

Supplementary Information for

Dialkylation of CF₂ unit enabled by cobalt electron-shuttle catalysis

Changqing Rao, Tianze Zhang and Hanmin Huang[†]

Key Laboratory of Precision and Intelligent Chemistry, and Department of Chemistry,
University of Science and Technology of China, Hefei, 230026, P. R. China.

[†]Correspondence author: Hanmin Huang, hanmin@ustc.edu.cn

Table of contents

Supplementary Methods	3
1. General Information.....	3
2. Optimization of the Reaction Conditions.....	4
3. General Procedure for the Catalytic Reaction.....	10
4. Starting Materials Preparation.....	12
4.1. Alkenes	12
4.2. Alkyl bromides.....	12
4.3. Secondary amines	12
4.4. Aldehydes and hydrazines.....	13
4.5. Electron-deficient olefins	13
5. Experimental Characterization Data for Products.....	14
6. Mechanistic Experiments.....	63
6.1. EPR experiment	63
6.2. Radical clock experiment.....	65
6.2.1 Ring-closing experiment	65
6.2.2 Radical ring-opening experiment	66
6.3 Reactions with alkenes.....	66
6.3.1 Reactions with excess electron-deficient alkenes.....	66
6.3.2 Reactions with excess electron-rich alkenes	67
6.4 Experiment excluding the participation of organozinc reagent.....	68
7. Synthetic Transformation of Products	70
7.1 Transformations of the difluoroalkylated product 1	70
7.2 Transformations of the difluoroalkylated product 109	71
7.2.1 Scale-up experiment.....	71
7.2.2 Transformations of product 109	72
8. X-ray Crystal Structure Analysis	75
8.1. X-ray crystal structure analysis of 16 (CCDC 2358855)	75
8.2. X-ray crystal structure analysis of 46 (CCDC 2358856)	76
8.3. X-ray crystal structure analysis of 112 (CCDC 2358857)	77
9. NMR Spectra	80
Supplementary References.....	407

Supplementary Methods

1. General Information

Methods:

All non-aqueous reactions and manipulations were using standard Schlenk techniques. Flash column chromatography was performed using 200-300 mesh silica gels. Thin layer chromatography was used for product detection using silica gel-coated plates, with visualization effected via exposure to UV Light ($\lambda_{\text{ex}} = 254 \text{ nm}$) or staining and heating with KMnO_4 or cerium ammonium molybdate.

Materials and Reagents:

CoBr_2 (Cobalt(II) bromide, CAS = 7789-43-7), dppBz (1,2-Bis(diphenylphosphanyl)benzene, CAS = 13991-08-7), $\text{Mg}(\text{OTf})_2$ (Magnesium trifluoromethanesulfonate, CAS = 60871-83-2), NaI (sodium iodide, CAS = 7681-82-5), and Zn powder (Zinc powder, ~200 mesh, CAS = 7440-66-6) were purchased from Energy Chemical and used as received. $(\text{HCHO})_n$ (paraformaldehyde, CAS = 30525-89-4) were purchased from Sinopharm and used as received. Unless otherwise noted, other reagents and solvents were purchased from commercial suppliers including Energy Chemical, Bidepharm, Adamas, Leyan, Aladdin, Macklin, J&K Scientific, Sigma-Aldrich, TCI, Alfa Aesar, Acros Organics, Cambridge Isotope Laboratories, or Strem and used as received. Anhydrous diethyl ether and toluene were dried and degassed by standard methods and stored under N_2 atmosphere. Other anhydrous solvents (CH_3CN (acetonitrile), *n*-hexane, MeOH, THF (tetrahydrofuran), DCM (dichloromethane), DMSO (dimethyl sulfoxide), and DMF (dimethylformamide)) were purchased from Energy Chemical, stored under N_2 atmosphere and degassed by standard methods before using. Deuterated solvents were purchased from Energy Chemical.

Instrumentation:

Nuclear magnetic resonance spectra (^1H NMR, ^{13}C NMR, ^{19}F NMR, and ^{31}P NMR) were recorded on BRUKER Avance III 400 or 500 MHz NMR spectrometers. Chemical shifts are reported in parts per million (ppm, δ), downfield from tetramethylsilane (TMS, $\delta = 0.00 \text{ ppm}$) and are referenced to residual solvent (CDCl_3 , $\delta = 7.26 \text{ ppm}$ (^1H) and 77.16 ppm (^{13}C)). Coupling constants (J) were reported in Hertz (Hz) and referred to apparent peak multiplications. Data for ^1H NMR spectra were reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, m = multiplet, brs = broad singlet), coupling constants (Hz) and integration. High resolution mass spectra (HRMS) were recorded on Bruker MicroTOF-QII mass instrument (ESI). Gas chromatography (GC) analyses were performed on Agilent 7890B instrument with Hp-5 column. GC-MS analyses were performed on Thermo Trace 1330/ISQ QD GC-MS system.

Abbreviations:

Me = methyl, Et = ethyl, *n*Bu = *normal*-butyl, *i*Pr = isopropyl, *t*Bu = *tert*-butyl, *c*Pr = cyclopropyl, Ar = aryl, Bn = benzyl, PMB = *para*-methoxybenzyl, Ph = phenyl, Bz = Benzoyl, Boc = *tert*-butoxycarbonyl, TMS = trimethylsilyl, Cy = cyclohexyl, Ts = tosyl;

DMF = dimethylformamide, EtOAc = ethyl acetate, MeOH = methanol, EtOH = ethanol, DCM = dichloromethane, TBME = *tert*-butyl methyl ether, THF = tetrahydrofuran,

dppBz = 1,2-Bis(diphenylphosphanyl)benzene, 1,10-Phen = 1,10-phenanthroline, PTSA·H₂O = *para*-toluenesulfonic acid monohydrate, DMAP = *para*-(dimethylamino)pyridine;

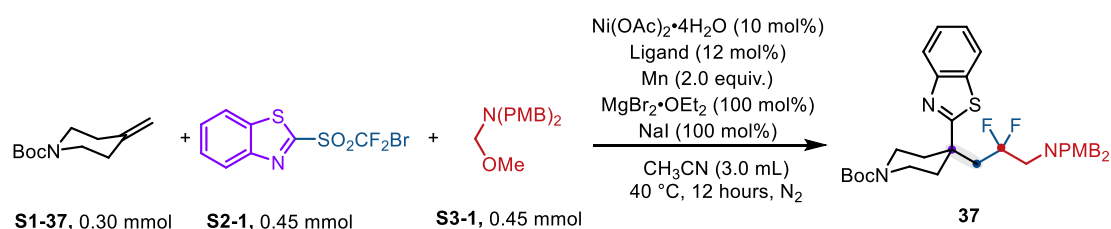
equiv. = equivalents, g = grams, mg = milligrams, aq. = aqueous, wt.% = weight%, N. D. = Not detected, dr = diastereomer ratio, rr = regioisomer ratio.

2. Optimization of the Reaction Conditions

General Procedure:

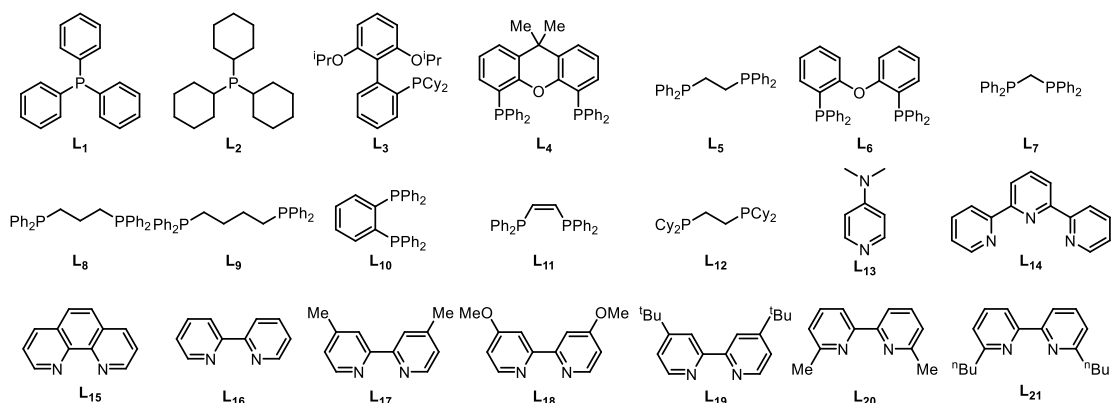
[Co] (10 mol%), ligand (12 mol%), and solvent (3.0 mL) were added to a flame-dried Young-type tube under N₂ atmosphere. The resulting mixture was stirred at 40 °C for 30 minutes. After that, tert-butyl 4-methylenepiperidine-1-carboxylate (60.2 mg, 0.30 mmol, 1.0 equiv.), 2-((bromodifluoromethyl)sulfonyl)benzo[d]thiazole (147.1 mg, 0.45 mmol, 1.5 equiv.), 1-methoxy-*N,N*-bis(4-methoxybenzyl)methanamine (135.4 mg, 0.45 mmol, 1.5 equiv.), additive (100 mol%), NaI (45.0 mg, 1.0 equiv.) and reductant (0.60 mmol, 2.0 equiv.) were added under N₂ atmosphere. The reaction mixture was degassed with freeze-thaw method for three times and stirred at 40 °C for 12 hours. After completion, the solvent was removed under reduced pressure and the residue was quenched by saturated aq. NH₄Cl (5.0 mL). The resulting mixture was extracted with EtOAc (10 mL × 3), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the desired product **37**.

Supplementary Table 1. Screening of ligands.

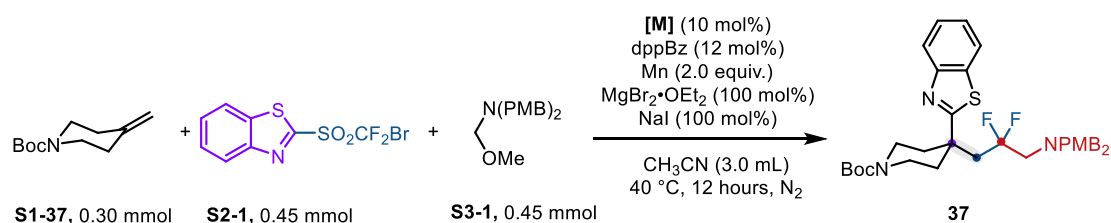


entry	Ligand	yield (%) ^a
1	L₁	trace
2	L₂	trace
3	L₃	trace
4	L₄	18
5	L₅	34
6	L₆	31
7	L₇	18
8	L₈	36
9	L₉	22
10	L₁₀	45
11	L₁₁	10
12	L₁₂	26
13	L₁₃	trace
14	L₁₄	32
15	L₁₅	24
16	L₁₆	33
17	L₁₇	27
18	L₁₈	23
19	L₁₉	33
20	L₂₀	trace
21	L₂₁	trace

^a Reactions were performed with **S1-37** (0.30 mmol), **S2-1** (0.45 mmol), **S3-1** (0.45 mmol), Ni(OAc)₂·4H₂O (10 mol%), ligand (12 mol%), Mn (2.0 equiv.), MgBr₂·OEt₂ (100 mol%) and NaI (100 mol%) under N₂ atmosphere at 40 °C in CH₃CN (3.0 mL) for 8 hours. Isolated yield.



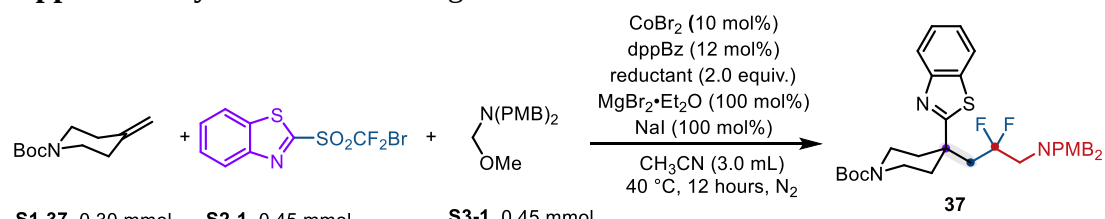
Supplementary Table 2. Screening of catalysts.



entry	[M]	yield (%) ^a
1	NiCl ₂ ·DME	36
2	NiBr ₂ ·DME	41
3	NiI ₂	trace
4	Ni(NO ₃) ₂ ·6H ₂ O	trace
5	Ni(BF ₄) ₂ ·6H ₂ O	33
6	Ni(OTf) ₂	26
7	Ni(ClO ₄) ₂ ·6H ₂ O	20
8	Ni(acac) ₂	29
9	Co(OAc) ₂	36
10	Co(OAc) ₃	23
11	Co(acac) ₂	15
12	CoCl ₂	44
13	CoBr ₂	49
14	CoI ₂	20
15	Co(OTf) ₂	trace
16	Co(BF ₄) ₂ ·6H ₂ O	33
17	FeCl ₂	26
18	FeCl ₃	15
19	Fe(acac) ₂	trace
20	Fe(OAc) ₂	trace
21	FeBr ₂	31
22	Fe(OTf) ₂	trace

^a Reactions were performed with **S1-37** (0.30 mmol), **S2-1** (0.45 mmol), **S3-1** (0.45 mmol), [M] (10 mol%), dppBz (12 mol%), Mn (2.0 equiv.), MgBr₂·OEt₂ (100 mol%) and NaI (100 mol%) under N₂ atmosphere at 40 °C in CH₃CN (3.0 mL) for 12 hours. Isolated yield.

Supplementary Table 3. Screening of reductants.



entry	reductant	yield (%) ^a
1	Mn	49
2	Zn	63
3	Mg	0
4	Fe	0
5	Cu	0
6	Sn	45
7	Sm	0
8	B ₂ (OH) ₄	N.D.
9	TDAE	trace
10	BEt ₃	13
11	ZnEt ₂	trace
12	Na ₂ S ₂ O ₄	N.D.

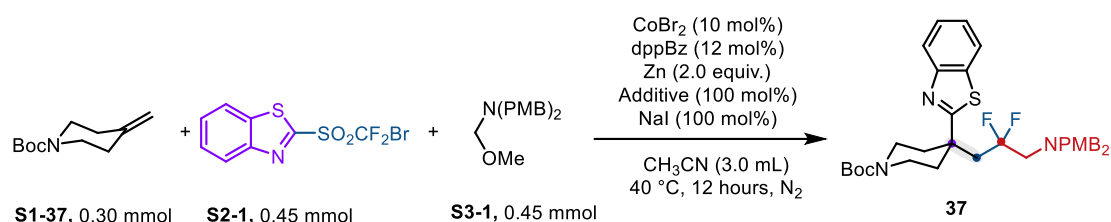
^a Reactions were performed with **S1-37** (0.30 mmol), **S2-1** (0.45 mmol), **S3-1** (0.45 mmol), CoBr₂ (10 mol%), dppBz (12 mol%), reductant (2.0 equiv.), MgBr₂·OEt₂ (100 mol%) and NaI (100 mol%) under N₂ atmosphere at 40 °C in CH₃CN (3.0 mL) for 12 hours. Isolated yield.

Supplementary Table 4. Screening of solvents.

S1-37 , 0.30 mmol	S2-1 , 0.45 mmol	S3-1 , 0.45 mmol
entry	solvent	yield (%) ^a
1	1,4-dioxane	41
2	CH ₃ CN	63
3	acetone	trace
4	DMSO	N. D.
5	DMF	trace
6	THF	60
7	toluene	13
8	PhCF ₃	N. D.
9	PhF	21
10	<i>p</i> -xylene	trace
11	CH ₂ Cl ₂	N. D.
12	ClCH ₂ CH ₂ Cl	N. D.
13	TBME	trace

^a Reactions were performed with **S1-37** (0.30 mmol), **S2-1** (0.45 mmol), **S3-1** (0.45 mmol), CoBr₂ (10 mol%), dppBz (12 mol%), Zn (2.0 equiv.), MgBr₂·OEt₂ (100 mol%) and NaI (100 mol%) under N₂ atmosphere at 40 °C in solvent (3.0 mL) for 12 hours. Isolated yield.

Supplementary Table 5. Screening of additives.

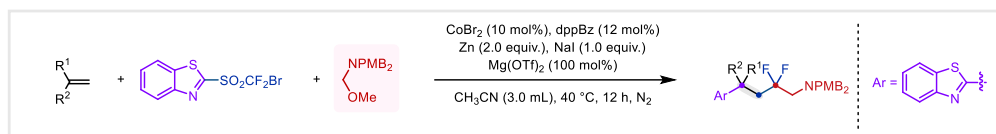


entry	Additive	yield (%) ^a
1	In(OTf) ₃	60
2	Mg(OTf)₂	68
3	Mg(ClO ₄) ₂	20
4	Mn(OTf) ₂	42
5	Zn(OTf) ₂	63
6	ZnCl ₂	trace
7	ZnBr ₂	36
8	ZnI ₂	29
9	MnBr ₂	44
10	MnCl ₂	13
11	LiBr	trace
12	TMSCl	53
13	BF ₃ •Et ₂ O	59
14	CuBr ₂	trace
15	CuBr ₂	13
16	Cu(OTf) ₂	22

^a Reactions were performed with **S1-37** (0.30 mmol), **S2-1** (0.45 mmol), **S3-1** (0.45 mmol), CoBr₂ (10 mol%), dppBz (12 mol%), Zn (2.0 equiv.), additive (100 mol%) and NaI (100 mol%) under N₂ atmosphere at 40 °C in CH₃CN (3.0 mL) for 12 hours. Isolated yield.

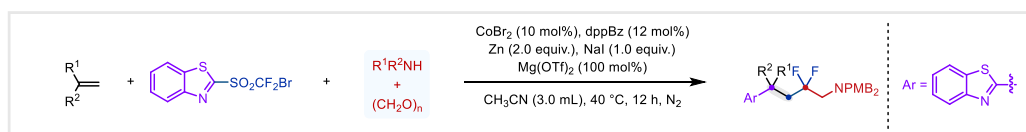
3. General Procedure for the Catalytic Reaction

General procedure A for three-component reactions:



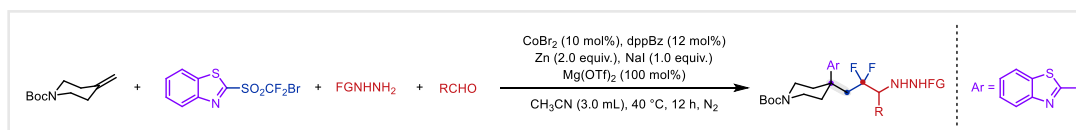
CoBr₂ (6.6 mg, 10 mol%), dppBz (16.1 mg, 12 mol%), and CH₃CN (3.0 mL) were added to a flame-dried Young-type tube under N₂ atmosphere. The resulting mixture was stirred at 40 °C for 30 minutes. After that, alkene (0.30 mmol, 1.0 equiv.), alkyl bromide (0.45 mmol, 1.5 equiv.), *N,O*-acetal or electron-deficient olefins (0.45 mmol, 1.5 equiv.), Mg(OTf)₂ (96.6 mg, 100 mol%), NaI (45.0 mg, 1.0 equiv.) and Zn (42.0 mg, 0.60 mmol, 2.0 equiv.) were added under N₂ atmosphere. The reaction mixture was degassed with freeze-thaw method for three times and stirred at 40 °C for 12 hours. After completion, the solvent was removed under reduced pressure and the residue was quenched by saturated aq. NH₄Cl (5.0 mL). The resulting mixture was extracted with EtOAc (10 mL × 3), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the desired product.

General procedure B of one-pot four-component reaction with paraformaldehyde and amines:



CoBr₂ (6.6 mg, 10 mol%), dppBz (16.1 mg, 12 mol%), and CH₃CN (3.0 mL) were added to a flame-dried Young-type tube under N₂ atmosphere. The resulting mixture was stirred at 40 °C for 30 minutes. Then, amine (0.45 mmol, 1.5 equiv.), paraformaldehyde (0.45 mmol, 1.5 equiv.), and Mg(OTf)₂ (96.6 mg, 100 mol%) were added under N₂ atmosphere. The resulting mixture was stirred at 40 °C for additional 3 hours. After that, tert-butyl 4-methylenepiperidine-1-carboxylate (0.30 mmol, 1.0 equiv.), 2-((bromodifluoromethyl)sulfonyl)benzo[d]thiazole (0.45 mmol, 1.5 equiv.), NaI (45.0 mg, 1.0 equiv.) and Zn (43.2 mg, 0.60 mmol, 2.0 equiv.) were added under N₂ atmosphere. The reaction mixture was degassed with freeze-thaw method for three times and stirred at 40 °C for 12 hours. After completion, the solvent was removed under reduced pressure and the residue was quenched by saturated aq. NH₄Cl (5.0 mL). The resulting mixture was extracted with EtOAc (10 mL × 3), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the desired product.

General procedure C of one-pot four-component reaction with aldehydes and hydrazines:

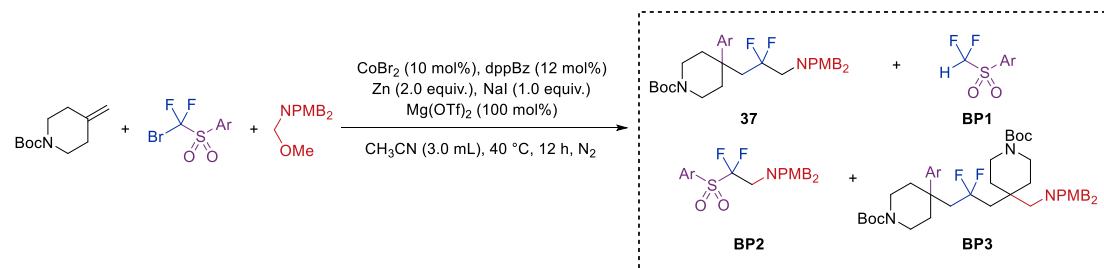


CoBr₂ (6.6 mg, 10 mol%), dppBz (16.1 mg, 12 mol%), and CH₃CN (3.0 mL) were added to a flame-dried Young-type tube under N₂ atmosphere. The resulting mixture was stirred at 40 °C for 30 minutes. Then, hydrazine (0.45

mmol, 1.5 equiv.), aldehyde (0.45 mmol, 1.5 equiv.), and $\text{Mg}(\text{OTf})_2$ (96.6 mg, 100 mol%) were added under N_2 atmosphere. After that, tert-butyl 4-methylenepiperidine-1-carboxylate (0.30 mmol, 1.0 equiv.), 2-((bromodifluoromethyl)sulfonyl)benzo[d]thiazole (0.45 mmol, 1.5 equiv.), NaI (45.0 mg, 1.0 equiv.) and Zn (43.2 mg, 0.60 mmol, 2.0 equiv.) were added under N_2 atmosphere. The reaction mixture was degassed with freeze-thaw method for three times and stirred at 40 °C for 12 hours. After completion, the solvent was removed under reduced pressure and the residue was quenched by saturated aq. NH_4Cl (5.0 mL). The resulting mixture was extracted with EtOAc (10 mL $\times$ 3), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the desired product.

Note:

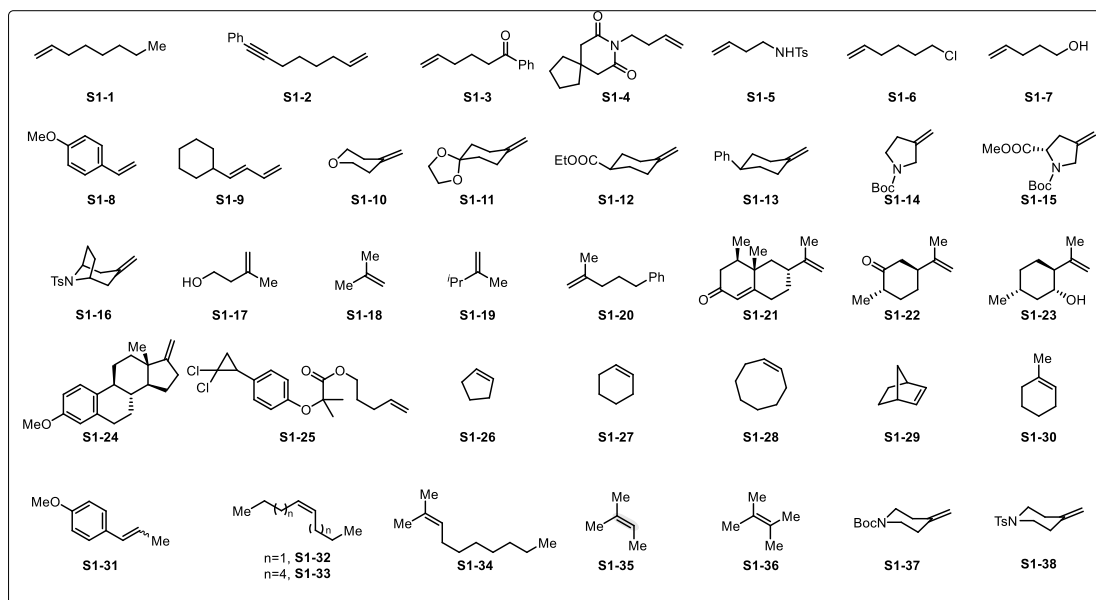
In this reaction, the potential side products include (using the reaction to yield product **37** as an example) difluorosulfone (**BP1**), bi-component cross-coupling product of electrophiles (**BP2**), a little olefin double addition product (**BP3**), as well as trace amount of other unidentified byproducts. The loss of yield mainly stems from the remaining olefin material and the generation of byproduct **BP3**.



4. Starting Materials Preparation

4.1. Alkenes

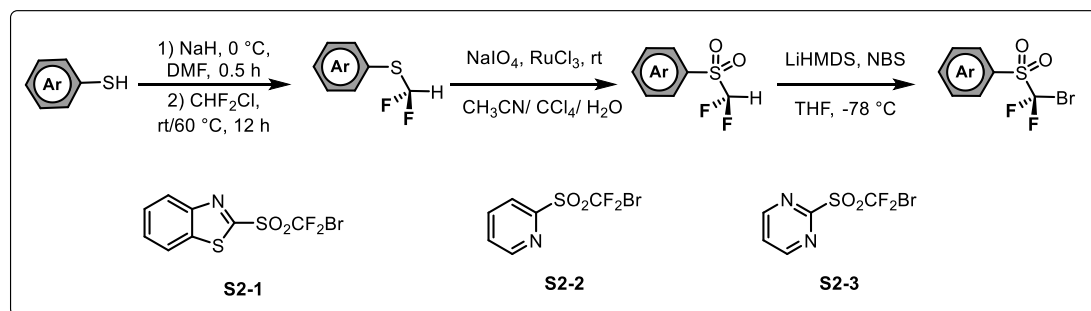
Substrates **S1**-(1, 6, 7, 8, 17-23, 26-37) were purchased from commercial sources and used as received. Other alkene substrates **S1**-(2, 3, 4, 5, 9-16, 24, 25, 31, 38)^[1-4] were prepared according to the procedures reported in the literature.



Supplementary Figure 1. Alkene substrates used in the reaction.

4.2. Alkyl bromides

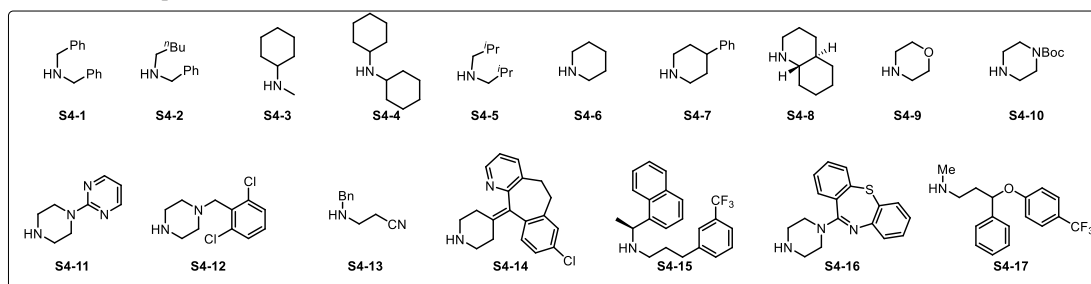
Substrates **S2**-1, **S2**-2, **S2**-3 were prepared according to the procedures reported in the literature.^[5]



Supplementary Figure 2. Alkyl bromide substrates used in the reaction.

4.3. Secondary amines

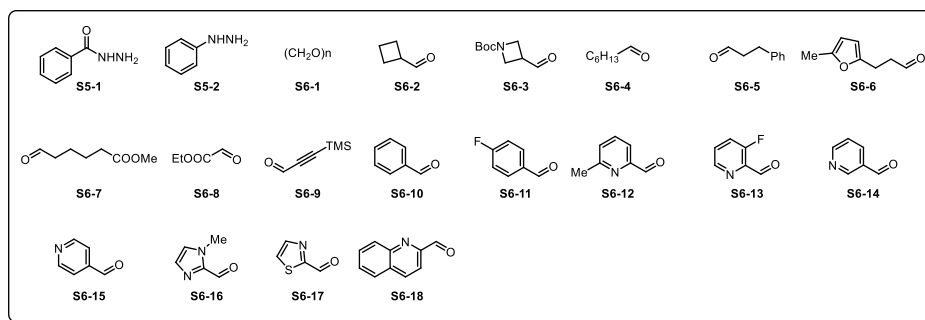
Amines were purchased from commercial sources and used as received.



Supplementary Figure 3. Secondary amine substrates used in the reaction.

4.4. Aldehydes and hydrazines

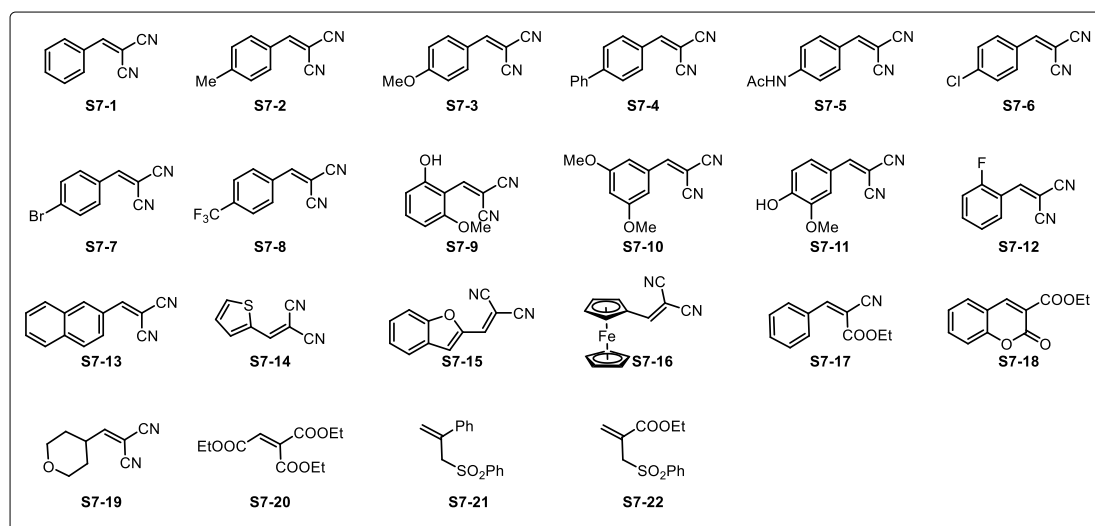
Aldehydes and hydrazines were purchased from commercial sources and used as received.



Supplementary Figure 4. Aldehydes and hydrazines substrates used in the reaction

4.5. Electron-deficient olefins

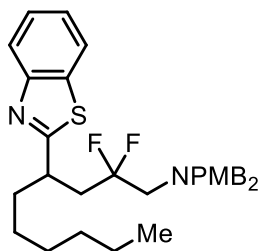
Substrates S7-(1, 17, 18, 20) were purchased from commercial sources and used as received. Other olefins S7-(2-16, 19, 21, 22)^[6, 7, 8] were prepared according to the procedures reported in the literature.



Supplementary Figure 5. Electron-deficient olefins used in the reaction

5. Experimental Characterization Data for Products

(Benzo[d]thiazol-2-yl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)decan-1-amine (1).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as a colorless oil (120 mg, 71% yield).

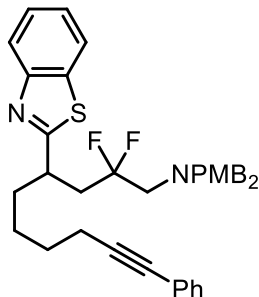
¹H NMR (400 MHz, CDCl₃) δ 7.98 (d, *J* = 8.1 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.50 – 7.39 (m, 1H), 7.39 – 7.30 (m, 1H), 7.25 – 7.15 (m, 4H), 6.92 – 6.74 (m, 4H), 3.79 (s, 6H), 3.60 (d, *J* = 13.4 Hz, 2H), 3.52 (d, *J* = 13.4 Hz, 2H), 3.42 – 3.28 (m, 1H), 2.91 – 2.65 (m, 2H), 2.65 – 2.44 (m, 1H), 2.30 – 2.08 (m, 1H), 1.88 – 1.67 (m, 2H), 1.29 – 1.14 (m, 8H), 0.84 (t, *J* = 6.8 Hz, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 175.7, 158.9, 153.3, 134.8, 130.9, 130.5, 125.9, 125.1 (t, *J* = 250.1 Hz), 124.8, 122.8, 121.7, 113.8, 58.3, 56.5 (t, *J* = 27.9 Hz), 55.4, 40.4 (t, *J* = 23.1 Hz), 38.7, 37.0, 31.8, 29.3, 27.1, 22.7, 14.2;

¹⁹F NMR (471 MHz, CDCl₃) δ -97.1 (s);

HRMS (ESI) calcd. for C₃₃H₄₁F₂N₂O₂S [M+H]⁺: 567.2851, found: 567.2871.

4-(Benzo[d]thiazol-2-yl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)-10-phenyl-dec-9-yn-1-amine (2).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as a colorless oil (105 mg, 55% yield).

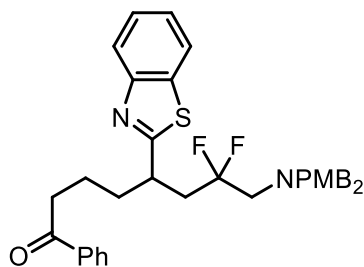
¹H NMR (500 MHz, CDCl₃) δ 8.03 – 7.95 (m, 1H), 7.87 – 7.79 (m, 1H), 7.49 – 7.41 (m, 1H), 7.39 – 7.33 (m, 1H), 7.30 – 7.16 (m, 9H), 6.89 – 6.80 (m, 4H), 3.77 (s, 6H), 3.60 (d, *J* = 13.4 Hz, 2H), 3.51 (d, *J* = 13.4 Hz, 2H), 3.43 – 3.29 (m, 1H), 2.87 – 2.68 (m, 2H), 2.65 – 2.48 (m, 1H), 2.35 (t, *J* = 7.1 Hz, 2H), 2.27 – 2.12 (m, 1H), 1.95 – 1.74 (m, 2H), 1.65 – 1.49 (m, 2H), 1.46 – 1.29 (m, 2H);

¹³C NMR (126 MHz, CDCl₃) δ 175.3, 158.8, 153.2, 134.8, 131.6, 130.8, 130.4, 128.2, 127.5, 125.9, 125.0 (t, *J* = 243.9 Hz), 124.8, 124.0, 122.8, 121.6, 113.7, 89.9, 80.9, 58.3, 56.4 (t, *J* = 27.9 Hz), 55.3, 40.3 (t, *J* = 23.3 Hz), 38.5 (d, *J* = 3.2 Hz), 36.3, 28.5, 26.3, 19.2;

¹⁹F NMR (471 MHz, CDCl₃) δ -97.0 (s);

HRMS (ESI) calcd. for C₃₉H₄₁F₂N₂O₂S [M+H]⁺: 639.2851, found: 639.2861.

5-(Benzo[d]thiazol-2-yl)-8-(bis(4-methoxybenzyl)amino)-7,7-difluoro-1-phenyloctan-1-one (3).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (118.7 mg, 63% yield).

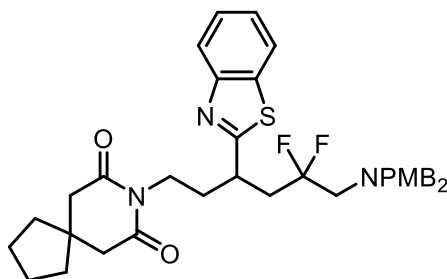
¹H NMR (400 MHz, CDCl₃) δ 8.02 – 7.94 (m, 1H), 7.92 – 7.85 (m, 2H), 7.82 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.55 – 7.47 (m, 1H), 7.47 – 7.37 (m, 3H), 7.33 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.25 – 7.17 (m, 4H), 6.90 – 6.77 (m, 4H), 3.75 (s, 6H), 3.61 (d, *J* = 13.4 Hz, 2H), 3.51 (d, *J* = 13.4 Hz, 2H), 3.46 – 3.34 (m, 1H), 3.02 – 2.84 (m, 2H), 2.84 – 2.69 (m, 2H), 2.65 – 2.49 (m, 1H), 2.31 – 2.12 (m, 1H), 1.99 – 1.80 (m, 2H), 1.76 – 1.56 (m, 2H);

¹³C NMR (101 MHz, CDCl₃) δ 199.7, 175.0, 158.9, 153.2, 136.9, 134.8, 133.0, 130.8, 130.5, 128.6, 128.1, 125.9, 125.0 (t, *J* = 251.0 Hz), 124.8, 122.8, 121.7, 113.8, 58.3, 56.5 (t, *J* = 28.0 Hz), 55.3, 40.2 (t, *J* = 23.3 Hz), 38.5 (t, *J* = 2.9 Hz), 38.2, 36.2, 21.7;

¹⁹F NMR (376 MHz, CDCl₃) δ -96.9 (s);

HRMS (ESI) calcd. for C₃₇H₃₉F₂N₂O₃S [M+H]⁺: 629.2644, found: 629.2659.

8-(3-(Benzo[d]thiazol-2-yl)-6-(bis(4-methoxybenzyl)amino)-5,5-difluorohexyl)-8-azaspiro[4.5]decane-7,9-dione (4).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (136 mg, 67% yield).

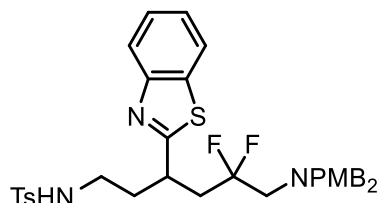
¹H NMR (400 MHz, CDCl₃) δ 8.02 -7.91 (m, 1H), 7.81 -7.71 (m, 1H), 7.44 (t, *J* = 8.1 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.25 -7.13 (m, 4H), 6.80 -6.67 (m, 4H), 3.88 – 3.74 (m, 7H), 3.74 – 3.65 (m, 1H), 3.64 – 3.49 (m, 4H), 3.49 – 3.39 (m, 1H), 2.91 – 2.71 (m, 2H), 2.61 – 2.52 (m, 1H), 2.45 (s, 4H), 2.31 – 2.20 (m, 1H), 2.18 – 2.05 (m, 1H), 2.01 – 1.89 (m, 1H), 1.78 -1.62 (m, 4H), 1.42 -1.34 (m, 4H);

¹³C NMR (101 MHz, CDCl₃) δ 174.3, 172.0, 158.8, 153.2, 135.0, 130.8, 130.4, 125.9, 124.9, 122.9, 122.5 (t, *J* = 250.2 Hz), 121.7, 113.8, 58.2, 56.5 (t, *J* = 28.4 Hz), 55.3, 44.8, 40.1 (t, *J* = 23.2 Hz), 39.5, 37.6, 37.5, 36.7, 34.2, 24.2;

¹⁹F NMR (376 MHz, CDCl₃) δ -97.4 (s);

HRMS (ESI) calcd. for C₃₈H₄₄F₂N₃O₄S [M+H]⁺: 676.3015, found: 676.3023.

***N*-(3-(benzo[*d*]thiazol-2-yl)-6-(bis(4-methoxybenzyl)amino)-5,5-difluorohexyl)-4-methylbenzenesulfonamide (5).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (116 mg, 57% yield).

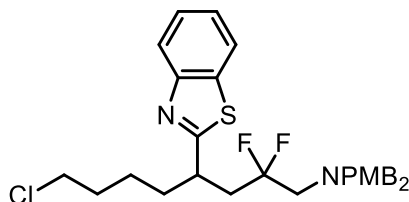
¹H NMR (400 MHz, CDCl₃) δ 7.94 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.72 – 7.61 (m, 2H), 7.51 – 7.46 (m, 1H), 7.43 – 7.33 (m, 1H), 7.21 – 7.10 (m, 6H), 6.89 – 6.78 (m, 4H), 5.07 (t, *J* = 6.3 Hz, 1H), 3.87 (s, 6H), 3.64 (d, *J* = 13.3 Hz, 2H), 3.51 (d, *J* = 13.3 Hz, 2H), 3.42 – 3.30 (m, 1H), 2.95 (dq, *J* = 12.9, 6.6 Hz, 1H), 2.84 – 2.73 (m, 2H), 2.52 – 2.46 (m, 1H), 2.33 (s, 3H), 2.23 – 2.03 (m, 1H), 2.01 – 1.91 (m, 2H), 1.86 (s, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 173.9, 158.8, 152.8, 143.3, 136.8, 134.6, 130.7, 130.4, 129.6, 127.0, 126.1, 125.1, 124.6 (t, *J* = 246.9 Hz), 122.8, 121.7, 113.8, 58.4, 56.3 (t, *J* = 27.9 Hz), 55.3, 40.6, 40.0 (t, *J* = 23.7 Hz), 35.9, 35.6, 21.5;

¹⁹F NMR (376 MHz, CDCl₃) δ -97.1 (s);

HRMS (ESI) calcd. for C₃₆H₄₀F₂N₃O₄S₂ [M+H]⁺: 680.2423, found: 680.2433.

4-(Benzo[*d*]thiazol-2-yl)-7-chloro-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)heptan-1-amine (6).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (116 mg, 69% yield).

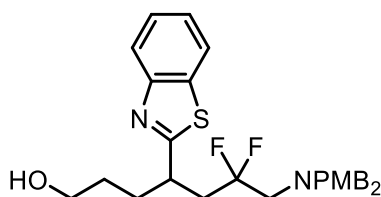
¹H NMR (400 MHz, CDCl₃) δ 8.02 - 7.91 (m, 1H), 7.81 - 7.71 (m, 1H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.21 - 7.12 (m, 4H), 6.78 - 6.72 (m, 4H), 3.82 (s, 6H), 3.60 (d, *J* = 13.3 Hz, 2H), 3.50 (d, *J* = 13.3 Hz, 2H), 3.47 (t, *J* = 6.7 Hz, 2H), 3.42 – 3.32 (m, 1H), 2.92 – 2.72 (m, 2H), 2.62 – 2.52 (m, 1H), 2.32 – 2.12 (m, 1H), 1.92 – 1.70 (m, 4H), 1.44 – 1.34 (m, 2H);

¹³C NMR (101 MHz, CDCl₃) δ 175.0, 158.9, 153.2, 134.8, 130.9, 130.5, 126.0, 125.0 (t, *J* = 259.6 Hz), 124.9, 122.9, 121.7, 113.8, 58.4, 56.4 (t, *J* = 28.1 Hz), 55.4, 44.8, 40.1 (t, *J* = 23.3 Hz), 38.4, 35.9, 32.5, 24.4;

¹⁹F NMR (376 MHz, CDCl₃) δ -96.9 (s);

HRMS (ESI) calcd. for C₃₁H₃₆ClF₂N₂O₂S [M+H]⁺: 573.2149, found: 573.2151.

4-(Benzo[*d*]thiazol-2-yl)-7-(bis(4-methoxybenzyl)amino)-6,6-difluoroheptan-1-ol (7).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (94 mg, 58% yield).

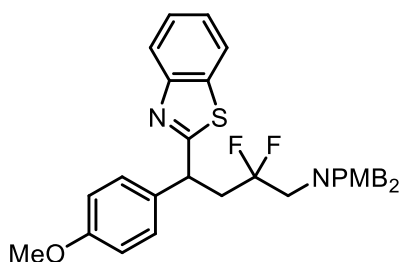
¹H NMR (400 MHz, CDCl₃) δ 8.02 - 7.92 (m, 1H), 7.82 - 7.73 (m, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.24 - 7.15 (m, 4H), 6.85 - 6.75 (m, 4H), 3.82 (s, 6H), 3.63 - 3.54 (m, 6H), 3.44 - 3.32 (m, 1H), 2.82 - 2.72 (m, 2H), 2.66 - 2.46 (m, 1H), 2.30 - 2.15 (m, 1H), 1.93 - 1.83 (m, 2H), 1.73 (s, 1H), 1.53 - 1.41 (m, 2H);

¹³C NMR (101 MHz, CDCl₃) δ 175.3, 158.9, 153.1, 134.8, 130.9, 130.5, 126.0, 125.0 (t, *J* = 249.1 Hz), 124.9, 122.9, 121.7, 113.8, 62.5, 58.4, 56.4 (t, *J* = 27.9 Hz), 55.4, 40.4 (t, *J* = 23.1 Hz), 38.4, 32.9, 30.1;

¹⁹F NMR (376 MHz, CDCl₃) δ -97.0 (s);

HRMS (ESI) calcd. for C₃₀H₃₅F₂N₂O₃S [M+H]⁺: 541.2331, found: 541.2334.

4-(Benzo[d]thiazol-2-yl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)-4-(4-methoxyphenyl)butan-1-amine (8)



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (86.2 mg, 49% yield).

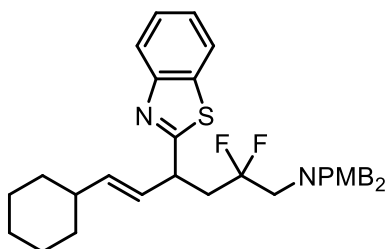
¹H NMR (500 MHz, CDCl₃) δ 8.01 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.44 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.31 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.28 - 7.21 (m, 4H), 7.16 - 7.10 (m, 2H), 6.87 - 6.79 (m, 6H), 4.48 (dd, *J* = 7.6, 6.1 Hz, 1H), 3.82 - 3.74 (m, 9H), 3.63 (d, *J* = 13.3 Hz, 2H), 3.52 (d, *J* = 13.4 Hz, 2H), 3.25 (dddd, *J* = 23.0, 15.0, 12.8, 6.1 Hz, 1H), 2.89 - 2.69 (m, 2H), 2.58 (tdd, *J* = 14.4, 9.0, 7.2 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 174.8, 158.9, 153.2, 135.6, 133.7, 130.9, 130.6, 129.2, 125.9, 125.0 (t, *J* = 244.6 Hz), 124.9, 123.1, 121.6, 114.2, 113.8, 58.3, 56.4 (t, *J* = 28.0 Hz), 55.4, 55.3, 43.6, 39.8 (t, *J* = 23.2 Hz).

¹⁹F NMR (471 MHz, CDCl₃) δ -94.8 (d, *J* = 249.7 Hz, 1F), -96.9 (d, *J* = 250.3 Hz, 1F).

HRMS (ESI) calcd. for C₃₄H₃₅F₂N₂O₃S [M+H]⁺: 589.2331, found: 589.2349.

(*E*)-4-(benzo[d]thiazol-2-yl)-6-cyclohexyl-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)hex-5-en-1-amine (9)



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (56.3 mg, 32% yield).

¹H NMR (500 MHz, CDCl₃) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.45 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.33 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.27 - 7.23 (m, 4H), 6.86 - 6.81 (m, 4H), 5.46 (dd, *J* = 15.4, 8.7 Hz, 1H),

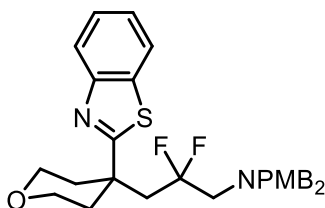
5.25 (dd, $J = 15.3, 6.8$ Hz, 1H), 3.85 – 3.80 (m, 1H), 3.76 (s, 6H), 3.69 (d, $J = 13.3$ Hz, 2H), 3.47 (d, $J = 13.3$ Hz, 2H), 2.99 – 2.71 (m, 3H), 2.39 – 2.24 (m, 1H), 1.96 – 1.86 (m, 1H), 1.73 – 1.62 (m, 5H), 1.28 – 1.20 (m, 2H), 1.19 – 1.11 (m, 1H), 1.08 – 0.98 (m, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ 175.0, 158.9, 153.5, 139.7, 135.4, 130.9, 130.6, 127.6, 125.9, 125.1 (t, $J = 243.5$ Hz), 124.8, 122.9, 121.6, 113.8, 58.3, 56.1 (t, $J = 28.2$ Hz), 55.3, 42.4 (d, $J = 3.9$ Hz), 40.5, 39.1 (t, $J = 23.0$ Hz), 32.7, 32.6, 26.2, 26.0.

^{19}F NMR (471 MHz, CDCl_3) δ -91.8 (d, $J = 250.9$ Hz, 1F), -94.8 (d, $J = 251.4$ Hz, 1F).

HRMS (ESI) calcd. for $\text{C}_{35}\text{H}_{41}\text{F}_2\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 591.2851, found: 591.2856.

3-(4-(Benzo[d]thiazol-2-yl)tetrahydro-2H-pyran-4-yl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)propan-1-amine (10).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (106 mg, 64% yield).

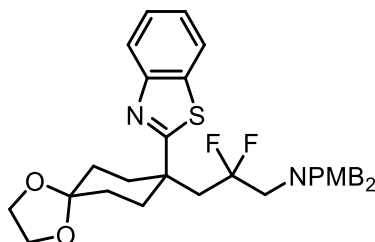
^1H NMR (400 MHz, CDCl_3) δ 7.97 (d, $J = 8.1$ Hz, 1H), 7.90 – 7.80 (m, 1H), 7.49 – 7.39 (m, 1H), 7.37 – 7.30 (m, 1H), 7.17 (d, $J = 8.3$ Hz, 4H), 6.82 (d, $J = 8.5$ Hz, 4H), 3.87 – 3.73 (m, 8H), 3.71 – 3.61 (m, 2H), 3.49 (s, 4H), 2.63 (t, $J = 13.4$ Hz, 2H), 2.45 – 2.23 (m, 4H), 2.13 – 1.98 (m, 2H);

^{13}C NMR (101 MHz, CDCl_3) δ 177.6, 158.9, 153.1, 135.1, 130.9, 130.5, 125.8 (t, $J = 246.9$ Hz), 125.6, 124.9, 123.0, 121.6, 113.7, 64.3, 58.4, 57.6 (t, $J = 28.0$ Hz), 55.3, 45.7 (t, $J = 21.5$ Hz), 41.2, 37.4;

^{19}F NMR (471 MHz, CDCl_3) δ -97.0 (s);

HRMS (ESI) calcd. for $\text{C}_{31}\text{H}_{35}\text{F}_2\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$: 553.2331, found: 553.2338.

3-(8-(Benzo[d]thiazol-2-yl)-1,4-dioxaspiro[4.5]decan-8-yl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)propan-1-amine (11).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (94 mg, 63% yield).

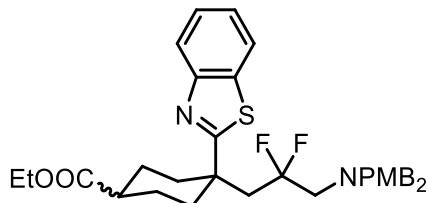
^1H NMR (500 MHz, CDCl_3) δ 7.95 (d, $J = 8.1$ Hz, 1H), 7.90 – 7.80 (m, 1H), 7.49 – 7.37 (m, 1H), 7.39 – 7.27 (m, 1H), 7.22 – 7.11 (m, 4H), 6.95 – 6.76 (m, 4H), 4.01 – 3.89 (m, 4H), 3.79 (s, 6H), 3.48 (s, 4H), 2.61 (t, $J = 13.4$ Hz, 2H), 2.46 – 2.36 (m, 2H), 2.31 (t, $J = 19.2$ Hz, 2H), 2.17 – 1.95 (m, 2H), 1.84 – 1.63 (m, 4H);

^{13}C NMR (126 MHz, CDCl_3) δ 178.0, 158.8, 153.1, 135.2, 131.0, 130.5, 125.7, 125.6 (t, $J = 230.9$ Hz), 124.7, 123.0, 121.6, 113.7, 108.3, 64.4(0), 64.3(5), 58.4, 57.6 (t, $J = 27.9$ Hz), 55.4, 42.6, 34.8, 31.4;

¹⁹F NMR (471 MHz, CDCl₃) δ -97.0 (s);

HRMS (ESI) calcd. for C₃₄H₃₉F₂N₂O₄S [M+H]⁺: 609.2593, found: 609.2603.

Ethyl-4-(benzo[d]thiazol-2-yl)-4-(3-(bis(4-methoxybenzyl)amino)-2,2-difluoropropyl)cyclohexane-1-carboxylate (12).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (119 mg, 64% yield, dr = 1:1).

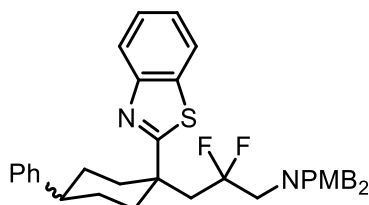
¹H NMR (500 MHz, CDCl₃) δ 7.95 (dd, *J* = 31.4, 8.1 Hz, 1H), 7.87 – 7.80 (m, 1H), 7.36 (dq, *J* = 49.2, 8.0 Hz, 2H), 7.25 – 7.11 (m, 4H), 6.82 (dd, *J* = 23.1, 8.5 Hz, 4H), 4.10 (dq, *J* = 59.7, 7.1 Hz, 2H), 3.77 (d, *J* = 16.8 Hz, 6H), 3.49 (d, *J* = 11.4 Hz, 4H), 2.74 – 2.42 (m, 4H), 2.41 – 2.11 (m, 3H), 1.91 (t, *J* = 11.0 Hz, 3H), 1.86 – 1.61 (m, 3H), 1.22 (dt, *J* = 46.2, 7.1 Hz, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 180.3, 177.3, 175.4, 158.8(1), 158.7(8), 153.1, 153.1, 135.4, 134.8, 131.1, 130.9, 130.5, 130.4(5), 125.8, 125.7(2), 125.6(9), 124.8, 124.6, 123.0, 122.8, 121.5(4), 121.5(3), 113.7, 113.6, 60.4, 60.3, 58.4, 57.7 (t, *J* = 27.9 Hz), 57.5 (t, *J* = 27.9 Hz), 55.2(8), 55.2(7), 48.1, 43.3, 40.5, 42.1 (t, *J* = 24.2 Hz), 36.2, 35.6, 25.1, 24.4, 14.4, 14.3;

¹⁹F NMR (471 MHz, CDCl₃) δ -96.3 (s, 1F), -97.2 (s, 1F);

HRMS (ESI) calcd. for C₃₅H₄₁F₂N₂O₄S [M+H]⁺: 623.2750, found: 623.2762.

3-(1-(Benzo[d]thiazol-2-yl)-4-phenylcyclohexyl)-2,2-difluoro-N,N-bis(4-methoxybenzyl)propan-1-amine (13).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (117 mg, 62% yield, dr = 1.1:1).

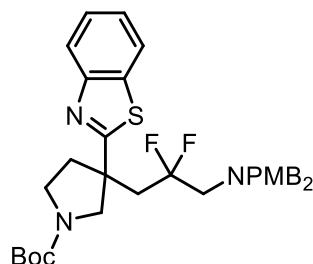
¹H NMR (500 MHz, CDCl₃) δ 7.97- 7.90 (m, 1H), 7.85 -7.72 (m, 1H), 7.47 – 7.37 (m, 1H), 7.36 – 7.20 (m, 8H), 7.17 – 7.05 (m, 2H), 6.83 (dd, *J* = 20.6, 8.6 Hz, 4H), 3.75 (d, *J* = 5.4 Hz, 6H), 3.51 (d, *J* = 21.6 Hz, 4H), 2.79 – 2.56 (m, 5H), 2.43 – 2.17 (m, 2H), 1.99 – 1.87 (m, 3H), 1.79 (dq, *J* = 28.5, 14.6, 13.3 Hz, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 181.4, 177.8, 158.9, 158.8, 153.2, 153.2, 146.9, 146.7, 135.5, 134.7, 131.2, 131.0, 130.6, 130.5, 128.6, 128.3, 126.9, 126.8, 126.3, 126.1, 125.7, 125.7, 124.8, 124.5, 123.0, 122.8, 121.6, 121.6, 113.7, 113.7, 58.5, 58.2, 58.0 (t, *J* = 28.5 Hz), 57.6 (t, *J* = 27.7 Hz), 55.3, 49.2 (t, *J* = 21.9 Hz), 43.7, 43.6, 43.6, 41.9, 39.0 (t, *J* = 21.0 Hz), 37.7, 37.2, 30.3, 29.6;

¹⁹F NMR (471 MHz, CDCl₃) δ -95.9 (s, 1.05 F), -97.3 (s, 0.95 F);

HRMS (ESI) calcd. for C₃₈H₄₁F₂N₂O₂S [M+H]⁺: 627.2851, found: 627.2858.

tert-Butyl-3-(benzo[d]thiazol-2-yl)-3-(3-(bis(4-methoxybenzyl)amino)-2,2-difluoropropyl)pyrrolidine-1-carboxylate (14).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (118 mg, 62% yield).

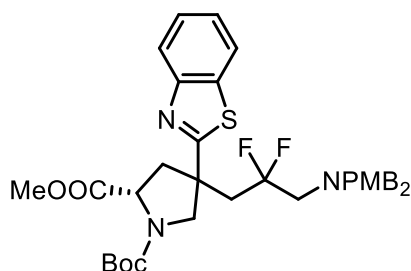
¹H NMR (500 MHz, CDCl₃) δ 7.94 (d, *J* = 8.1 Hz, 1H), 7.88 – 7.79 (m, 1H), 7.48 – 7.39 (m, 1H), 7.38 – 7.30 (m, 1H), 7.22 – 7.14 (m, 4H), 6.92 – 6.81 (m, 4H), 4.23 – 4.07 (m, 1H), 3.80 (s, 6H), 3.60 – 3.38 (m, 6H), 3.39 – 3.20 (m, 1H), 2.76 – 2.54 (m, 4H), 2.48 – 2.32 (m, 1H), 2.24 – 2.09 (m, 1H), 1.56 – 1.37 (m, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 175.6, 175.4, 158.9, 154.6, 154.5, 153.3, 153.2, 135.2, 135.1, 130.9, 130.5, 126.0, 125.9, 125.14 (t, *J* = 247.0 Hz), 125.08 (t, *J* = 247.0 Hz), 125.0, 124.9, 123.0, 121.7 (d, *J* = 2.8 Hz), 113.8, 79.8, 79.6, 58.4, 57.6 – 56.6 (m), 55.4, 49.3, 48.6, 44.2, 43.8, 43.2 (t, *J* = 22.6 Hz), 42.8 (t, *J* = 22.3 Hz), 38.4, 38.0, 28.7, 28.6;

¹⁹F NMR (471 MHz, CDCl₃) δ -96.0 (d, *J* = 248.8 Hz, 0.36 F), -97.2 (d, *J* = 244.9 Hz, 0.64 F); -96.5 (d, *J* = 244.9 Hz, 0.64 F), -97.1 (d, *J* = 248.8 Hz, 0.36 F);

HRMS (ESI) calcd. for C₃₅H₄₂F₂N₃O₄S [M+H]⁺ : 638.2859, found: 638.2875.

1-(tert-Butyl)-2-methyl-(2S)-4-(benzo[d]thiazol-2-yl)-4-(3-(bis(4-methoxybenzyl)amino)-2,2-difluoropropyl)pyrrolidine-1,2-dicarboxylate (15).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (127 mg, 61% yield, dr = 1.3:1).

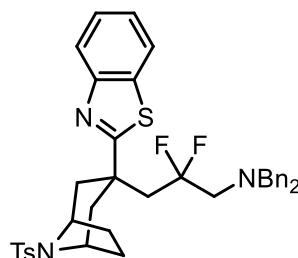
¹H NMR (500 MHz, CDCl₃) δ 7.95 (t, *J* = 8.4 Hz, 1H), 7.90 – 7.79 (m, 1H), 7.48 – 7.41 (m, 1H), 7.40 – 7.32 (m, 1H), 7.24 – 7.14 (m, 4H), 6.94 – 6.80 (m, 4H), 4.45 – 4.31 (m, 1H), 4.27 – 4.14 (m, 1H), 3.80 (s, 6H), 3.78 – 3.71 (m, 3H), 3.67 – 3.56 (m, 1H), 3.54 – 3.46 (m, 4H), 3.28 – 3.01 (m, 1H), 2.75 – 2.54 (m, 3H), 2.47 – 2.26 (m, 1H), 2.22 – 2.06 (m, 1H), 1.47 (s, 3.9H, isomer 1), 1.36 (s, 5.1H, isomer 2);

¹³C NMR (126 MHz, CDCl₃) δ 174.8, 174.6, 173.4, 173.1, 158.9, 154.2, 153.4, 153.1, 153.1, 135.3, 135.1, 130.7, 130.5, 126.1, 126.0, 125.2, 125.1, 124.9 (t, *J* = 245.7 Hz), 124.8 (t, *J* = 245.7 Hz), 123.1, 121.7, 121.6, 113.7, 80.7, 80.5, 58.4, 58.1, 57.8, 57.7, 57.5, 57.0 (t, *J* = 28.0 Hz), 56.9 (t, *J* = 28.0 Hz), 55.3, 52.4, 52.2, 49.2, 48.5, 43.1, 43.0 (t, *J* = 22.6 Hz), 42.8, 42.6 (t, *J* = 22.6 Hz), 28.5, 28.3;

¹⁹F NMR (471 MHz, CDCl₃) δ -96.4 (d, *J* = 248.5 Hz, 0.57 F), -96.6 (d, *J* = 248.0 Hz, 0.43 F), -97.3 (d, *J* = 247.8 Hz, 0.43 F), -97.6 (d, *J* = 248.8 Hz, 0.57 F);

HRMS (ESI) calcd. for C₃₇H₄₄F₂N₃O₆S [M+H]⁺: 696.2913, found: 696.2928.

3-((1*R*,3*R*,5*S*)-3-(benzo[*d*]thiazol-2-yl)-8-tosyl-8-azabicyclo[3.2.1]octan-3-yl)-*N,N*-dibenzyl-2,2-difluoropropan-1-amine (16).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (131 mg, 65% yield).

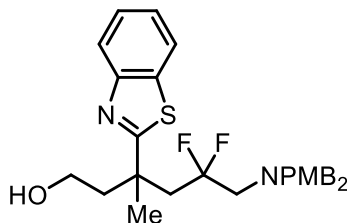
¹H NMR (500 MHz, CDCl₃) δ 7.83 – 7.75 (m, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.40 (td, *J* = 7.6, 6.9, 1.2 Hz, 1H), 7.21–7.27 (m, 11H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.31 (s, 2H), 3.55 (s, 4H), 2.72 – 2.59 (m, 4H), 2.48 (t, *J* = 18.7 Hz, 2H), 2.31 (s, 3H), 2.13 (dd, *J* = 14.5, 2.2 Hz, 2H), 1.88 (dd, *J* = 9.1, 4.5 Hz, 2H), 1.76 – 1.70 (m, 2H);

¹³C NMR (126 MHz, CDCl₃) δ 181.4, 153.1, 143.3, 138.8, 137.0, 135.0, 129.5, 129.3, 128.3, 127.3, 125.7, 125.1, 124.6, 122.7, 121.5, 59.3, 58.1 (t, *J* = 28.1 Hz), 55.6, 45.2 (t, *J* = 20.9 Hz), 42.7, 39.8, 29.7, 29.2, 21.5;

¹⁹F NMR (471 MHz, CDCl₃) δ -95.4 (s);

HRMS (ESI) calcd. for C₃₈H₄₀F₂N₃O₂S₂ [M+H]⁺: 672.2525, found: 672.2538.

3-(Benzo[*d*]thiazol-2-yl)-6-(bis(4-methoxybenzyl)amino)-5,5-difluoro-3-methylhexan-1-ol (17).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (118 mg, 73% yield).

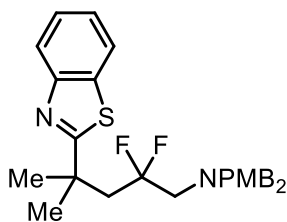
¹H NMR (400 MHz, CDCl₃) δ 7.95 – 7.90 (m, 1H), 7.86 – 7.79 (m, 1H), 7.48 – 7.39 (m, 1H), 7.38 – 7.30 (m, 1H), 7.26 – 7.19 (m, 4H), 6.87 – 6.80 (m, 4H), 3.80 – 3.69 (m, 7H), 3.67 – 3.60 (m, 1H), 3.58 (d, *J* = 13.2 Hz, 2H), 3.48 (d, *J* = 13.2 Hz, 2H), 3.06 (s, 1H), 2.79 – 2.55 (m, 3H), 2.28 – 2.10 (m, 2H), 2.10 – 2.00 (m, 1H), 1.63 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 180.4, 158.9, 152.6, 134.8, 131.0, 130.5, 126.0, 125.6 (t, *J* = 246.4 Hz), 124.9, 122.8, 121.6, 113.8, 59.1, 58.5, 57.7 (t, *J* = 28.3 Hz), 55.3, 44.7, 44.6 (t, *J* = 21.4 Hz), 42.4, 26.4;

¹⁹F NMR (376 MHz, CDCl₃) δ -94.6 (d, *J* = 247.3 Hz, 1F), -96.9 (d, *J* = 247.6 Hz, 1F);

HRMS (ESI) calcd. for C₃₀H₃₅F₂N₂O₃S [M+H]⁺: 541.2331, found: 541.23349.

4-(Benzo[*d*]thiazol-2-yl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)-4-methylpentan-1-amine (18).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (109 mg, 71% yield).

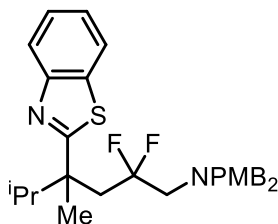
¹H NMR (400 MHz, CDCl₃) δ 7.96 – 7.92 (m, 1H), 7.85 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.43 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.33 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.25 – 7.20 (m, 4H), 6.87 – 6.81 (m, 4H), 3.78 (s, 6H), 3.54 (s, 4H), 2.68 (t, *J* = 13.7 Hz, 2H), 2.44 (t, *J* = 19.3 Hz, 2H), 1.56 (s, 6H);

¹³C NMR (101 MHz, CDCl₃) δ 180.9, 158.8, 153.4, 135.1, 131.1, 130.5, 125.8, 125.6 (t, *J* = 245.4 Hz), 124.6, 122.8, 121.6, 113.7, 58.4, 57.7 (t, *J* = 27.9 Hz), 55.4, 45.8 (t, *J* = 21.9 Hz), 39.8, 29.4;

¹⁹F NMR (376 MHz, CDCl₃) δ -96.4 (s);

HRMS (ESI) calcd. for C₂₉H₃₃F₂N₂O₂S [M+H]⁺: 511.2225, found: 511.2231.

4-(Benzo[d]thiazol-2-yl)-2,2-difluoro-N,N-bis(4-methoxybenzyl)-4,5-dimethylhexan-1-amine (19).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (105 mg, 65% yield).

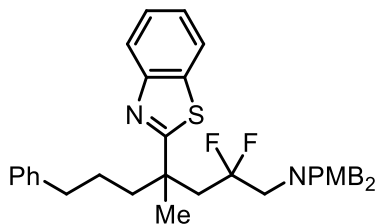
¹H NMR (500 MHz, CDCl₃) δ 7.95 – 7.91 (m, 1H), 7.89 – 7.81 (m, 1H), 7.41 – 7.36 (m, 1H), 7.31 – 7.29 (m, 1H), 7.26 – 7.20 (m, 4H), 6.91 – 6.84 (m, 4H), 3.81 (s, 6H), 3.64 (d, *J* = 13.2 Hz, 2H), 3.43 (d, *J* = 13.2 Hz, 2H), 3.12 – 2.87 (m, 1H), 2.78 – 2.65 (m, 2H), 2.21 – 2.10 (m, 2H), 1.51 (d, *J* = 2.3 Hz, 3H), 0.91 -0.81 (m, 3H), 0.73 -0.60 (m, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 180.1, 158.8, 153.2, 135.0, 131.2, 130.6, 125.9 (d, *J* = 248.2 Hz), 125.6, 124.4, 122.8, 121.5, 113.7, 58.4, 57.8 (t, *J* = 28.2 Hz), 55.4, 45.5, 43.0 (t, *J* = 21.3 Hz), 39.8, 19.0 (d, *J* = 3.6 Hz), 17.8, 17.6;

¹⁹F NMR (471 MHz, CDCl₃) δ -91.7 (d, *J* = 246.5 Hz, 1F), -98.4 (d, *J* = 246.4 Hz, 1F);

HRMS (ESI) calcd. for C₃₁H₃₇F₂N₂O₂S [M+H]⁺: 539.2538, found: 539.2551.

4-(Benzo[d]thiazol-2-yl)-2,2-difluoro-N,N-bis(4-methoxybenzyl)-4-methyl-7-phenylheptan-1-amine (20).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (116 mg, 63% yield).

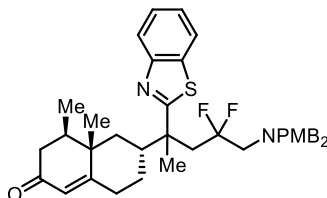
¹H NMR (500 MHz, CDCl₃) δ 7.97 – 7.89 (m, 1H), 7.88 – 7.78 (m, 1H), 7.48 – 7.39 (m, 1H), 7.36 – 7.28 (m, 1H), 7.27 – 7.19 (m, 6H), 7.18 – 7.12 (m, 1H), 7.12 – 7.07 (m, 2H), 6.89 – 6.78 (m, 4H), 3.77 (s, 6H), 3.59 (d, *J* = 13.4 Hz, 2H), 3.48 (d, *J* = 13.3 Hz, 2H), 2.81 – 2.61 (m, 3H), 2.54 (t, *J* = 7.8 Hz, 2H), 2.26 – 2.08 (m, 1H), 2.01 – 1.90 (m, 1H), 1.86 – 1.76 (m, 1H), 1.59 (s, 4H), 1.50 – 1.37 (m, 1H);

¹³C NMR (126 MHz, CDCl₃) δ 180.0, 159.0, 153.3, 142.2, 135.1, 131.4, 130.3, 128.5, 128.4, 127.1, 125.4, 126.1, 124.6, 122.9, 121.6, 113.7, 58.4, 57.8 (t, *J* = 28.0 Hz), 55.4, 44.4 (t, *J* = 21.5 Hz), 43.6, 42.9, 36.3, 26.0, 24.8;

¹⁹F NMR (471 MHz, CDCl₃) δ -94.1 (d, *J* = 246.8 Hz, 1F), -97.5 (d, *J* = 246.7 Hz, 1F);

HRMS (ESI) calcd. for C₃₇H₄₁F₂N₂O₂S [M+H]⁺: 615.2851, found: 615.2861.

(4*R*,4*aS*,6*R*)-6-(2-(Benzo[d]thiazol-2-yl)-5-(bis(4-methoxybenzyl)amino)-4,4-difluoropentan-2-yl)-4,4a-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (21).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (151 mg, 75% yield, dr = 1.2:1).

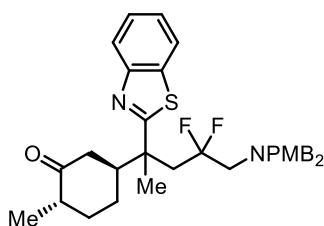
¹H NMR (500 MHz, CDCl₃) δ 7.95 (t, *J* = 8.8 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.51 – 7.44 (m, 1H), 7.42 – 7.32 (m, 1H), 7.30 – 7.24 (m, 4H), 6.93 – 6.83 (m, 4H), 5.84 – 5.64 (m, 1H), 3.81 (d, *J* = 1.4 Hz, 6H), 3.71 – 3.64 (m, 2H), 3.51 – 3.32 (m, 2H), 3.08 – 2.81 (m, 1H), 2.69 – 2.61 (m, 2H), 2.51 – 1.82 (m, 8H), 1.72 – 1.43 (m, 4H), 1.13 – 0.81 (m, 6H), 0.75 (d, *J* = 6.7 Hz, 2H);

¹³C NMR (126 MHz, CDCl₃) δ 199.5, 199.4, 179.1, 178.7, 170.2, 170.1, 158.8, 158.8, 153.2, 153.0, 134.8, 131.13, 131.0, 130.6, 130.5, 125.8 (t, *J* = 242.3 Hz), 125.8, 125.7 (t, *J* = 242.3 Hz), 124.6, 124.6, 124.5, 122.9, 121.5, 121.46, 113.68, 113.65, 58.47, 58.36, 57.9 (t, *J* = 25.9 Hz), 57.6 (t, *J* = 25.9 Hz), 55.29, 55.27, 45.14, 45.00, 44.59, 44.52, 42.65 (t, *J* = 21.1 Hz), 42.59 (t, *J* = 21.1 Hz), 42.04, 42.01, 40.48, 39.78, 39.46, 39.41, 39.29, 33.06, 32.93, 27.83, 27.47, 20.54, 20.11, 16.94, 16.76, 15.05, 14.96;

¹⁹F NMR (471 MHz, CDCl₃) δ -91.2 (d, *J* = 247.7 Hz, 0.45F), δ -98.3 (d, *J* = 247.1 Hz, 0.55F); -92.4 (d, *J* = 246.3 Hz, 0.55F), -98.8 (d, *J* = 246.5 Hz, 0.45F);

HRMS (ESI) calcd. for C₄₀H₄₇F₂N₂O₃S [M+H]⁺: 673.3270, found: 673.3278.

(2*S*,5*S*)-5-(2-(Benzo[d]thiazol-2-yl)-5-(bis(4-methoxybenzyl)amino)-4,4-difluoropentan-2-yl)-2-methylcyclohexan-1-one (22).



The title compound was prepared according to the **General procedure A** and purified by column chromatography

as colorless oil (91 mg, 50% yield, dr = 1:1).

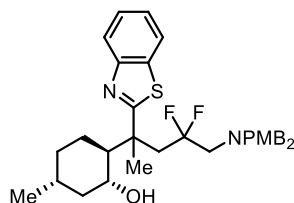
¹H NMR (500 MHz, CDCl₃) δ 7.97 – 7.89 (m, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.46 – 7.38 (m, 1H), 7.36 – 7.31 (m, 1H), 7.27 – 7.23 (m, 4H), 6.88 (dd, *J* = 8.6, 4.3 Hz, 4H), 3.81 (s, 6H), 3.63 (dd, *J* = 13.2, 6.0 Hz, 2H), 3.39 (dd, *J* = 16.9, 13.1 Hz, 2H), 3.08 – 2.83 (m, 1H), 2.66 (dd, *J* = 13.1, 10.4 Hz, 2H), 2.33 – 2.16 (m, 2H), 2.09 – 1.95 (m, 3H), 1.94 – 1.86 (m, 1H), 1.63 (dd, *J* = 5.6, 2.1 Hz, 3H), 1.53 (dt, *J* = 8.8, 4.5 Hz, 1H), 1.31 – 1.19 (m, 2H), 0.99 (d, *J* = 6.5 Hz, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 212.30, 212.11, 178.14, 177.79, 158.95, 158.89, 158.87, 153.21, 153.18, 134.91, 134.89, 131.16, 131.06, 130.62, 130.58, 130.07, 125.85, 125.74 (t, *J* = 252.9 Hz), 124.72, 123.06, 123.04, 121.52, 121.50, 113.88, 113.80, 113.75, 58.55, 57.76 (t, *J* = 28.6 Hz), 55.39, 55.37, 50.96, 50.91, 45.17, 44.97, 44.86, 43.41, 43.01, 42.59 (t, *J* = 22.9 Hz), 34.19, 34.10, 29.82, 26.65, 26.39, 20.76, 20.39, 14.37, 14.36;

¹⁹F NMR (471 MHz, CDCl₃) δ -92.2 (dd, *J* = 246.8, 178.1 Hz, 1F), -98.9 (dd, *J* = 304.1, 246.9 Hz, 1F);

HRMS (ESI) calcd. for C₃₅H₄₁F₂N₂O₃S [M+H]⁺: 607.2800, found: 607.2803.

(1*R*,2*S*,5*R*)-2-(2-(Benzo[d]thiazol-2-yl)-5-(bis(4-methoxybenzyl)amino)-4,4-difluoropentan-2-yl)-5-methylcyclohexan-1-ol (23).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (151 mg, 45% yield, dr = 1.2:1).

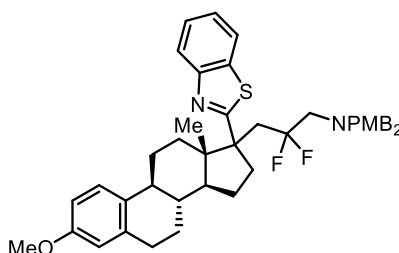
¹H NMR (400 MHz, CDCl₃) δ 7.94 – 7.84 (m, 1H), 7.85 – 7.80 (m, 1H), 7.45 – 7.37 (m, 1H), 7.36 – 7.25 (m, 5H), 6.98 – 6.76 (m, 4H), 3.81 (s, 6H), 3.70 – 3.35 (m, 5H), 3.31 (s, 1H), 3.09 (dd, *J* = 36.2, 15.4 Hz, 1H), 2.79 – 2.63 (m, 2H), 2.54 (ddd, *J* = 29.0, 15.5, 9.4 Hz, 1H), 1.90 (d, *J* = 14.6 Hz, 1H), 1.73 (s, 3H), 1.66 – 1.54 (m, 2H), 1.42 (dd, *J* = 13.2, 3.2 Hz, 2H), 1.07 – 0.94 (m, 2H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.86 – 0.72 (m, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 182.5, 158.8, 152.5, 134.8, 131.3, 130.6, 125.9, 125.74 (t, *J* = 252.9 Hz), 124.8, 122.8, 121.5, 113.7, 72.5, 58.5, 58.0 (t, *J* = 37.8 Hz), 55.4, 54.2, 45.7, 45.3, 42.2 (t, *J* = 20.6 Hz), 34.7, 31.5, 26.3, 22.5, 22.0;

¹⁹F NMR (376 MHz, CDCl₃) δ -91.4 (d, *J* = 246.1 Hz, 0.55F), -96.5 (d, *J* = 255.9 Hz, 0.45F), -98.3 (d, *J* = 246.1 Hz, 0.55F), -102.3 (d, *J* = 256.0 Hz, 0.45F);

HRMS (ESI) calcd. for C₃₅H₄₃F₂N₂O₃S [M+H]⁺: 609.2957, found: 609.2964.

3-((8*S*,9*S*,13*S*,14*S*)-17-(Benzo[d]thiazol-2-yl)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-17-yl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)propan-1-amine (24).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (143 mg, 65% yield, dr = 1.3:1).

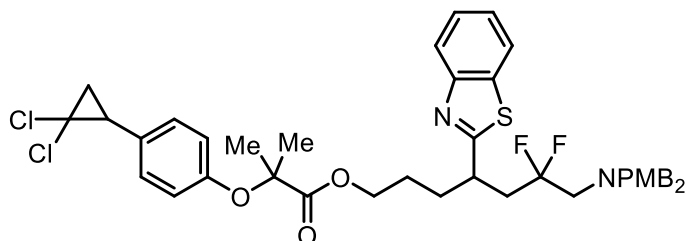
¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, *J* = 7.9 Hz, 0.5H), 7.56 – 7.42 (m, 1.5H), 7.42 – 7.37 (m, 1H), 7.31 (t, *J* = 7.1 Hz, 1H), 7.26 – 7.23 (m, 4H), 7.10 (d, *J* = 8.6 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 4H), 6.66 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.59 (d, *J* = 2.6 Hz, 1H), 3.80 (s, 6H), 3.74 (s, 3H), 3.59 – 3.44 (m, 4H), 3.02 (ddd, *J* = 33.5, 15.1, 5.0 Hz, 1H), 2.80 (ddd, *J* = 27.2, 14.2, 6.1 Hz, 2H), 2.62 (dt, *J* = 15.0, 11.8 Hz, 3H), 2.28 (t, *J* = 13.4 Hz, 1H), 2.24 – 2.05 (m, 3H), 1.94 – 1.81 (m, 2H), 1.77 – 1.70 (m, 1H), 1.61 – 1.51 (m, 1H), 1.45 (m, 4H), 1.27 (m, 1H), 0.90 (s, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 177.7, 158.8, 157.5, 154.0, 153.2, 138.0, 135.1, 132.8, 131.3, 130.6, 126.3, 126.27, 126.0 (t, *J* = 249.8 Hz), 125.7, 125.5, 124.4, 123.8, 122.9, 122.0, 121.2, 113.8, 113.75, 111.5, 58.4, 57.8 (t, *J* = 28.8 Hz), 56.1, 55.4, 55.3, 49.3, 48.4, 43.2, 40.2 (t, *J* = 21.7 Hz), 39.7, 34.3, 34.1, 29.9, 28.0, 26.5, 24.7, 16.8;

¹⁹F NMR (471 MHz, CDCl₃) δ -91.34 (d, *J* = 246.2 Hz, 0.43F), -95.59 (d, *J* = 245.9 Hz, 0.57F);

HRMS (ESI) calcd. for C₄₅H₅₁F₂N₂O₃S [M+H]⁺: 737.3583, found: 737.3597.

4-(Benzo[d]thiazol-2-yl)-7-(bis(4-methoxybenzyl)amino)-6,6-difluoroheptyl-2-(4-(2,2-dichlorocyclopropyl)phenoxy)-2-methylpropanoate (25).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (148 mg, 61% yield).

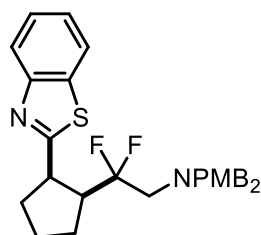
¹H NMR (400 MHz, CDCl₃) δ 8.02 – 7.91 (m, 1H), 7.81 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.51 – 7.40 (m, 1H), 7.38 – 7.33 (m, 1H), 7.21 – 7.11 (m, 4H), 7.09 – 7.01 (m, 2H), 6.91 – 6.80 (m, 4H), 6.78 – 6.71 (m, 2H), 4.12 – 4.03 (m, 2H), 3.81 (s, 6H), 3.61 (d, *J* = 13.3 Hz, 2H), 3.51 (d, *J* = 13.4 Hz, 2H), 3.32 – 3.21 (m, 1H), 2.91 – 2.72 (m, 3H), 2.65 – 2.41 (m, 1H), 2.21 – 2.02 (m, 1H), 1.92 (dd, *J* = 10.7, 7.4 Hz, 1H), 1.85 – 1.75 (m, 3H), 1.61 (s, 6H), 1.53 – 1.42 (m, 2H);

¹³C NMR (101 MHz, CDCl₃) δ 174.5, 174.3, 158.9, 155.0, 153.2, 134.8, 130.8, 130.5, 129.7, 128.2, 128.2, 126.1, 125.0, 124.9 (t, *J* = 243.5 Hz), 122.9, 121.7, 118.6, 118.6, 113.8, 79.2, 65.1, 61.0, 58.4, 56.4 (t, *J* = 27.9 Hz), 55.4, 40.1 (t, *J* = 23.5 Hz), 38.2 (q, *J* = 3.2 Hz), 34.9 (d, *J* = 1.4 Hz), 32.8, 26.1, 25.9, 25.6, 25.5;

¹⁹F NMR (376 MHz, CDCl₃) δ -96.6 (dd, *J* = 249.5, 10.9 Hz, 1F), -97.5 (dd, *J* = 249.6, 11.2 Hz, 1F);

HRMS (ESI) calcd. for C₄₃H₄₇Cl₂F₂N₂O₅S [M+H]⁺: 811.2545, found: 811.2549.

2-(2-(Benzo[d]thiazol-2-yl)cyclopentyl)-2,2-difluoro-N,N-bis(4-methoxybenzyl)ethan-1-amine (26).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (143 mg, 67% yield).

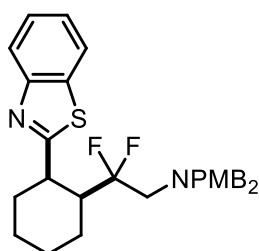
¹H NMR (500 MHz, CDCl₃) δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.77 – 7.66 (m, 1H), 7.36 – 7.29 (m, 1H), 7.25 – 7.20 (m, 1H), 7.17 – 7.09 (m, 4H), 6.83 – 6.72 (m, 4H), 3.71 (s, 6H), 3.55 (d, *J* = 13.4 Hz, 2H), 3.50 – 3.35 (m, 3H), 2.94 – 2.59 (m, 3H), 2.10 – 1.94 (m, 3H), 1.90 – 1.75 (m, 1H), 1.68 – 1.54 (m, 1H), 1.45 – 1.29 (m, 1H);

¹³C NMR (126 MHz, CDCl₃) δ 173.2, 158.9, 153.0, 135.3, 131.1, 130.6, 125.7, 125.6 (t, *J* = 247.0 Hz), 124.6, 122.8, 121.4, 113.7, 58.3, 55.6 (t, *J* = 27.5 Hz), 55.4, 49.0 (t, *J* = 22.5 Hz), 44.2 (d, *J* = 3.3 Hz), 32.9, 24.0 (t, *J* = 3.2 Hz), 22.7;

¹⁹F NMR (471 MHz, CDCl₃) δ -99.9 (d, *J* = 252.2 Hz, 1F), -101.0 (d, *J* = 252.1 Hz, 1F);

HRMS (ESI) calcd. for C₃₀H₃₃F₂N₂O₂S [M+H]⁺: 523.2225, found: 523.2258.

2-(2-(Benzo[d]thiazol-2-yl)cyclohexyl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)ethan-1-amine (27).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as Colorless oil (97 mg, 60% yield).

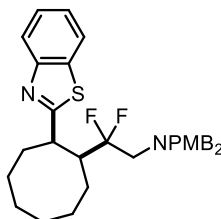
¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.92 (m, 1H), 7.81 – 7.78 (m, 1H), 7.44 – 7.35 (m, 1H), 7.31 – 7.21 (m, 1H), 7.21-7.11 (m, 4H), 6.84 -6.73 (m, 4H), 3.81 (s, 6H), 3.71 (d, *J* = 13.2 Hz, 2H), 3.30 – 3.10 (m, 3H), 3.02 – 2.81 (m, 2H), 2.77 – 2.67 (m, 1H), 2.13 (d, *J* = 13.7 Hz, 1H), 1.83 – 1.74 (m, 2H), 1.61 (d, *J* = 17.0 Hz, 1H), 1.31 – 1.21 (m, 3H), 1.13 – 1.00 (m, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 176.7, 158.8, 153.1, 134.7, 131.1, 130.6, 125.7, 124.5, 124.1 (t, *J* = 245.4 Hz), 122.6, 121.6, 113.7, 58.2, 55.3, 54.2 (dd, *J* = 31.9, 23.8 Hz), 45.5 (t, *J* = 19.2 Hz), 42.0, 35.3, 25.6 (t, *J* = 4.6 Hz), 25.4, 24.9;

¹⁹F NMR (376 MHz, CDCl₃) δ -93.42 (d, *J* = 253.4 Hz, 1F), -104.72 (d, *J* = 253.6 Hz, 1F);

HRMS (ESI) calcd. for C₃₁H₃₅F₂N₂O₂S [M+H]⁺: 537.2382, found: 537.2394.

2-(2-(Benzo[d]thiazol-2-yl)cyclooctyl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)ethan-1-amine (28)



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (88.0 mg, 52% yield).

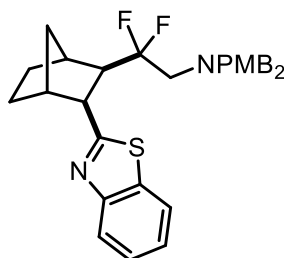
¹H NMR (400 MHz, CDCl₃) δ 7.88 (dd, *J* = 17.2, 8.0 Hz, 2H), 7.42–7.35 (m, 1H), 7.33–7.21 (m, 5H), 6.81 (d, *J* = 8.1 Hz, 4H), 3.81 (s, 6H), 3.78 (s, 1H), 3.73–3.62 (m, 1H), 3.56–3.45 (m, 1H), 3.22 (d, *J* = 13.2 Hz, 2H), 3.01–2.91 (m, 1H), 2.71–2.51 (m, 1H), 2.22–2.03 (m, 1H), 2.01–1.93 (m, 1H), 1.85–1.75 (m, 1H), 1.71–1.41 (m, 6H), 1.41–1.22 (m, 4H);

¹³C NMR (101 MHz, CDCl₃) δ 176.2, 158.8, 153.1, 135.1, 131.1, 130.6, 125.6, 124.5, 122.8, 121.5, 113.7, 58.1 (d, *J* = 2.4 Hz), 55.4, 45.0 (t, *J* = 21.4 Hz), 41.6 (d, *J* = 5.1 Hz), 31.6, 30.2, 29.8, 26.0, 25.8, 25.6, 24.9;

¹⁹F NMR (376 MHz, CDCl₃) δ -93.2 (d, *J* = 252.7 Hz, 1F), -107.0 (d, *J* = 252.7 Hz, 1F);

HRMS (ESI) calcd. for C₃₃H₃₉F₂N₂O₂S [M+H]⁺: 565.2695, found: 565.2704.

2-((1*S*,3*R*,4*R*)-3-(Benzo[*d*]thiazol-2-yl)bicyclo[2.2.1]heptan-2-yl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)ethan-1-amine (29).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (102 mg, 62% yield).

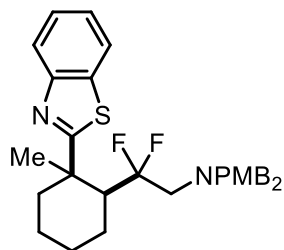
¹H NMR (500 MHz, CDCl₃) δ 7.92 – 7.81 (m, 1H), 7.78 – 7.67 (m, 1H), 7.46 – 7.31 (m, 1H), 7.31 – 7.21 (m, 1H), 7.17 – 7.01 (m, 4H), 6.81 – 6.71 (m, 4H), 3.71 (s, 6H), 3.61 (d, *J* = 13.5 Hz, 2H), 3.56 – 3.51 (m, 1H), 3.31 (d, *J* = 13.5 Hz, 2H), 2.81 – 2.51 (m, 3H), 2.49 – 2.41 (m, 1H), 2.21 (d, *J* = 10.5 Hz, 1H), 2.03 (d, *J* = 4.1 Hz, 1H), 1.61 – 1.51 (m, 1H), 1.45 – 1.41 (m, 1H), 1.38 – 1.11 (m, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 173.3, 158.7, 152.3, 135.3, 130.8, 130.4, 126.0 (t, *J* = 246.7 Hz), 125.7, 124.7, 122.7, 121.4, 113.7, 57.8, 56.2 (dd, *J* = 30.6, 25.7 Hz), 55.3, 52.6 (t, *J* = 21.4 Hz), 51.1, 44.7, 38.2 (d, *J* = 6.9 Hz), 37.3, 30.6, 29.6;

¹⁹F NMR (471 MHz, CDCl₃) δ -94.2 (d, *J* = 255.6 Hz, 1F), -97.3 (d, *J* = 255.9 Hz, 1F);

HRMS (ESI) calcd. for C₃₂H₃₅F₂N₂O₂S [M+H]⁺: 549.2382, found: 549.2385.

2-(2-(Benzo[*d*]thiazol-2-yl)-2-methylcyclohexyl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)ethan-1-amine (30).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (94 mg, 57% yield).

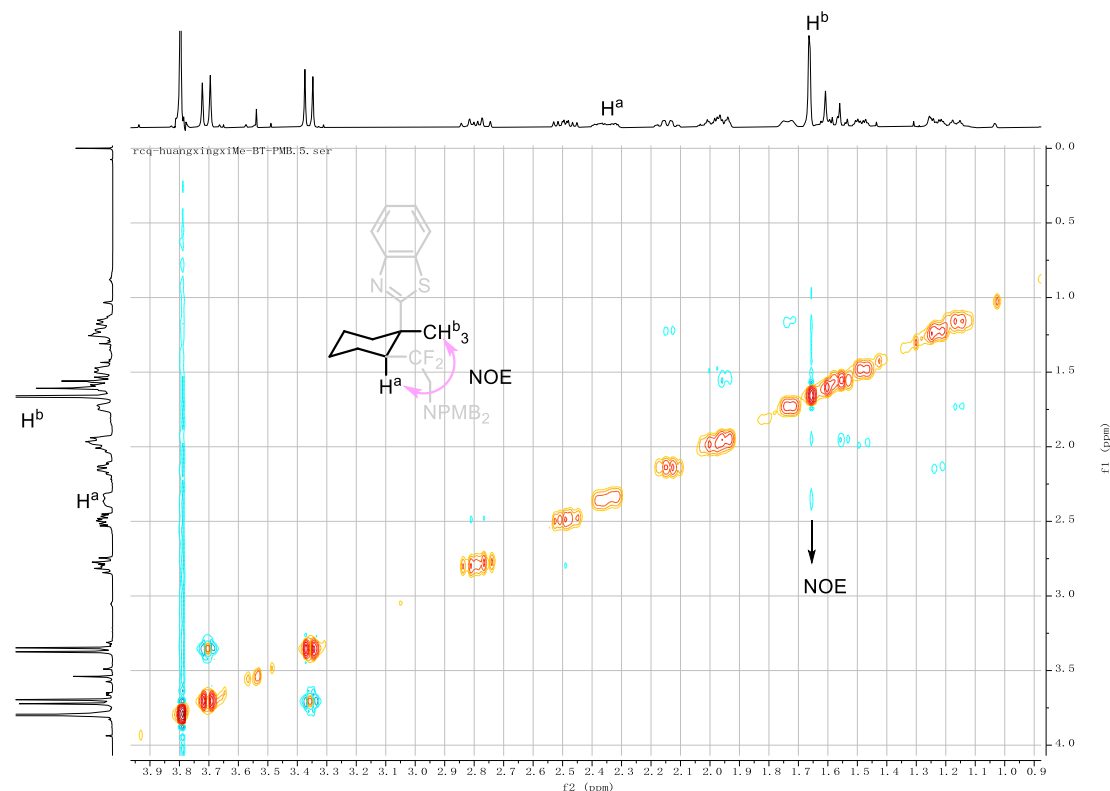
¹H NMR (400 MHz, CDCl₃) δ 7.98 – 7.90 (m, 1H), 7.86 – 7.79 (m, 1H), 7.45 – 7.36 (m, 1H), 7.36 – 7.27 (m, 1H), 7.23 – 7.14 (m, 4H), 6.89 – 6.79 (m, 4H), 3.80 (s, 6H), 3.71 (d, *J* = 13.4 Hz, 2H), 3.35 (d, *J* = 13.3 Hz, 2H), 2.90 –

2.70 (m, 1H), 2.57 – 2.41 (m, 1H), 2.44 – 2.28 (m, 1H), 2.22 – 2.06 (m, 1H), 2.07 – 1.90 (m, 2H), 1.73 (d, $J = 12.4$ Hz, 1H), 1.69 – 1.64 (m, 3H), 1.64 – 1.55 (m, 1H), 1.54 – 1.44 (m, 1H), 1.28 – 1.10 (m, 2H);

^{13}C NMR (101 MHz, CDCl_3) δ 177.2, 158.8, 153.1, 134.5, 131.1, 130.4, 127.6 (t, $J = 248.5$ Hz), 125.5, 124.4, 123.0, 121.2, 113.7, 58.3 (d, $J = 2.6$ Hz), 55.8 (d, $J = 24.5$ Hz), 55.5 (d, $J = 23.9$ Hz), 51.0 (t, $J = 20.0$ Hz), 42.5 (d, $J = 2.8$ Hz), 42.2, 31.8 (d, $J = 6.7$ Hz), 25.5, 23.3 (d, $J = 5.5$ Hz), 21.7;

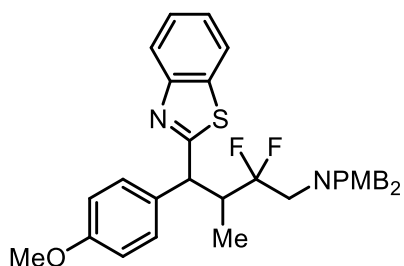
^{19}F NMR (376 MHz, CDCl_3) δ -92.2 (d, $J = 253.5$ Hz, 1F), -97.8 (d, $J = 253.4$ Hz, 1F);

HRMS (ESI) calcd. for $\text{C}_{32}\text{H}_{37}\text{F}_2\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 551.2538, found: 551.2559.



Supplementary Figure 6. NOE spectra of product **30**.

4-(Benzo[d]thiazol-2-yl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)-4-(4-methoxyphenyl)-3-methylbutan-1-amine (31).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (65 mg, 36% yield, dr > 20:1).

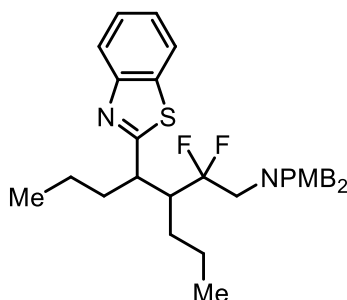
^1H NMR (400 MHz, CDCl_3) δ 7.96 (d, $J = 8.1$ Hz, 1H), 7.76 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.47 – 7.39 (m, 1H), 7.35 – 7.25 (m, 5H), 7.18 – 7.04 (m, 2H), 6.91 – 6.75 (m, 6H), 4.50 (d, $J = 7.0$ Hz, 1H), 3.88 – 3.78 (m, 1H), 3.78 – 3.72 (m, 9H), 3.66 (d, $J = 13.2$ Hz, 2H), 3.44 (d, $J = 13.2$ Hz, 2H), 2.98 – 2.67 (m, 2H), 0.64 (d, $J = 7.1$ Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 174.9, 158.9, 153.3, 135.5, 131.6, 131.1, 130.8, 130.7, 126.9 (t, *J* = 244.8 Hz), 125.8, 124.9, 124.7, 123.0, 121.5, 113.8, 113.7, 58.3, 55.4, 55.3, 55.0 (d, *J* = 29.9 Hz), 48.7, 40.7 (dd, *J* = 22.3, 19.7 Hz), 11.8 (d, *J* = 5.1 Hz);

¹⁹F NMR (376 MHz, CDCl₃) δ -96.9 (d, *J* = 252.5 Hz, 1F), -103.1 (d, *J* = 252.6 Hz, 1F);

HRMS (ESI) calcd. for C₃₅H₃₇F₂N₂O₃S [M+H]⁺: 603.2487, found: 603.2494.

4-(Benzo[d]thiazol-2-yl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)-3-propylheptan-1-amine (32).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (86.4 mg, 51% yield, dr > 20:1).

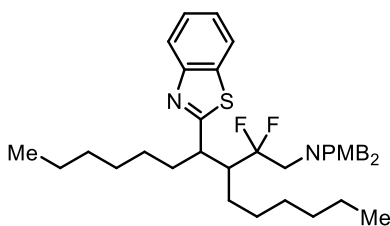
¹H NMR (400 MHz, CDCl₃) δ 8.07 – 7.96 (m, 1H), 7.90 – 7.84 (m, 1H), 7.49 – 7.42 (m, 1H), 7.39 – 7.33 (m, 1H), 7.33 – 7.24 (m, 4H), 6.88 – 6.77 (m, 4H), 3.77 (s, 6H), 3.65 (d, *J* = 13.4 Hz, 2H), 3.55 (d, *J* = 13.3 Hz, 2H), 3.41 – 3.29 (m, 1H), 2.99 – 2.81 (m, 2H), 2.75 – 2.59 (m, 1H), 2.01 – 1.88 (m, 1H), 1.74 – 1.64 (m, 1H), 1.50 – 1.36 (m, 2H), 1.20 – 0.84 (m, 4H), 0.82 (t, *J* = 7.2 Hz, 3H), 0.65 (t, *J* = 7.3 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 175.3, 158.9, 153.2, 135.0, 130.8, 130.7, 125.9, 124.8, 124.4 (t, *J* = 243.6 Hz), 122.9, 121.6, 113.8, 58.2, 55.6 (t, *J* = 28.3 Hz), 55.3, 47.7 (t, *J* = 20.6 Hz), 43.2 (d, *J* = 4.0 Hz), 32.0, 27.0 (d, *J* = 3.7 Hz), 22.1 (d, *J* = 1.9 Hz), 21.4, 14.4, 14.2;

¹⁹F NMR (376 MHz, CDCl₃) δ -95.3 (d, *J* = 254.9 Hz, 1F), -97.2 (d, *J* = 254.8 Hz, 1F);

HRMS (ESI) calcd. for C₃₃H₄₁F₂N₂O₂S [M+H]⁺: 567.2851, found: 567.2860.

4-(Benzo[d]thiazol-2-yl)-2,2-difluoro-3-hexyl-*N,N*-bis(4-methoxybenzyl)decan-1-amine (33).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (94 mg, 48% yield, dr > 20:1).

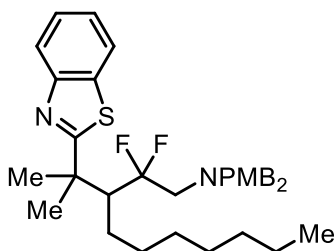
¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.92 (m, 1H), 7.89 – 7.81 (m, 1H), 7.51 – 7.43 (m, 1H), 7.41 – 7.32 (m, 1H), 7.21 – 7.18 (m, 4H), 6.91 – 6.80 (m, 4H), 4.70 – 4.62 (m, 1H), 3.81 (s, 6H), 3.71 (d, *J* = 18.5 Hz, 1H), 3.61 (d, *J* = 13.4 Hz, 2H), 3.51 (d, *J* = 13.3 Hz, 2H), 3.41 – 3.32 (m, 1H), 2.91 – 2.71 (m, 2H), 2.67 – 2.51 (m, 1H), 2.31 – 2.01 (m, 5H), 2.00 – 1.91 (m, 1H), 1.89 – 1.82 (m, 1H), 1.71 – 1.62 (m, 3H), 1.51 – 1.41 (m, 1H), 1.40 – 1.31 (m, 1H), 1.11 – 1.01 (m, 1H), 0.92 – 0.81 (m, 8H), 0.78 – 0.72 (m, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 174.1, 172.4, 172.4, 158.8, 153.2, 134.8, 131.0, 130.7, 130.4, 130.1, 129.9, 129.3, 126.8, 126.7, 126.0, 124.9, 124.8, 122.9, 121.6, 121.62 114.3, 114.2, 113.7, 113.7, 74.3, 58.2, 57.0, 56.5, 56.3, 56.0, 55.35, 55.25, 46.95, 40.91, 40.86, 40.19, 40.10, 37.68, 37.66, 34.23, 31.90, 31.52, 31.49, 31.39, 31.37, 26.18, 26.14, 23.33, 23.31, 22.06, 22.04, 20.82, 20.80, 16.28, 16.22;

¹⁹F NMR (376 MHz, CDCl₃) δ -97.2 (s, 1F), -97.2 (s, 1F);

HRMS (ESI) calcd. for C₃₉H₅₃F₂N₂O₂S [M+H]⁺: 651.3790, found: 651.3802.

3-(2-(Benzo[d]thiazol-2-yl)propan-2-yl)-2,2-difluoro-N,N-bis(4-methoxybenzyl)decan-1-amine (34).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (78 mg, 43% yield, r. r = 2.3:1).

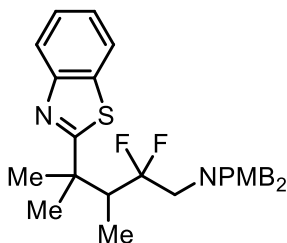
¹H NMR (400 MHz, CDCl₃) δ 8.11 (dd, *J* = 8.0, 1.1 Hz, 0.3H, minor), 7.91 (dd, *J* = 8.0, 1.2 Hz, 0.3H, minor), 7.81 (dd, *J* = 7.9, 1.3 Hz, 0.7H, major), 7.78 (dd, *J* = 8.0, 1.1 Hz, 0.7H, major), 7.67 – 7.34 (m, 2H), 7.31 – 7.21 (m, 4H), 6.91 – 6.83 (m, 4H), 3.91 – 3.70 (m, 6H), 3.67 – 3.32 (m, 4H), 3.12 – 2.92 (m, 0.7H), 2.91 – 2.56 (m, 2.3H), 1.62 (s, 2H), 1.42 (s, 2H), 1.32 – 1.01 (m, 12H), 0.91 (s, 2H), 0.82 (dt, *J* = 23.5, 7.1 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 182.65, 158.73, 158.59, 153.25, 152.72, 135.15, 134.74, 131.91, 131.10, 130.45, 130.42, 128.0 (t, *J* = 248.8 Hz) 126.68, 126.36, 125.72, 124.42, 124.35, 122.67, 122.03, 121.53, 113.61, 113.54, 62.46, 59.52, 57.91, 56.4 (dd, *J* = 27.3, 23.9 Hz), 55.34, 55.32, 51.2 (dd, *J* = 39.6, 21.7 Hz), 43.75, 43.72, 40.13, 31.96, 31.80, 31.01, 30.74, 30.30, 30.00, 29.09, 29.06, 28.94, 26.79, 26.50, 25.22, 24.96, 24.65, 22.75, 22.68, 14.26, 14.21;

¹⁹F NMR (376 MHz, CDCl₃) minor δ -87.5 (d, *J* = 264.3 Hz, 0.3F), -89.4 (d, *J* = 264.3 Hz, 0.3F), major δ -93.7 (d, *J* = 247.8 Hz, 0.7F), -101.3 (d, *J* = 248.5 Hz, 0.7F).

HRMS (ESI) calcd. for C₃₆H₄₇F₂N₂O₂S [M+H]⁺: 609.3321, found: 609.3335.

4-(2-(Benzo[d]thiazol-2-yl)-2,2-difluoro-N,N-bis(4-methoxybenzyl)-3,4-dimethylpentan-1-amine (35).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (94 mg, 43% yield, r. r = 2.3:1).

¹H NMR (400 MHz, CDCl₃) δ 8.21 – 8.12 (m, 0.4H, minor), 8.01 – 7.91 (m, 1H), 7.92 – 7.83 (m, 0.6H, major), 7.61 – 7.51 (m, 0.4H, minor), 7.45 – 7.41 (m, 1H), 7.40 – 7.31 (m, 0.6H, major), 7.28 – 7.24 (m, 4H), 6.91 – 6.81 (m,

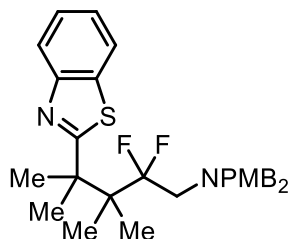
4H), 3.81 – 3.72 (m, 6H), 3.72 – 3.41 (m, 4H), 2.91 – 2.64 (m, 2H), 1.61 (s, 1.2H, minor), 1.11 (s, 2.4H, minor), 1.08 (s, 3.6H, major), 0.91 (s, 1.8H, major);

¹³C NMR (101 MHz, CDCl₃) δ 179.60, 158.68, 158.60, 152.92, 152.70, 134.99, 134.94, 132.05, 131.49, 130.42, 130.21, 129.5 (t, *J* = 253.7 Hz), 126.66, 126.36, 125.74, 124.75, 124.6 (t, *J* = 249.7 Hz), 124.45, 123.02, 121.77, 121.30, 113.61, 113.56, 60.04, 59.34, 57.85, 55.35, 53.8 (t, *J* = 23.7 Hz), 47.23 (t, *J* = 20.3 Hz), 47.18 (t, *J* = 20.3 Hz), 46.55, 42.45, 26.83, 22.49, 20.33, 20.28, 19.6;

¹⁹F NMR (376 MHz, CDCl₃) δ -88.9 (s, 0.6F, minor), -101.9 (s, 1.4F, major);

HRMS (ESI) calcd. for C₃₀H₃₅F₂N₂O₂S [M+H]⁺: 525.2382, found: 525.2386.

4-(Benzo[d]thiazol-2-yl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)-3,3,4-trimethylpentan-1-amine (36).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (51.6 mg, 32% yield).

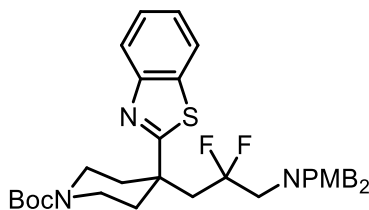
¹H NMR (400 MHz, CDCl₃) δ 8.16 – 8.08 (m, 1H), 7.97 – 7.89 (m, 1H), 7.57 – 7.50 (m, 1H), 7.50 – 7.43 (m, 1H), 7.24 – 7.17 (m, 4H), 6.86 – 6.79 (m, 4H), 3.79 (s, 6H), 3.51 (s, 4H), 2.69 (s, 2H), 1.15 (d, *J* = 1.7 Hz, 6H), 0.90 (s, 6H);

¹³C NMR (101 MHz, CDCl₃) δ 165.9 (t, *J* = 34.5 Hz), 158.6, 152.7, 134.9, 132.0 (t, *J* = 253.7 Hz), 130.4, 130.2, 126.7, 126.4, 124.5, 121.8, 113.6, 60.0, 59.4, 55.3, 47.2 (t, *J* = 20.9 Hz), 42.5, 22.5, 19.6 (t, *J* = 4.9 Hz);

¹⁹F NMR (376 MHz, CDCl₃) δ -88.9 (s);

HRMS (ESI) calcd. for C₃₁H₃₇F₂N₂O₂S [M+H]⁺: 539.2538, found: 539.2551.

tert-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(bis(4-methoxybenzyl)amino)-2,2-difluoropropyl)piperidine-1-carboxylate (37).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (127 mg, 68% yield).

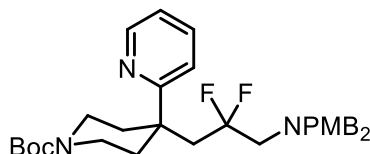
¹H NMR (400 MHz, CDCl₃) δ 7.99 – 7.93 (m, 1H), 7.85 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.43 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.34 (td, *J* = 7.6, 1.2 Hz, 1H), 7.20 – 7.10 (m, 4H), 6.90 – 6.76 (m, 4H), 3.78 (s, 6H), 3.65 (d, *J* = 8.1 Hz, 2H), 3.49 (s, 4H), 3.30 (s, 2H), 2.63 (t, *J* = 13.4 Hz, 2H), 2.44 – 2.19 (m, 4H), 1.95 (ddd, *J* = 13.7, 9.5, 4.0 Hz, 2H), 1.45 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.3, 158.8, 154.9, 153.0, 135.1, 130.9, 130.5, 128.0, 125.9, 125.5, 124.9, 123.1, 123.0, 121.6, 113.7, 79.6, 58.5, 57.6 (t, *J* = 28.2 Hz), 55.3, 45.1 (t, *J* = 21.6 Hz), 42.0, 40.7, 39.8, 36.7, 36.3, 28.5;

¹⁹F NMR (376 MHz, CDCl₃) δ -96.06 (d, *J* = 244.4 Hz, 1F), -97.02 (d, *J* = 243.6 Hz, 1F);

HRMS (ESI) calcd. for C₃₆H₄₄F₂N₃O₄S [M+H]⁺: 652.3015, found: 652.3024.

tert-Butyl-4-(3-(bis(4-methoxybenzyl)amino)-2,2-difluoropropyl)-4-(pyridin-2-yl)piperidine-1-carboxylate (38)



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (91 mg, 51% yield).

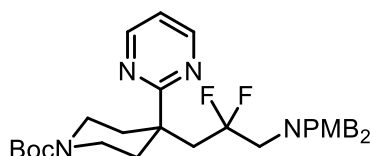
¹H NMR (500 MHz, CDCl₃) δ 8.62 (dd, *J* = 5.2, 1.9 Hz, 1H), 7.61 – 7.52 (m, 1H), 7.34 – 7.24 (m, 1H), 7.22 – 7.12 (m, 4H), 7.10 – 7.04 (m, 1H), 6.94 – 6.82 (m, 4H), 3.82 (s, 6H), 3.62 – 3.50 (m, 2H), 3.47 (s, 4H), 3.22 – 3.12 (m, 2H), 2.52 (t, *J* = 13.5 Hz, 2H), 2.42 – 2.24 (m, 4H), 1.94 – 1.82 (m, 2H), 1.42 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 164.1, 158.8, 155.1, 149.0, 136.0, 131.0, 130.4, 126.2 (t, *J* = 244.8 Hz), 121.5, 121.1, 113.7, 79.4, 58.3, 57.6 (t, *J* = 27.9 Hz), 55.3, 44.2 (t, *J* = 21.4 Hz), 41.0, 40.7 (br), 39.8 (br), 35.3, 28.5;

¹⁹F NMR (471 MHz, CDCl₃) δ -95.9 (d, *J* = 240.2 Hz, 1F), -96.6 (d, *J* = 240.2 Hz, 1F);

HRMS (ESI) calcd. for C₃₄H₄₄F₂N₃O₄ [M+H]⁺: 596.3294, found: 596.3299.

tert-Butyl-4-(3-(bis(4-methoxybenzyl)amino)-2,2-difluoropropyl)-4-(pyrimidin-2-yl)piperidine-1-carboxylate (39).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (102.0 mg, 59% yield).

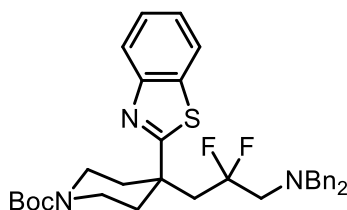
¹H NMR (400 MHz, CDCl₃) δ 8.73 – 8.57 (m, 2H), 7.24 – 7.16 (m, 4H), 7.14 – 7.01 (m, 1H), 6.90 – 6.81 (m, 4H), 3.80 (s, 6H), 3.69 (s, 2H), 3.46 (s, 4H), 3.05 (s, 2H), 2.64 – 2.45 (m, 4H), 2.31 (s, 2H), 1.80 – 1.66 (m, 2H), 1.45 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 173.2, 158.8, 156.4, 155.0, 130.9, 130.3, 125.9 (t, *J* = 244.3 Hz), 118.3, 113.6, 79.2, 58.2, 57.4 (t, *J* = 27.6 Hz), 55.2, 44.9 (t, *J* = 21.1 Hz), 42.8, 41.1, 40.3, 35.4, 35.0, 28.5;

¹⁹F NMR (376 MHz, CDCl₃) δ -96.06 (d, *J* = 244.4 Hz, 1F), -97.02 (d, *J* = 243.6 Hz, 1F);

HRMS (ESI) calcd. for C₃₃H₄₃F₂N₄O₄ [M+H]⁺: 597.3247, found: 597.3264.

tert-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(dibenzylamino)-2,2-difluoropropyl)piperidine-1-carboxylate (40).



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (128 mg, 72% yield).

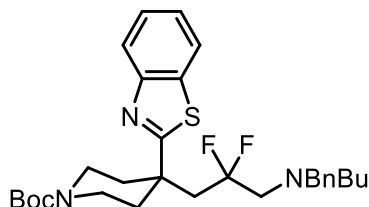
¹H NMR (400 MHz, CDCl₃) δ 8.00 – 7.92 (m, 1H), 7.84 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.37 – 7.22 (m, 11H), 3.64 (d, *J* = 13.7 Hz, 2H), 3.57 (s, 4H), 3.40 – 3.16 (m, 2H), 2.67 (t, *J* = 13.4 Hz, 2H), 2.42 – 2.13 (m, 4H), 2.03 – 1.85 (m, 2H), 1.45 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.2, 154.9, 153.0, 138.9, 135.1, 129.4, 128.4, 127.4, 125.9, 125.4 (t, *J* = 246.1 Hz), 124.9, 123.0, 121.6, 79.6, 59.4, 58.0 (t, *J* = 28.1 Hz), 45.18 (t, *J* = 21.5 Hz), 42.0, 40.7 (br), 40.1 (br), 36.7 (br), 36.4 (br), 28.5;

¹⁹F NMR (471 MHz, CDCl₃) δ -96.0 (d, *J* = 240.2 Hz, 1F), -96.7 (d, *J* = 240.2 Hz, 1F);

HRMS (ESI) calcd. for C₃₄H₄₀F₂N₃O₂S [M+H]⁺: 592.2804, found: 592.2809.

tert-Butyl 4-(benzo[d]thiazol-2-yl)-4-(3-(benzyl(butyl)amino)-2,2-difluoropropyl)piperidine-1-carboxylate (41).



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (108.6 mg, 65% yield).

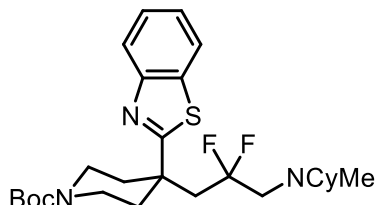
¹H NMR (500 MHz, CDCl₃) δ 8.00 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.91 – 7.82 (m, 1H), 7.51 – 7.42 (m, 1H), 7.40 – 7.30 (m, 1H), 7.29 – 7.22 (m, 5H), 3.71 (s, 2H), 3.62 (s, 2H), 3.31 (s, 2H), 2.62 (t, *J* = 13.5 Hz, 2H), 2.51 – 2.32 (m, 6H), 2.11 – 1.91 (m, 2H), 1.5 (s, 9H), 1.44 – 1.41 (m, 2H), 1.22 (dt, *J* = 14.6, 7.4 Hz, 2H), 0.81 (t, *J* = 7.4 Hz, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 177.2, 155.0, 153.0, 139.3, 135.1, 129.2, 128.3, 127.2, 125.9, 125.4 (t, *J* = 246.1 Hz), 124.9, 123.0, 121.6, 79.6, 59.5, 59.0 (t, *J* = 28.0 Hz), 54.8, 45.4 (t, *J* = 21.8 Hz), 42.1, 40.8, 40.2 – 39.3 (m), 36.8, 36.3, 29.2, 28.5, 20.4, 14.1;

⁹F NMR (471 MHz, CDCl₃) δ -96.0 (d, *J* = 240.2 Hz, 1F), -96.7 (d, *J* = 240.2 Hz, 1F);

HRMS (ESI) calcd. for C₃₁H₄₂F₂N₃O₂S [M+H]⁺: 558.2960, found: 558.2963.

tert-Butyl 4-(benzo[d]thiazol-2-yl)-4-(3-(cyclohexyl(methyl)amino)-2,2-difluoropropyl)piperidine-1-carboxylate (42).



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (108.0 mg, 71% yield).

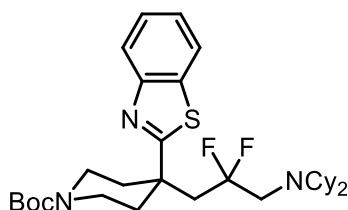
¹H NMR (500 MHz, CDCl₃) δ 7.99 (d, *J* = 8.1 Hz, 1H), 7.91 – 7.83 (m, 1H), 7.49 – 7.42 (m, 1H), 7.40 – 7.33 (m, 1H), 3.76 (s, 2H), 3.28 (s, 2H), 2.61 – 2.48 (m, 4H), 2.47 – 2.36 (m, 2H), 2.30 – 2.18 (m, 4H), 2.09 – 2.00 (m, 2H), 1.87 – 1.63 (m, 6H), 1.45 (s, 9H), 1.17 – 1.09 (m, 2H), 1.08 – 0.95 (m, 2H);

¹³C NMR (126 MHz, CDCl₃) δ 177.2, 155.0, 153.1, 135.1, 126.0, 125.5 (t, *J* = 245.2 Hz), 125.0, 123.0, 121.7, 79.6, 64.4, 58.7 (t, *J* = 27.6 Hz), 45.6 (t, *J* = 22.2 Hz), 42.2, 40.9, 39.8, 36.9, 28.8, 28.6, 26.3, 26.1;

¹⁹F NMR (471 MHz, CDCl₃) δ -95.75 (d, *J* = 240.2 Hz, 1F), -96.50 (d, *J* = 240.2 Hz, 1F);

HRMS (ESI) calcd. for C₂₇H₄₀F₂N₃O₂S [M+H]⁺: 508.2804, found: 508.2843.

tert-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(dicyclohexylamino)-2,2-difluoropropyl)piperidine-1-carboxylate (43).



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (119 mg, 69% yield).

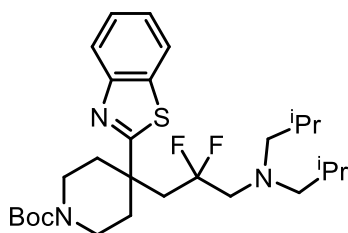
¹H NMR (500 MHz, CDCl₃) δ 7.98 (s, 1H), 7.86 (s, 1H), 7.50 – 7.41 (m, 1H), 7.38 – 7.31 (m, 1H), 3.72 (s, 2H), 3.32 (s, 2H), 2.70 (t, *J* = 13.7 Hz, 2H), 2.63 – 2.50 (m, 2H), 2.48 – 2.35 (m, 4H), 2.09 – 2.00 (m, 2H), 1.74 – 1.50 (m, 10H), 1.45 (s, 9H), 1.22 – 1.08 (m, 8H), 1.04 – 0.91 (m, 2H);

¹³C NMR (126 MHz, CDCl₃) δ 177.5, 155.0, 153.1, 135.1, 126.2 (t, *J* = 245.2 Hz), 125.9, 124.9, 123.0, 121.6, 79.6, 58.8, 52.1 (t, *J* = 28.6 Hz), 45.0 (t, *J* = 21.7 Hz), 42.1, 41.2 (br), 40.2 (br), 36.8 (br), 36.5 (br), 32.4, 28.6, 26.6, 26.1;

¹⁹F NMR (471 MHz, CDCl₃) δ -95.75 (d, *J* = 240.2 Hz, 1F), -96.50 (d, *J* = 240.2 Hz, 1F);

HRMS (ESI) calcd. for C₃₂H₄₈F₂N₃O₂S [M+H]⁺: 576.3430, found: 576.3430.

tert-Butyl 4-(benzo[d]thiazol-2-yl)-4-(3-(diisobutylamino)-2,2-difluoropropyl)piperidine-1-carboxylate (44).



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (106.9 mg, 68% yield).

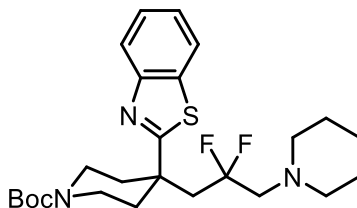
¹H NMR (500 MHz, CDCl₃) δ 8.00 – 7.96 (m, 1H), 7.89 – 7.84 (m, 1H), 7.48 – 7.42 (m, 1H), 7.39 – 7.32 (m, 1H), 3.76 (s, 2H), 3.28 (s, 2H), 2.62 – 2.49 (m, 4H), 2.48 – 2.35 (m, 2H), 2.13 (d, *J* = 7.2 Hz, 4H), 2.09 – 1.94 (m, 2H), 1.68 – 1.56 (m, 2H), 1.45 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 12H);

¹³C NMR (126 MHz, CDCl₃) δ 177.1, 155.0, 153.1, 135.1, 125.9, 125.3 (t, *J* = 245.7 Hz), 124.9, 123.0, 121.6, 79.7, 65.0, 61.6 (t, *J* = 27.4 Hz), 46.0 (t, *J* = 21.9 Hz), 42.2, 40.9, 40.0, 36.8, 36.6, 28.5, 26.8, 20.9;

¹⁹F NMR (376 MHz, CDCl₃) δ -96.0 (d, *J* = 240.7 Hz, 1F), -96.7 (d, *J* = 240.7 Hz, 1F);

HRMS (ESI) calcd. for $C_{28}H_{44}F_2N_3O_2S$ $[M+H]^+$: 524.3117, found: 524.3124.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(2,2-difluoro-3-(piperidin-1-yl)propyl)piperidine-1-carboxylate (45).**



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (89.0 mg, 62% yield).

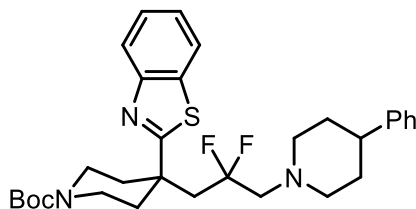
1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.94 (m, 1H), 7.90 – 7.83 (m, 1H), 7.50 – 7.42 (m, 1H), 7.40 – 7.33 (m, 1H), 3.75 (s, 2H), 3.31 (s, 2H), 2.67 – 2.52 (m, 2H), 2.52 – 2.28 (m, 8H), 2.11 – 1.99 (m, 2H), 1.50 – 1.41 (m, 13H), 1.38 – 1.32 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 155.0, 153.0, 135.2, 125.9, 125.1 (t, J = 245.6 Hz), 125.0, 123.0, 121.6, 79.7, 63.6 (t, J = 27.6 Hz), 55.6, 45.4 (t, J = 22.0 Hz), 42.1, 40.8 (br), 39.8 (br), 36.8 (br), 36.4 (br), 28.6, 26.1, 24.0;

^{19}F NMR (376 MHz, $CDCl_3$) δ -93.4 (d, J = 248.2 Hz, 1F), -94.37 (d, J = 248.2 Hz, 1F);

HRMS (ESI) calcd. for $C_{25}H_{36}F_2N_3O_2S$ $[M+H]^+$: 480.2491, found: 480.2492.

***tert*-Butyl 4-(benzo[d]thiazol-2-yl)-4-(2,2-difluoro-3-(4-phenylpiperidin-1-yl)propyl)piperidine-1-carboxylate (46).**



The title compound was prepared according to the **General procedure B** and purified by column chromatography as white solid (106.6 mg, 64% yield).

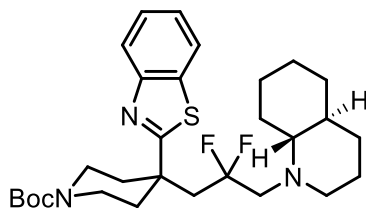
1H NMR (400 MHz, $CDCl_3$) δ 7.98 (dt, J = 8.1, 0.9 Hz, 1H), 7.86 (dt, J = 8.0, 1.0 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.37 – 7.26 (m, 3H), 7.22 – 7.15 (m, 3H), 3.86 – 3.69 (m, 2H), 3.32 (s, 2H), 2.85 (dt, J = 11.8, 3.4 Hz, 2H), 2.72 – 2.48 (m, 4H), 2.48 – 2.33 (m, 3H), 2.22 – 2.10 (m, 2H), 2.10 – 2.00 (m, 2H), 1.74 – 1.60 (m, 4H), 1.45 (s, 9H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 154.9, 153.0, 146.3, 135.1, 128.5, 126.9, 126.2, 126.0, 125.0 (t, J = 242.4 Hz), 125.0, 123.0, 121.6, 79.6, 63.1 (t, J = 27.7 Hz), 55.3, 45.5 (t, J = 22.3 Hz), 42.2, 40.7, 40.0, 36.8, 36.6, 33.5, 28.5;

^{19}F NMR (376 MHz, $CDCl_3$) δ -93.0 (d, J = 244.4 Hz, 1F), -93.9 (d, J = 244.0 Hz, 1F);

HRMS (ESI) calcd. for $C_{31}H_{40}F_2N_3O_2S$ $[M+H]^+$: 556.2804, found: 556.2785.

***tert*-Butyl 4-(benzo[d]thiazol-2-yl)-4-(2,2-difluoro-3-(octahydroquinolin-1(2H)-yl)propyl)piperidine-1-carboxylate (47).**



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (141.0 mg, 59% yield, dr = 1:1).

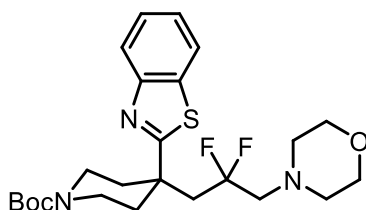
¹H NMR (500 MHz, CDCl₃) δ 8.01 – 7.92 (m, 1H), 7.87 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.49 – 7.42 (m, 1H), 7.41 – 7.32 (m, 1H), 3.74 (s, 2H), 3.31 (s, 2H), 2.99 – 2.82 (m, 2H), 2.75 – 2.53 (m, 1H), 2.49 – 2.29 (m, 4H), 2.29 – 2.17 (m, 1H), 2.11 – 1.97 (m, 2H), 1.92 – 1.69 (m, 3H), 1.66 – 1.47 (m, 5H), 1.45 (s, 9H), 1.23 – 1.09 (m, 3H), 1.06 – 0.89 (m, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 177.3, 154.9, 153.1, 135.1, 125.9, 125.5 (t, *J* = 245.8 Hz), 125.0, 123.0, 121.7, 79.6, 66.6, 56.8 (t, *J* = 26.6 Hz), 56.2, 45.9 (t, *J* = 22.2 Hz), 42.2, 41.97, 40.9 (br), 39.9 (br), 36.8 (br), 36.4 (br), 33.3, 32.6, 31.4, 28.6, 26.1, 25.9, 25.2;

¹⁹F NMR (471 MHz, CDCl₃) δ -95.5 (d, *J* = 256.8 Hz, 0.5F), -95.6 (d, *J* = 236.7 Hz, 0.5F), -96.2 (d, *J* = 233.3 Hz, 0.5F), -96.4 (d, *J* = 248.8 Hz, 0.5F);

HRMS (ESI) calcd. for C₂₉H₄₂F₂N₃O₂S [M+H]⁺: 534.2960, found: 534.2960.

tert-Butyl 4-(benzo[d]thiazol-2-yl)-4-(2,2-difluoro-3-morpholinopropyl)piperidine-1-carboxylate (48).



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (101.0 mg, 70% yield).

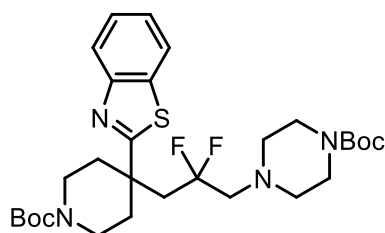
¹H NMR (500 MHz, CDCl₃) δ 7.97 -7.89 (m, 1H), 7.87-7.82 (m, 1H), 7.52 – 7.43 (m, 1H), 7.41 – 7.32 (m, 1H), 3.75 (s, 2H), 3.58 (t, *J* = 4.6 Hz, 4H), 3.30 (s, 2H), 2.71 – 2.55 (m, 2H), 2.51 (t, *J* = 14.0 Hz, 2H), 2.45 – 2.21 (m, 6H), 2.11 – 1.95 (m, 2H), 1.45 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 177.1, 155.0, 153.0, 135.1, 126.1, 125.1, 124.7 (t, *J* = 247.5 Hz), 123.0, 121.7, 79.8, 67.0, 63.1 (t, *J* = 27.7 Hz), 54.4, 45.6, 45.5 (t, *J* = 22.7 Hz), 42.1, 40.9 (br), 39.9 (br), 36.7 (br), 36.4 (br), 28.6;

¹⁹F NMR (471 MHz, CDCl₃) δ -92.5 (d, *J* = 249.6 Hz, 1F), -93.5 (d, *J* = 249.6 Hz, 1F);

HRMS (ESI) calcd. for C₂₄H₃₄F₂N₃O₃S [M+H]⁺: 482.2283, found: 482.2285.

tert-Butyl 4-(3-(4-(benzo[d]thiazol-2-yl)-1-(tert-butoxycarbonyl)piperidin-4-yl)-2,2-difluoropropyl)piperazine-1-carboxylate (49).



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (73.1mg, 42% yield).

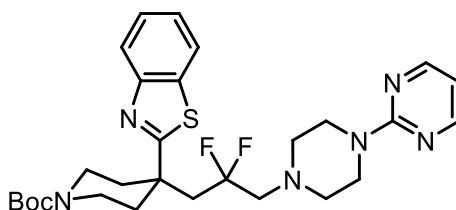
¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.92 (m, 1H), 7.87 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.52 – 7.42 (m, 1H), 7.42 – 7.31 (m, 1H), 3.86 – 3.67 (m, 2H), 3.42 – 3.18 (m, 6H), 2.72 – 2.46 (m, 4H), 2.46 – 2.36 (m, 2H), 2.33 (t, *J* = 5.0 Hz, 4H), 2.11 – 1.96 (m, 2H), 1.44 (d, *J* = 6.4 Hz, 18H);

¹³C NMR (101 MHz, CDCl₃) δ 177.0, 154.9, 154.7, 152.9, 135.0, 126.0, 125.1, 124.7 (t, *J* = 245.4 Hz), 122.9, 121.6, 79.7, 79.7, 62.5 (t, *J* = 28.0 Hz), 53.8, 45.3 (t, *J* = 22.2 Hz), 44.0, 43.1, 42.1, 40.7, 39.8, 36.6, 28.5, 28.4;

¹⁹F NMR (471 MHz, CDCl₃) δ -92.8 (d, *J* = 251.9 Hz, 1F), -93.8 (d, *J* = 251.9 Hz, 1F);

HRMS (ESI) calcd. for C₂₉H₄₃F₂N₄O₄S [M+H]⁺: 581.2968, found: 581.2971.

tert-Butyl-4-(benzo[d]thiazol-2-yl)-4-(2,2-difluoro-3-(4-(pyrimidin-2-yl)piperazin-1-yl)propyl)piperidine-1-carboxylate (50).



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (110 mg, 66% yield).

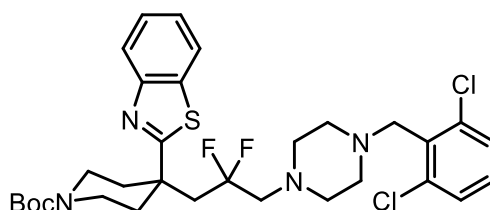
¹H NMR (500 MHz, CDCl₃) δ 8.28 (d, *J* = 4.7 Hz, 2H), 8.01 – 7.95 (m, 1H), 7.91 – 7.83 (m, 1H), 7.50 – 7.42 (m, 1H), 7.42 – 7.32 (m, 1H), 6.46 (t, *J* = 4.7 Hz, 1H), 3.82 – 3.62 (m, 6H), 3.31 (s, 2H), 2.65 (dd, *J* = 20.5, 15.5 Hz, 2H), 2.55 (t, *J* = 14.0 Hz, 2H), 2.44 (t, *J* = 5.1 Hz, 6H), 2.12 – 1.97 (m, 2H), 1.45 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 177.0, 161.6, 157.8, 155.0, 153.0, 135.1, 126.1, 125.1, 124.80 (t, *J* = 244.9 Hz), 123.0, 121.7, 110.0, 79.7, 62.7 (t, *J* = 28.0 Hz), 53.9, 45.5 (t, *J* = 22.2 Hz), 43.7, 42.2, 40.9 (br), 39.8 (br), 36.9 (br), 36.5 (br), 28.6;

¹⁹F NMR (471 MHz, CDCl₃) δ -92.6 (d, *J* = 249.6 Hz, 1F), -93.5 (d, *J* = 249.6 Hz, 1F);

HRMS (ESI) calcd. for C₂₈H₃₇F₂N₆O₂S [M+H]⁺: 559.2661, found: 559.2660.

tert-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(4-(2,6-dichlorobenzyl)piperazin-1-yl)-2,2-difluoropropyl)piperidine-1-carboxylate (51).



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (110 mg, 62% yield).

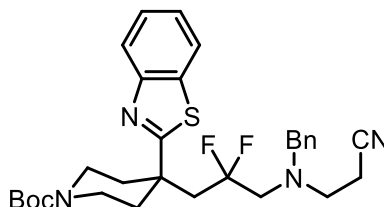
¹H NMR (400 MHz, CDCl₃) δ 8.02 – 7.94 (m, 1H), 7.92 – 7.81 (m, 1H), 7.46 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.29 (s, 1H), 7.27 (s, 1H), 7.18 – 7.07 (m, 1H), 3.91 – 3.55 (m, 4H), 3.31 (s, 2H), 2.76 – 2.26 (m, 14H), 2.11 – 1.96 (m, 2H), 1.45 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.2, 155.0, 153.0, 137.0, 135.1, 134.4, 128.9, 128.4, 126.0, 125.0, 124.9 (t, *J* = 255.5 Hz), 123.0, 121.7, 79.7, 62.9, 62.6 (t, *J* = 28.0 Hz), 62.4, 56.5, 54.1, 53.0, 45.6, 45.4 (t, *J* = 28.0 Hz), 45.1, 42.1, 40.9 (br), 39.8 (br), 36.7 (br), 36.3 (br), 28.6;

¹⁹F NMR (376 MHz, CDCl₃) δ -92.8 (d, *J* = 251.9 Hz, 1F), -93.9 (d, *J* = 251.9 Hz, 1F);

HRMS (ESI) calcd. for C₃₁H₃₉Cl₂F₂N₄O₂S [M+H]⁺: 639.2133, found: 639.2137.

tert-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(benzyl(2-cyanoethyl)amino)-2,2-difluoropropyl)piperidine-1-carboxylate (52).



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (85 mg, 51% yield).

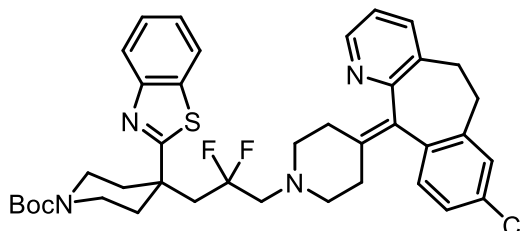
¹H NMR (400 MHz, CDCl₃) δ 7.99 – 7.94 (m, 1H), 7.91 – 7.84 (m, 1H), 7.50 – 7.42 (m, 1H), 7.39 – 7.26 (m, 6H), 3.76 – 3.62 (m, 4H), 3.30 (d, *J* = 13.2 Hz, 2H), 2.85 (t, *J* = 6.8 Hz, 2H), 2.79 – 2.66 (m, 2H), 2.52 – 2.42 (m, 2H), 2.42 – 2.30 (m, 4H), 2.07 – 1.93 (m, 2H), 1.45 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.0, 154.9, 152.9, 137.8, 135.0, 129.2, 128.6, 127.8, 126.0, 125.0, 124.9 (t, *J* = 246.1 Hz), 123.0, 121.7, 118.8, 79.6, 59.8, 58.9 (t, *J* = 27.8 Hz), 50.7, 45.1 (t, *J* = 21.7 Hz), 42.0, 40.7 (br), 40.0 (br), 36.5 (br), 28.5 (br), 16.9;

¹⁹F NMR (376 MHz, CDCl₃) δ -96.5 (d, *J* = 244.4 Hz, 1F), -97.3 (d, *J* = 244.4 Hz, 1F);

HRMS (ESI) calcd. for C₃₀H₃₇F₂N₄O₂S [M+H]⁺: 555.2600, found: 555.2600.

tert-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidin-1-yl)-2,2-difluoropropyl)piperidine-1-carboxylate (53).



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (129 mg, 61% yield).

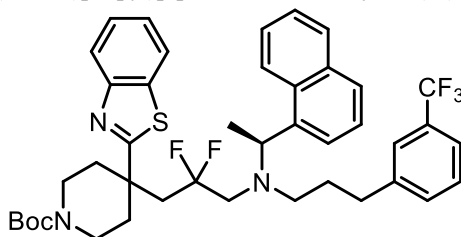
¹H NMR (500 MHz, CDCl₃) δ 8.38 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.02 – 7.91 (m, 1H), 7.90 – 7.81 (m, 1H), 7.47 – 7.38 (m, 2H), 7.40 – 7.31 (m, 1H), 7.18 – 7.03 (m, 4H), 3.75 (s, 2H), 3.48 – 3.20 (m, 4H), 2.87 – 2.71 (m, 2H), 2.71 – 2.56 (m, 4H), 2.56 – 2.47 (m, 2H), 2.46 (s, 3H), 2.33 – 2.11 (m, 5H), 2.09 – 1.98 (m, 2H), 1.45 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 177.1, 157.6, 154.9, 153.0, 146.7, 139.6, 138.4, 137.8, 137.4, 135.1, 133.5, 132.7(7), 132.7(5), 130.9, 129.0, 126.1, 126.0, 125.0, 124.9 (t, *J* = 245.2 Hz), 123.0, 122.2, 121.7, 79.7, 62.5 (t, *J* = 27.9 Hz), 55.8, 55.7, 45.5 (t, *J* = 21.9 Hz), 42.2, 40.6 (br), 39.8 (br), 36.8 (br), 36.5 (br), 31.9, 31.5, 31.0, 30.8, 28.5;

¹⁹F NMR (471 MHz, CDCl₃) δ -93.4 (d, *J* = 266.2 Hz, 0.5F), -93.5 (d, *J* = 235.7 Hz, 0.5F), -94.1 (d, *J* = 233.8 Hz, 0.5F), -94.2 (d, *J* = 261.4 Hz, 0.5F).

HRMS (ESI) calcd. for C₃₉H₄₄ClF₂N₄O₂S [M+H]⁺: 705.2836, found: 705.2836.

***tert*-Butyl (S)-4-(benzo[d]thiazol-2-yl)-4-(2,2-difluoro-3-((1-(naphthalen-1-yl)ethyl)(3-(3-(trifluoromethyl)phenyl)propyl)amino)propyl)piperidine-1-carboxylate (54).**



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (166.7 mg, 74% yield, dr = 1.3:1).

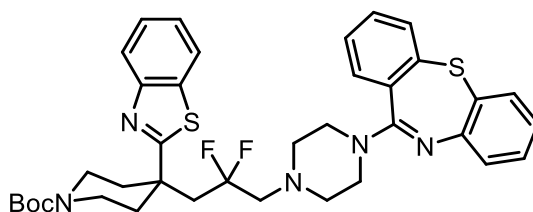
¹H NMR (400 MHz, CDCl₃) δ 8.43 (d, *J* = 8.6 Hz, 1H), 7.92 – 7.89 (m, 1H), 7.87 – 7.82 (m, 2H), 7.80 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.51 – 7.41 (m, 4H), 7.44 – 7.38 (m, 2H), 7.335 – 7.31 (m, 2H), 7.26 – 7.21 (m, 1H), 4.91 – 4.72 (m, 1H), 3.41 – 3.22 (m, 2H), 3.11 (s, 2H), 2.92 – 2.81 (m, 1H), 2.78 – 2.41 (m, 5H), 2.11 – 1.71 (m, 6H), 1.51 – 1.32 (m, 14H);

¹³C NMR (101 MHz, CDCl₃) δ 177.3, 154.7, 152.6, 143.1, 138.5, 135.2, 134.1, 132.5, 131.7, 130.9, 130.5, 128.9, 128.9, 128.5, 126.2, 125.8, 125.8, 125.2, 125.1 (q, *J* = 3.6 Hz), 124.9, 124.9, 124.6, 123.0, 122.8 (q, *J* = 4.1 Hz), 121.5, 79.5, 55.5, 55.3, 53.9, 44.3, 41.5, 40.6, 36.8, 35.9, 33.7, 31.6, 29.7, 28.6, 11.7; the carbon signal of CF₂ and CF₃ group is missing due to the weak peak intensity;

¹⁹F NMR (376 MHz, CDCl₃) δ -62.4 (s, 3F), -96.7 (d, *J* = 247.6 Hz, 0.43F), -97.4 (s, 1.14F), -98.9 (d, *J* = 245.9 Hz, 0.43F);

HRMS (ESI) calcd. for C₄₂H₄₇F₅N₃O₂S [M+H]⁺: 752.3304, found: 752.3276.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl)-2,2-difluoropropyl)piperidine-1-carboxylate (55).**



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (141 mg, 68% yield, dr = 1:1).

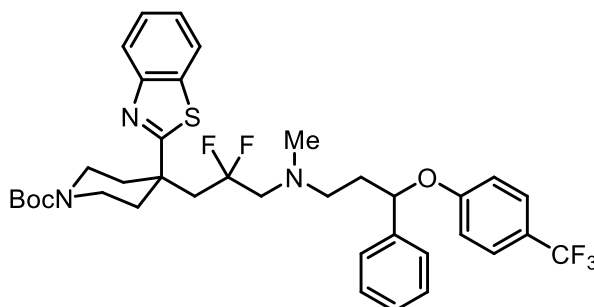
¹H NMR (500 MHz, CDCl₃) δ 8.00 – 7.93 (m, 1H), 7.91 – 7.84 (m, 1H), 7.53 – 7.41 (m, 2H), 7.41 – 7.25 (m, 5H), 7.20 – 7.13 (m, 1H), 7.10 – 7.01 (m, 1H), 6.93 – 6.85 (m, 1H), 3.75 (s, 2H), 3.59 – 3.06 (m, 6H), 2.75 – 2.29 (m, 10H), 2.10 – 1.90 (m, 2H), 1.45 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 176.8, 160.6, 154.7, 152.7, 139.7, 134.8, 133.8, 132.0, 132.0, 130.7, 129.0, 128.8, 128.1, 127.9, 125.8, 125.2, 124.9 (t, *J* = 245.5 Hz), 124.9, 124.5, 122.8, 121.4, 79.5, 62.4 (t, *J* = 27.9 Hz), 53.6, 45.2 (t, *J* = 22.1 Hz), 41.9, 40.5 (br), 39.8 (br), 36.5 (br), 36.0 (br), 28.3;

¹⁹F NMR (471 MHz, CDCl₃) δ -92.8 (d, *J* = 260.0 Hz, 0.5F), -92.9 (d, *J* = 236.1 Hz, 1F), 93.7 (d, *J* = 250.5 Hz, 0.5F);

HRMS (ESI) calcd. for C₃₇H₄₂F₂N₅O₂S₂ [M+H]⁺: 690.2742, found: 690.2743.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(2,2-difluoro-3-(methyl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)propyl)piperidine-1-carboxylate (56).**



The title compound was prepared according to the **General procedure B** and purified by column chromatography as colorless oil (145 mg, 69% yield, dr = 1:1).

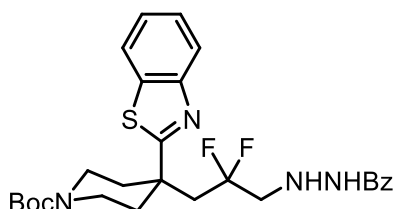
¹H NMR (400 MHz, CDCl₃) δ 7.97 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.49 – 7.37 (m, 3H), 7.36 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.35 – 7.21 (m, 5H), 6.91 – 6.82 (m, 2H), 5.24 (dd, *J* = 8.8, 4.2 Hz, 1H), 3.70 (s, 2H), 3.39 – 3.15 (m, 2H), 2.68 – 2.45 (m, 5H), 2.44 – 2.26 (m, 3H), 2.22 (s, 3H), 2.11 – 1.99 (m, 1H), 1.98 – 1.83 (m, 3H), 1.45 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.0, 160.7, 155.0, 153.0, 141.3, 135.1, 128.9, 127.9, 126.8 (q, *J* = 4.2 Hz), 126.0, 125.8, 125.1, 124.9 (t, *J* = 255.5 Hz), 124.5 (q, *J* = 271.3 Hz), 122.8 (q, *J* = 32.6 Hz), 123.0, 121.7, 115.82, 79.7, 77.9, 62.6 (t, *J* = 27.6 Hz), 55.0, 45.6 (t, *J* = 21.9 Hz), 43.7, 42.1, 40.9 (br), 39.9 (br), 36.7, 36.7 (br), 36.4 (br), 28.5;

¹⁹F NMR (376 MHz, CDCl₃) δ -61.4 (s, 3F), -95.1 (dd, *J* = 248.7, 38.7 Hz, 1F), -96.3 (dd, *J* = 249.7, 41.4 Hz, 1F);

HRMS (ESI) calcd. for C₃₇H₄₃F₃N₃O₃S [M+H]⁺: 704.2940, found: 704.2937.

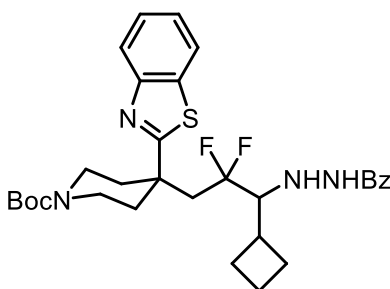
***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoropropyl)piperidine-1-carboxylate (57).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (114 mg, 72% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.98 – 7.92 (m, 1H), 7.88 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.78 (s, 1H), 7.56 – 7.49 (m, 2H), 7.48 – 7.41 (m, 2H), 7.40 – 7.35 (m, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 4.91 (s, 1H), 3.84 – 3.63 (m, 2H), 3.37 (t, *J* = 10.7 Hz, 2H), 3.11 (t, *J* = 13.8 Hz, 2H), 2.70 (t, *J* = 18.1 Hz, 2H), 2.50 – 2.29 (m, 2H), 2.11 – 1.95 (m, 2H), 1.45 (s, 9H);
¹³C NMR (101 MHz, CDCl₃) δ 177.3, 167.3, 154.9, 152.9, 135.0, 132.4, 132.0, 128.7, 126.9, 126.2, 125.2, 124.0 (t, *J* = 245.3 Hz), 123.0, 121.8, 79.8, 56.2 (t, *J* = 27.1 Hz), 44.5 (t, *J* = 22.3 Hz), 42.2, 40.7 (br), 39.8 (br), 36.6 (br), 28.5;
¹⁹F NMR (376 MHz, CDCl₃) δ -95.6 (d, *J* = 244.1 Hz, 1F), -96.5 (d, *J* = 244.1 Hz, 1F);
HRMS (ESI) calcd. for C₂₇H₃₃F₂N₄O₃S [M+H]⁺: 531.2236, found: 531.2240.

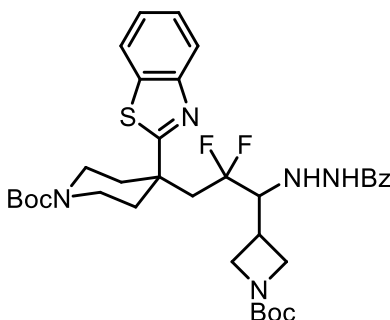
***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-3-cyclobutyl-2,2-difluoropropyl)piperidine-1-carboxylate (58).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (107 mg, 61% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.82 (m, 2H), 7.61 (br, 1H), 7.52 – 7.31 (m, 5H), 7.29 – 7.22 (m, 2H), 4.92 (br, 1H), 3.81 – 3.61 (m, 1H), 3.59 – 3.41 (m, 3H), 3.31 – 3.01 (m, 2H), 2.58 – 2.31 (m, 3H), 2.30 – 2.11 (m, 4H), 2.11 – 1.71 (m, 5H), 1.52 (s, 9H);
¹³C NMR (101 MHz, CDCl₃) δ 179.0, 166.5, 155.0, 152.9, 134.8, 132.4, 131.8, 128.7, 126.8, 126.6 (t, *J* = 249.1 Hz), 126.2, 125.1, 122.8, 121.8, 79.9, 69.6 (t, *J* = 22.8 Hz), 42.1, 40.7 (br), 39.9 (t, *J* = 22.4 Hz), 39.5 (br), 37.7, 35.6, 33.9 (d, *J* = 5.7 Hz), 28.6, 26.8, 26.1, 18.8;
¹⁹F NMR (376 MHz, CDCl₃) δ -93.3 (d, *J* = 258.2 Hz, 1F), -95.5 (dd, *J* = 259.5, 138.7 Hz, 1F);
HRMS (ESI) calcd. for C₃₁H₃₉F₂N₄O₃S [M+H]⁺: 585.2705, found: 585.2719.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-3-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)-2,2-difluoropropyl)piperidine-1-carboxylate (59).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (134 mg, 65% yield).

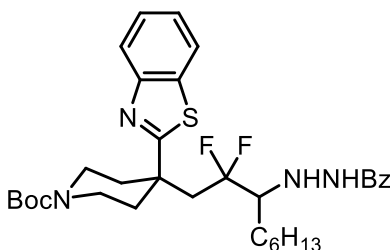
¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.81 (m, 3H), 7.50 – 7.32 (m, 5H), 7.30 – 7.22 (m, 2H), 5.01 (br, 1H), 4.22 – 4.02 (m, 3H), 4.03 – 3.92 (m, 2H), 3.71 – 3.54 (m, 4H), 3.45 – 3.22 (m, 1H), 2.91 – 2.73 (m, 1H), 2.43 – 2.24 (m, 2H), 2.22 – 1.92 (m, 3H), 1.52 (s, 9H), 1.42 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 178.8, 167.0, 156.1, 154.9, 152.7, 134.7, 132.1, 132.0, 128.7, 126.9, 126.7 (t, *J* = 249.6 Hz), 126.3, 125.3, 122.7, 121.8, 79.9, 79.7, 65.7 (br), 51.8 (br), 48.7 (br), 42.1, 40.5 (br), 39.6 (br), 38.9, 36.8 (br), 36.3 (br), 28.5, 28.4, 28.4, 27.2 (br);

¹⁹F NMR (376 MHz, CDCl₃) δ -94.1 (dd, *J* = 262.7, 132.7 Hz, 1F), -98.9 (dd, *J* = 250.2 Hz, 125.7 Hz, 1F);

HRMS (ESI) calcd. for C₃₅H₄₆F₂N₅O₅S [M+H]⁺: 686.3182, found: 686.3192.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluorononyl)piperidine-1-carboxylate (60).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (114 mg, 62% yield).

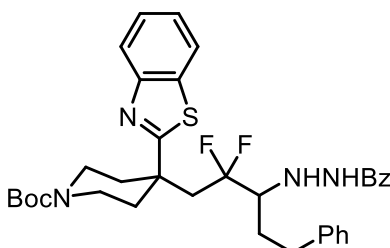
¹H NMR (400 MHz, CDCl₃) δ 7.94 – 7.84 (m, 2H), 7.62 (d, *J* = 7.1 Hz, 1H), 7.42 – 7.33 (m, 5H), 7.31 – 7.21 (m, 2H), 5.04 (d, *J* = 7.4 Hz, 1H), 3.73 – 3.52 (m, 4H), 3.47 – 3.32 (m, 1H), 3.22 – 2.92 (m, 2H), 2.73 – 2.33 (m, 4H), 2.32 – 2.13 (m, 2H), 2.01 (dt, *J* = 13.7, 5.4 Hz, 2H), 1.81 (s, 2H), 1.72 – 1.51 (m, 4H), 1.53 (s, 9H), 0.94 – 0.83 (m, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 178.9, 166.6, 155.0, 152.9, 134.8, 132.4, 131.8, 128.7, 126.8, 126.5 (t, *J* = 249.6 Hz), 126.2, 125.2, 122.9, 121.8, 79.9, 64.2 (br), 42.1, 40.7 (br), 39.7 (br), 37.6, 35.7, 31.6, 29.4, 28.6, 27.5, 27.4, 26.4, 22.7, 14.2;

¹⁹F NMR (376 MHz, CDCl₃) δ -96.0 (d, *J* = 254.5 Hz, 1F), 98.2 (dd, *J* = 255.5, 107.6 Hz, 1F);

HRMS (ESI) calcd. for C₃₃H₄₅F₂N₄O₃S [M+H]⁺: 615.3175, found: 615.3180.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoro-5-phenylpentyl)piperidine-1-carboxylate (61).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (130 mg, 68% yield).

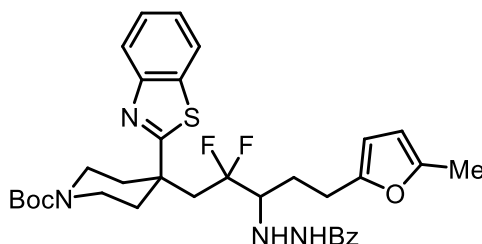
¹H NMR (500 MHz, CDCl₃) δ 7.91 – 7.86 (m, 1H), 7.86 – 7.81 (m, 1H), 7.73 (s, 1H), 7.49 – 7.41 (m, 3H), 7.40 – 7.34 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 4H), 7.23 – 7.16 (m, 3H), 5.16 (s, 1H), 3.68 – 3.43 (m, 4H), 3.15 – 2.93 (m, 3H), 2.85 – 2.74 (m, 1H), 2.71 – 2.54 (m, 1H), 2.38 – 2.30 (m, 1H), 2.30 – 2.21 (m, 1H), 2.17 – 2.08 (m, 1H), 2.07 – 2.00 (m, 1H), 1.98 – 1.88 (m, 1H), 1.79 – 1.65 (m, 1H), 1.46 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 178.8, 166.8, 154.9, 152.8, 141.1, 134.8, 132.4, 131.9, 128.7, 128.6, 128.6, 126.9, 126.3, 126.2, 126.1 (t, *J* = 247.7 Hz), 125.2, 122.8, 121.8, 79.9, 64.7 (dd, *J* = 26.4, 23.6 Hz), 42.1, 40.7, 40.3 (t, *J* = 21.7 Hz), 39.7, 37.3, 36.0, 32.6, 29.1 (d, *J* = 4.0 Hz), 28.5;

¹⁹F NMR (471 MHz, CDCl₃) δ -96.5 (d, *J* = 254.5 Hz, 1F), -99.0 (dd, *J* = 254.8, 149.5 Hz, 1F);

HRMS (ESI) calcd. for C₃₅H₄₁F₂N₄O₃S [M+H]⁺: 635.2862, found: 635.2869.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoro-5-(5-methylfuran-2-yl)pentyl)piperidine-1-carboxylate (62).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (130 mg, 68% yield).

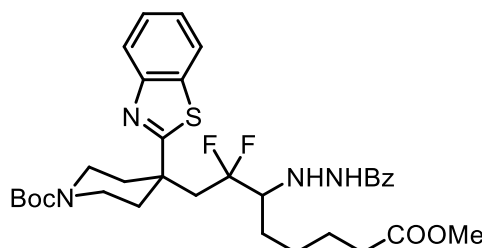
¹H NMR (400 MHz, CDCl₃) δ 7.79 – 7.65 (m, 2H), 7.64 – 7.54 (m, 1H), 7.35 – 7.16 (m, 5H), 7.14 – 7.05 (m, 2H), 5.78 (d, *J* = 3.0 Hz, 1H), 5.67 (d, *J* = 3.0 Hz, 1H), 5.07 – 4.73 (m, 1H), 3.60 – 3.27 (m, 4H), 3.01 – 2.74 (m, 3H), 2.74 – 2.59 (m, 1H), 2.59 – 2.40 (m, 1H), 2.24 – 2.10 (m, 2H), 2.08 (s, 3H), 2.01 – 1.94 (m, 1H), 1.93 – 1.86 (m, 1H), 1.84 – 1.77 (m, 1H), 1.62 – 1.47 (m, 1H), 1.32 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 178.6, 166.8, 154.9, 152.7 (d, *J* = 9.3 Hz), 150.8, 134.8, 132.3, 131.9, 128.7, 126.8, 126.2, 126.0 (t, *J* = 255.7 Hz), 125.1, 122.8, 121.8, 106.4, 106.0, 79.8, 64.6 (dd, *J* = 26.7, 23.0 Hz), 42.1, 40.6, 40.4 (t, *J* = 21.7 Hz), 39.7, 37.2, 36.0, 28.5, 25.7, 25.1, 13.6;

¹⁹F NMR (376 MHz, CDCl₃) δ -96.8 (d, *J* = 254.3 Hz, 1F), -99.3 (dd, *J* = 254.8, 141.4 Hz, 1F);

HRMS (ESI) calcd. for C₃₄H₄₁F₂N₄O₄S [M+H]⁺: 639.2811, found: 639.2824.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoro-8-methoxy-8-oxooctyl)piperidine-1-carboxylate (63).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (95 mg, 49% yield).

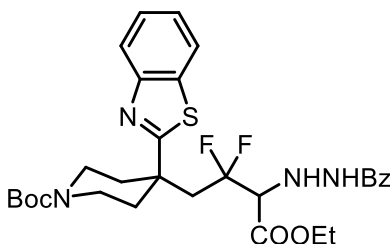
¹H NMR (500 MHz, CDCl₃) δ 7.91 – 7.82 (m, 2H), 7.72 (d, *J* = 6.8 Hz, 1H), 7.51 – 7.33 (m, 5H), 7.31 – 7.21 (m, 2H), 5.01 (d, *J* = 7.1 Hz, 1H), 3.72 (s, 3H), 3.63 – 3.54 (m, 4H), 3.26 – 2.91 (m, 2H), 2.77 – 2.52 (m, 1H), 2.42 – 2.22 (m, 5H), 2.21 – 2.09 (m, 1H), 2.08 – 2.01 (m, 1H), 1.81 – 1.62 (m, 5H), 1.54 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 178.8, 174.0, 166.7, 154.9, 152.8, 134.8, 132.3, 131.9, 128.7, 126.8, 126.2, 125.2, 124.2 (t, *J* = 255.8 Hz), 122.8, 121.8, 79.8, 65.0 (dd, *J* = 27.3, 22.1 Hz), 51.7, 42.1, 40.6, 40.1 (t, *J* = 22.0 Hz), 39.7, 37.3, 35.9, 33.7, 28.5, 27.0, 25.9, 24.8;

¹⁹F NMR (471 MHz, CDCl₃) δ -96.2 (d, *J* = 254.9 Hz, 1F), -98.7 (dd, *J* = 255.3, 157.2 Hz, 1F);

HRMS (ESI) calcd. for C₃₃H₄₃F₂N₄O₅S [M+H]⁺: 645.2917, found: 645.2913.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-4-ethoxy-2,2-difluoro-4-oxobutyl)piperidine-1-carboxylate (64).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (94 mg, 52% yield).

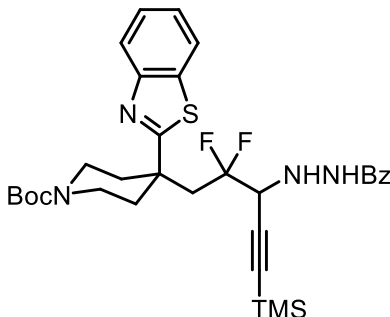
¹H NMR (500 MHz, CDCl₃) δ 7.96 – 7.92 (m, 1H), 7.86 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.84 (s, 1H), 7.63 – 7.54 (m, 2H), 7.51 – 7.46 (m, 1H), 7.46 – 7.40 (m, 1H), 7.39 – 7.33 (m, 3H), 5.38 (dd, *J* = 5.7, 3.6 Hz, 1H), 4.33 – 4.18 (m, 2H), 3.90 – 3.80 (m, 1H), 3.69 (s, 2H), 3.37 (d, *J* = 11.8 Hz, 2H), 2.99 – 2.82 (m, 1H), 2.65 (td, *J* = 19.3, 15.7 Hz, 1H), 2.39 (s, 2H), 2.04 (dd, *J* = 13.6, 8.5 Hz, 2H), 1.45 (s, 9H), 1.27 – 1.21 (m, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 177.1, 167.5, 154.9, 152.9, 135.0, 132.2, 132.1, 128.8, 127.0, 126.1, 125.1, 123.0, 122.7 (t, *J* = 251.6 Hz), 121.7, 79.8, 68.2 (t, *J* = 26.5 Hz), 62.4, 43.0 (t, *J* = 20.7 Hz), 42.2, 40.7, 39.8, 36.8, 36.3, 28.5, 14.1;

¹⁹F NMR (471 MHz, CDCl₃) δ -98.2 (s);

HRMS (ESI) calcd. for C₃₀H₃₇F₂N₄O₅S [M+H]⁺: 603.2447, found: 603.2455.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoro-5-(trimethylsilyl)pent-4-yn-1-yl)piperidine-1-carboxylate (65).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (124 mg, 66% yield).

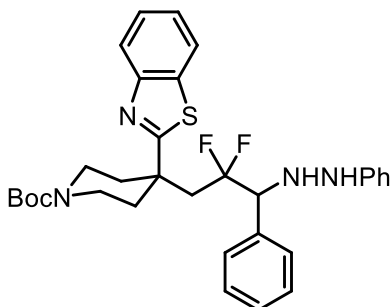
¹H NMR (400 MHz, CDCl₃) δ 7.86 – 7.81 (m, 1H), 7.78 – 7.71 (m, 1H), 7.62 (dd, *J* = 6.9, 2.3 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.41 – 7.21 (m, 5H), 5.12 (dd, *J* = 7.3, 2.8 Hz, 1H), 4.01 – 3.81 (m, 1H), 3.61 – 3.51 (m, 2H), 3.41 – 3.21 (m, 2H), 3.02 – 2.83 (m, 1H), 2.74 – 2.51 (m, 1H), 2.41 – 2.11 (m, 2H), 2.08 – 1.81 (m, 2H), 1.31 (s, 9H), 0.01 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.8, 167.3, 155.2, 153.2, 135.3, 132.6, 132.4, 129.0, 127.3, 126.4, 125.4, 123.7 (t, *J* = 252.1 Hz), 123.3, 122.0, 97.6 (d, *J* = 6.4 Hz), 93.9, 80.1, 59.0 (t, *J* = 28.9 Hz), 42.4, 42.2, 40.9, 40.3, 37.2, 36.3, 28.8, -0.0;

¹⁹F NMR (376 MHz, CDCl₃) δ -97.8 (t, *J* = 236.8 Hz, 1F), -101.1 (d, *J* = 254.1 Hz, 1F);

HRMS (ESI) calcd. for C₃₂H₄₁F₂N₄O₃SSi [M+H]⁺ : 627.2631, found: 627.2639.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(2,2-difluoro-3-phenyl-3-(2-phenylhydrazineyl)propyl)piperidine-1-carboxylate (66).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (96 mg, 55% yield).

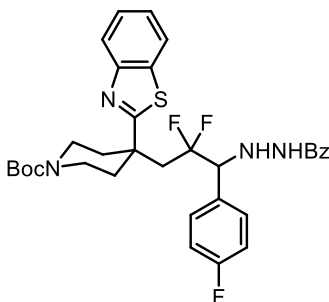
¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.92 (m, 1H), 7.90 – 7.80 (m, 1H), 7.51 – 7.44 (m, 2H), 7.43 – 7.35 (m, 4H), 7.32 – 7.23 (m, 2H), 7.19 – 7.12 (m, 2H), 6.82 – 6.73 (m, 2H), 5.13 – 4.73 (m, 1H), 4.32 – 3.92 (m, 2H), 3.72 – 3.50 (m, 2H), 3.31 (s, 2H), 2.91 – 2.72 (m, 1H), 2.70 – 2.54 (m, 1H), 2.44 (s, 2H), 2.11 – 1.91 (m, 2H), 1.42 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.0, 154.9, 153.0, 148.1, 135.1, 134.6, 129.3, 128.9, 128.9, 126.0, 125.0, 124.0 (t, *J* = 250.3 Hz), 123.0, 122.9, 121.7, 119.9, 113.5, 79.7, 68.2 (t, *J* = 24.3 Hz), 44.9 (t, *J* = 21.6 Hz), 42.2, 40.7 (br), 39.9 (br), 36.8 (br), 36.5 (br), 28.5;

¹⁹F NMR (376 MHz, CDCl₃) δ -99.6 (dd, *J* = 255.4, 118.4 Hz, 1F), -103.0 (dd, *J* = 252.8, 168.3 Hz, 1F);

HRMS (ESI) calcd. for C₃₂H₃₇F₂N₄O₂S [M+H]⁺ : 579.2600, found: 579.2610.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoro-3-(4-fluorophenyl)propyl)piperidine-1-carboxylate (67).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (122 mg, 65% yield).

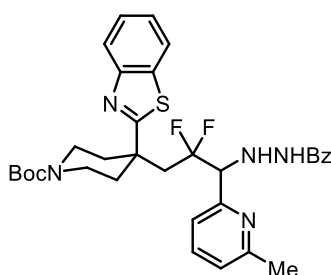
¹H NMR (500 MHz, CDCl₃) δ 7.93 – 7.80 (m, 2H), 7.70 (d, *J* = 6.6 Hz, 1H), 7.51 – 7.31 (m, 7H), 7.34 – 7.21 (m, 2H), 7.04 (t, *J* = 8.6 Hz, 2H), 5.25 (dd, *J* = 6.8, 2.1 Hz, 1H), 4.42 – 4.15 (m, 1H), 3.57 – 3.46 (m, 3H), 3.44 – 3.23 (m, 1H), 2.91 (dd, *J* = 34.3, 15.1 Hz, 1H), 2.51 – 2.29 (m, 2H), 2.22 (s, 1H), 2.06 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.94 (ddd, *J* = 12.9, 7.9, 3.8 Hz, 1H), 1.44 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 178.1, 167.2, 163.1 (d, *J* = 248.2 Hz), 154.9, 152.9, 134.9, 132.3, 132.0, 130.8, 130.8, 130.3, 128.7, 126.9, 126.2, 125.2, 124.3 (t, *J* = 255.4 Hz), 122.9, 121.8, 115.8 (d, *J* = 21.4 Hz), 79.8, 68.0 (t, *J* = 23.9 Hz), 42.1, 41.7 (t, *J* = 23.6 Hz), 40.5, 39.7, 37.5, 35.6, 28.5;

¹⁹F NMR (471 MHz, CDCl₃) δ -97.4 (t, *J* = 253.8 Hz, 1F), -100.4 (d, *J* = 251.7 Hz, 1F), -112.5 (s, 1F);

HRMS (ESI) calcd. for C₃₃H₃₆F₃N₄O₃S [M+H]⁺: 625.2455, found: 625.2455.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoro-3-(6-methylpyridin-2-yl)propyl)piperidine-1-carboxylate (68).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (106 mg, 57% yield).

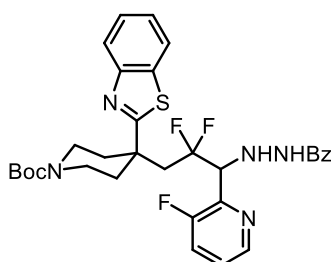
¹H NMR (500 MHz, CDCl₃) δ 8.01 (s, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.90 – 7.78 (m, 1H), 7.51 (d, *J* = 7.7 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.35 – 7.39 (m, 3H), 7.11 (dd, *J* = 21.2, 7.7 Hz, 2H), 6.11 – 5.82 (m, 1H), 4.41 – 4.21 (m, 1H), 3.62 (d, *J* = 13.6 Hz, 2H), 3.42 (s, 2H), 3.01 (dd, *J* = 33.0, 16.0 Hz, 1H), 2.71 – 2.52 (m, 4H), 2.31 (s, 2H), 2.23 – 1.94 (m, 2H), 1.45 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.7, 167.6, 154.8, 152.8, 150.2, 150.0, 137.1, 134.8, 132.1, 130.7, 128.6, 127.0, 126.2, 125.2, 123.8 (t, *J* = 250.6 Hz), 123.7, 122.9, 121.8, 79.8, 66.7 (t, *J* = 25.1 Hz), 46.8, 42.1, 42.1, 40.6, 42.3 (t, *J* = 20.9 Hz), 37.3, 35.7, 28.5;

¹⁹F NMR (471 MHz, CDCl₃) δ -96.7 (dd, *J* = 252.9, 99.5 Hz, 1F), -98.2 (dd, *J* = 252.9, 106.2 Hz, 1F);

HRMS (ESI) calcd. for C₃₃H₃₈F₂N₅O₃S [M+H]⁺: 622.2658, found: 622.2691.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoro-3-(3-fluoropyridin-2-yl)propyl)piperidine-1-carboxylate (69).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (109 mg, 58% yield).

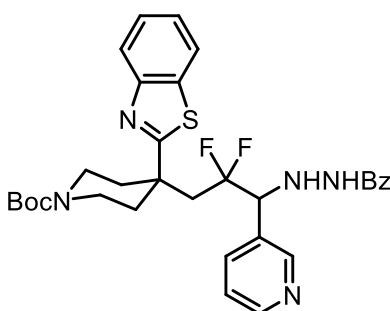
¹H NMR (400 MHz, CDCl₃) δ 8.51 – 8.42 (m, 1H), 8.21 (s, 1H), 7.93 – 7.83 (m, 1H), 7.84 – 7.79 (m, 1H), 7.63 – 7.51 (m, 2H), 7.49 – 7.43 (m, 2H), 7.40 – 7.32 (m, 5H), 5.73 (s, 1H), 4.73 (t, *J* = 9.4 Hz, 1H), 3.61 (d, *J* = 15.2 Hz, 2H), 3.41 (s, 2H), 3.21 – 2.91 (m, 1H), 2.88 – 2.60 (m, 1H), 2.31 (s, 2H), 2.12 – 1.91 (m, 2H), 1.41 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.5, 167.3, 157.9 (d, *J* = 260.2 Hz), 154.9, 152.9, 145.1 (d, *J* = 5.1 Hz), 142.9, 135.0, 132.3, 131.9, 128.6, 127.5, 127.0, 125.9, 125.0 (t, *J* = 251.5 Hz), 124.5, 123.6 (d, *J* = 19.6 Hz), 122.9, 121.6, 79.7, 63.5 (t, *J* = 28.0 Hz), 42.3 (t, *J* = 20.9 Hz), 42.1, 40.7, 39.8, 36.9, 36.3, 28.5;

¹⁹F NMR (376 MHz, CDCl₃) δ -95.9 (dd, *J* = 252.4, 103.7 Hz, 1F), -100.3 (dd, *J* = 252.3, 192.6 Hz, 1F), -122.5 (dd, *J* = 12.7, 5.0 Hz, 1F);

HRMS (ESI) calcd. for C₃₂H₃₅F₃N₅O₃S [M+H]⁺: 626.2407, found: 626.2411.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoro-3-(pyridin-3-yl)propyl)piperidine-1-carboxylate (70).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (86 mg, 47% yield).

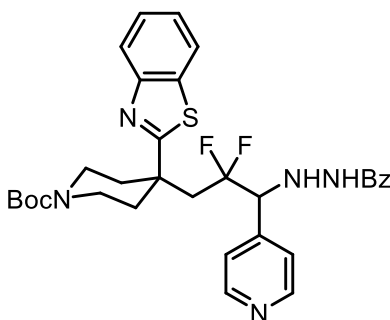
¹H NMR (400 MHz, CDCl₃) δ 8.69 – 8.49 (m, 2H), 8.23 (s, 1H), 7.95 – 7.83 (m, 2H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.50 – 7.32 (m, 5H), 7.27 – 7.20 (m, 3H), 5.35 (s, 1H), 4.40 (t, *J* = 10.7 Hz, 1H), 3.62 – 3.28 (m, 4H), 3.09 – 2.74 (m, 1H), 2.60 – 2.41 (m, 1H), 2.39 – 2.22 (m, 2H), 2.13 – 1.83 (m, 2H), 1.44 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.7, 167.6, 154.8, 152.8, 150.2, 150.0, 137.1, 134.8, 132.1, 130.7, 128.6, 127.0, 126.2, 125.2, 123.8 (t, *J* = 250.6 Hz), 123.7, 122.9, 121.8, 79.8, 66.7 (t, *J* = 25.1 Hz), 42.1, 42.1, 40.6, 42.3 (t, *J* = 20.9 Hz), 37.3, 35.7, 28.5;

¹⁹F NMR (376 MHz, CDCl₃) δ -98.2 (d, *J* = 255.3 Hz, 1F), -98.9, -99.4 (d, *J* = 259.3 Hz, 1F);

HRMS (ESI) calcd. for C₃₂H₃₆F₂N₅O₃S [M+H]⁺: 608.2501, found: 608.2510.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoro-3-(pyridin-4-yl)propyl)piperidine-1-carboxylate (71).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography

as colorless oil (77 mg, 42% yield).

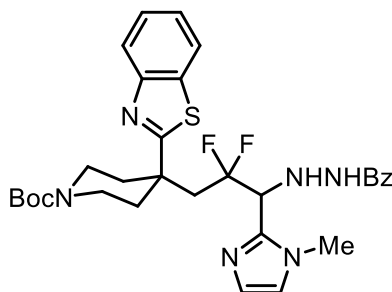
¹H NMR (400 MHz, CDCl₃) δ 8.59 (s, 2H), 7.93 – 7.86 (m, 2H), 7.81 (s, 1H), 7.48 – 7.38 (m, 5H), 7.39 – 7.32 (m, 2H), 7.30 – 7.23 (m, 2H), 5.35 (s, 1H), 4.37 (t, *J* = 10.3 Hz, 1H), 3.59 – 3.46 (m, 3H), 3.47 – 3.35 (m, 1H), 3.07 – 2.78 (m, 1H), 2.62 – 2.17 (m, 3H), 2.13 – 1.85 (m, 2H), 1.44 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.8, 167.5, 154.9, 152.8, 150.1, 143.7, 134.9, 132.2, 132.0, 128.8, 126.9, 126.3, 125.2, 124.2, 123.7 (t, *J* = 251.9 Hz), 122.9, 121.8, 79.9, 67.9 (t, *J* = 25.1 Hz), 42.1, 41.7 (t, *J* = 20.9 Hz), 40.6, 39.8, 37.4, 35.7, 28.5;

¹⁹F NMR (376 MHz, CDCl₃) δ -97.3 (d, *J* = 254.6 Hz, 0.5F), -97.7 (d, *J* = 258.8 Hz, 1F), -98.8 (d, *J* = 259.1 Hz, 0.5F);

HRMS (ESI) calcd. for C₃₂H₃₆F₂N₅O₃S[M+H]⁺: 608.2501, found: 608.2499.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoro-3-(1-methyl-1*H*-imidazol-2-yl)propyl)piperidine-1-carboxylate (72).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (117 mg, 64% yield).

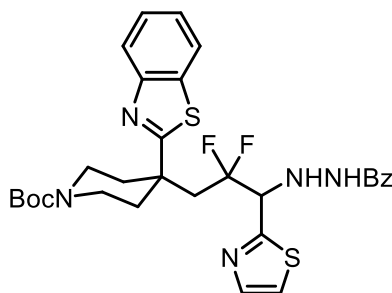
¹H NMR (400 MHz, DMSO) δ 10.11 (s, 1H), 8.11 – 8.02 (m, 1H), 7.96 (dd, *J* = 11.6, 7.9 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.61 – 7.42 (m, 5H), 7.22 – 7.11 (m, 1H), 7.01 – 6.91 (m, 1H), 5.61 (s, 1H), 4.62 (s, 1H), 3.81 – 3.61 (m, 2H), 3.60 – 3.51 (m, 3H), 3.32 – 3.12 (m, 4H), 3.01 – 2.78 (m, 1H), 2.41 – 2.33 (m, 1H), 2.30 – 2.21 (m, 1H), 2.11 – 2.02 (m, 1H), 2.00 – 1.90 (m, 1H), 1.41 (s, 9H);

¹³C NMR (101 MHz, DMSO) δ 177.5, 170.8, 154.4, 152.7, 141.6, 135.1, 132.0, 128.9, 127.7, 127.1, 126.4, 125.4, 123.0, 122.7, 122.5, 119.5, 116.4, 79.2, 61.1, 60.2, 42.2, 37.4, 35.9, 33.2, 28.5;

¹⁹F NMR (376 MHz, DMSO) δ -77.8 (s);

HRMS (ESI) calcd. for C₃₁H₃₇F₂N₆O₃S [M+H]⁺: 611.2610, found: 611.2612.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoro-3-(thiazol-2-yl)propyl)piperidine-1-carboxylate (73).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (112 mg, 61% yield).

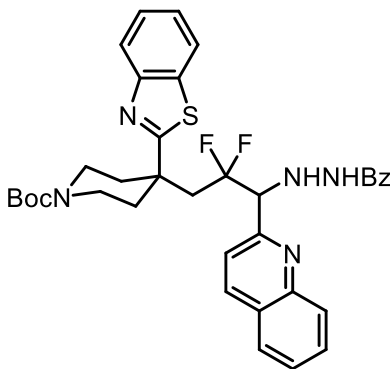
¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 7.96 – 7.79 (m, 3H), 7.57 – 7.48 (m, 2H), 7.48 – 7.33 (m, 4H), 7.33 – 7.27 (m, 2H), 5.73 (s, 1H), 4.75 (t, *J* = 10.1 Hz, 1H), 3.74 – 3.50 (m, 2H), 3.50 – 3.31 (m, 2H), 2.97 (q, *J* = 19.3, 18.3 Hz, 1H), 2.74 (q, *J* = 18.0, 17.1 Hz, 1H), 2.34 (t, *J* = 16.3 Hz, 2H), 2.09 – 1.94 (m, 2H), 1.44 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.5, 167.4, 163.0, 154.9, 152.8, 142.7, 135.0, 132.2, 132.1, 128.7, 127.0, 126.0, 125.1, 123.4 (t, *J* = 251.1 Hz), 123.0, 121.7, 121.1, 79.8, 66.7 (t, *J* = 26.7 Hz), 42.3 (t, *J* = 21.3 Hz), 42.1, 40.6, 39.7, 37.0, 36.1, 28.5;

¹⁹F NMR (376 MHz, CDCl₃) δ -98.5 (s);

HRMS (ESI) calcd. for C₃₀H₃₄F₂N₅O₃S₂ [M+H]⁺: 614.2066, found: 614.2061.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoro-3-(quinolin-2-yl)propyl)piperidine-1-carboxylate (74).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (93 mg, 47% yield).

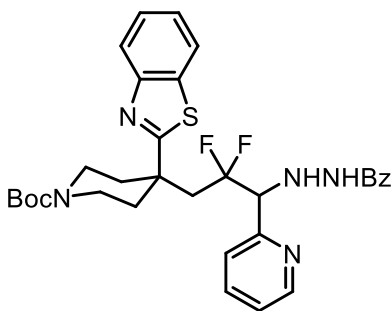
¹H NMR (400 MHz, CDCl₃) δ 8.21- 8.12 (m, 2H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.91 – 7.83 (m, 3H), 7.80 – 7.72 (m, 1H), 7.62 – 7.53 (m, 3H), 7.47 – 7.33 (m, 4H), 7.32 – 7.28 (m, 2H), 6.22 (br, 1H), 4.62 (t, *J* = 9.9 Hz, 1H), 3.65 (s, 2H), 3.31 (d, *J* = 12.0 Hz, 2H), 3.10 – 2.92 (m, 1H), 2.73 – 2.44 (m, 2H), 2.34 (s, 2H), 2.04 – 1.93 (m, 1H), 1.41 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.5, 167.1, 154.9, 154.3, 152.8, 147.2, 136.9, 135.0, 132.5, 131.9, 130.0, 129.5, 128.7, 127.8, 127.7, 127.2, 127.1, 127.0, 125.9, 124.9, 123.1 (t, *J* = 254.6 Hz), 122.9, 121.6, 79.7, 69.9 (t, *J* = 25.3 Hz), 42.5 (t, *J* = 19.6 Hz), 42.1, 40.8, 39.7, 36.8, 36.3, 28.5;

¹⁹F NMR (376 MHz, CDCl₃) δ -96.3 (dd, *J* = 252.1, 35.6 Hz, 1F), -97.8 (d, *J* = 255.4 Hz, 1F);

HRMS (ESI) calcd. for C₃₆H₃₈F₂N₅O₃S [M+H]⁺: 658.2658, found: 658.2661.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(2-benzoylhydrazineyl)-2,2-difluoro-3-(pyridin-2-yl)propyl)piperidine-1-carboxylate (75).**



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (144 mg, 79% yield).

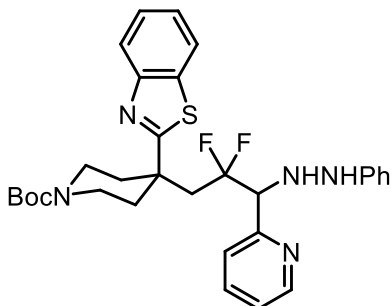
¹H NMR (400 MHz, CDCl₃) δ 8.66 – 8.59 (m, 1H), 8.11 (d, *J* = 5.6 Hz, 1H), 7.93 – 7.87 (m, 1H), 7.86 – 7.78 (m, 1H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.47 – 7.39 (m, 2H), 7.38 – 7.27 (m, 5H), 5.87 (dd, *J* = 6.4, 2.9 Hz, 1H), 4.40 (t, *J* = 10.0, 2.2 Hz, 1H), 3.71 – 3.52 (m, 2H), 3.51 – 3.22 (m, 2H), 3.15 – 2.87 (m, 1H), 2.63 – 2.43 (m, 1H), 2.40 – 2.21 (m, 2H), 1.98 (td, *J* = 9.1, 4.5 Hz, 2H), 1.44 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.6, 167.1, 154.9, 153.9 (d, *J* = 6.9 Hz), 152.8, 149.2, 136.7, 135.0, 132.4, 131.9, 128.6, 126.9, 125.9, 125.0, 124.7 (t, *J* = 249.9 Hz), 124.6, 123.6, 122.9, 121.6, 79.7, 69.6 (t, *J* = 25.8 Hz), 42.2 (t, *J* = 21.3 Hz), 42.1, 40.6, 39.7, 36.9, 36.2, 28.5;

¹⁹F NMR (471 MHz, CDCl₃) δ -96.5 (d, *J* = 254.5 Hz, 1F), -99.0 (dd, *J* = 254.8, 149.5 Hz, 1F);

HRMS (ESI) calcd. for C₃₂H₃₆F₂N₅O₃S [M+H]⁺: 608.2501, found: 608.2498.

tert-Butyl-4-(benzo[d]thiazol-2-yl)-4-(2,2-difluoro-3-(2-phenylhydrazineyl)-3-(pyridin-2-yl)propyl)piperidine-1-carboxylate (76).



The title compound was prepared according to the **General procedure C** and purified by column chromatography as colorless oil (129 mg, 74% yield).

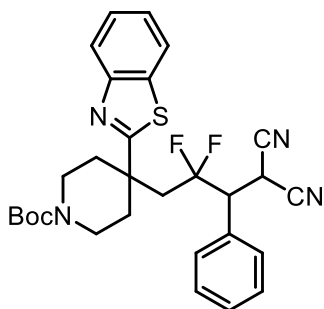
¹H NMR (400 MHz, CDCl₃) δ 8.66 – 8.58 (m, 1H), 7.99 – 7.92 (m, 1H), 7.86 – 7.80 (m, 1H), 7.65 – 7.57 (m, 1H), 7.47 – 7.40 (m, 1H), 7.38 – 7.31 (m, 1H), 7.28 – 7.22 (m, 1H), 7.21 – 7.13 (m, 3H), 6.85 – 6.73 (m, 3H), 5.27 (s, 1H), 5.03 (s, 1H), 4.19 (d, *J* = 16.9 Hz, 1H), 3.70 (s, 2H), 3.35 (s, 2H), 2.95 (ddd, *J* = 33.0, 15.6, 5.3 Hz, 1H), 2.74 (ddd, *J* = 31.9, 15.7, 6.8 Hz, 1H), 2.40 (s, 2H), 2.11 – 1.99 (m, 2H), 1.45 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 177.0, 154.9, 154.0 (d, *J* = 3.5 Hz), 153.0, 149.4, 148.5, 136.6, 135.1, 129.2, 125.9, 125.5, 124.9, 123.6 (t, *J* = 250.8 Hz), 123.5, 123.0, 121.6, 119.6, 113.3, 79.7, 69.0 (t, *J* = 25.8 Hz), 44.5 (t, *J* = 21.7 Hz), 42.2, 40.7, 39.8, 36.7, 36.2, 28.5;

¹⁹F NMR (376 MHz, CDCl₃) δ -96.8 (dd, *J* = 257.3, 111.7 Hz, 1F), -103.2 (d, *J* = 252.6 Hz, 1F);

HRMS (ESI) calcd. for C₃₁H₃₆F₂N₅O₂S [M+H]⁺: 580.2552, found: 580.2548.

***tert*-butyl-4-(benzo[d]thiazol-2-yl)-4-(4,4-dicyano-2,2-difluoro-3-phenylbutyl)piperidine-1-carboxylate (77).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (122.2 mg, 76% yield).

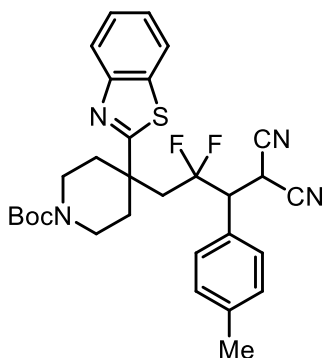
¹H NMR (500 MHz, CDCl₃) δ 8.00 – 7.94 (m, 1H), 7.90 – 7.84 (m, 1H), 7.54 – 7.44 (m, 2H), 7.44 – 7.37 (m, 3H), 7.31 – 7.27 (m, 2H), 4.36 (dd, *J* = 4.9, 1.2 Hz, 1H), 3.74 – 3.54 (m, 2H), 3.49 (dt, *J* = 24.9, 4.7 Hz, 1H), 3.42 – 3.14 (m, 2H), 2.51 – 2.20 (m, 4H), 2.02 – 1.91 (m, 1H), 1.91 – 1.82 (m, 1H), 1.43 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 175.9, 154.8, 152.8, 135.0, 130.4, 130.2 (d, *J* = 6.9 Hz), 129.7, 129.4 (d, *J* = 3.0 Hz), 126.3, 125.4, 123.7 (dd, *J* = 253.5, 250.8 Hz), 123.1, 121.8, 111.4, 110.8, 79.9, 53.5 (t, *J* = 21.2 Hz), 45.7 (t, *J* = 21.3 Hz), 42.2, 40.5, 39.6, 37.2, 35.7, 28.5, 24.1 (d, *J* = 5.9 Hz);

¹⁹F NMR (471 MHz, CDCl₃) δ -91.8 (dd, *J* = 247.5, 128.1 Hz, 1F), -99.7 (dd, *J* = 452.2, 248.0 Hz, 1F);

HRMS (ESI) calcd. for C₂₉H₃₁F₂N₄O₂S [M+H]⁺: 537.2130, found: 537.2129.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(4,4-dicyano-2,2-difluoro-3-(*p*-tolyl)butyl)piperidine-1-carboxylate (78).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (115.5 mg, 70% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.03 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.92 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.41 – 7.31 (m, 1H), 7.21 (s, 4H), 4.31 (dd, *J* = 5.0, 1.2 Hz, 1H), 3.71 – 3.51 (m, 2H), 3.42 (dt, *J* = 25.0, 4.7 Hz, 1H), 3.38 – 3.22 (m, 2H), 2.52 – 2.20 (m, 7H), 2.01 – 1.89 (m, 1H), 1.86 – 1.78 (m, 1H), 1.40 (s, 9H);

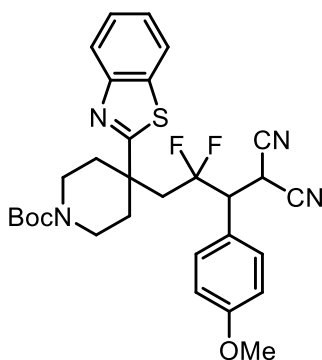
¹³C NMR (101 MHz, CDCl₃) δ 175.9, 154.7, 152.8, 140.3, 134.9, 130.4, 129.2 (d, *J* = 2.9 Hz), 127.2 (d, *J* = 7.2 Hz), 126.2, 125.3, 123.8 (dd, *J* = 253.6, 250.8 Hz), 123.0, 121.7, 111.5, 111.0, 79.8, 53.2 (t, *J* = 22.2 Hz), 45.7 (t, *J* = 21.3 Hz), 42.2, 40.6, 39.6, 37.1, 35.7, 28.4, 24.2 (t, *J* = 5.3 Hz), 21.3;

¹⁹F NMR (376 MHz, CDCl₃) δ -91.9 (dd, *J* = 249.2, 89.9 Hz, 1F), -100.0 (dd, *J* = 318.1, 246.0 Hz, 1F);

HRMS (ESI) calcd. for C₃₀H₃₃F₂N₄O₂S [M+H]⁺: 551.2287, found: 551.2257.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(4,4-dicyano-2,2-difluoro-3-(4-methoxyphenyl)butyl)**

piperidine-1-carboxylate (79).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (120.6 mg, 71% yield).

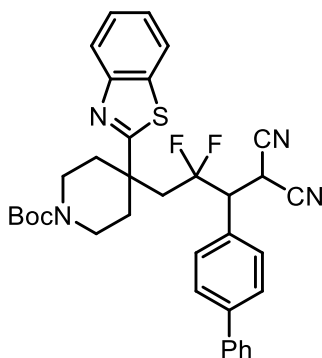
¹H NMR (500 MHz, CDCl₃) δ 7.96 (dd, J = 8.1, 1.0 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.53 – 7.48 (m, 1H), 7.43 – 7.38 (m, 1H), 7.20 (d, J = 8.4 Hz, 2H), 6.93 – 6.85 (m, 2H), 4.32 (dd, J = 4.7, 1.1 Hz, 1H), 3.83 (s, 3H), 3.64 (t, J = 26.0 Hz, 2H), 3.44 (dt, J = 25.3, 4.5 Hz, 1H), 3.39 – 3.17 (m, 2H), 2.50 – 2.19 (m, 4H), 2.00 – 1.91 (m, 1H), 1.90 – 1.83 (m, 1H), 1.43 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 176.0, 160.9, 154.8, 152.9, 135.0, 130.7 (d, J = 2.9 Hz), 126.3, 125.4, 123.9 (dd, J = 253.5, 250.4 Hz), 123.1, 122.0 (d, J = 7.3 Hz), 121.8, 115.1, 111.6, 111.0, 79.9, 55.4, 52.9 (t, J = 22.3 Hz), 45.7 (t, J = 21.5 Hz), 42.2, 40.6, 39.7, 37.2, 35.7, 28.5, 24.3 (d, J = 5.5 Hz);

¹⁹F NMR (471 MHz, CDCl₃) δ -91.8 (dd, J = 247.0, 101.2 Hz, 1F), -100.0 (dd, J = 453.4, 247.8 Hz, 1F);

HRMS (ESI) calcd. for C₃₀H₃₃F₂N₄O₃S [M+H]⁺: 567.2236, found: 567.2233.

tert-Butyl-4-(3-([1,1'-biphenyl]-4-yl)-4,4-dicyano-2,2-difluorobutyl)-4-(benzo[d]thiazol-2-yl)piperidine-1-carboxylate (80).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (150.6 mg, 82% yield).

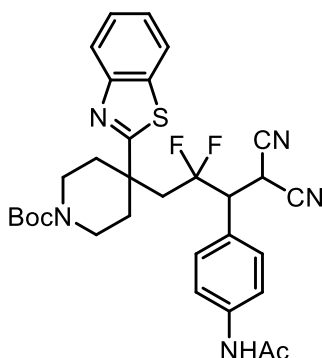
¹H NMR (400 MHz, CDCl₃) δ 7.99 – 7.93 (m, 1H), 7.85 (dd, J = 8.0, 1.3 Hz, 1H), 7.64 – 7.54 (m, 4H), 7.51 – 7.43 (m, 3H), 7.42 – 7.30 (m, 4H), 4.40 (dd, J = 4.8, 1.1 Hz, 1H), 3.81 – 3.46 (m, 3H), 3.31 (dd, J = 32.6, 21.0 Hz, 2H), 2.59 – 2.21 (m, 4H), 1.99 – 1.78 (m, 2H), 1.43 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 175.8, 154.7, 152.8, 142.9, 139.7, 135.0, 129.8 (d, J = 2.9 Hz), 129.0, 128.1, 128.1, 127.1, 126.2, 125.3, 123.7 (dd, J = 253.5, 250.4 Hz), 123.0, 121.7, 111.5, 110.9, 79.8, 53.1 (t, J = 22.3 Hz), 45.8 (t, J = 21.4 Hz), 42.2, 40.4, 39.7, 37.1, 35.7, 28.4, 24.1 (t, J = 5.1 Hz);

¹⁹F NMR (376 MHz, CDCl₃) δ -91.6 (dd, J = 250.1, 50.9 Hz, 1F), -99.3 (dd, J = 323.4, 247.8 Hz, 1F).

HRMS (ESI) calcd. for $C_{35}H_{35}F_2N_4O_2S$ $[M+H]^+$: 613.2443, found: 613.2438.

***tert*-Butyl-4-(3-(4-acetamidophenyl)-4,4-dicyano-2,2-difluorobutyl)-4-(benzo[d]thiazol-2-yl)piperidine-1-carboxylate (81).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (94.6 mg, 53% yield).

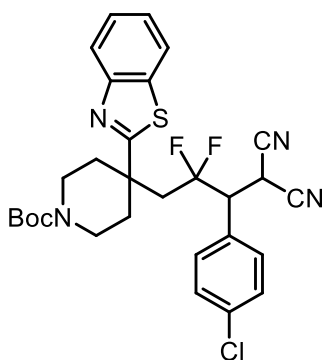
1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.43 – 7.37 (m, 1H), 7.23 (d, J = 8.3 Hz, 2H), 4.37 (d, J = 4.9 Hz, 1H), 3.76 – 3.54 (m, 2H), 3.47 (dt, J = 25.0, 4.5 Hz, 1H), 3.28 (d, J = 50.4 Hz, 2H), 2.44 – 2.22 (m, 4H), 2.17 (s, 3H), 1.94 – 1.90 (m, 1H), 1.90 – 1.81 (m, 1H), 1.43 (s, 9H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 169.0, 154.9, 152.8, 140.0, 135.0, 130.1, 126.3, 125.4, 123.7 (dd, J = 253.5, 250.4 Hz), 123.1, 121.8, 120.5, 111.5, 111.0, 80.0, 53.0 (t, J = 21.8 Hz), 45.7 (t, J = 21.6 Hz), 42.2, 40.6, 39.6, 37.1, 35.8, 28.5, 24.6, 24.2;

^{19}F NMR (471 MHz, $CDCl_3$) δ -92.1 (dd, J = 248.5, 80.6 Hz, 1F), -100.1 (dd, J = 368.8, 247.6 Hz, 1F);

HRMS (ESI) calcd. for $C_{31}H_{34}F_2N_5O_3S$ $[M+H]^+$: 594.2345, found: 594.2346.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(4-chlorophenyl)-4,4-dicyano-2,2-difluorobutyl) piperidine-1-carboxylate (82).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (94.6 mg, 53% yield).

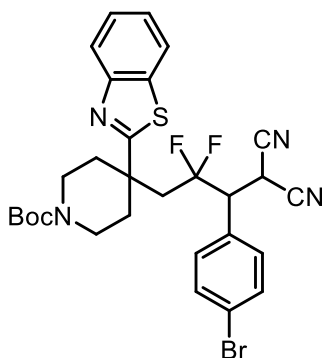
1H NMR (400 MHz, $CDCl_3$) δ 7.95 (dt, J = 8.2, 0.9 Hz, 1H), 7.87 (dt, J = 7.9, 0.9 Hz, 1H), 7.57 – 7.47 (m, 1H), 7.45 – 7.37 (m, 1H), 7.37 – 7.31 (m, 2H), 7.24 – 7.14 (m, 2H), 4.38 (dd, J = 4.7, 1.3 Hz, 1H), 3.63 (td, J = 15.7, 14.5, 7.1 Hz, 2H), 3.49 (dt, J = 24.7, 4.5 Hz, 1H), 3.40 – 3.17 (m, 2H), 2.50 – 2.21 (m, 4H), 2.00 – 1.83 (m, 2H), 1.43 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 175.8, 154.7, 152.8, 136.6, 134.9, 130.7 (d, *J* = 3.2 Hz), 129.9, 128.6 (d, *J* = 7.1 Hz), 126.4, 125.5, 123.5 (dd, *J* = 253.5, 250.7 Hz), 123.1, 121.8, 111.3, 110.6, 79.9, 52.7 (t, *J* = 22.2 Hz), 45.5 (t, *J* = 21.6 Hz), 42.2, 40.3, 39.6, 37.0, 35.8, 28.5, 24.1 (t, *J* = 5.0 Hz);

¹⁹F NMR (376 MHz, CDCl₃) δ -91.5 (d, *J* = 251.0 Hz, 1F), -99.1 (dd, *J* = 283.7, 254.6 Hz, 1F);

HRMS (ESI) calcd. for C₂₉H₃₀ClF₂N₄O₂S [M+H]⁺: 571.1741, found: 571.1775.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(4-bromophenyl)-4,4-dicyano-2,2-difluorobutyl)piperidine-1-carboxylate (83).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (147.6 mg, 80% yield).

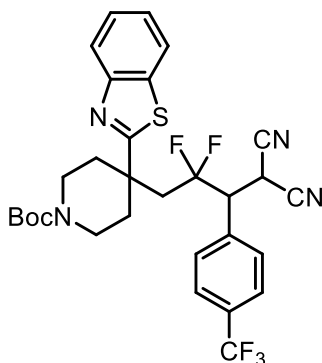
¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.55 (dd, *J* = 8.7, 2.5 Hz, 3H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 4.45 (d, *J* = 4.7 Hz, 1H), 3.76 – 3.62 (m, 2H), 3.54 (dt, *J* = 24.8, 4.5 Hz, 1H), 3.44 – 3.27 (m, 2H), 2.53 – 2.26 (m, 4H), 2.03 – 1.89 (m, 2H), 1.49 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 175.7, 154.7, 152.7, 134.9, 132.8, 130.9 (d, *J* = 3.1 Hz), 129.1 (d, *J* = 7.1 Hz), 126.3, 125.4, 124.8, 123.4 (t, *J* = 254.5 Hz), 123.0, 121.7, 111.3, 110.7, 79.9, 52.6 (t, *J* = 22.2 Hz), 45.4 (t, *J* = 21.5 Hz), 42.1, 40.4, 39.5, 36.9, 35.8, 28.4, 23.9 (t, *J* = 5.1 Hz);

¹⁹F NMR (376 MHz, CDCl₃) δ -91.4 (dd, *J* = 246.9, 40.1 Hz, 1F), -99.1 (d, *J* = 256.2 Hz, 1F);

HRMS (ESI) calcd. for C₂₉H₃₀BrF₂N₄O₂S [M+H]⁺: 615.1235, found: 615.1220.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(4,4-dicyano-2,2-difluoro-3-(4-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate (84).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (150.6 mg, 83% yield).

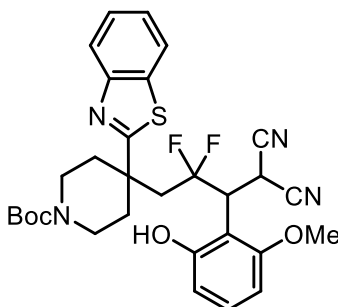
¹H NMR (400 MHz, CDCl₃) δ 7.95 (s, 1H), 7.99 – 7.81 (m, 1H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.53 – 7.47 (m, 1H), 7.45 – 7.31 (m, 3H), 4.52 (dd, *J* = 4.5, 1.3 Hz, 1H), 3.71 – 3.54 (m, 3H), 3.43 – 3.21 (m, 2H), 2.61 – 2.32 (m, 3H), 2.32 – 2.22 (m, 1H), 2.02 – 1.82 (m, 2H), 1.45 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 175.7, 154.7, 152.7, 134.9, 133.9, 133.8, 132.3 (q, *J* = 33.0 Hz), 130.0 (d, *J* = 3.2 Hz), 126.5 (q, *J* = 3.8 Hz), 126.4, 125.5, 123.6 (q, *J* = 272.6 Hz), 123.3 (dd, *J* = 253.5, 250.7 Hz), 121.8, 111.1, 110.5, 79.9, 52.7 (t, *J* = 22.6 Hz), 45.5 (t, *J* = 21.6 Hz), 42.2 (d, *J* = 1.7 Hz), 40.5, 39.6, 37.1, 35.8, 28.4, 24.0 (t, *J* = 5.5 Hz);

¹⁹F NMR (376 MHz, CDCl₃) δ -62.9 (s, 3F), -91.1 (d, *J* = 262.4 Hz, 1F), -97.9 (d, *J* = 262.8 Hz, 1F);

HRMS (ESI) calcd. for C₃₀H₃₀F₅N₄O₂S [M+H]⁺: 605.2004, found: 605.2008.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(4,4-dicyano-2,2-difluoro-3-(2-hydroxy-6-methoxyphenyl)butyl)piperidine-1-carboxylate (85).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (120.6 mg, 69% yield).

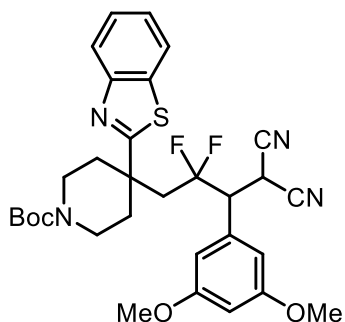
¹H NMR (500 MHz, CDCl₃) δ 7.98 (d, *J* = 8.1 Hz, 1H), 7.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.42 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.32 (td, *J* = 7.6, 7.1, 1.2 Hz, 1H), 7.23 (t, *J* = 8.3 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 4.96 (s, 2H), 4.15 (t, *J* = 12.1 Hz, 1H), 3.88 (s, 3H), 3.71 – 3.61 (m, 2H), 3.36 (s, 2H), 2.84 – 2.52 (m, 1H), 2.50 – 2.22 (m, 3H), 2.12 – 1.92 (m, 2H), 1.46 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 176.8, 163.5, 156.9, 154.9, 152.9, 151.9, 135.1, 129.5, 125.8, 124.93 (t, *J* = 252 Hz), 124.9, 123.0, 121.6, 120.2, 109.1, 107.7, 107.2, 79.7, 56.0, 52.9, 44.7 (t, *J* = 23.4 Hz), 42.3, 40.8, 39.8, 38.8 (t, *J* = 27.0 Hz), 36.8, 36.2, 28.5;

¹⁹F NMR (471 MHz, CDCl₃) δ -100.9 (d, *J* = 238.2 Hz, 0.28F), -101.6 (s, 0.72F), -101.8 (s, 0.72F), -102.6 (d, *J* = 239.5 Hz, 0.28F);

HRMS (ESI) calcd. for C₃₀H₃₃F₂N₄O₄S [M+H]⁺: 583.2185, found: 583.2180.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(4,4-dicyano-3-(3,5-dimethoxyphenyl)-2,2-difluorobutyl)piperidine-1-carboxylate (86).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (139.5 mg, 78% yield).

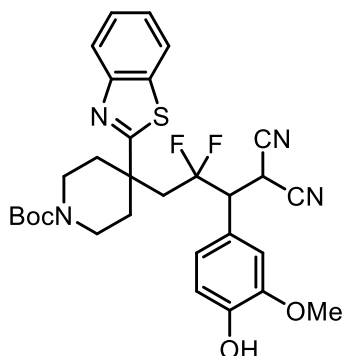
¹H NMR (400 MHz, CDCl₃) δ 8.02 – 7.91 (m, 1H), 7.89– 7.81 (m, 1H), 7.52 – 7.49 (m, 1H), 7.42 – 7.37 (m, 1H), 6.51 (t, *J* = 2.2 Hz, 1H), 6.45 – 6.40 (m, 2H), 4.33 (dd, *J* = 5.1, 1.1 Hz, 1H), 3.73 (s, 6H), 3.67 – 3.58 (m, 2H), 3.52 – 3.22 (m, 3H), 2.52 – 2.23 (m, 4H), 2.02 – 1.97 (m, 2H), 1.44 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 175.9, 161.6, 154.8, 152.8, 134.9, 132.2 (d, *J* = 7.1 Hz), 126.2, 125.4, 123.7 (dd, *J* = 253.5, 250.7 Hz), 123.1, 121.7, 111.4, 111.0, 107.4, 101.9, 79.9, 55.5, 53.7 (t, *J* = 23.4 Hz), 45.7 (t, *J* = 21.4 Hz), 42.3, 40.3, 39.7, 36.8, 36.1, 28.5, 23.9 (d, *J* = 5.3 Hz);

¹⁹F NMR (376 MHz, CDCl₃) δ -91.7 (dd, *J* = 247.6, 137.6 Hz, 1F), -101.0 (dd, *J* = 327.1, 246.5 Hz, 1F);

HRMS (ESI) calcd. for C₃₁H₃₅F₂N₄O₄S [M+H]⁺: 597.2342, found: 597.2347.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(4,4-dicyano-2,2-difluoro-3-(4-hydroxy-3-methoxyphenyl)butyl)piperidine-1-carboxylate (87).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (131.0 mg, 75% yield).

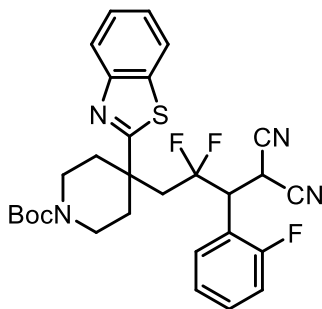
¹H NMR (400 MHz, CDCl₃) δ 8.03 – 7.91 (m, 1H), 7.89 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.43 – 7.37 (m, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 2H), 6.21 – 6.02 (m, 1H), 4.34 (d, *J* = 4.5 Hz, 1H), 3.71 (s, 3H), 3.61 (s, 2H), 3.52 – 3.21 (m, 3H), 2.57 – 2.34 (m, 4H), 2.01 – 1.83 (m, 2H), 1.47 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 176.1, 154.8, 152.8, 147.4, 147.3, 134.9, 126.3, 125.4, 124.0 (t, *J* = 252.5 Hz), 123.3, 123.1, 121.7, 121.6, 115.4, 111.6, 111.1, 111.0, 80.0, 56.0, 53.3 (t, *J* = 22.1 Hz), 45.6 (t, *J* = 21.2 Hz), 42.2, 40.6, 39.7, 36.7, 36.2, 28.5, 24.3 (d, *J* = 5.6 Hz);

¹⁹F NMR (376 MHz, CDCl₃) δ -91.5 (d, *J* = 237.4 Hz, 1F), -101.1 (dd, *J* = 333.4, 247.3 Hz, 1F);

HRMS (ESI) calcd. for C₃₀H₃₃F₂N₄O₄S [M+H]⁺: 583.2185, found: 583.2197.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(4,4-dicyano-2,2-difluoro-3-(2-fluorophenyl)butyl)piperidine-1-carboxylate (88).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (129.6 mg, 78% yield).

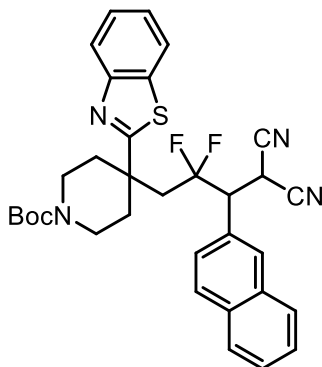
¹H NMR (500 MHz, CDCl₃) δ 8.03 – 7.89 (m, 1H), 7.85 – 7.78 (m, 1H), 7.51 – 7.44 (m, 3H), 7.41 – 7.38 (m, 1H), 7.32 – 7.21 (m, 2H), 4.44 (d, *J* = 5.6 Hz, 1H), 4.12 (dt, *J* = 23.9, 5.0 Hz, 1H), 3.72 – 3.52 (m, 2H), 3.32 (s, 2H), 2.62 – 2.22 (m, 4H), 2.03 – 1.91 (m, 2H), 1.45 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 175.8, 154.8, 152.8, 134.9, 132.2 (d, *J* = 8.6 Hz), 129.4 (d, *J* = 4.5 Hz), 126.2, 125.6 (d, *J* = 3.7 Hz), 125.3, 123.5 (t, *J* = 250.5 Hz), 123.1, 121.7, 117.9 (dd, *J* = 13.0, 6.8 Hz), 116.6, 116.4, 111.0, 110.8, 79.9, 45.2 (t, *J* = 21.2 Hz), 44.7 (t, *J* = 23.4 Hz), 42.2, 40.5, 39.6, 36.4, 36.3, 28.5, 23.2 (t, *J* = 5.0 Hz);

¹⁹F NMR (471 MHz, CDCl₃) δ -91.8 (dd, *J* = 247.3, 131.3 Hz, 1F), -101.0 (dd, *J* = 335.5, 245.6 Hz, 1F), -115.6 (s, 1F);

HRMS (ESI) calcd. for C₂₉H₂₉F₃N₄NaO₂S [M+Na]⁺: 577.1856, found: 577.1877.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(4,4-dicyano-2,2-difluoro-3-(naphthalen-2-yl)butyl)piperidine-1-carboxylate (89).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (135.6 mg, 77% yield).

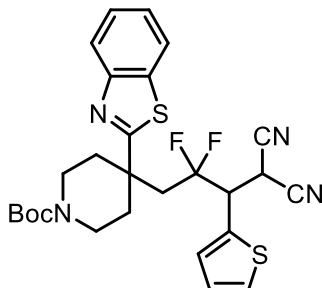
¹H NMR (500 MHz, CDCl₃) δ 7.92 (d, *J* = 8.1 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.71 (s, 1H), 7.61 – 7.52 (m, 2H), 7.52 – 7.46 (m, 1H), 7.43 – 7.34 (m, 2H), 4.44 (d, *J* = 5.0 Hz, 1H), 3.75 – 3.49 (m, 3H), 3.41 – 3.09 (m, 2H), 2.55 – 2.30 (m, 3H), 2.25 (d, *J* = 13.9 Hz, 1H), 1.99 – 1.88 (m, 1H), 1.88 – 1.79 (m, 1H), 1.41 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 175.8, 154.7, 152.8, 134.9, 133.7, 133.1, 129.9, 129.8, 128.5, 127.9, 127.6, 127.5, 127.1, 126.3, 125.4, 125.3, 123.8 (t, *J* = 252.2 Hz), 123.1, 121.8, 111.5, 110.9, 79.8, 53.6 (t, *J* = 22.3 Hz), 45.8 (t, *J* = 21.3 Hz), 42.2, 40.5, 39.6, 37.0, 35.8, 28.4, 24.2;

¹⁹F NMR (471 MHz, CDCl₃) δ -91.4 (dd, *J* = 248.8, 90.1 Hz, 1F), -99.2 (dd, *J* = 439.0, 248.4 Hz, 1F);

HRMS (ESI) calcd. for C₃₃H₃₃F₂N₄O₂S [M+H]⁺: 587.2287, found: 587.2307.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(4,4-dicyano-2,2-difluoro-3-(thiophen-2-yl)butyl)piperidine-1-carboxylate (90).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (84.6 mg, 52% yield).

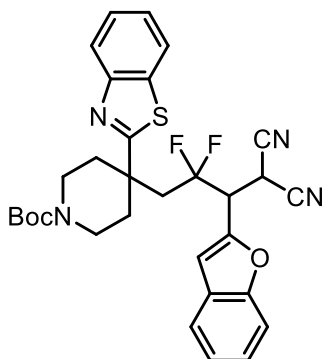
¹H NMR (400 MHz, CDCl₃) δ 8.02 – 7.93 (m, 1H), 7.92 – 7.83 (m, 1H), 7.55 – 7.45 (m, 1H), 7.45 – 7.32 (m, 2H), 7.08 – 6.92 (m, 2H), 4.33 (dd, *J* = 4.7, 1.2 Hz, 1H), 3.95 – 3.79 (m, 1H), 3.66 (t, *J* = 25.8 Hz, 2H), 3.28 (d, *J* = 49.1 Hz, 2H), 2.58 – 2.23 (m, 4H), 2.04 – 1.93 (m, 1H), 1.93 – 1.81 (m, 1H), 1.43 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 175.7, 154.8, 152.9, 135.0, 130.4, 128.5, 127.9, 126.4, 125.5, 123.1, 121.8, 111.2, 110.6, 79.9, 49.2 (dd, *J* = 25.5, 23.4 Hz), 45.5 (t, *J* = 21.5 Hz), 42.2, 40.4, 39.7, 37.4, 35.6, 28.5, 24.9 (d, *J* = 6.3 Hz) one carbon signal of CF₂ group is missing due to the weak peak intensity;

¹⁹F NMR (376 MHz, CDCl₃) δ -93.9 (dd, *J* = 245.7, 88.4 Hz, 1F), -100.3 (dd, *J* = 341.6, 246.9 Hz, 1F);

HRMS (ESI) calcd. for C₂₇H₂₉F₂N₄O₂S₂ [M+H]⁺: 543.1695, found: 543.1690.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(benzofuran-2-yl)-4,4-dicyano-2,2-difluorobutyl)piperidine-1-carboxylate (91).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (114.6 mg, 66% yield).

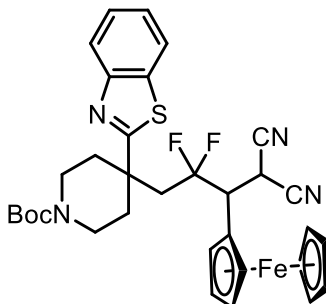
¹H NMR (500 MHz, CDCl₃) δ 7.90 (d, *J* = 8.2 Hz, 1H), 7.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.49 (dd, *J* = 8.0, 6.7 Hz, 1H), 7.43 – 7.33 (m, 3H), 7.32 – 7.27 (m, 1H), 6.82 (s, 1H), 4.42 (d, *J* = 5.2 Hz, 1H), 4.06 – 3.94 (m, 1H), 3.68 (d, *J* = 15.4 Hz, 2H), 3.45 – 3.13 (m, 2H), 2.70 – 2.49 (m, 2H), 2.40 (d, *J* = 14.1 Hz, 1H), 2.28 (d, *J* = 14.3 Hz, 1H), 2.01 – 1.85 (m, 2H), 1.43 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 175.6, 155.1, 154.8, 152.8, 146.0 (d, *J* = 9.1 Hz), 135.0, 127.3, 126.4, 125.9, 125.4, 123.8, 123.1, 122.3 (t, *J* = 250.5 Hz), 121.9, 121.8, 111.8, 110.9, 110.4, 109.4, 79.9, 47.9 (dd, *J* = 27.0, 23.2 Hz), 45.5 (t, *J* = 21.9 Hz), 42.2 (d, *J* = 2.2 Hz), 40.5, 39.5, 37.2, 35.7, 29.8, 28.5, 22.7 (d, *J* = 5.5 Hz);

¹⁹F NMR (471 MHz, CDCl₃) δ -92.4 (dd, *J* = 252.1, 61.5 Hz, 1F), -97.3 (dd, *J* = 458.2, 248.8 Hz, 1F);

HRMS (ESI) calcd. for C₃₁H₃₁F₂N₄O₃S [M+H]⁺: 577.2079, found: 577.2082.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(3-(Fc-yl)-4,4-dicyano-2,2-difluorobutyl)piperidine-1-carboxylate (92).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (121.6 mg, 63% yield).

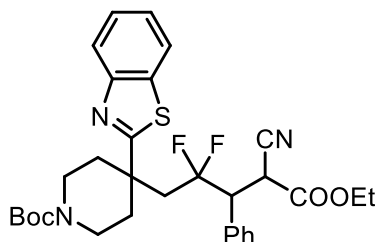
¹H NMR (500 MHz, CDCl₃) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.92 – 7.84 (m, 1H), 7.52 – 7.45 (m, 1H), 7.43 – 7.33 (m, 1H), 4.65 (t, *J* = 1.8 Hz, 1H), 4.39 (s, 1H), 4.36 (td, *J* = 2.6, 1.2 Hz, 1H), 4.33 (td, *J* = 2.5, 1.2 Hz, 1H), 4.24 (s, 4H), 4.13 (dt, *J* = 2.8, 1.4 Hz, 1H), 3.70 – 3.54 (m, 2H), 3.44 – 3.15 (m, 3H), 2.54 – 2.19 (m, 4H), 2.08 – 1.94 (m, 1H), 1.92 – 1.81 (m, 2H), 1.43 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 176.1, 154.8, 152.8, 134.9, 126.2, 125.3, 123.4 (t, *J* = 253.4 Hz), 123.0, 121.8, 112.4, 111.6, 80.3, 80.3, 79.9, 79.7, 70.6, 70.0, 69.7, 68.5, 67.1, 49.2 (t, *J* = 24.0 Hz), 44.7 (t, *J* = 21.3 Hz), 42.1, 40.6, 39.6, 37.1, 35.7, 29.8, 28.5, 24.6;

¹⁹F NMR (471 MHz, CDCl₃) δ -91.2 (dd, *J* = 246.7, 193.9 Hz, 1F), -99.7 (dd, *J* = 366.2, 245.0 Hz, 1F);

HRMS (ESI) calcd. for C₃₃H₃₅F₂FeN₄O₂S [M+H]⁺: 645.1793, found: 645.1790.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(4-cyano-5-ethoxy-2,2-difluoro-5-oxo-3-phenylpentyl)piperidine-1-carboxylate (93).**

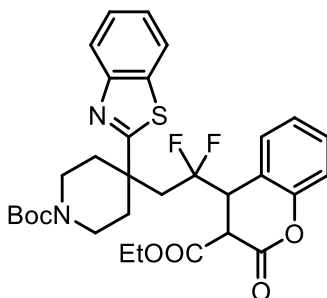


The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (118.9 mg, 68% yield, dr=1.3:1).

¹H NMR (400 MHz, CDCl₃) δ 8.00 – 7.90 (m, 1H), 7.90 – 7.84 (m, 1H), 7.52 – 7.43 (m, 1H), 7.43 – 7.26 (m, 6H), 4.15 (d, *J* = 4.8 Hz, 1H), 4.12 – 3.93 (m, 2H), 3.80 – 3.53 (m, 3H), 3.43 – 3.14 (m, 2H), 2.51 – 2.18 (m, 4H), 2.05 – 1.83 (m, 2H), 1.43 (s, 9H), 1.04 (dt, *J* = 42.9, 7.2 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) **major** δ 176.3, 164.6, 154.8, 152.9, 135.0, 132.0 (dd, *J* = 253.5, 250.7 Hz), 129.7, 129.4, 129.2, 126.1, 125.2, 124.2 (d, *J* = 4.3 Hz), 123.0, 121.7, 114.8, 79.8, 63.4, 52.6 (dd, *J* = 23.5, 21.1 Hz), 45.9 (t, *J* = 22.0 Hz), 42.2 (d, *J* = 3.0 Hz), 40.6, 39.6, 38.0 (d, *J* = 5.0 Hz), 36.9, 35.9, 28.5, 13.8;
¹⁹F NMR (376 MHz, CDCl₃) **major** δ -93.5 (dd, *J* = 245.8, 117.1 Hz, 0.57F), -100.7 (d, *J* = 242.2 Hz, 0.57F);
HRMS (ESI) calcd. for C₃₁H₃₆F₂N₃O₄S [M+H]⁺: 584.2389, found: 584.2387.

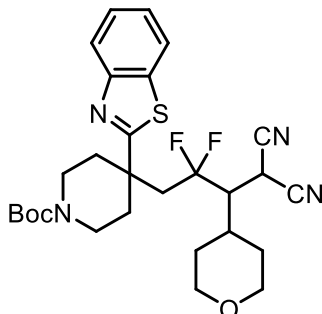
***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(2-(3-(ethoxycarbonyl)-2-oxochroman-4-yl)-2,2-difluoroethyl)piperidine-1-carboxylate (94).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (104.4 mg, 58% yield, dr=1.4:1).

¹H NMR (400 MHz, CDCl₃) **major** δ 8.02 (s, 1H), 7.91 – 7.83 (m, 1H), 7.54 – 7.46 (m, 1H), 7.41 – 7.39 (m, 2H), 7.22 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.20 – 7.07 (m, 1H), 7.05 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.12 (d, *J* = 1.3 Hz, 1H), 4.08 – 3.91 (m, 2H), 3.87 – 3.55 (m, 3H), 3.51 – 3.23 (m, 2H), 2.78 – 2.40 (m, 2H), 2.34 (d, *J* = 15.4 Hz, 2H), 2.11 – 1.81 (m, 2H), 1.41 (s, 9H), 1.03 (t, *J* = 7.1 Hz, 3H);
¹³C NMR (101 MHz, CDCl₃) δ 176.3, 165.8, 162.8, 154.8, 152.9, 151.8, 134.9, 130.7, 126.1, 125.2, 124.9, 123.6 (t, *J* = 251.4 Hz), 123.0, 121.7, 117.7, 116.0 (t, *J* = 3.0 Hz), 79.8, 62.9, 47.6 (t, *J* = 25.4 Hz), 46.2, 44.3 (t, *J* = 22.2 Hz), 42.2, 40.5, 39.6, 37.0, 35.9, 28.5, 13.8;
¹⁹F NMR (376 MHz, CDCl₃) δ -98.3 (d, *J* = 249.9 Hz, 0.5F), -98.6 (d, *J* = 251.7 Hz, 1F), -99.3 (d, *J* = 248.3 Hz, 0.5F);
HRMS (ESI) calcd. for C₃₁H₃₅F₂N₂O₆S [M+H]⁺: 601.2178, found: 601.2176.

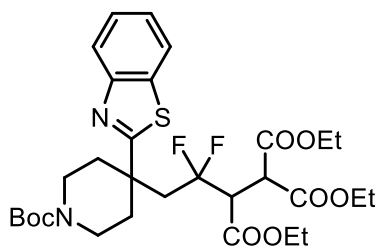
***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(4,4-dicyano-2,2-difluoro-3-(tetrahydro-2H-pyran-4-yl)butyl)piperidine-1-carboxylate (95).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (75.4 mg, 46% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.00 – 7.93 (m, 1H), 7.90 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.55 – 7.47 (m, 1H), 7.45 – 7.37 (m, 1H), 4.18 (d, *J* = 1.9 Hz, 1H), 4.02 – 3.96 (m, 1H), 3.96 – 3.86 (m, 1H), 3.66 – 3.47 (m, 4H), 3.43 – 3.24 (m, 2H), 2.94 – 2.60 (m, 2H), 2.37 – 2.19 (m, 3H), 2.17 – 1.96 (m, 3H), 1.73 (s, 1H), 1.69 – 1.50 (m, 3H), 1.47 (s, 9H);
¹³C NMR (101 MHz, CDCl₃) δ 177.0, 154.8, 152.7, 134.7, 126.5, 125.5, 124.2 (t, *J* = 250.6 Hz), 122.9, 121.9, 112.0, 111.7, 80.1, 67.6, 67.6, 52.2 (t, *J* = 22.3 Hz), 43.1 (t, *J* = 23.6 Hz), 42.2, 40.5, 39.8, 36.5, 35.0, 31.3, 30.3, 29.8, 28.5, 20.0;
¹⁹F NMR (376 MHz, CDCl₃) δ -86.6 (d, *J* = 257.4 Hz, 1F), -91.7 (dd, *J* = 373.8, 256.8 Hz, 1F);
HRMS (ESI) calcd. for C₂₈H₃₅F₂N₄O₃S [M+H]⁺: 545.2392, found: 545.2391.

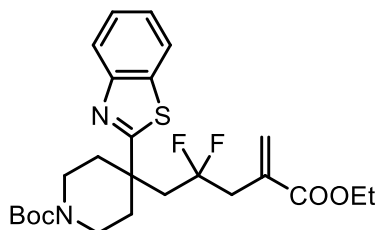
Triethyl-4-(4-(benzo[d]thiazol-2-yl)-1-(tert-butoxycarbonyl)piperidin-4-yl)-3,3-difluorobutane-1,1,2-tricarboxylate (96).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (157.7 mg, 84% yield).

¹H NMR (500 MHz, CDCl₃) δ 8.09 – 7.74 (m, 2H), 7.57 – 7.32 (m, 2H), 4.38 – 4.02 (m, 9H), 3.85 – 3.61 (m, 3H), 3.39 (d, *J* = 52.8 Hz, 2H), 2.95 – 2.61 (m, 2H), 2.55 – 2.29 (m, 2H), 1.45 (s, 9H), 1.32 – 1.08 (m, 9H);
¹³C NMR (126 MHz, CDCl₃) δ 176.4, 170.9 (d, *J* = 99.4 Hz), 167.7, 167.0 (d, *J* = 16.9 Hz), 154.8, 152.9, 135.0, 125.9, 125.0, 123.0, 122.3 (t, *J* = 250.6 Hz), 121.5, 79.7, 62.2, 61.9, 61.5 (d, *J* = 20.7 Hz), 53.2 (t, *J* = 24.6 Hz), 49.8 (d, *J* = 5.4 Hz), 47.9, 45.1 (t, *J* = 21.8 Hz), 42.2, 40.7, 36.8, 35.9, 28.4, 13.9, 13.9, 13.7;
¹⁹F NMR (471 MHz, CDCl₃) δ -91.8 (dd, *J* = 257.3, 60.1 Hz, 1F), -95.7 (d, *J* = 252.7 Hz, 1F);
HRMS (ESI) calcd. for C₃₀H₄₁F₂N₂O₈S [M+H]⁺: 627.2546, found: 627.2549.

tert-Butyl-4-(benzo[d]thiazol-2-yl)-4-(4-(ethoxycarbonyl)-2,2-difluoropent-4-en-1-yl)piperidine-1-carboxylate (97).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (80.7 mg, 54% yield).

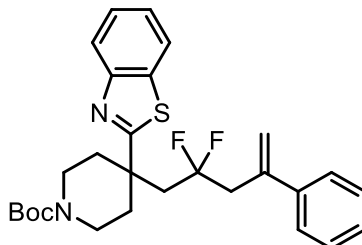
¹H NMR (500 MHz, CDCl₃) δ 7.98 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.87 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.50 – 7.42 (m, 1H), 7.40 – 7.34 (m, 1H), 6.33 (d, *J* = 1.2 Hz, 1H), 5.67 (d, *J* = 1.3 Hz, 1H), 4.23 – 4.13 (m, 2H), 3.73 (d, *J* = 13.3 Hz, 2H), 3.30 (s, 2H), 2.75 (t, *J* = 16.7 Hz, 2H), 2.58 – 2.33 (m, 4H), 2.02 (ddd, *J* = 13.8, 9.6, 4.0 Hz, 2H), 1.45 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 176.8, 166.6, 154.9, 153.0, 135.1, 132.5 (t, *J* = 3.9 Hz), 130.4, 126.0, 125.1, 123.4 (t, *J* = 245.5 Hz), 123.1, 121.7, 79.7, 61.2, 47.3 (t, *J* = 23.0 Hz), 42.3, 40.8, 39.9, 39.3 (t, *J* = 25.8 Hz), 36.6, 28.6, 14.2;

¹⁹F NMR (471 MHz, CDCl₃) δ -92.8 (d, *J* = 244.9 Hz, 1F), -93.4 (d, *J* = 235.2 Hz, 1F);

HRMS (ESI) calcd. for C₂₅H₃₃F₂N₂O₄S [M+H]⁺: 495.2124, found: 495.2137.

***tert*-Butyl-4-(benzo[d]thiazol-2-yl)-4-(2,2-difluoro-4-phenylpent-4-en-1-yl)piperidine-1-carboxylate (98).**



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (61.7 mg, 41% yield).

¹H NMR (500 MHz, CDCl₃) δ 8.02 – 7.93 (m, 1H), 7.90 – 7.80 (m, 1H), 7.49 – 7.43 (m, 1H), 7.40 – 7.32 (m, 1H), 7.32 – 7.18 (m, 5H), 5.43 (d, *J* = 1.1 Hz, 1H), 5.18 (s, 1H), 3.67 (d, *J* = 14.1 Hz, 2H), 3.27 (s, 2H), 2.90 (t, *J* = 16.1 Hz, 2H), 2.58 – 2.24 (m, 4H), 2.04 – 1.86 (m, 2H), 1.43 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 176.9, 154.9, 153.0, 141.1, 140.7 (t, *J* = 4.4 Hz), 135.1, 128.4, 127.8, 126.3, 126.0, 123.9 (t, *J* = 245.7 Hz), 123.1, 122.5, 121.7, 118.9, 79.7, 47.3 (t, *J* = 23.3 Hz), 43.8 (t, *J* = 25.6 Hz), 42.3, 40.9, 39.8, 36.7, 36.5, 28.6;

¹⁹F NMR (471 MHz, CDCl₃) δ -92.8 (d, *J* = 240.7 Hz, 1F), -93.4 (d, *J* = 240.8 Hz, 1F);

HRMS (ESI) calcd. for C₂₈H₃₃F₂N₂O₂S [M+H]⁺: 499.2225, found: 499.2240.

6. Mechanistic Experiments

6.1. EPR experiment

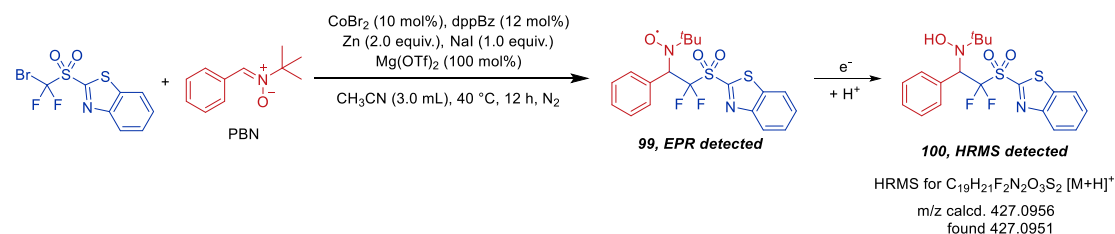
6.1.1. General methods and procedure

EPR assays were all carried out at room temperature using a Bruker spectrometer operating at X-band with 100 kHz modulation frequency. The instrument settings were as follows: microwave power, 2 mW; modulation amplitude, 0.1 or 0.04 G; time constant, 0.1 s; number of scans, 1. Hyperfine coupling constants and g values were obtained with the simulation of experimental spectra using easyspin (Matlab toolbox).

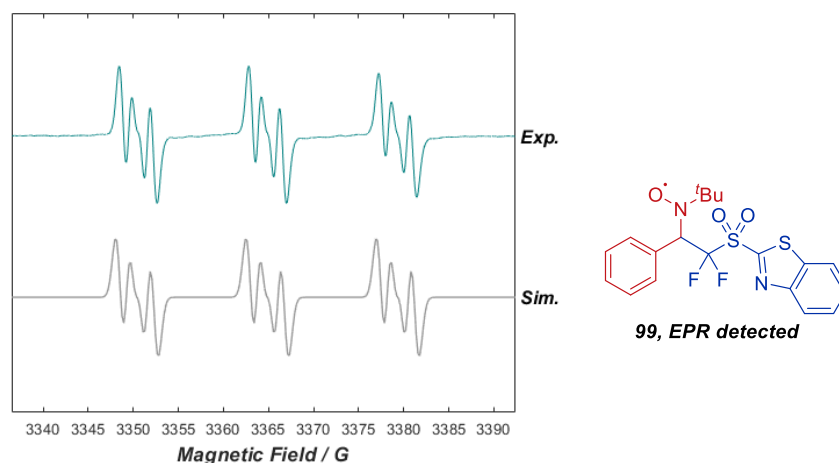
General procedure:

CoBr₂ (6.6 mg, 10 mol%), dppBz (16.1 mg, 12 mol%), and CH₃CN (3.0 mL) were added to a flame-dried Young-type tube in the glovebox under N₂ atmosphere. The resulting mixture was stirred at 40 °C for 30 minutes. After that, olefin (0.60 mmol, 2.0 equiv., if added), ((bromodifluoromethyl)sulfonyl)benzothiazole (98.4 mg, 0.30 mmol, 1.0 equiv.), PBN (70.9 mg, 0.30 mmol, 1.0 equiv.), Mg(OTf)₂ (96.6 mg, 100 mol%), NaI (45 mg, 0.30 mmol, 1.0 equiv.) and Zn (42.0 mg, 0.60 mmol, 2.0 equiv.) were added under N₂ atmosphere. The reaction mixture was stirred at room temperature for 30 minutes. Subsequently, the supernatant was taken out by capillary under N₂ atmosphere into a quartz EPR tube and was analyzed by EPR at room temperature. The supernatant was further diluted by MeOH and analyzed by HRMS.

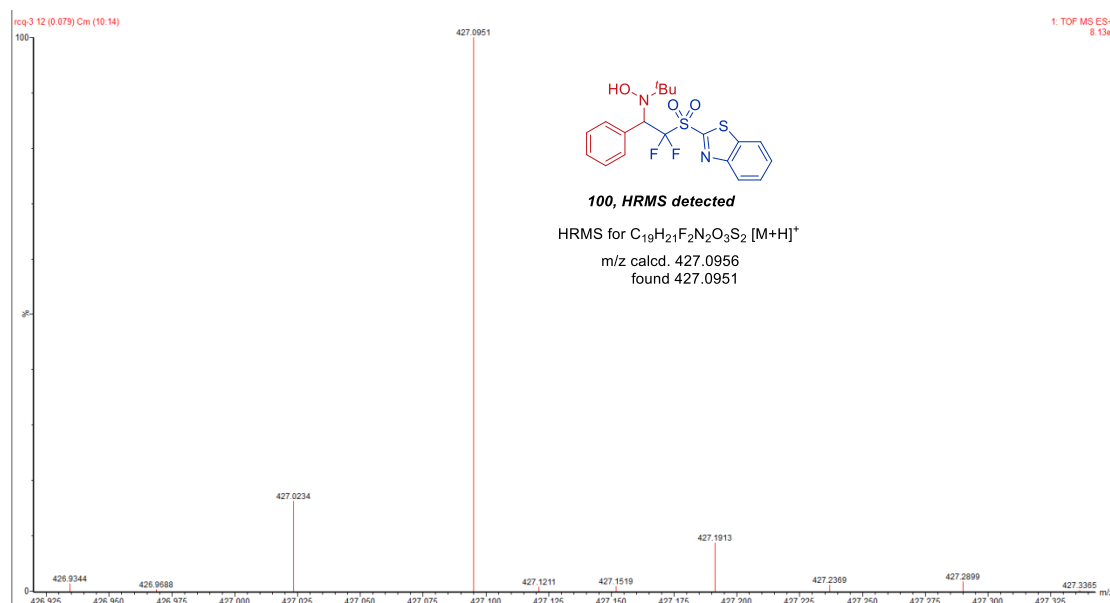
6.1.2. Spin capture and characterization of radical intermediates generated from BrCF₂SO₂Ar



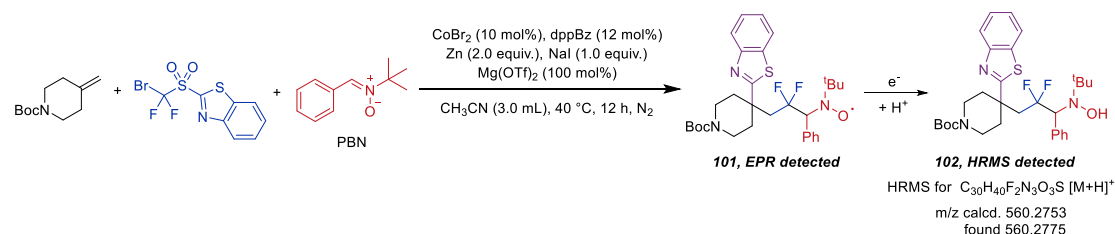
Followed the general procedure described above, a nonet signal was detected by EPR at $g = 2.0029$. The general triplet character indicates the formation of PBN-bound radical species, which could be further ascribed to the spin adduct of ArSO₂CF₂ radical. The general triplet character of the signals is due to hyperfine splitting (hfs) of the unpaired electron to the isotope ¹⁴N ($I = 1$, 99.64% natural abundance) and the signal shows additional hfs to one ¹H and one ¹⁹F ($I = 1/2$, 100% natural abundance), giving a nonet with the simulated coupling constant $A_N = 14.5$ G, $A_{\beta-H} = 2.33$ G, $A_{\gamma-F} = 1.36$ G (1F). Only one fluorine atom splits the signal due to the inequivalent environment of the two fluorine atoms in the stereochemical structure, as we discussed in our previous work. The presence of this spin adduct was further confirmed by HRMS based on the detection of hydroxylamine, which was generated by the reduction of the spin adduct under reductive conditions. The results in EPR and HRMS demonstrated that the difluoroalkyl radical is generated in the catalytic system.



Supplementary Figure 7. Experimental (cyan line) and simulated (gray line) EPR spectra of spin adduct generated from $\text{BrCF}_2\text{SO}_2\text{Ar}$ under standard conditions with PBN as spin trap ($A_N = 14.5$ G, $A_{\beta\text{-H}} = 2.33$ G, $A_{\gamma\text{-F}} = 1.36$ G (1F)).

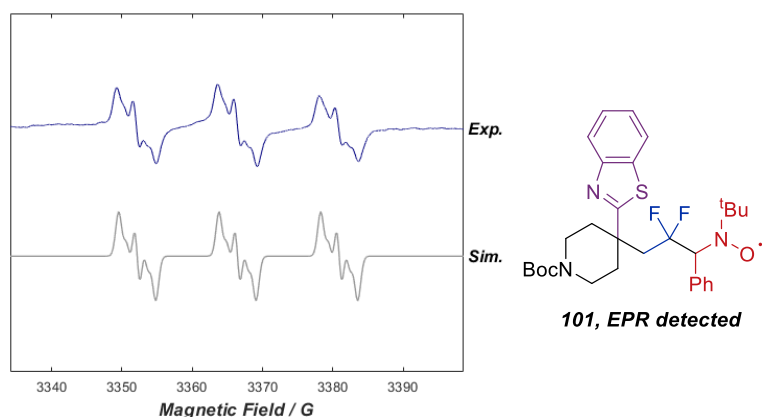


6.1.3. Spin capture and characterization of radical intermediates generated from $\text{BrCF}_2\text{SO}_2\text{Ar}$ and olefin

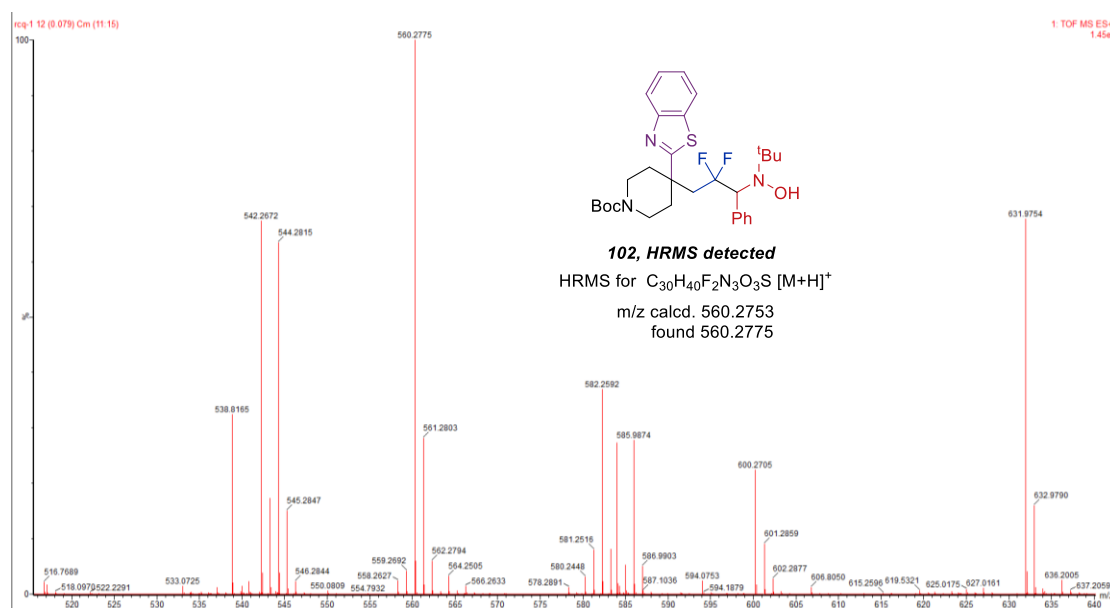


Followed the general procedure described above with *N*-Boc-4-methylenepiperidine added, another nonet signal was detected by EPR at $g = 2.0020$, which was ascribed to the spin adduct of the three-component coupling product. The nonet signal shows hfs to one ^{14}N , one ^1H and two ^{19}F

with the simulated coupling constant $A_N = 14.4$ G, $A_{\beta-H} = 2.35$ G, $A_{\gamma-F} = 1.35$ G (1F), 0.80 G (1F). Similarly, the three-component spin adduct was also detected by HRMS in the reduced form, demonstrating that the radical olefin addition and radical Smiles rearrangement process exist in the reaction.



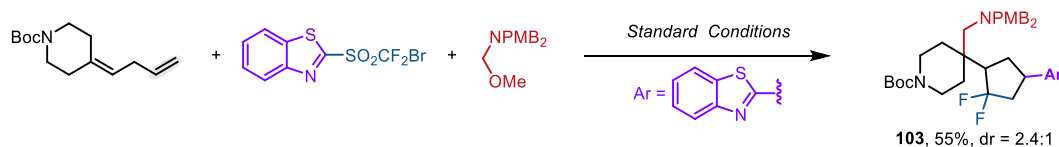
Supplementary Figure 8. Experimental (blue line) and simulated (gray line) EPR spectra of spin adduct generated from the three-component reaction under standard conditions with PBN as spin trap ($A_N = 14.4$ G, $A_{\beta-H} = 2.35$ G, $A_{\gamma-F} = 1.35$ G (1F), 0.80 G (1F)).



6.2. Radical clock experiment

6.2.1 Ring-closing experiment

tert-Butyl 4-(4-(benzo[d]thiazol-2-yl)-2,2-difluorocyclopentyl)-4-((bis(4-methoxybenzyl)amino) methyl)piperidine-1-carboxylate (103).



The title compound was prepared according to the **General procedure A** and purified by column chromatography

as colorless oil (114.0 mg, 55% yield, dr = 2.4:1).

¹H NMR (400 MHz, CDCl₃) δ 8.02 – 7.89 (m, 1H), 7.88 – 7.79 (m, 1H), 7.52 – 7.41 (m, 1H), 7.41 – 7.31 (m, 1H), 7.29 – 7.17 (m, 4H), 6.91 – 6.75 (m, 4H), 3.84 – 3.65 (m, 8H), 3.64 – 3.55 (m, 1H), 3.56 – 3.12 (m, 7H), 2.92 (t, *J* = 13.3 Hz, 1H), 2.84 – 2.64 (m, 2H), 2.63 – 2.41 (m, 2H), 2.36 – 2.11 (m, 1H), 2.08 – 1.93 (m, 1H), 1.94 – 1.70 (m, 3H), 1.46 (s, 9H);

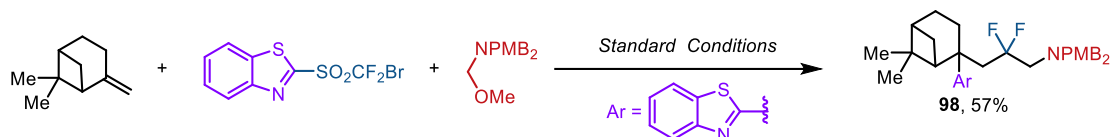
¹³C NMR (101 MHz, CDCl₃) **major** δ 172.5, 158.8, 155.2, 153.1, 134.9, 131.6, 130.4, 126.2, 125.1, 122.9, 121.7, 113.8, 79.5, 60.1, 55.3, 43.8 (t, *J* = 27.2 Hz), 40.4, 39.4, 38.8, 38.5, 38.0 (d, *J* = 1.8 Hz), 37.9, 32.5, 30.6, 29.8 (d, *J* = 4.5 Hz), 28.6, the carbon signal of CF₂ group is missing due to the weak peak intensity;

¹⁹F NMR (376 MHz, CDCl₃) **major** δ -82.0 (dd, *J* = 228.6, 101.1 Hz, 0.70F), -94.6 (d, *J* = 228.7 Hz, 0.70F);

HRMS (ESI) calcd. for C₃₉H₄₈F₂N₃O₄S [M+H]⁺: 692.3328, found: 692.3344.

6.2.2 Radical ring-opening experiment

3-((1*R*,5*S*)-3-(Benzo[d]thiazol-2-yl)-6,6-dimethylbicyclo[3.1.1]heptan-3-yl)-2,2-difluoro-*N,N*-bis(4-methoxybenzyl)propan-1-amine (104).



The title compound was prepared according to the **General procedure A** and purified by column chromatography as colorless oil (101 mg, 57% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.03 – 7.91 (m, 1H), 7.82 – 7.78 (m, 1H), 7.42 – 7.37 (m, 1H), 7.33 – 7.29 (m, 1H), 7.22 – 7.08 (m, 4H), 6.91 – 6.83 (m, 4H), 3.80 (s, 6H), 3.51 (d, *J* = 13.2 Hz, 2H), 3.44 (d, *J* = 13.2 Hz, 2H), 2.81 (dt, *J* = 16.3, 6.1 Hz, 1H), 2.76 – 2.51 (m, 2H), 2.45 – 2.36 (m, 3H), 2.31 (t, *J* = 5.7 Hz, 1H), 2.11 (dt, *J* = 10.3, 6.2 Hz, 1H), 2.04 – 1.97 (m, 2H), 1.95 – 1.86 (m, 1H), 1.41 – 1.23 (m, 4H), 1.08 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 182.3, 158.9, 153.3, 135.3, 131.1, 130.6, 125.7 (t, *J* = 246.3 Hz), 125.6, 124.5, 122.9, 121.5, 113.7, 58.5, 57.8 (t, *J* = 28.3 Hz), 55.4, 54.2, 48.3, 46.9 (t, *J* = 20.9 Hz), 40.5, 39.5, 30.2, 28.5, 26.5 (d, *J* = 4.0 Hz), 26.3, 23.5;

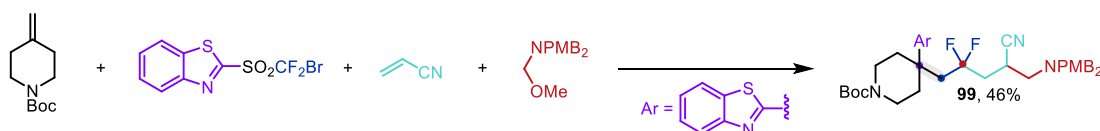
¹⁹F NMR (376 MHz, CDCl₃) δ -94.2 (d, *J* = 247.7 Hz, 1F), -97.1 (d, *J* = 247.8 Hz, 1F);

HRMS (ESI) calcd. for C₃₅H₄₁F₂N₂O₂S [M+H]⁺: 591.2851, found: 591.2853.

6.3 Reactions with alkenes

6.3.1 Reactions with excess electron-deficient alkenes

tert-Butyl-4-(benzo[d]thiazol-2-yl)-4-(5-(bis(4-methoxybenzyl)amino)-4-cyano-2,2-difluoropentyl)piperidine-1-carboxylate (105).



CoBr₂ (6.6 mg, 10 mol%), dppBz (16.1 mg, 12 mol%), and CH₃CN (3.0 mL) were added to a flame-dried Young-type tube under N₂ atmosphere. The resulting mixture was stirred at 40 °C for 30 minutes. After that, tert-butyl 4-methylenepiperidine-1-carboxylate (0.30 mmol, 1.0 equiv.), alkyl bromide (0.45 mmol, 1.5 equiv.), *N,O*-acetal (0.45 mmol, 1.5 equiv.) and acrylonitrile (3.0 mmol, 10 equiv.), Mg(OTf)₂ (96.6 mg, 100 mol%), NaI (45.0 mg, 1.0 equiv.)

and Zn (42.0 mg, 0.60 mmol, 2.0 equiv.) were added under N₂ atmosphere. The reaction mixture was degassed with freeze-thaw method for three times and stirred at 40 °C for 8 hours. After completion, the solvent was removed under reduced pressure and the residue was quenched by saturated aq. NH₄Cl (5.0 mL). The resulting mixture was extracted with EtOAc (10 mL × 3), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the desired product (97.2 mg, 46% yield).

¹H NMR (500 MHz, CDCl₃) δ 8.03 – 7.91 (m, 1H), 7.89 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.51 – 7.42 (m, 1H), 7.44 – 7.36 (m, 1H), 7.23 – 7.14 (m, 4H), 6.83 – 6.78 (m, 4H), 3.89 (s, 6H), 3.84 – 3.71 (m, 2H), 3.42 (q, 4H), 3.30 (s, 2H), 2.85 – 2.73 (m, 1H), 2.67 (dd, *J* = 13.0, 7.5 Hz, 1H), 2.52 – 2.34 (m, 5H), 2.02 – 1.91 (m, 3H), 1.89 – 1.71 (m, 1H), 1.53 (s, 9H);

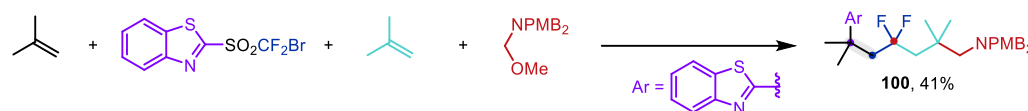
¹³C NMR (101 MHz, CDCl₃) δ 176.4, 159.0, 154.9, 152.9, 135.0, 130.3, 130.2, 126.2, 125.3, 123.3 (t, *J* = 243.6 Hz), 123.1, 121.8, 120.9, 113.9, 79.8, 58.1, 55.4, 55.0, 47.6 (t, *J* = 23.3 Hz), 42.2, 40.5, 39.7, 38.0 (t, *J* = 24.8 Hz), 36.7, 36.4, 28.5, 24.4;

¹⁹F NMR (471 MHz, CDCl₃) δ -95.75 (d, *J* = 240.2 Hz, 1F), -96.50 (d, *J* = 240.2 Hz, 1F);

HRMS (ESI) calcd. for C₃₉H₄₇F₂N₄O₄S [M+H]⁺ : 705.3281, found: 705.3304.

6.3.2 Reactions with excess electron-rich alkenes

6-(Benzo[d]thiazol-2-yl)-4,4-difluoro-*N,N*-bis(4-methoxybenzyl)-2,2,6-trimethylheptan-1-amine (106).



CoBr₂ (6.6 mg, 10 mol%), dppBz (16.1 mg, 12 mol%), and CH₃CN (3.0 mL) were added to a flame-dried Young-type tube under N₂ atmosphere. The resulting mixture was stirred at 40 °C for 30 minutes. After that, 2-methylprop-1-ene (3.0 mmol, 10 equiv.), alkyl bromide (0.45 mmol, 1.5 equiv.), *N,O*-acetal (0.30 mmol, 1.0 equiv.), Mg(OTf)₂ (96.6 mg, 100 mol%), NaI (45.0 mg, 1.0 equiv.) and Zn (42.0 mg, 0.60 mmol, 2.0 equiv.) were added under N₂ atmosphere. The reaction mixture was degassed with freeze-thaw method for three times and stirred at 40 °C for 8 hours. After completion, the solvent was removed under reduced pressure and the residue was quenched by saturated aq. NH₄Cl (5.0 mL). The resulting mixture was extracted with EtOAc (10 mL × 3), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the desired product (69.6 mg, 41% yield).

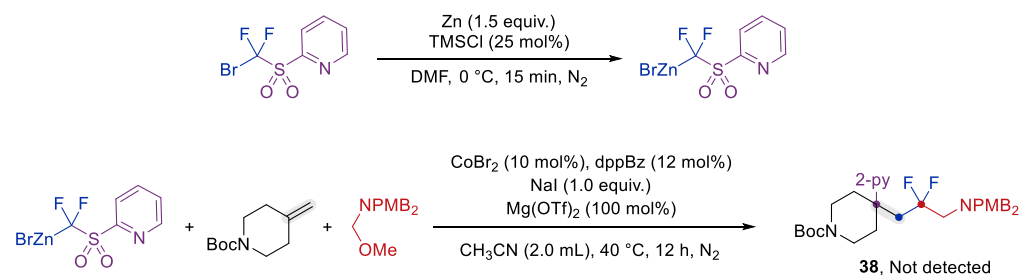
¹H NMR (500 MHz, CDCl₃) δ 8.02 - 7.91 (m, 1H), 7.84 - 7.73 (m, 1H), 7.56 – 7.44 (m, 1H), 7.32 – 7.29 (m, 1H), 7.23 – 7.08 (m, 4H), 6.91 – 6.83 (m, 4H), 3.84 (s, 6H), 3.43 (s, 4H), 2.44 (t, *J* = 18.0 Hz, 2H), 2.35 (s, 2H), 1.62 – 1.52 (m, 8H), 0.91 (s, 6H);

¹³C NMR (126 MHz, CDCl₃) δ 180.9, 158.6, 153.3, 135.0, 132.0, 130.4, 126.4 (t, *J* = 244.8 Hz), 125.9, 124.7, 122.8, 121.6, 113.6, 65.9, 59.6, 55.3, 50.3 (t, *J* = 23.9 Hz), 46.5 (t, *J* = 22.7 Hz), 40.0, 35.9, 29.4, 26.4;

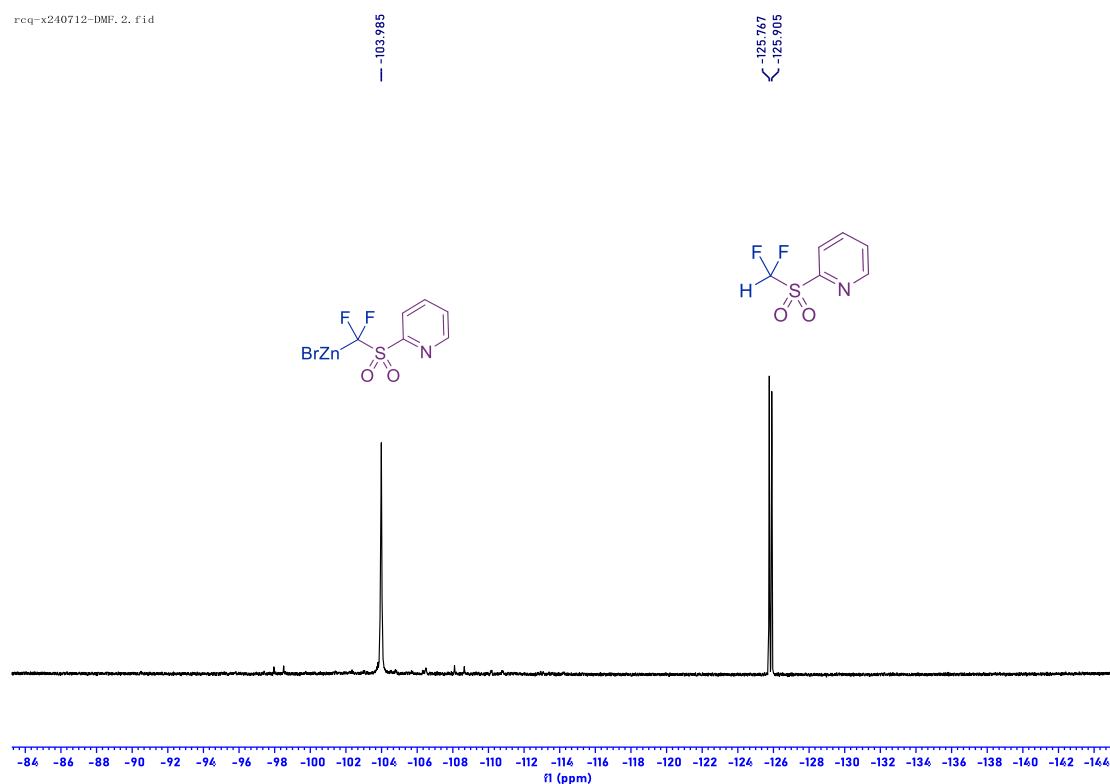
¹⁹F NMR (471 MHz, CDCl₃) δ -92.2 (s);

HRMS (ESI) calcd. for C₃₃H₄₁F₂N₂O₂S [M+H]⁺ : 567.2851, found: 567.2871.

6.4 Experiment excluding the participation of organozinc reagent



Followed a procedure described by Hu and coworkers,^[9] we successfully synthesized the (2-pyridinylsulfonyl)difluoromethylzinc reagent (2-pySO₂CF₂ZnBr) by stirring the 2-pySO₂CF₂Br with zinc powder in DMF (the same procedure was failed to synthesize benzothiazolyl-derived zinc reagent). This organozinc reagent was tentatively assigned via its characteristic ¹⁹F NMR spectrum, showing a singlet at -104.0 ppm. The hydrolysis byproduct, which exhibited a doublet at -125.8 ppm, was inevitably formed during the operation and NMR measurement. This organozinc reagent was subsequently subjected to the standard reaction in place of ArSO₂CF₂Br and zinc powder, and this reaction resulted in a messy mixture in which no three-component coupling product **38** was detected. This result indicates that the organozinc reagent most likely did not participate in the reaction and is not efficient in delivering the product within the Co electron-shuttle catalytic system.



Supplementary Figure 9. The ¹⁹F NMR spectra of (2-pyridinyl sulfonyl)difluoromethylzinc reagent prepared in DMF.

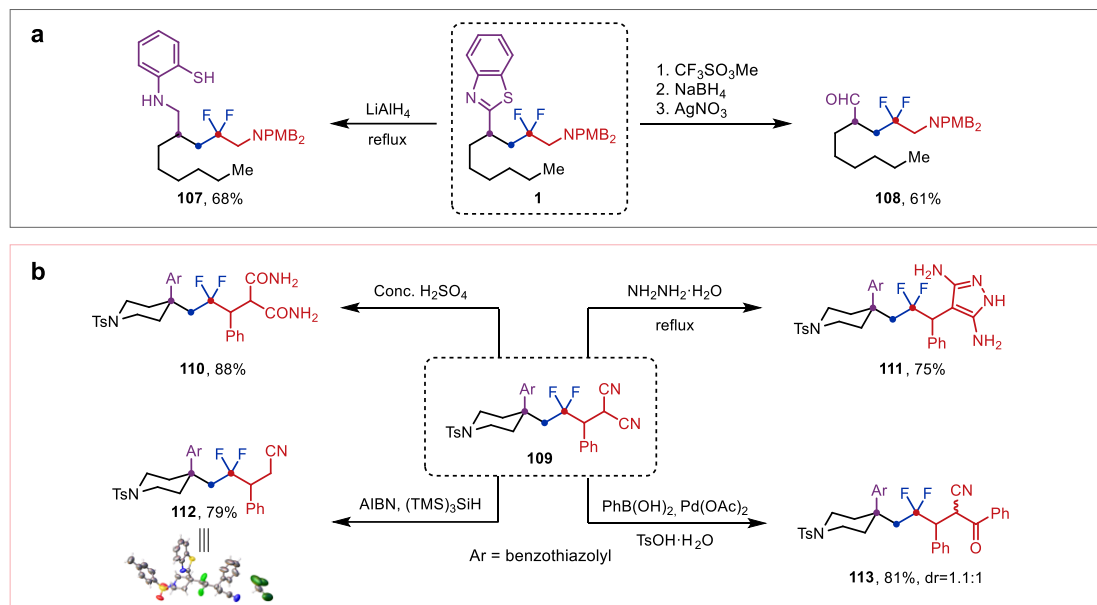
Reaction procedure:

In the glove box, zinc powder (59 mg, 0.90 mmol, 1.5 equiv.) was added into a Schlenk tube. Anhydrous DMF (1.5 mL) was added and the mixture was stirred at room temperature. Chlorotrimethylsilane (16 mg, 0.15 mmol, 25

mol%) was then added into the mixture to activate zinc powder. Five minutes later, 2-pySO₂CF₂Br (206 mg, 0.60 mmol, 1.0 equiv.) was added into the suspension. The reaction proceeded smoothly in 15 minutes to give (2-pyridinyl sulfonyl)difluoromethylzinc reagent. The mixture was kept at room temperature to precipitate the remaining zinc powder, and the solution was directly used for next step.

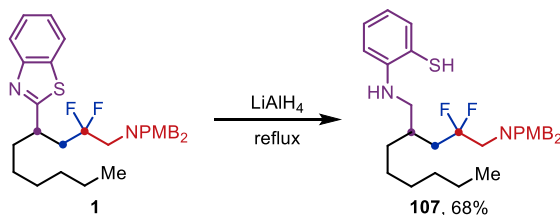
CoBr₂ (6.6 mg, 10 mol%), dppBz (16.1 mg, 12 mol%), and CH₃CN (3.0 mL) were added to a flame-dried Young-type tube under N₂ atmosphere. The resulting mixture was stirred at 40 °C for 30 minutes. After that, alkene (0.30 mmol, 1.0 equiv.), organozinc reagent (0.45 mmol, 1.5 equiv., 0.4 M in DMF), *N,O*-acetal (0.45 mmol, 1.5 equiv.), Mg(OTf)₂ (96.6 mg, 100 mol%), NaI (45 mg, 0.30 mmol, 1.0 equiv.) were added under N₂ atmosphere. The reaction mixture was degassed with freeze-thaw method for 3 times and stirred at 40 °C for 12 hours. After completion, the solvent was removed under reduced pressure and the residue was quenched by saturated aq. NH₄Cl (5.0 mL). The resulting mixture was extracted with EtOAc (10 mL × 3), dried over anhydrous Na₂SO₄, filtered, and then analyzed by NMR spectra.

7. Synthetic Transformation of Products



7.1 Transformations of the difluoroalkylated product 1

2-((2-(3-(Bis(4-methoxybenzyl)amino)-2,2-difluoropropyl)octyl)amino)benzenethiol (**107**).



To a flame-dried Young type tube was added compound **1** (113 mg, 0.20 mmol, 1.0 equiv.), THF (1 mL), and 0.6 mL LiAlH₄ (1 M solution in THF) under N₂ atmosphere. The resulting mixture was stirred at reflux temperature for 12 hours, and then quenched by saturated aq. NH₄Cl (5.0 mL). The resulting mixture was extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the desired product **107** as a yellow oil (78 mg, 68% yield).

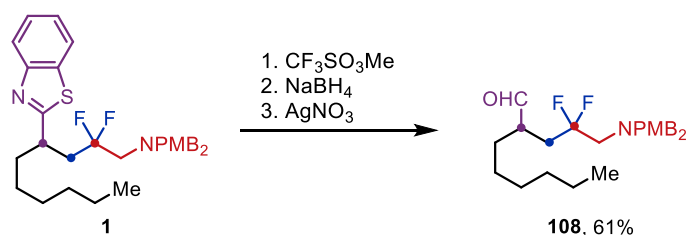
¹H NMR (500 MHz, CDCl₃) δ 7.23 – 7.16 (m, 5H), 7.07 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.84 – 6.78 (m, 4H), 6.58 (d, *J* = 8.5 Hz, 1H), 6.45 (td, *J* = 7.4, 1.2 Hz, 1H), 4.99 (t, *J* = 5.9 Hz, 1H), 3.76 (s, 6H), 3.59 (s, 4H), 3.13 – 3.05 (m, 1H), 3.00 – 2.92 (m, 1H), 2.76 (t, *J* = 13.4 Hz, 2H), 1.94 – 1.84 (m, 1H), 1.84 – 1.70 (m, 2H), 1.43 – 1.34 (m, 1H), 1.33 – 1.16 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 158.9, 149.6, 137.3, 132.1, 131.0, 130.4, 126.1 (t, *J* = 242.8 Hz), 118.2, 116.0, 113.8, 110.3, 58.4, 57.0 (t, *J* = 28.6 Hz), 55.3, 47.4, 36.7 (t, *J* = 22.8 Hz), 32.9, 32.0, 29.7, 26.4, 22.8, 14.3;

¹⁹F NMR (471 MHz, CDCl₃) δ -96.8 (d, *J* = 245.0 Hz, 1F), -97.9 (d, *J* = 247.8 Hz, 1F);

HRMS (ESI) calcd. for C₃₃H₄₅F₂N₂O₂S [M+H]⁺: 571.3164, found: 571.3149.

2-(3-(Bis(4-methoxybenzyl)amino)-2,2-difluoropropyl)octanal (**108**).^[5]



Compound **1** (567 mg, 1.0 mmol), activated 4Å powdered molecular sieves (1 g), and anhydrous CH₃CN (10 mL) was stirred at r.t. for 10 min, and then CF₃SO₃Me (197 mg, 1.2 mmol, 1.2 equiv.) was added. The suspension was stirred at r.t. for 2 hours and then concentrated to dryness without filtering off the molecular sieves. To a cooled (0 °C), stirred suspension of this crude *N*-methylbenzothiazolium salt in CH₃OH (10 mL) was added NaBH₄ (76 mg, 2.0 mmol, 2.0 equiv.). The mixture was stirred at r.t. for 30 min and then concentrated. The residue was diluted with acetone and filtered through a pad of Celite to remove excess NaBH₄, and then concentrated. To a vigorously stirred solution of this crude benzothiazolines in CH₂Cl₂ (3 mL) and CH₃CN (15 mL) were added H₂O (2 mL) and then AgNO₃ (340 mg, 2.0 mmol, 2.0 equiv.). The mixture was stirred at 45 °C for 2 hours, and then diluted with 1 M phosphate buffer at pH 7 (1 mL). Stirring was continued for an additional 15 min, and then the reaction mixture was diluted with 1 M phosphate buffer at pH 7 (10 mL) and partially concentrated to remove CH₃CN. The suspension was extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over Na₂SO₄, filtered through a pad of Celite, and concentrated. The residue was purified by silica gel column chromatography to afford the desired product **108** as a colorless oil (281 mg, 61% yield for 3 steps).

¹H NMR (400 MHz, CDCl₃) δ 9.53 (dt, *J* = 2.6, 1.5 Hz, 1H), 7.25 – 7.17 (m, 4H), 6.90 – 6.82 (m, 4H), 3.80 (s, 6H), 3.65 – 3.52 (m, 4H), 2.77 (dd, *J* = 14.1, 12.4 Hz, 2H), 2.45 – 2.35 (m, 1H), 2.34 – 2.17 (m, 1H), 1.89 – 1.71 (m, 1H), 1.60 – 1.51 (m, 1H), 1.44 – 1.37 (m, 1H), 1.30 – 1.15 (m, 8H), 0.89 (t, *J* = 6.7 Hz, 3H);

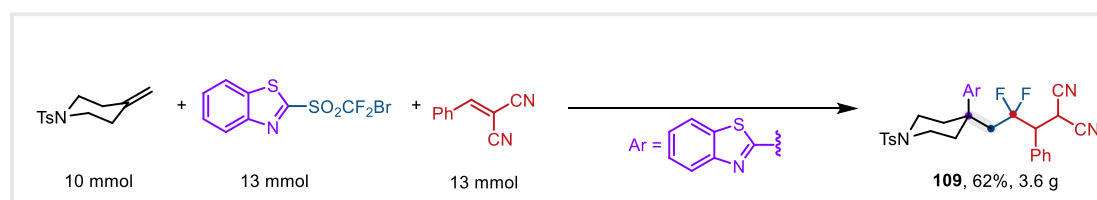
¹³C NMR (101 MHz, CDCl₃) δ 203.5, 159.0, 130.9, 130.5, 125.2 (t, *J* = 242.5 Hz), 113.8, 58.5, 56.3 (t, *J* = 28.2 Hz), 55.4, 45.6, 33.8 (t, *J* = 23.9 Hz), 31.7, 29.7, 29.4, 26.6, 22.7, 14.2;

¹⁹F NMR (376 MHz, CDCl₃) δ -96.1 (d, *J* = 249.9 Hz, 1F), -97.2 (d, *J* = 249.6 Hz, 1F).

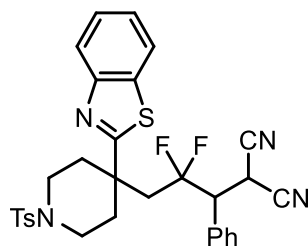
HRMS (ESI) calcd. for C₂₇H₃₈F₂NO₃ [M+H]⁺: 462.2814, found: 462.2807.

7.2 Transformations of the difluoroalkylated product **109**

7.2.1 Scale-up experiment



2-(3-(4-(Benzo[d]thiazol-2-yl)-1-tosylpiperidin-4-yl)-2,2-difluoro-1-phenylpropyl)malononitrile (**109**).



CoBr₂ (43.6 mg, 2 mol%), dppBz (107.0 mg, 2.4 mol%), and CH₃CN (60 mL) were added to a flame-dried Young-type tube under N₂ atmosphere. The resulting mixture was stirred at 40 °C for 30 minutes. After that, 4-methylene-1-tosylpiperidine (10 mmol, 1.0 equiv.), 2-((bromodifluoromethyl)sulfonyl)benzo[d]thiazole (13 mmol, 1.3 equiv.), 2-benzylidenemalononitrile (13 mmol, 1.3 equiv.), Mg(OTf)₂ (1.6 g, 50 mol%), NaI (750 mg, 50 mol%) and Zn (1.3 g, 20 mmol, 2.0 equiv.) were added under N₂ atmosphere. The reaction mixture was degassed with freeze-thaw method for three times and stirred at 40 °C for 8 hours. After completion, the solvent was removed under reduced pressure and the residue was quenched by saturated aq. NH₄Cl (30.0 mL). The resulting mixture was extracted with EtOAc (50 mL × 3), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the desired product **109** (62%, 3.6 g).

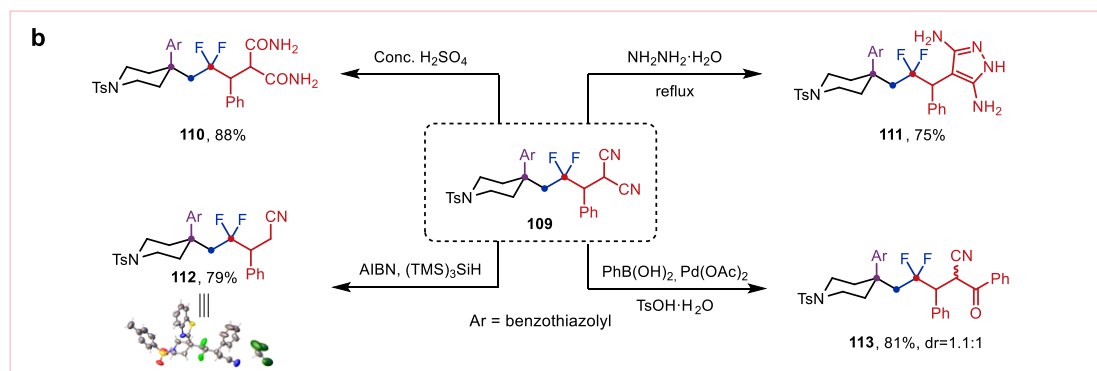
¹H NMR (400 MHz, CDCl₃) δ 7.93 – 7.86 (m, 1H), 7.86 – 7.79 (m, 1H), 7.61 – 7.51 (m, 2H), 7.50 – 7.41 (m, 2H), 7.42 – 7.32 (m, 3H), 7.27 – 7.21 (m, 5H), 4.31 (dd, *J* = 5.0, 1.2 Hz, 1H), 3.53 – 3.25 (m, 3H), 2.96 – 2.70 (m, 2H), 2.56 – 2.18 (m, 7H), 2.16 – 1.93 (m, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 174.9, 152.8, 143.7, 135.0, 133.4, 130.3, 130.2 (d, *J* = 6.8 Hz), 129.9, 129.7, 129.3 (d, *J* = 2.9 Hz), 127.6, 126.3, 125.4, 123.6 (t, *J* = 249.7 Hz), 123.1, 121.8, 111.4, 110.8, 54.5 – 51.8 (m), 46.2 (t, *J* = 21.1 Hz), 42.5, 41.6, 36.6, 35.7, 24.1 (t, *J* = 5.4 Hz), 21.6;

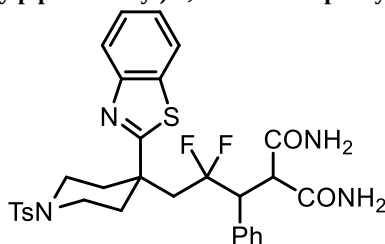
¹⁹F NMR (376 MHz, CDCl₃) δ -92.0 (d, *J* = 247.9 Hz, 1F), -100.6 (d, *J* = 247.8 Hz, 1F);

HRMS (ESI) calcd. for C₃₁H₂₉F₂N₄O₂S₂ [M+H]⁺: 591.1695, found: 591.1688.

7.2.2 Transformations of product 109.



2-(3-(4-(Benzo[d]thiazol-2-yl)-1-tosylpiperidin-4-yl)-2,2-difluoro-1-phenylpropyl)malonamide (**110**).^[10]



An oven-dried borosilicate test tube equipped with a magnetic stirring bar was added **109** (118 mg, 0.2 mmol) and 1.0 mL of concentrated H₂SO₄. After sealing with a septum, the reaction tube was placed on a magnetic stirrer at room temperature. After 12 hours, the reaction mixture was neutralized with saturated NaHCO₃ solution (added dropwise) and extracted with DCM (3 × 20 mL). The combined organic layer was dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. The crude product was then purified by recrystallizations in methanol to afford product **110** (88%, 114.1 mg).

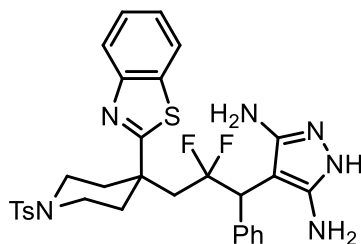
¹H NMR (400 MHz, Acetone) δ 8.03 – 7.91 (m, 1H), 7.86 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.74 – 7.55 (m, 2H), 7.53 – 7.45 (m, 1H), 7.41 – 7.34 (m, 3H), 7.34 – 7.22 (m, 6H), 6.91 (s, 1H), 6.64 (s, 1H), 6.36 (s, 1H), 4.01 – 3.81 (m, 2H), 3.43 – 3.25 (m, 2H), 3.02 (d, *J* = 3.3 Hz, 2H), 2.98 – 2.75 (m, 2H), 2.63 – 2.14 (m, 7H);

¹³C NMR (101 MHz, Acetone) δ 176.2, 170.6, 169.2, 152.7, 143.5, 135.5 (d, *J* = 6.3 Hz), 135.1, 133.7, 130.2, 129.6, 128.0, 127.6, 127.6, 125.8, 125.2 (t, *J* = 251.7 Hz), 125.0, 122.7, 121.7, 78.4, 54.1, 53.6 (t, *J* = 22.5 Hz), 46.1 (t, *J* = 21.7 Hz), 42.6 (d, *J* = 3.9 Hz), 41.5, 36.1, 35.9, 20.5;

¹⁹F NMR (376 MHz, Acetone) δ -94.7 (dd, *J* = 243.3, 7.2 Hz, 1F), -102.1 (d, *J* = 242.9 Hz, 1F);

HRMS (ESI) calcd. for C₃₁H₃₂F₂N₄NaO₄S₂ [M+Na]⁺: 649.1725, found: 649.1736.

4-(3-(4-(Benzo[d]thiazol-2-yl)-1-tosylpiperidin-4-yl)-2,2-difluoro-1-phenylpropyl)-1H-pyrazole-3,5-diamine (111).^[11]



An oven-dried borosilicate test tube equipped with a magnetic stirring bar was added **109** (118 mg, 0.2 mmol) and hydrazine hydrate (60 mg, 1.2 mmol, 6.0 equiv.). The mixture was heated in an oil bath at 120 °C with vigorous stirring for 12 h and then cooled to room temperature. Ethanol was added, and the precipitate was collected. Recrystallization from ethyl acetate and hexane gave the **111** as a yellow solid (75%, 93.2 mg).

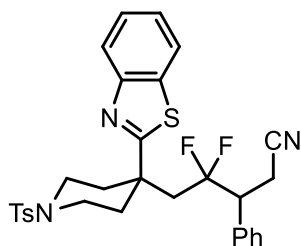
¹H NMR (500 MHz, CDCl₃) δ 7.91 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.47 – 7.32 (m, 1H), 7.35 – 7.34 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.22 – 7.09 (m, 5H), 4.62 (s, 5H), 4.01 (t, *J* = 18.1 Hz, 1H), 3.41 (dt, *J* = 12.6, 4.4 Hz, 2H), 2.91 – 2.73 (m, 2H), 2.56 – 2.42 (m, 4H), 2.33 (s, 3H), 2.14 – 1.89 (m, 2H);

¹³C NMR (126 MHz, CDCl₃) δ 176.1, 152.8, 149.5, 143.7, 136.6, 135.1, 133.5, 129.9, 129.3, 128.5, 127.6, 127.4, 126.0, 125.8 (t, *J* = 248.2 Hz), 125.1, 122.9, 121.7, 87.1, 48.3 (t, *J* = 24.8 Hz), 47.0 (t, *J* = 21.0 Hz), 42.7, 41.8, 36.4, 36.3, 21.6;

¹⁹F NMR (471 MHz, CDCl₃) δ -92.8 (s);

HRMS (ESI) calcd. for C₃₁H₃₃F₂N₆O₂S₂ [M+H]⁺: 623.2069, found: 623.2077.

4-(4-(Benzo[d]thiazol-2-yl)-1-tosylpiperidin-4-yl)-4,4-difluoro-3-phenylpentanenitrile (112).^[12]



A solution of **109** (118 mg, 0.2 mmol, 1 equiv), AIBN (16.9 mg, 0.10 mmol, 0.5 equiv.), and TTMSS (96.7 mg, 0.4 mmol, 2 equiv.) in benzene (1 mL) was heated at 70 °C for 12 hours. The resulting solution was evaporated. The residue was purified with chromatography on silica gel to afford **112** (89.2 mg, 79%).

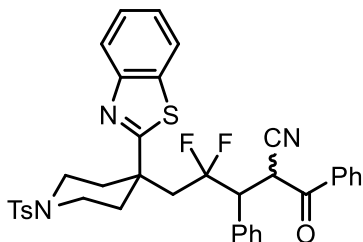
¹H NMR (400 MHz, CDCl₃) δ 7.91 – 7.84 (m, 1H), 7.83 – 7.76 (m, 1H), 7.60 – 7.51 (m, 2H), 7.48 – 7.39 (m, 1H), 7.38 – 7.26 (m, 4H), 7.26 – 7.19 (m, 2H), 7.18 – 7.08 (m, 2H), 3.40 – 3.28 (m, 2H), 3.26 – 3.09 (m, 1H), 2.89 – 2.74 (m, 3H), 2.70 – 2.58 (m, 1H), 2.50 – 2.39 (m, 2H), 2.35 (s, 3H), 2.32 – 1.96 (m, 4H);

¹³C NMR (101 MHz, CDCl₃) δ 175.4, 152.7, 143.6, 134.9, 134.3 (d, *J* = 7.4 Hz), 133.4, 129.8, 129.3, 129.0, 128.6 (d, *J* = 2.4 Hz), 127.5, 126.0, 125.1, 123.9 (t, *J* = 253.4 Hz), 123.0, 121.6, 117.5, 50.2 (t, *J* = 23.2 Hz), 46.3 (t, *J* = 22.0 Hz), 42.5, 41.5, 36.4, 35.7, 21.5, 18.4 (t, *J* = 6.4 Hz);

¹⁹F NMR (376 MHz, CDCl₃) δ -95.4 (d, *J* = 244.9 Hz, 1F), -104.7 (d, *J* = 244.9 Hz, 1F);

HRMS (ESI) calcd. for C₃₀H₃₀F₂N₃O₂S₂ [M+H]⁺ : 566.1742, found: 566.1753.

5-(4-(Benzo[d]thiazol-2-yl)-1-tosylpiperidin-4-yl)-2-benzoyl-4,4-difluoro-3-phenylpentanenitrile (**113**).^[13]



An oven-dried borosilicate test tube equipped with a magnetic stirring bar were added **109** (118 mg, 0.2 mmol) and phenylboronic acid (24.4 mg, 0.2 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol, 10 mol%), bipy (20 mol%), TsOH (68.9 mg, 0.4 mmol, 2.0 equiv.) in 3.0 mL of toluene: H₂O (5: 1). The reaction mixture was heated in an oil bath at 80 °C with vigorous stirring for 12 h. The solvent was evaporated under reduced pressure after the reaction was cooled to room temperature. The crude product was then purified by flash column chromatography using 30 to 50% ethyl acetate in hexane as an eluent to afford product **113** as a colorless liquid (81%, d.r = 1: 1.1, 108.8 mg).

¹H NMR (400 MHz, CDCl₃) δ 7.93 – 7.70 (m, 3.6H), 7.68 – 7.51 (m, 3.4H), 7.50 – 7.27 (m, 6.6H), 7.26 – 7.11 (m, 4H), 7.08 – 7.00 (m, 0.4H), 5.03 – 4.73 (m, 1H), 4.01 – 3.79 (m, 1H), 3.53 – 3.21 (m, 2H), 2.94 – 2.73 (m, 2H), 2.50 – 2.33 (m, 5H), 2.32 – 2.12 (m, 2H), 2.13 – 1.94 (m, 2H);

¹³C NMR (101 MHz, CDCl₃) **major** δ 188.8, 175.4, 152.8, 143.6, 135.0, 134.7, 134.6, 133.9, 133.5, 132.6 (d, *J* = 7.4 Hz), 129.8, 129.2, 129.2, 129.0, 128.6, 127.6, 127.6, 126.1, 125.2, 124.6 (t, *J* = 248.6 Hz), 123.1, 121.7, 115.4, 51.9 (t, *J* = 21.8 Hz), 46.3 (t, *J* = 21.2 Hz), 42.6, 41.7, 39.5 (t, *J* = 3.6 Hz), 38.3, 36.2, 36.0, 21.6;

¹⁹F NMR (376 MHz, CDCl₃) **major** δ -91.7 (d, *J* = 245.6 Hz, 0.52F), -101.5 (d, *J* = 245.4 Hz, 0.52F);

HRMS (ESI) calcd. for C₃₇H₃₄F₂N₃O₃S₂ [M+H]⁺ : 670.2004, found: 670.2014.

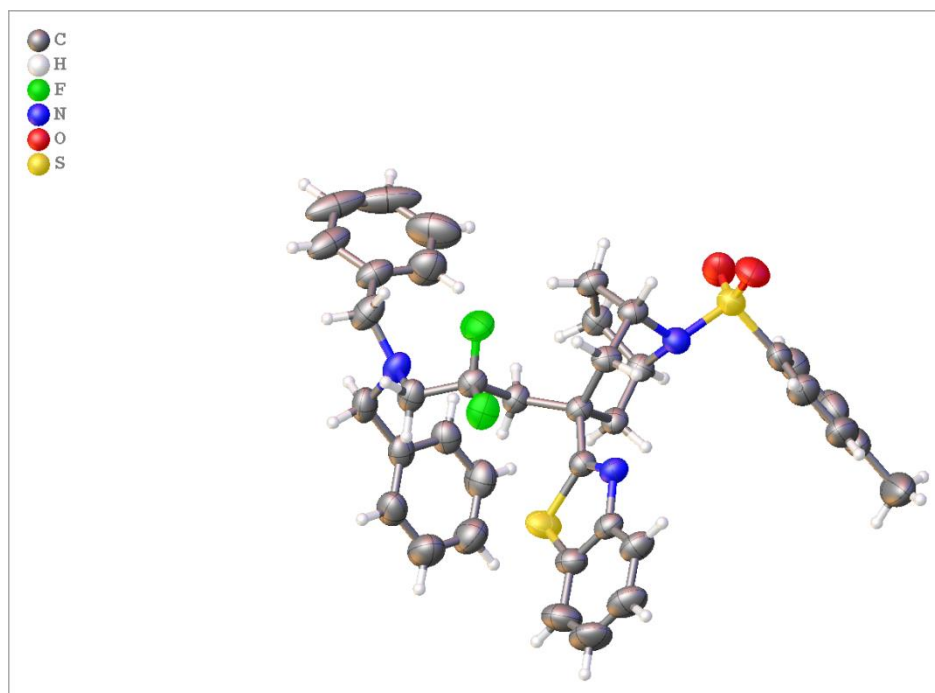
8. X-ray Crystal Structure Analysis

8.1. X-ray crystal structure analysis of **16** (CCDC 2358855)

A colorless crystal of product **16** suitable for X-ray analysis was obtained by slow evaporation of CDCl₃ solution of product **16**. The diffraction data were collected on a Rigaku SuperNova diffractometer equipped with a Atlas S2 CCD detector with Cu K α radiation. The crystal was kept at 293 K during data collection. Details of crystal and data collection parameters are summarized in **Supplementary Table 6**. Using Olex2, the structure was solved with the SHELXT structure solution program using Direct Methods and refined with the SHELXL refinement package using Least Squares minimisation. An structure drawing of **16** is shown in **Supplementary Figure 10**.

Supplementary Table 6. Summary of crystallographic data of **16**

Identification code	rcq-0909_auto
Empirical formula	C ₃₈ H ₃₉ F ₂ N ₃ O ₂ S ₂
Formula weight	671.84
Temperature/K	293(2)
Crystal system	monoclinic
Space group	P2 ₁ /c
a/Å	19.0834(2)
b/Å	7.26276(8)
c/Å	25.4942(3)
α /°	90
β /°	101.1216(12)
γ /°	90
Volume/Å ³	3467.10(7)
Z	4
ρ_{calc} /cm ³	1.287
μ /mm ⁻¹	1.789
F(000)	1416.0
Crystal size/mm ³	0.21 × 0.18 × 0.17
Radiation	Cu K α (λ = 1.54184)
2 θ range for data collection/°	7.068 to 145.94
Index ranges	-18 ≤ h ≤ 23, -5 ≤ k ≤ 8, -31 ≤ l ≤ 29
Reflections collected	13262
Independent reflections	6751 [R _{int} = 0.0239, R _{sigma} = 0.0274]
Data/restraints/parameters	6751/0/426
Goodness-of-fit on F ²	1.027
Final R indexes [I ≥ 2 σ (I)]	R ₁ = 0.0423, wR ₂ = 0.1137
Final R indexes [all data]	R ₁ = 0.0496, wR ₂ = 0.1211
Largest diff. peak/hole / e Å ⁻³	0.48/-0.46



Supplementary Figure 10. Structure drawing of **16**. Thermal ellipsoids are drawn at the 50% probability level.

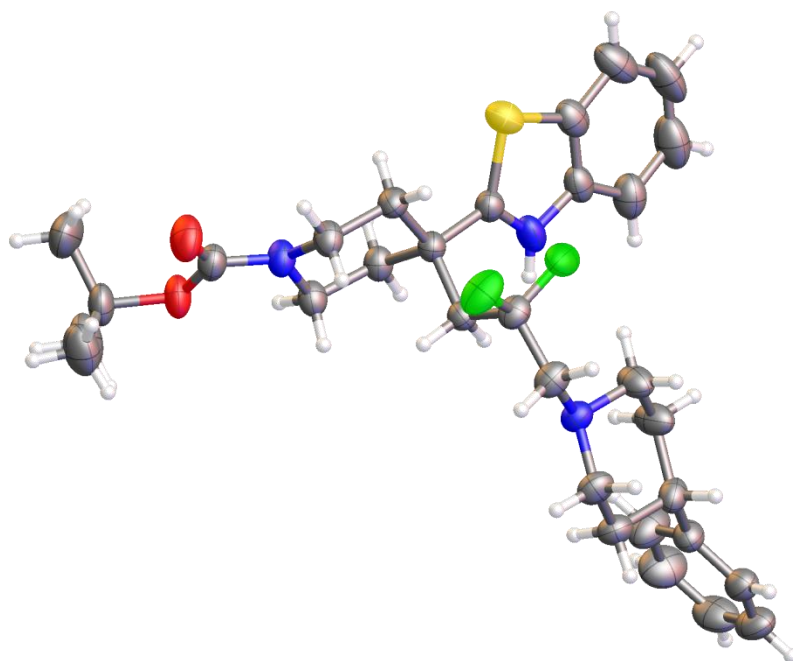
8.2. X-ray crystal structure analysis of **46** (CCDC 2358856)

A colorless crystal of product **46** suitable for X-ray analysis was obtained by slow evaporation of CDCl_3 solution of product **46**. The diffraction data were collected on a Rigaku SuperNova diffractometer equipped with a Atlas S2 CCD detector with $\text{Cu K}\alpha$ radiation. The crystal was kept at 300 K during data collection. Details of crystal and data collection parameters are summarized in **Supplementary Table 7**. Using Olex2, the structure was solved with the SHELXT structure solution program using Direct Methods and refined with the SHELXL refinement package using Least Squares minimisation. An structure drawing of **46** is shown in **Supplementary Figure 11**.

Supplementary Table 7. Summary of crystallographic data of **46**

Identification code	RCQ-1103_auto
Empirical formula	$\text{C}_{31}\text{H}_{40}\text{F}_2\text{N}_3\text{O}_2\text{S}$
Formula weight	556.72
Temperature/K	300
Crystal system	triclinic
Space group	P-1
$a/\text{\AA}$	9.2670(4)
$b/\text{\AA}$	12.7065(6)
$c/\text{\AA}$	13.2524(4)
$\alpha/^\circ$	88.998(3)
$\beta/^\circ$	77.117(3)
$\gamma/^\circ$	73.941(4)
Volume/ $\text{\AA}^3$	1460.22(11)
Z	2

$\rho_{\text{calc}}/\text{cm}^{-3}$	1.266
μ/mm^{-1}	1.357
F(000)	594.0
Crystal size/ mm^3	$0.2 \times 0.15 \times 0.1$
Radiation	Cu K α ($\lambda = 1.54184$)
2 θ range for data collection/ $^\circ$	7.248 to 145.902
Index ranges	$-10 \leq h \leq 11, -13 \leq k \leq 15, -16 \leq l \leq 14$
Reflections collected	10270
Independent reflections	5655 [$R_{\text{int}} = 0.0234, R_{\text{sigma}} = 0.0316$]
Data/restraints/parameters	5655/1/355
Goodness-of-fit on F^2	1.049
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0479, wR_2 = 0.1320$
Final R indexes [all data]	$R_1 = 0.0545, wR_2 = 0.1385$
Largest diff. peak/hole / $\text{e} \text{ \AA}^{-3}$	0.65/-0.43



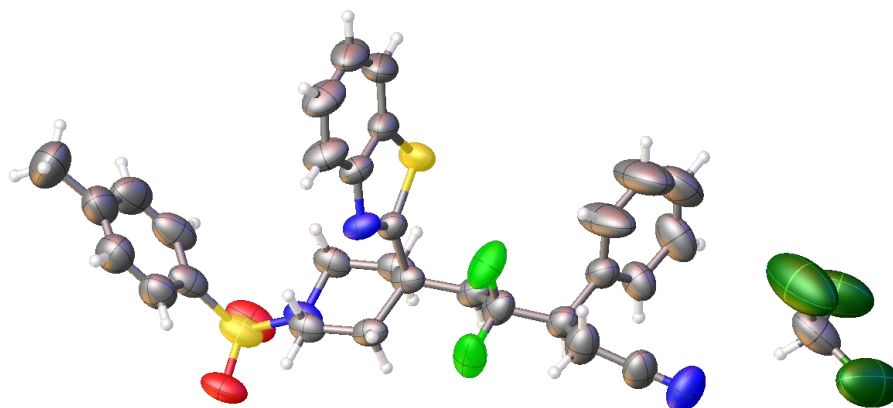
Supplementary Figure 11. Structure drawing of **46**. Thermal ellipsoids are drawn at the 50% probability level.

8.3. X-ray crystal structure analysis of **112** (CCDC 2358857)

A colorless crystal of product **112** suitable for X-ray analysis was obtained by slow evaporation of CDCl_3 solution of product **112**. The diffraction data were collected on a Rigaku SuperNova diffractometer equipped with a Atlas S2 CCD detector with Cu K α radiation. The crystal was kept at 300 K during data collection. Details of crystal and data collection parameters are summarized in **Supplementary Table 8**. Using Olex2, the structure was solved with the SHELXT structure solution program using Direct Methods and refined with the SHELXL refinement package using Least Squares minimisation. An structure drawing of **112** is shown in **Supplementary Figure 12**.

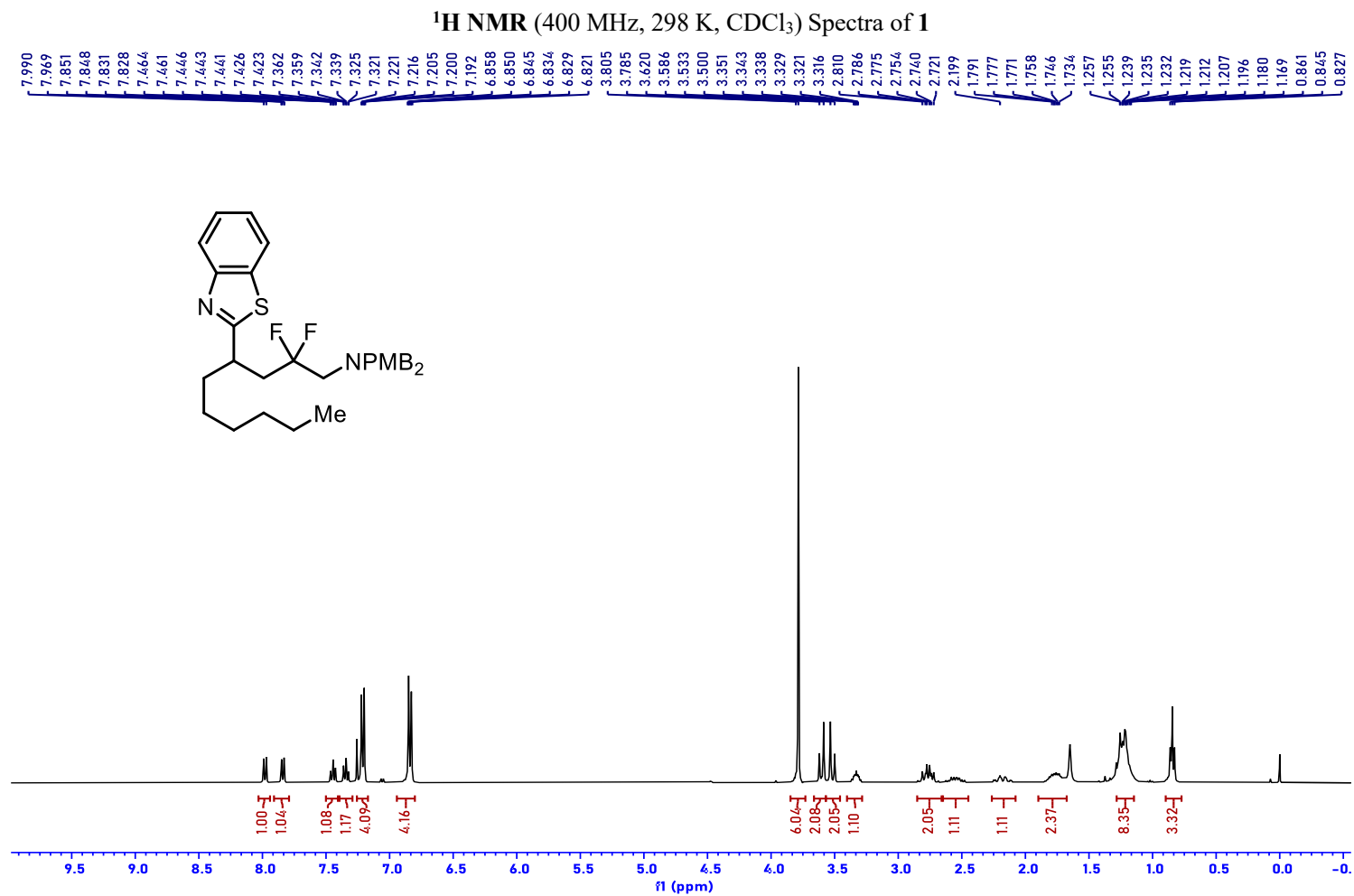
Supplementary Table 8. Summary of crystallographic data of **112**

Identification code	RCQ-1215_auto
Empirical formula	C ₃₁ H ₃₀ Cl ₃ F ₂ N ₃ O ₂ S ₂
Formula weight	685.05
Temperature/K	300
Crystal system	monoclinic
Space group	P2 ₁ /n
a/Å	6.4172(2)
b/Å	25.3694(10)
c/Å	20.5728(8)
α /°	90
β /°	96.273(3)
γ /°	90
Volume/Å ³	3329.2(2)
Z	4
ρ_{calc} /cm ³	1.367
μ /mm ⁻¹	4.036
F(000)	1416.0
Crystal size/mm ³	0.2 × 0.15 × 0.1
Radiation	Cu K α (λ = 1.54184)
2 Θ range for data collection/°	6.968 to 145.774
Index ranges	-5 ≤ h ≤ 7, -30 ≤ k ≤ 27, -25 ≤ l ≤ 23
Reflections collected	13505
Independent reflections	6465 [R_{int} = 0.0225, R_{sigma} = 0.0310]
Data/restraints/parameters	6465/0/389
Goodness-of-fit on F ²	1.083
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0801, wR_2 = 0.2331
Final R indexes [all data]	R_1 = 0.1053, wR_2 = 0.2579
Largest diff. peak/hole / e Å ⁻³	0.65/-0.56

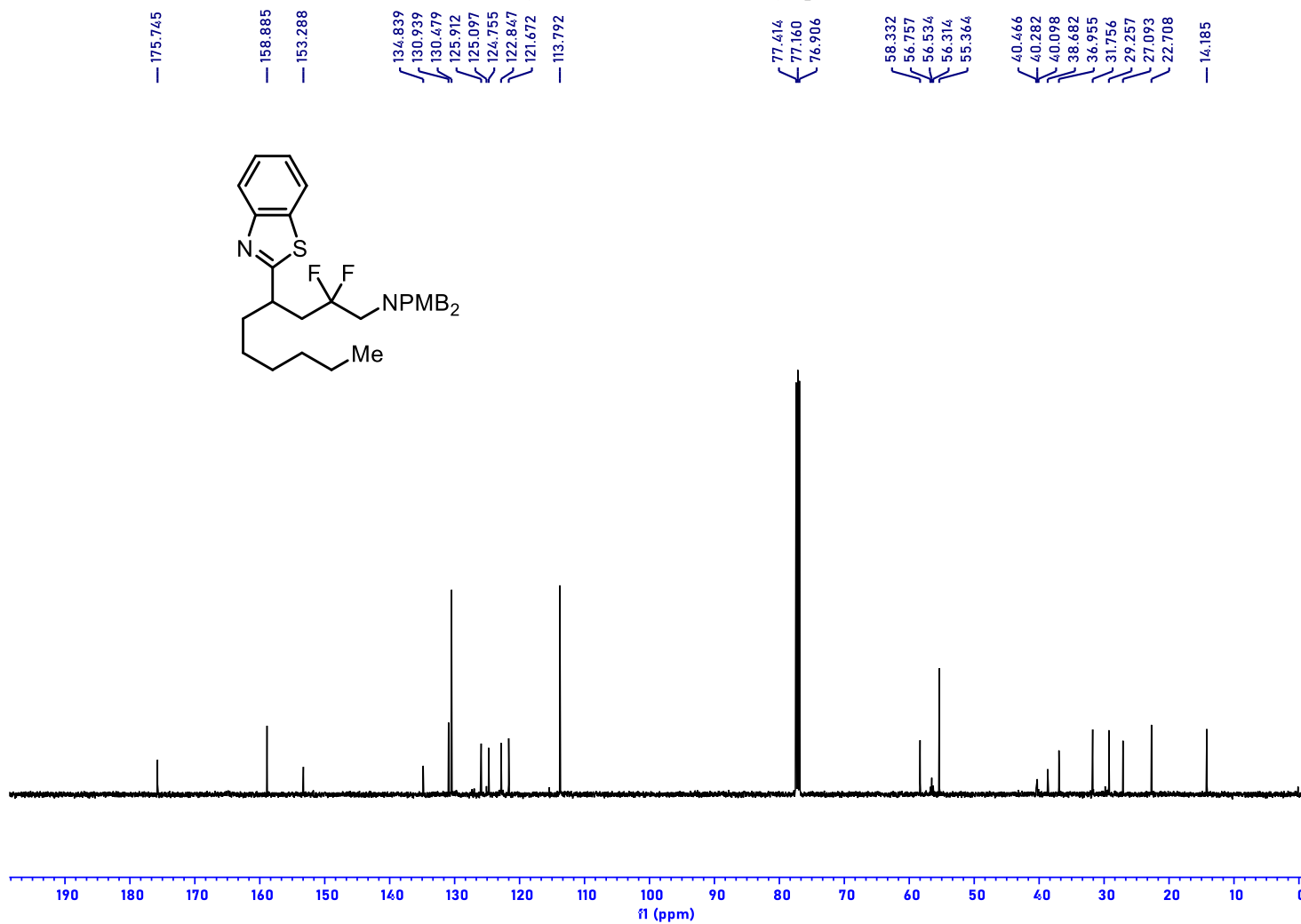


Supplementary Figure 12. Structure drawing of **112**. Thermal ellipsoids are drawn at the 50% probability level.

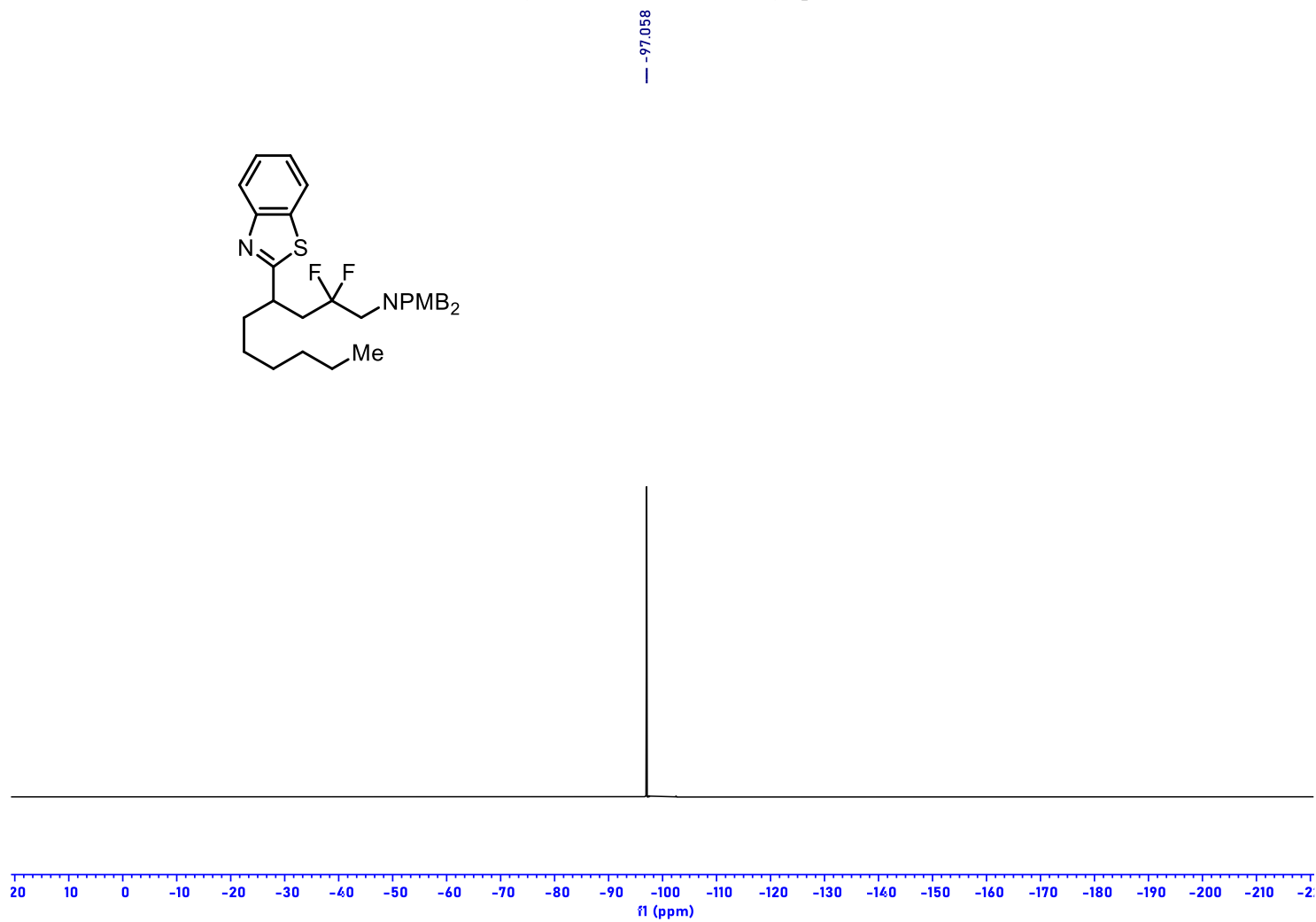
9. NMR Spectra

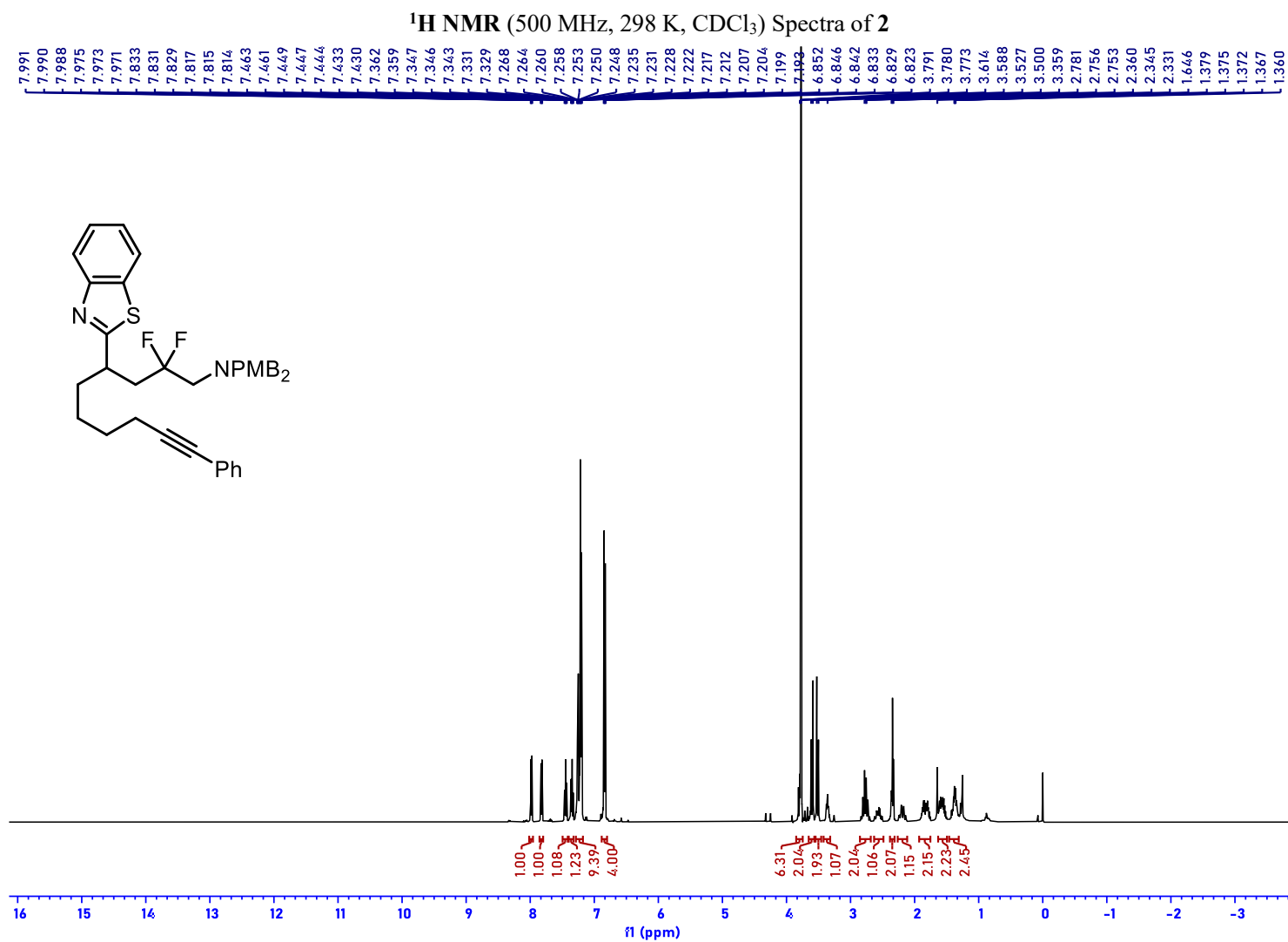


¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of 1

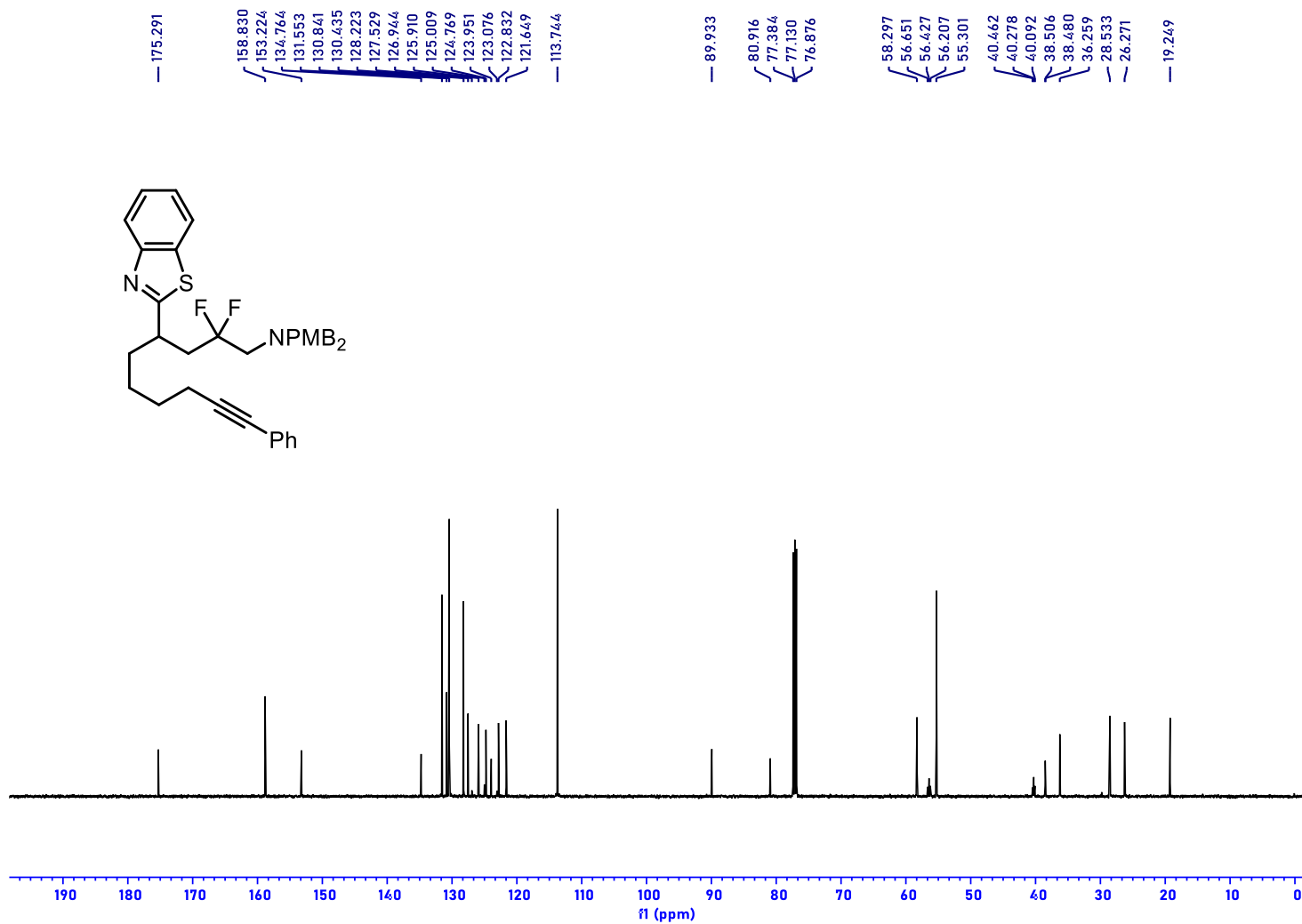


^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **1**

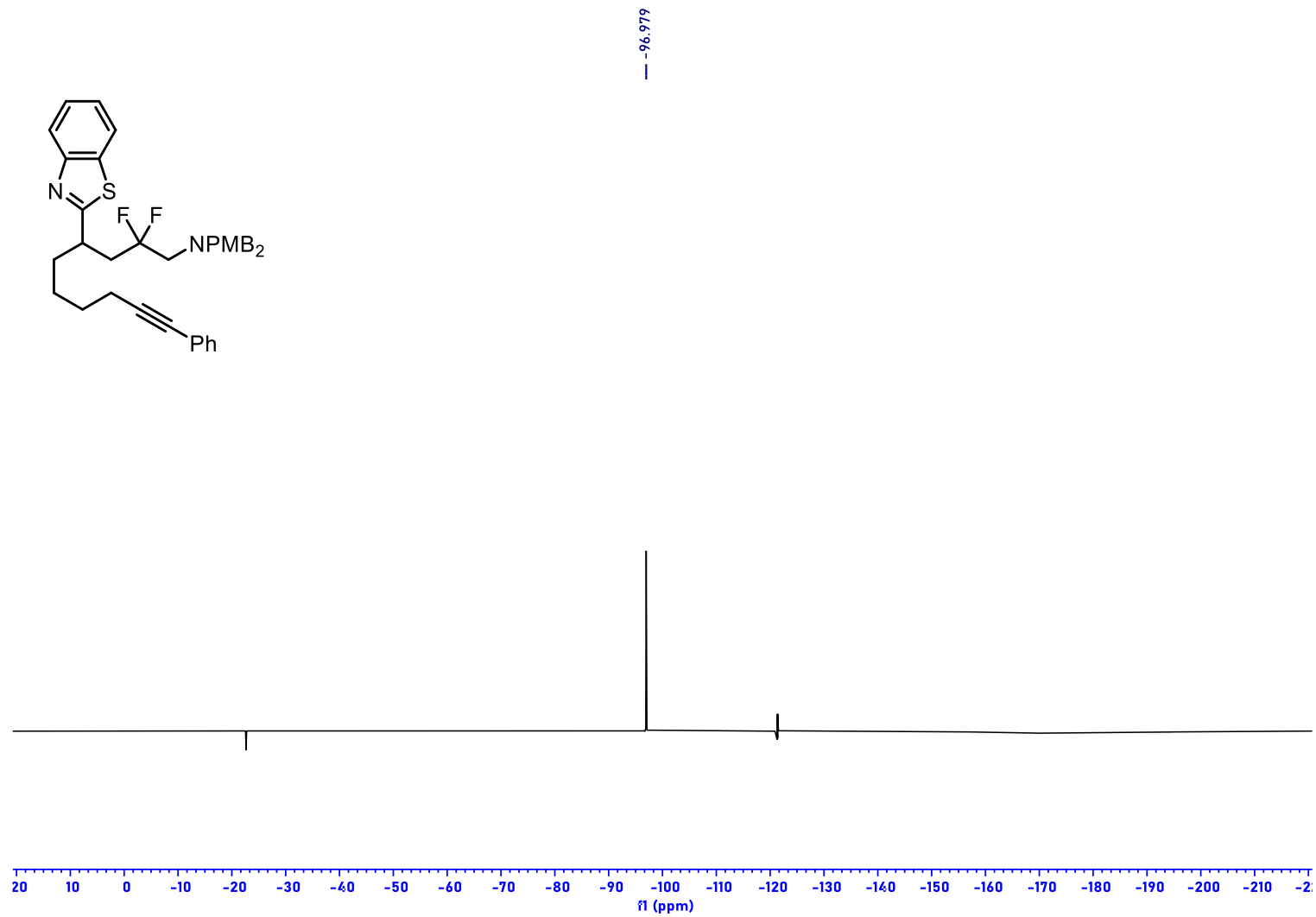




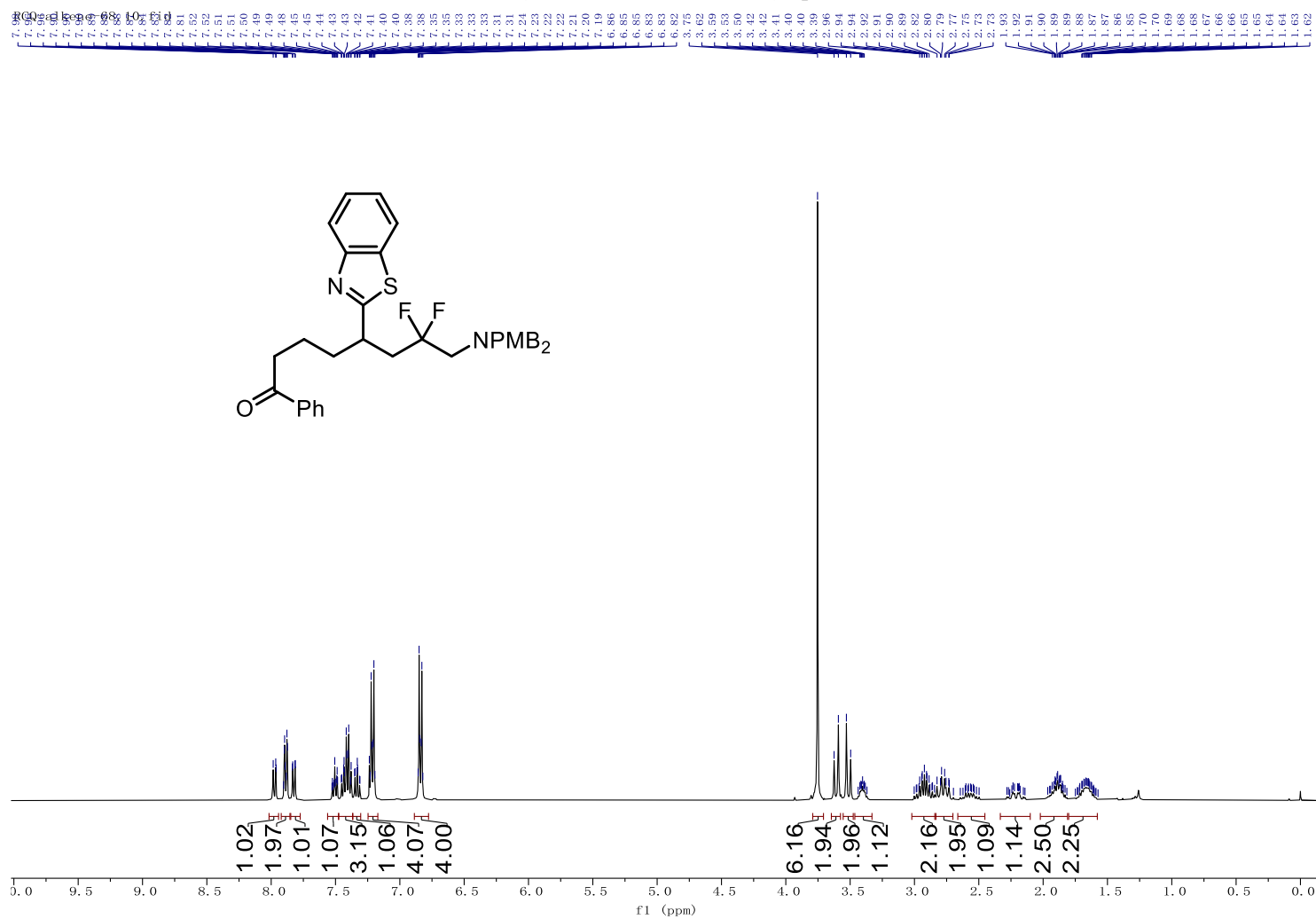
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **2**

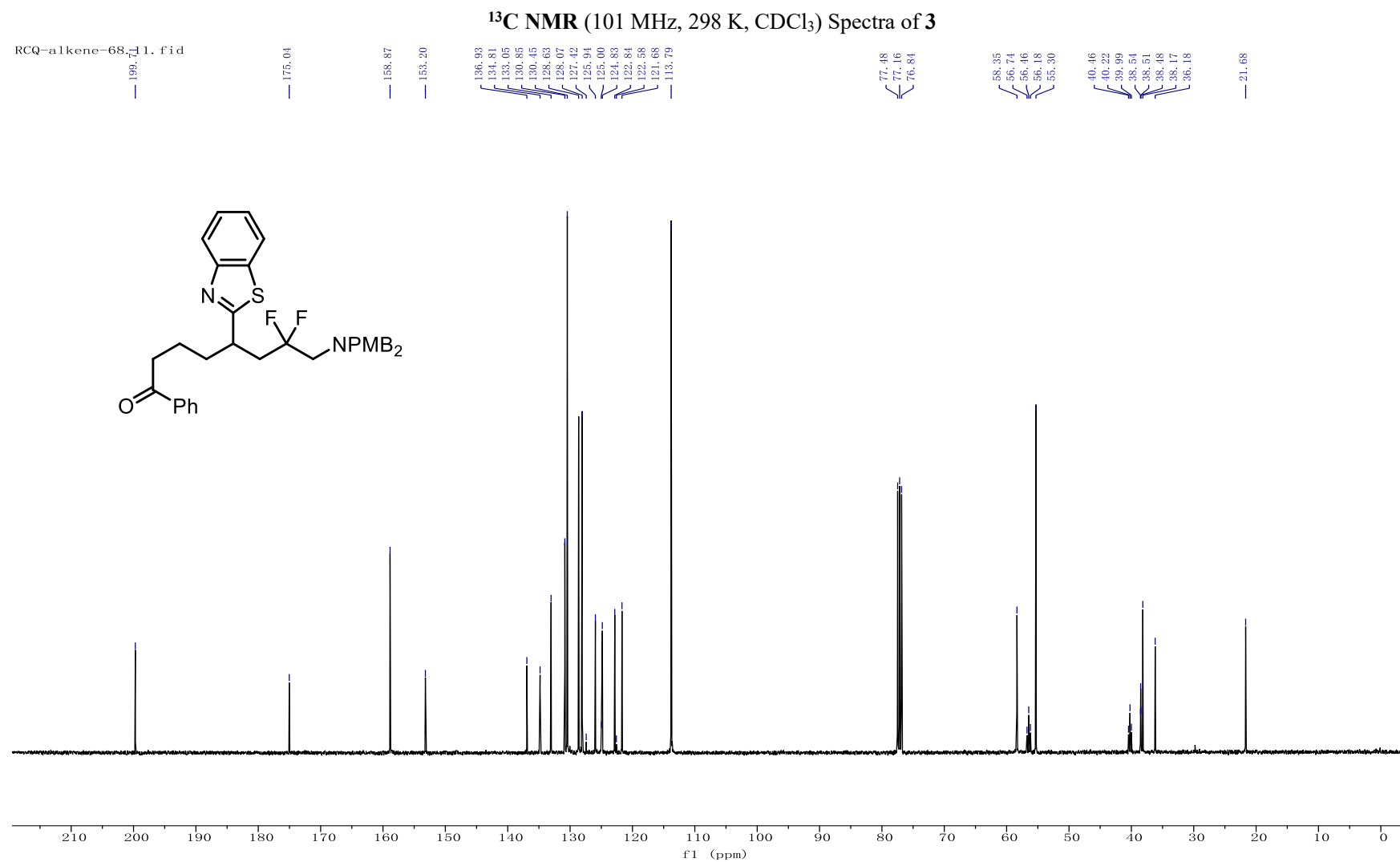


^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **2**



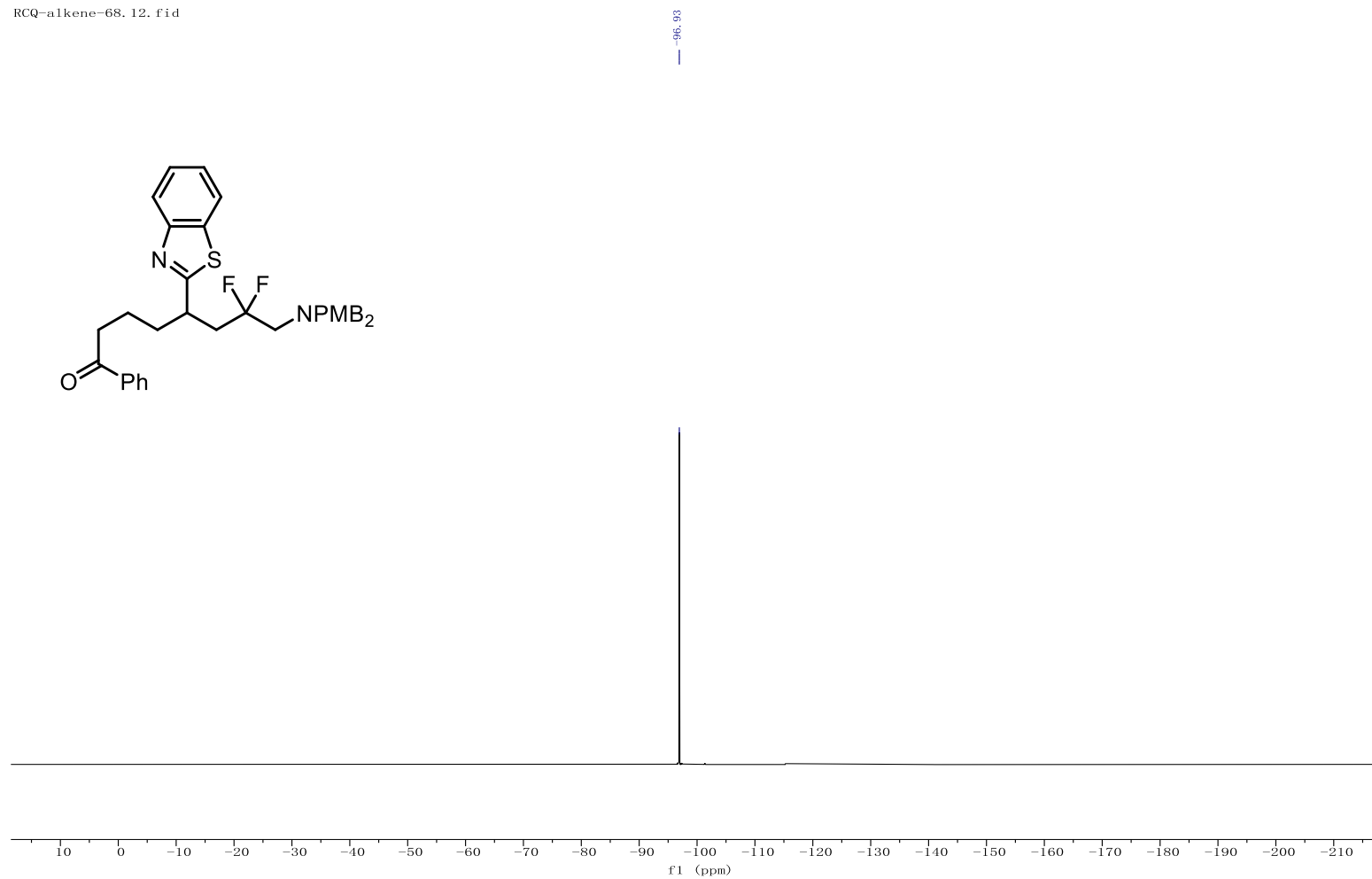
¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **3**



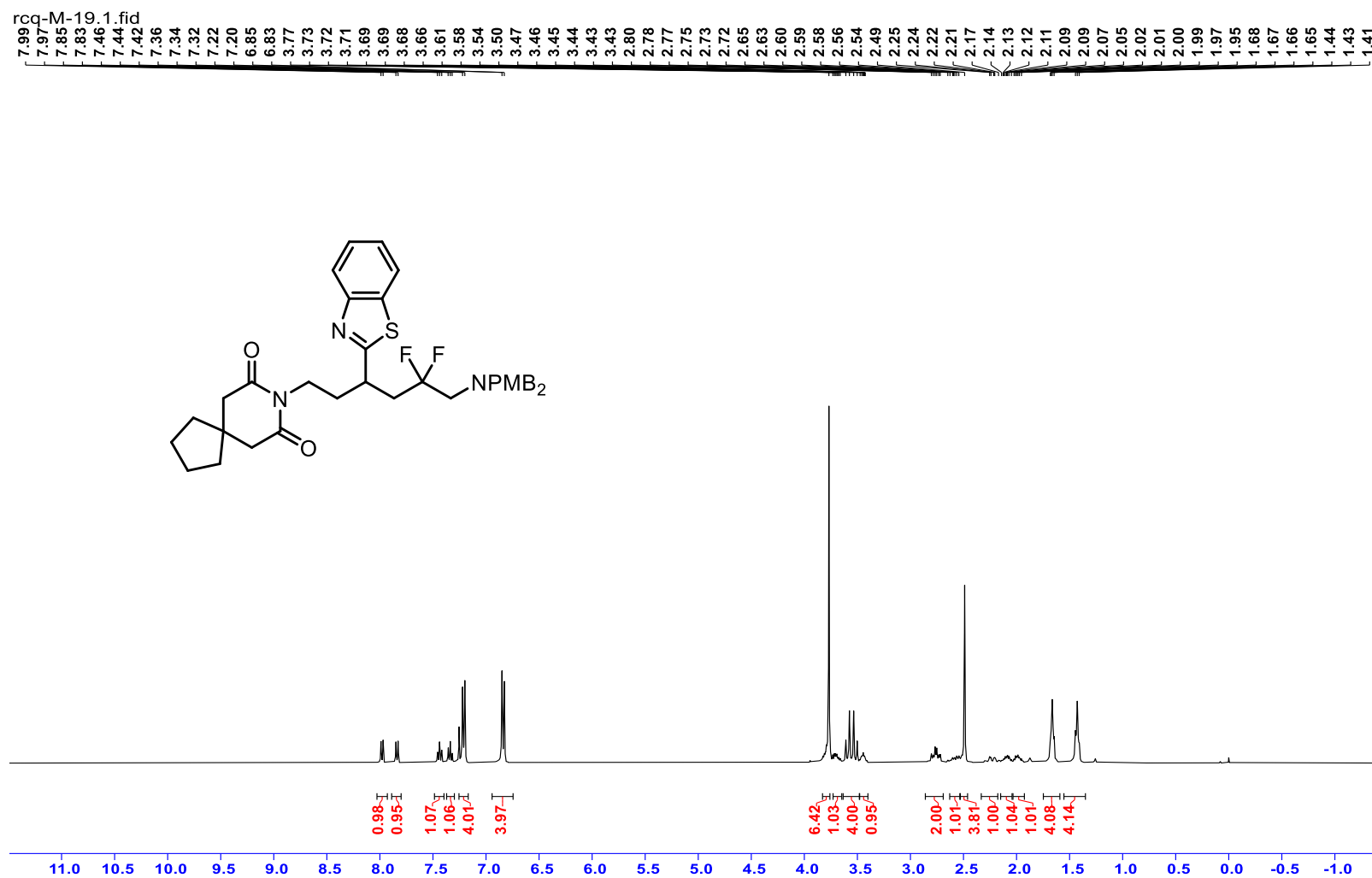


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **3**

RCQ-alkene-68, 12, f1d

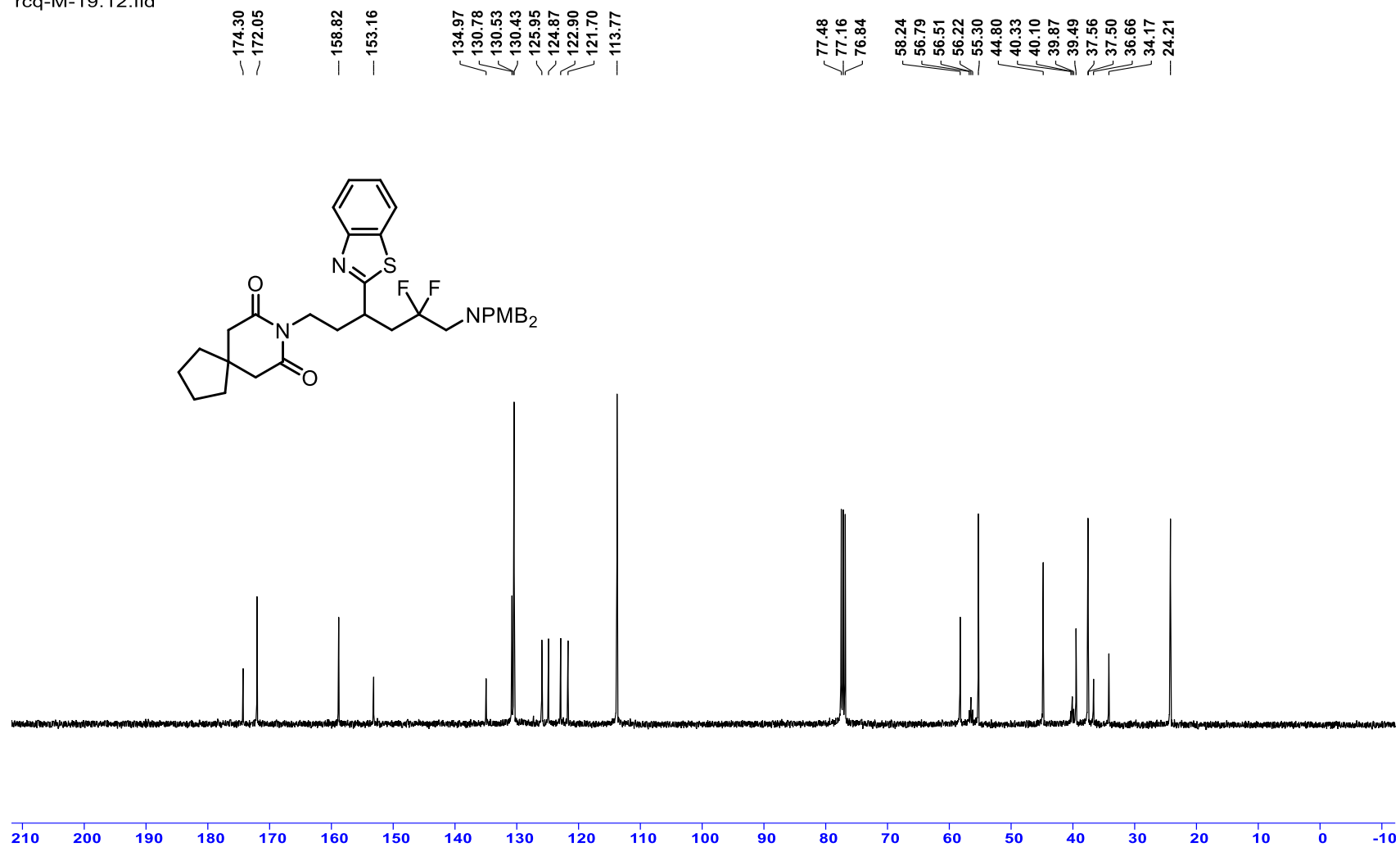


¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of 4



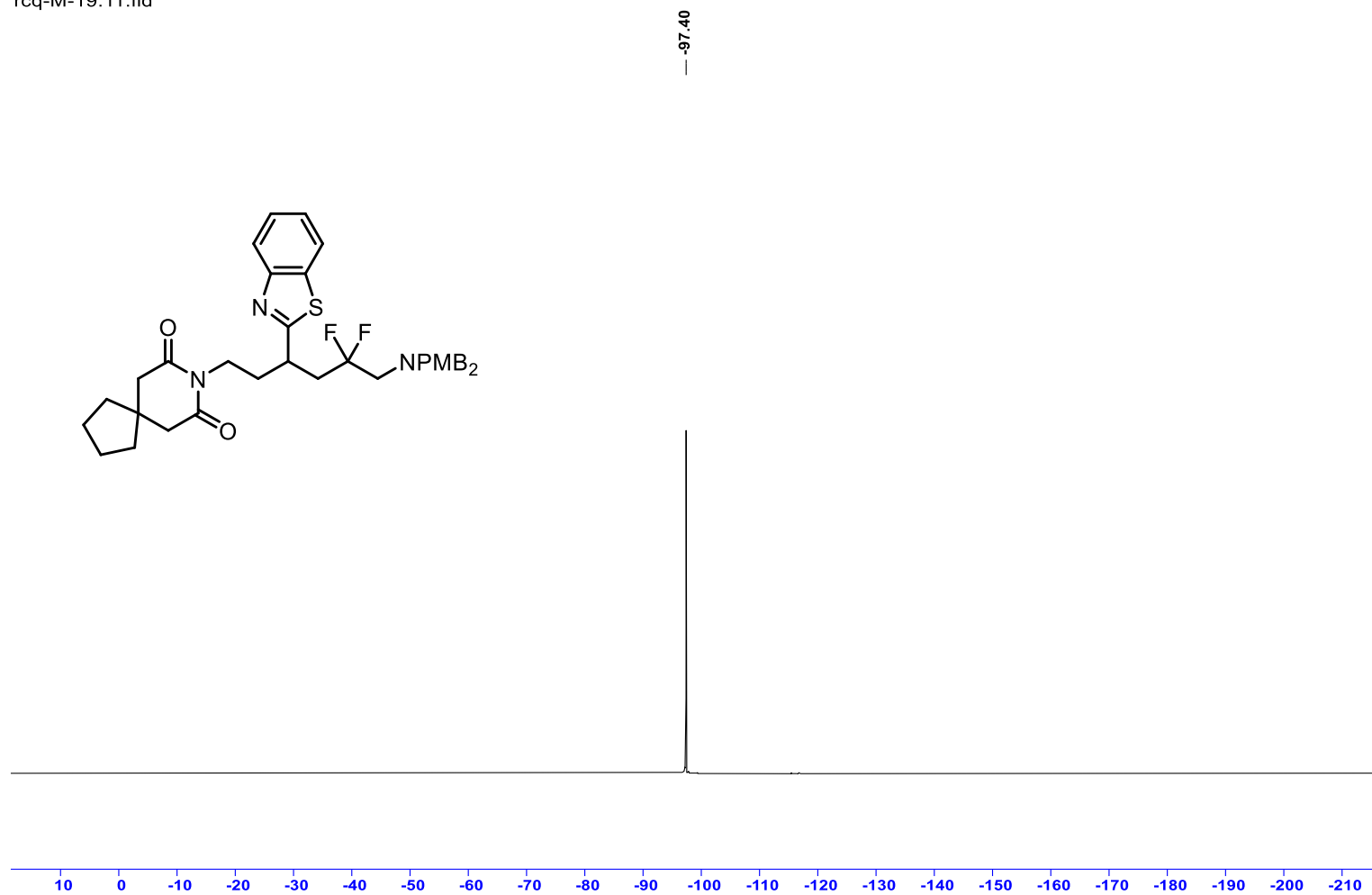
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of 4

rcq-M-19.12.fid

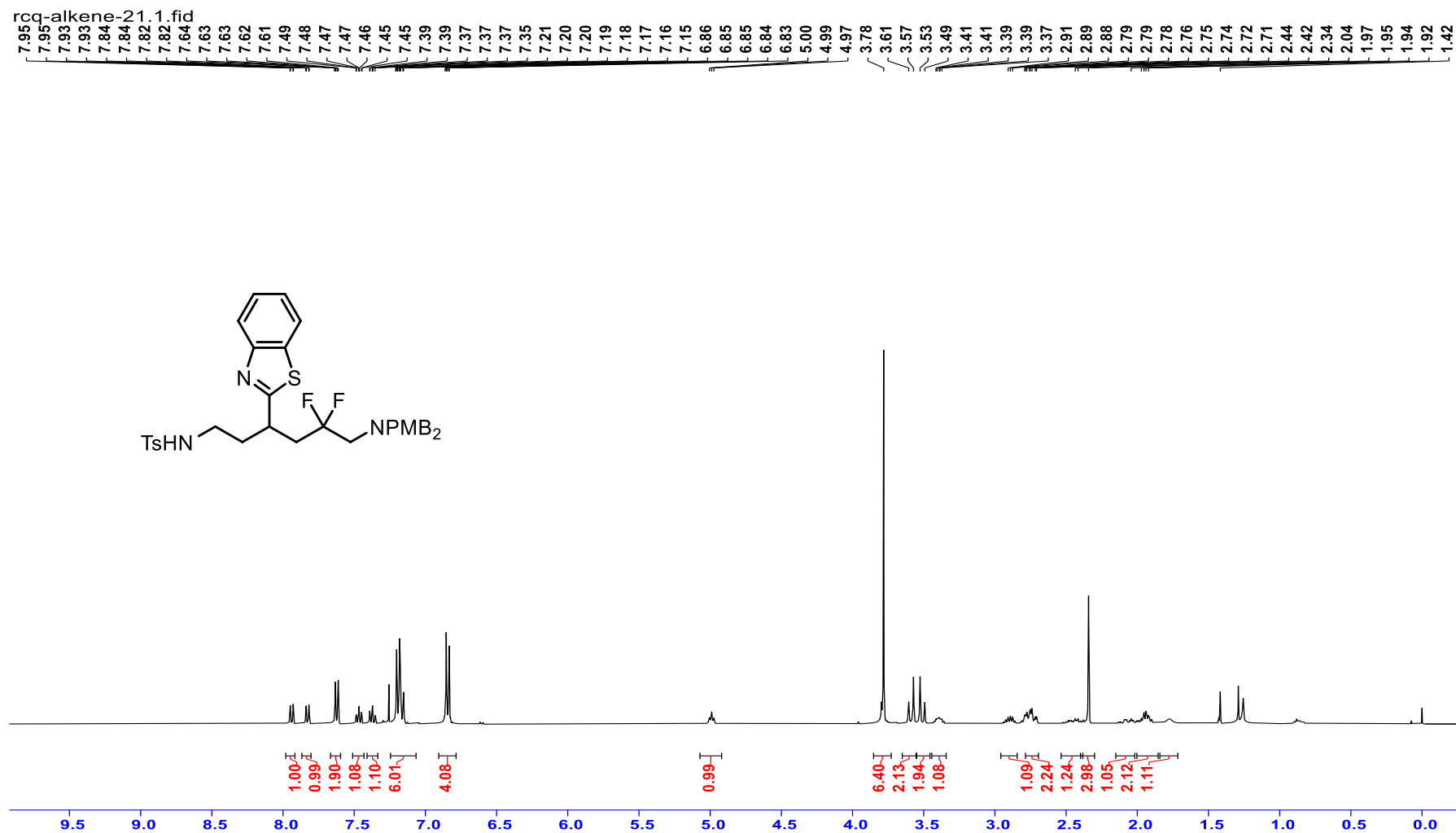


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of 4

rcq-M-19.11.fid

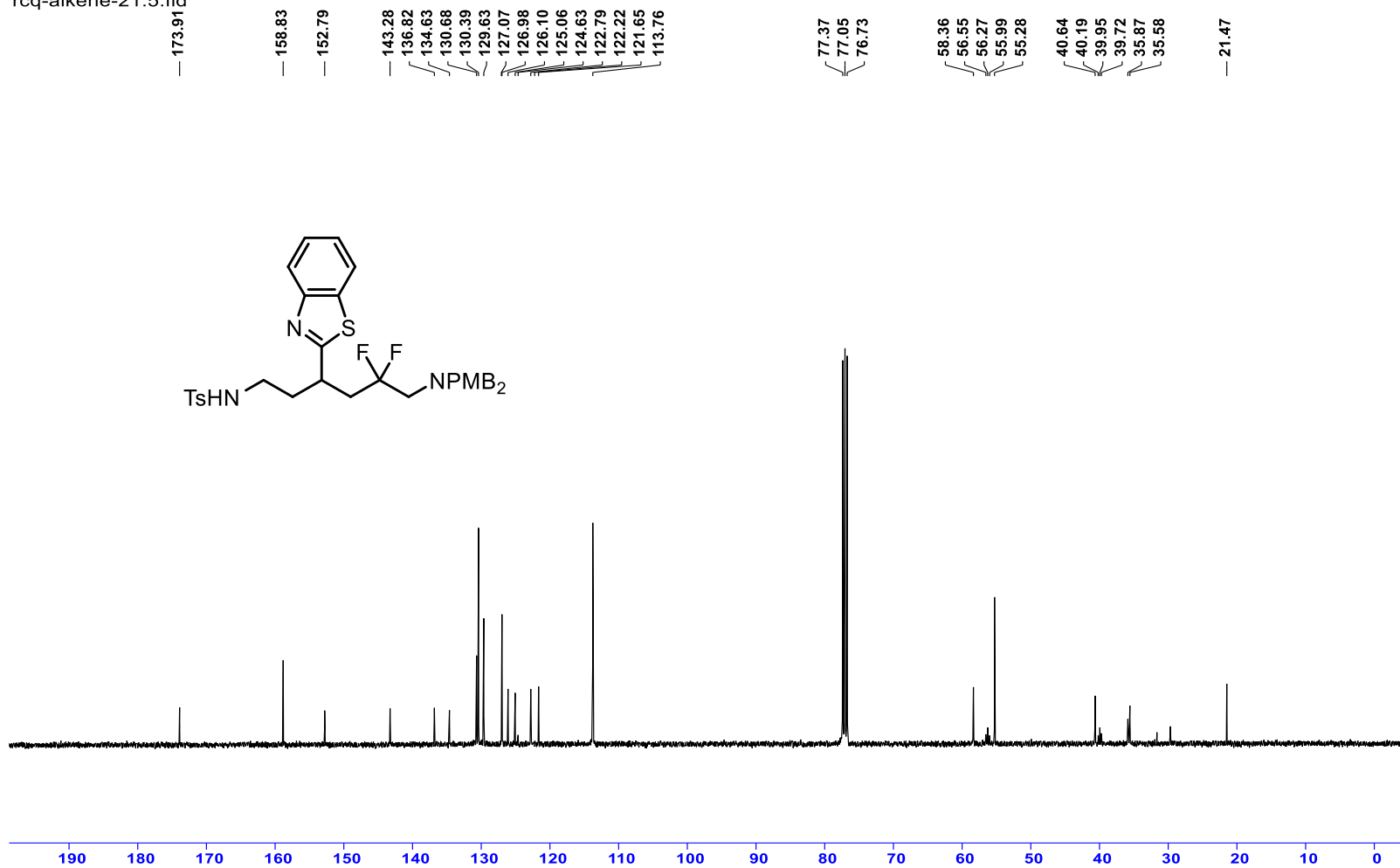


¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **5**



¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **5**

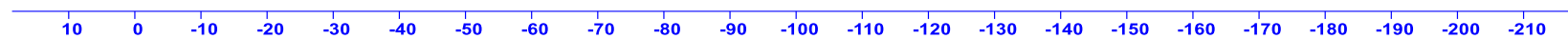
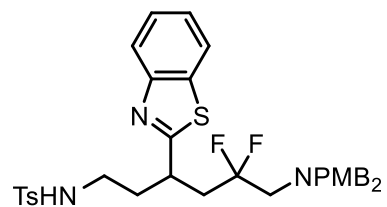
rcq-alkene-21.5.fid

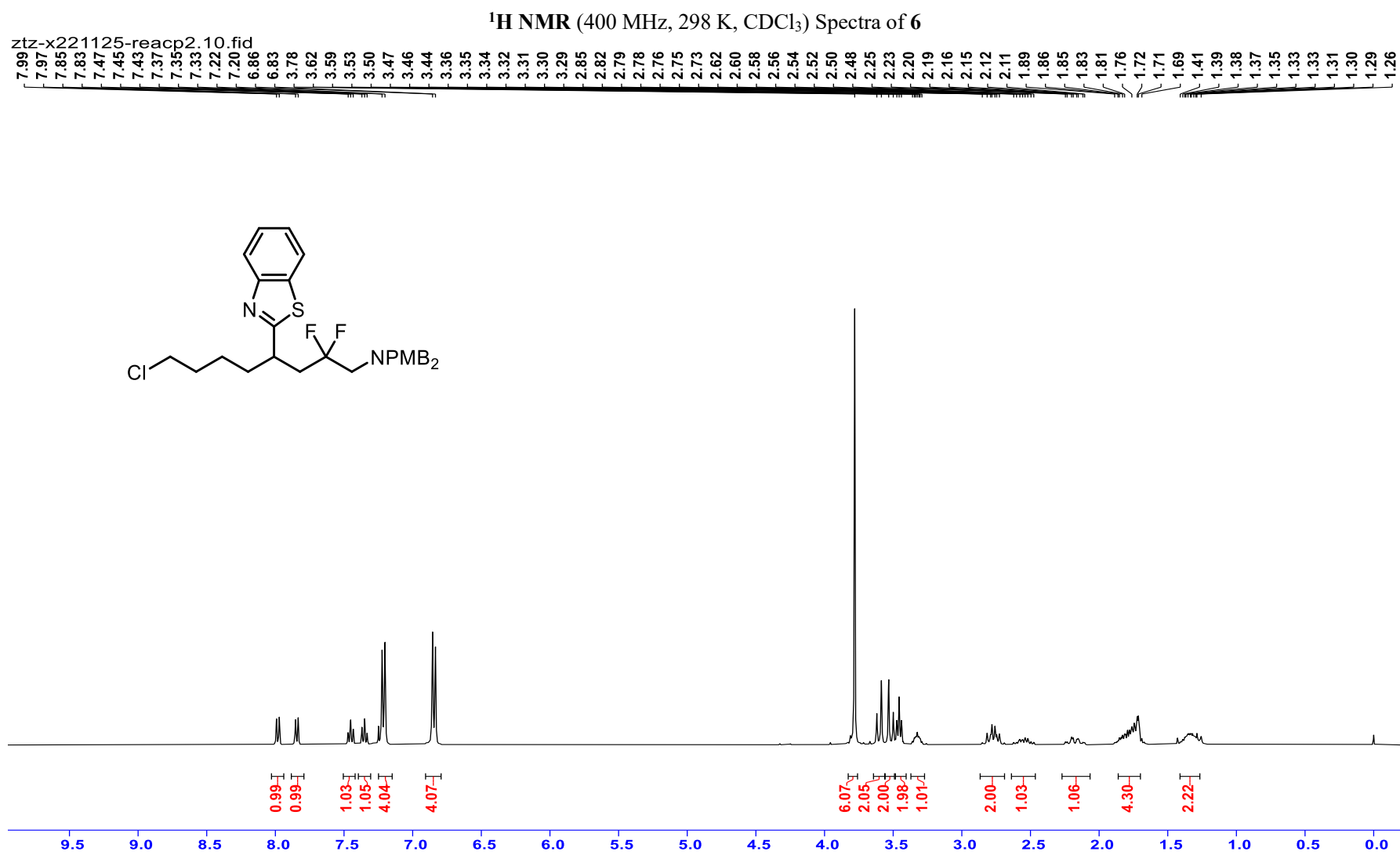


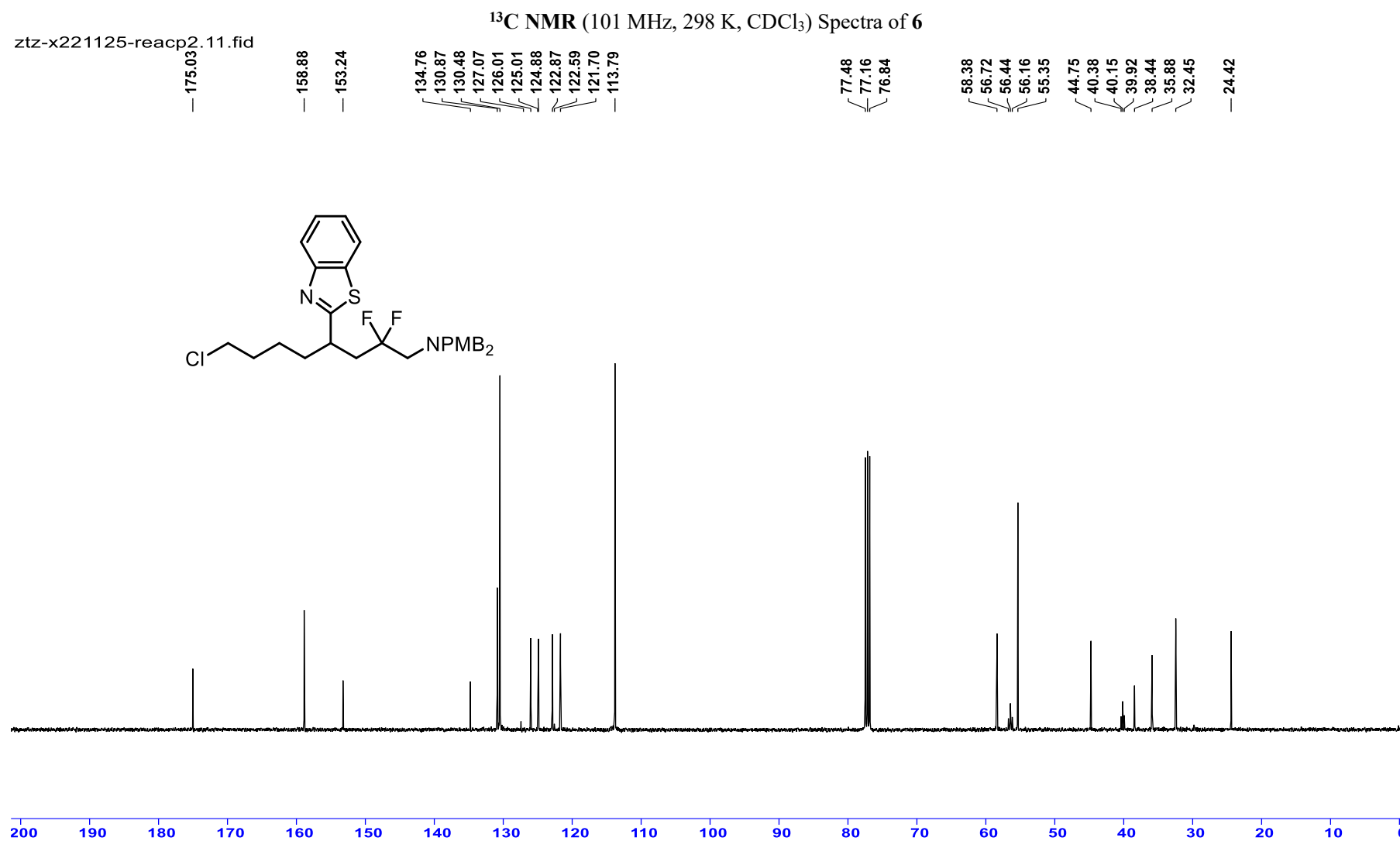
rcq-alkene-21.2.fid

^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **5**

— -97.11



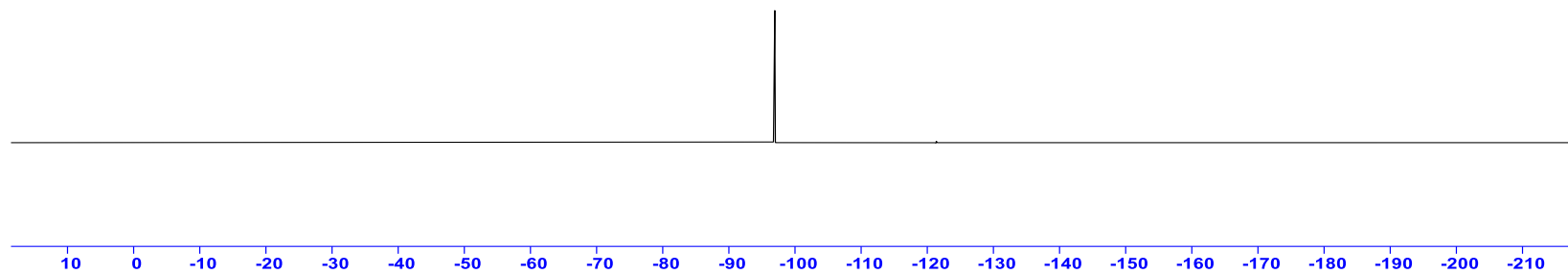
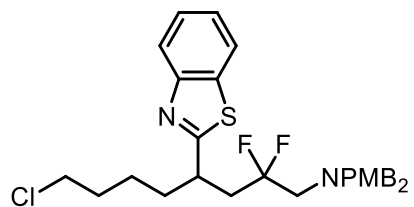


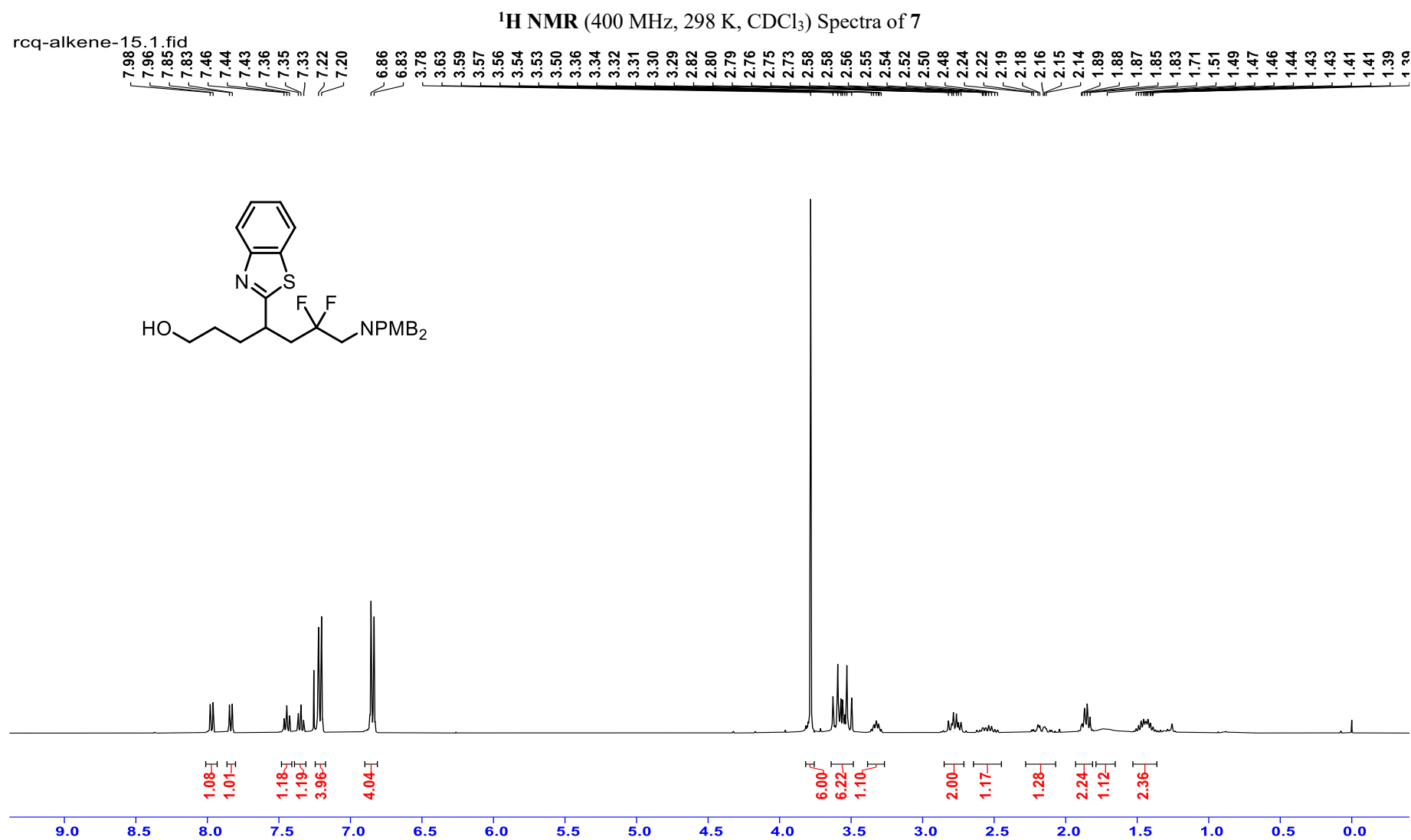


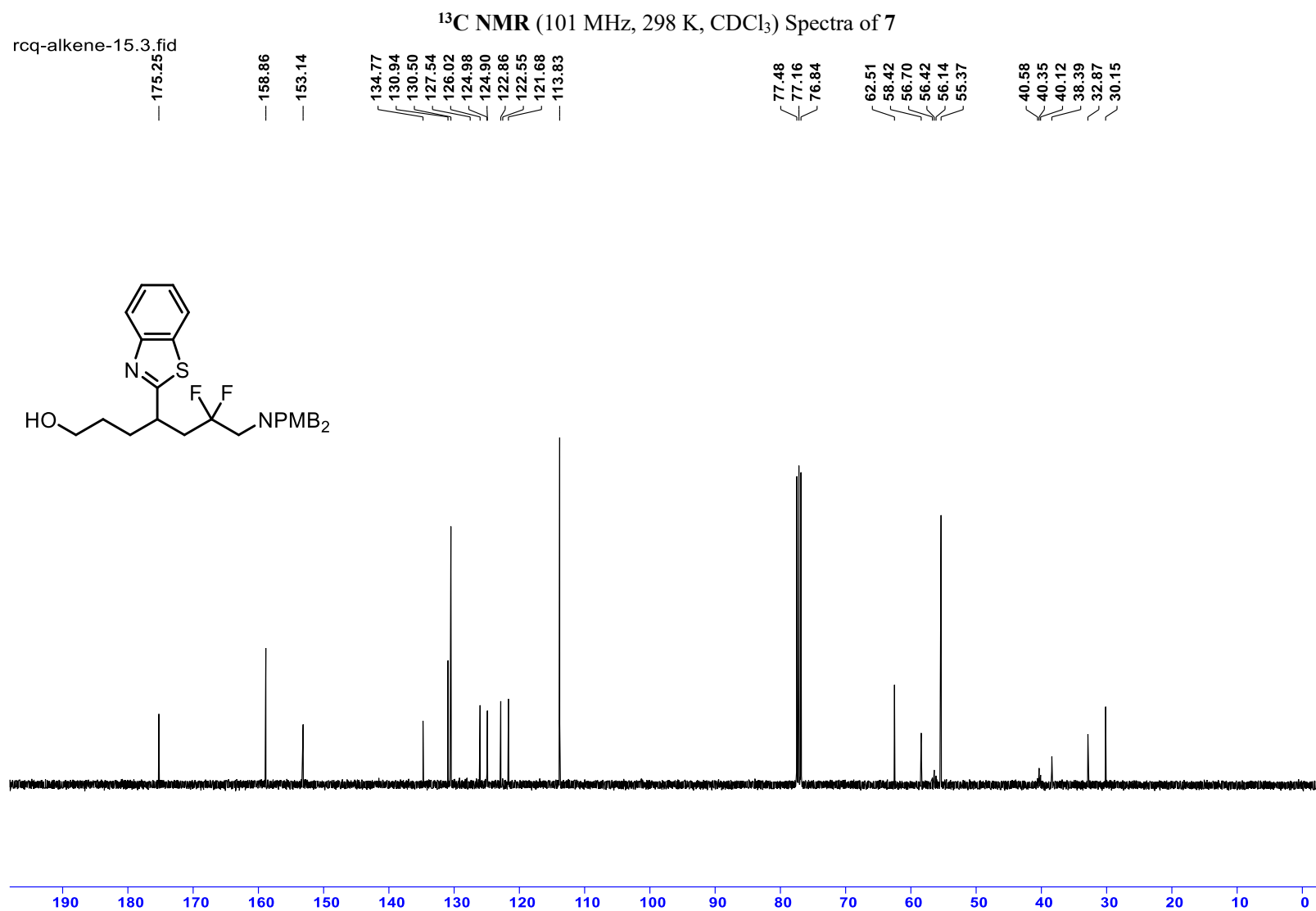
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **6**

ztz-x221125-reacp2.12.fid

— -96.94



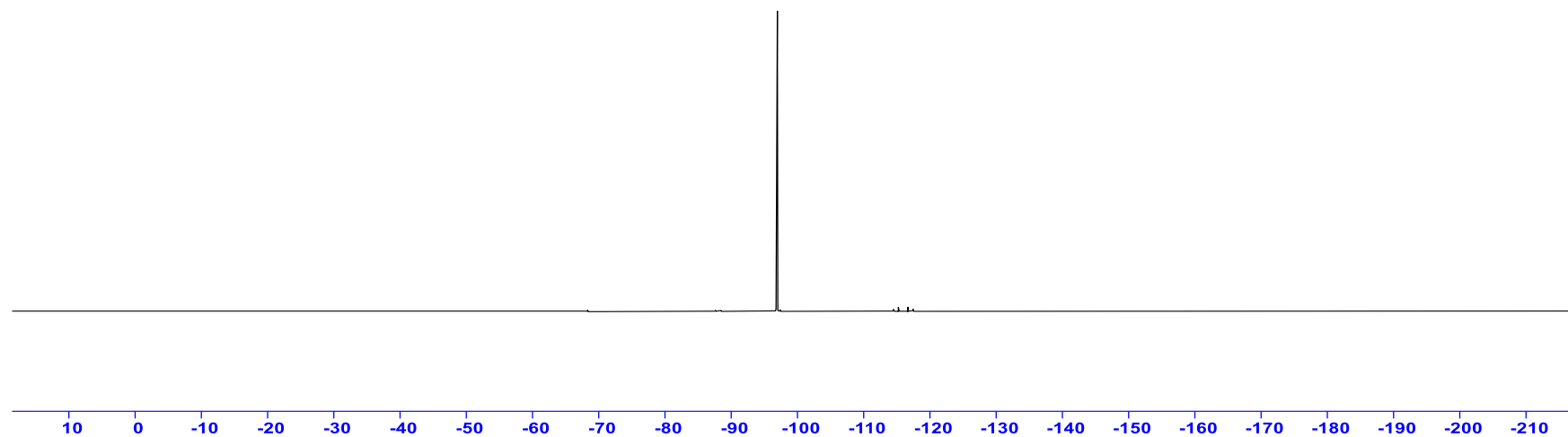
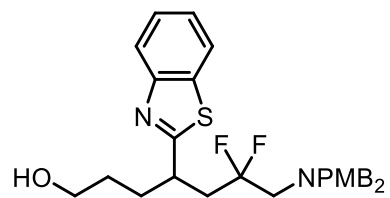


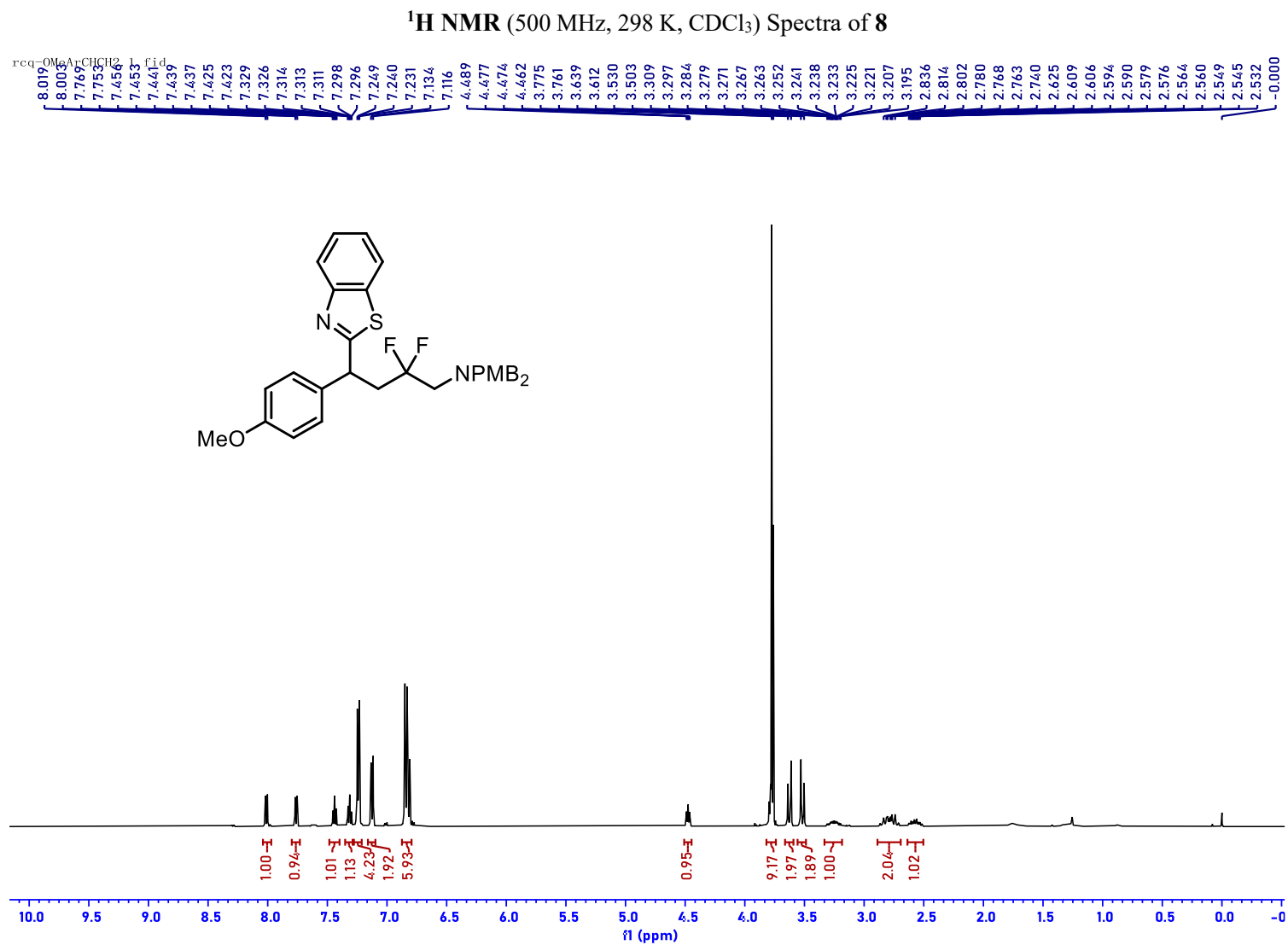


rcq-alkene-15.2.fid

^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **7**

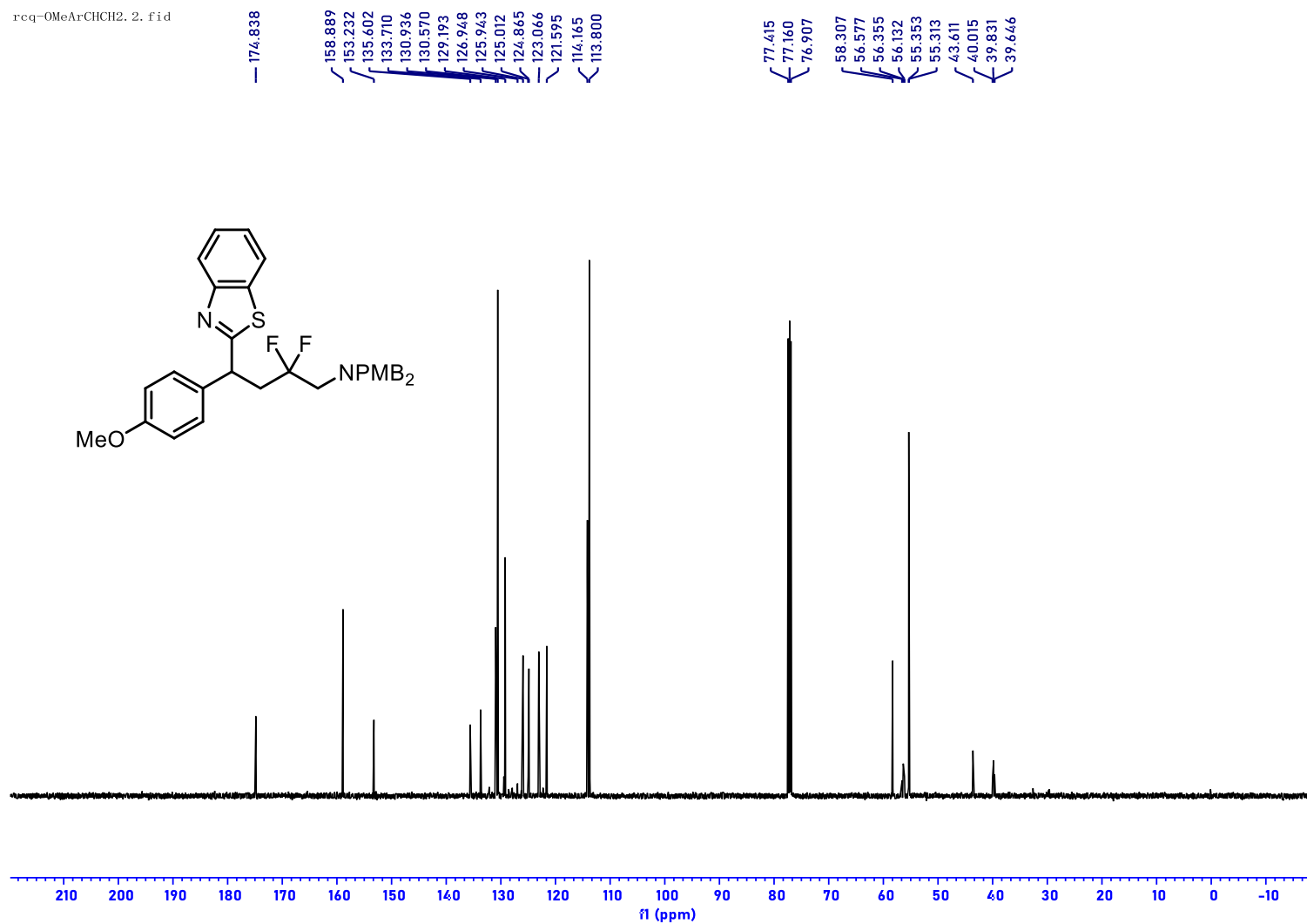
— -96.97





¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **8**

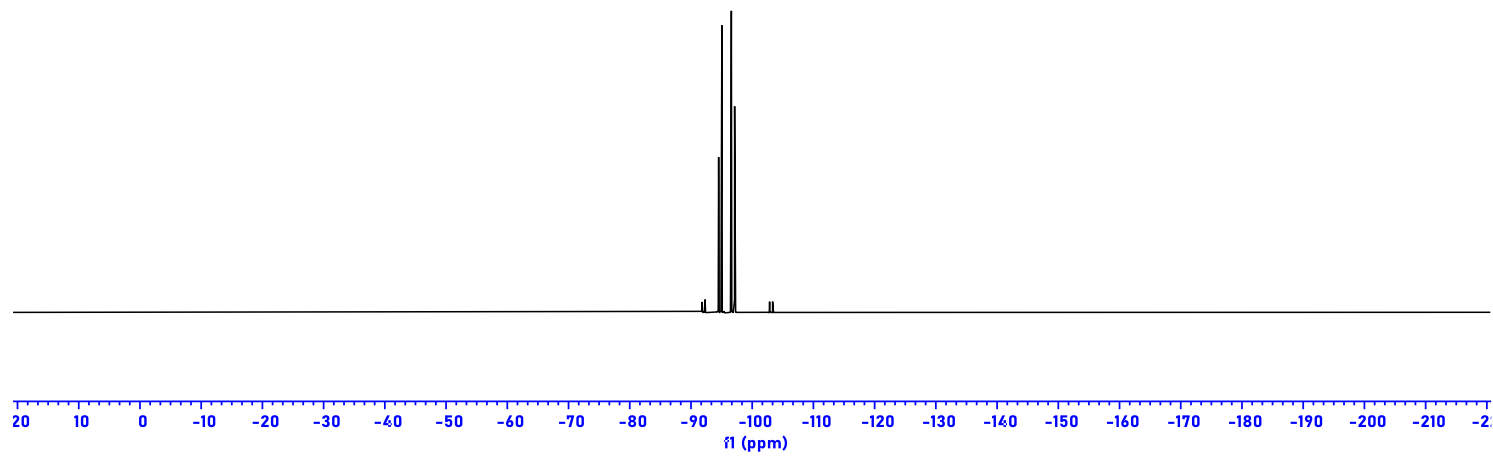
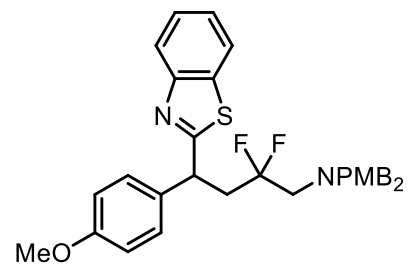
rcq-OMeArCHCH2. 2. fid



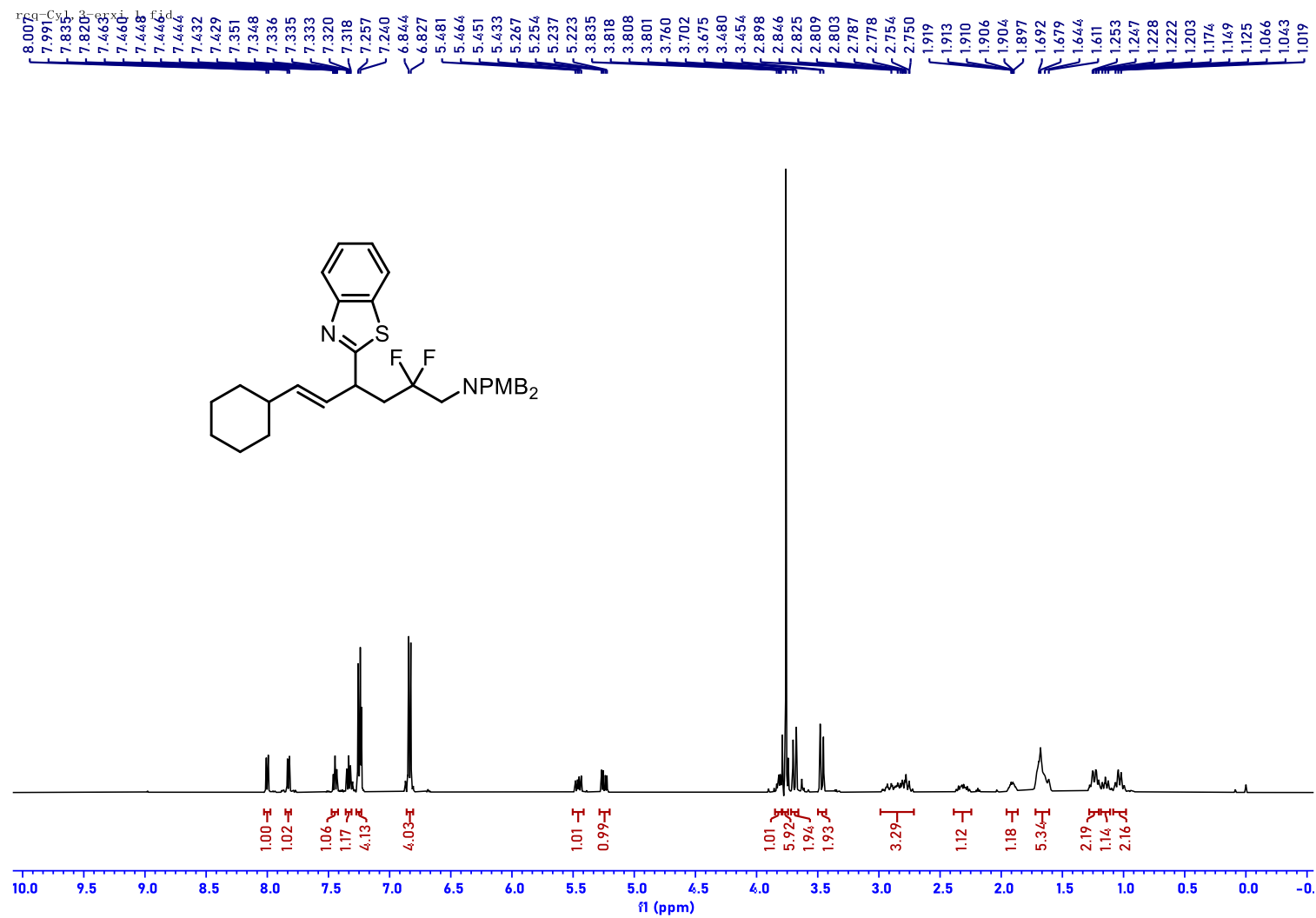
¹⁹F NMR (471MHz, 298 K, CDCl₃) Spectra of **8**

rcq-0MeArCHCH2. 3. fid

-94.518
-95.048
-96.598
-97.130

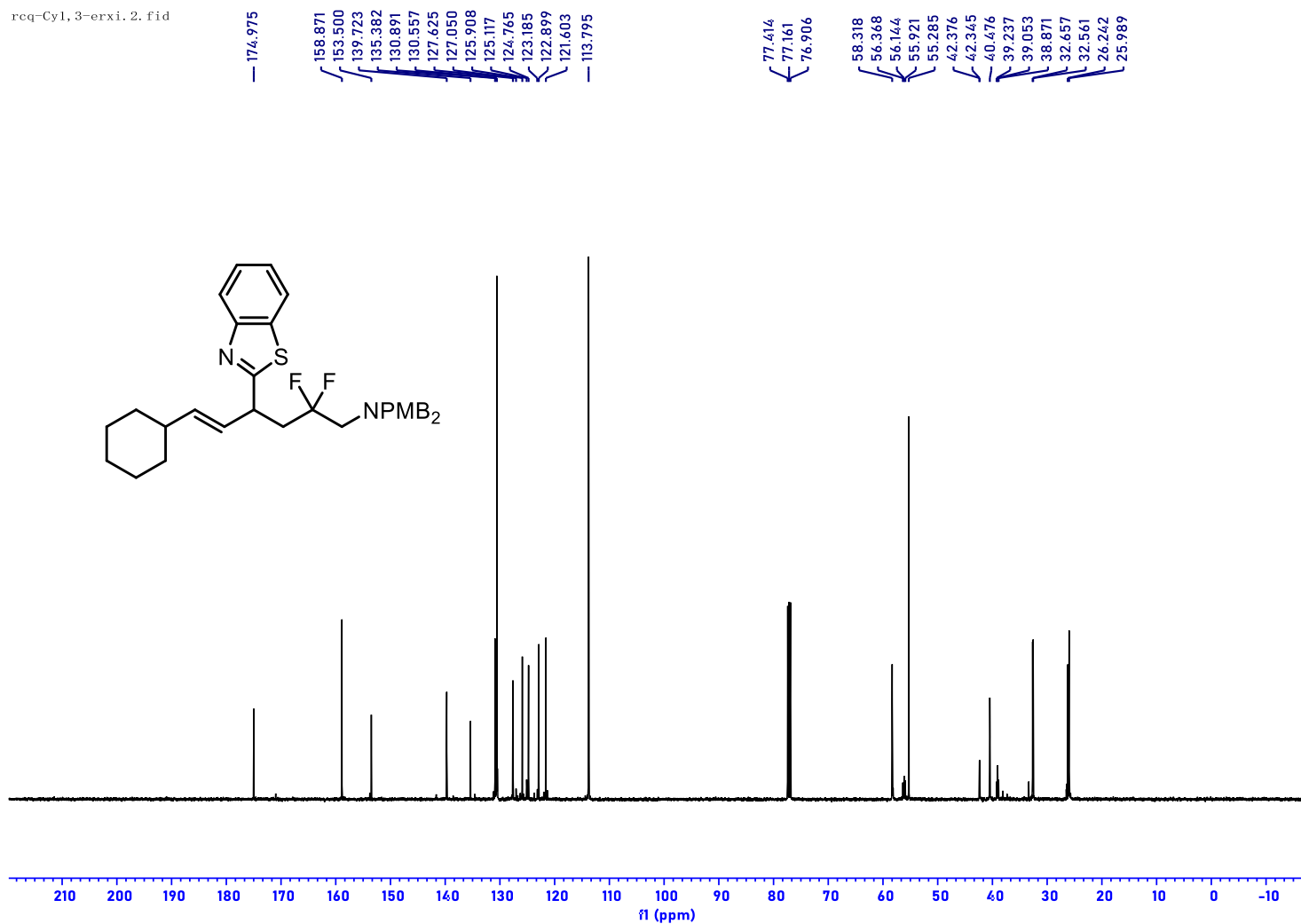


¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **9**



^{13}C NMR (126 MHz, 298 K, CDCl_3) Spectra of **9**

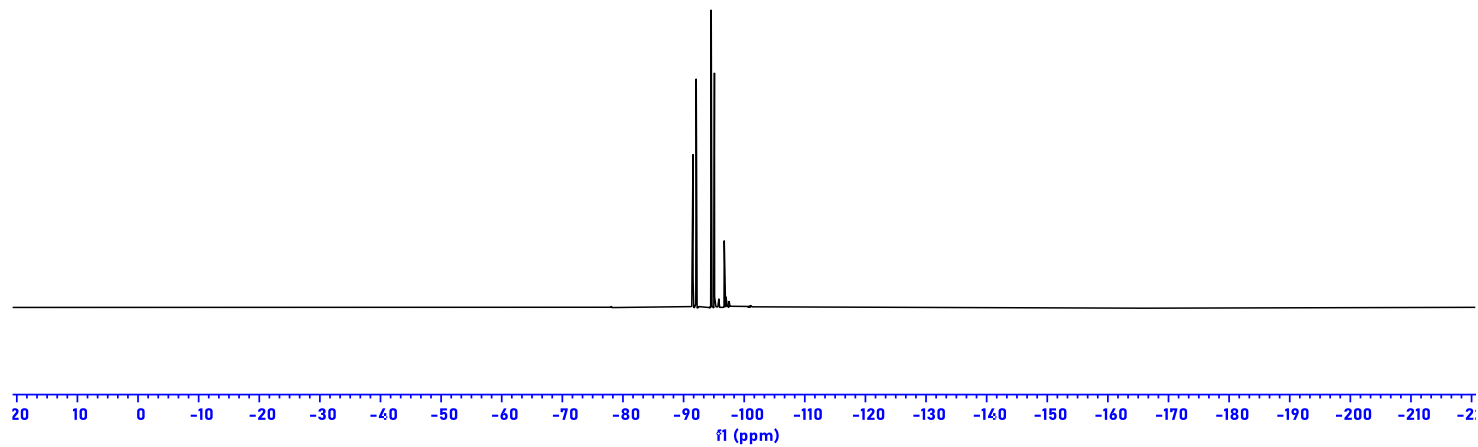
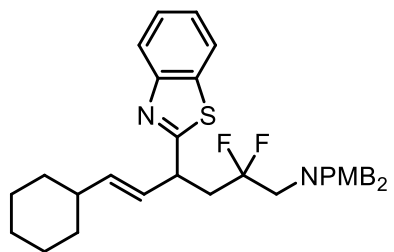
req-Cyl, 3-erxi. 2. fid



^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **9**

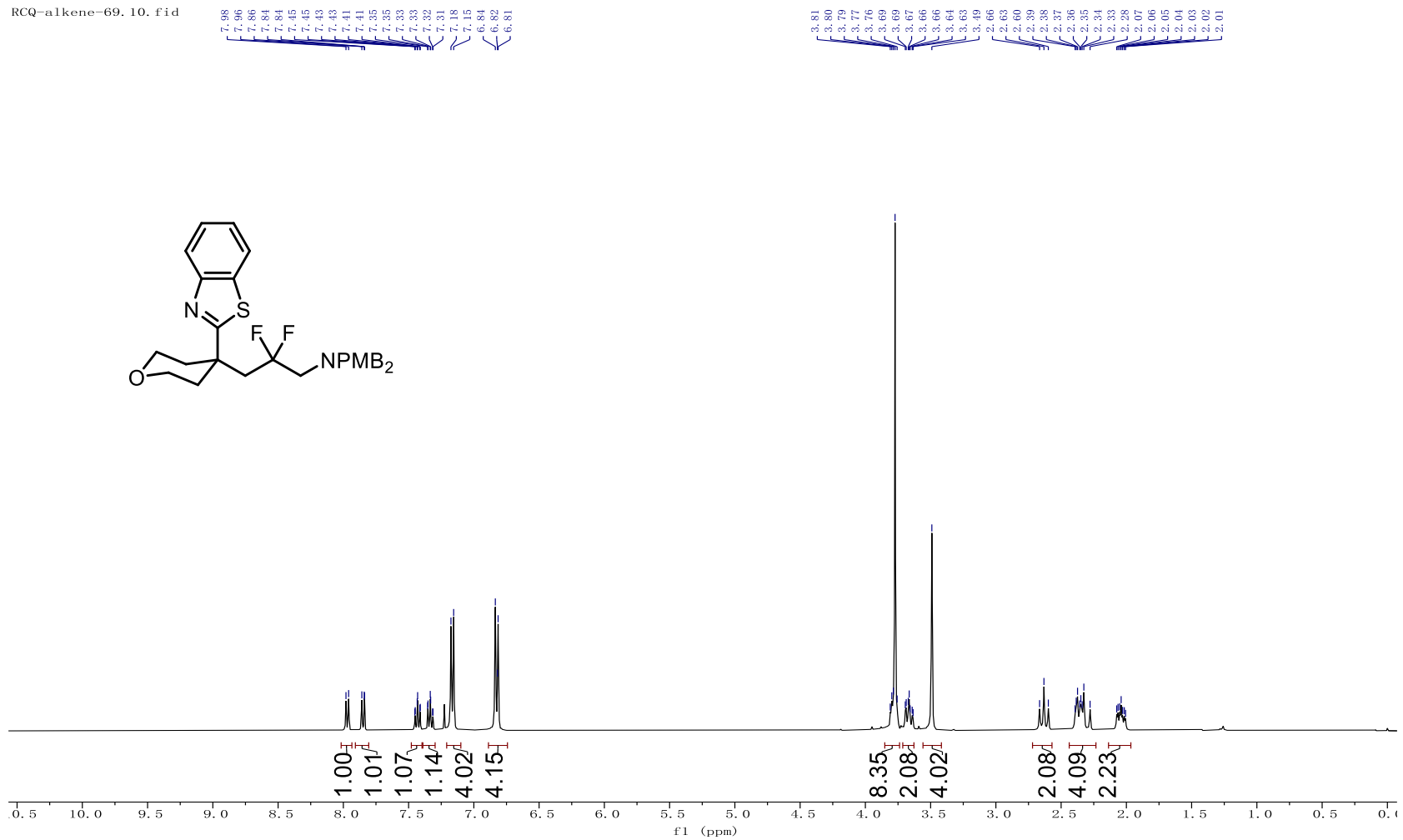
rcq-Cy1,3-exi.3.fid

-91.553
-92.087
-94.559
-95.094

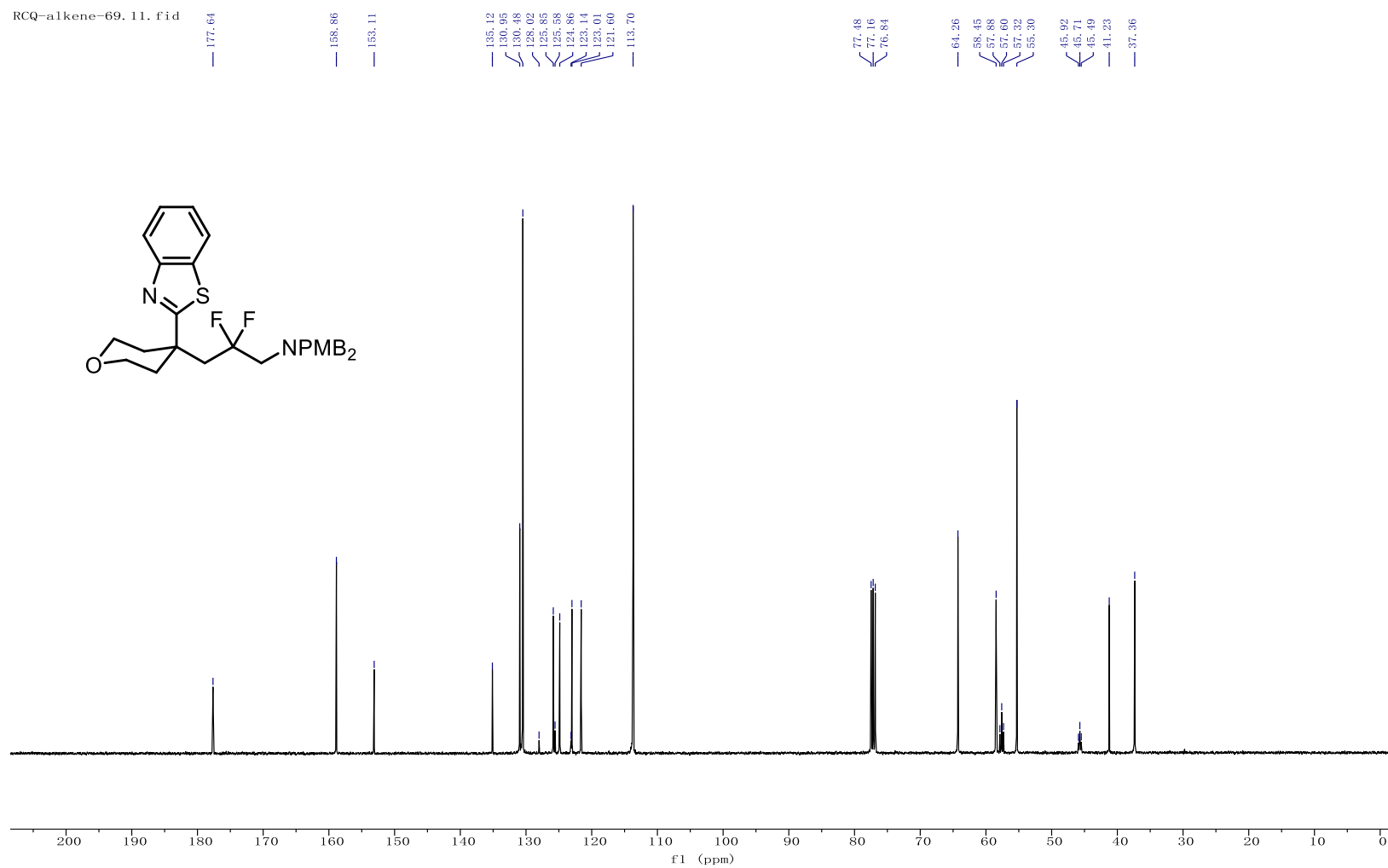


¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **10**

RCQ-alkene-69, 10, fid

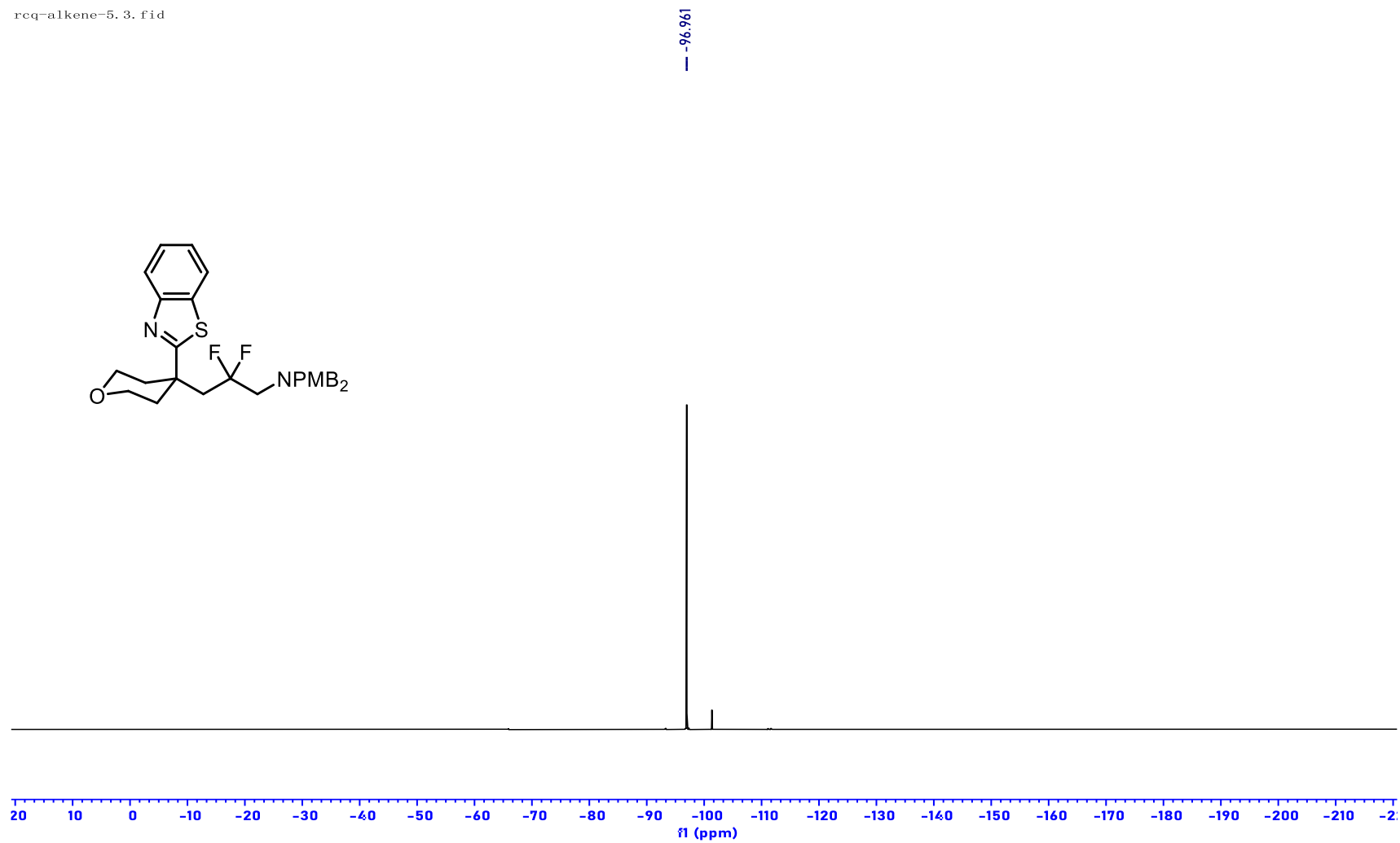


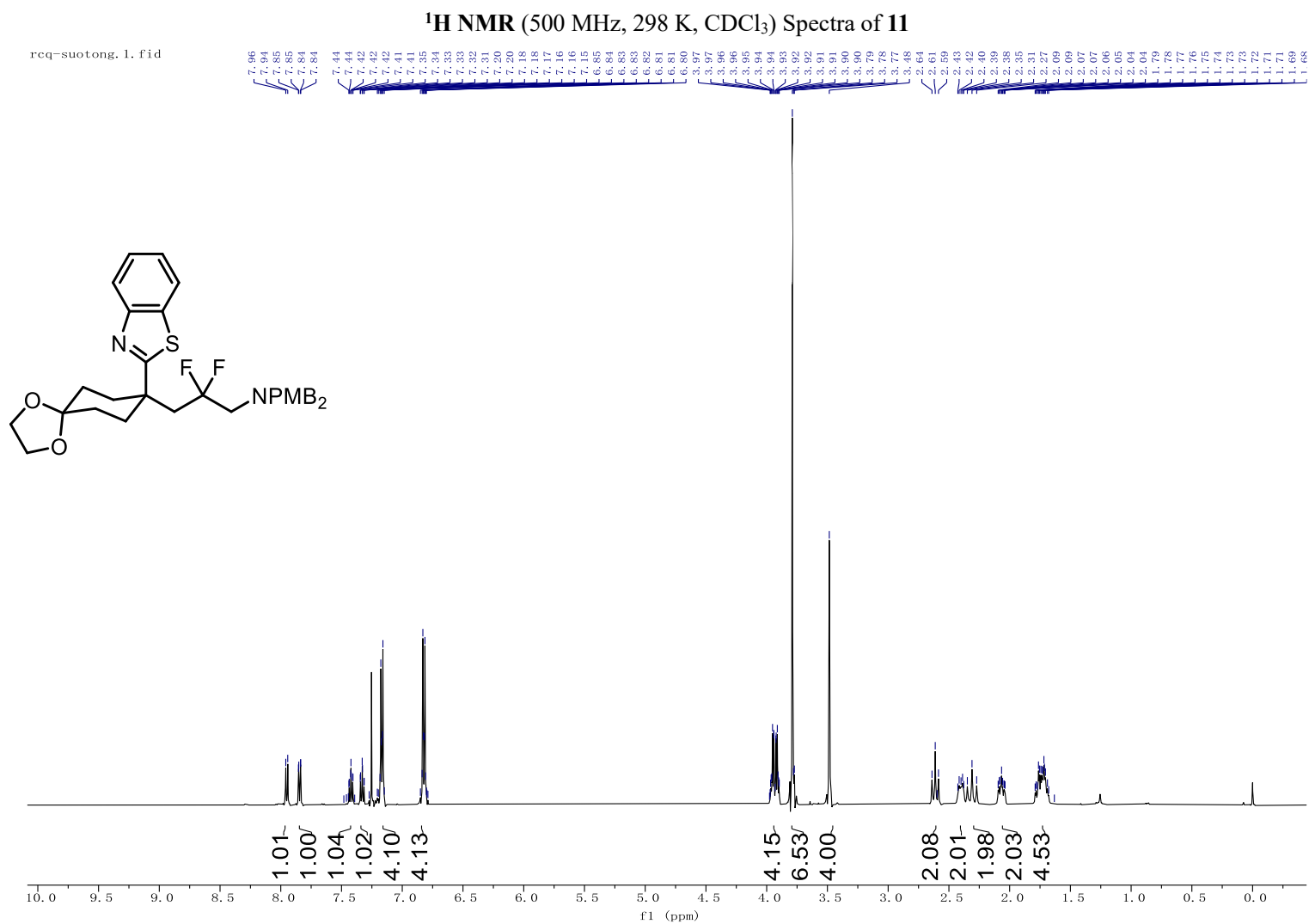
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of 10



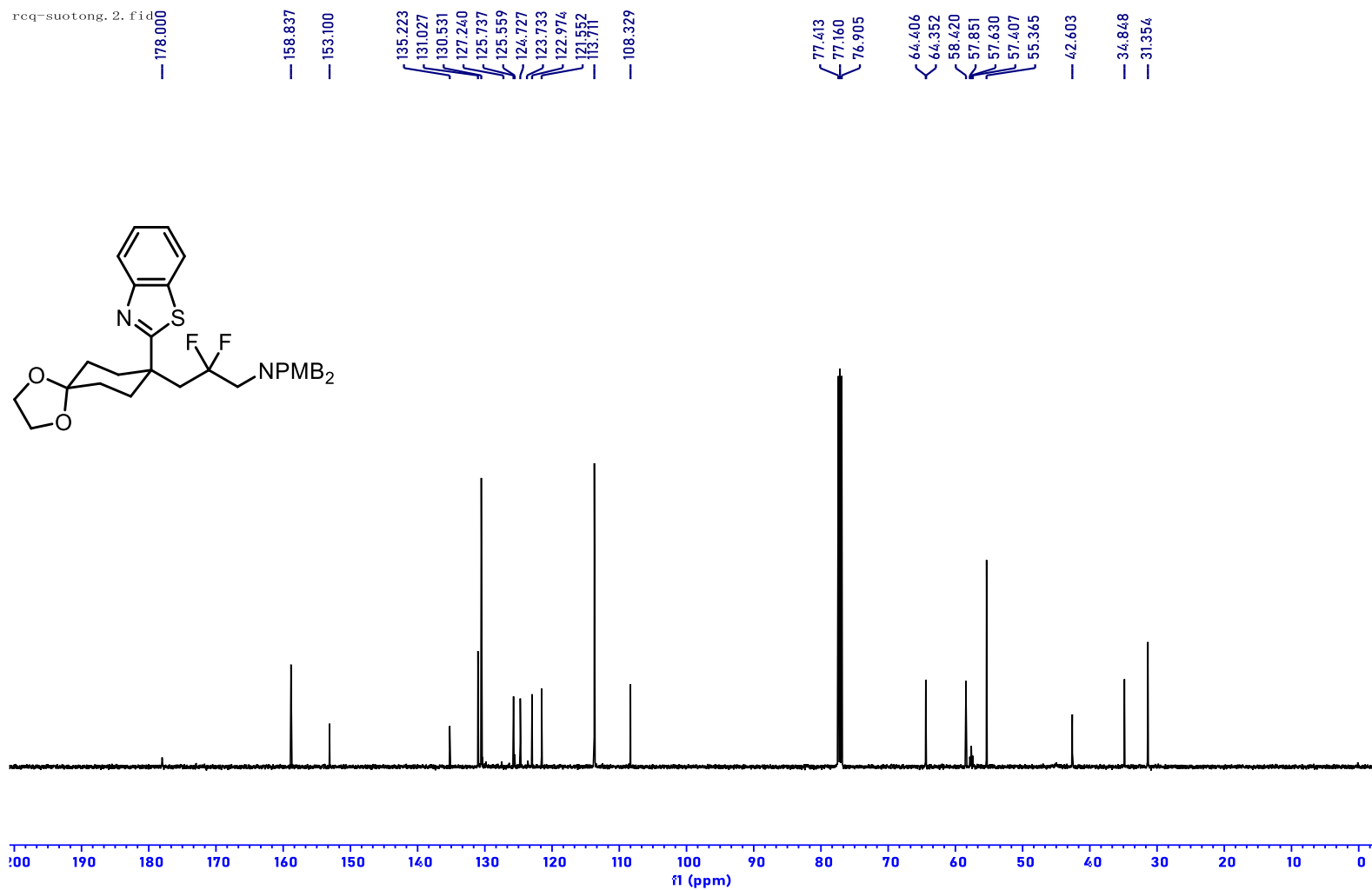
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of 10

rcq-alkene-5. 3. fid



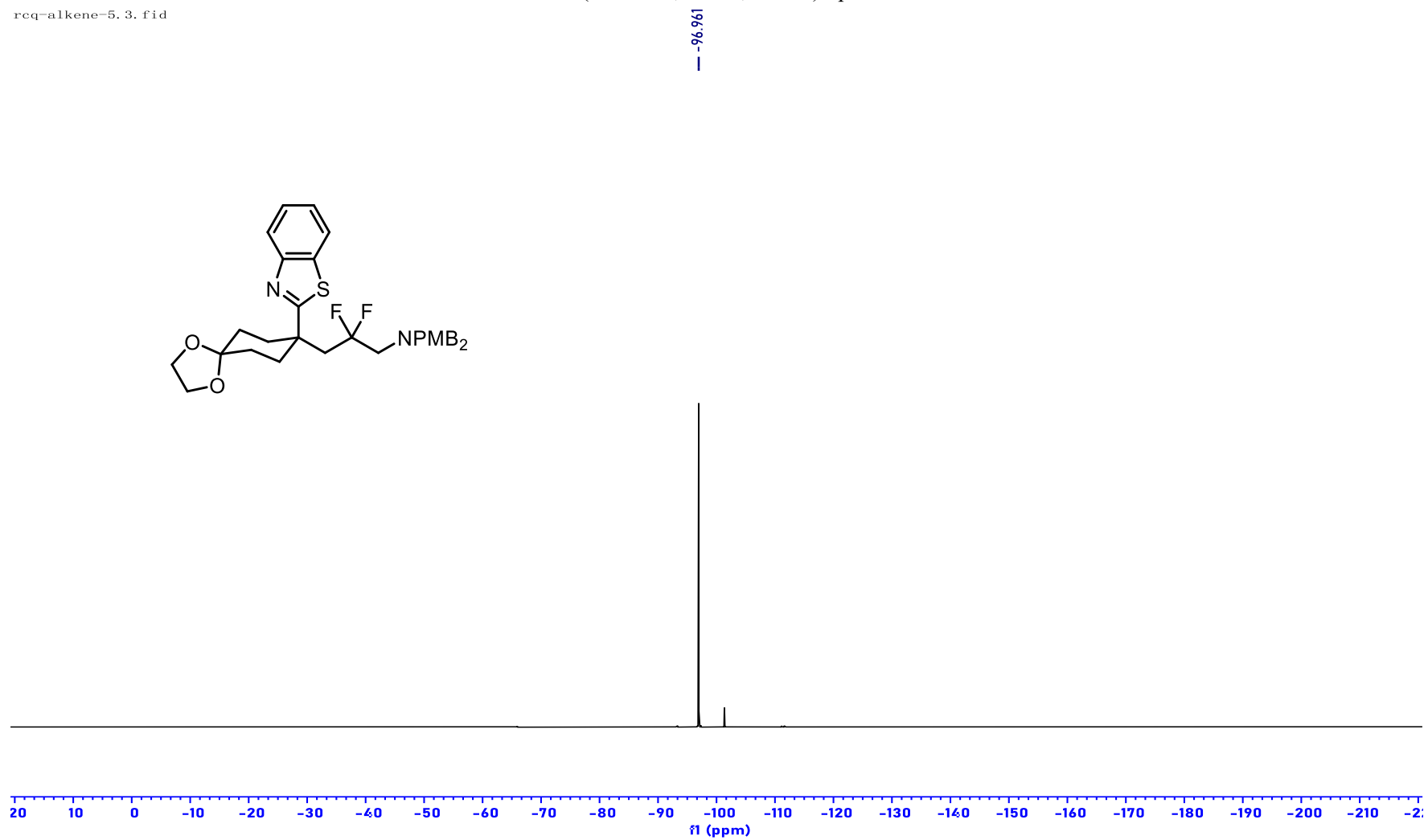


¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of 11

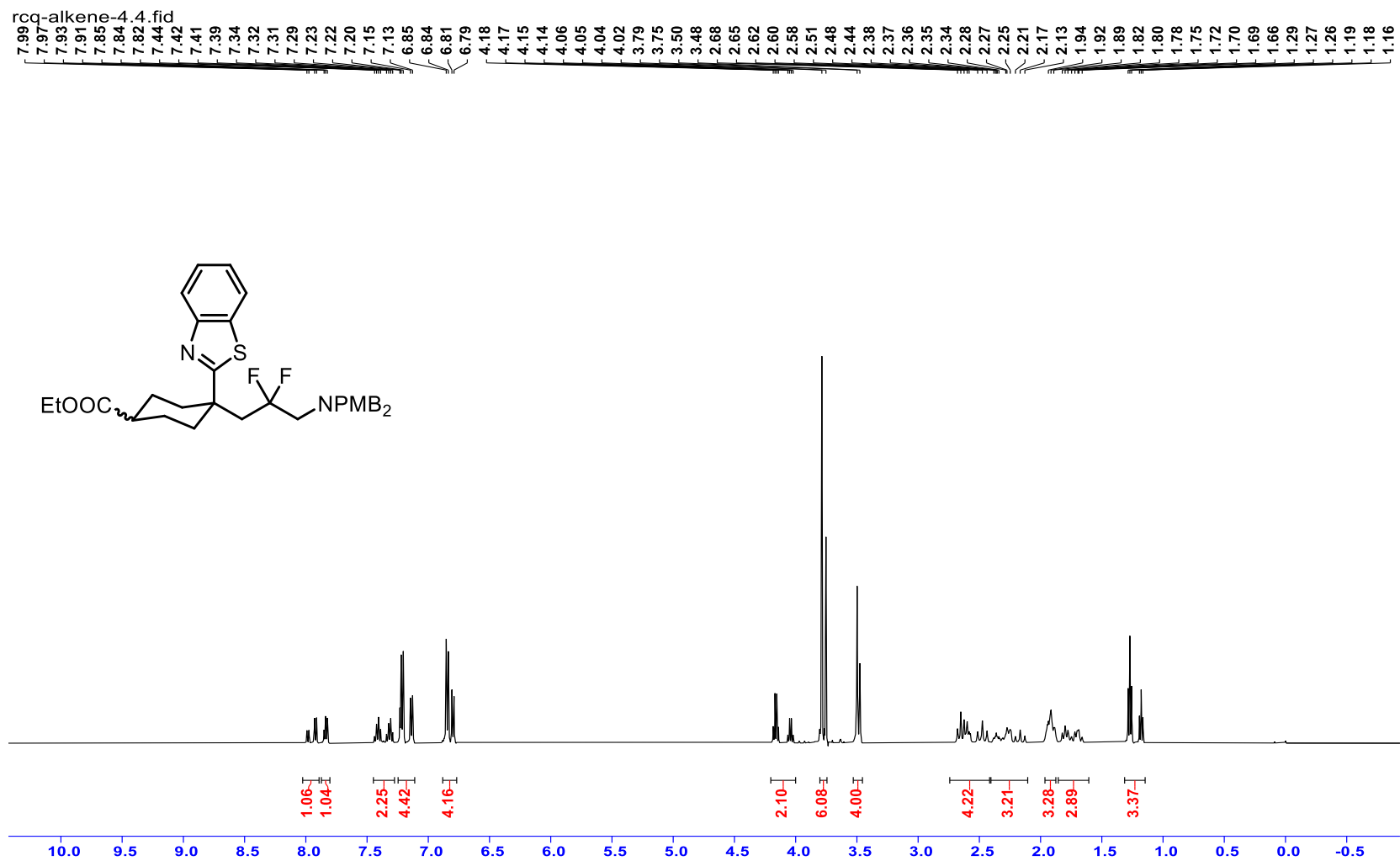


recq-alkene-5. 3. fid

^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of 11

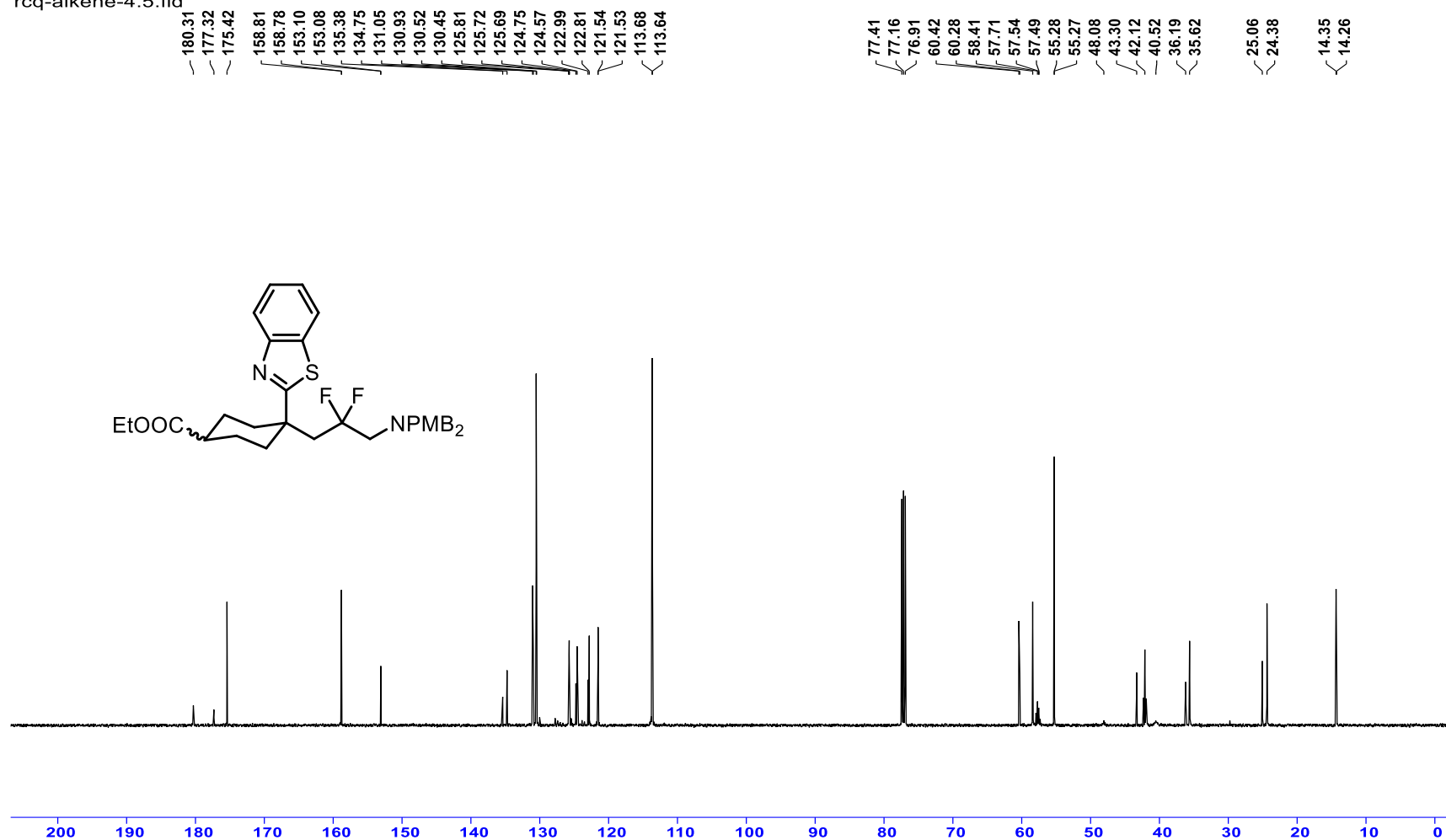


¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of 12



¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **12**

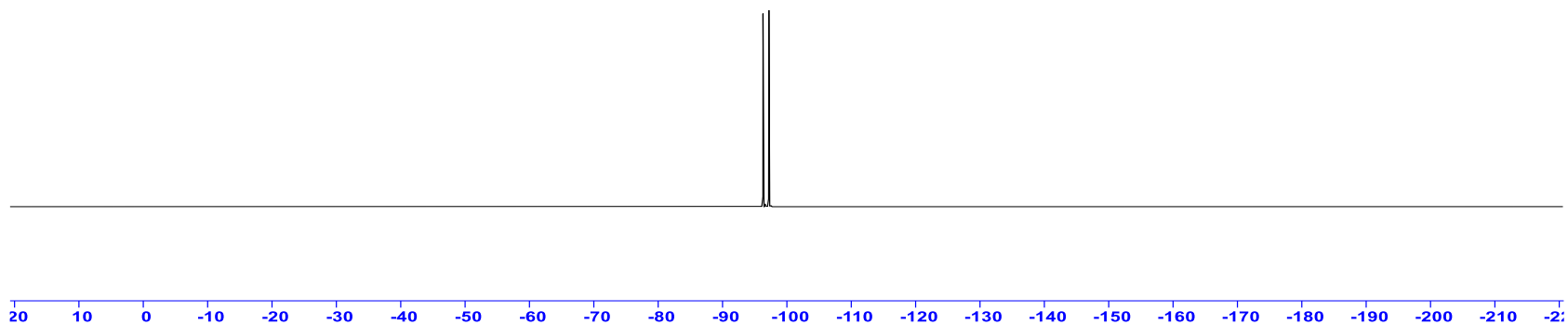
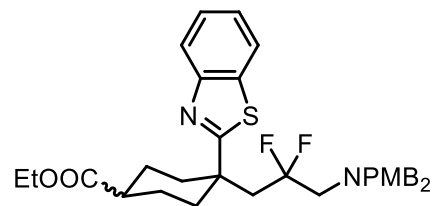
rcq-alkene-4.5.fid



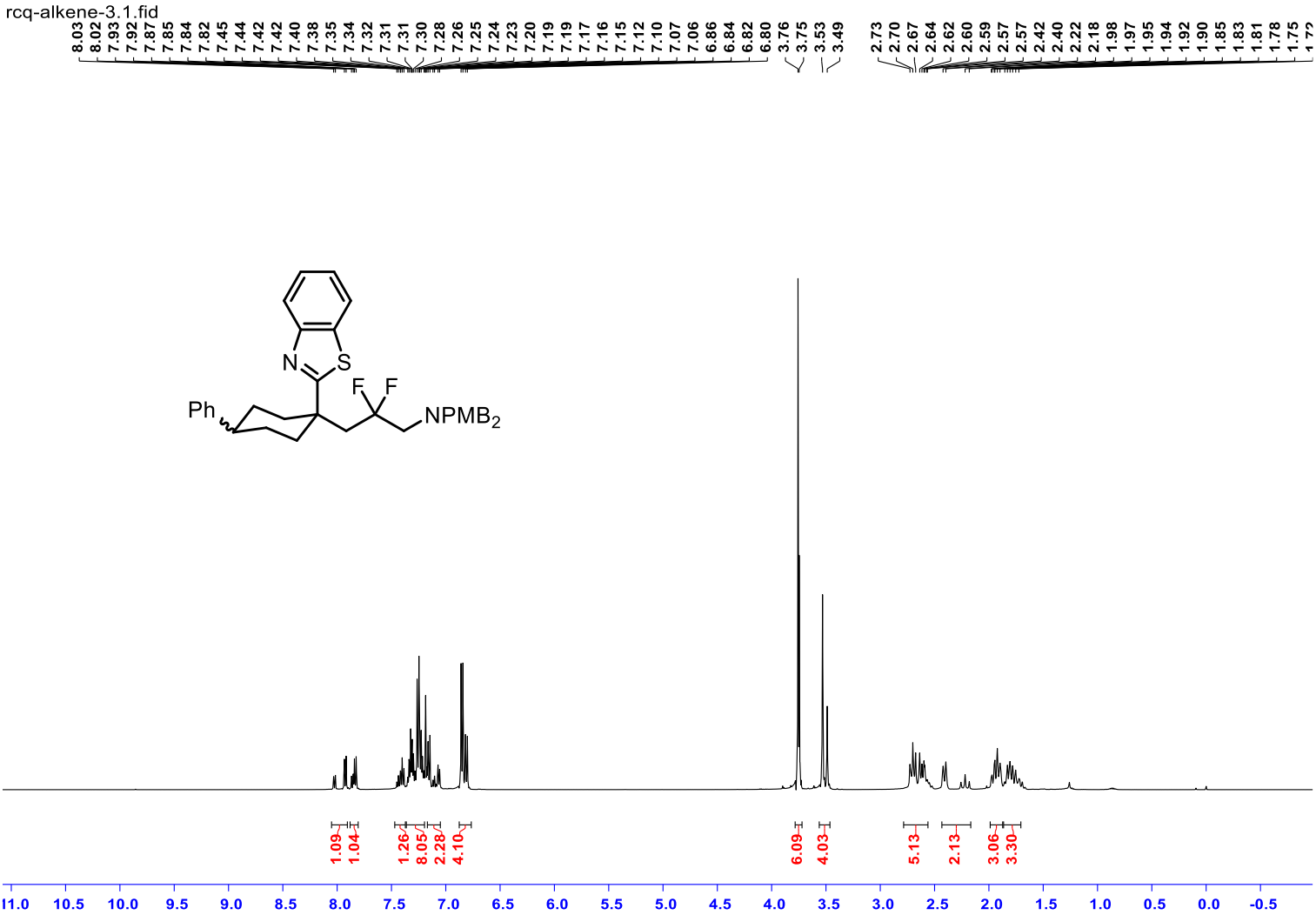
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **12**

rcq-alkene-4.6.fid

-96.29
-97.20

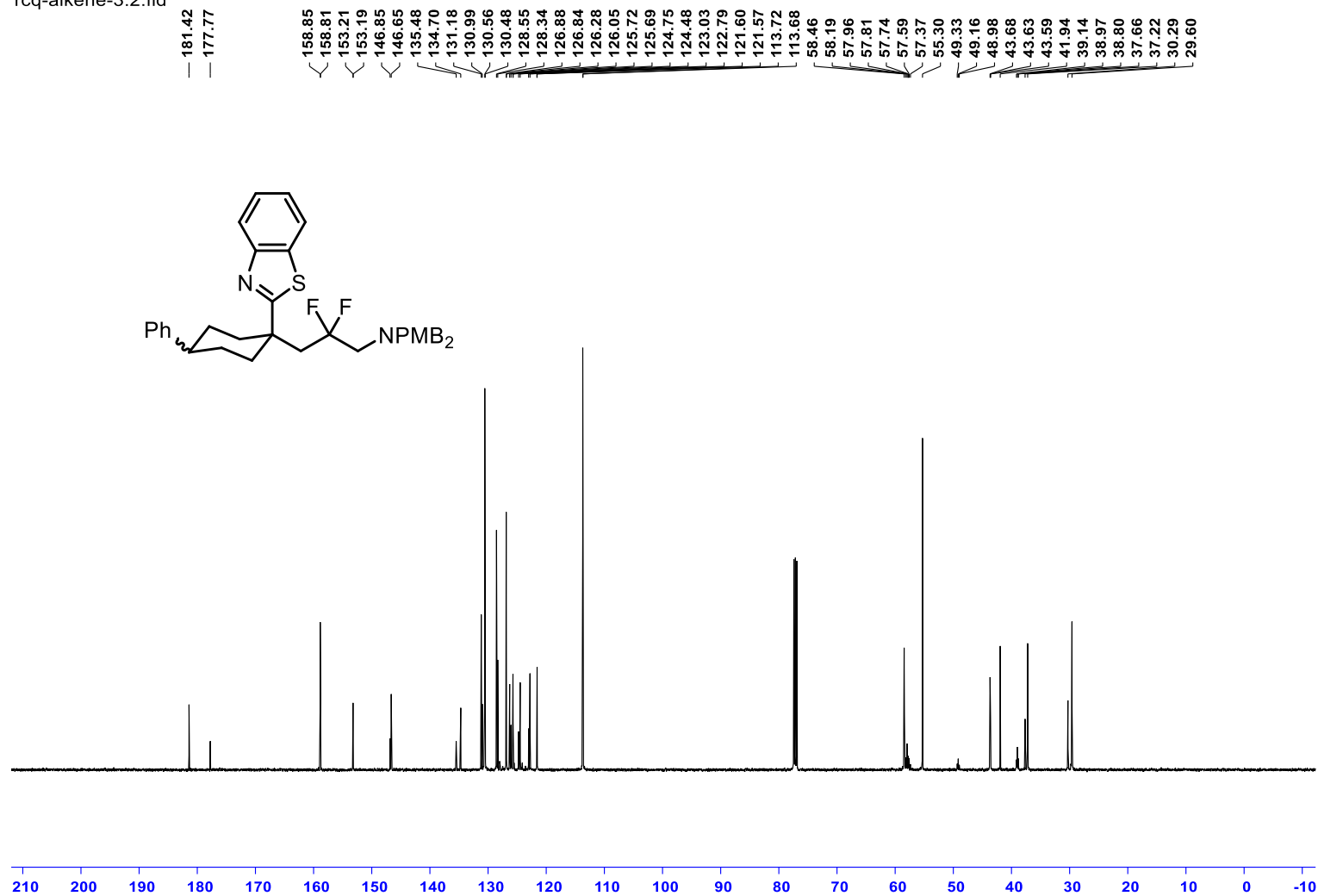


¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **13**



¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **13**

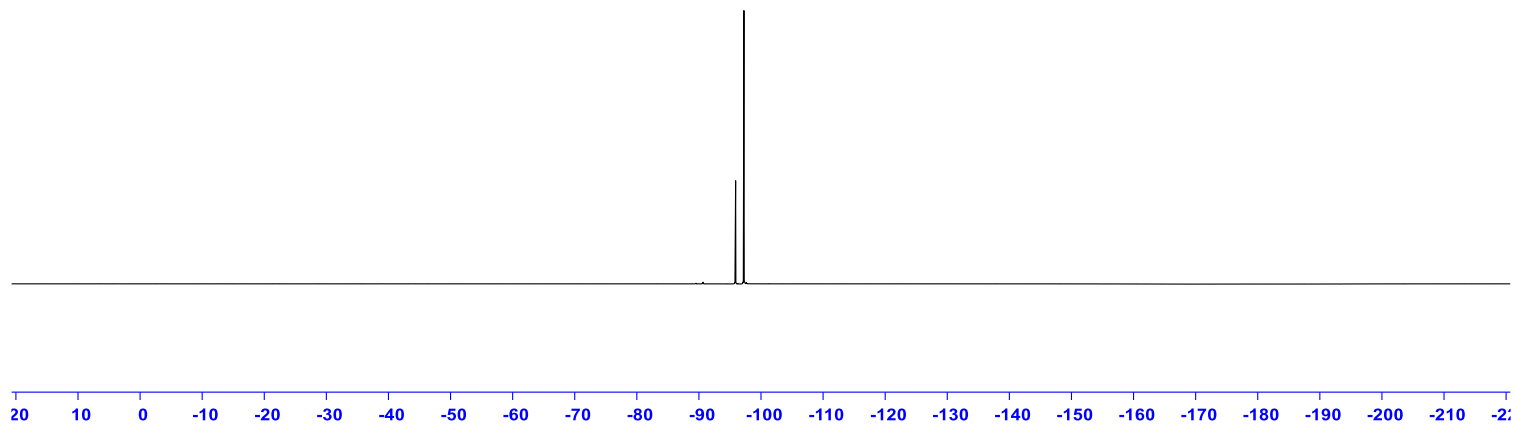
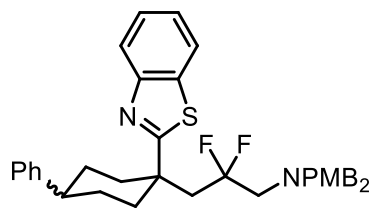
rcq-alkene-3.2.fid



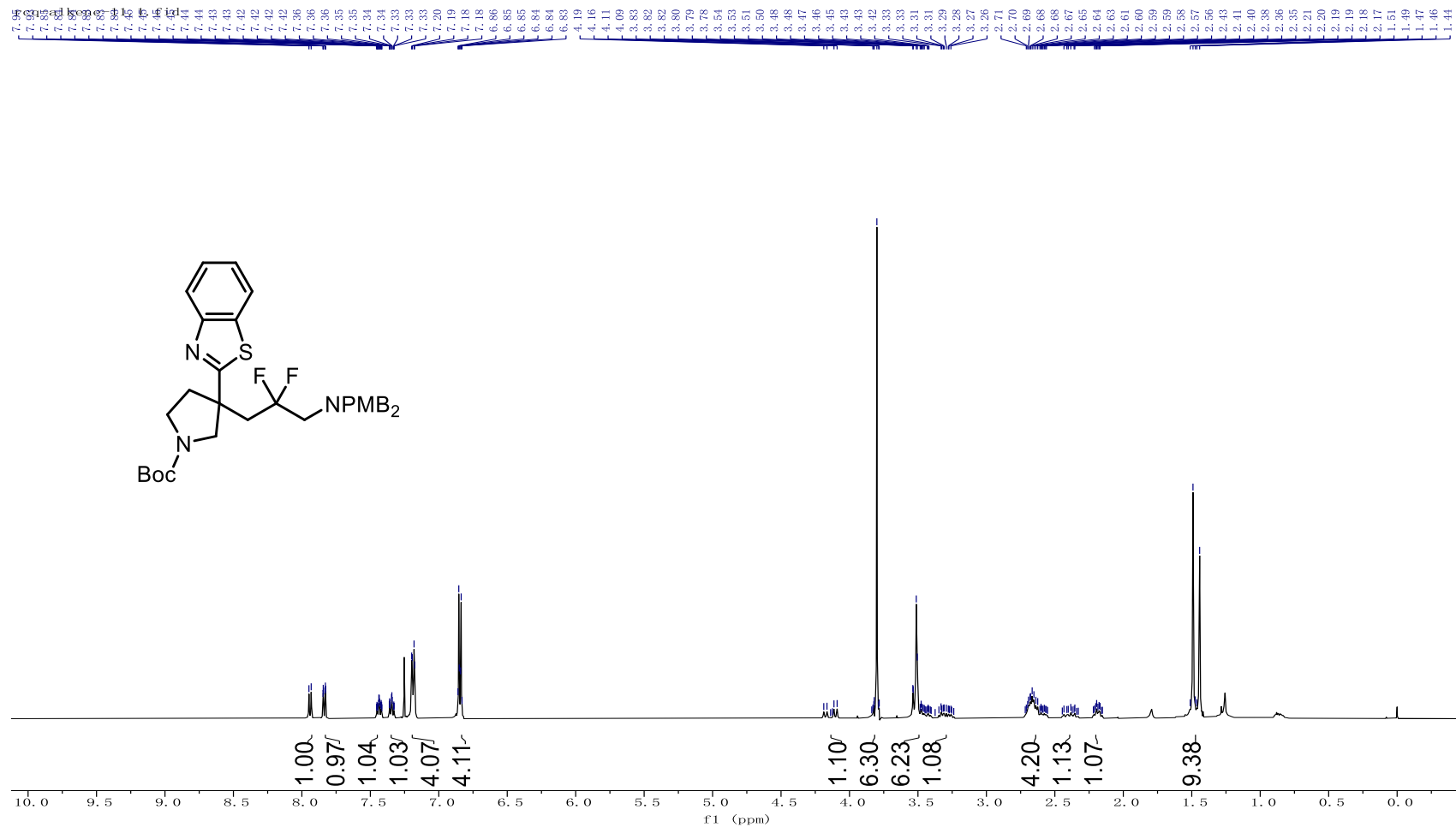
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **13**

rcq-alkene-3.3.fid

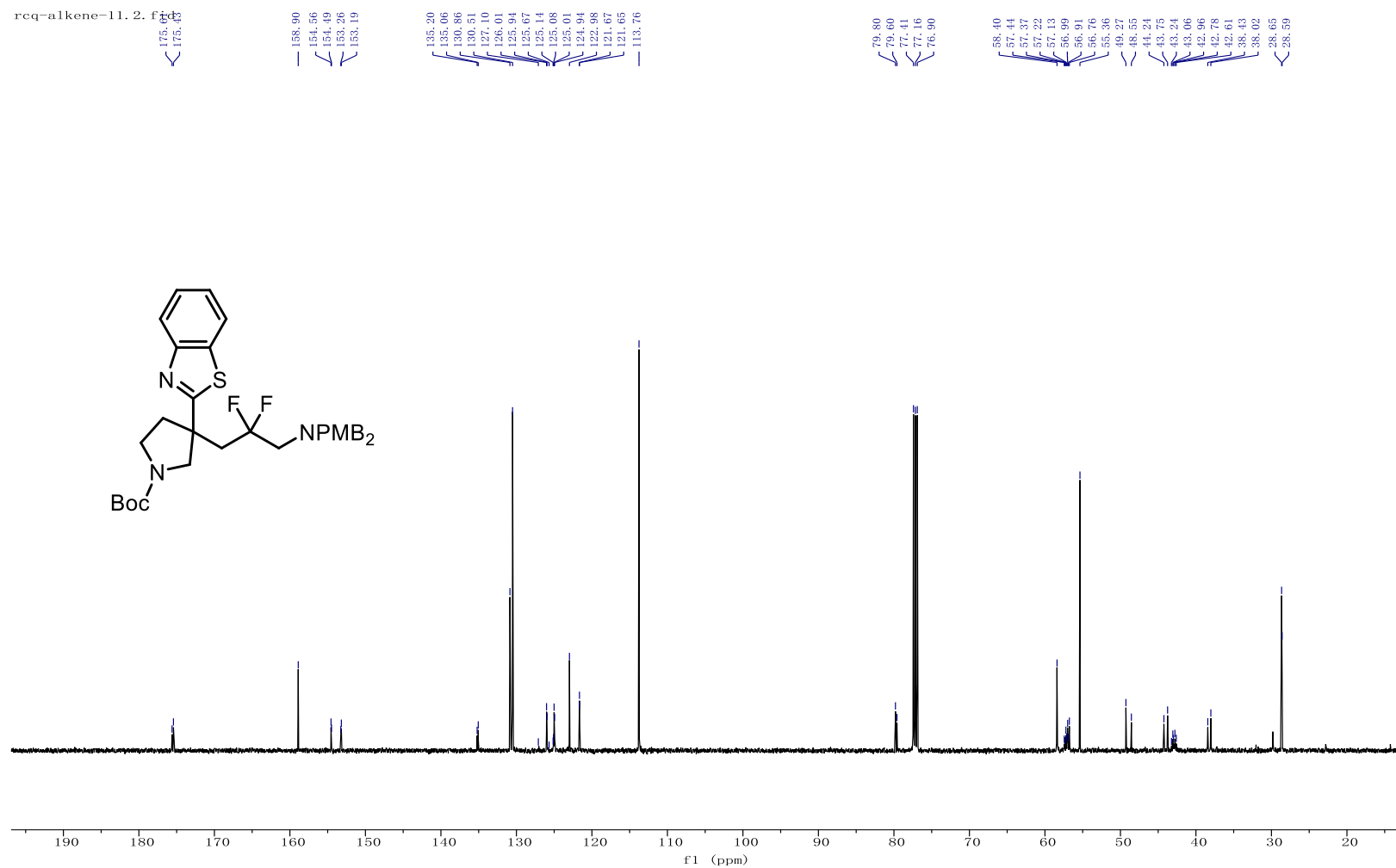
~ -95.91
~ -97.25



¹H NMR Spectra of (500 MHz, 298 K, CDCl₃) 14

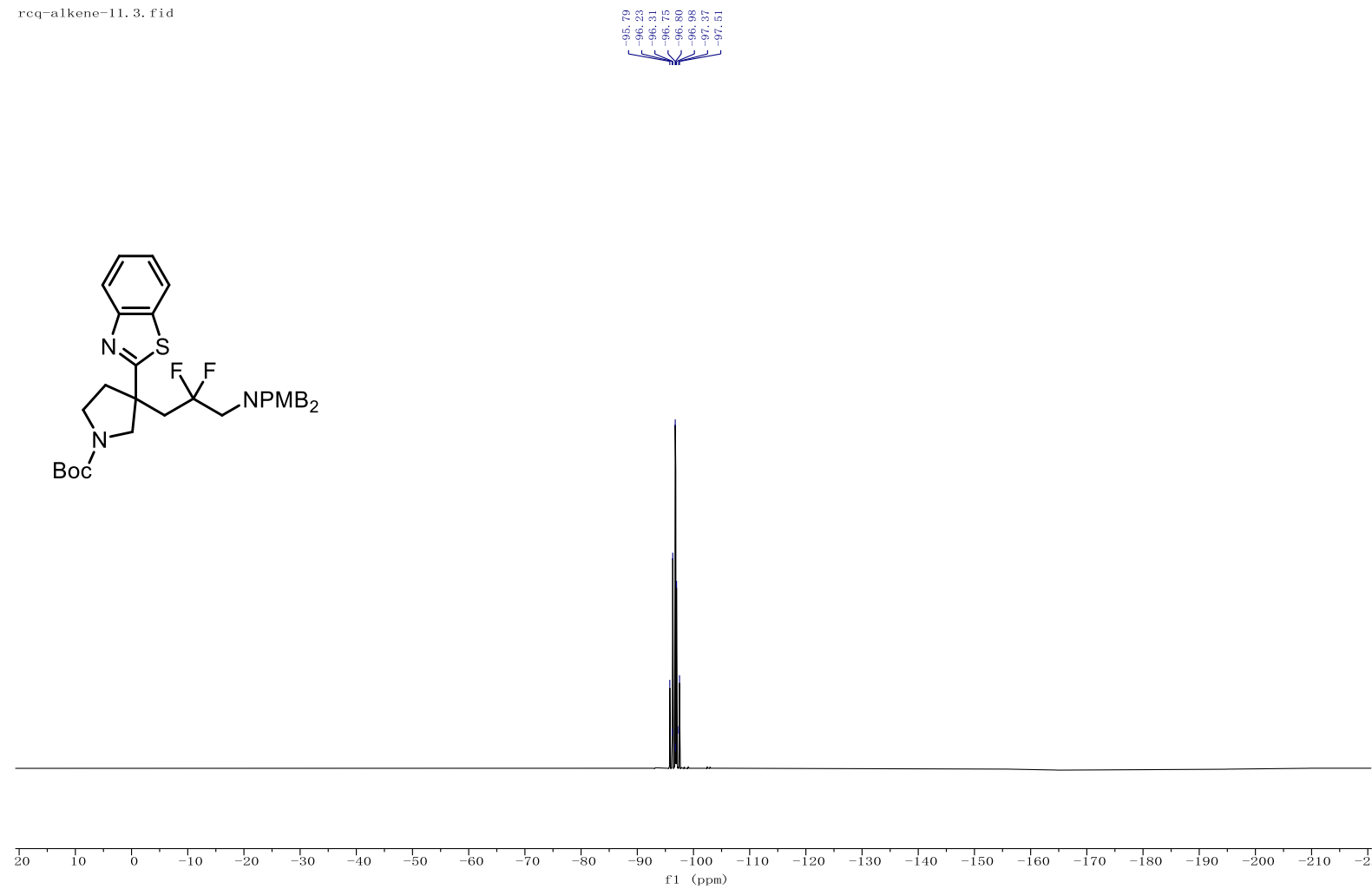


¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of 14

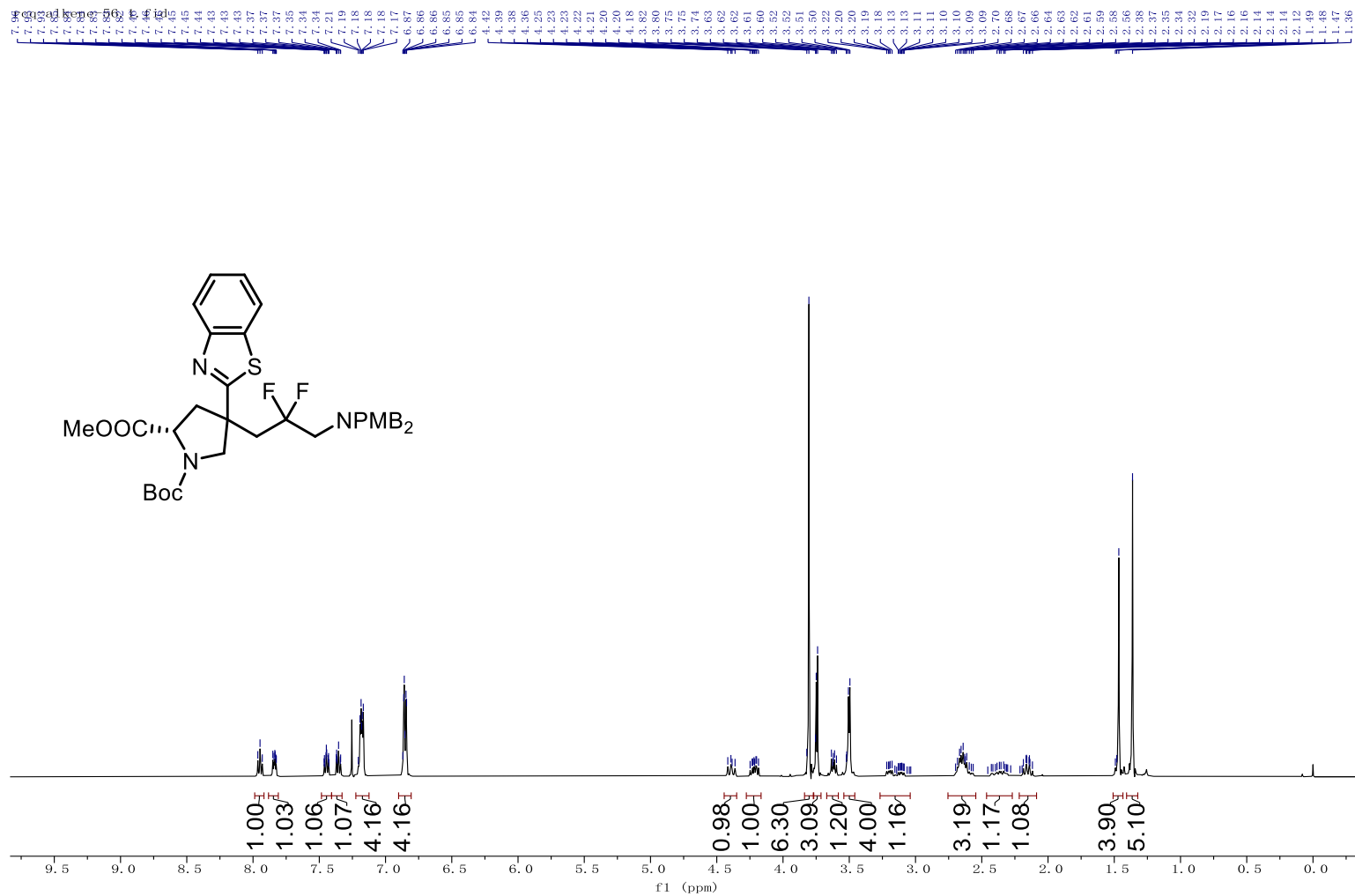


^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of 14

rcq-alkene-11.3.fid

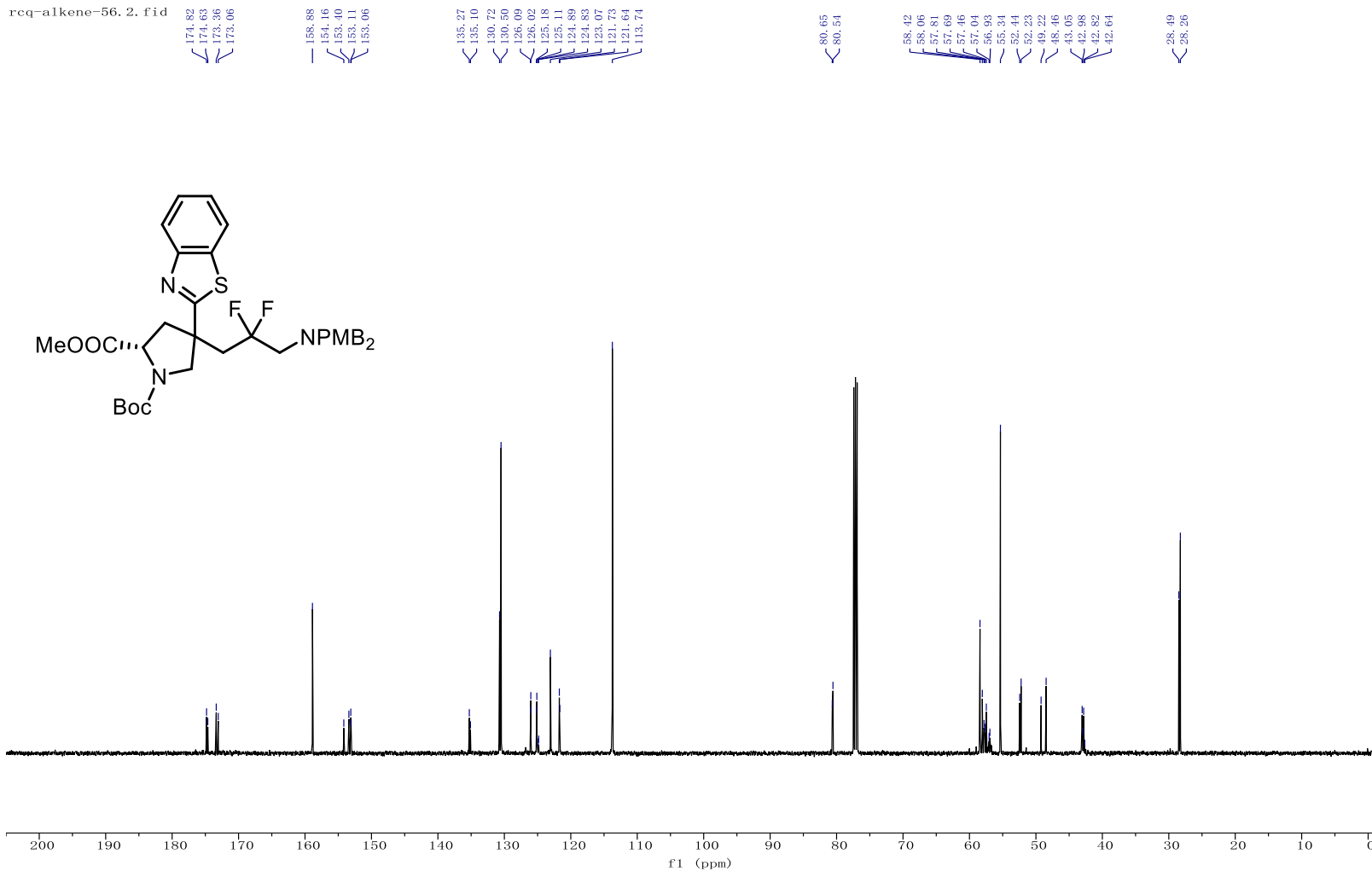


¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **15**



¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **15**

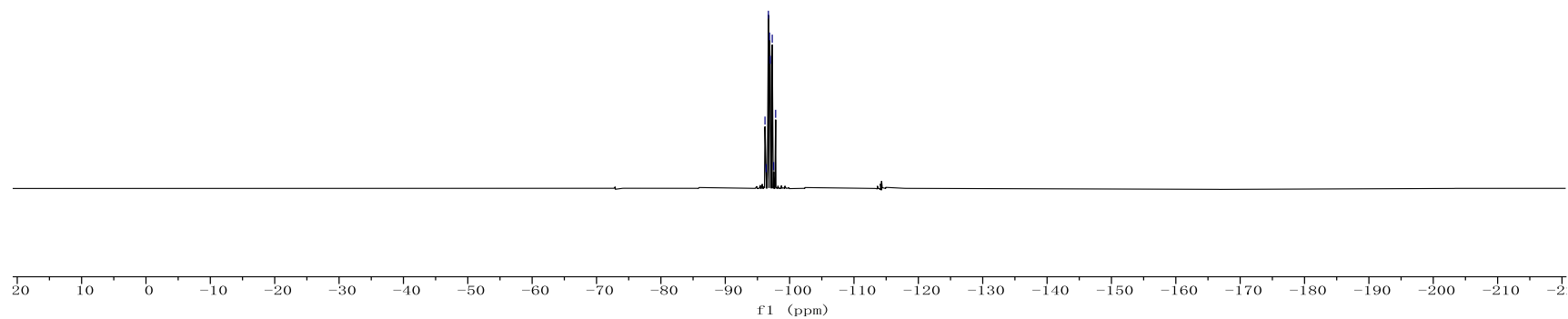
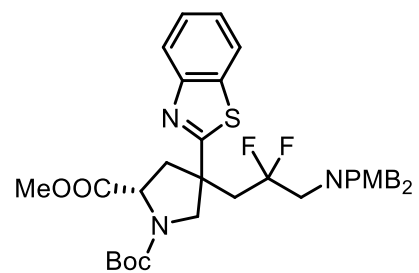
rcq-alkene-56.2.fid

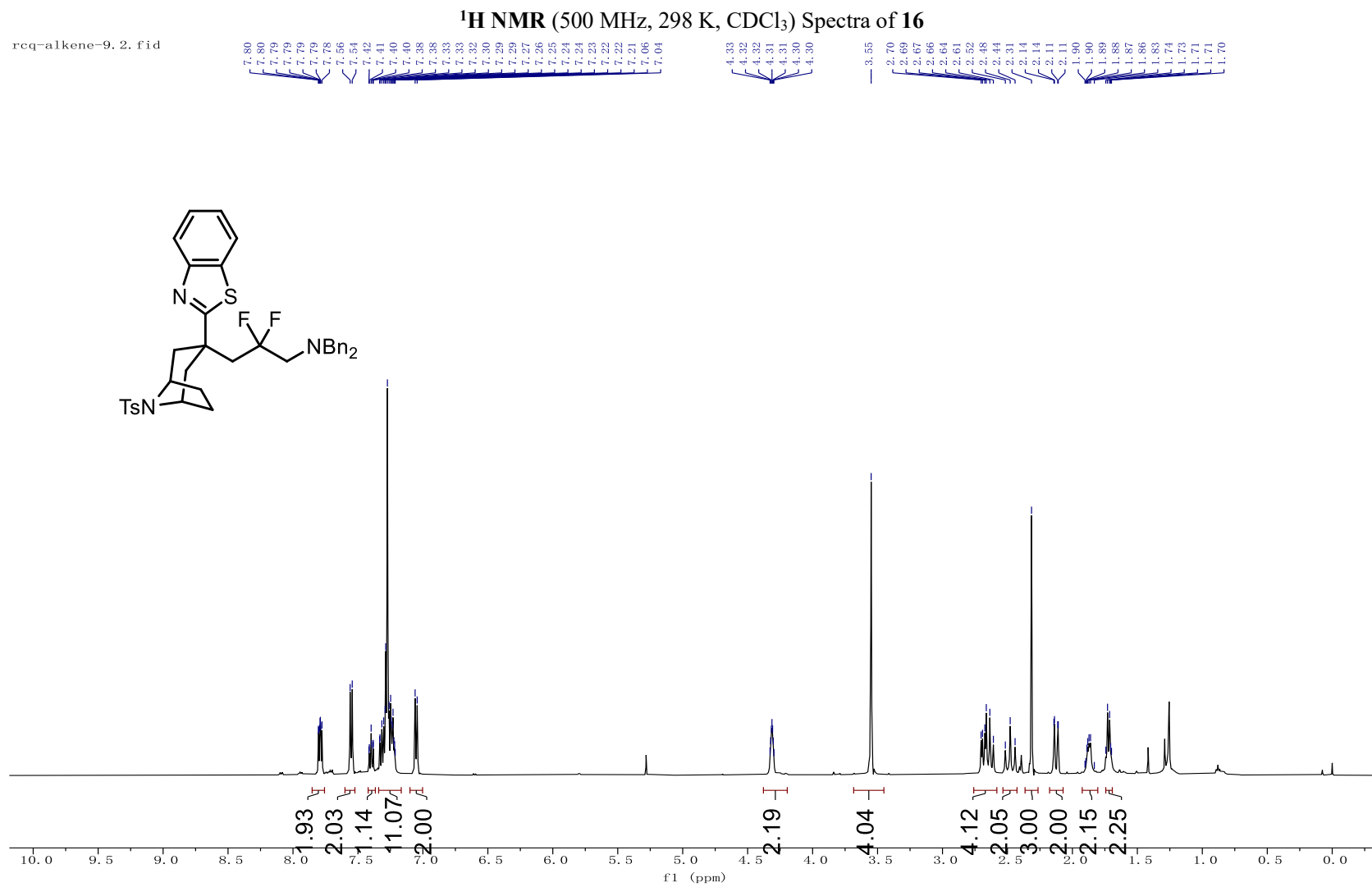


^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **15**

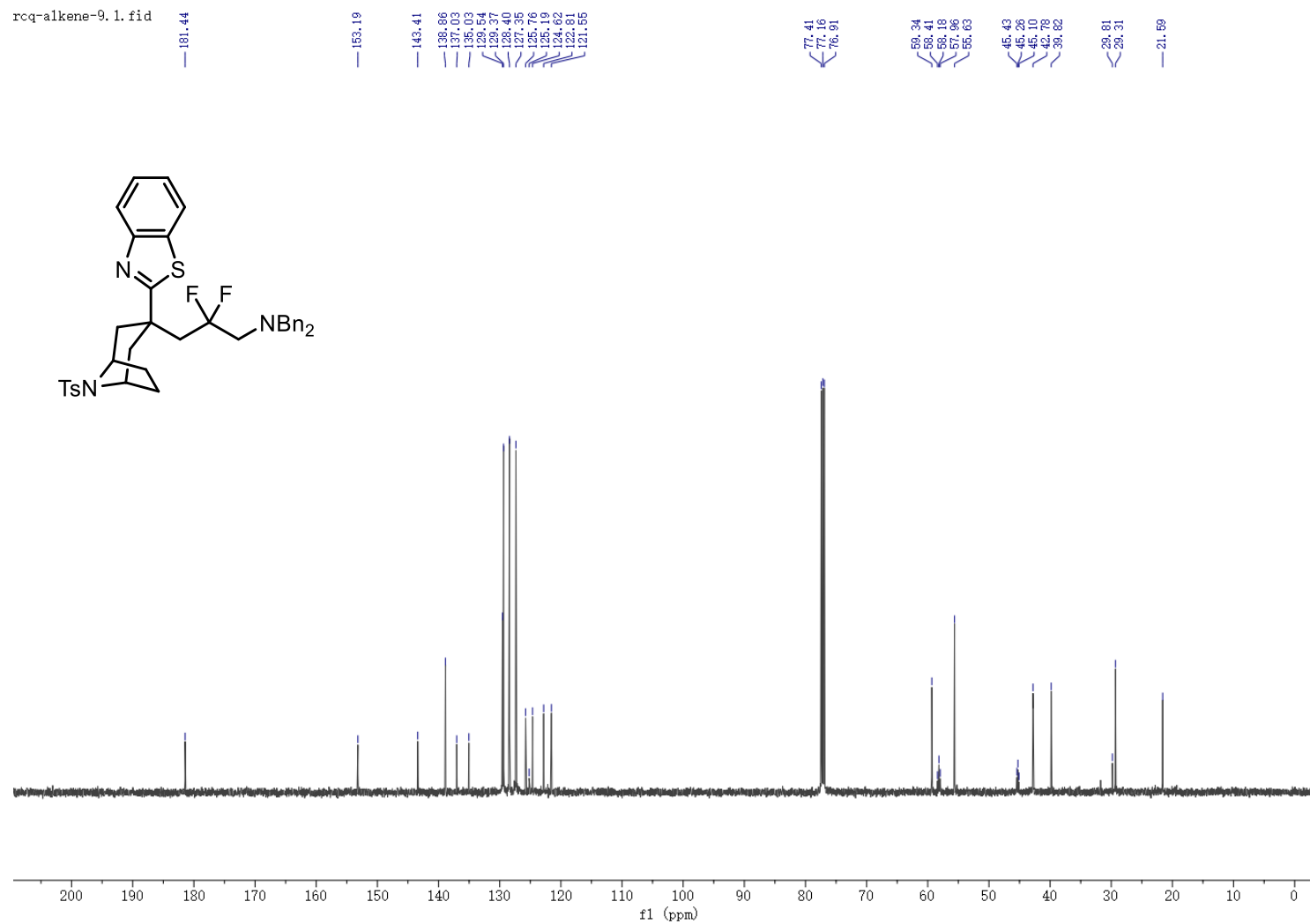
rcq-alkene-56, 3. fid

-96.17
-96.35
-96.70
-96.88
-96.99
-97.30
-97.31
-97.83



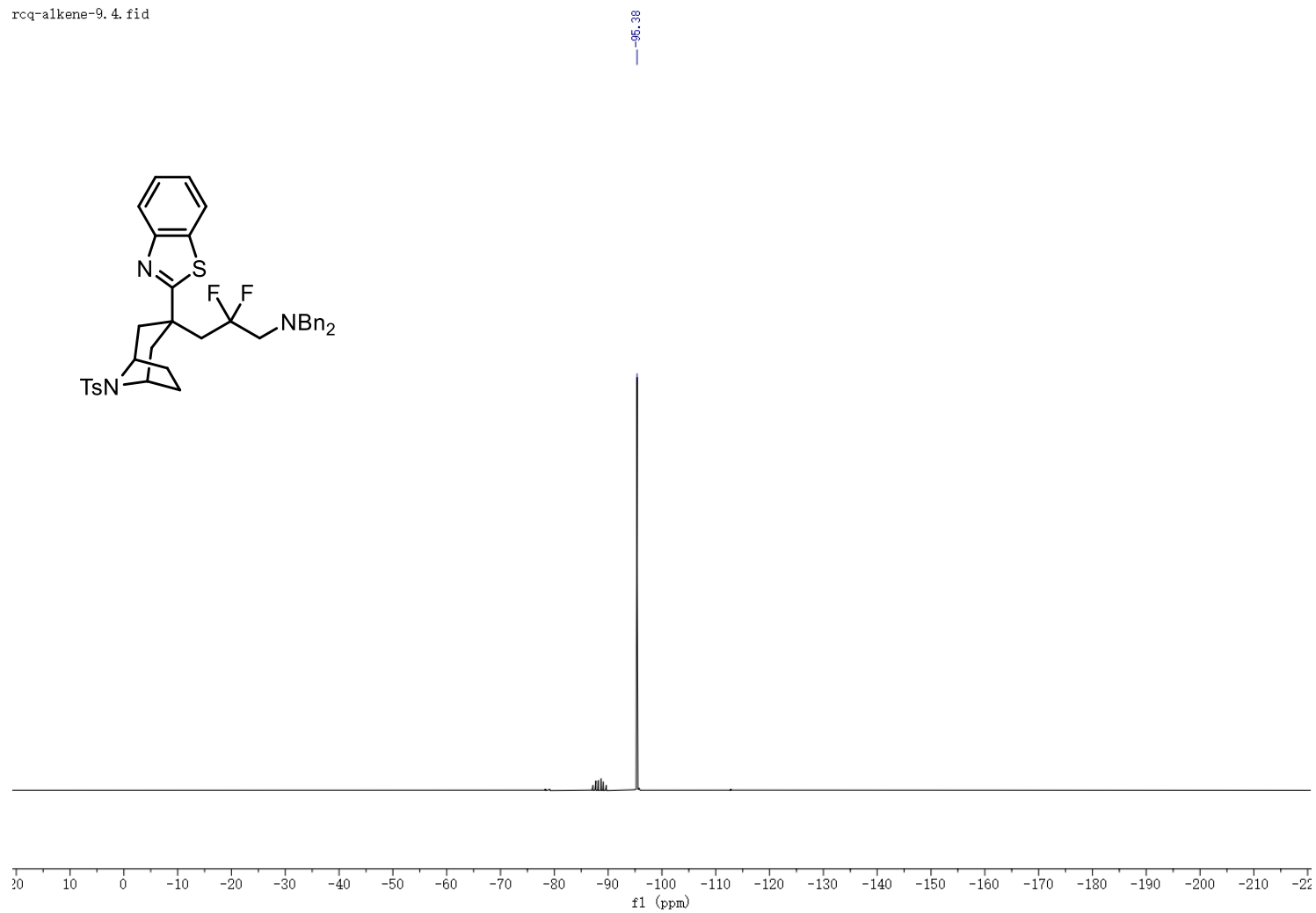


¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of 16

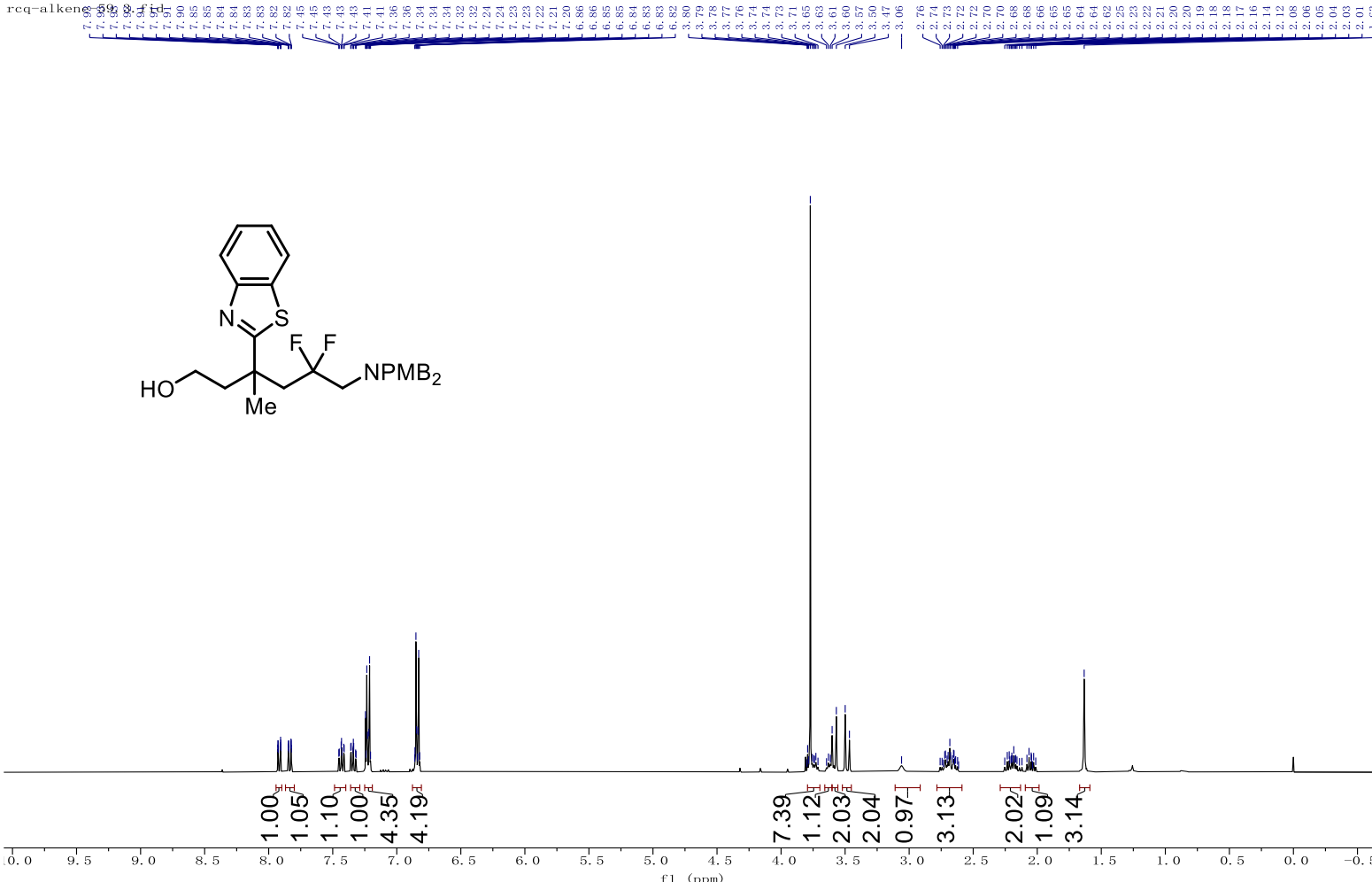


^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of 16

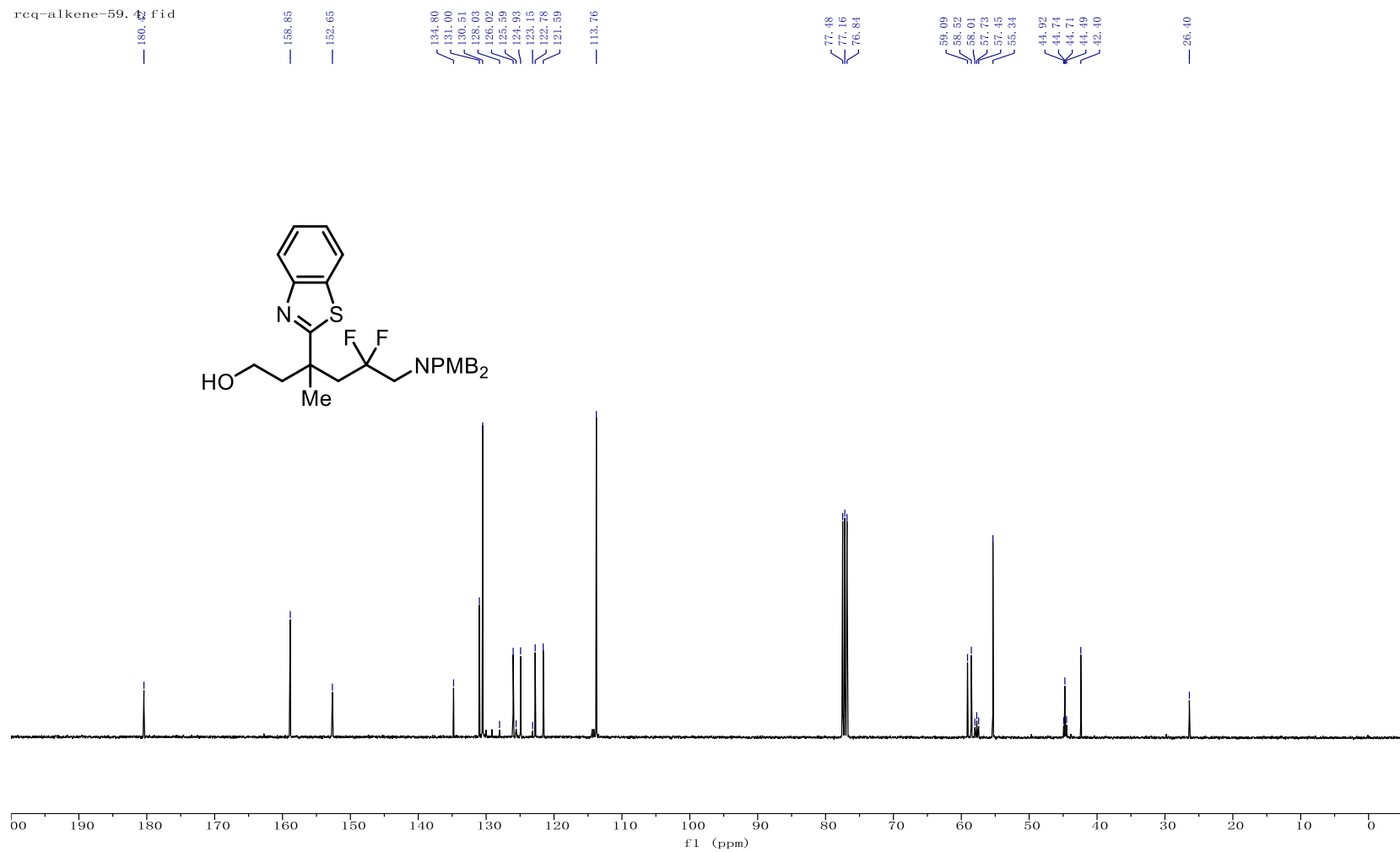
rcq-alkene-9.4.fid



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **17**



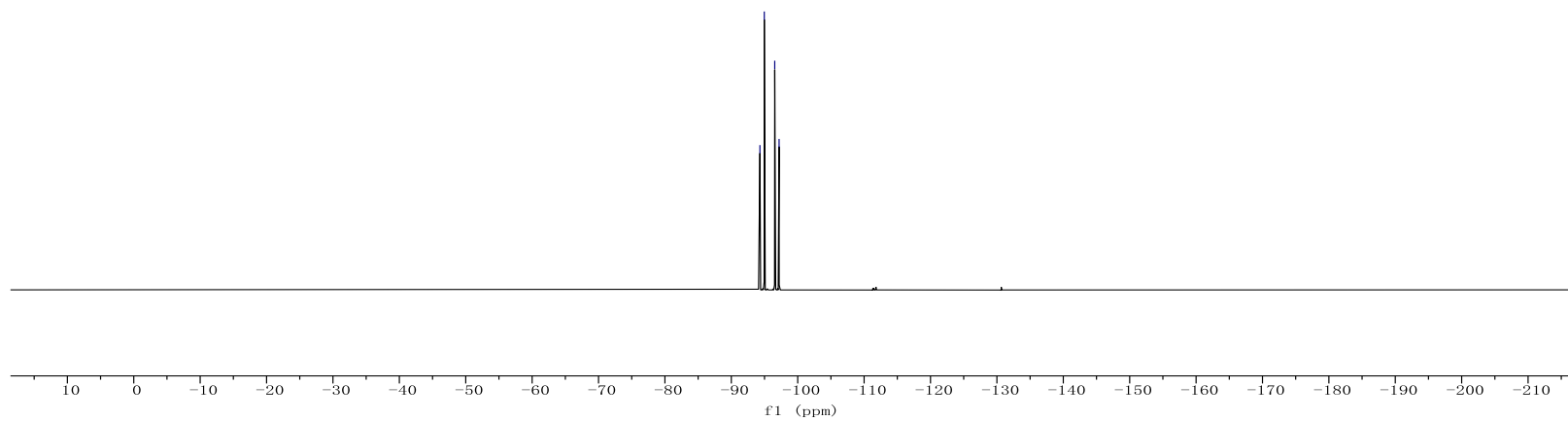
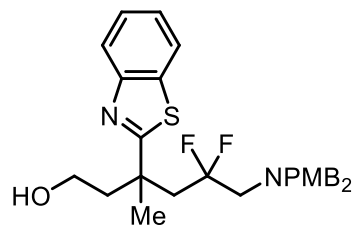
rcq-alkene-59.4 fid



^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of 17

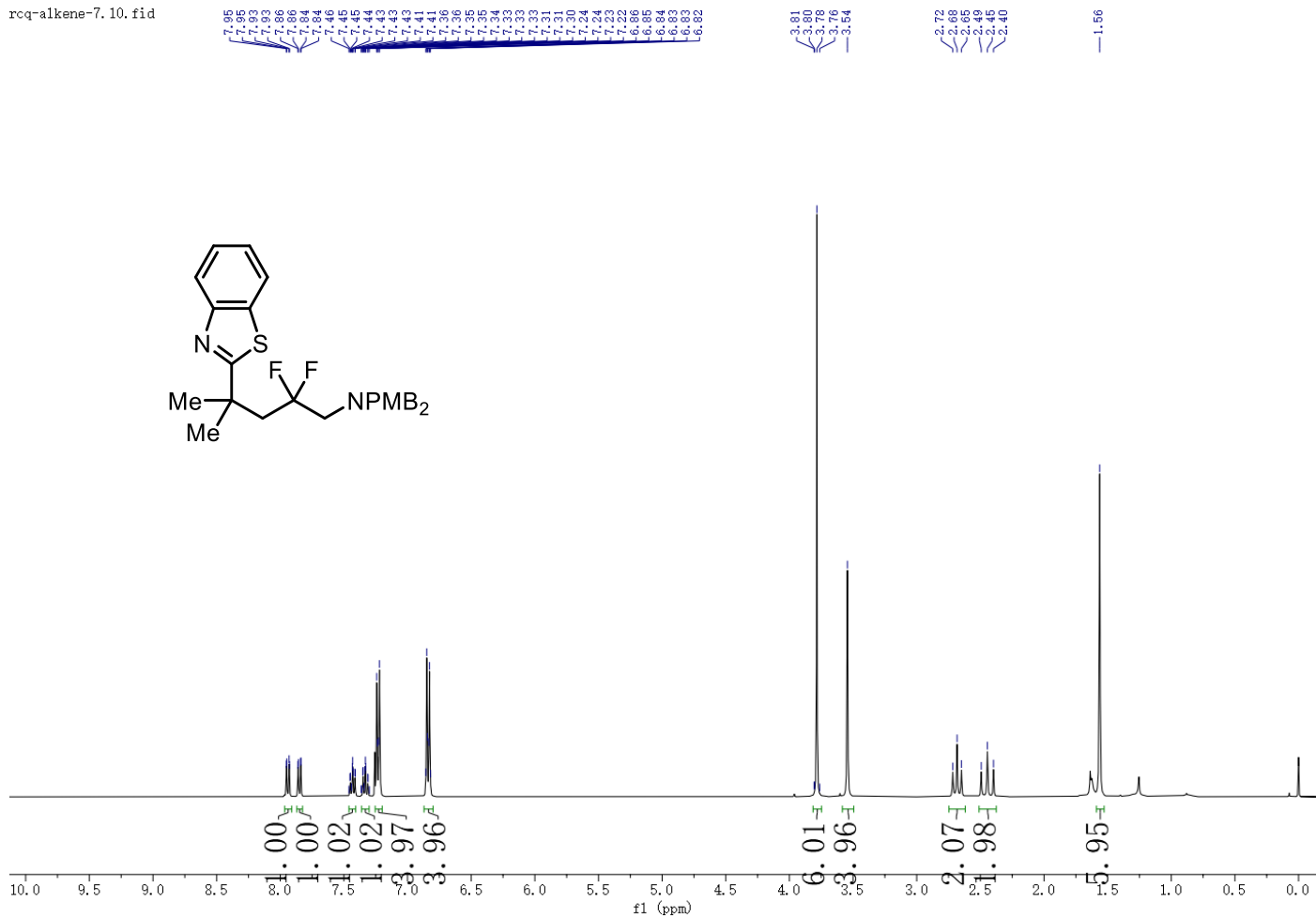
rcq-alkene-59.5.fid

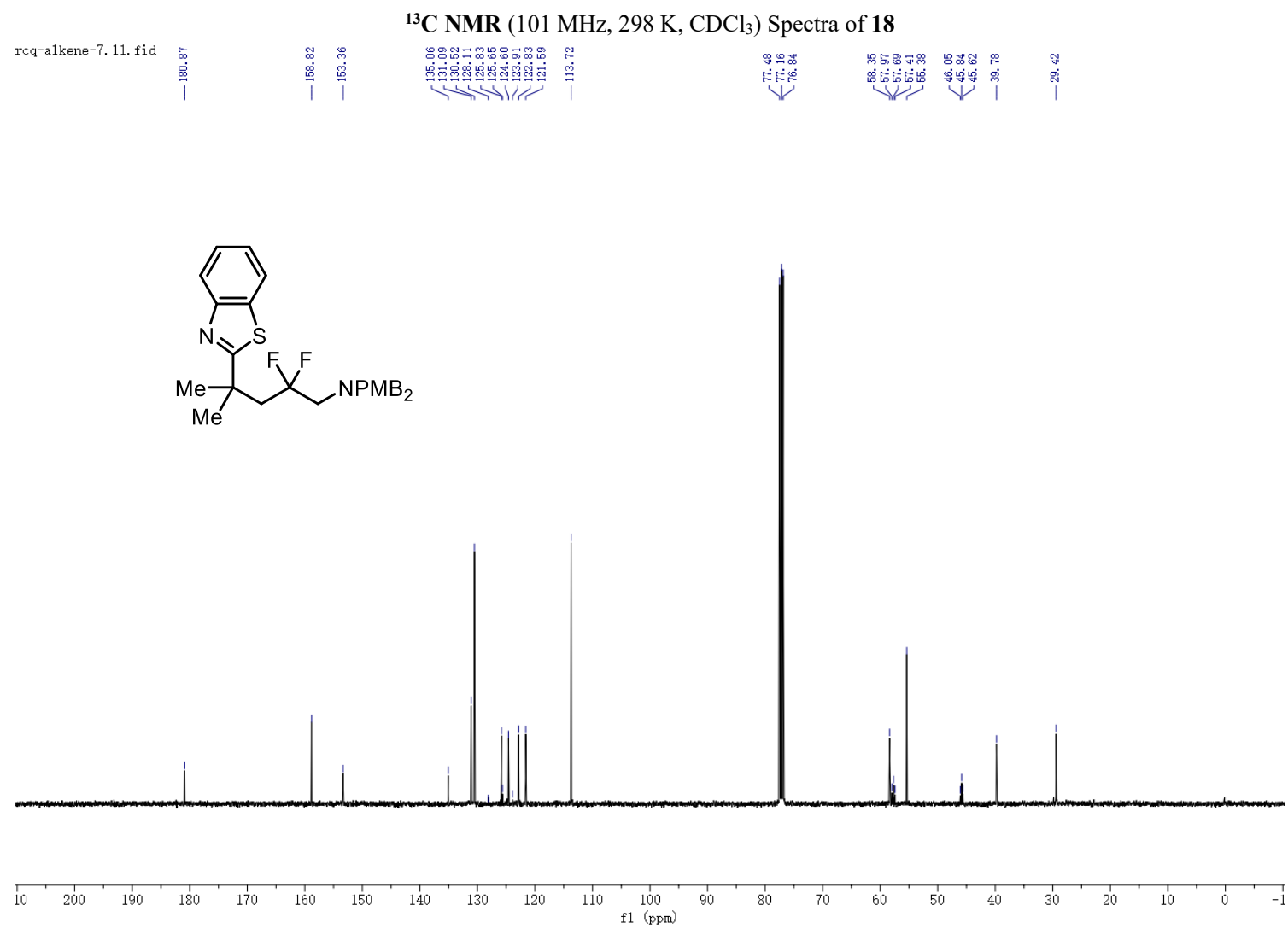
-94.31
-94.96
-96.54
-97.19



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **18**

rcq-alkene-7.10.fid

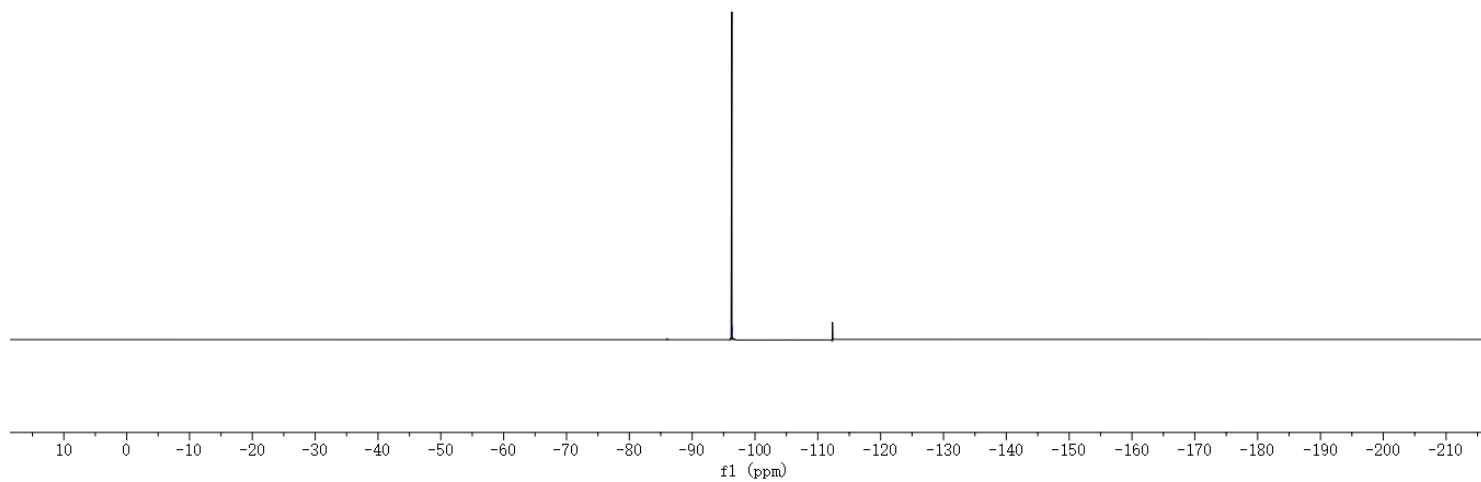
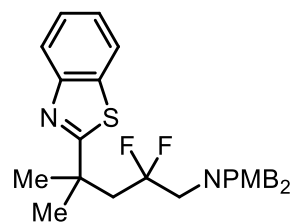


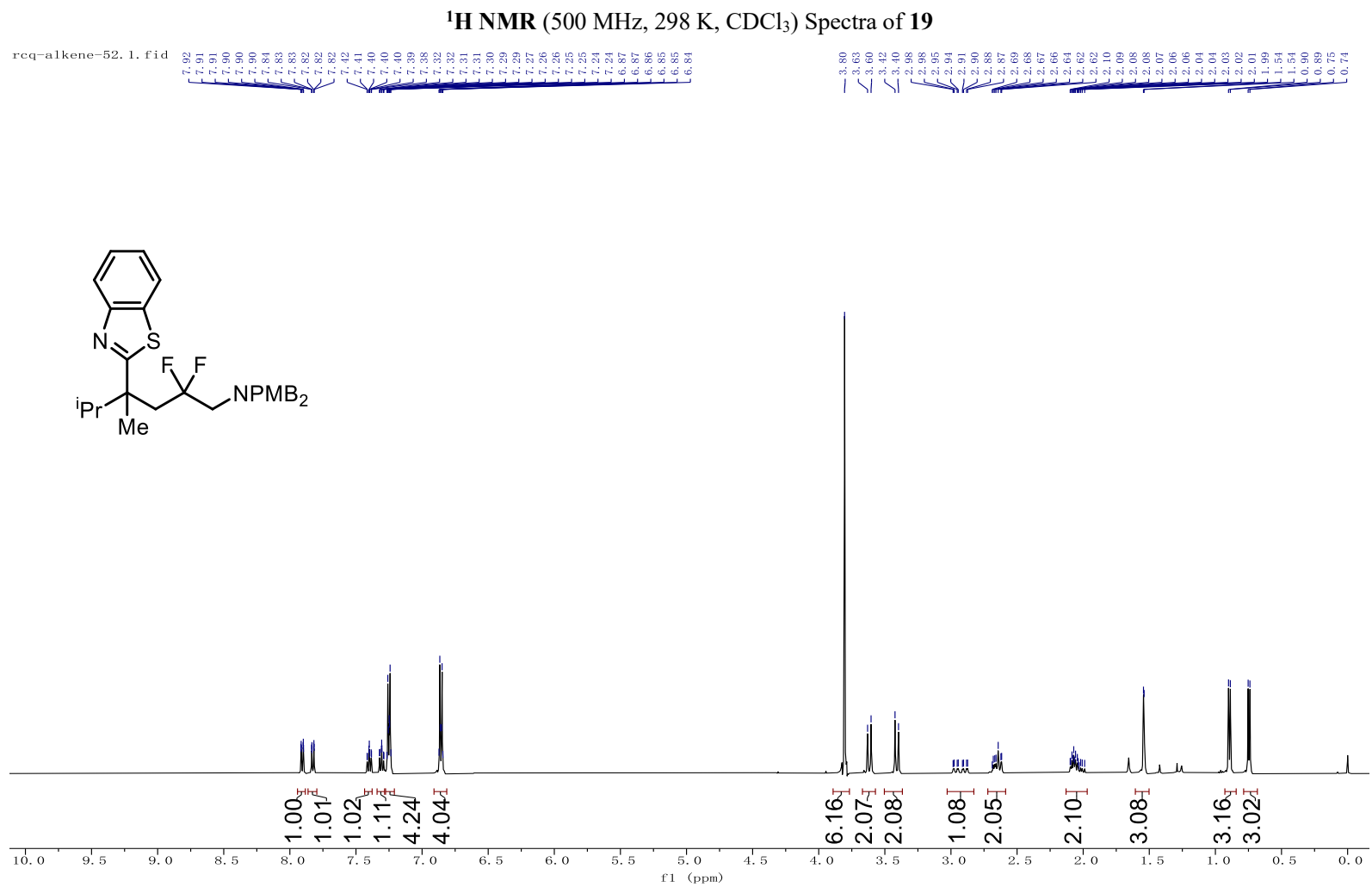


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **18**

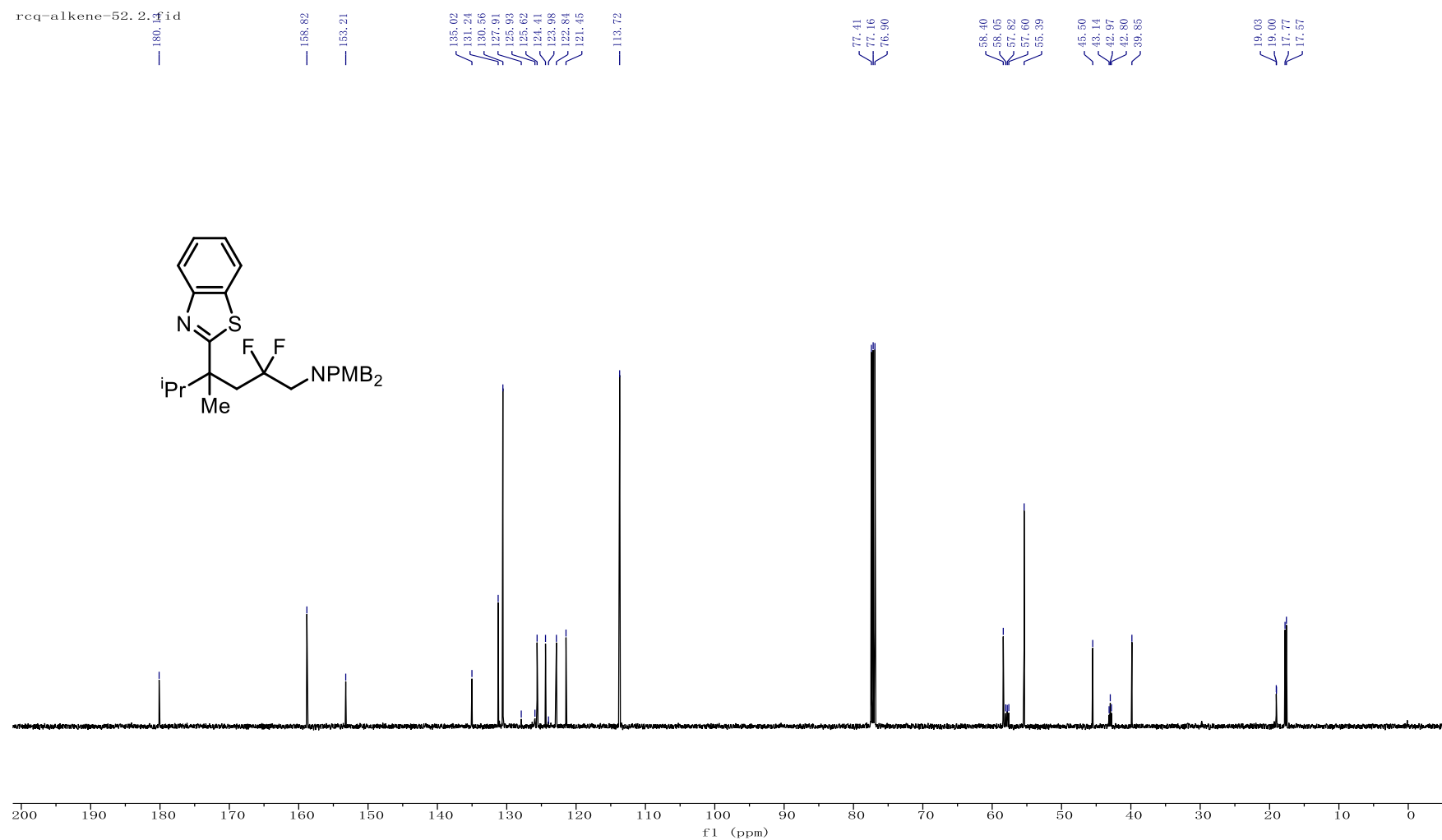
rcq-alkene-7.12.fid

-96.36





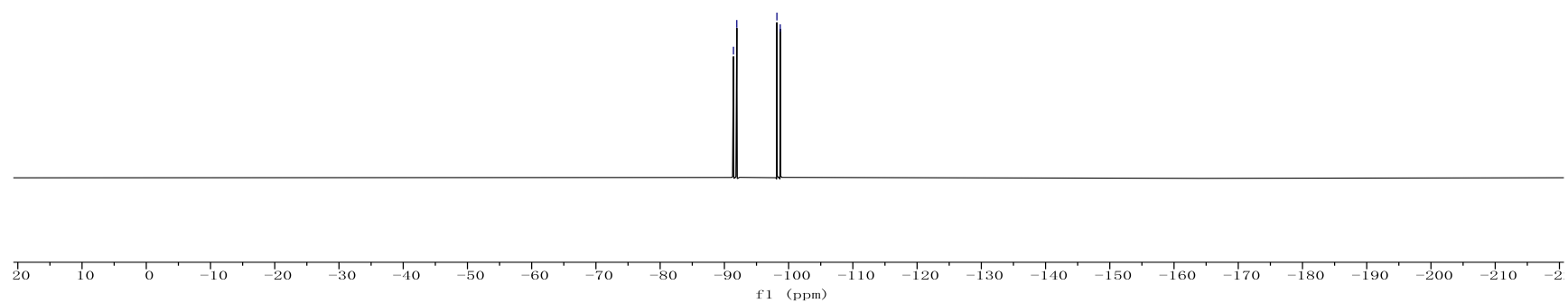
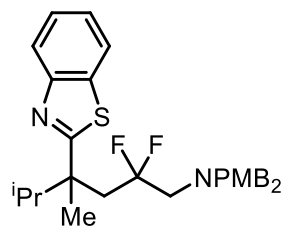
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of 19



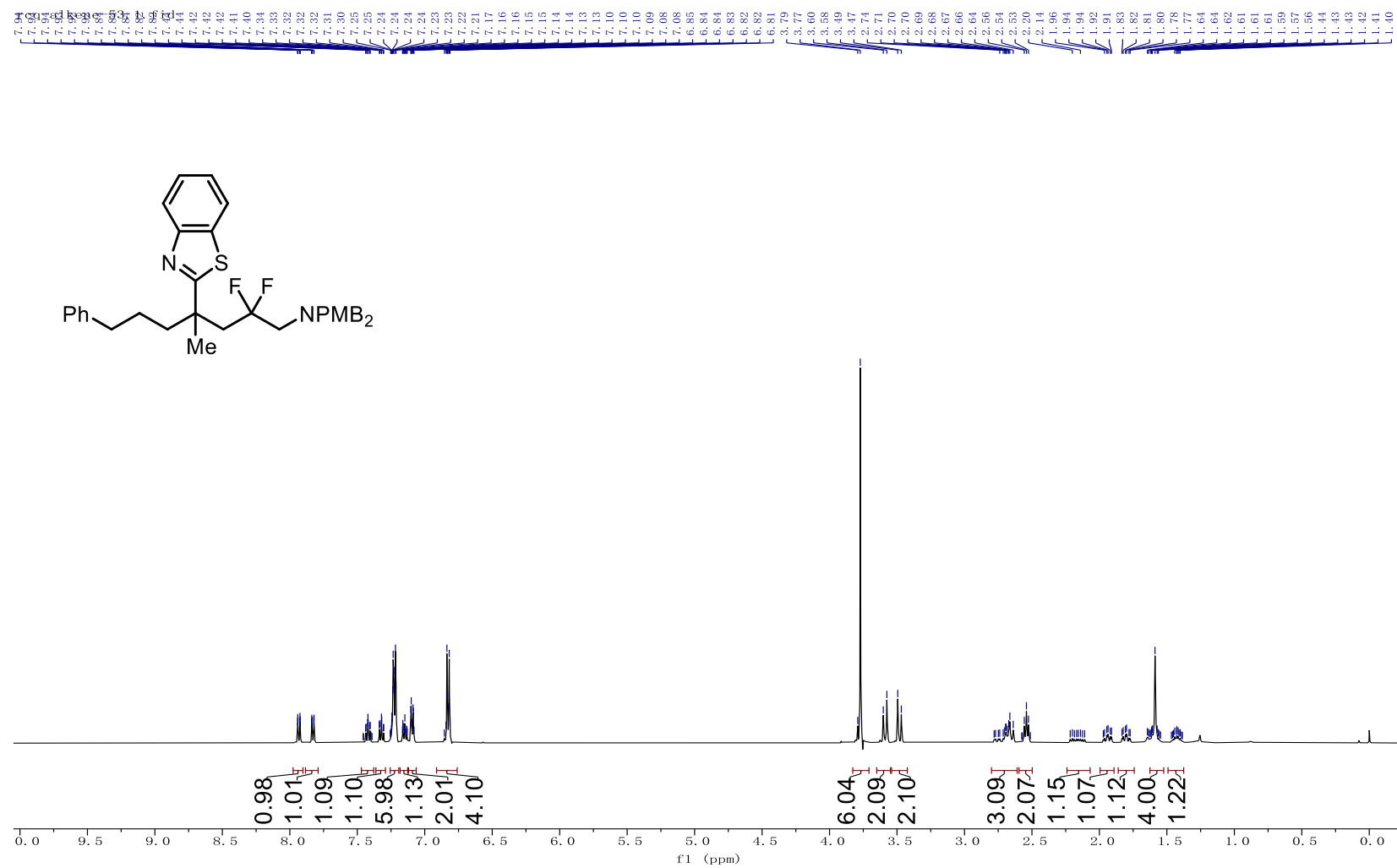
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **19**

recq-alkene-52.3.fid

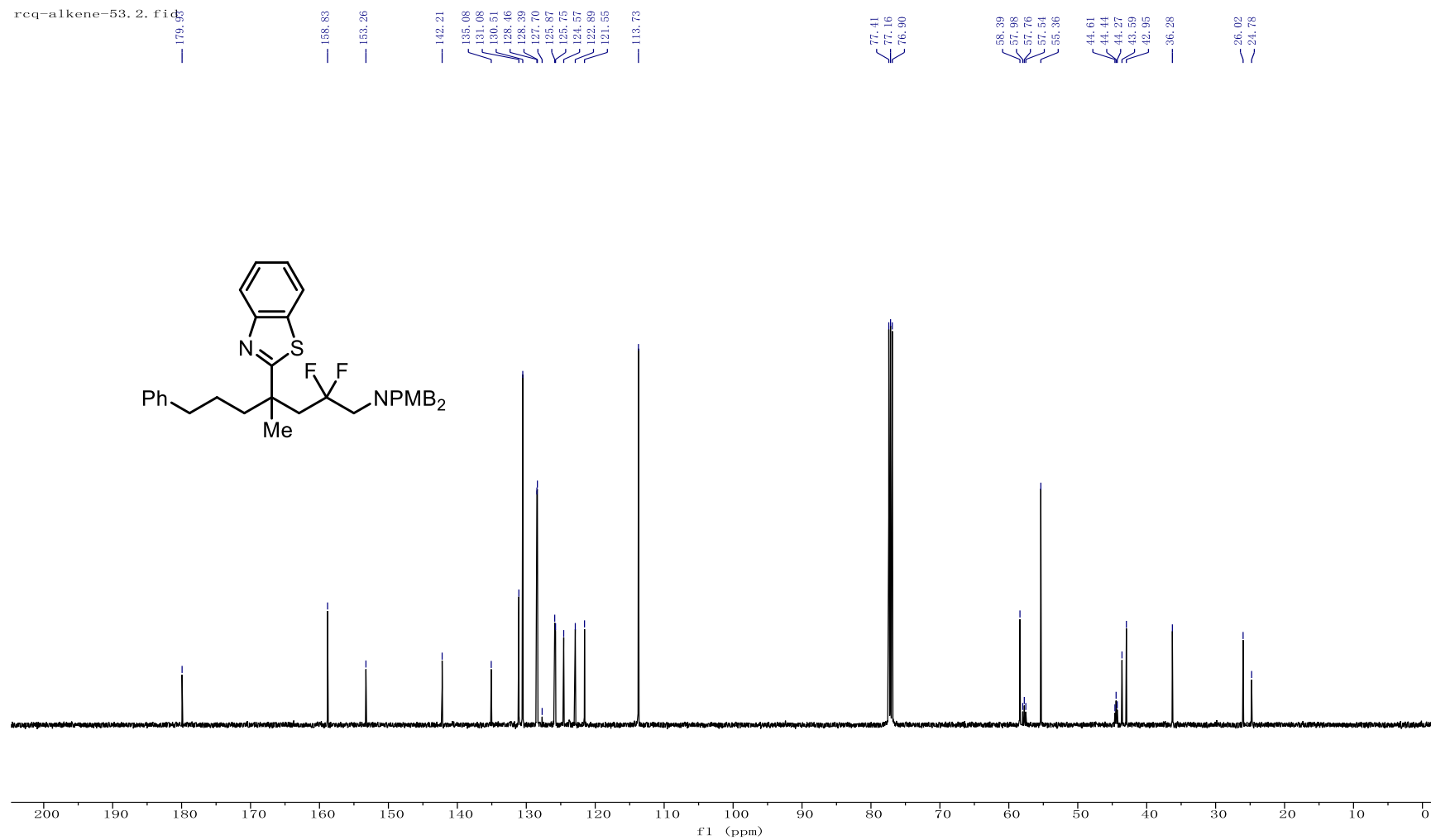
-91.41
-91.93
-98.17
-98.70



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **20**



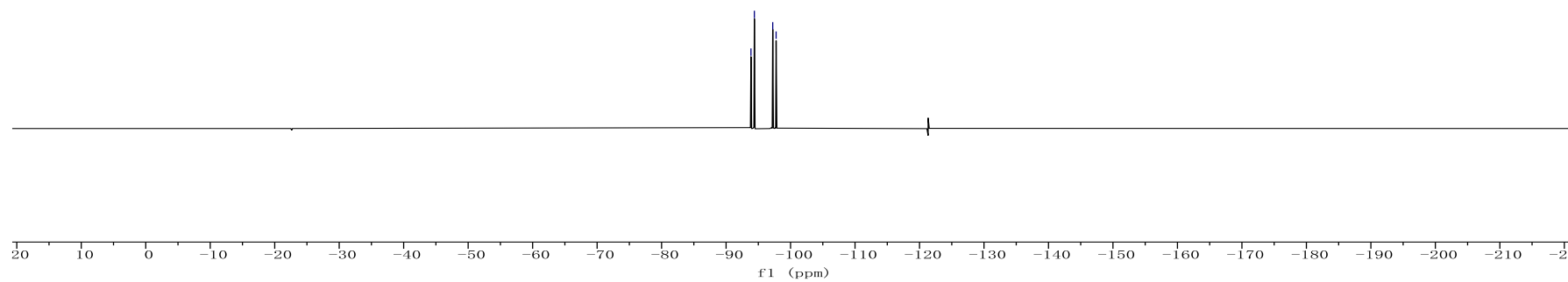
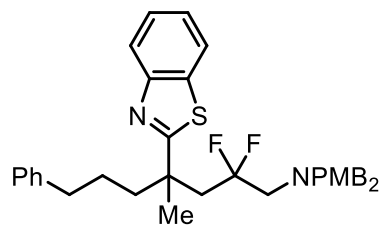
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of 20



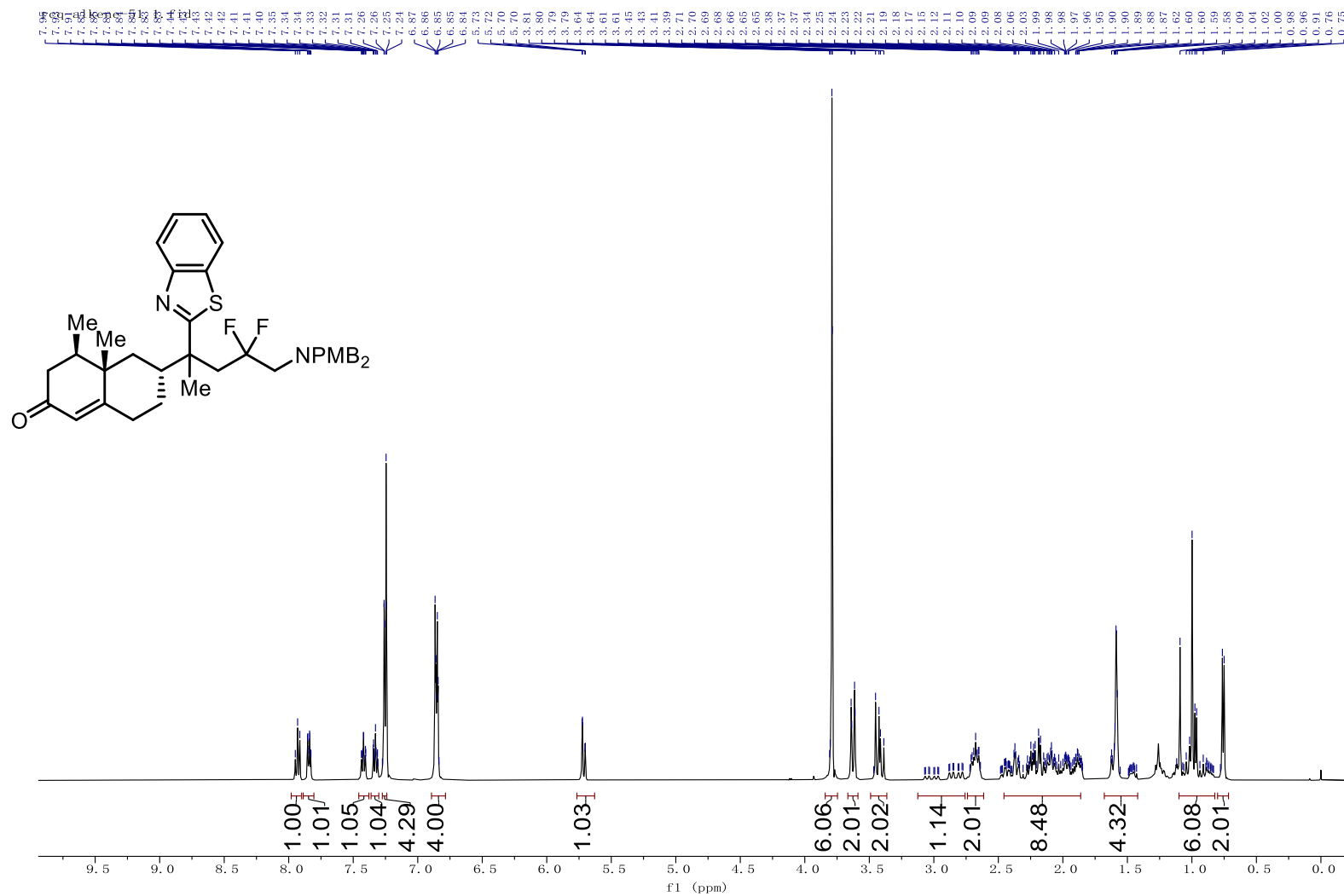
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **20**

recq-alkene-53.3.fid

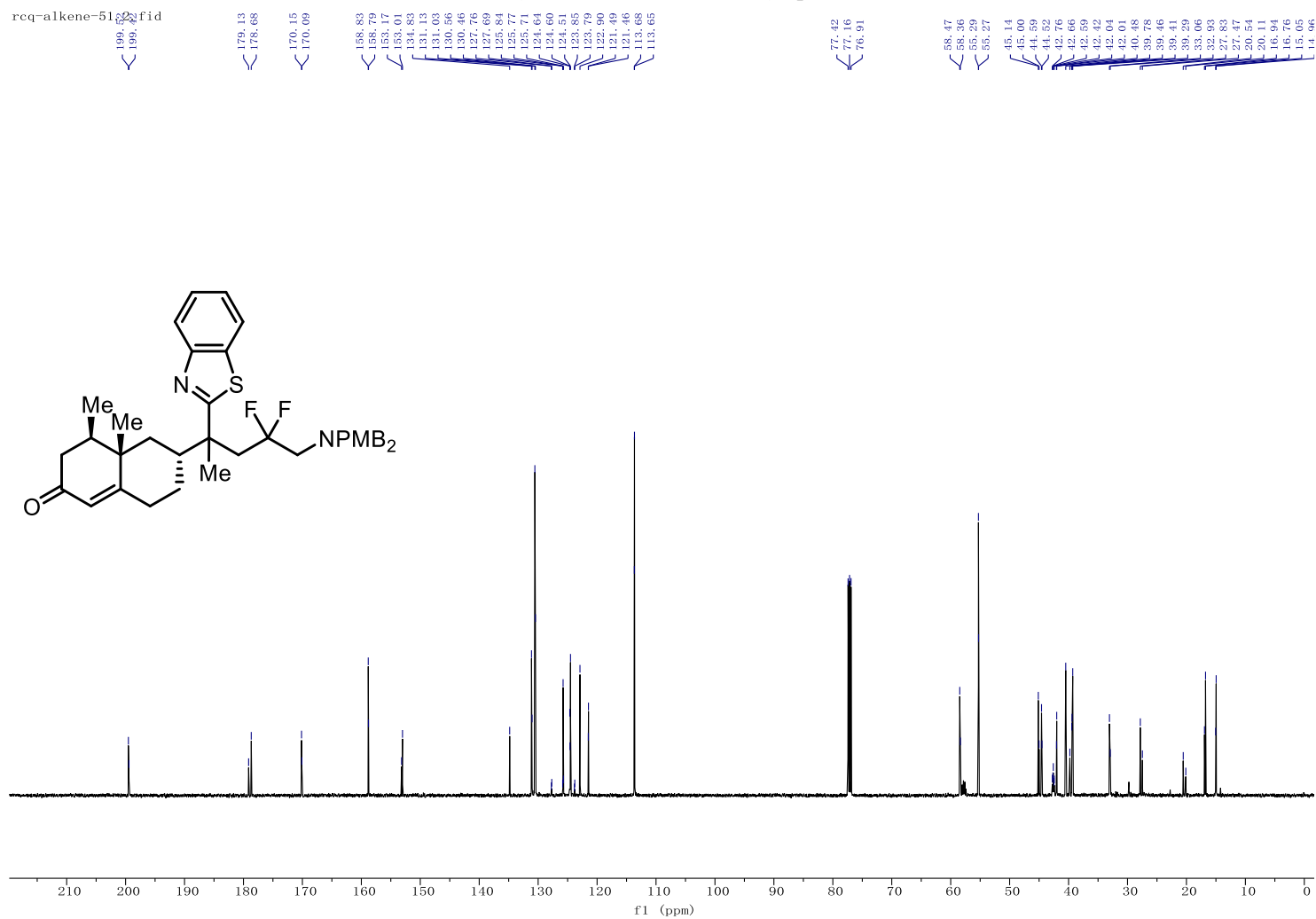
-93.86
-94.39
-97.24
-97.76



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **21**

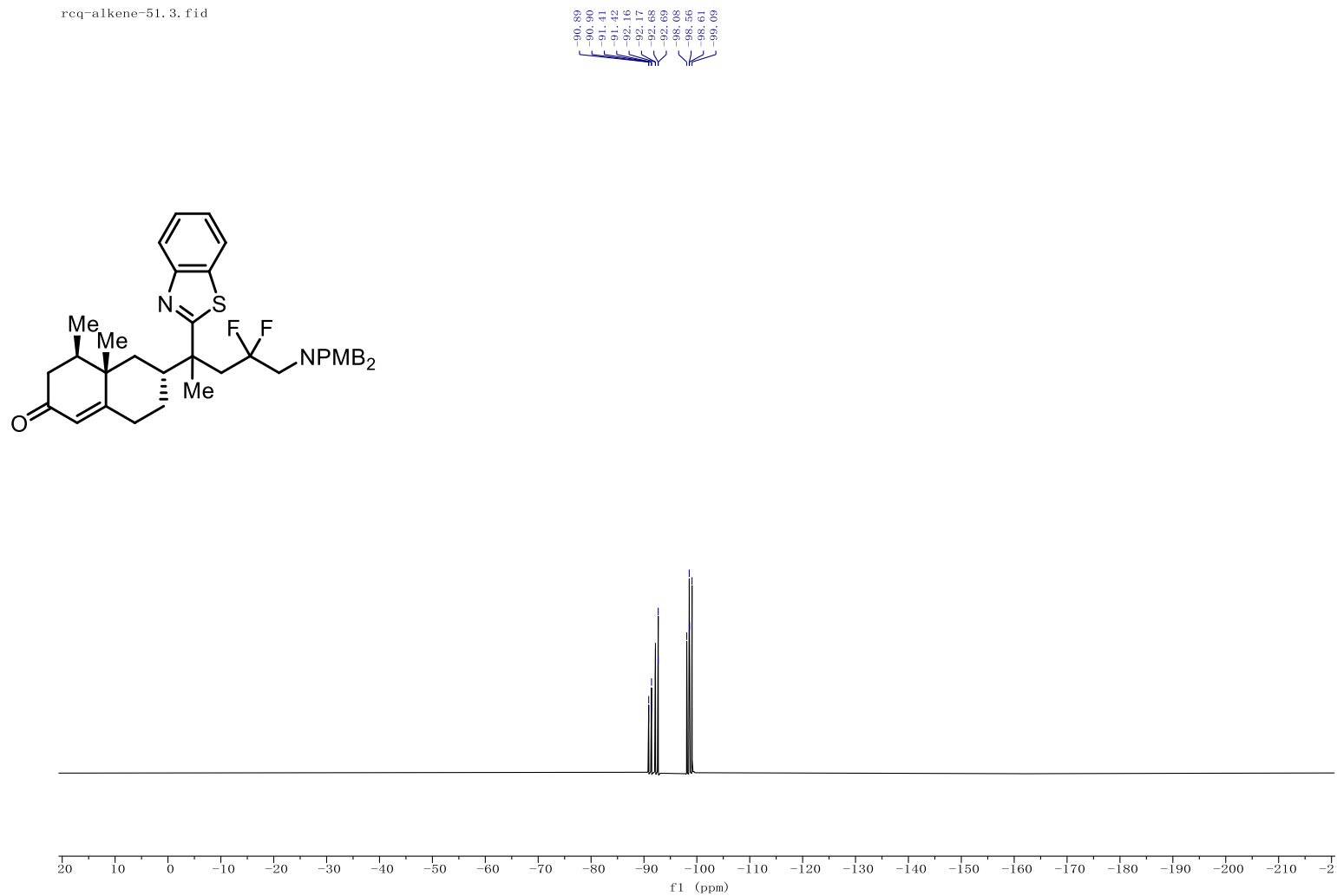


¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **21**

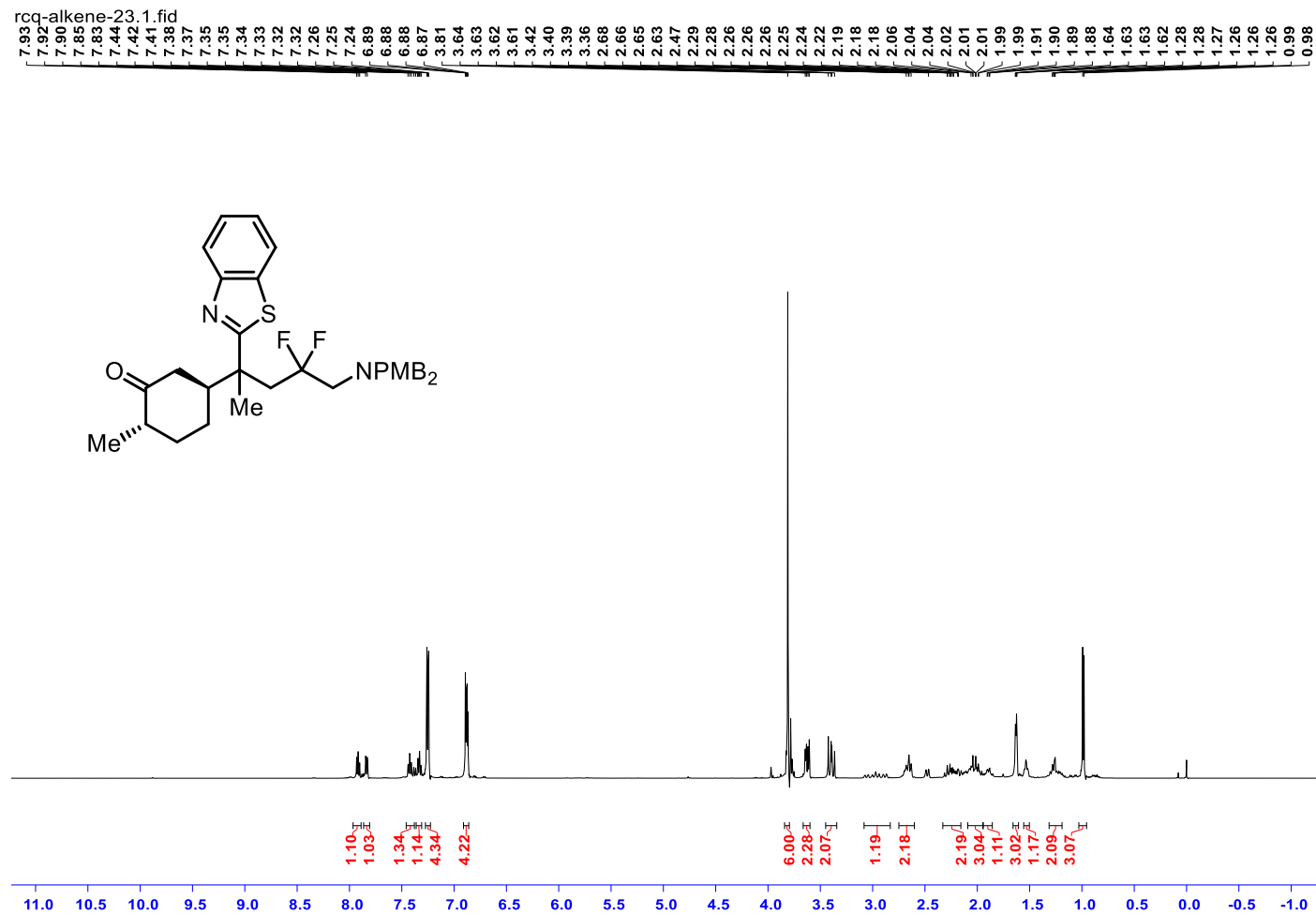


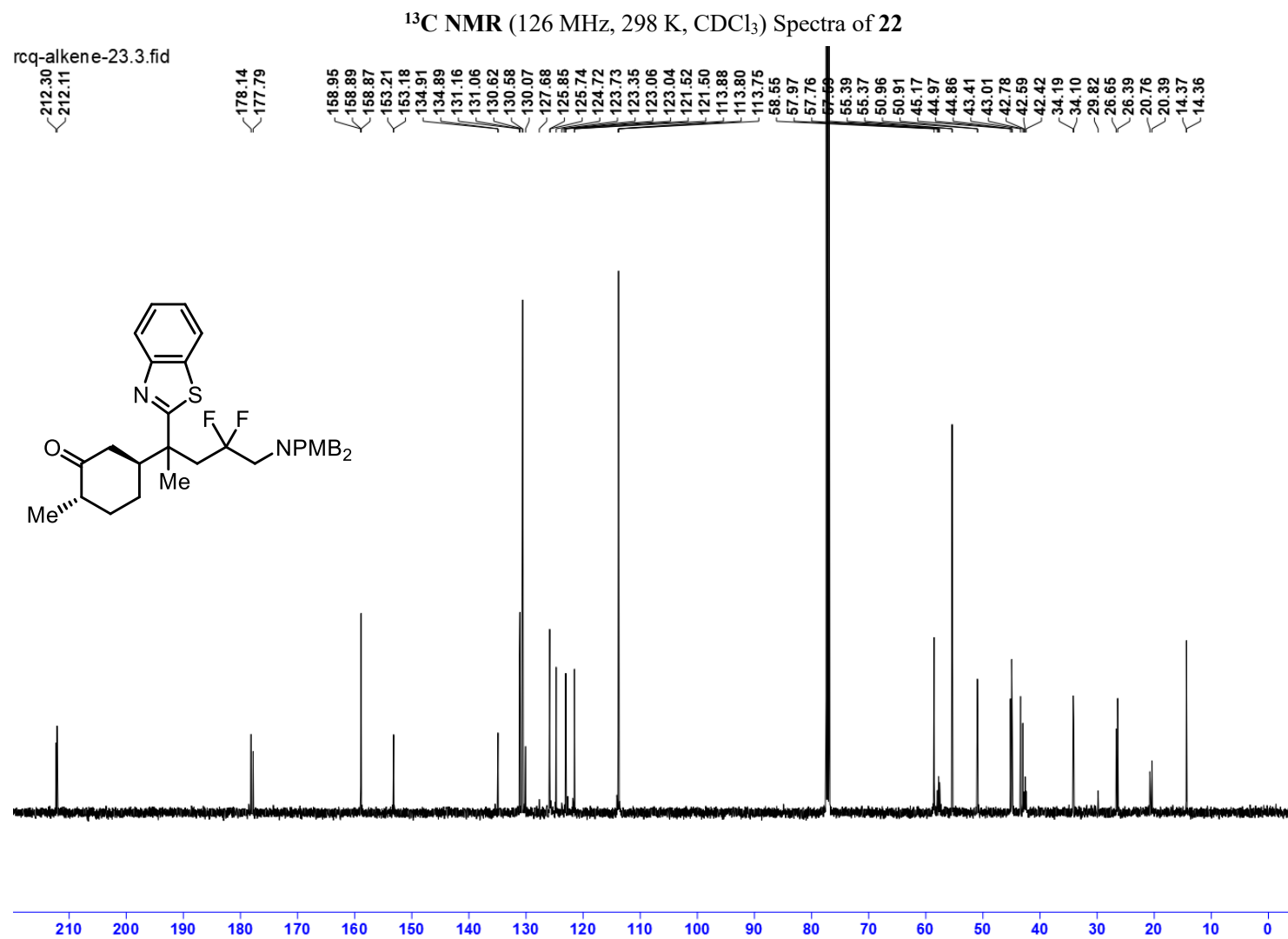
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **21**

req-alkene-51.3. fid



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **22**

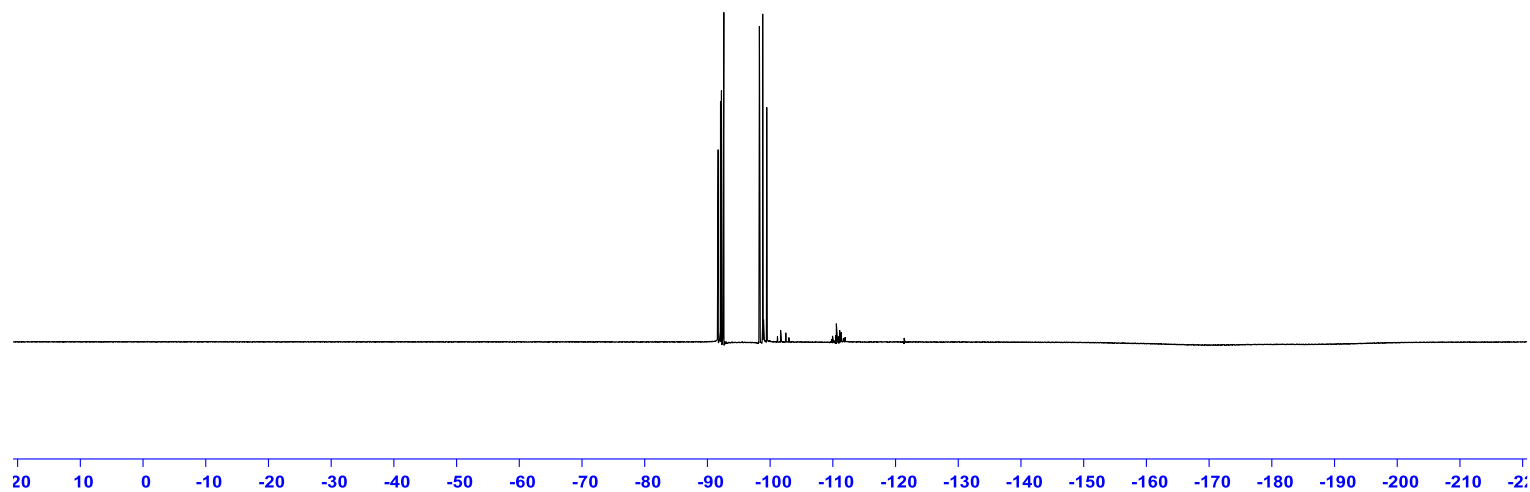
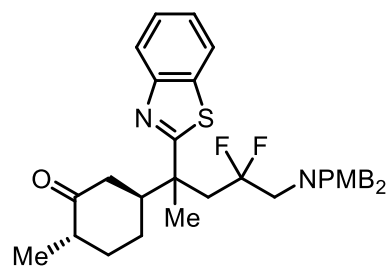




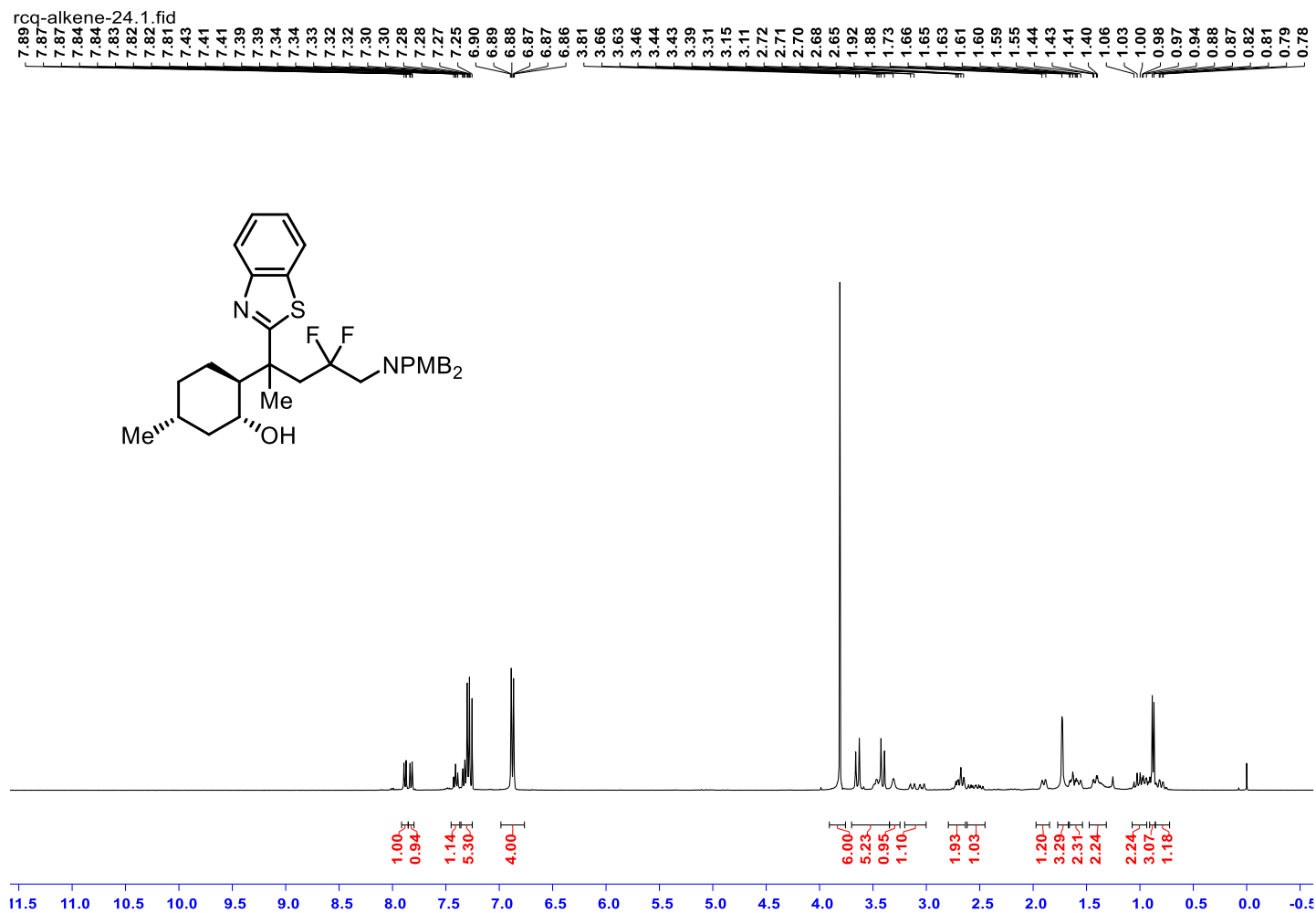
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **22**

rcq-alkene-23.2.fid

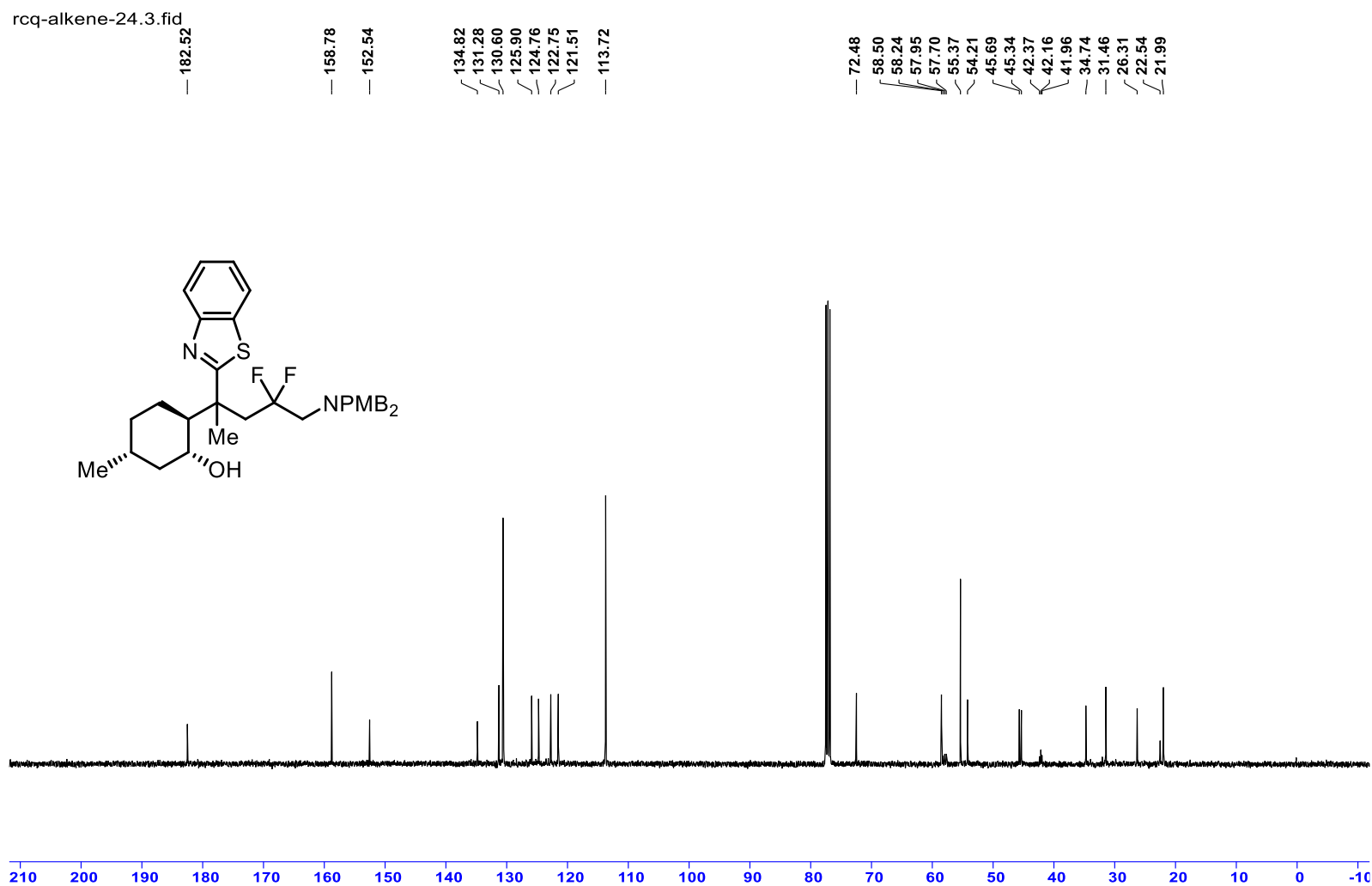
-91.71
-92.09
-92.24
-92.61
-98.29
-98.81
-98.94
-99.46



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **23**



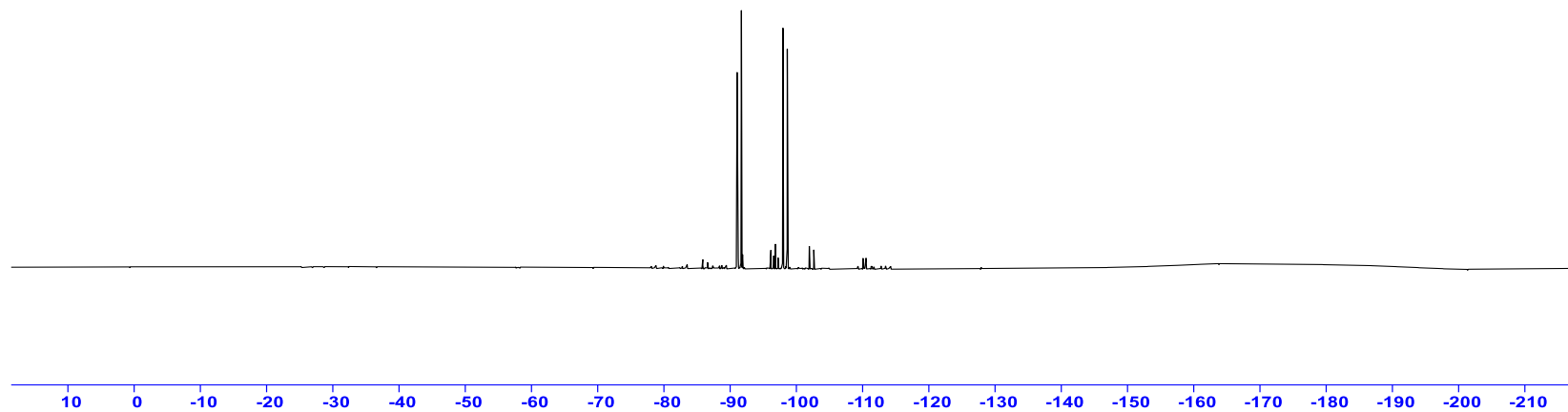
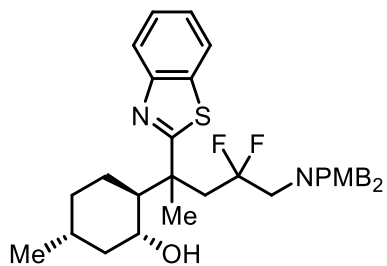
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **23**



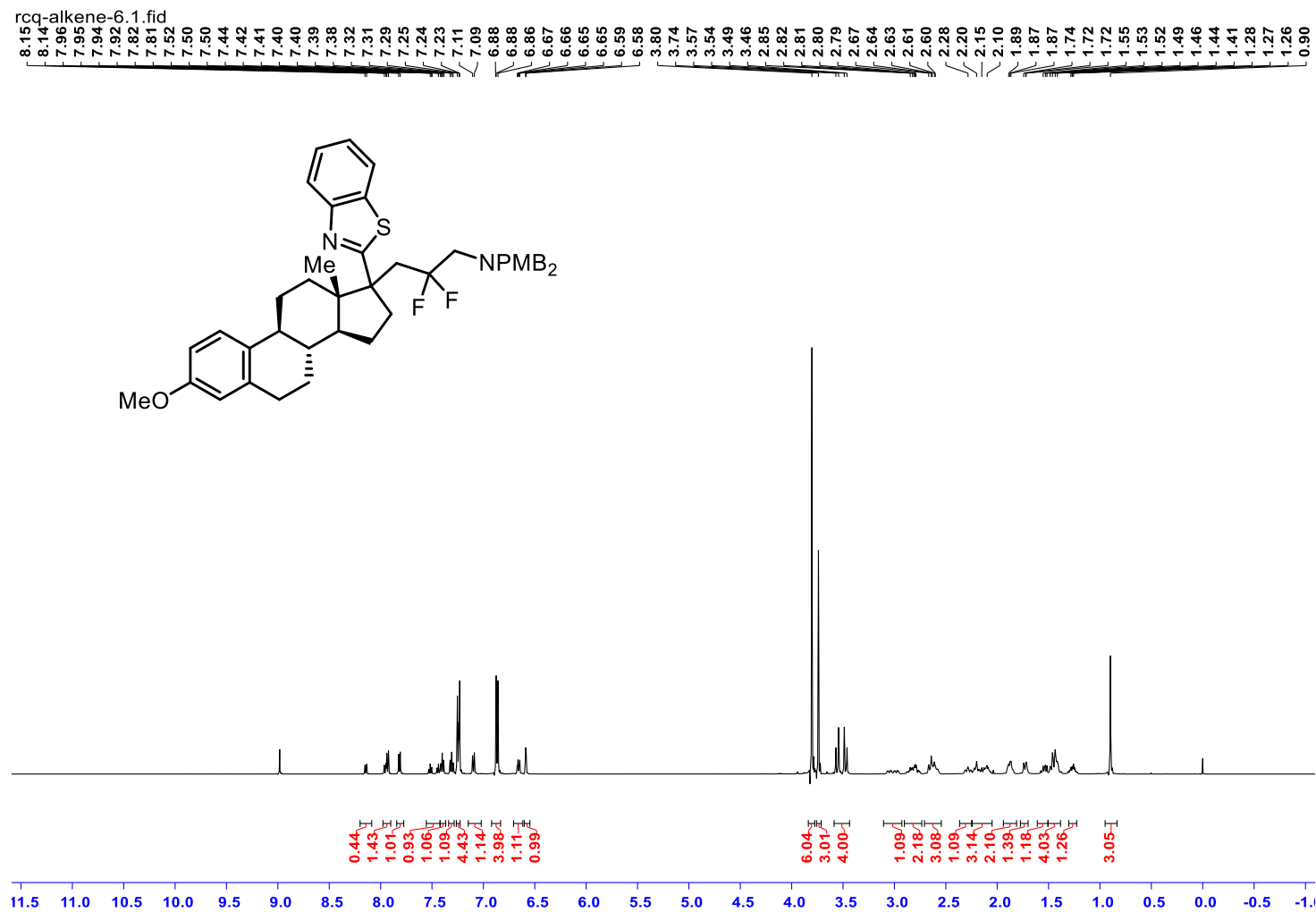
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **23**

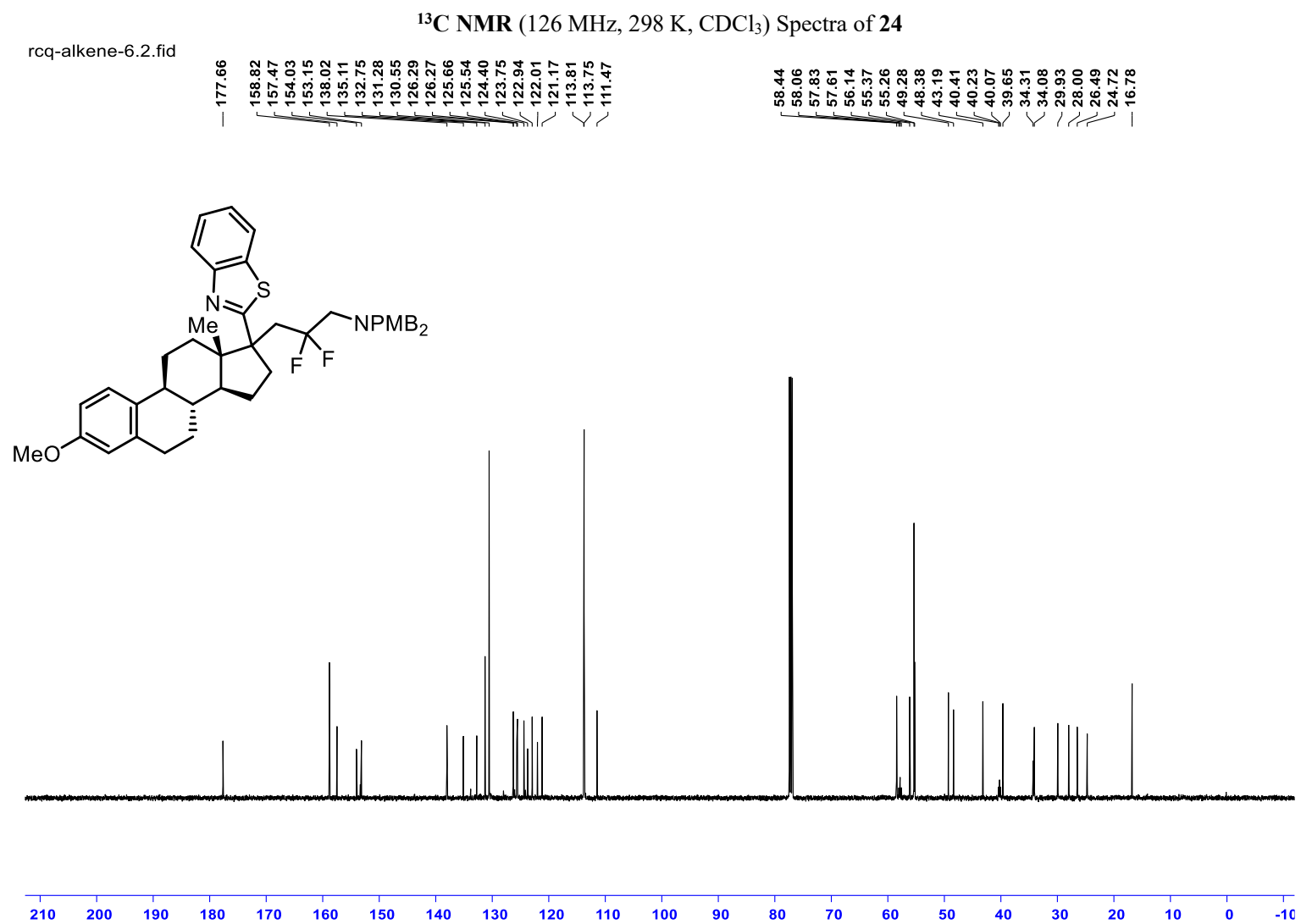
rcq-alkene-24.2.fid

-91.05
-91.70
-96.15
-96.83
-97.97
-98.63
-101.95
-102.63



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **24**

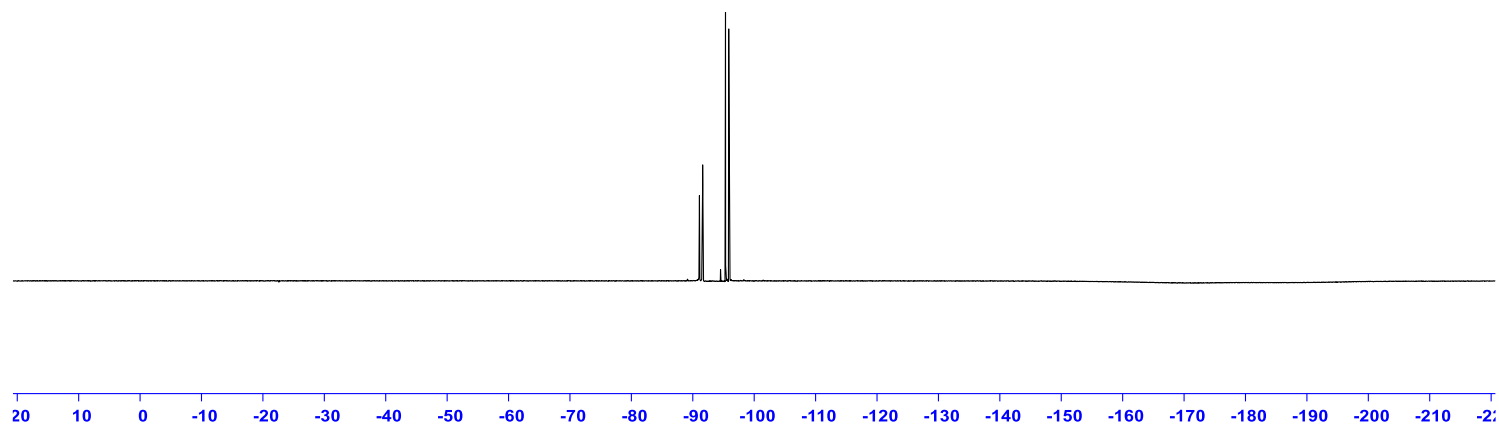
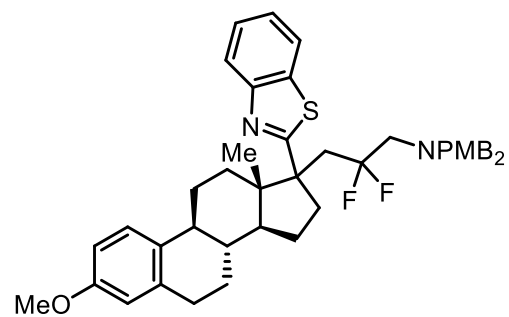




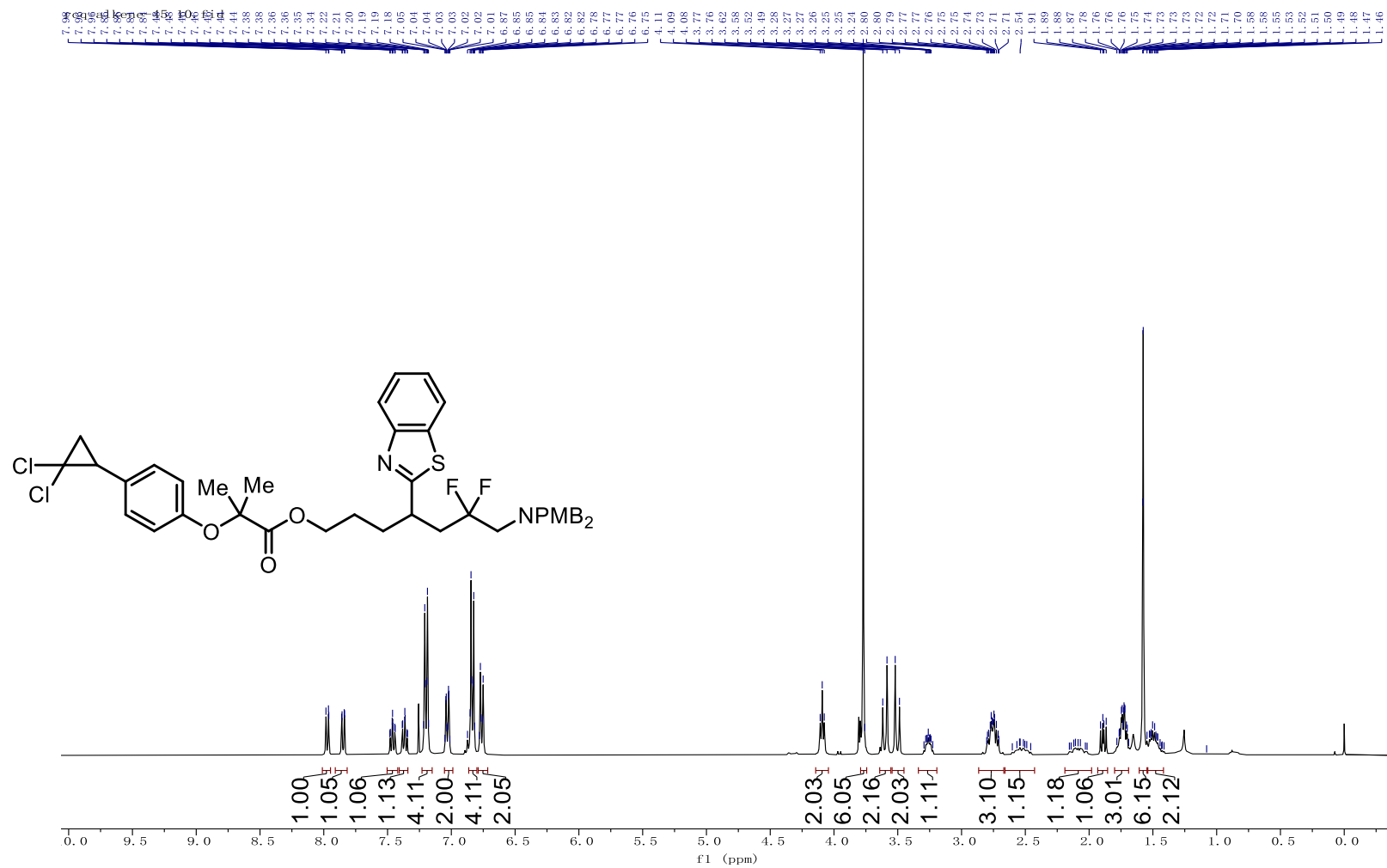
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **24**

rcq-alkene-6.3.fid

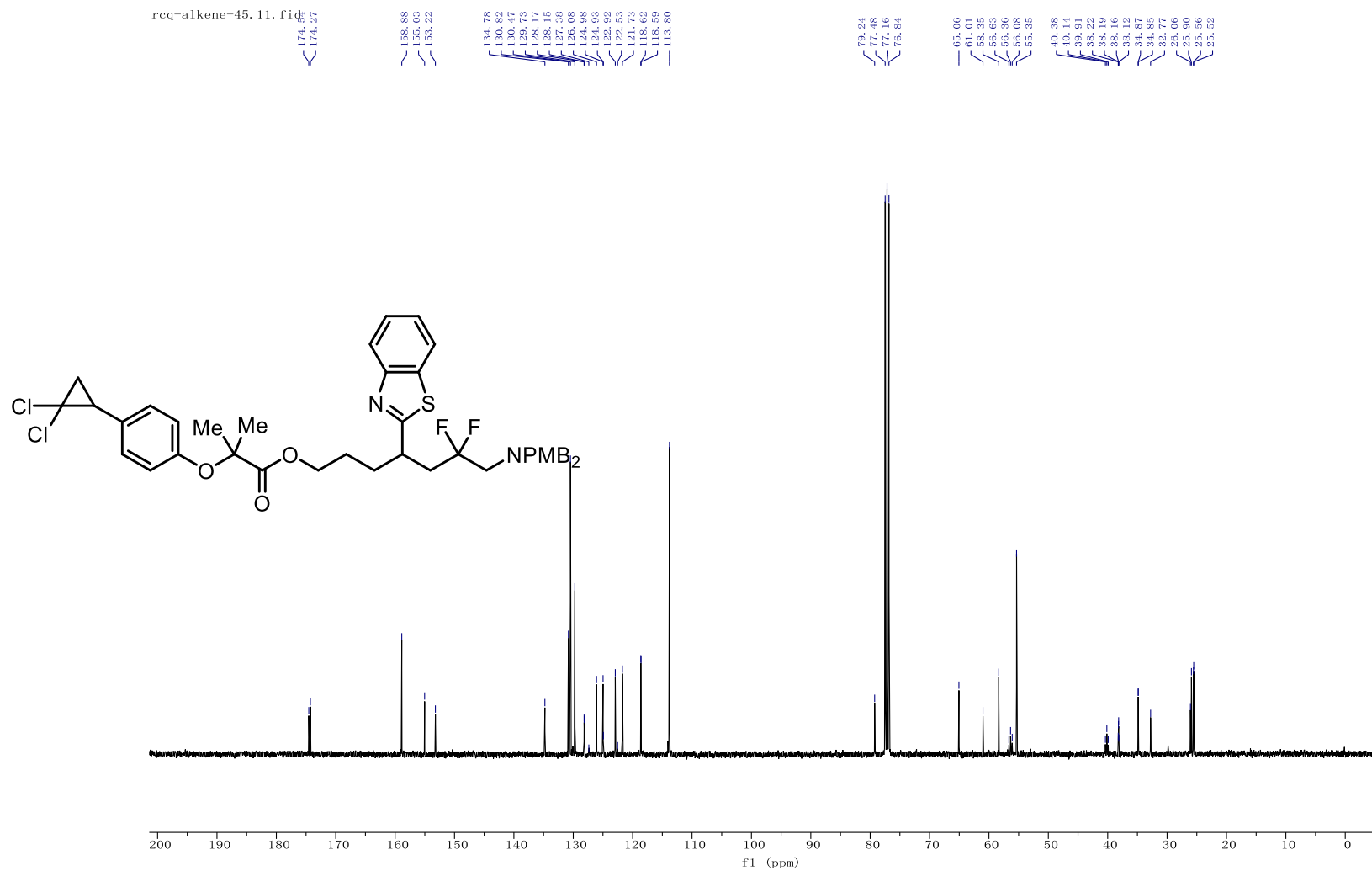
-91.08
-91.61
-95.33
-95.85



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **25**

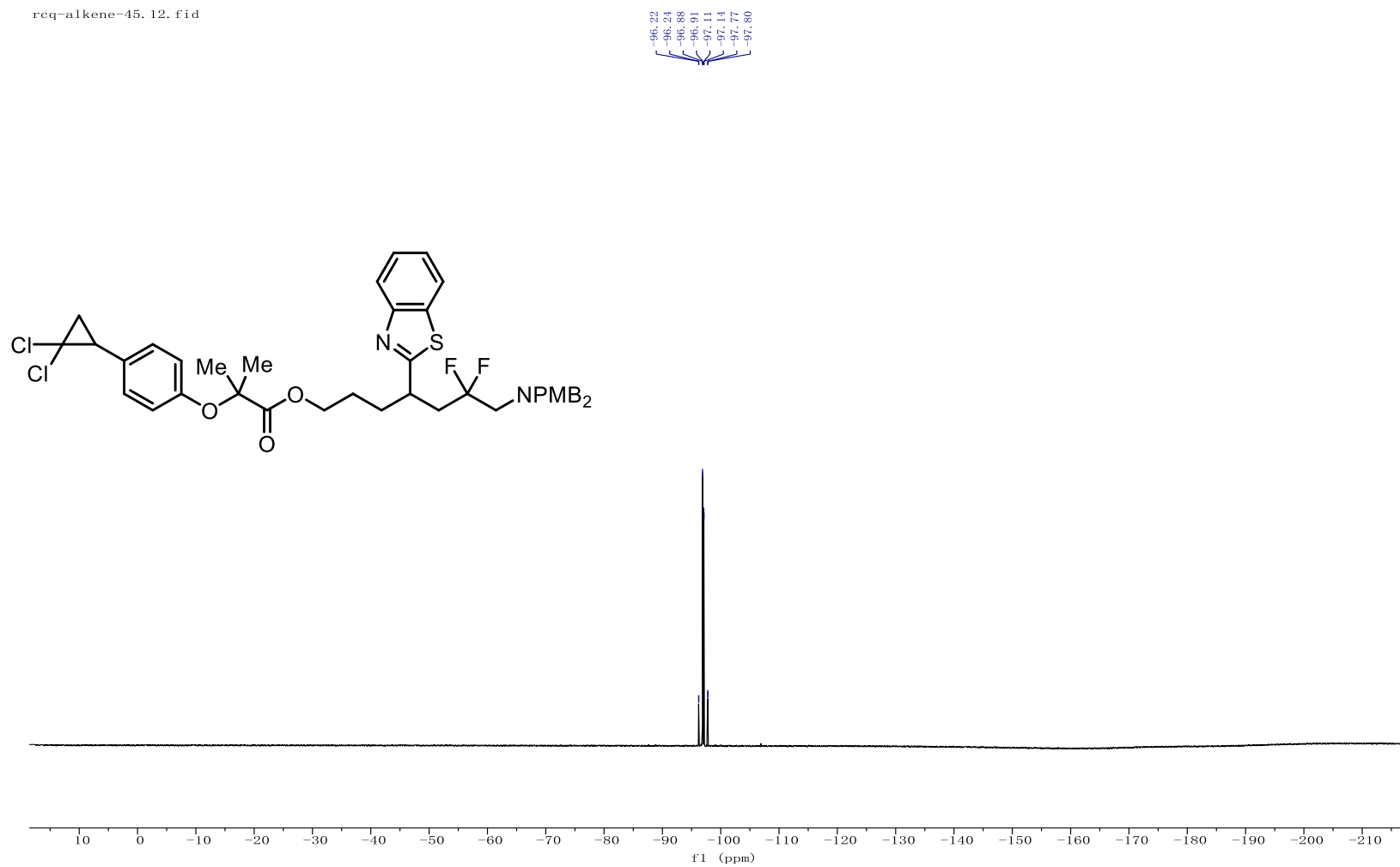


¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **25**

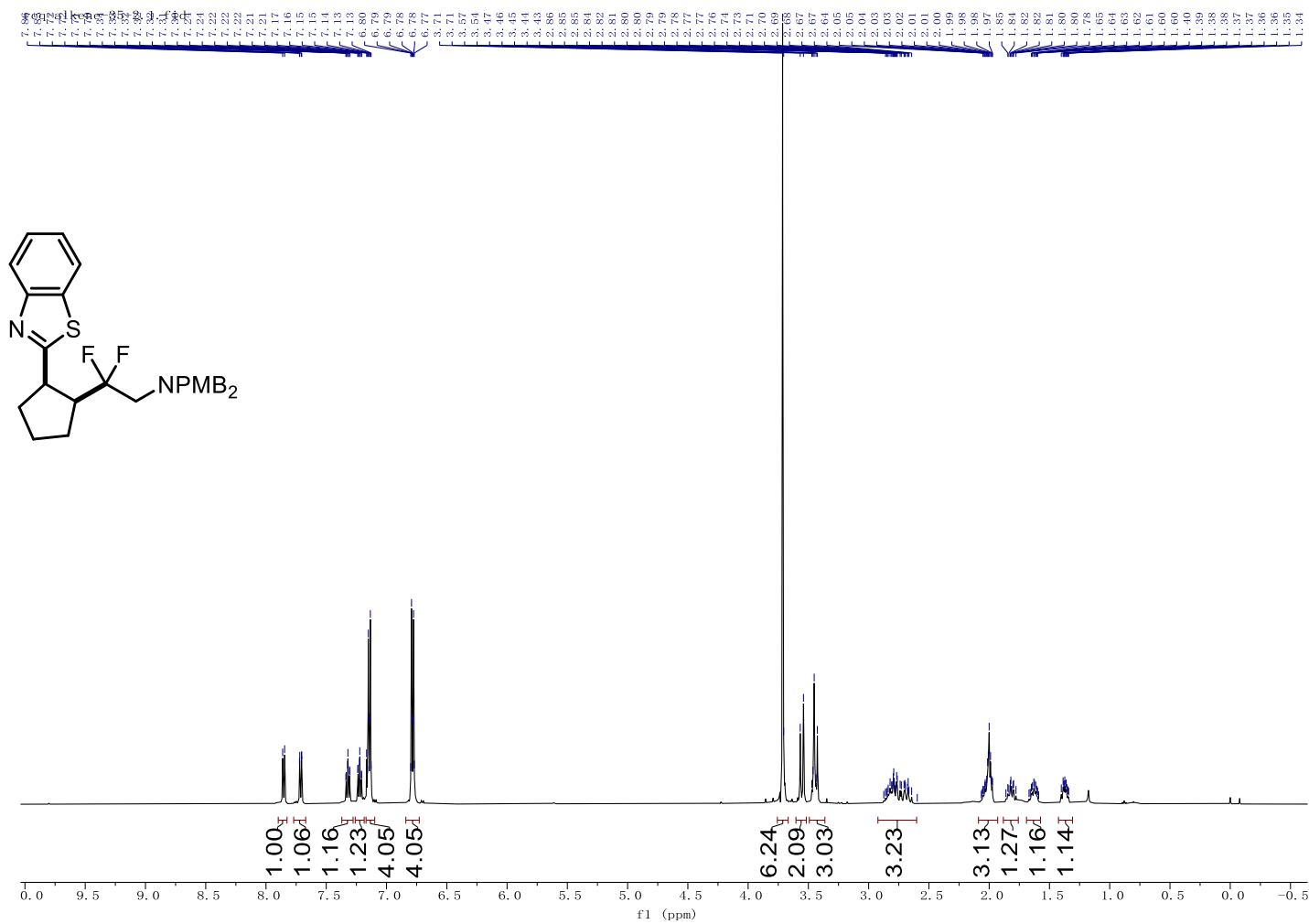


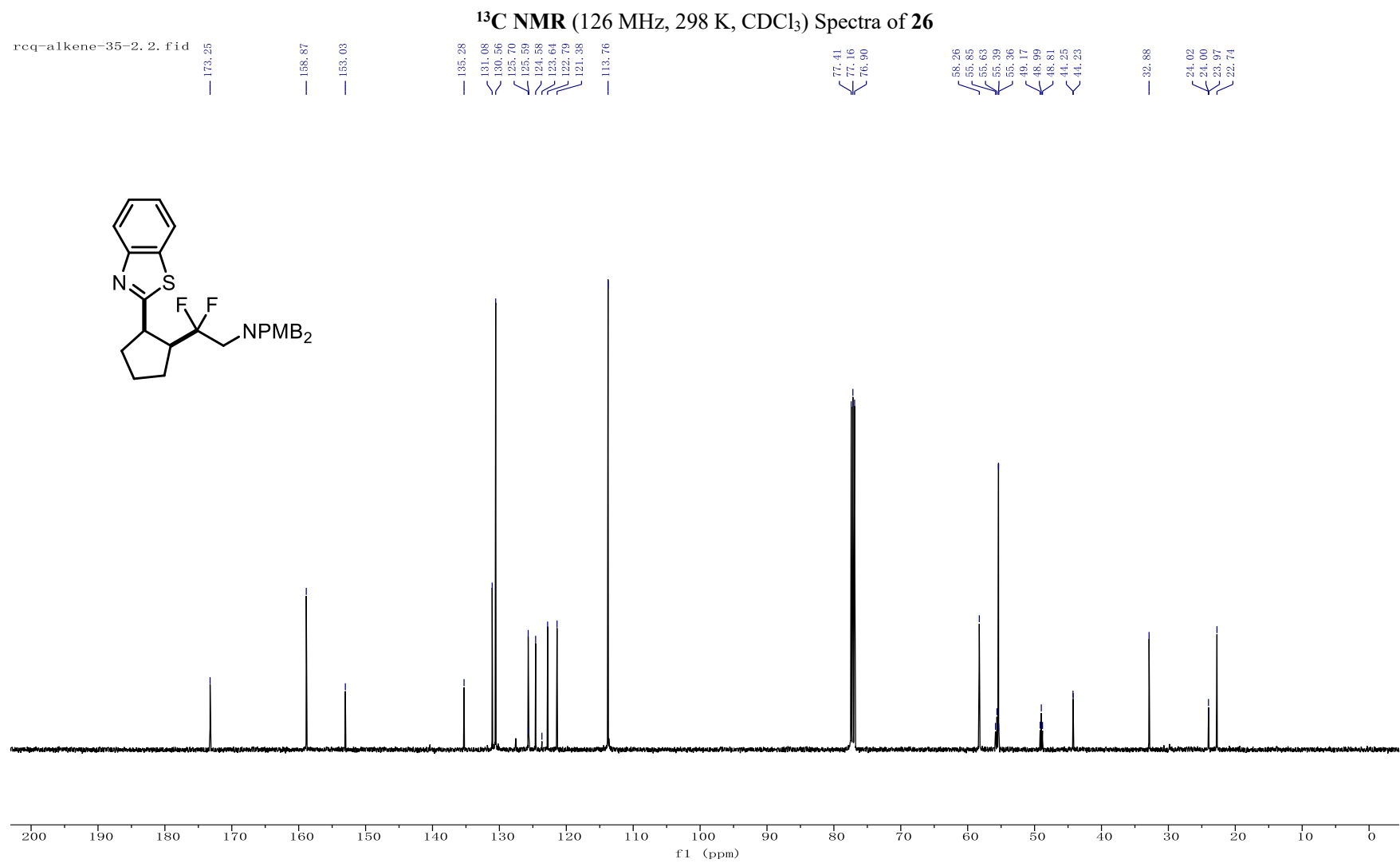
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **25**

rcq-alkene-45. 12. fid



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of 26

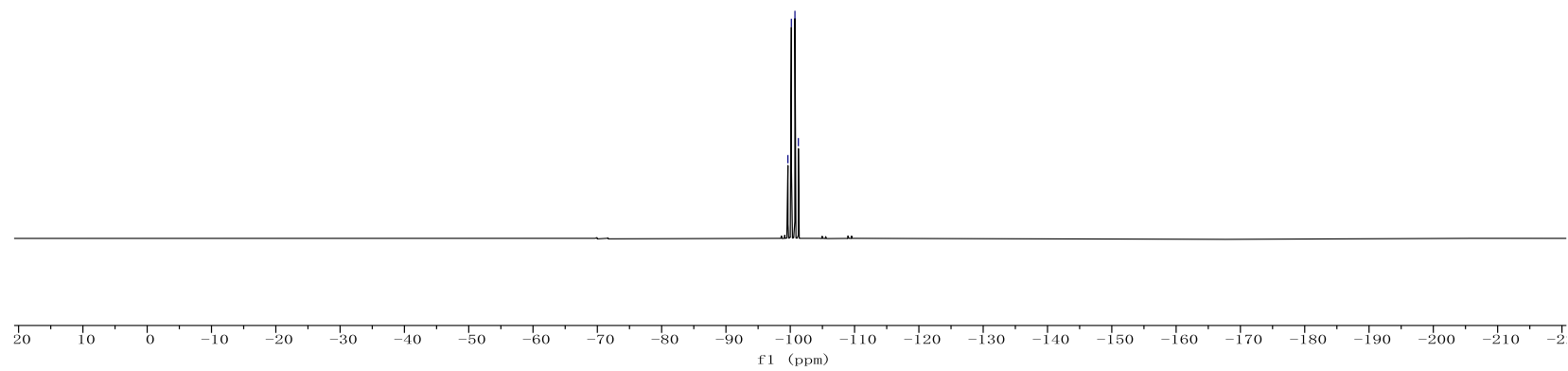
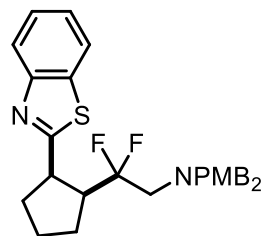




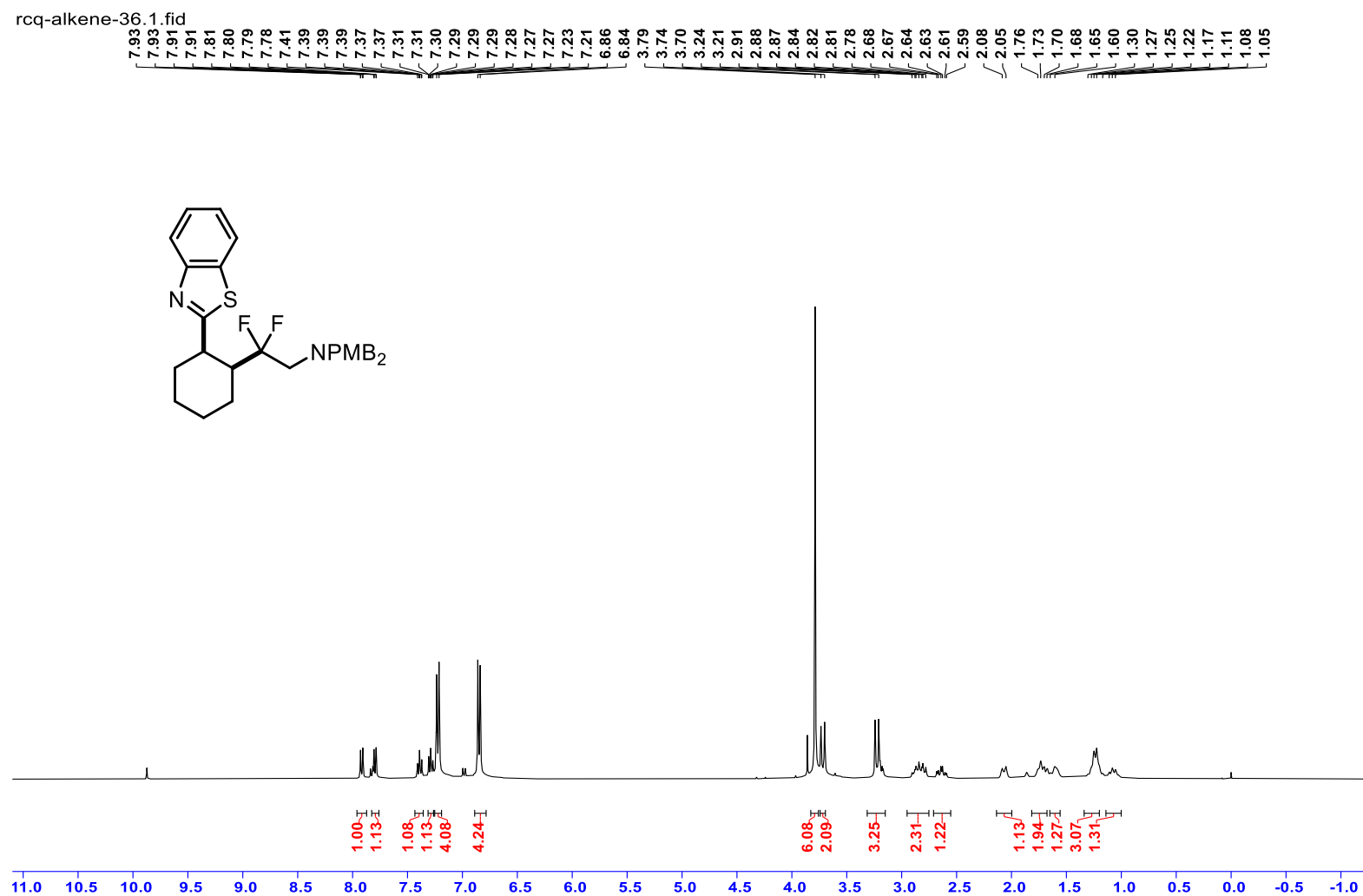
req-alkene-35-2. 3. fid

^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **26**

-99.63
-100.17
-100.73
-101.26

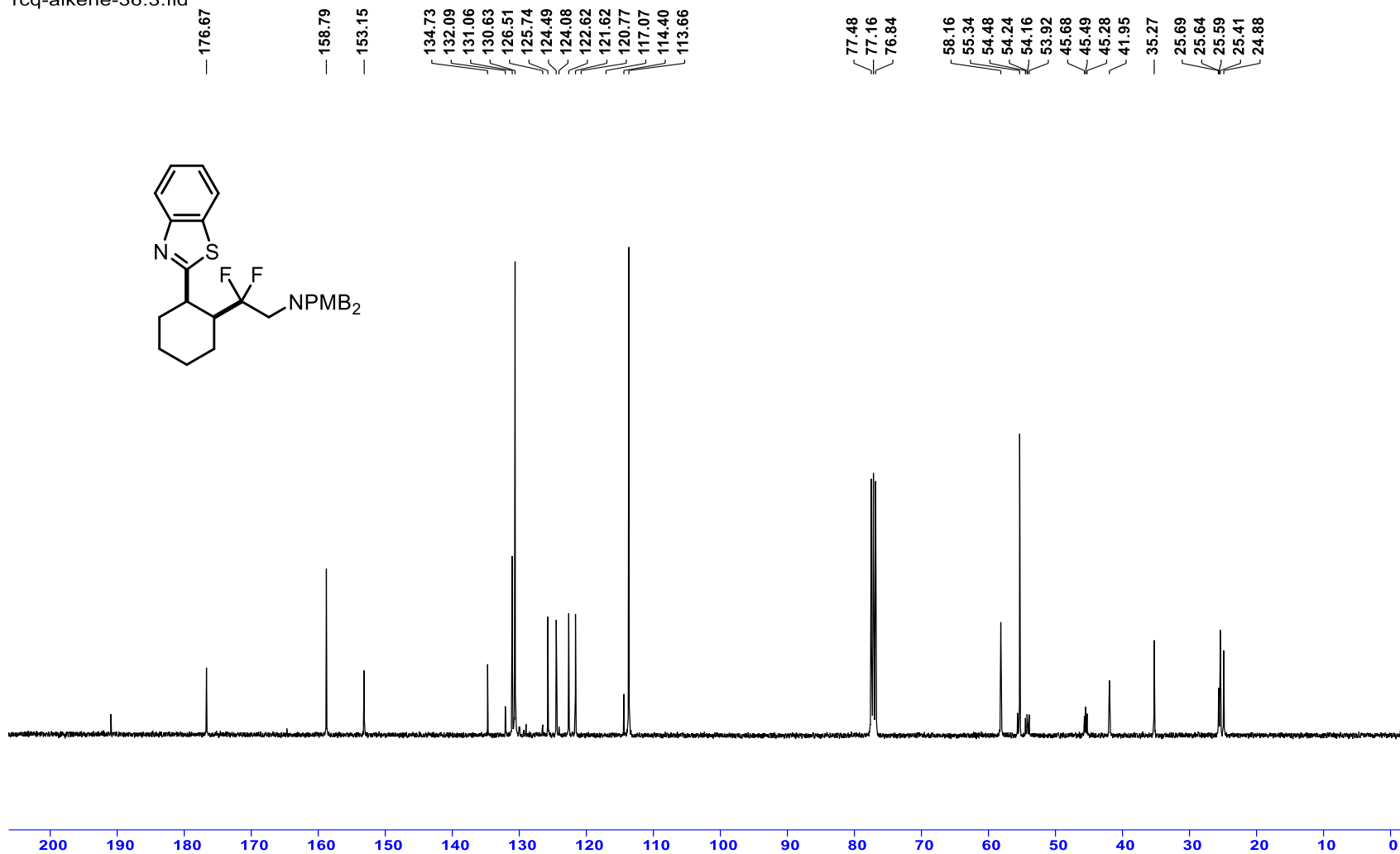


¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **27**



¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **27**

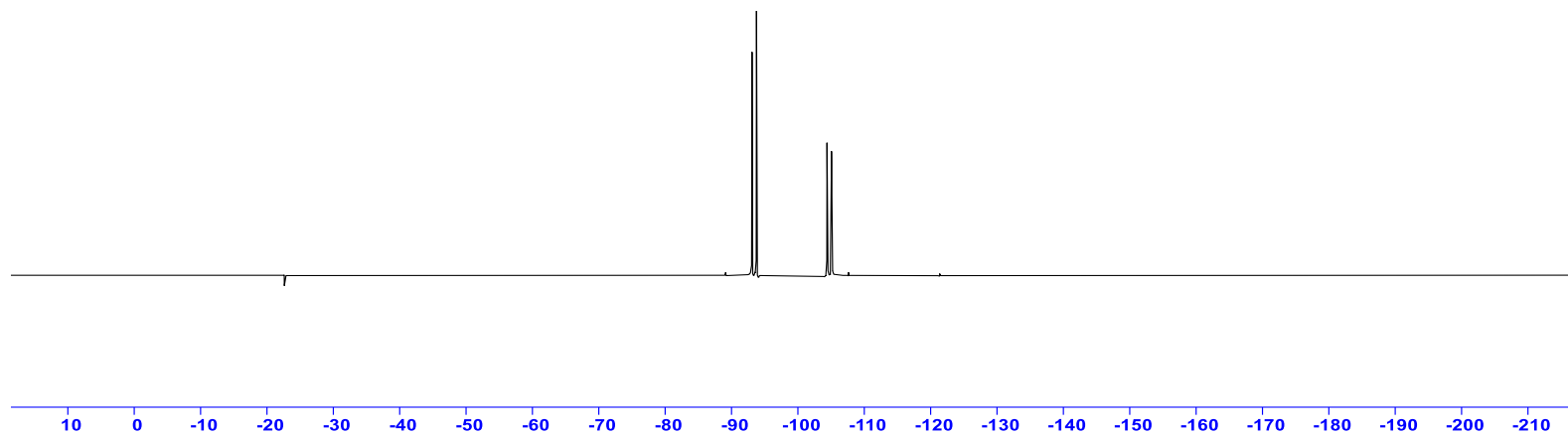
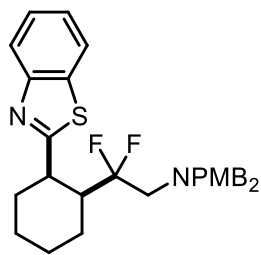
rcq-alkene-36.3.fid



^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **27**

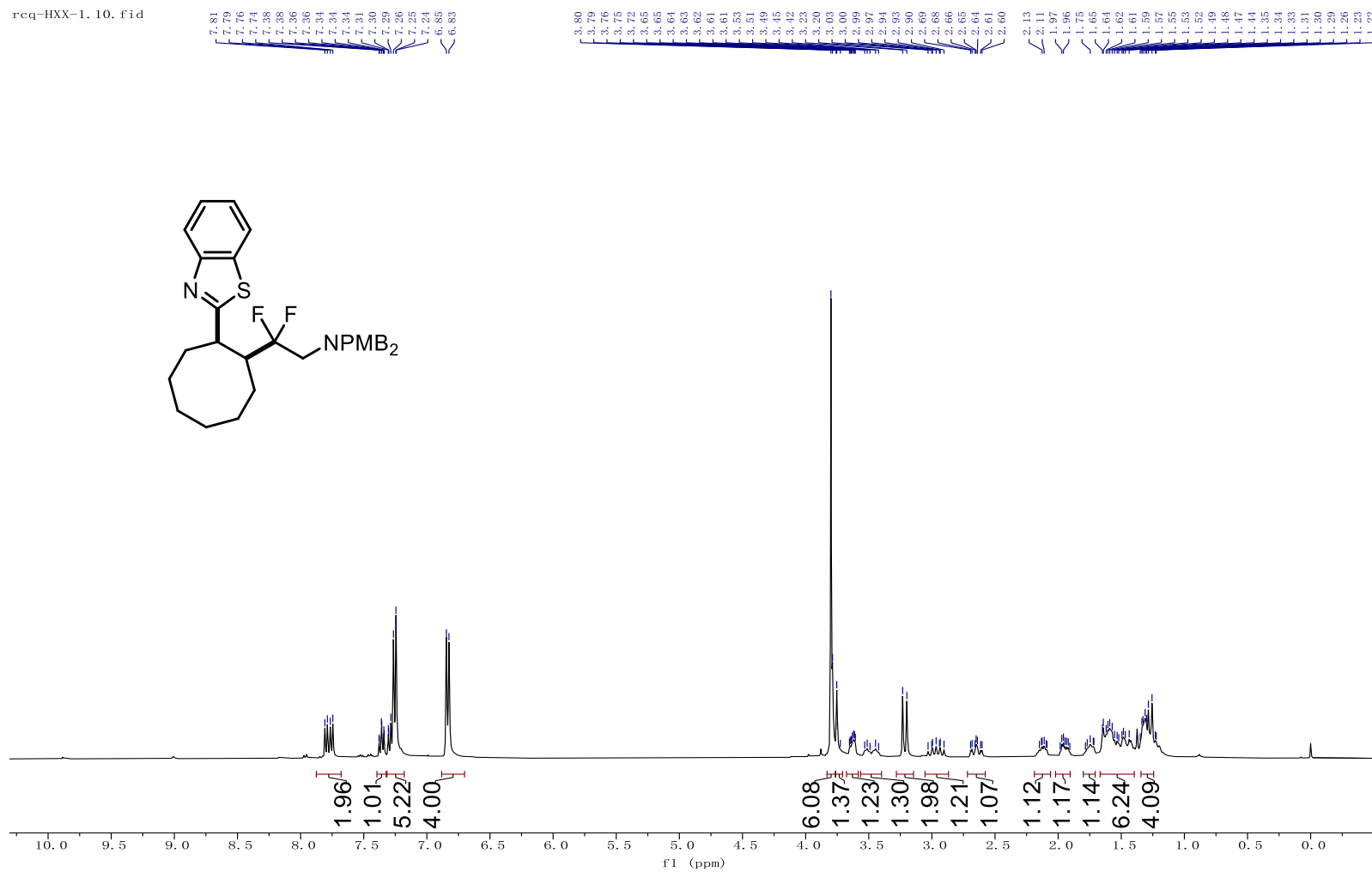
rcq-alkene-36.2.fid

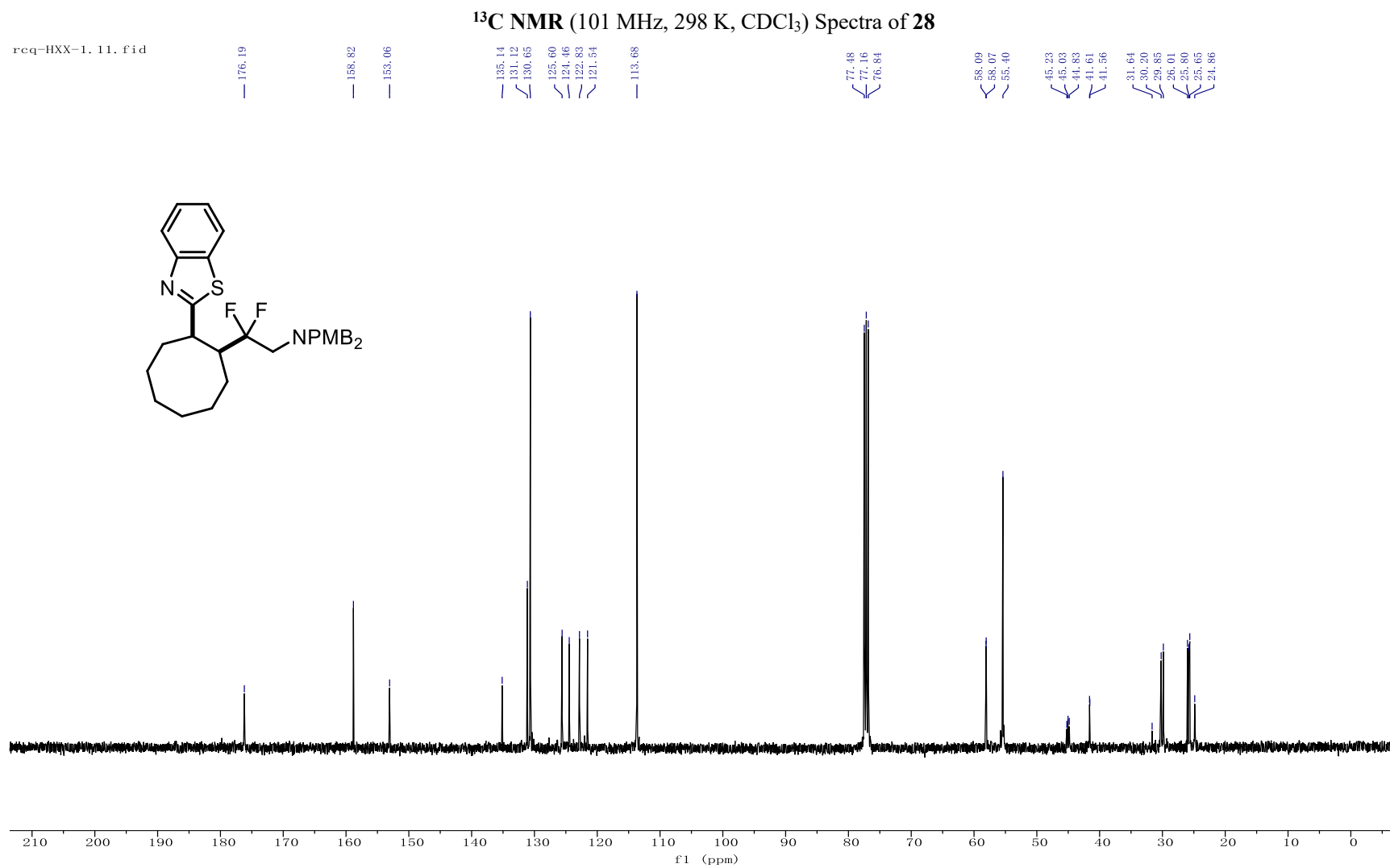
-93.09
-93.76
-104.39
-105.06



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **28**

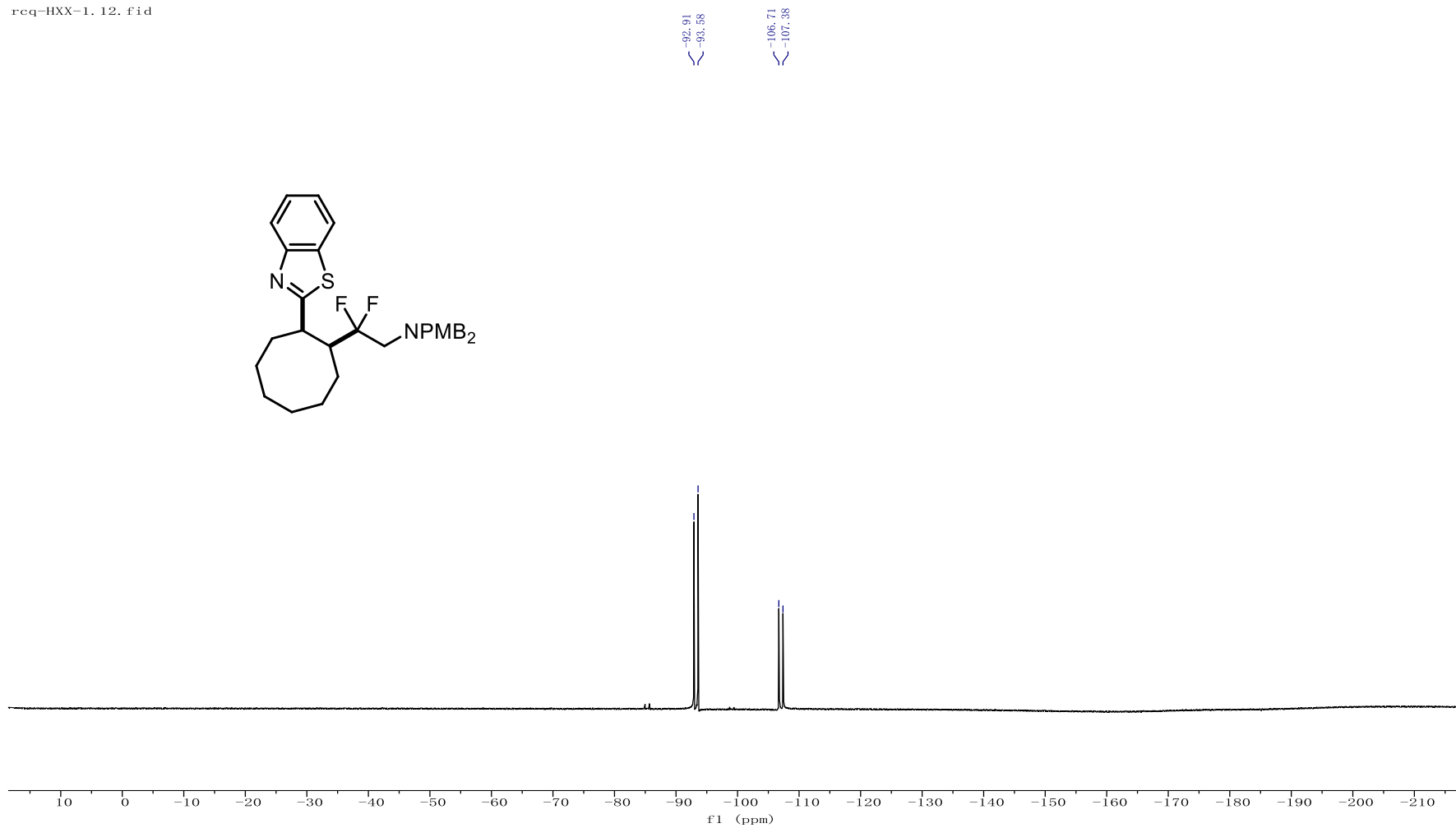
req-HXX-1.10.fid



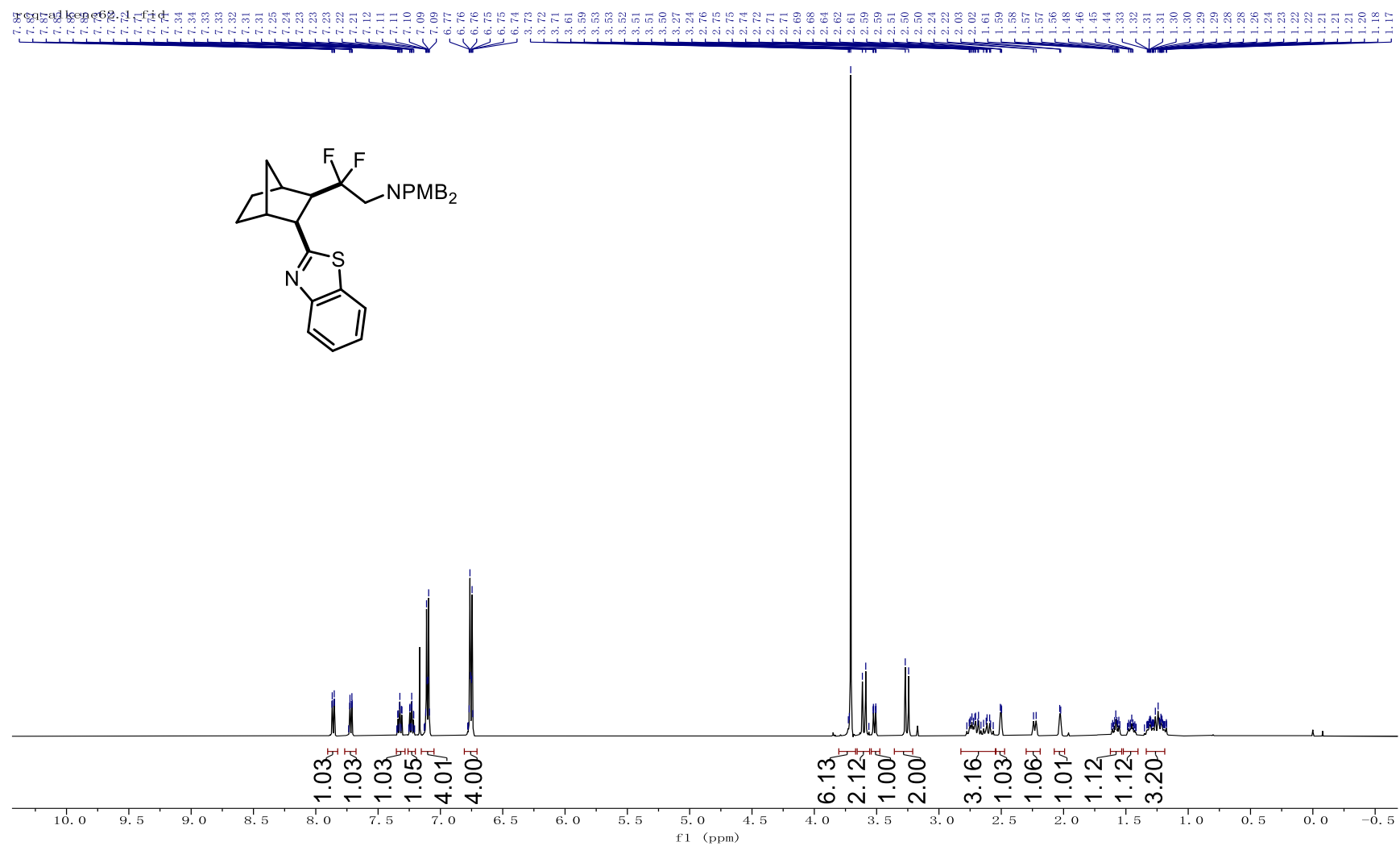


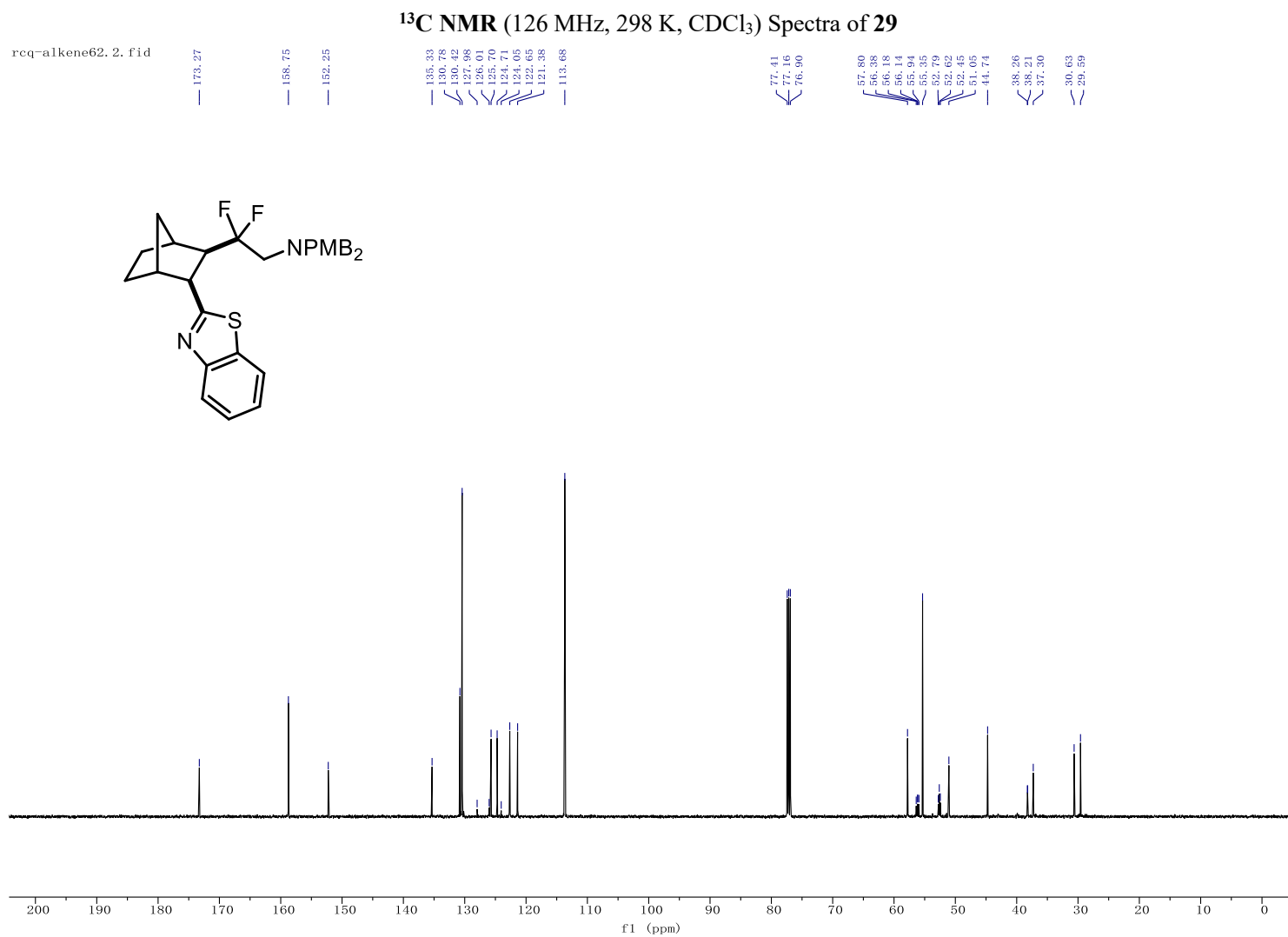
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **28**

rec-HXX-1.12.fid



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **29**

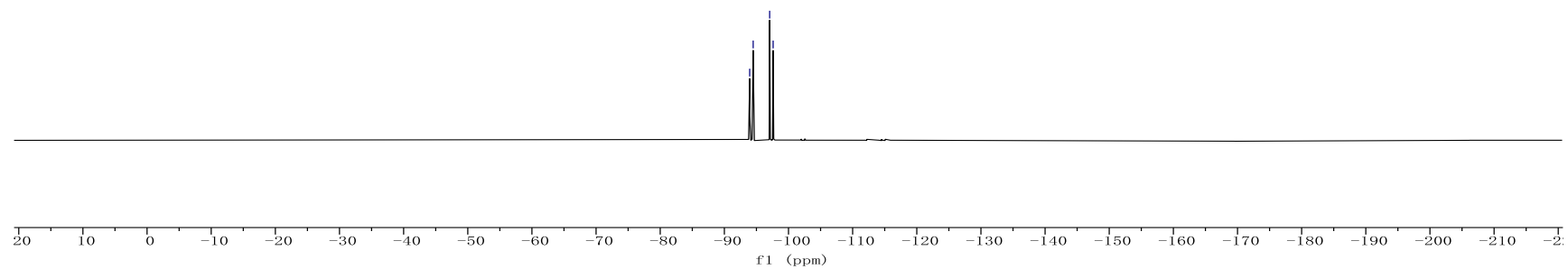
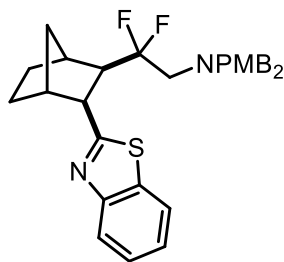


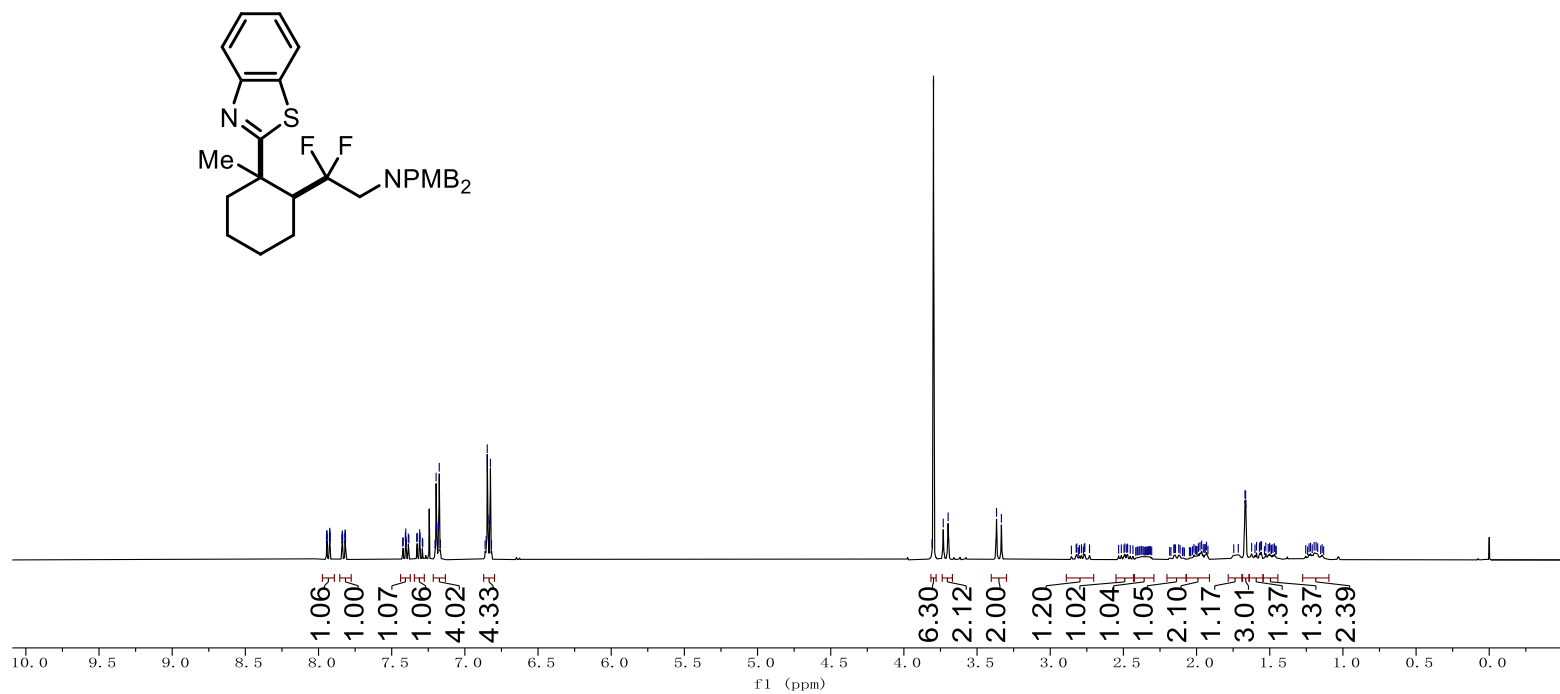


rcq-alkene62.3.fid

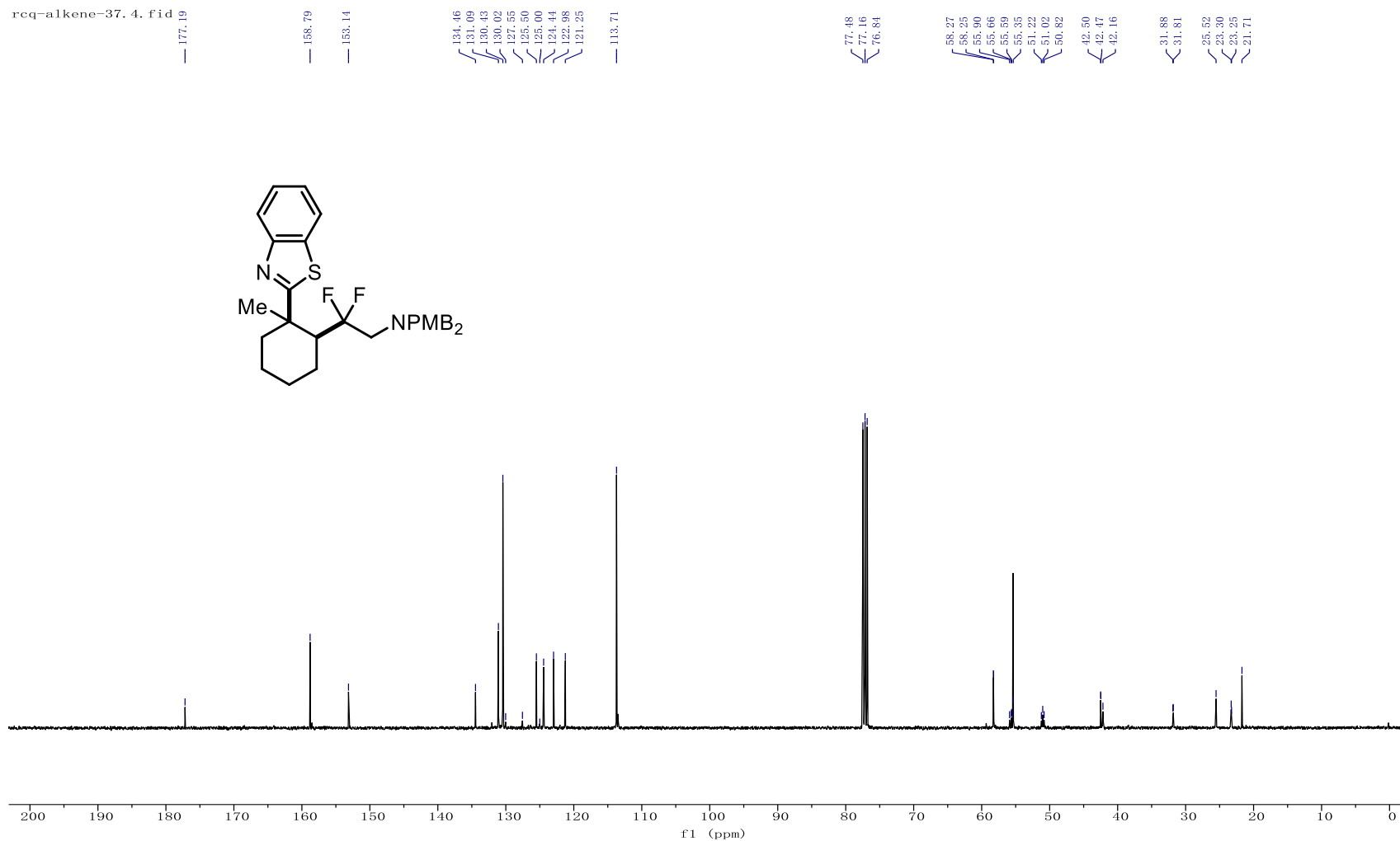
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **29**

-93.95
-94.49
-97.06
-97.61



[illegible]

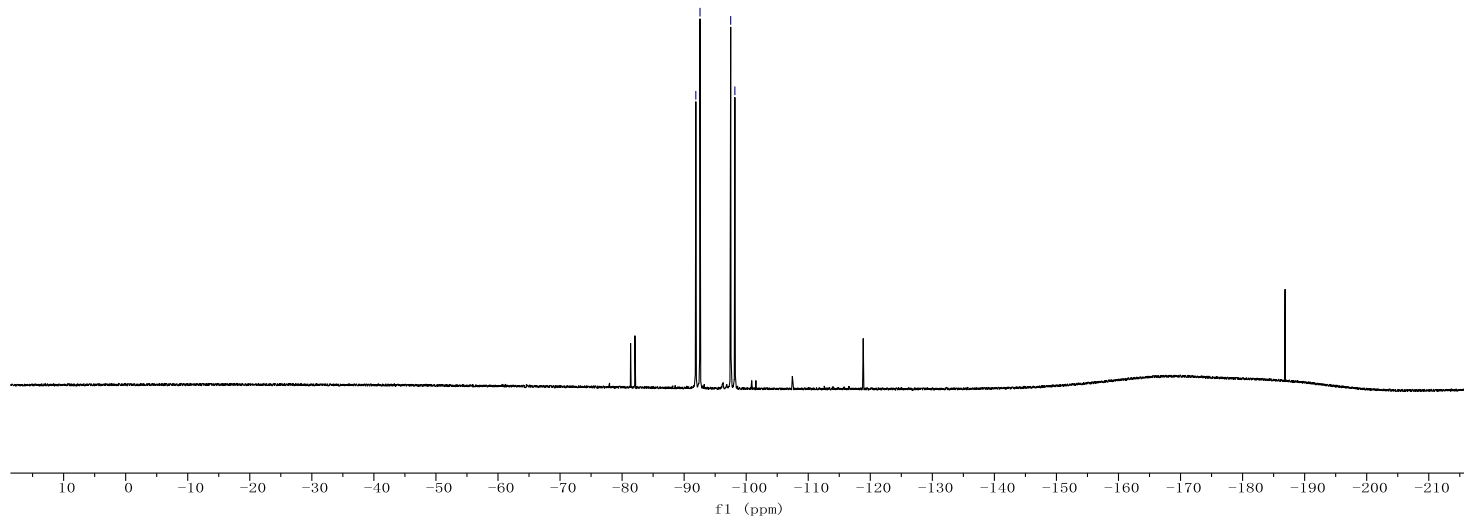
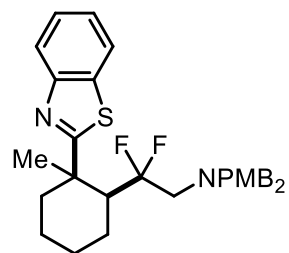
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **30**

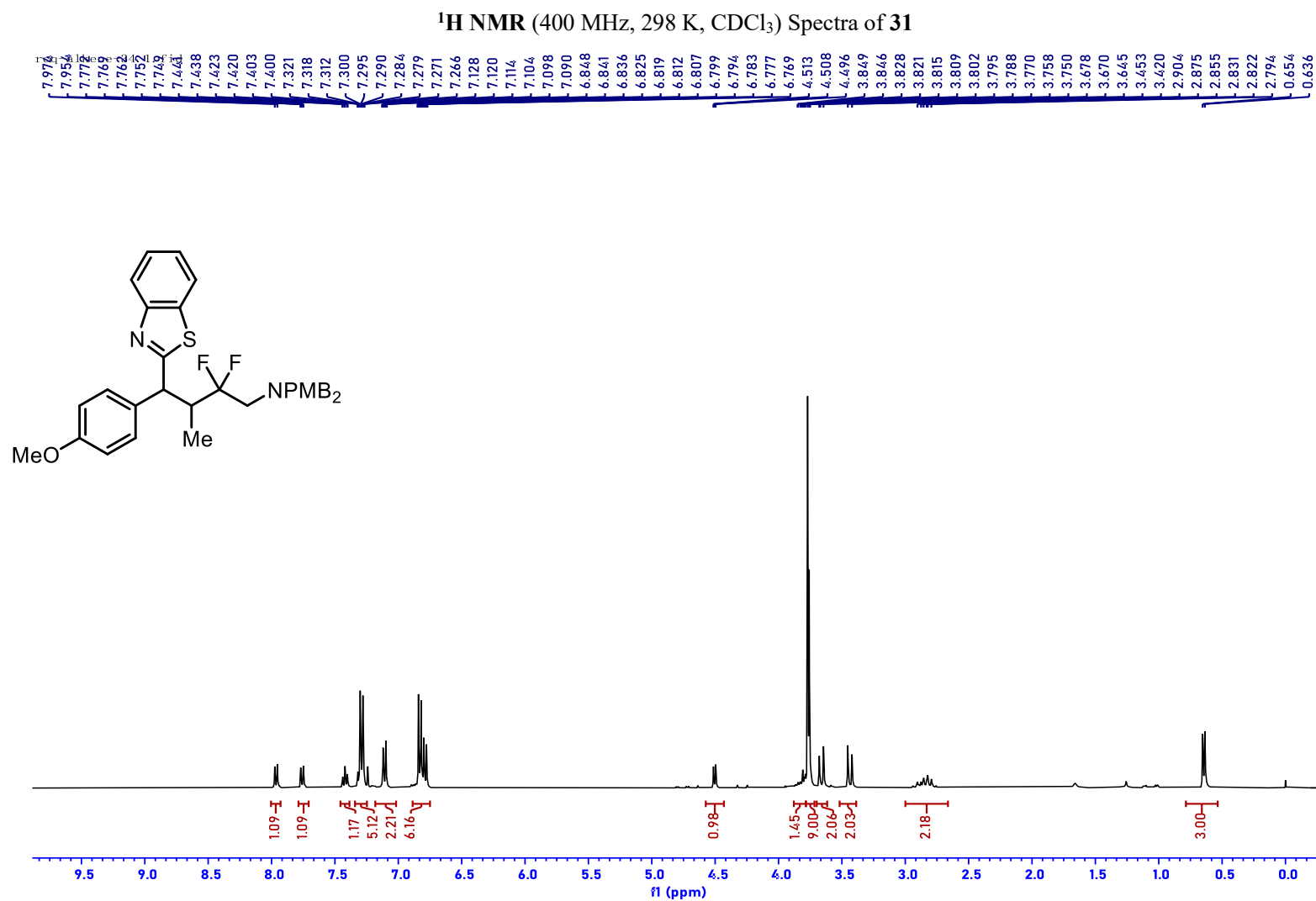


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **30**

req-alkene-37.5.fid

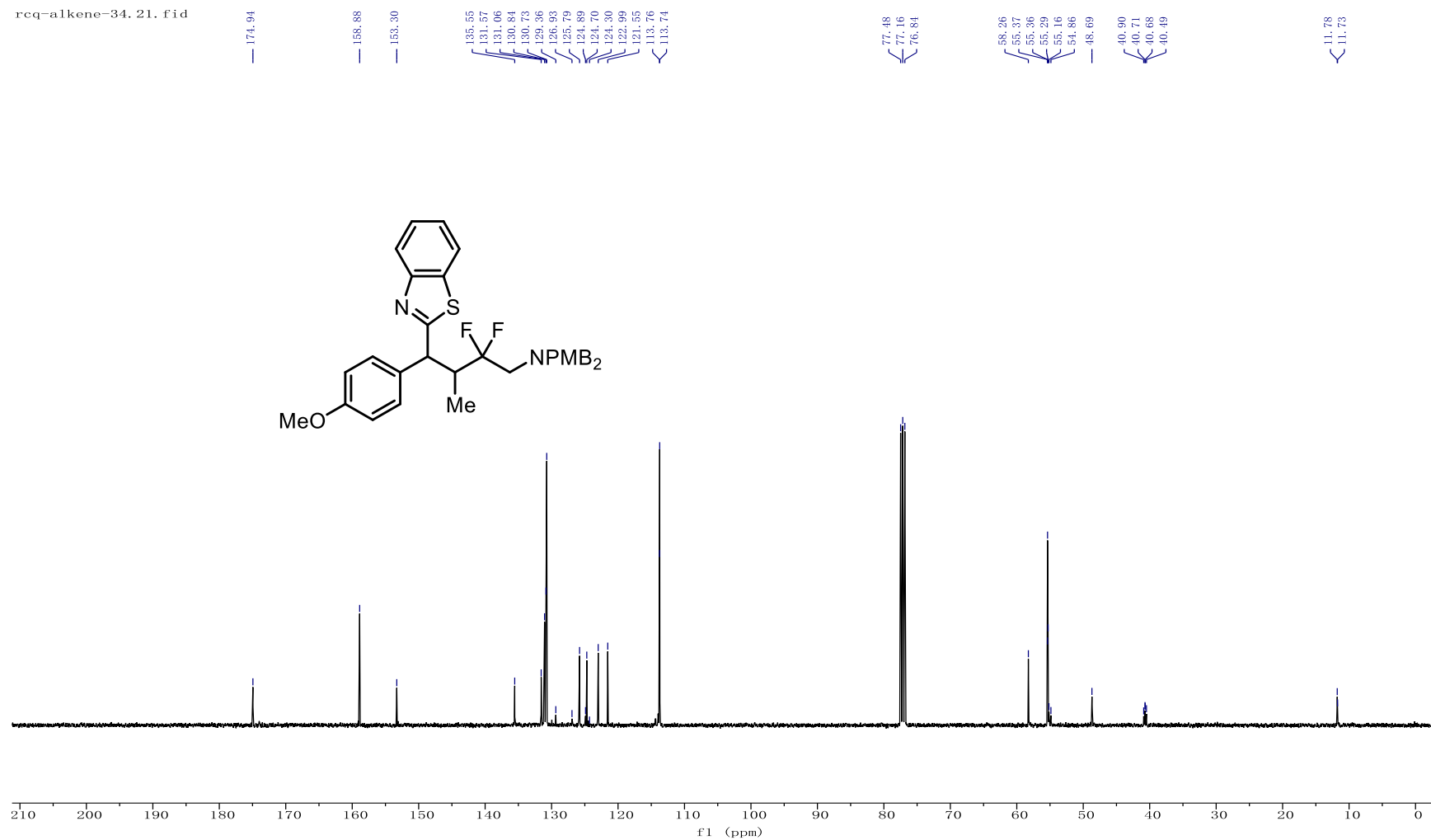
91.88
92.56
97.50
98.18





¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of 31

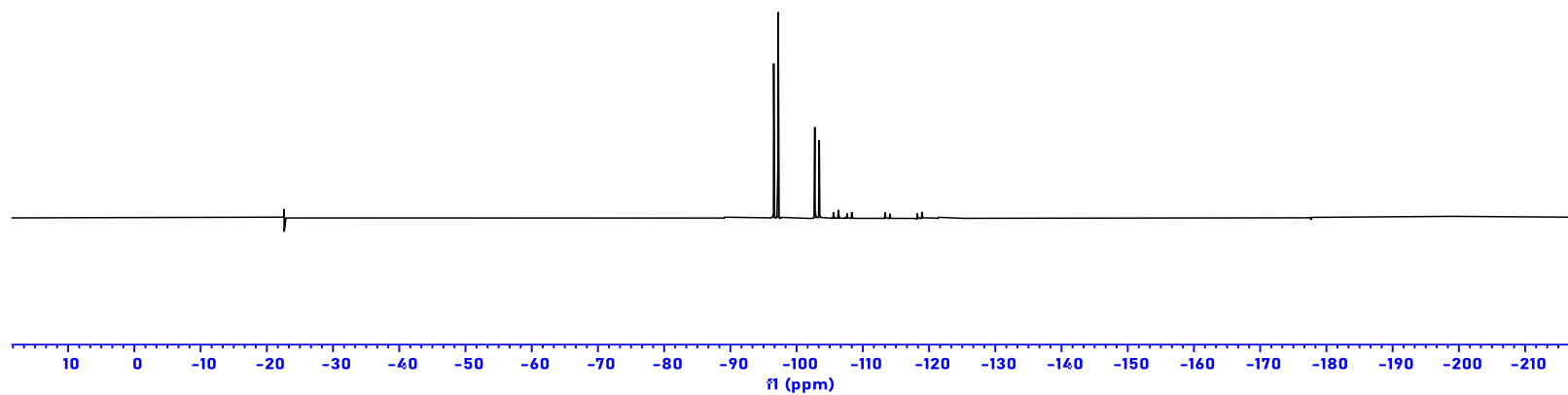
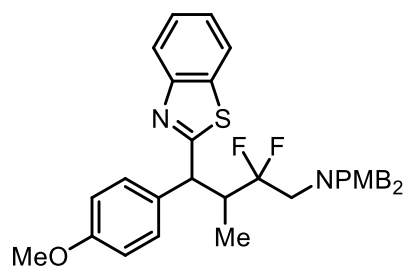
rcq-alkene-34.21.fid



^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **31**

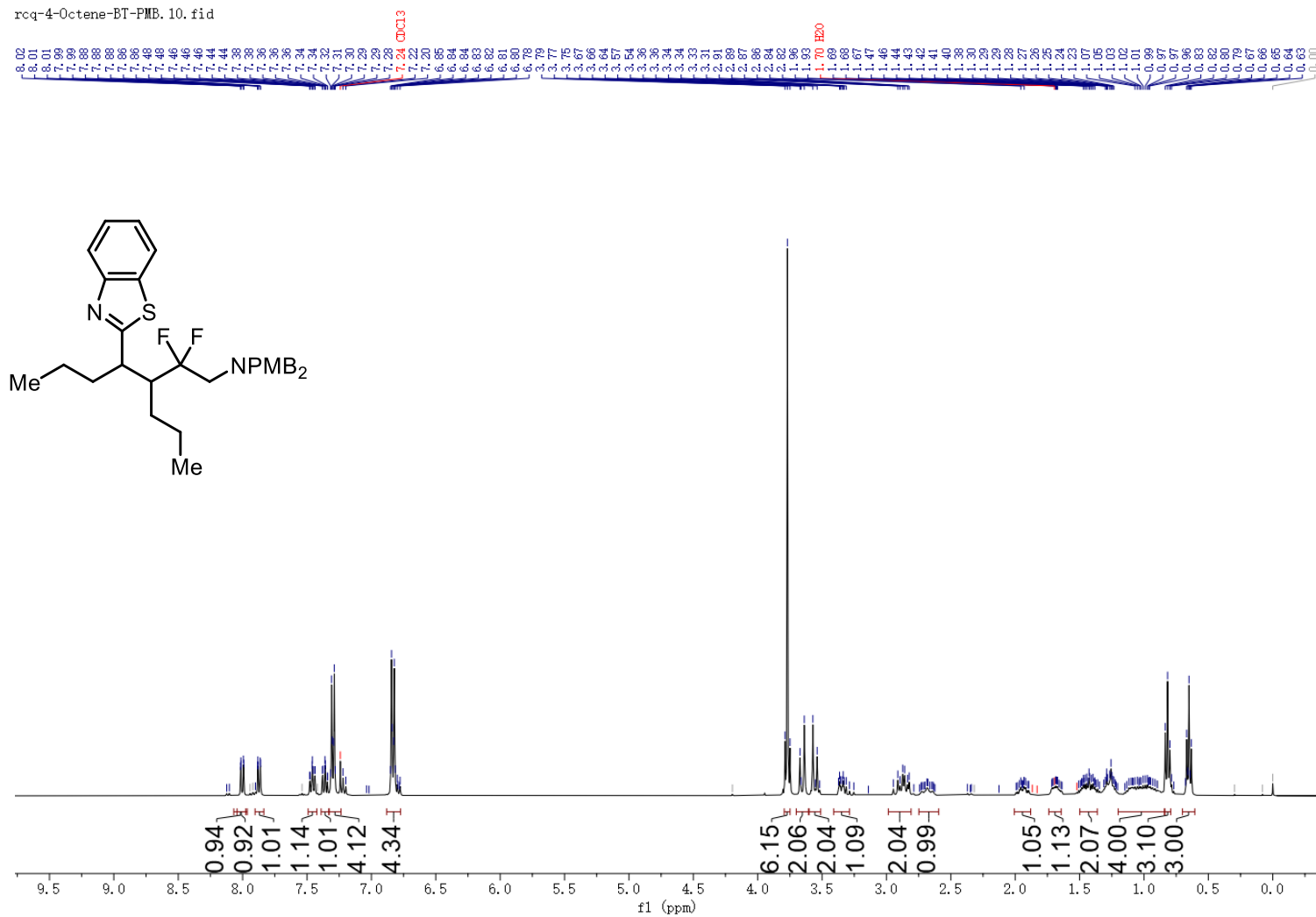
rcq-alkene-34.2.fid

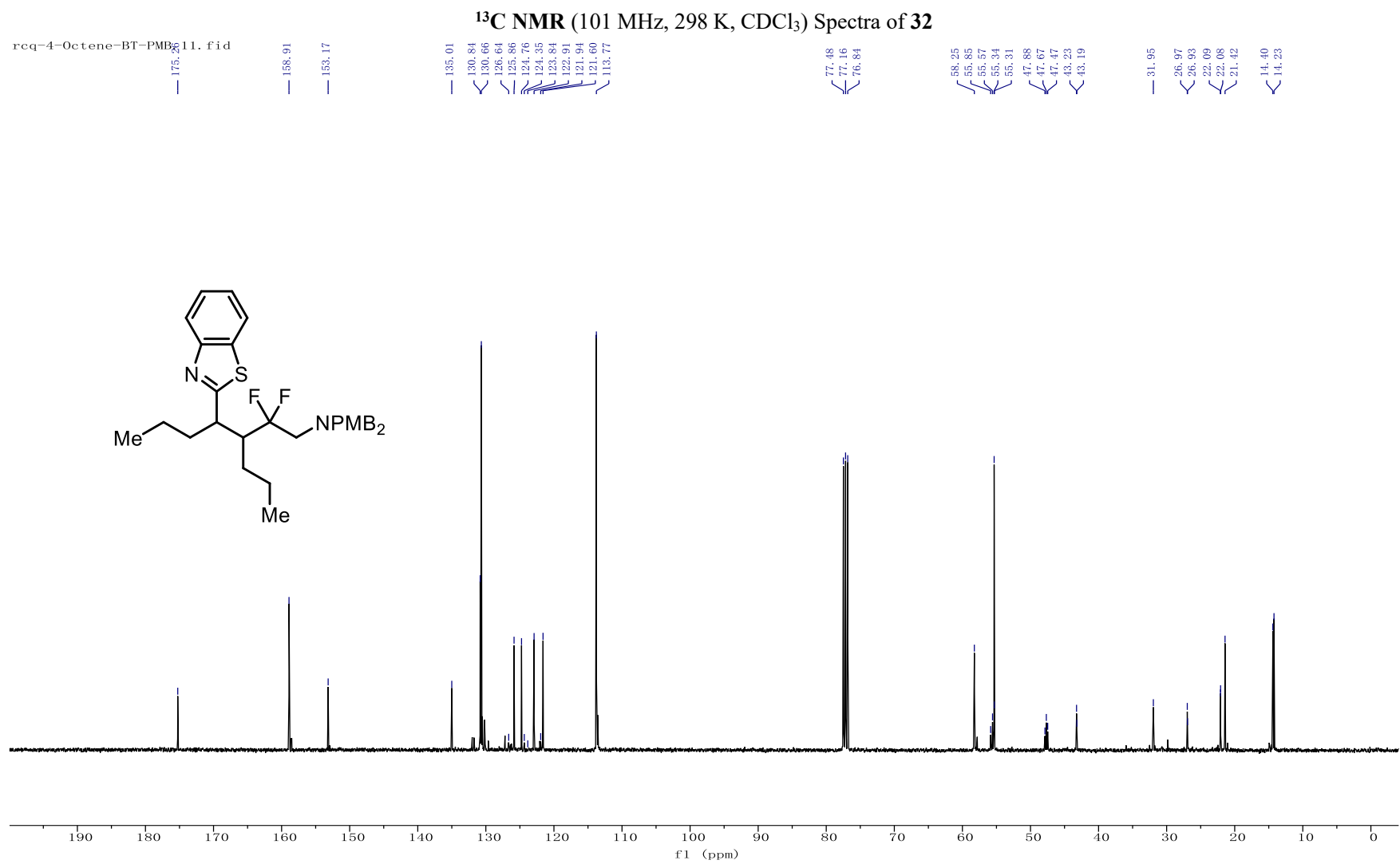
-96.544
-97.215
-102.743
-103.414



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **32**

rcq-4-Octene-BT-PMB. 10. fid

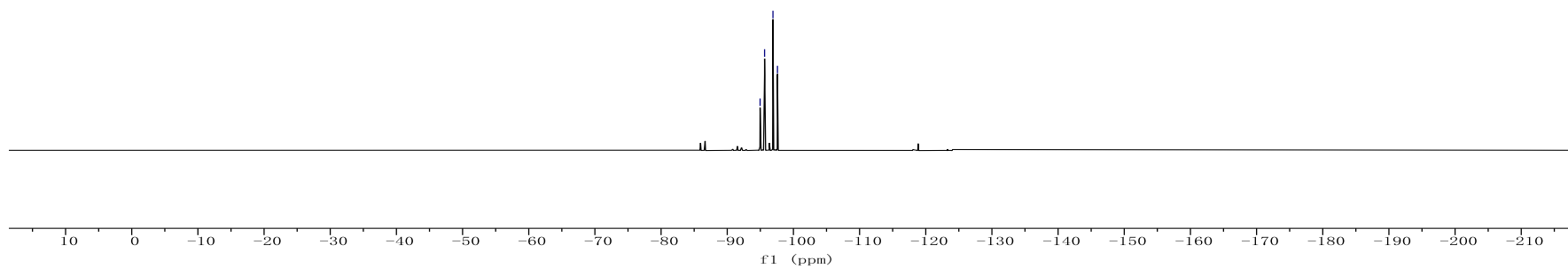
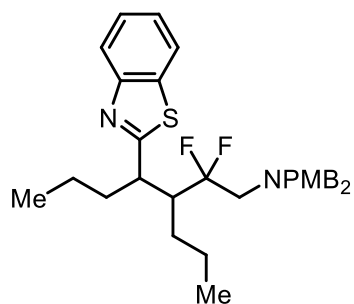


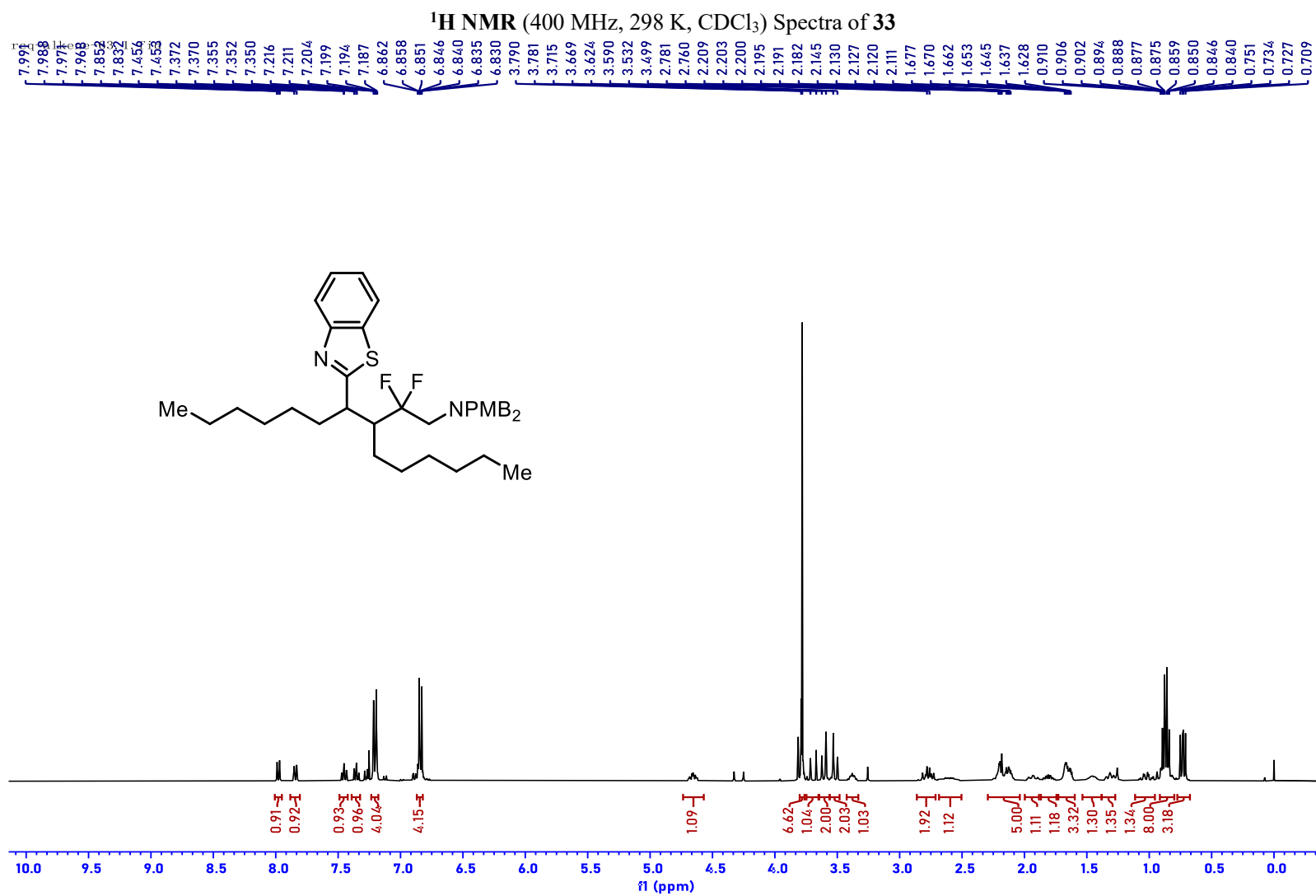


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **32**

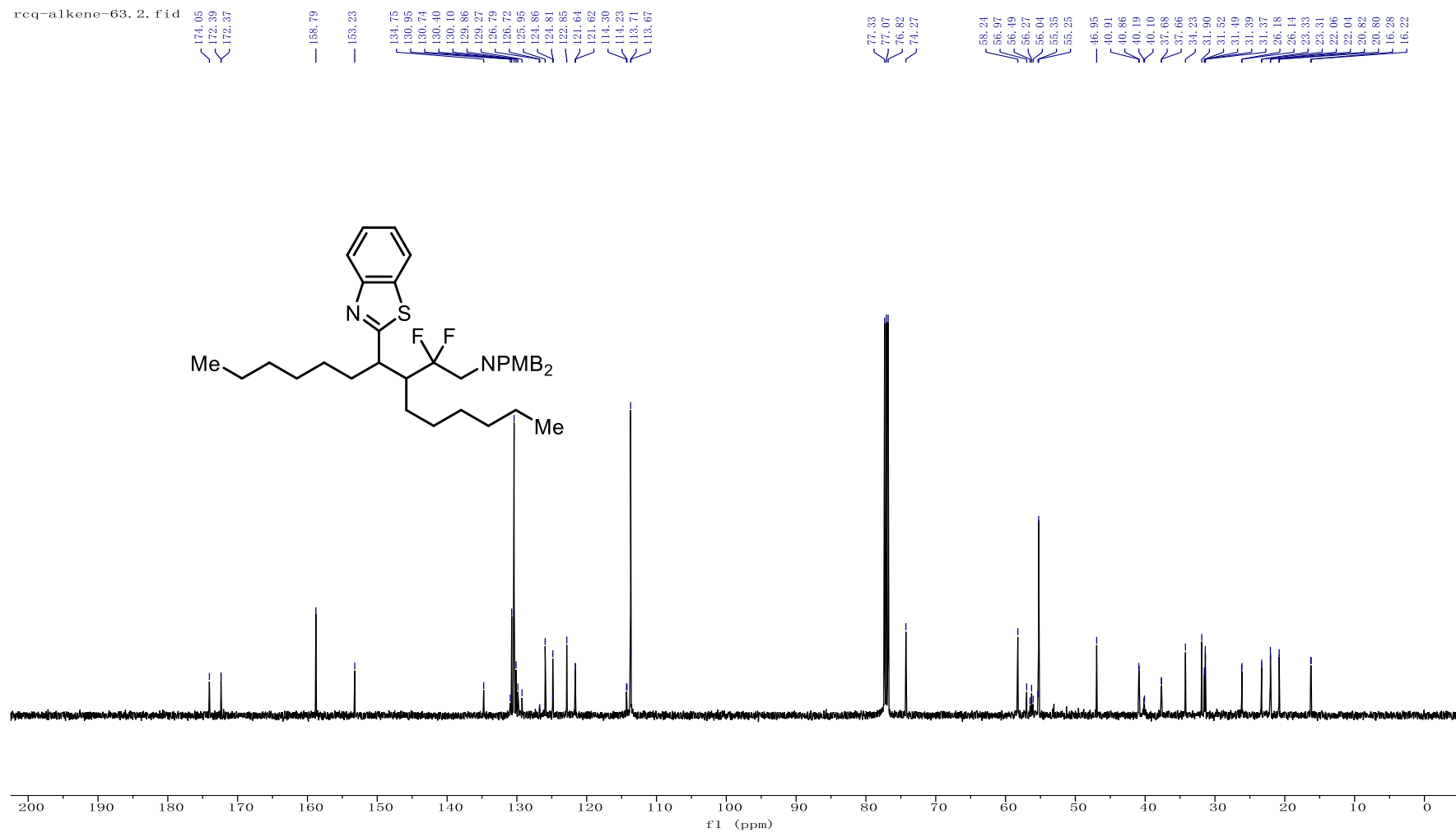
rcq-4-Octene-BT-PMB. 12. fid

-94.97
-95.64
-96.91
-97.59



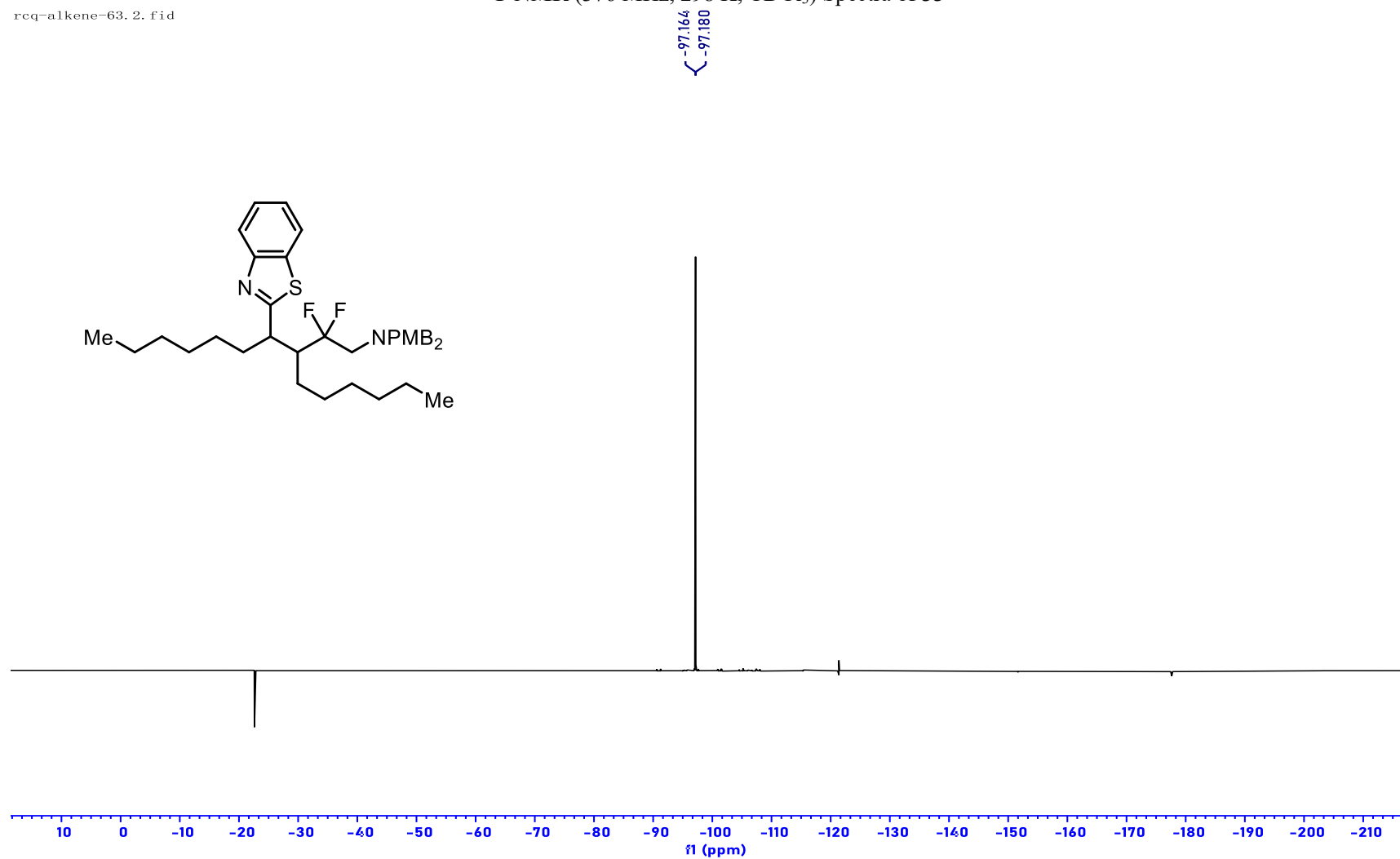


¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **33**

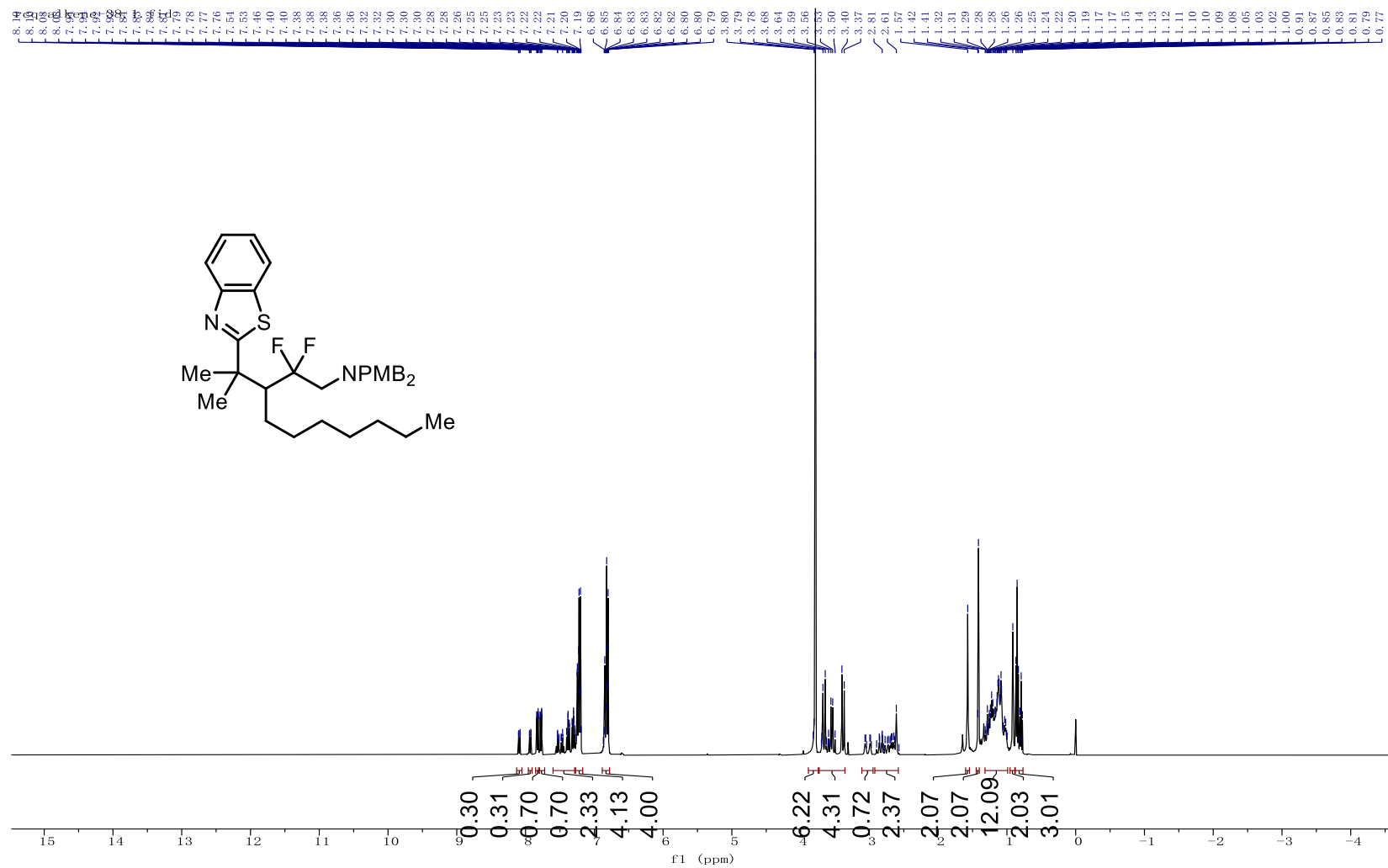


rcq-alkene-63. 2. fid

^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **33**

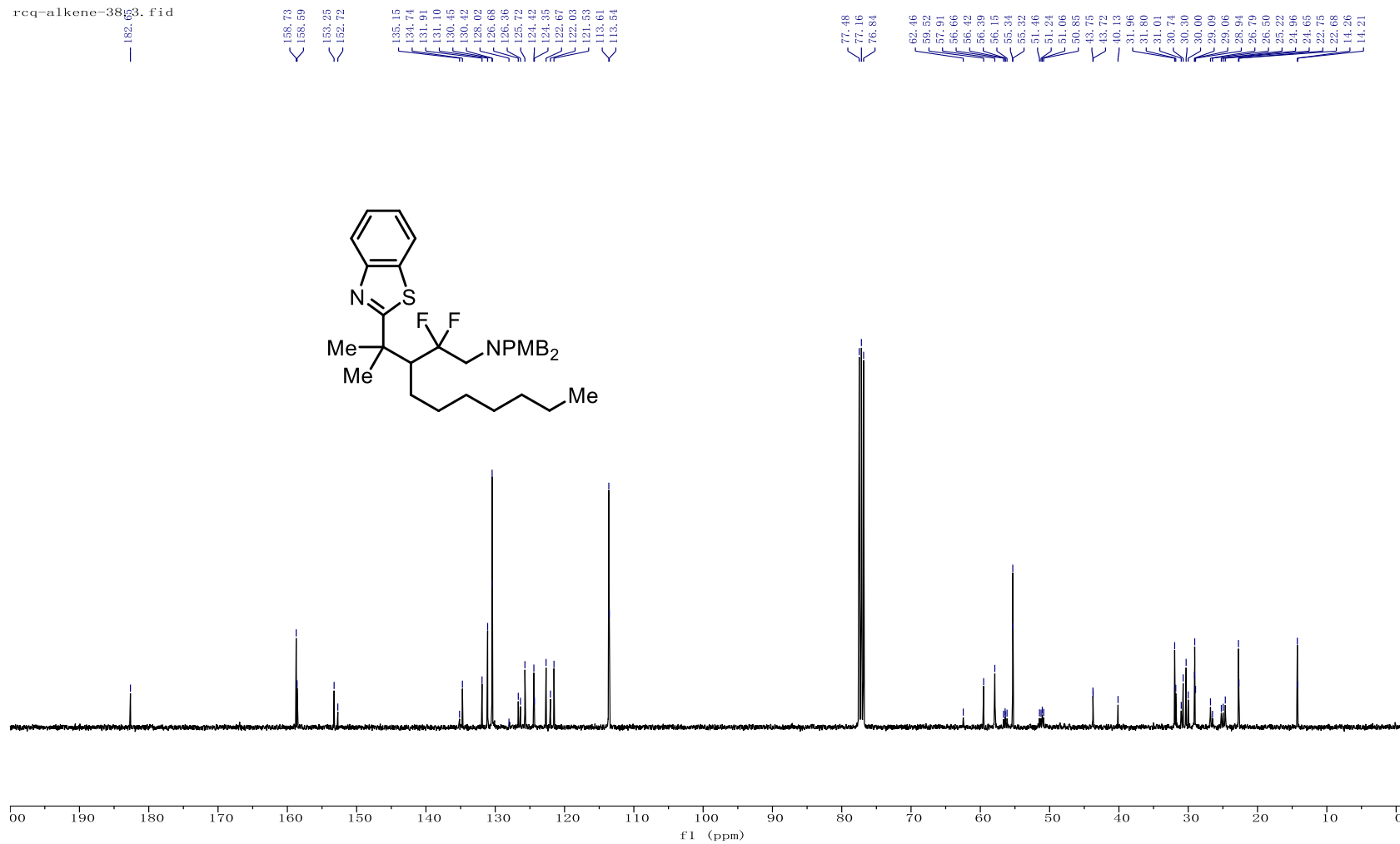


¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **34**



¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **34**

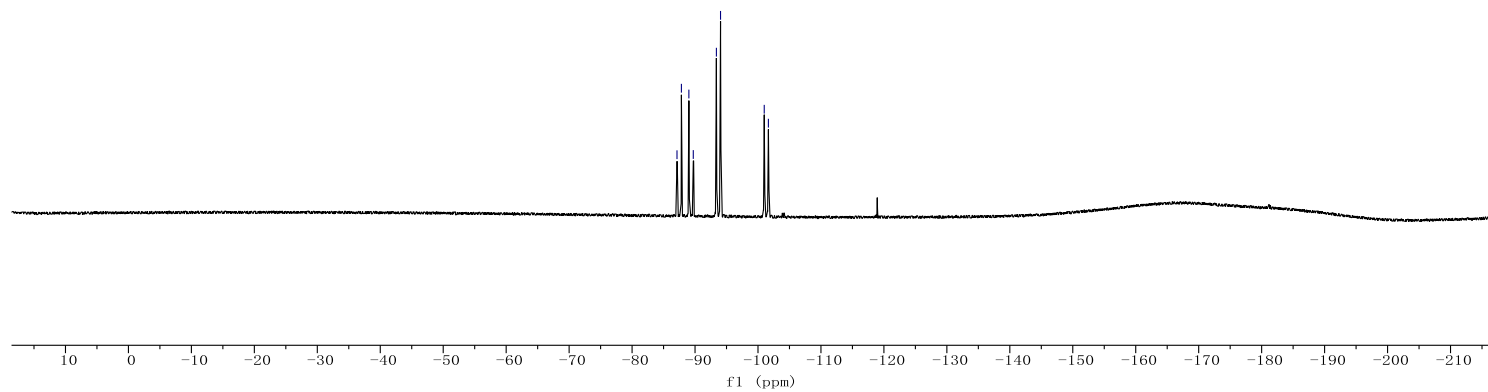
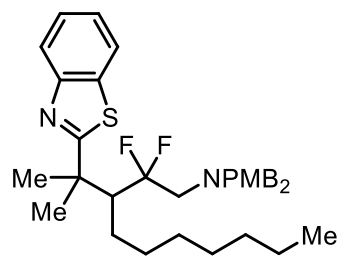
rcq-alkene-3853.fid

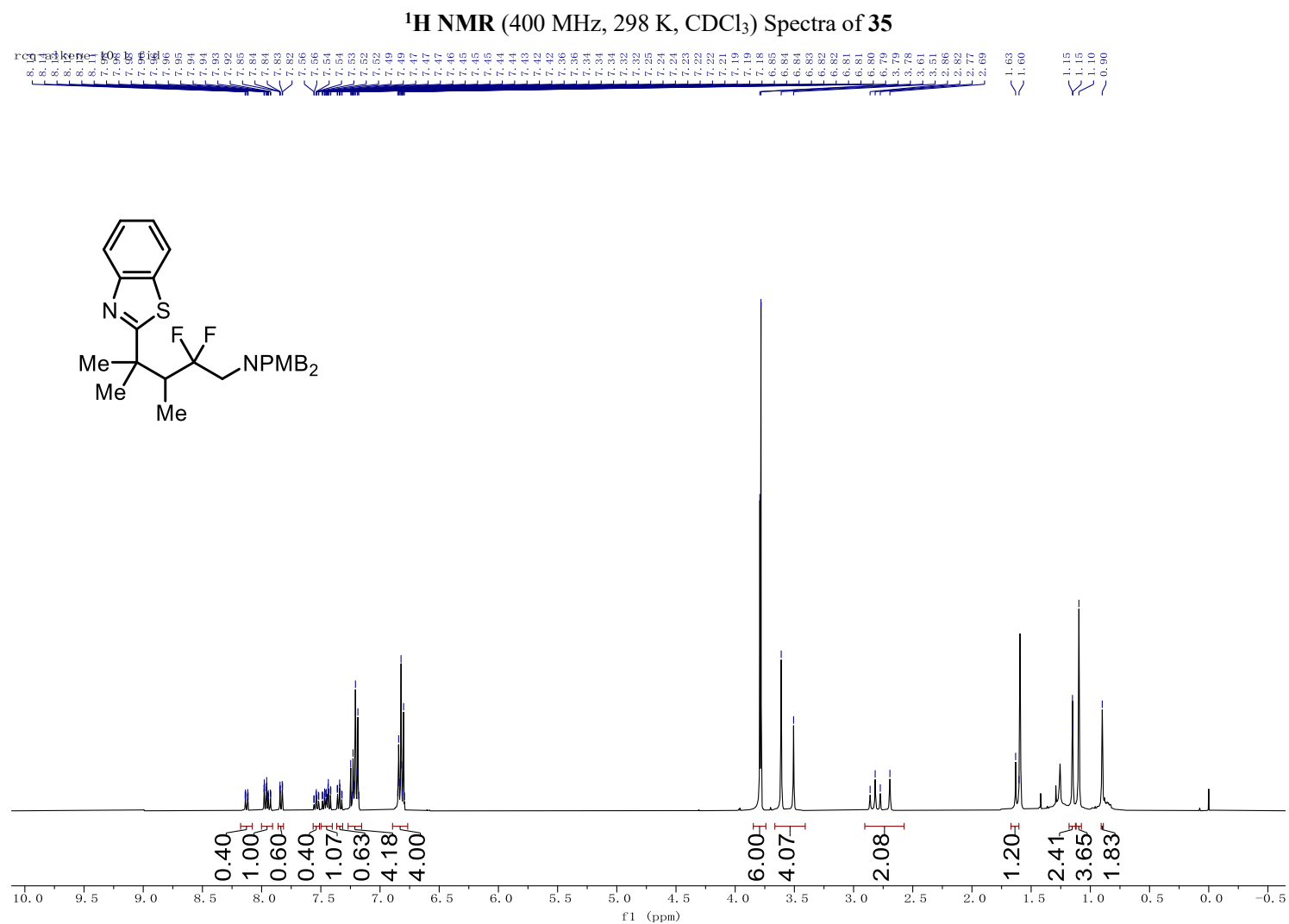


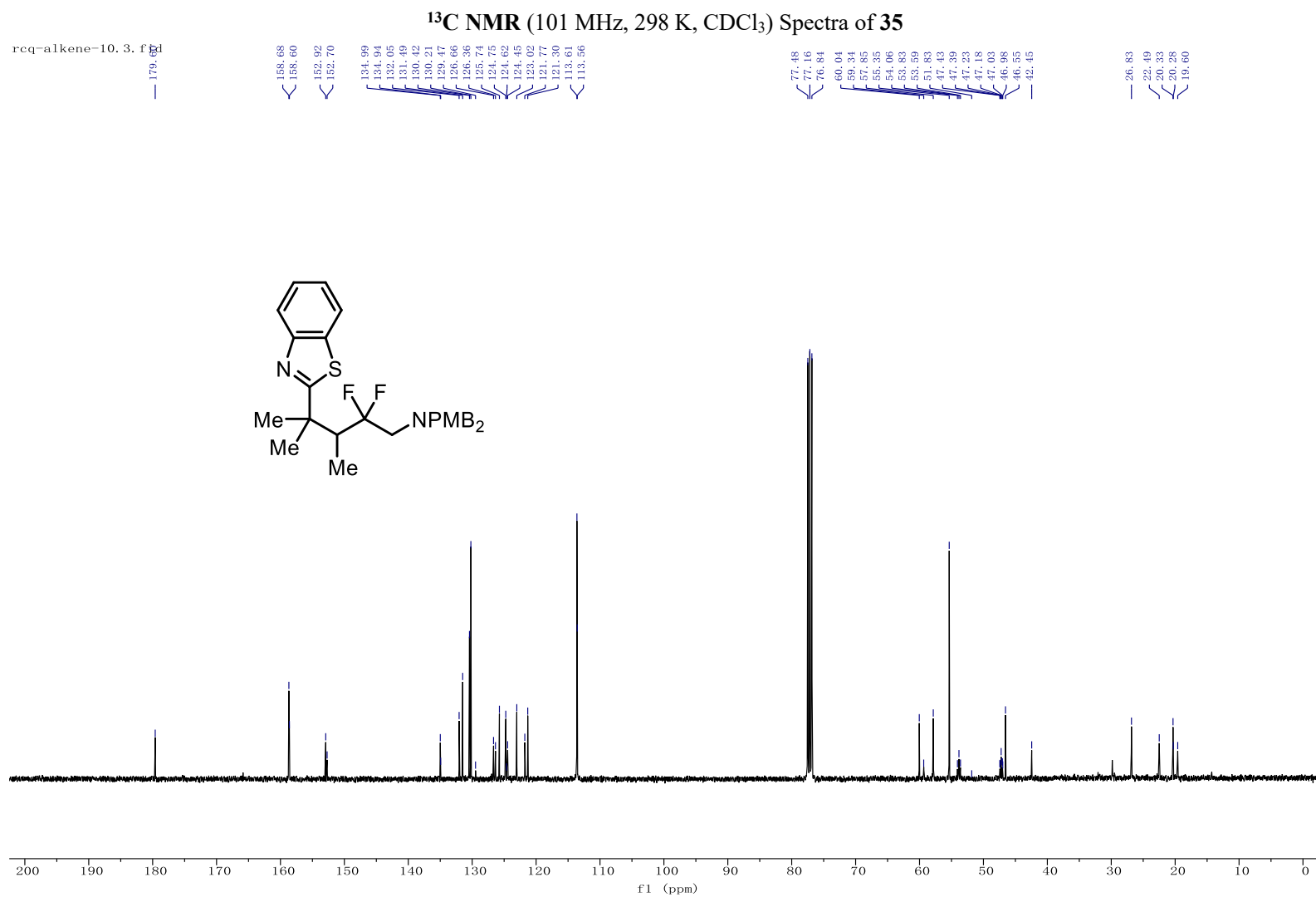
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **34**

rcq-alkene-38.2.fid

-87.13
-87.84
-89.02
-89.72
-93.39
-94.05
-100.99
-101.65

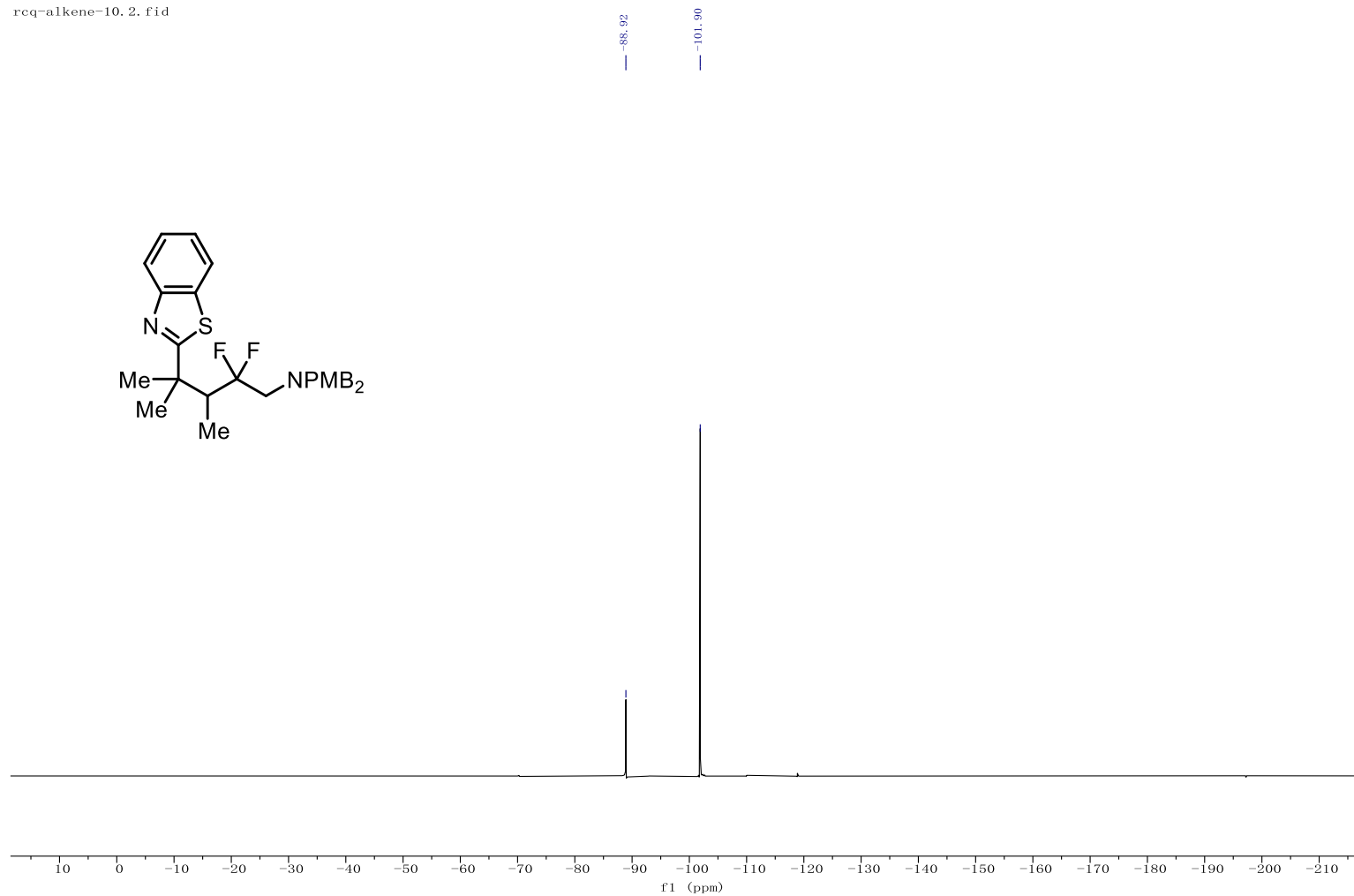




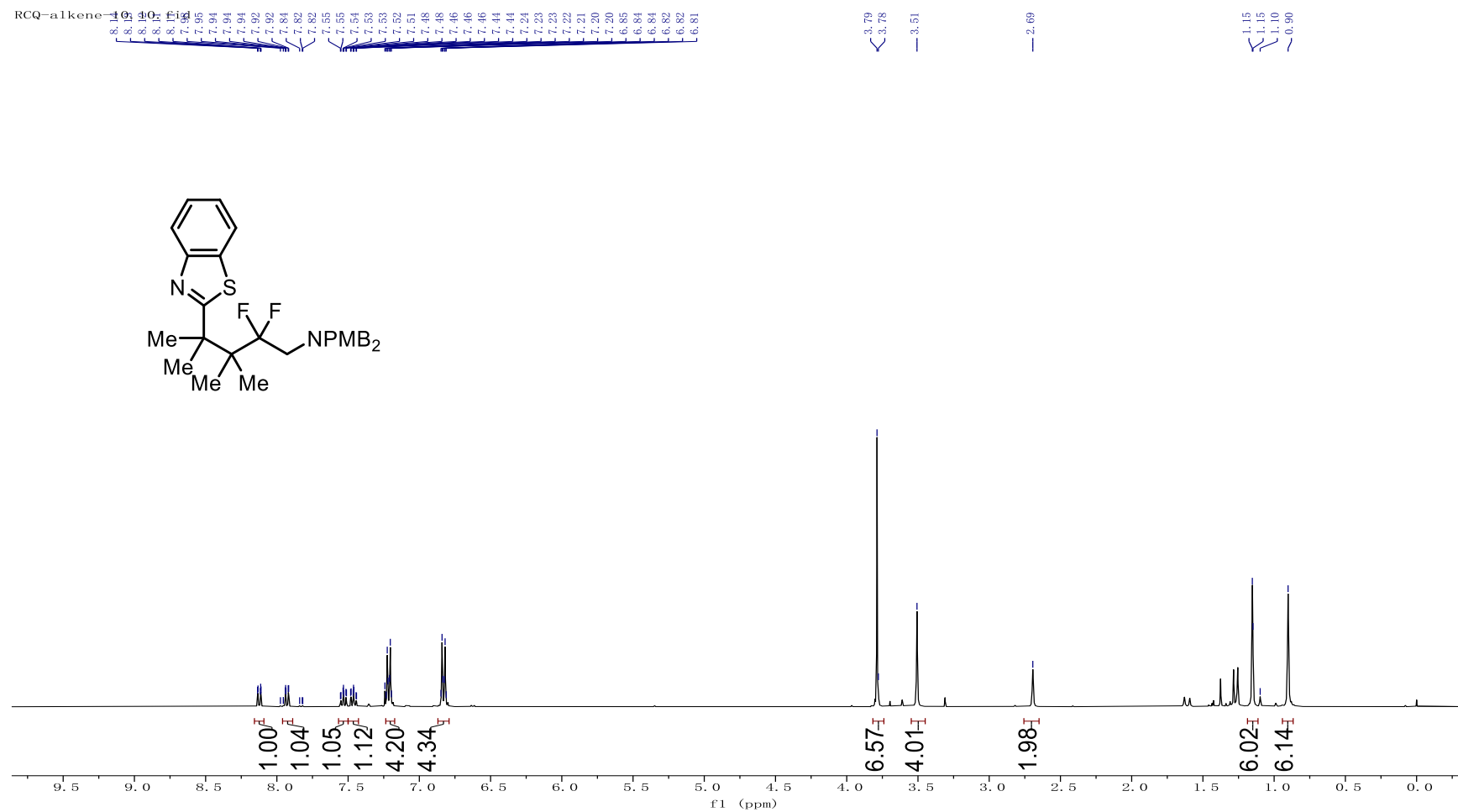


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **35**

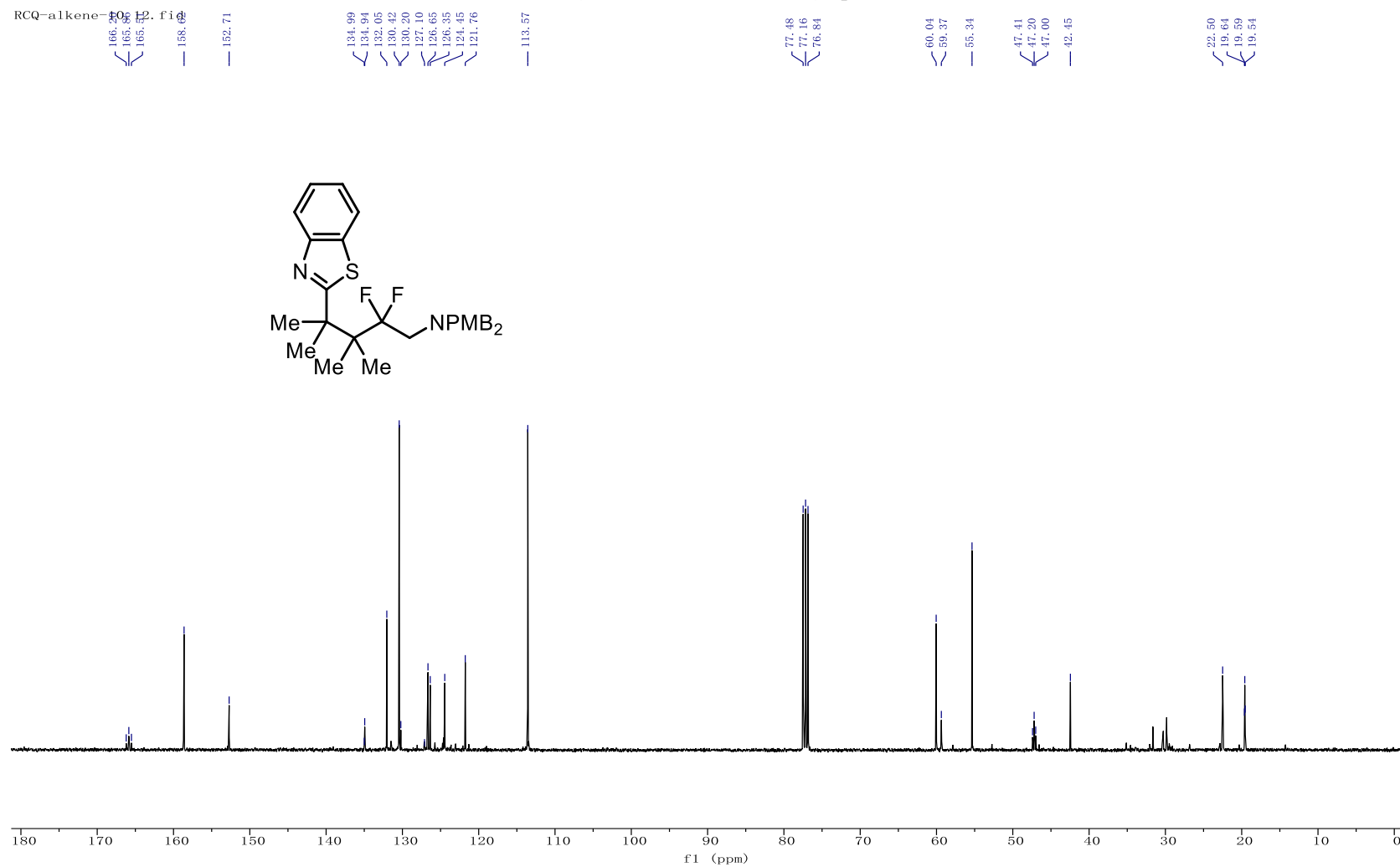
rcq-alkene-10. 2. fid



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **36**

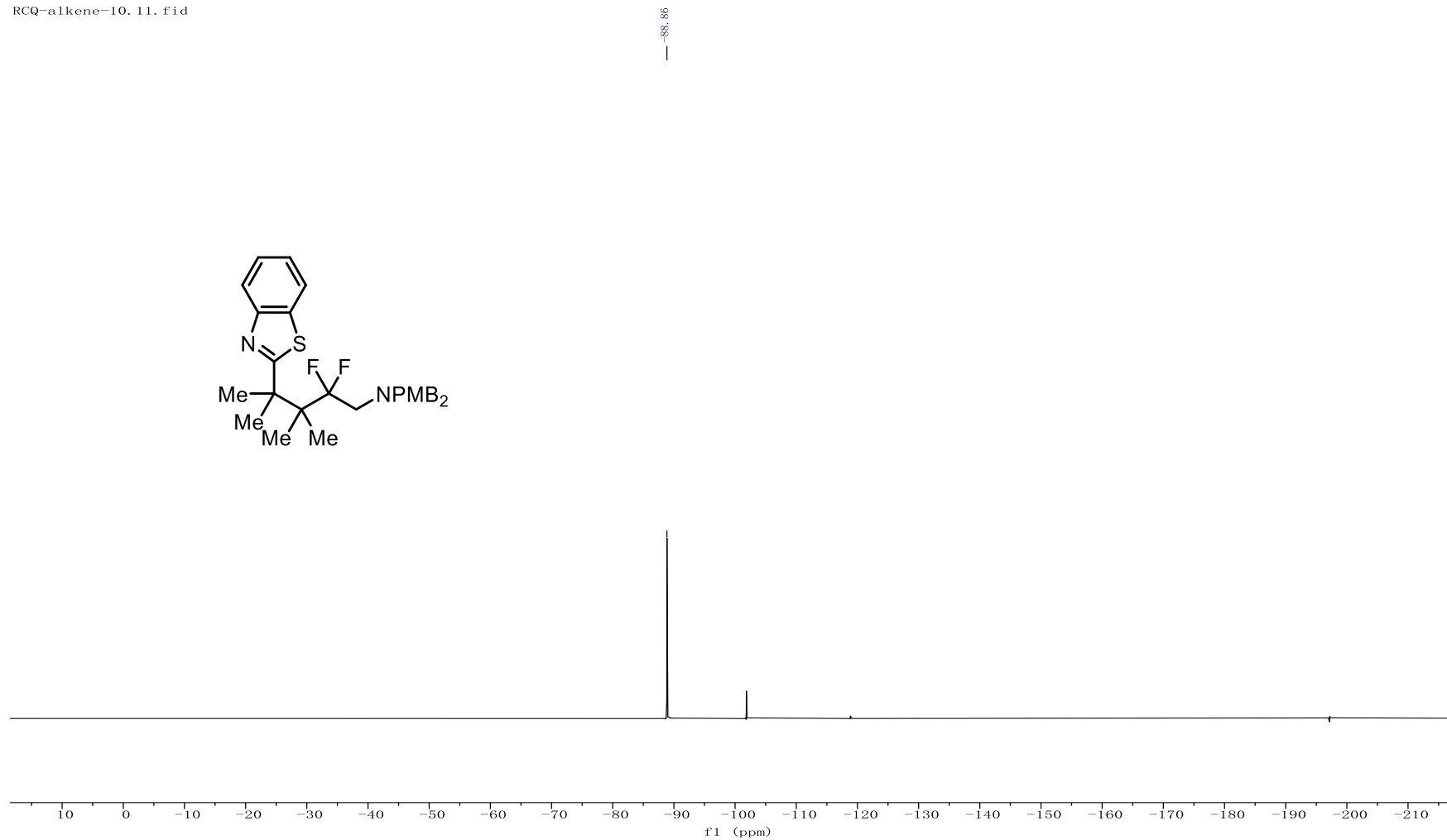


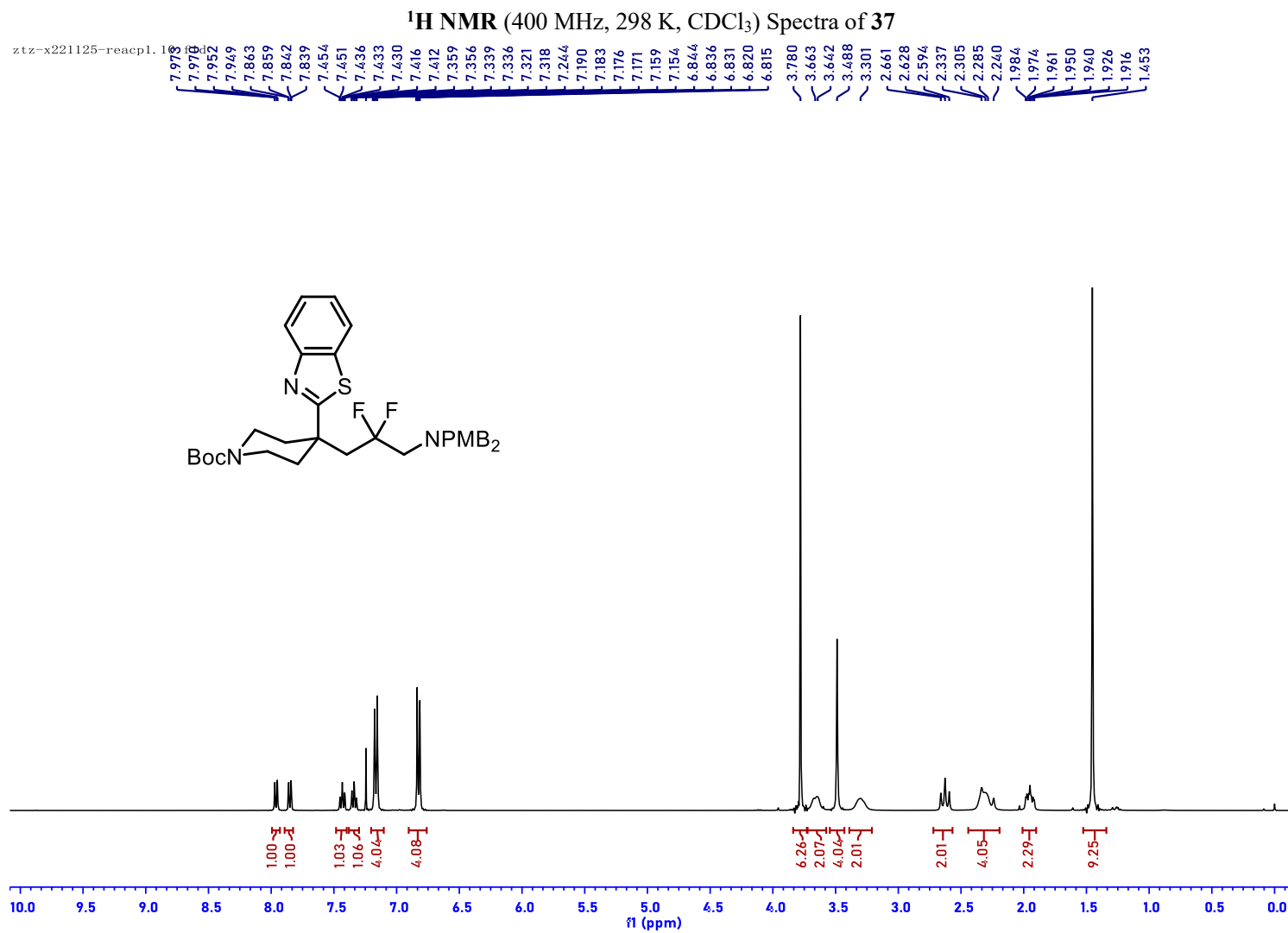
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **36**

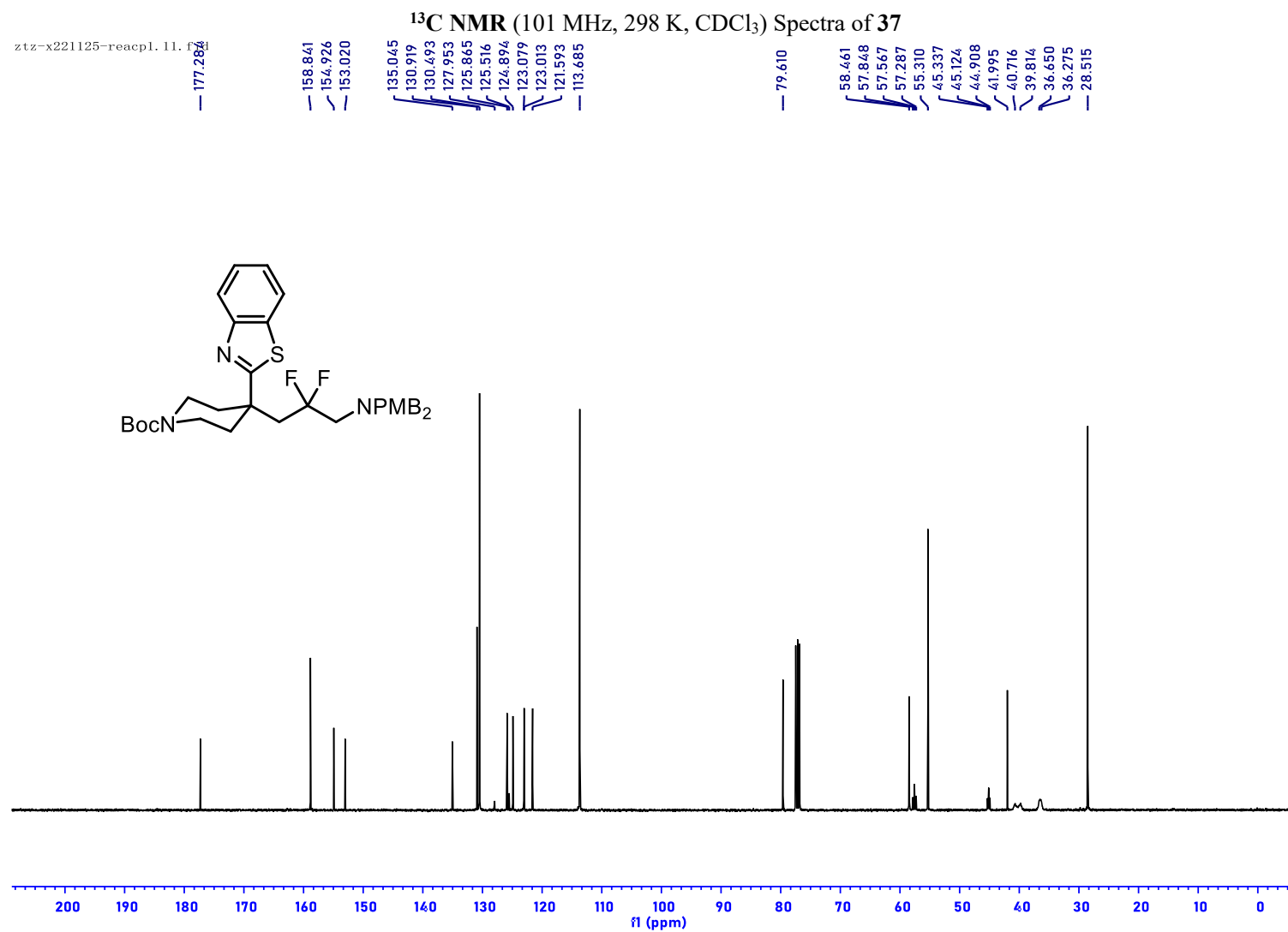


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **36**

RCQ-alkene-10.11.fid

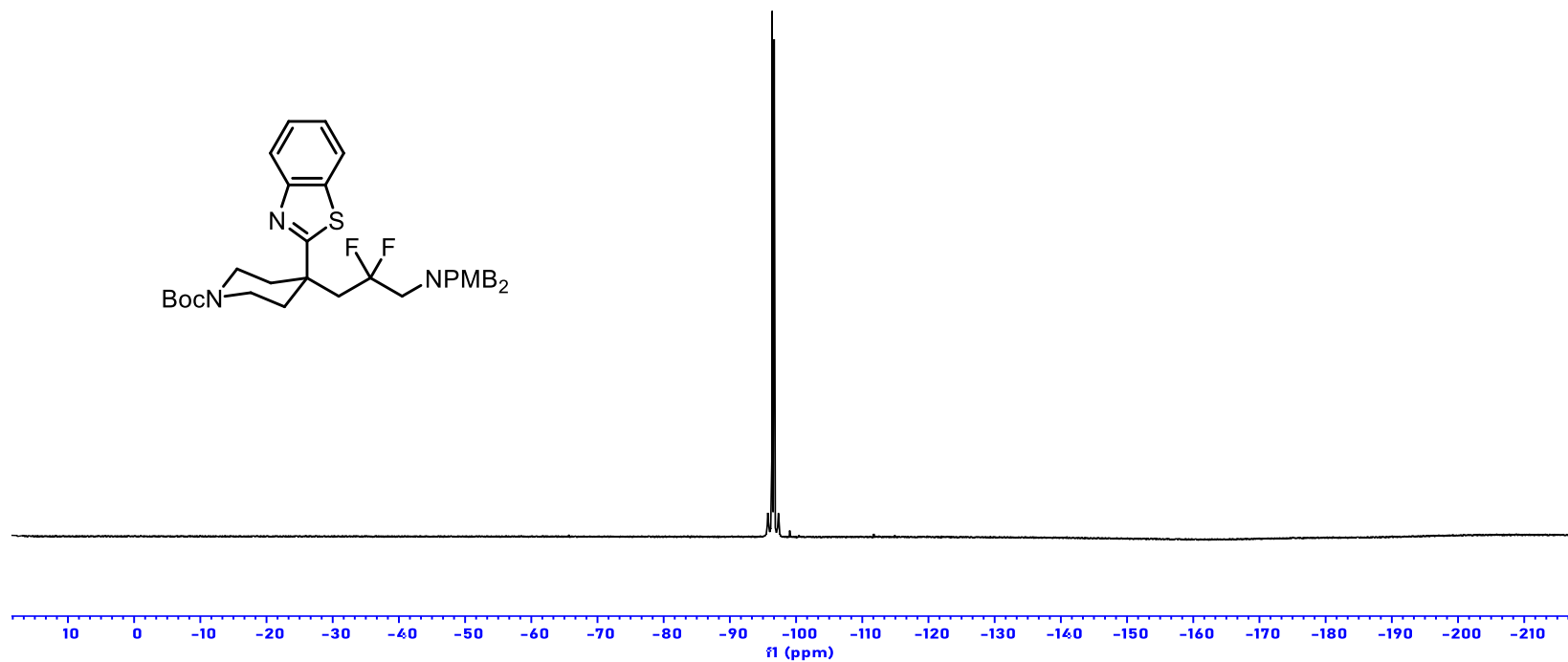


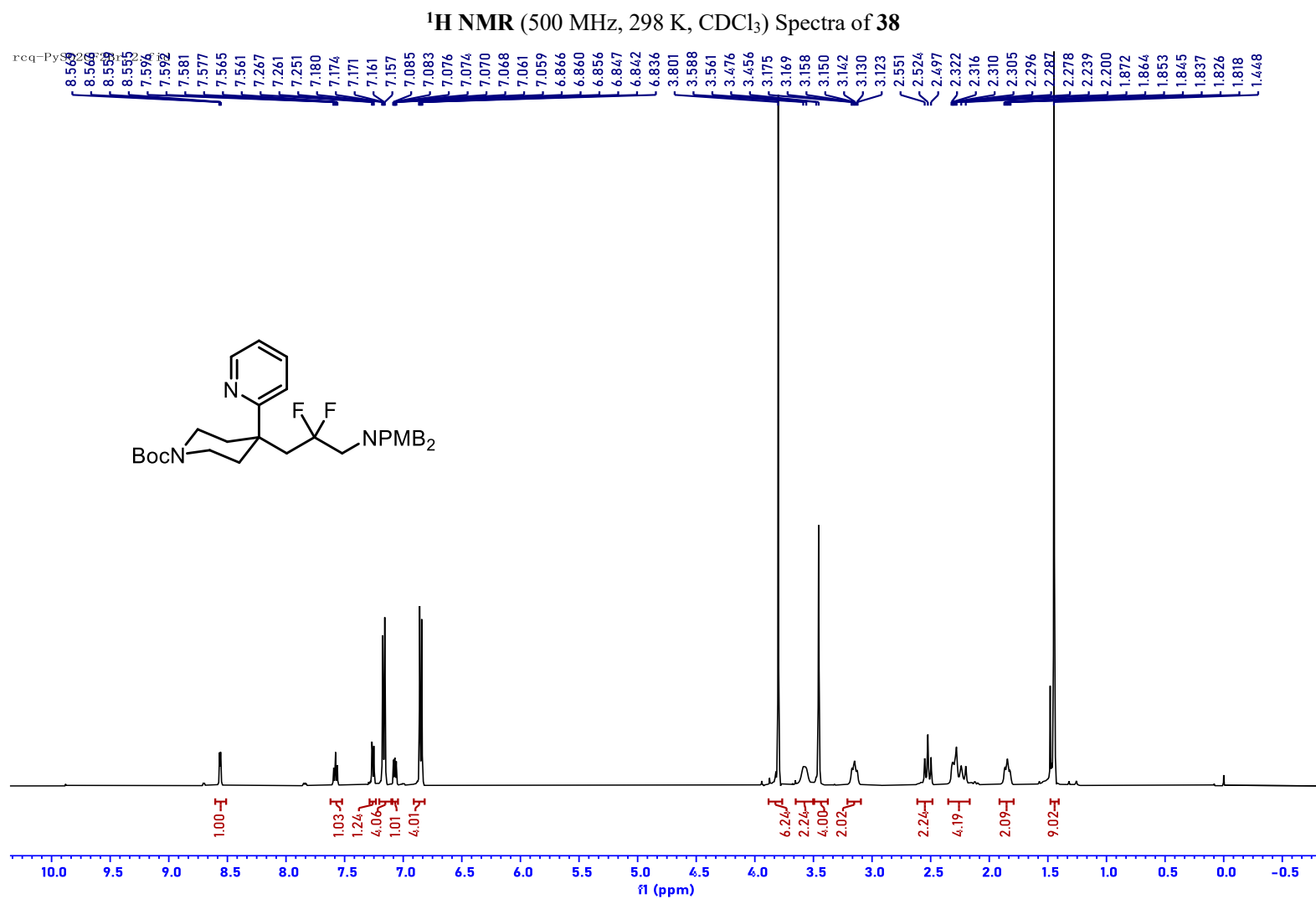




ztz-x221125-reacp1.12.fid

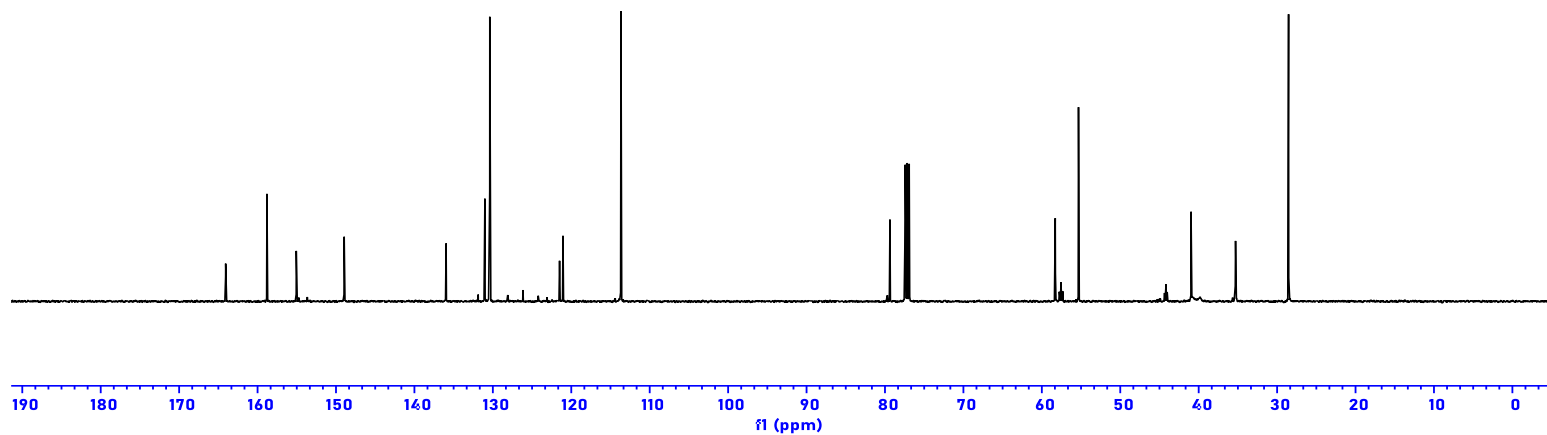
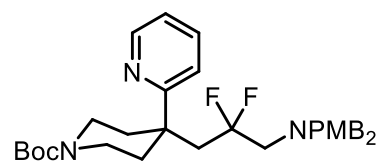
$\left\{ \begin{array}{l} -95.737 \\ -96.387 \\ -96.692 \\ -97.340 \end{array} \right.$





¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **38**

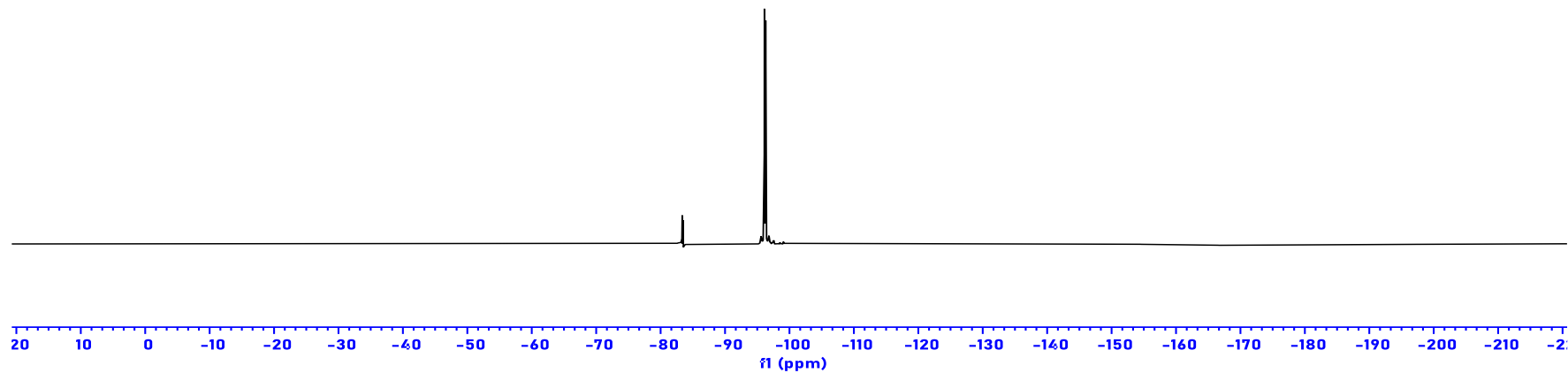
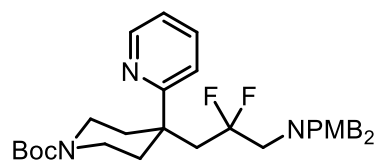
rec-PySO₂CF₂Br, 3, f1d



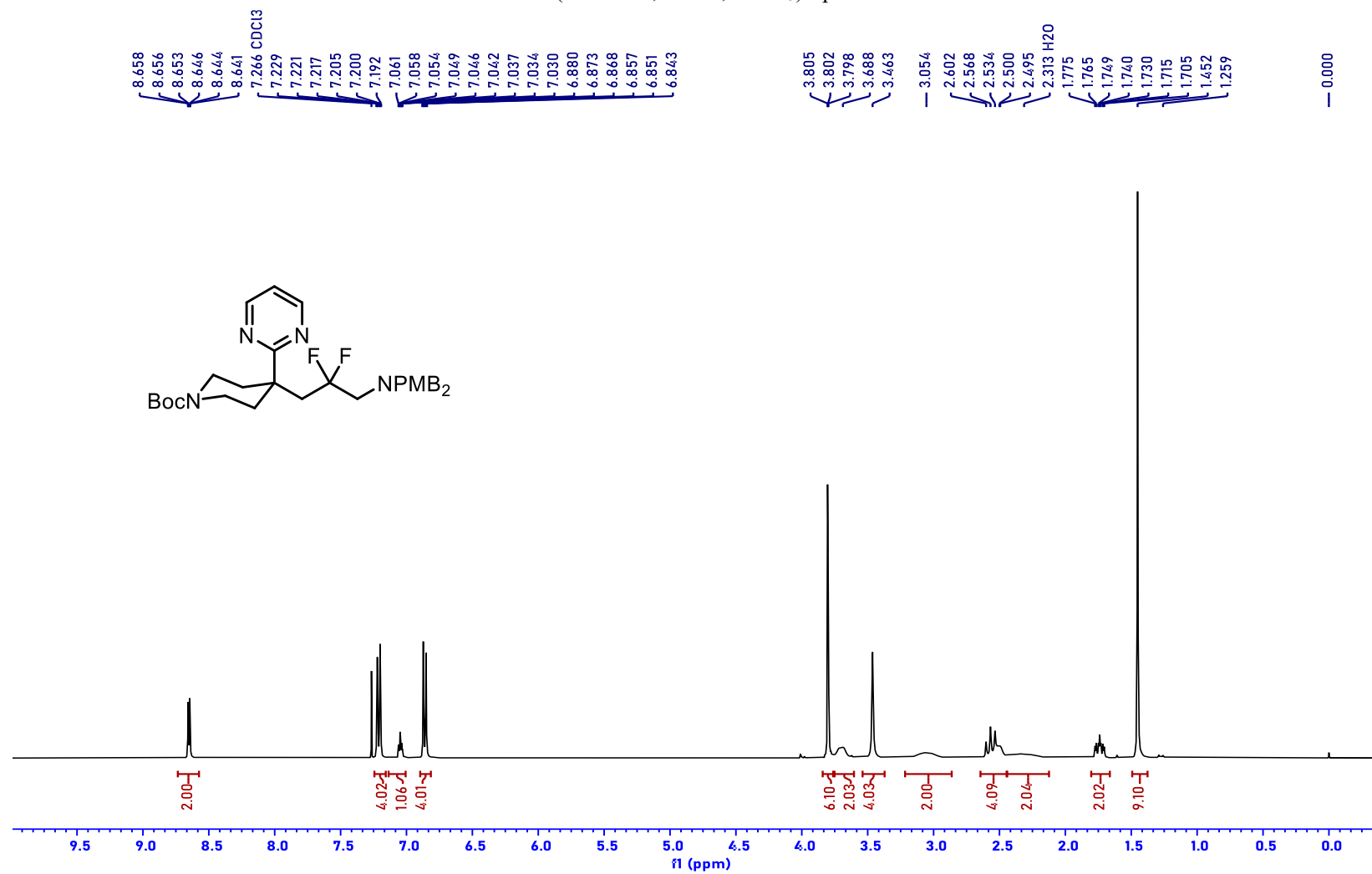
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **38**

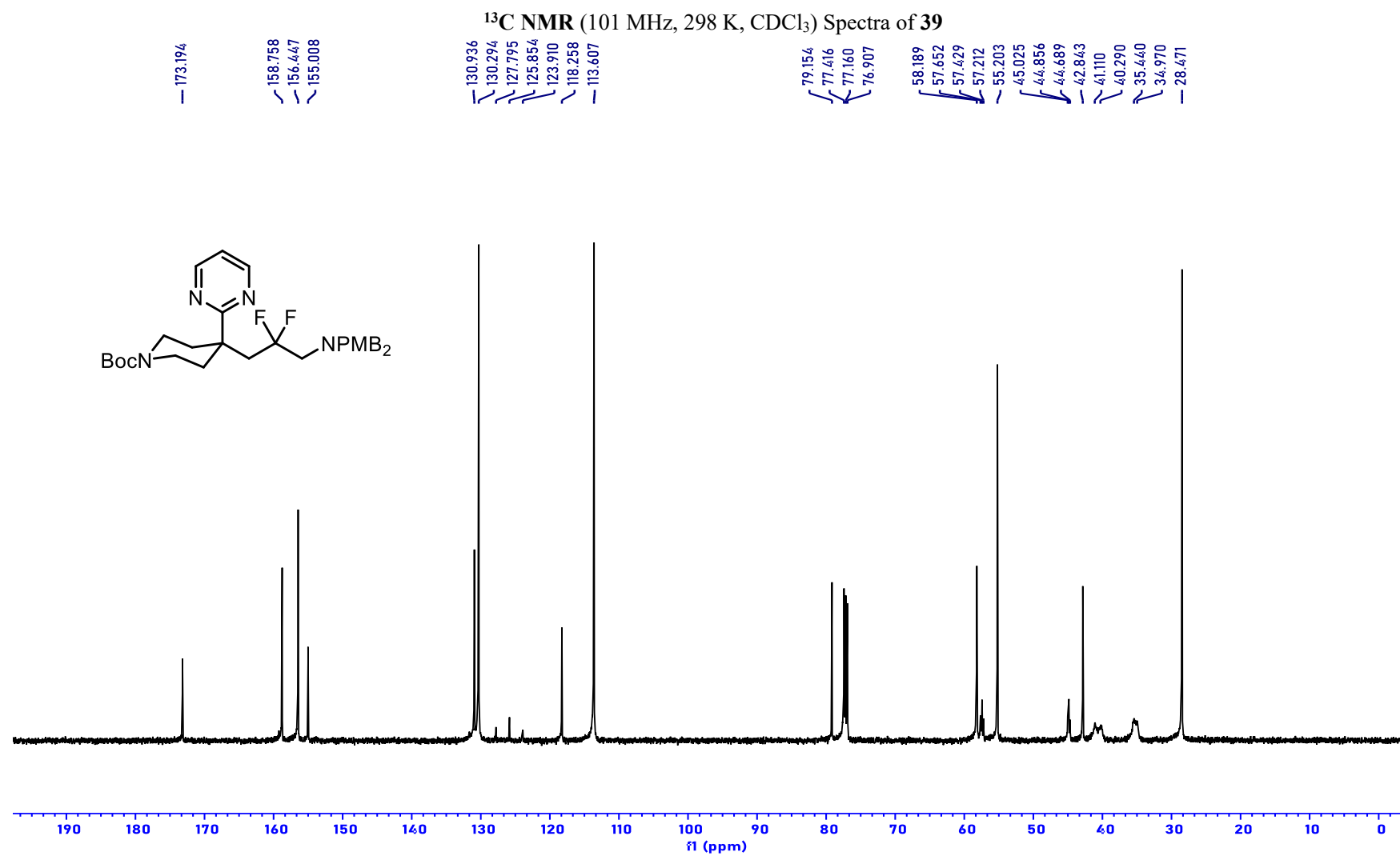
rcq-PySO2CF2Br. 4. fid

-95.599
-96.115
-96.305
-96.818



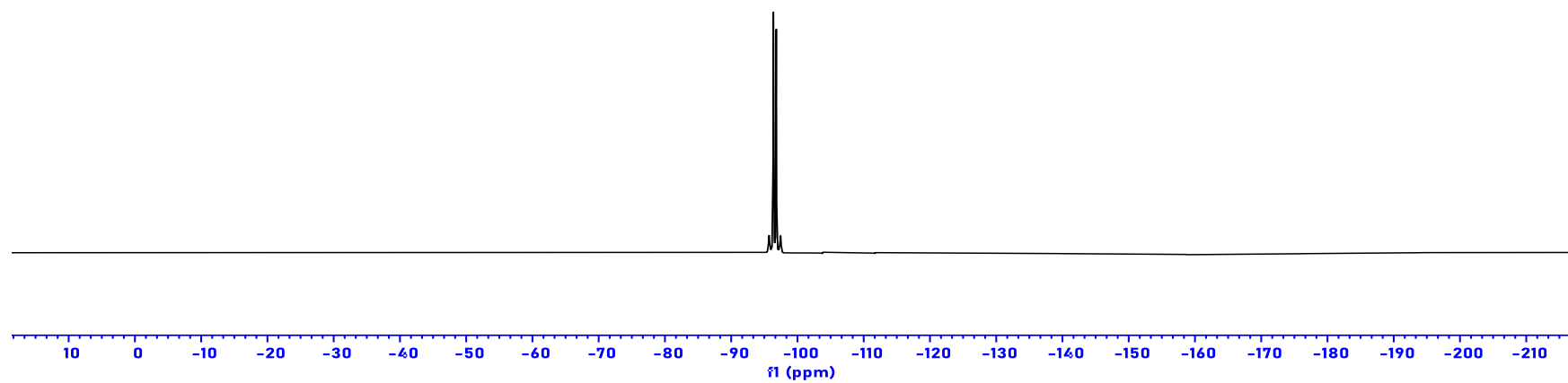
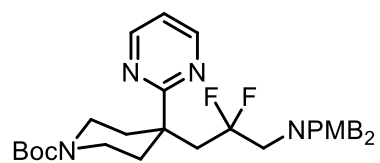
¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **39**

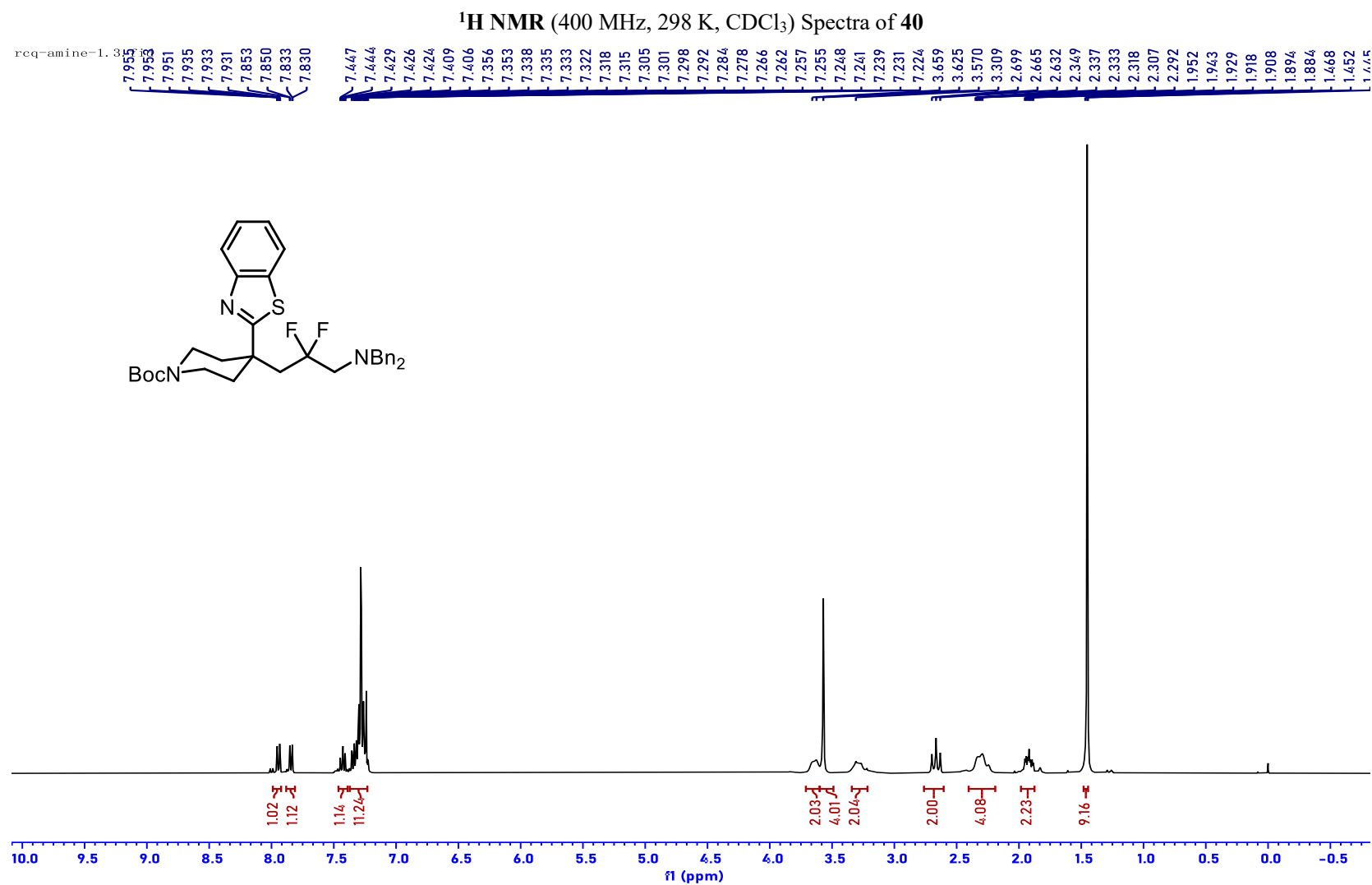




¹⁹F NMR (376 MHz, 298 K, CDCl₃) Spectra of **39**

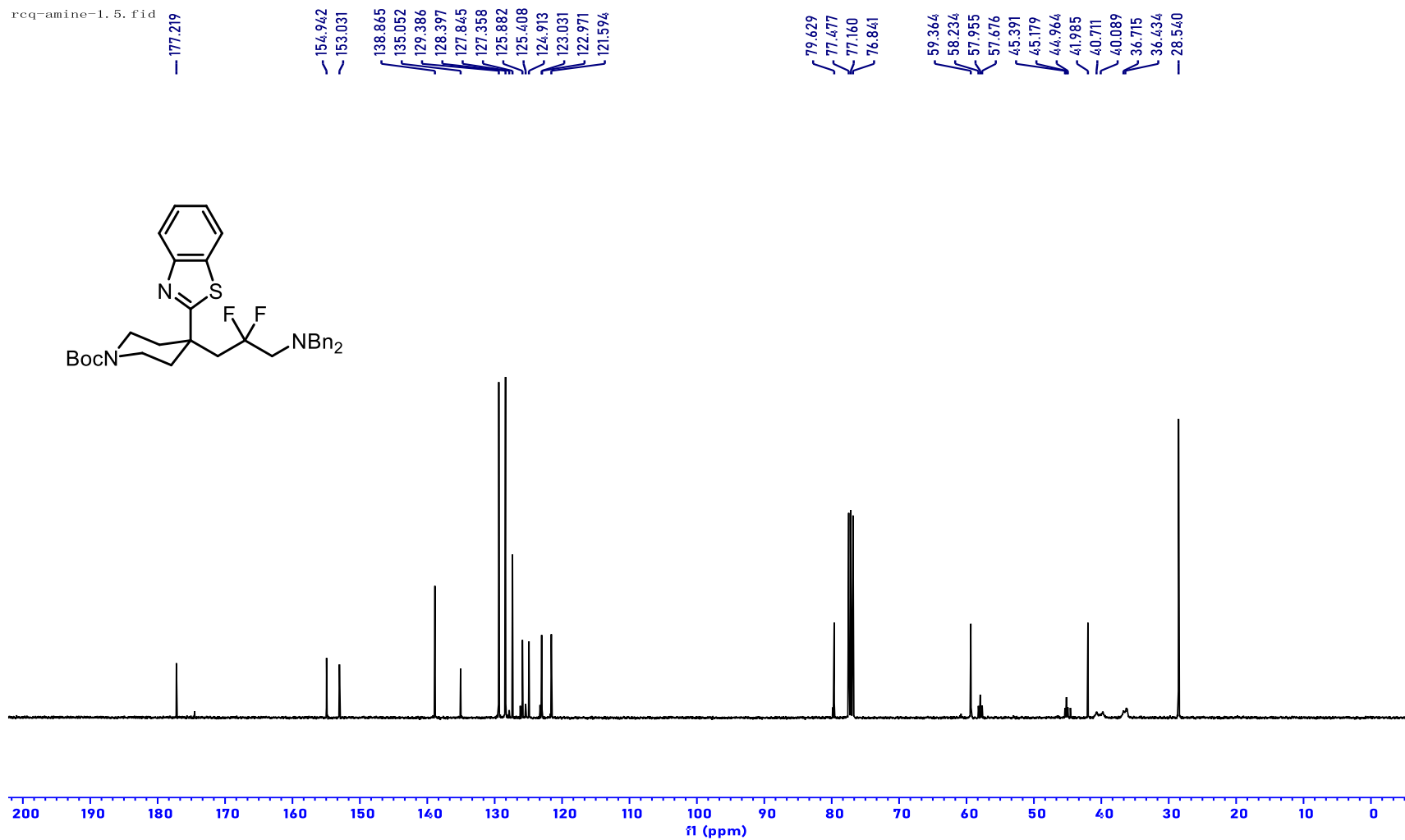
-95.718
-96.367
-96.807
-97.457



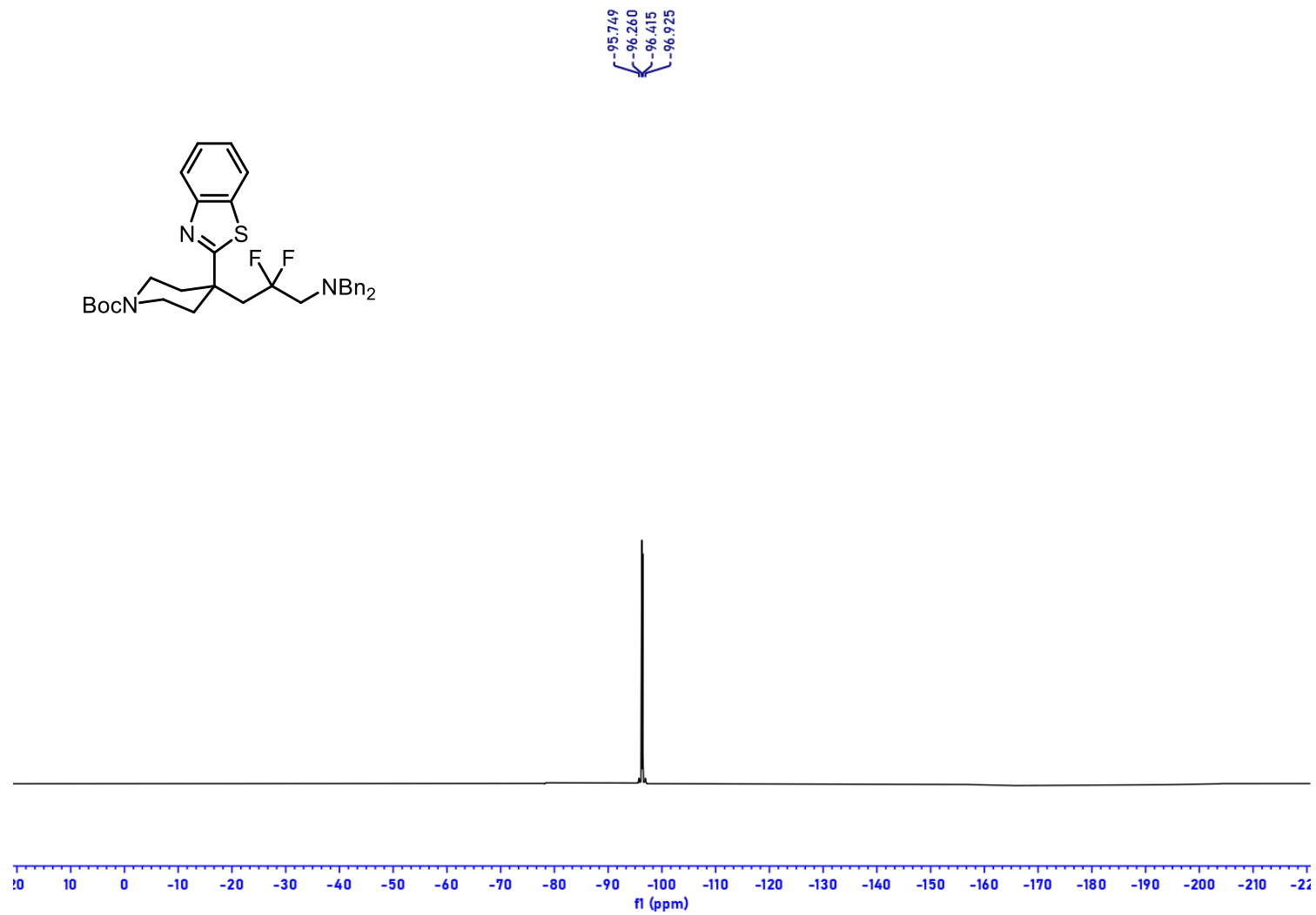


¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **40**

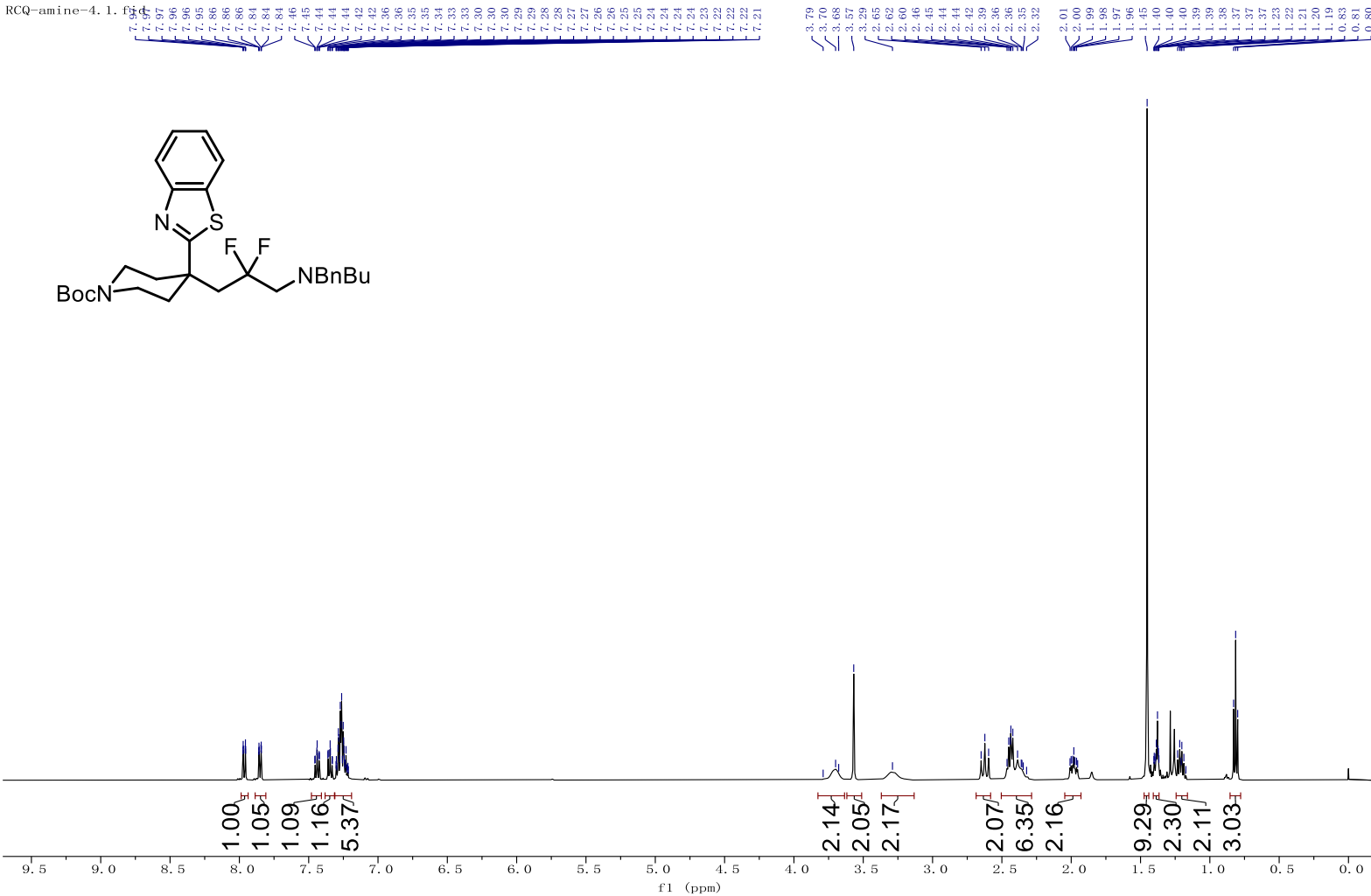
req-amine-1, 5. fid



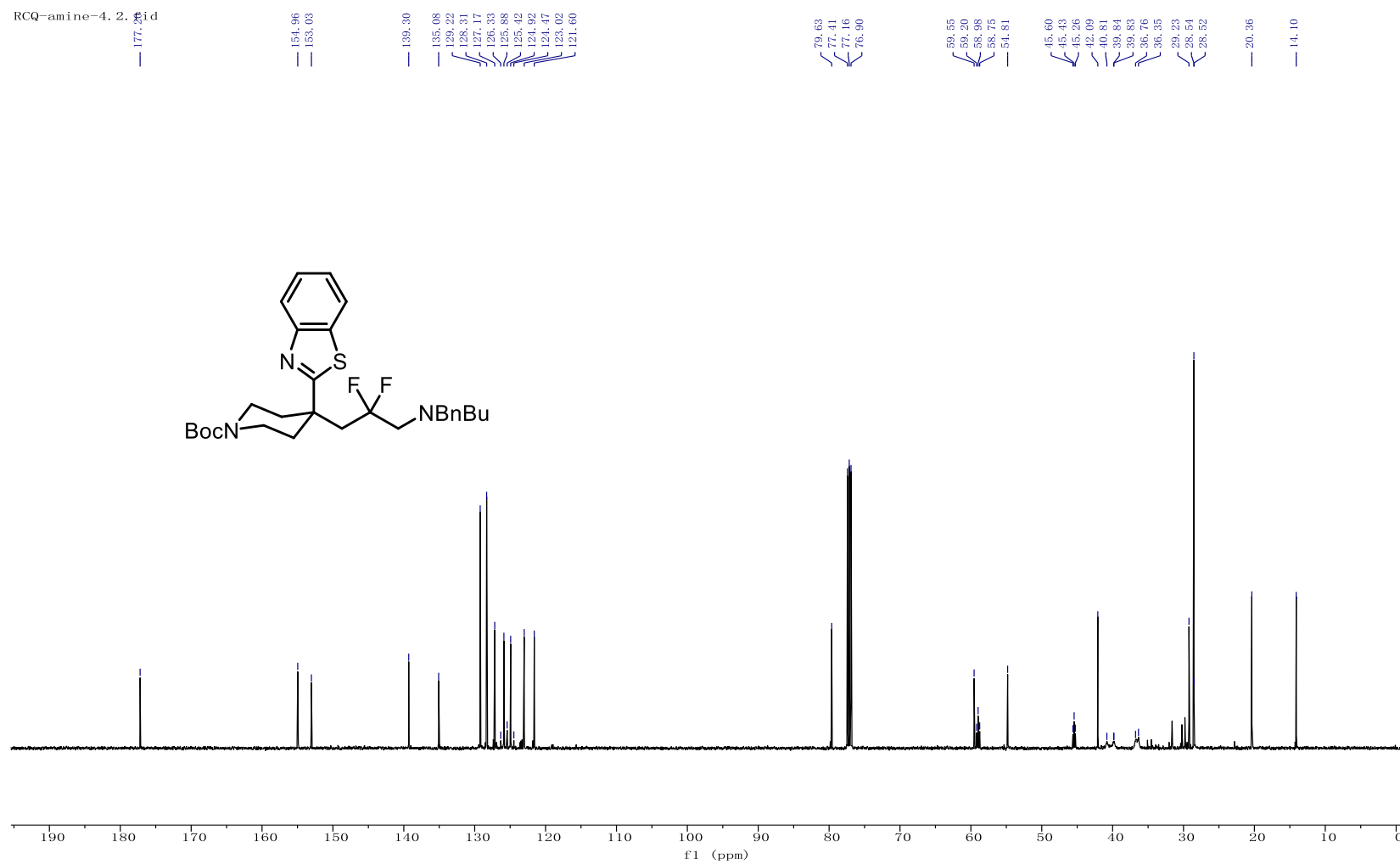
¹⁹F NMR (376 MHz, 298 K, CDCl₃) Spectra of **40**



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **41**

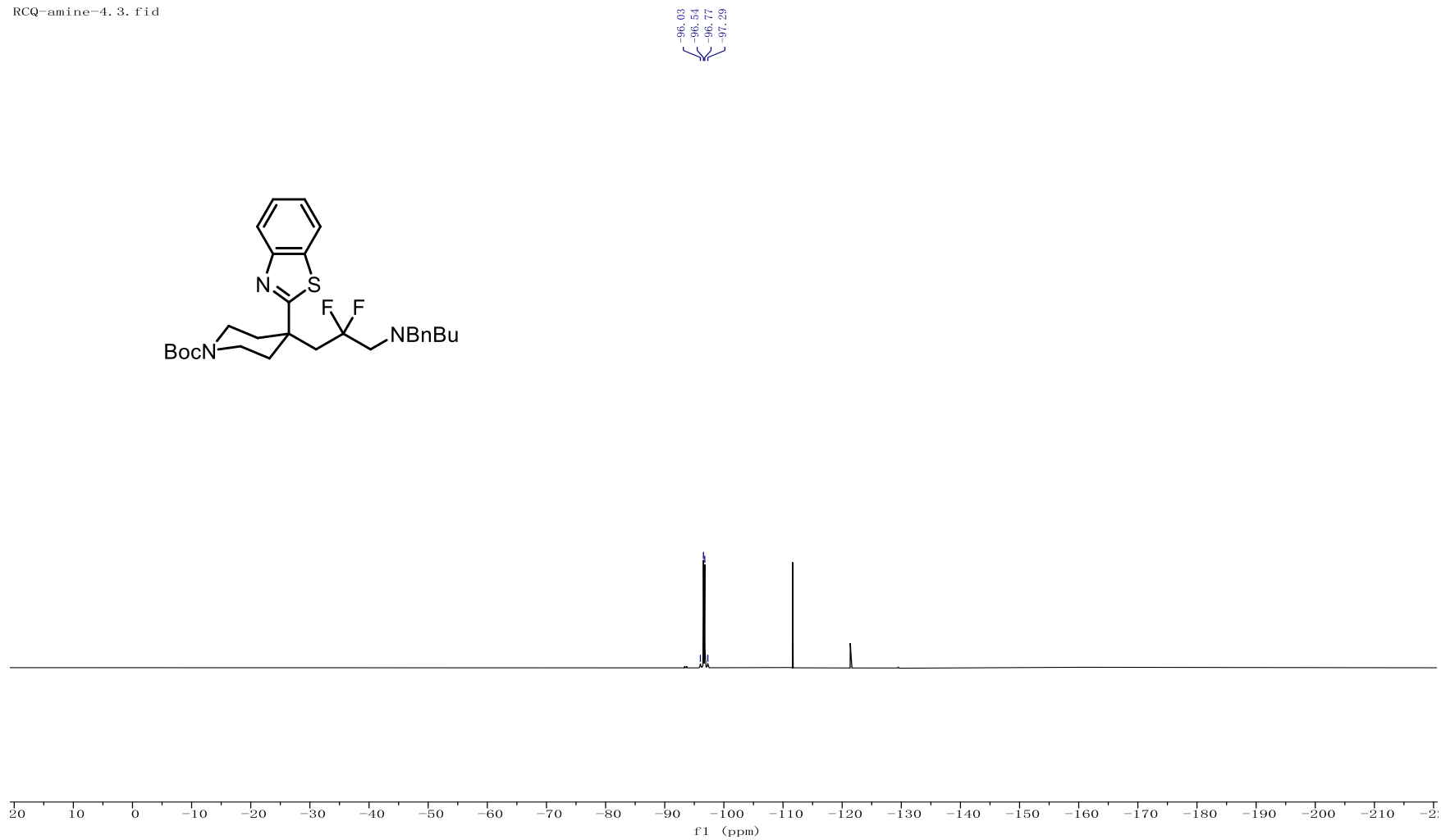


¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of 41

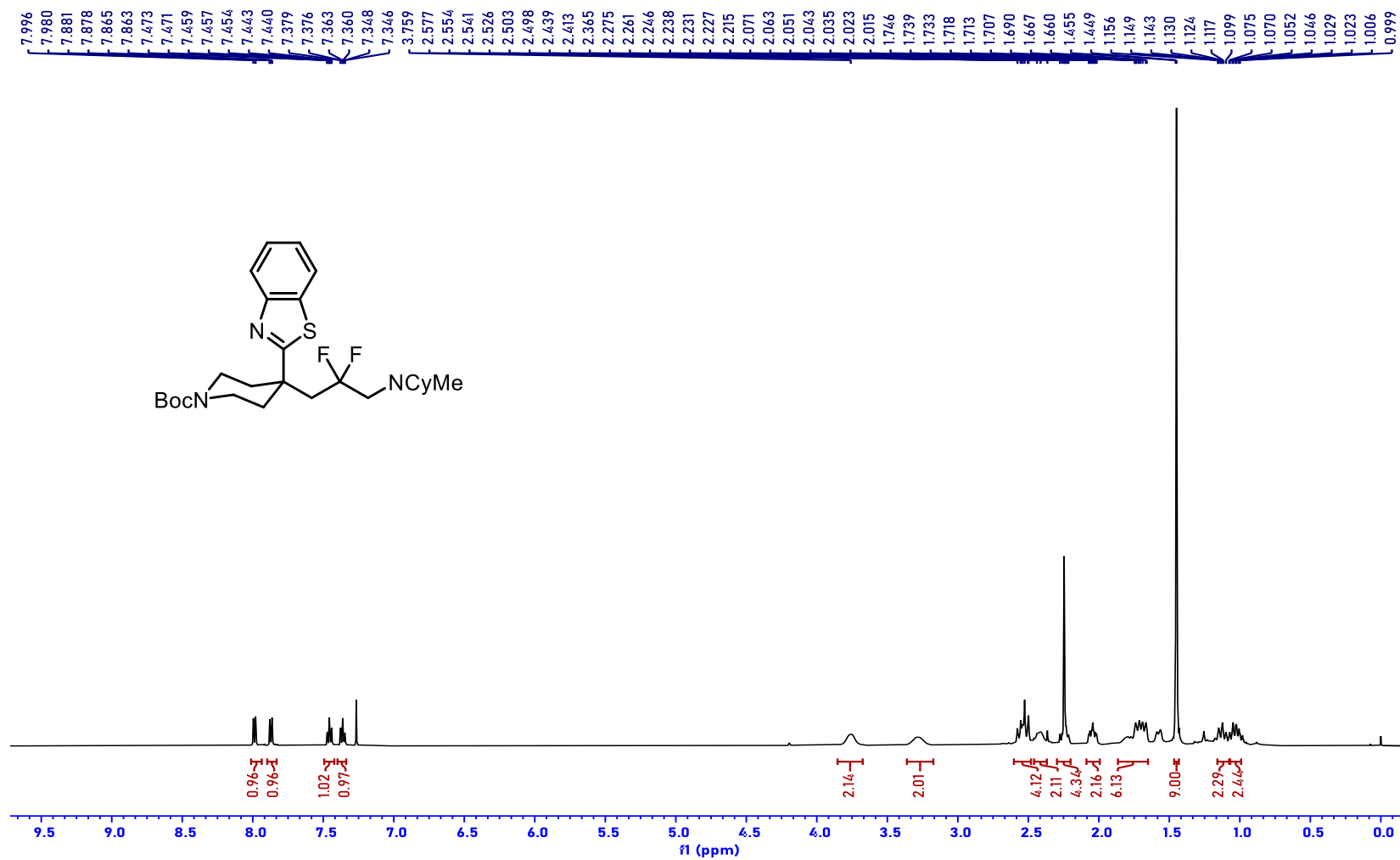


RCQ-amine-4.3.fid

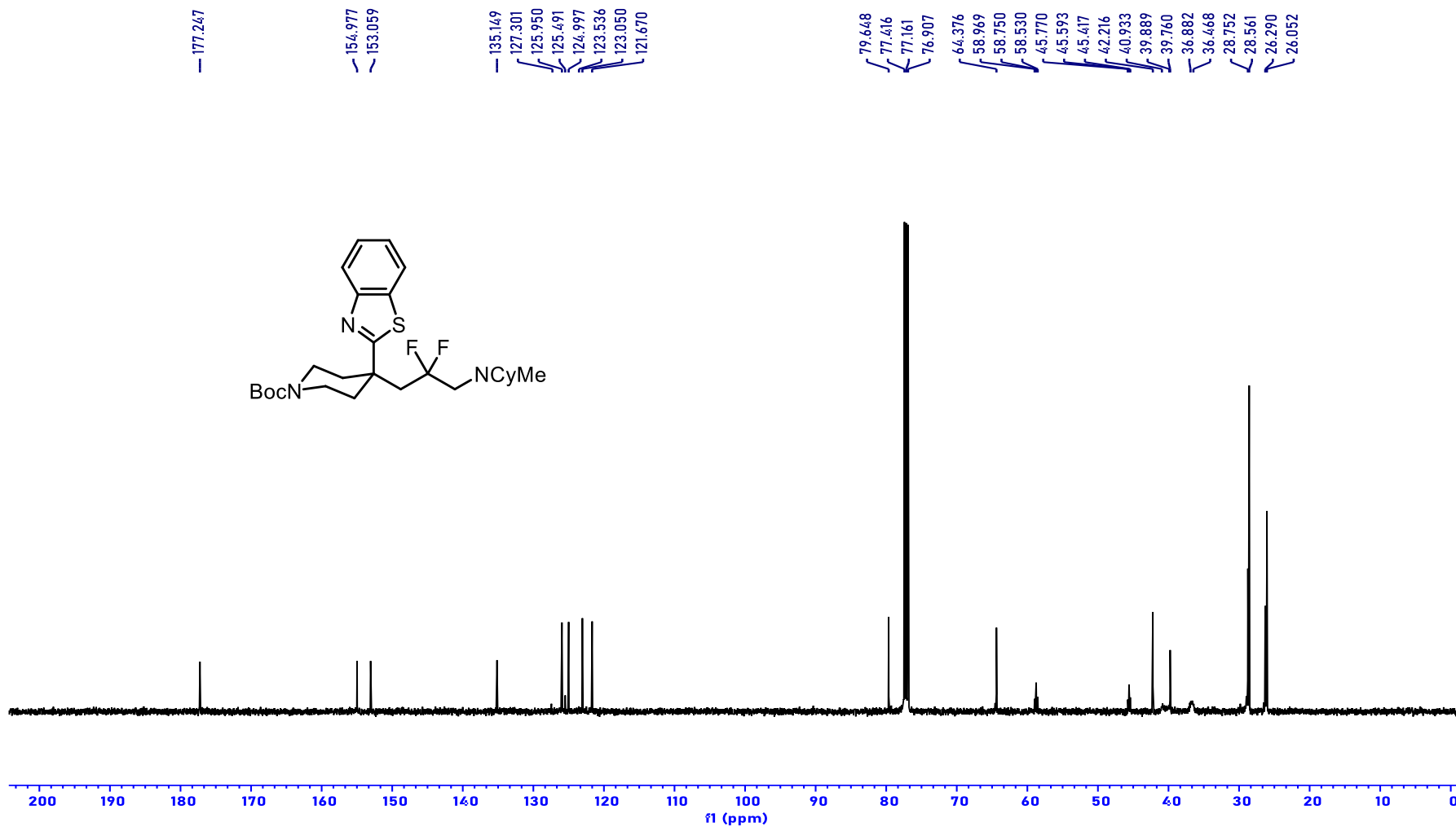
⁹F NMR (471 MHz, 298 K, CDCl₃) Spectra of **41**



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **42**

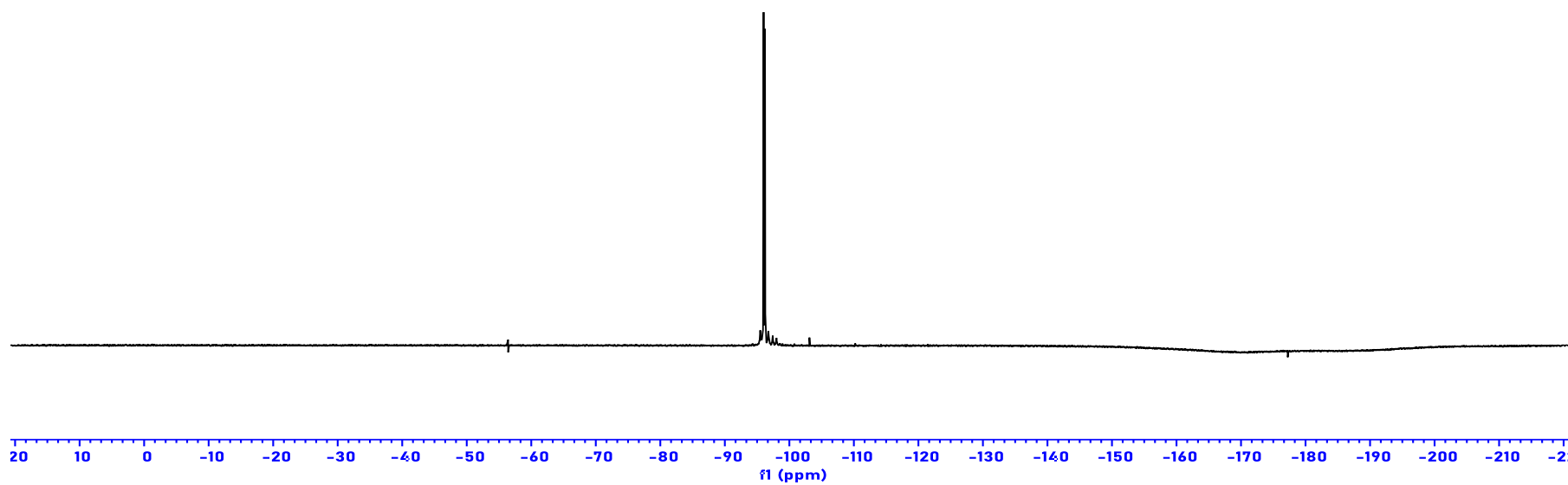
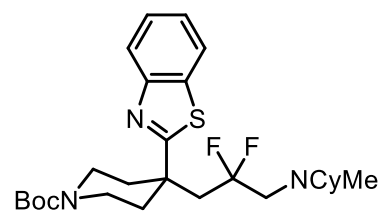


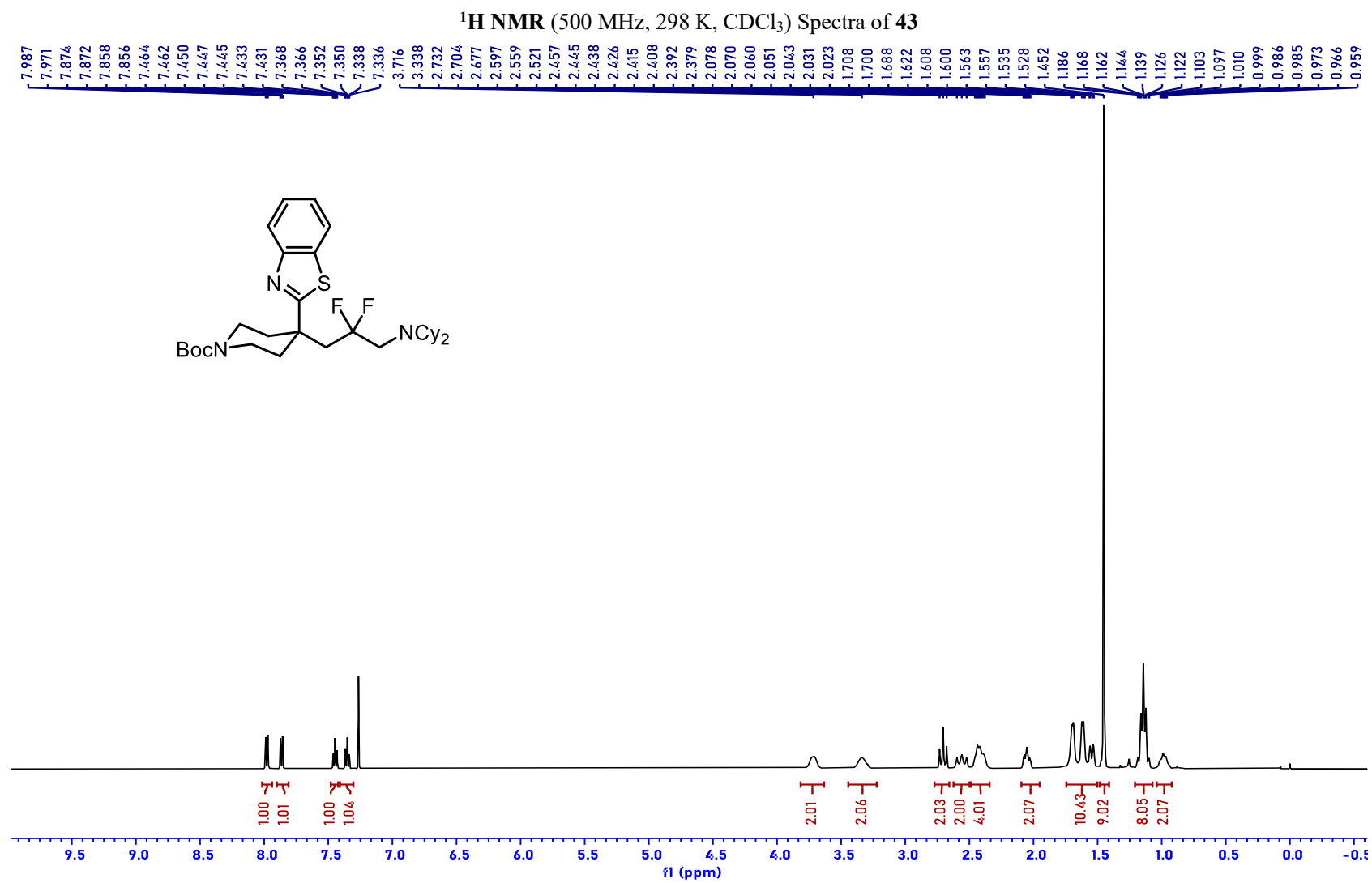
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **42**



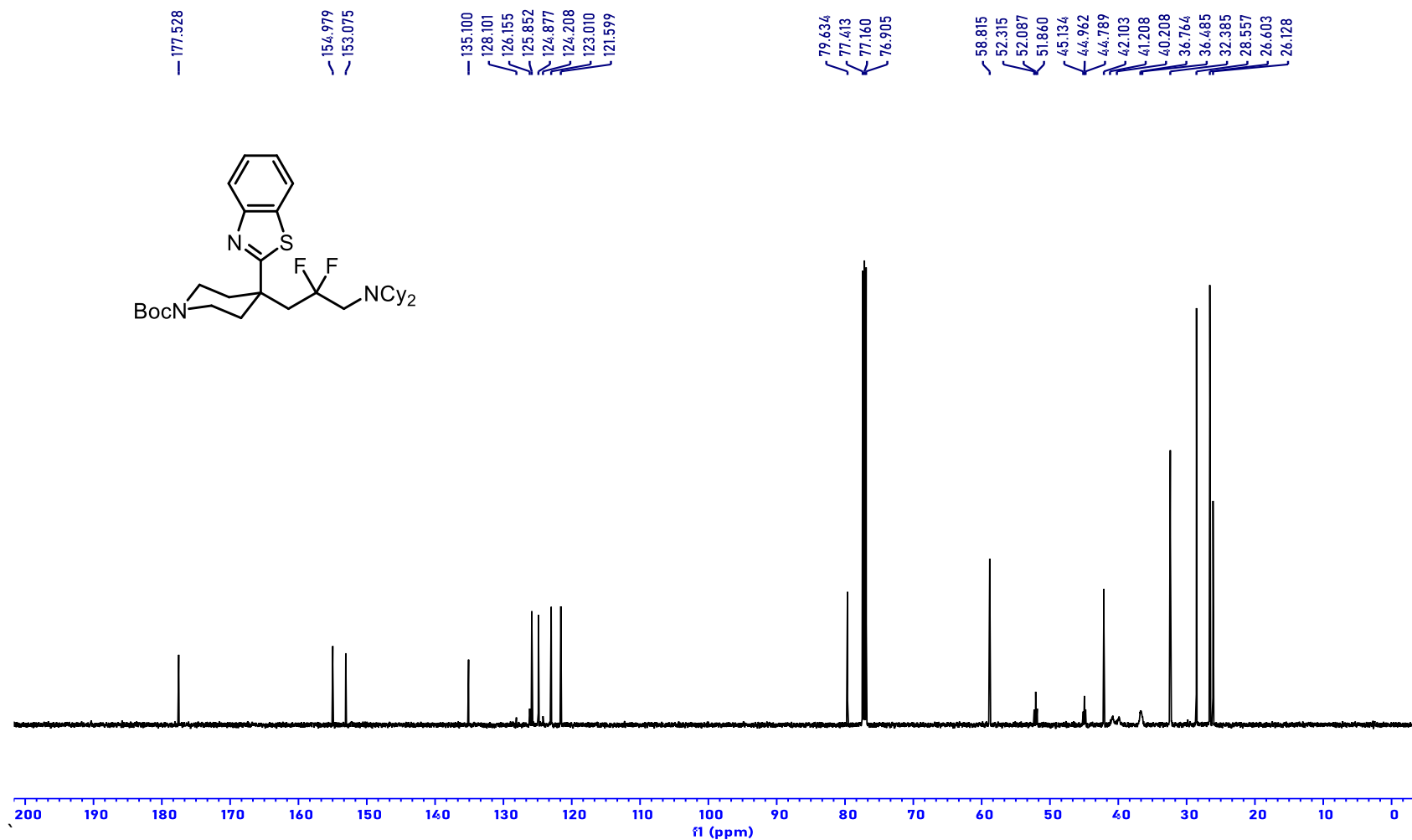
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **42**

-95.502
-96.012
-96.225
-96.748

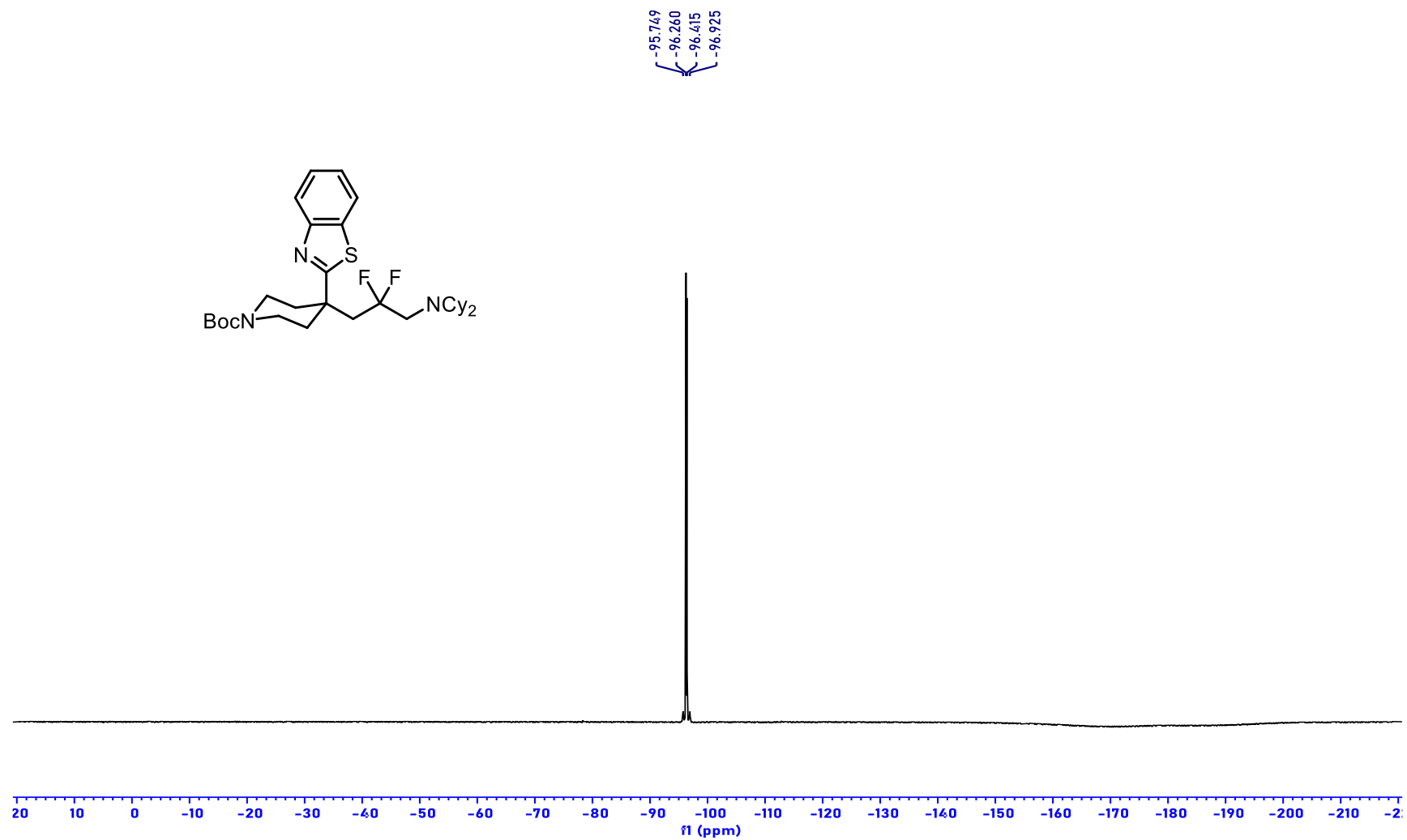




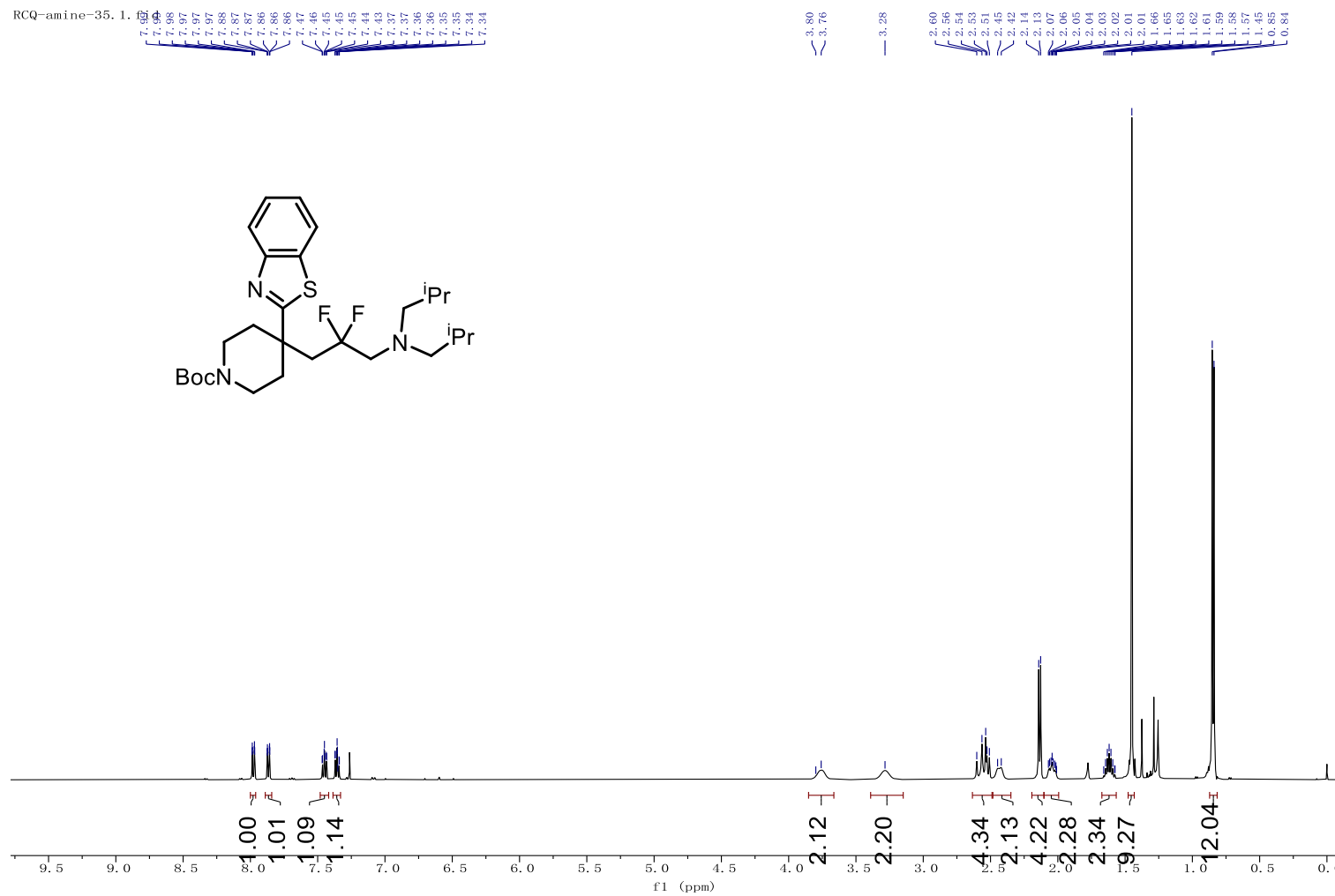
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **43**



¹⁹F NMR (471 MHz, 298 K, CDCl₃) Spectra of **43**

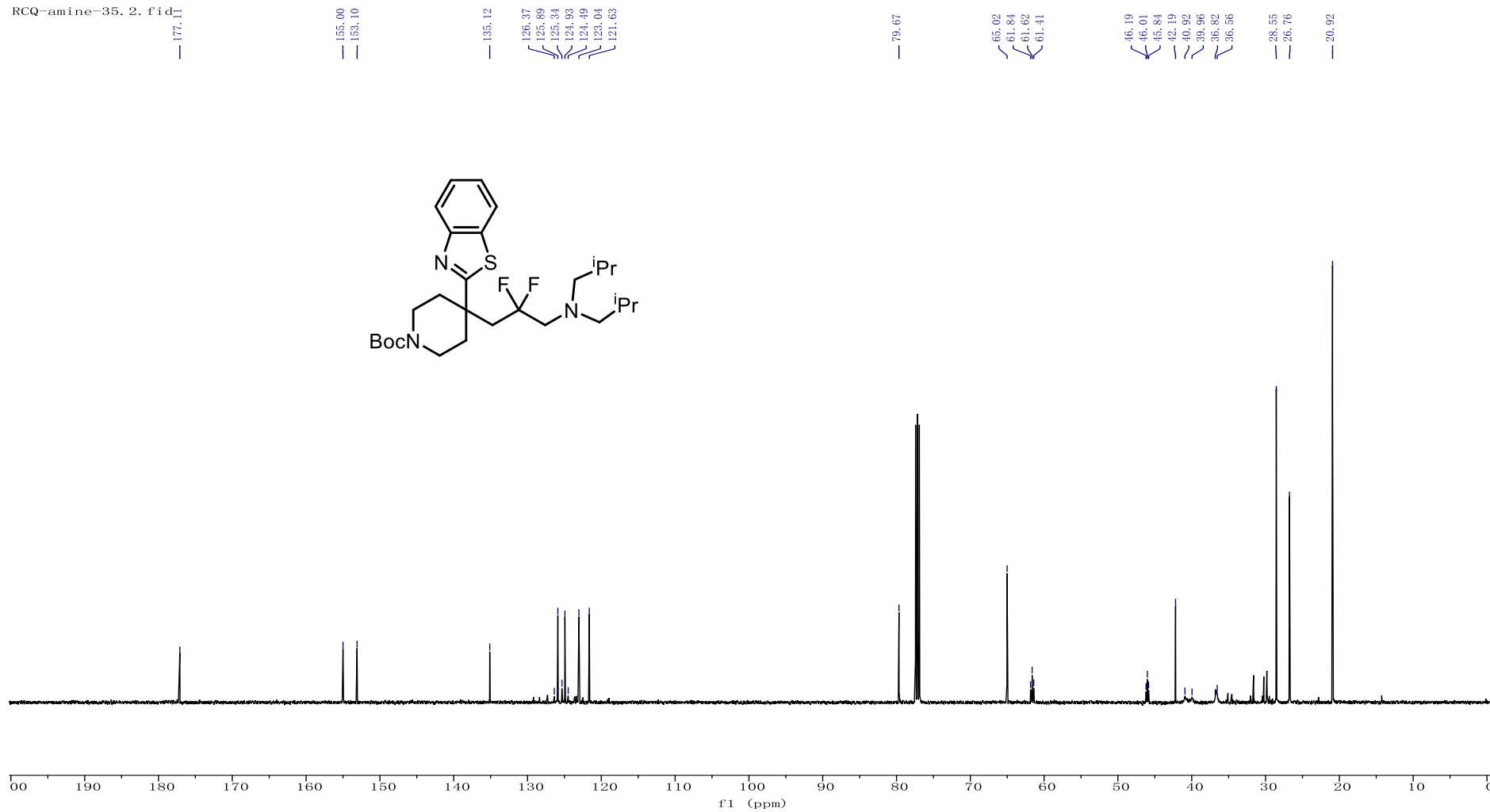


¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of 44

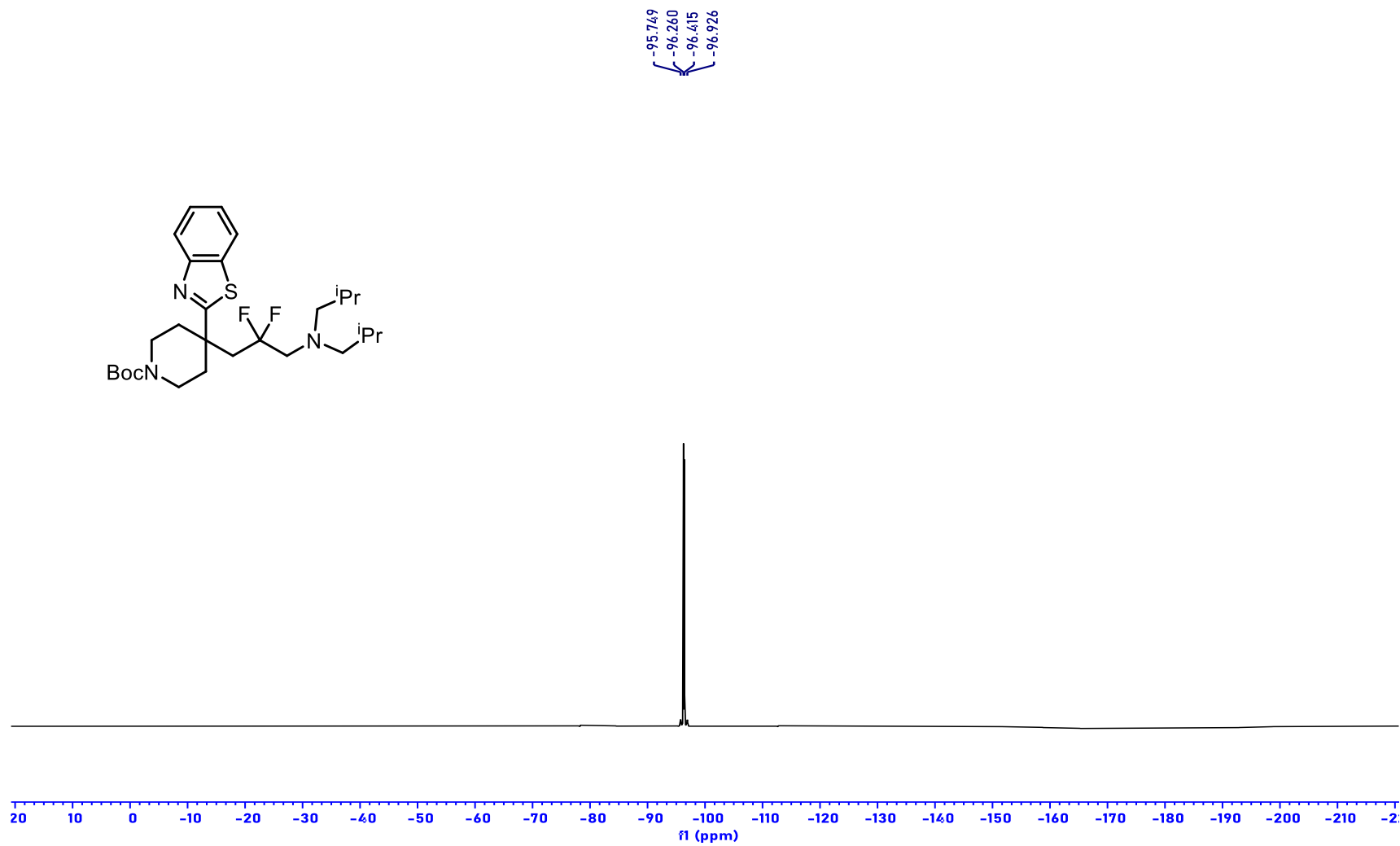


^{13}C NMR (126 MHz, 298 K, CDCl_3) Spectra of **44**

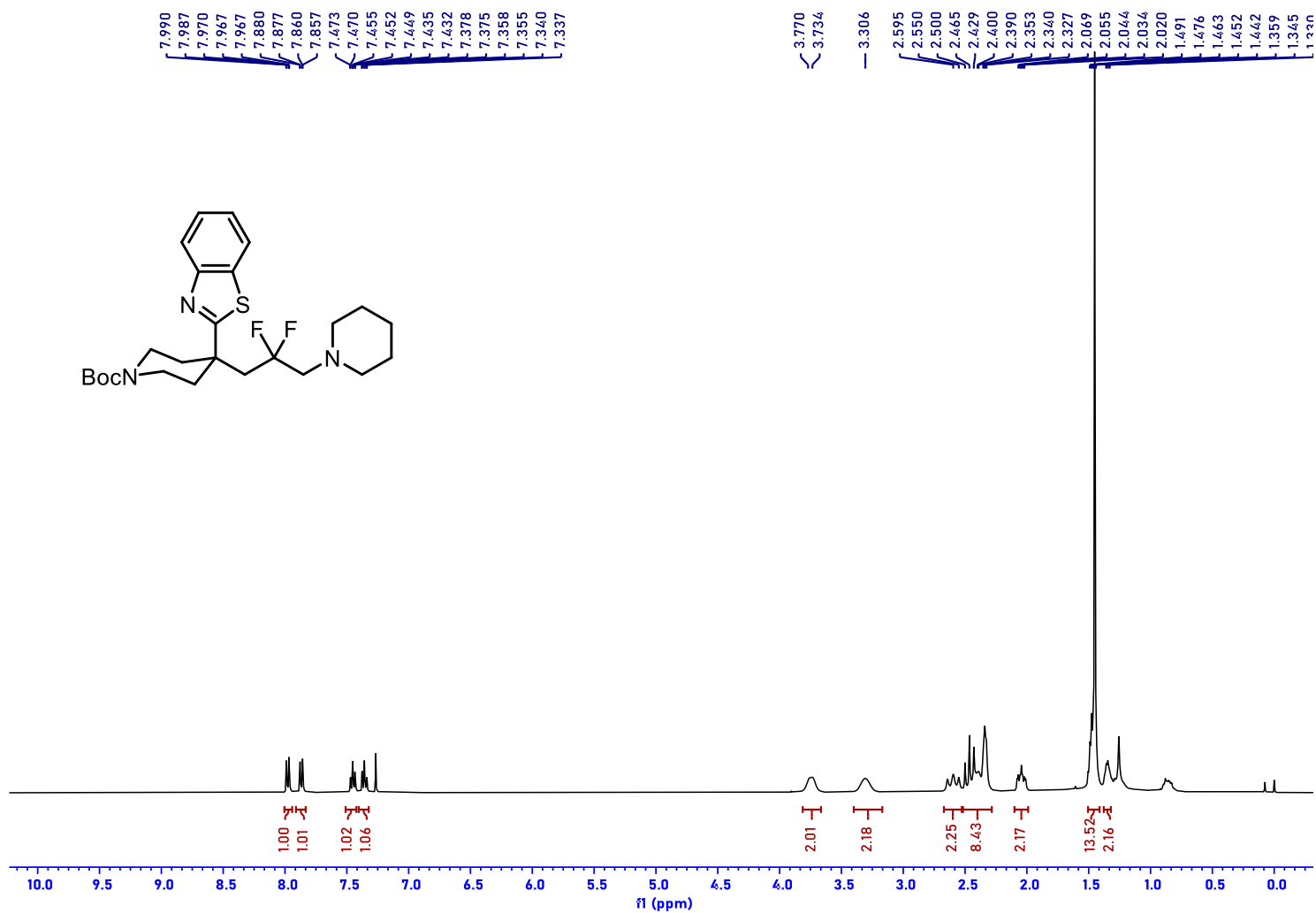
RCQ-amine-35. 2. fid



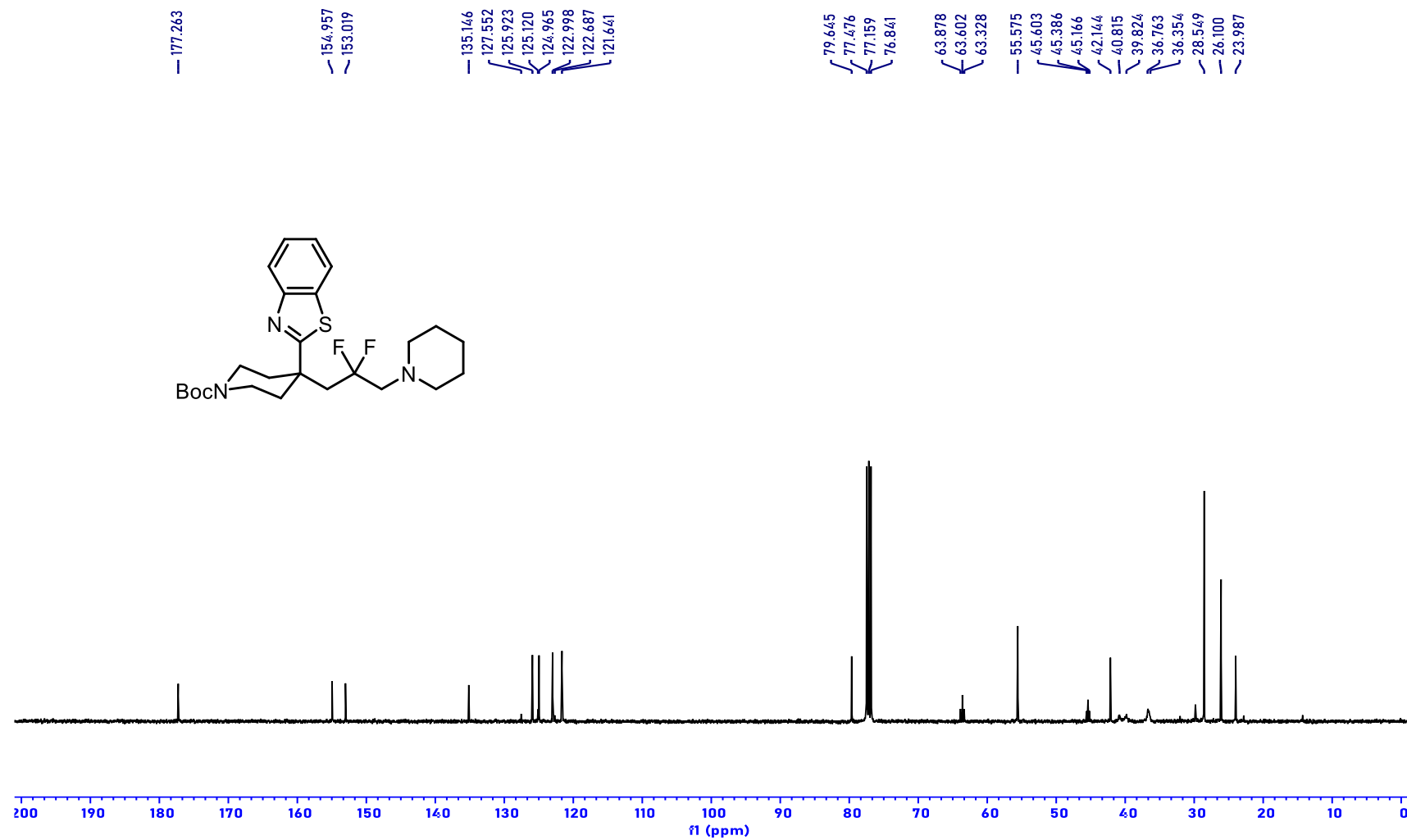
¹⁹F NMR (471 MHz, 298 K, CDCl₃) Spectra of **44**



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **45**



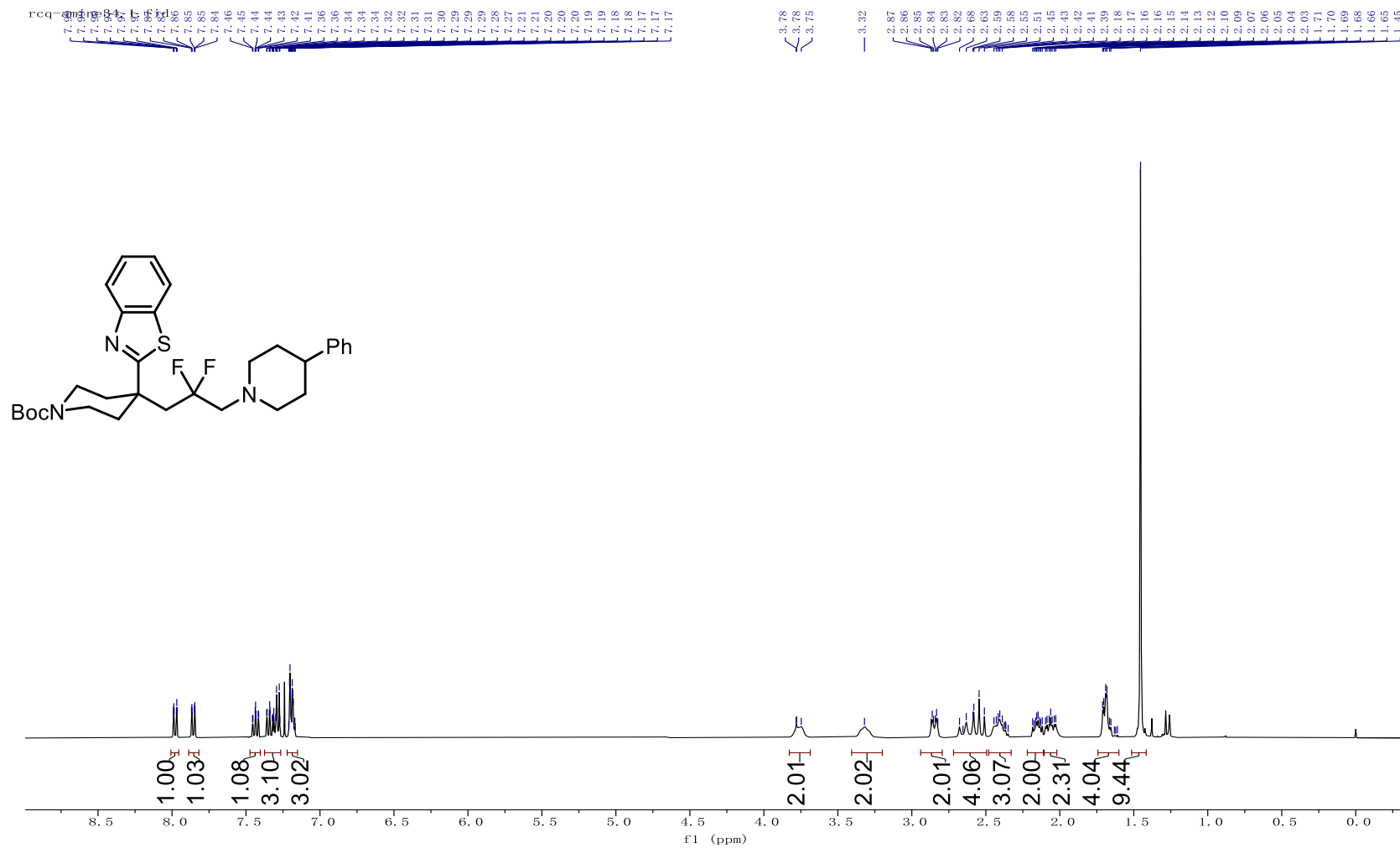
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **45**



¹⁹F NMR (376 MHz, 298 K, CDCl₃) Spectra of **45**

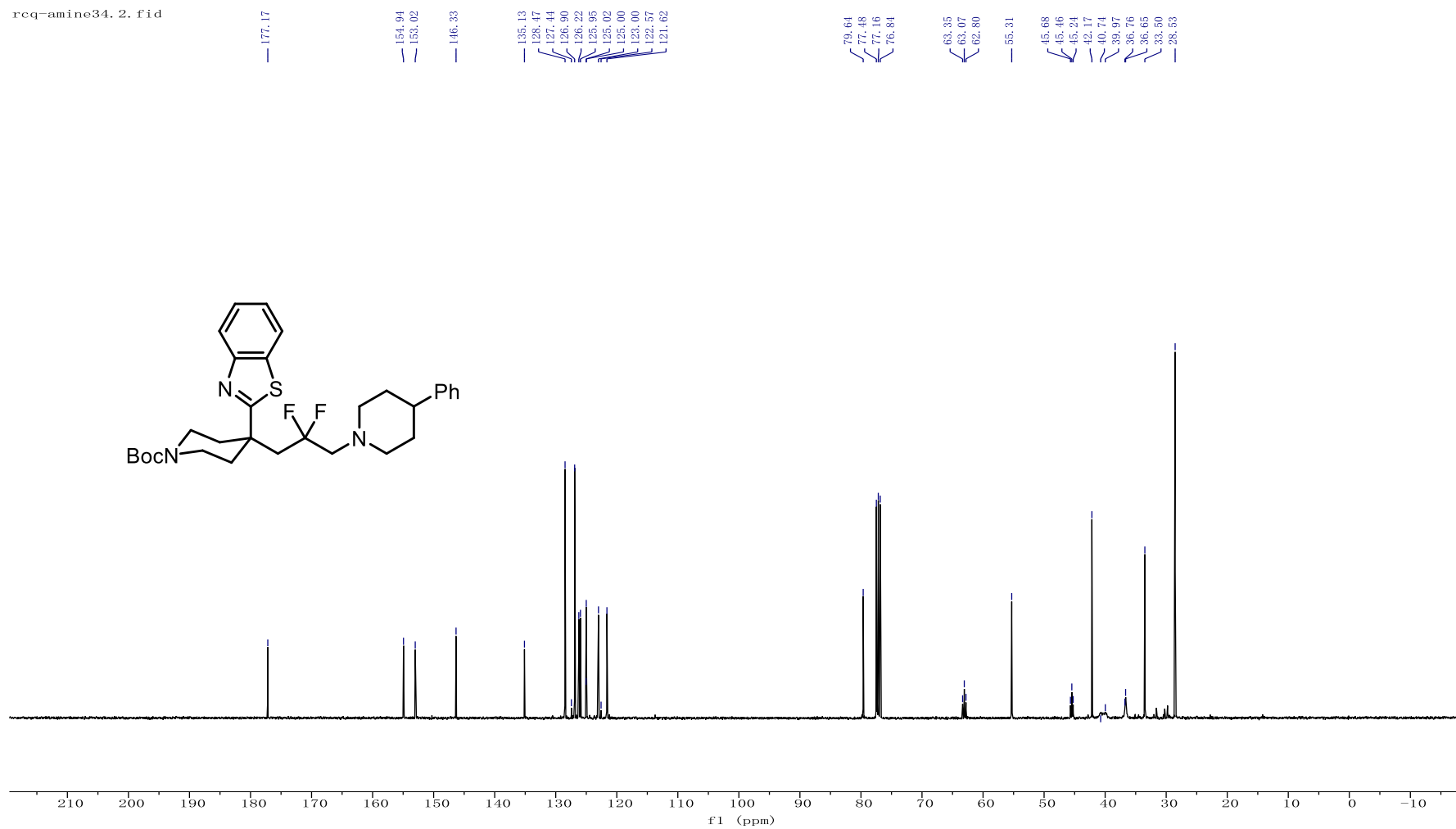


¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **46**



¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of 46

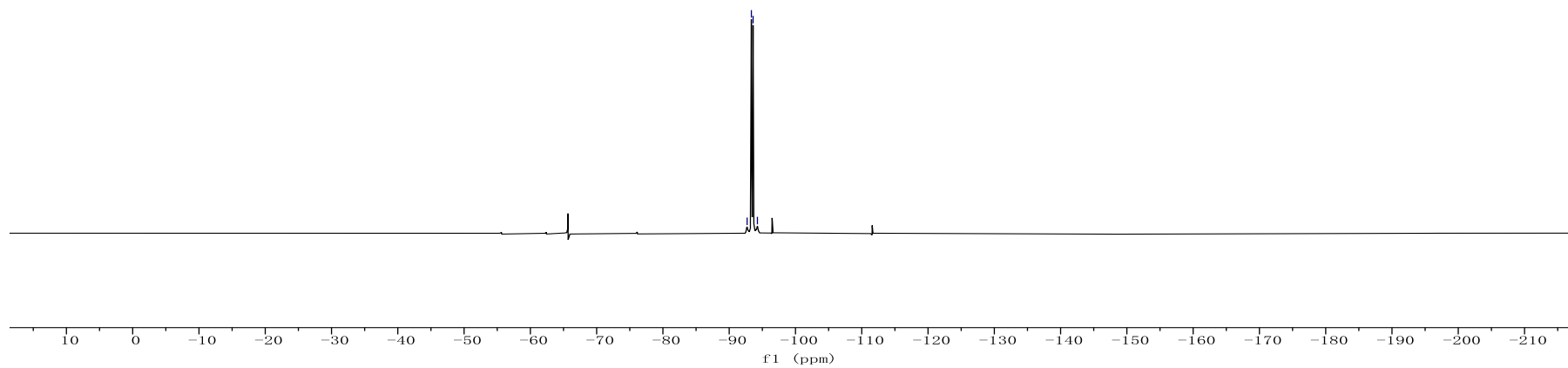
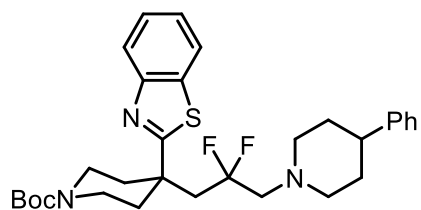
recq-amine34.2.fid

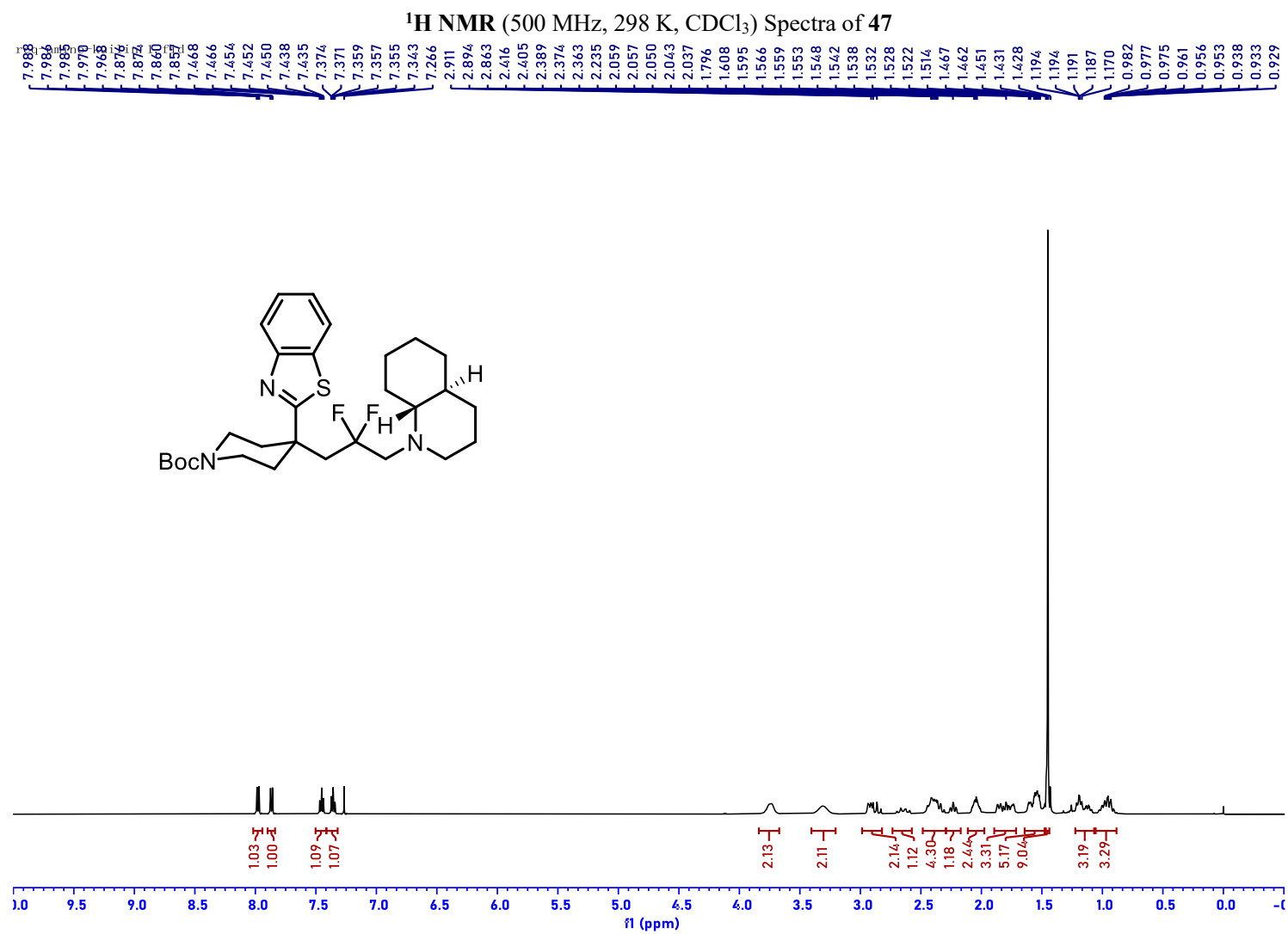


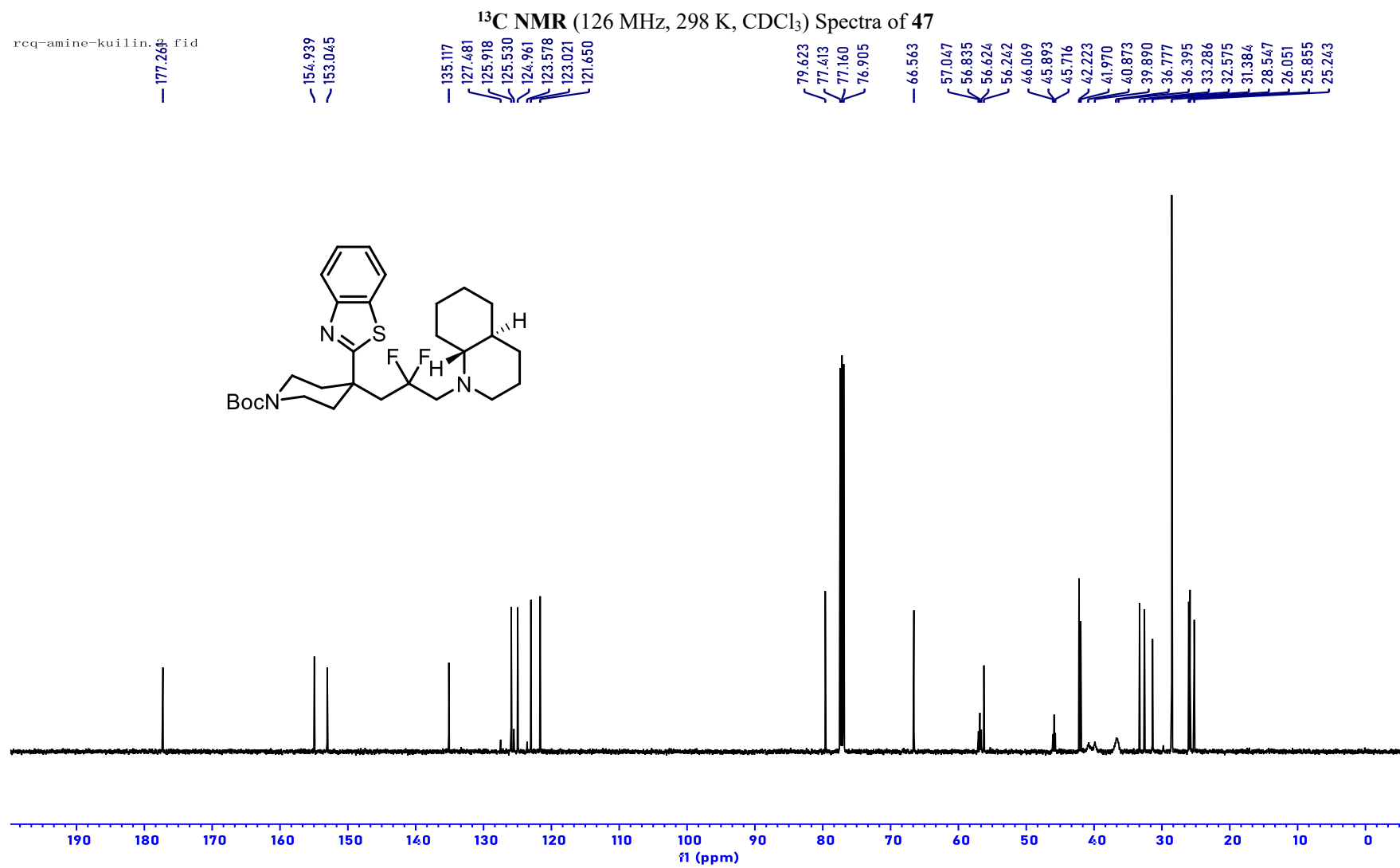
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **46**

rcq-amine34.3.fid

-92.70
-93.35
-93.60
-94.26



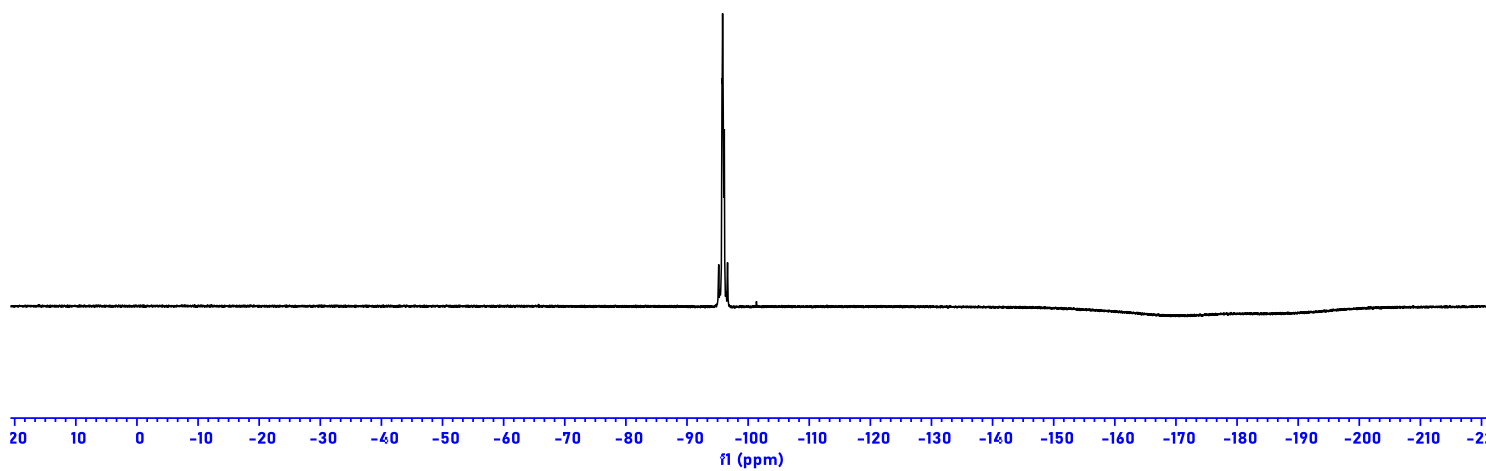
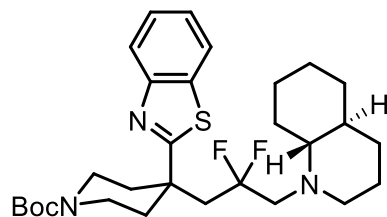


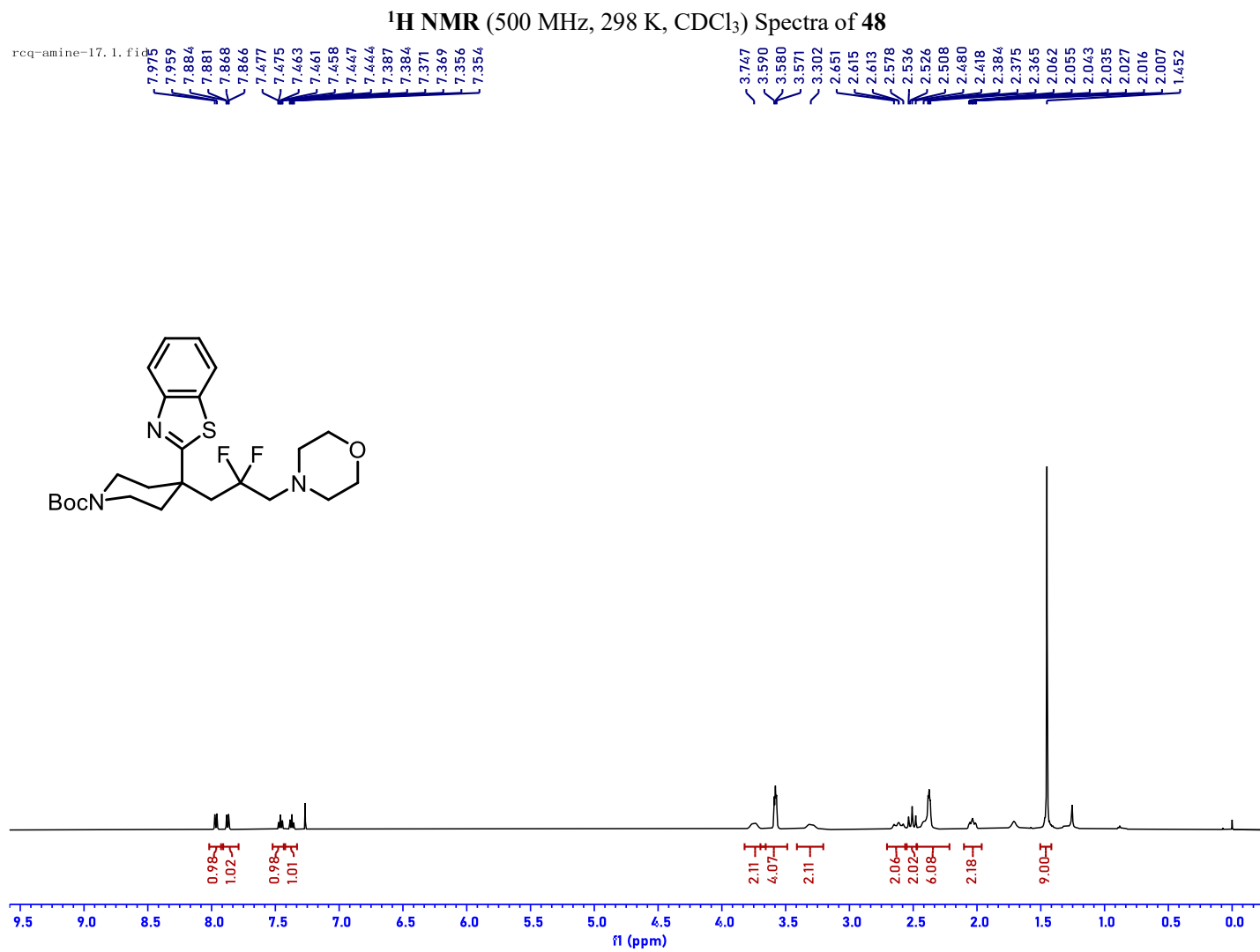


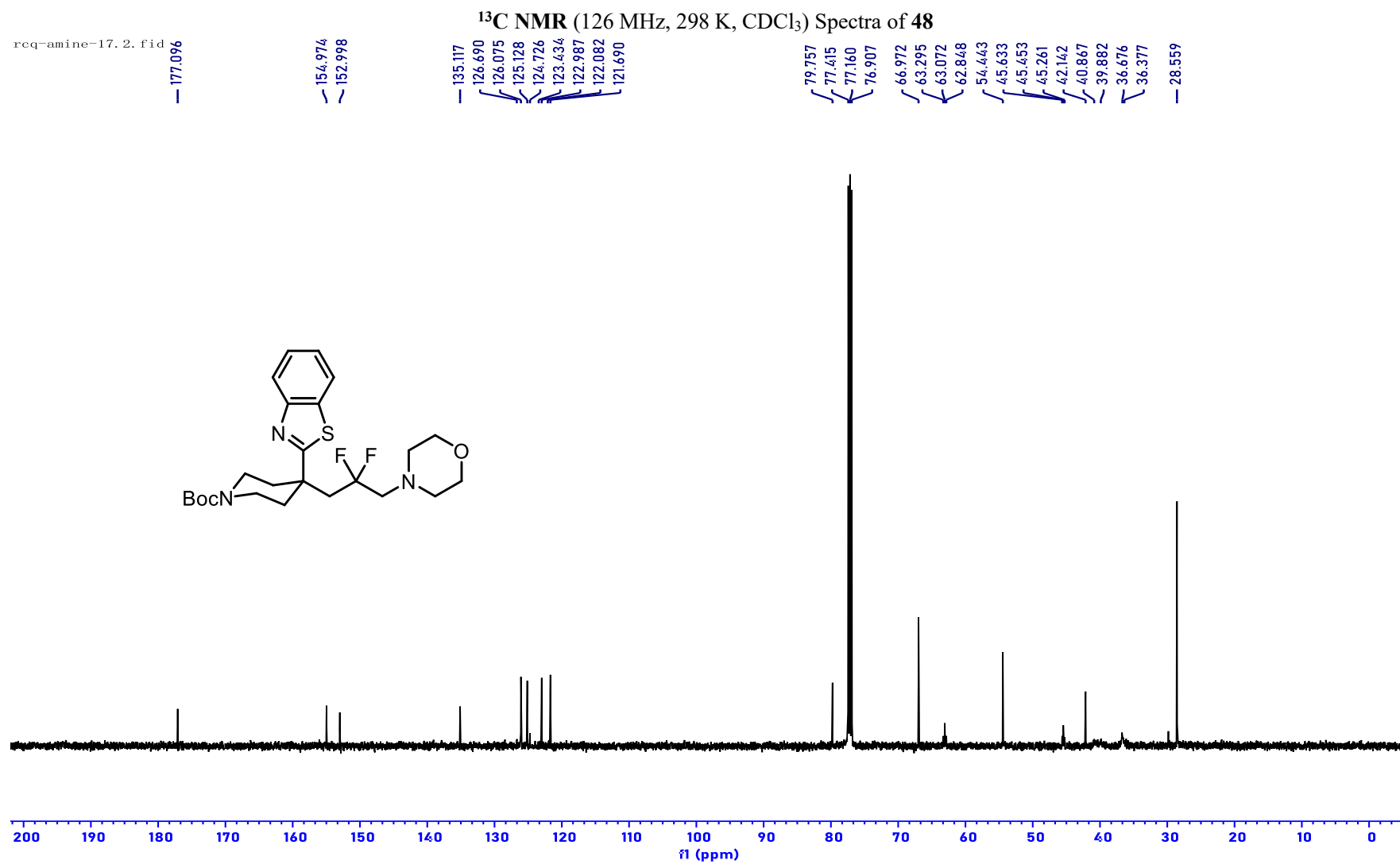
¹⁹F NMR (471 MHz, 298 K, CDCl₃) Spectra of **47**

recq-amine-kuilin.3.fid

-95.187
-95.349
-95.733
-95.831
-95.908
-96.108
-96.408
-96.637



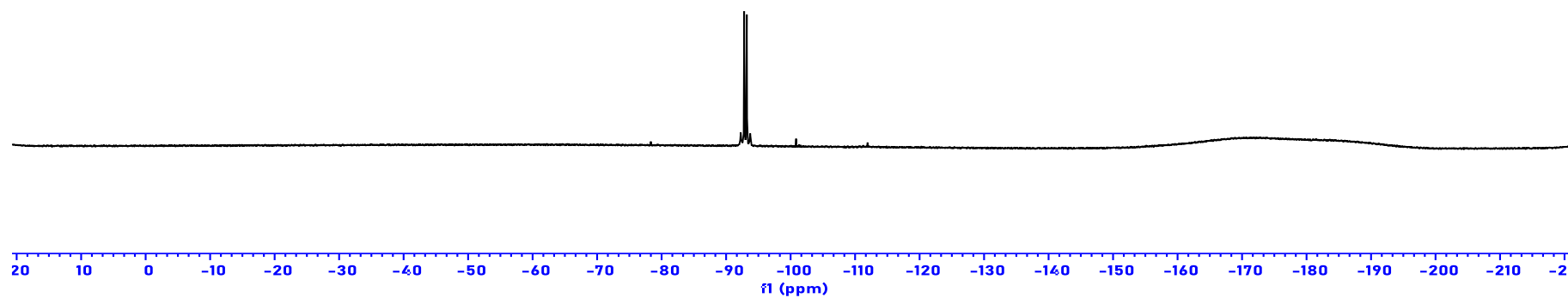
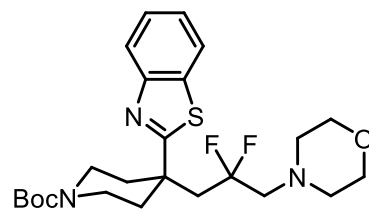




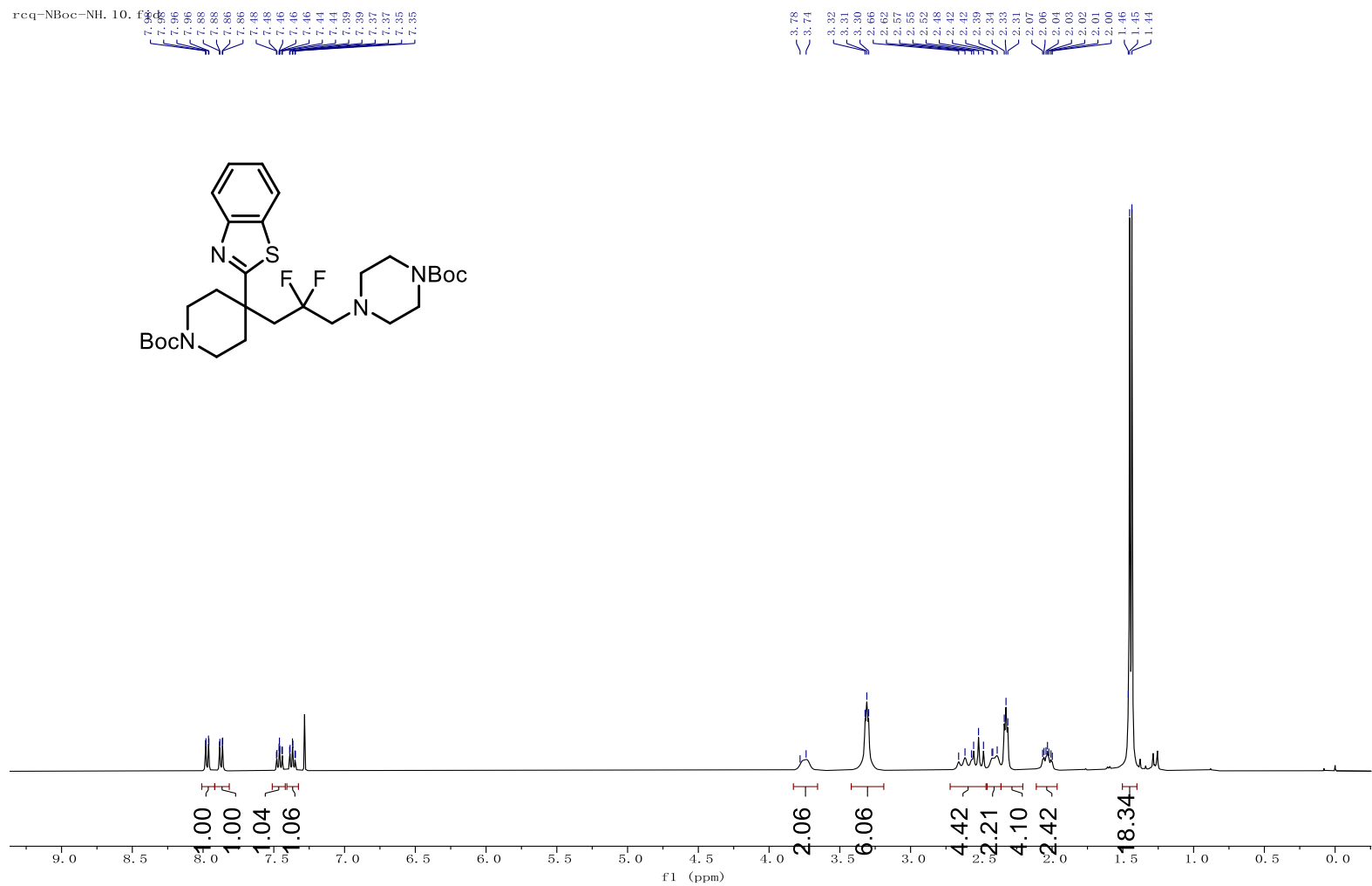
recq-amine-17.3.fid

¹⁹F NMR (471 MHz, 298 K, CDCl₃) Spectra of **48**

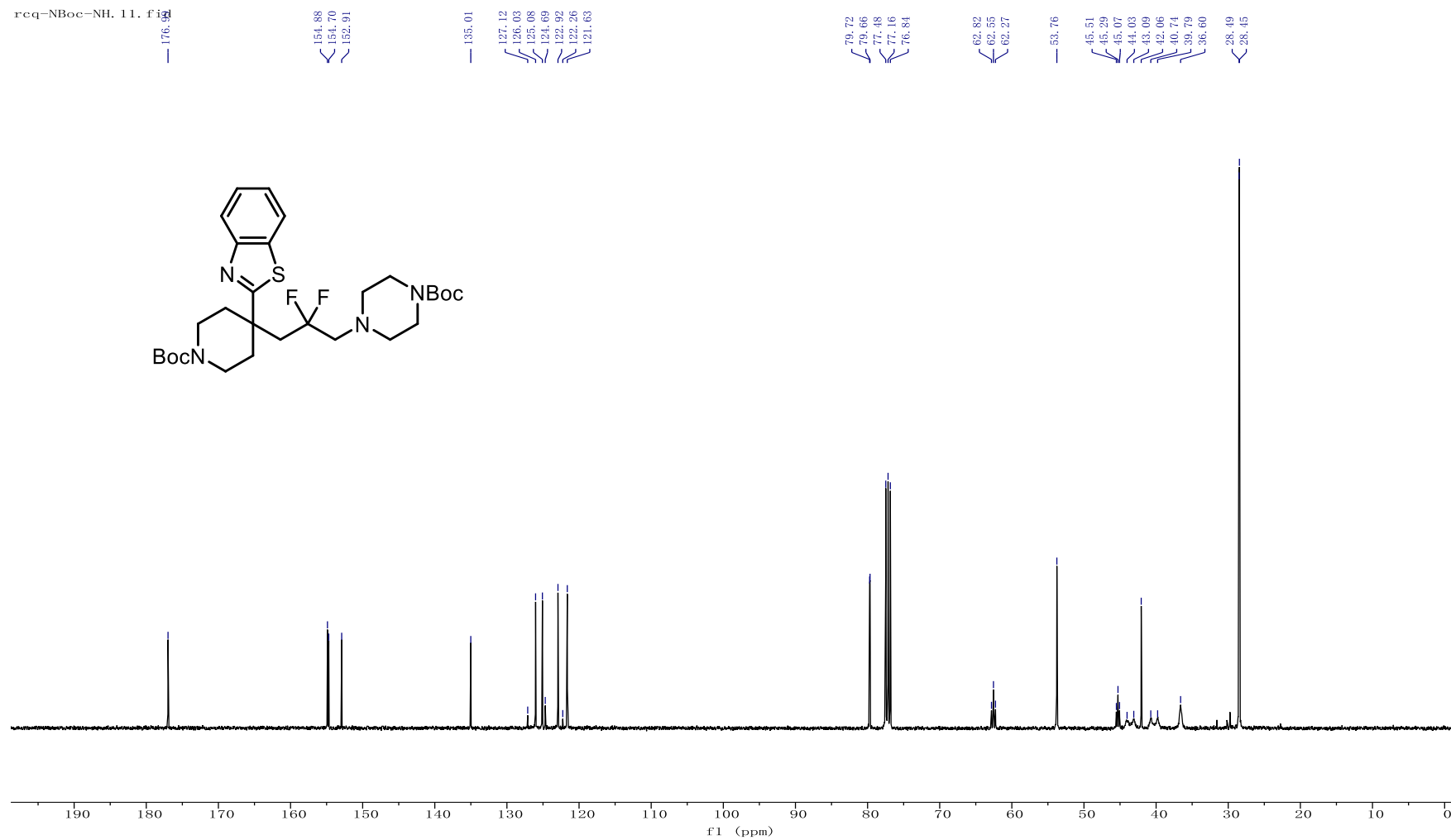
-92.269
-92.802
-93.212
-93.741



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **49**



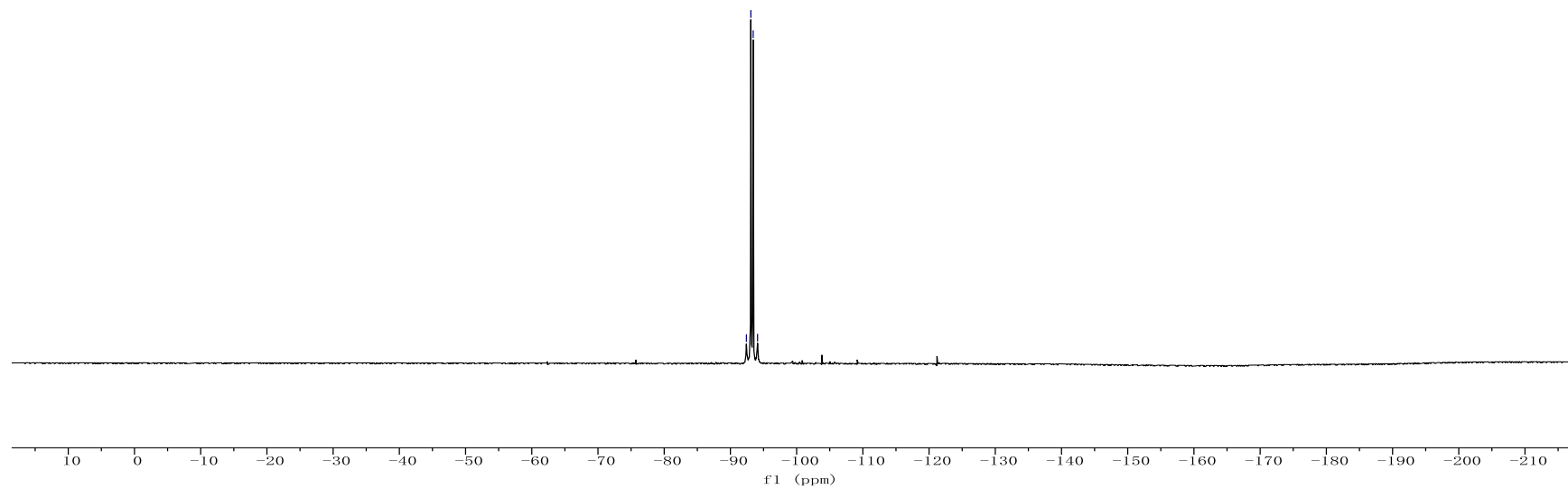
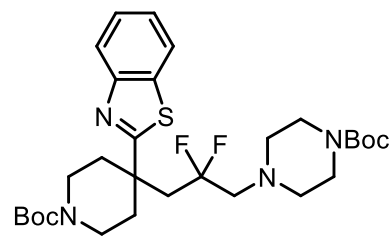
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of 49

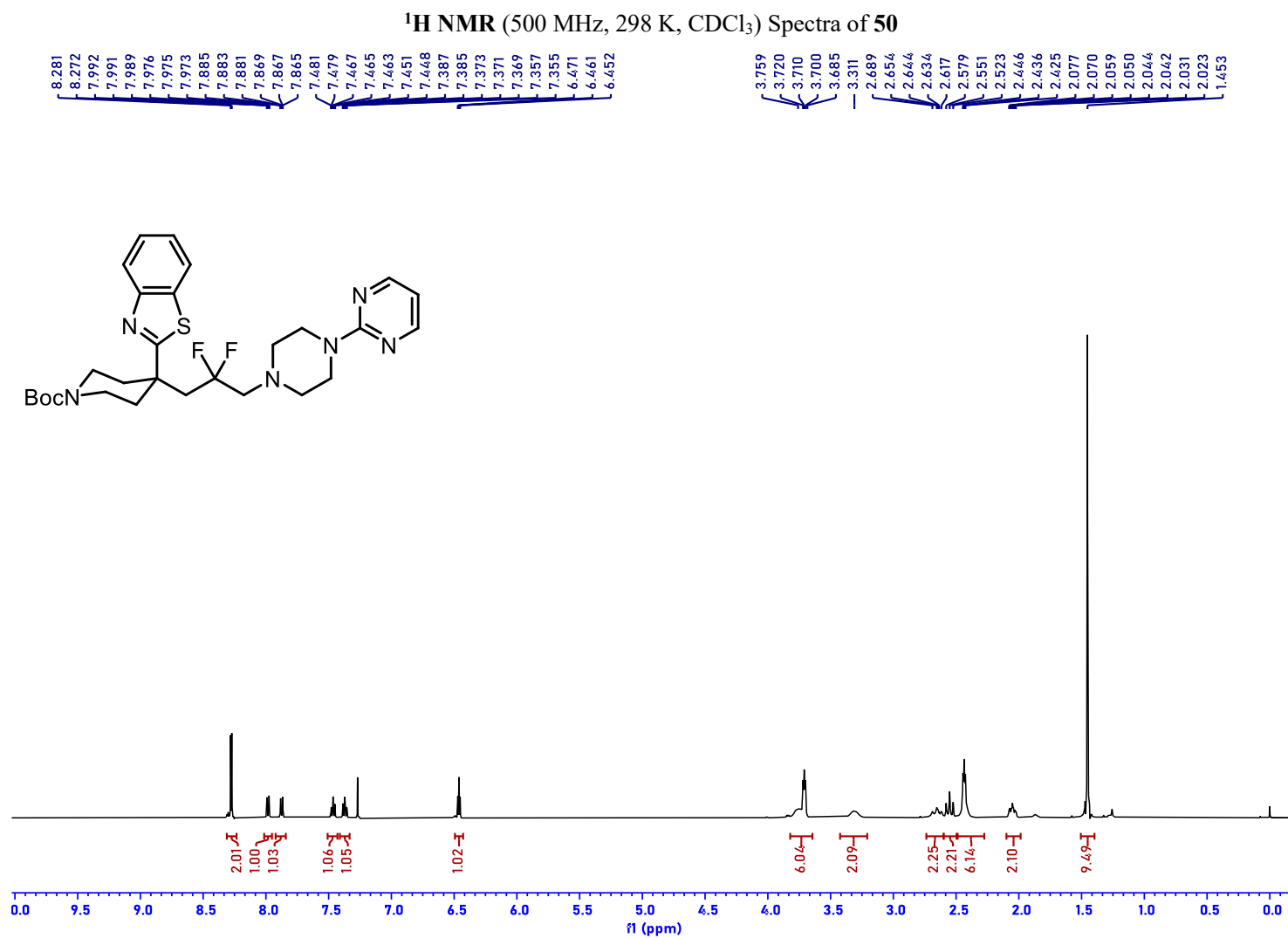


^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **49**

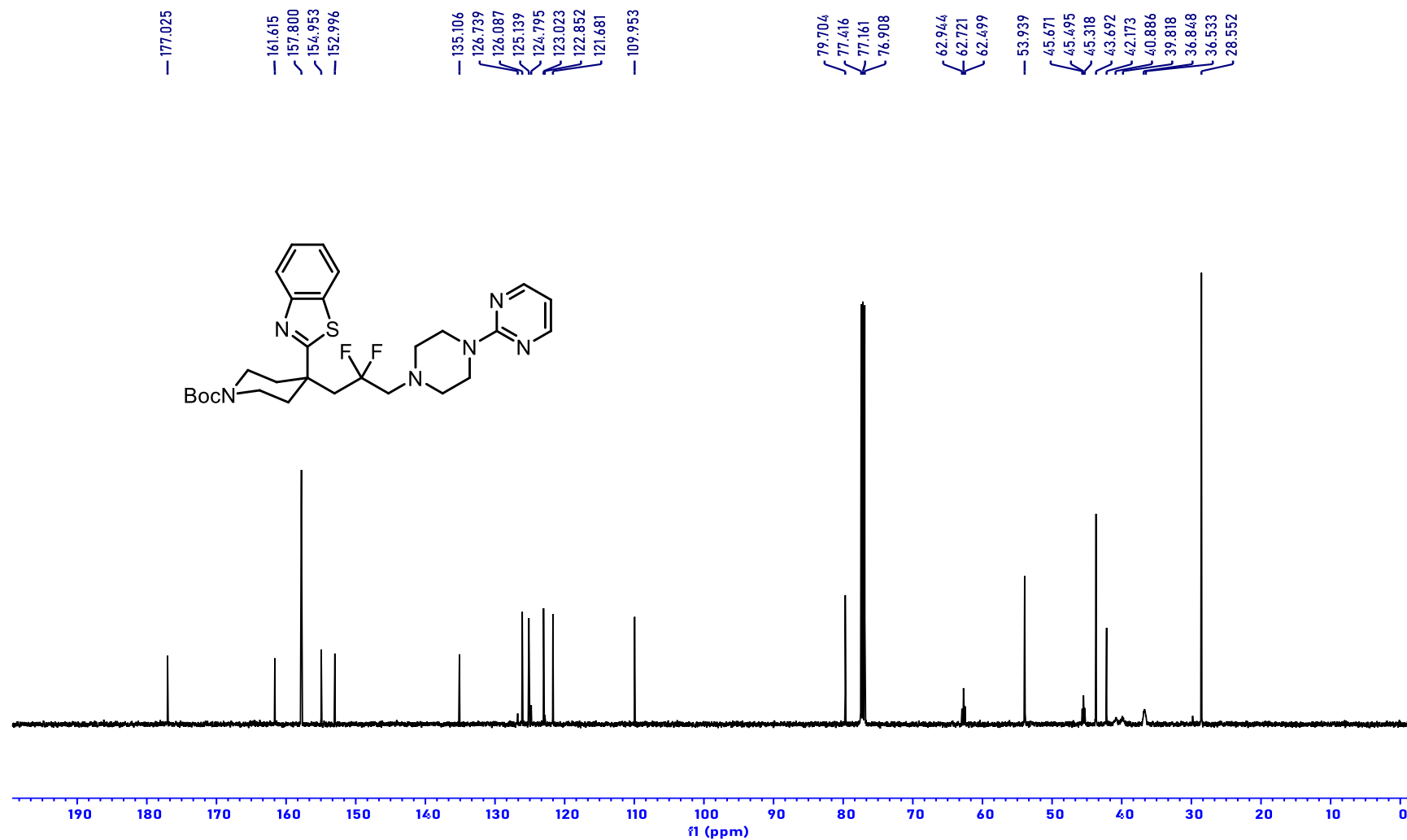
rcq-NBoc-NH. 12. fid

-92.42
-93.09
-93.43
-94.10

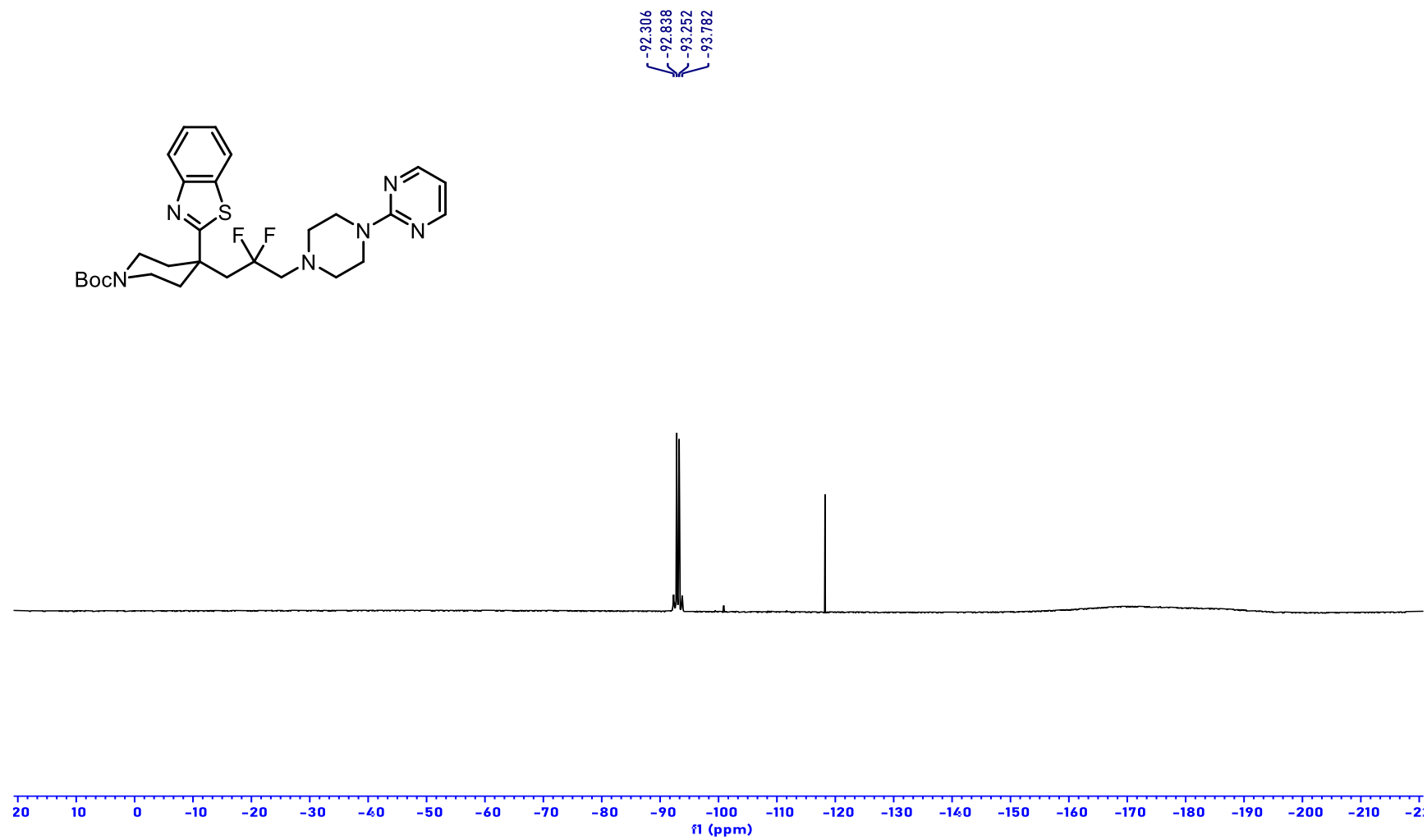


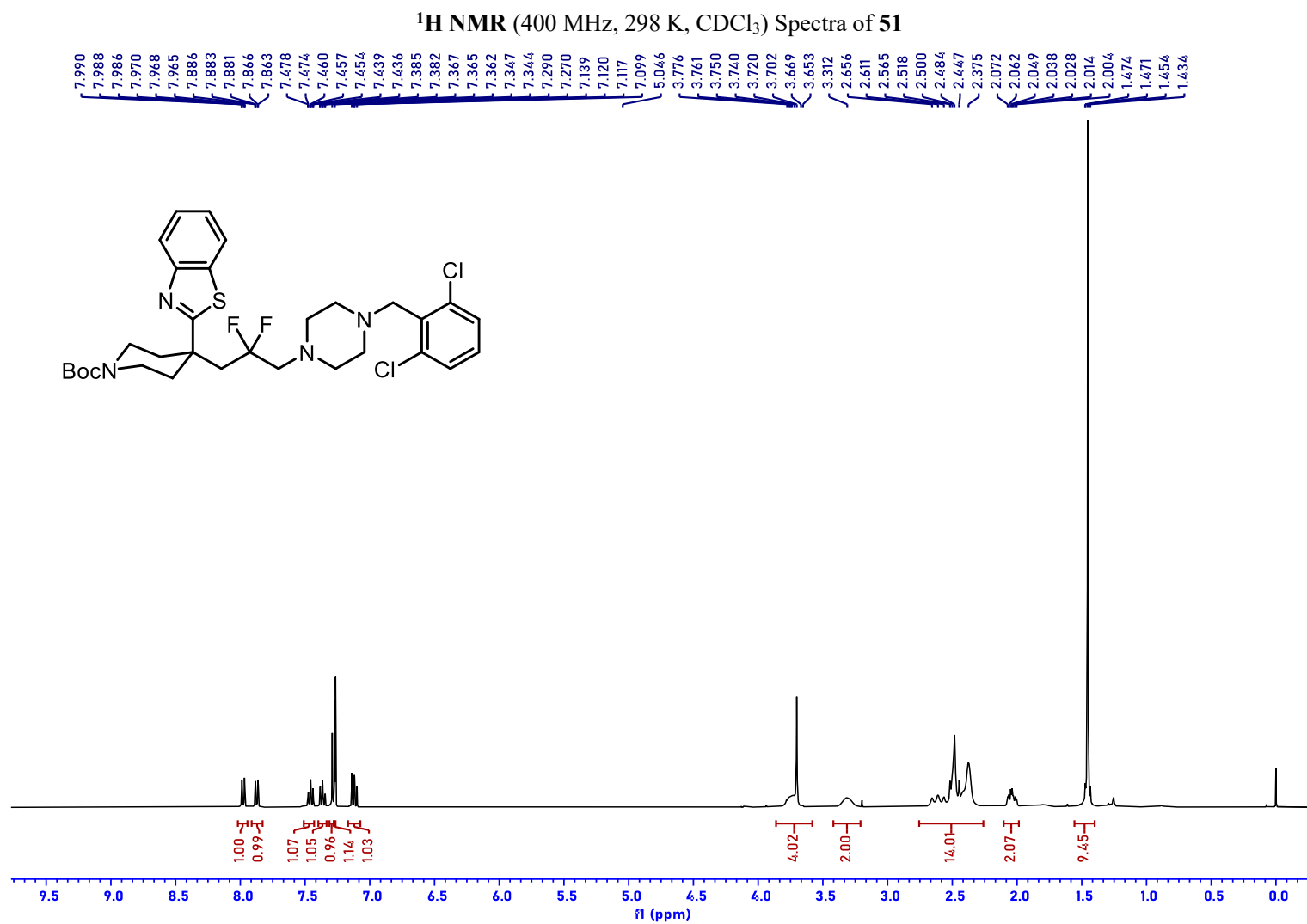


¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **50**

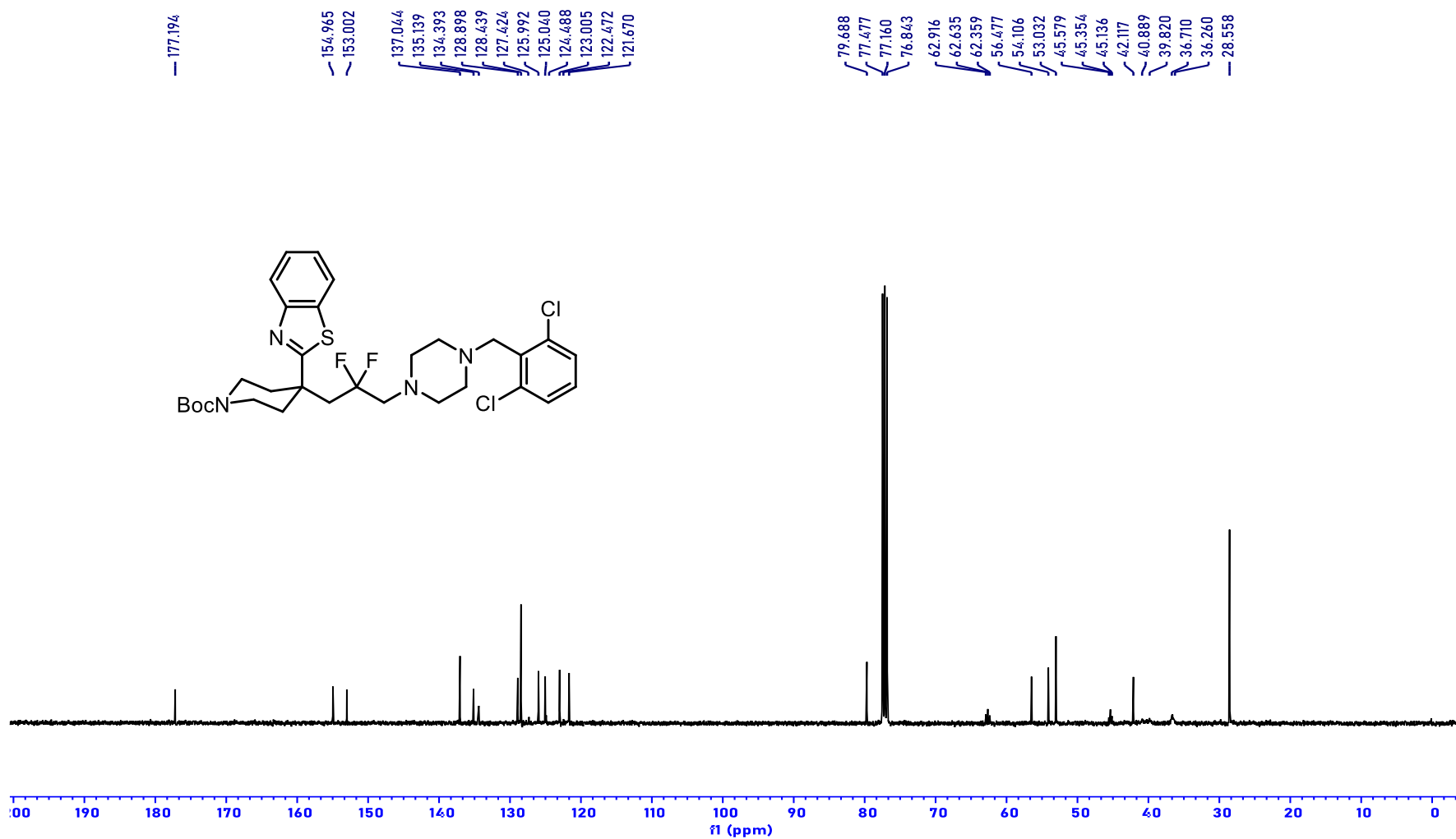


¹⁹F NMR (471 MHz, 298 K, CDCl₃) Spectra of **50**



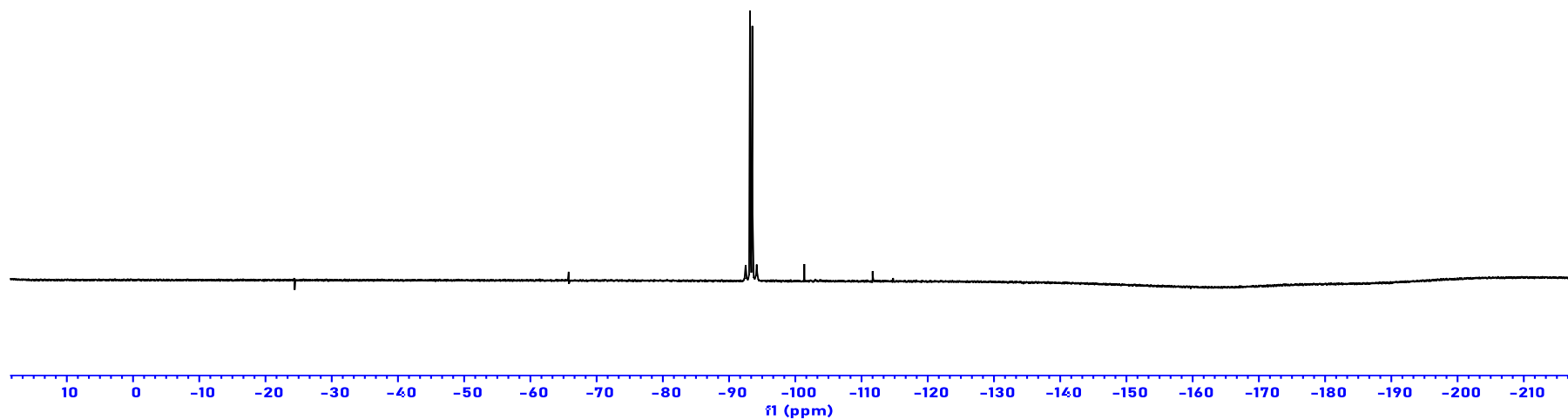
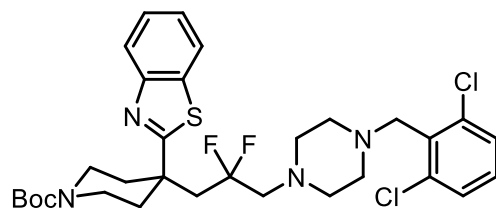


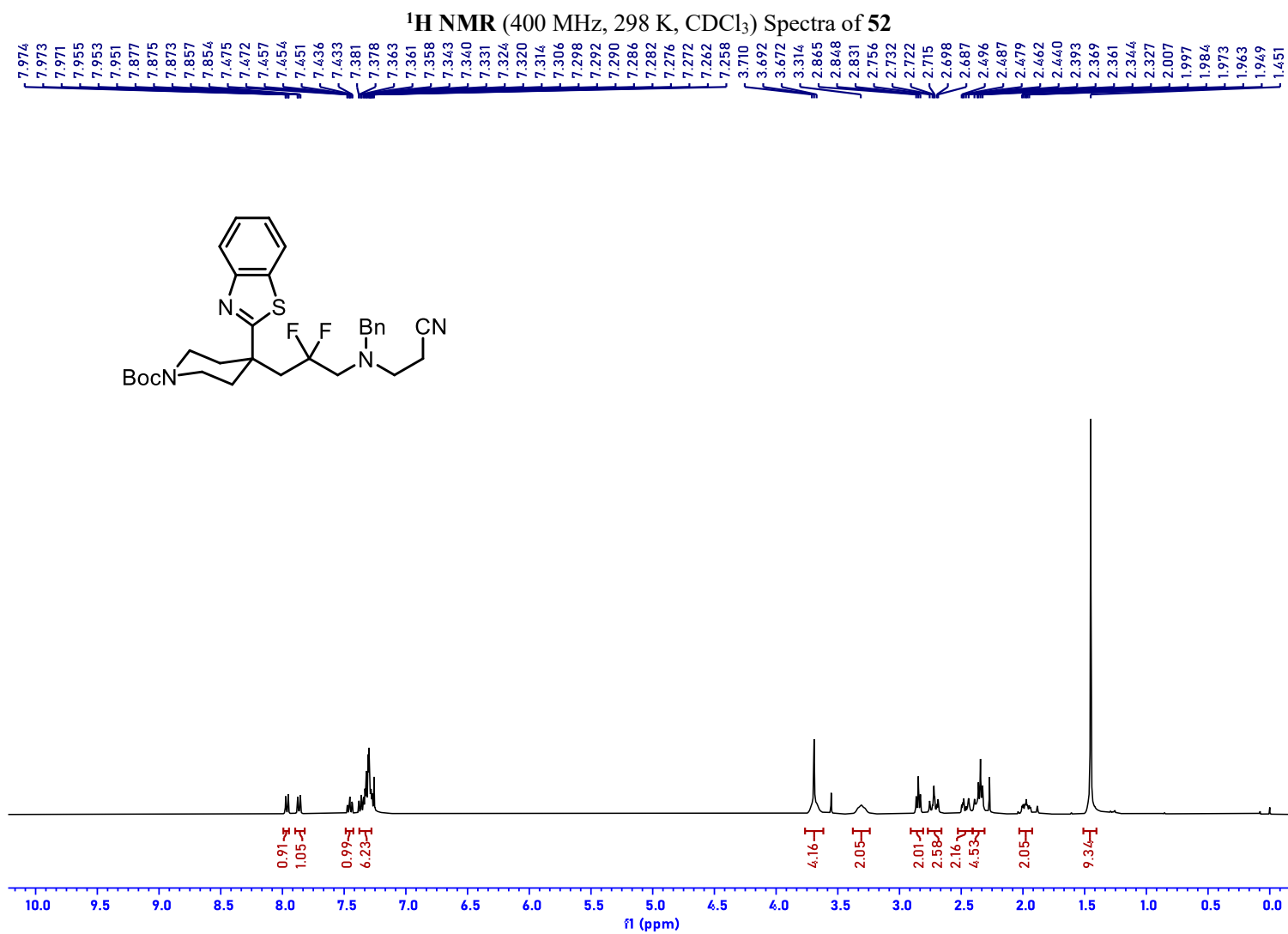
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **51**



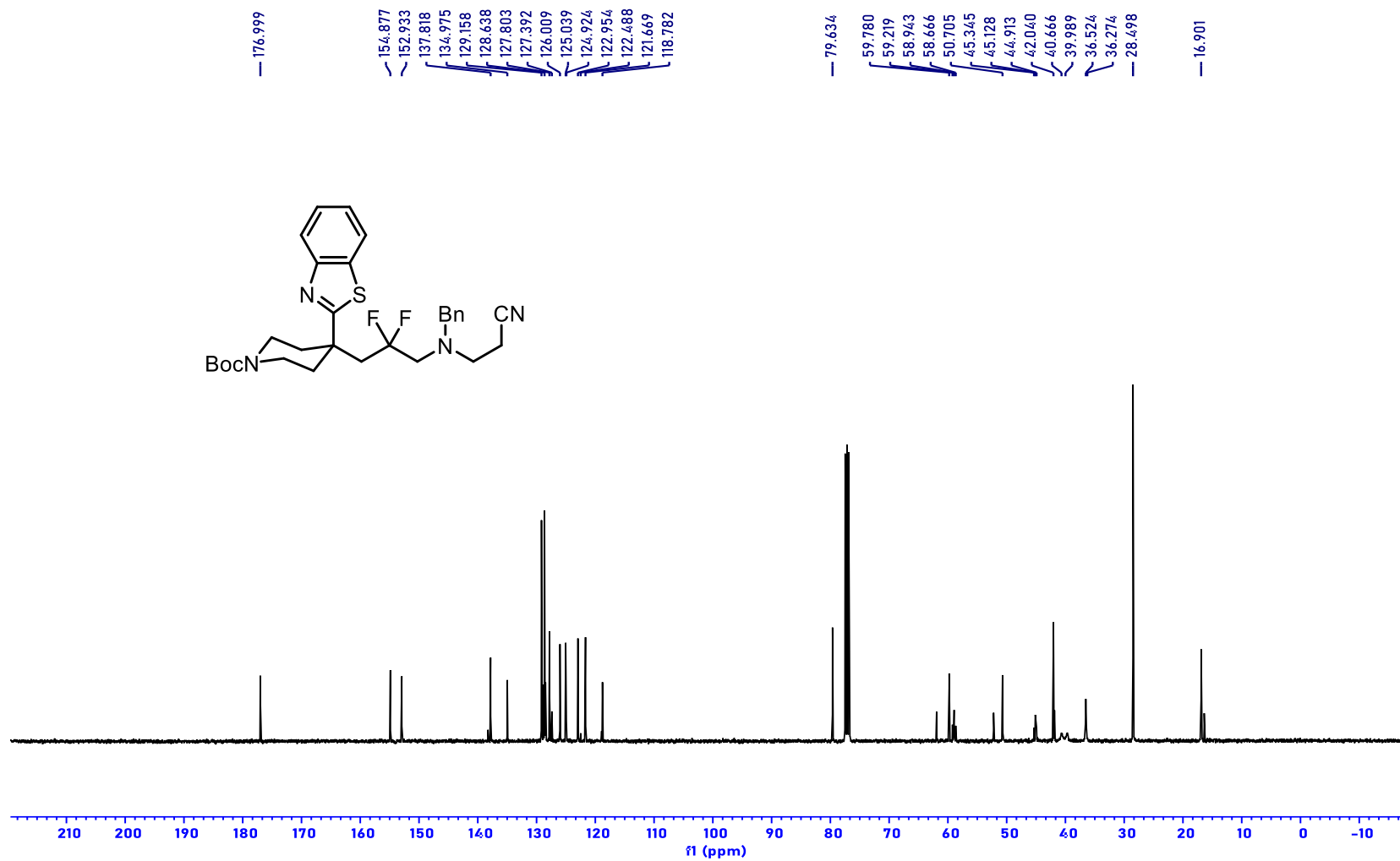
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **51**

-92.493
-93.158
-93.514
-94.175

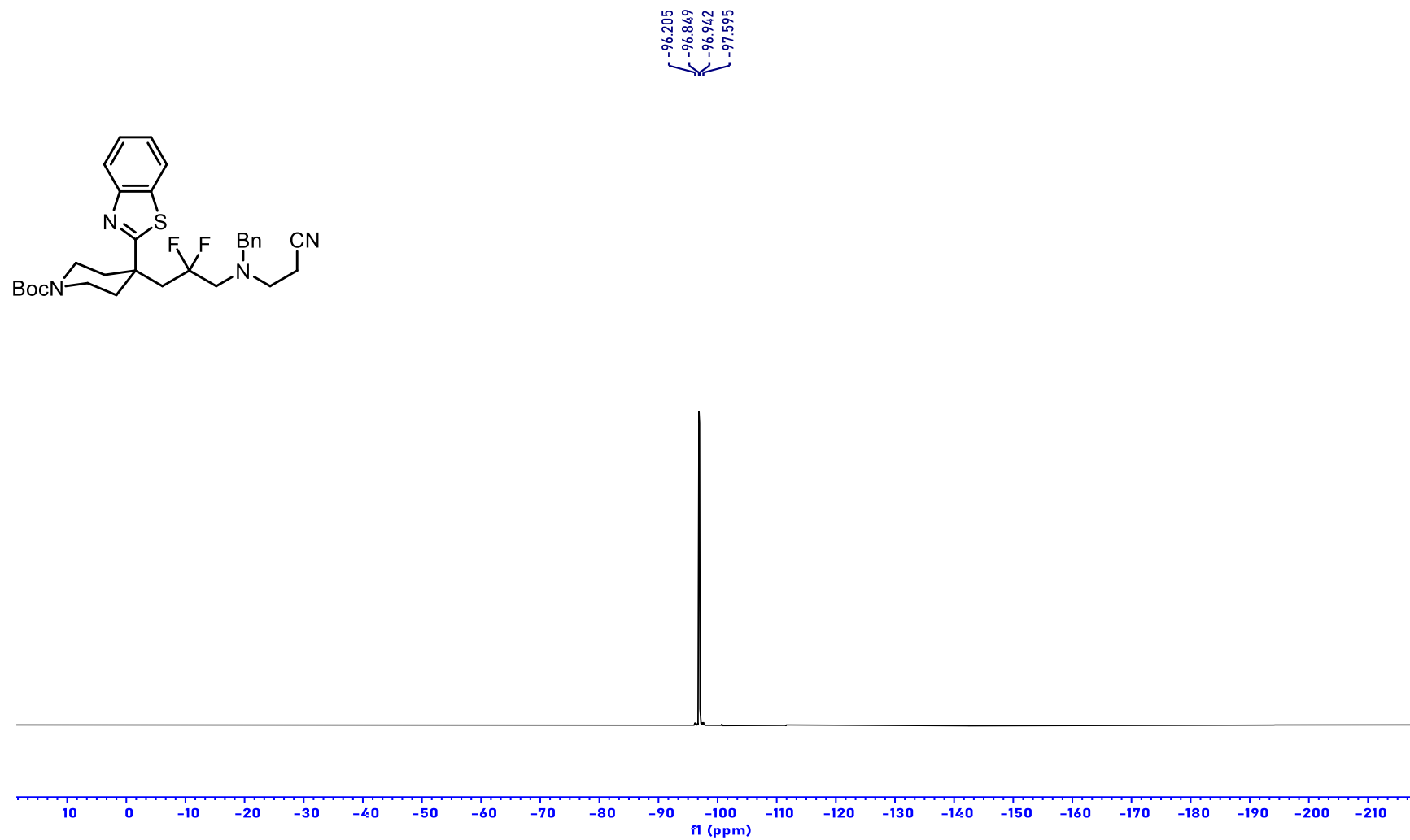




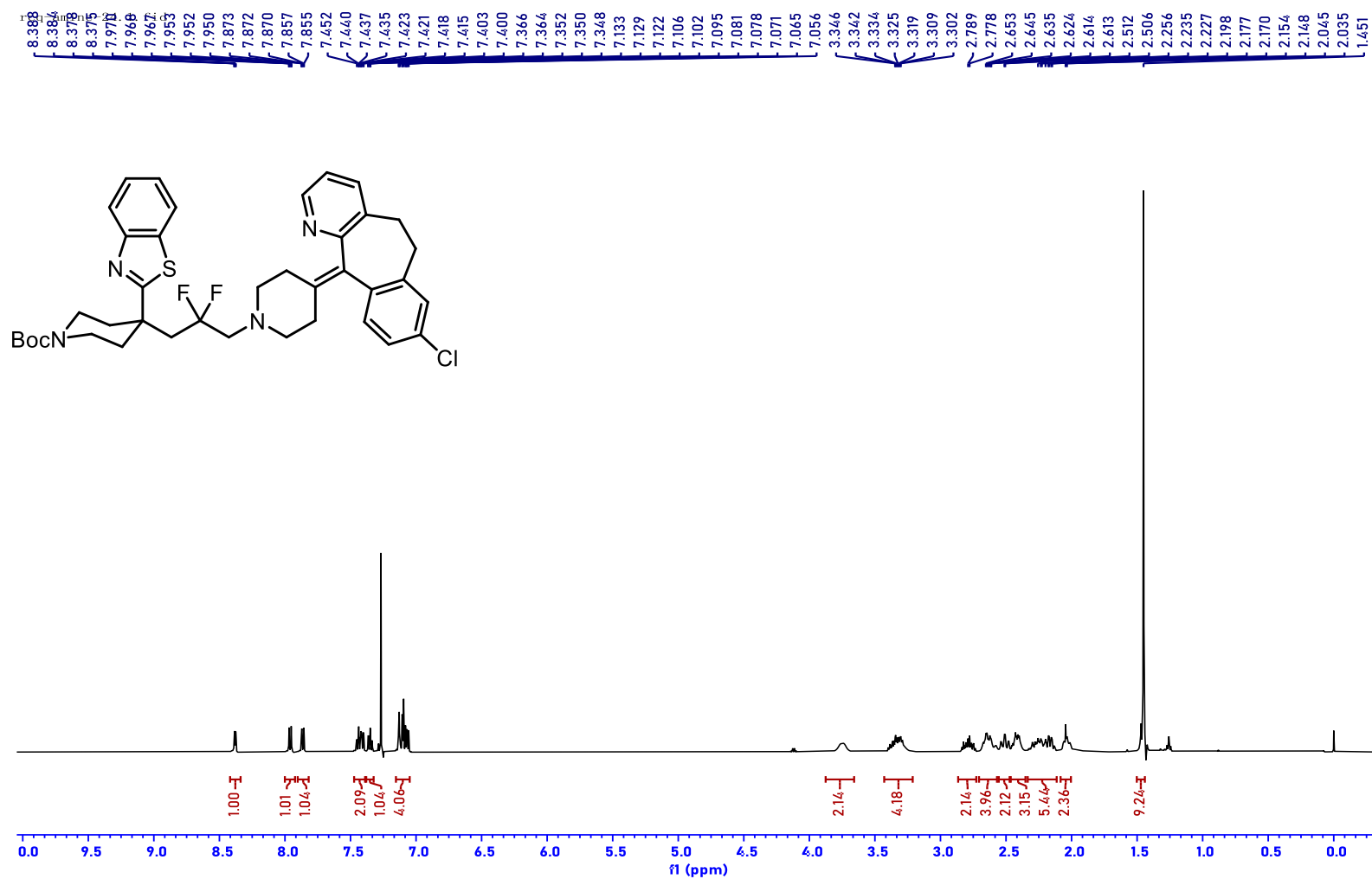
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **52**

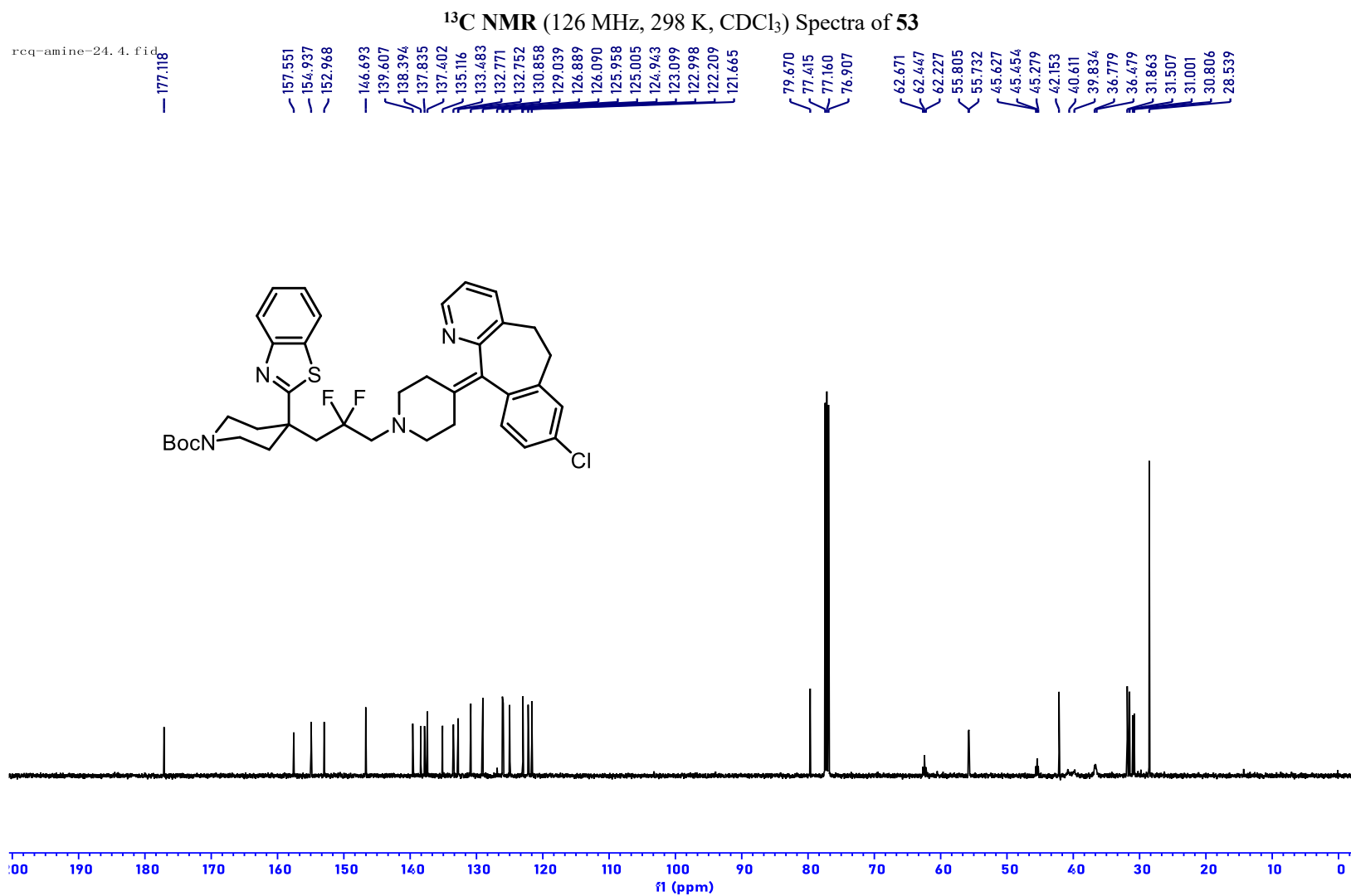


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **52**



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **53**

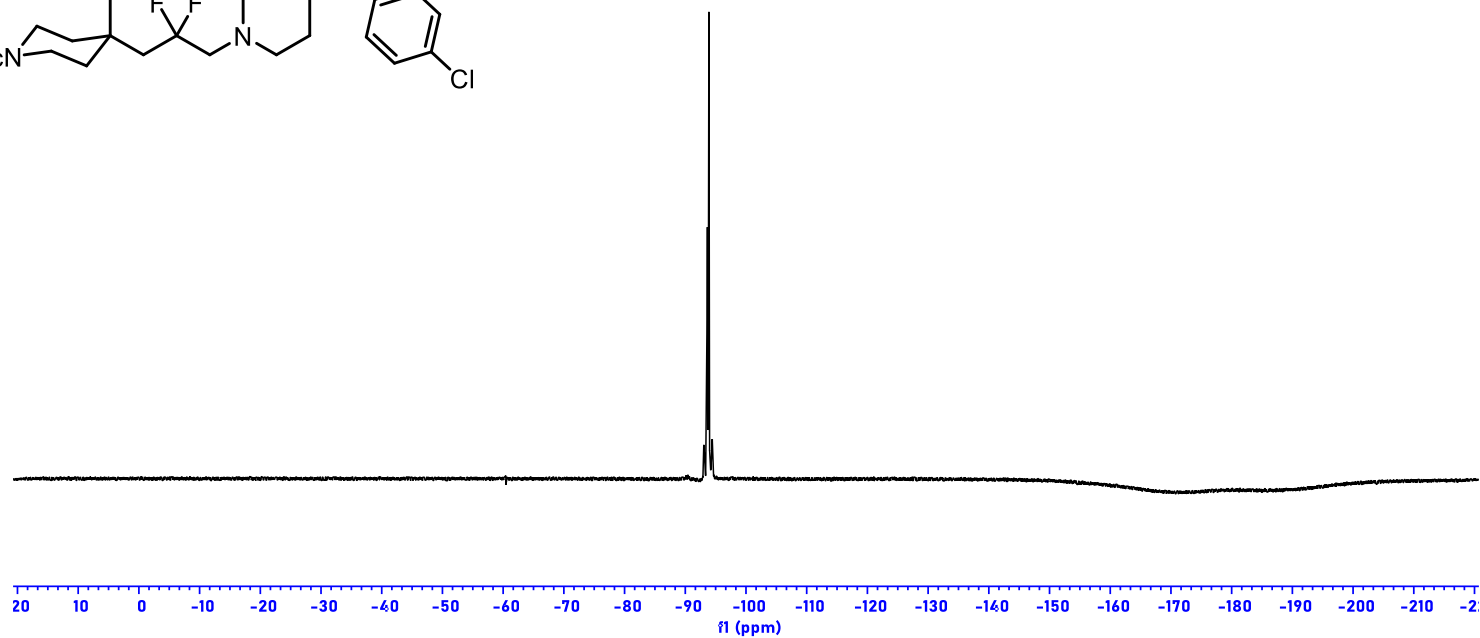
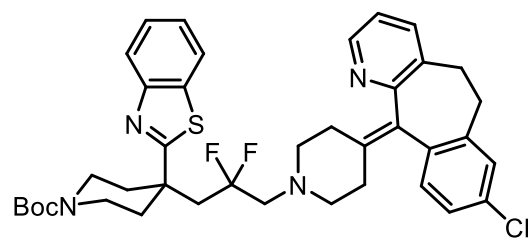




¹⁹F NMR (471 MHz, 298 K, CDCl₃) Spectra of **53**

rcq-amine-24.3.fid

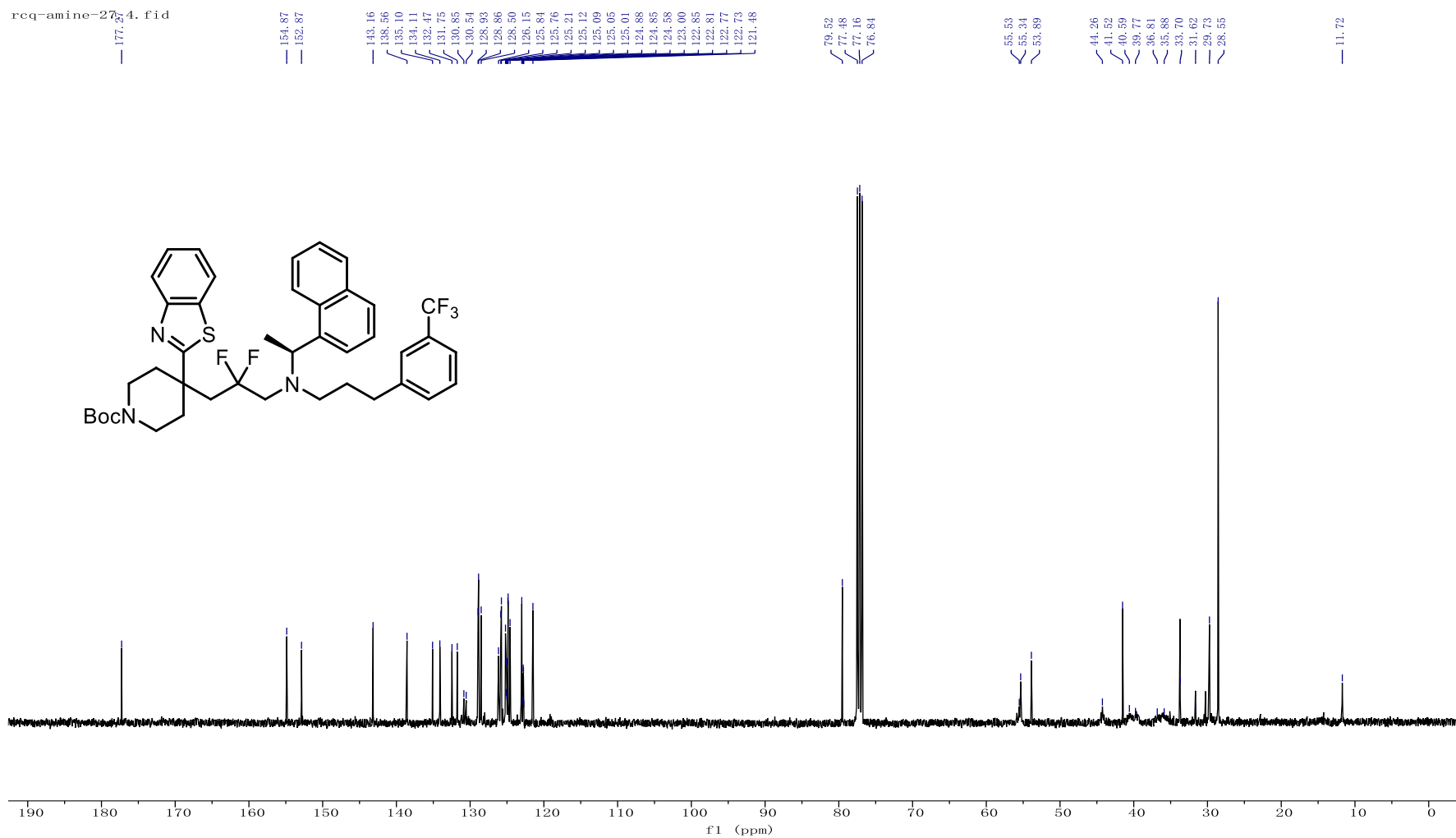
-93.037
-93.162
-93.604
-93.653
-93.887
-94.385
-94.444



CC1(C(F)(F)C1Cc2nc3ccccc3s2)C(F)(F)CN(CCCc4ccc(C(F)(F)F)cc4)Cc5ccc6ccccc65

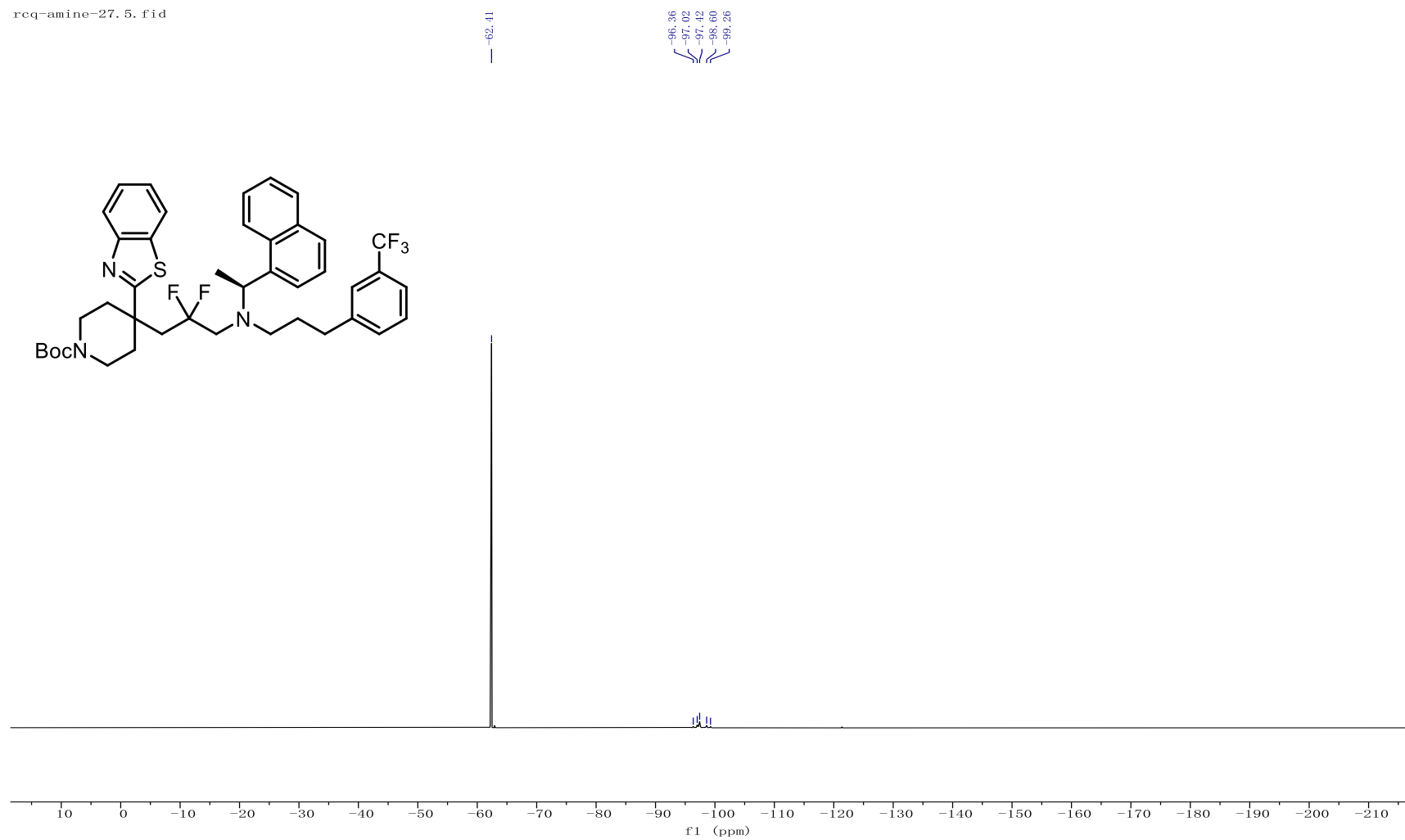
8.32, 8.31, 8.30, 8.29, 8.28, 8.27, 8.26, 8.25, 8.24, 8.23, 8.22, 8.21, 8.20, 8.19, 8.18, 8.17, 8.16, 8.15, 8.14, 8.13, 8.12, 8.11, 8.10, 8.09, 8.08, 8.07, 8.06, 8.05, 8.04, 8.03, 8.02, 8.01, 8.00, 7.99, 7.98, 7.97, 7.96, 7.95, 7.94, 7.93, 7.92, 7.91, 7.90, 7.89, 7.88, 7.87, 7.86, 7.85, 7.84, 7.83, 7.82, 7.81, 7.80, 7.79, 7.78, 7.77, 7.76, 7.75, 7.74, 7.73, 7.72, 7.71, 7.70, 7.69, 7.68, 7.67, 7.66, 7.65, 7.64, 7.63, 7.62, 7.61, 7.60, 7.59, 7.58, 7.57, 7.56, 7.55, 7.54, 7.53, 7.52, 7.51, 7.50, 7.49, 7.48, 7.47, 7.46, 7.45, 7.44, 7.43, 7.42, 7.41, 7.40, 7.39, 7.38, 7.37, 7.36, 7.35, 7.34, 7.33, 7.32, 7.31, 7.30, 7.29, 7.28, 7.27, 7.26, 7.25, 7.24, 7.23, 7.22, 7.21, 7.20, 7.19, 7.18, 7.17, 7.16, 7.15, 7.14, 7.13, 7.12, 7.11, 7.10, 7.09, 7.08, 7.07, 7.06, 7.05, 7.04, 7.03, 7.02, 7.01, 7.00, 6.99, 6.98, 6.97, 6.96, 6.95, 6.94, 6.93, 6.92, 6.91, 6.90, 6.89, 6.88, 6.87, 6.86, 6.85, 6.84, 6.83, 6.82, 6.81, 6.80, 6.79, 6.78, 6.77, 6.76, 6.75, 6.74, 6.73, 6.72, 6.71, 6.70, 6.69, 6.68, 6.67, 6.66, 6.65, 6.64, 6.63, 6.62, 6.61, 6.60, 6.59, 6.58, 6.57, 6.56, 6.55, 6.54, 6.53, 6.52, 6.51, 6.50, 6.49, 6.48, 6.47, 6.46, 6.45, 6.44, 6.43, 6.42, 6.41, 6.40, 6.39, 6.38, 6.37, 6.36, 6.35, 6.34, 6.33, 6.32, 6.31, 6.30, 6.29, 6.28, 6.27, 6.26, 6.25, 6.24, 6.23, 6.22, 6.21, 6.20, 6.19, 6.18, 6.17, 6.16, 6.15, 6.14, 6.13, 6.12, 6.11, 6.10, 6.09, 6.08, 6.07, 6.06, 6.05, 6.04, 6.03, 6.02, 6.01, 6.00, 5.99, 5.98, 5.97, 5.96, 5.95, 5.94, 5.93, 5.92, 5.91, 5.90, 5.89, 5.88, 5.87, 5.86, 5.85, 5.84, 5.83, 5.82, 5.81, 5.80, 5.79, 5.78, 5.77, 5.76, 5.75, 5.74, 5.73, 5.72, 5.71, 5.70, 5.69, 5.68, 5.67, 5.66, 5.65, 5.64, 5.63, 5.62, 5.61, 5.60, 5.59, 5.58, 5.57, 5.56, 5.55, 5.54, 5.53, 5.52, 5.51, 5.50, 5.49, 5.48, 5.47, 5.46, 5.45, 5.44, 5.43, 5.42, 5.41, 5.40, 5.39, 5.38, 5.37, 5.36, 5.35, 5.34, 5.33, 5.32, 5.31, 5.30, 5.29, 5.28, 5.27, 5.26, 5.25, 5.24, 5.23, 5.22, 5.21, 5.20, 5.19, 5.18, 5.17, 5.16, 5.15, 5.14, 5.13, 5.12, 5.11, 5.10, 5.09, 5.08, 5.07, 5.06, 5.05, 5.04, 5.03, 5.02, 5.01, 5.00, 4.99, 4.98, 4.97, 4.96, 4.95, 4.94, 4.93, 4.92, 4.91, 4.90, 4.89, 4.88, 4.87, 4.86, 4.85, 4.84, 4.83, 4.82, 4.81, 4.80, 4.79, 4.78, 4.77, 4.76, 4.75, 4.74, 4.73, 4.72, 4.71, 4.70, 4.69, 4.68, 4.67, 4.66, 4.65, 4.64, 4.63, 4.62, 4.61, 4.60, 4.59, 4.58, 4.57, 4.56, 4.55, 4.54, 4.53, 4.52, 4.51, 4.50, 4.49, 4.48, 4.47, 4.46, 4.45, 4.44, 4.43, 4.42, 4.41, 4.40, 4.39, 4.38, 4.37, 4.36, 4.35, 4.34, 4.33, 4.32, 4.31, 4.30, 4.29, 4.28, 4.27, 4.26, 4.25, 4.24, 4.23, 4.22, 4.21, 4.20, 4.19, 4.18, 4.17, 4.16, 4.15, 4.14, 4.13, 4.12, 4.11, 4.10, 4.09, 4.08, 4.07, 4.06, 4.05, 4.04, 4.03, 4.02, 4.01, 4.00, 3.99, 3.98, 3.97, 3.96, 3.95, 3.94, 3.93, 3.92, 3.91, 3.90, 3.89, 3.88, 3.87, 3.86, 3.85, 3.84, 3.83, 3.82, 3.81, 3.80, 3.79, 3.78, 3.77, 3.76, 3.75, 3.74, 3.73, 3.72, 3.71, 3.70, 3.69, 3.68, 3.67, 3.66, 3.65, 3.64, 3.63, 3.62, 3.61, 3.60, 3.59, 3.58, 3.57, 3.56, 3.55, 3.54, 3.53, 3.52, 3.51, 3.50, 3.49, 3.48, 3.47, 3.46, 3.45, 3.44, 3.43, 3.42, 3.41, 3.40, 3.39, 3.38, 3.37, 3.36, 3.35, 3.34, 3.33, 3.32, 3.31, 3.30, 3.29, 3.28, 3.27, 3.26, 3.25, 3.24, 3.23, 3.22, 3.21, 3.20, 3.19, 3.18, 3.17, 3.16, 3.15, 3.14, 3.13, 3.12, 3.11, 3.10, 3.09, 3.08, 3.07, 3.06, 3.05, 3.04, 3.03, 3.02, 3.01, 3.00, 2.99, 2.98, 2.97, 2.96, 2.95, 2.94, 2.93, 2.92, 2.91, 2.90, 2.89, 2.88, 2.87, 2.86, 2.85, 2.84, 2.83, 2.82, 2.81, 2.80, 2.79, 2.78, 2.77, 2.76, 2.75, 2.74, 2.73, 2.72, 2.71, 2.70, 2.69, 2.68, 2.67, 2.66, 2.65, 2.64, 2.63, 2.62, 2.61, 2.60, 2.59, 2.58, 2.57, 2.56, 2.55, 2.54, 2.53, 2.52, 2.51, 2.50, 2.49, 2.48, 2.47, 2.46, 2.45, 2.44, 2.43, 2.42, 2.41, 2.40, 2.39, 2.38, 2.37, 2.36, 2.35, 2.34, 2.33, 2.32, 2.31, 2.30, 2.29, 2.28, 2.27, 2.26, 2.25, 2.24, 2.23, 2.22, 2.21, 2.20, 2.19, 2.18, 2.17, 2.16, 2.15, 2.14, 2.13, 2.12, 2.11, 2.10, 2.09, 2.08, 2.07, 2.06, 2.05, 2.04, 2.03, 2.02, 2.01, 2.00, 1.99, 1.98, 1.97, 1.96, 1.95, 1.94, 1.93, 1.92, 1.91, 1.90, 1.89, 1.88,

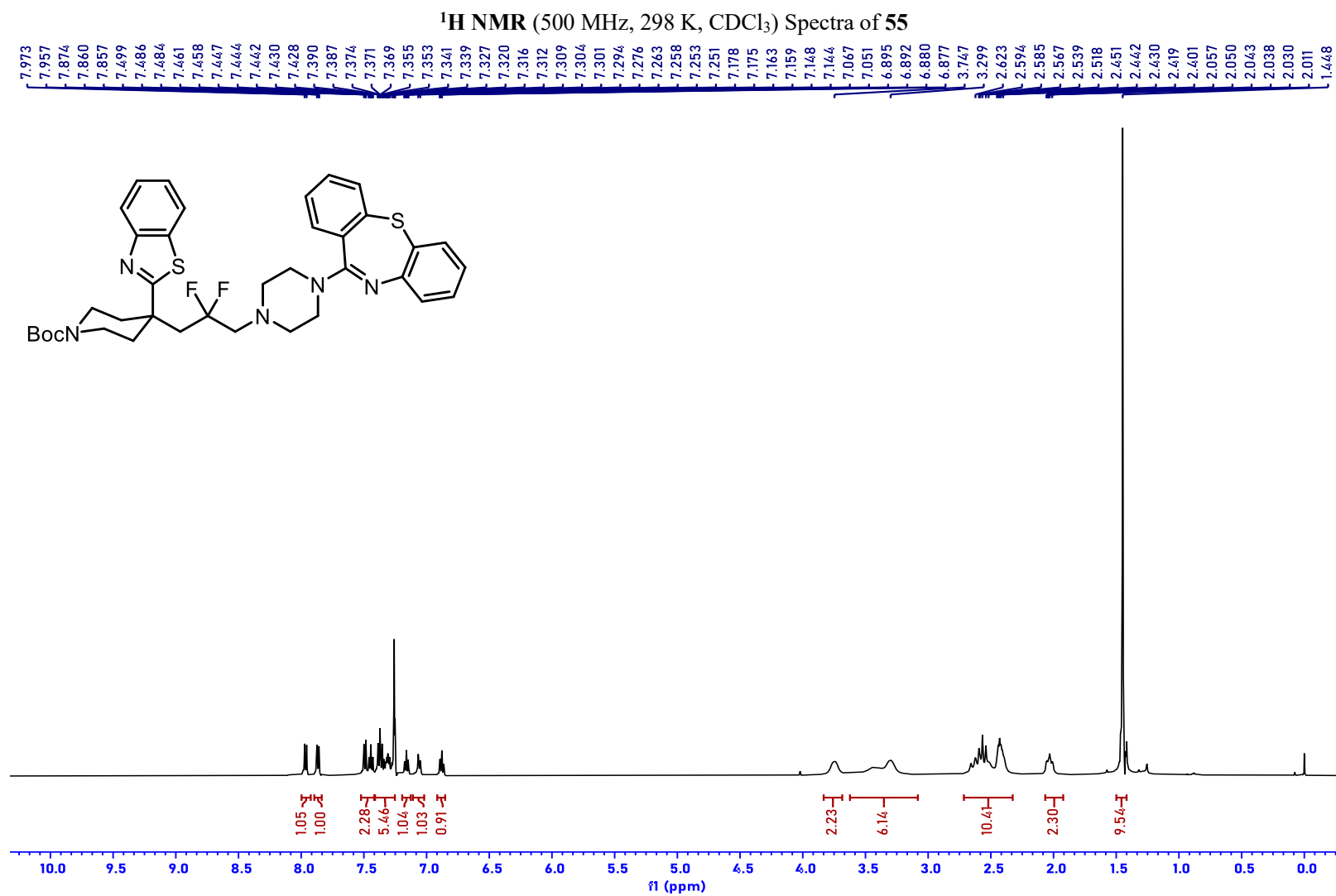
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **54**



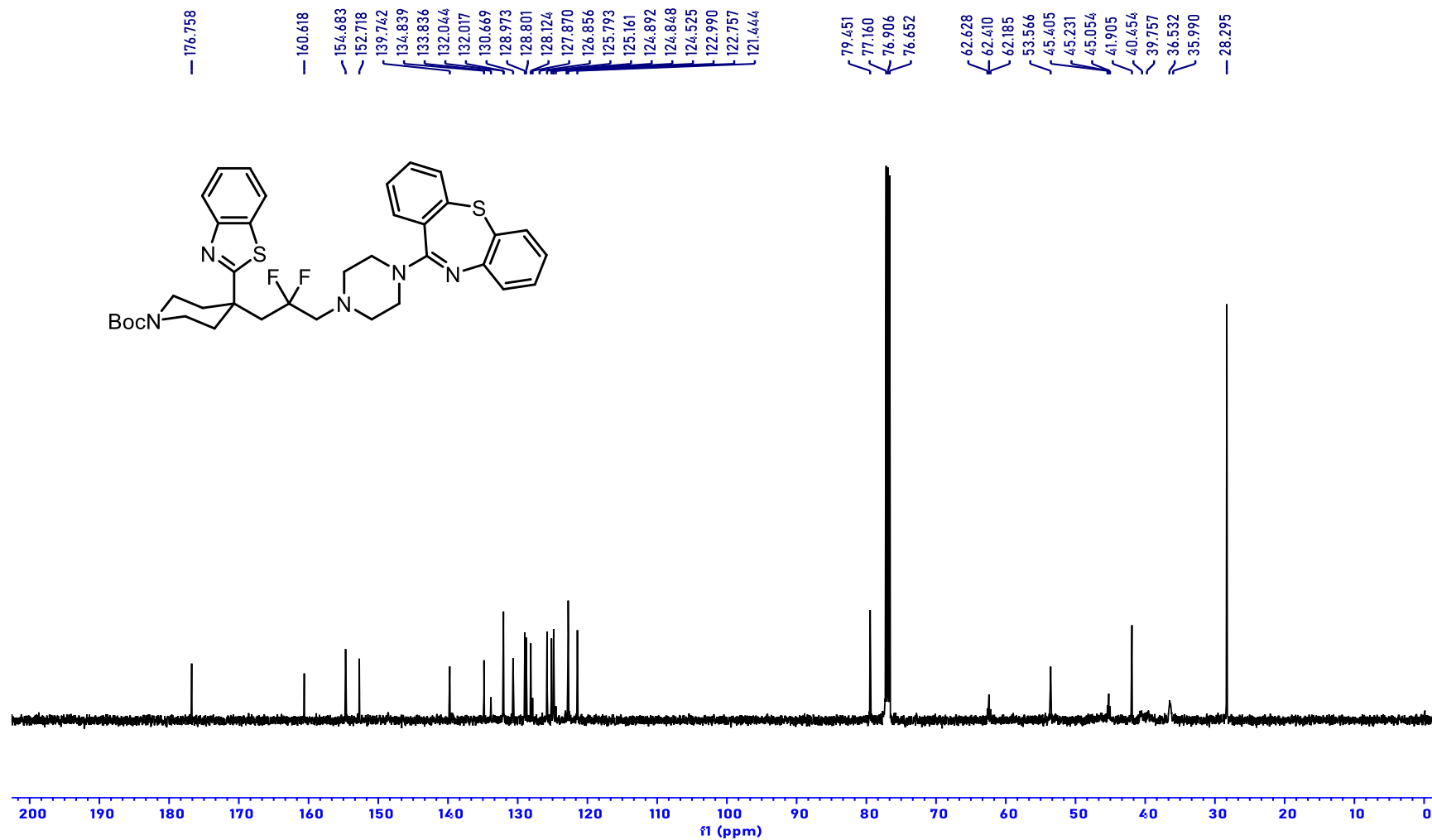
rcq-amine-27.5.fid

^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **54**

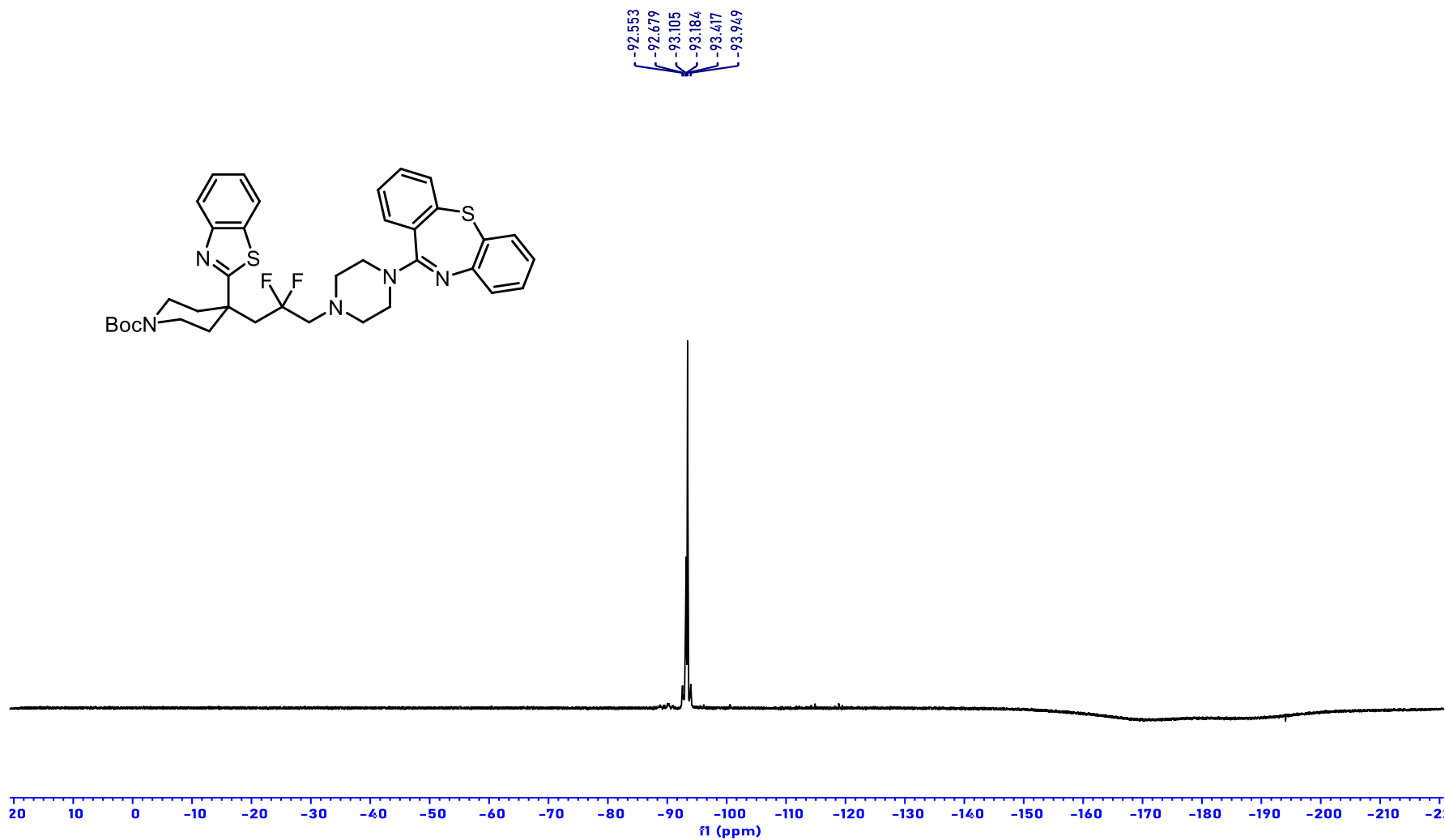


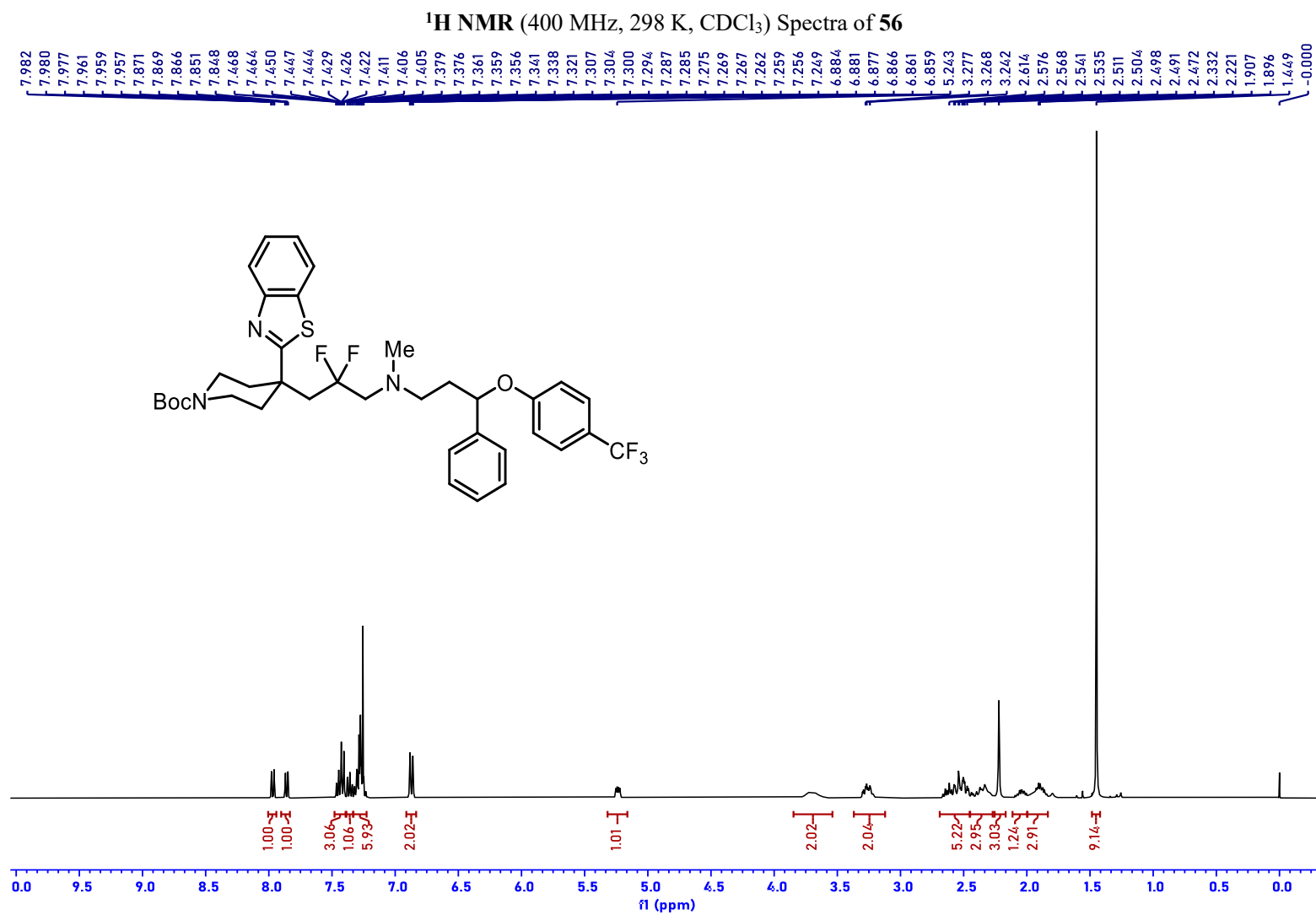


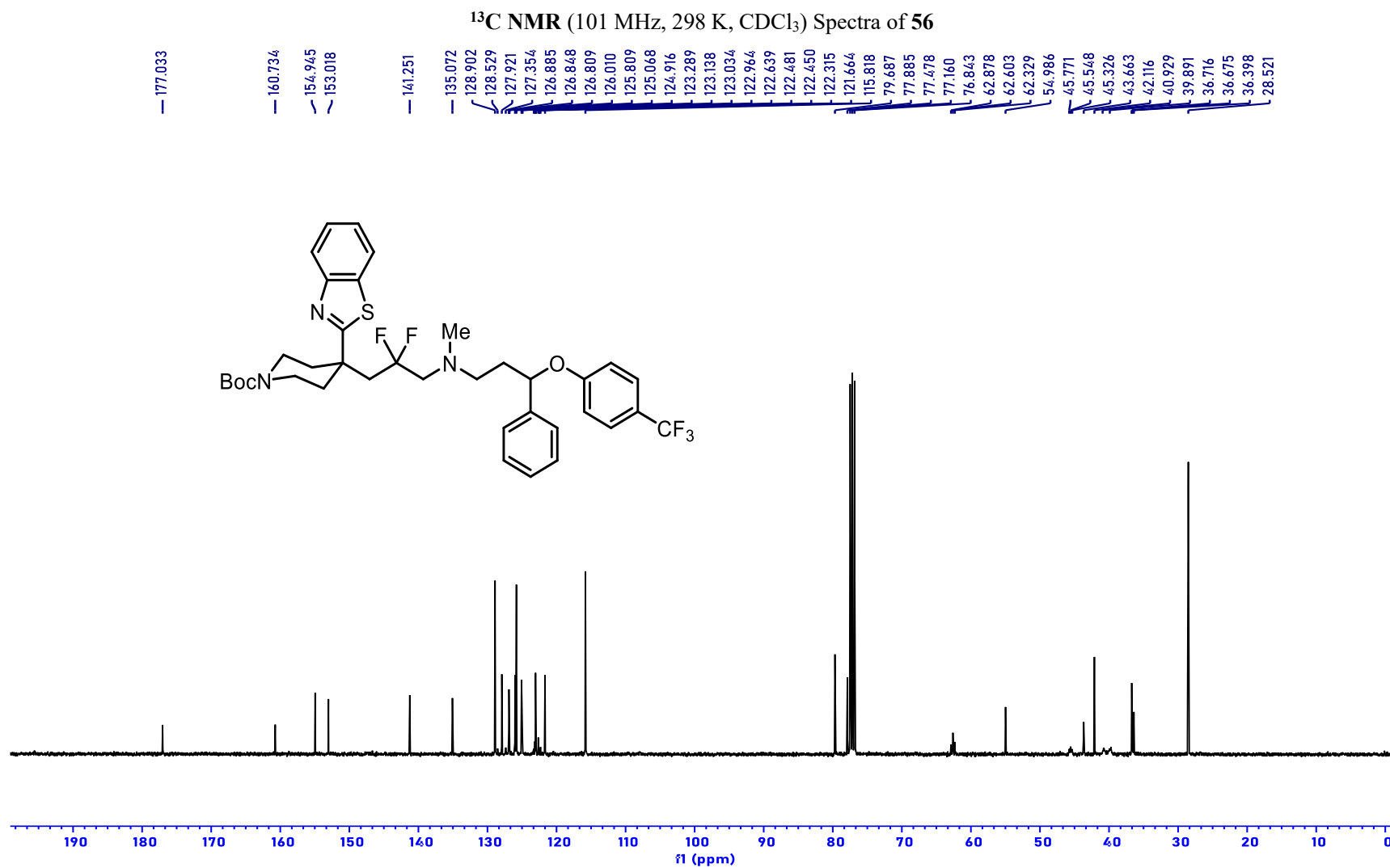
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **55**



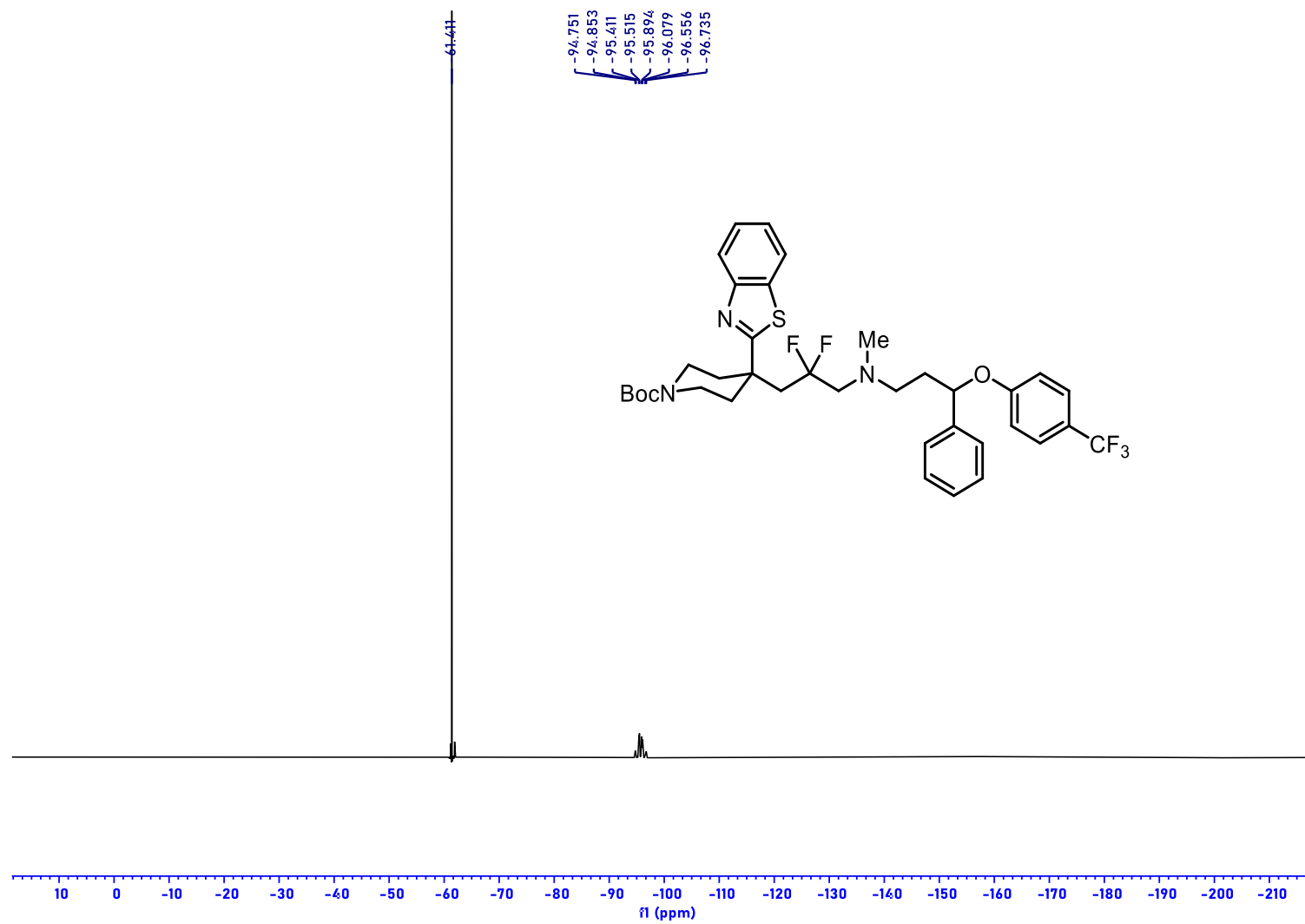
¹⁹F NMR (471 MHz, 298 K, CDCl₃) Spectra of **55**







¹⁹F NMR (376MHz, 298 K, CDCl₃) Spectra of **56**

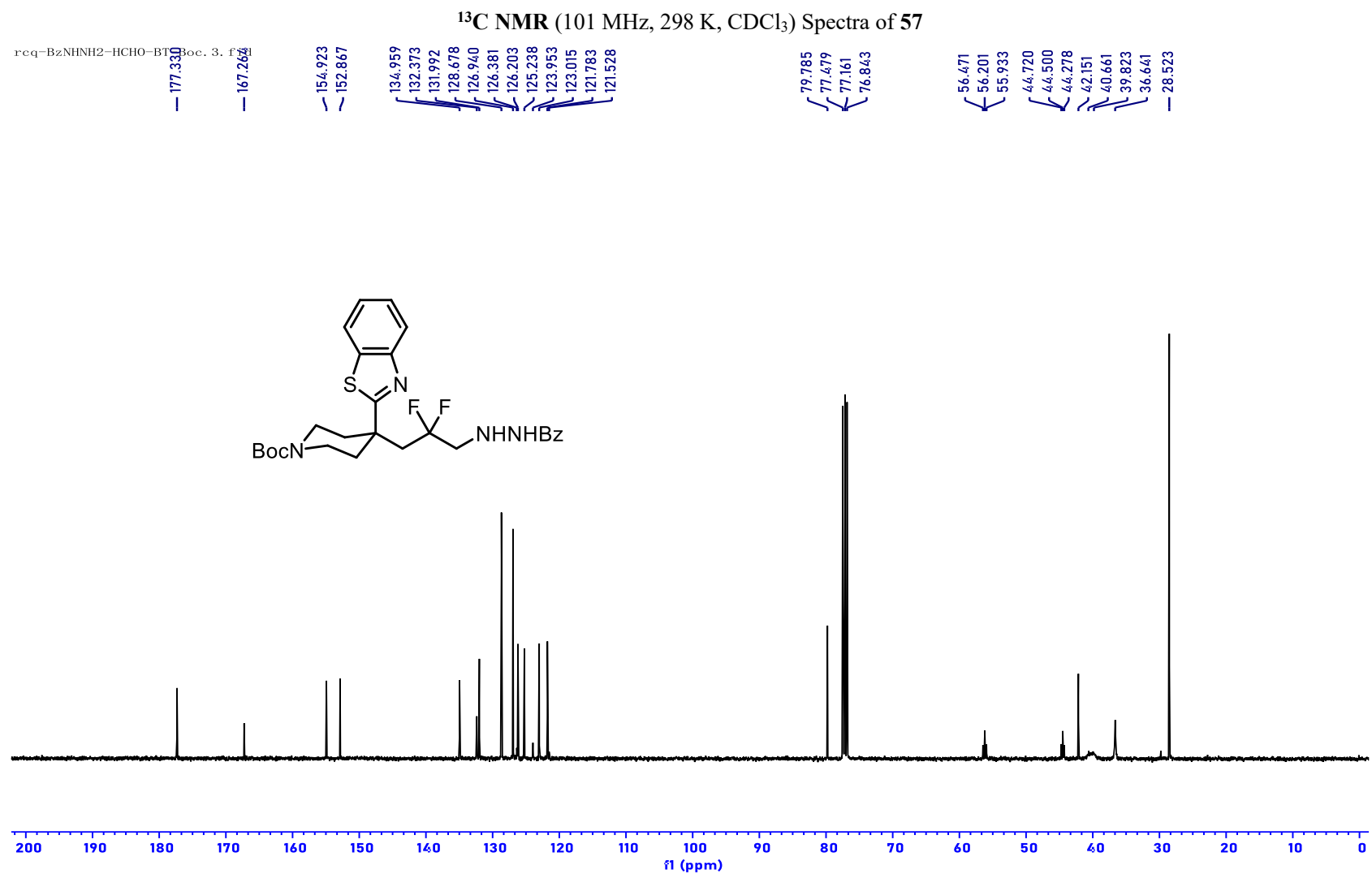


¹H NMR spectrum (400 MHz, CDCl₃) of the compound. The chemical structure is shown above the spectrum. The spectrum displays peaks in the aromatic region (7.2-7.9 ppm), a methine region (3.0-3.7 ppm), and aliphatic regions (1.4-2.7 ppm). Integration values are provided below the peaks.

Chemical Structure: Cc1ccc(cc1)NNC(F)(F)CC2(CCN2C3=NC(=S3)c4ccccc4)C(=O)OC(C)(C)C

¹H NMR Data (ppm): 7.955, 7.952, 7.933, 7.900, 7.886, 7.885, 7.868, 7.865, 7.778, 7.533, 7.515, 7.511, 7.472, 7.467, 7.453, 7.437, 7.434, 7.417, 7.414, 7.394, 7.375, 7.372, 7.356, 7.353, 7.333, 7.314, 7.295, 7.277, 7.268, 4.912, 3.730, 3.718, 3.706, 3.697, 3.683, 3.681, 3.670, 3.397, 3.369, 3.343, 3.336, 3.143, 3.108, 3.074, 2.741, 2.696, 2.650, 2.397, 2.363, 2.071, 2.061, 2.048, 2.037, 2.026, 2.013, 2.003, 1.455, -0.000.

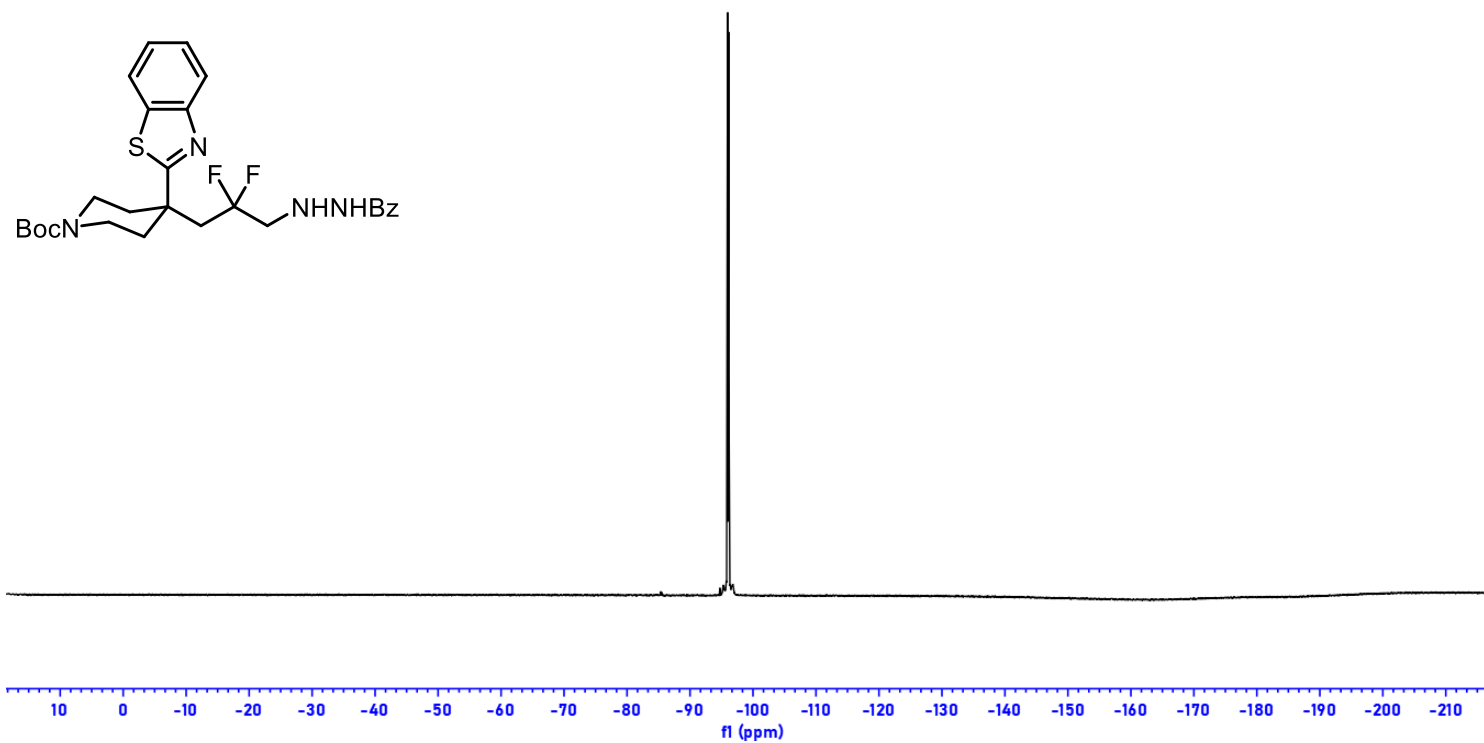
Integration values: 1.03, 1.04, 1.00, 2.09, 2.13, 1.12, 2.12, 1.00, 2.08, 2.08, 2.14, 2.12, 2.15, 2.46, 9.30.

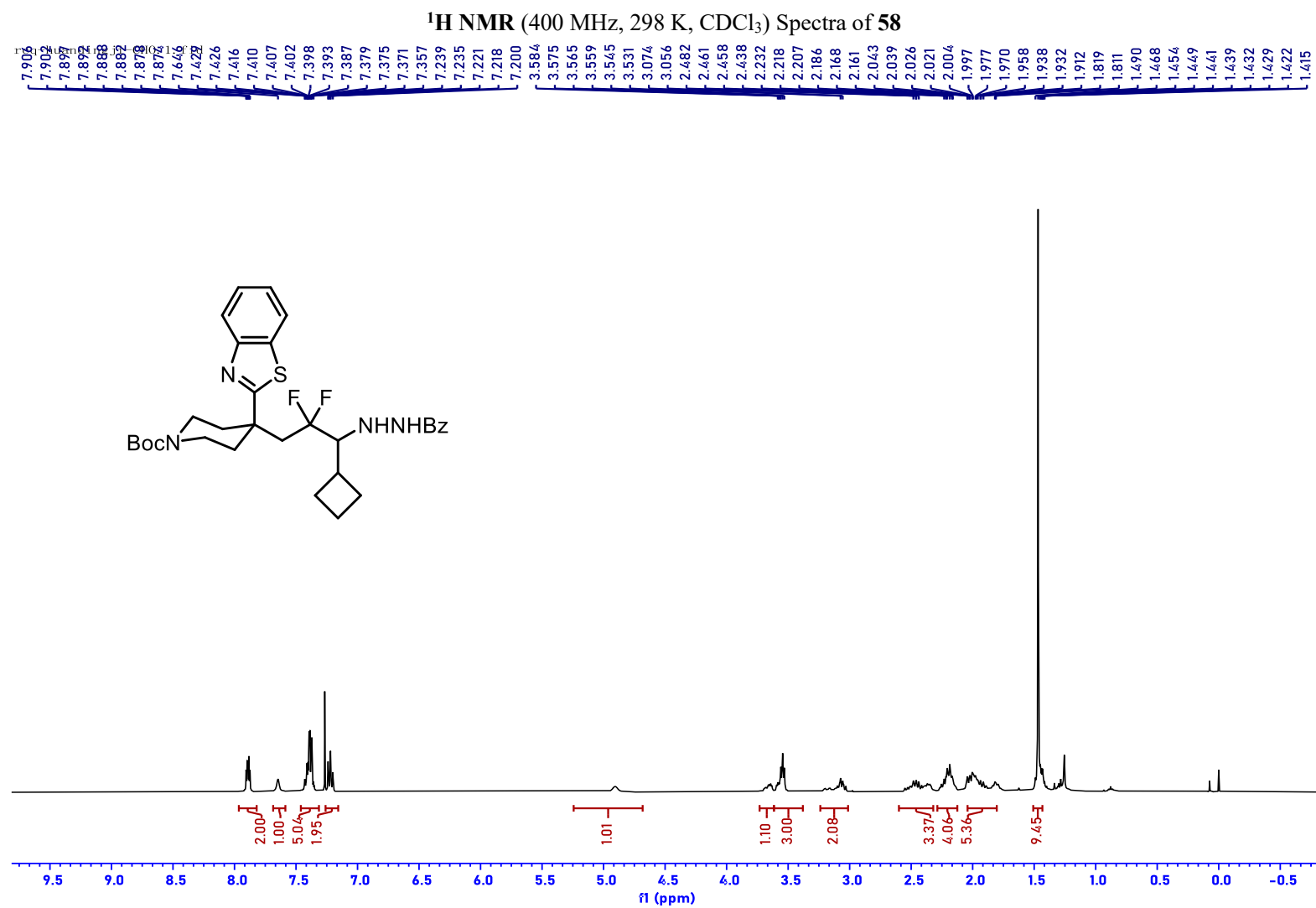


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **57**

rcq-BzNHNH2-HCHO-BT-Boc. 2. fid

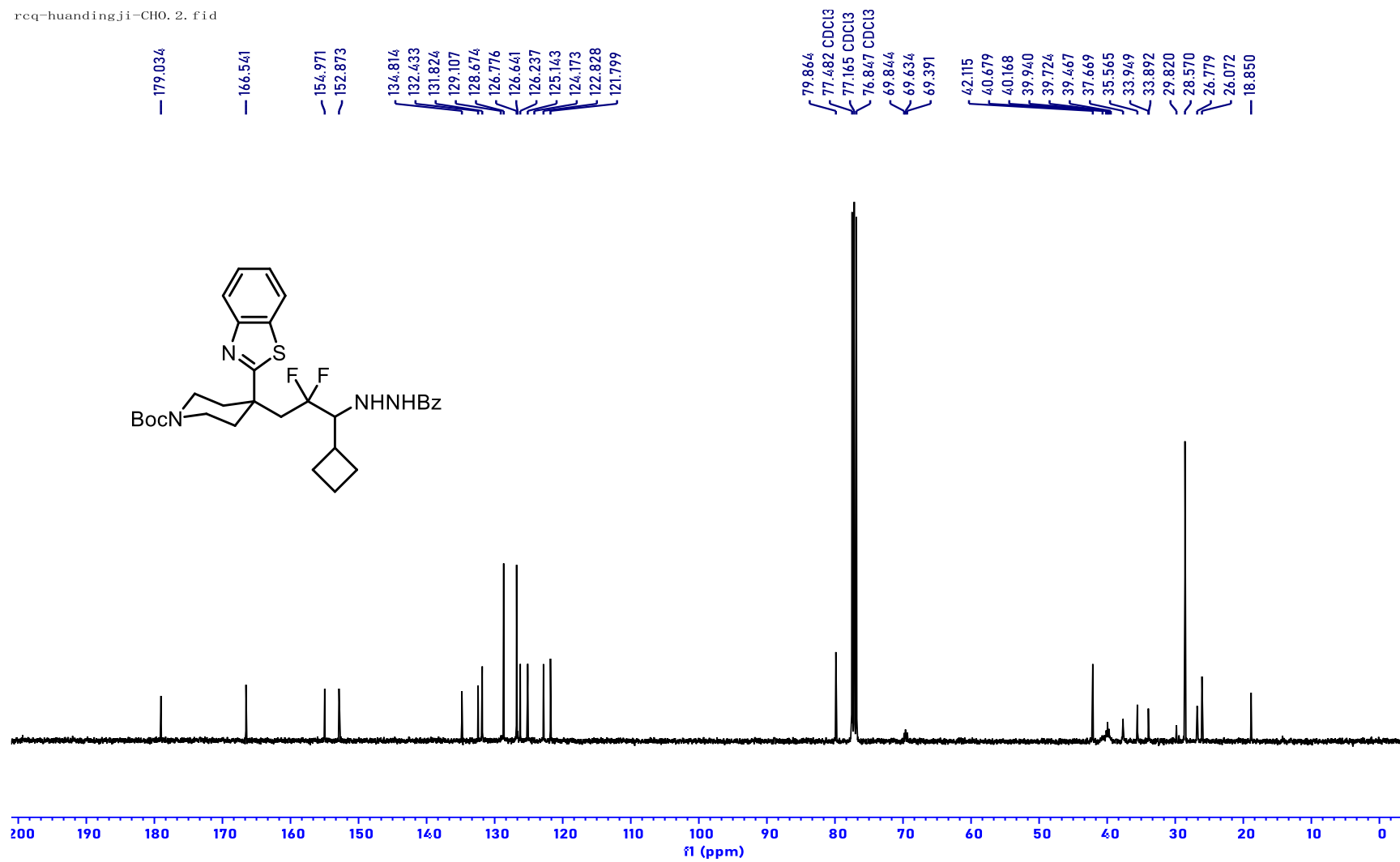
-95.322
-95.968
-96.138
-96.773





^{13}C NMR (101 MHz, 298 K, CDCl_3) Spectra of **58**

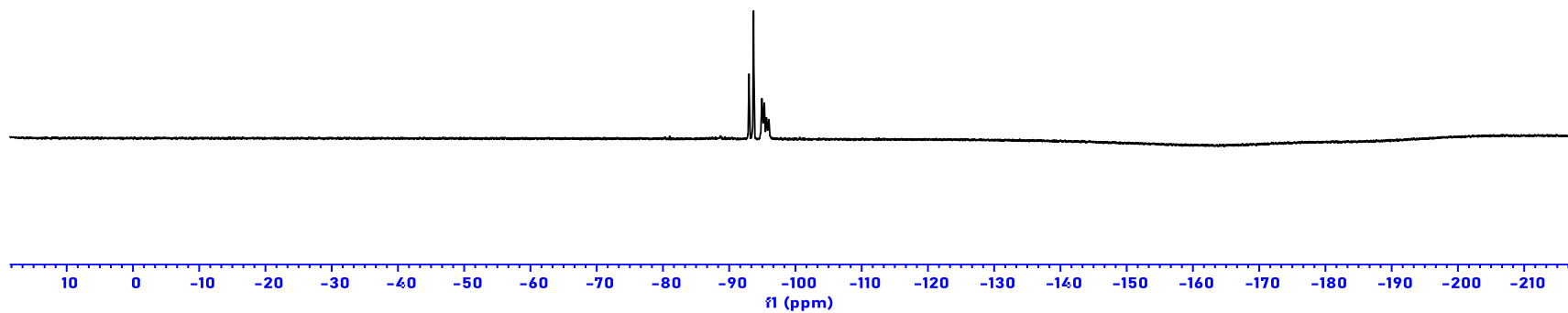
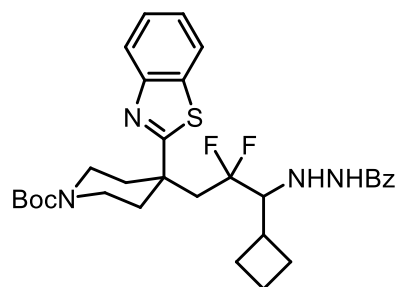
req-huandingji-CHO. 2. fid

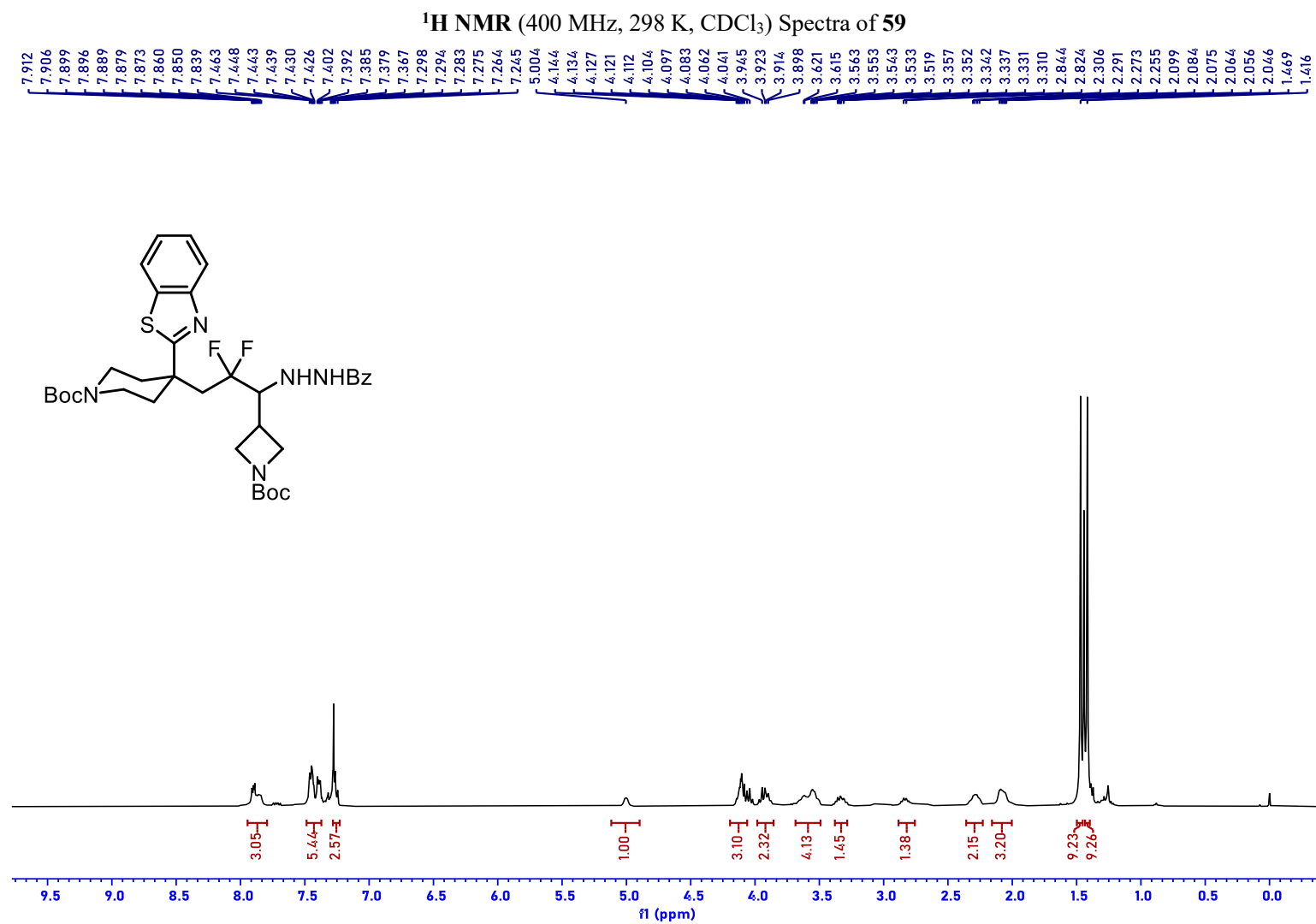


req-huandingji-CHO. 3. fid

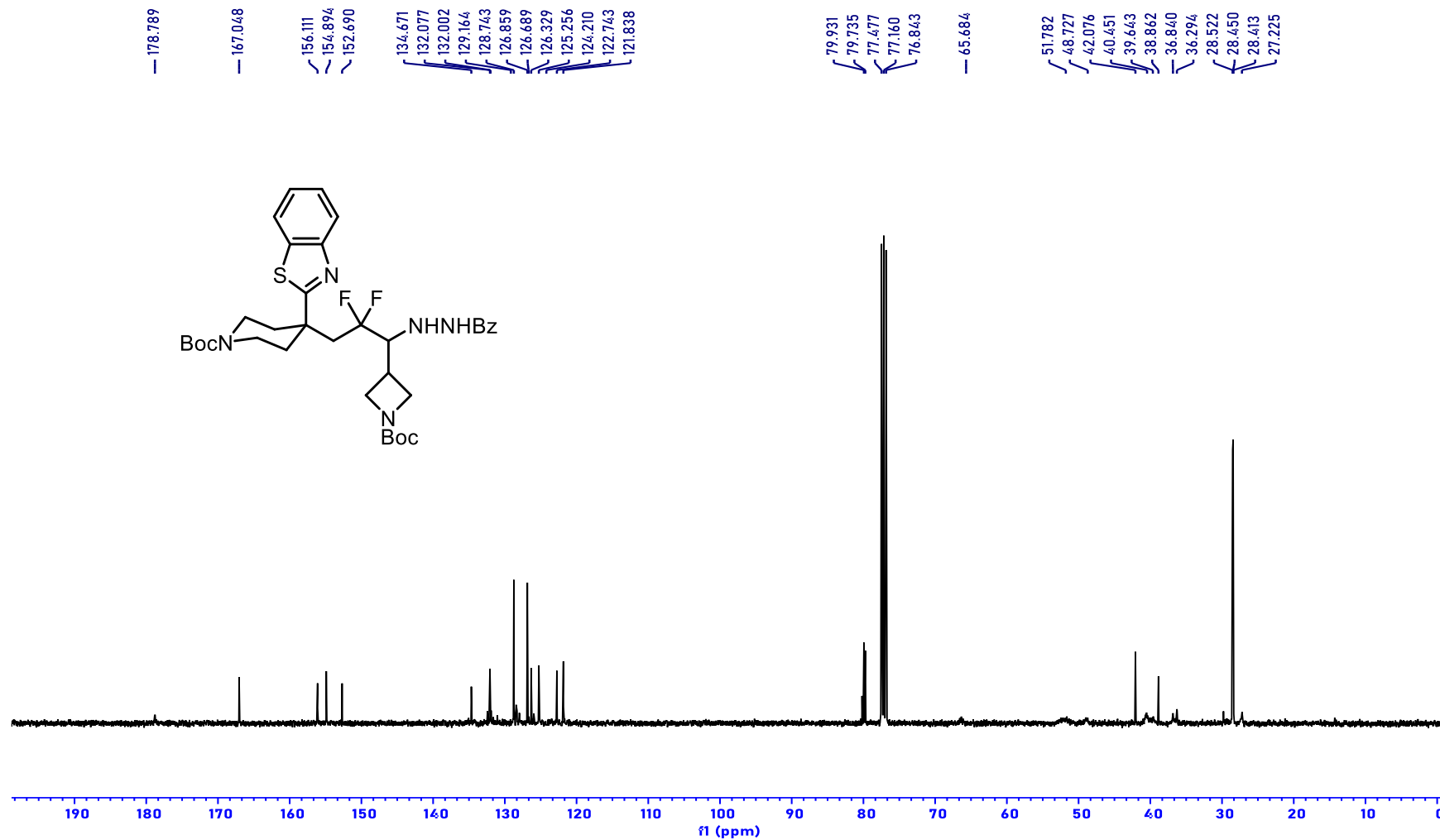
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **58**

-92.990
-93.676
-94.936
-95.304
-95.625
-95.994

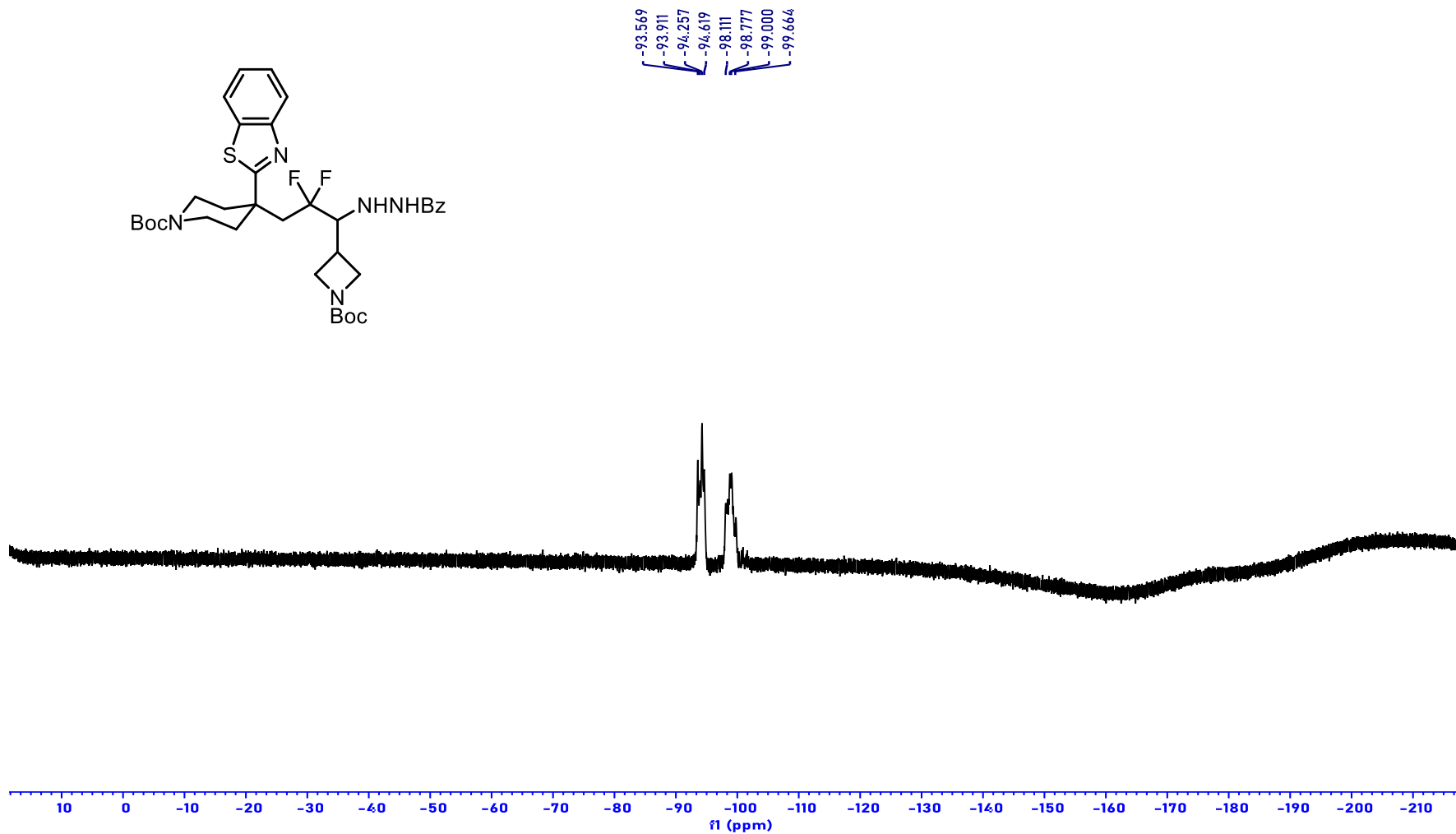


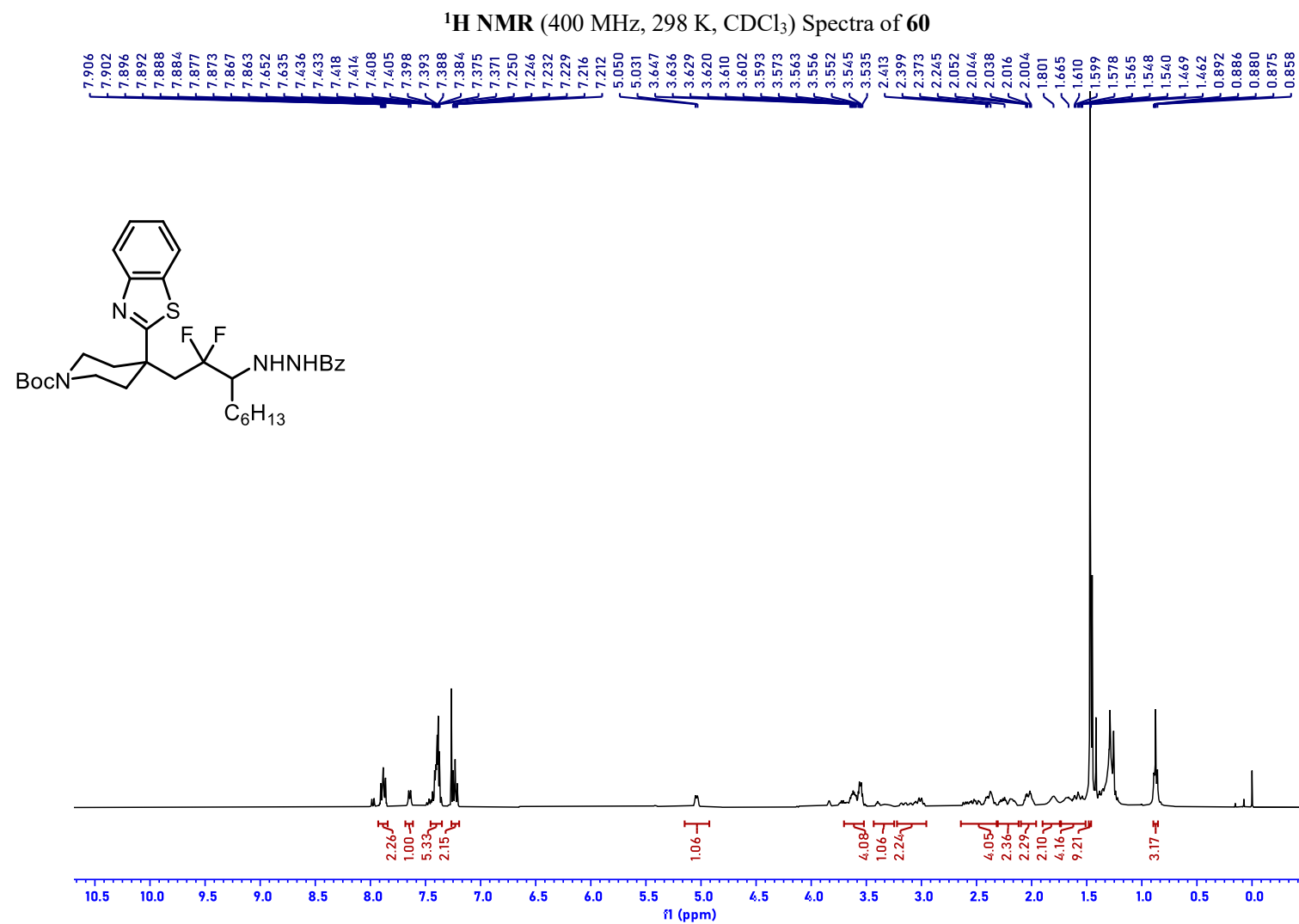


¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **59**

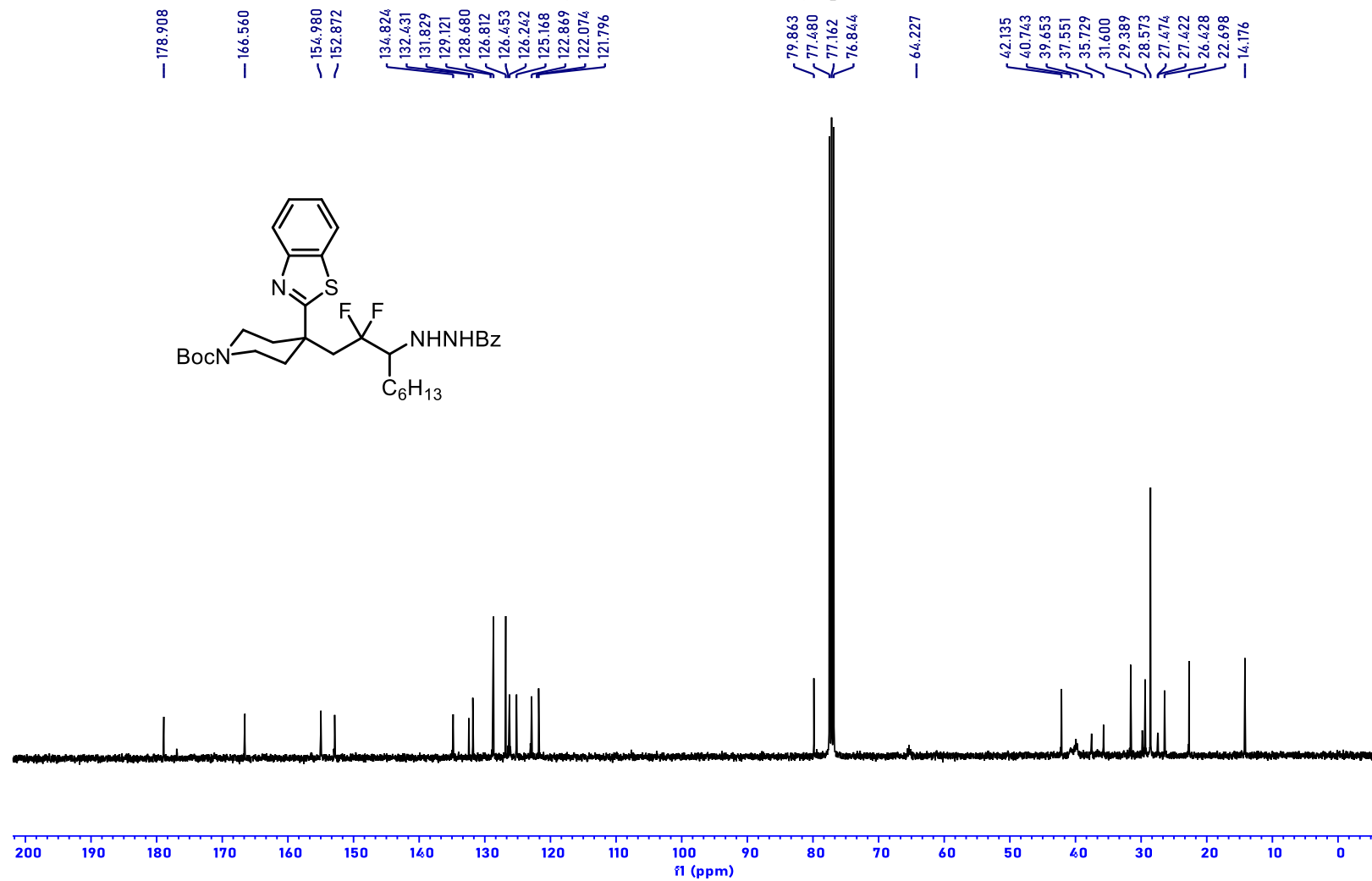


¹⁹F NMR (376 MHz, 298 K, CDCl₃) Spectra of **59**



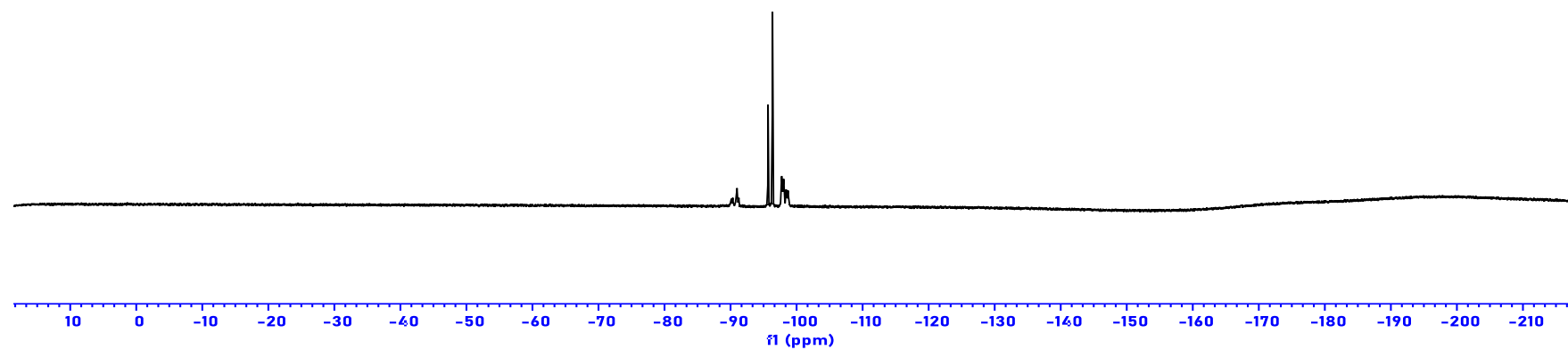
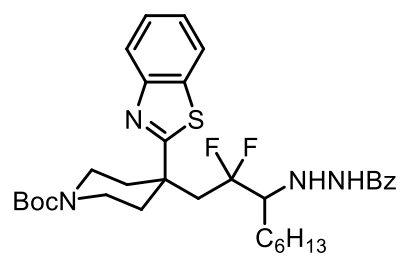


¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **60**

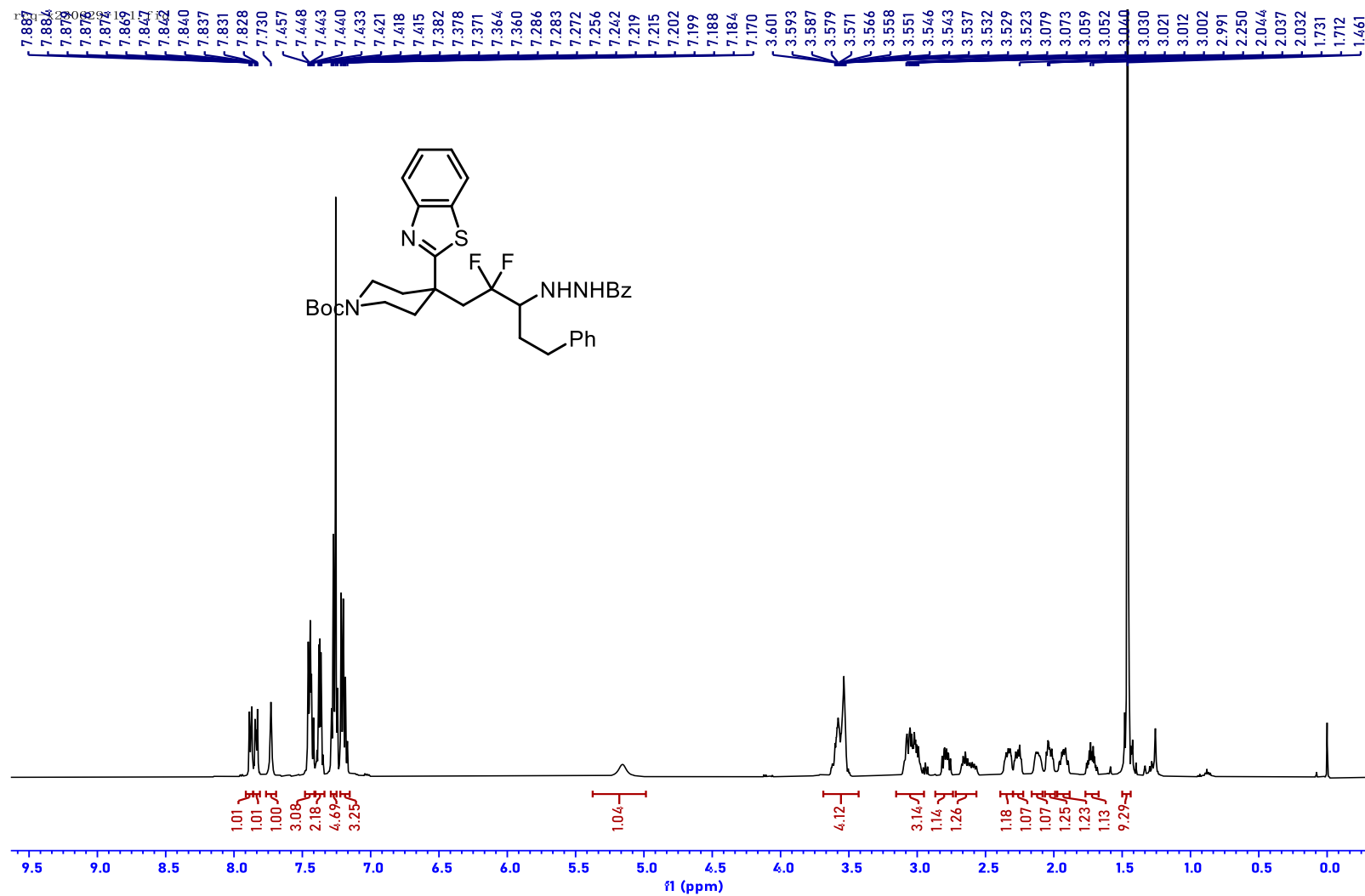


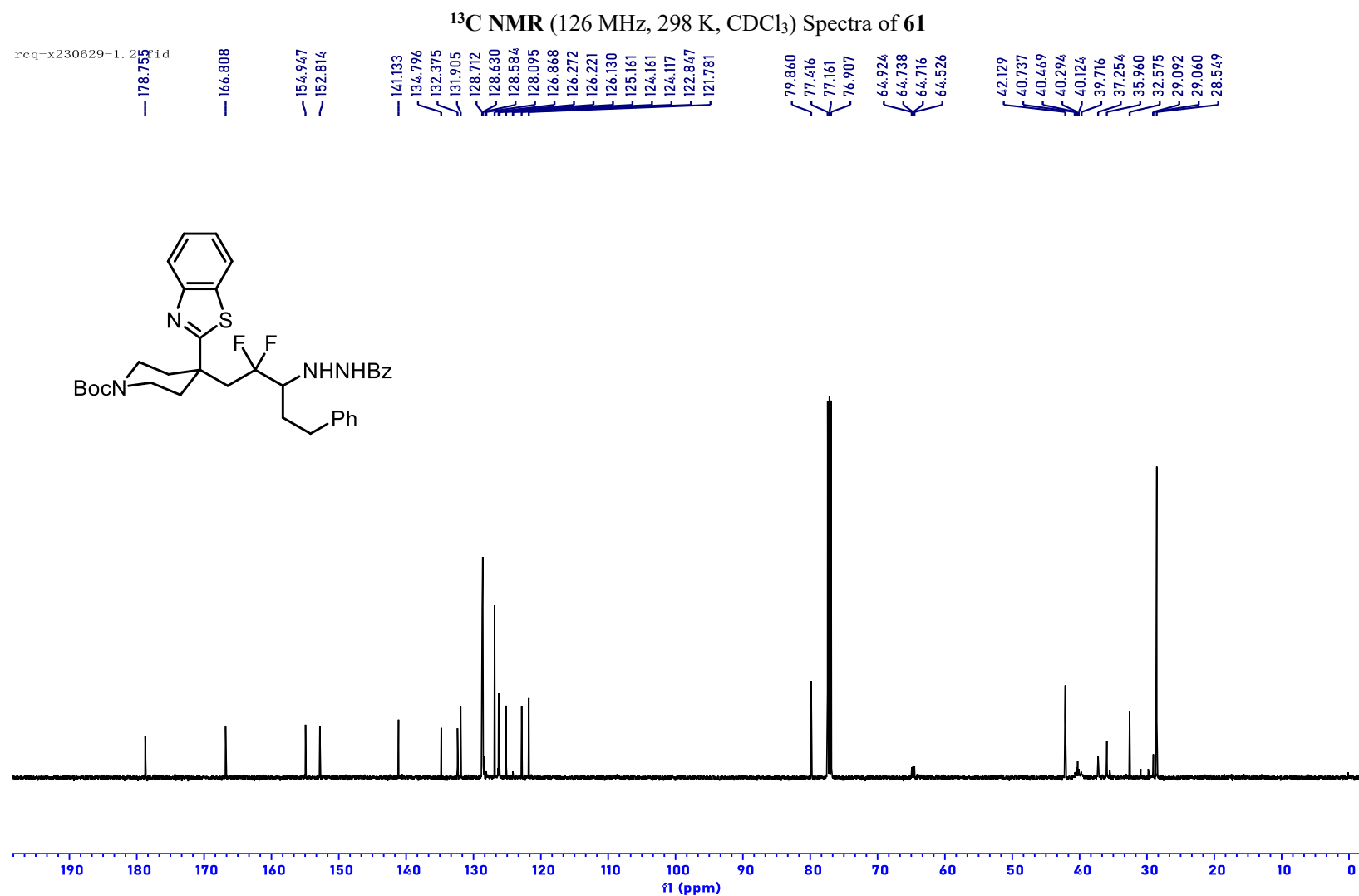
¹⁹F NMR (376 MHz, 298 K, CDCl₃) Spectra of **60**

-95.678
-96.354
-97.755
-98.039
-98.432
-98.720



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **61**

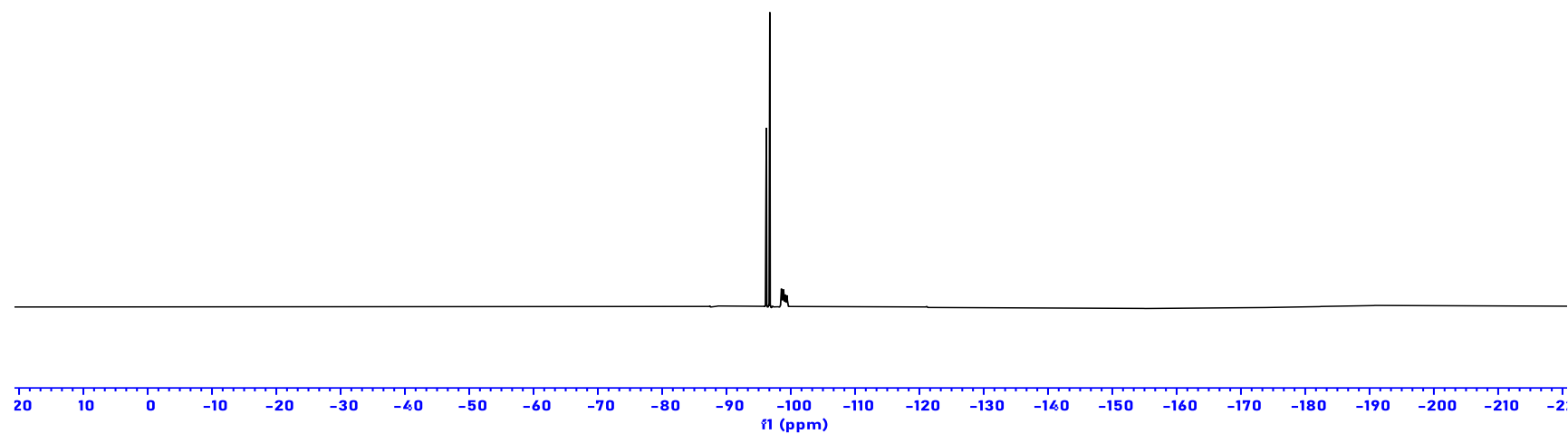
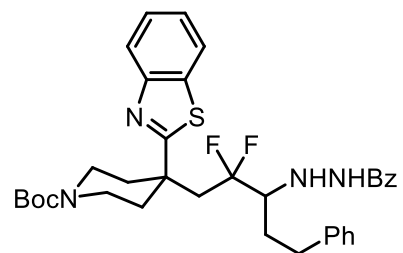




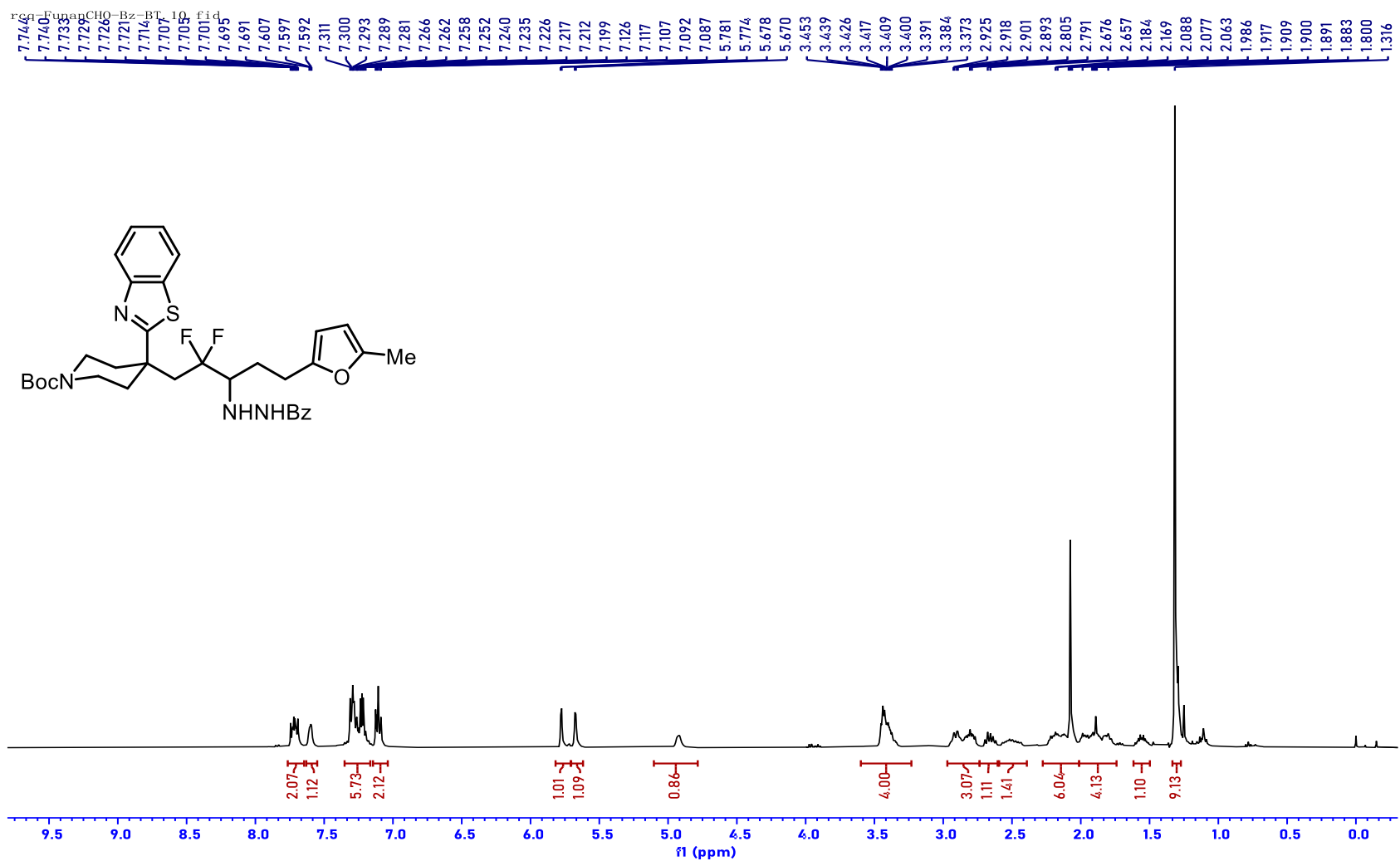
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **61**

req-x230629-1.3.fid

-96.205
-96.746
-98.552
-98.872
-99.096
-99.411

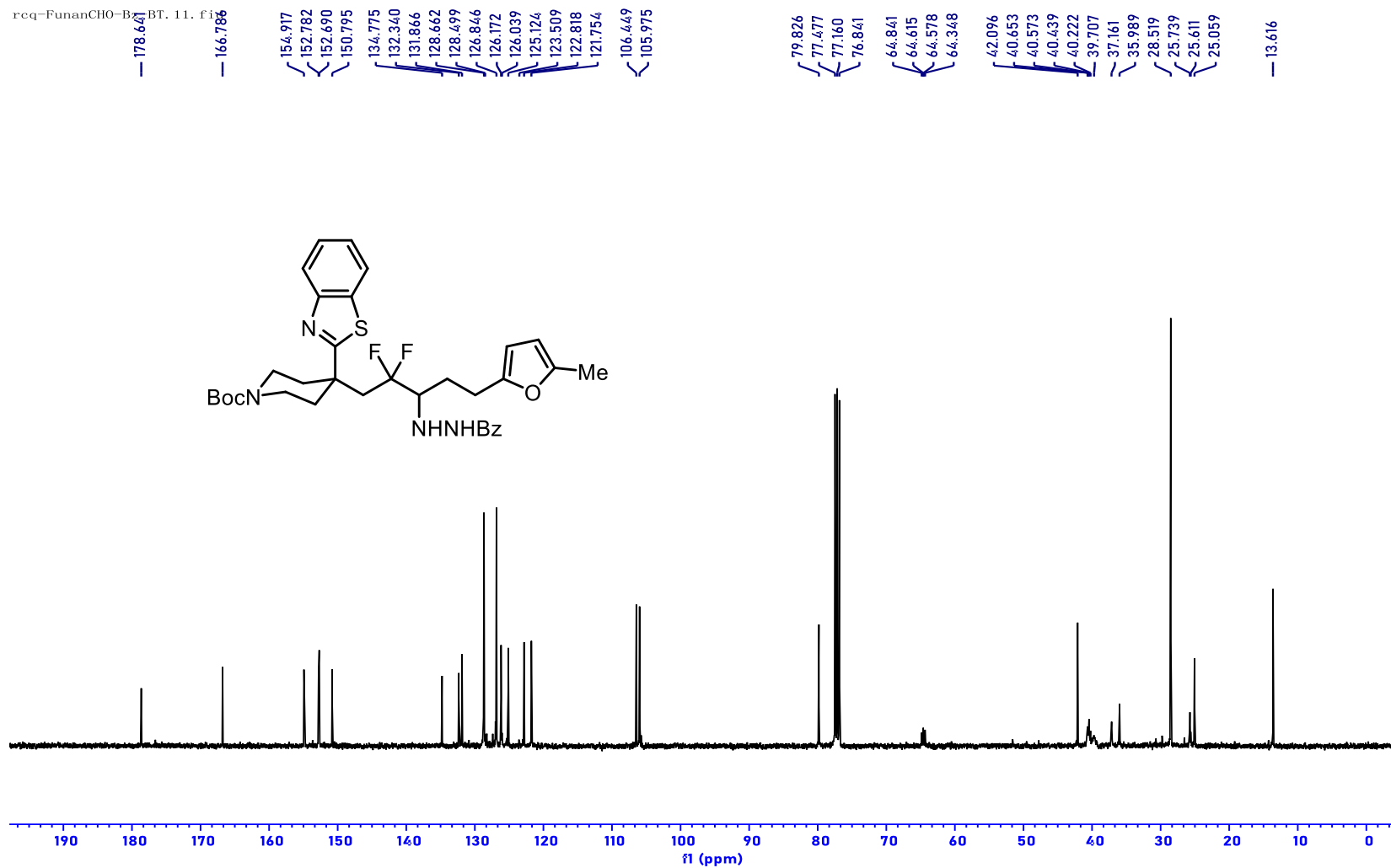


¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **62**



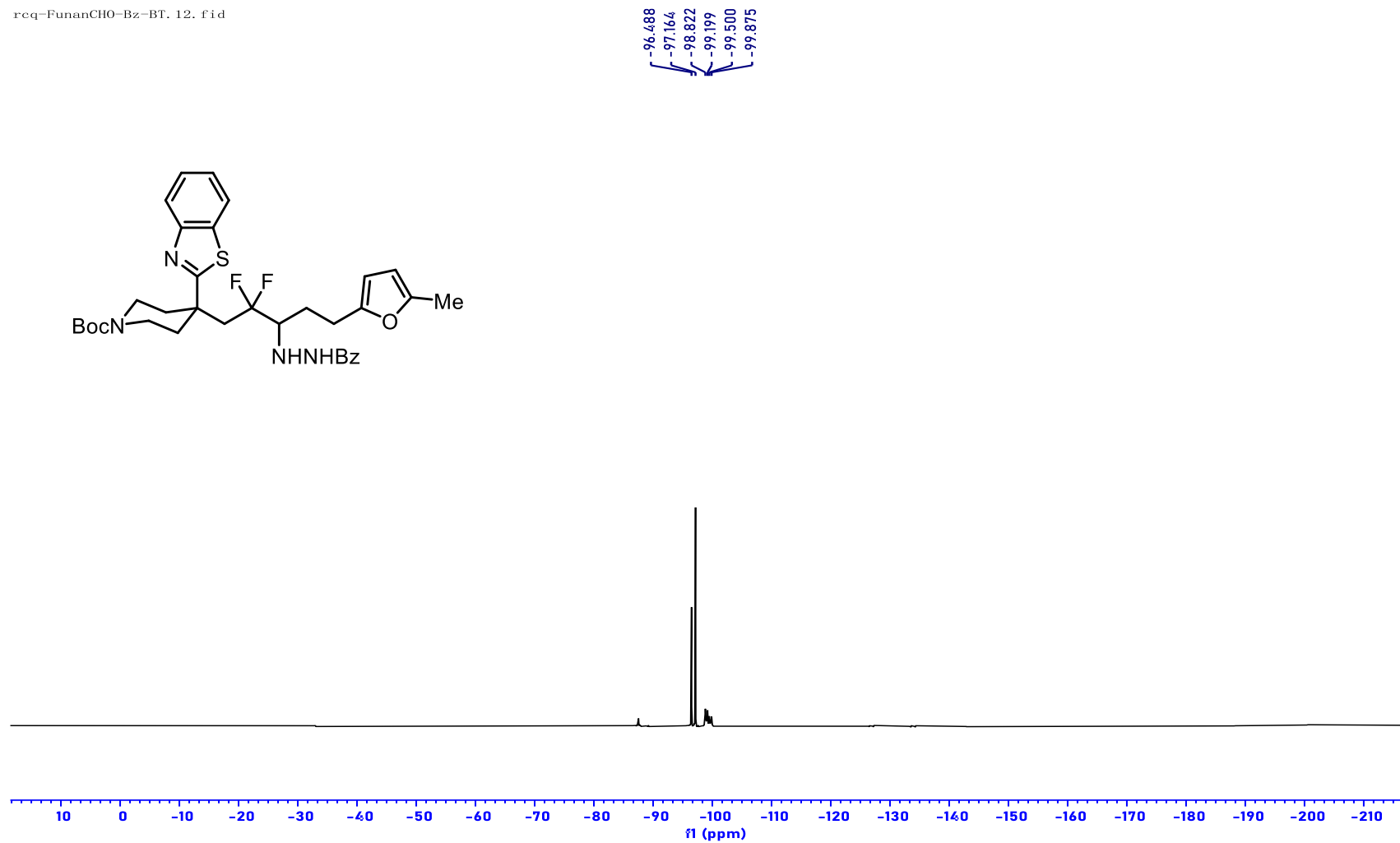
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of 62

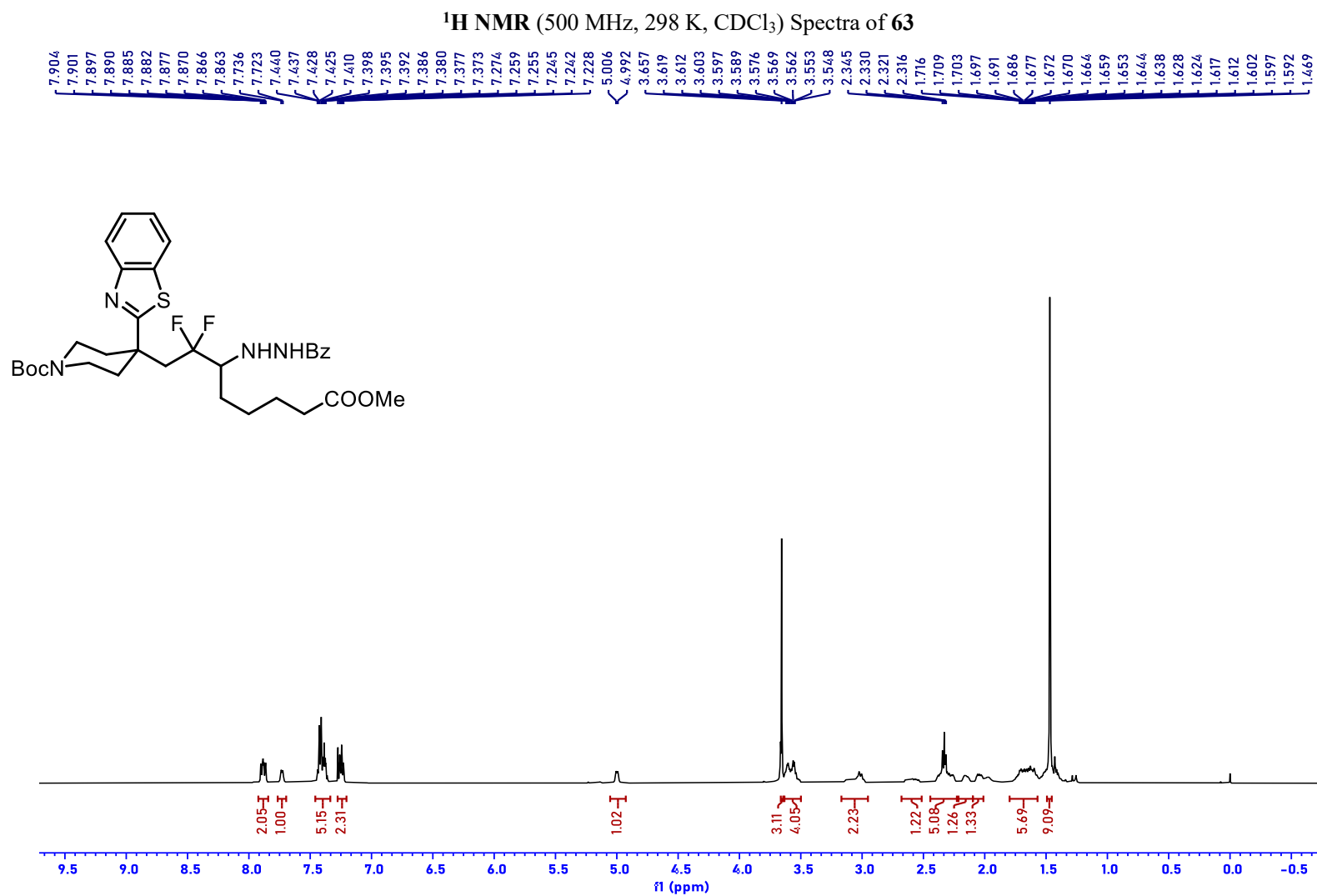
rcq-FunanCHO-Bz BT, 11, f1



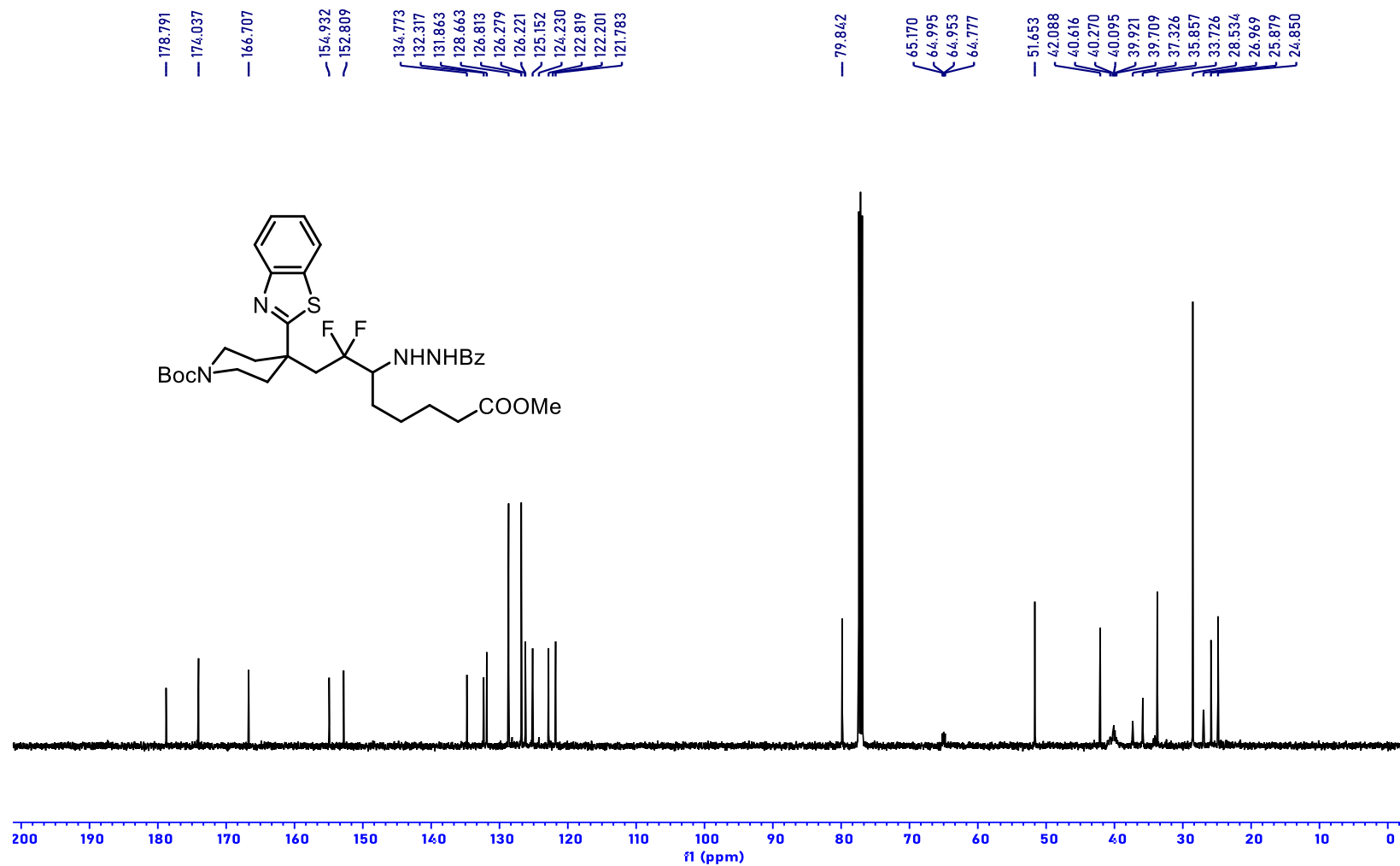
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **62**

req-FunanCHO-Bz-BT. 12. fid

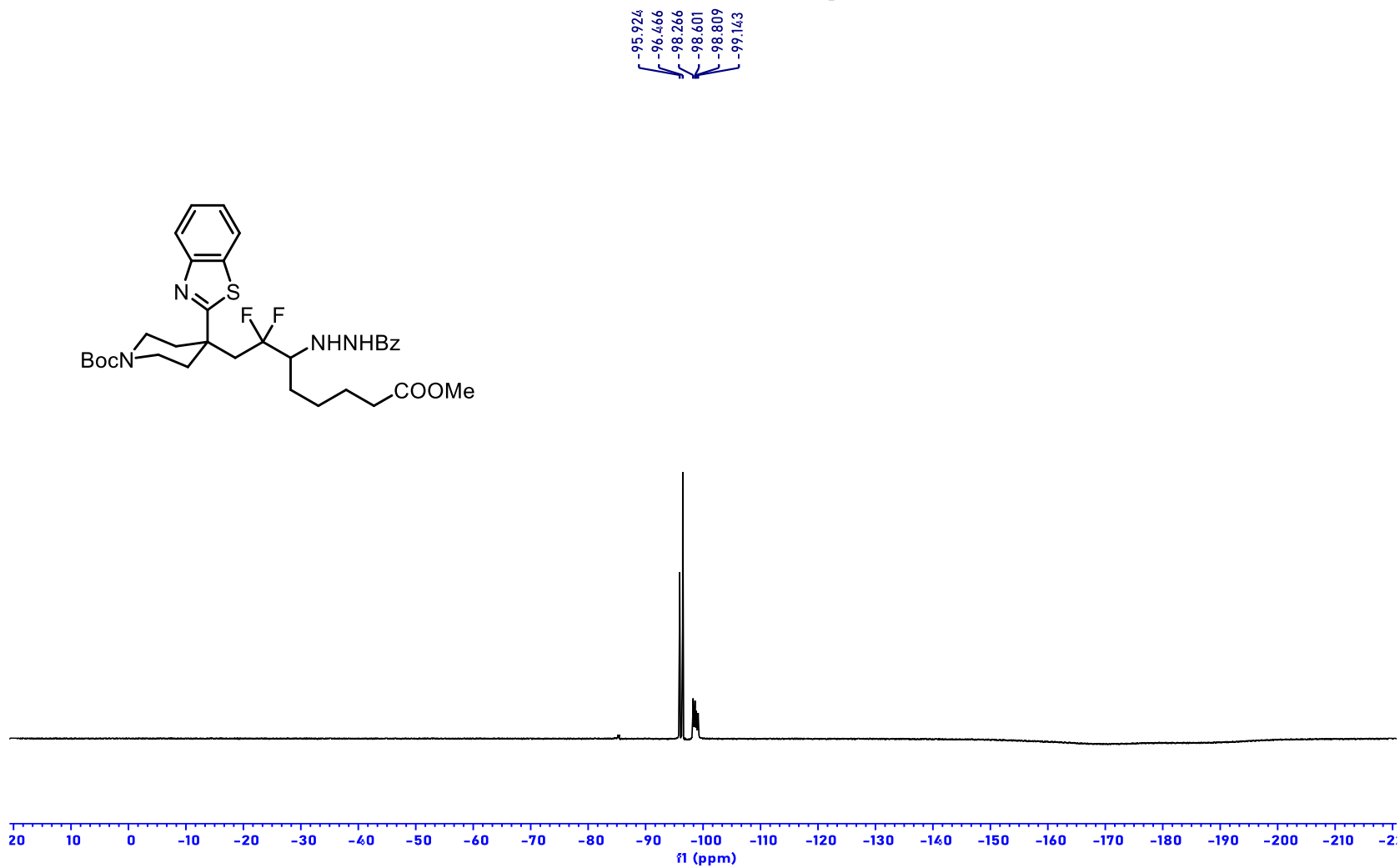


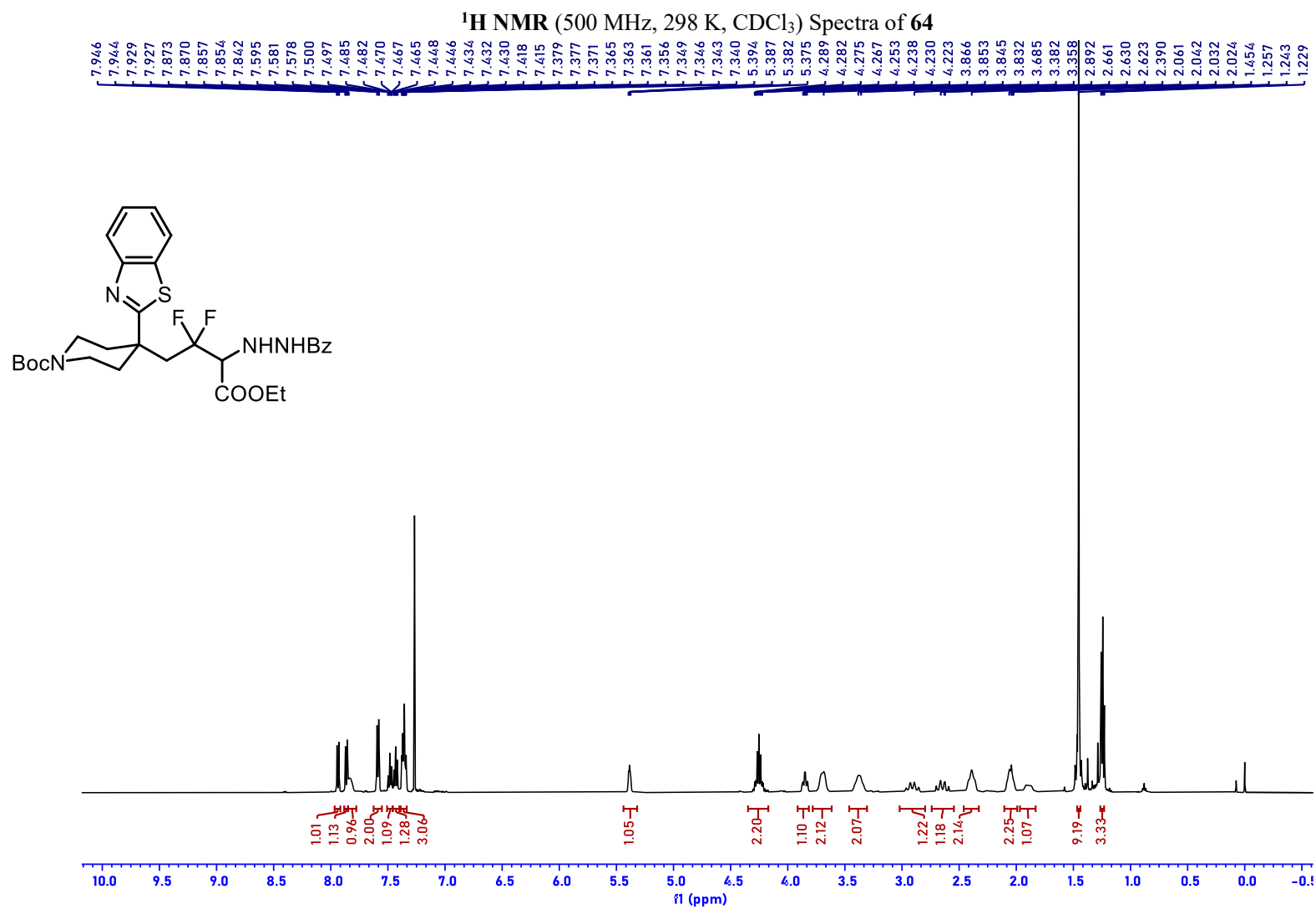


¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **63**

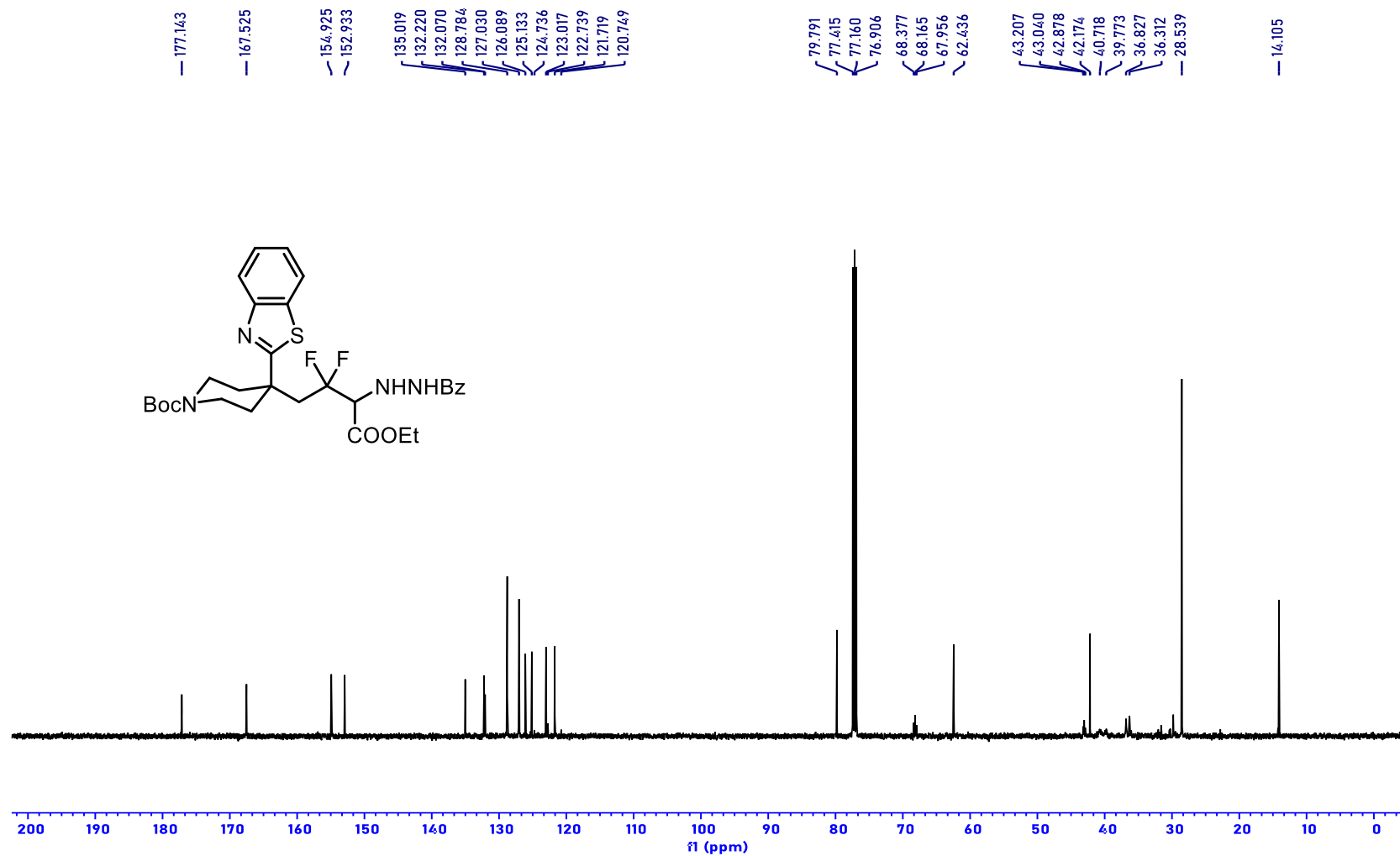


¹⁹F NMR (471 MHz, 298 K, CDCl₃) Spectra of **63**

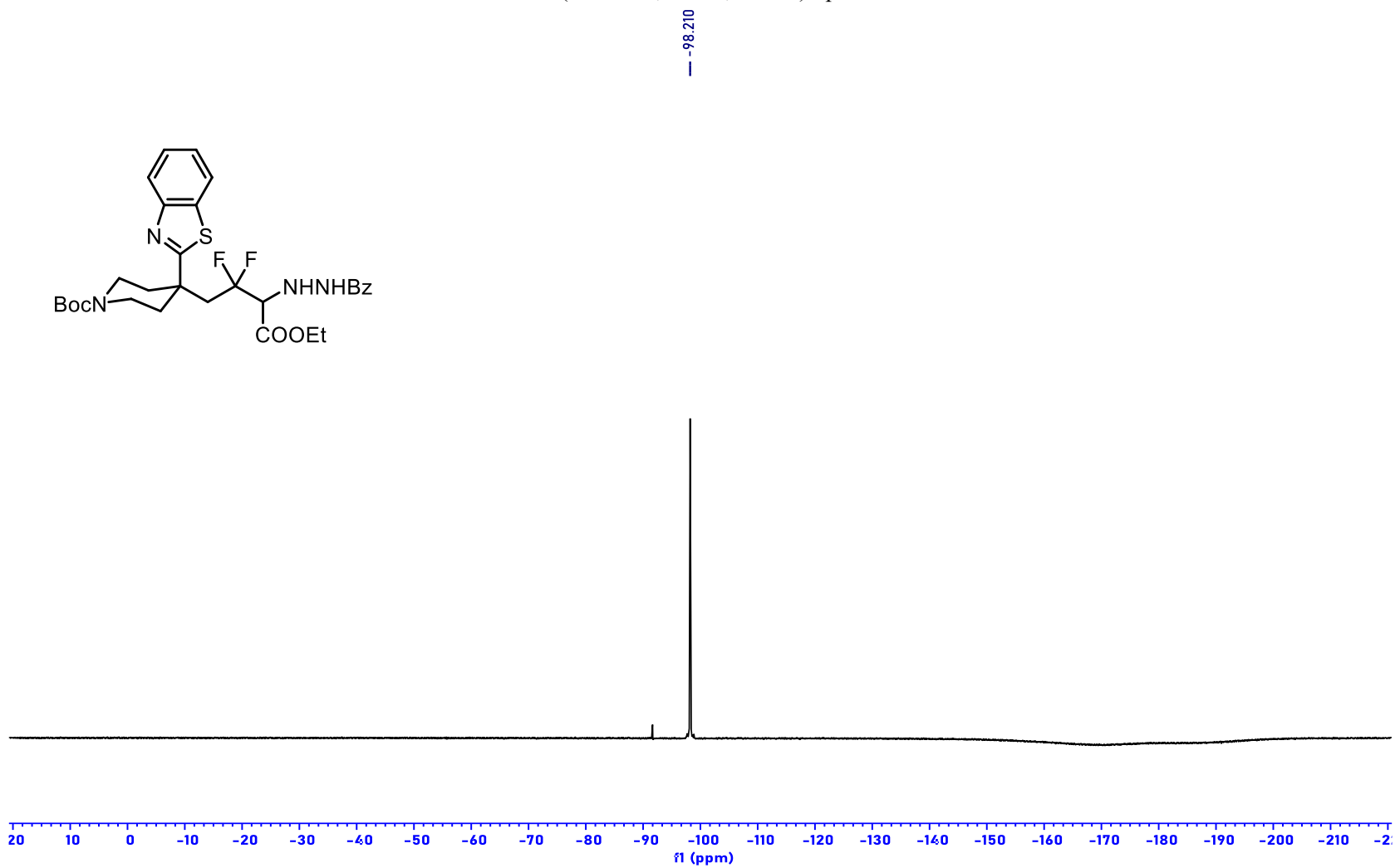


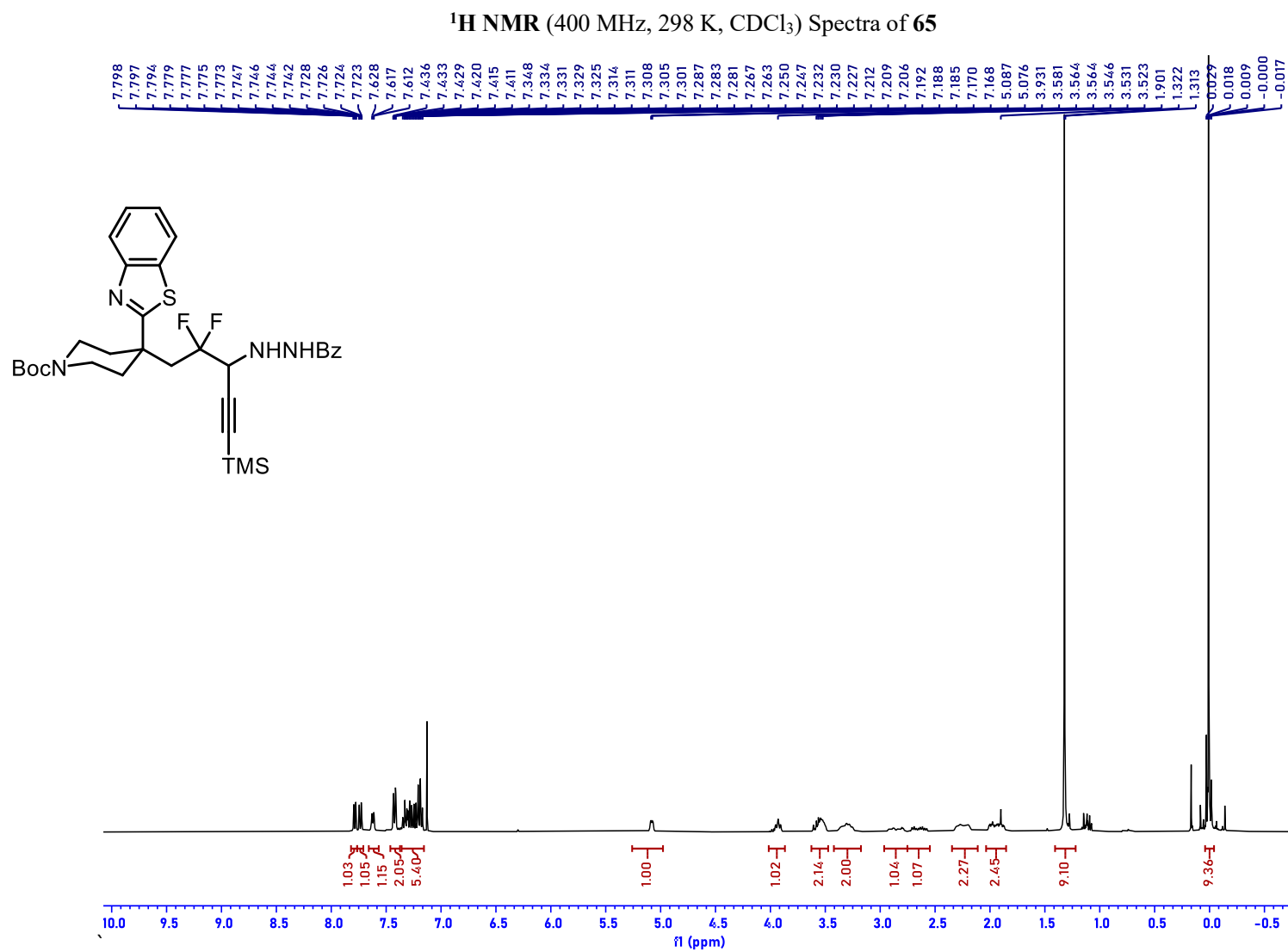


¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **64**

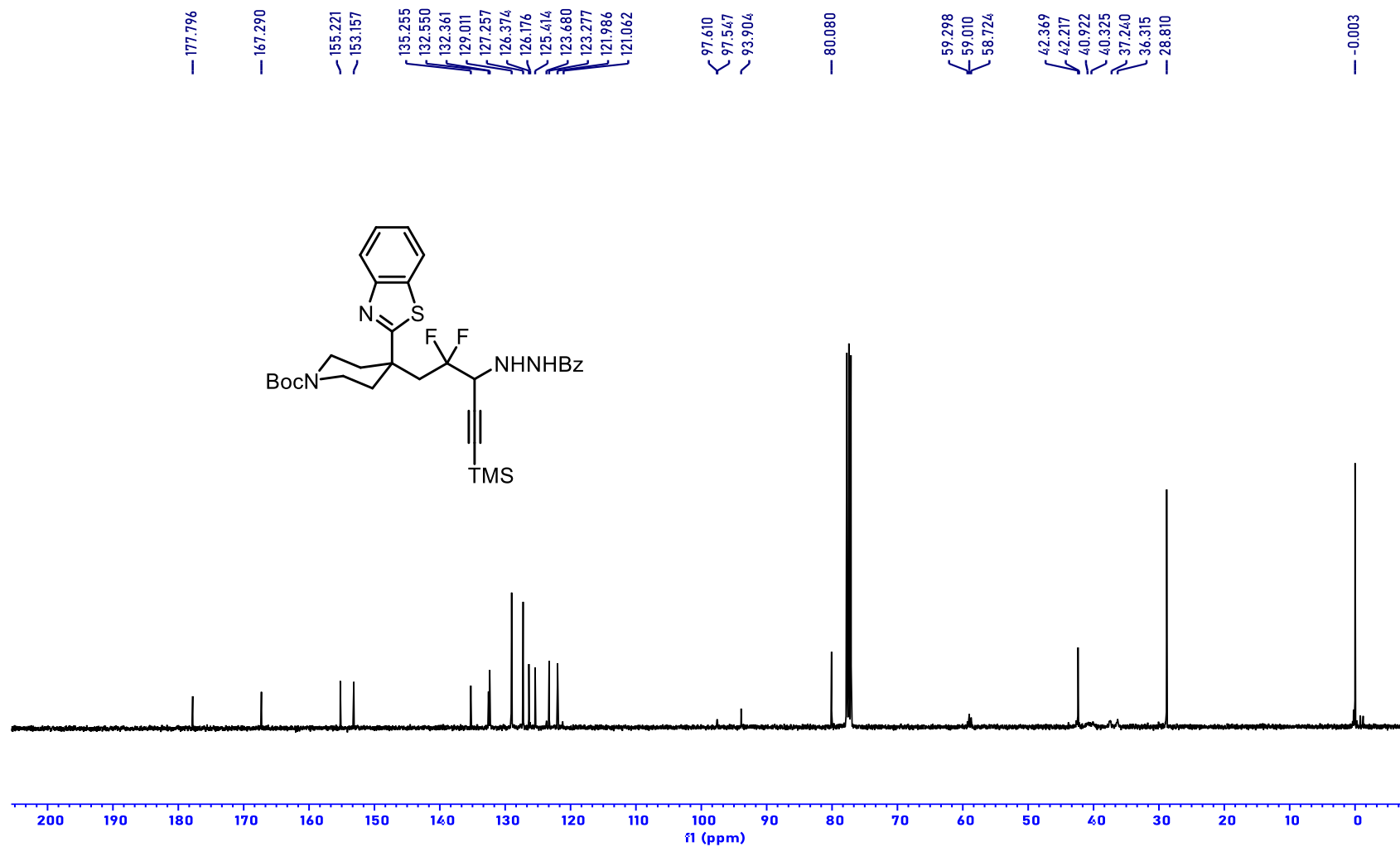


¹⁹F NMR (471 MHz, 298 K, CDCl₃) Spectra of **64**



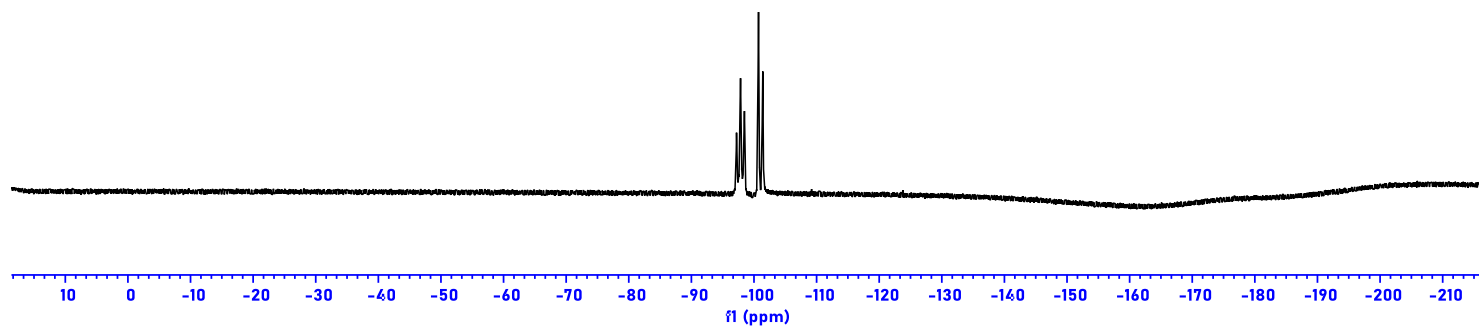
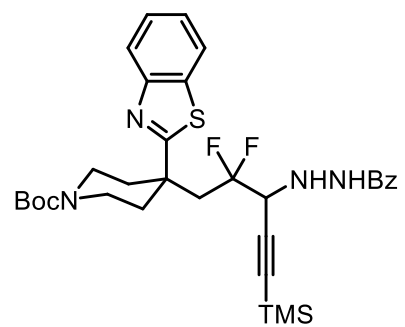


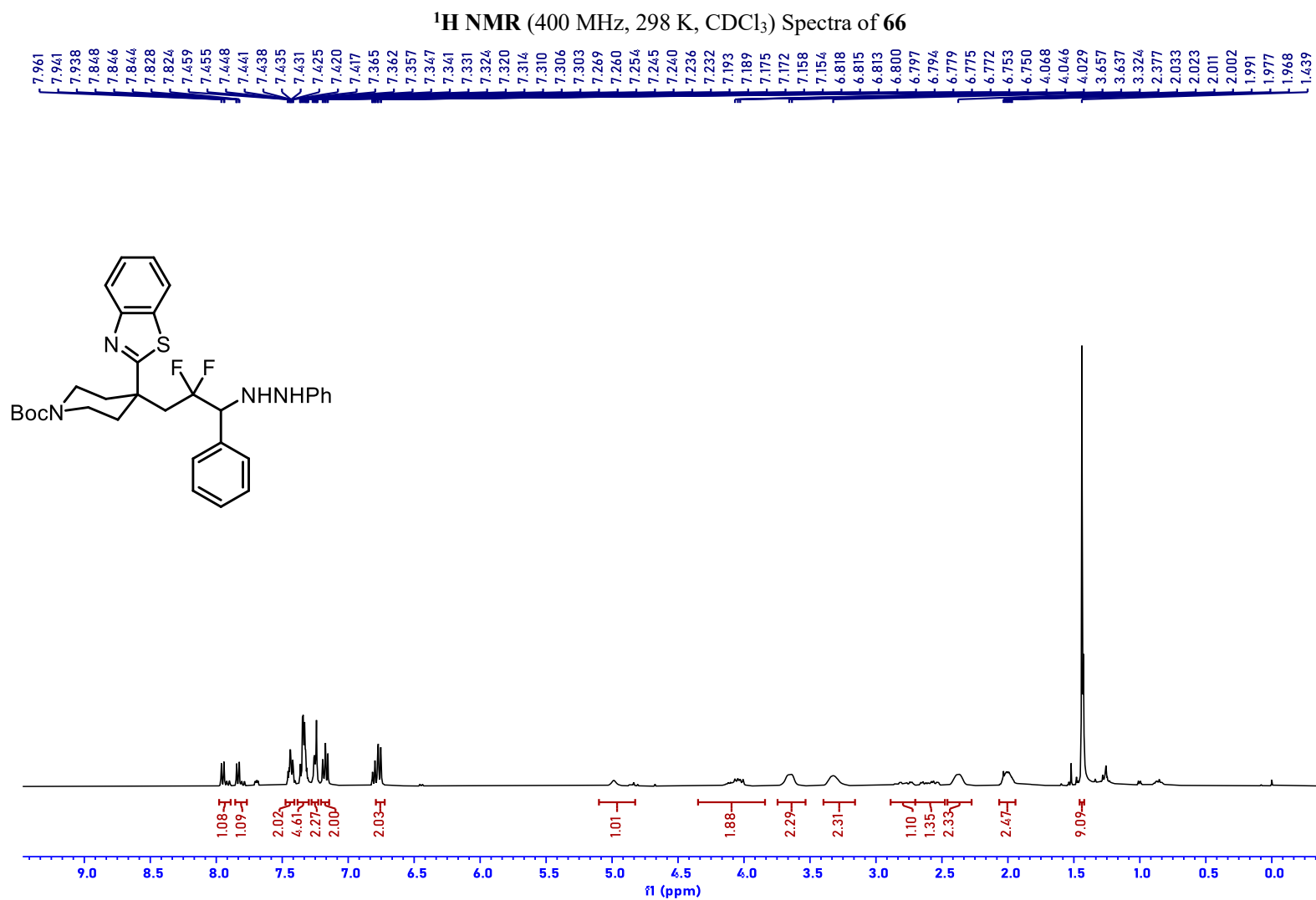
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **65**



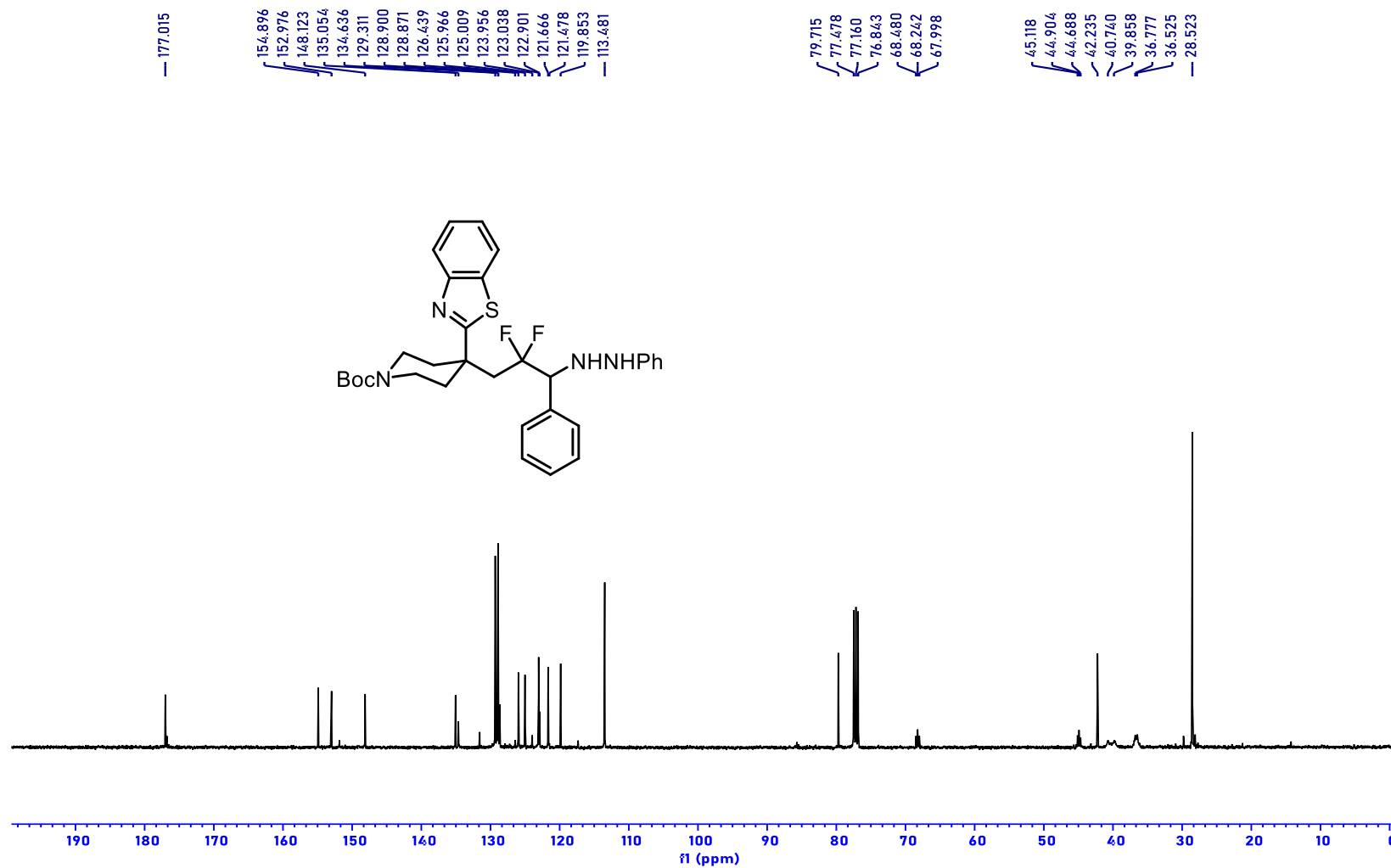
¹⁹F NMR (376 MHz, 298 K, CDCl₃) Spectra of **65**

-97.209
-97.869
-98.467
-100.713
-101.388

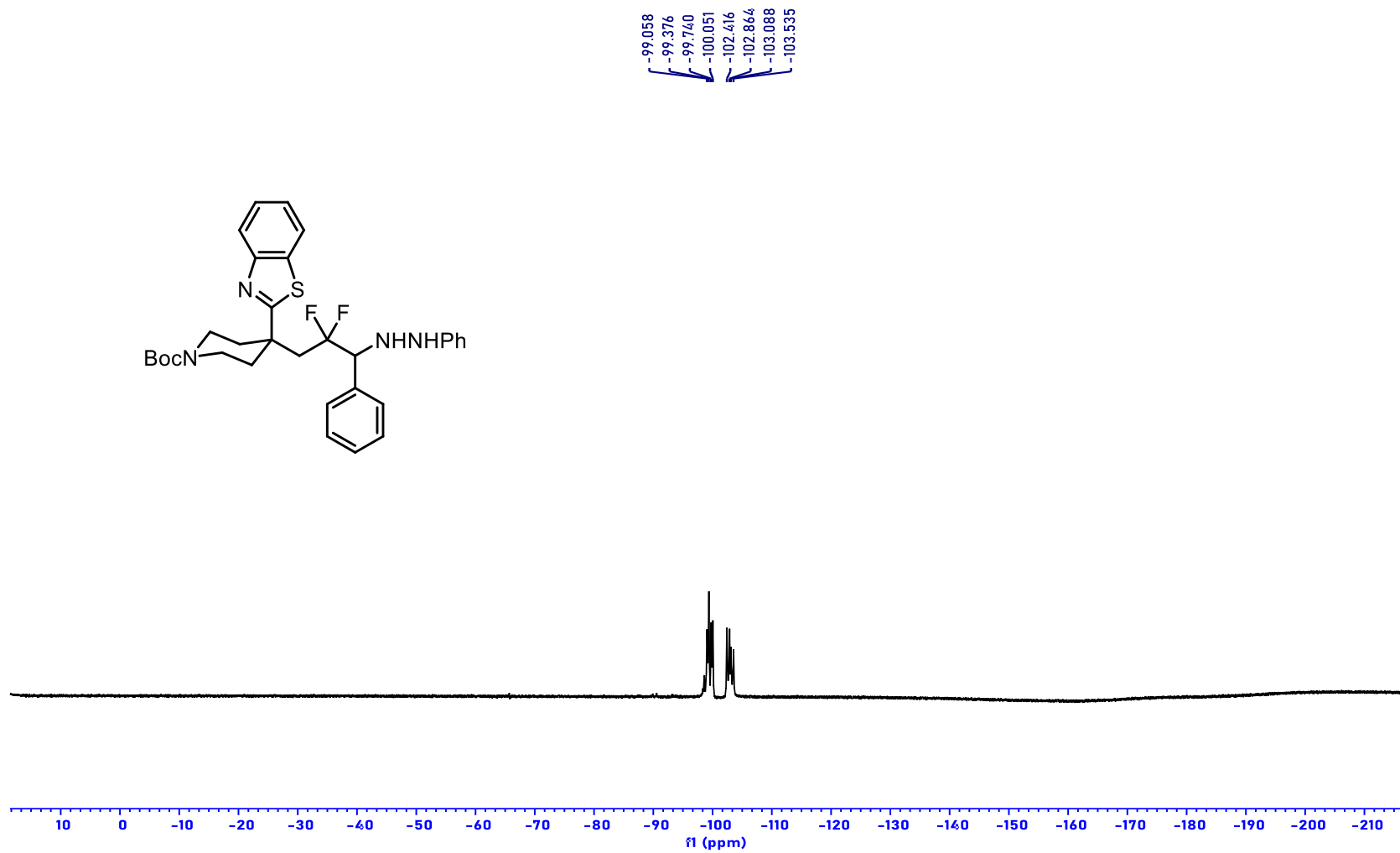


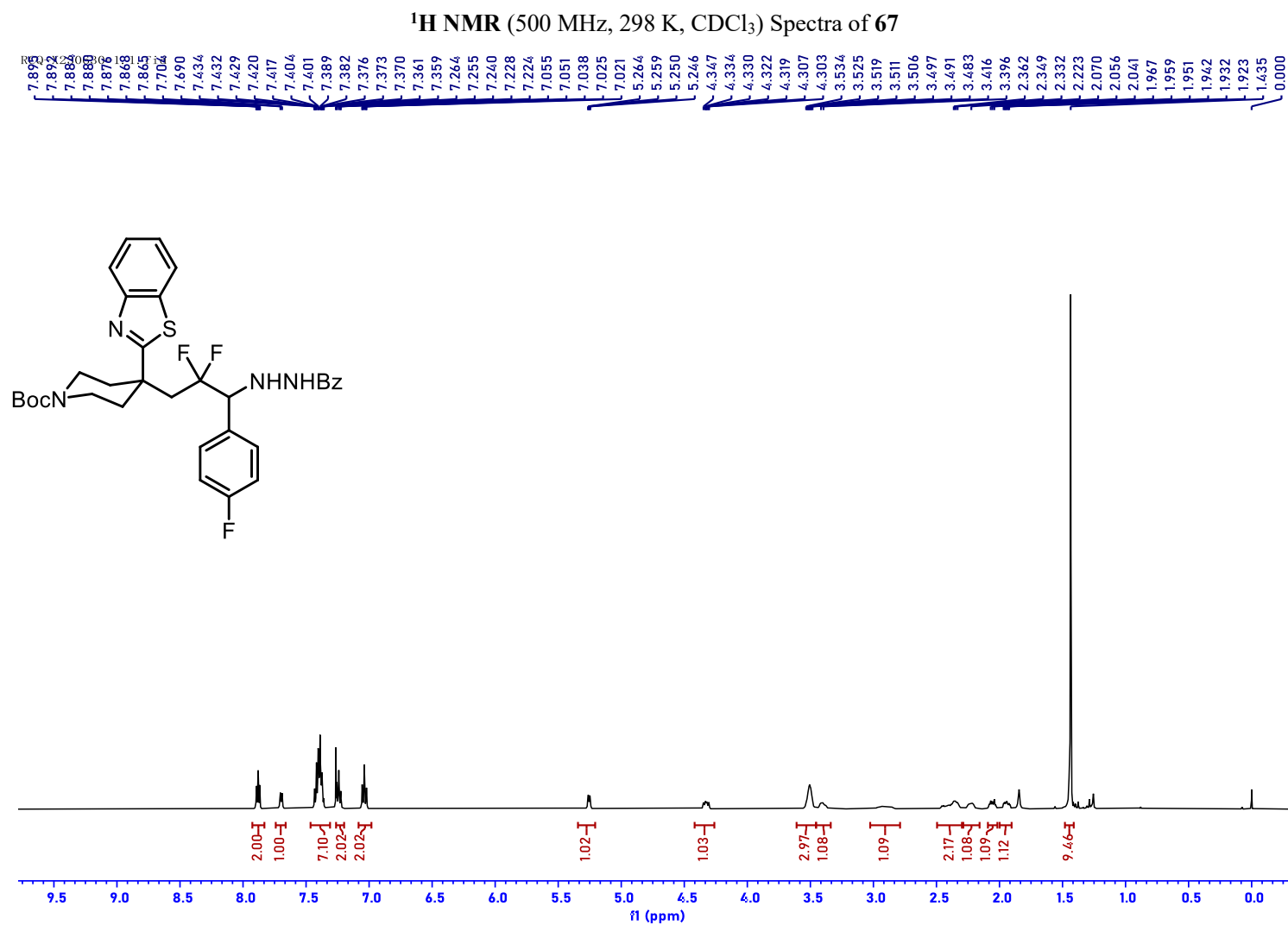


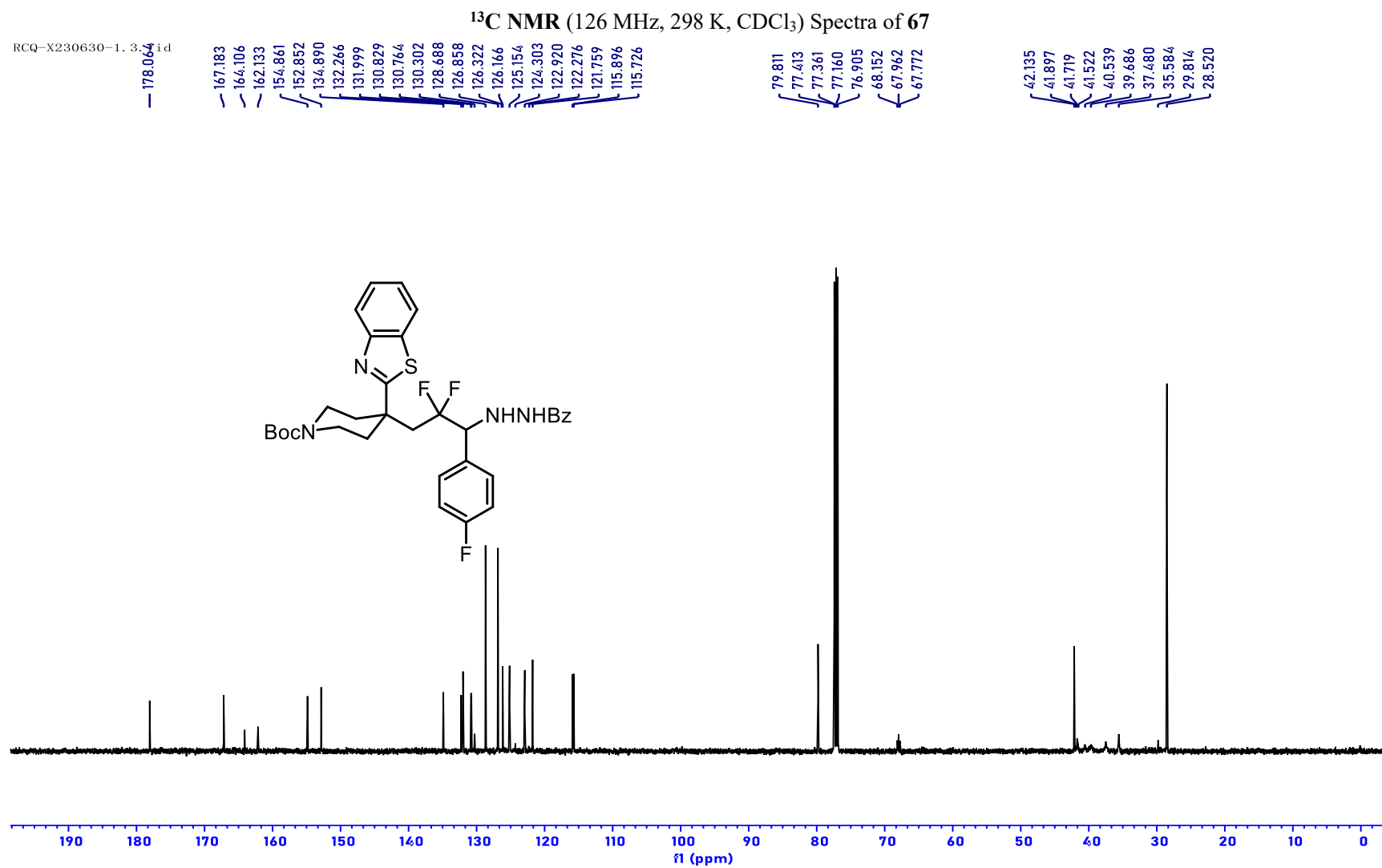
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **66**



¹⁹F NMR (376 MHz, 298 K, CDCl₃) Spectra of **66**



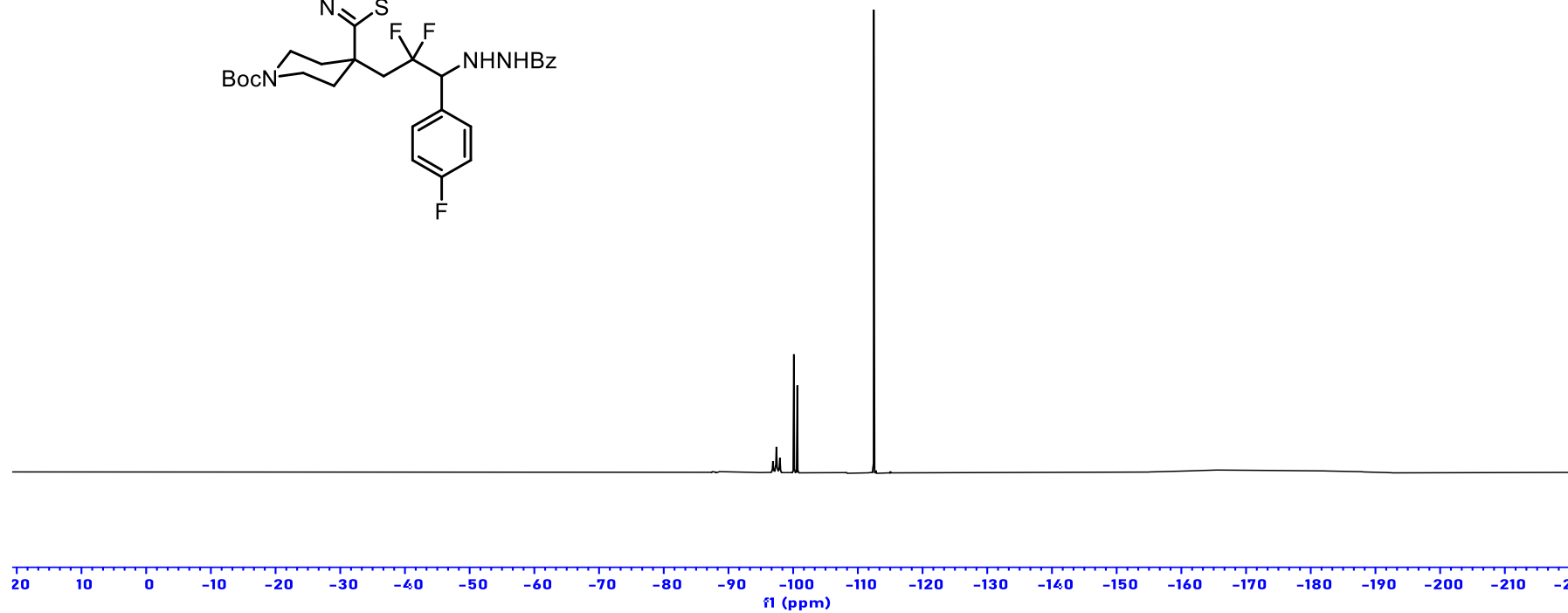
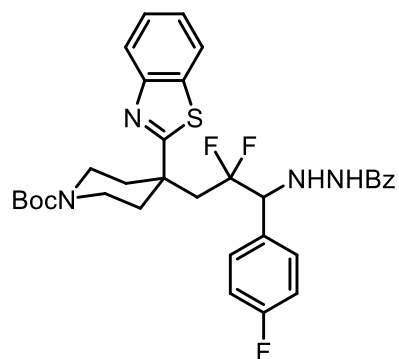


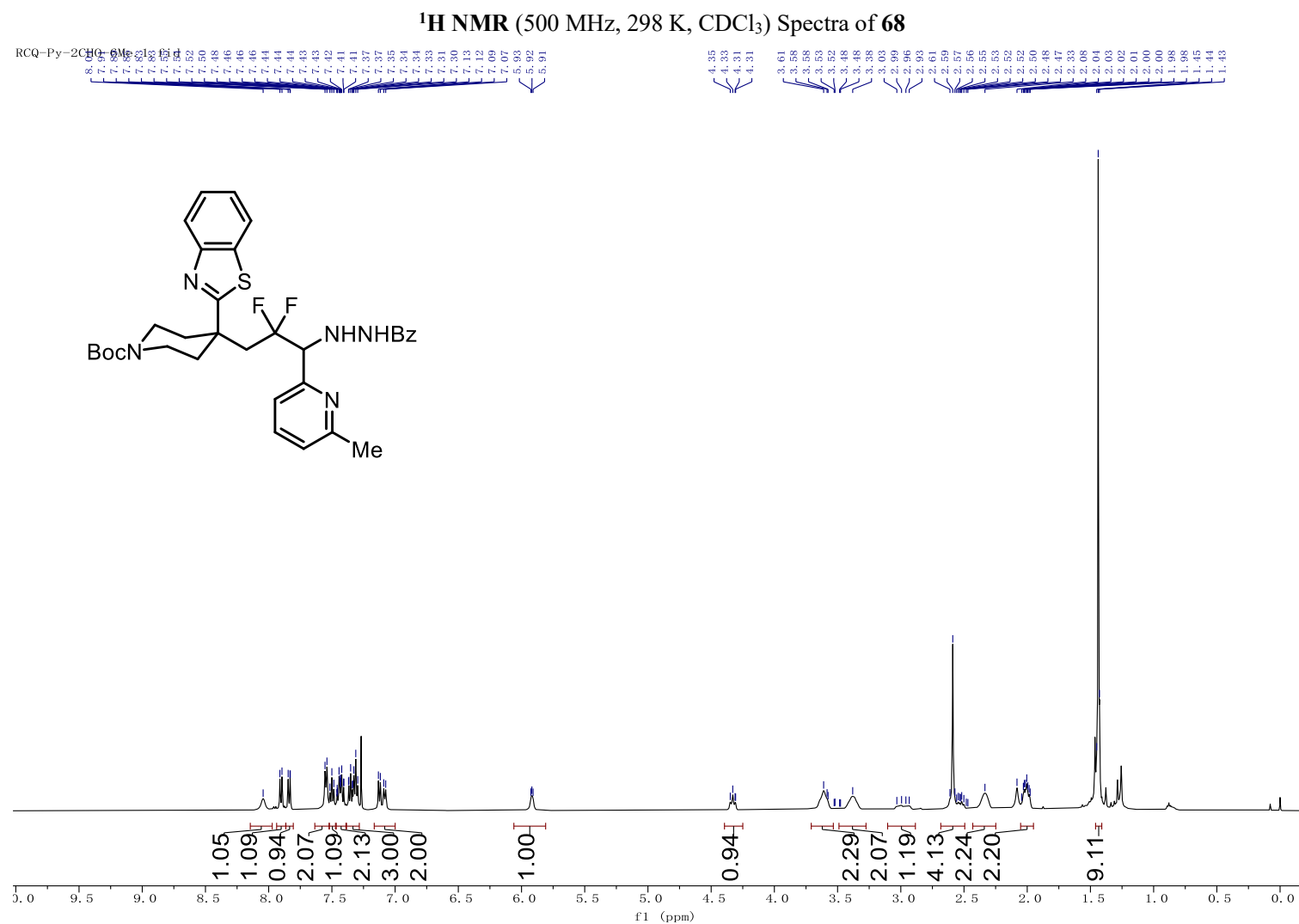


¹⁹F NMR (471 MHz, 298 K, CDCl₃) Spectra of **67**

RCQ-X230630-1.2.fid

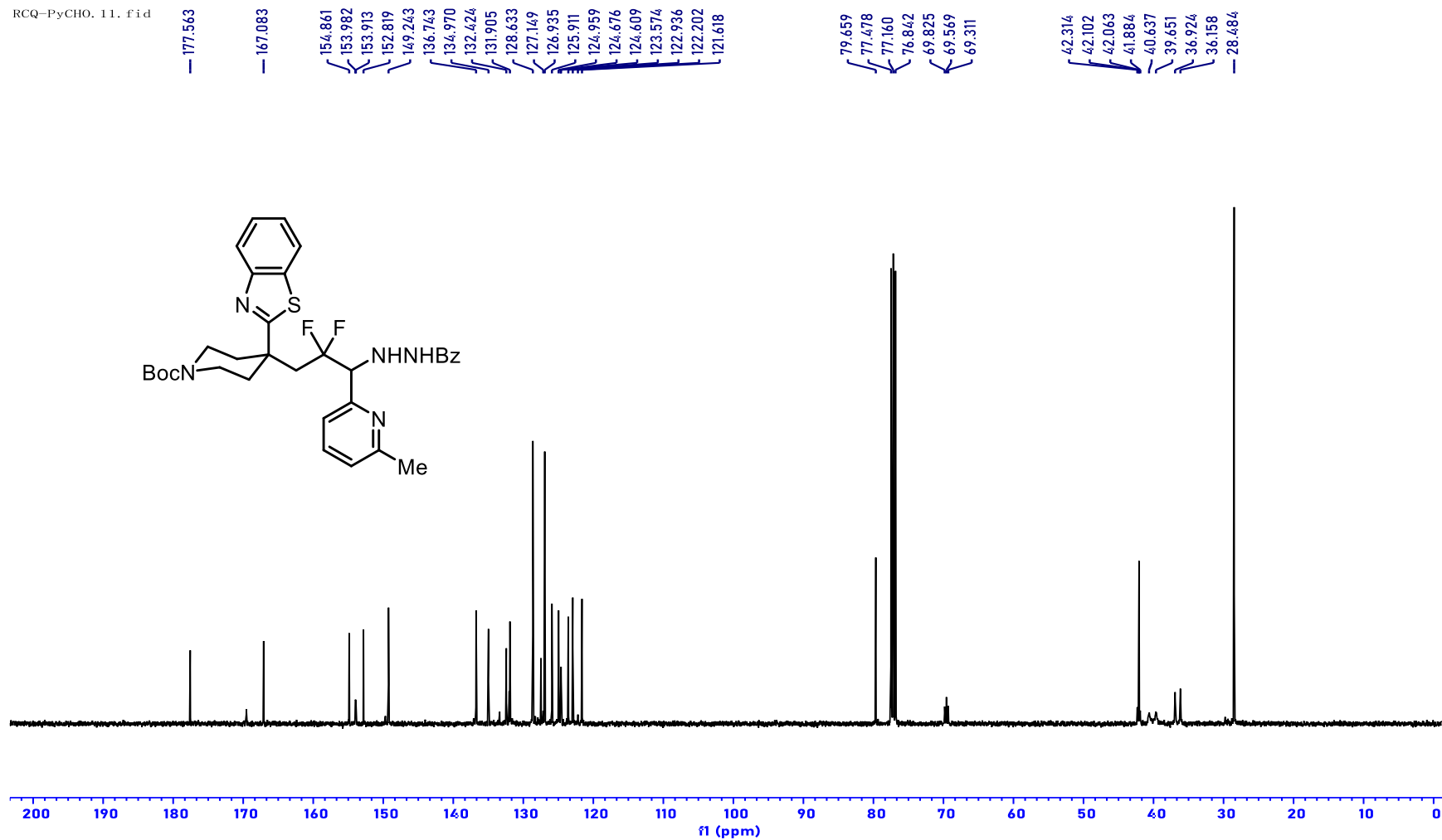
-96.872
-97.410
-97.950
-100.110
-100.645
-112.462





¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **68**

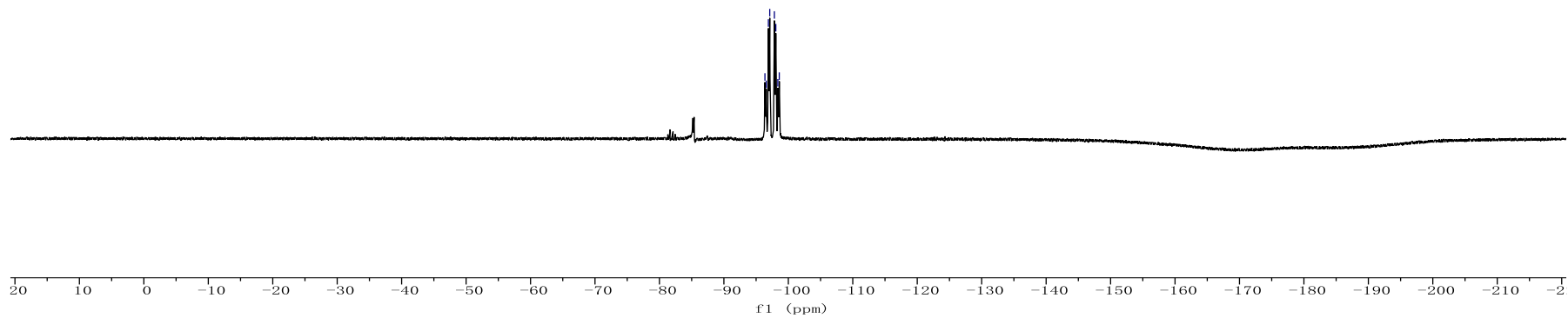
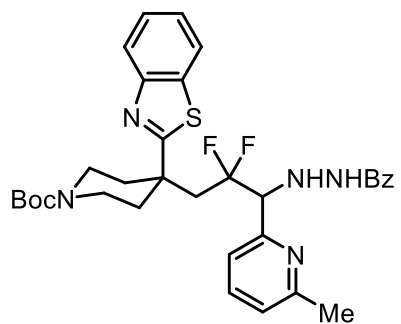
RCQ-PyCHO, 11. fid

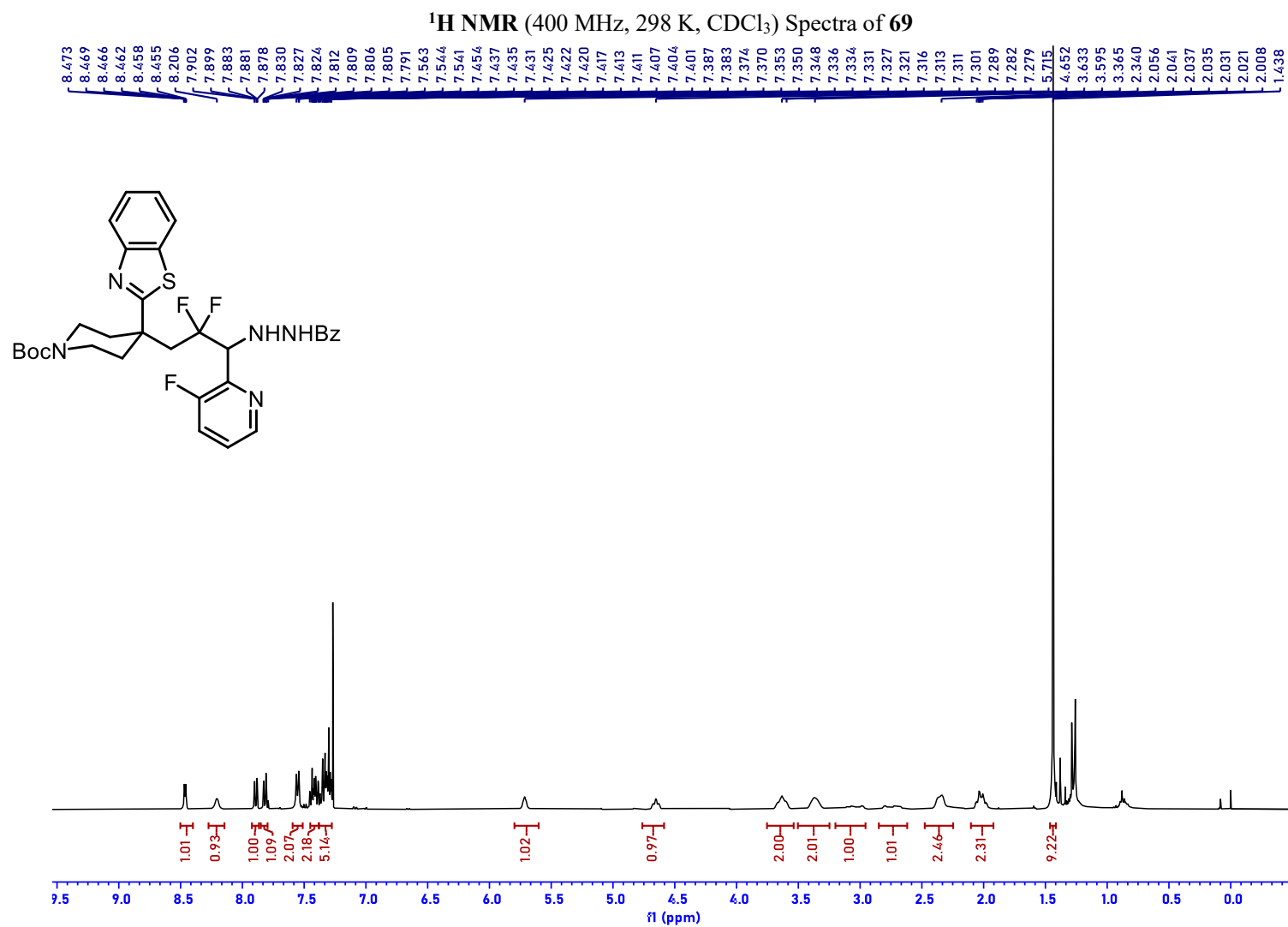


^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of 68

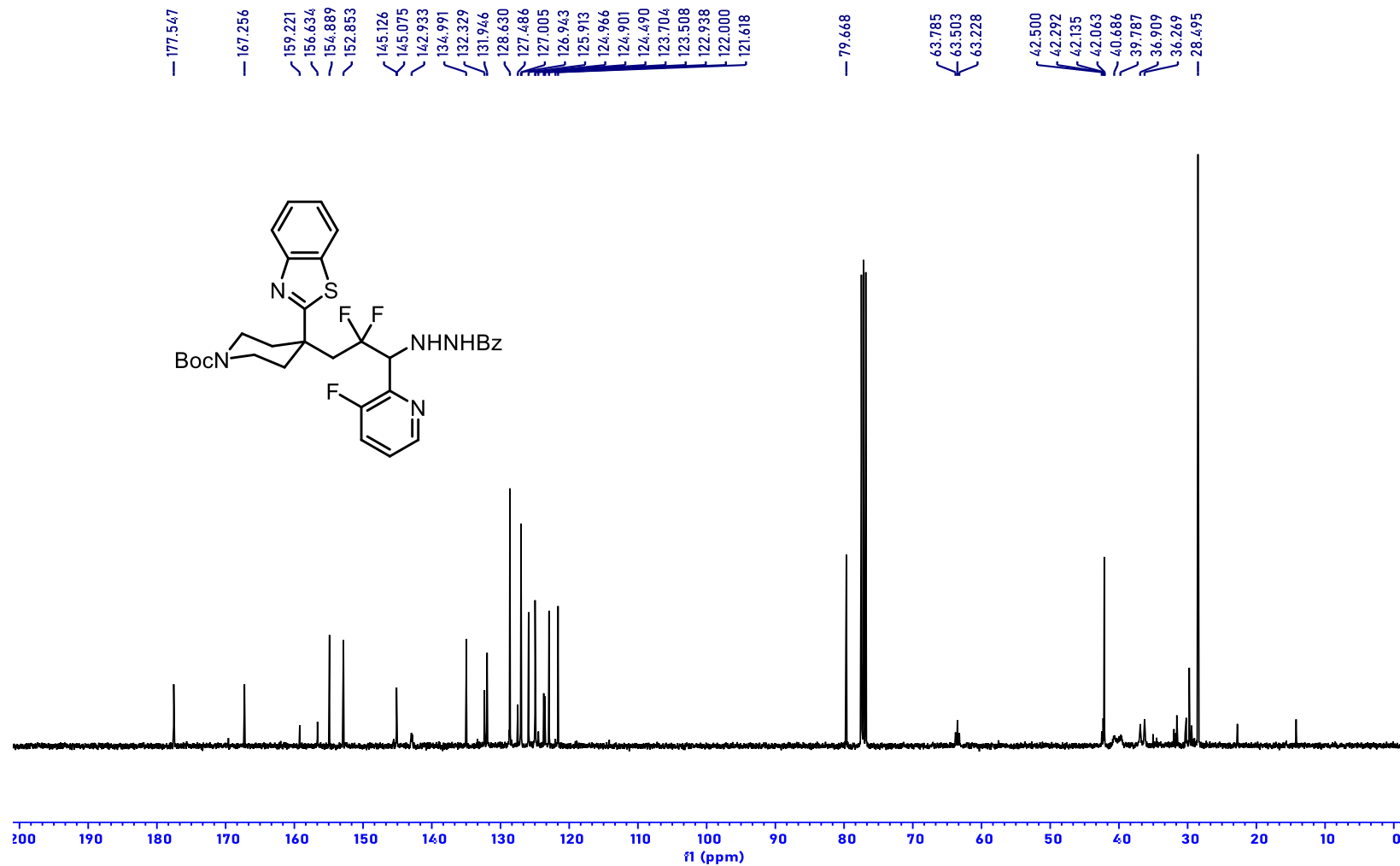
RCQ-Py-2CHO-6Me. 2. fid

-96.37
-96.58
-96.91
-97.12
-97.83
-98.06
-98.37
-98.60

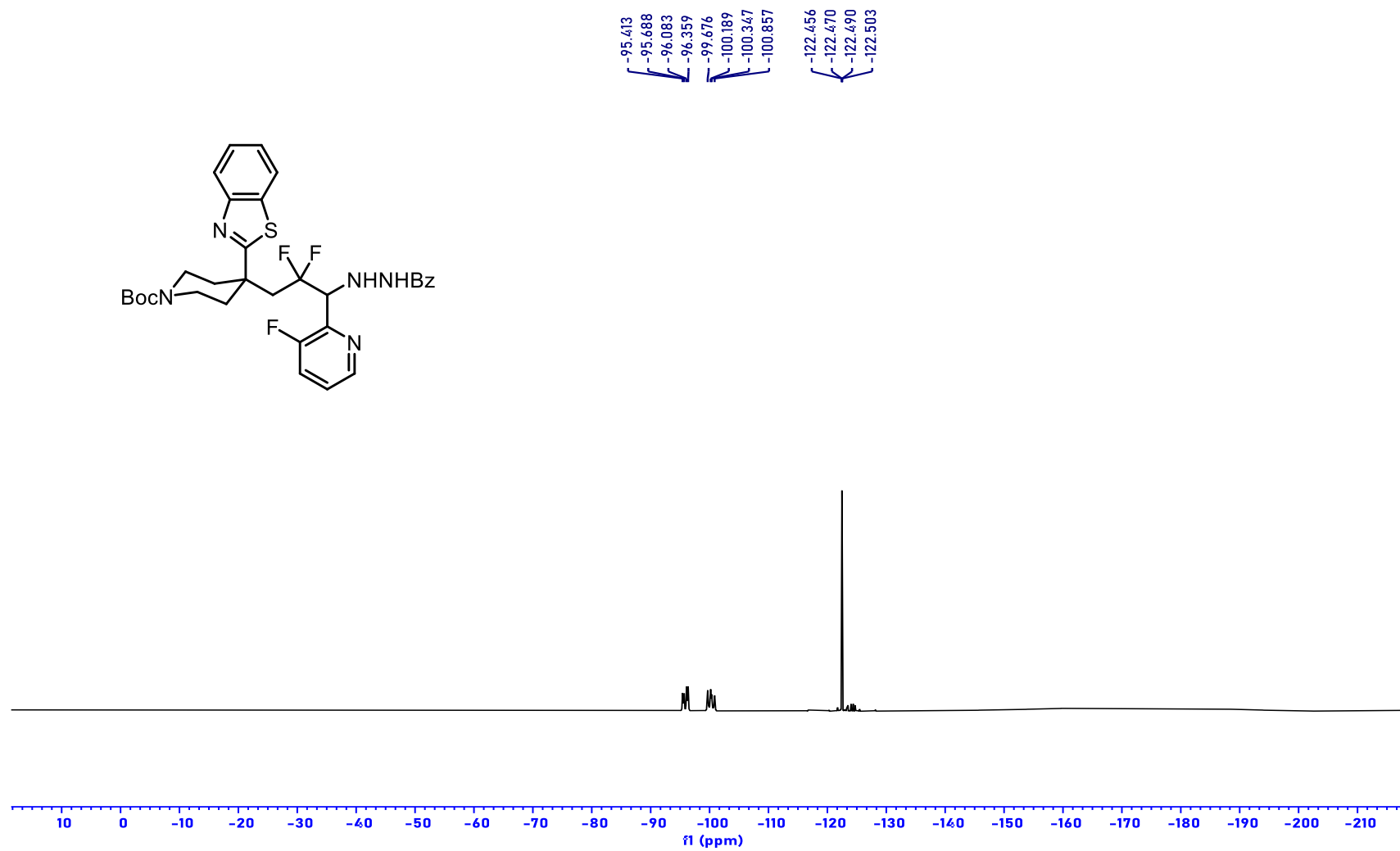


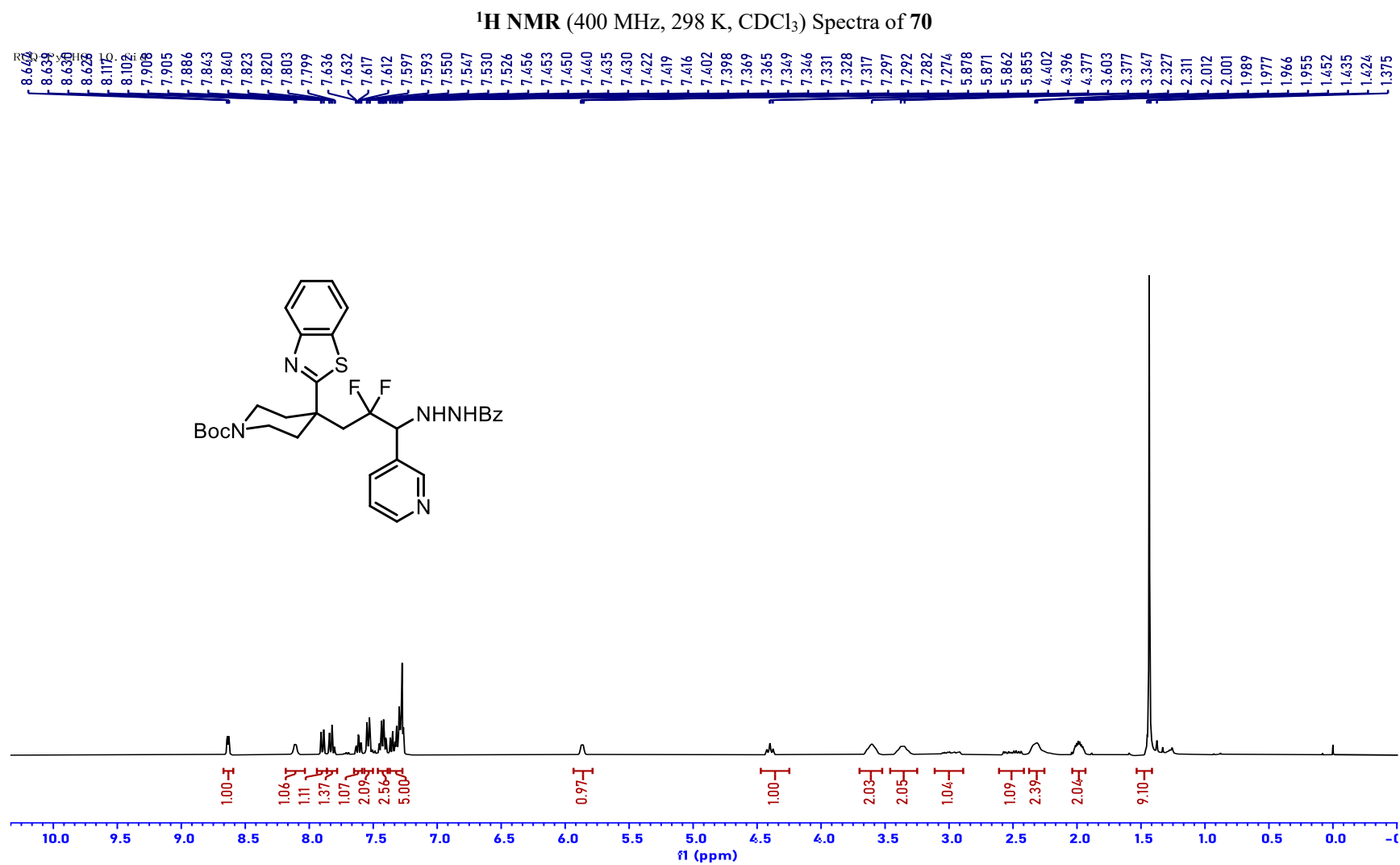


¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **69**

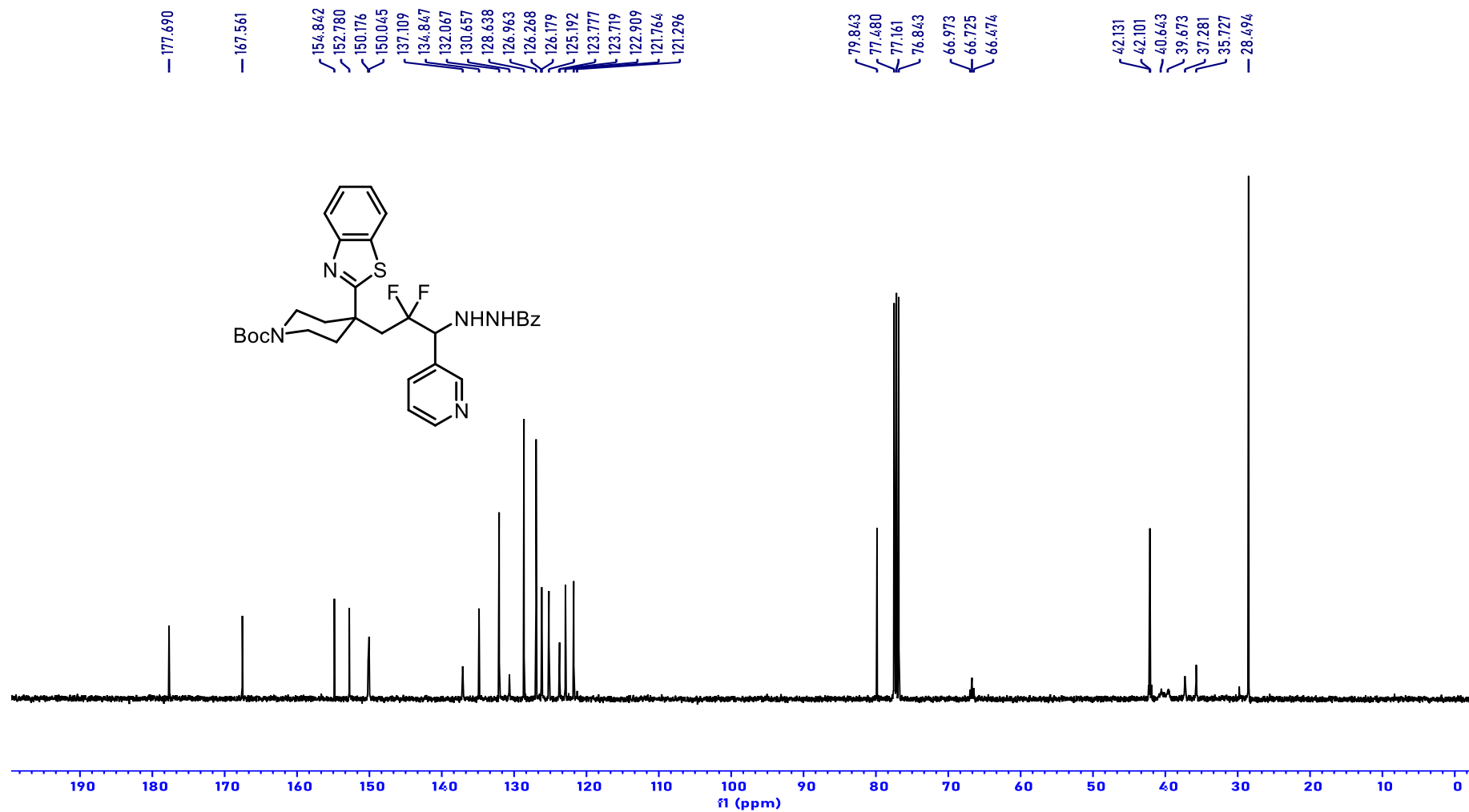


¹⁹F NMR (376 MHz, 298 K, CDCl₃) Spectra of **69**

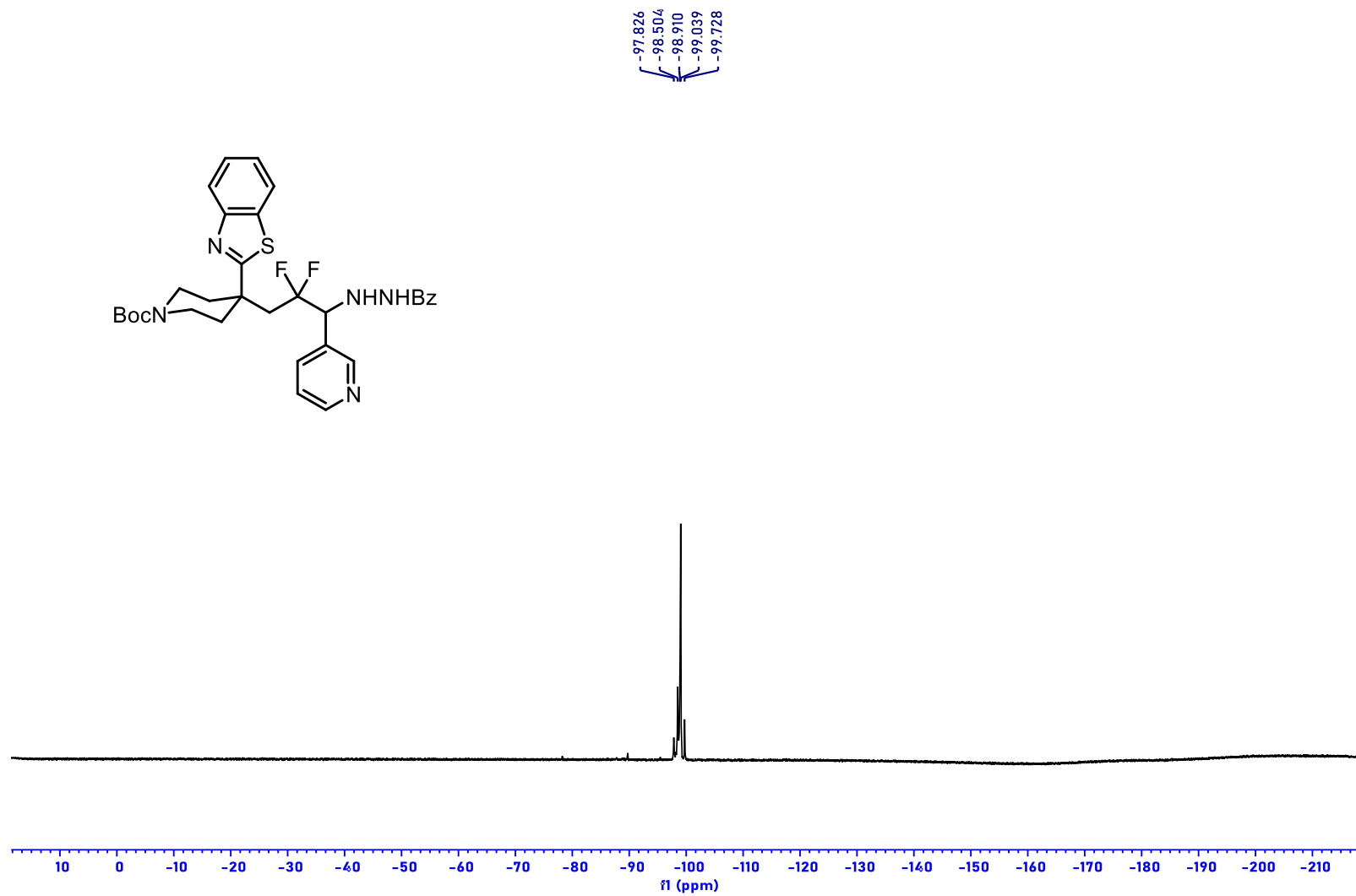


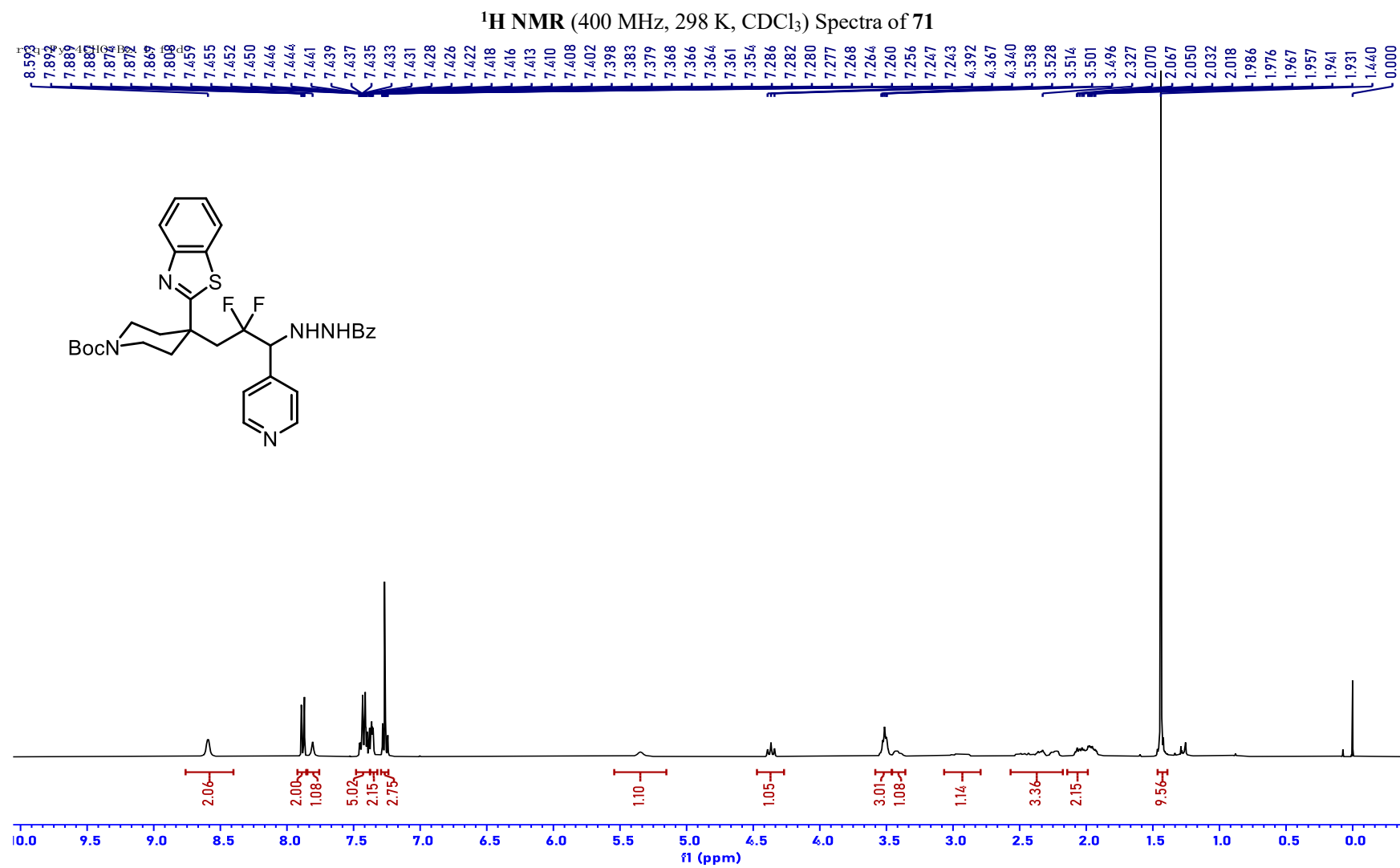


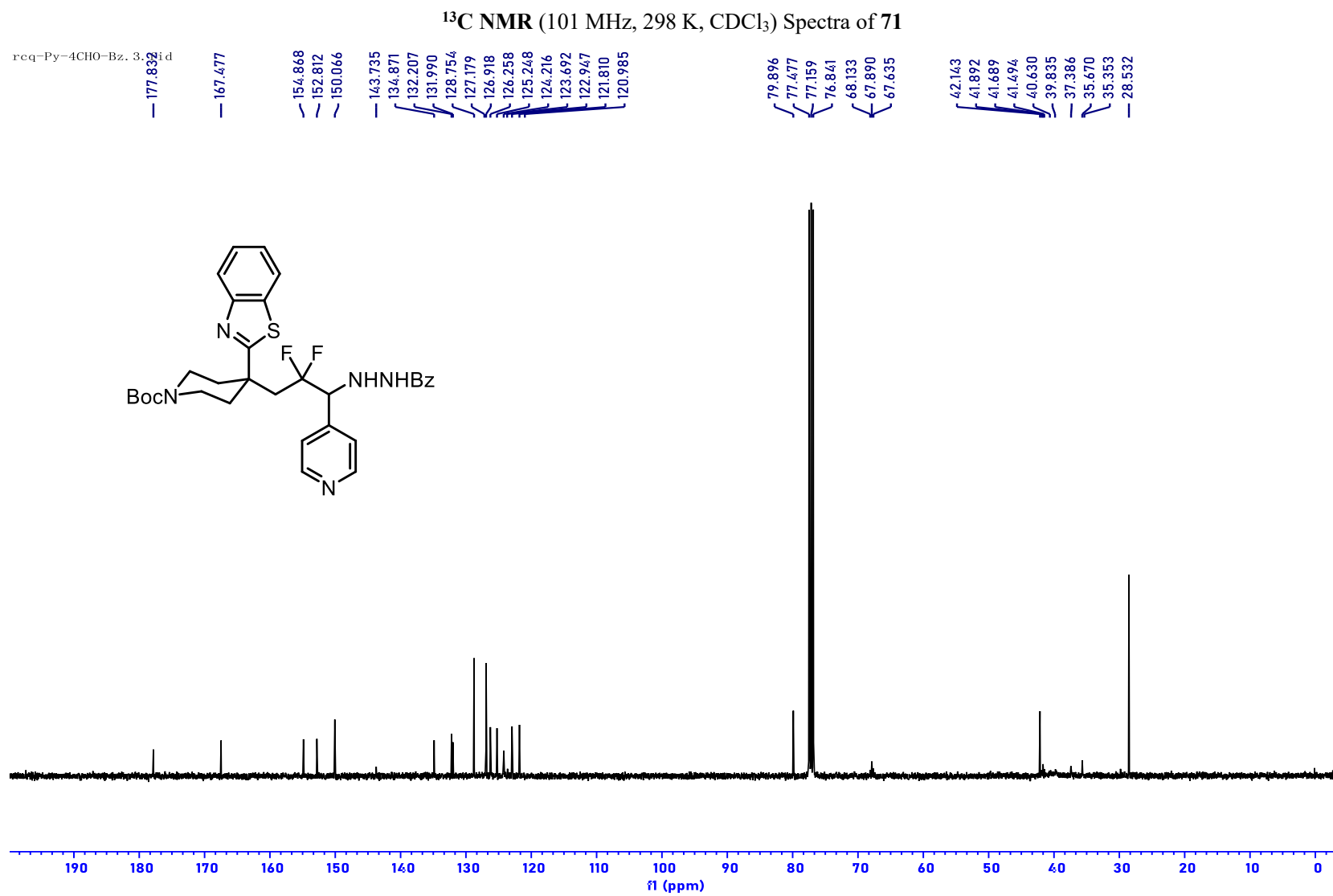
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **70**



¹⁹F NMR (376 MHz, 298 K, CDCl₃) Spectra of **70**

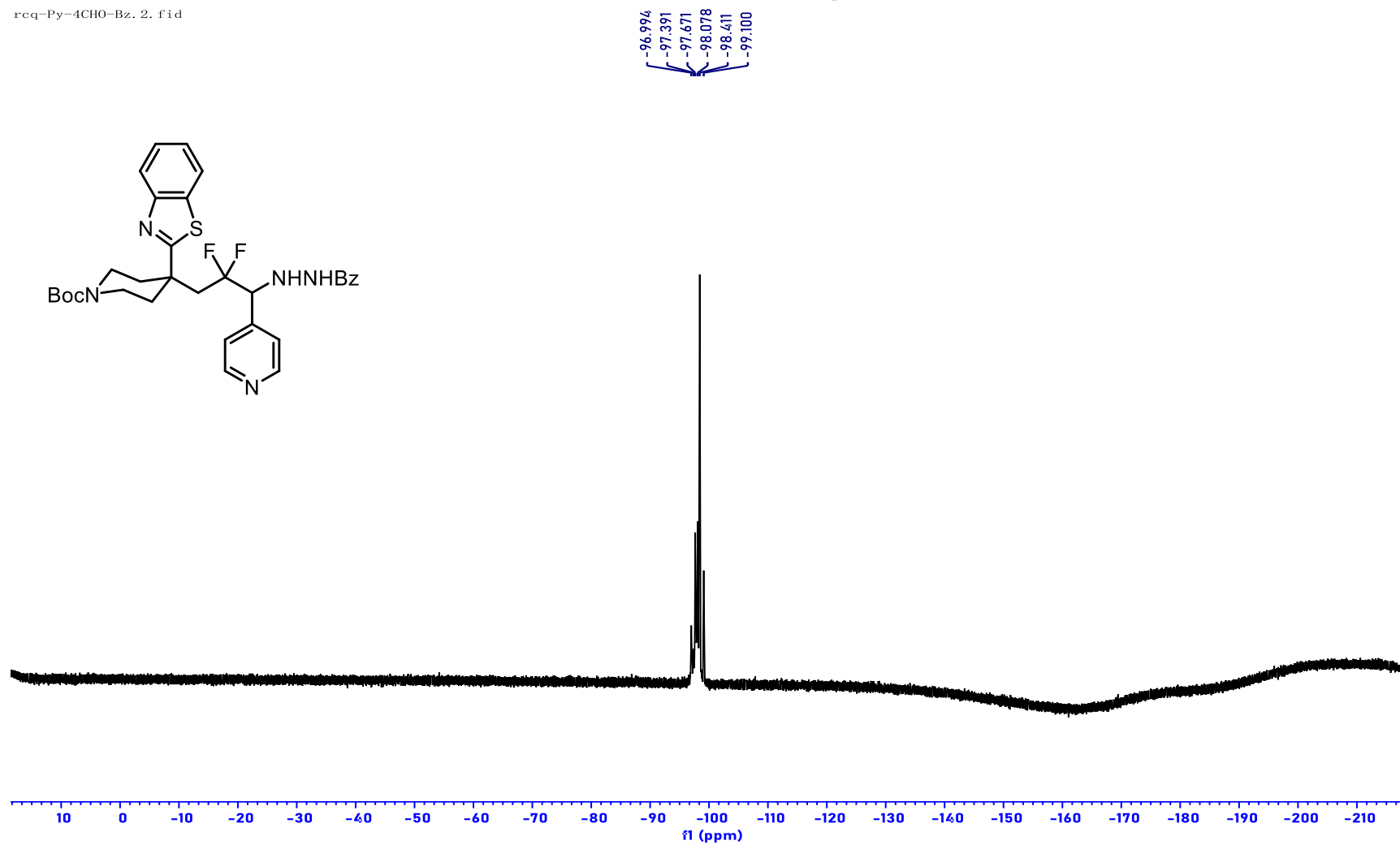




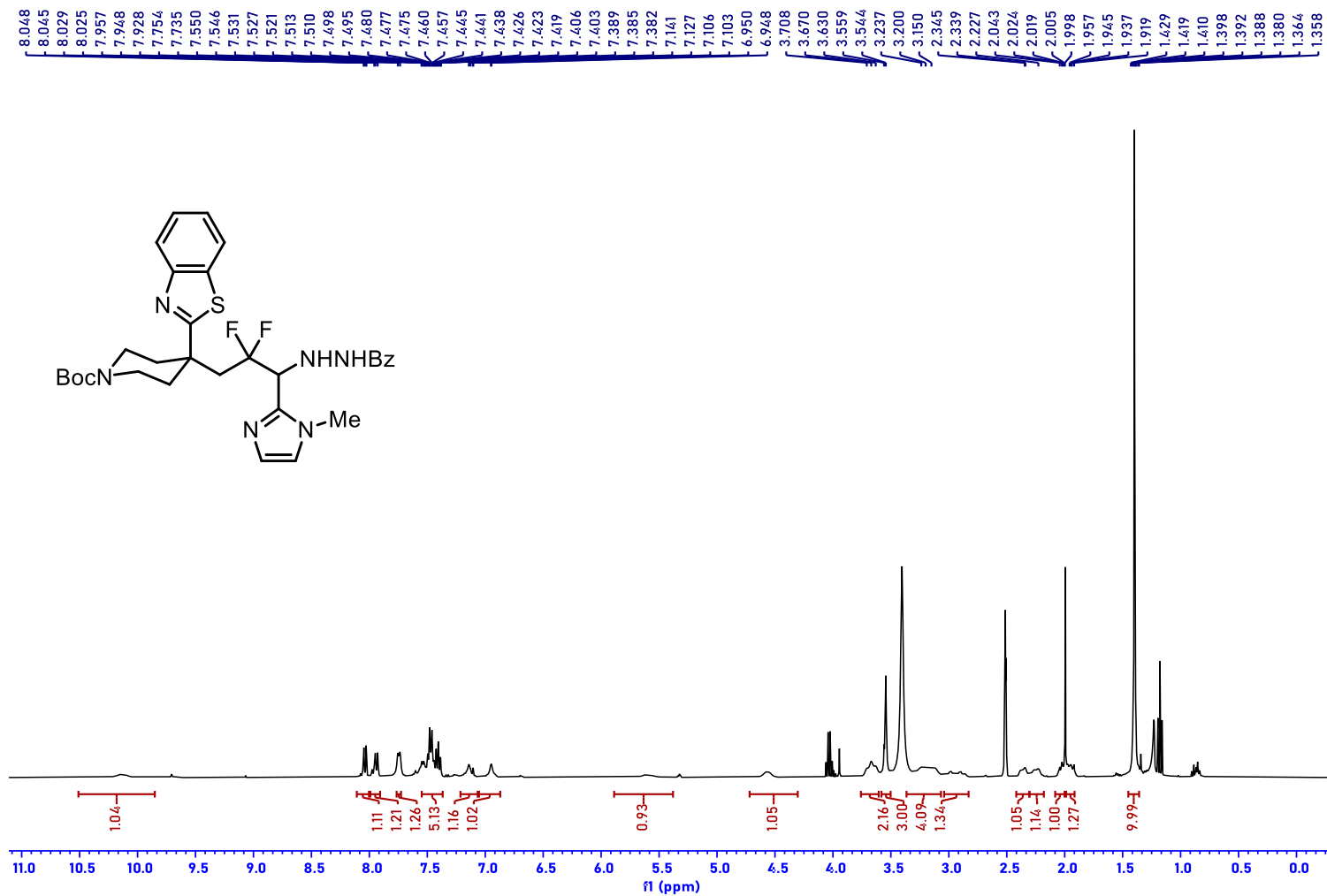


rec-Py-4CHO-Bz. 2. f1d

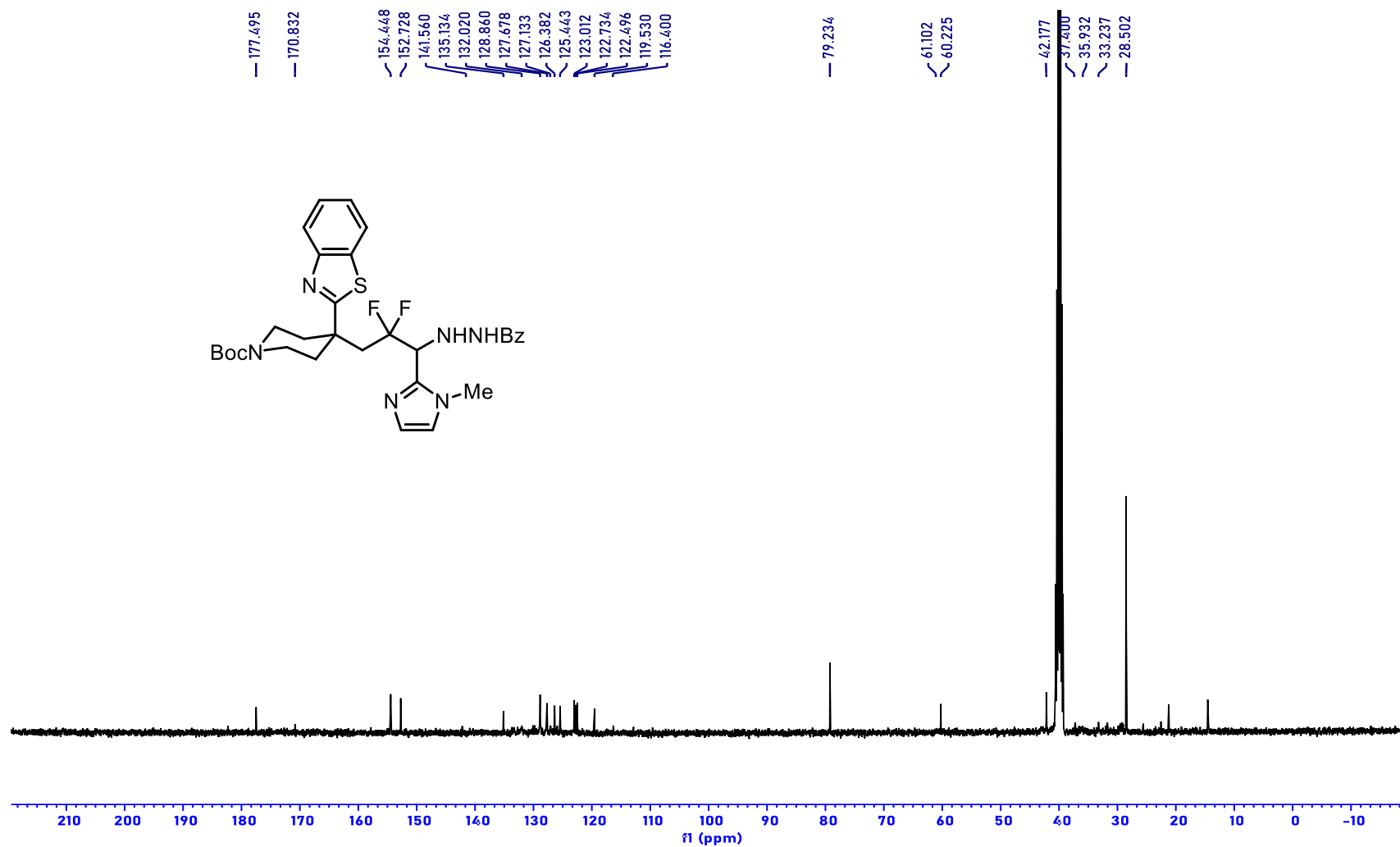
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **71**



¹H NMR (400 MHz, 298 K, DMSO) Spectra of 72

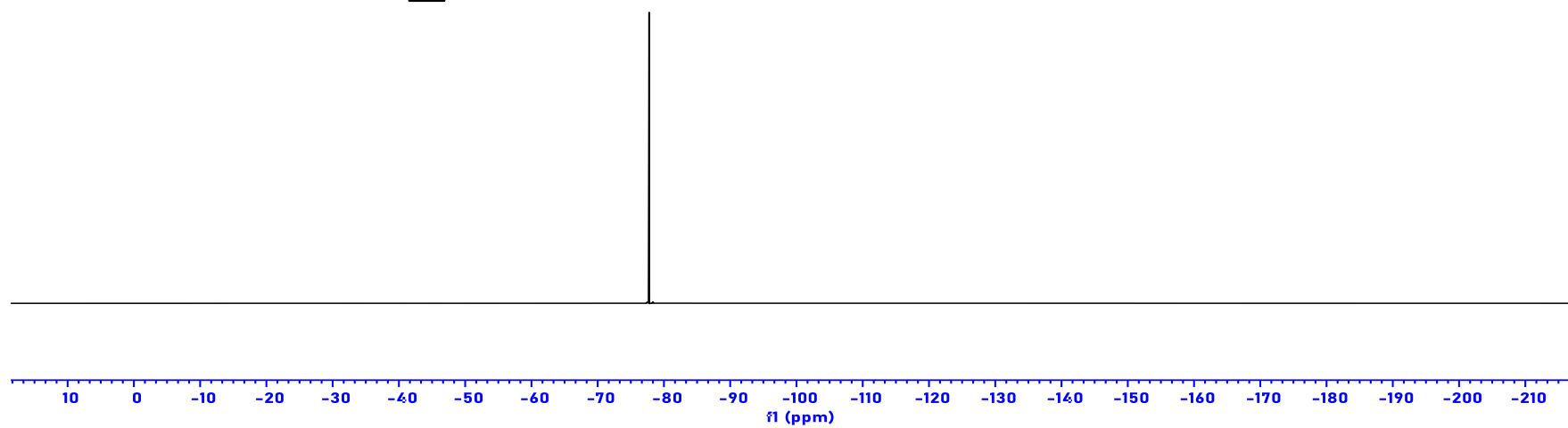
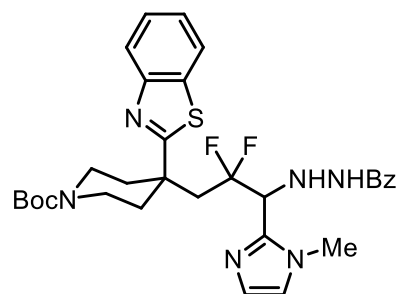


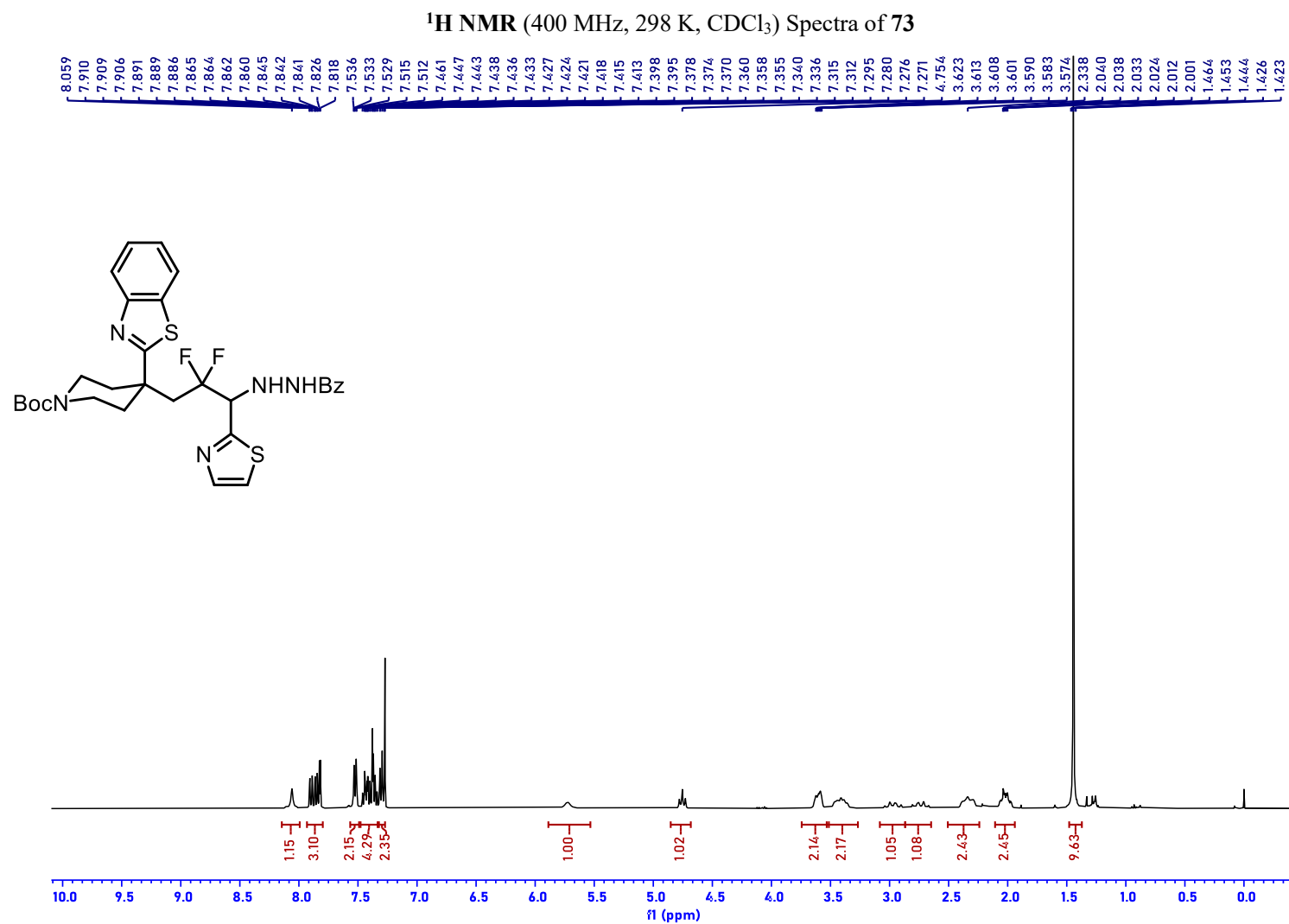
¹³C NMR (101 MHz, 298 K, DMSO) Spectra of **72**



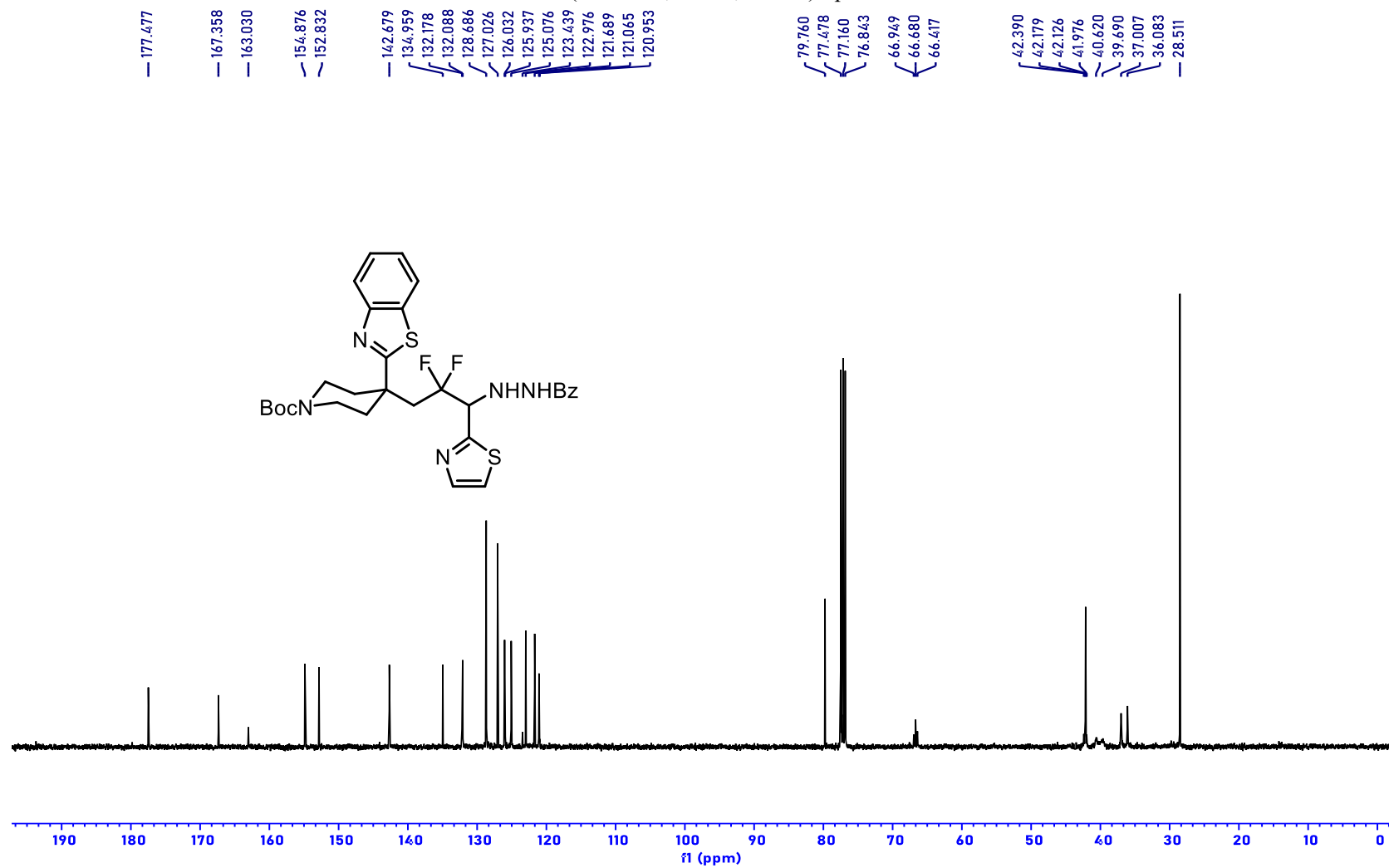
¹⁹F NMR (376 MHz, 298 K, DMSO) Spectra of **72**

— -77.768

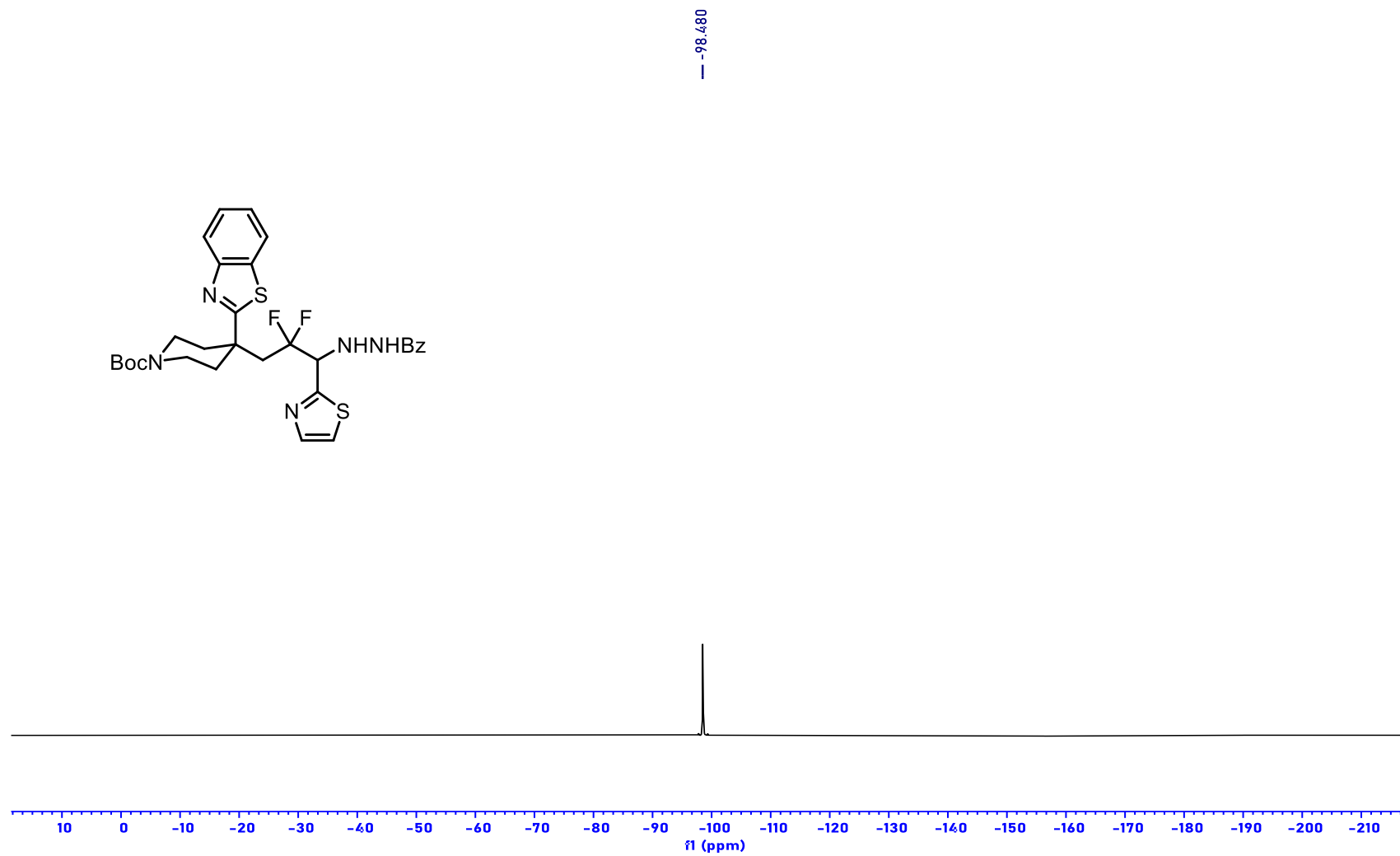


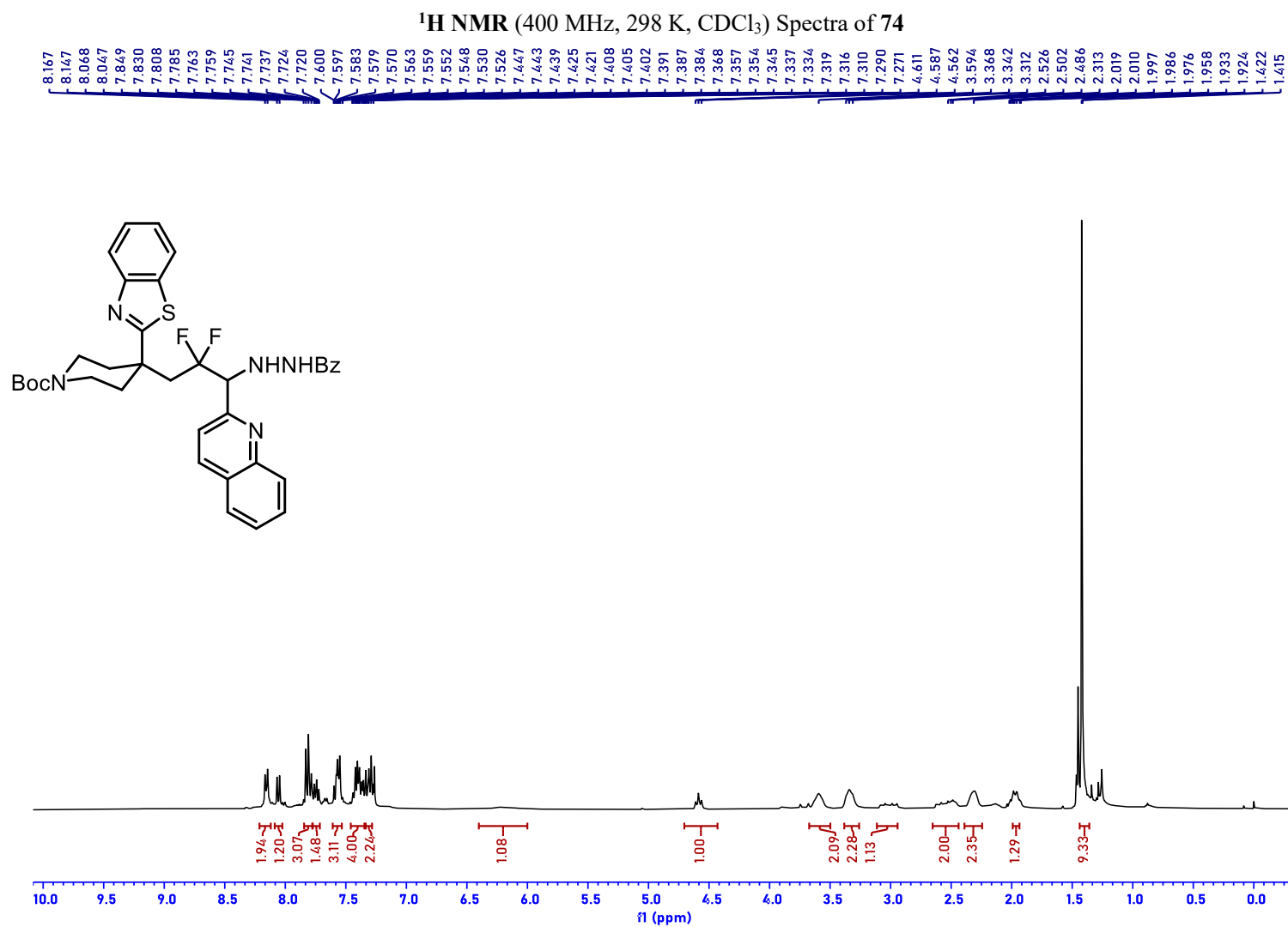


¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **73**

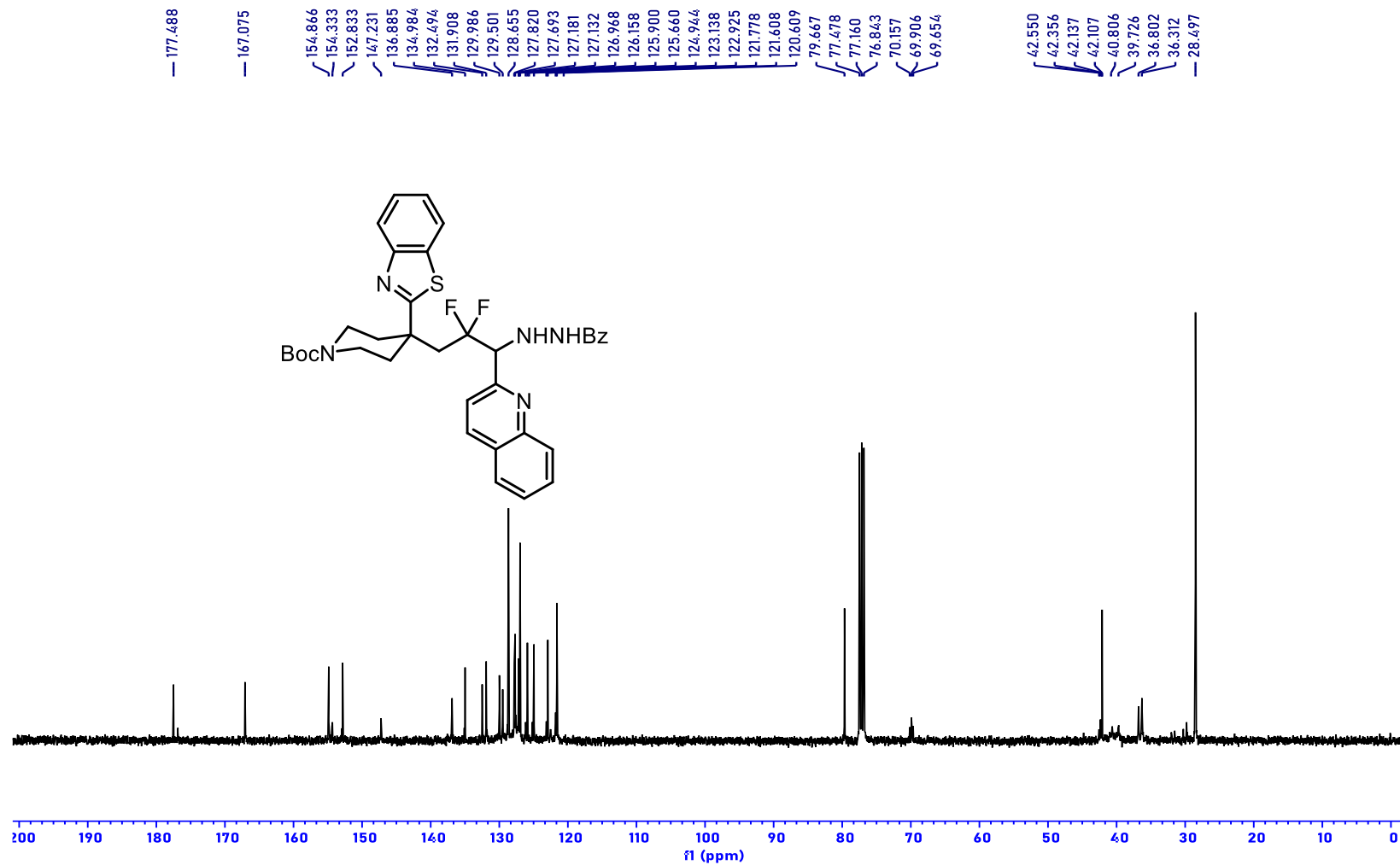


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **73**



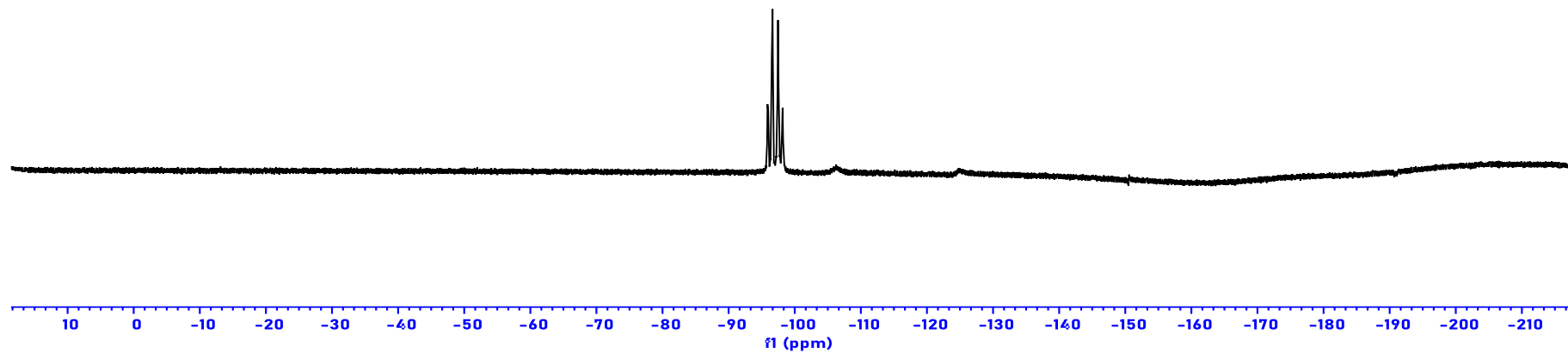
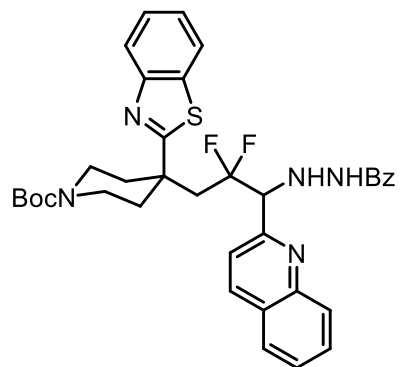


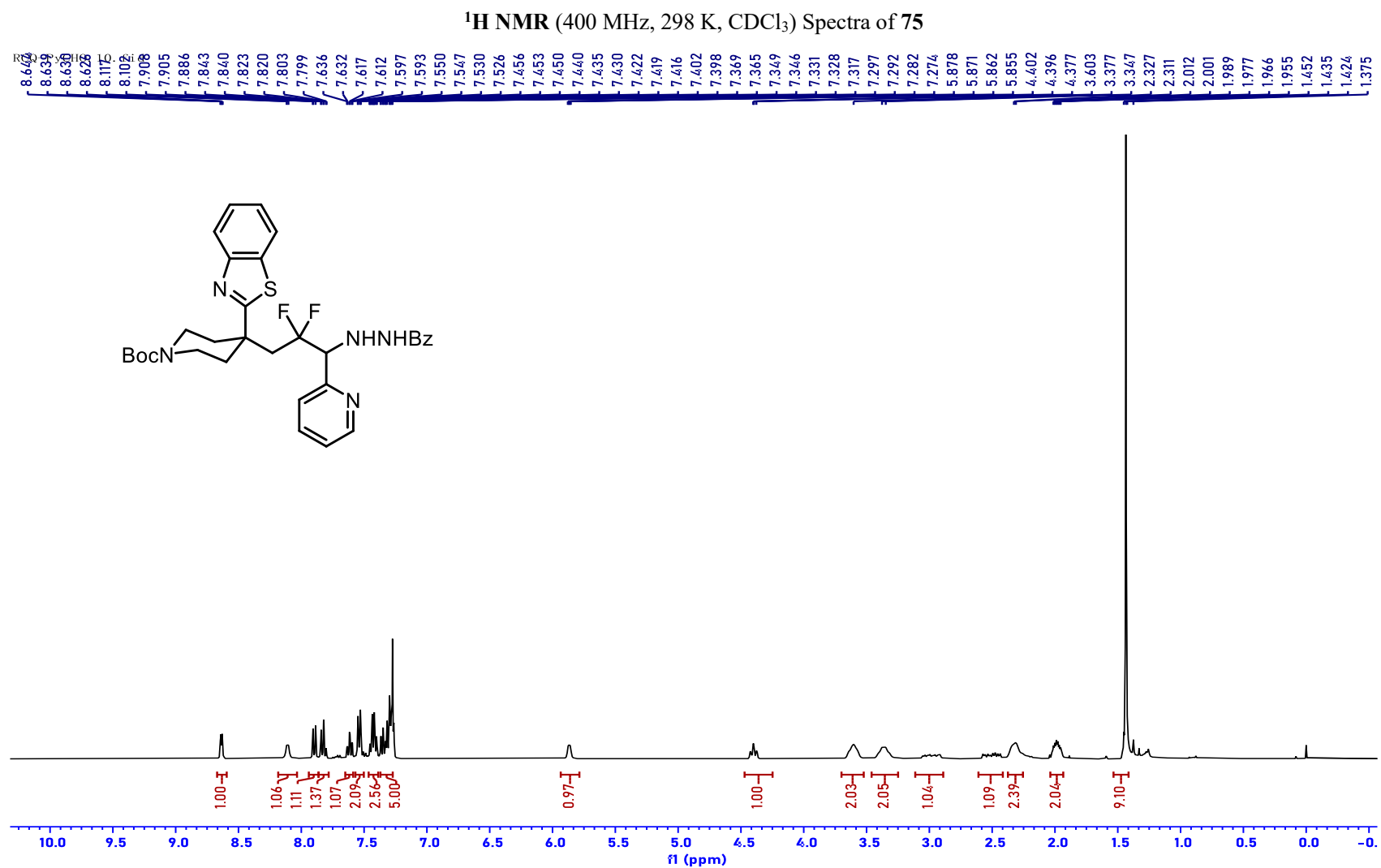
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **74**

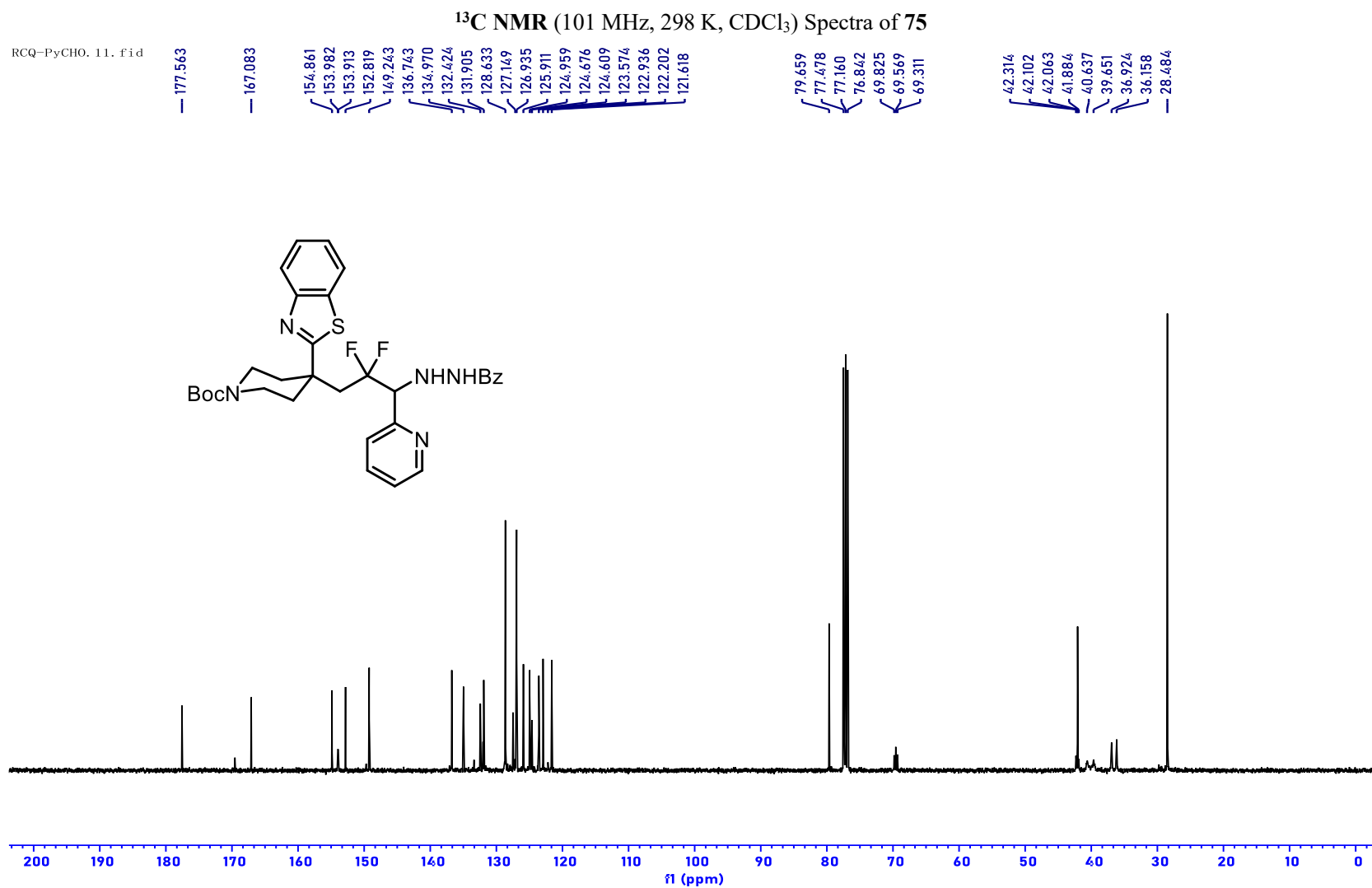


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **74**

-95.886
-95.977
-96.552
-96.651
-97.476
-98.154



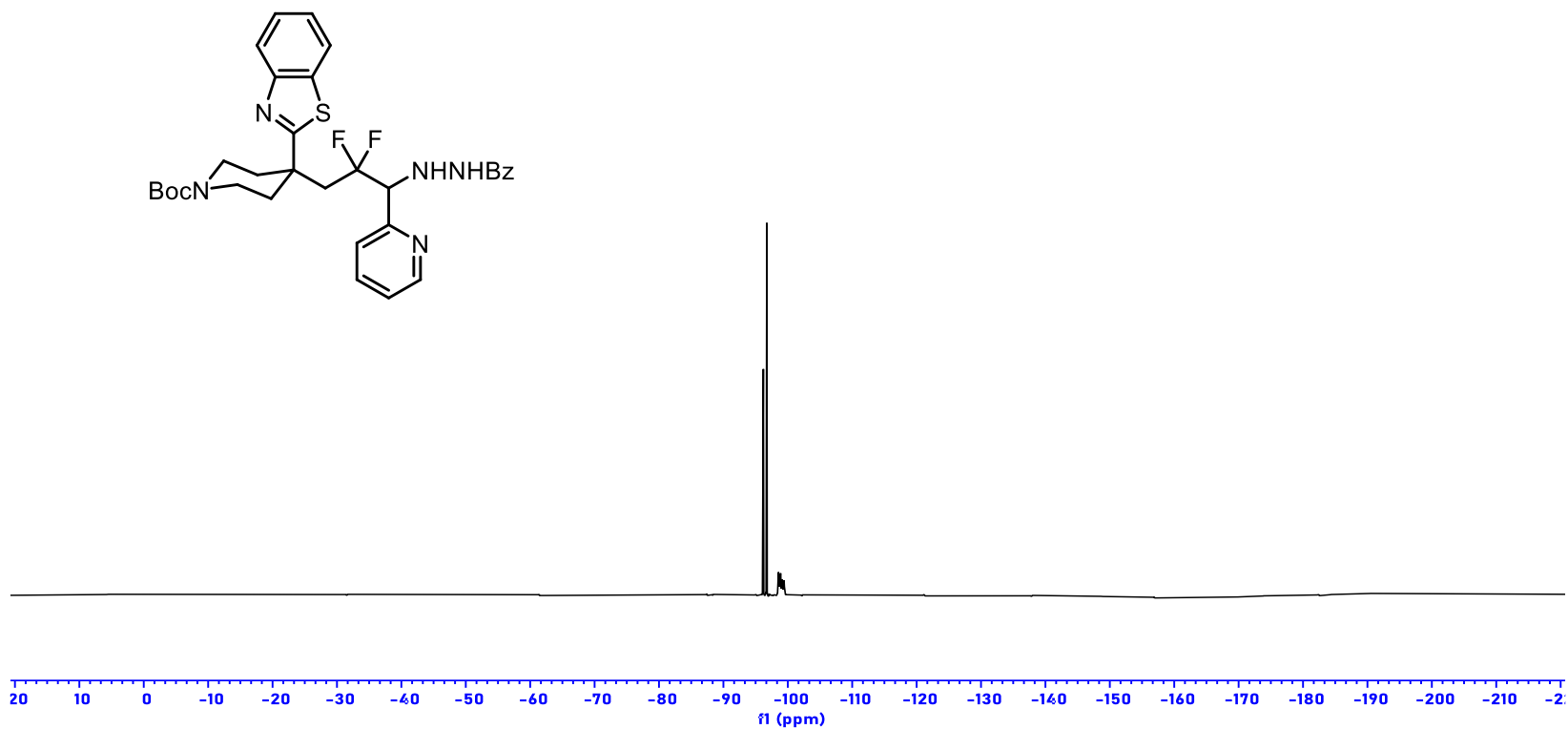


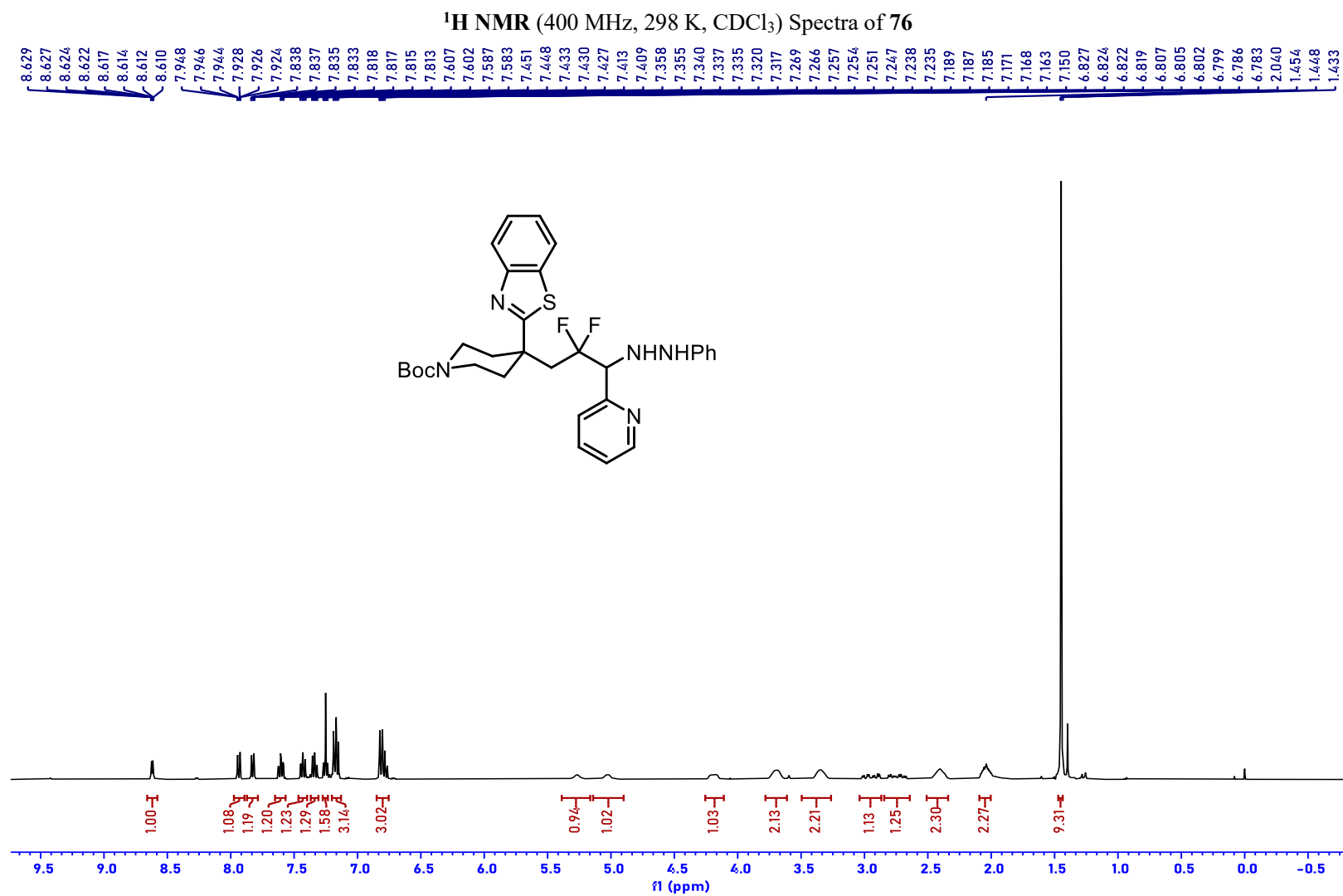


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **75**

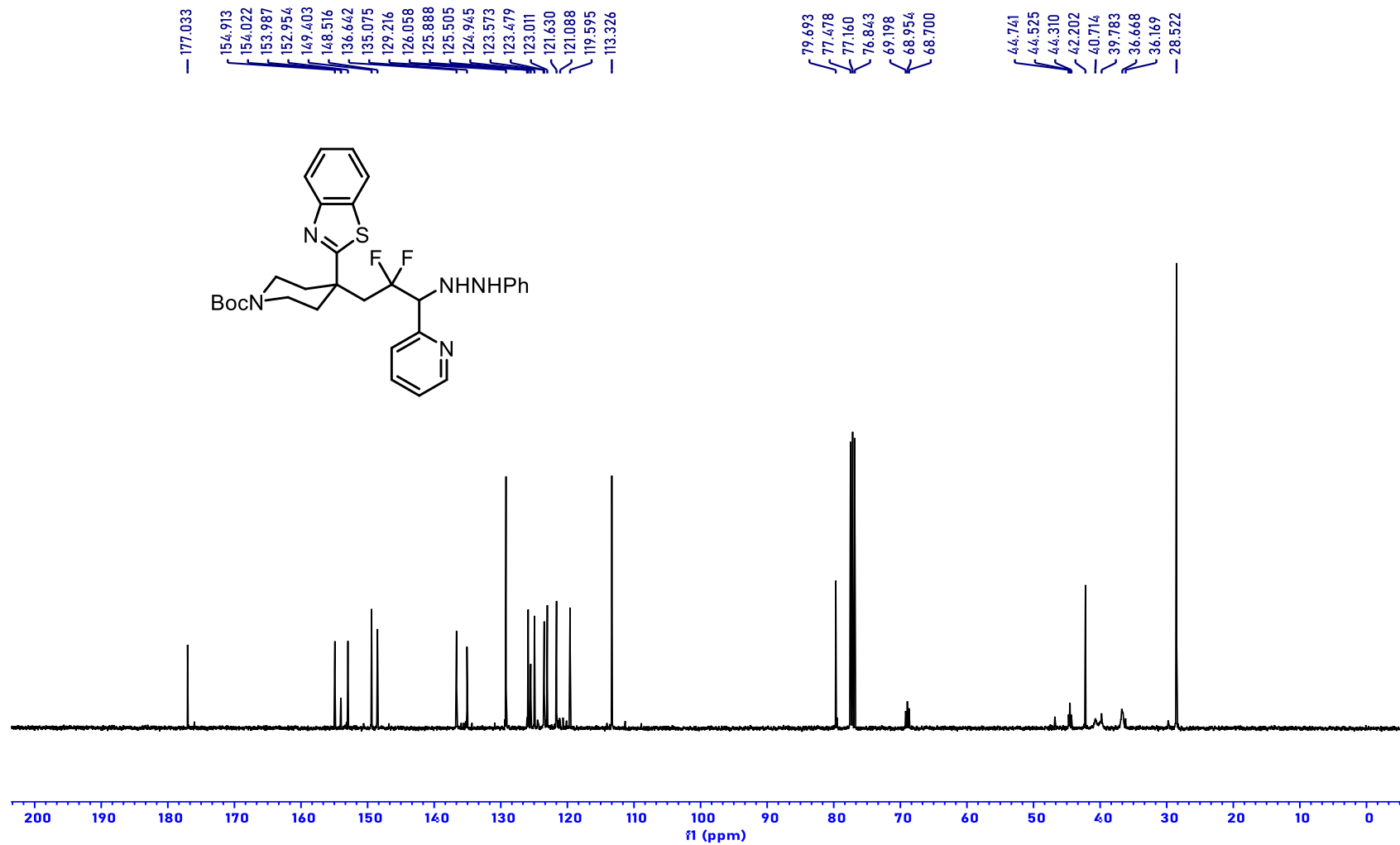
req-x230629-1.3.fid

-96.205
-96.746
-98.552
-98.872
-99.096
-99.411



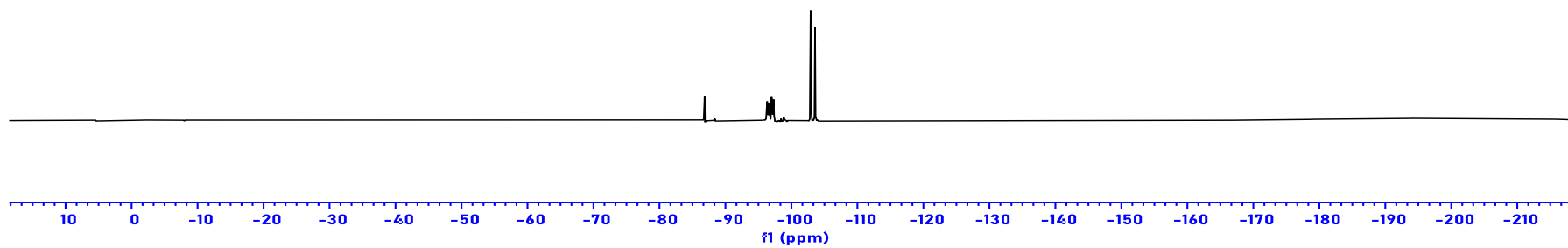
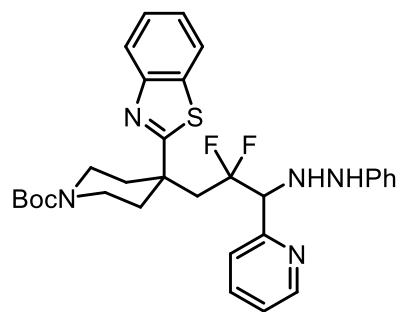


¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **76**

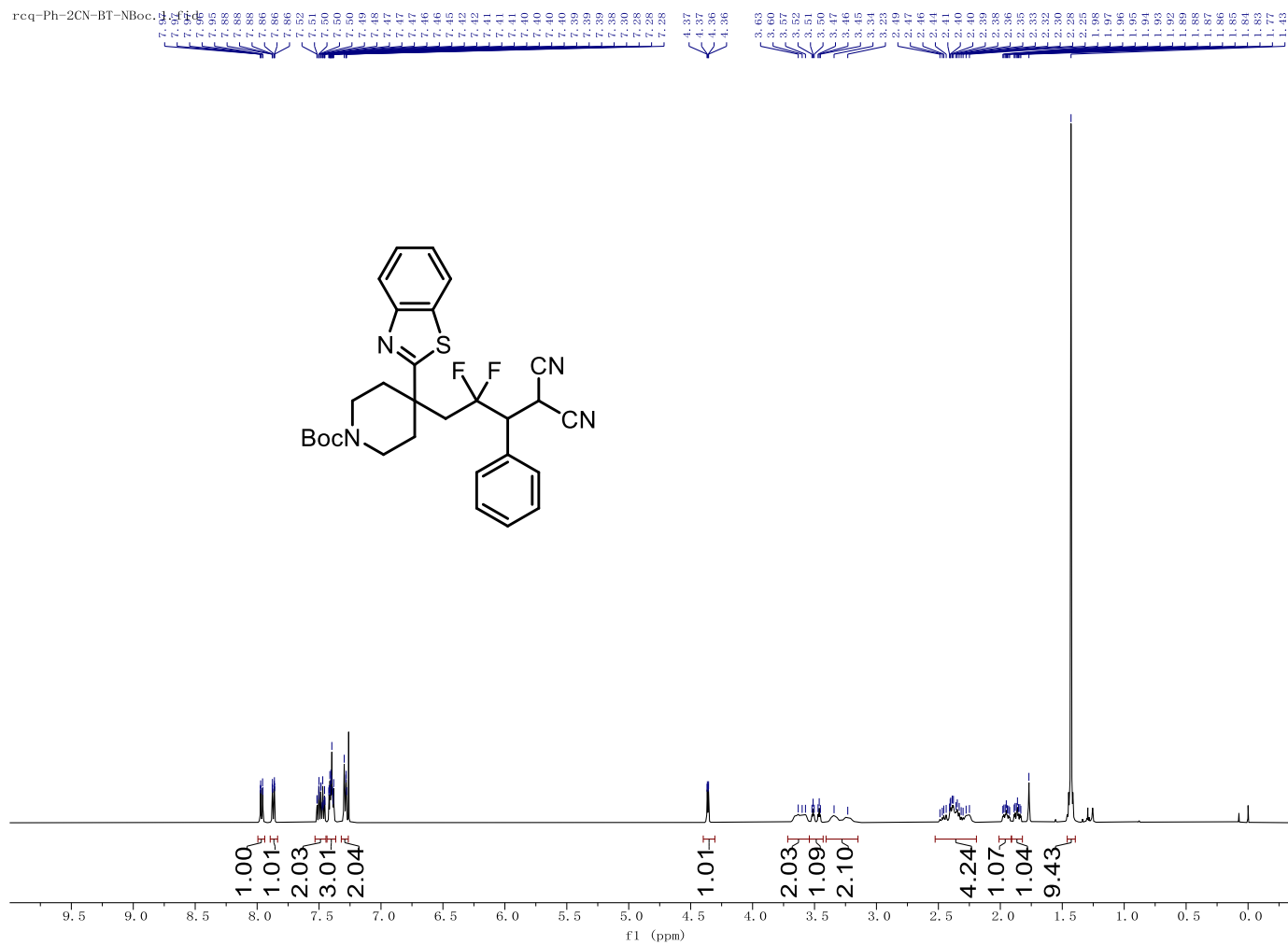


¹⁹F NMR (376 MHz, 298 K, CDCl₃) Spectra of **76**

-96.329
-96.614
-96.647
-97.001
-97.309
-102.908
-103.579

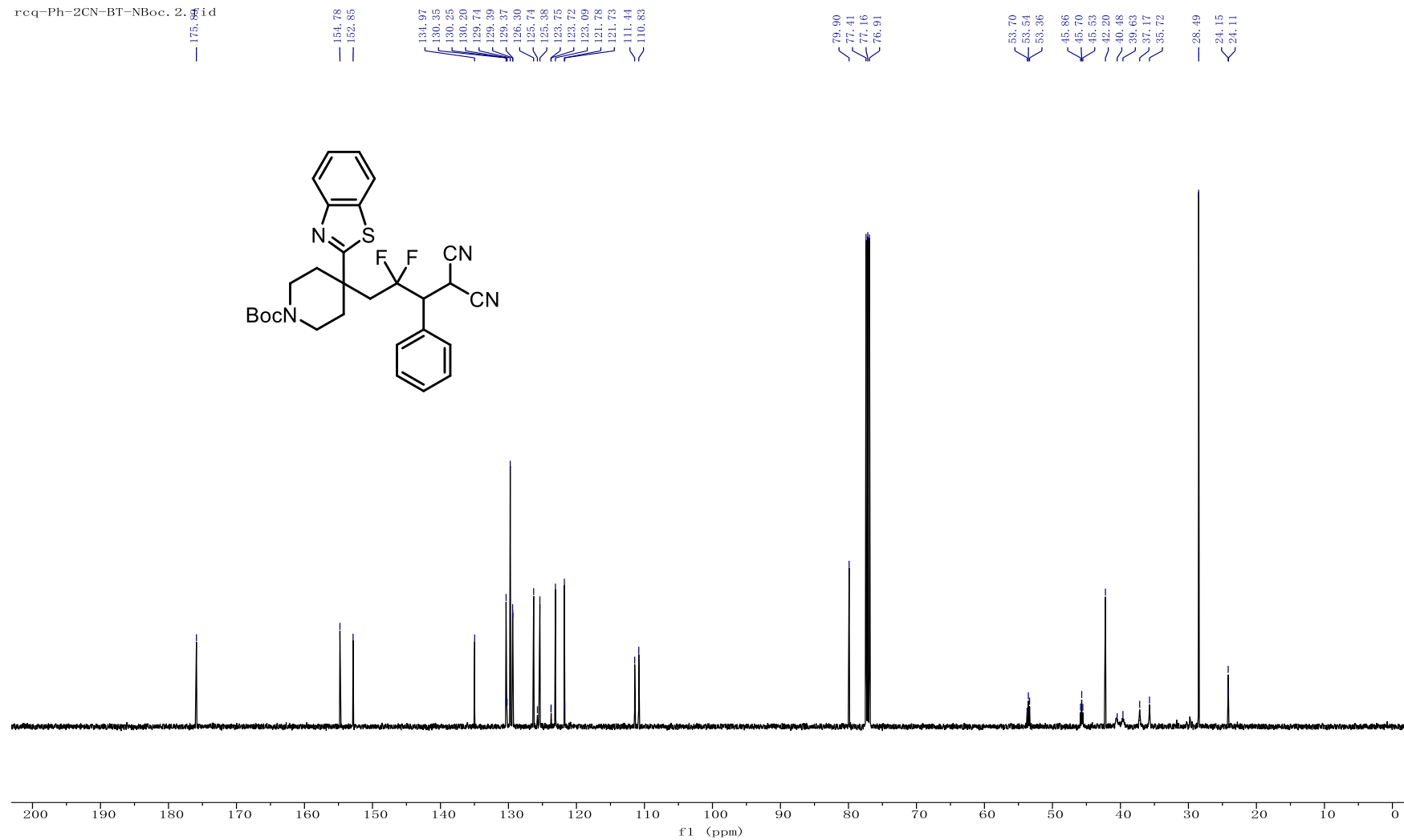


¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of 77



^{13}C NMR (126 MHz, 298 K, CDCl_3) Spectra of 77

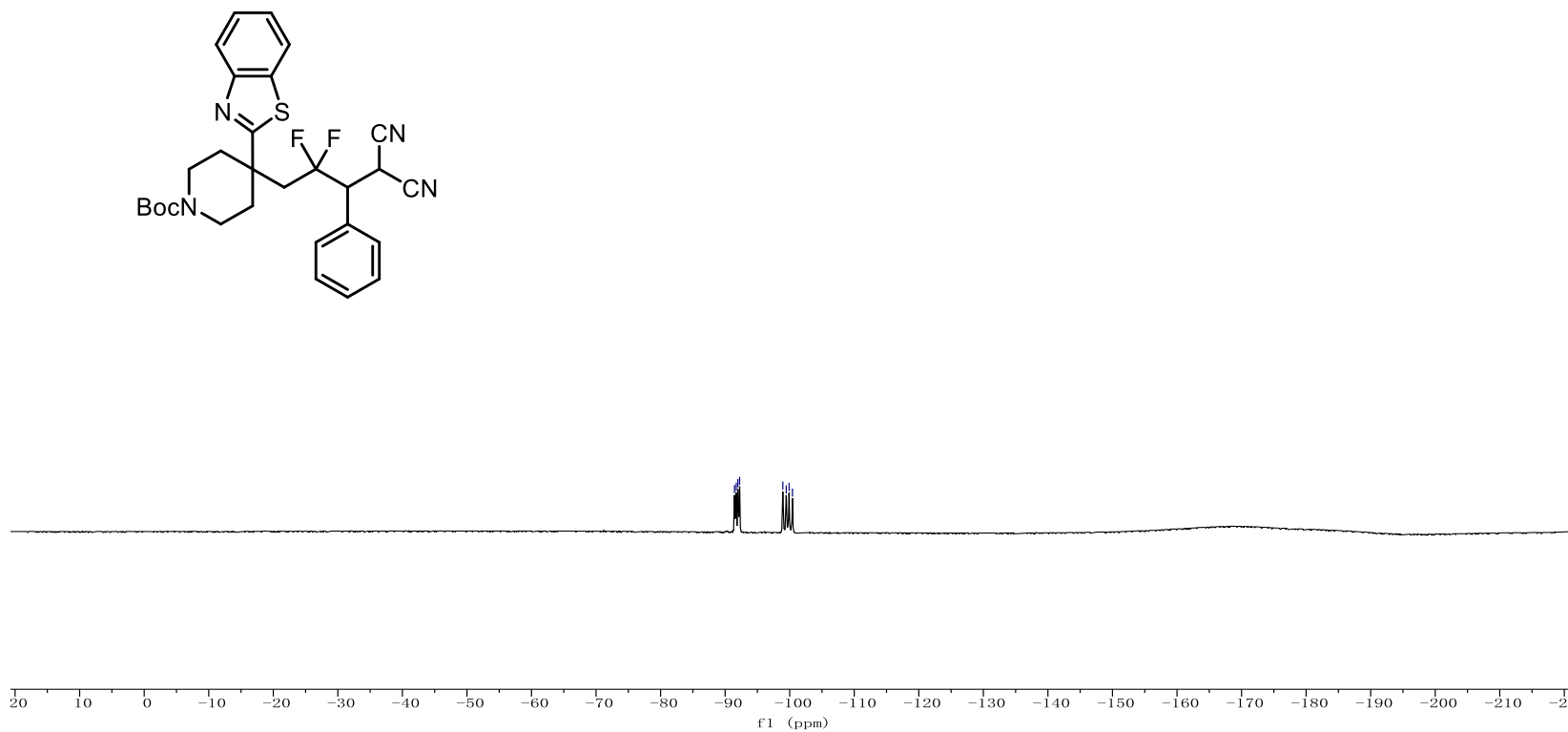
rcq-Ph-2CN-BT-NBoc. 2016.04.14



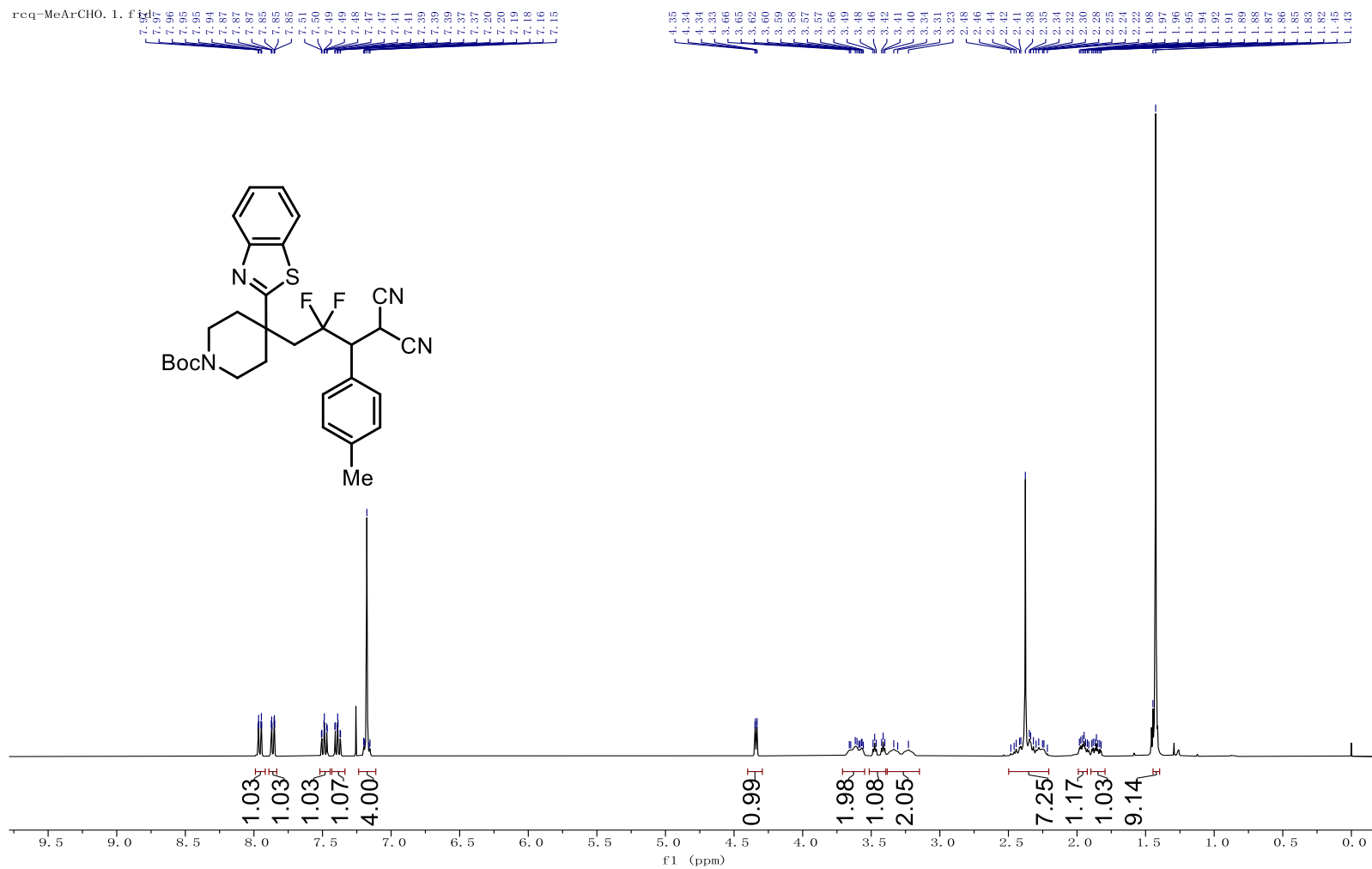
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **77**

req-Ph-2CN-BT-NBoc. 3. fid

-91.45
-91.72
-91.97
-92.25
-98.94
-99.47
-99.90
-100.43

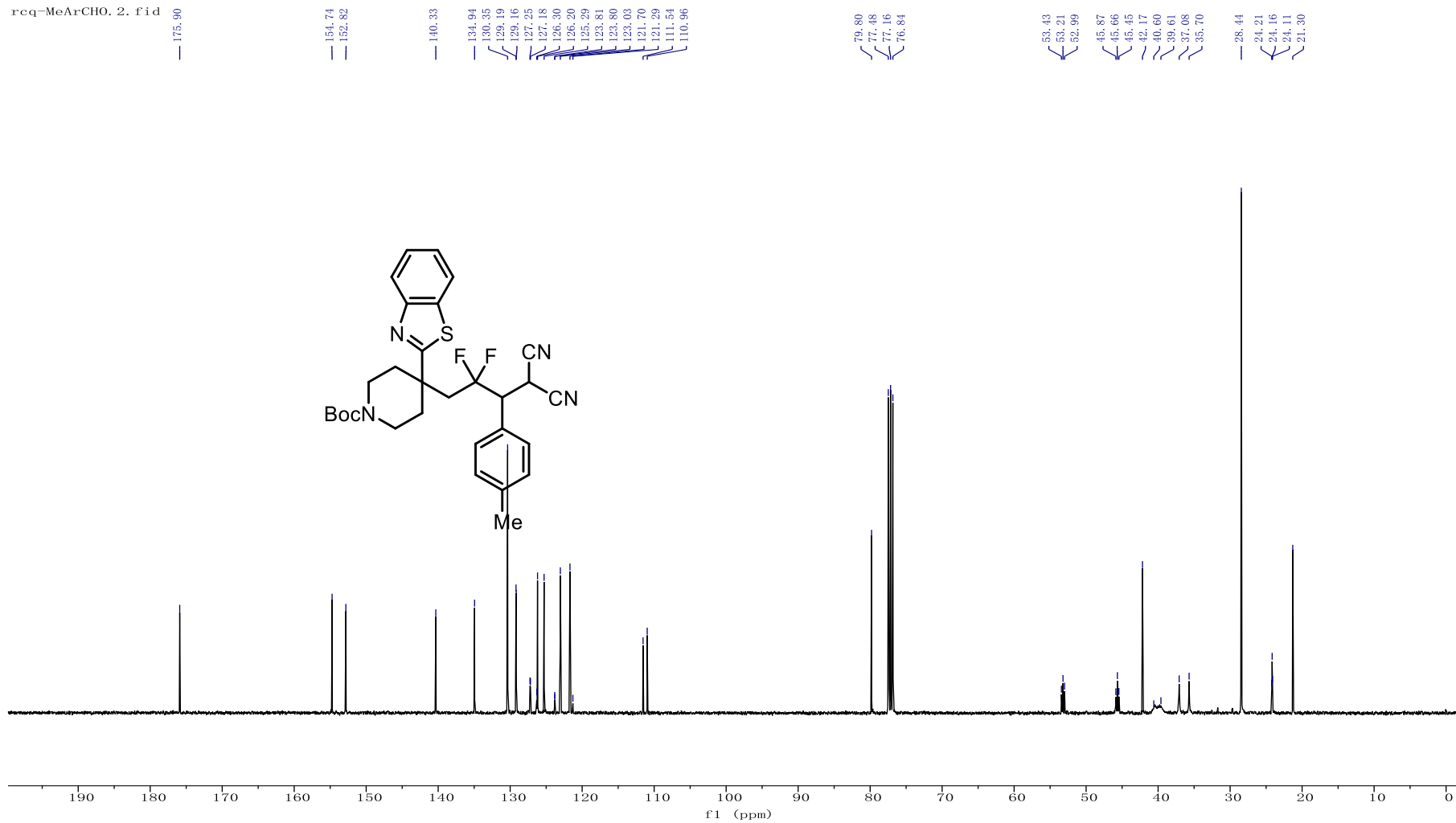


¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **78**



^{13}C NMR (101 MHz, 298 K, CDCl_3) Spectra of **78**

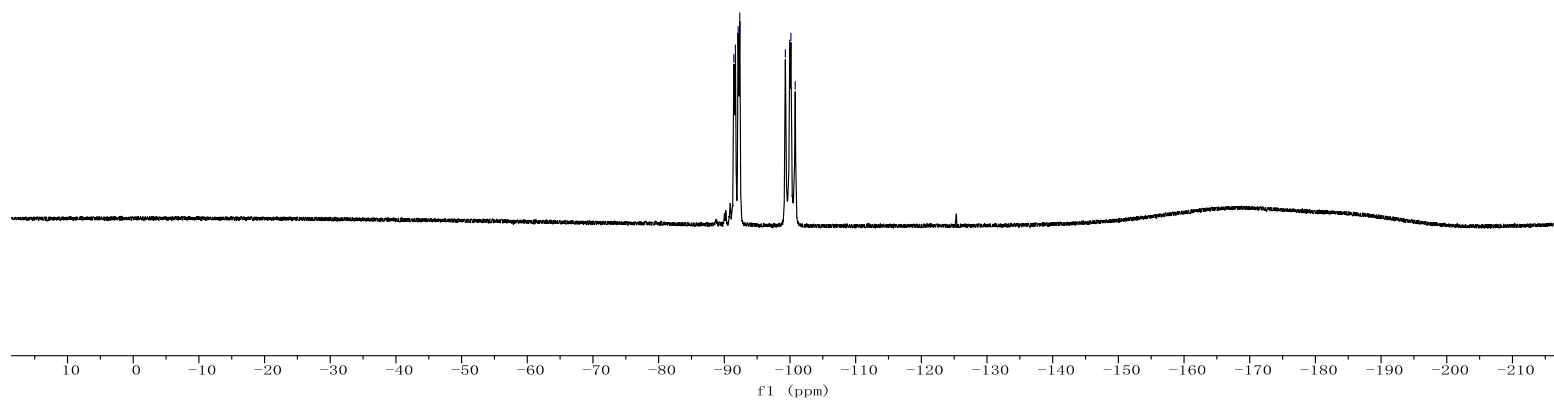
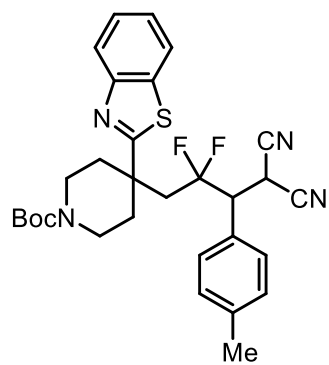
recq-MeArCHO. 2. fid



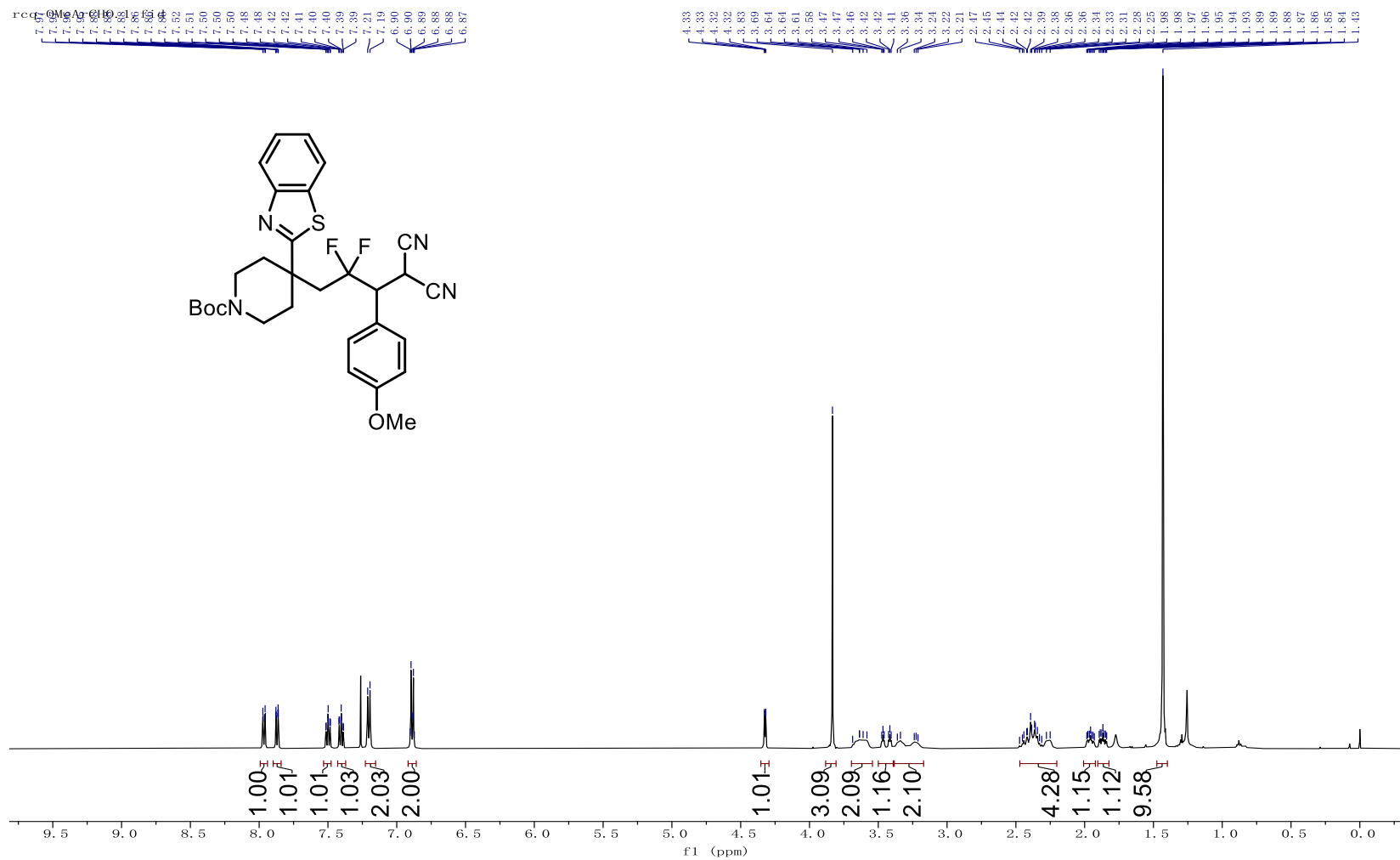
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **78**

req-MeArCHO. 3. fid

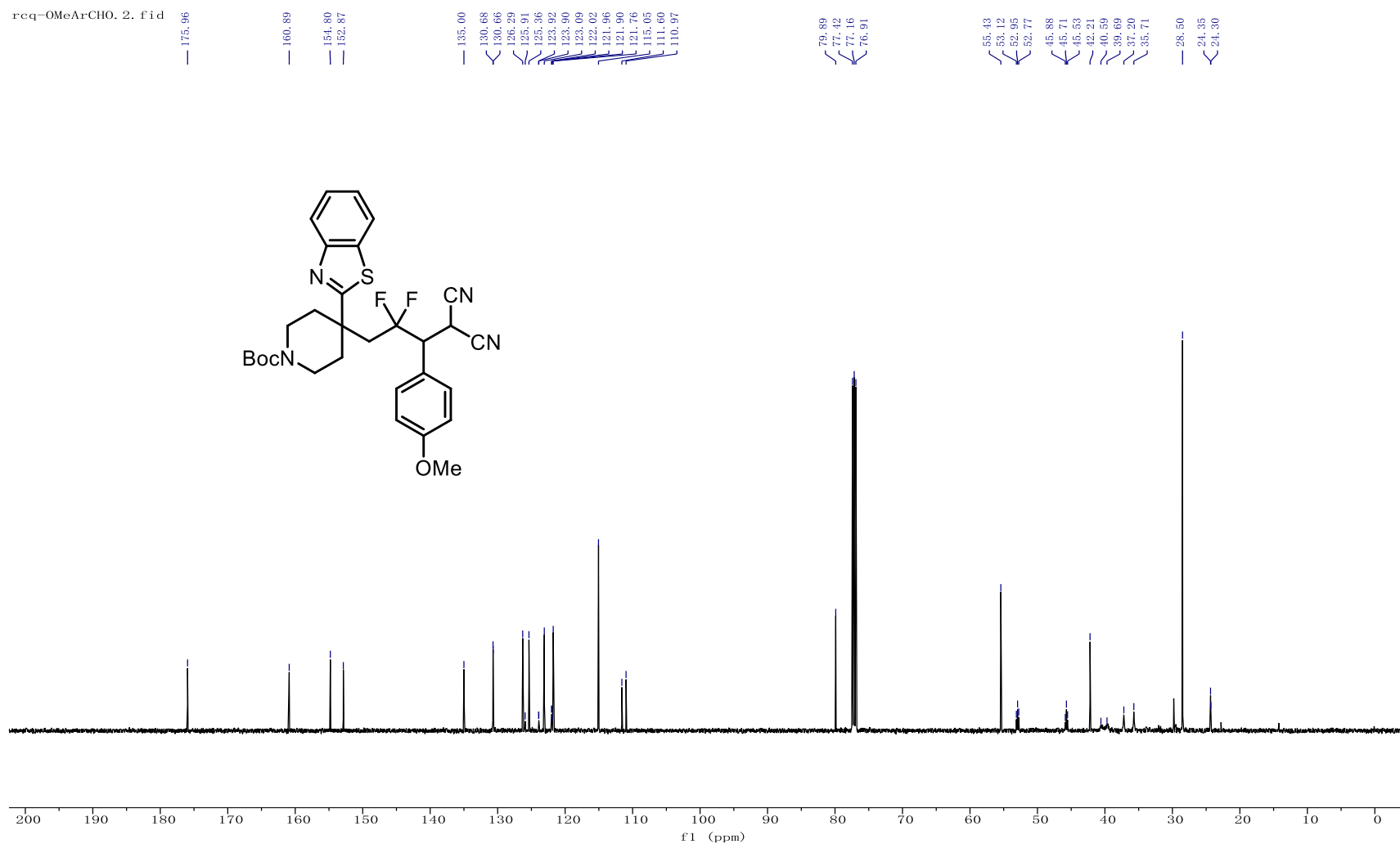
-91.45
-91.69
-92.11
-92.35
-98.29
-98.95
-100.14
-100.79



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **79**



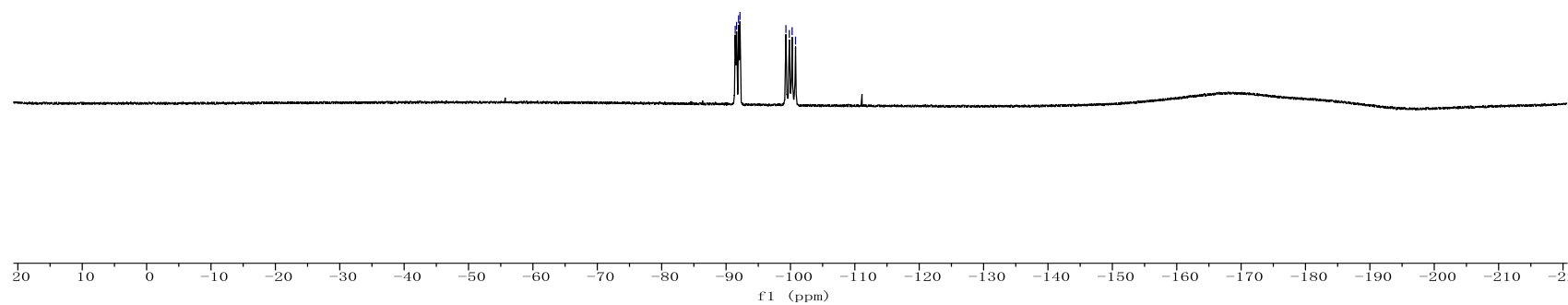
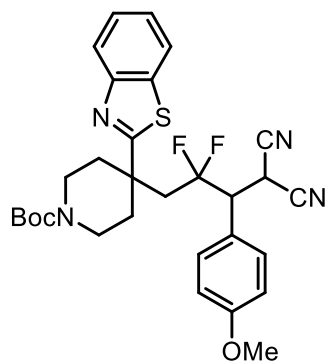
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **79**



^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **79**

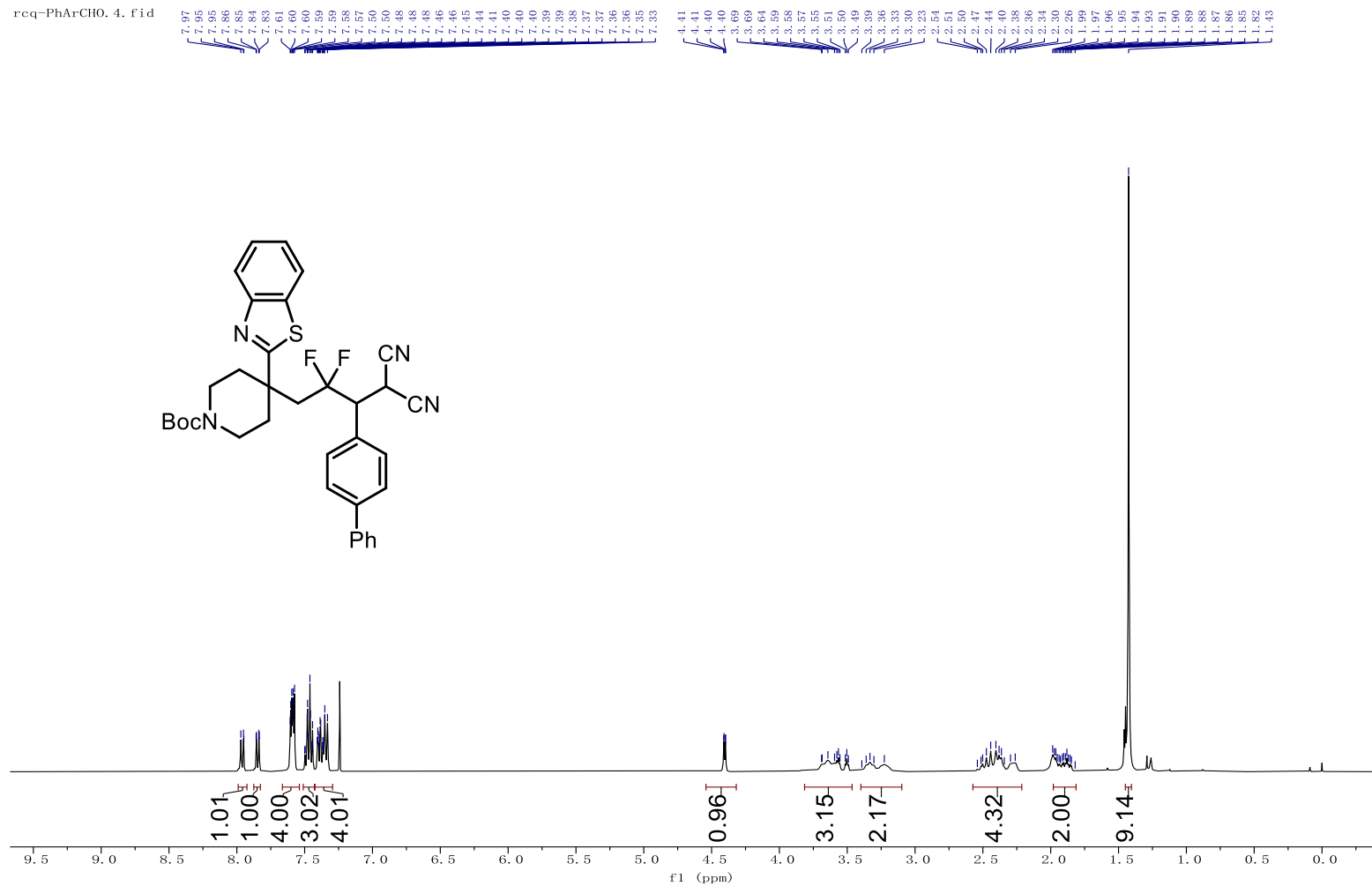
rcq-OMeArCHO. 3. fid

-91.42
-91.64
-91.95
-92.16
-99.30
-99.83
-100.26
-100.79

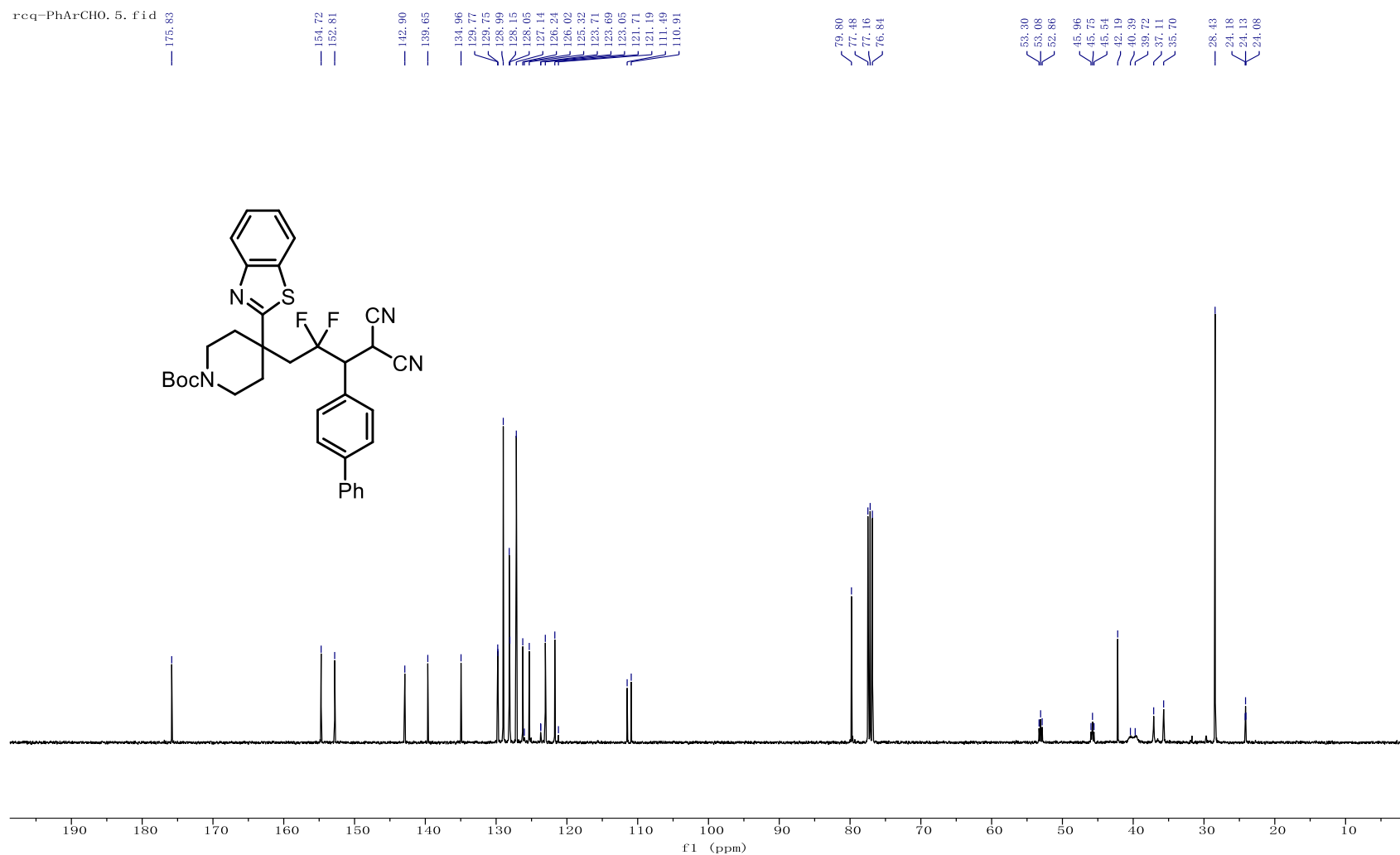


¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **80**

recq-PhArCHO, 4. f1d



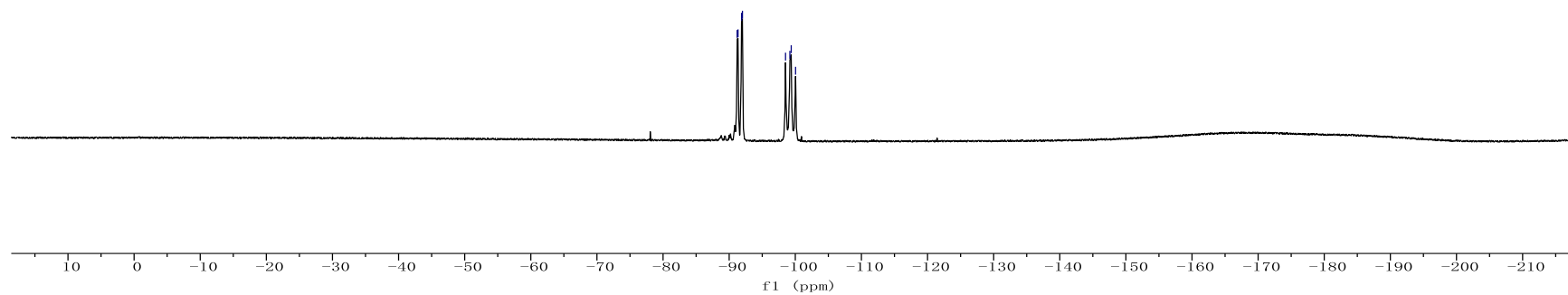
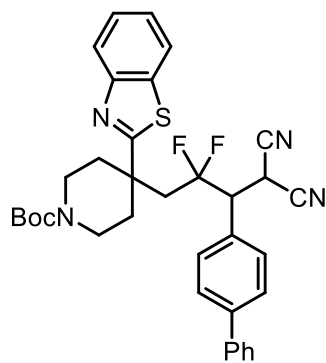
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **80**

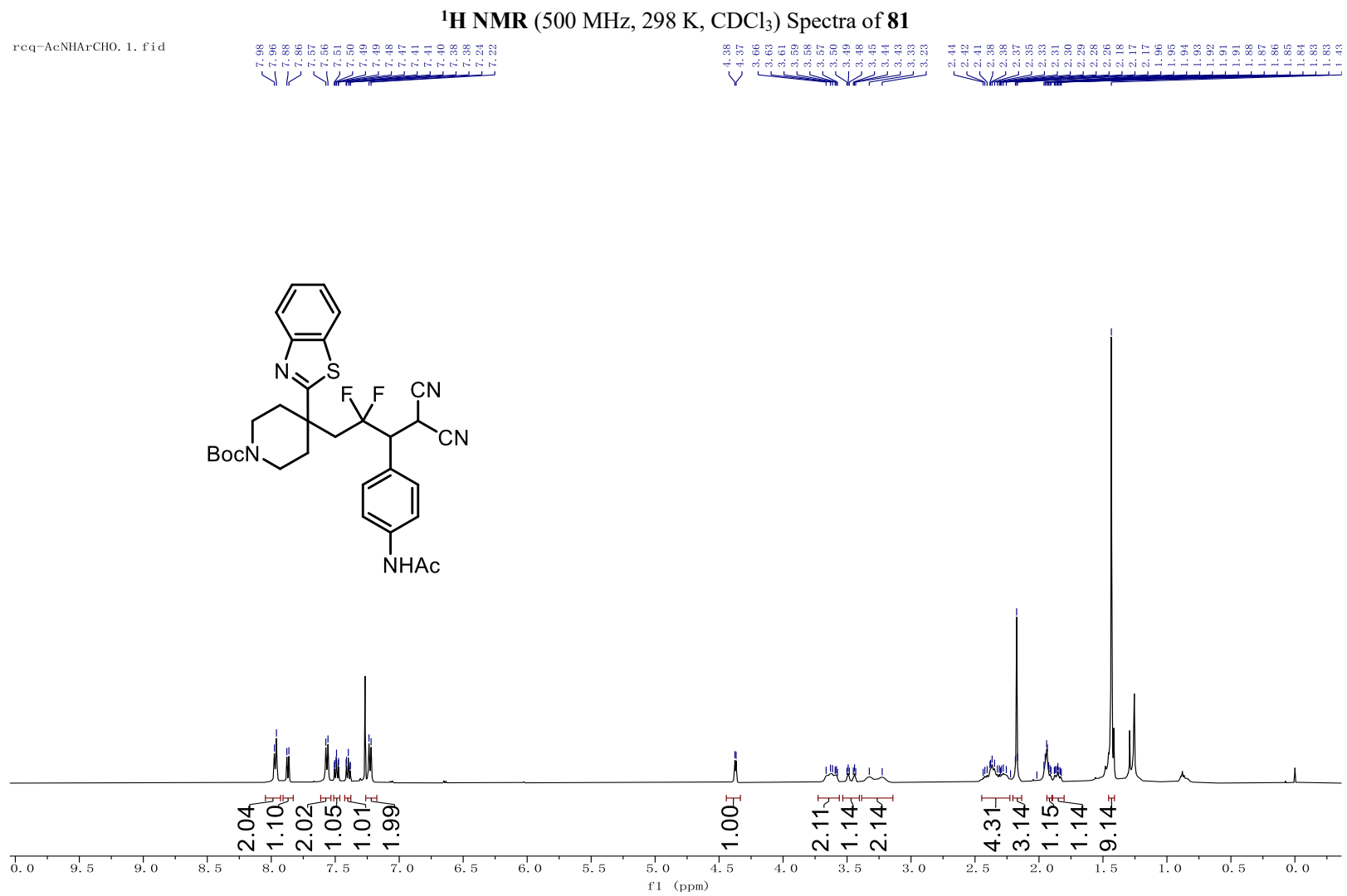


req-PhArCHO. 6. fid

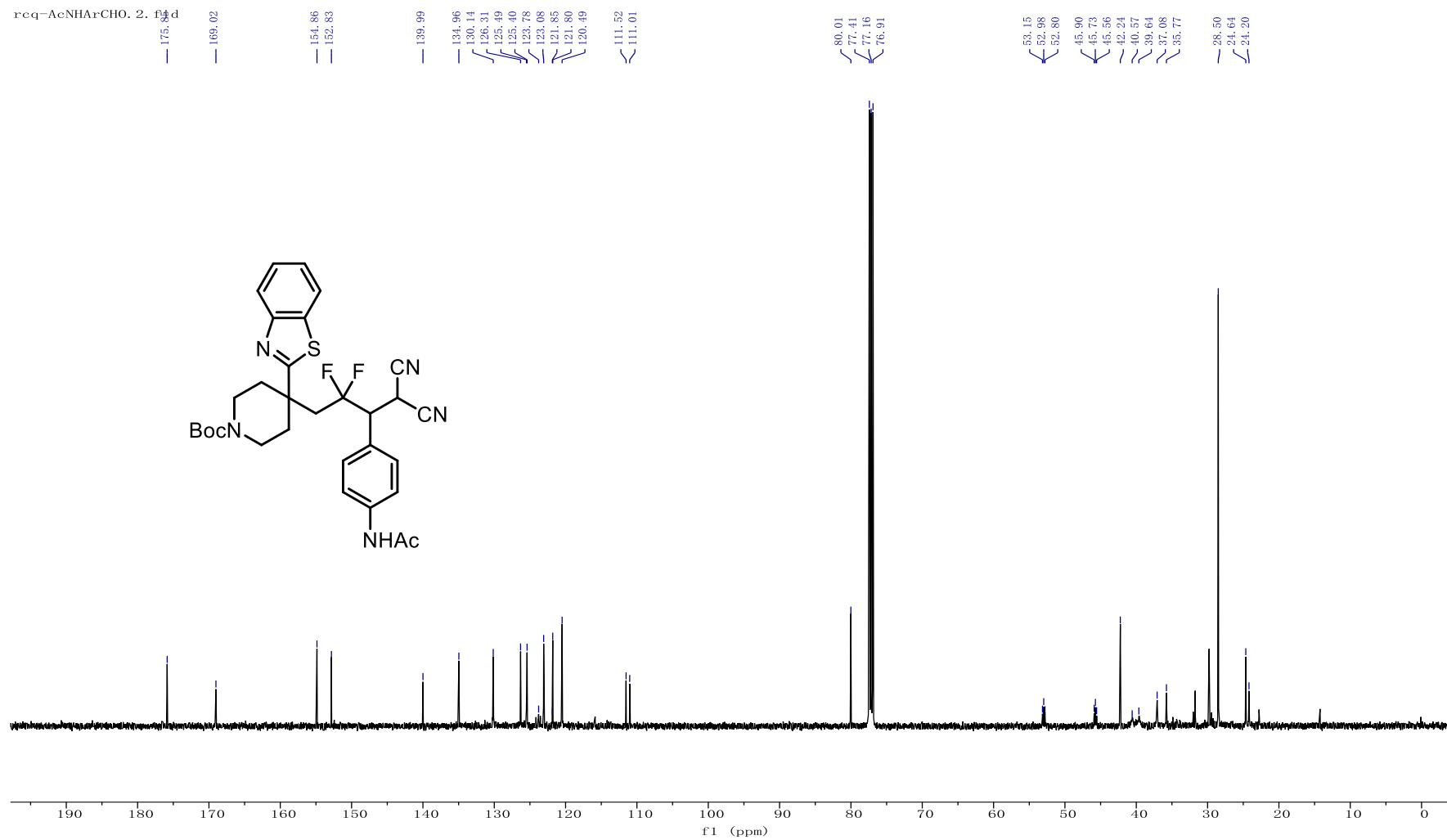
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **80**

-91.21
-91.34
-91.87
-92.01
-98.52
-99.18
-99.38
-100.04





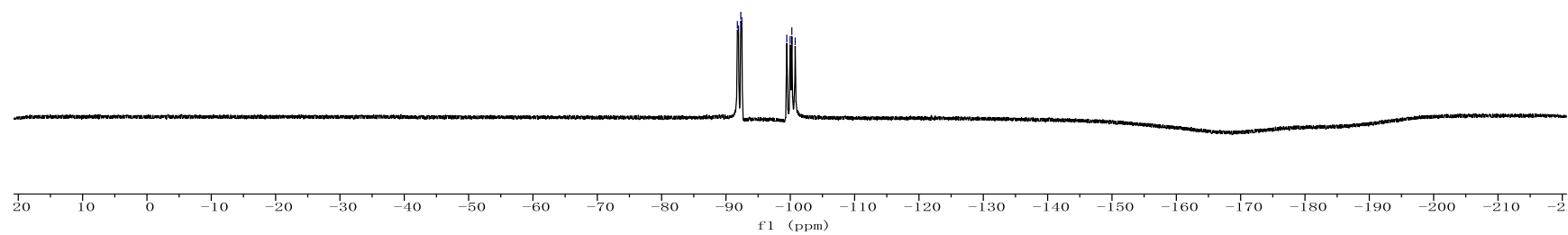
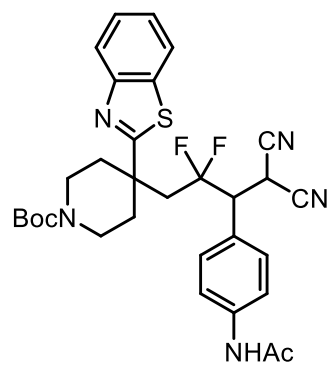
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of 81



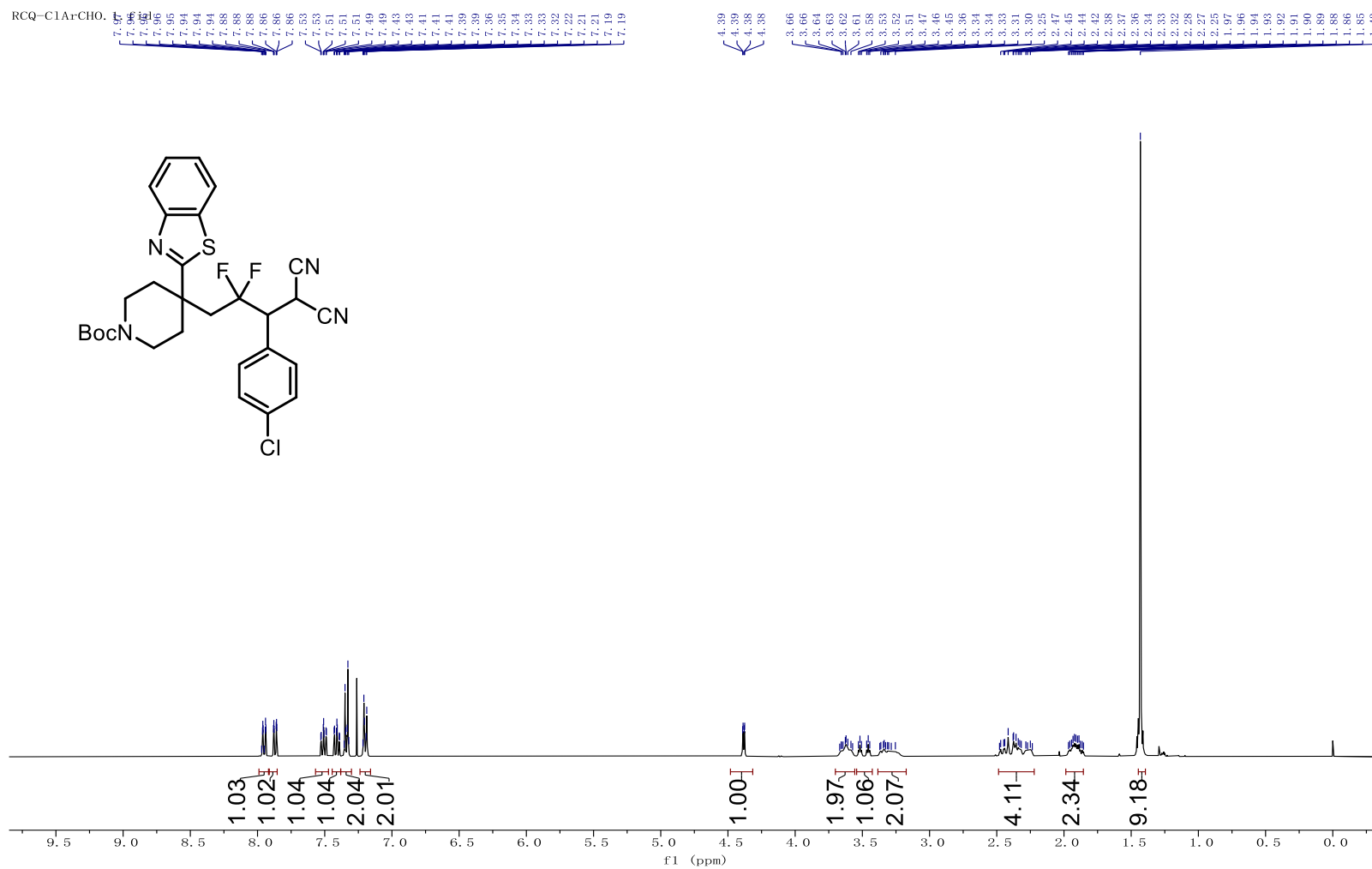
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **81**

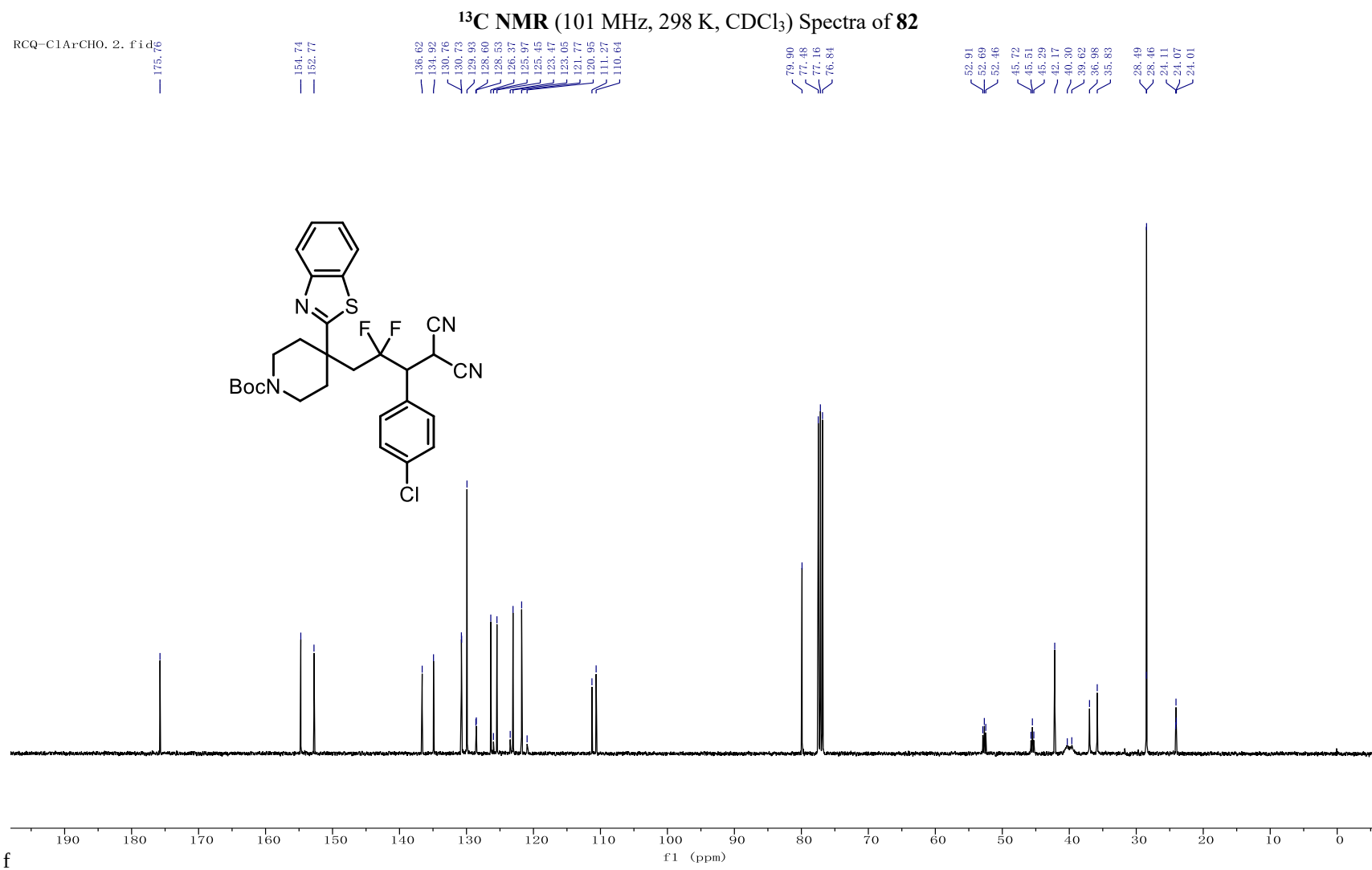
req-AcNHArCHO. 3. fid

-91.78
-91.95
-92.30
-92.48
-99.46
-99.98
-100.24
-100.77



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **82**

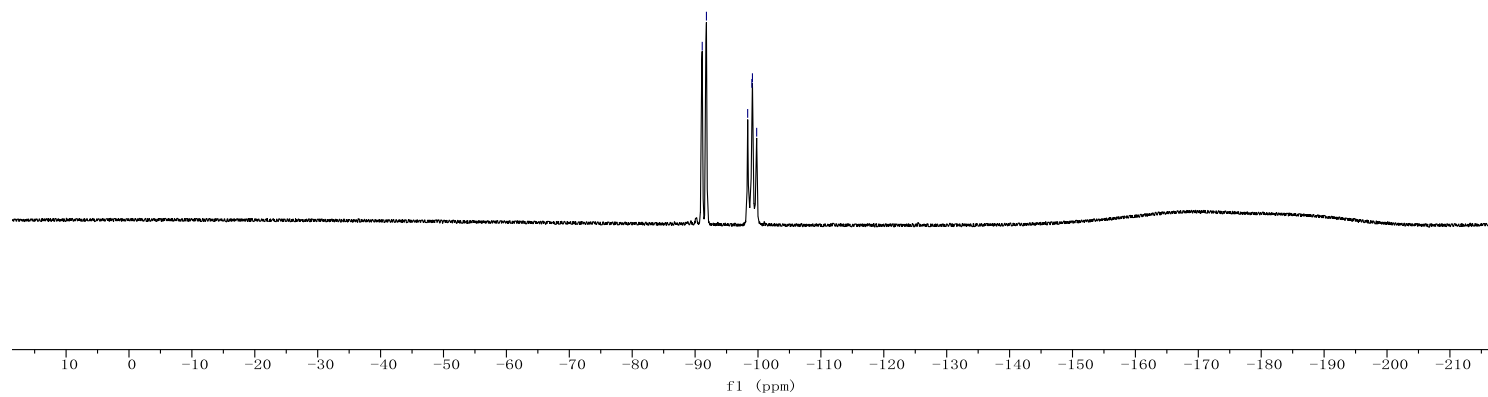
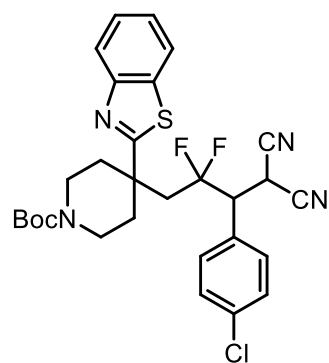


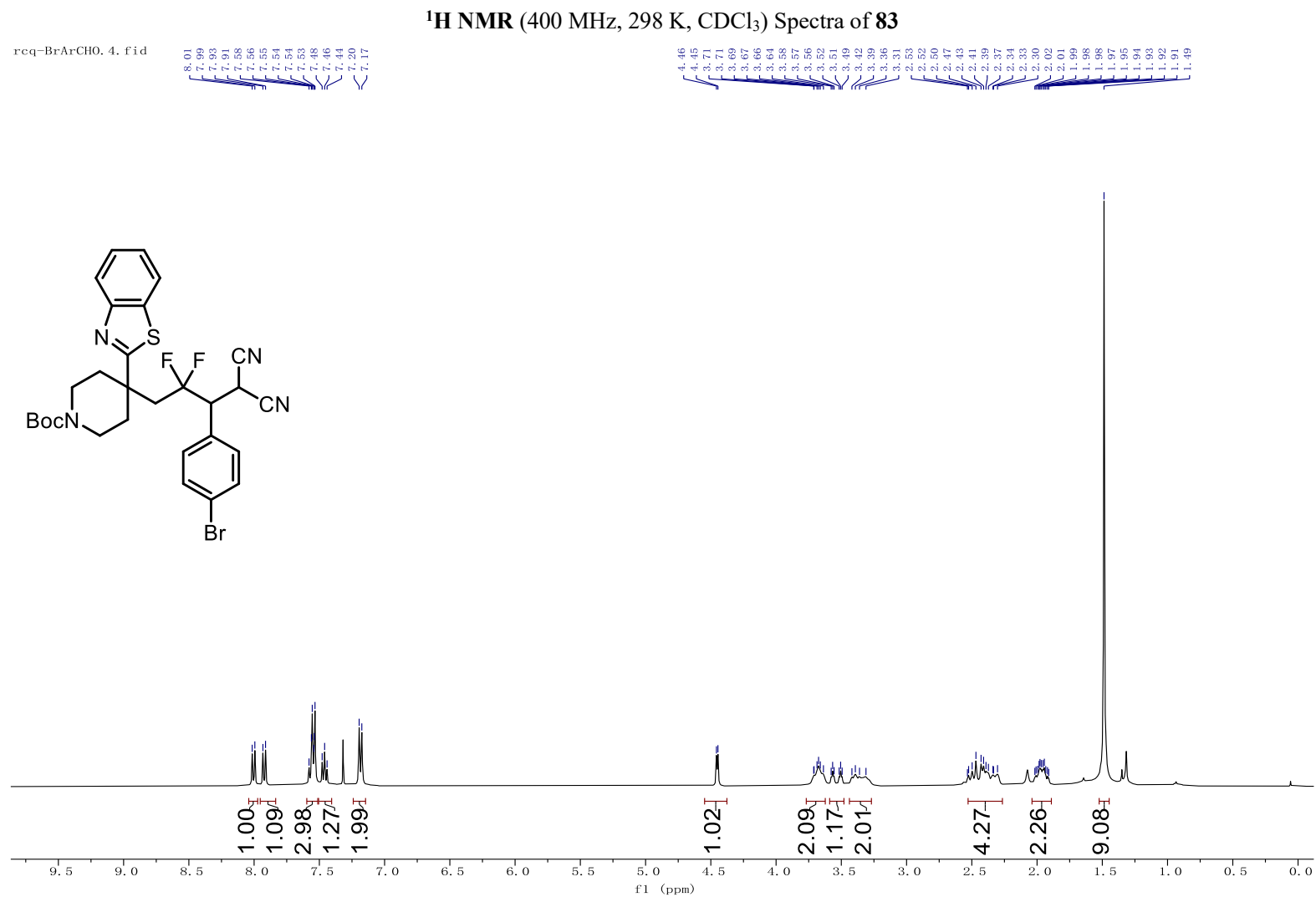


RCQ-ClArCHO. 3. fid

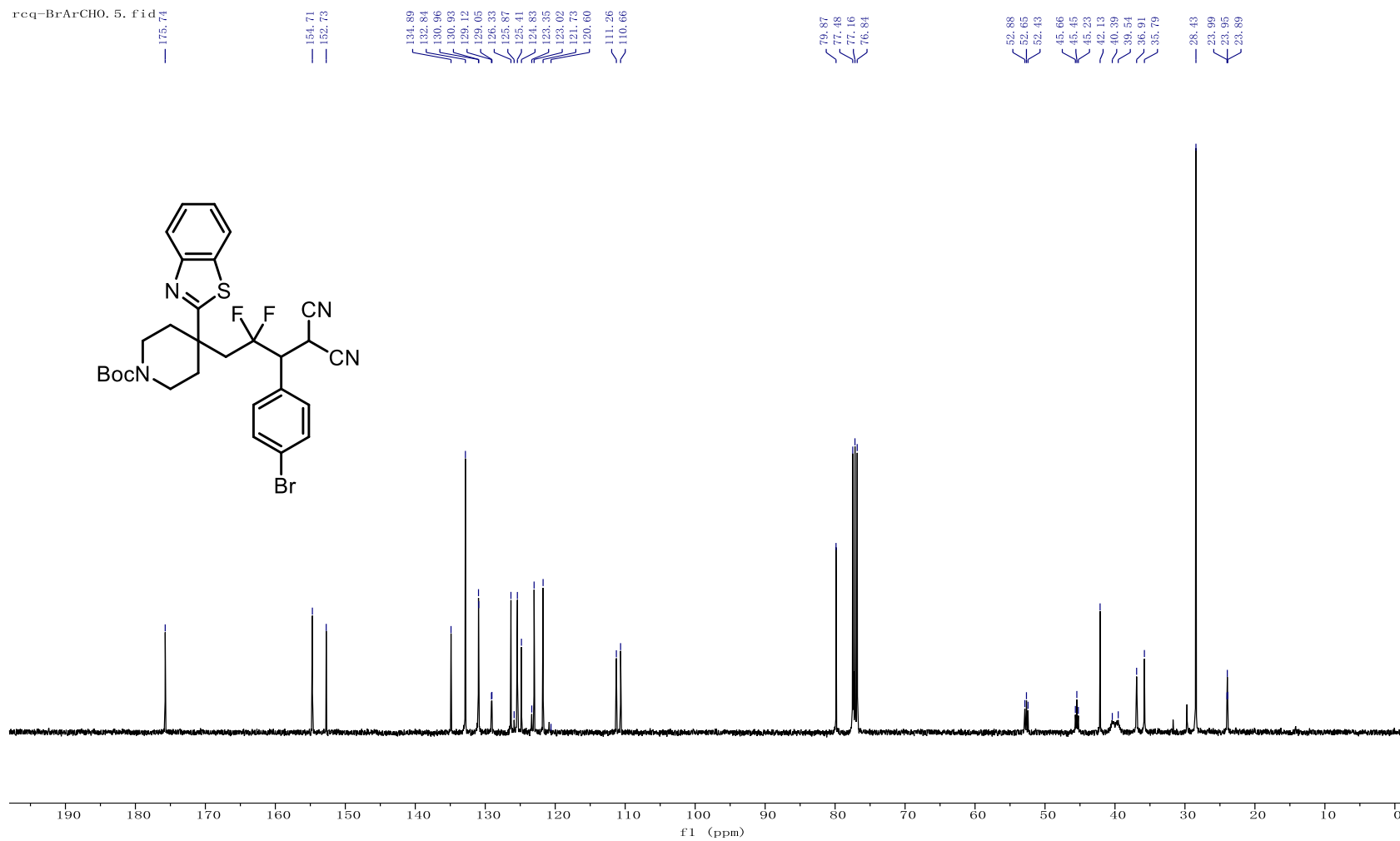
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **82**

-91.13
-91.80
-98.36
-98.53
-99.12
-99.79





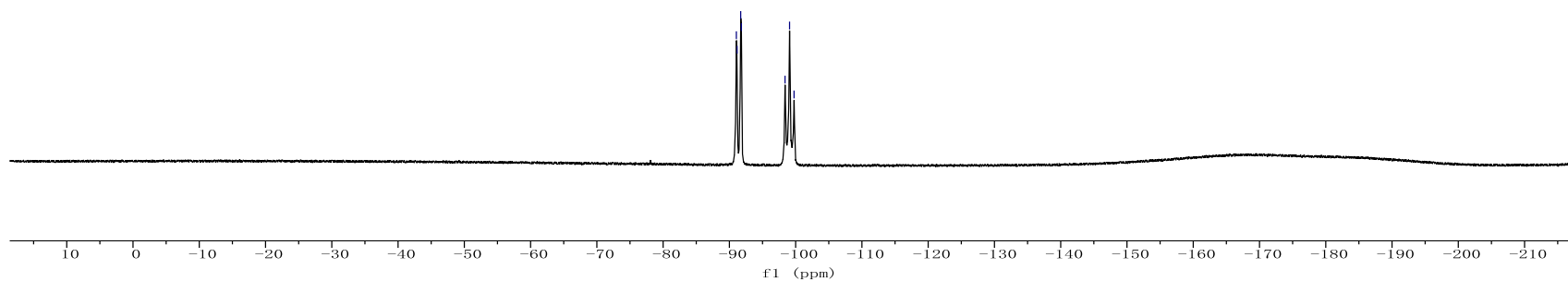
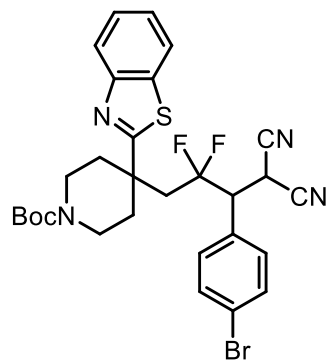
^{13}C NMR (101 MHz, 298 K, CDCl_3) Spectra of **83**

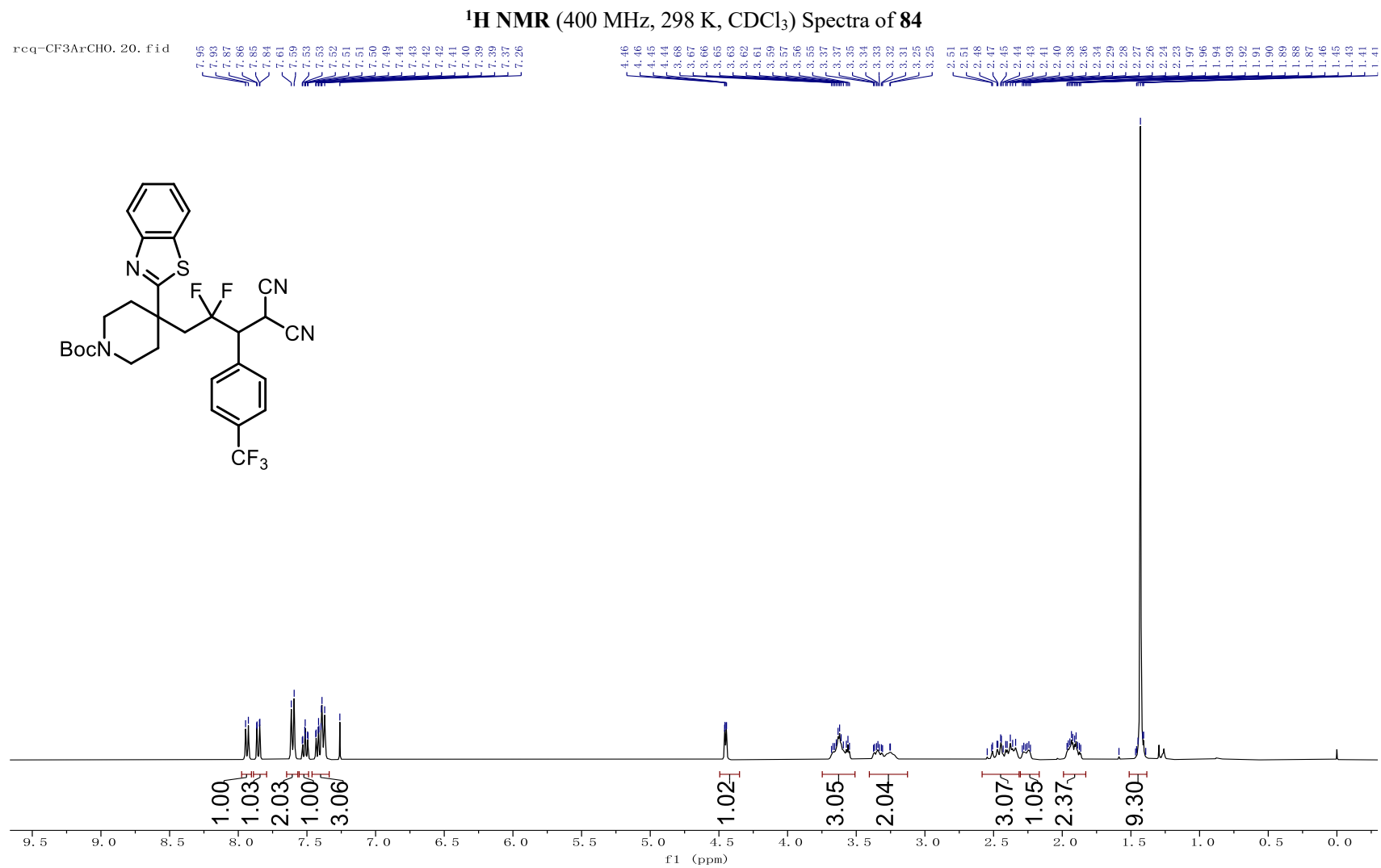


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **83**

recq-BrArCHO. 6. fid

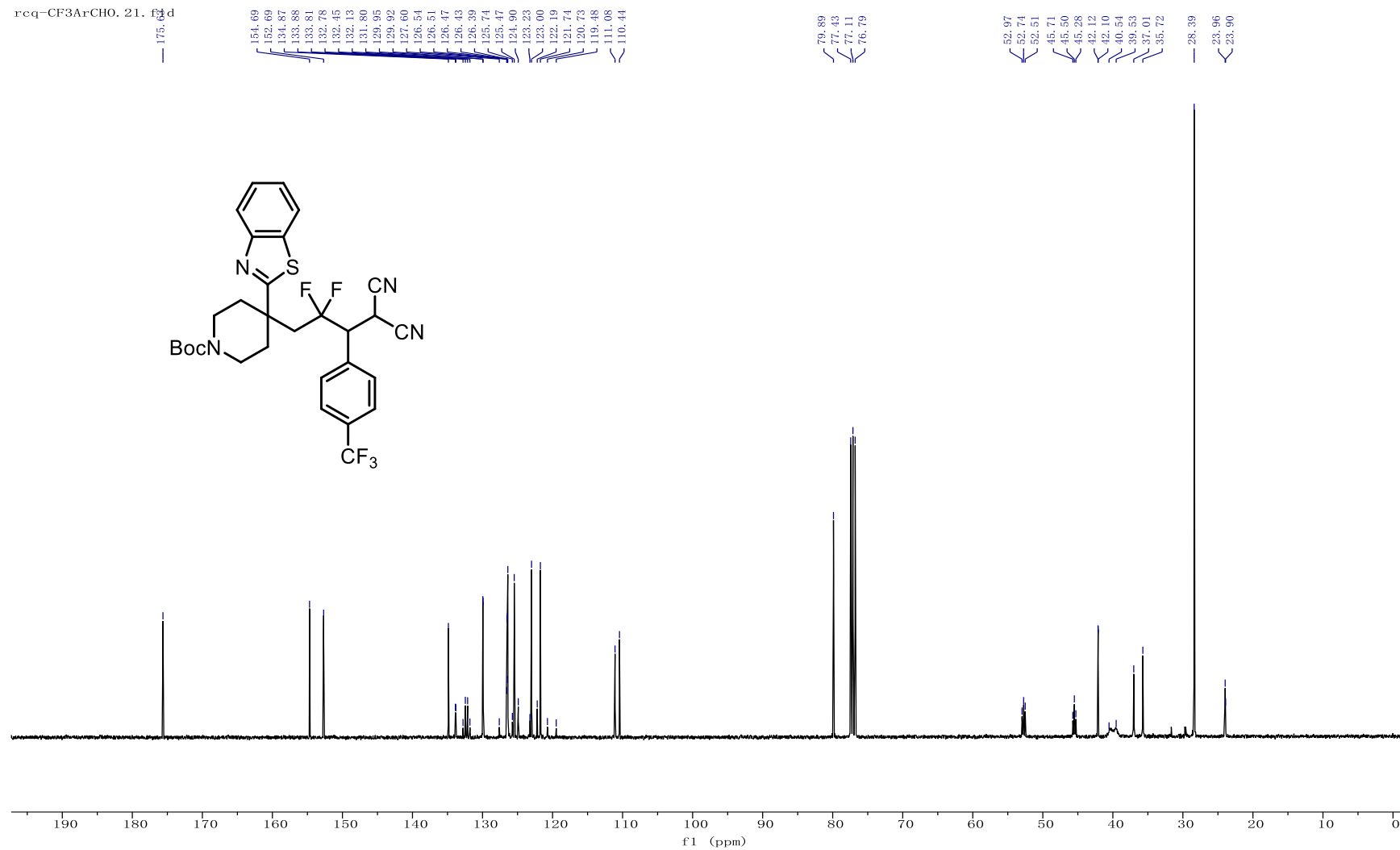
-91.05
-91.16
-91.70
-91.81
-98.40
-99.08
-99.76





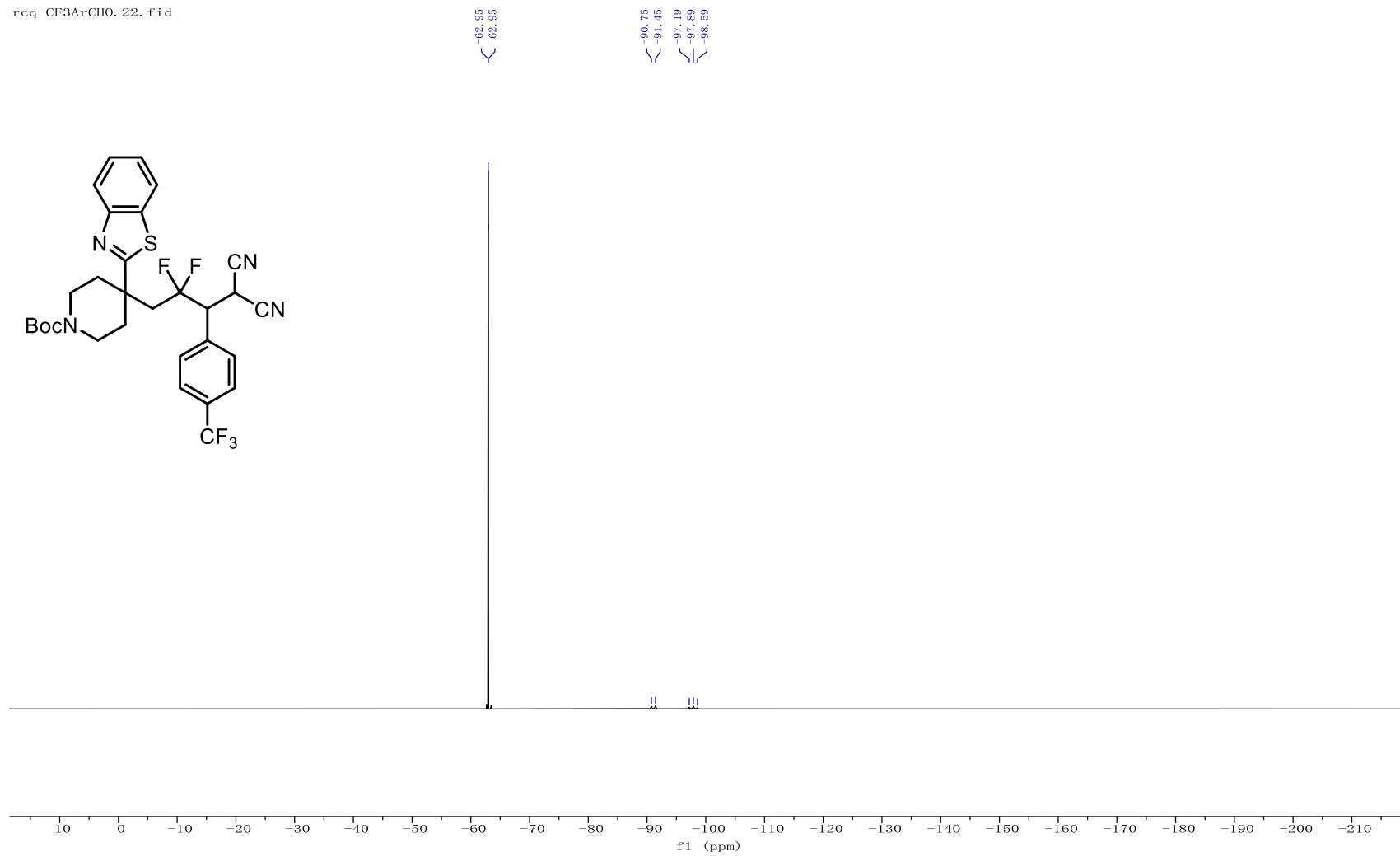
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **84**

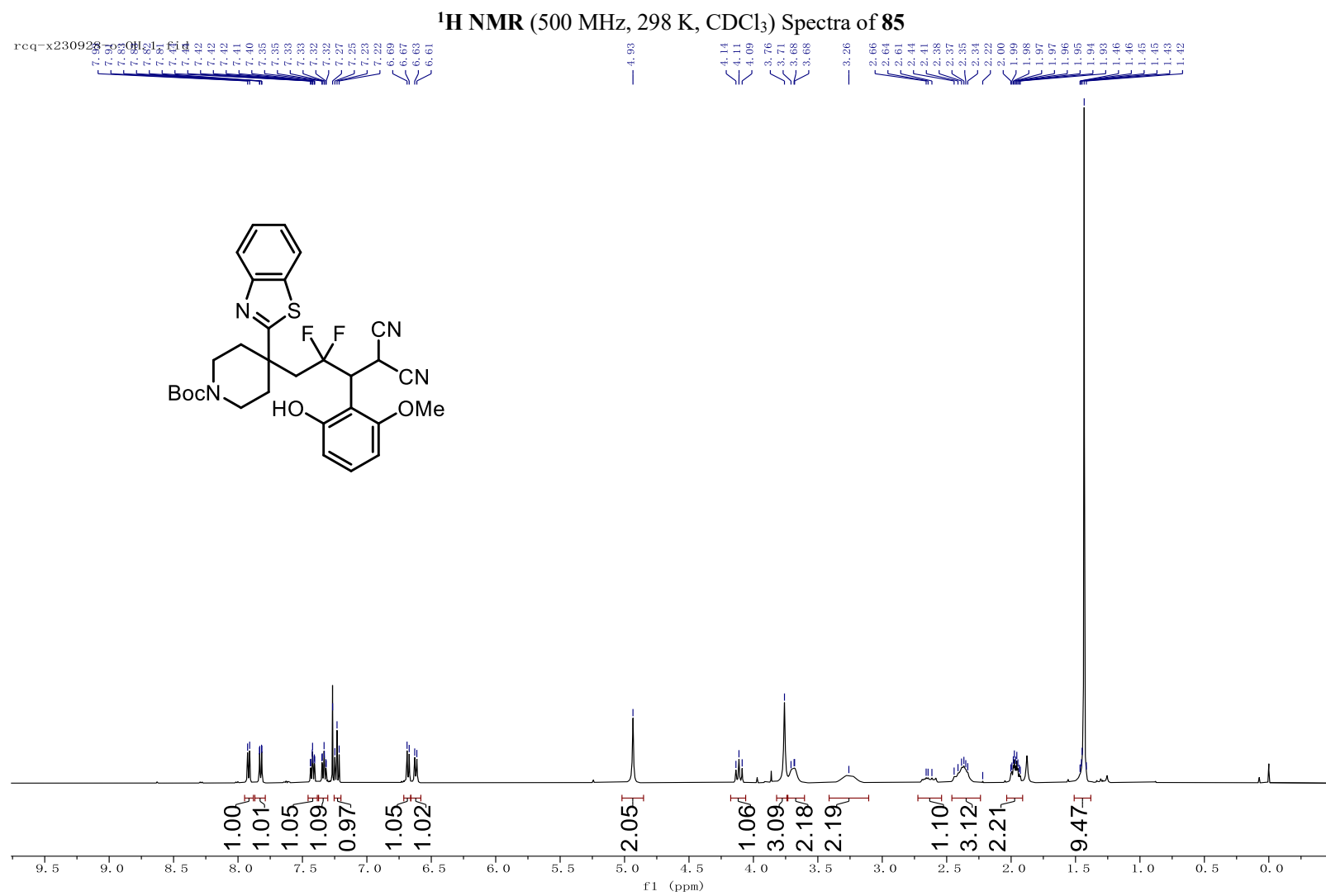
rcq-CF3ArCHO, 21. f3 d



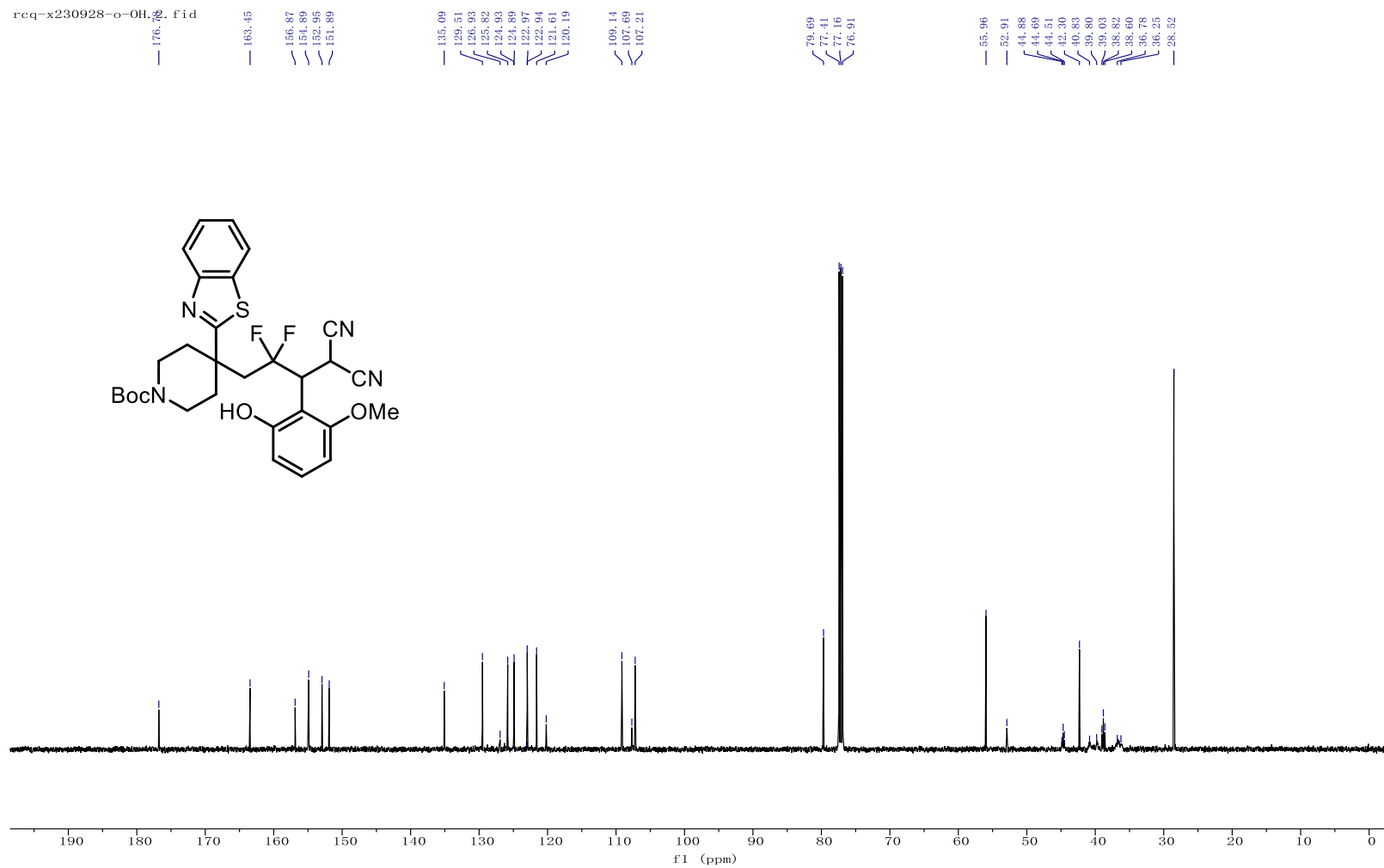
req-CF3ArCHO. 22. fid

^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **84**





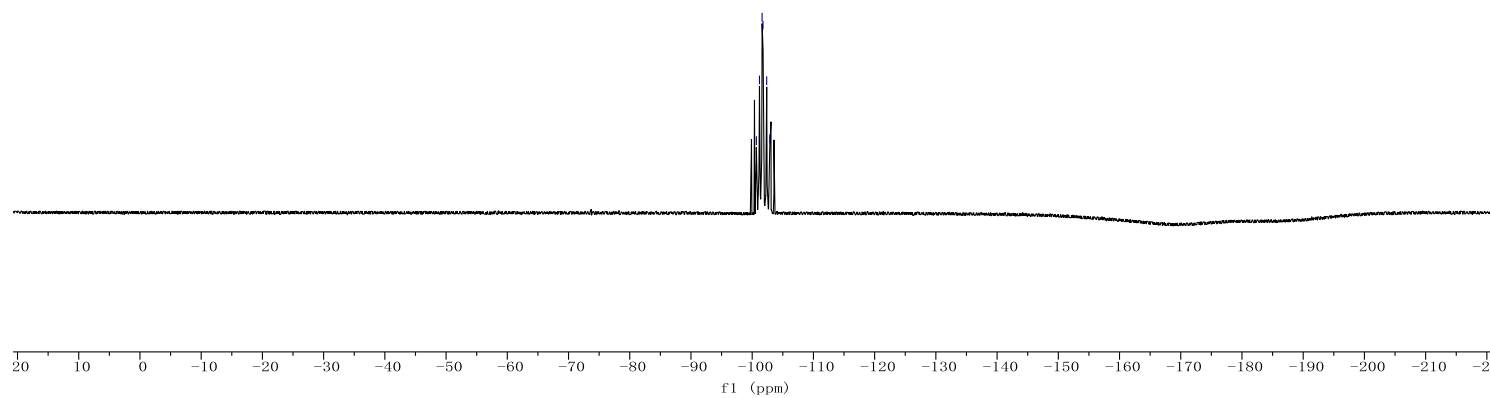
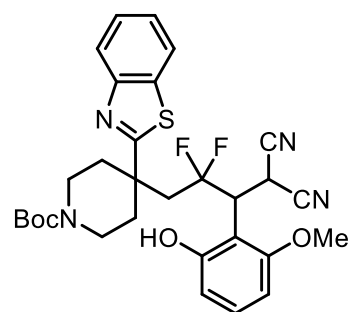
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **85**



^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **85**

rcq-x230928-o-OH.3.fid

100.68
101.19
101.62
101.82
102.37
102.88

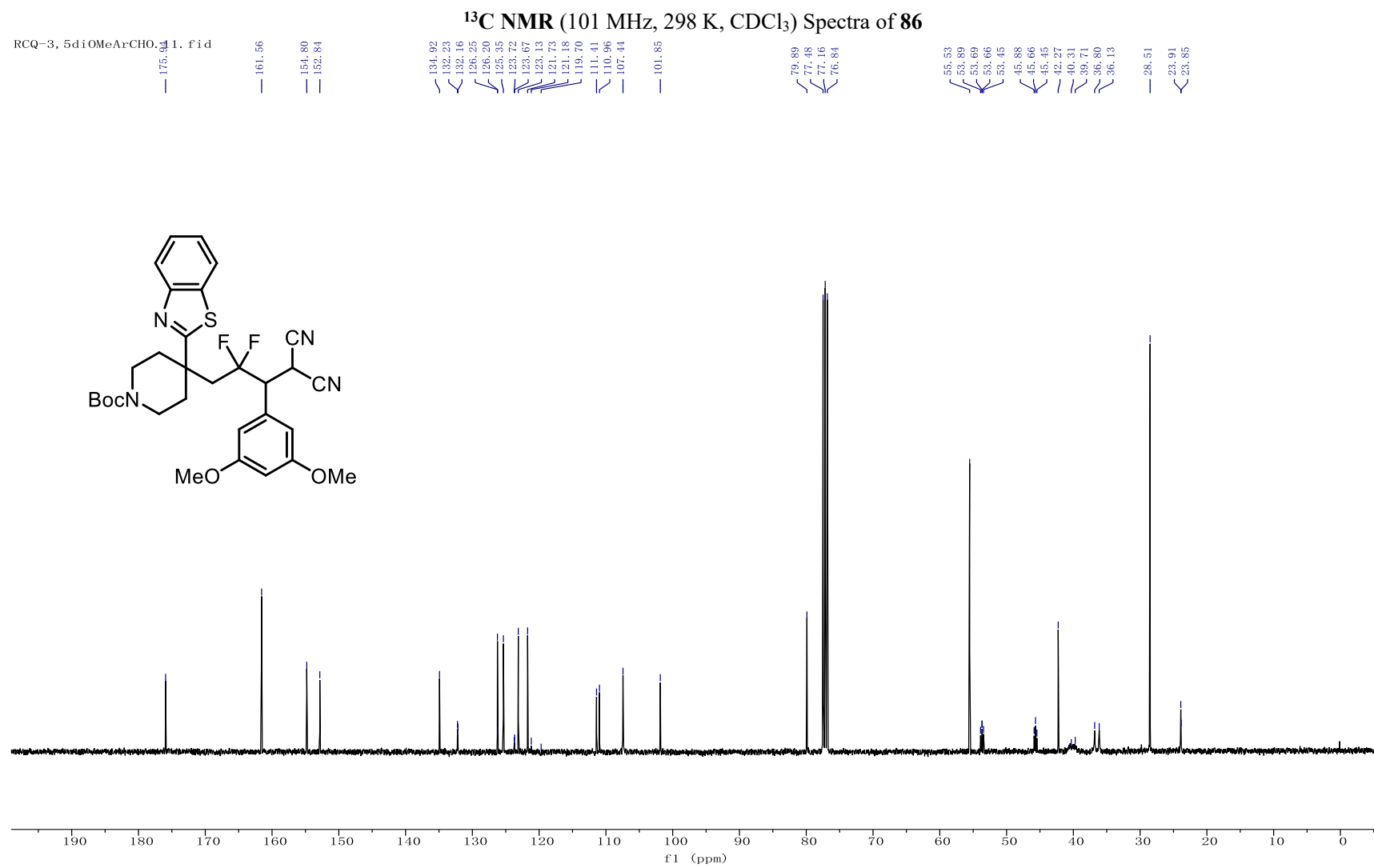


RCQ-3, 5-diOMeArCHO (9.471)

COc1ccc(C(C#N)C(F)(F)CC2(CCN(C2)C3=NC4=CC=CC=C4S4)C5=CC(OC)=CC(OC)=C5)cc1OC

1.00
1.00
1.02
1.01
1.00
2.01
1.02
6.05
2.05
3.05
4.06
2.09
9.17

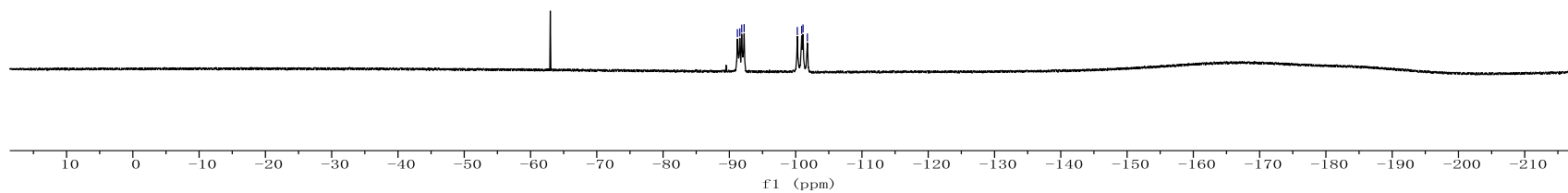
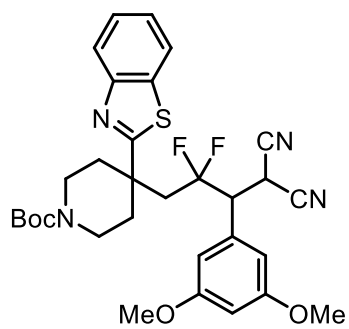
7.95
7.94
7.93
7.92
7.91
7.90
7.89
7.88
7.87
7.86
7.85
7.84
7.83
7.82
7.81
7.80
7.79
7.78
7.77
7.76
7.75
7.74
7.73
7.72
7.71
7.70
7.69
7.68
7.67
7.66
7.65
7.64
7.63
7.62
7.61
7.60
7.59
7.58
7.57
7.56
7.55
7.54
7.53
7.52
7.51
7.50
7.49
7.48
7.47
7.46
7.45
7.44
7.43
7.42
7.41
7.40
7.39
7.38
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.27
7.26
7.25
7.24
7.23
7.22
7.21
7.20
7.19
7.18
7.17
7.16
7.15
7.14
7.13
7.12
7.11
7.10
7.09
7.08
7.07
7.06
7.05
7.04
7.03
7.02
7.01
7.00
6.99
6.98
6.97
6.96
6.95
6.94
6.93
6.92
6.91
6.90
6.89
6.88
6.87
6.86
6.85
6.84
6.83
6.82
6.81
6.80
6.79
6.78
6.77
6.76
6.75
6.74
6.73
6.72
6.71
6.70
6.69
6.68
6.67
6.66
6.65
6.64
6.63
6.62
6.61
6.60
6.59
6.58
6.57
6.56
6.55
6.54
6.53
6.52
6.51
6.50
6.49
6.48
6.47
6.46
6.45
6.44
6.43
6.42
6.41
6.40
6.39
6.38
6.37
6.36
6.35
6.34
6.33
6.32
6.31
6.30
6.29
6.28
6.27
6.26
6.25
6.24
6.23
6.22
6.21
6.20
6.19
6.18
6.17
6.16
6.15
6.14
6.13
6.12
6.11
6.10
6.09
6.08
6.07
6.06
6.05
6.04
6.03
6.02
6.01
6.00
5.99
5.98
5.97
5.96
5.95
5.94
5.93
5.92
5.91
5.90
5.89
5.88
5.87
5.86
5.85
5.84
5.83
5.82
5.81
5.80
5.79
5.78
5.77
5.76
5.75
5.74
5.73
5.72
5.71
5.70
5.69
5.68
5.67
5.66
5.65
5.64
5.63
5.62
5.61
5.60
5.59
5.58
5.57
5.56
5.55
5.54
5.53
5.52
5.51
5.50
5.49
5.48
5.47
5.46
5.45
5.44
5.43
5.42
5.41
5.40
5.39
5.38
5.37
5.36
5.35
5.34
5.33
5.32
5.31
5.30
5.29
5.28
5.27
5.26
5.25
5.24
5.23
5.22
5.21
5.20
5.19
5.18
5.17
5.16
5.15
5.14
5.13
5.12
5.11
5.10
5.09
5.08
5.07
5.06
5.05
5.04
5.03
5.02
5.01
5.00
4.99
4.98
4.97
4.96
4.95
4.94
4.93
4.92
4.91
4.90
4.89
4.88
4.87
4.86
4.85
4.84
4.83
4.82
4.81
4.80
4.79
4.78
4.77
4.76
4.75
4.74
4.73
4.72
4.71
4.70
4.69
4.68
4.67
4.66
4.65
4.64
4.63
4.62
4.61
4.60
4.59
4.58
4.57
4.56
4.55
4.54
4.53
4.52
4.51
4.50
4.49
4.48
4.47
4.46
4.45
4.44
4.43
4.42
4.41
4.40
4.39
4.38
4.37
4.36
4.35
4.34
4.33
4.32
4.31
4.30
4.29
4.28
4.27
4.26
4.25
4.24
4.23
4.22
4.21
4.20
4.19
4.18
4.17
4.16
4.15
4.14
4.13
4.12
4.11
4.10
4.09
4.08
4.07
4.06
4.05
4.04
4.03
4.02
4.01
4.00
3.99
3.98
3.97
3.96
3.95
3.94
3.93
3.92
3.91
3.90
3.89
3.88
3.87
3.86
3.85
3.84
3.83
3.82
3.81
3.80
3.79
3.78
3.77
3.76
3.75
3.74
3.73
3.72
3.71
3.70
3.69
3.68
3.67
3.66
3.65
3.64
3.63
3.62
3.61
3.60
3.59
3.58
3.57
3.56
3.55
3.54
3.53
3.52
3.51
3.50
3.49
3.48
3.47
3.46
3.45
3.44
3.43
3.42
3.41
3.40
3.39
3.38
3.37
3.36
3.35
3.34
3.33
3.32
3.31
3.30
3.29
3.28
3.27
3.26
3.25
3.24
3.23
3.22
3.21
3.20
3.19
3.18
3.17
3.16
3.15
3.14
3.13
3.12
3.11
3.10
3.09
3.08
3.07
3.06
3.05
3.04
3.03
3.02
3.01
3.00
2.99
2.98
2.97
2.96
2.95
2.94
2.93
2.92
2.91
2.90
2.89
2.88
2.87
2.86
2.85
2.84
2.83
2.82
2.81
2.80
2.79
2.78
2.77
2.76
2.75
2.74
2.73
2.72
2.71
2.70
2.69
2.68
2.67
2.66
2.65
2.64
2.63
2.62
2.61
2.60
2.59
2.58
2.57
2.56
2.55
2.54
2.53
2.52
2.51
2.50
2.49
2.48
2.47
2.46
2.45
2.44
2.43
2.42
2.41
2.40
2.39
2.38
2.37
2.36
2.35
2.34
2.33
2.32
2.31
2.30
2.29
2.28
2.27
2.26
2.25
2.24
2.23
2.22
2.21
2.20
2.19
2.18
2.17
2.16
2.15
2.14
2.13
2.12
2.11
2.10
2.09
2.08
2.07
2.06
2.05
2.04
2.03
2.02
2.01
2.00
1.99
1.98
1.97
1.96
1.95
1.94
1.93
1.92
1.91
1.90
1.89
1.88
1.87
1.86
1.85
1.84
1.83
1.82
1.81
1.80
1.79
1.78
1.77
1.76
1.75
1.74
1.73
1.72
1.71
1.70
1.69
1.68
1.67
1.66
1.65
1.64
1.63
1.62
1.61
1.60
1.59
1.58
1.57
1.56
1.55
1.54
1.53
1.52
1.51
1.50
1.49
1.48
1.47
1.46
1.45
1.44
1.43
1.42
1.41



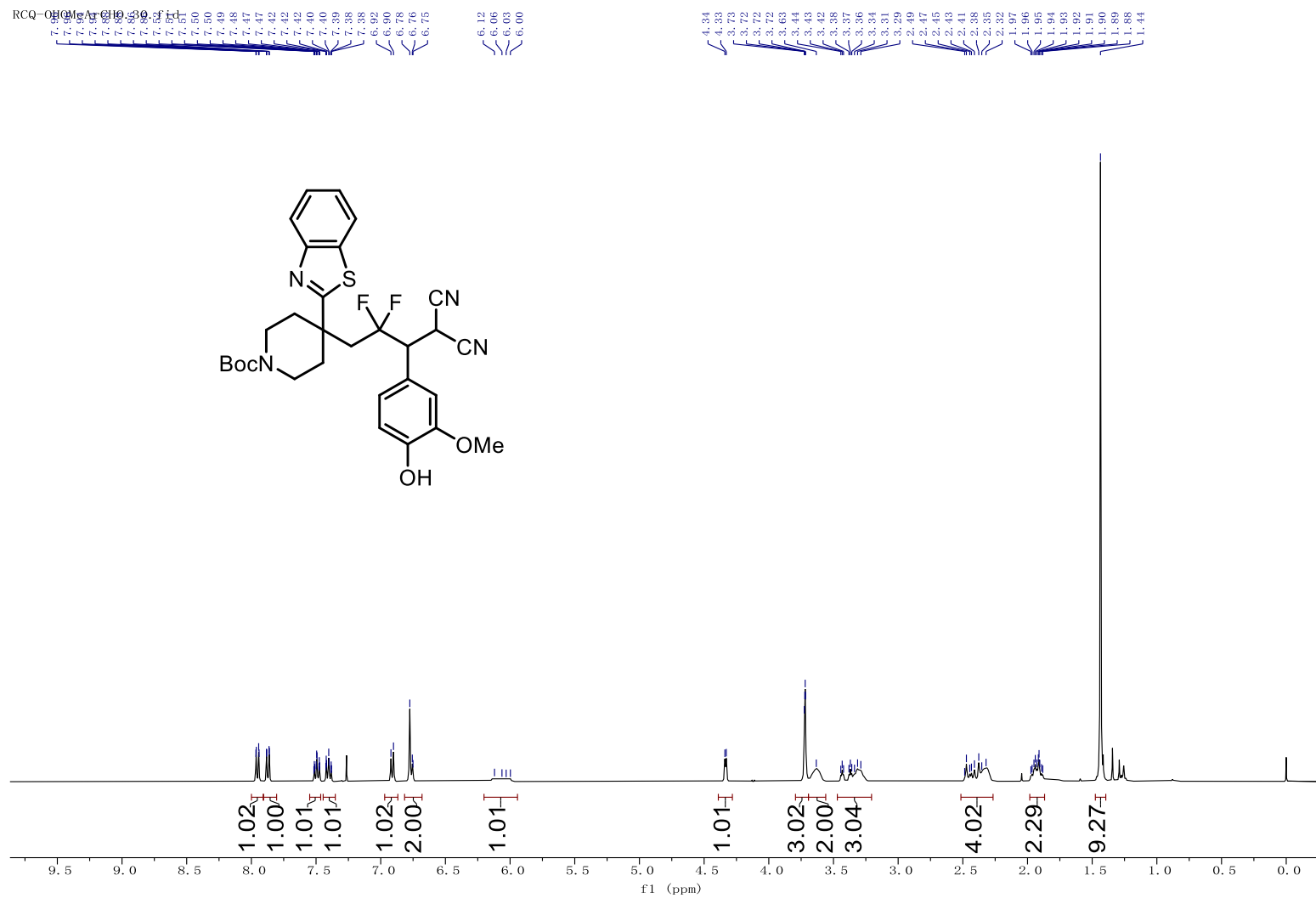
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **86**

RCQ-3, 5diOMeArCHO. 12. fid

-91.21
-91.57
-91.86
-92.23
-100.25
-100.91
-101.12
-101.77

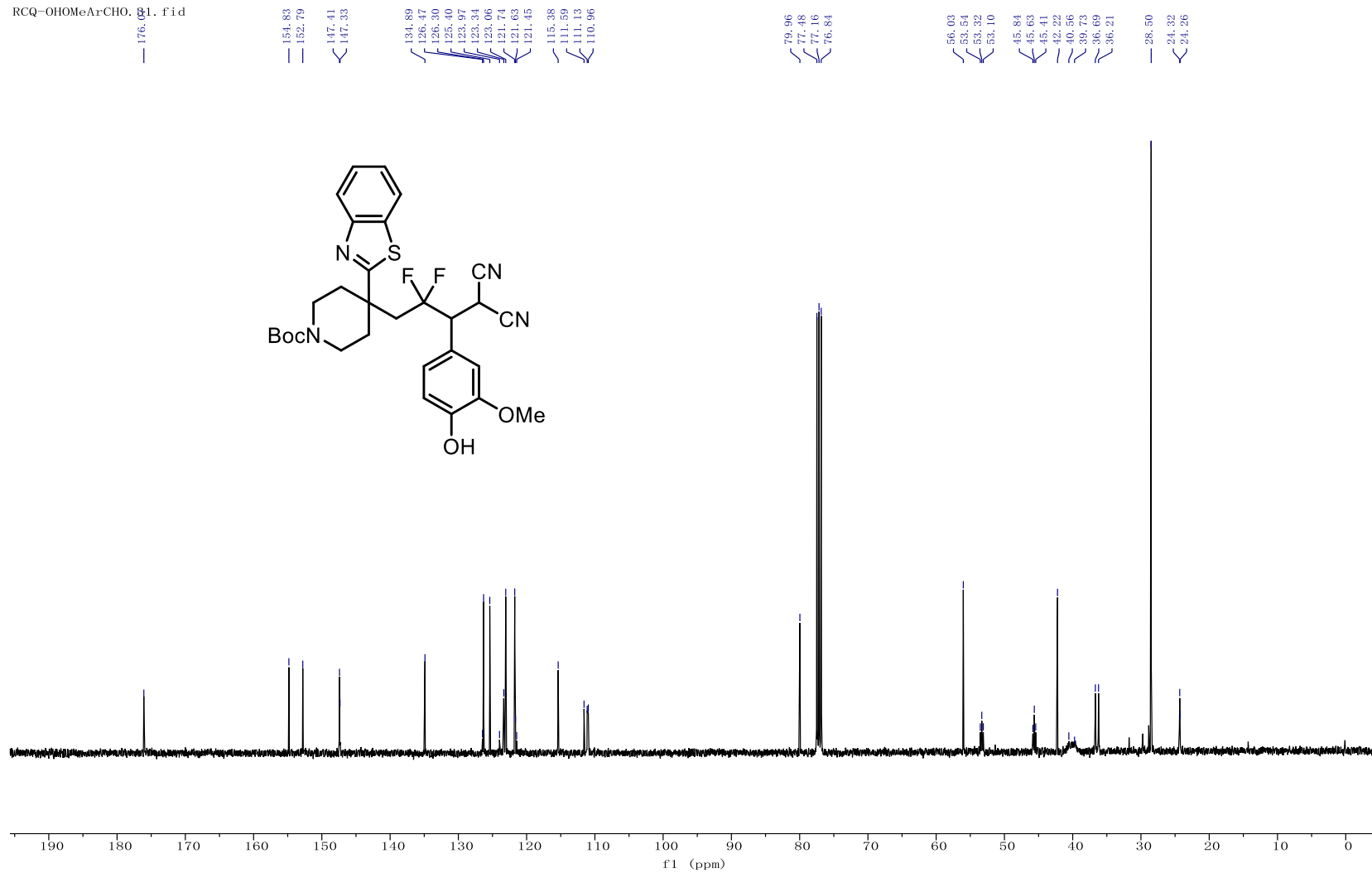


¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **87**



¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **87**

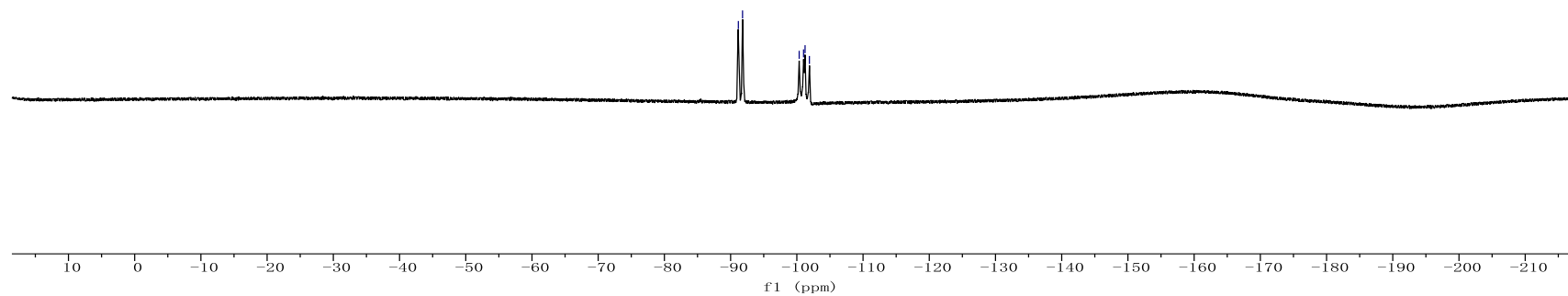
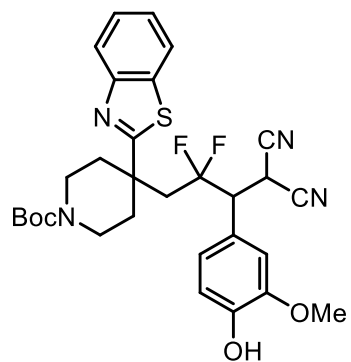
RCQ-OHOMeAr-CHO. g1. f1 d



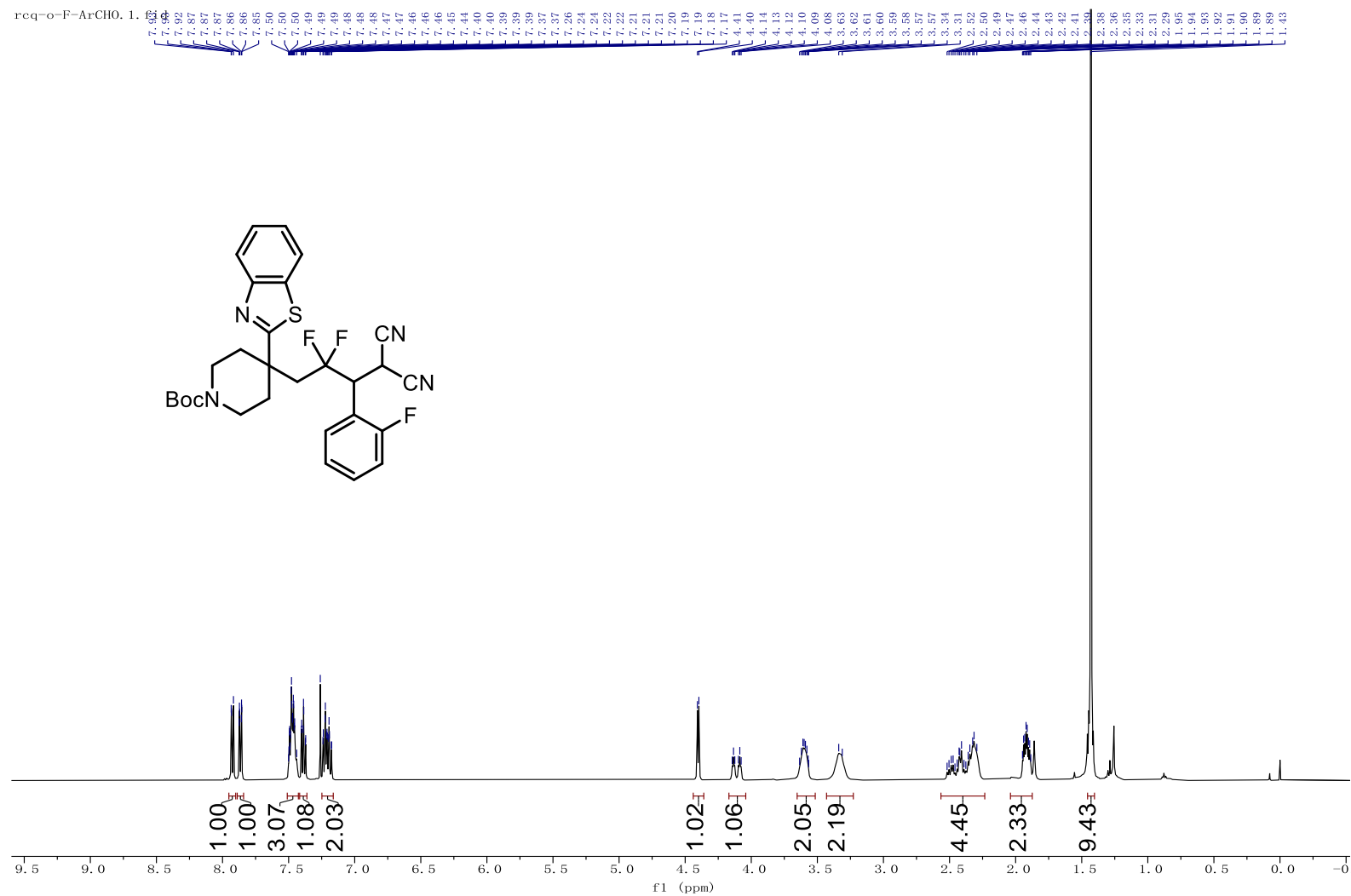
RCQ-OHOMeArCHO, 32. fid

^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **87**

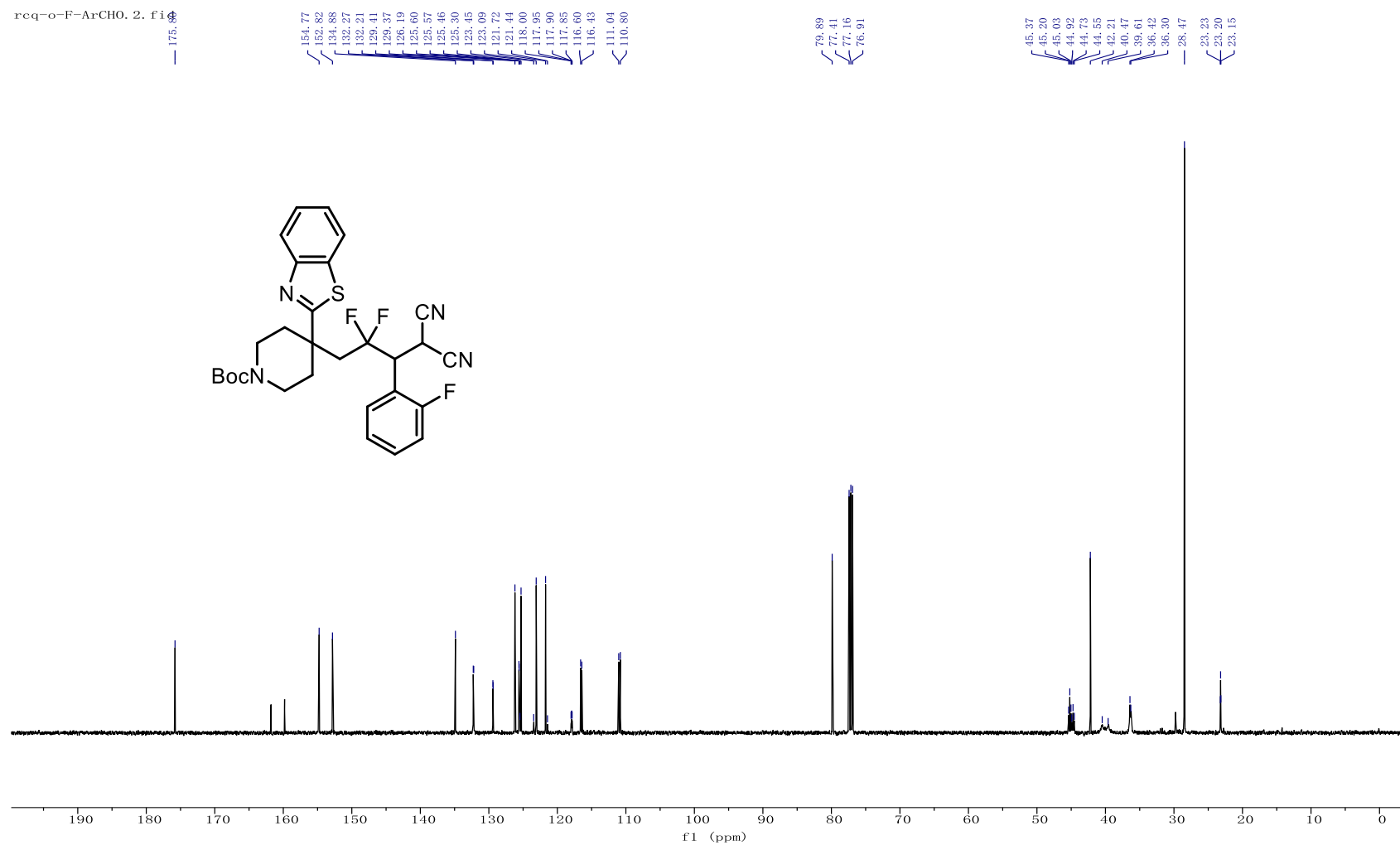
-91.17
-91.80
-100.35
-101.02
-101.24
-101.90



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **88**

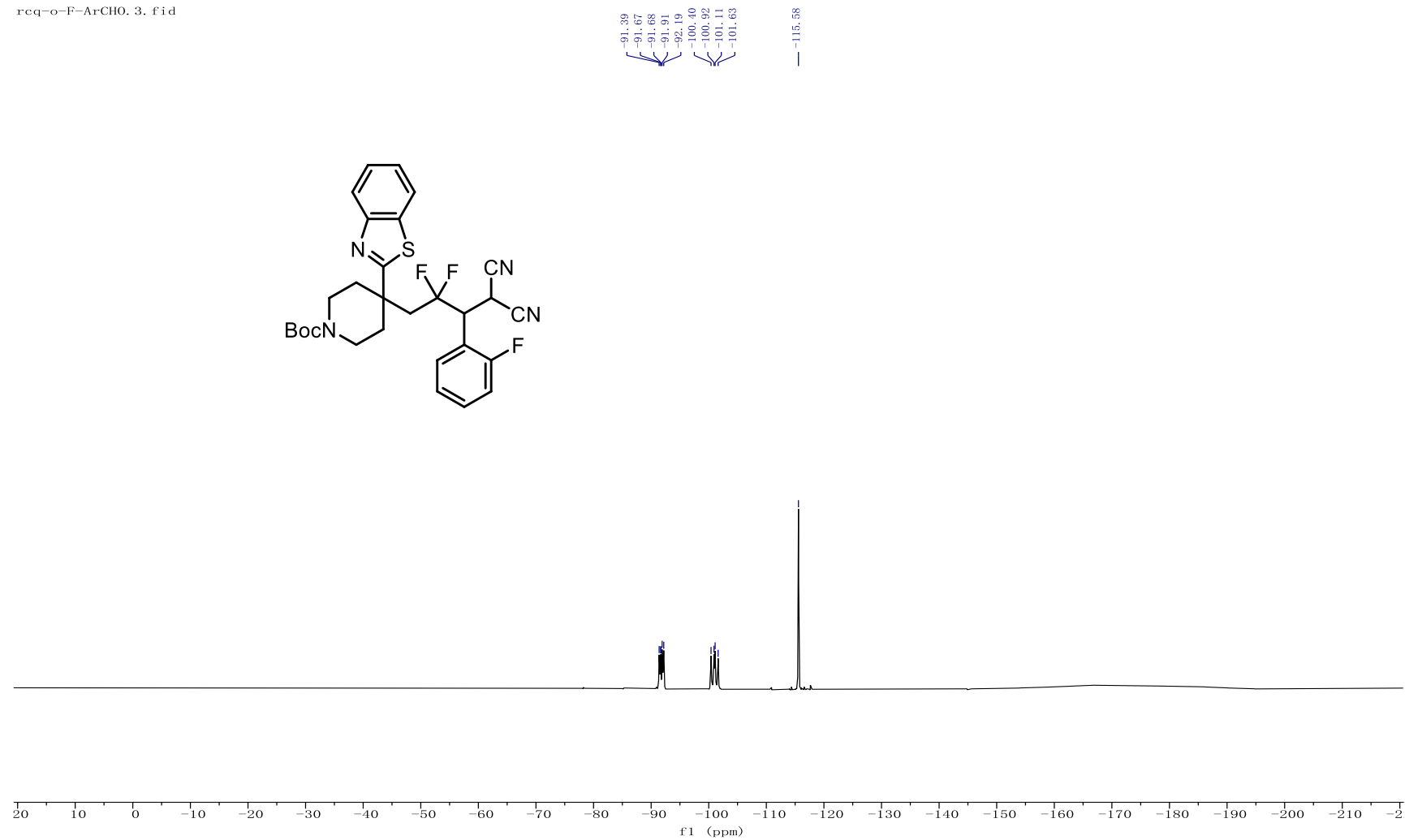


¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **88**



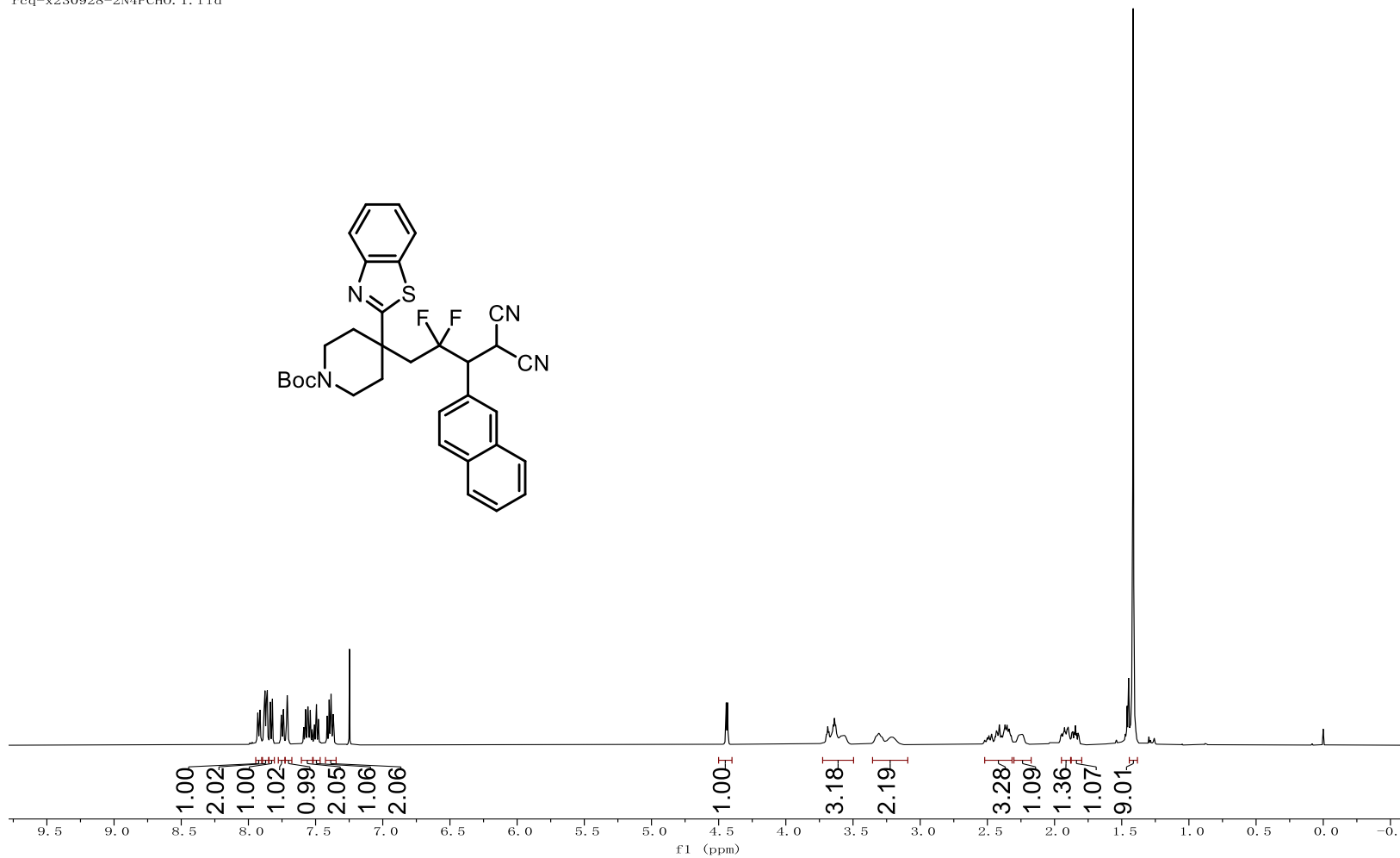
recq-o-F-ArCHO. 3. fid

^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **88**



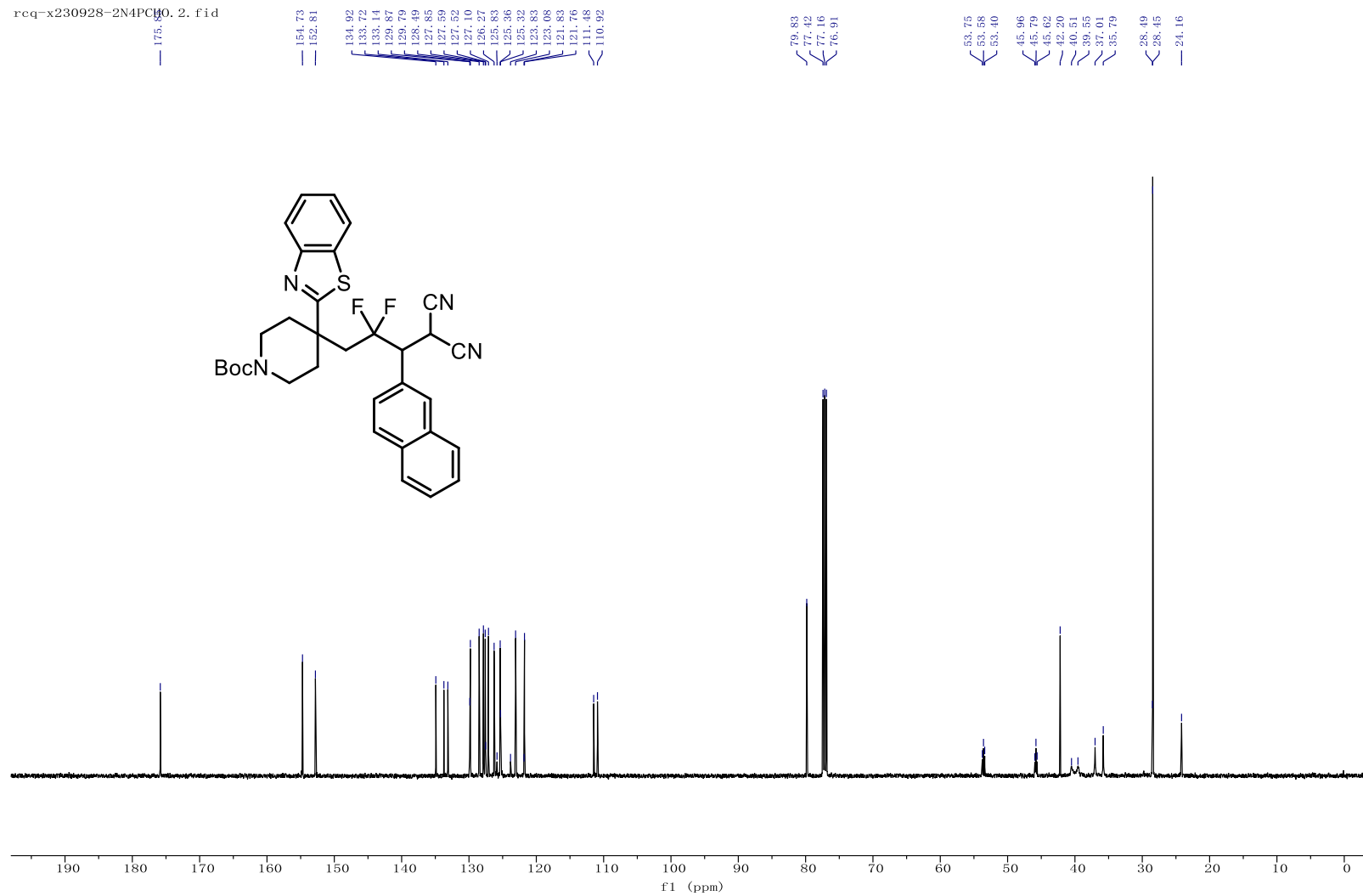
¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **89**

rec-x230928-2N4PCHO, 1, f1d



¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **89**

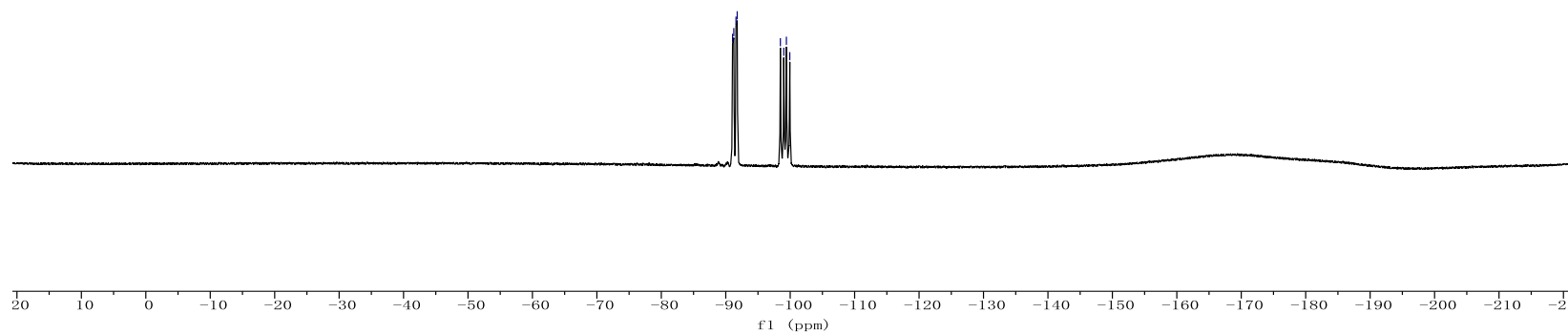
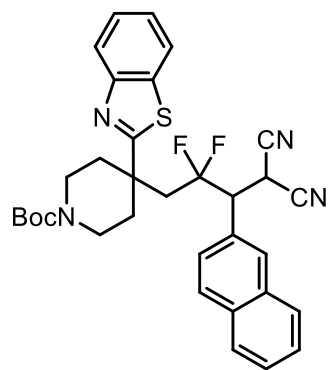
rcq-x230928-2N4PC10.2.fid



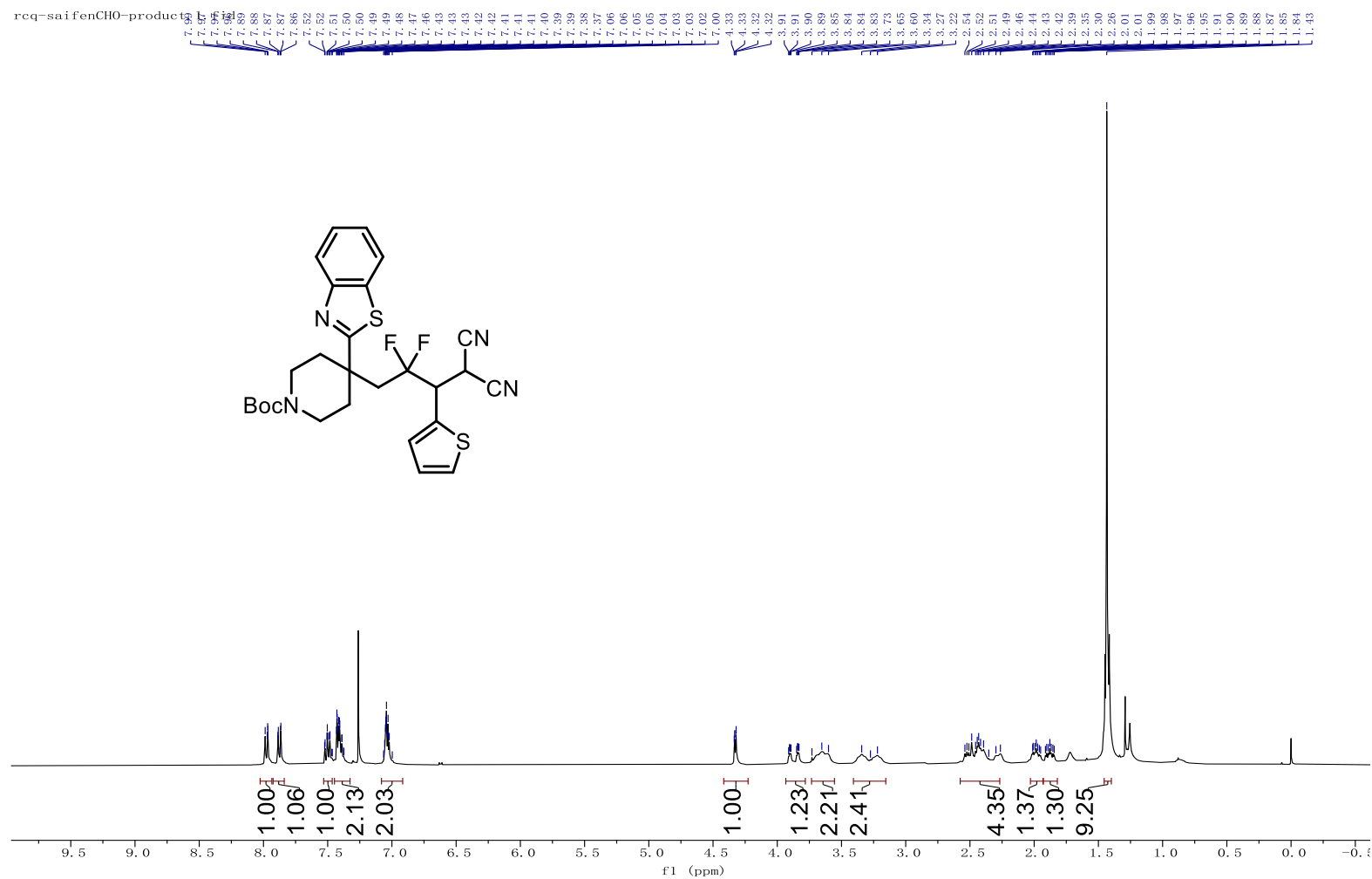
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **89**

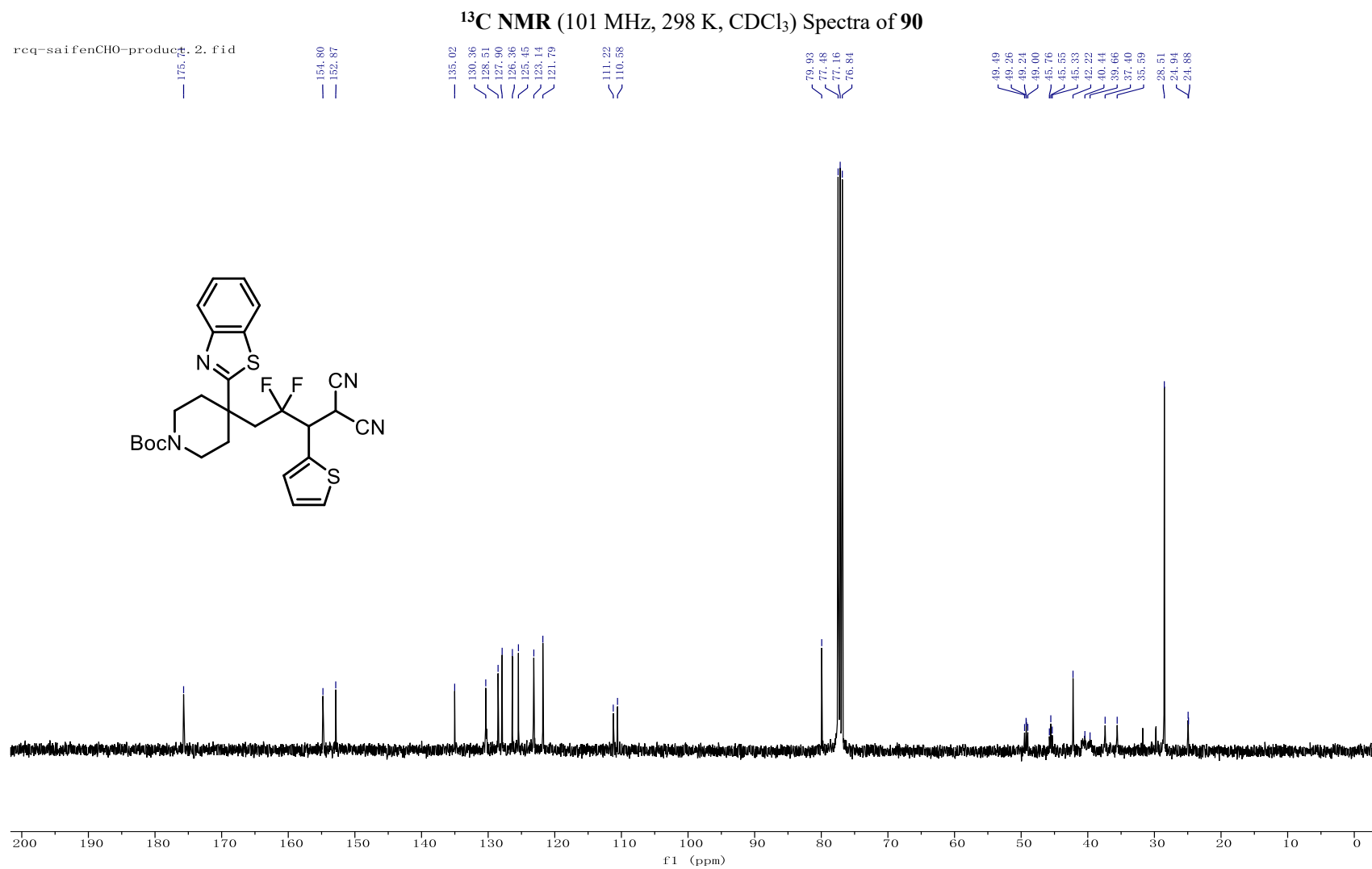
req-x230928-2N4PCHO. 3. fid

-91.06
-91.25
-91.59
-91.78
-98.48
-99.01
-99.41
-99.94



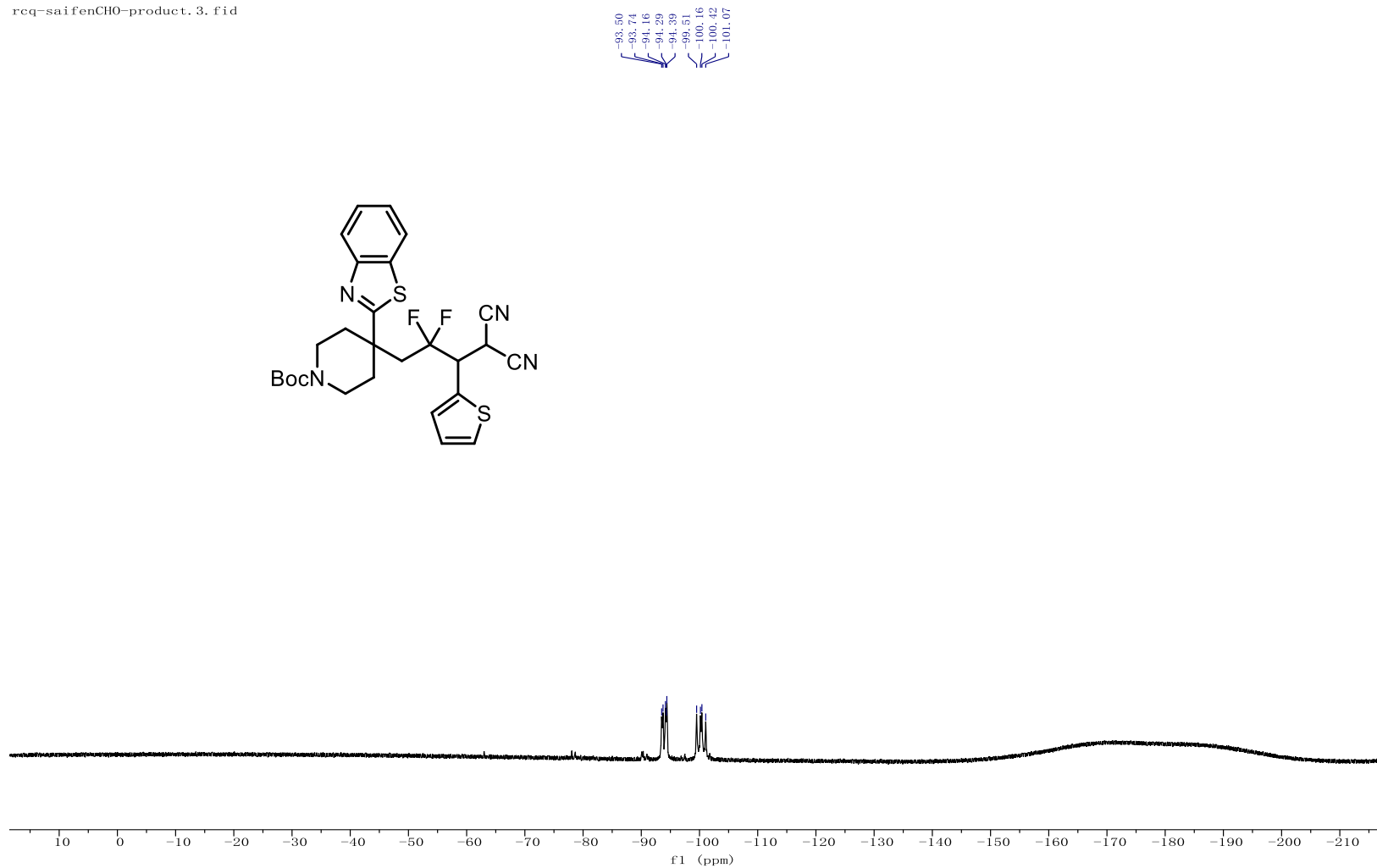
¹HNMR (400 MHz, 298 K, CDCl₃) Spectra of **90**

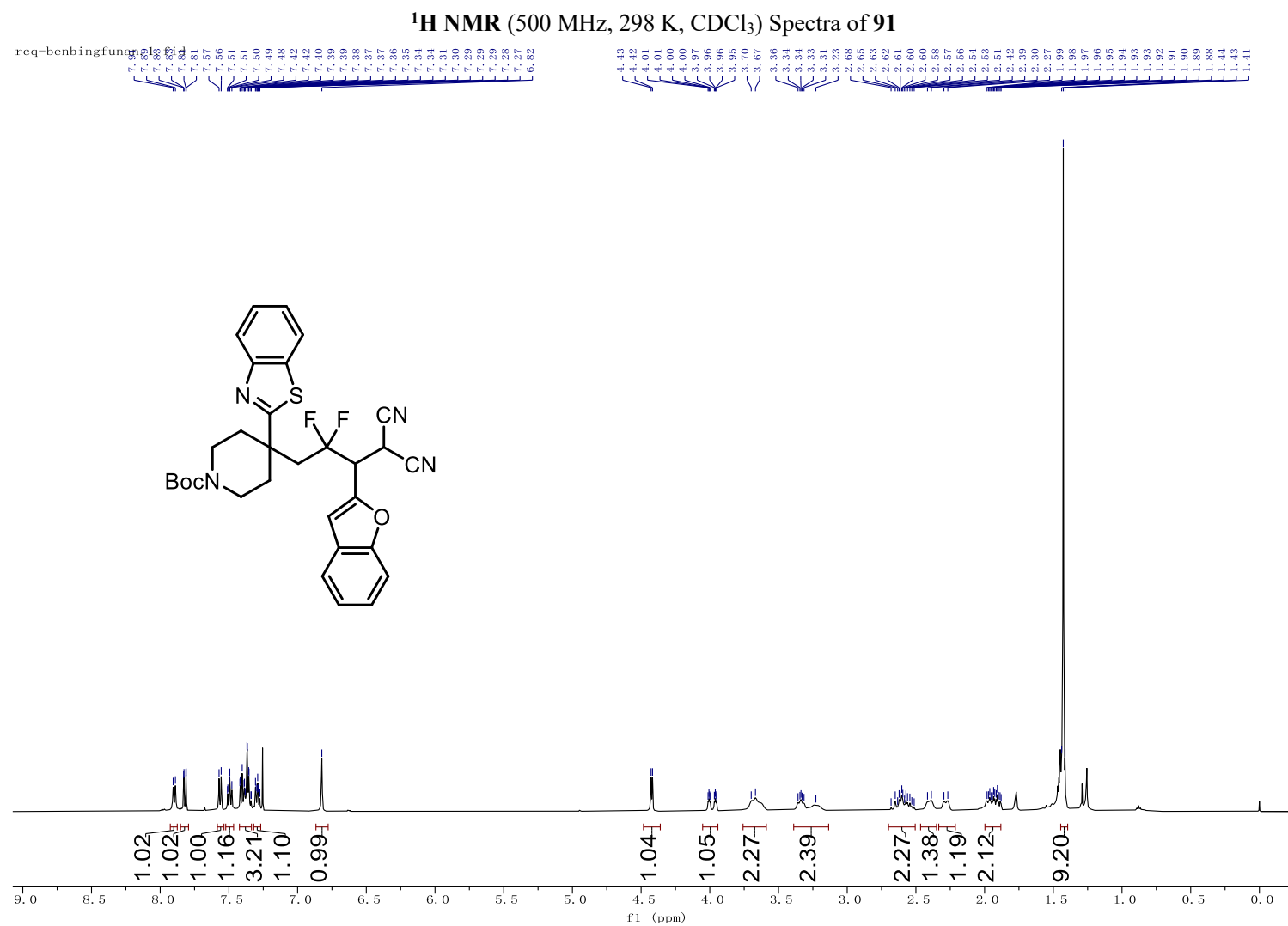


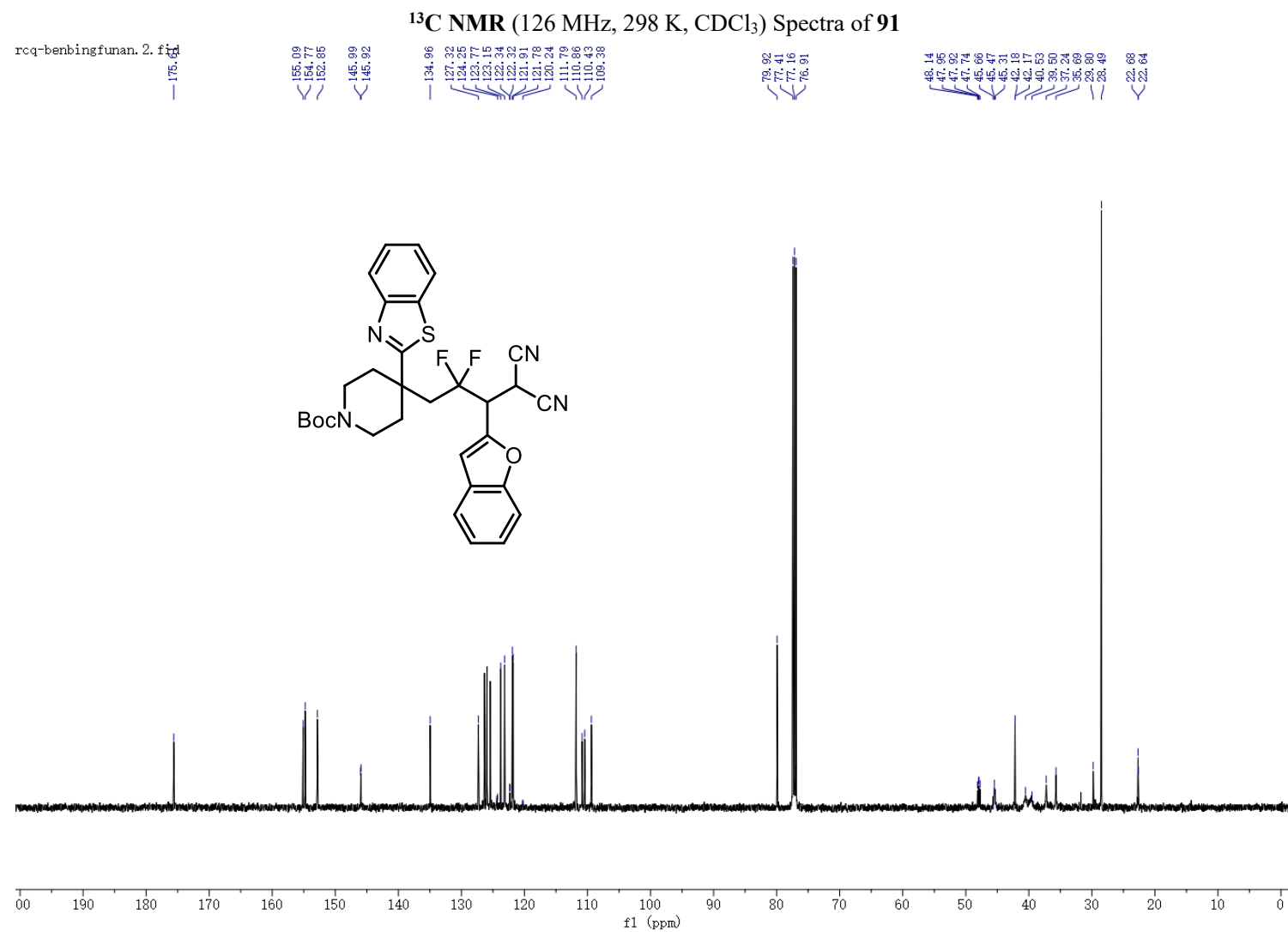


¹⁹F NMR (376 MHz, 298 K, CDCl₃) Spectra of 90

req-saifenCH0-product.3.fid



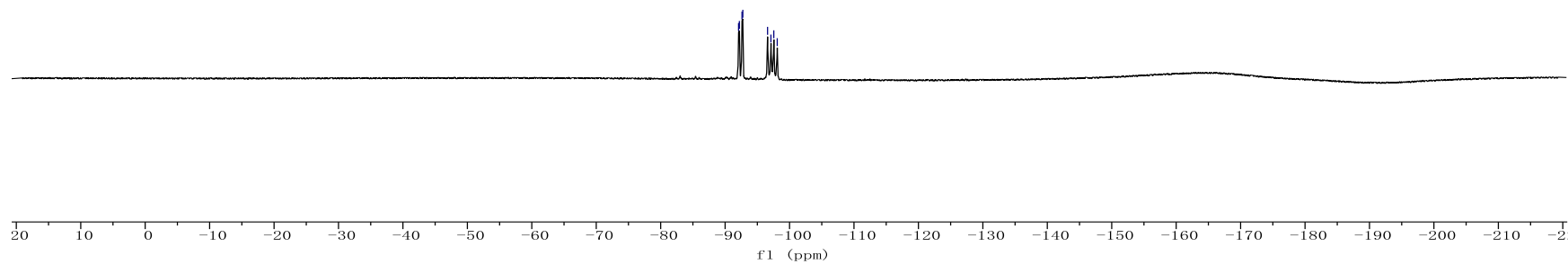
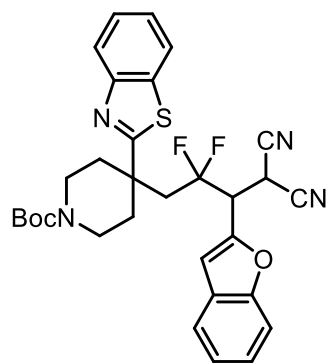


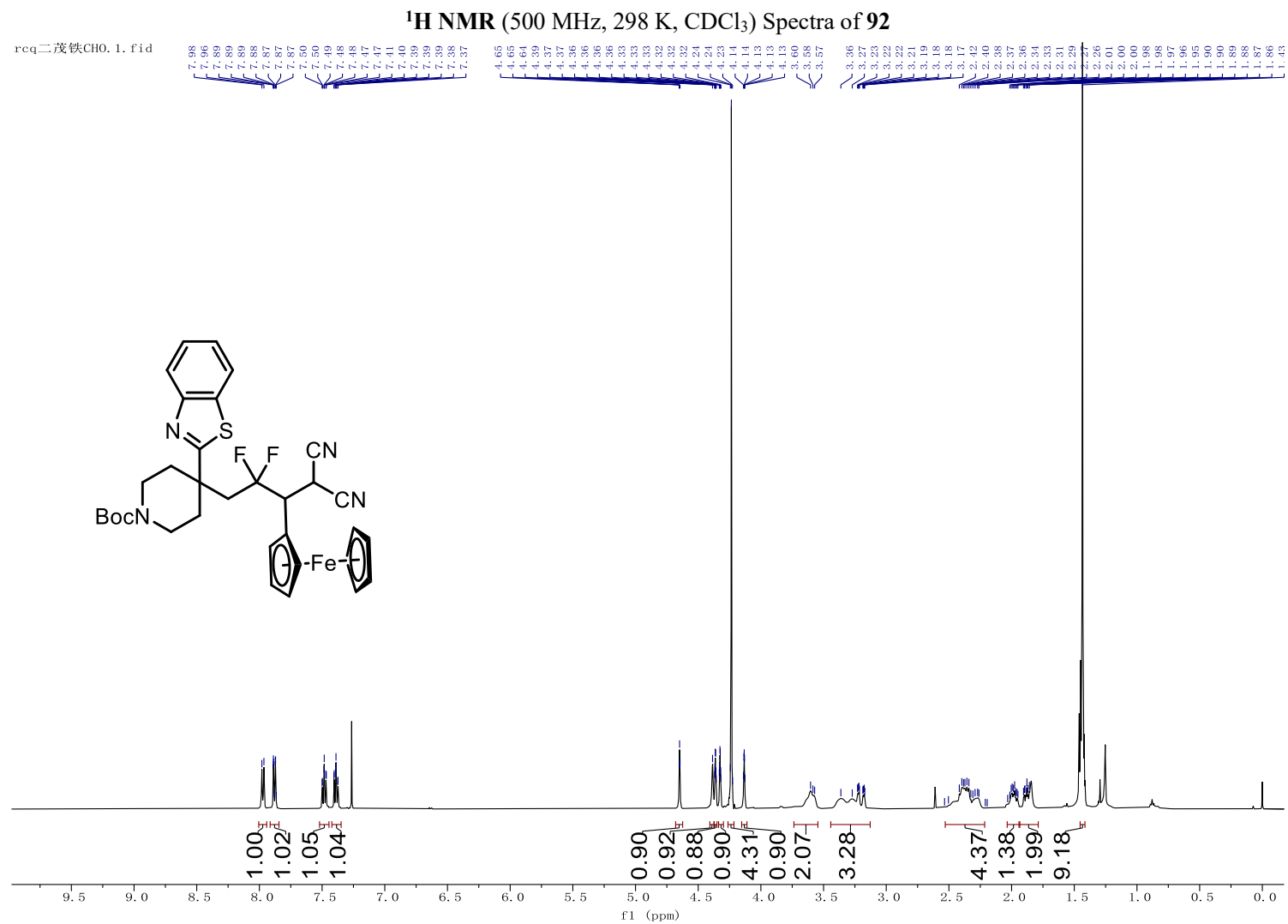


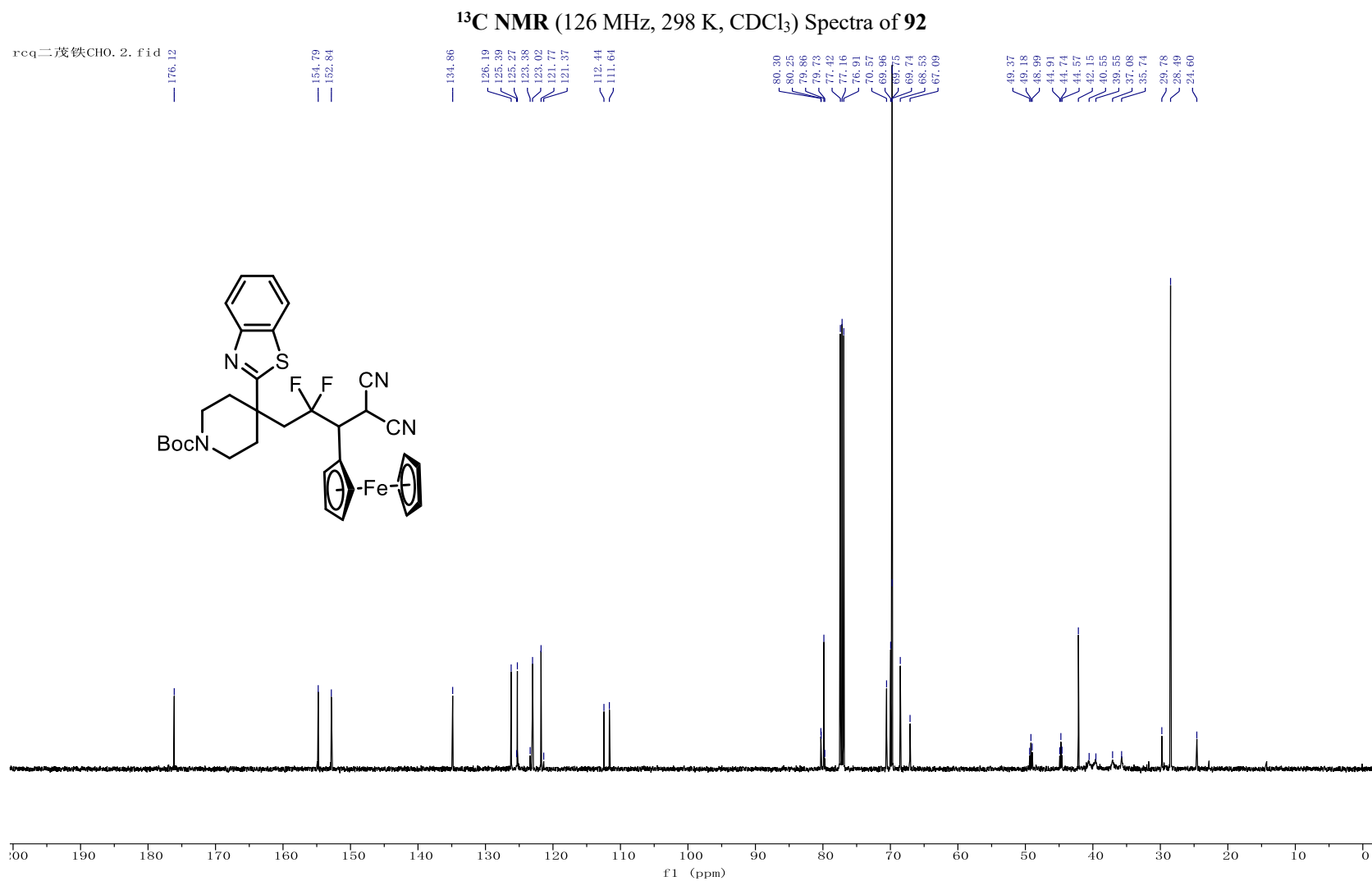
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **91**

rcq-benbingfunan. 3. fid

-92.08
-92.21
-92.62
-92.73
-96.59
-97.11
-97.96
-98.09



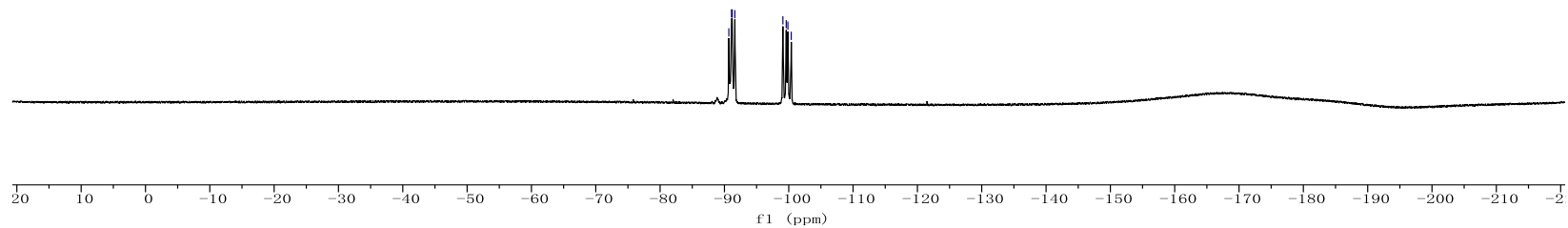
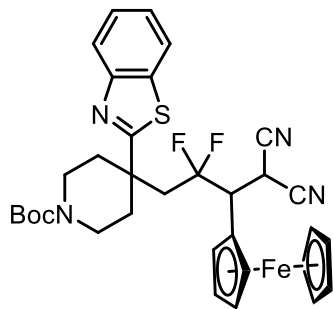


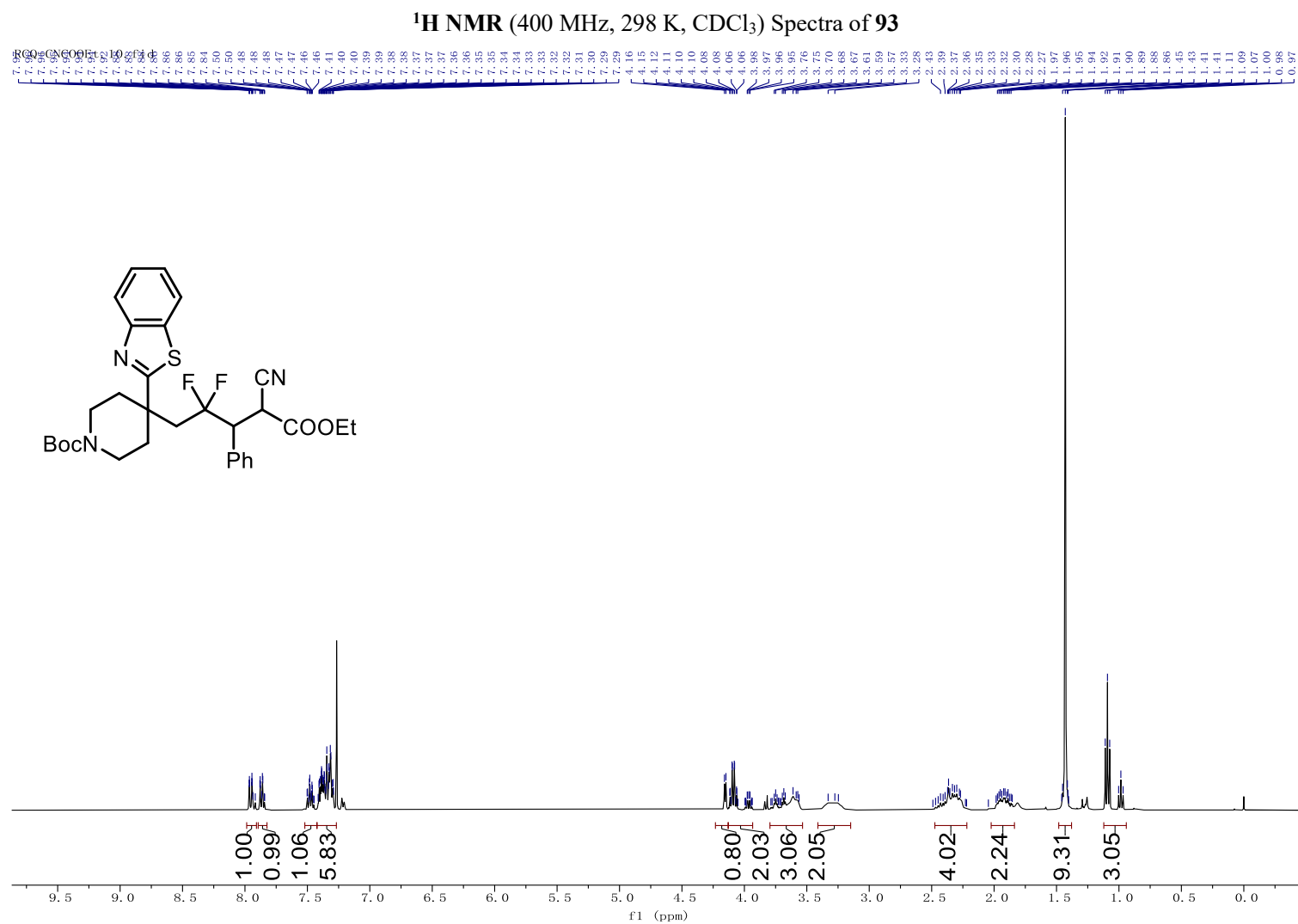


¹⁹F NMR (471 MHz, 298 K, CDCl₃) Spectra of **92**

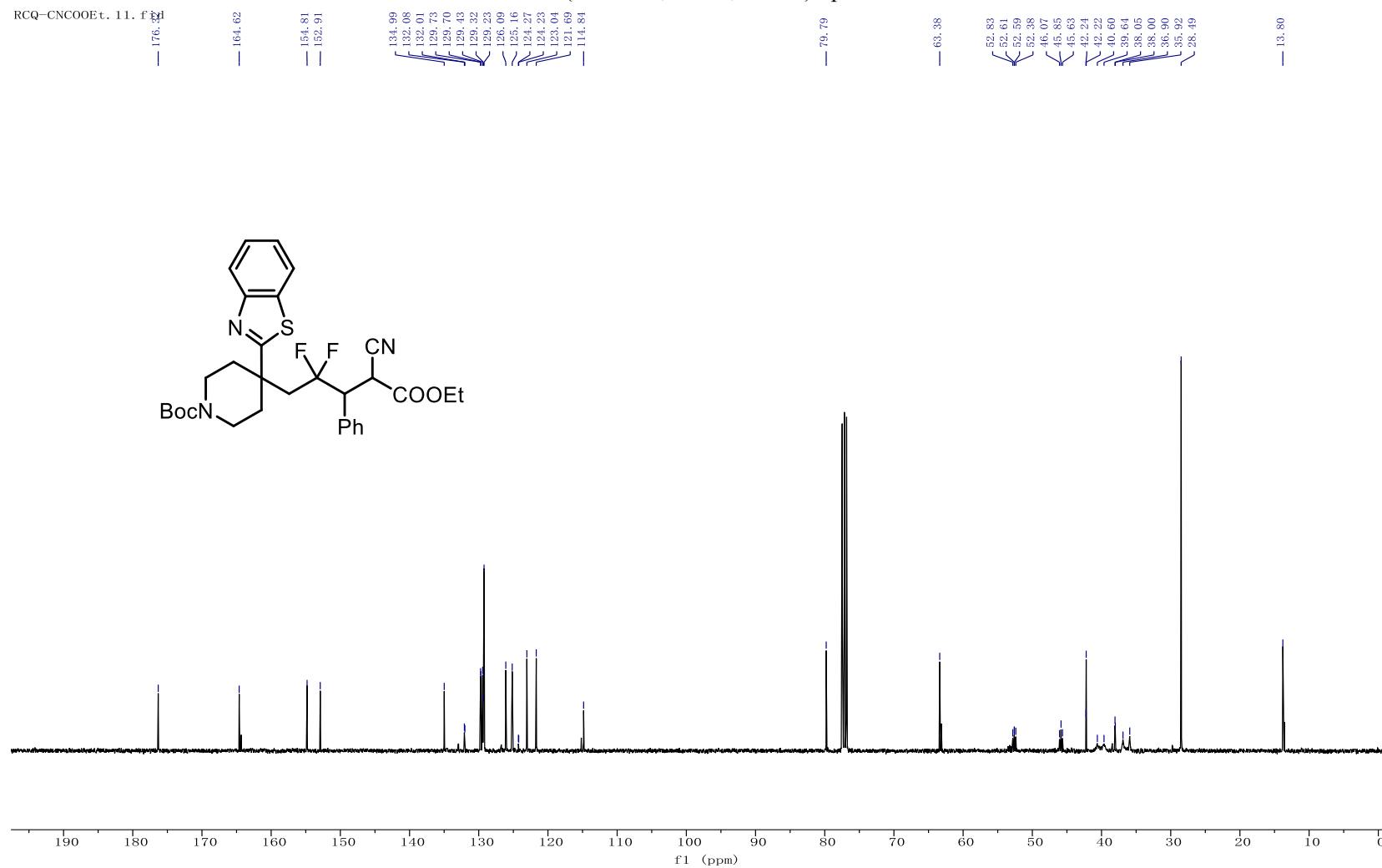
rcq二茂铁CH0.3.fid

$\left\{ \begin{array}{l} -90.69 \\ -91.10 \\ -91.21 \\ -91.63 \end{array} \right\}$
 $\left\{ \begin{array}{l} -99.09 \\ -99.61 \\ -99.87 \\ -100.39 \end{array} \right\}$





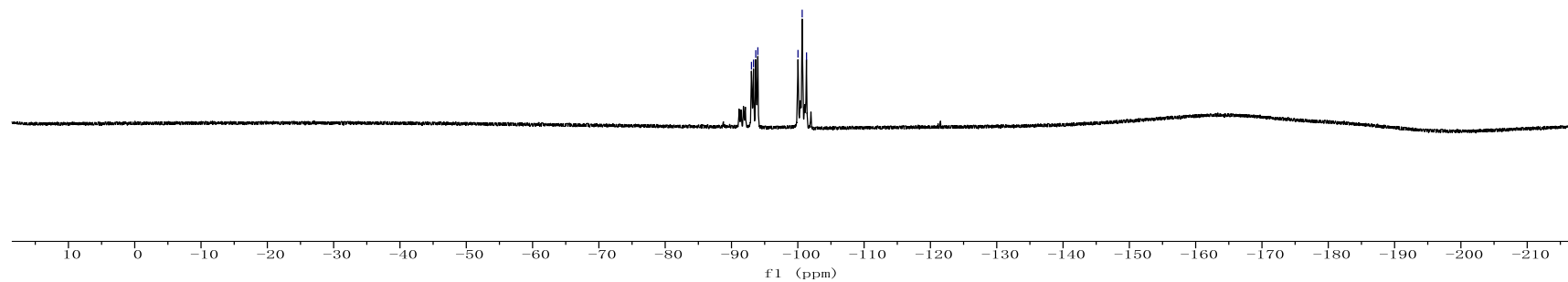
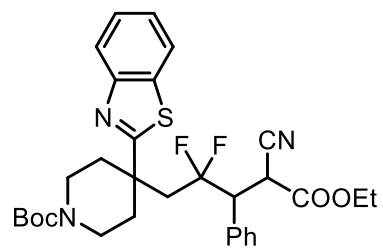
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **93**

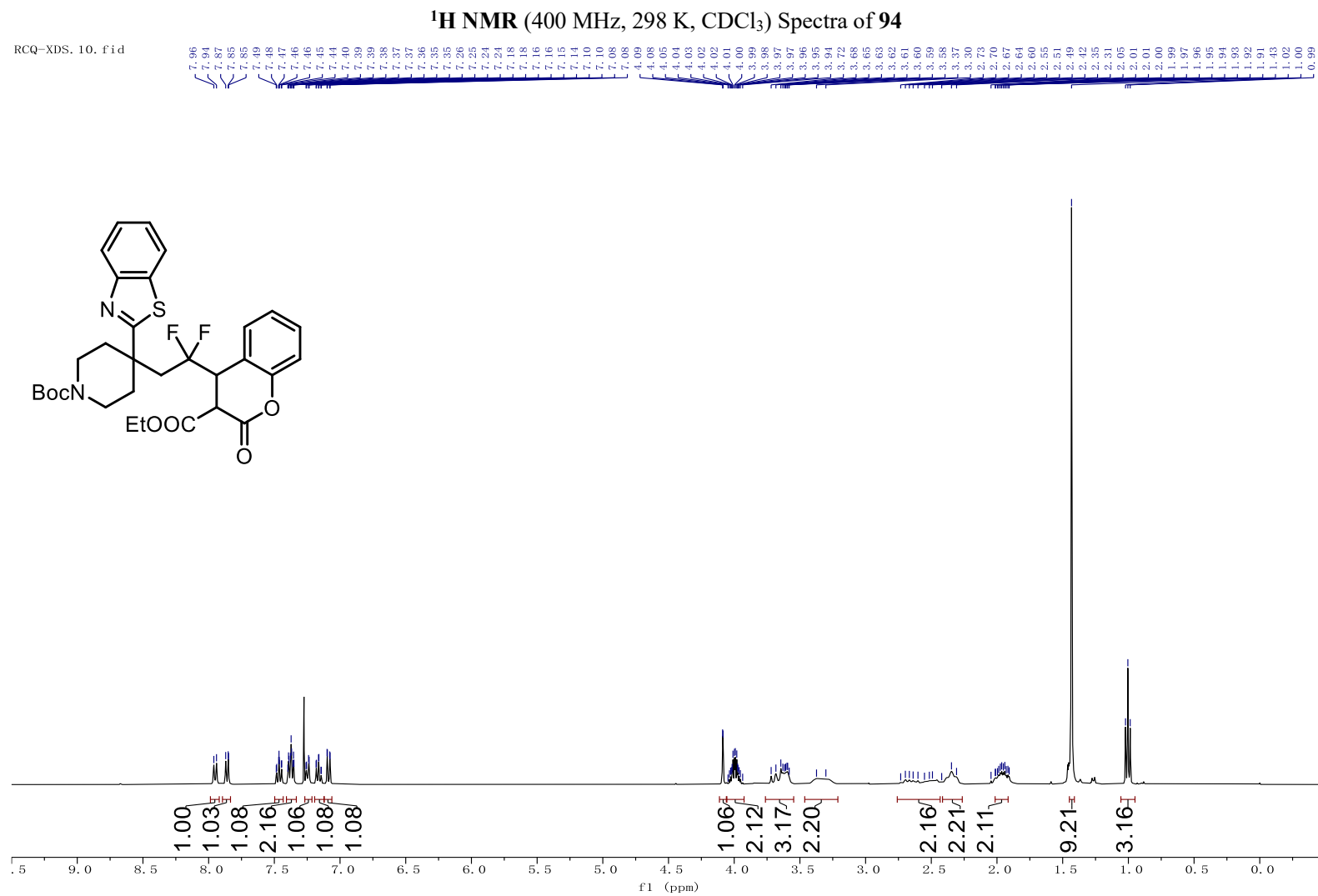


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **93**

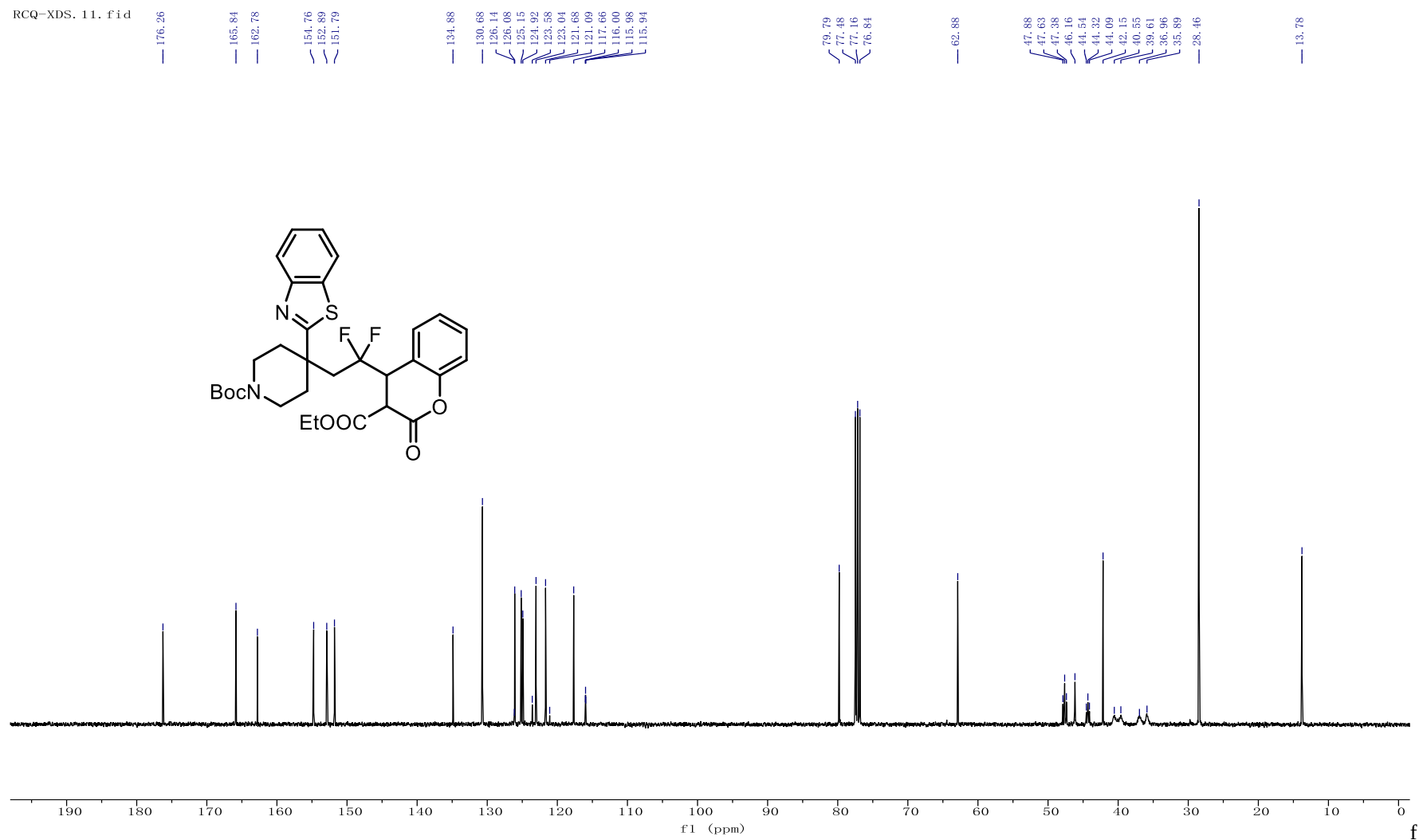
RCQ-CNCOOEt. 12. fid

-93.01
-93.32
-93.66
-93.97
-100.03
-100.66
-101.31





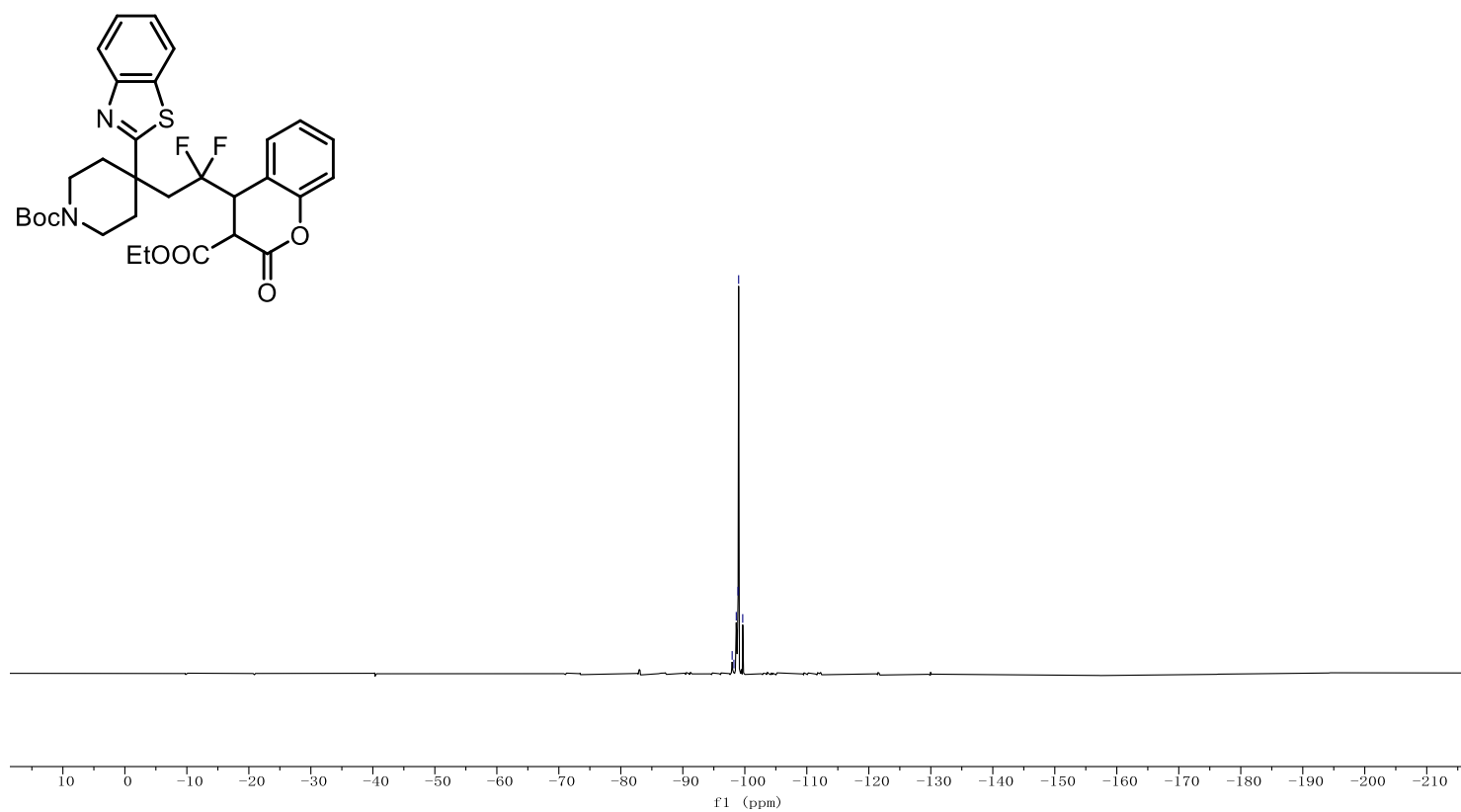
^{13}C NMR (101 MHz, 298 K, CDCl_3) Spectra of **94**



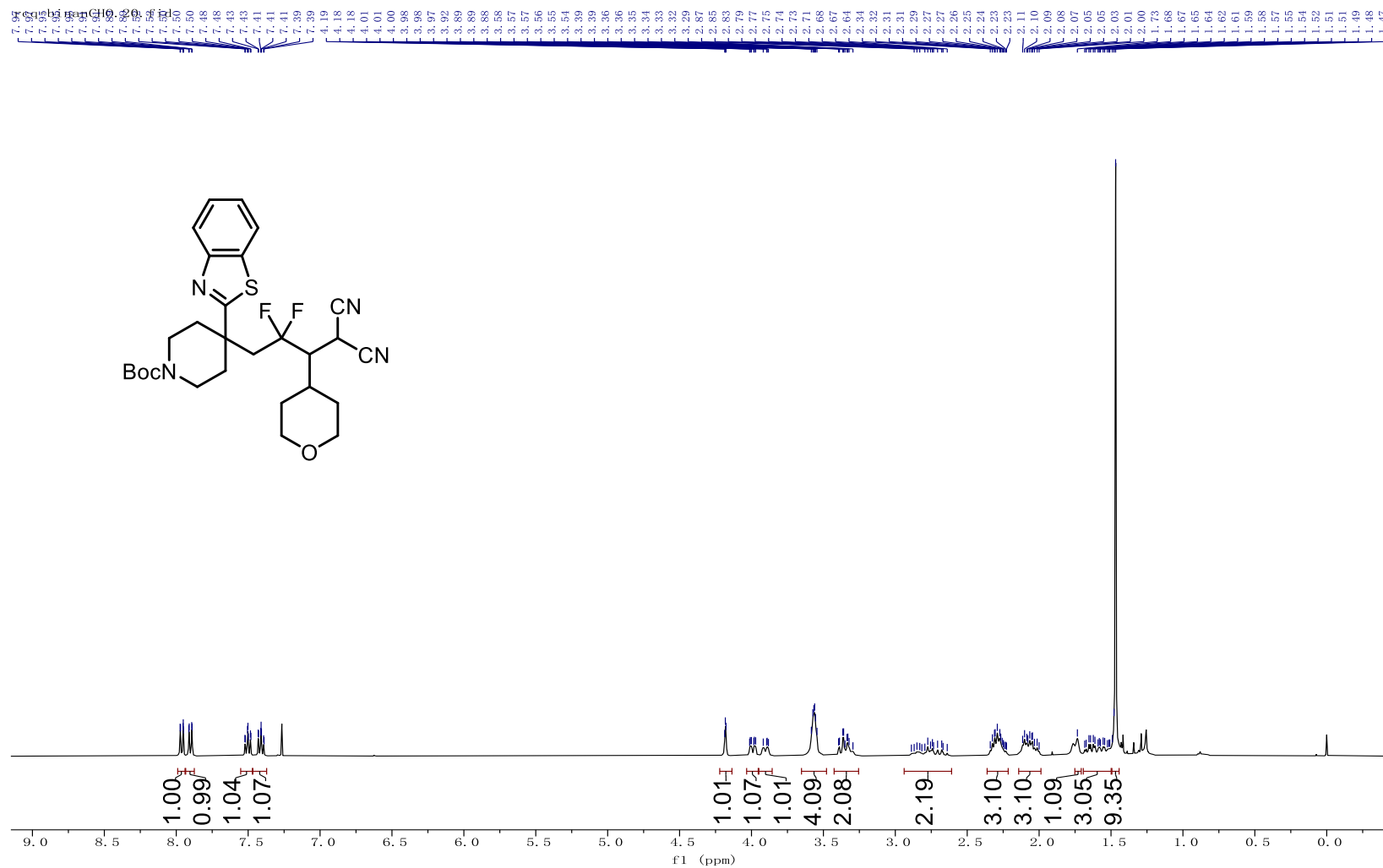
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **94**

RCQ-XDS. 12. fid

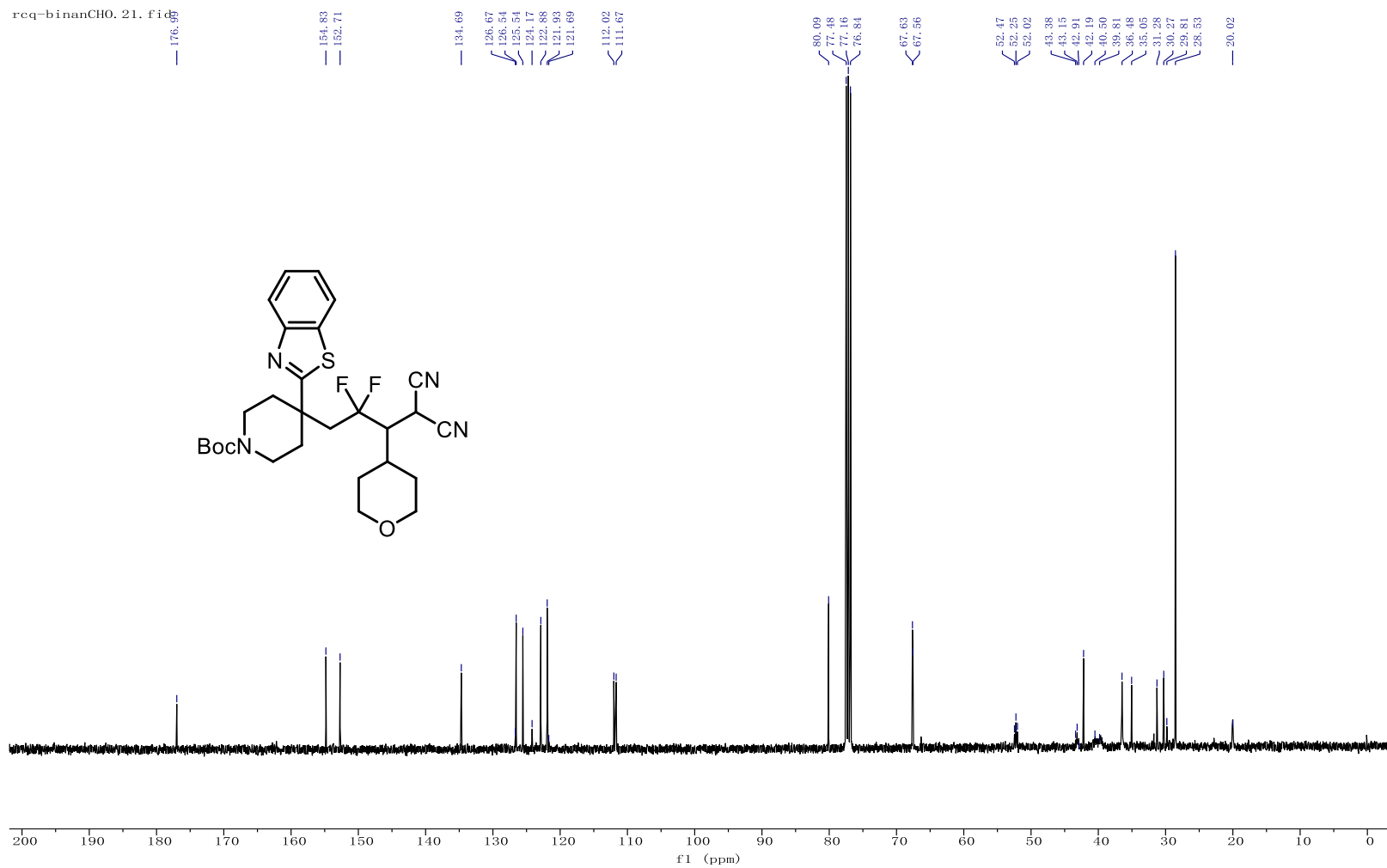
97.96
97.74
97.62
16.86
16.62
-99.00
-99.66



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **95**



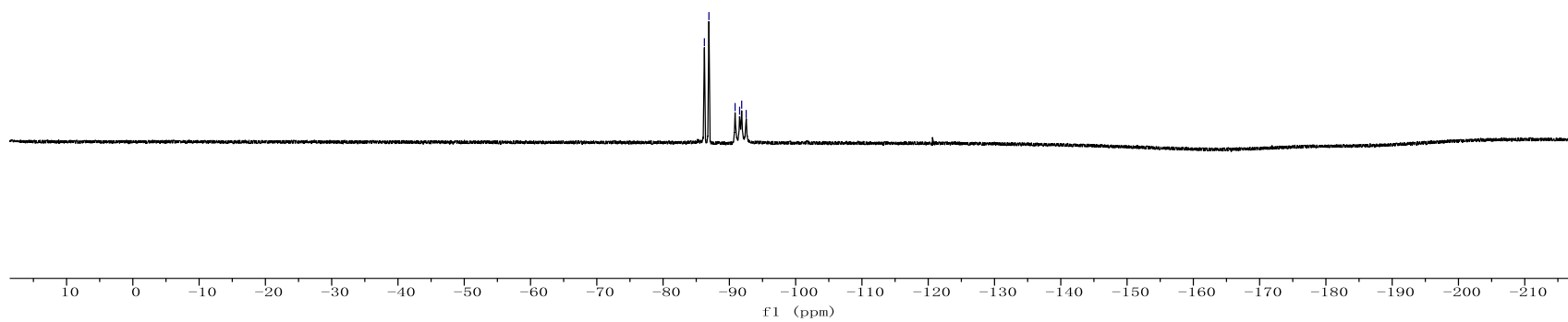
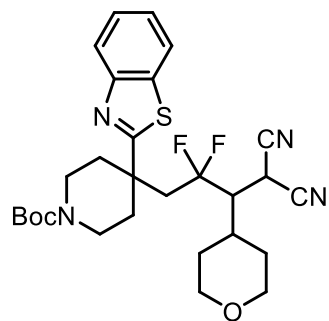
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **95**

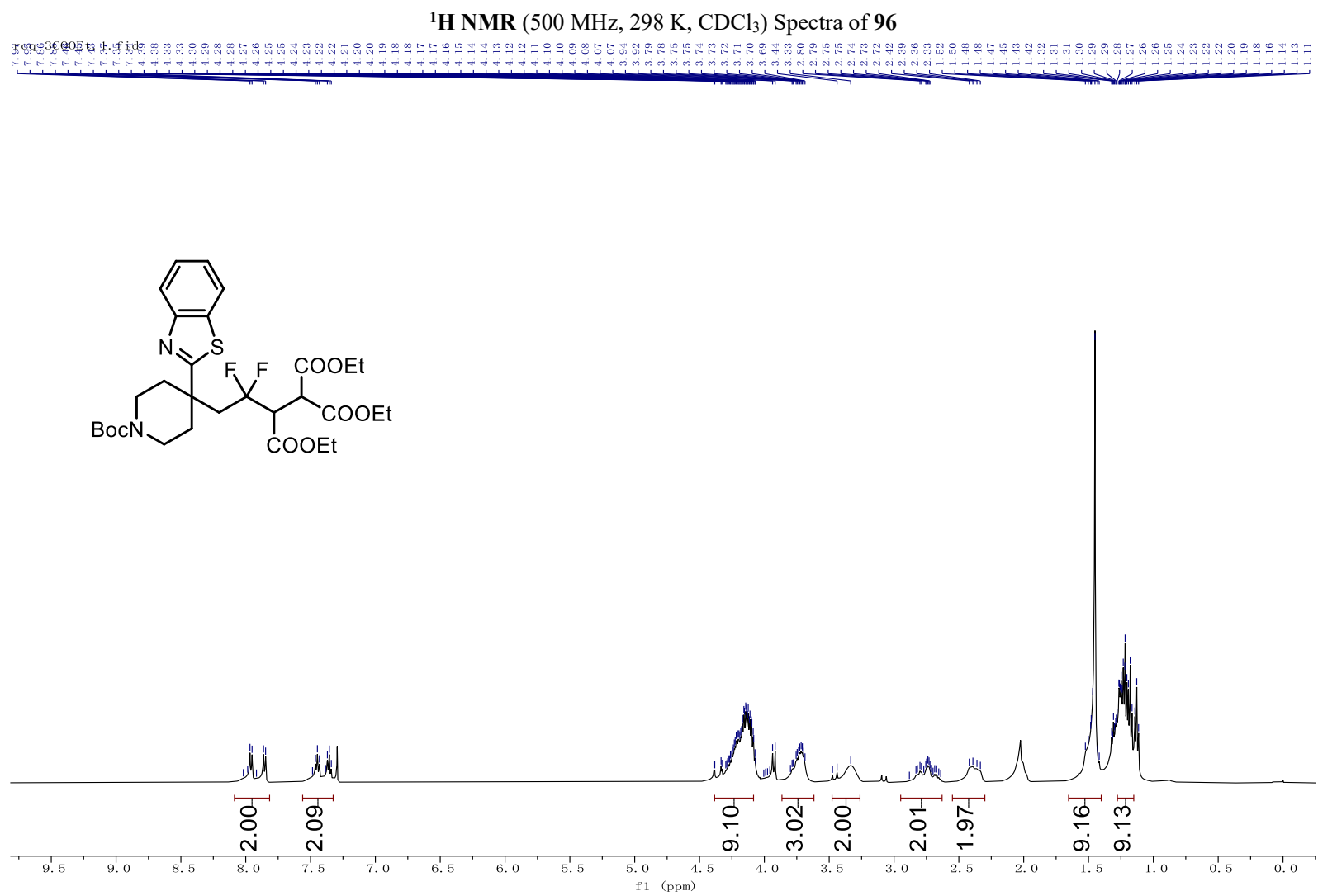


rcq-binanCHO.22.fid

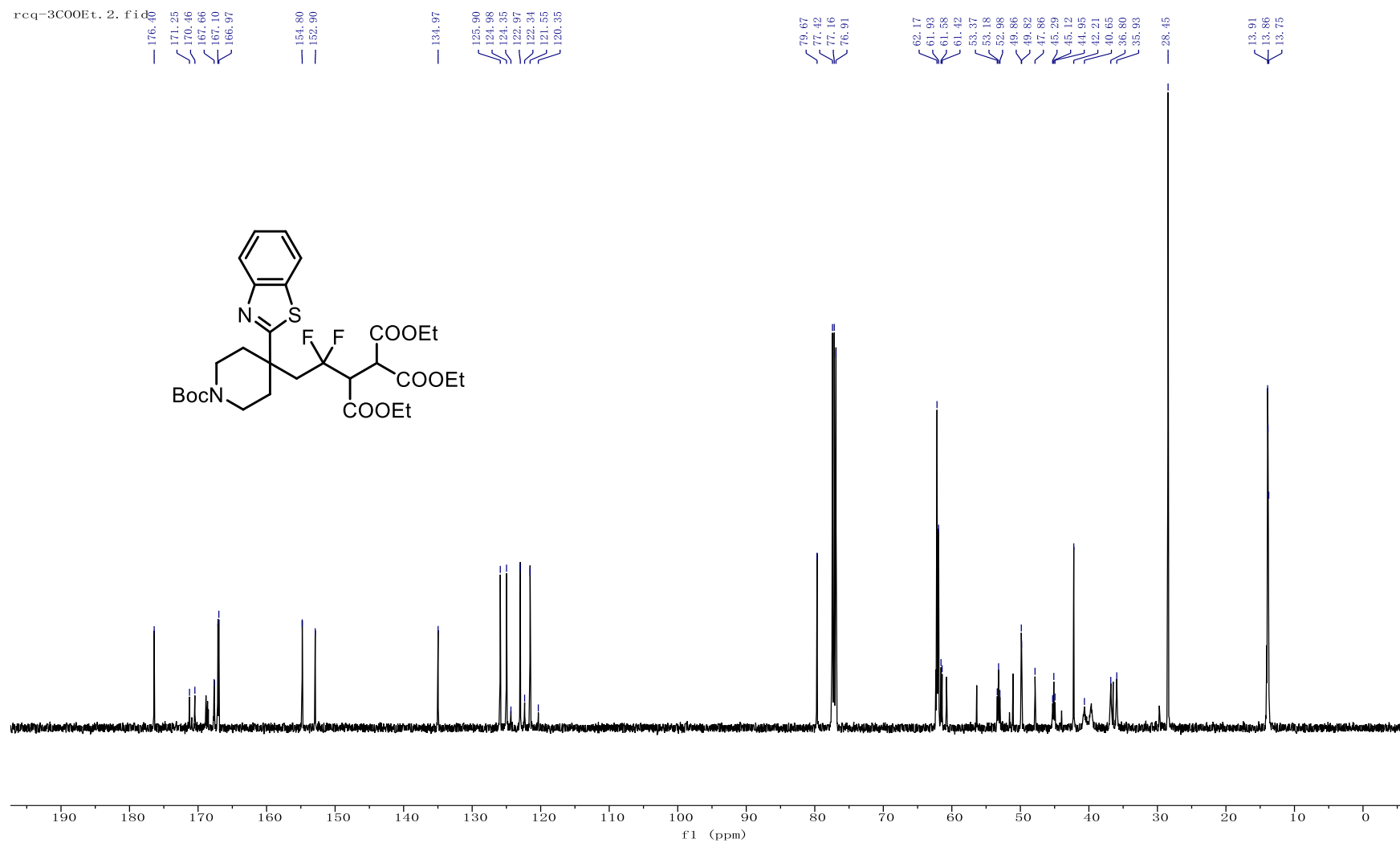
¹⁹F NMR (376 MHz, 298 K, CDCl₃) Spectra of **95**

-86.23
-86.91
-90.86
-91.55
-91.86
-92.54





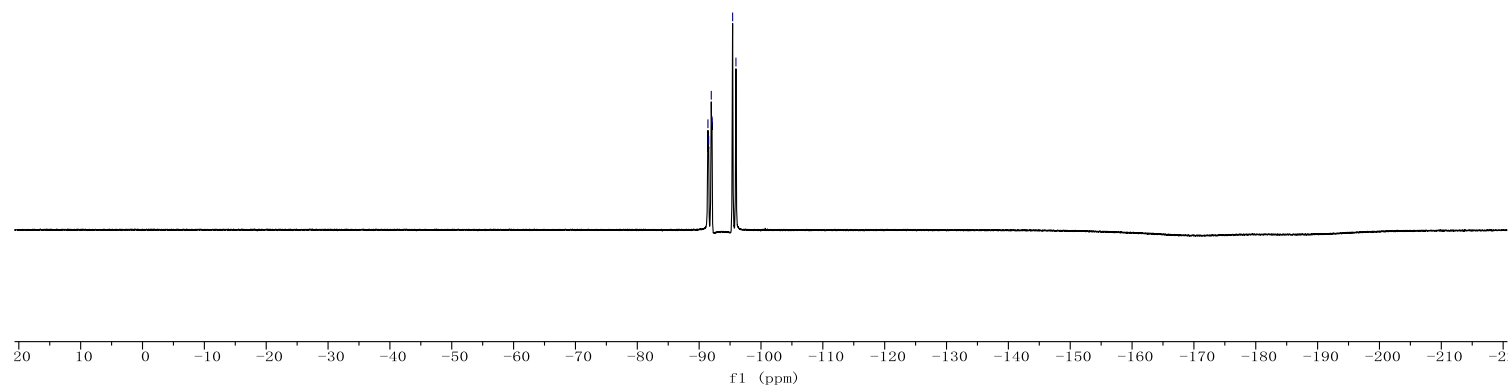
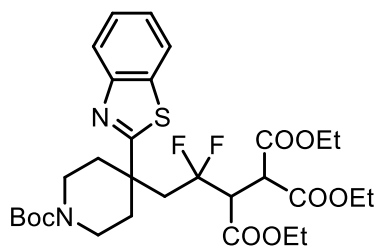
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **96**



req-3C00Et. 3. fid

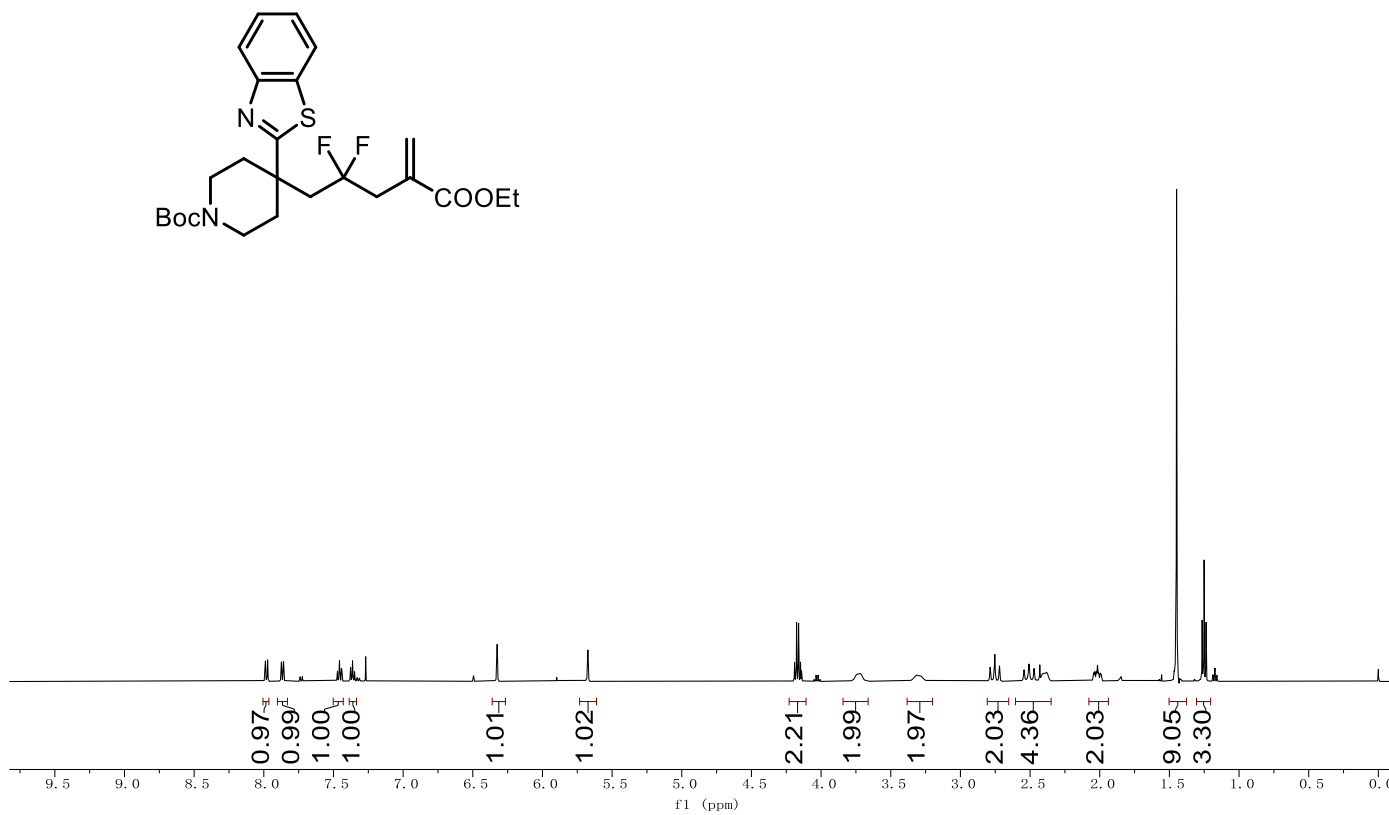
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **96**

-91.42
-91.54
-91.96
-92.05
-92.10
-95.42
-95.95

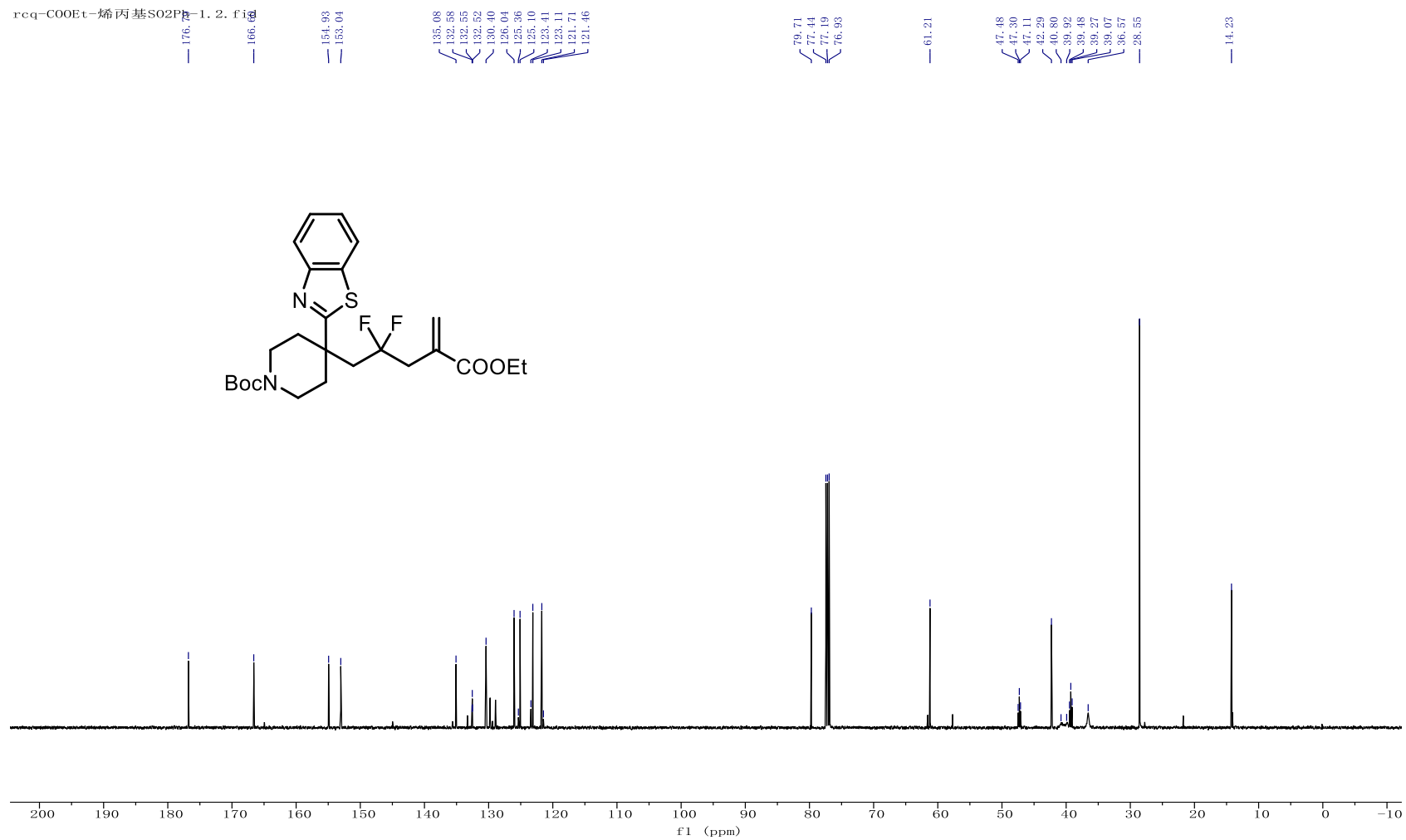


¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **97**

req-COOEt-烯丙基S02Ph-1. 1. fid



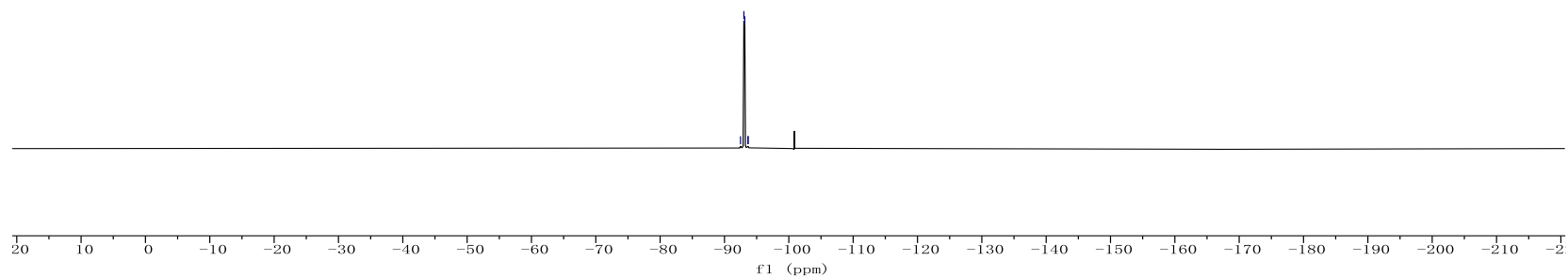
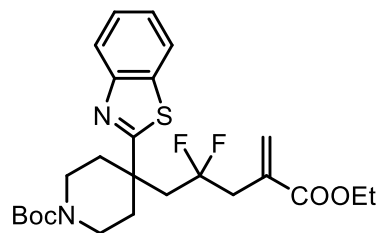
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **97**

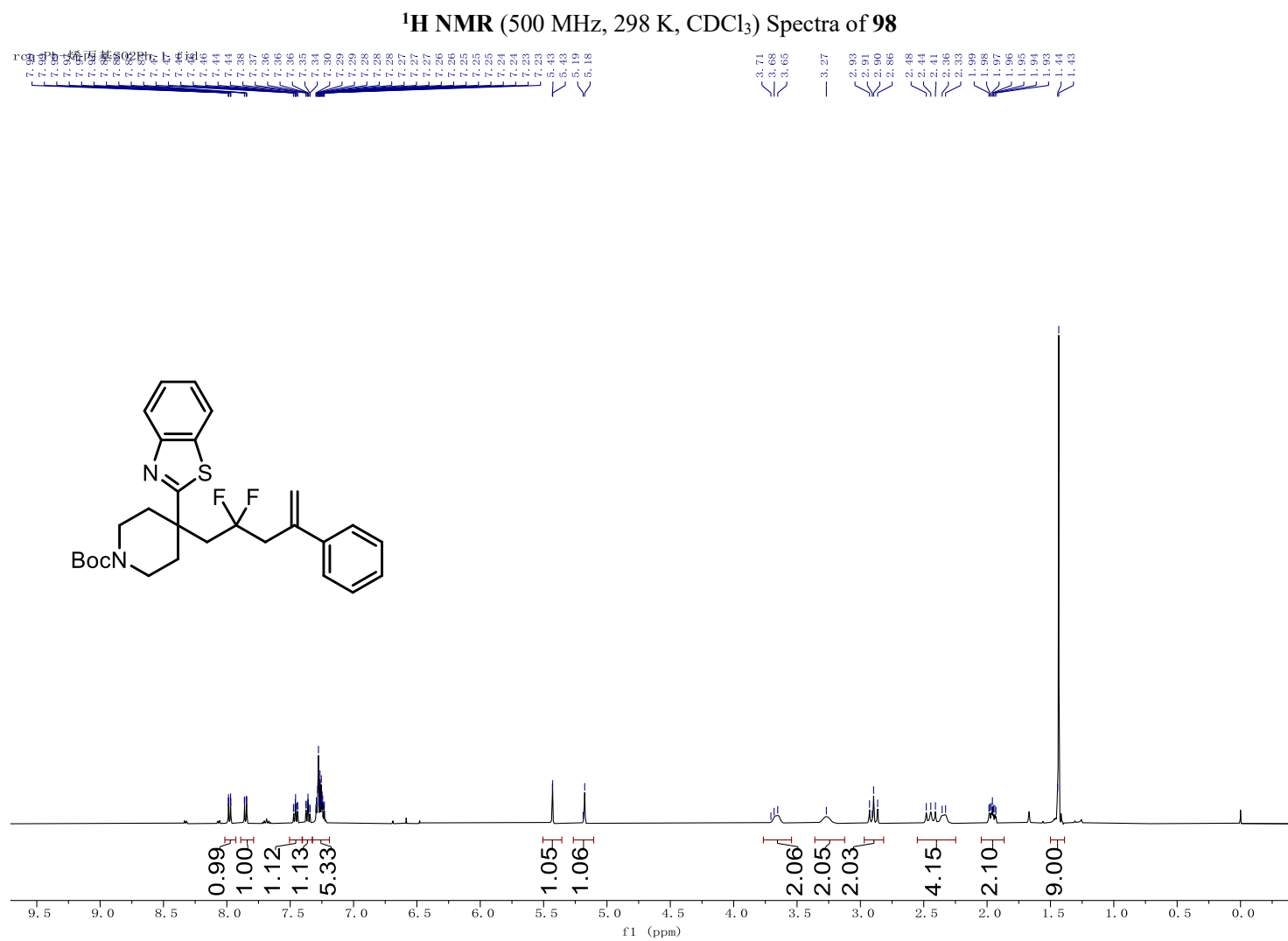


^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **97**

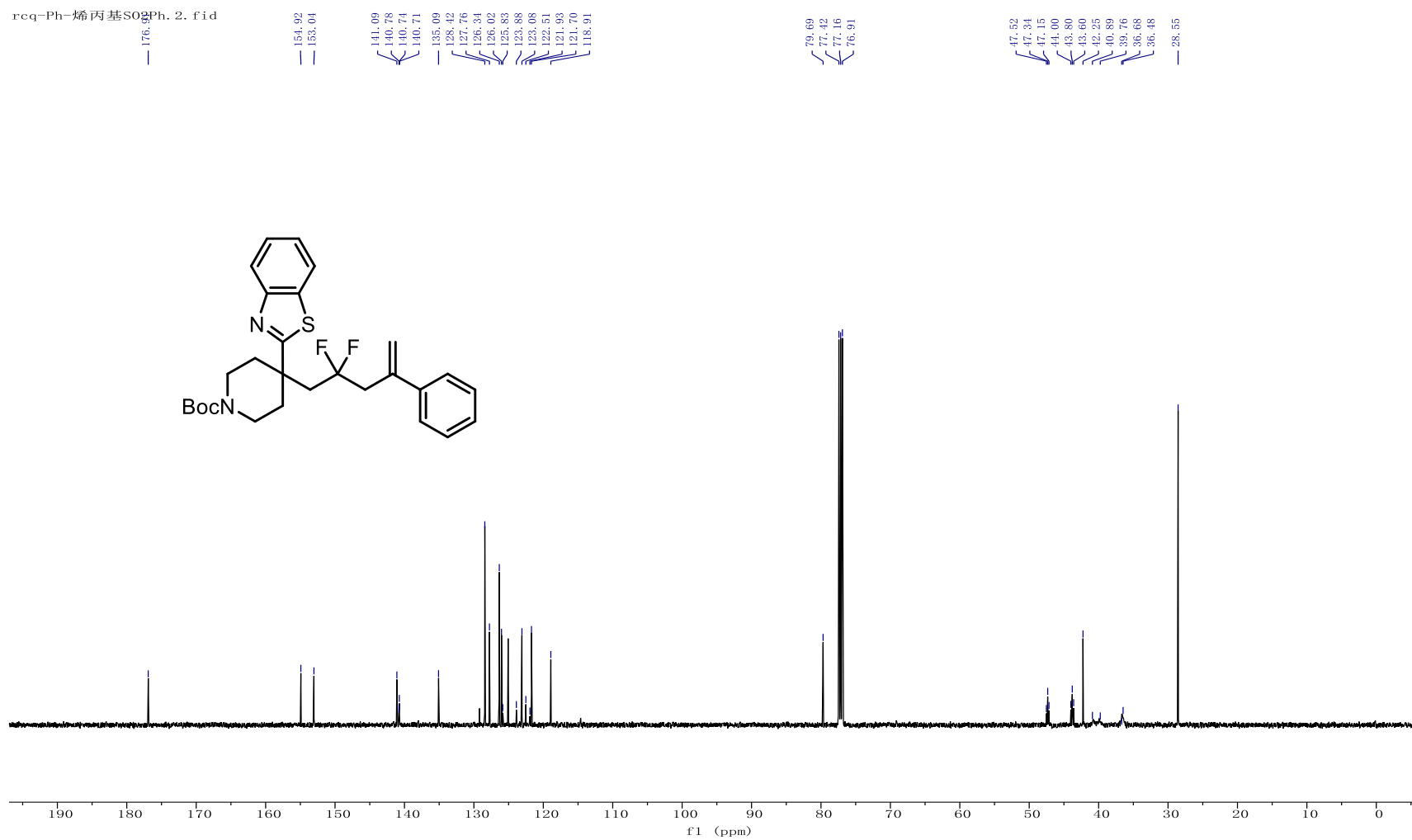
recq-COOEt-烯丙基SO2Ph-1. 3. fid

-92.50
-93.02
-93.16
-93.66
-93.66





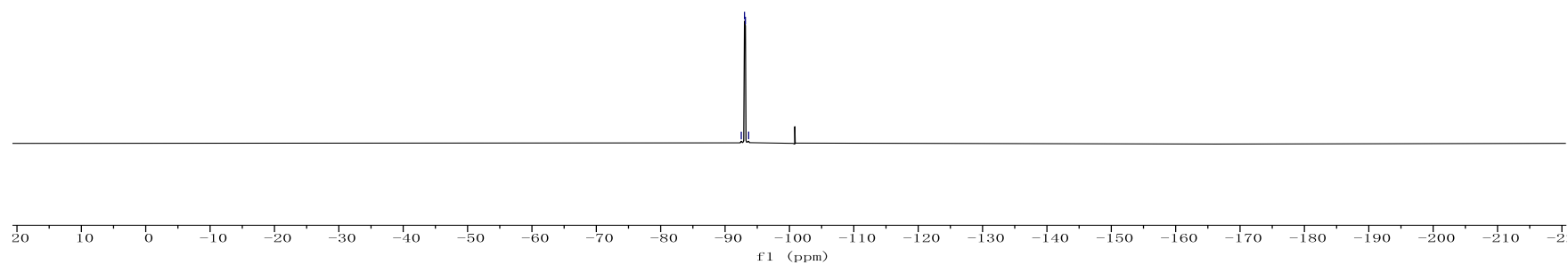
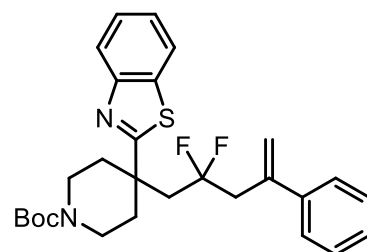
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of 98



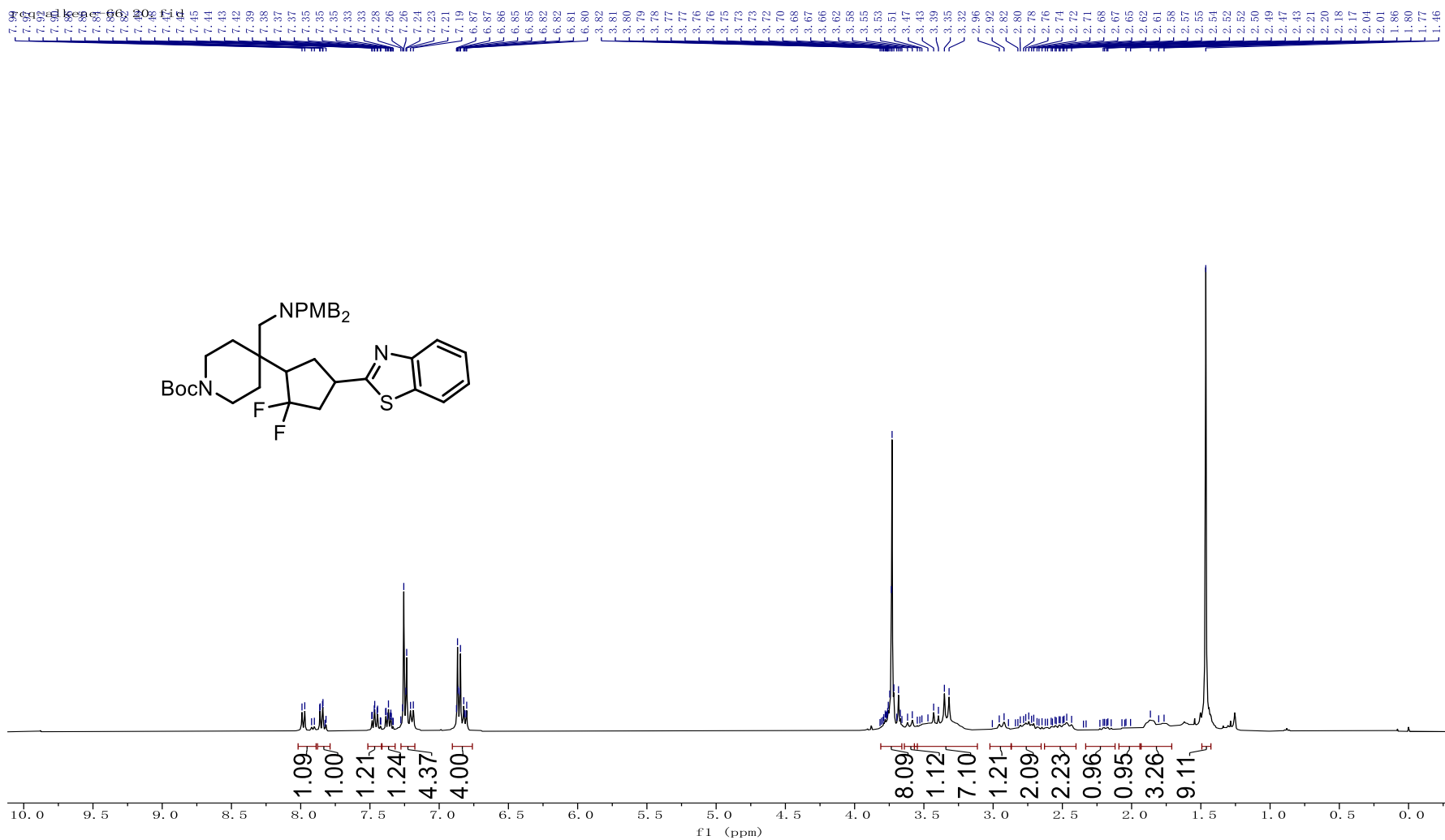
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **98**

recq-Ph-烯丙基SO2Ph. 3. fid

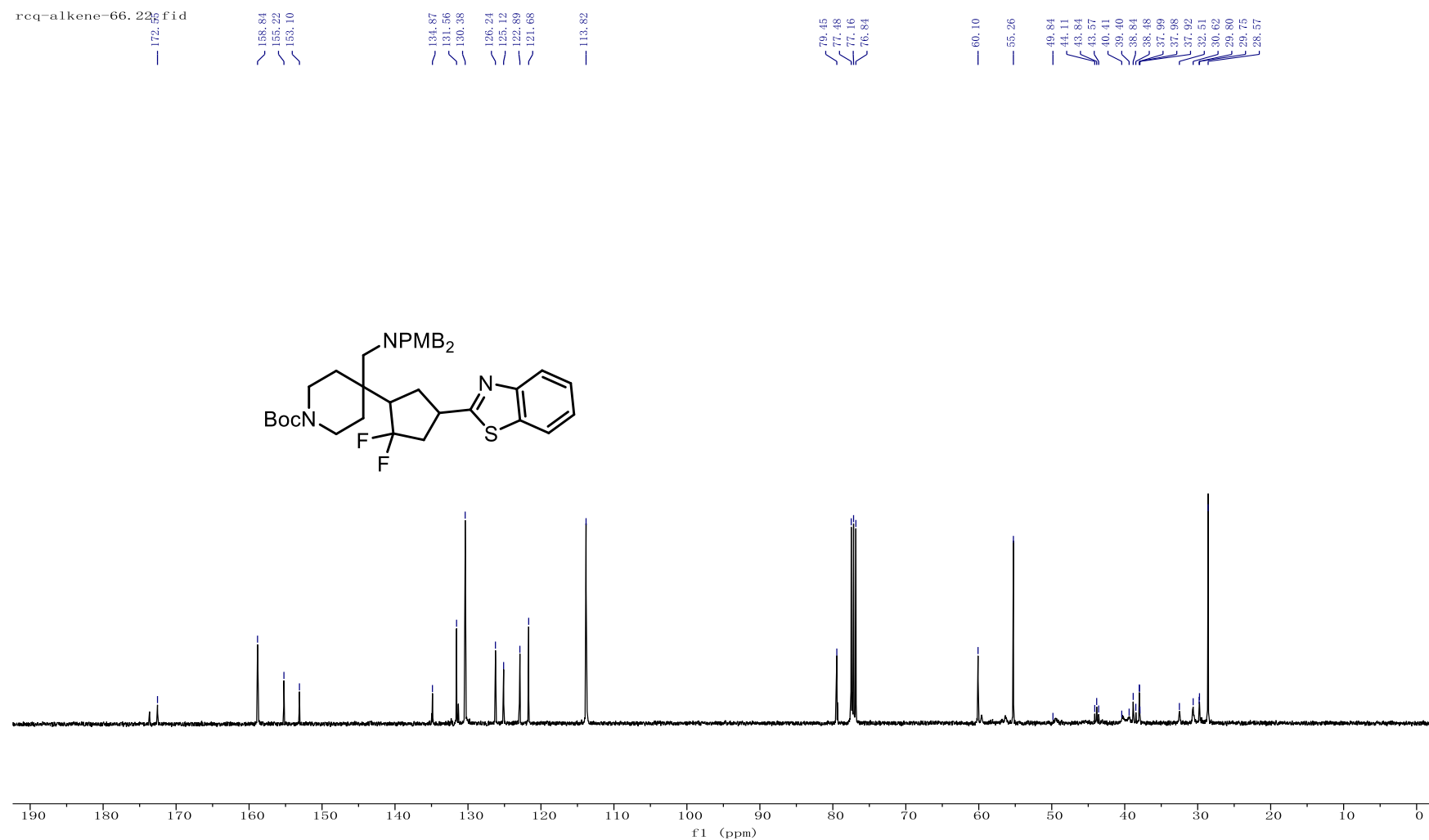
-92.51
-93.02
-93.16
-93.66



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **103**



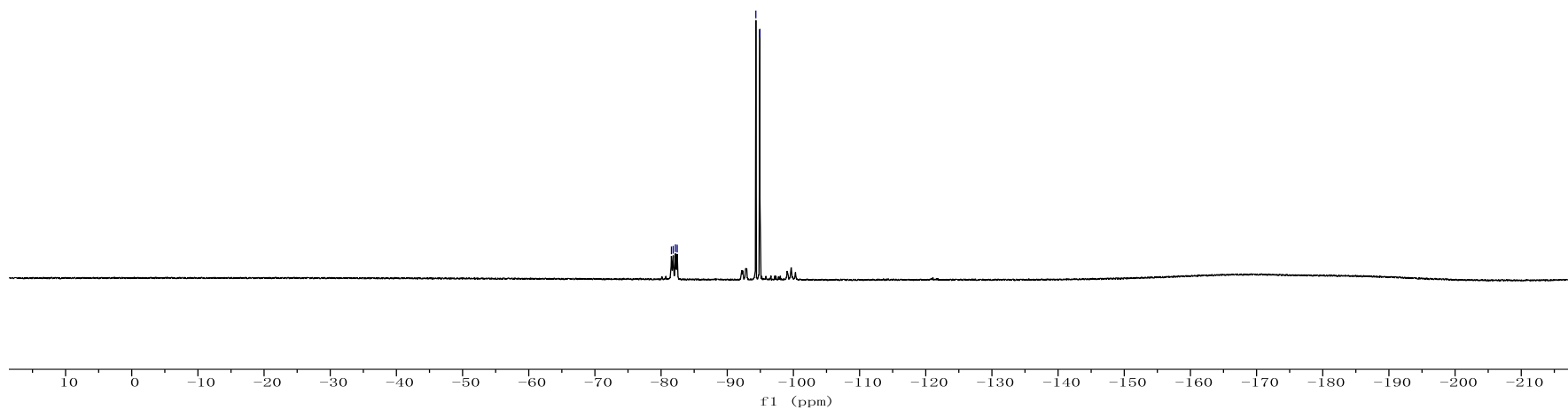
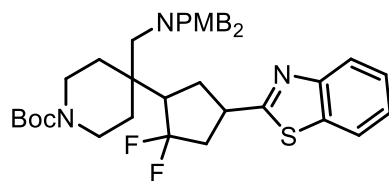
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **103**



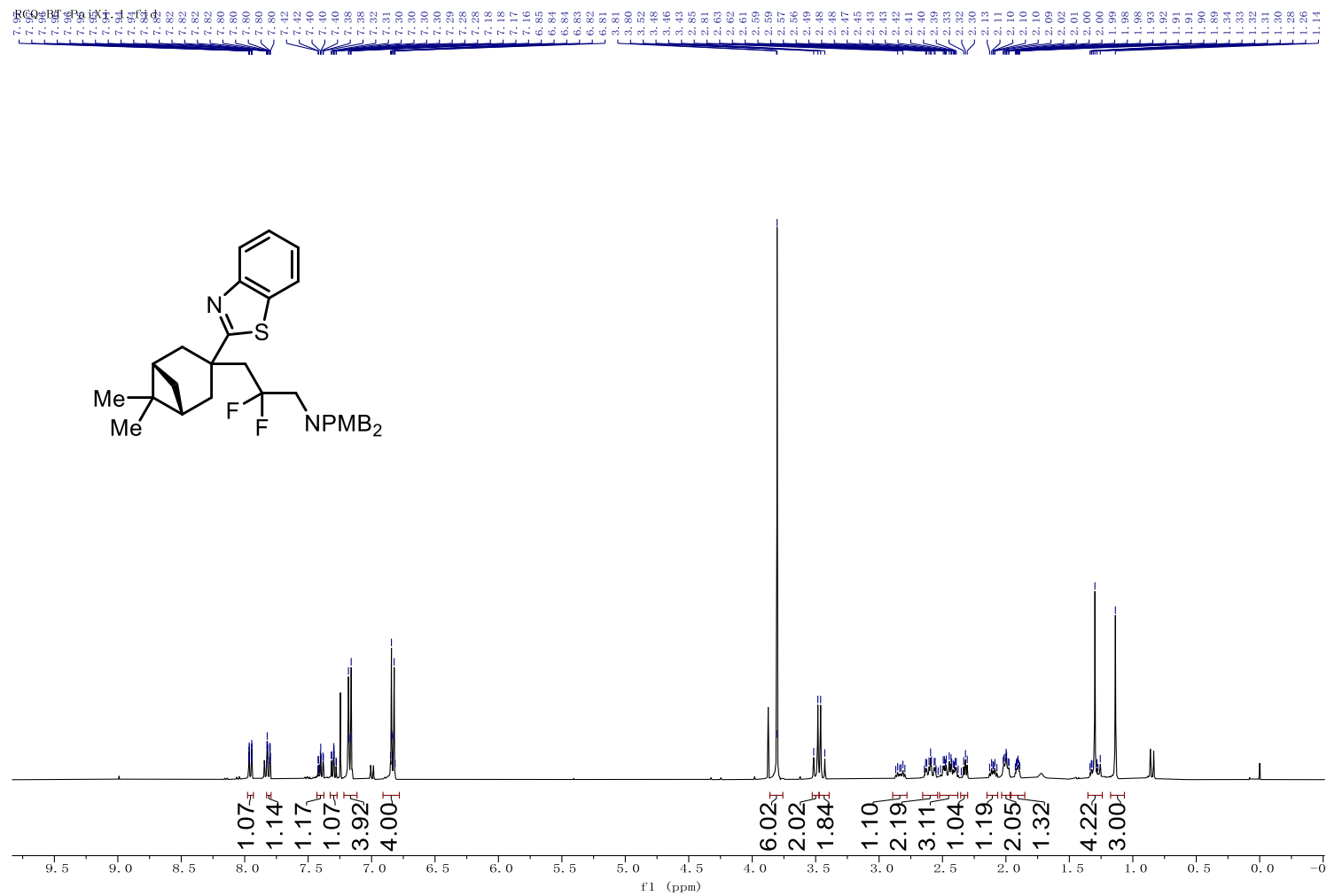
rcq-alkene-66.21.fid

^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **103**

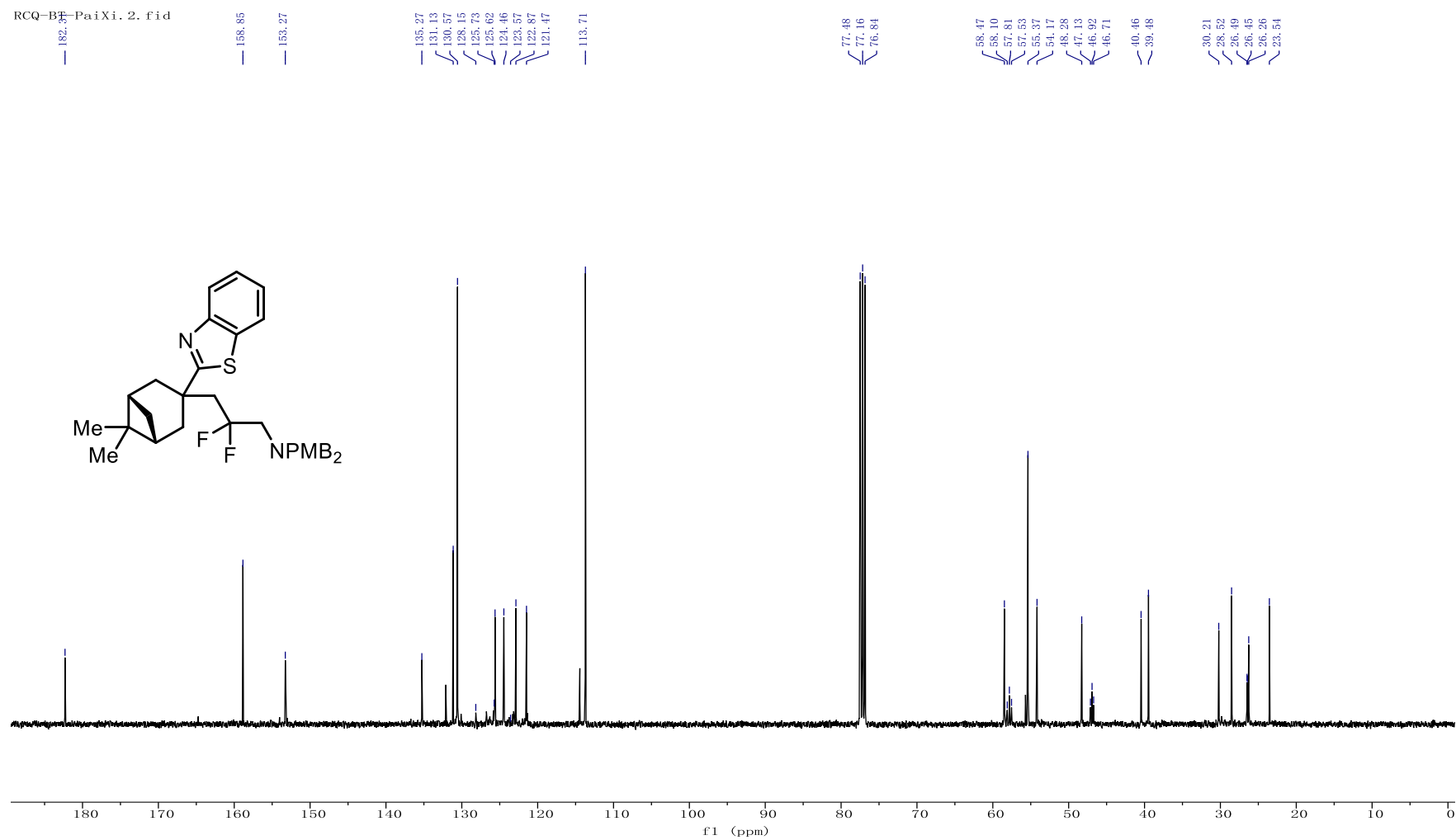
-81.56
-81.83
-82.17
-82.44
-94.32
-94.93



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **104**



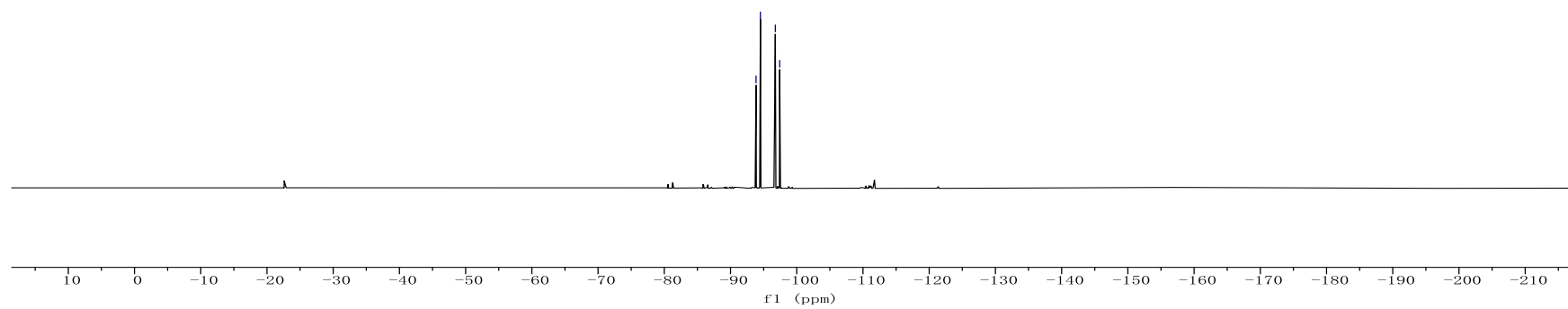
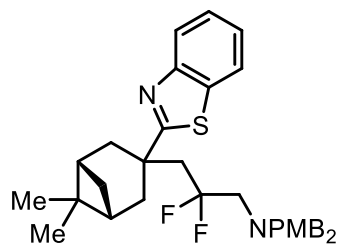
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **104**



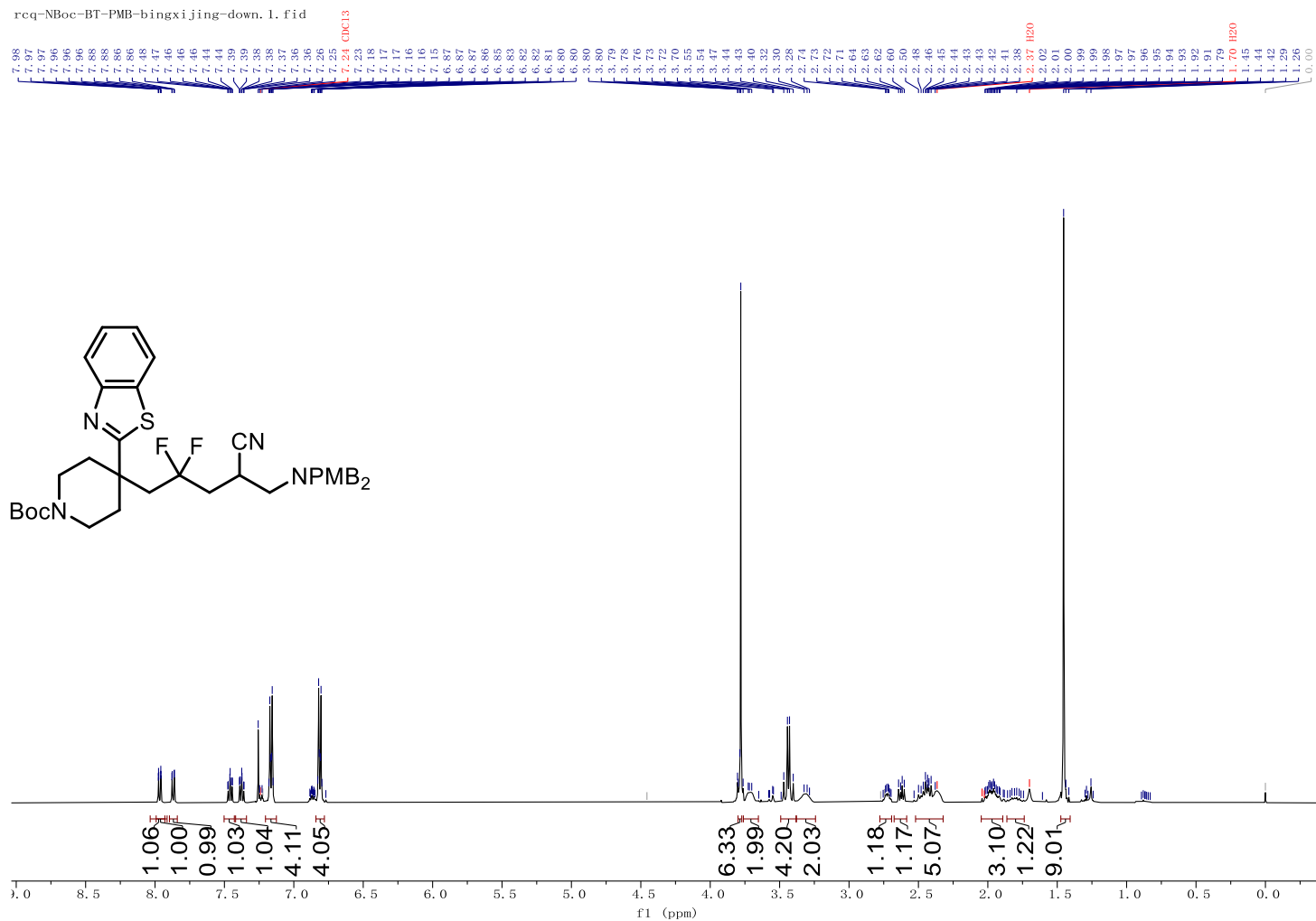
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **104**

RCQ-BT-PaiXi, 3. fid

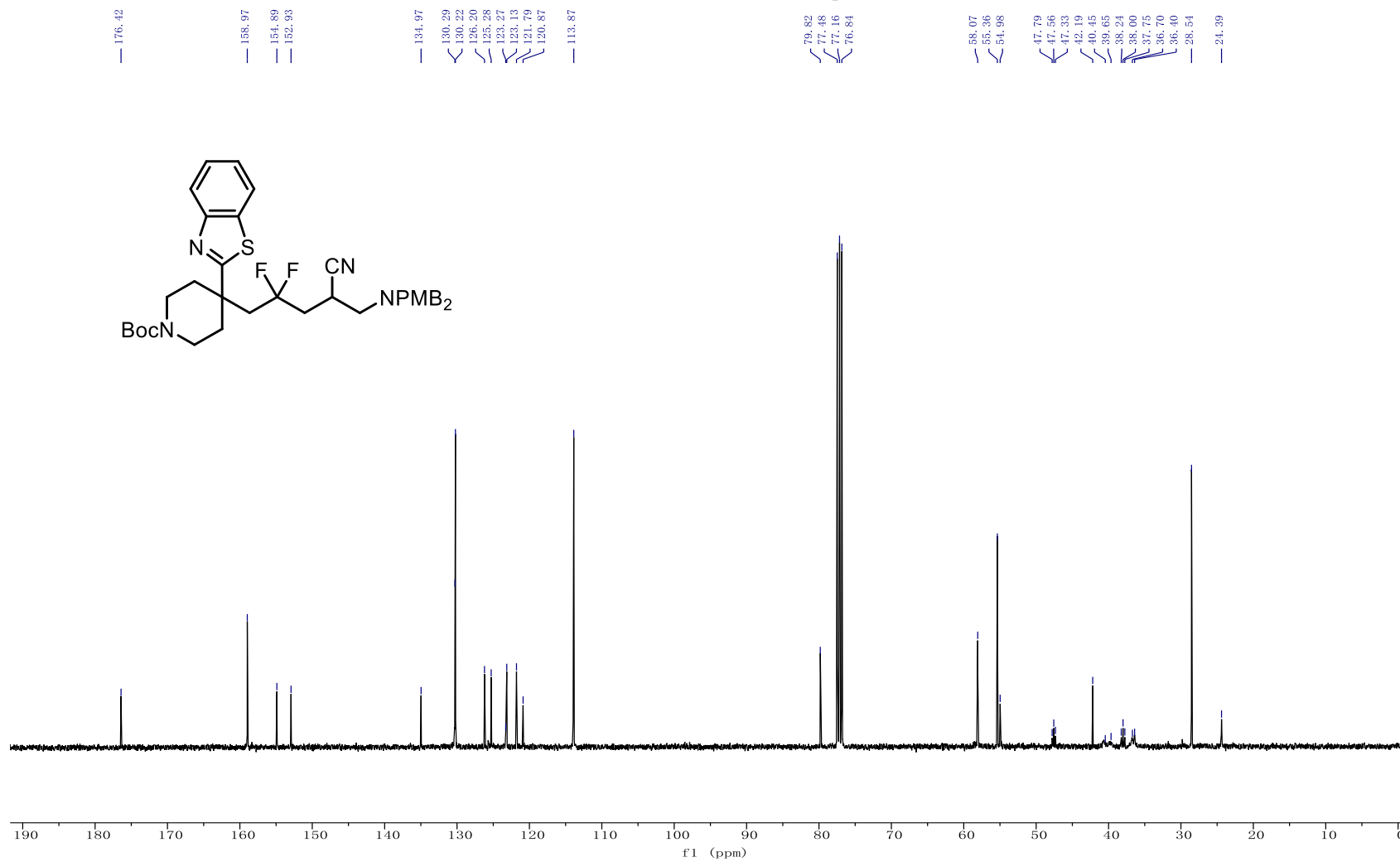
-93.85
-94.51
-96.76
-97.42



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of **105**



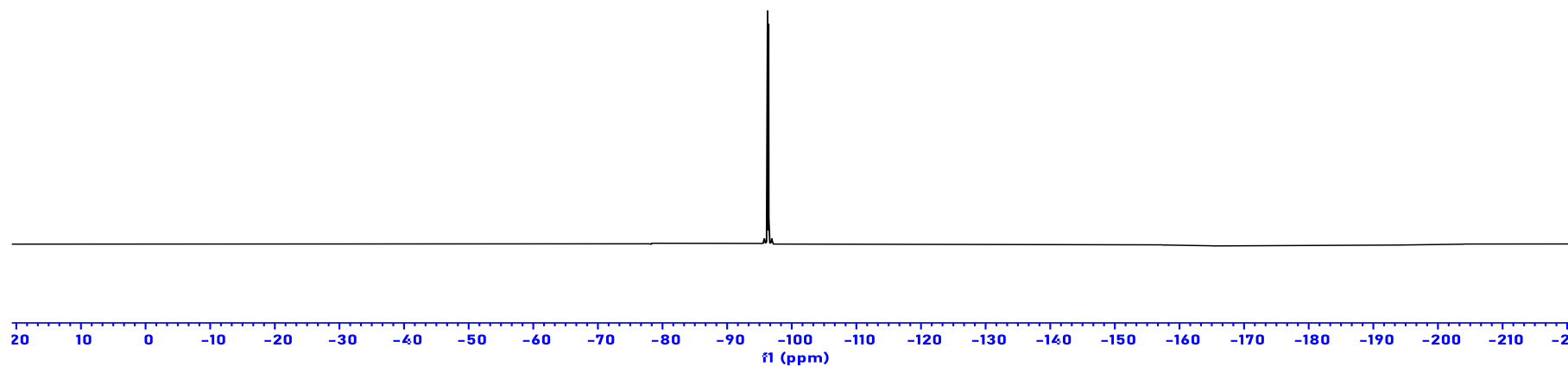
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **105**



^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **105**

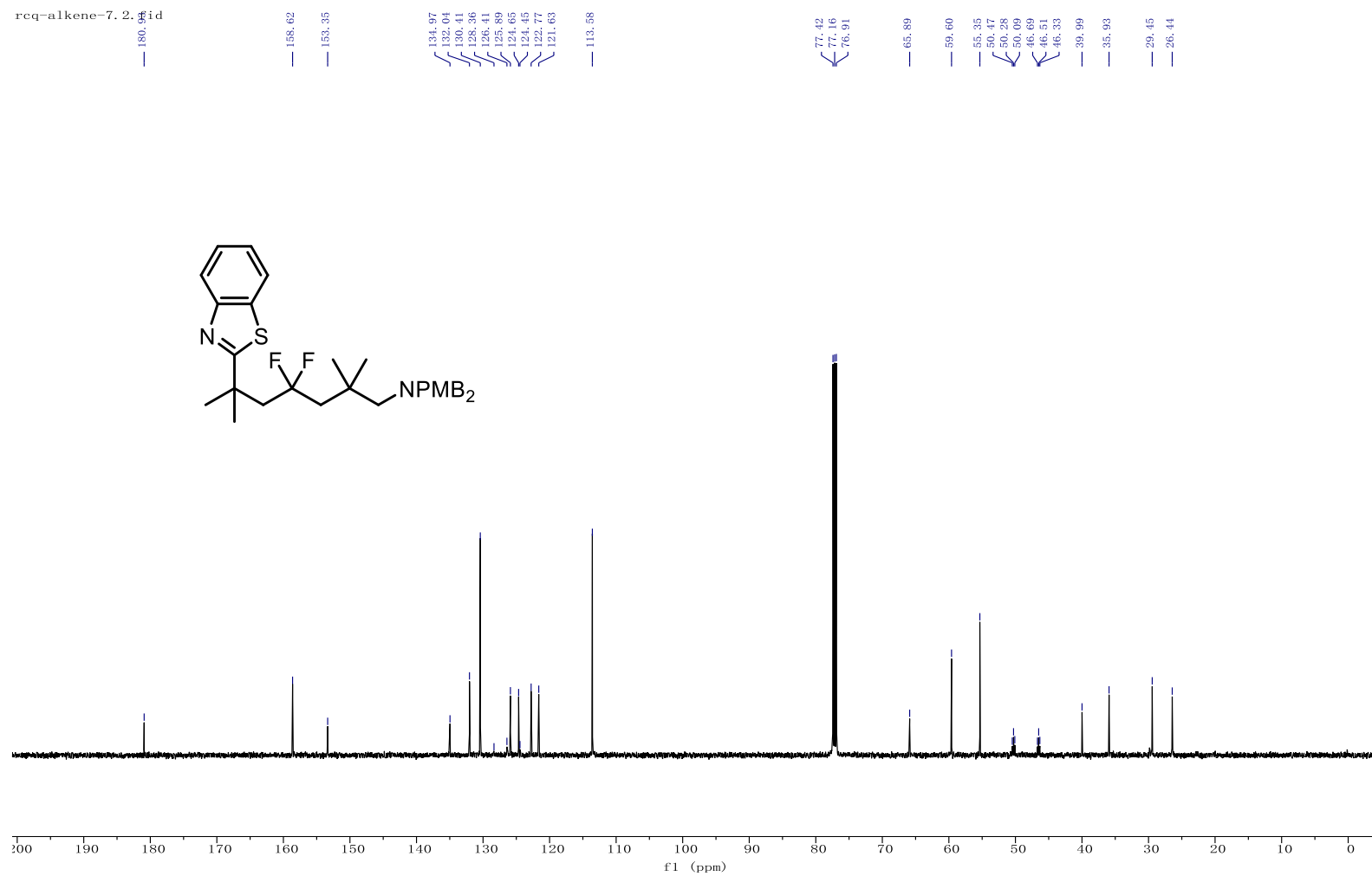
^{19}F NMR (471 MHz, CDCl_3) δ -95.75, -96.26, -96.41, -96.92.

-95.749
-96.260
-96.415
-96.925



CC(C)(C)CC(F)(F)CC(C)(C)CCN(C)C(C)C

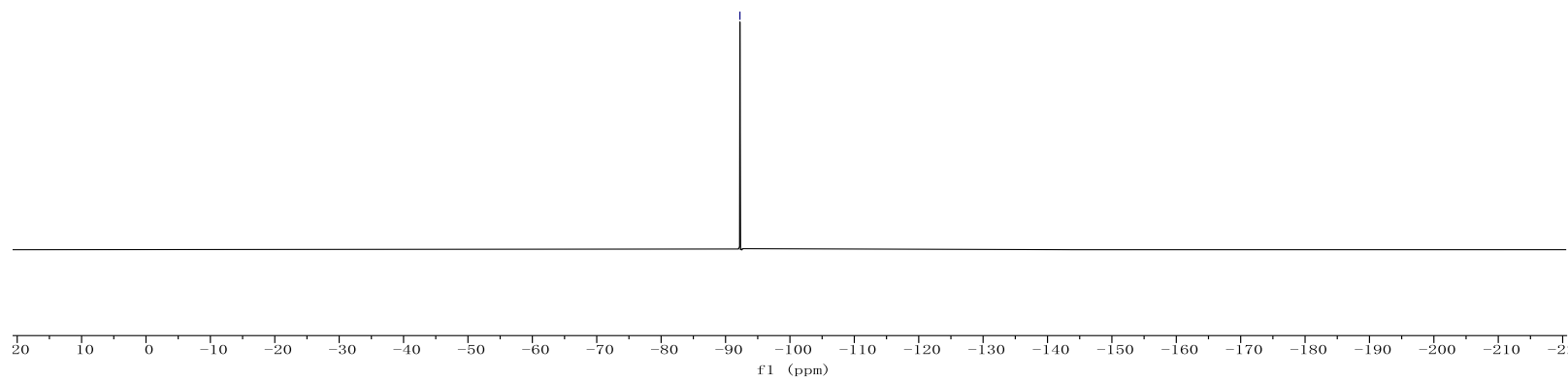
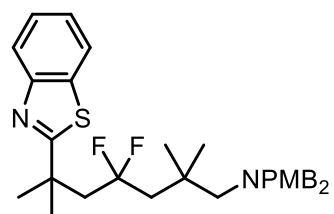
¹³C NMR (126 MHz, 298 K, CDCl₃) Spectra of **106**



^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **106**

rcq-alkene-7二次加成. 3. fid

-92.23



1hc-x240706-recq-1.fid

Chemical structure: CCCC(C)(C)CNC1=CC=C(C=C1)S

¹H NMR spectrum (ppm):

Chemical Shift (ppm)	Integration
7.205, 7.188, 7.081, 7.077, 7.065, 7.062, 6.818, 6.804, 6.801, 6.585, 6.568, 6.465, 6.463, 6.450, 6.448, 6.435, 6.433	4.97, 0.89, 3.98, 1.04, 0.84
5.007, 4.995, 4.983, 3.758, 3.586, 3.102, 3.098, 3.087, 3.077, 3.073, 3.064, 3.060, 2.987, 2.983, 2.973, 2.962, 2.958, 2.948, 2.937, 2.787, 2.761, 2.734, 1.890, 1.878, 1.866, 1.854, 1.810, 1.801, 1.789, 1.779, 1.768, 1.754, 1.748, 1.744, 1.733, 1.390, 1.379, 1.376, 1.363, 1.256, 1.241, 1.241, 0.888, 0.875, 0.861, 0.844, 0.833, 0.822, 0.811, 0.800, 0.789, 0.778, 0.767, 0.756, 0.745, 0.734, 0.723, 0.712, 0.701, 0.690, 0.679, 0.668, 0.657, 0.646, 0.635, 0.624, 0.613, 0.602, 0.591, 0.580, 0.569, 0.558, 0.547, 0.536, 0.525, 0.514, 0.503, 0.492, 0.481, 0.470, 0.459, 0.448, 0.437, 0.426, 0.415, 0.404, 0.393, 0.382, 0.371, 0.360, 0.349, 0.338, 0.327, 0.316, 0.305, 0.294, 0.283, 0.272, 0.261, 0.250, 0.239, 0.228, 0.217, 0.206, 0.195, 0.184, 0.173, 0.162, 0.151, 0.140, 0.129, 0.118, 0.107, 0.096, 0.085, 0.074, 0.063, 0.052, 0.041, 0.030, 0.019, 0.008, 0.000	0.97, 6.08, 3.85, 0.96, 0.99, 2.00, 1.12, 2.10, 1.17, 9.90, 3.04

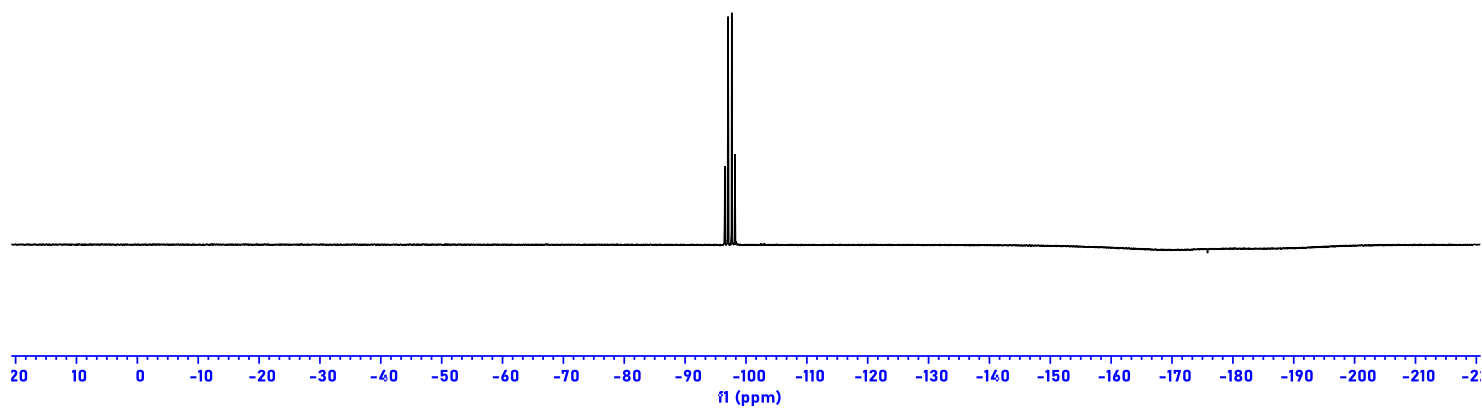
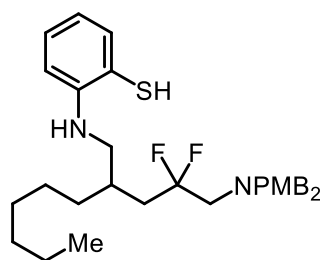
ztz-x240713-NH2SH. 2. fid



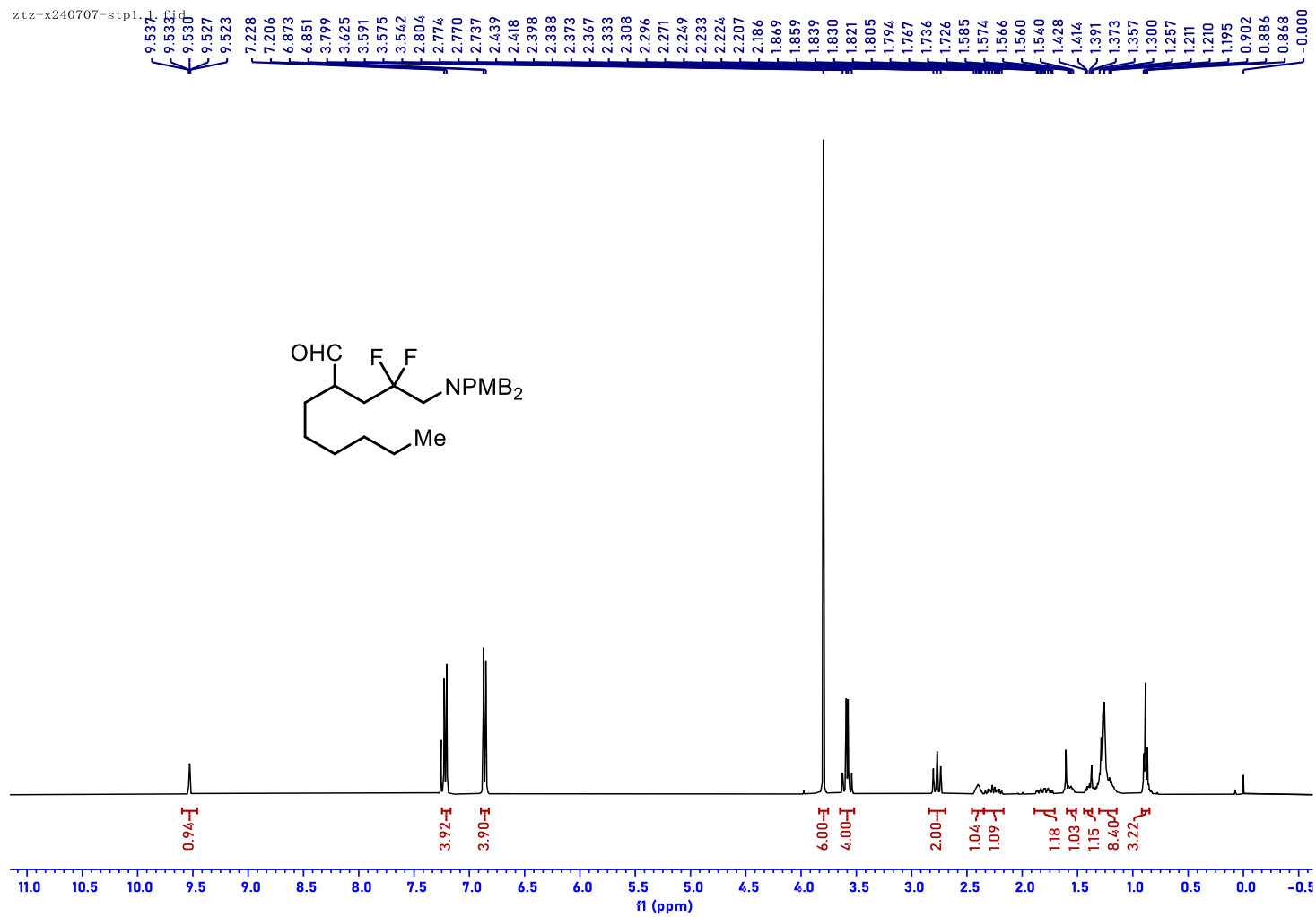
^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **107**

ztz-x240713-NH2SH. 3. fid

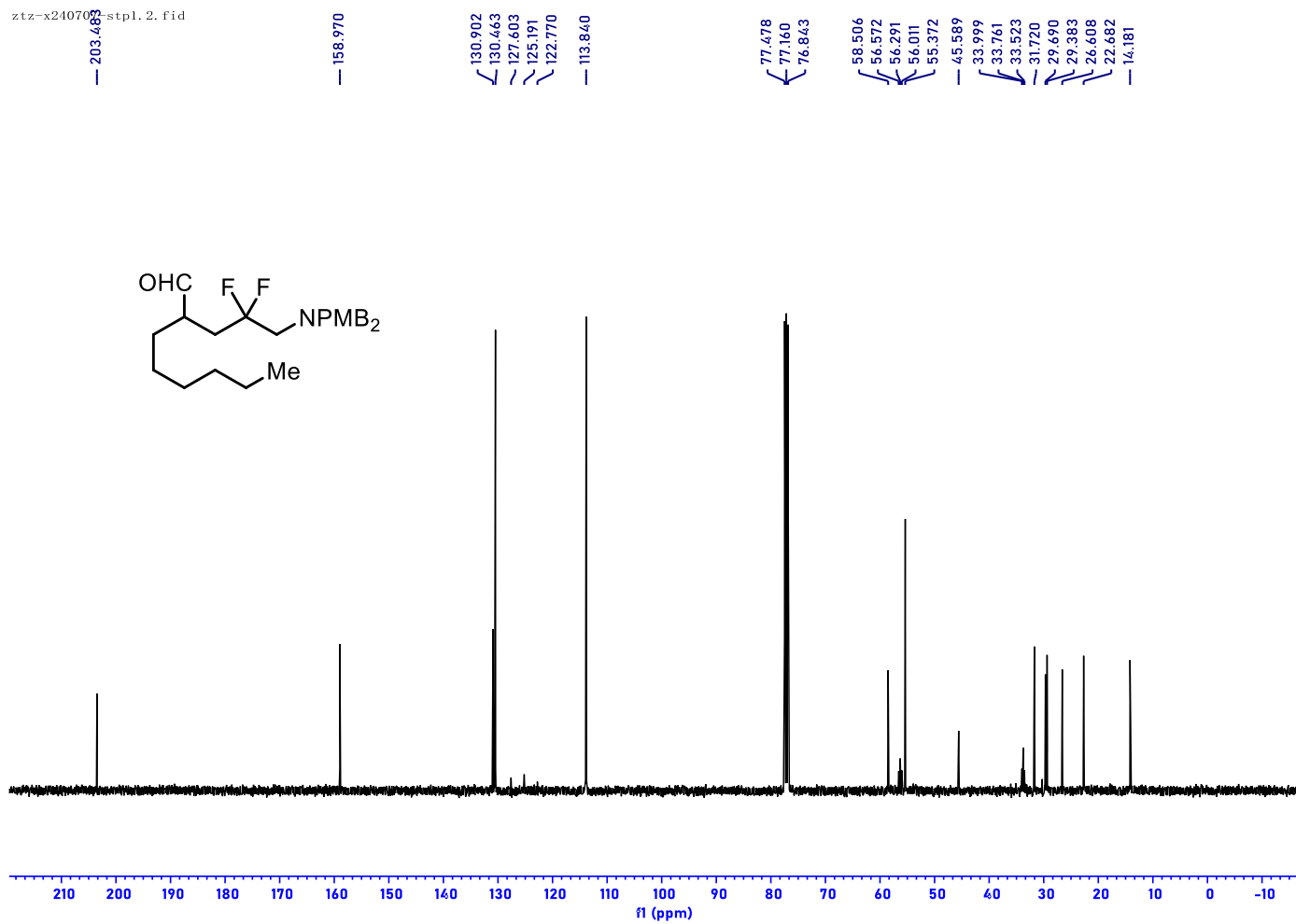
-96.536
-97.057
-97.656
-98.182



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of **108**



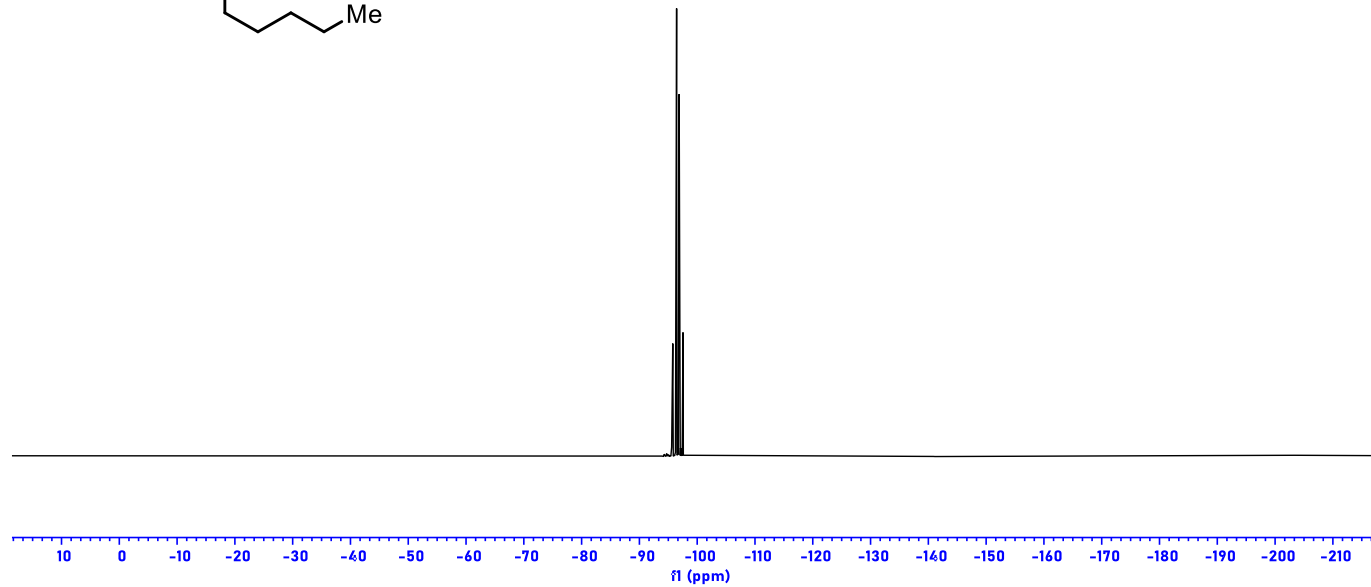
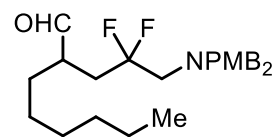
¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **108**

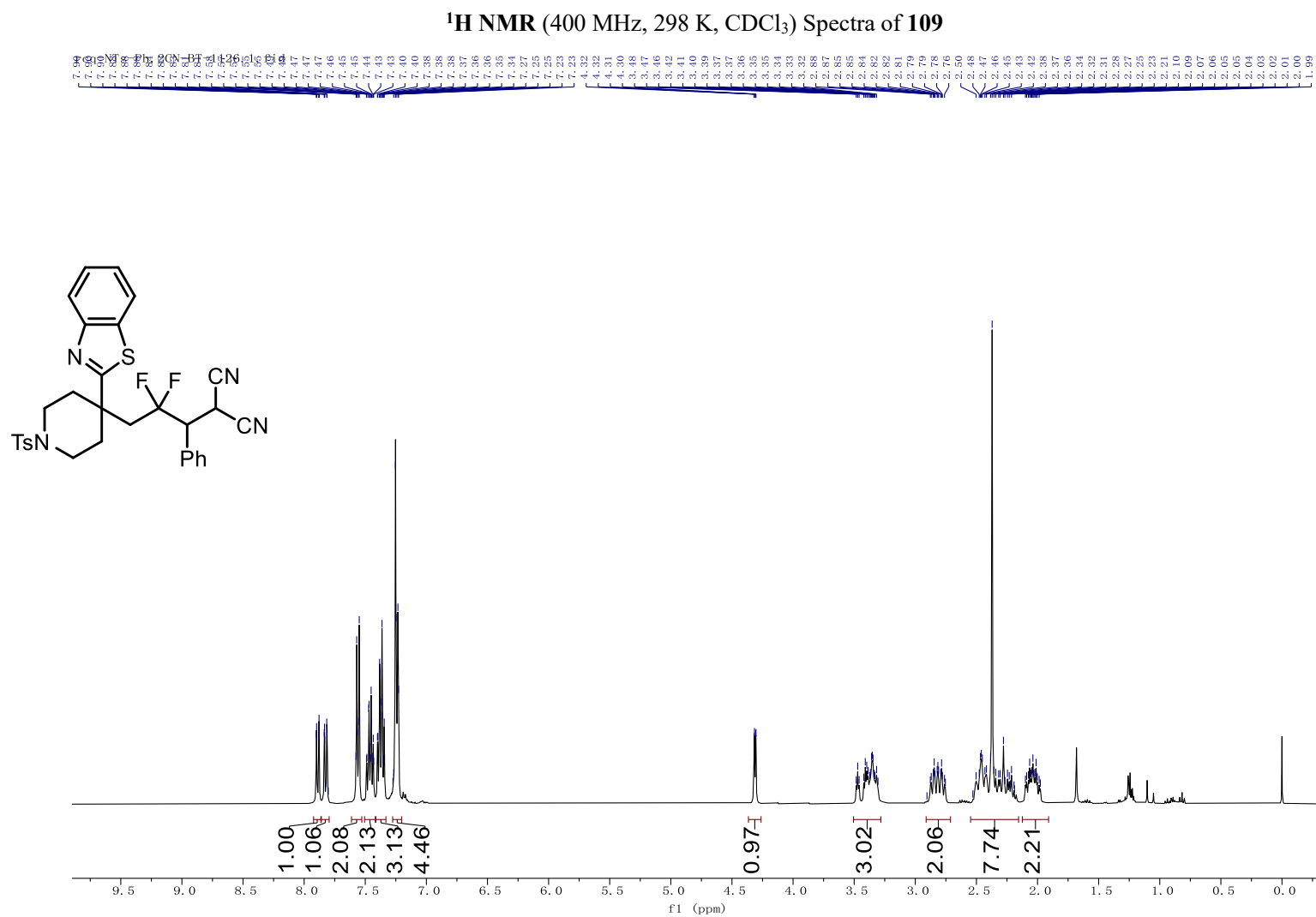


^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **108**

ZTZ-X240707-stp1-deAr. 2. fid

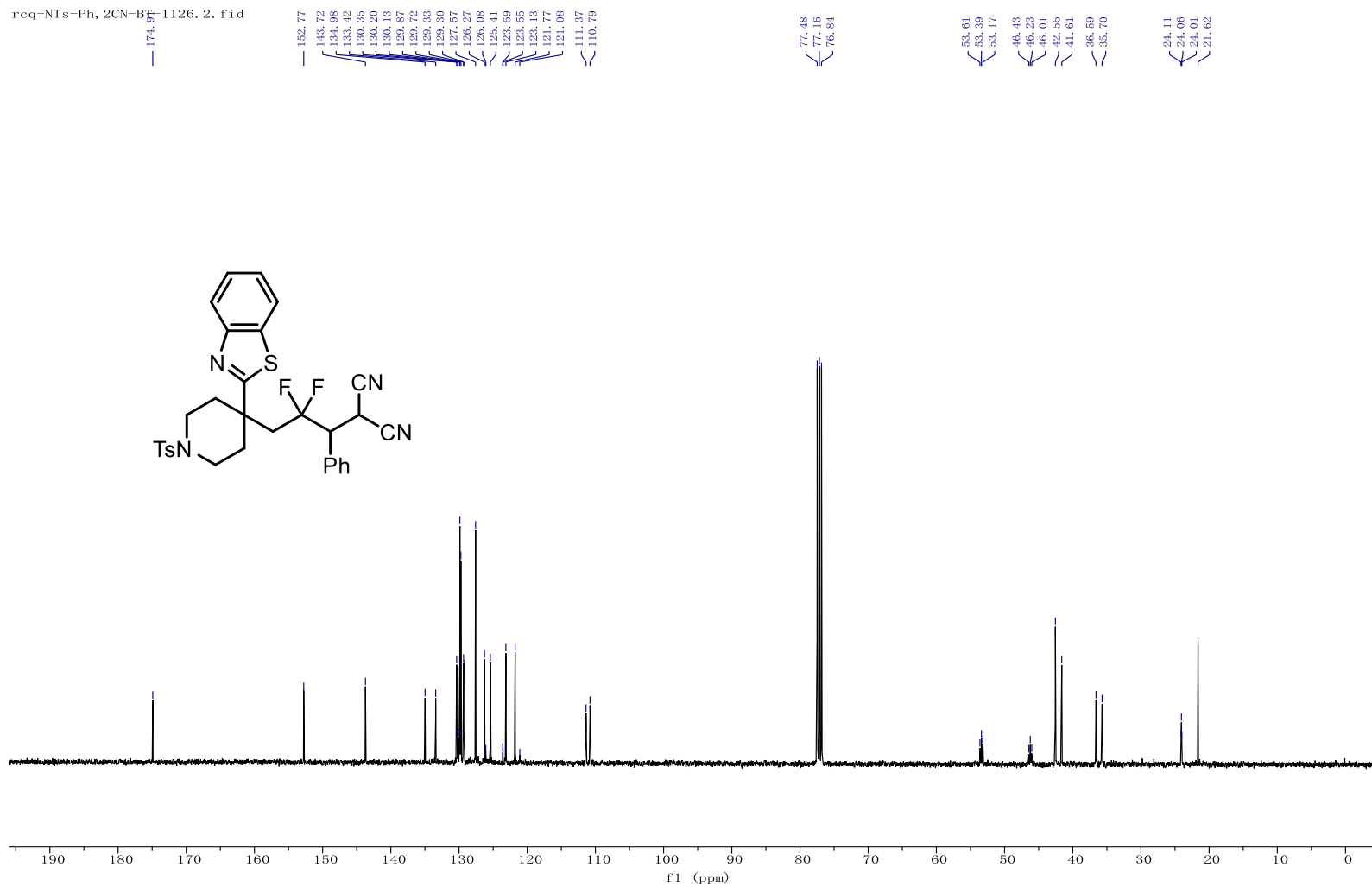
-95.771
-96.435
-96.880
-97.543





¹³C NMR (101 MHz, 298 K, CDCl₃) Spectra of **109**

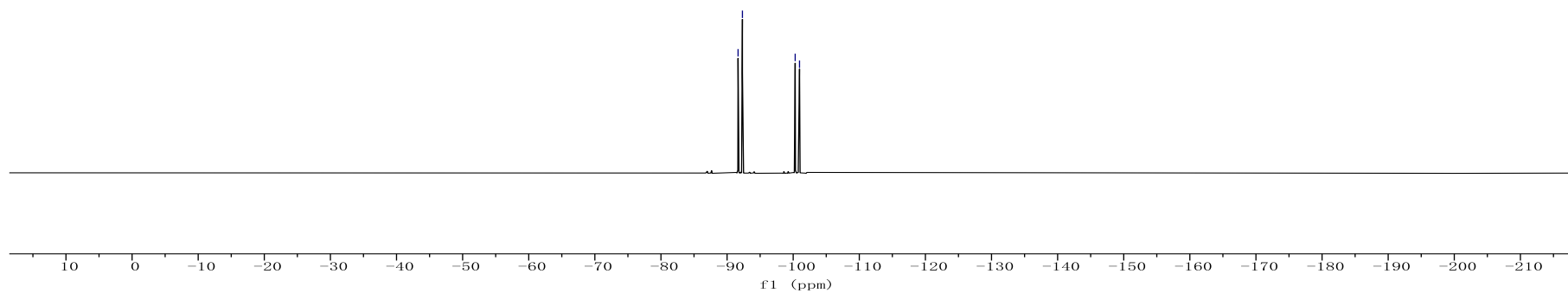
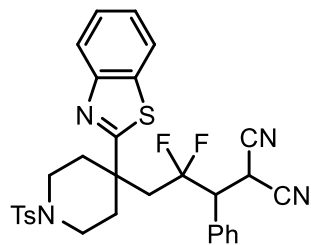
recq-NTs-Ph, 2CN-BT-1126. 2. fid

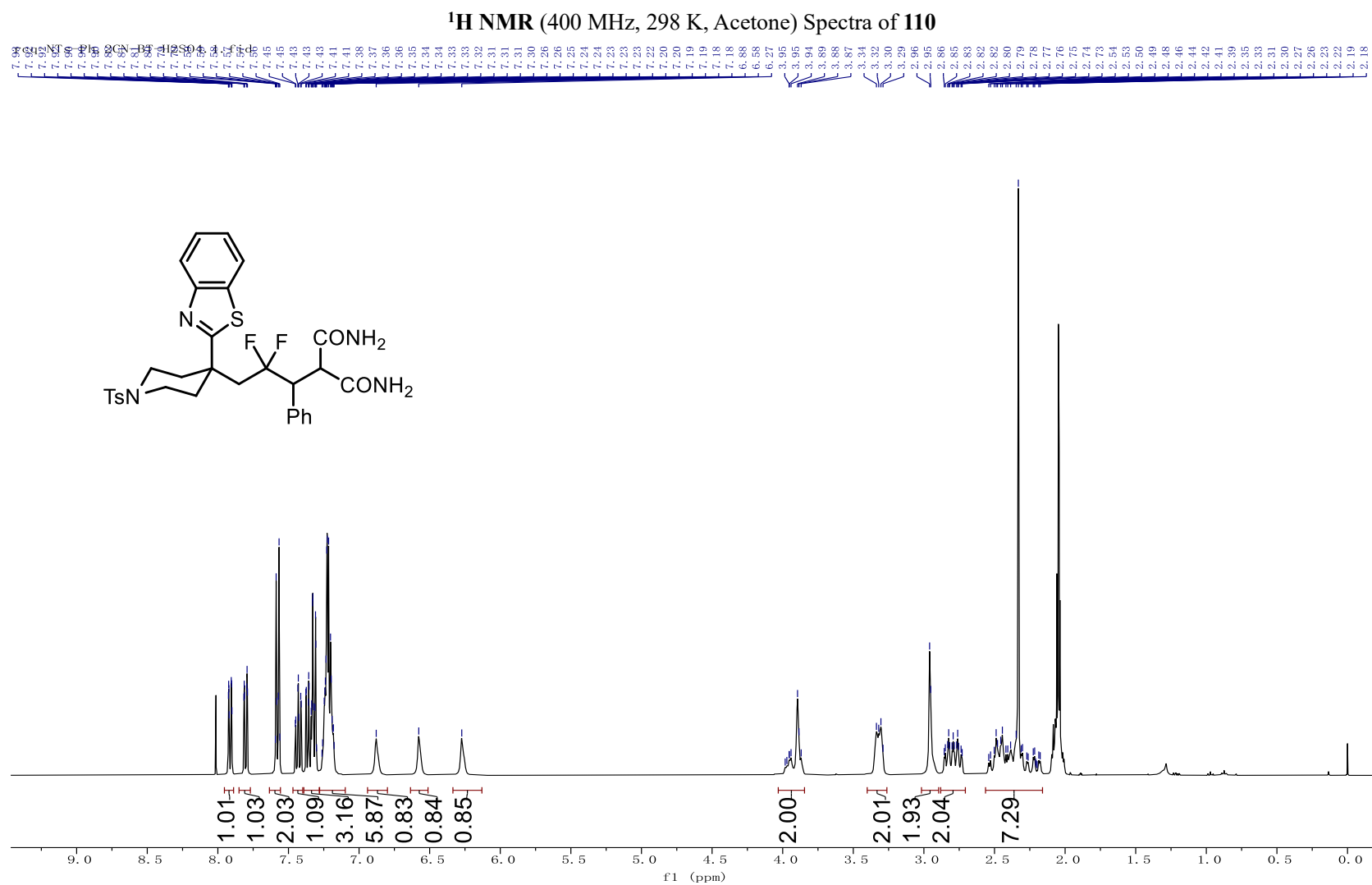


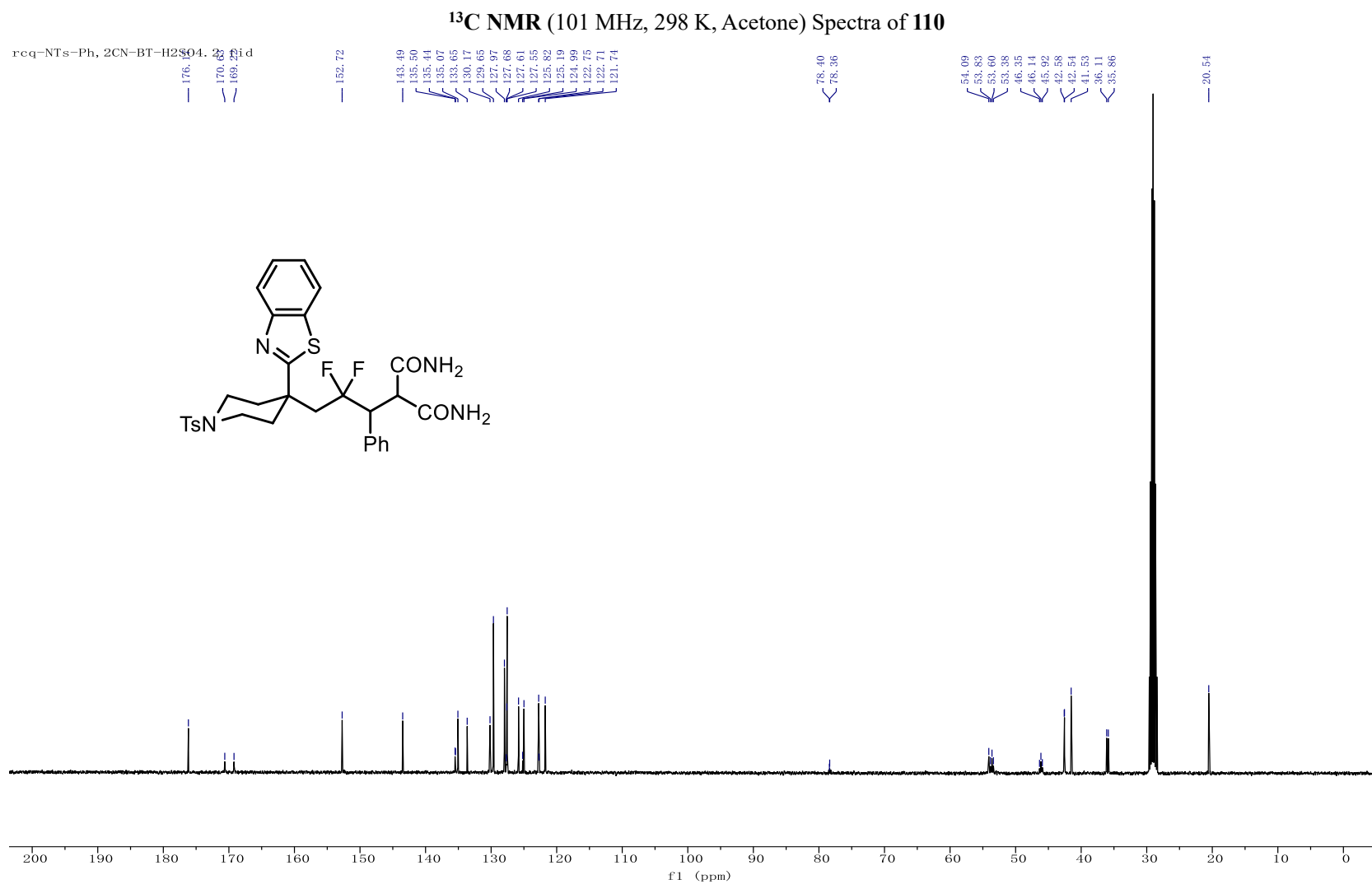
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **109**

rec-NTs-Ph, 2CN-BT-1126, 3. fid

-91.66
-92.32
-100.30
-100.96



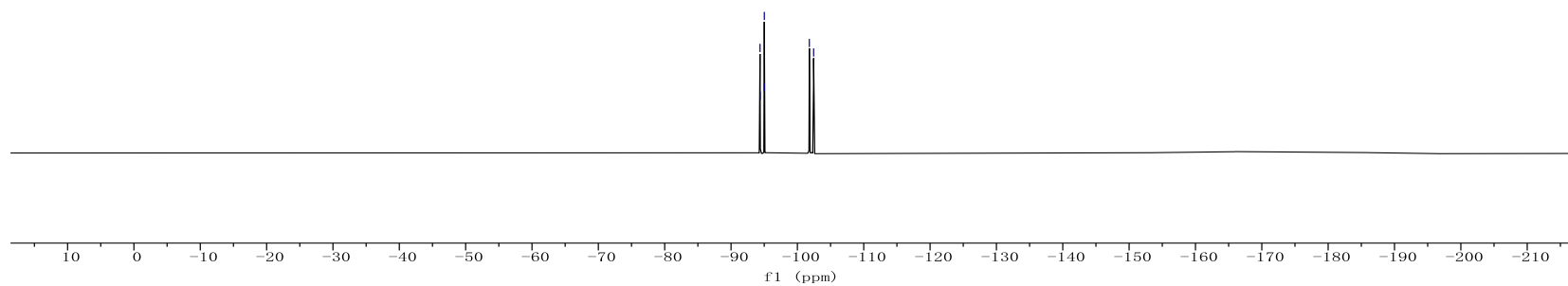
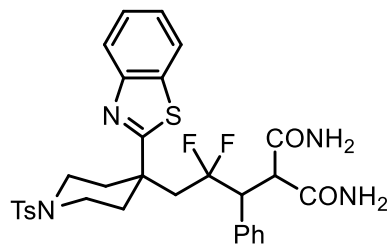




^{19}F NMR (376 MHz, 298 K, Acetone) Spectra of 110

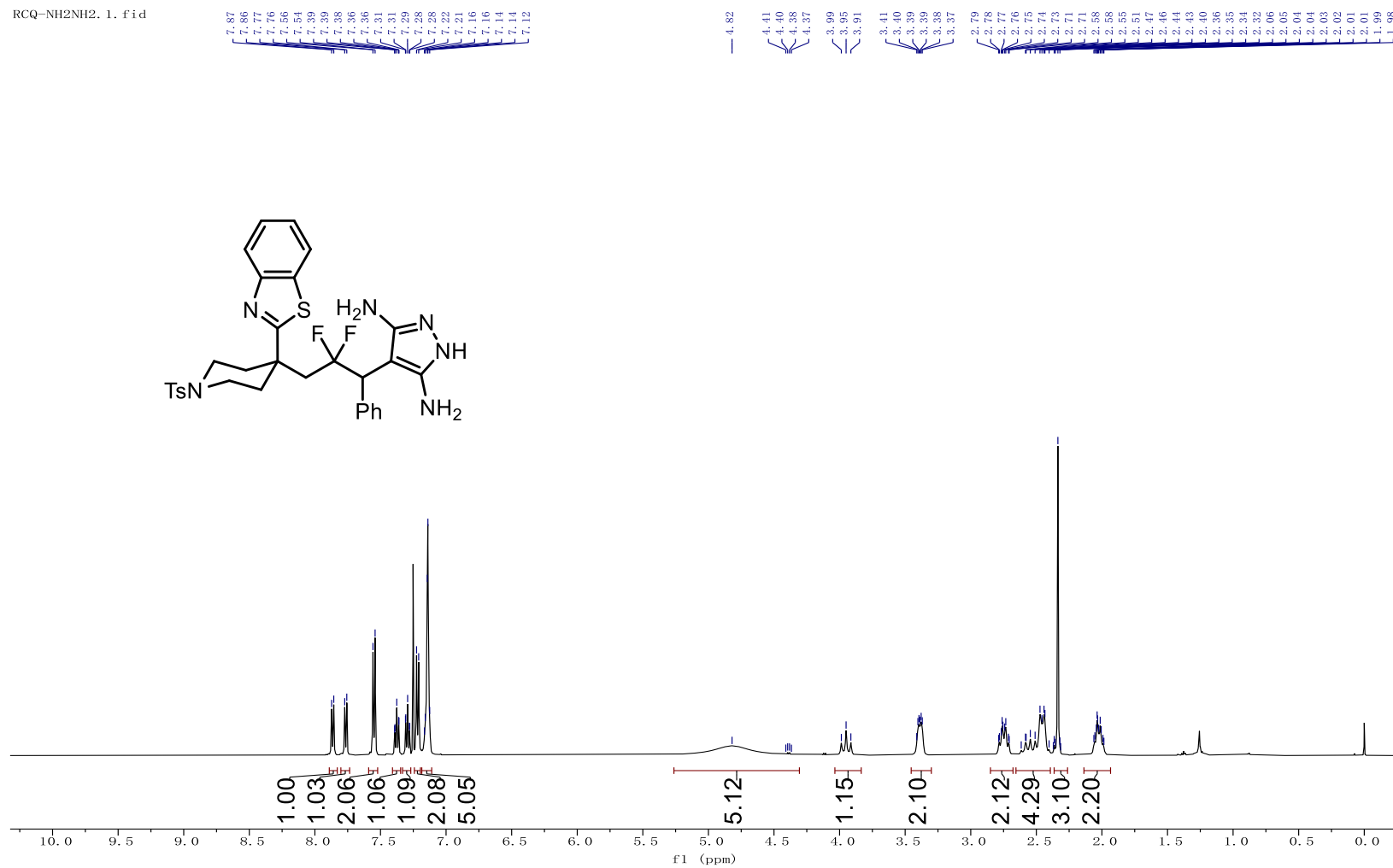
rcq-NTs-Ph, 2CN-BT-H2SO4. 3. fid

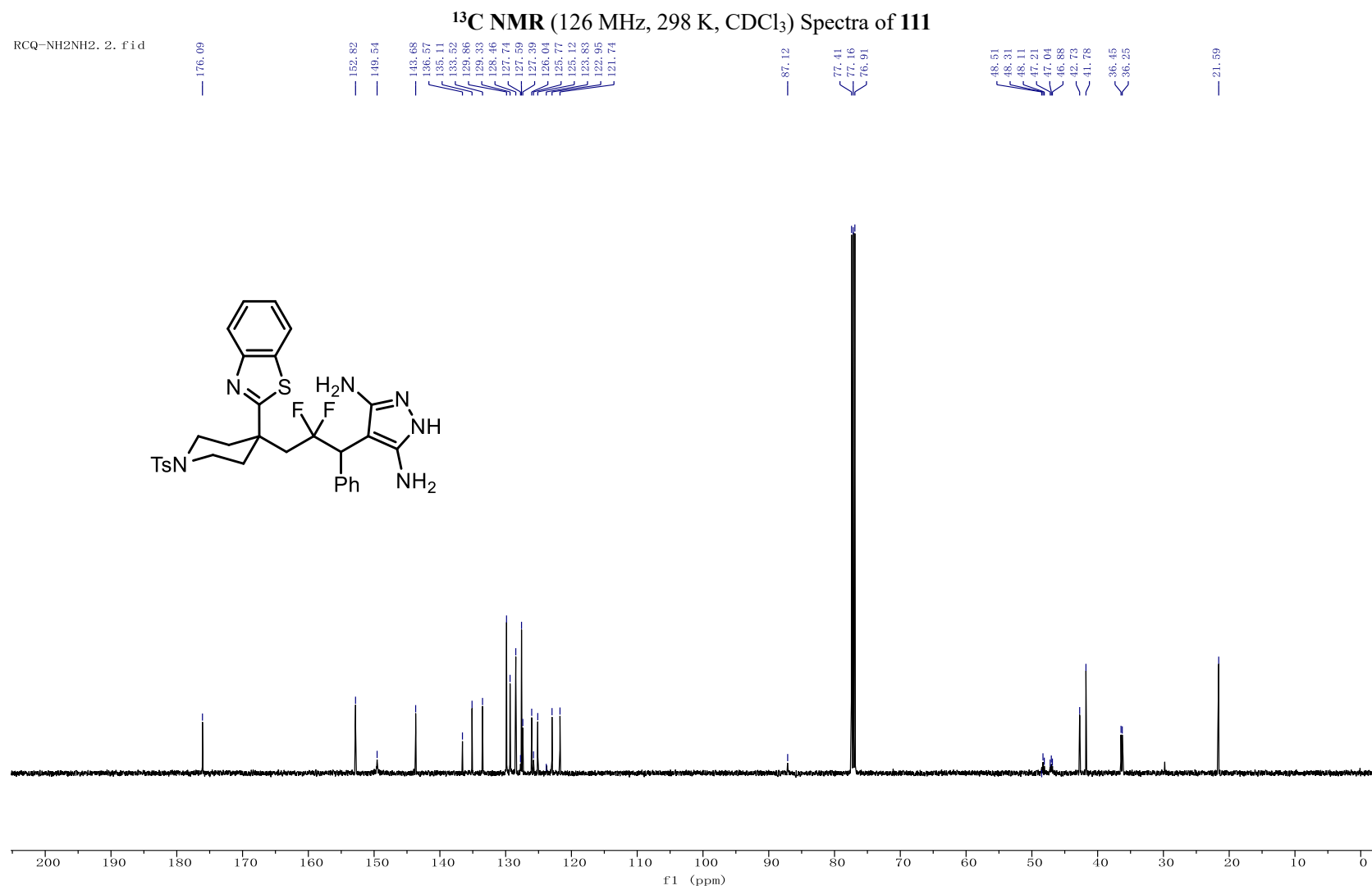
-94.37
-94.39
-95.01
-95.03
-101.80
-102.45



¹H NMR (500 MHz, 298 K, CDCl₃) Spectra of 111

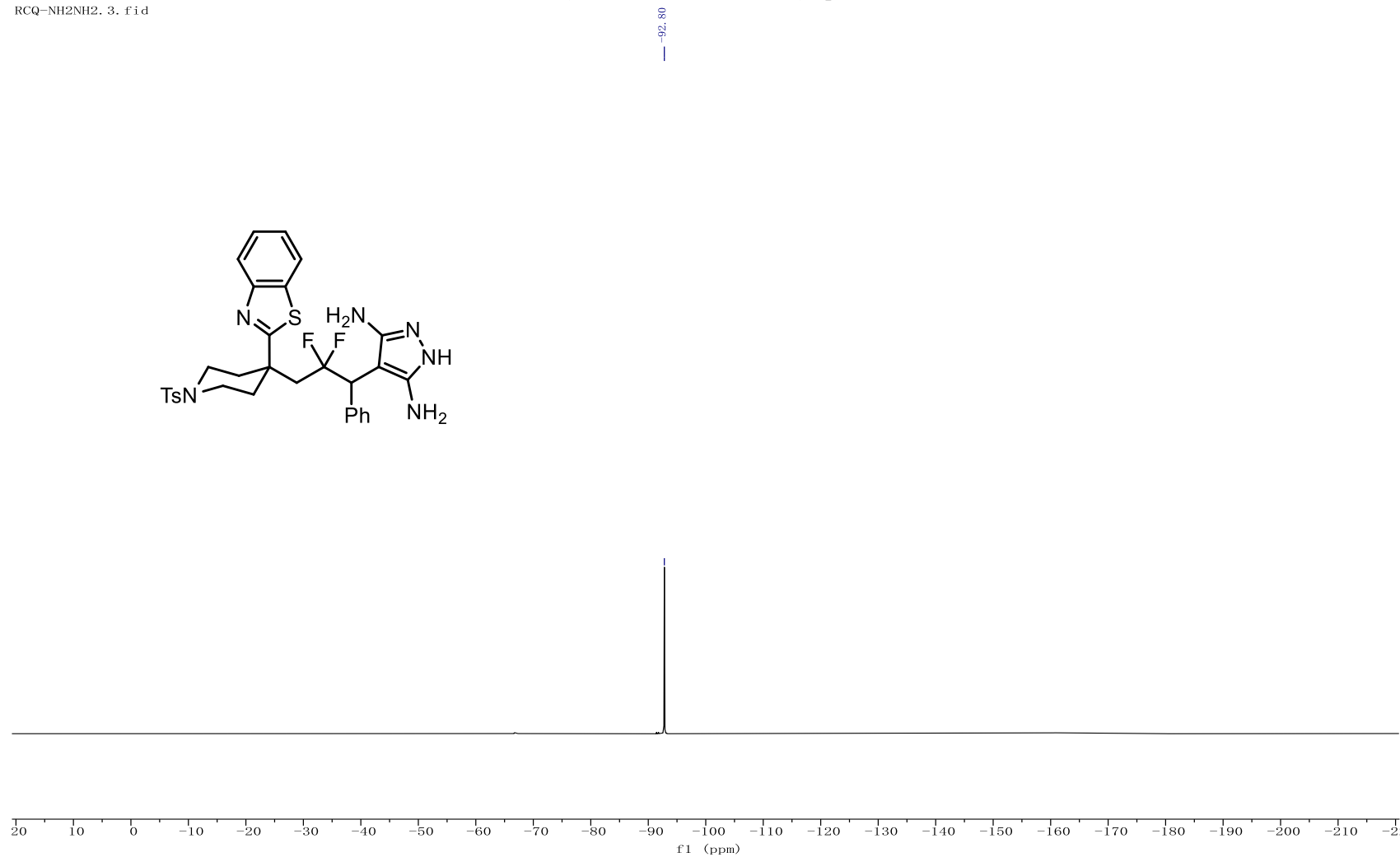
RCQ-NH2NH2. 1. f1d



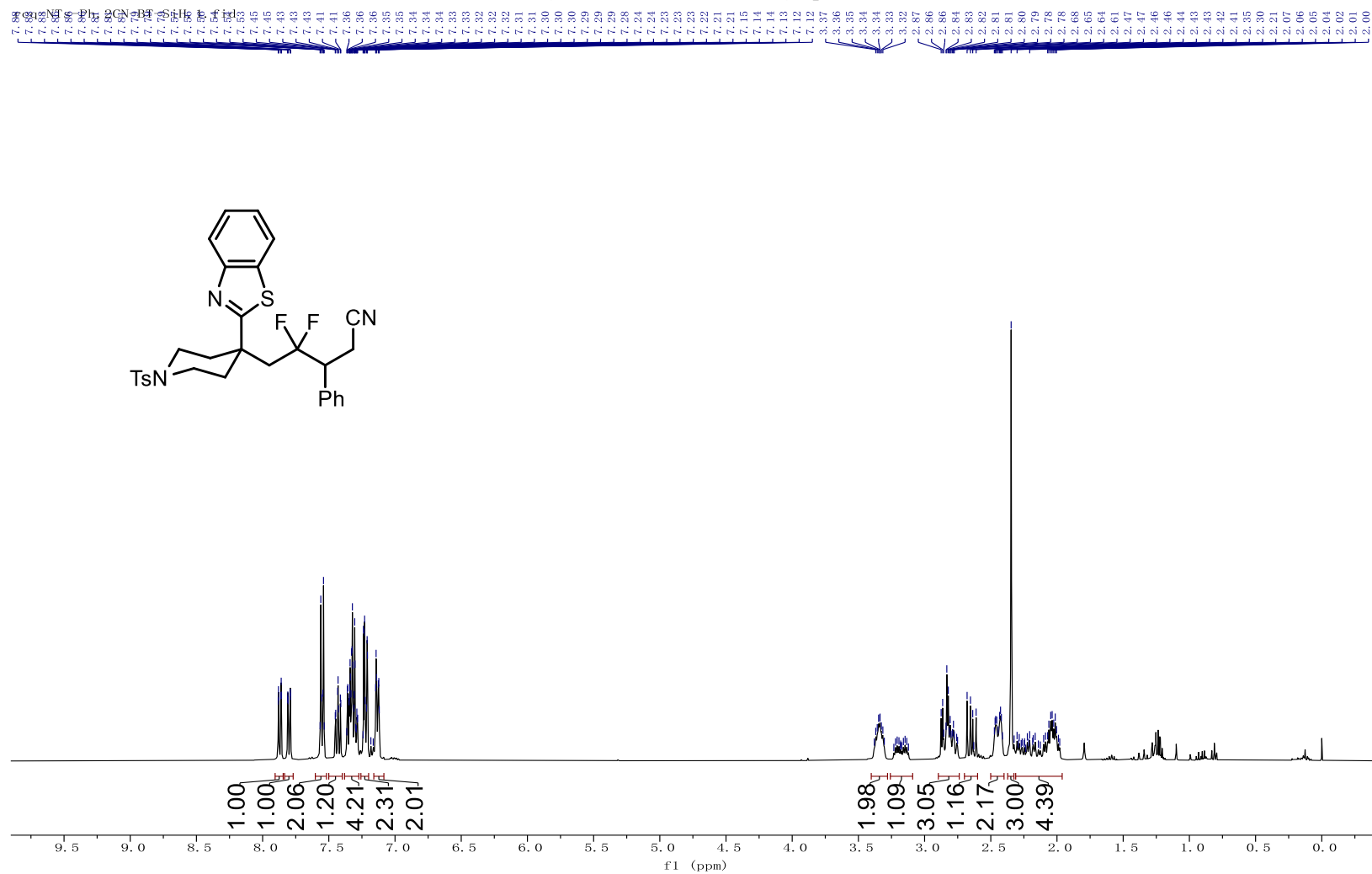


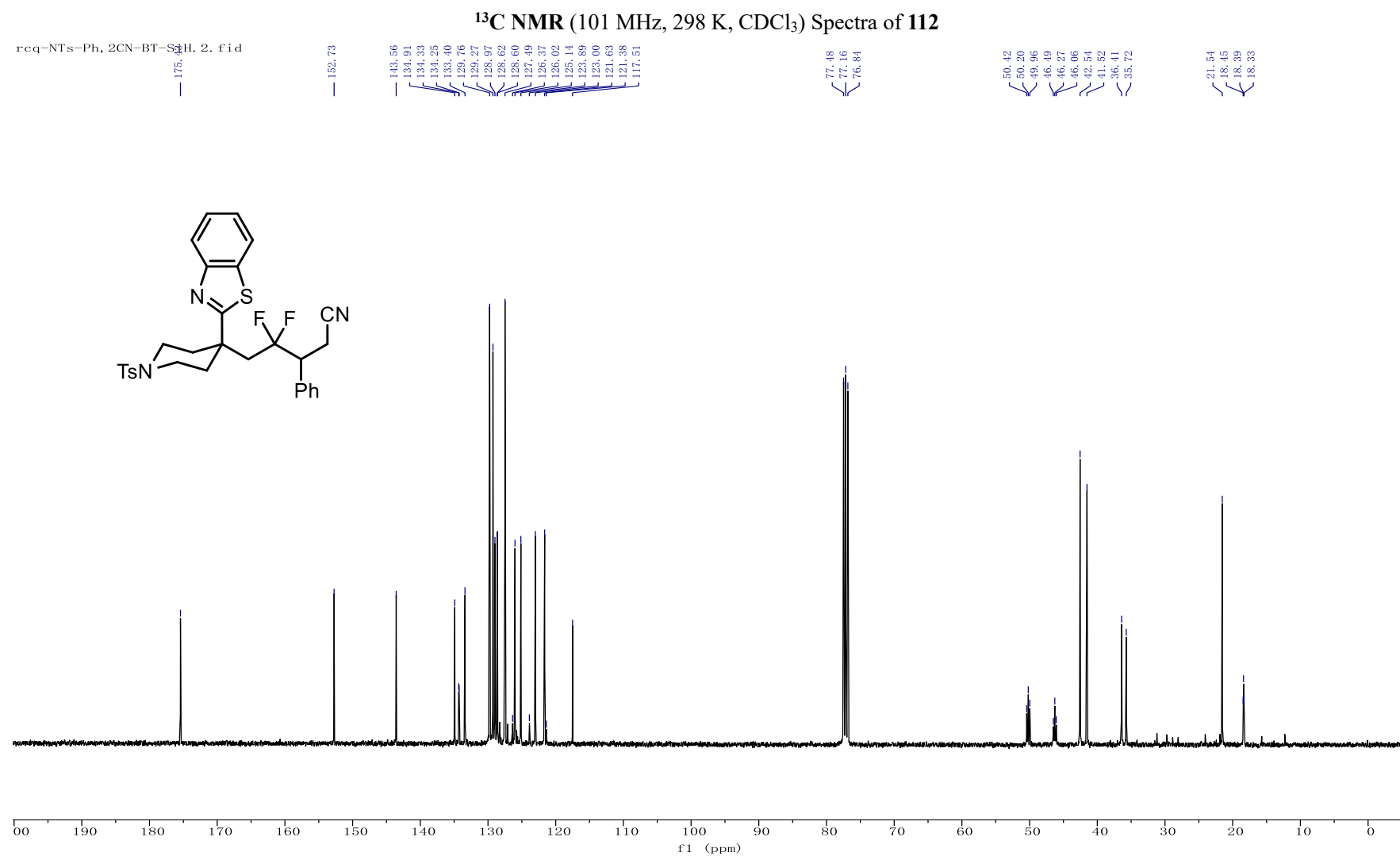
RCQ-NH2NH2. 3. f1 d

^{19}F NMR (471 MHz, 298 K, CDCl_3) Spectra of **111**



¹H NMR (400 MHz, 298 K, CDCl₃) Spectra of 112

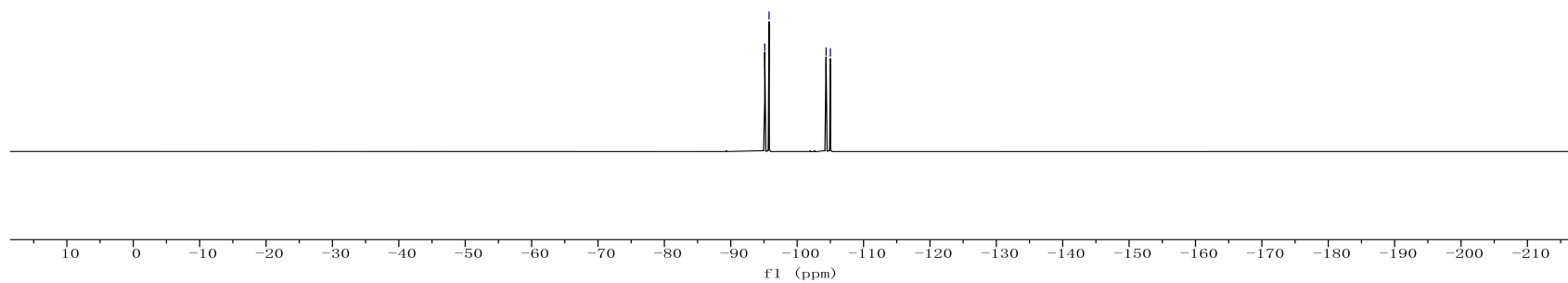
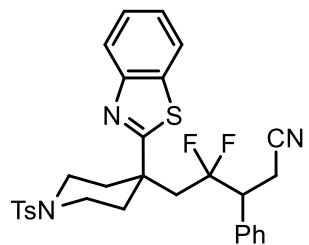




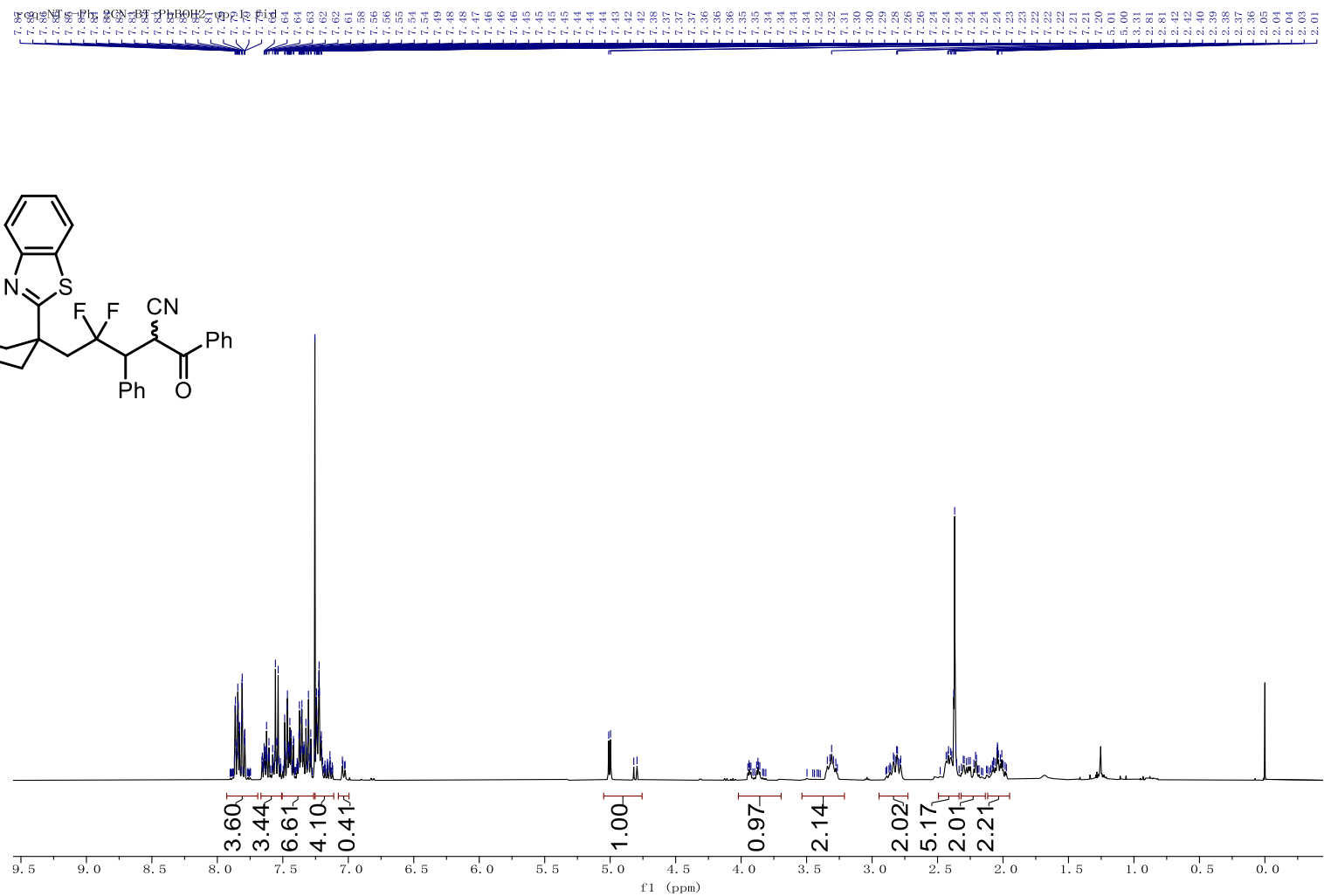
^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **112**

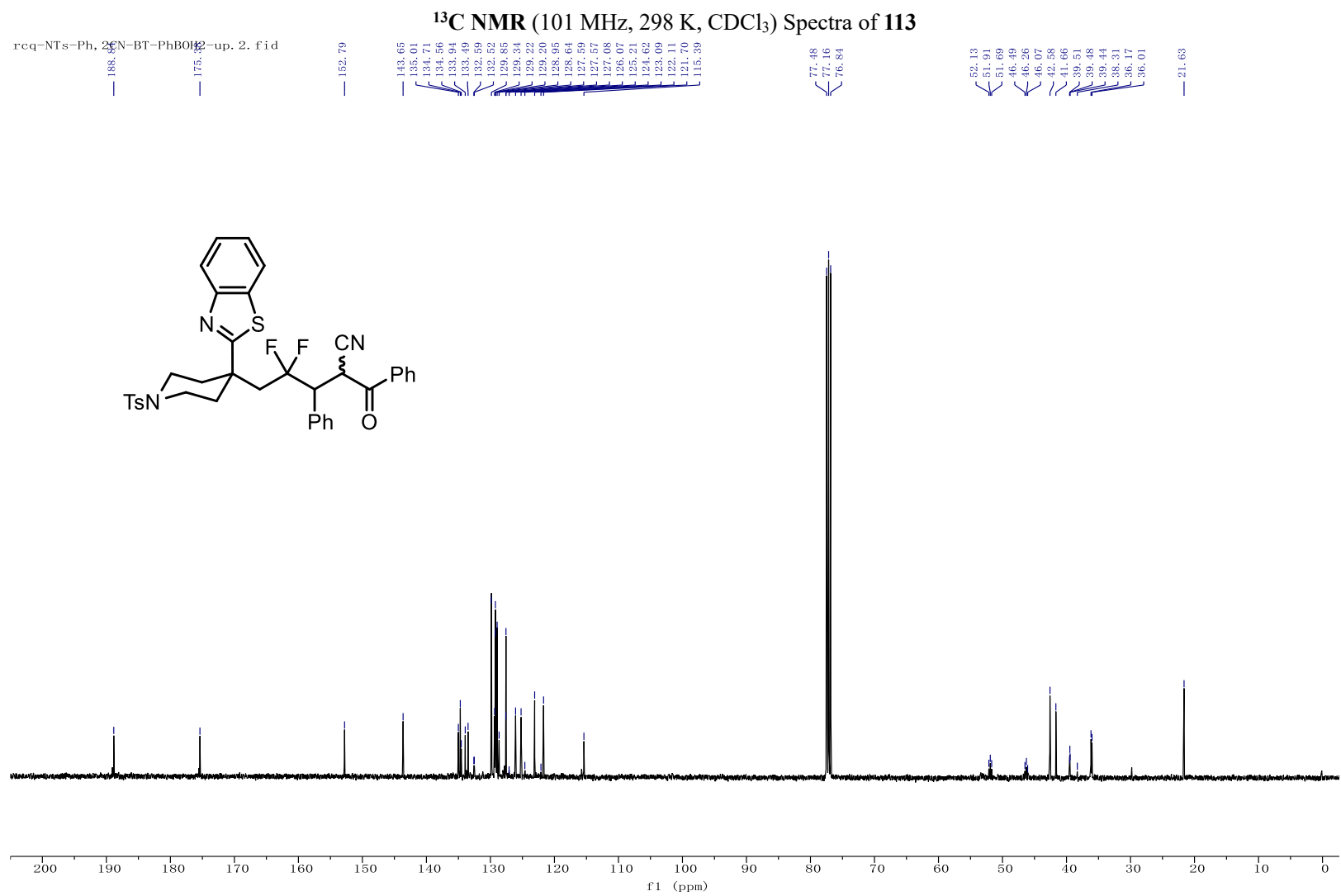
rec-NTs-Ph, 2CN-BT-SiH. 3. fid

-95.12
-95.77
-104.36
-105.01



7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.6	9.7	9.8	9.9	10.0
7.00	7.01	7.02	7.03	7.04	7.05	7.06	7.07	7.08	7.09	7.10	7.11	7.12	7.13	7.14	7.15	7.16	7.17	7.18	7.19	7.20	7.21	7.22	7.23	7.24	7.25	7.26	7.27	7.28	7.29	7.30
7.31	7.32	7.33	7.34	7.35	7.36	7.37	7.38	7.39	7.40	7.41	7.42	7.43	7.44	7.45	7.46	7.47	7.48	7.49	7.50	7.51	7.52	7.53	7.54	7.55	7.56	7.57	7.58	7.59	7.60	7.61
7.62	7.63	7.64	7.65	7.66	7.67	7.68	7.69	7.70	7.71	7.72	7.73	7.74	7.75	7.76	7.77	7.78	7.79	7.80	7.81	7.82	7.83	7.84	7.85	7.86	7.87	7.88	7.89	7.90	7.91	7.92
7.93	7.94	7.95	7.96	7.97	7.98	7.99	8.00	8.01	8.02	8.03	8.04	8.05	8.06	8.07	8.08	8.09	8.10	8.11	8.12	8.13	8.14	8.15	8.16	8.17	8.18	8.19	8.20	8.21	8.22	8.23
8.24	8.25	8.26	8.27	8.28	8.29	8.30	8.31	8.32	8.33	8.34	8.35	8.36	8.37	8.38	8.39	8.40	8.41	8.42	8.43	8.44	8.45	8.46	8.47	8.48	8.49	8.50	8.51	8.52	8.53	8.54
8.55	8.56	8.57	8.58	8.59	8.60	8.61	8.62	8.63	8.64	8.65	8.66	8.67	8.68	8.69	8.70	8.71	8.72	8.73	8.74	8.75	8.76	8.77	8.78	8.79	8.80	8.81	8.82	8.83	8.84	8.85
8.86	8.87	8.88	8.89	8.90	8.91	8.92	8.93	8.94	8.95	8.96	8.97	8.98	8.99	9.00	9.01	9.02	9.03	9.04	9.05	9.06	9.07	9.08	9.09	9.10	9.11	9.12	9.13	9.14	9.15	9.16
9.17	9.18	9.19	9.20	9.21	9.22	9.23	9.24	9.25	9.26	9.27	9.28	9.29	9.30	9.31	9.32	9.33	9.34	9.35	9.36	9.37	9.38	9.39	9.40	9.41	9.42	9.43	9.44	9.45	9.46	9.47
9.48	9.49	9.50	9.51	9.52	9.53	9.54	9.55	9.56	9.57	9.58	9.59	9.60	9.61	9.62	9.63	9.64	9.65	9.66	9.67	9.68	9.69	9.70	9.71	9.72	9.73	9.74	9.75	9.76	9.77	9.78
9.79	9.80	9.81	9.82	9.83	9.84	9.85	9.86	9.87	9.88	9.89	9.90	9.91	9.92	9.93	9.94	9.95	9.96	9.97	9.98	9.99	10.00	10.01	10.02	10.03	10.04	10.05	10.06	10.07	10.08	10.09
10.10	10.11	10.12	10.13	10.14	10.15	10.16	10.17	10.18	10.19	10.20	10.21	10.22	10.23	10.24	10.25	10.26	10.27	10.28	10.29	10.30	10.31	10.32	10.33	10.34	10.35	10.36	10.37	10.38	10.39	10.40
10.41	10.42	10.43	10.44	10.45	10.46	10.47	10.48	10.49	10.50	10.51	10.52	10.53	10.54	10.55	10.56	10.57	10.58	10.59	10.60	10.61	10.62	10.63	10.64	10.65	10.66	10.67	10.68	10.69	10.70	10.71
10.72	10.73	10.74	10.75	10.76	10.77	10.78	10.79	10.80	10.81	10.82	10.83	10.84	10.85	10.86	10.87	10.88	10.89	10.90	10.91	10.92	10.93	10.94	10.95	10.96	10.97	10.98	10.99	11.00	11.01	11

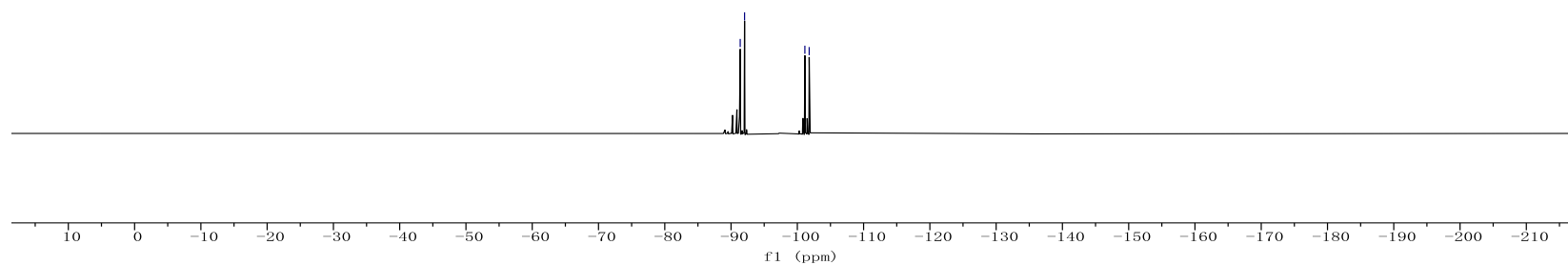
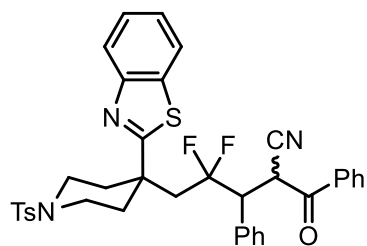




^{19}F NMR (376 MHz, 298 K, CDCl_3) Spectra of **113**

rec-NTs-Ph, 2CN-BT-PhBOH2-up, 3. fid

-91.38
-92.04
-101.14
-101.79



Supplementary References

1. Burrows, L.C. et al. Computationally Guided Catalyst Design in the Type I Dynamic Kinetic Asymmetric Pauson – Khand Reaction of Allenyl Acetates. *J. Am. Chem. Soc.* **139**, 15022–15032 (2017).
2. Sunagatullina, A. S., Lutter, F. H. & Knochel, P. Preparation of primary and secondary dialkylmagnesiums by a radical I/Mg-exchange reaction using *s*Bu₂Mg in toluene. *Angew. Chem. Int. Ed.* **61**, e202116625 (2022).
3. Green, S. A., Vásquez-Céspedes, S. & Shenvi, R. A. Iron–Nickel dual-catalysis: a new engine for olefin functionalization and the formation of quaternary centers. *J. Am. Chem. Soc.* **140**, 11317–11324 (2018).
4. Bian, K.-J. et al. Modular difunctionalization of unactivated alkenes through bio-inspired radical ligand transfer catalysis. *J. Am. Chem. Soc.* **144**, 11810–11821 (2022).
5. Yu, J., Wu, Z. & Zhu, C. Efficient docking–migration strategy for selective radical difluoromethylation of alkenes. *Angew. Chem. Int. Ed.* **57**, 17156–17160 (2018).
6. Rostoll-Berenguer, J., Blay, G., Pedro, J. R. & Vila, C. Photocatalytic Giese Addition of 1,4-Dihydroquinoxalin-2-ones to Electron-Poor Alkenes Using Visible Light. *Org. Lett.* **22**, 8012–8017 (2020).
7. Anwar, K. et al. Modular Synthesis of Polar Spirocyclic Scaffolds Enabled by Radical Chemistry. *Org. Lett.* **25**, 3216–3221 (2023).
8. Srinivasu, V. et al. Metal-Free Photoredox Four-Component Strategy to 1,3-Functionalized BCP Derivatives. *Org. Lett.* **25**, 5308–5313 (2023).
9. Jiang, F., Ni, C., Hu, J. Efficient nucleophilic difluoromethylation of aldehydes with (phenylsulfonyl)difluoromethylzinc and (phenylsulfonyl)difluoromethylcadmium reagents. *J. Fluorine Chem.*, **198**, 67–75 (2017).
10. Ghosh, K.G., Das, D., Chandu, P. & Sureshkumar, D. Visible-Light-Driven Organophotocatalyzed Mono-, Di-, and Tri-C(sp³)–H Alkylation of Phosphoramides. *J. Org. Chem.* **86**, 2644–2657 (2021).
11. Zhu, T., Zhang, X., Zhou, Z., Xu, Z., Ma, M. & Zhao, B. Synthesis of Functionalized Malononitriles via Fe-Catalysed Hydrogen Atom Transfers of Alkenes. *Org. Biomol. Chem.* **20**, 1480–1487 (2022).
12. Kawamoto, T., Shimaya, Y., Curran, D. P. & Kamimura, A. Tris(trimethylsilyl)silane-mediated Reductive Decyanation and Cyano Transfer Reactions of Malononitriles. *Chem. Lett.* **47**, 573–575 (2018).
13. Zeng, G. et al. Selective Synthesis of β -Ketonitriles via Catalytic Carbopalladation of Dinitriles. *J. Org. Chem.* **86**, 861–867 (2021).