Supporting Information

Design, synthesis and *in vitro* evaluation of novel SARS-CoV-2 3CL^{pro} covalent inhibitors.

Julia K. Stille,[#,1] Jevgenijs Tjutrins,[#,1] Guanyu Wang,[#,1] Felipe A. Venegas,[#,1] Christopher Hennecker,[1] Andrés M. Rueda [1] Itai Sharon,[2] Nicole Blaine [1] Caitlin E. Miron,[1] Sharon Pinus,[1] Anne Labarre,[1] Jessica Plescia,[1] Mihai Burai Patrascu,[1] Xiaocong Zhang,[1] Alexander S. Wahba,[1] Danielle Vlaho,[1] Mitchell J. Huot,[1] T. Martin Schmeing,[2] Anthony K. Mittermaier,[1] and Nicolas Moitessier*,[1]*

[1] Department of Chemistry, McGill University, 801 Sherbrooke St W, Montreal, QC, Canada H3A 0B8. [2] Department of Biochemistry, McGill University, 3649 Promenade Sir William Osler Montreal, QC, Canada H3G 0B1.

nicolas.moitessier@mcgill.ca

anthony.mittermaier@mcgill.ca

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1. Purification of 3CL^{pro}.

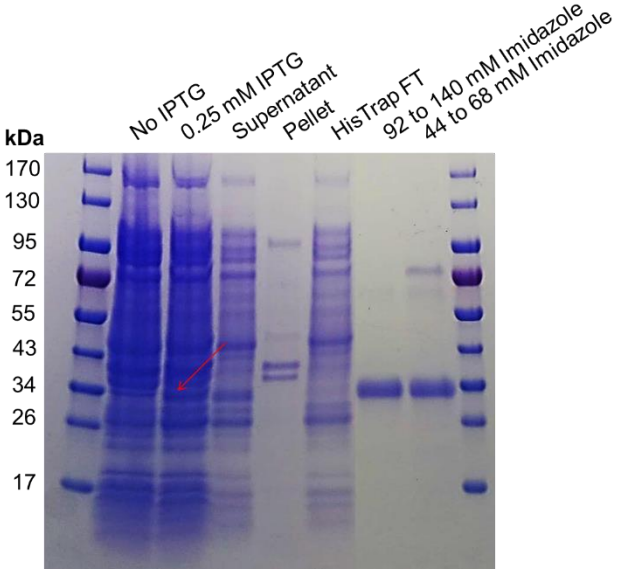


Figure S1. SDS-PAGE at each of the purification step.

2. Dose-response curves

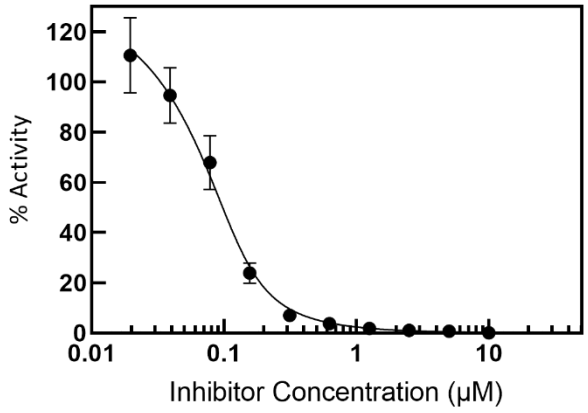


Figure S2a. Dose-response curves. **GC376:** IC_{50} = 0.11 ± 0.06.

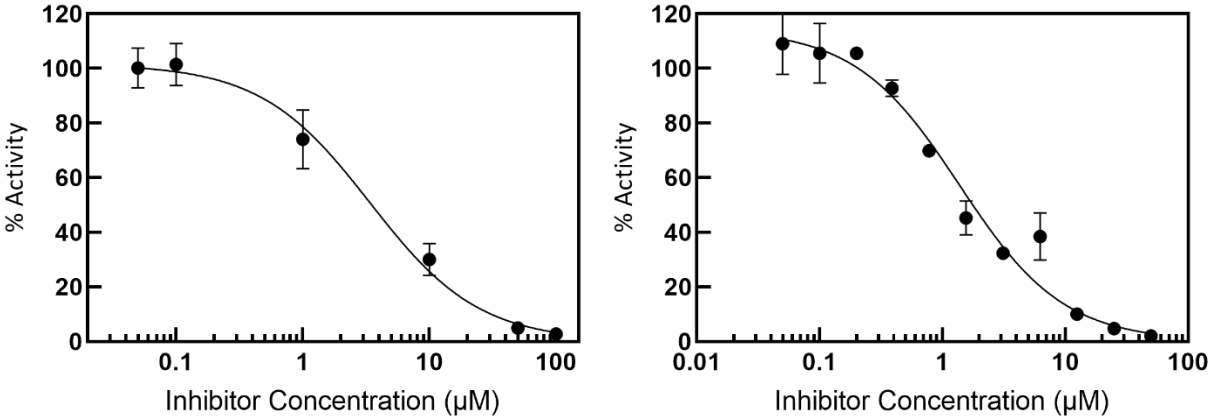


Figure S2b. Dose-response curves. Top: **X77:** IC_{50} = 4.1 ± 1; **ML188**: IC_{50} = 1.4 ± 0.4.

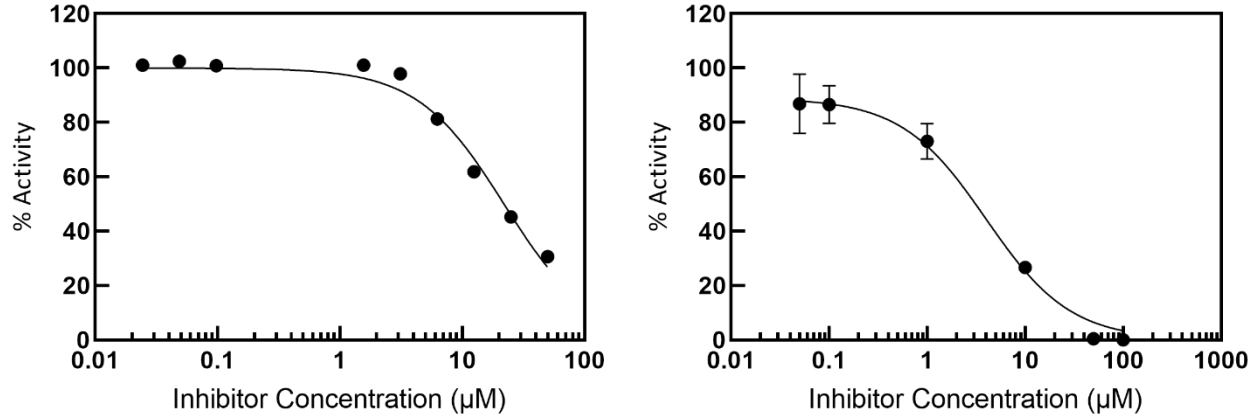


Figure S2c. 6a: IC_{50} = 11.1 ± 1.5; **13a**: IC_{50} = 5.3 ± 0.8.

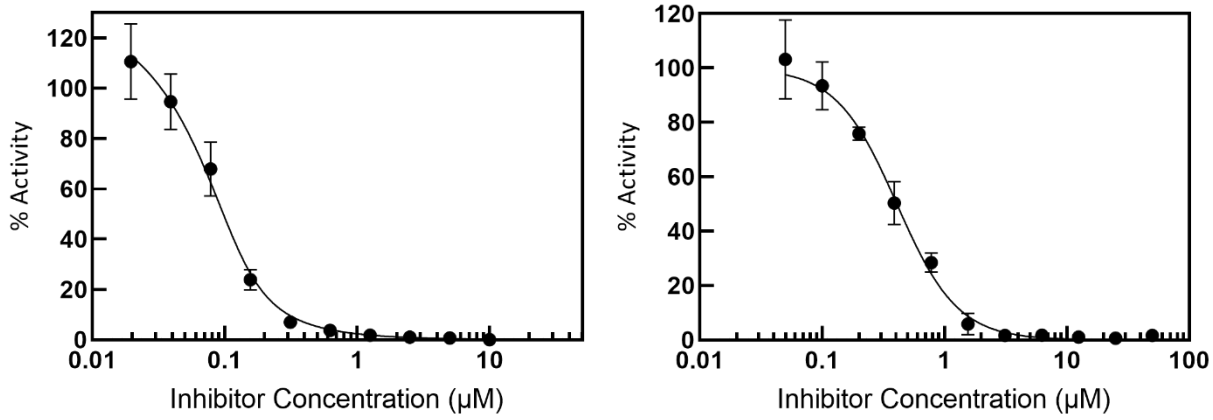


Figure S2d. 14a: IC_{50} = 0.50 ± 0.1; **16a**: IC_{50} =0.40 ± 0.16.

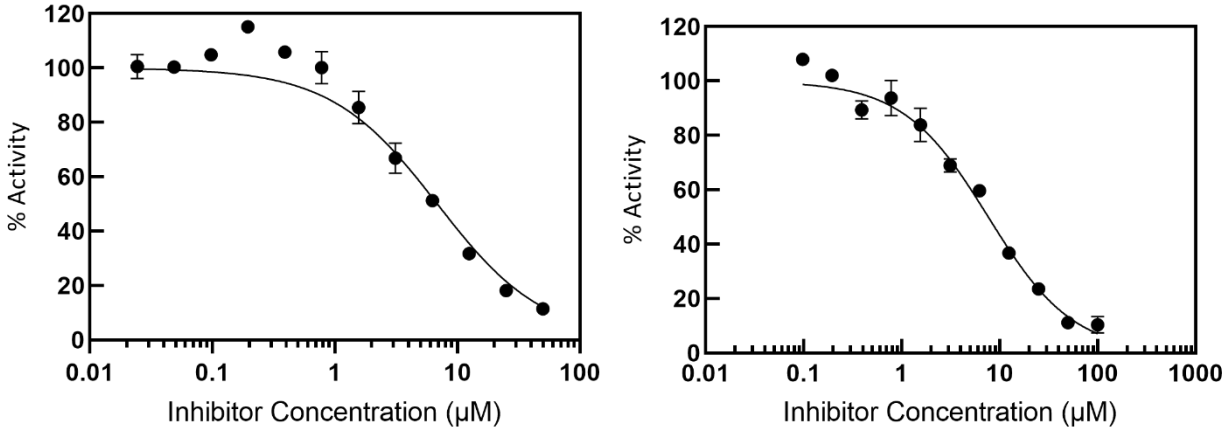


Figure S2e. 18a: IC_{50} = 5.2 ± 1.2; **20a**: IC_{50} = 7.0 ± 0.2.

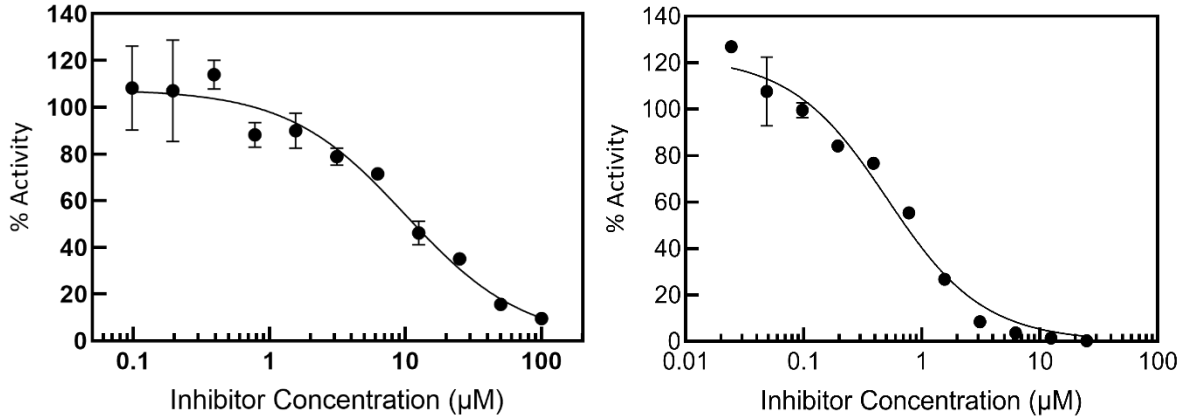


Figure S2f. 22a: IC_{50} = 12.4 ± 5.2; **23a**: IC_{50} = 0.85 ± 0.42.

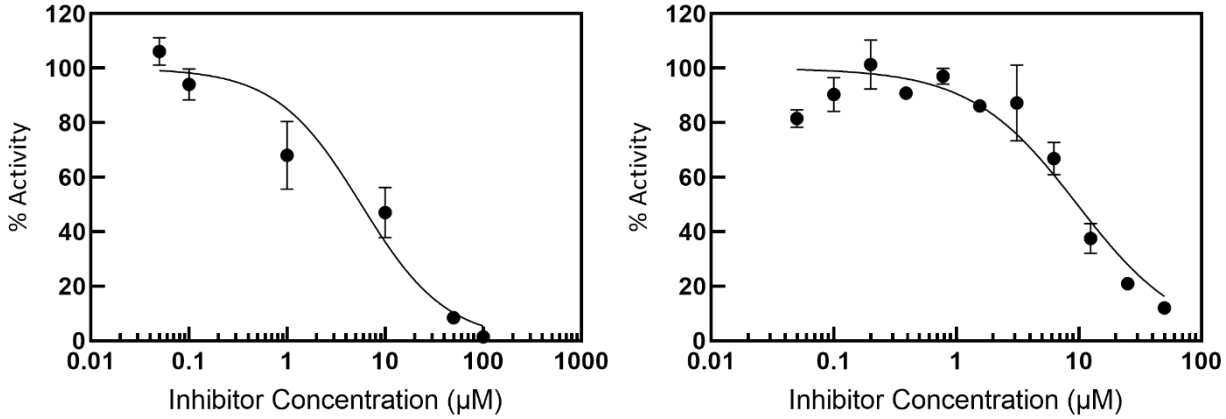


Figure S2g. 13b: IC_{50} = 15.0 ± 9.3; **13c**: IC_{50} = 9.7 ± 3.8.

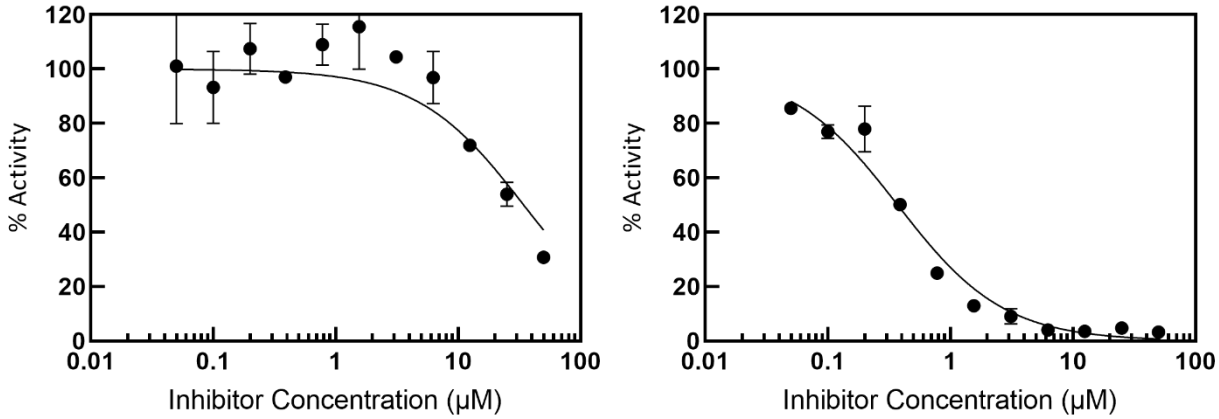


Figure S2h. 13d: IC_{50} > 30; **16b**: IC_{50} = 0.38 ± 0.09.

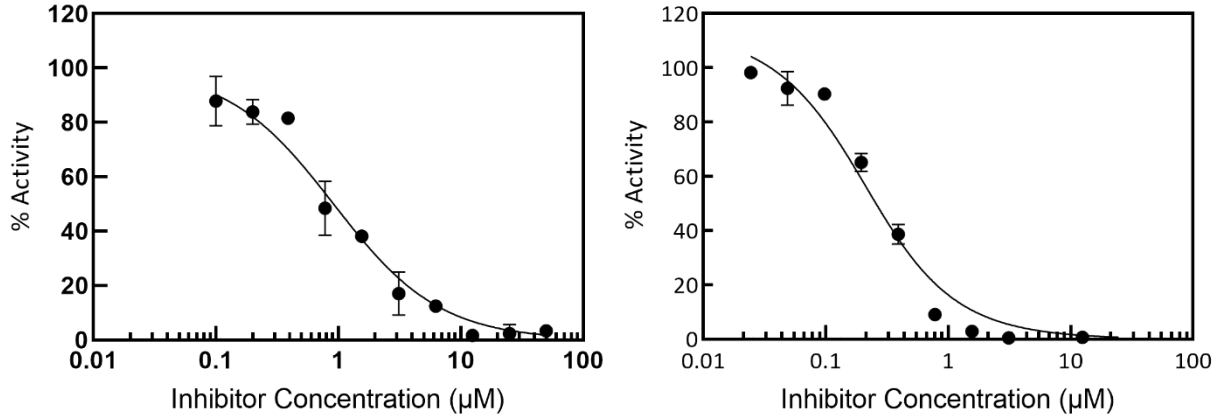


Figure S2i. 16c: IC_{50} = 0.92 ± 0.24; **14b**: IC_{50} = 0.28 ± 0.10;

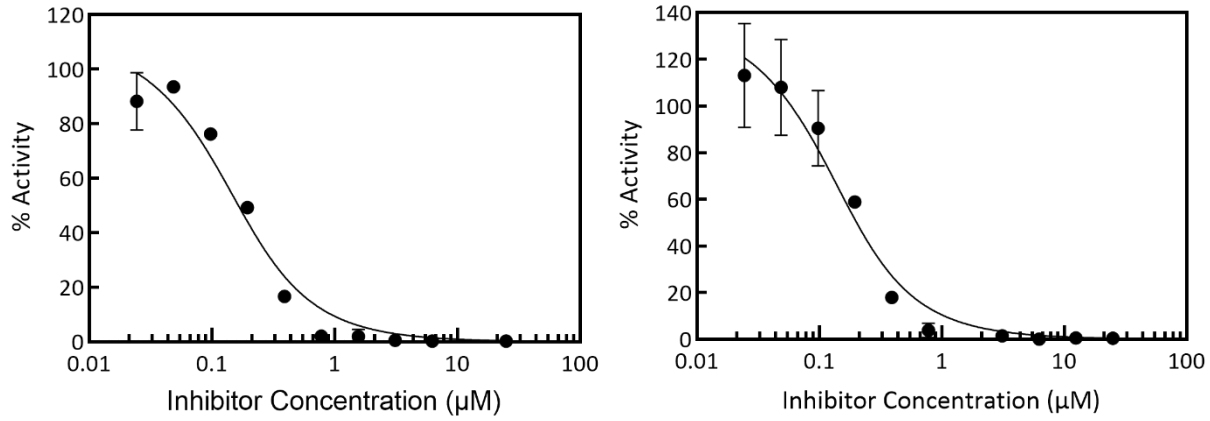


Figure S2j. 14c: IC_{50} = 0.17 ± 0.07; **14d**: IC_{50} = 0.24 ± 0.15.

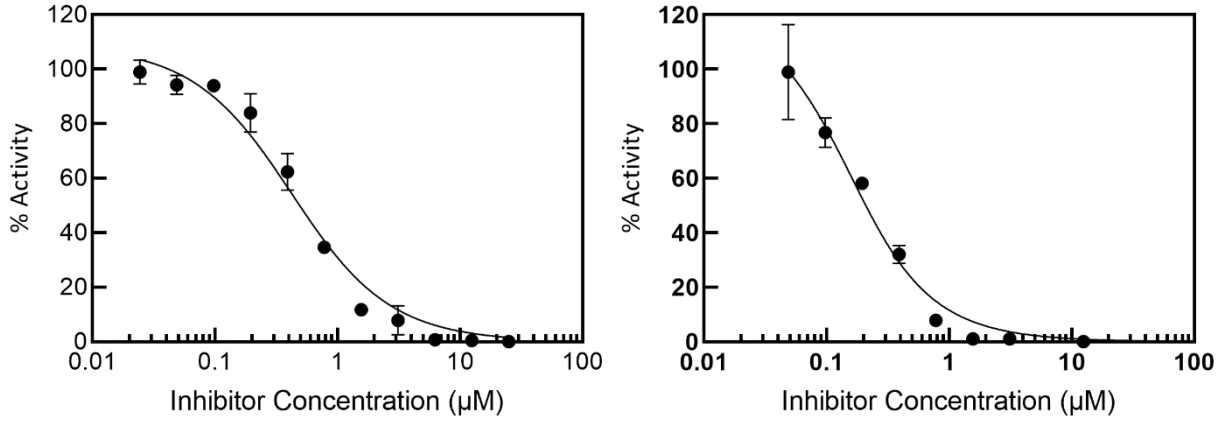


Figure S2k. 14e: IC_{50} = 0.52 ± 0.16; **14f**: IC_{50} = 0.22 ± 0.08

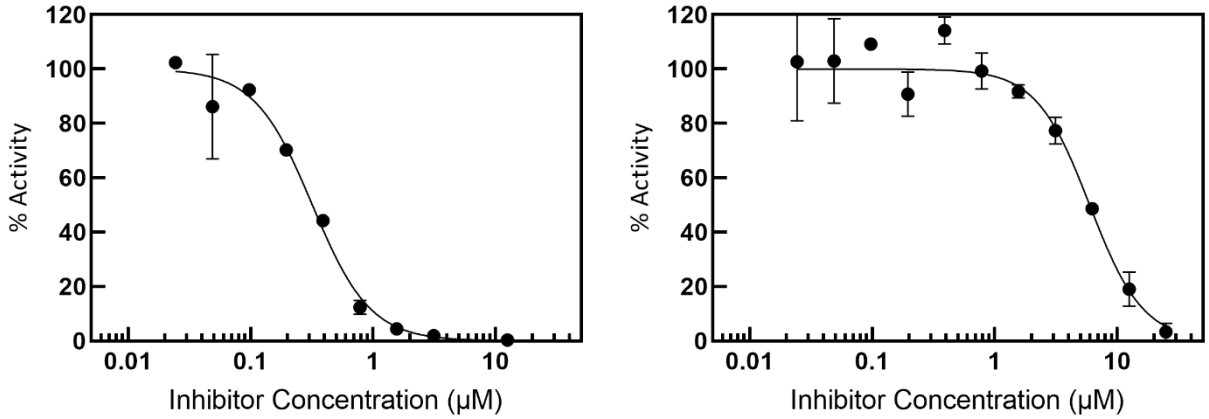


Figure S2l. 14g: IC_{50} = 0.32 ± 0.10; **14h**: IC_{50} = 6.0 ± 2.7.

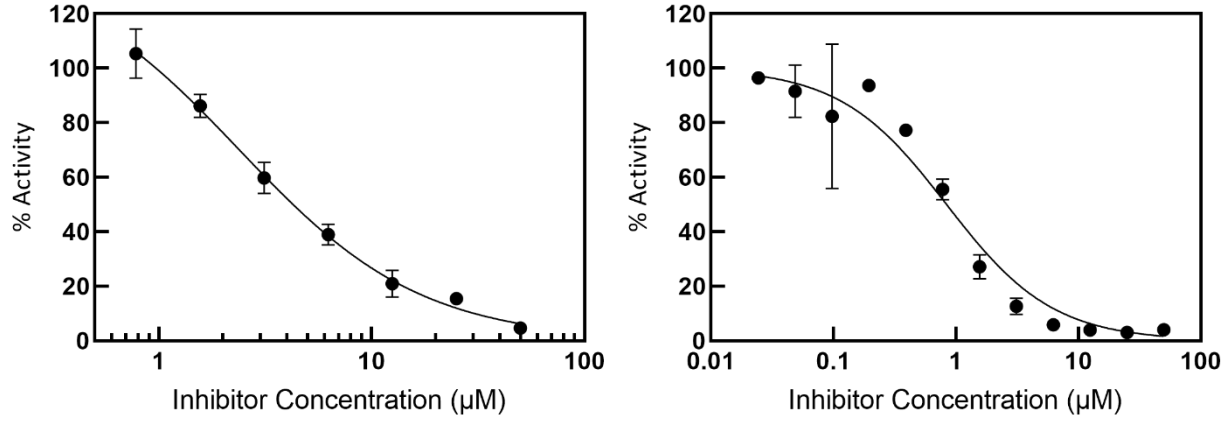


Figure S2m. 13e: IC_{50} = 5.0 ± 2.3; **16e**: IC_{50} = 0.84 ± 0.30.

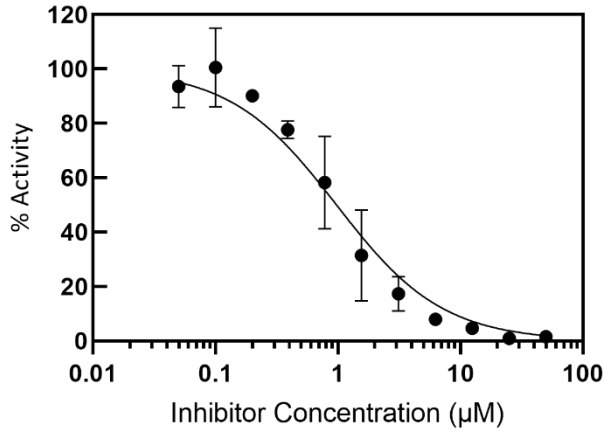


Figure S2m. 16f: IC_{50} = 0.98 ± 0.35.

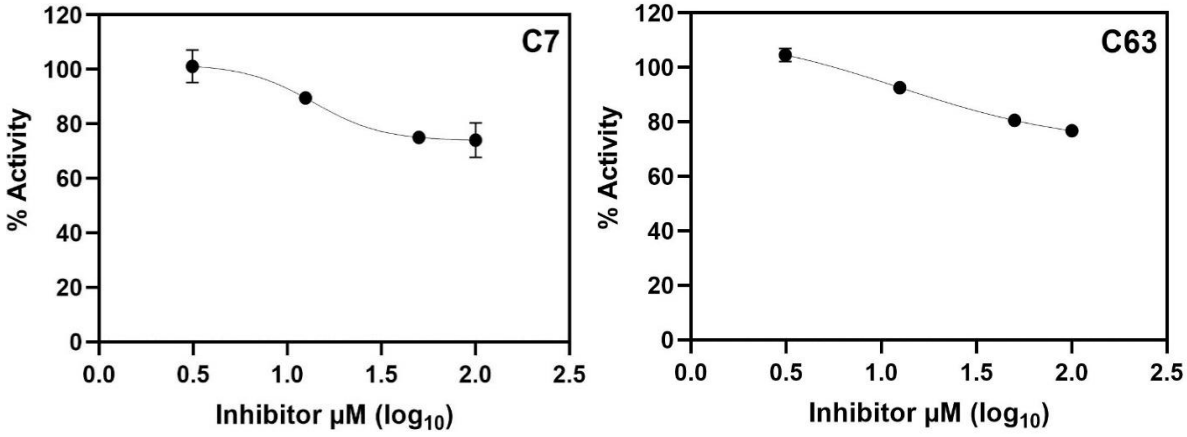


Figure S3a. Cathepsin L inhibition: **16a** and **14a**.

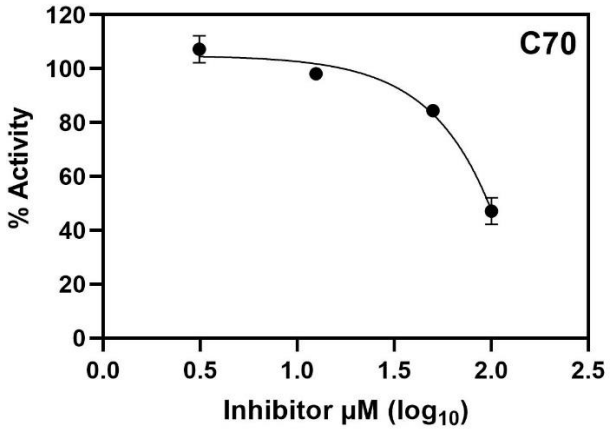


Figure S3b. Cathepsin L inhibition: **14c**.

3. Time dependent IC_{50}'s and Mass Spectrometry

Covalent binding. To evaluate the covalent inhibition hypothesis, we measured the time dependence of the inhibition of our most potent inhibitor, **16a**. As can be seen in Figure 6, the level of inhibition increases over time when the inhibitor is used close to its IC_{50} concentration, while it remains constant for the non-covalent inhibitor **X77**. This observation is consistent with the slow formation of a covalent adduct. Furthermore, the presence of the 3CL^{pro}-**16a** and 3CL^{pro}-**14a** adducts were confirmed by LC-MS (Figures S4 and S5). When the protease was incubated with inhibitor **16a**, the population of unmodified protein decreases as a new population with mass of the protease-inhibitor complex (3CL^{pro} + **16a**) appears, persists while denaturation occurs.

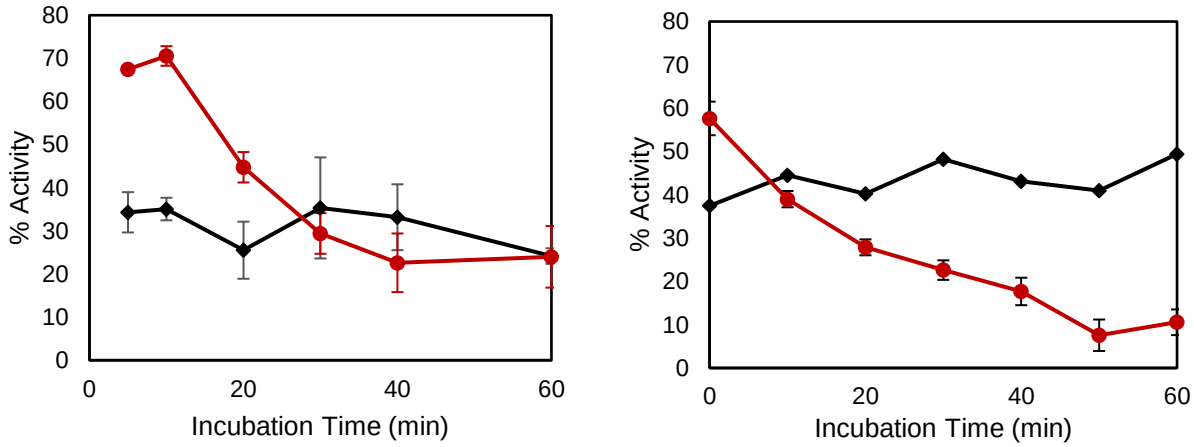


Figure S4. Time-dependent potency for **X77** (black) and **16a** (left, red) and **14a** (right, red).

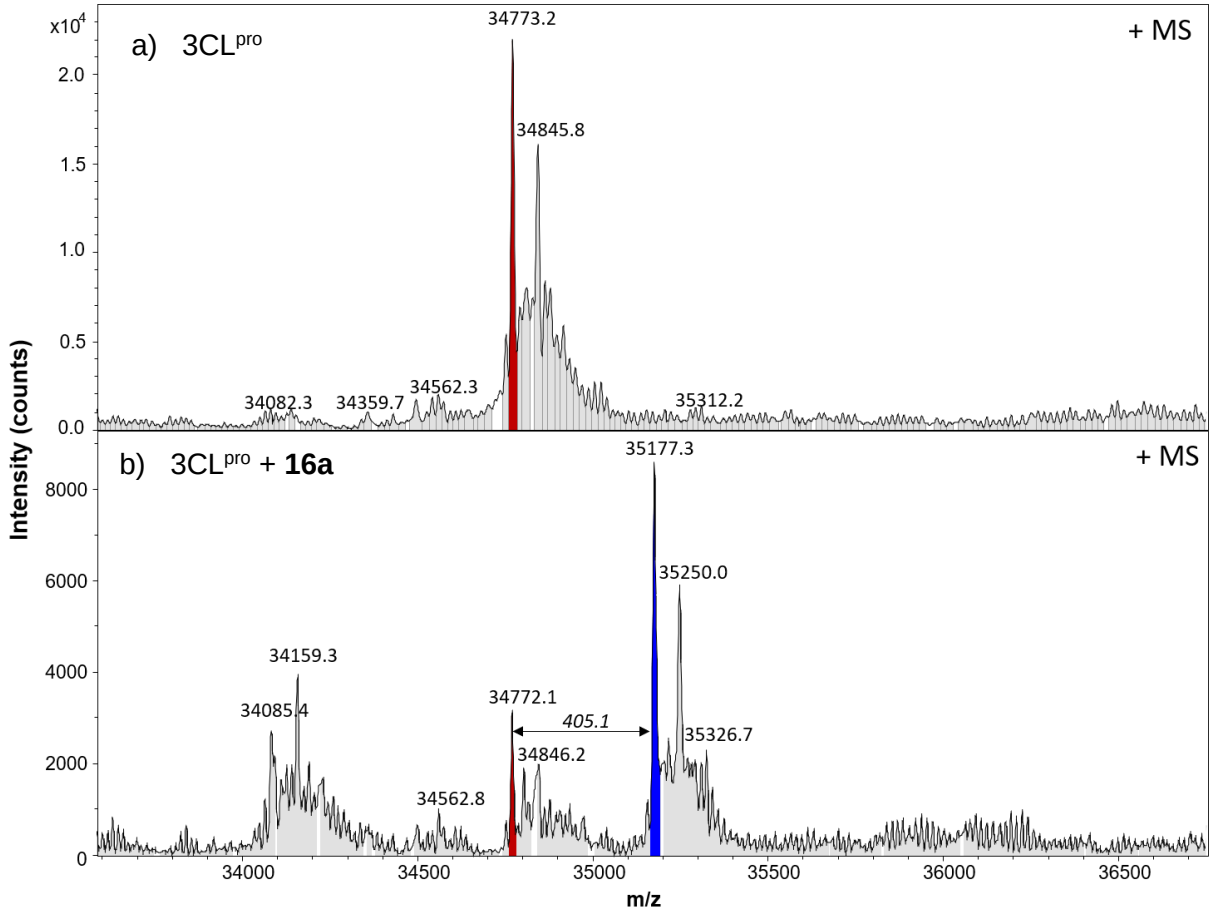


Figure S5a. Deconvoluted mass spectra of 3CL^{pro} in the absence, a), and presence, b), of **16a**. While the mass of 3CL^{pro} (red) is present in both spectra, the mass corresponding to the covalent 3CL^{pro}-**16a** adduct (blue) is only observed in the presence of **16a**.

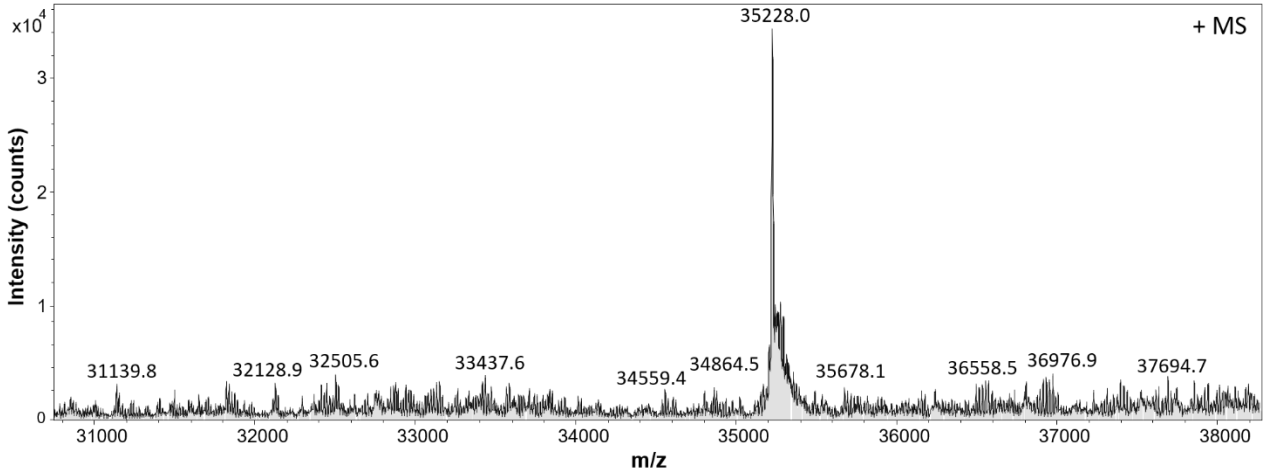


Figure S5b. Deconvoluted mass spectrum for 3CL^{pro} in the presence of **14a**. The expected mass for 3CL^{pro}-**14a** adduct is 35228.

4. Isothermal Titration Calorimetry

Enzyme Fitting Scripts. All curve fitting was performed with MATLAB. Differential equations shown below describing Michaelis-Menten kinetics, competitive inhibition, and covalent inhibition were integrated using MATLAB's built in ODE solver ode15s.

Michaelis-Menten Kinetics

$$[E]_{inj} = [E]_{cell} + \frac{V_{inj}[E]_{syringe}}{V_{cell}}$$

$$\frac{d[S]}{dt} = -\frac{\left(k_{cat}[E]_{inj}[S]_t\right)}{K_m + [S]_t}$$

$$\frac{d[P]}{dt} = \frac{\left(k_{cat}[E]_{inj}[S]_t\right)}{K_m + [S]_t}$$

Rapid equilibrium inhibition

$$[E]_{inj} = [E]_{cell} + \frac{V_{inj}[E]_{syringe}}{V_{cell}}$$

$$K_{m(app)} = K_m * \left(1 + \frac{[I]}{K_i}\right)$$

$$\frac{d[S]}{dt} = -\frac{\left(k_{cat}[E]_{inj}[S]_t\right)}{K_{m(app)} + [S]_t}$$

$$\frac{d[P]}{dt} = \frac{\left(k_{cat}[E]_{inj}[S]_t\right)}{K_{m(app)} + [S]_t}$$

Irreversible inhibition

$$[E]_{inj} = [E]_{cell} + \frac{V_{inj}[E]_{syringe}}{V_{cell}}$$

$$\frac{d[S]}{dt} = -\frac{\left(k_{cat}[E]_{inj}[S]_t\right)}{K_{m(app)} + [S]_t}$$

$$\frac{d[P]}{dt} = \frac{\left(k_{cat}[E]_{inj}[S]_t\right)}{K_{m(app)} + [S]_t}$$

$$[E]_{free} = [E]_{inj} * \left(1 - \frac{[S]_t}{[S]_t + K_m}\right)$$

$$\frac{d[E]_{inj}}{dt} = -k_{on}[I][E]_{free}$$

Pre-equilibrium irreversible inhibition

$$[E]_{inj} = [E]_{cell} + \frac{V_{inj}[E]_{syringe}}{V_{cell}}$$

$$[ES]_t = \frac{K_i[S]_t[E]_{inj}}{K_m K_i + K_i[S]_t + K_m[I]}$$

$$[EI]_t = \frac{K_i[I]_t[ES]_t}{K_i[S]_t}$$

$$\frac{d[S]}{dt} = -\frac{\left(k_{\text{inact}}[E]_{inj}[S]_t\right)}{K_m + [S]_t}$$

$$\frac{d[P]}{dt} = \frac{\left(k_{\text{inact}}[E]_{inj}[S]_t\right)}{K_m + [S]_t}$$

$$\frac{d[E]_{inj}}{dt} = -\mathrm{k}_{\text{inact}}[EI]$$

where k_{cat} and K_m are the catalytic rate and the Michaelis constant respectively, and $[E]_t$, $[S]_t$, and $[P]_t$ are the total concentrations of enzyme, substrate, and product at time = t. $[E]_{cell}$ and $[E]_{syringe}$ are the concentrations of enzyme in the cell and syringe respectively. V_{inj} and V_{cell} are the volume of each injection and total volume of the cell respectively. The instantaneous heat *h(t)* is calculated from the enthalpy of the reaction, dH_{react}, and the total volume of the cell according to

$$h(t) = \Delta H_{cat} * V_{cell} * \frac{d[P]}{dt}$$

to account for injection artifacts, only the last half of each injection was used for fitting. Furthermore, a linear baseline was fit to account for any baseline drift during the experiment. Enzyme kinetic parameters were globally fit to both data sets by minimizing the target function

$$RSS = \sum_{n=0}^{N} [\, h(t) - \Delta P(t)]^2$$

where the RSS is the residual sum of squared differences and $\Delta P(t)$ is the change in experimental heat from the baseline. Errors for fitted parameters were calculated using a bootstrapping approach, in which each bootstrap sample was obtained by random resampling of the original data. For example, if the original dataset contained N points, each bootstrap sample was constructed by randomly selecting N of these data points, such that points may be selected more than once or not at all. 500 bootstrap samples were constructed and fitted using the thermodynamic models described above. The errors in the extracted parameters were taken as the standard deviations of the 500 sets of parameters obtained for all bootstrap samples.[1]

Table S1: Best fit kinetic parameters

3CL^{pro}	k_{cat} (s^{-1})	K_m (μM)	ΔH (kcal/mol)	*RSS*
	2.9 ± 0.2	80 ± 10	-1.91 ± 0.06	0.70

	Pre-equilibrium		Irreversible		Pre-equilibrium Reversible		
	K_i (nM)	*RSS*	k_{on} (μM^{-1} s^{-1})	*RSS*	k_{inact} (s^{-1})	K_i (μM)	*RSS*
16a	1.0e5 ± 1e4	0.40	3.9e2 ± 0.5e2	1.1	3e-3 ± 1e-3	16 ± 2	0.20
14a	870 ± 80	4.09	1.7e3 ± 0.3	1.55	6.1e-3 ± 0.5e-3	4.5 ± 0.3	0.19
14c	35 ± 9	2.75	6.1e3 ± 0.9e3	2.11	1.7e-2 ± 0.2e-2	2.3 ± 0.3	2.00

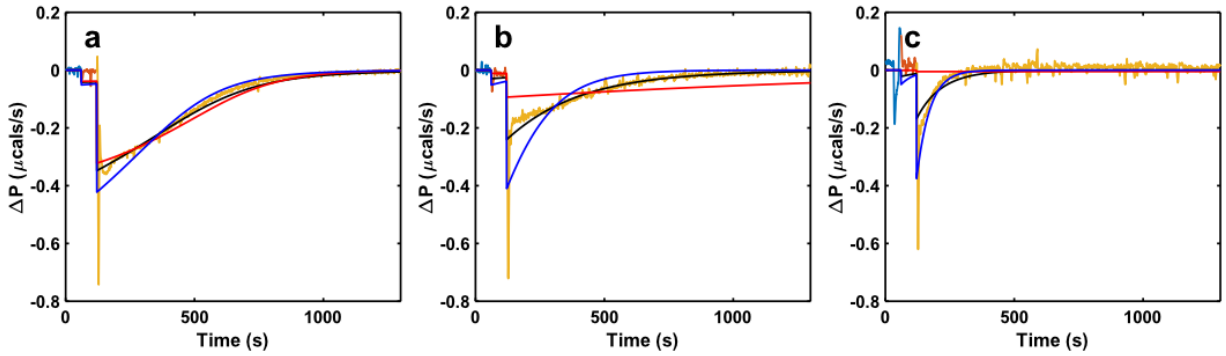


Figure S6. ITC enzyme activity assay in the presence of a) **16a**, b) **14a**, c) **14c**, each successive injection is shown in separate color, ITC simulations corresponding to the minimized kinetic parameters for a pre-equilibrium inhibition are shown in red, irreversible inhibition are shown as blue, and pre-equilibrium irreversible inhibition is shown in black.

5. Crystallography

Table S2. Statistics for crystallography data and structure refinement.

	3CL^{pro} – 16a	**3CL^{pro} – 14a**
Wavelength (Å)	1.521	0.97918
Resolution range	38.38 - 2.6 (2.693 - 2.6)	48.06 - 2.5 (2.59 - 2.5)
Space group	C 1 2 1	C 1 2 1
Unit cell	116.81 53.54 45.33 90 98.917 90	113.45 53.318 45.4745 90 101.876 90
Total reflections	16512 (1645)	17032 (1708)
Unique reflections	8544 (862)	9105 (901)
Multiplicity	1.9 (1.9)	2.9 (3.1)
Completeness (%)	93.18 (48.82)	97.59 (98.79)
Mean I/sigma(I)	6.00 (0.45)	9.37 (1.14)
Wilson B-factor	71.23	54.62
R-merge	0.04975 (1.3)	0.03943 (0.2481)
R-meas	0.07036 (1.838)	0.05576 (0.3509)
R-pim	0.04975 (1.3)	0.03943 (0.2481)
CC1/2	0.996 (0.679)	0.997 (0.777)
CC*	0.999 (0.899)	0.999 (0.935)
Reflections used in refinement	8072 (435)	9104 (901)
Reflections used for R-free	417 (20)	434 (40)
R-work	0.2146	0.2242 (0.3611)
R-free	0.2677	0.2680 (0.3928)
Number of non-hydrogen atoms	2417	2407
macromolecules	2347	2347
ligands	30	32
solvent	40	28
Protein residues	304	304
RMS(bonds)	0.013	0.012
RMS(angles)	1.67	1.65
Ramachandran favored (%)	96.36	96.36
Ramachandran allowed (%)	3.31	3.64
Ramachandran outliers (%)	0.33	0
Rotamer outliers (%)	0	0.38
Clashscore	1.5	3.83
Average B-factor	65.04	63.73
macromolecules	65.15	63.38
ligands	79.53	107.2
solvent	47.9	43.37

6. Additional figures

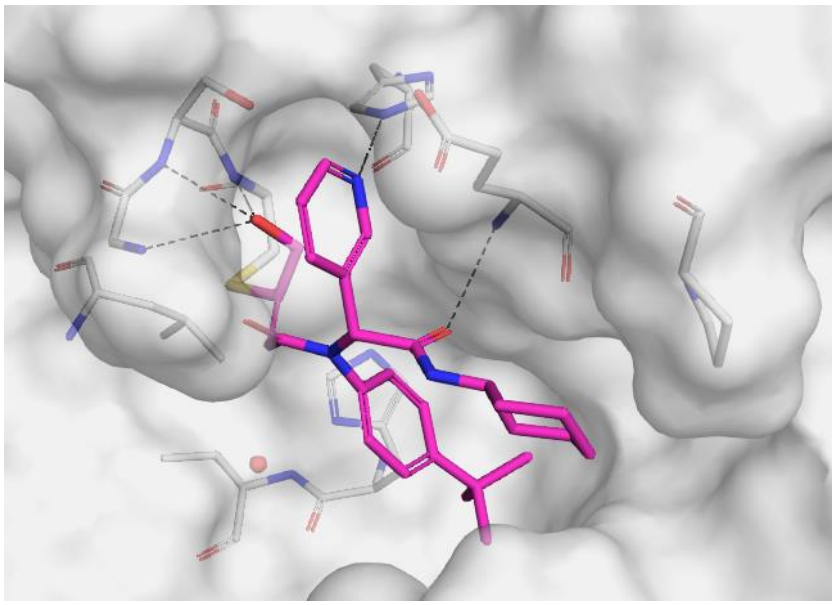


Figure S7. Docked molecule **13a** to 3CLpro catalytic site.

7. Compound purity

Table S3. Purity of Biologically Tested Compounds

Entry	Compound	Retention time (min.)[a]	Purity (%)[b]
1	**X77**	15.45	99.1
2	**ML188**	15.09	98.9
3	**4a**	14.52	95.6
4	**4b**	13.99	97.8
5	**5a**	15.77	96.7
6	**6a**	15.18	98.9
7	**6b**	14.72	99.6
8	**7a**	16.59	97.6
9	**8a**	15.53	99.8
10	**8b**	14.89	99.8
11	**8c**	15.10	97.5
12	**9a**	15.56	96.4
13	**10a**	15.34	95.2
14	**11a**	16.06	95.1
15	**11b**	15.77	97.1

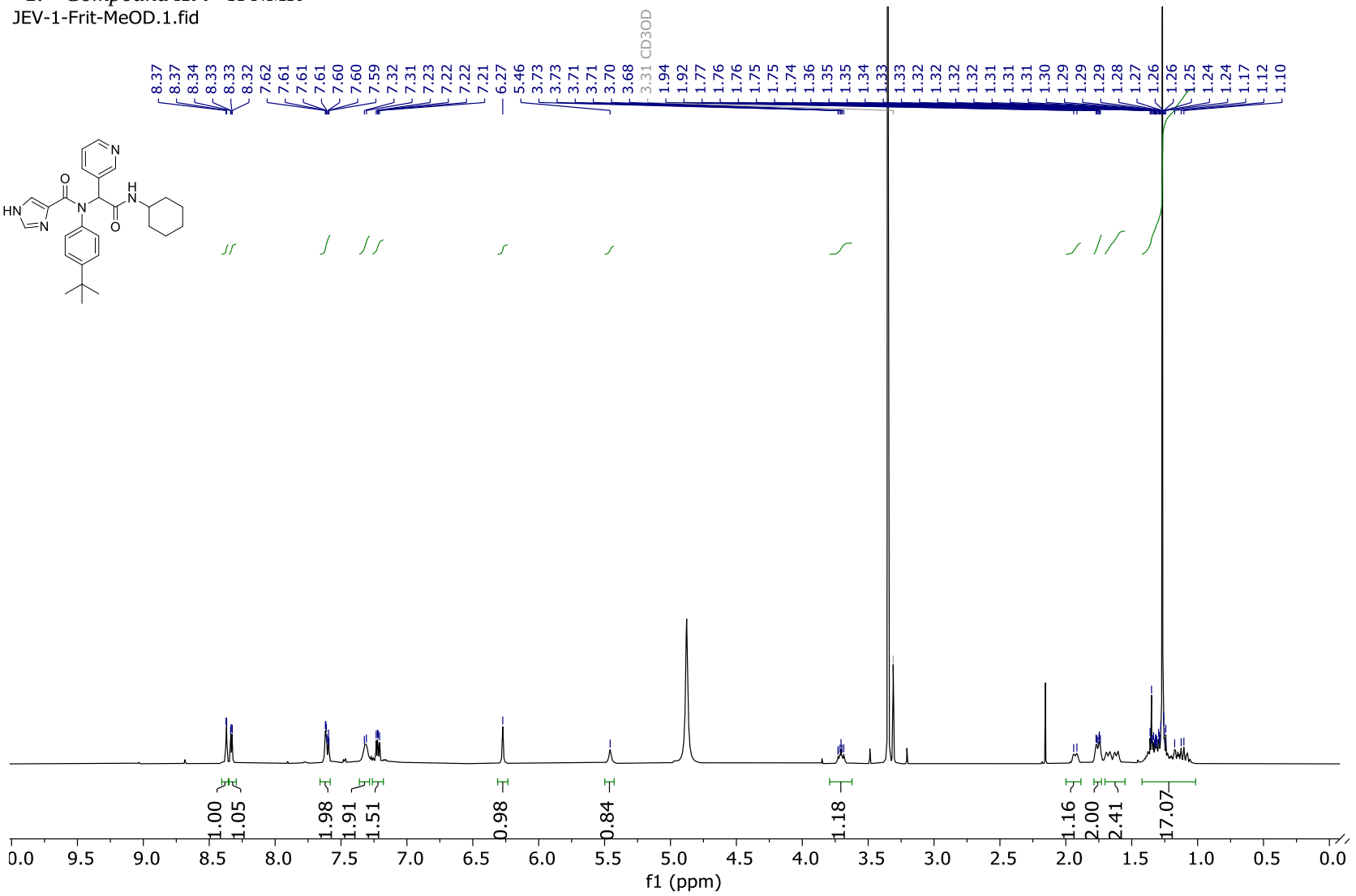
16	**11c**	17.45	95.1
17	**11d**	17.03	98.37
18	**11e**	15.54	95.7
19	**11f**	16.17	95.7
20	**11g**	16.04	96.4
21	**11h**	16.93	99.5
22	**11i**	14.50	98.3
23	**12a**	16.37	94.0
24	**13a**	15.25	94.2
25	**13b**	14.69	97.2
26	**13c**	15.1	96.0
27	**13d**	14.53	97.5
28	**13e**	16.80	99.5
29	**13f**	16.30	95.1
30	**13g**	15.56	95.7
31	**13h**	17.41	91.8
32	**13i**	14.61	99.5
33	**13j**	14.84	97.6
34	**13k**	14.01	97.5
35	**13l**	15.46	99.0
36	**13m**	12.96	92.3
37	**13n**	15.88	96.1
38	**13o**	15.67	95.8
39	**13p**	14.52	98.0
40	**13q**	14.07	95.9
41	**14a**	15.76	91.0
42	**14b**	15.39	99.4
43	**14c**	15.93	97.4
44	**14d**	15.45	99.2
45	**14e**	15.84	94.5
46	**14f**	11.6	87.8
47	**14g**	15.58	92.7
48	**14h**	15.42	95.3
49	**15a**	15.03	94.7

50	**16a**	15.37	95.6
51	**16b**	12.80	96.1
52	**16c**	15.3	91.2
53	**16d**	15.52	93.5
54	**16e**	15.46	95.4
55	**16f**	15.84	90.6
56	**17a**	16.00	99.5
57	**18a**	15.34	97.7
58	**18b**	14.224	76.6
59	**19a**	15.80	99.8
60	**20a**	15.08	90.9
61	**21a**	15.71	98.5
62	**22a**	15.32	97.7
63	**23a**	14.52	98.2
64	**24a**	11.99	96.7
65	**25a**	12.05	93.1

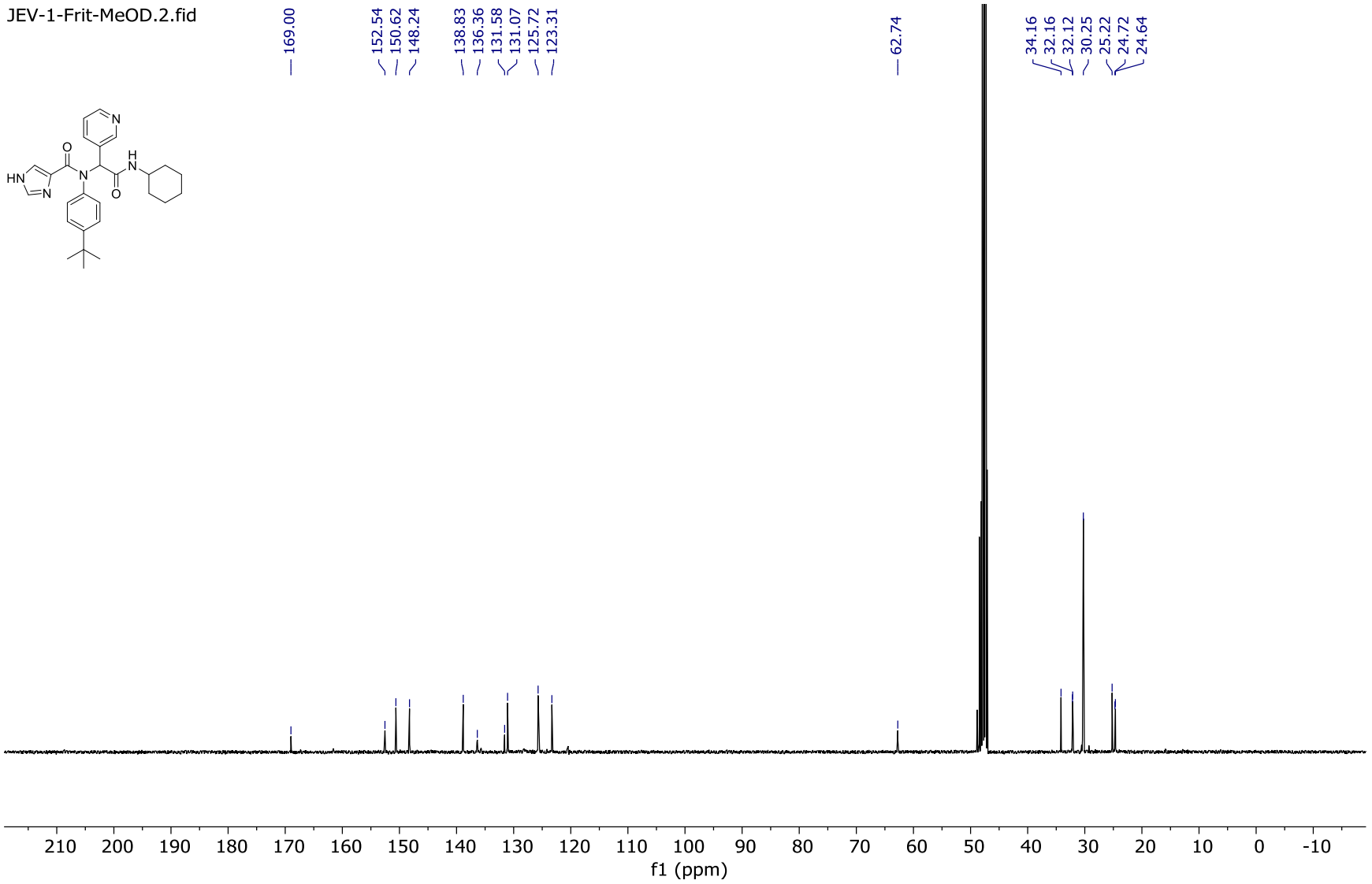
[a] Conditions: (gradient of 95% water, 5% MeOH or MeCN, 1 mL/min). [b] UV detection at 254 nm.

8. ^{1}H and ^{13}C NMR spectra

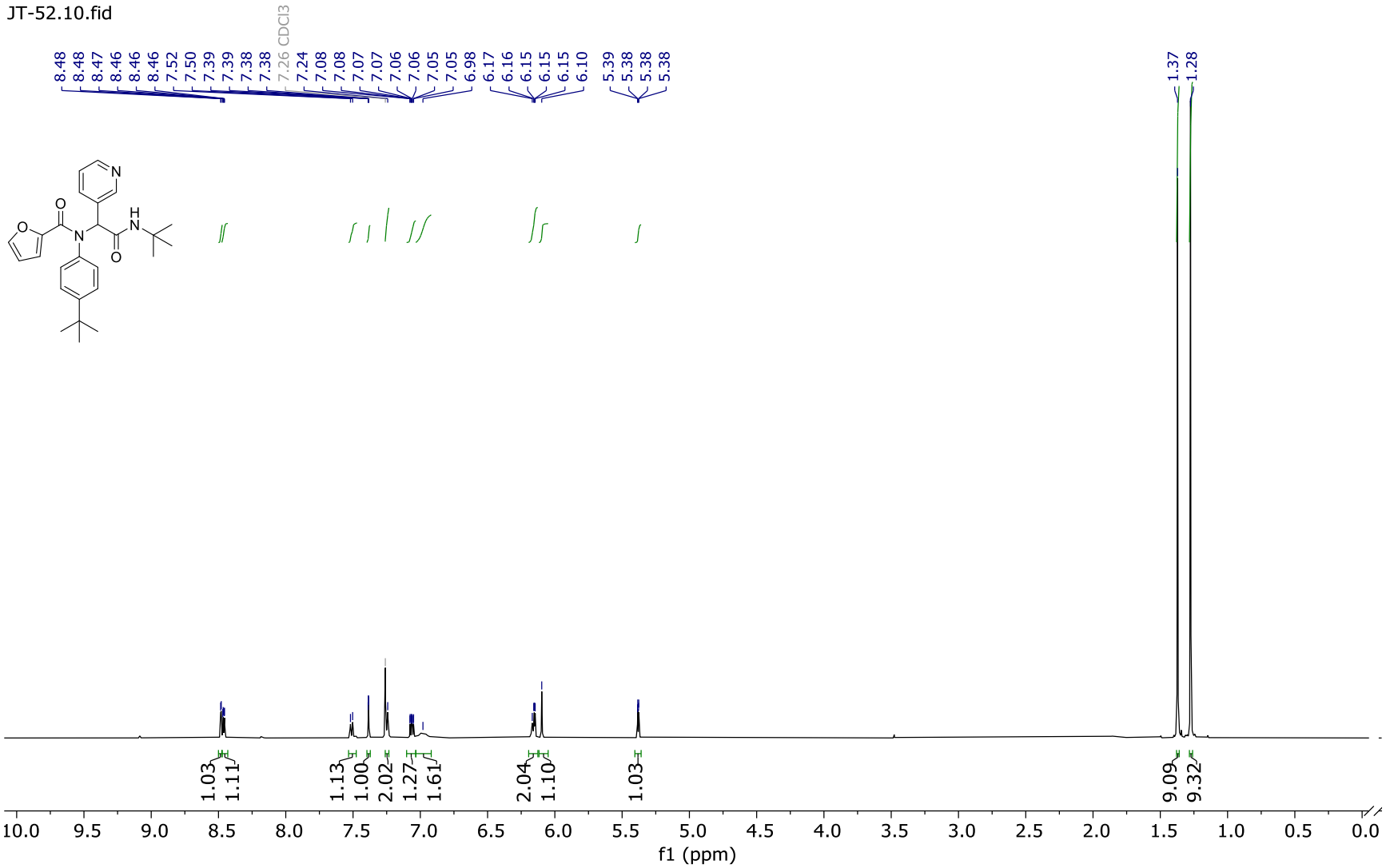
*1. Compound **X77** ^{1}H NMR*



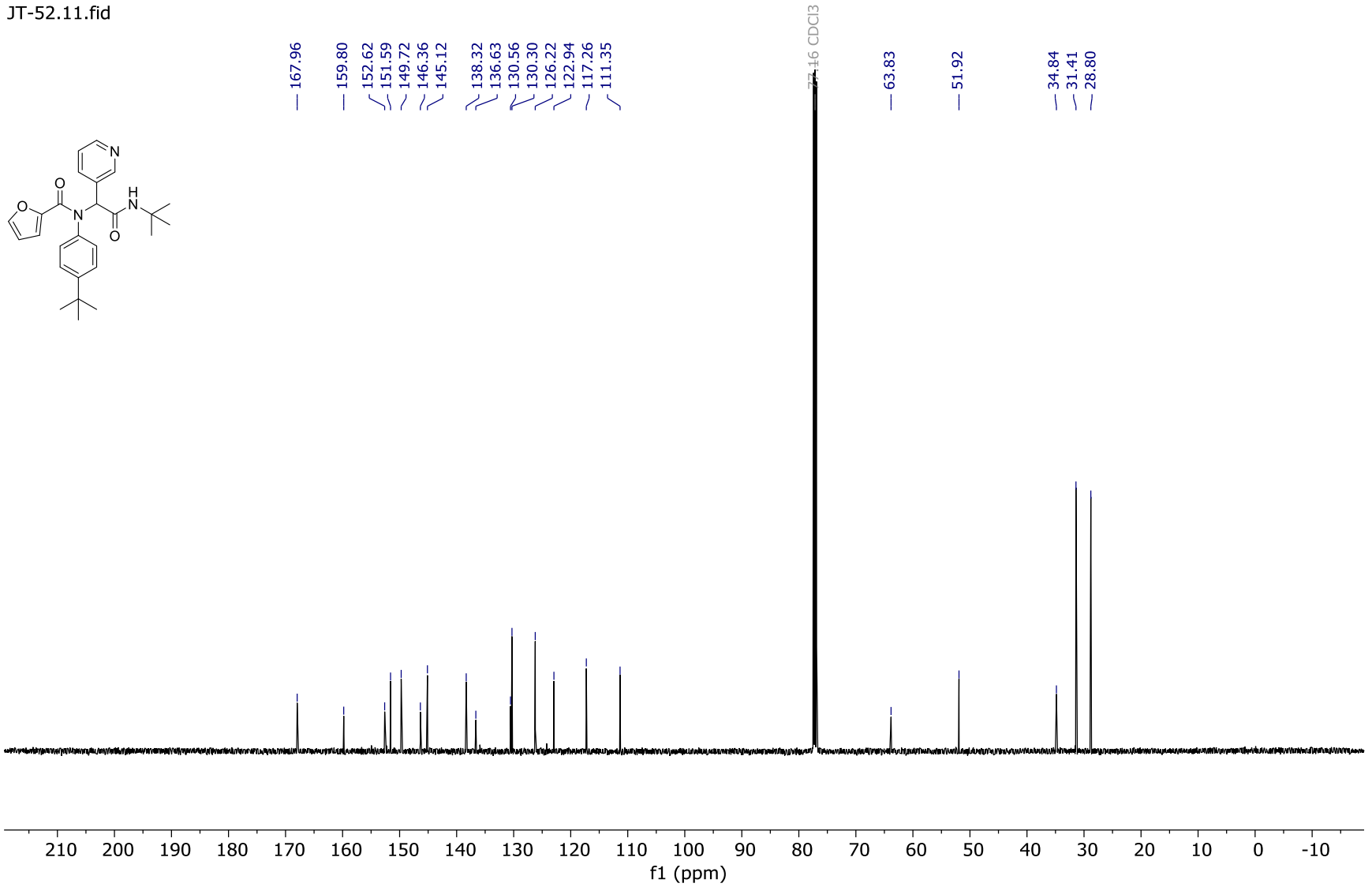
2. *Compound **X77** ^{13}C NMR*



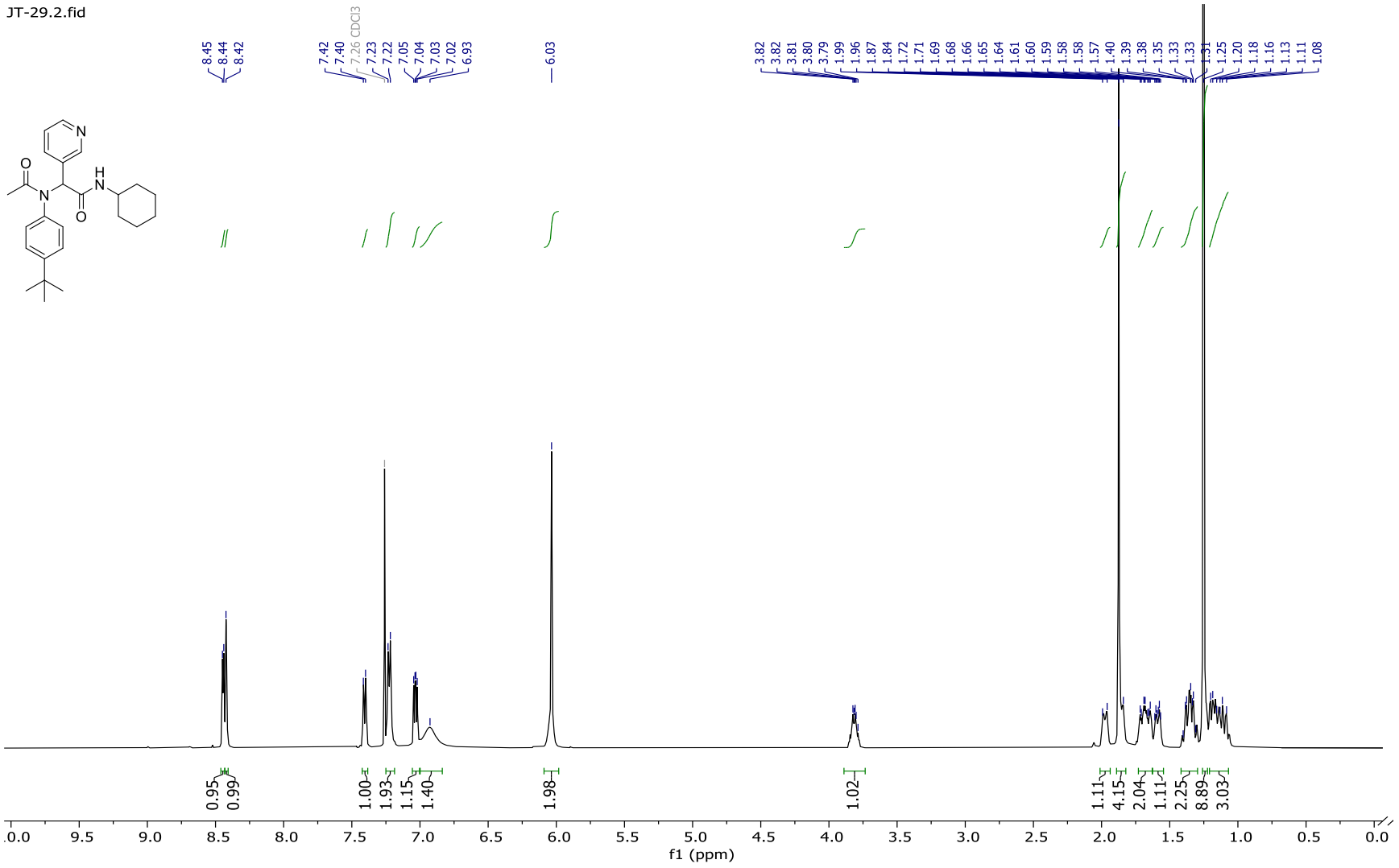
*3. Compound **ML188** ^{1}H NMR*



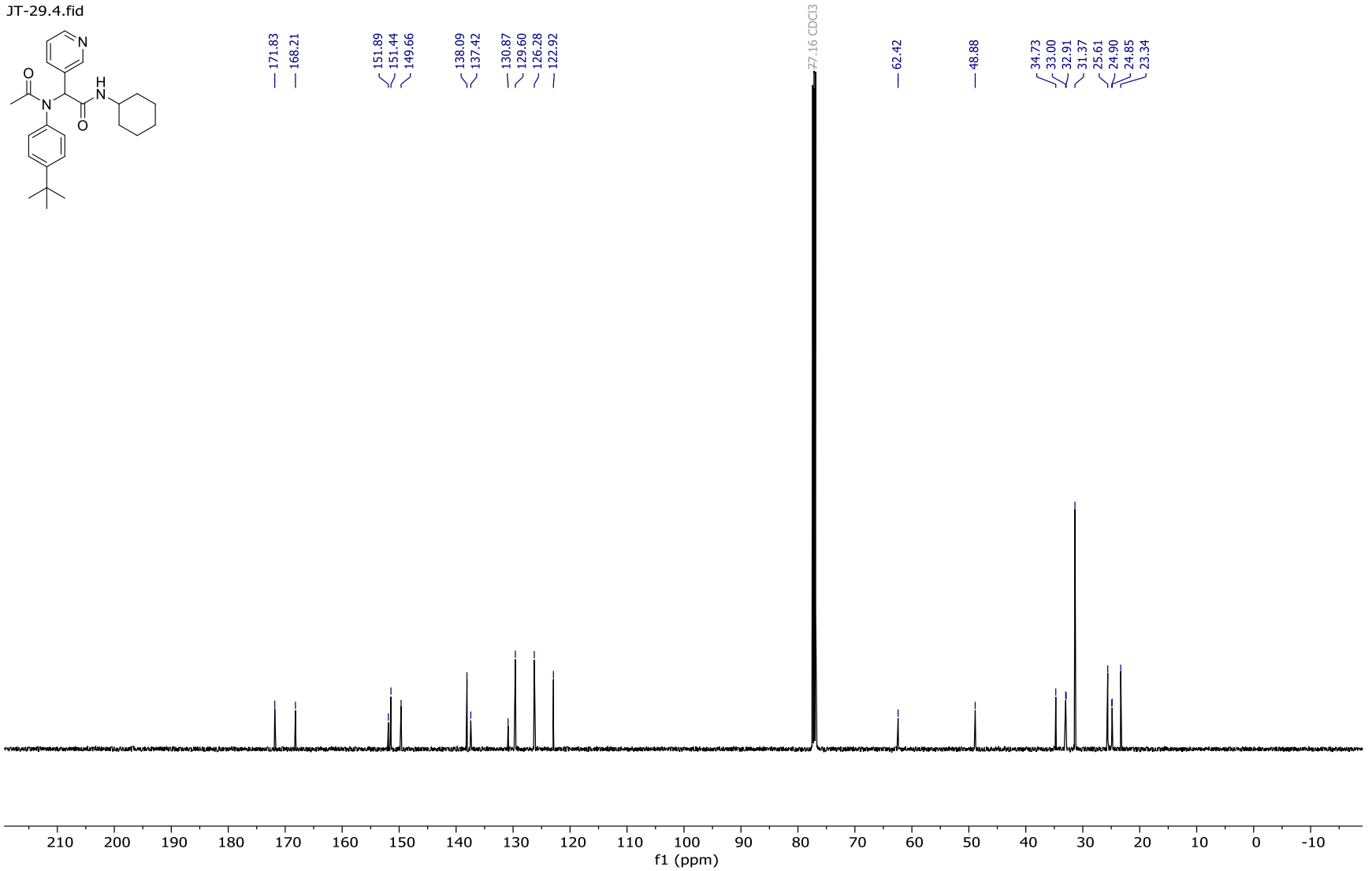
*4. Compound **ML188** ^{13}C NMR*



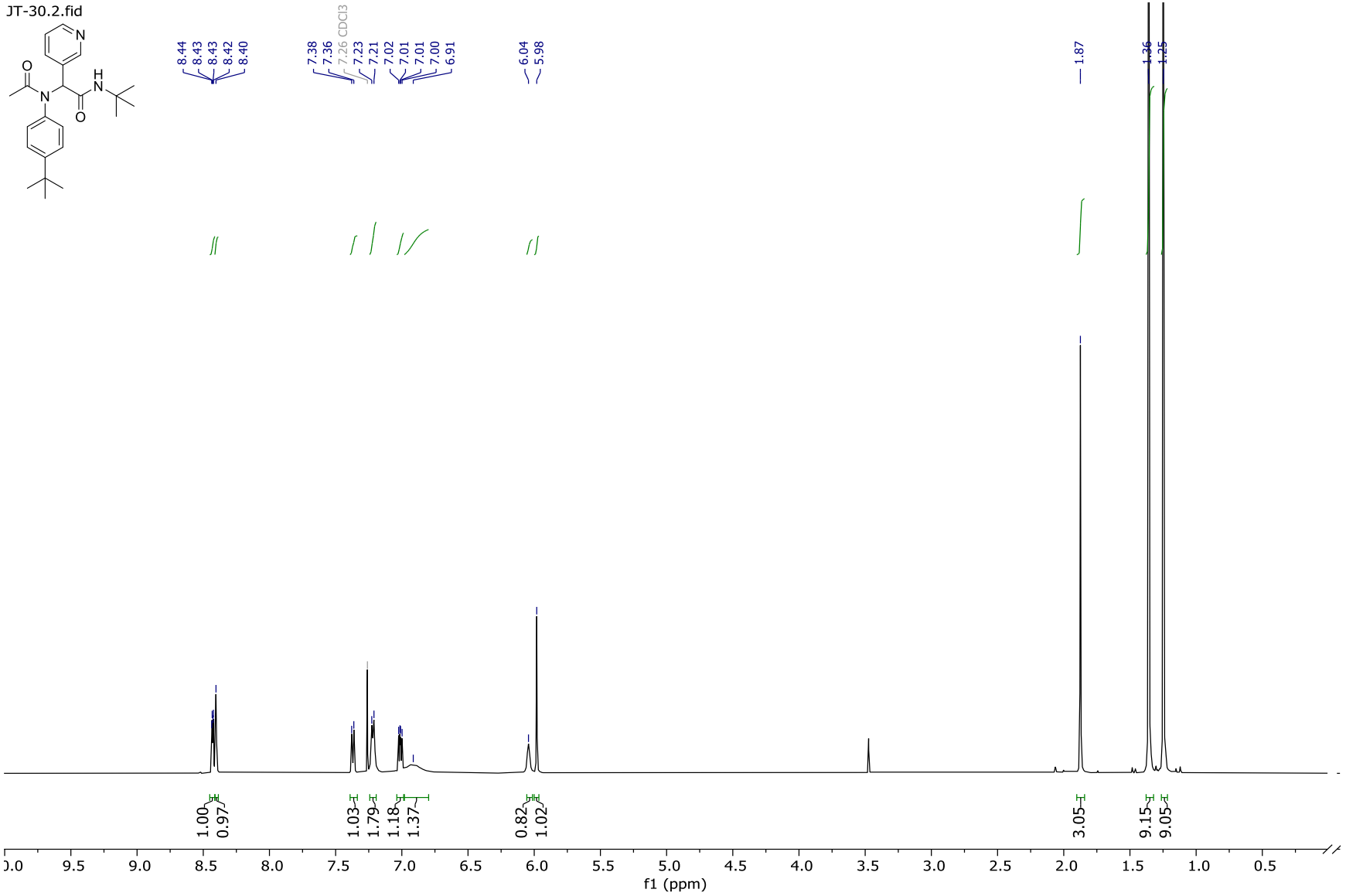
5. *Compound **4a** ^{1}H NMR*



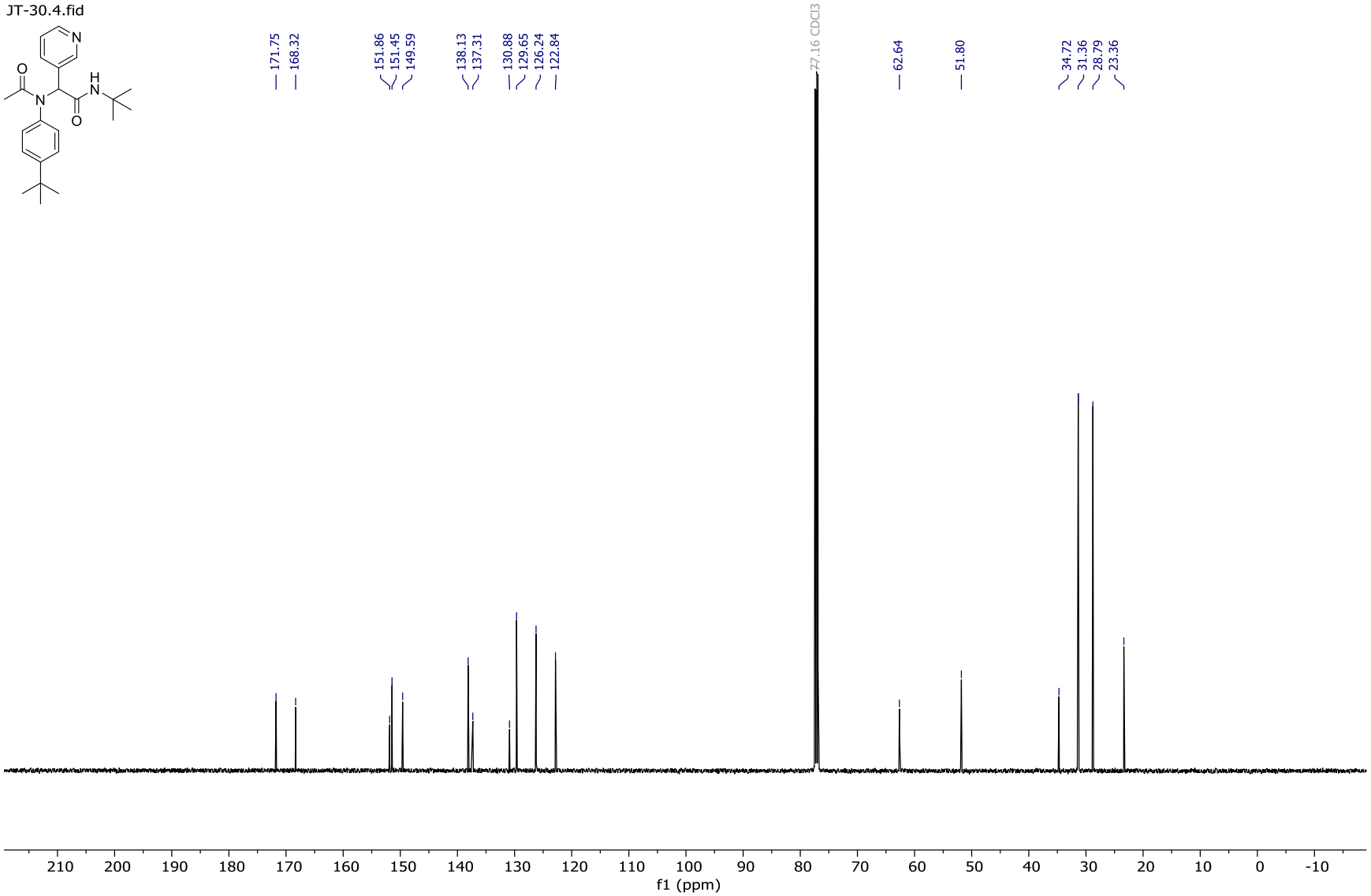
6. *Compound **4a** ^{13}C NMR*



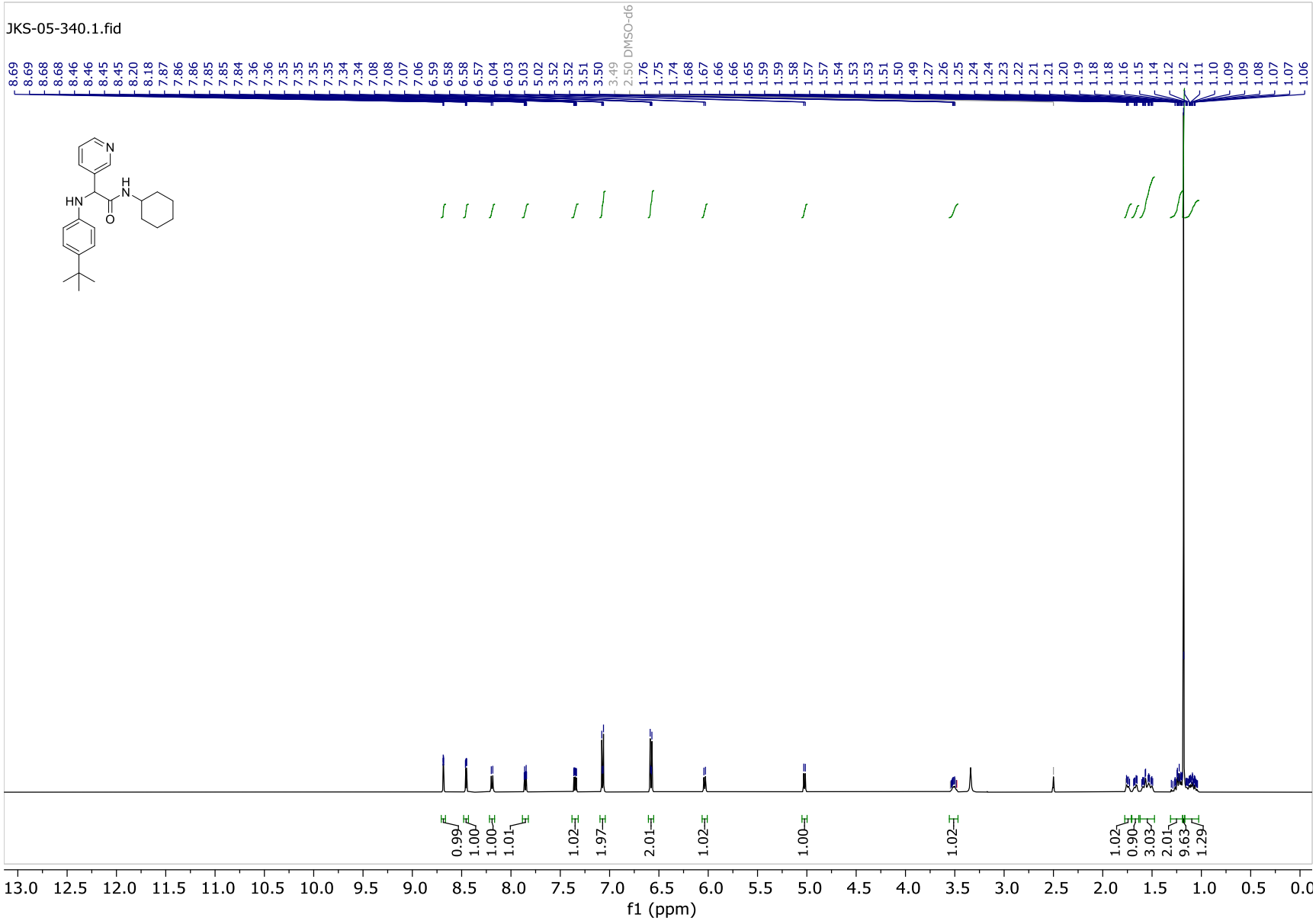
*7. Compound **4b** ^{1}H NMR*



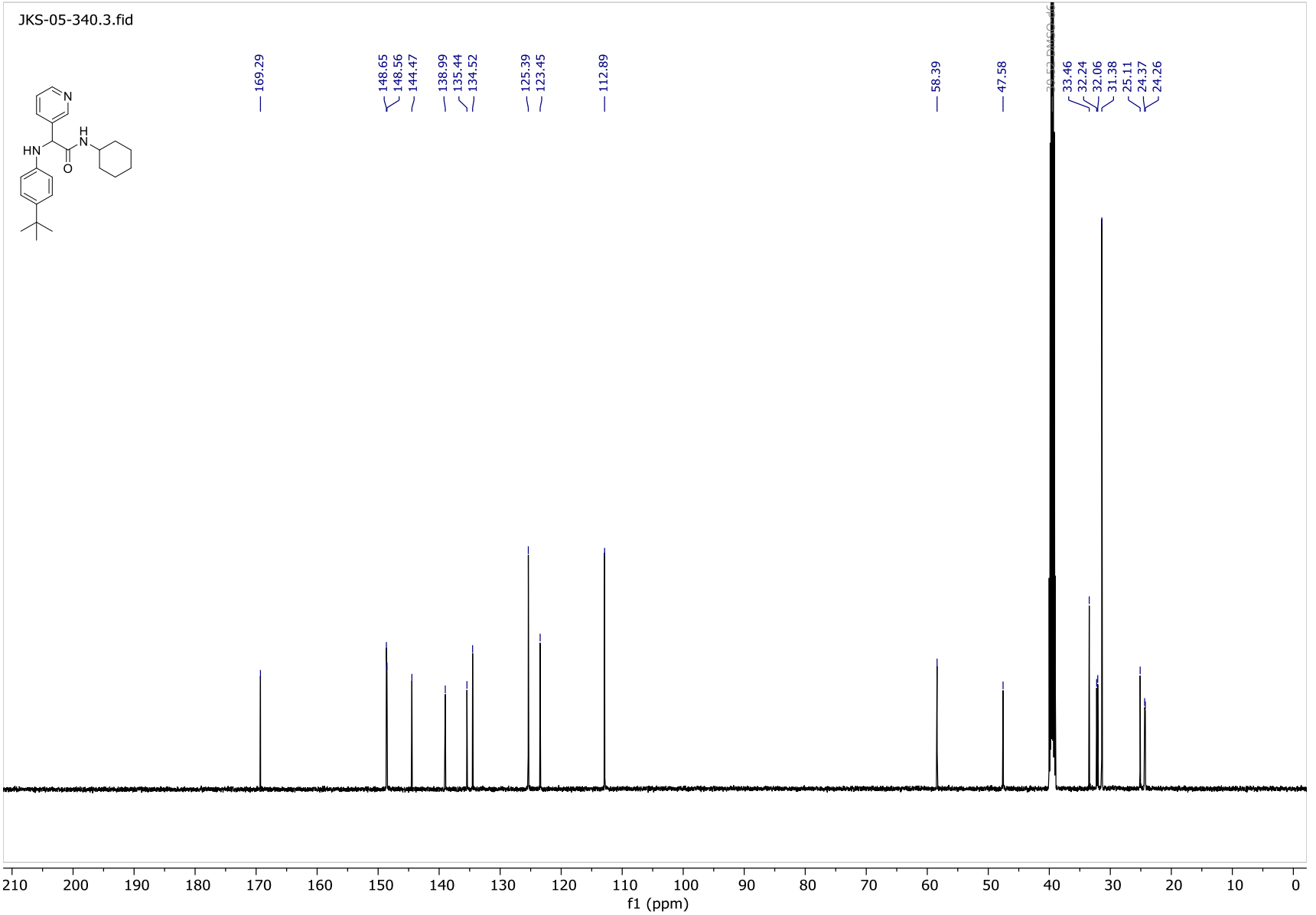
*8. Compound **4b** ^{13}C NMR*



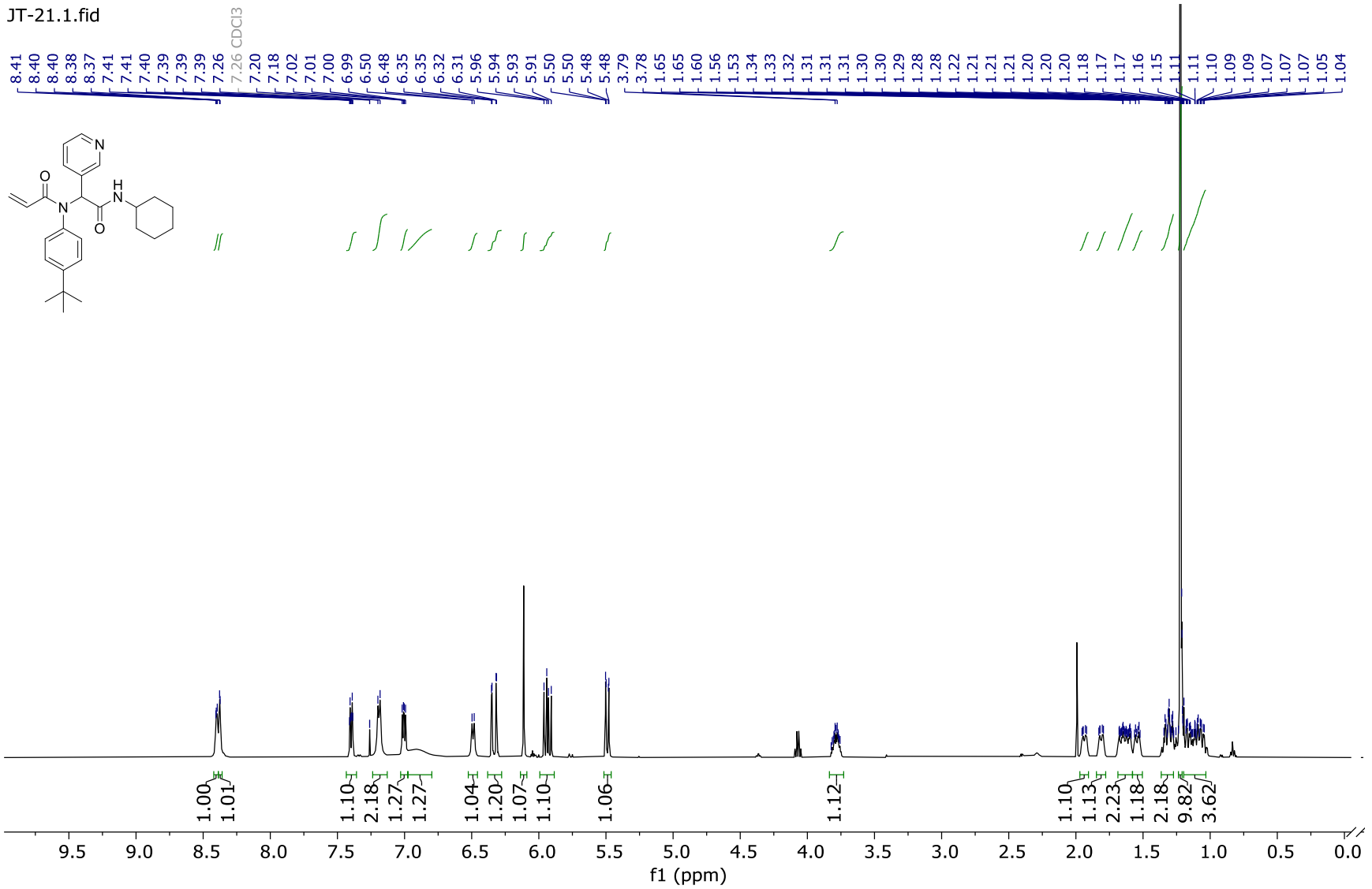
*9. Compound **5a** ^{1}H NMR*



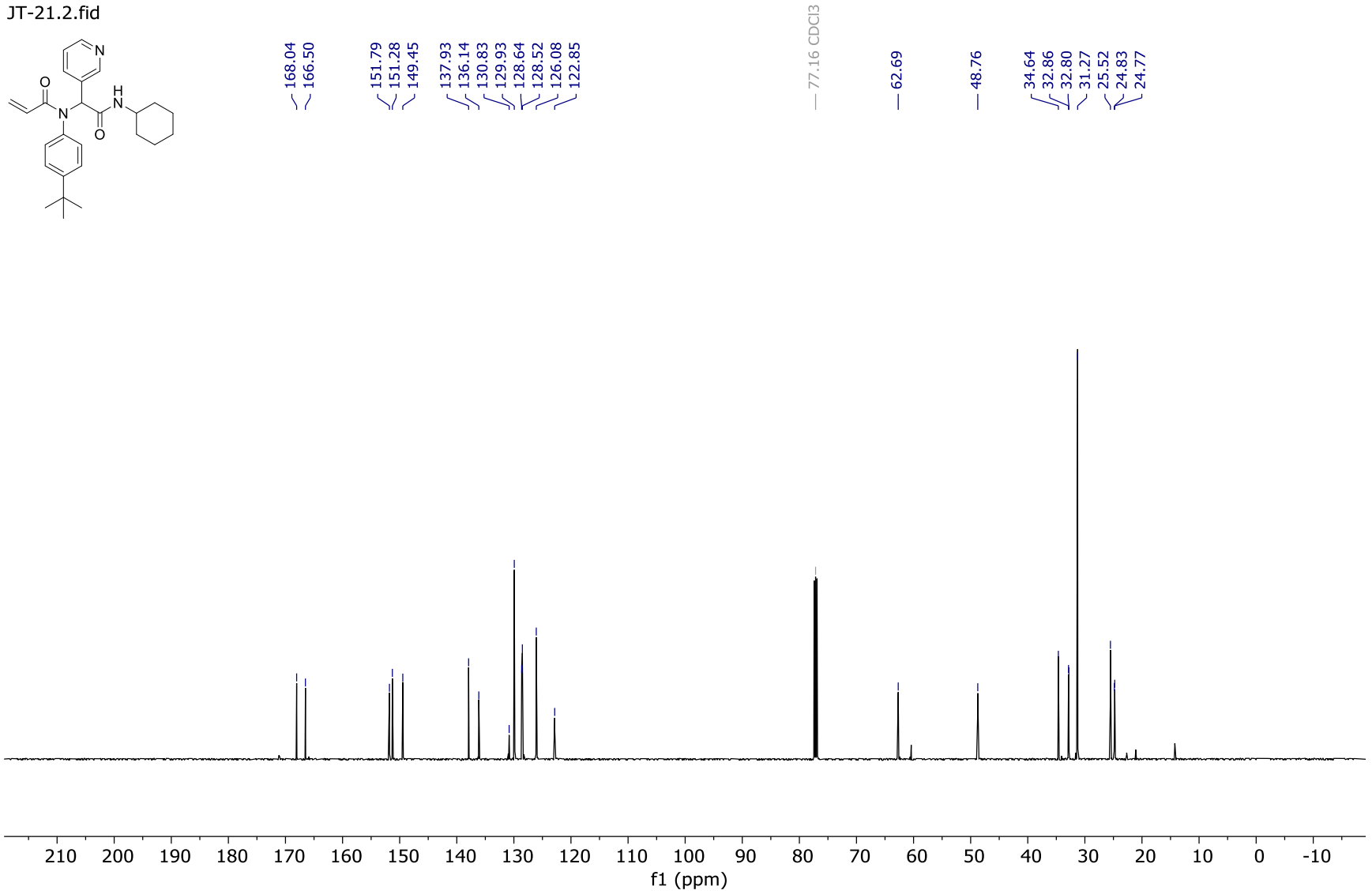
*10. Compound **5a** ^{13}C NMR*



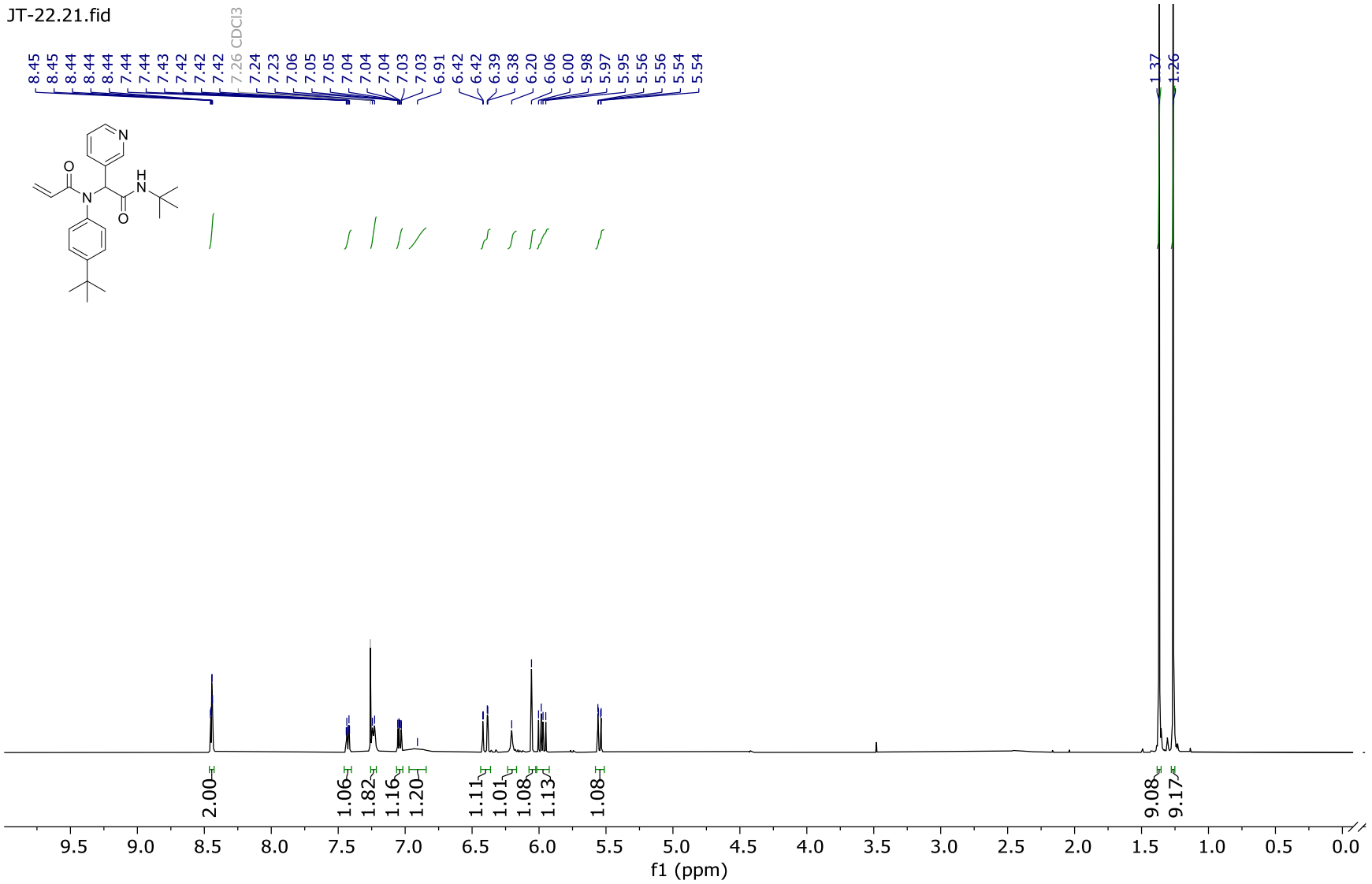
*11. Compound **6a** ^{1}H NMR*



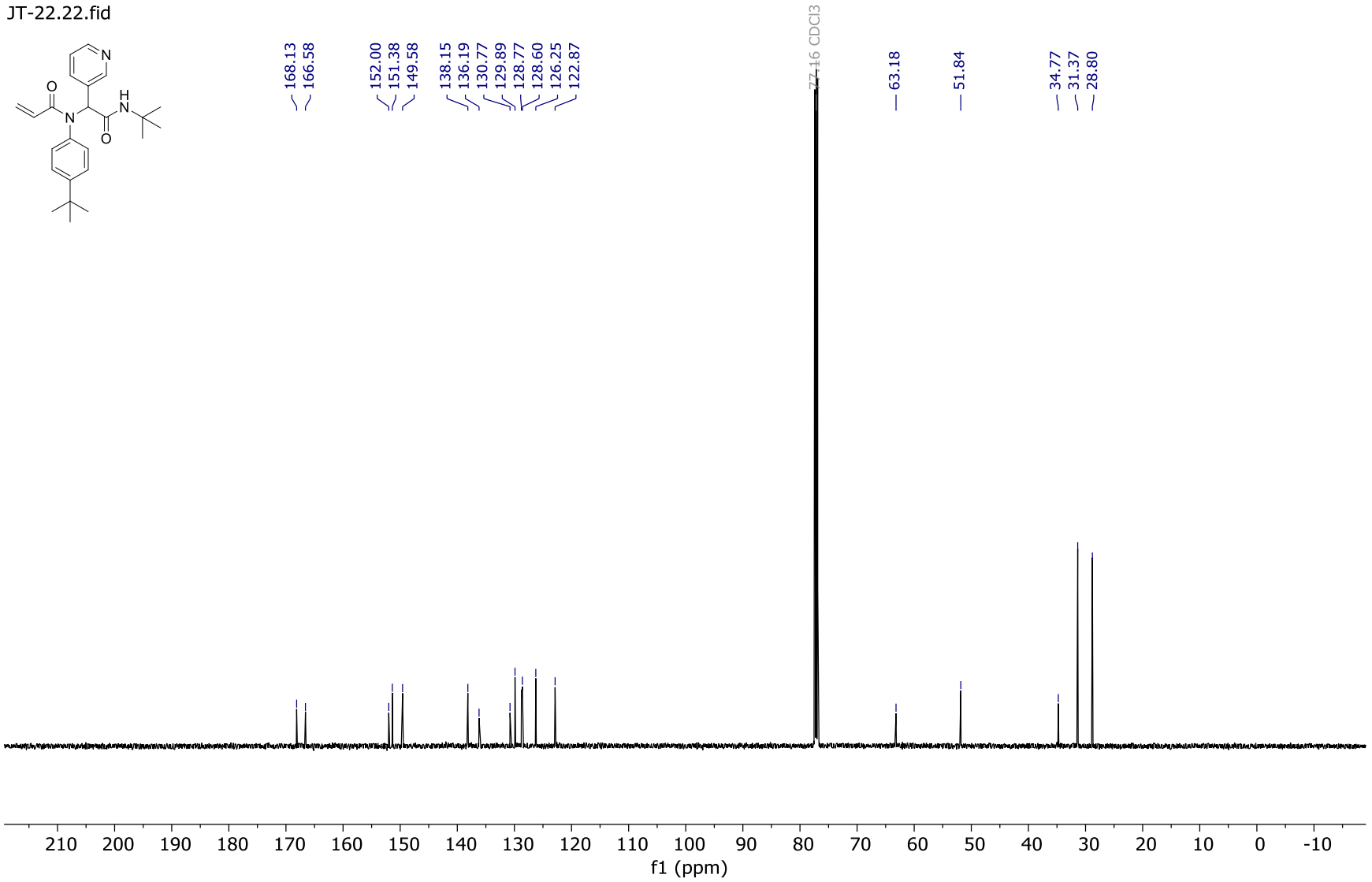
*12. Compound **6a** ^{13}C NMR*



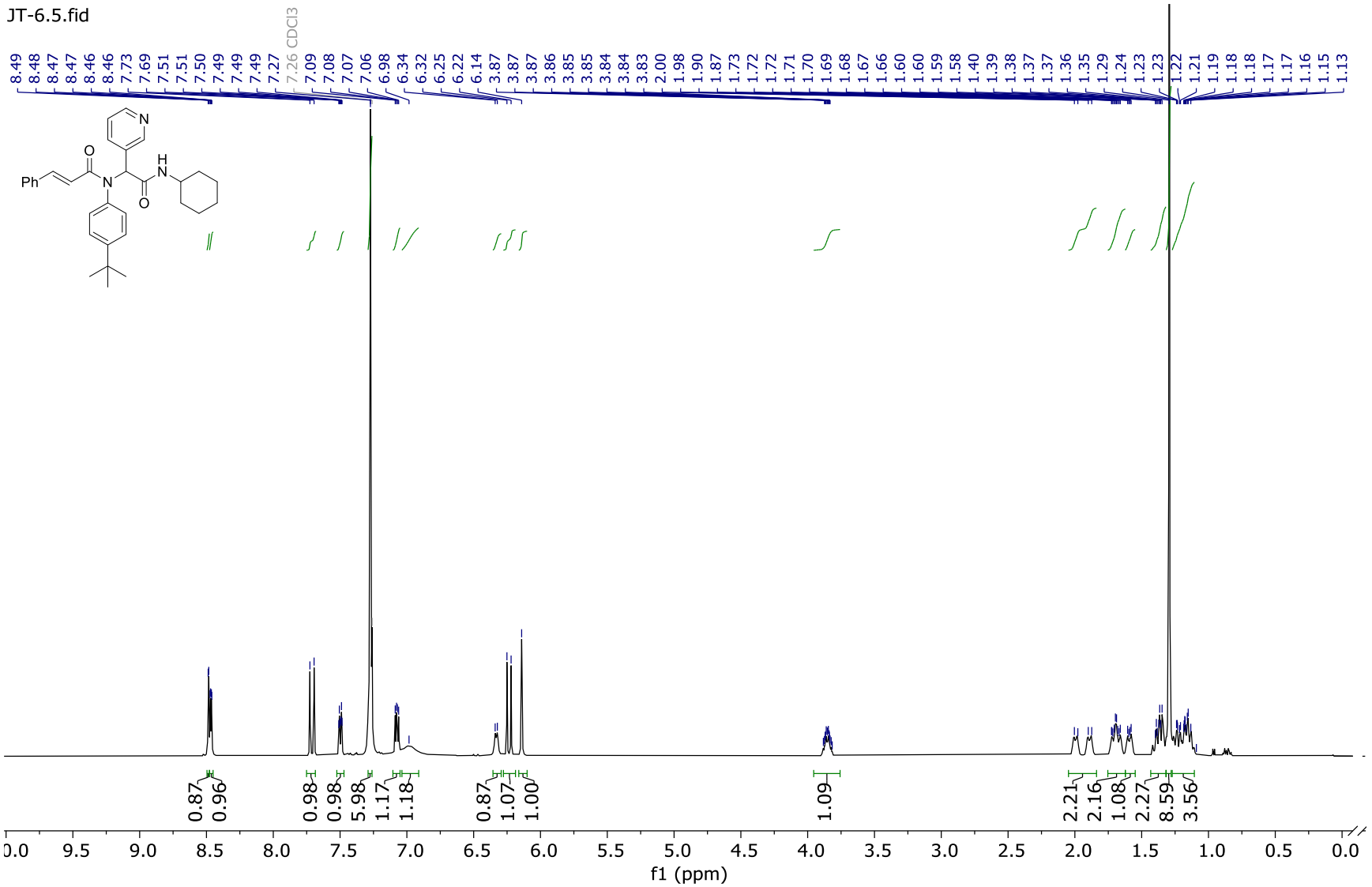
*13. Compound **6b** ^{1}H NMR*



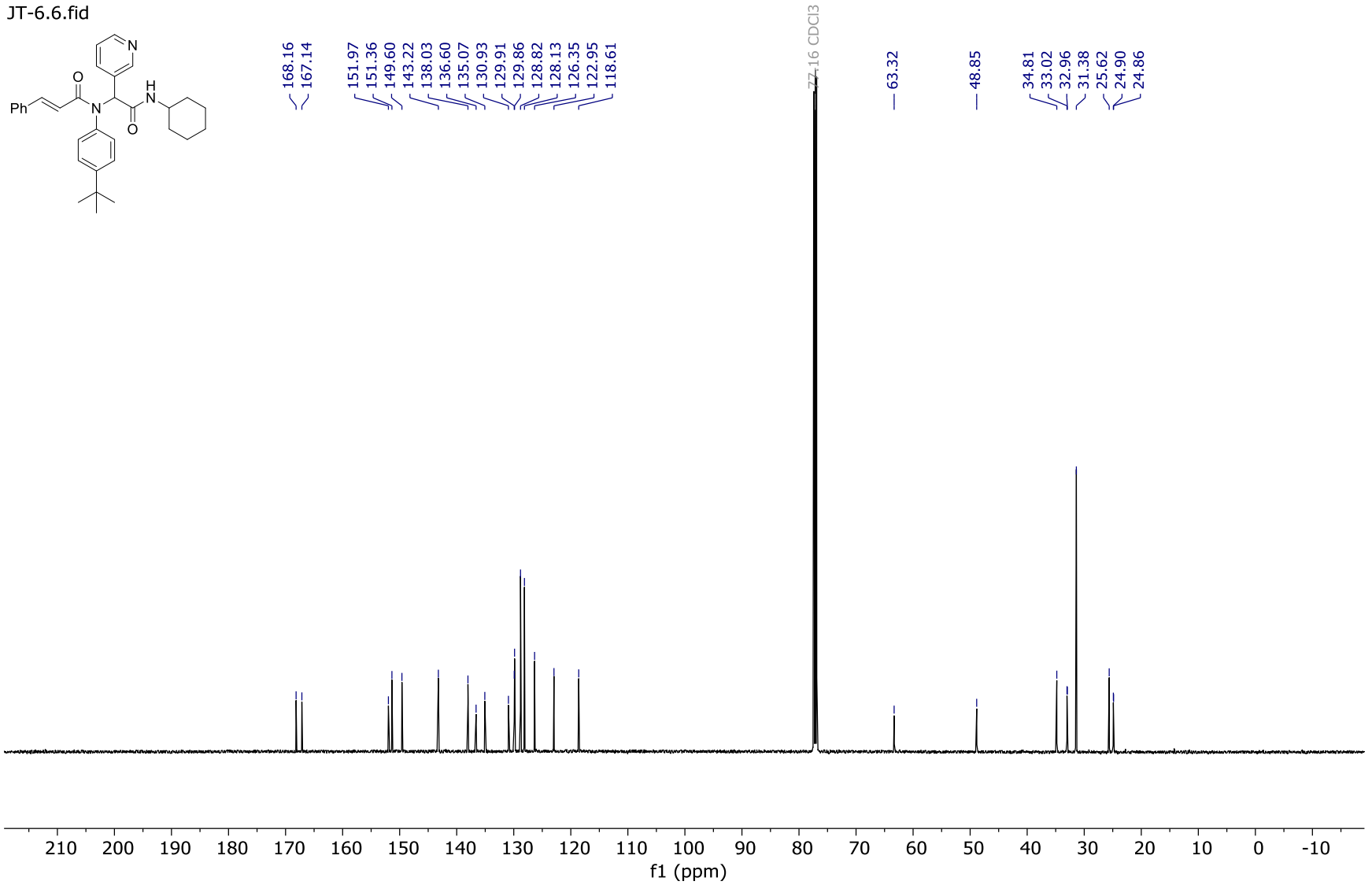
*14. Compound **6b** ^{13}C NMR*



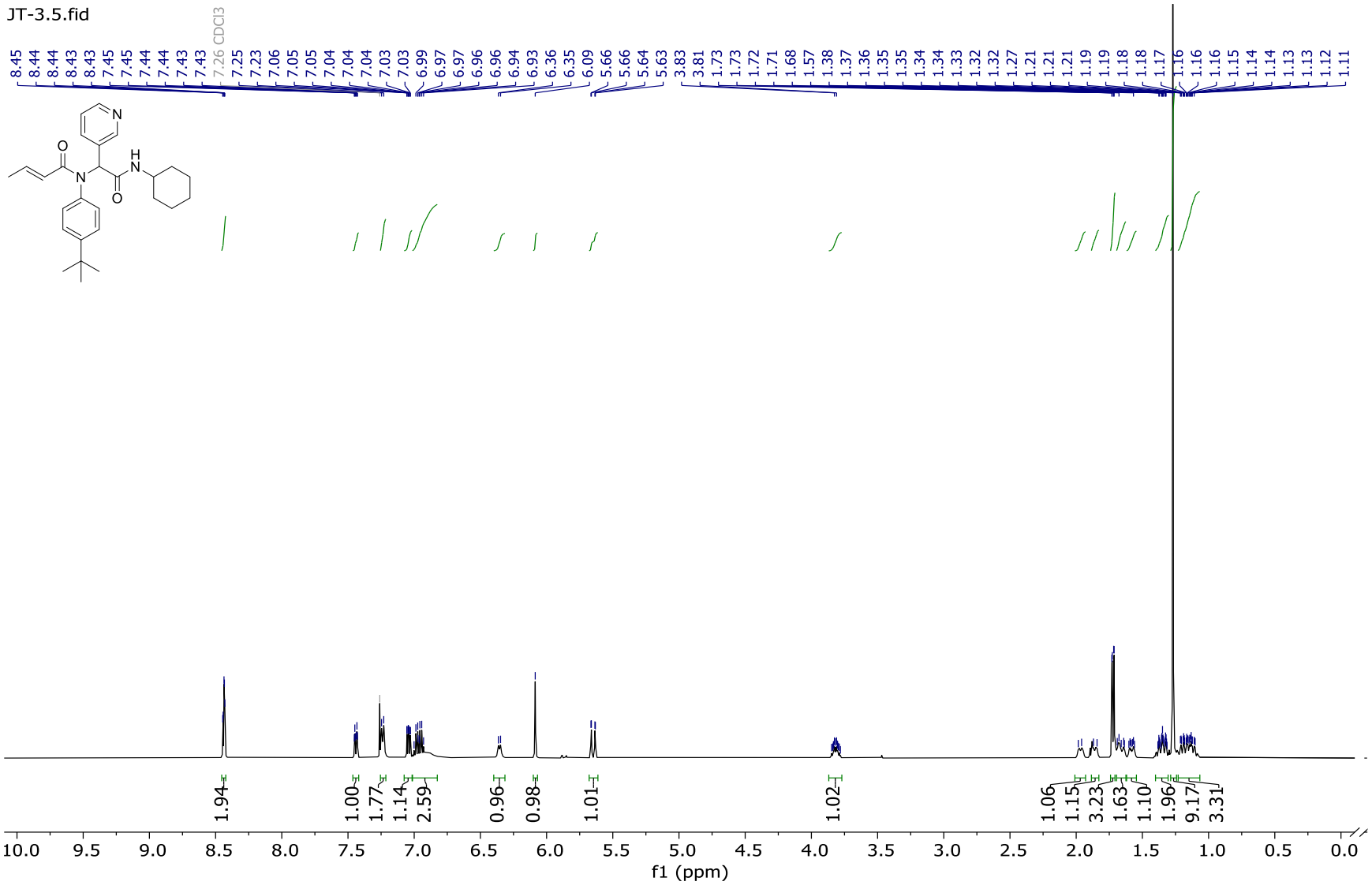
*15. Compound **7a** ^{1}H NMR*



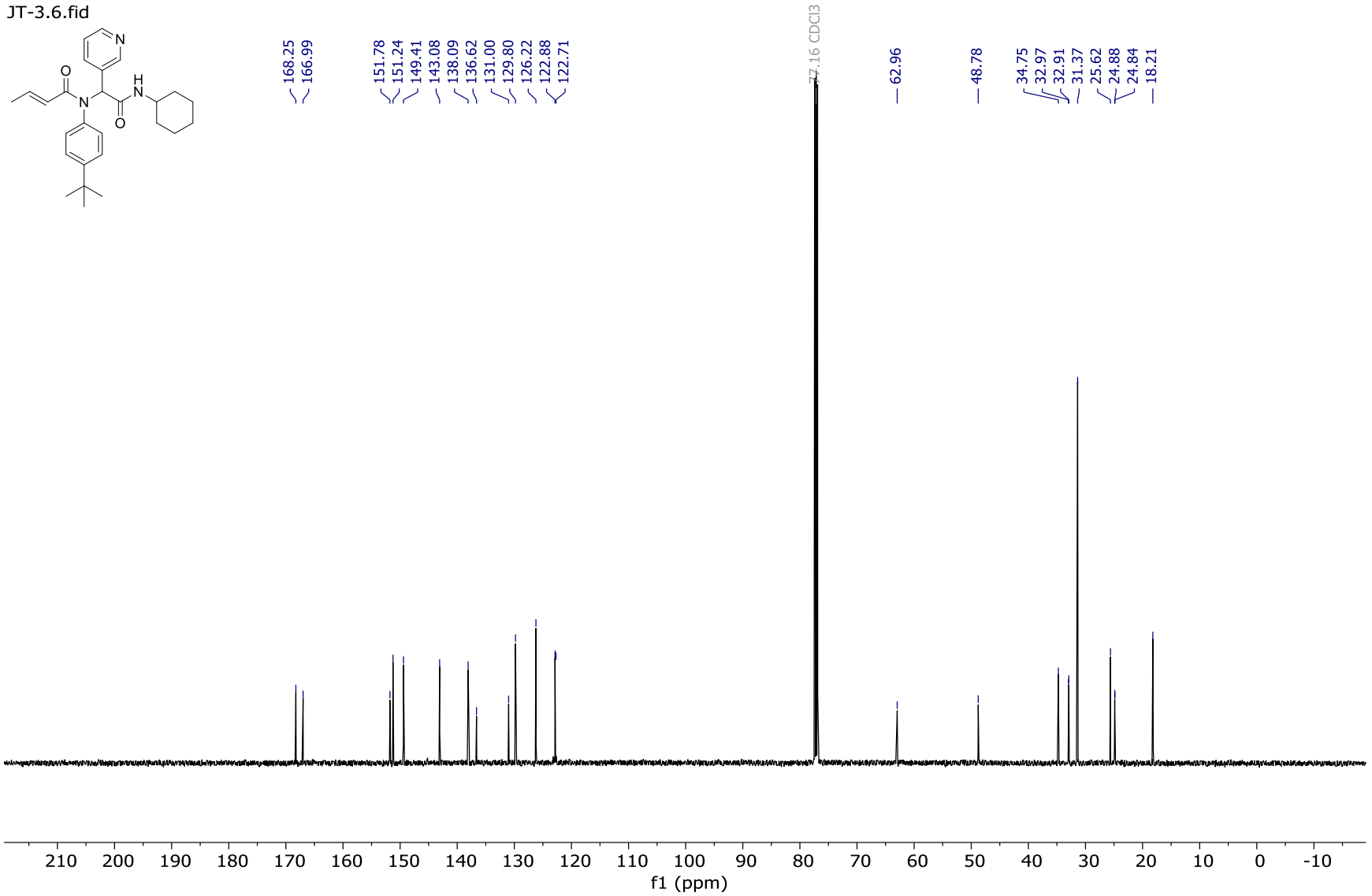
*16. Compound **7a** ^{13}C NMR*



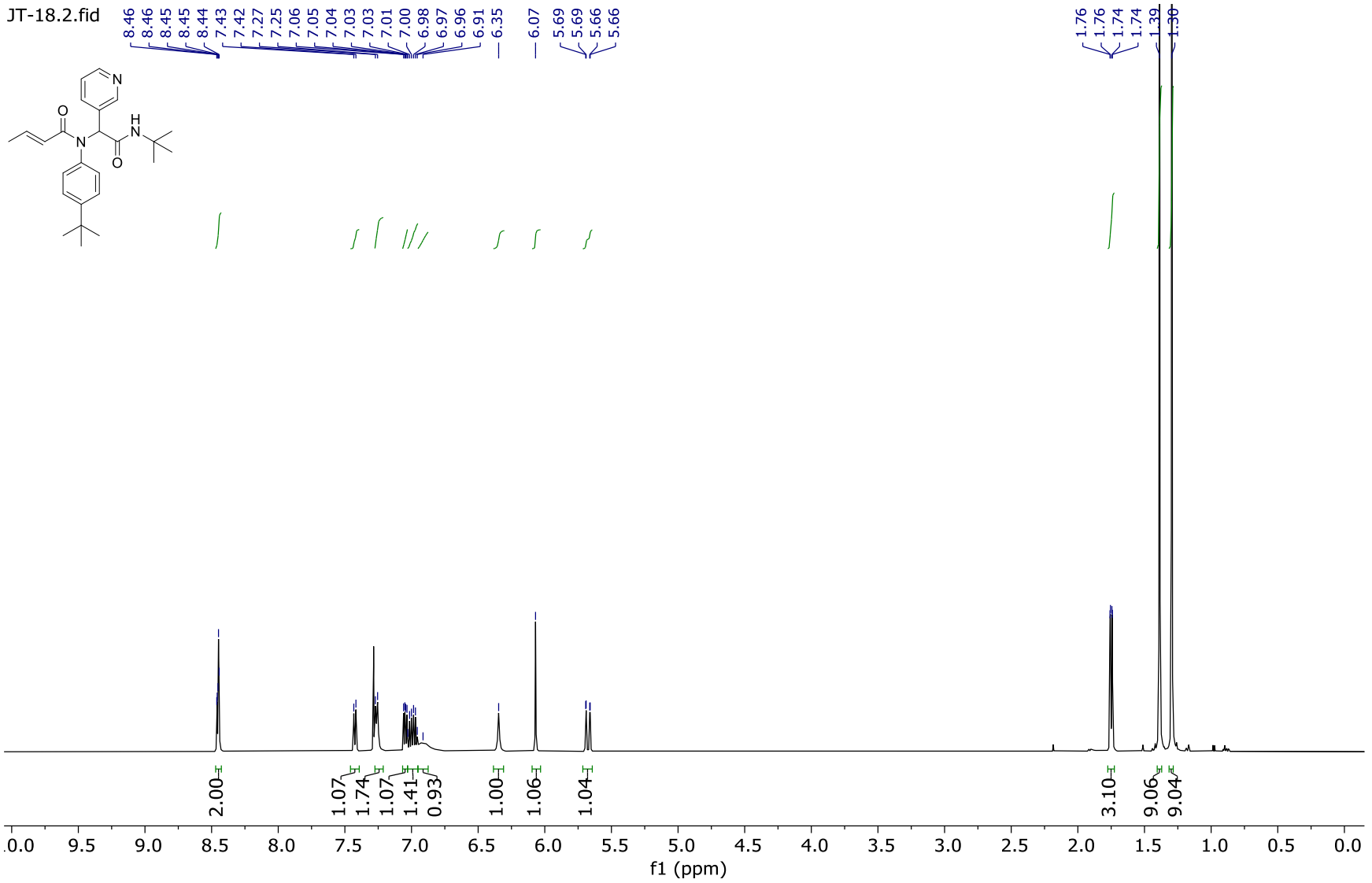
*17. Compound **8a** ^{1}H NMR*



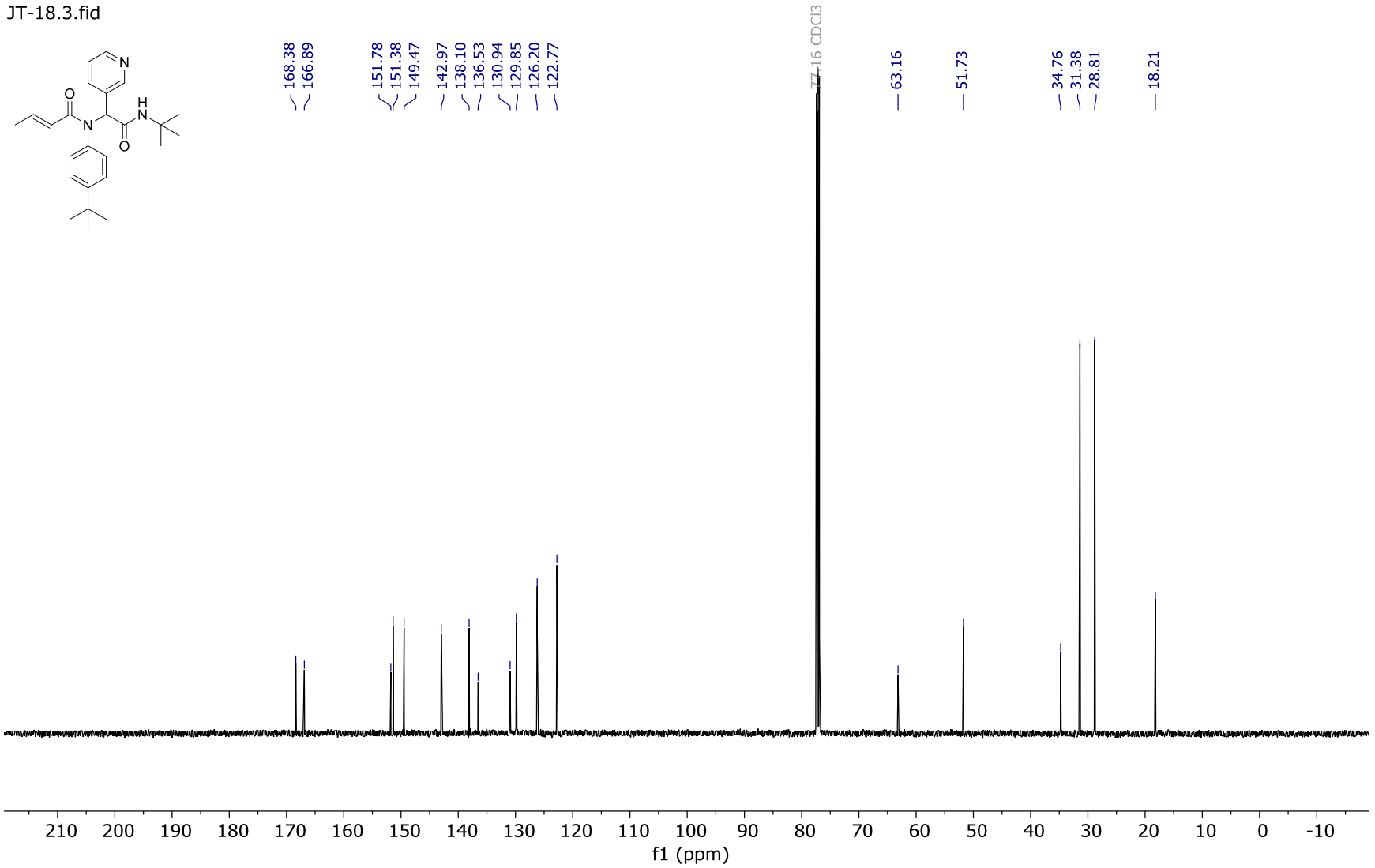
*18. Compound **8a** ^{13}C NMR*



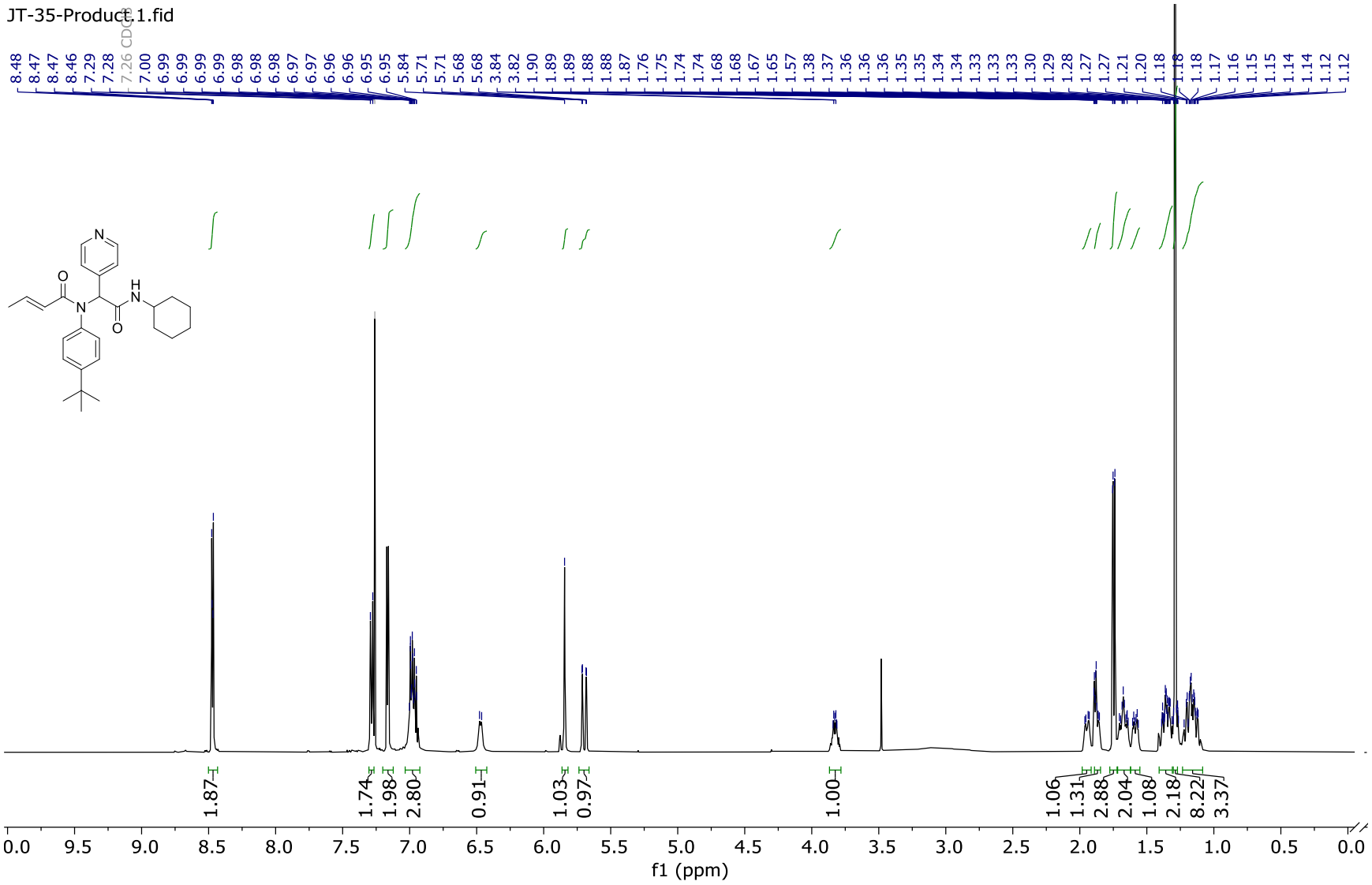
*19. Compound **8b** ^{1}H NMR*



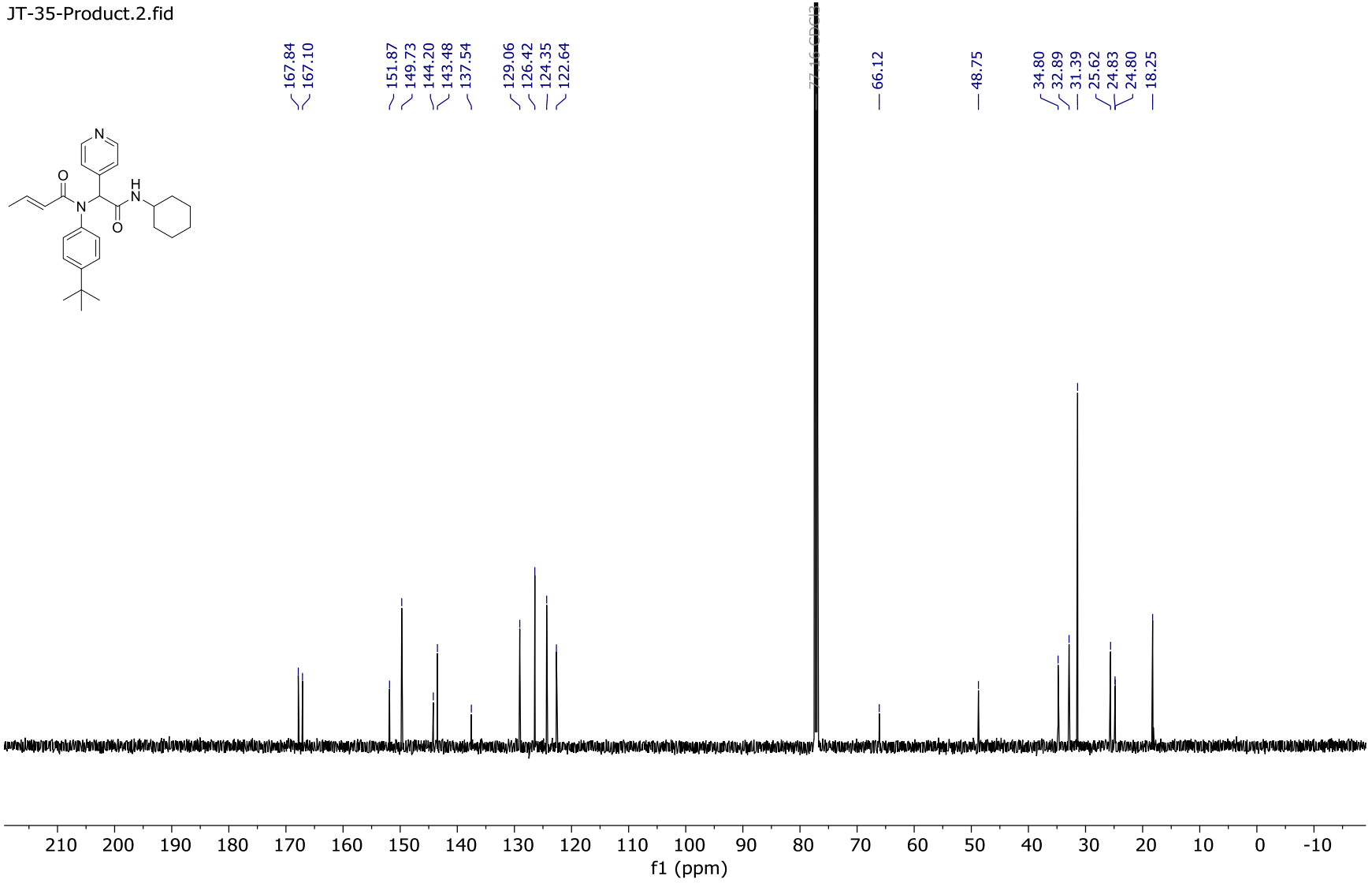
*20. Compound **8b** ^{13}C NMR*



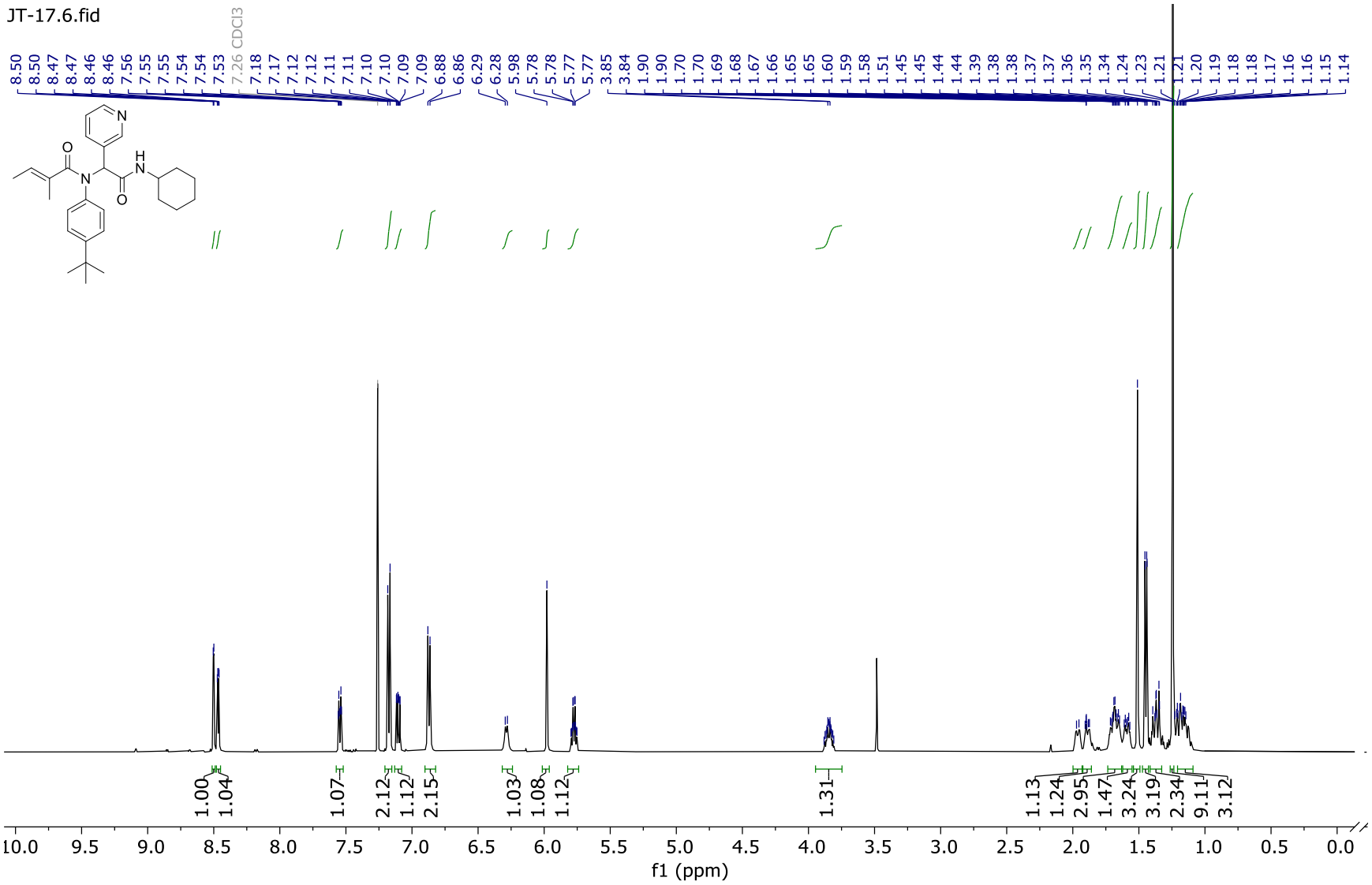
21. Compound ***8c*** *^{1}H NMR*



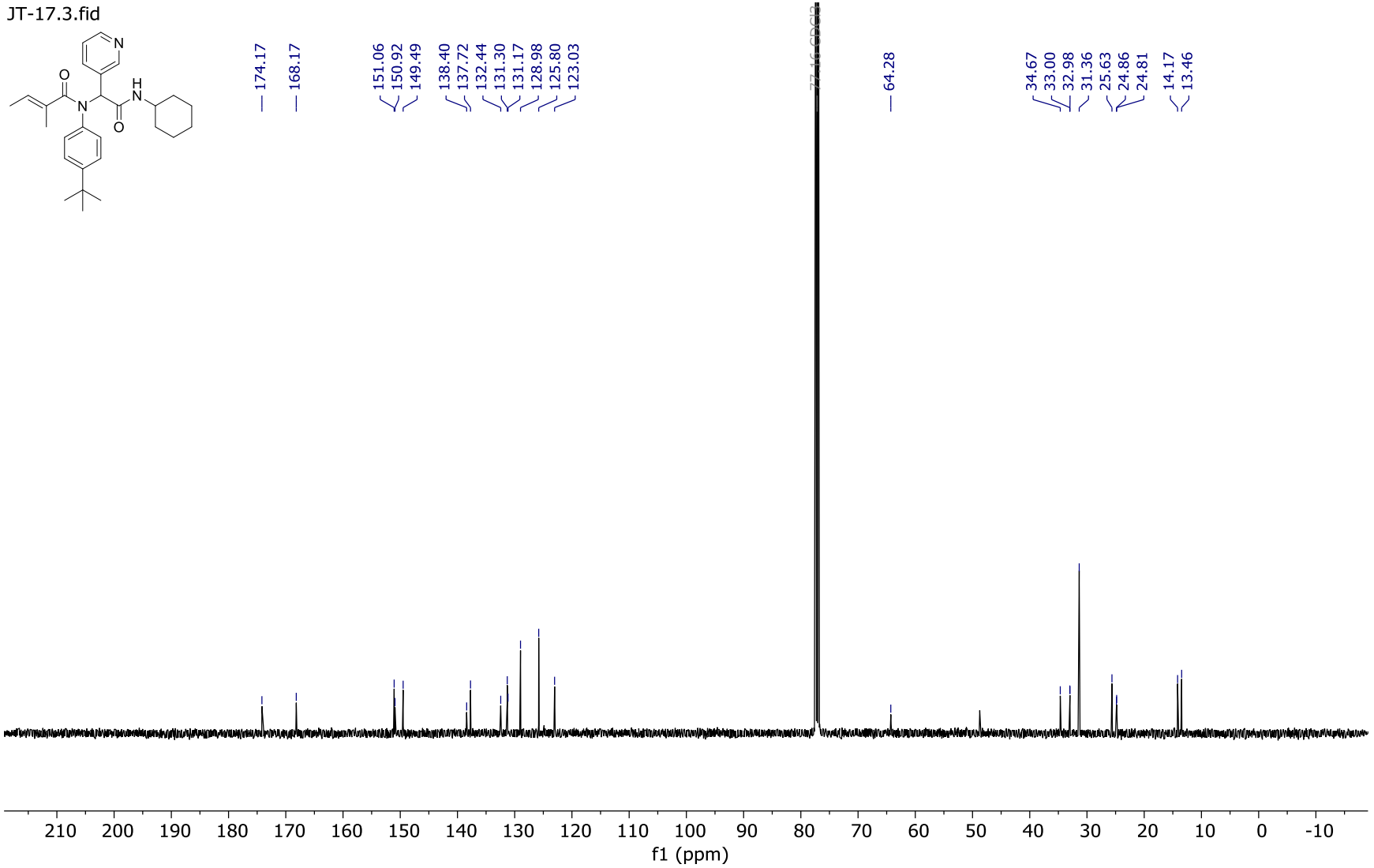
*22. Compound **8c** ^{13}C NMR*



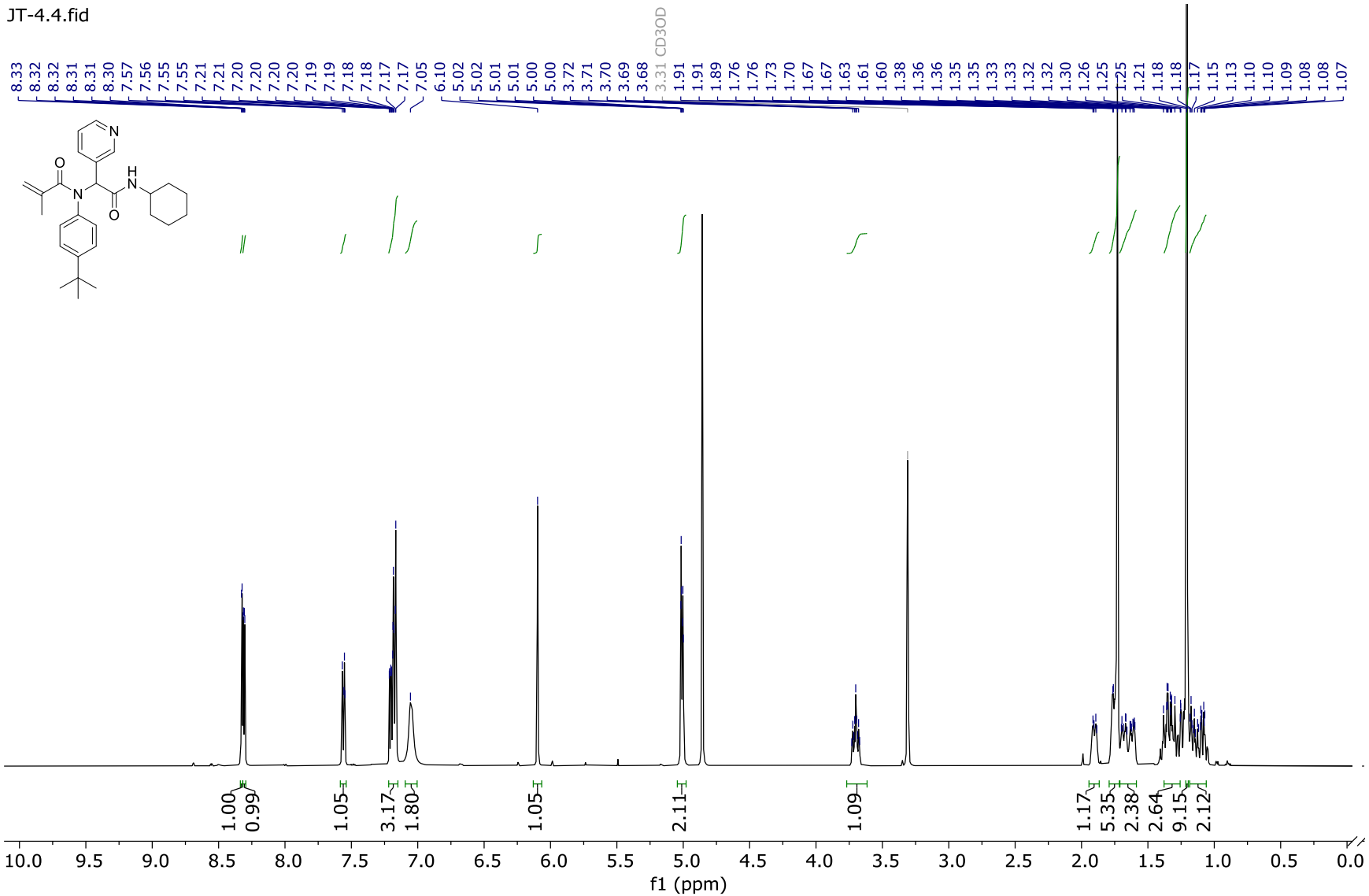
*23. Compound **9a** ^{1}H NMR*



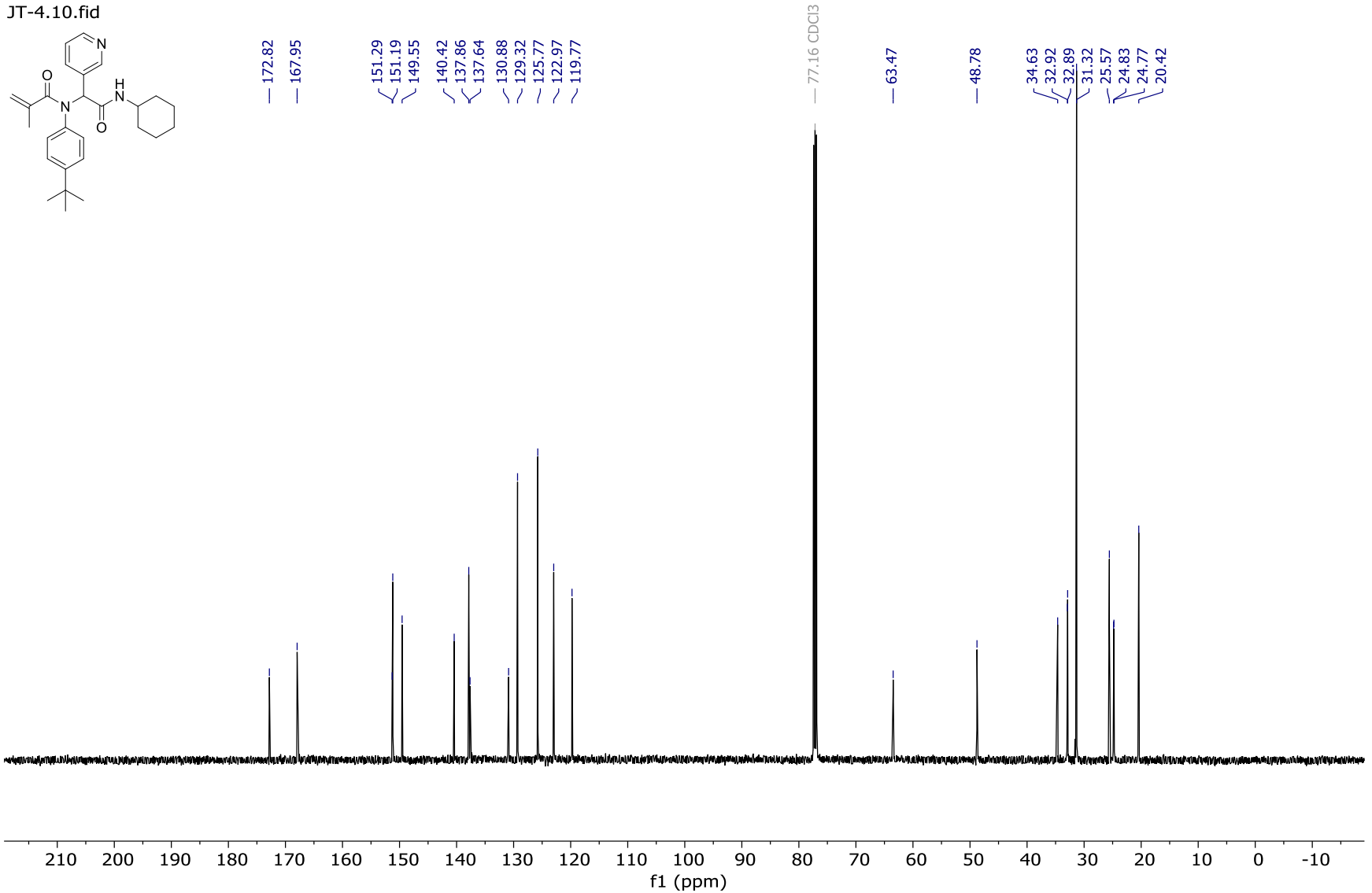
*24. Compound **9a** ^{13}C NMR*



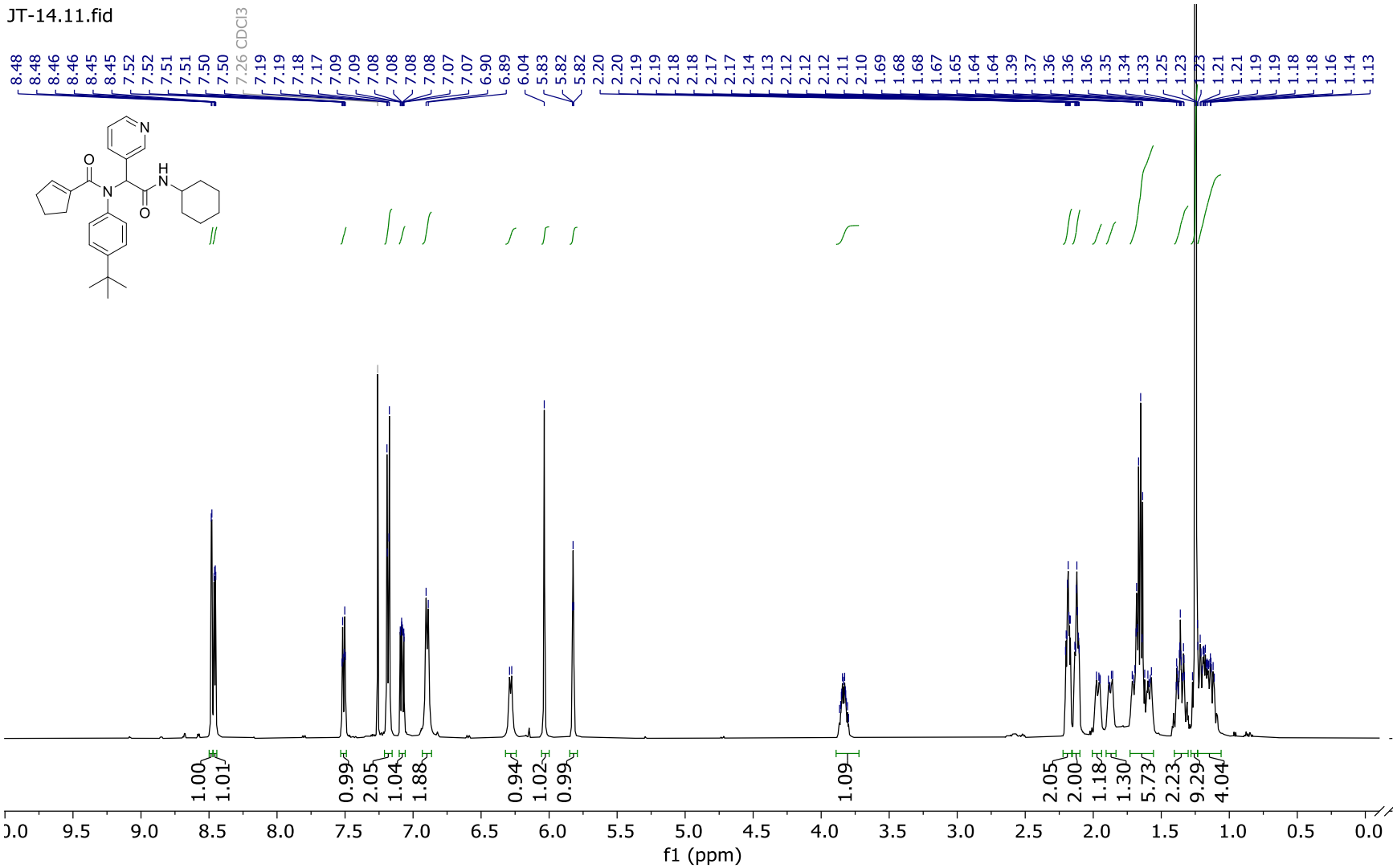
*25. Compound **10a** ^{1}H NMR*



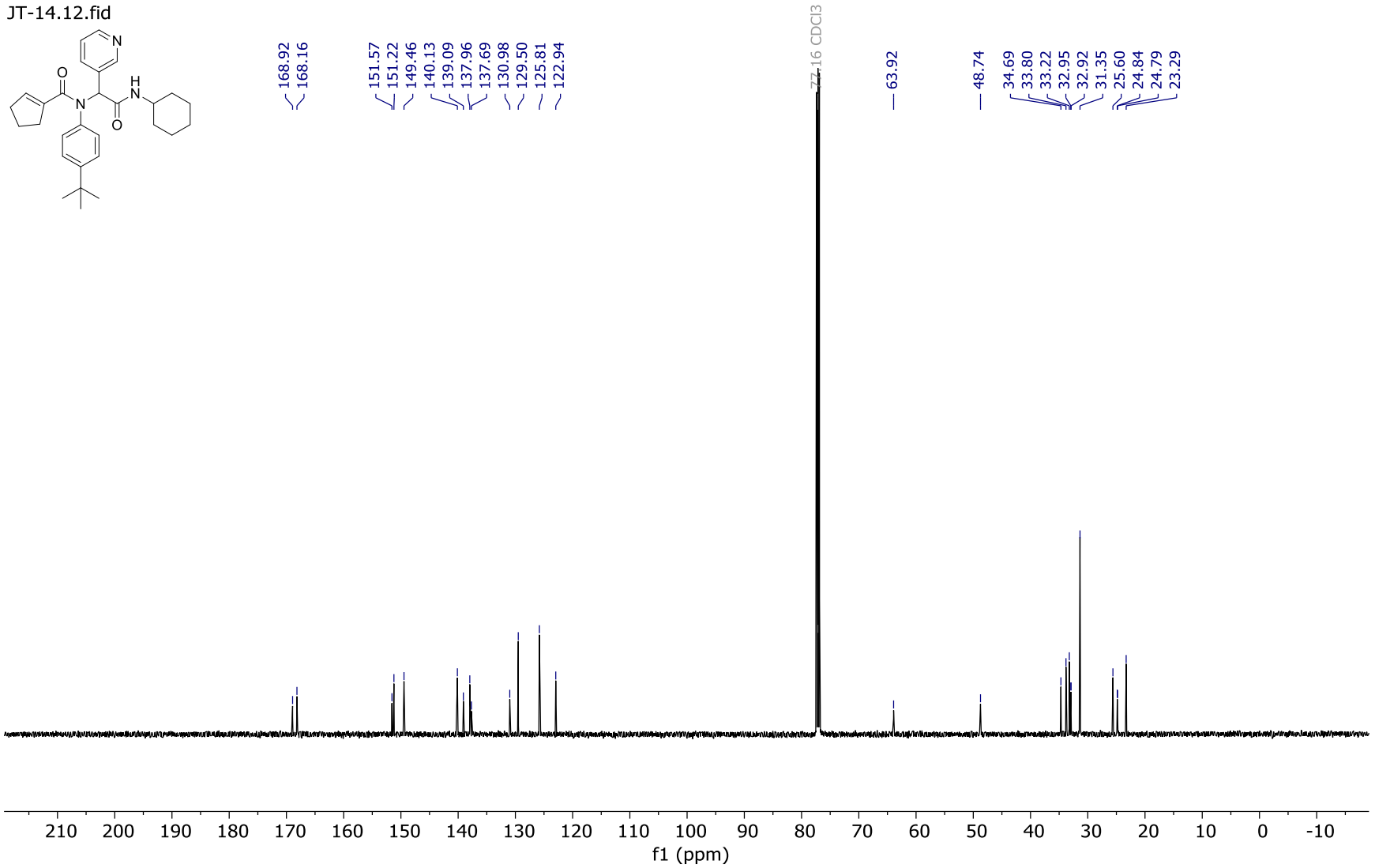
*26. Compound **10a** ^{13}C NMR*



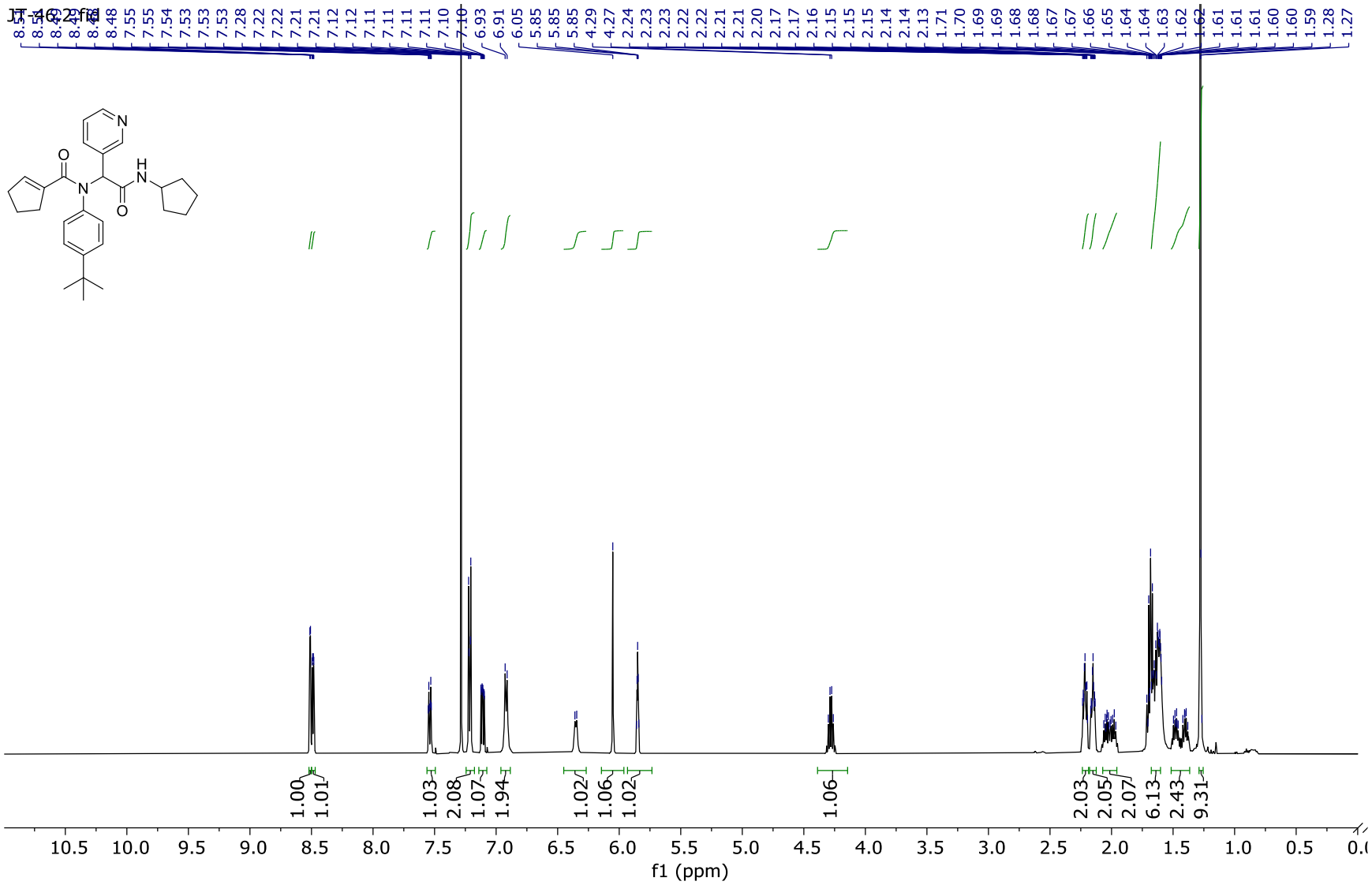
*27. Compound **11a** ^{1}H NMR*



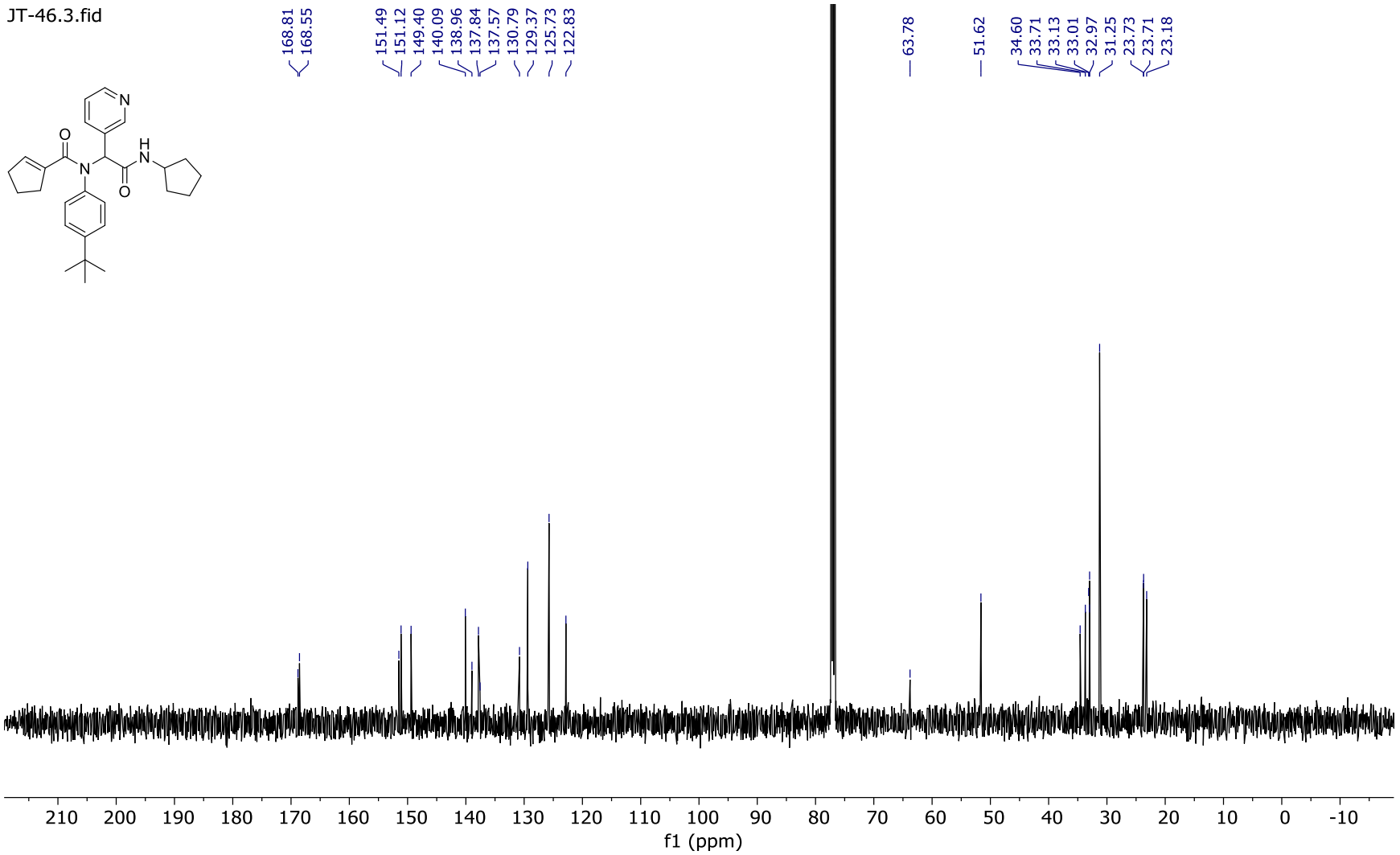
*28. Compound **11a** ^{13}C NMR*



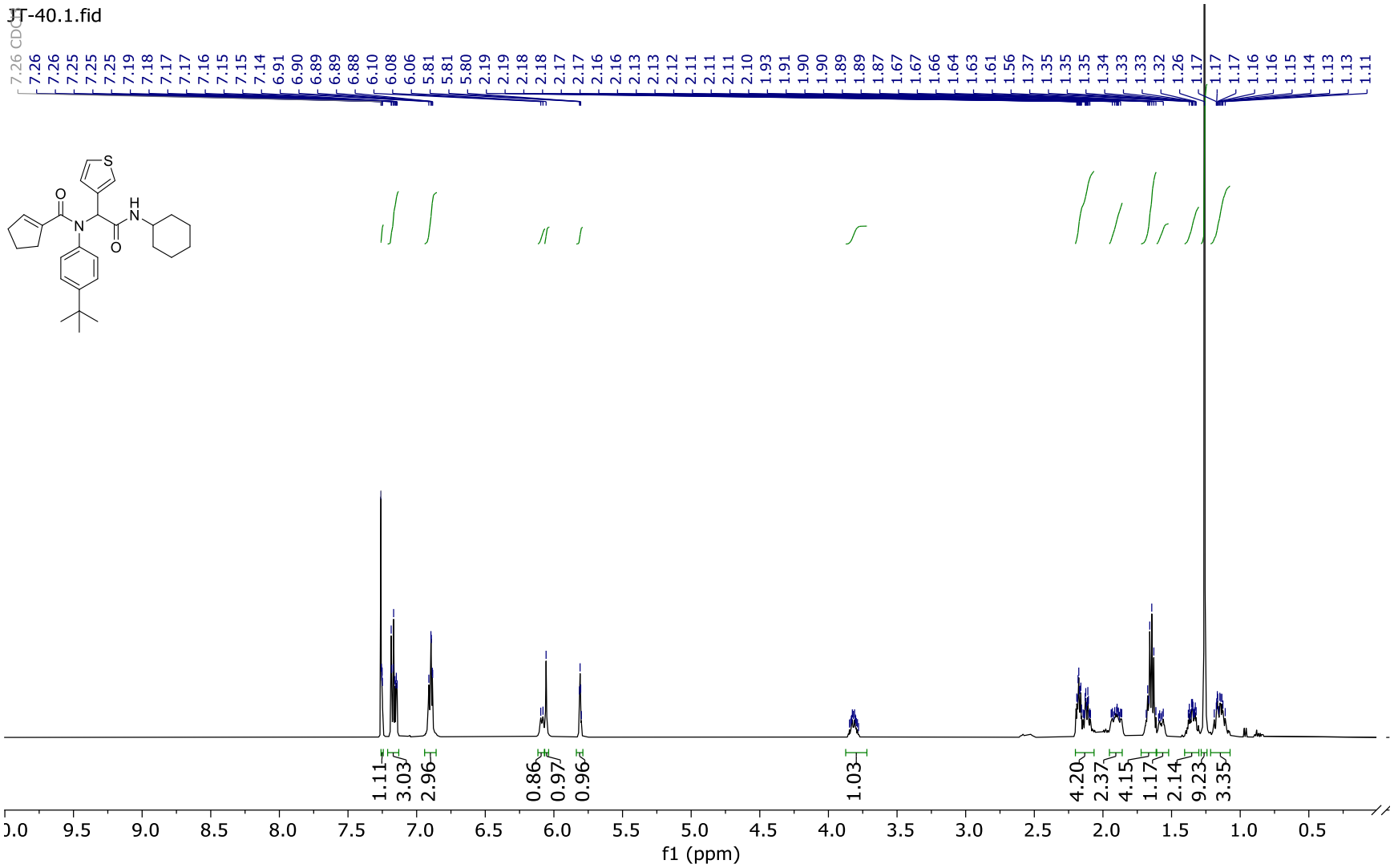
*29. Compound **11b** ^{1}H NMR*



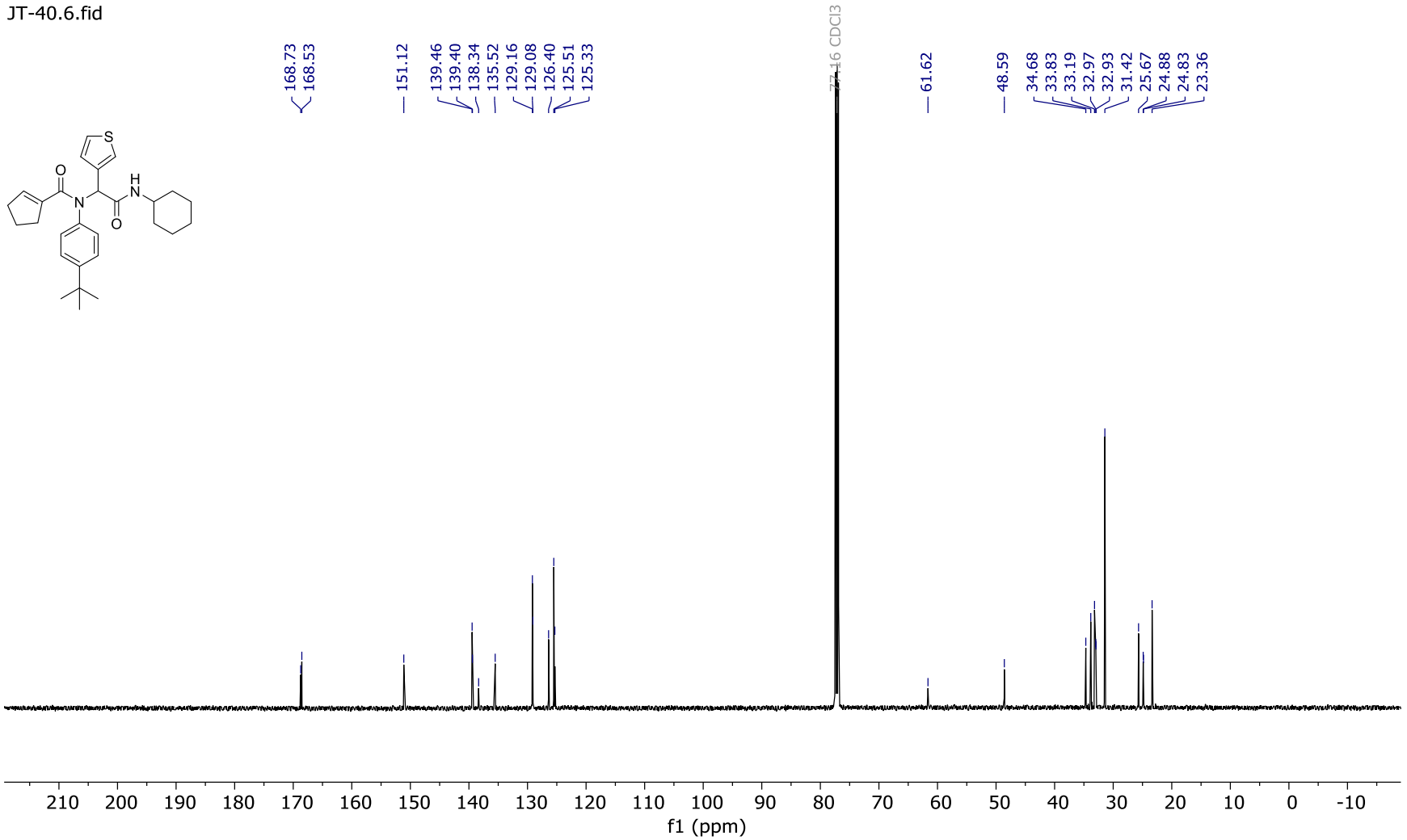
*30. Compound **11b** ^{13}C NMR*



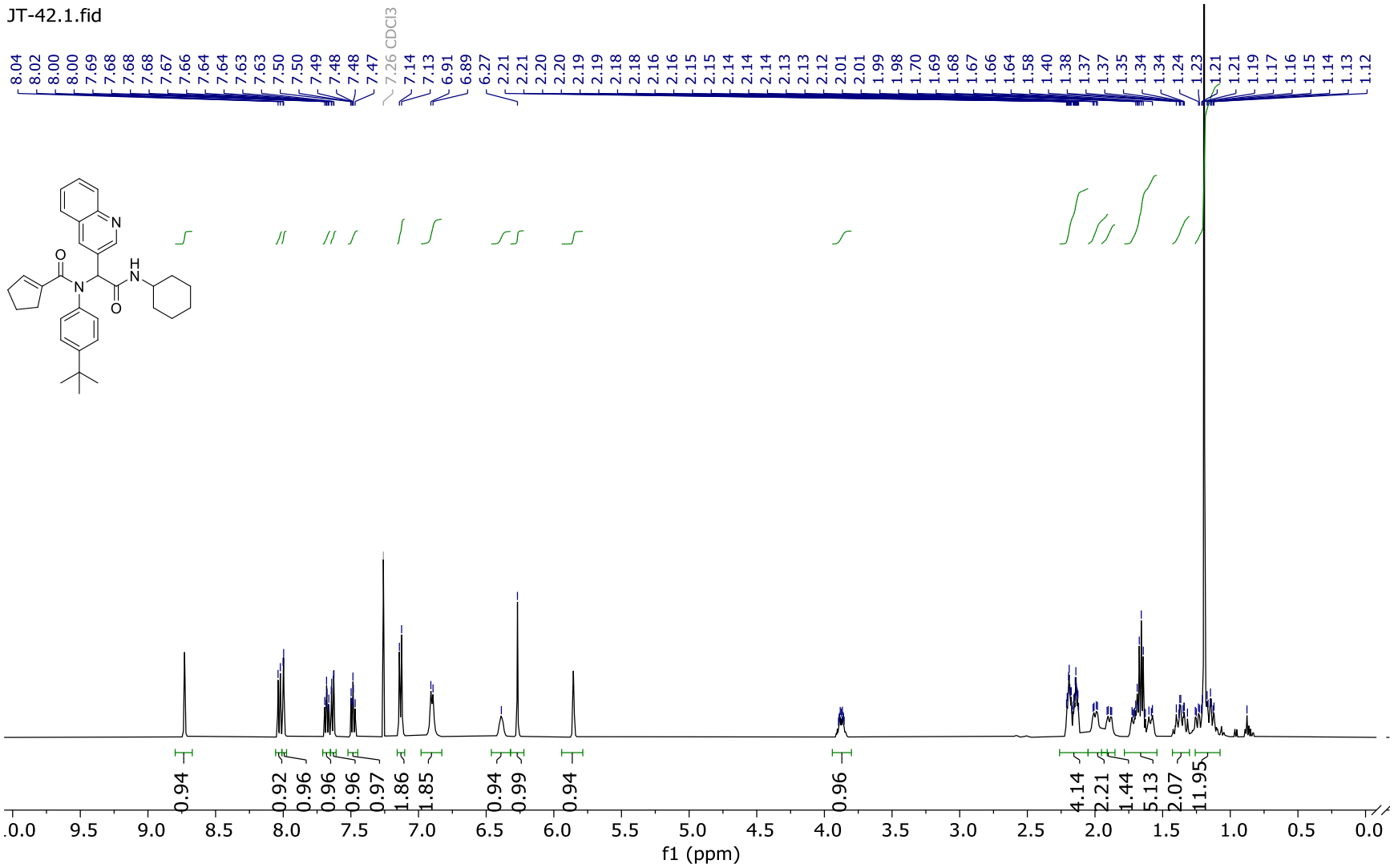
*31. Compound **11c** ^{1}H NMR*



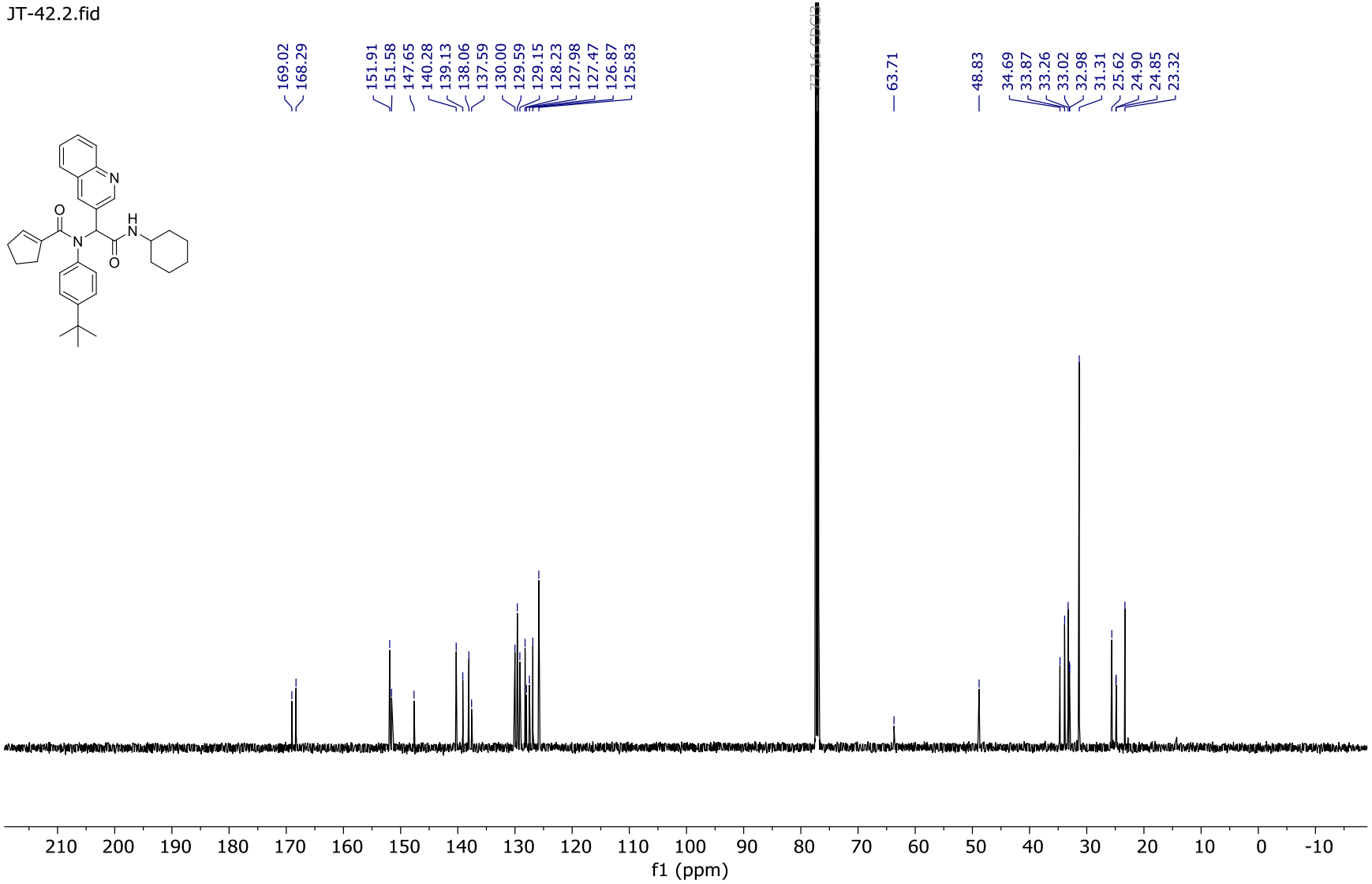
*32. Compound **11c** ^{13}C NMR*



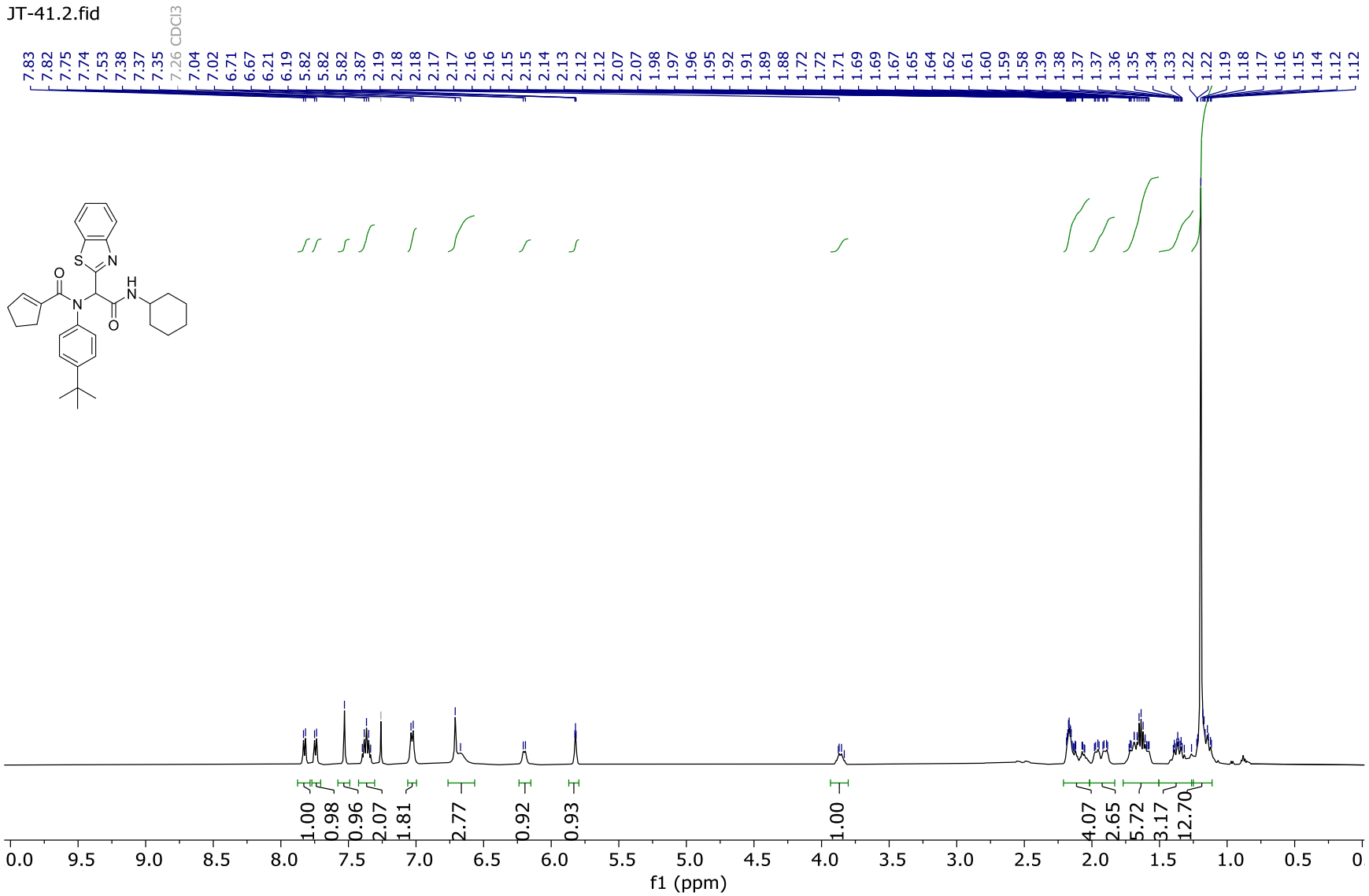
*33. Compound **11d** ^{1}H NMR*



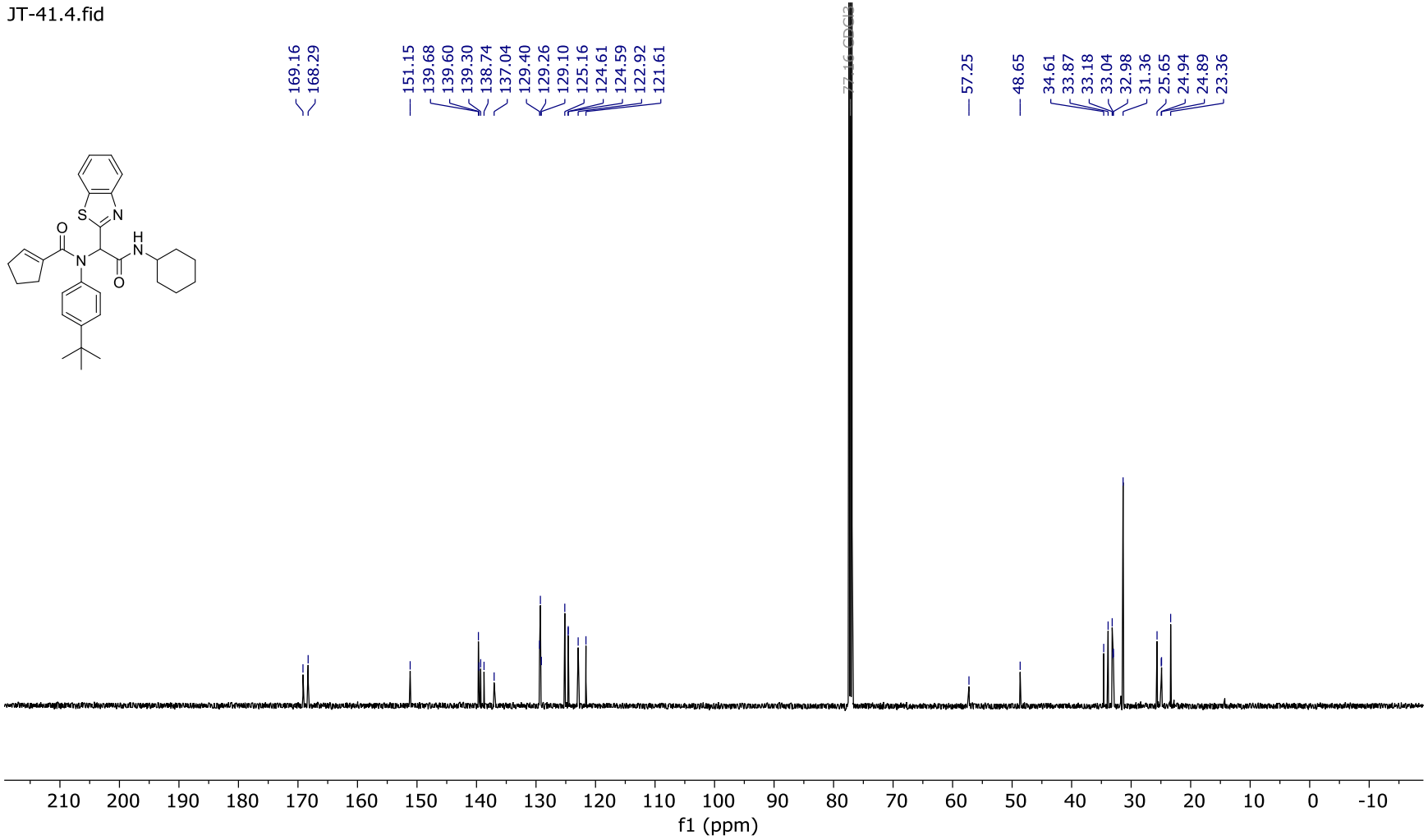
*34. Compound **11d** ^{13}C NMR*



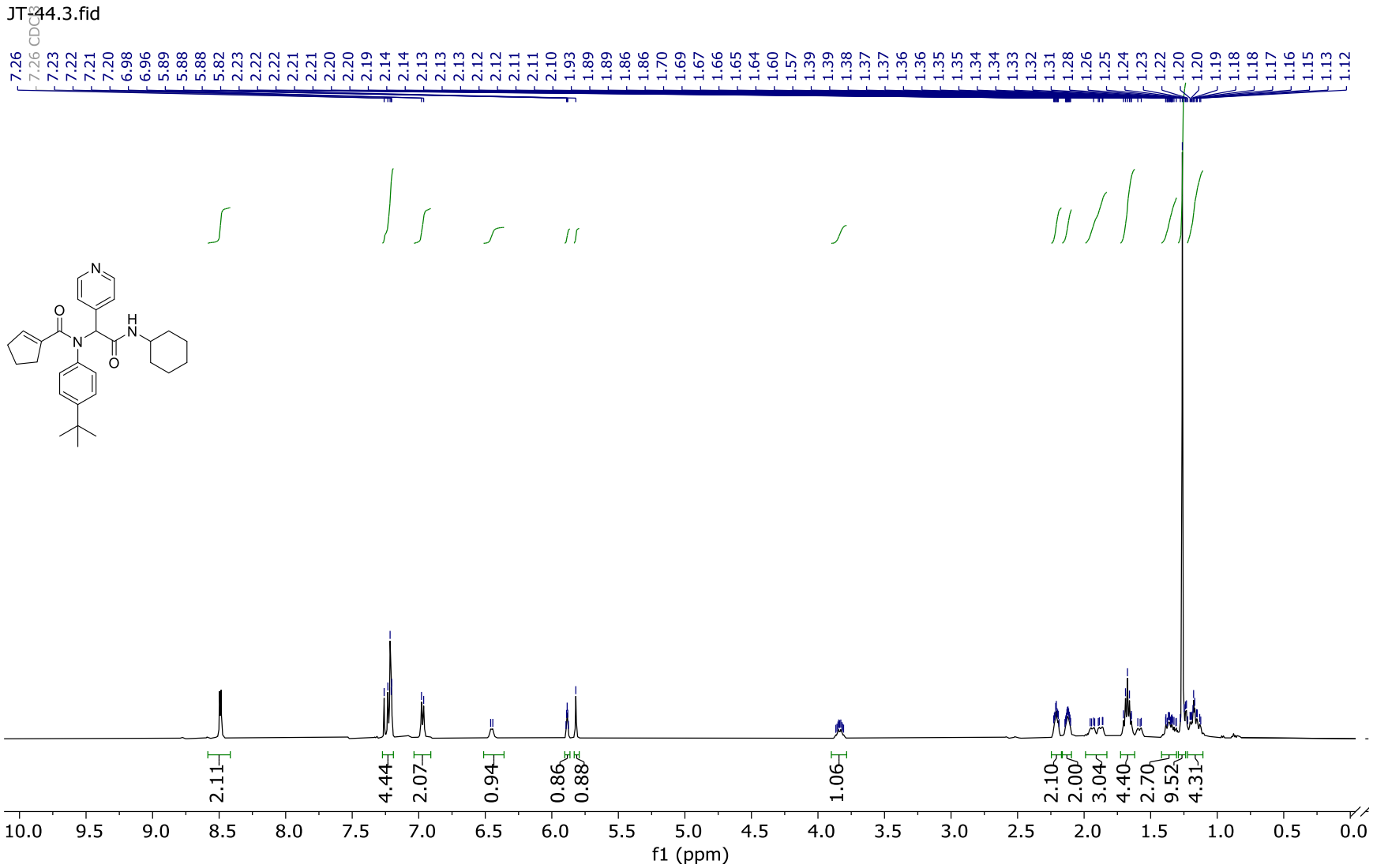
*35. Compound **11e** ^{1}H NMR*



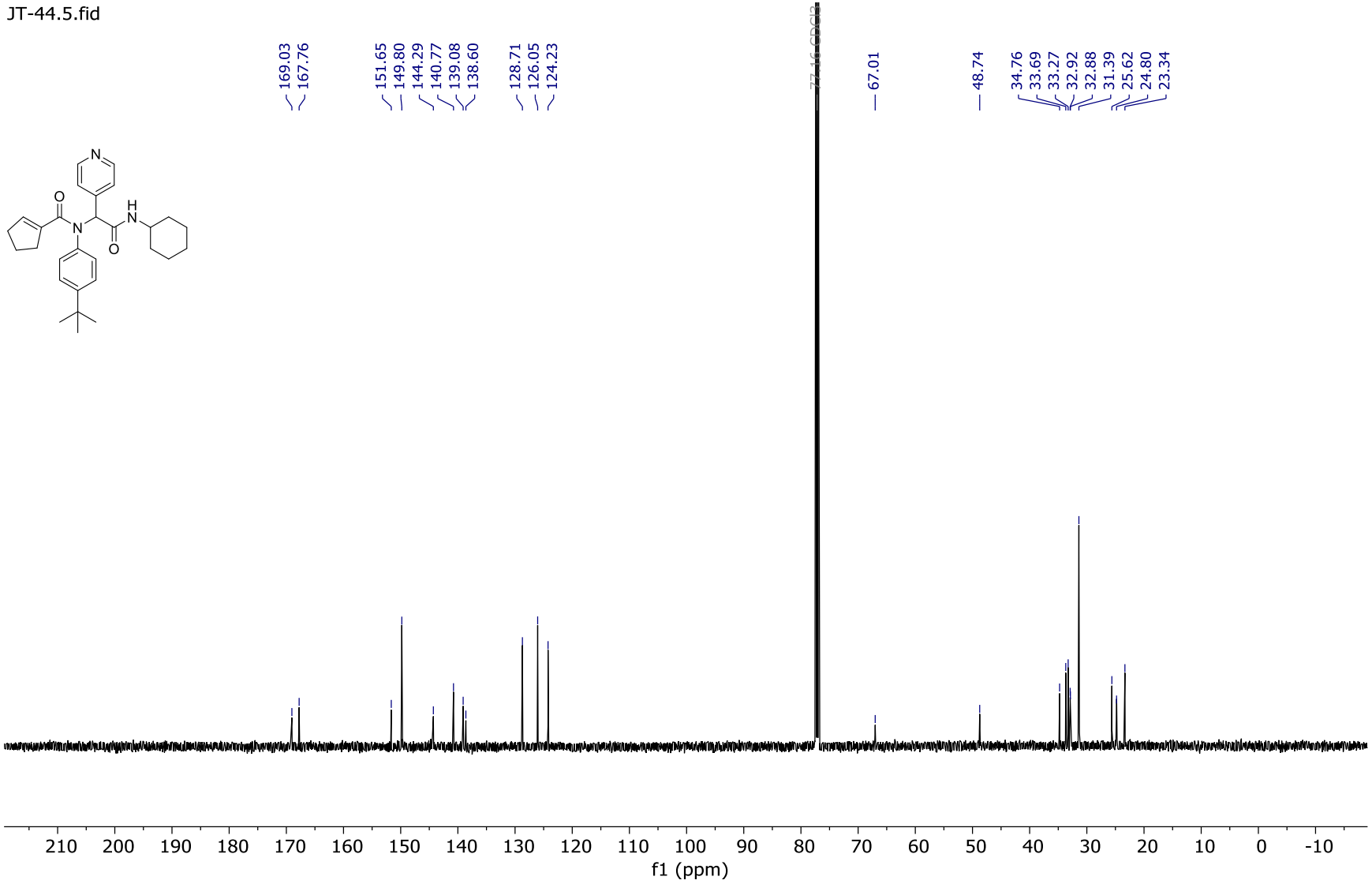
*36. Compound **11e** ^{13}C NMR*



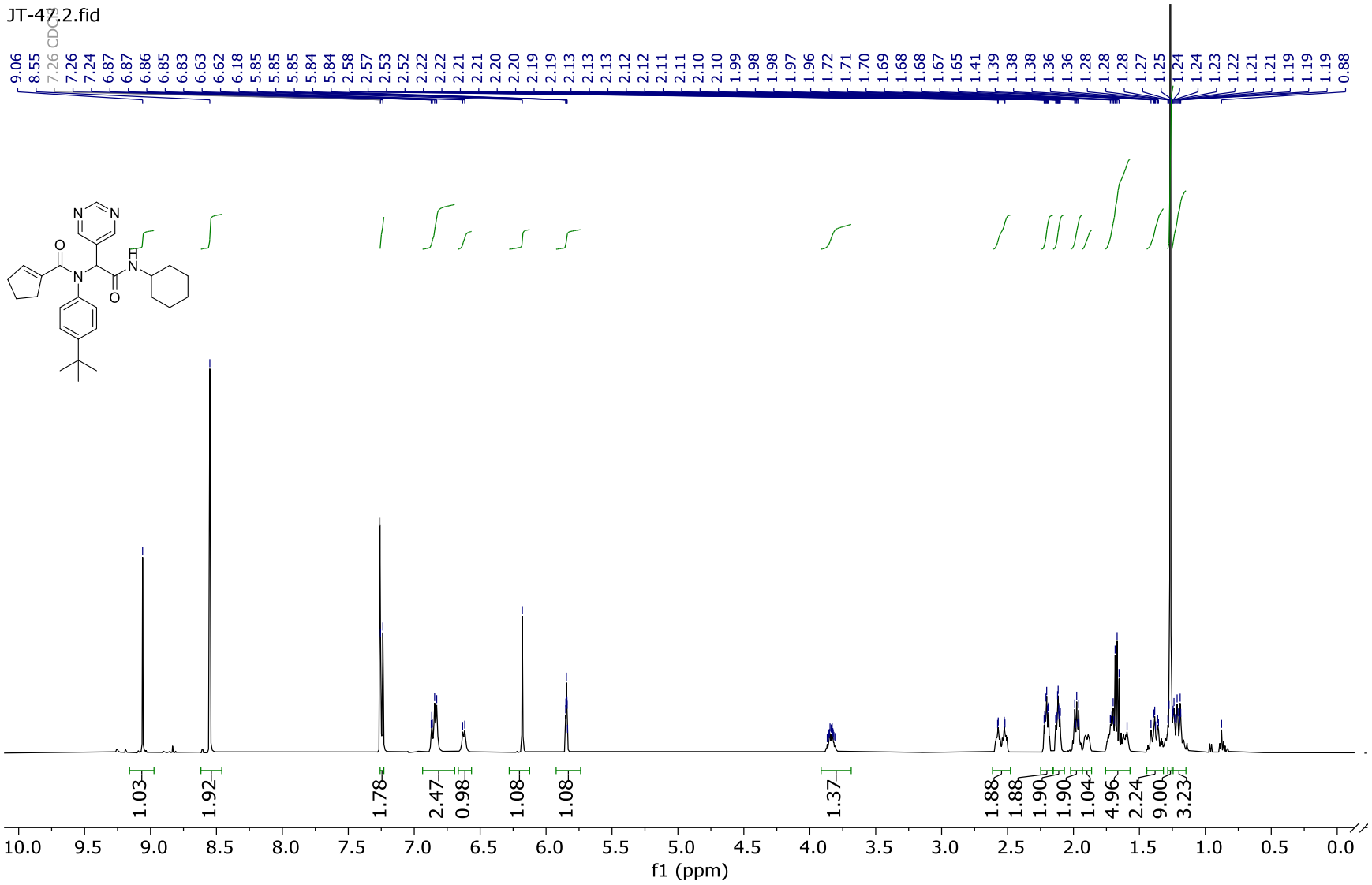
37. Compound ***11f*** *^{1}H NMR*



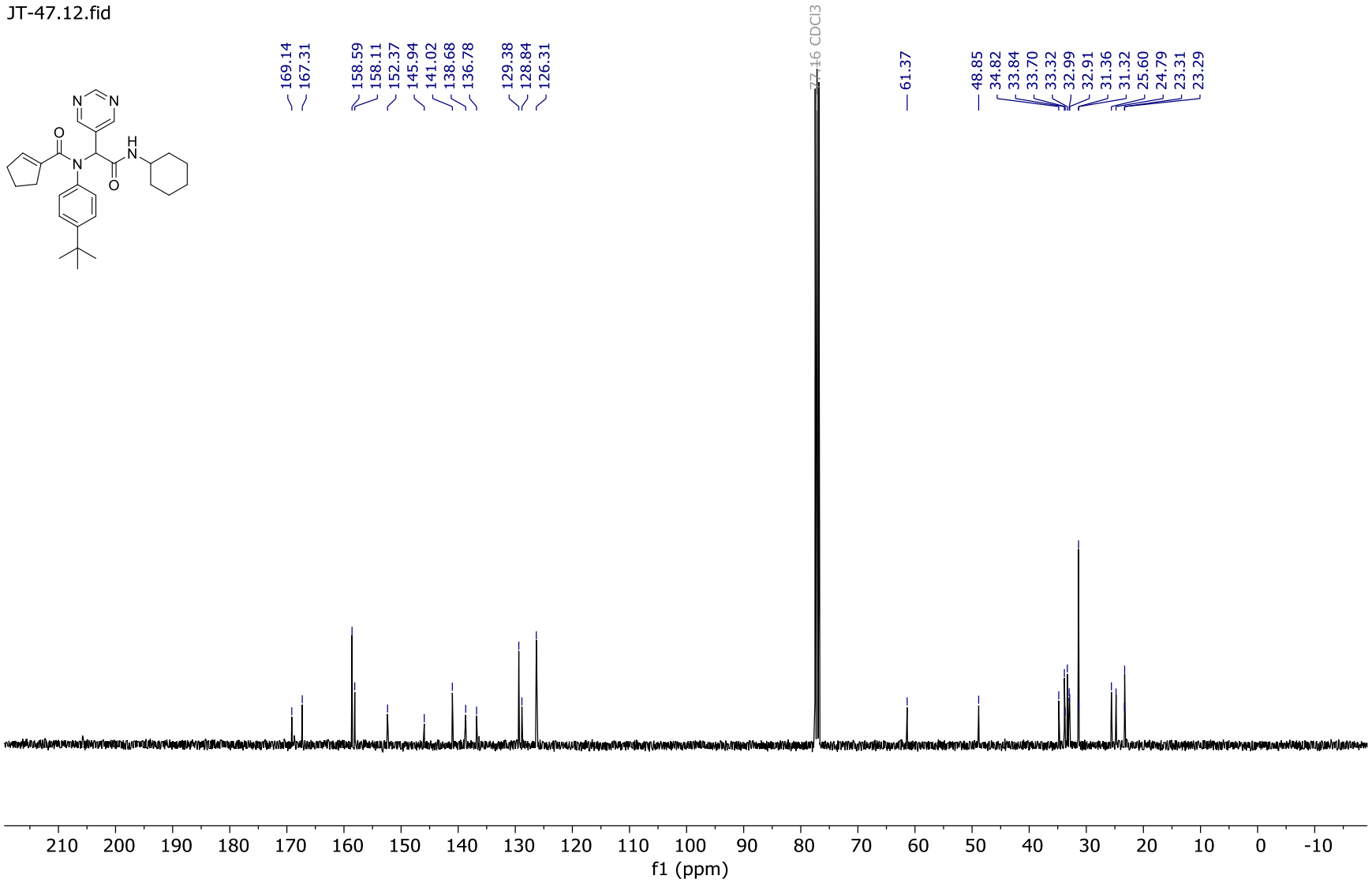
*38. Compound **11f** ^{13}C NMR*



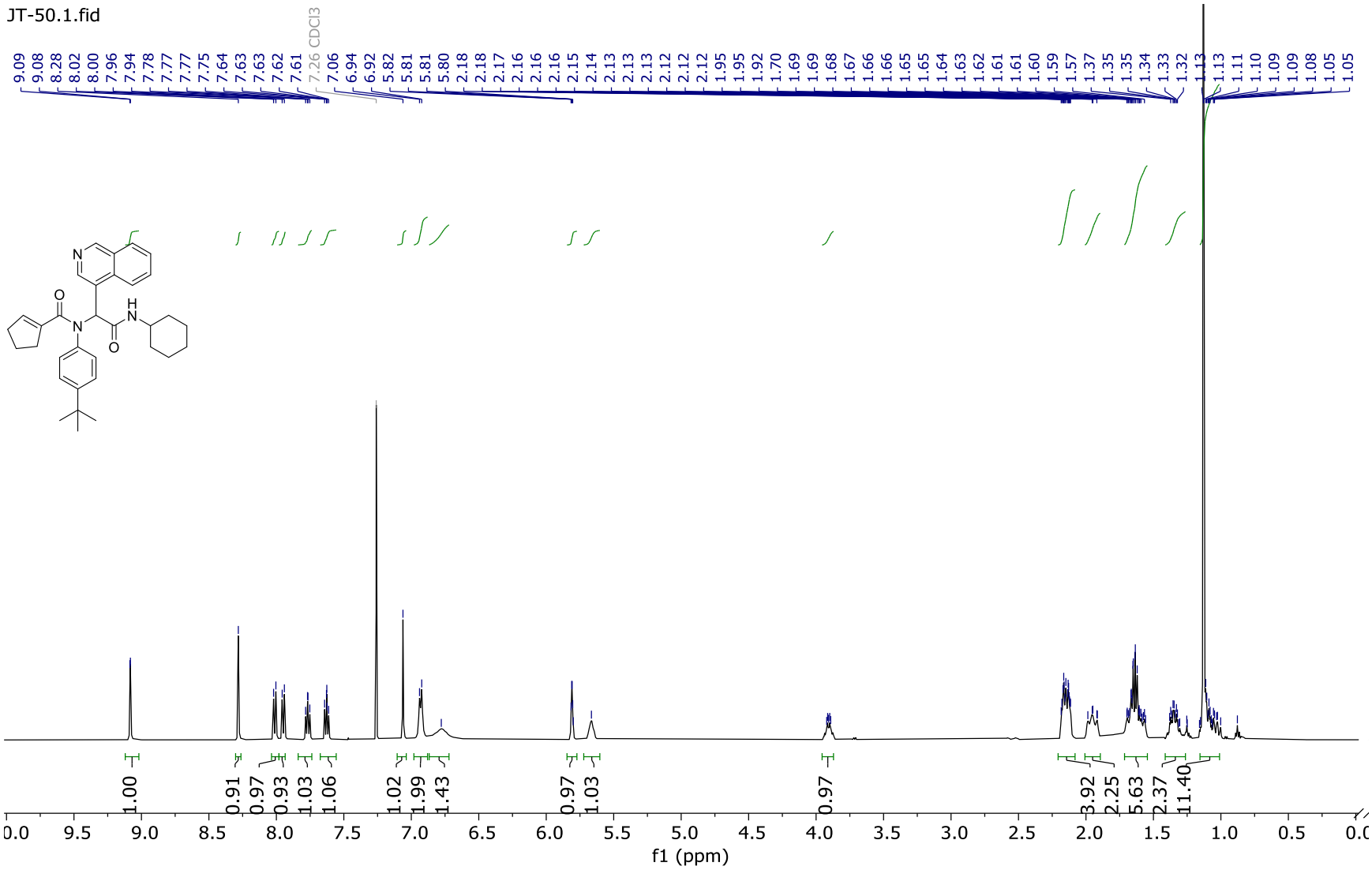
*39. Compound **11g** ^{1}H NMR*



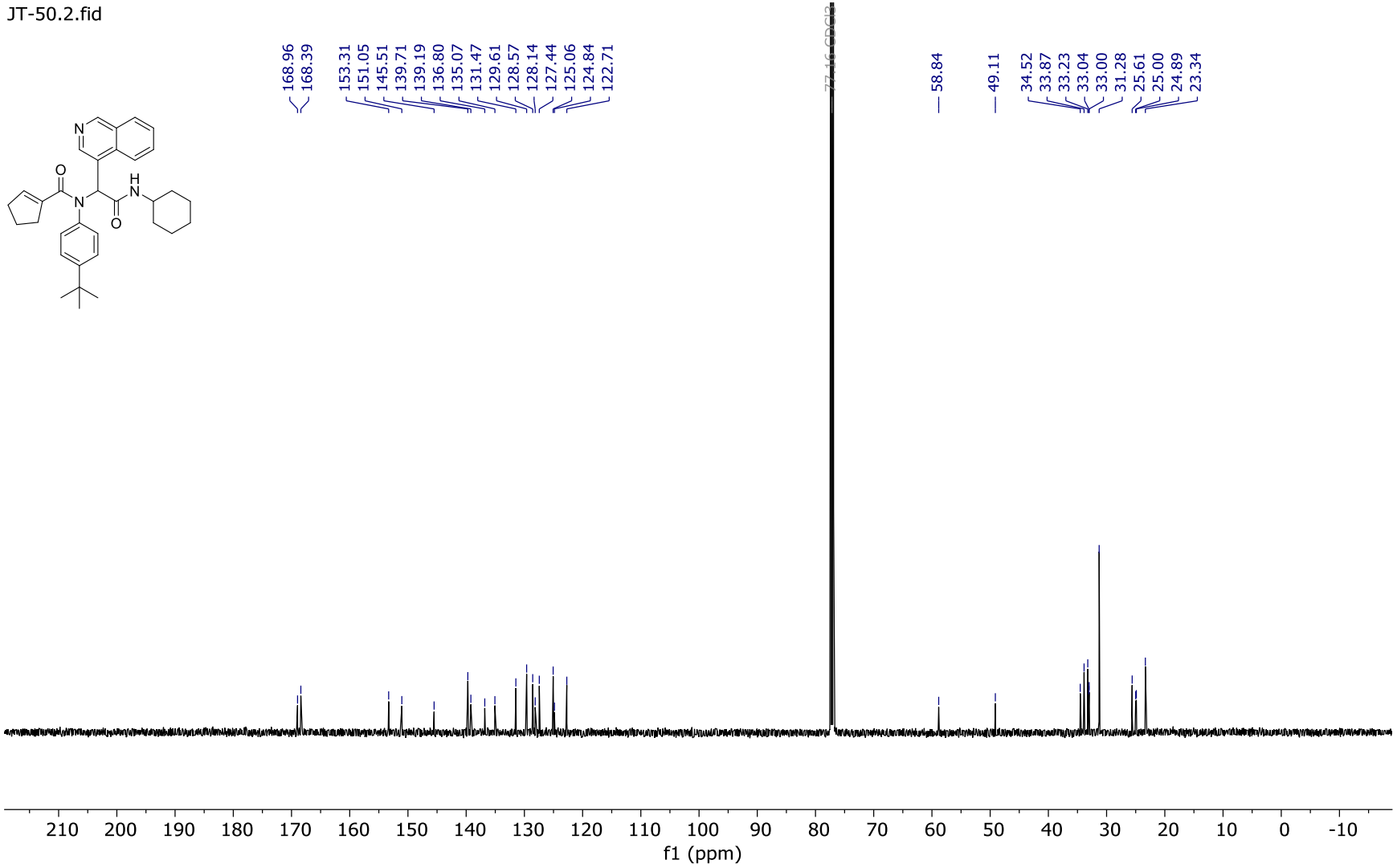
*40. Compound **11g** ^{13}C NMR*



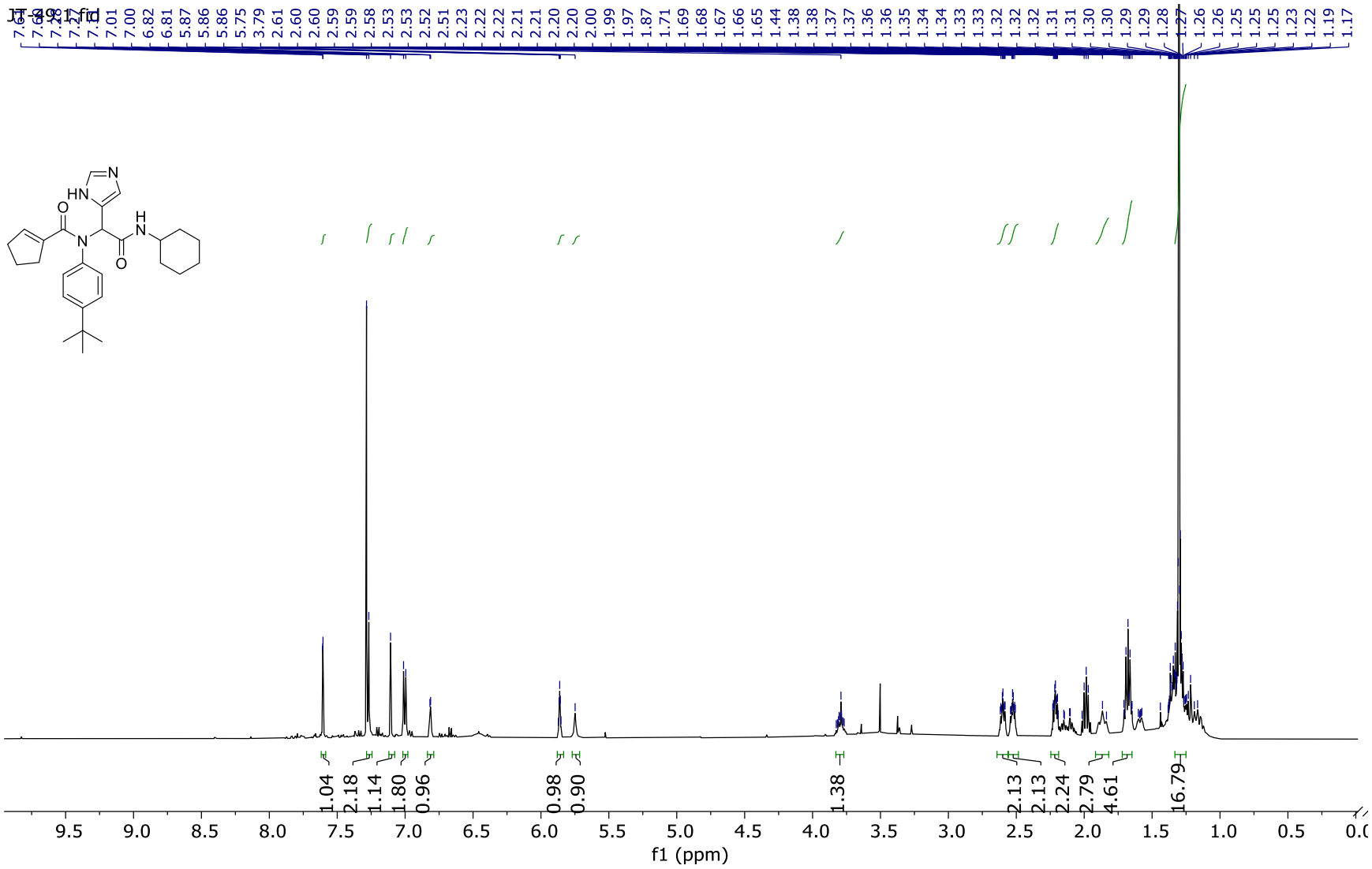
*41. Compound **11h** ^{1}H NMR*



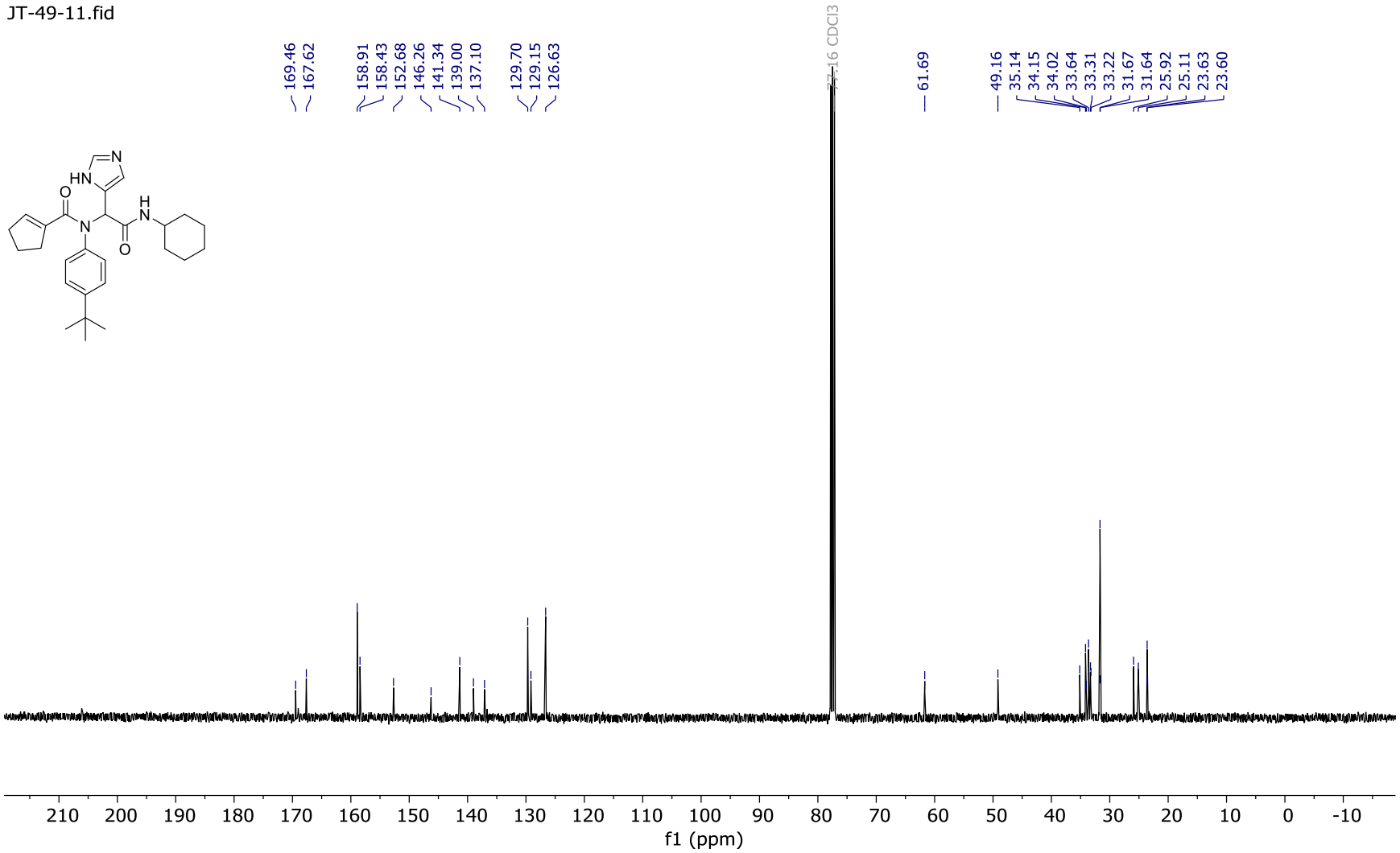
*42. Compound **11h** ^{13}C NMR*



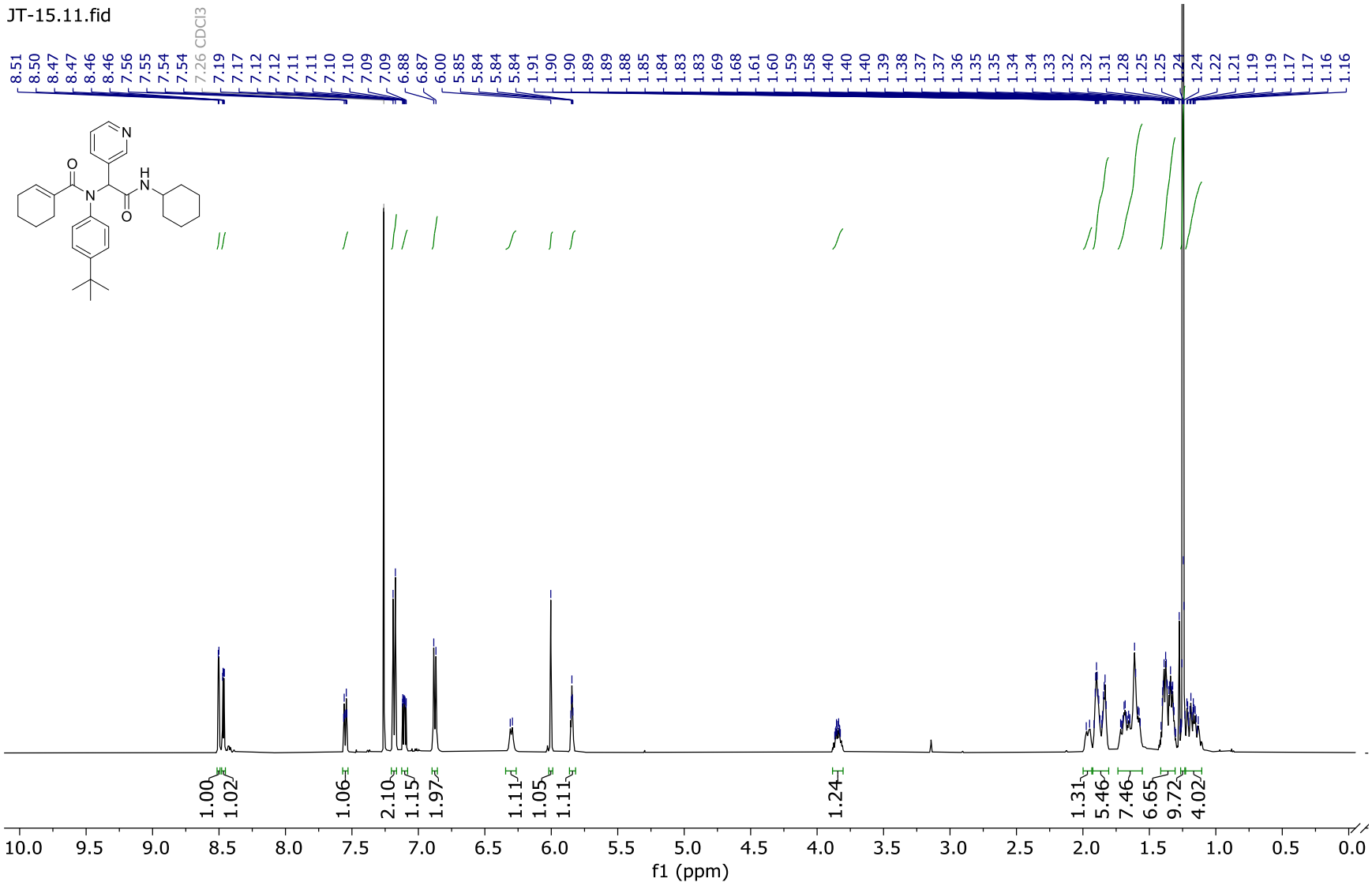
*43. Compound **11i** ^{1}H NMR*



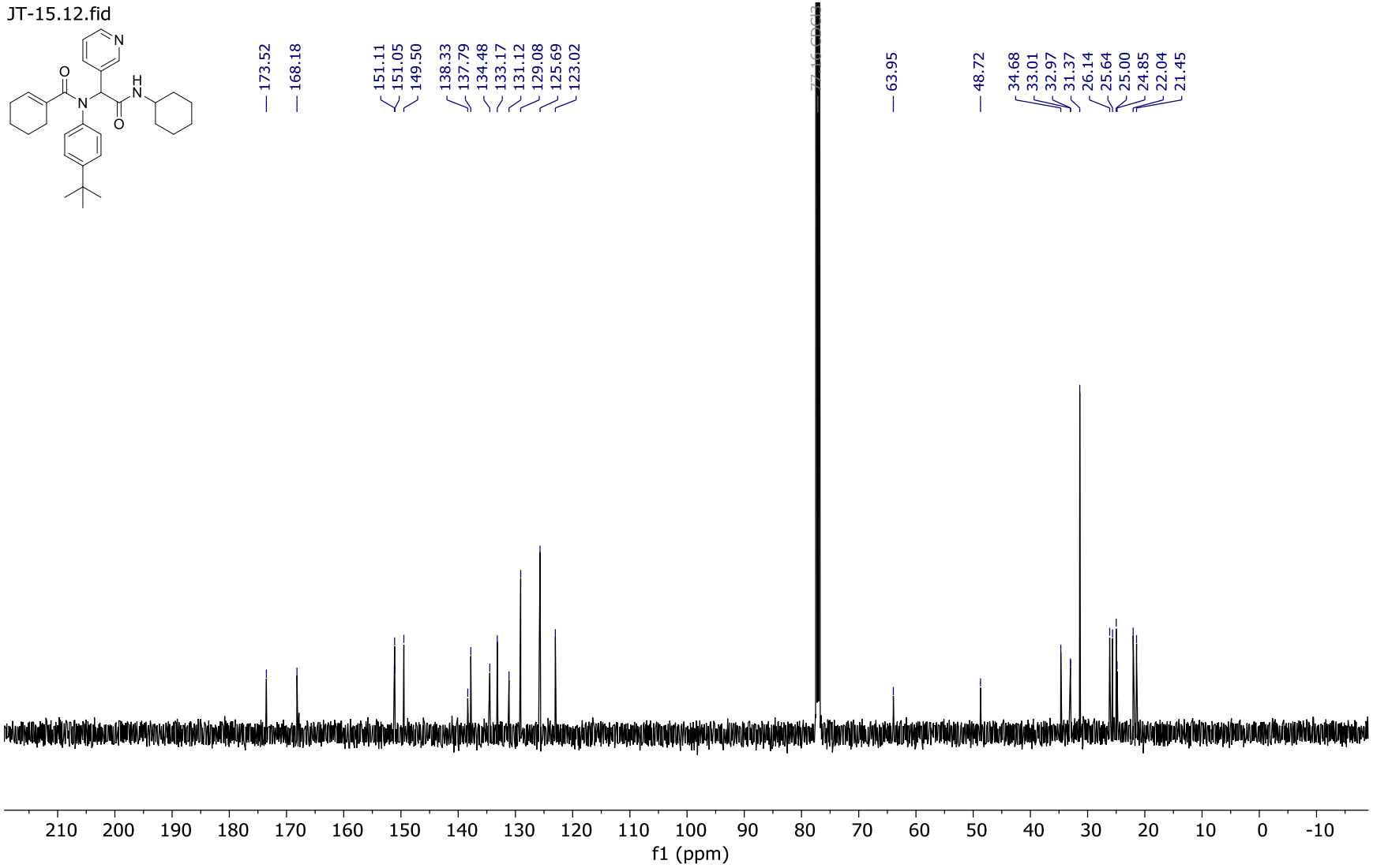
*44. Compound **11i** ^{13}C NMR*



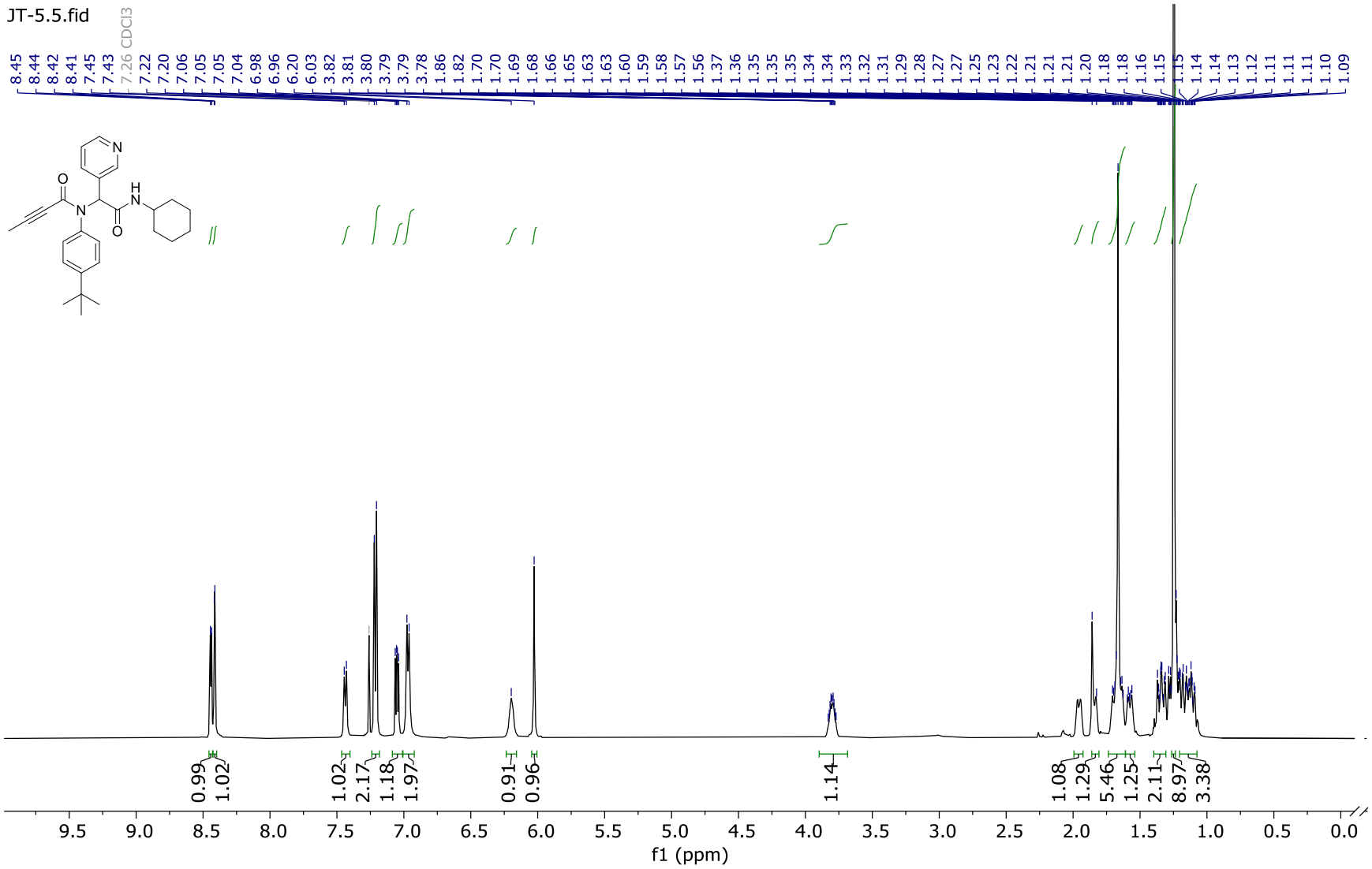
45. Compound ***12a*** *^{1}H NMR*



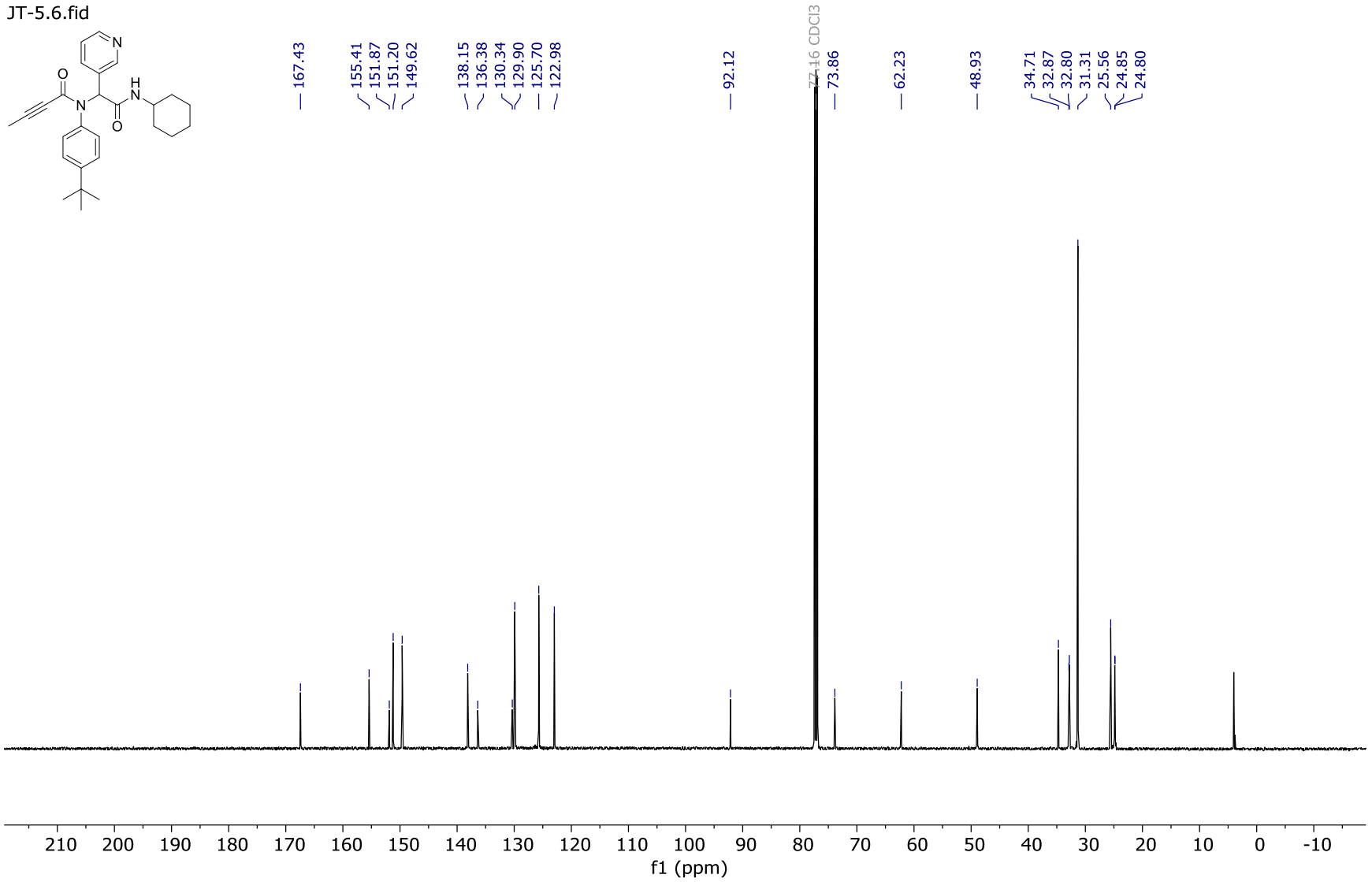
*46. Compound **12a** ^{13}C NMR*



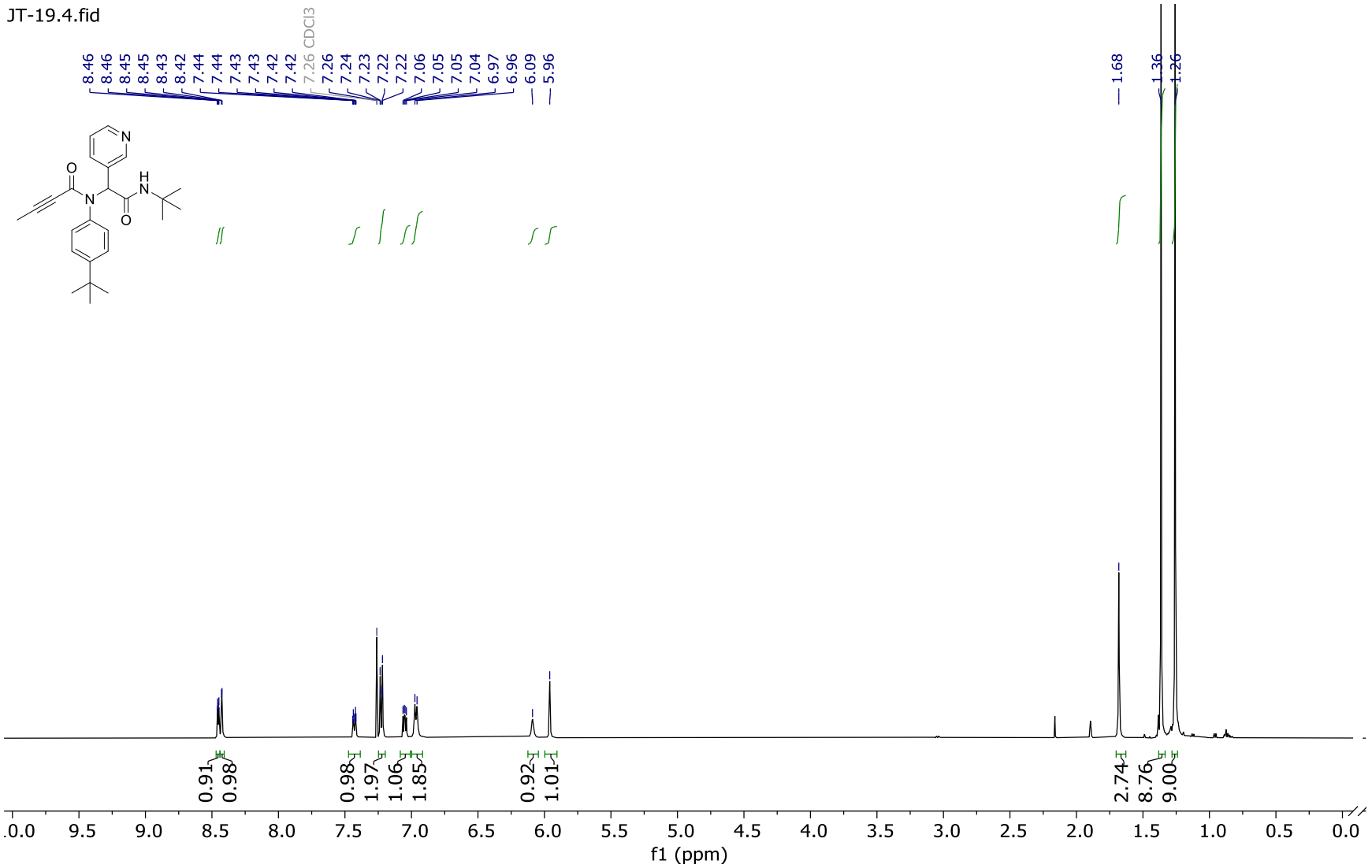
*47. Compound **13a** ^{1}H NMR*



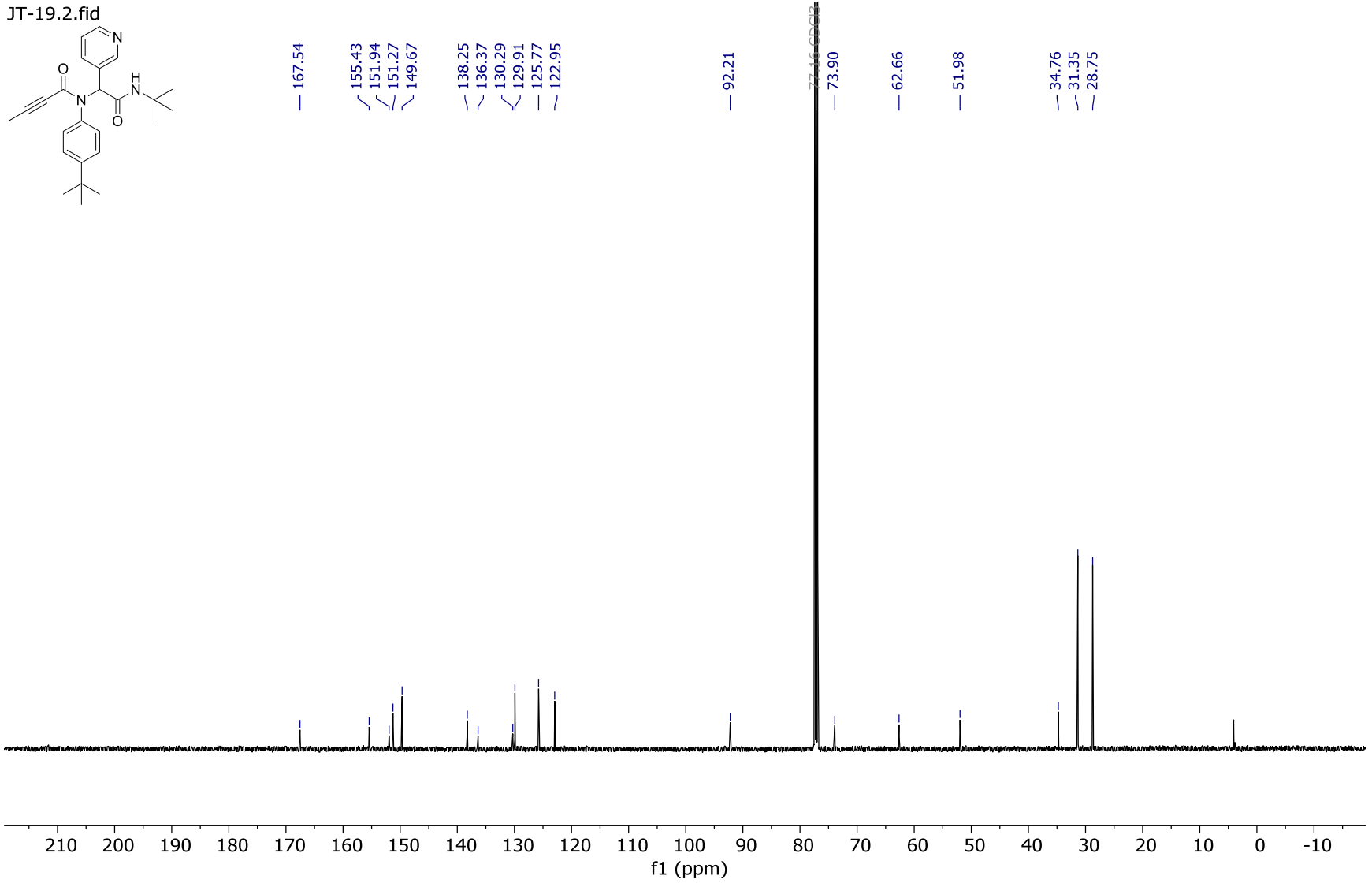
*48. Compound **13a** ^{13}C NMR*



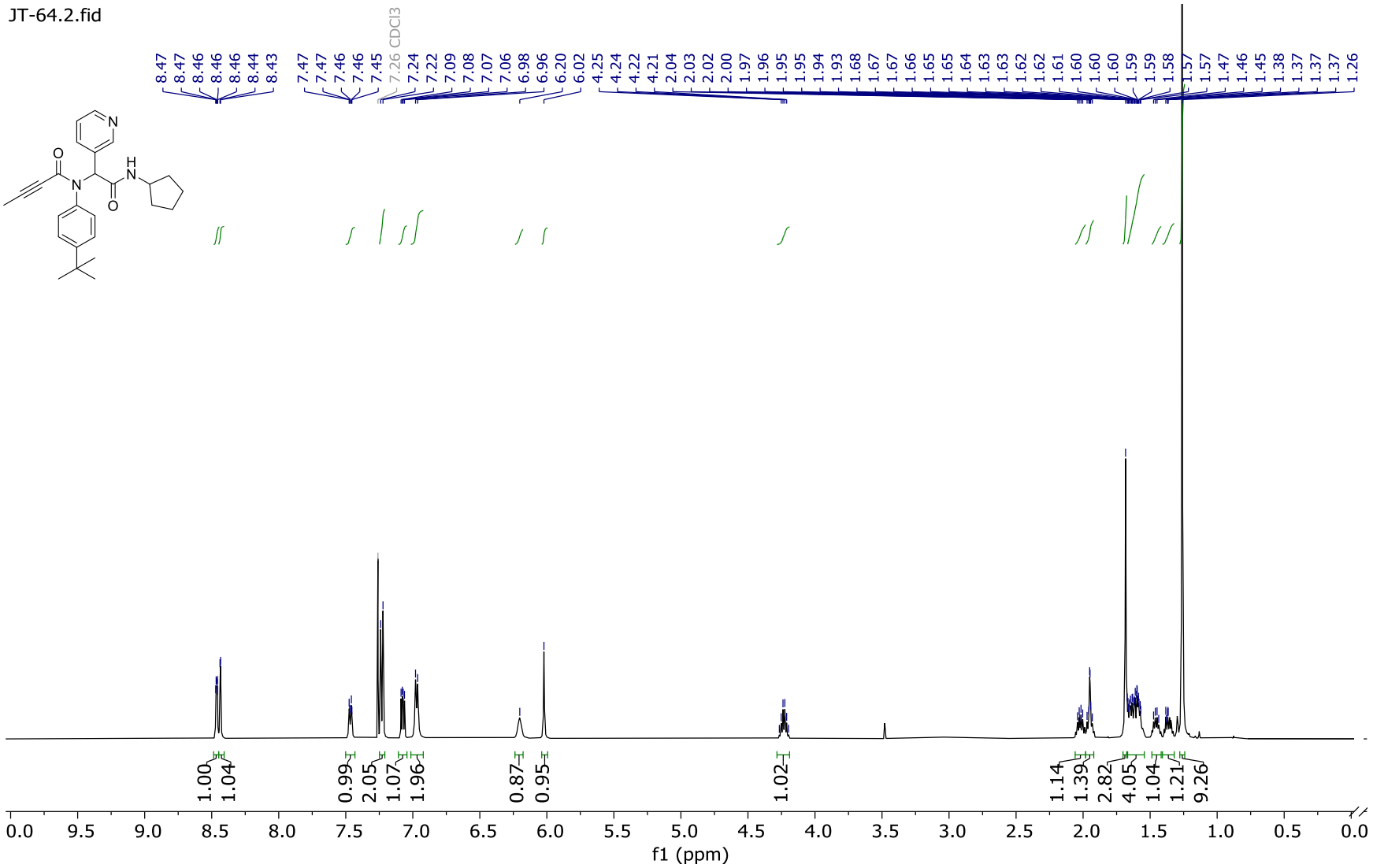
*49. Compound **13b** ^{1}H NMR*



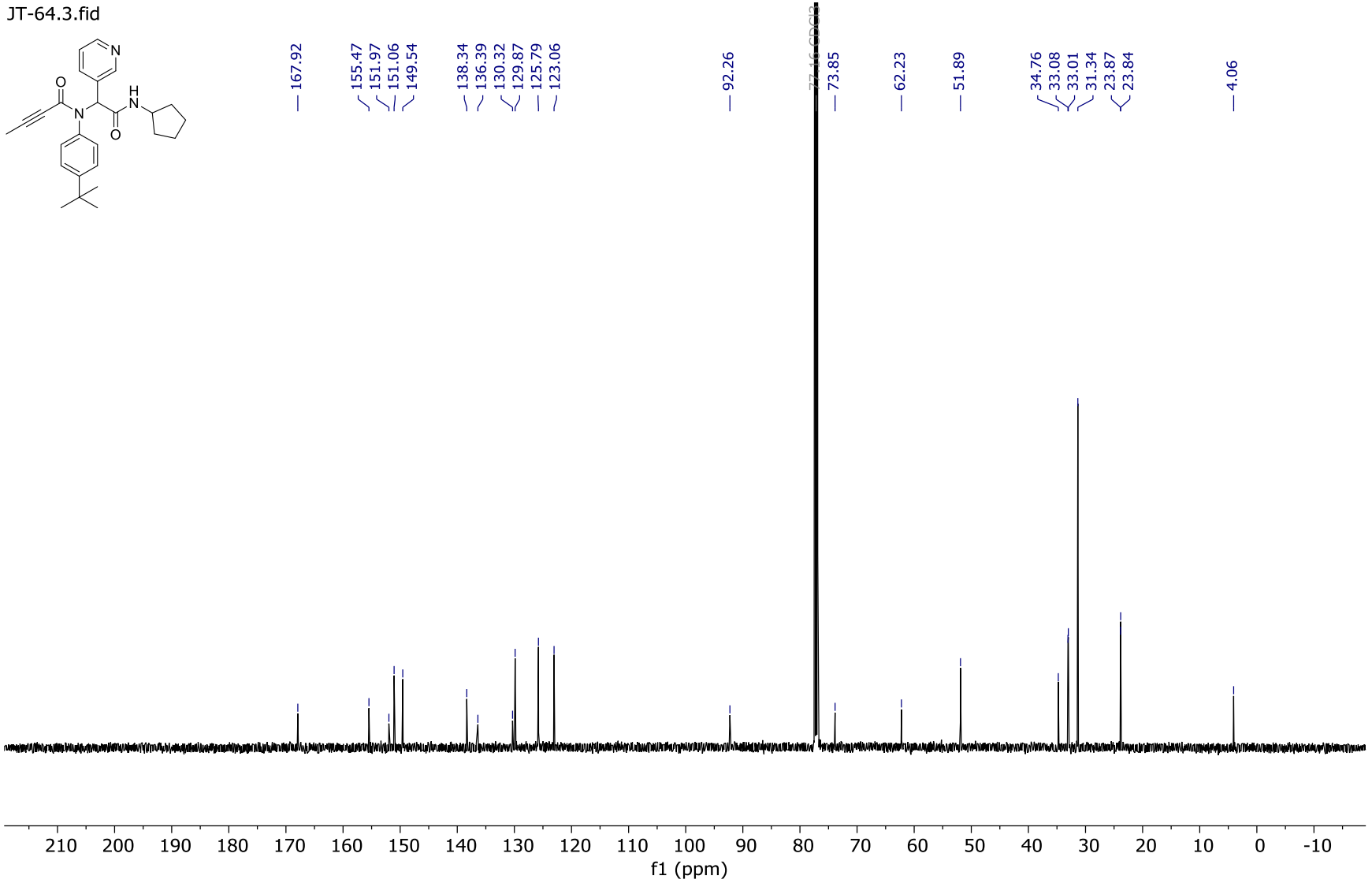
*50. Compound **13b** ^{13}C NMR*



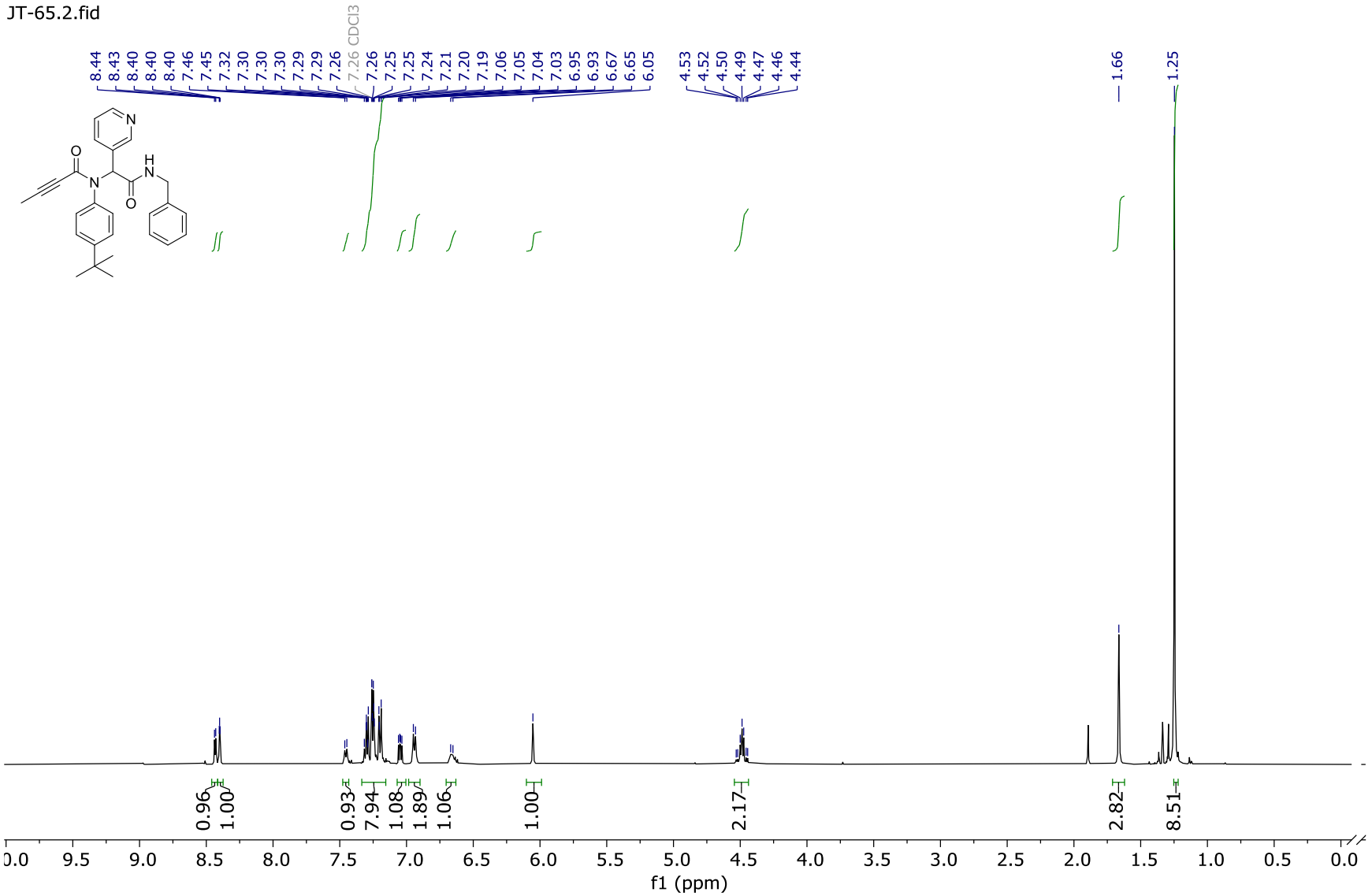
51. Compound ***13c*** *^{1}H NMR*



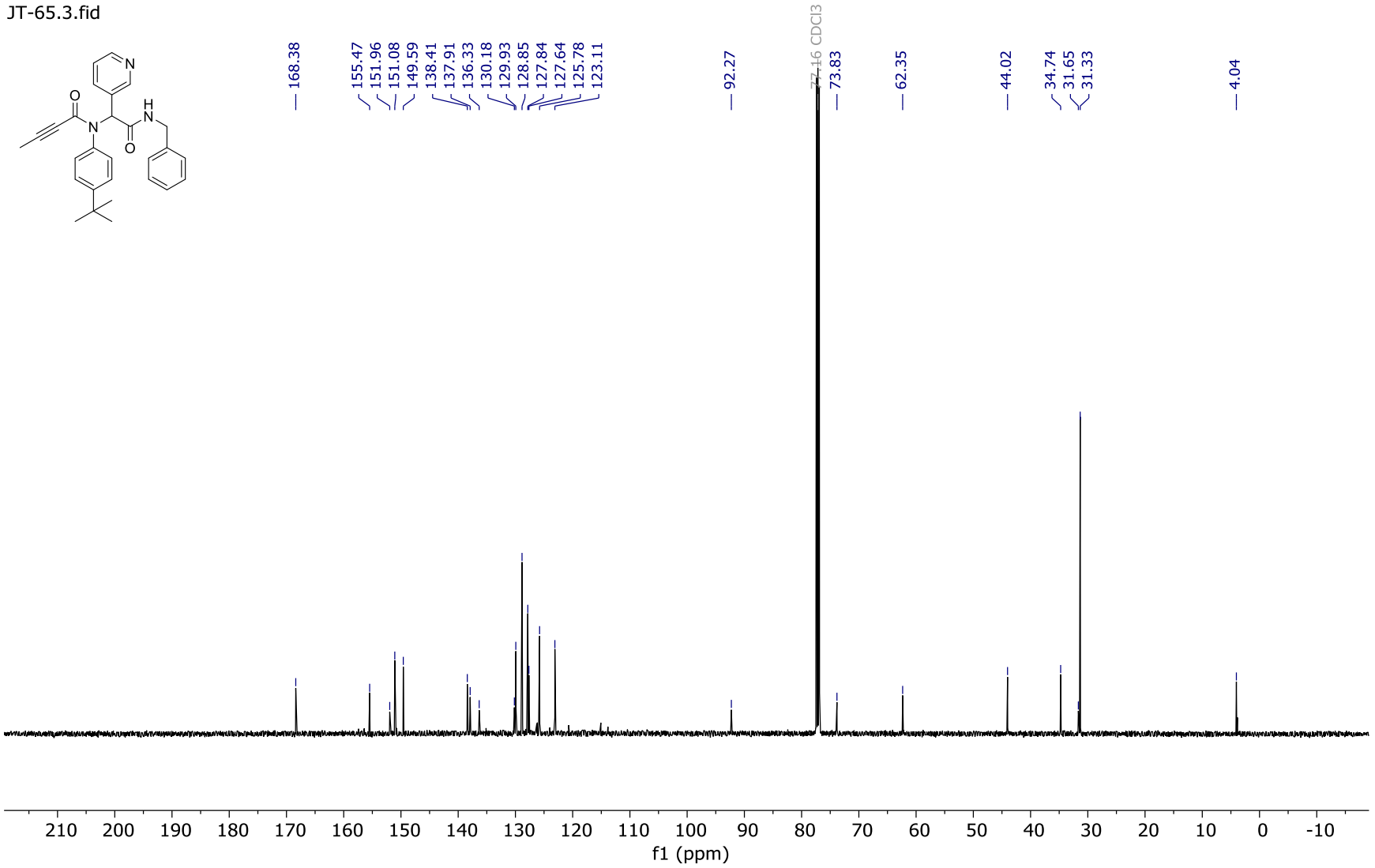
*52. Compound **13c** ^{13}C NMR*



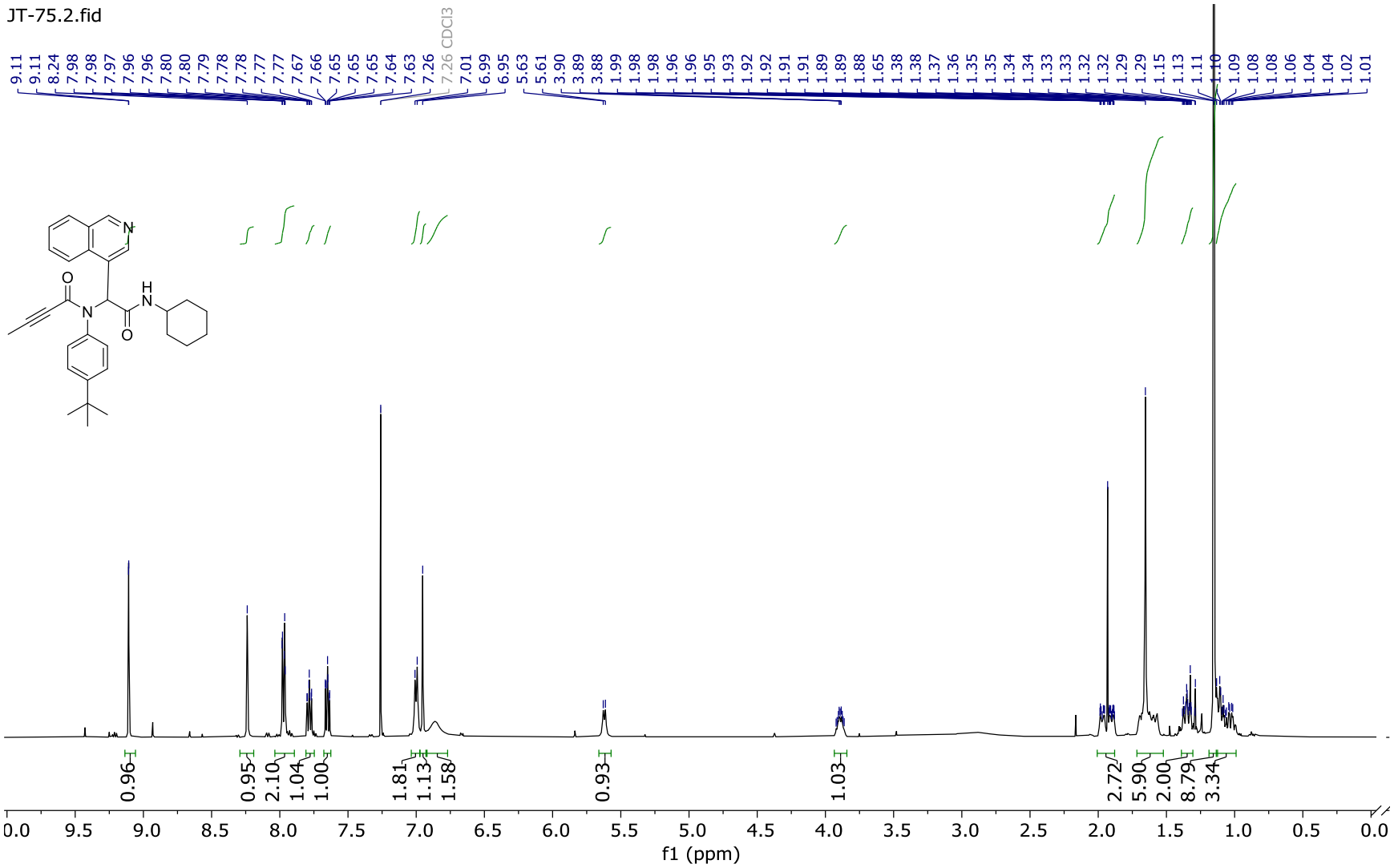
*53. Compound **13d** ^{1}H NMR*



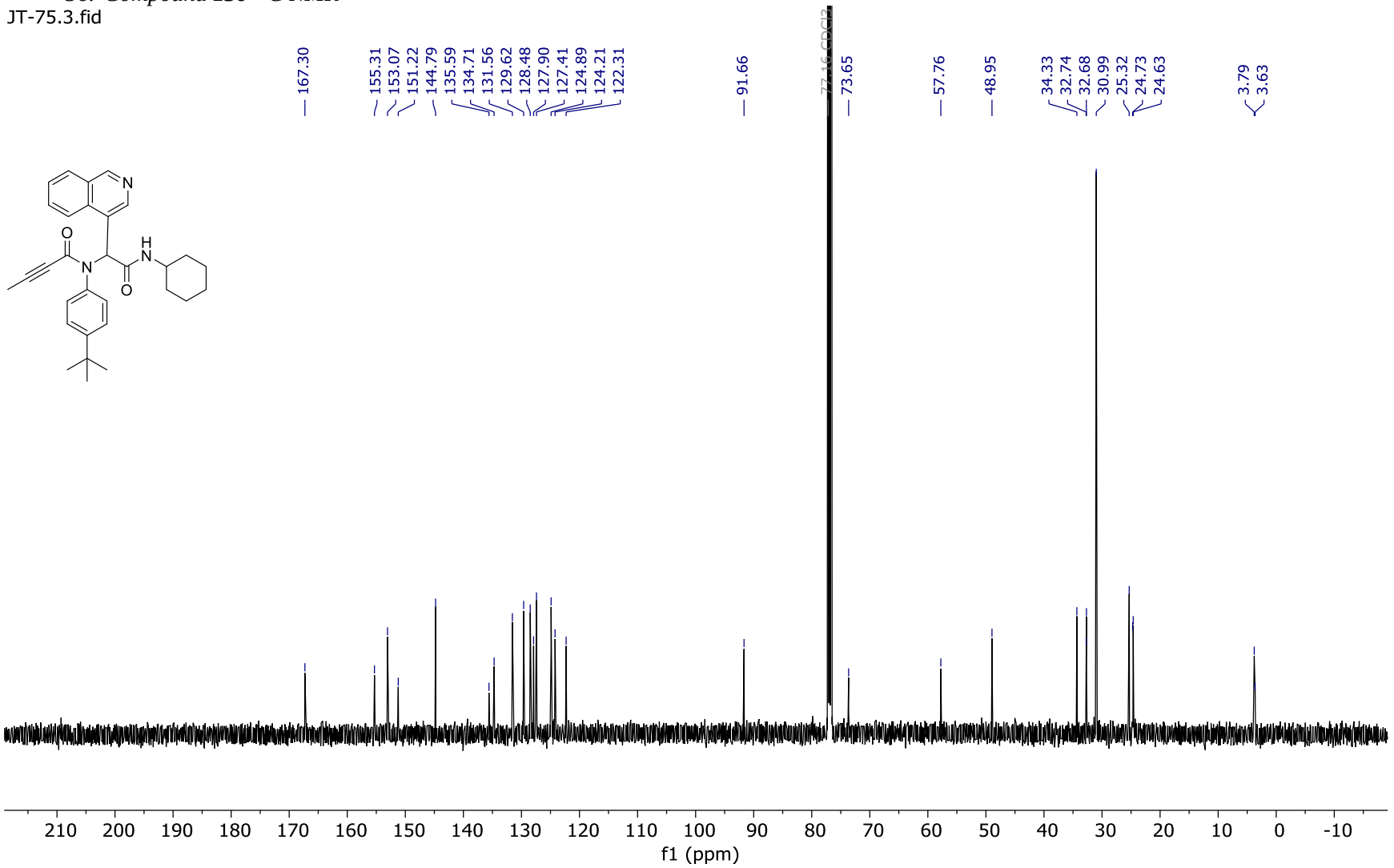
*54. Compound **13d** ^{13}C NMR*



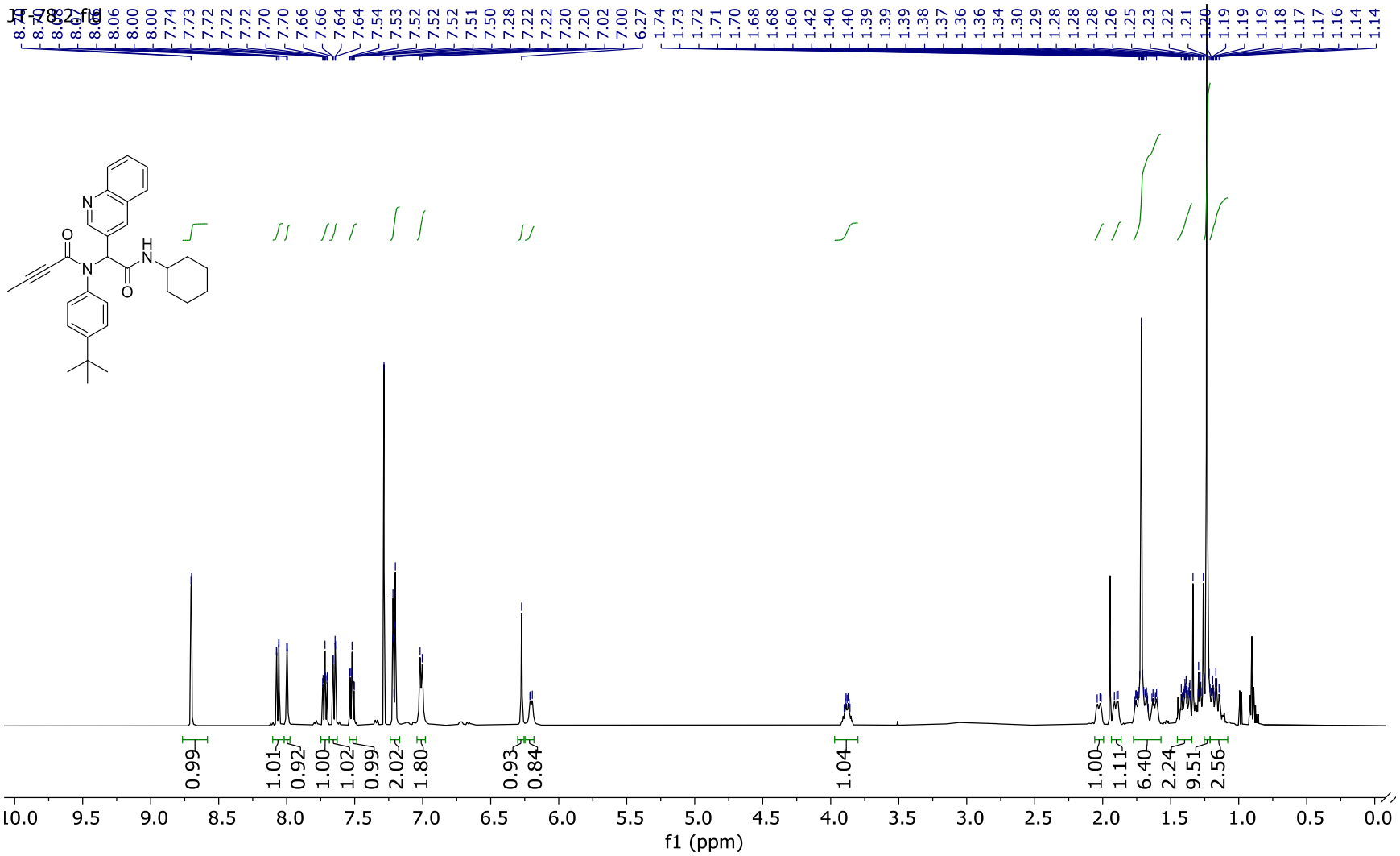
*55. Compound **13e** ^{1}H NMR*



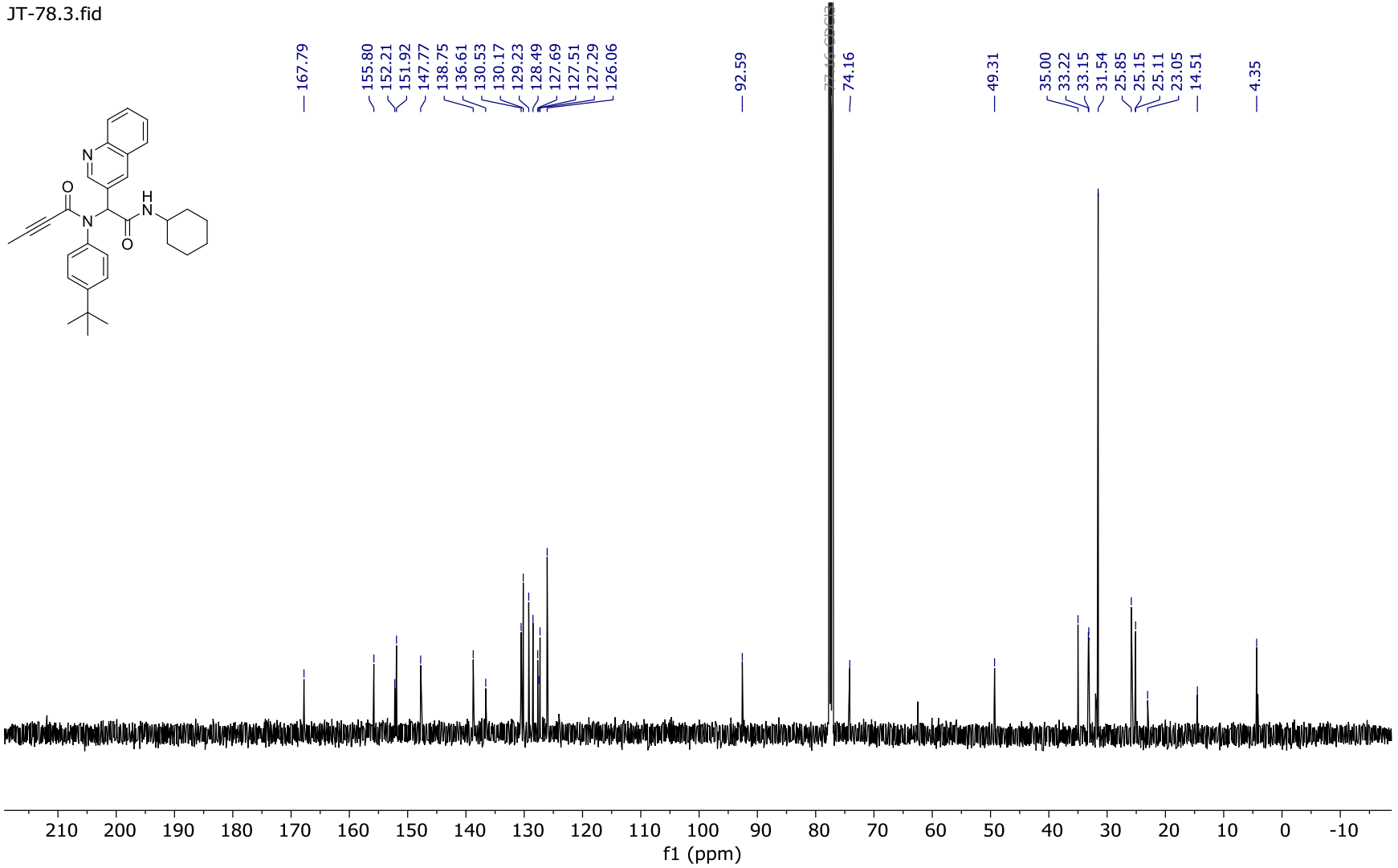
56. Compound ***13e*** *^{13}C NMR*



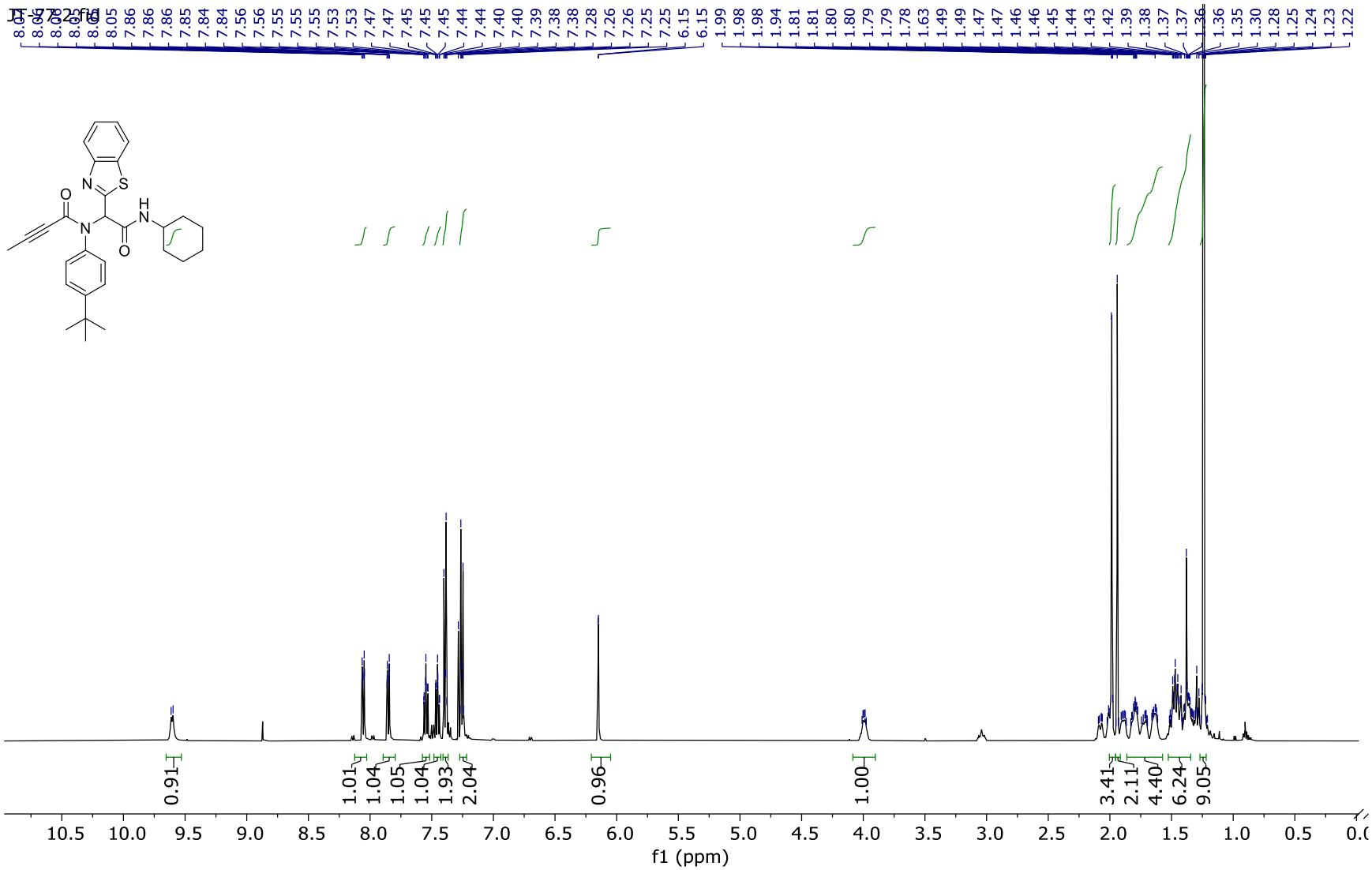
57. Compound ***13f*** *^{1}H NMR*



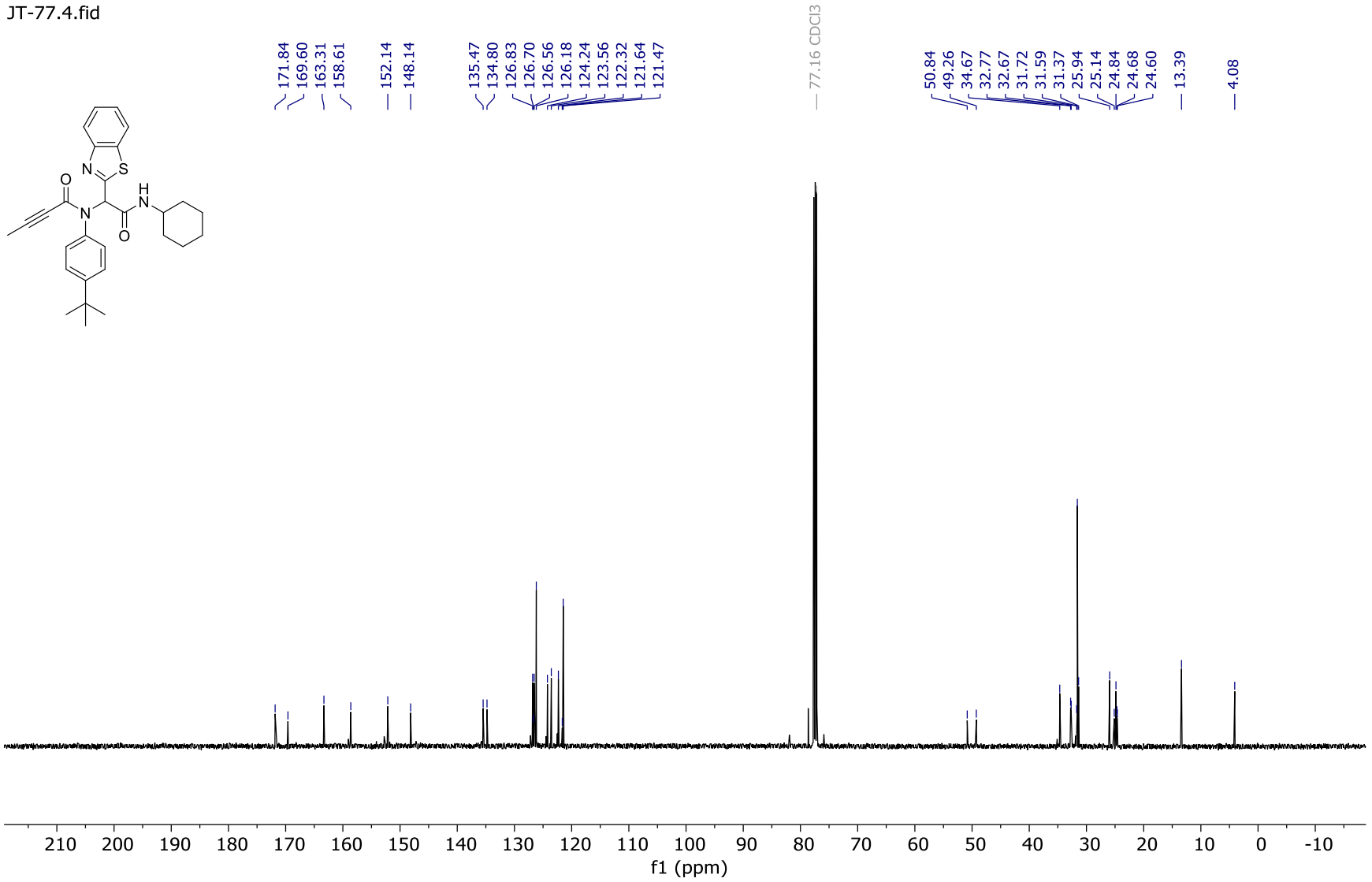
*58. Compound **13f** ^{13}C NMR*



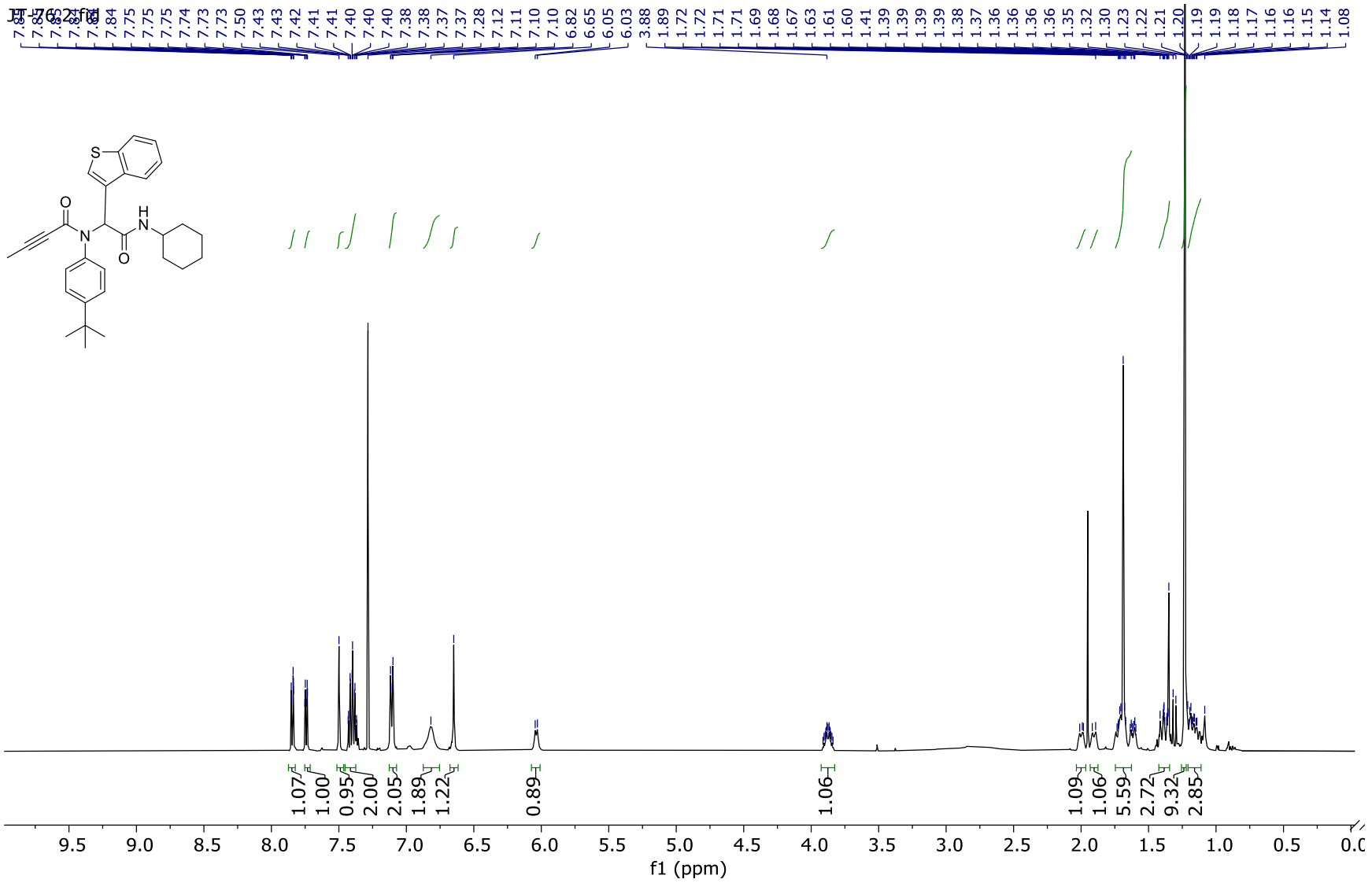
*59. Compound **13g** ^{1}H NMR*



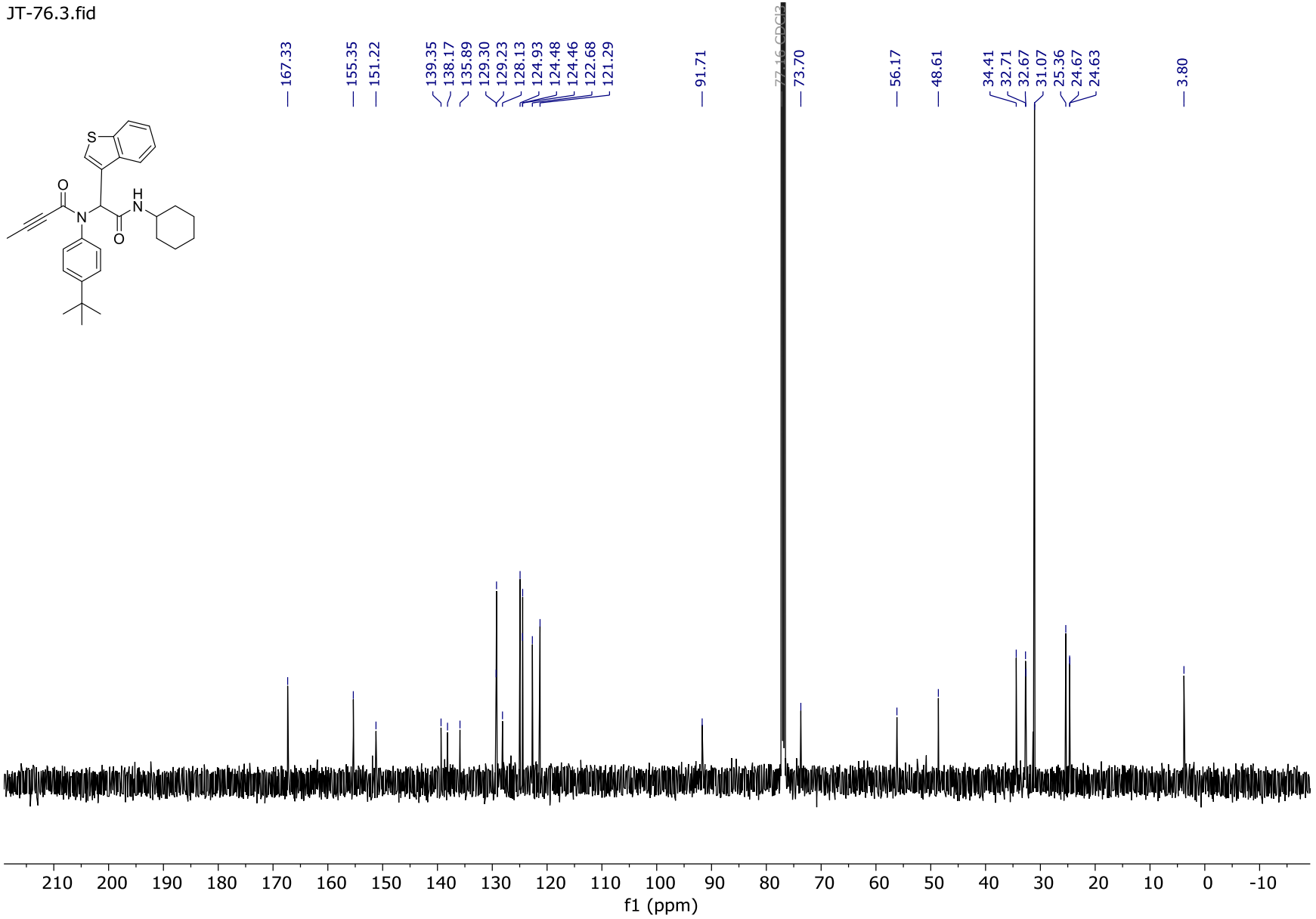
*60. Compound **13g** ^{13}C NMR*



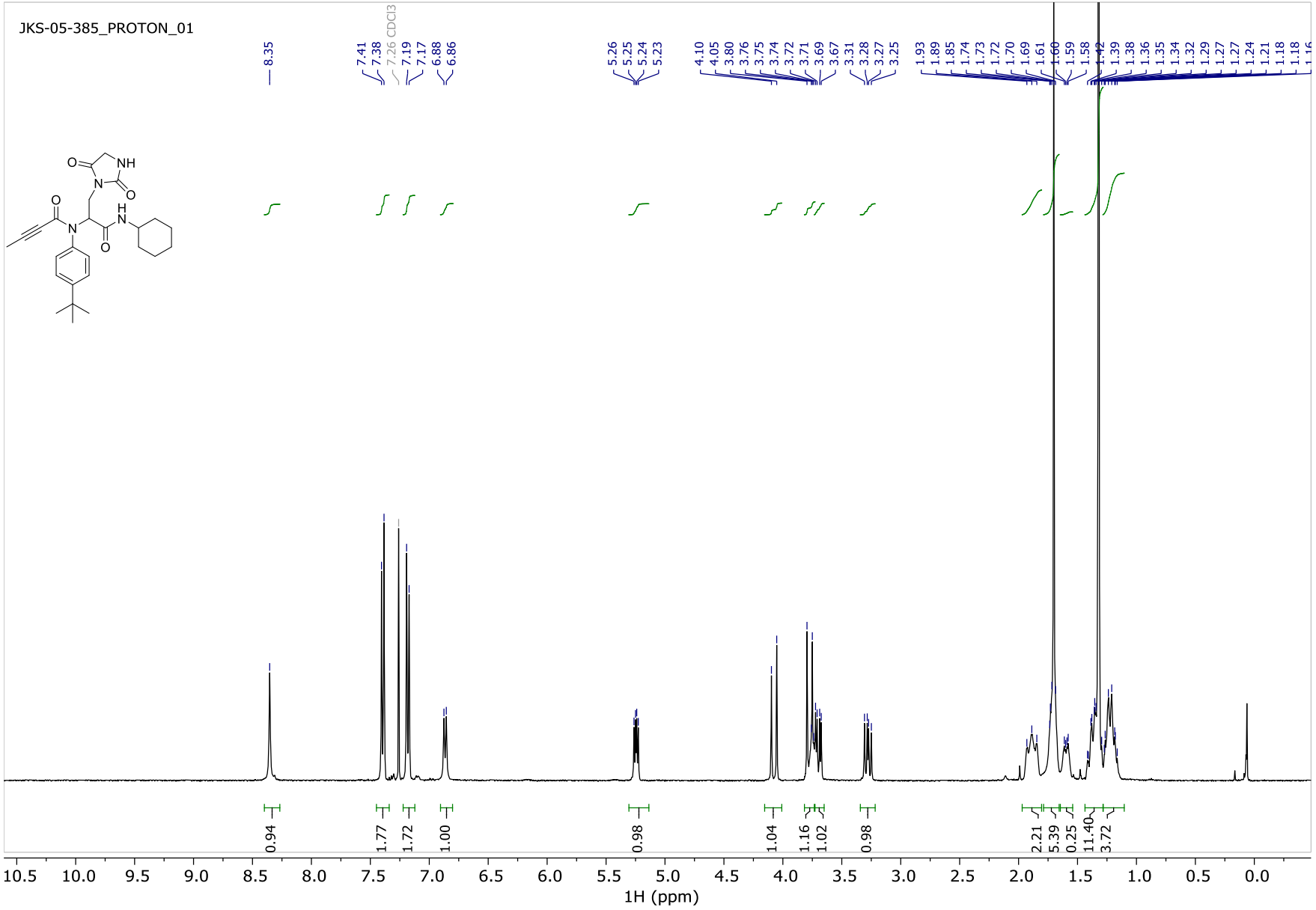
61. Compound ***13h*** *^{1}H NMR*



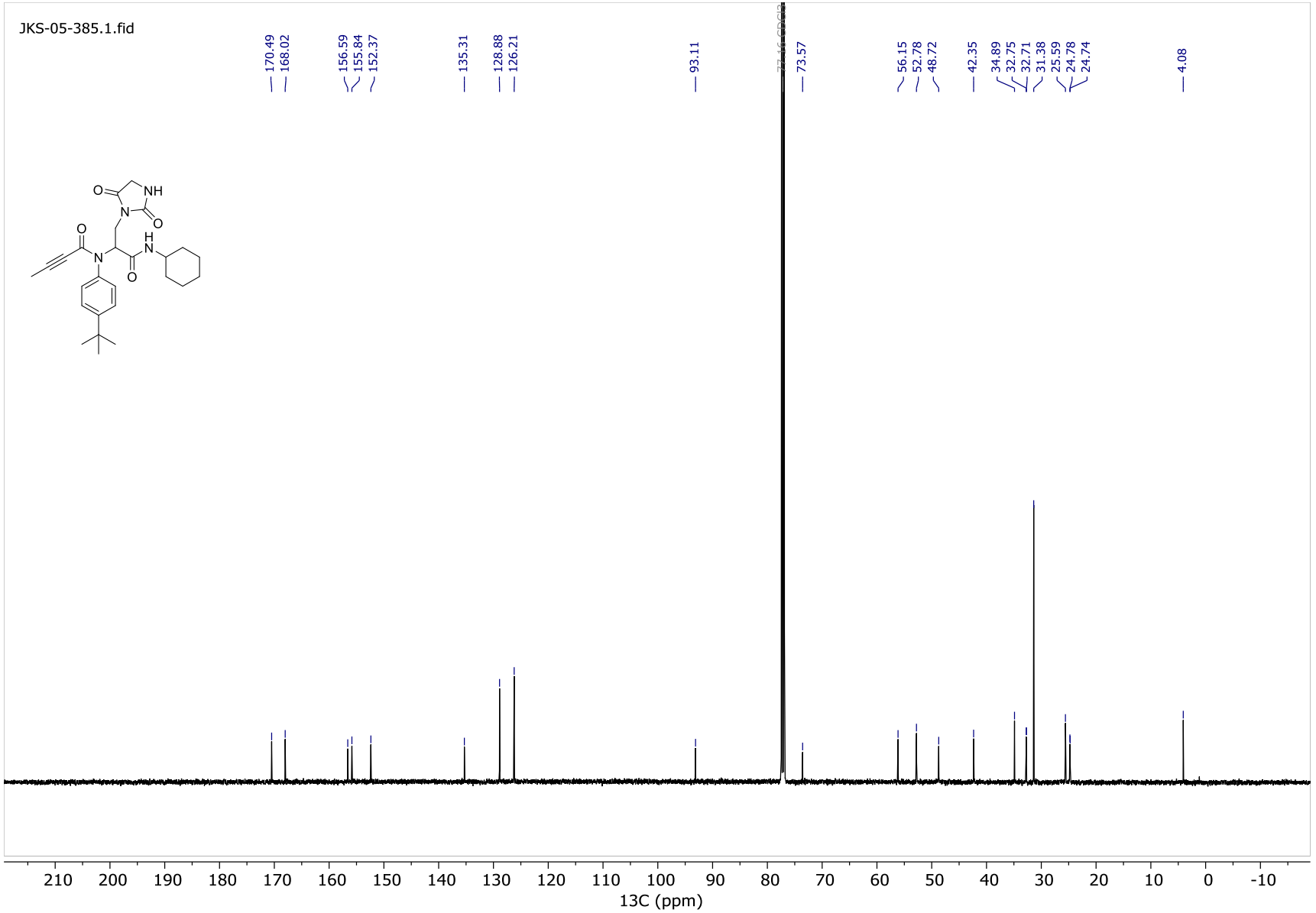
*62. Compound **13h** ^{13}C NMR*



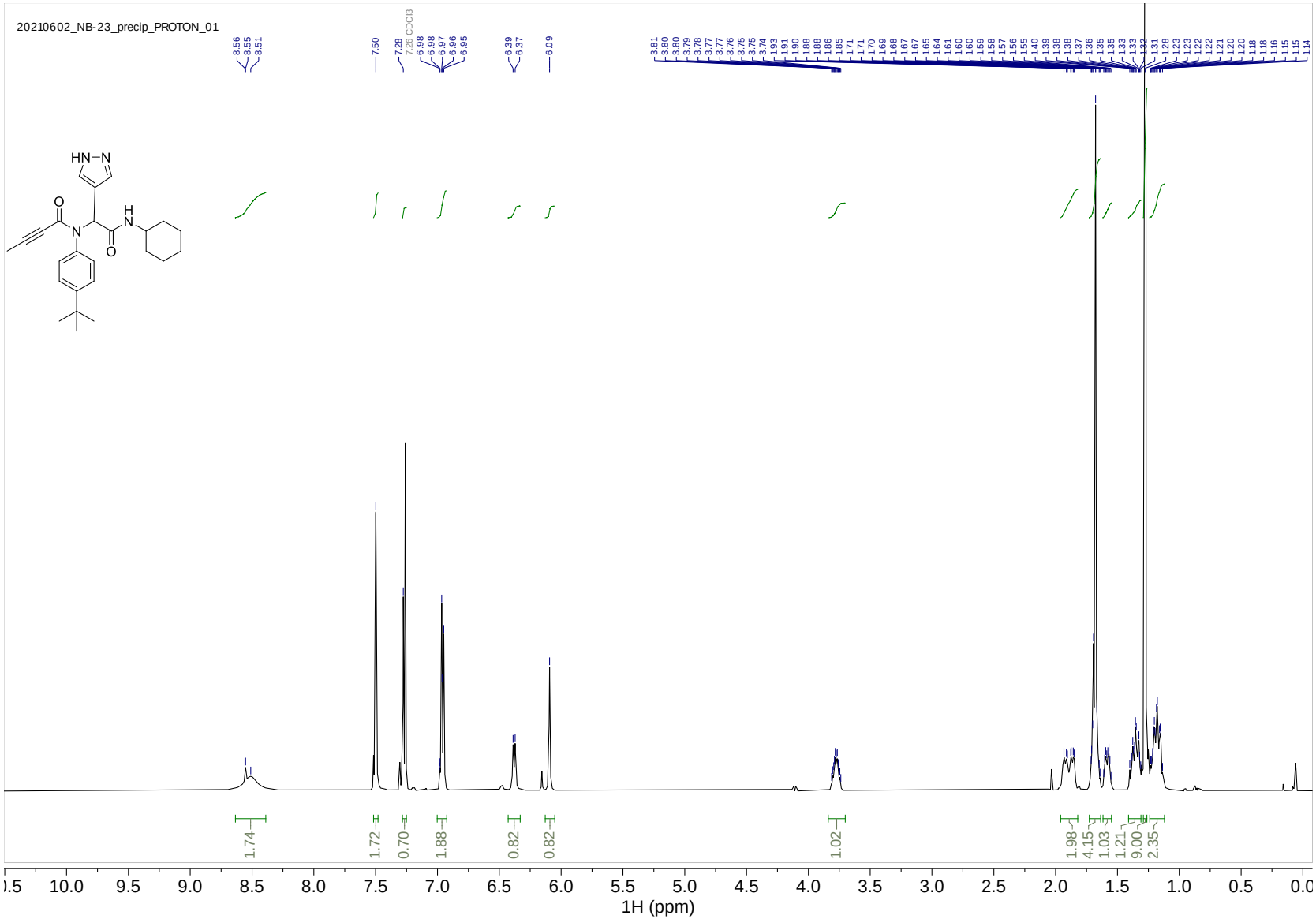
*63. Compound **13i** ^{1}H NMR*



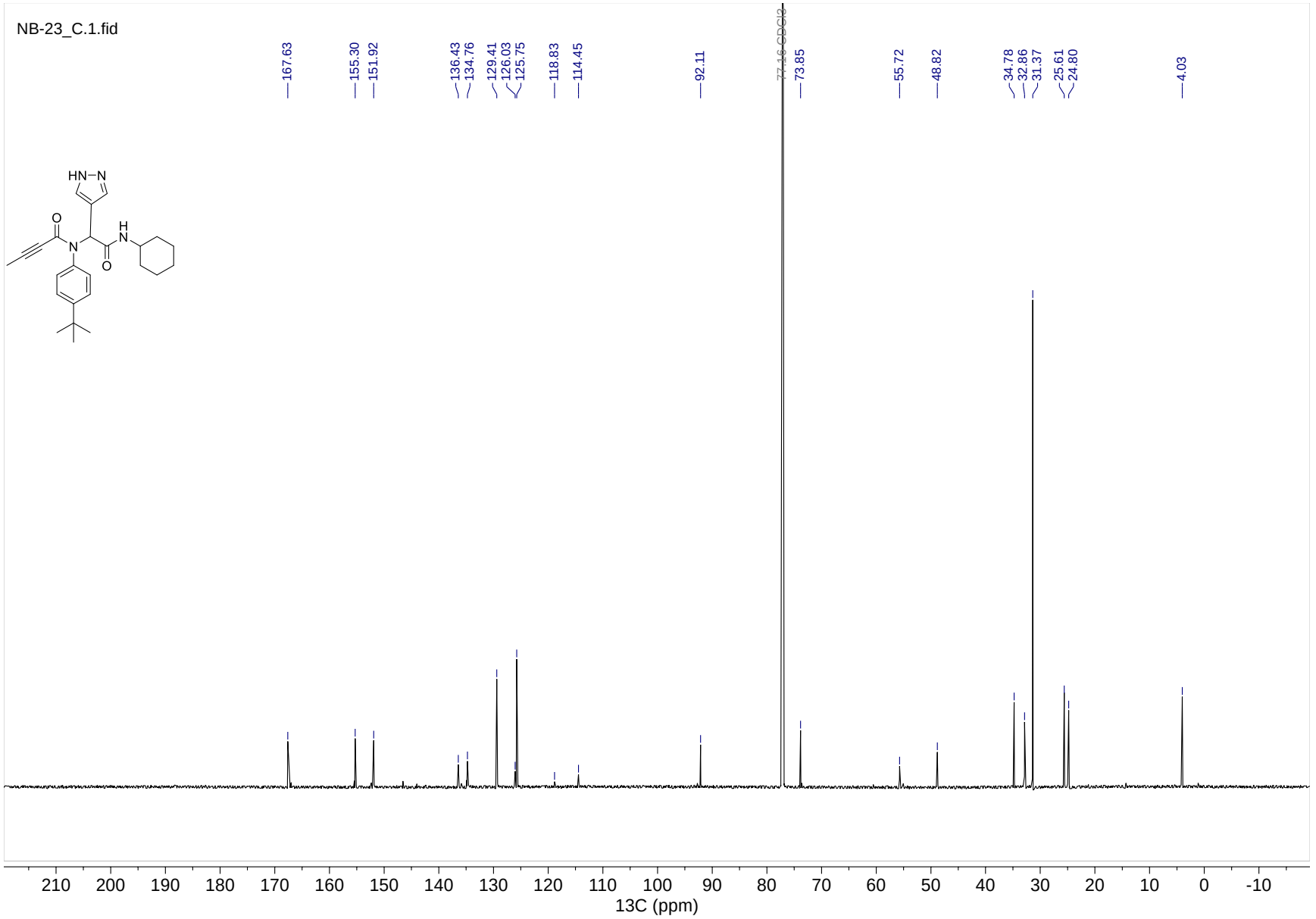
*64. Compound **13i** ^{13}C NMR*



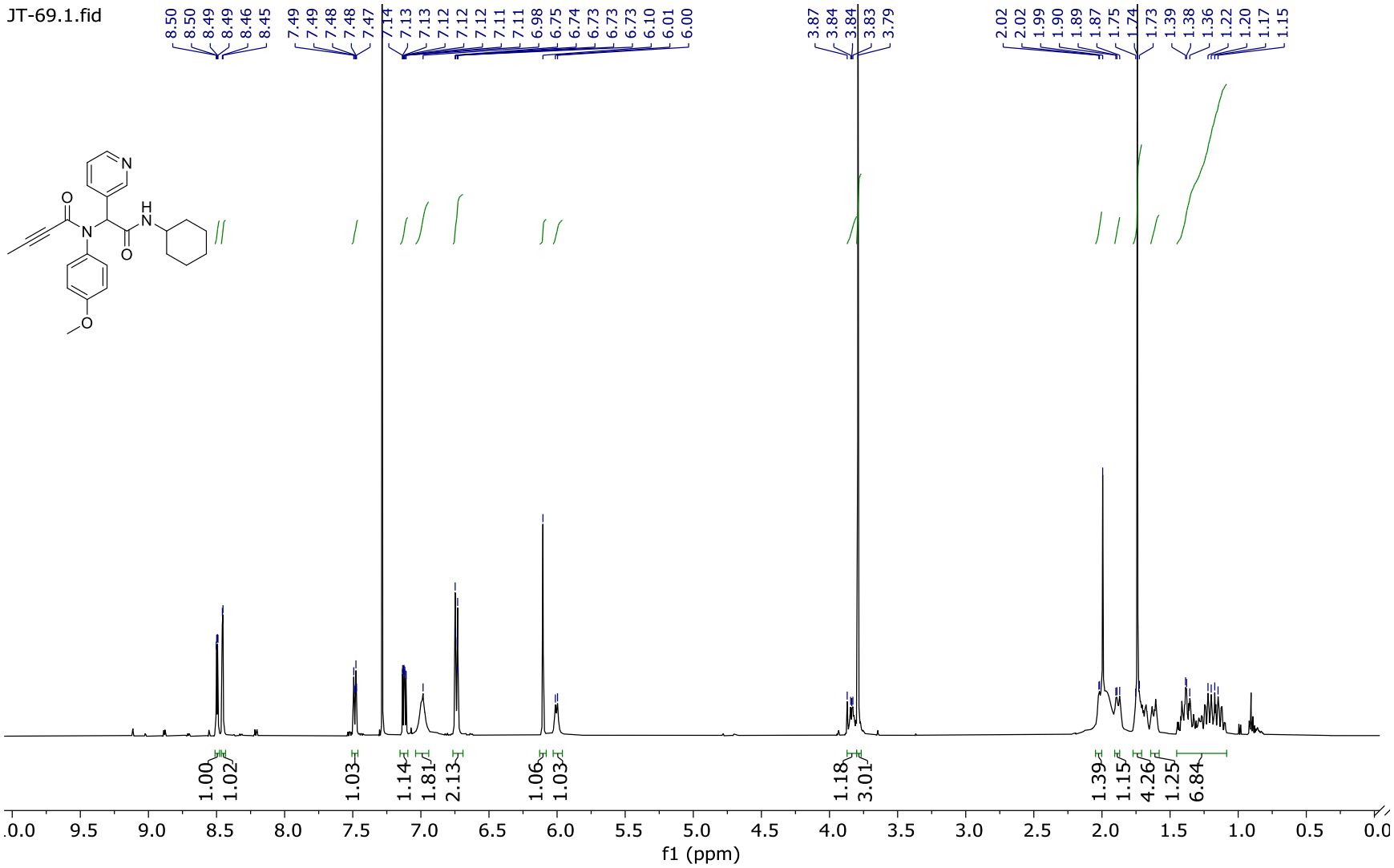
*65. Compound **13j** ^{1}H NMR*



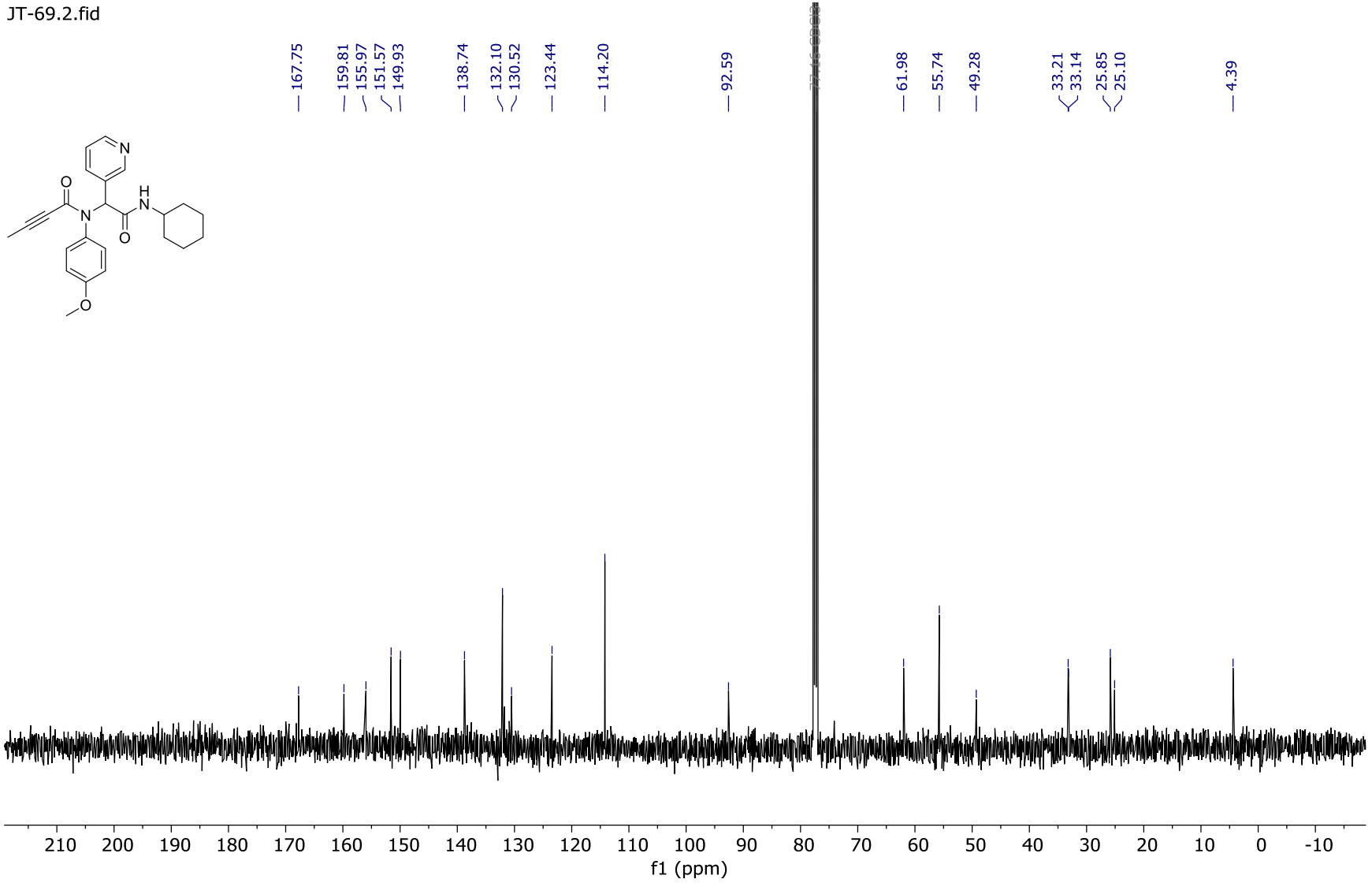
*66. Compound **13j** ^{13}C NMR*



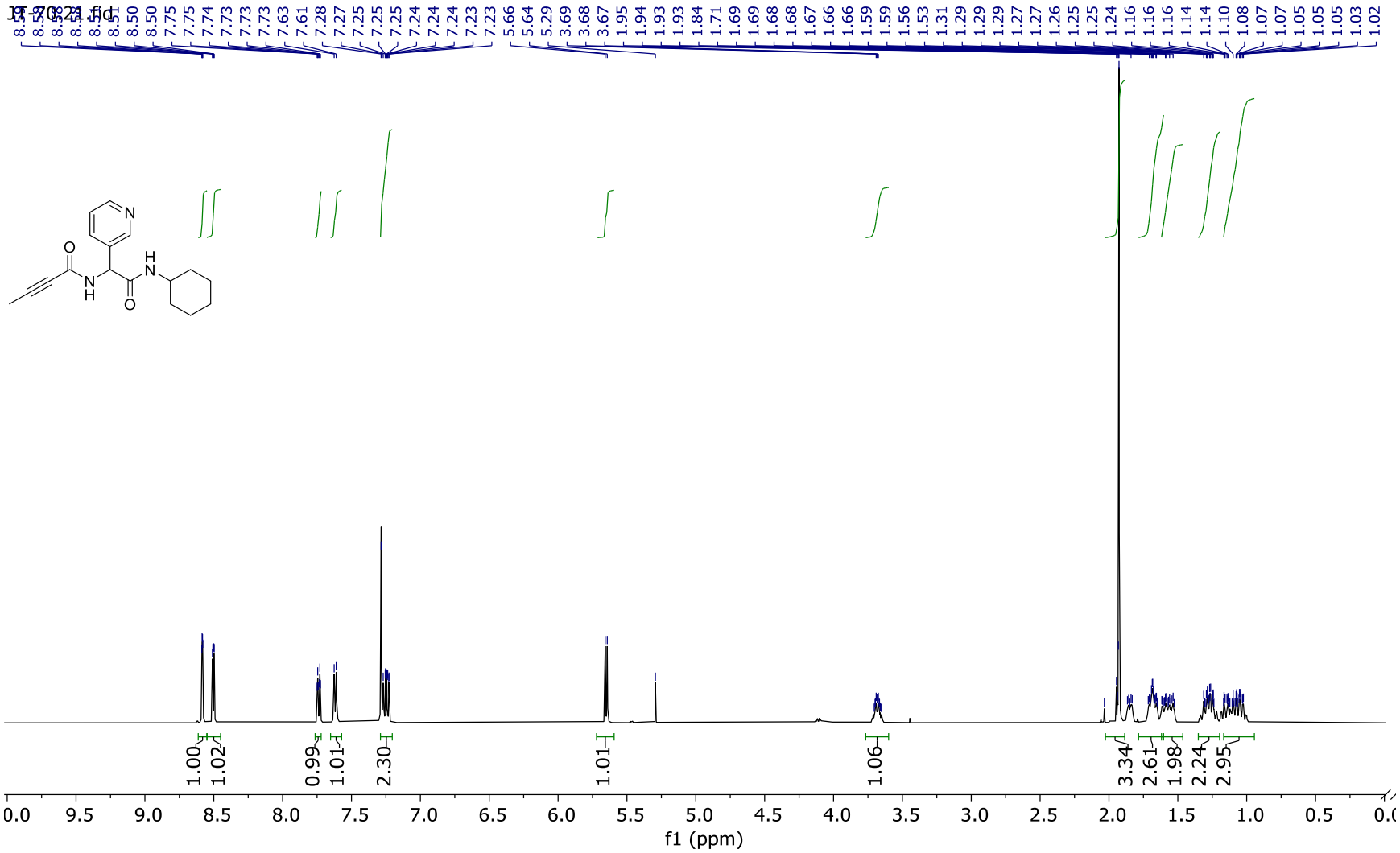
67. Compound ***13k*** *^{1}H NMR*



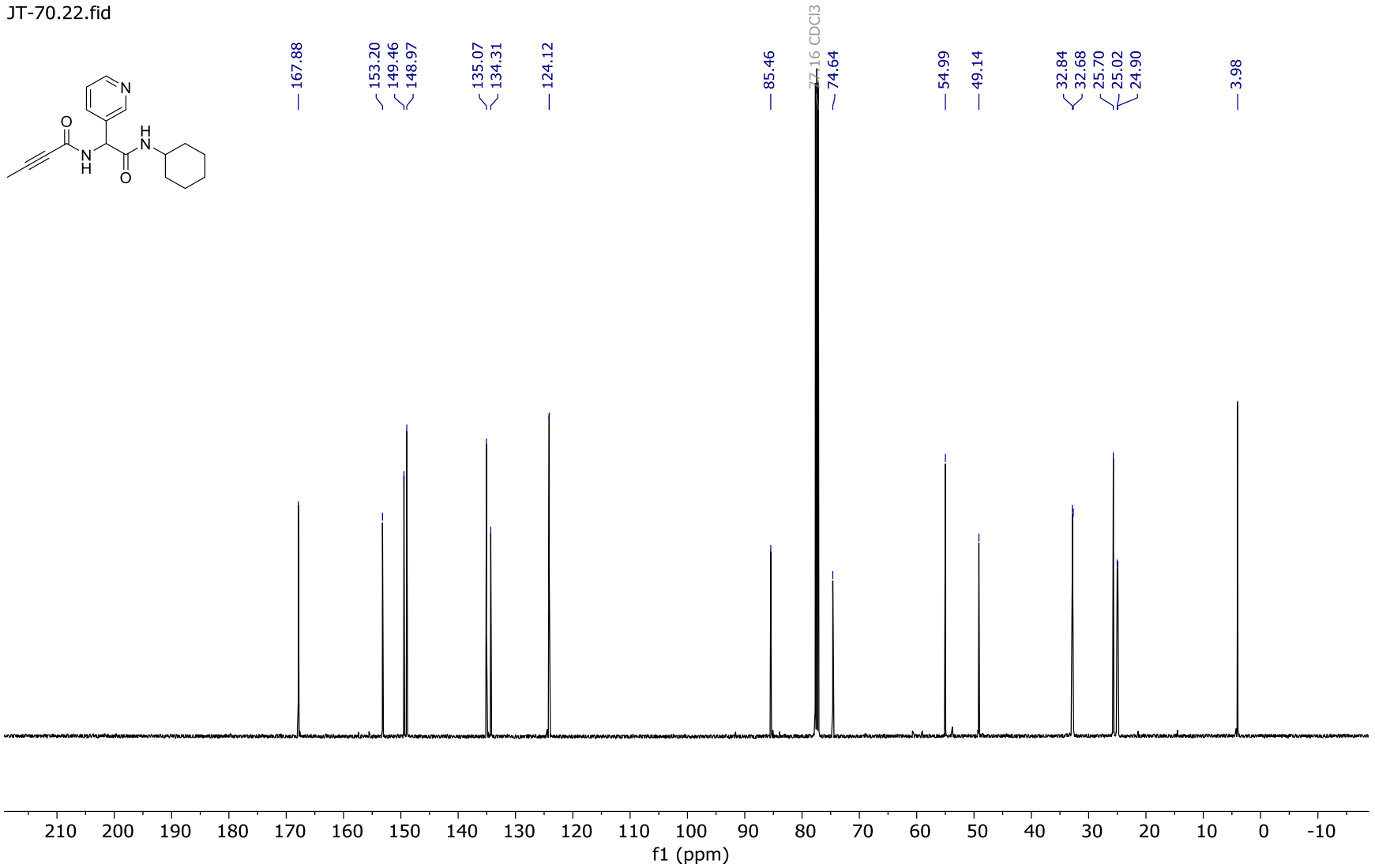
*68. Compound **13k** ^{13}C NMR*



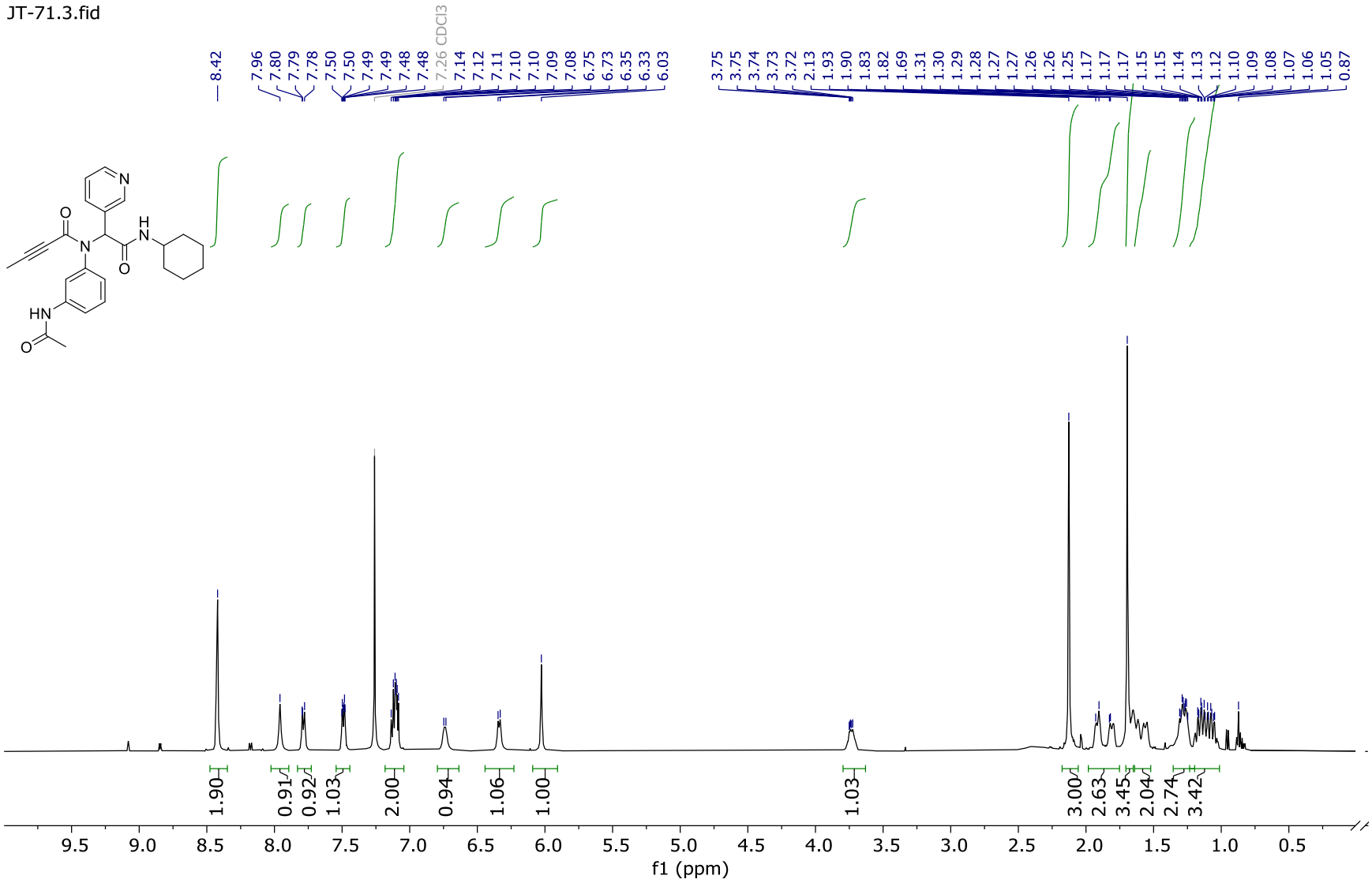
69. Compound ***13l*** *^{1}H NMR*



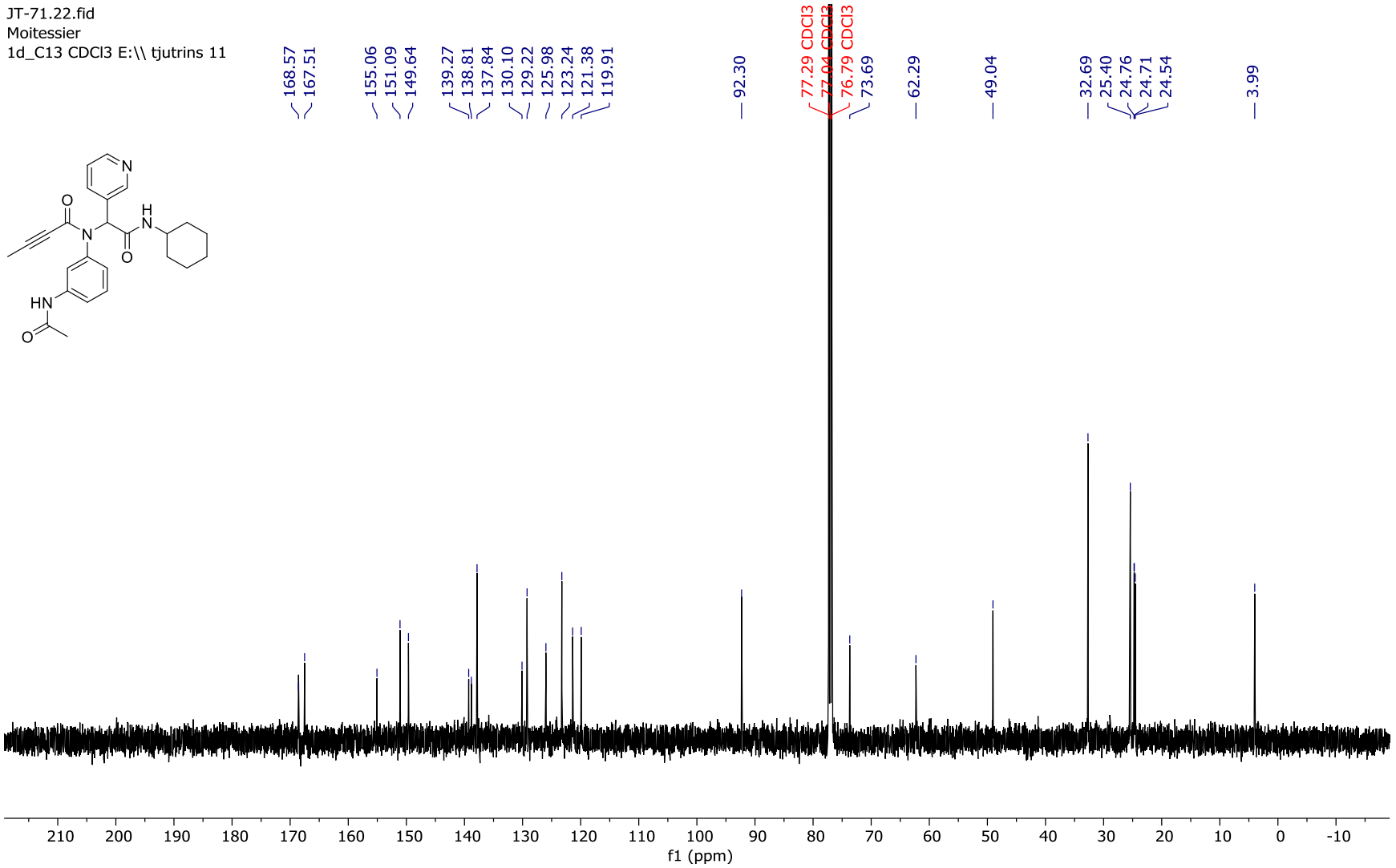
*70. Compound **13l** ^{13}C NMR*



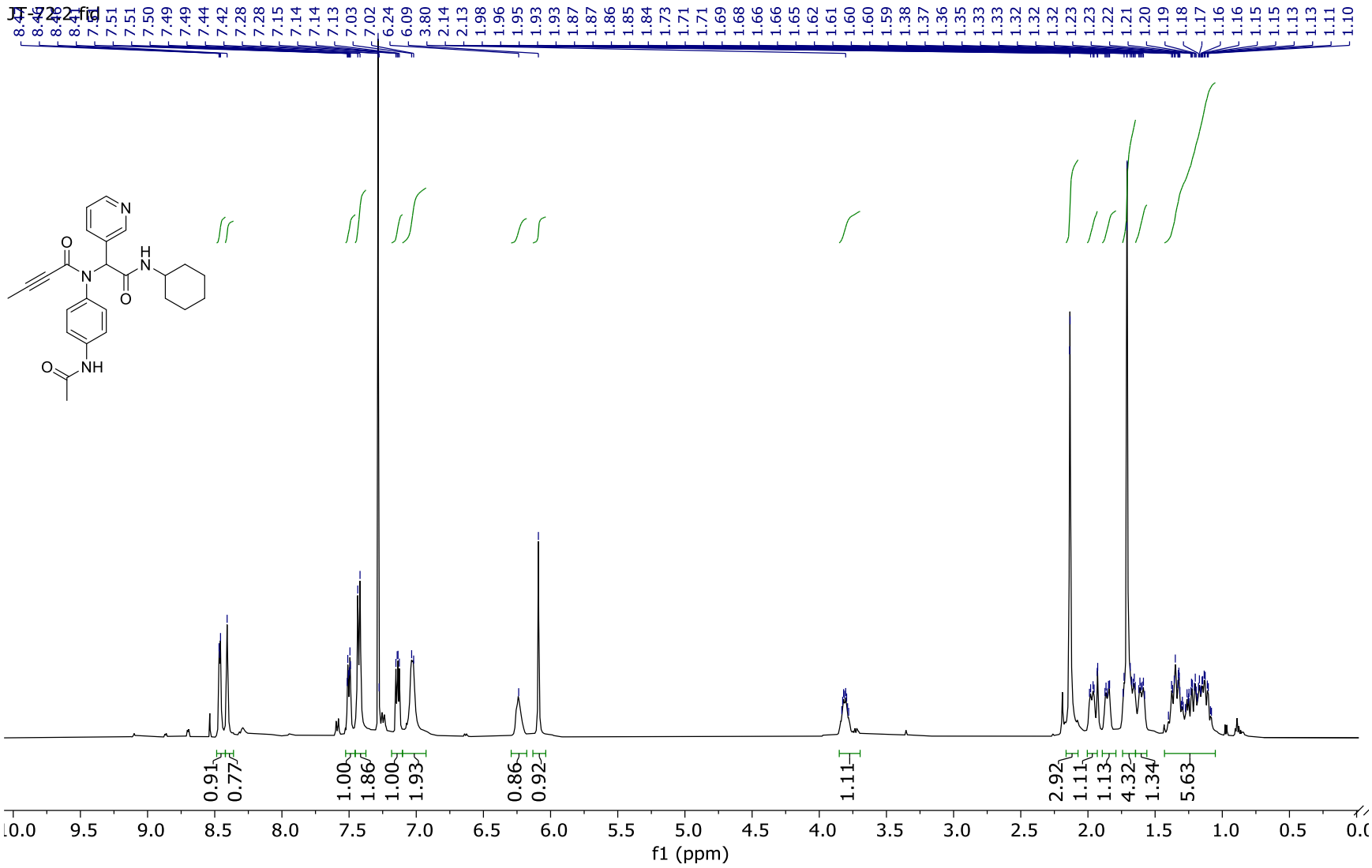
*71. Compound **13m** ^{1}H NMR*



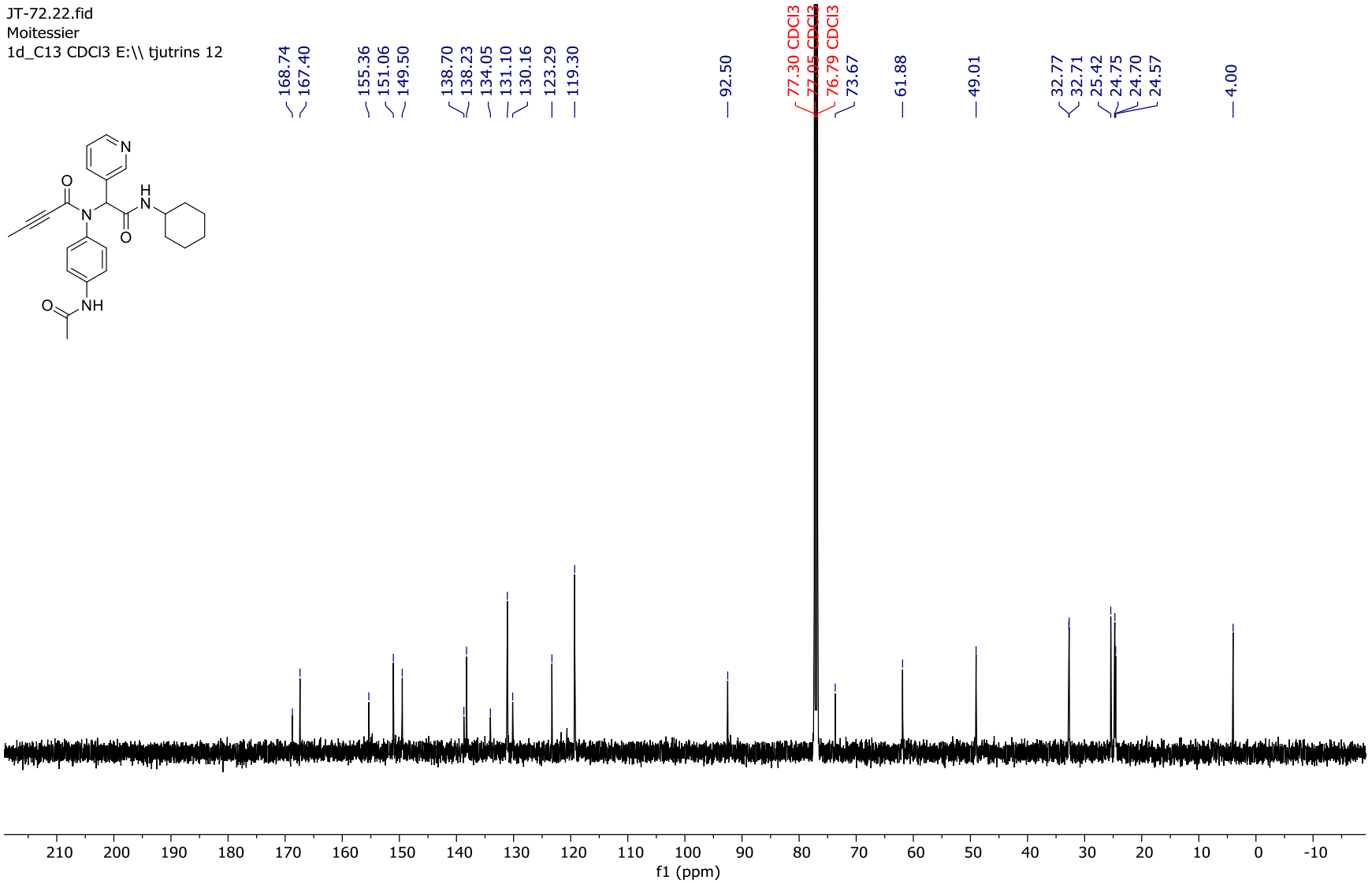
*72. Compound **13m** ^{13}C NMR*



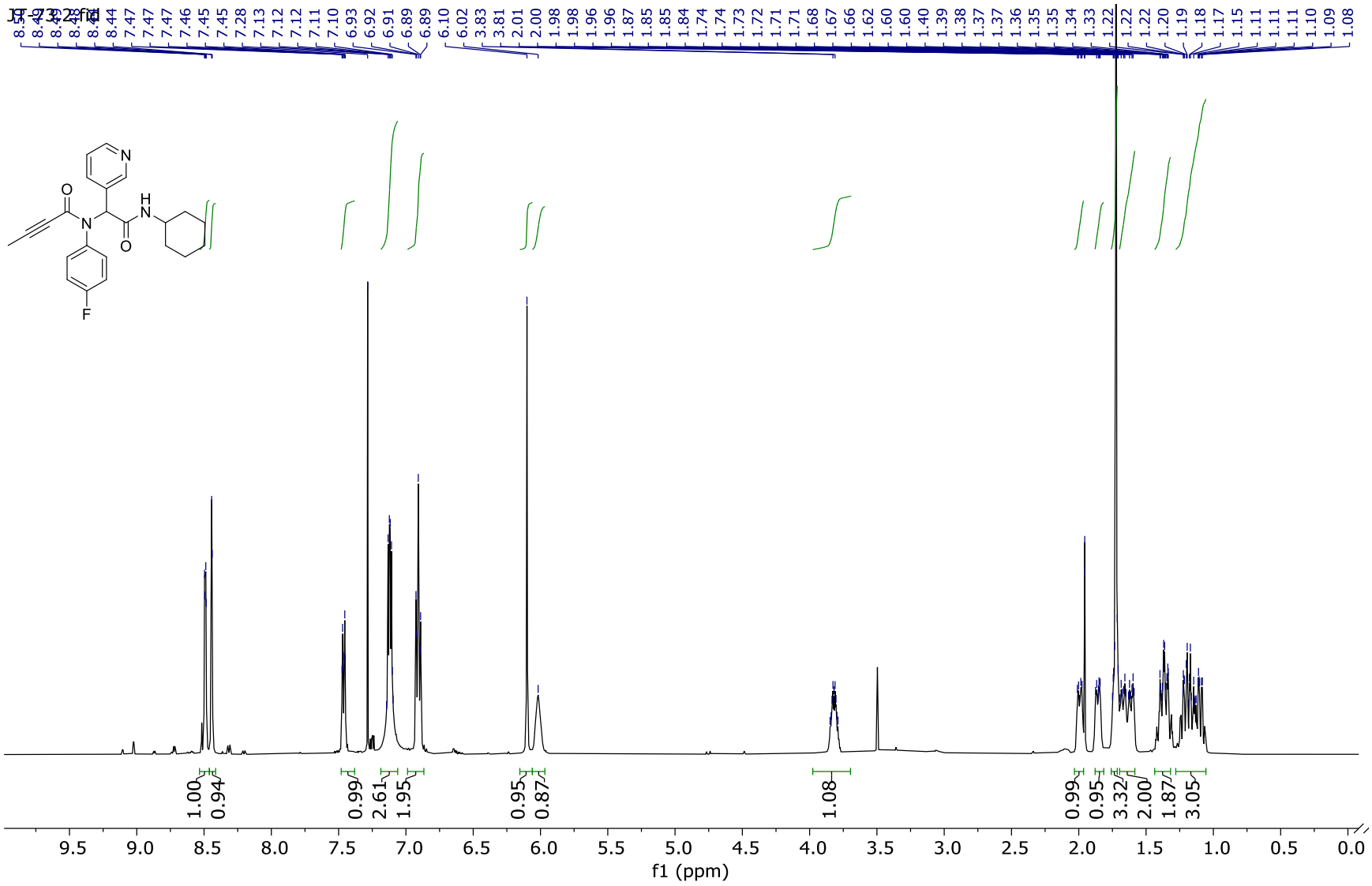
73. Compound ***13n*** *^{1}H NMR*



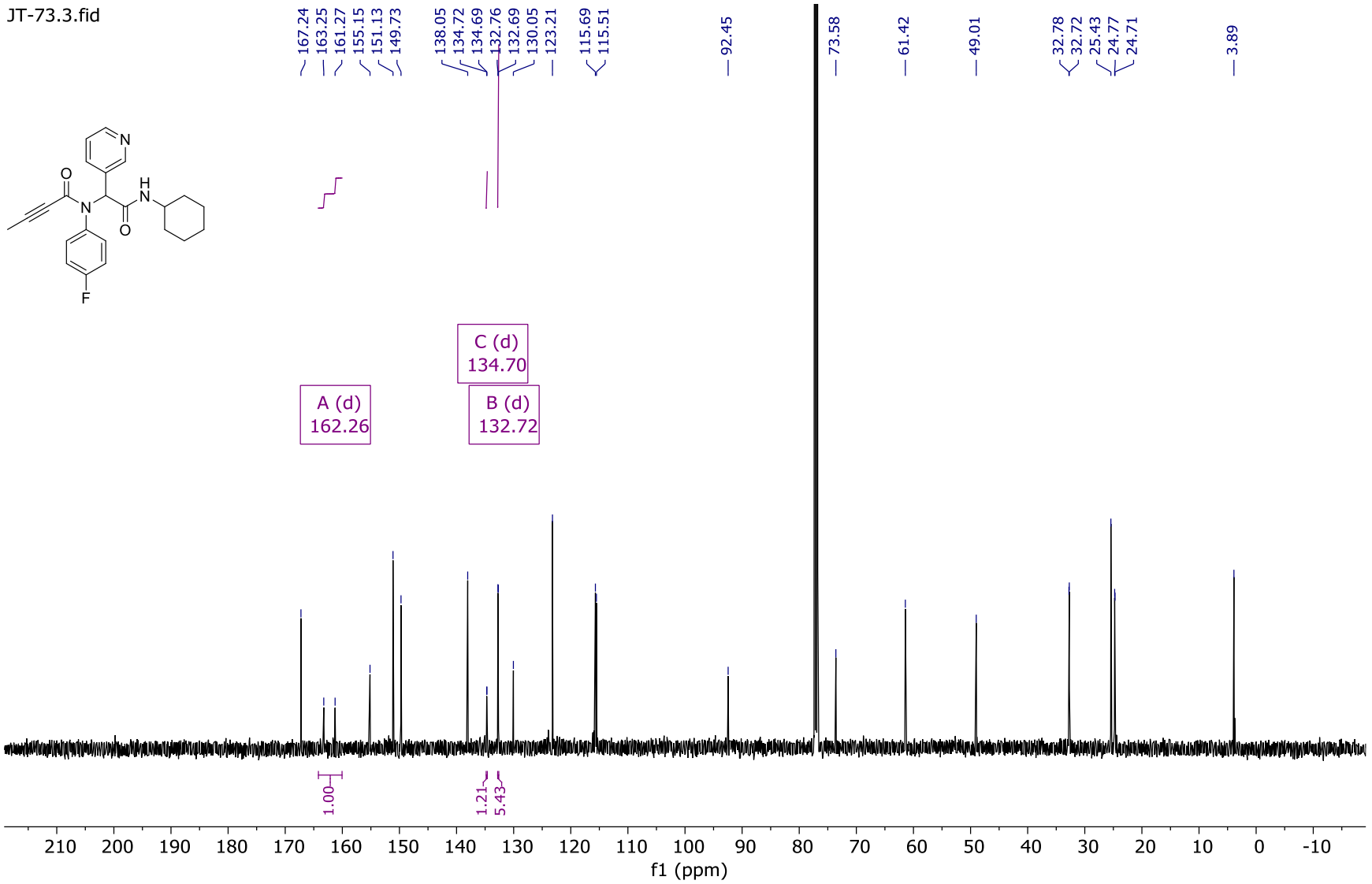
74. Compound ***13n*** *^{13}C NMR*



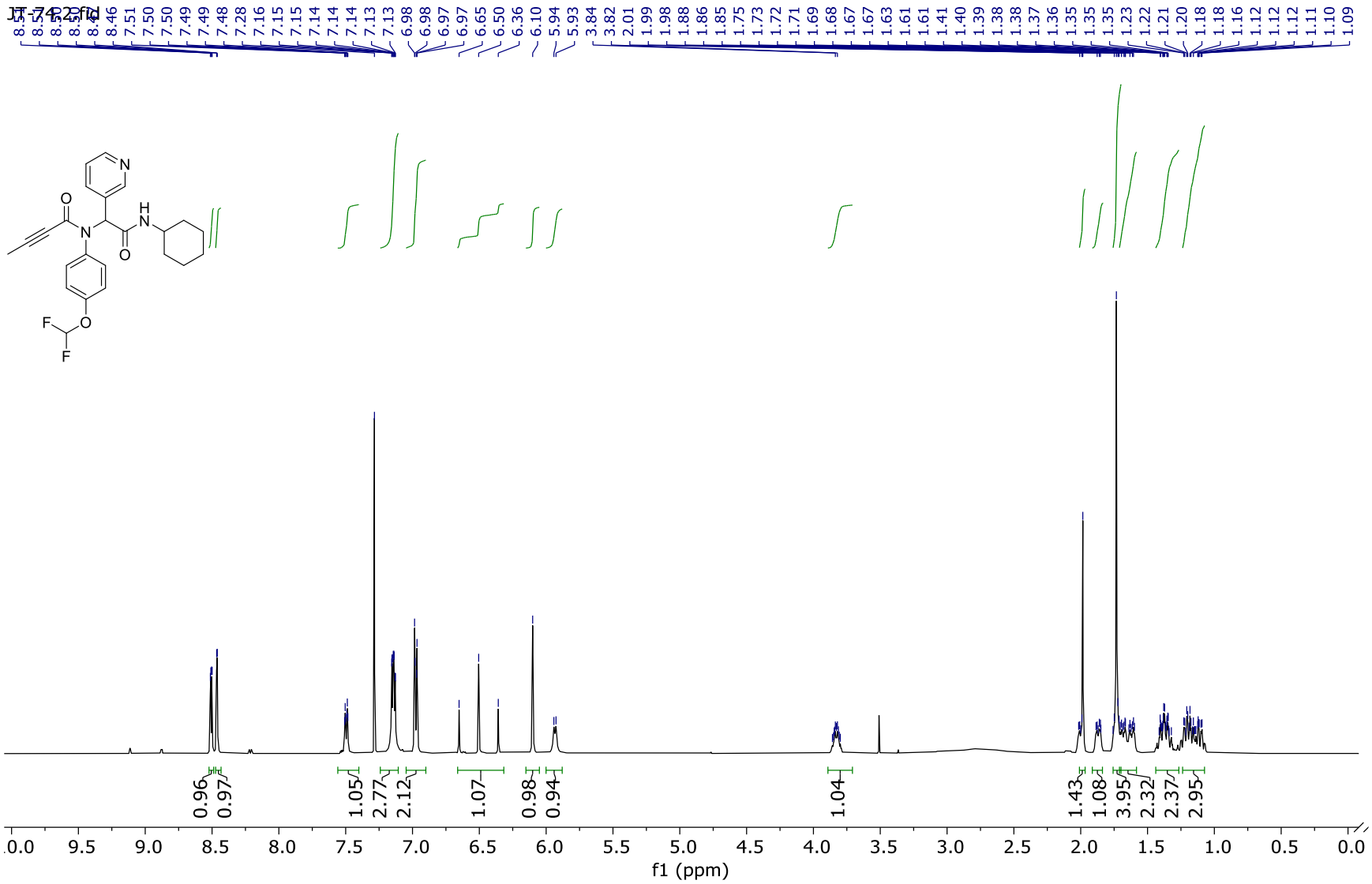
*75. Compound **13o** ^{1}H NMR*



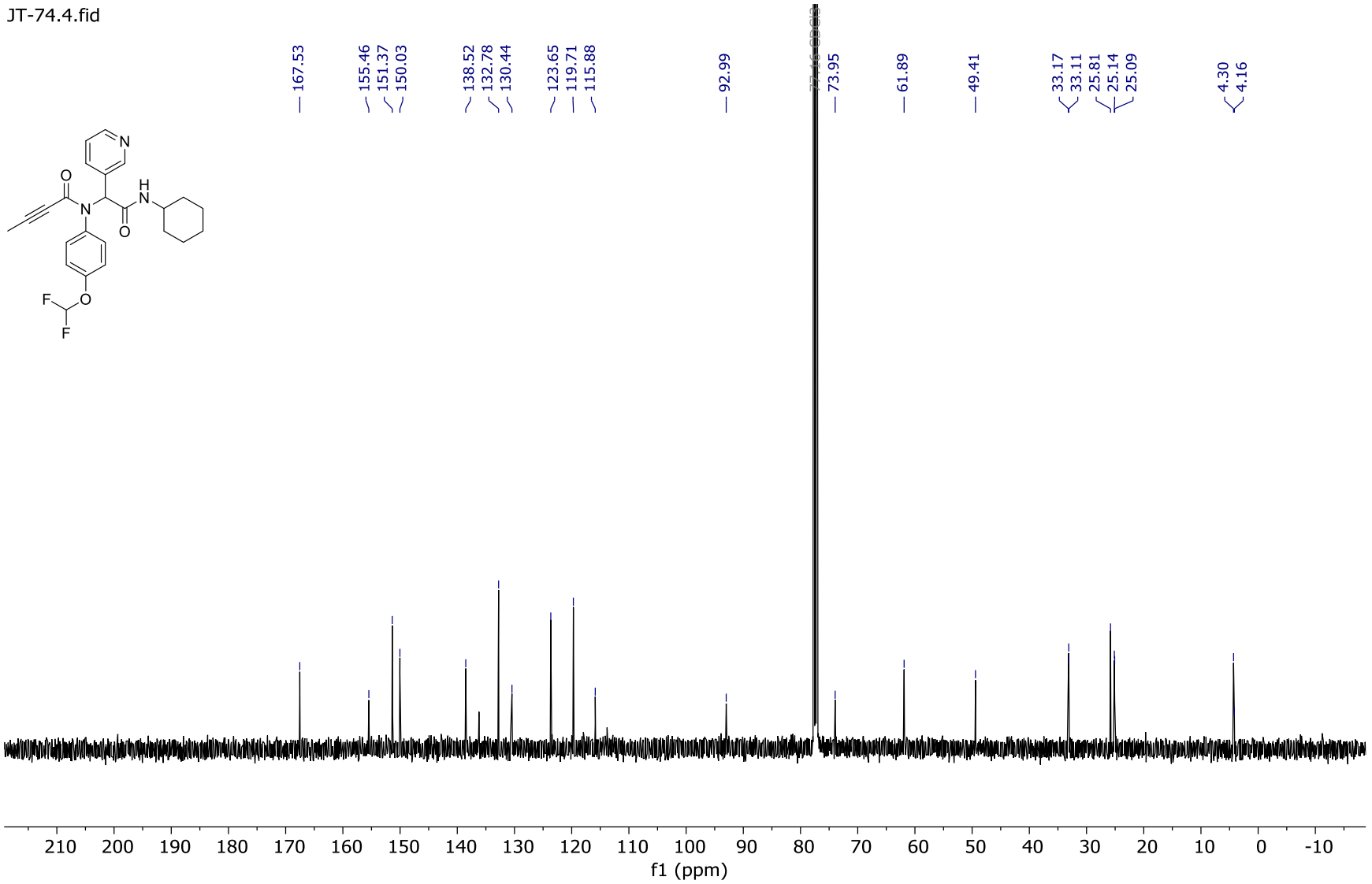
*76. Compound **13o** ^{13}C NMR*



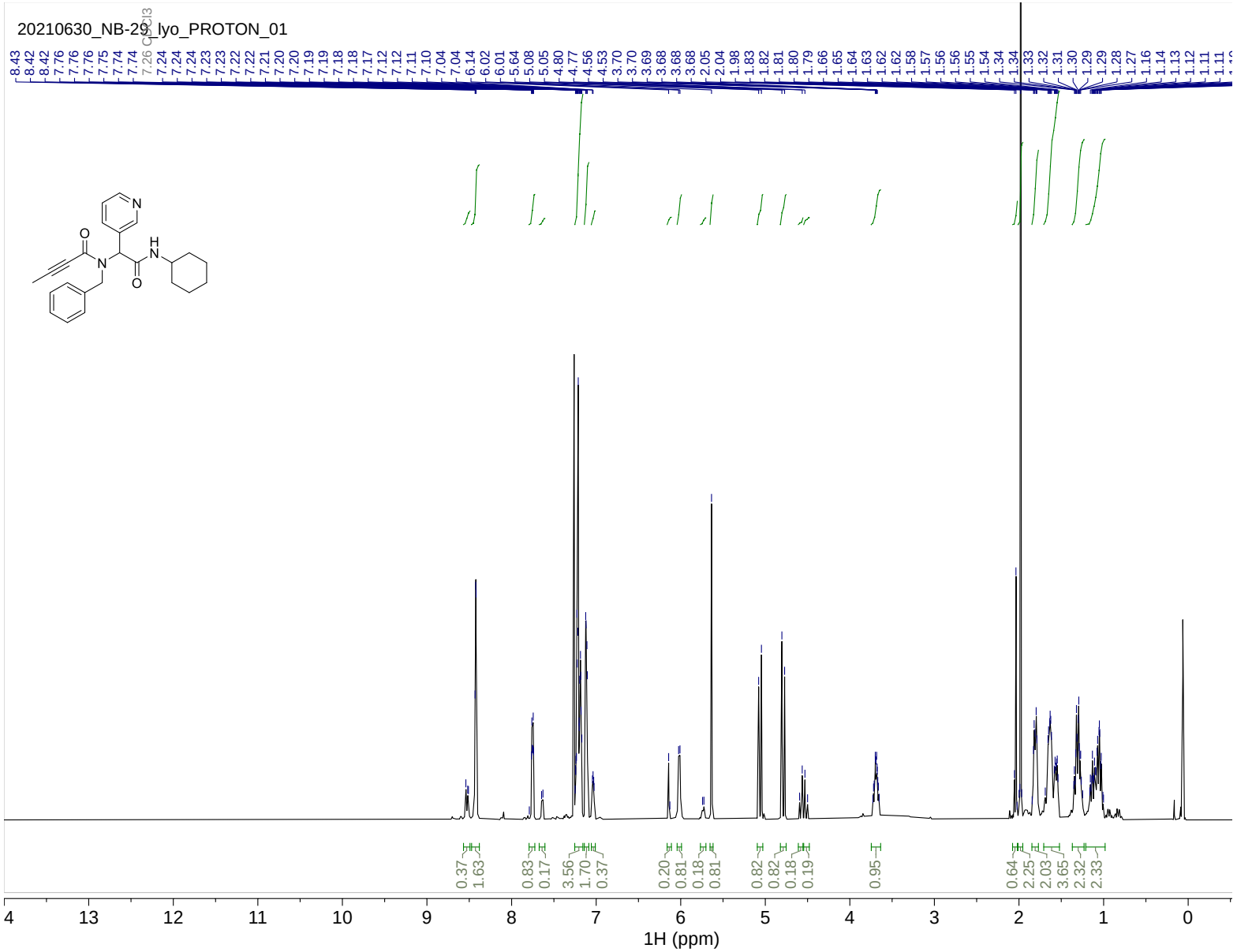
77. Compound ***13p*** *^{1}H NMR*



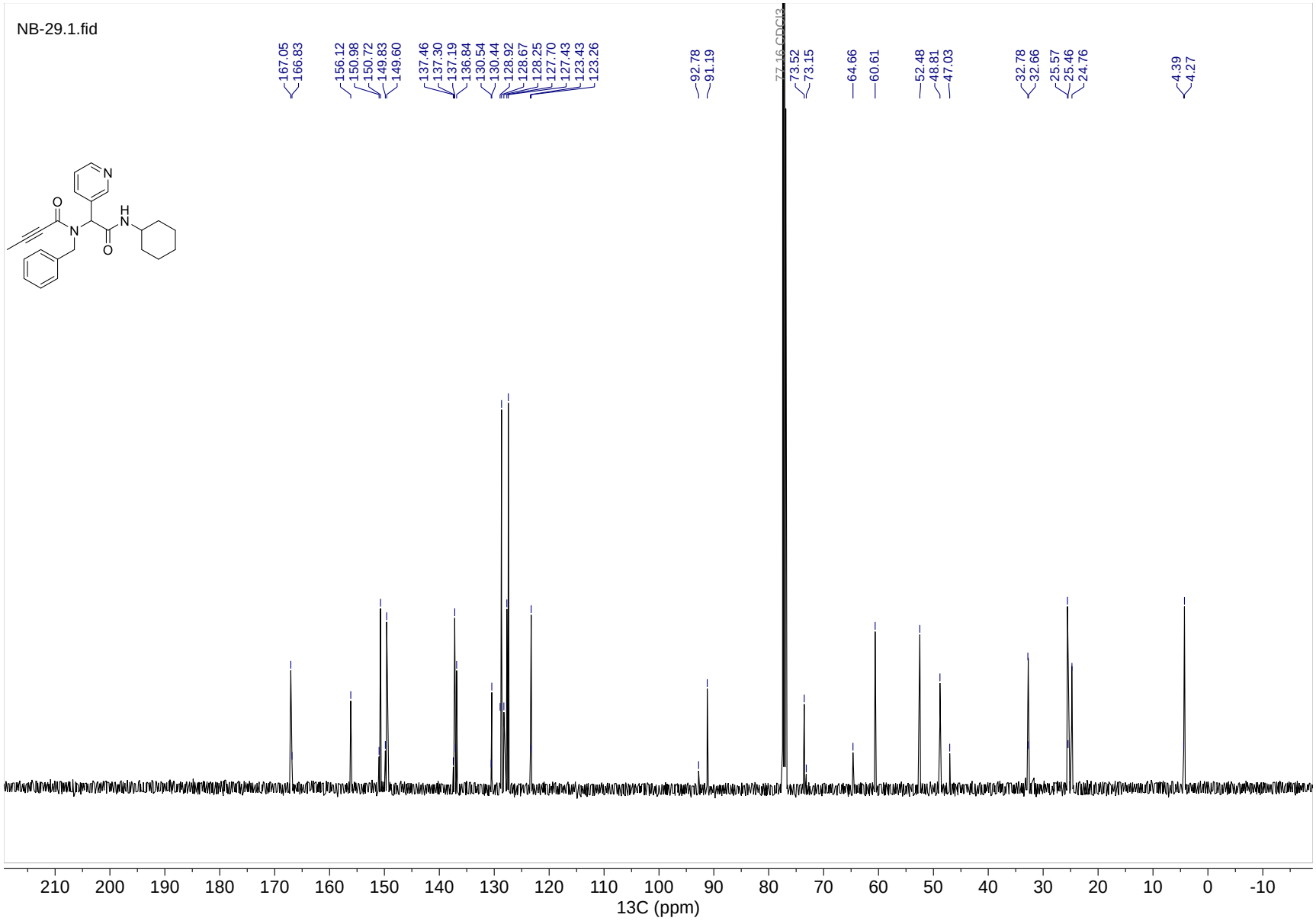
*78. Compound **13p** ^{13}C NMR*



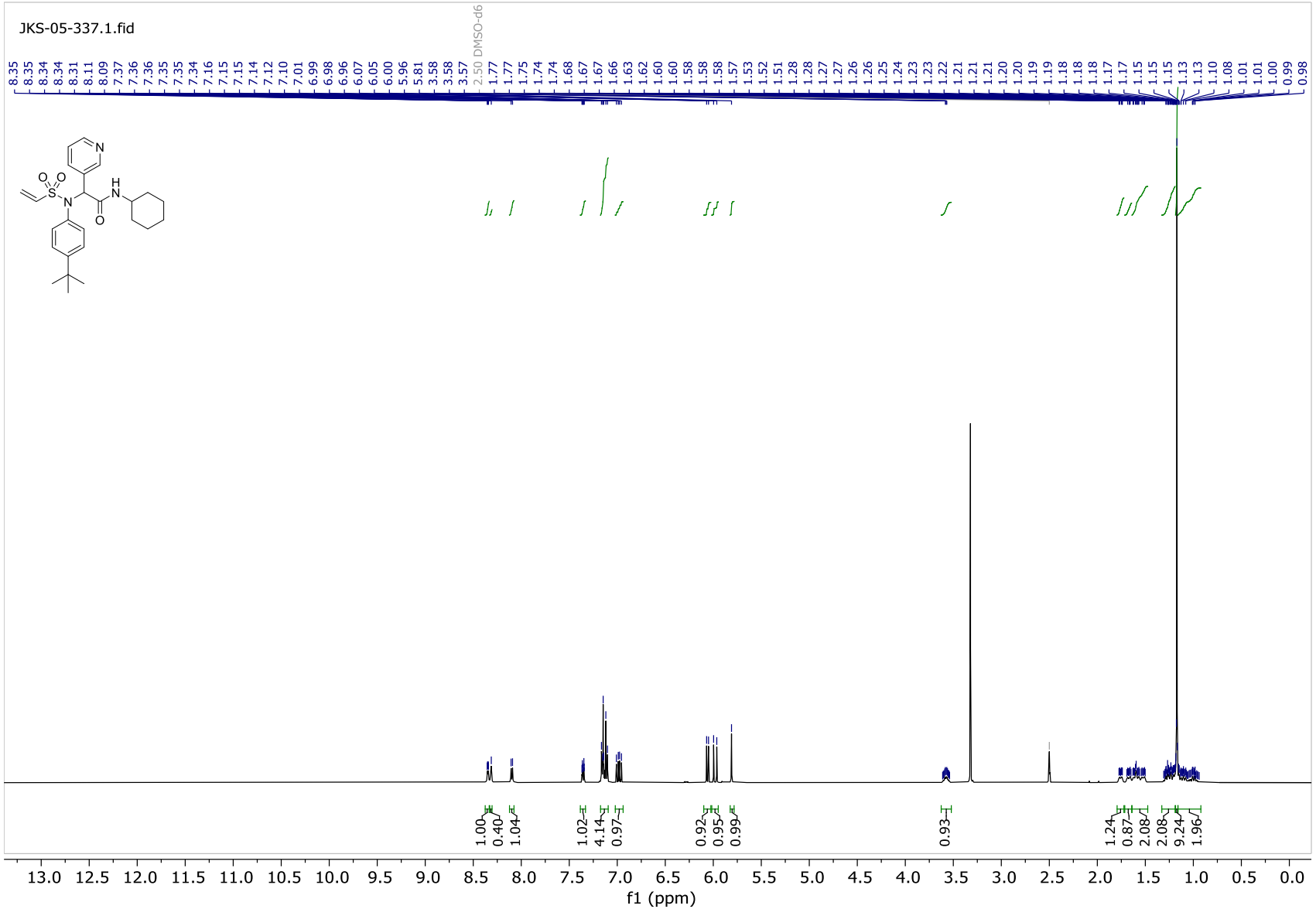
79. Compound ***13q*** *^{13}C NMR*



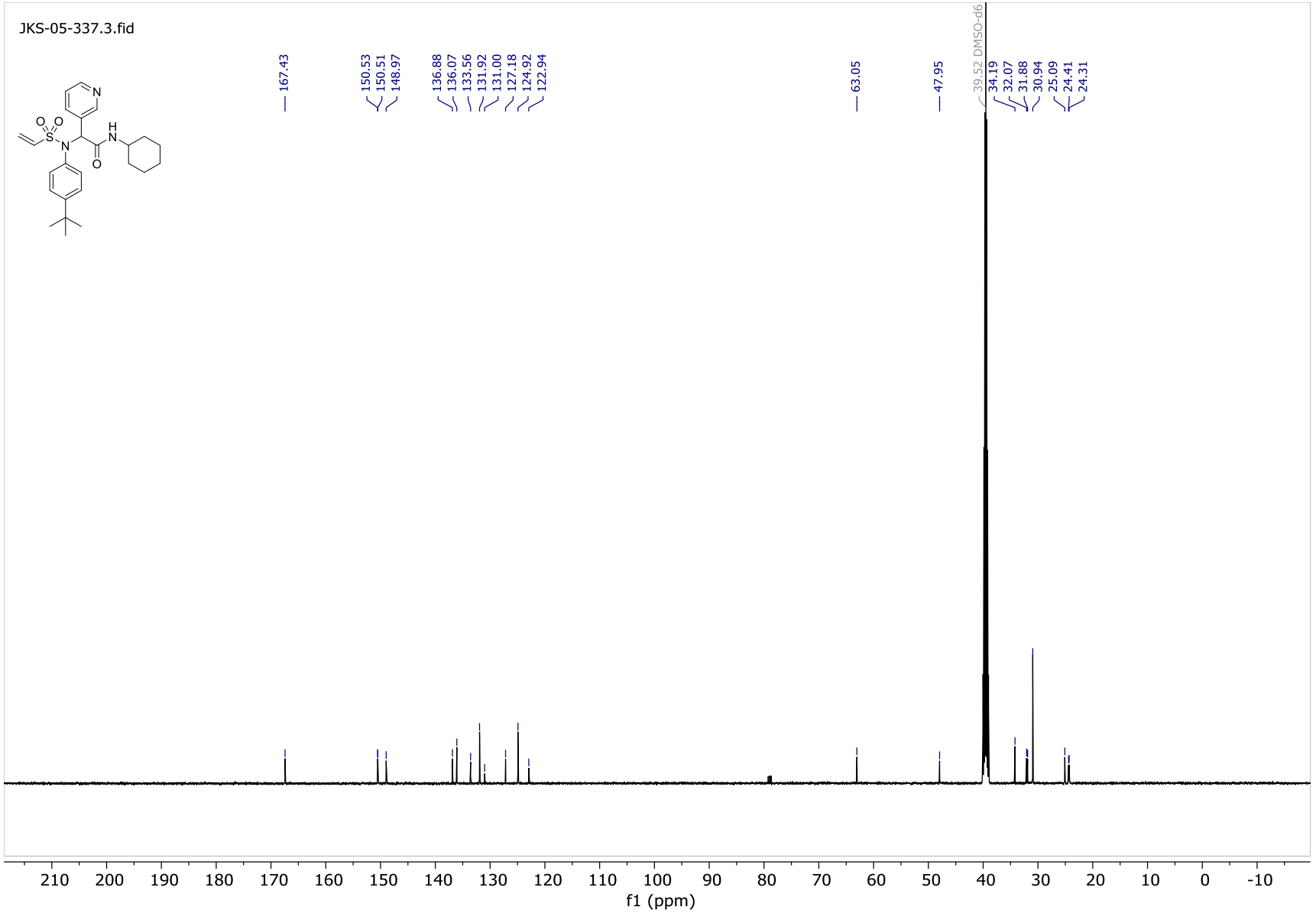
80. Compound ***13q*** *^{13}C NMR*



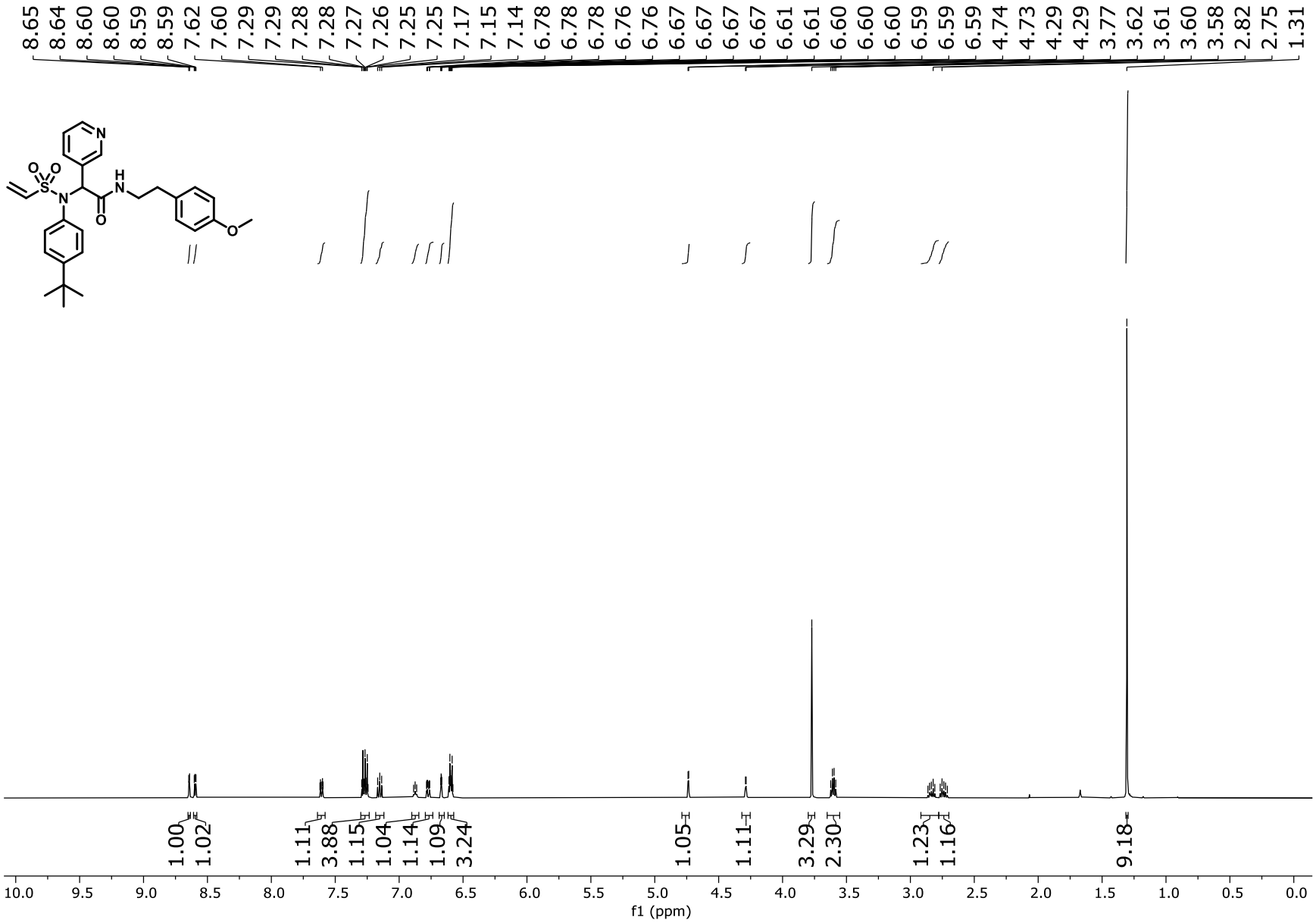
*81. Compound **14a** ^{1}H NMR*



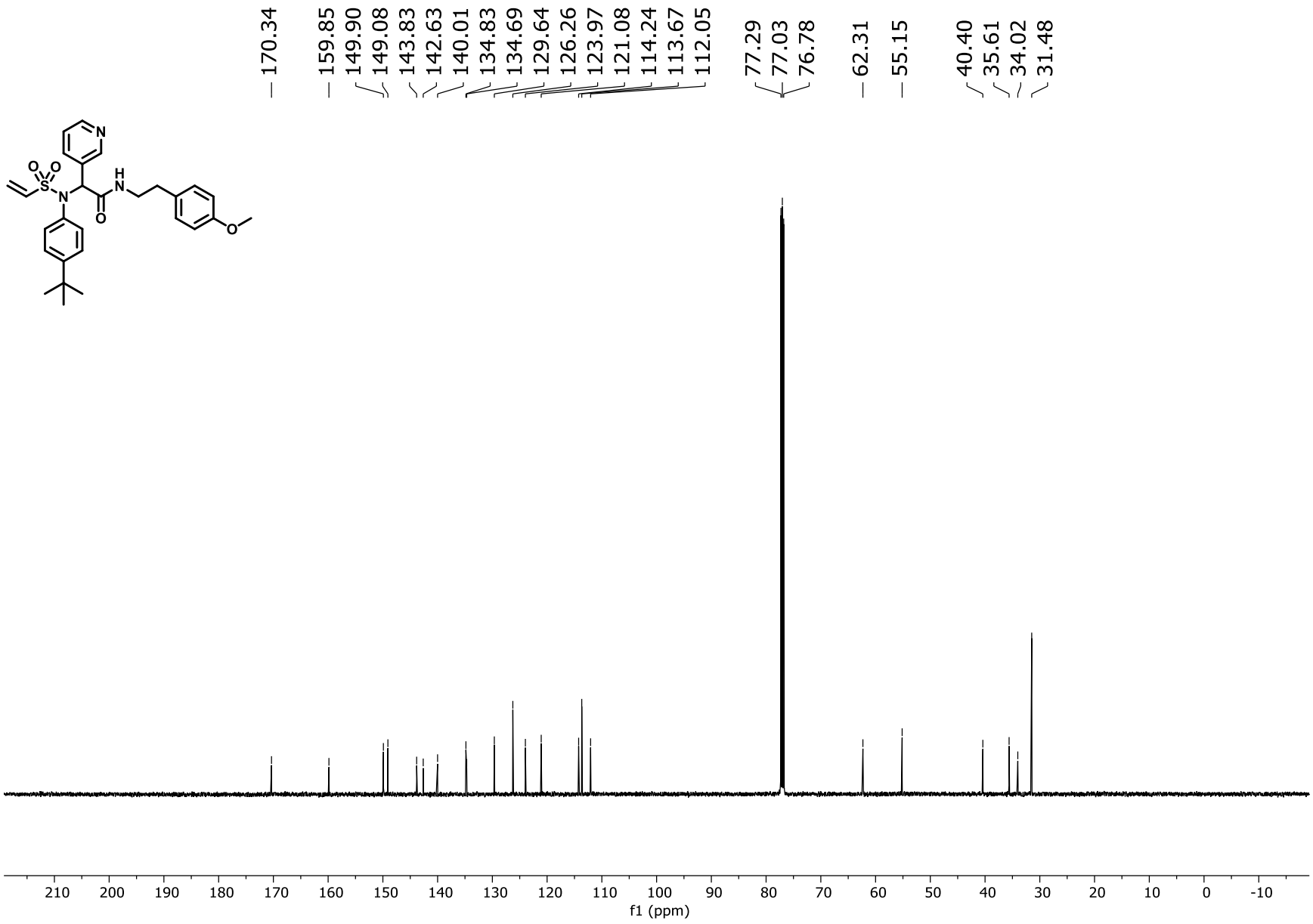
*82. Compound **14a** ^{13}C NMR*



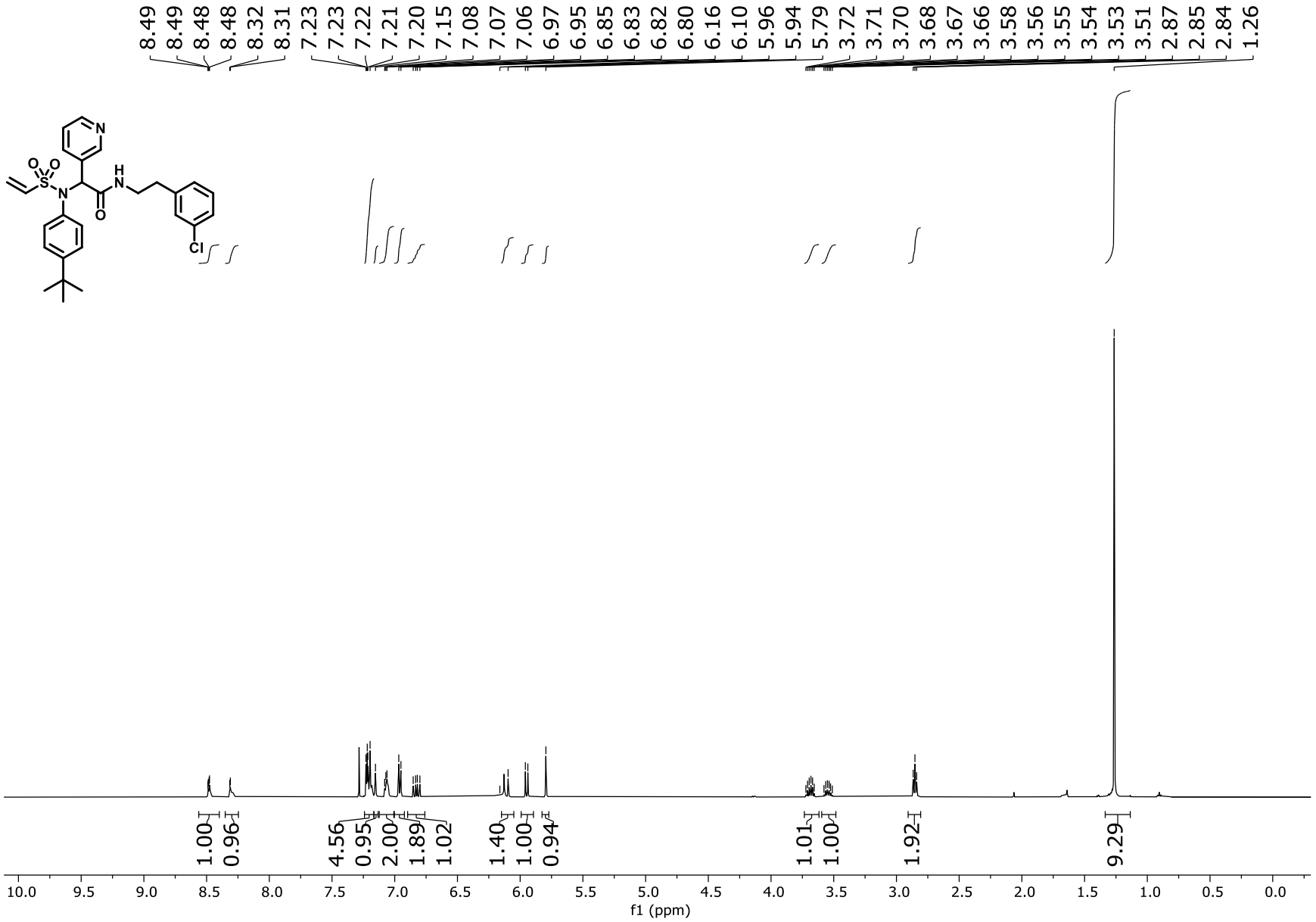
*83. Compound **14b** ^{1}H NMR*



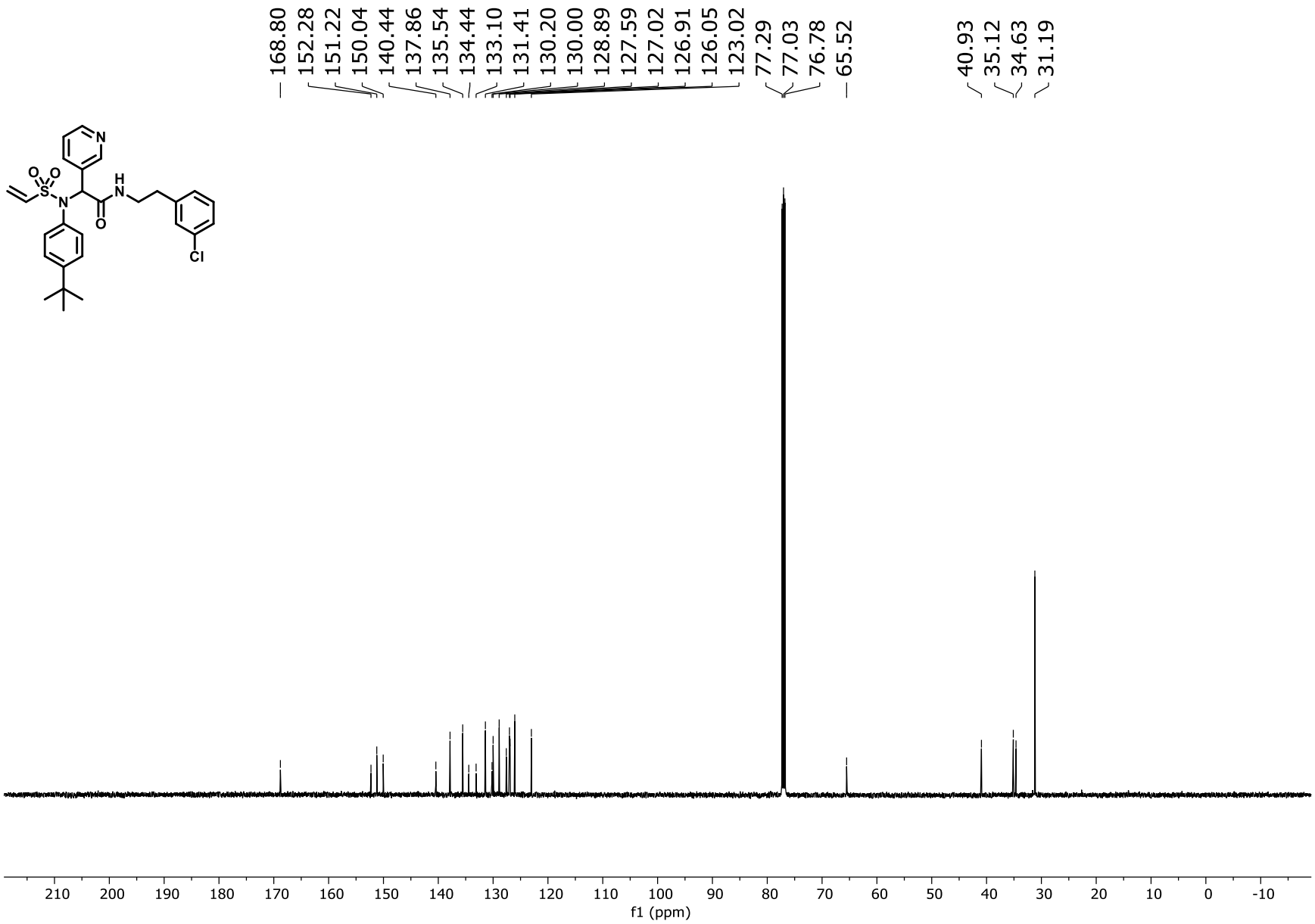
*84. Compound **14b** ^{13}C NMR*



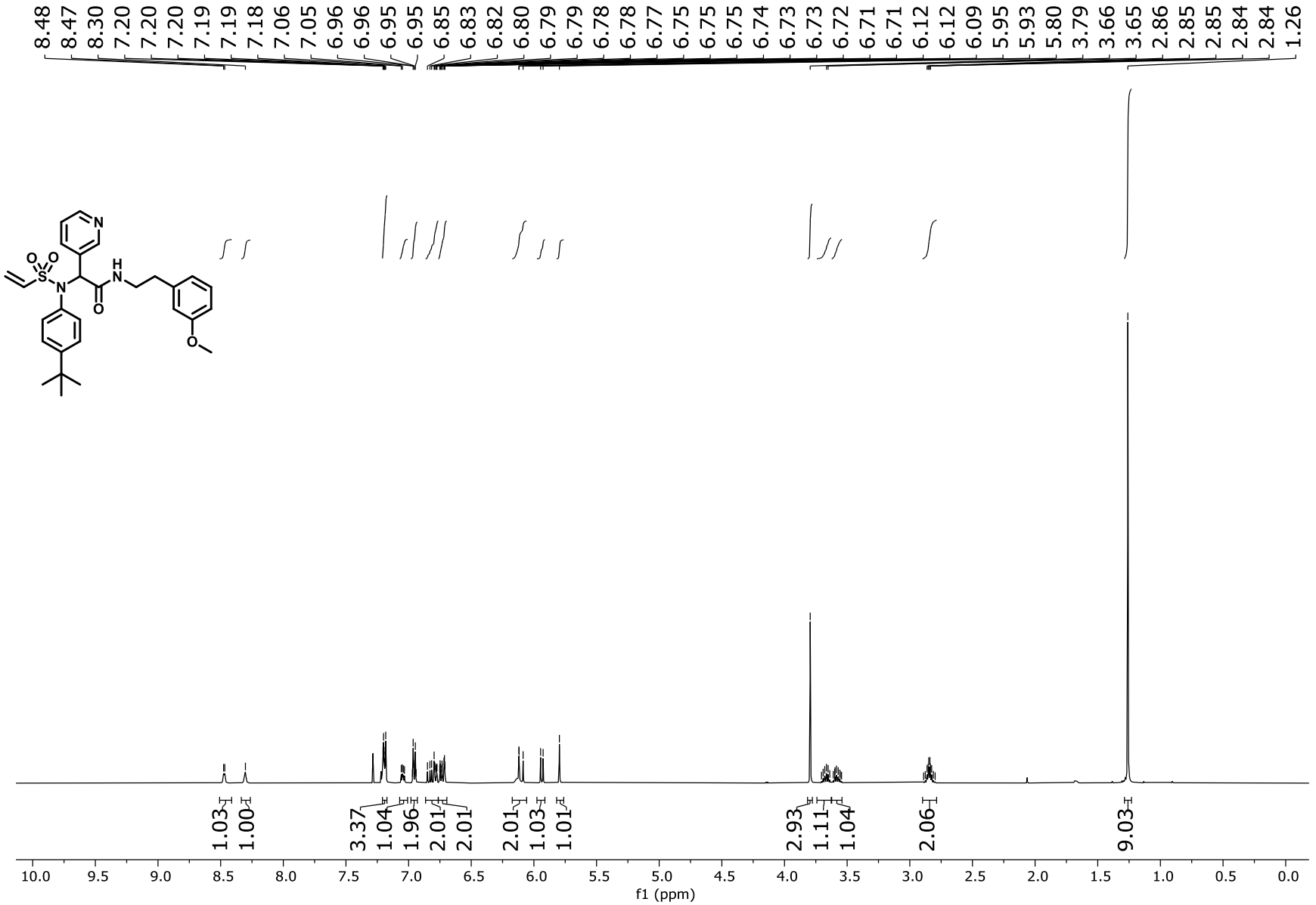
*85. Compound **14c** ^{1}H NMR*



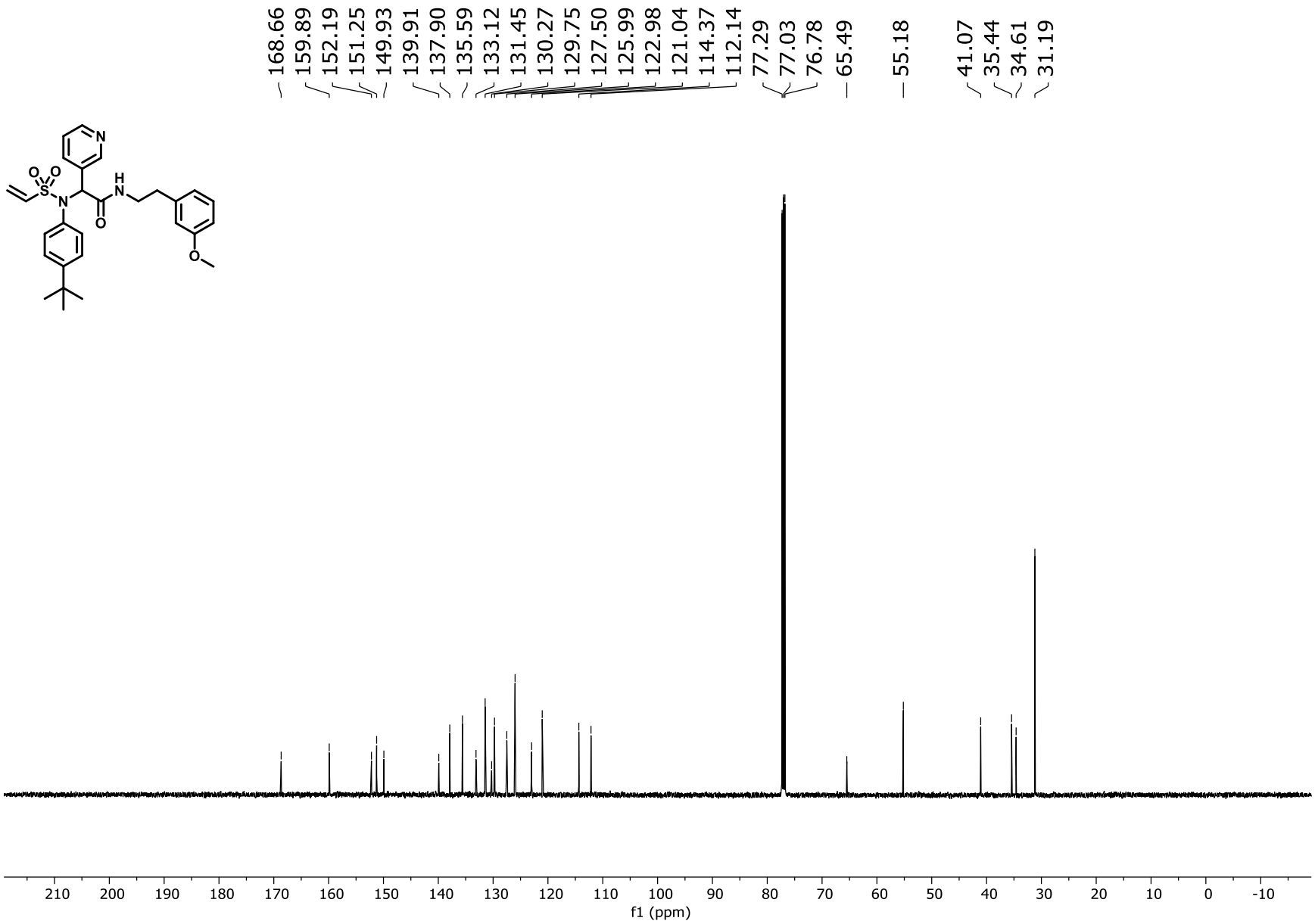
*86. Compound **14c** ^{13}C NMR*



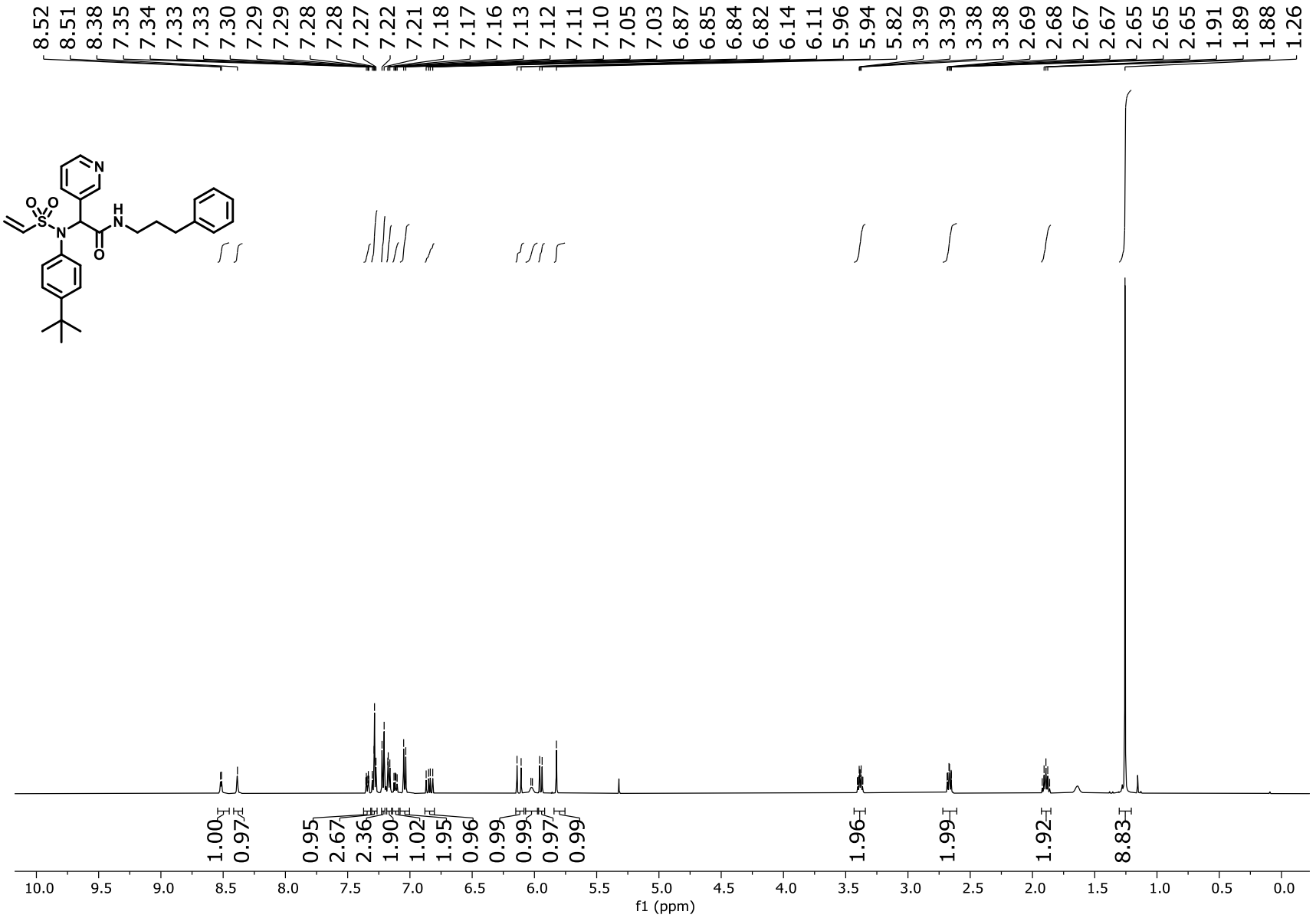
*87. Compound **14d** ^{1}H NMR*



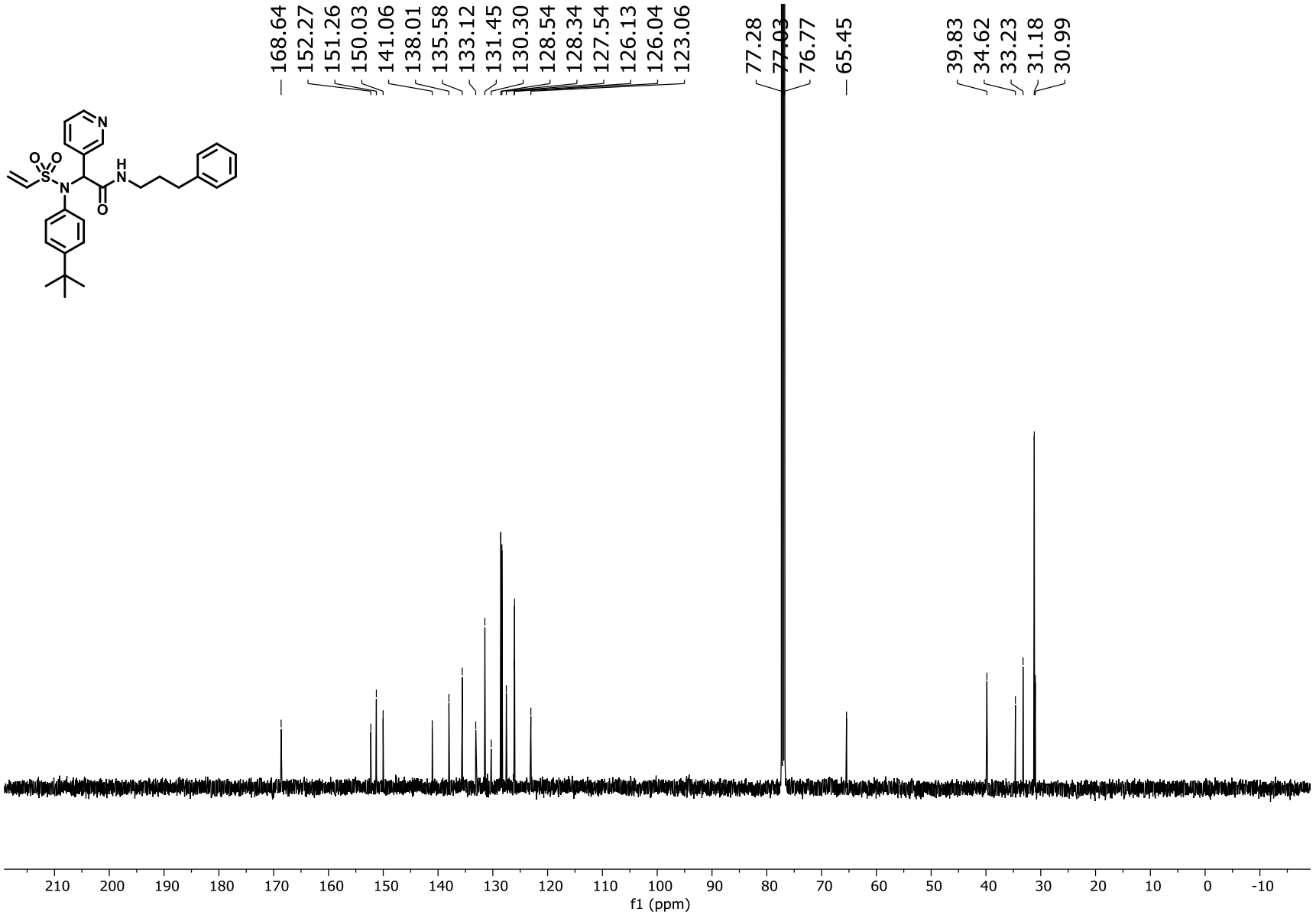
*88. Compound **14d** ^{13}C NMR*



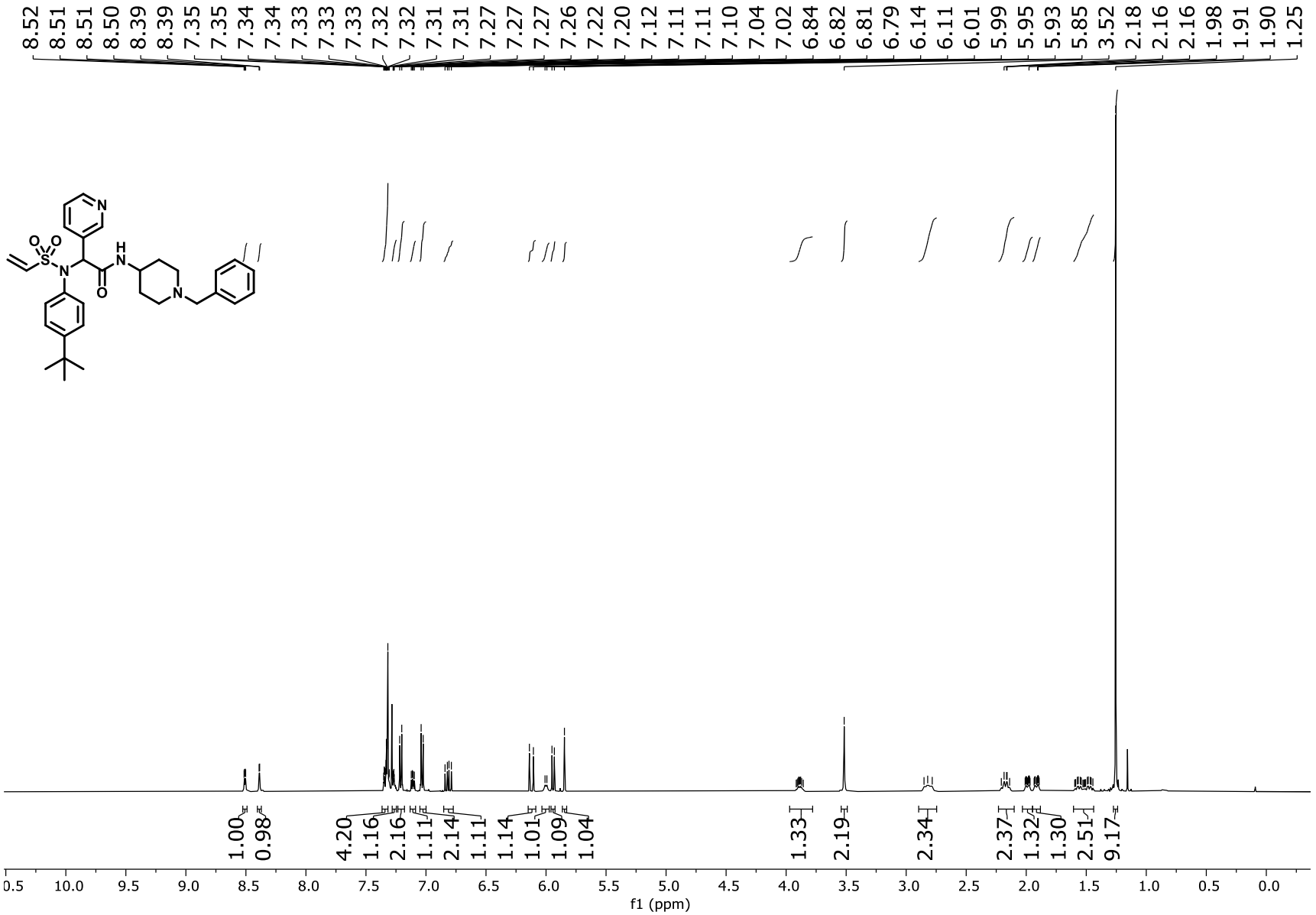
*89. Compound **14e** 1H NMR*



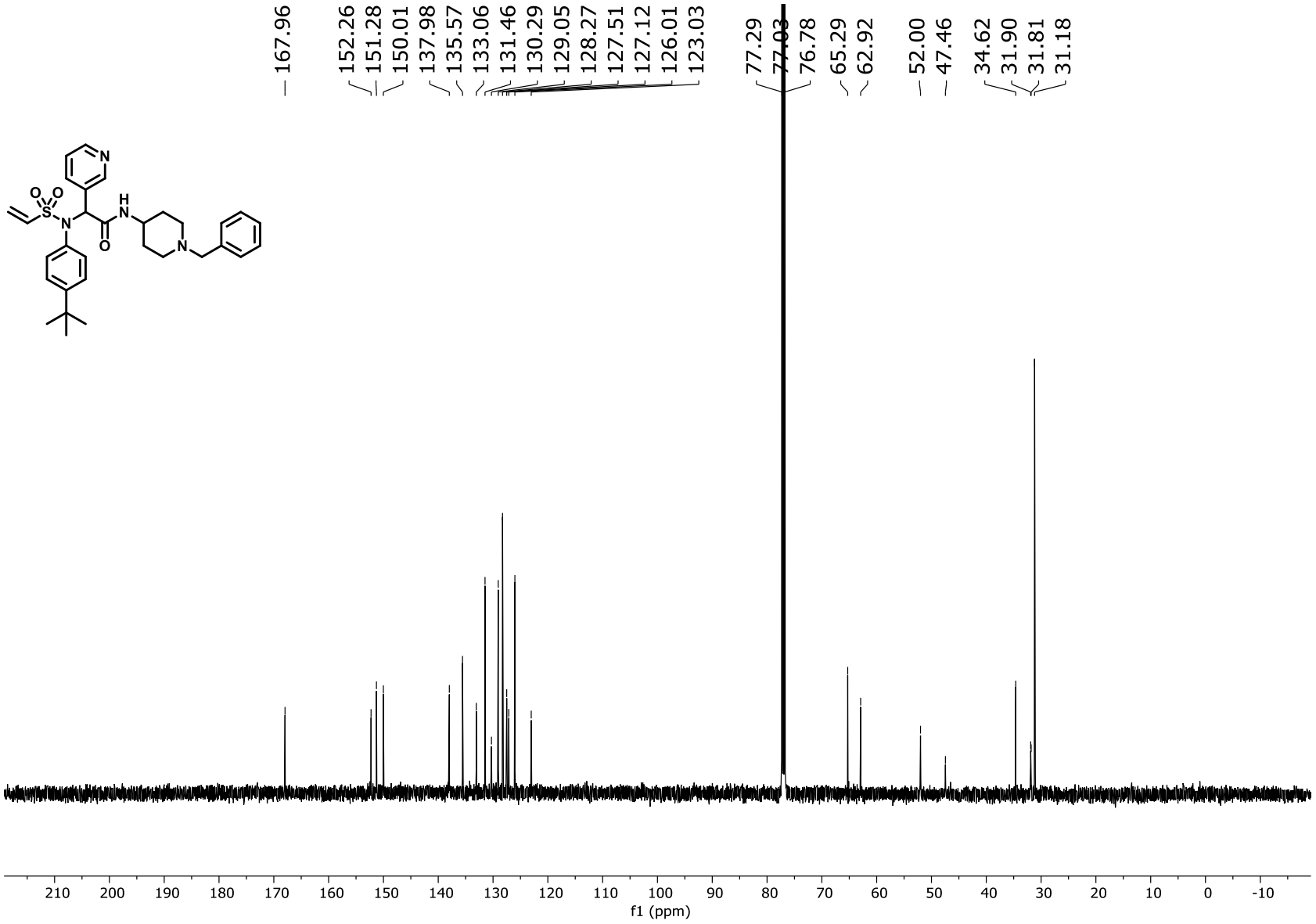
*90. Compound **14e** 13C NMR*



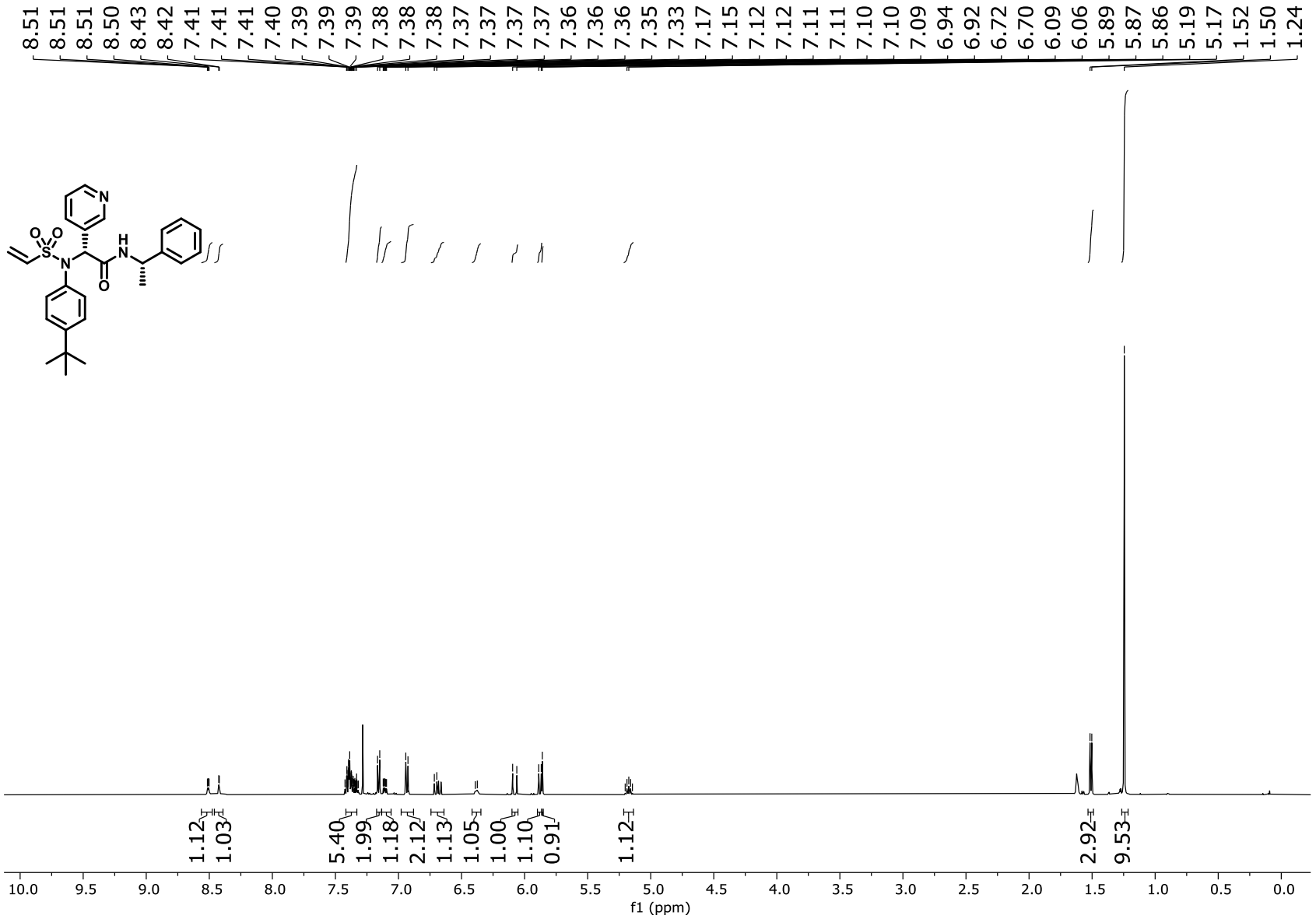
*91. Compound **14f** 1H NMR*



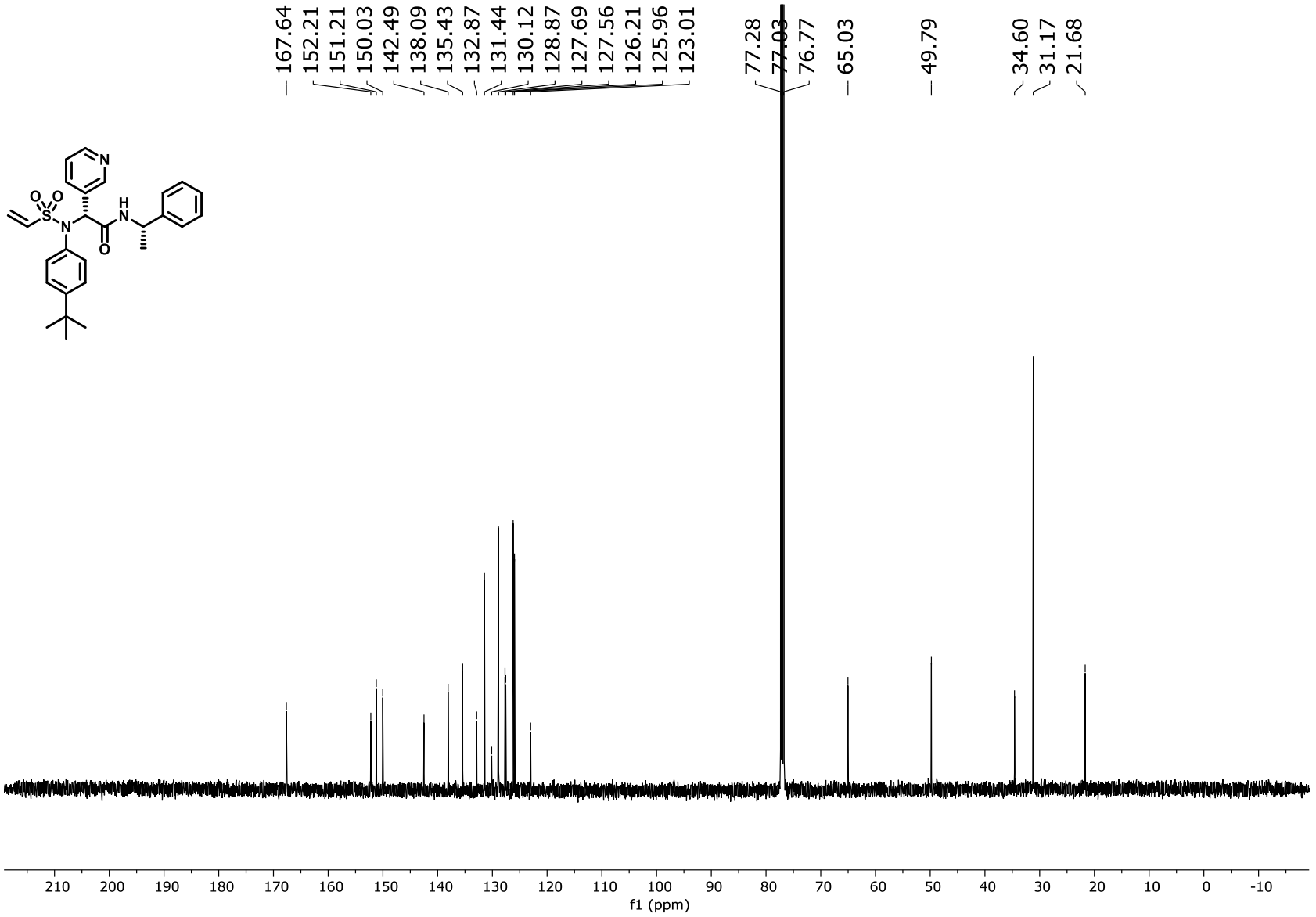
*92. Compound **14f** 13C NMR*



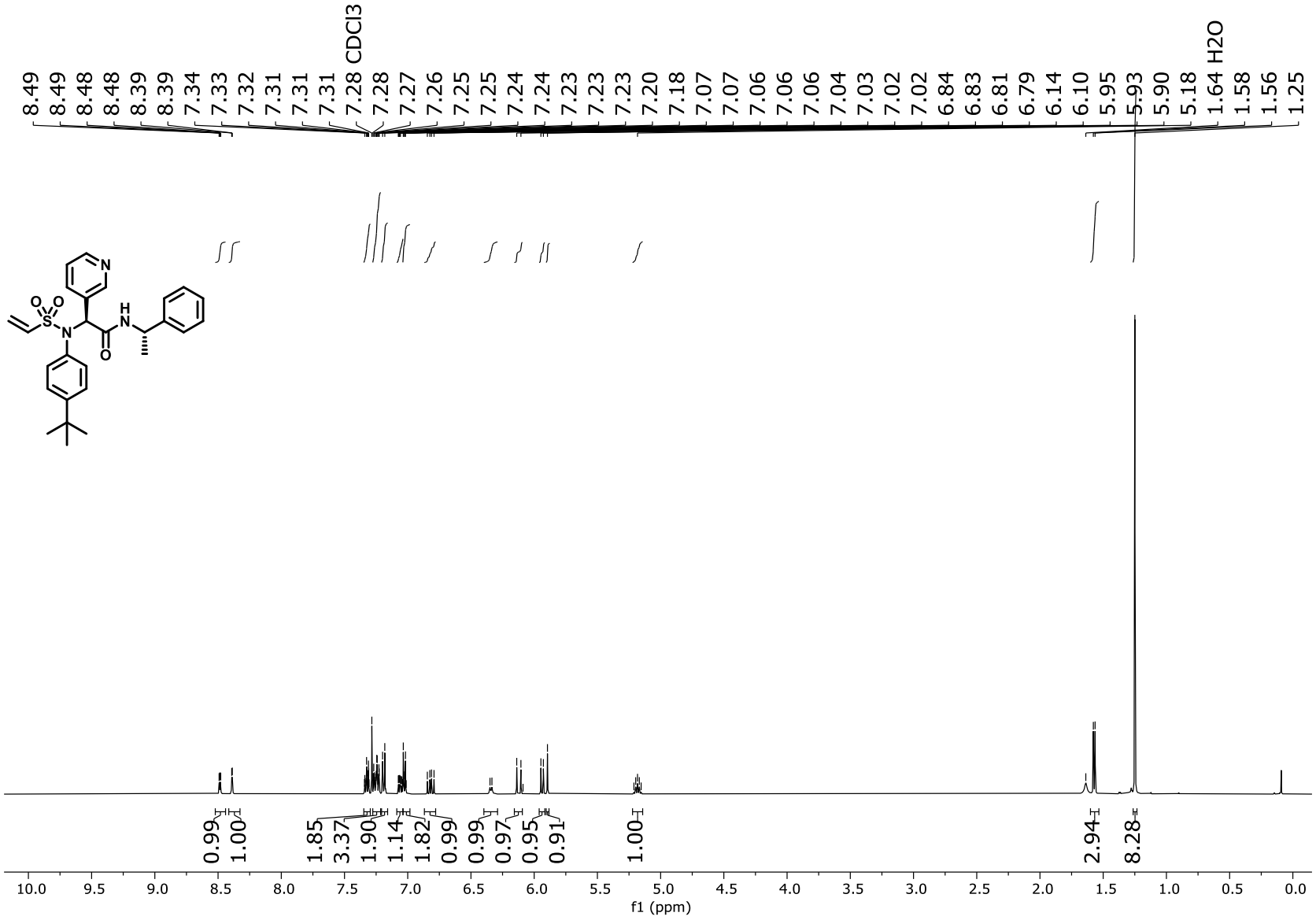
*93. Compound **14g** ^{1}H NMR*



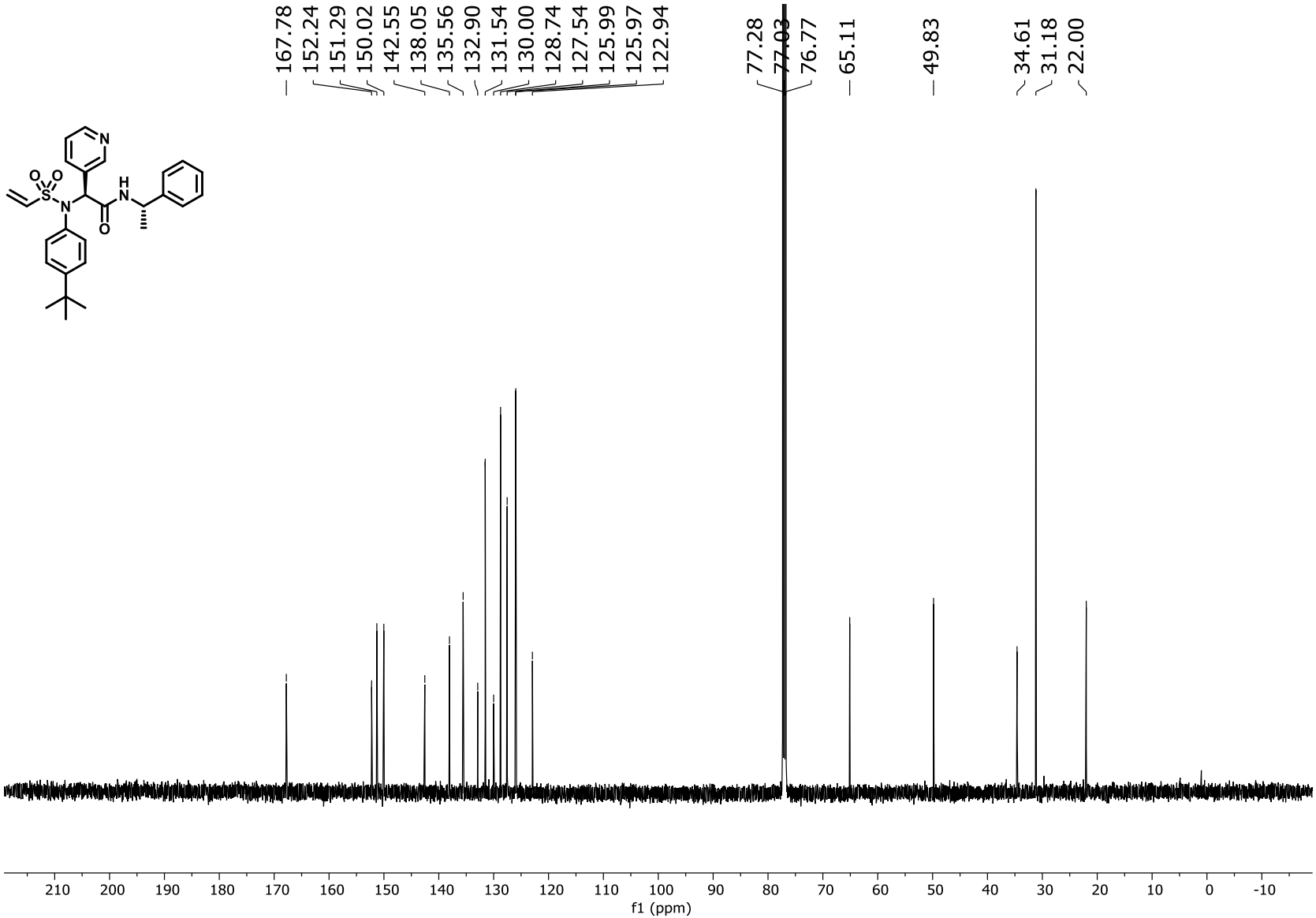
*94. Compound **14g** ^{13}C NMR*



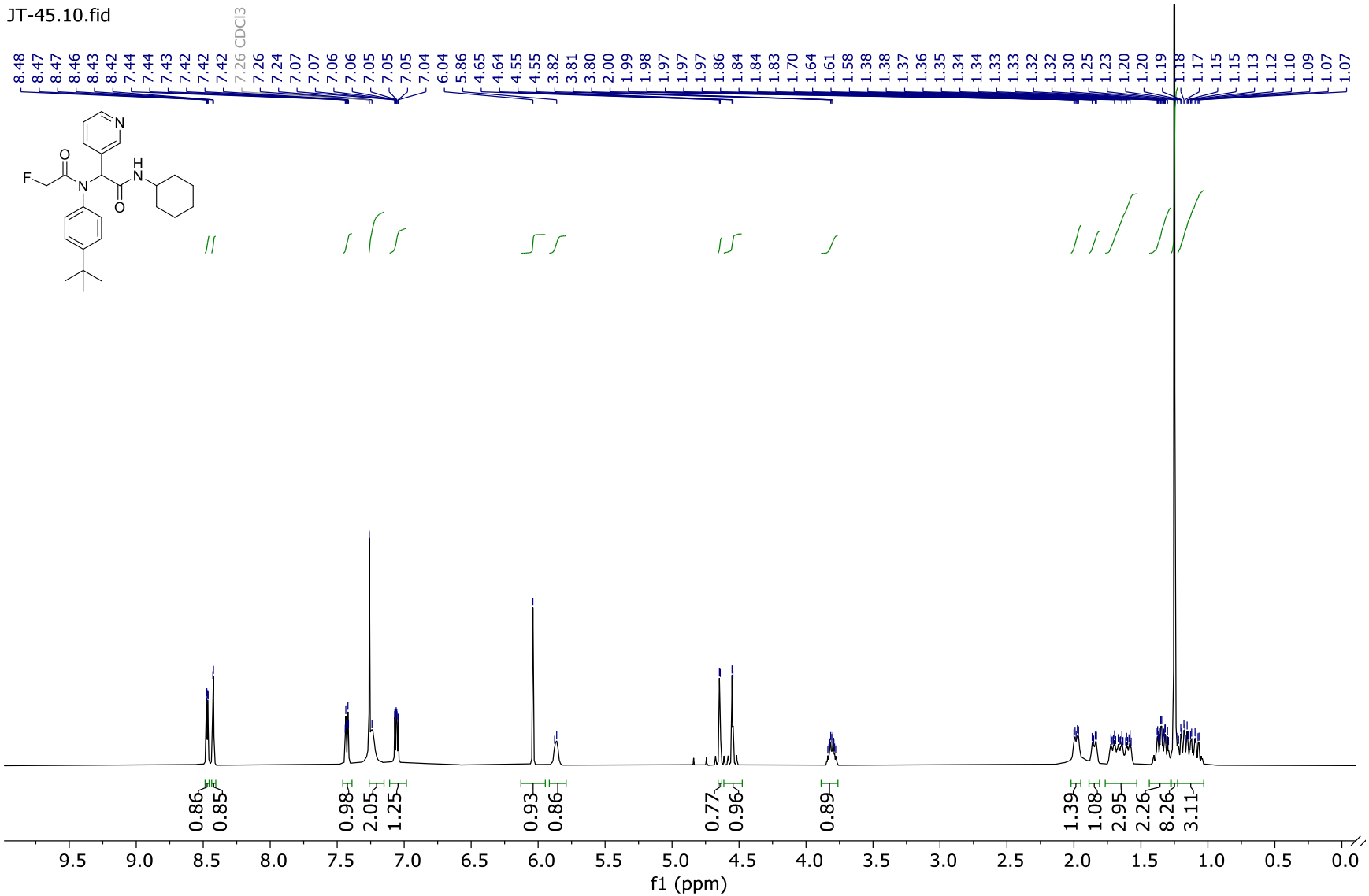
*95. Compound **14h** ^{1}H NMR*



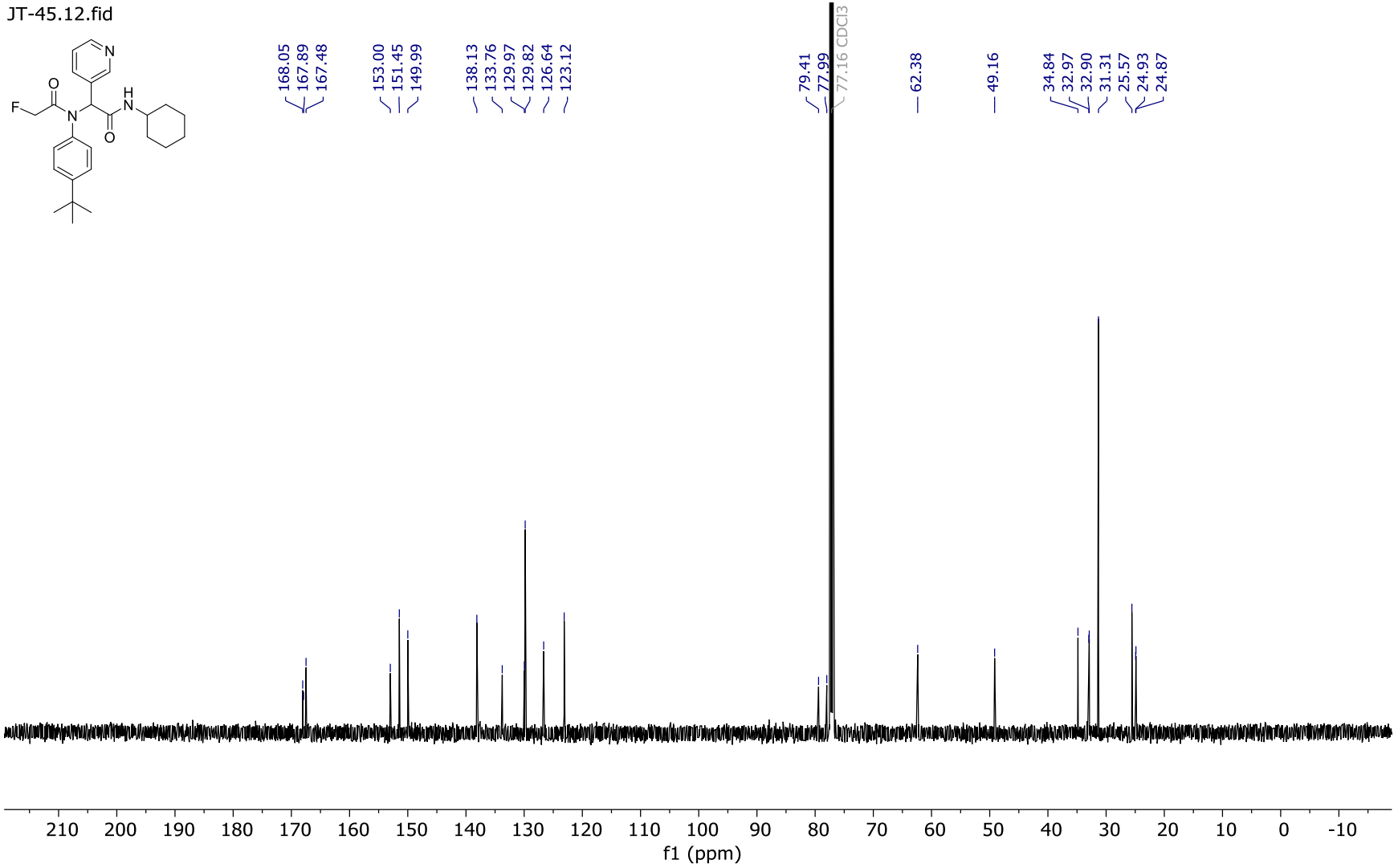
*96. Compound **14h** ^{13}C NMR*



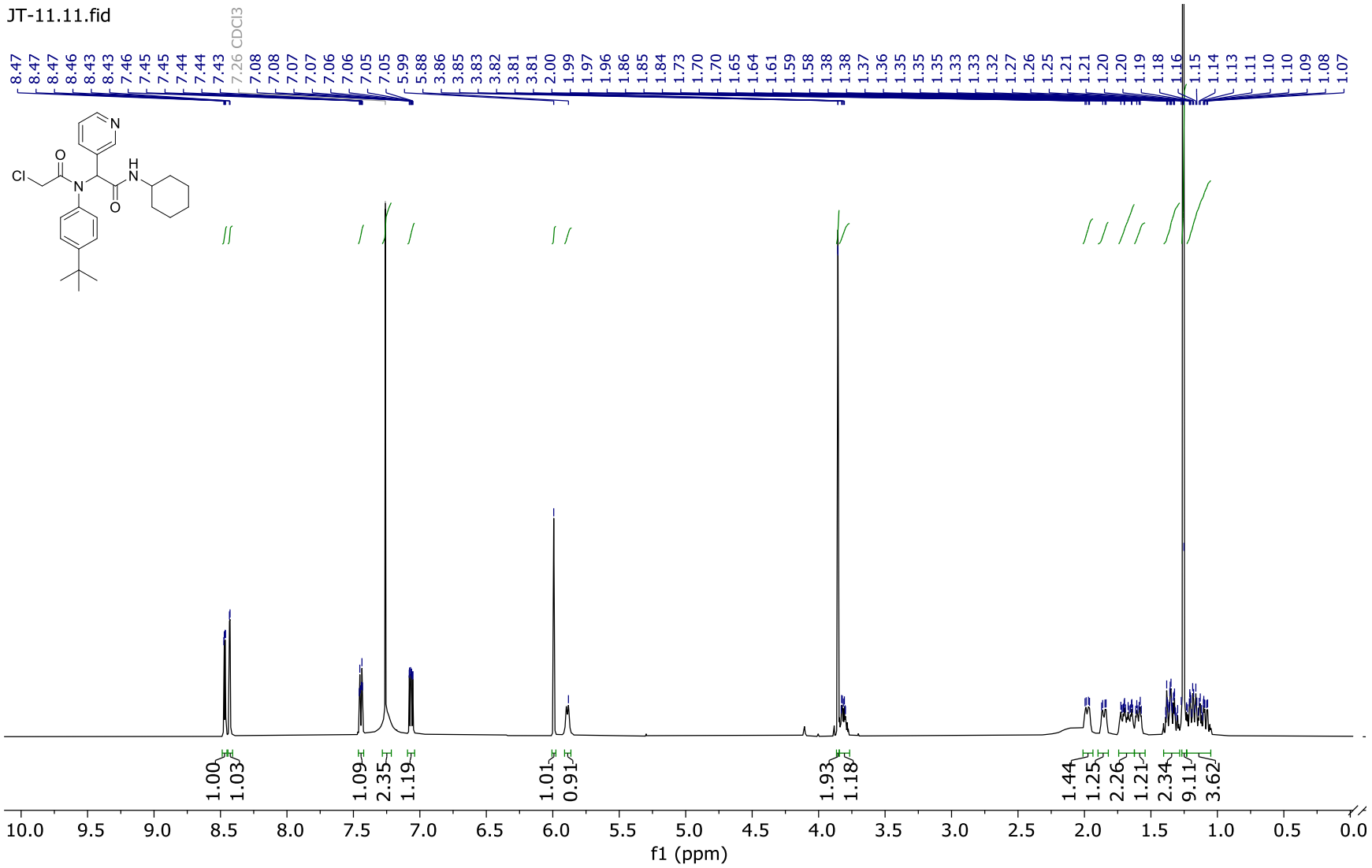
*97. Compound **15a** ^{1}H NMR*



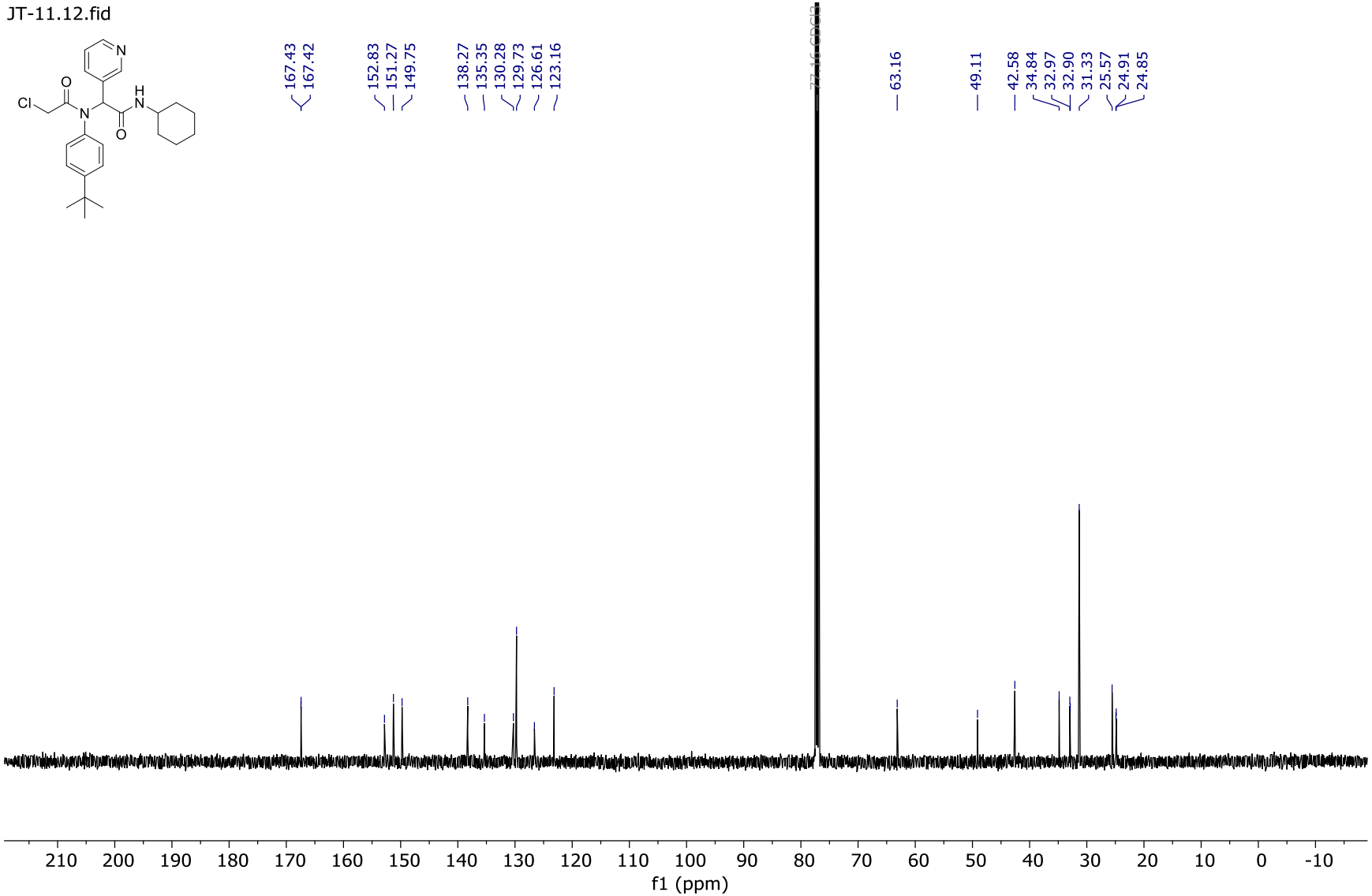
*98. Compound **15a** ^{13}C NMR*



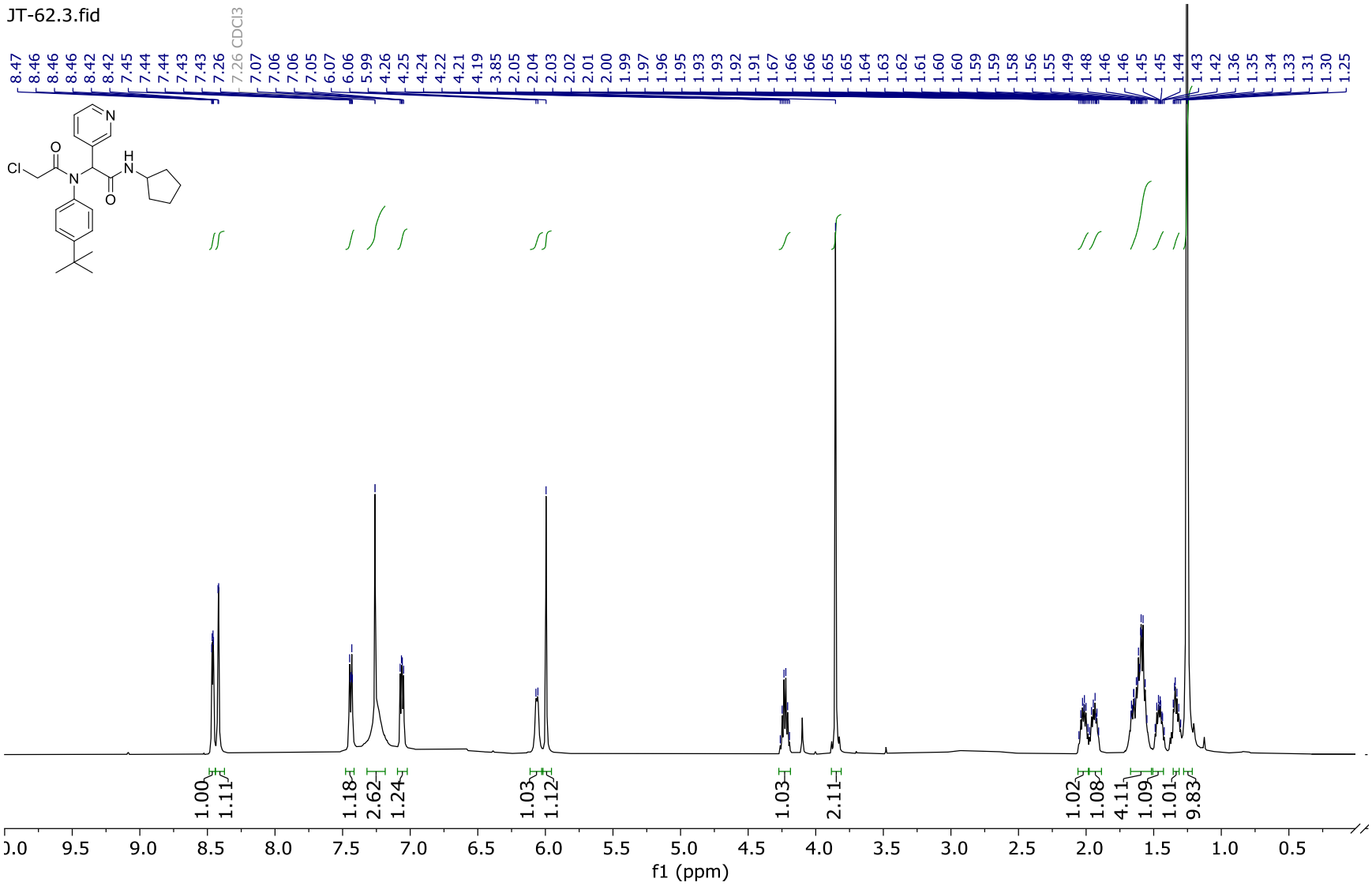
*99. Compound **16a** ^{1}H NMR*



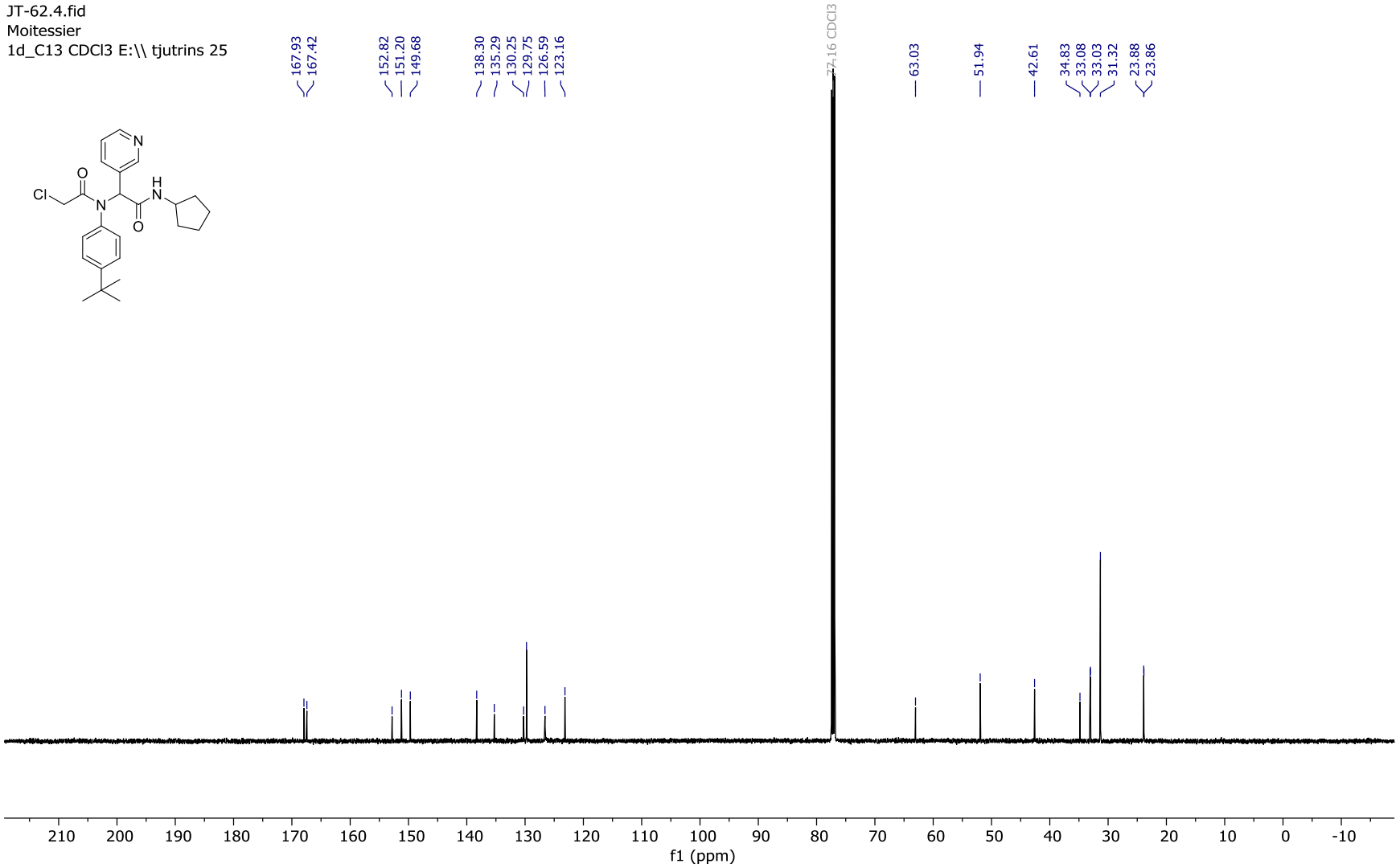
*100. Compound **16a** ^{13}C NMR*



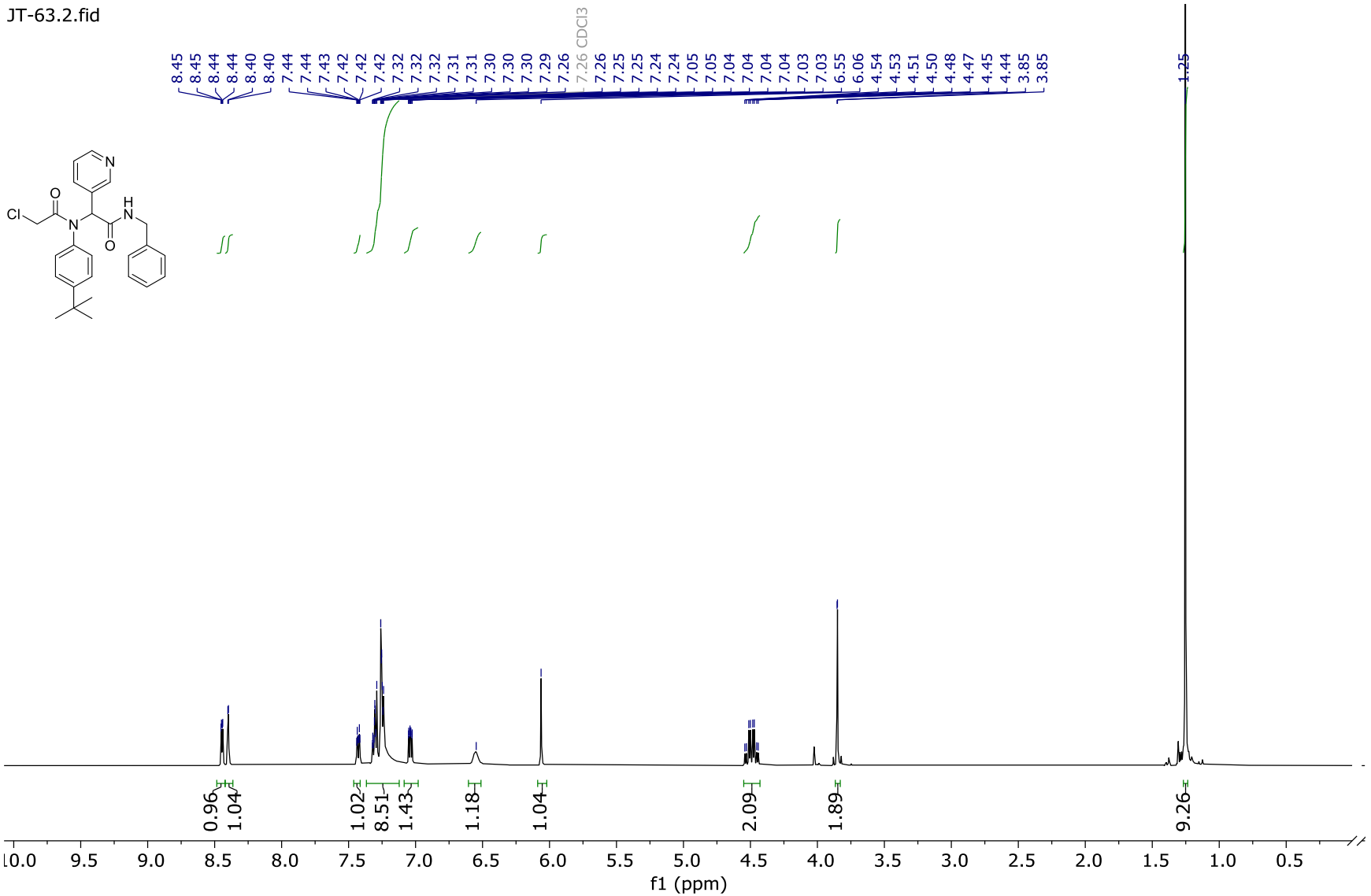
*101. Compound **16b** ^{1}H NMR*



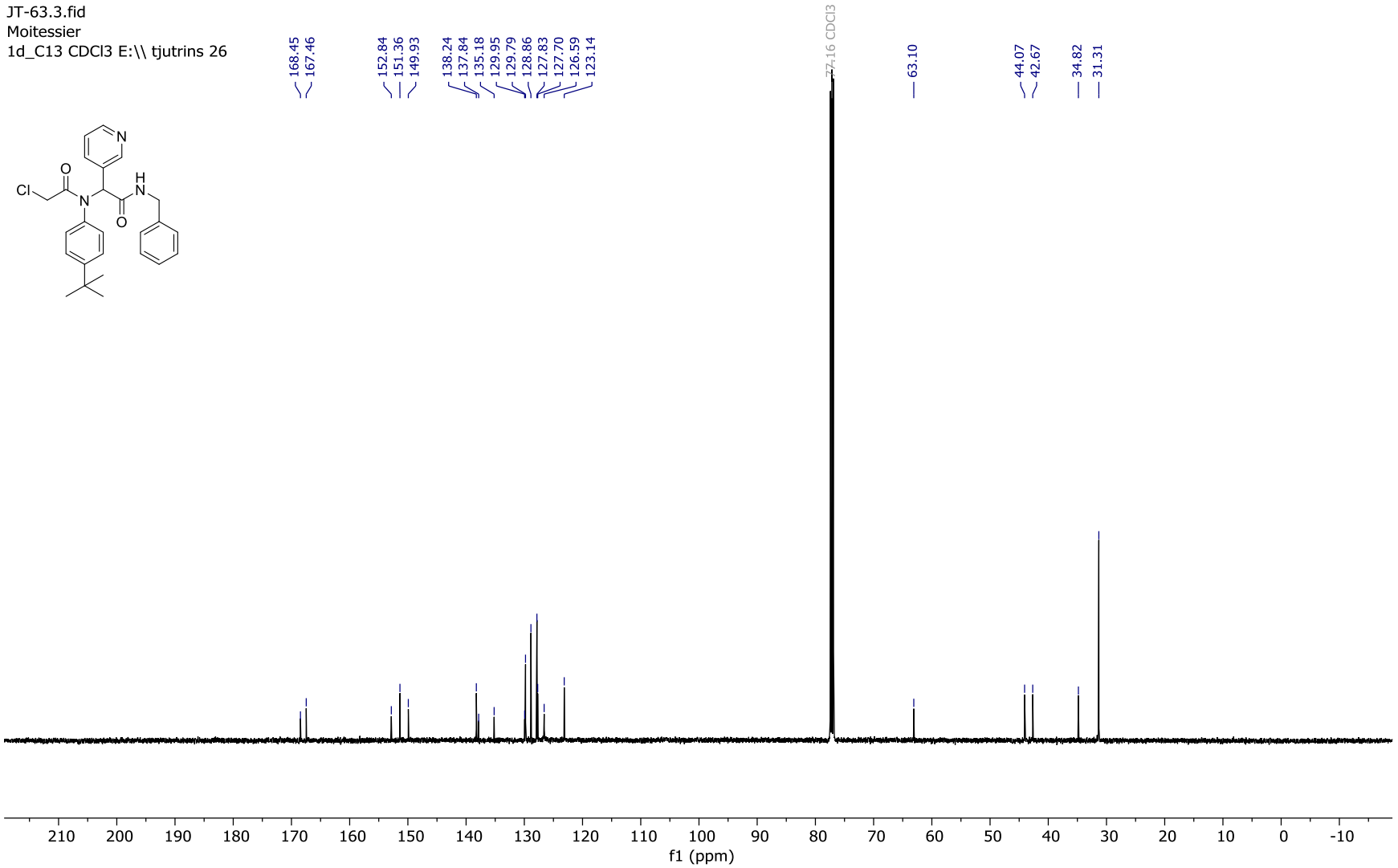
*102. Compound **16b** ^{13}C NMR*



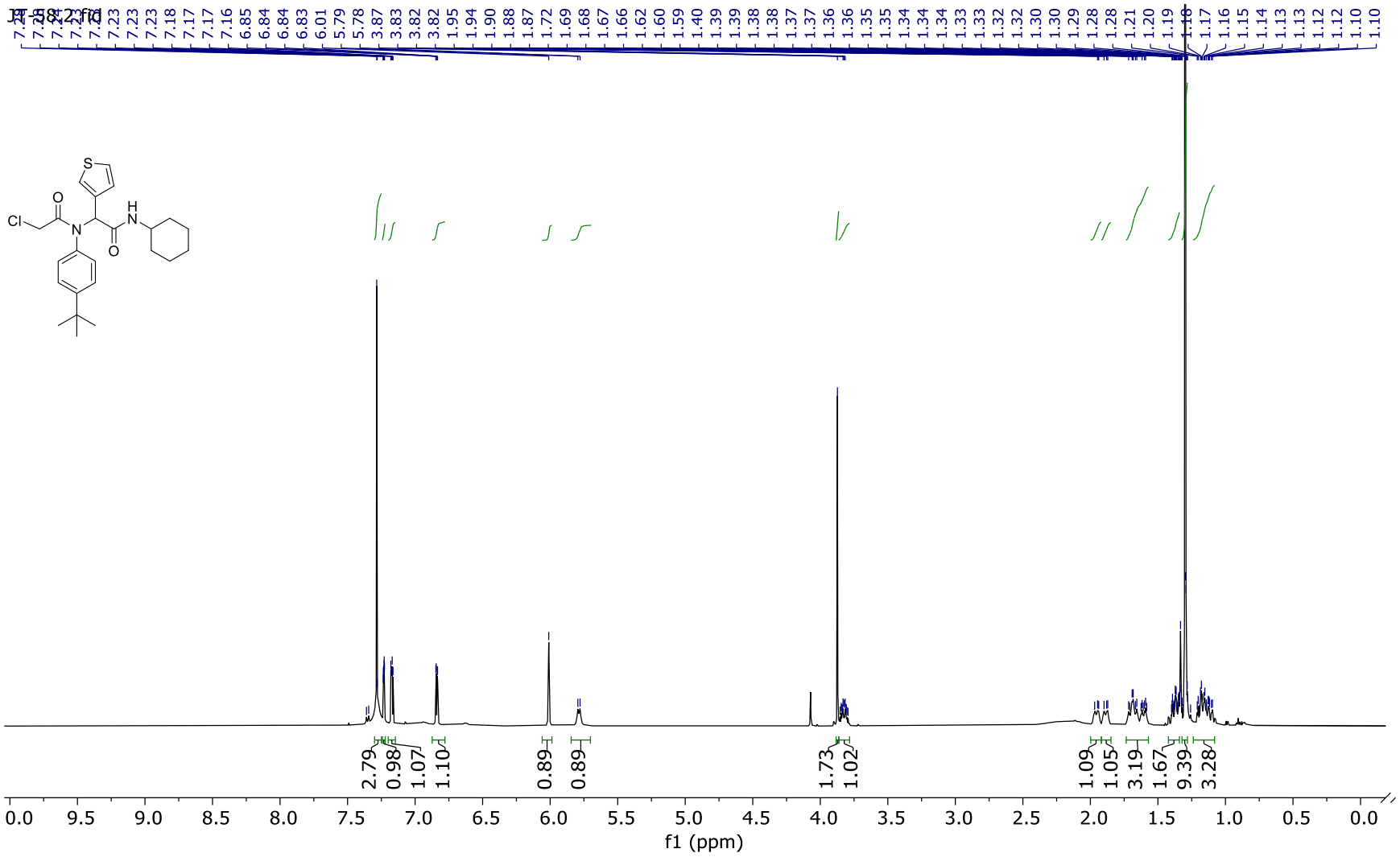
*103. Compound **16c** ^{1}H NMR*



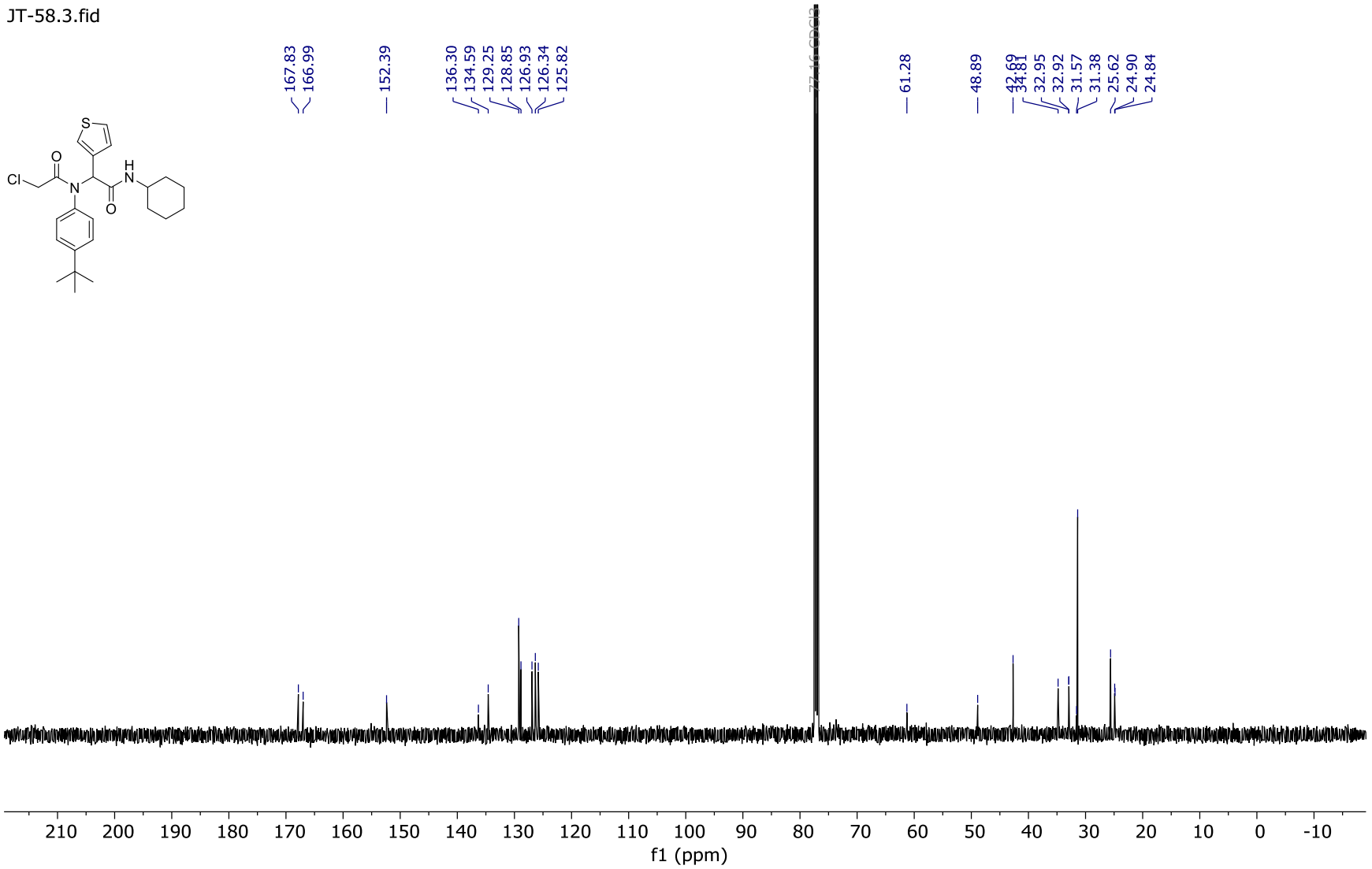
*104. Compound **16c** ^{13}C NMR*



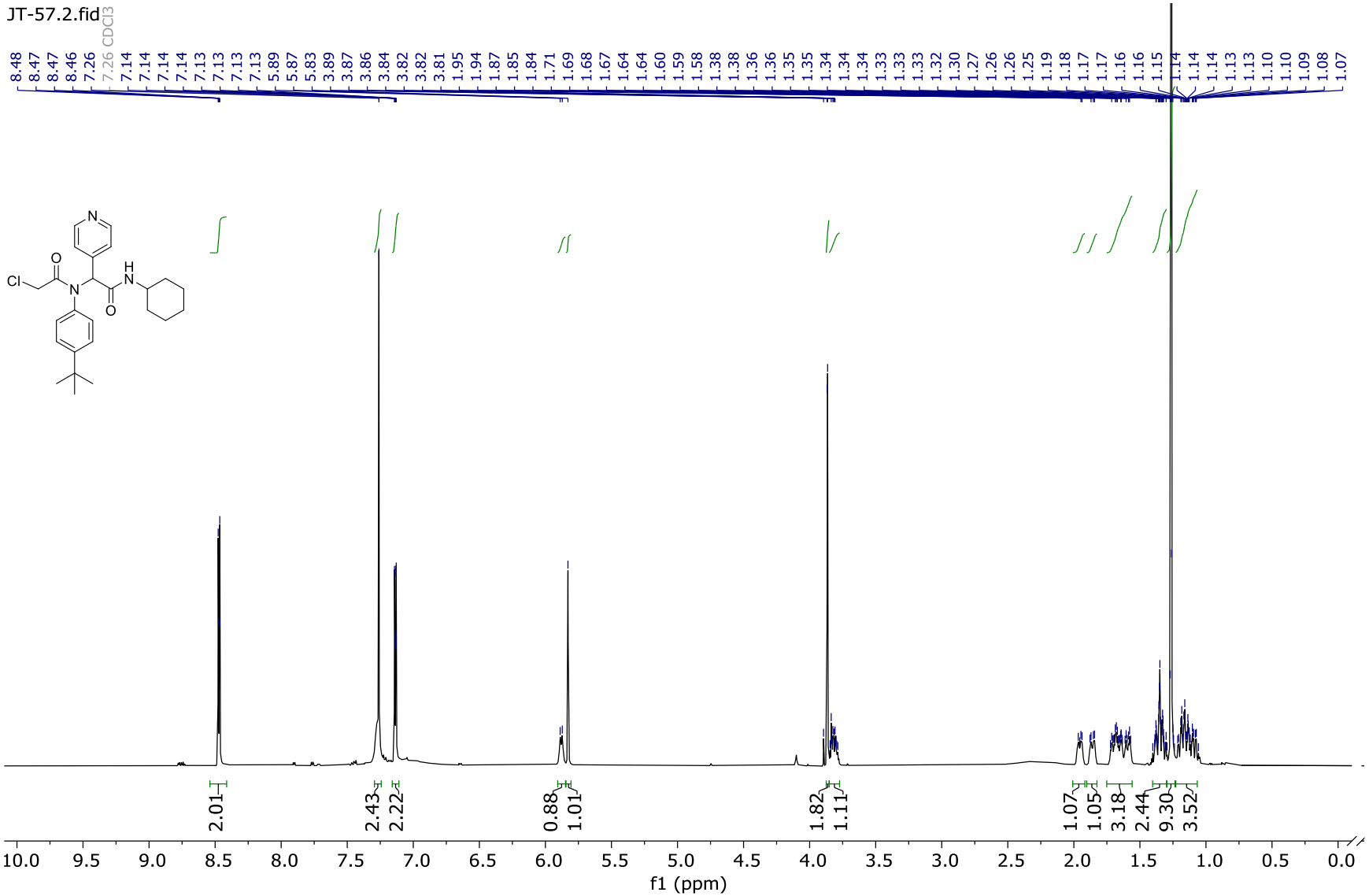
*105. Compound **16d** ^{1}H NMR*



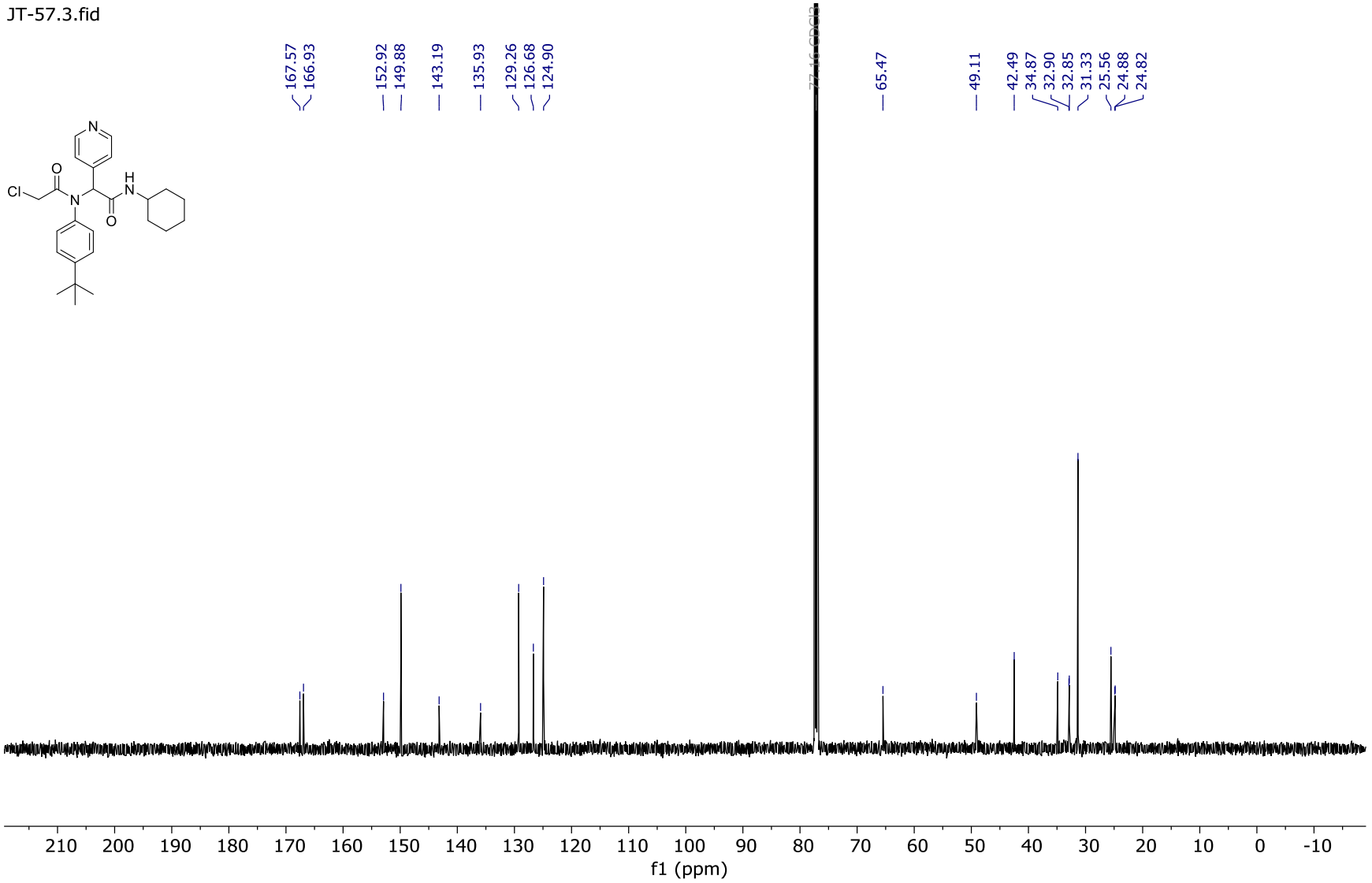
*106. Compound **16d** ^{13}C NMR*



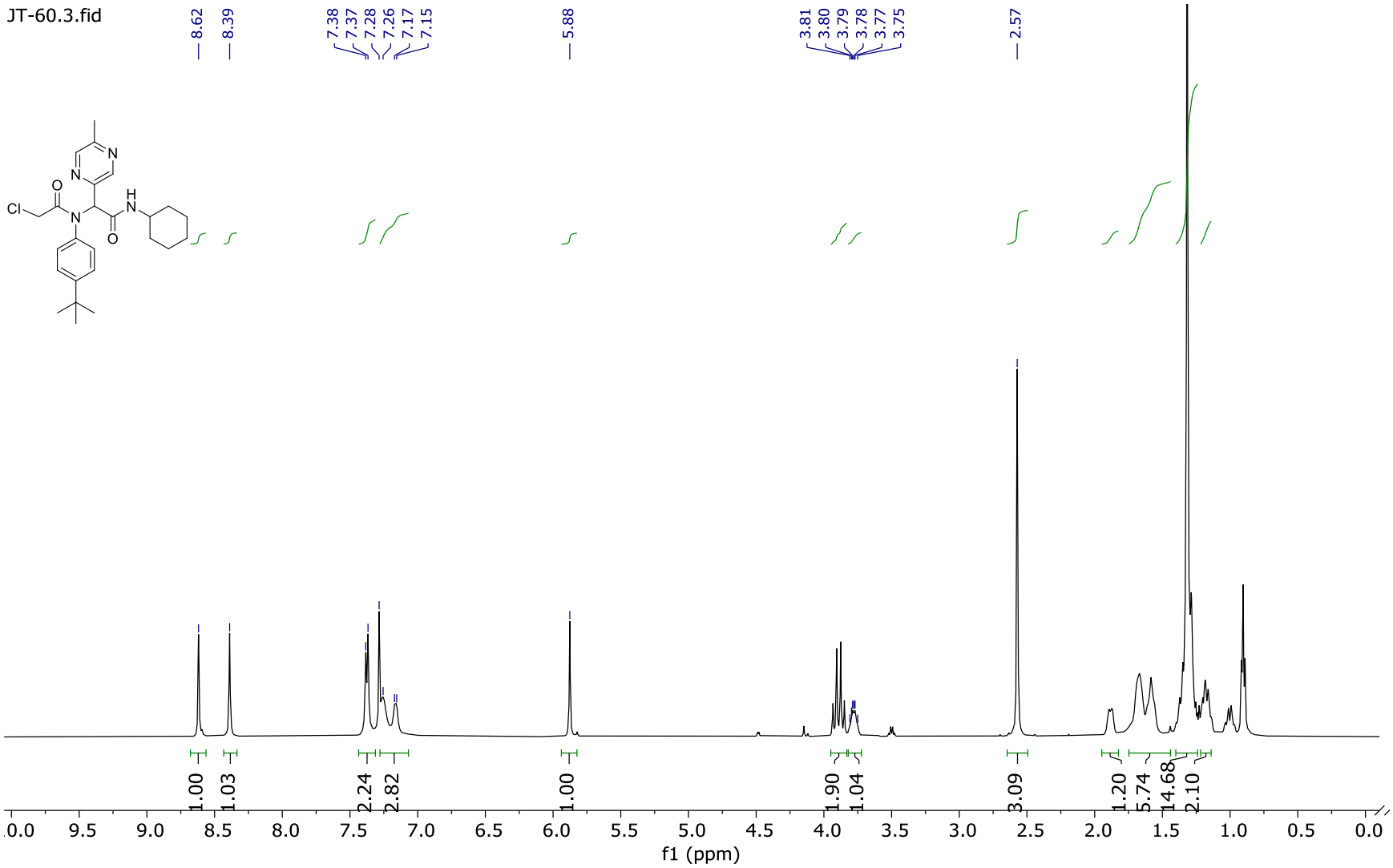
*107. Compound **16e** ^{1}H NMR*



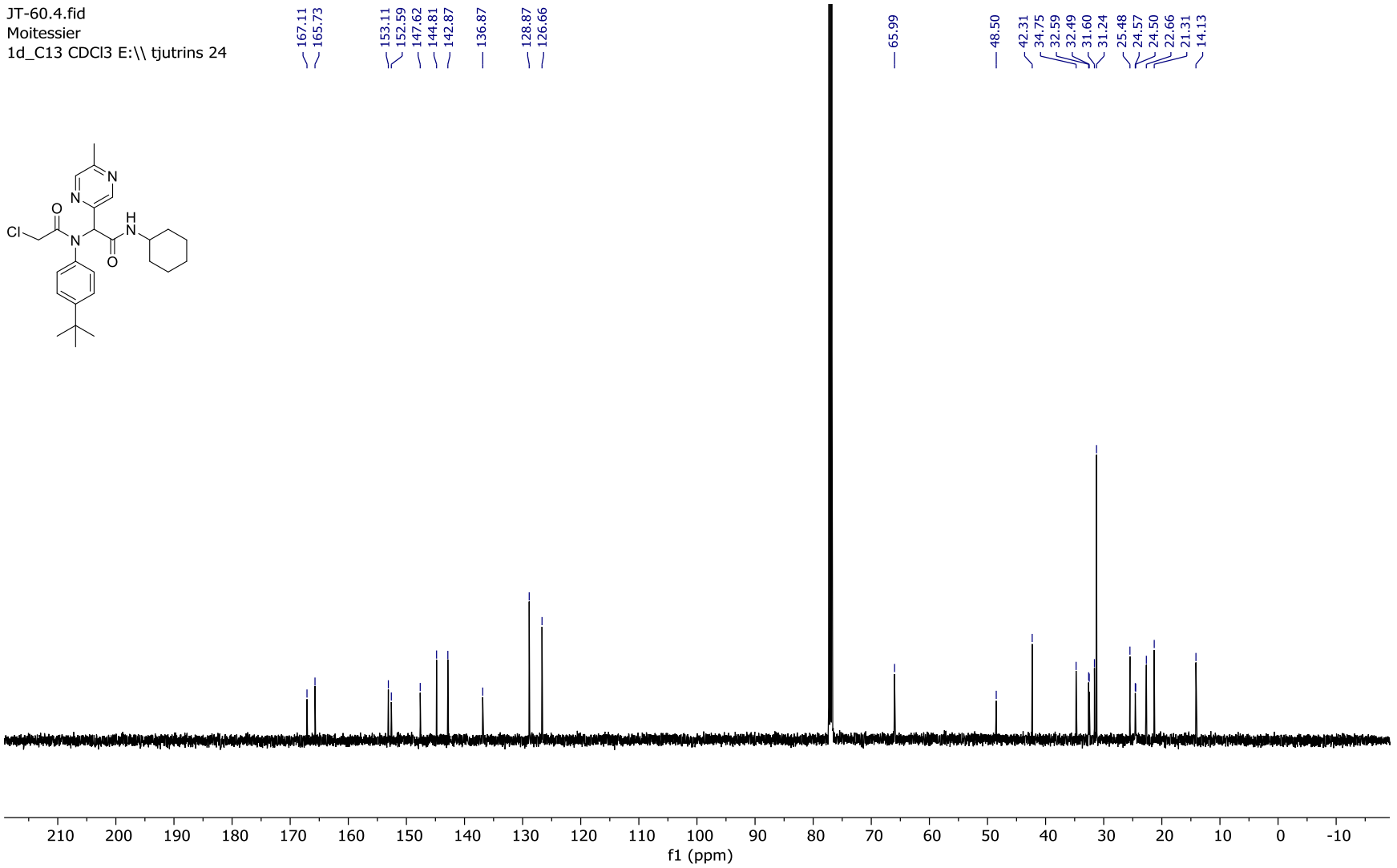
*58. Compound **16e** ^{3}C NMR*



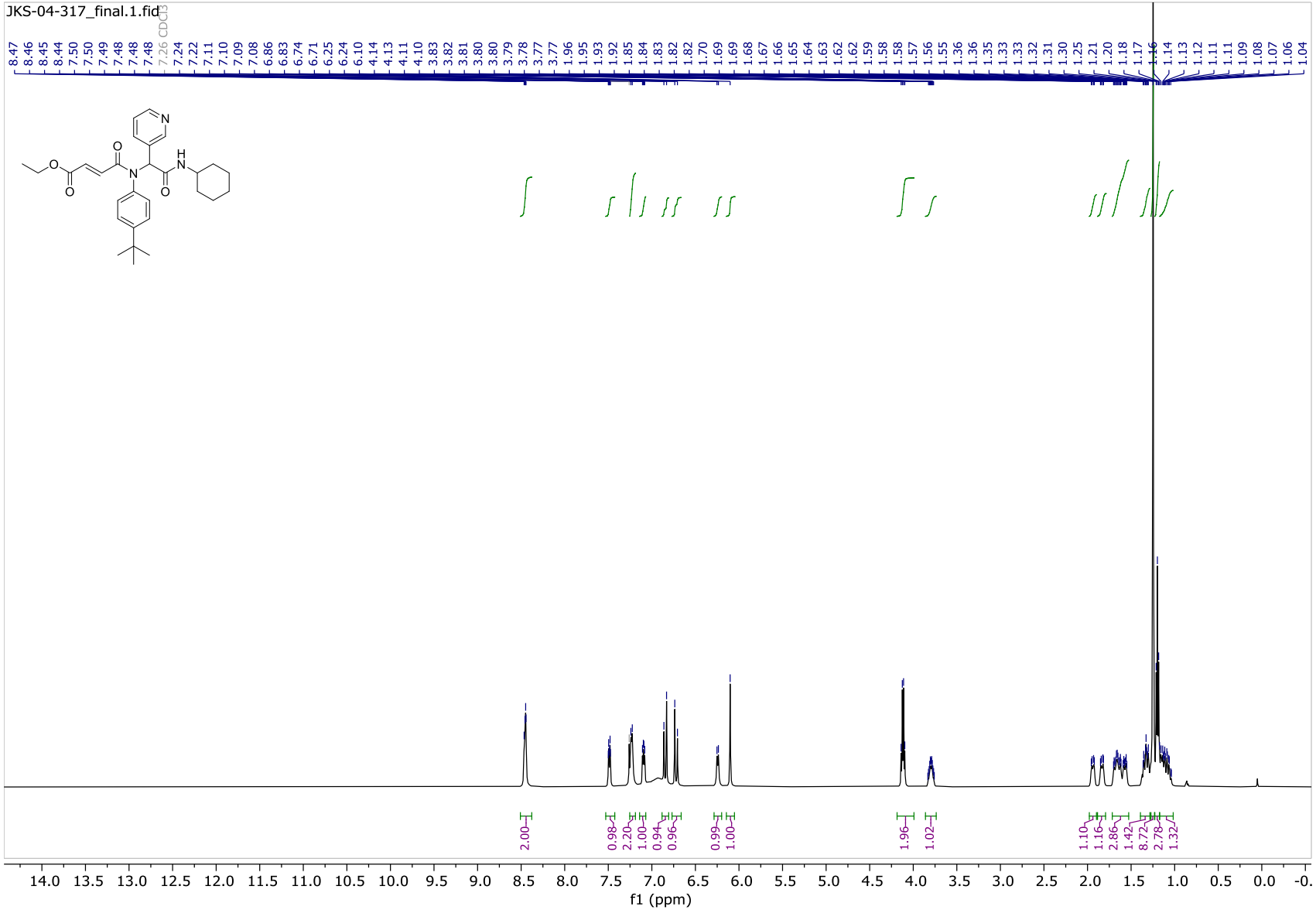
*59. Compound **16f** ^{1}H NMR*



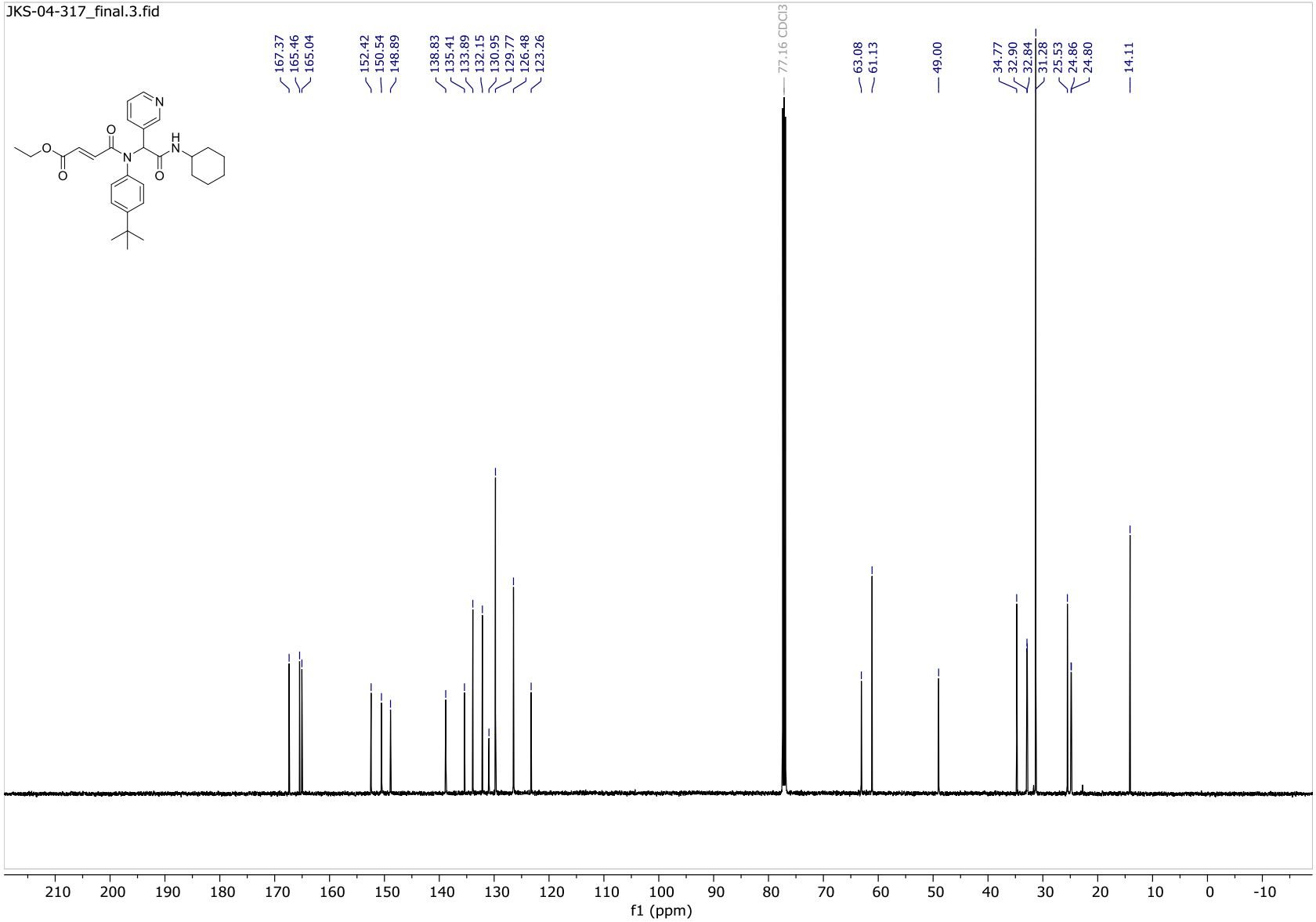
*60. Compound **16f** ^{13}C NMR*



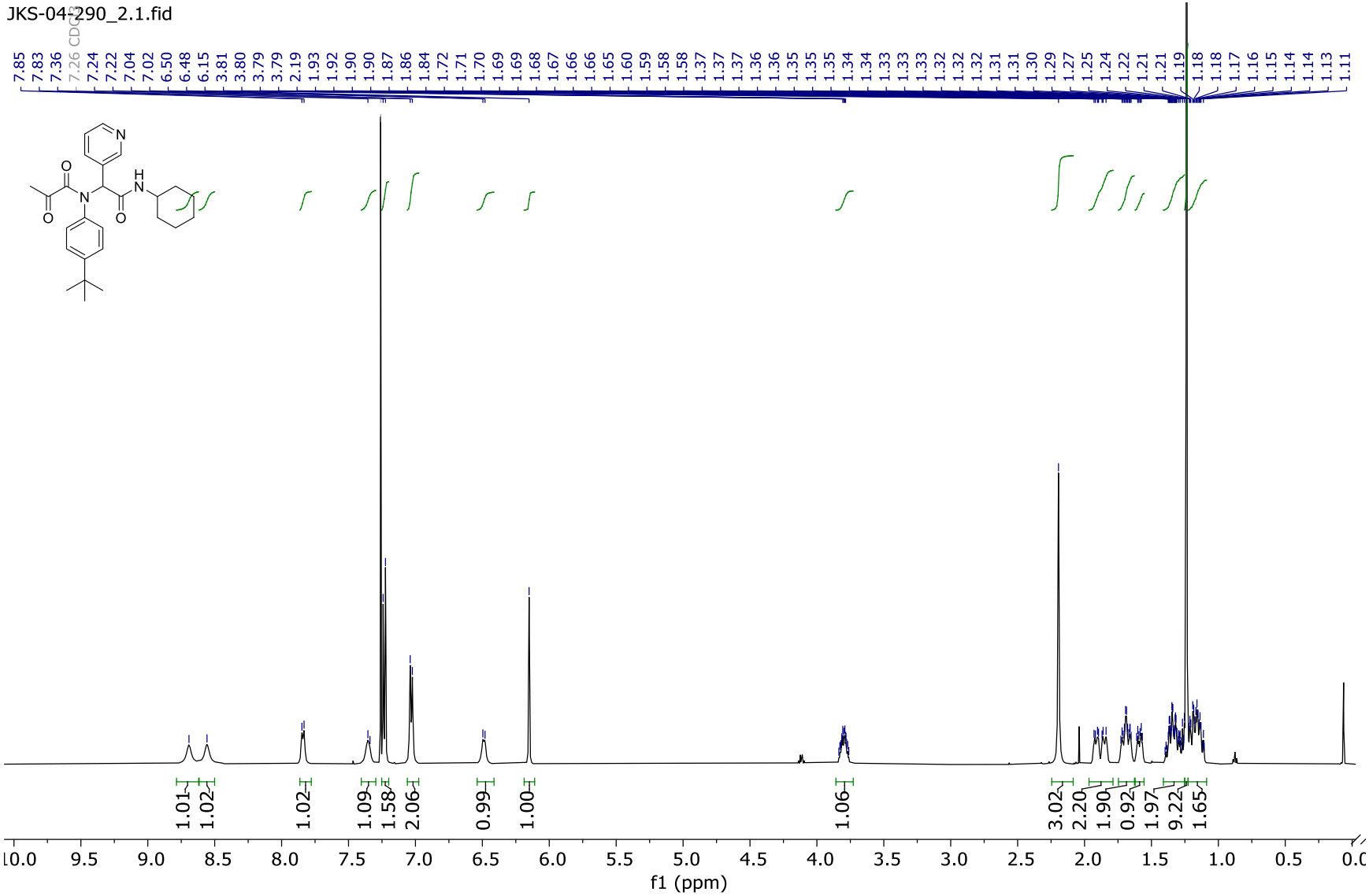
*61. Compound **17a** ^{1}H NMR*



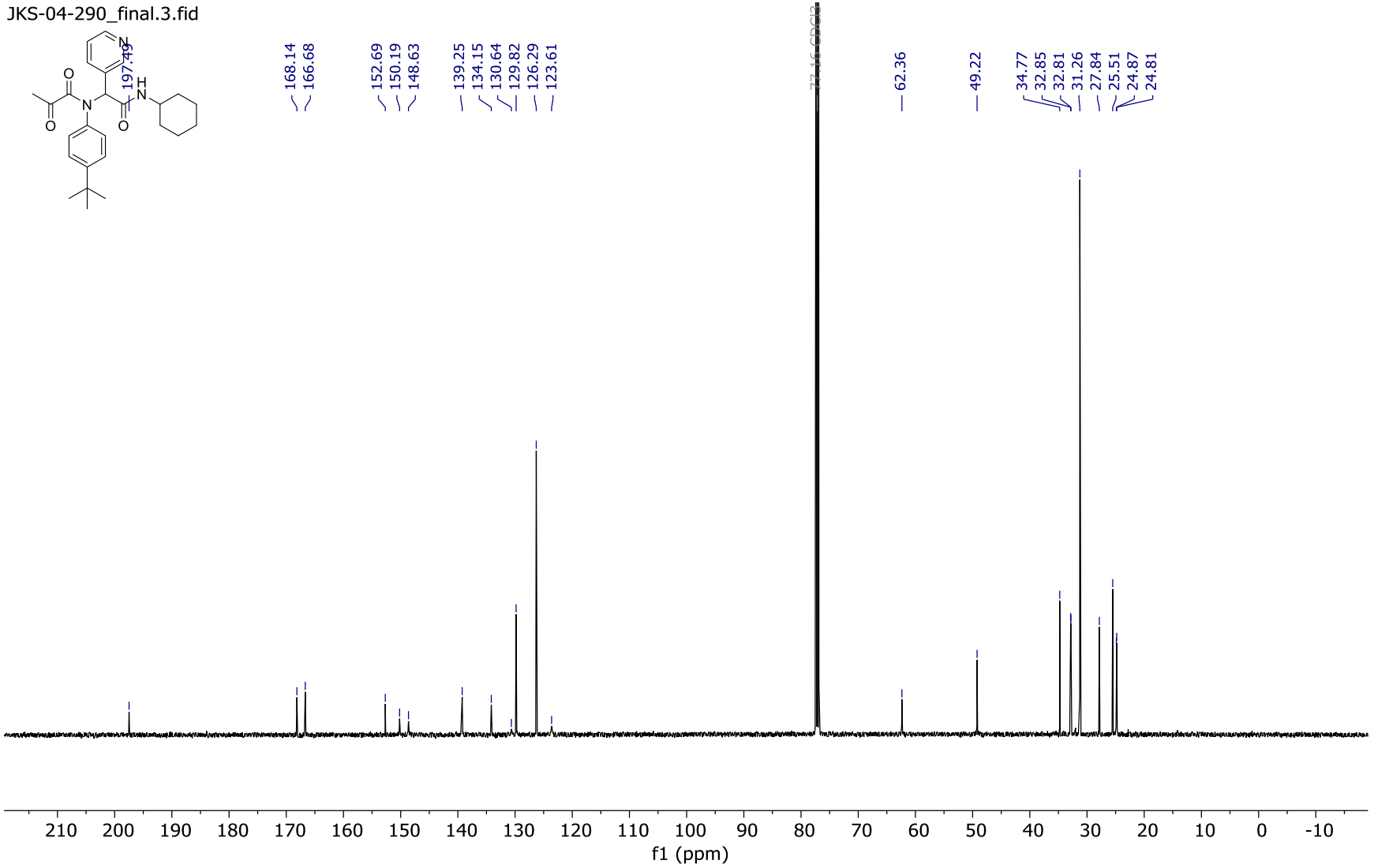
*62. Compound **17a** ^{13}C NMR*



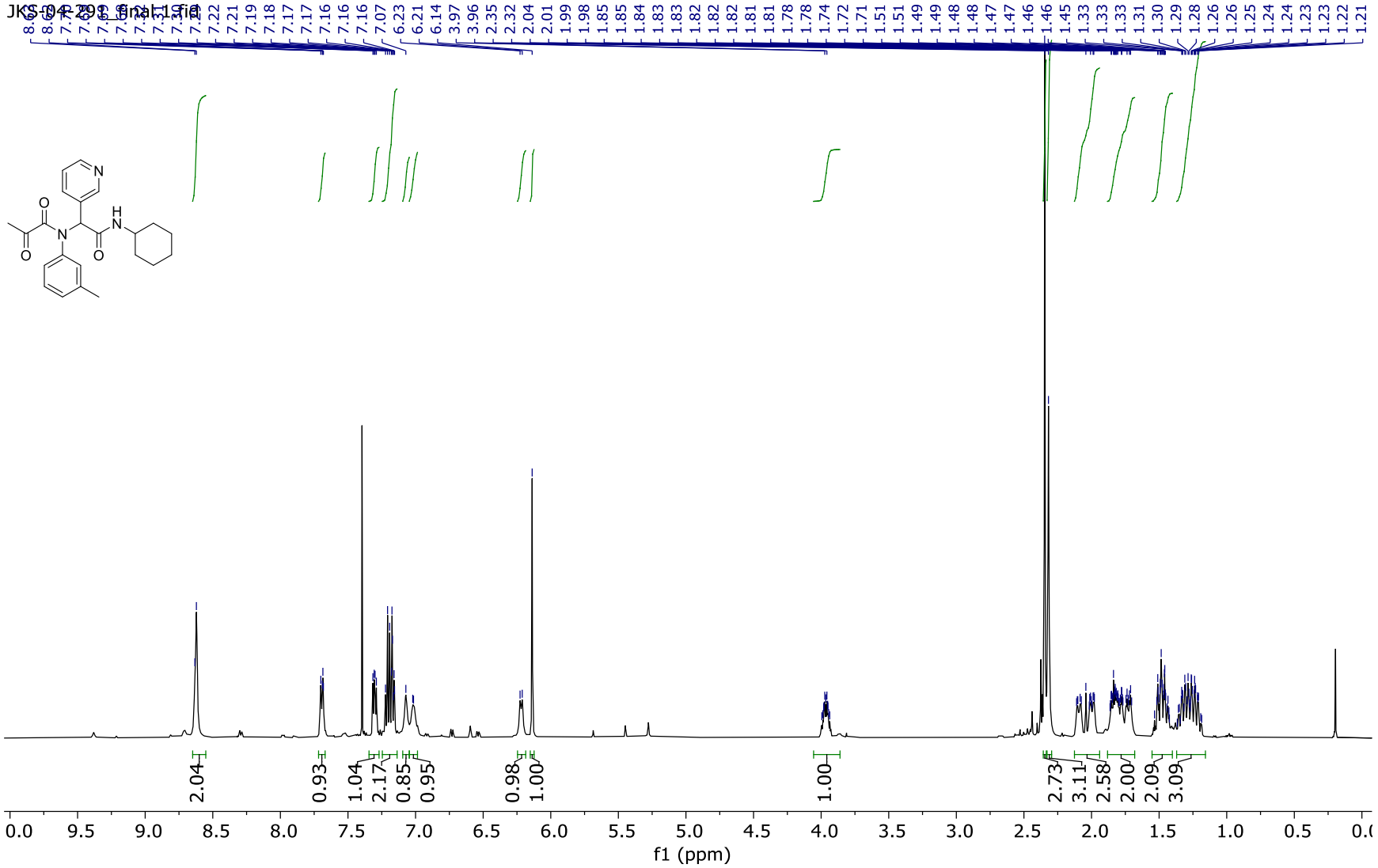
*63. Compound **18a** ^{1}H NMR*



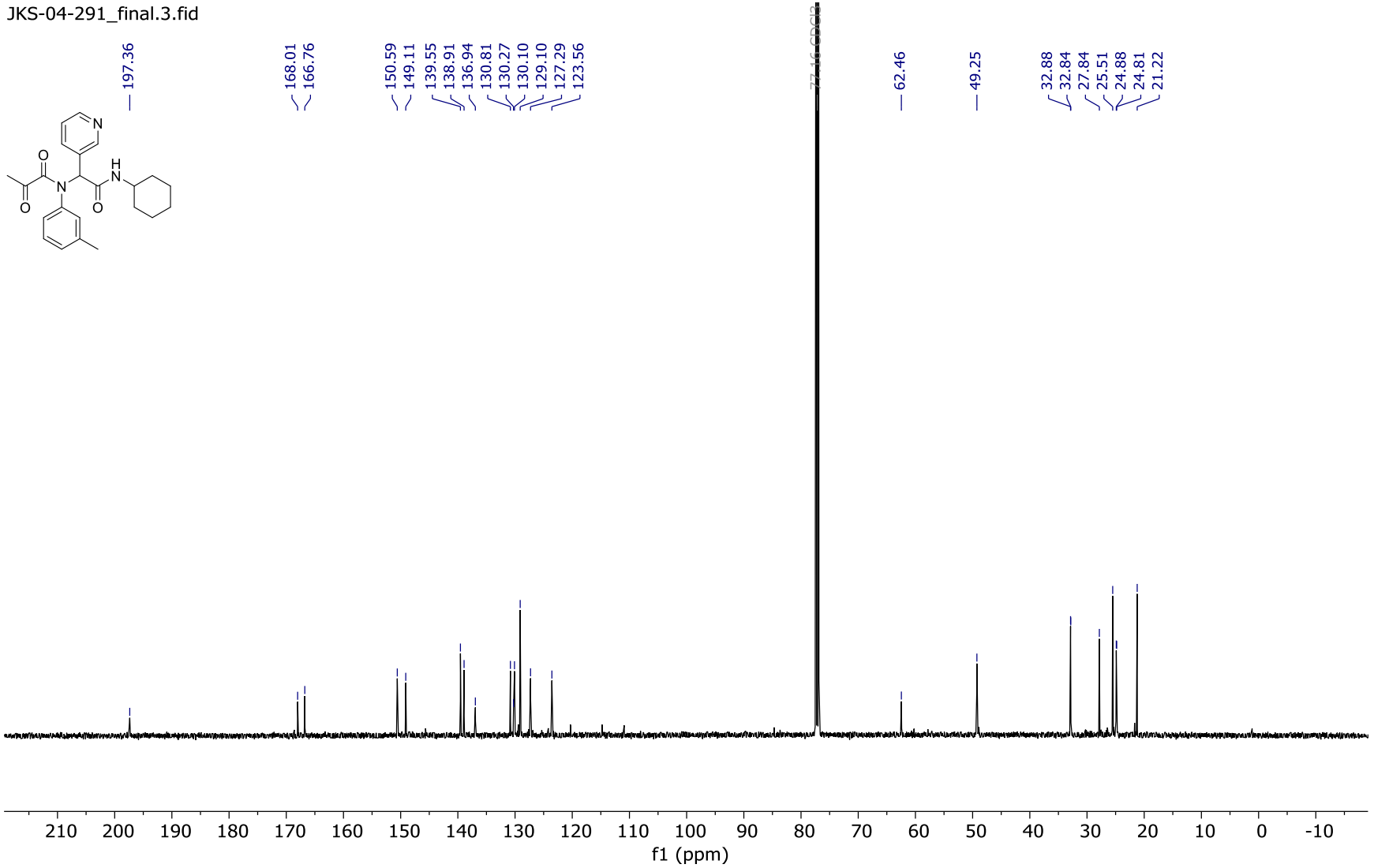
*64. Compound **18a** ^{13}C NMR*



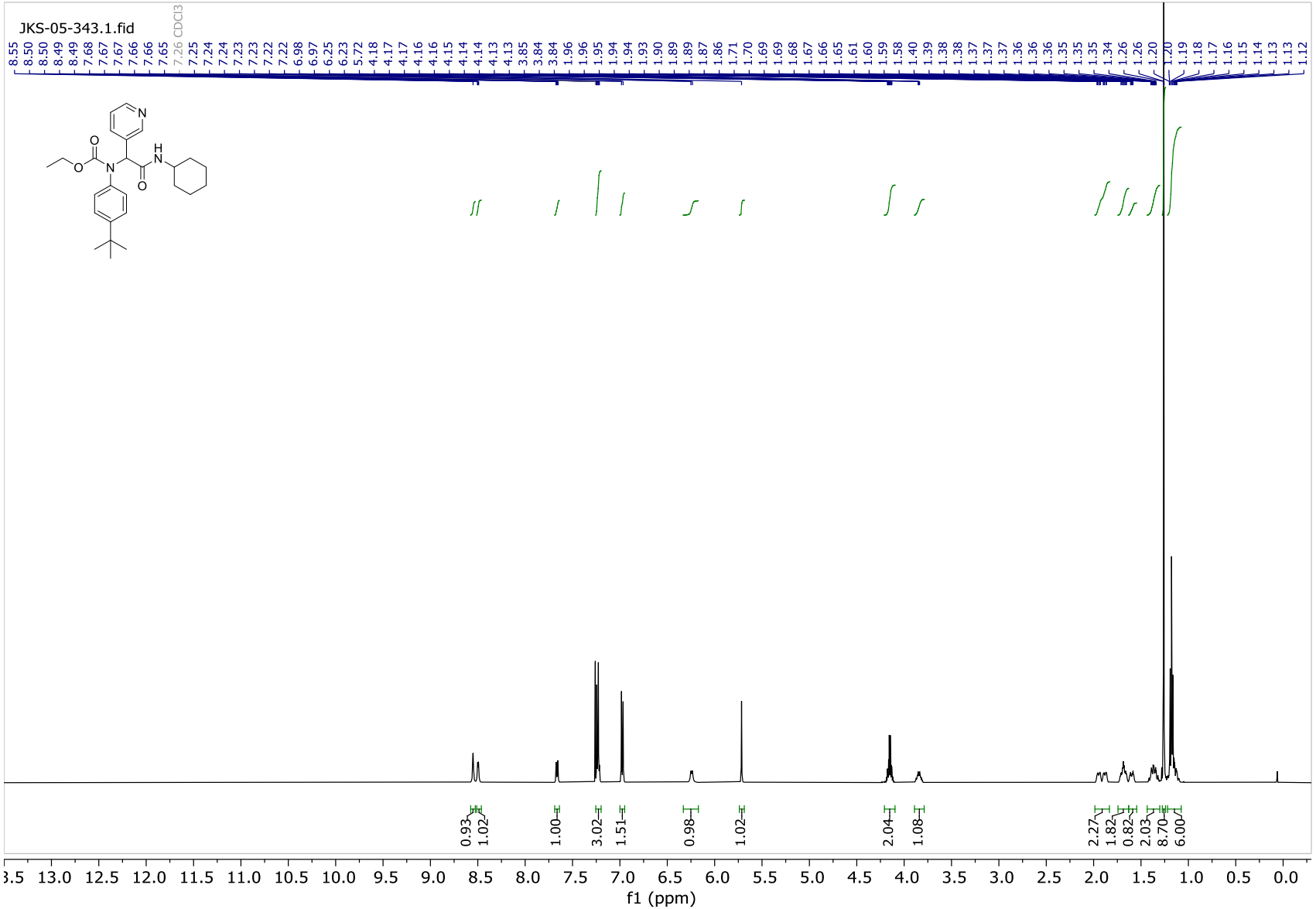
*65. Compound **18b** ^{1}H NMR*



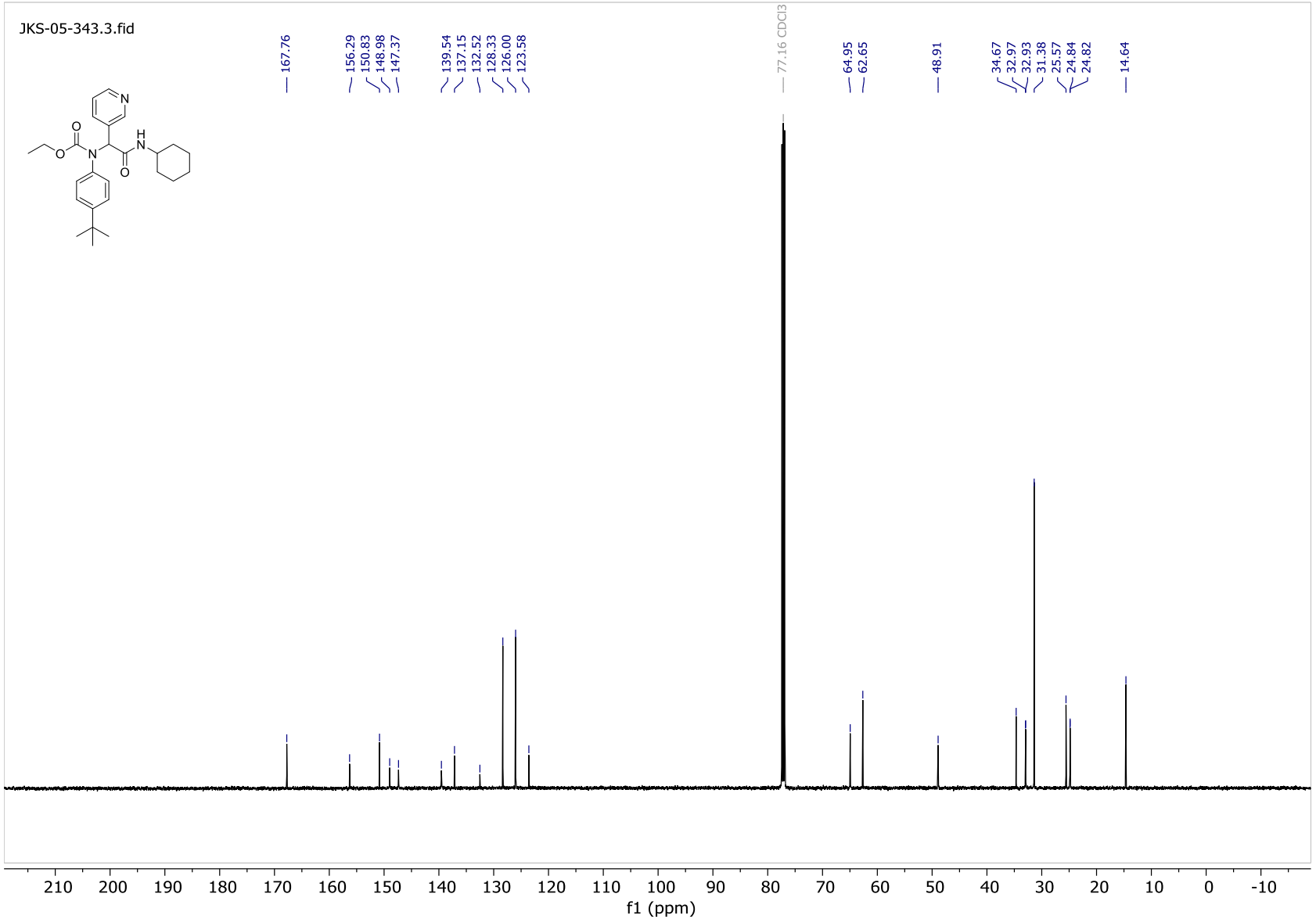
*66. Compound **18b** ^{13}C NMR*



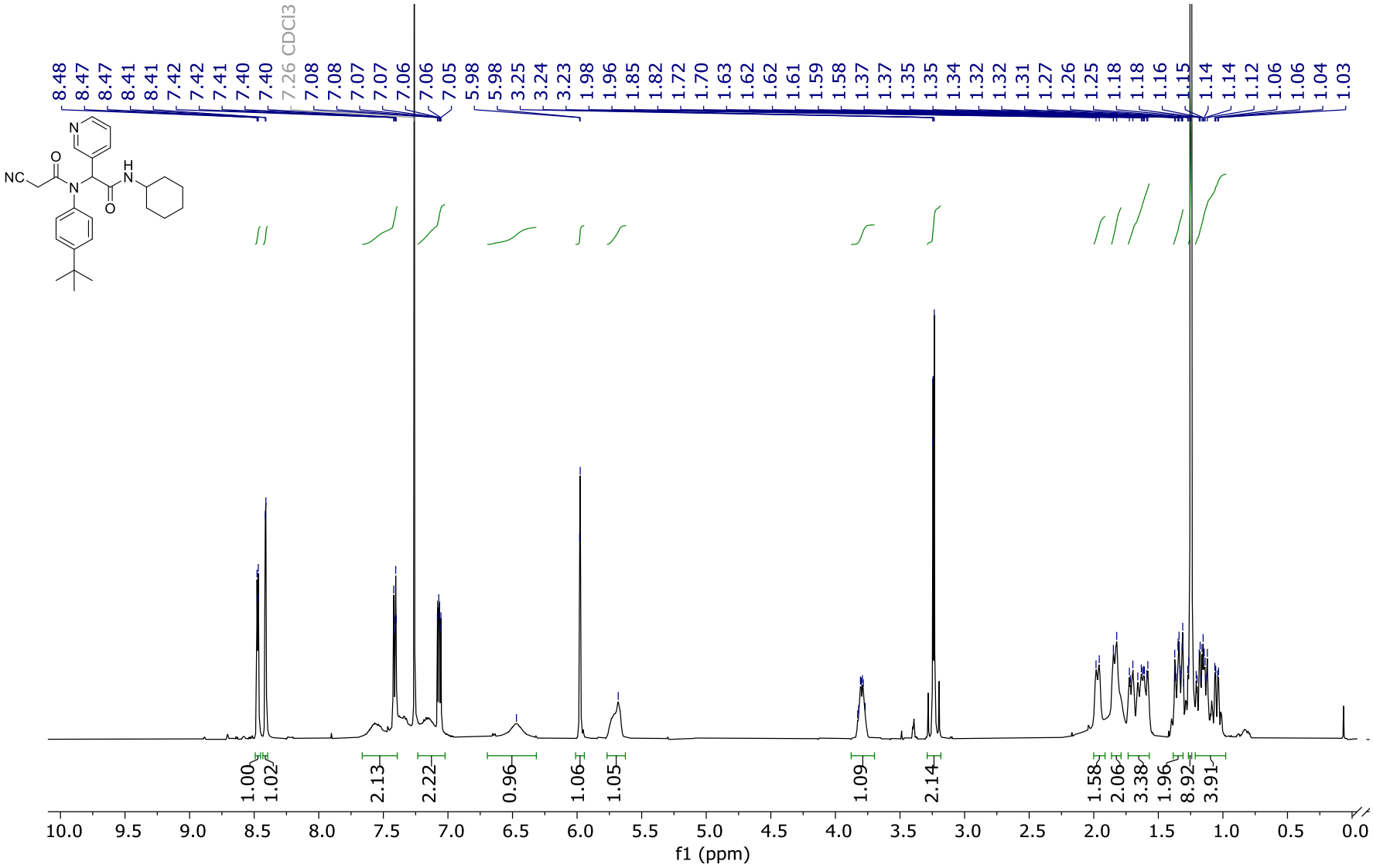
*67. Compound **19a** ^{1}H NMR*



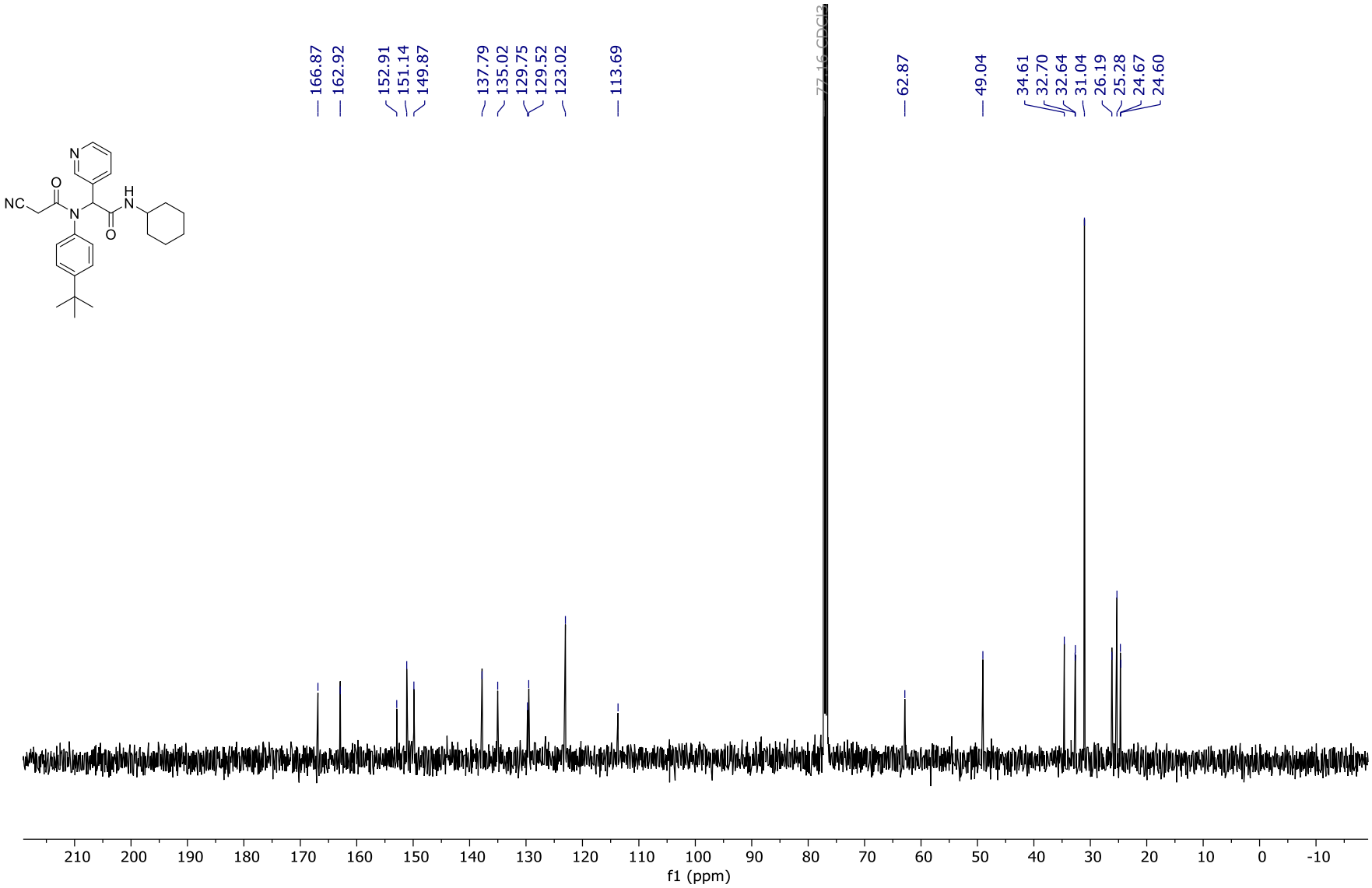
*68. Compound **19a** ^{13}C NMR*



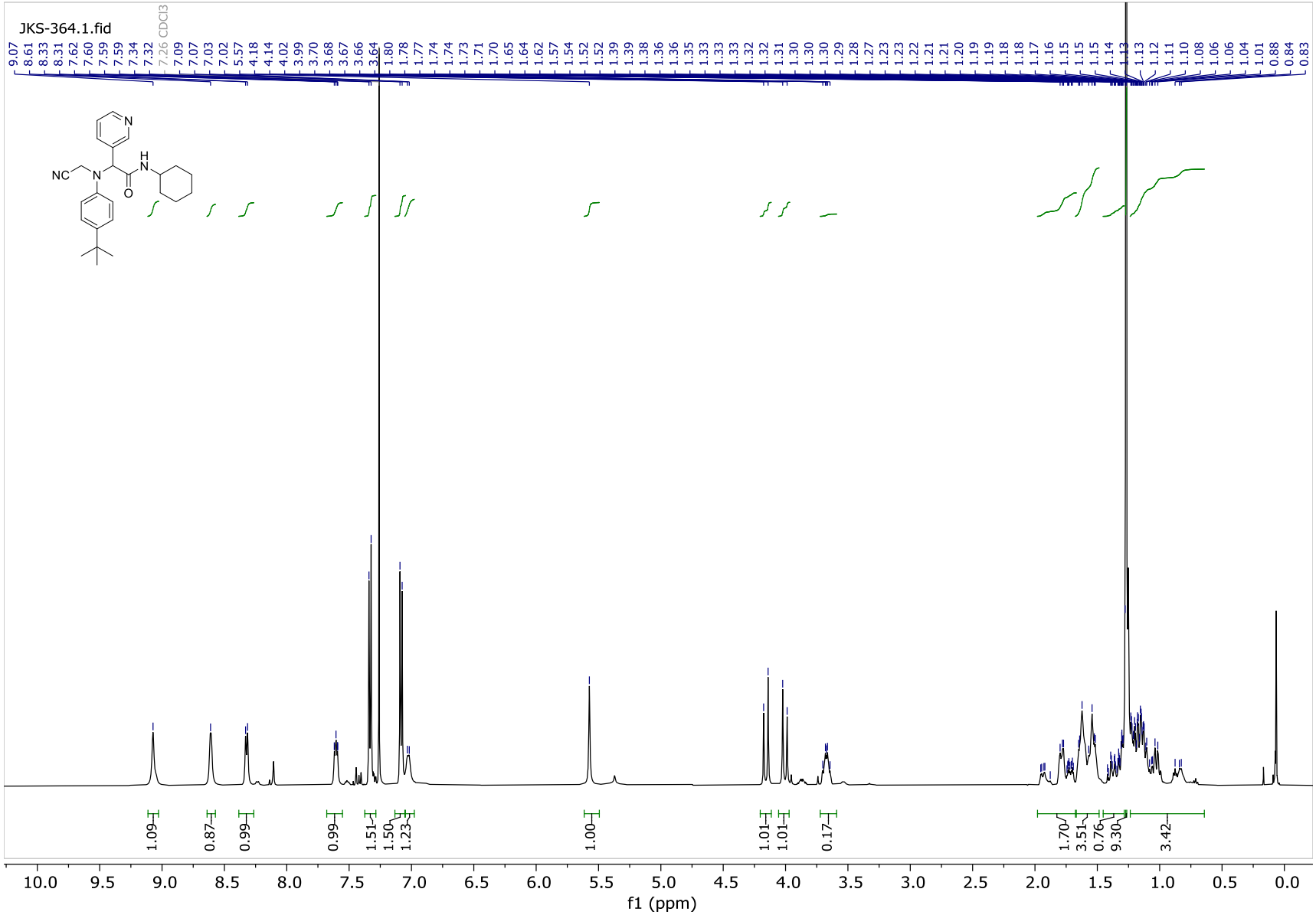
69. Compound ***20a*** *^{1}H NMR*



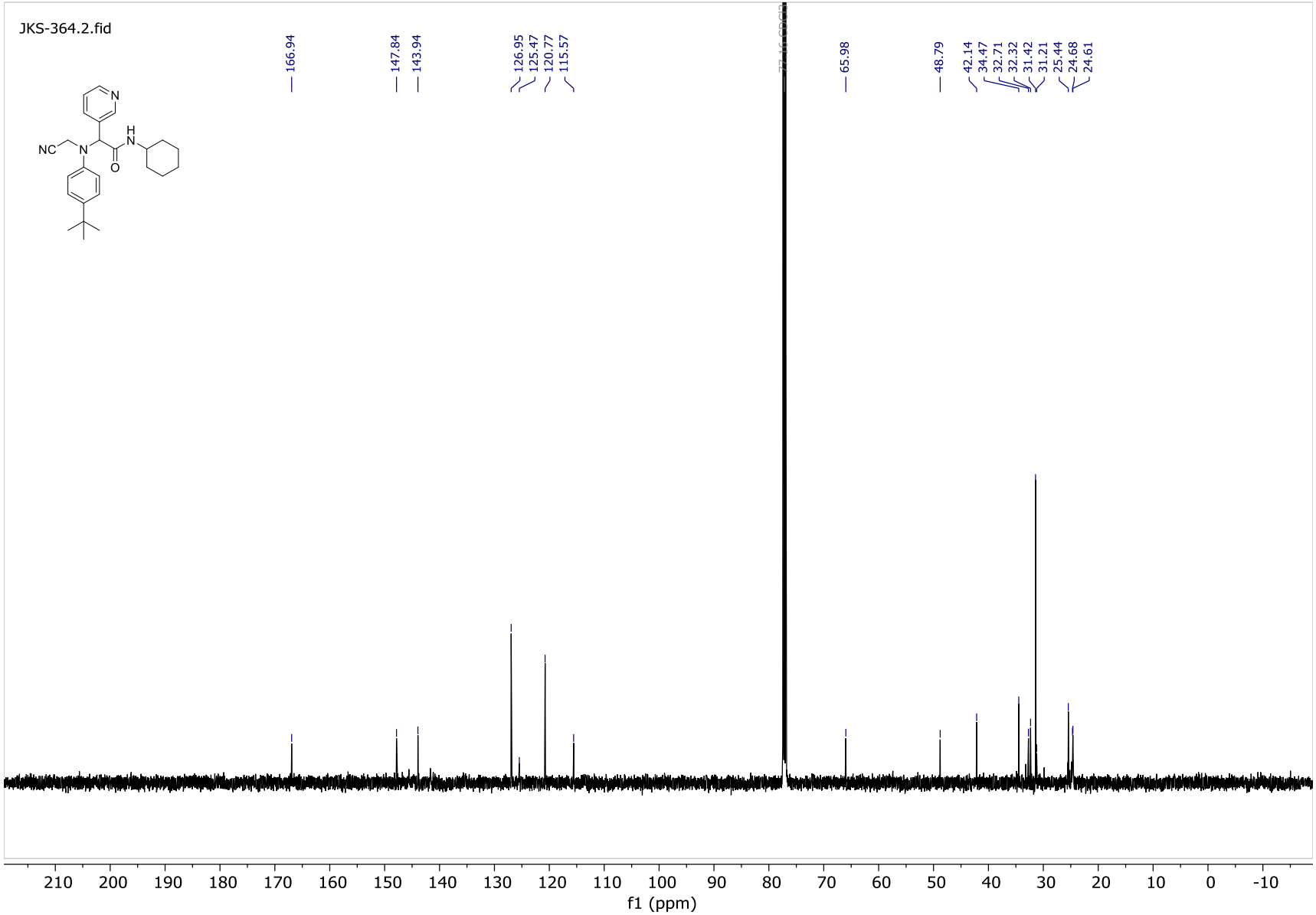
*70. Compound **20a** ^{13}C NMR*



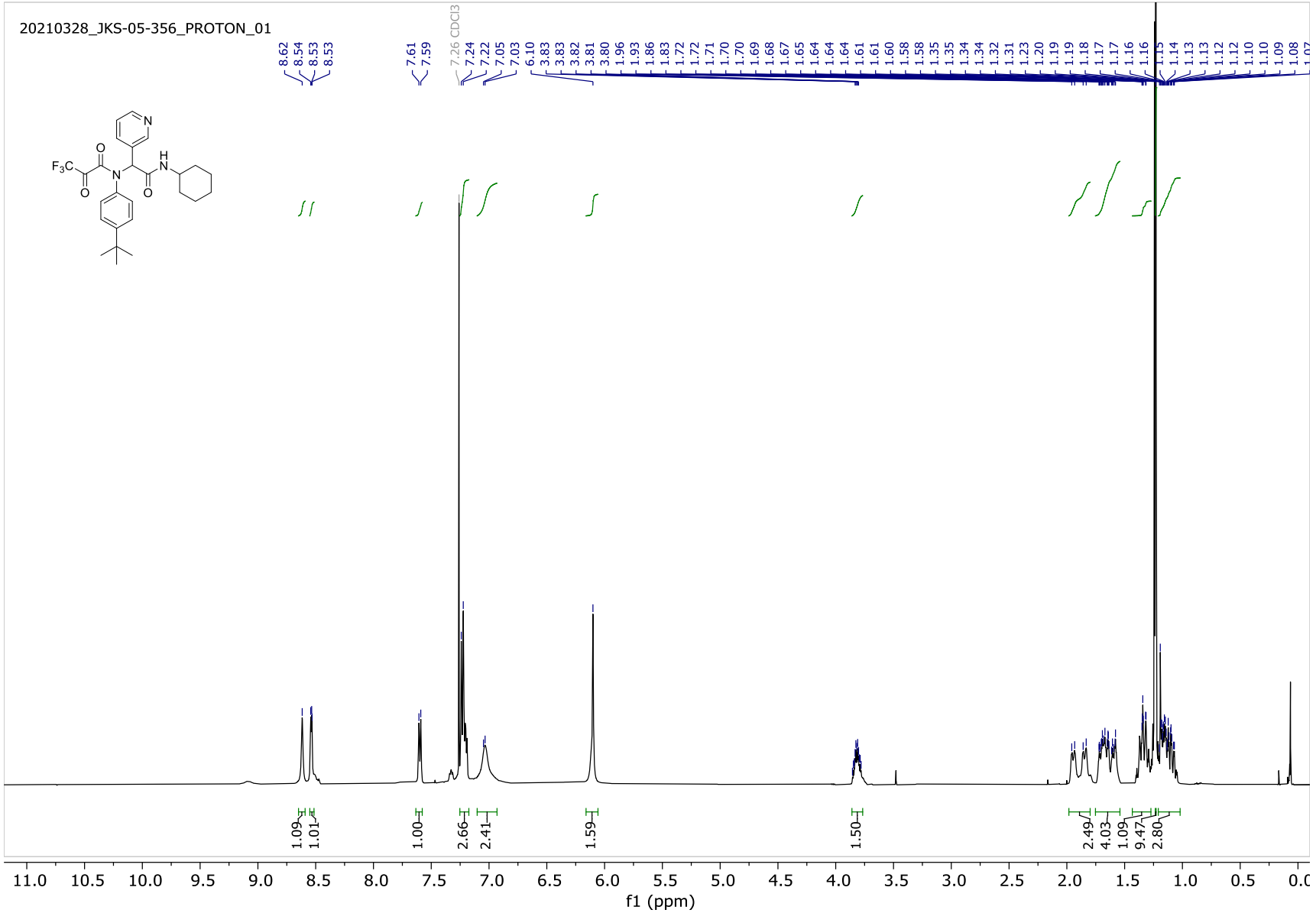
*71. Compound **21a** ^{1}H NMR*



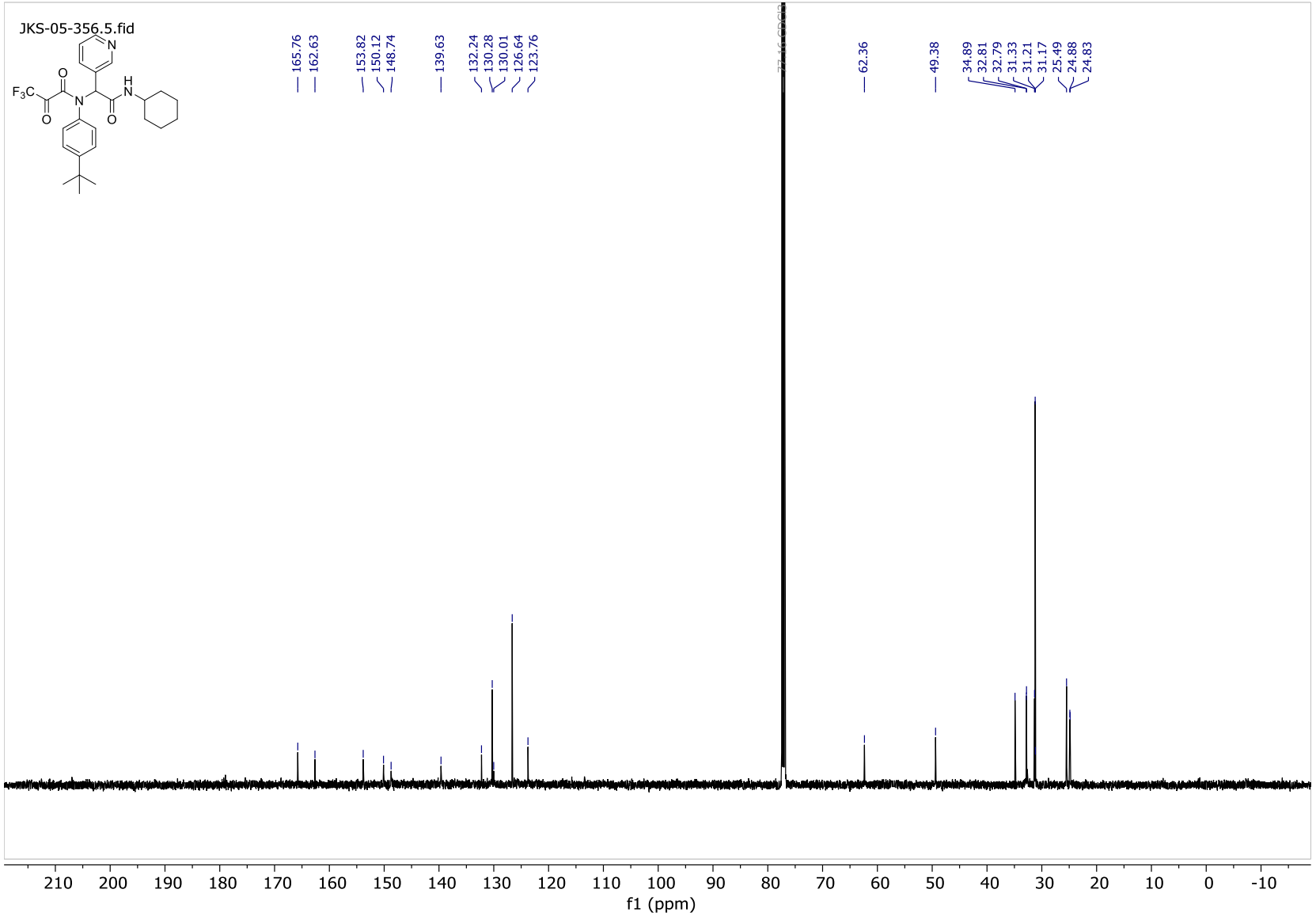
*72. Compound **21a** ^{13}C NMR*



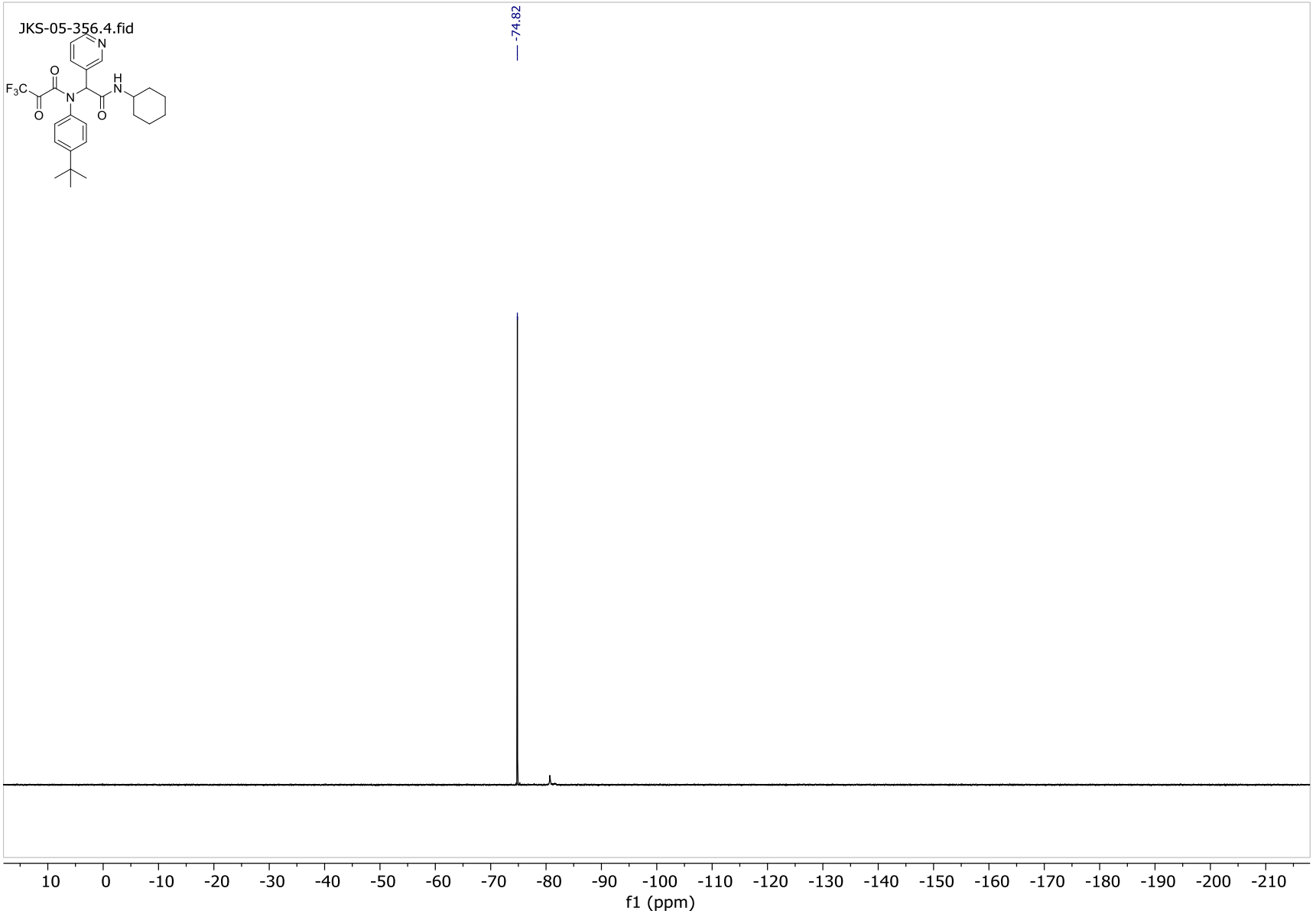
73. Compound ***22a*** *^{1}H NMR*



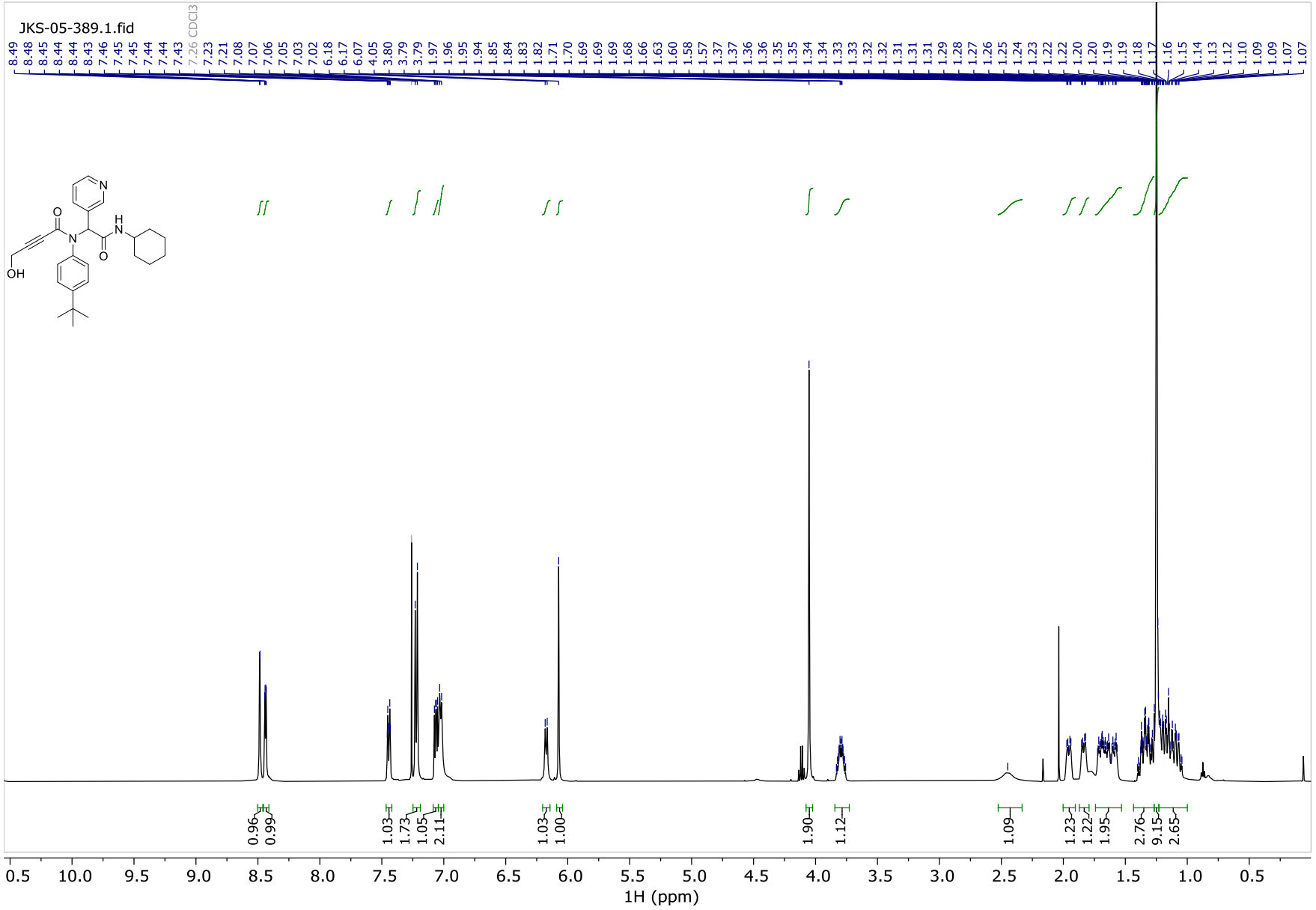
*74. Compound **22a** ^{13}C NMR*



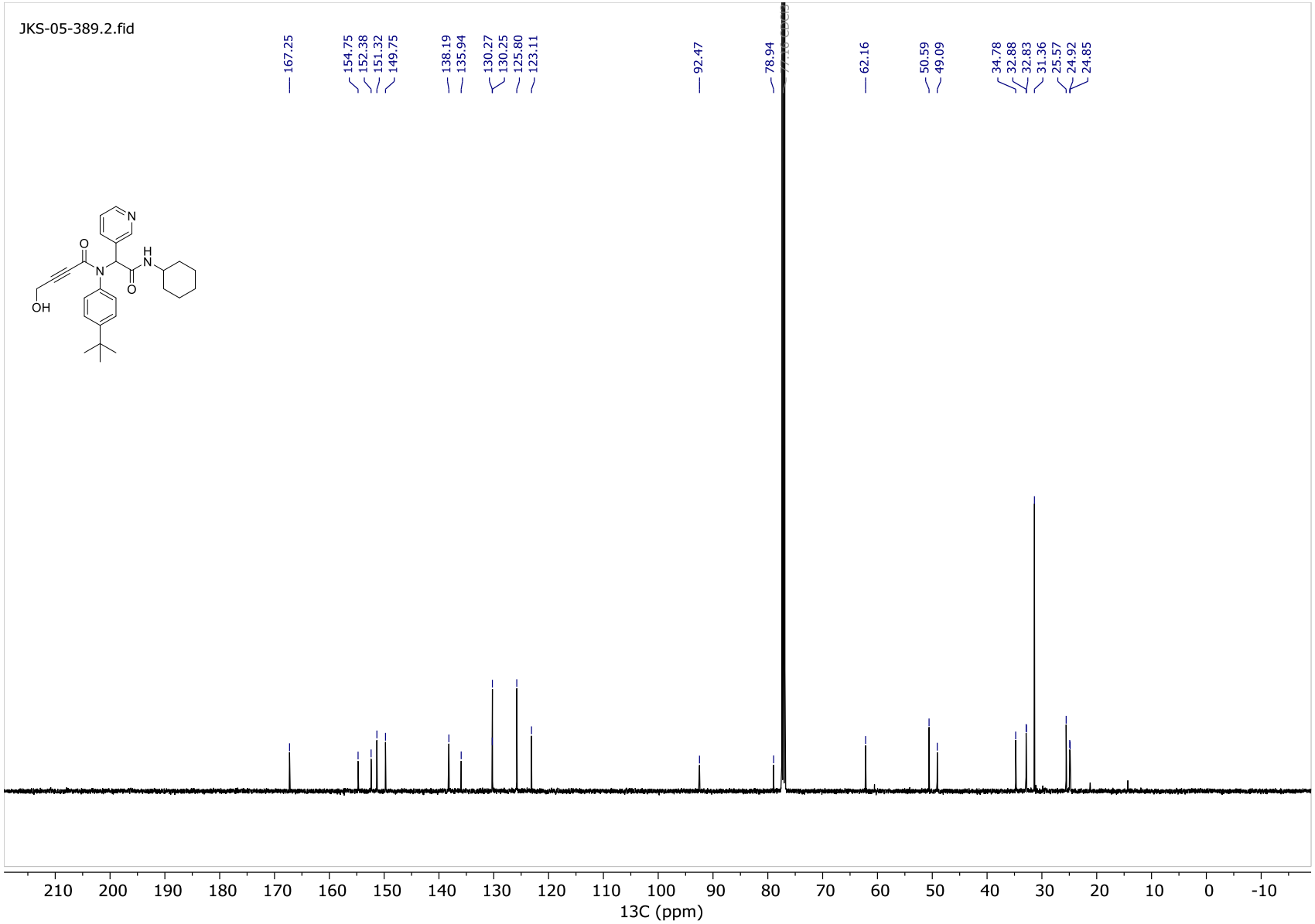
*75. Compound **22a** ^{19}F NMR*



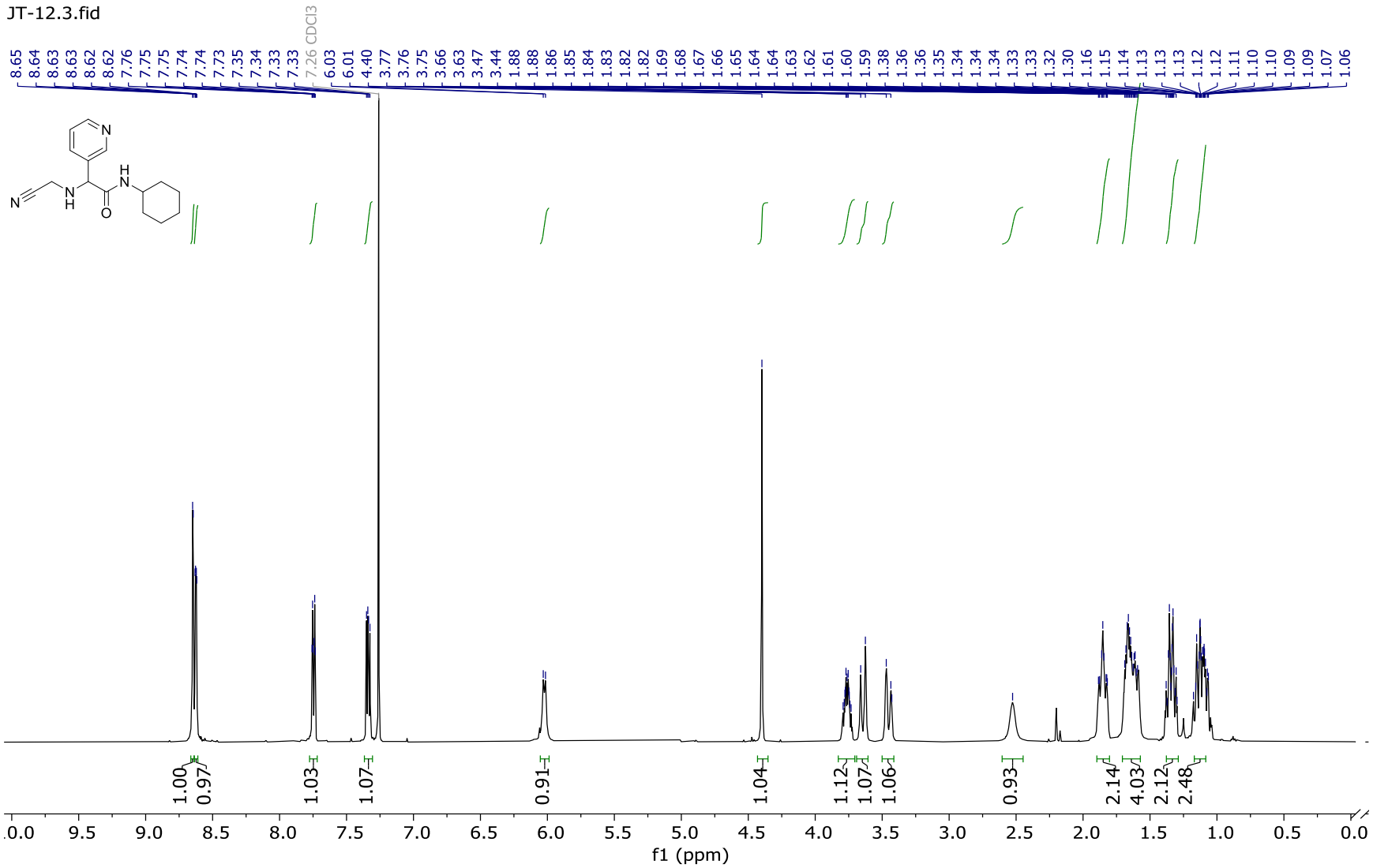
*76. Compound **23a** ^{1}H NMR*



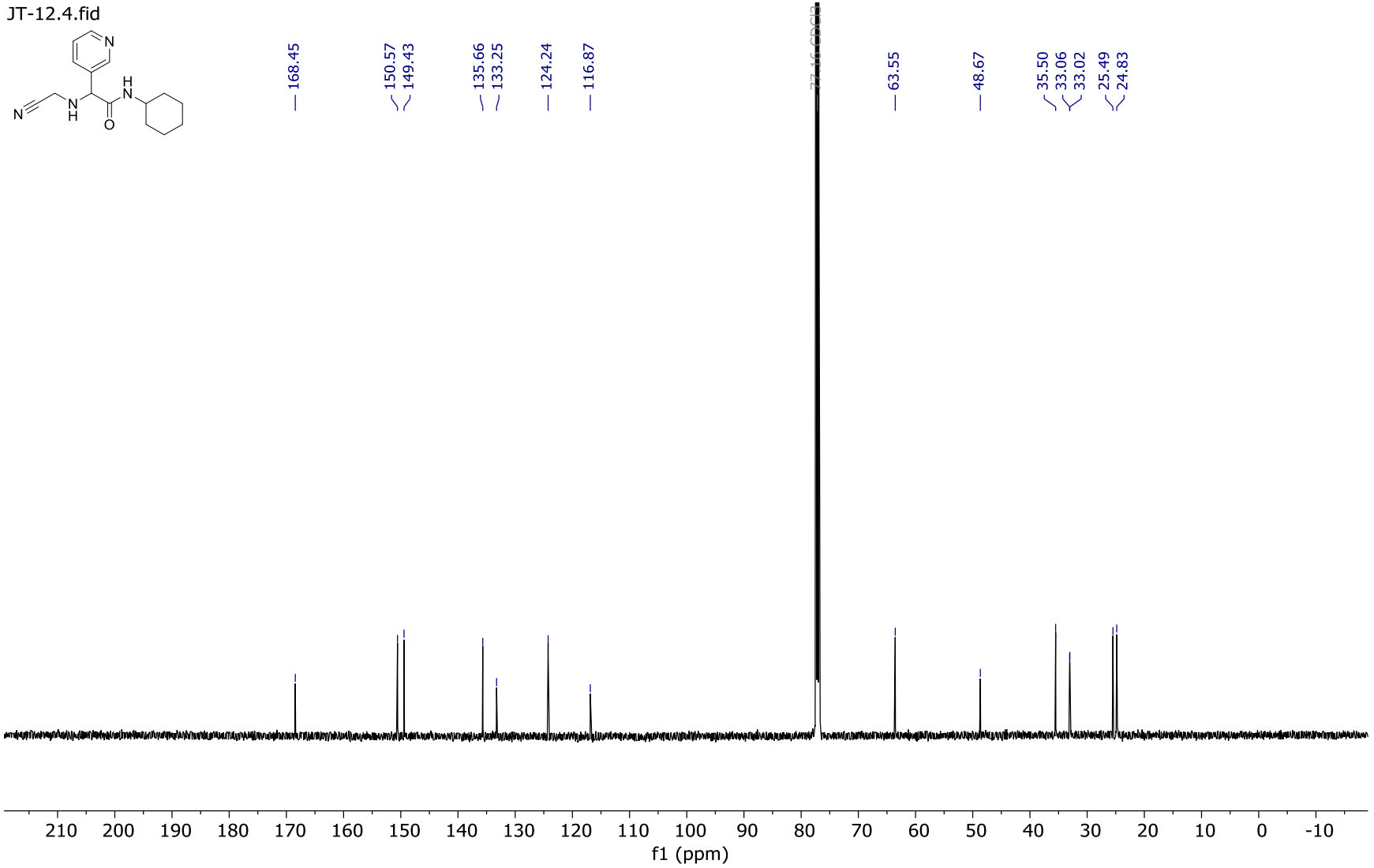
*77. Compound **23a** ^{13}C NMR*



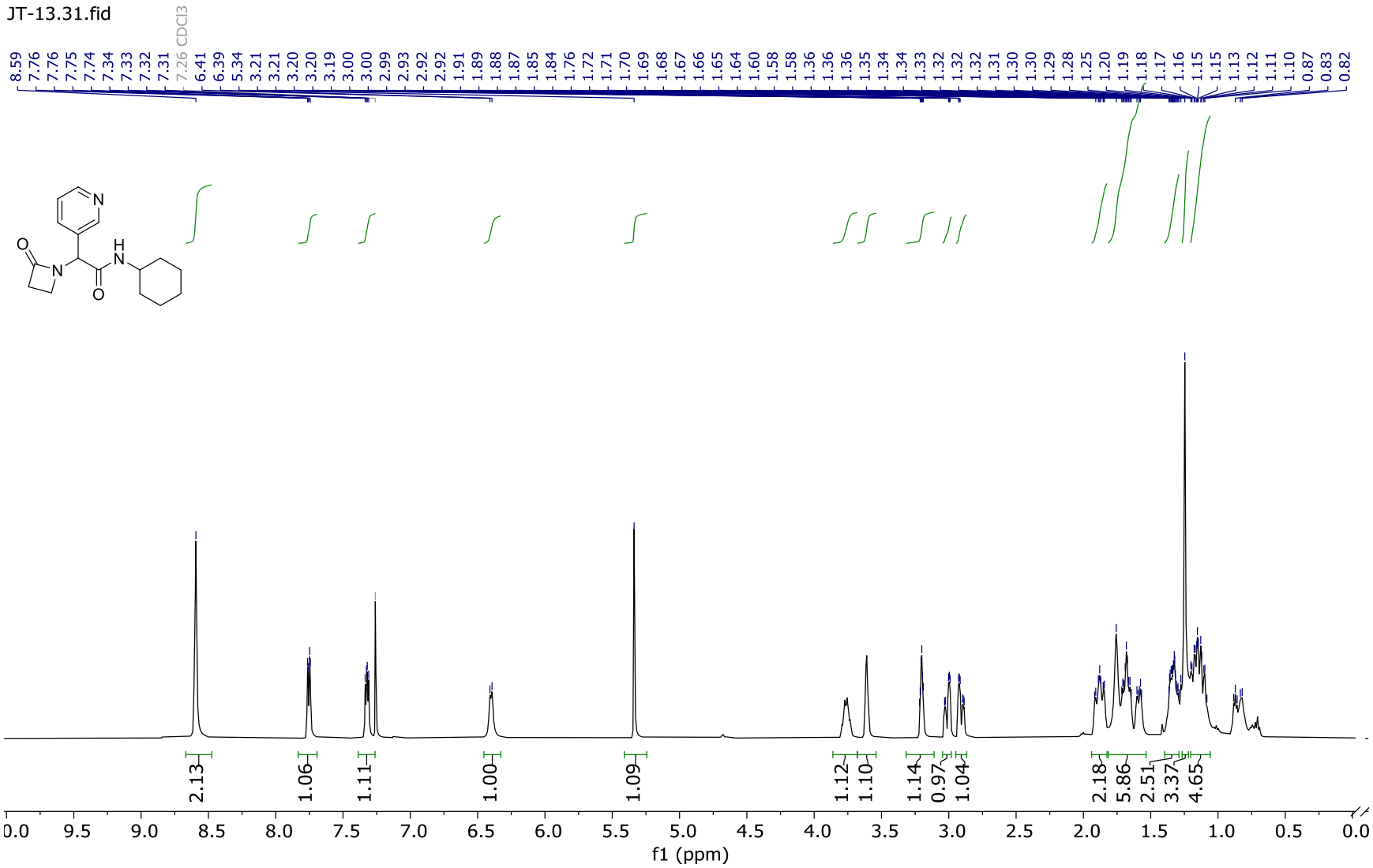
*78. Compound **24a** ^{1}H NMR*



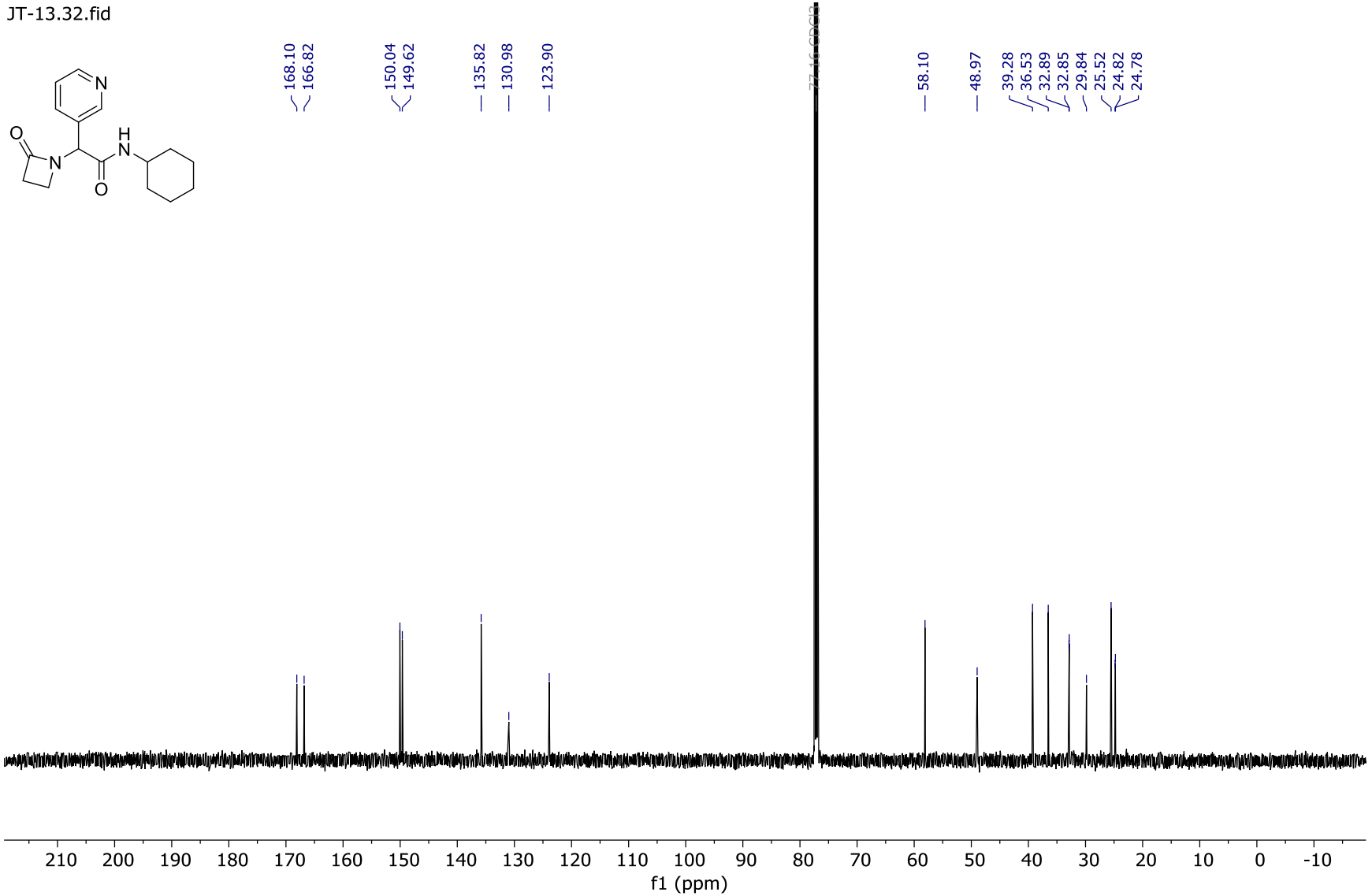
*79. Compound **24a** ^{13}C NMR*



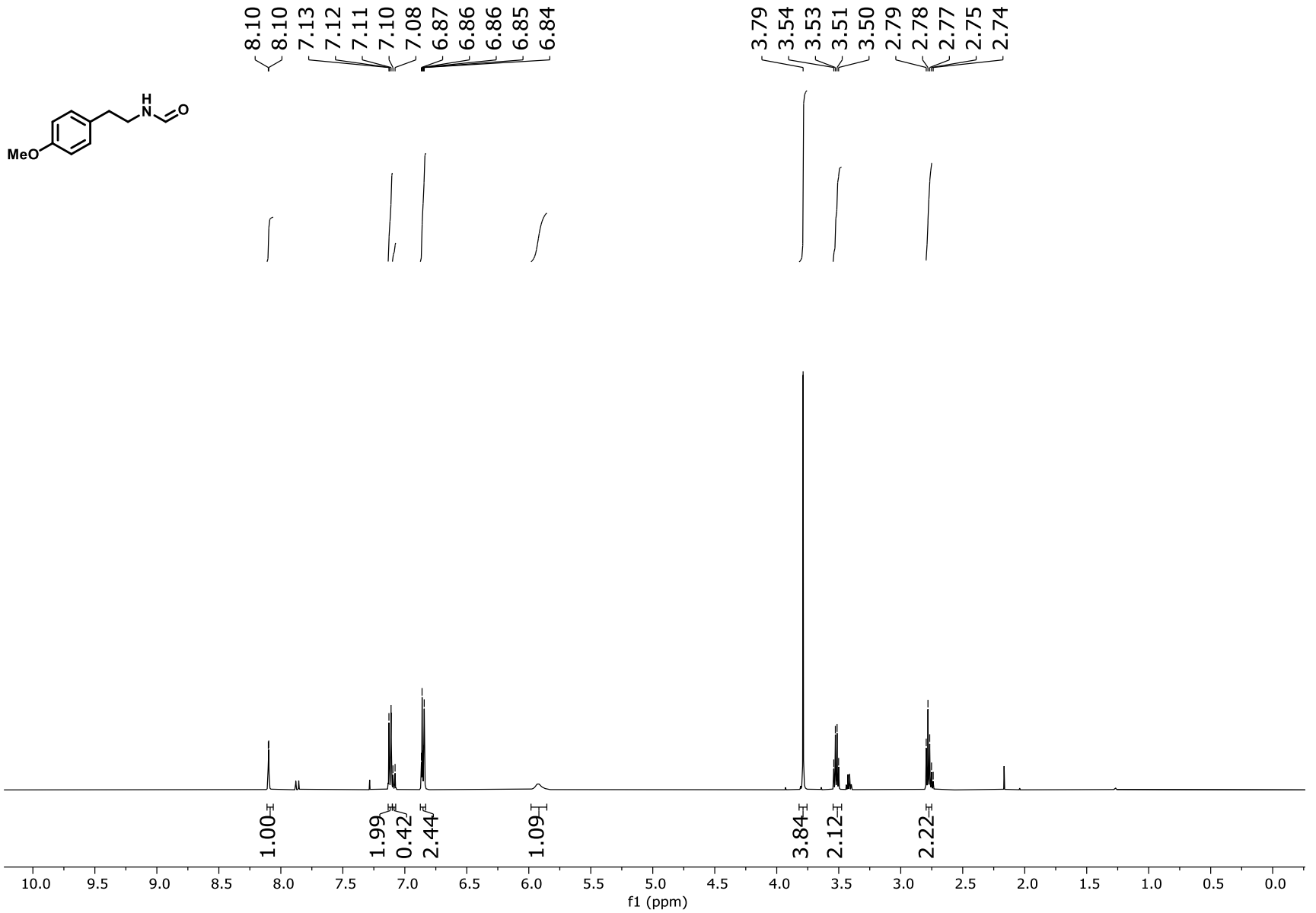
*80. Compound **25a** ^{1}H NMR*



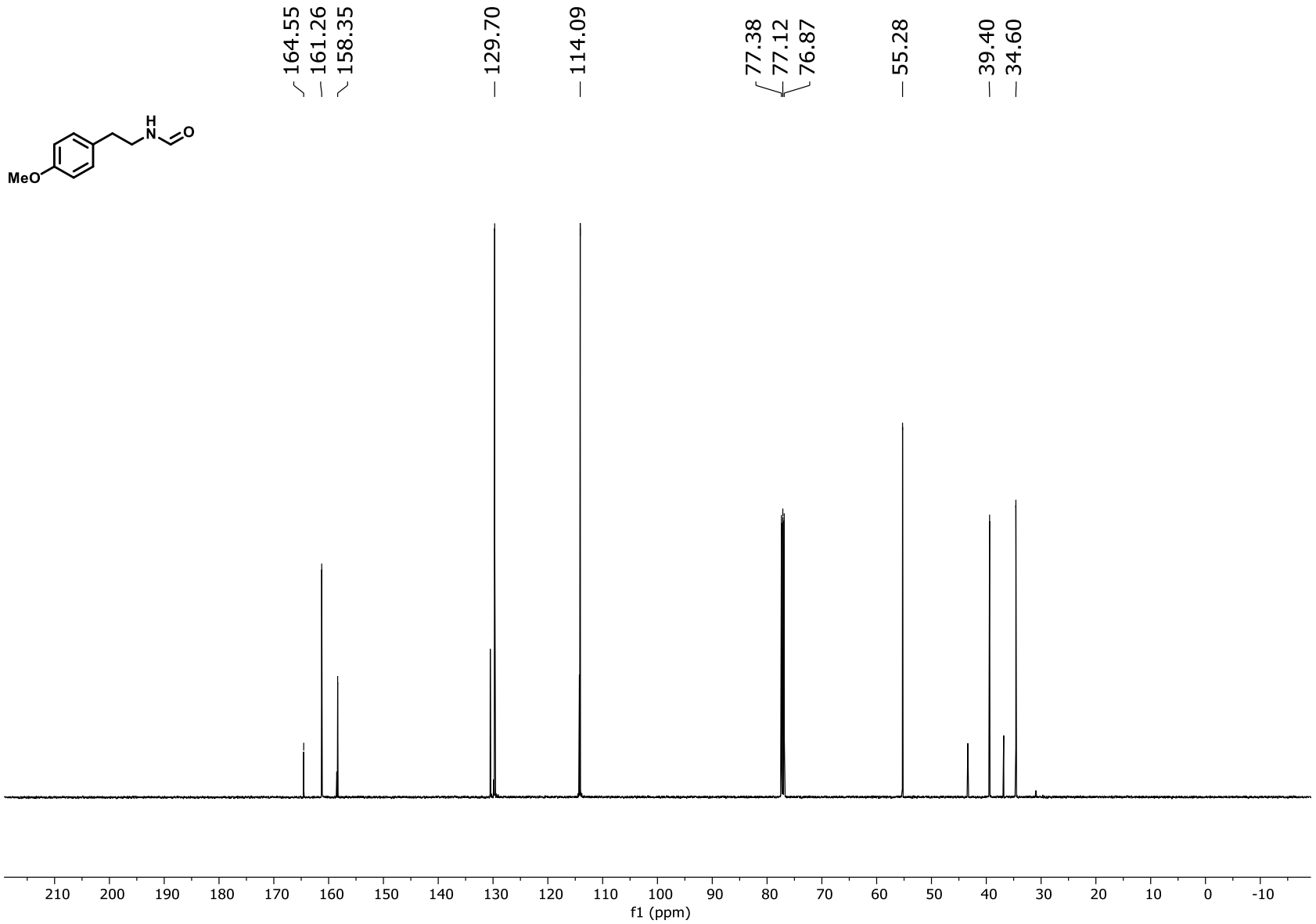
*81. Compound **25a** ^{13}C NMR*



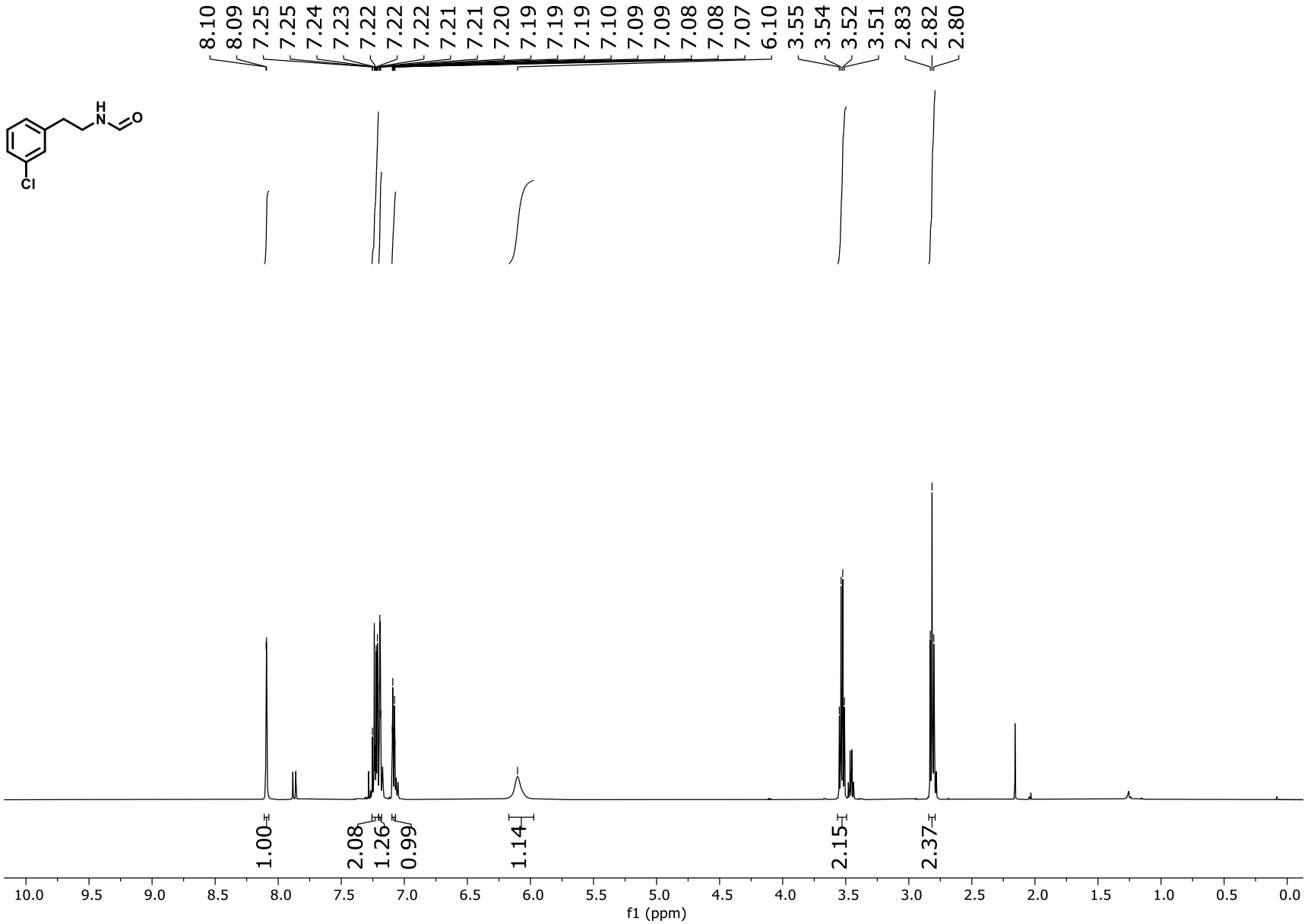
*82. Compound **26b** ^{1}H NMR*



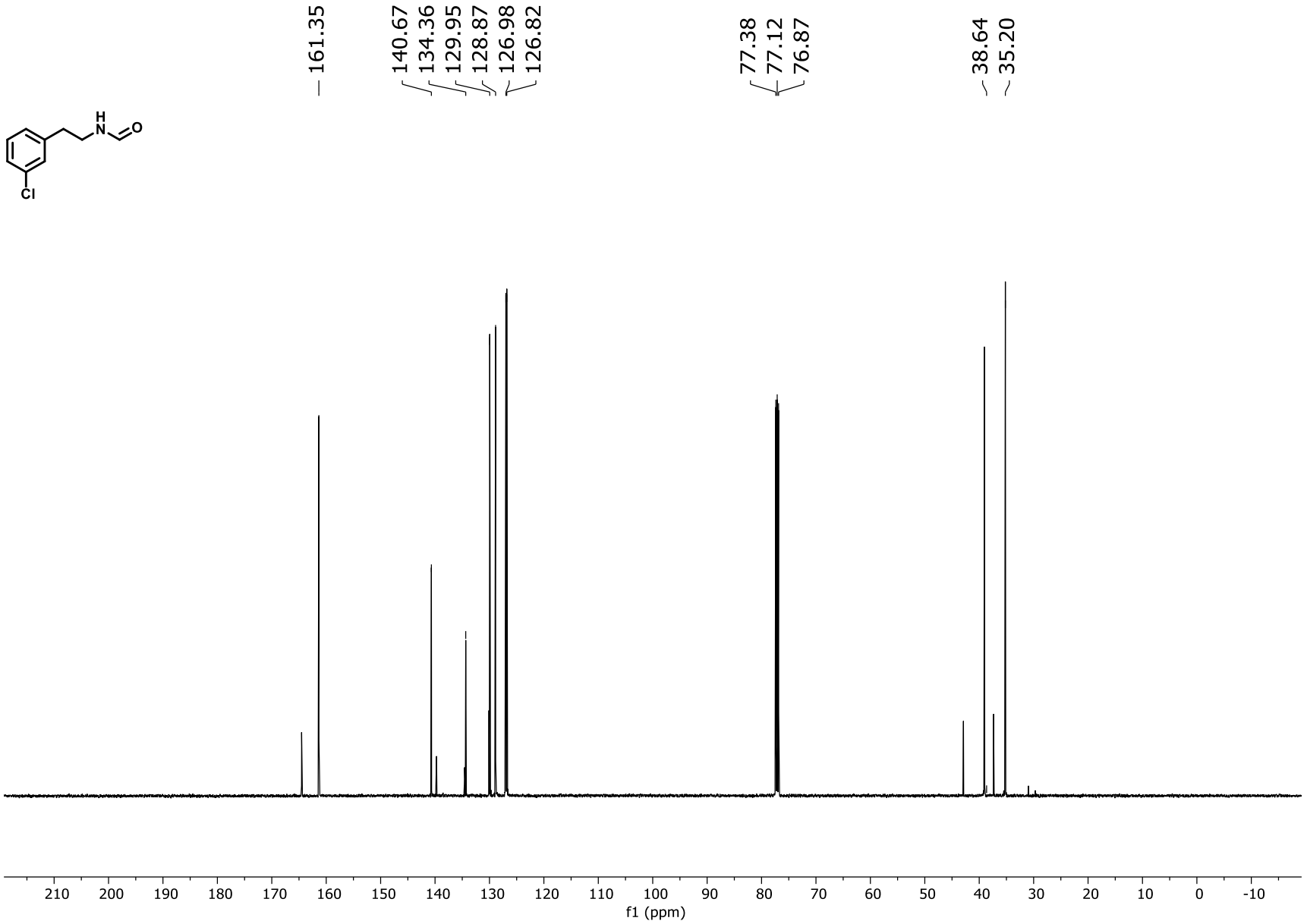
*83. Compound **26b** ^{13}C NMR*



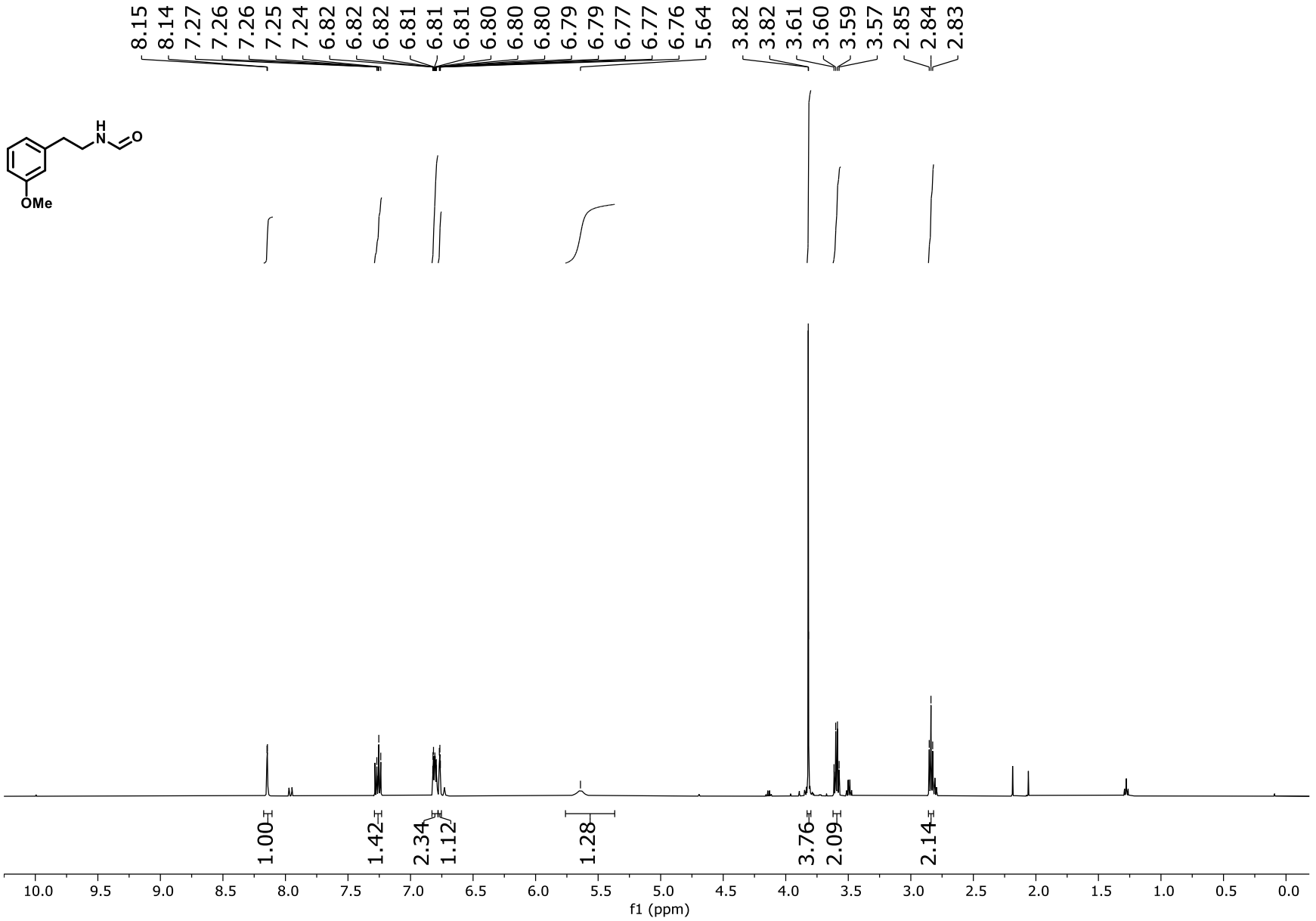
*84. Compound **26c** ^{1}H NMR*


8.10
8.09
7.25
7.25
7.24
7.23
7.22
7.22
7.22
7.21
7.21
7.20
7.19
7.19
7.19
7.10
7.09
7.09
7.08
7.08
7.07
6.10
3.55
3.54
3.52
3.51
2.83
2.82
2.80
H
N
O
Cl
1.00
2.08
1.26
0.99
1.14
2.15
2.37
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

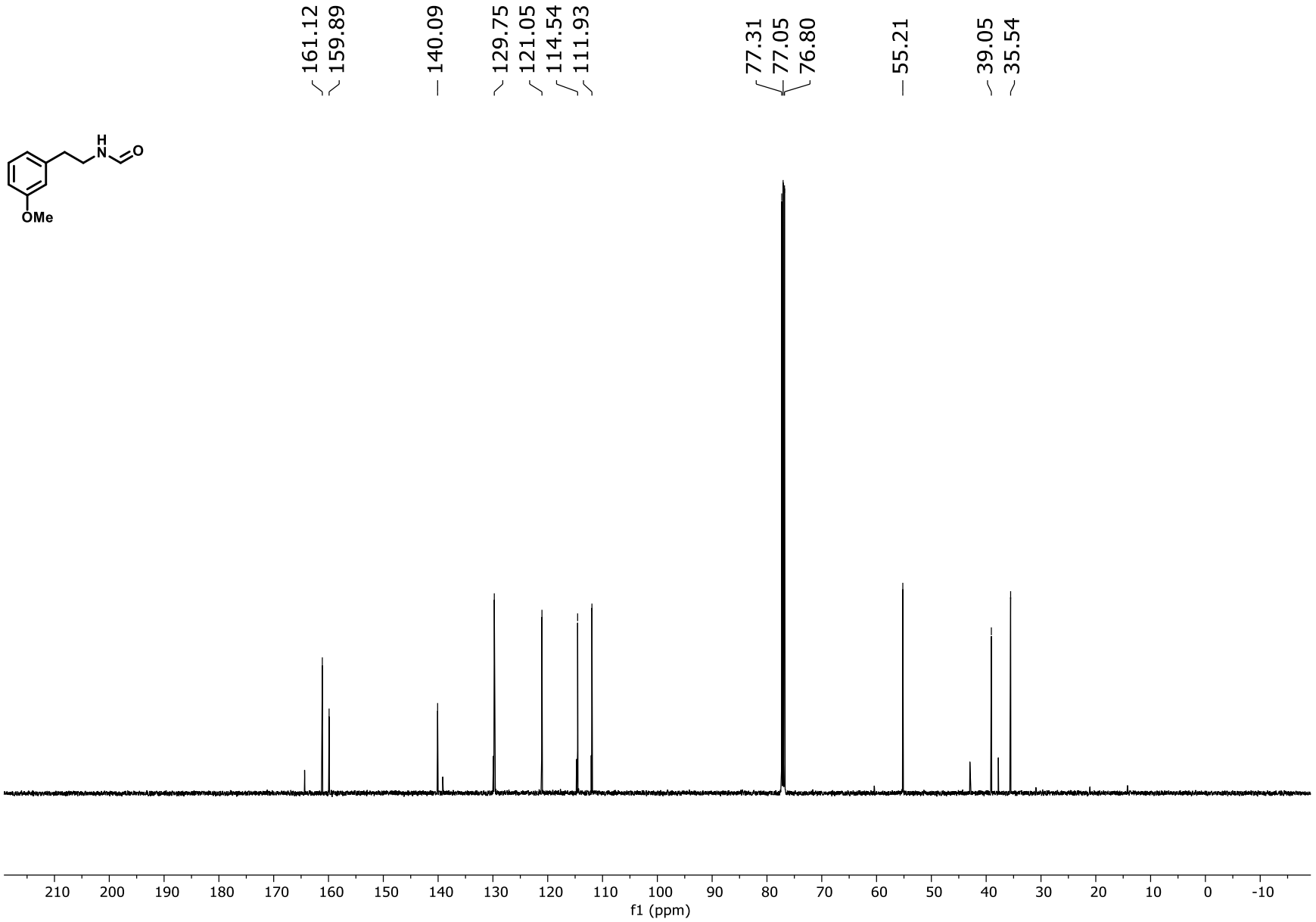
*85. Compound **26c** ^{13}C NMR*



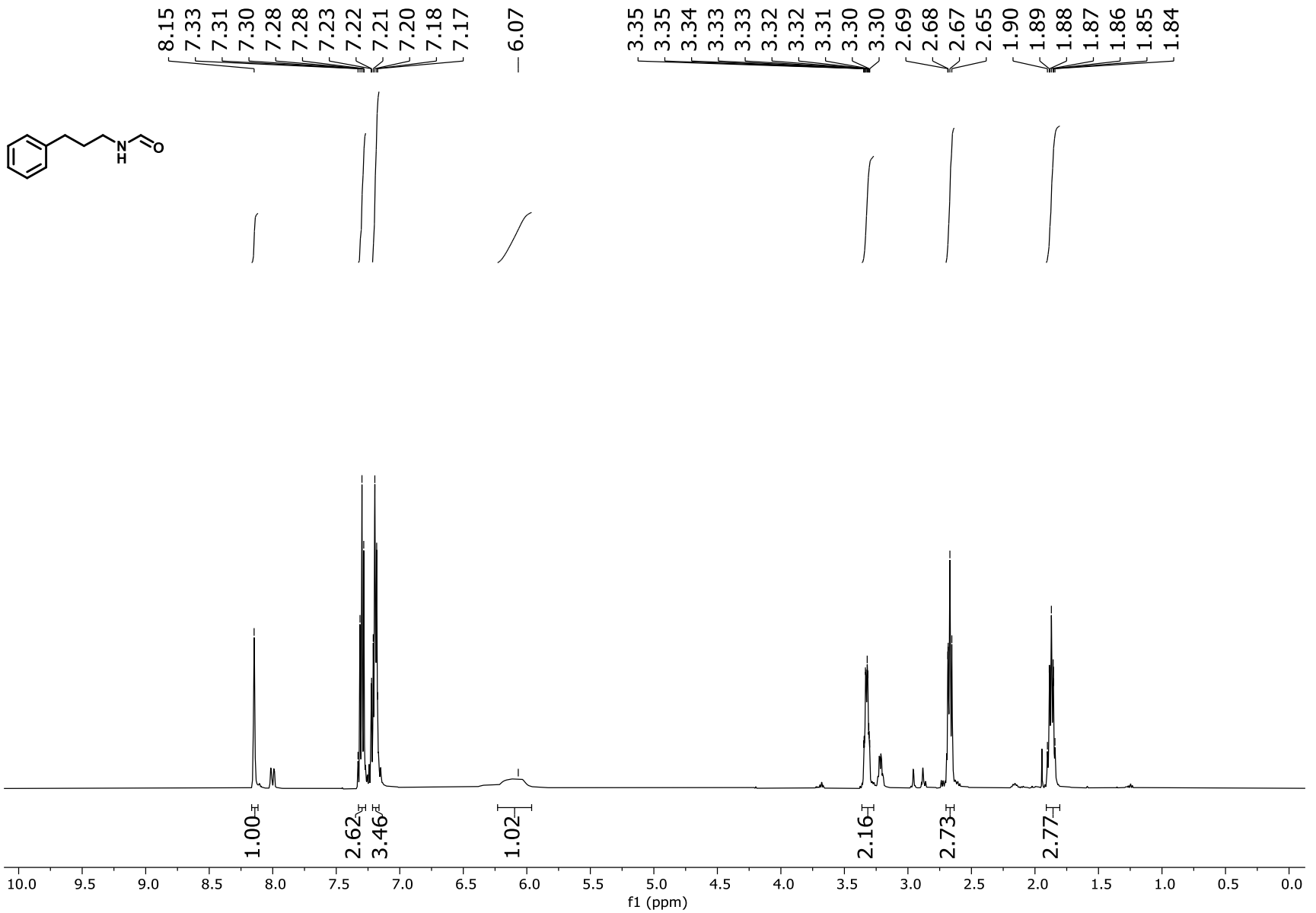
*86. Compound **26d** ^{1}H NMR*



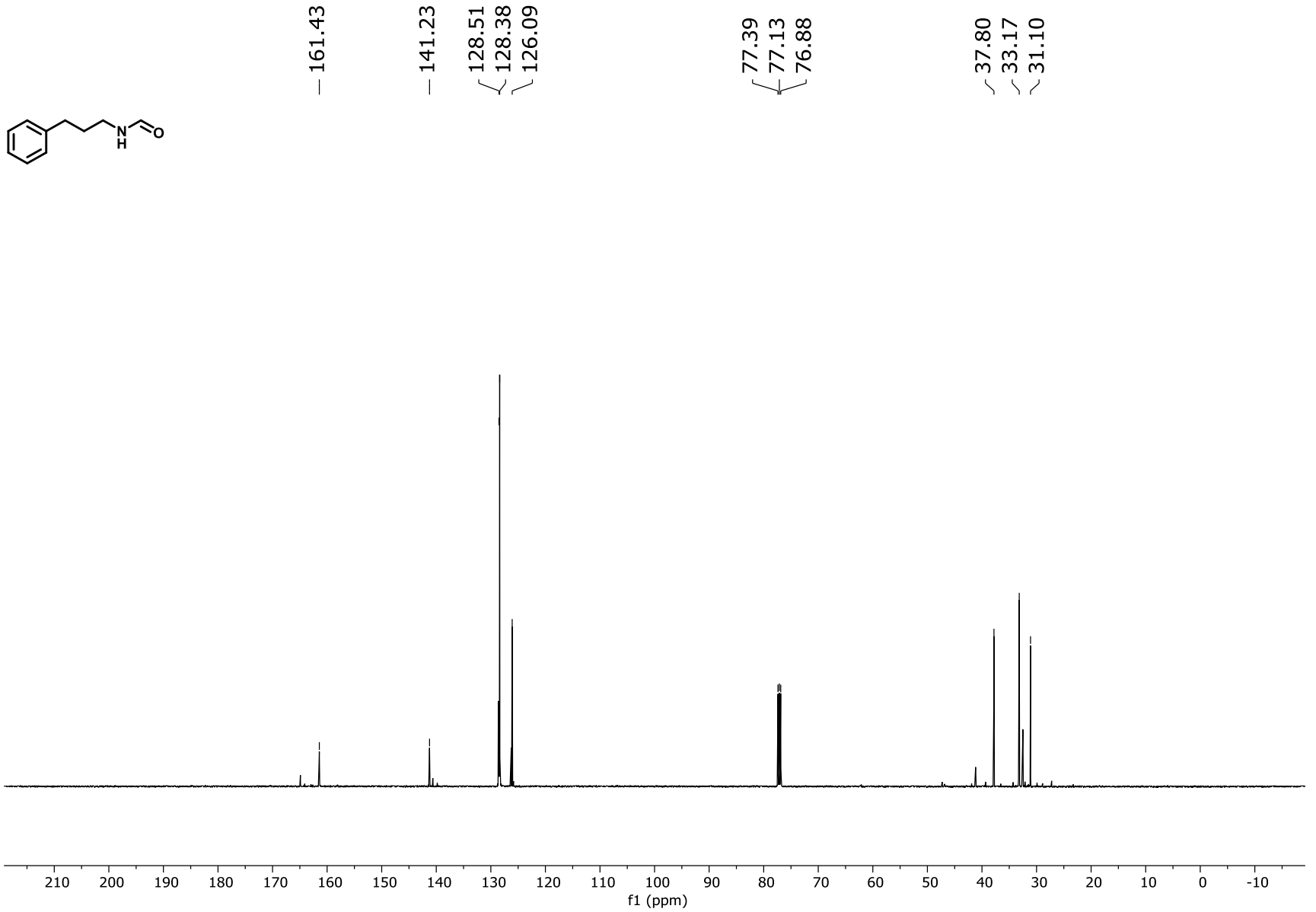
*87. Compound **26d** ^{13}C NMR*



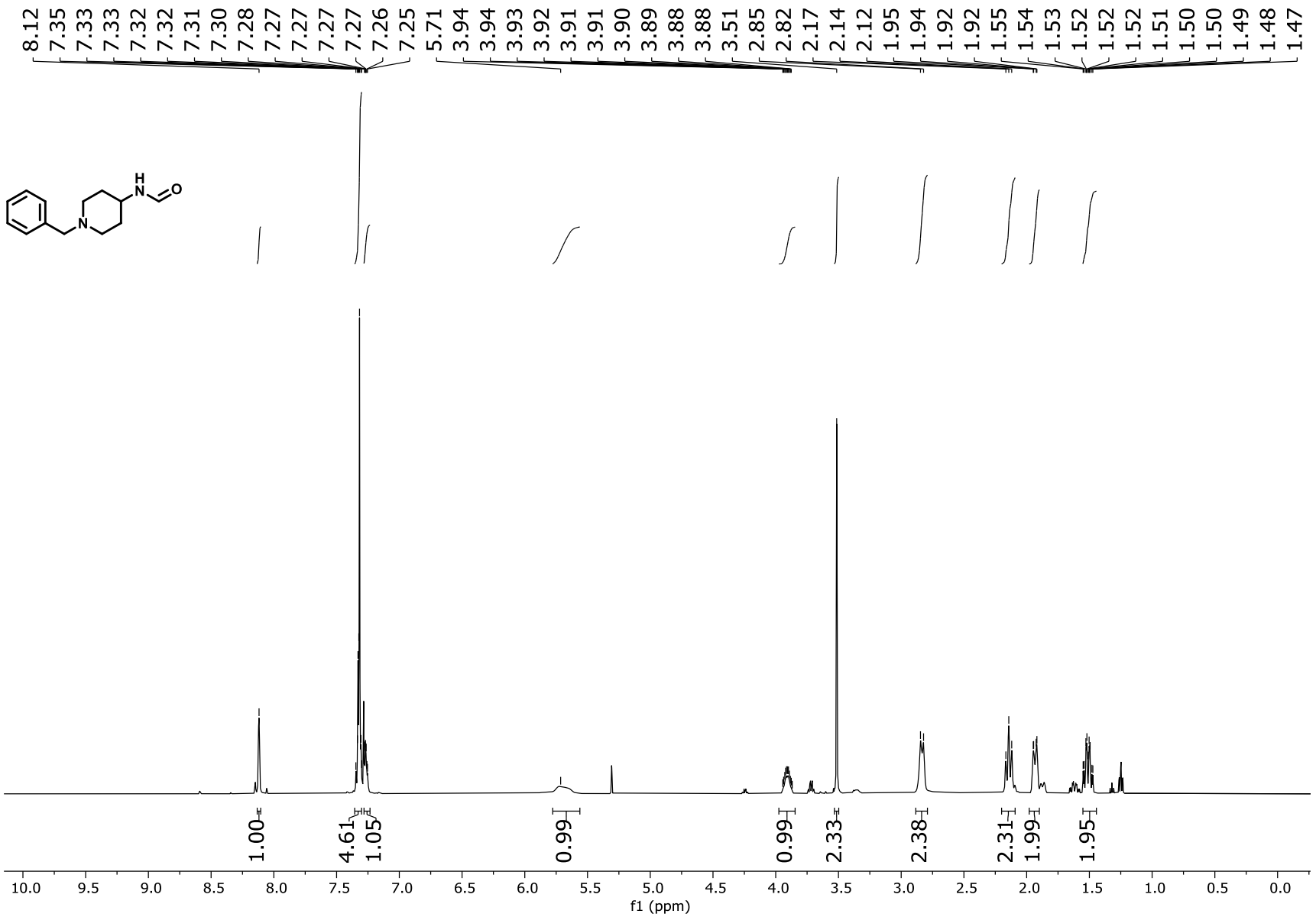
*88. Compound **26e** ^{1}H NMR*



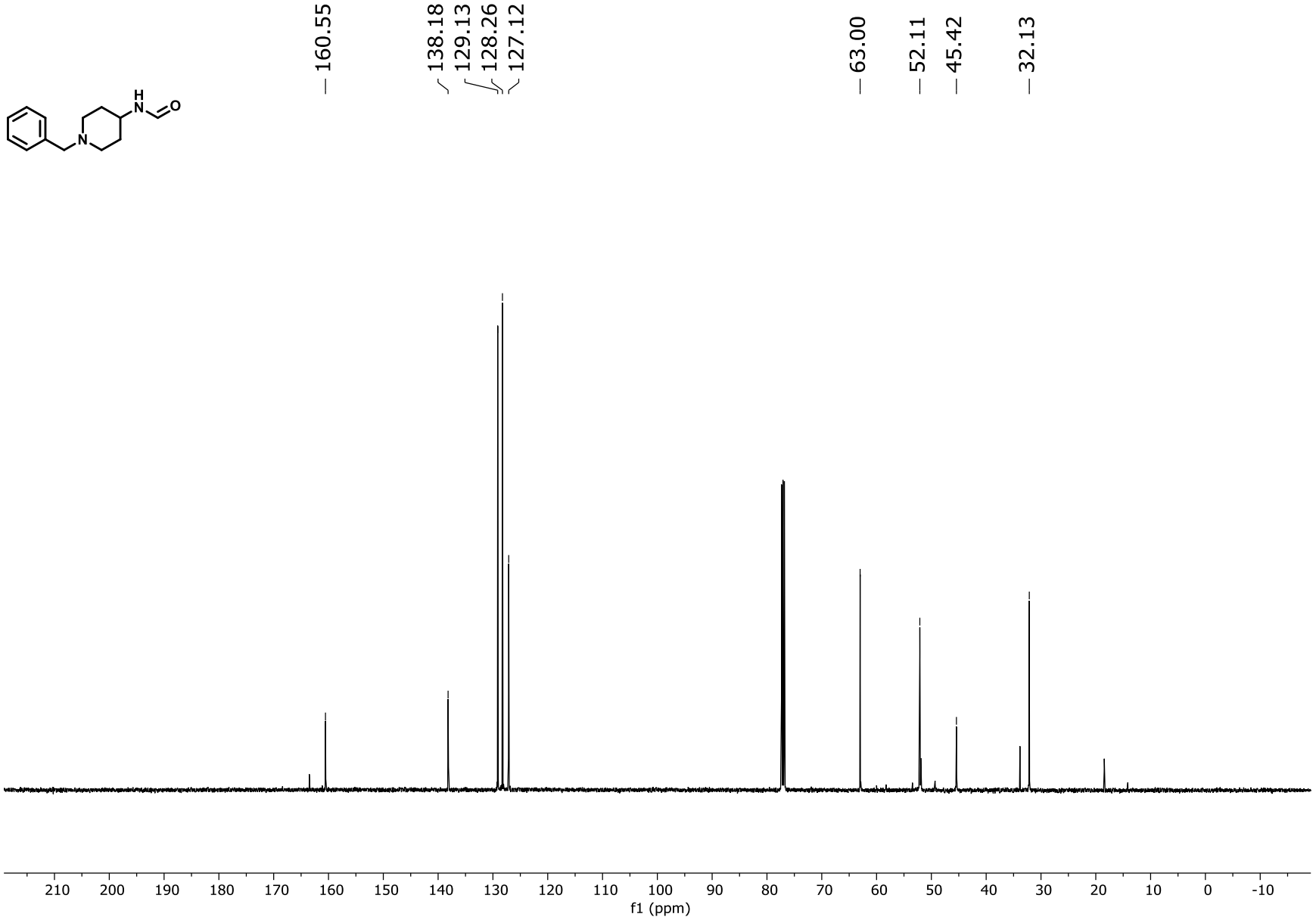
*89. Compound **26e** ^{13}C NMR*



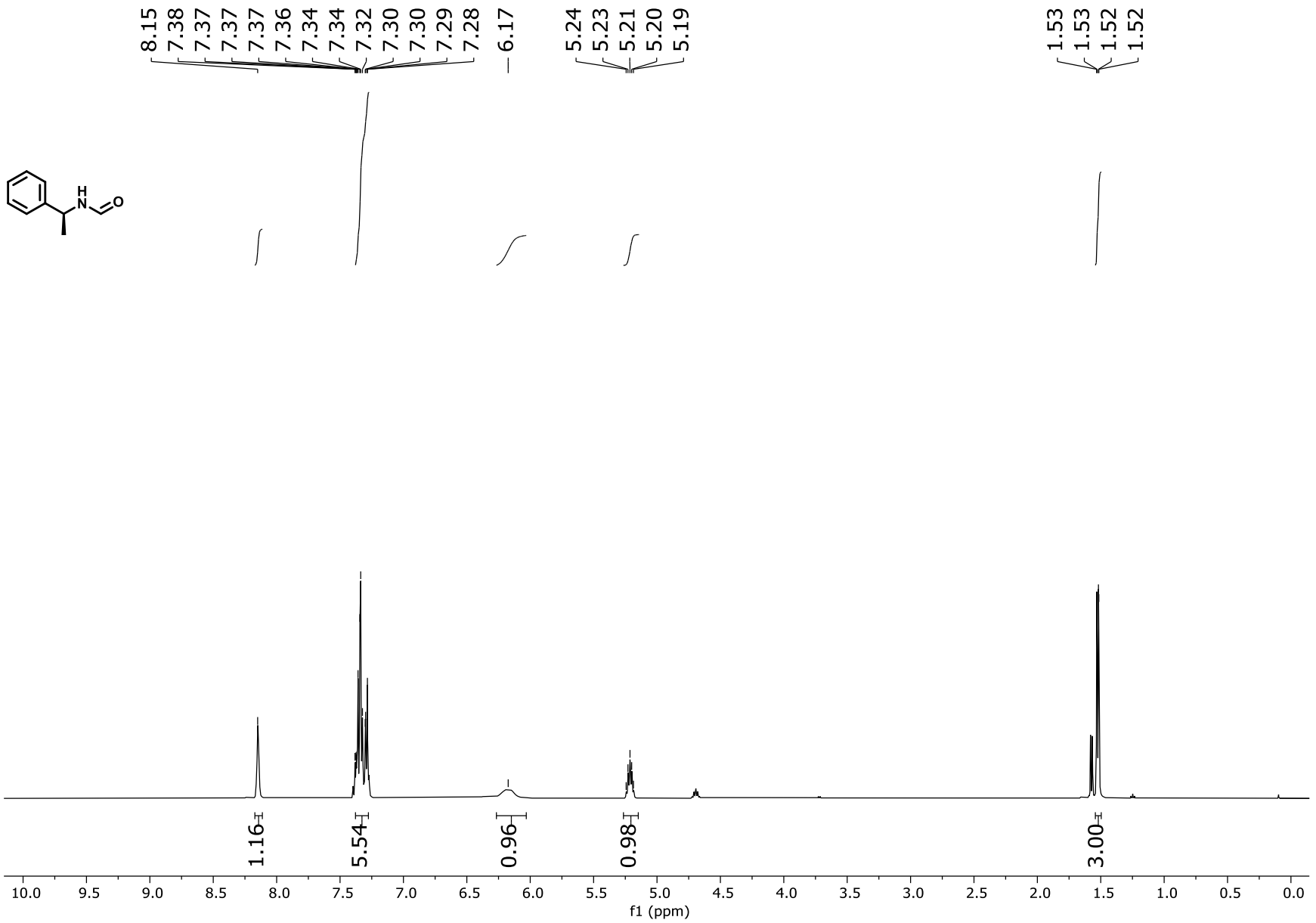
*90. Compound **26f** ^{1}H NMR*



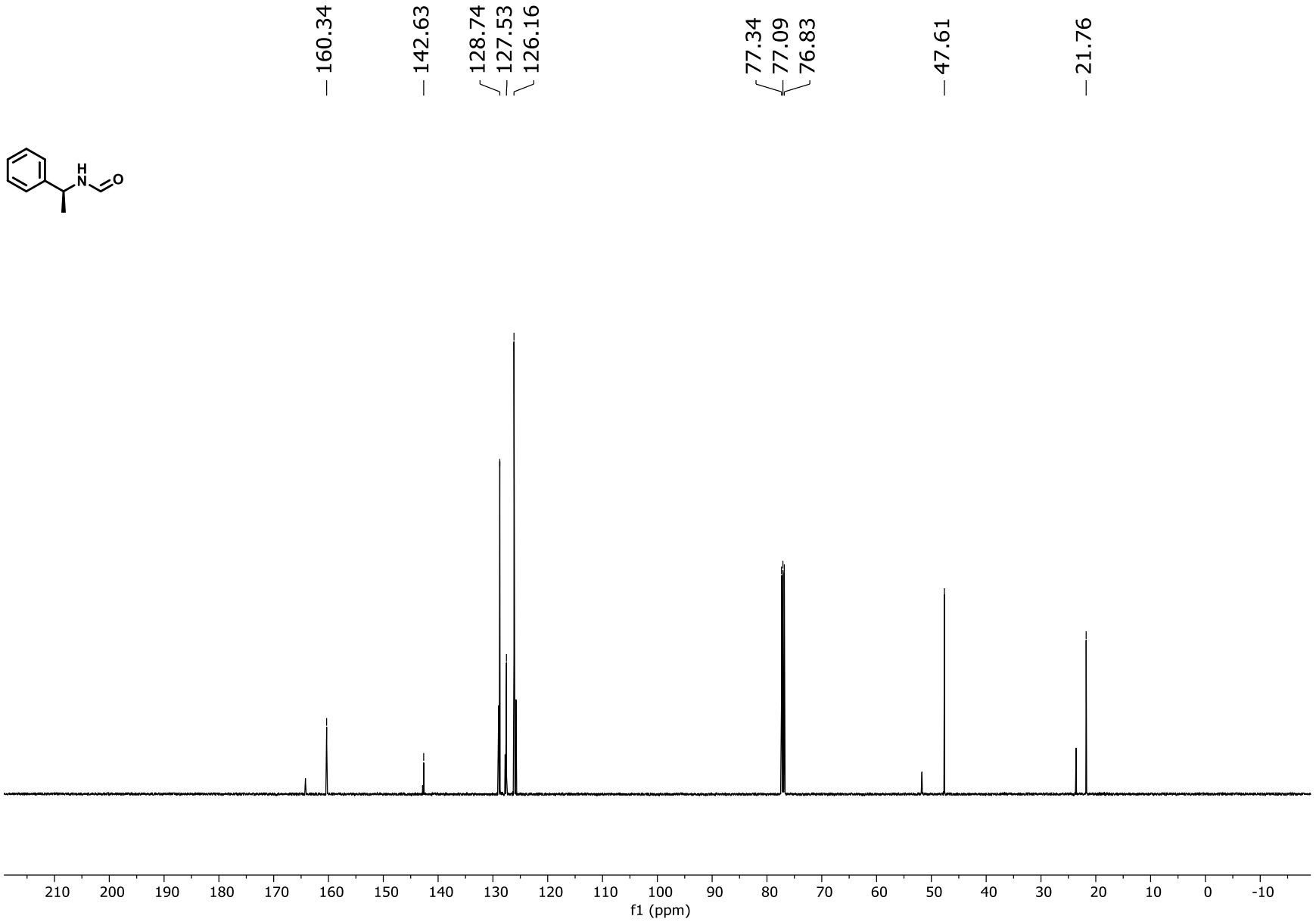
*91. Compound **26f** ^{13}C NMR*



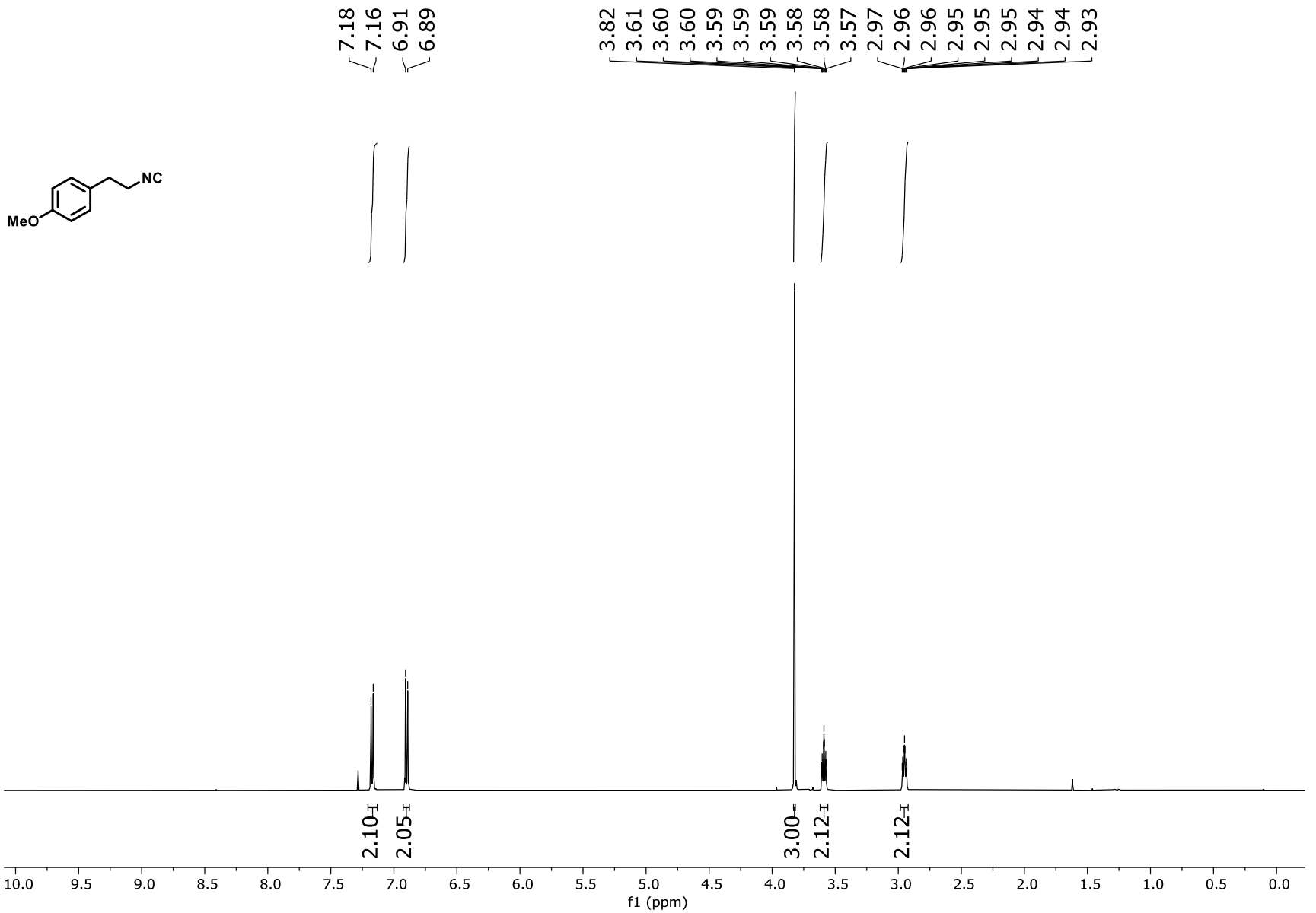
*92. Compound **26g** ^{1}H NMR*



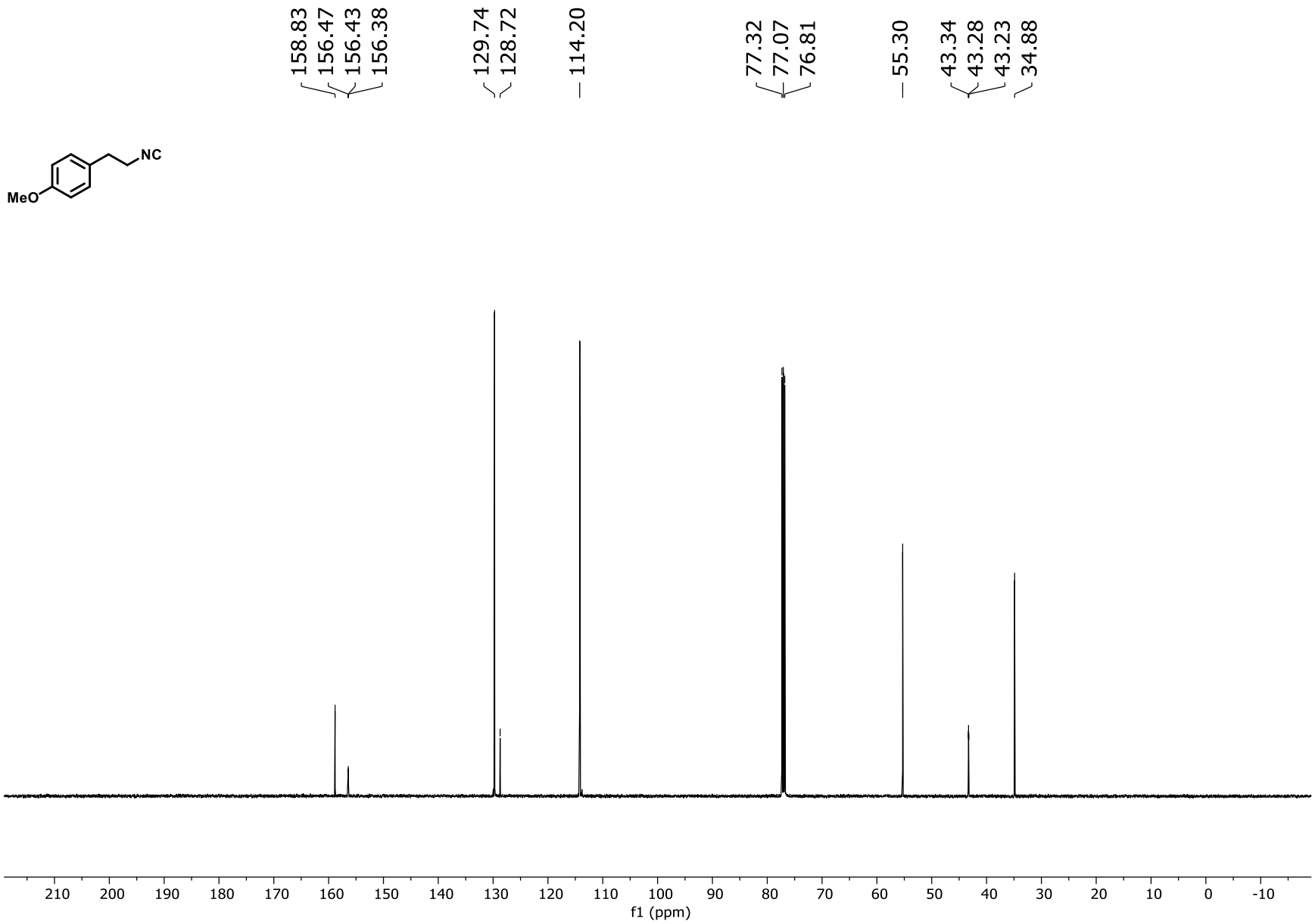
*93. Compound **26g** ^{13}C NMR*



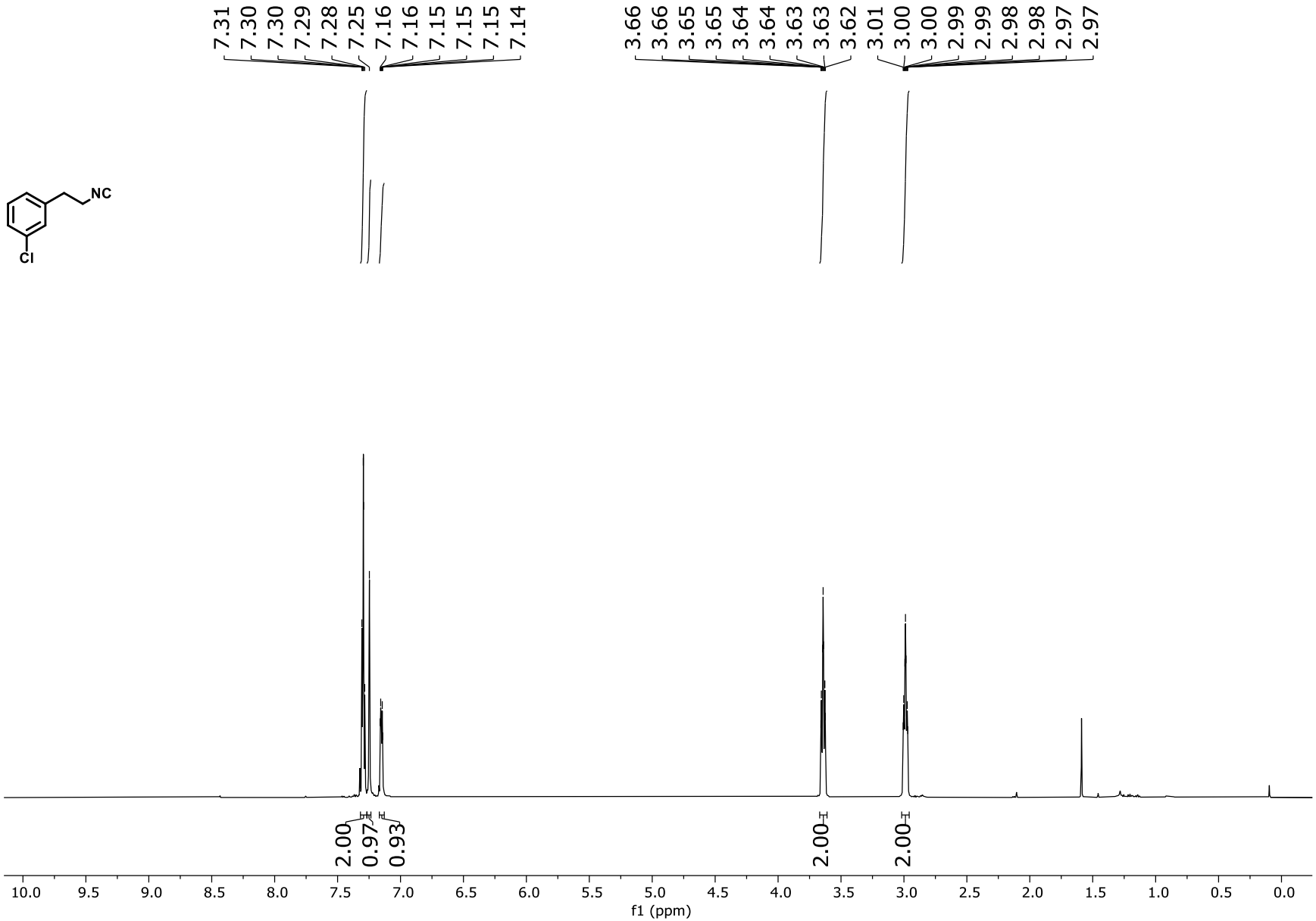
*94. Compound **27b** ^{1}H NMR*



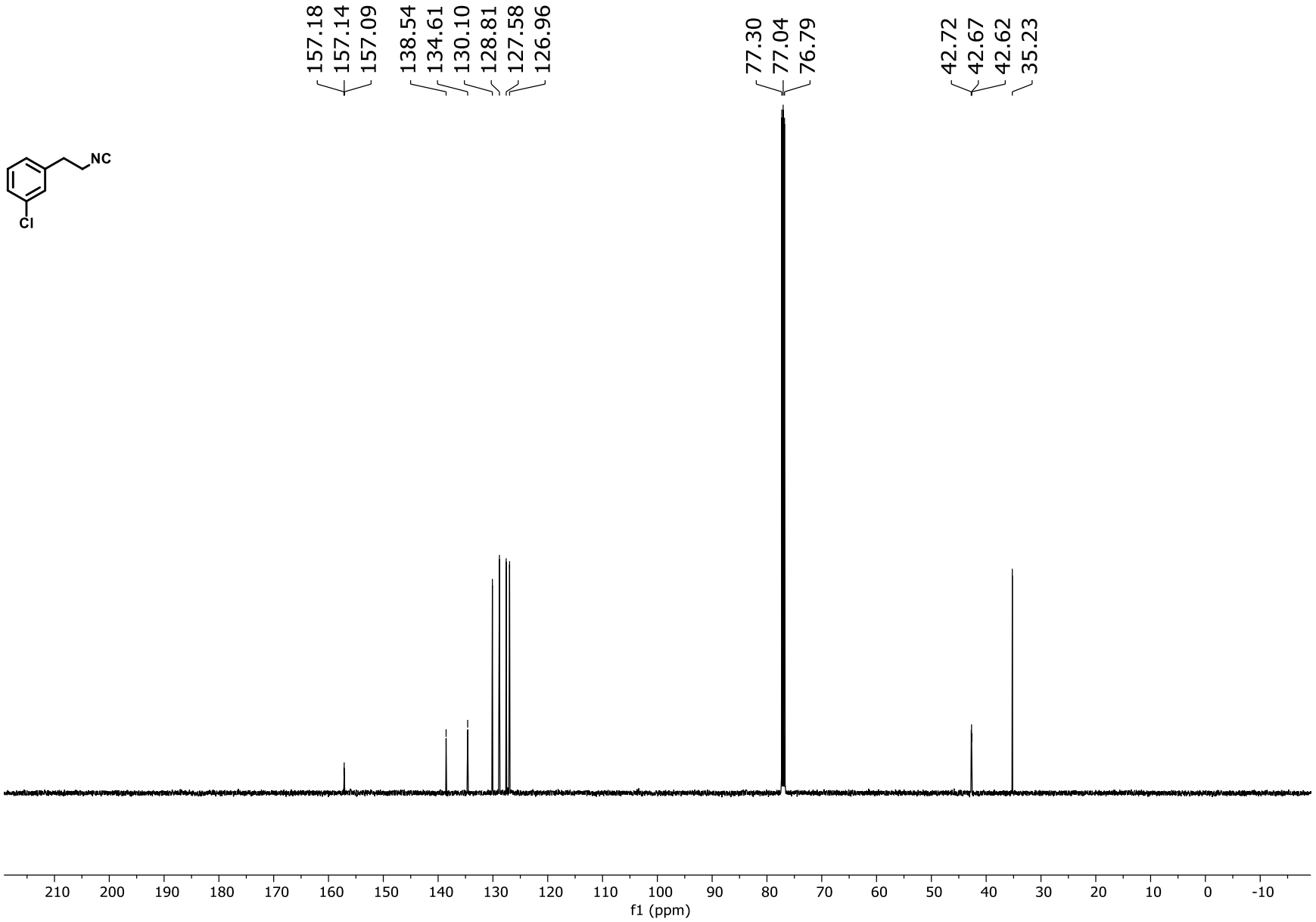
*95. Compound **27b** ^{13}C NMR*



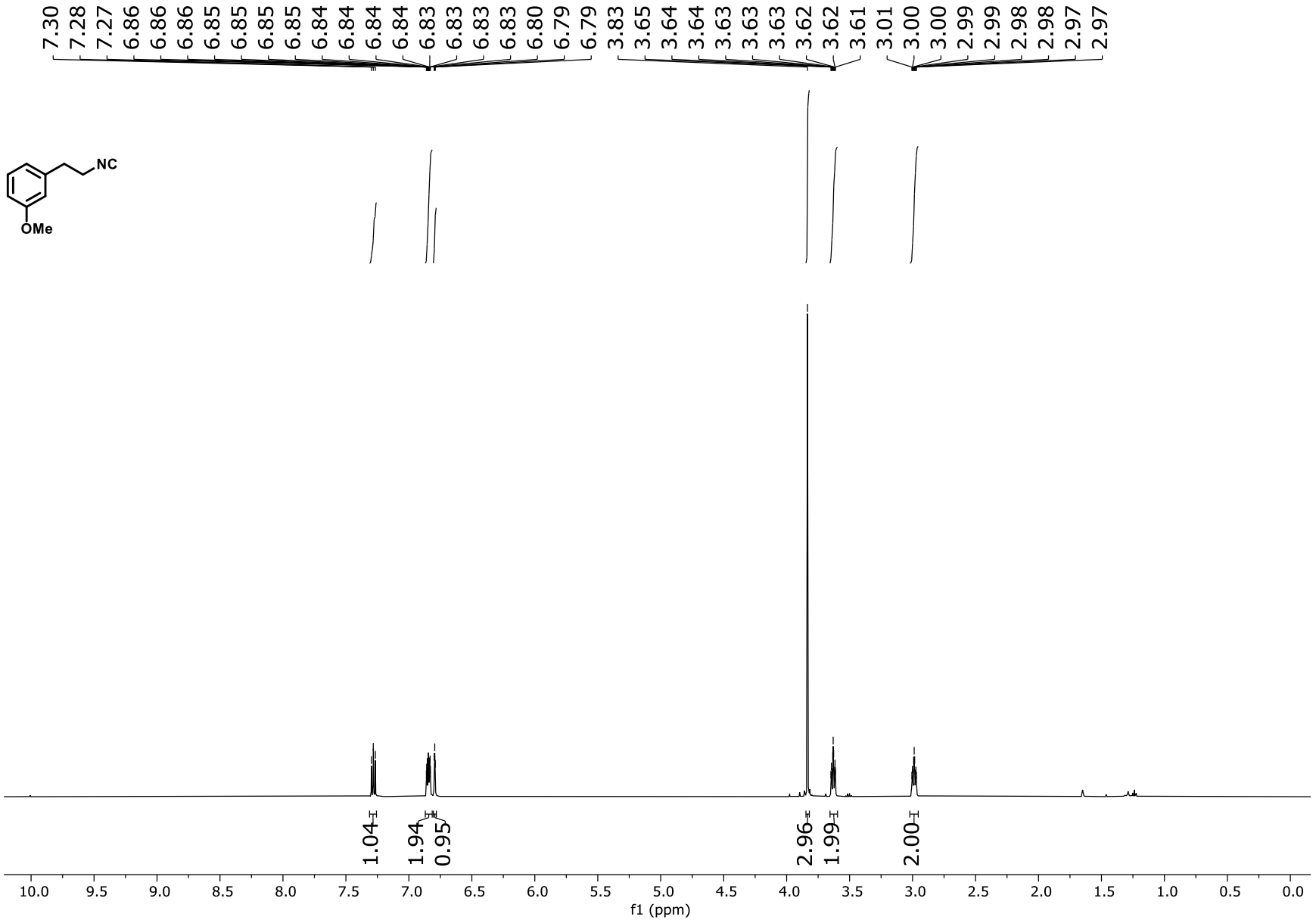
*96. Compound **27c** ^{1}H NMR*



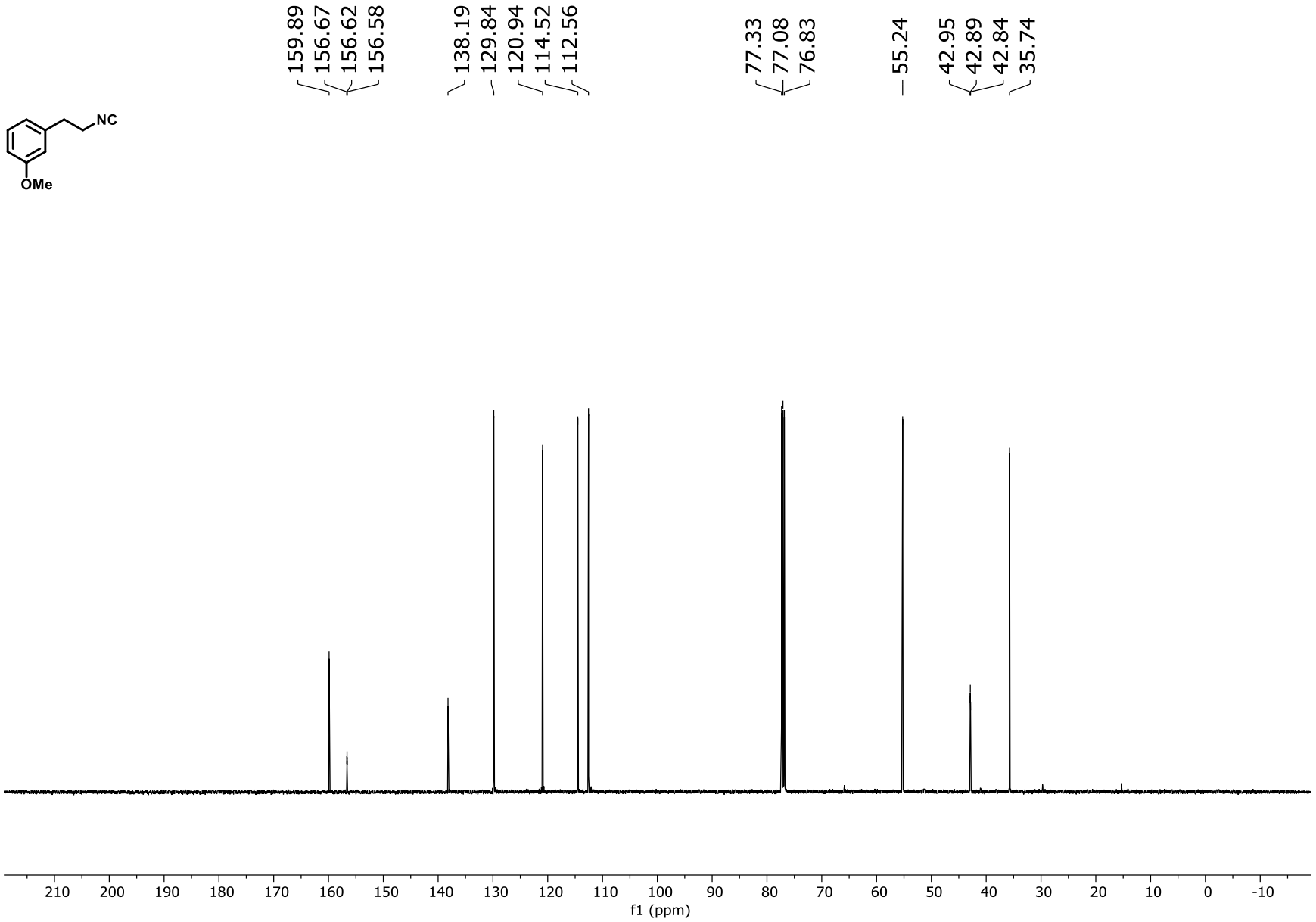
*97. Compound **27c** ^{13}C NMR*



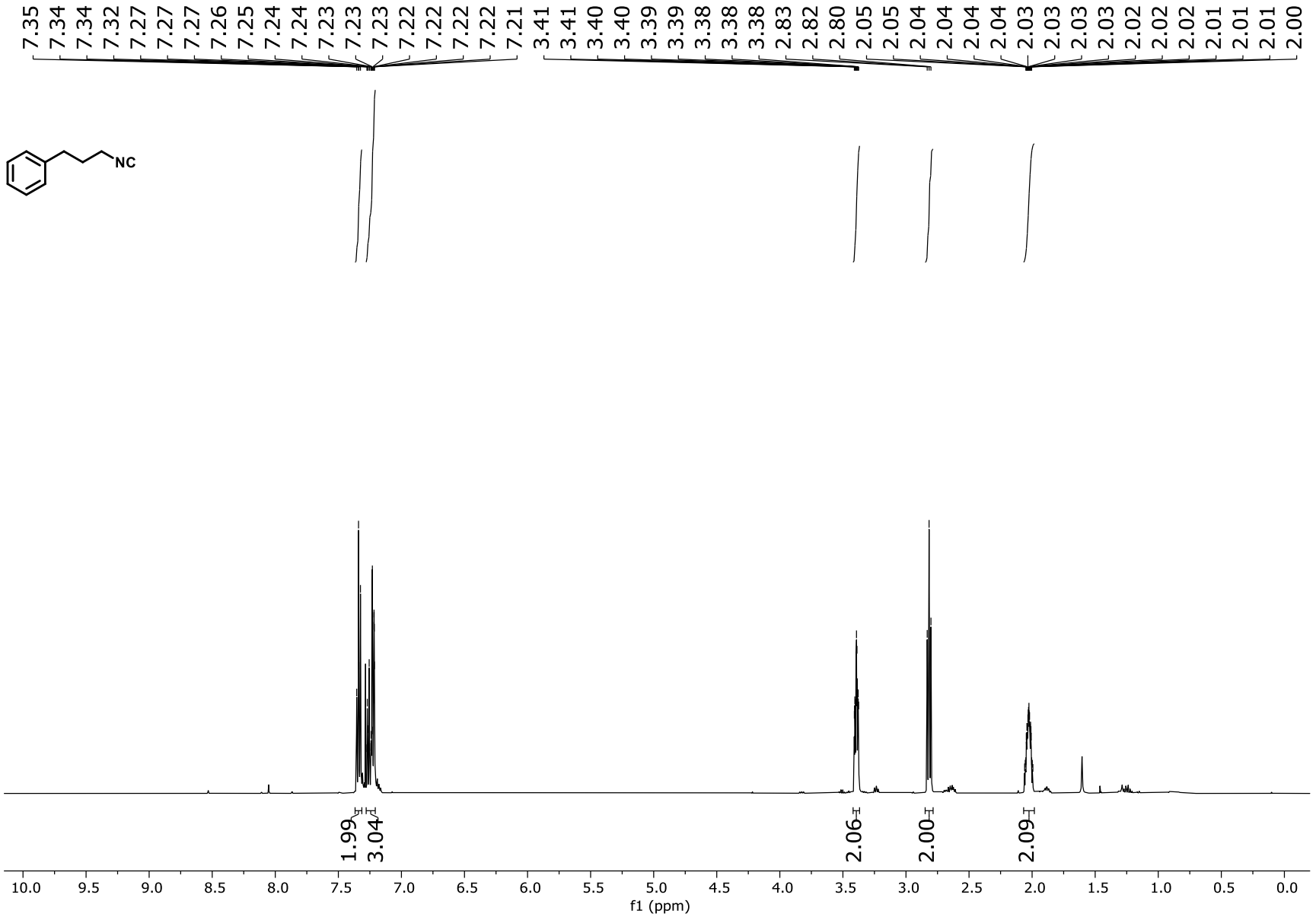
*98. Compound **27d** ^{1}H NMR*



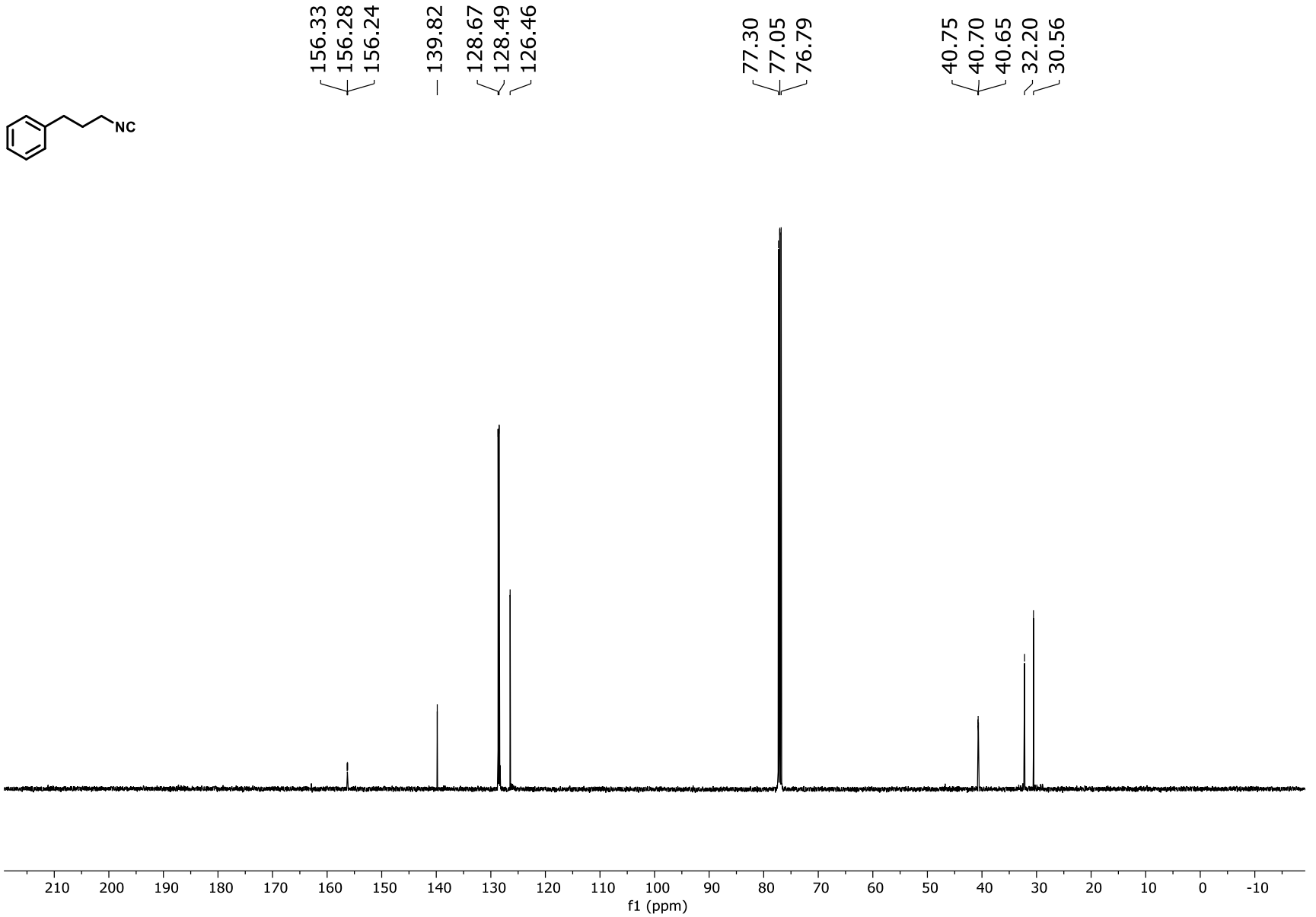
*99. Compound **27d** ^{13}C NMR*



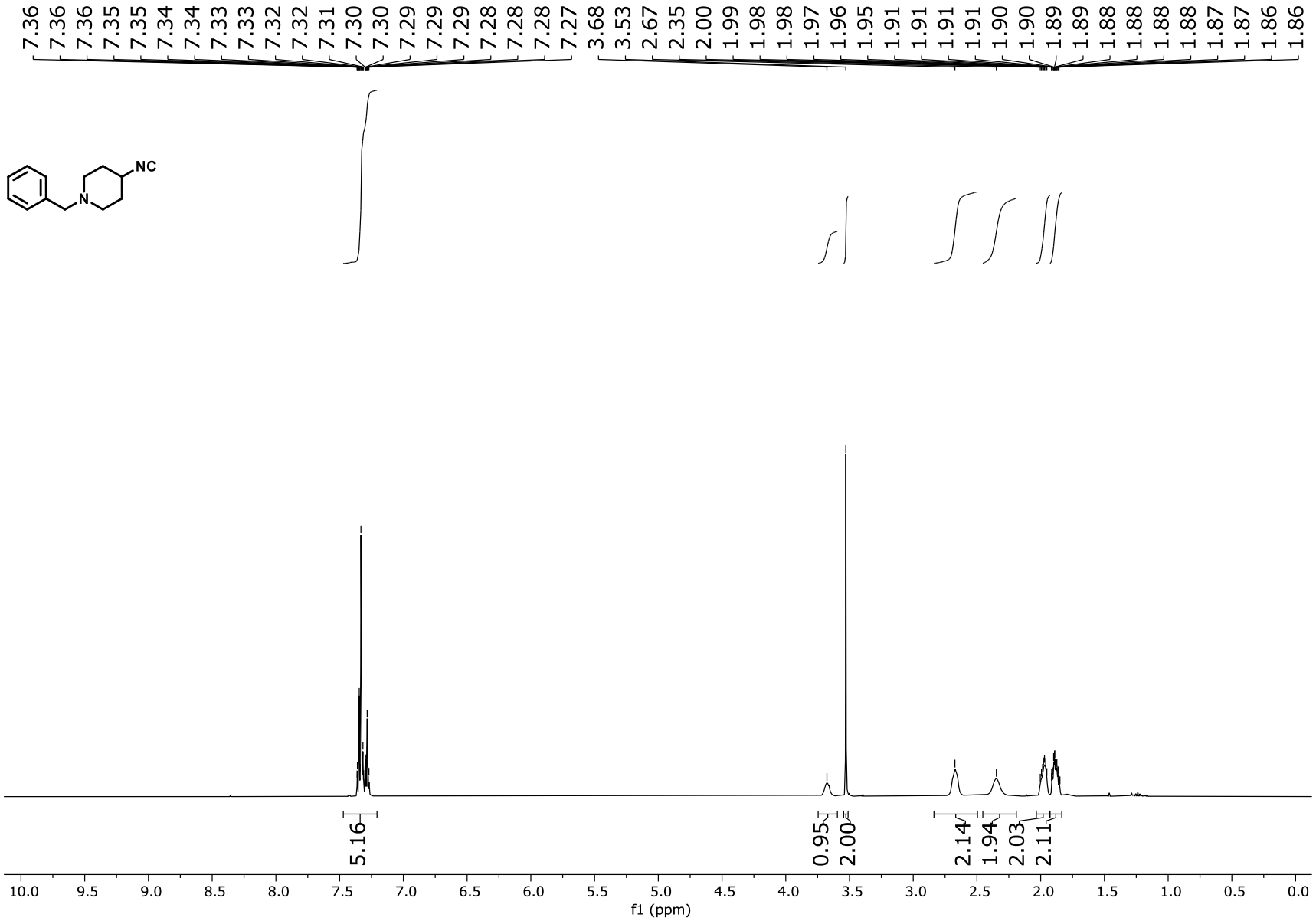
*100. Compound **27e** ^{1}H NMR*



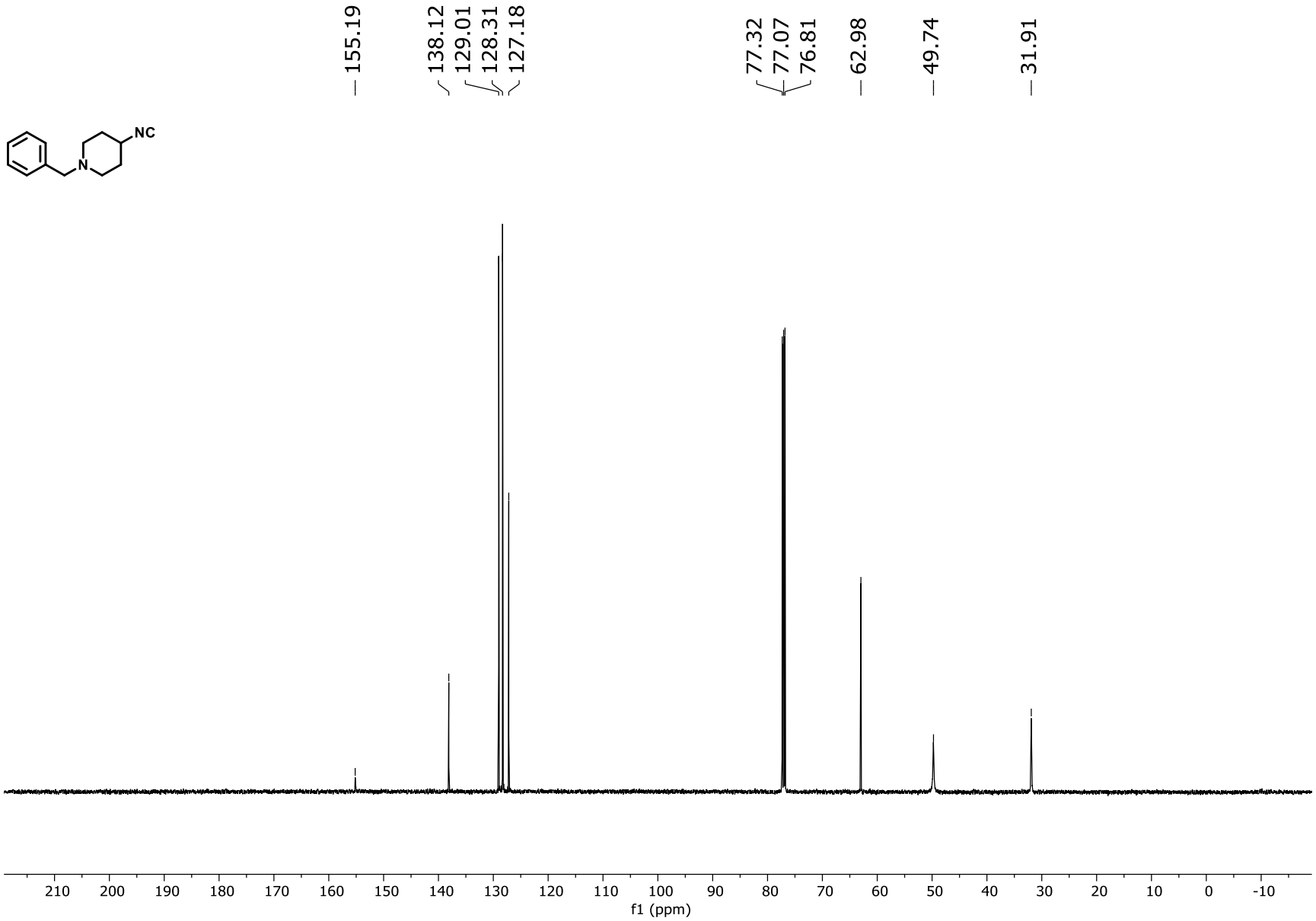
*101. Compound **27e** ^{13}C NMR*



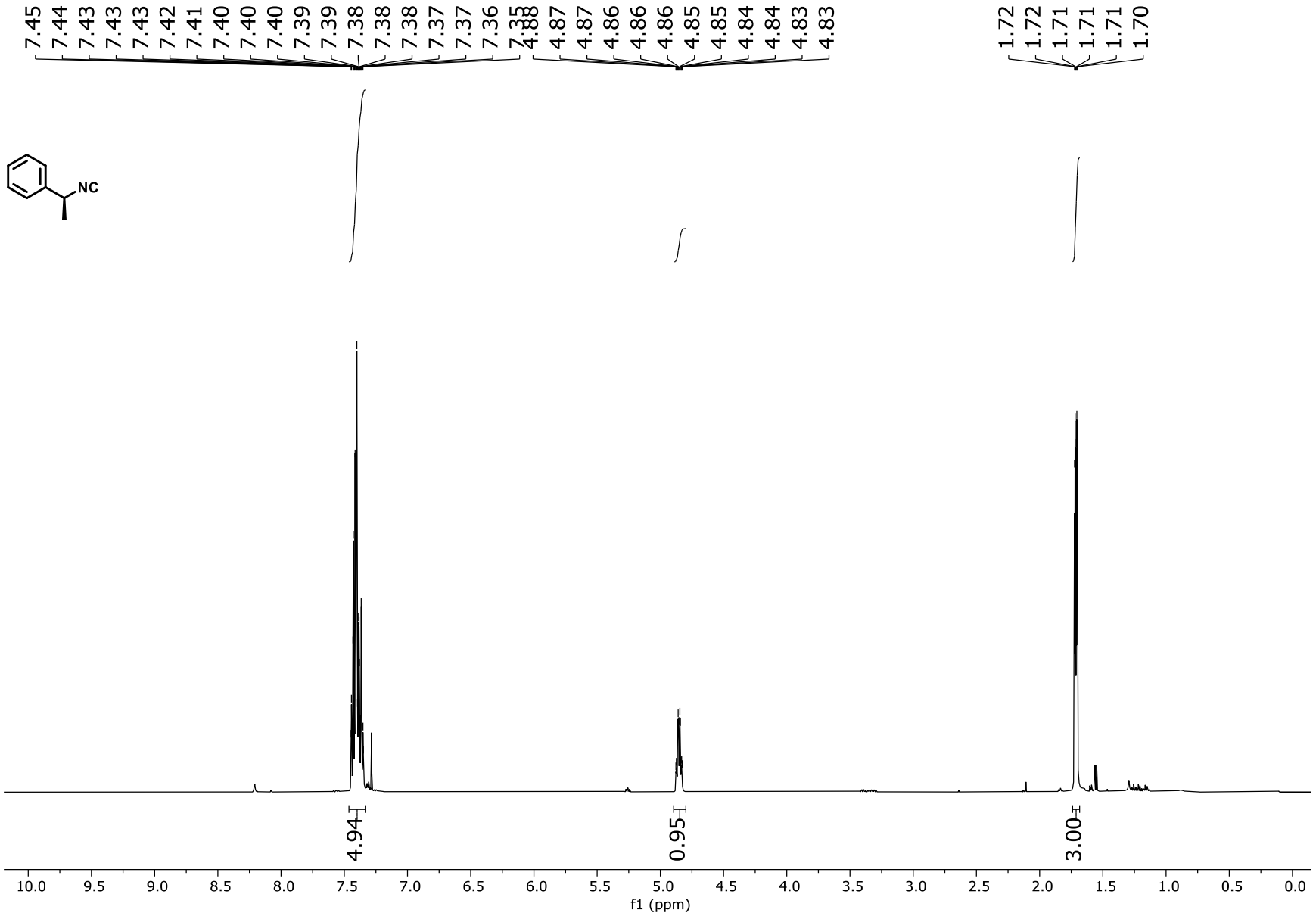
*102. Compound **27f** ^{1}H NMR*



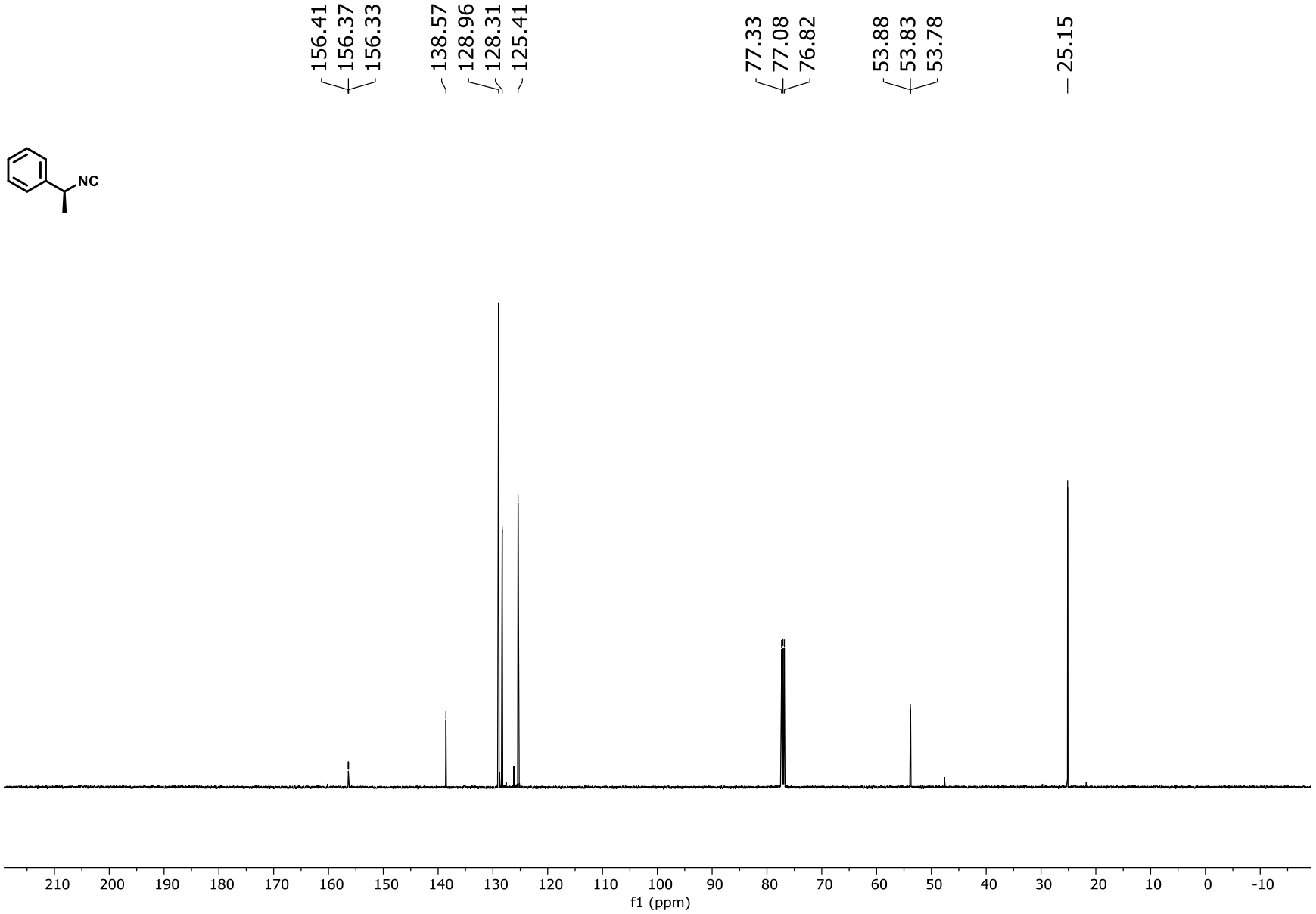
*103. Compound **27f** ^{13}C NMR*



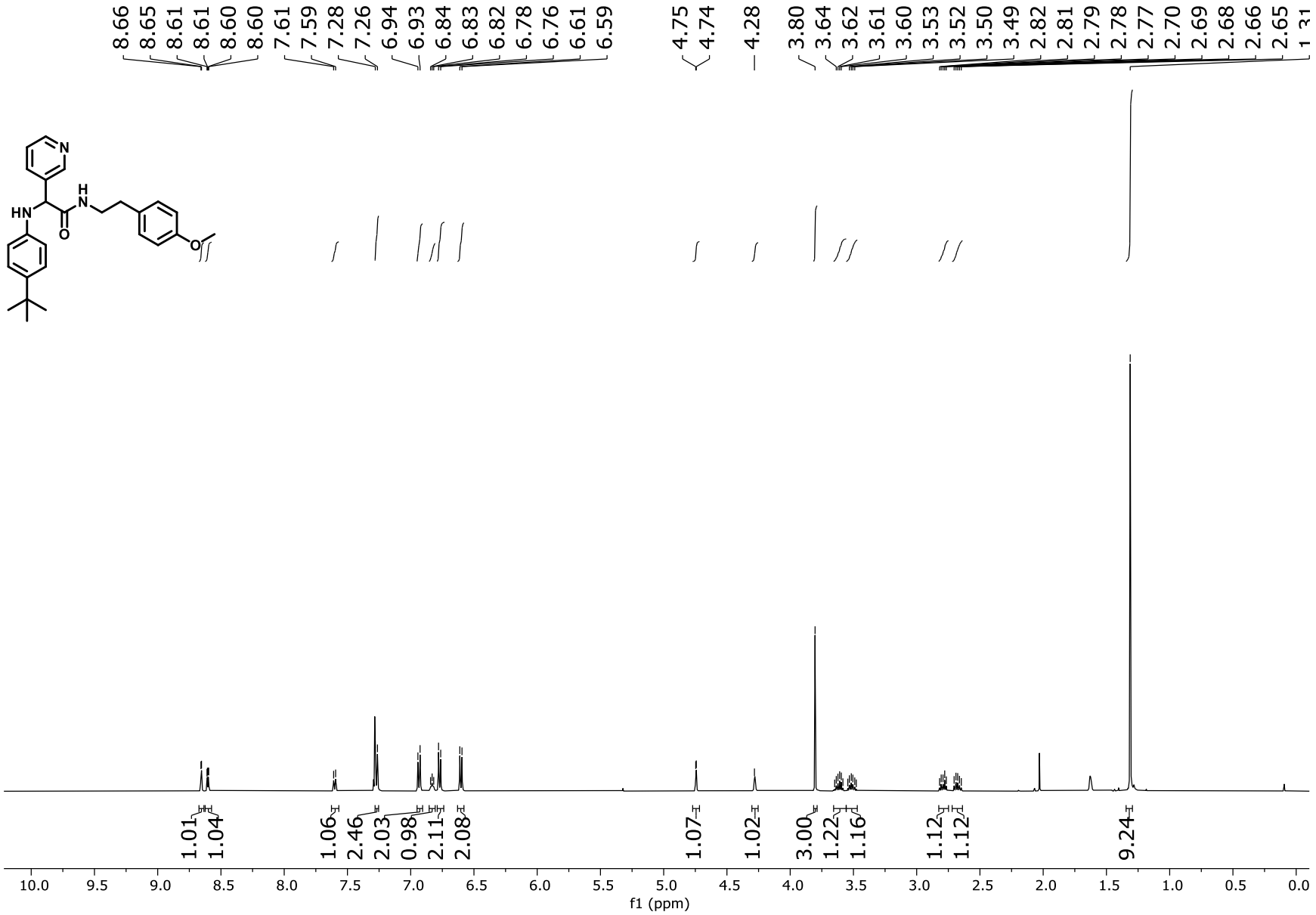
*104. Compound **27g** ^{1}H NMR*



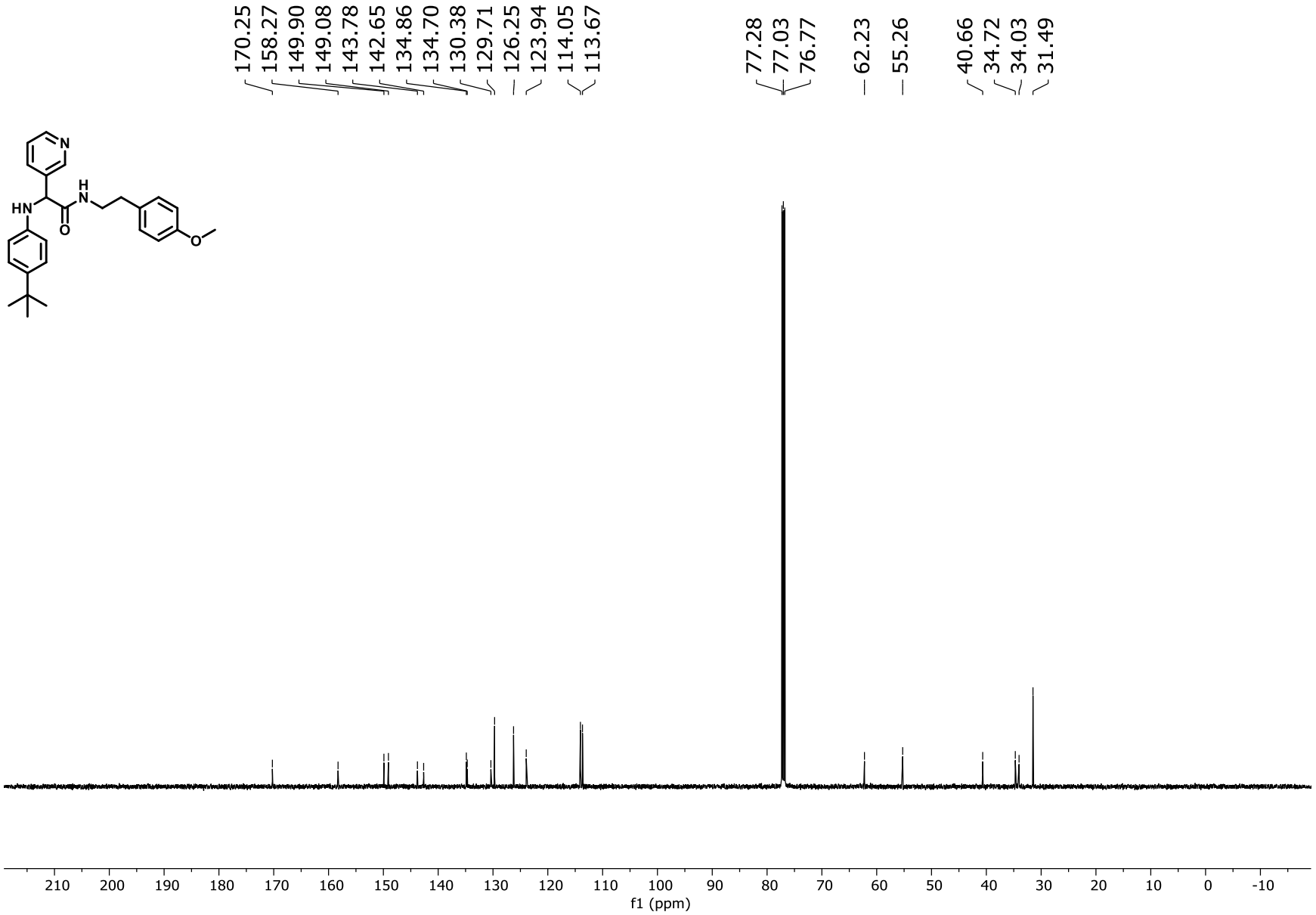
*105. Compound **27g** ^{13}C NMR*



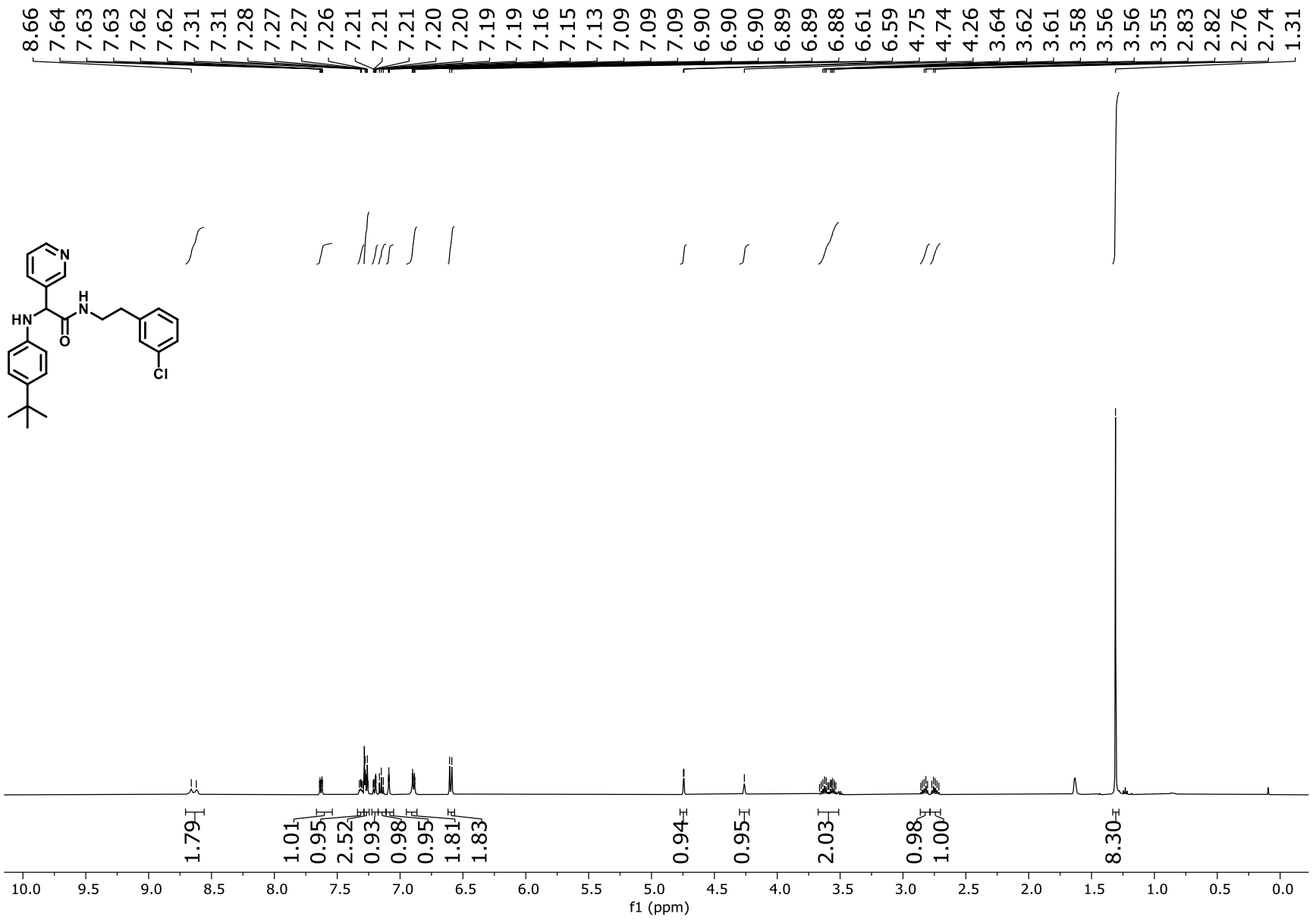
*106. Compound **28b** ^{1}H NMR*



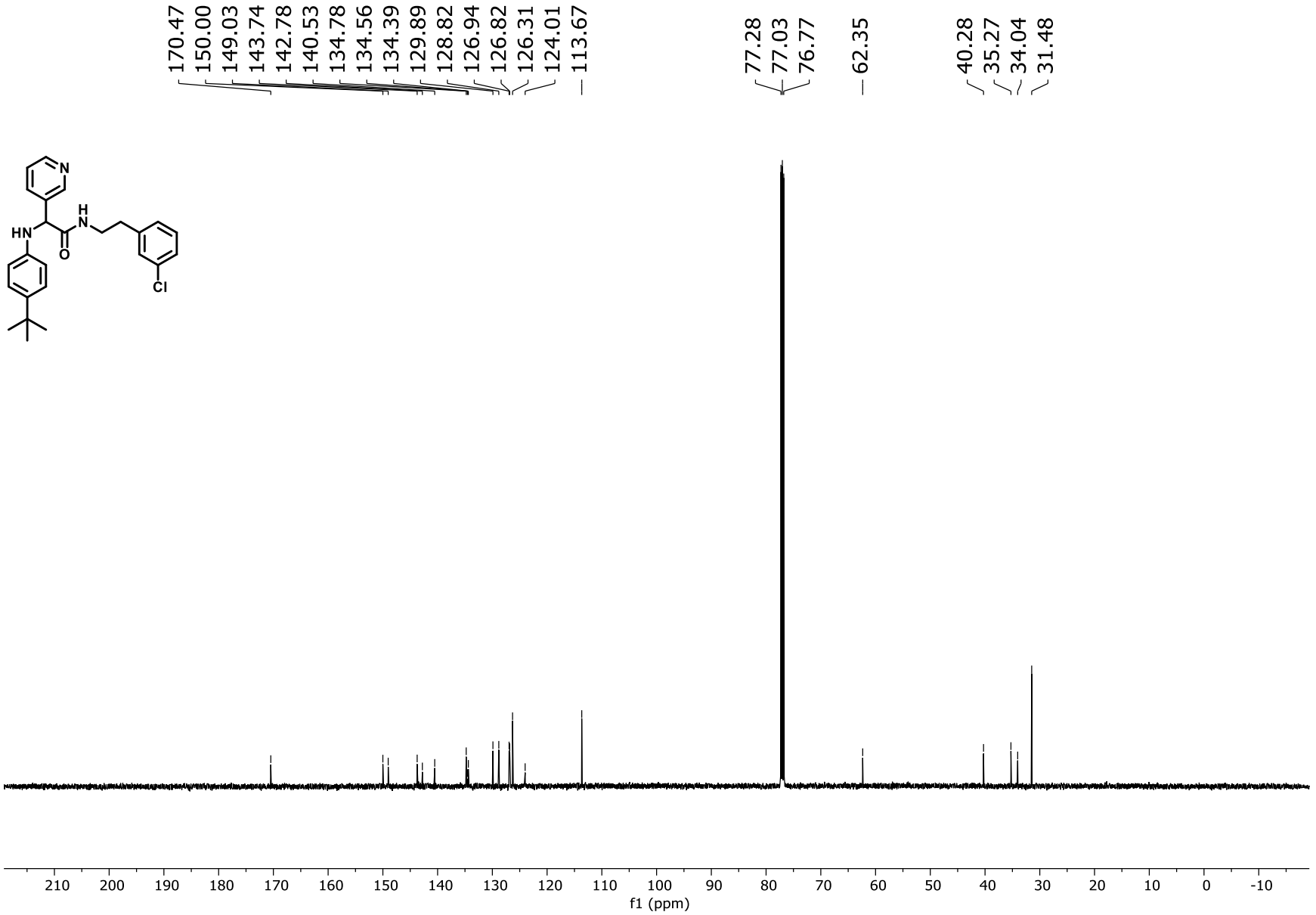
*107. Compound **28b** ^{13}C NMR*



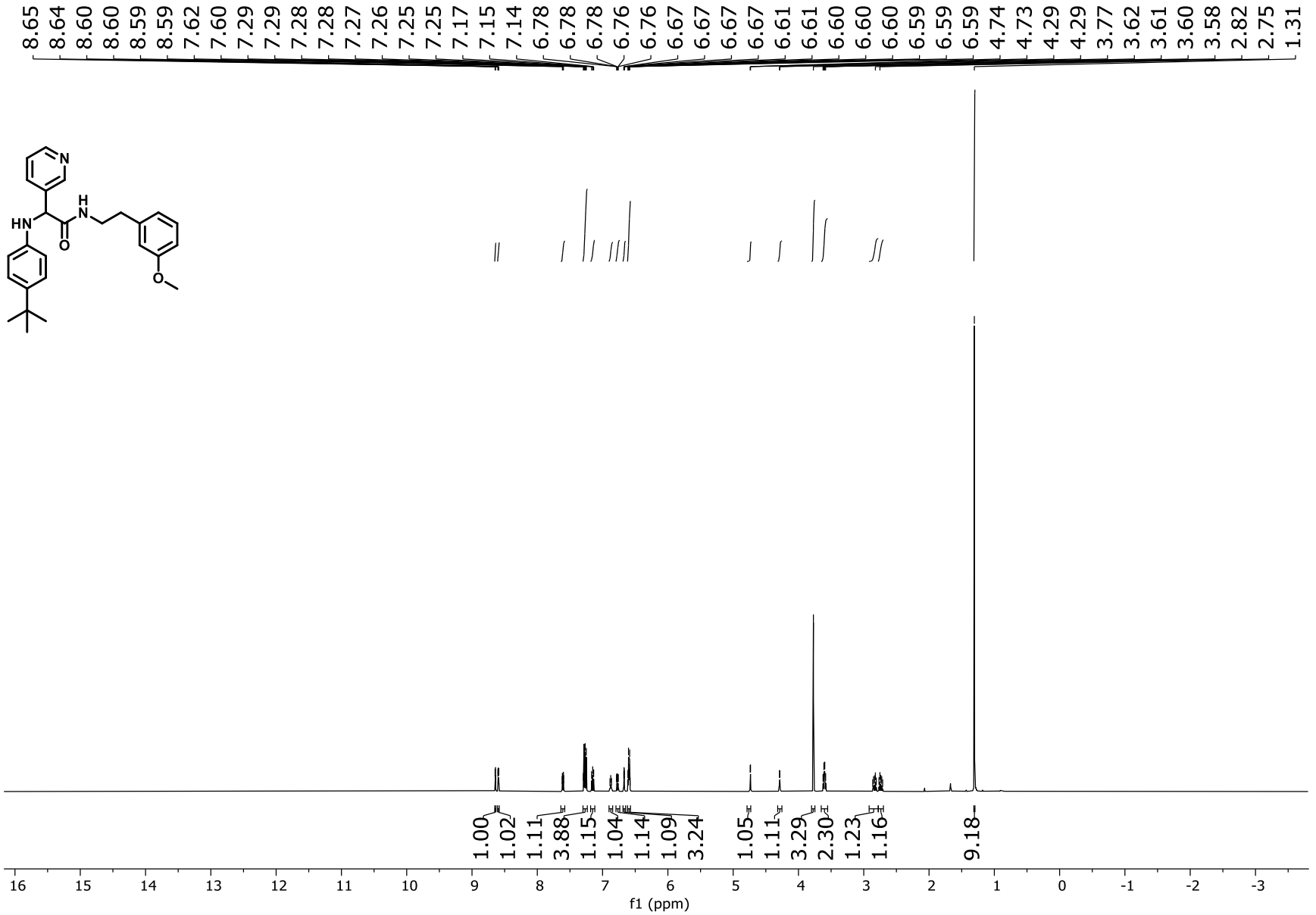
*108. Compound **28c** ^{1}H NMR*



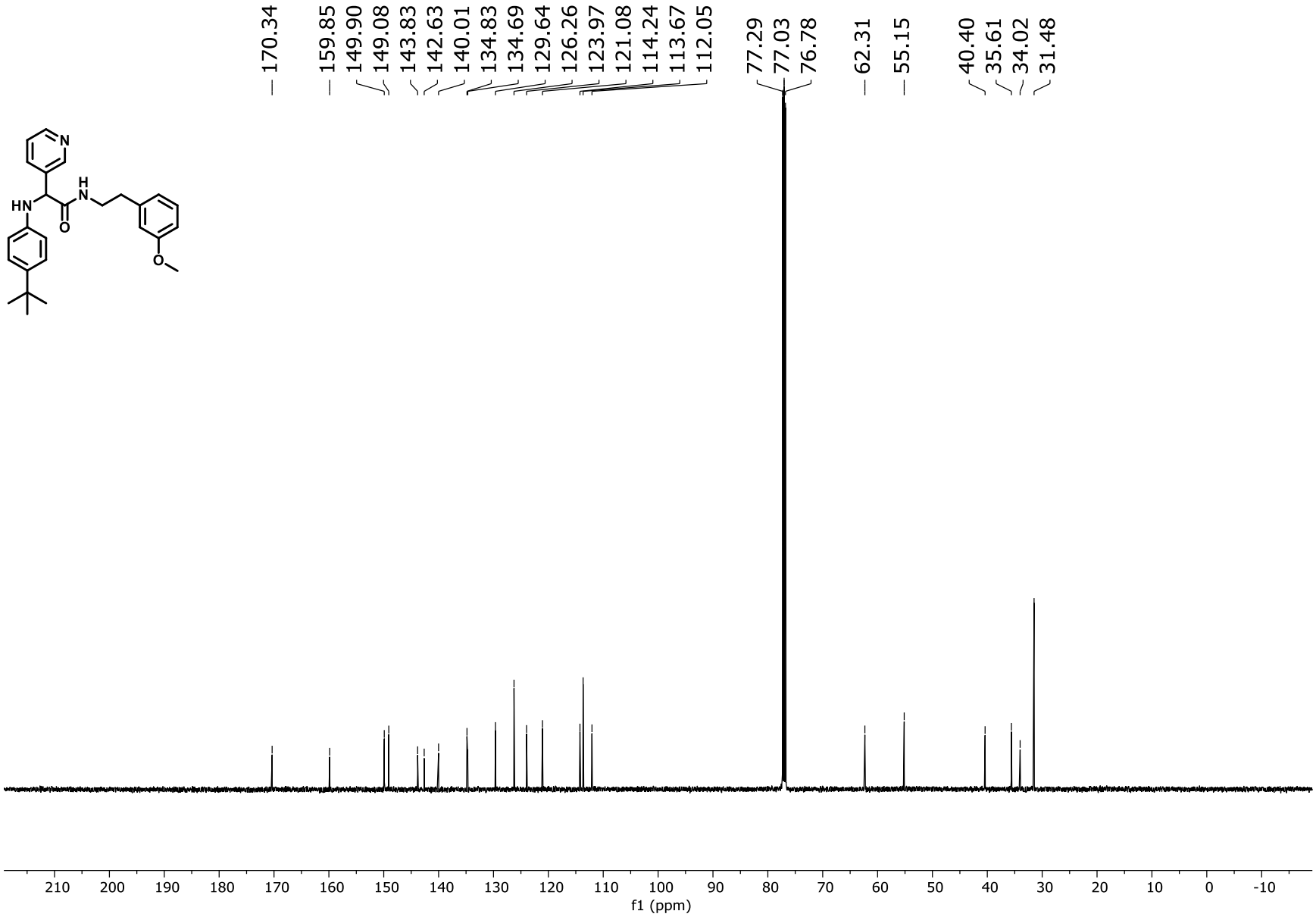
*109. Compound **28c** ^{13}C NMR*



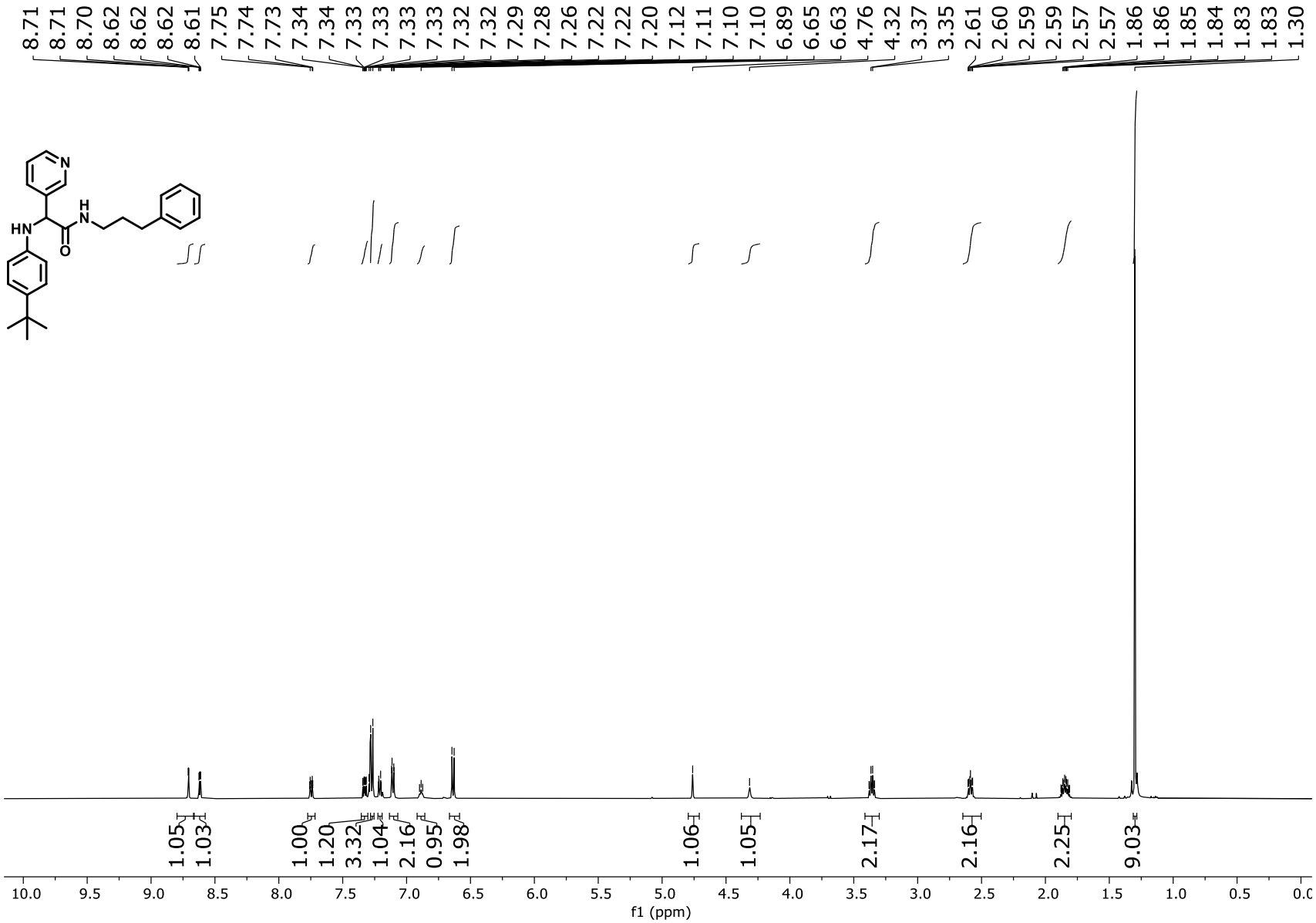
*110. Compound **28d** ^{1}H NMR*



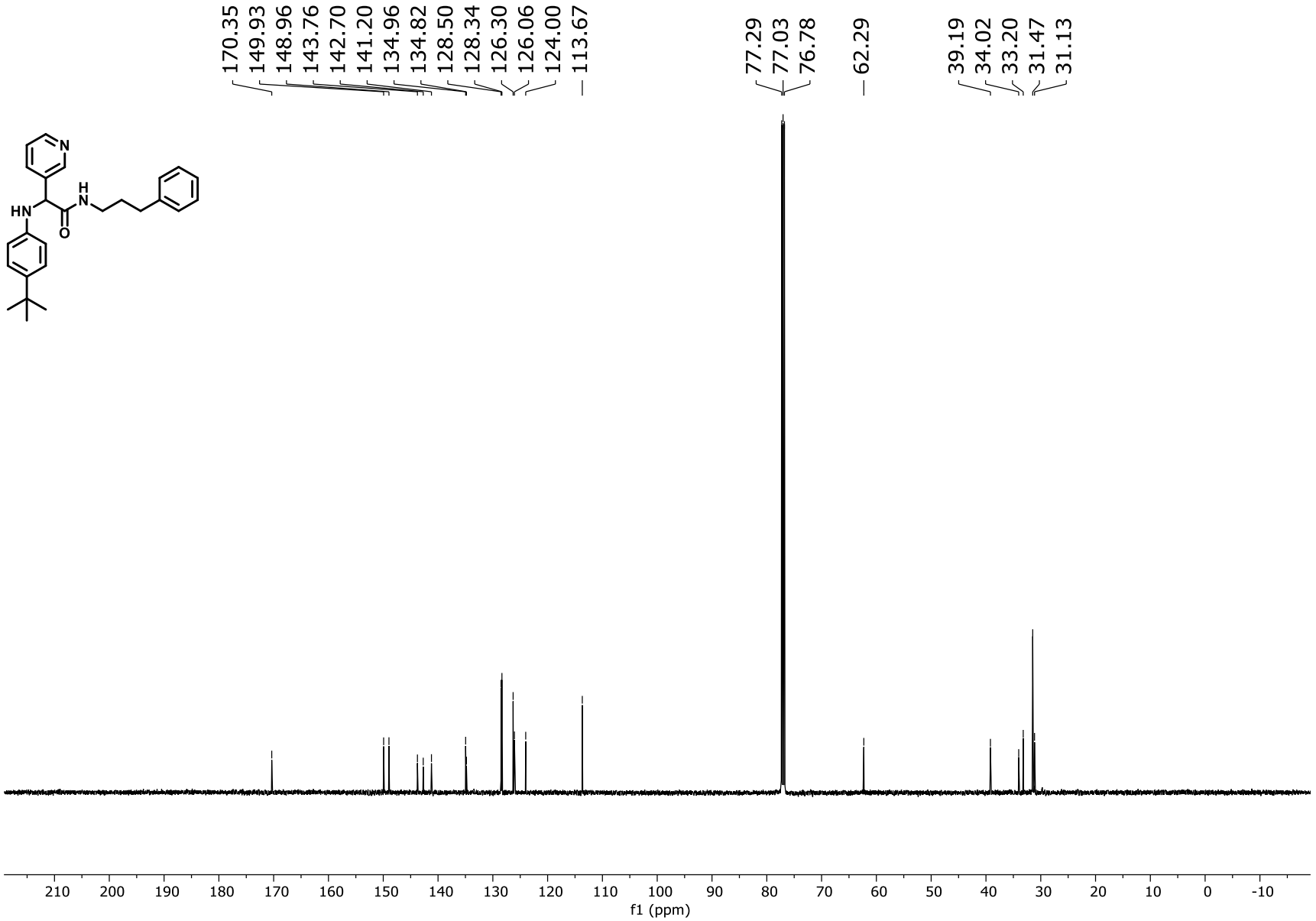
*111. Compound **28d** ^{13}C NMR*



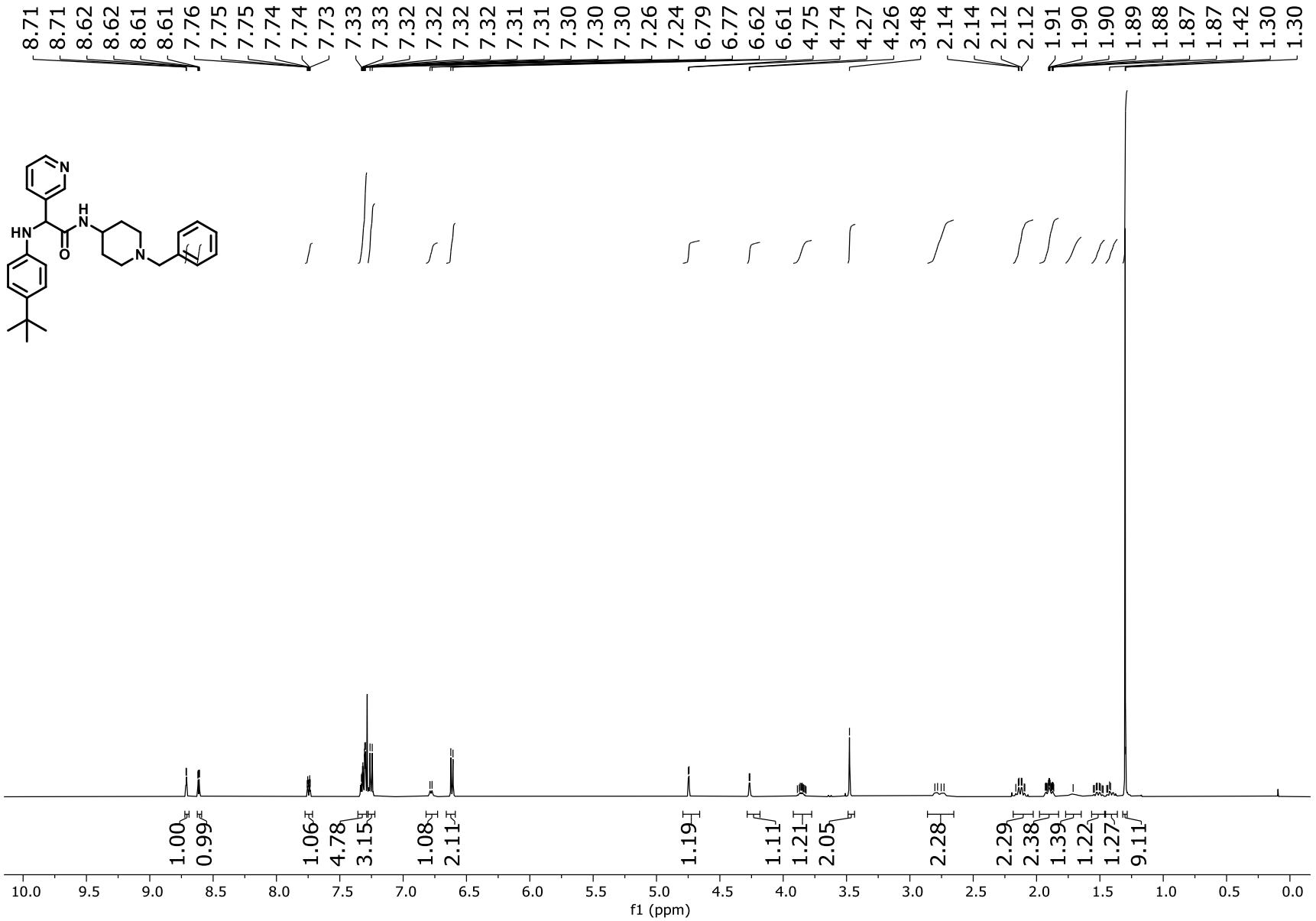
*112. Compound **28e** ^{1}H NMR*



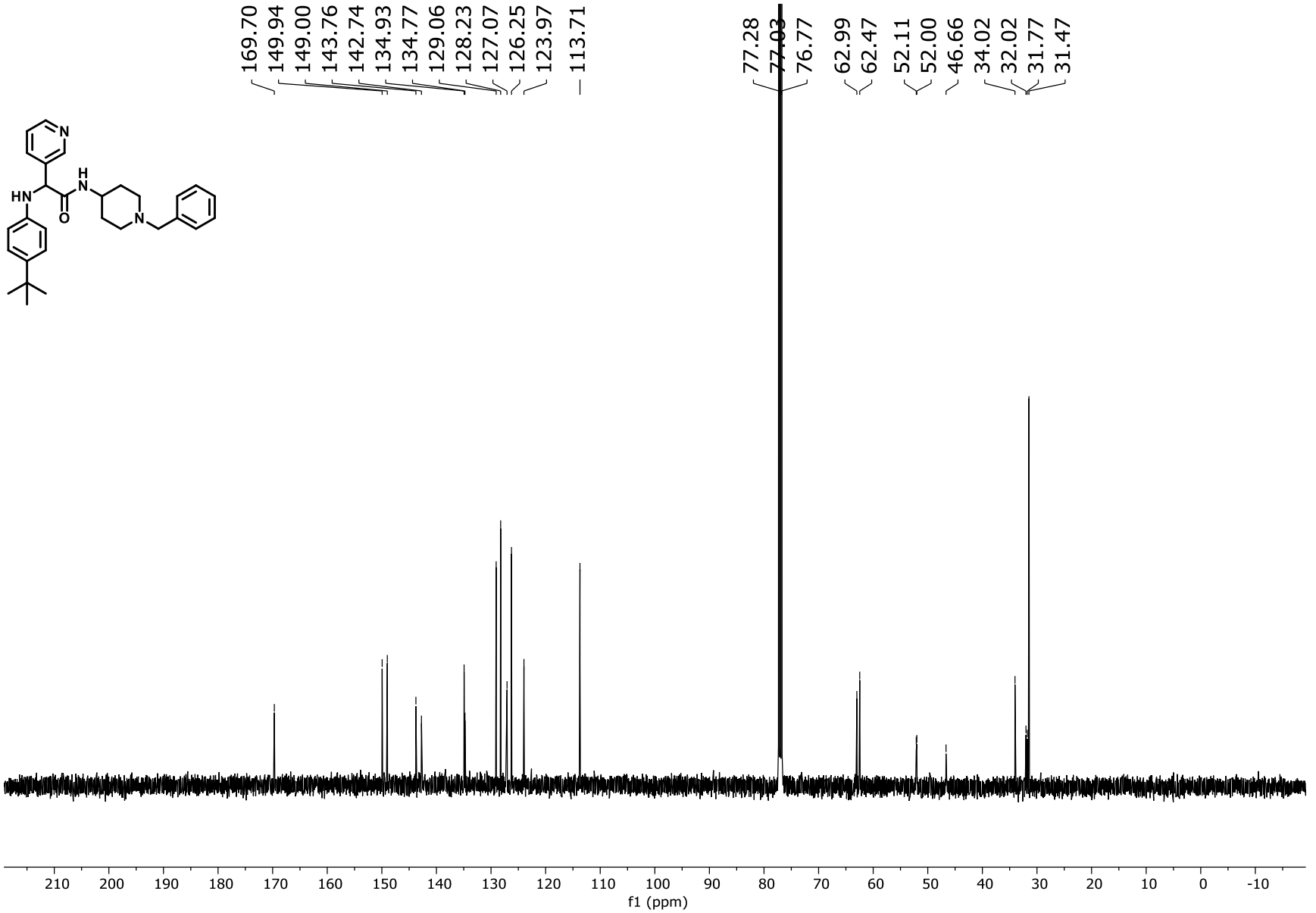
*113. Compound **28e** ^{13}C NMR*



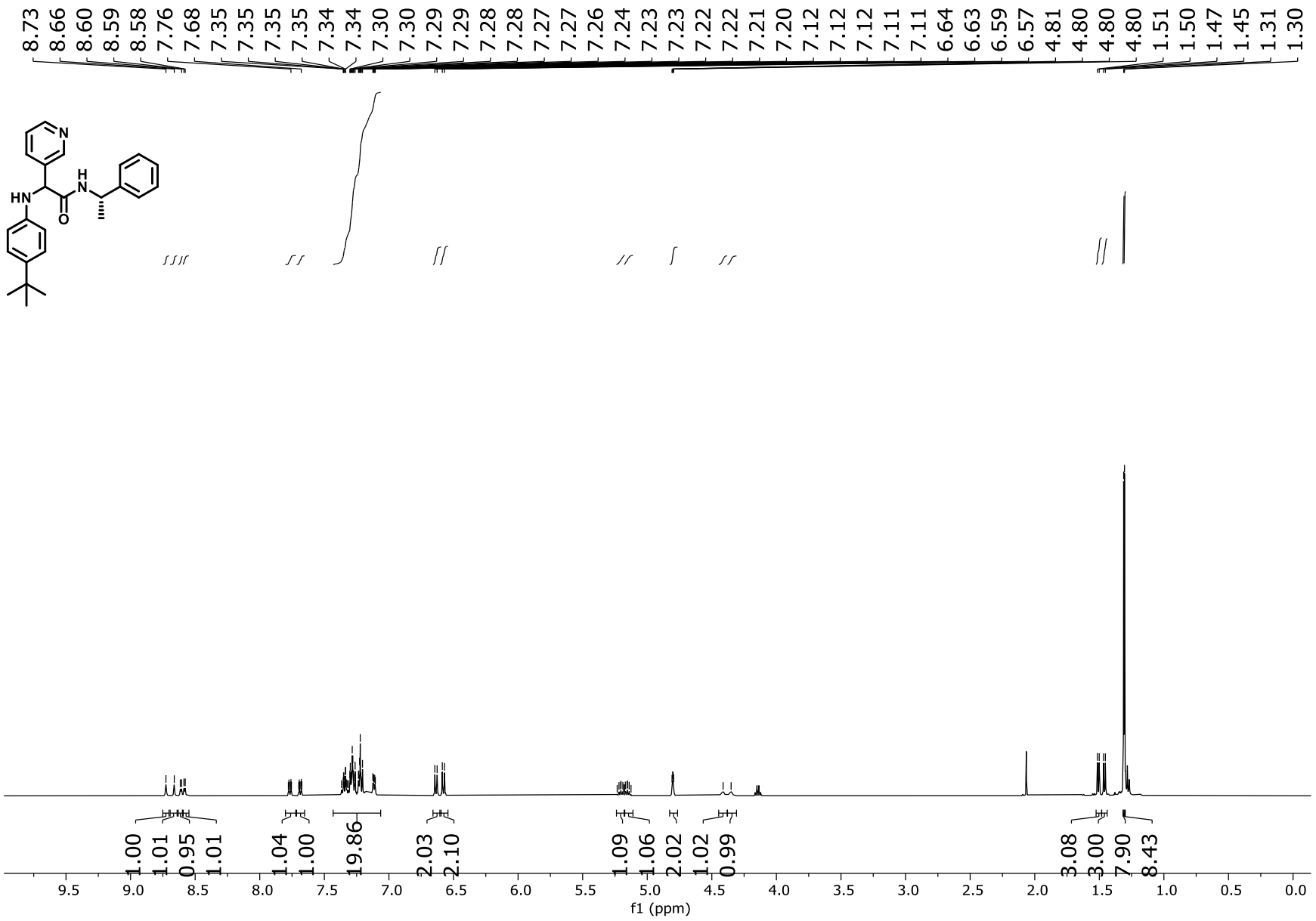
*114. Compound **28f** ^{1}H NMR*



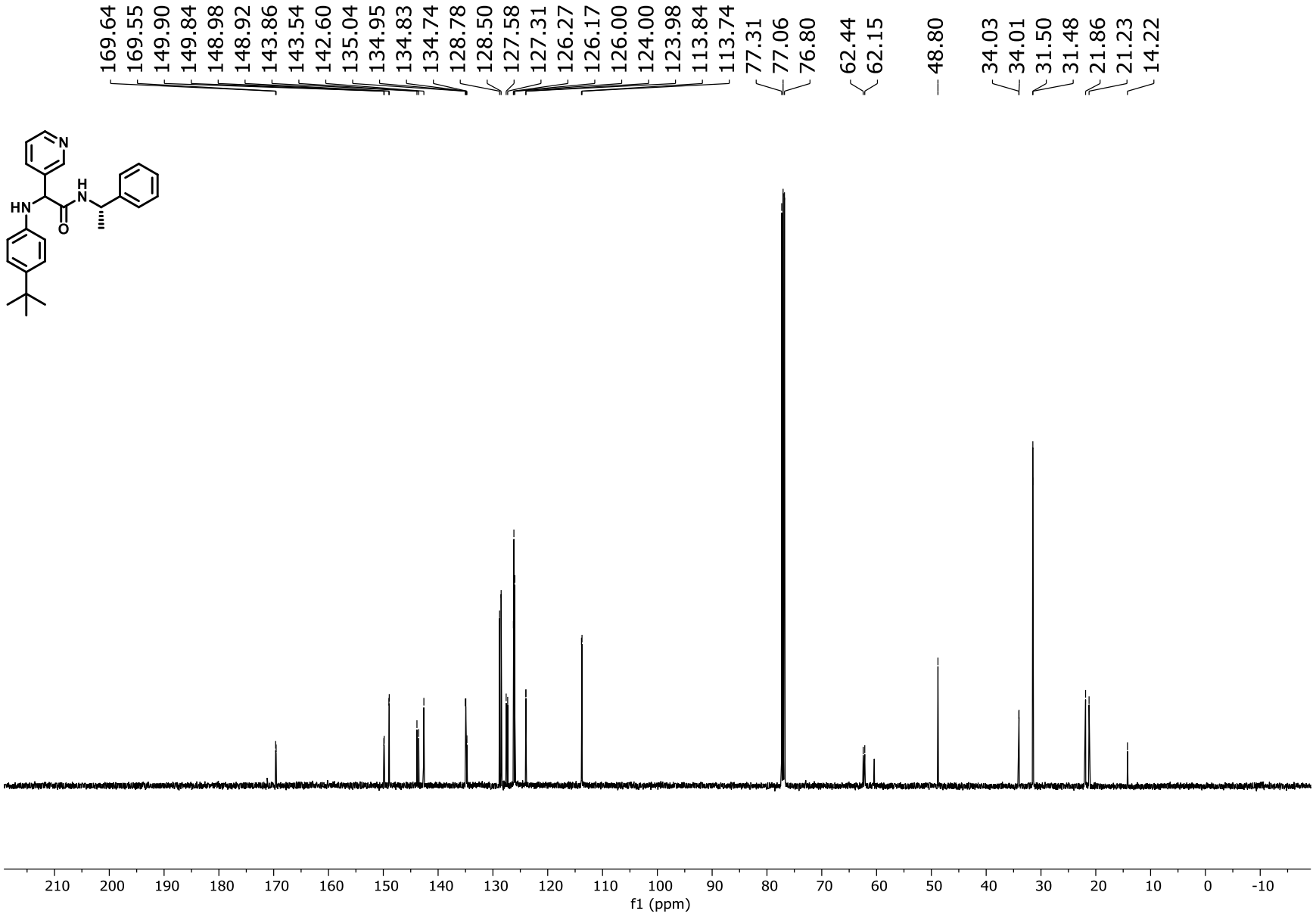
*115. Compound **28f** ^{13}C NMR*



*116. Compound **28g** ^{1}H NMR*



*117. Compound **28g** ^{13}C NMR*



9. References

(1) Efron, B.; Tibshirani, R. Bootstrap Methods for Standard Errors, Confidence Intervals, and Other Measures of Statistical Accuracy. *Stat. Sci.* **1986**, *1*, 54-75.