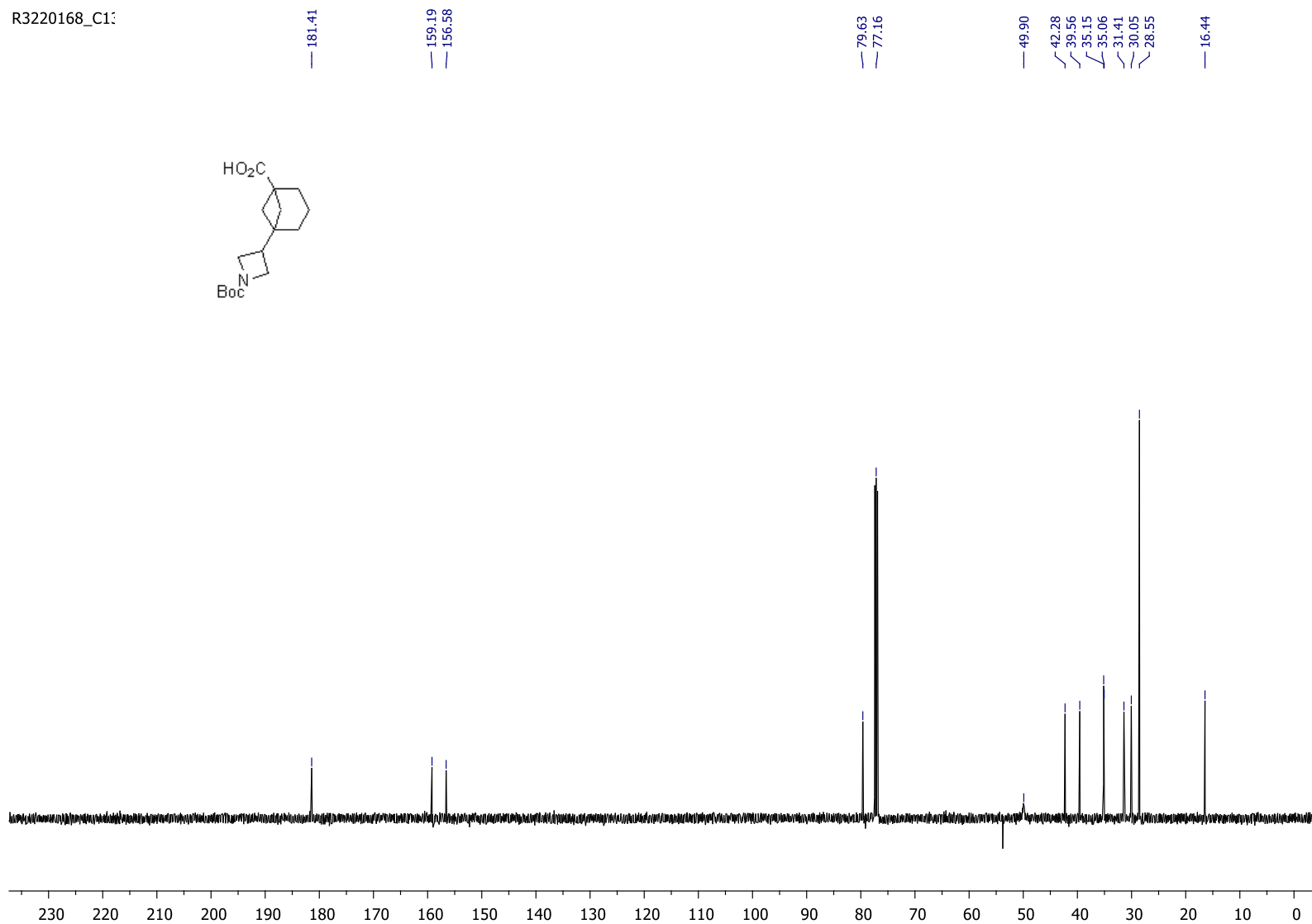
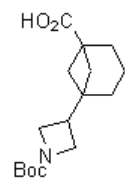


Compound 80k



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

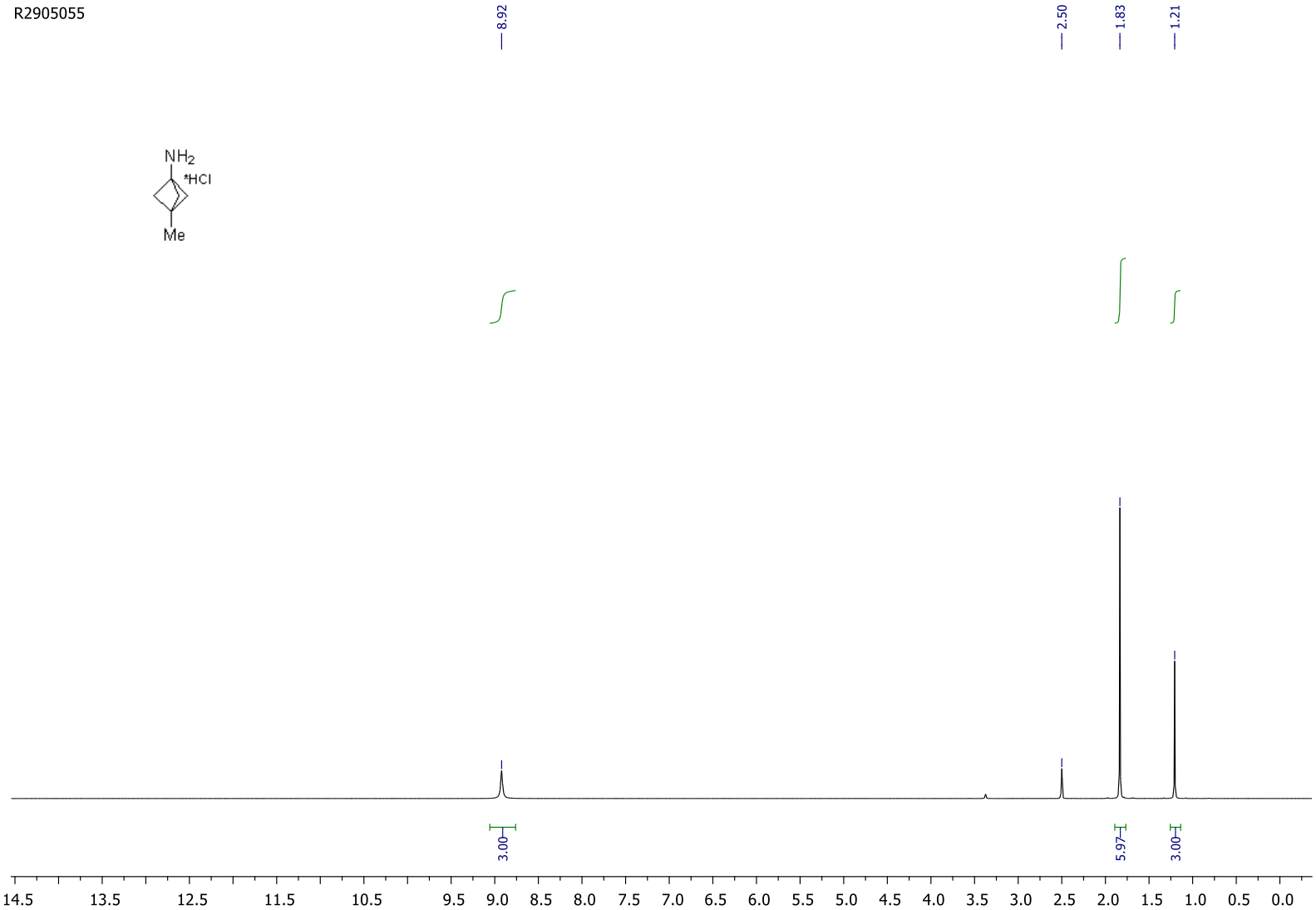
R3220168_C13



Compound 1l

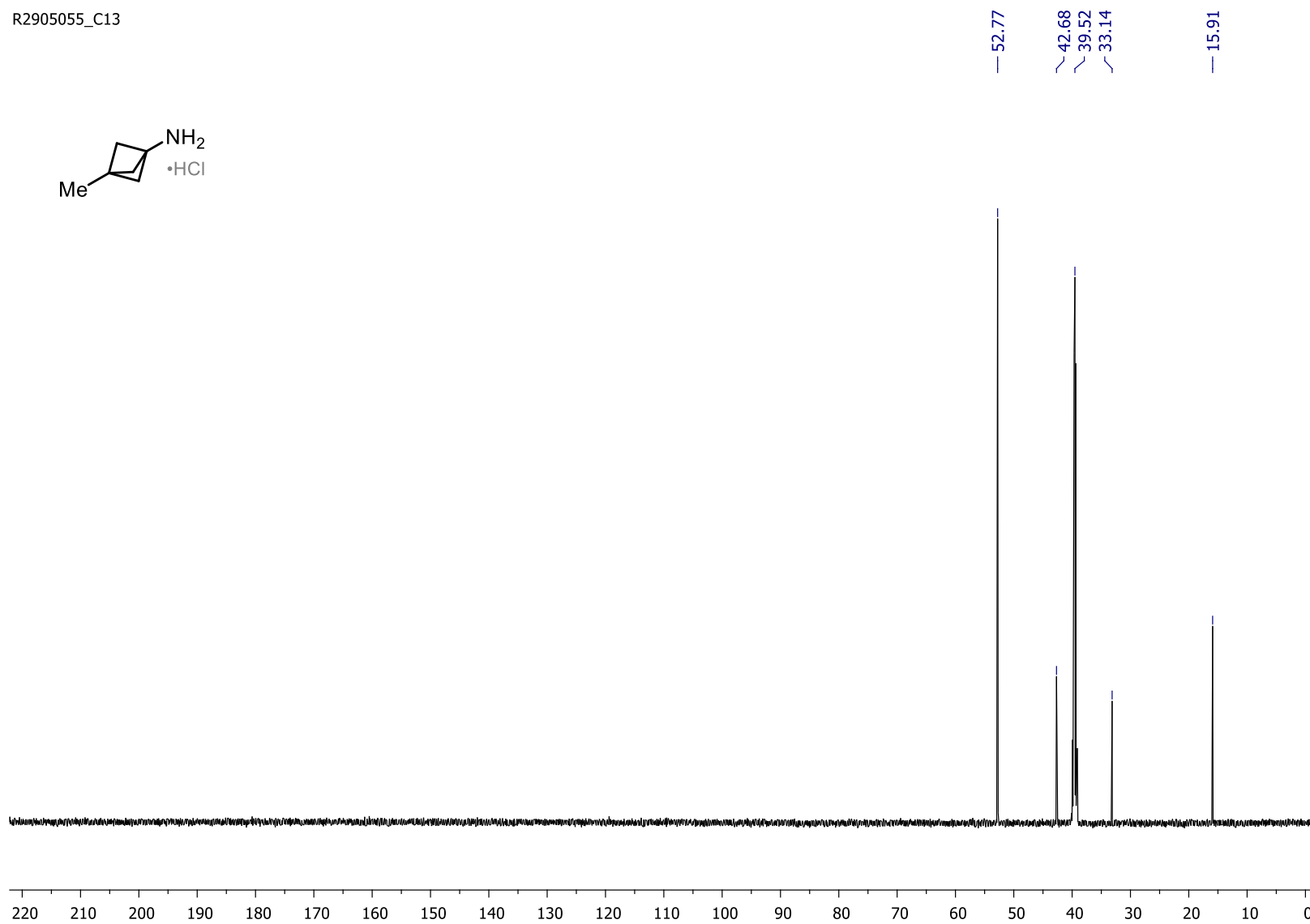
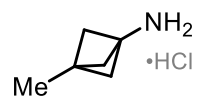
R2905055

¹H NMR (500 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

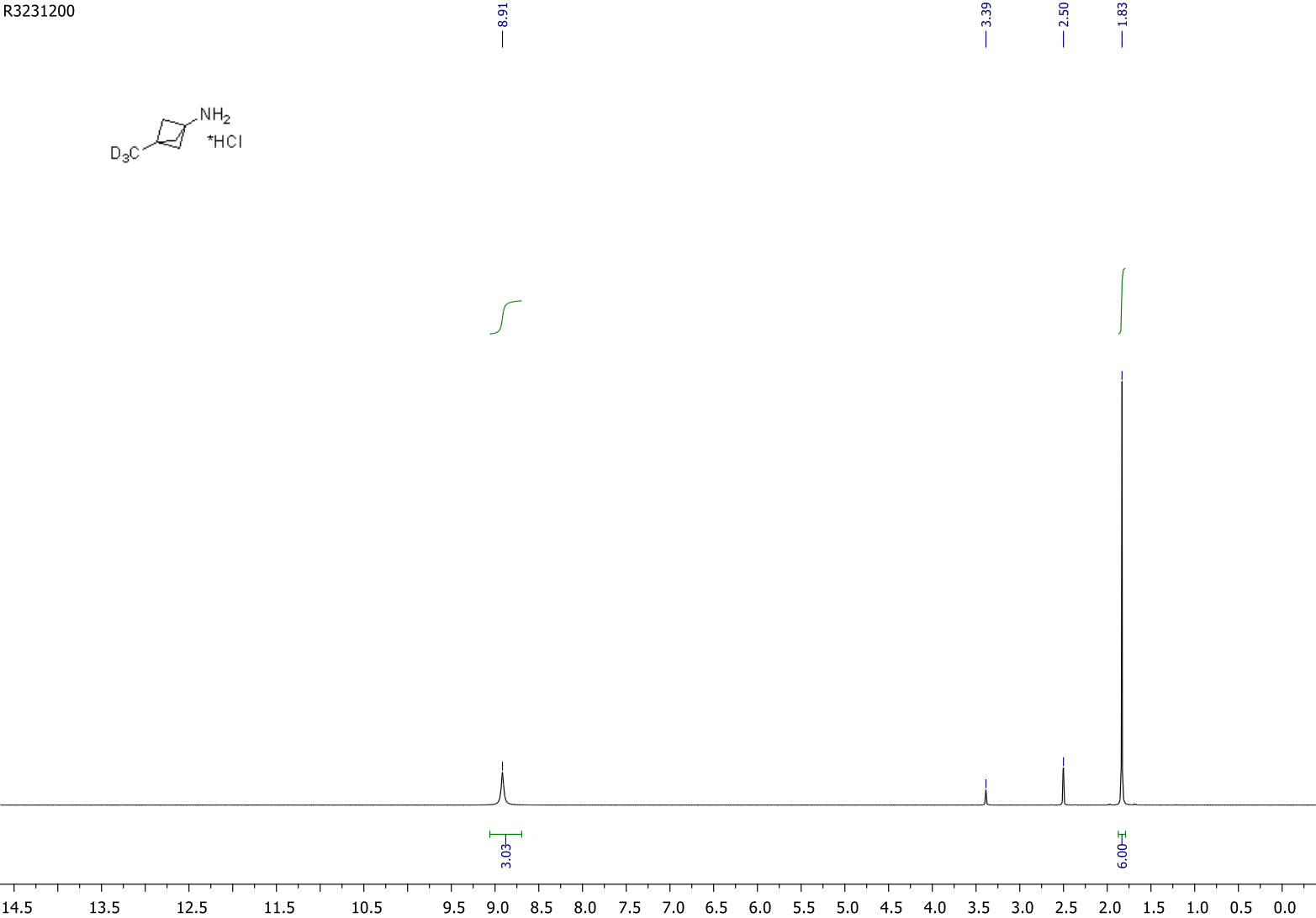
R2905055_C13



Compound (D3-1)l

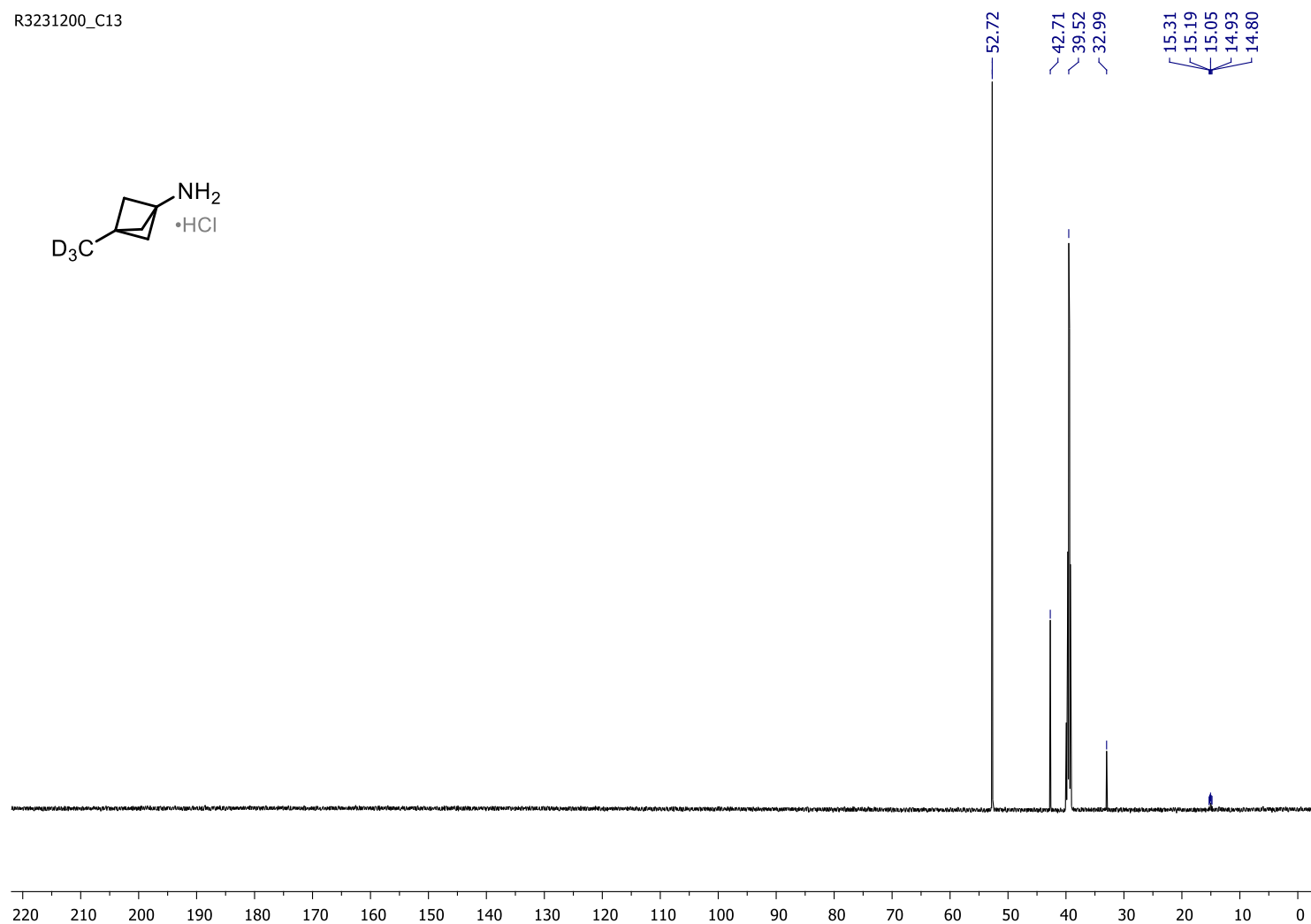
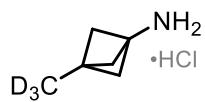
R3231200

¹H NMR (500 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

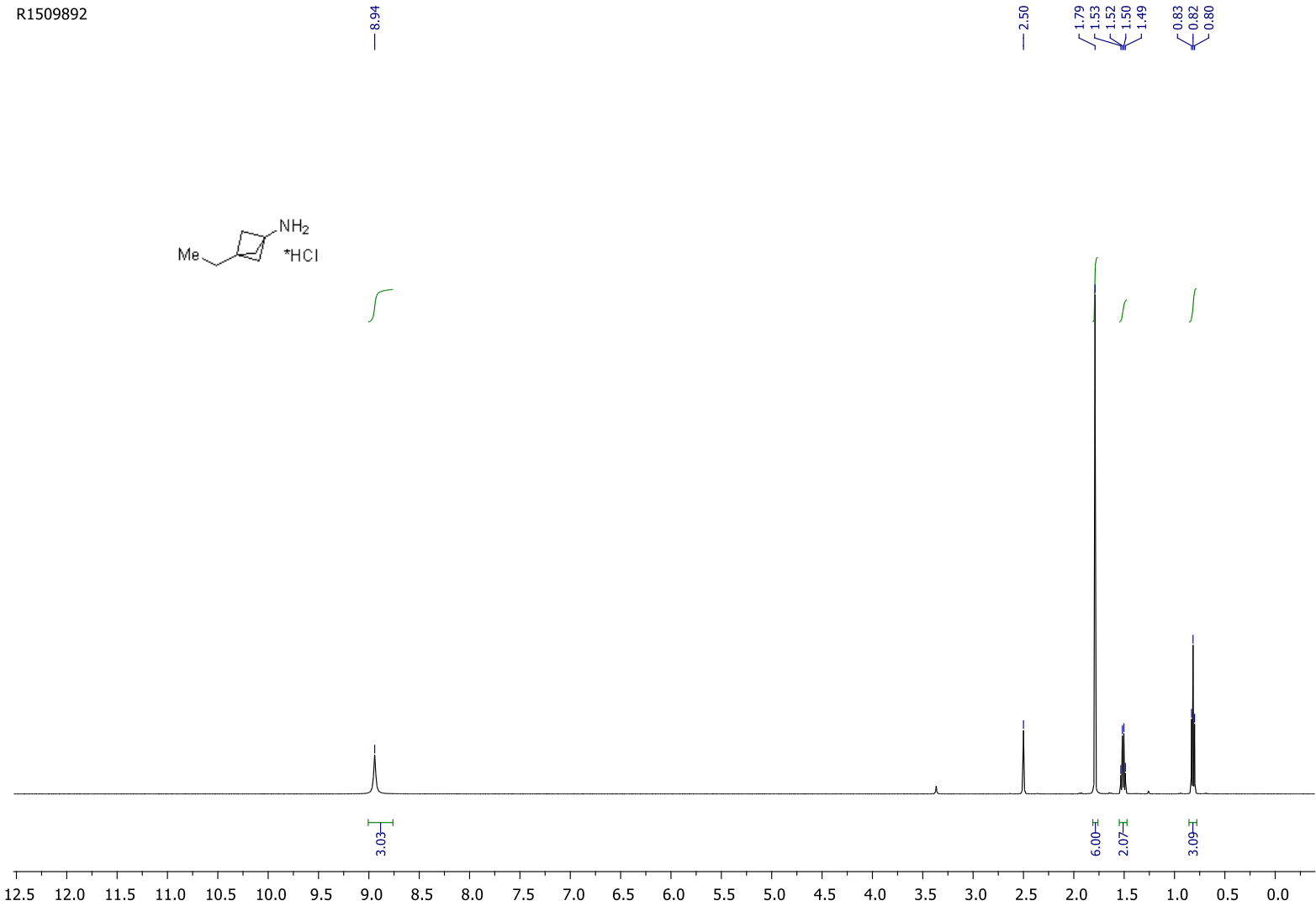
R3231200_C13



Compound 2l

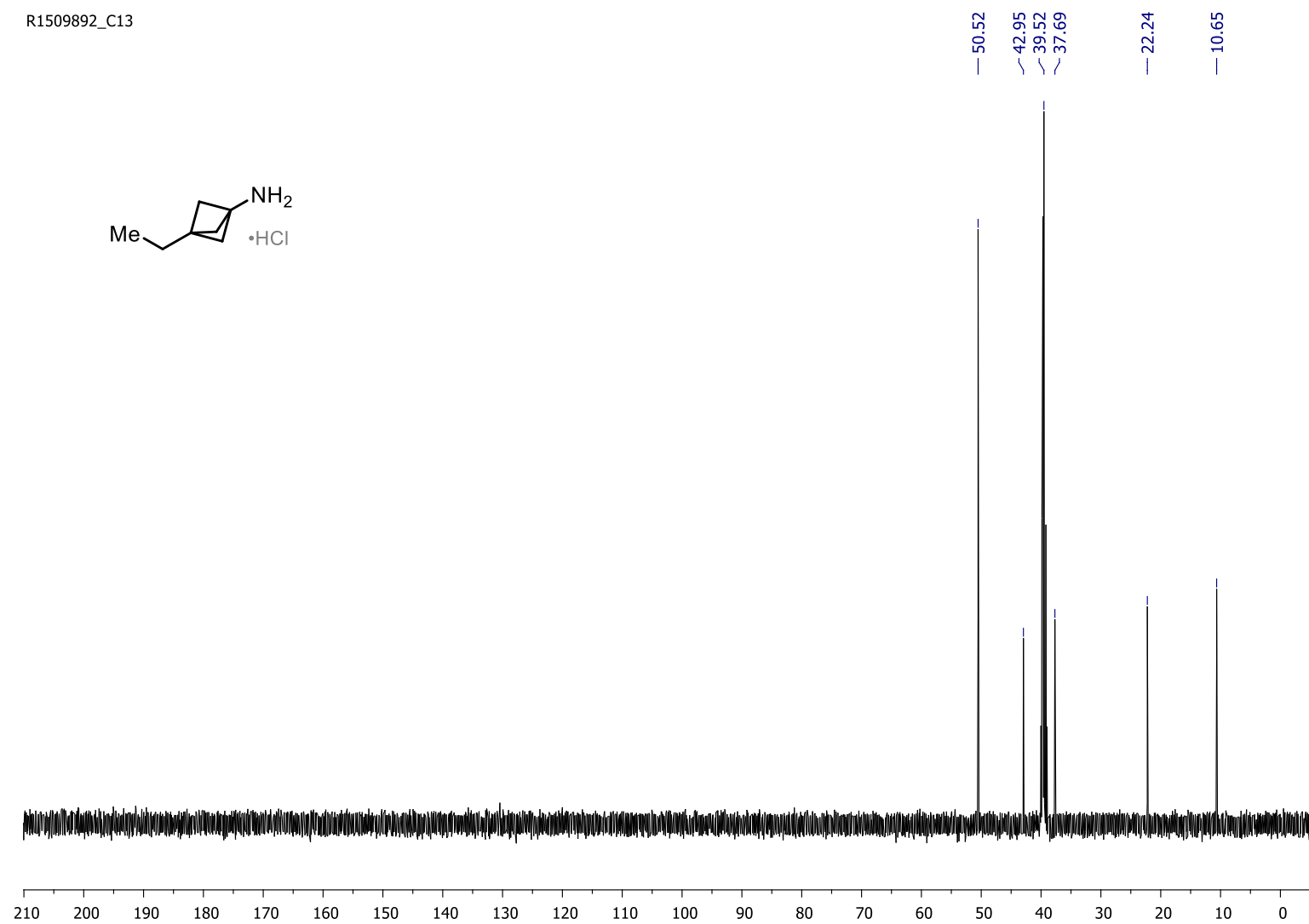
¹H NMR (500 MHz, DMSO-d₆)

R1509892



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

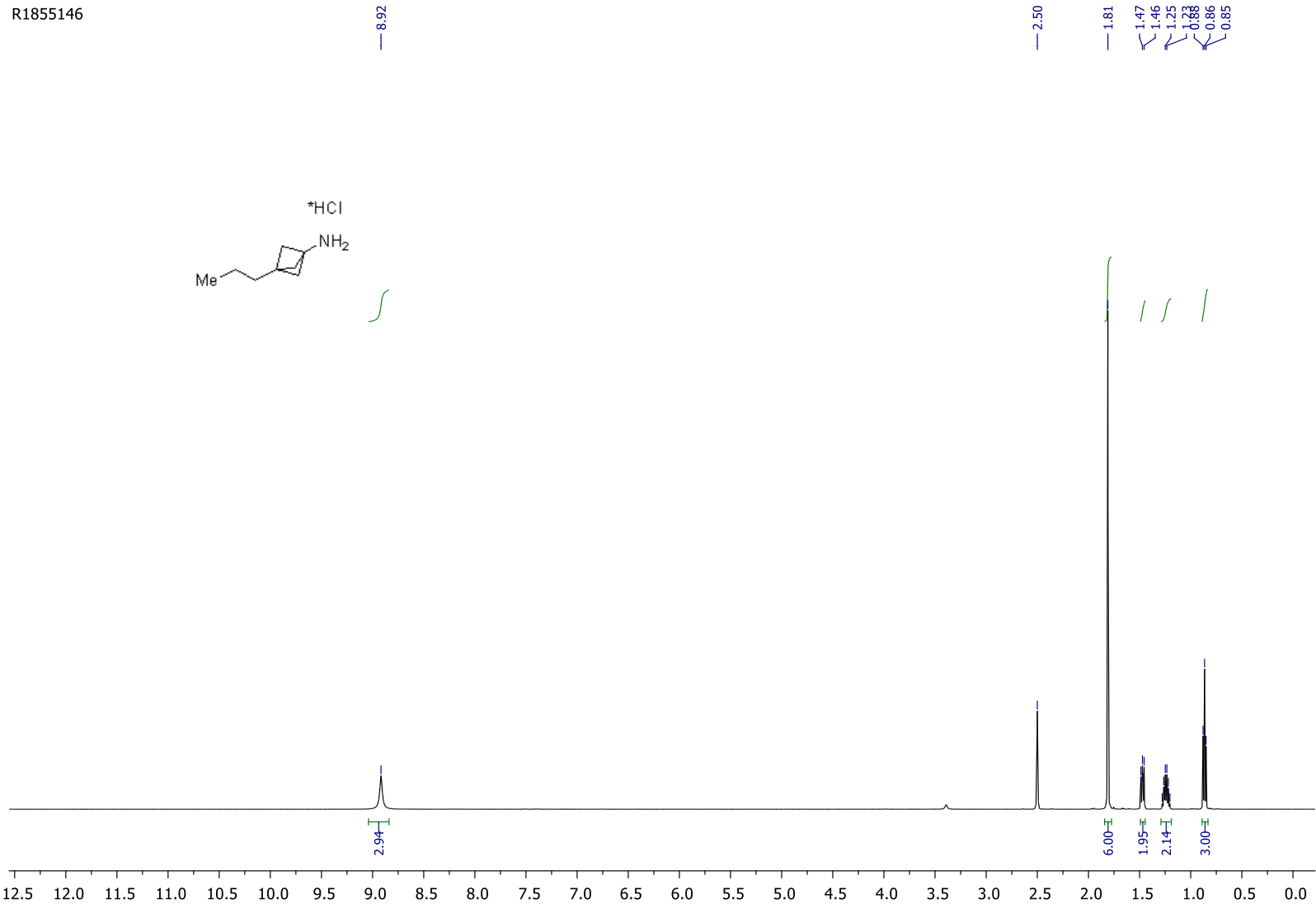
R1509892_C13



Compound 3l

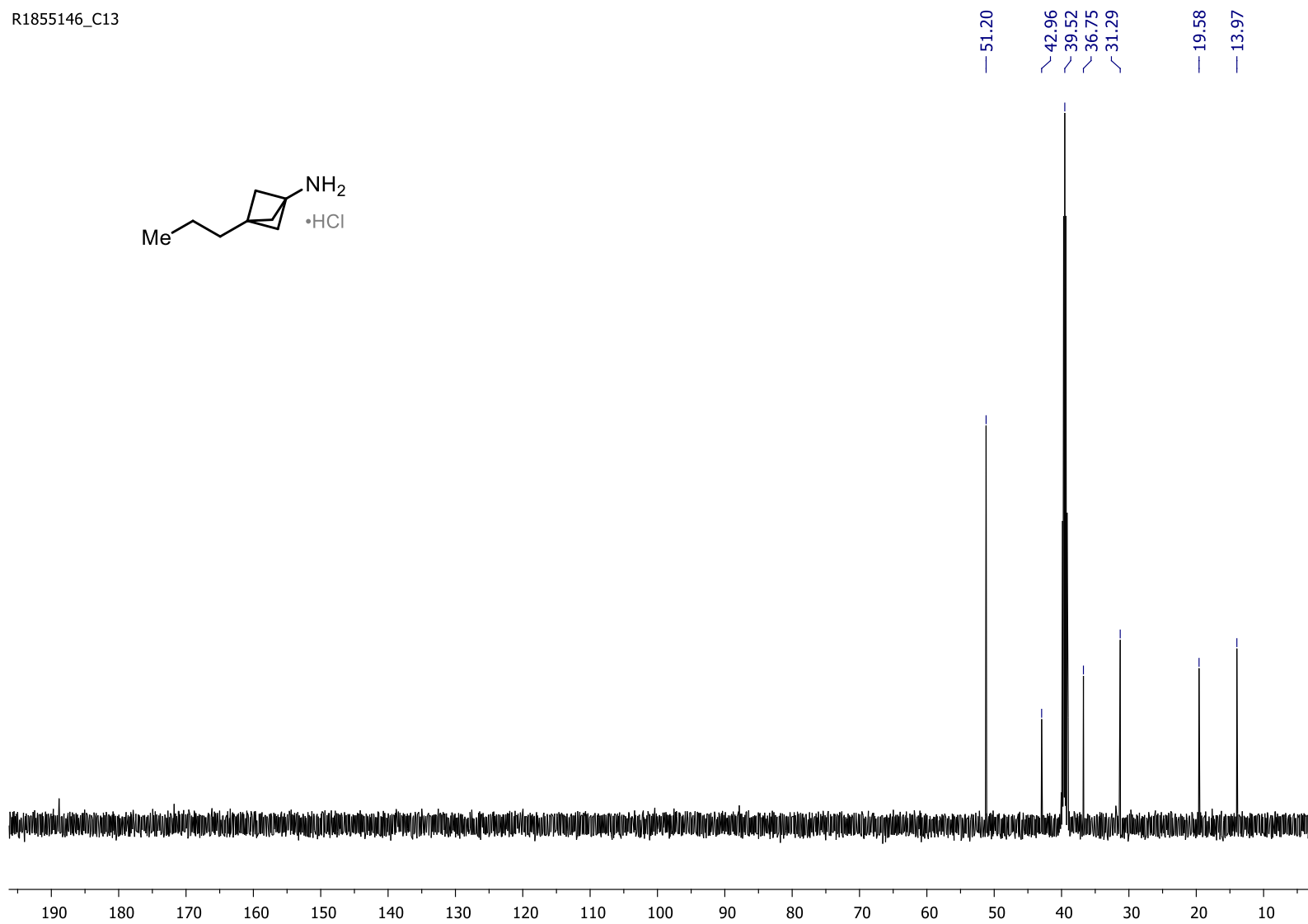
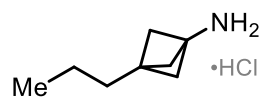
¹H NMR (400 MHz, DMSO-d₆)

R1855146



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

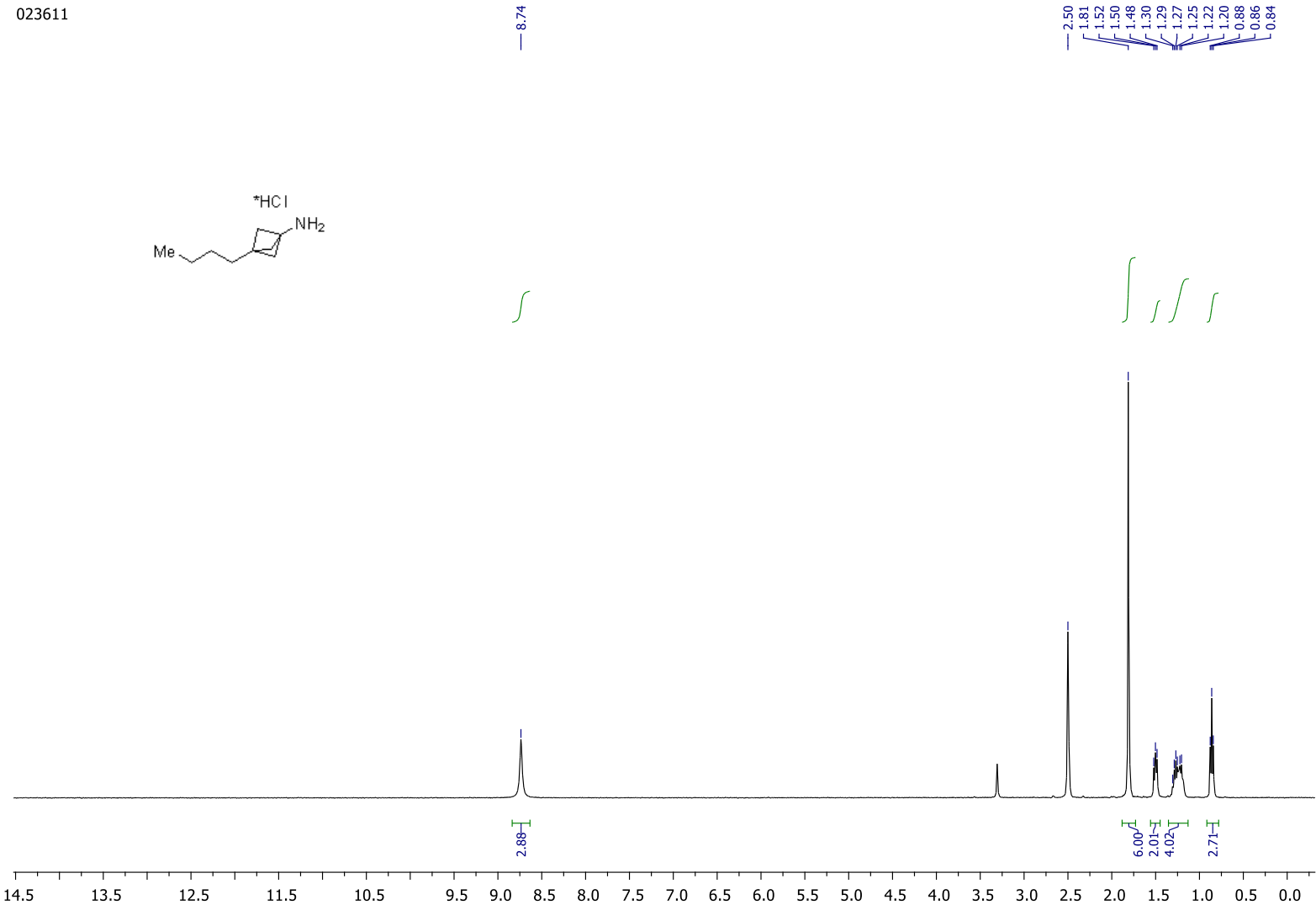
R1855146_C13



Compound 4l

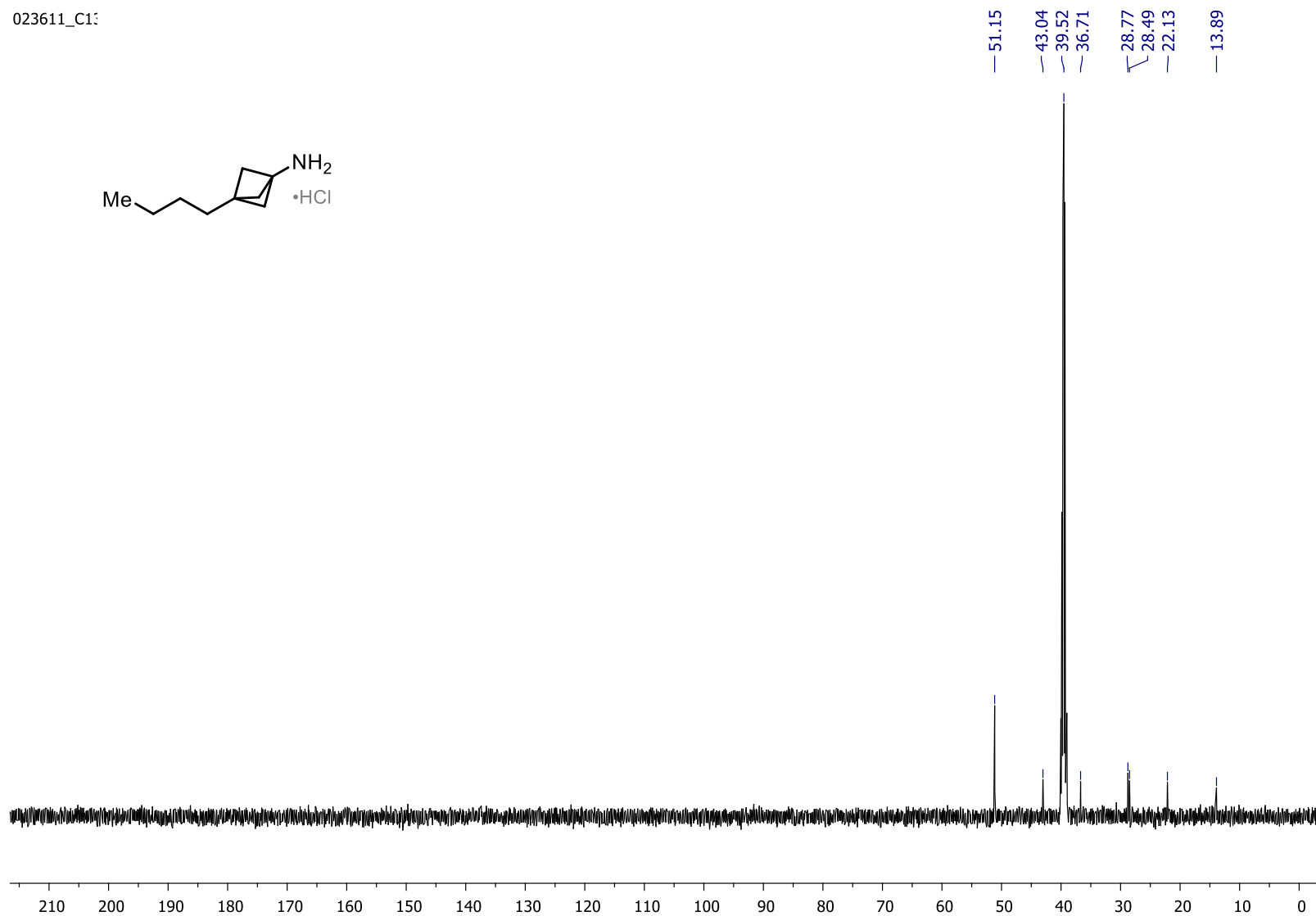
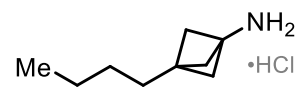
023611

¹H NMR (400 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

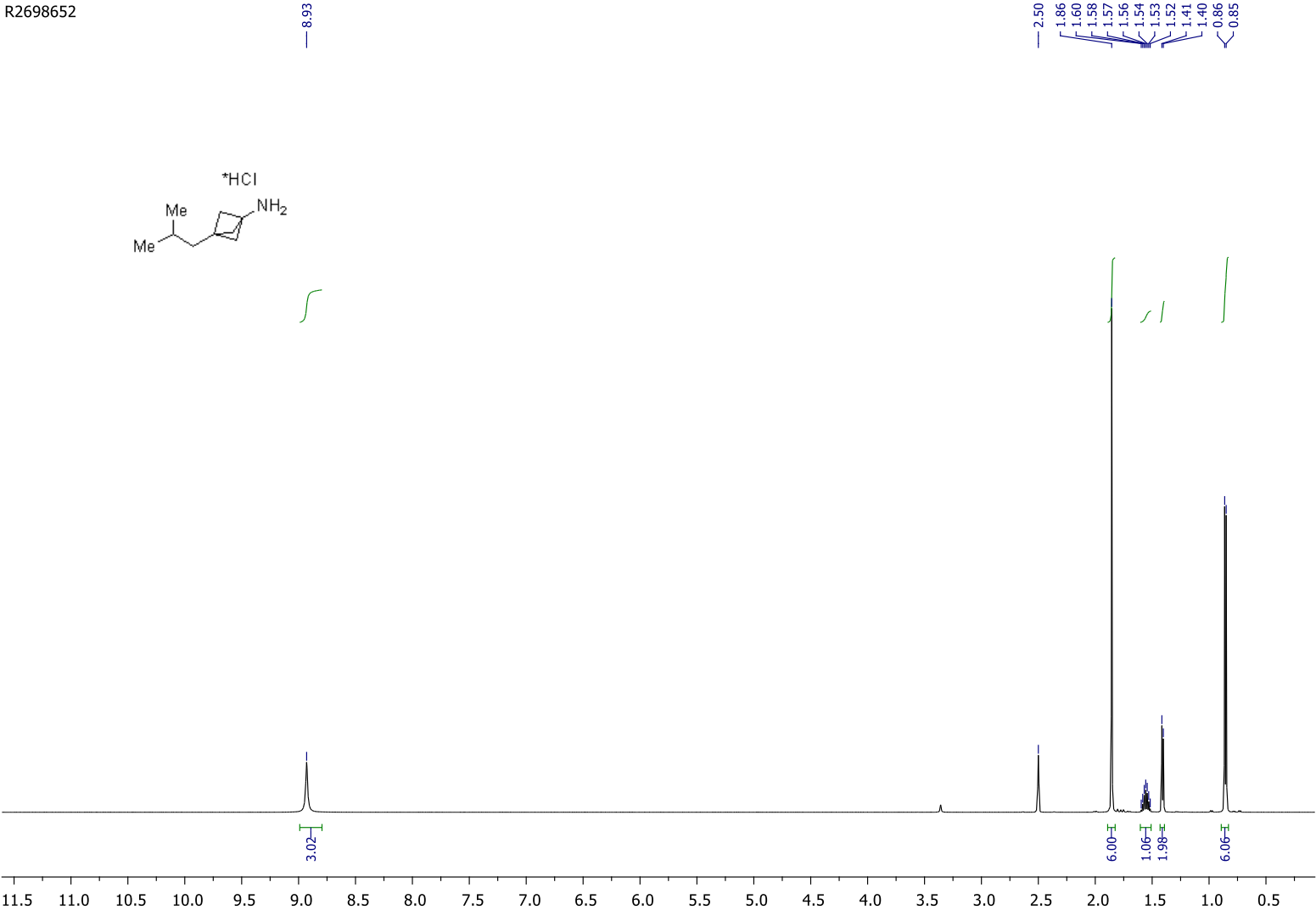
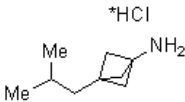
023611_C13



Compound 5l

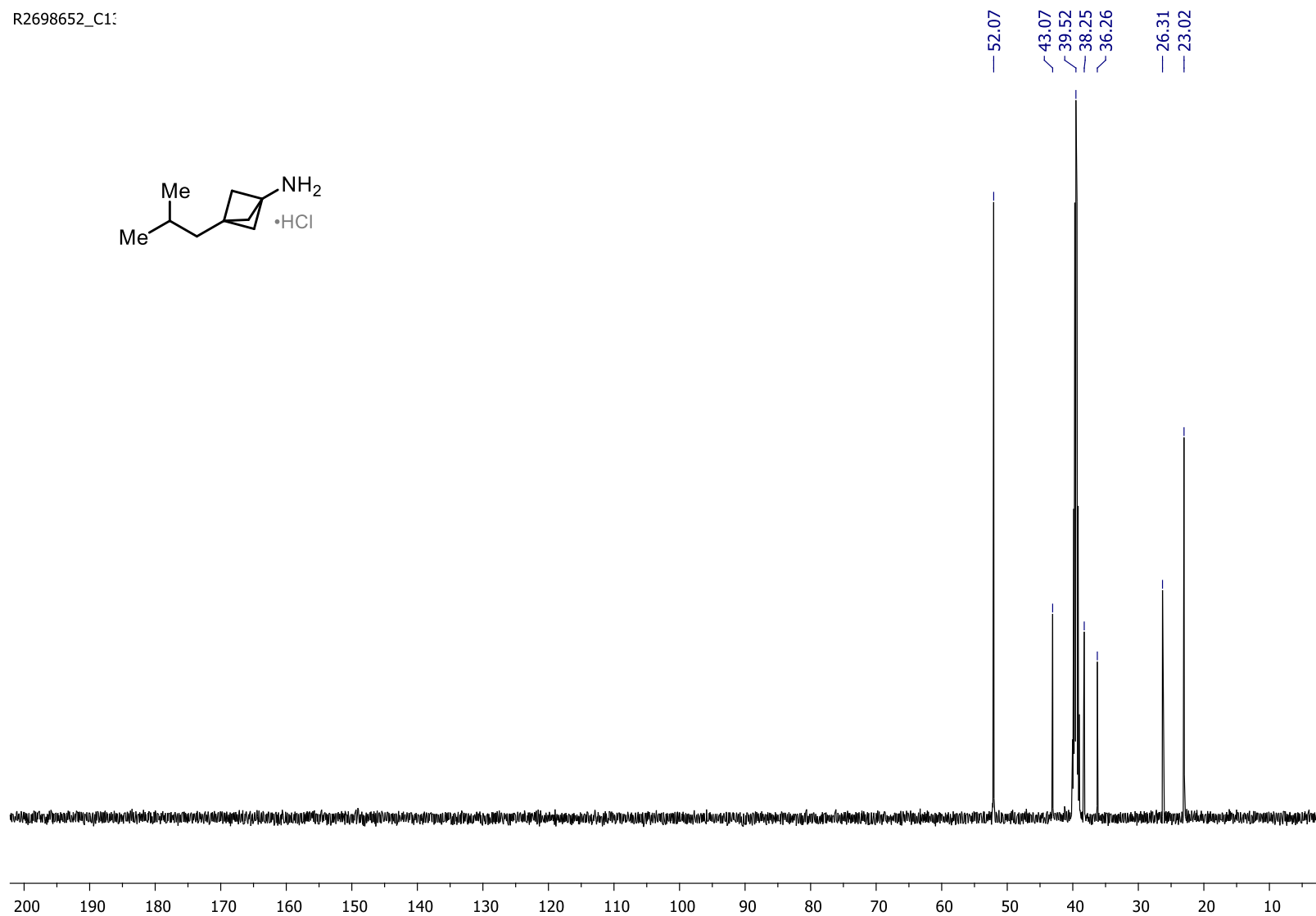
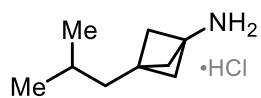
¹H NMR (500 MHz, DMSO-d₆)

R2698652



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

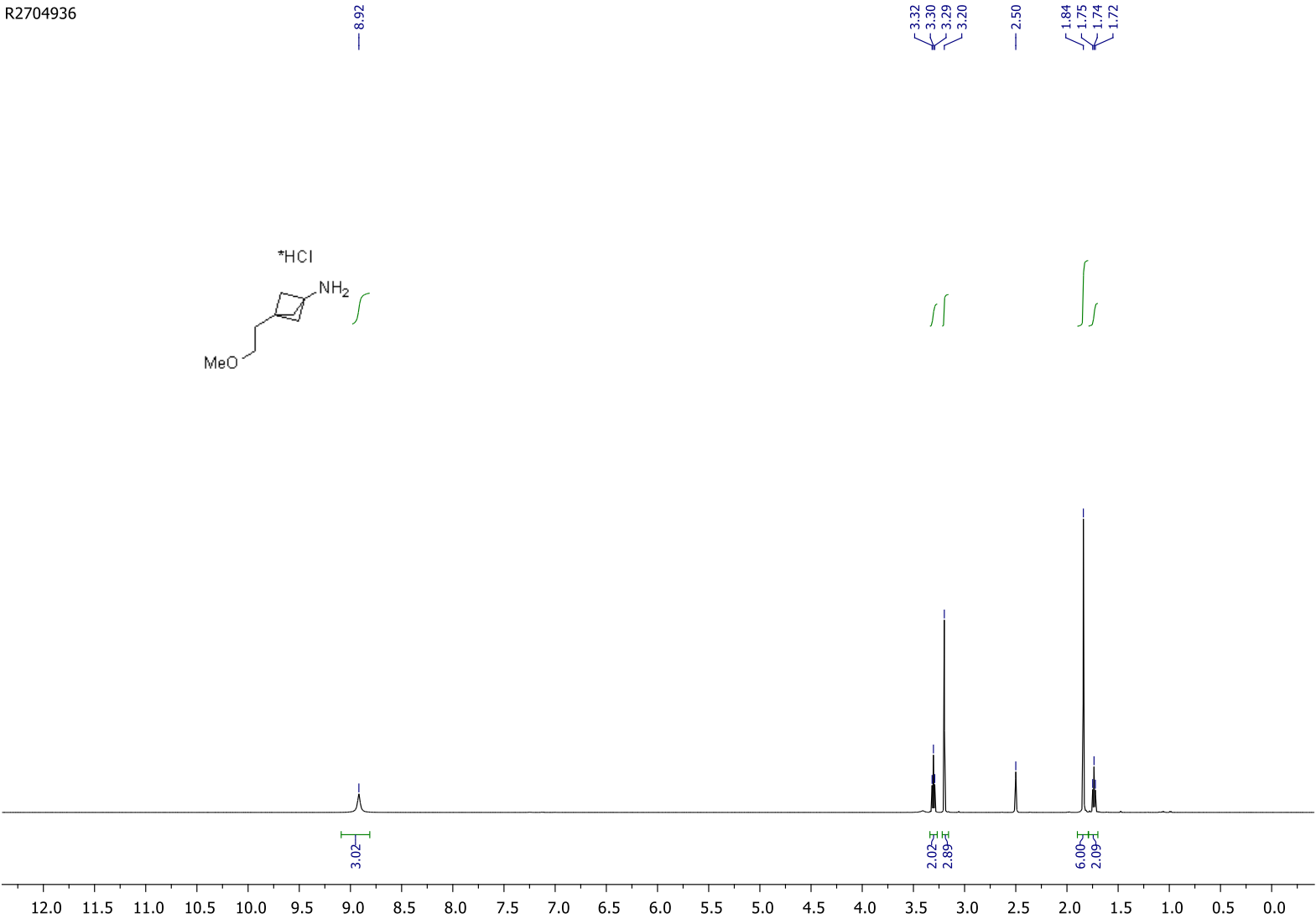
R2698652_C1:



Compound 7l

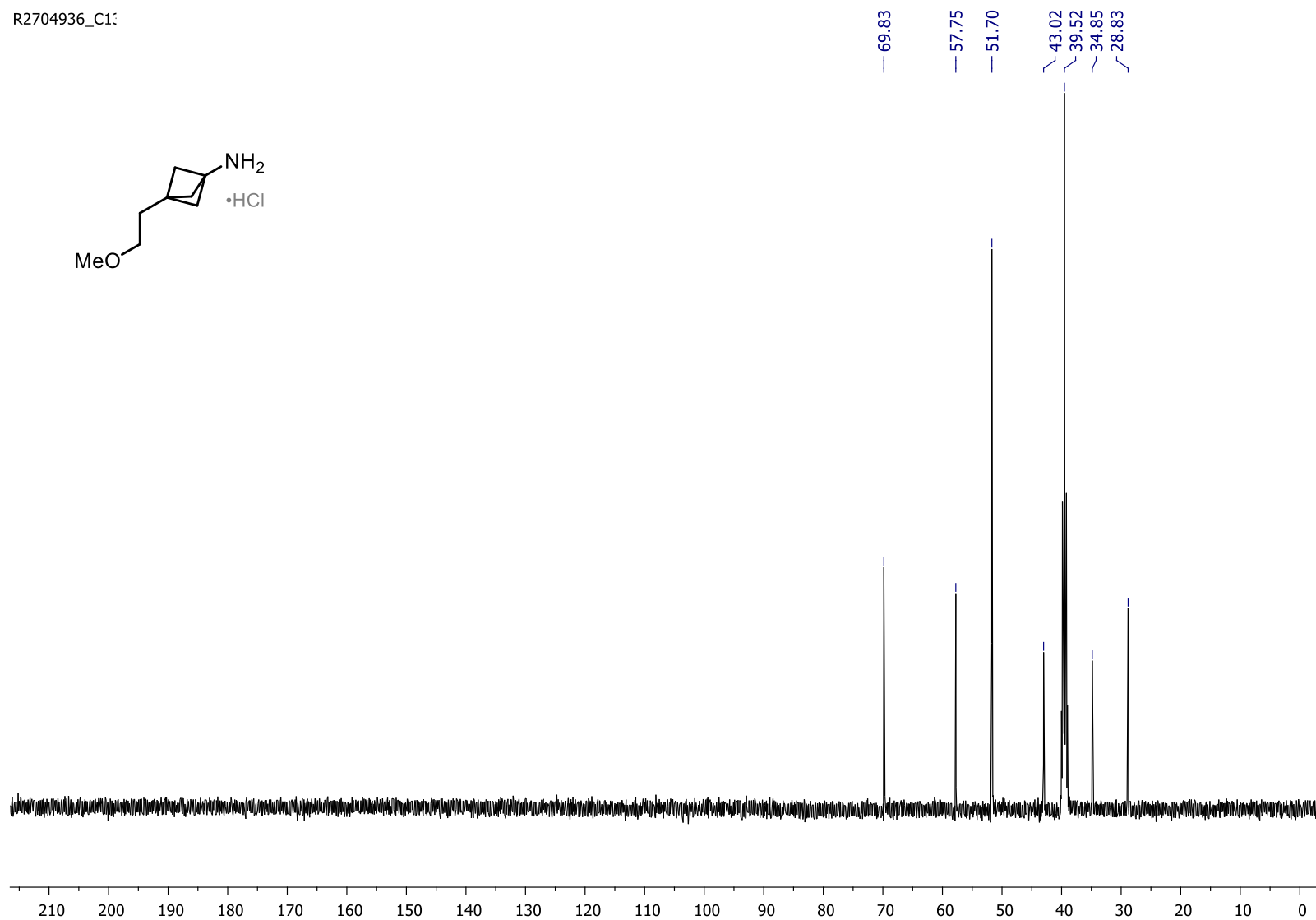
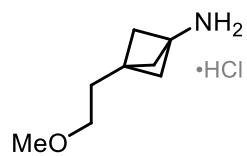
¹H NMR (500 MHz, DMSO-d₆)

R2704936



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

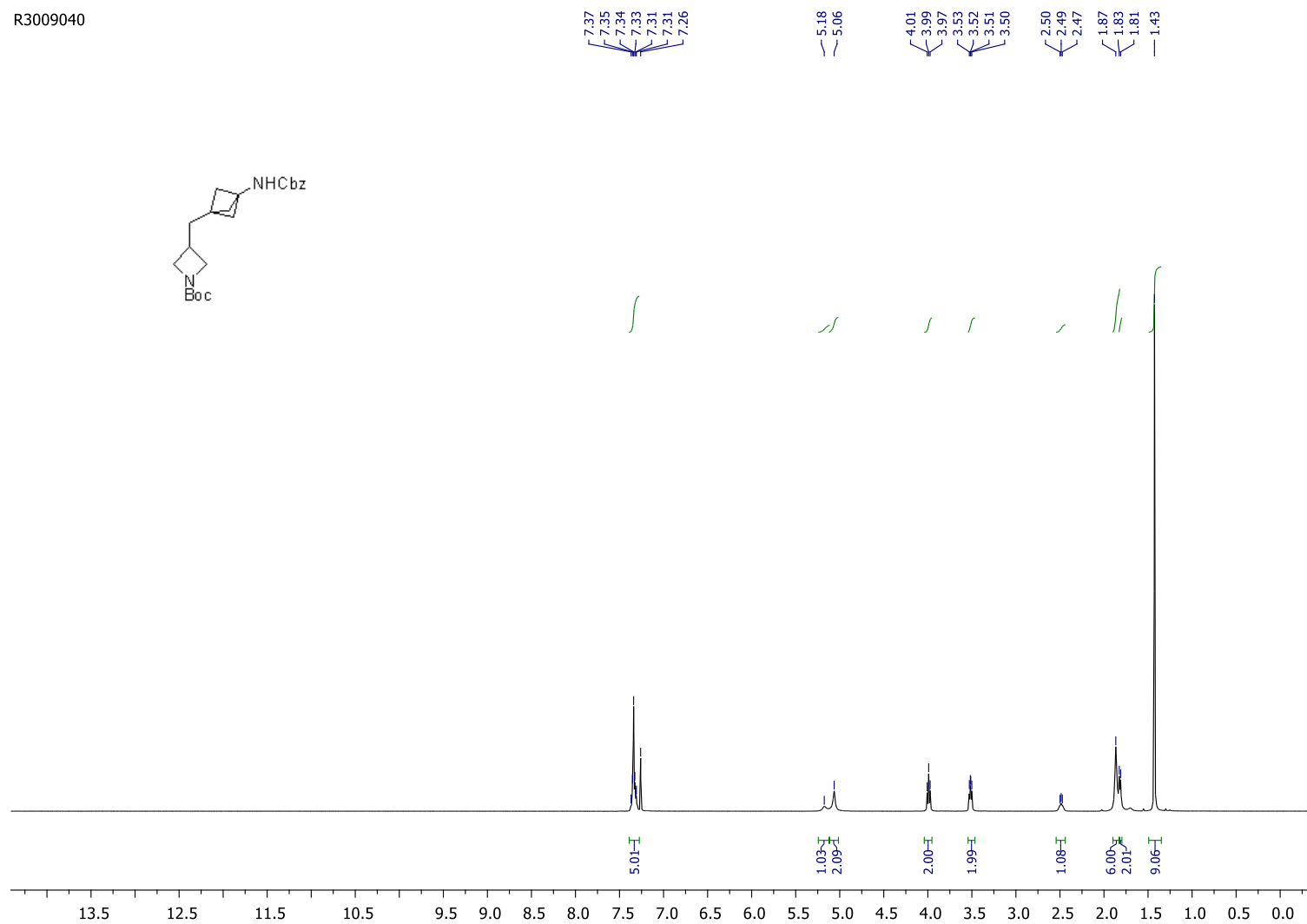
R2704936_C1:



***Tert*-butyl 3-((3-(((benzyloxy)carbonyl)amino)bicyclo[1.1.1]pentan-1-yl)methyl)azetidine-1-carboxylate**

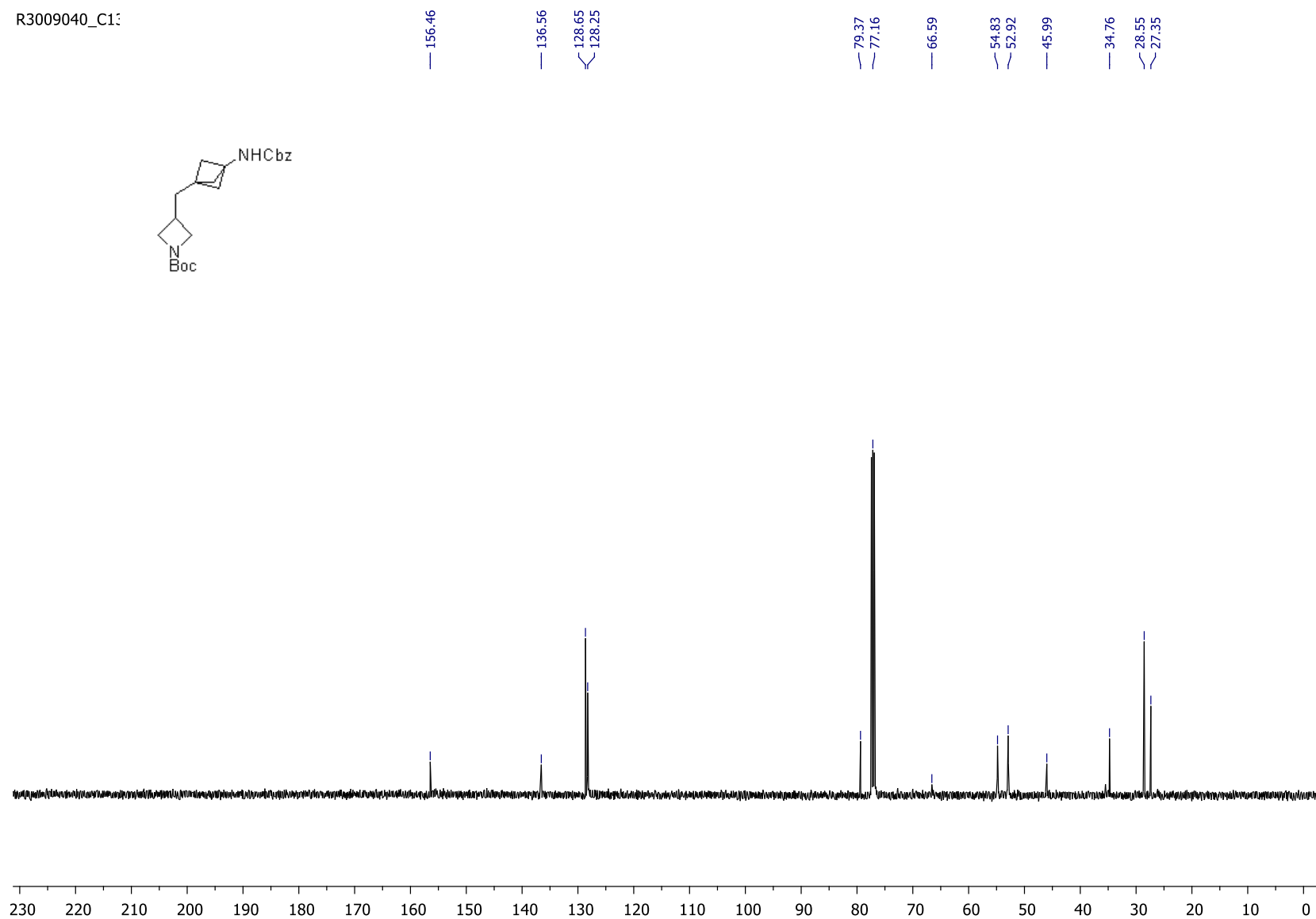
^1H NMR (500 MHz, CDCl_3)

R3009040



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

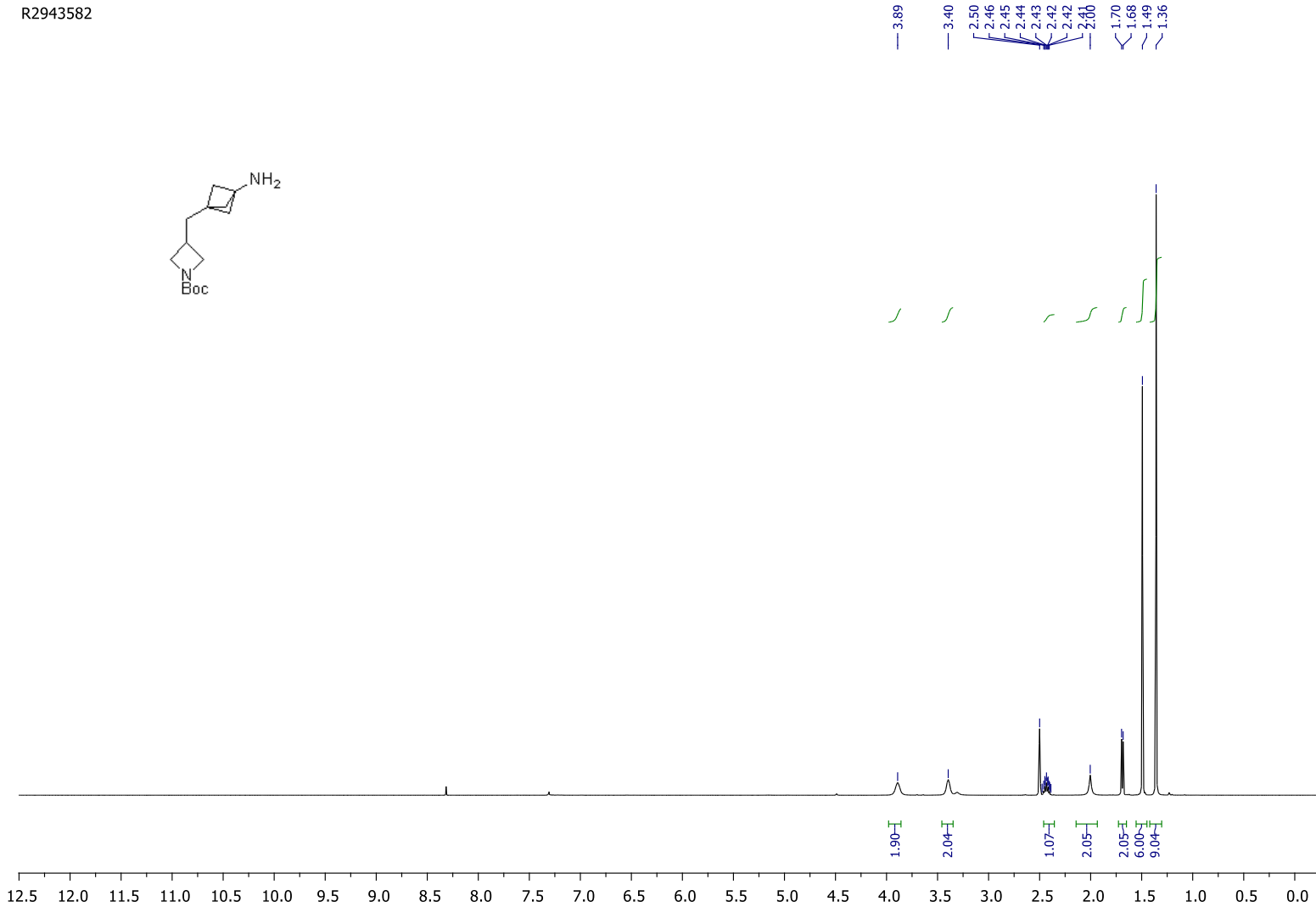
R3009040_C1:



Compound 14l

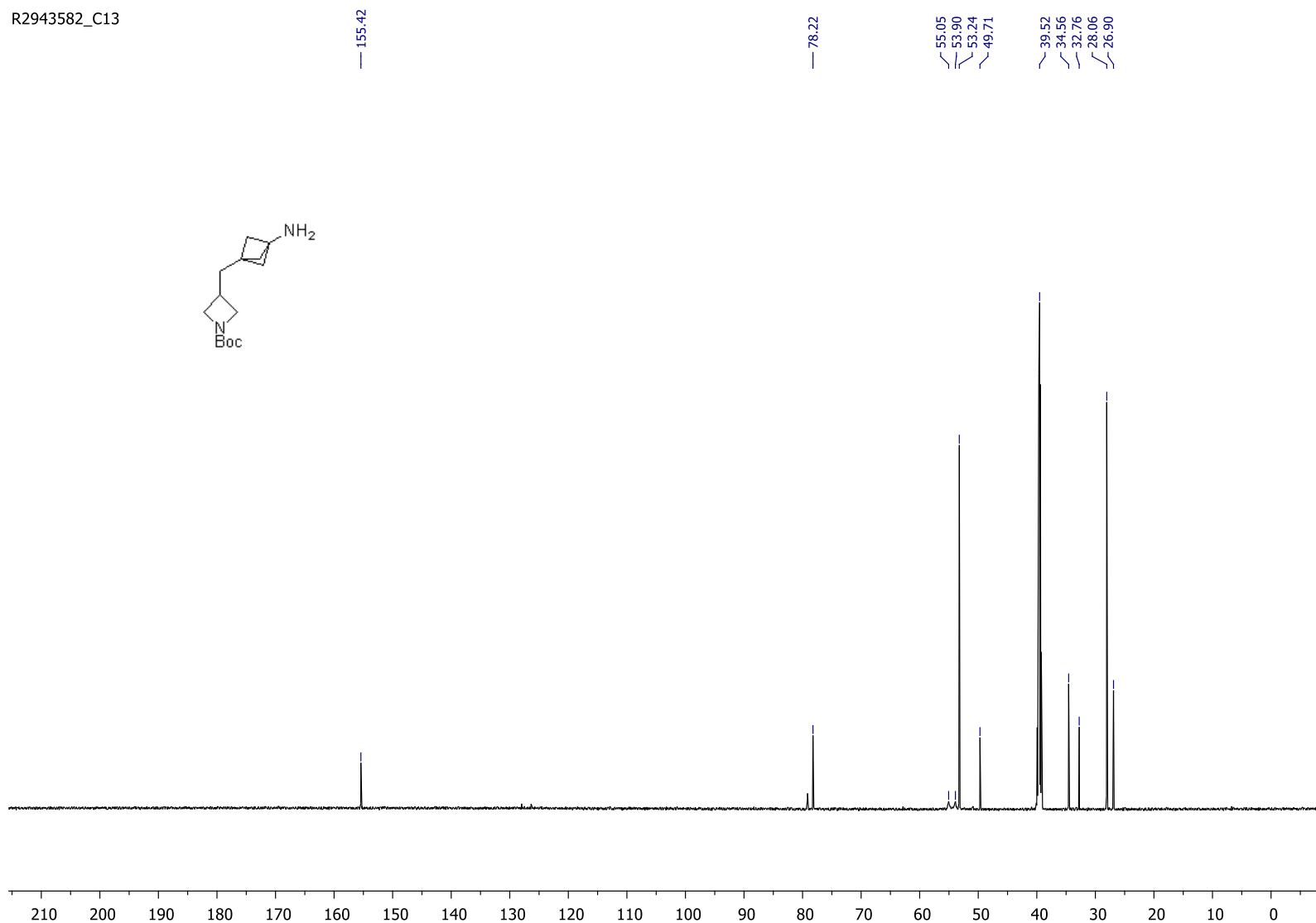
¹H NMR (500 MHz, DMSO-d₆)

R2943582



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

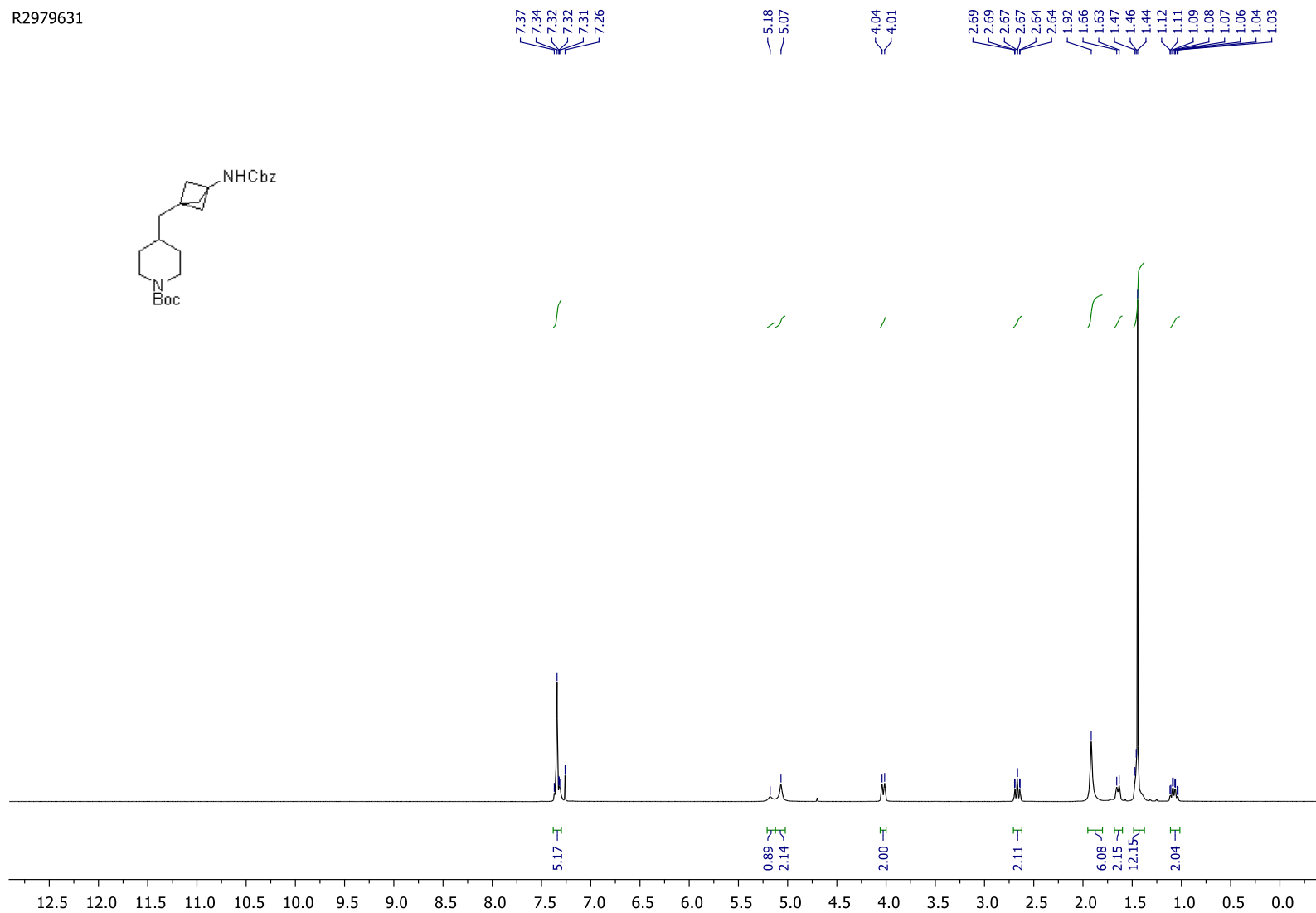
R2943582_C13

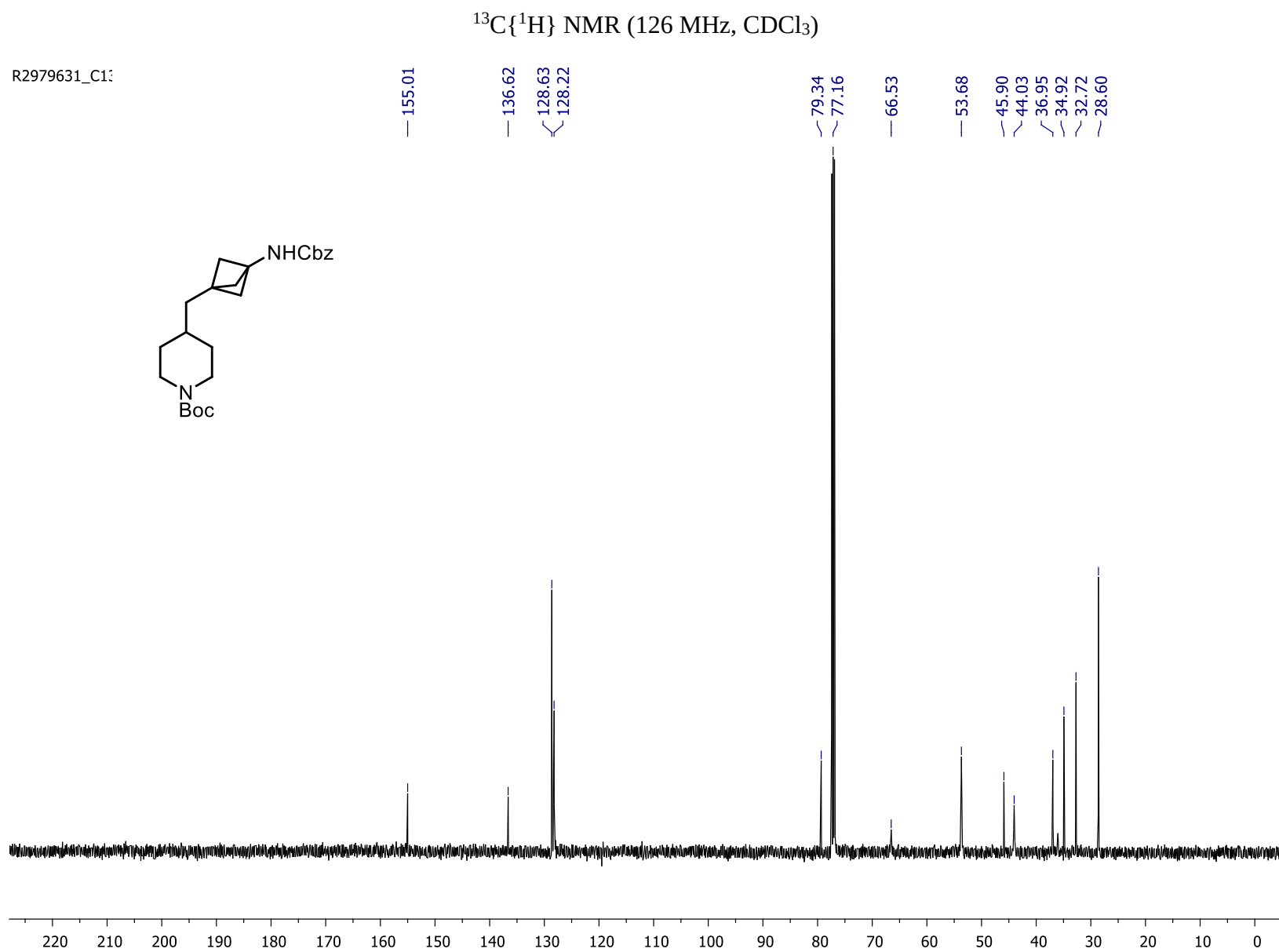


***Tert*-butyl 4-((3-(((benzyloxy)carbonyl)amino)bicyclo[1.1.1]pentan-1-yl)methyl)piperidine-1-carboxylate**

^1H NMR (500 MHz, CDCl_3)

R2979631

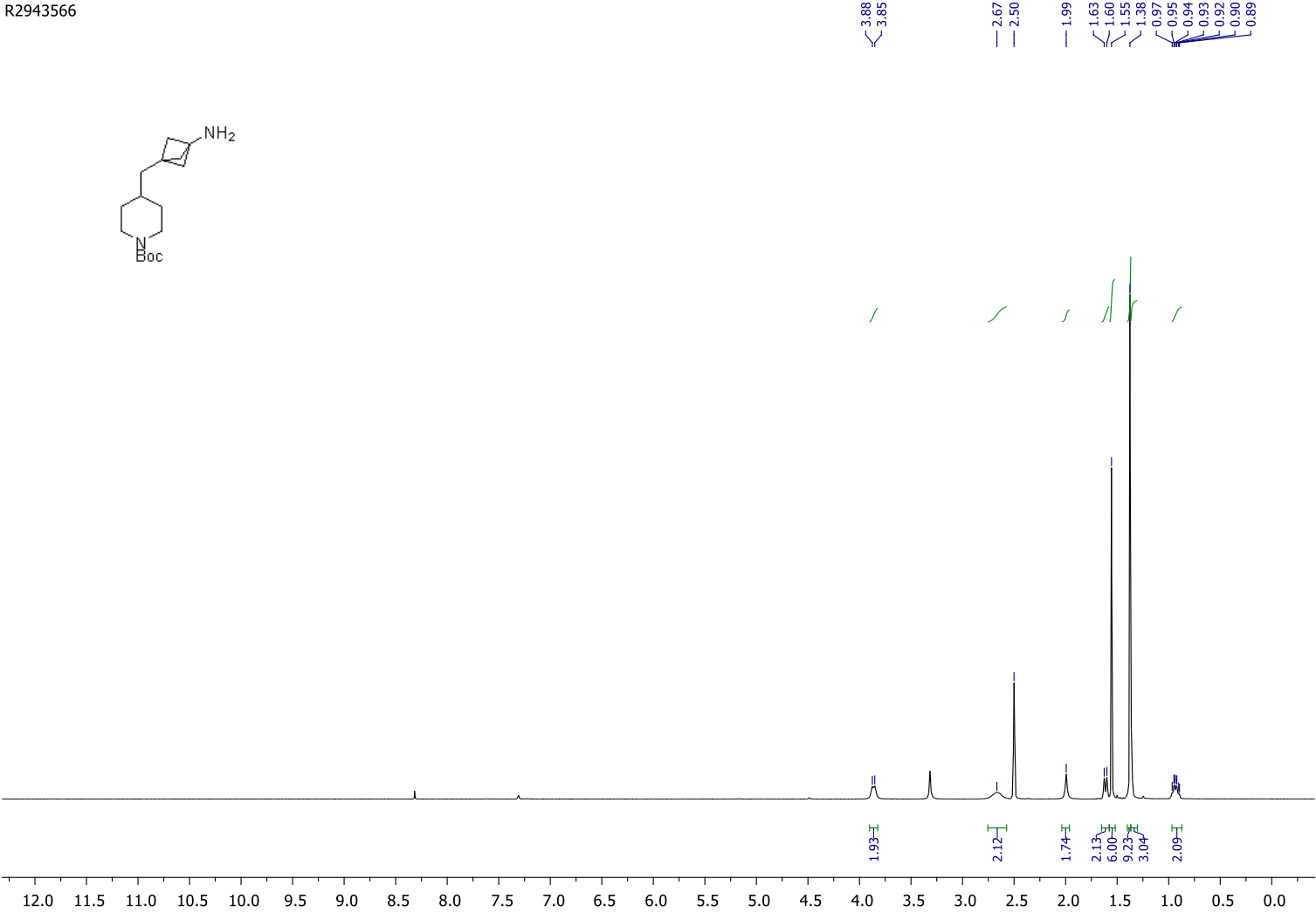
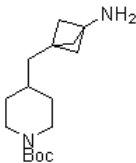


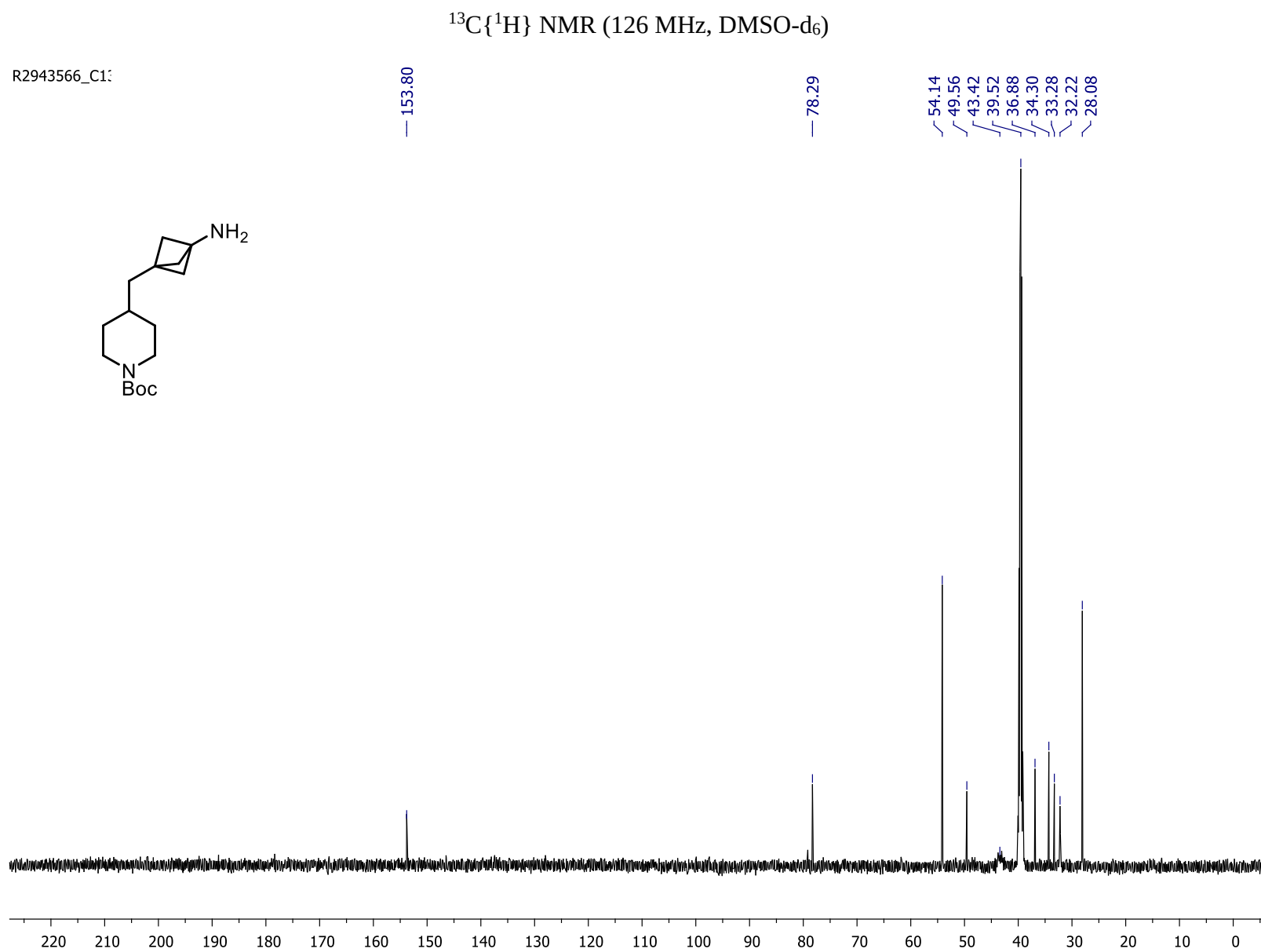


Compound 16l

¹H NMR (500 MHz, DMSO-d₆)

R2943566

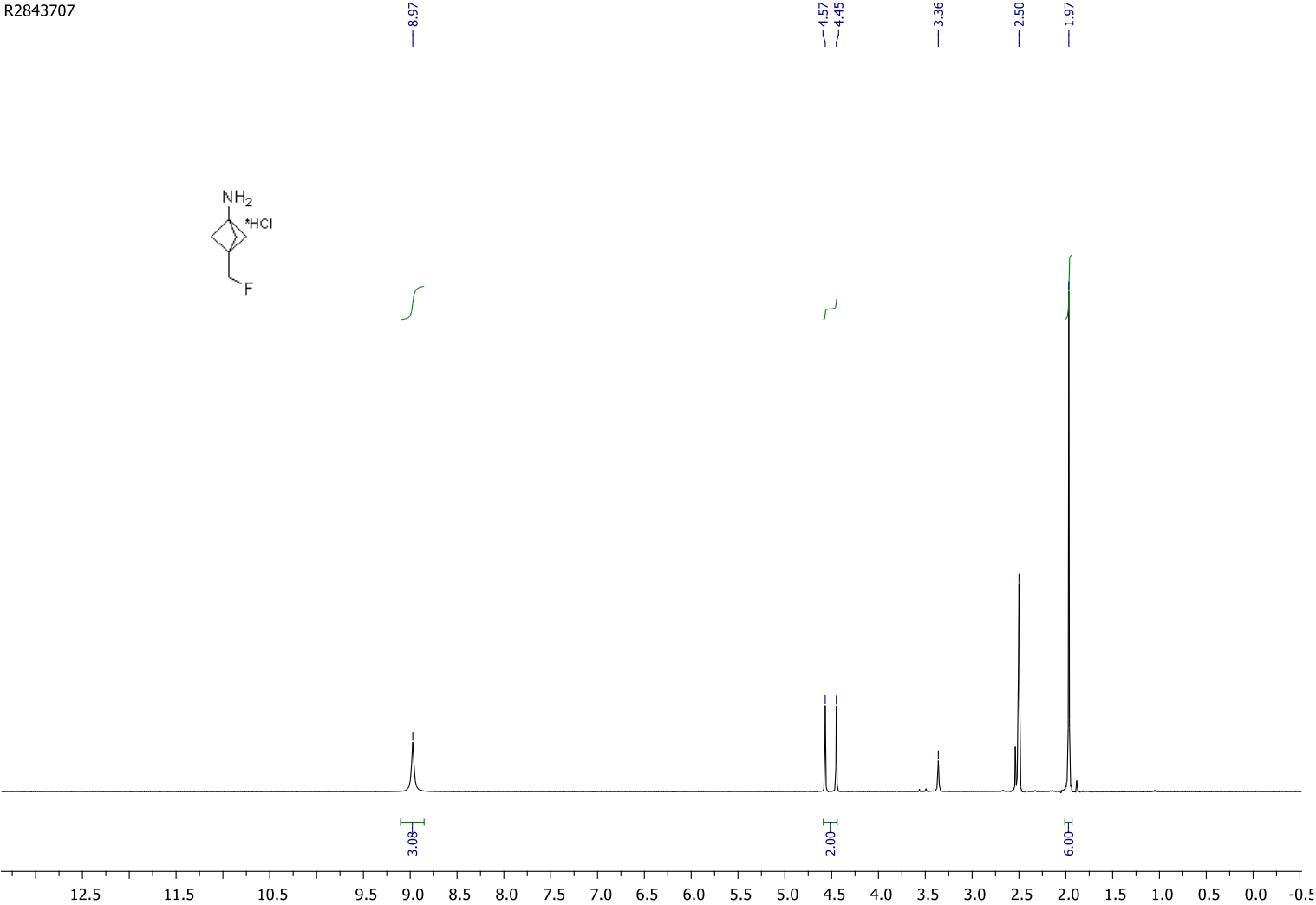




Compound 21l

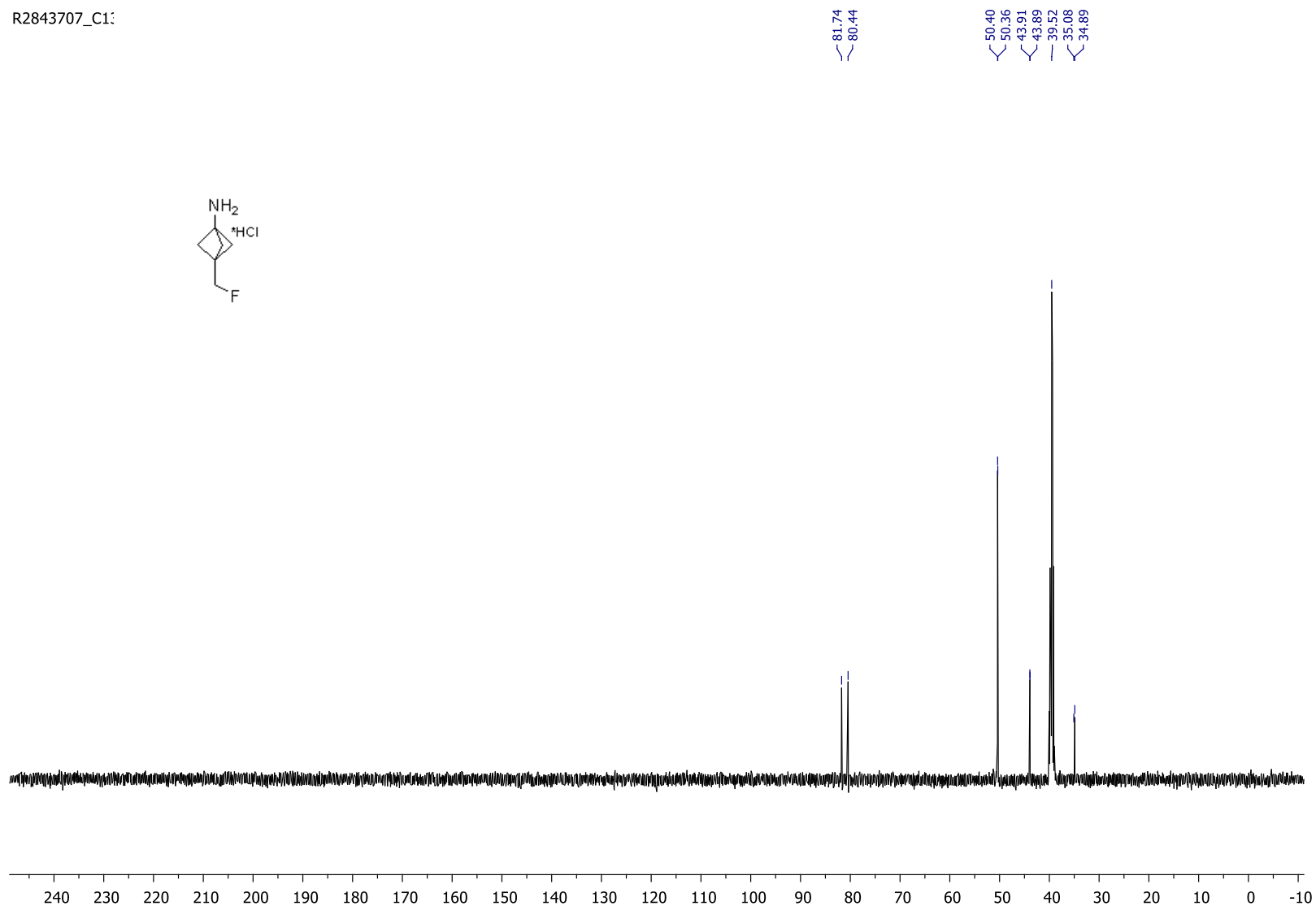
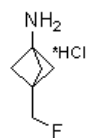
¹H NMR (400 MHz, DMSO-d₆)

R2843707



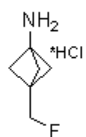
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2843707_C11

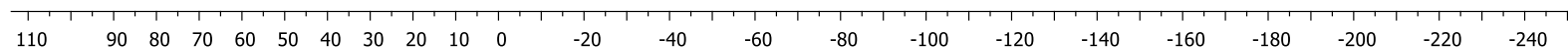


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2843707_F19{H}
19F-{1H}



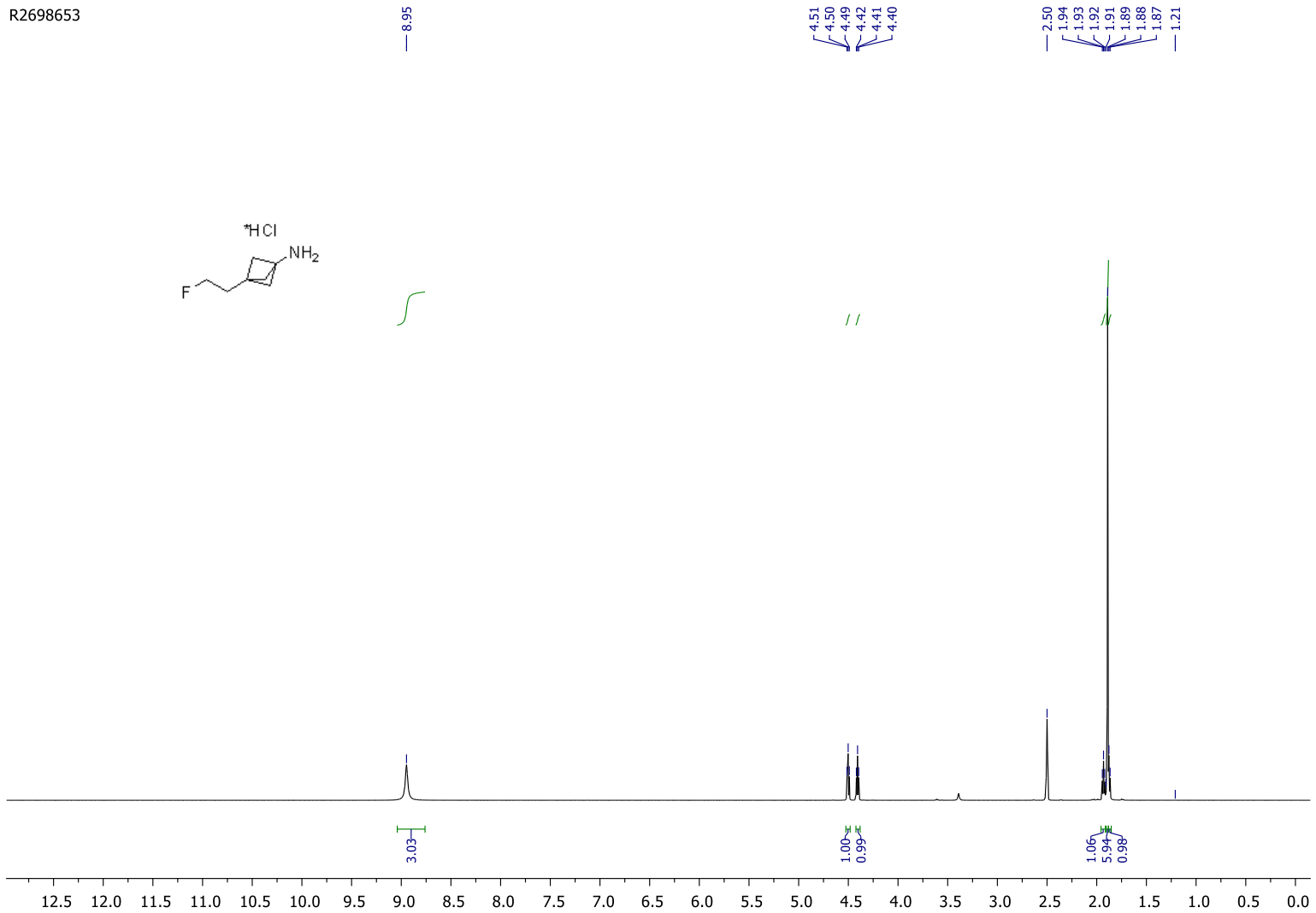
— -221.35



Compound 22l

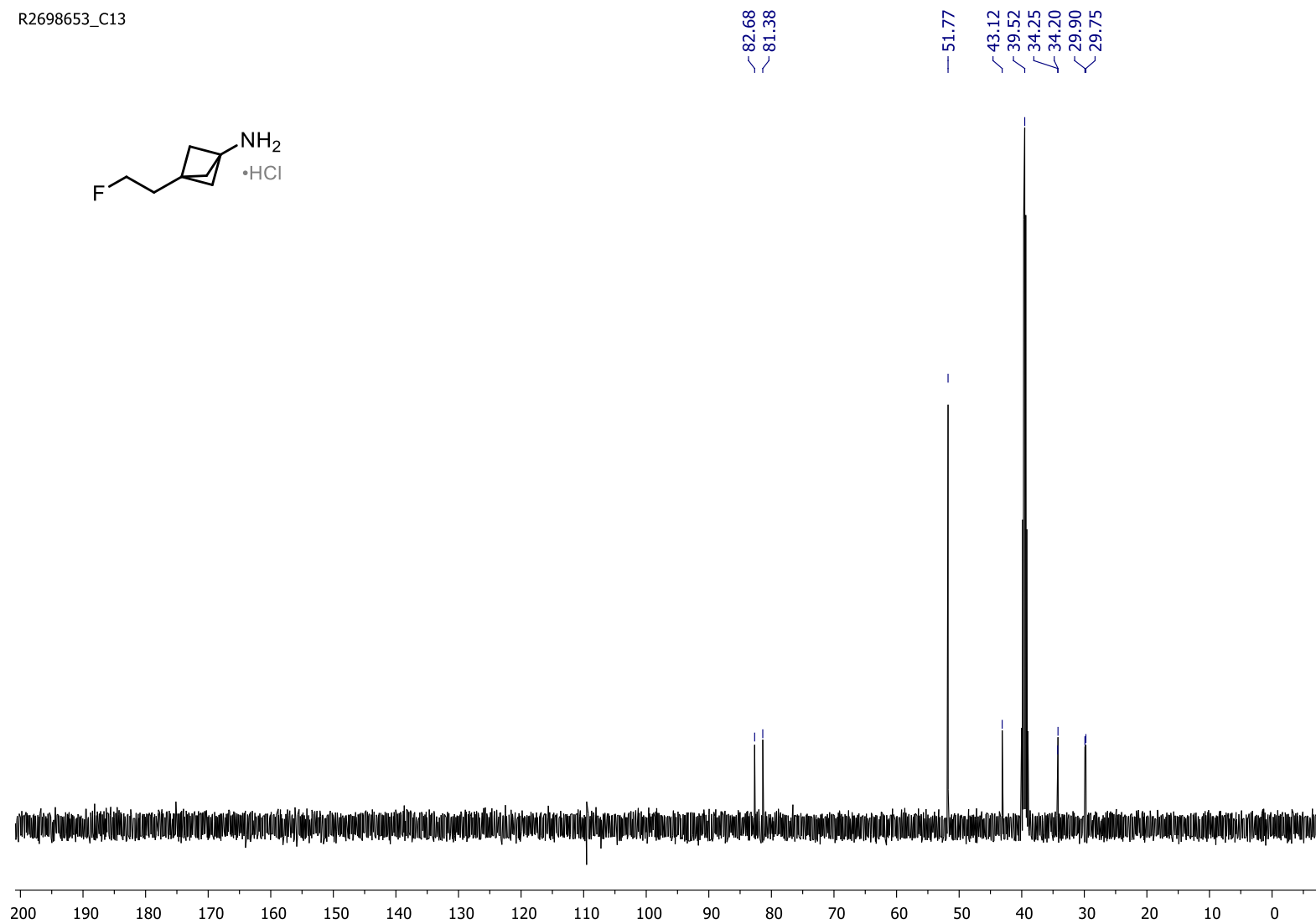
¹H NMR (500 MHz, DMSO-d₆)

R2698653



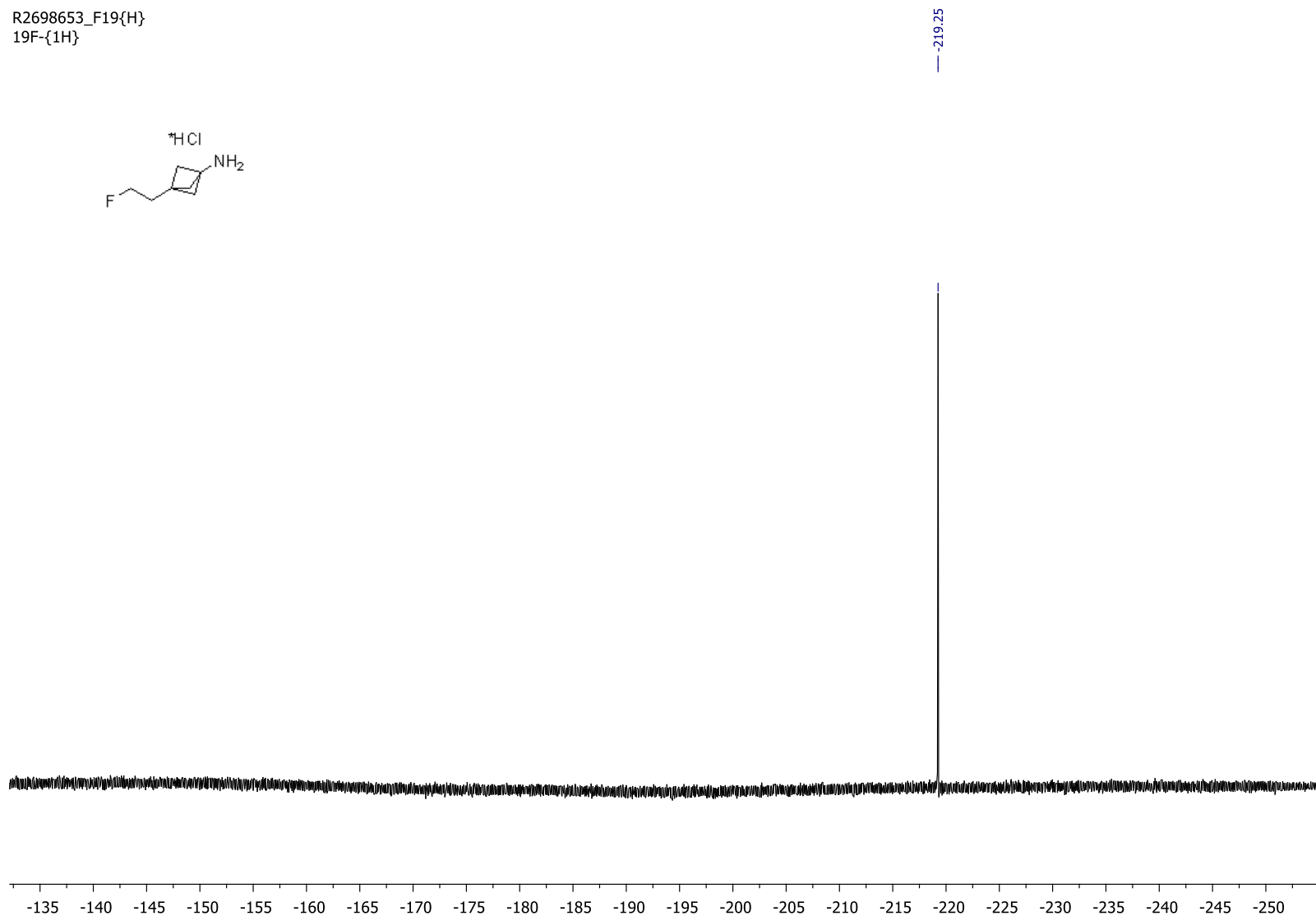
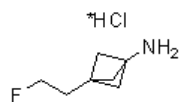
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2698653_C13



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

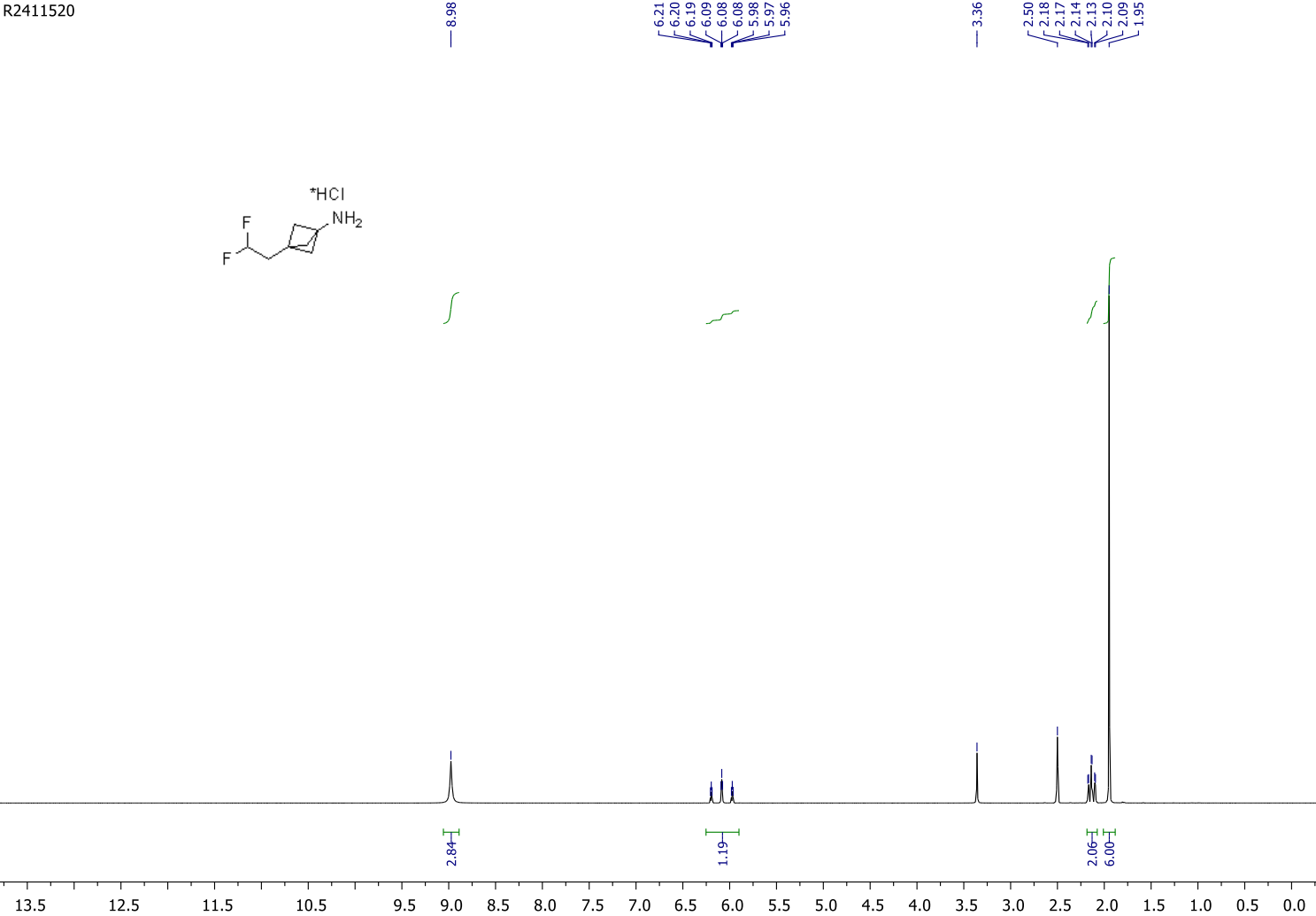
R2698653_F19{H}
19F-{1H}



Compound 24l

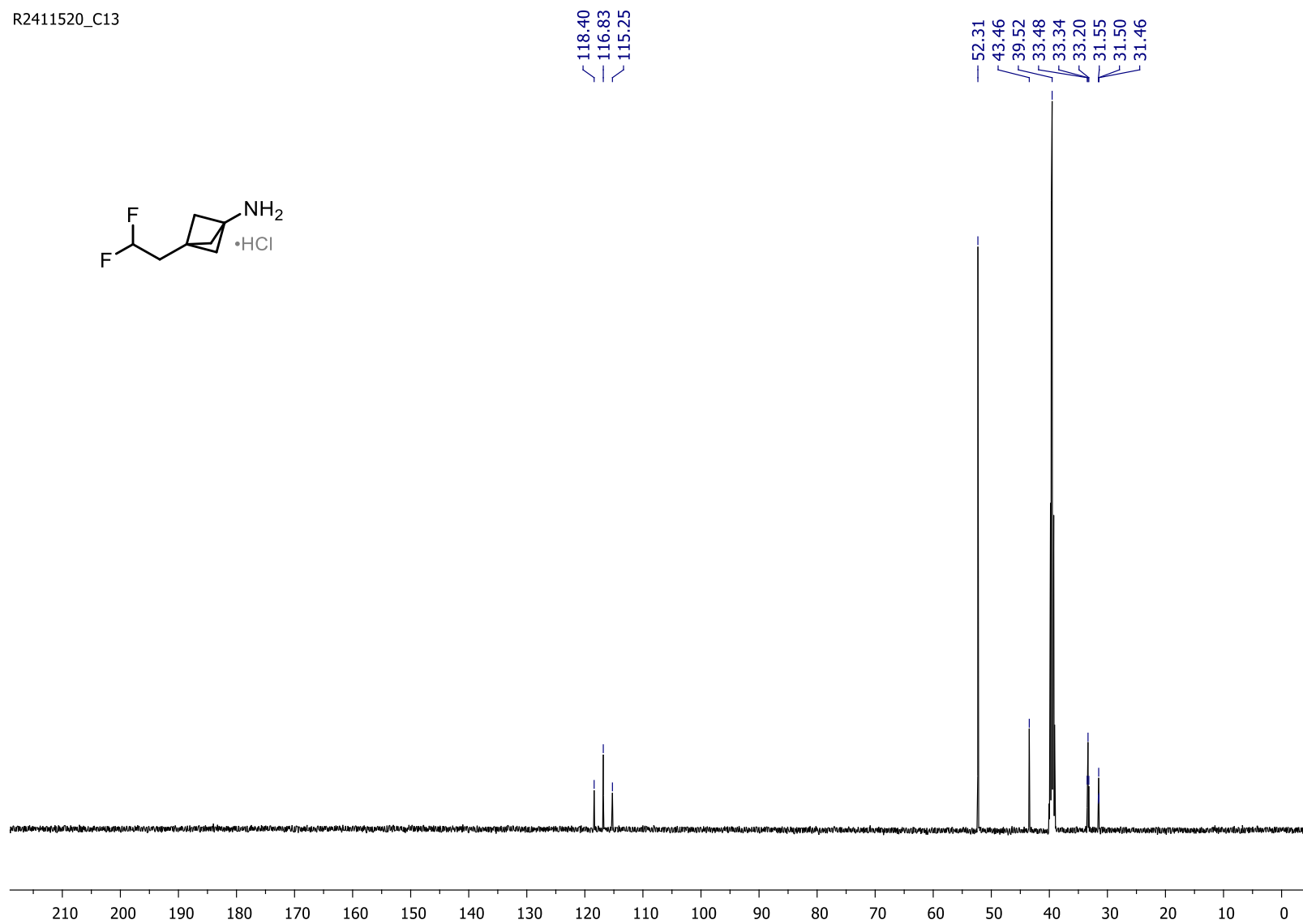
¹H NMR (500 MHz, DMSO-d₆)

R2411520



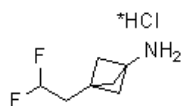
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2411520_C13

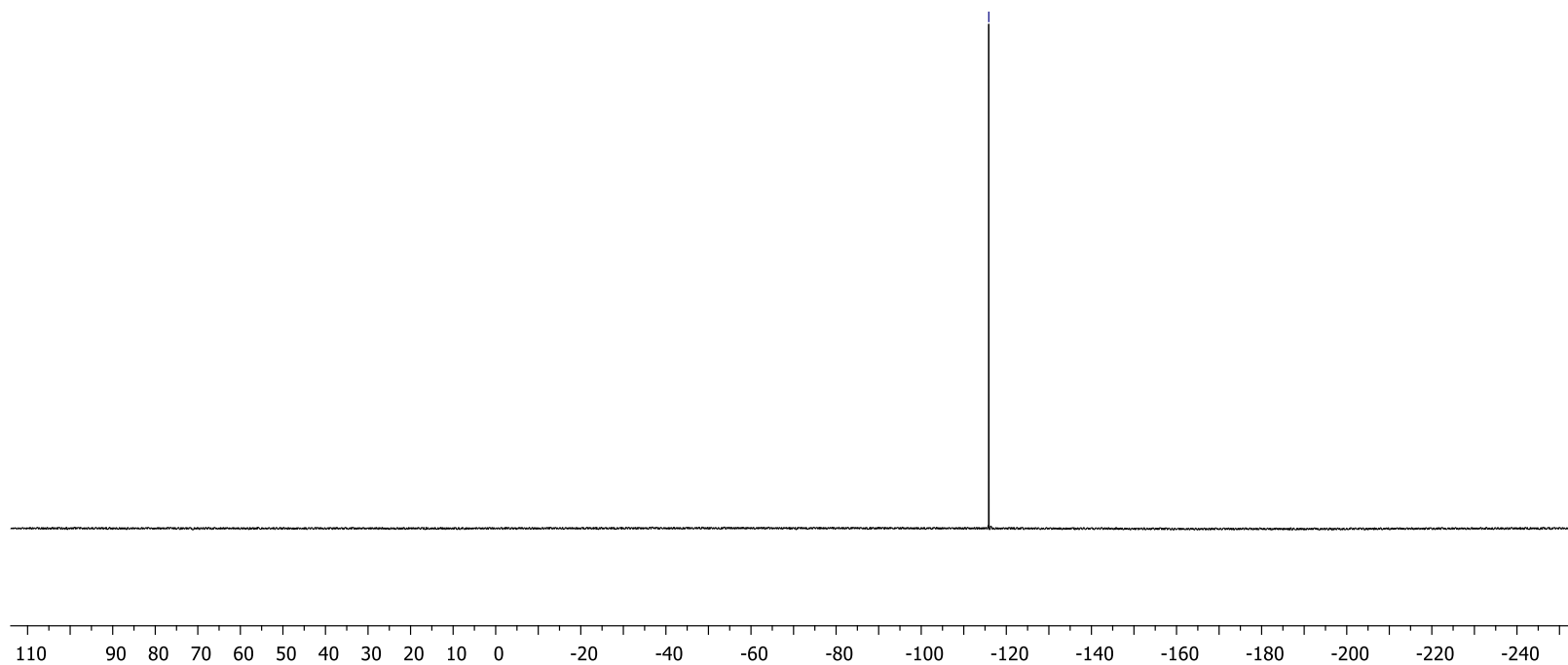


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2411520_F19
 $^{19}\text{F}\{^1\text{H}\}$



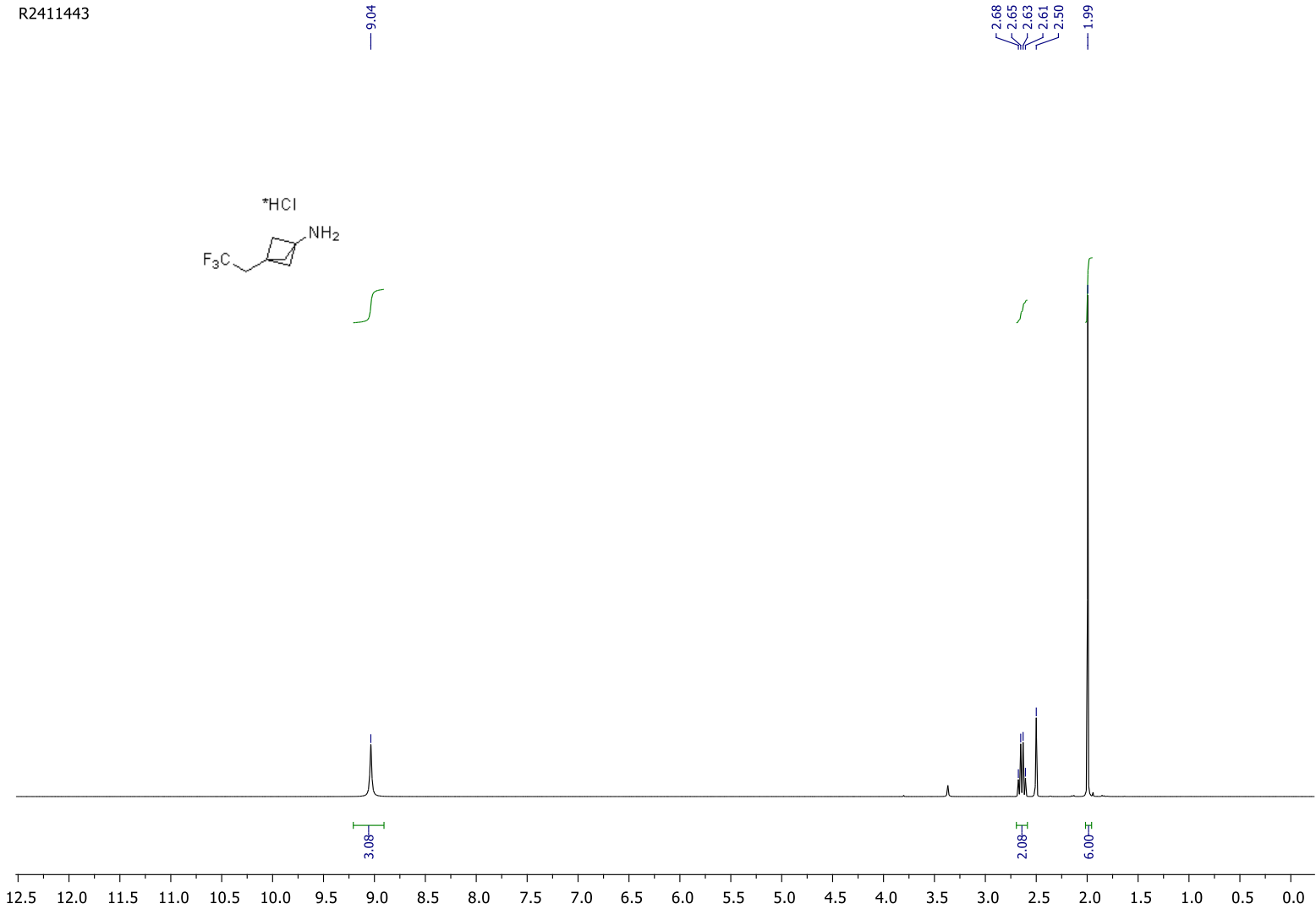
— -115.88

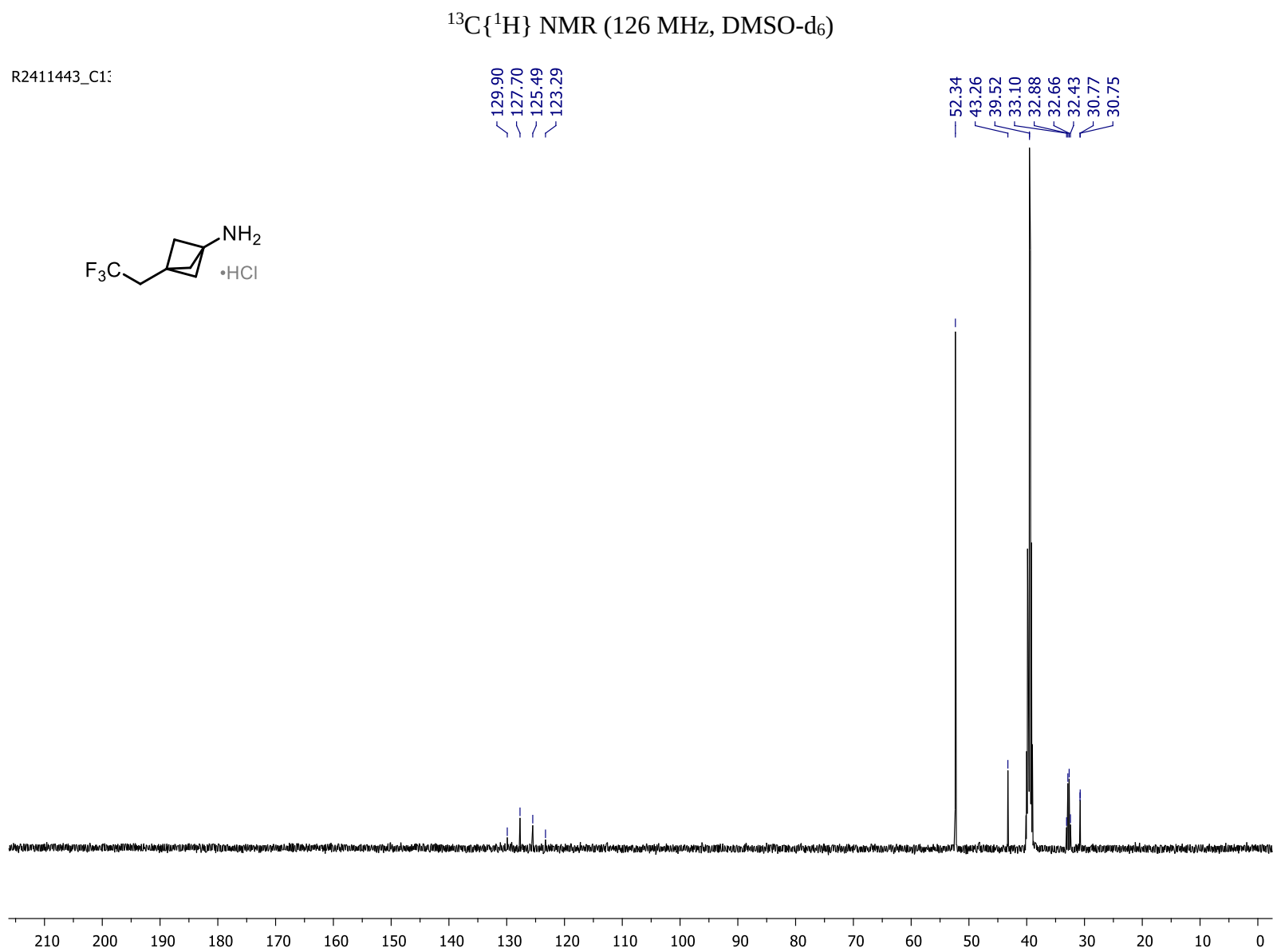


Compound 25l

¹H NMR (500 MHz, DMSO-d₆)

R2411443

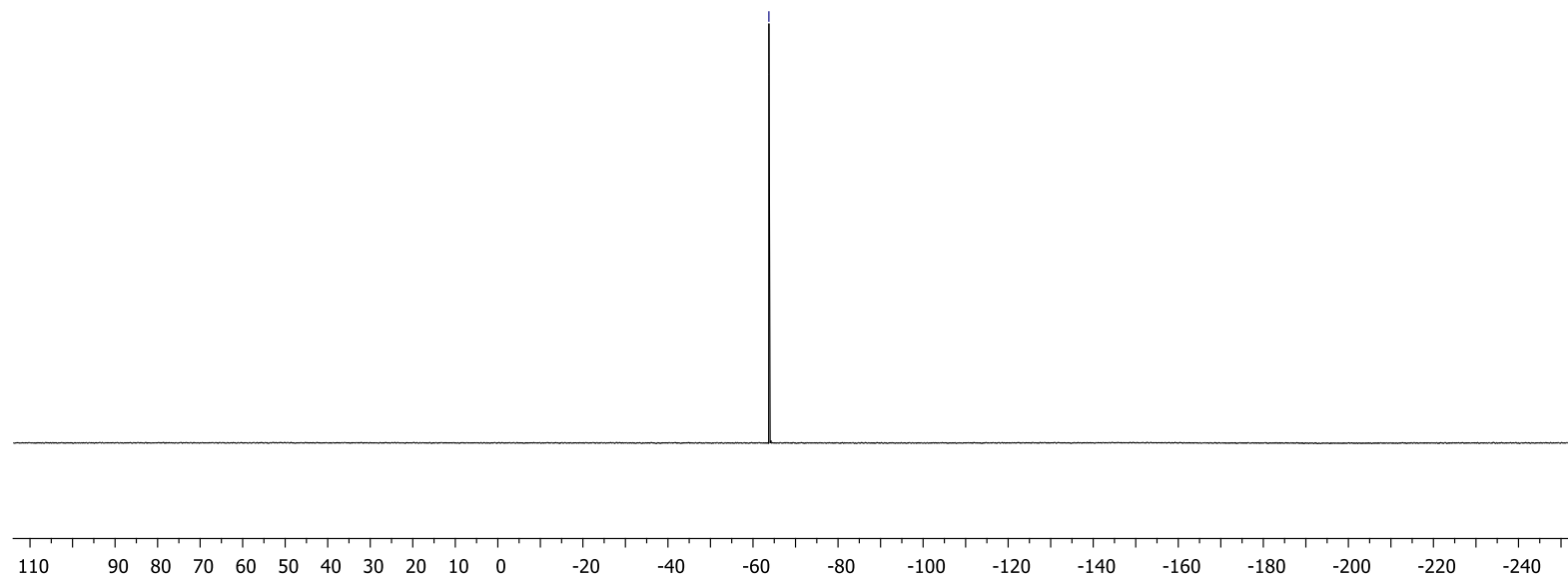
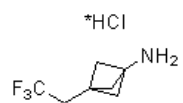




$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2411443_F19{H}

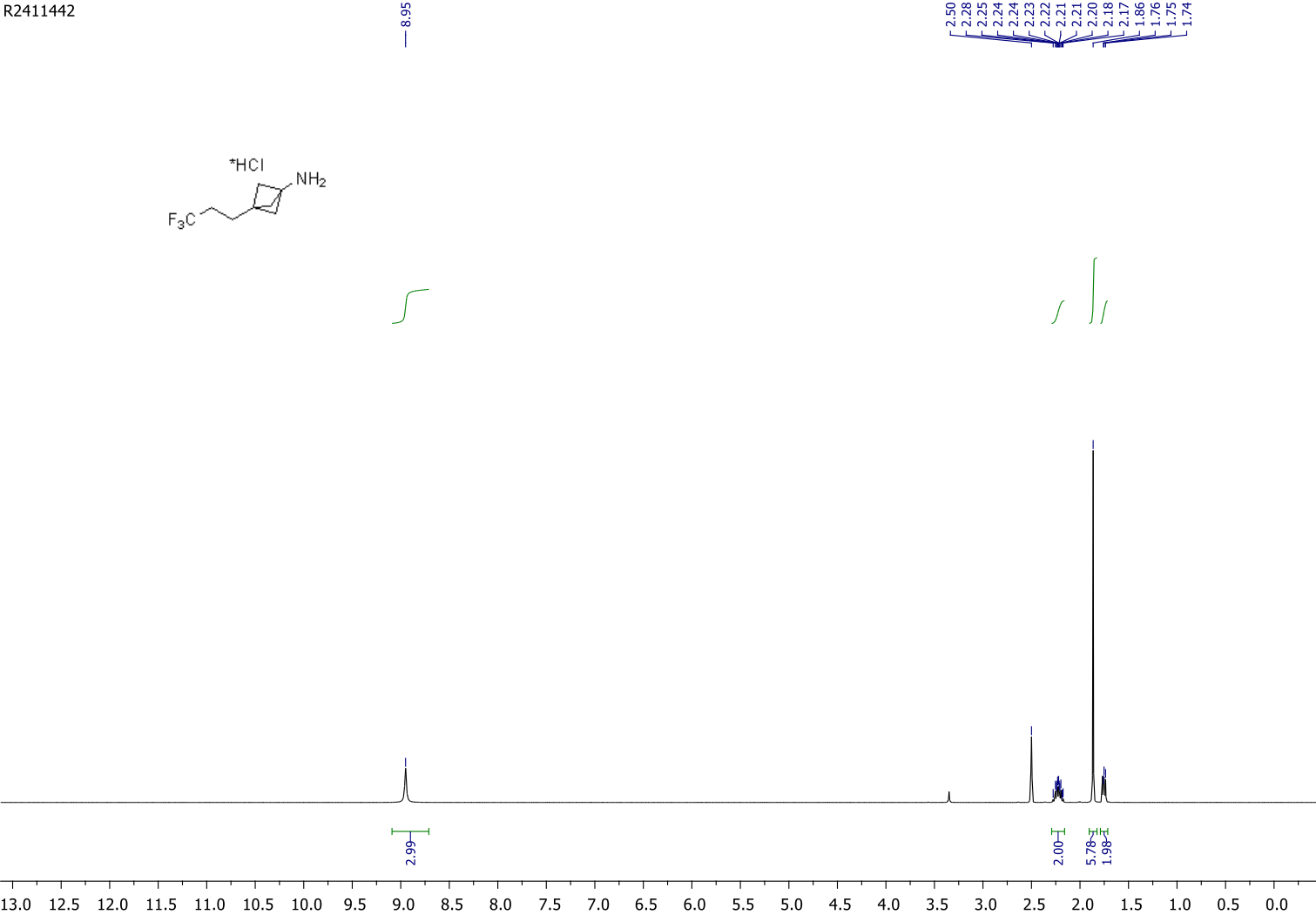
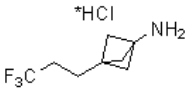
— -63.74

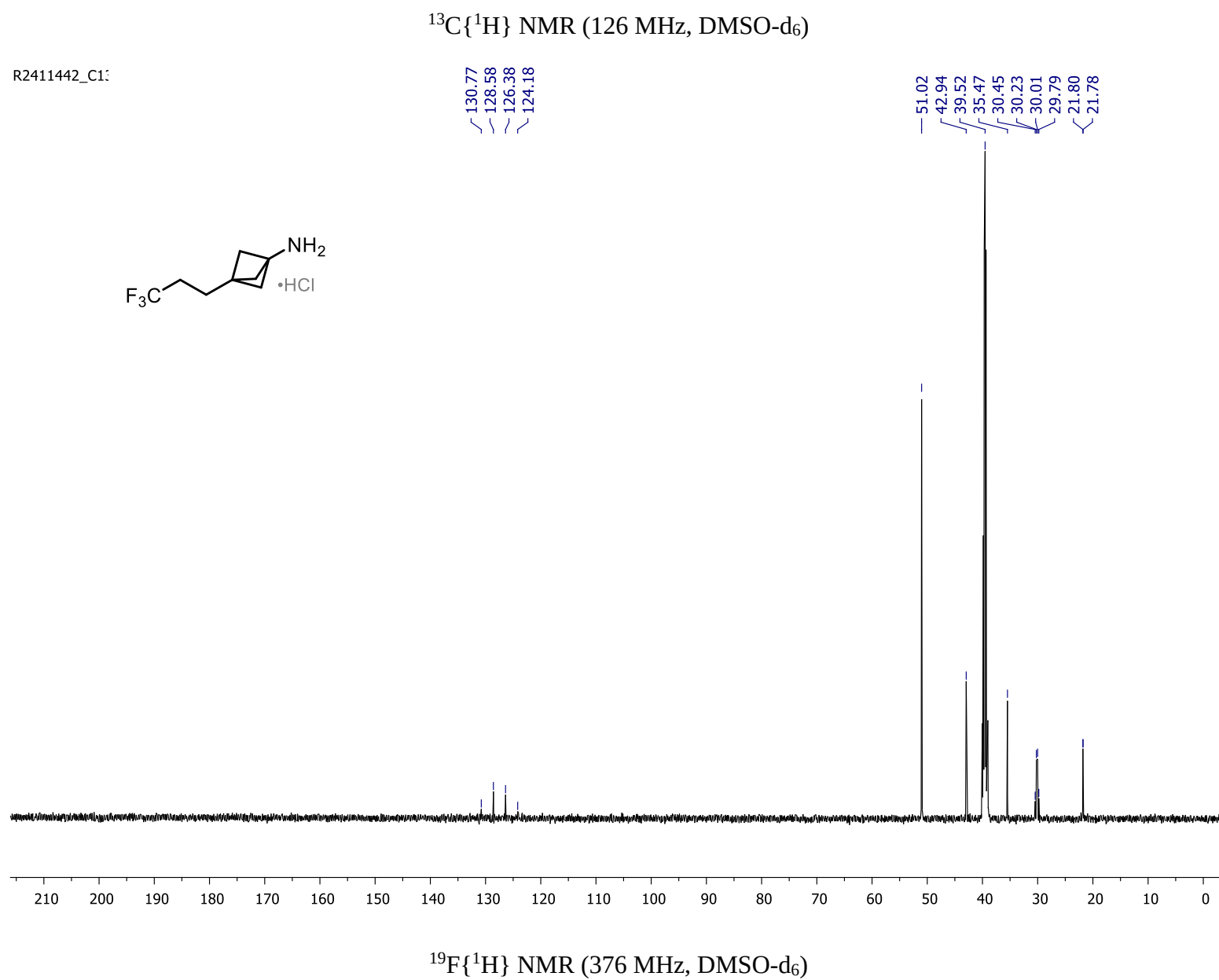


Compound 26l

¹H NMR (500 MHz, DMSO-d₆)

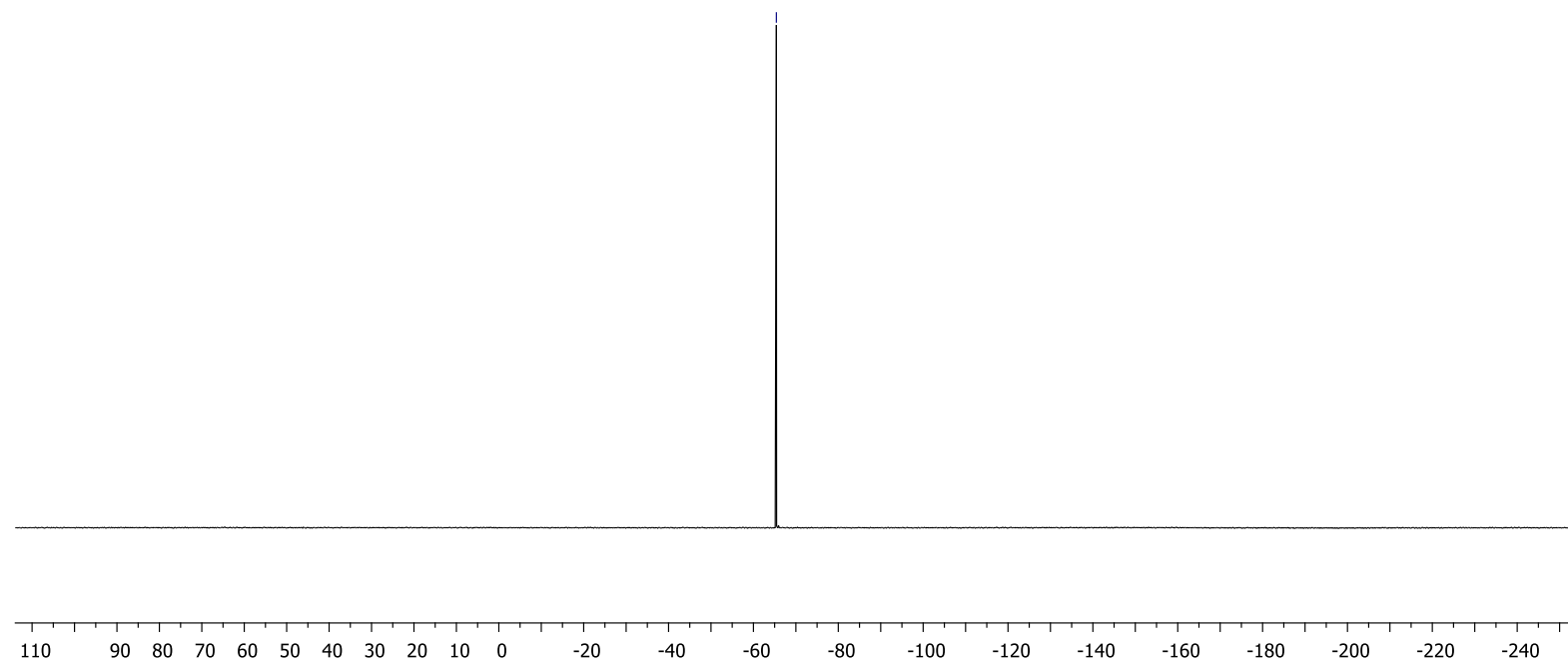
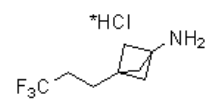
R2411442





R2411442_F19{H}

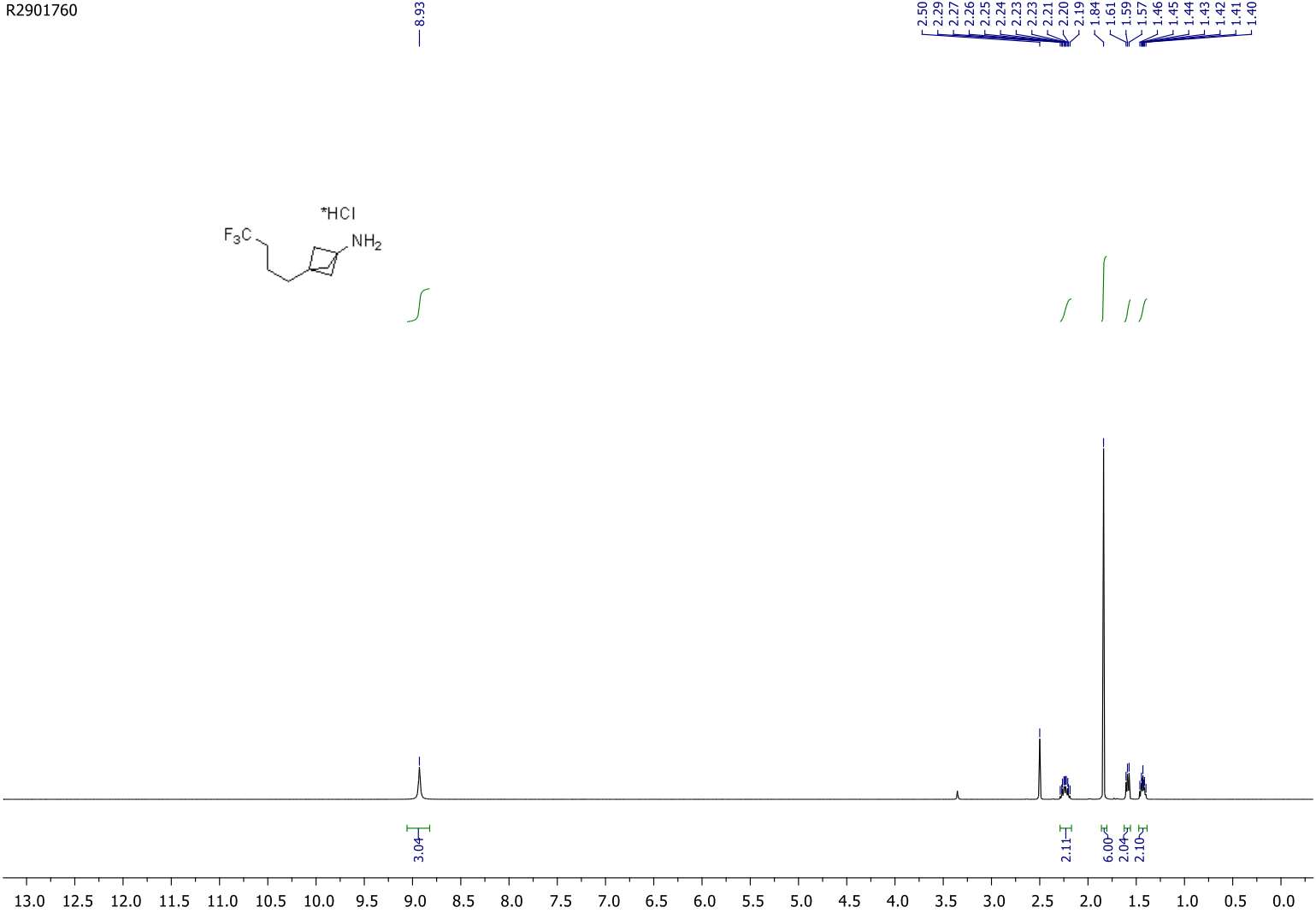
— -65.40



Compound 27l

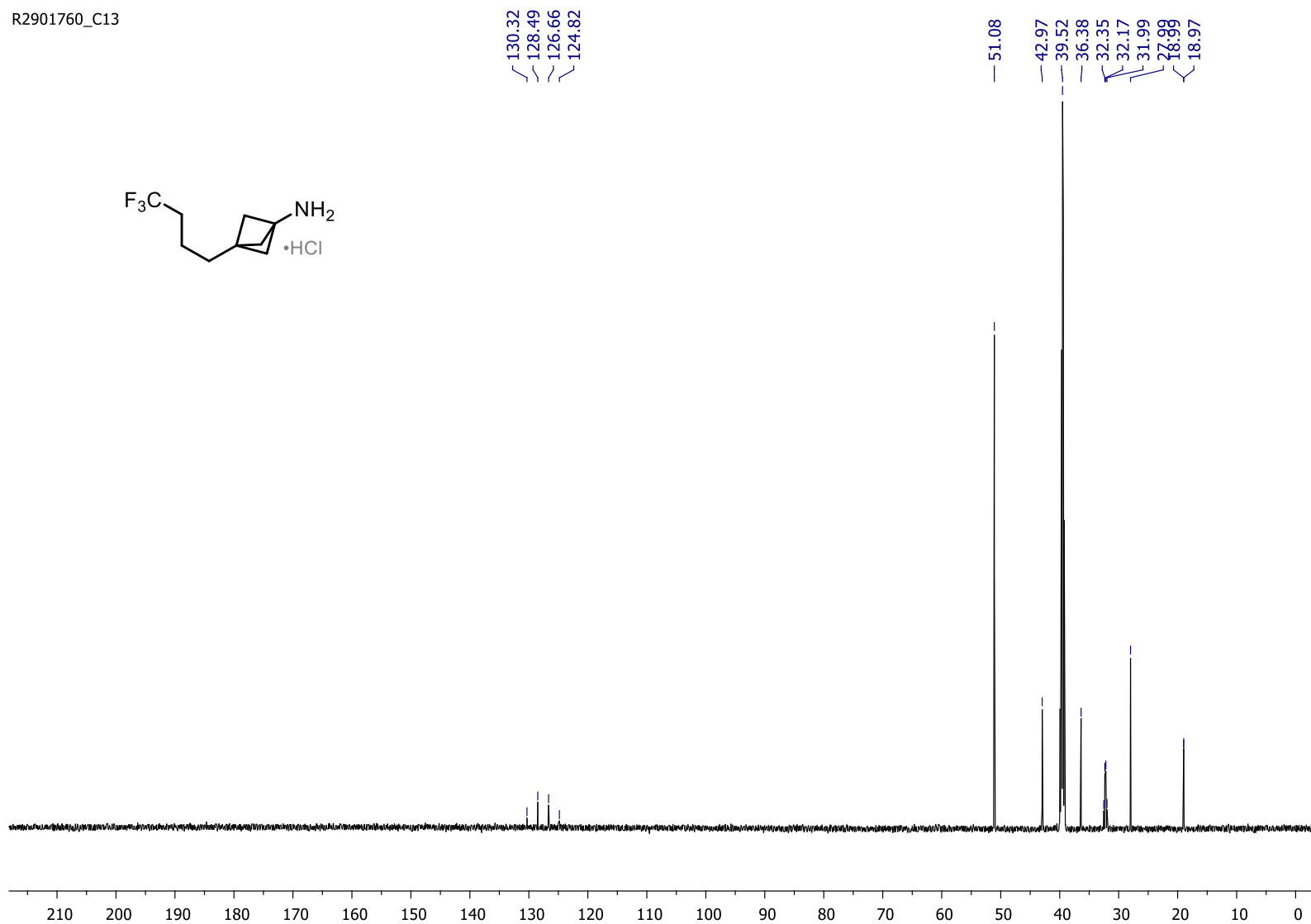
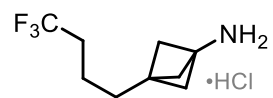
¹H NMR (500 MHz, DMSO-d₆)

R2901760



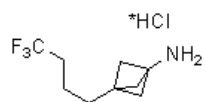
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2901760_C13

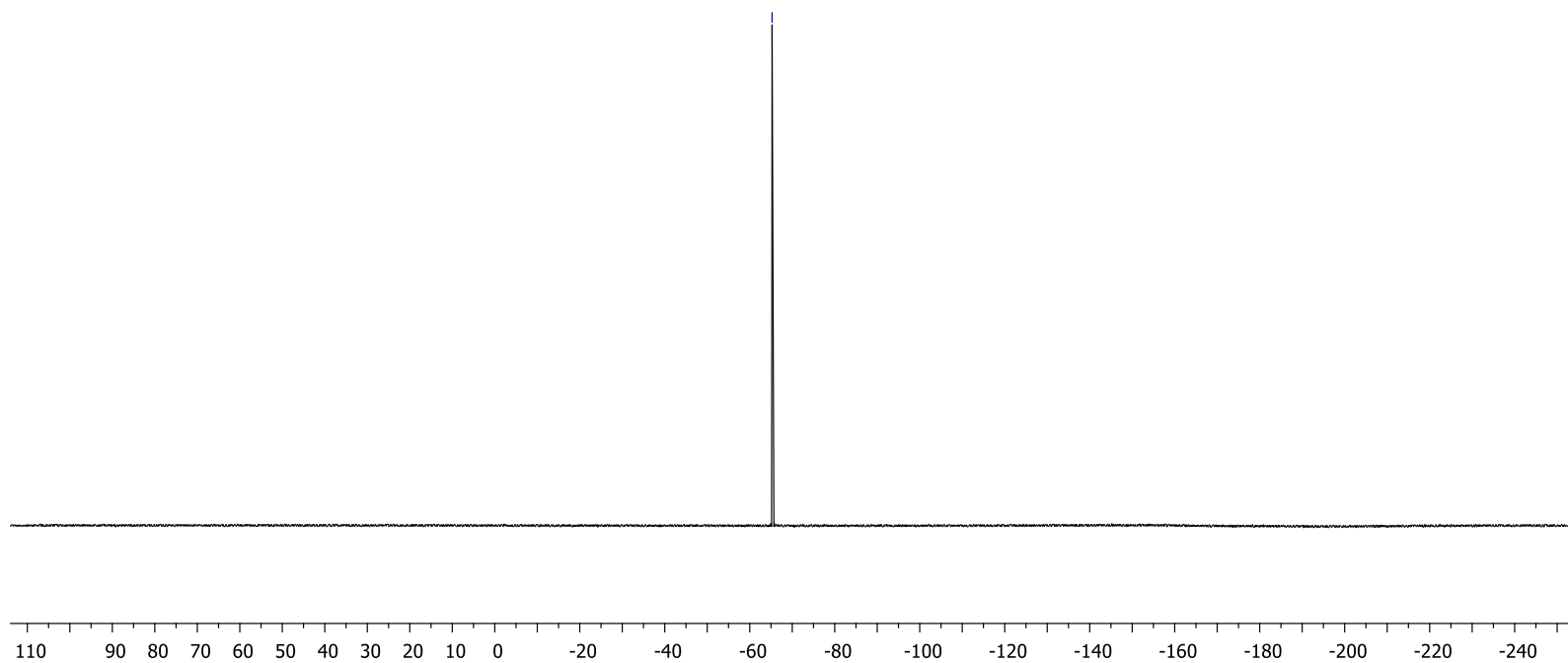


$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R2901760_F19{H}
19F-{1H}

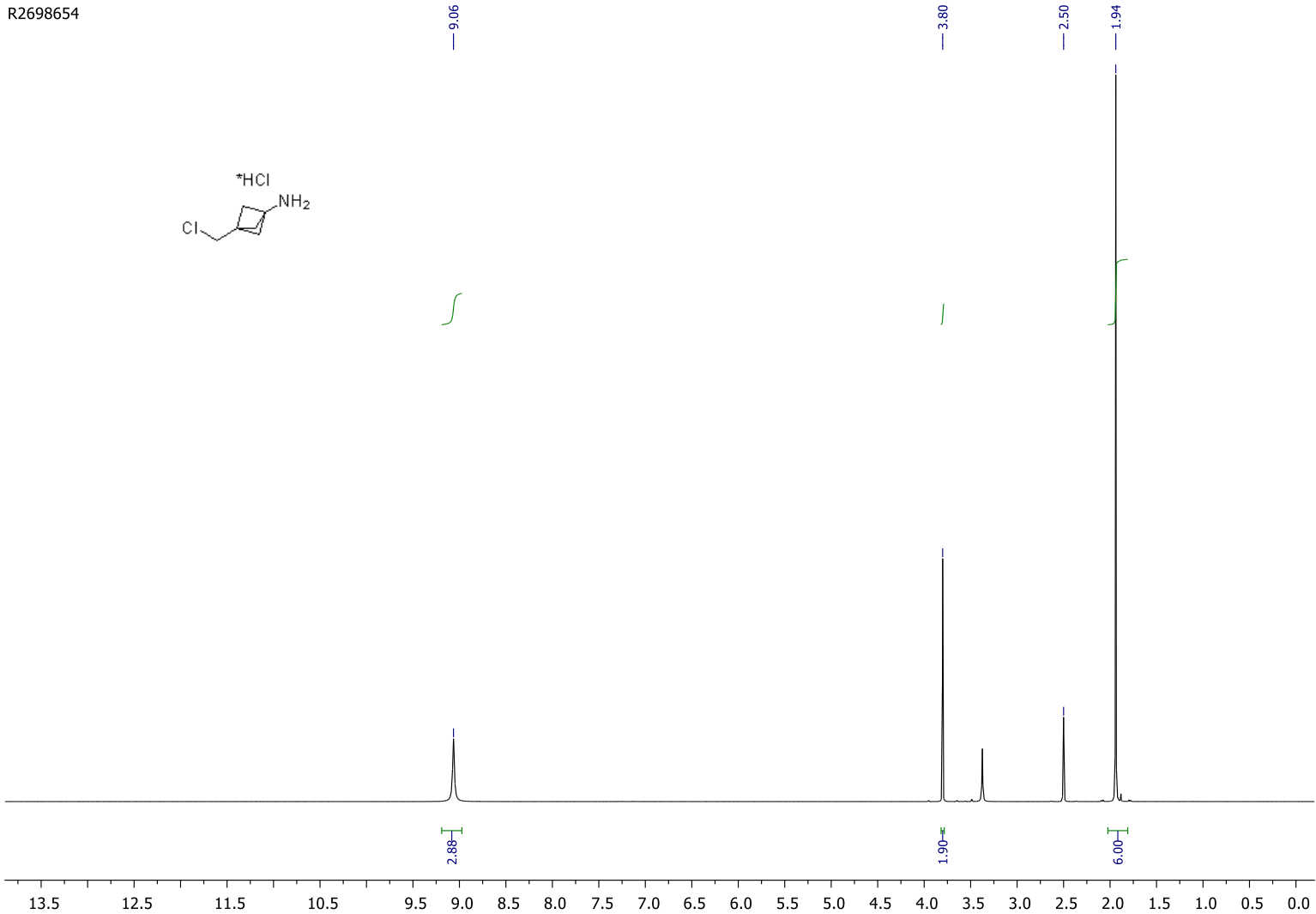


-65.26



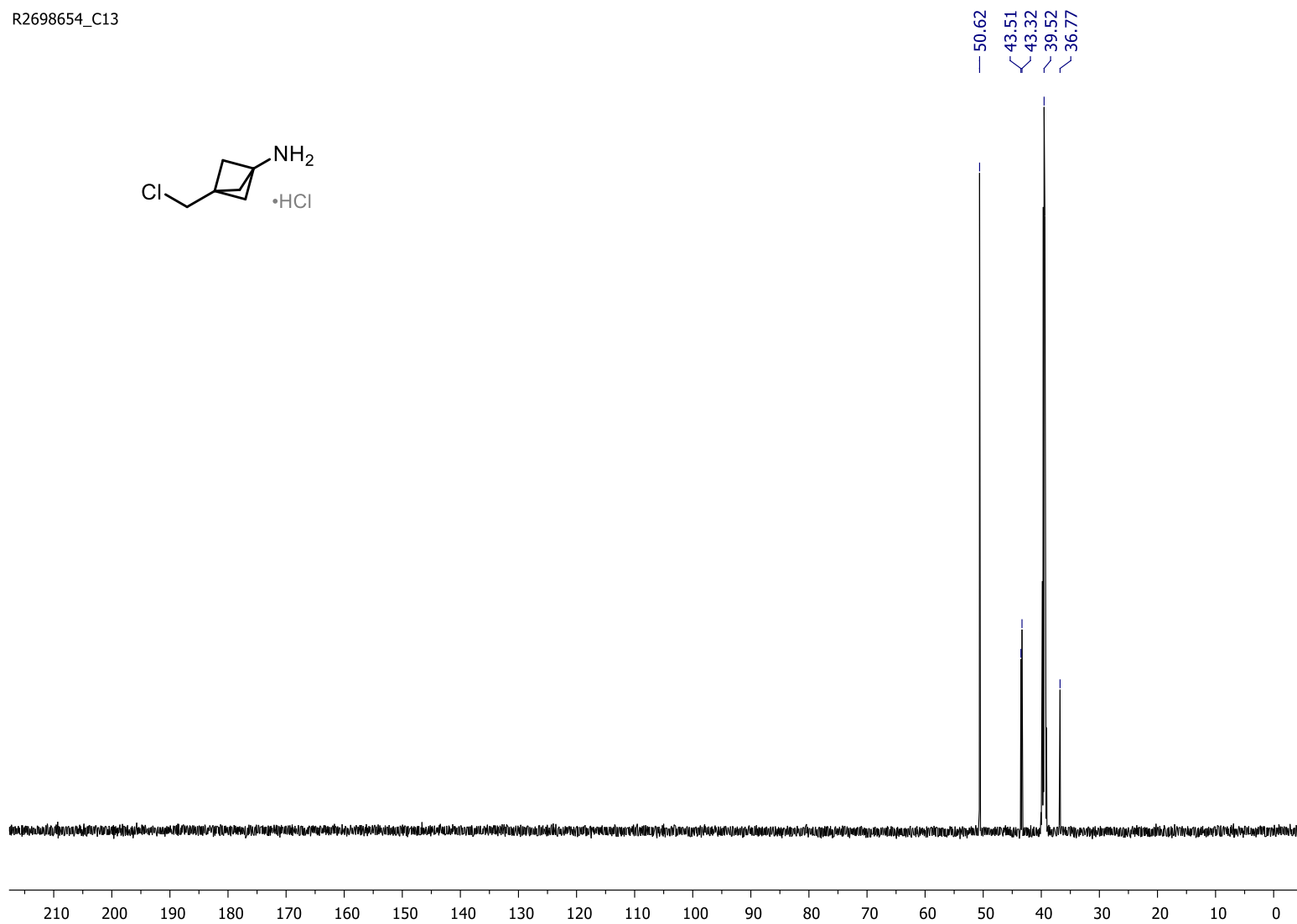
Compound 34l

¹H NMR (500 MHz, DMSO-d₆)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

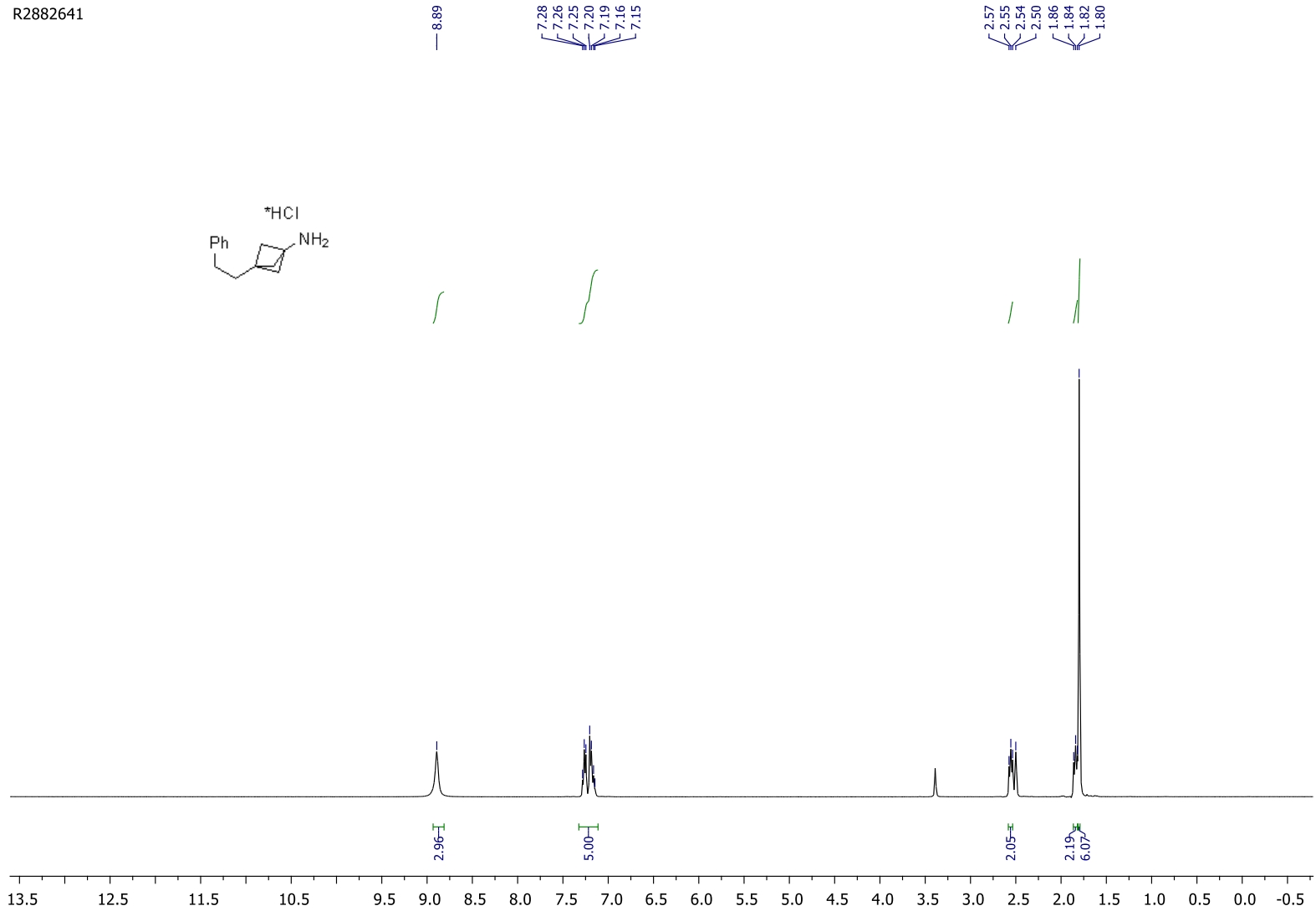
R2698654_C13



Compound 41l

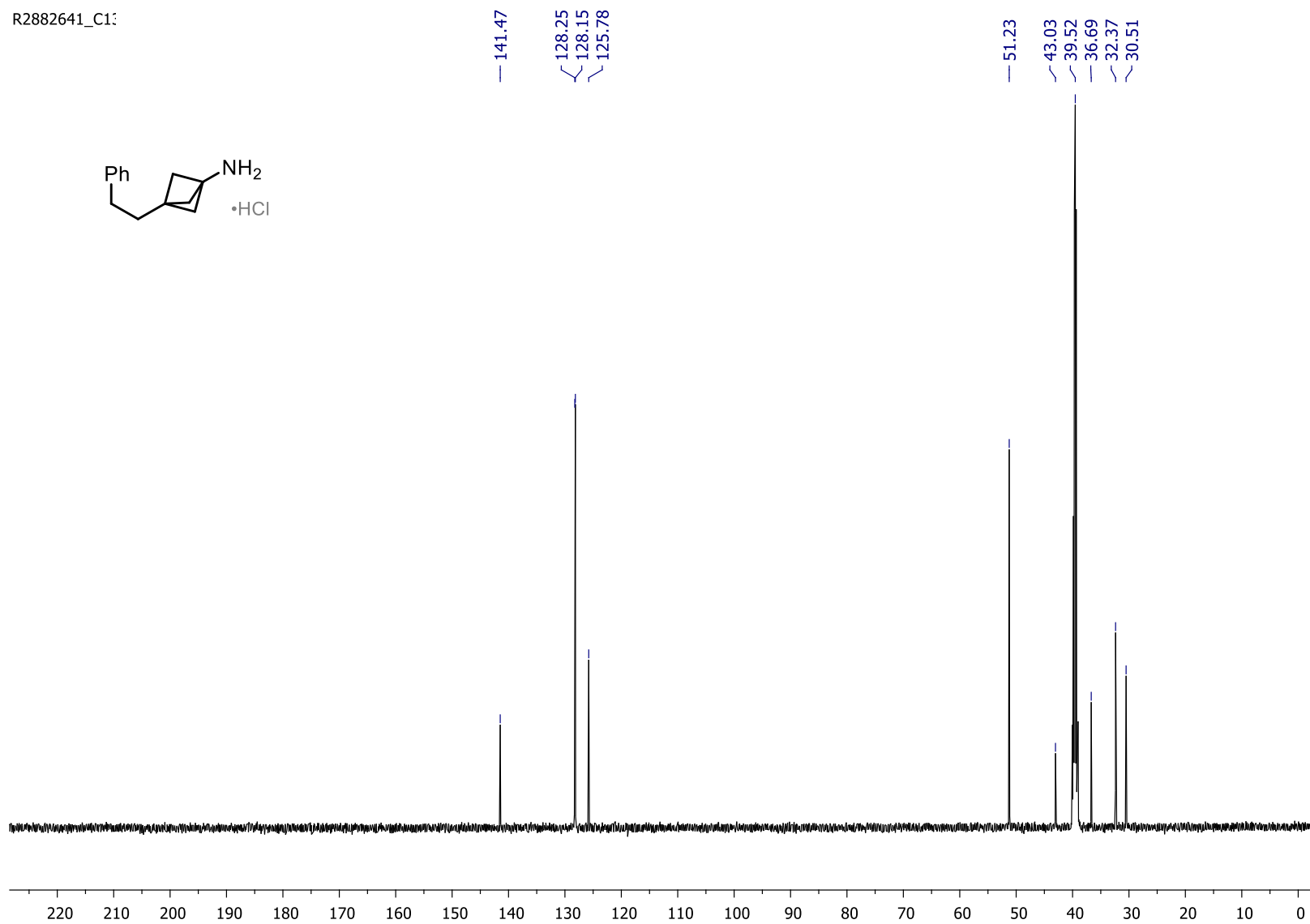
¹H NMR (400 MHz, DMSO-d₆)

R2882641



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

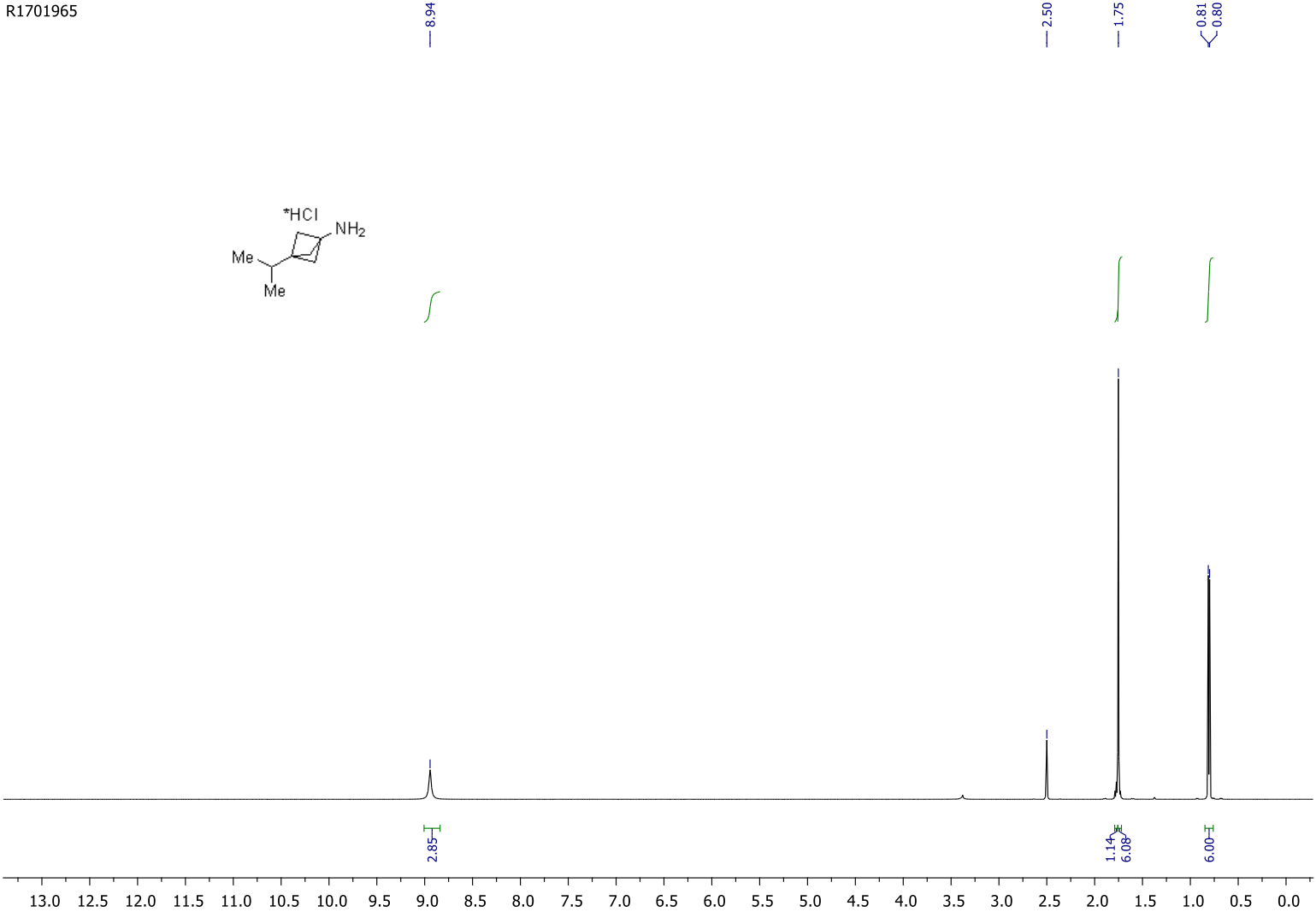
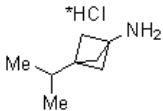
R2882641_C1:



Compound 48l

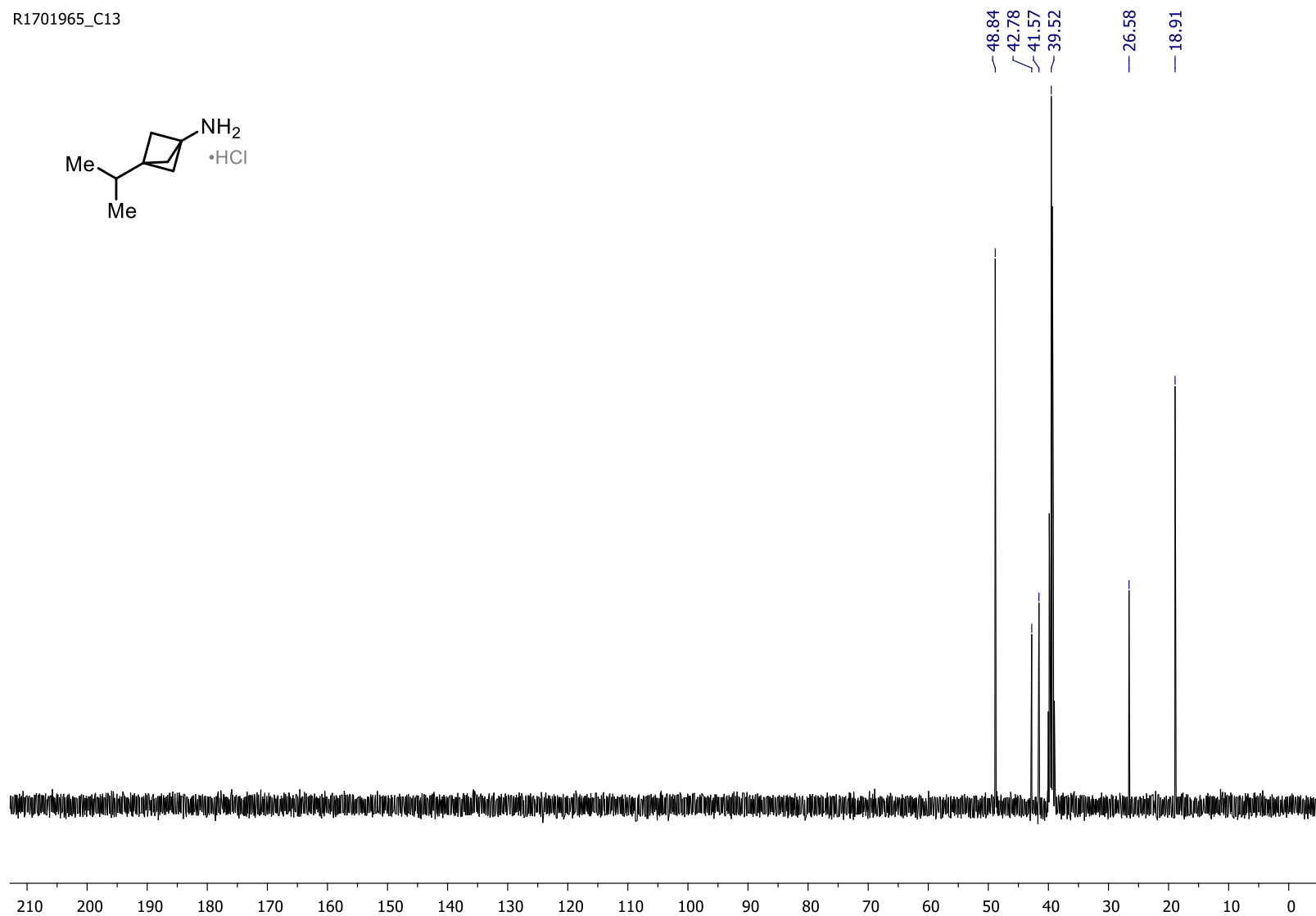
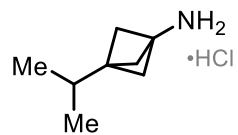
¹H NMR (500 MHz, DMSO-d₆)

R1701965



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

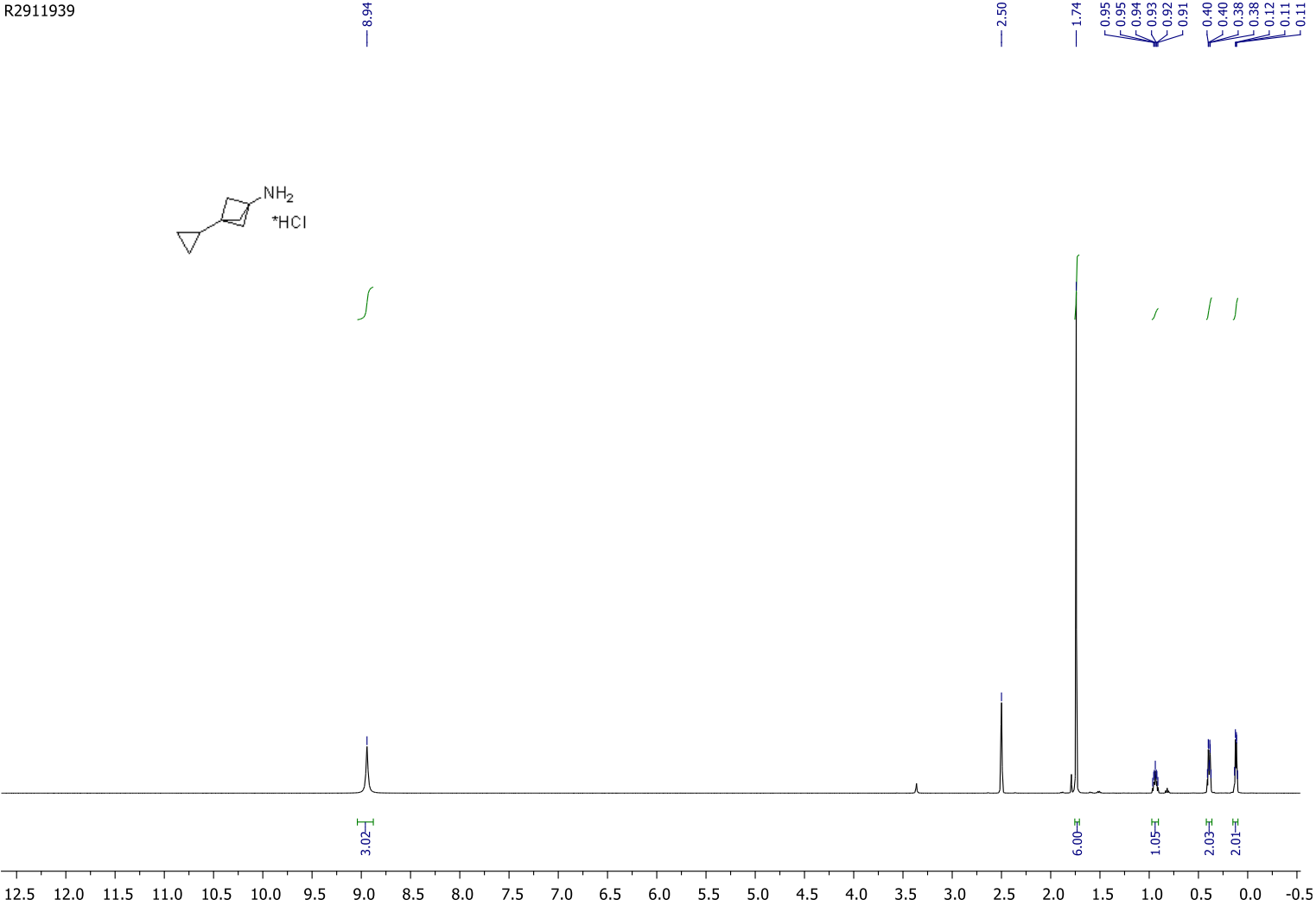
R1701965_C13



Compound 50l

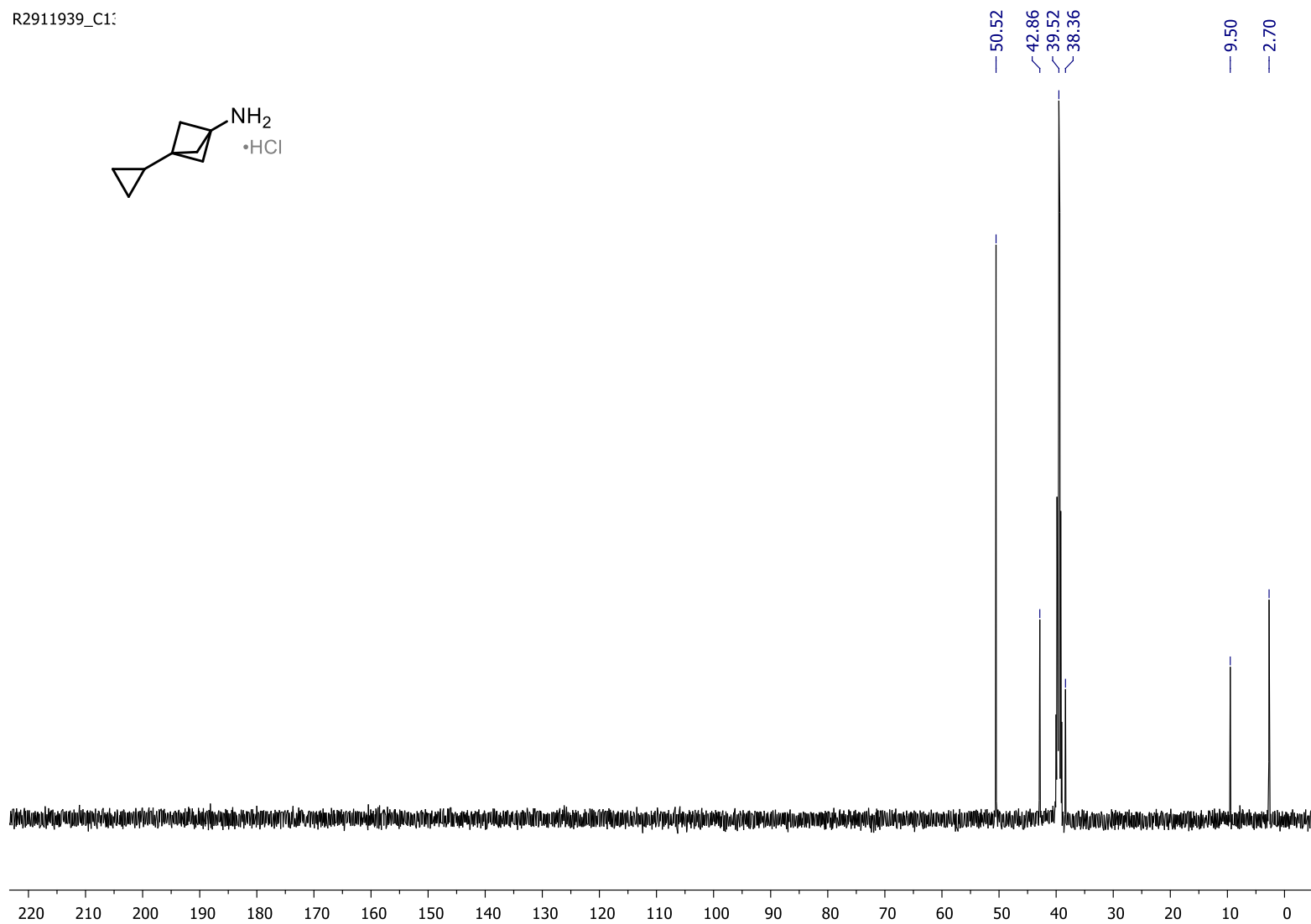
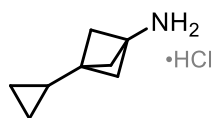
¹H NMR (500 MHz, DMSO-d₆)

R2911939



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

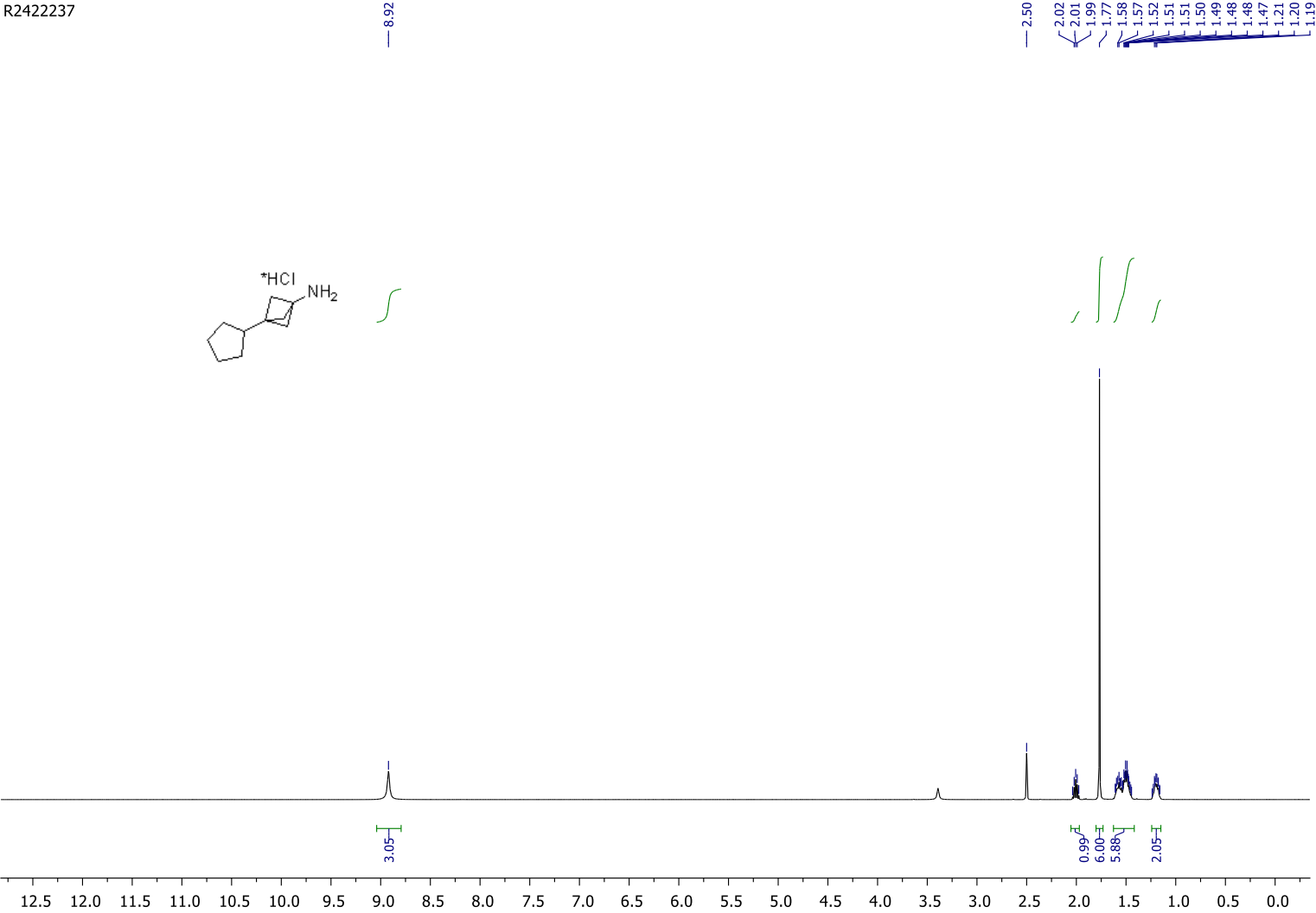
R2911939_C1:



Compound 52I

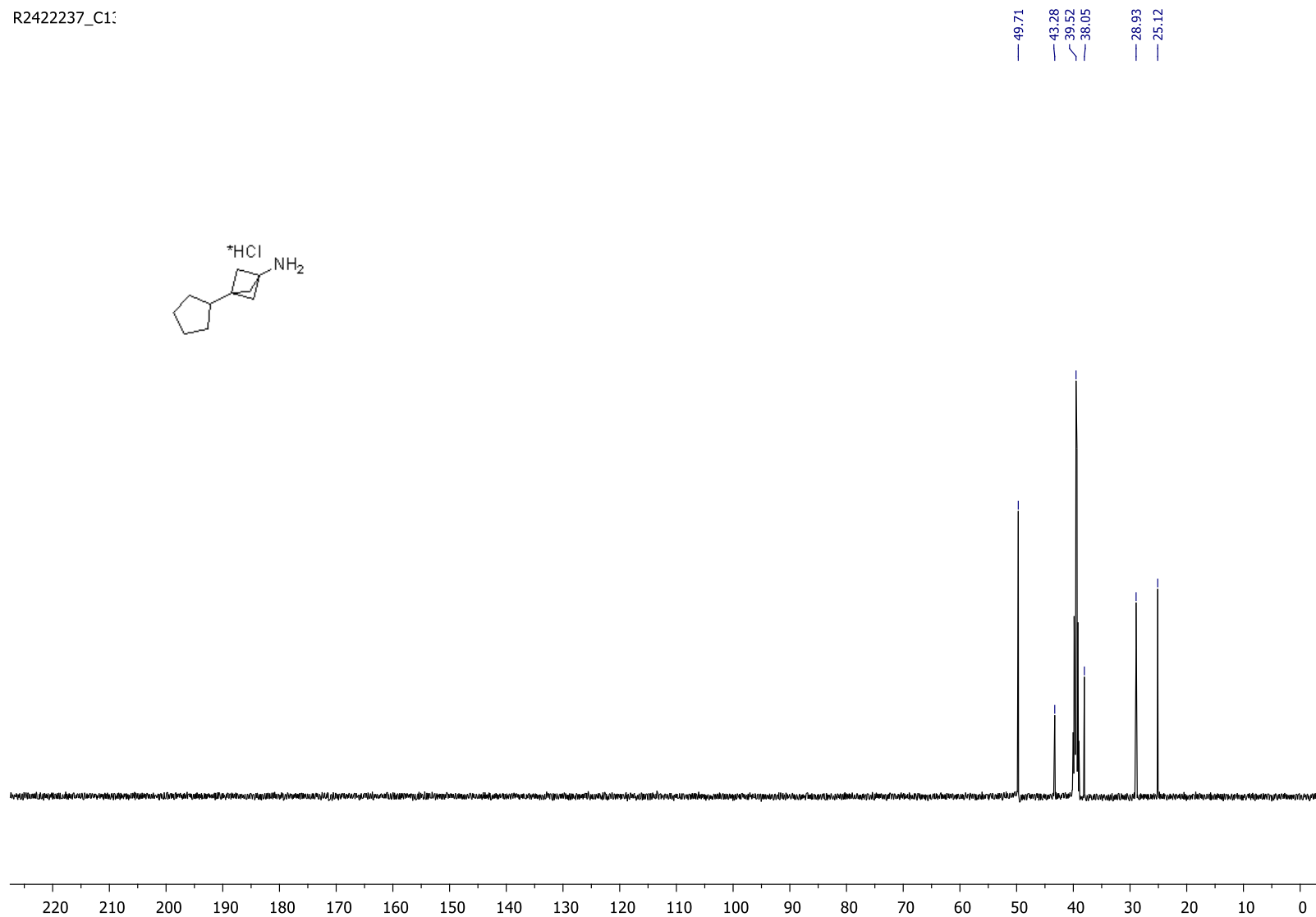
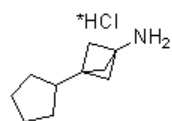
¹H NMR (500 MHz, DMSO-d₆)

R2422237



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

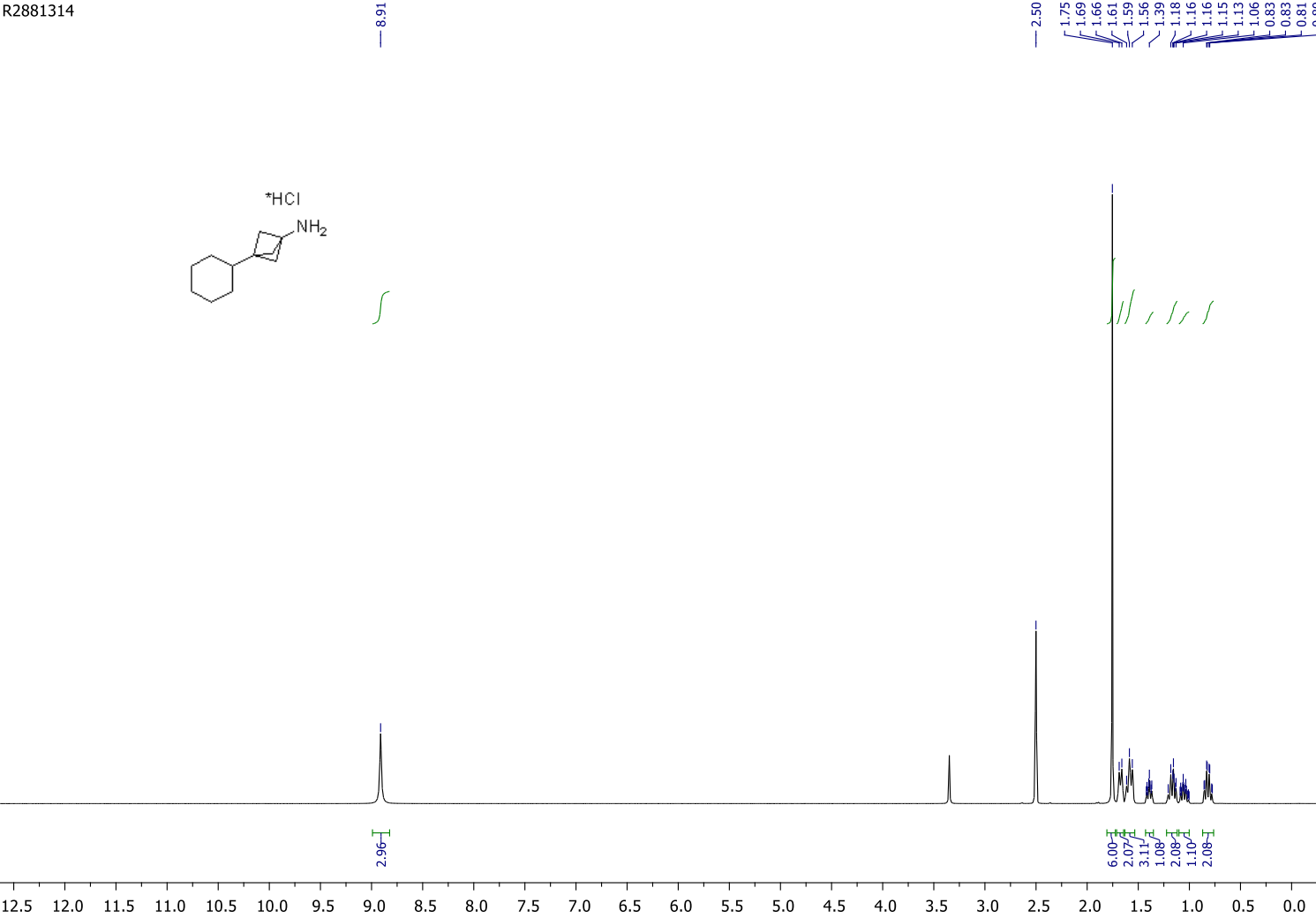
R2422237_C11



Compound 53I

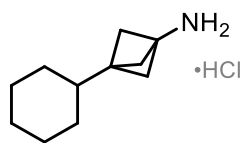
¹H NMR (500 MHz, DMSO-d₆)

R2881314

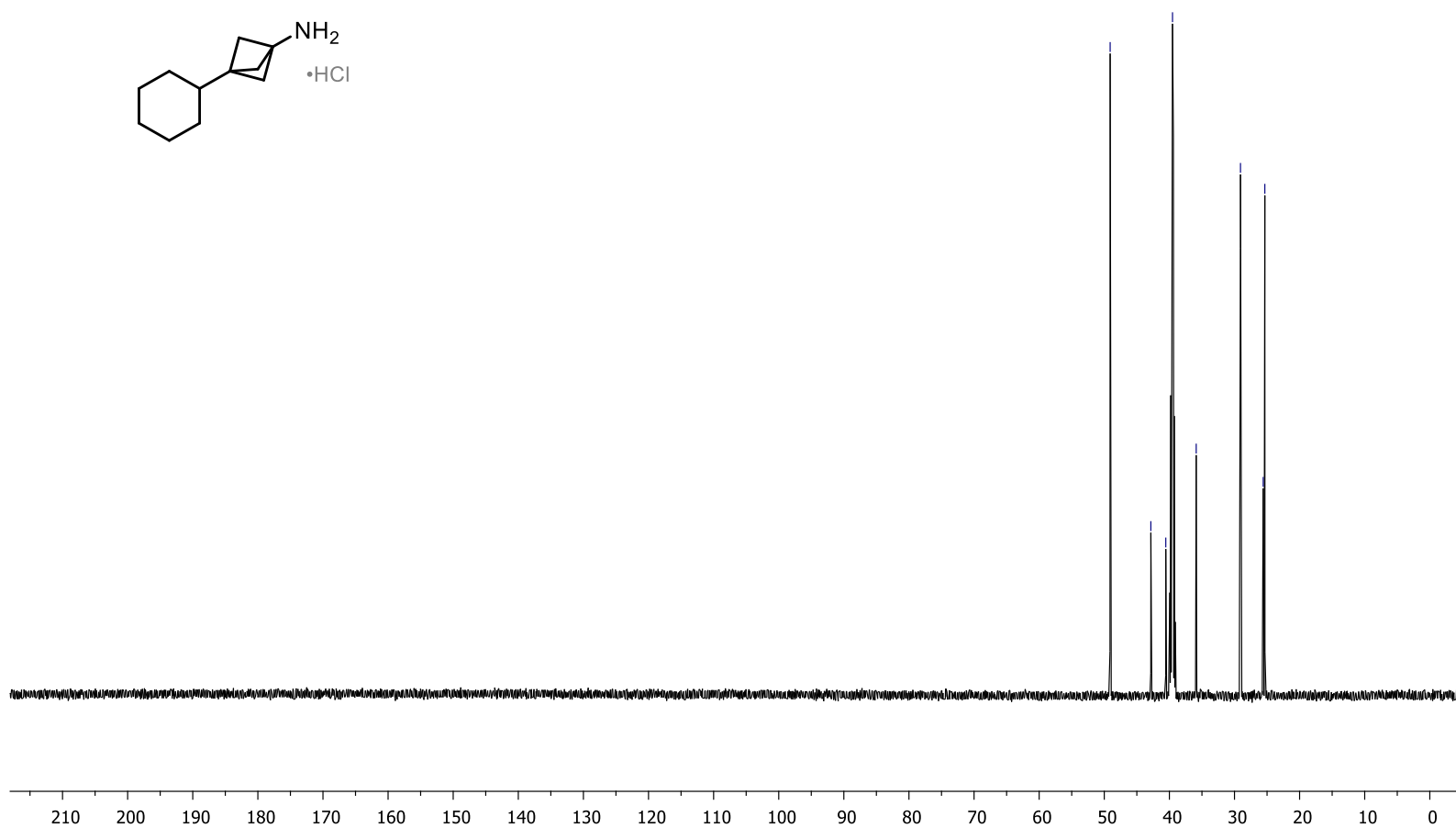


$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R2881314_C13



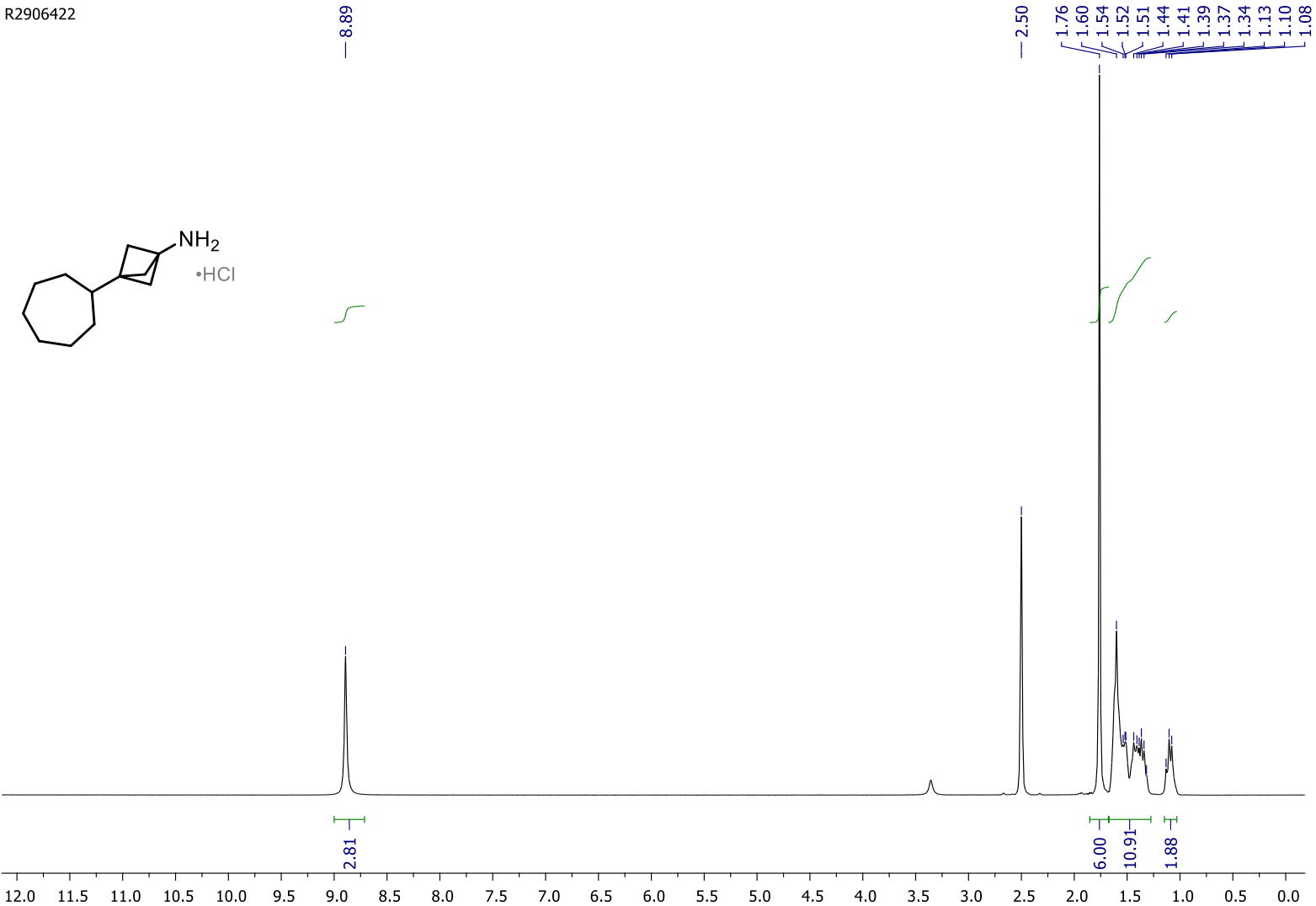
49.09
42.84
40.55
39.52
35.88
29.08
25.59
25.34



Compound 54I

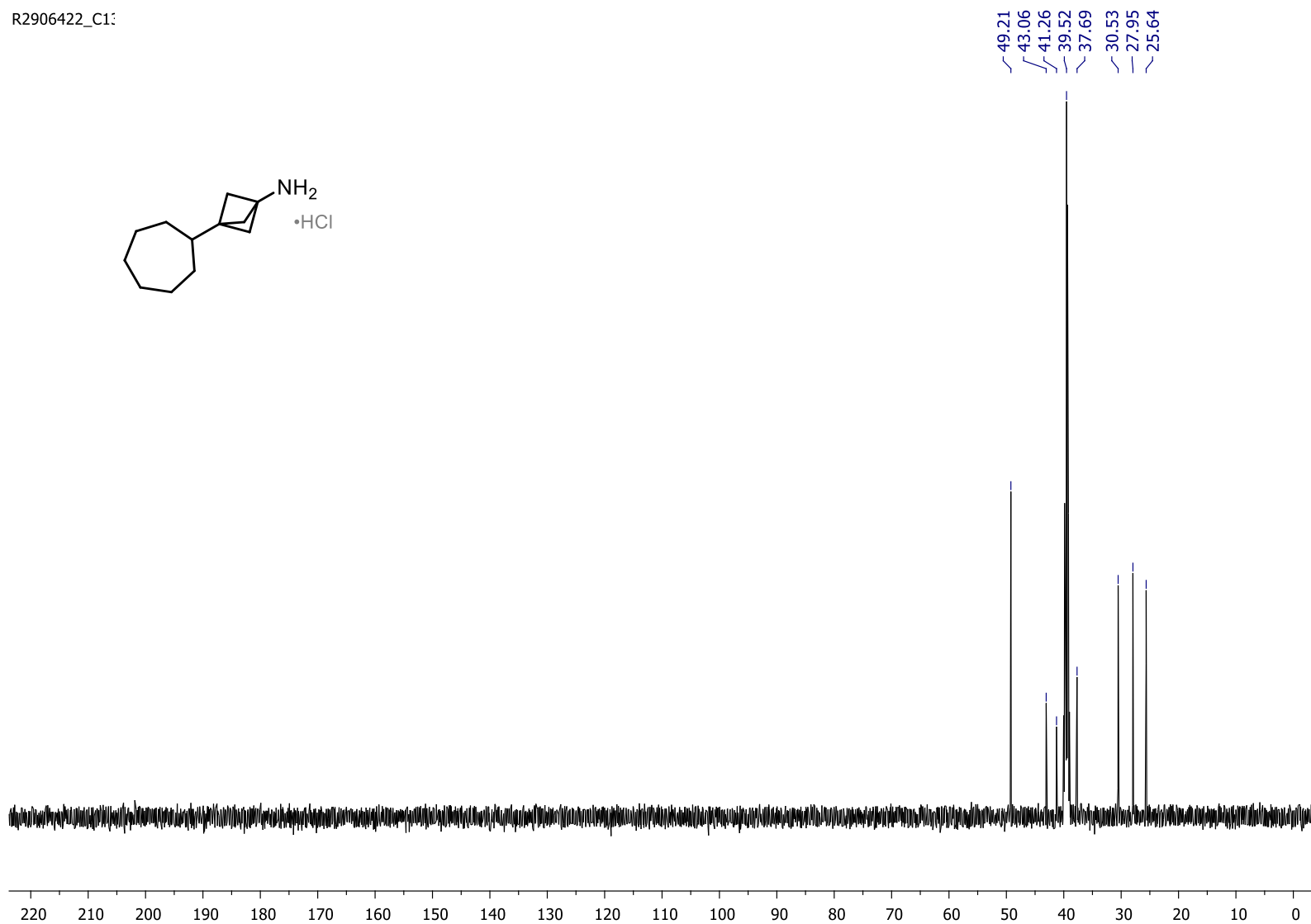
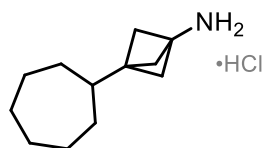
¹H NMR (400 MHz, DMSO-d₆)

R2906422



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

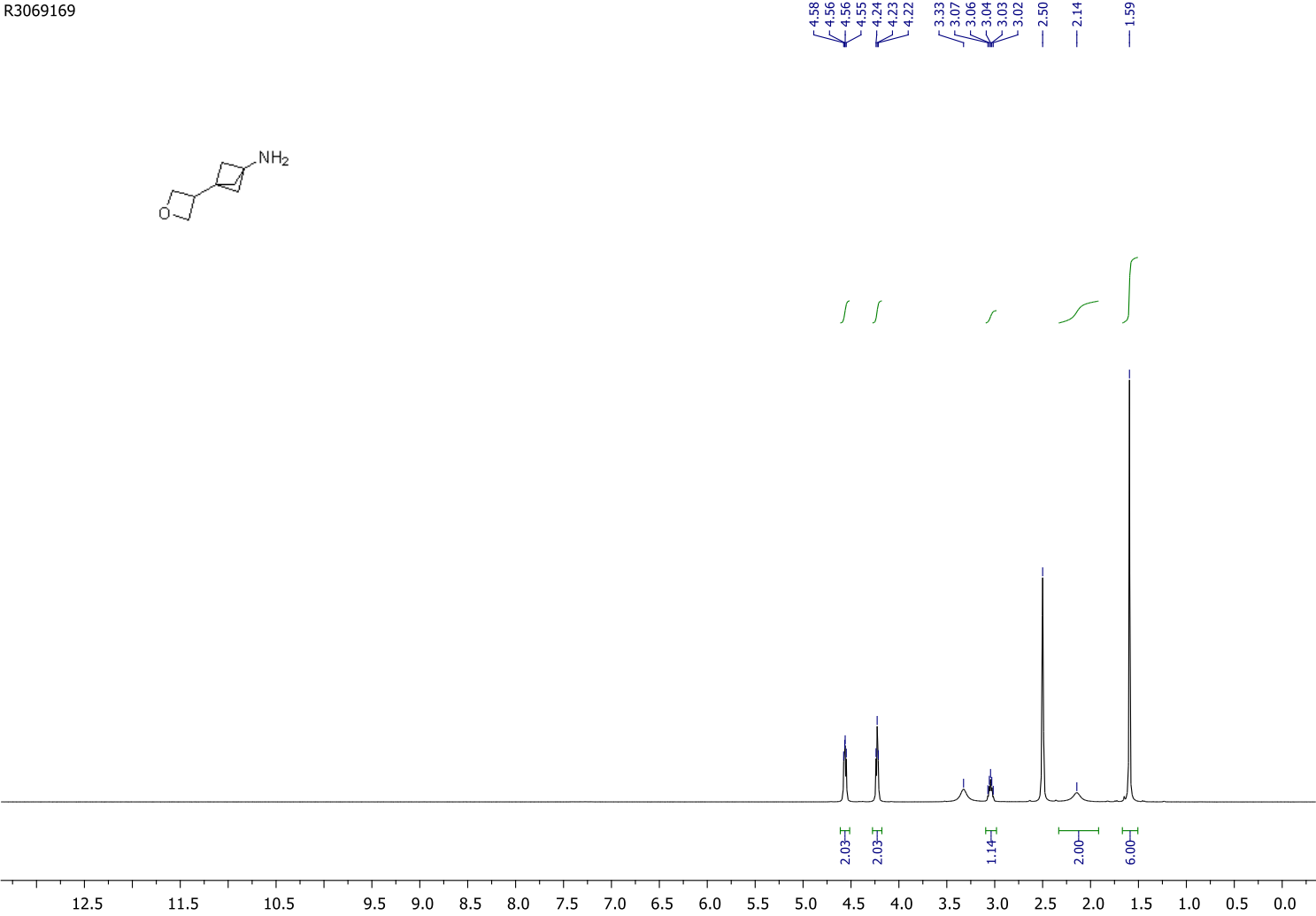
R2906422_C13



Compound 55l

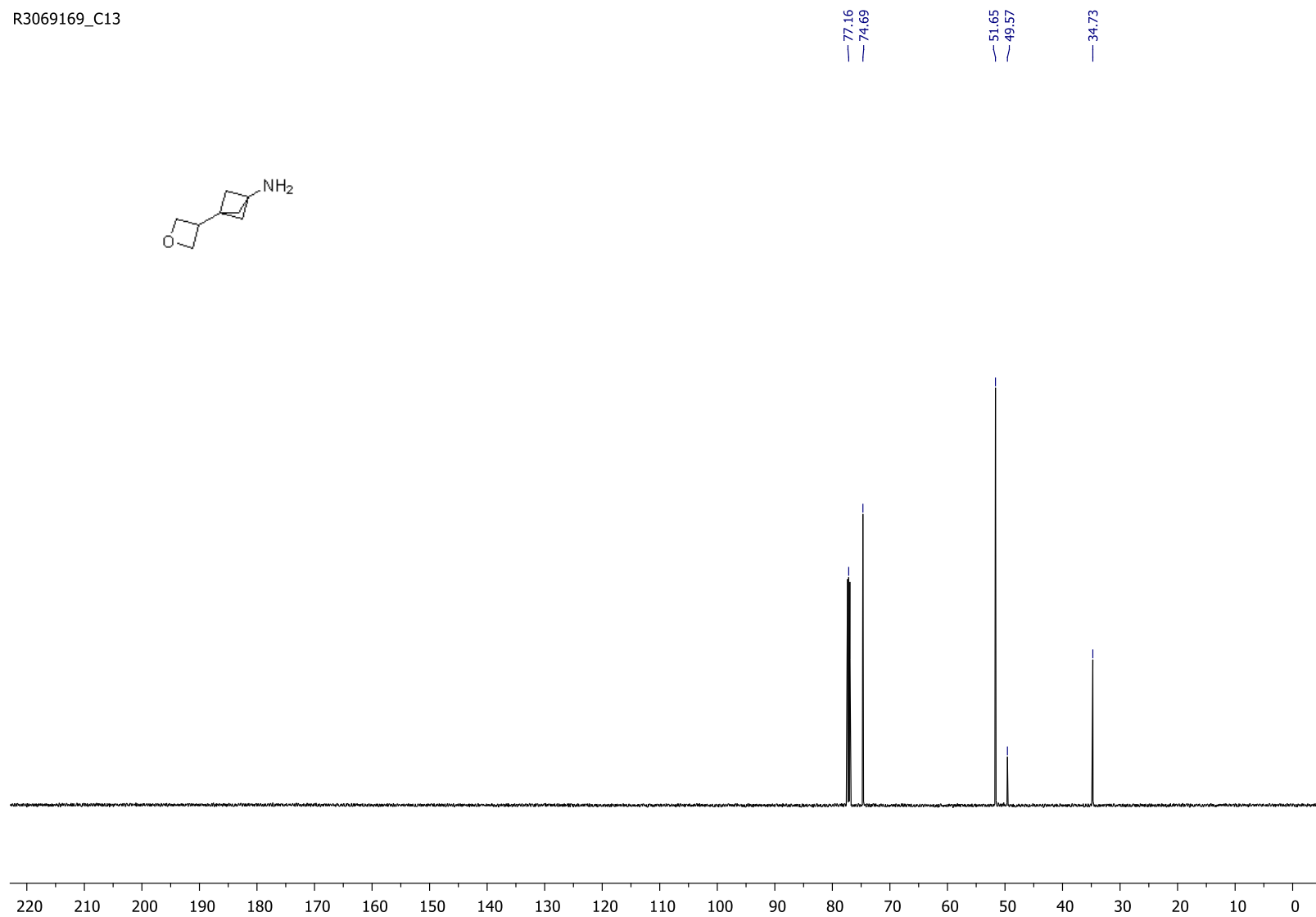
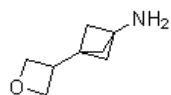
¹H NMR (500 MHz, DMSO-d₆)

R3069169



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

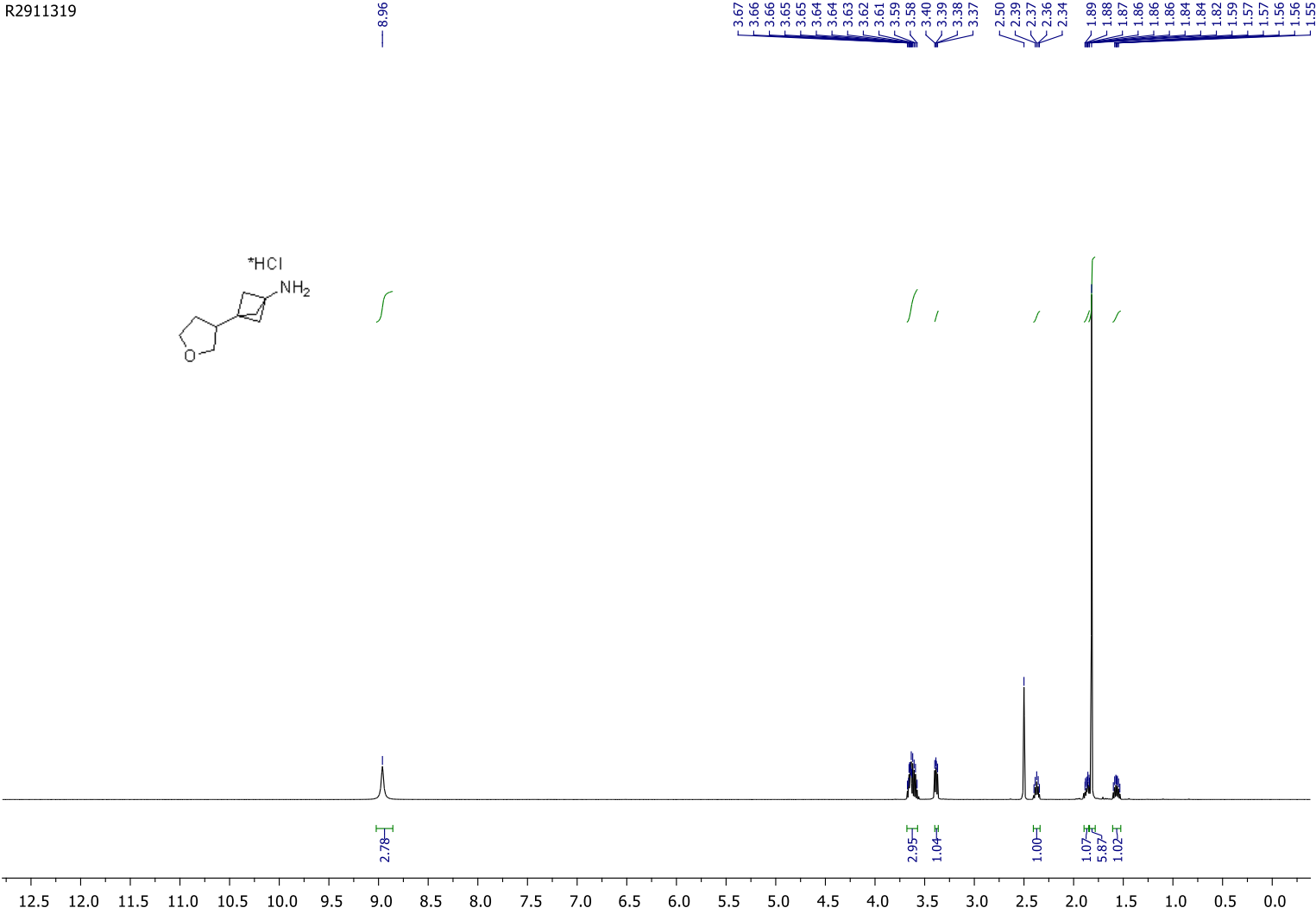
R3069169_C13



Compound 56l

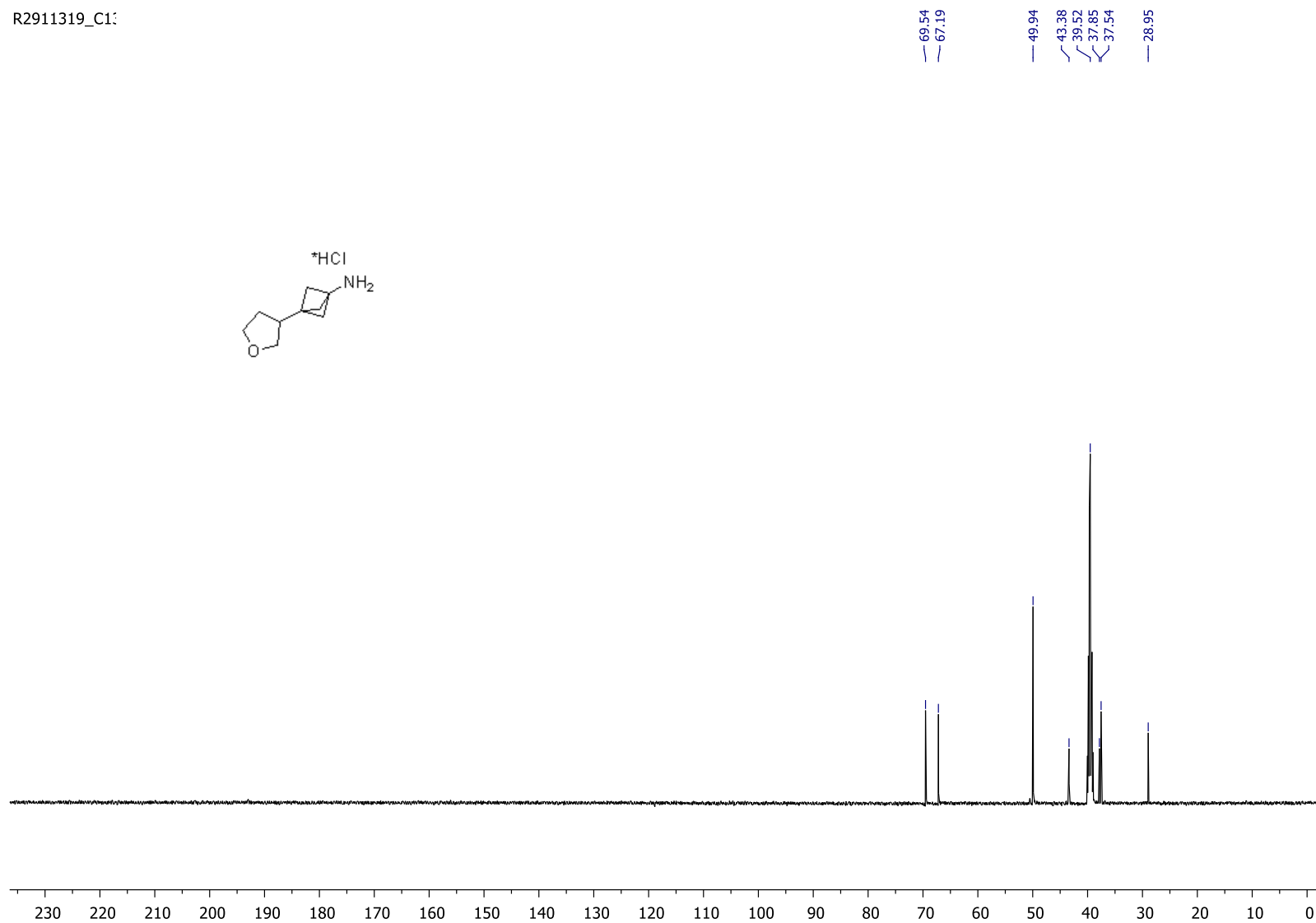
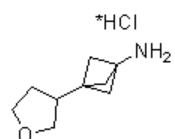
¹H NMR (500 MHz, DMSO-d₆)

R2911319



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

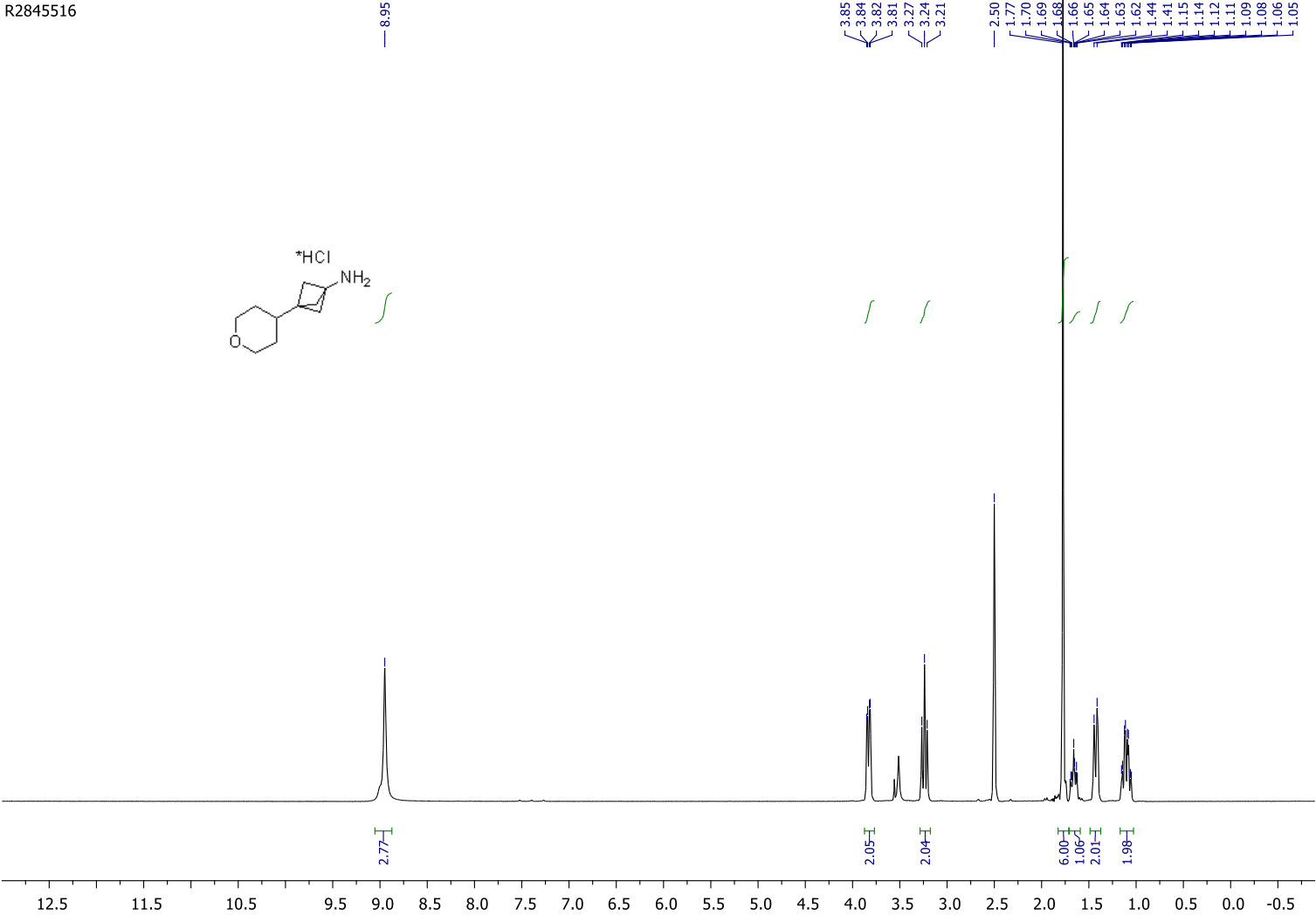
R2911319_C13



Compound 57l

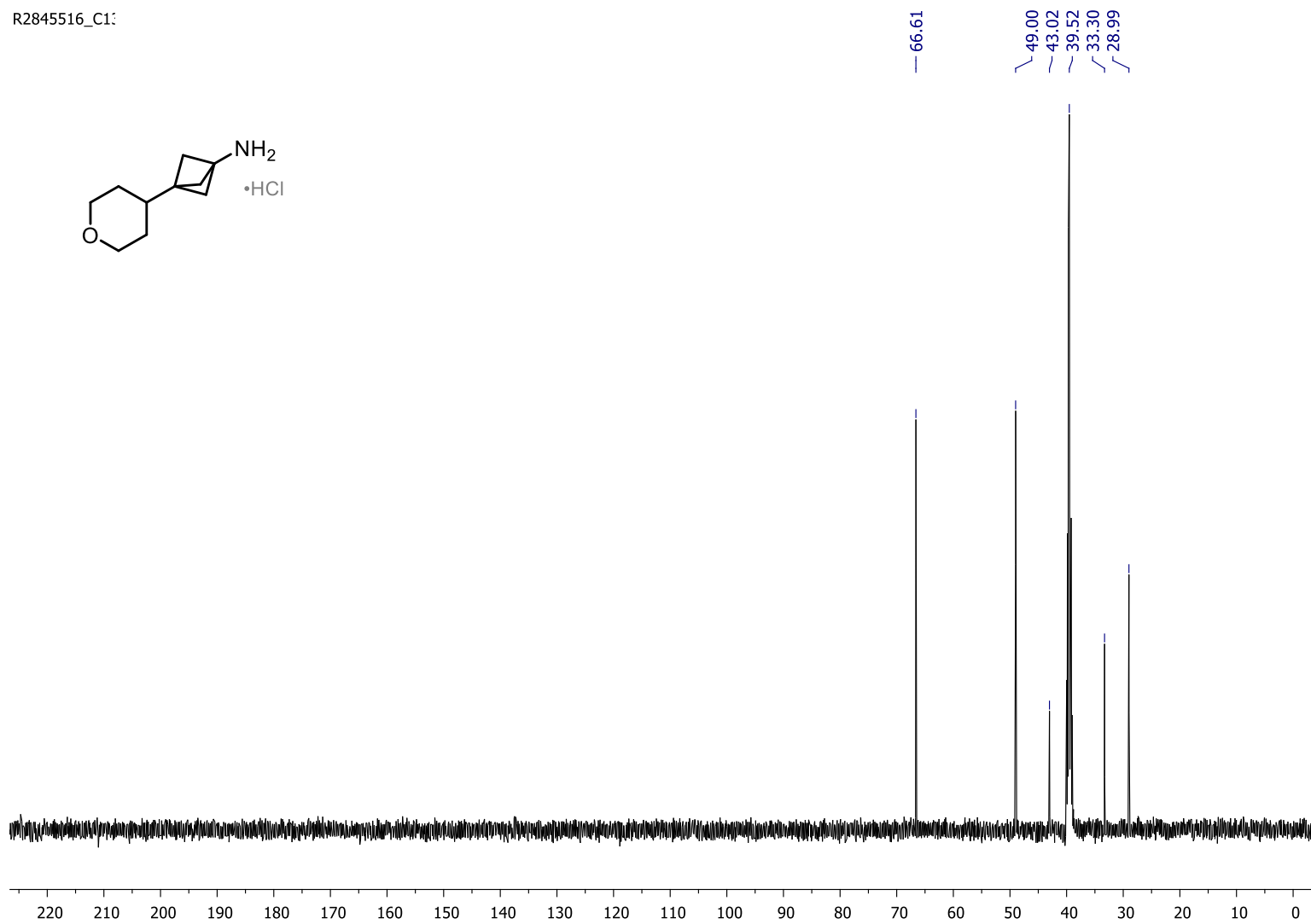
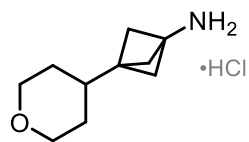
¹H NMR (400 MHz, DMSO-d₆)

R2845516



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

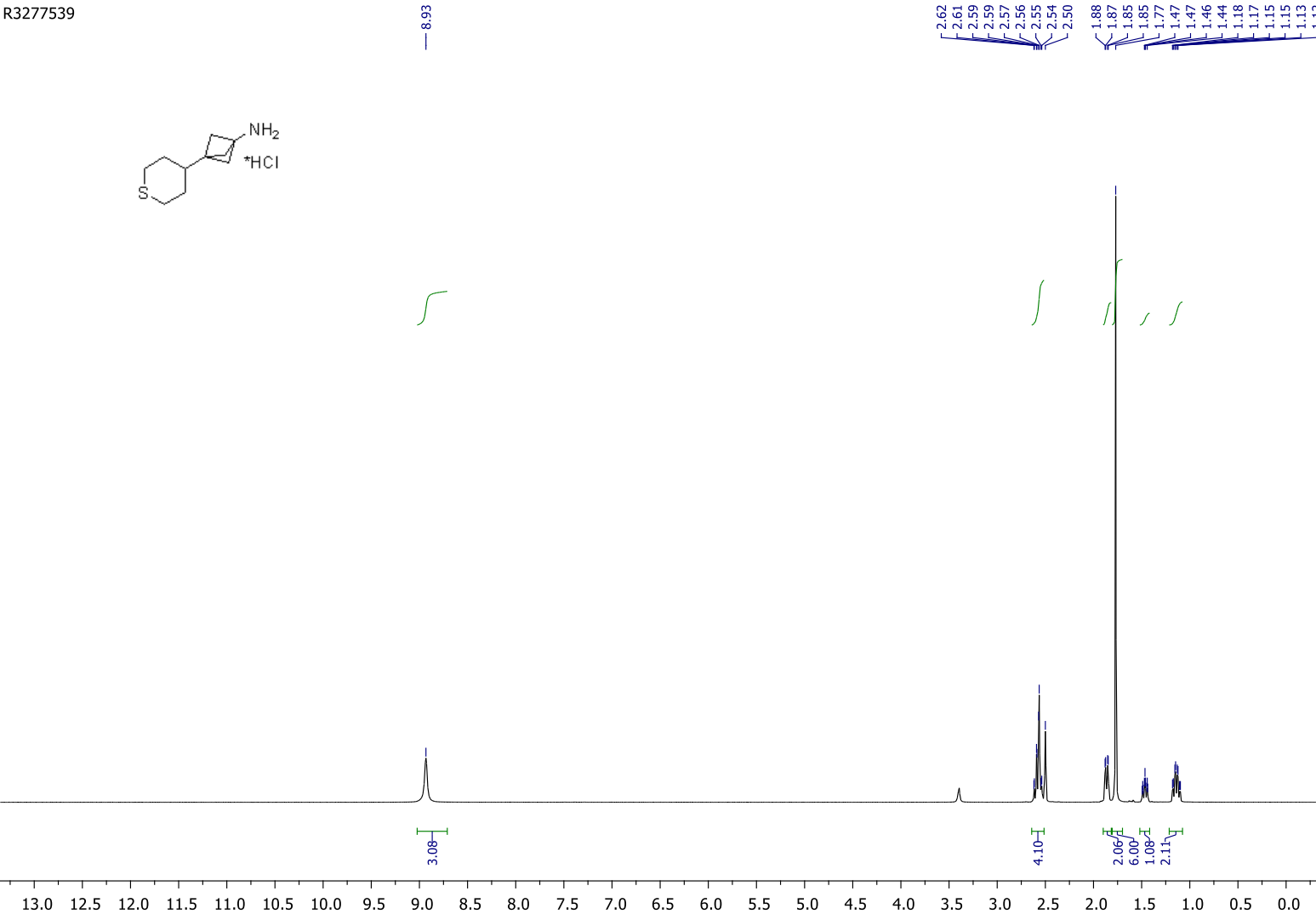
R2845516_C1:



Compound 59l

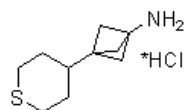
R3277539

¹H NMR (500 MHz, DMSO-d₆)

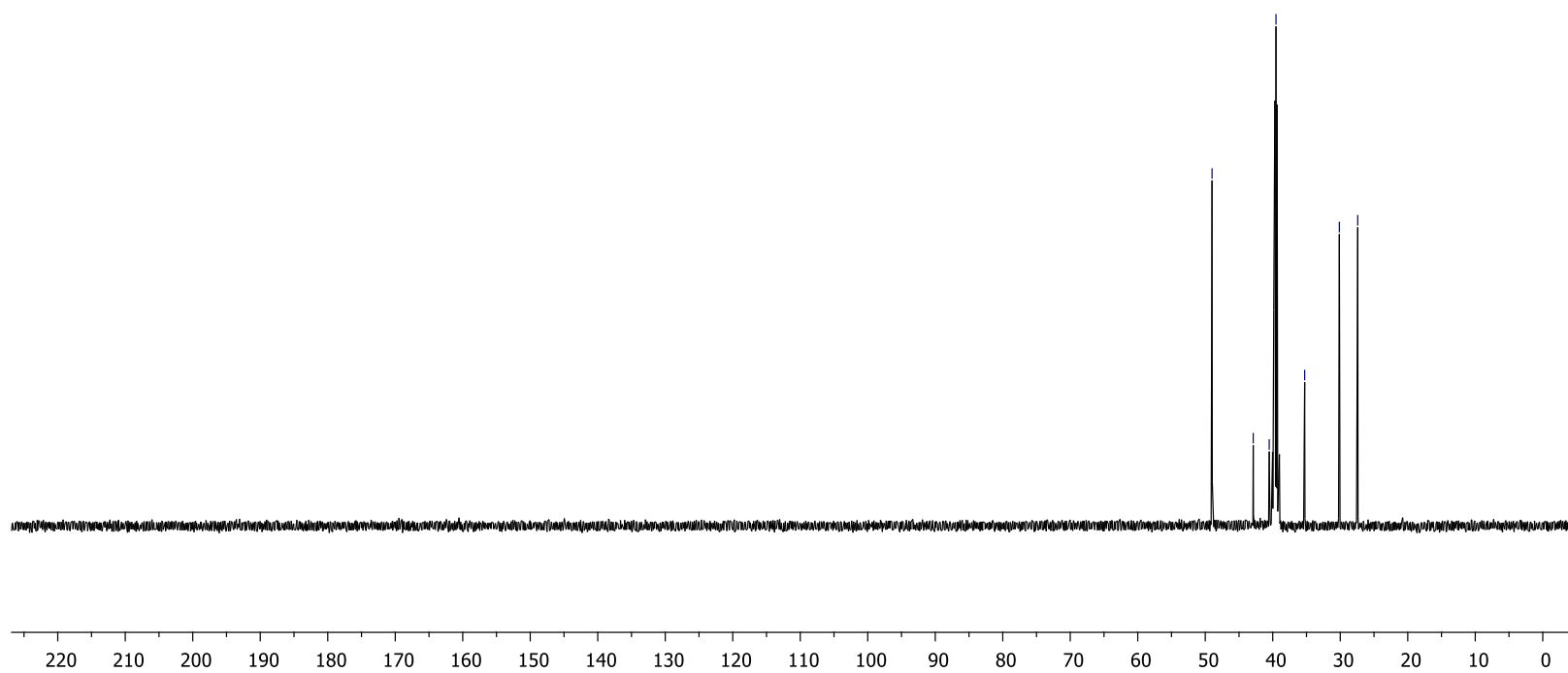


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R3277539_C13



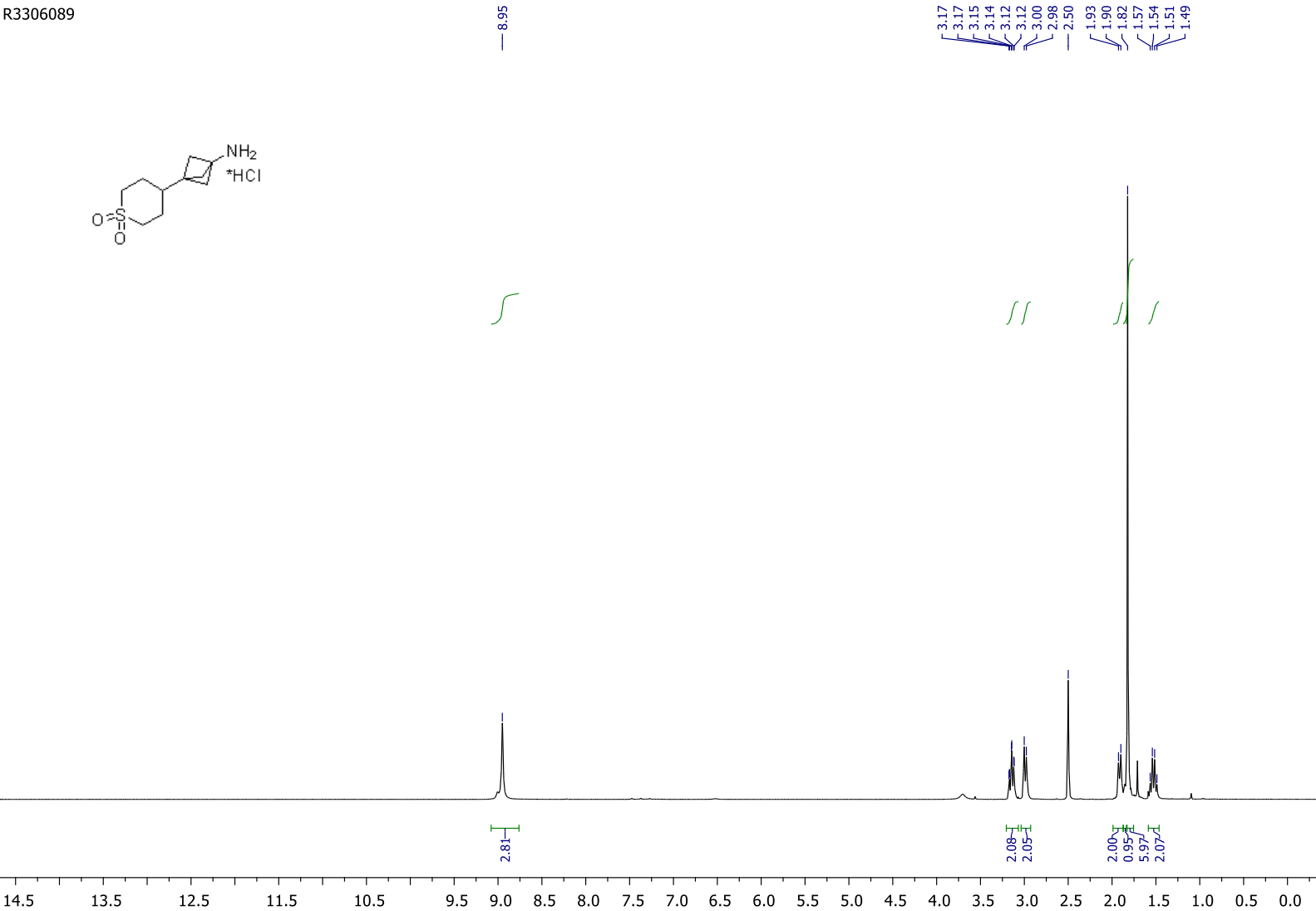
48.99
42.89
40.53
39.52
35.27
30.13
27.41



Compound O2-59I

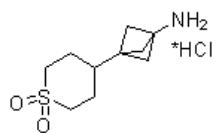
R3306089

¹H NMR (500 MHz, DMSO-d₆)

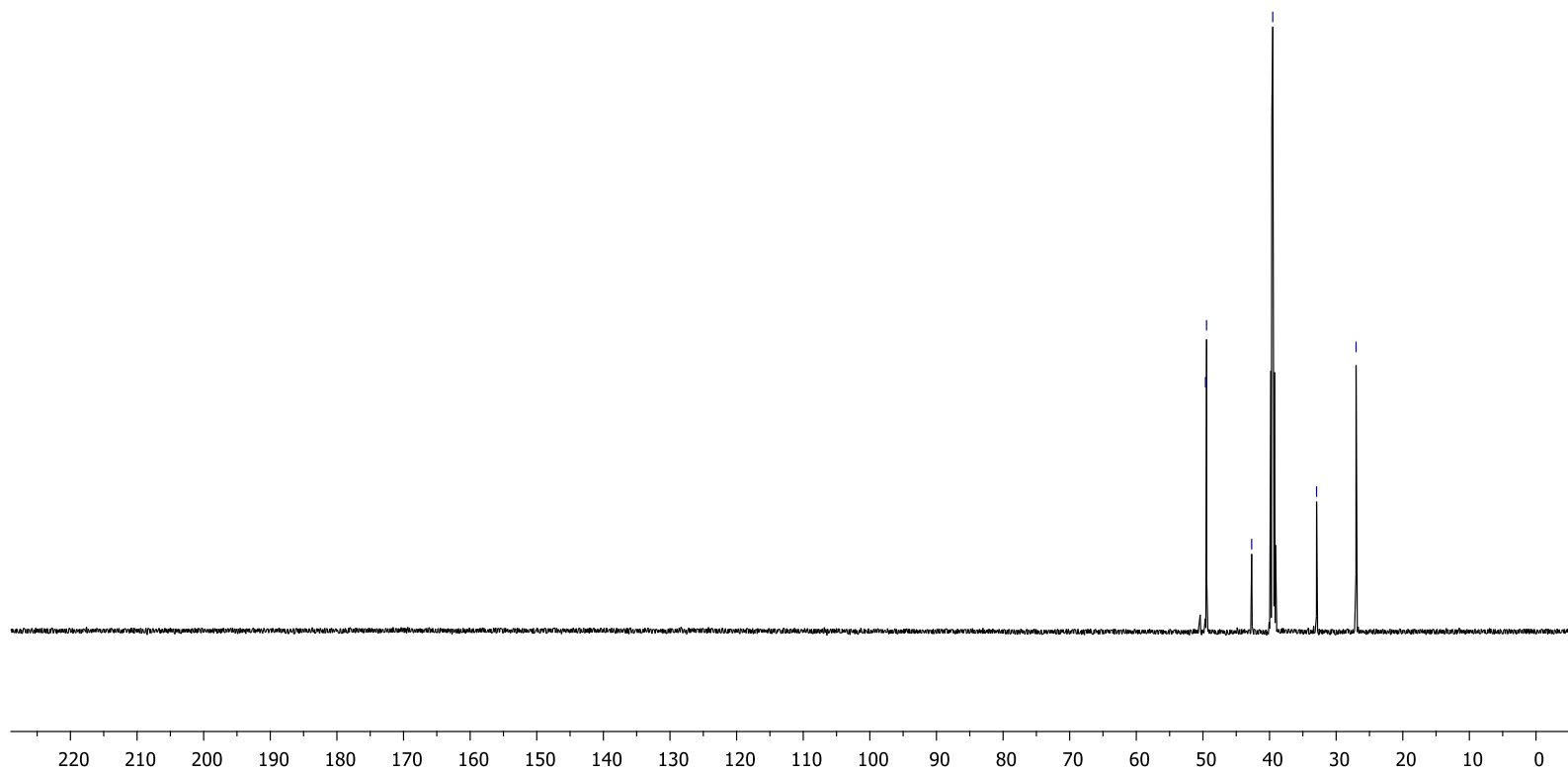


$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R3306089_C13



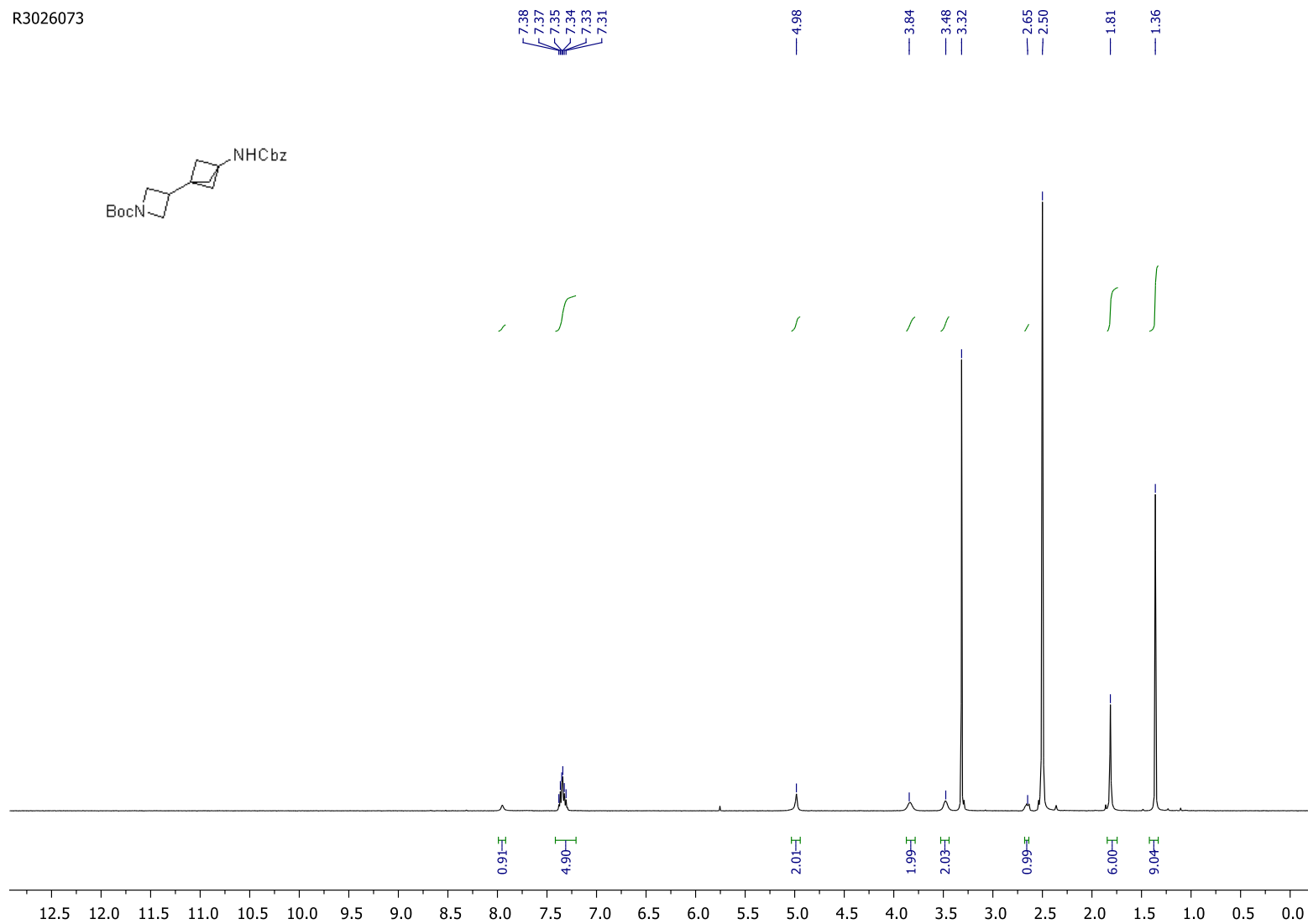
49.62
49.46
42.68
39.52
32.94
27.01



***Tert*-butyl 3-(3-(((benzyloxy)carbonyl)amino)bicyclo[1.1.1]pentan-1-yl)azetidine-1-carboxylate**

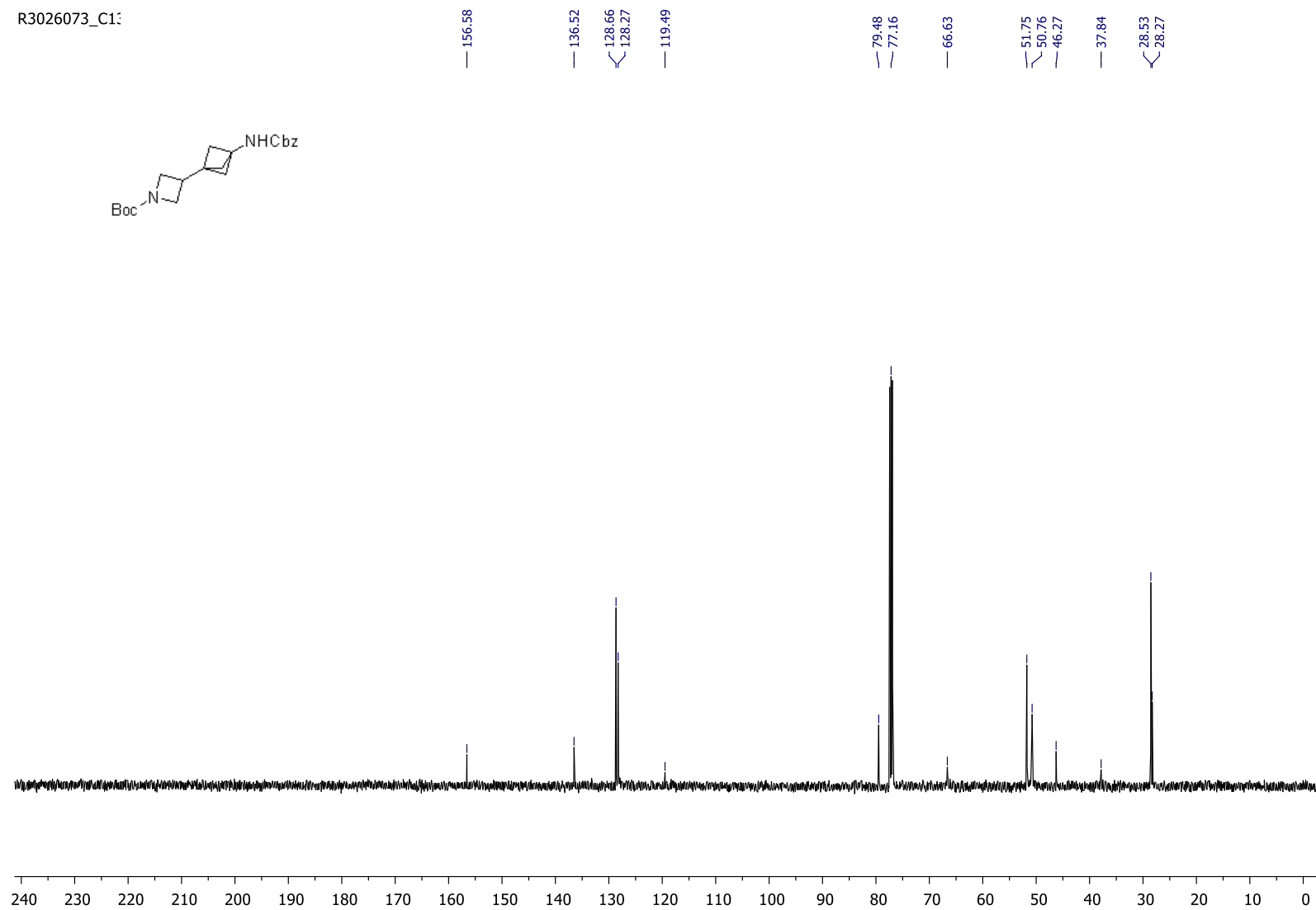
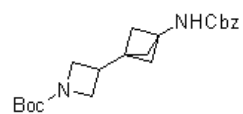
^1H NMR (500 MHz, DMSO- d_6)

R3026073



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

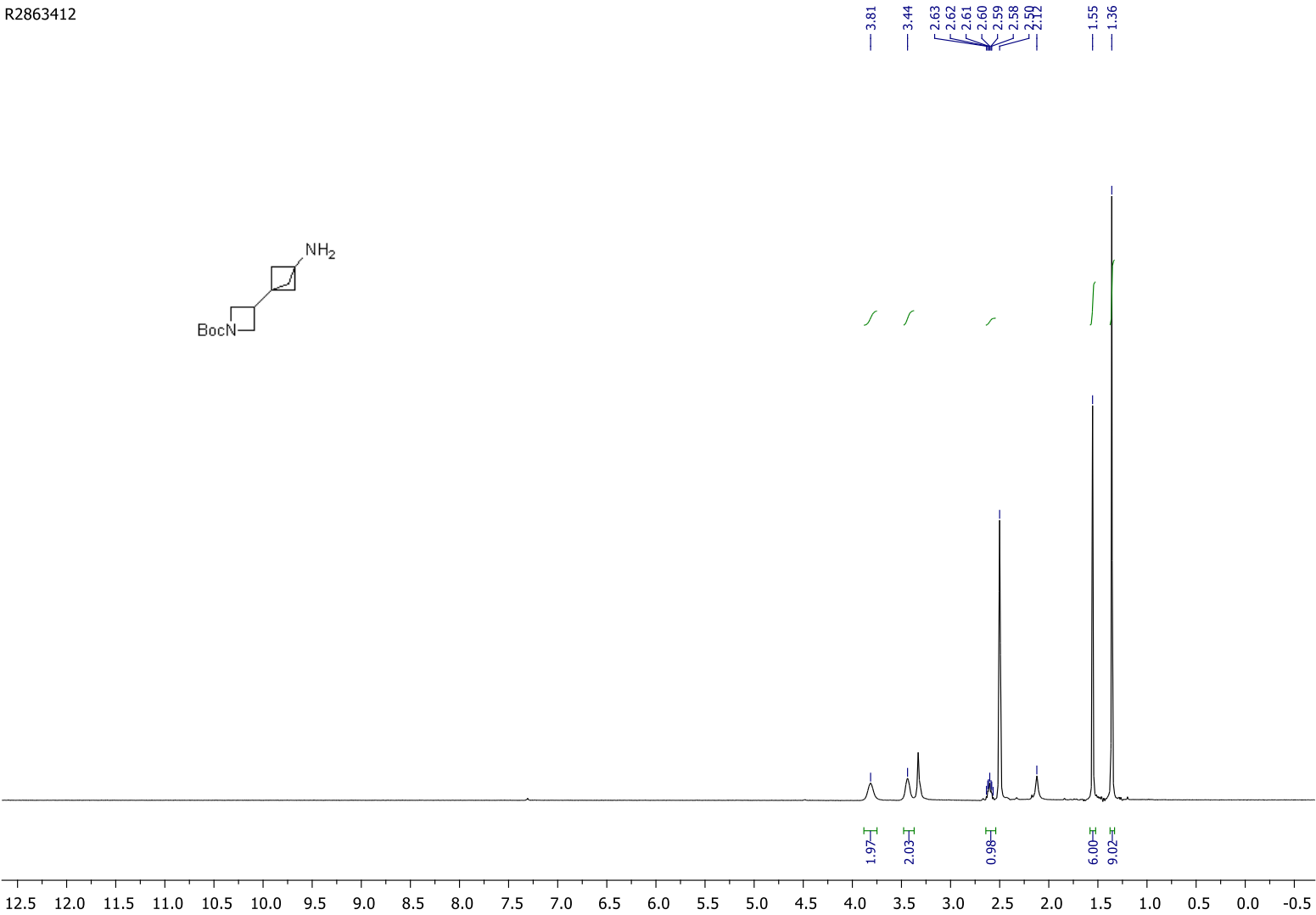
R3026073_C1:



Compound 60l

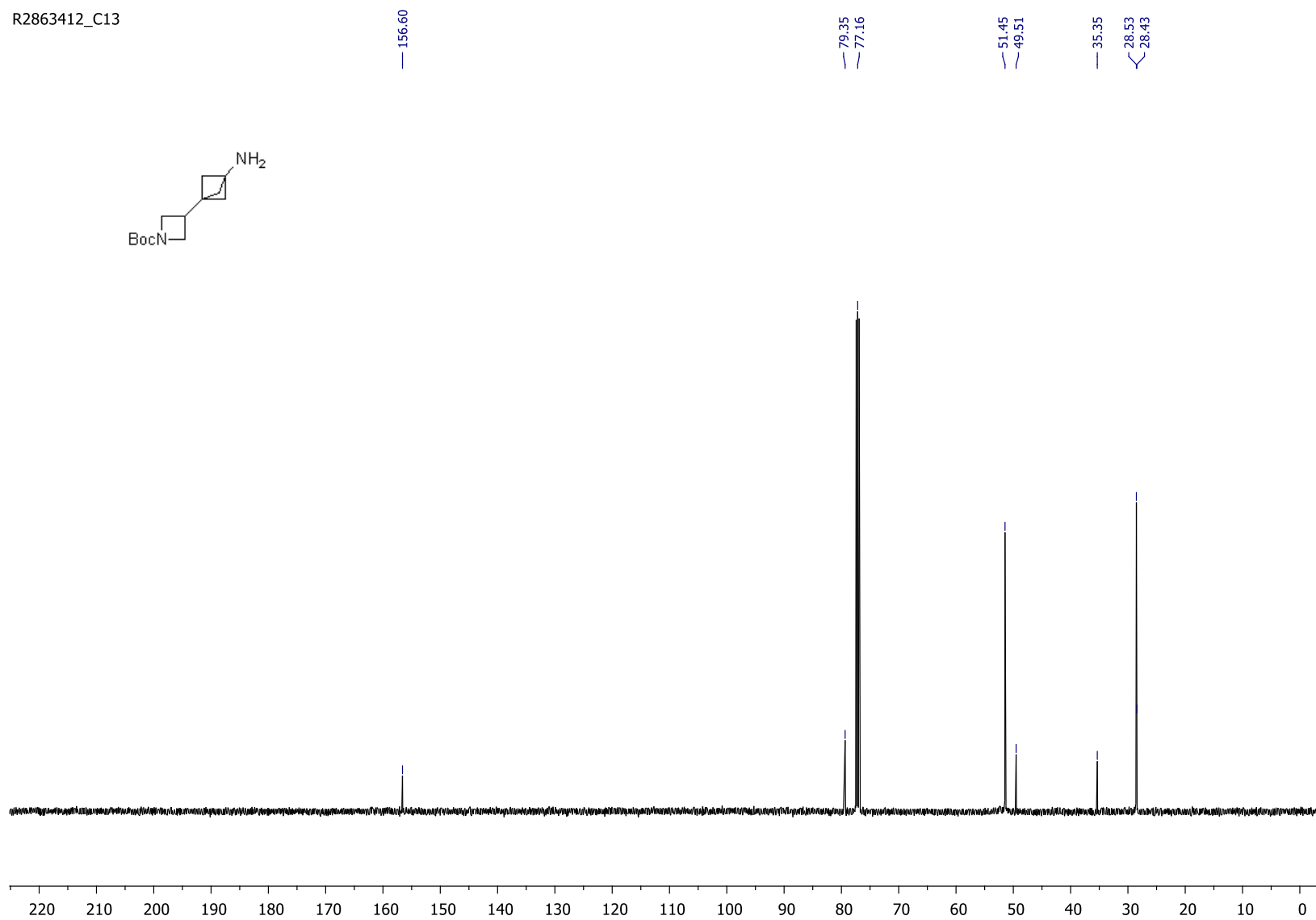
¹H NMR (400 MHz, DMSO-d₆)

R2863412



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

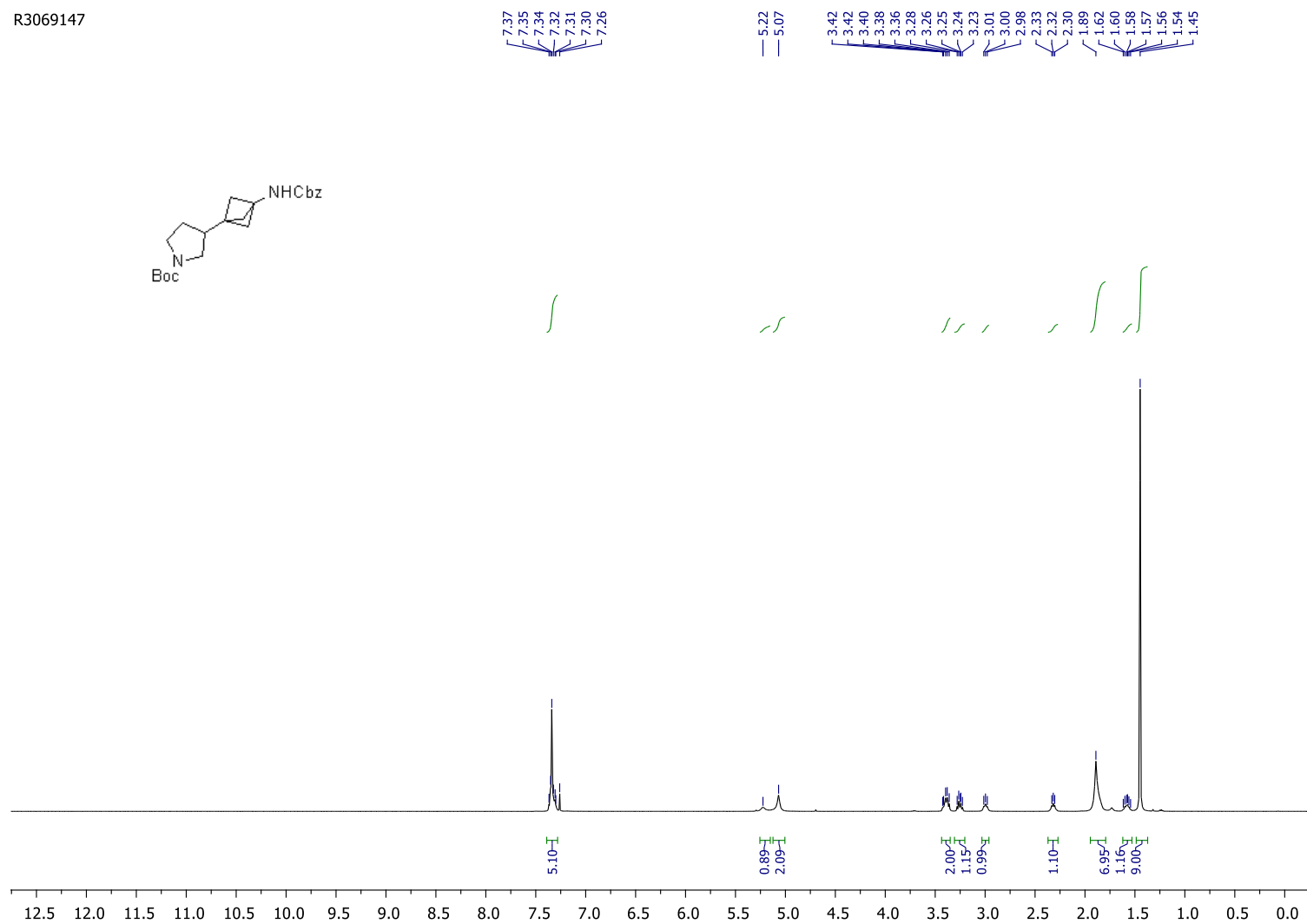
R2863412_C13



(±)-Tert-butyl 3-(3-(((benzyloxy)carbonyl)amino)bicyclo[1.1.1]pentan-1-yl)pyrrolidine-1-carboxylate

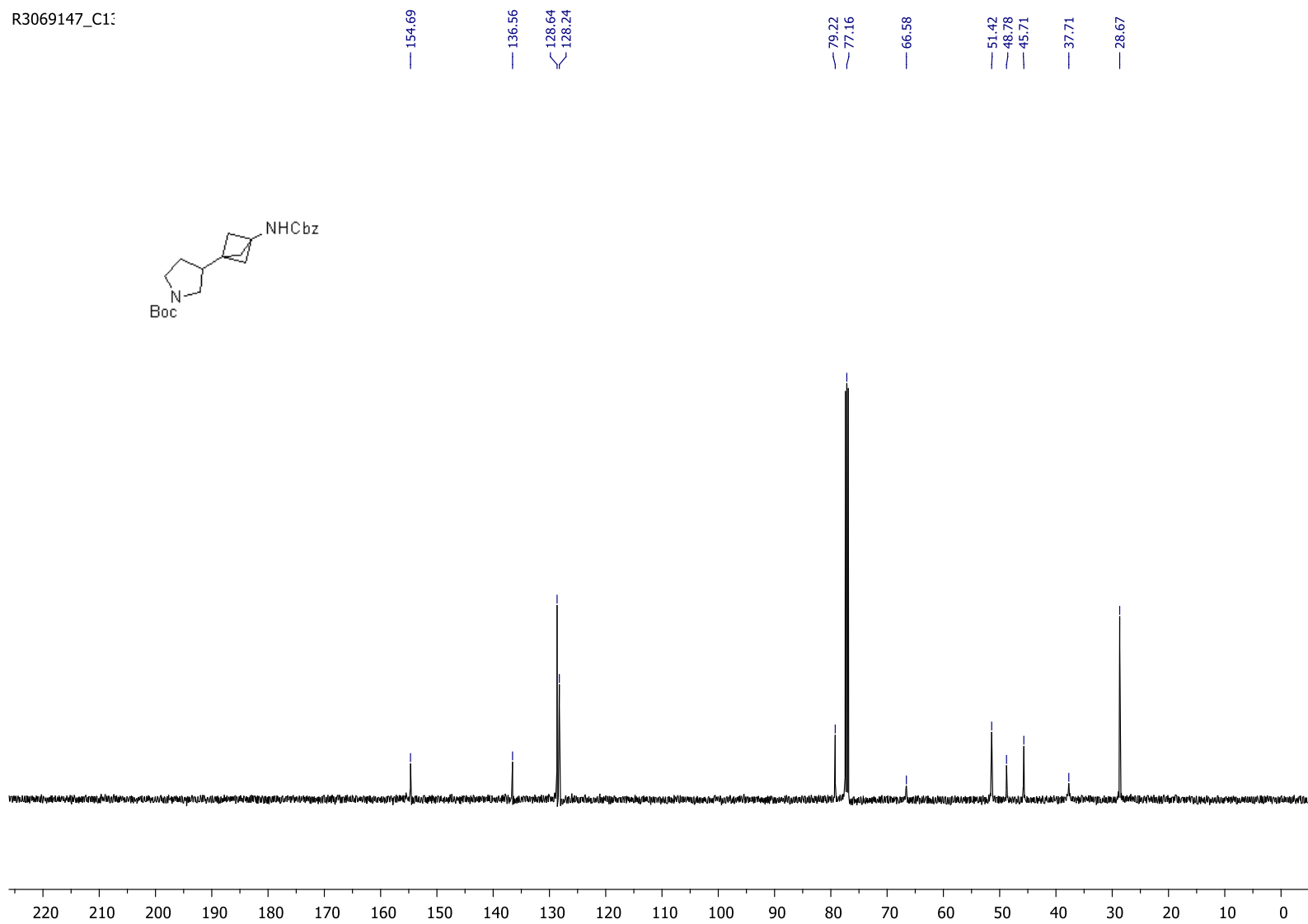
¹H NMR (500 MHz, CDCl₃)

R3069147



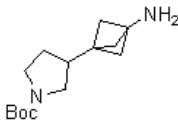
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

R3069147_C1:

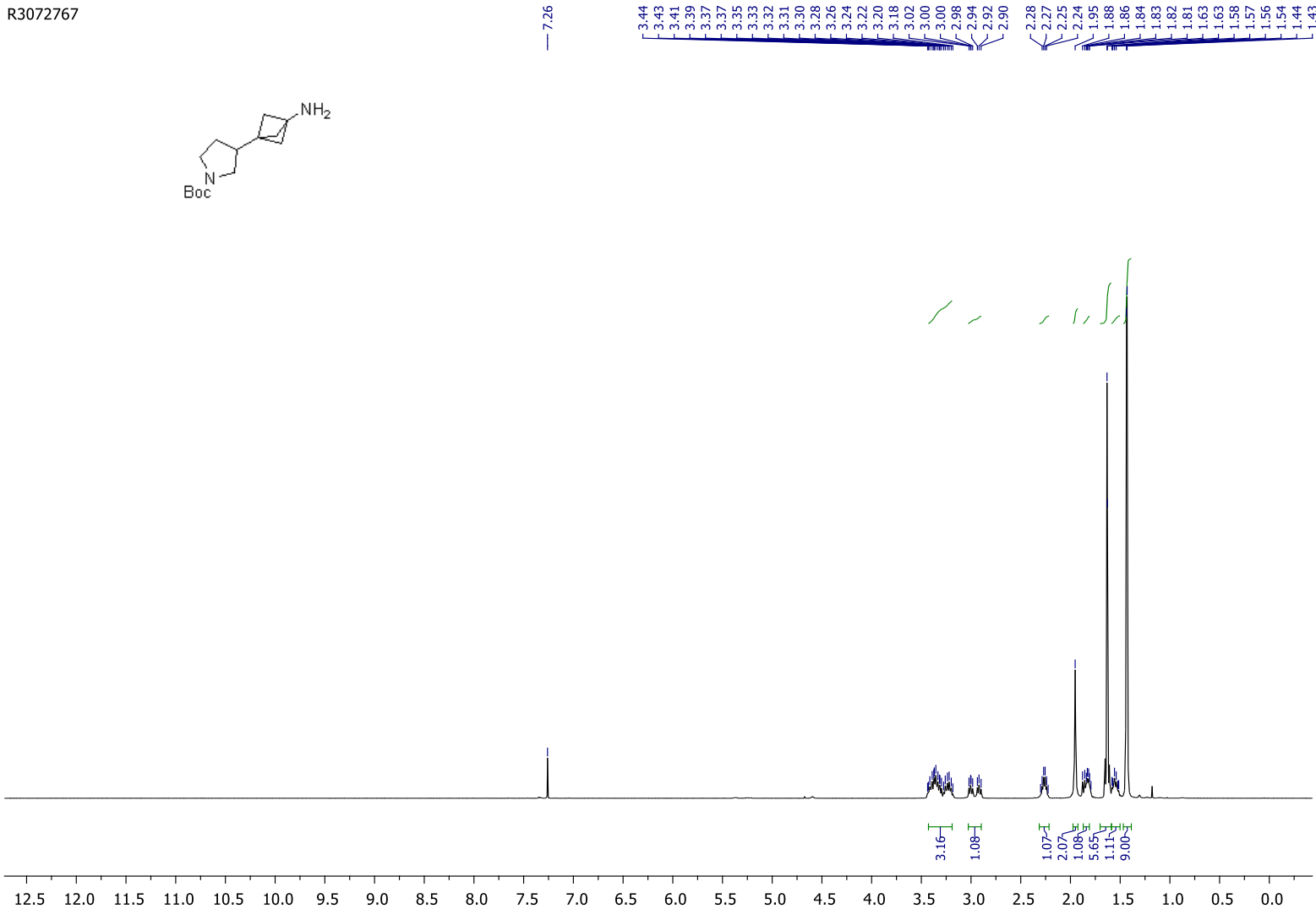


Compound 61l

R3072767

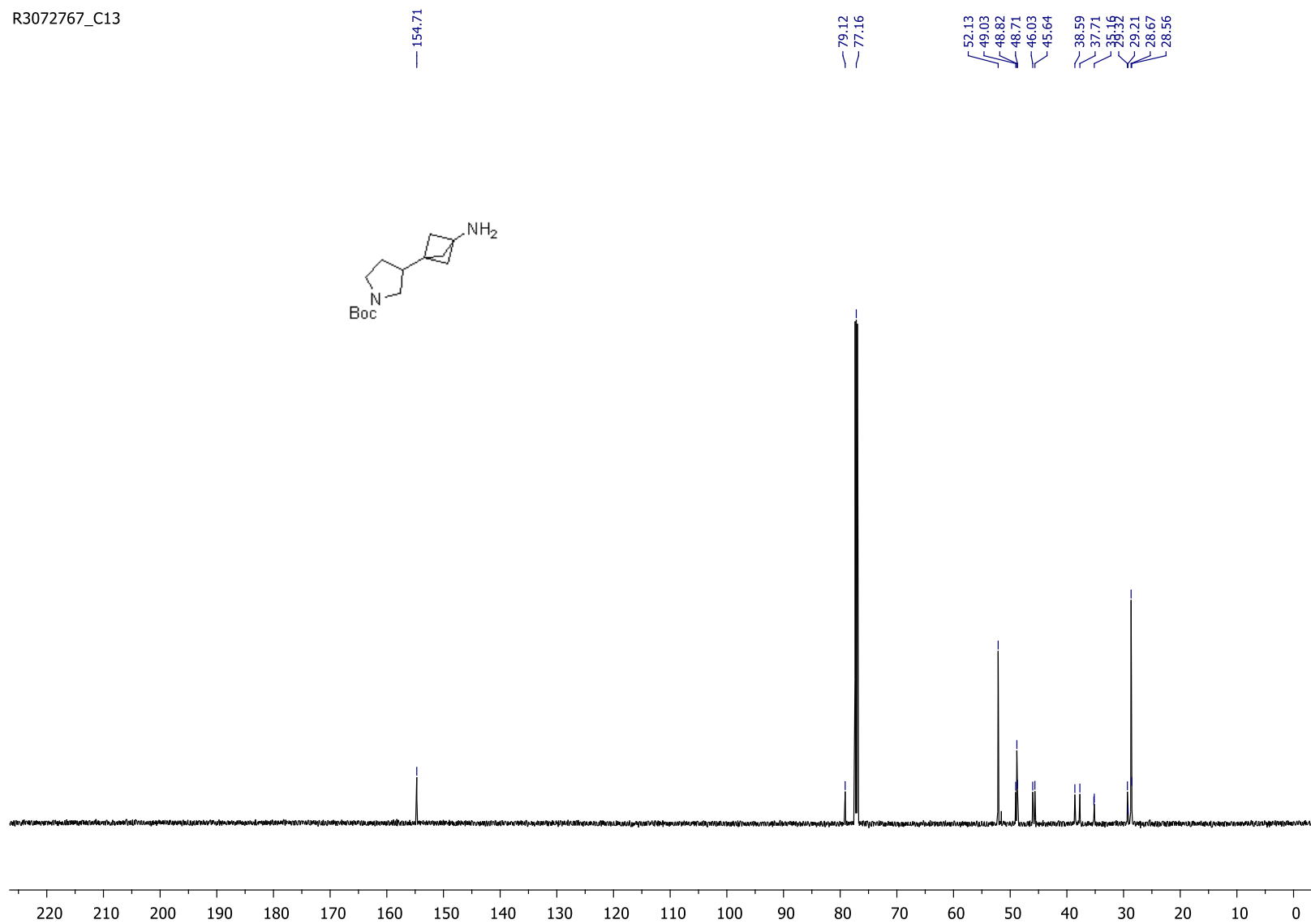
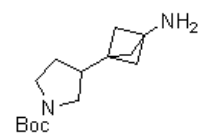


¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3)

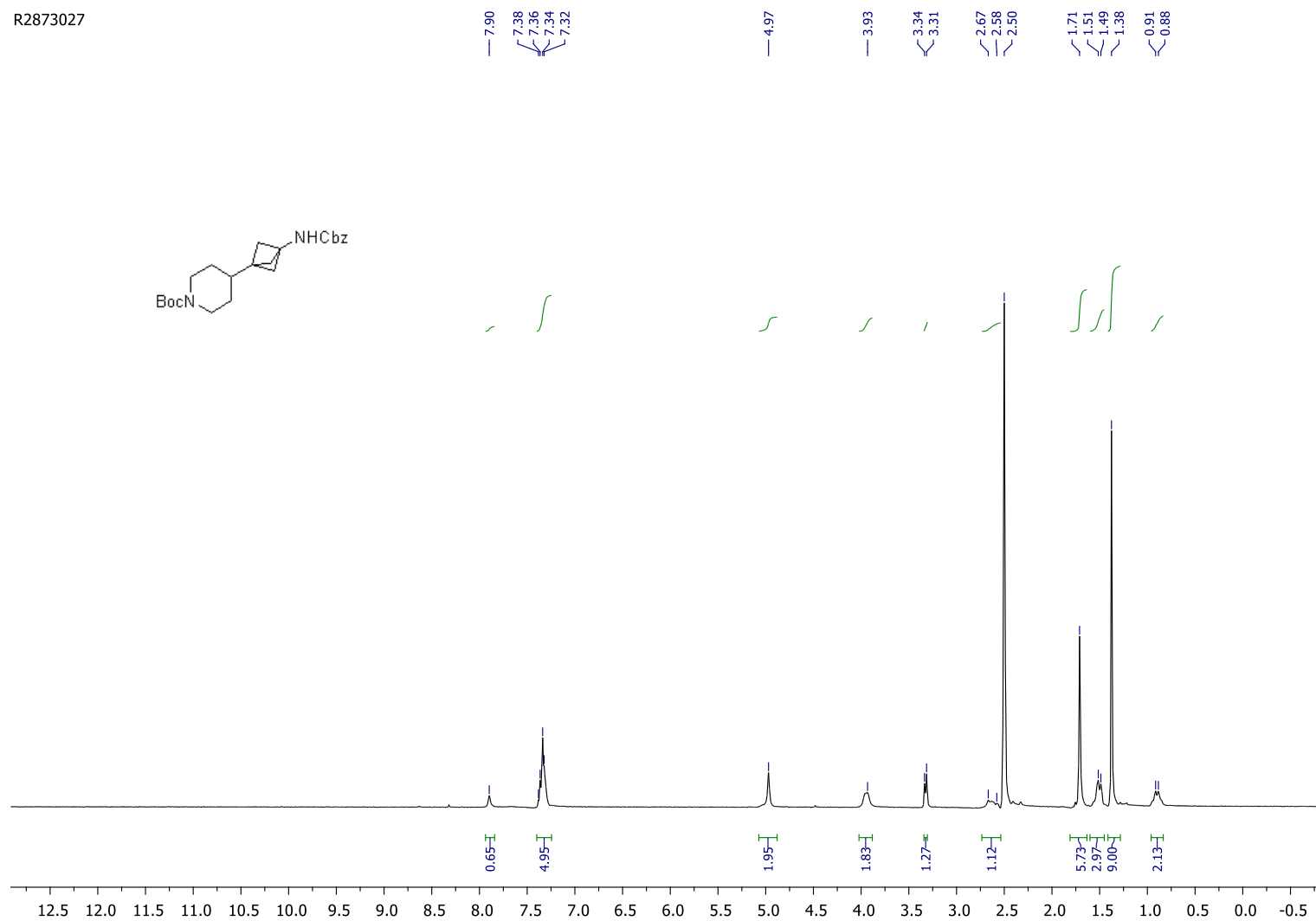
R3072767_C13

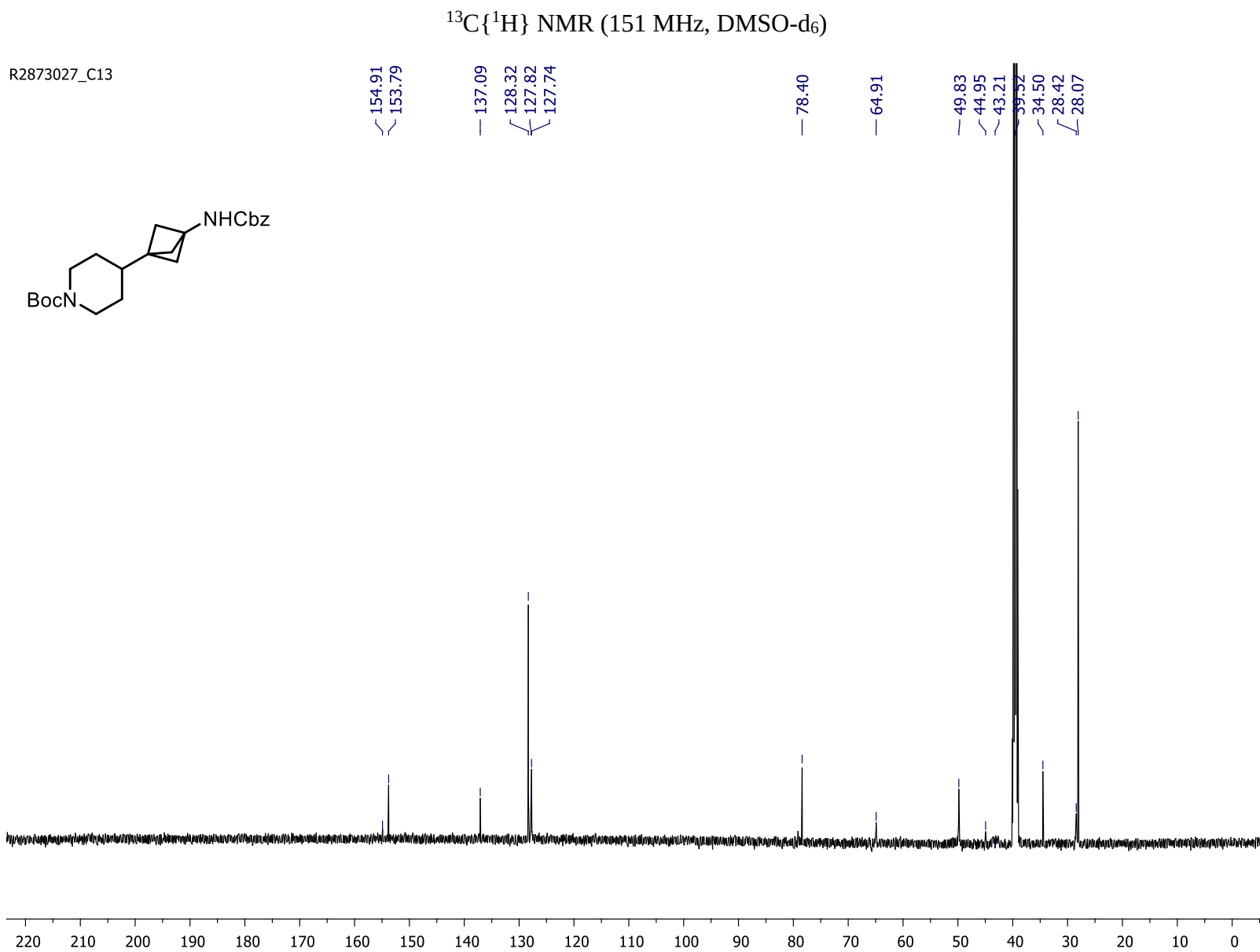


***Tert*-butyl 4-(3-(((benzyloxy)carbonyl)amino)bicyclo[1.1.1]pentan-1-yl)piperidine-1-carboxylate**

¹H NMR (400 MHz, DMSO-d₆)

R2873027

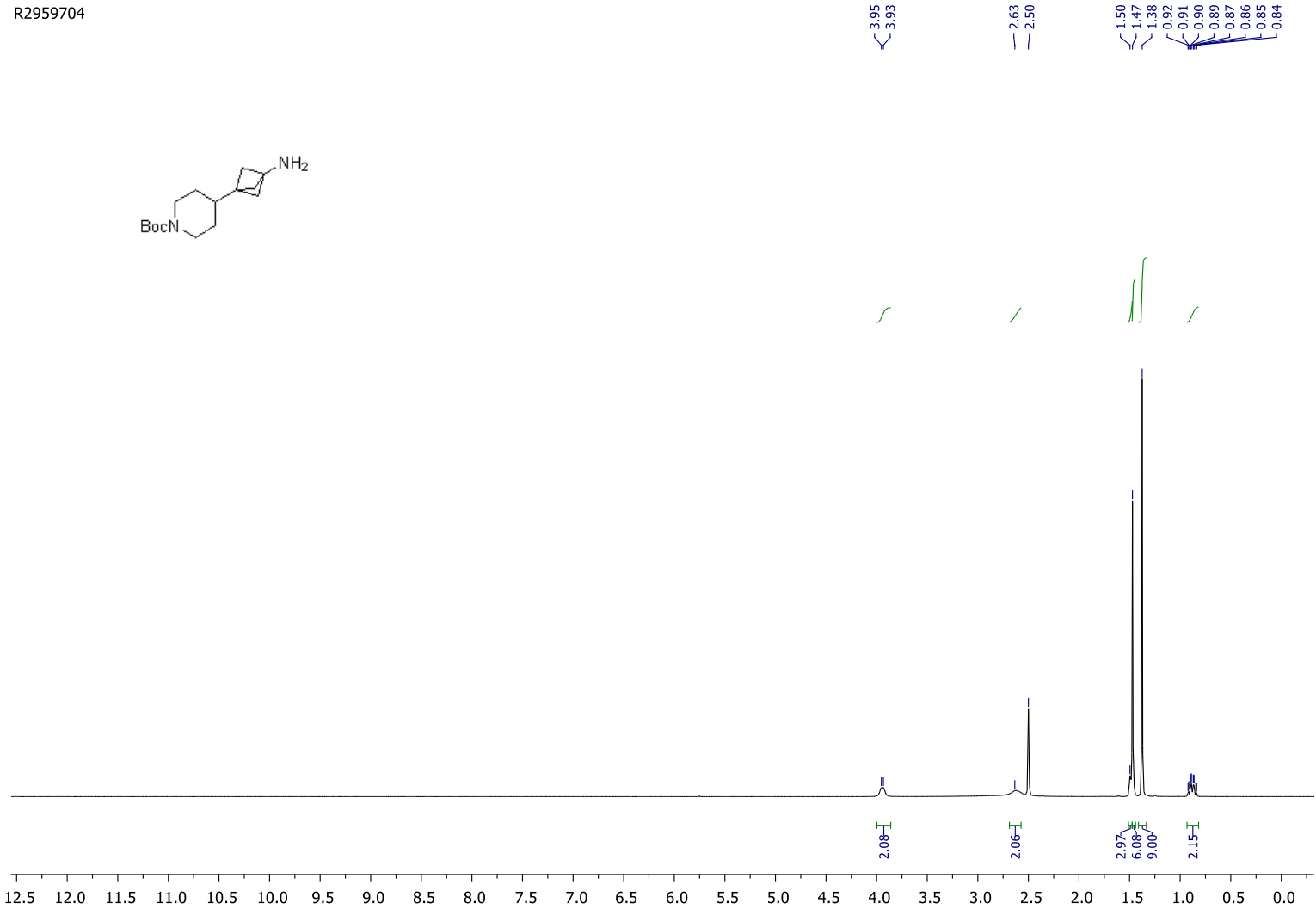
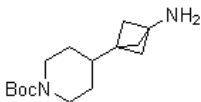




Compound 63I

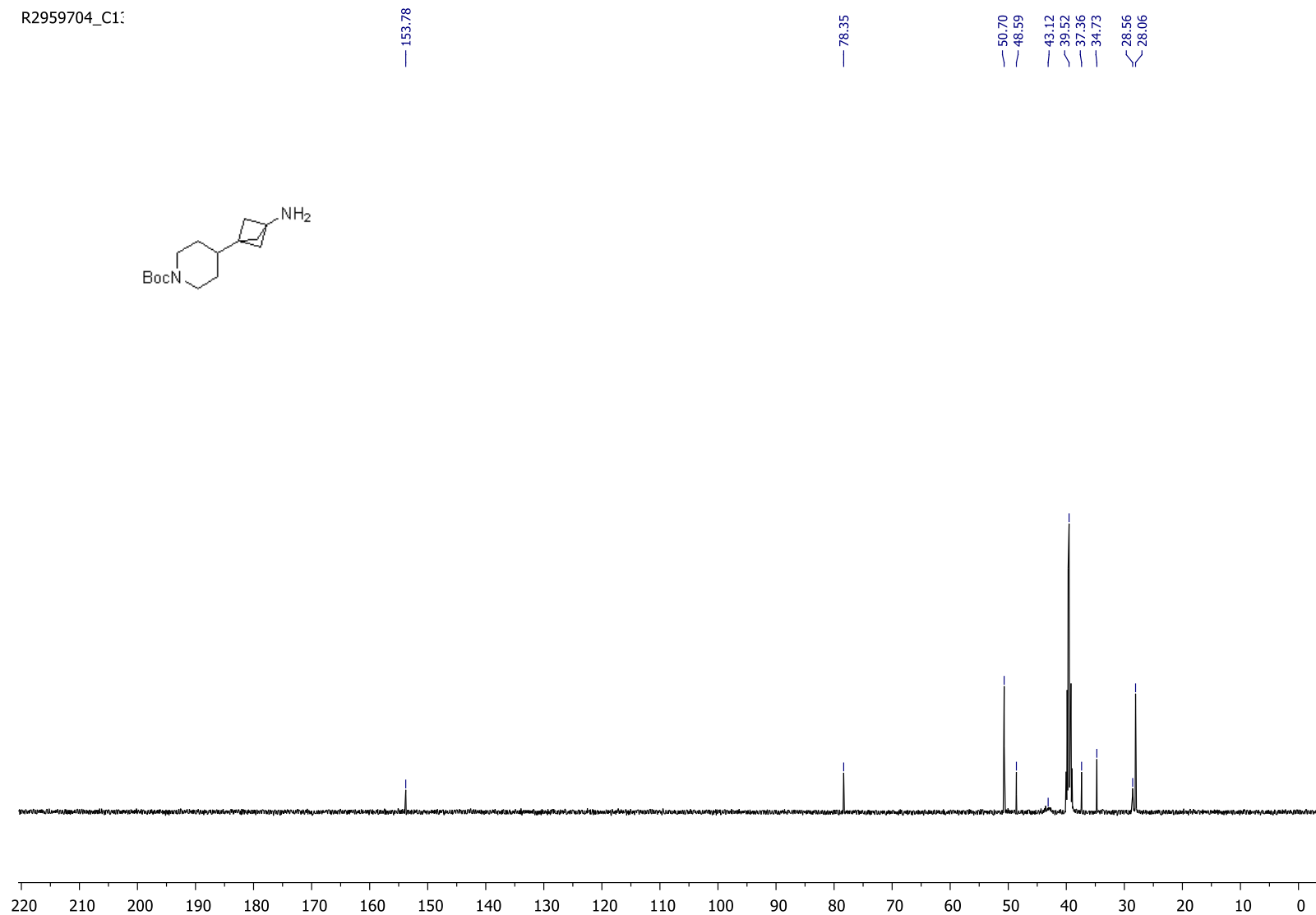
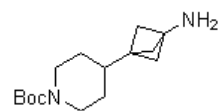
¹H NMR (500 MHz, DMSO-d₆)

R2959704



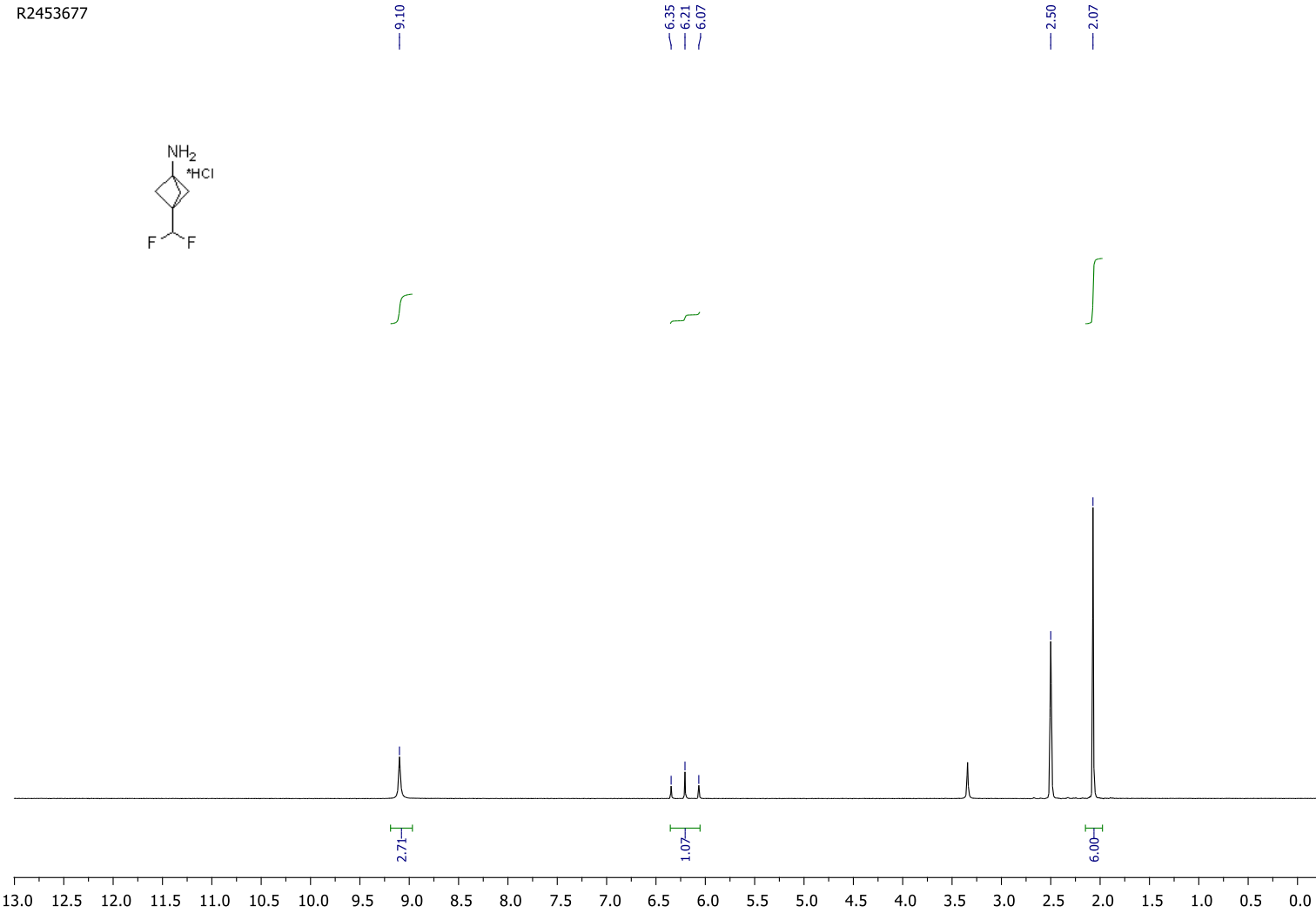
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2959704_C1:



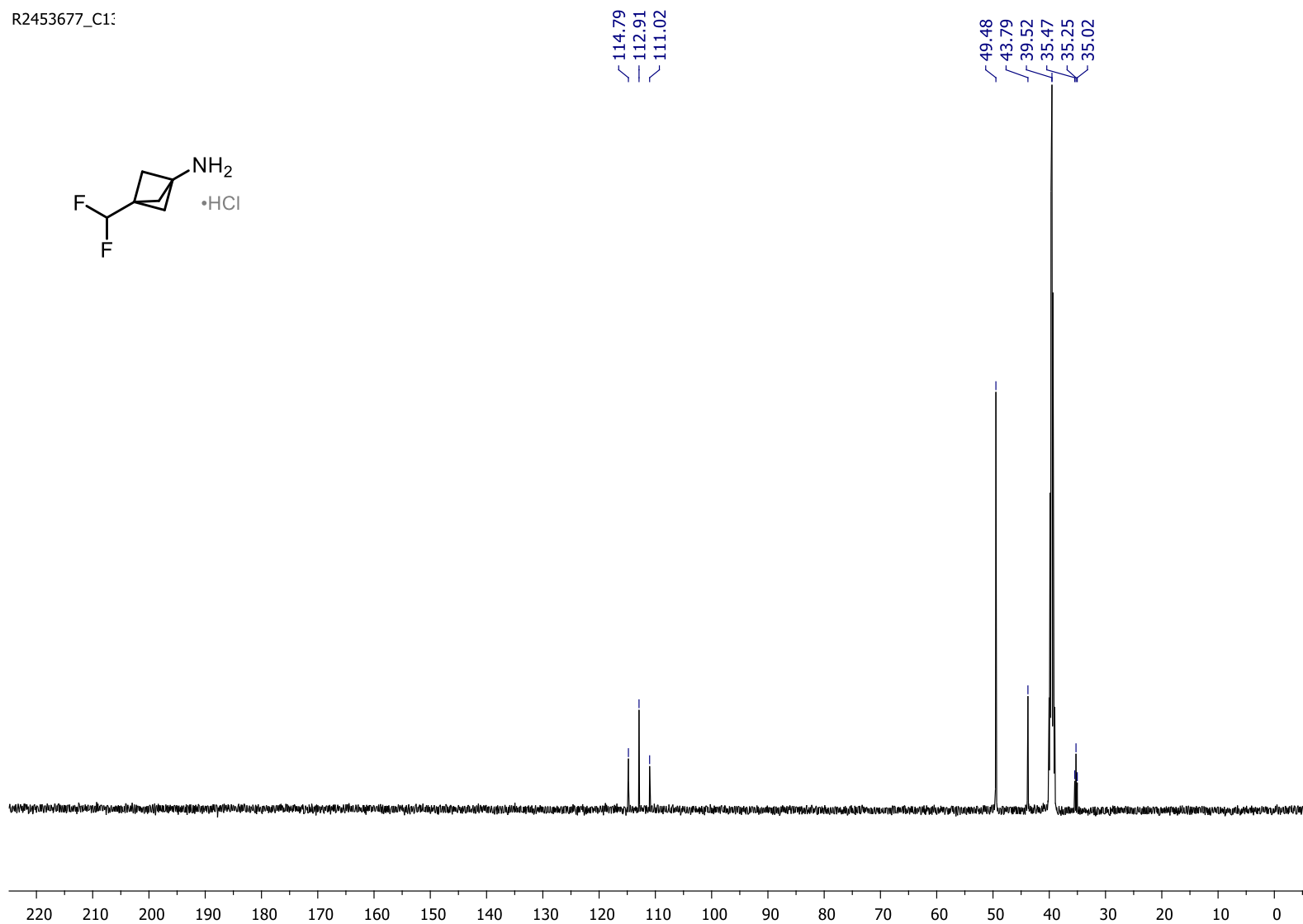
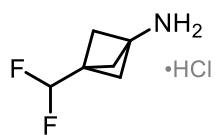
Compound 67l

¹H NMR (400 MHz, DMSO-d₆)



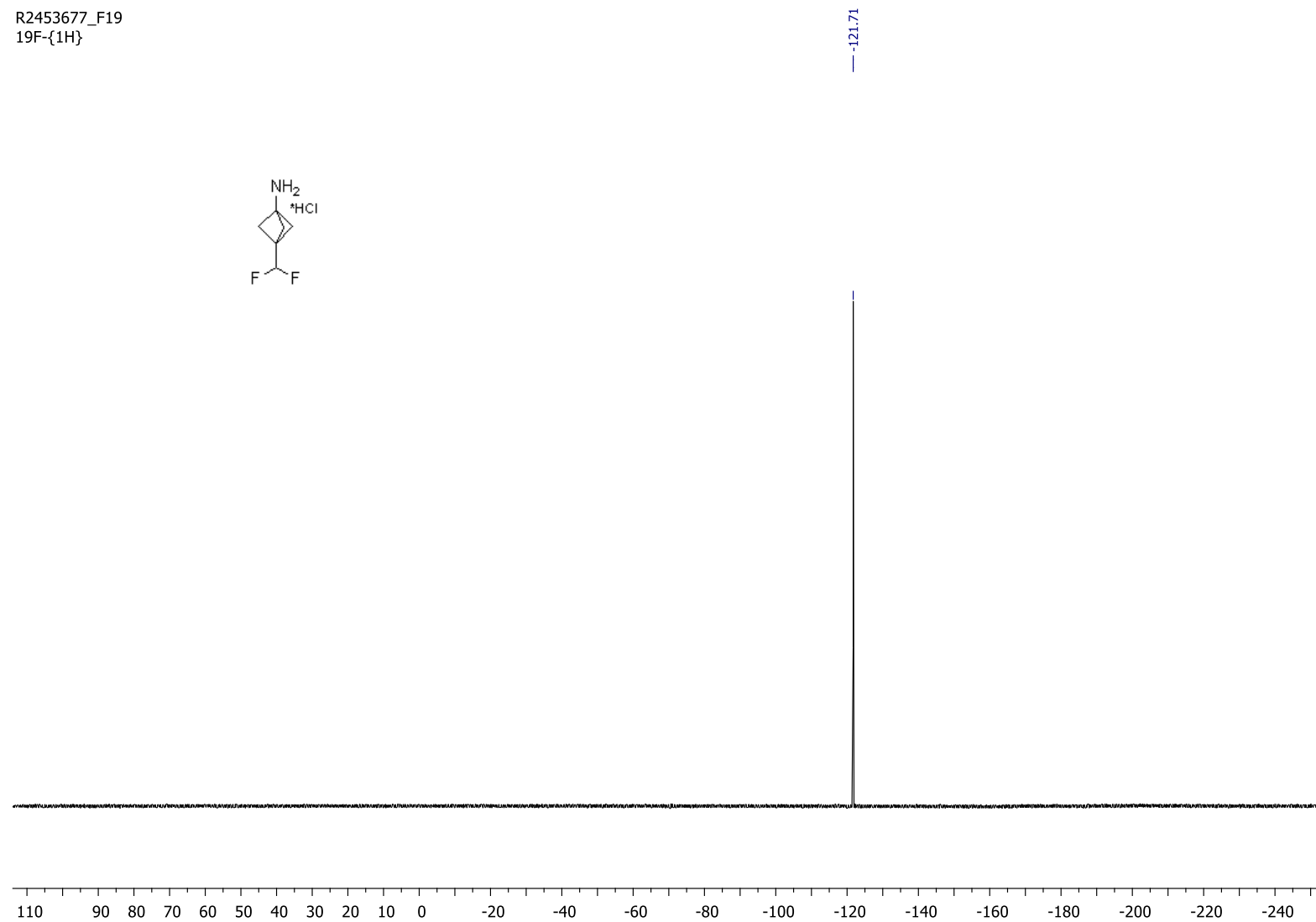
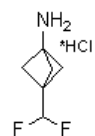
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

R2453677_C1:



$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

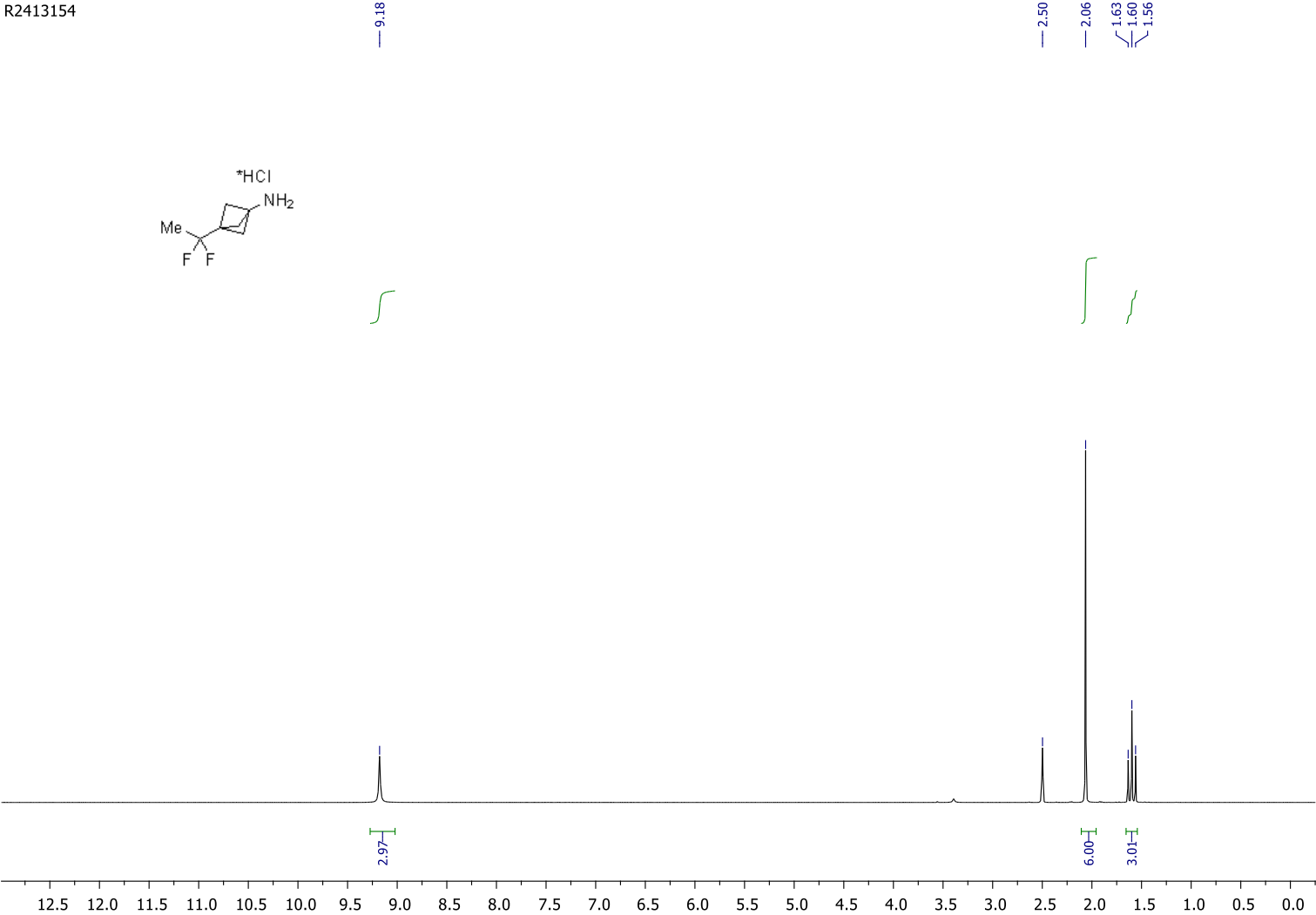
R2453677_F19
 $^{19}\text{F}\{^1\text{H}\}$

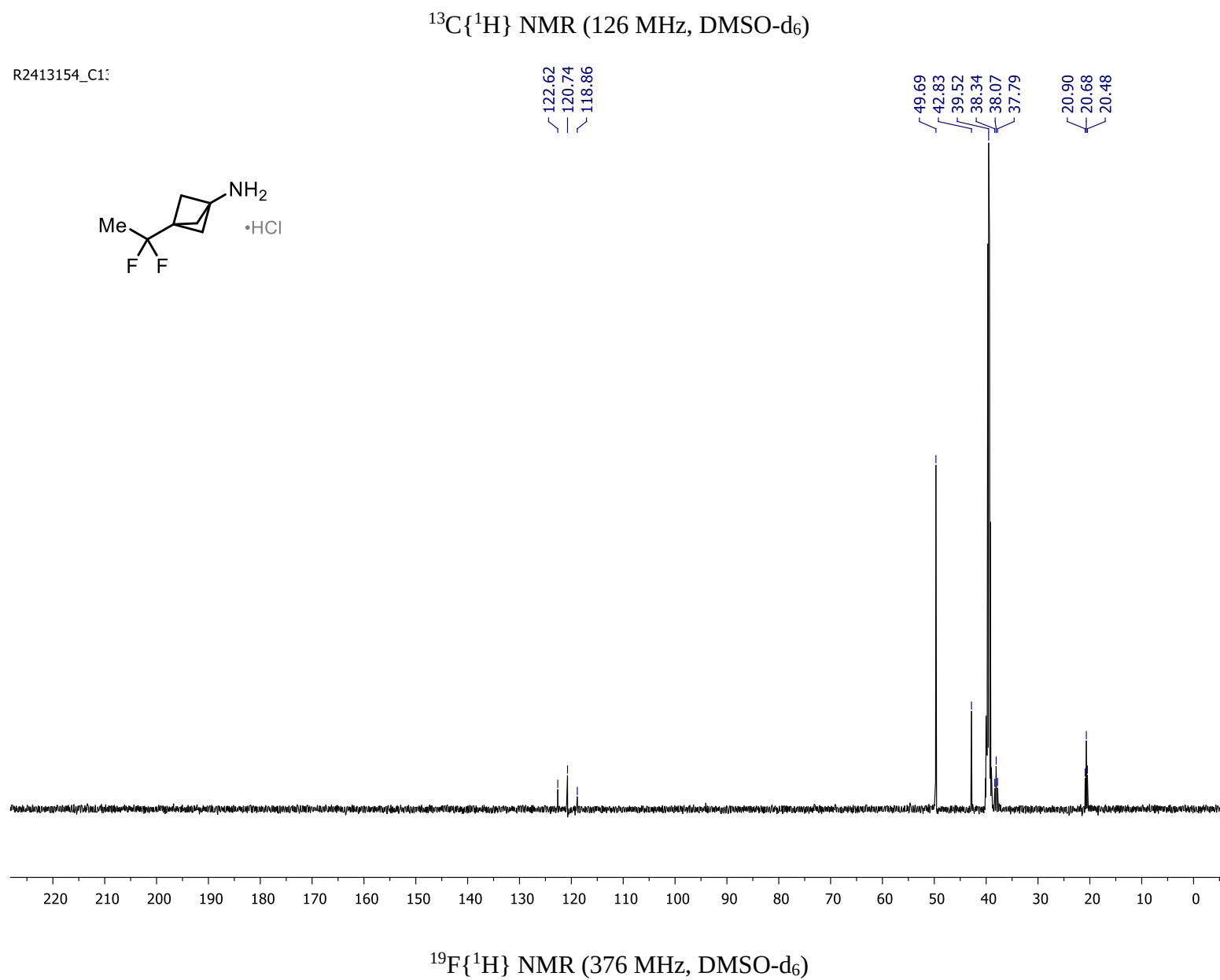


Compound 68l

¹H NMR (500 MHz, DMSO-d₆)

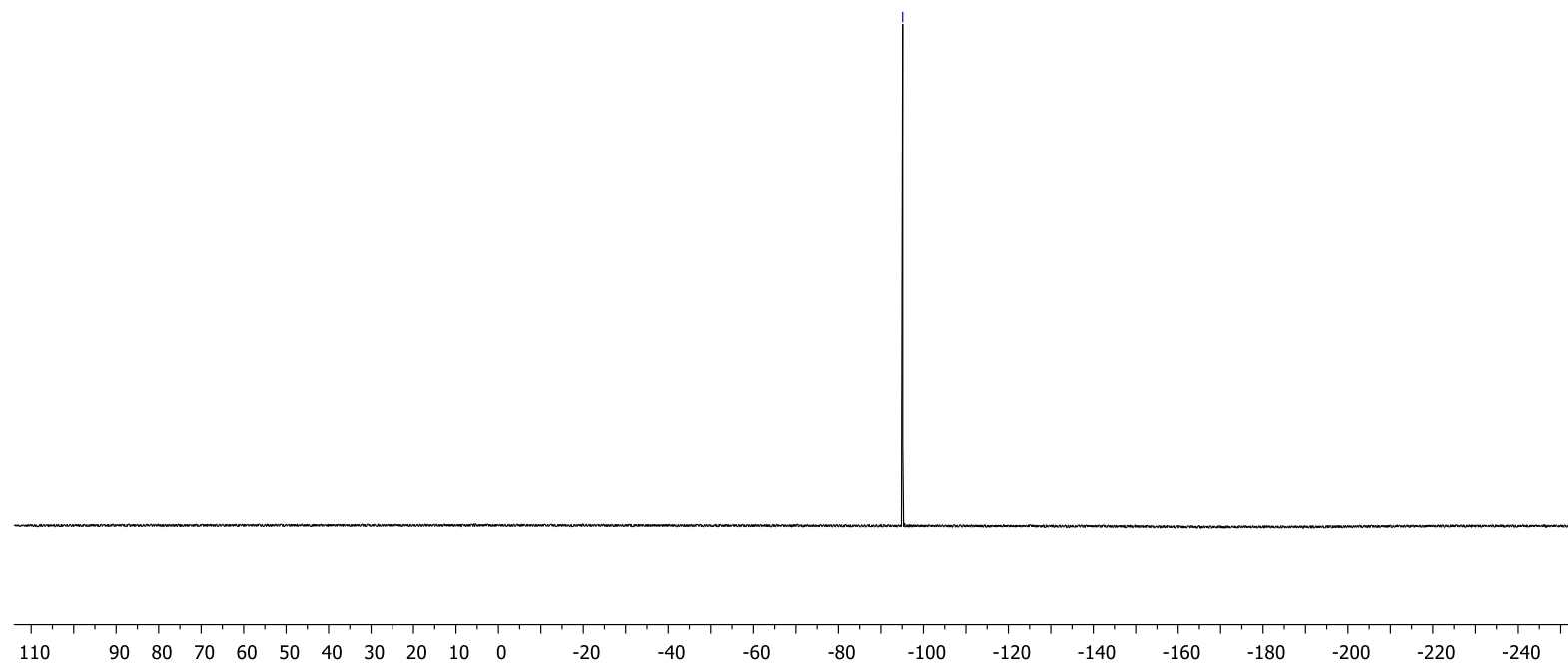
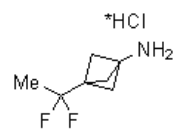
R2413154





R2413154_F19{H}

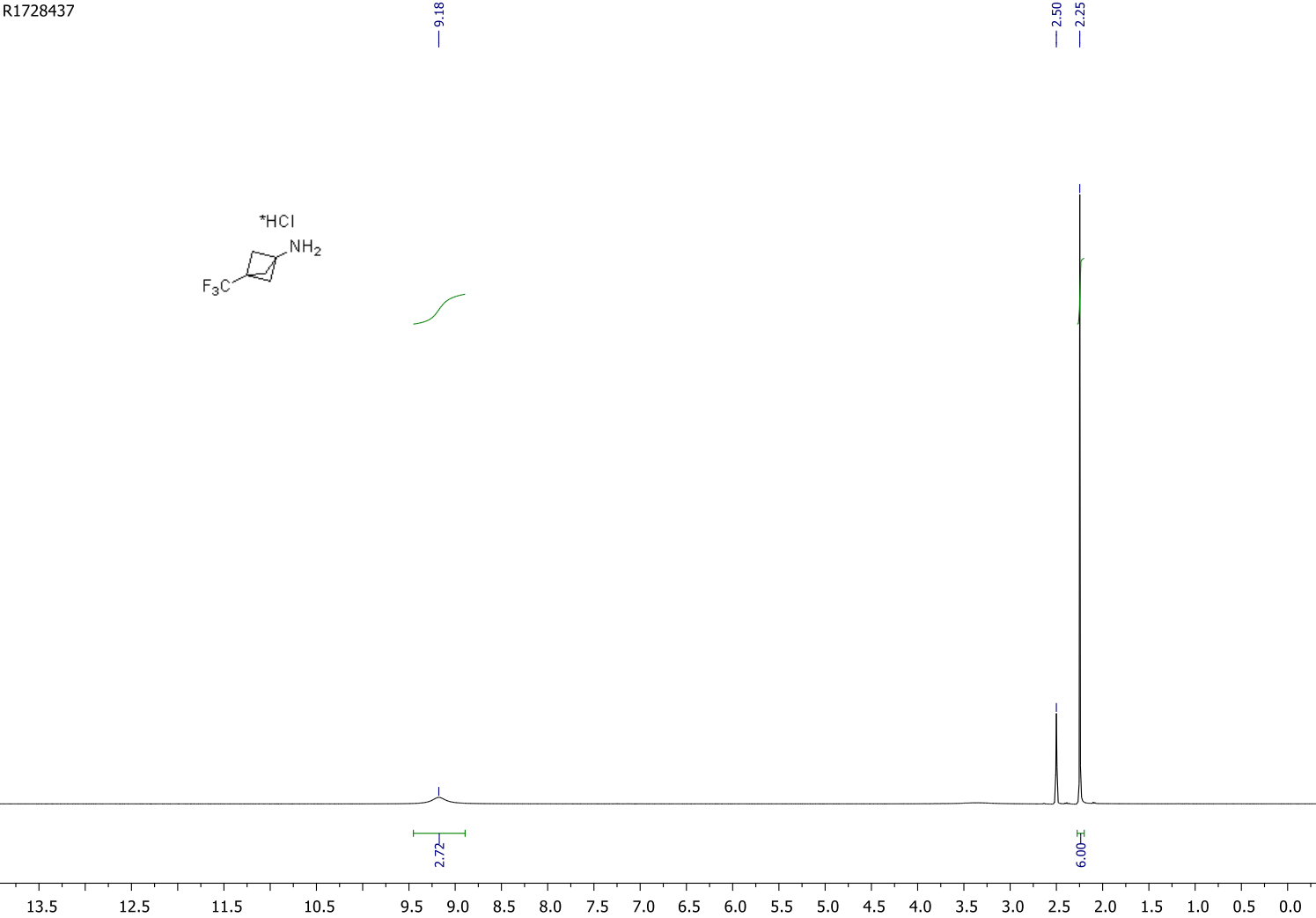
— 95.13



Compound 69I

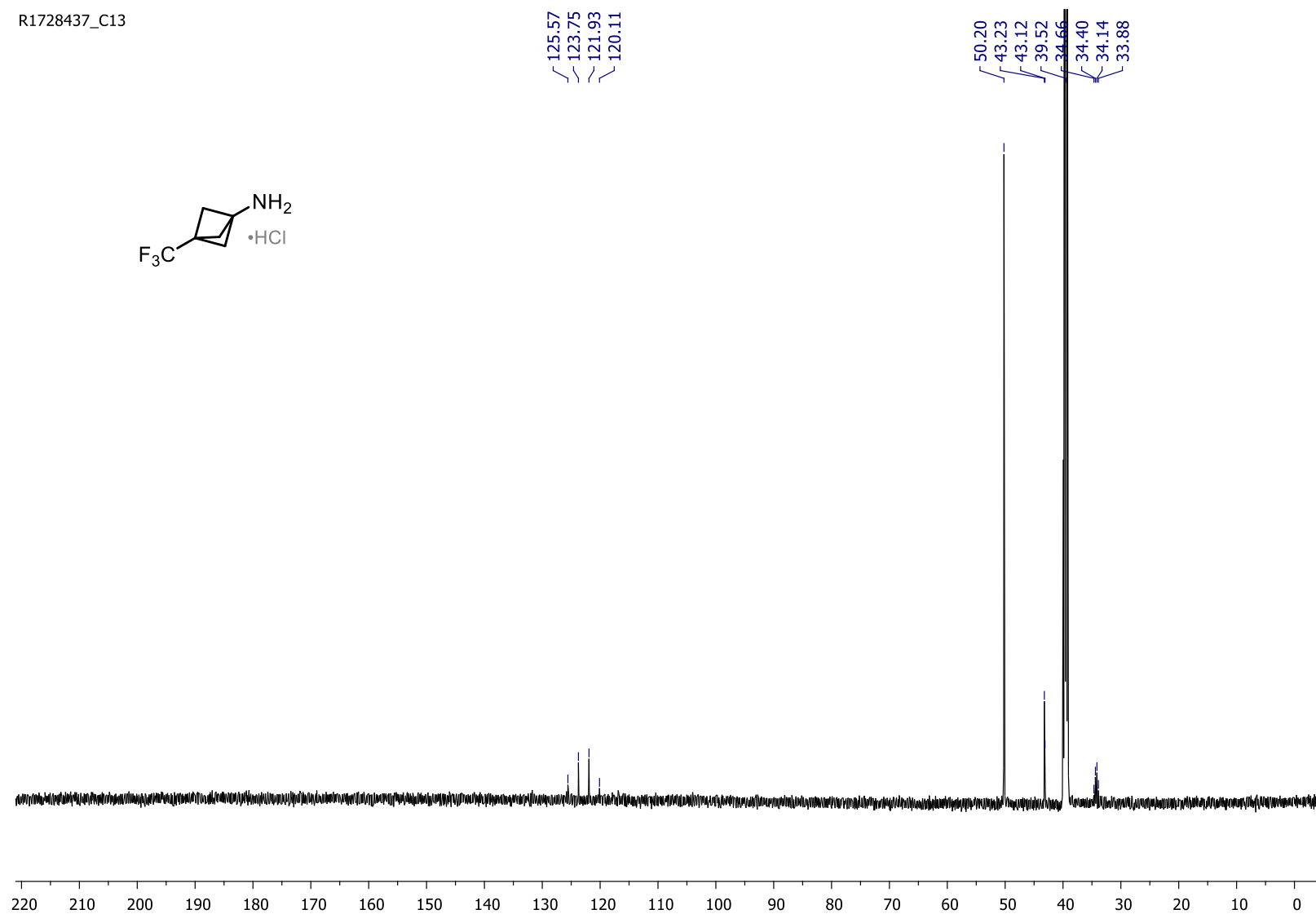
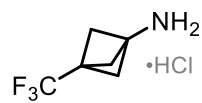
¹H NMR (500 MHz, DMSO-d₆)

R1728437



$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

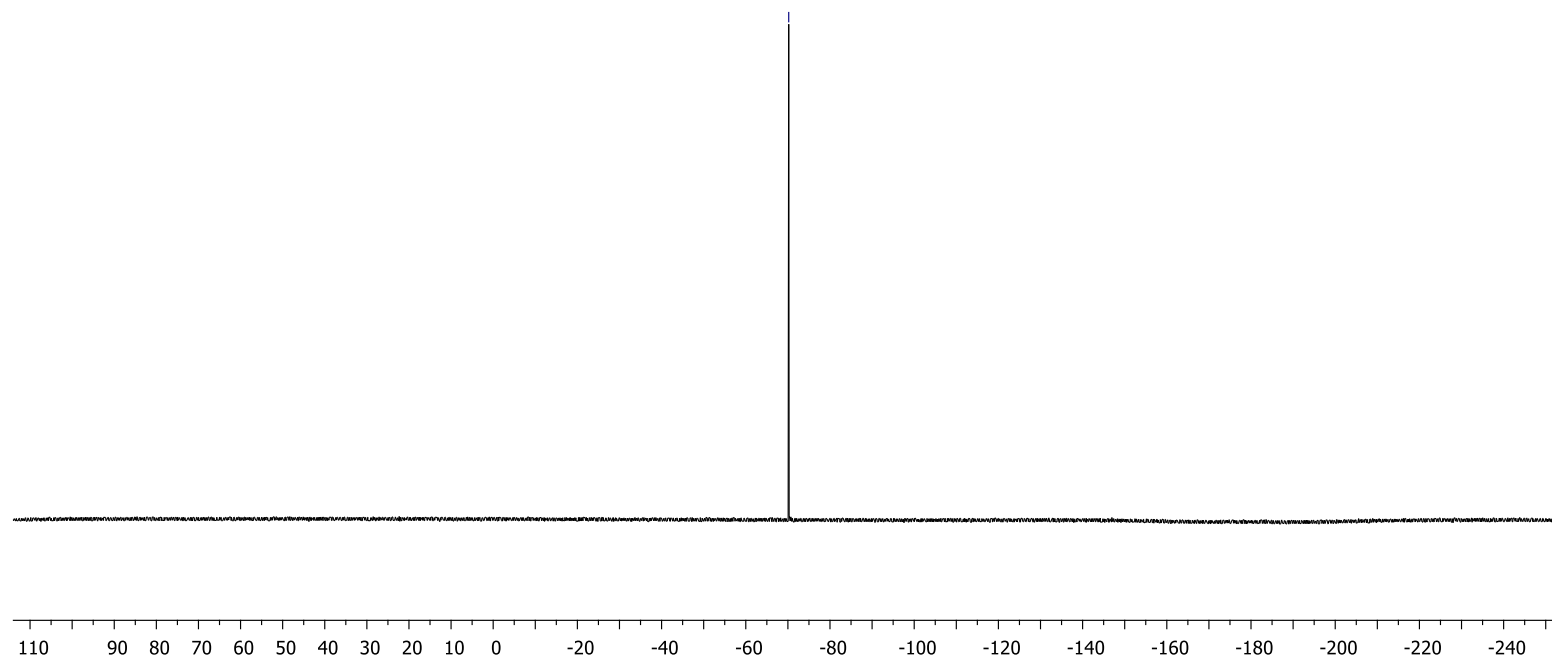
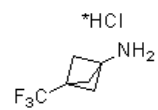
R1728437_C13



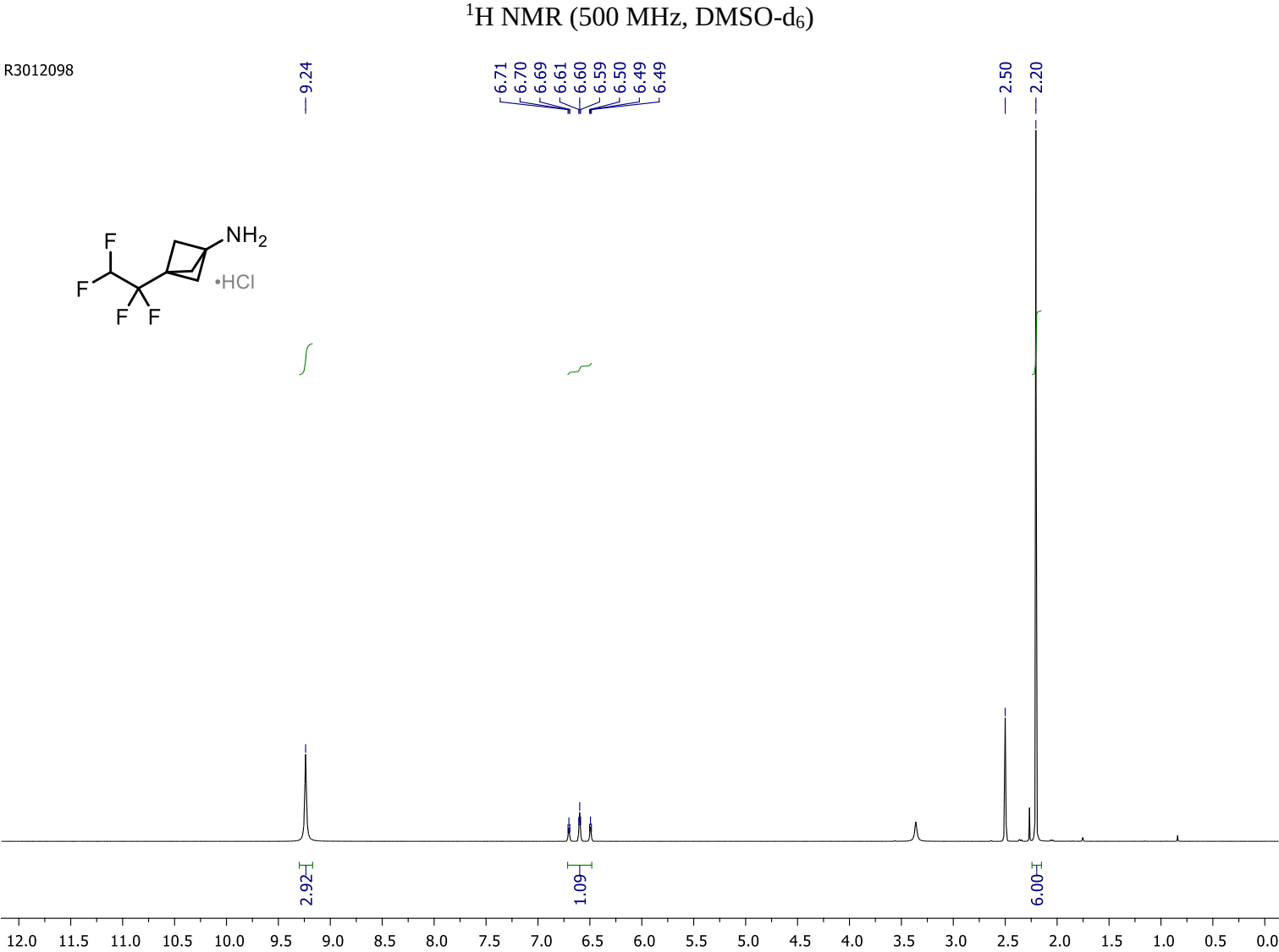
$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

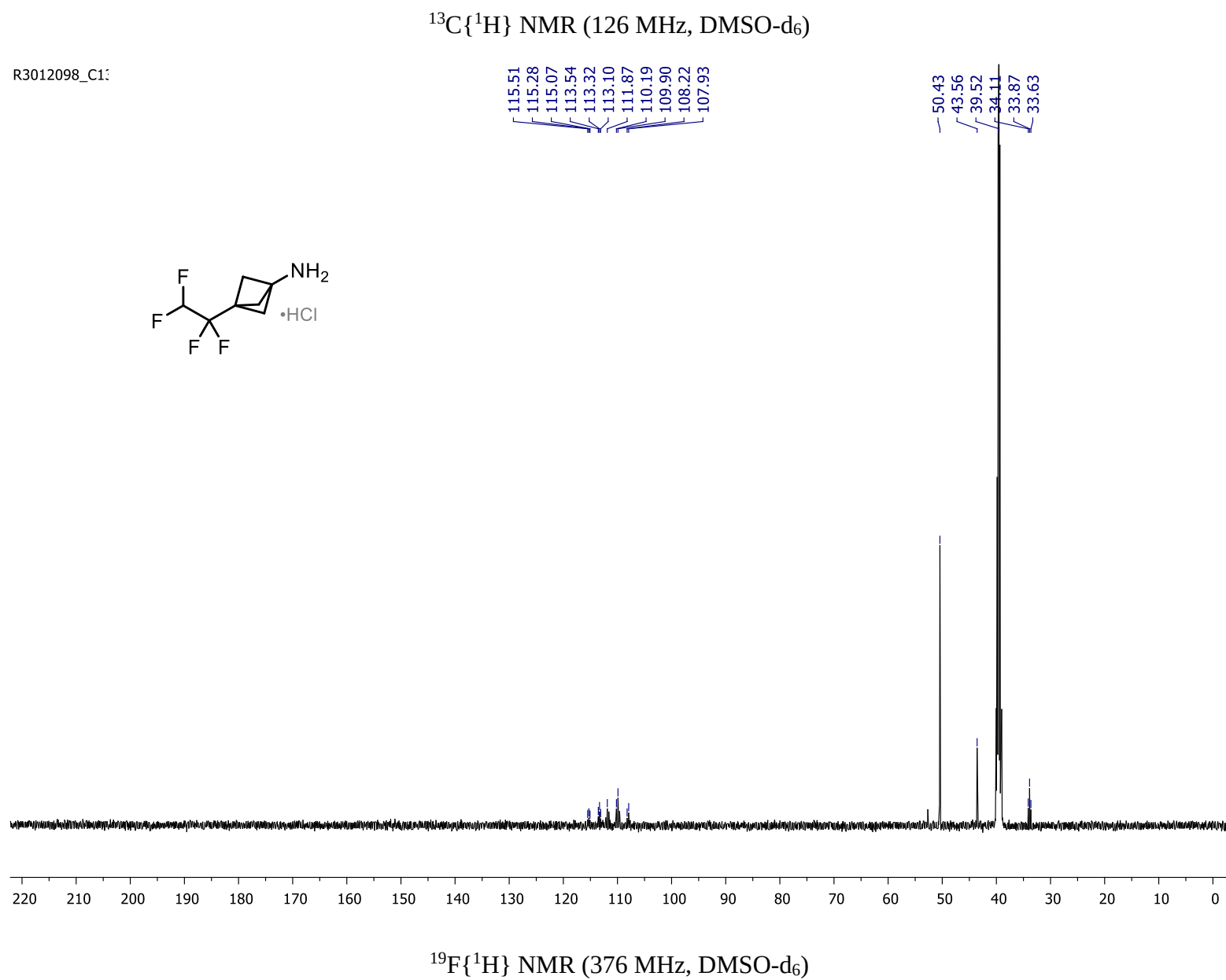
R1728437_F19{H}
19F-{1H}

— -70.20

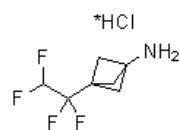


Compound 70l



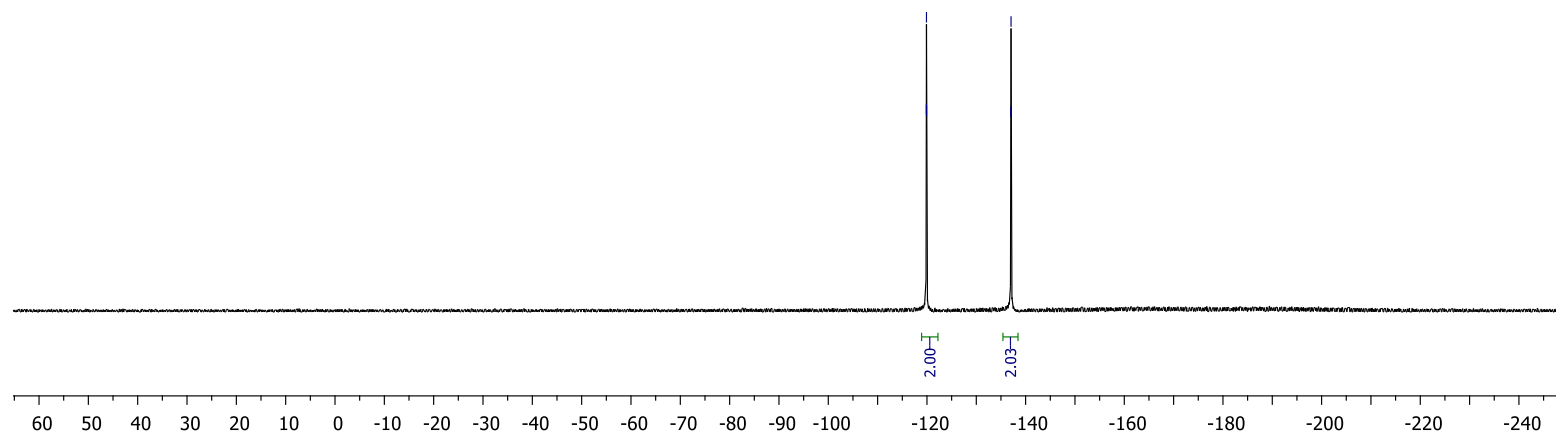


R3012098_F19{H}



-119.88
-119.90
-119.92

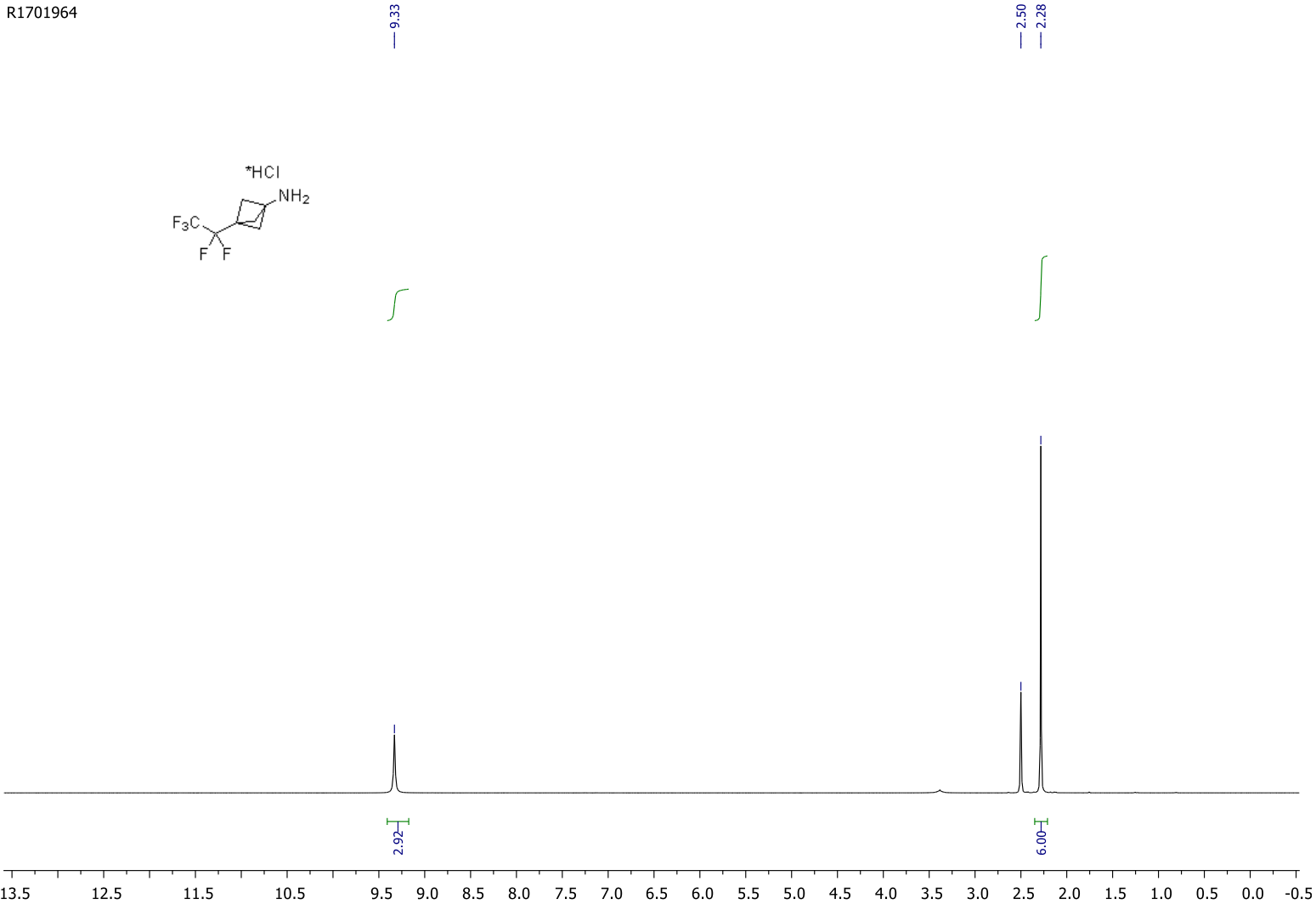
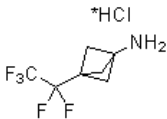
-137.03
-137.04
-137.06



Compound 71I

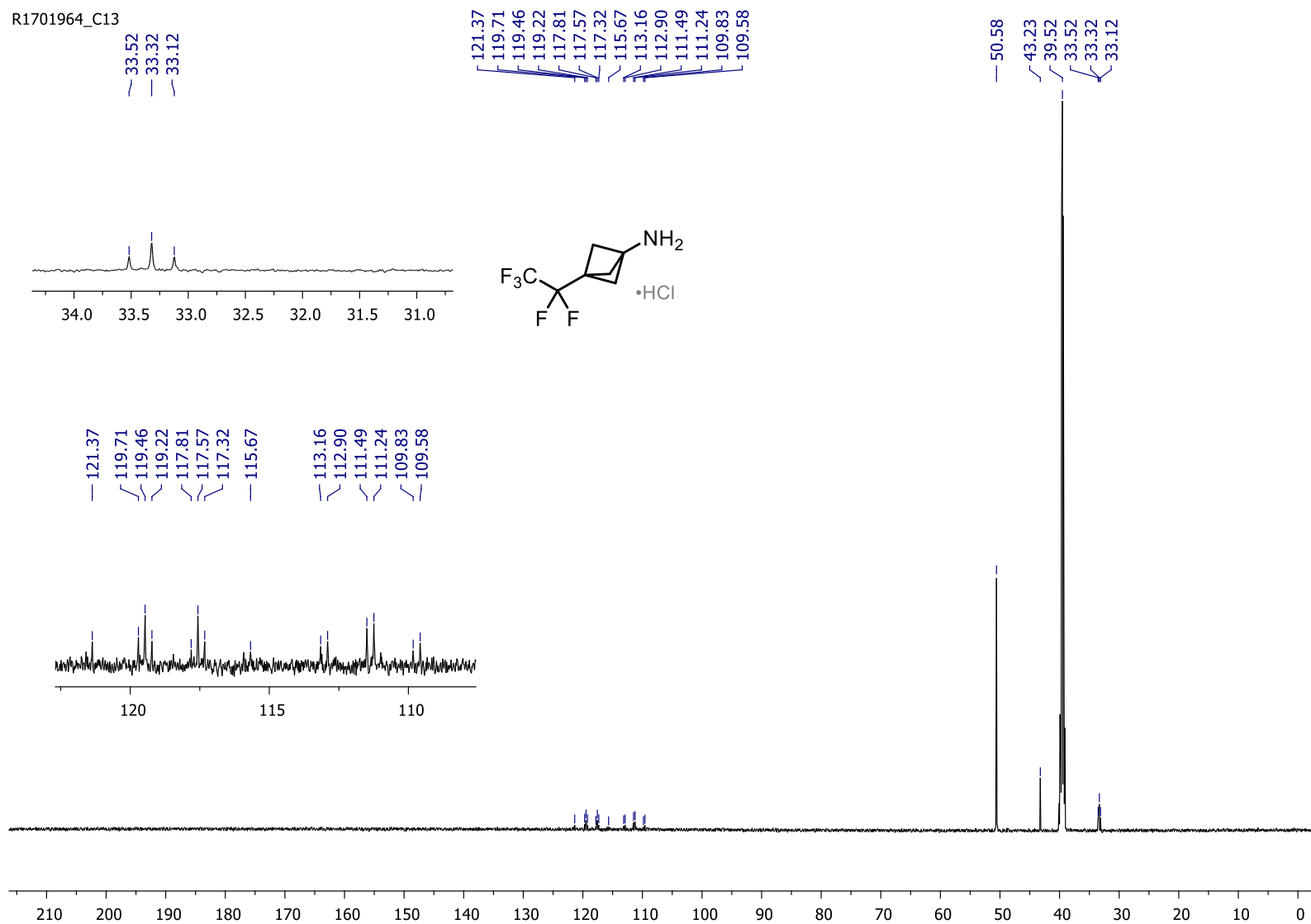
¹H NMR (500 MHz, DMSO-d₆)

R1701964



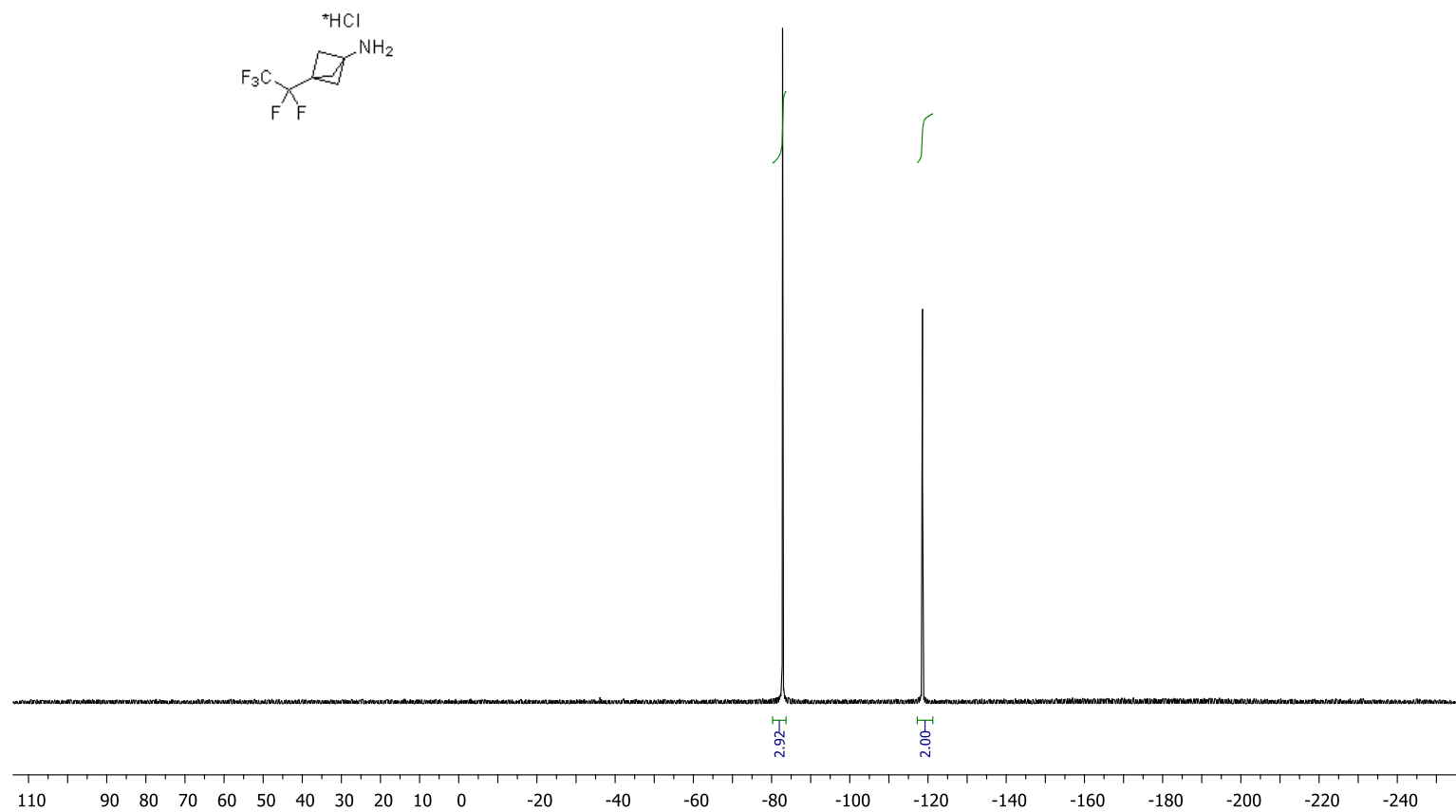
$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, DMSO- d_6)

R1701964_C13

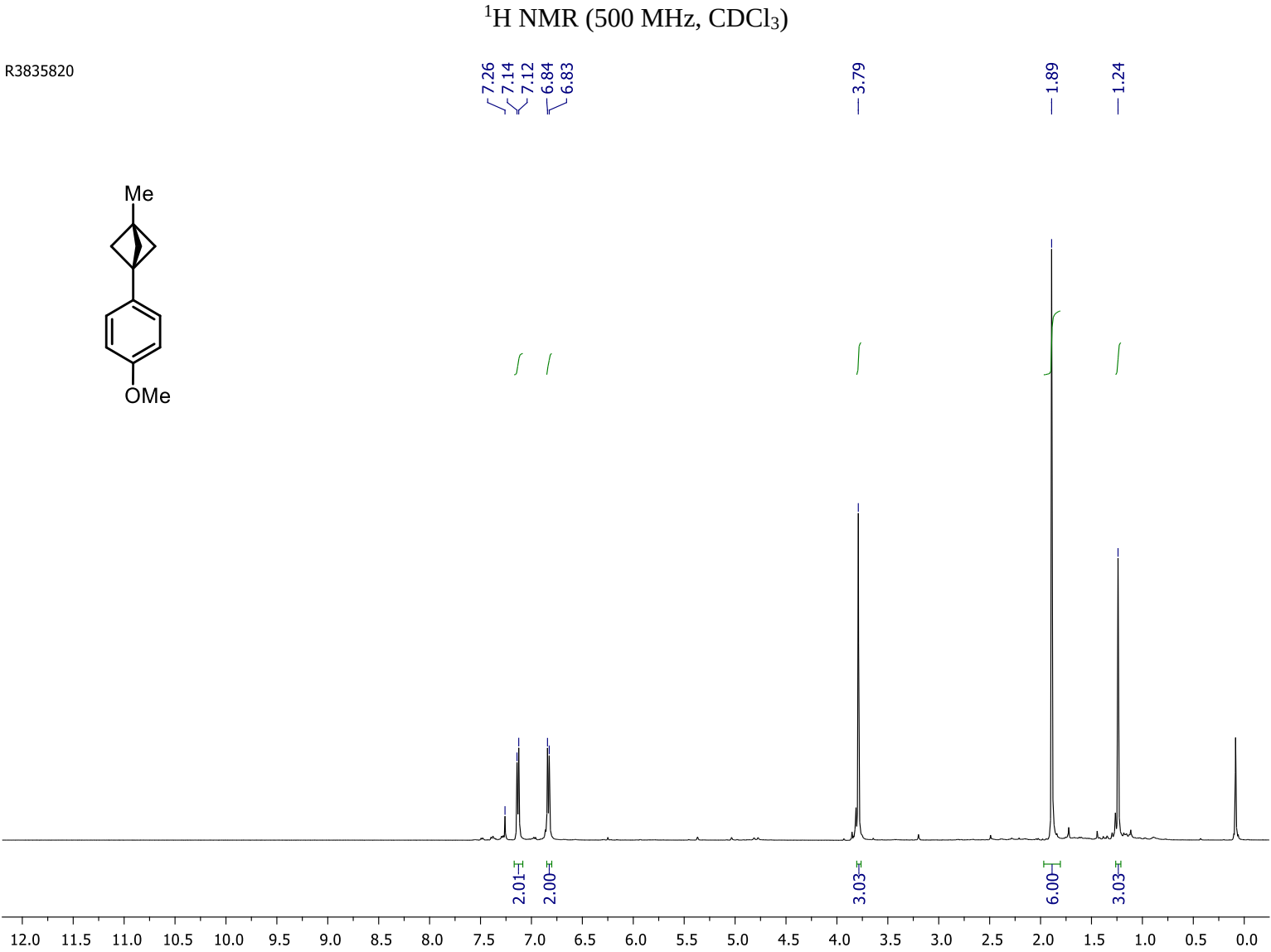


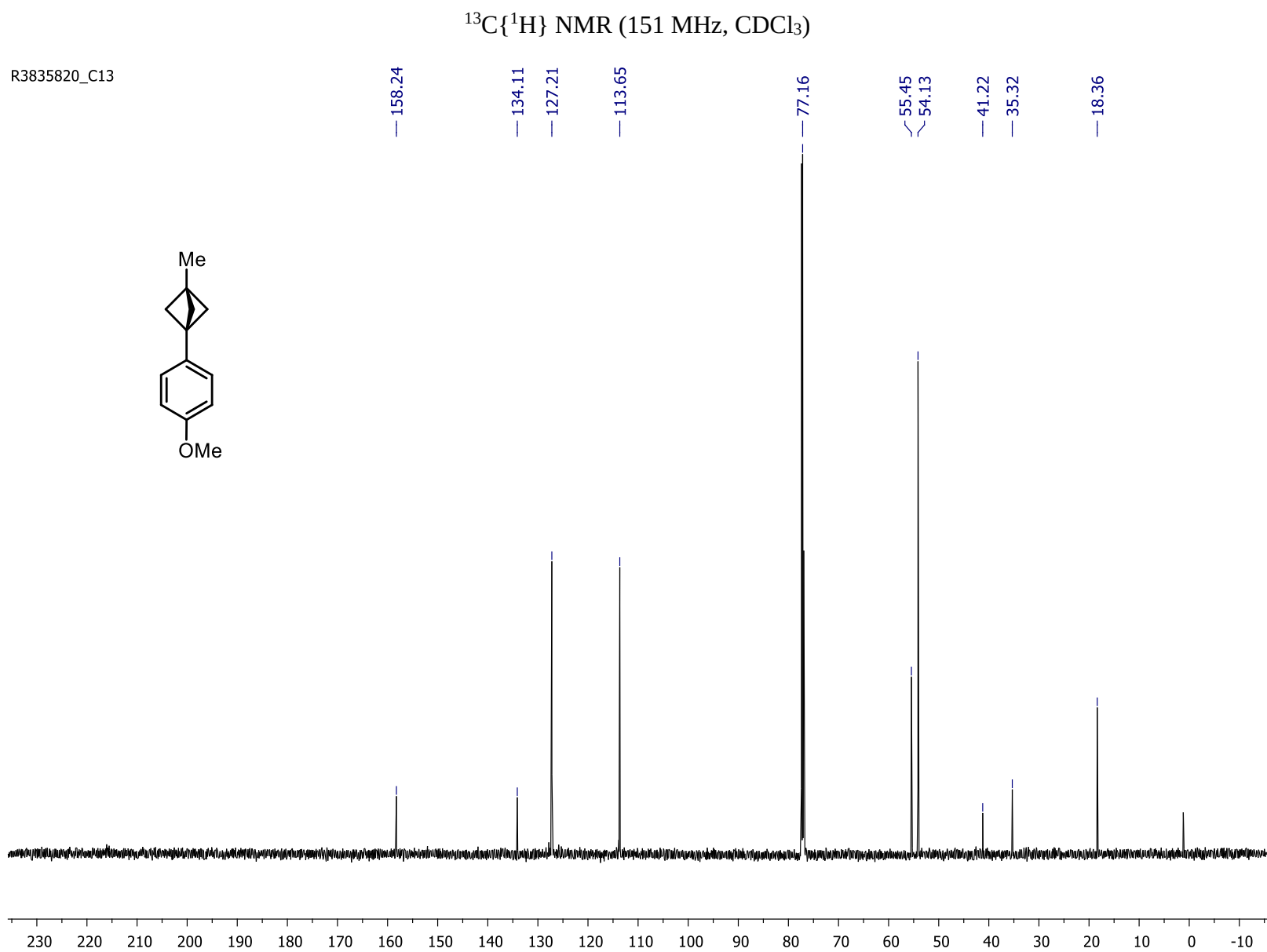
$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, DMSO- d_6)

R1701964_F19{H}
19F-{1H}



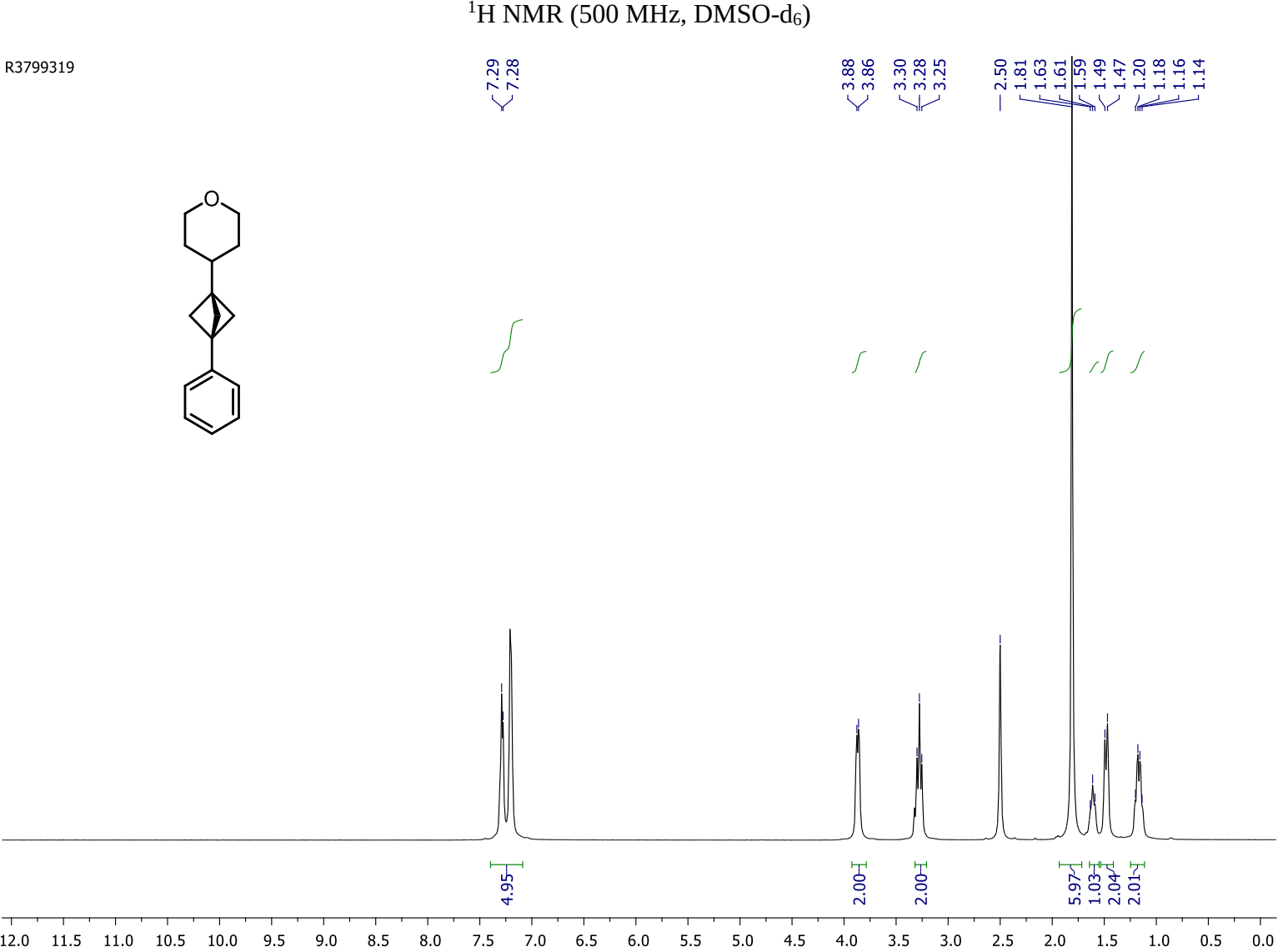
Compound 1m

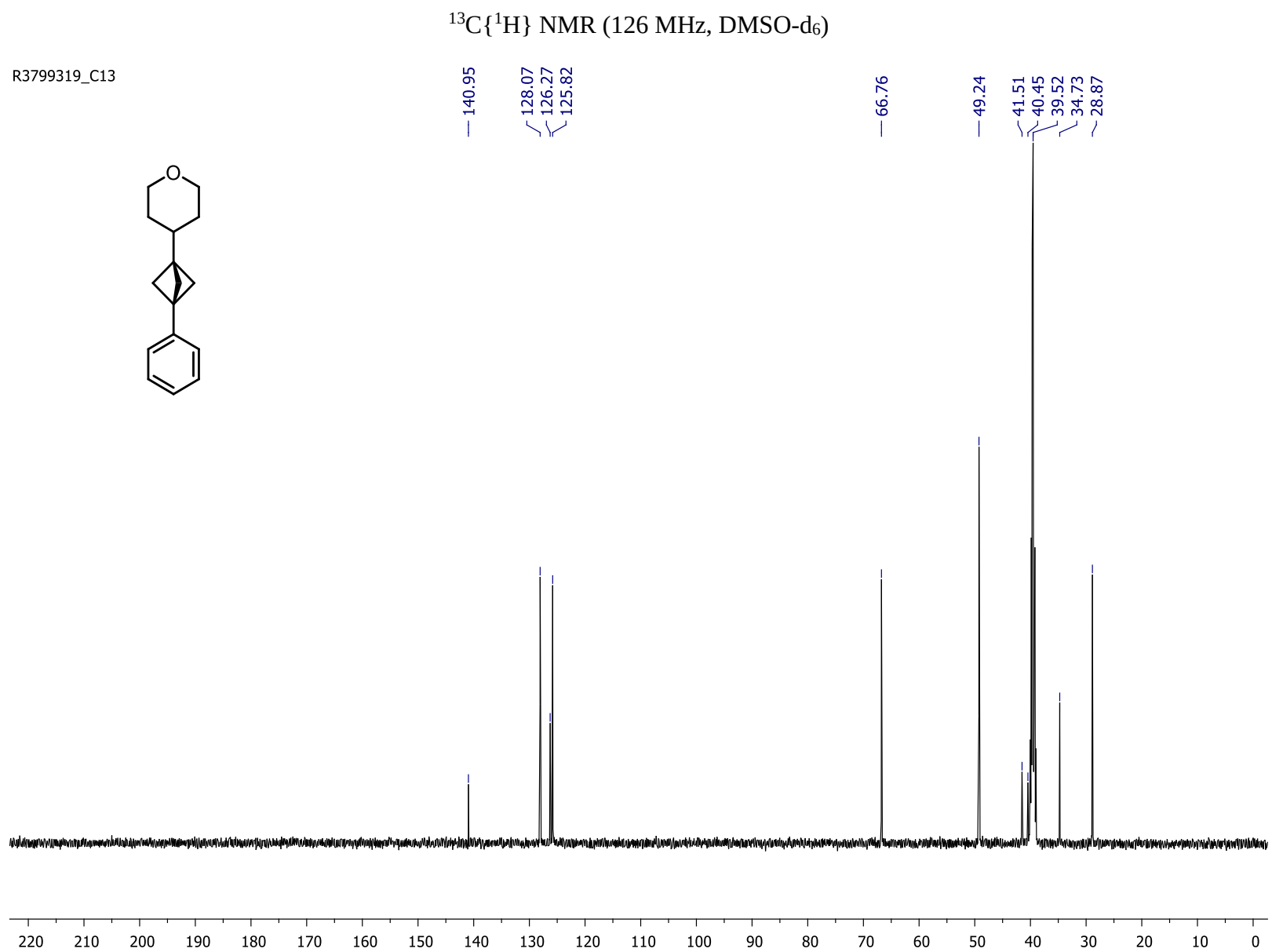




Compound 2m

R3799319

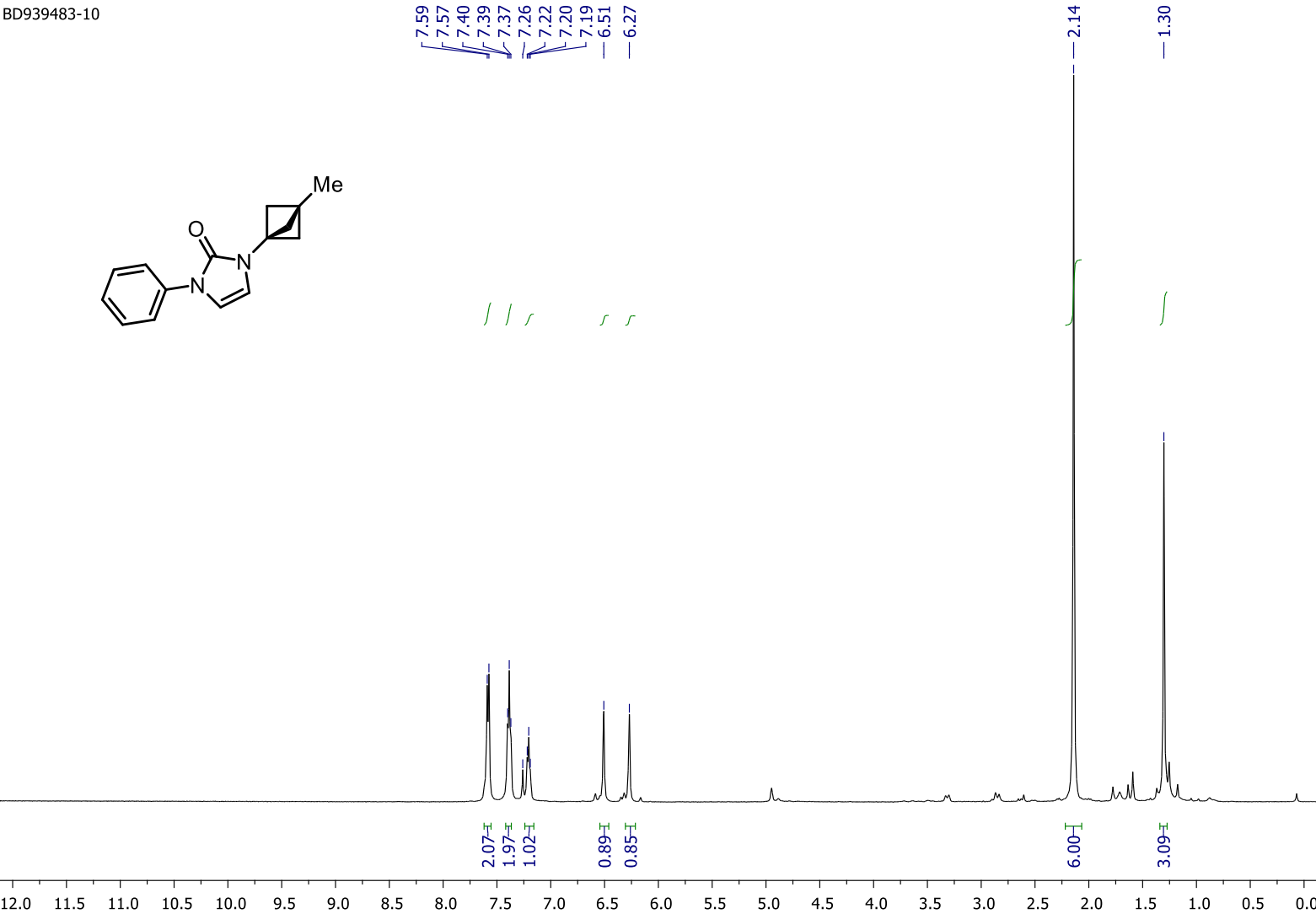


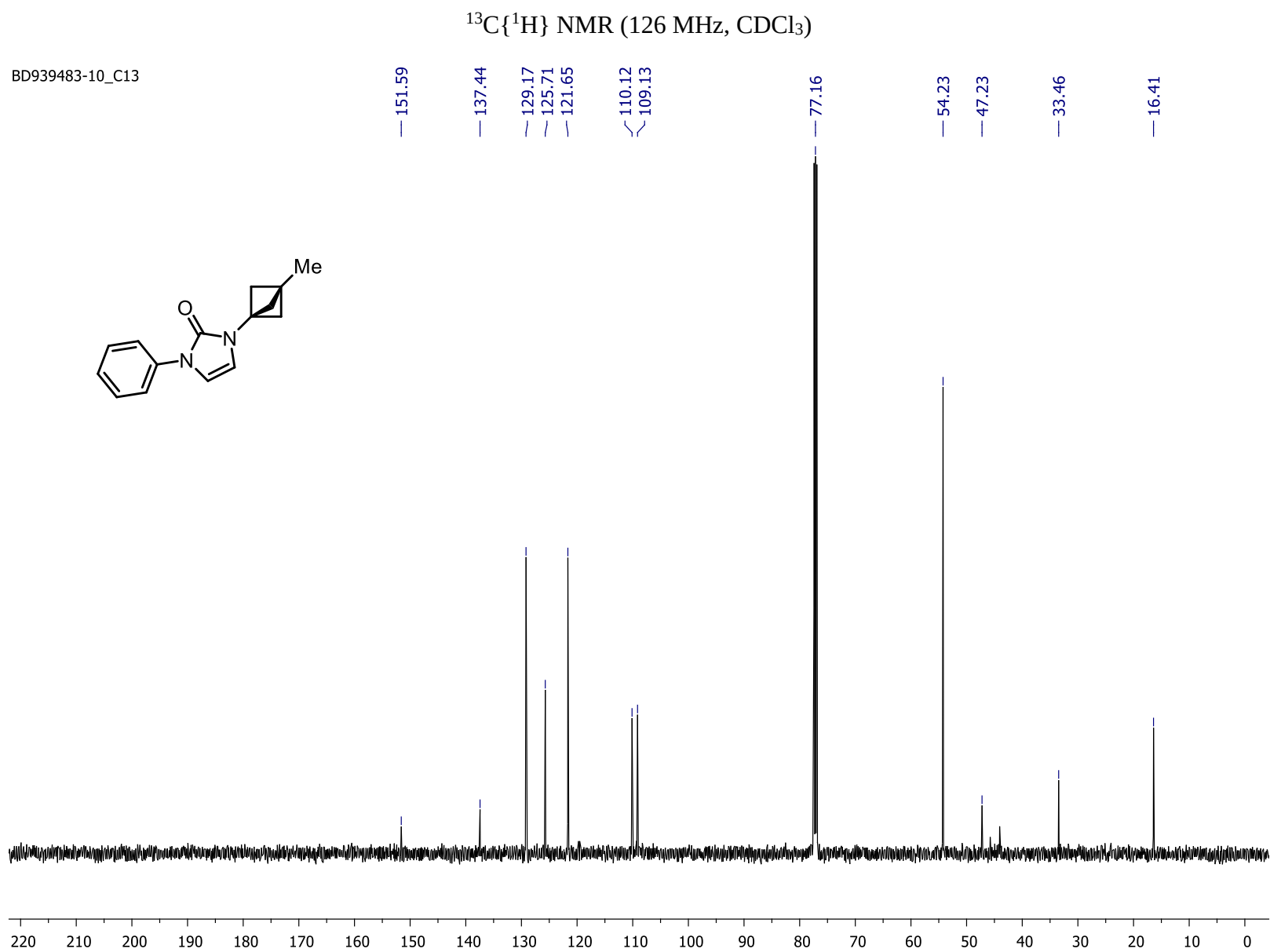


Compound 1n

BD939483-10

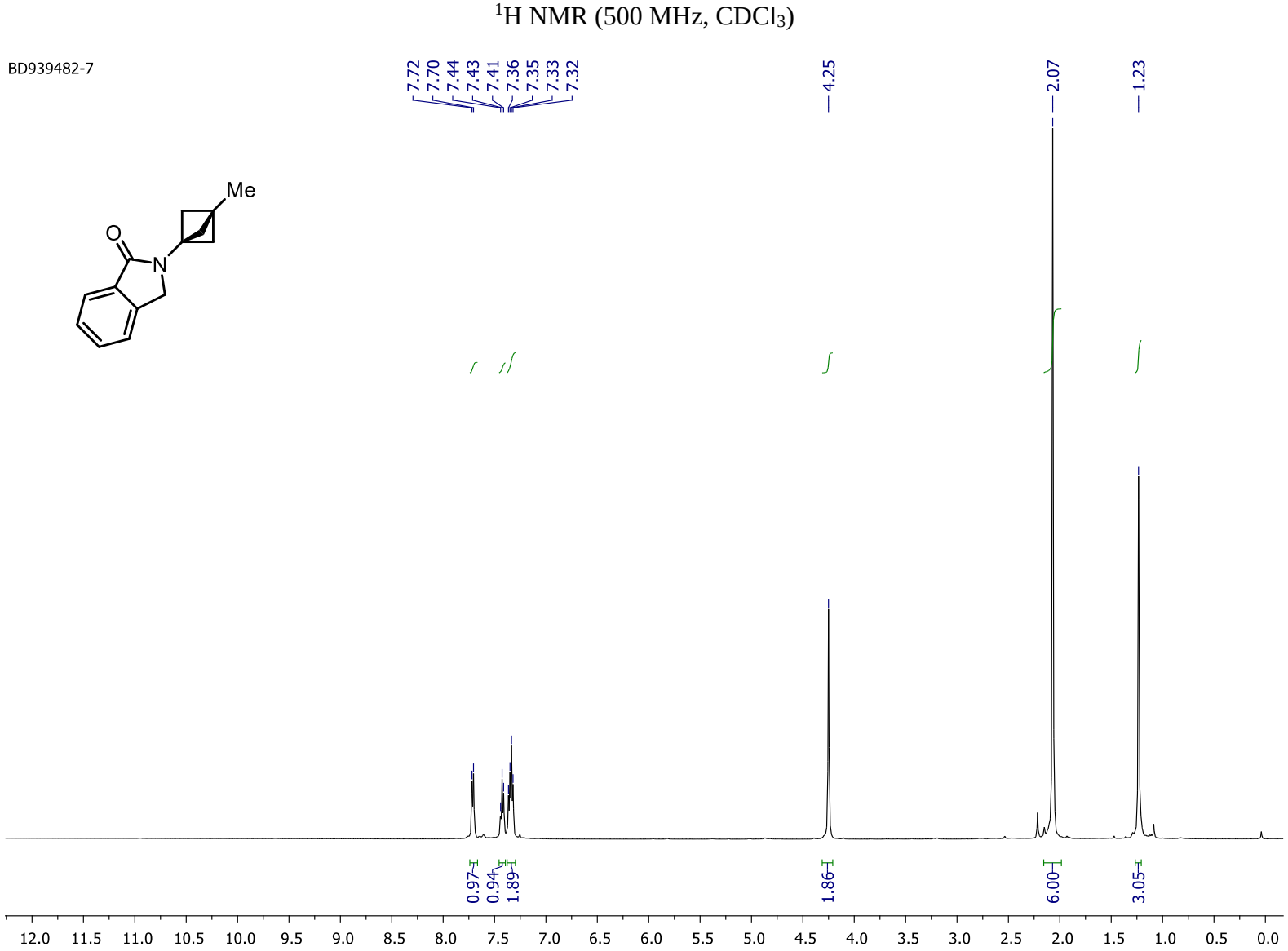
¹H NMR (500 MHz, CDCl₃)





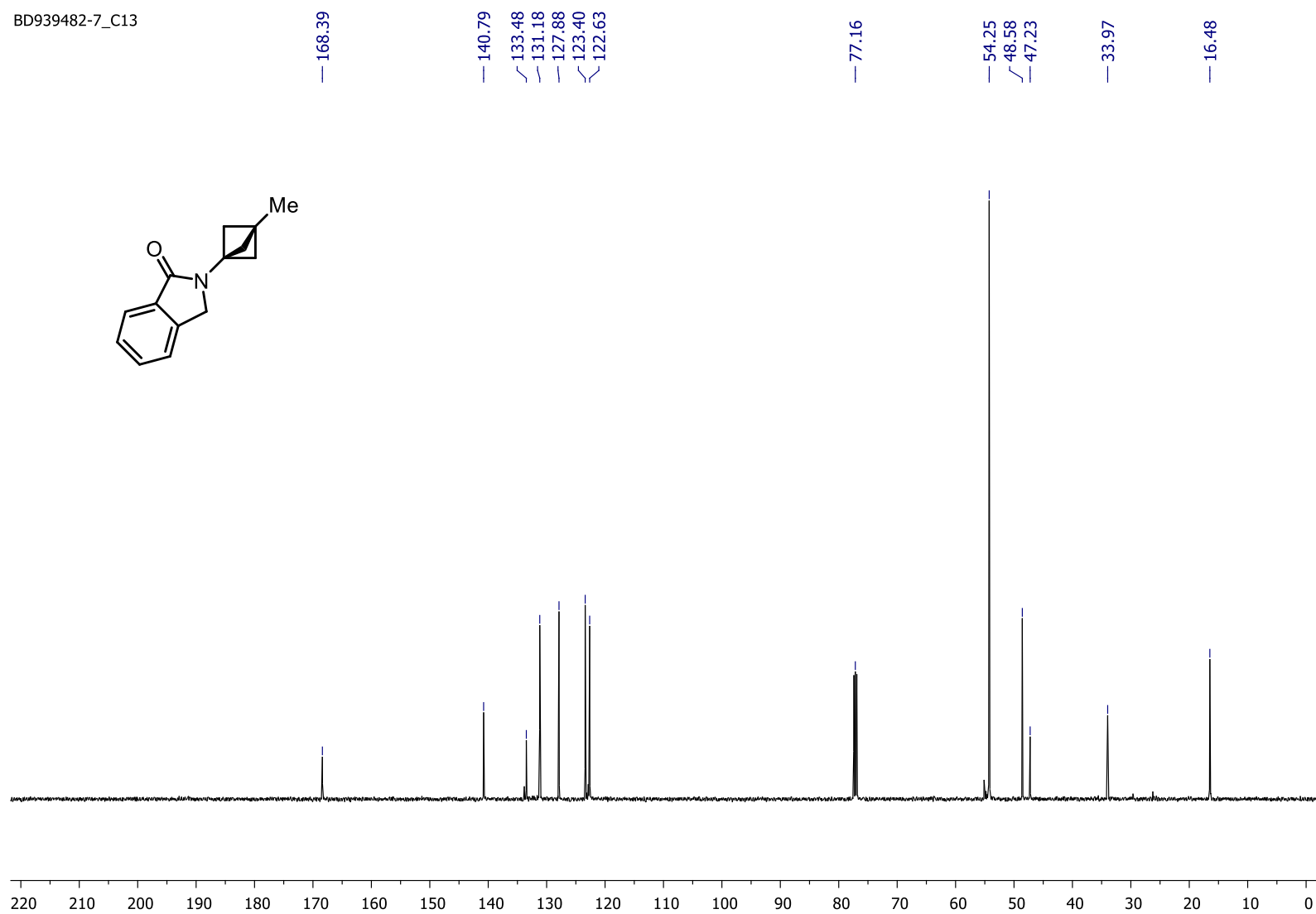
Compound 2n

BD939482-7

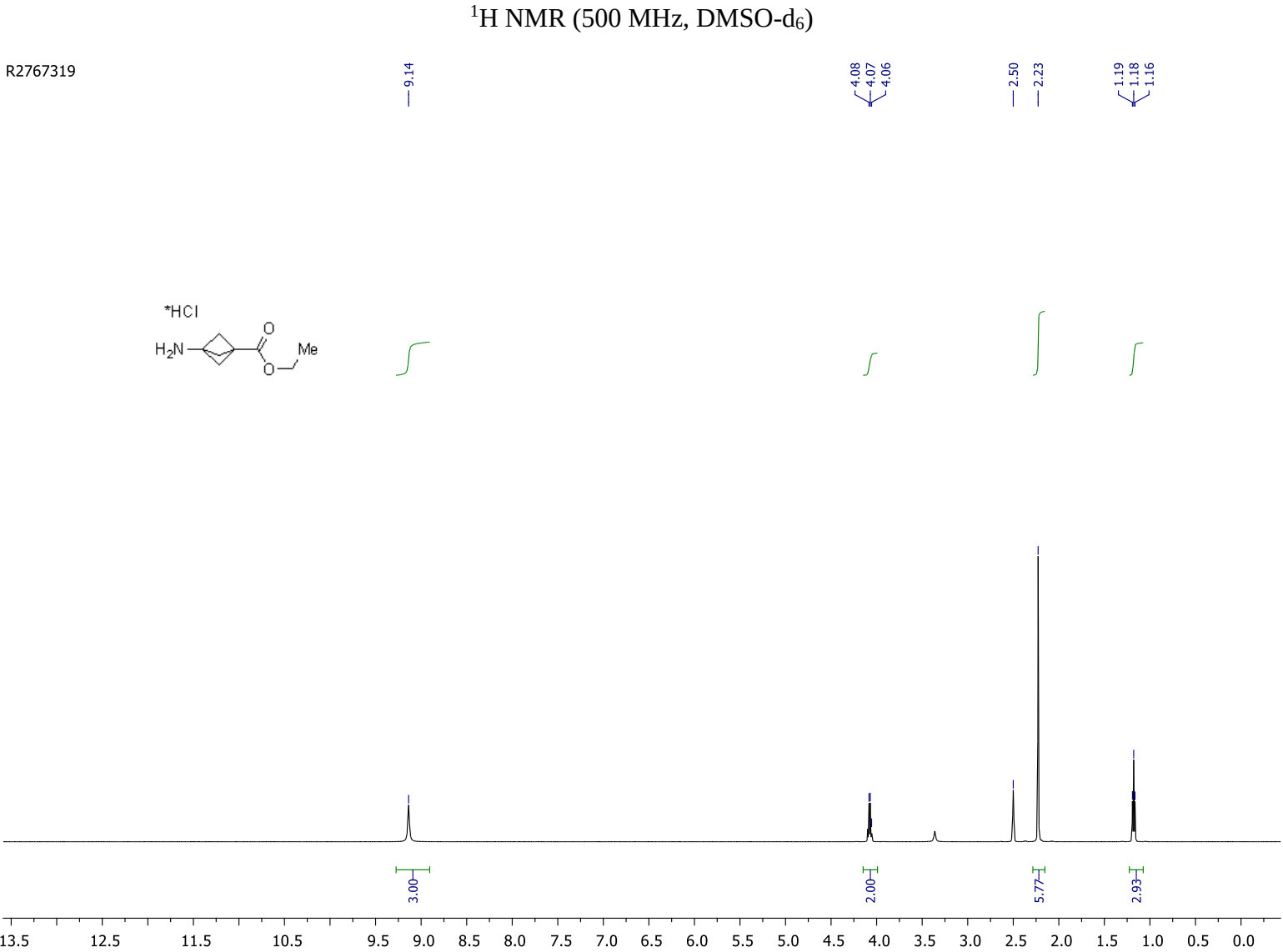


$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

BD939482-7_C13

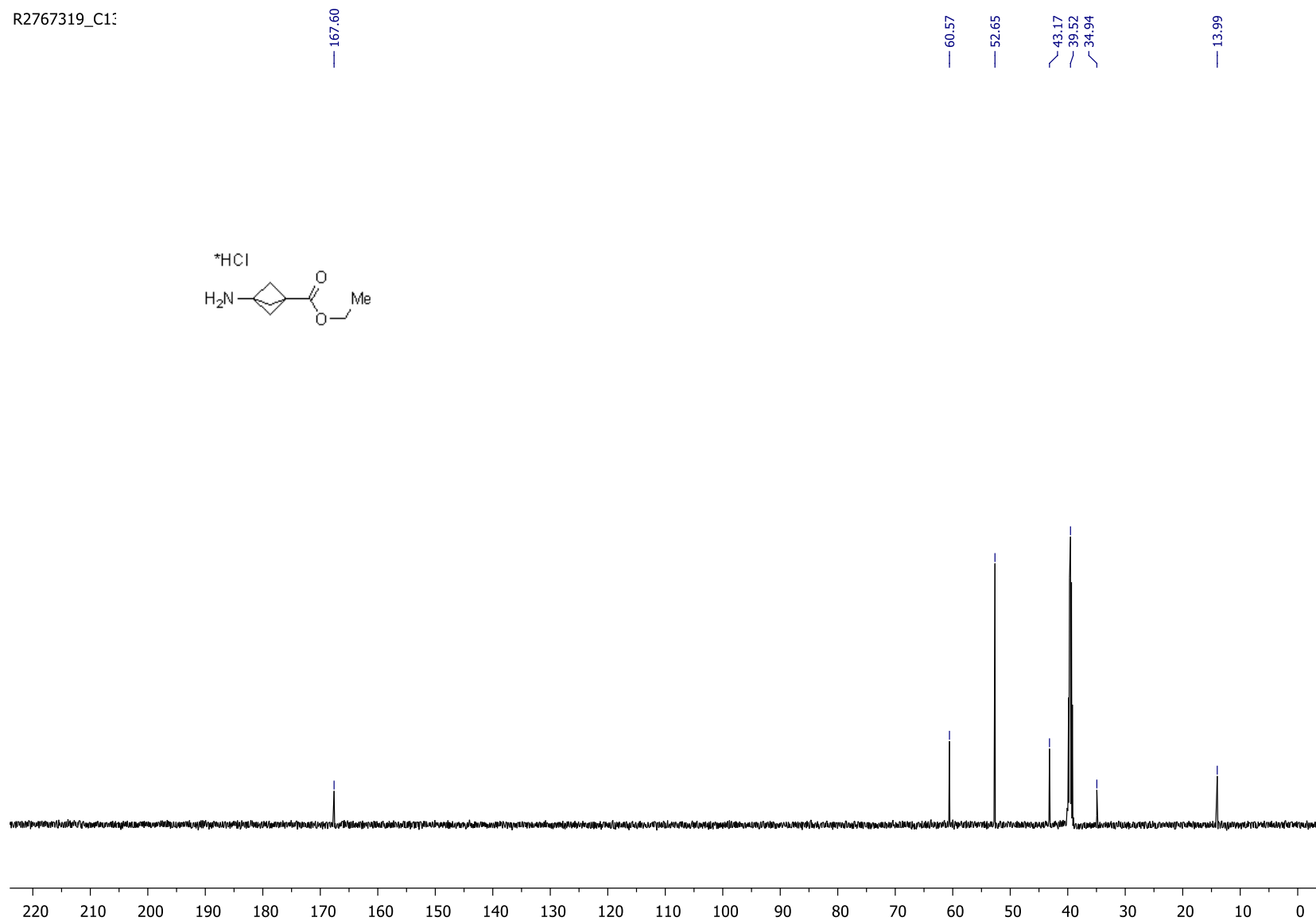
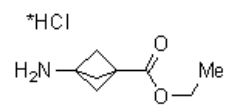


Compound 91



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO- d_6)

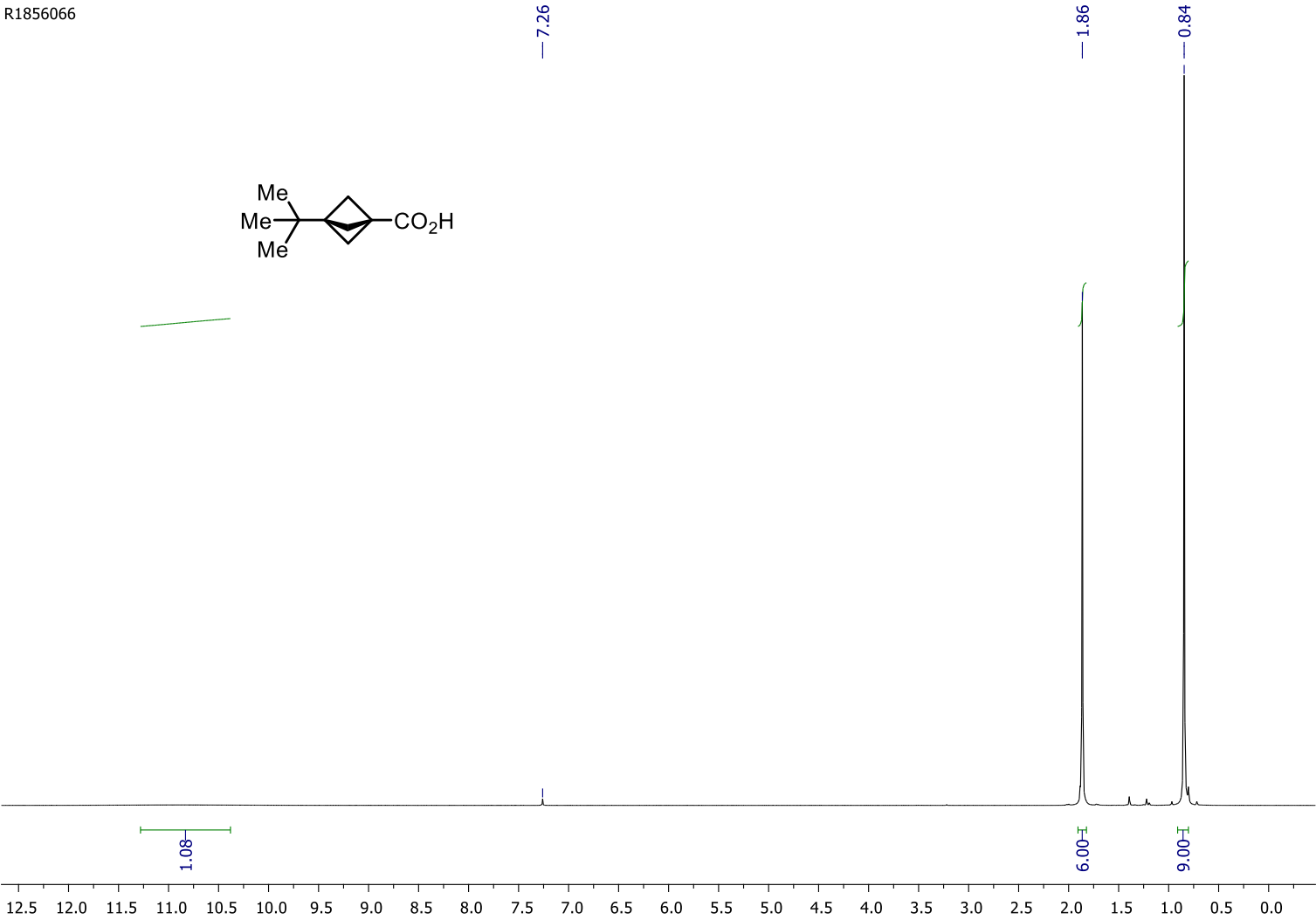
R2767319_C1:



Compound 92

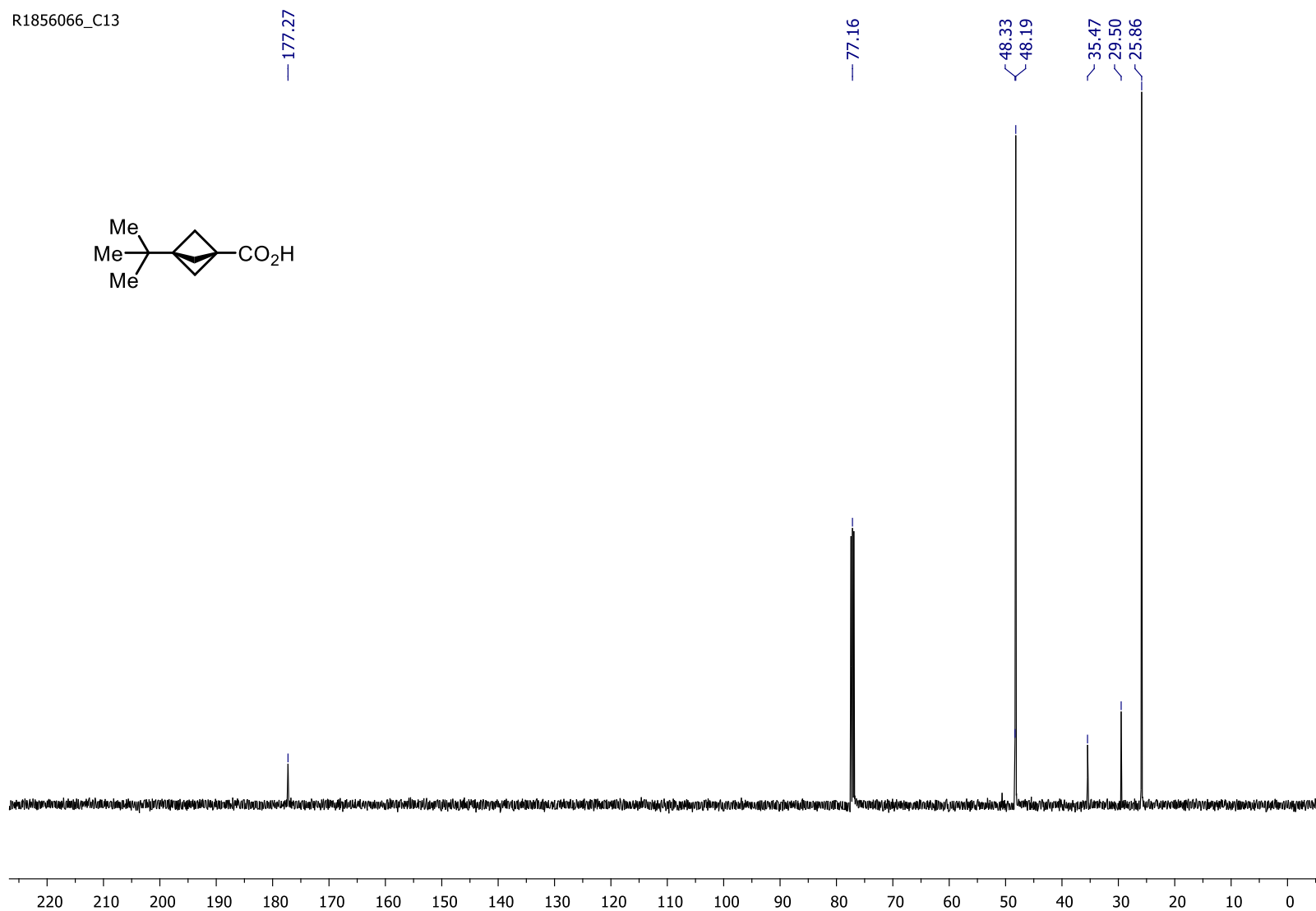
R1856066

¹H NMR (500 MHz, CDCl₃)



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)

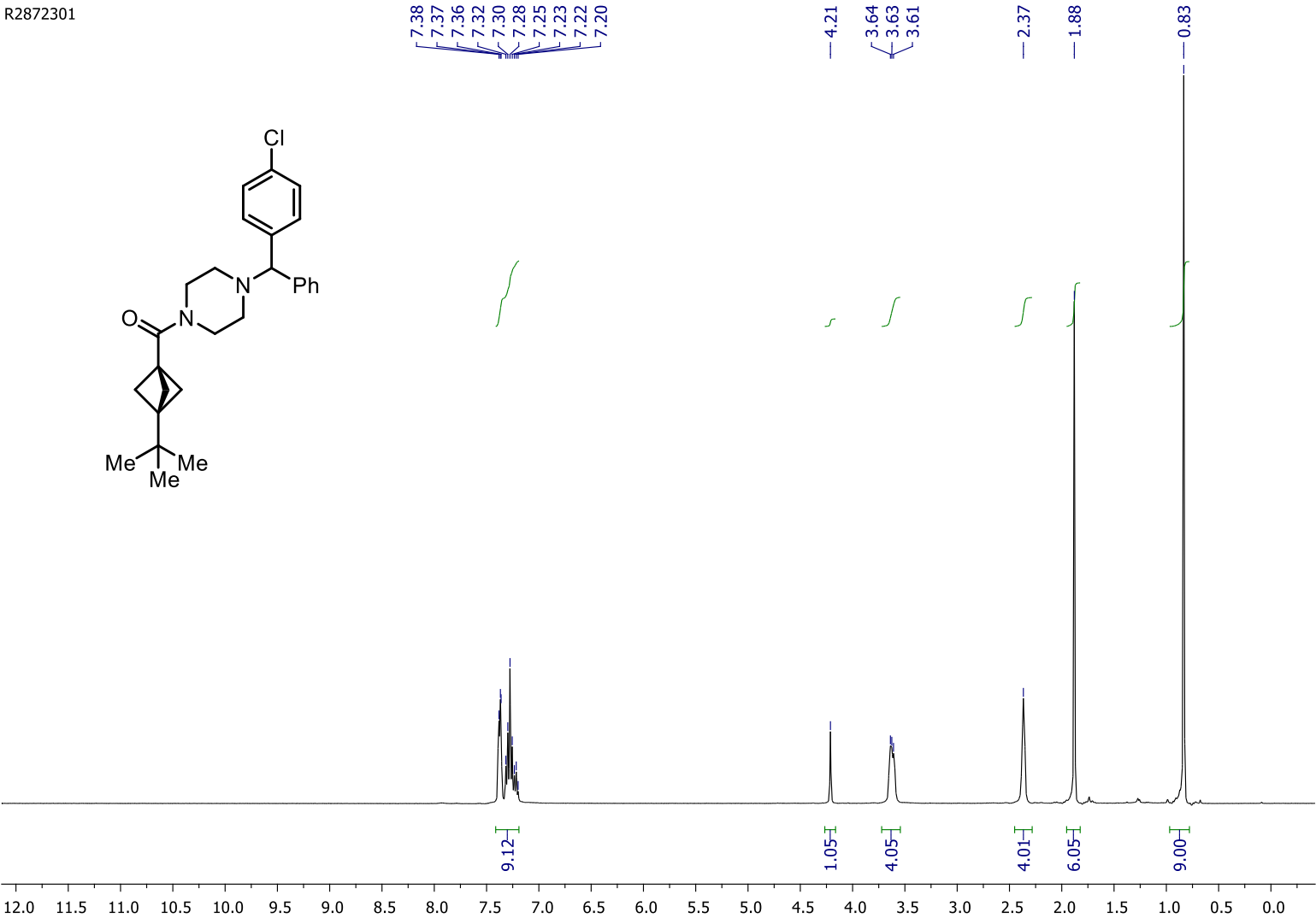
R1856066_C13

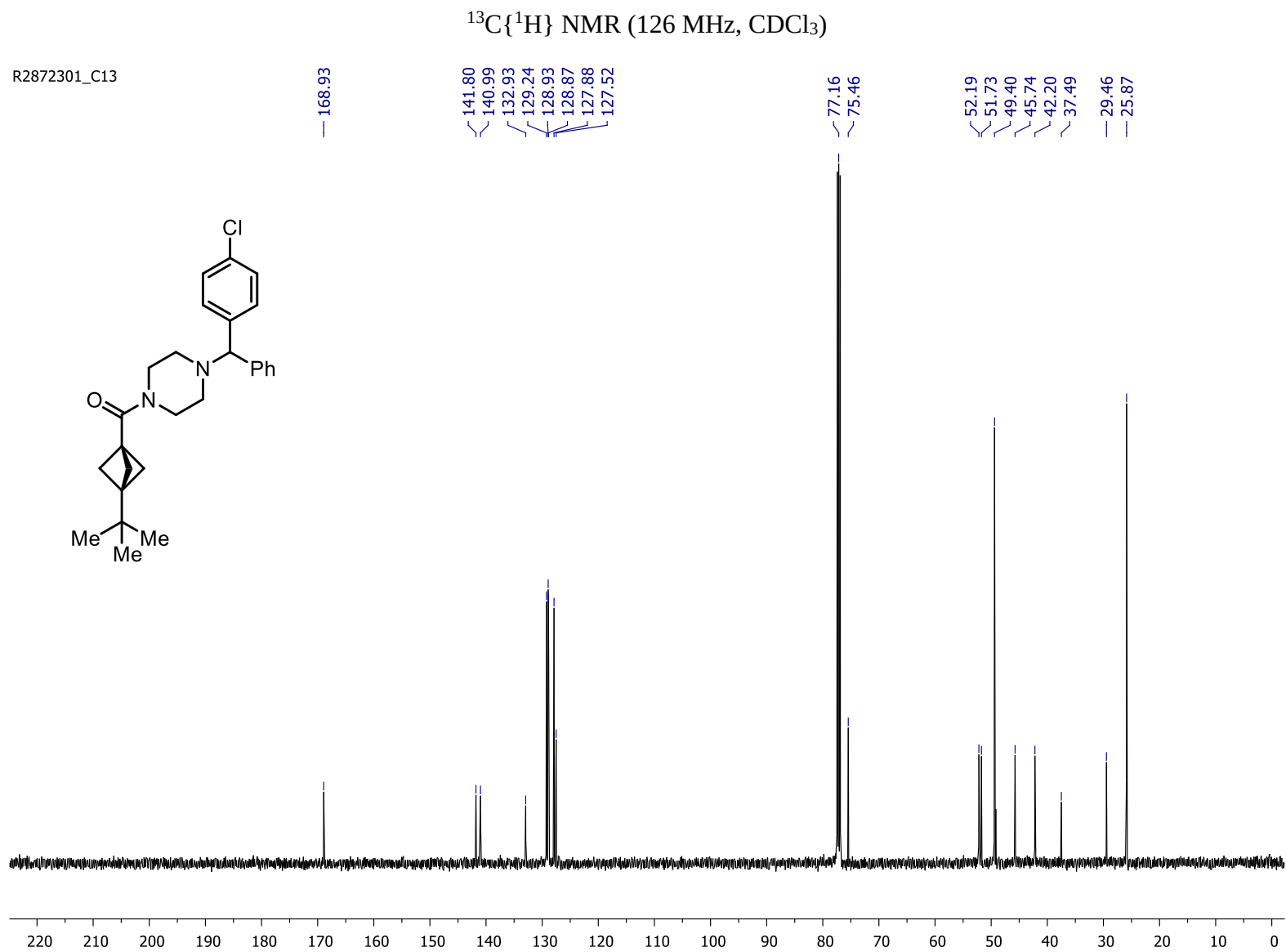


Compound 93

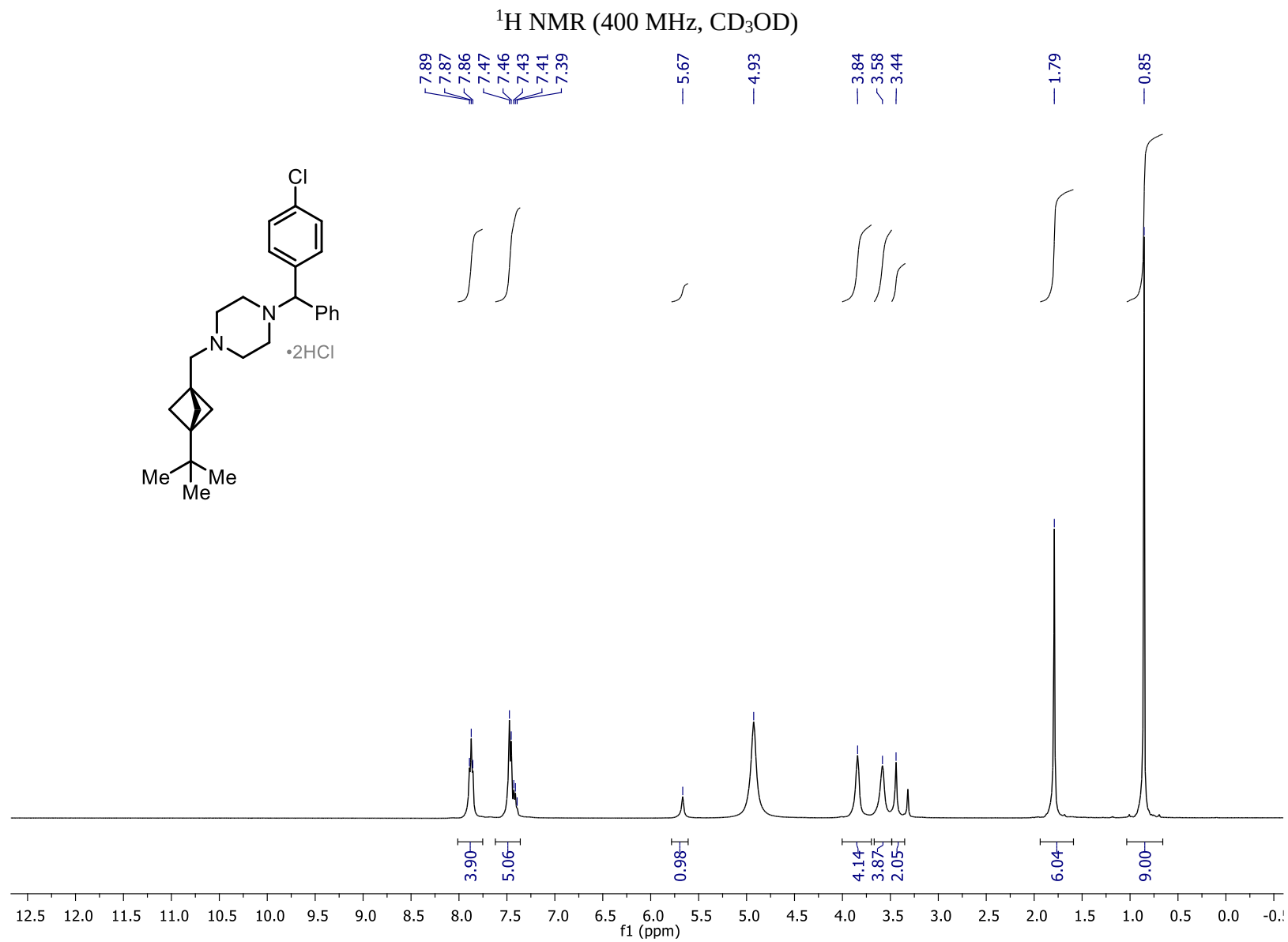
R2872301

¹H NMR (400 MHz, CDCl₃)





Compound 94



Crystallographic data (X-ray)

Crystals of compounds **14**, **19**, **55**, **2k**, and **22k** suitable for X-ray diffraction studies were obtained by a low evaporation of a solution in CHCl₃. Diffraction data were collected at room temperature on an Xcalibur-3 diffractometer with graphite-monochromated Mo K α radiation ($\lambda = 0.71073$ Å) operating in the ω -scans mode. The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the SHELXTL program package. Crystallographic data for the structure in this paper has been deposited at the Cambridge Crystallographic Data Centre. CCDC number: **14** (2260408), **19** (2244857), **55** (2244859), **2k** (2237112) and **21k** (2244856). Copies of the data can be obtained, free of charge, by application to CCDC, 12 Union Road, Cambridge CB21EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Compound **14**

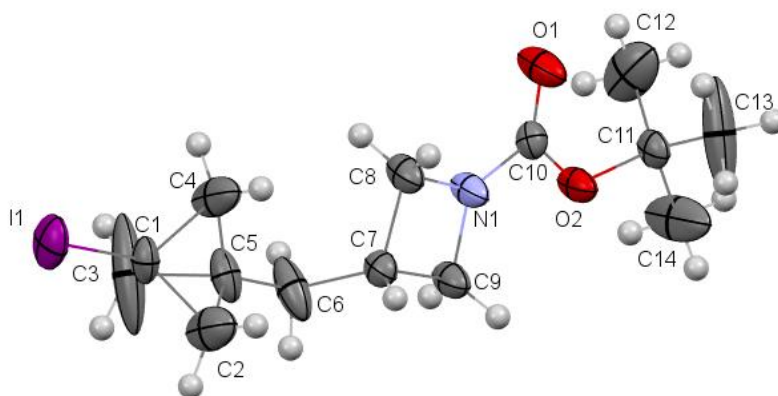


Figure S1. Molecular structure of **14** according to X-ray diffraction data. Thermal ellipsoids are shown at a 50% probability level.

Crystal structure determination of **14**

data_vd93

_chemical_formula_moiety	C ₁₄ H ₂₂ INO ₂
_chemical_formula_sum	C ₁₄ H ₂₂ INO ₂
_chemical_formula_weight	363.22
_space_group_crystal_system	'triclinic'
_space_group_IT_number	2

_space_group_name_H-M_alt	'P -1'
_space_group_name_Hall	'-P 1'
_cell_length_a	6.4845(8)
_cell_length_b	11.2145(13)
_cell_length_c	11.3838(14)
_cell_angle_alpha	81.994(6)
_cell_angle_beta	79.538(6)
_cell_angle_gamma	81.736(6)
_cell_volume	800.15(17)
_cell_formula_units_Z	2
_cell_measurement_reflns_used	3878
_cell_measurement_temperature	273.15
_cell_measurement_theta_max	26.09
_cell_measurement_theta_min	2.45
_shelx_estimated_absorpt_T_max	0.857
_shelx_estimated_absorpt_T_min	0.691
_exptl_absorpt_coefficient_mu	1.997
_exptl_absorpt_correction_T_max	0.7454
_exptl_absorpt_correction_T_min	0.5121
_exptl_absorpt_correction_type	multi-scan
_exptl_absorpt_process_details	SADABS
_exptl_crystal_colour	colourless
_exptl_crystal_colour_primary	colourless
_exptl_crystal_density_diffn	1.508
_exptl_crystal_description	block
_exptl_crystal_F_000	364
_exptl_crystal_size_max	0.2
_exptl_crystal_size_mid	0.18
_exptl_crystal_size_min	0.08
_diffn_reflns_av_R_equivalents	0.0419
_diffn_reflns_av_unetI/netI	0.0412
_diffn_reflns_Laue_measured_fraction_full	0.999
_diffn_reflns_Laue_measured_fraction_max	0.999
_diffn_reflns_limit_h_max	6
_diffn_reflns_limit_h_min	-7

_diffn_reflns_limit_k_max	13
_diffn_reflns_limit_k_min	-13
_diffn_reflns_limit_l_max	13
_diffn_reflns_limit_l_min	-13
_diffn_reflns_number	9684
_diffn_reflns_point_group_measured_fraction_full	0.999
_diffn_reflns_point_group_measured_fraction_max	0.999
_diffn_reflns_theta_full	24.997
_diffn_reflns_theta_max	24.997
_diffn_reflns_theta_min	2.446
_diffn_ambient_temperature	273.15
_diffn_measured_fraction_theta_full	0.999
_diffn_measured_fraction_theta_max	0.999
_diffn_measurement_device_type	'Bruker APEX-II CCD'
_diffn_measurement_method	'\f and \w scans'
_diffn_radiation_type	MoK\alpha
_diffn_radiation_wavelength	0.71073
_diffn_source_current	30.0
_diffn_source_power	1.2
_diffn_source_voltage	40.0
_diffn_standards_number	0
_reflns_Friedel_coverage	0.000
_reflns_number_gt	2366
_reflns_number_total	2830

Compound 19

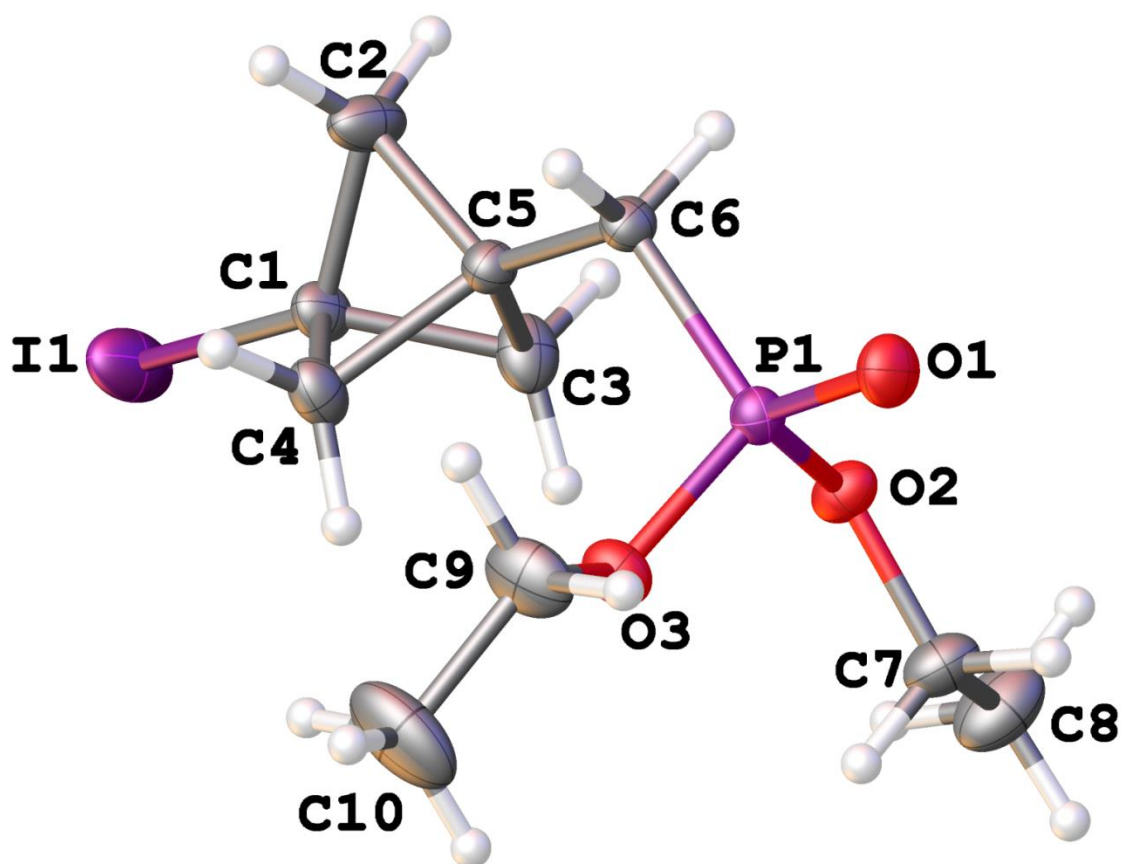


Figure S2. Molecular structure of **19** according to X-ray diffraction data. Thermal ellipsoids are shown at a 50% probability level.

Crystal structure determination of 19

data_vd91

_chemical_formula_moiety	C ₁₀ H ₁₈ IO ₃ P
_chemical_formula_sum	C ₁₀ H ₁₈ IO ₃ P
_chemical_formula_weight	344.11
_space_group_crystal_system	'triclinic'
_space_group_IT_number	2
_space_group_name_H-M_alt	'P -1'
_space_group_name_Hall	'-P 1'
_cell_length_a	8.2203(4)
_cell_length_b	8.6129(4)
_cell_length_c	10.9415(5)
_cell_angle_alpha	84.123(3)

_cell_angle_beta	86.147(3)
_cell_angle_gamma	63.830(3)
_cell_volume	691.39(6)
_cell_formula_units_Z	2
_cell_measurement_reflns_used	6345
_cell_measurement_temperature	296.15
_cell_measurement_theta_max	30.10
_cell_measurement_theta_min	2.64
_shelx_estimated_absorpt_T_max	0.728
_shelx_estimated_absorpt_T_min	0.606
_exptl_absorpt_coefficient_mu	2.419
_exptl_absorpt_correction_T_max	0.7460
_exptl_absorpt_correction_T_min	0.3870
_exptl_absorpt_correction_type	multi-scan
_exptl_absorpt_process_details	SADABS
_exptl_crystal_colour	yellow
_exptl_crystal_colour_primary	yellow
_exptl_crystal_density_diffn	1.653
_exptl_crystal_description	block
_exptl_crystal_F_000	340
_exptl_crystal_size_max	0.23
_exptl_crystal_size_mid	0.19
_exptl_crystal_size_min	0.14
_diffn_reflns_av_R_equivalents	0.0481
_diffn_reflns_av_unetI/netI	0.0507
_diffn_reflns_Laue_measured_fraction_full	1.000
_diffn_reflns_Laue_measured_fraction_max	0.998
_diffn_reflns_limit_h_max	11
_diffn_reflns_limit_h_min	-11
_diffn_reflns_limit_k_max	12
_diffn_reflns_limit_k_min	-11
_diffn_reflns_limit_l_max	15
_diffn_reflns_limit_l_min	-15
_diffn_reflns_number	11627
_diffn_reflns_point_group_measured_fraction_full	1.000

_diffraction_reflections_point_group_measured_fraction_max	0.998
_diffraction_reflections_theta_full	25.242
_diffraction_reflections_theta_max	29.997
_diffraction_reflections_theta_min	1.872
_diffraction_ambient_temperature	296.15
_diffraction_measured_fraction_theta_full	1.000
_diffraction_measured_fraction_theta_max	0.998
_diffraction_measurement_device_type	'Bruker APEX-II CCD'
_diffraction_measurement_method	'\f and \w scans'
_diffraction_radiation_type	MoK\alpha
_diffraction_radiation_wavelength	0.71073
_diffraction_source_current	30.0
_diffraction_source_power	1.2
_diffraction_source_voltage	40.0
_reflections_Friedel_coverage	0.000
_reflections_number_gt	3487
_reflections_number_total	4032

Compound 55

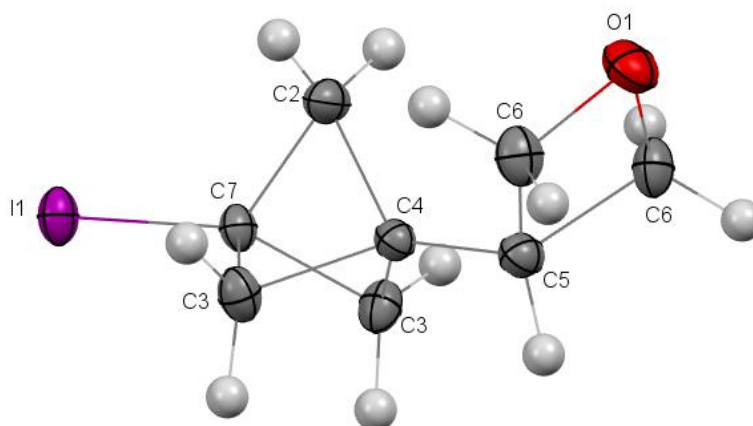


Figure S3. Molecular structure of **55** according to X-ray diffraction data. Thermal ellipsoids are shown at a 50% probability level.

Crystal structure determination of 55

data_v94

_chemical_formula_moiety	'C ₈ H ₁₁ IO'
_chemical_formula_sum	C ₈ H ₁₁ IO
_chemical_formula_weight	250.07
_space_group_crystal_system	'monoclinic'
_space_group_IT_number	11
_space_group_name_H-M_alt	'P 1 21/m 1'
_space_group_name_Hall	'-P 2yb'
_cell_length_a	5.5590(3)
_cell_length_b	8.6711(5)
_cell_length_c	8.8350(5)
_cell_angle_alpha	90
_cell_angle_beta	95.146(3)
_cell_angle_gamma	90
_cell_volume	424.15(4)
_cell_formula_units_Z	2
_cell_measurement_reflns_used	5895
_cell_measurement_temperature	273.15
_cell_measurement_theta_max	30.59

_cell_measurement_theta_min 2.31
 _shelx_estimated_absorpt_T_max 0.866
 _shelx_estimated_absorpt_T_min 0.524
 _exptl_absorpt_coefficient_mu 3.707
 _exptl_absorpt_correction_T_max 0.7461
 _exptl_absorpt_correction_T_min 0.3653
 _exptl_absorpt_correction_type multi-scan
 _exptl_absorpt_process_details SADABS
 _exptl_crystal_colour colourless
 _exptl_crystal_colour_primary colourless
 _exptl_crystal_density_diffn 1.958
 _exptl_crystal_description plate
 _exptl_crystal_F_000 240
 _exptl_crystal_size_max 0.2
 _exptl_crystal_size_mid 0.19
 _exptl_crystal_size_min 0.04
 _diffn_reflms_av_R_equivalents 0.0668
 _diffn_reflms_av_unetI/netI 0.0418
 _diffn_reflms_Laue_measured_fraction_full 0.999
 _diffn_reflms_Laue_measured_fraction_max 0.999
 _diffn_reflms_limit_h_max 7
 _diffn_reflms_limit_h_min -7
 _diffn_reflms_limit_k_max 12
 _diffn_reflms_limit_k_min -12
 _diffn_reflms_limit_l_max 12
 _diffn_reflms_limit_l_min -12
 _diffn_reflms_number 7702
 _diffn_reflms_point_group_measured_fraction_full 0.999
 _diffn_reflms_point_group_measured_fraction_max 0.999
 _diffn_reflms_theta_full 25.242
 _diffn_reflms_theta_max 29.998
 _diffn_reflms_theta_min 3.298
 _diffn_ambient_temperature 273.15
 _diffn_measured_fraction_theta_full 0.999
 _diffn_measured_fraction_theta_max 0.999

_diffraction_measurement_device_type 'Bruker APEX-II CCD'
_diffraction_measurement_method '\f and \w scans'
_diffraction_radiation_type MoK\alpha
_diffraction_radiation_wavelength 0.71073
_diffraction_source_current 30.0
_diffraction_source_power 1.2
_diffraction_source_voltage 40.0
_reflections_Friedel_coverage 0.000
_reflections_number_gt 1237
_reflections_number_total 1320

Compound **2k**

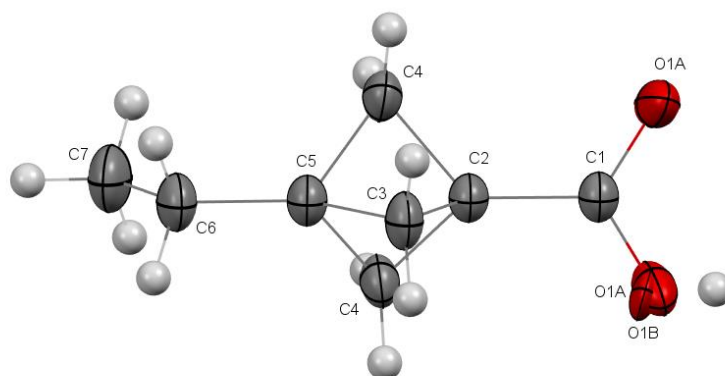


Figure S4. Molecular structure of **2k** according to X-ray diffraction data. Thermal ellipsoids are shown at a 50% probability level.

Crystal structure determination of **2k**

data_v59

_chemical_formula_sum	'C ₈ H ₁₂ O ₂ '
_chemical_formula_weight	140.18
_space_group_crystal_system	'monoclinic'
_space_group_IT_number	12
_space_group_name_H-M_alt	'C 1 2/m 1'
_space_group_name_Hall	'-C 2y'
_cell_length_a	13.2367(9)
_cell_length_b	9.0277(9)
_cell_length_c	8.0716(5)
_cell_angle_alpha	90
_cell_angle_beta	123.741(6)
_cell_angle_gamma	90
_cell_volume	802.06(12)
_cell_formula_units_Z	4
_cell_measurement_reflns_used	1075

_cell_measurement_temperature	296.15
_cell_measurement_theta_max	21.75
_cell_measurement_theta_min	2.92
_shelx_estimated_absorpt_T_max	0.993
_shelx_estimated_absorpt_T_min	0.984
_exptl_absorpt_coefficient_mu	0.082
_exptl_crystal_colour	colourless
_exptl_crystal_density_diffn	1.161
_exptl_crystal_description	block
_exptl_crystal_F_000	304
_exptl_crystal_size_max	0.2
_exptl_crystal_size_mid	0.1
_exptl_crystal_size_min	0.09
_diffn_reflms_av_R_equivalents	0.0842
_diffn_reflms_av_unetI/netI	0.0373
_diffn_reflms_Laue_measured_fraction_full	1.000
_diffn_reflms_Laue_measured_fraction_max	1.000
_diffn_reflms_limit_h_max	15
_diffn_reflms_limit_h_min	-15
_diffn_reflms_limit_k_max	10
_diffn_reflms_limit_k_min	-10
_diffn_reflms_limit_l_max	9
_diffn_reflms_limit_l_min	-8
_diffn_reflms_number	5879
_diffn_reflms_point_group_measured_fraction_full	1.000
_diffn_reflms_point_group_measured_fraction_max	1.000
_diffn_reflms_theta_full	24.995
_diffn_reflms_theta_max	24.995
_diffn_reflms_theta_min	2.918
_diffn_ambient_temperature	296.15
_diffn_measured_fraction_theta_full	1.000
_diffn_measured_fraction_theta_max	1.000
_diffn_measurement_method	'\f and \w scans'
_diffn_radiation_type	MoK\alpha
_diffn_radiation_wavelength	0.71073

_diffn_source_current	30.0
_diffn_source_power	1.2
_diffn_source_voltage	40.0
_reflns_Friedel_coverage	0.000
_reflns_number_gt	609
_reflns_number_total	758

Compound 22k

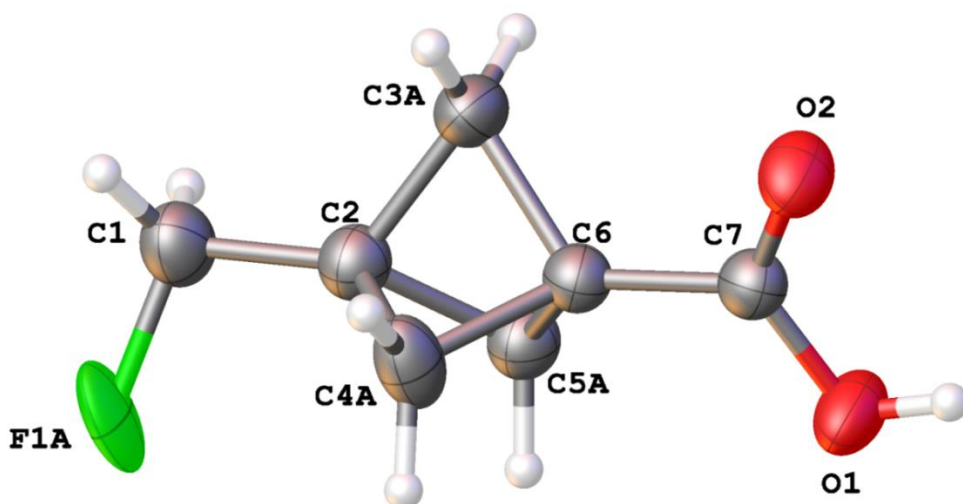


Figure S5. Molecular structure of **22k** according to X-ray diffraction data. Thermal ellipsoids are shown at a 50% probability level.

Crystal structure determination of 22k

data_v90

_chemical_formula_moiety	'C ₇ H ₉ FO ₂ '
_chemical_formula_weight	144.14
_cell_length_a	5.7180(3)
_cell_length_b	9.6081(4)
_cell_length_c	13.0730(6)
_cell_angle_alpha	90
_cell_angle_beta	91.709(3)
_cell_angle_gamma	90
_cell_volume	717.90(6)
_cell_formula_units_Z	4
_cell_measurement_reflns_used	3192
_cell_measurement_temperature	273.15
_cell_measurement_theta_max	26.36
_cell_measurement_theta_min	2.63
_shelx_estimated_absorpt_T_max	0.982
_shelx_estimated_absorpt_T_min	0.978
_exptl_absorpt_coefficient_mu	0.113

_exptl_crystal_colour	colourless
_exptl_crystal_colour_primary	colourless
_exptl_crystal_density_diffn	1.334
_exptl_crystal_description	block
_exptl_crystal_F_000	304
_exptl_crystal_size_max	0.2
_exptl_crystal_size_mid	0.2
_exptl_crystal_size_min	0.16
_diffn_reflms_av_R_equivalents	0.0353
_diffn_reflms_av_unetI/netI	0.0198
_diffn_reflms_Laue_measured_fraction_full	1.000
_diffn_reflms_Laue_measured_fraction_max	1.000
_diffn_reflms_limit_h_max	6
_diffn_reflms_limit_h_min	-6
_diffn_reflms_limit_k_max	10
_diffn_reflms_limit_k_min	-11
_diffn_reflms_limit_l_max	15
_diffn_reflms_limit_l_min	-15
_diffn_reflms_number	8777
_diffn_reflms_point_group_measured_fraction_full	1.000
_diffn_reflms_point_group_measured_fraction_max	1.000
_diffn_reflms_theta_full	25.000
_diffn_reflms_theta_max	25.000
_diffn_reflms_theta_min	2.631
_diffn_ambient_temperature	273.15
_diffn_measured_fraction_theta_full	1.000
_diffn_measured_fraction_theta_max	1.000
_diffn_measurement_device_type	'Bruker APEX-II CCD'
_diffn_measurement_method	'\f and \w scans'
_diffn_radiation_type	MoK\alpha
_diffn_radiation_wavelength	0.71073
_diffn_source_current	30.0
_diffn_source_power	1.2
_diffn_source_voltage	40.0
_reflms_Friedel_coverage	0.000

_reflns_number_gt	1094
_reflns_number_total	1268

Analysis of Aqueous Solubility

Study Objective

Test articles (**EN300-1653315 (91)**, **EN300-16170 (Benzocaine)**, **EN300-37158947 (94)**, **EN300-7414506 (Buclizine)**) and a reference compound (Ondansetron) were assessed for kinetic solubility in phosphate-buffered saline, pH 7.4 and a reference compound (Ondansetron) were assessed for kinetic solubility in phosphate-buffered saline, pH 7.4.

Reagents and consumables

Phosphate buffered saline, pH 7.4 (Sigma-Aldrich, USA; Cat #P3813)

Acetonitrile Chromasolv, gradient grade, for HPLC, $\geq 99.9\%$ (Sigma-Aldrich, USA; Cat #34851)

Methanol, for HPLC, $\geq 99.9\%$ (Sigma-Aldrich, Cat #34860)

Ondansetron base powder (Enamine, Ukraine, Cat # EN300-117273)

Verapamil hydrochloride (Sigma Aldrich, USA; Cat #V4629)

DMSO (Sigma-Aldrich, USA; Cat # 34869)

Costar 96 Well Assay Blocks (Corning, USA; Cat # 3958)

MultiScreen HTS 96 Well Filter Plates (Millipore, Ireland; Cat # MSSLBPC10)

UV-Star® 96 Well Microplate (Greiner Bio-One, Germany; Cat #655801)

Matrix Disposable pipette tips (ThermoScientific, USA; Cat ## 8041, 7622, 7321)

Flex-Tubes Microcentrifuge Tubes, 1.5 mL (Eppendorf, Germany; Cat # 22364111)

Matrix Storage tubes, 1.4 mL (ThermoScientific, USA; Cat # 4247)

Phenomenex Luna® C18 HPLC column, 2.0×30 mm, 3 μ m (Cat #00A-4162-B0)

Equipment

Water purification system Millipore Milli-Q Gradient A10 (Sartorius Arium™ Mini)

Thermomixer R Block, 1.5 mL (Eppendorf, Germany; Cat # 5355)

Matrix Multichannel Electronic Pipette 2-125 μ L, 5-250 μ L, 15-1250 μ L (Thermo Scientific, USA; Cat ## 2011, 2012, 2004)

Triple quadrupole mass-detector API 5000 with Turbo V Ion Source (AB Sciex, Canada)

SpectraMax Paradigm™ Reader (Multi-Mode Detection Platform, Product # 33270-1279)

Multi-Well Plate Vacuum Manifold (Pall Corporation, USA; Product # 5014)

Vacuum pump (Millipore, USA; Model # XX5500000)

Analytical System

The measurements were performed using a SpectraMax Paradigm reader in UV-Vis mode. The data were acquired and analyzed using SoftMax Pro v.5.4 (Molecular Devices) and Excel 2010 data analysis software. The measurements for poorly UV-adsorbing compounds (**EN300-1653315 (91)**, **EN300-37158947 (94)**, and **EN300-7414506 (Buclizine)**) were performed using the Shimadzu Prominence

HPLC system including vacuum degasser, gradient pumps, reverse phase column, column oven, and autosampler. The HPLC system was coupled with a tandem mass spectrometer API 5000 (PE Sciex). The TurboIonSpray ion source was used in both positive and negative ion modes. Acquisition and analysis of the data were performed using Analyst 1.6.3 software.

Methods

Kinetic solubility assay was performed according to Enamine's aqueous solubility SOP. Briefly, using a 20 mM stock solution of the compound in 100% DMSO dilutions were prepared to a theoretical concentration of 400 μ M in duplicates in phosphate-buffered saline pH 7.4 (138 mM NaCl, 2.7 mM KCl, 10 mM K-phosphate) with 2% final DMSO. The experimental compound dilutions in PBS were further allowed to equilibrate at 25°C on a thermostatic shaker for two hours and then filtered through HTS filter plates using a vacuum manifold. The filtrates of test compounds were diluted 2-fold with acetonitrile with 2% DMSO before measuring.

In parallel, compound dilutions in 50% acetonitrile/PBS were prepared to theoretical concentrations of 1 μ M, 10 μ M, 25 μ M, 50 μ M, 100 μ M, and 200 μ M with 2% final DMSO to generate calibration curves. Ondansetron was used as a reference compound to control proper assay performance. The calibration solutions and incubation samples were diluted 2-fold with acetonitrile containing internal standard and were analyzed using the HPLC system coupled with a tandem mass spectrometer. The effective range of this assay is approximately 1-400 μ M, and the compounds returning values close to the upper limit of the range may have higher actual solubility (e.g. 5'-deoxy-5-fluorouridine).

Results

The solubility data of the test and reference compounds are listed in the table below. The calibration curves are shown in Appendix*.

Table S1. Solubility data (1st batch)

Compound ID	PBS solubility, pH 7.4, μM			SE
	Incubation 1	Incubation 2	Mean	
Ondansetron	113	108	111**	2.5
EN300-1653315 (91)	322	315	319	3.5
EN300-16170 (Benzocaine)	386	384	385	1.4

*Goodness of fit (R^2) in all titration curves as well as the variations between repeat measurements indicates a high quality of the experimental data in the current batch of test articles.

**Ondansetron solubility data are consistent with those previously obtained.

Table S2. Solubility data (2nd batch)

Compound ID	PBS solubility, pH 7.4, μM			SE
	Incubation 1	Incubation 2	Mean	
Ondansetron	118	111	115**	3.4
EN300-7414506 (Buclizine)	0.3	0.1	≤ 1	-
EN300-37158947 (94)	0.1	0.04	≤ 1	-

*Goodness of fit (R^2) in all titration curves as well as the variations between repeat measurements indicates a high quality of the experimental data in the current batch of test articles.

**Ondansetron solubility data are consistent with those previously obtained.

APPENDIX

1st batch

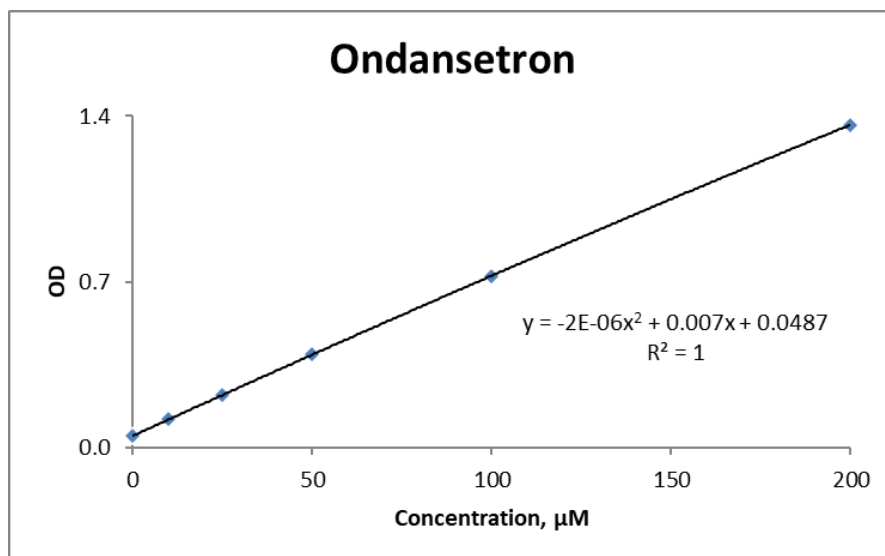


Figure S6. Calibration curve for **Ondansetron**

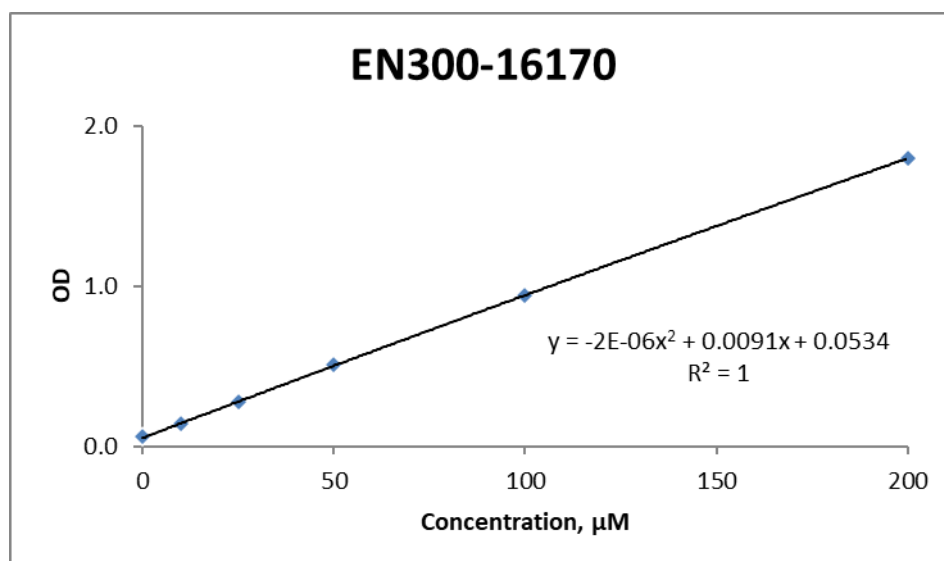


Figure S7. Calibration curve for **EN300-16170 (Benzocaine)**

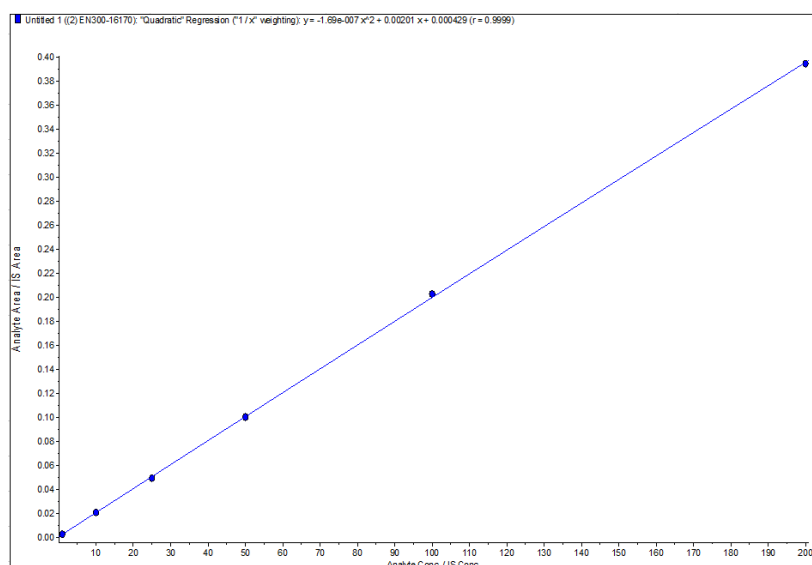


Figure S8. Calibration curve for EN300-1653315 (91)

2nd batch

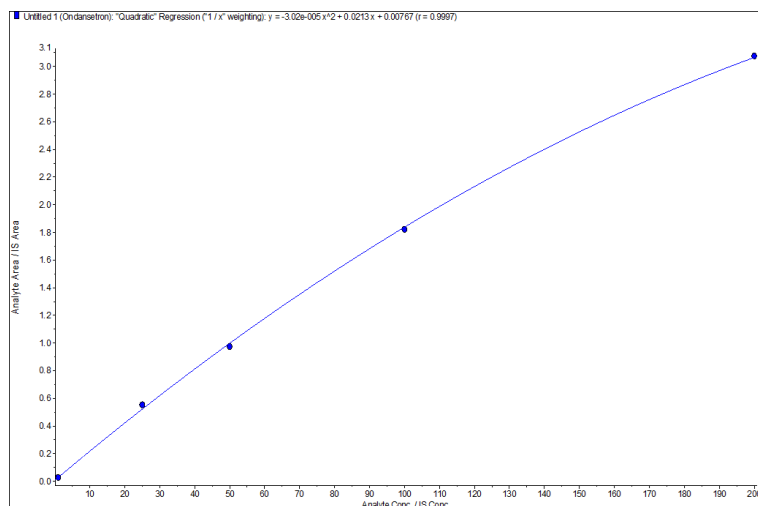


Figure S9. Calibration curve for Ondansetron

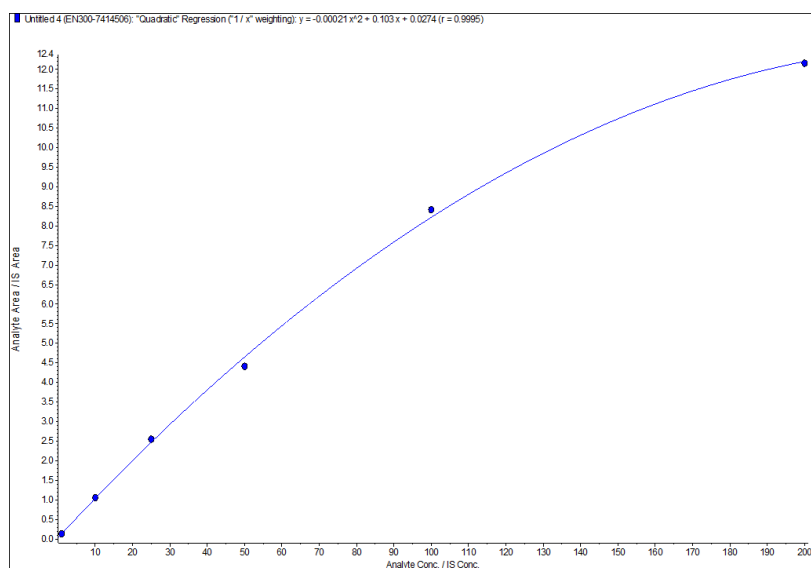


Figure S10. Calibration curve for EN300-7414506 (Buclizine)

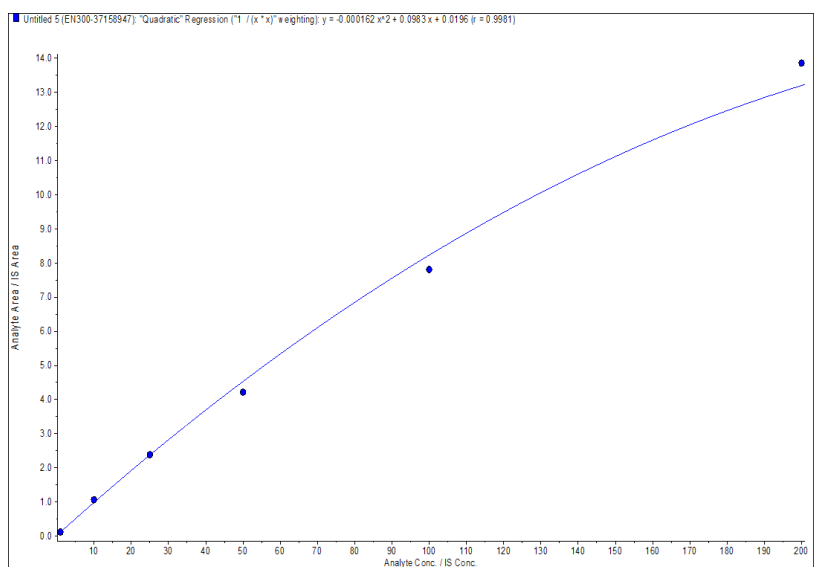


Figure S11. Calibration curve for EN300-37158947 (94)

Determination of Distribution Coefficient (LogD, pH 7.4)

The aim of this study was to determine distribution coefficients for the test articles (**EN300-1653315 (91)**, **EN300-16170 (Benzocaine)**, **EN300-37158947 (94)**, **EN300-7414506 (Buclizine)**) and reference compound (Mebendazole) in *n*-octanol – phosphate-buffered saline (PBS), pH 7.4. The distribution coefficient (or LogD) is a logarithm of the ratio of drug concentrations in two immiscible solvents, typically pH-buffered water and *n*-octanol. It is a measure of the hydrophobic/hydrophilic properties of a given molecule. The partition of test compounds is determined using a shake-flask method, which involves mixing a certain amount of the solute of interest in defined volumes of *n*-octanol and an aqueous buffer of choice followed by equilibration of the mixture by incubation with efficient mixing. Then, the distribution of the compounds in each solvent was controlled using LC-MS/MS.

Reagents and consumables

DMSO Chromasolv Plus, HPLC grade, $\geq 99.7\%$ (Sigma-Aldrich, USA; Cat #34869)

Acetonitrile Chromasolv, gradient grade, for HPLC, $\geq 99.9\%$ (Sigma-Aldrich, USA; Cat #34851)

Formic acid for mass spectrometry, $\sim 98\%$ (Fluka, USA; Cat #94318)

Phosphate buffered saline, tablet (Sigma-Aldrich, USA; Cat # P4417)

1-Octanol ACS grade, $\geq 99\%$ (Sigma-Aldrich, USA; Cat # 472328)

Mebendazole analytical standard, $\geq 98\%$, HPLC (Sigma-Aldrich, USA; Cat # M2523)

DMSO stock solutions of the test compounds 10 mM

Phenomenex Luna® C18 HPLC column, 2.0 × 30 mm, 3 μm (Cat #00A-4162-B0)

1.1 mL microtubes in microracks, pipettor tips (Thermo Scientific, USA).

National Scientific MicroTube™ Rack (Thermo Fisher Scientific, USA; Cat # TN094612R)

Equipment

Gradient HPLC system (Shimadzu, Japan)

Triple quadrupole mass-detector API 5000 with Turbo V Ion Source (AB Sciex, Canada)

VWR Membrane Nitrogen Generators N2-04-L1466, nitrogen purity 99%+ (VWR, USA)

MTR22 Multi Mix Rotator (UNICO, USA)

Laboratory Centrifuge, Sigma 4-15C, Qiagen (SIGMA GmbH, Germany)

Water purification system Millipore Milli-Q Gradient A10 (Millipore, France)

Multichannel Electronic Pipettes 2-125 μL , 5-250 μL , 15-1250 μL , Matrix (Thermo Scientific, USA; Cat ## 2001, 2002, 2004)

Analytical System

All measurements were performed using the Shimadzu Prominence HPLC system including vacuum degasser, gradient pumps, reverse phase column, column oven, and autosampler. Mass spectrometric analysis was performed using a tandem mass spectrometer API 5000 (PE Sciex) with Turbo V ion source and TurboIonSpray interface. The TurboIonSpray ion source was used in both positive and negative ion modes. Acquisition and analysis of the data were performed using Analyst 1.6.3 software.

Methods

Incubations were carried out in Eppendorf-type polypropylene microtubes in triplicates. A 2.5 μL aliquot of 20 mM DMSO stock of a test compound was added into the previously mutually saturated mixture containing 500 μL of PBS (pH 7.4) and 500 μL of octanol. The solution was mixed in a rotator for 1 hour at 30 rpm. Phase separation was assured by centrifugation for 2 min at 6000 rpm. The octanol phase was diluted 100-fold with 40% acetonitrile, and the aqueous phase (PBS buffer) was diluted 10-fold, the aqueous phase was analyzed without dilution. The samples (both phases) were analyzed using an HPLC system coupled with a tandem mass spectrometer. Mebendazole was used as a reference compound.

Calculations of the partition ratios were carried out using the equation below.

$$D = \frac{d_o \cdot S_o}{d_p \cdot S_p}$$

where: S_o – peak area of the analyte in octanol phase

S_p – peak area of the analyte in PBS buffer

d_o – dilution coefficient for octanol phase

d_p – dilution coefficient for aqueous phase

Results

LogD data for the reference compound (Mebendazole) and test compounds are provided in the table below.

Table S3. Experimental LogD, pH 7.4, batch 1st

Compound ID	Incuba-tion	S _p	S _o	D	LogD, pH 7.4	
Mebendazole	1	4.91E+04	4.43E+06	9.01E+02	2.96	2.9
	2	5.21E+04	4.44E+06	8.52E+02	2.93	
	3	5.46E+04	4.55E+06	8.33E+02	2.92	
	3	1.65E+04	2.68E+05	1.62E+02	2.21	
EN300-1653315 (91)	1	6.11E+04	8.19E+03	1.34E+00	0.13	0.1
	2	5.99E+04	7.79E+03	1.30E+00	0.12	
	3	5.95E+04	6.04E+03	1.02E+00	0.01	
EN300-16170 (Benzocaine)	1	2.58E+04	1.52E+05	5.86E+01	1.77	1.8
	2	2.42E+04	1.57E+05	6.48E+01	1.81	
	3	2.55E+04	1.44E+05	5.65E+01	1.75	

*Reliable measurable range is approximately -1 to 4.5.

Table S4. Experimental LogD, pH 7.4, batch 2nd

Compound ID	Injection	S _P	S _O	D	LogD, pH 7.4	
Mebendazole	1	8.72E+03	6.34E+05	7.27E+02	2.862	2.91
	2	9.34E+03	7.46E+05	7.99E+02	2.903	
	3	8.10E+03	7.22E+05	8.91E+02	2.951	
EN300-7414506 (Buclizine)	1	4.04E+02	1.18E+06	2.92E+04	4.466	4.46
	2	4.44E+02	1.22E+06	2.75E+04	4.439	
	3	4.35E+02	1.28E+06	2.94E+04	4.469	
EN300-37158947 (94)	1	7.31E+03	1.34E+06	1.83E+03	3.264	3.26
	2	7.67E+03	1.36E+06	1.77E+03	3.249	
	3	7.73E+03	1.37E+06	1.77E+03	3.249	

*Reliable measurable range is approximately -1 to 4.5.

Assessment of Metabolic Stability in Human Liver Microsomes

The objective of this study was to determine the metabolic stability of test articles (**EN300-1653315 (91)**, **EN300-16170 (Benzocaine)**, **EN300-37158947 (94)**, **EN300-7414506 (Buclizine)**) and reference compounds in human liver microsomes at five-time points over 40 minutes using HPLC-MS. Metabolic stability is defined as the percentage of parent compound lost over time in the presence of a metabolically active test system.

Reagents and consumables

DMSO Chromasolv Plus, HPLC grade, $\geq 99.7\%$ (Sigma-Aldrich, USA; Cat# 34869)

Acetonitrile Chromasolv, gradient grade, for HPLC, $\geq 99.9\%$ (Sigma-Aldrich, USA; Cat# 34851)

Methanol, HiPerSolv, HPLC-gradient grade, $\geq 99.9\%$ (VWR Chemicals, USA, Cat# 20864.320)

Potassium phosphate monobasic (Bio-Basic, Canada; Lot #N9016010)

Potassium phosphate dibasic (Bio-Basic, Canada; Lot #MA7100050)

Magnesium chloride hexahydrate (Santa Cruz Biotechnology, Inc., USA; sc-203126A)

Human Liver Microsomes: pooled, mixed gender (XenoTech, H0630/lot N#1210097)

Glucose-6-phosphate dehydrogenase from baker's yeast, type XV (Sigma-Aldrich, USA; Cat #G6378)

D-Glucose-6-phosphate monosodium salt (Santa Cruz Biotechnology, Inc., USA; sc-210728)

NADPH tetrasodium salt (BLD Pharmatech Ltd., Cat #BD116582)

Formic acid (Sigma-Aldrich, 94318)

Verapamil hydrochloride (Sigma Aldrich, USA; Cat #V4629)

Niclosamide (Sigma-Aldrich, USA; Cat #N3510)

DMSO stock solutions of the tested compounds 20 mM

(+,-) Propranolol hydrochloride (Sigma-Aldrich, P0884)

Imipramine hydrochloride (Sigma-Aldrich, I7379)

Diclofenac sodium salt (Sigma-Aldrich, D6899)

Phenomenex Luna® C18 HPLC column, 2.1 × 50 mm, 5 µm (Cat #5291-126)

Matrix™ 0.75 mL blank tubes (Cat #4170), pipettor tips (Thermo Scientific).

Equipment

Gradient HPLC system (Shimadzu)

Hybrid triple quadrupole/linear ion trap mass-detector 4000 QTRAP with Turbo V ion source (AB Sciex, Canada)

Triple quadrupole mass-detector API 5000 with Turbo V Ion Source (AB Sciex, Canada)

Nitrogen generator N2-04-L1466, nitrogen purity 99%+ (Whatman)

Environmental Incubator Shaker G24; Digital Refrigerated Incubator/Shaker Innova 4330 (New Brunswick Scientific)

Water purification system Millipore Milli-Q Gradient A10 (Millipore, France)

Multichannel pipettors 1-30 μL , 2-125 μL , 30-850 μL (Thermo Scientific)

Analytical System

All measurements were performed using the Shimadzu HPLC system including vacuum degasser, gradient pumps, reverse phase HPLC column, column oven, and autosampler. Mass spectrometric analysis was performed using an API 4000 QTRAP and API 5000 mass spectrometers from Applied Biosystems/ MDS Sciex (AB Sciex) with Turbo V ion source and TurboIonSpray interface. The TurboIonSpray ion source was used in both positive and negative ion modes. The data acquisition and system control was performed using Analyst 1.6.3 software from AB Sciex.

Methods

Microsomal incubations were carried out in 96-well plates in 5 aliquots of 30 μL each (one for each time point). Liver microsomal incubation medium comprised of phosphate buffer (100 mM, pH 7.4), MgCl_2 (3.3 mM), NADPH (3 mM), glucose-6-phosphate (5.3 mM), glucose-6-phosphate dehydrogenase (0.67 units/mL) with 0.42 mg of liver microsomal protein per mL. In the control reactions, the NADPH-cofactor system was substituted with phosphate buffer. Test compounds (2 μM , final solvent concentration 1.6 %) were incubated with microsomes at 37°C, shaking at 100 rpm. Five time points over 40 minutes were analyzed. The reactions were stopped by adding 5 volumes of acetonitrile with internal standard to incubation aliquots, followed by protein sedimentation by centrifuging at 5500 rpm for 5 minutes. Each reaction was performed in duplicates. Supernatants were analyzed using the HPLC system coupled with a tandem mass spectrometer.

The elimination constant (k_{el}), half-life ($t_{1/2}$), and intrinsic clearance (Cl_{int}) were determined in a plot of $\ln(\text{AUC})$ versus time, using linear regression analysis:³

$$k_{\text{el}} = -\text{slope}$$

$$t_{1/2} = \frac{0.693}{k}$$

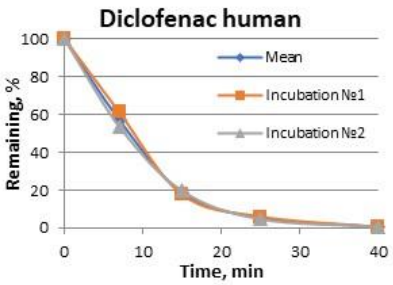
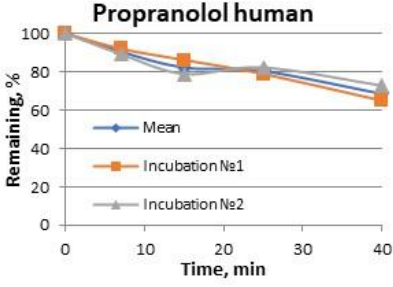
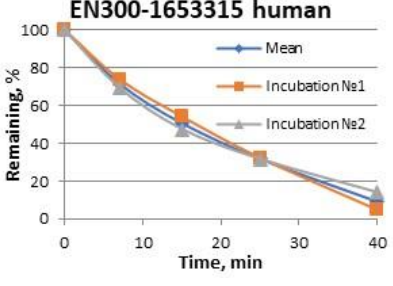
$$Cl_{\text{int}} = \frac{0.693}{t_{1/2}} \times \frac{\mu\text{L}_{\text{incubation}}}{\text{mg}_{\text{microsomes}}}$$

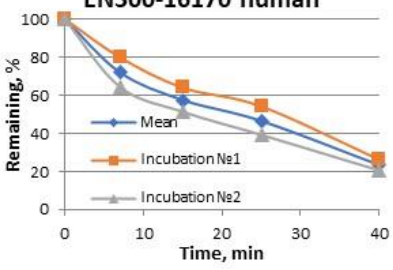
³ In order to indicate the quality of the linear regression analysis, the R^2 (determination coefficient) values are provided. In some cases, the last time point is excluded from the calculations to ensure acceptable logarithmic linearity of decay.

Results

Human microsomal stability data for reference and test compounds are provided in the tables below.

Table S5. Human microsomal stability, 1st batch

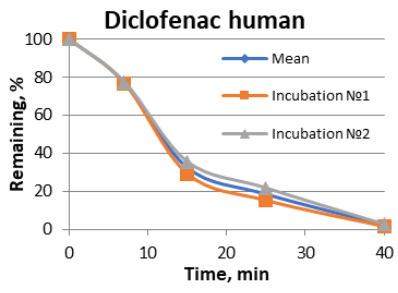
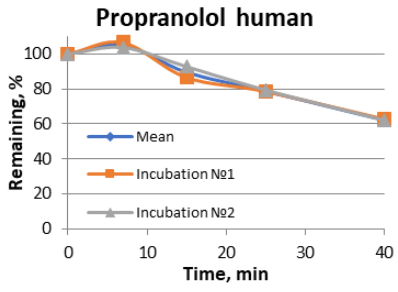
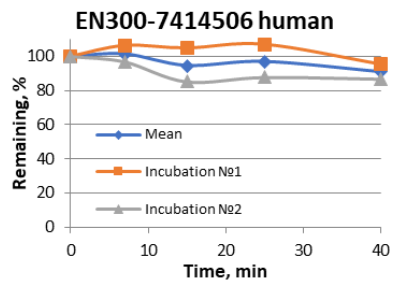
Compound ID	Time, min	Analyte Peak Area		Analyte Peak Area, Mean of 2	% Remaining, Mean of 2	R ²	k _{el} , min ⁻¹	t _{1/2} , min	Cl _{int} , µl/min/mg	% Remaining without cofactor, Mean of 2
		Inc. 1	Inc. 2							
Diclofenac human	0	2.88E-02	3.39E-02	3.14E-02	100	0.996	0.127	5.4	307	100
	7	1.76E-02	1.82E-02	1.79E-02	57					
	15	5.06E-03	6.74E-03	5.90E-03	19					
	25	1.68E-03	1.68E-03	1.68E-03	5					
	40	1.20E-04	3.03E-04	2.11E-04	1					97
Propranolol human	0	5.77E-02	5.95E-02	5.86E-02	100	0.962	0.009	79.8	21	100
	7	5.31E-02	5.31E-02	5.31E-02	91					
	15	4.97E-02	4.69E-02	4.83E-02	82					
	25	4.55E-02	4.89E-02	4.72E-02	81					
	40	3.75E-02	4.33E-02	4.04E-02	69					107
EN300-1653315 human (91)	0	3.03E-03	3.14E-03	3.09E-03	100	0.975	0.058	12.0	140	100
	7	2.24E-03	2.18E-03	2.21E-03	72					
	15	1.64E-03	1.49E-03	1.56E-03	51					
	25	9.78E-04	9.93E-04	9.85E-04	32					
	40	1.42E-04	4.35E-04	2.89E-04	9					5#

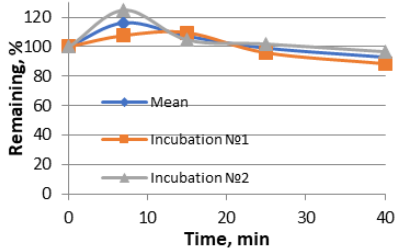
EN300-16170 human Benzocaine	0	2.25E-02	2.36E-02	2.31E-02	100	0.982	0.034	20.1	83	100
	7	1.80E-02	1.52E-02	1.66E-02	72					
	15	1.44E-02	1.21E-02	1.32E-02	57					
	25	1.22E-02	9.24E-03	1.07E-02	47					
	40	5.95E-03	4.84E-03	5.40E-03	23					20#

* Parameter should be considered as approximate due to the high stability of the compound

#“No cofactor” control data indicates the instability of the compound in the test system without cofactors

Table S6. Human microsomal stability, 2nd batch

Compound ID	Time, min	Peak Area Ratio		Peak Area Ratio, Mean of 2	% Remaining, Mean of 2	R	k_{el} , min ⁻¹	$t_{1/2}$, min	Cl_{int} , μ L/min/mg	% Remaining without cofactor, Mean of 2
		Inc. 1	Inc. 2							
Diclofenac human	0	3.41E-02	3.41E-02	3.41E-02	100	0.980	0.096	7.2	231	100
	7	2.62E-02	2.64E-02	2.63E-02	77					
	15	1.00E-02	1.21E-02	1.11E-02	32					
	25	5.24E-03	7.38E-03	6.31E-03	19					
	40	5.84E-04	8.68E-04	7.26E-04	2					90
Propranolol human	0	3.58E-02	3.64E-02	3.61E-02	100	0.968	0.013	53.5	31	100
	7	3.82E-02	3.78E-02	3.80E-02	105					
	15	3.10E-02	3.38E-02	3.24E-02	90					
	25	2.81E-02	2.89E-02	2.85E-02	79					
	40	2.24E-02	2.26E-02	2.25E-02	62					85
EN300-7414506 human (Buclizine)	0	7.42E-01	8.30E-01	7.86E-01	100	0.873	0.002*	284.3*	6*	100
	7	7.90E-01	8.04E-01	7.97E-01	101					
	15	7.79E-01	7.08E-01	7.44E-01	95					
	25	7.95E-01	7.29E-01	7.62E-01	97					
	40	7.08E-01	7.21E-01	7.15E-01	91					94

EN300-37158947 human (94)	0	6.60E-01	6.52E-01	6.56E-01	100	0.650	0.004*	194.9*	9*	100
	7	7.09E-01	8.16E-01	7.63E-01	116					
	15	7.21E-01	6.84E-01	7.03E-01	107					
	25	6.33E-01	6.66E-01	6.50E-01	99					
	40	5.85E-01	6.32E-01	6.09E-01	93					88

* Parameter should be considered as approximate due to the high stability of the compound

** “No cofactor” control data indicates the instability of the compound in the test system without cofactors

#Due to the rapid degradation of the compound, the metabolic stability parameters are considered ambiguous

Interpretation of microsomal stability assay data

The test compounds can be classified in terms of their microsomal stability into low, medium, and high clearance groups. Intrinsic Clearance (*in vitro*) can be recalculated to Intrinsic Clearance (*in vivo*) using literature data for liver weight and liver blood flow with the next equation¹:

$$\text{Predicted } in\ vivo\ CL_{int,u} = \frac{in\ vitro\ CL_{int} \times PBSF \times LW}{f_{u\ mic}\ or\ f_{u\ heps}}$$

where,

in vivo $CL_{int,u}$ – predicted *in vivo* intrinsic clearance, mL/min/kg

in vitro CL_{int} – *in vitro* microsomal clearance, mL/min/mg

PBSF – physiologically based scaling factor – the microsomal average recovery factor for microsomal predictions and hepatocellularity for hepatocyte predictions, mg/g

LW – liver weight/kg bodyweight, g/kg

$f_{u\ mic}\ or\ f_{u\ heps}$ – fraction unbound in either microsomes or hepatocytes (can be determined from Plasma Protein Binding study or assumed as 1, if it is unknown)

Using *in vivo* CL_{int} hepatic clearance can be predicted based on a “well-stirred” liver model using the next formula²:

$$CL_H = \frac{Q_H \times f_u \times CL_{int}}{Q_H + f_u \times CL_{int}}$$

where,

CL_H – predicted hepatic clearance, mL/min/kg

Q_H – liver blood flow, mL/min/kg

f_u – fraction unbound in the blood

CL_{int} – predicted *in vivo* clearance, mL/min/kg

¹. Wood, F. L., Houston, J. B., & Hallifax, D. (2017). Clearance prediction methodology needs fundamental improvement: Trends common to rat and human hepatocytes/microsomes and implications for experimental methodology. *Drug Metabolism and Disposition*, 45 (11), 1178–1188. <https://doi.org/10.1124/dmd.117.077040>.

². Laveé, T., & Funk, C. (2007). *In vivo* absorption, distribution, metabolism, and excretion studies in Discovery and Development. *Comprehensive Medicinal Chemistry II*, 31–50. <https://doi.org/10.1016/b0-08-045044-x/00118-8>.

³. Barter, Z. E., *et al.*, Scaling factors for the extrapolation of *in vivo* metabolic drug clearance from *in vitro* data: reaching a consensus on values of human microsomal protein and hepatocellularity per gram of liver, *Current Drug Metabolism*, 2007, 8, 33-45.

⁴. Iwatsubo T., *et al.*, Prediction of species differences (rats, dogs, humans) in the *in vivo* metabolic clearance of YM796 by the liver from *in vitro* data, *Journal of Pharmacology and Experimental Therapeutics*, 1997, 283, 462-469.

Antinociceptive effect of Benzocaine and its saturated analog **91**

Efficacy study for compounds **EN300-16170-HCl** (Benzocaine*HCl) and **EN300-1653315-HCl** (compound **91***HCl) in the tail flick test in CD-1 female mice

List of abbreviations

AUC	The area under the curve
G	Gauge
SC	Subcutaneous

Study objective

The study aimed to investigate the antinociceptive effect of compound **91** in the tail-flick test in mice. The effect of a single local subcutaneous administration of compound **EN300-2848707 (91)** at the dose of 6.5 mg/mice was tested in female CD-1 mice. The tail-flick latency was registered by analgesia meter 5, 15, 30, 60, 120, and 180 min after a single compound administration. Benzocaine hydrochloride **EN300-16170 (Benzocaine)** was used as a reference compound. The mice of the control group were treated with glycerol.

Materials

The test compounds were provided from the Enamine store.

Reagents and materials used for formulation of the test substances

Physiological saline (Pharmaceutical Firm “Yuria-Pharm”, Ukraine, Cat # AA1807/1-1)

Glycerol (“Arterium”, Ukraine, Lot# 233142)

Sodium hydroxide (Bio Basic Canada Inc., Canada, Cat # SB0617)

Reagents for anesthesia

CO₂

Other Materials

Syringes for injection, 1 mL, 29G needle, Medicare S-3SI1,0 (Dopomoga-1 Ltd, Ukraine)

Plastic tubes of different volumes (Falcon, Eppendorf)

CODA® Animal Holders (Kent Scientific Corporation, USA, Cat # HLD-MS)

Analytical balances Sartorius LE225D (Germany, calibration weight class E2)

Balance Scout Pro SP2001 (USA, Class B)

Vortex mixer “Fisher Scientific” (Fisher Scientific. KG, Germany; IP-40)

pH-meter (Beckman Coulter PHI410 with Mettler Toledo LE422)

Dosing pipettes Eppendorf Research (100-1000µl; 10-100µl; 2-20 µl) (Germany)

Analgesia meter (Columbus Instruments, USA).

Test systems

Animals

	Male	Female
Species/strain:	—	Mice, CD-1
Age:	—	11-13 weeks
Body weight:	—	22.3 - 25.6 g
Number of animals ordered:	—	20
Number of animals in the study:	—	15

Animal care

Study design, animal selection, handling, and treatment were all by the Bienta efficacy study protocols and Standard Operation Procedure, and the Animal Care Guidelines. Breeders. The animals were obtained from the Animal Facility of Bienta.

The hygienic class was conventional at arrival. The animals were kept in standard conventional conditions during the study.

Animal species and strain selection

CD-1 mouse strain is commonly used for the mouse model of antinociception.

Animal identification

The animals were individually identified by an earmark. The cages were labeled with tags indicating the ID numbers and earmarks of the mice, the study code, sex, administration route, and start/finish dates of the experimental period.

Housing conditions

Hygienic level:	Good conventional
Type of animal cages:	Polypropylene bottoms with stainless steel wire mesh lids
Cage size:	H x W x D: 12.0 × 17.5 × 28.0 cm
Cage enrichment:	Mouse Hut, 3.75"L X 3"W X 1.75" H (Bio-Serv)
Cleaning:	Changing the bedding twice a week
Number of animals per cage:	5

Environmental conditions

Air exchange:	15-20 times/hour
Temperature:	22 ± 3 °C
Relative humidity:	40 – 70%
Lighting:	12-hour light/dark cycles.

Feed. Mice had free access to standardized rodent diets.

Drinking. Mice had free access to acidified boiled tap water.

Acclimatization period

During the seven days of the acclimatization period, two animals were kept per cage with an enriched environment. All animals were under observation and only animals without any clinical symptoms of illness were taken into the study.

Randomization

Animals were randomized based on body weight and assigned to the groups by the Bienta SOP RD-01.

Ethical statement

All *in vivo* protocols were approved by Bienta's Animal Care and Use Committee and in adherence with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes⁴. The experiments were performed according to the Standard Operating Procedures/Manuals of the Bienta.

⁴The European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (1986, ETS 123, ISSN 0070-105X)

Study design

Dose levels, group division

15 mice were randomly divided into 3 groups based on body weight: Benzocaine hydrochloride, **EN300-16170 (Benzocaine)**, **EN300-1653315 (91)**, and **Vehicle** (glycerol), 5 mice per group.

Groups characteristics

15 female CD-1 mice 11-12 weeks old were taken into the study. Body weights ranged from 22.3 to 26.8 g with an average body weight across all groups of 24.4 g (SD = 1.53; CV = 6.27%).

Compound administration

Drug formulation. Route and volume of administration

Benzocaine hydrochloride **EN300-16170 (Benzocaine)** served as a reference compound. Benzocaine hydrochloride was dissolved in glycerol at a concentration of 13%. **EN300-1653315 (91)** testing compound was dissolved in 0.9% sodium chloride at the same concentration; the pH of the solution was adjusted to pH 5.6 with 2M NaOH. Glycerol was served as a **Vehicle**. The final concentration for all compounds' formulations was 130 mg/mL.

Subcutaneous (SC) route of administration was used in the study for all drugs. Only a freshly prepared formulation of **EN300-16170 (Benzocaine)** and **EN300-1653315 (91)** was used for each dosing; each working formulation batch was prepared immediately before the administration. The dosing volume for **EN300-16170 (Benzocaine)** and **EN300-1653315 (91)** was 50 µL/mouse. The working formulations were administered as transparent clear solutions for all doses for all compounds.

Frequency and application duration

Each animal was randomly single-treated with one of the tested substances **EN300-16170 (Benzocaine)**, **EN300-1653315 (91)**, or **Vehicle** 5 min before the first response-to-heat latency assay.

Duration of the experimental period

Seven days of an acclimatization period and two days of the experiment, 1 day for data analysis and reporting.

Examinations

Tail flick test

The antinociceptive effect of benzocaine and its analogs was assessed by the tail-flick assay, which was based on exposure of the tail to localized infrared irradiation and further registration of the animal response-to-heat latency. The site of tail exposure to infrared radiation was leveled and is at a distance of

2-3 cm below the base of the tail. Tail flick latency was registered by an analgesia meter (Columbus Instruments, USA). Each measurement was performed in triplicates. The cut-off time for the heat source was set at 12 sec to avoid tissue damage. The 50 µl of test formulations or vehicle was slowly subcutaneously injected 2 cm distally from the tail base by a 29G needle, which remained for a few seconds at the site of injection to prevent leakage of the solution from the hole. Treatment of mice from one group was conducted inconsistently to provide unbiased measurement results. The level of analgesia for each mouse was measured by tail flick assay 5, 10, 15, 30, 60, 120, and 180 min after compound injection. Each mouse was immobilized by a holder and kept in it for 1 min before time-point measurement to exclude a false-positive response. The normal reaction time for all animals (zero point) was determined in the tail flick assay before administration of the test compound.

Body weight

Animals were weighed once on the day of randomization.

Euthanasia

Euthanasia was performed by CO₂ inhalation by trained personnel according to the Bienta Standard Operation Procedures. All procedures were approved by the Bienta's Animal Care and Use Committee by the OECD recommendations⁵.

Statistical analysis

Student's t-test was used for statistical comparisons according to the Standard Operating Procedures/Manuals of the Bienta. Results of the tail flick assay are represented as means ± SEM. The trapezoidal rule was used to determine the area under the curve (AUC) of withdrawal latency. The difference between the mean AUC for the vehicle group was compared with the mean AUC for every other group. P value < 0.05 was considered statistically significant. No mice were excluded from the results.

Data management

Original data were recorded, collected, and stored in a single Study File and maintained according to the Standard Operating Procedure.

⁵OECD Guidance Document on the Recognition, Assessment and Use of Clinical Signs as Humane End Points for Experimental Animals Used in Safety Evaluation, Series on Testing and Assessment, N°19, ENV/JM/MONO (2000)7, OECD, Paris. (2000).

Results

Table S7. Withdrawal latency (sec) and AUC of the antinociceptive effect of the benzocaine analog in the tail flick test

Groups	Mice #	Time after administration, min							AUC
		0	5	15	30	60	120	180	
Vehicle	8	2.70	6.00	3.90	3.27	4.15	2.42	2.3	215.0
	11	2.95	1.02	4.28	3.61	3.36	2.64	2.03	163.0
	16	2.32	2.40	3.52	1.91	2.53	3.10	2.65	130.4
	21	1.67	2.50	2.25	2.46	2.30	2.19	2.6	59.63
	26	4.16	3.18	1.36	1.53	1.90	1.60	2.39	17.95
M		2.76	3.02	3.06	2.56	2.85	2.39	2.39	117.20
SD		0.92	1.84	1.22	0.88	0.90	0.55	0.25	79.06
SE		0.41	0.82	0.55	0.39	0.40	0.25	0.11	35.36
Benzocaine	2	3.57	12.00	12.00	12.00	12.00	7.32	3.75	1251.0
	13	2.77	4.36	12.00	9.87	2.65	3.02	2.97	441.3
	17	3.54	2.85	12.00	10.34	12.00	12.00	12.00	1673.0
	22	3.37	4.76	9.25	12.00	9.97	3.13	2.6	784.2
	28	4.13	3.73	9.80	12.00	1.72	9.70	3.49	835.3
M		3.48	5.54	11.01	11.24	7.67	7.03	4.96	996.96
SD		0.49	3.68	1.37	1.05	5.08	3.98	3.96	474.80
SE		0.22	1.65	0.61	0.47	2.27	1.78	1.77	212.34
<i>t</i> -criteria compared to Vehicle Group		0.081	0.104	0.000005	0.0000003	0.035	0.016	0.093	0.002
Compound 91	5	2.62	12.00	12.00	3.28	2.21	2.53	5.61	379.9
	10	2.60	2.63	7.00	2.81	4.30	4.86	3.18	397.5
	12	2.50	1.09	3.71	2.67	1.70	4.76	2.53	204.2
	14	2.39	12.00	1.65	4.23	9.31	2.59	1.89	483.8
	15	3.07	7.30	4.96	4.00	3.68	2.54	12.00	532.4
M		2.64	7.00	5.86	3.40	4.24	3.46	5.04	399.56
SD		0.26	5.10	3.94	0.70	3.02	1.24	4.14	125.80
SE		0.12	2.28	1.76	0.31	1.35	0.55	1.85	56.26
<i>t</i> -criteria compared to Benzocaine group		0.008	0.447	0.024	0.000008	0.279	0.121	0.979	0.080
<i>t</i> -criteria compared to Vehicle Group		0.700	0.097	0.142	0.225	0.420	0.053	0.230	0.026

The tested compound **EN300-1653315 (91)** demonstrated weak antinociceptive activity compared to the reference substance.

Cytostatic effect by Buclizine and its saturated analog 94

Translationally controlled tumor protein (TCTP) is a promising target for cancer differentiation therapy due to its extreme down-regulation upon induction of transformation of malignant cell phenotype into normal that occurs in tumor reversion experiments. TCTP may be inhibited by antihistaminic drugs since the protein is involved in histamine signaling. Buclizine is a piperazine-derived antihistamine drug that has been used for the treatment of allergy symptoms and the prevention of nausea and vomiting. On the cellular level, buclizine demonstrates growth inhibition also known as cytostatic effect, which implies inhibition of cellular growth and proliferation without inflicting cell death. Resazurin reduction assay may be used to investigate the effect of the growth inhibition of buclizine and its analogs in human cancer cells (see reference: E.-J. Seo and T. Efferth, Interaction of antihistaminic drugs with human translationally controlled tumor protein (TCTP) as a novel approach for differentiation therapy, *Oncotarget* **2016**, 7, 16818-16839). The assay is based on the reduction of the indicator dye, resazurin, to the highly fluorescent resorufin by viable cells upon their respiration. Non-viable cells' mitochondria rapidly lose the metabolic capacity to reduce resazurin and do not produce fluorescent signal. Thus, the resazurin reduction assay was chosen for quantification of the drug's cytostatic effect.

Another indicator of the cell cycle arrest and cellular differentiation is the formation of lipid droplets that has been observed in breast cancer cells (see reference: H. Lee, A. Horbath, L. Kondiparthi et al. Cell cycle arrest induces lipid droplet formation and confers ferroptosis resistance, *Nat. Commun.* **2024**, 15, 79). Nile Red is a fluorescent dye that stains polar membrane lipids. It was chosen for quantification of the level of lipid droplet formation upon treatment with compounds using confocal fluorescent microscopy.

Cytostatic effect in resazurin assay

To assess cytostatic effect of tested compounds, MCF-7 cell line (ATCC, #HTB-2) was thawed and cultured in DMEM complete medium (10% FBS, 0.01 g L⁻¹ insulin, 1% non-essential amino acids, 1% sodium pyruvate). When cells reached 70-80% confluency, they were detached from the flask surface and seeded to sterile black wall 384-well plates (Falcon, #353962) at seeding density 6000 cells per well in 20 µL of 1% FBS Opti-MEM (ThermoFisher, #31985062) medium in each well. The plate was centrifuged at 40×g for 15 seconds and cultivated at 37 °C in the presence of 5% carbon dioxide overnight. On the next day, compounds in a volume of 30 µL per well were added. After that, the plate was centrifuged at 40×g for 15 seconds and incubated 72 hours in a carbon dioxide incubator. 10 mM stock of resazurin (Cayman Chemical, #14322) prepared earlier was diluted in sterile DPBS (pH = 7.4) to 250 µM concentration in the dark and then added at the volume of 12.5 µL per well to each well of the plate to outcome the final resazurin concentration of 50 µM. The plate was centrifuged at 40×g for 15 seconds and incubated at 37 °C for 3.5 hours.

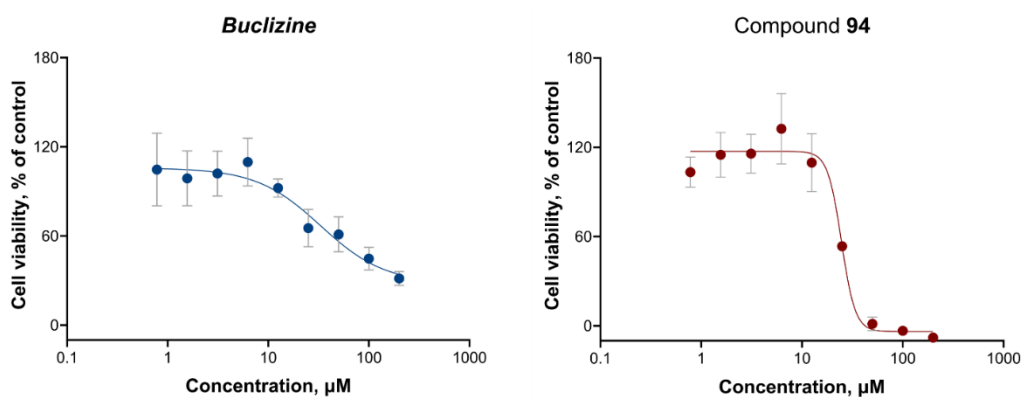


Figure S12. Resazurin reduction assay results for **Buclizine** and analog **94**, in MCF-7 cells. Data are represented as mean $\pm$ standard error for three technical repeats. Data are normalized to vehicle-treated cells (100% viability), and to cells treated with 200 μ M doxorubicin (0% viability).

After that, the fluorescent signal was detected using SpectraMax Paradigm Multi-Mode Microplate Reader (bottom read) with an excitation wavelength of 544 nm and an emission wavelength of 590 nm (Figure S12). Collected data were normalized by setting 0% cell viability for non-viable cells resulted from treatment with 200 μ M of reference compound doxorubicin, and 100% cell viability for the vehicle-treated cells (0.5% DMSO) using GraphPad Prism 10. Four-parameter nonlinear regression function was used to build the dose-response curves for tested compounds.

Results

Tested compounds exhibited a cytostatic effect on human cancer cell line MCF-7 at the following concentrations:

Buclizine: $IC_{50} = 31.3 \pm 7.8 \mu$ M,

94: $IC_{50} = 24.5 \pm 1.5 \mu$ M.

In comparison to the parent molecule buclizine ($IC_{50} = 31.3 \pm 7.8 \mu$ M), compound **94** demonstrated some level of cytostatic (or cytotoxic) activity.

Lipid droplets fluorescent imaging assay (Buclizine and analog **94**)

To assess lipid droplet formation, MCF-7 cell line (ATCC, #HTB-2) was thawed and cultured in DMEM complete medium (10% FBS, 1% non-essential amino acids, 1% sodium pyruvate). Insulin was not added due to its ability to promote cellular differentiation by itself. When cells reached 70-80% confluency, they were detached from the flask surface and seeded to sterile black wall 384-well plates (PerkinElmer, #6057302) at seeding density 6000 cells per well in 20 μ L of 1% FBS Opti-MEM (ThermoFisher, #31985062) medium in each well. The plate was centrifuged at 40 $\times$ g for 15 seconds and incubated at 37 $^{\circ}$ C in the presence of 5% carbon dioxide overnight. On the next day, compounds in volumes of 30 μ L per well were added.

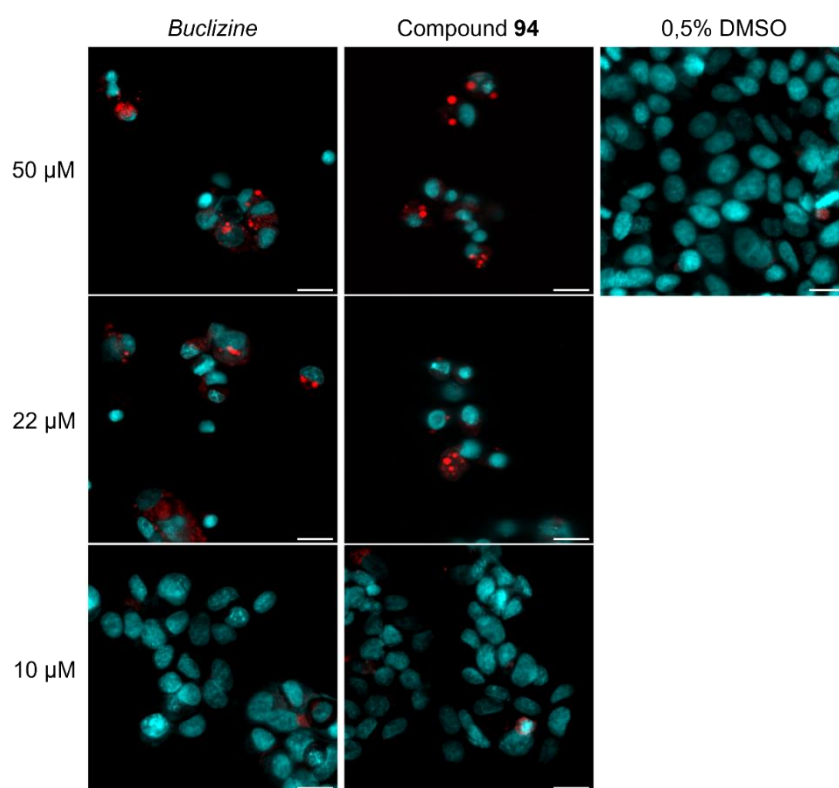


Figure S13. Confocal images of the lipid droplets formation in MCF-7 cells upon incubation with buclizine and analog **94**, for 72 hours. Nuclei were stained with Hoechst 33342 (cyan), lipid droplets were stained with Nile Red (red). Scale bars are 20 μ m.

After that, the plate was centrifuged at 40 $\times$ g for 15 seconds and incubated 72 hours in the carbon dioxide incubator. After 72 hours, 20% PFA stock (Thermo Fisher, #047340.9M) was pre-warmed at 37 $^{\circ}$ C and mixed with Hoechst 33342 dye (Thermo Scientific, #62249) stock solution (20 mM). The prepared PFA/Hoechst 33342 mix was dispensed at the volume of 12.5 μ L per well to each well of the plate to result in a final Hoechst 33342 concentration of 5 μ M and 4% PFA. The plate was centrifuged at 40 $\times$ g for 15 seconds and incubated at room temperature for 20 minutes in the dark. Then, the plate was washed twice with PBS using an automated plate washer (BioTek EL-406). 10 mM DMSO stock solution

of Nile Red (BLDpharm, #CGW360) prepared separately was diluted in DPBS (pH = 7.4) to a concentration of 250 nM in the dark and then added at the volume of 50 μ L per well. The plate was centrifuged at 40 $\times$ g for 15 seconds and incubated at room temperature for 20 minutes in the dark. Then, the plate was washed twice with PBS. The plate was filled with 80 μ L PBS per well and sealed with aluminum film. Confocal microscopy analysis was performed using the automated High Content Imaging system InCell Analyzer 6500 HS. 9 images were taken with 20 $\times$ obj. lens (NA = 0.95) as shown in Figure S13. All samples were acquired at the same intensity/exposure/laser power parameters. Images were analyzed using InCarta v.1.17 software (Molecular Devices). Nuclei were segmented using Hoechst 33342 staining, lipid droplets were identified and counted using Nile Red staining. At least 500 cells were analyzed per tested condition, three technical replicates were run per concentration of the compounds. Three independent experiments were conducted. Collected data were normalized to vehicle control (0.5% DMSO) using GraphPad Prism 10. Four-parameter nonlinear regression function was used to build the dose-response curves for tested compounds.

Results

Treatment with buclizine and its analog **94**, resulted in the induction of lipid droplet formation. The images are shown in Figure S13. The number of lipid droplets with an area of more than 1 μ m² and fluorescence intensity higher than background intensity per cell was used for the determination of the EC₅₀ values of test compounds (Figure S14):

Buclizine: EC₅₀ = 19.11 $\pm$ 1.45 μ M,

94: EC₅₀ = 16.49 $\pm$ 0.56 μ M.

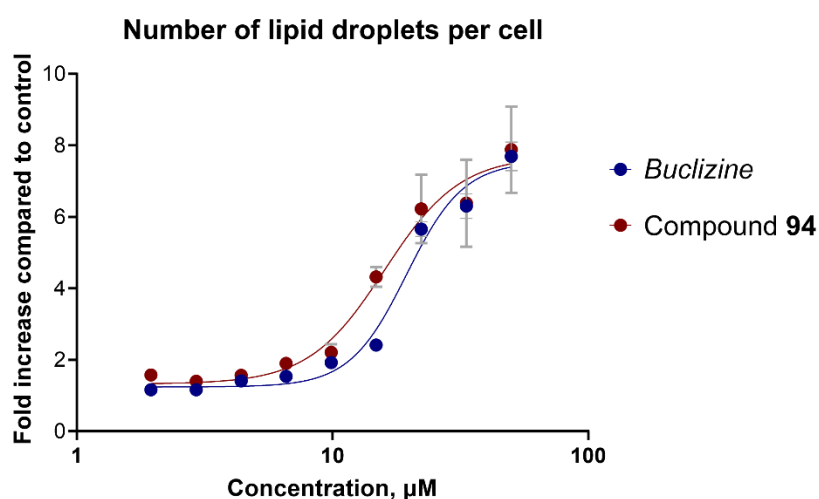


Figure S14. Lipid droplet formation induced by the addition of buclizine and its analog **94**. The number of lipid droplets per cell was quantified and normalized to vehicle control (cells treated with 0.5% DMSO). At least 500 cells were analyzed per tested concentration, 3 technical replicates were conducted per each tested concentration of the compounds. Data are represented as mean $\pm$ standard error.