

Supporting Information for:

Modulation of Amide Bond Rotamers in 5-Acyl-6,7-dihydrothieno[3,2-*c*]pyridines.

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1. NMR Analysis of Conformational Characteristics

1.1. 1-(4-phenyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)ethanone (**1**)

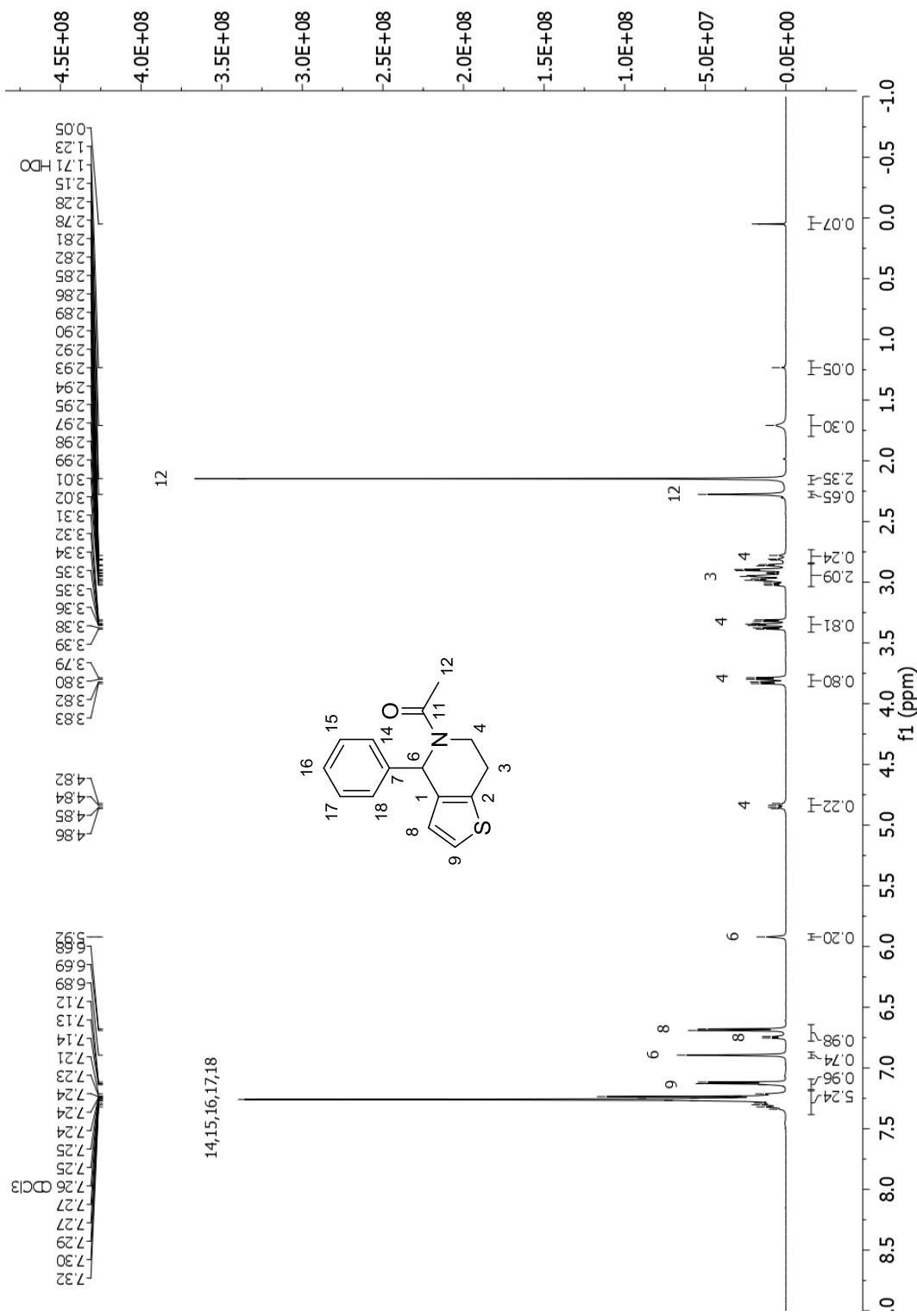


Figure S1. ^1H NMR (500 MHz, CDCl_3) of **1**.

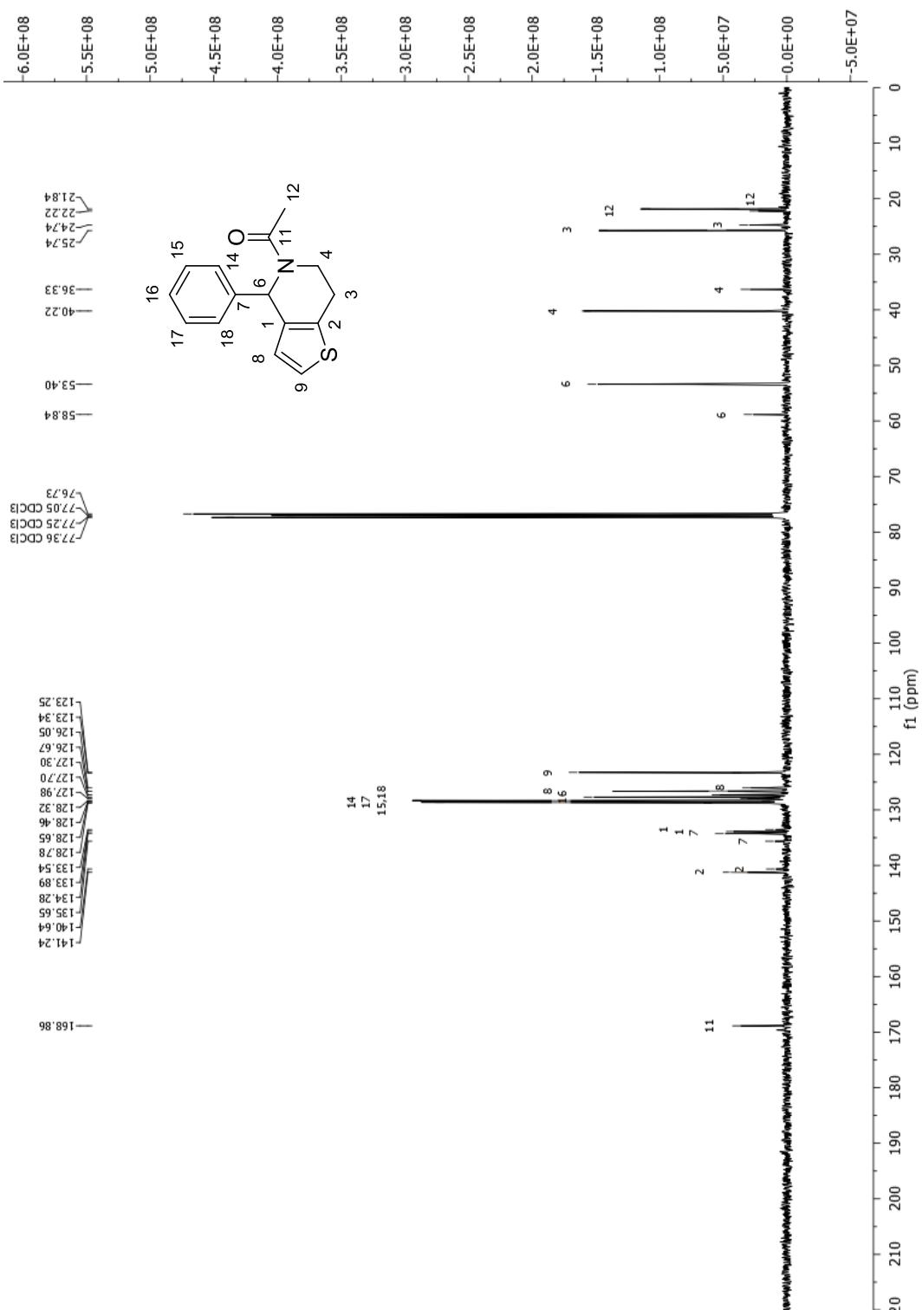


Figure S2. ^{13}C NMR (400 MHz, CDCl_3) of 1.

1.1.1. Low Temperature 2D-NOESY and 1D Selective NOE of 1

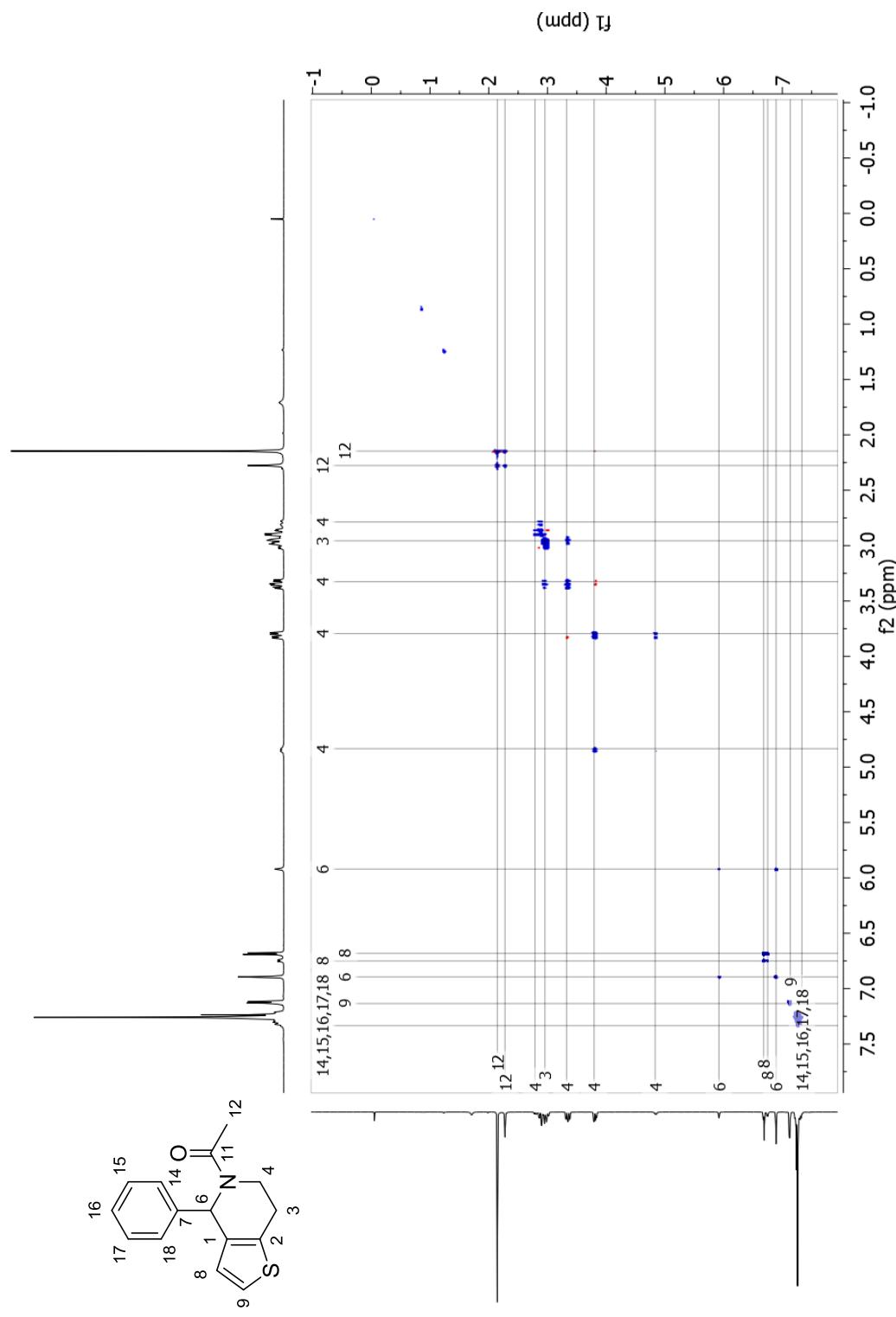


Figure S3. 2D-NOESY (400 MHz, CDCl₃) at 298 K of 1.

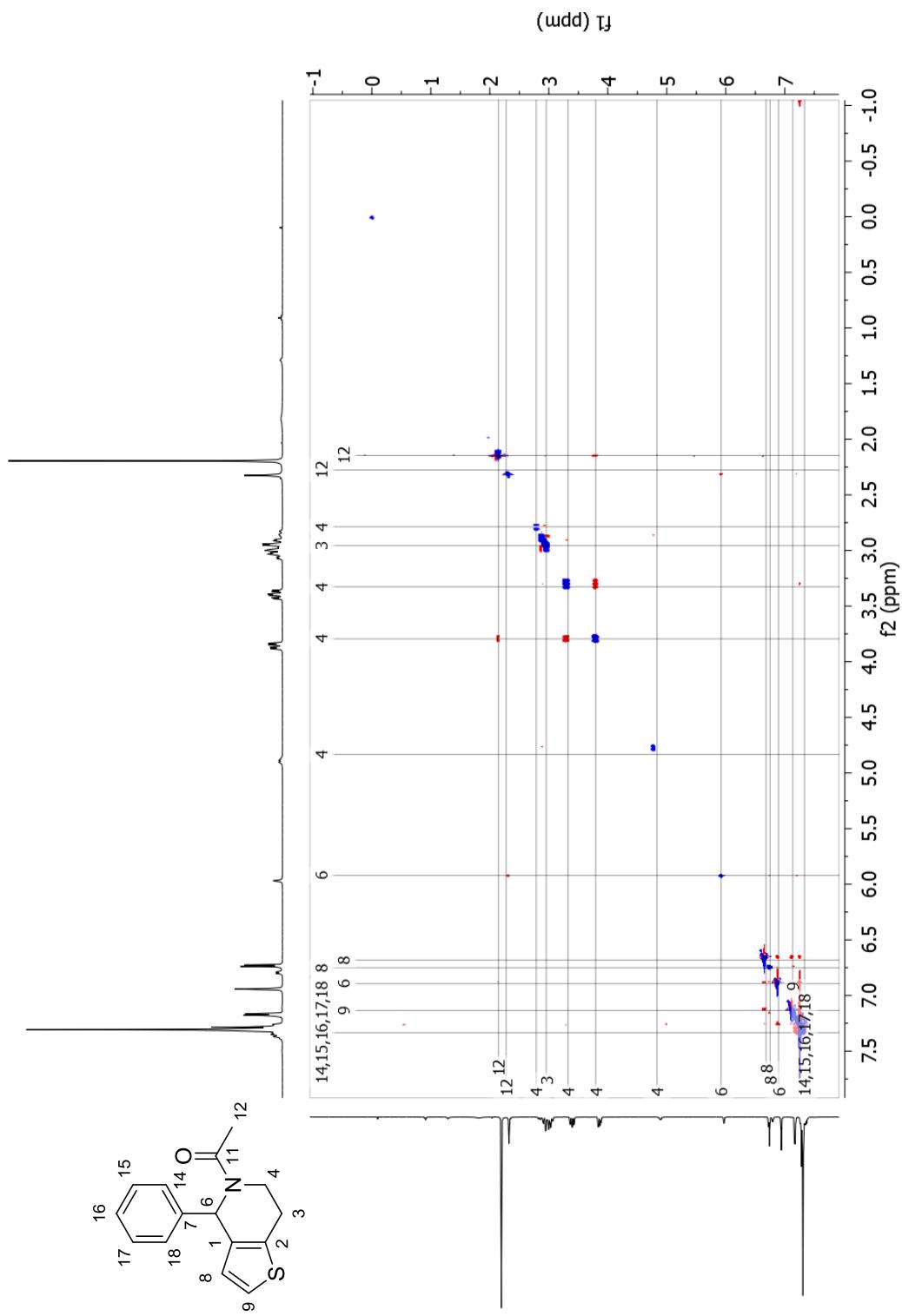


Figure S4. 2D-NOESY (400 MHz, CDCl₃) at 221 K of **1**.

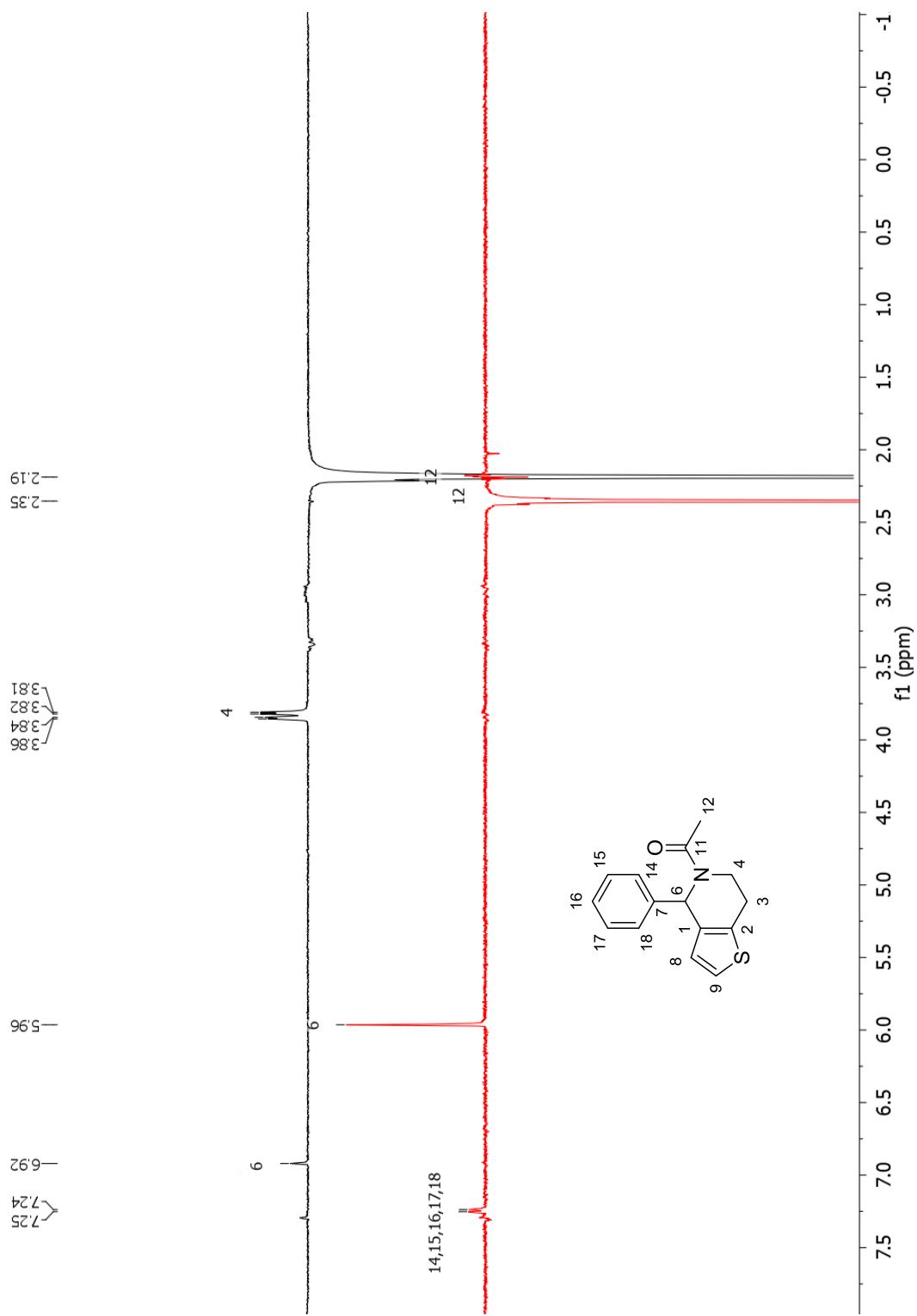


Figure S5. 1D selective NOE spectra of **1** at 2.19 ppm (black) and 2.35 ppm (red) (400 MHz, CDCl₃, 218 K).

1.1.2. Comparison of the Population of the *E*- and *Z*-Conformers of **1 Derived from Lowest Energy Calculations and NMR Measurements**

Table S1. Boltzmann population distribution of the *E*- and *Z*-conformers of **1** derived from the lowest energy calculations.

Energy Level No.	Conformation	Energy [kcal/mol]	Energy [J/mol]	Boltzmann Factor	Population (N_i/N_{total})	
					<i>E</i>	<i>Z</i>
1	<i>Z</i>	0.0	0.0	1.00		0.84
2	<i>E</i>	3.3	13807.2	0.00	0.00	
3	<i>Z</i>	3.5	14644.0	0.00		0.00
4	<i>E</i>	1.0	4184.0	0.18	0.16	
				Total	0.16	0.84

Table S2. Population of the *E*- and *Z*-conformers of **1** derived from the ^1H NMR.

Proton Nr.	Integral		Ratio (<i>E/Z</i>)
	<i>E</i>	<i>Z</i>	
4	0.22	0.81	0.27
6	0.20	0.74	0.27
8	0.22	0.78	0.28
12	0.65	2.35	0.28
	Average		0.28
	E		0.22
	Z		0.78

1.1.3. Comparison of Shifts from Lowest Energy Structure Calculations and ^1H NMR of 1

Table S3. Comparison of chemical shifts derived from the lowest energy structure calculations and the ^1H NMR spectrum of the Z-conformation of 1.

Proton-No.	Lowest Energy Structure Calculations [ppm] Level 1 (0.0 kcal/mol) 84%	^1H NMR Data of 1 [ppm]			Δ [ppm]
		From	To	Average	
3 (ax)	2.96	3.02	2.85	2.94	0.02
3 (eq)	2.71	3.02	2.85	2.94	0.23
4 (ax)	3.24	3.39	3.31	3.35	0.11
4 (eq)	3.57	3.83	3.79	3.81	0.24
6	7.06	6.89	6.89	6.89	0.17
7	6.90	6.75	6.74	6.74	0.17
8	7.37	7.13	7.12	7.13	0.26
	2.15				
12	2.05	2.01	2.15	2.15	0.14
	1.84				
14	8.29	7.34	7.21	7.28	1.01
15	7.78	7.34	7.21	7.28	0.50
16	7.67	7.34	7.21	7.28	0.39
17	7.59	7.34	7.21	7.28	0.31
18	7.17	7.34	7.21	7.28	0.11

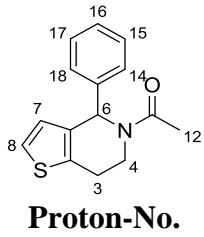


Table S4. Comparison of chemical shifts derived from the lowest energy structure calculations and the ^1H NMR spectrum of the *E*-conformation of **1**.

Proton-No.	Chemical Structure with Proton Labels	<u>Lowest Energy Structure Calculations [ppm]</u>		<u>^1H NMR Data of 1 [ppm]</u>			Δ [ppm]
		Level 1 (0.0 kcal/mol)	16%	From	To	Average	
3 (ax)	2.93			3.02	2.85	2.94	0.01
3 (eq)	2.57			3.02	2.85	2.94	0.37
4 (ax)	2.62			2.82	2.78	2.80	0.18
4 (eq)	4.38			4.86	4.82	4.84	0.46
6	6.09			5.92	5.92	5.92	0.17
7	6.92			6.75	6.74	6.75	0.18
8	7.4			7.15	7.14	7.15	0.26
	1.99						
12	2.75	2.36		2.28	2.28	2.28	0.08
	2.33						
14	8.02			7.34	7.21	7.28	0.74
15	7.81			7.34	7.21	7.28	0.53
16	7.69			7.34	7.21	7.28	0.41
17	7.61			7.34	7.21	7.28	0.33
18	7.12			7.34	7.21	7.28	0.16

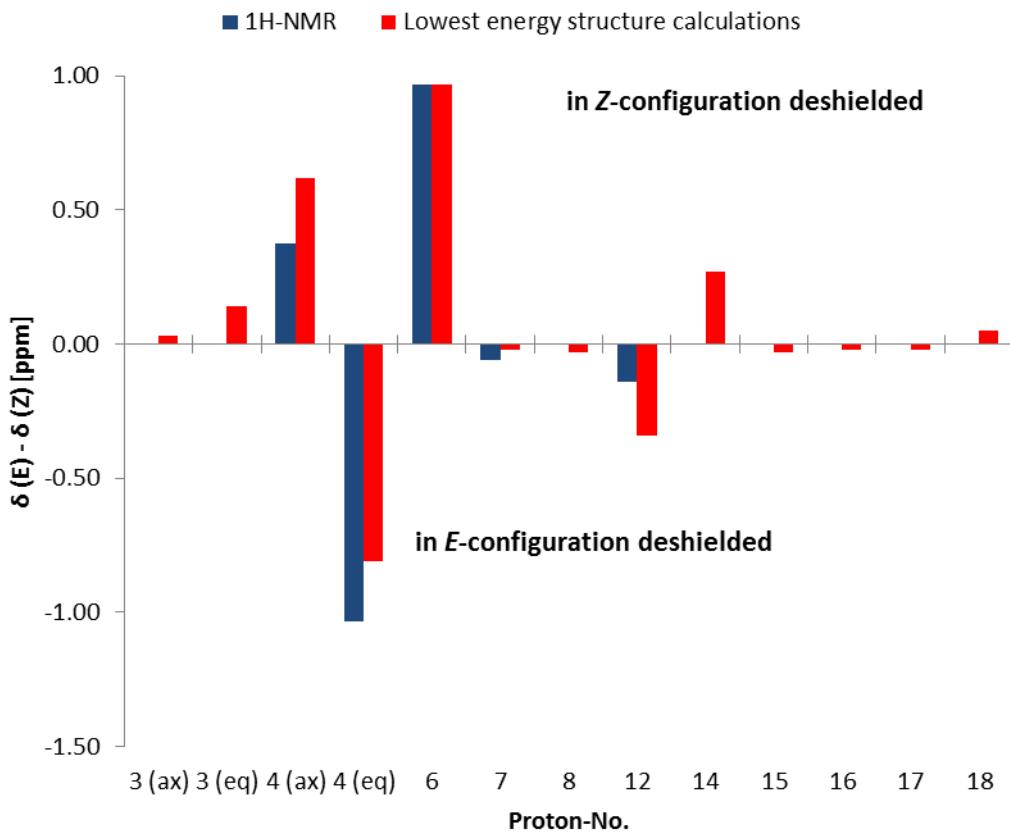


Figure S6. Differences between the chemical shifts of all protons of the *E*- and the *Z*-conformation of **1** derived from the ^1H NMR spectrum and the lowest energy structure calculations, respectively. The protons are deshielded in the *Z*-conformation in the case of positive values and deshielded in the *E*-conformation in the case of negative values.

1.2. 1-[4-(3-methylphenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl]prop-2-en-1-one (2)

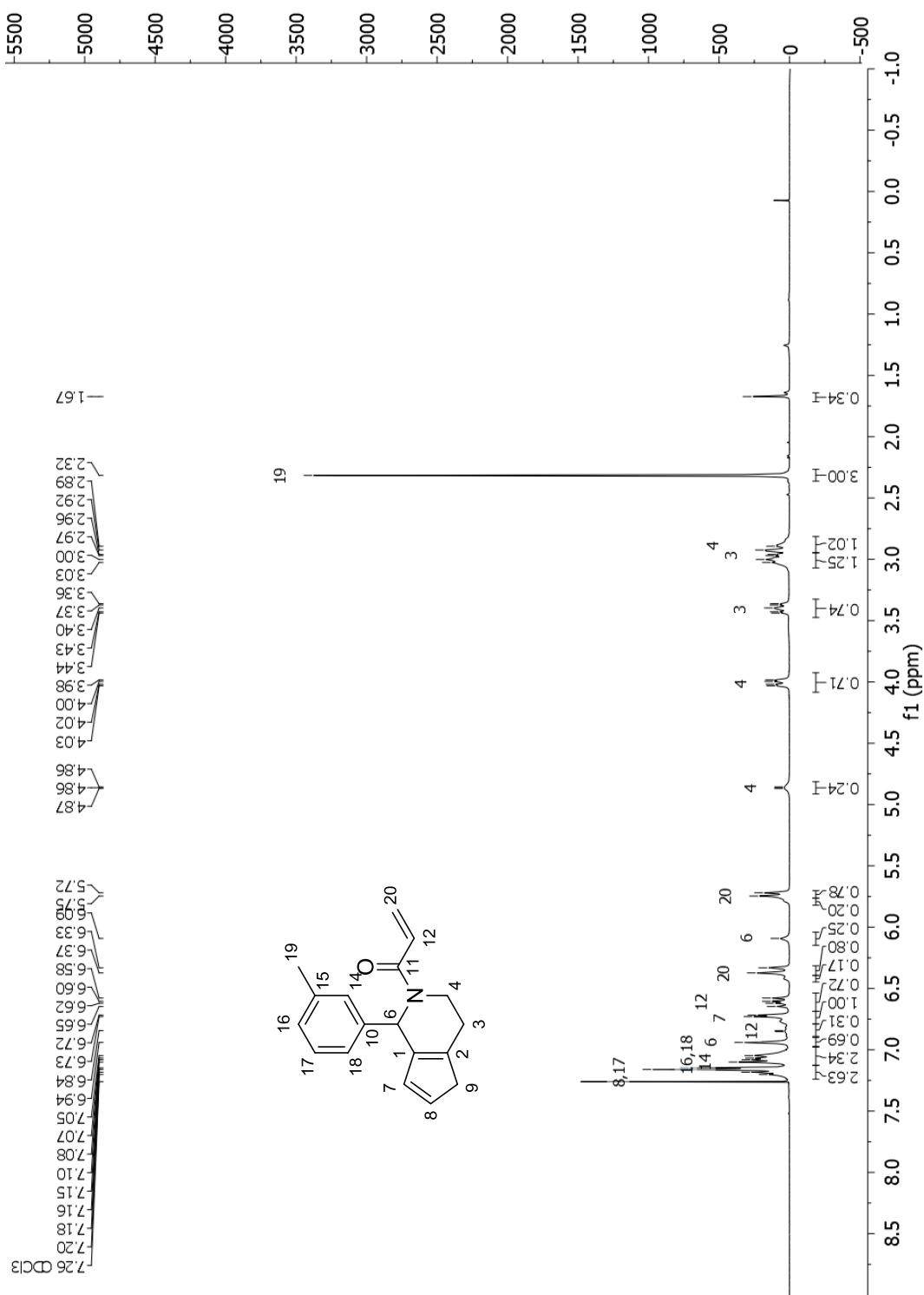


Figure S7. ^1H NMR (400 MHz, CDCl₃) at 298 K of 2.

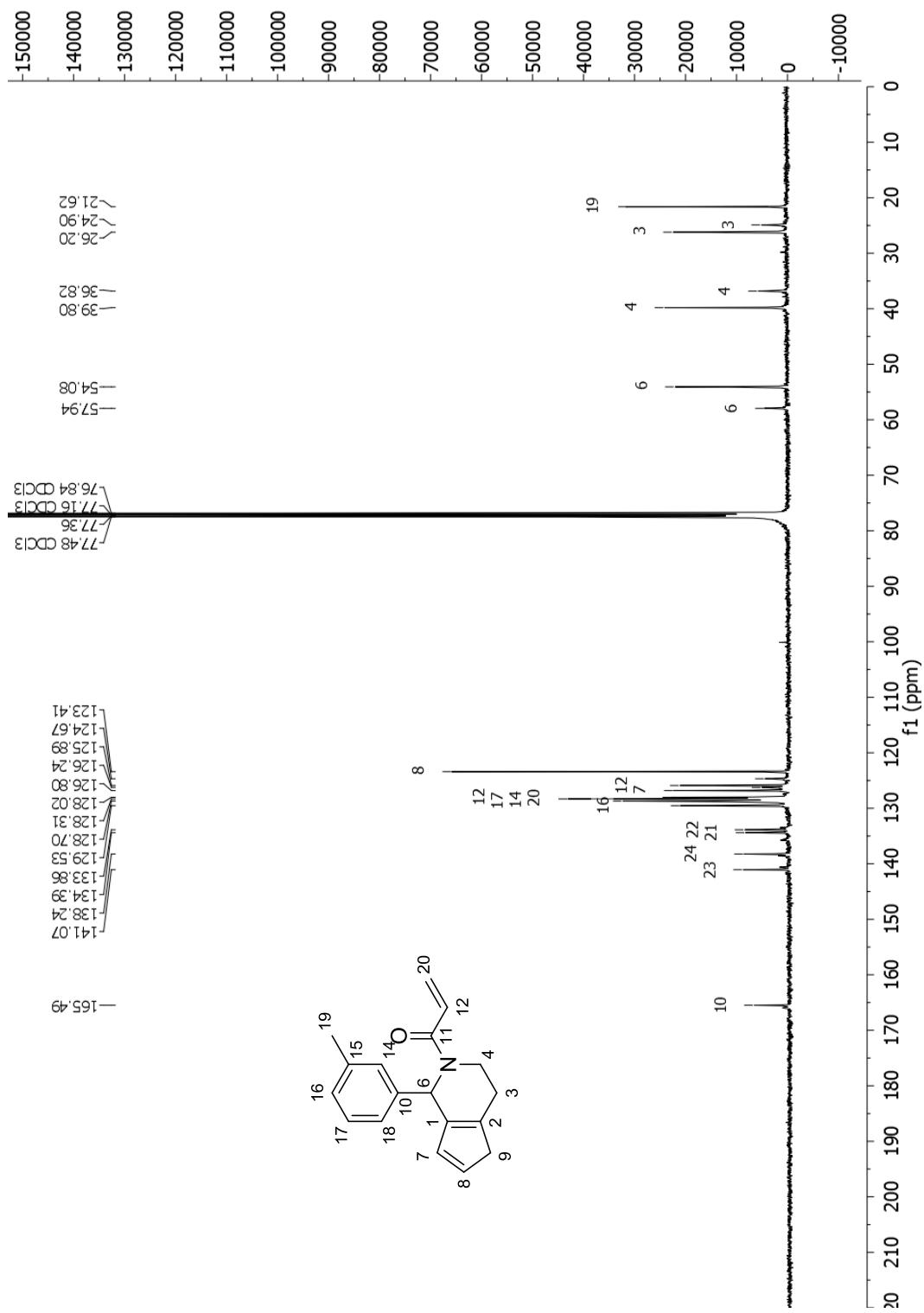


Figure S8. ^{13}C NMR (400 MHz, CDCl_3) at 298 K of 2.

1.2.1. Low Temperature 2D-NOESY and 1D Selective NOE of 2

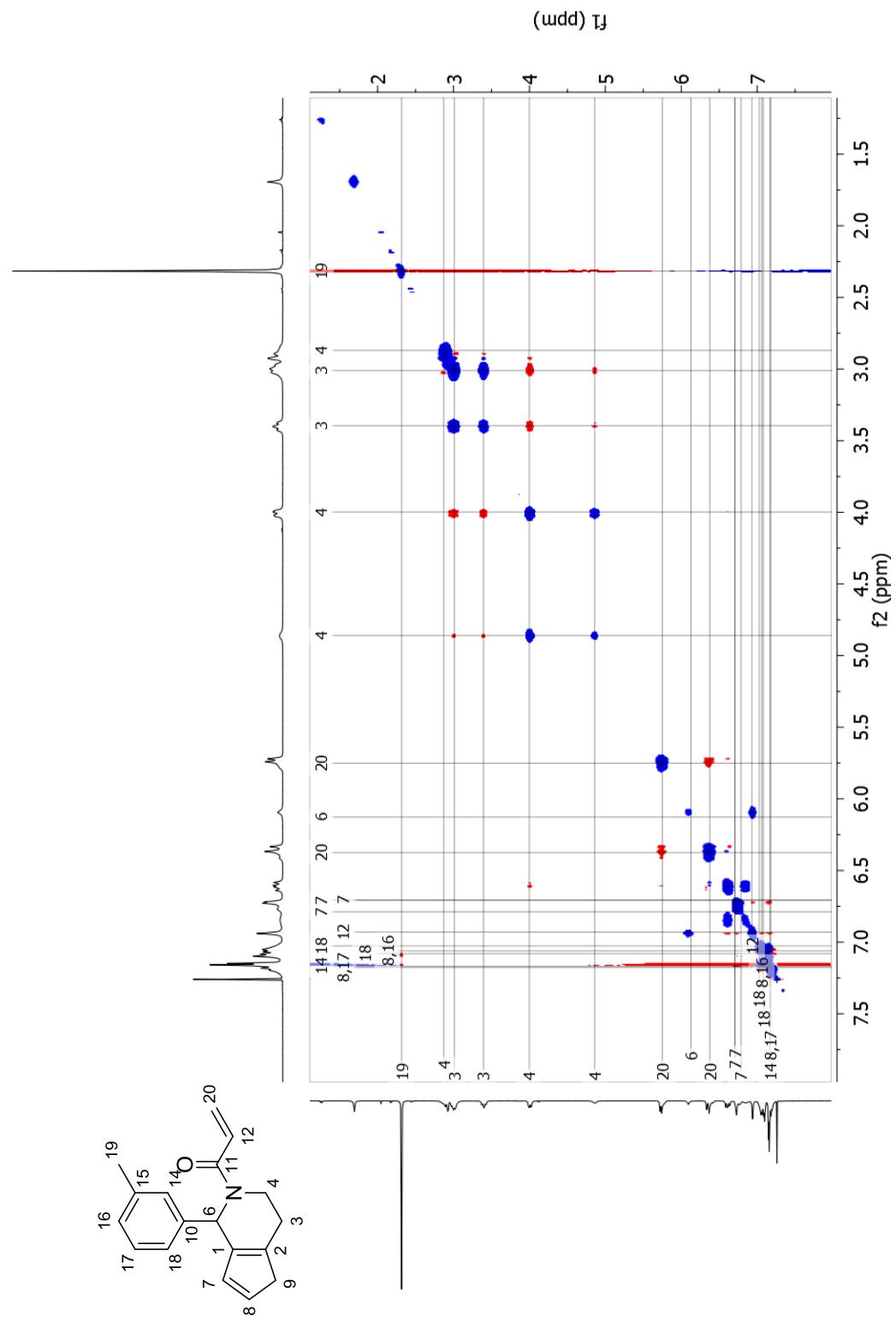


Figure S9. 2D-NOESY (500 MHz, CDCl₃) at 298 K of **2**.

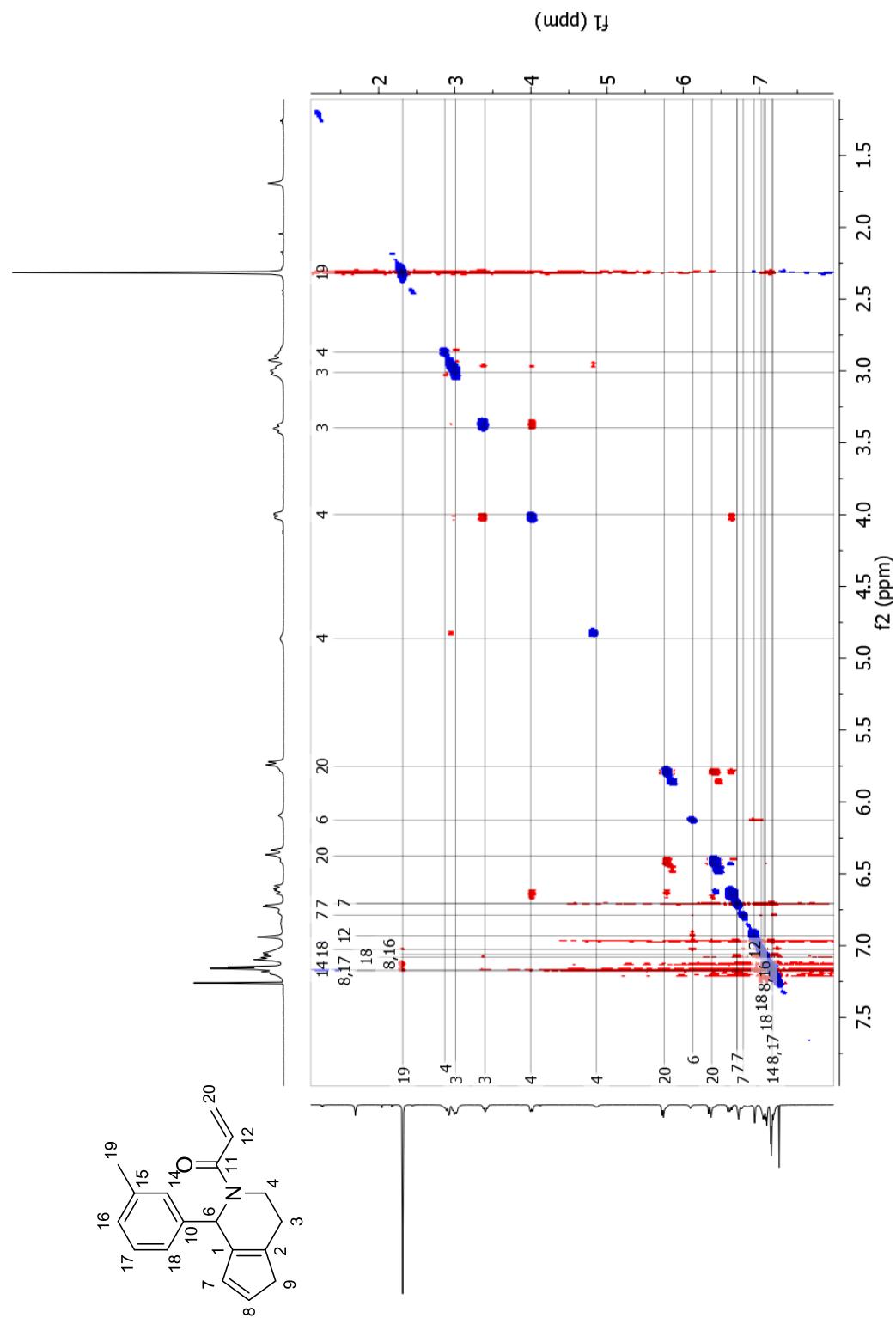


Figure S10. 2D-NOESY (500 MHz, CDCl_3) at 218 K of 2.

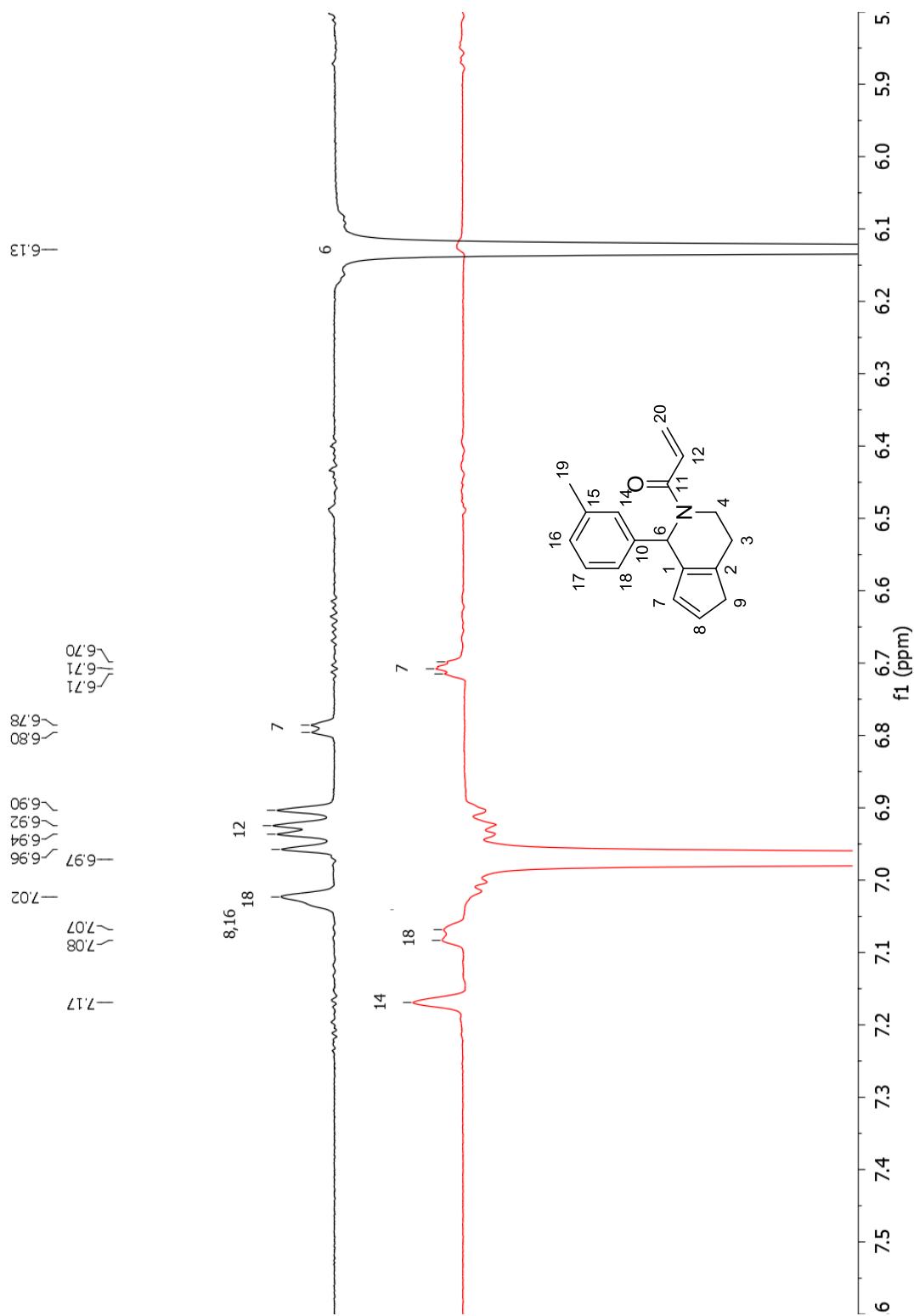


Figure S11. 1D selective NOE spectra of **2** at 6.13 ppm (black) and 6.97 ppm (red) (500 MHz, CDCl₃, 218 K).

1.3. 1-[4-(3-methylphenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl]prop-2-en-1-one (3)

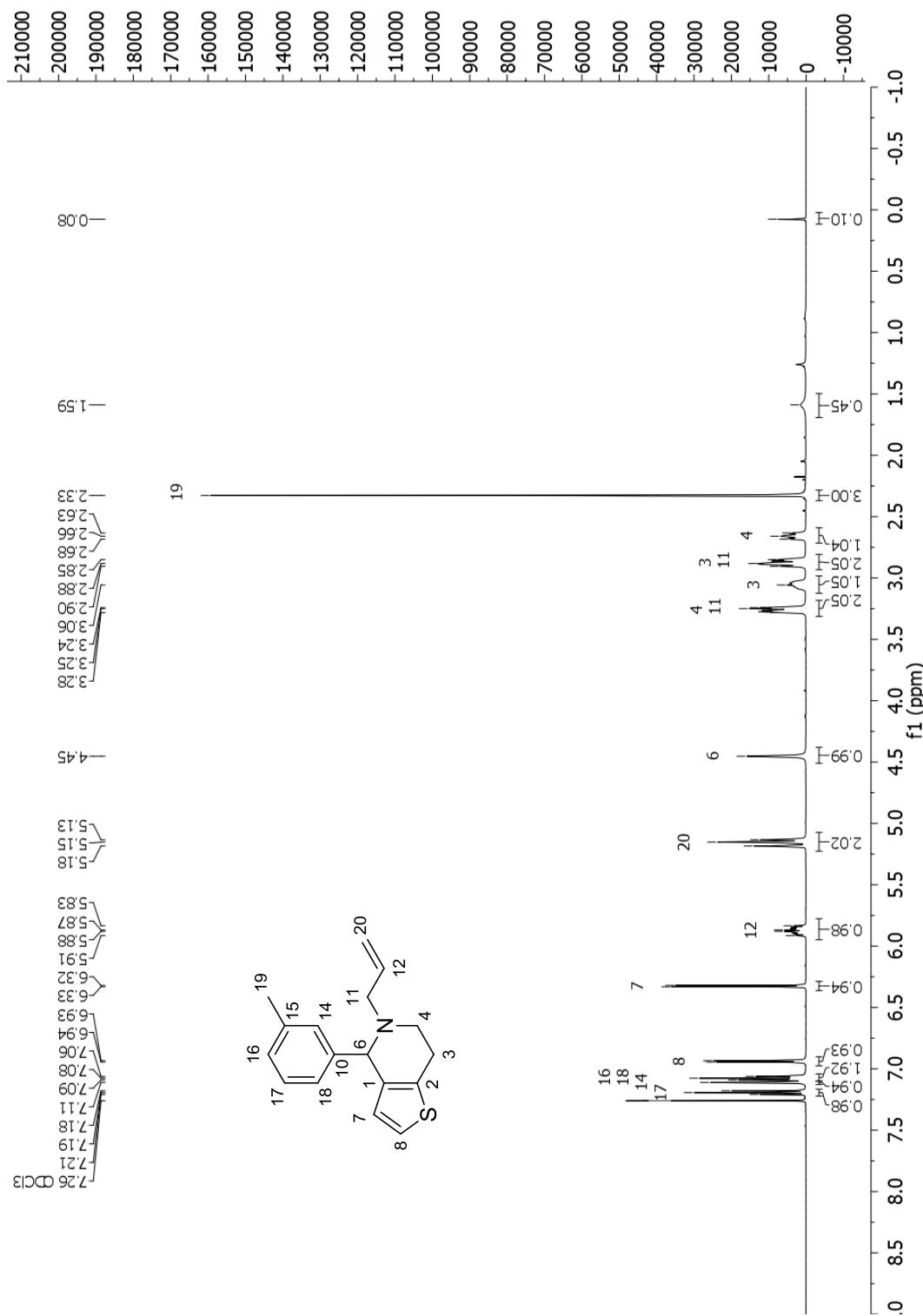


Figure S12. ^1H NMR (500 MHz, CDCl_3) at 298 K of 3.

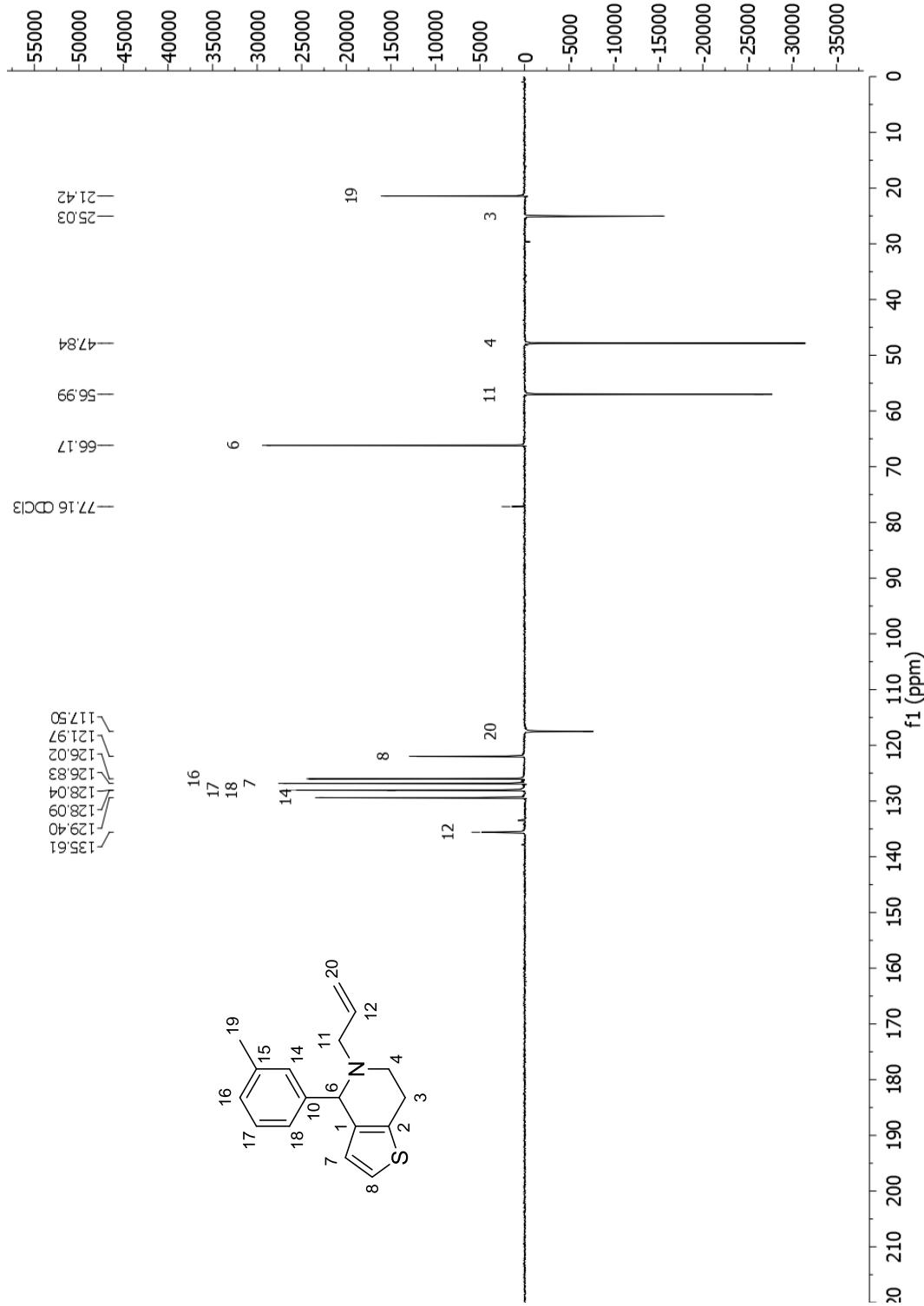


Figure S13. DEPT ^{13}C NMR (500 MHz, CDCl_3) at 298 K of 3.

1.4. 1-(4-cyclohexyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)ethanone (4)

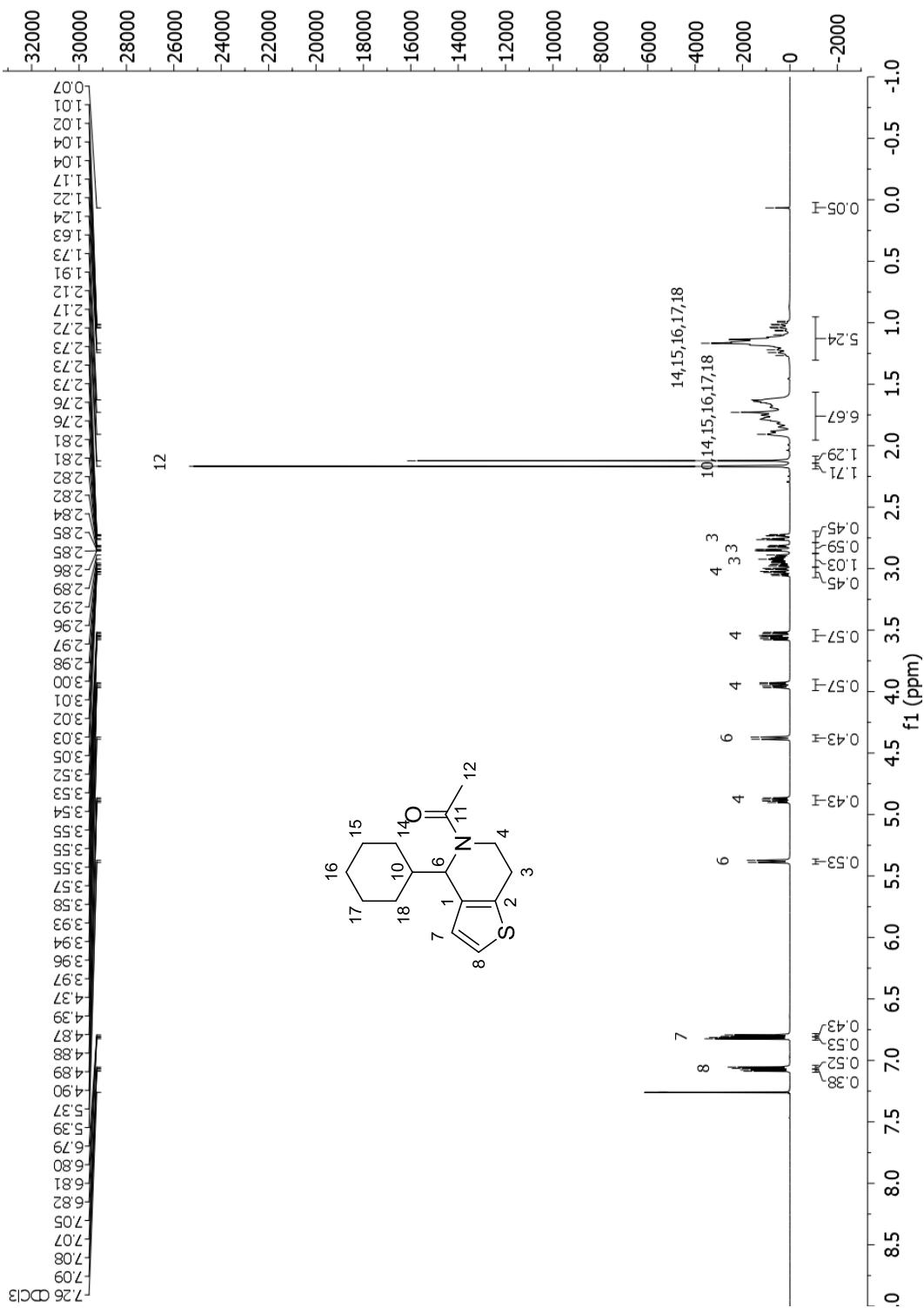


Figure S14. ^1H NMR (500 MHz, CDCl_3) at 298 K of **4**.

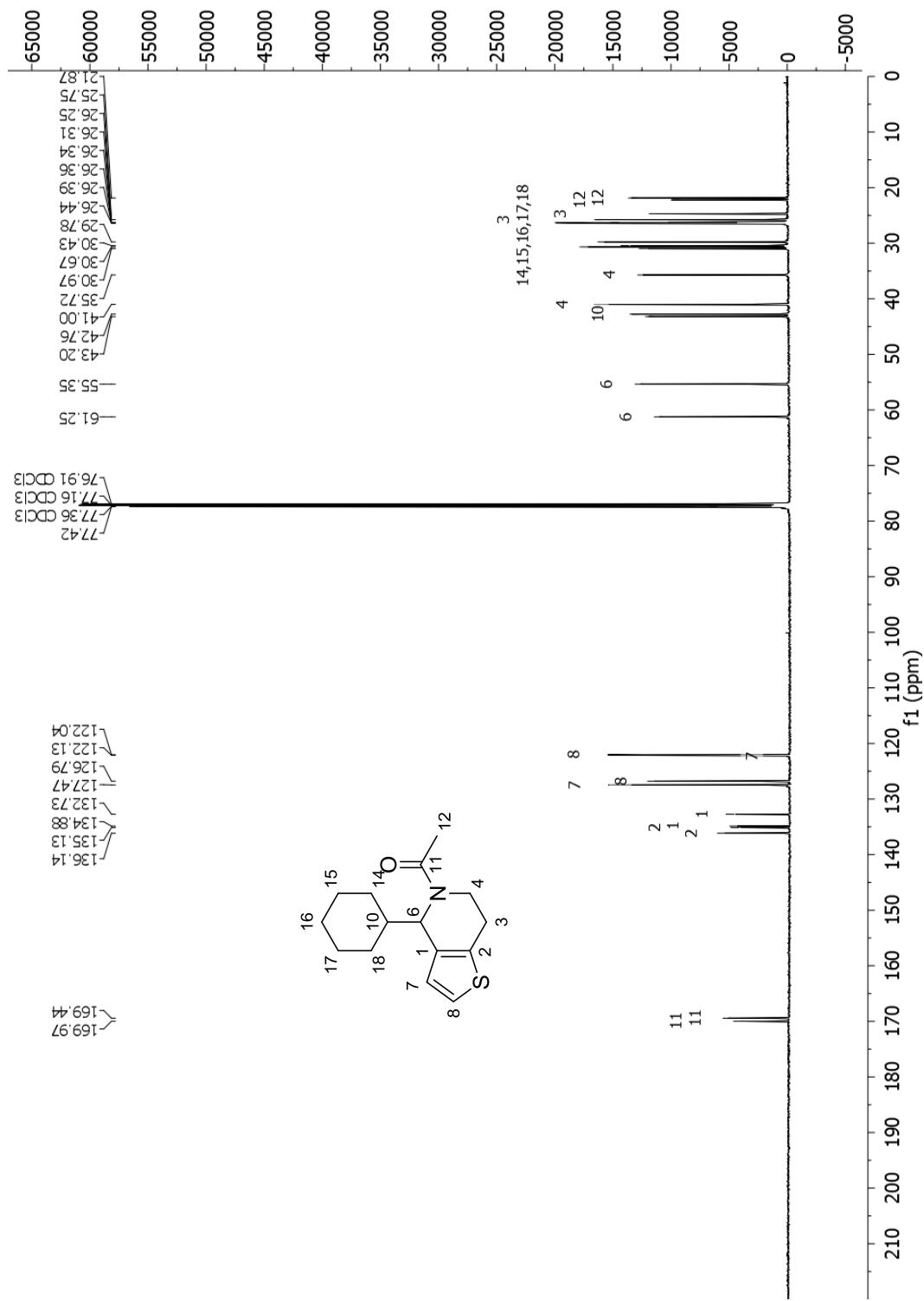


Figure S15. ^{13}C NMR (500 MHz, CDCl_3) at 298 K of **4**.

1.4.1. Low Temperature 2D-NOESY and 1D Selective NOE of 4

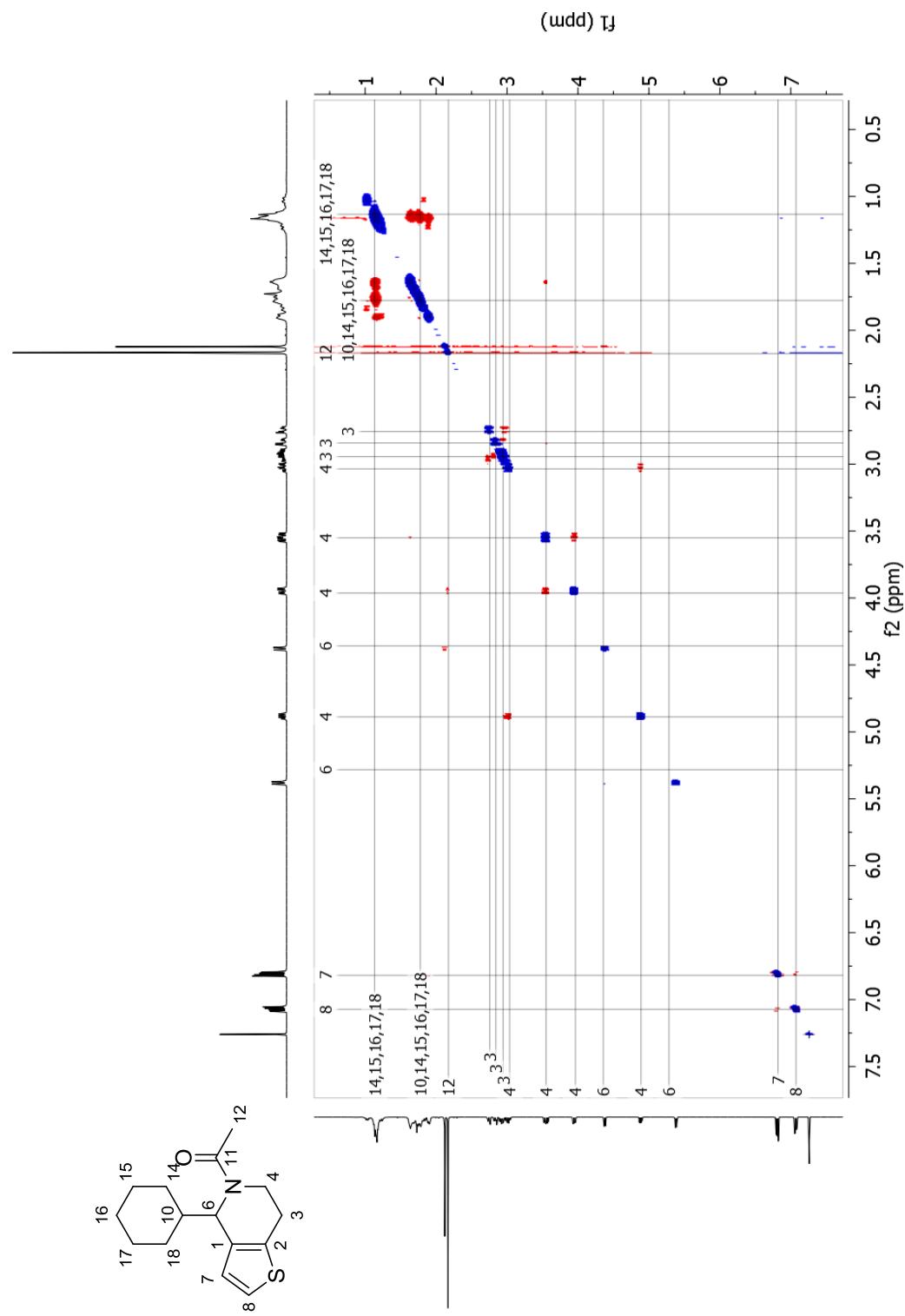


Figure S16. 2D-NOESY (500 MHz, CDCl₃) at 298 K of 4.

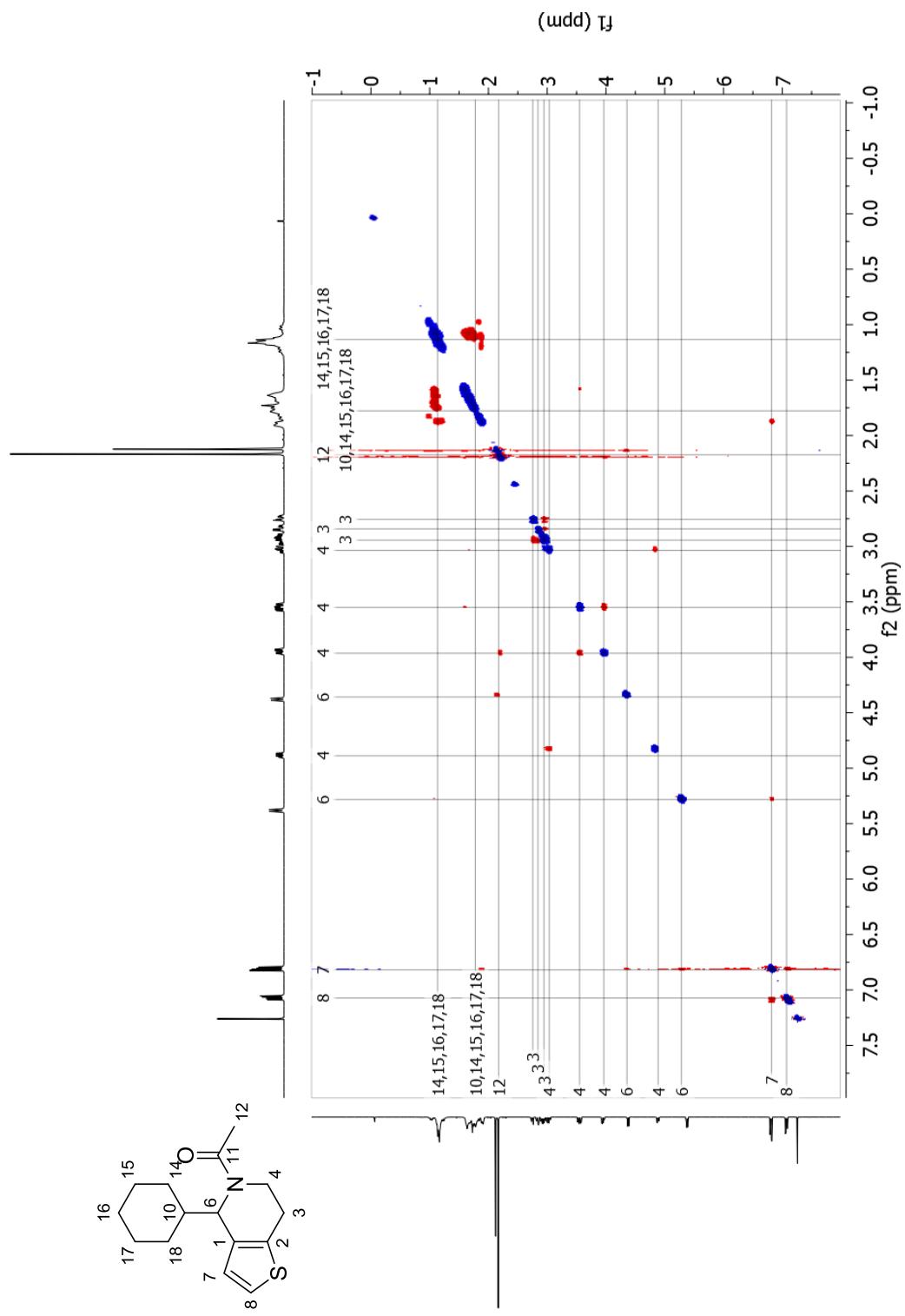


Figure S17. 2D-NOESY (500 MHz, CDCl₃) at 218 K of **4**.

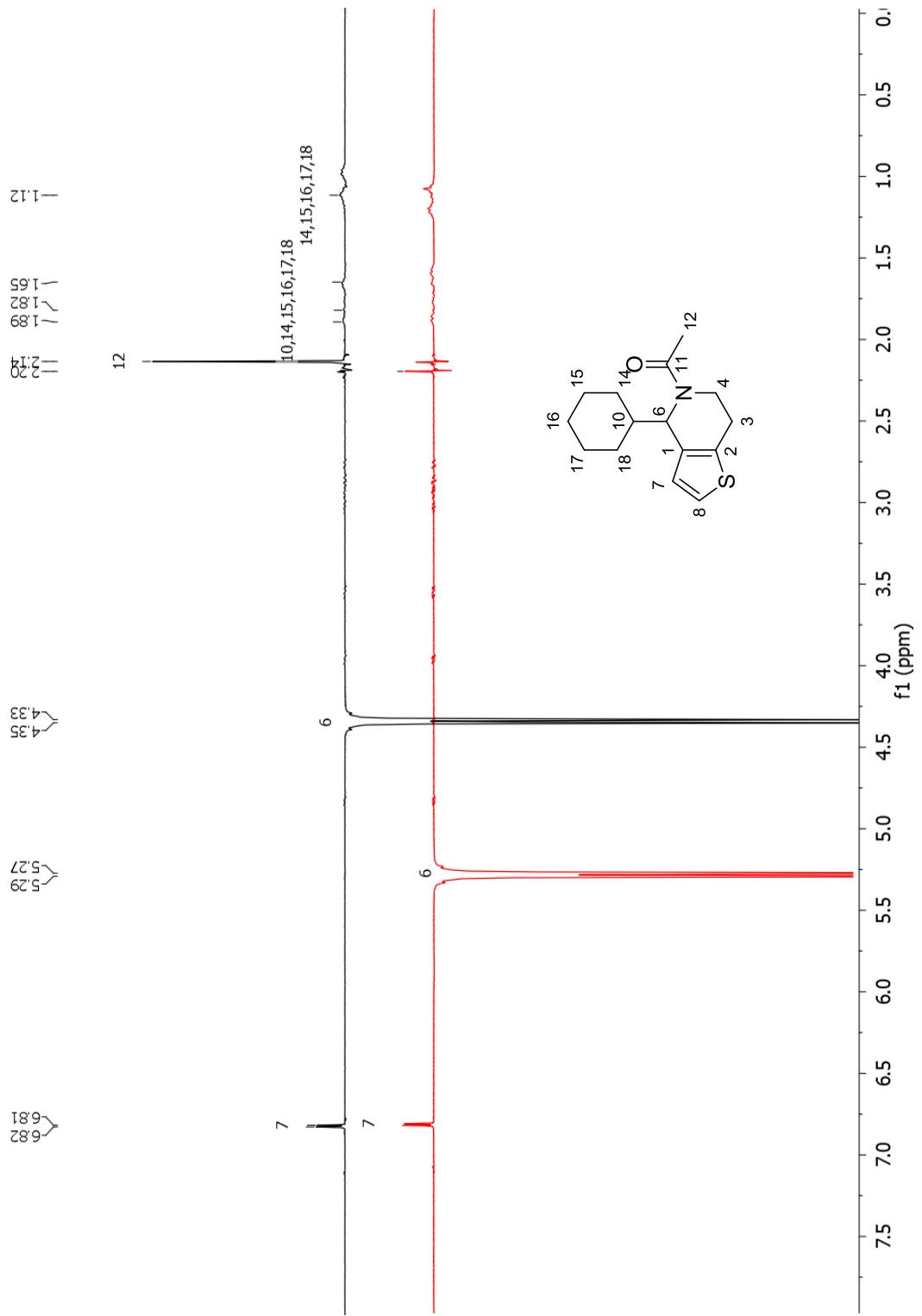


Figure S18. 1D selective NOE spectra of **4** at 4.34 ppm (black) and 5.28 ppm (red) (500 MHz, CDCl₃, 218 K).

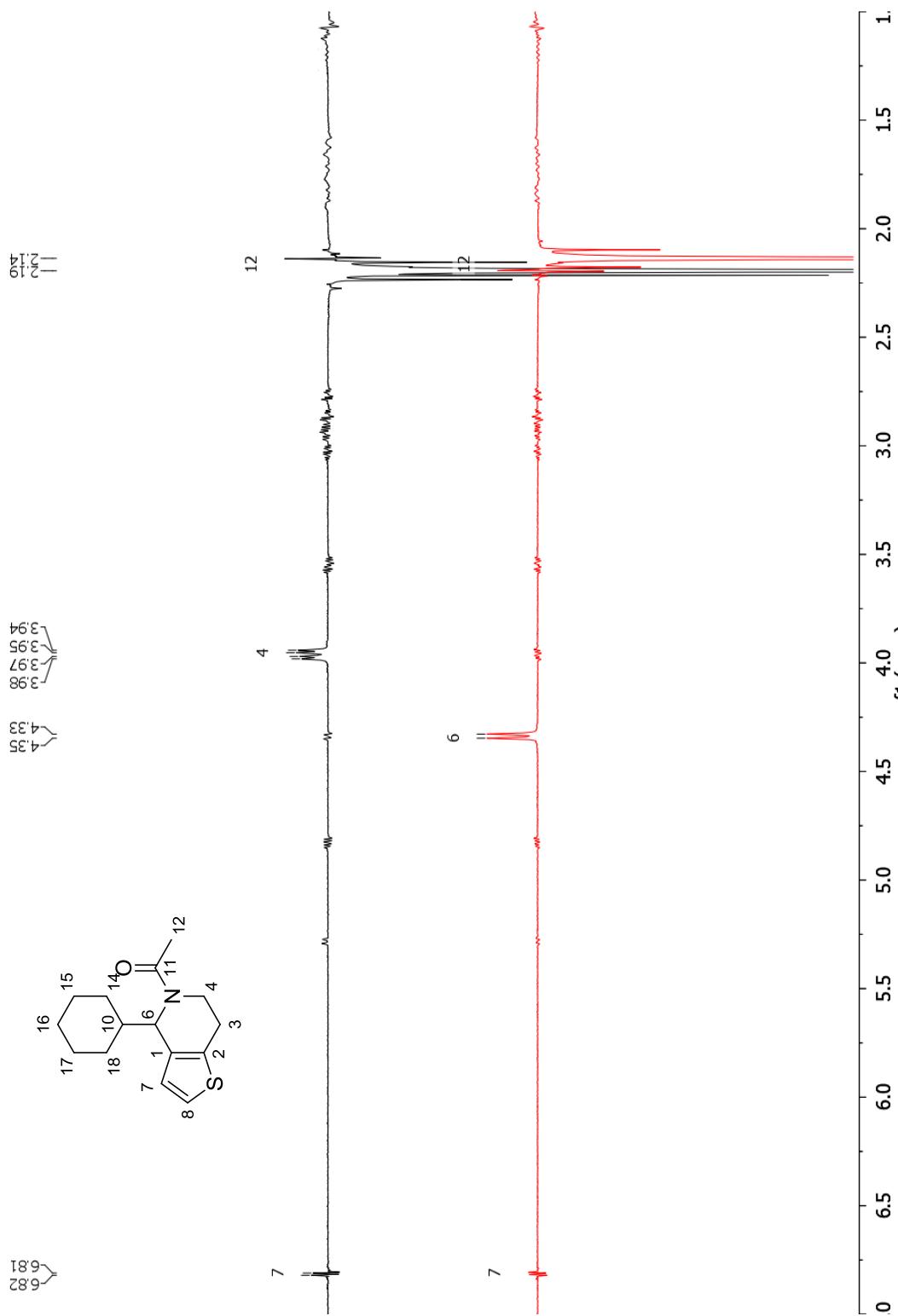


Figure S19. 1D selective NOE spectra of **4** at 2.19 ppm (black) and 2.14 ppm (red) (500 MHz, CDCl_3 , 218 K).

1.4.2. Comparison of the Population of the *E*- and *Z*-Conformers of **4** Derived from Lowest Energy Calculations and NMR Measurements

Table S5. Boltzmann population distribution of the *E*- and *Z*-conformers of **4** derived from the lowest energy calculations.

Energy Level No.	Conformation	Energy [kcal/mol]	Energy [J/mol]	Boltzmann Factor	Population (N_i/N_{total})	
					<i>E</i>	<i>Z</i>
1	<i>Z</i>	0.0	0.0	1.00		0.37
2	<i>E</i>	3.4	14225.6	0.00	0.00	
3	<i>Z</i>	2.6	10878.4	0.01		0.00
4	<i>E</i>	0.0	0.0	1.00	0.37	
5	<i>E</i>	0.6	2510.4	0.36	0.13	
6	<i>Z</i>	1.1	4602.4	0.16		0.06
7	<i>Z</i>	4.8	20083.2	0.00		0.00
8	<i>E</i>	1.1	4602.4	0.16	0.06	
		Total			0.57	0.43

Table S6. Population of the *E*- and *Z*-conformers of **4** derived from the ^1H NMR.

Proton Nr.	Integral		Ratio (<i>E/Z</i>)
	<i>E</i>	<i>Z</i>	
4	0.57	0.43	1.33
6	0.53	0.43	1.23
8	0.52	0.38	1.37
12	1.71	1.29	1.33
Average		1.31	
<i>E</i>		0.57	
<i>Z</i>			0.43

1.4.3. Comparison of Shifts from Lowest Energy Structure Calculations and ^1H NMR of 4

Table S7. Comparison of chemical shifts derived from lowest energy structure calculations and ^1H NMR spectrum of the Z-conformation of 4.

Proton-No.	Lowest Energy Structure Calculations [ppm]			^1H NMR Data of 10 [ppm]			Δ [ppm]
	Level 1 (0.0 kcal/mol)		Average	From	To	Average	
	37.2%	5.8%					
3 (ax)	2.88	2.66	2.85	2.98	2.89	2.94	0.06
3 (eq)	2.64	2.5	2.62	2.86	2.81	2.84	0.20
4 (ax)	3.74	2.95	3.63	3.97	3.93	3.95	0.21
4 (eq)	3.53	4.92	3.72	3.58	3.52	3.55	0.02
6	5.26	4.68	5.18	5.39	5.37	5.38	0.12
7	7.04	7.06	7.04	6.82	6.81	6.82	0.23
8	7.28	7.34	7.29	7.07	7.05	7.06	0.22
10	1.59	1.95	1.64	1.91	1.63	1.77	0.13
	2.20	2.39					
12	2.13	2.03	2.04	2.08	2.03	2.17	0.14
	1.75		1.8				
14 (ax)	1.09	1.45	1.14	1.27	0.99	1.13	0.01
14 (eq)	1.66	1.84	1.68	1.91	1.63	1.77	0.09
15 (ax)	1.13	1.39	1.17	1.27	0.99	1.13	0.04
15 (eq)	1.63	1.75	1.65	1.91	1.63	1.77	0.12
16 (ax)	1.17	1.16	1.17	1.27	0.99	1.13	0.04
16 (eq)	1.53	1.54	1.53	1.91	1.63	1.77	0.24
17 (ax)	1.12	1.05	1.11	1.27	0.99	1.13	0.02
17 (eq)	1.69	1.6	1.68	1.91	1.63	1.77	0.09
18 (ax)	1.26	1.1	1.24	1.27	0.99	1.13	0.11
18 (eq)	1.96	1.37	1.88	1.91	1.63	1.77	0.11

Table S8. Comparison of chemical shifts derived from the lowest energy structure calculations and the ^1H NMR spectrum of the *E*-conformation of **4**.

Proton-No.	Lowest Energy Structure Calculations [ppm]				Average	^1H NMR Data of 10 [ppm]			Δ [ppm]
	Level 1 (0.0 kcal/mol)	Level 2 (0.6 kcal/mol)	Level 3 (1.1 kcal/mol)			From	To	Average	
	37.2%	13.5%	5.8 %						
3 (ax)	2.81	2.47	2.66		2.79	2.98	2.89	2.94	0.13
3 (eq)	2.58	2.58	2.5		2.57	2.76	2.72	2.74	0.16
4 (ax)	3.01	3.46	2.95		3.00	3.06	3	3.03	0.02
4 (eq)	4.71	3.86	4.92		4.74	4.9	4.87	4.89	0.18
6	4.23	5.59	4.68		4.29	4.39	4.37	4.38	0.15
7	7.00	7.11	7.06		7.01	6.8	6.79	6.80	0.21
8	7.29	7.34	7.34		7.30	7.09	7.08	7.09	0.21
10	1.70	1.95	1.95		1.73	1.91	1.63	1.77	0.04
	2.24	2.27	2.39	2.08	2.00				
12	2.02	1.99	2.17	2.09	2.04	2.02	2.12	2.12	0.12
	1.72		1.82		1.8		1.73		
14 (ax)	1.05		1.14		1.45		1.10	1.27	0.99
14 (eq)	1.85		1.95		1.84		1.85	1.91	1.63
15 (ax)	1.18		1.34		1.39		1.21	1.27	0.99
15 (eq)	1.67		1.66		1.75		1.68	1.91	1.63
16 (ax)	1.18		1.13		1.16		1.18	1.27	0.99
16 (eq)	1.56		1.53		1.54		1.56	1.91	1.63
17 (ax)	1.14		1.08		1.05		1.13	1.27	0.99
17 (eq)	1.69		1.57		1.6		1.68	1.91	1.63
18 (ax)	1.19		1.05		1.1		1.18	1.27	0.99
18 (eq)	1.94		1.33		1.37		1.86	1.91	1.63

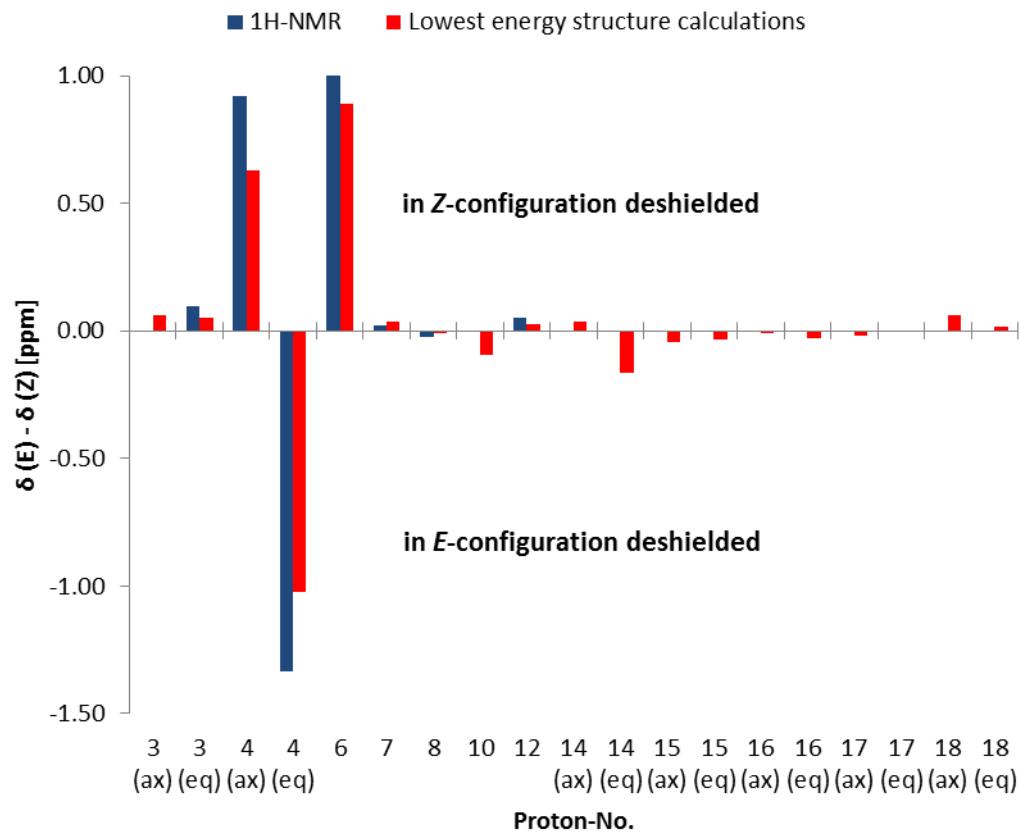


Figure S20. Differences between the chemical shifts of all protons of the ***E***- and the ***Z***-conformation of **4** derived from the ^1H NMR spectrum and the lowest energy structure calculations, respectively. The protons are deshielded in the *Z*-conformation in the case of positive values and deshielded in the *E*-conformation in the case of negative values.

1.5. 1-(4-phenyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)ethanethione (5**)**

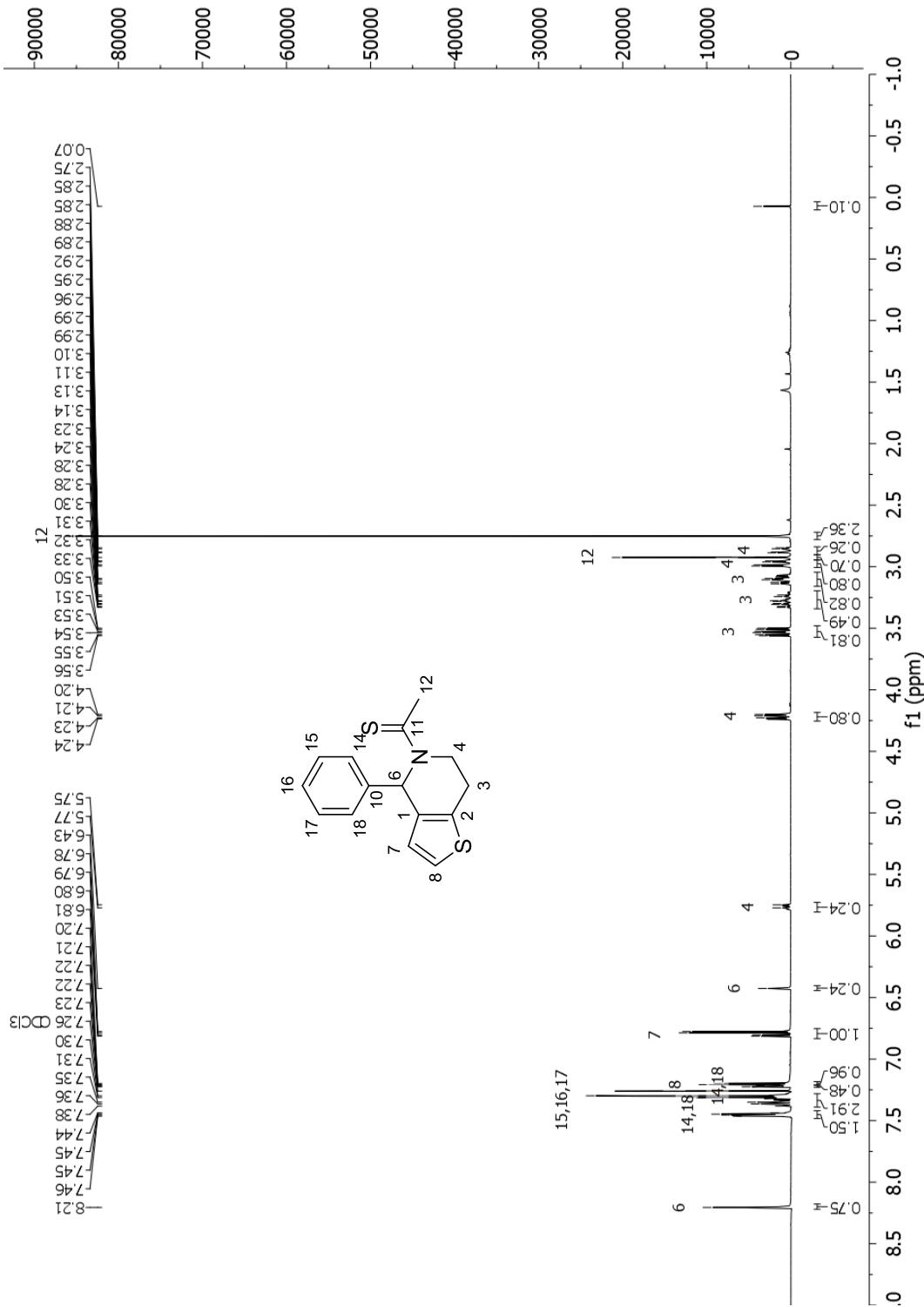


Figure S21. ^1H NMR (500 MHz, CDCl_3) at 298 K of **5**.

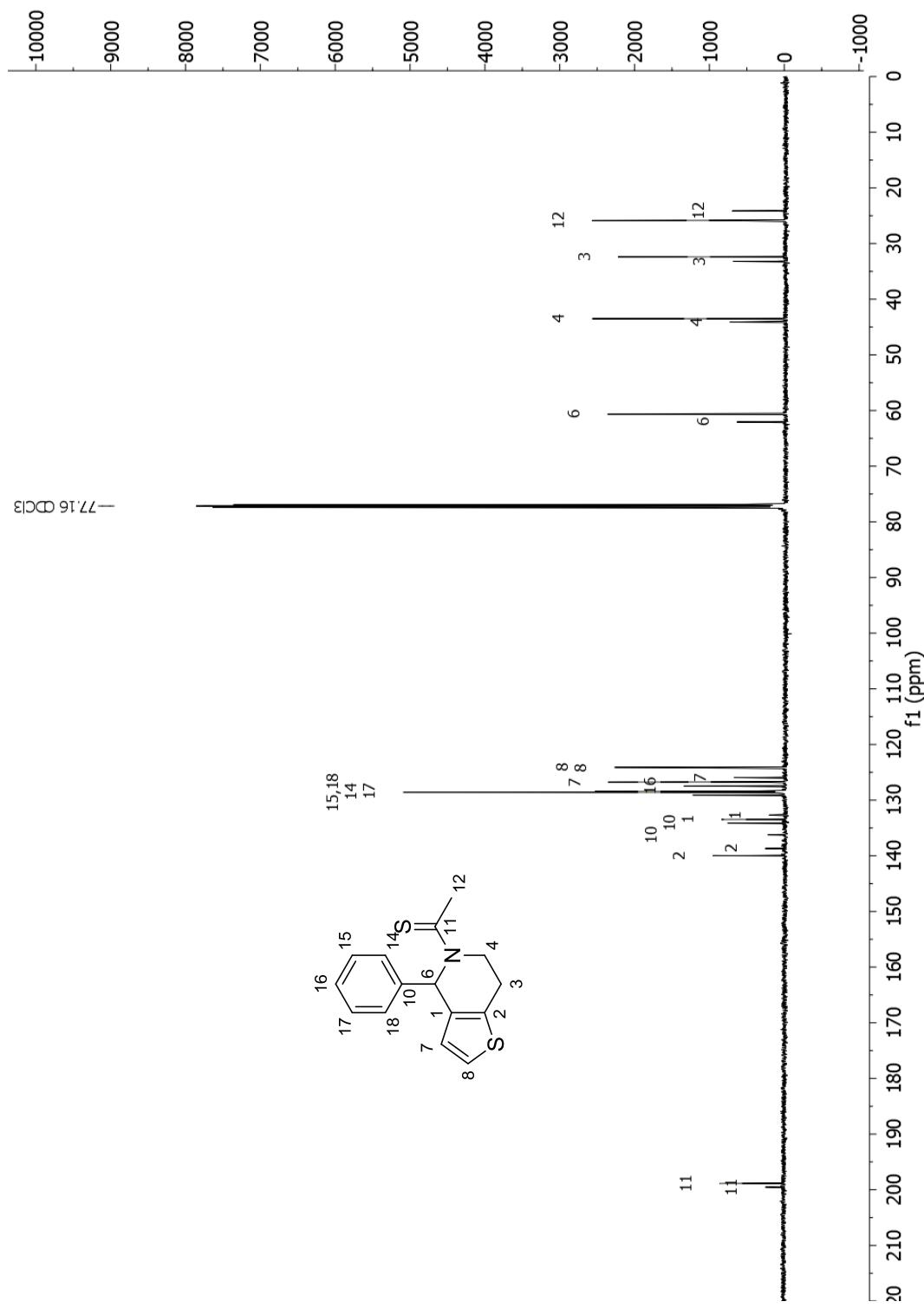


Figure S22. ^{13}C NMR (500 MHz, CDCl_3) at 298 K of 5.

1.5.1. Low Temperature 2D-NOESY and 1D Selective NOE of 5

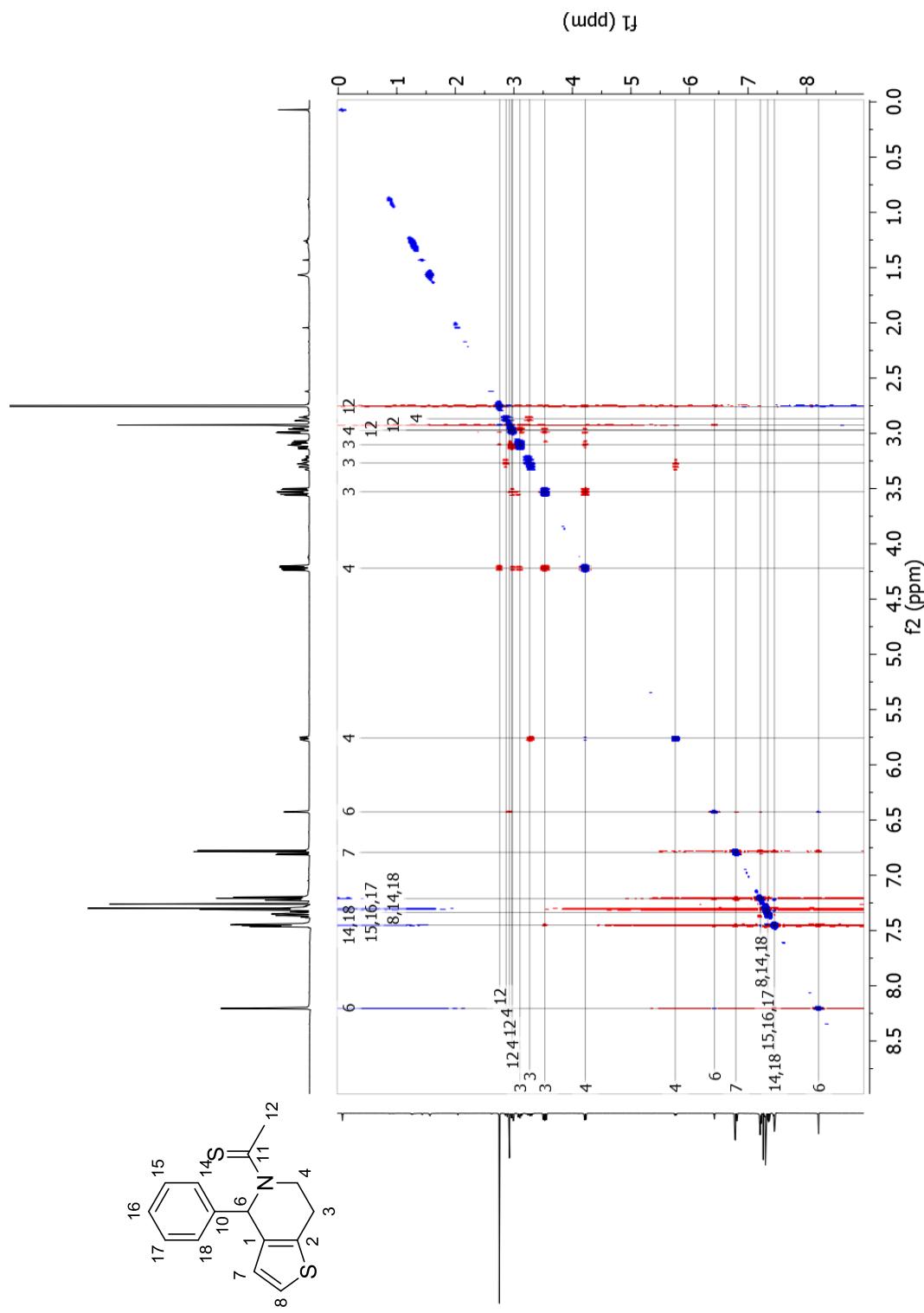


Figure S23. 2D-NOESY (500 MHz, CDCl₃) at 298 K of **5**.

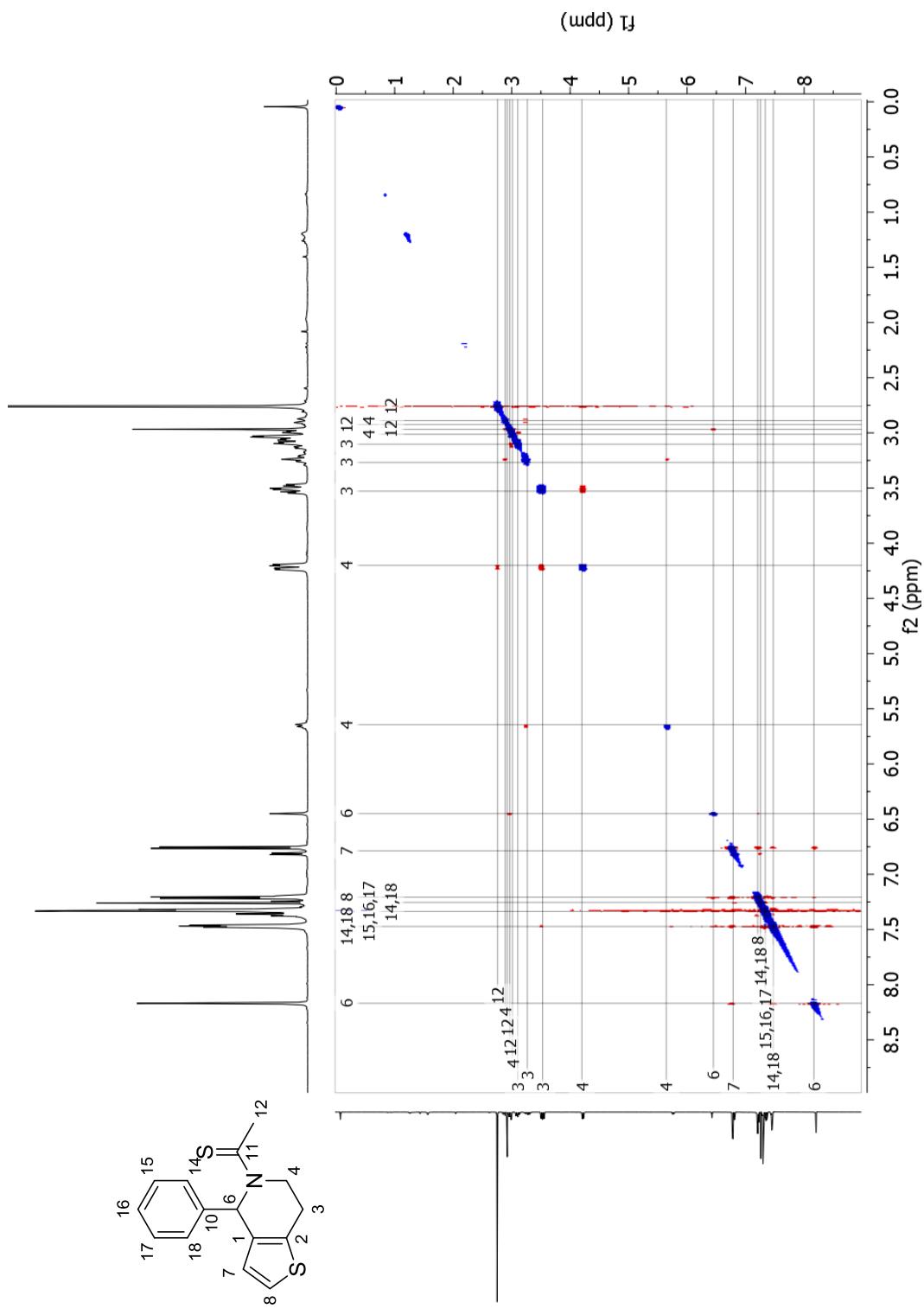


Figure S24. 2D-NOESY (500 MHz, CDCl_3) at 218 K of 5.

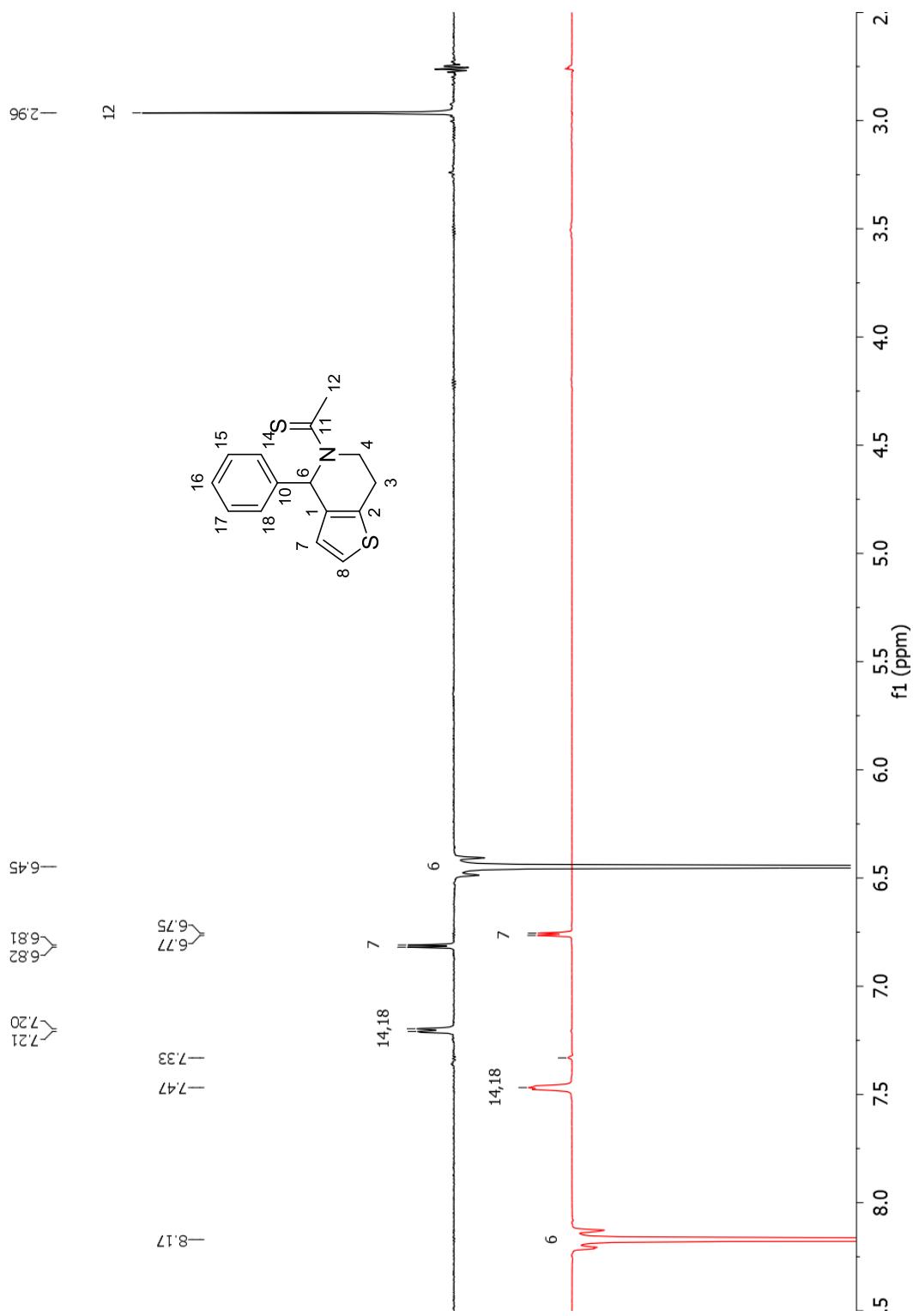


Figure S25. 1D selective NOE spectra of **5** at 6.45 ppm (black) and 8.17 ppm (red) (500 MHz, CDCl_3 , 218 K).

1.6. 1-[4-(pyridin-2-yl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl]ethanone (6**)**

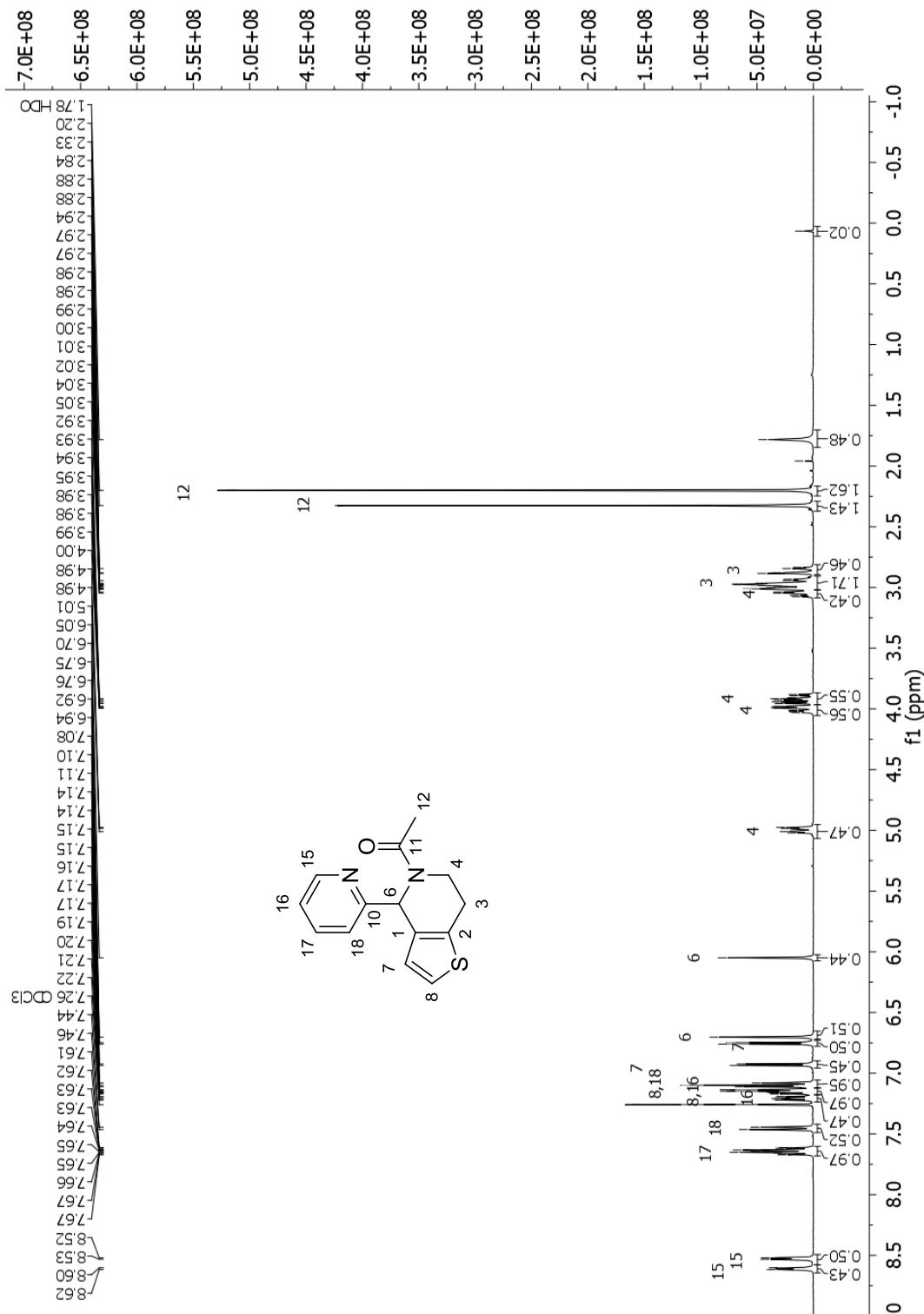


Figure S26. ^1H NMR (500 MHz, CDCl_3) at 298 K of **6**.

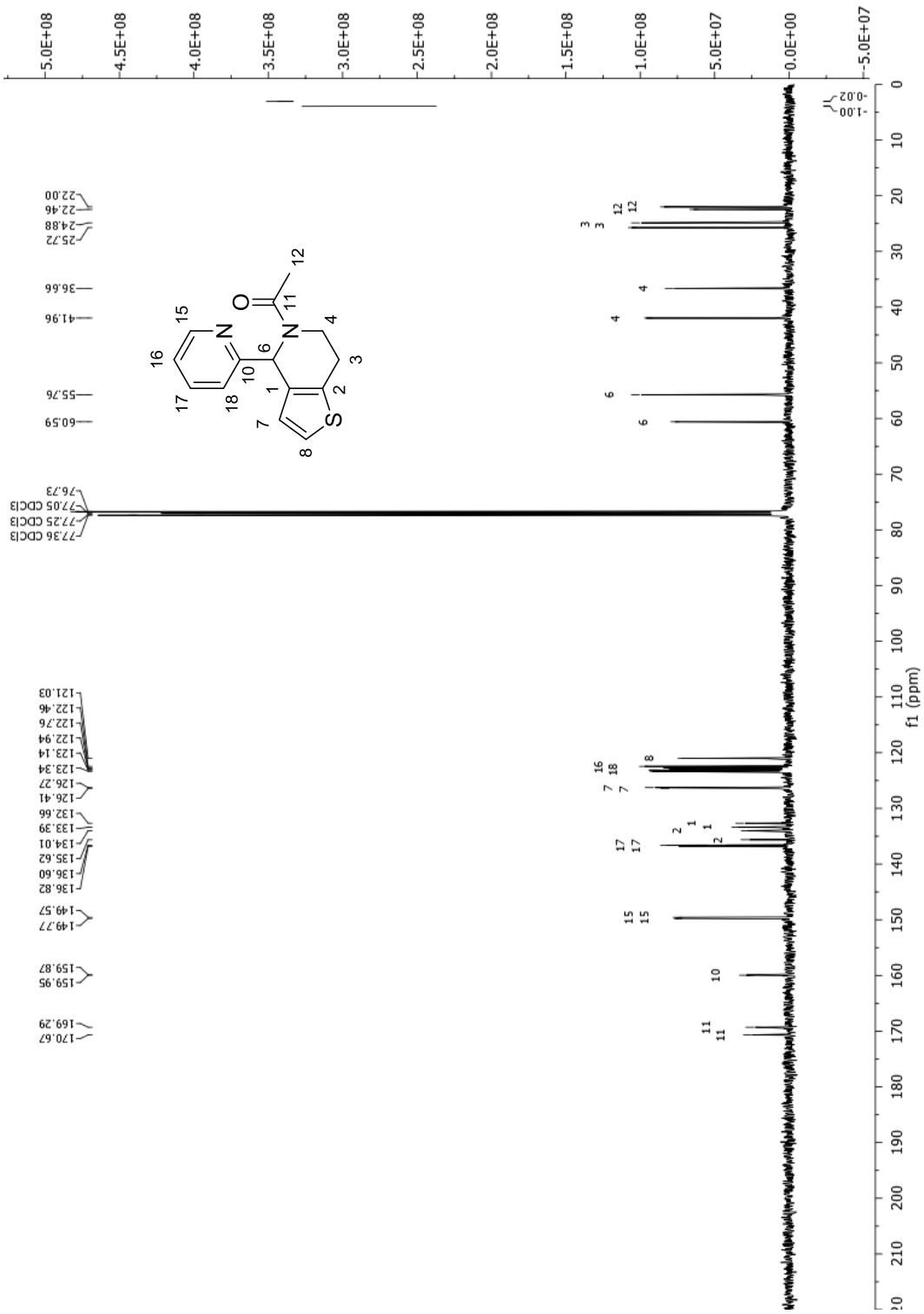


Figure S27. ^{13}C NMR (400 MHz, CDCl_3) at 298 K of 6

1.6.1. Low Temperature 2D-NOESY and 1D Selective NOE of 6

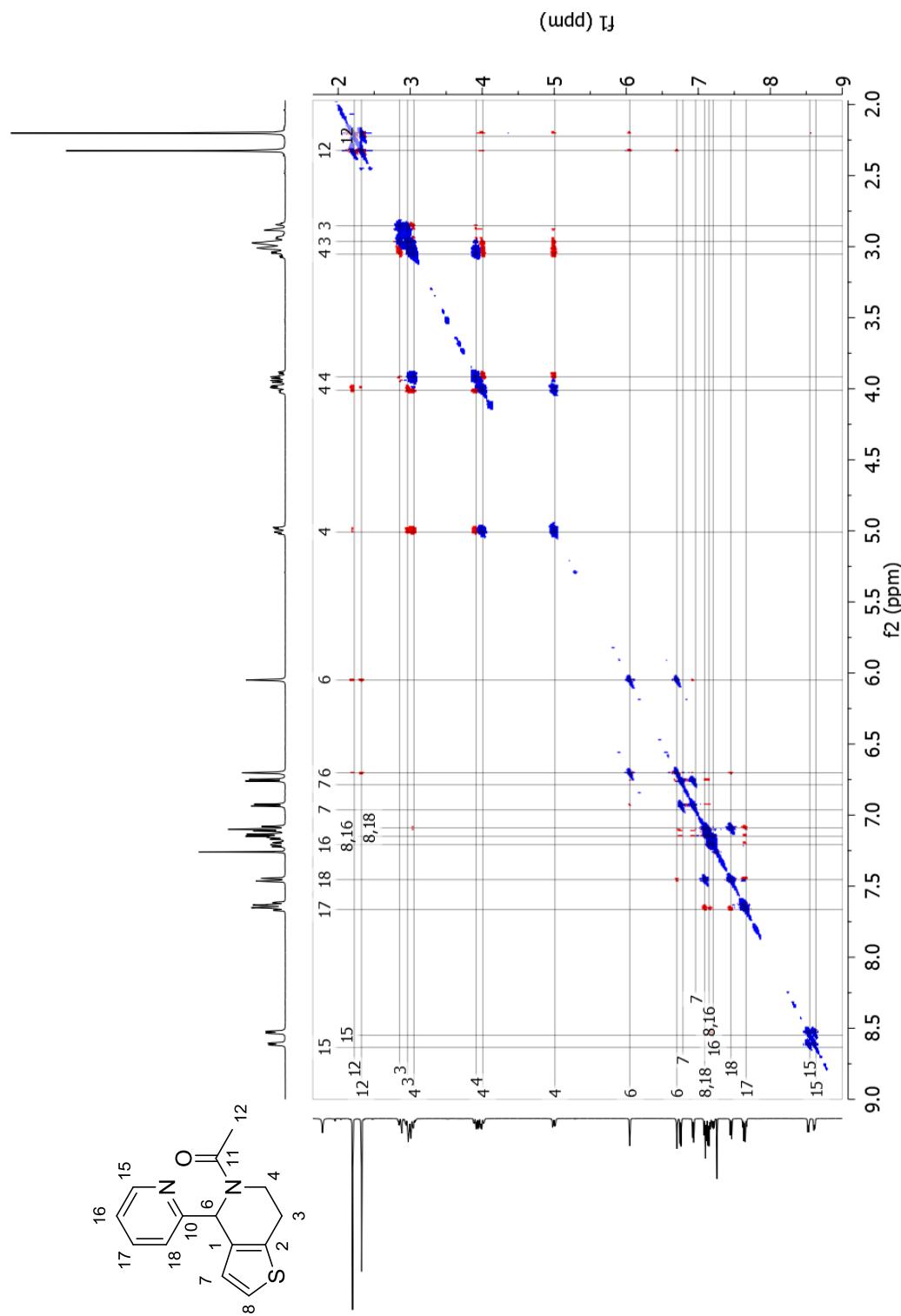


Figure S28. 2D-NOESY (400 MHz, CDCl₃) at 298 K of 6.

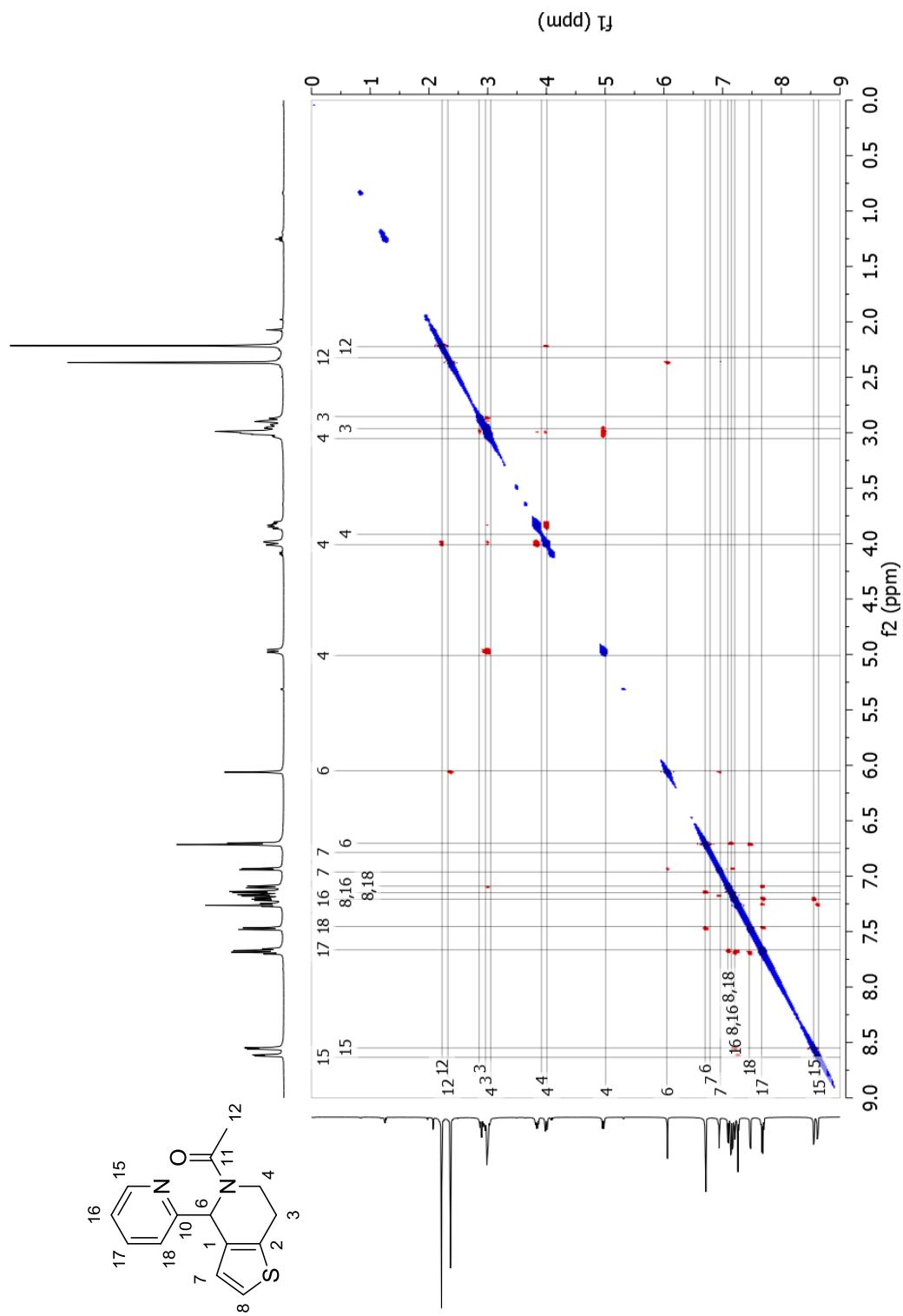


Figure S29. 2D-NOESY (400 MHz, CDCl_3) at 221 K of **6**.

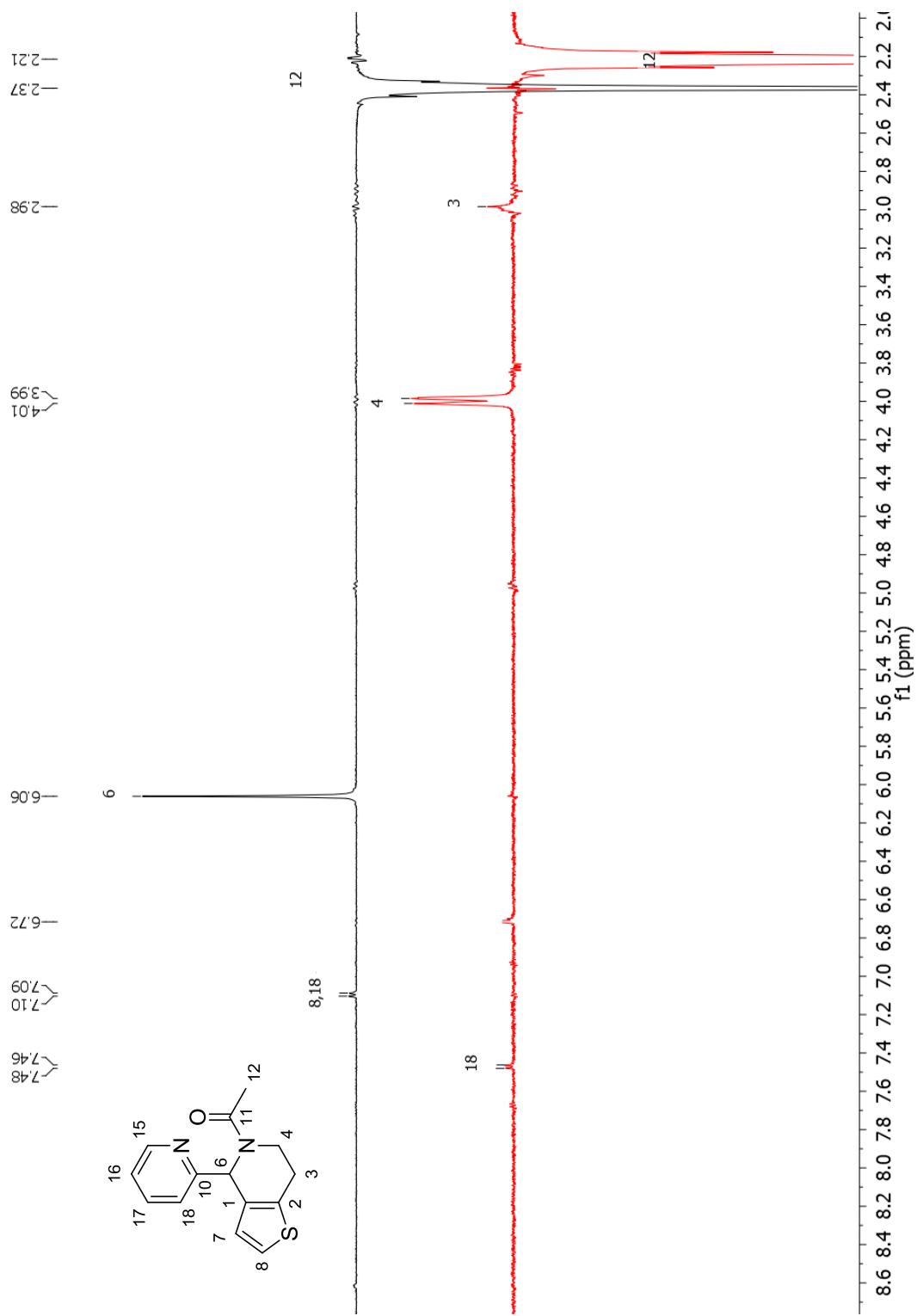


Figure S30. 1D selective NOE spectra of **6** at 2.79 ppm (black) and 2.21 ppm (red) (400 MHz, CDCl_3 , 218 K).

1.6.2. Comparison of the Population of the *E*- and *Z*-Conformers of **6** Derived from Lowest Energy Calculations and NMR Measurements

Table S9. Boltzmann population distribution of the *E*- and *Z*-conformers of **6** derived from the lowest energy calculations.

Energy Level No.	Conformation	Energy [kcal/mol]	Energy [J/mol]	Boltzmann Factor	Population (N_i/N_{total})	
					<i>E</i>	<i>Z</i>
1	<i>Z</i>	2.7	11296.8	0.01		0.00
2	<i>E</i>	3.1	12970.4	0.01	0.00	
3	<i>Z</i>	1.1	4602.4	0.16		0.07
4	<i>E</i>	0.0	0.0	1.00	0.46	
5	<i>E</i>	2.2	9204.8	0.02	0.01	
6	<i>Z</i>	2.6	10878.4	0.01		0.01
7	<i>Z</i>	0.2	836.8	0.71		0.33
8	<i>E</i>	0.8	3347.2	0.26	0.12	
		Total		0.59	0.41	

Table S10. Population of the *E*- and *Z*-conformers of **6** derived from the ^1H NMR.

Proton Nr.	Integral		Ratio (<i>E/Z</i>)
	<i>E</i>	<i>Z</i>	
4	0.47	0.50	0.94
6	0.44	0.51	0.86
7	0.45	0.50	0.90
12	1.43	1.62	0.88
		Average	0.91
		E	0.48
		Z	0.52

1.6.3. Comparison of Shifts from Lowest Energy Structure Calculations and ^1H NMR of 6

Table S11. Comparison of chemical shifts derived from the lowest energy structure calculations and the ^1H NMR spectrum of the Z-conformation of 6.

Proton-No.	Lowest Energy Structure Calculations [ppm]				Average	^1H NMR Data of 6 [ppm]			Δ [ppm]
	Level 1 (1.1 kcal/mol) 32.7%	Level 2 (1.1 kcal/mol) 7.2%	Level 3 (2.6 kcal/mol) 0.6%	From		To	Average		
3 (ax)	2.97	2.97	3.10	2.89	2.99	2.82	2.91	0.07	
3 (eq)	2.80	2.67	2.92	2.71	2.99	2.82	2.91	0.13	
4 (ax)	4.35	3.07	3.16	2.86	3.97	3.87	3.92	0.19	
4 (eq)	3.74	3.59	4.55	4.63	4.04	3.96	4.00	0.28	
6	6.57	7.12	5.97	6.09	6.71	6.71	6.71	0.05	
7	6.69	6.98	7.46	6.87	6.76	6.75	6.76	0.00	
8	7.25	7.41	7.24	7.35	7.11	7.1	7.11	0.17	
	1.75	2.16	1.58						
12	2.03	1.99	1.86	2.05	1.65	1.82	2.51	2.2	2.20
	2.18		2.12		2.23				0.21
15	8.74	8.94	8.83		8.91	8.53	8.52	8.53	0.25
16	7.53	7.51	7.46		7.57	7.2	7.19	7.20	0.33
17	8.12	7.94	8.04		8.03	7.68	7.61	7.65	0.44
18	8.02	7.08	7.75		7.28	7.46	7.44	7.45	0.40

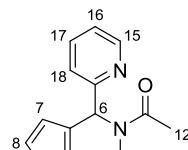


Table S12. Comparison of chemical shifts derived from the lowest energy structure calculations and the ^1H NMR spectrum of the *E*-conformation of **6**.

Proton-No.	Lowest Energy Structure Calculations [ppm]				Average	^1H NMR Data of 6 [ppm]			Δ [ppm]		
	Level 1 (0.0 kcal/mol) 45.9%	Level 2 (0.8 kcal/mol) 11.9%	Level 3 (2.2 kcal/mol) 1.1%			From	To	Average			
3 (ax)	2.88	2.82	3.79	2.89	2.89	2.99	2.82	2.91	0.02		
3 (eq)	2.68	2.79	2.84	2.71	2.71	2.99	2.82	2.91	0.20		
4 (ax)	2.52	4.16	3.17	2.86	2.86	3.08	3.04	3.06	0.20		
4 (eq)	4.53	5.02	4.51	4.63	4.63	5.02	4.98	5.00	0.37		
6	6.20	5.70	5.87	6.09	6.09	6.05	6.05	6.05	0.04		
7	6.90	6.71	7.18	6.87	6.87	6.94	6.92	6.93	0.06		
8	7.39	7.21	7.21	7.35	7.35	7.17	7.16	7.17	0.19		
	2.37	2.33	2.25								
12	1.87	2.64	2.02	2.04	2.04	1.64	1.82	2.51	2.33	2.33	0.18
	3.69		1.76		1.58						
15	8.94	8.83	8.78	8.91	8.91	8.62	8.6	8.61	0.30		
16	7.57	7.56	7.46	7.57	7.57	7.24	7.2	7.22	0.35		
17	7.99	8.16	8.04	8.03	8.03	7.68	7.61	7.65	0.38		
18	7.15	7.76	7.71	7.28	7.28	7.12	7.07	7.10	0.19		

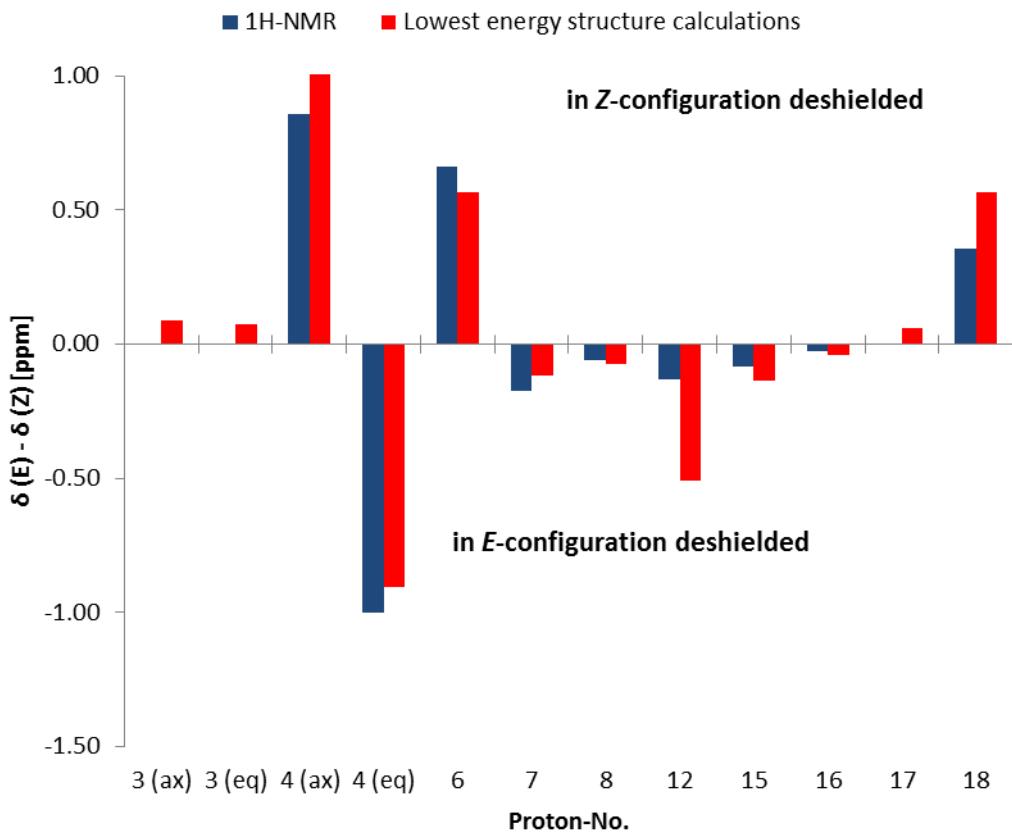


Figure S31. Differences between the chemical shifts of all protons of the *E*- and the *Z*-conformation of **4** derived from the ^1H NMR spectrum and the lowest energy structure calculations, respectively. The protons are deshielded in the *Z*-conformation in the case of positive values and deshielded in the *E*-conformation in the case of negative values.

1.7. 1-[4-(2-methoxyphenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl]ethanone (7)

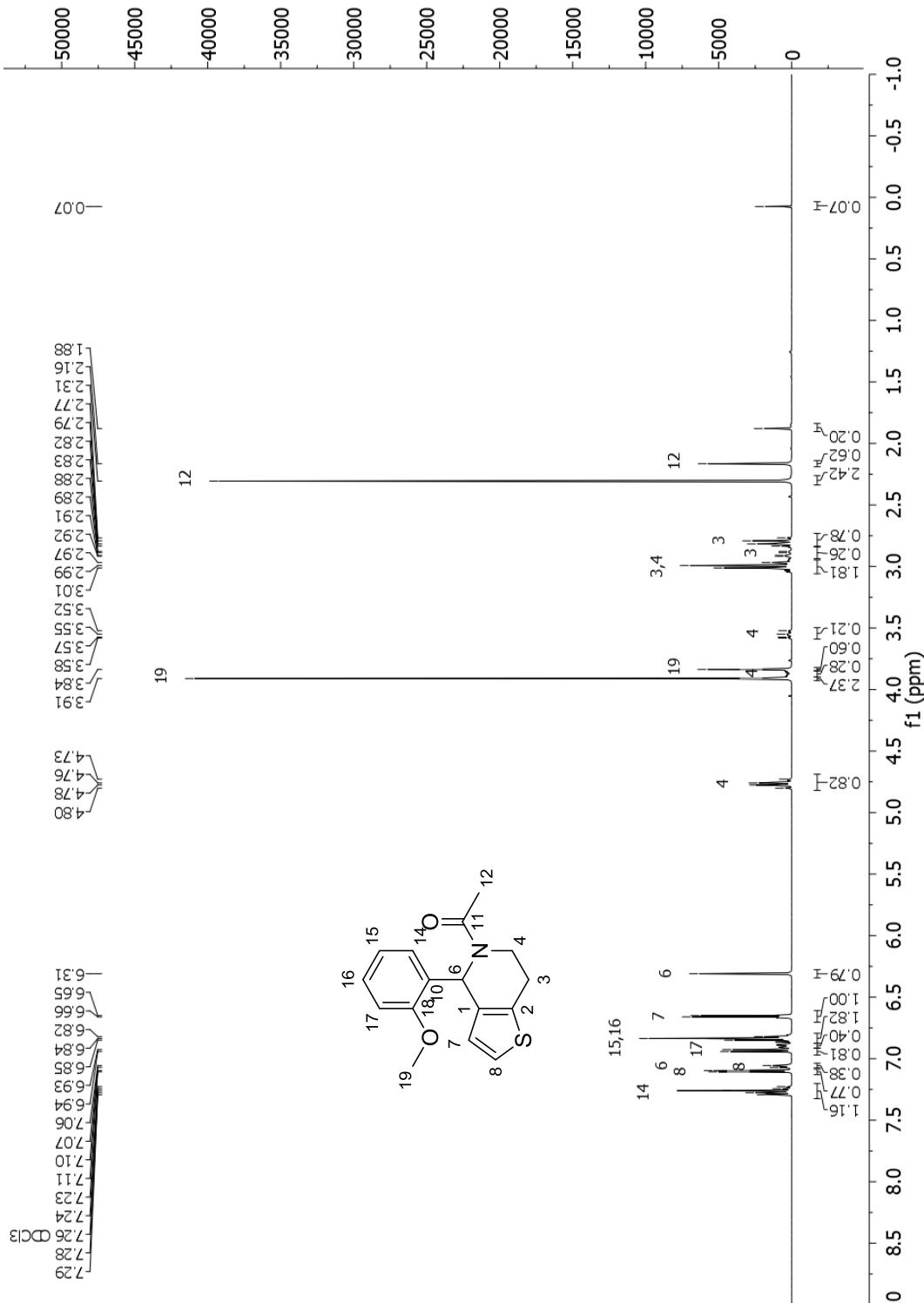


Figure S32. ^1H NMR (500 MHz, CDCl₃) at 298 K of 7.

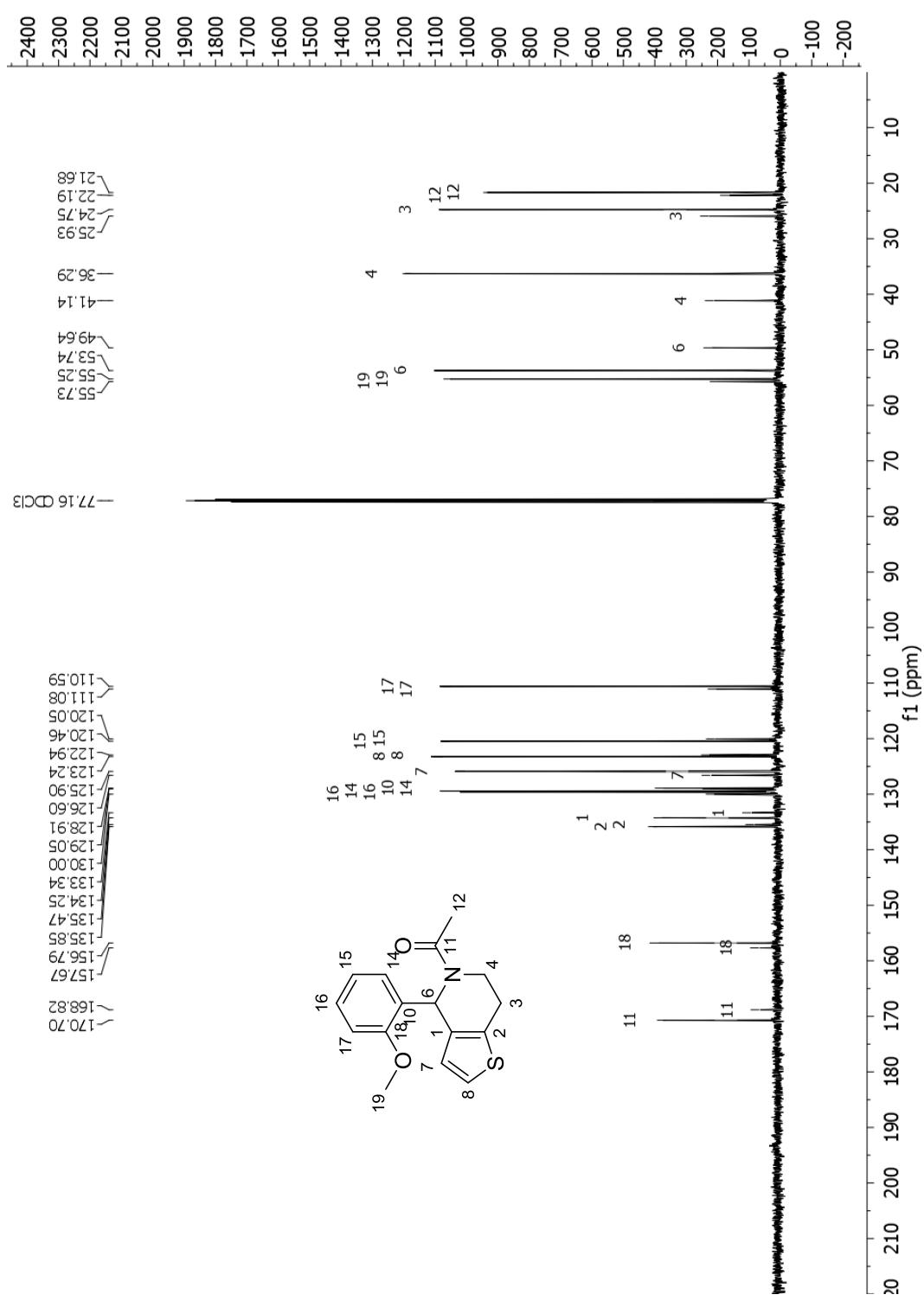


Figure S33. ^{13}C NMR (500 MHz, CDCl_3) at 298 K of 7.

1.7.1. Low Temperature 2D-NOESY and 1D Selective NOE of 7

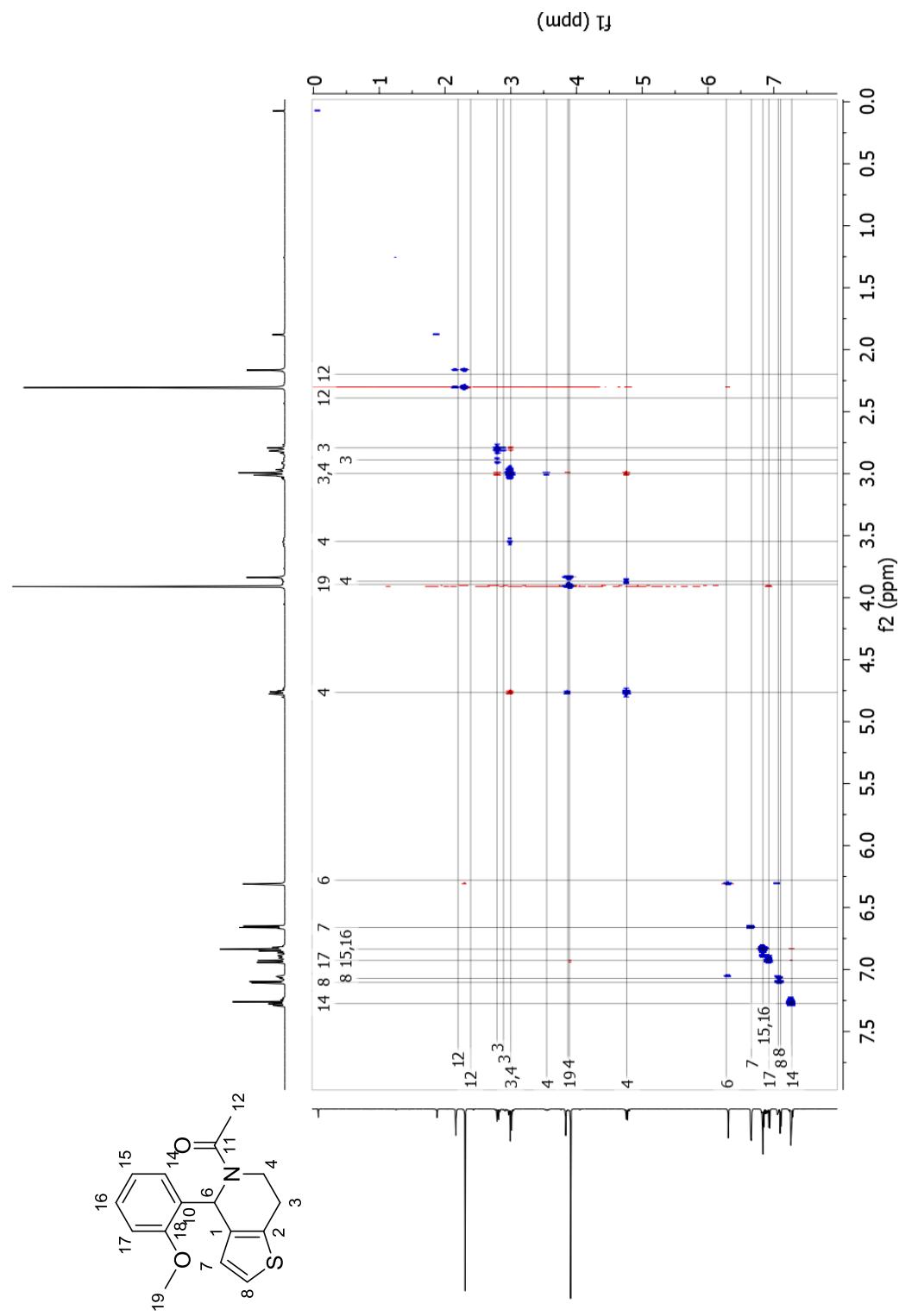


Figure S34. 2D-NOESY (500 MHz, CDCl₃) at 298 K of 7.

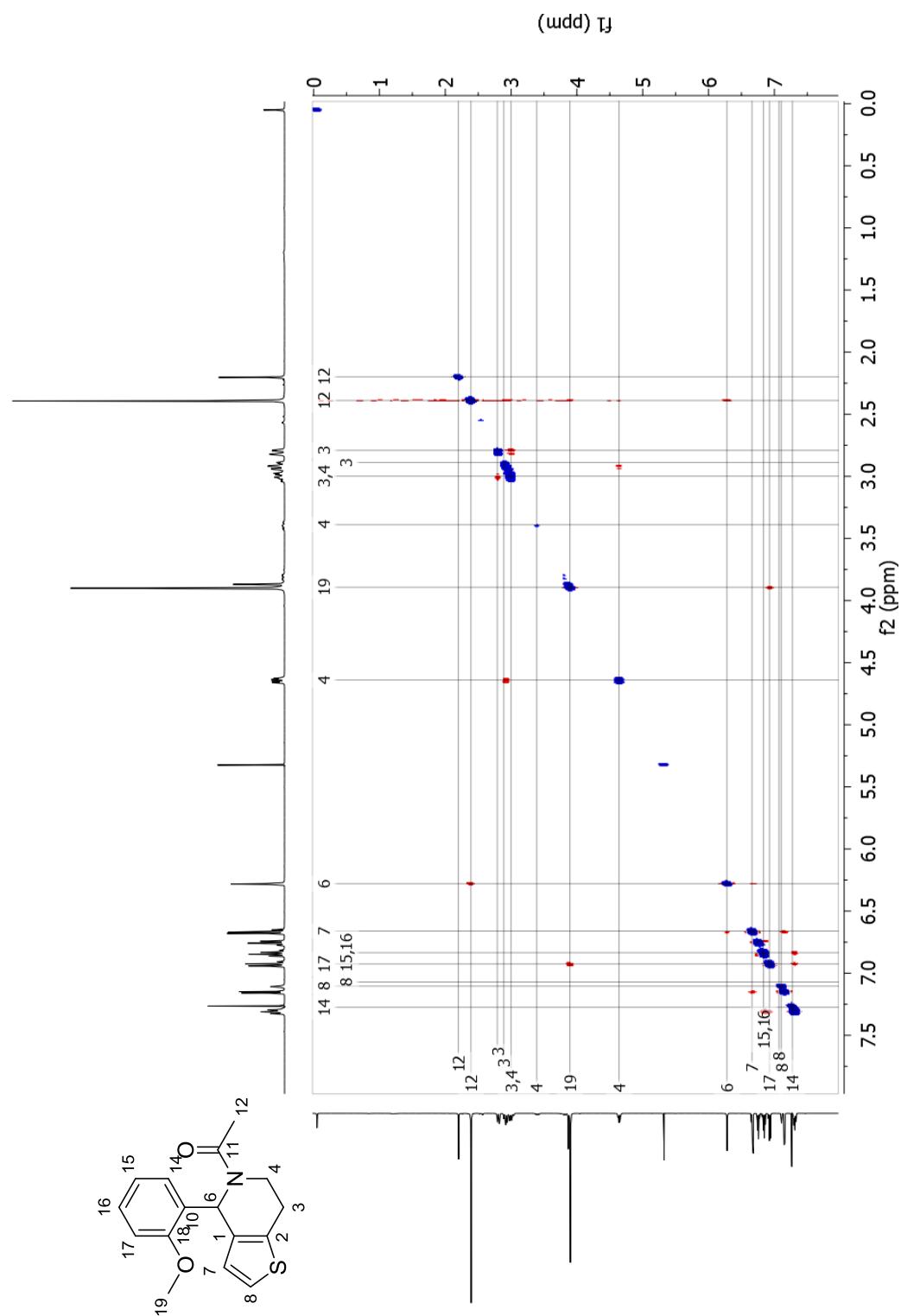


Figure S35. 2D-NOESY (500 MHz, CDCl_3) at 218 K of 7.

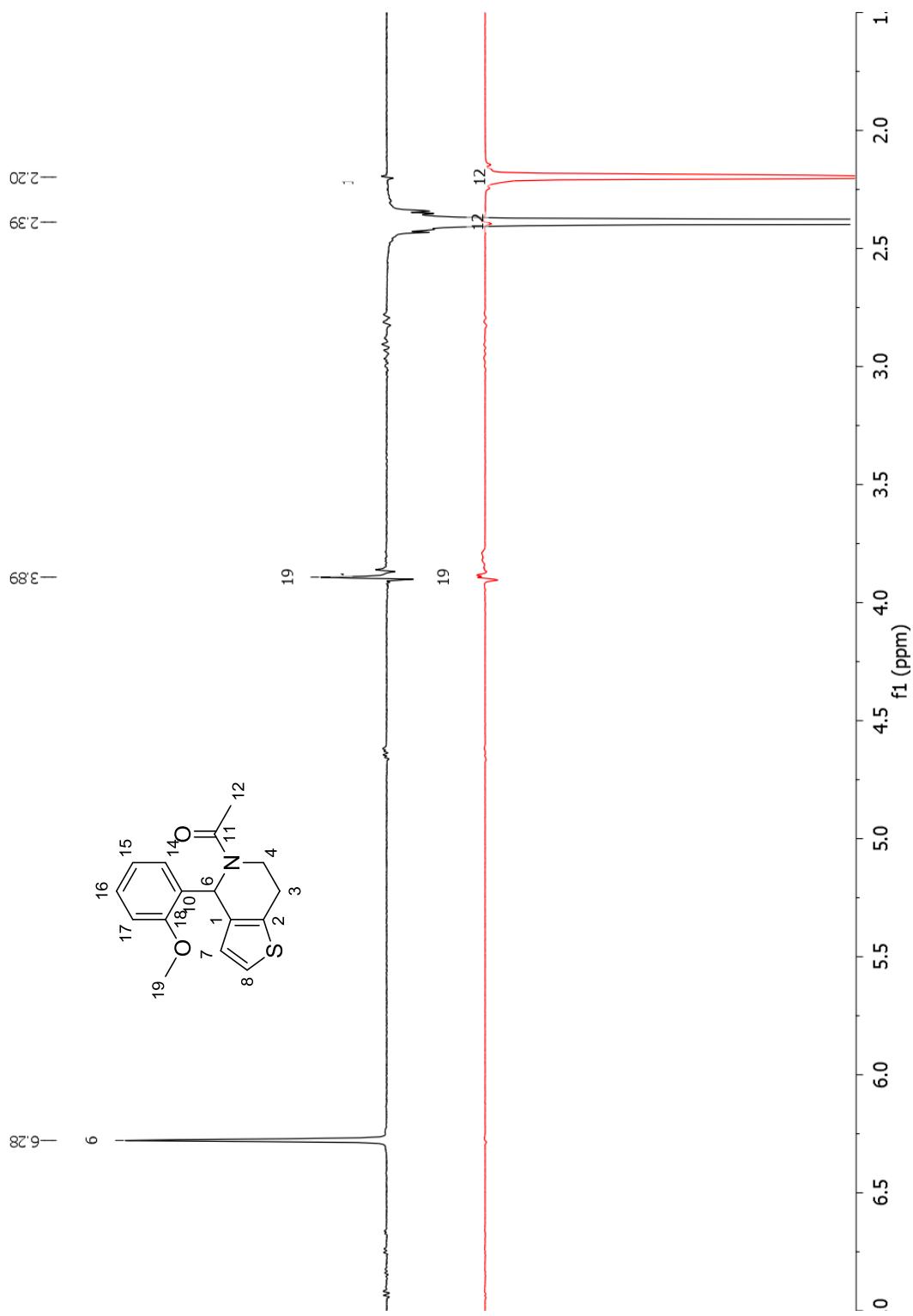


Figure S36. 1D selective NOE spectra of **7** at 2.39 ppm (black) and 2.20 ppm (red) (500 MHz, CDCl_3 , 218 K).

1.8. 1-[4-(2-hydroxyphenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl]ethanone (8)

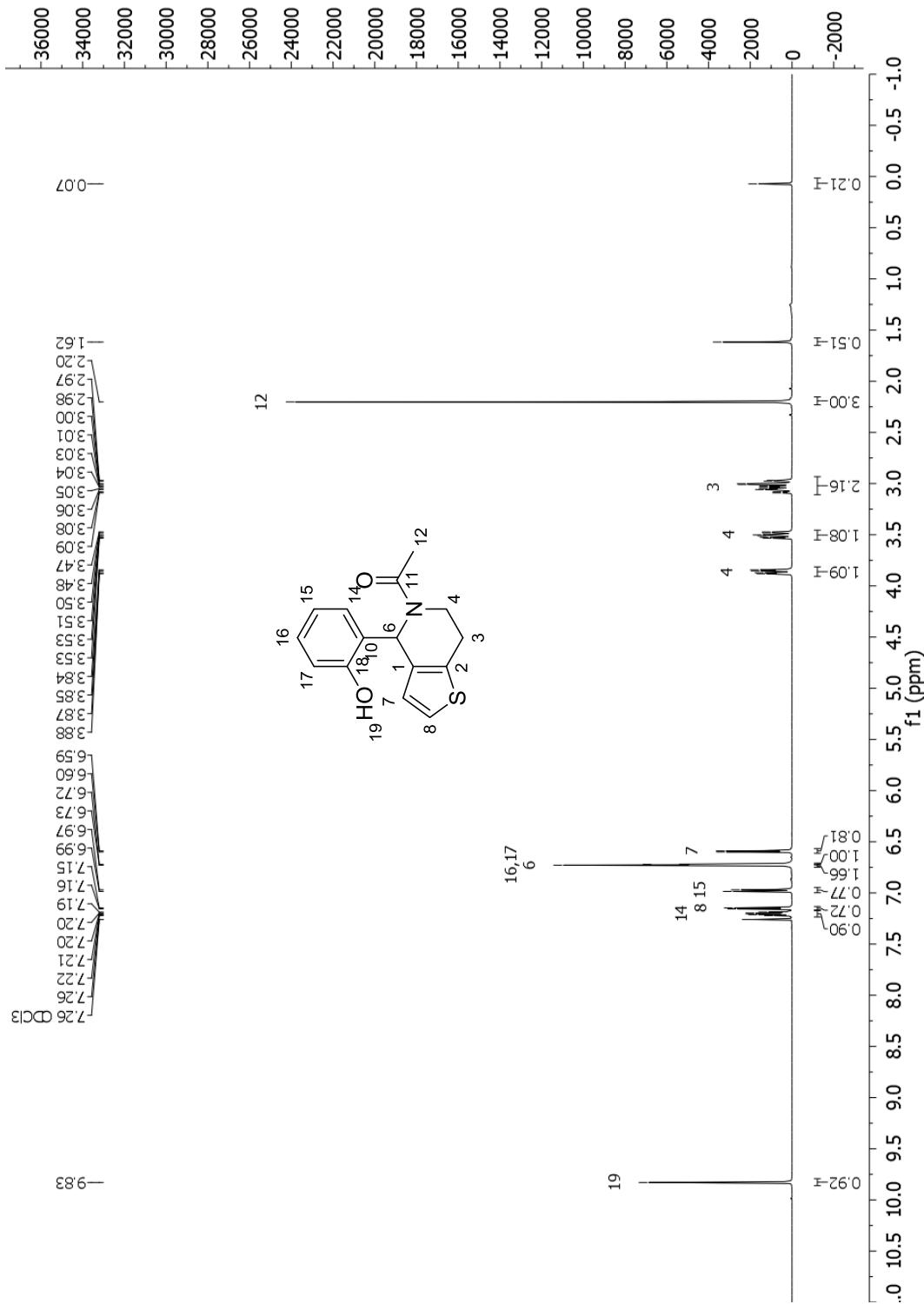


Figure S37. ^1H NMR (500 MHz, CDCl_3) at 298 K of 8.

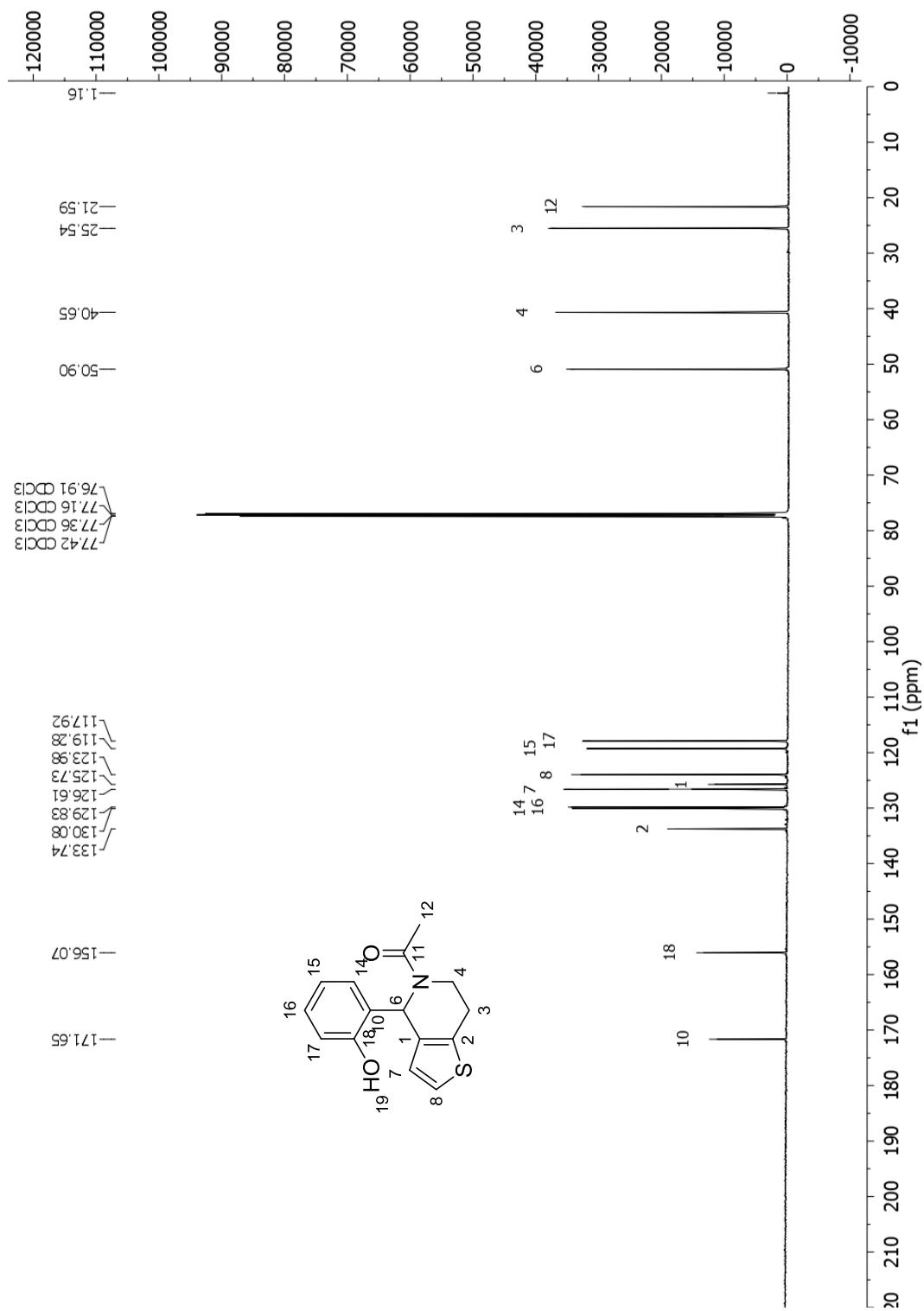


Figure S38. ${}^{13}\text{C}$ NMR (500 MHz, CDCl_3) at 298 K of 8.

1.8.1. Low Temperature 2D-NOESY and 1D Selective NOE of 8

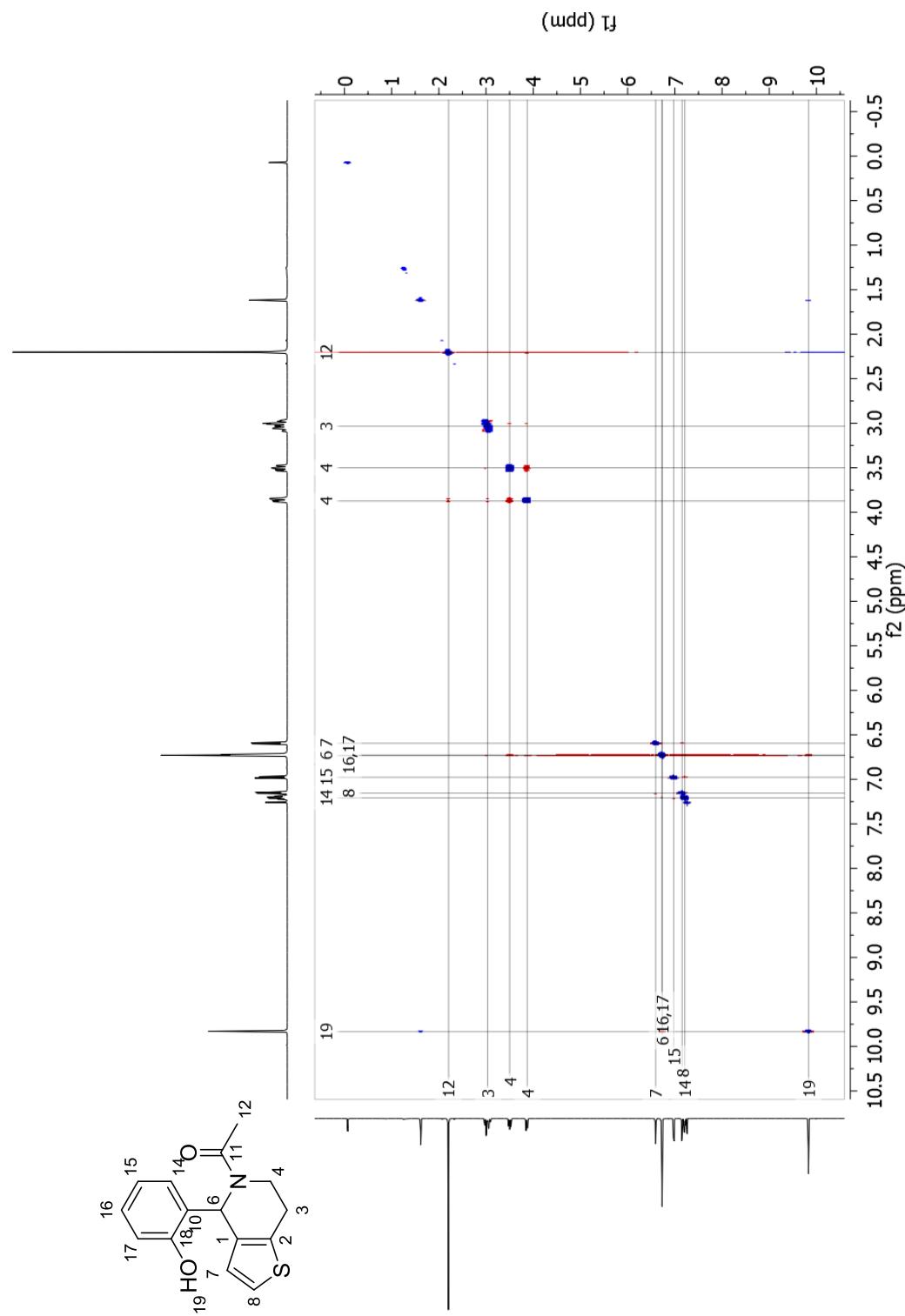


Figure S39. 2D-NOESY (500 MHz, CDCl₃) at 298 K of 8.

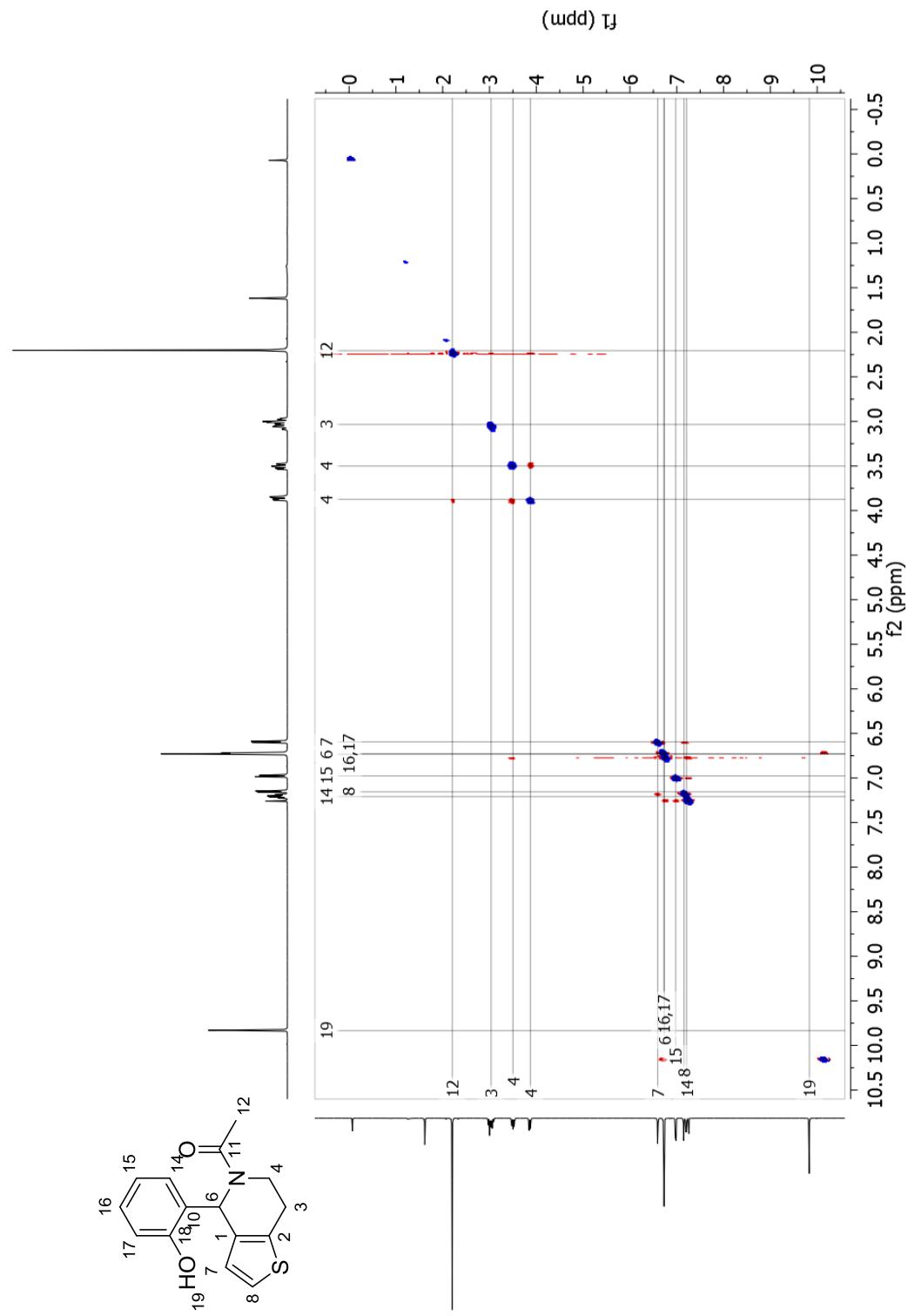


Figure S40. 2D-NOESY (500 MHz, CDCl₃) at 218 K of **8**.

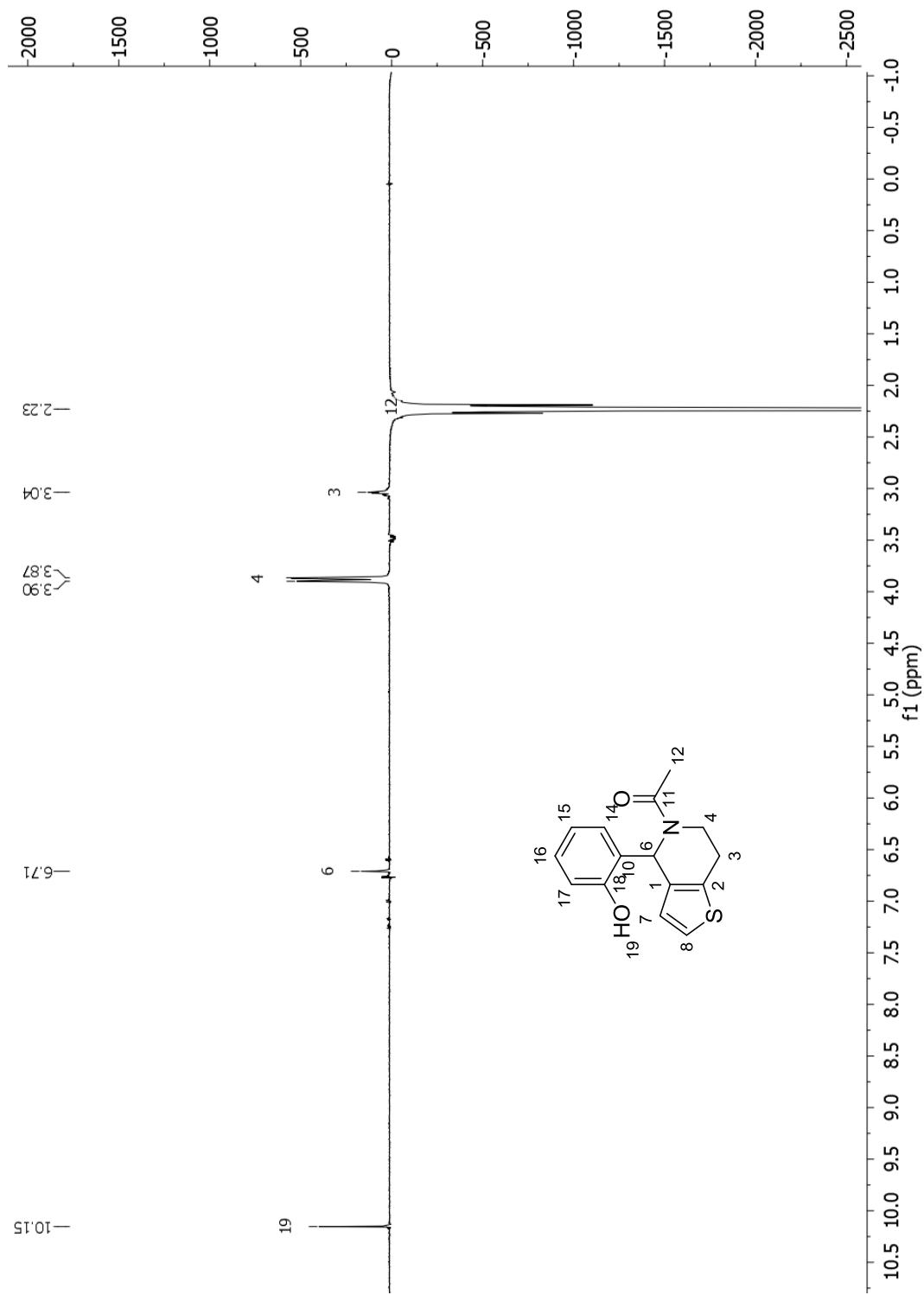


Figure S41. 1D selective NOE spectra of **8** at 2.23 ppm (black) (500 MHz, CDCl₃, 298 K).

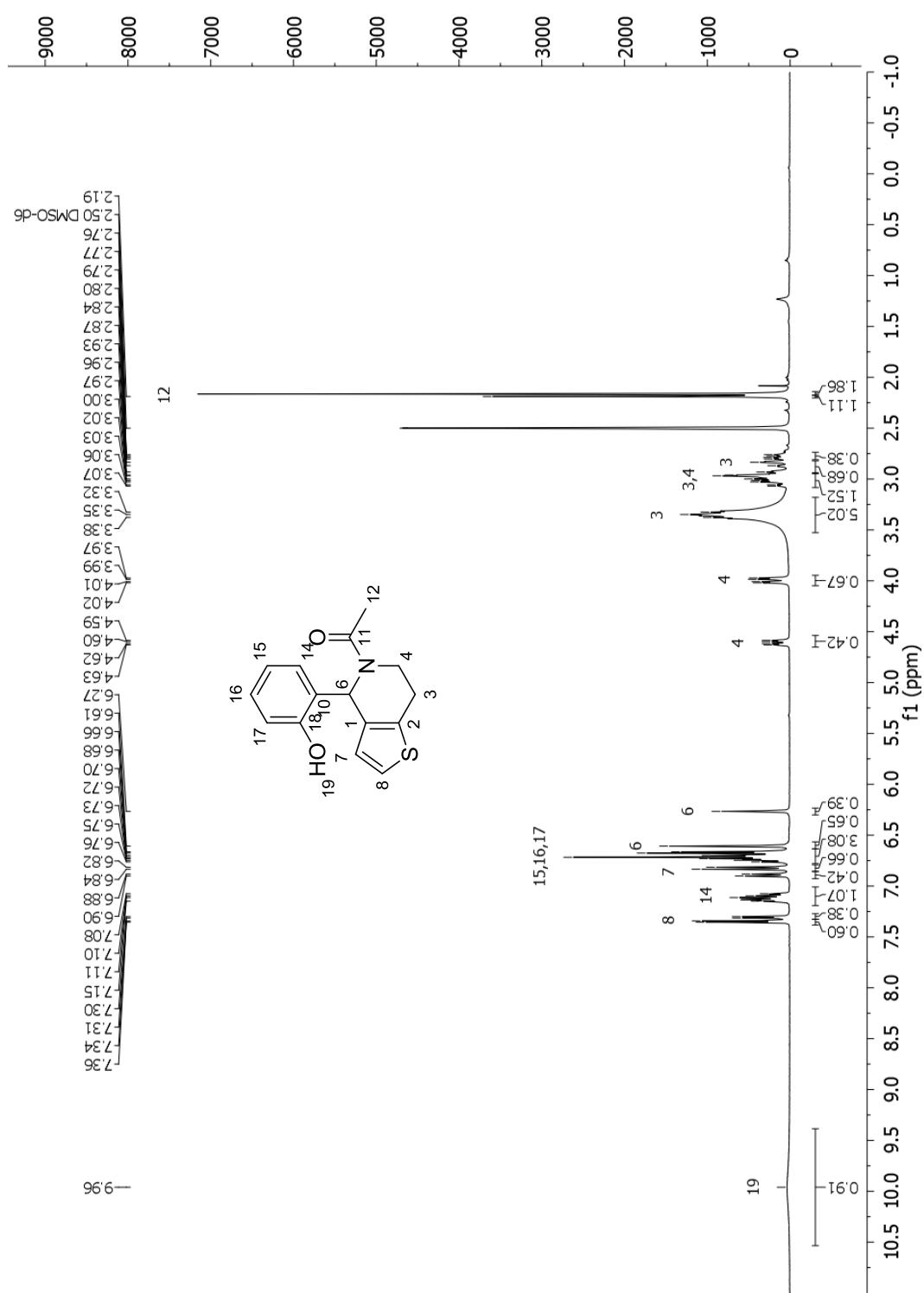


Figure S42. ^1H NMR (400 MHz, DMSO-d6) at 298 K of **8**.

1.8.2. Calculation of the Boltzmann Population of the *E*- and *Z*-Conformers of **8**

Table S13. Boltzmann population distribution of the *E*- and *Z*-conformers of **8** derived from the lowest energy calculations.

Energy Level No.	Conformation	Energy [kcal/mol]	Energy [J/mol]	Boltzmann Factor	Population (N _i /N _{total})	
					<i>E</i>	<i>Z</i>
1	<i>Z</i>	4.8	20083.2	0.00		0.0003
2	<i>E</i>	7.8	32635.2	0.00	0.0000	
3	<i>Z</i>	0.0	0.0	1.00		0.9993
4	<i>E</i>	5.1	21338.4	0.00	0.0002	
5	<i>E</i>	9.7	40584.8	0.00	0.0000	
6	<i>Z</i>	7.9	33053.6	0.00		0.0000
7	<i>Z</i>	5.0	20920.0	0.00		0.0002
8	<i>E</i>	7.2	30124.8	0.00	0.0000	
					Total	0.00 1.00

1.8.3. Comparison of Shifts from Lowest Energy Structure Calculations and ^1H NMR of 8

Table S14. Comparison of chemical shifts derived from the lowest energy structure calculations and the ^1H NMR spectrum of the Z-conformation of 8.

Proton-No.	Lowest Energy Structure Calculations [ppm]		^1H NMR Data of 8 [ppm]			Δ [ppm]
	Level 1 (0.0 kcal/mol)	100%	From	To	Average	
3 (ax)	3.03		3.09	2.97	3.03	0.00
3 (eq)	2.80		3.09	2.97	3.03	0.23
4 (ax)	3.66		3.88	3.84	3.86	0.20
4 (eq)	3.44		3.53	3.47	3.50	0.06
6	6.50		6.73	6.72	6.73	0.23
7	6.75		6.6	6.59	6.60	0.15
8	7.34		7.16	7.15	7.16	0.18
	2.17					
12	2.15	2.09	2.2	2.2	2.20	0.05
	1.96					
14	7.11		6.73	6.73	6.73	0.38
15	6.96		6.73	6.72	6.73	0.24
16	7.59		7.22	7.19	7.21	0.39
17	7.29		6.99	6.97	6.98	0.31
19	9.94		9.83	9.83	9.83	0.11

1.8.4. IR Spectra of 8

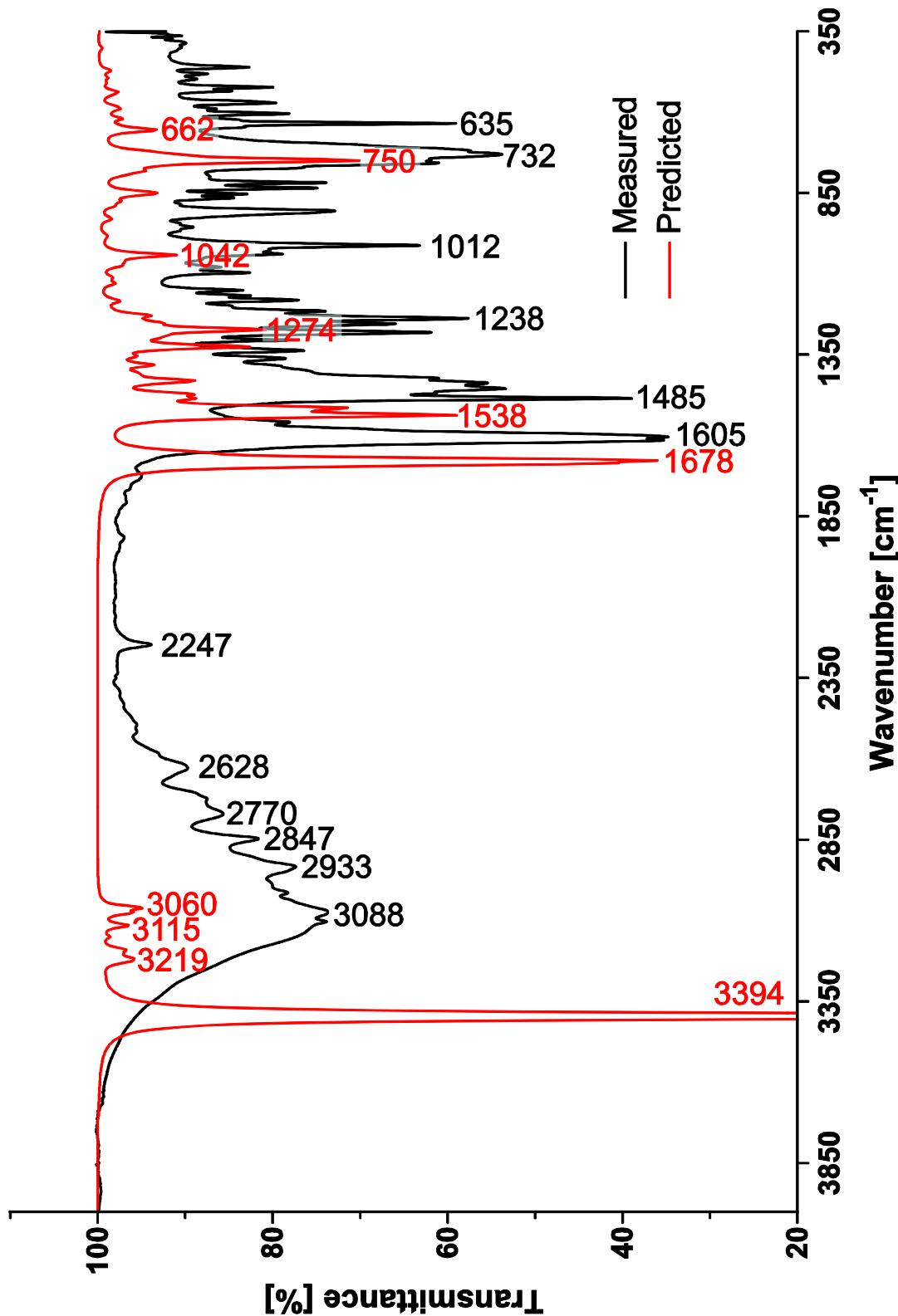


Figure S43. Measured and Predicted IR of 8. The spectrum was recorded in the solid state.

2. NMR spectra of intermediates 9a-13ca

2.1. N-[2-(2-Thienyl)ethyl]benzamide (9a)

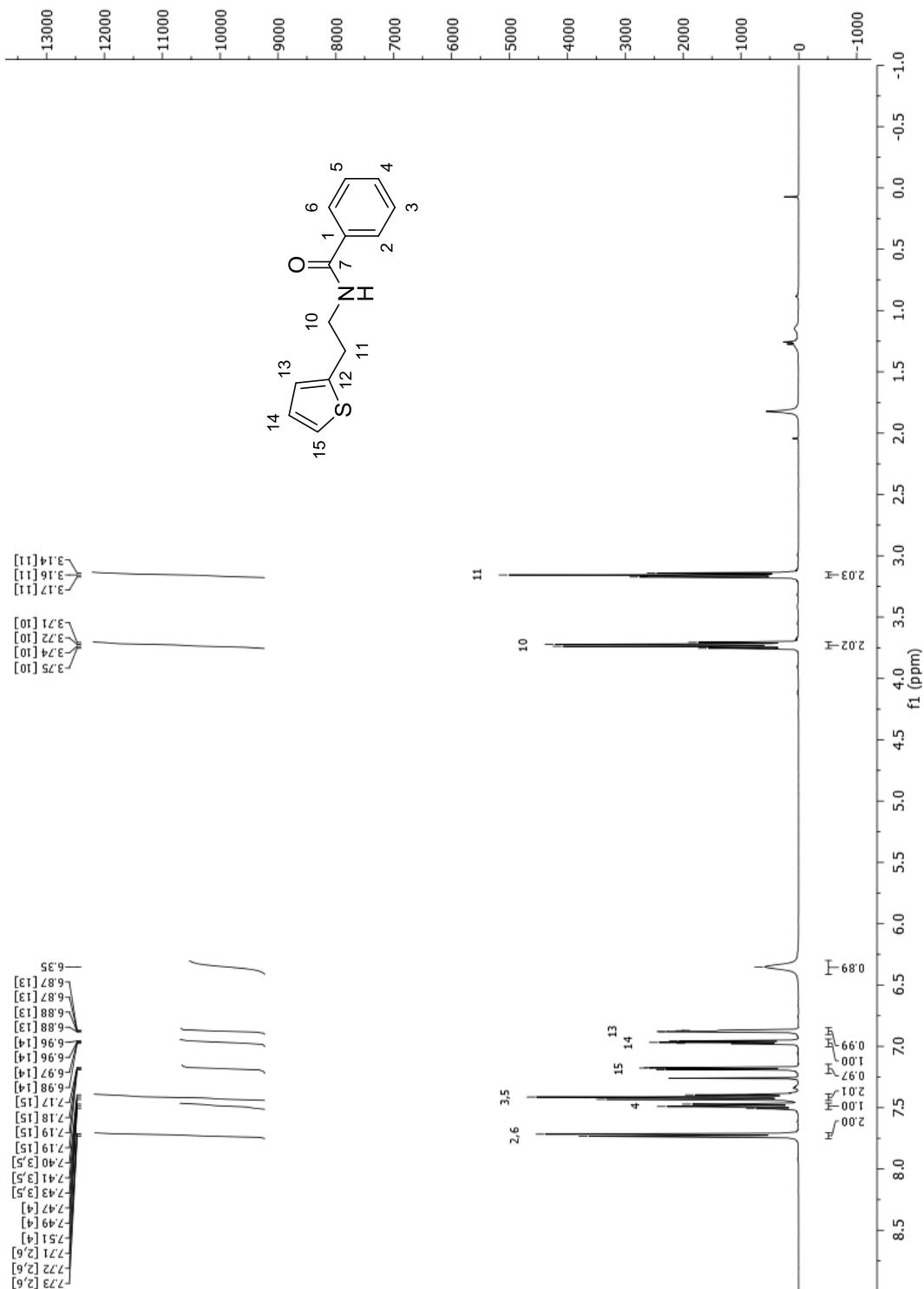


Figure S44. ^1H NMR (400 MHz, CDCl_3) at 298 K of **9a**.

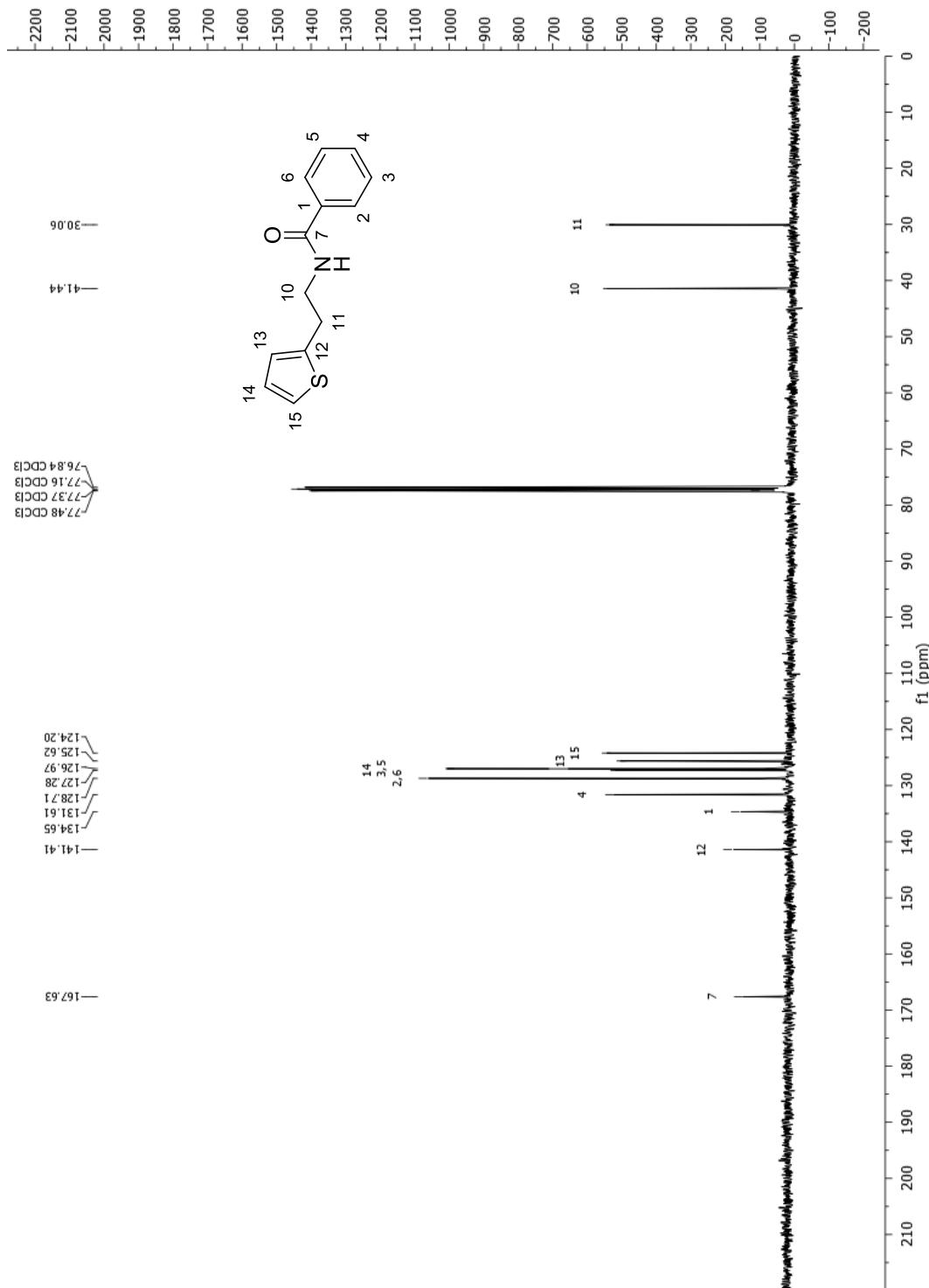


Figure S45. ^{13}C NMR (400 MHz, CDCl_3) at 298 K of 9a.

2.2. 4-Phenyl-6,7-dihydrothieno[3,2-*c*]pyridine (9b)

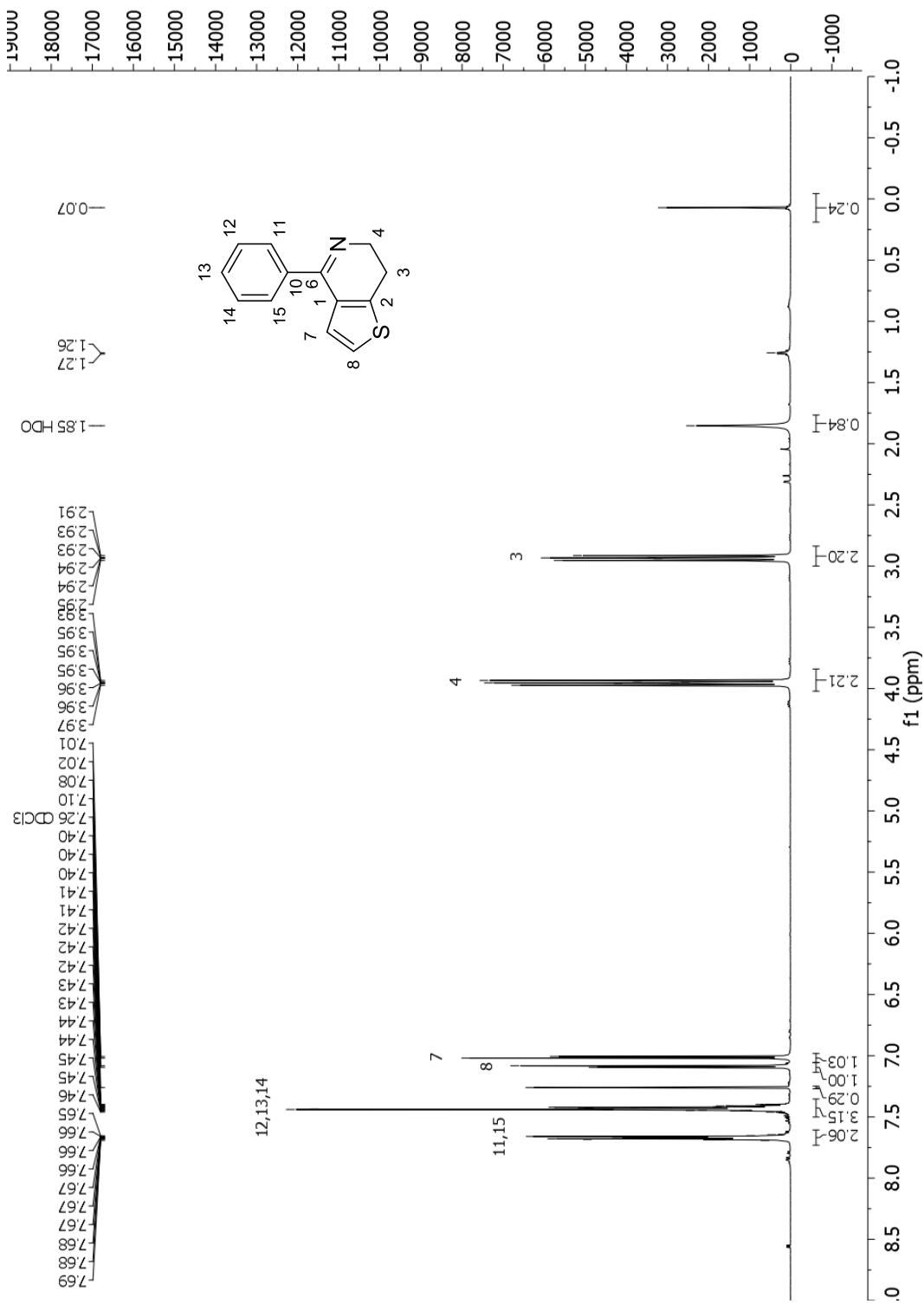


Figure S46. ^1H NMR (400 MHz, CDCl_3) at 298 K of 9b.

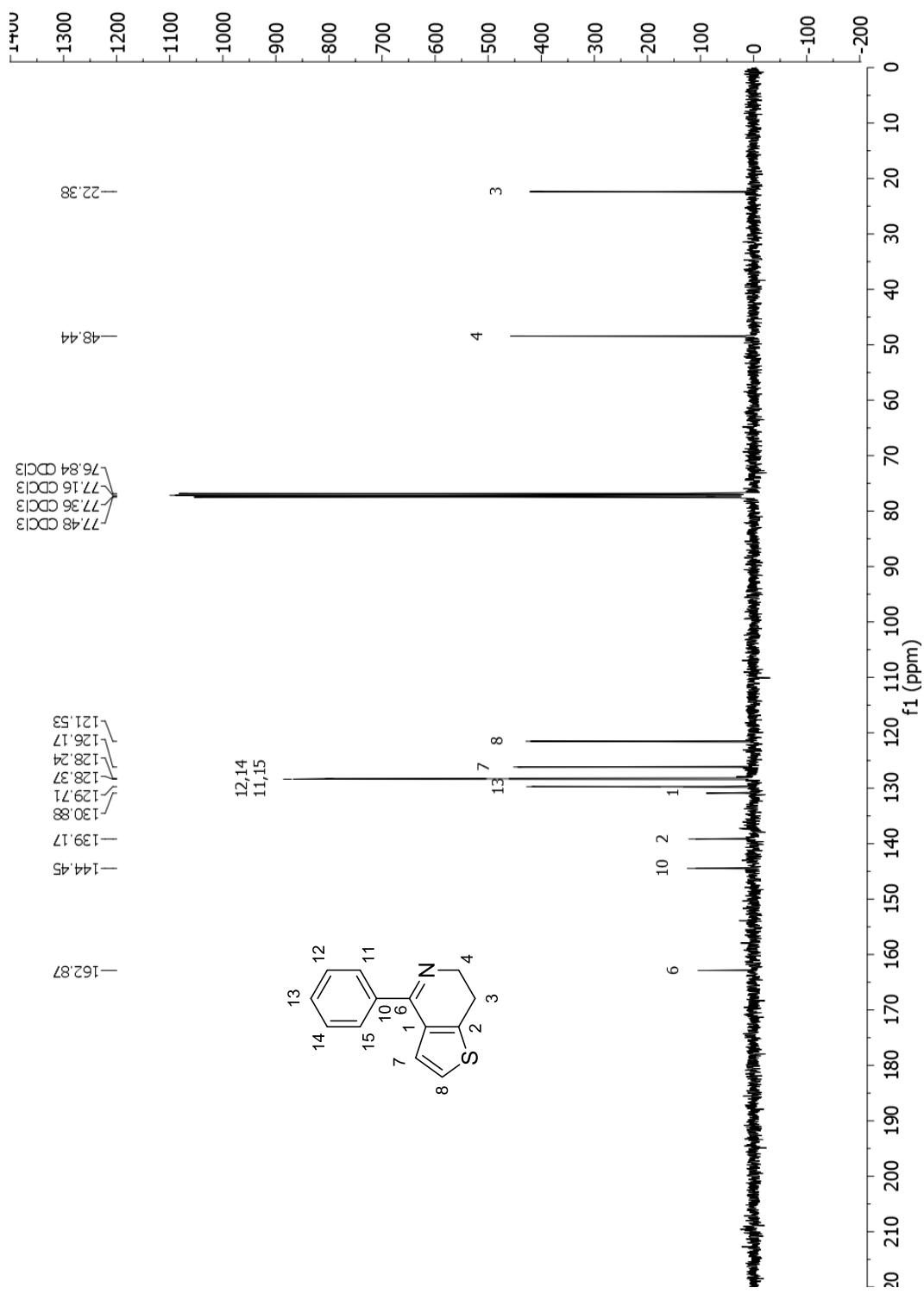


Figure S47. ^{13}C NMR (400 MHz, CDCl₃) at 298 K of **9b**.

2.3. 4-Phenyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**9c**)

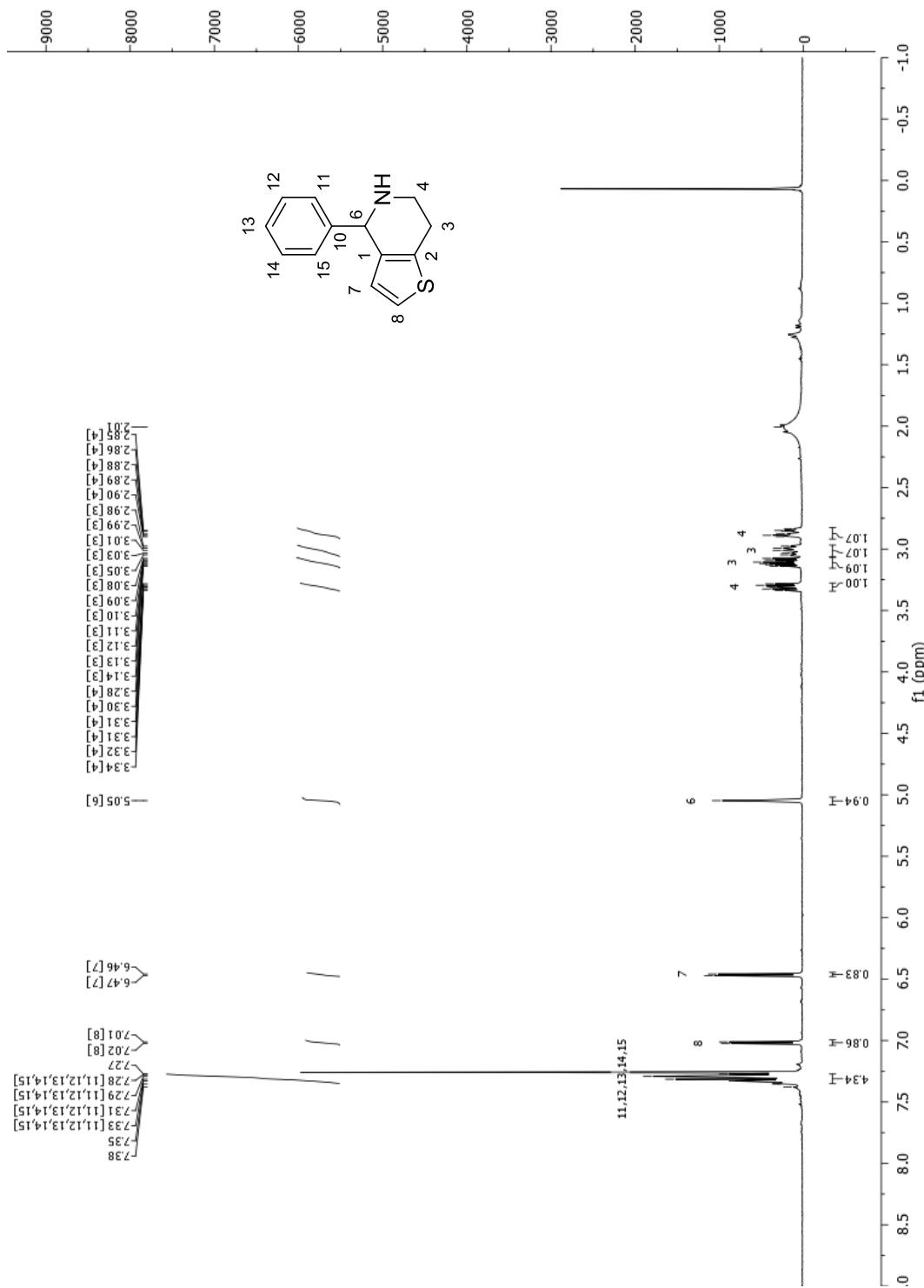


Figure S48. ^1H NMR (400 MHz, CDCl_3) at 298 K of **9c**.

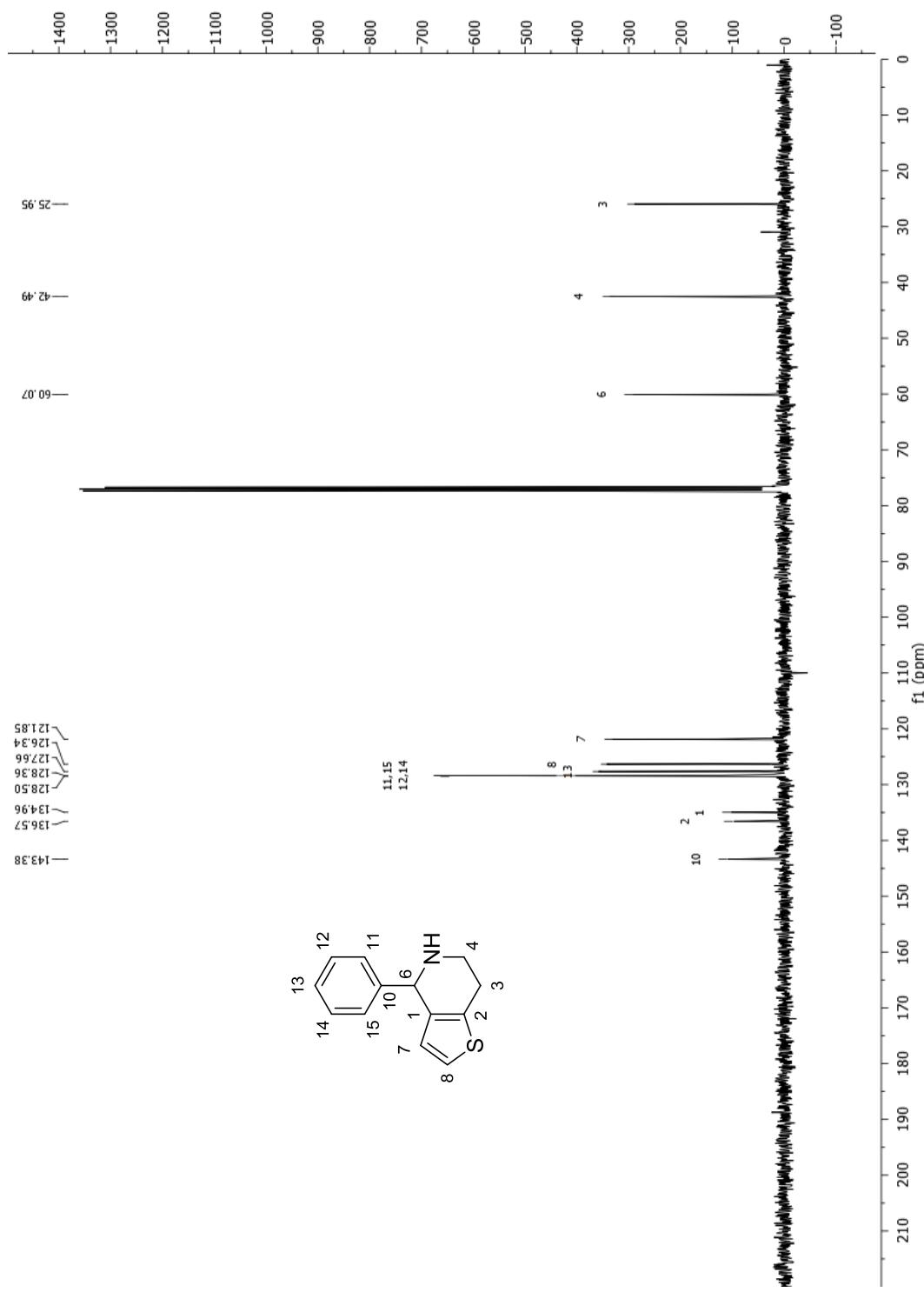


Figure S49. ^{13}C NMR (400 MHz, CDCl_3) at 298 K of 9c.

2.4. [2-(2-Thienyl)ethylamino](m-tolyl)formaldehyde (10a)

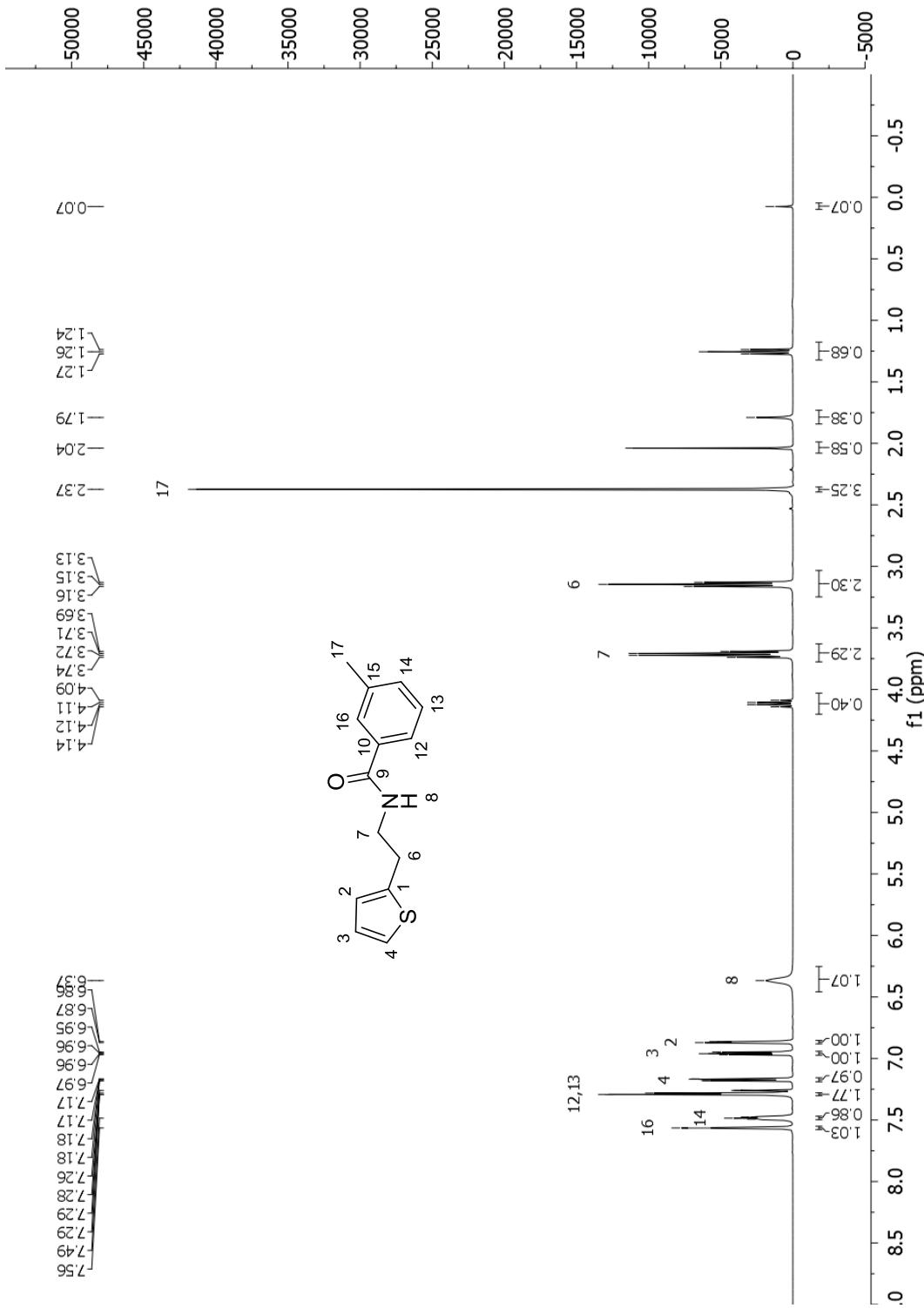


Figure S50. ^1H NMR (400 MHz, CDCl_3) at 298 K of 10a.

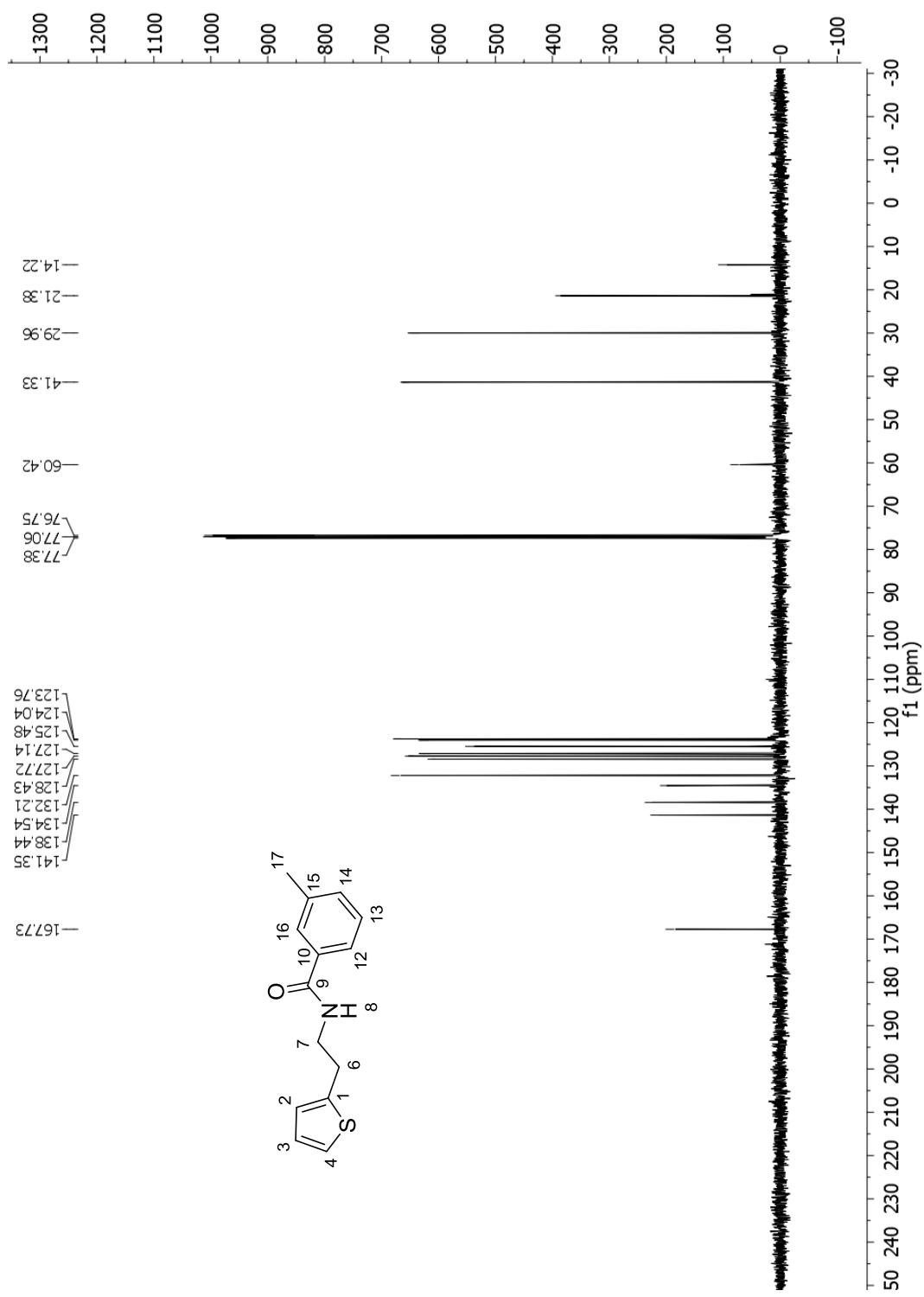


Figure S51. ^{13}C NMR (400 MHz, CDCl_3) at 298 K of 10a.

2.5. 4-(m-Tolyl)-6,7-dihydrothieno[3,2-*c*]pyridine (10b**)**

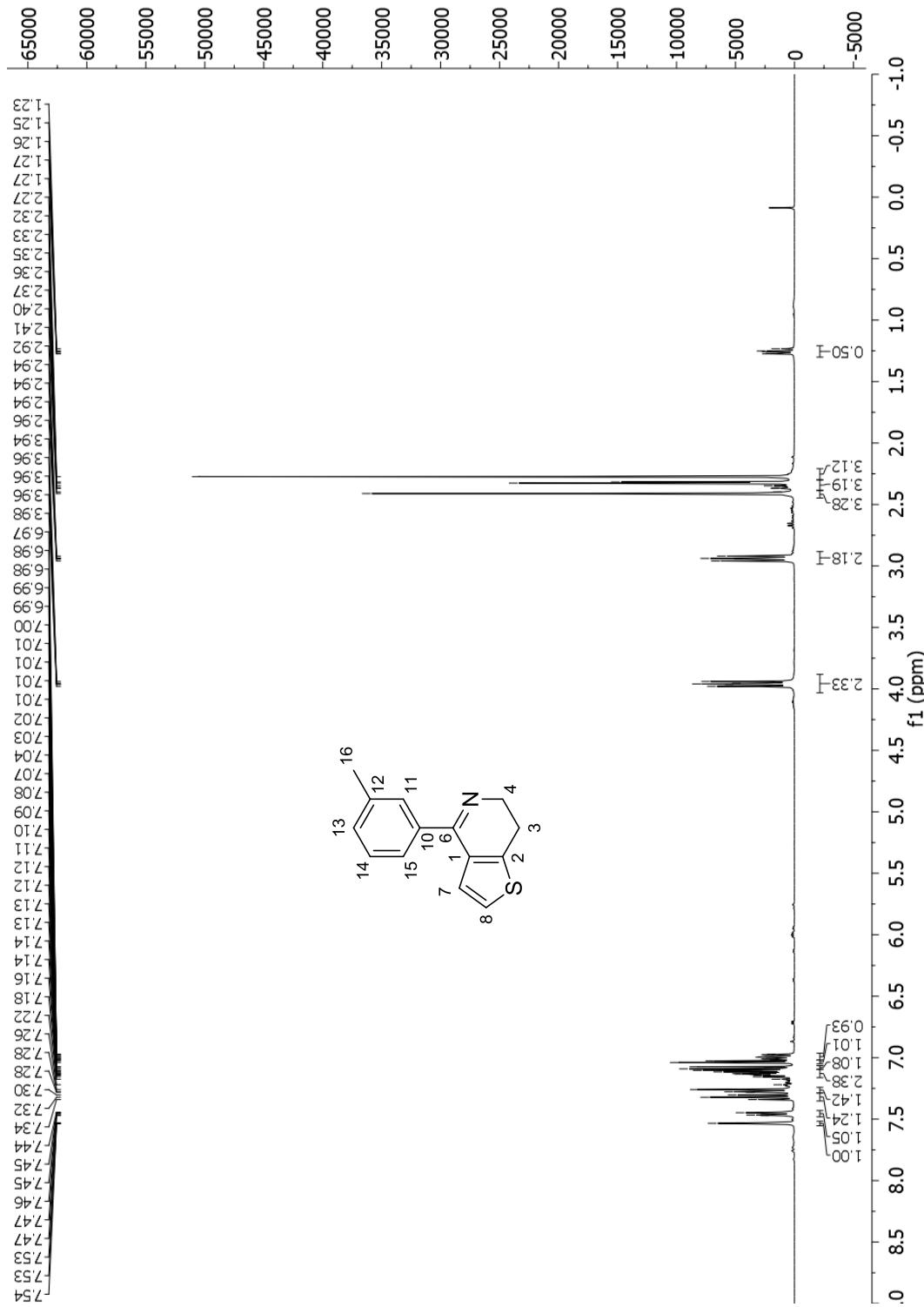


Figure S52. Crude ^1H NMR (400 MHz, CDCl_3) at 298 K of **10b**.

2.6. 4-(m-Tolyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (10c)

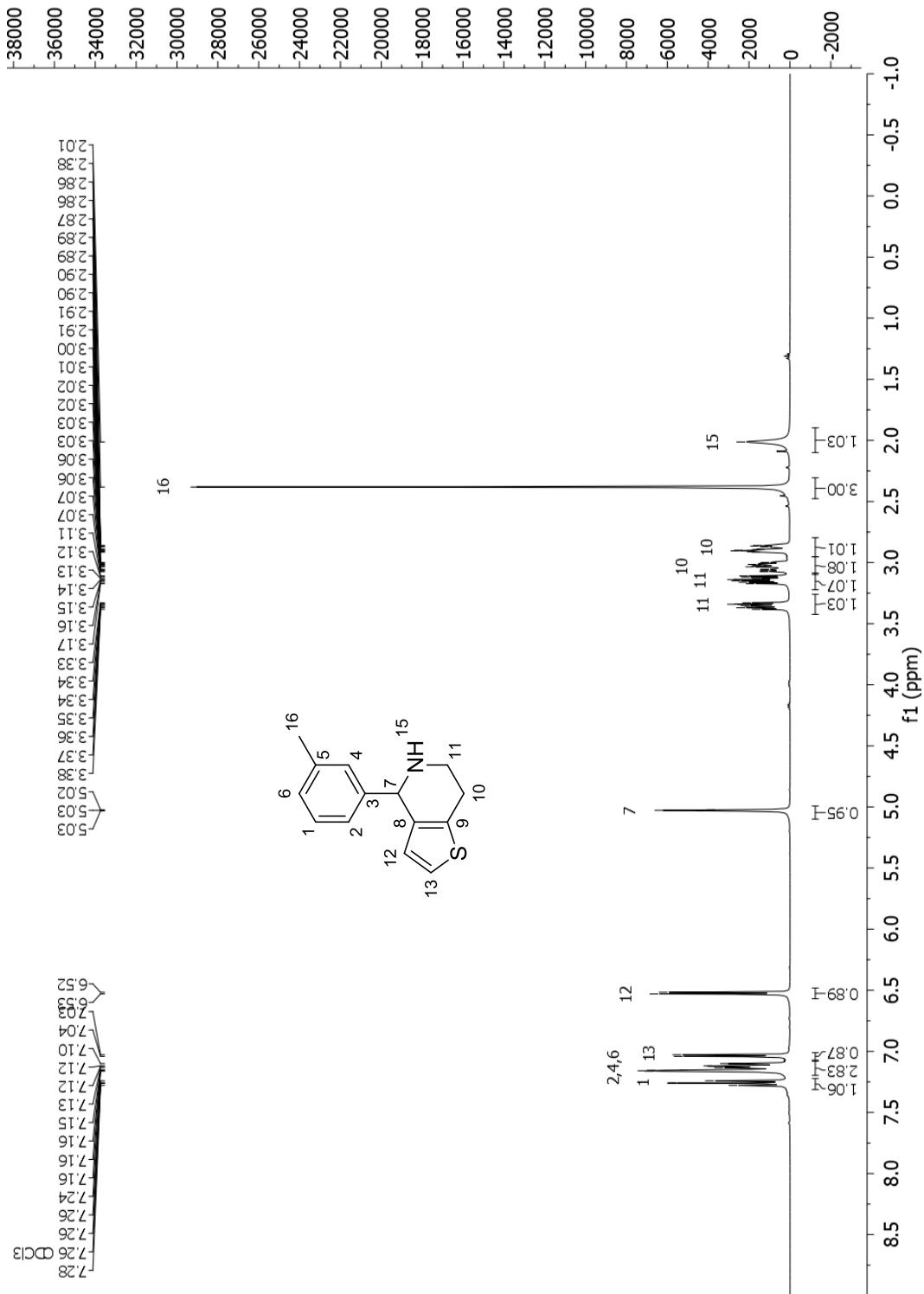


Figure S53. ^1H NMR (400 MHz, CDCl_3) at 298 K of 10c.

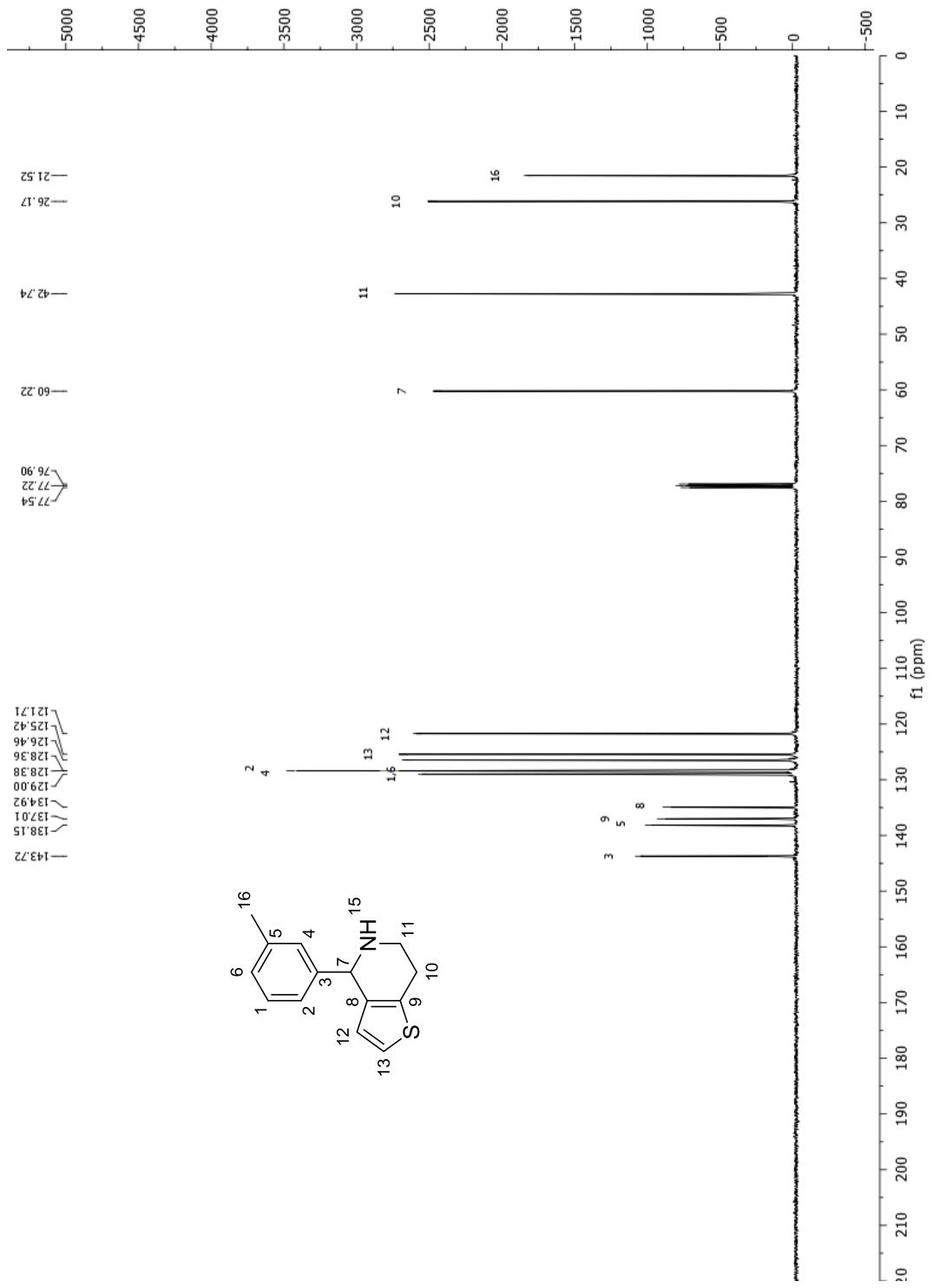


Figure S54. ^{13}C NMR (400 MHz, CDCl_3) at 298 K of **10c**.

2.7. Cyclohexanecarboxylic acid (2-thiophen-2-ylethyl)amide (11a)

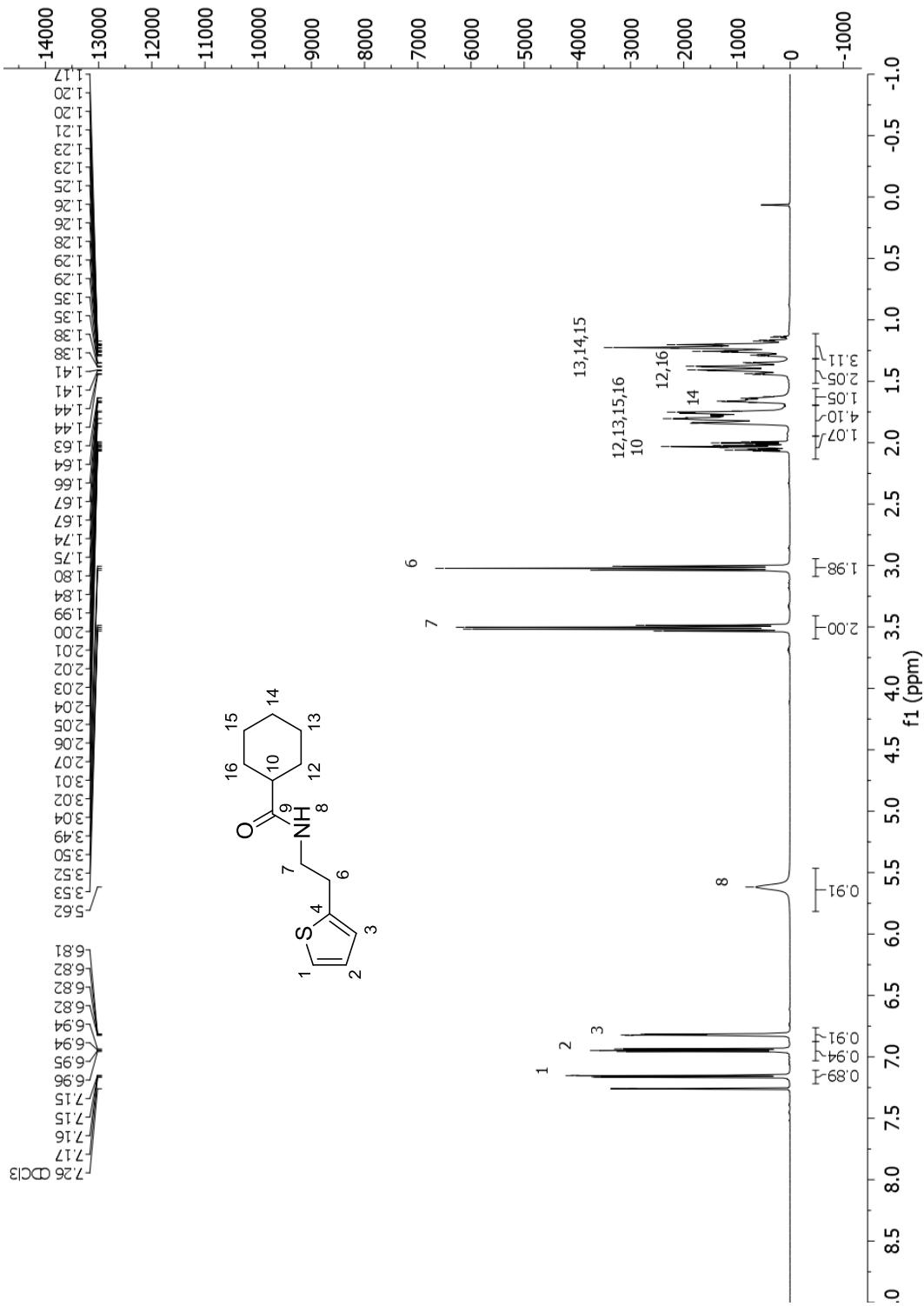


Figure S55. ^1H NMR (400 MHz, CDCl_3) at 298 K of 11a.

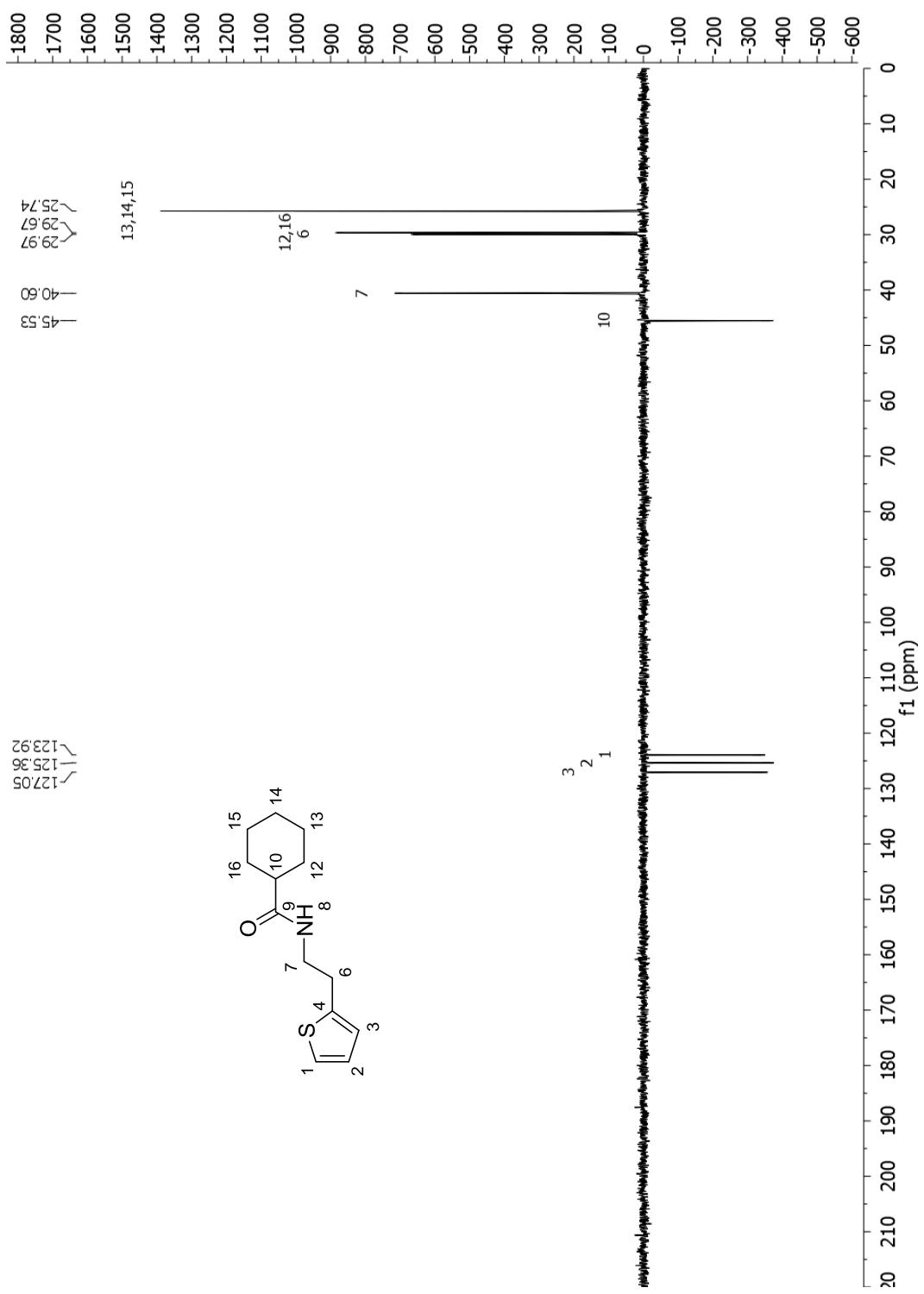


Figure S56. DEPT ^{13}C NMR (400 MHz, CDCl_3) at 298 K of 11a.

2.8. 7-Cyclohexyl-6,7-dihydrothieno[3,2-*c*]pyridine (11b**)**

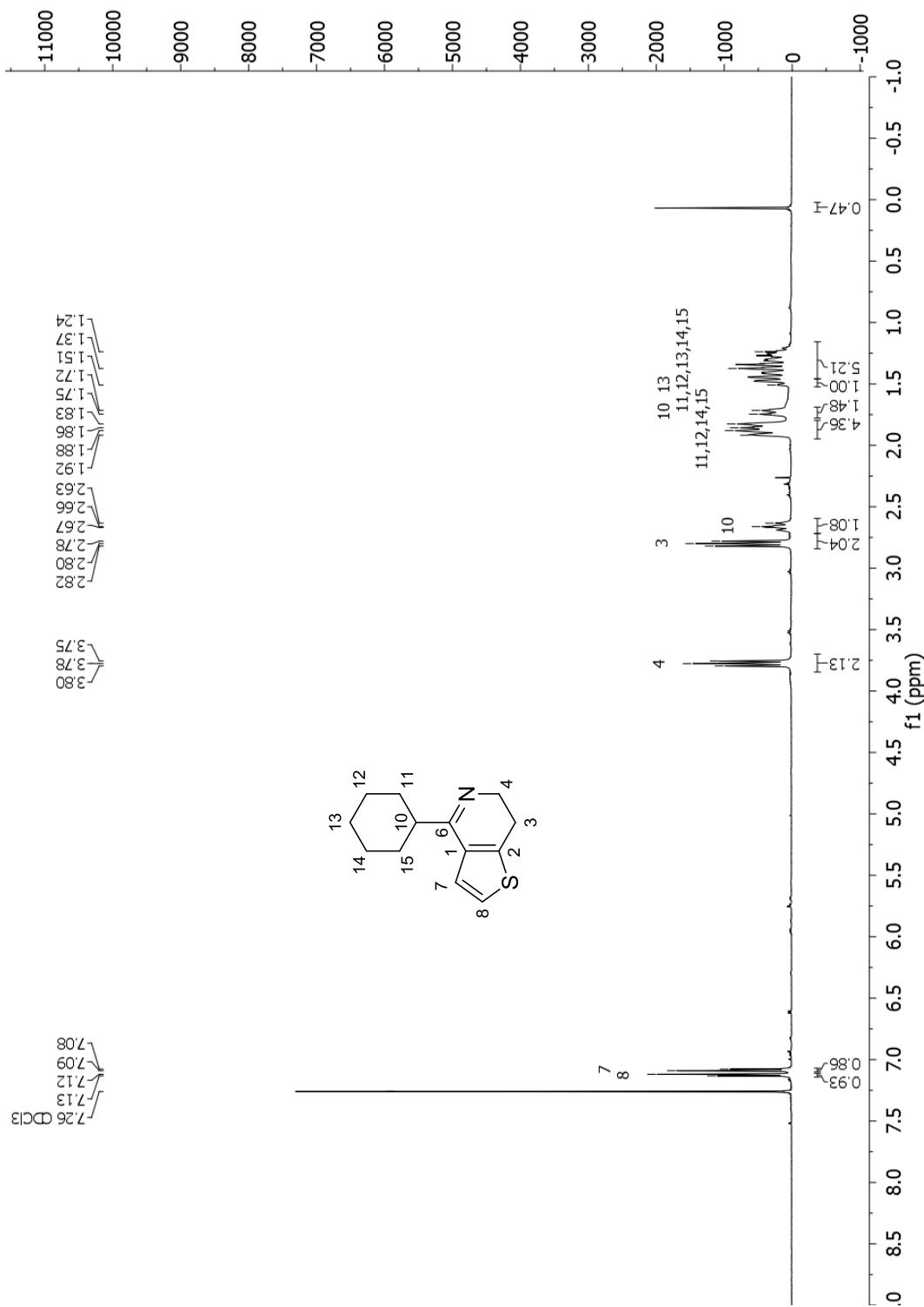


Figure S57. ^1H NMR (400 MHz, CDCl_3) at 298 K of **11b**

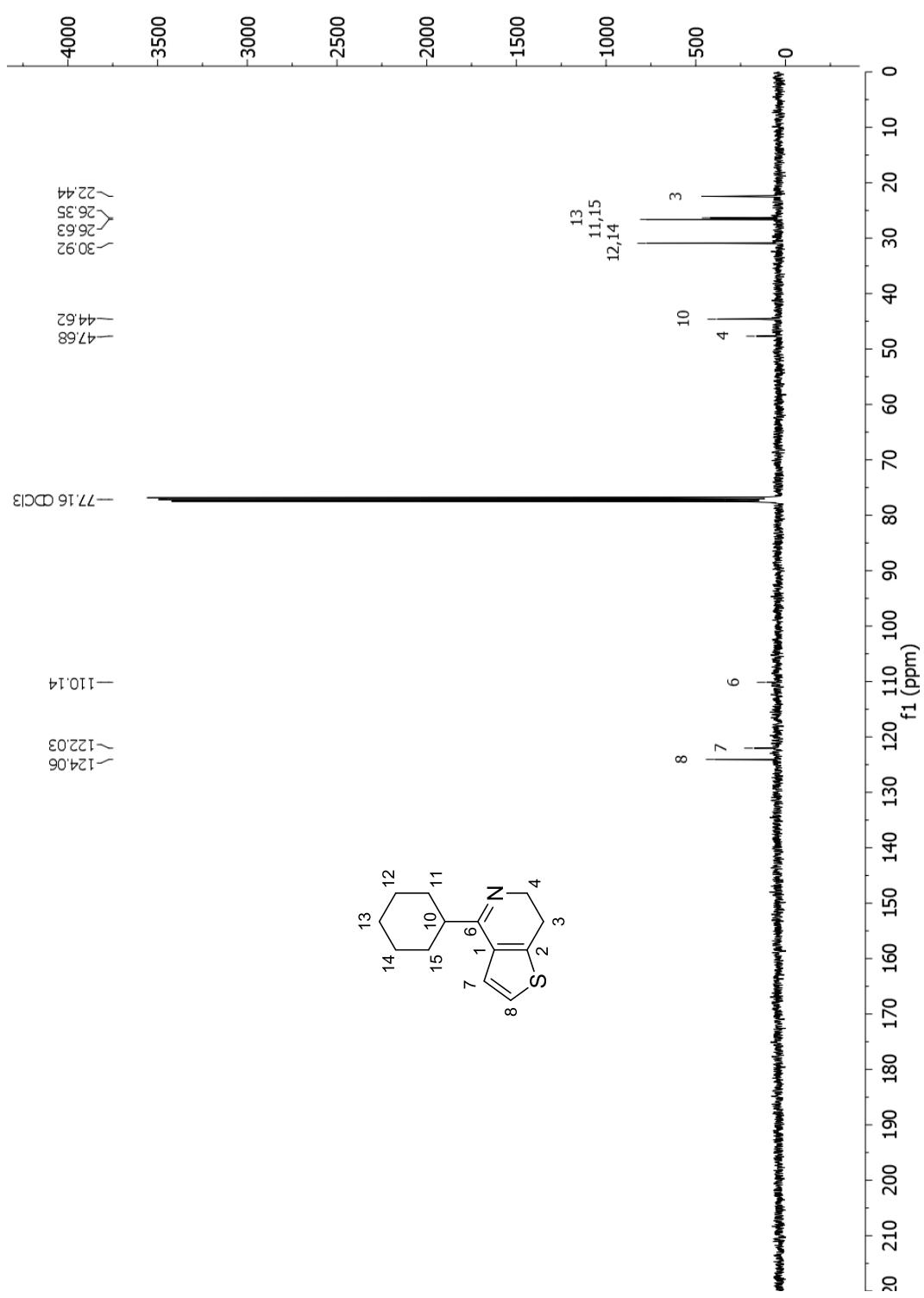


Figure S58. ^{13}C NMR (400 MHz, CDCl_3) at 298 K of 11b

2.9. 7-Cyclohexyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (11c)

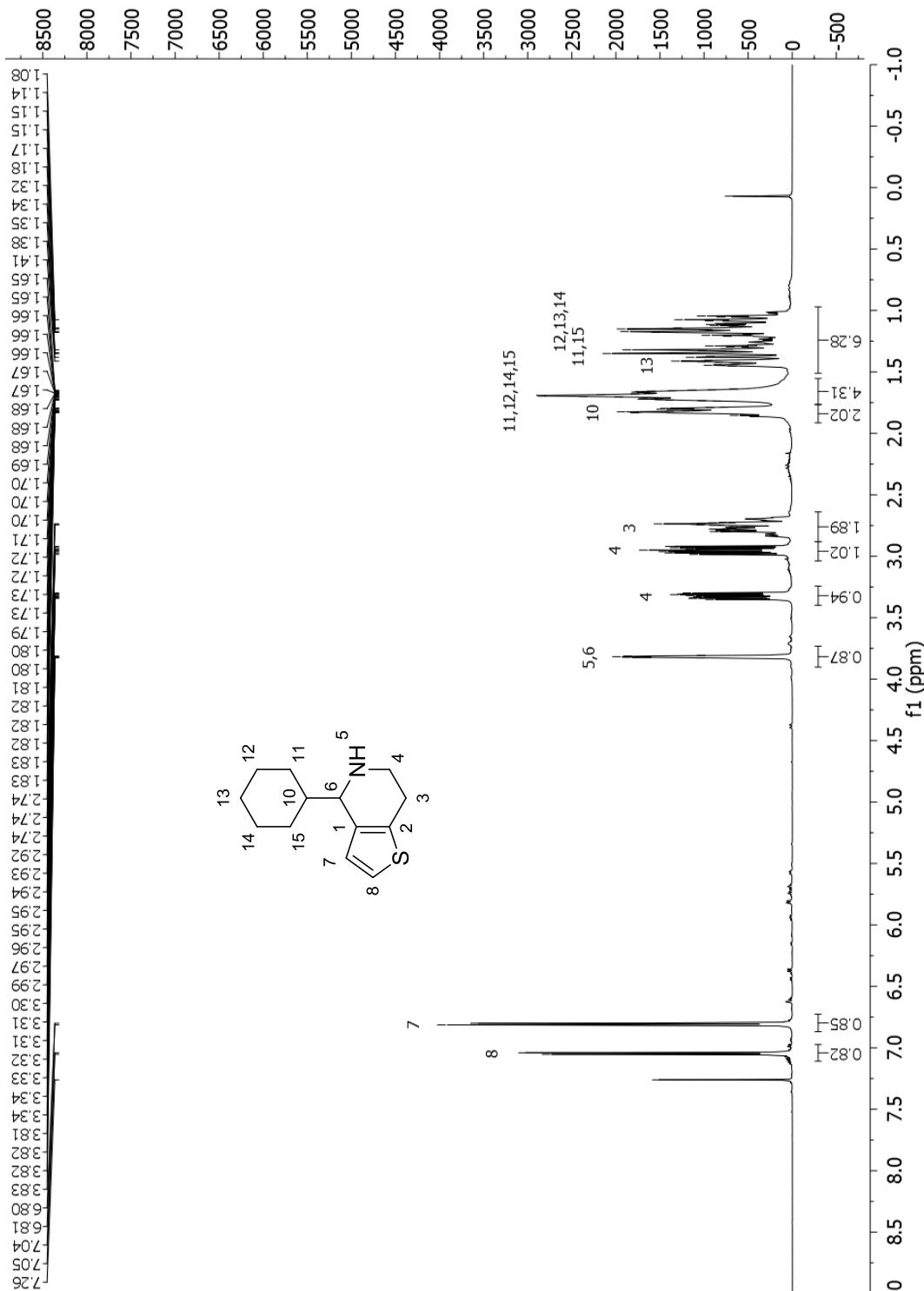


Figure S59. ^1H NMR (400 MHz, CDCl_3) at 298 K of 11c

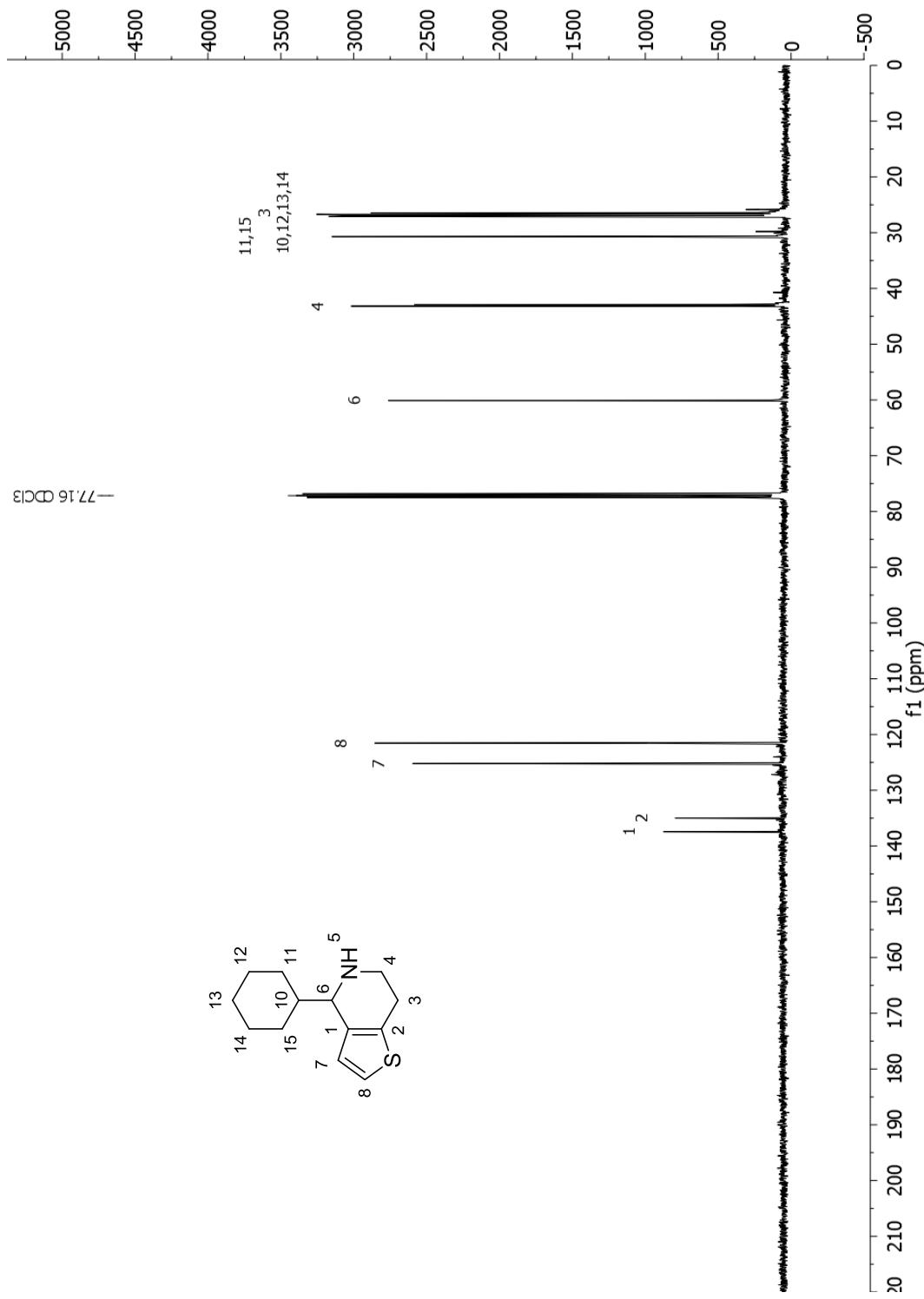


Figure S60. ^{13}C NMR (400 MHz, CDCl_3) at 298 K of 11c

2.10. 2-Picolinic acid (2-thiophen-2-ylethyl)amide (12a).

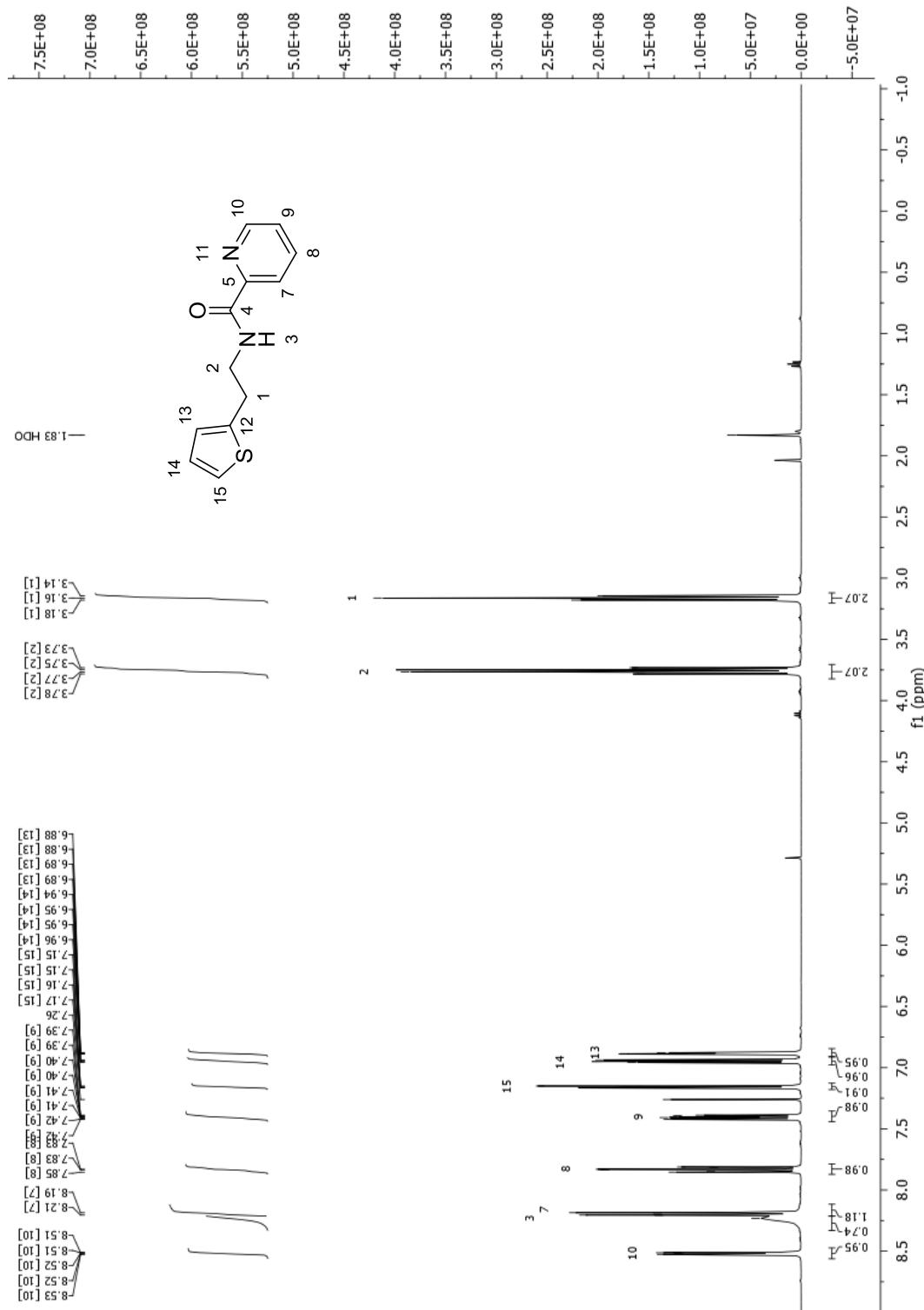


Figure S61. ^1H NMR (400 MHz, CDCl_3) at 298 K of 12a

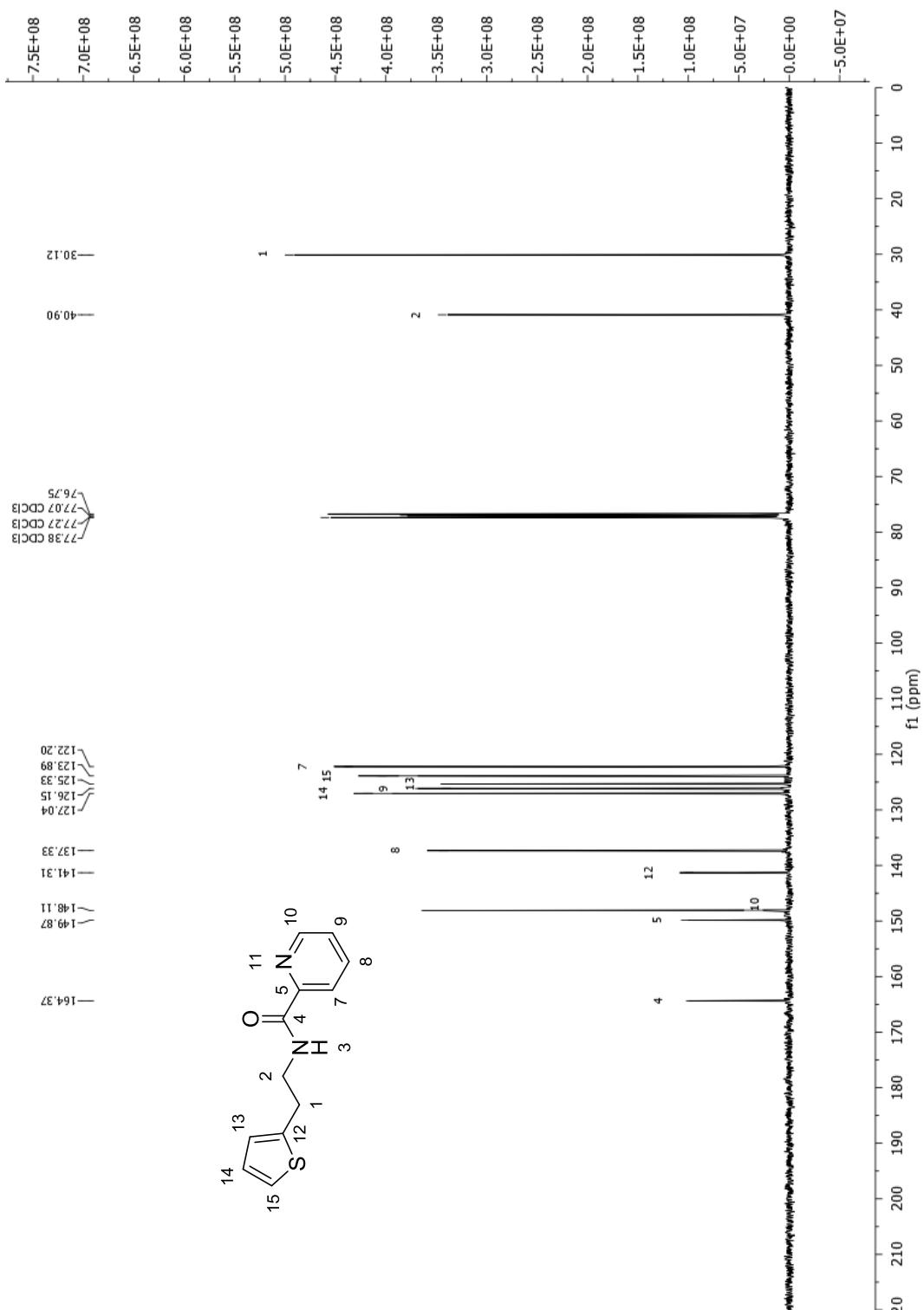


Figure S62. ^{13}C NMR (400 MHz, CDCl_3) at 298 K of 12a

2.11. 7-(2-Pyridyl)-6,7-dihydrothieno[3,2-*c*]pyridine (12b)

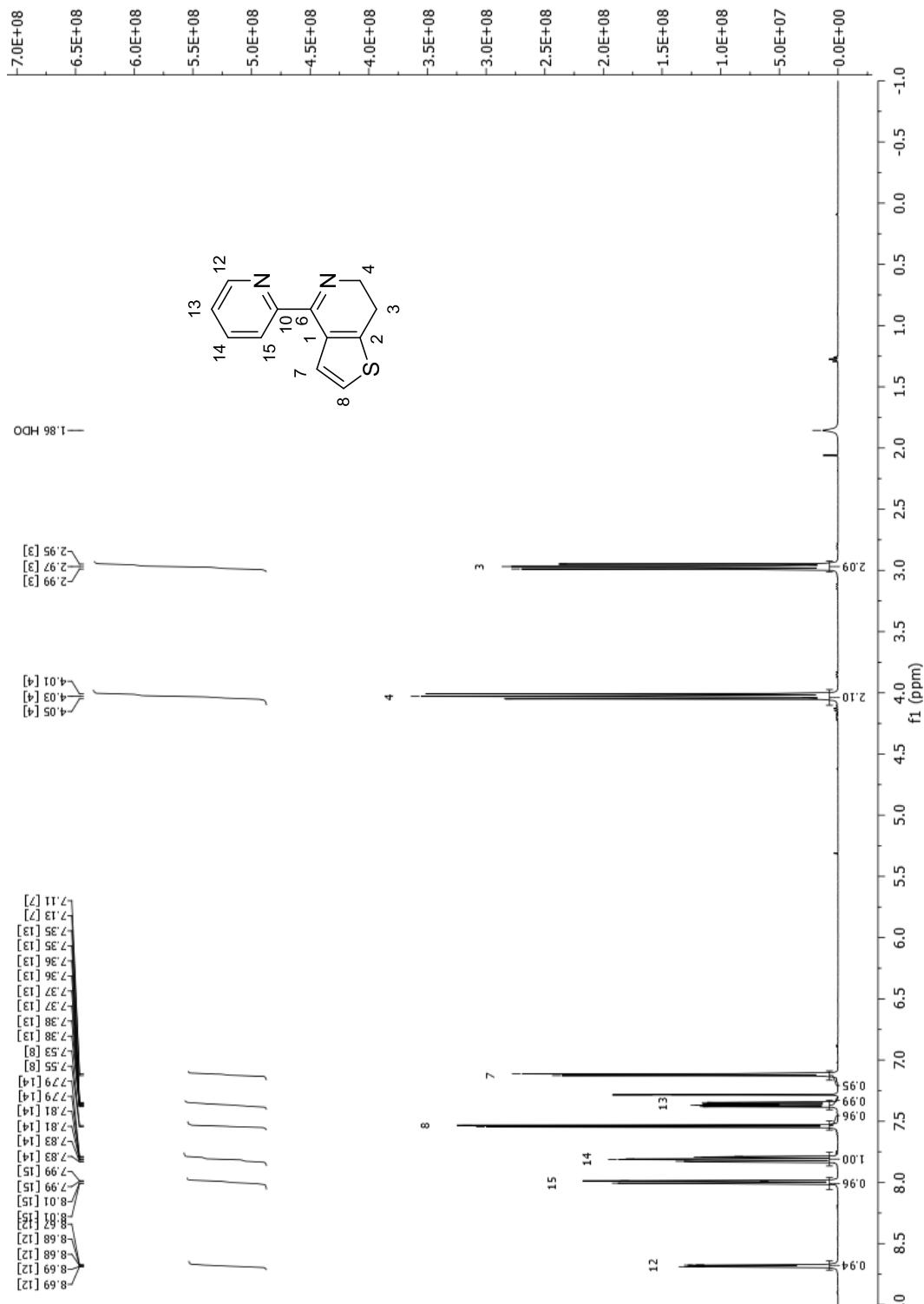


Figure S63. ^1H NMR (400 MHz, CDCl_3) at 298 K of 12b

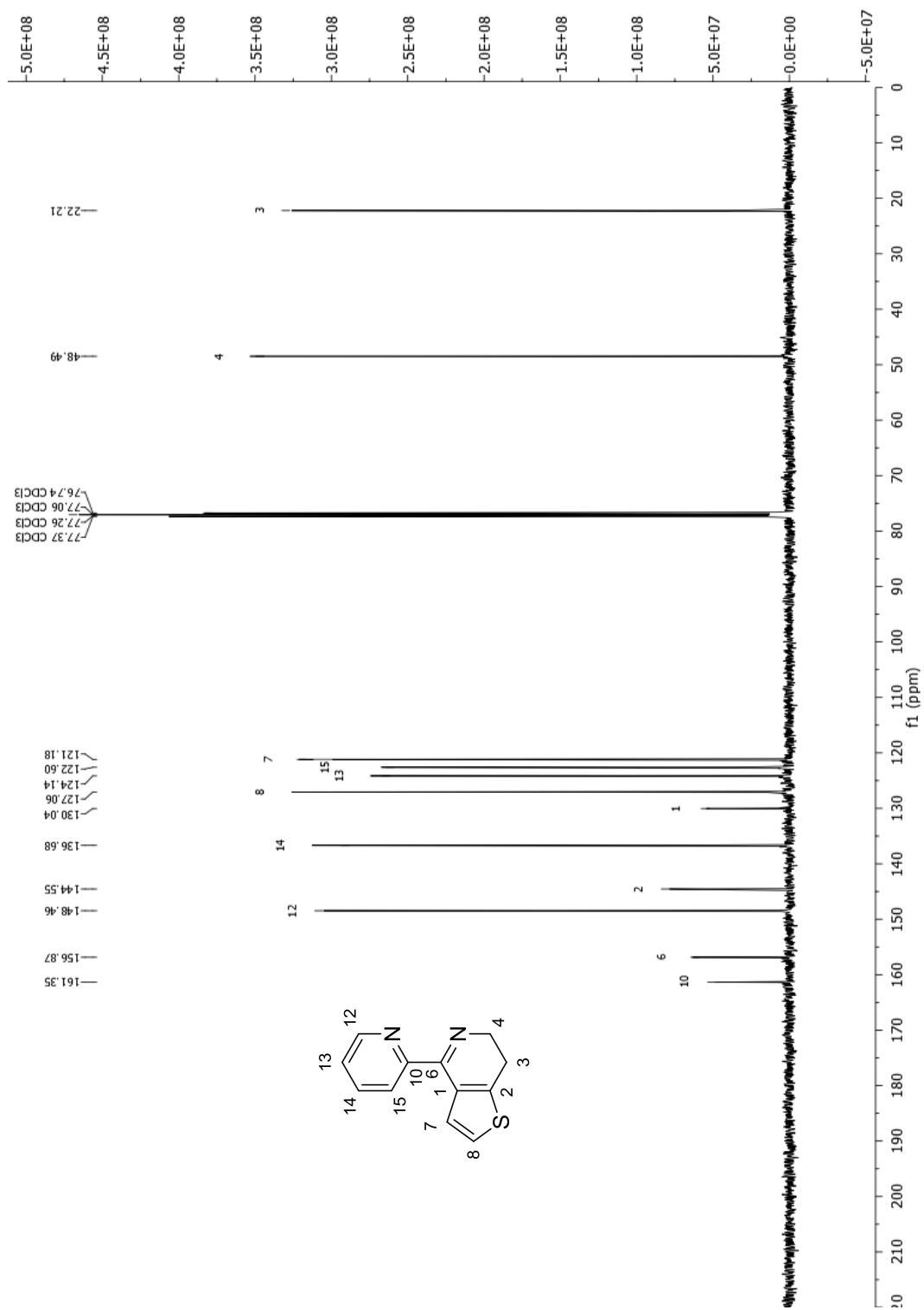


Figure S64. ^{13}C NMR (400 MHz, CDCl₃) at 298 K of **12b**

2.12. 7-(2-Pridyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (12c)

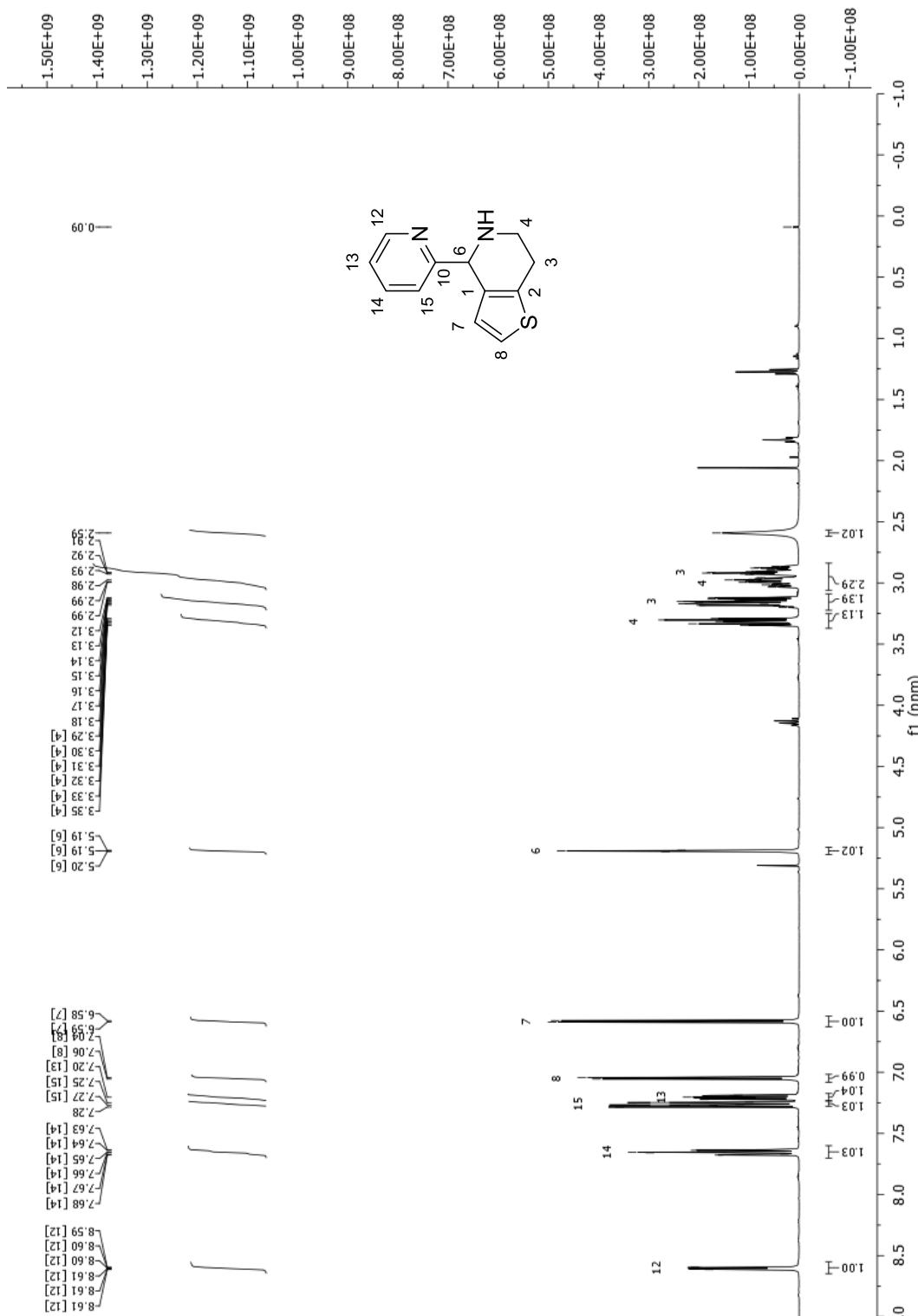


Figure S65. ^1H NMR (400 MHz, CDCl_3) at 298 K of 12c

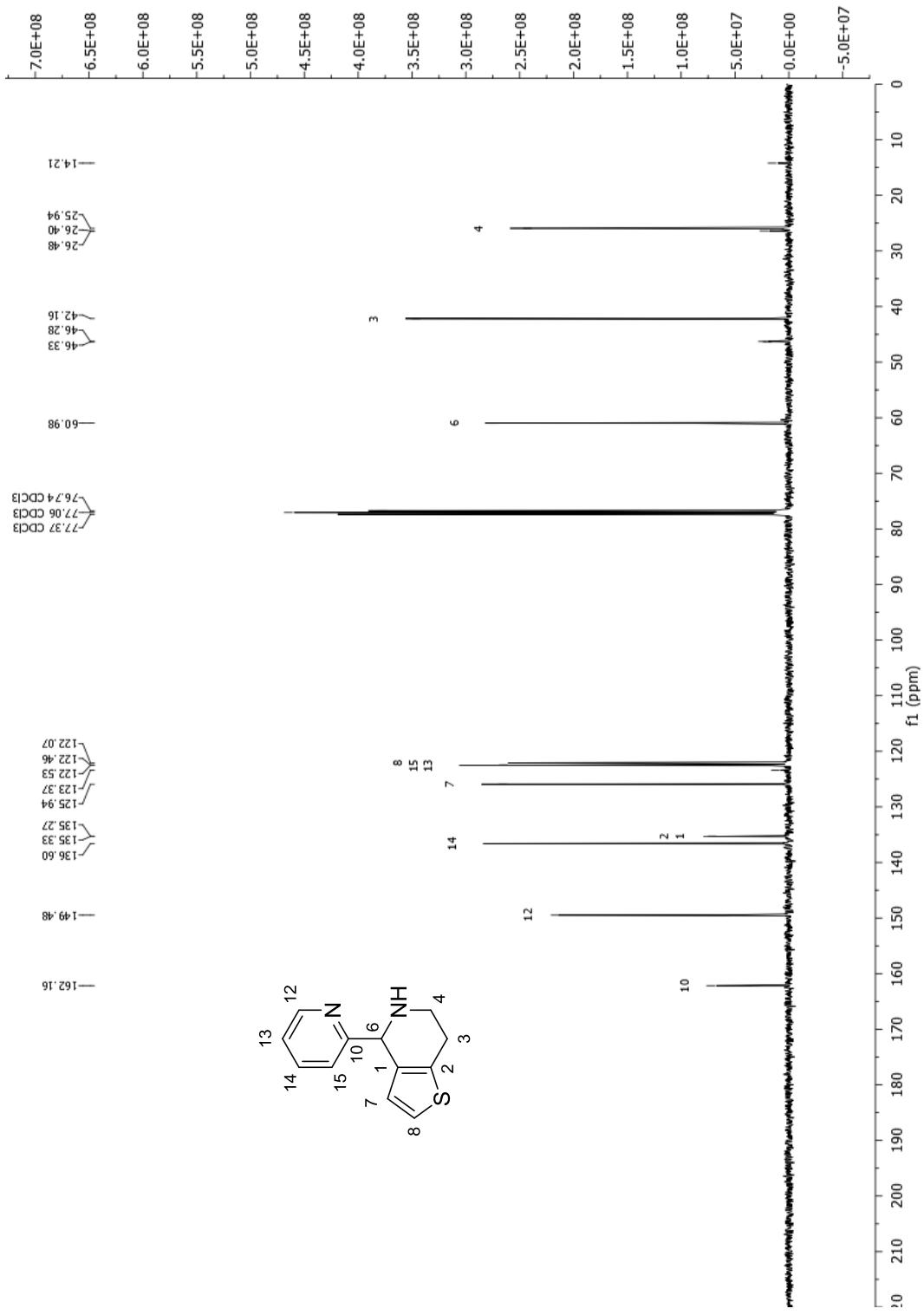
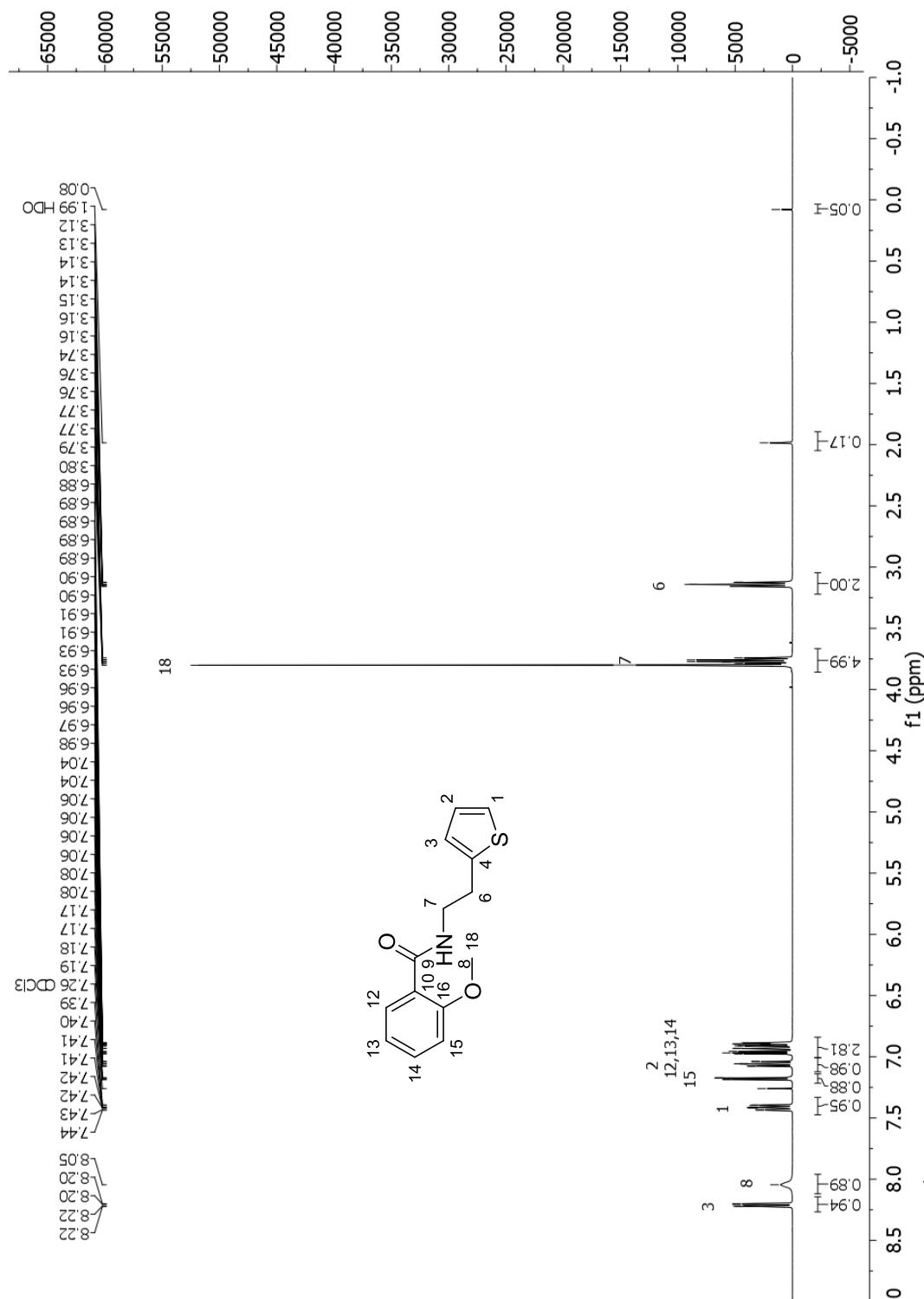


Figure S66. ^{13}C NMR (400 MHz, CDCl_3) at 298 K of **12c**

2.13. 2-Methoxybenzoic acid (2-thiophen-2-ylethyl)amide (13a)



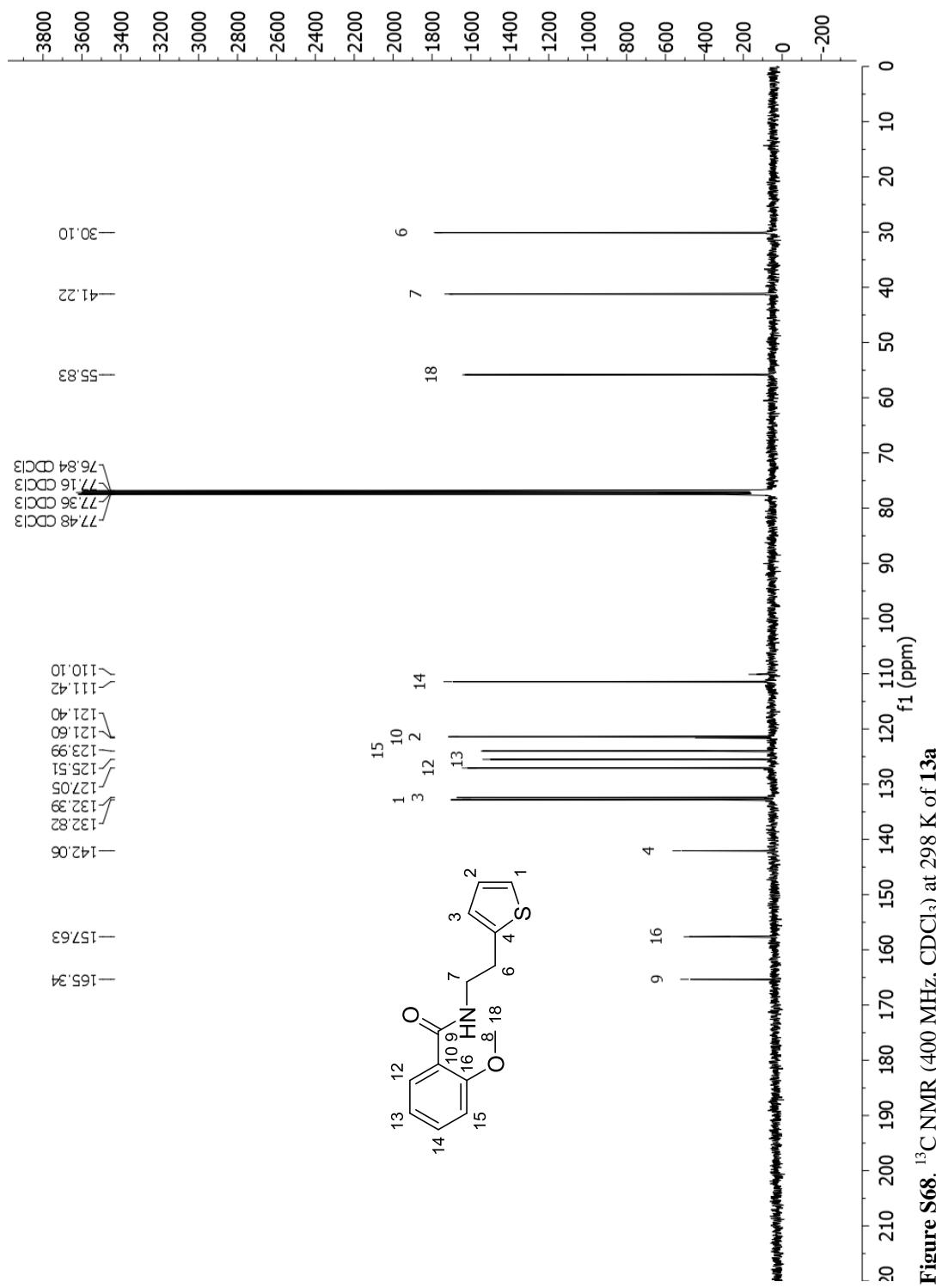


Figure S68 ^{13}C NMR (400 MHz, CDCl₃) at 298 K of 13a

2.14. 7-(2-Methoxyphenyl)-6,7-dihydrothieno[3,2-*c*]pyridine (13b)

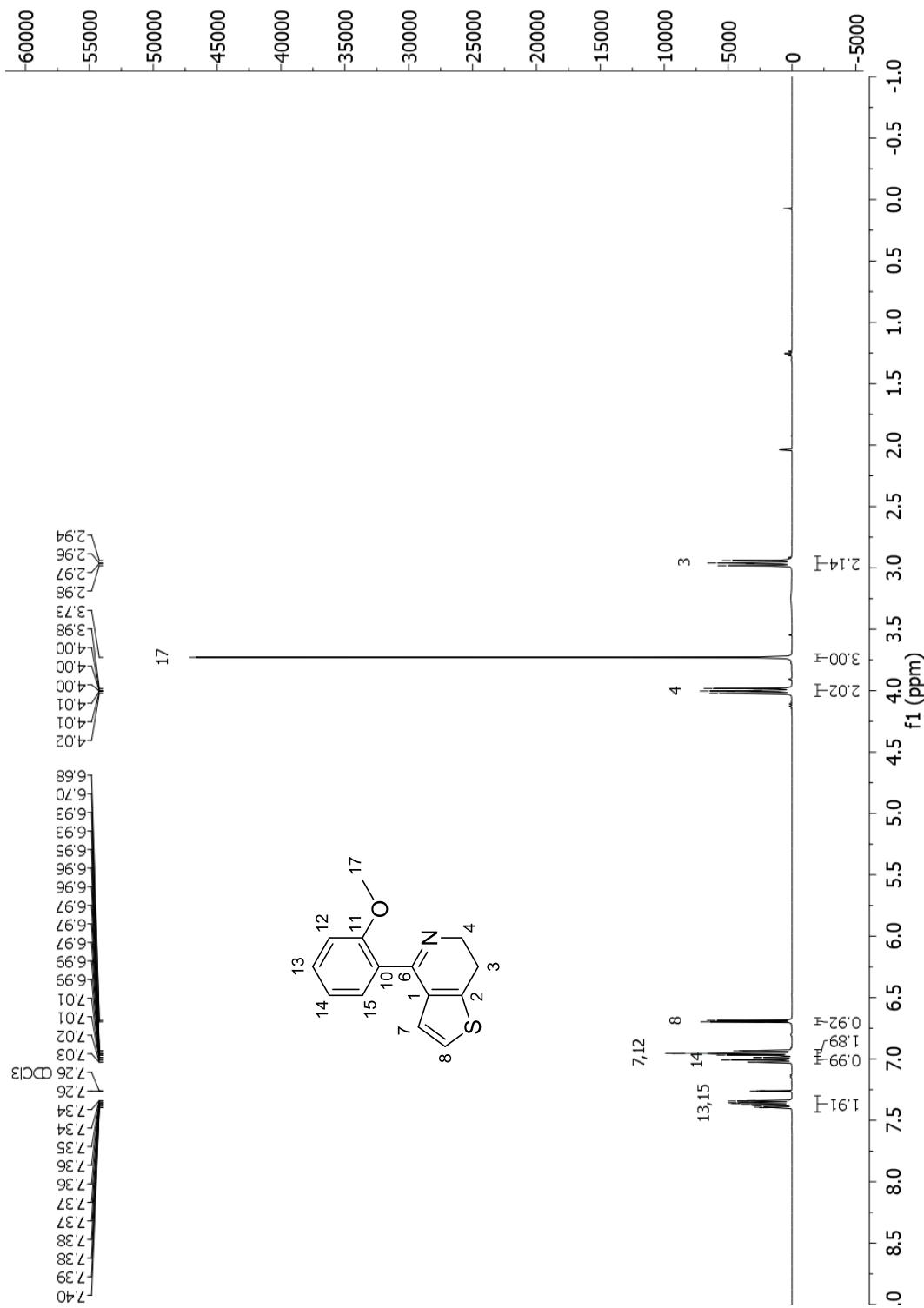


Figure S69. ^1H NMR (400 MHz, CDCl₃) at 298 K of 13b

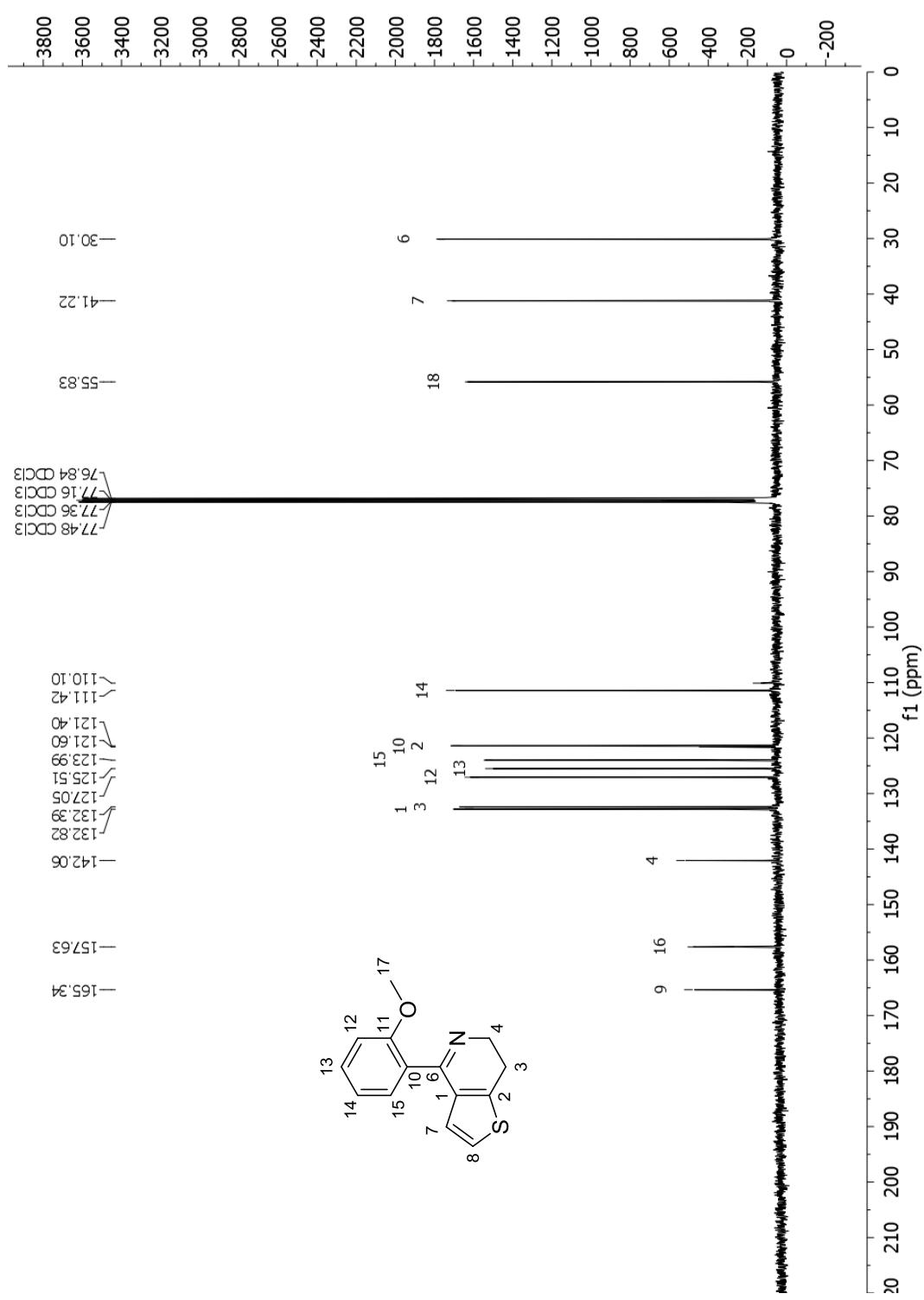


Figure S70. ^{13}C NMR (400 MHz, CDCl_3) at 298 K of 13b

2.15. 7-(2-Methoxyphenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (13c)

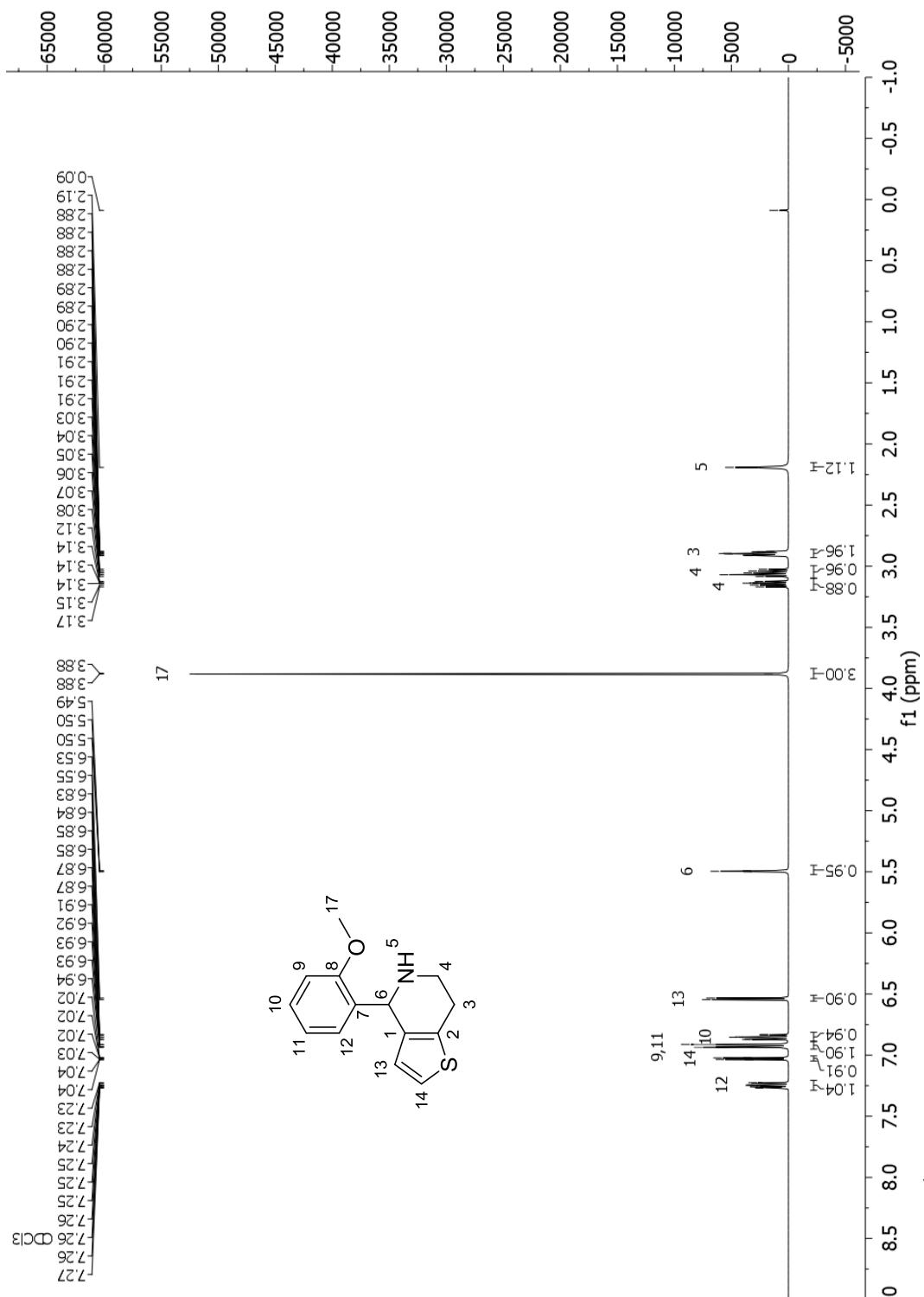


Figure S71. ^1H NMR (400 MHz, CDCl_3) at 298 K of 13c

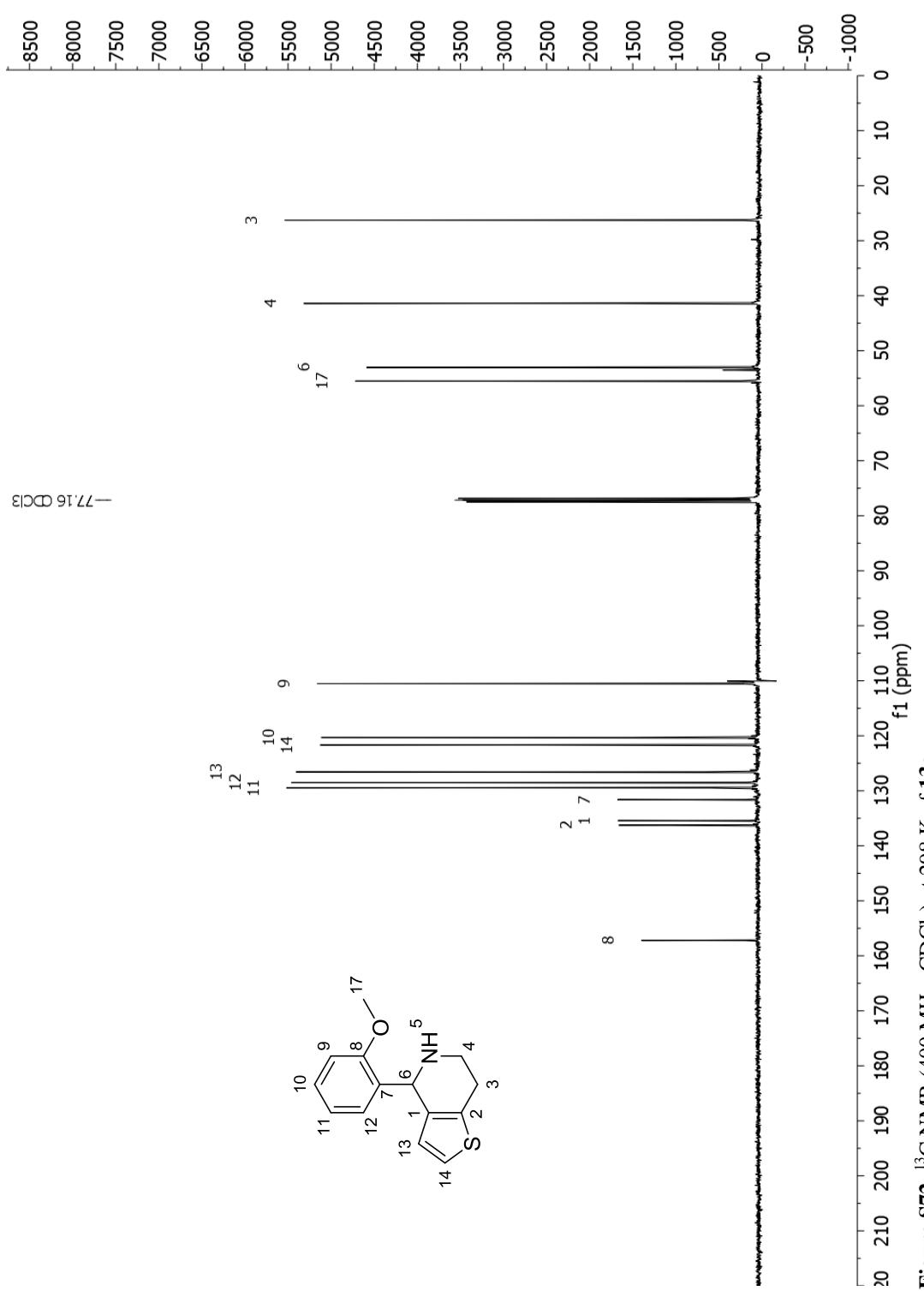


Figure S72. ^{13}C NMR (400 MHz, CDCl_3) at 298 K of **13c**

2.16. Determination of the Coalescence Temperature of **4** and **6**

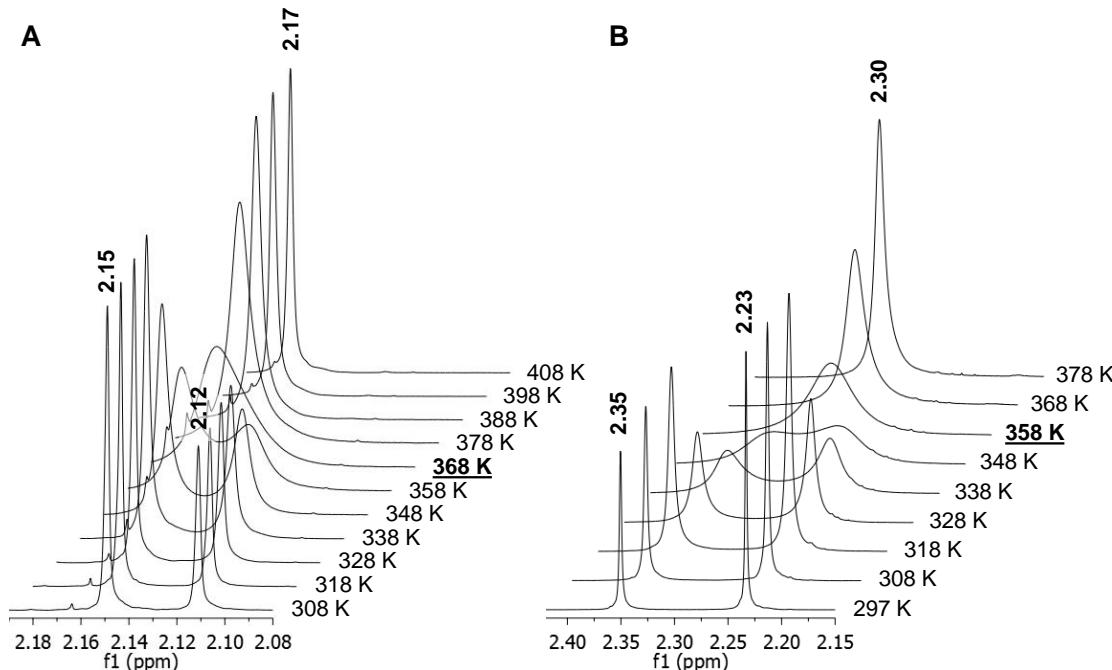


Figure S73. ^1H NMR spectra from 2.18-2.08 ppm of **4** at 308-408 K (**A**) and from 2.40-2.15 ppm of **6** at 297-378 K (**B**) (500 MHz, $\text{C}_2\text{D}_2\text{Cl}_4$).

The coalescence temperatures at 368 K and 358 K are highlighted as bold and underlined values, respectively. The corresponding rate constants of the exchange processes can be calculated using:

$$k_c = \frac{\pi \Delta \nu}{\sqrt{2}} = 2.22 \Delta \nu$$

Compound **4** exhibits a rate constant of 44.4 Hz and **6** a value of 42.4 Hz. Subsequently, the activation energy of the exchange processes can be calculated using the Eyring equation:

$$\Delta G^\ddagger = RT \left[23.760 + \ln \left(\frac{T}{k_c} \right) \right]$$

Considering a coalescence temperature of 368 K for **4** and 358 K for **6** (cf. Figure S73) and assuming a 1:1 mixture of both conformers, the activation energies constitute 18.9 kcal/mol and 18.4 kcal/mol, respectively.

3. Analysis of Cambridge Crystallographic Database Structures Containing the 2-Substituted *N*-acyl Piperidine Motif.

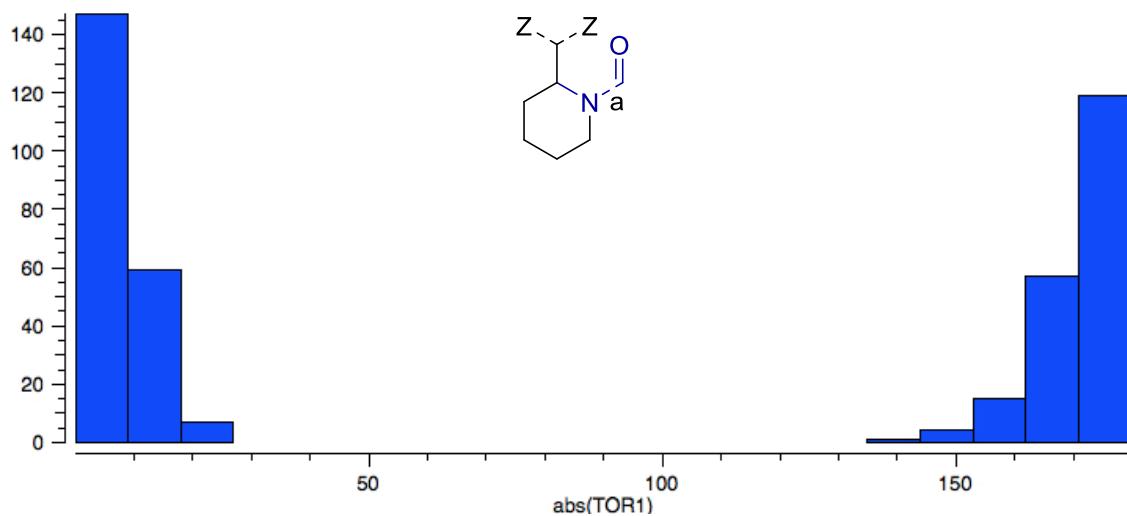


Figure S74. Torsion angles of the amide bond (shown in blue) of all structures of the Cambridge Crystallographic Database that contain the 2-substituted *N*-acyl piperidine motif. The corresponding key structure used for the query is shown (*Z* = any atom apart from hydrogen; dashed bonds = any bond). The *N*-C-bond was specified as acyclic (*a*). Moreover, no disorders and no errors were specified. 186 search results were obtained.

4. Calculation of cLogP Values.

Table S15. cLogP values were calculated using ChemBio3D Ultra (Version 13.0.2.3021, CambridgeSoft).

No.	1	6	7	8	9	10
Structure						
cLogP	2.03	0.35	1.76	1.13	2.03	2.81