UNIVERSITÀ DEGLI STUDI DI MILANO

CORSO DI DOTTORATO IN SCIENZE FARMACEUTICHE (XXXVI ciclo)

DIPARTIMENTO DI SCIENZE FARMACEUTICHE (DISFARM)

Synthesis of pharmacologically active molecules through biocatalytic approaches: study of their stereochemistry and polymorphism by means of spectroscopic and crystallographic methods.

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COORDINATORE: Prof. GIULIO VISTOLI

A.A. 2022/2023

Supplementary Materials

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Elagolix

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Elagolix

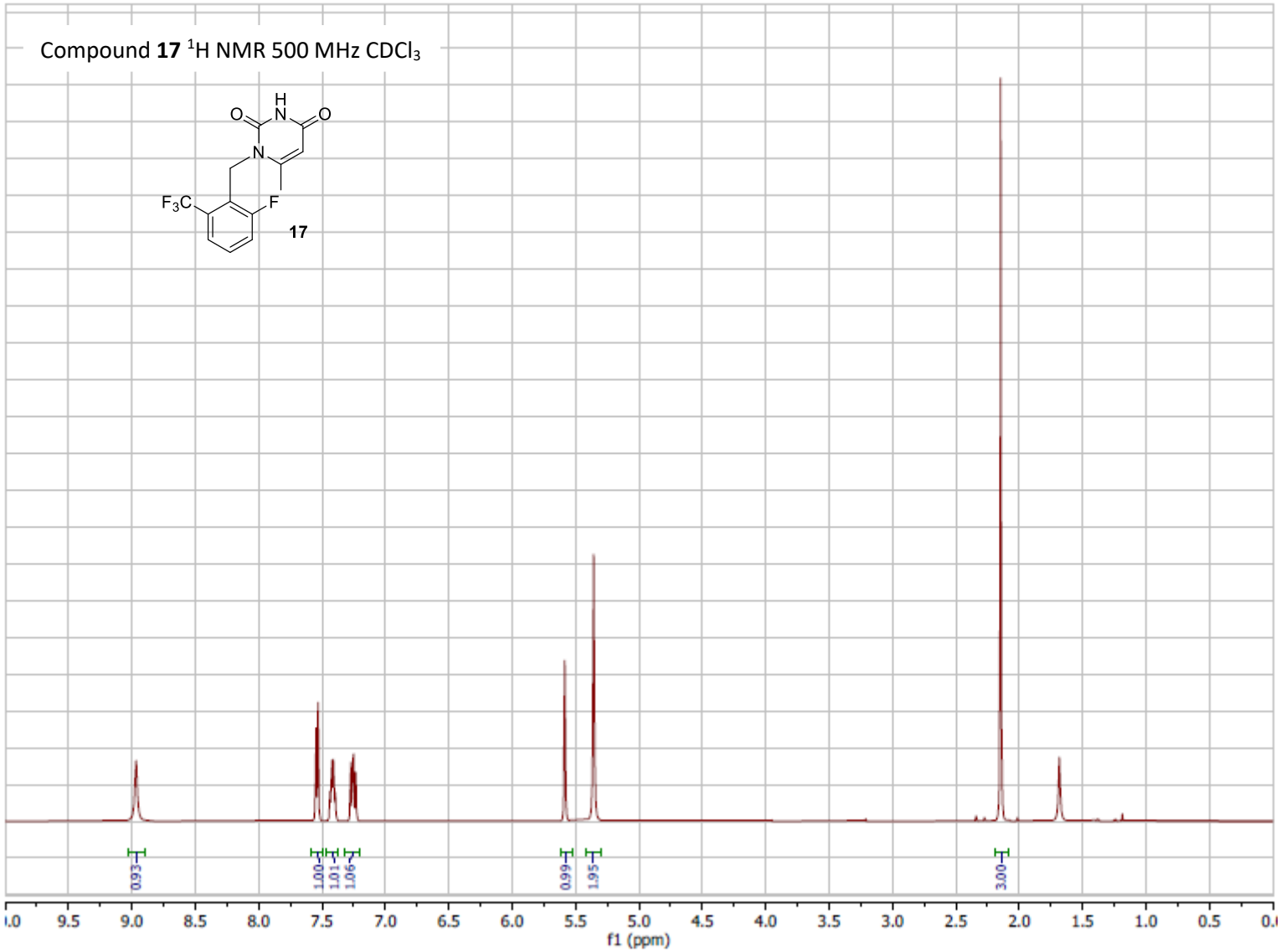


Figure S1. ^{1}H NMR of compound **17**

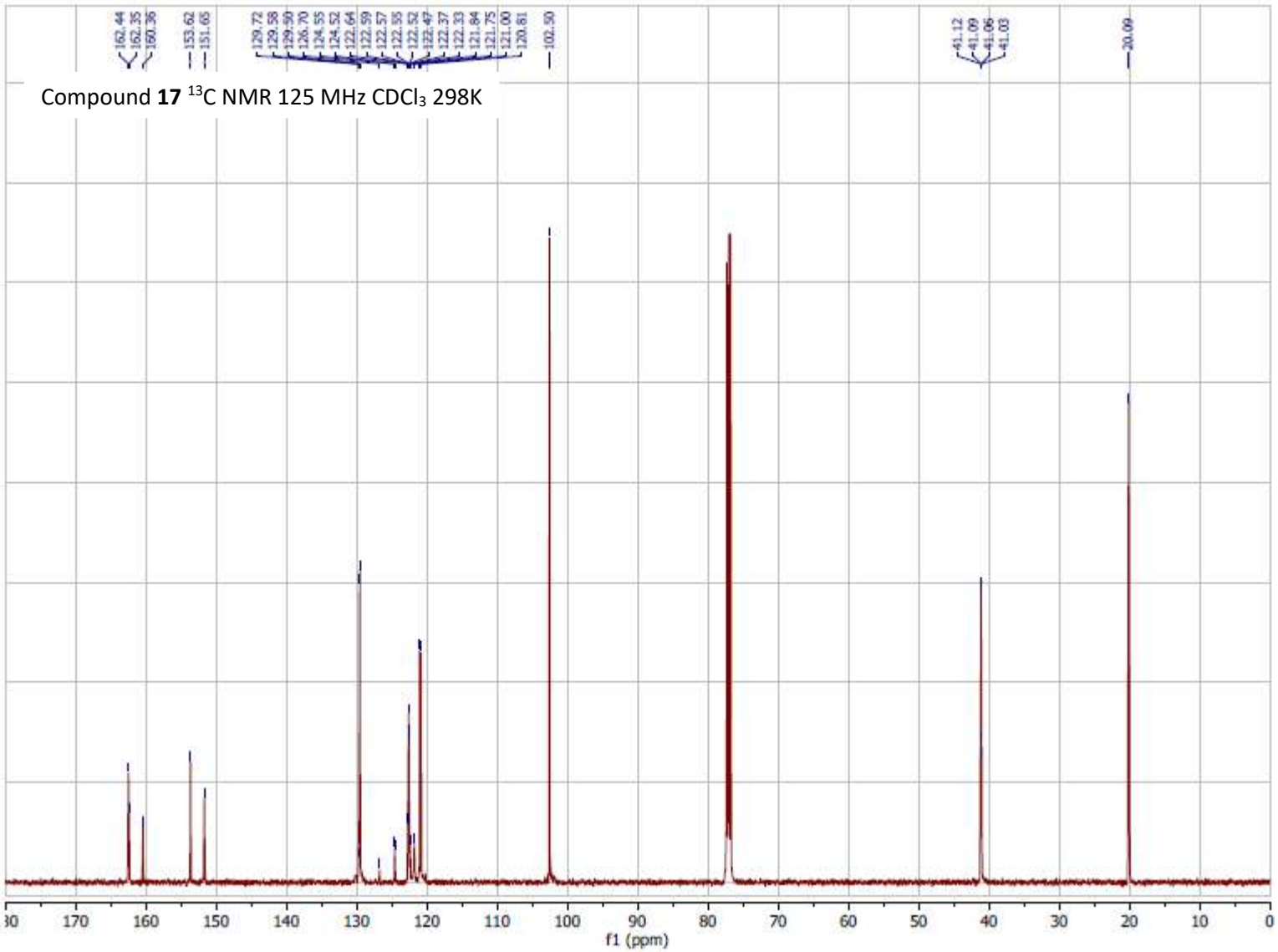


Figure S2. ^{13}C NMR of compound **17**

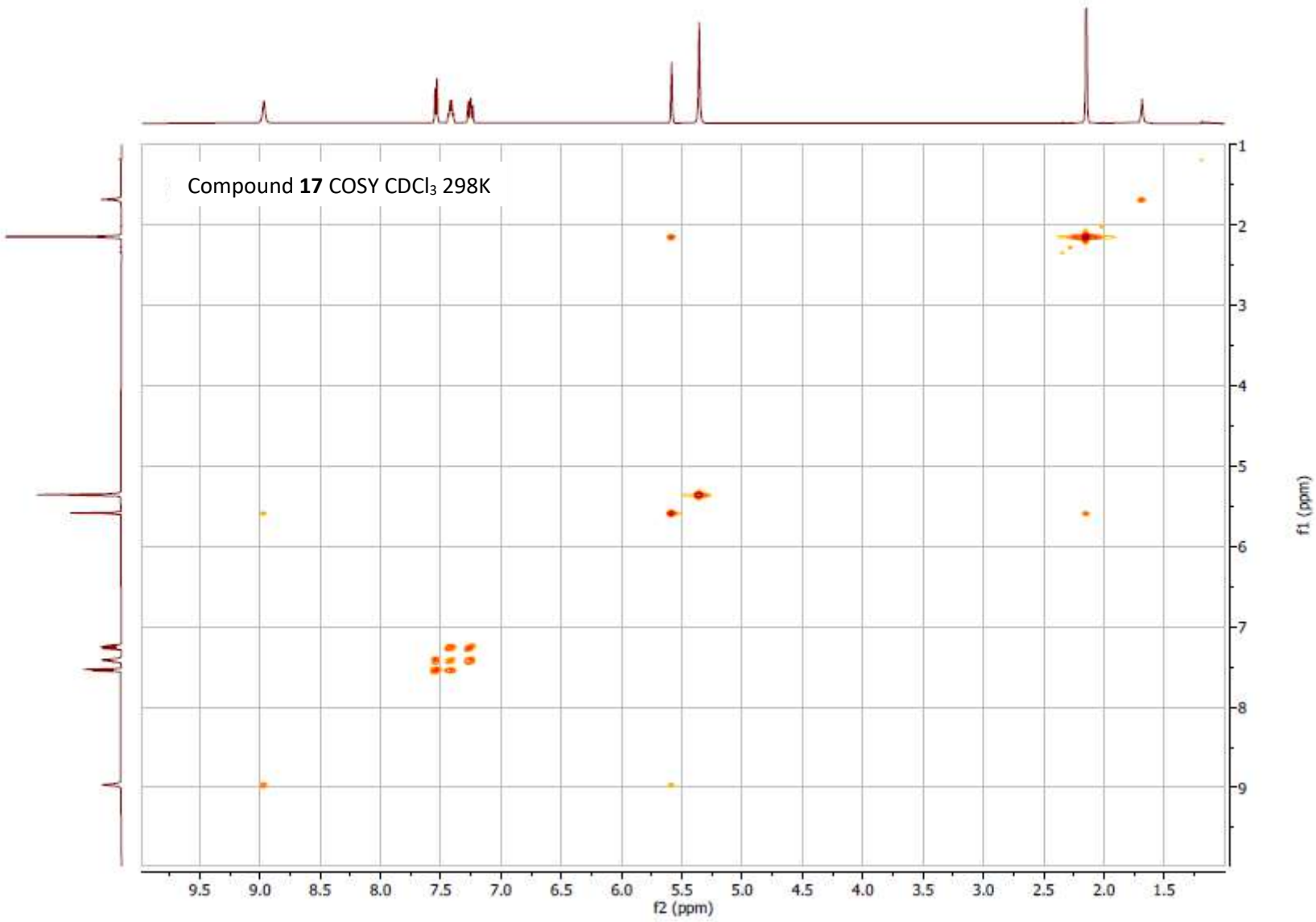


Figure S3. COSY of compound **17**

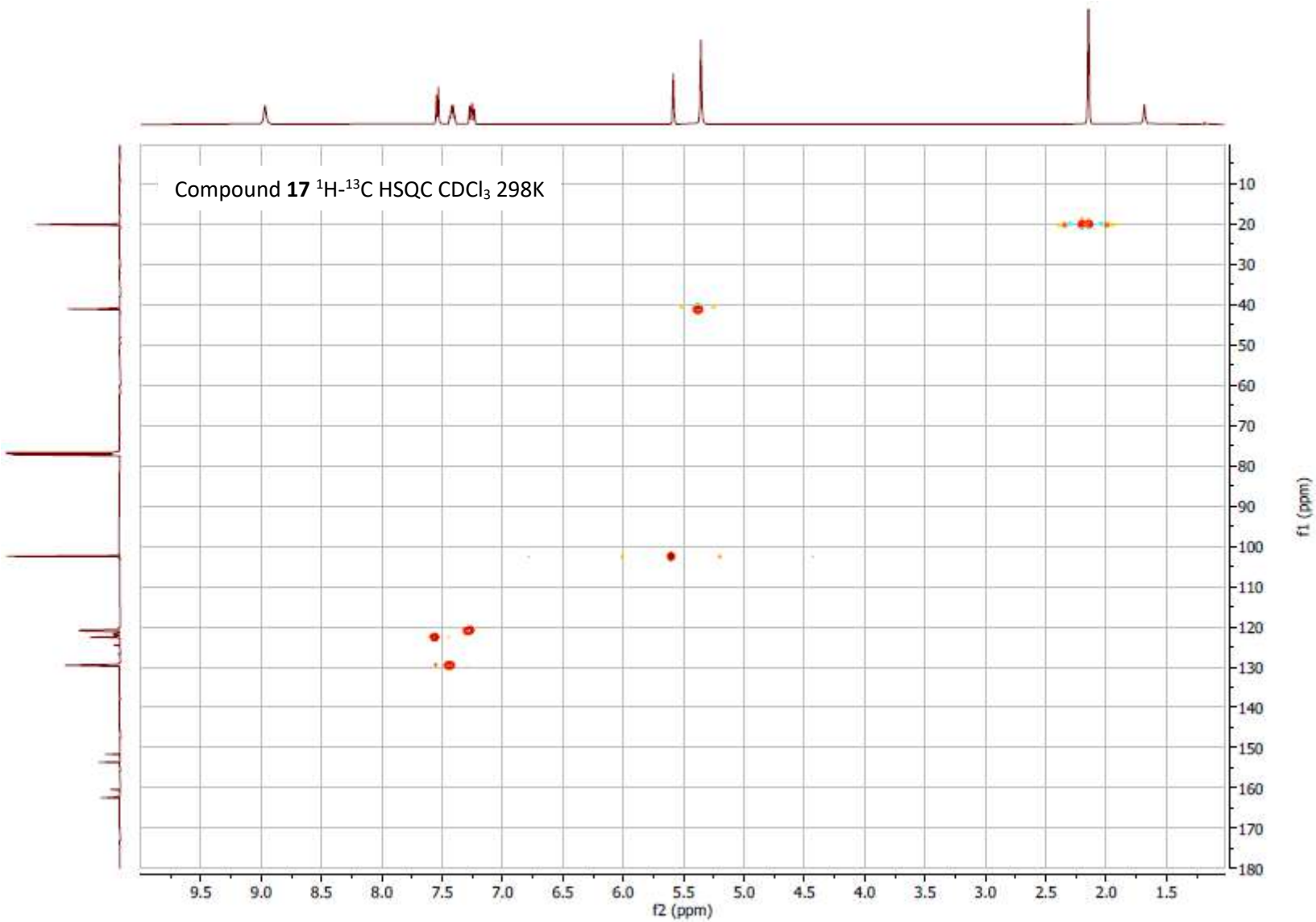


Figure S4. ^{1}H-^{13}C HSQC of compound **17**

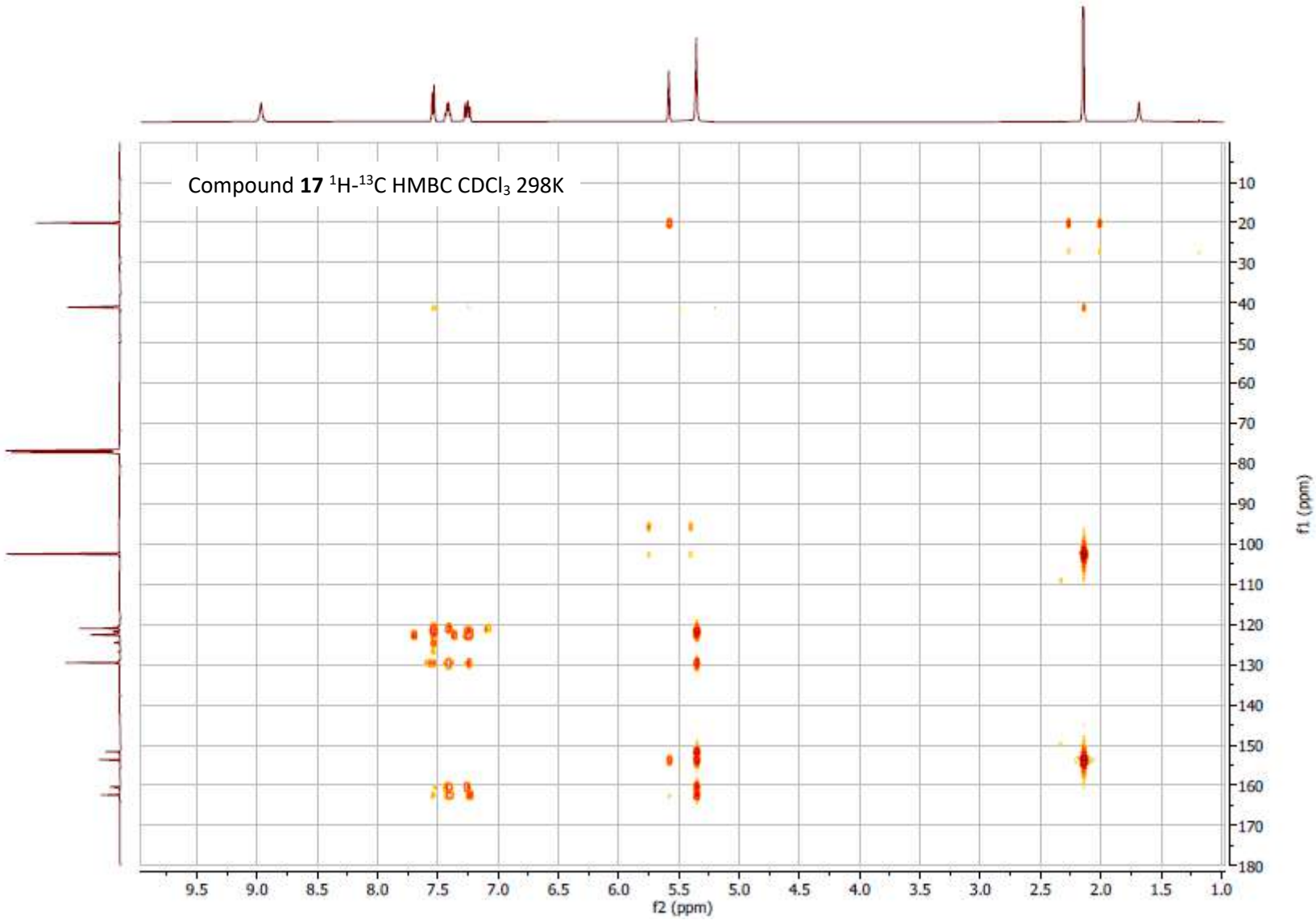


Figure S5. ^{1}H-^{13}C HMBC of compound **17**

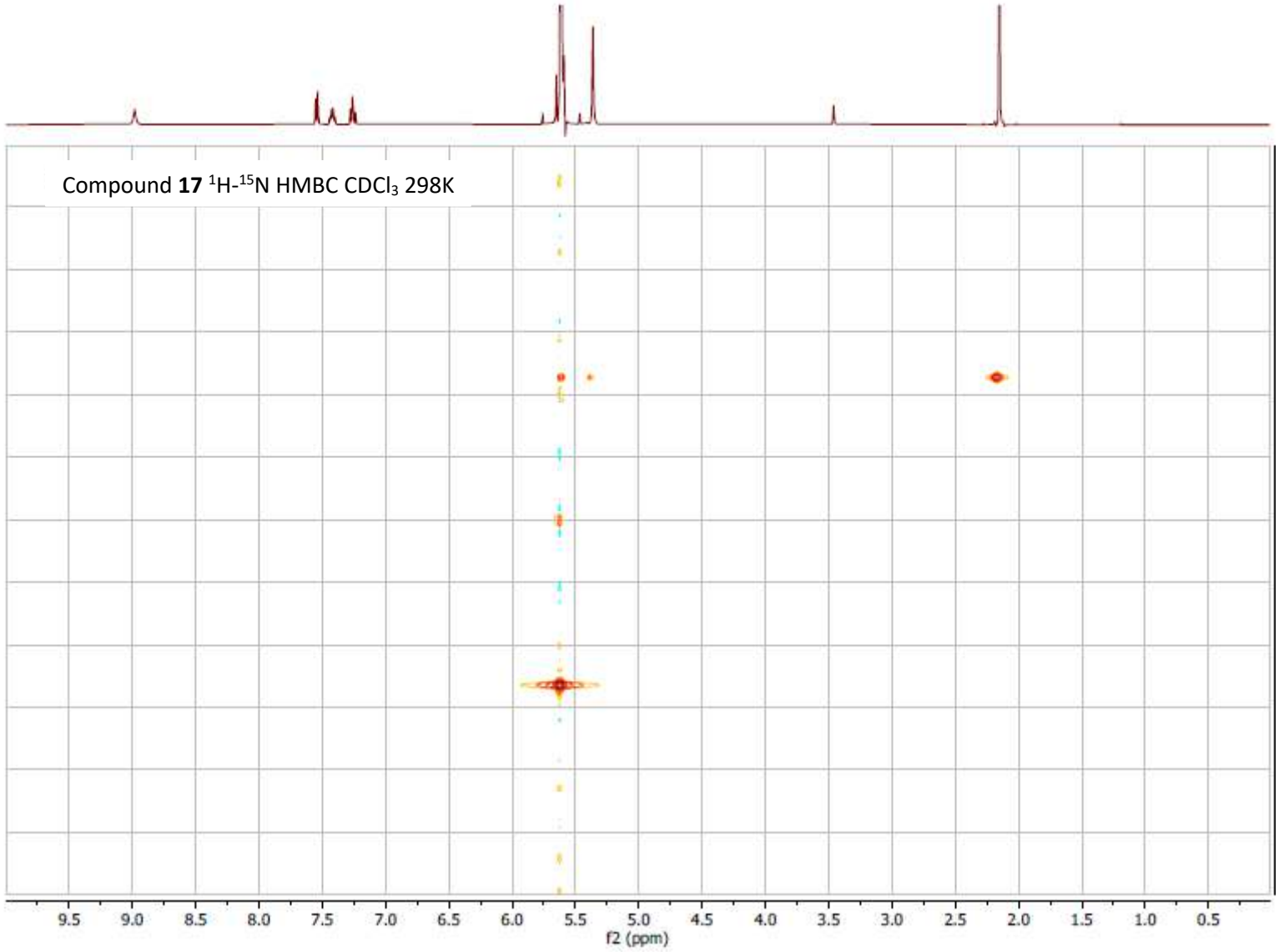


Figure S6. ^{1}H-^{15}N HMBC of compound **17**

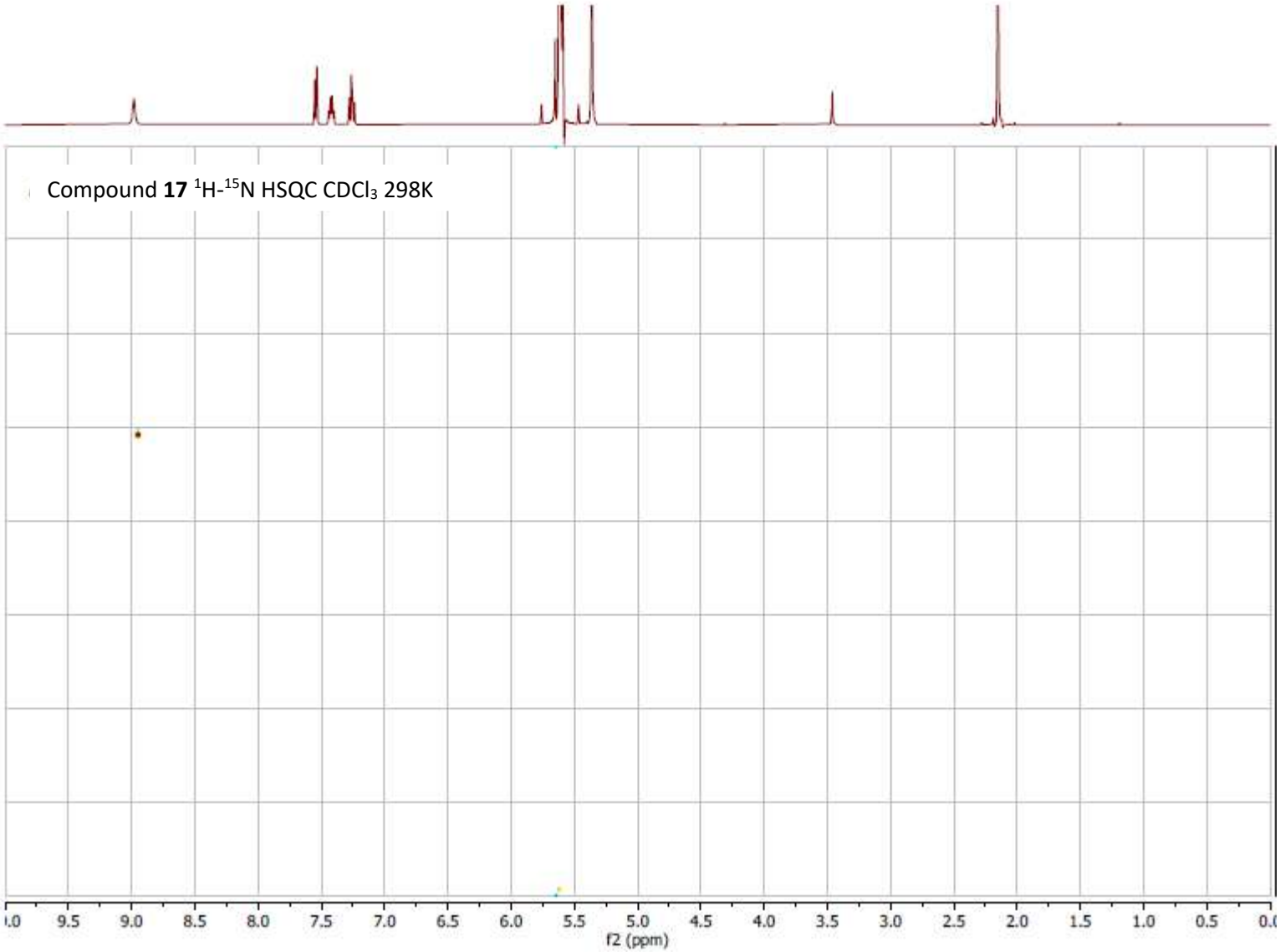


Figure S7. ^{1}H-^{15}N HSQC of compound **17**

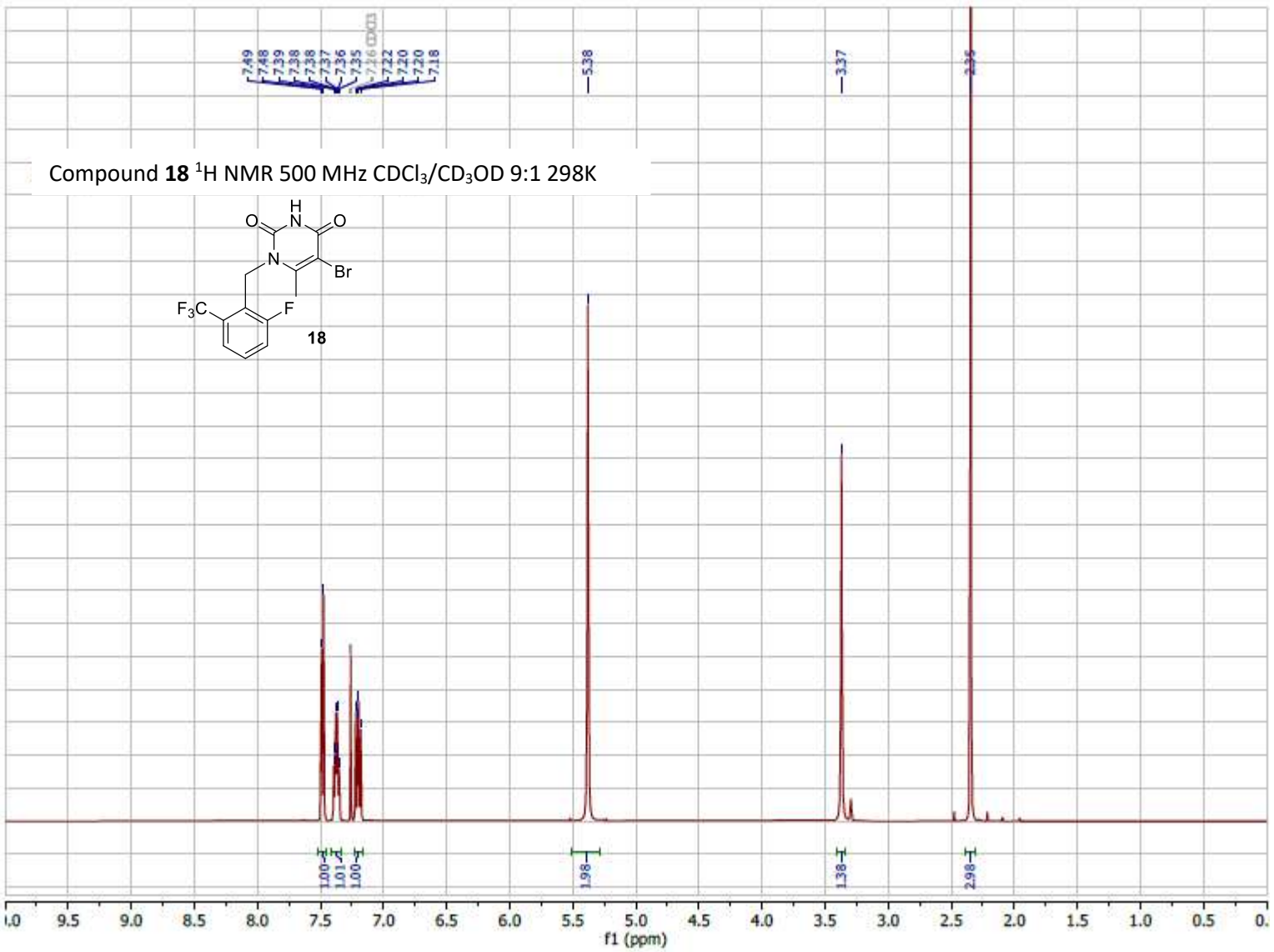


Figure S8. ^{1}H NMR of compound **18**

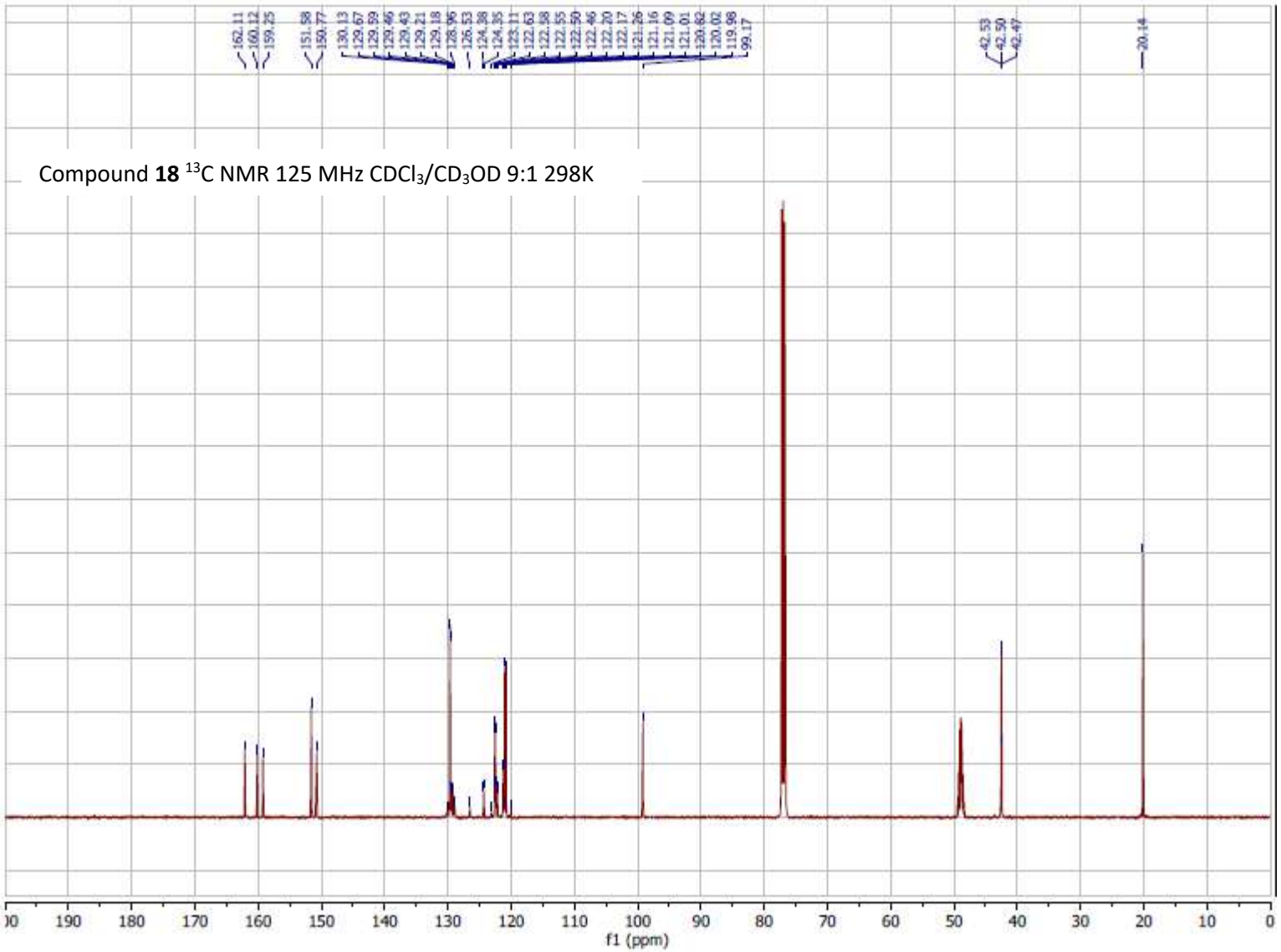


Figure S9. ^{13}C NMR of compound **18**

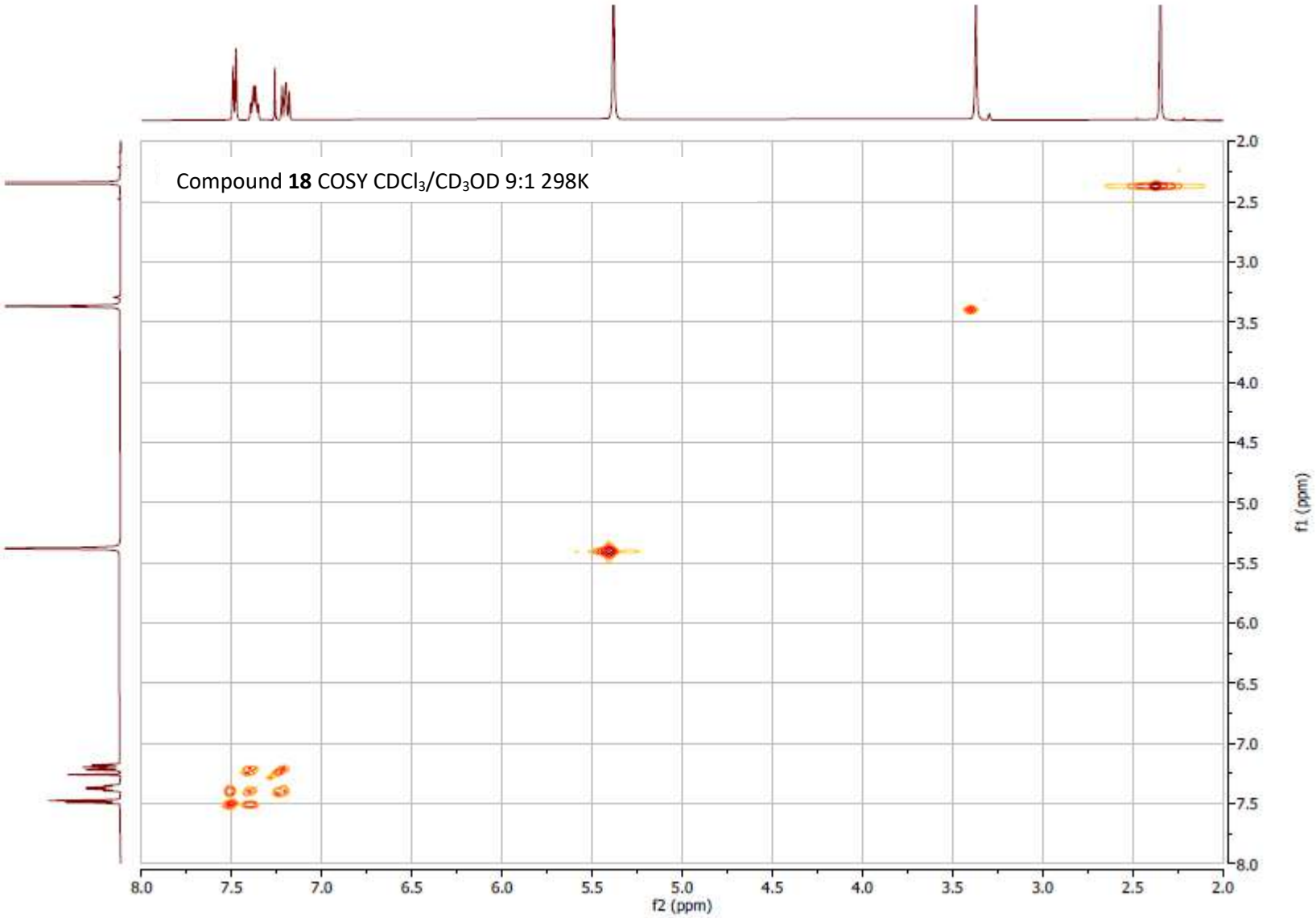


Figure S10. COSY of compound **18**

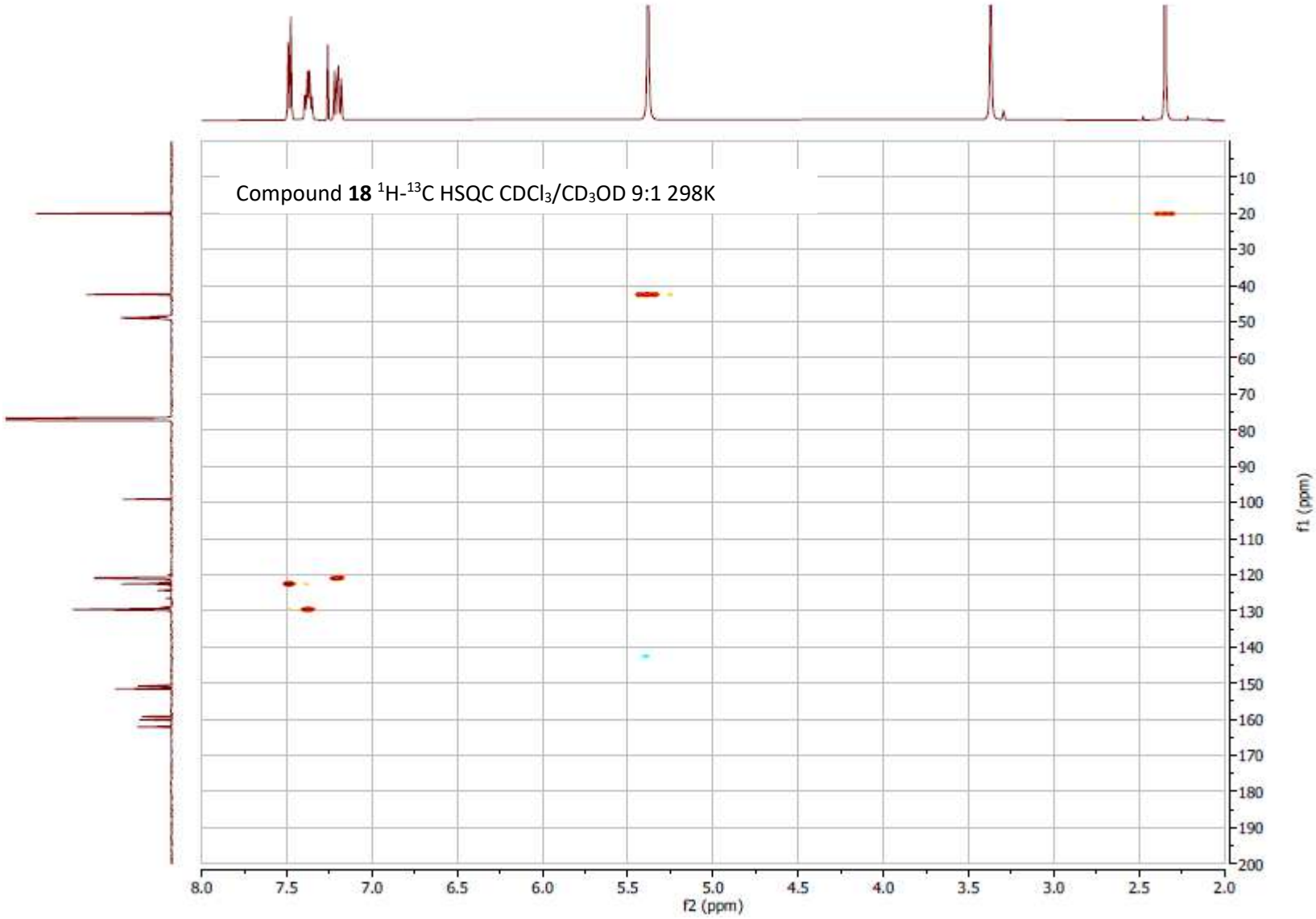


Figure S11. ^{1}H-^{13}C HSQC of compound **18**

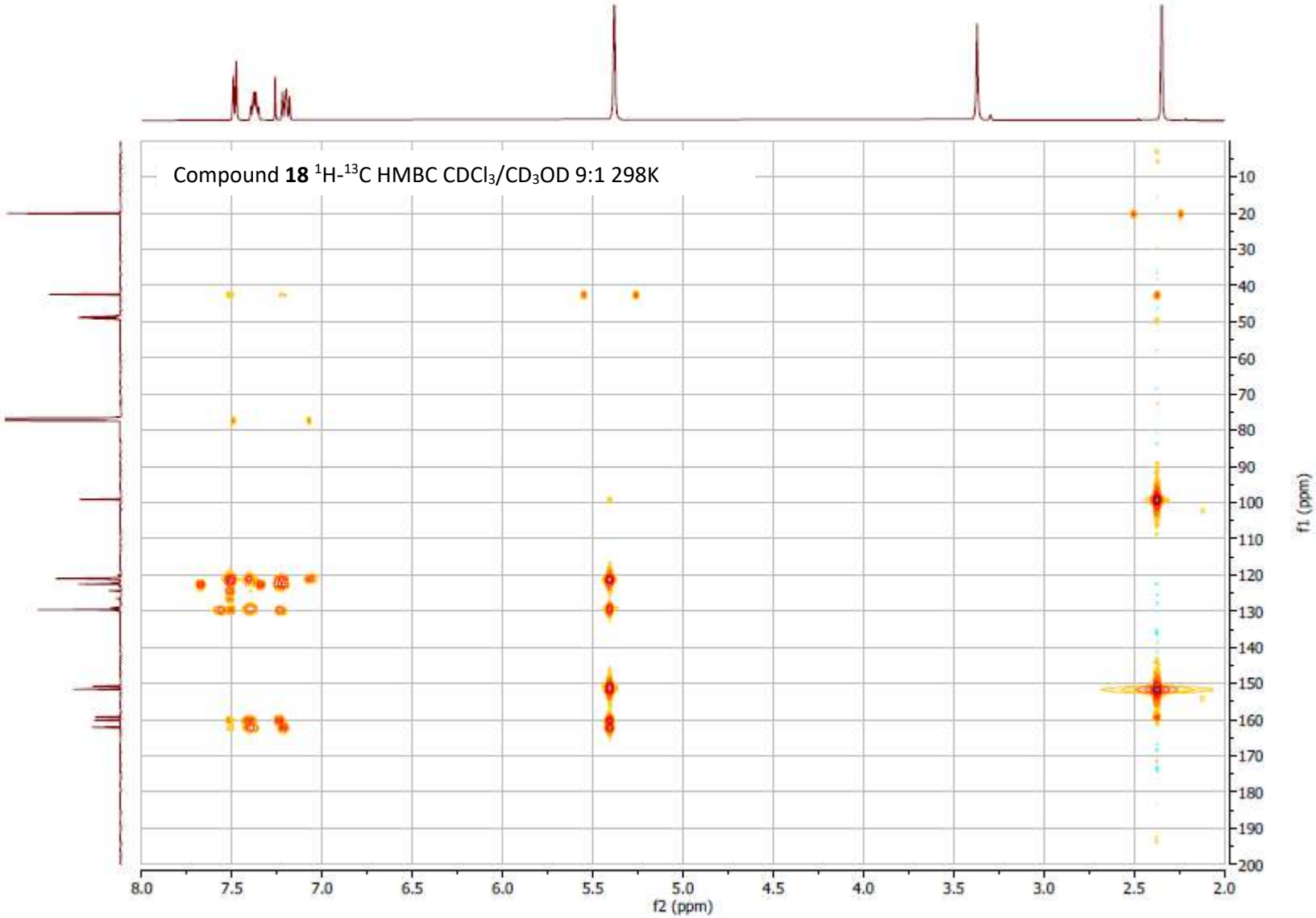


Figure S12. ^{1}H-^{13}C HMBC of compound **18**

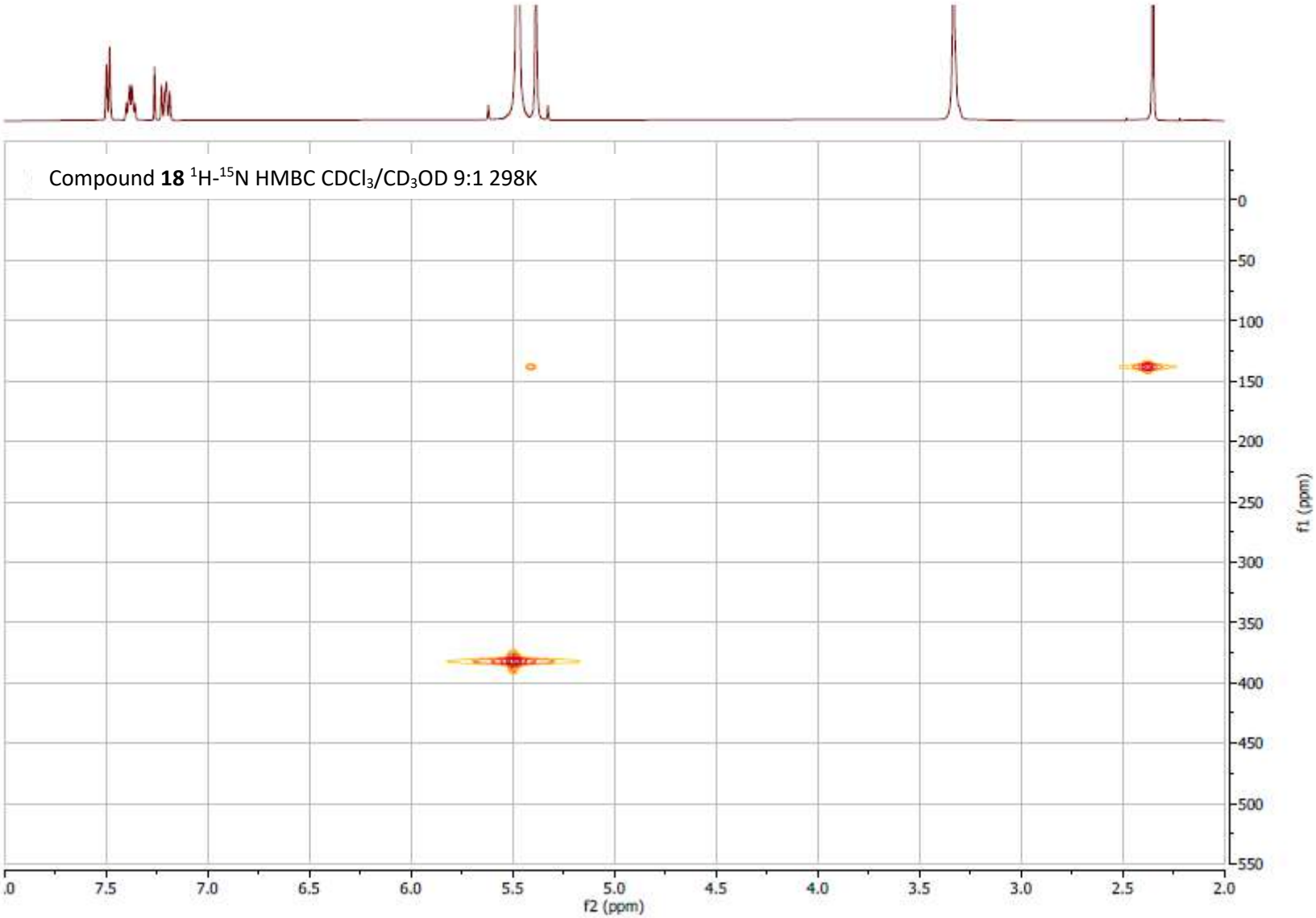


Figure S13. ^{1}H-^{15}N HMBC of compound **18**

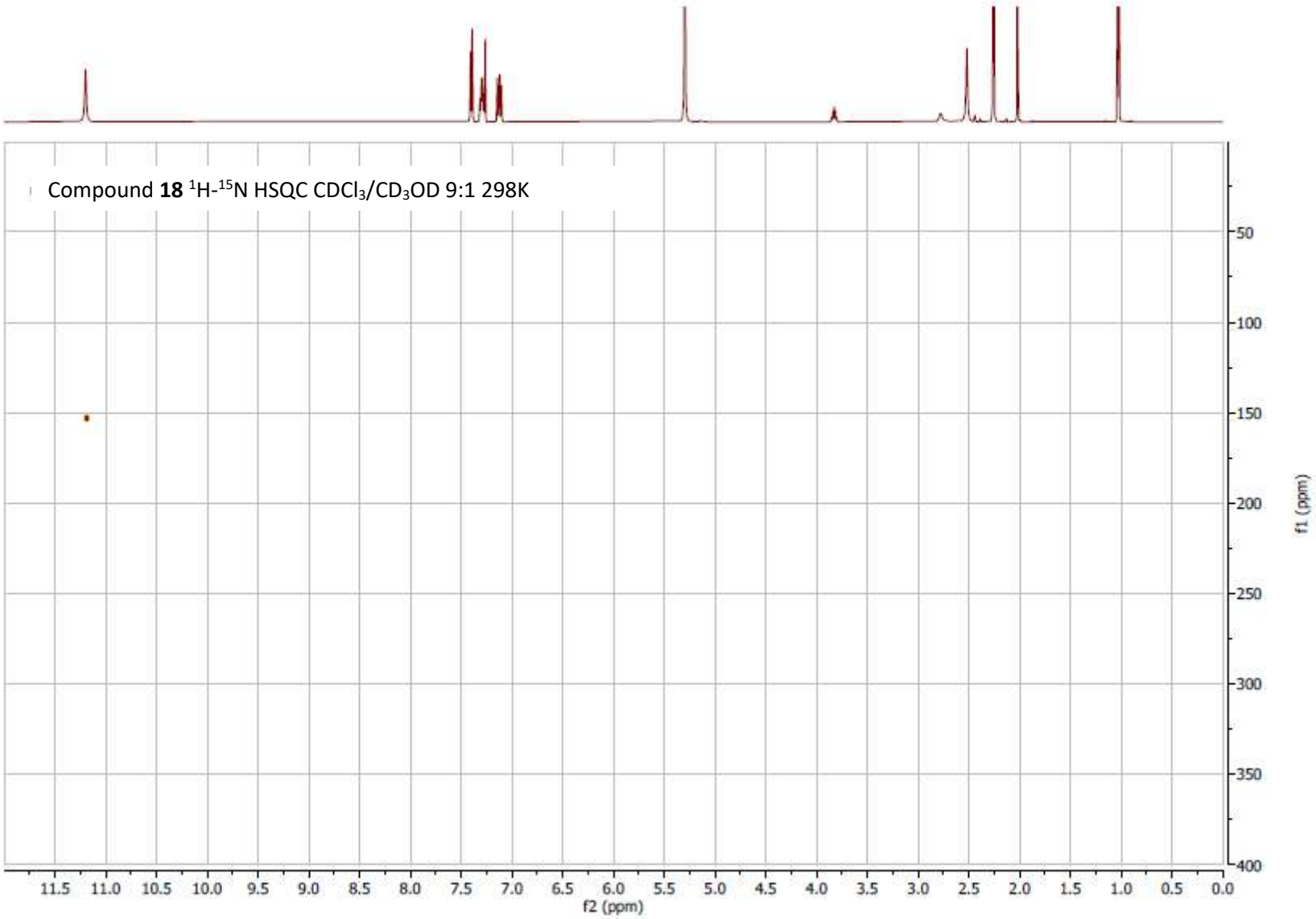


Figure S14. ^{1}H-^{15}N HSQC of compound **18**

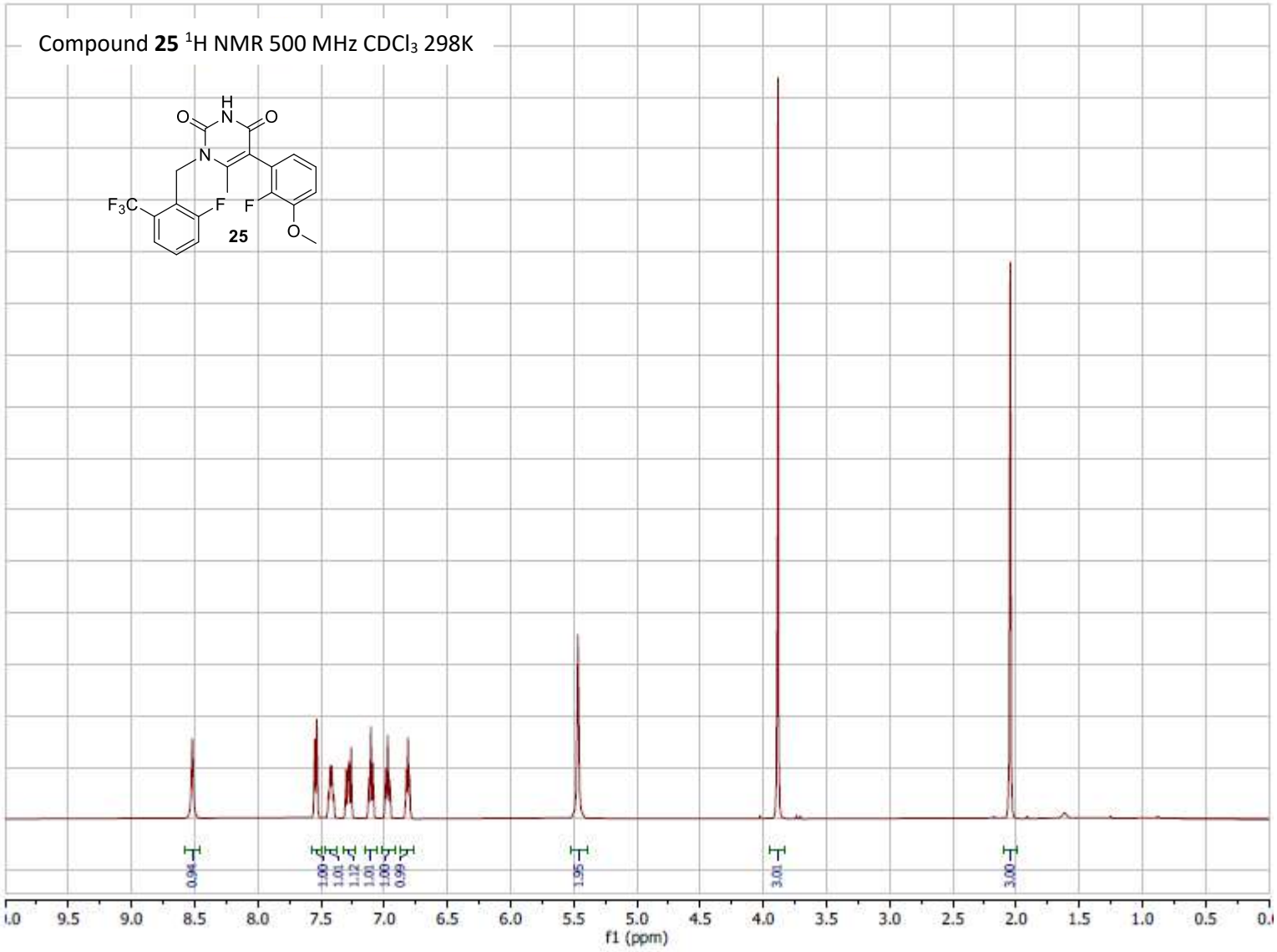


Figure S15. ^{1}H NMR of compound **25**

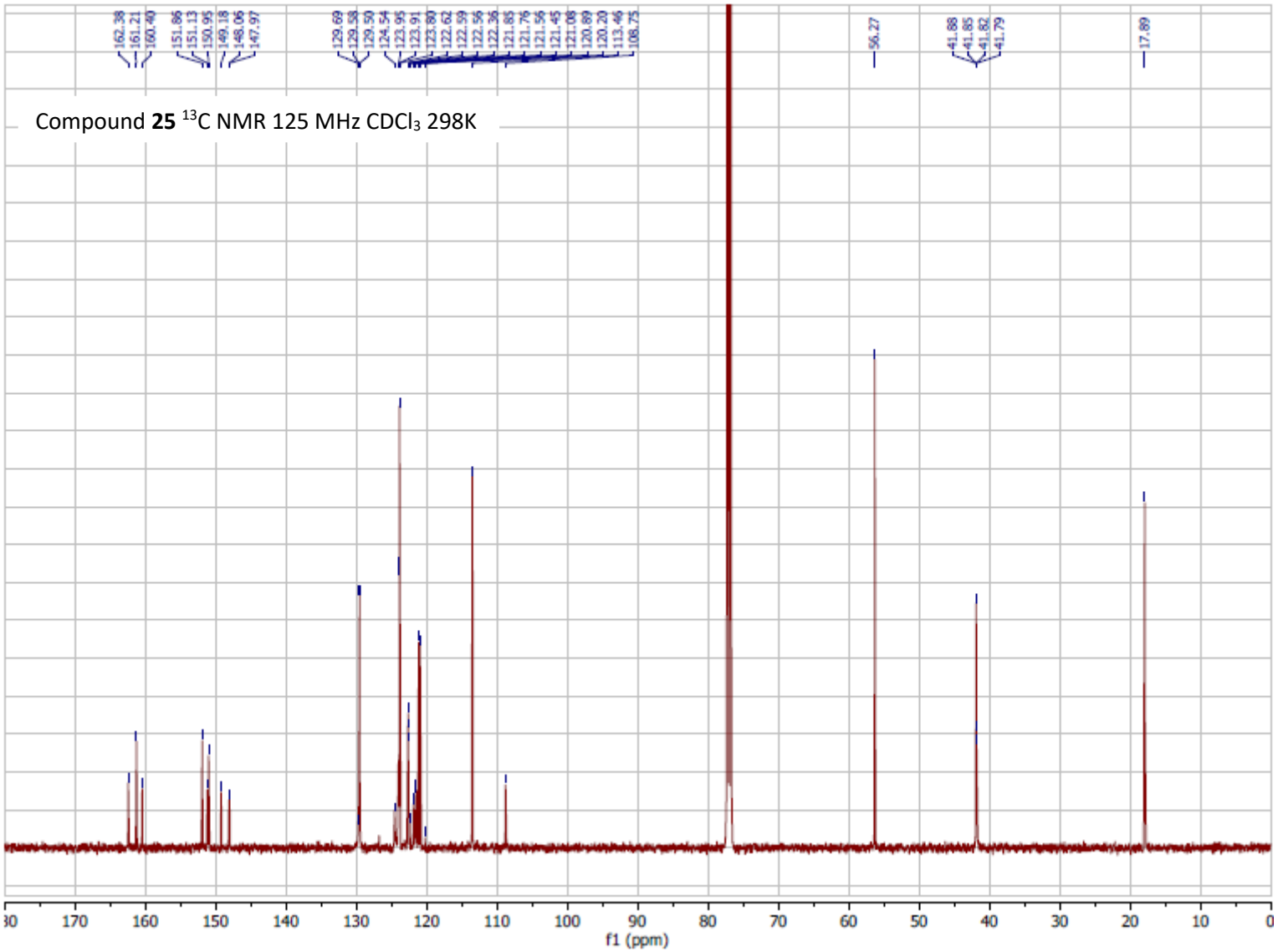


Figure S16. ^{13}C NMR of compound **25**

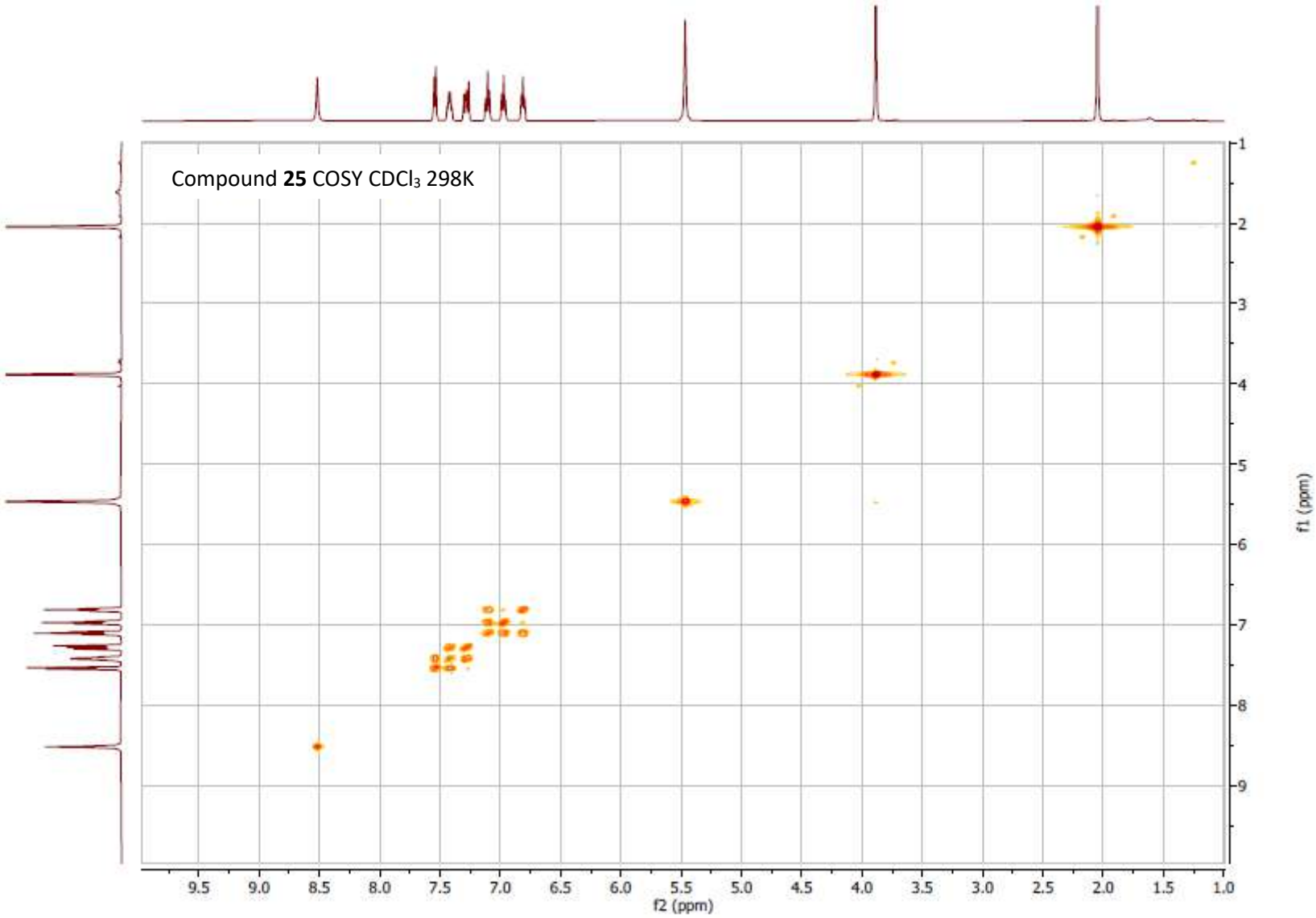


Figure S17. COSY of compound **25**

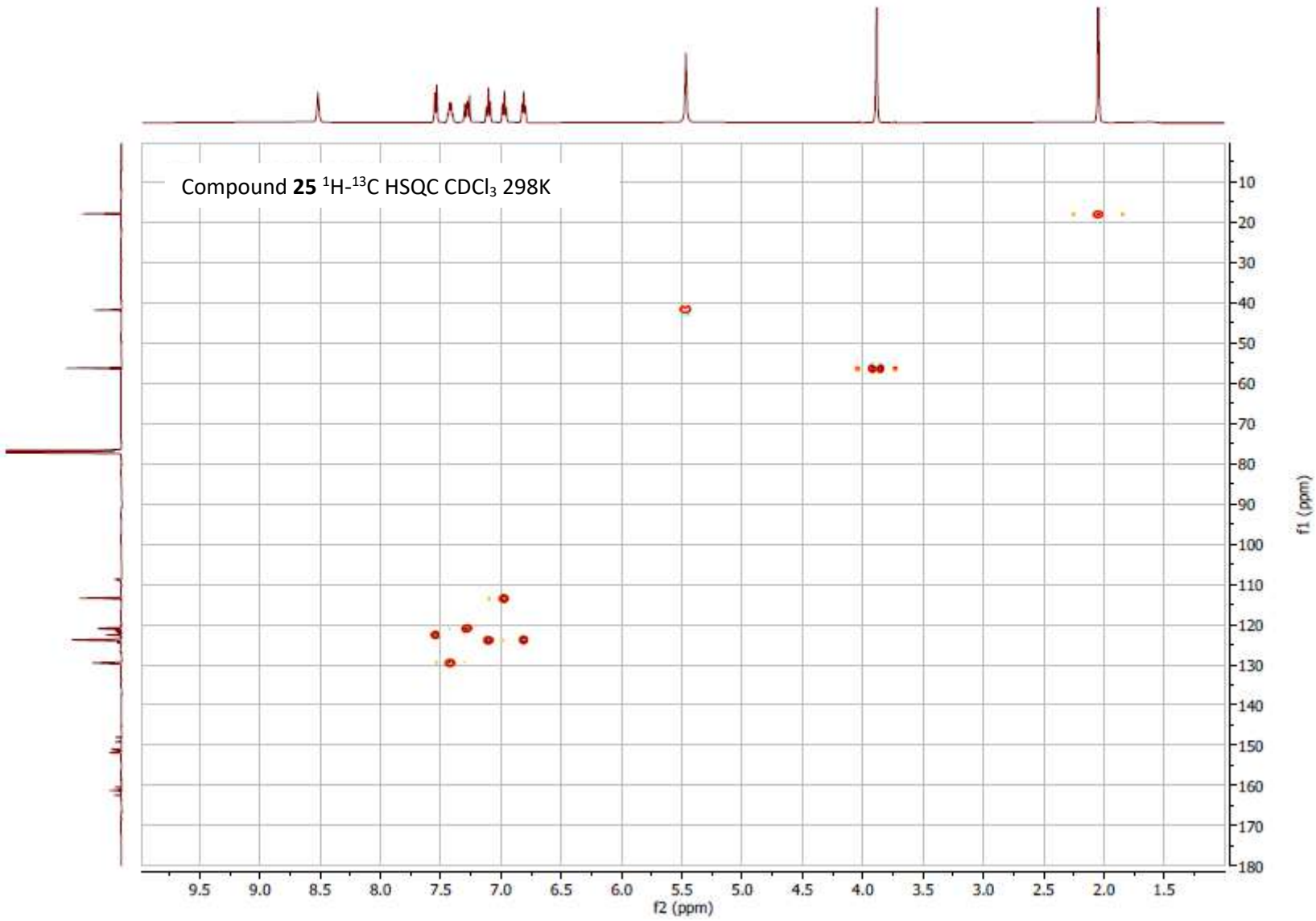


Figure S18. ^{1}H-^{13}C HSQC of compound **25**

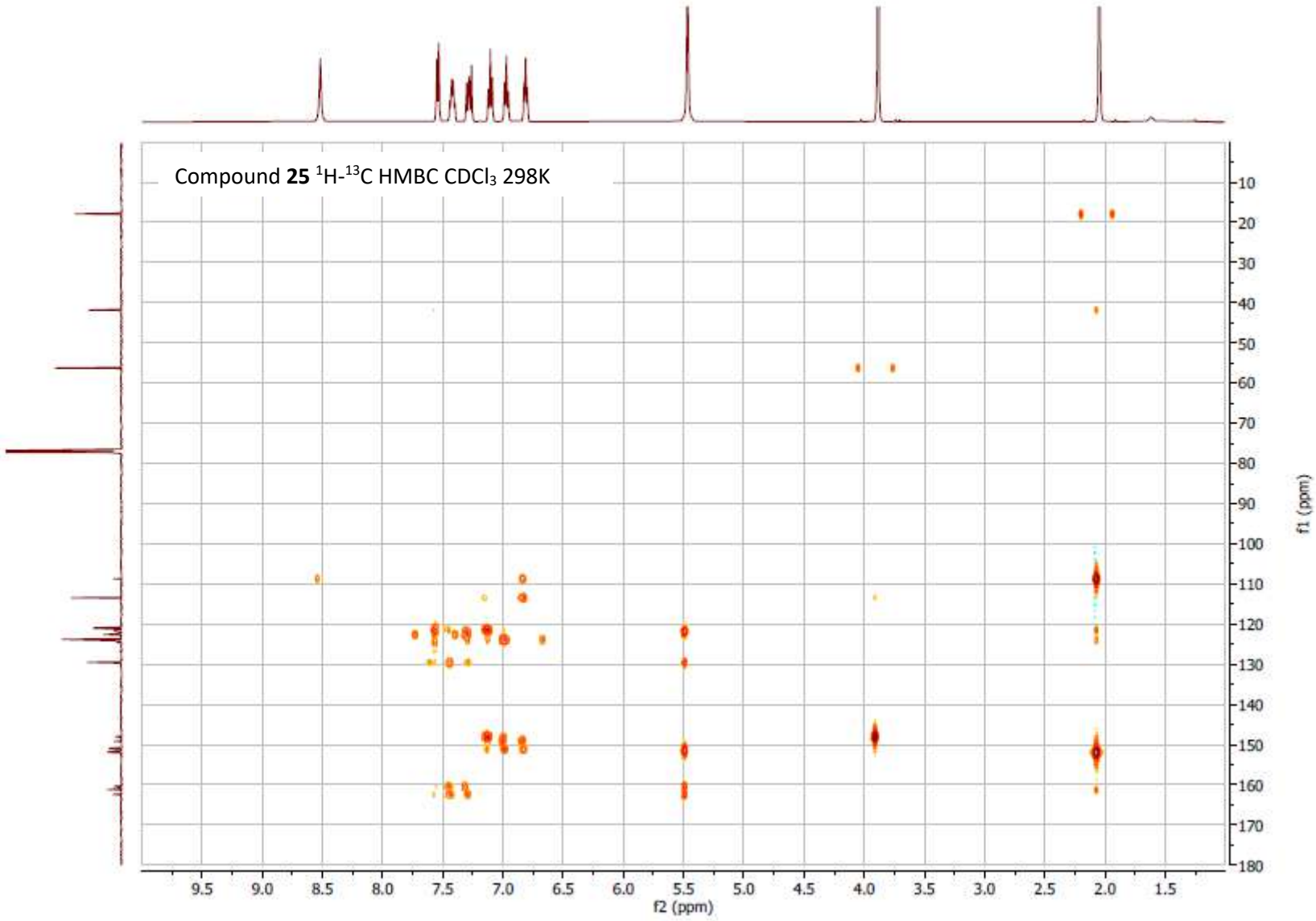


Figure S19. ^{1}H-^{13}C HMBC of compound **25**

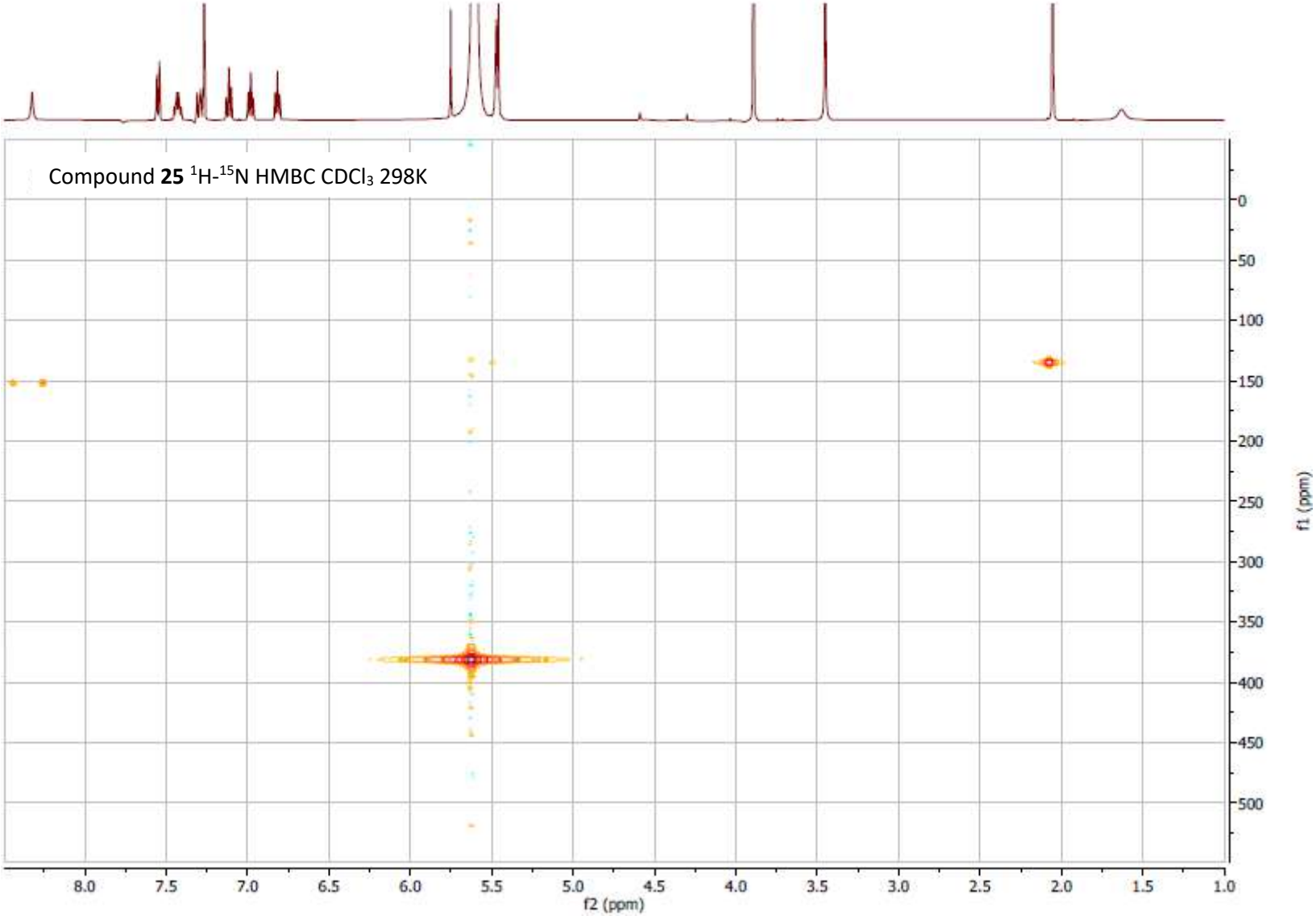


Figure S20. ^{1}H-^{15}N HMBC of compound **25**

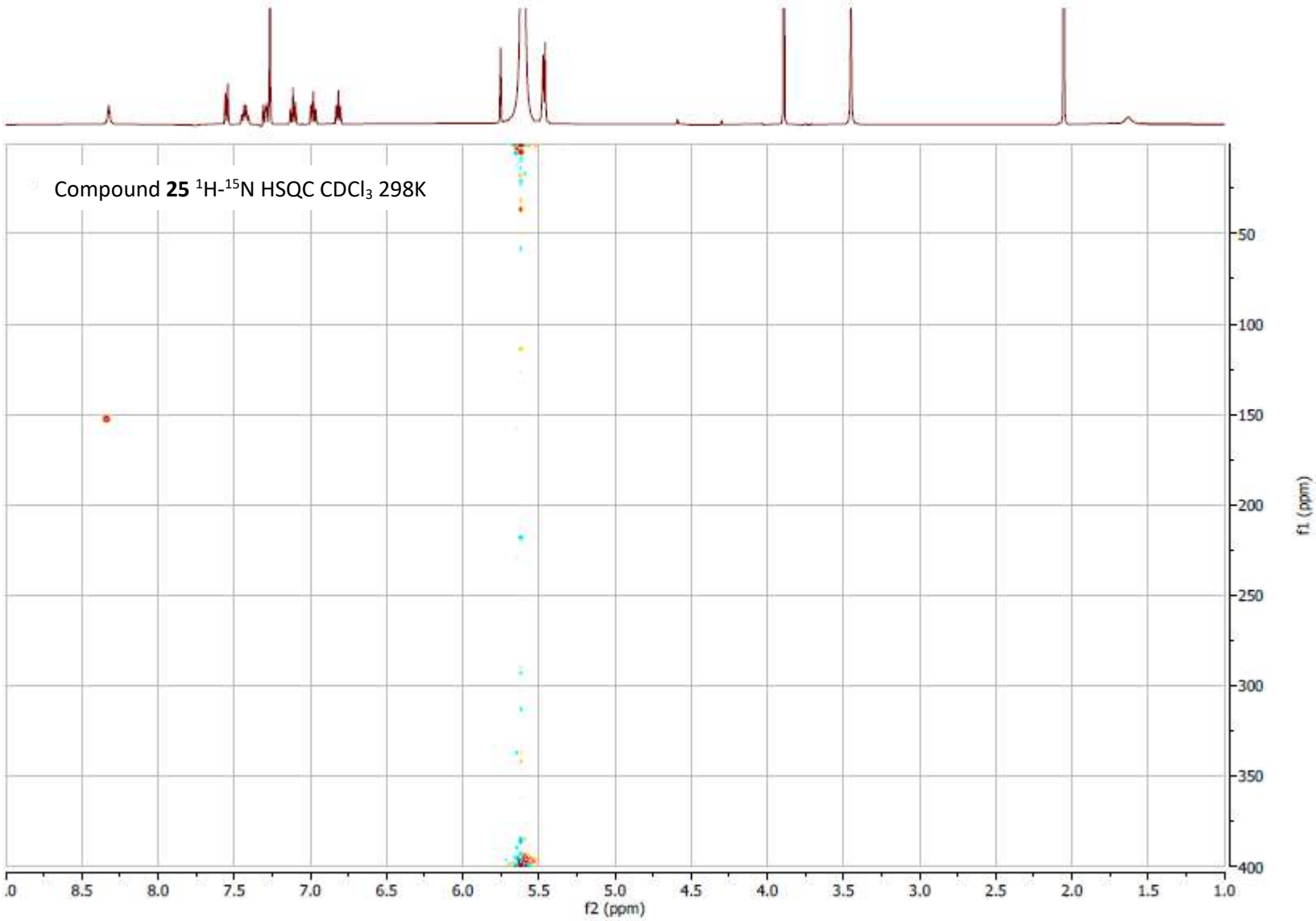


Figure S21. ^{1}H-^{15}N HSQC of compound **25**

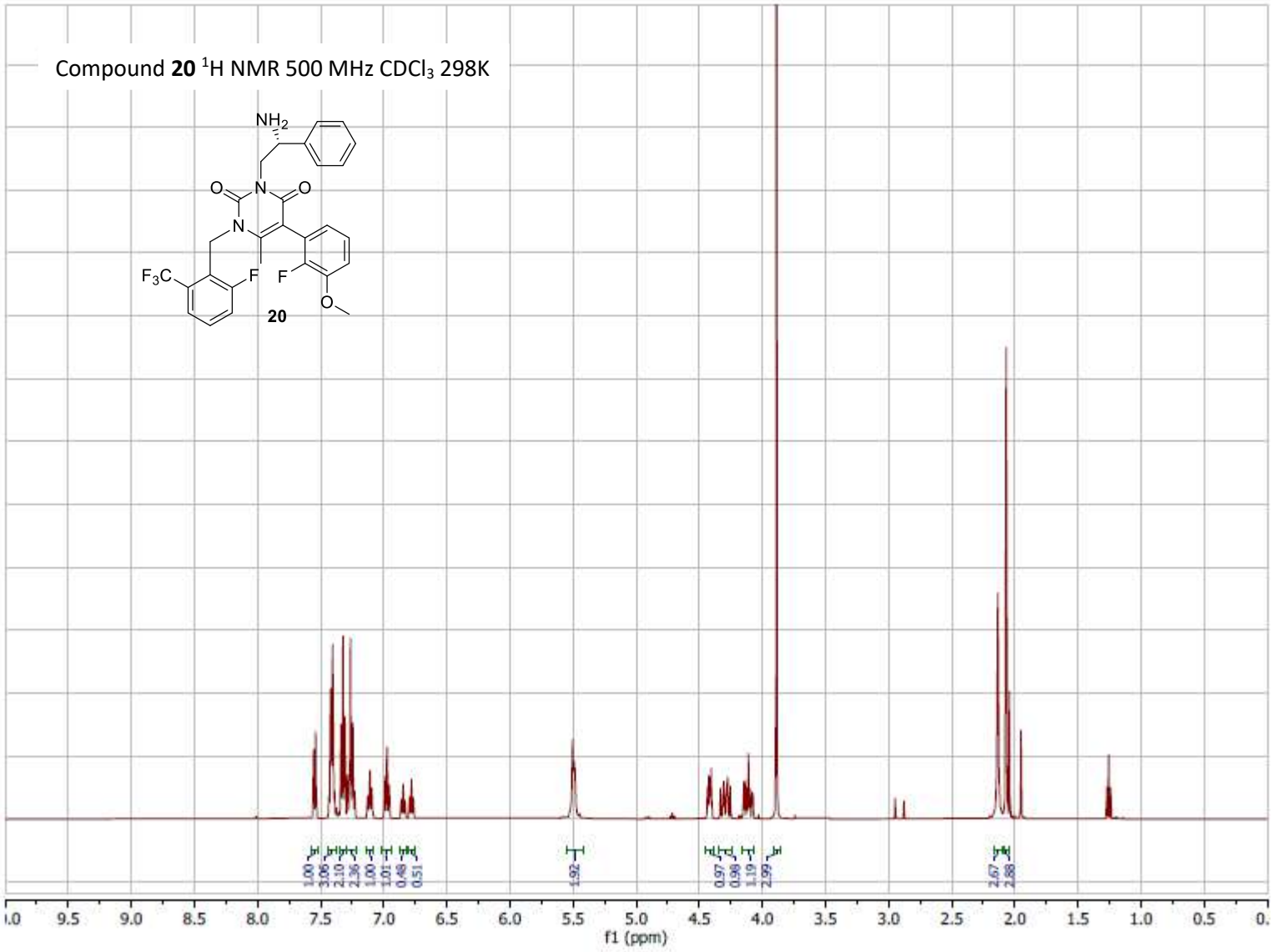


Figure S22. ^{1}H NMR of compound **20**

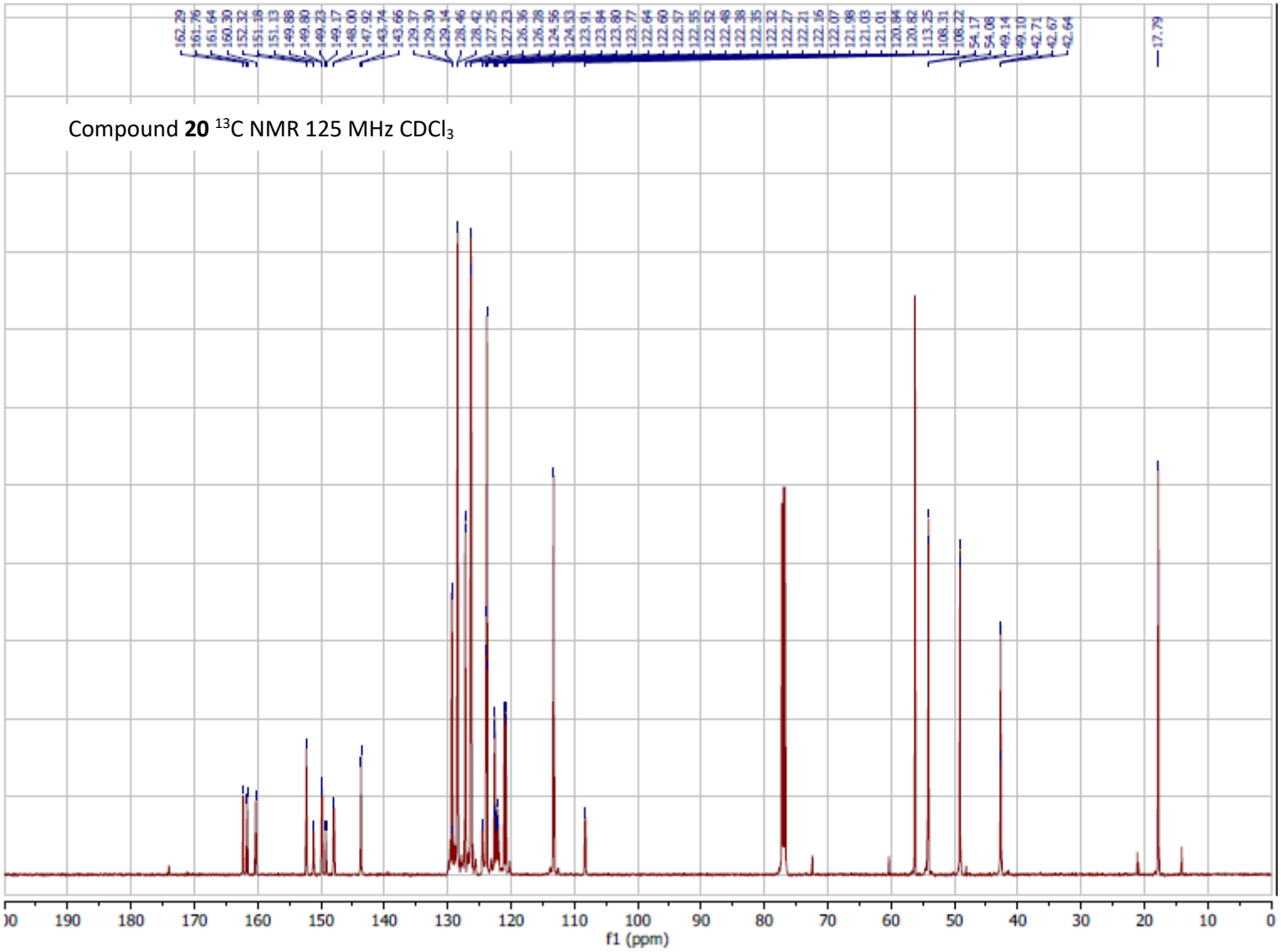


Figure S23. ^{13}C NMR of compound **20**

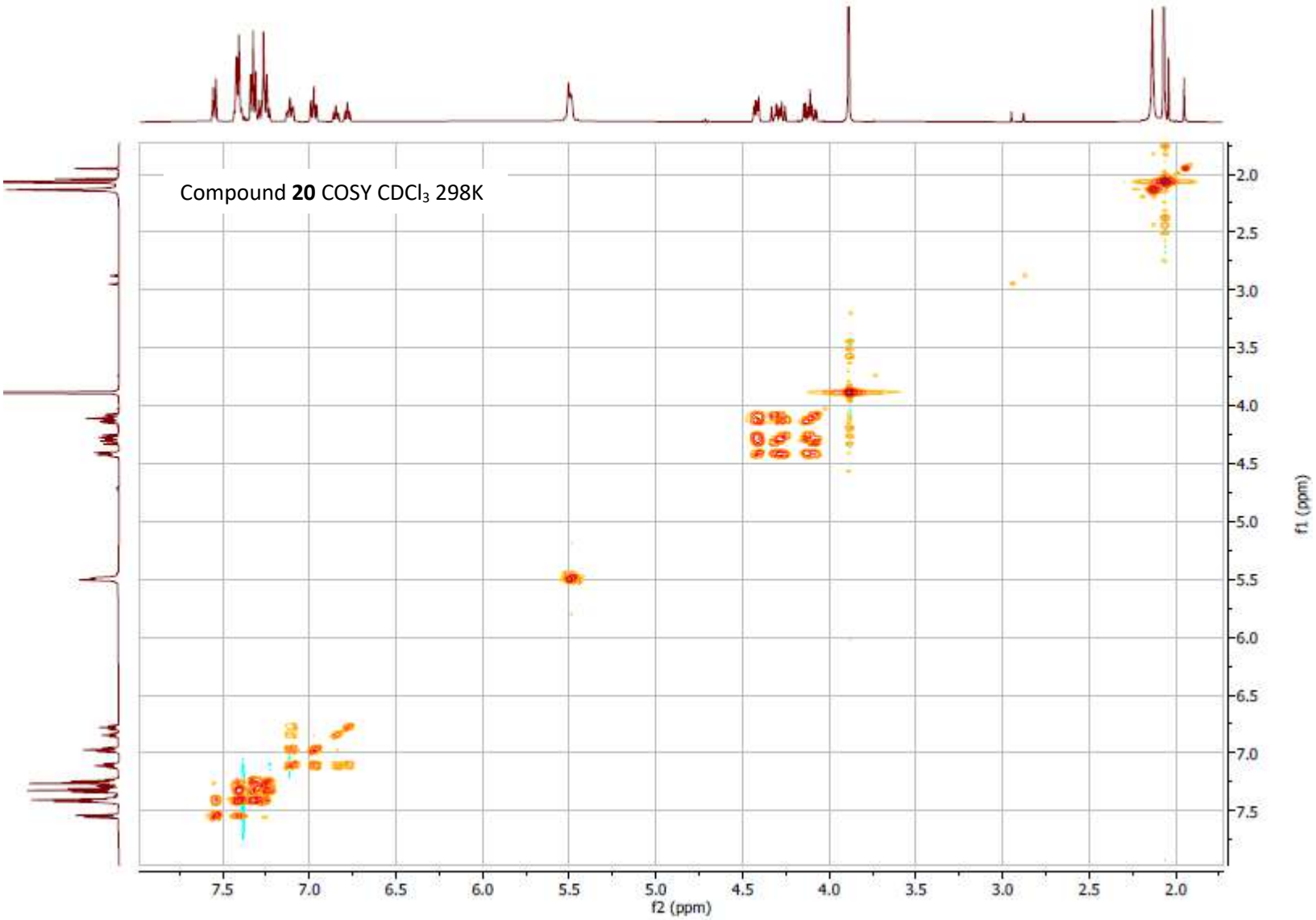


Figure S24. COSY of compound **20**

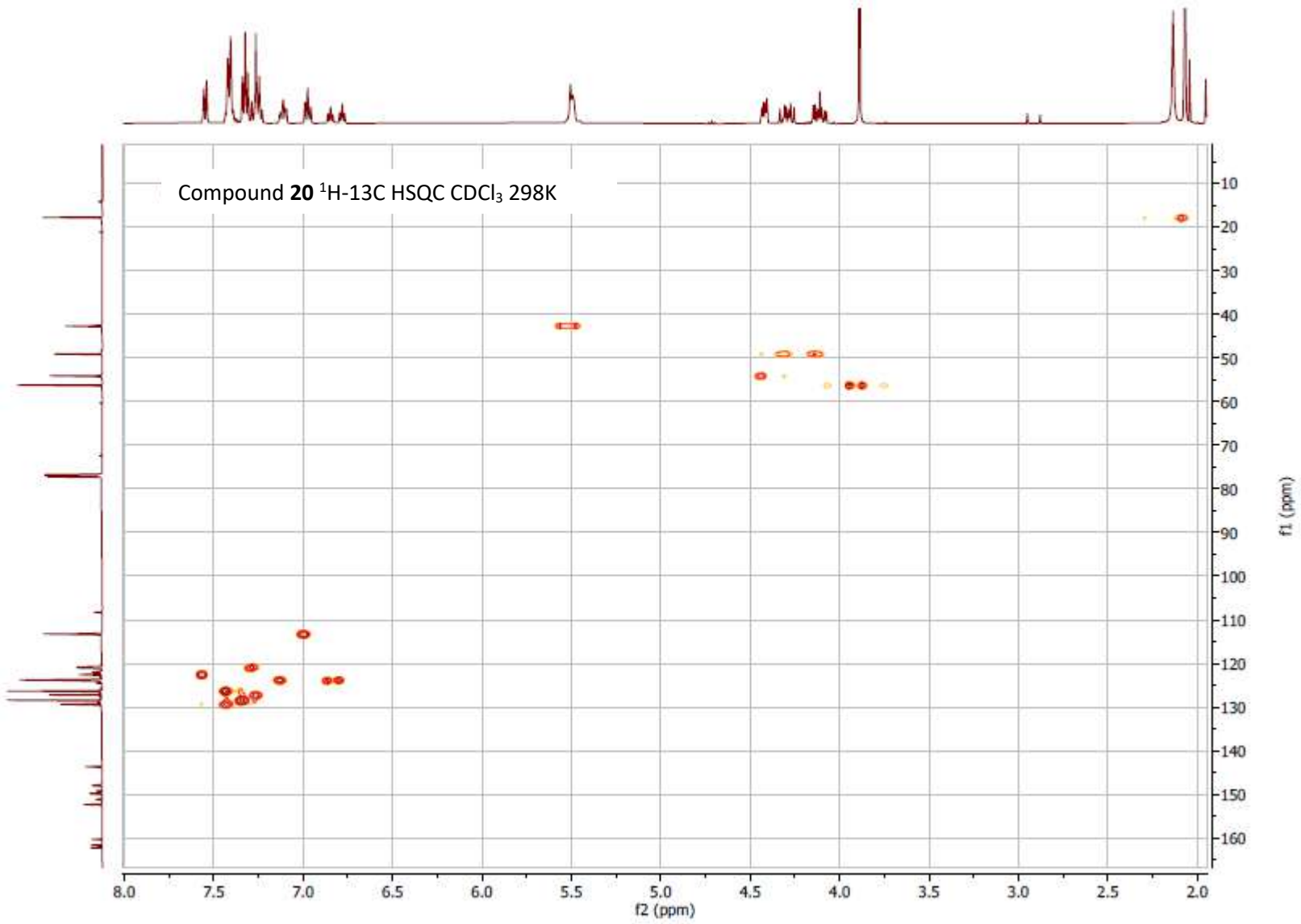


Figure S25. ^{1}H-^{13}C HSQC of compound **20**

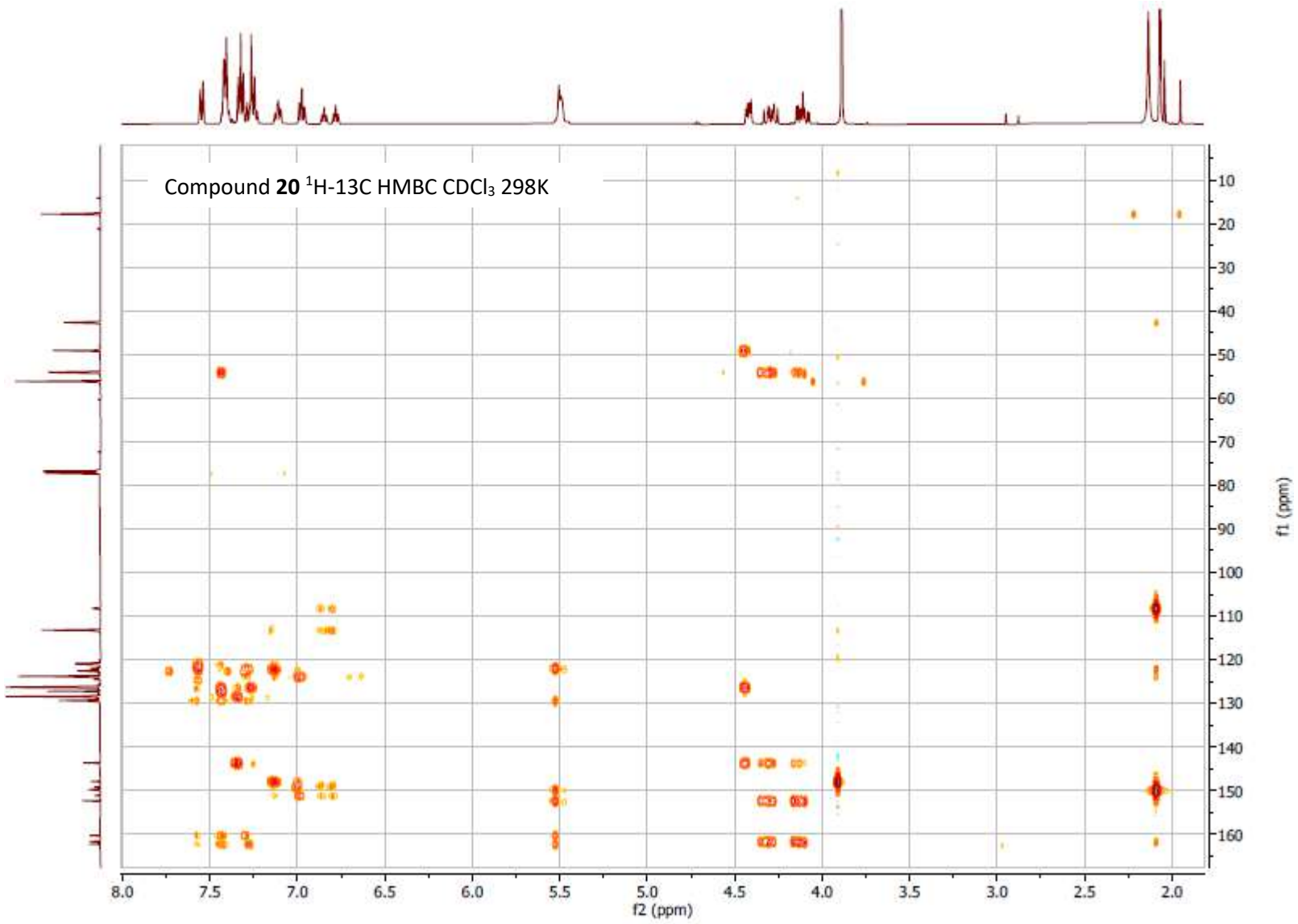


Figure S26. ^{1}H-^{13}C HMBC of compound **20**

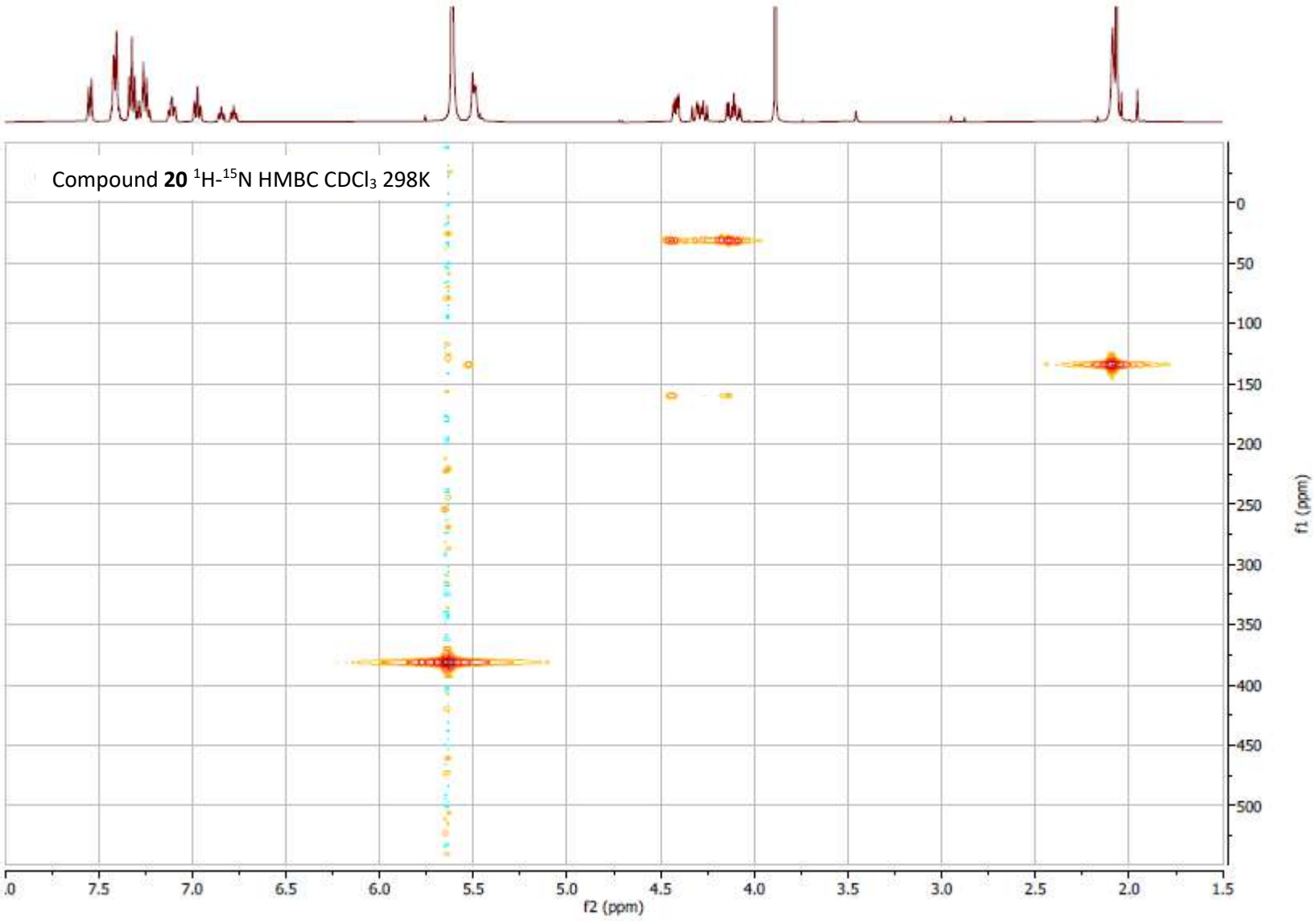


Figure S27. ^{1}H-^{15}N HMBC of compound **20**

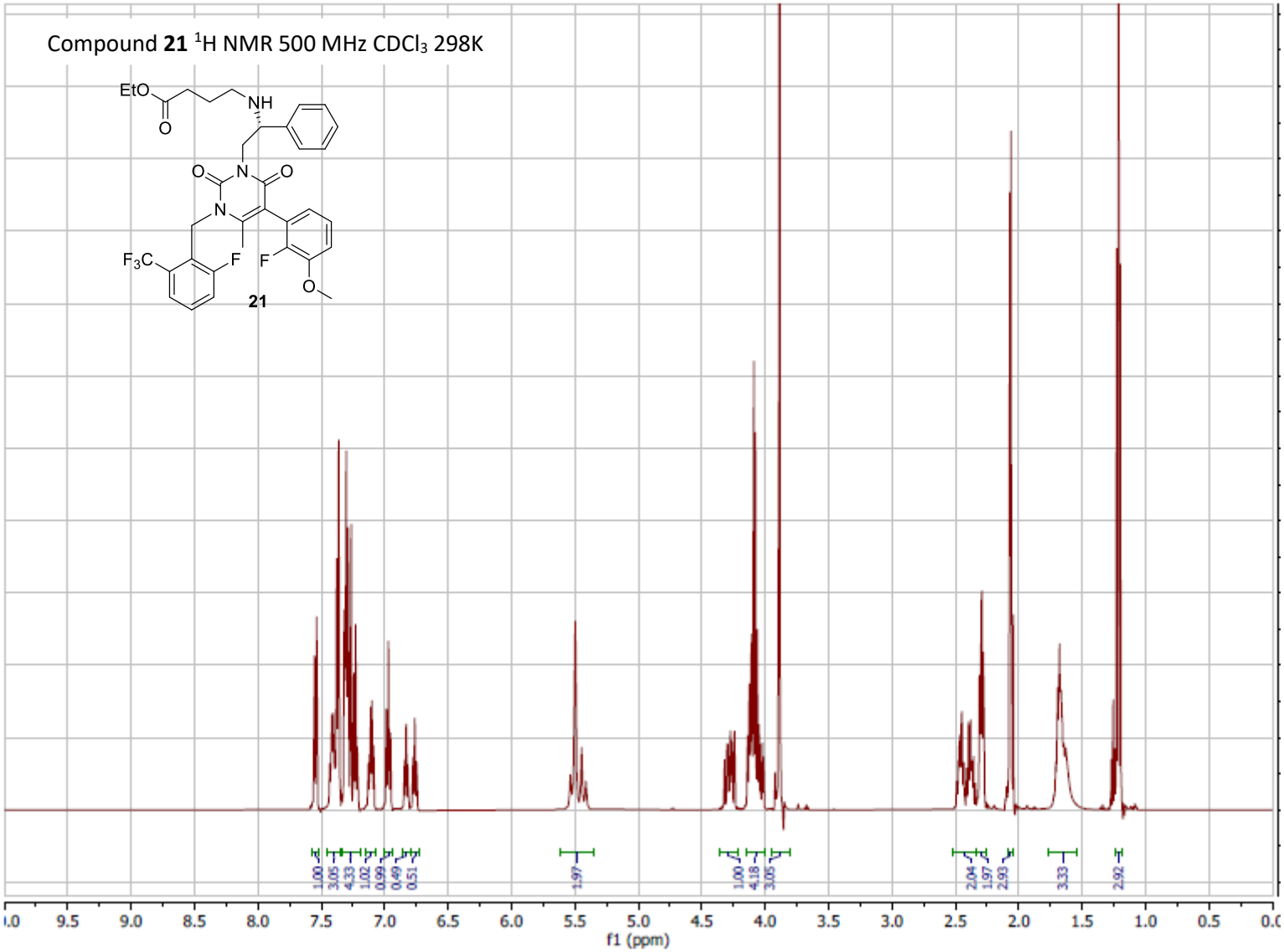


Figure S28. ^{1}H NMR of compound **21**

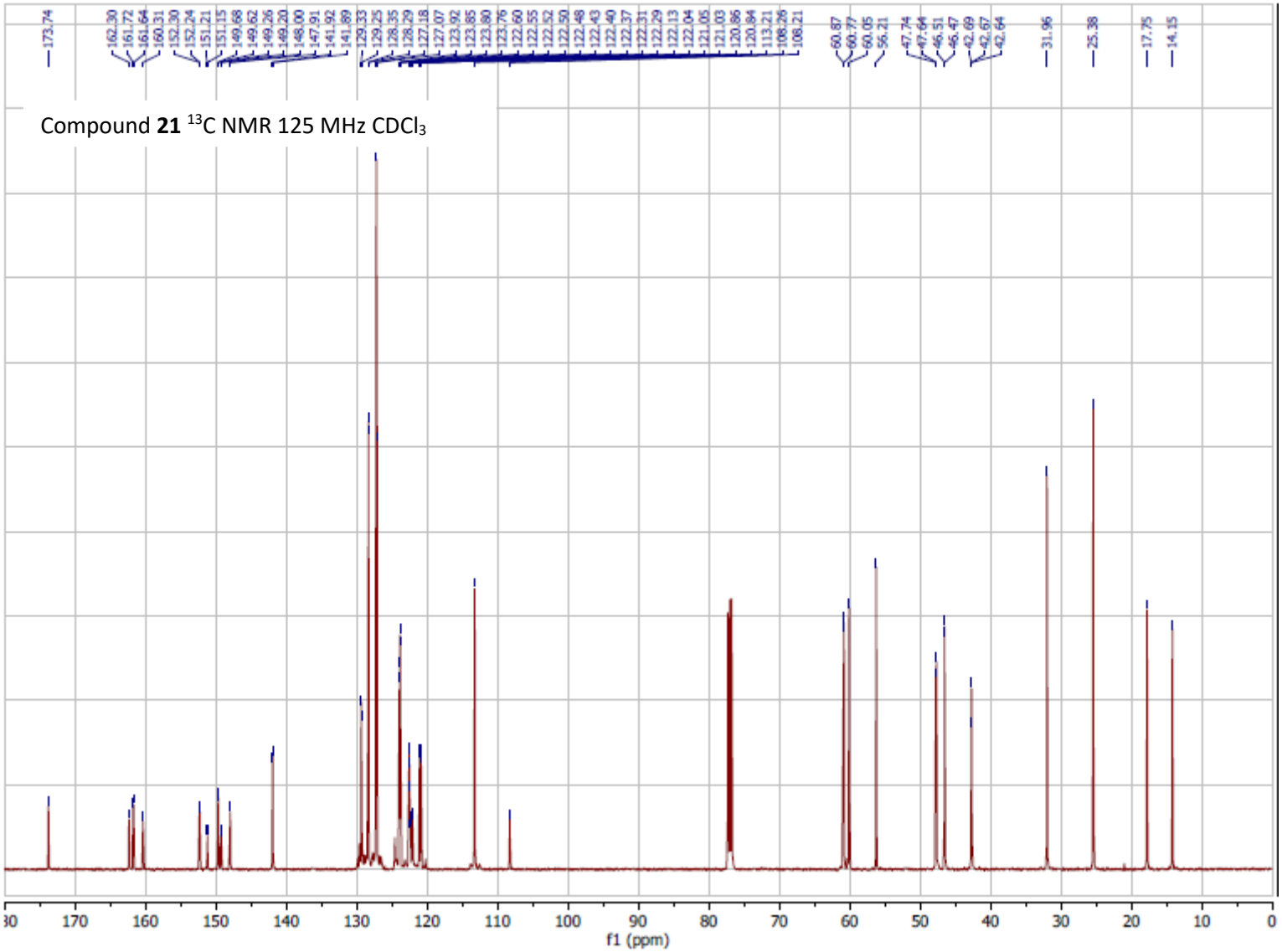


Figure S29. ^{13}C NMR of compound **21**

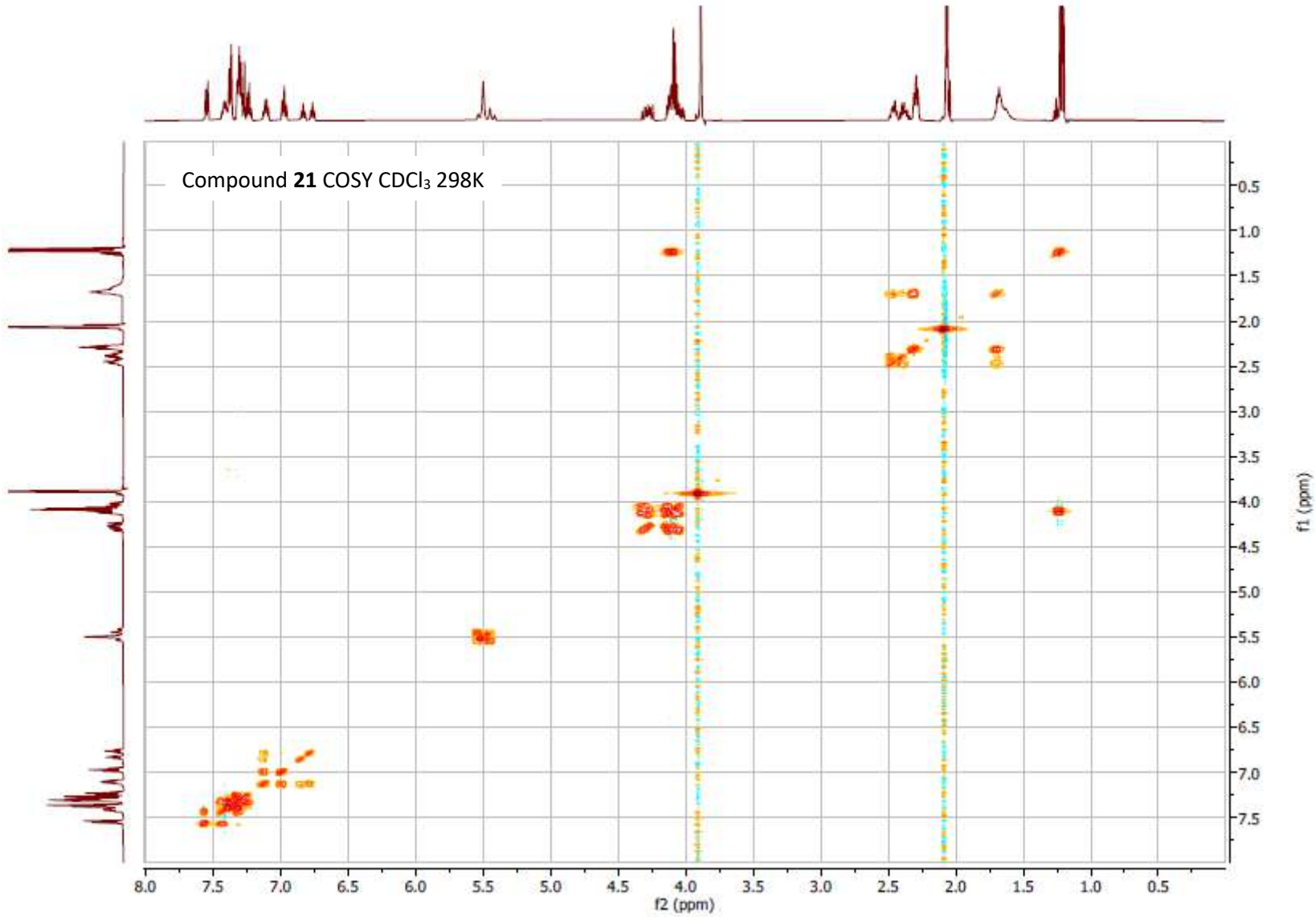


Figure S30. COSY of compound **21**

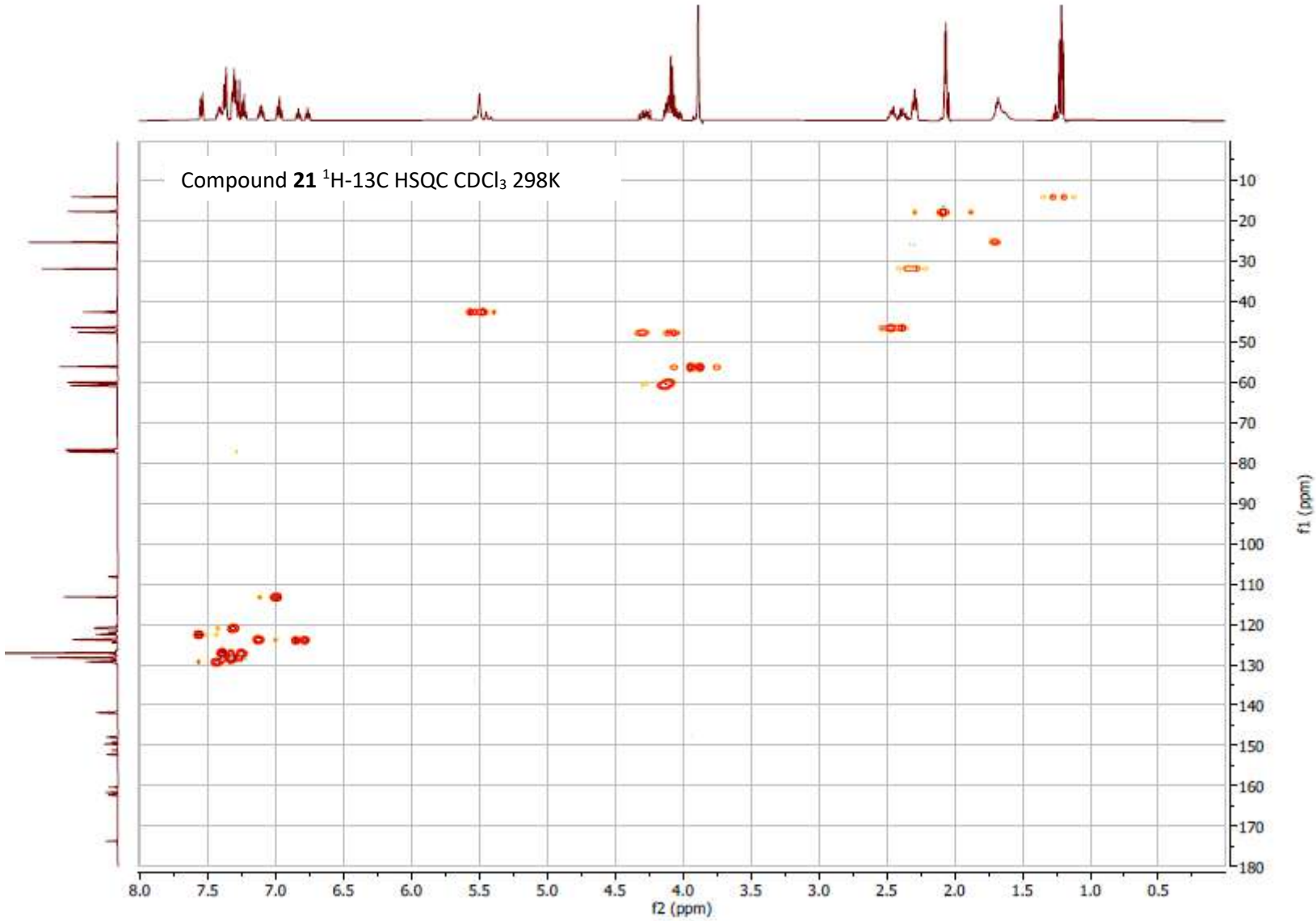


Figure S31. ^{1}H-^{13}C HSQC of compound **21**

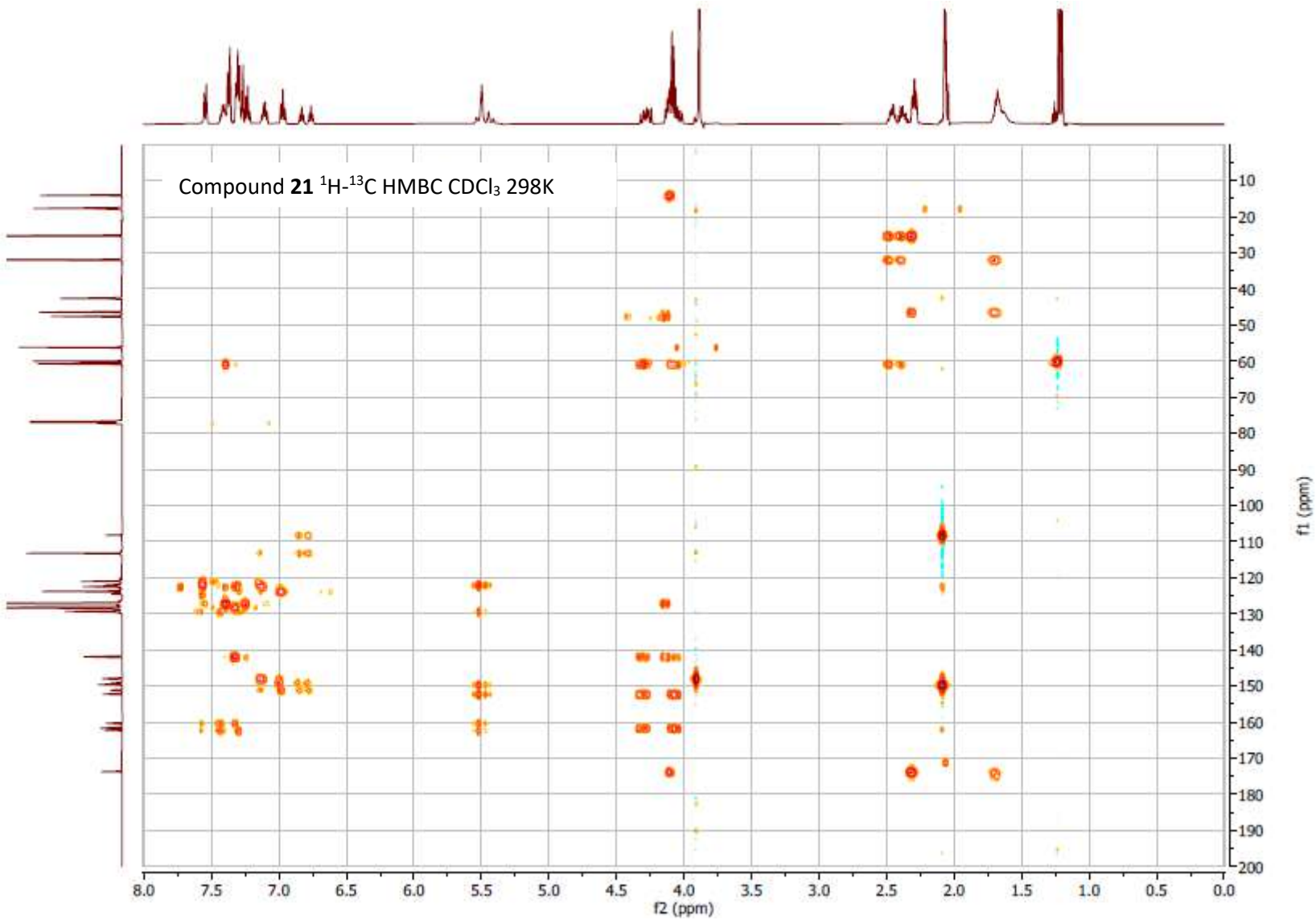


Figure S32. ^{1}H-^{13}C HMBC of compound **9**

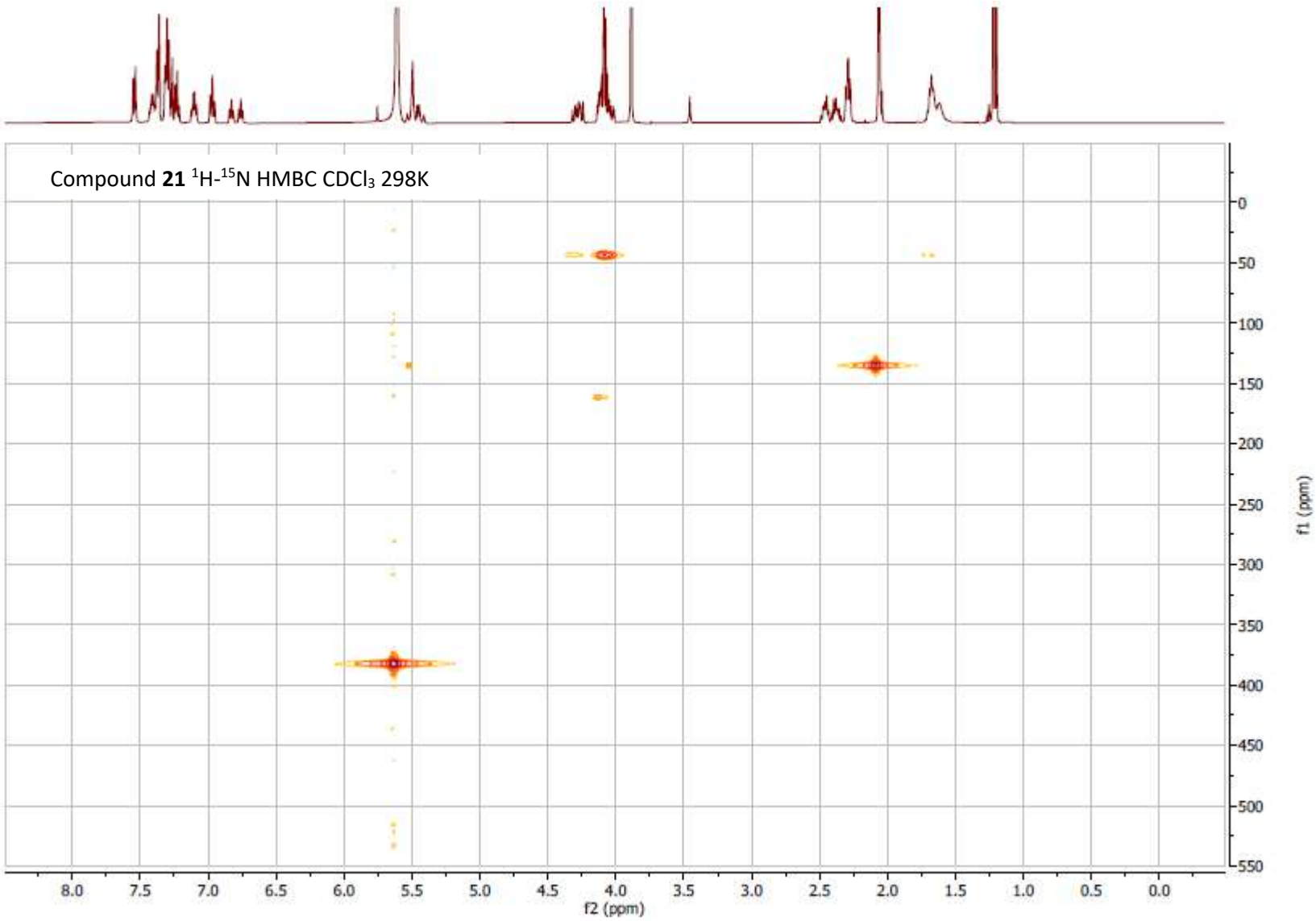


Figure S33. ^{1}H-^{15}N HMBC of compound **21**

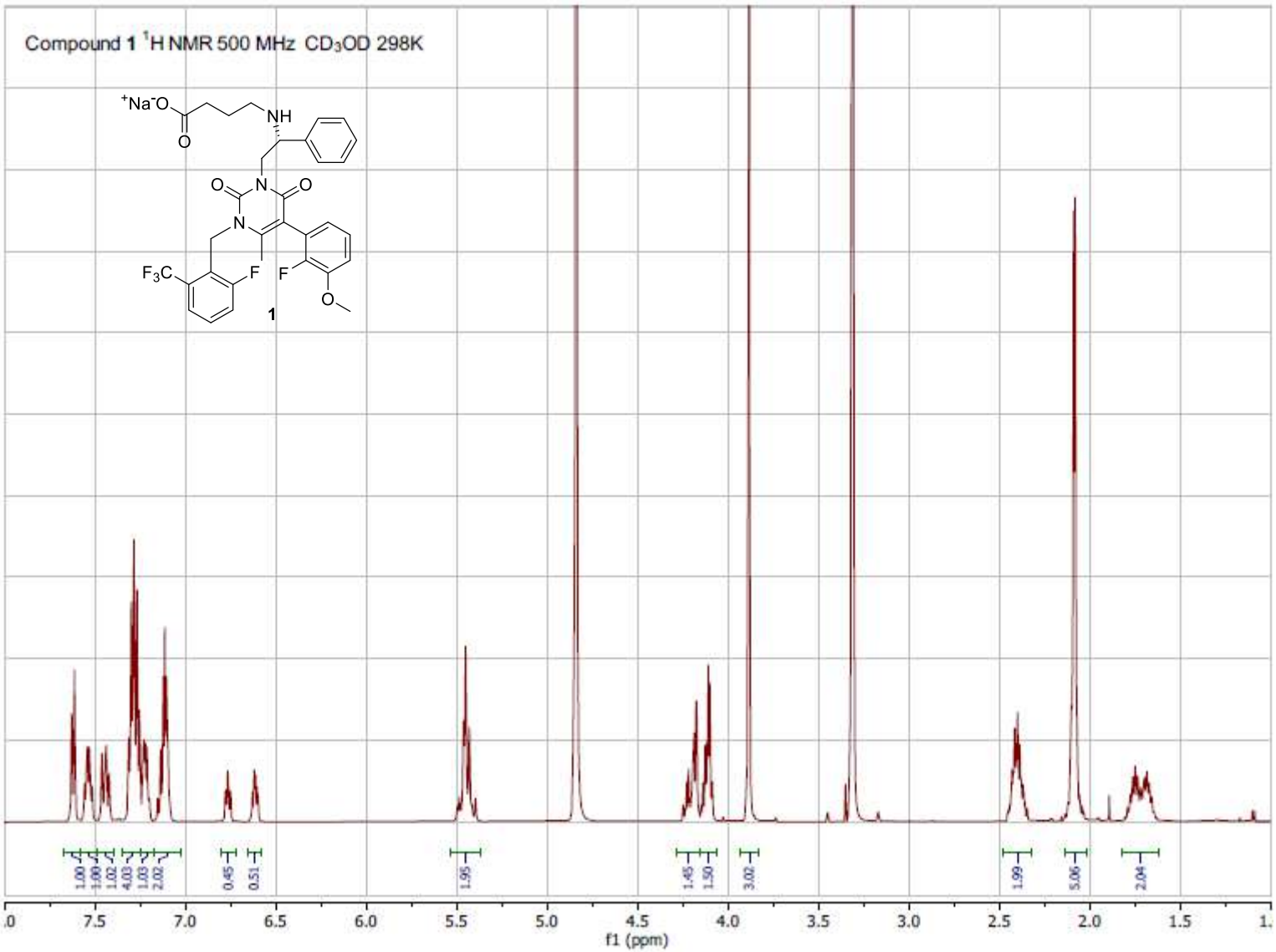


Figure S34. ^{1}H NMR of compound **1**

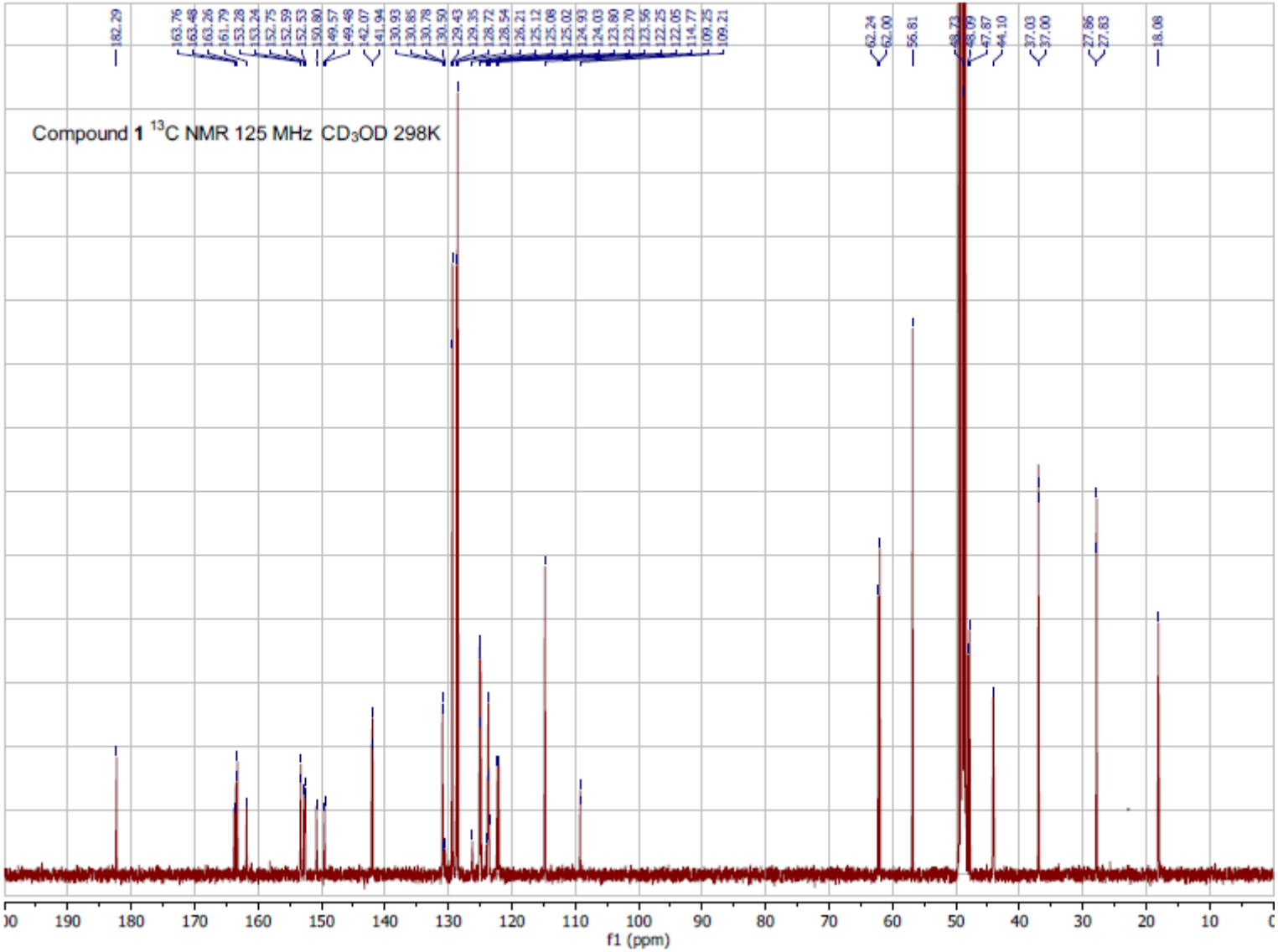


Figure S35. ^{13}C NMR of compound **1**

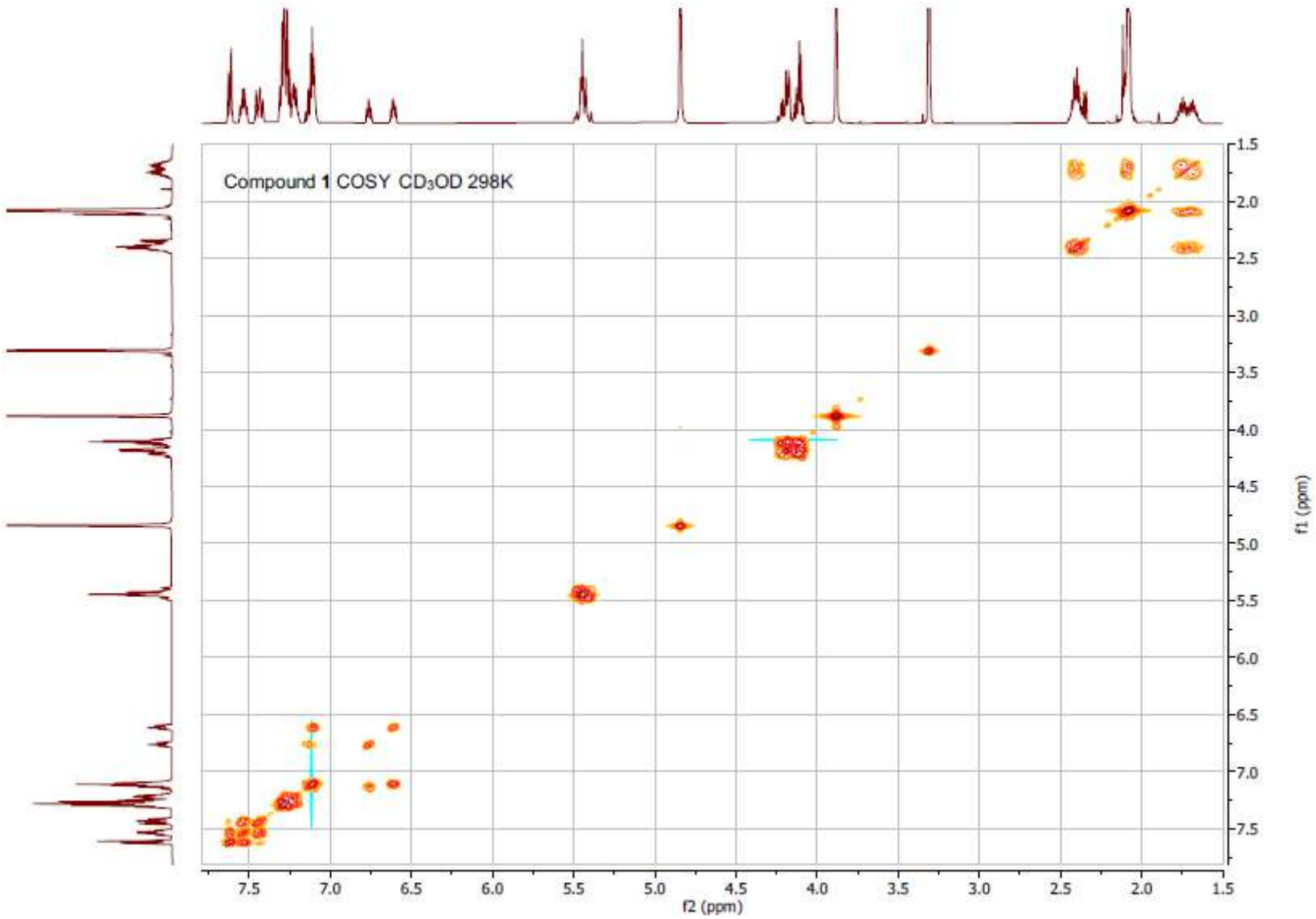


Figure S36. COSY of compound **1**

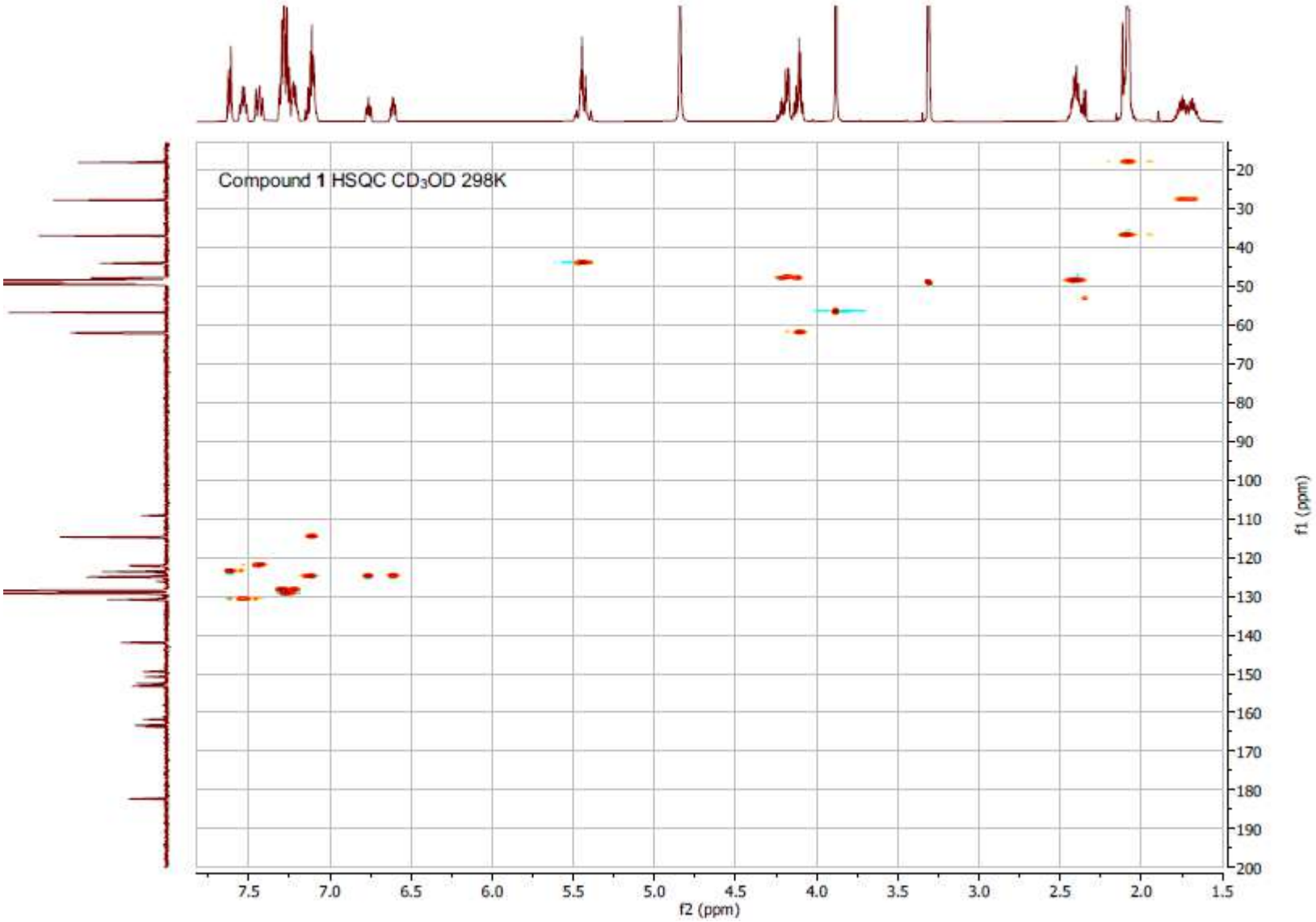


Figure S37. ^{1}H-^{13}C HSQC of compound **1**

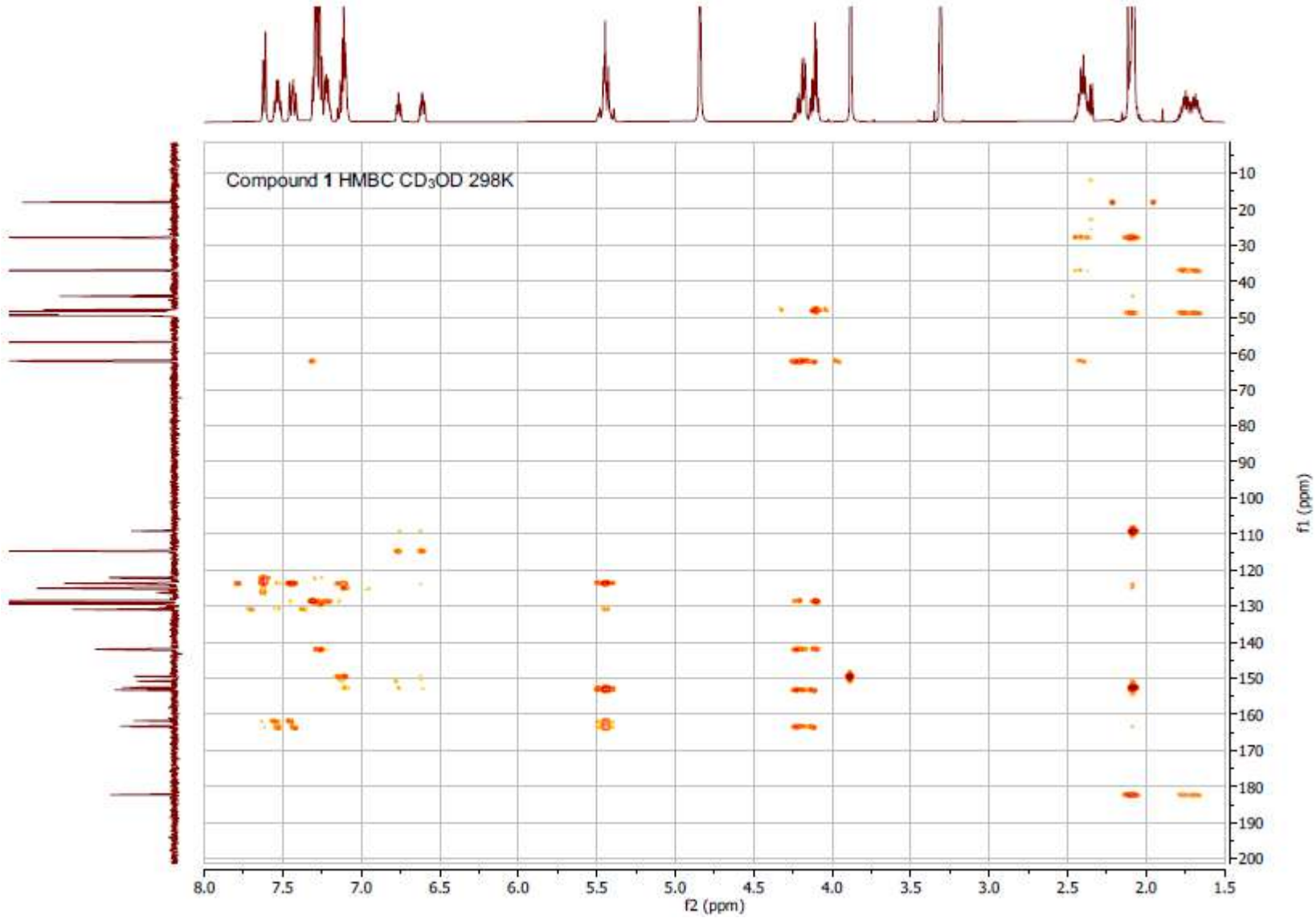


Figure S38. ^{1}H-^{13}C HMBC of compound **1**

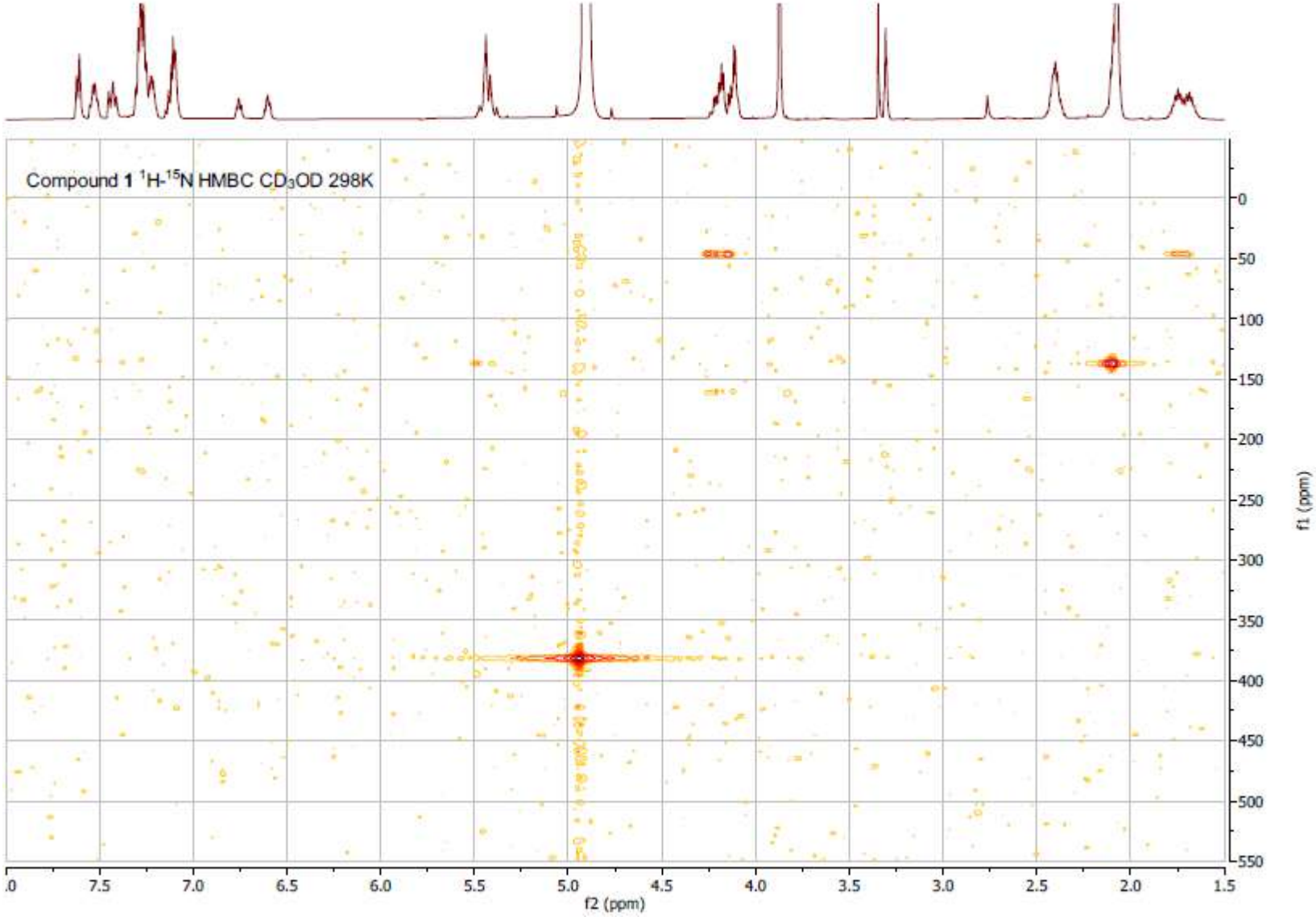


Figure S39. ^{1}H-^{15}N HMBC of compound **1**

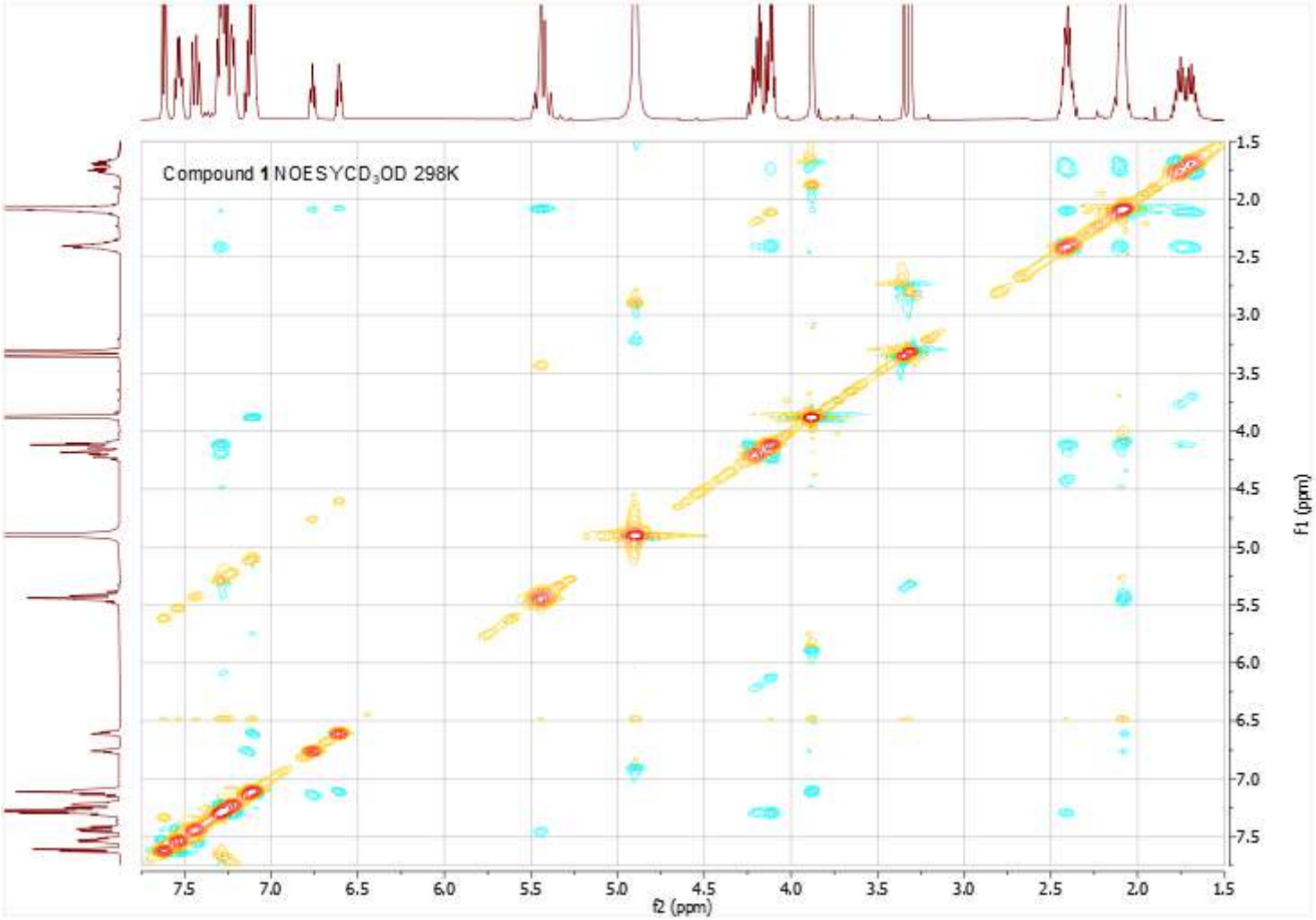


Figure S40. NOESY of compound **1**

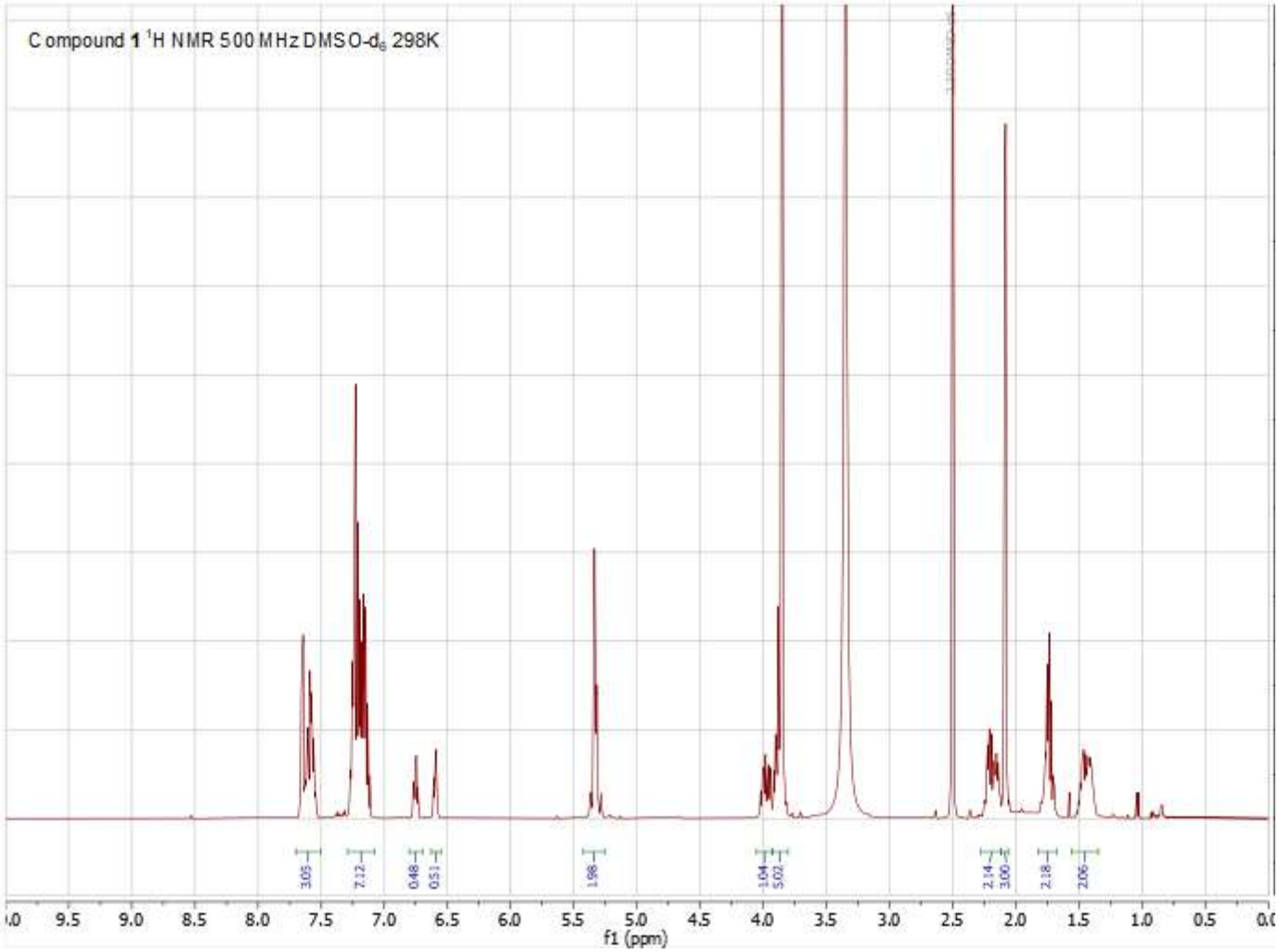


Figure S41. ^{1}H NMR of compound **1** in DMSO-d$_6$

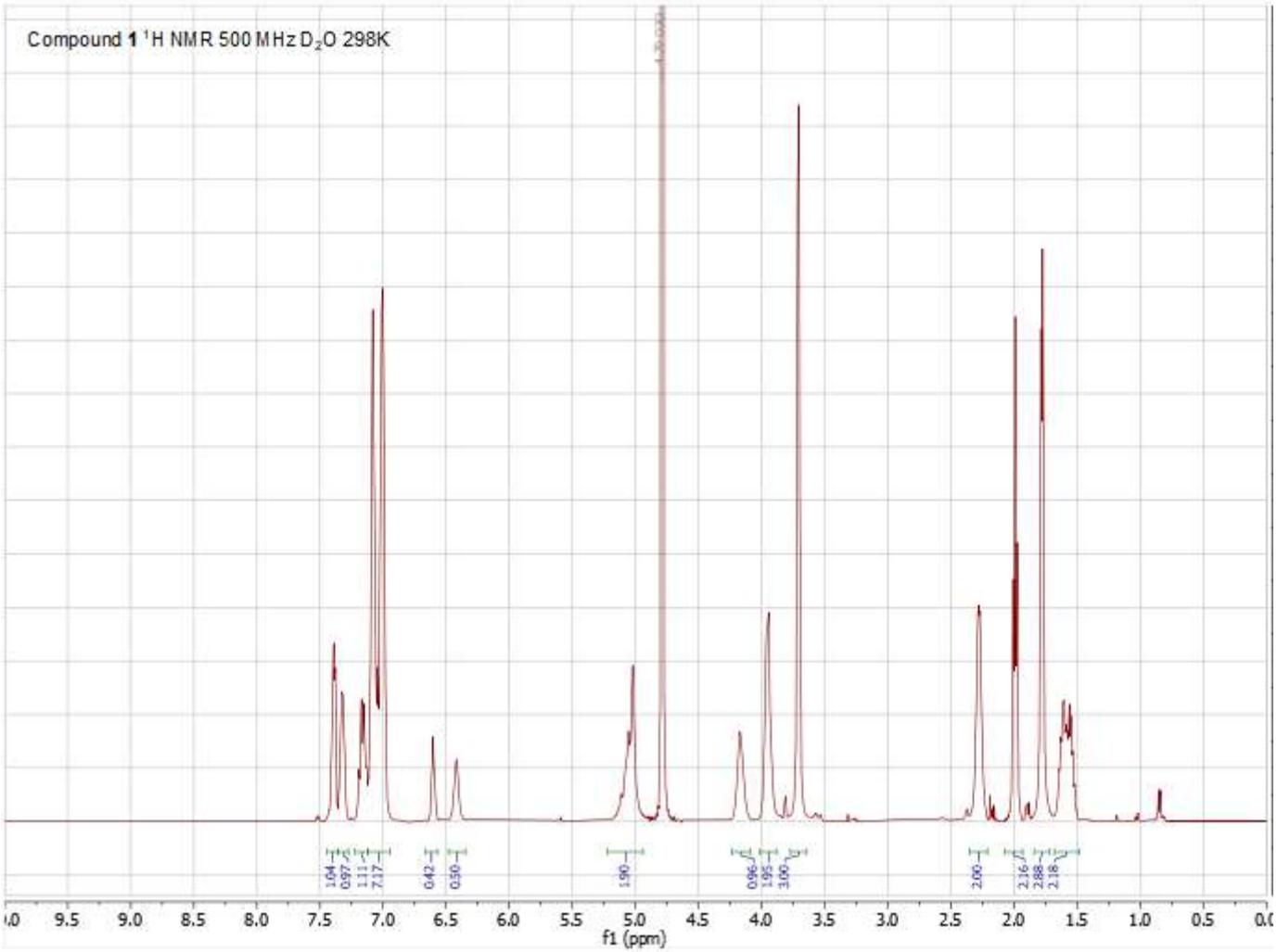


Figure S42. ^{1}H NMR of compound **1** in D_2O

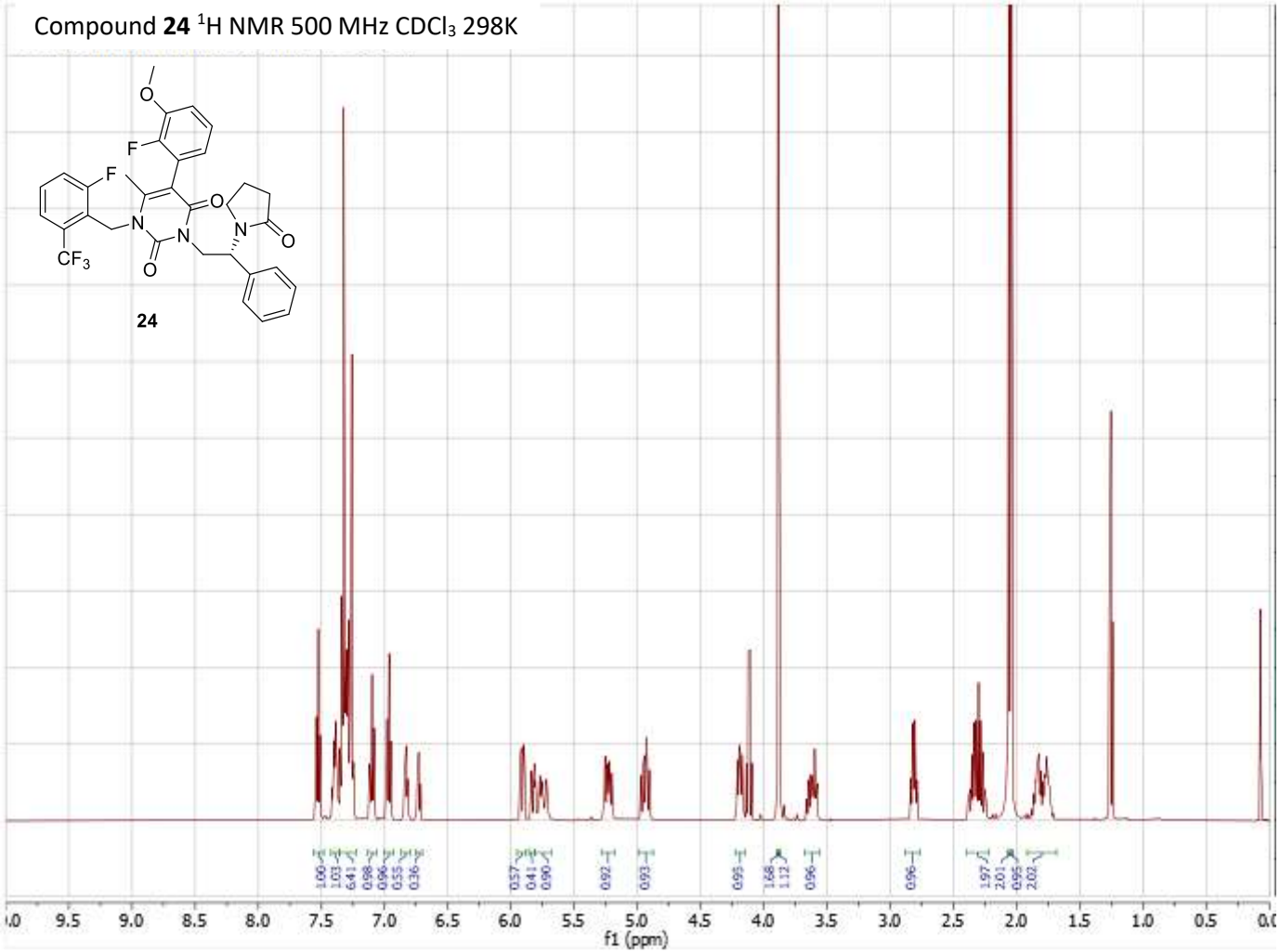


Figure S43. ^{1}H NMR of compound **24**

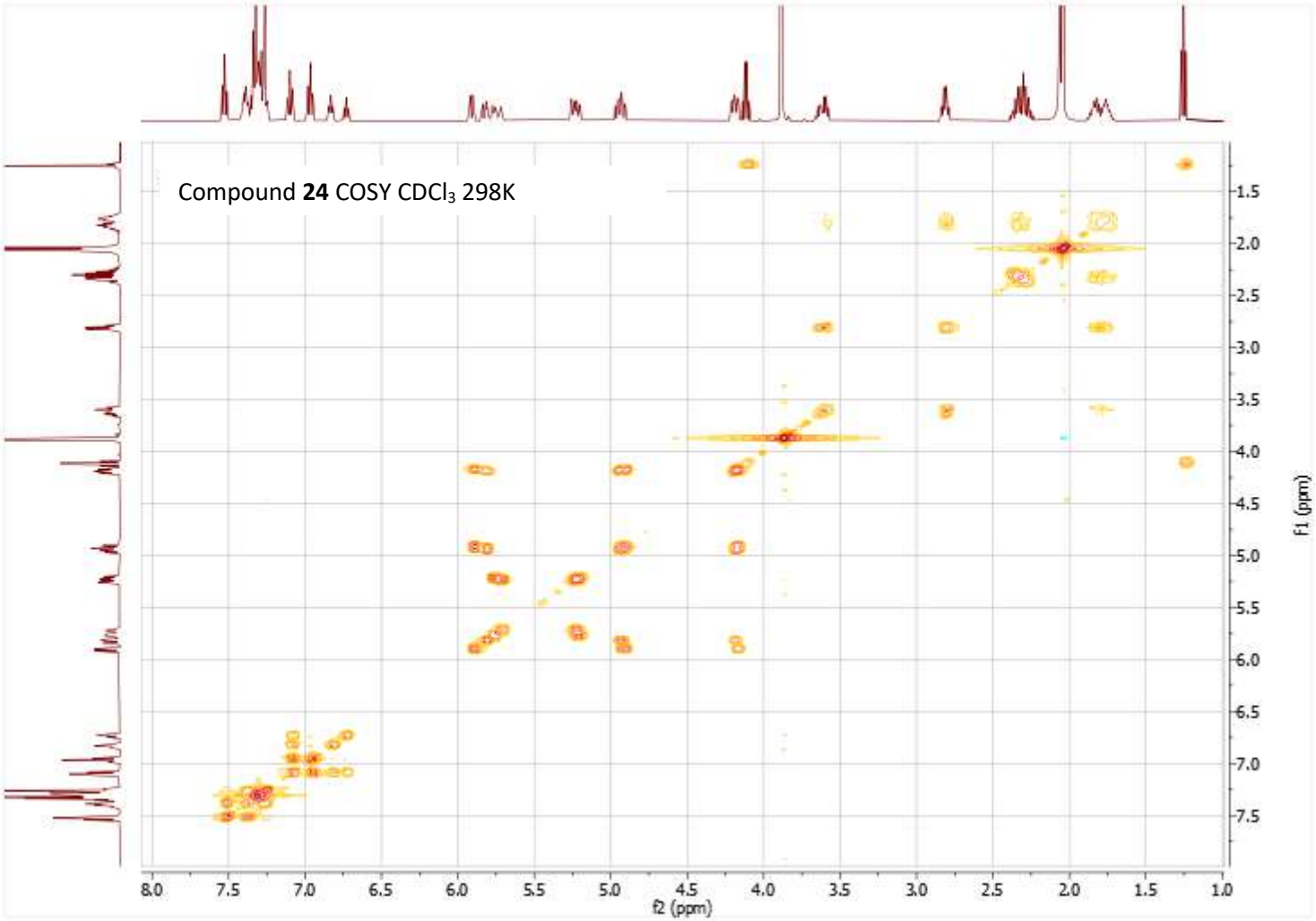


Figure S44. COSY of compound **24**

Modifications at the 4-position

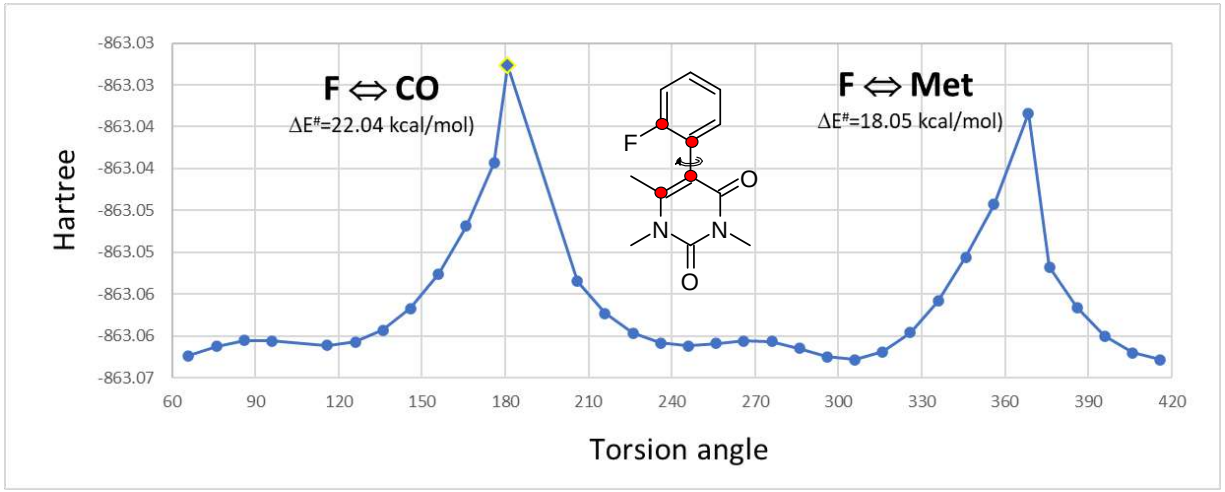


Figure S45. Potential energy scan obtained rotating the torsion angle indicated by the red arrow. The red dots highlight the atoms selected for the scan.

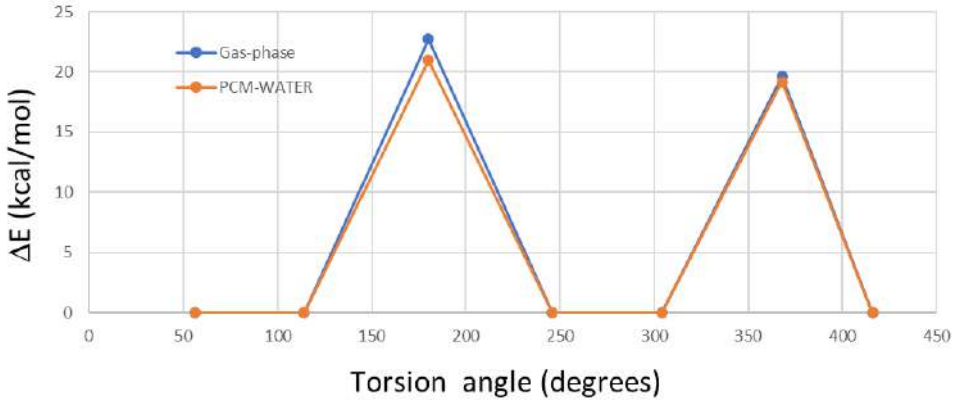


Figure S46. Comparison between the potential energy plots obtained optimizing the energy minima and the TS structures derived from the potential energy scan (Figure S45) in gas-phase (cyan line) and in PCM implicit water solvent model (orange line). Calculations were performed at DFT/B3LYP/6-31g(d,p) level.

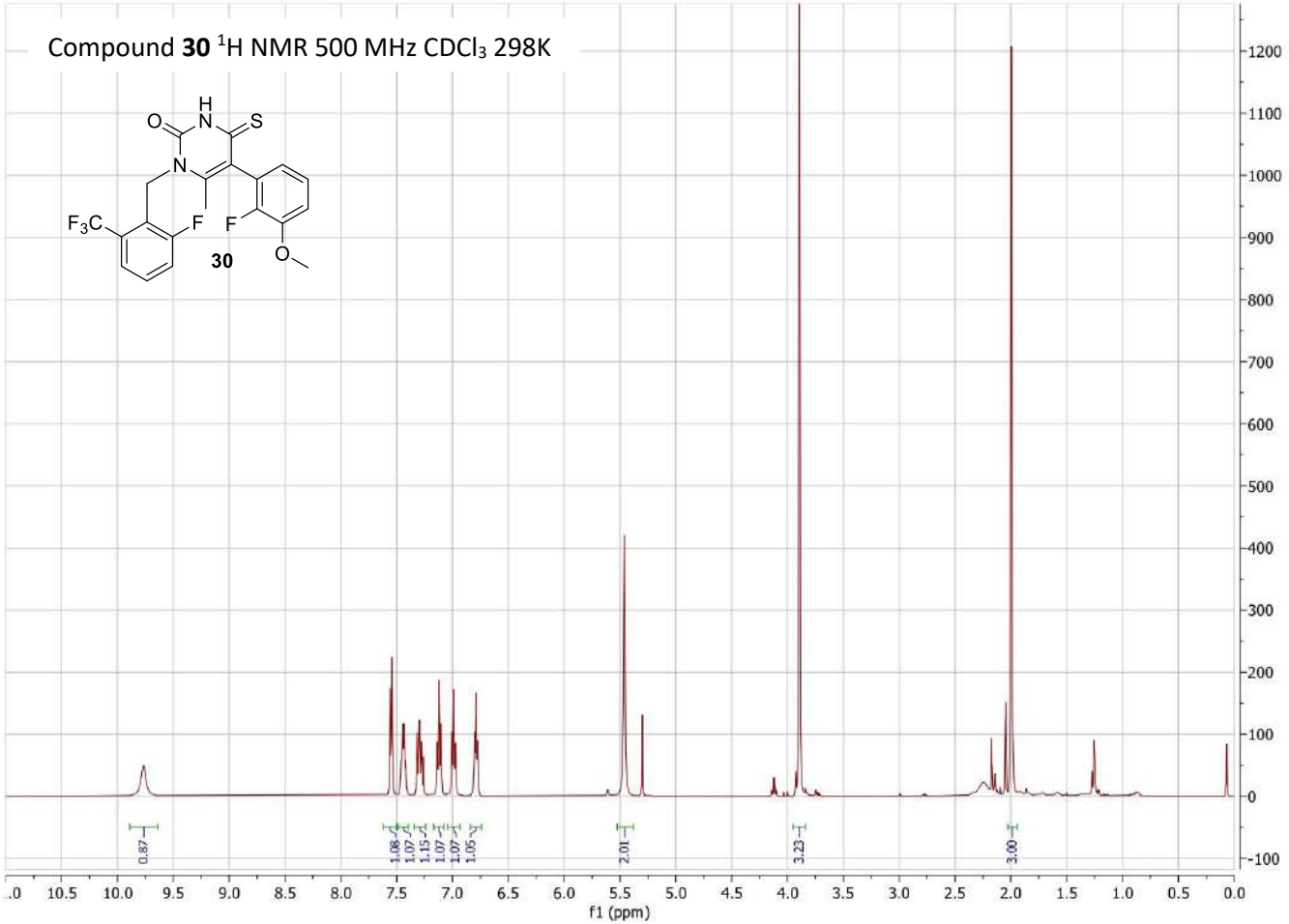


Figure S47. ^{1}H NMR of compound **30**

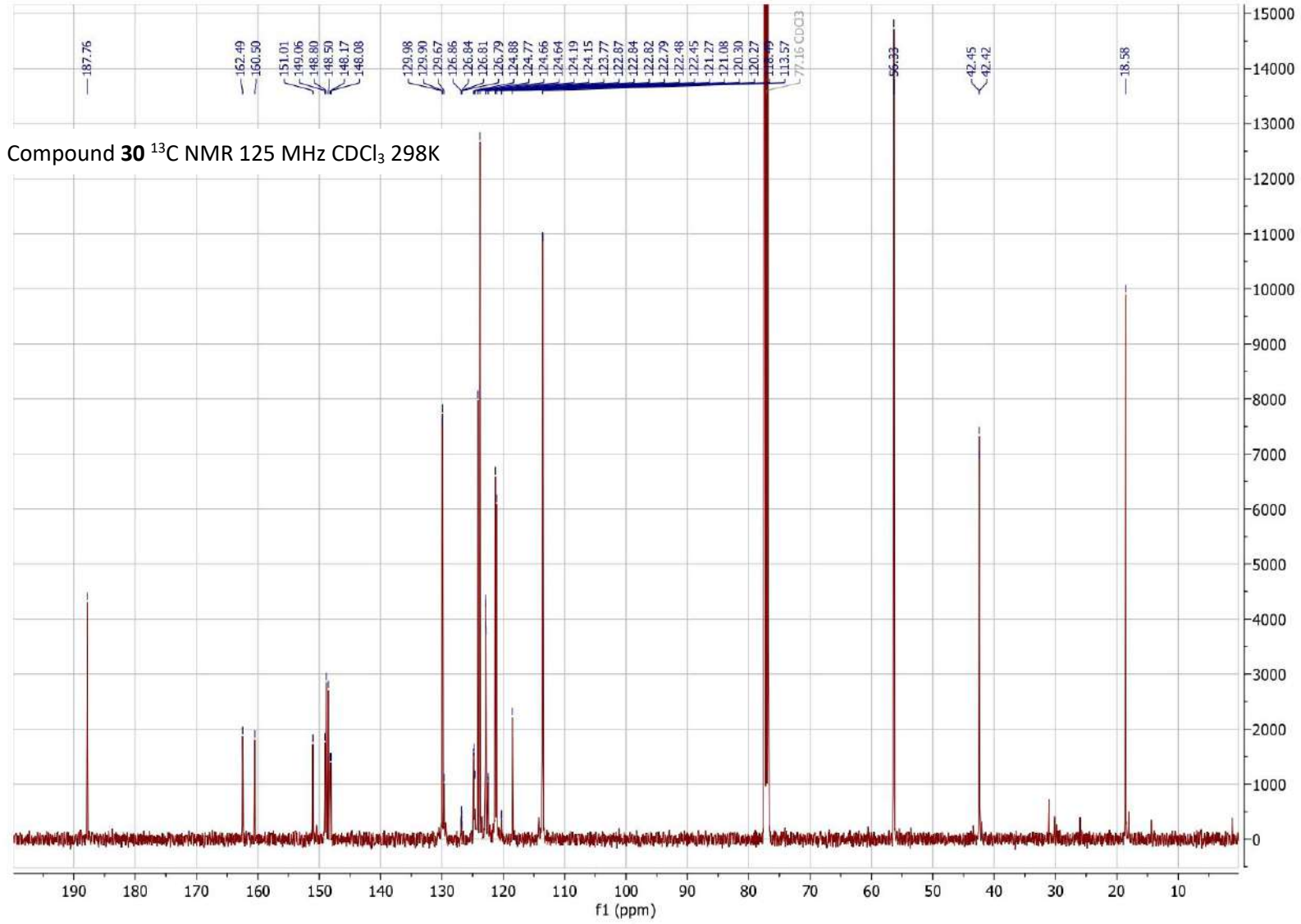


Figure S48. ^{13}C NMR of compound **30**

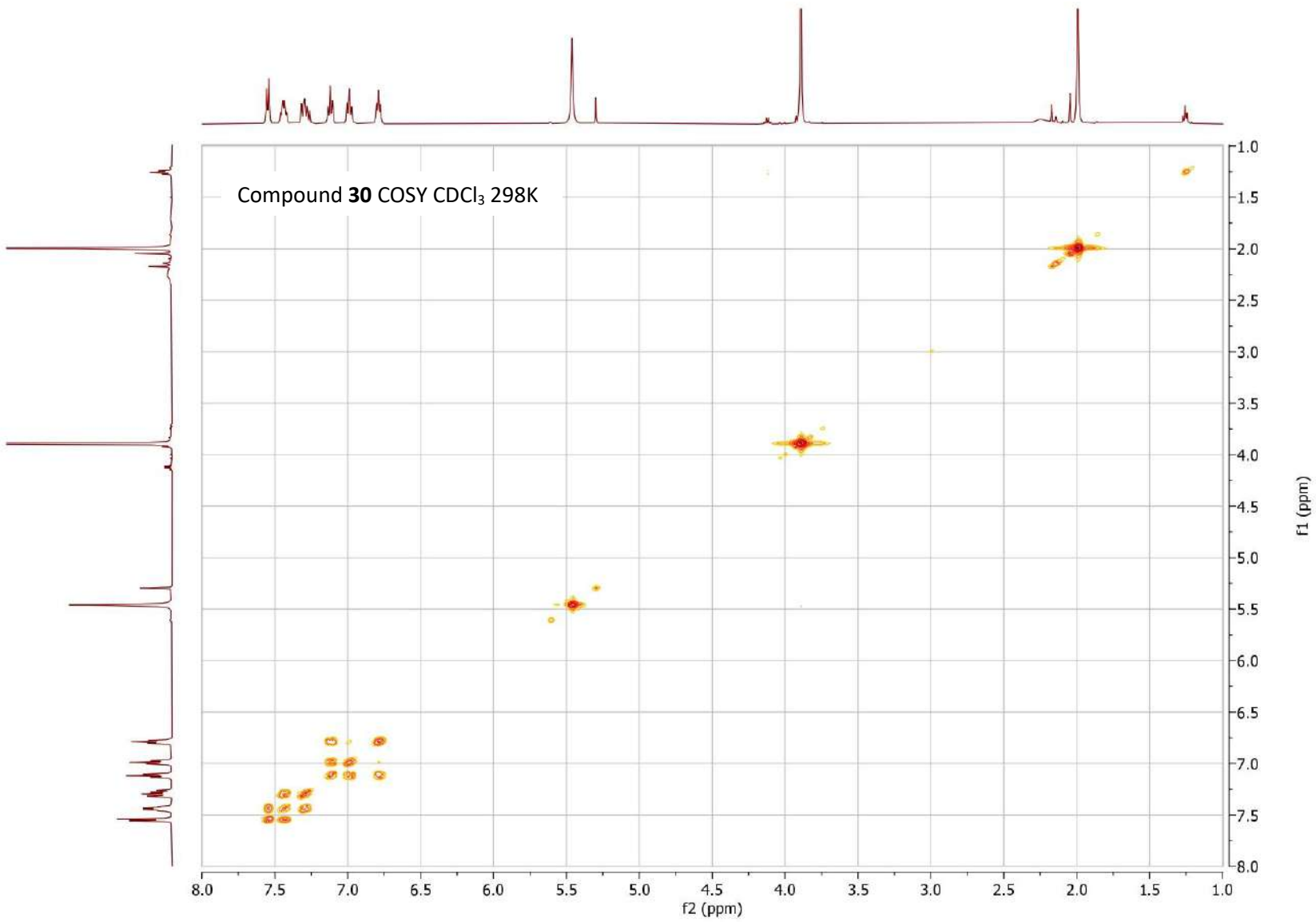


Figure S49. COSY of compound **30**

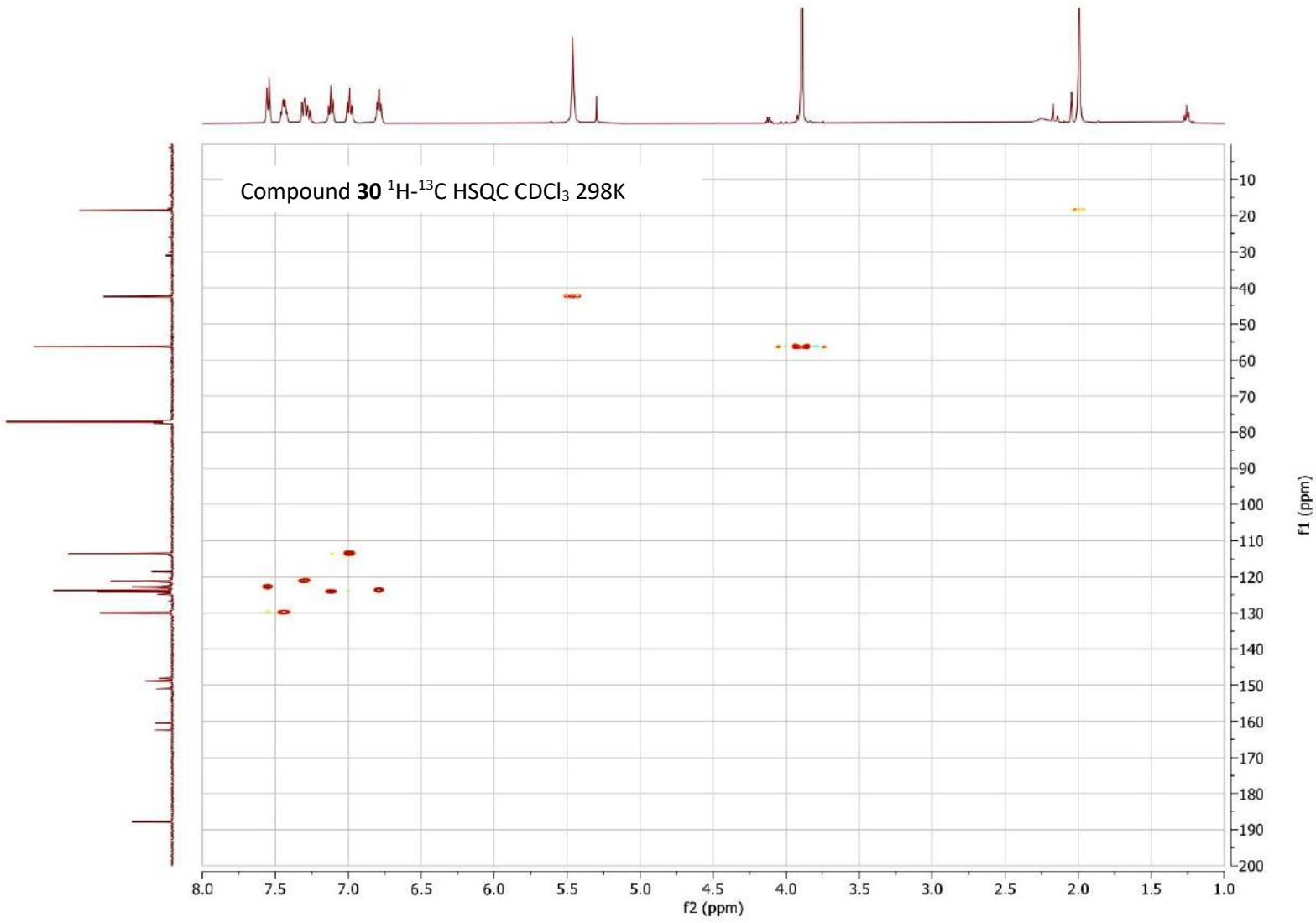


Figure S50. ^{1}H-^{13}C HSQC of compound **30**

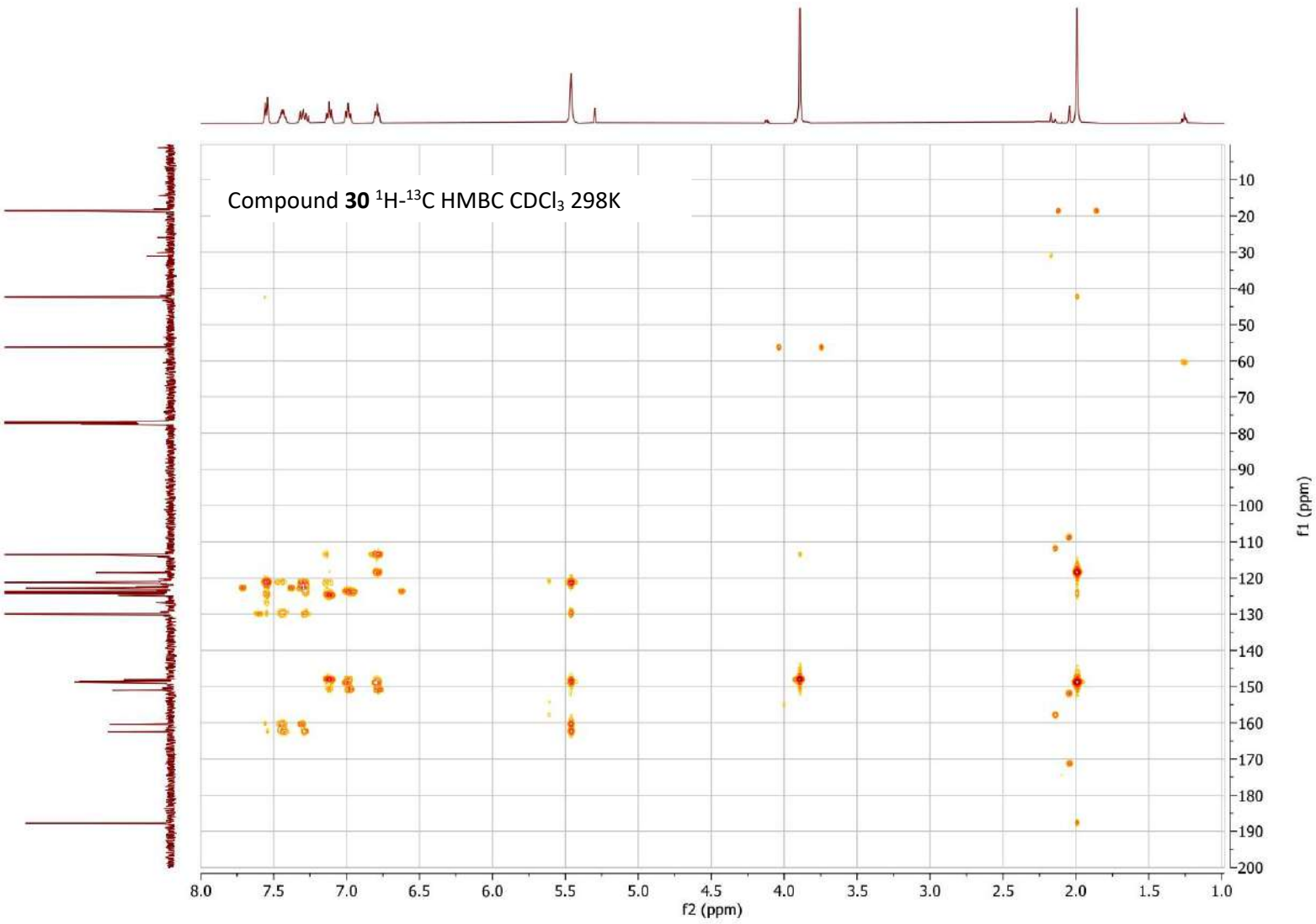


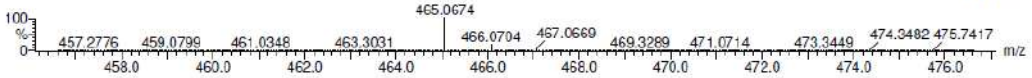
Figure S51. ^{1}H-^{13}C HMBC of compound **30**

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -5.0, max = 300.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

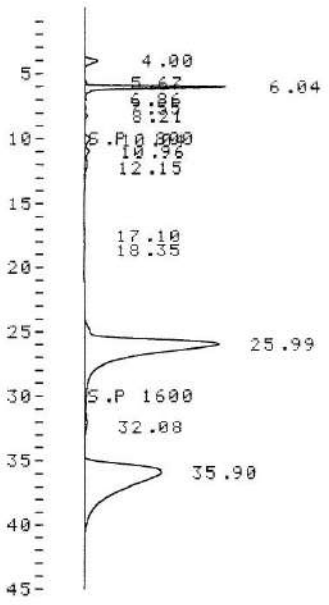
Monoisotopic Mass, Even Electron Ions
13 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 20-20 H: 14-16 N: 2-2 O: 2-2 Na: 0-4 S: 1-1 K: 0-2 F: 5-5

INT10Z 30 (0.603) AM2 (Ar,40000.0,0.00,0.00); Cm (30:50) 1: TOF MS ES+ 1.44e+007



Minimum:				-5.0				
Maximum:		5.0	5.0	300.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
465.0674	465.0672	0.2	0.4	11.5	1840.8	n/a	n/a	C20 H15 N2 O2 Na S F5

Figure S52. HRMS analysis of compound **30**



D-2500

METHOD: TAG: 1 CH: 1

FILE: 0 CALC-METHOD: AREA% TABLE: 0 CONC: AREA

NO.	RT	AREA	CONC	BC
1	4.00	25897	1.390	BB
2	5.67	1504	0.081	BV
3	6.04	125743	6.751	VV
4	6.86	1396	0.075	TBB
5	7.55	2418	0.130	BB
6	8.21	4038	0.217	BB
7	10.04	13171	0.707	BV
8	10.96	11535	0.619	VV
9	12.15	13815	0.742	VB
10	17.10	967	0.052	BB
11	18.35	1550	0.083	BB
12	25.99	863597	46.365	BV
13	32.08	13236	0.711	TBB
14	35.90	783753	42.078	BB
TOTAL		1862620	100.000	

PEAK REJ : 0

RAW DATA STORAGE NO. 1

Figure S53. Chiral HPLC analysis of compound **30**

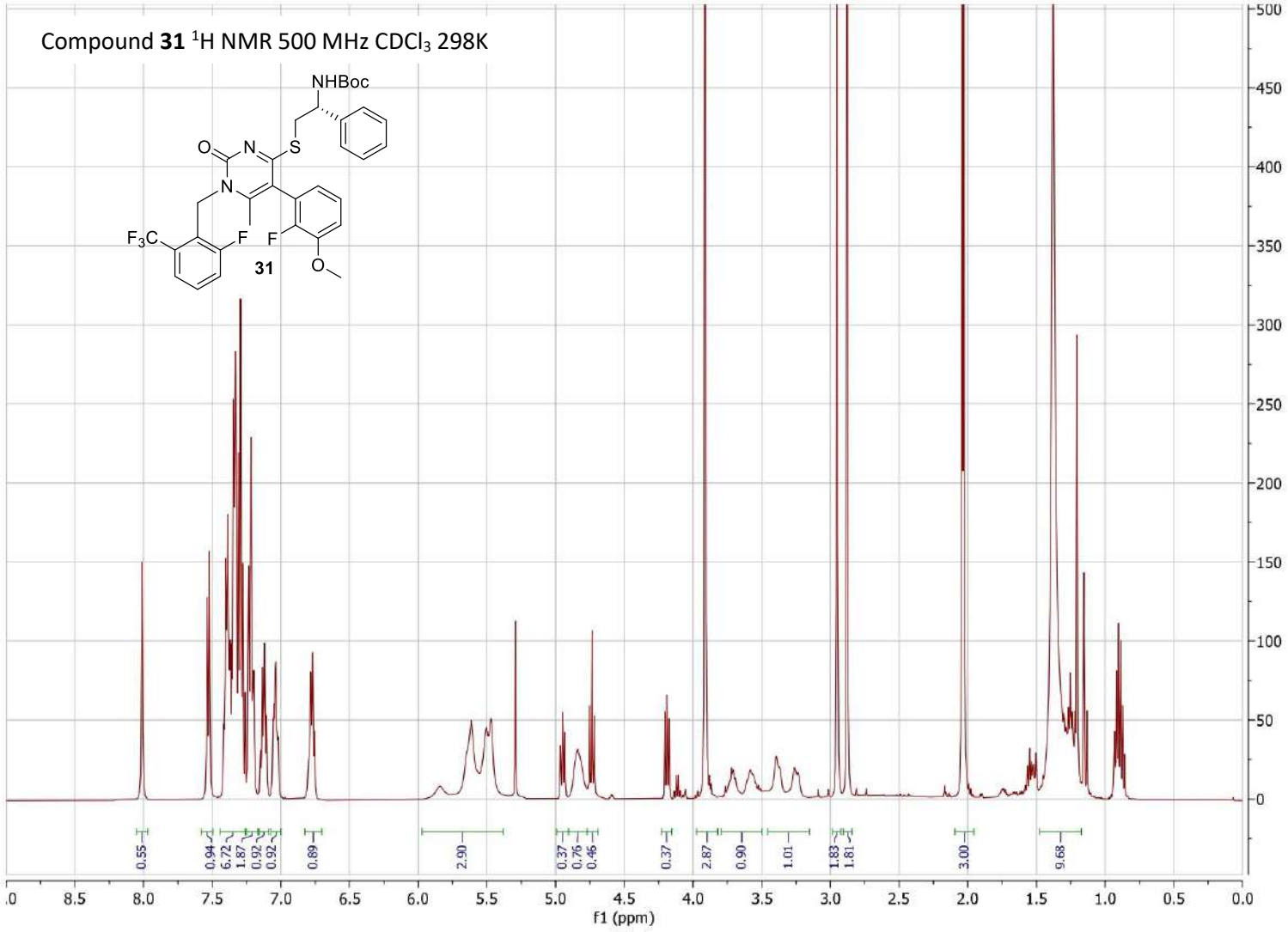


Figure S54. ^{1}H NMR of compound **31**

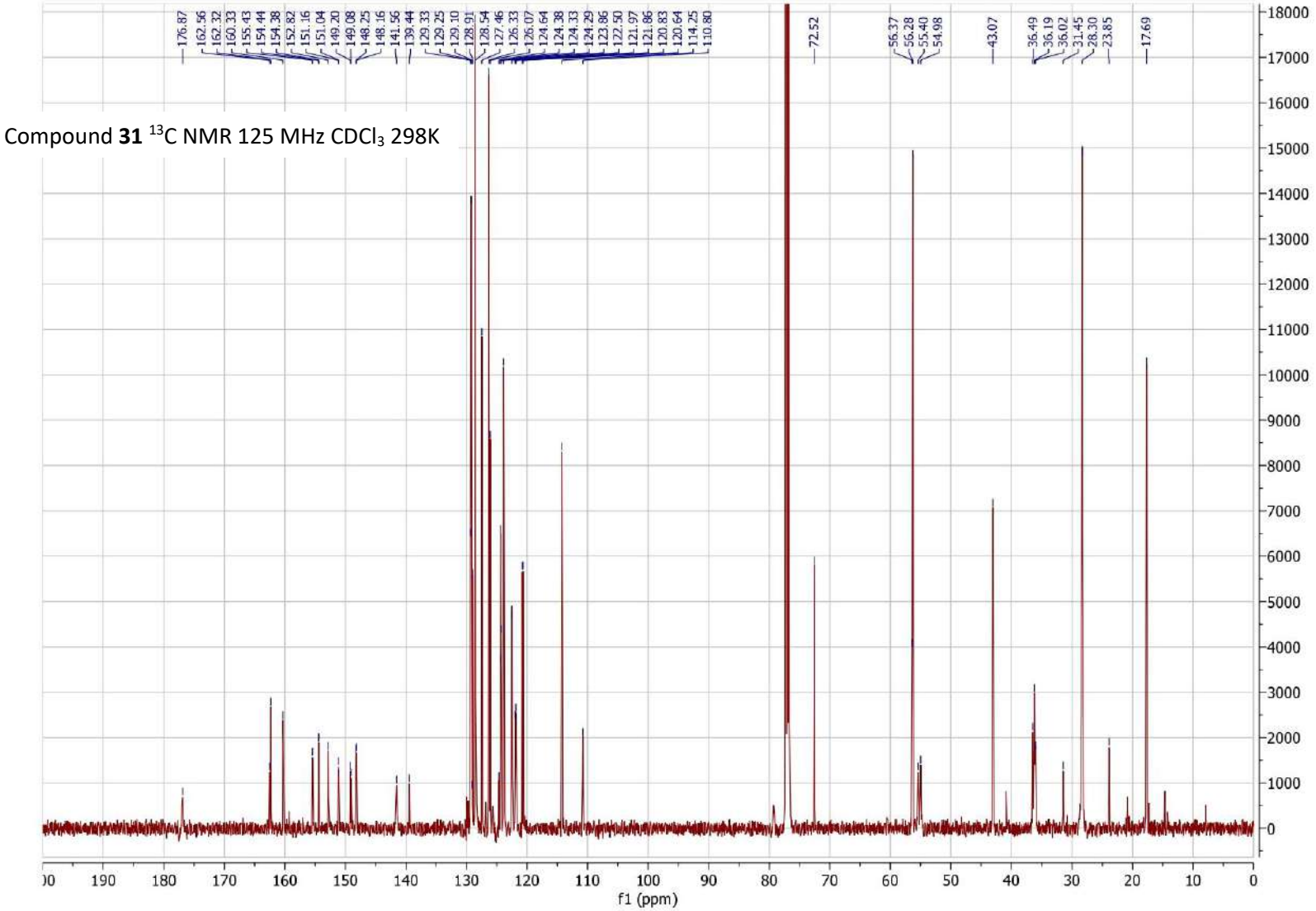


Figure S55. ^{13}C NMR of compound **31**

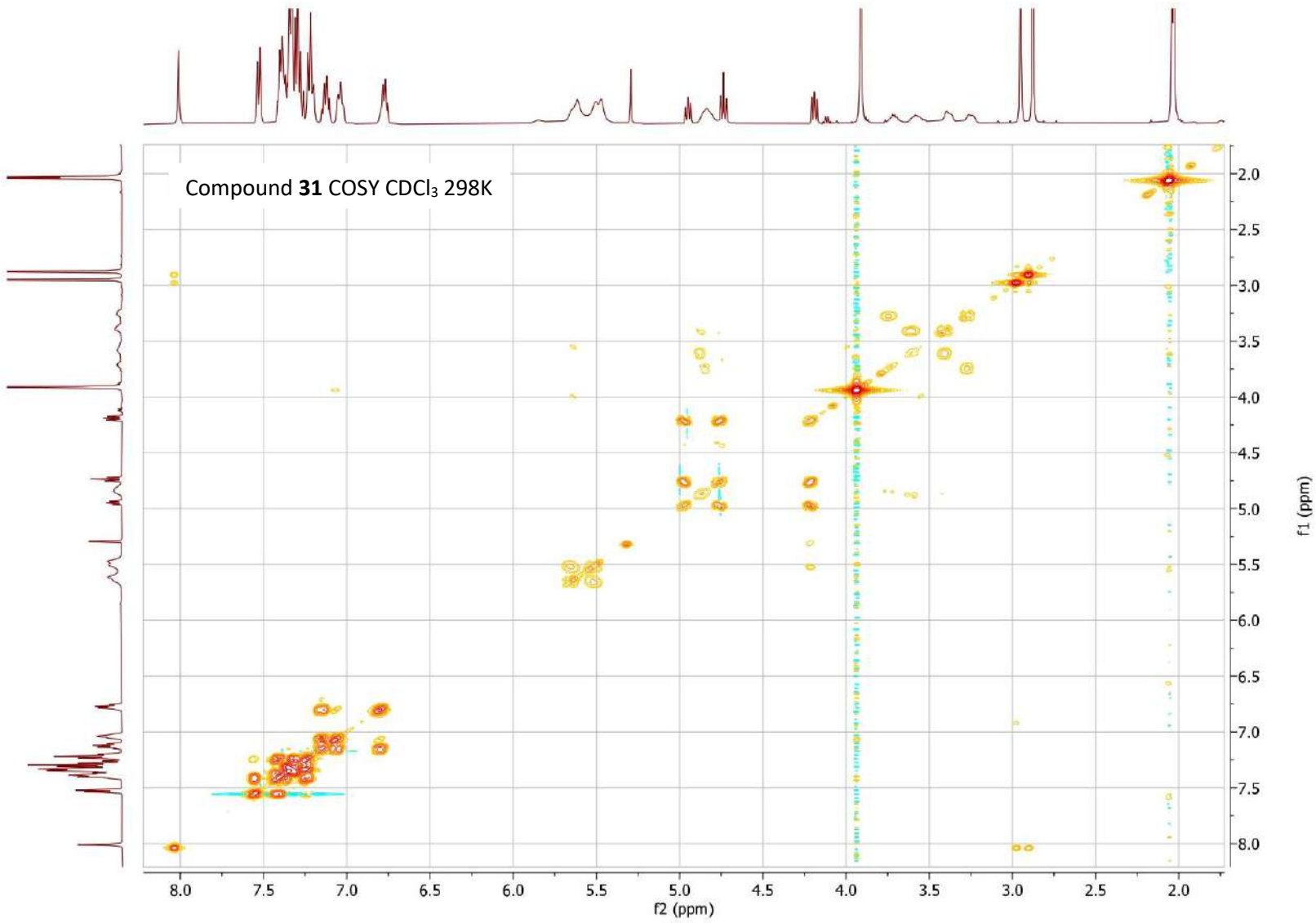


Figure S56. COSY of compound **31**

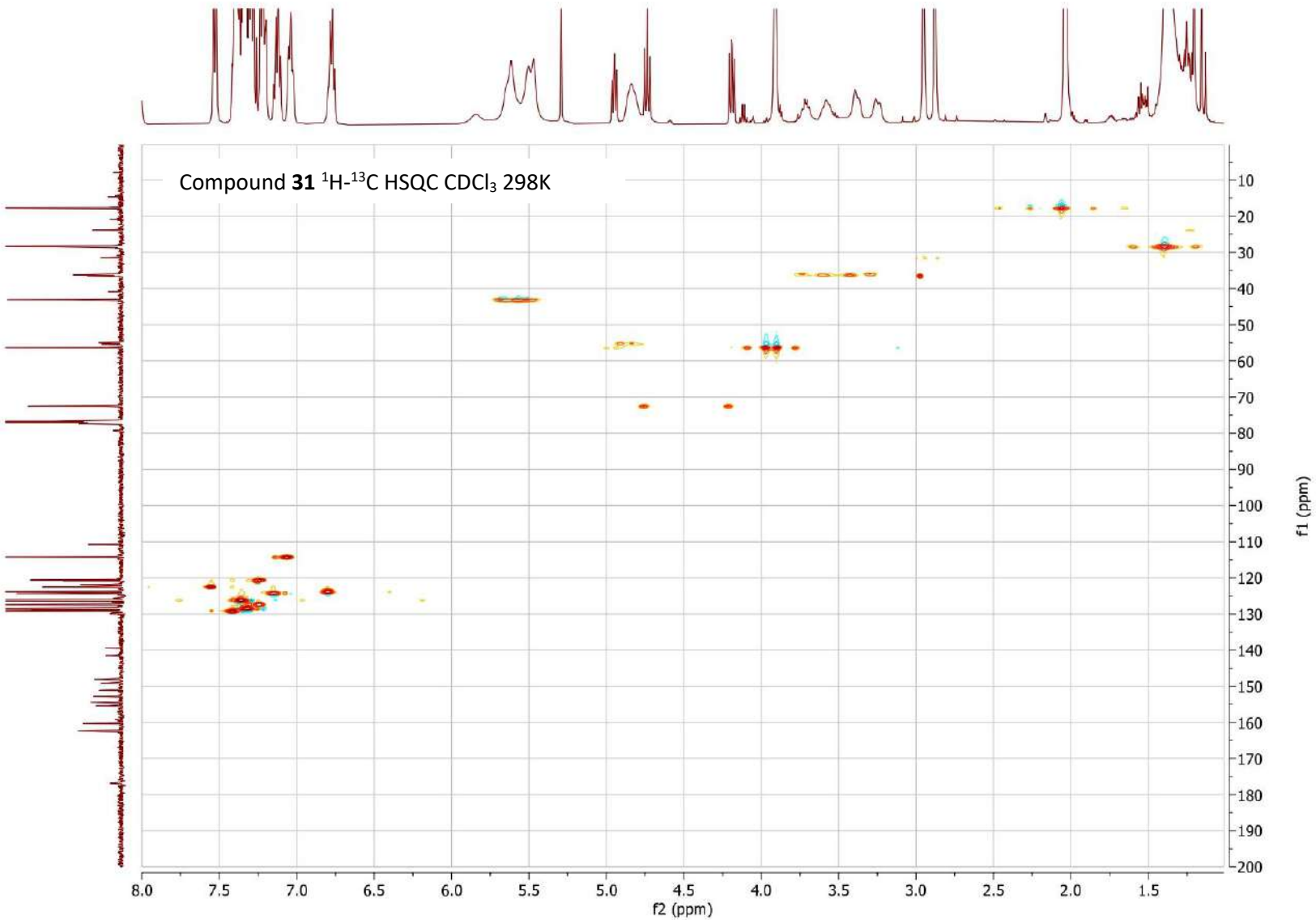


Figure S57. ^{1}H-^{13}C HSQC of compound **31**

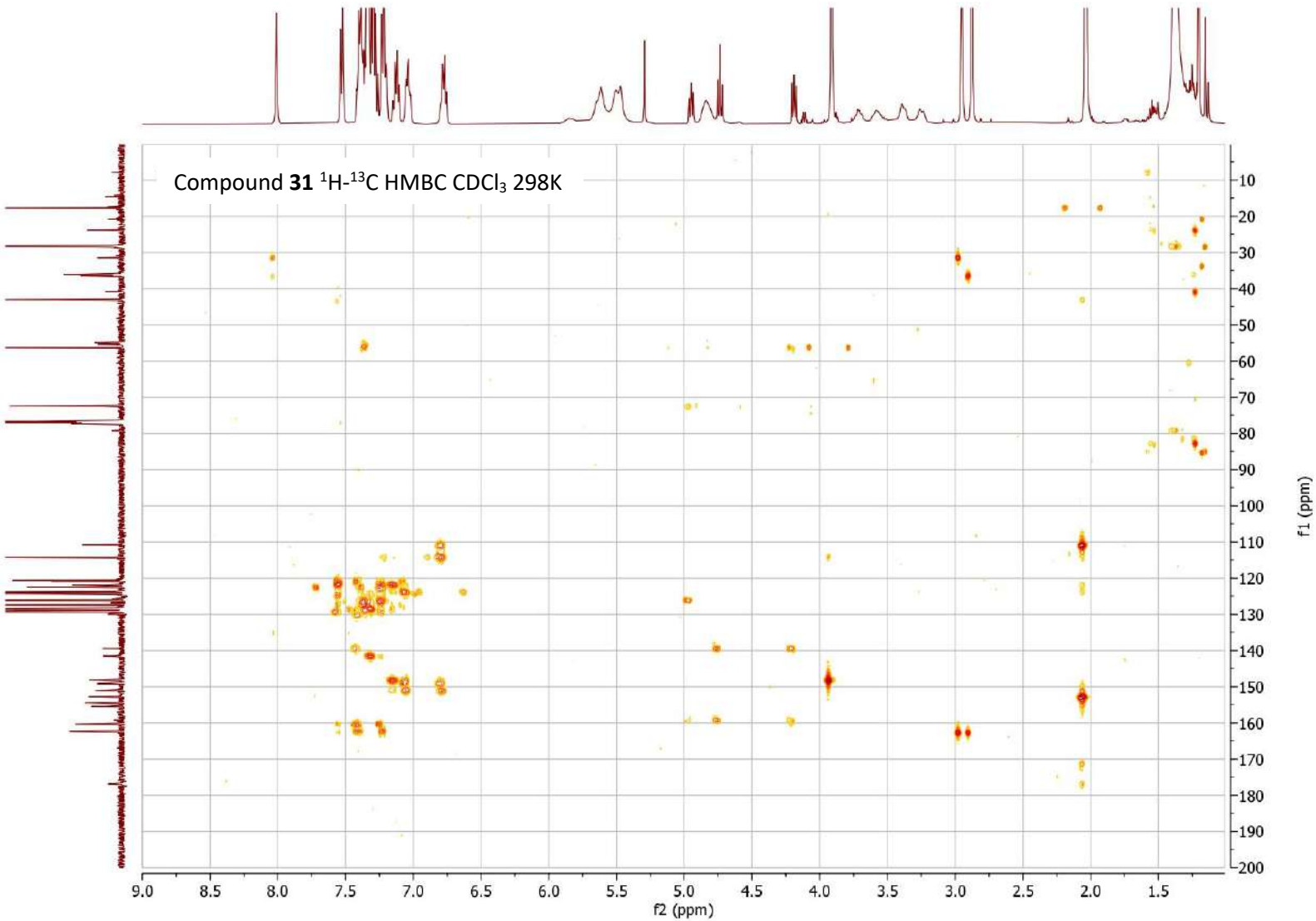


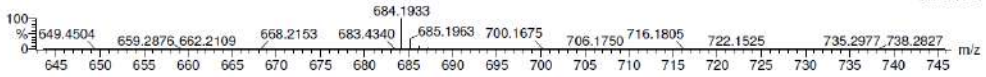
Figure S58. ^{1}H-^{13}C HMBC of compound **31**

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -5.0, max = 300.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

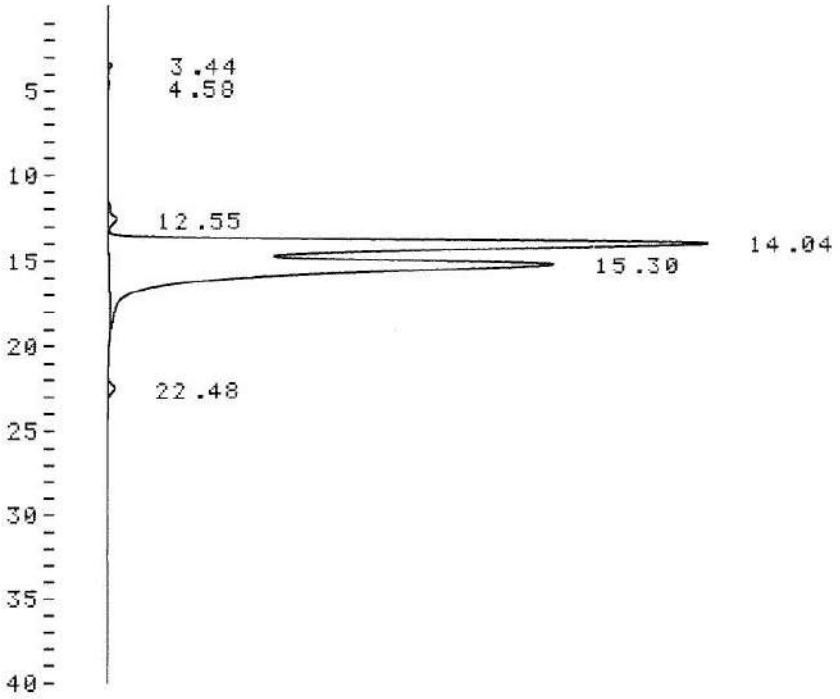
Monoisotopic Mass, Even Electron Ions
12 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 33-33 H: 31-33 N: 3-3 O: 4-4 Na: 0-4 S: 1-1 K: 0-2 F: 5-5

INT5Z 41 (0.829) AM2 (Ar,40000.0,0.00,0.00); Cm (30:50) 1: TOF MS ES+ 9.09e+006



Minimum:				-5.0				
Maximum:		5.0	5.0	300.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
684.1933	684.1931	0.2	0.3	16.5	1281.5	n/a	n/a	C33 H32 N3 O4 Na S F5

Figure S59. HRMS analysis of compound **31**



D-2500

METHOD: TAG: 5 CH: 1

FILE: 0 CALC-METHOD: AREA% TABLE: 0 CONC: AREA

NO.	RT	AREA	CONC	BC
1	3.44	1260	0.083	BB
2	4.58	924	0.061	BB
3	12.55	10798	0.712	BV
4	14.04	718177	47.332	VV
5	15.30	778529	51.310	VB
6	22.48	7619	0.502	BB
TOTAL		1517307	100.000	

PEAK REJ : 0

Figure S60. Chiral HPLC analysis of compound **31**

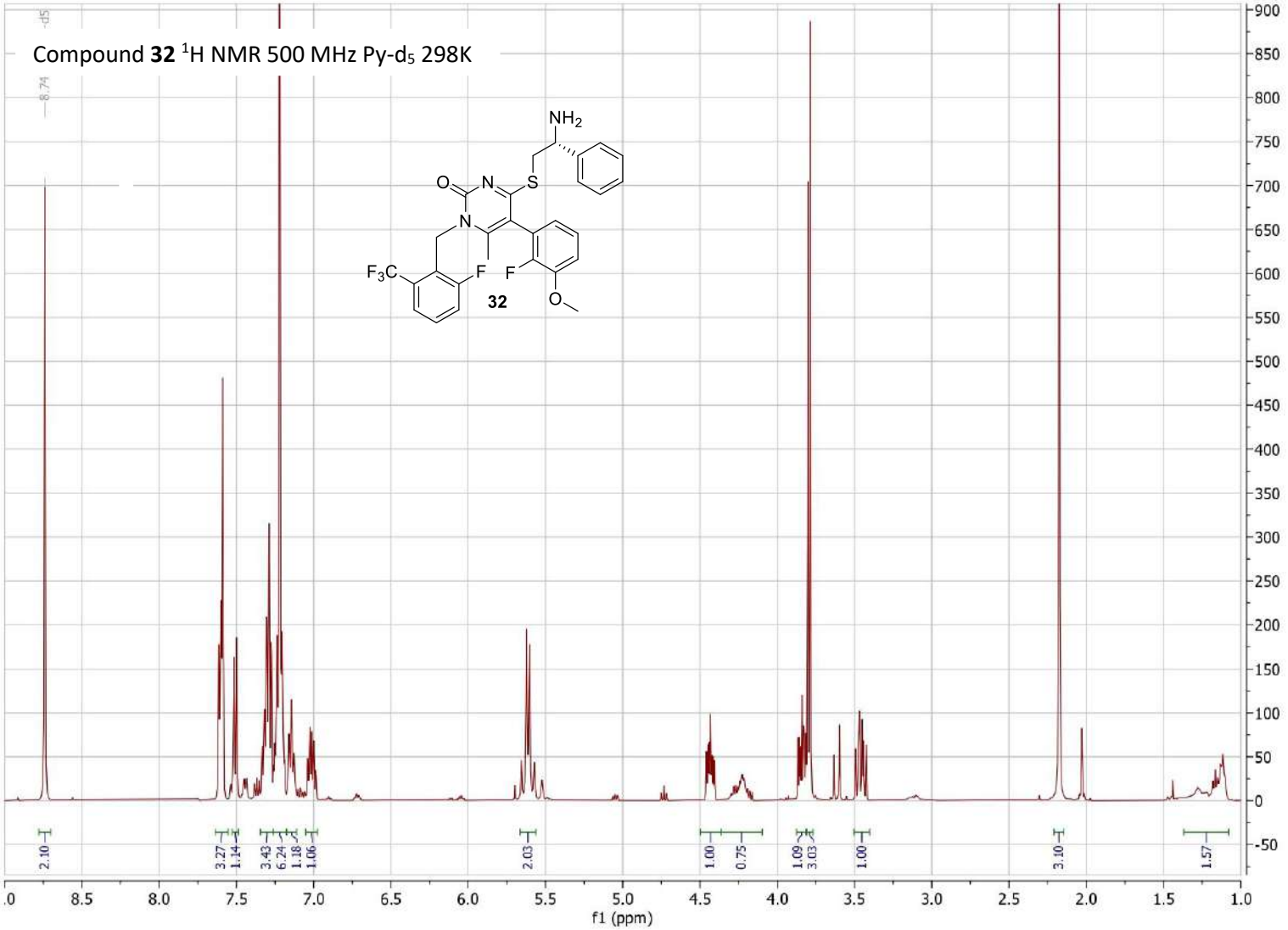


Figure S61. ^{1}H NMR of compound **32**

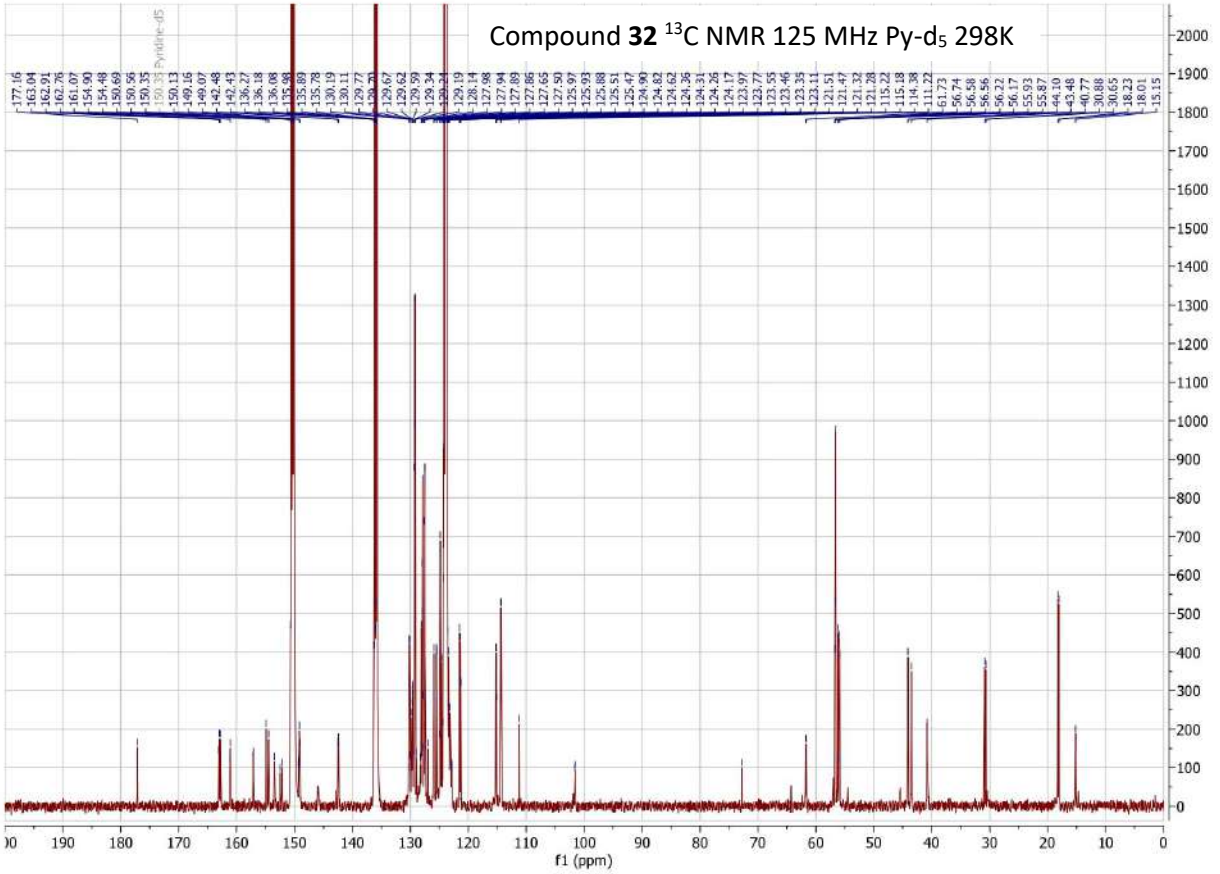


Figure S62. ^{13}C NMR of compound **32**

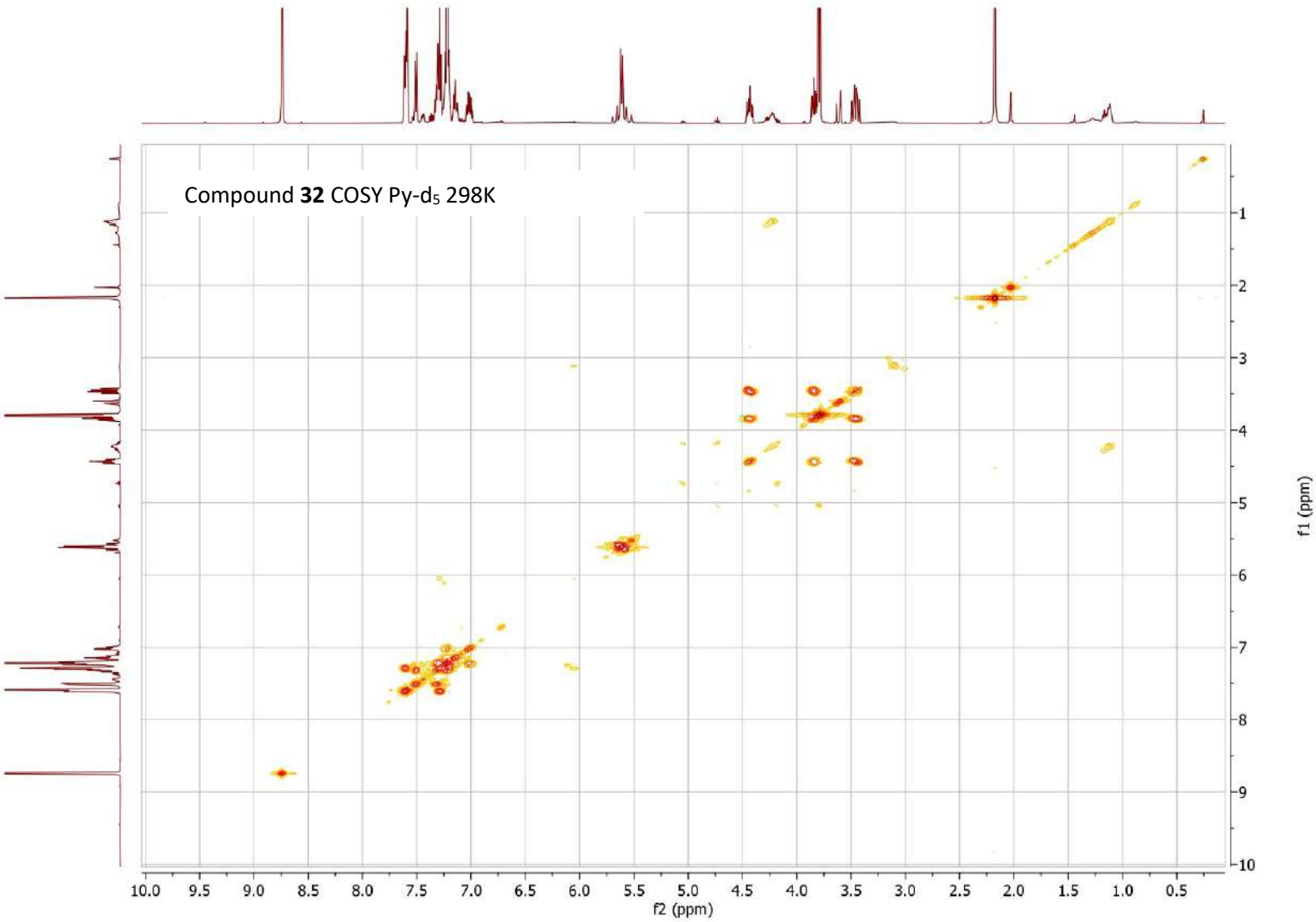


Figure S63. COSY of compound **32**

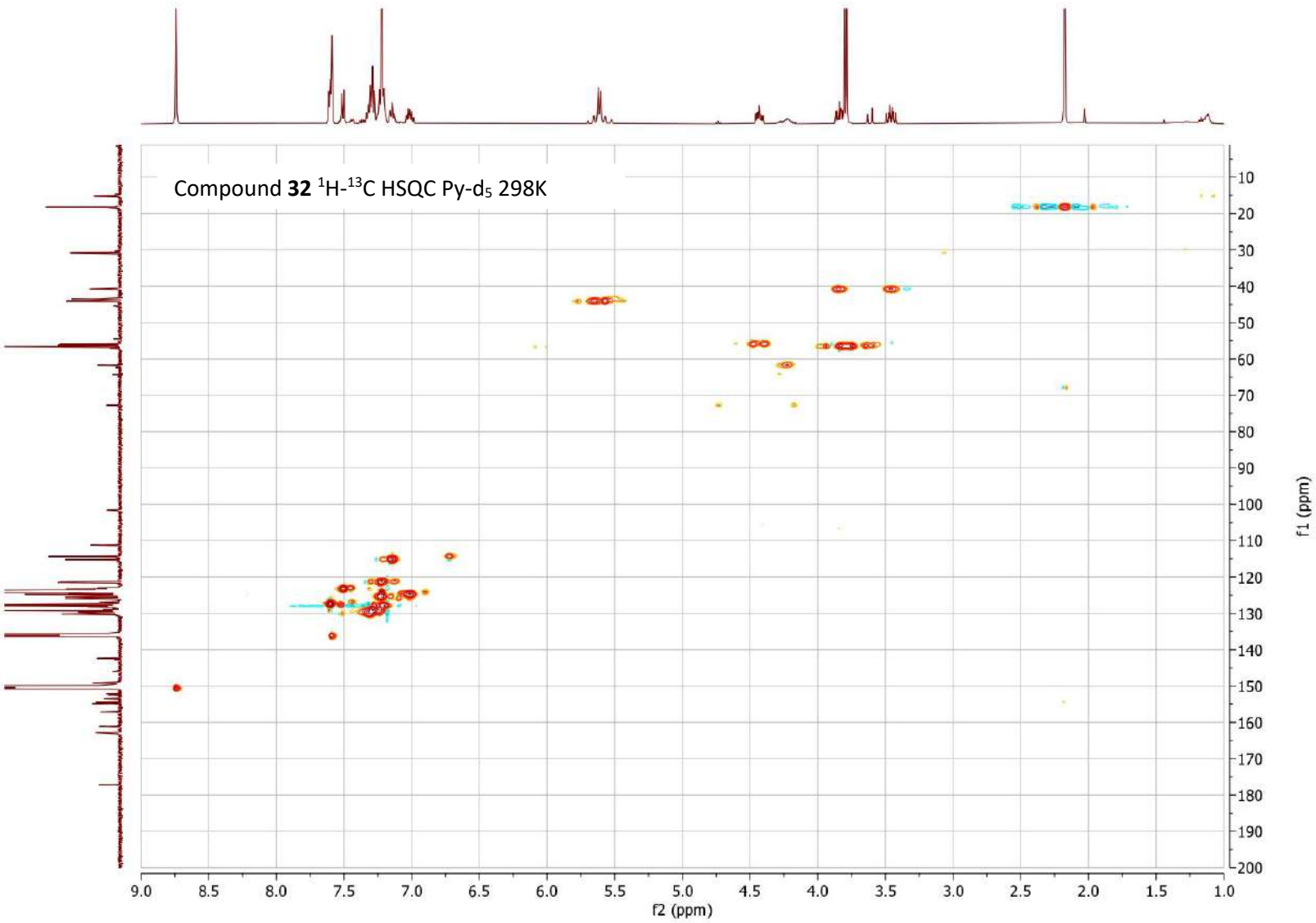


Figure S64. ^{1}H-^{13}C HSQC of compound **32**

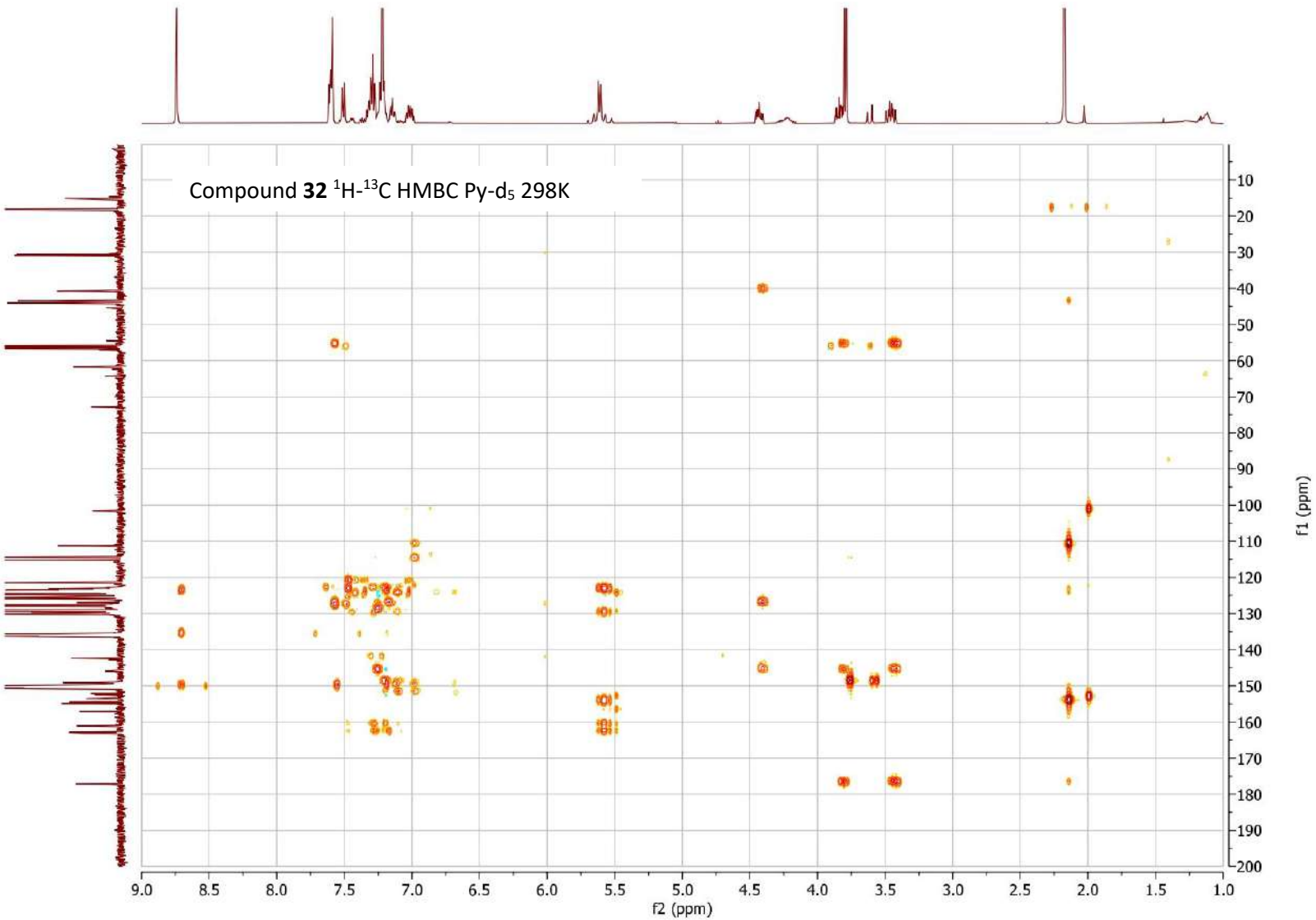


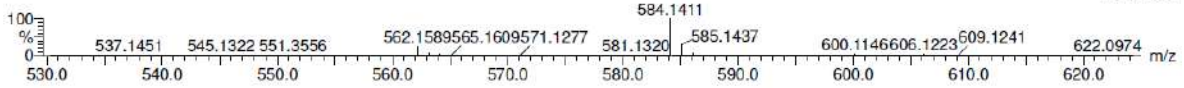
Figure S65. ^{1}H-^{13}C HMBC of compound **32**

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -5.0, max = 300.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
12 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 28-28 H: 23-25 N: 3-3 O: 2-2 Na: 0-4 S: 1-1 K: 0-2 F: 5-5

INT5Zdep 49 (0.984) AM2 (Ar,40000.0,0.00,0.00); Cm (30:50) 1: TOF MS ES+ 1.44e+007



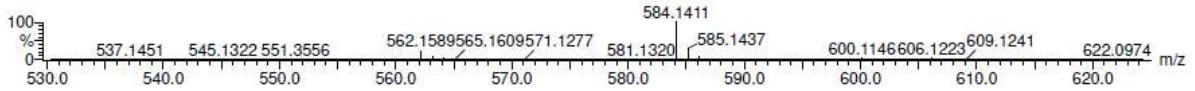
Minimum:				-5.0				
Maximum:		5.0	5.0	300.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
584.1411	584.1407	0.4	0.7	15.5	1472.7	n/a	n/a	C28 H24 N3 O2 Na S F5

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -5.0, max = 300.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
14 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 28-28 H: 23-25 N: 3-3 O: 2-2 Na: 0-4 S: 1-1 K: 0-2 F: 5-5

INT5Zdep 49 (0.984) AM2 (Ar,40000.0,0.00,0.00); Cm (30:50) 1: TOF MS ES+ 1.44e+007



Minimum:				-5.0				
Maximum:		5.0	5.0	300.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
562.1589	562.1588	0.1	0.2	15.5	1553.9	n/a	n/a	C28 H25 N3 O2 S F5

Figure S66. HRMS analysis of compound **32**

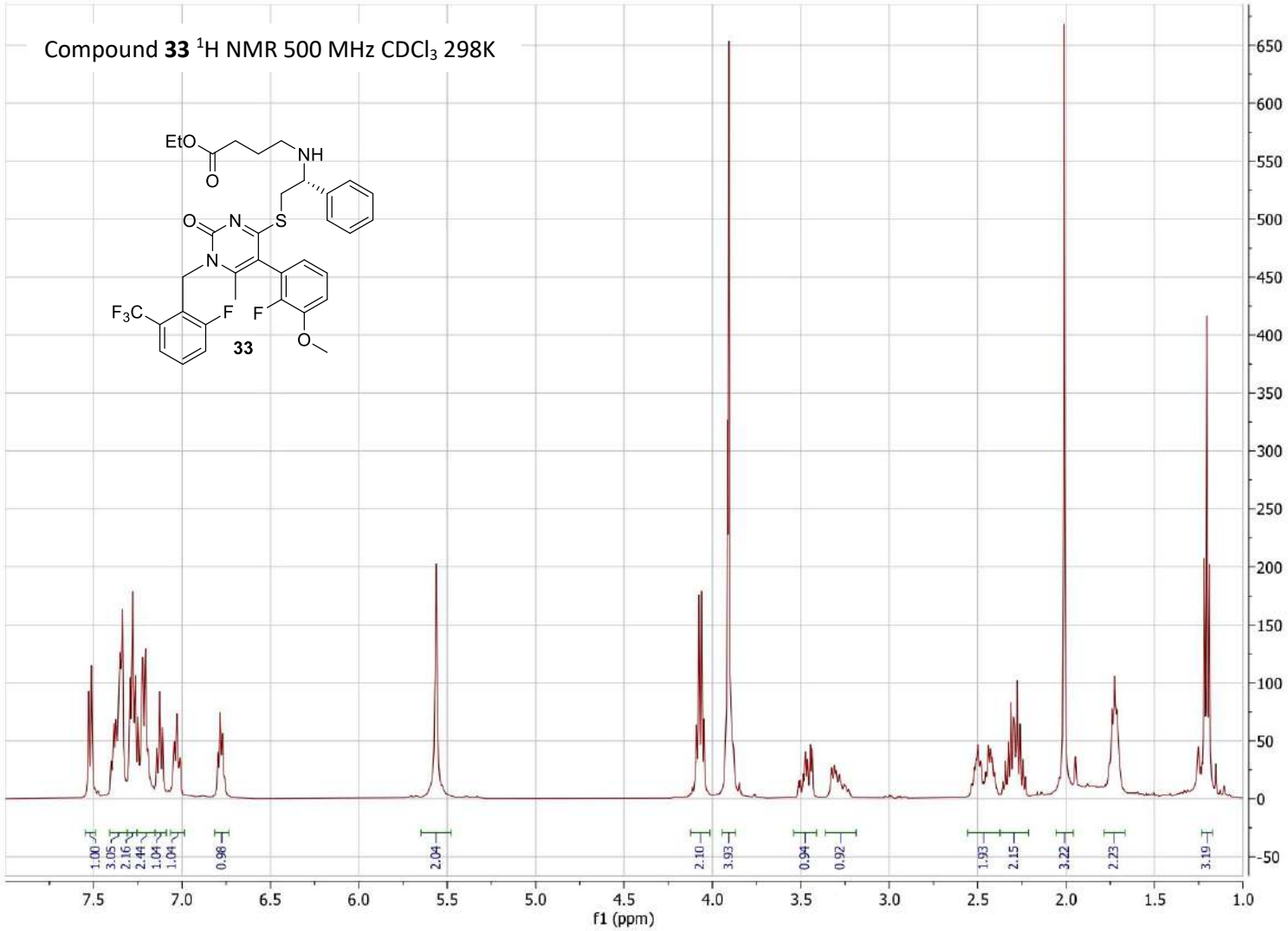


Figure S67. ^{1}H NMR of compound **33**

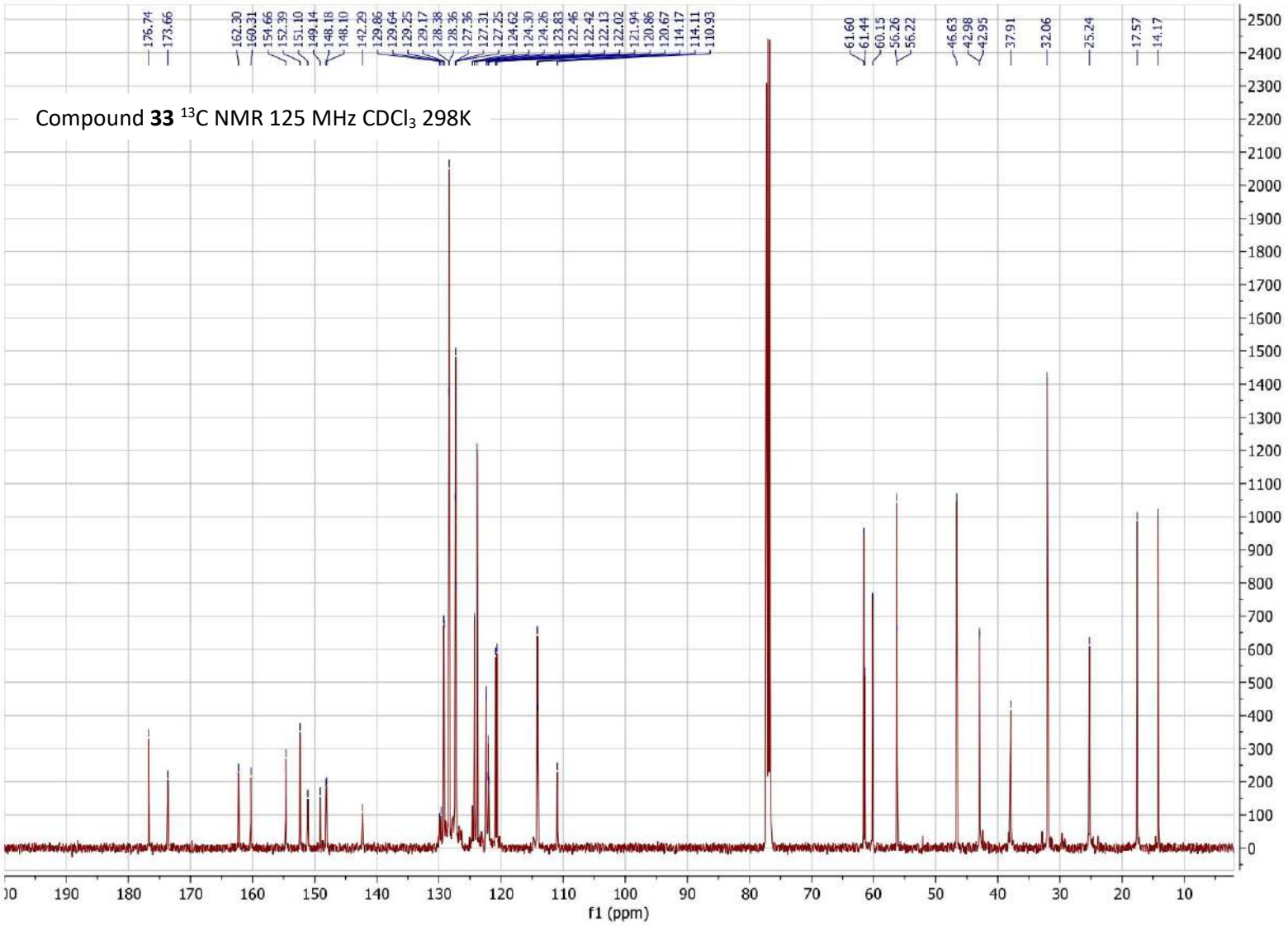


Figure S68. ^{13}C NMR of compound **33**

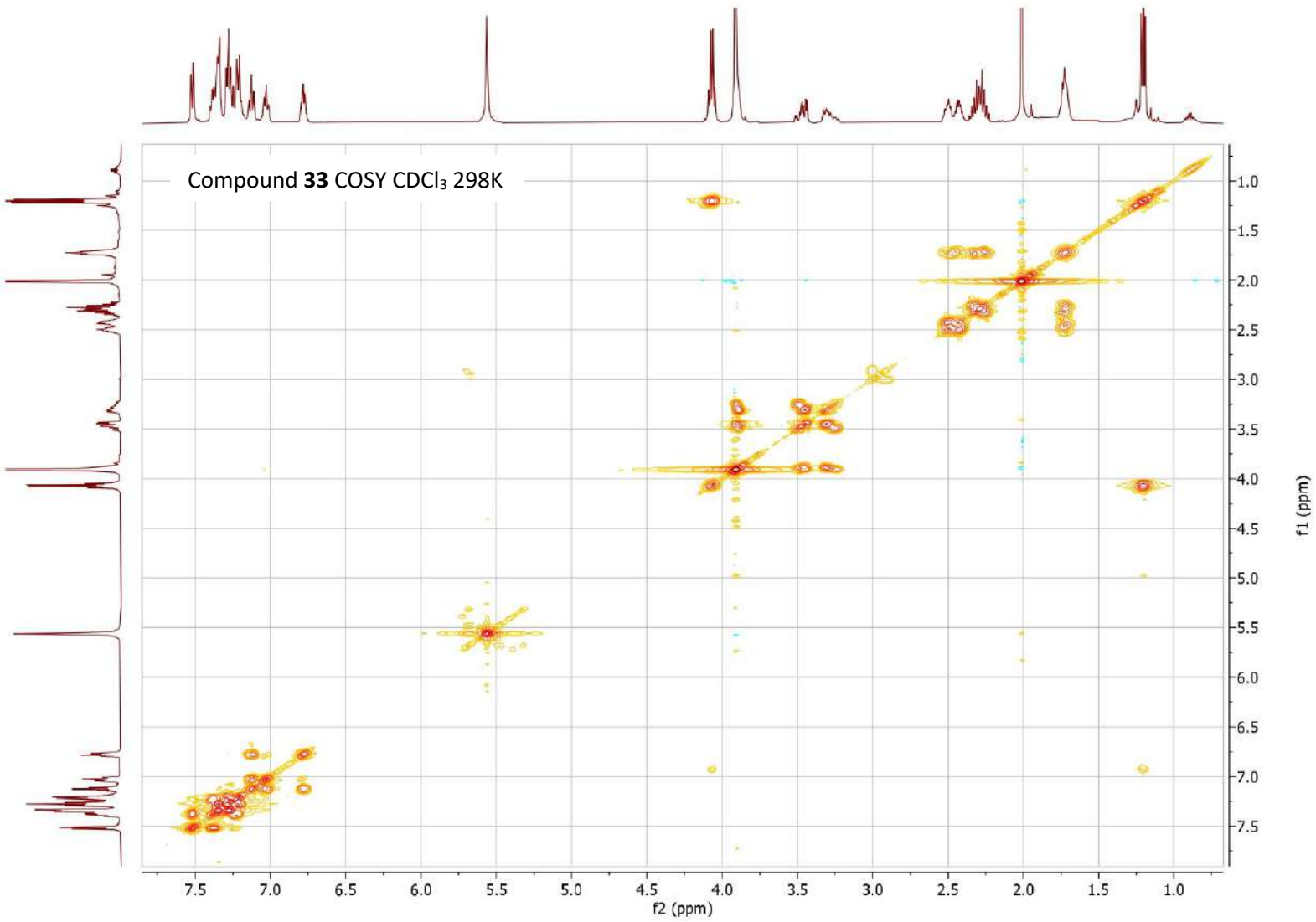


Figure S69. COSY of compound **33**

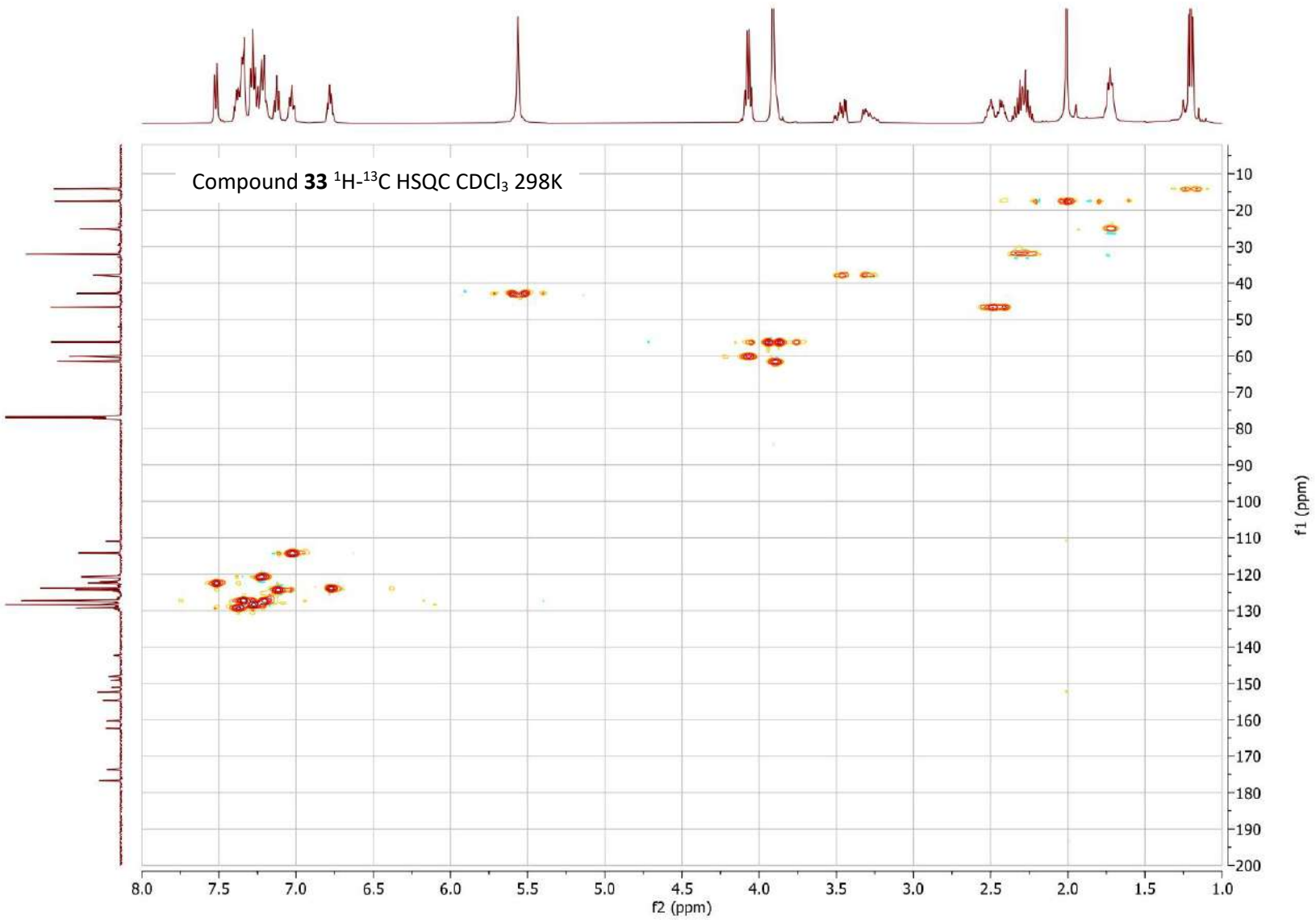


Figure S70. ^{1}H-^{13}C HSQC of compound **33**

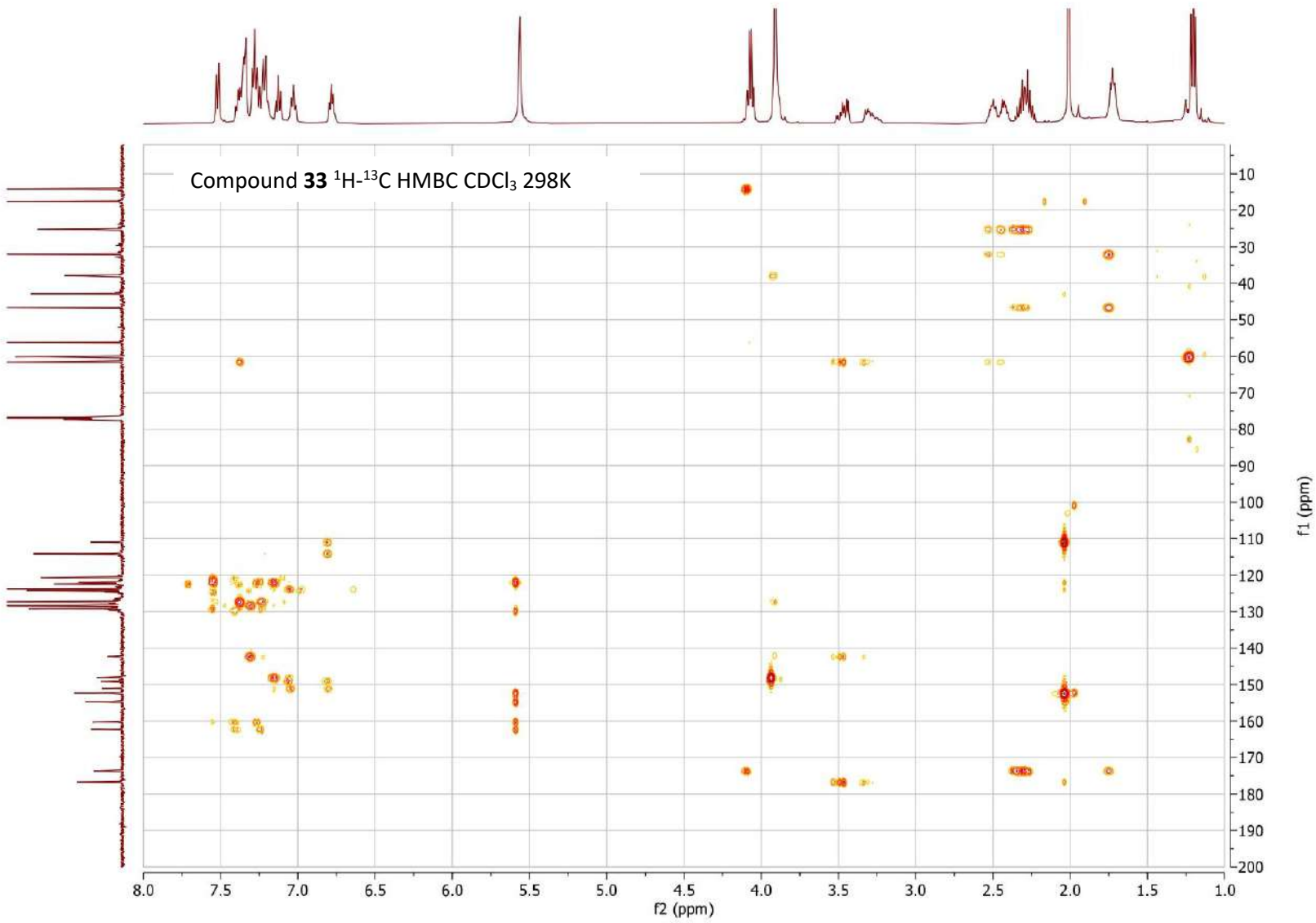


Figure S71. ^{1}H-^{13}C HMBC of compound **33**

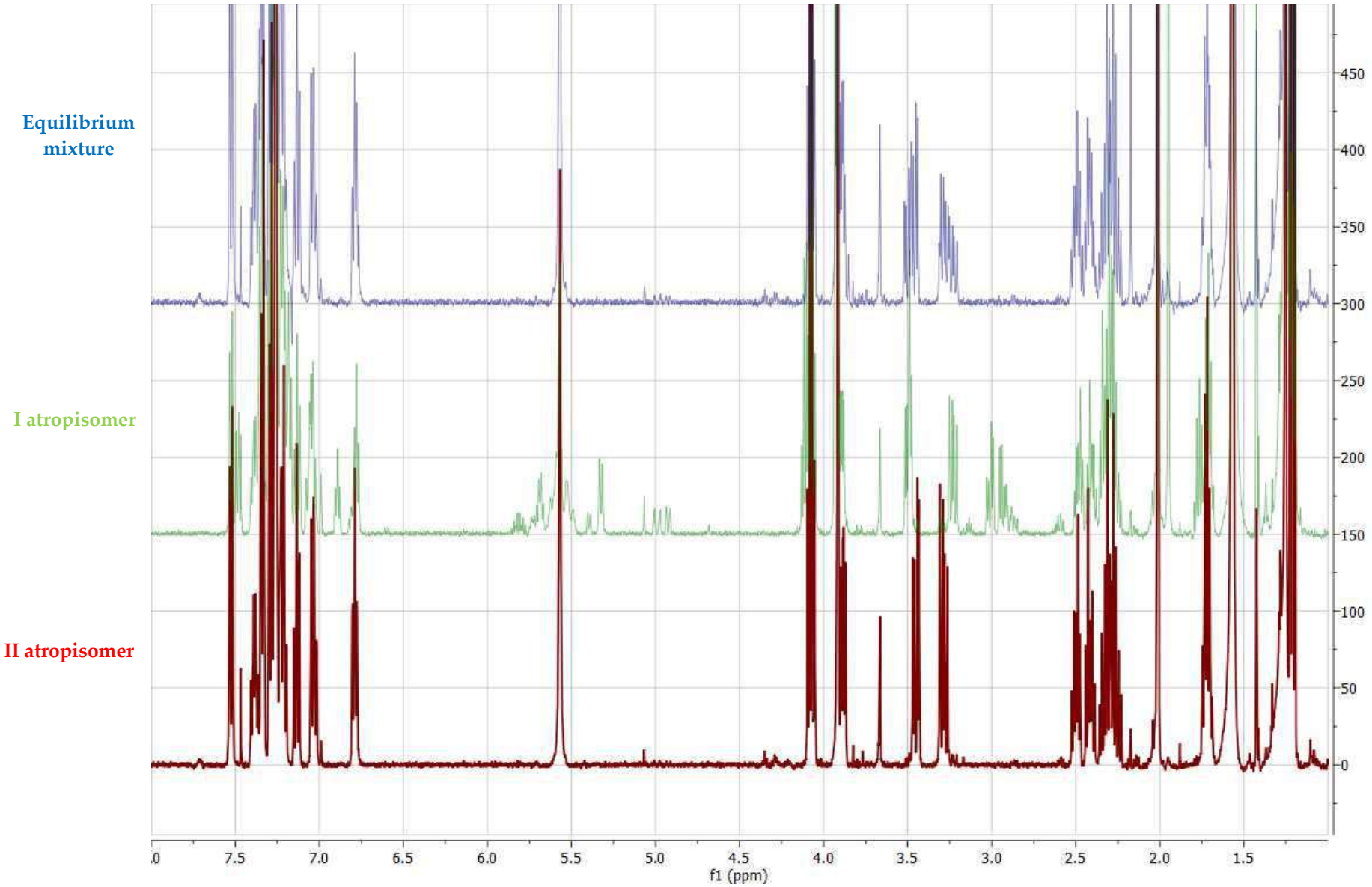


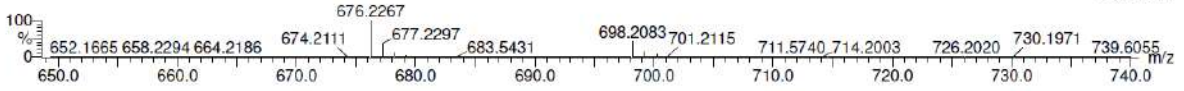
Figure S72. Superimposed spectra of I and II atropisomer of **33**, and equilibrium mixture

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -5.0, max = 300.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 7

Monoisotopic Mass, Even Electron Ions
4 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 34-34 H: 34-35 N: 3-3 O: 4-4 Na: 0-4 S: 1-1 F: 5-5

INT6ZIII 49 (0.984) AM2 (Ar,40000.0,0.00,0.00); Cm (10:50) 1: TOF MS ES+ 2.52e+007



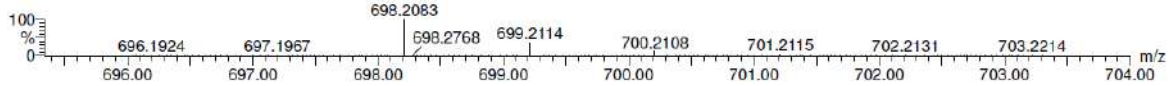
Minimum:				-5.0				
Maximum:		5.0	5.0	300.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
676.2267	676.2268	-0.1	-0.1	16.5	2248.4	n/a	n/a	C34 H35 N3 O4 S F5

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -5.0, max = 300.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 7

Monoisotopic Mass, Even Electron Ions
3 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 34-34 H: 34-35 N: 3-3 O: 4-4 Na: 0-4 S: 1-1 F: 5-5

INT6ZIII 49 (0.984) AM2 (Ar,40000.0,0.00,0.00); Cm (10:50) 1: TOF MS ES+ 1.02e+007



Minimum:				-5.0				
Maximum:		5.0	5.0	300.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
698.2083	698.2088	-0.5	-0.7	16.5	1635.3	n/a	n/a	C34 H34 N3 O4 Na S F5

Figure S73. HRMS analysis of compound **33**

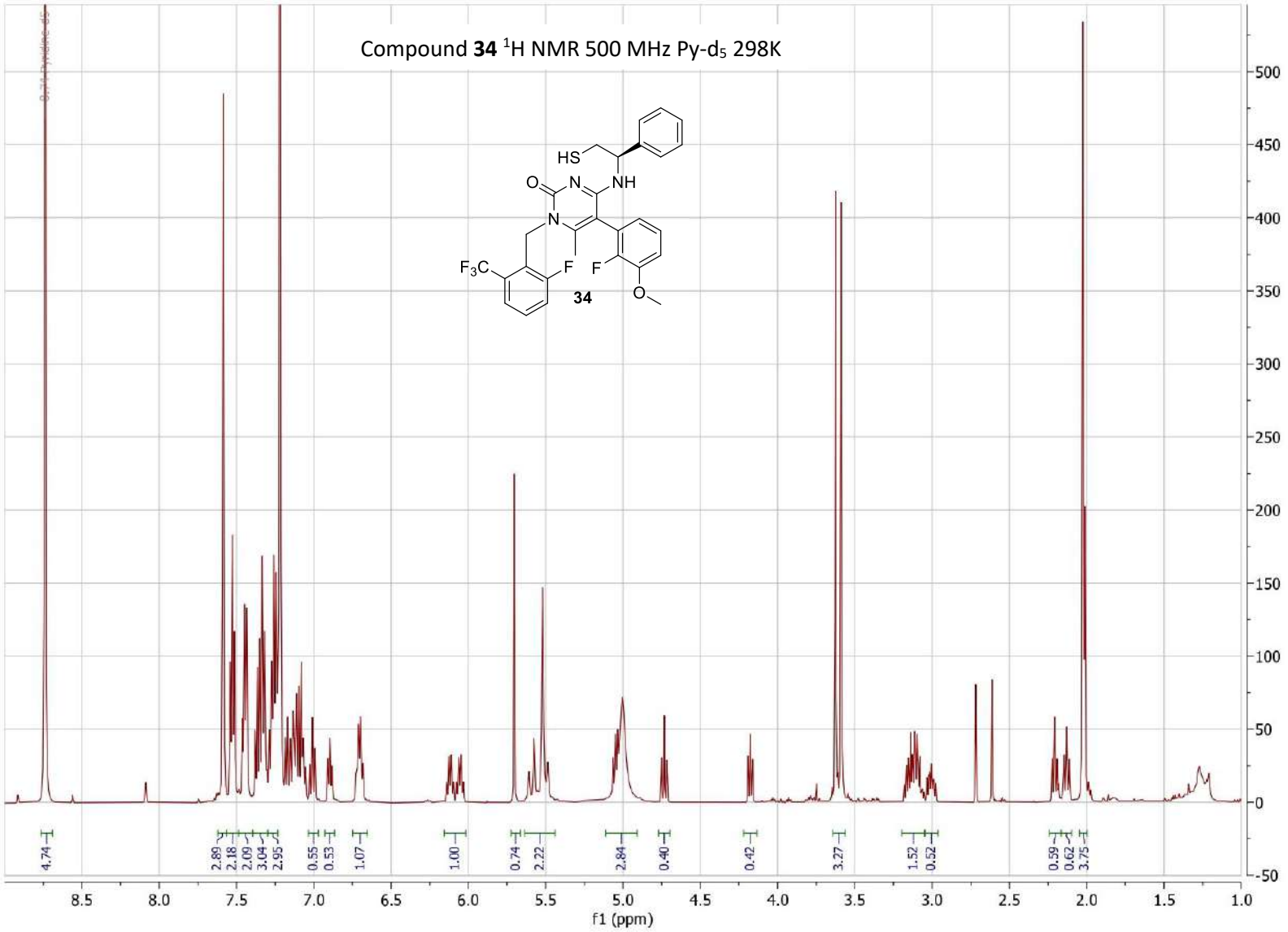


Figure S74. ^{1}H NMR of compound **34**

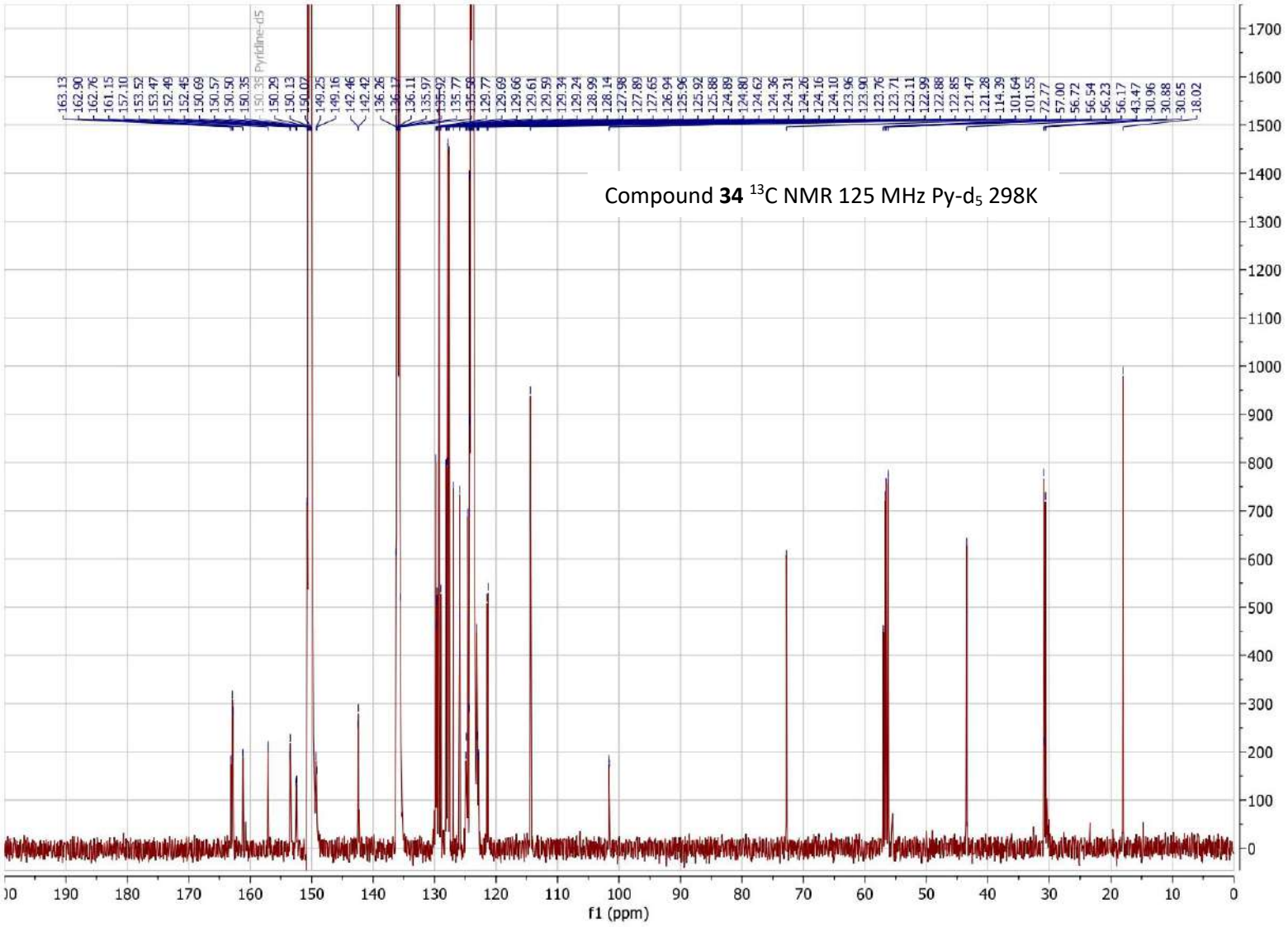


Figure S75. ^{13}C NMR of compound **34**

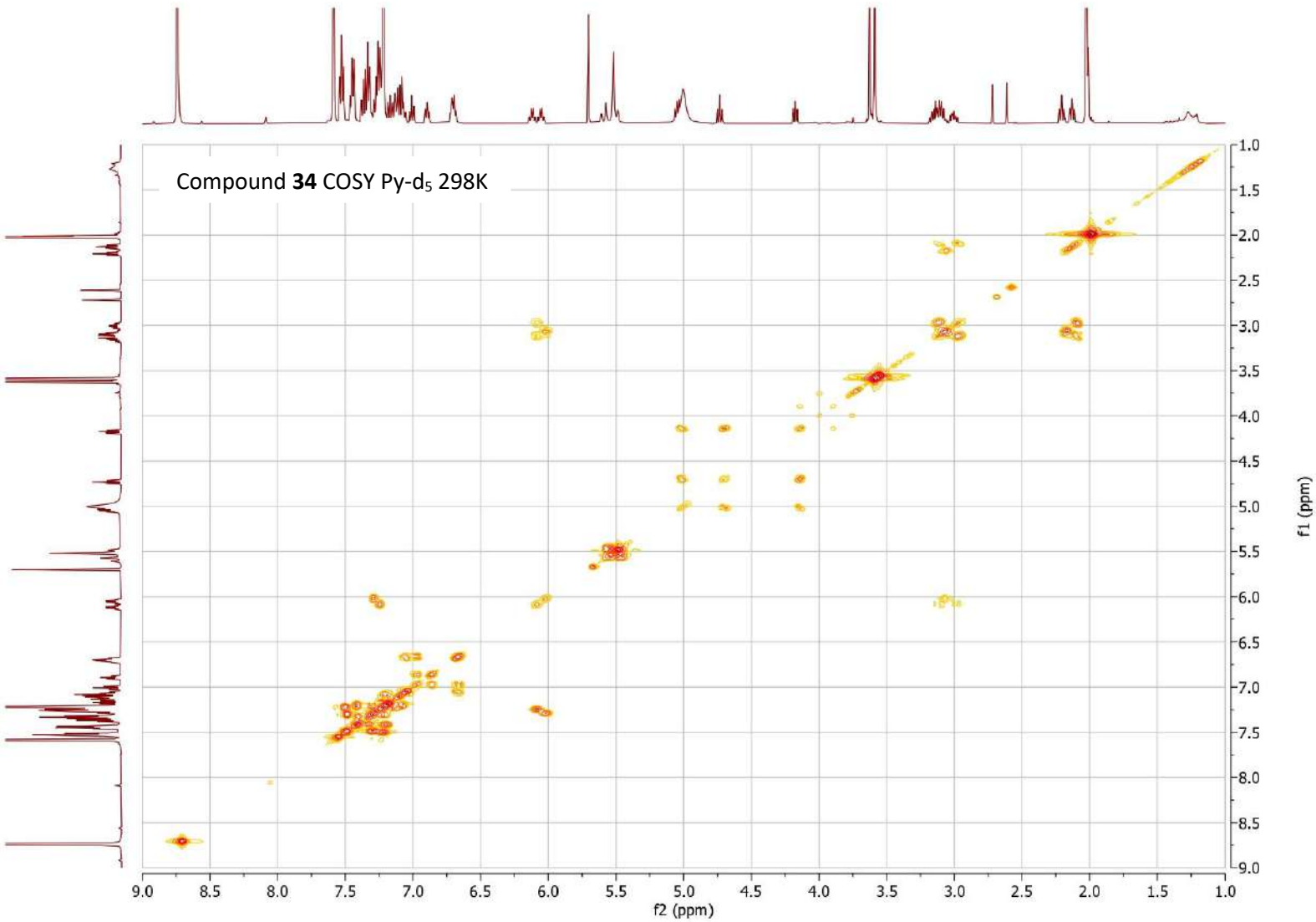


Figure S76. COSY of compound **34**

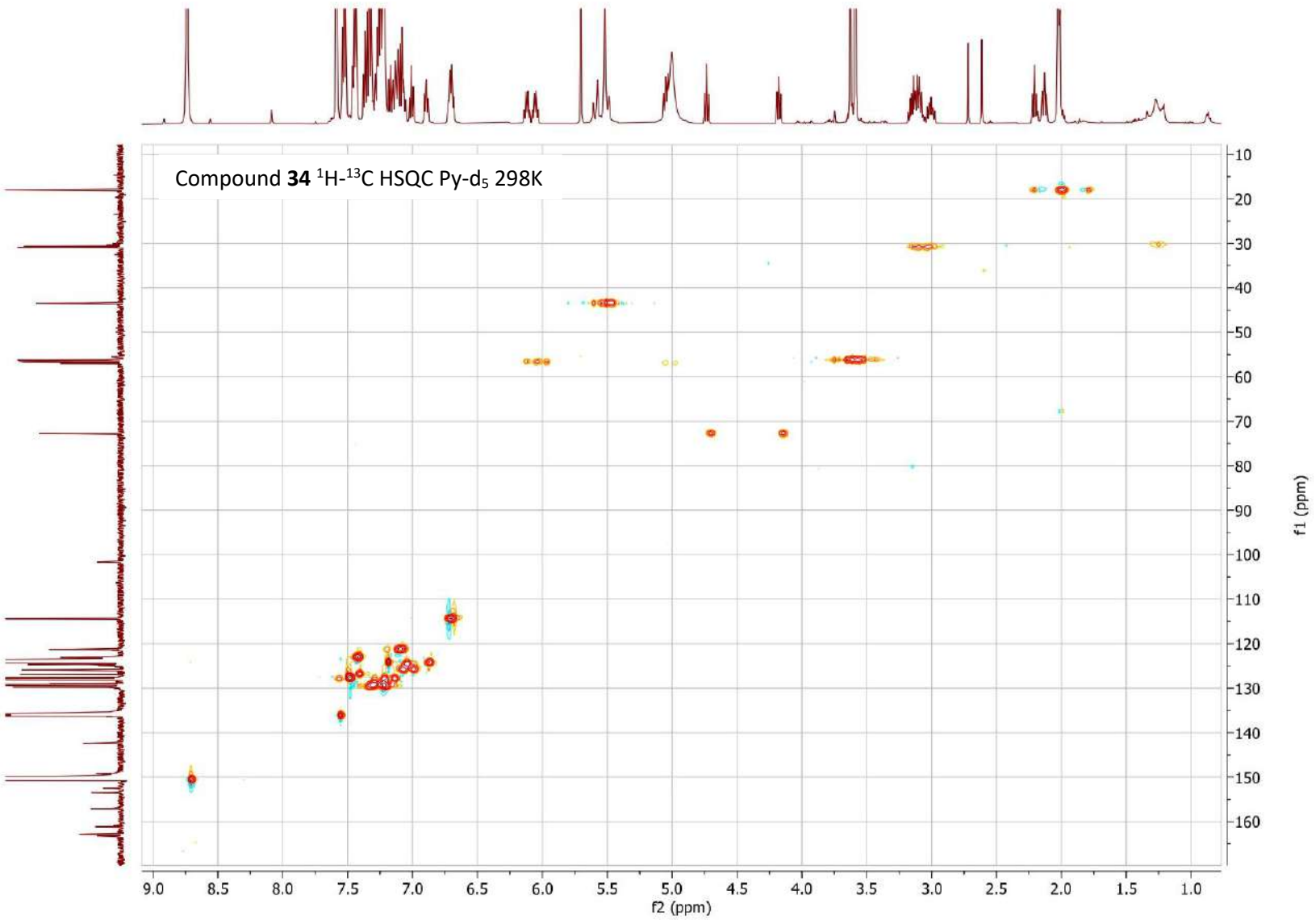


Figure S77. ^{1}H-^{13}C HSQC of compound **34**

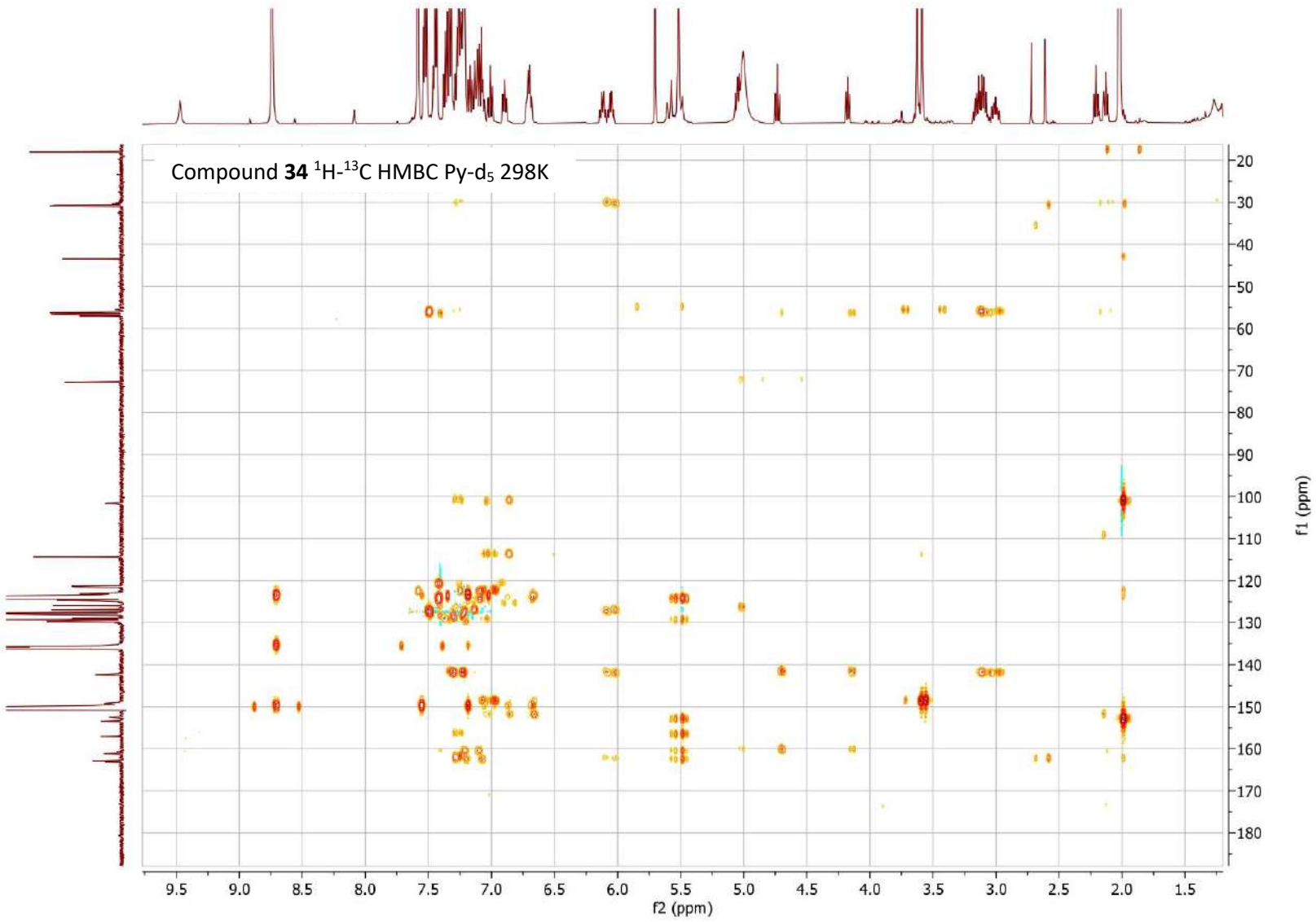


Figure S78. ^{1}H-^{13}C HMBC of compound **34**

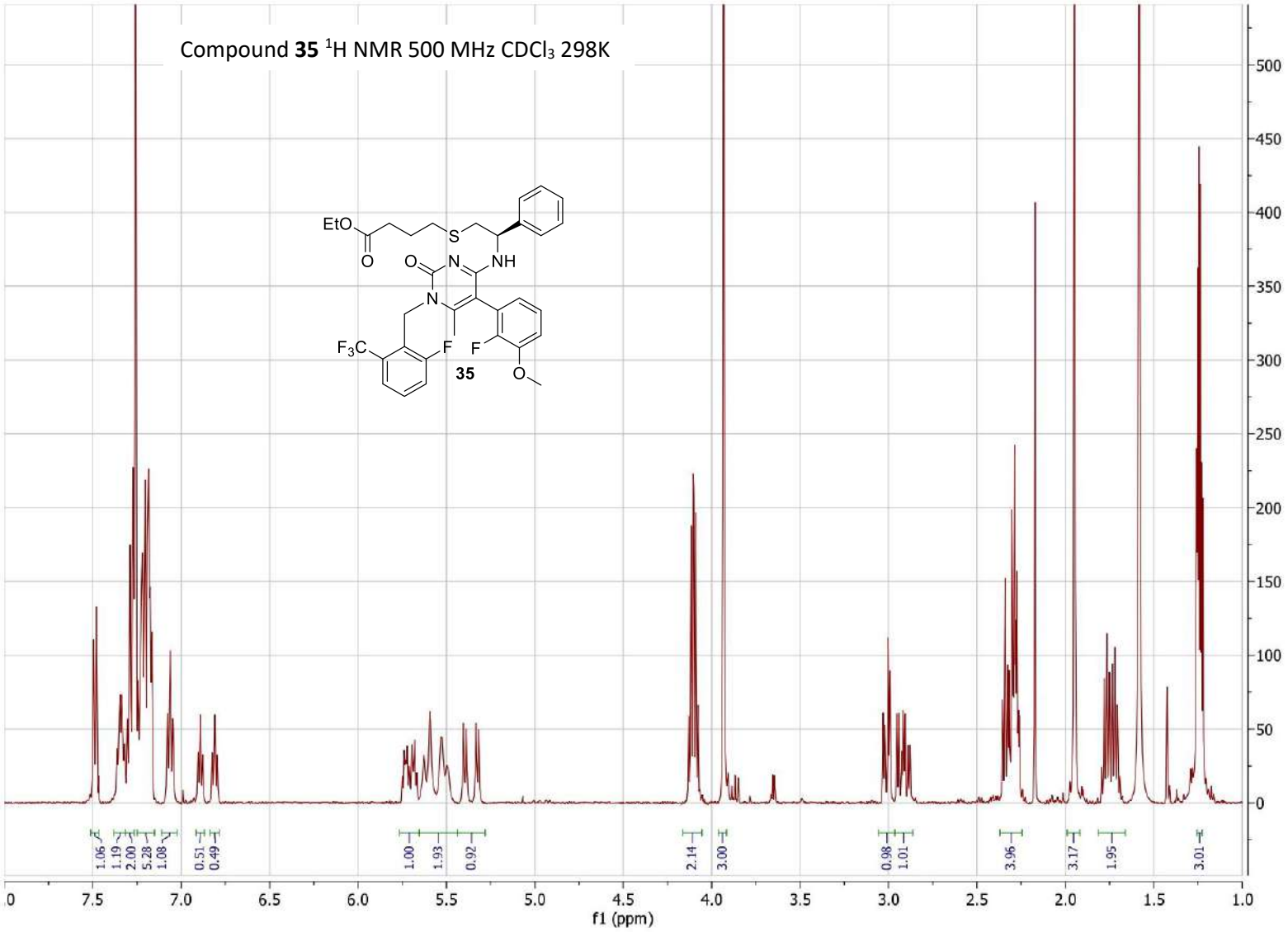


Figure S79. ^{1}H NMR of compound **35**

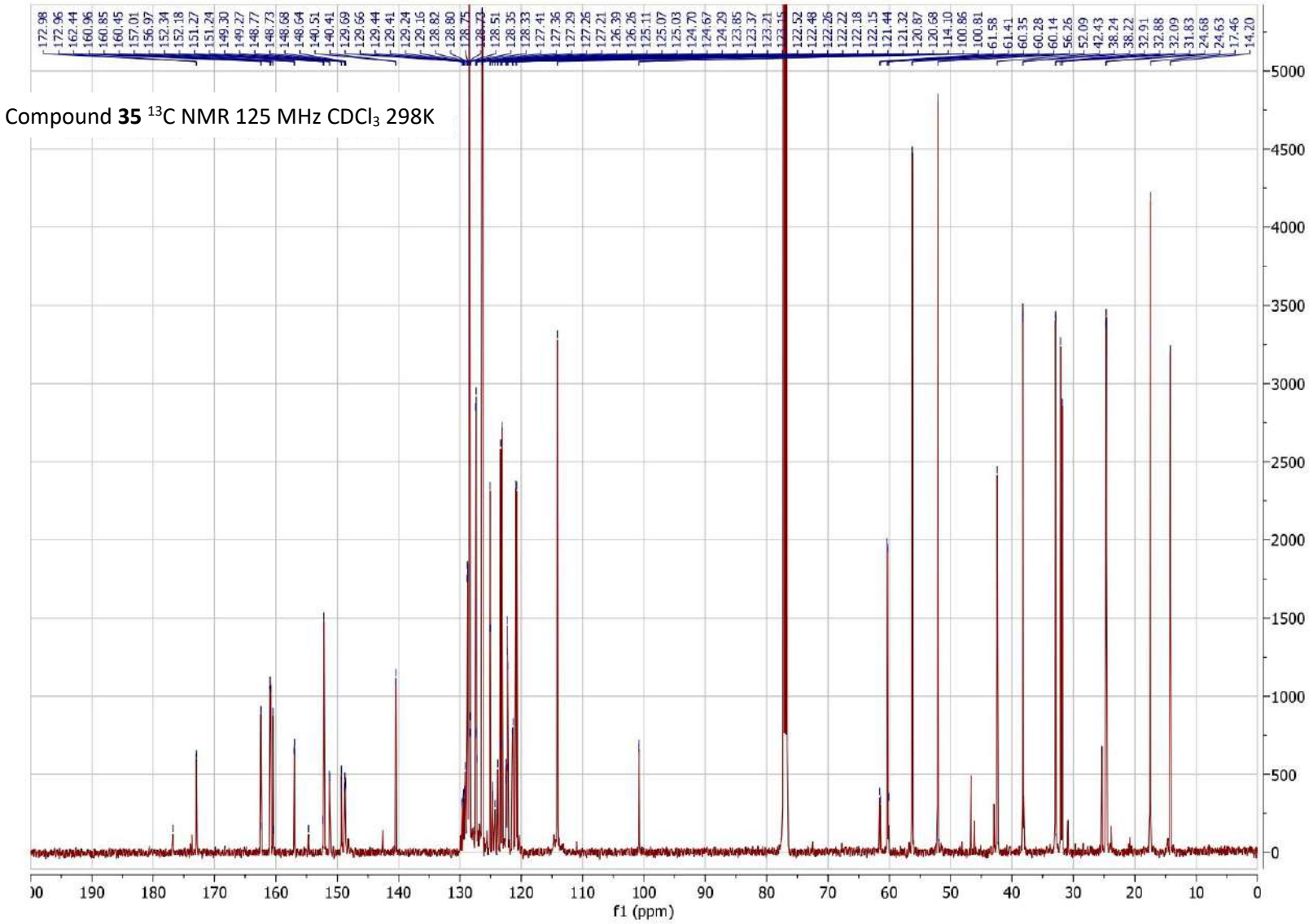


Figure S80. ^{13}C NMR of compound **35**

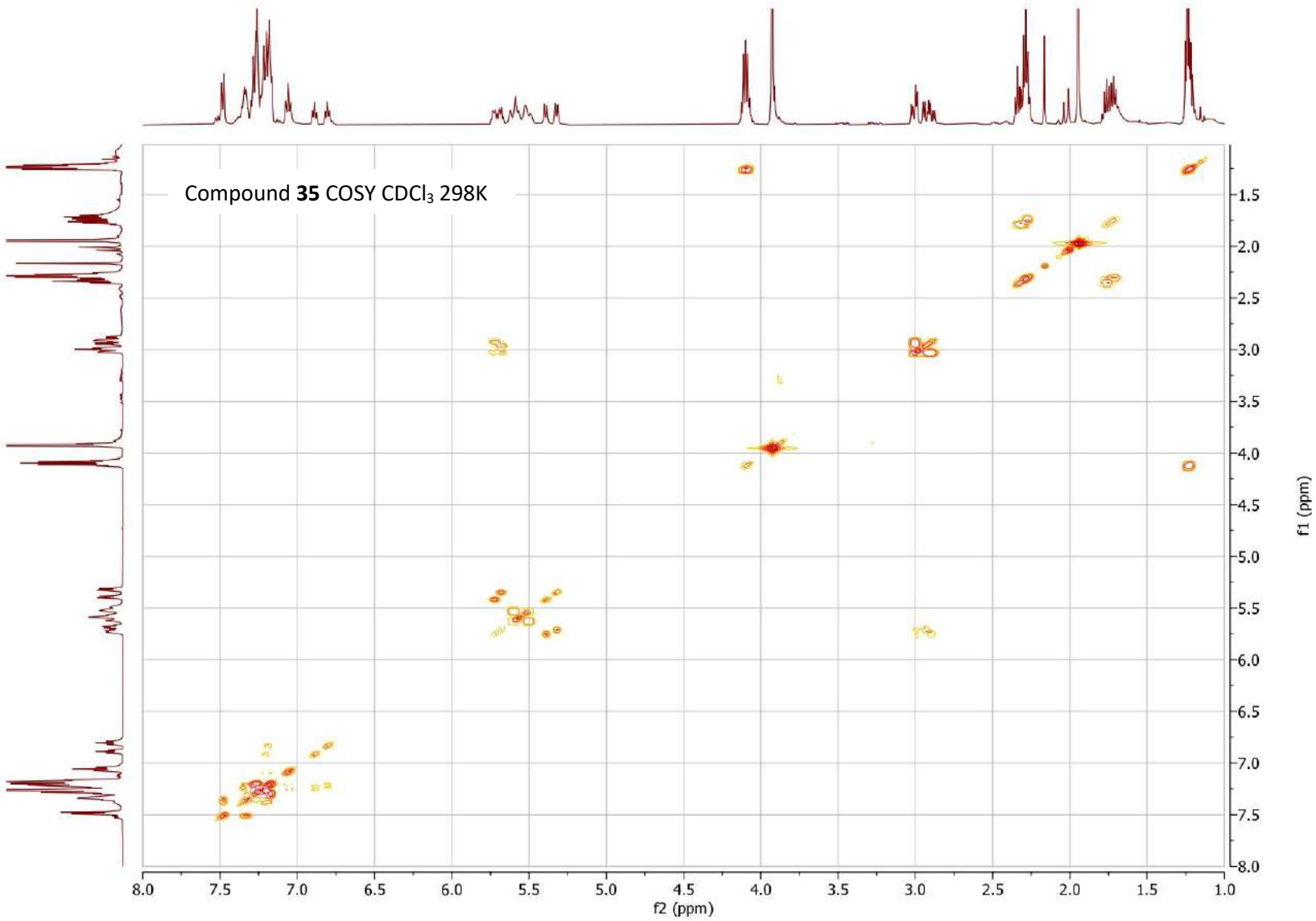


Figure S81. COSY of compound **35**

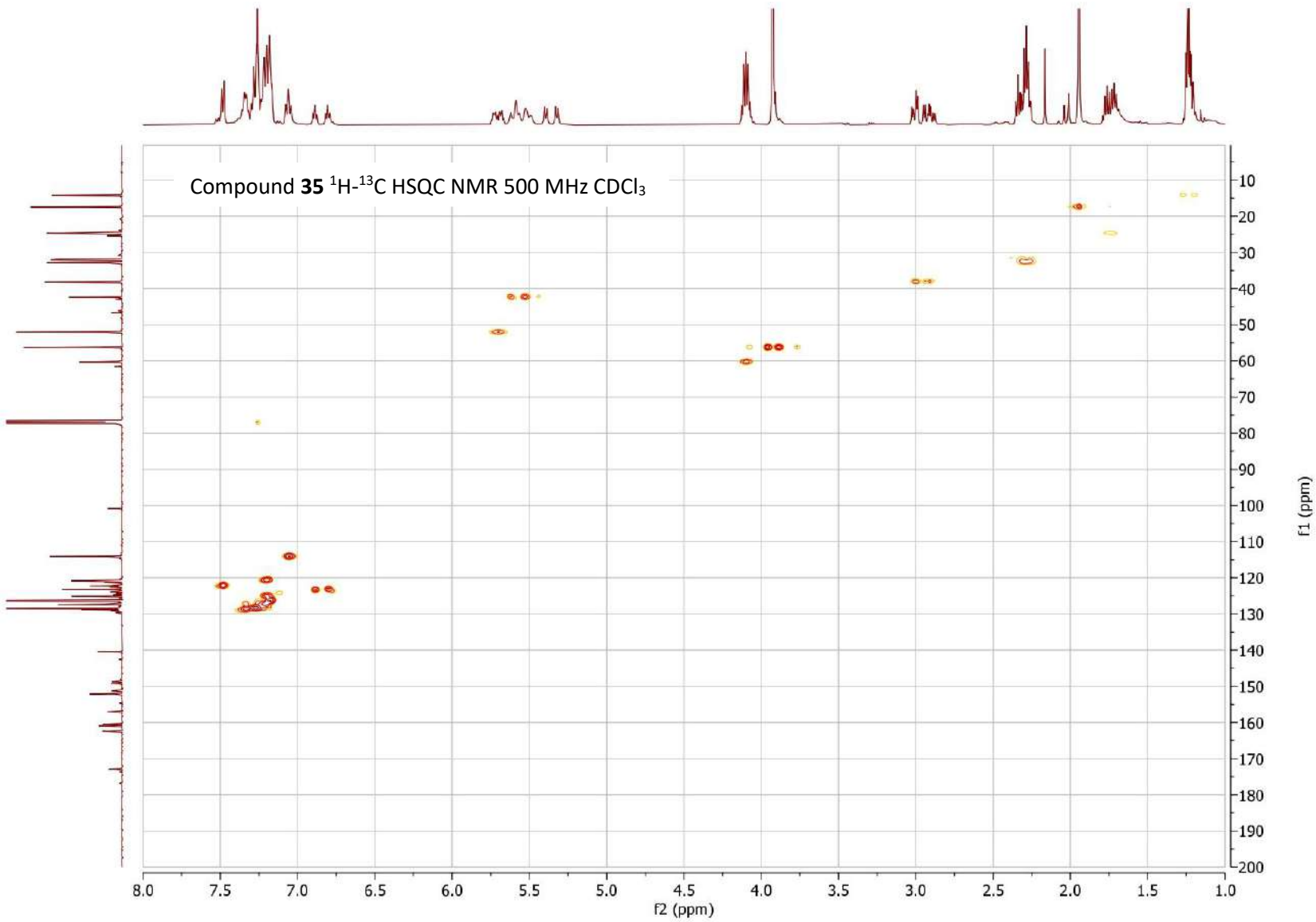


Figure S82. ^{1}H-^{13}C HSQC of compound **35**

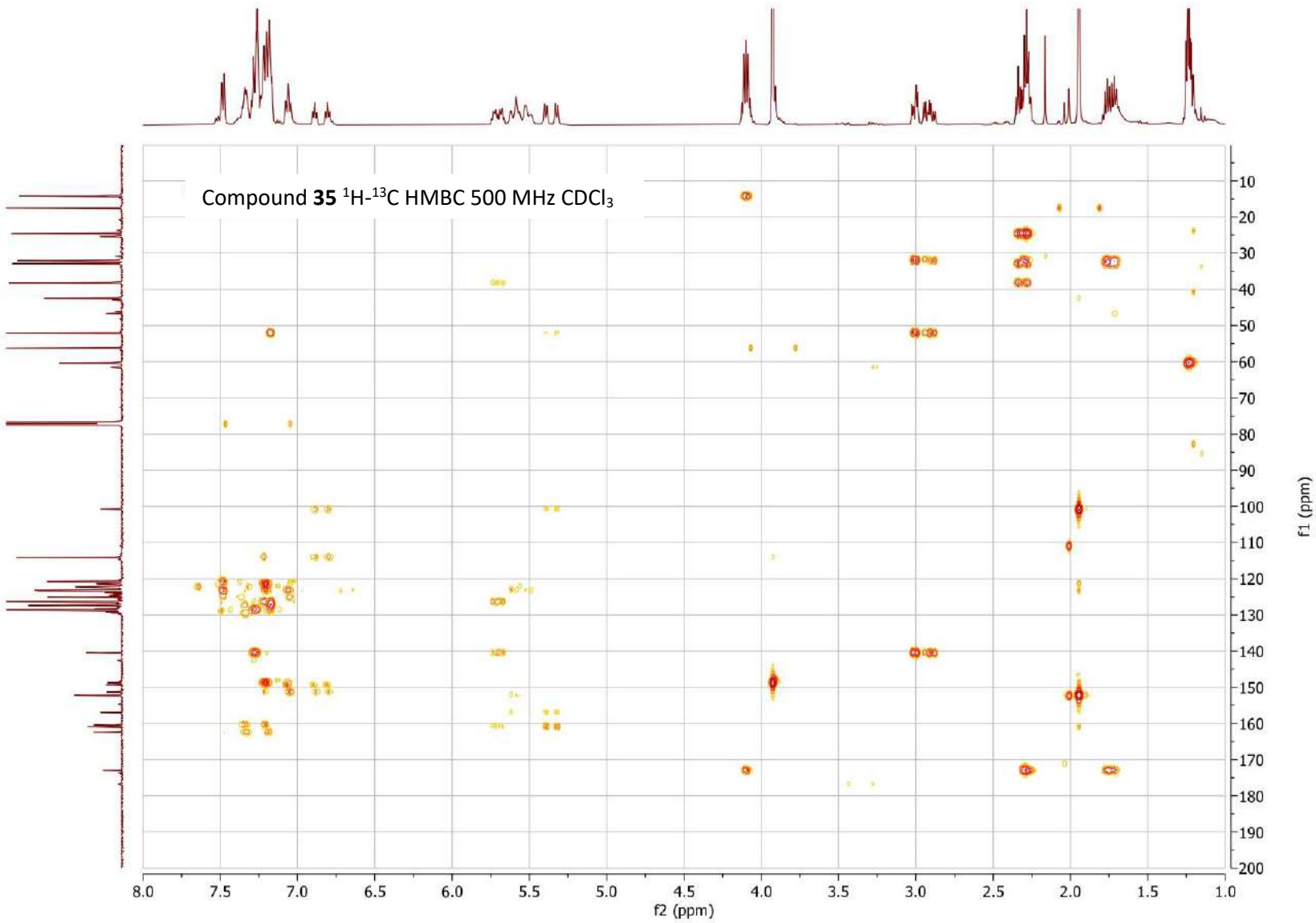


Figure S83. ^{1}H-^{13}C HMBC of compound **35**

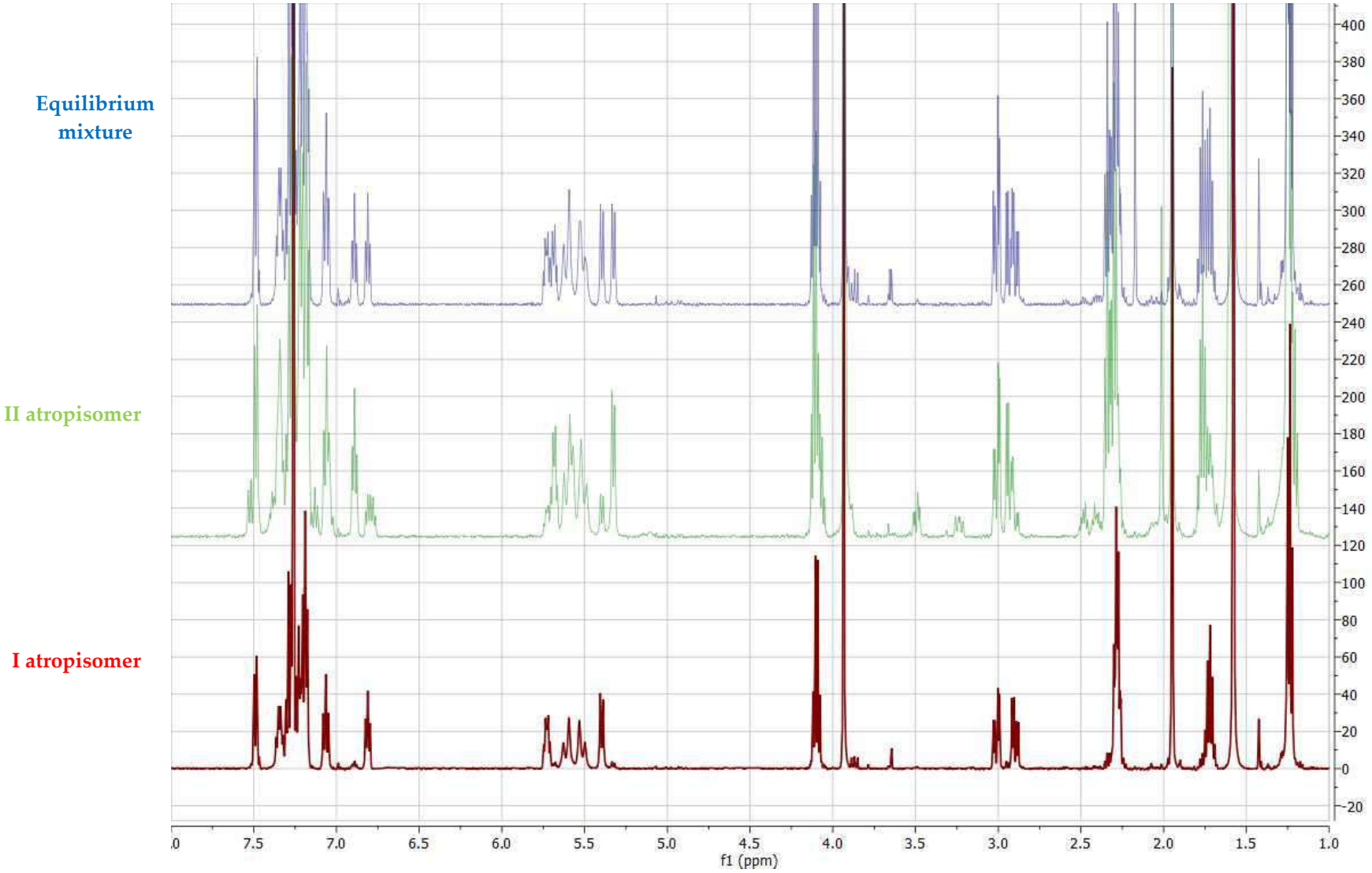


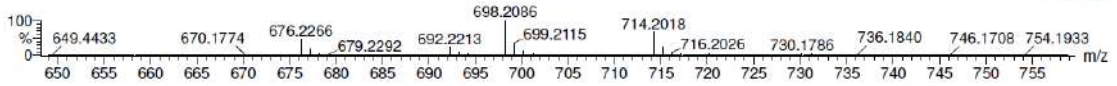
Figure S84. Superimposed spectra of I and II atropisomer of **35**, and equilibrium mixture

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -5.0, max = 300.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
13 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 34-34 H: 34-35 N: 3-3 O: 4-4 Na: 0-4 S: 1-1 K: 0-2 F: 5-5

INT6Z 49 (0.984) AM2 (Ar,40000.0,0.00,0.00); Cm (30:50) 1: TOF MS ES+ 9.75e+006



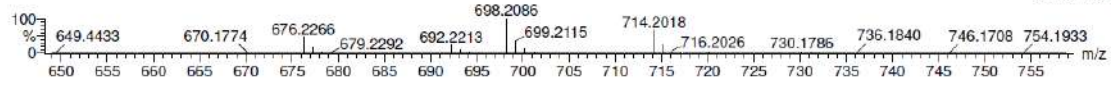
Minimum:				-5.0				
Maximum:		5.0	5.0	300.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
676.2266	676.2268	-0.2	-0.3	16.5	1290.6	n/a	n/a	C34 H35 N3 O4 S F5

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -5.0, max = 300.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
11 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 34-34 H: 34-35 N: 3-3 O: 4-4 Na: 0-4 S: 1-1 K: 0-2 F: 5-5

INT6Z 49 (0.984) AM2 (Ar,40000.0,0.00,0.00); Cm (30:50) 1: TOF MS ES+ 9.75e+006



Minimum:				-5.0				
Maximum:		5.0	5.0	300.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
698.2086	698.2088	-0.2	-0.3	16.5	1333.5	n/a	n/a	C34 H34 N3 O4 Na S F5

Figure S85. HRMS analysis of compound **35**

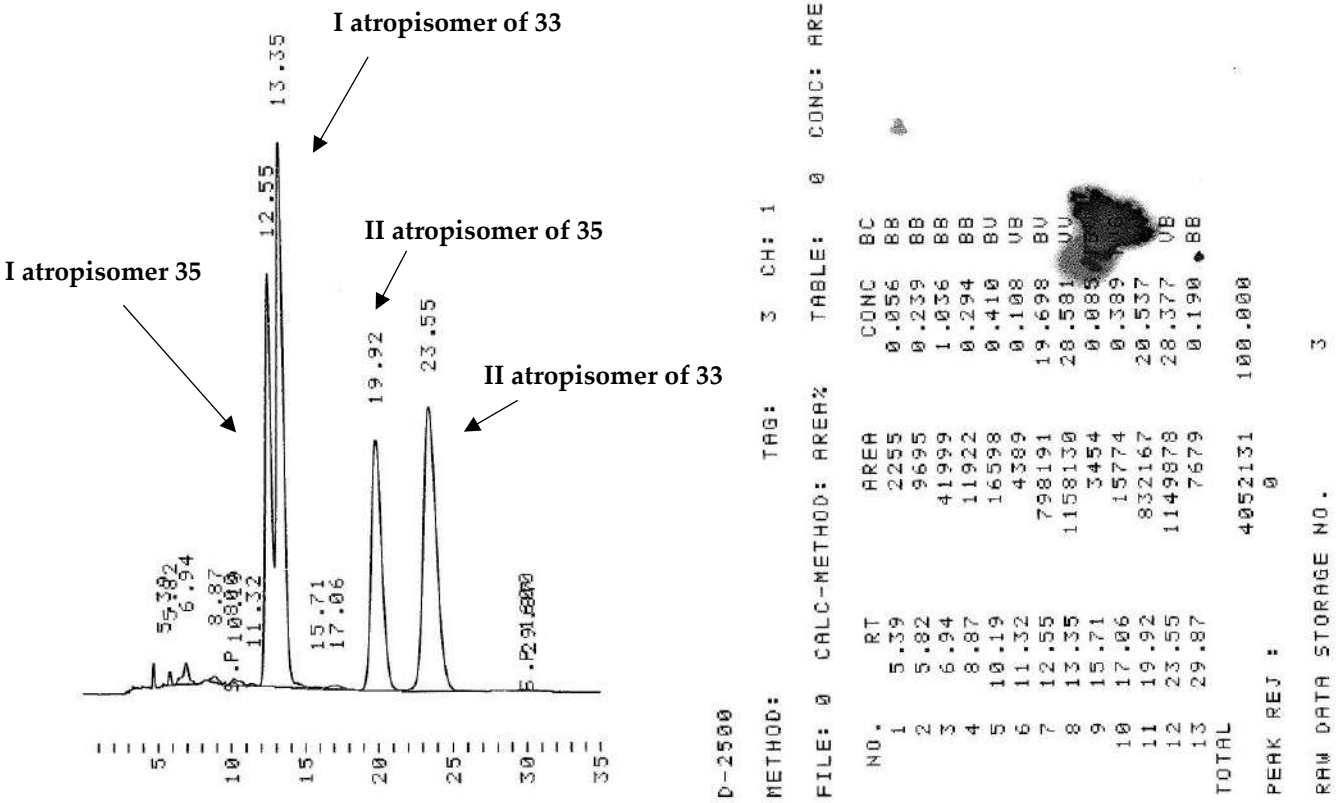


Figure S86. Chiral HPLC analysis of the obtained crude mixture of compounds **33** and **35**

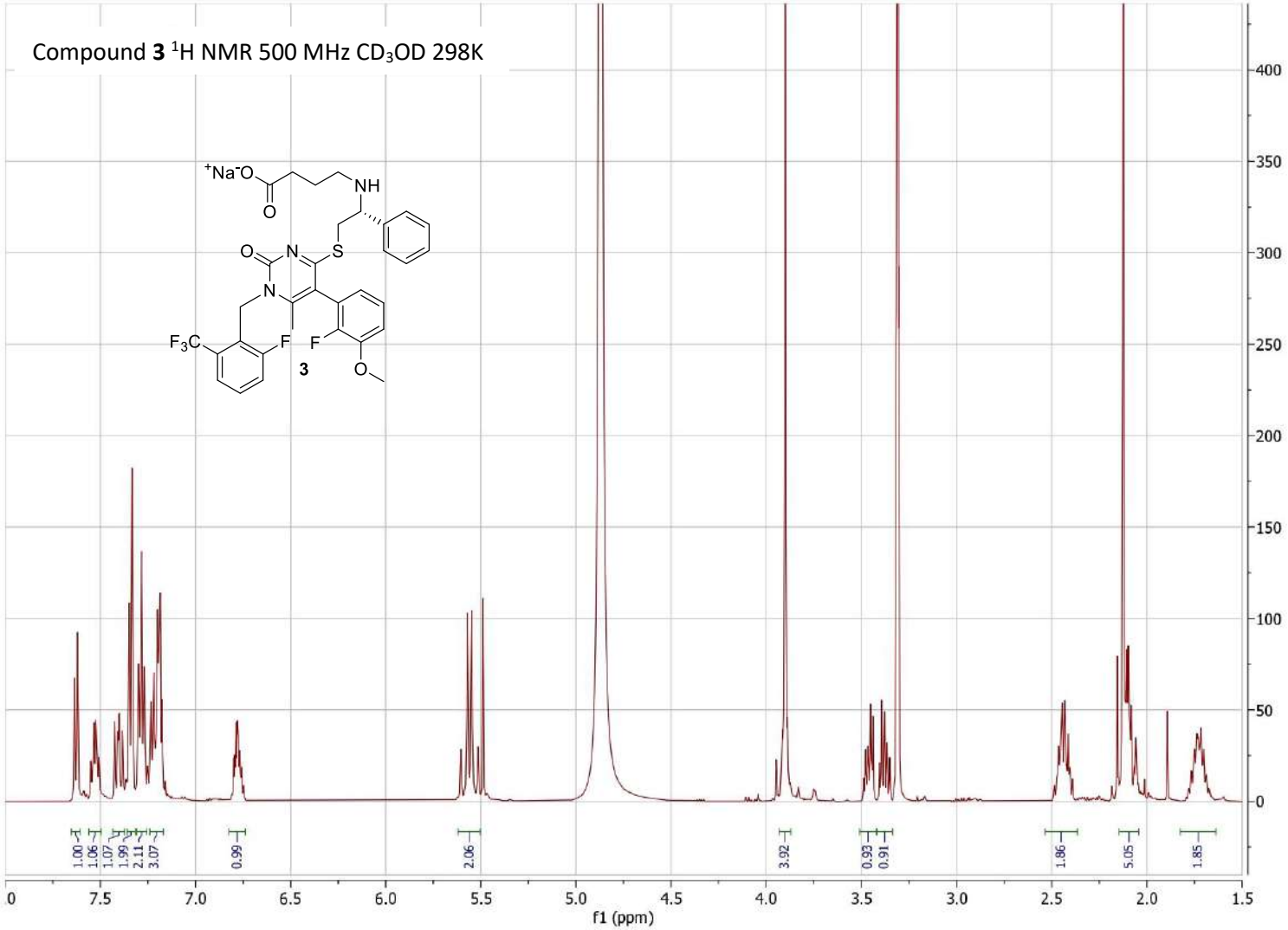


Figure S87. [1]H NMR of compound **3**

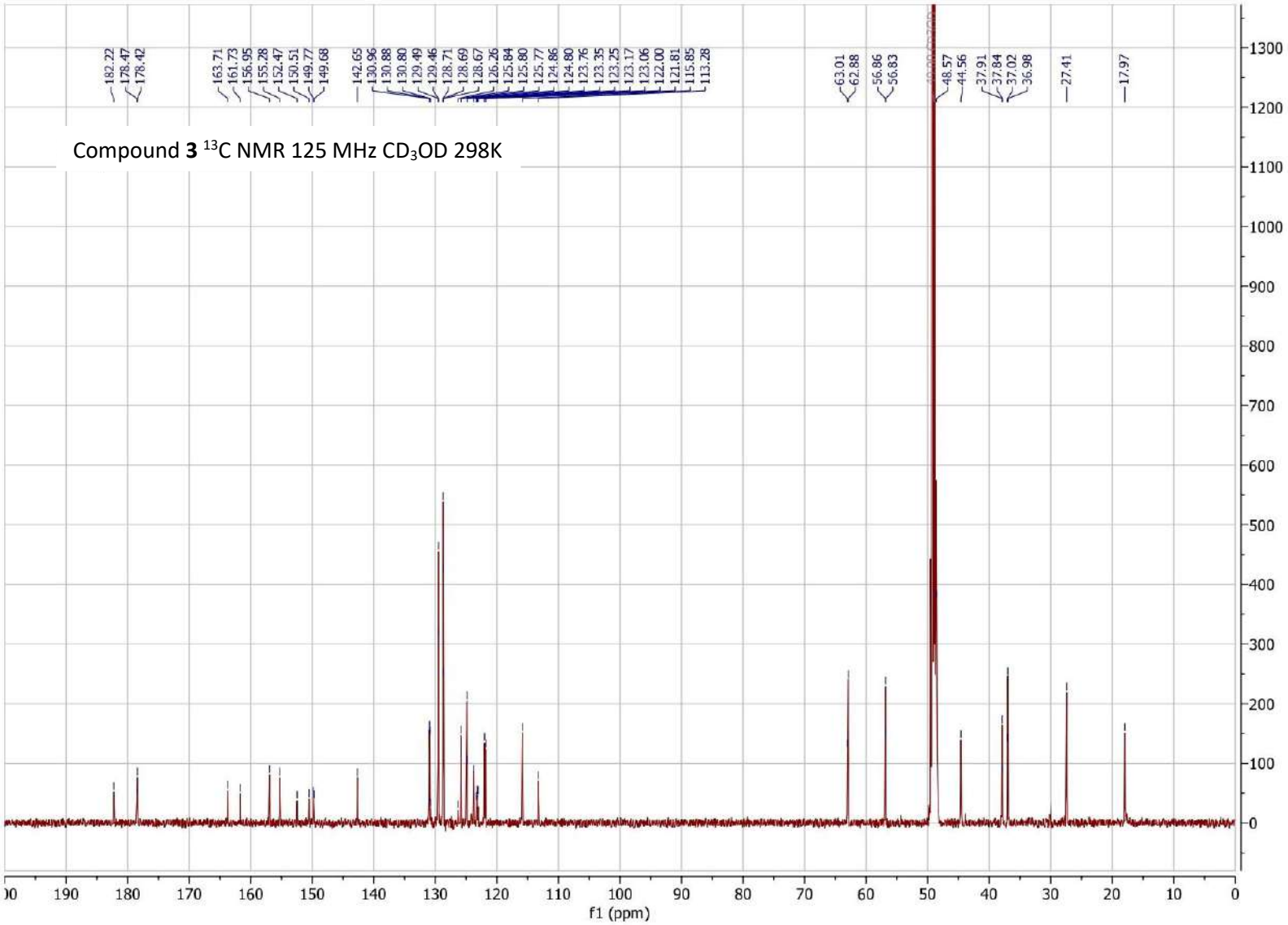


Figure S88. ^{13}C NMR of compound **3**

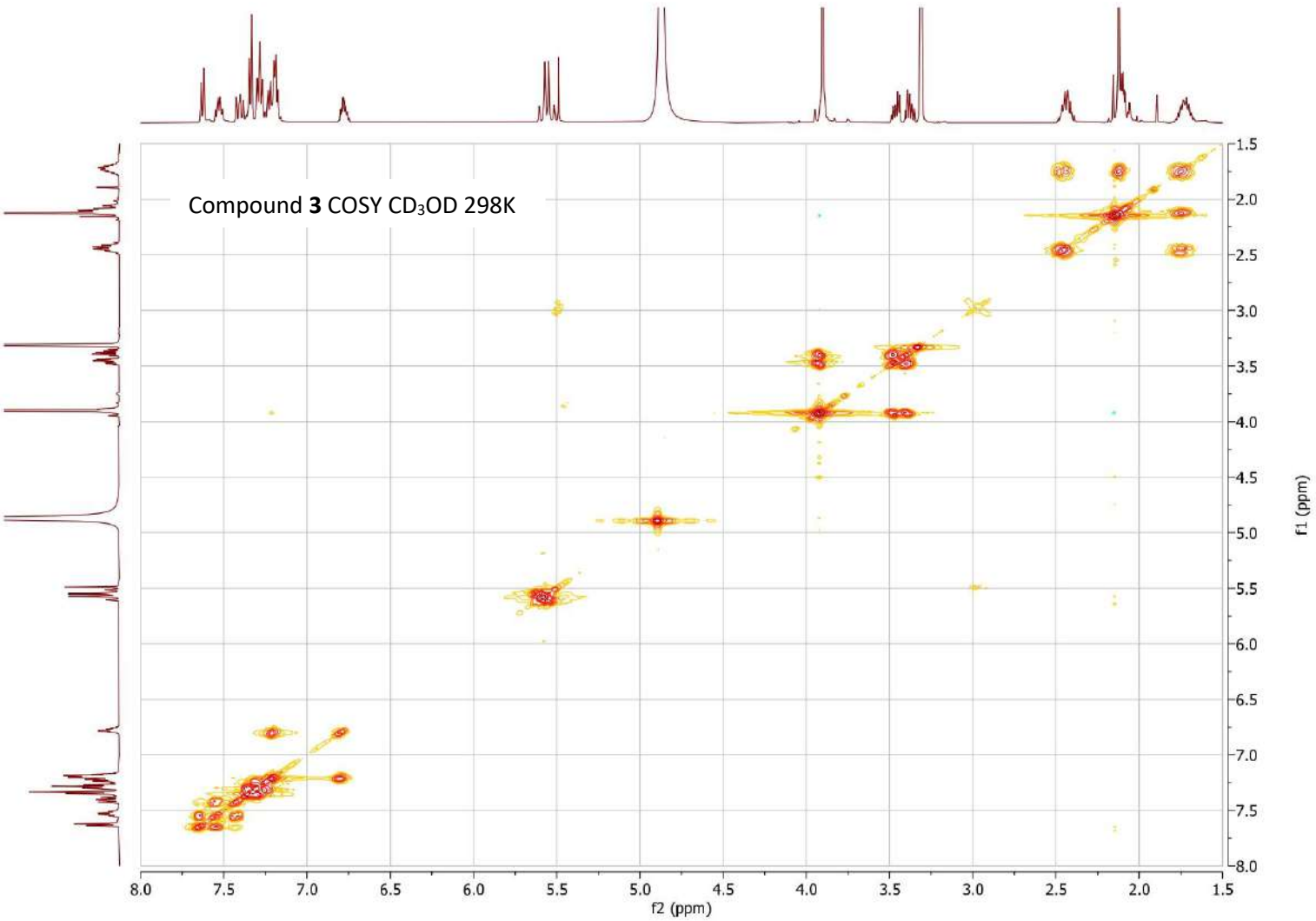


Figure S89. COSY of compound **3**

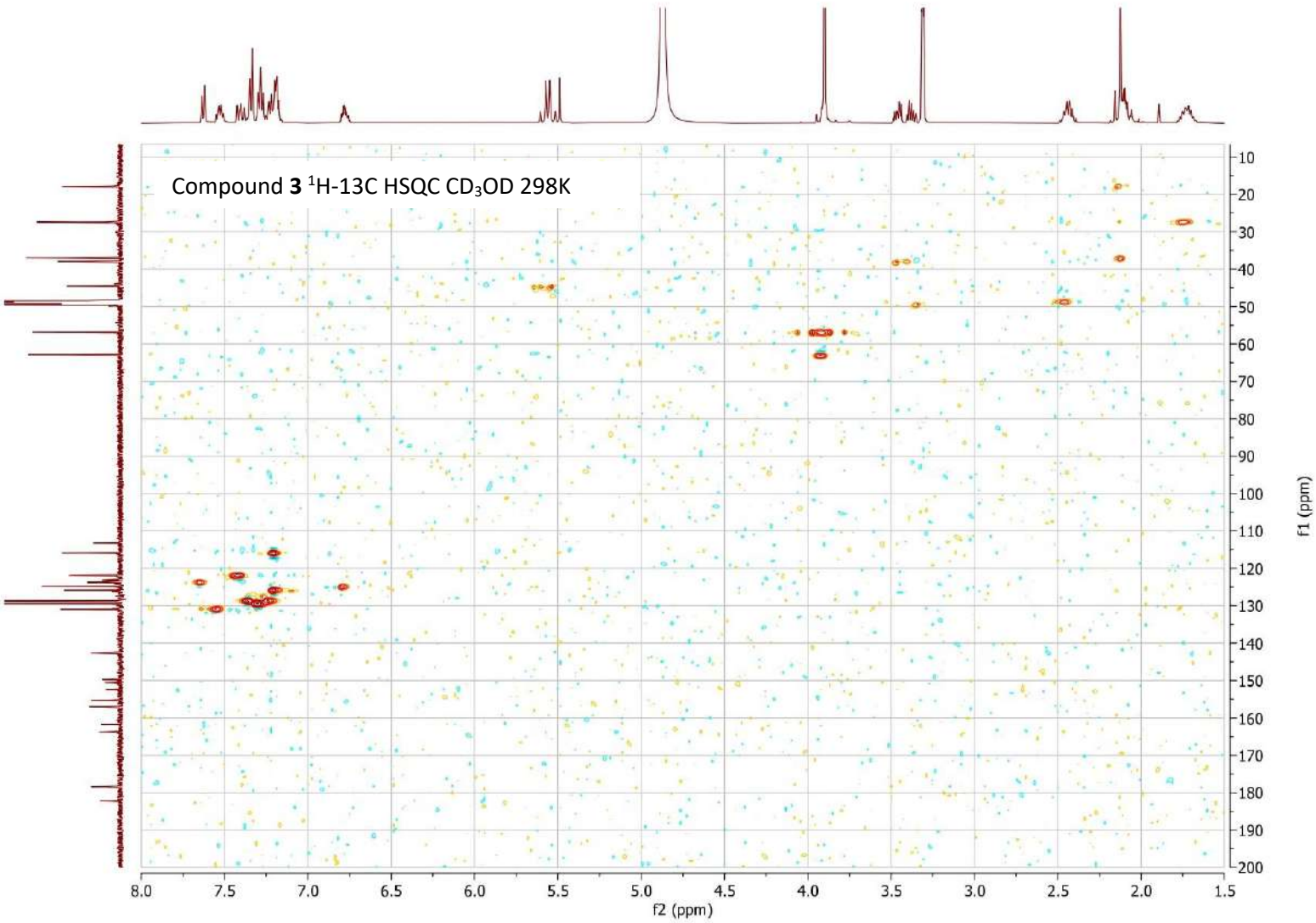


Figure S90. ^{1}H-^{13}C HSQC of compound **3**

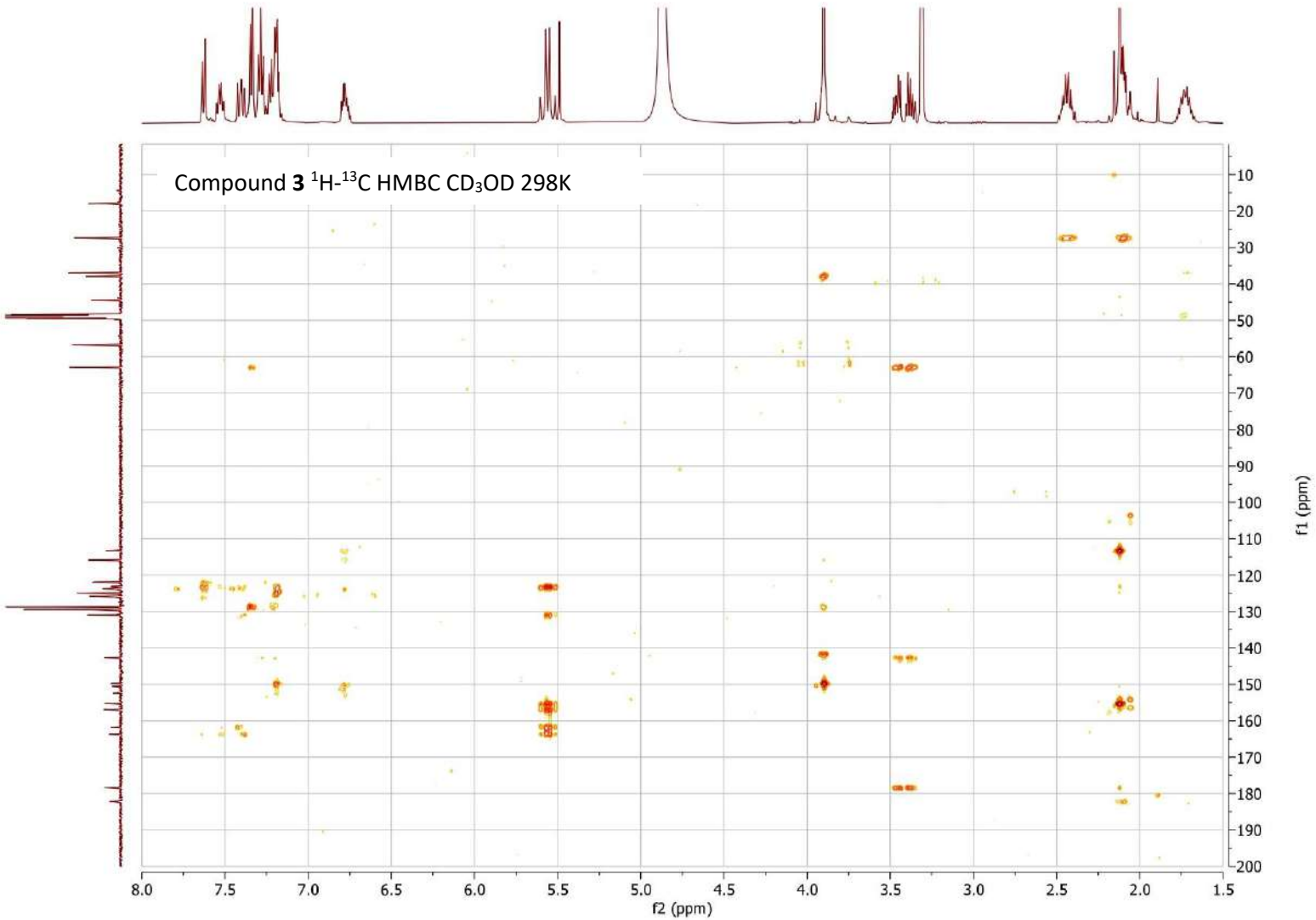


Figure S91. ^{1}H-^{13}C HMBC of compound **3**

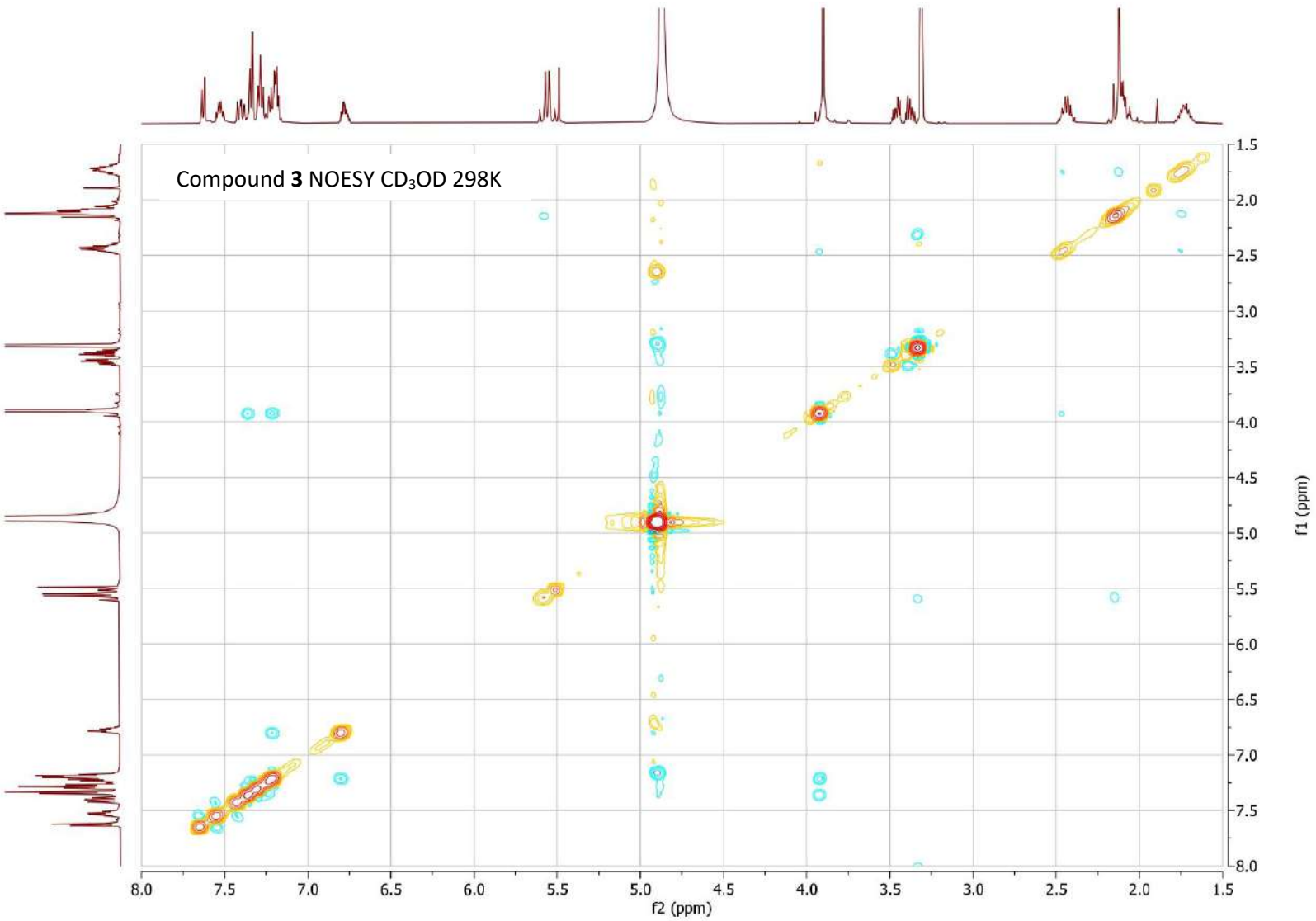


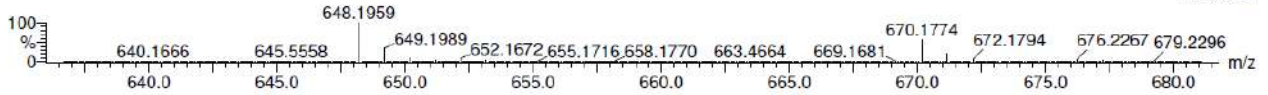
Figure S92. NOESY of compound **3**

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -5.0, max = 300.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 7

Monoisotopic Mass, Even Electron Ions
4 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 32-32 H: 30-31 N: 3-3 O: 4-4 Na: 0-4 S: 1-1 F: 5-5

SC1iso2 11 (0.242) AM2 (Ar,40000.0,0.00,0.00); Cm (10:50) 1: TOF MS ES+ 2.29e+007



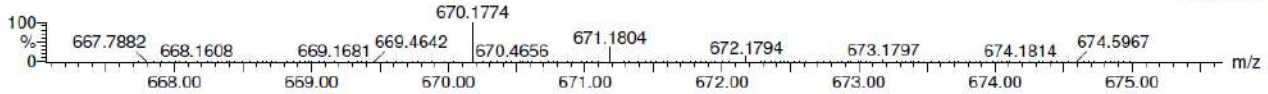
Minimum:				-5.0				
Maximum:		5.0	5.0	300.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
648.1959	648.1955	0.4	0.6	16.5	2386.6	n/a	n/a	C32 H31 N3 O4 S F5

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -5.0, max = 300.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 7

Monoisotopic Mass, Even Electron Ions
3 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 32-32 H: 30-31 N: 3-3 O: 4-4 Na: 0-4 S: 1-1 F: 5-5

SC1iso2 11 (0.242) AM2 (Ar,40000.0,0.00,0.00); Cm (10:50) 1: TOF MS ES+ 1.27e+007



Minimum:				-5.0				
Maximum:		5.0	5.0	300.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
670.1774	670.1775	-0.1	-0.1	16.5	1650.2	n/a	n/a	C32 H30 N3 O4 Na S F5

Figure S93. HRMS analysis of compound **3**

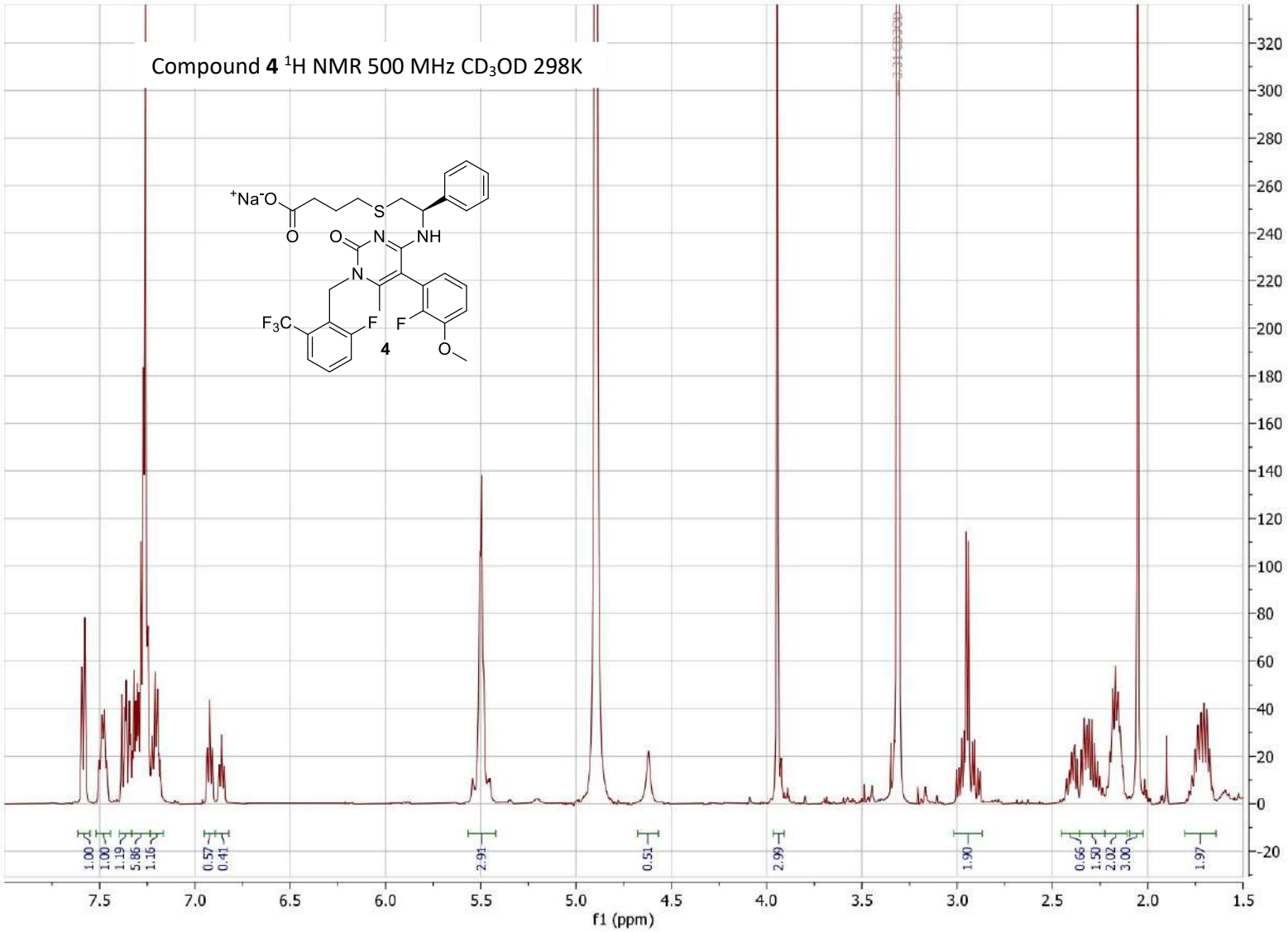


Figure S94. ^{1}H NMR of compound **4**

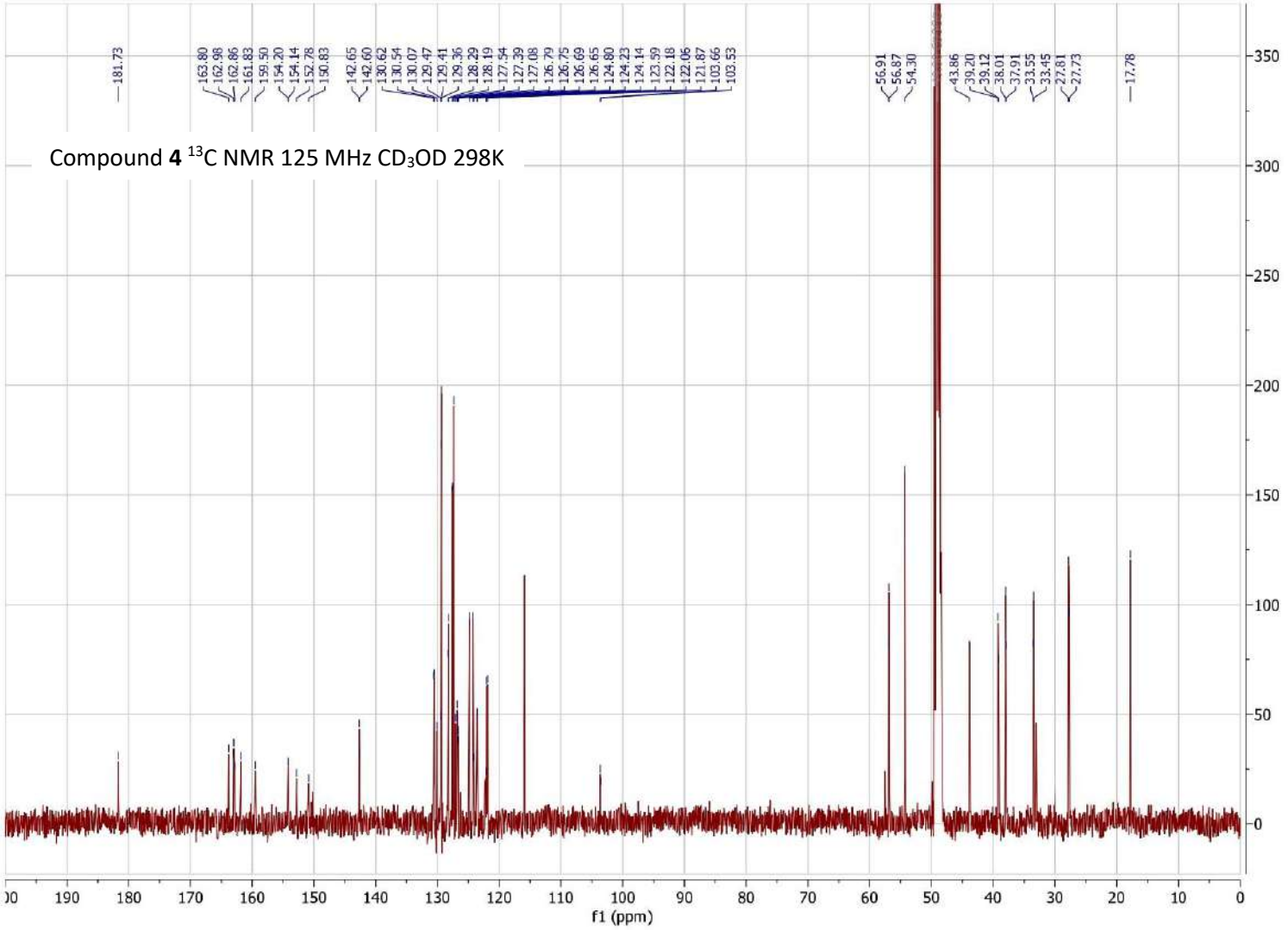


Figure S95. ^{13}C NMR of compound **4**

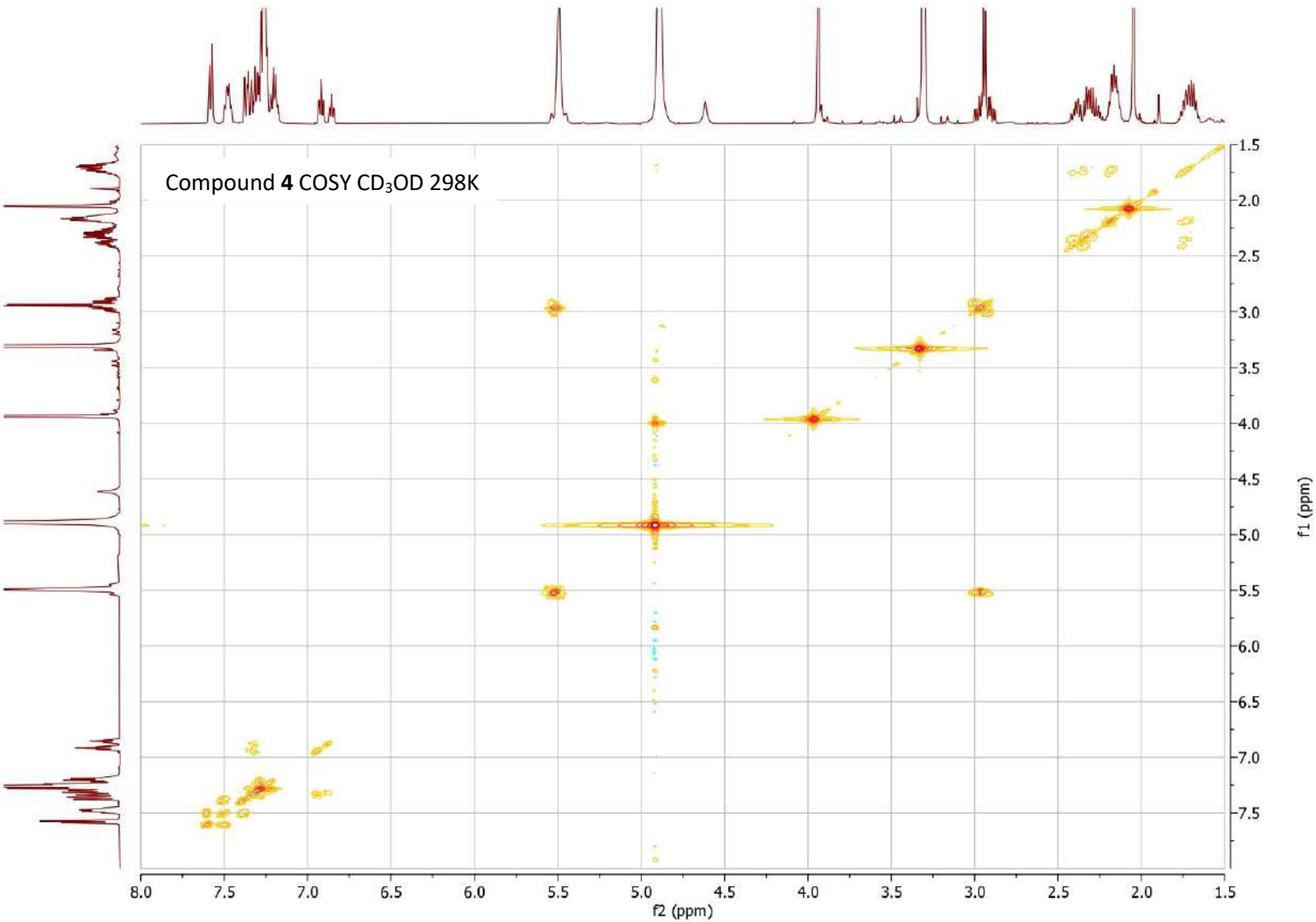


Figure S96. COSY of compound **4**

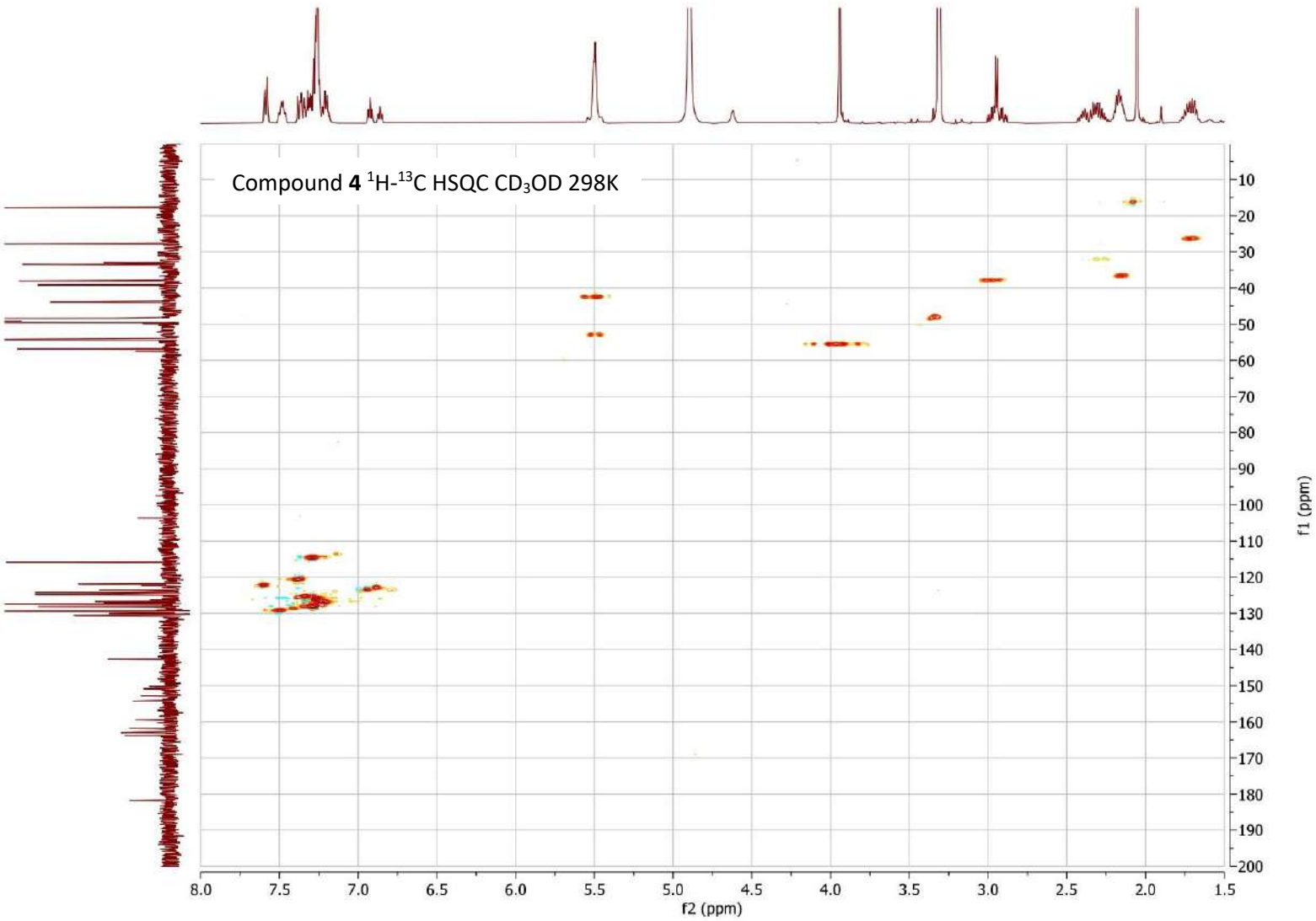


Figure S97. ^{1}H-^{13}C HSQC of compound **4**

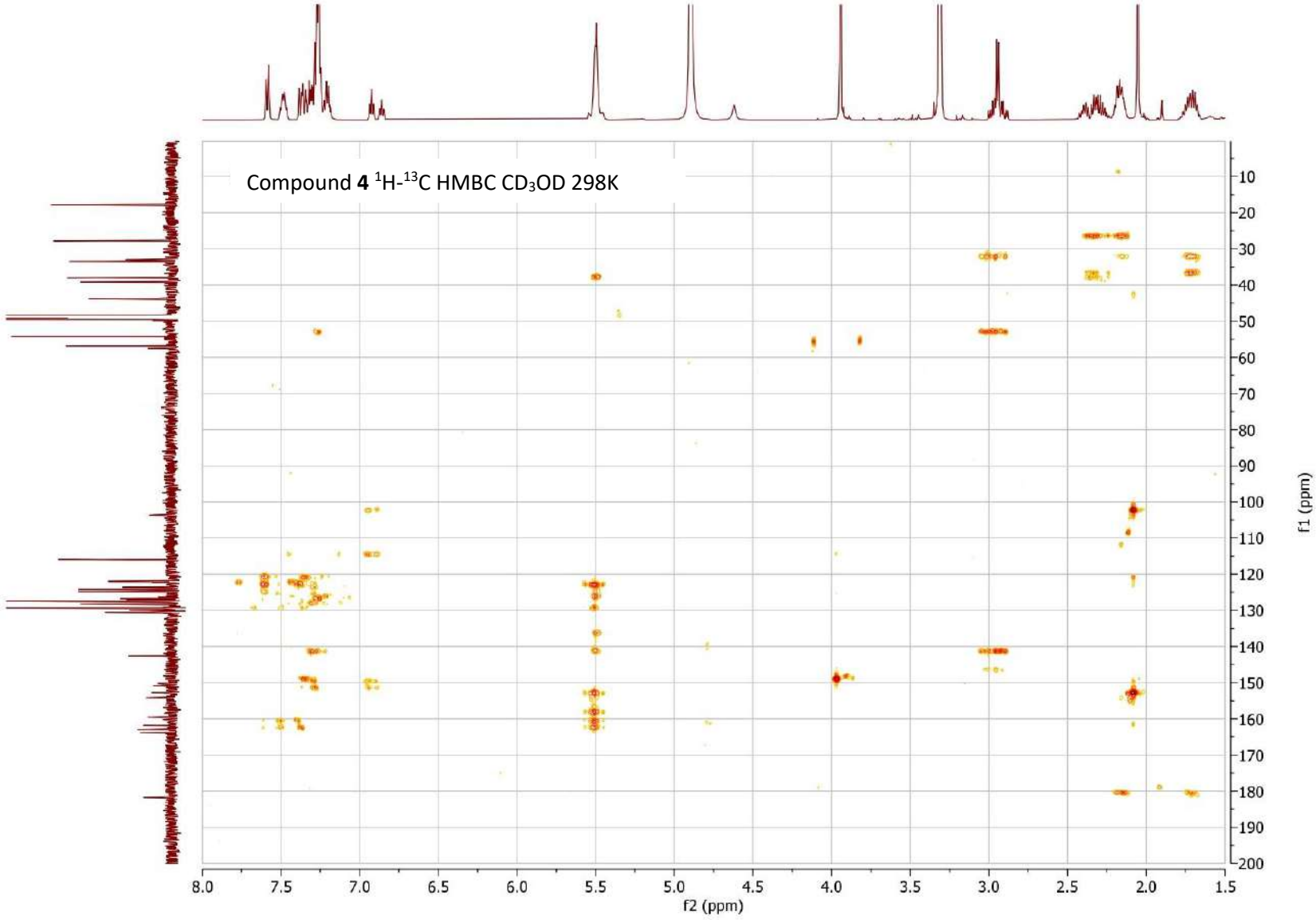


Figure S98. ^{1}H-^{13}C HMBC of compound **4**

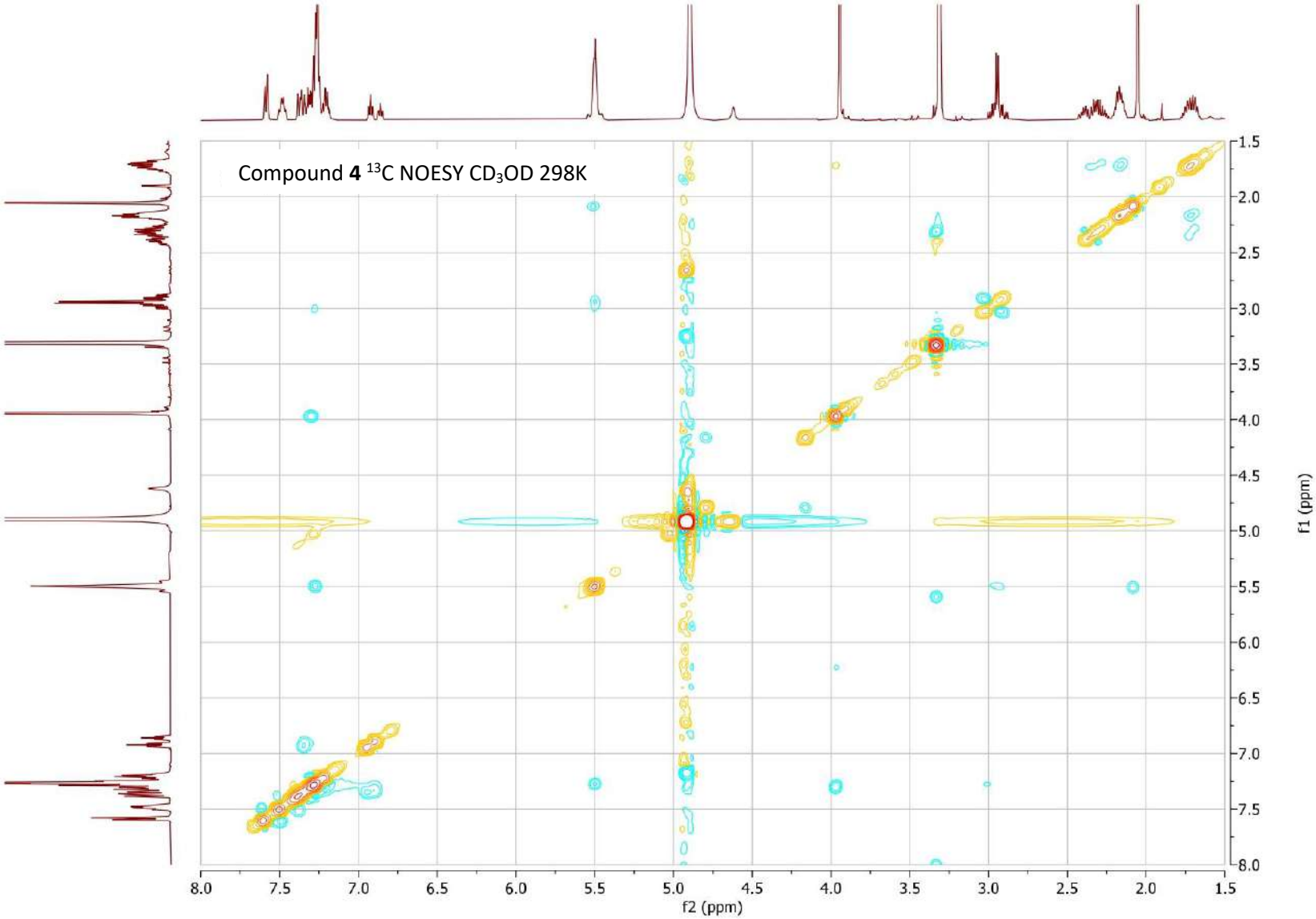


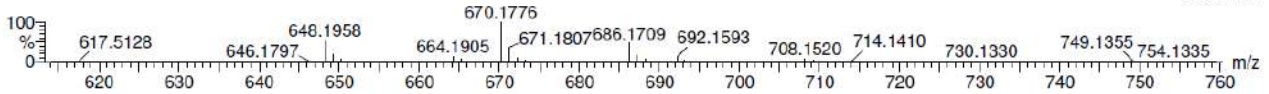
Figure S99. NOESY of compound **4**

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -5.0, max = 300.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
14 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 32-32 H: 28-31 N: 3-3 O: 4-4 F: 5-5 Na: 0-4 S: 1-1 K: 0-2

SC1_isomero 33 (0.674) AM2 (Ar,40000.0,0.00,0.00); Cm (30:49) 1: TOF MS ES+ 3.65e+007



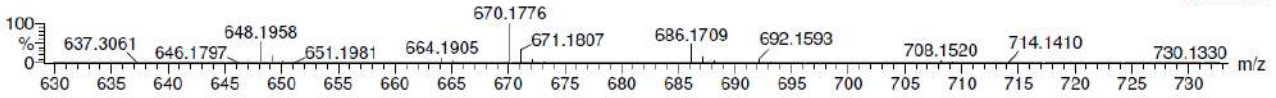
Minimum:				-5.0				
Maximum:		5.0	5.0	300.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
648.1958	648.1955	0.3	0.5	16.5	1498.5	n/a	n/a	C32 H31 N3 O4 F5 S

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -5.0, max = 300.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
12 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 32-32 H: 28-31 N: 3-3 O: 4-4 F: 5-5 Na: 0-4 S: 1-1 K: 0-2

SC1_isomero 33 (0.674) AM2 (Ar,40000.0,0.00,0.00); Cm (30:49) 1: TOF MS ES+ 3.65e+007



Minimum:				-5.0				
Maximum:		5.0	5.0	300.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
670.1776	670.1775	0.1	0.1	16.5	1497.2	n/a	n/a	C32 H30 N3 O4 F5 Na S

Figure S100. HRMS analysis of compound **4**

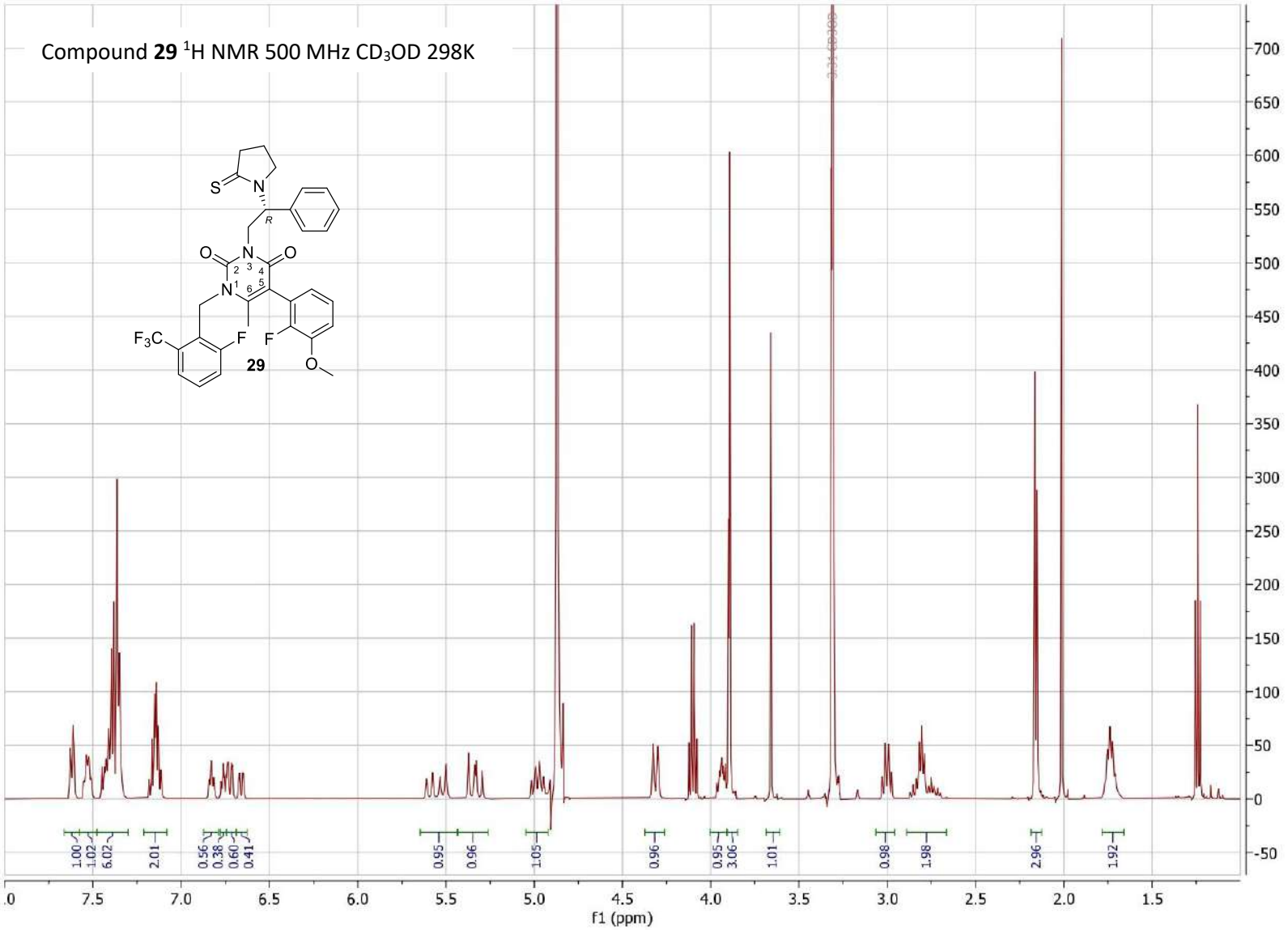


Figure S101. ^{1}H NMR of compound **29**

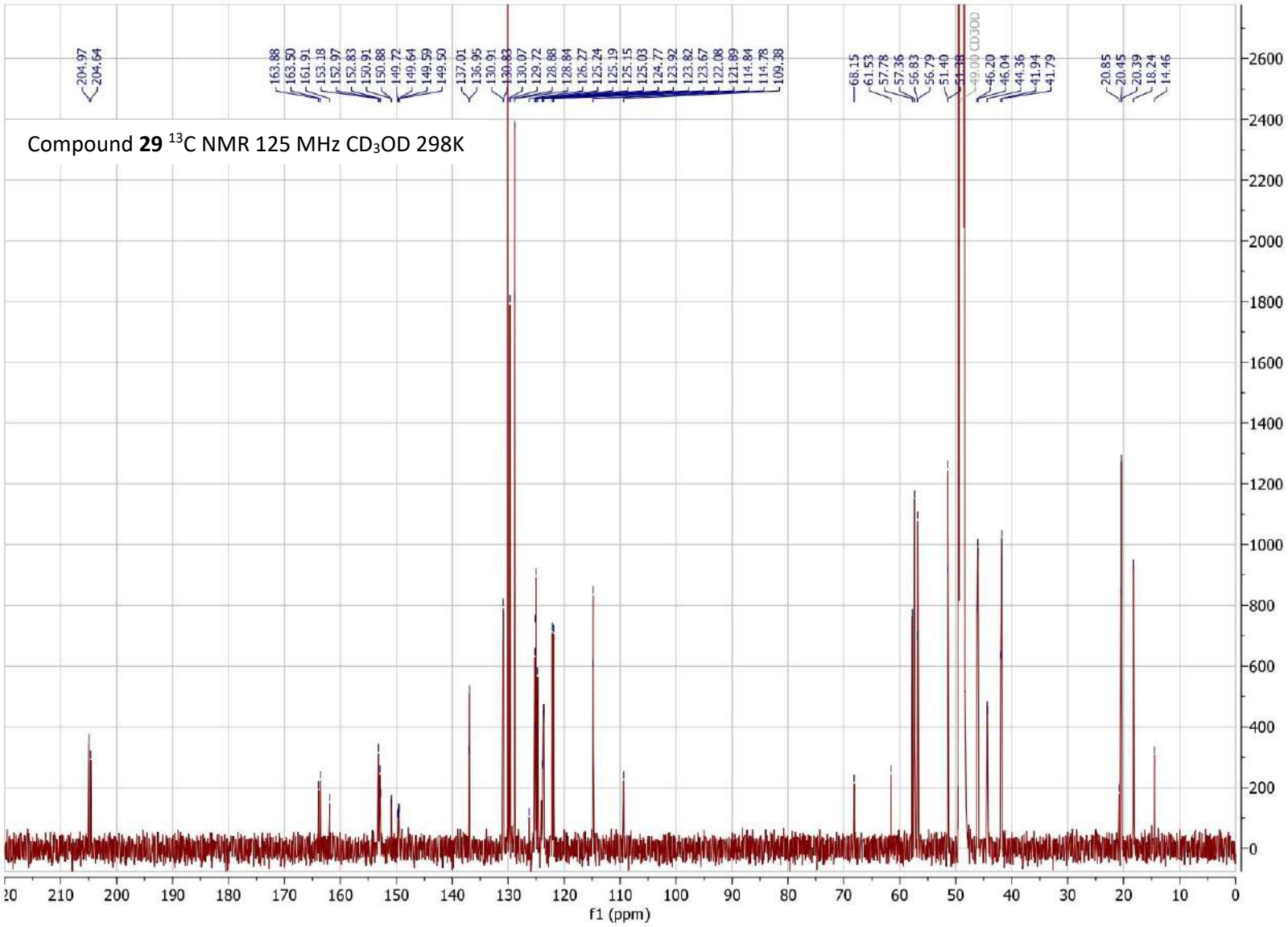


Figure S102. ^{13}C NMR of compound **29**

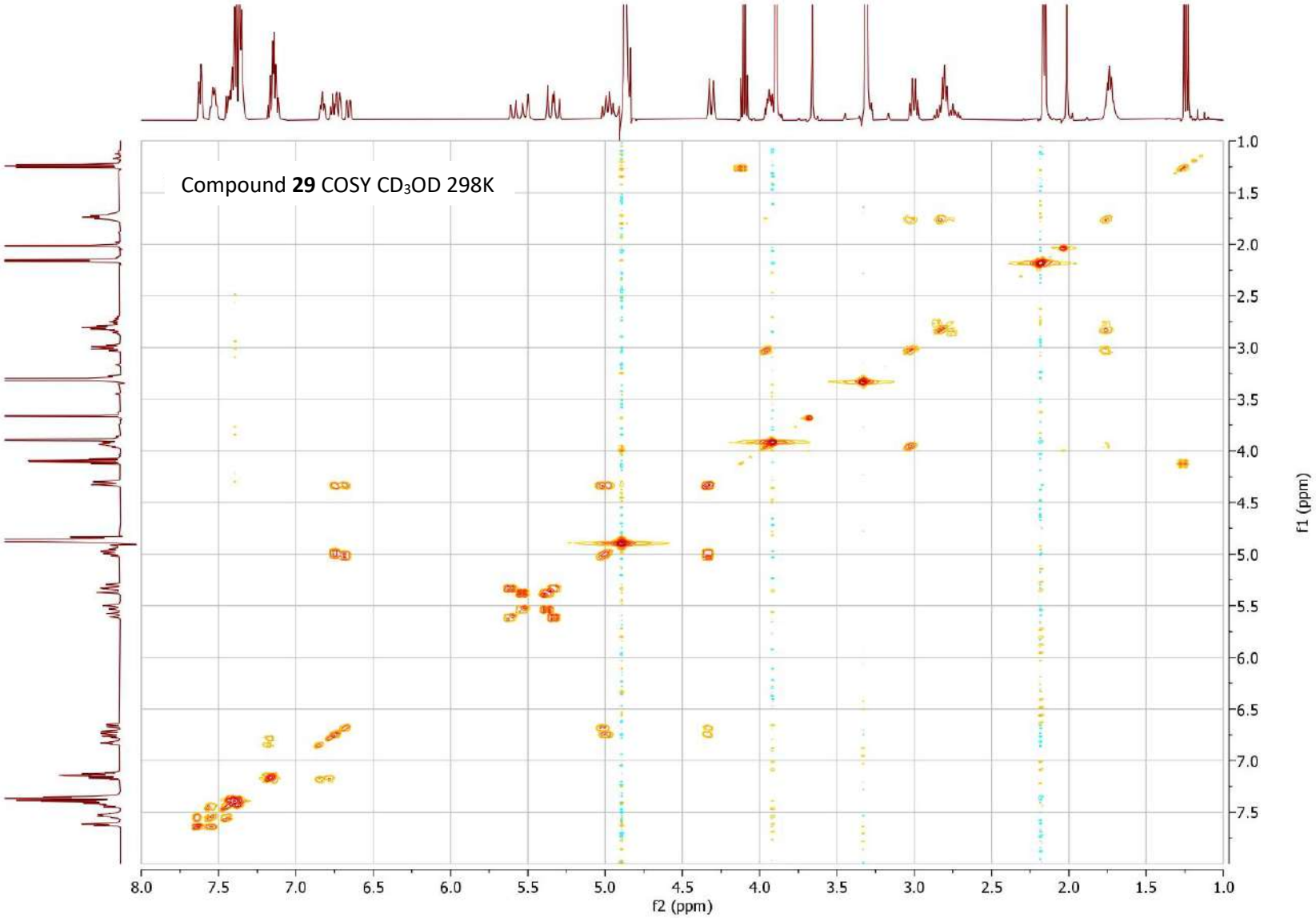


Figure S103. COSY of compound **29**

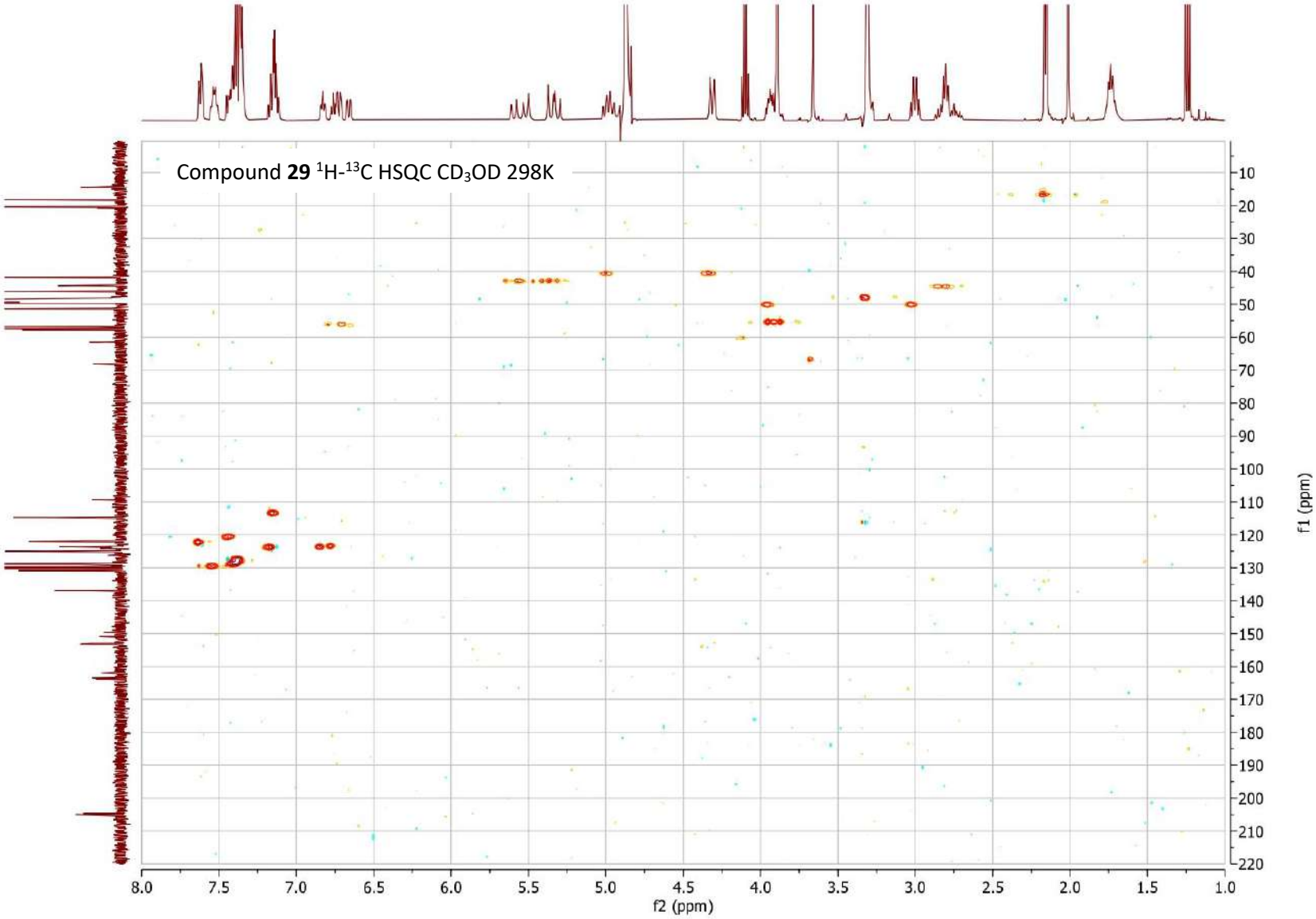


Figure S104. ^{1}H-^{13}C HSQC of compound **29**

Modifications at the 6-position

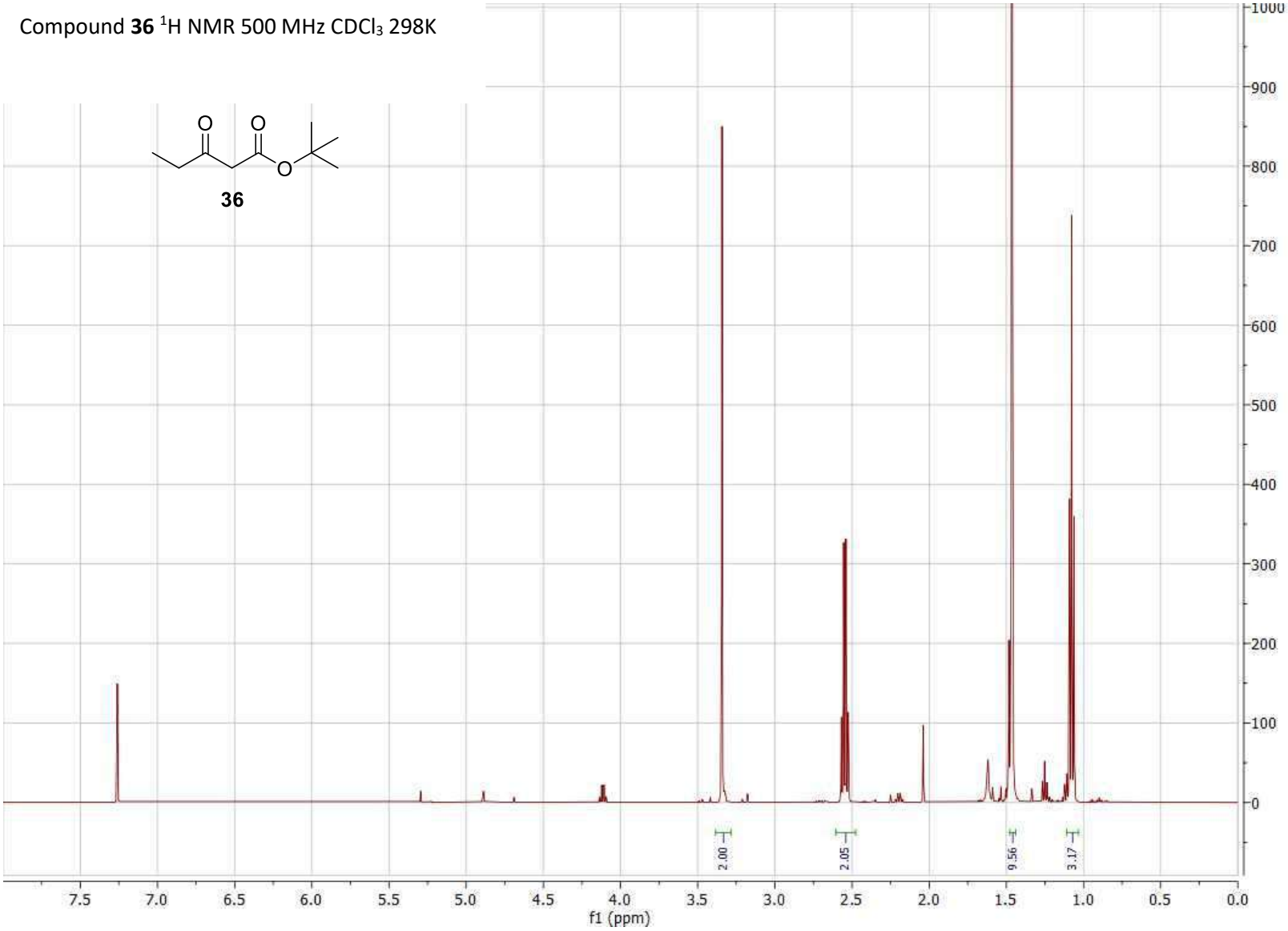


Figure S105. ^{1}H NMR of compound **36**

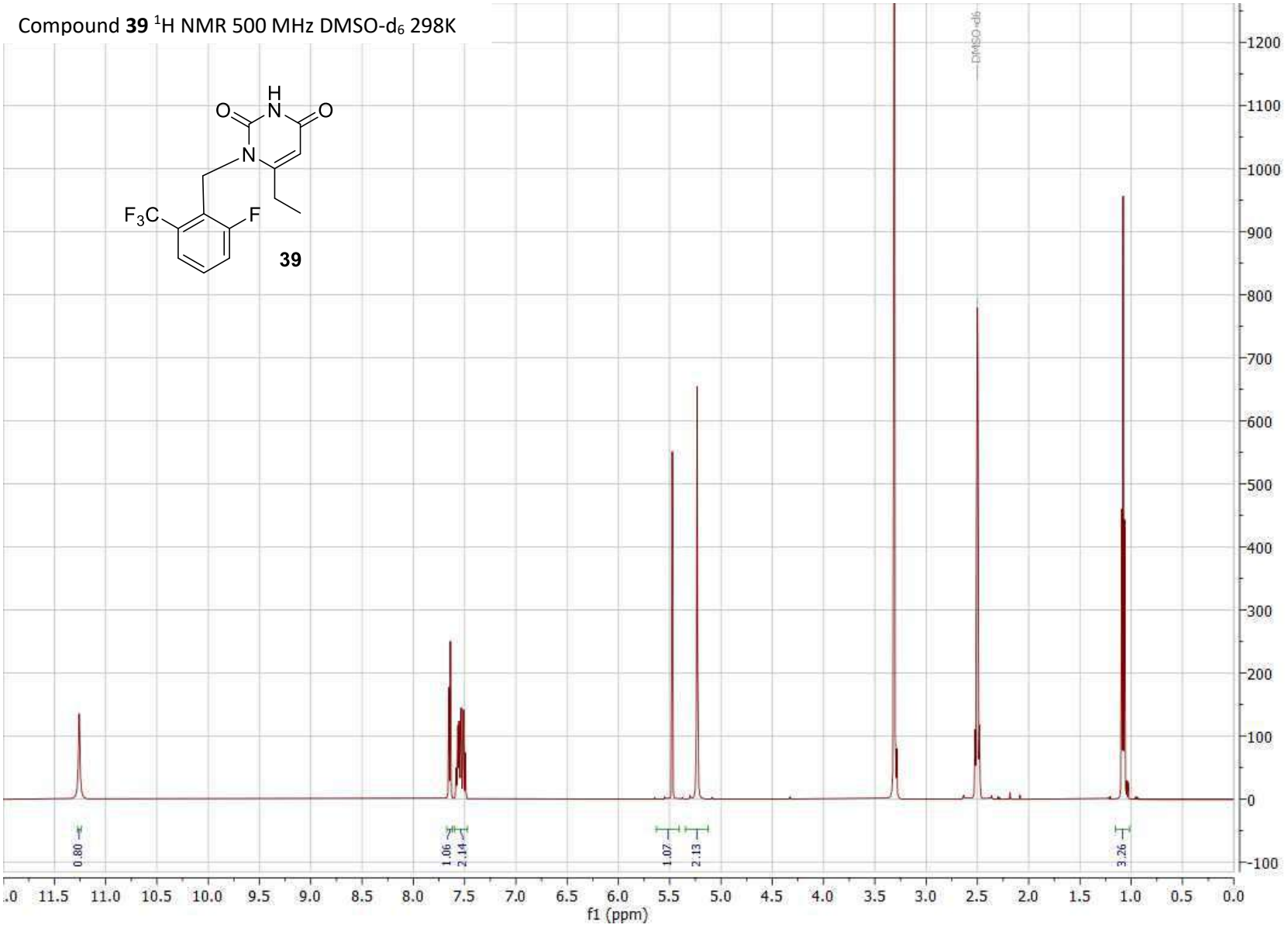


Figure S106. ^{1}H NMR of compound **39**

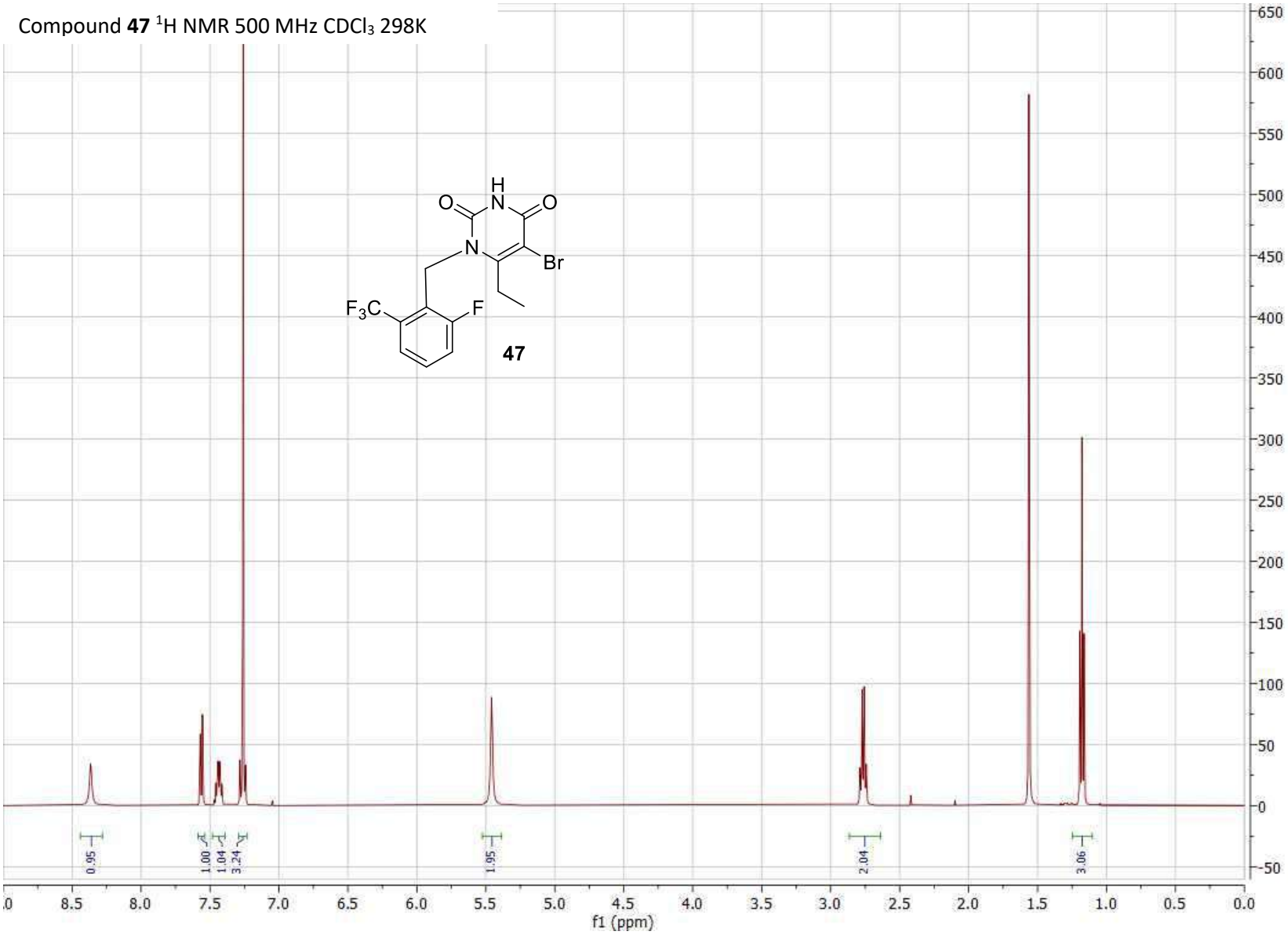


Figure S107. ^{1}H NMR of compound **47**

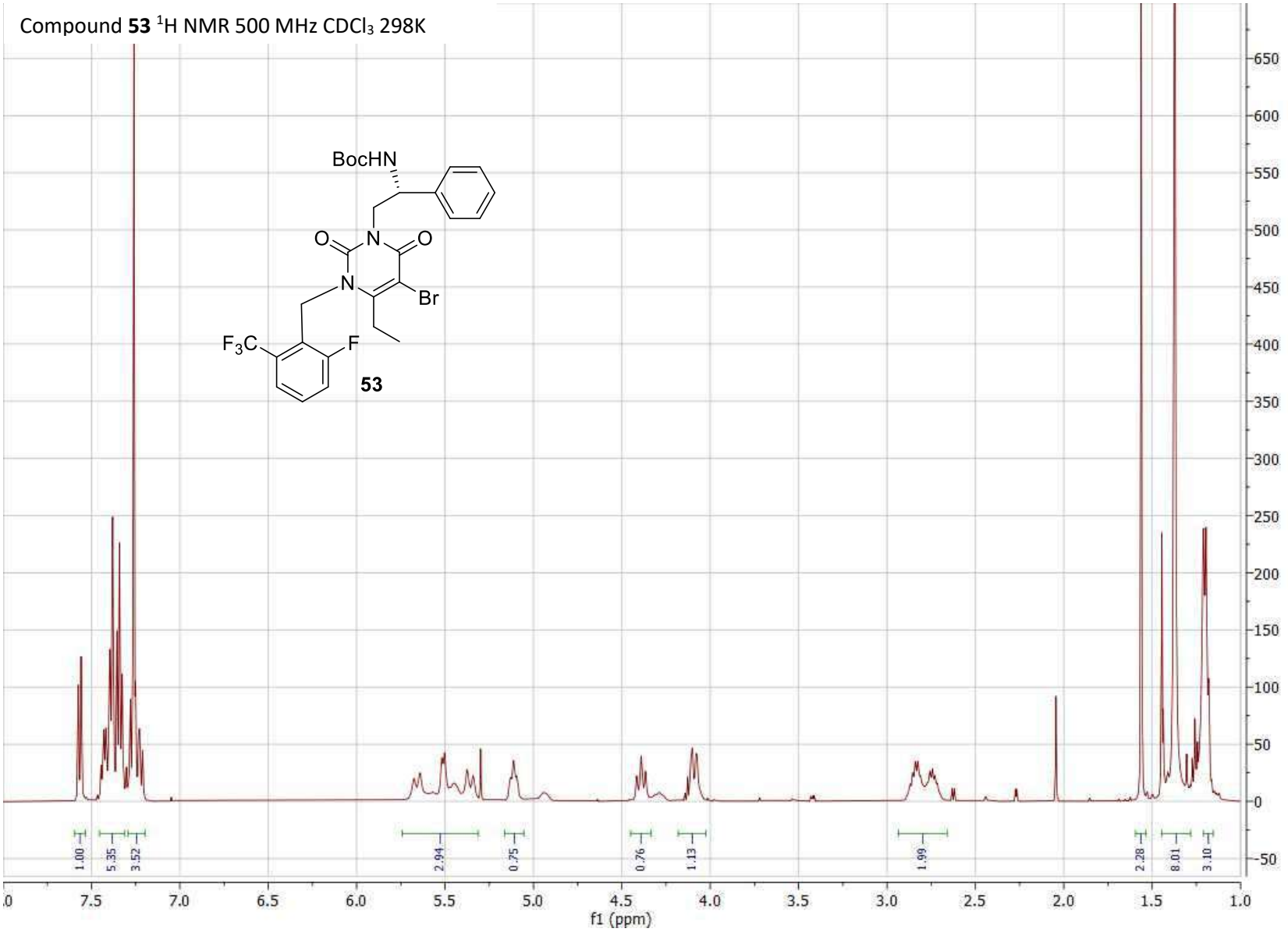


Figure S108. ^{1}H NMR of compound **53**

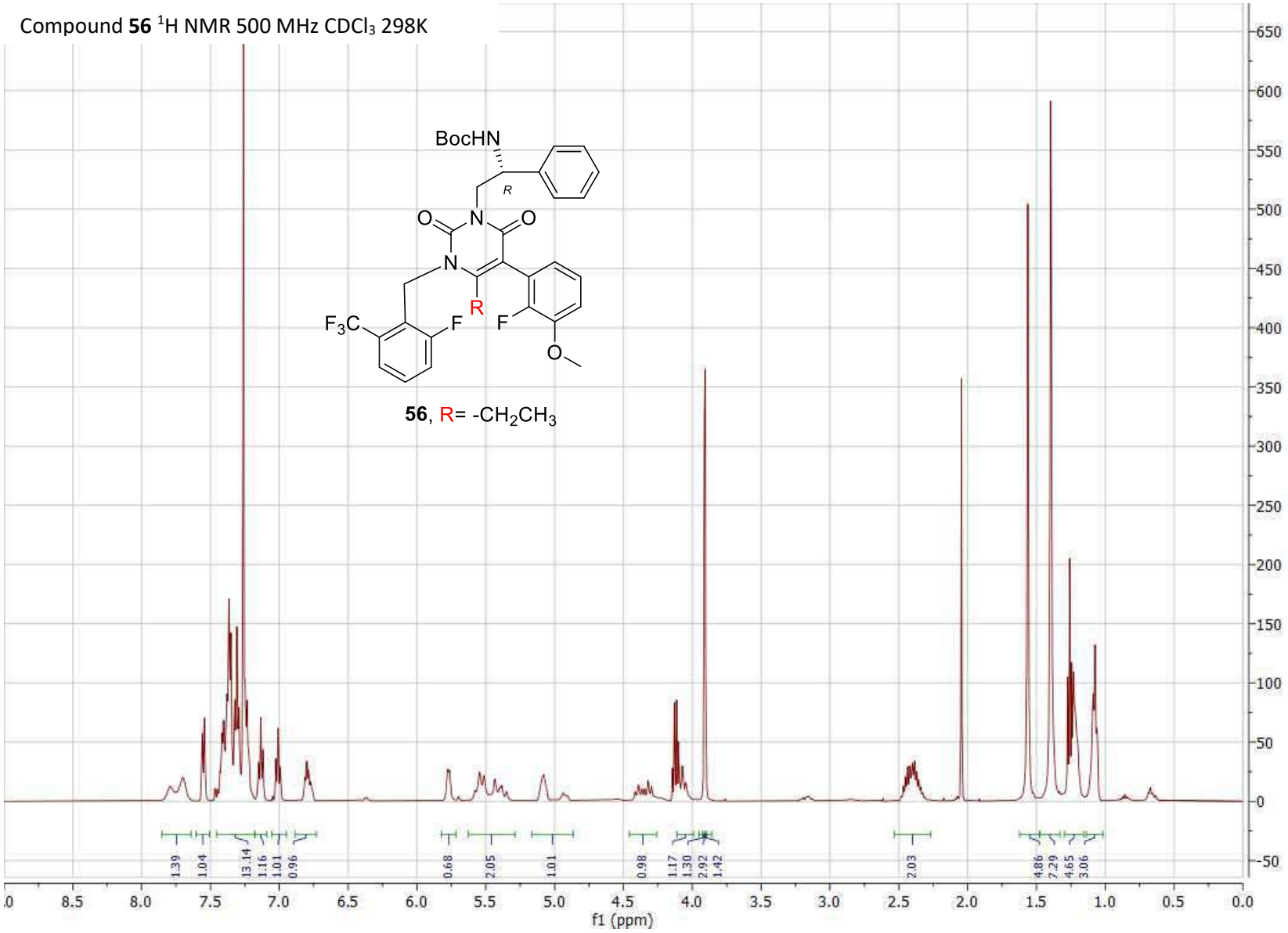


Figure S109. [1]H NMR of compound **56**

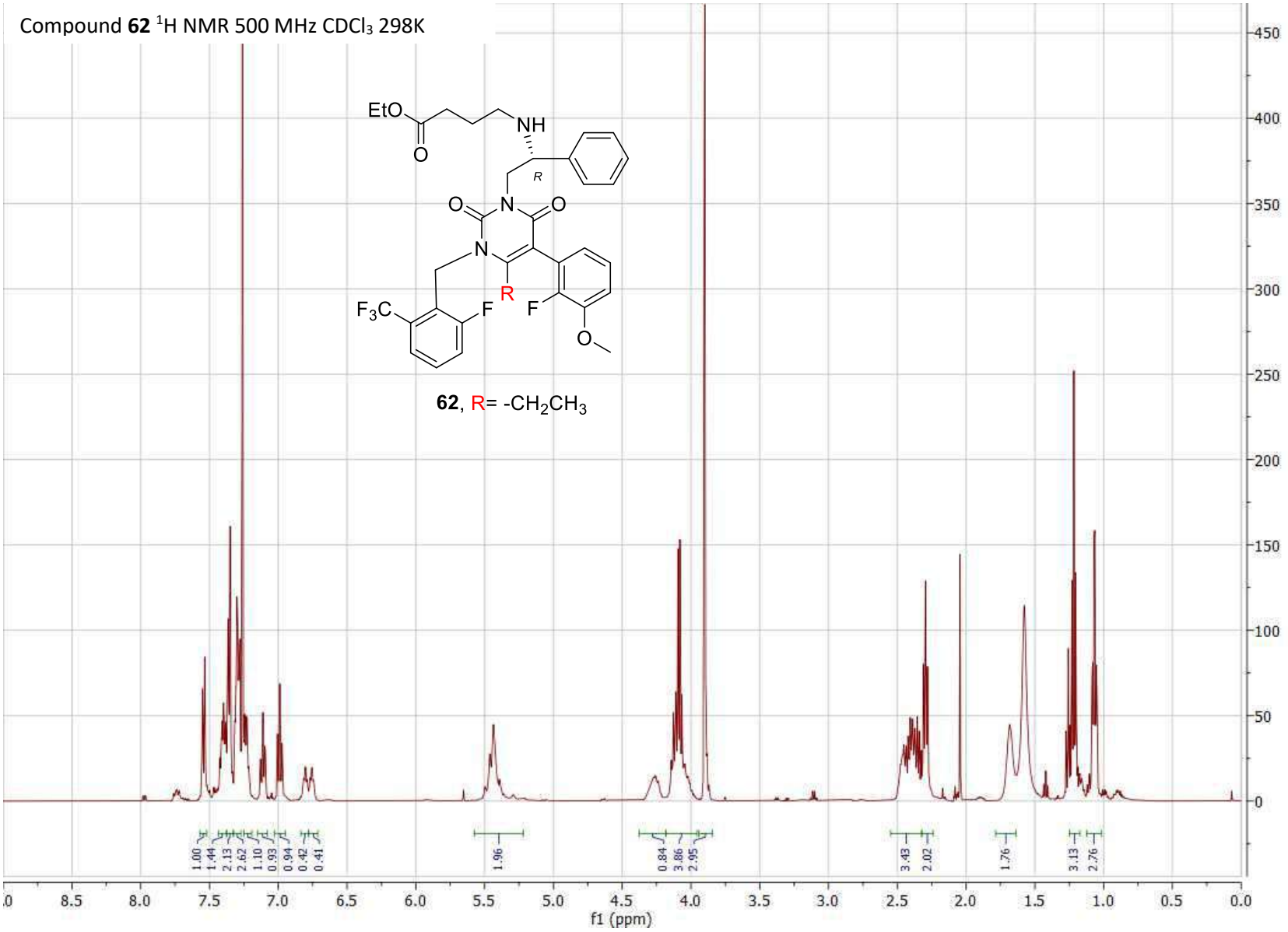


Figure S110. ^{1}H NMR of compound **62**

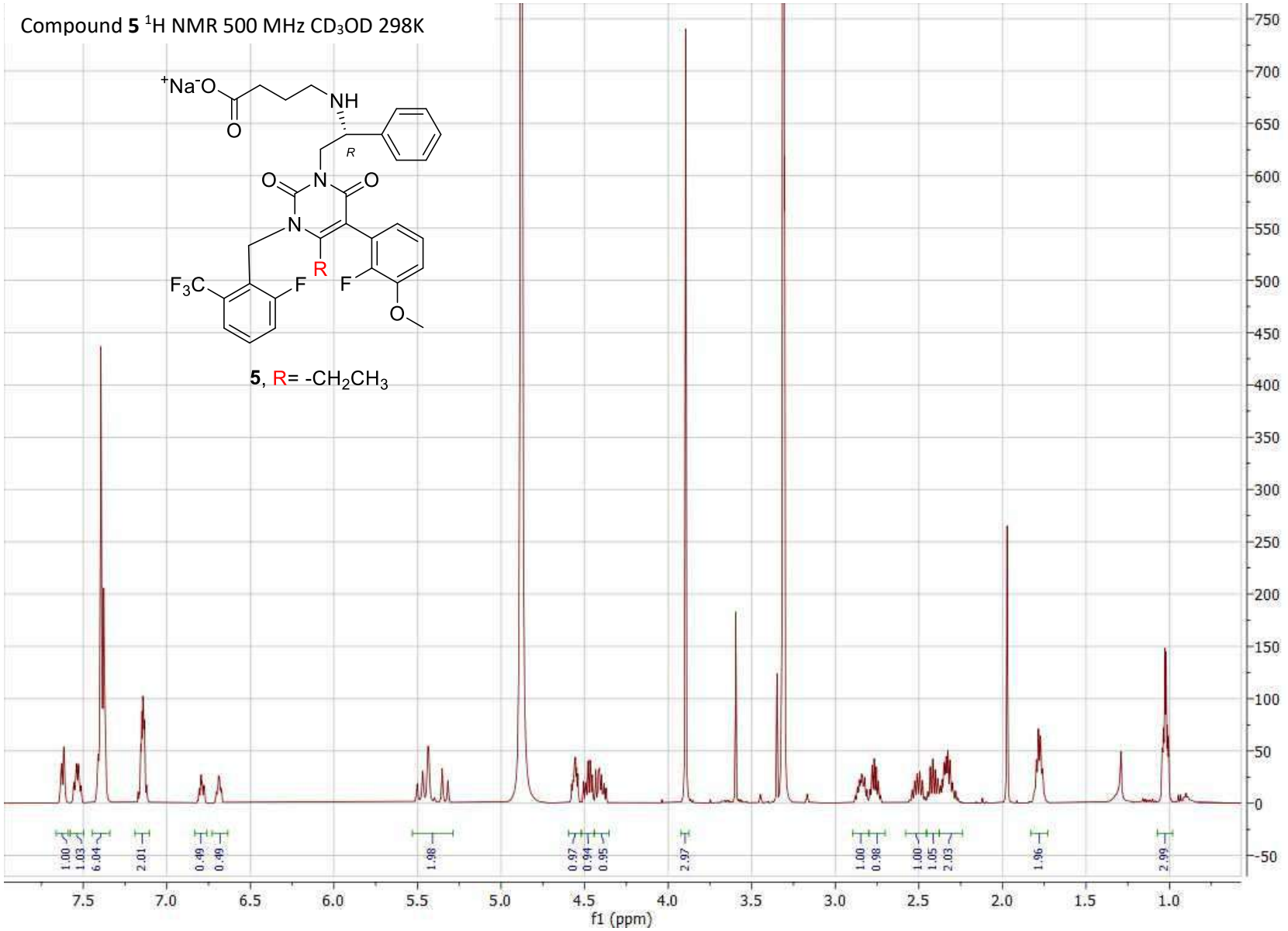


Figure S111. ¹H NMR of compound **5**

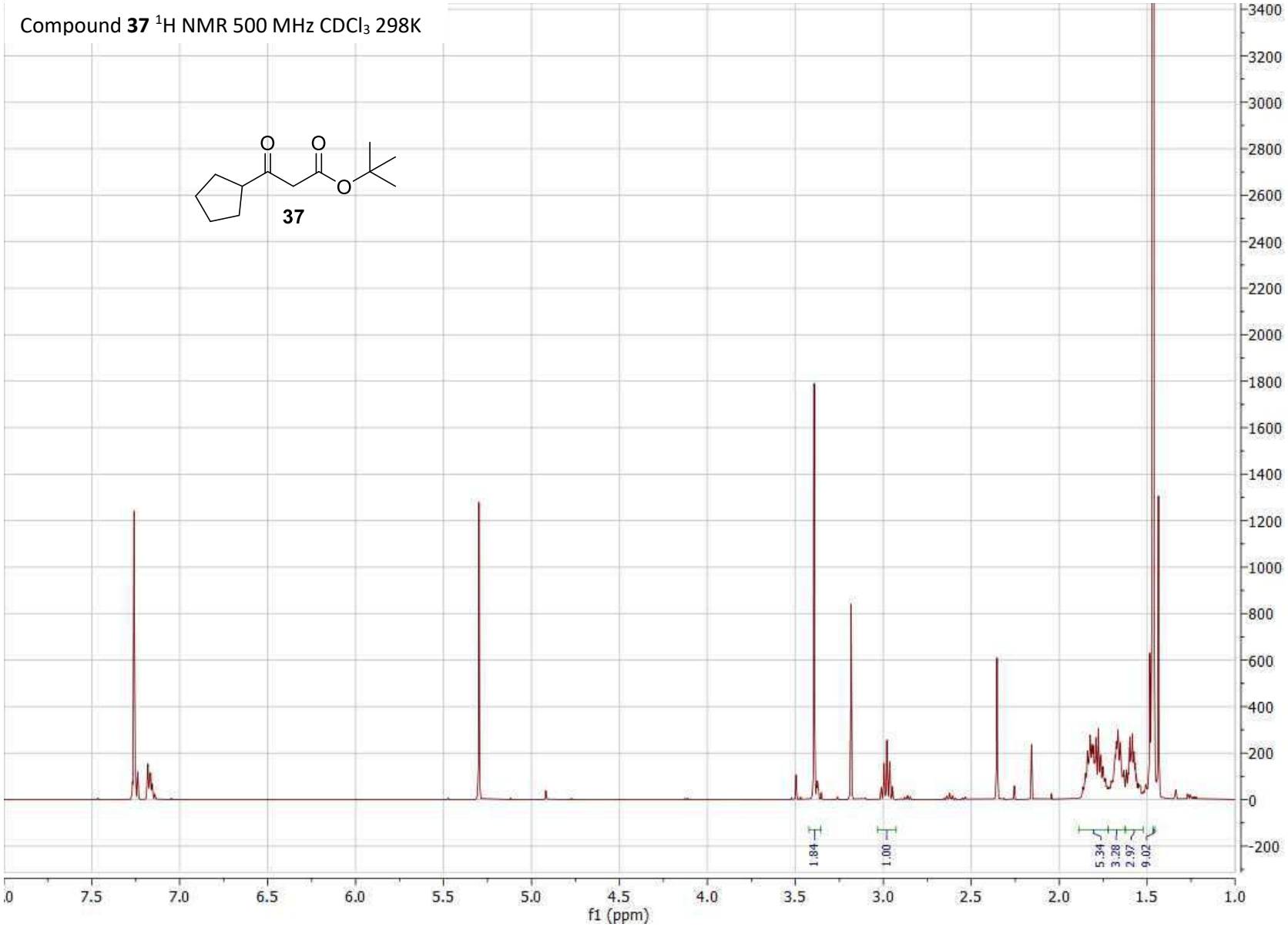


Figure S112. ^{1}H NMR of compound **37**

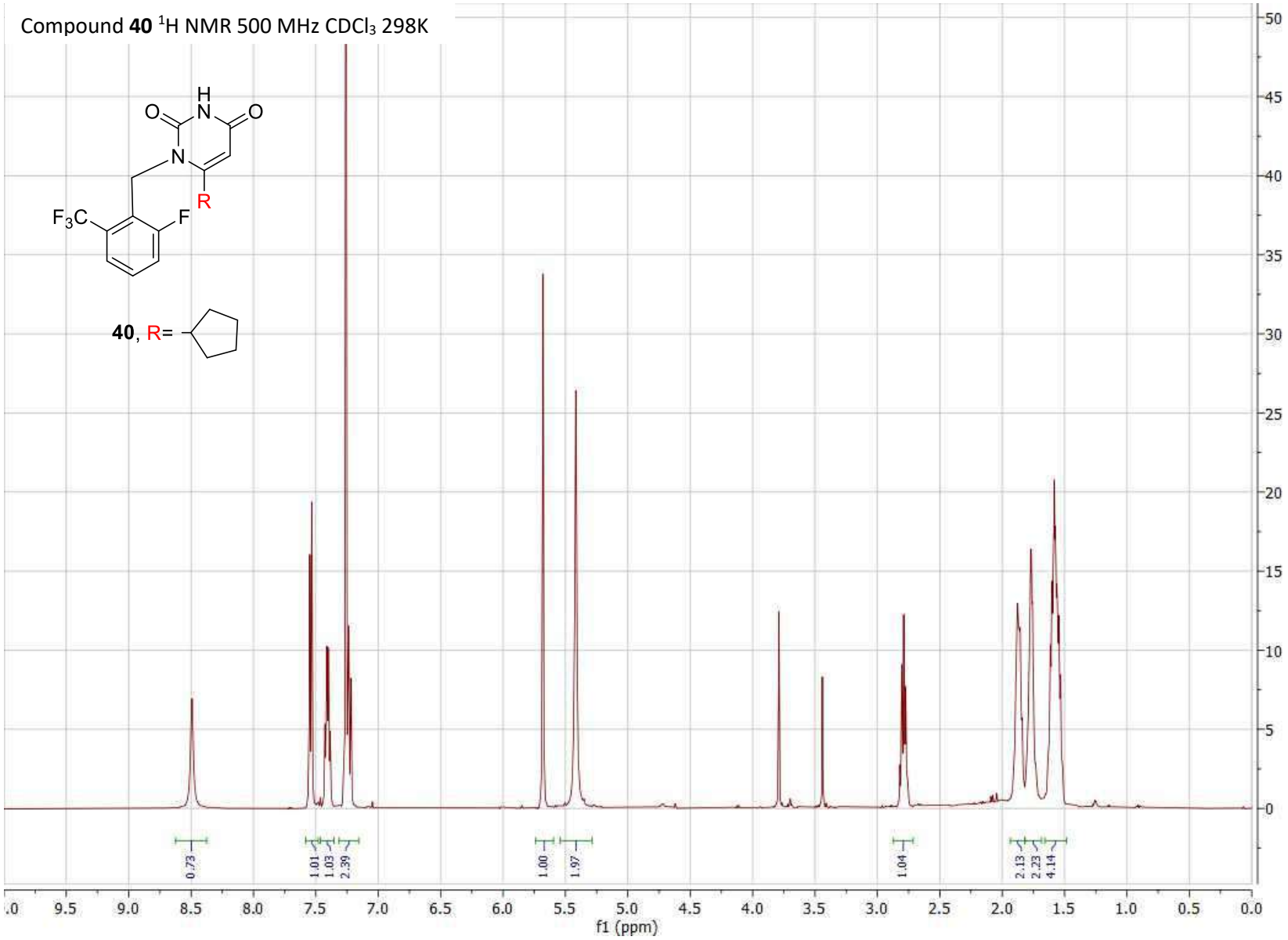


Figure S113. ^{1}H NMR of compound **40**

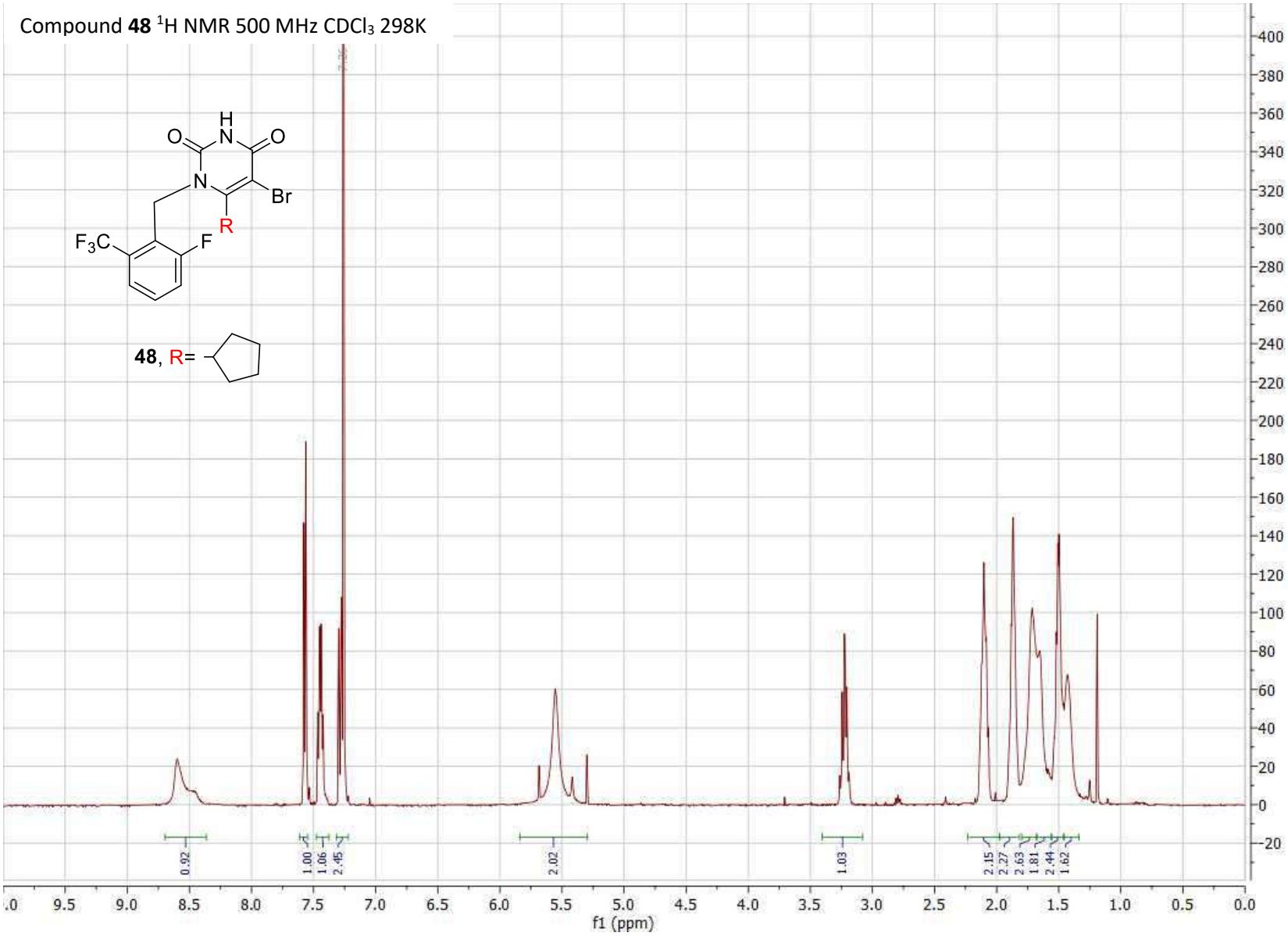


Figure S114. ^{1}H NMR of compound **48**

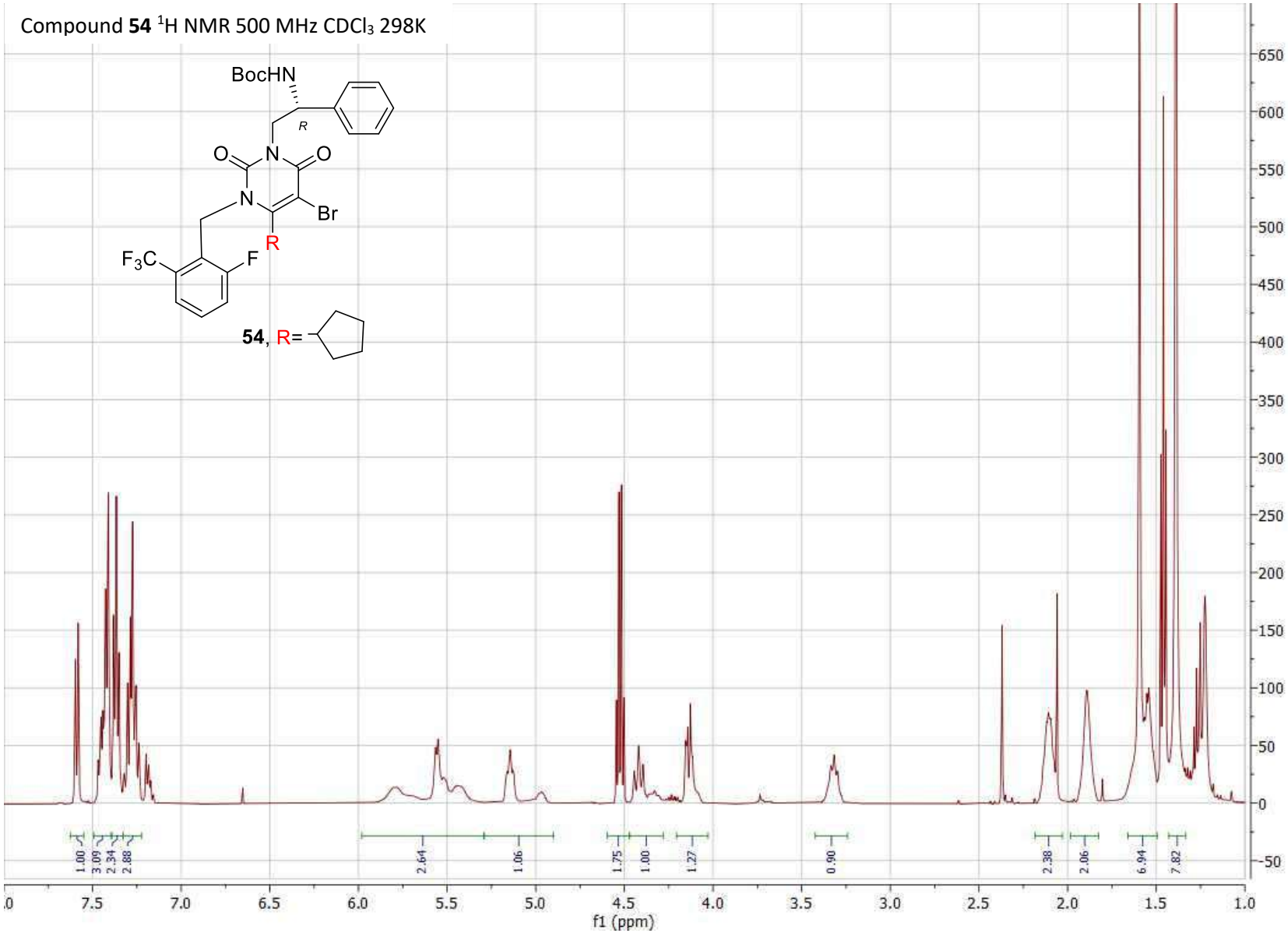


Figure S115. ^{1}H NMR of compound **54**

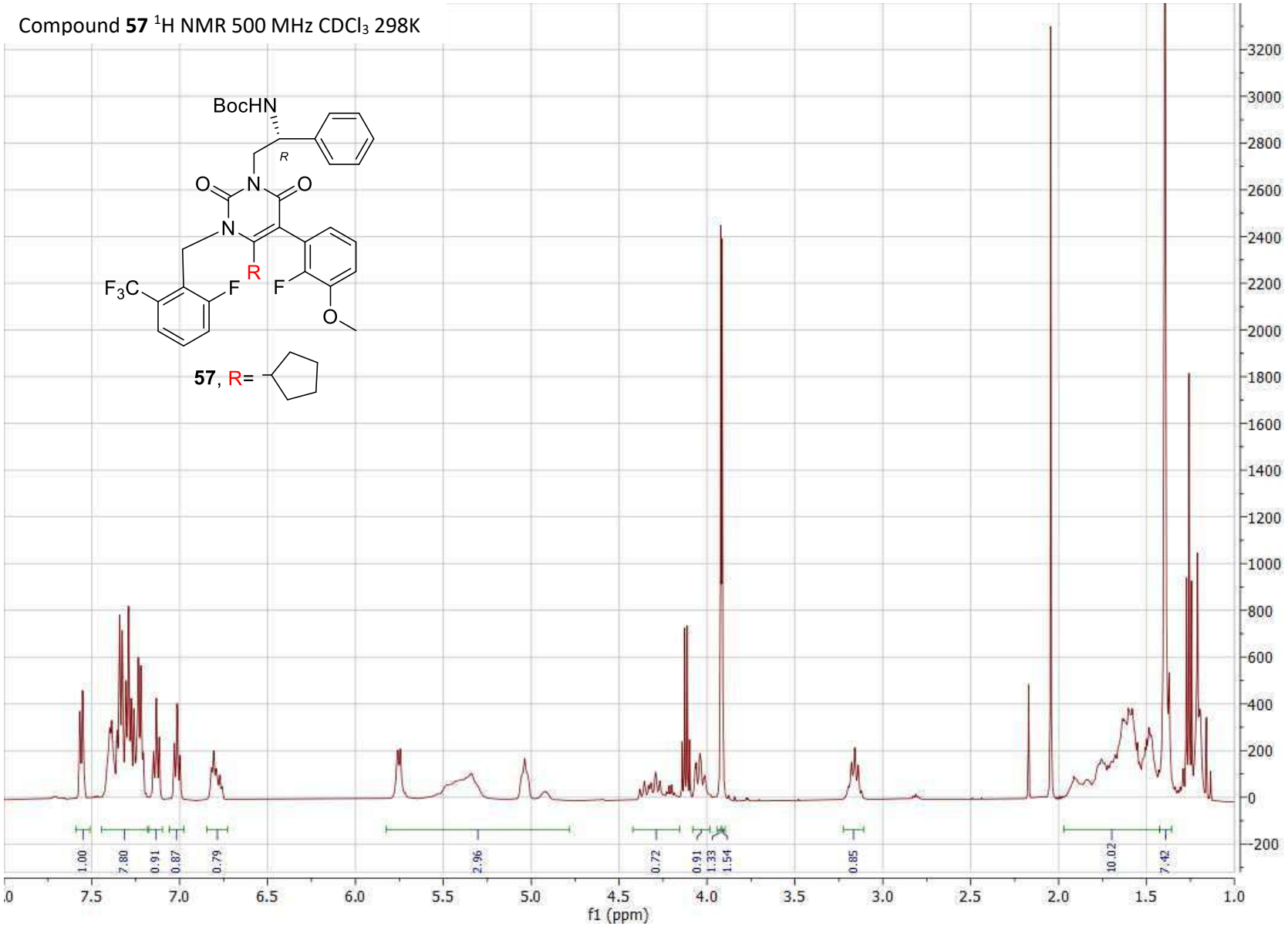


Figure S116. ^{1}H NMR of compound **57**

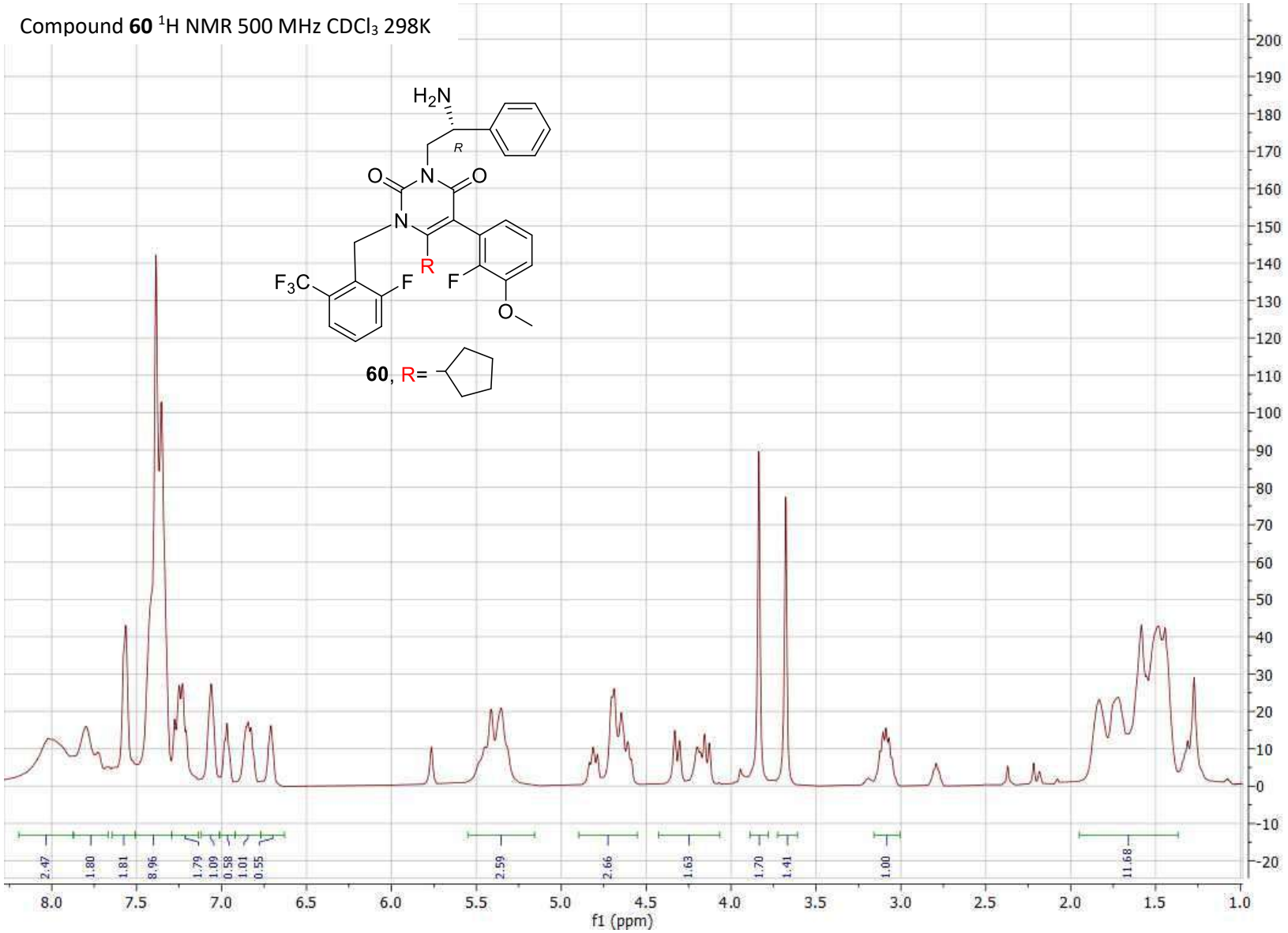


Figure S117. [1]H NMR of compound **60**

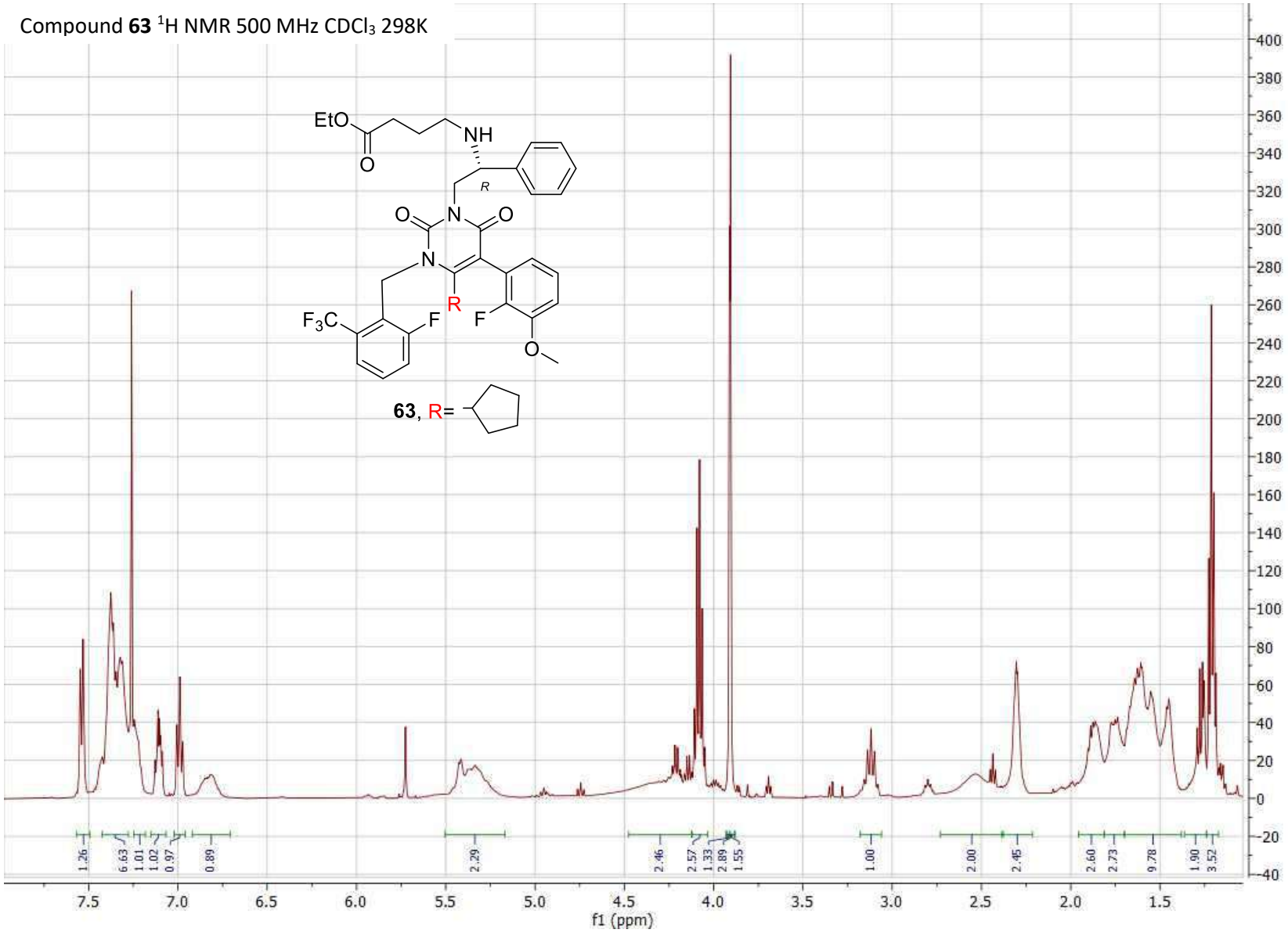


Figure S118. ^{1}H NMR of compound **63**

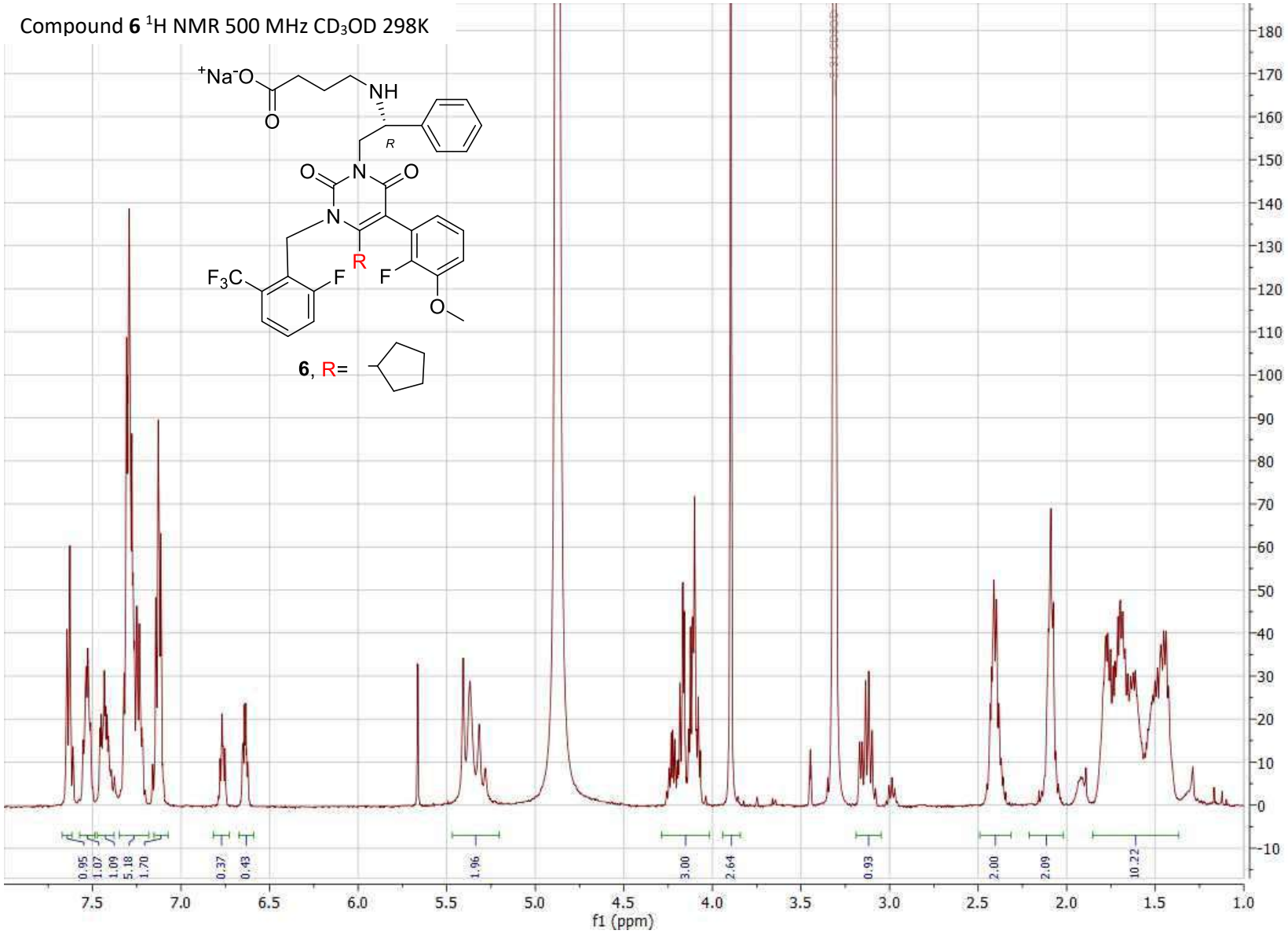


Figure S119. ^{1}H NMR of compound **6**

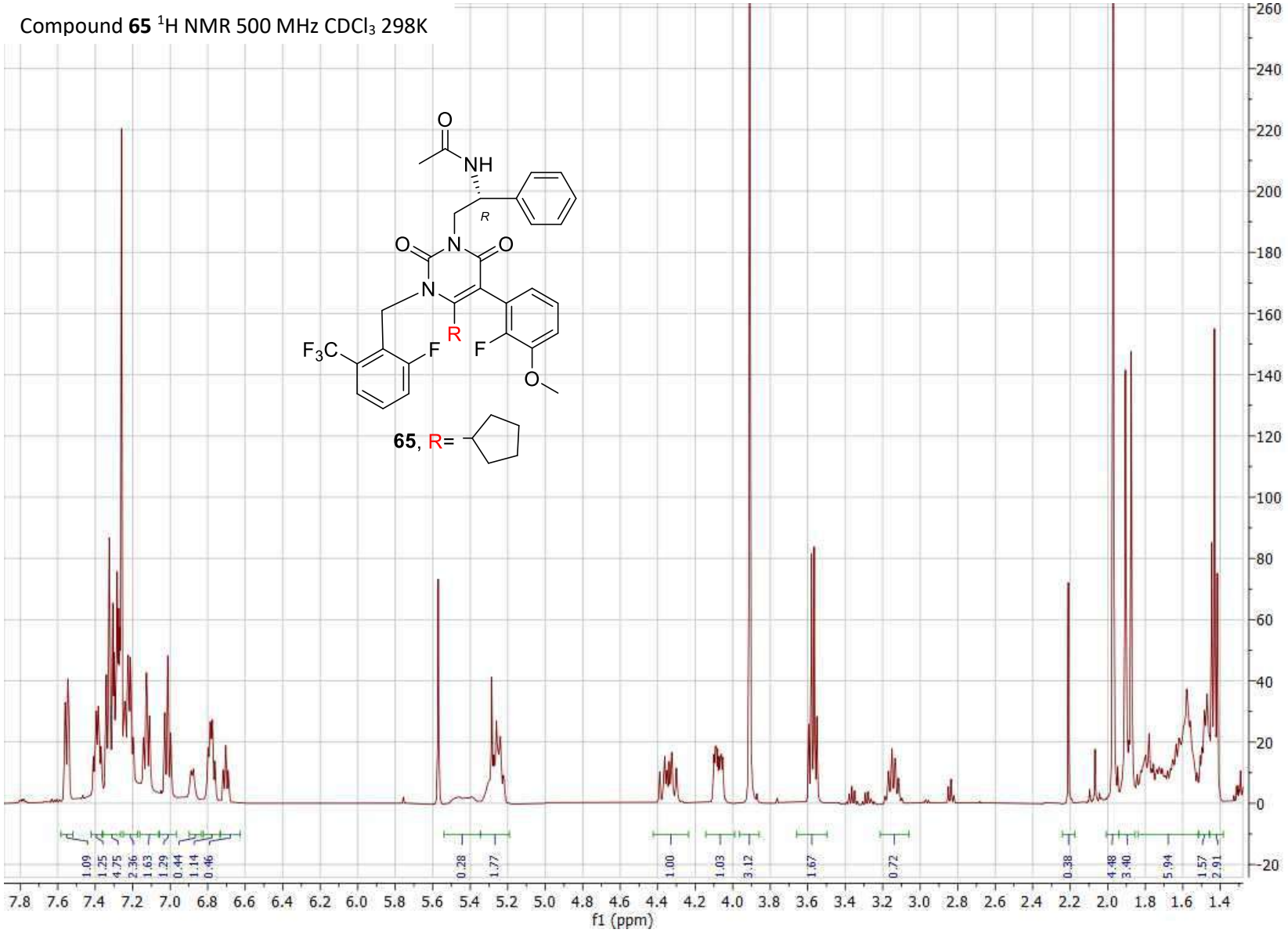


Figure S120. ^{1}H NMR of compound **65**

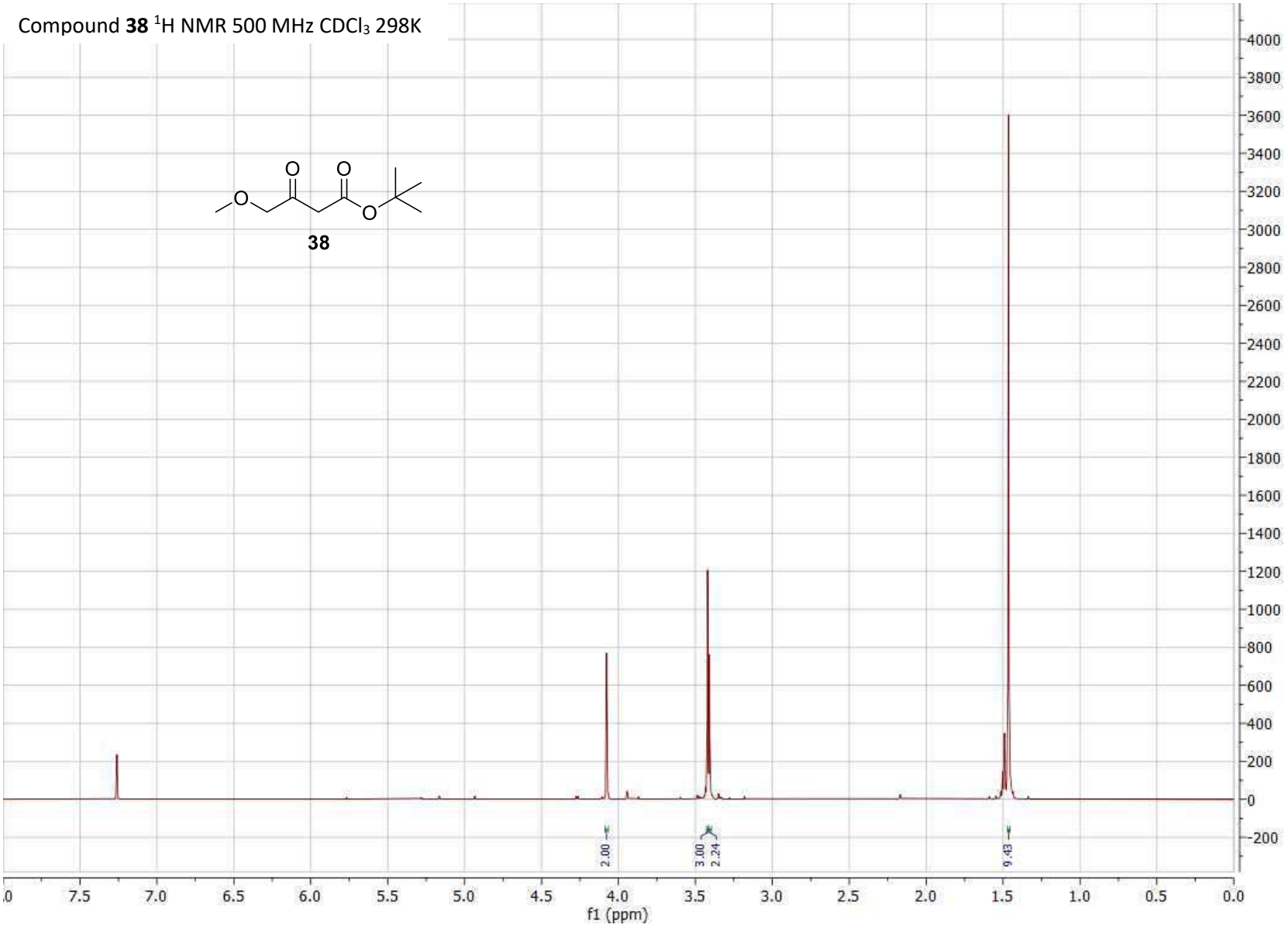


Figure S121. ^{1}H NMR of compound **38**

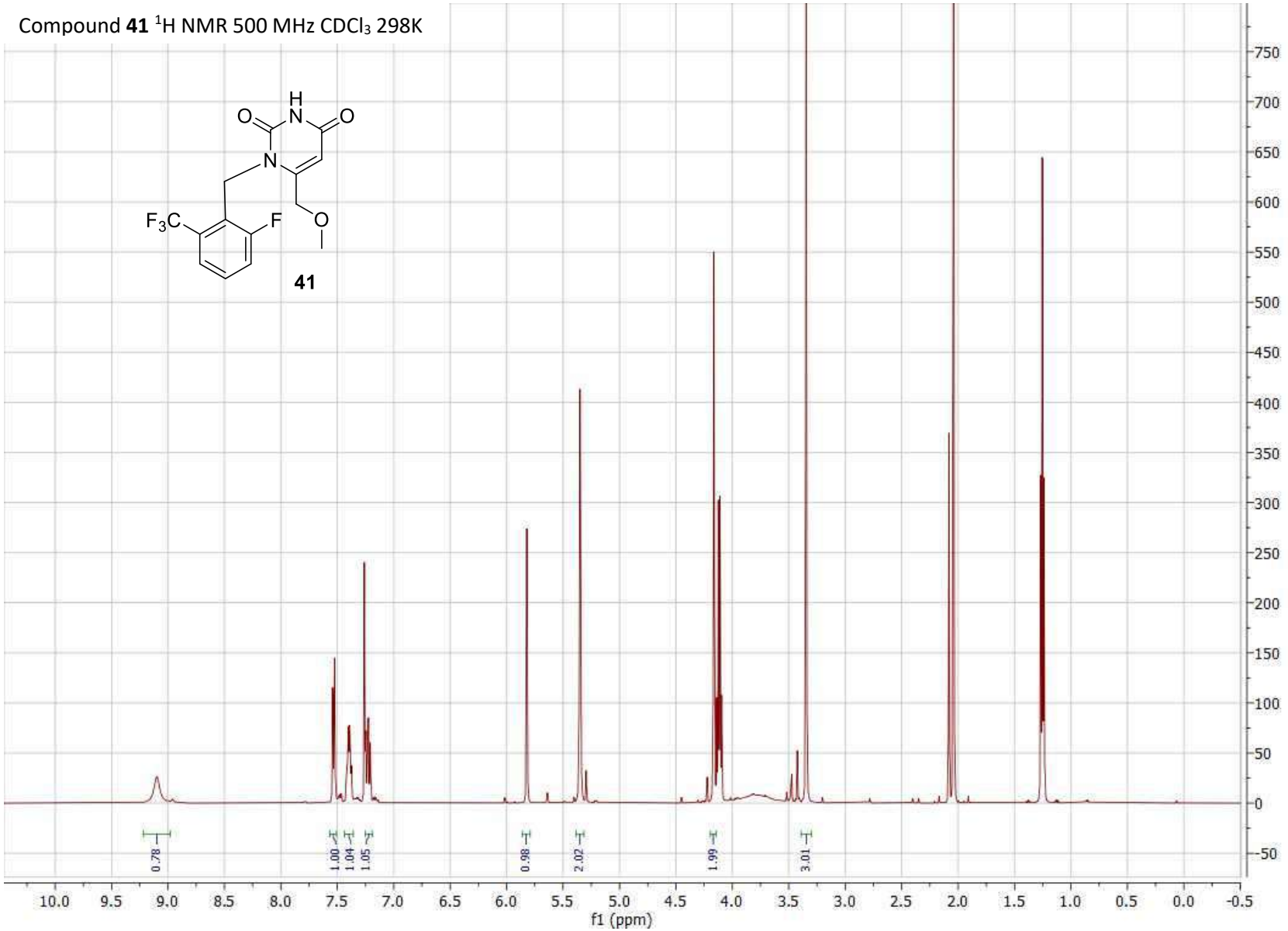


Figure S122. ^{1}H NMR of compound **41**

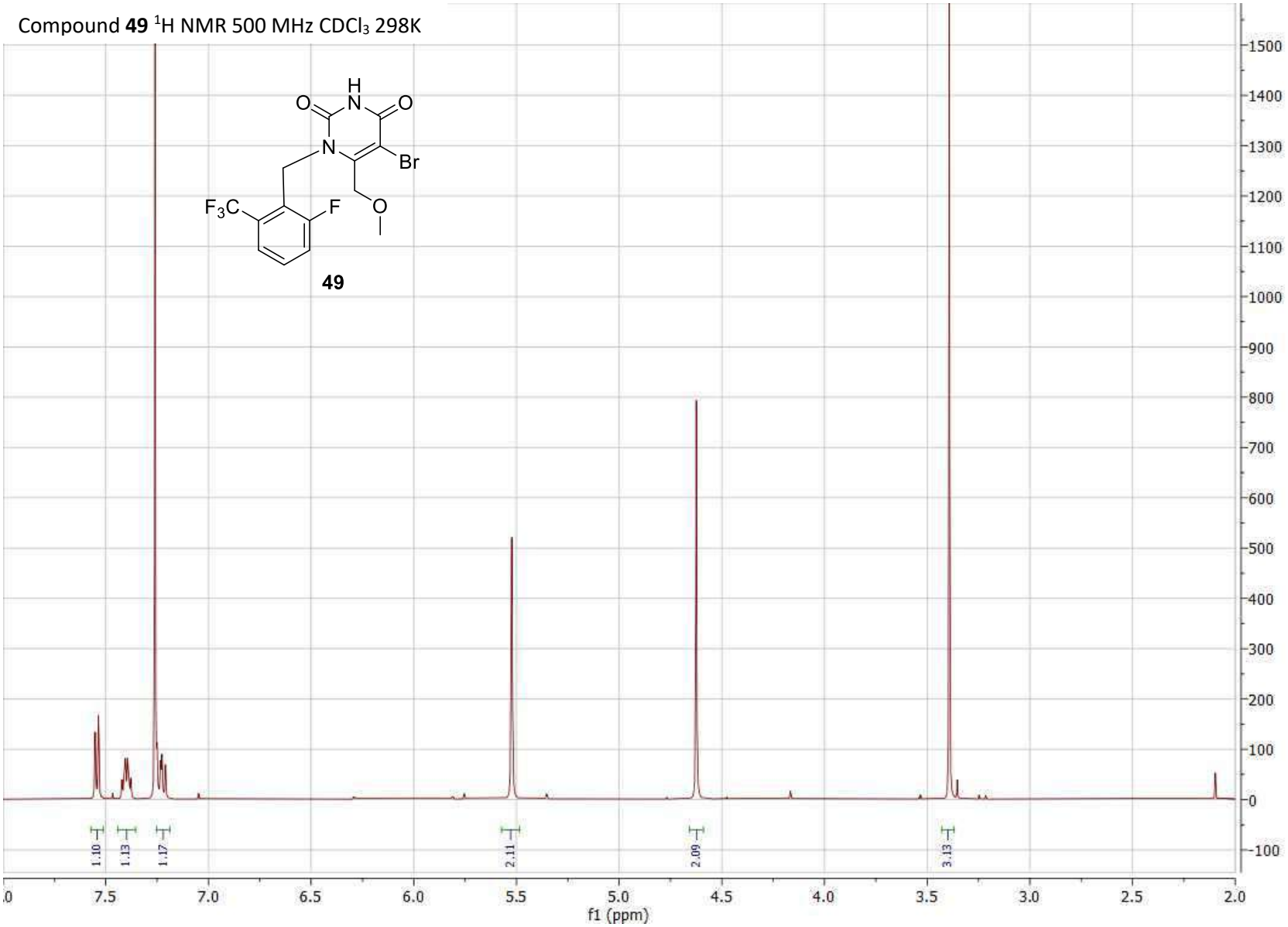


Figure S123. ^{1}H NMR of compound **49**

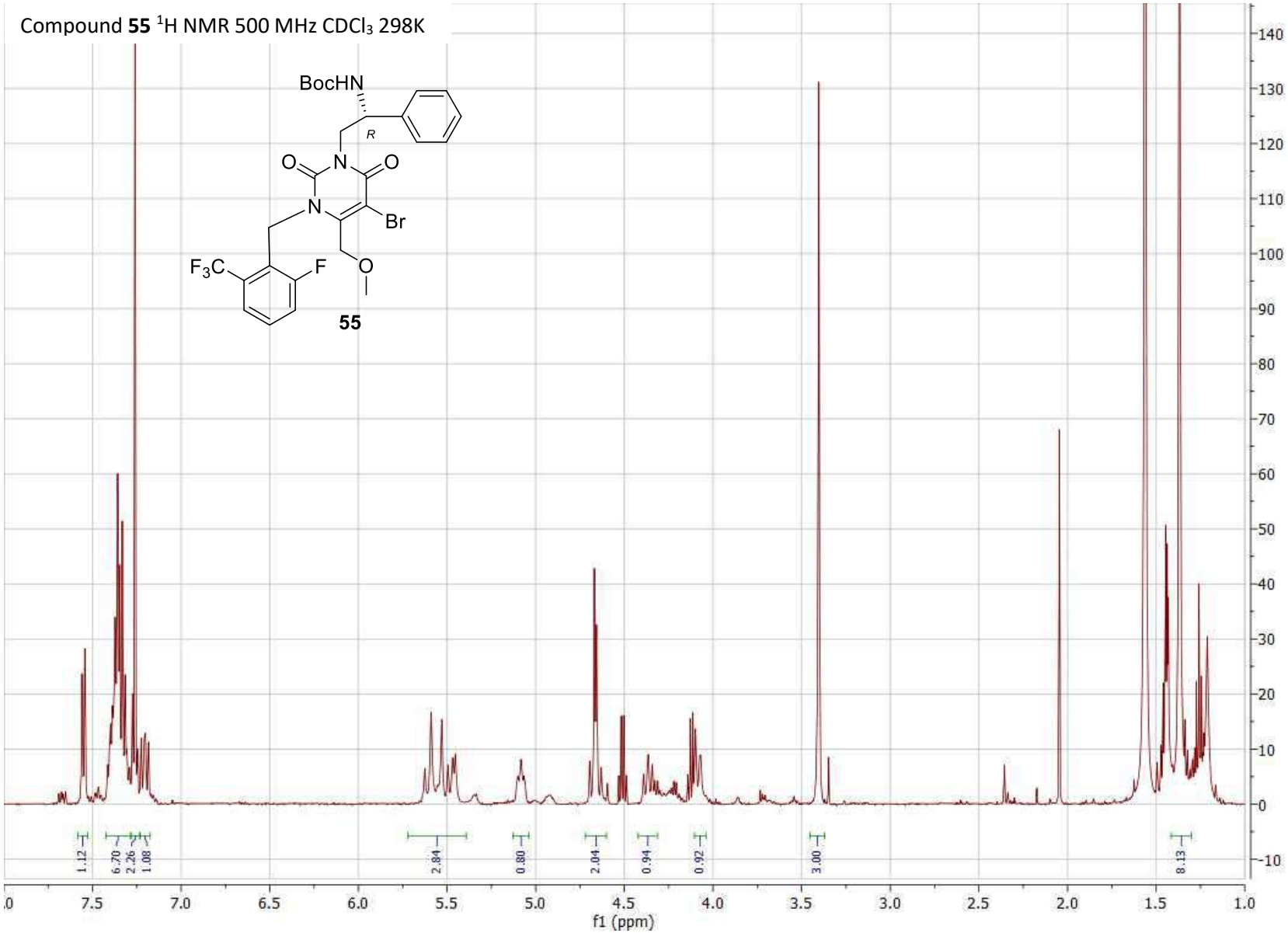


Figure S124. ^{1}H NMR of compound **55**

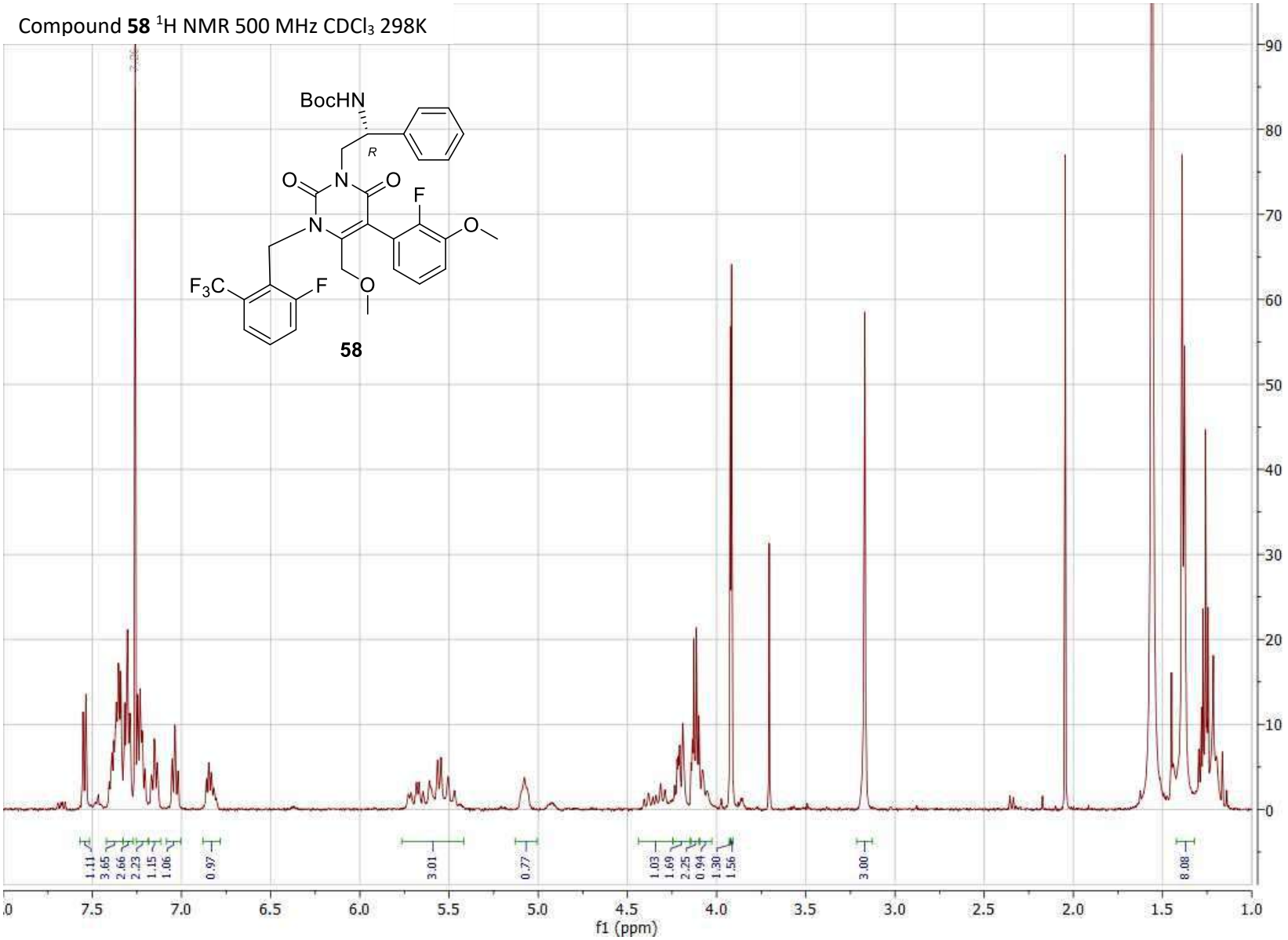


Figure S125. [1]H NMR of compound **58**

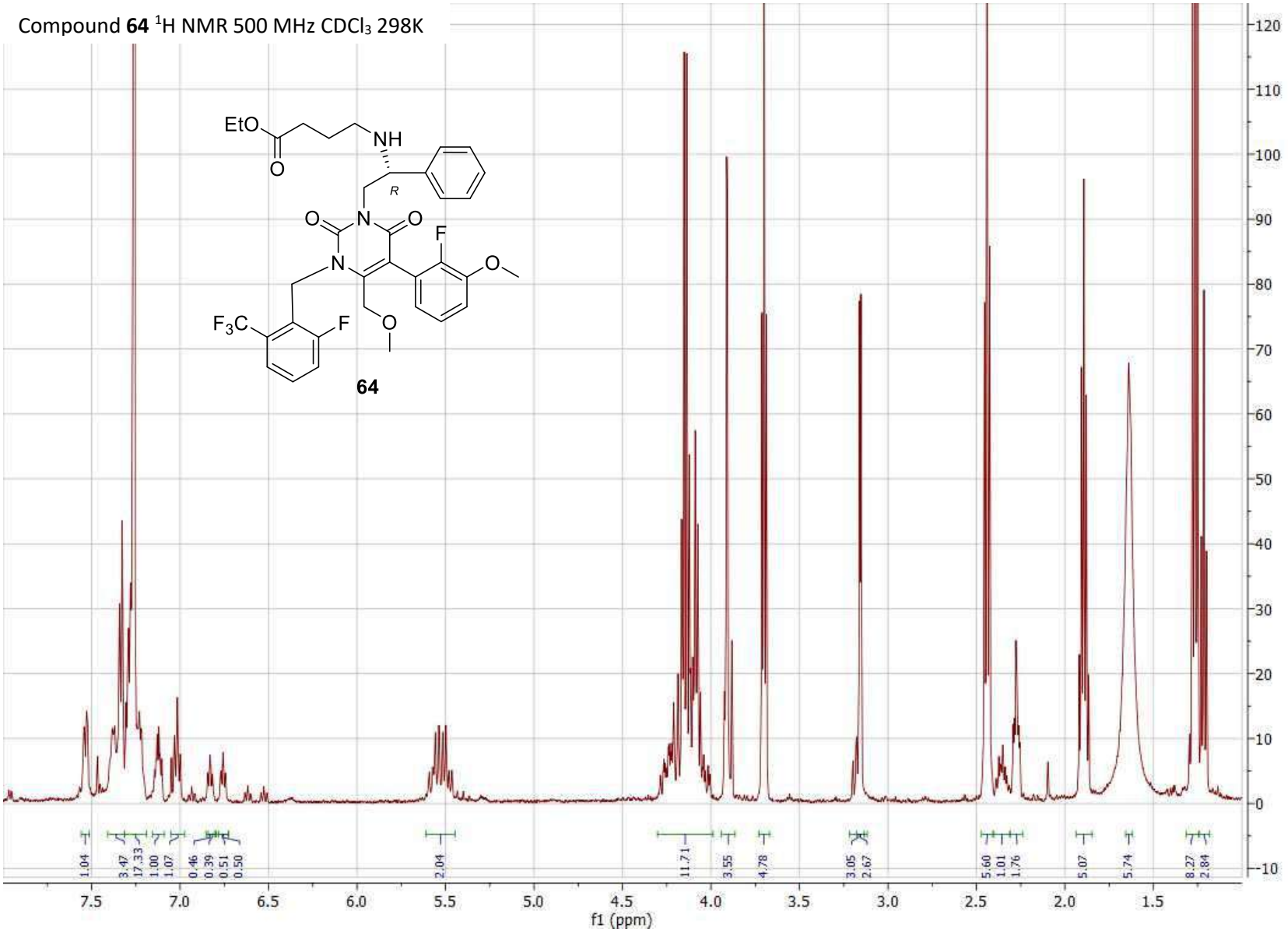


Figure S126. [1]H NMR of compound **64**

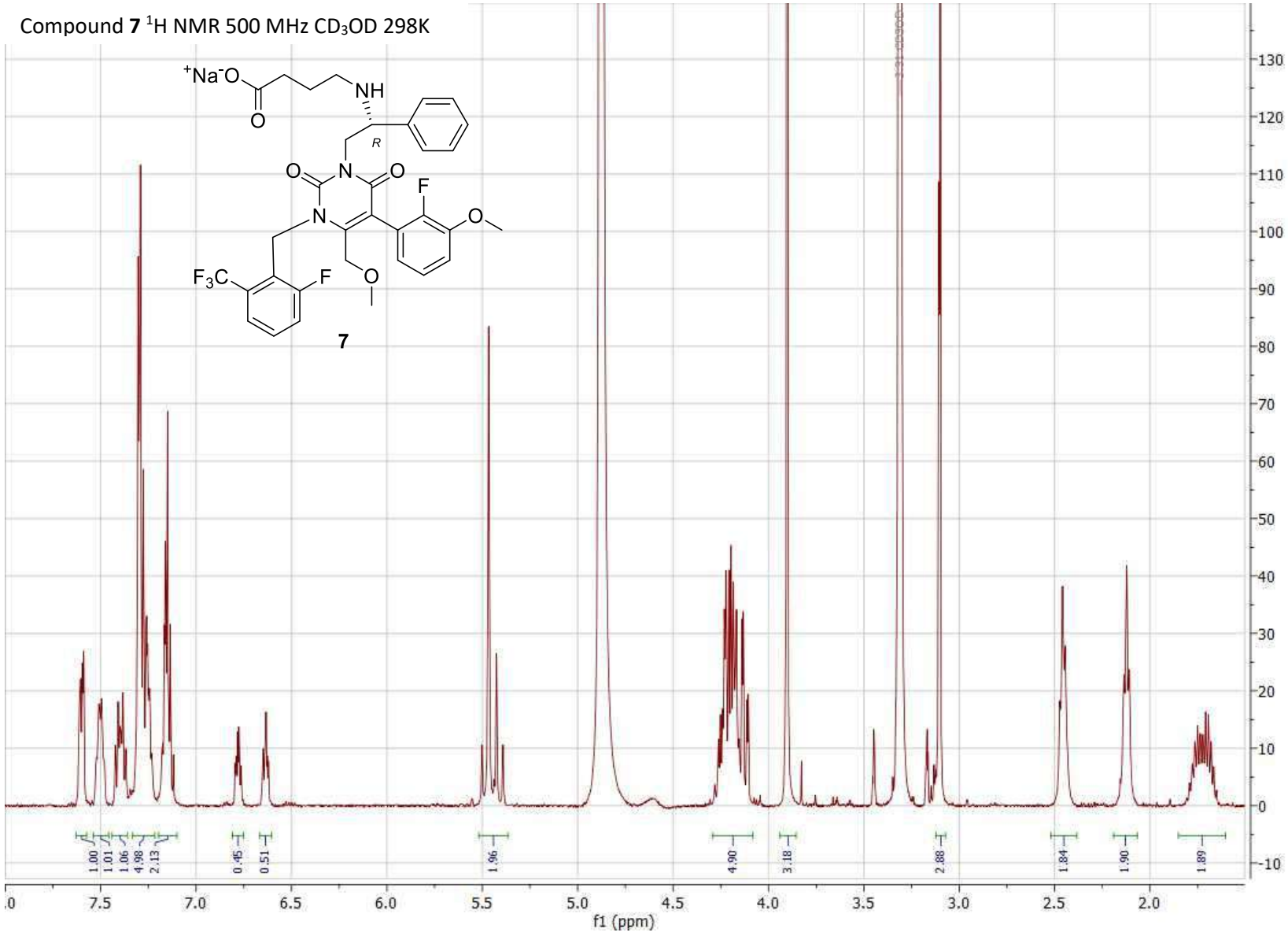


Figure S127. [1]H NMR of compound **7**

Modifications at the 21-position

Compound **14** ^{1}H NMR 500 MHz $CDCl_3$ 298K

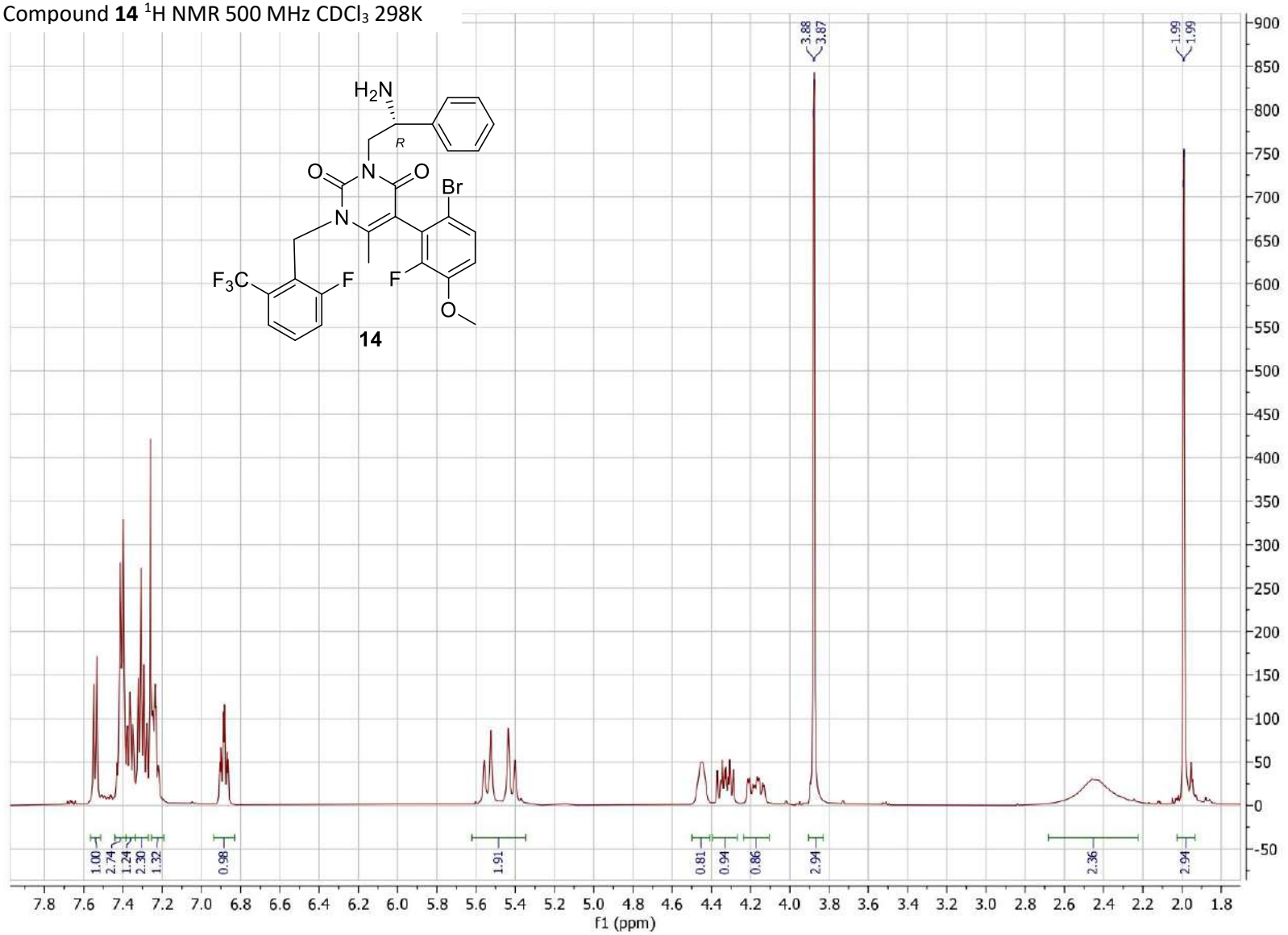


Figure S128. ^{1}H NMR of compound **14**

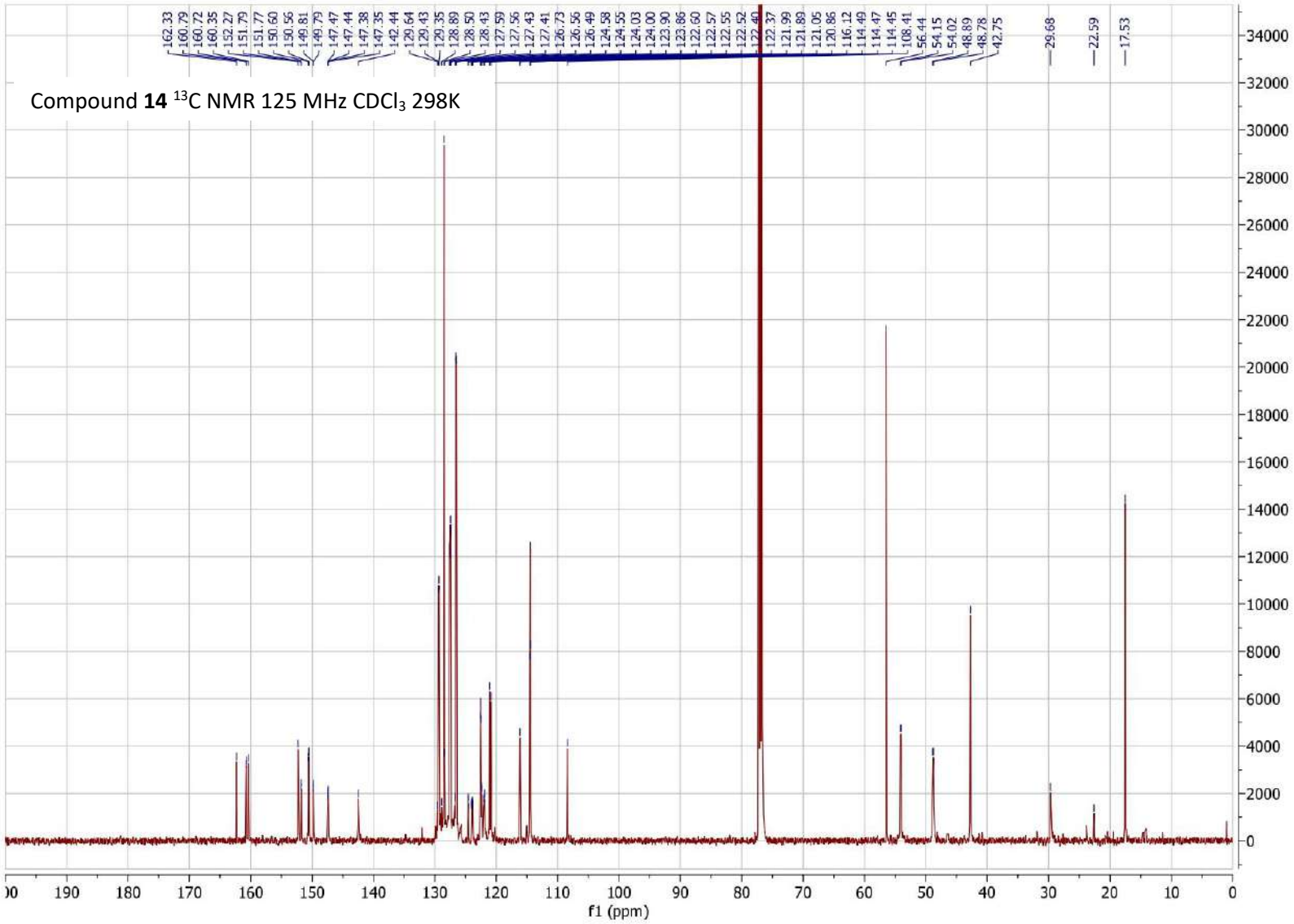


Figure S129. ^{13}C NMR of compound **14**

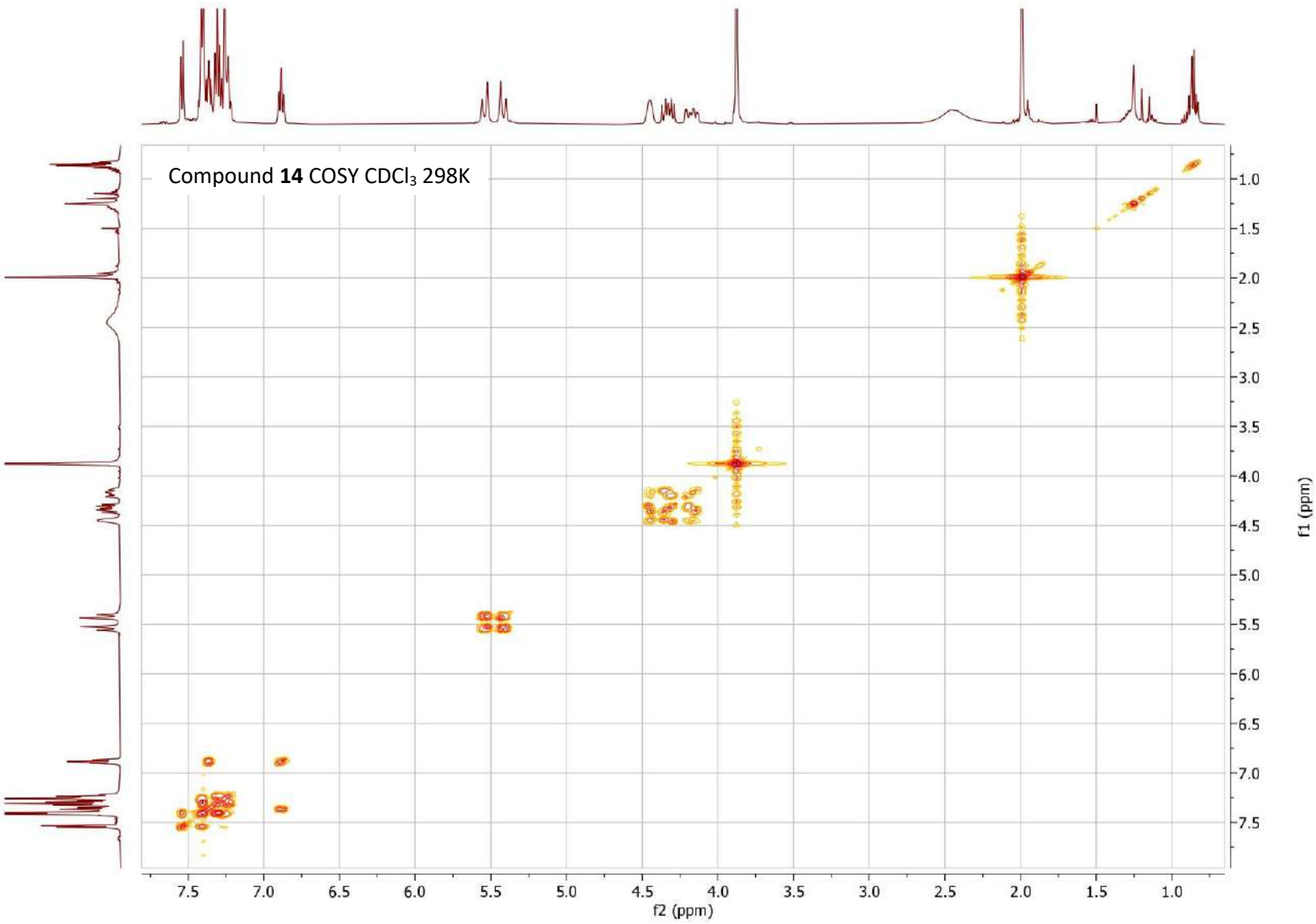


Figure S130. COSY of compound **14**

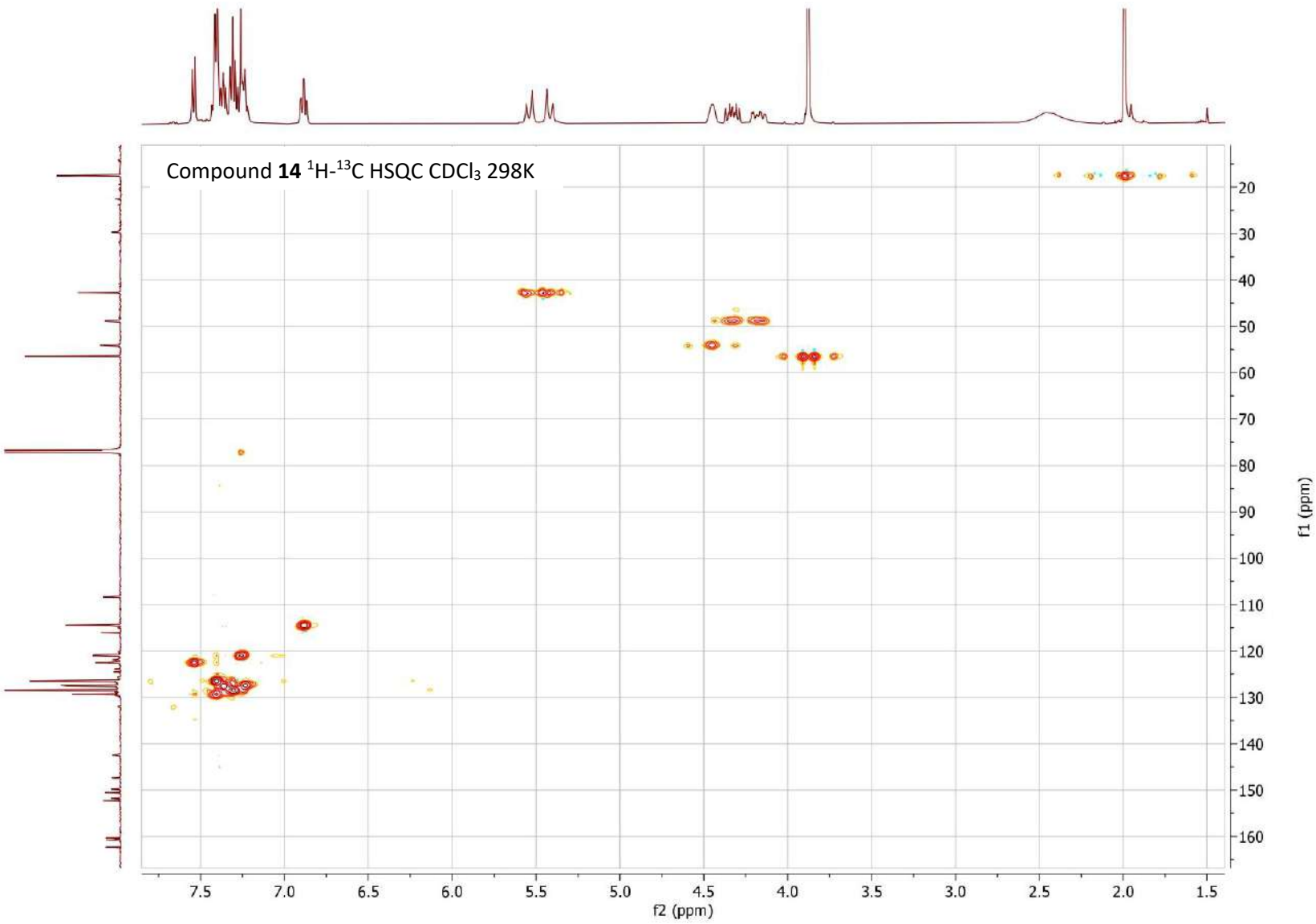


Figure S131. ^{1}H-^{13}C HSQC of compound **14**

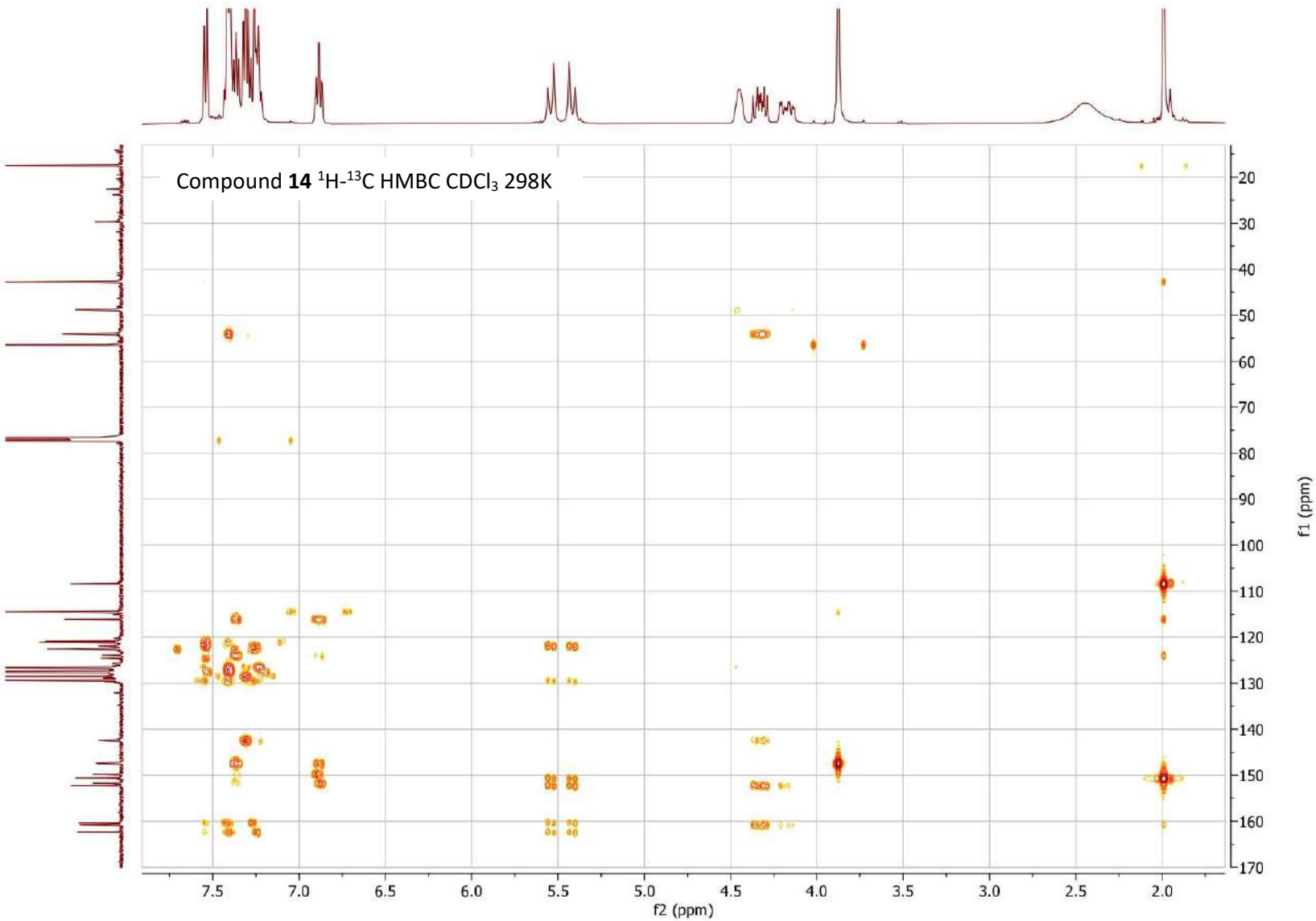
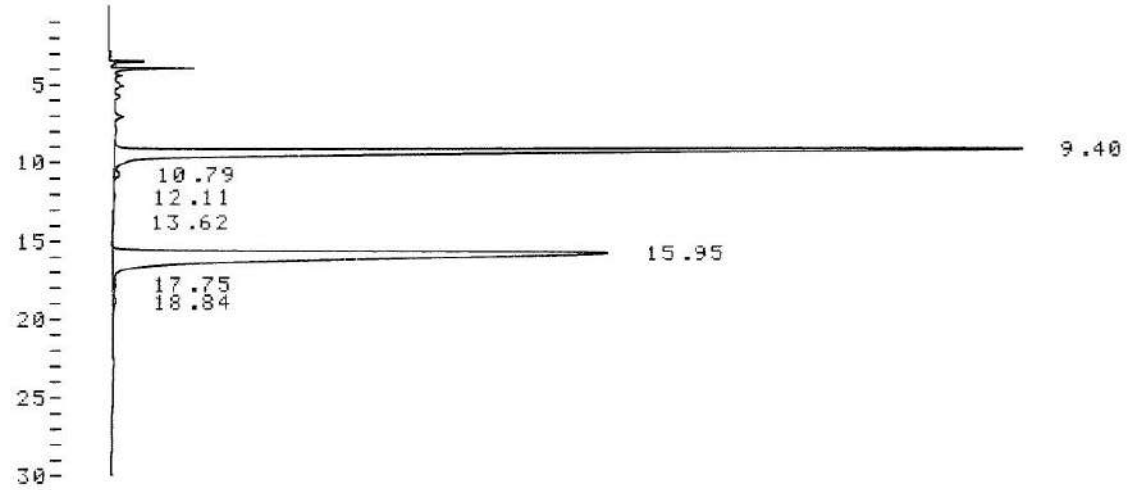


Figure S132. ^{1}H-^{13}C HMBC of compound **14**



D-2500

METHOD: TAG: 2 CH: 1

FILE: 0 CALC-METHOD: AREA% TABLE: 0 CONC: AREA

NO.	RT	AREA	CONC	BC
1	9.40	2205007	49.374	BV
2	10.79	13245	0.297	TBB
3	12.11	8950	0.200	BB
4	13.62	3625	0.081	BB
5	15.95	2220043	49.710	BV
6	17.75	5248	0.118	TBB
7	18.84	9830	0.220	TBB
TOTAL		4465948	100.000	

PEAK REJ : 0

Figure S133. Chiral HPLC analysis of compound **14**

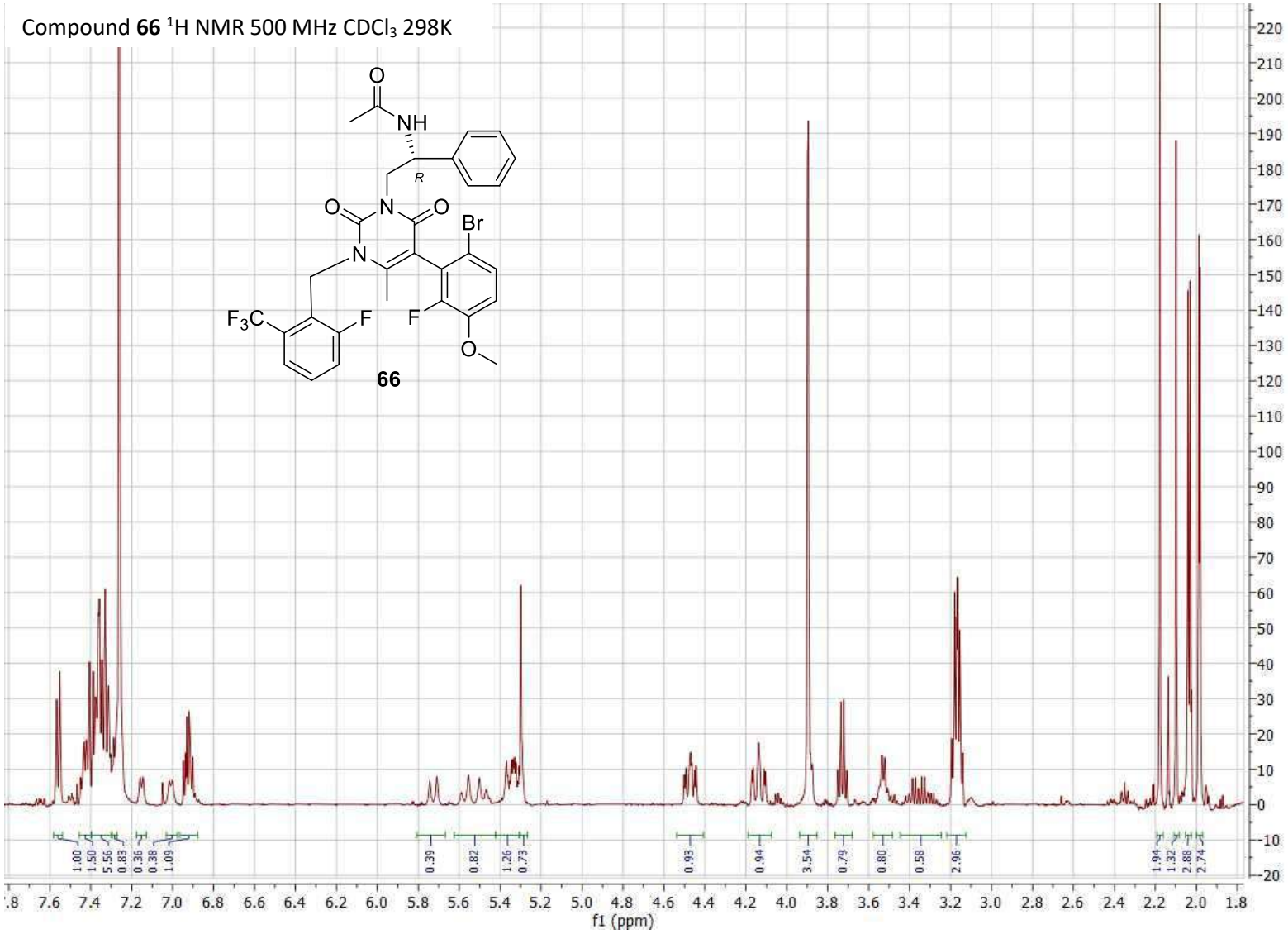
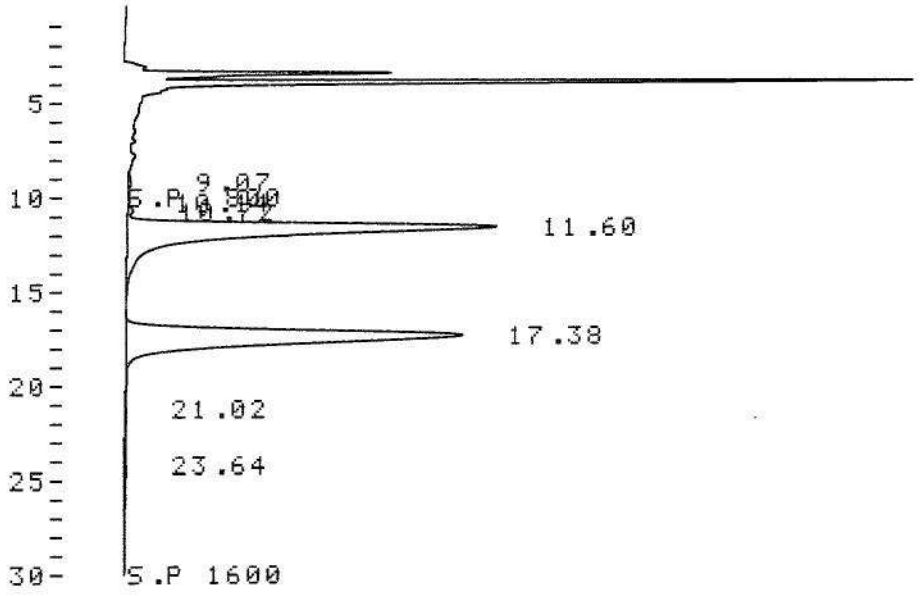


Figure S134. ^{1}H NMR of compound **66**



D-2500

METHOD: TAG: 5 CH: 1

FILE: 0 CALC-METHOD: AREA% TABLE: 0 CONC: AREA

NO.	RT	AREA	CONC	BC
1	9.07	3618	0.209	BB
2	10.14	864	0.050	BV
3	10.72	5573	0.322	VV
4	11.60	835360	48.209	VB
5	17.38	875953	50.552	BV
6	21.02	2831	0.163	TBB
7	23.64	8581	0.495	TBB
TOTAL		1732780	100.000	

PEAK REJ : 0

Figure S135. Chiral HPLC analysis of compound **66**

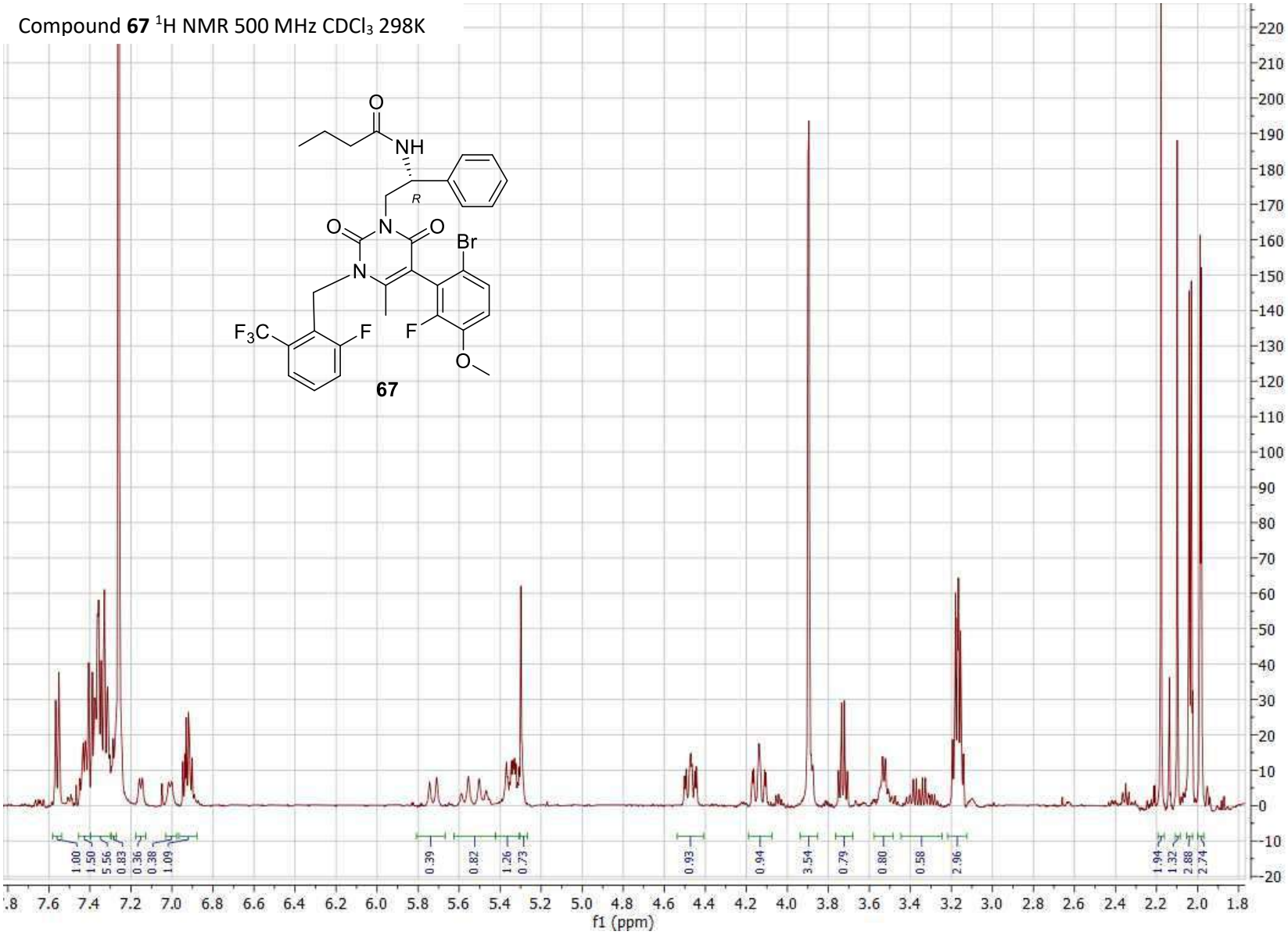
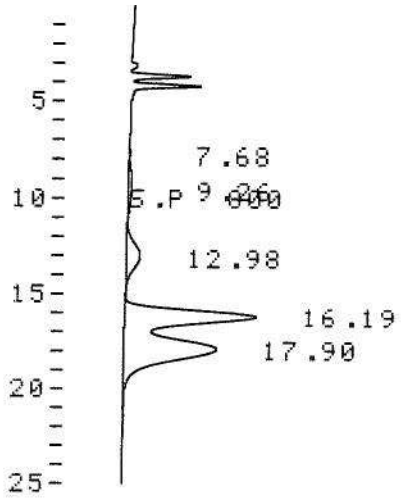


Figure S136. ^{1}H NMR of compound **67**



D-2500

METHOD: TAG: 2 CH: 1

FILE: 0 CALC-METHOD: AREA% TABLE: 0 CONC: AREA

NO.	RT	AREA	CONC	BC
1	7.68	825	0.105	BB
2	9.26	15576	1.979	BB
3	12.98	64674	8.215	BB
4	16.19	336024	42.684	BV
5	17.90	370132	47.017	VB
TOTAL		787231	100.000	

PEAK REJ : 0

Figure S137. Chiral HPLC analysis of compound **67**