

SUPPORTING INFORMATION

Poly(ethylene) glycols and mechanochemistry for the preparation of bioactive 3,5-disubstituted hydantoins.

Laure Konnert, Myriam Dimassi, Lori Gonnet, Frédéric Lamaty, Jean Martinez and Evelina Colacino*

Université Montpellier, Institut des Biomolécules Max Mousseron, UMR 5247 CNRS – UM - ENSCM, Place E. Bataillon, Campus Triolet, cc 1703, 34095 Montpellier (France).

*e-mail: evelina.colacino@umontpellier.fr

General Remarks and Experimental Procedures S1

Table S1. Screening of mechanochemical parameters to prepare **2** by Method A. S2

Table S2. Synthesis of hydantoins. Comparison between mechanochemical (BM) and solution methods. S2

Chiral HPLC Analyses for compound **4** (Methods A and B, with and without MeO-PEG-2000-OMe) (Table 4) S3-S5

¹H NMR, ¹³C NMR and IR spectra of compounds **2**, **4-19**, **21**, **24** (Table 2), and **25-26** (Scheme 2). S6-S68

General Remarks and Experimental Procedures

All reagents were commercially available. All the starting α -amino esters were in the *L*-form. 5-Phenyl hydantoin was prepared as previously described.¹ NMR spectra were recorded at room temperature with the appropriate deuterated solvent (CDCl₃ or *d*₆-DMSO). Chemical shifts (δ) of ¹H NMR and ¹³C NMR spectra are reported in ppm relative to residual solvent signals (CHCl₃ in CDCl₃: δ = 7.26 ppm for ¹H and CDCl₃: δ = 77.04 ppm for ¹³C NMR); *J* values are given in Hz. ¹H and ¹³C NMR spectra were registered at 300 MHz or 400 MHz, the samples were prepared by dissolving 15 mg of hydantoin in 0.7 mL of deuterated solvent. ¹H and ¹³C NMR were recorded using 32 and 4096 scans respectively. The identity of analytically pure final products was assessed by comparison of their ¹H NMR data previously described in the literature and by their fragmentation in LC/MS. HRMS measurements were performed on a TOF mass analyser. Analytical high performance liquid chromatography (HPLC) was performed with a UV-detector at 214 nm using a CHROMOLITH RP18 column (50 x 4.6 mm), flow 5 mL/min, linear gradient CH₃CN in water 0-100% (+ 0.1% TFA) in 3 min. LC-MS analyses were performed by HPLC, column Onyx C₁₈, (25 x 4.6 mm), flow 3 mL/min linear gradient CH₃CN in water 0-100% (+ 0.1% HCO₂H) in 2.5 min. Melting points were measured on a Büchi Melting Point 510 apparatus and are uncorrected. Infrared spectra were recorded on a NexusTM E.S.P. (Thermo Nicolet, USA) FT-IR spectrometer equipped with high pressure diamond cell. The ball-milling experiments were performed in a MM200 vibrational ball mill (Retsch GmbH, Haan, Germany) using 5 mL stainless steel jar (2 stainless steel balls, 5 mm Ø), a PM100 planetary mill (Retsch GmbH, Haan, Germany) using a 12 mL stainless steel jar (25 or 50 stainless steel balls, 5 mm Ø) or a Pulverisette 7 Premium (Fritsch GmbH, Idar-Oberstein, Germany) using a 20 mL stainless steel jar (40 stainless steel

balls, 5 mm Ø). All compounds displayed identical spectral data compared to literature. Enantiomeric excess (*e.e.*) and ratio (*e.r.*) were measured using a Beckman Coulter System Gold 126 Solvent Module HPLC machine and Beckman Coulter System Gold 168 Detector. Column: direct phase CHIRACEL OD-RH (0.46 x 25 cm) for compound **4**, using *n*-hexanes and 2-propanol as solvents (ratio 90:10 v/v, Flow: 1 mL/min, $\lambda = 214$ nm).

Table S1. Screening of mechanochemical parameters to prepare **2 by Method A.**

Ball-Mill	Jar Material	Frequency (Hz) / Rotation speed (rpm)	Time (min.)	Yield (%)
PBM	Stainless steel	450 rpm	120	76
VBM	Stainless steel	30 Hz	120	75
VBM	WC	30 Hz	120	74

Table S2. Synthesis of hydantoins. Comparison between mechanochemical (BM) and solution methods.

Product	Yield (%)	
	BM (A or B) ^a	In Solution ^b
2	84, B	82 ²
11	79, A	94 ³
12	40, B	70 ⁴ , 60 ⁵
13	75, B	29 ⁶
14	58, B	54 ⁶
16	65, B	92 ⁷
17	25, B	68 ⁸
18	85, A	84 ²

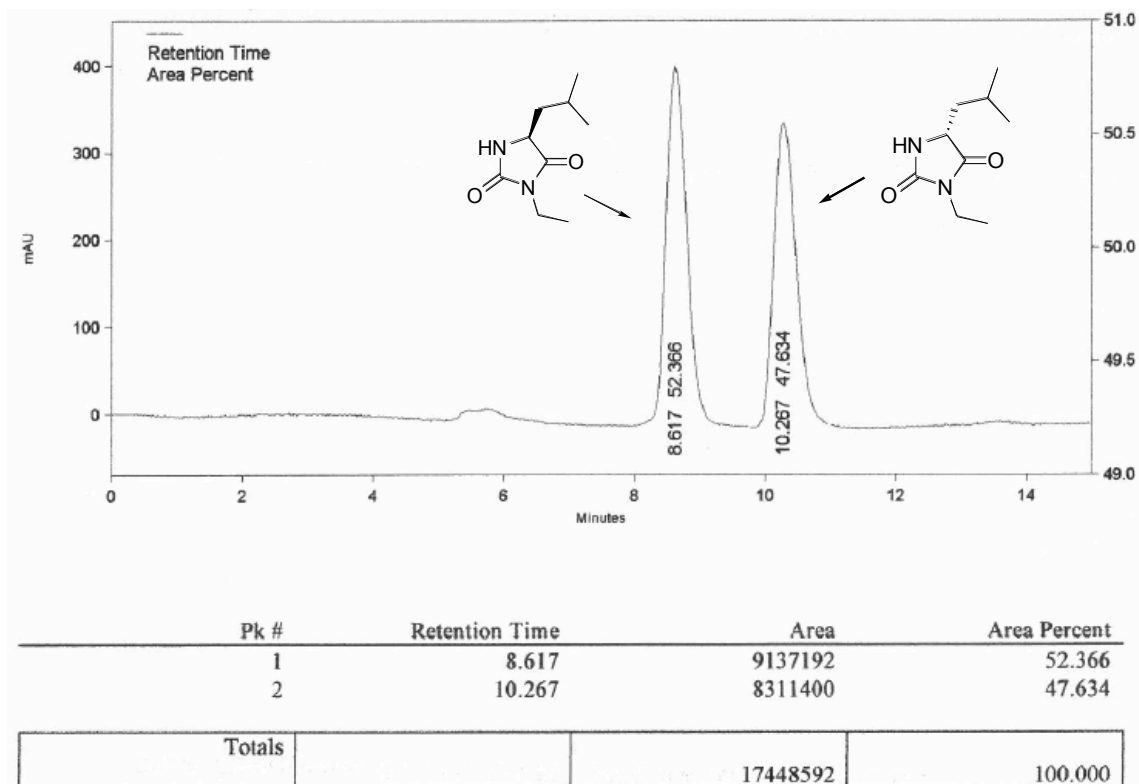
^a For the same compound, the method giving the better yield was reported. Method A: α -amino ester (1 equiv.), R²NCO (3 equiv.), K₂CO₃ (3 equiv.), 30 Hz, 120 min; Method B: (*step 1*) α -amino ester (1 equiv.), CDI (1.3 equiv.), 450 rpm, 40 min.; (*step 2*) R₂NH₂ (1.6 equiv.), K₂CO₃ (3.6 equiv.), 450 rpm, 120 min.; ^b For some compounds no comparison with solution procedure is possible: compounds **4-6**, **9** and **15** are hitherto unknown; compounds **7** and **8** are commercially available (509€/g) but the preparation in solution was never reported in the literature.

REFERENCES

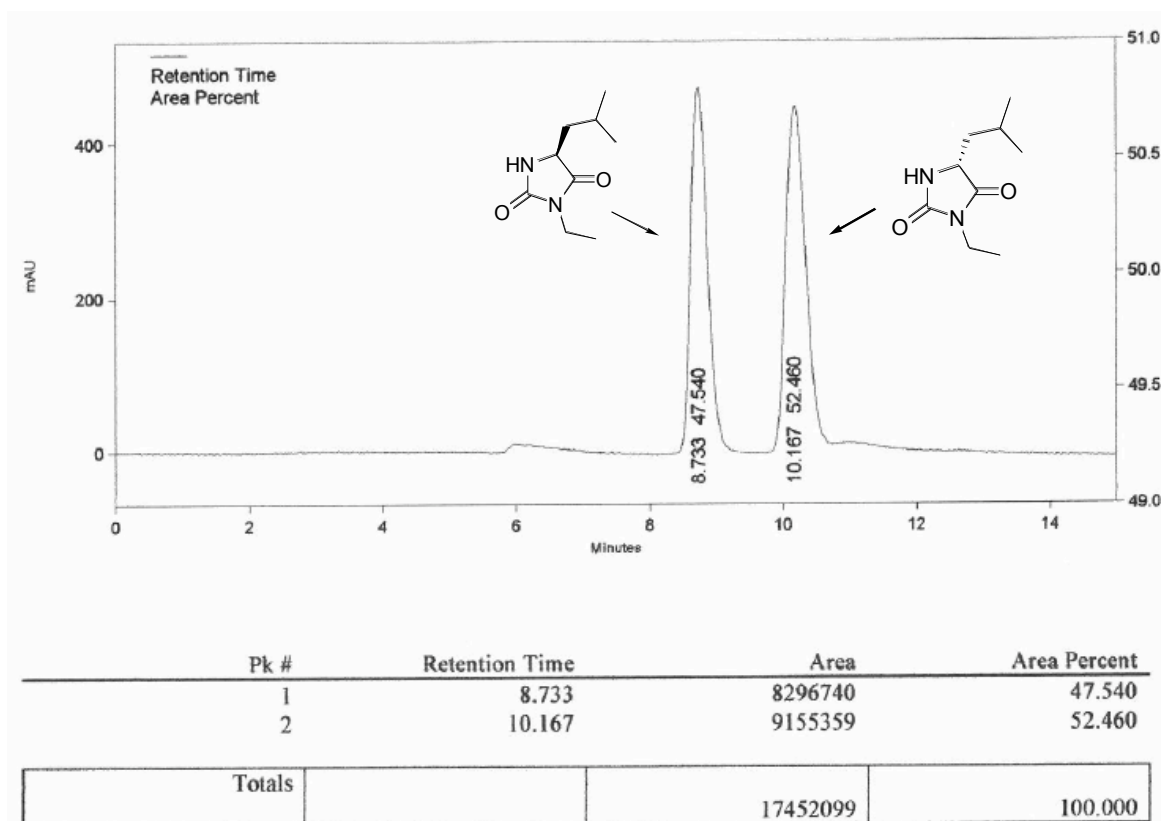
- (1) Konnert, L.; Reneaud, B.; de Figueiredo, R. M.; Campagne, J.-M.; Lamaty, F.; Martinez, J.; Colacino, E. *J. Org. Chem.* **2014**, *79*, 10132-10142.
- (2) Dumbris, S. M.; Di'az, D. J.; McElwee-White, L. *J. Org. Chem.* **2009**, *74*, 8862-8865.
- (3) Chen, Z.; Sun, Y. *Ind. Eng. Chem. Res.* **2006**, *45*, 2634-2640.
- (4) Dudley, K. H.; Bius, D. L. *J. Heterocycl. Chem.* **1973**, *10*, 173-80.
- (5) Liu, H.; Yang, Z.; Pan, Z. *Organic Letters* **2014**, *16*, 5902-5905.
- (6) Dewitt, S. H. H.; Kiely, J. S.; Pavia, M. R.; Schroeder, M. C.; Stankovic, C. J.; Warner-Lambert Co., USA . 1998, p 67 pp., Cont.-in-part of U.S. Ser.5,612,002.
- (7) Xi, G.; Xiu, Y.; Wang, L.; Liu, X. *J. Appl. Polym. Sci.* **2015**, *132*, 41824/1-41824/7
- (8) Trisovic, N.; Timic, T.; Divljakovic, J.; Rogan, J.; Poleti, D.; Savic, M. M.; Uscumlic, G. *Monatsh. Chem.* **2012**, *143*, 1451-1457.

Chiral HPLC analyses of compound 4 prepared with Method B (Table 4):

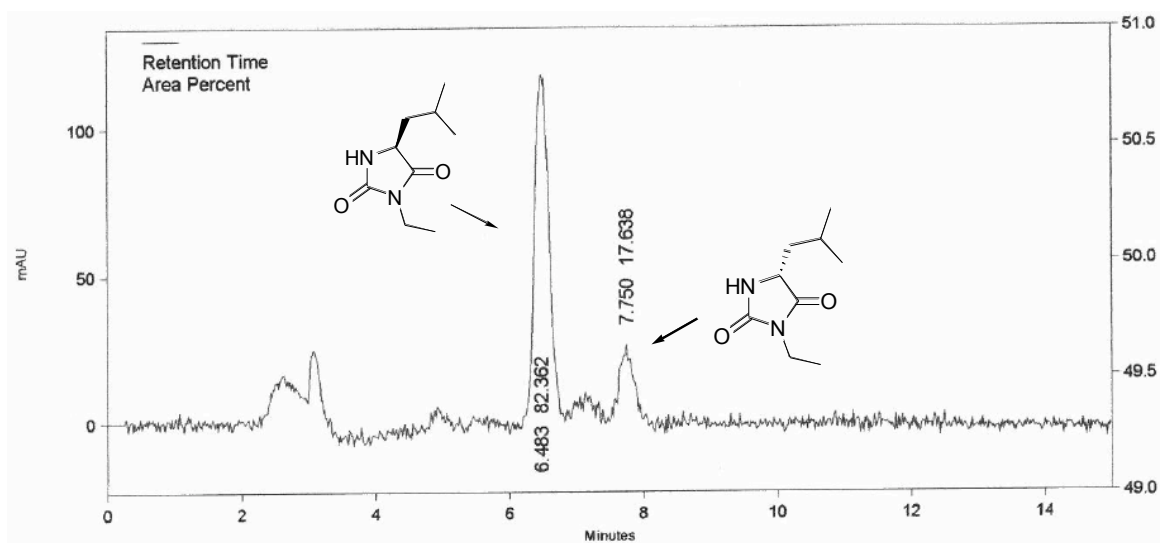
Reaction performed from H-L-Leu-OMe*HCl, without MeO-PEG-2000-OMe



Reaction performed from H-D-Leu-OMe*HCl, without MeO-PEG-2000-OMe



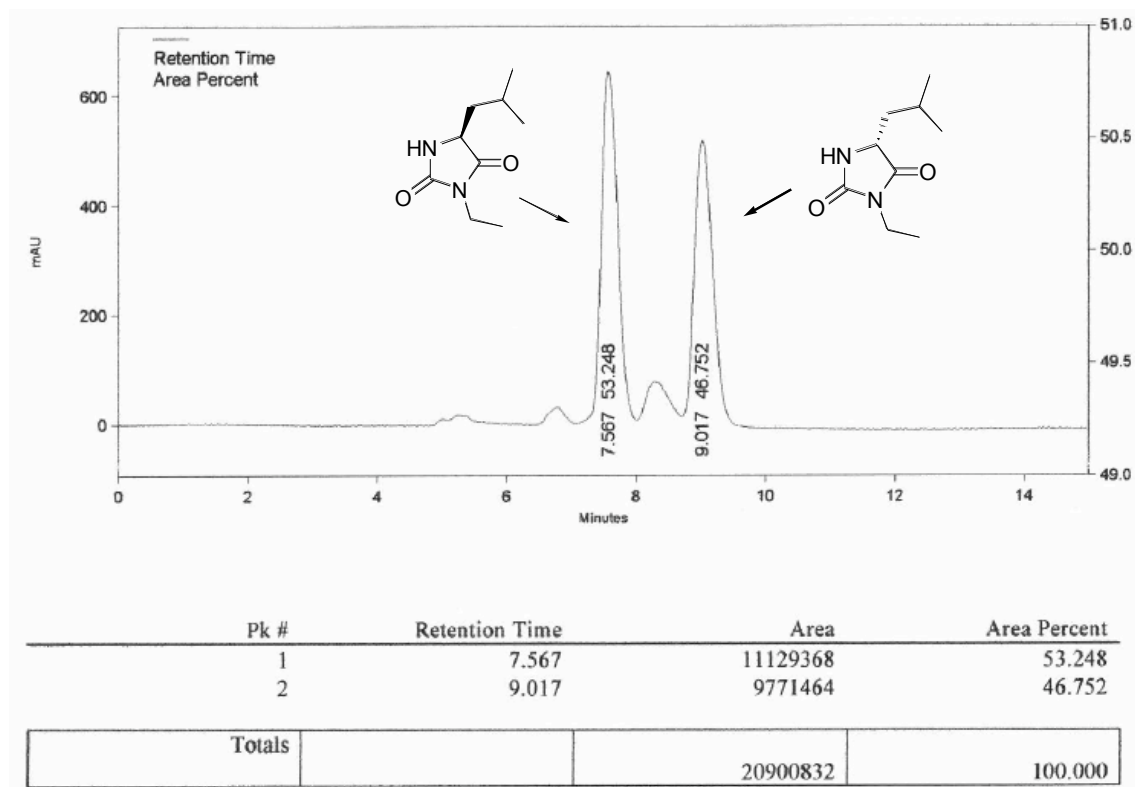
Reaction performed from H-L-Leu-OMe*HCl, with MeO-PEG-2000-OMe



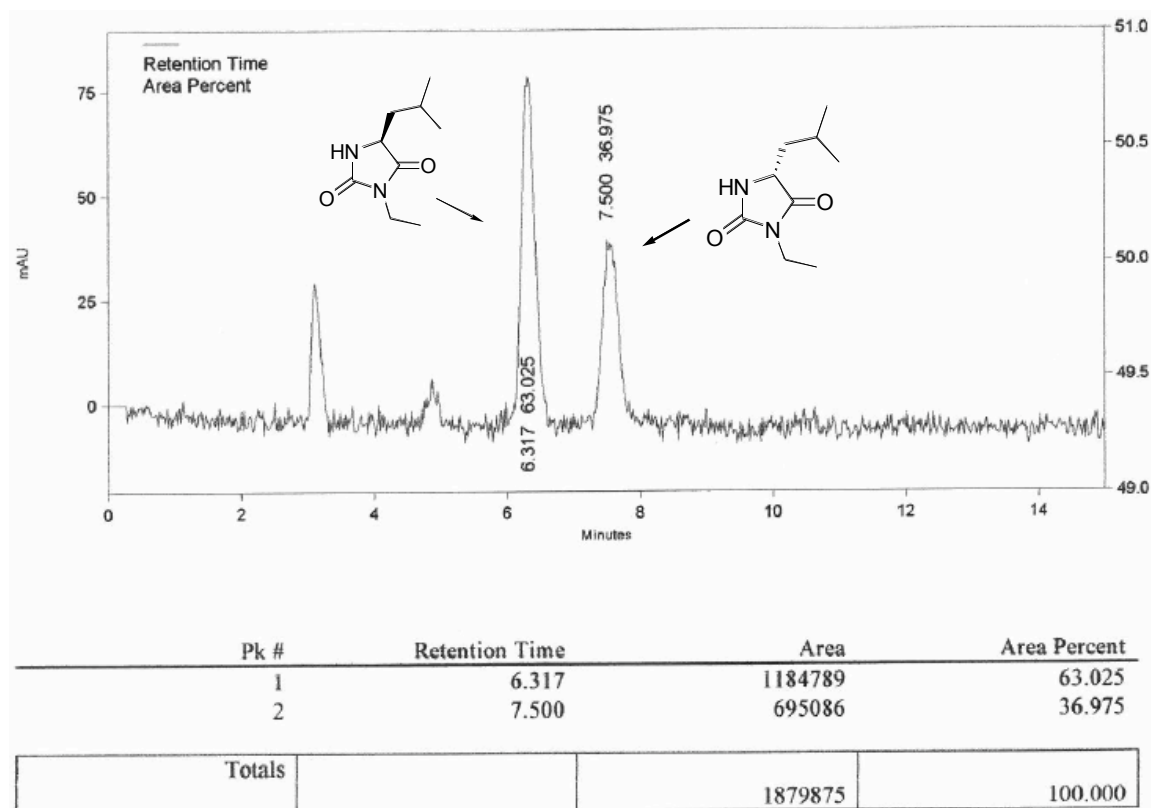
Pk #	Retention Time	Area	Area Percent
1	6.483	1819680	82.362
2	7.750	389687	17.638
Totals		2209367	100.000

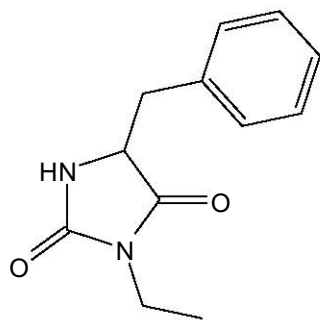
Chiral HPLC analyses of compound 4 prepared with method A (Table 4):

Reaction performed from H-L-Leu-OMe*HCl, without MeO-PEG-2000-OMe

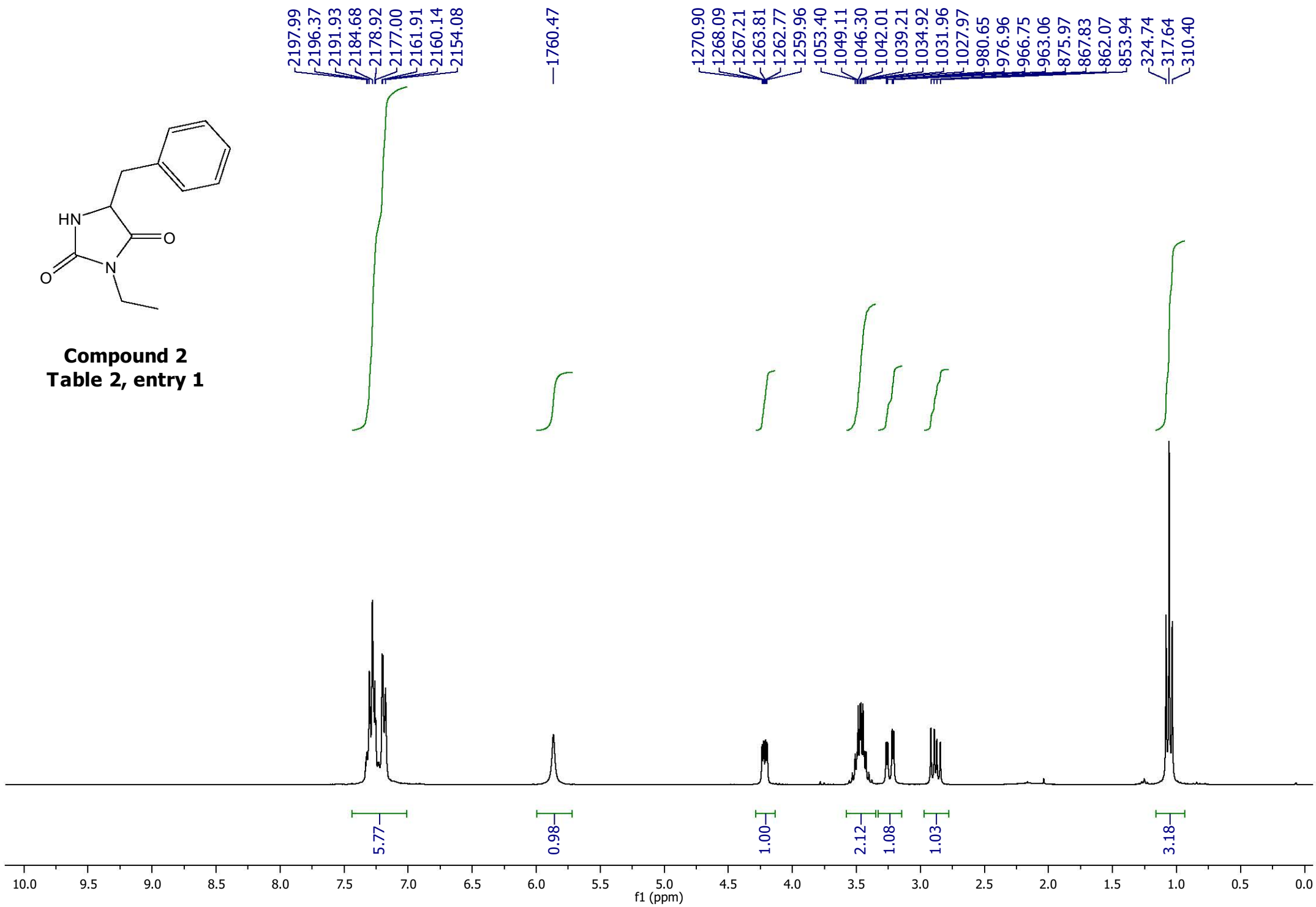


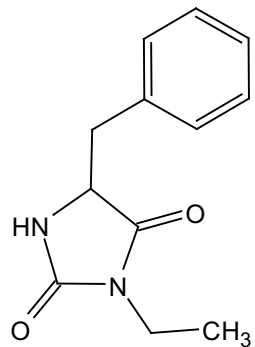
Reaction performed from H-L-Leu-OMe*HCl, with MeO-PEG-2000-OMe



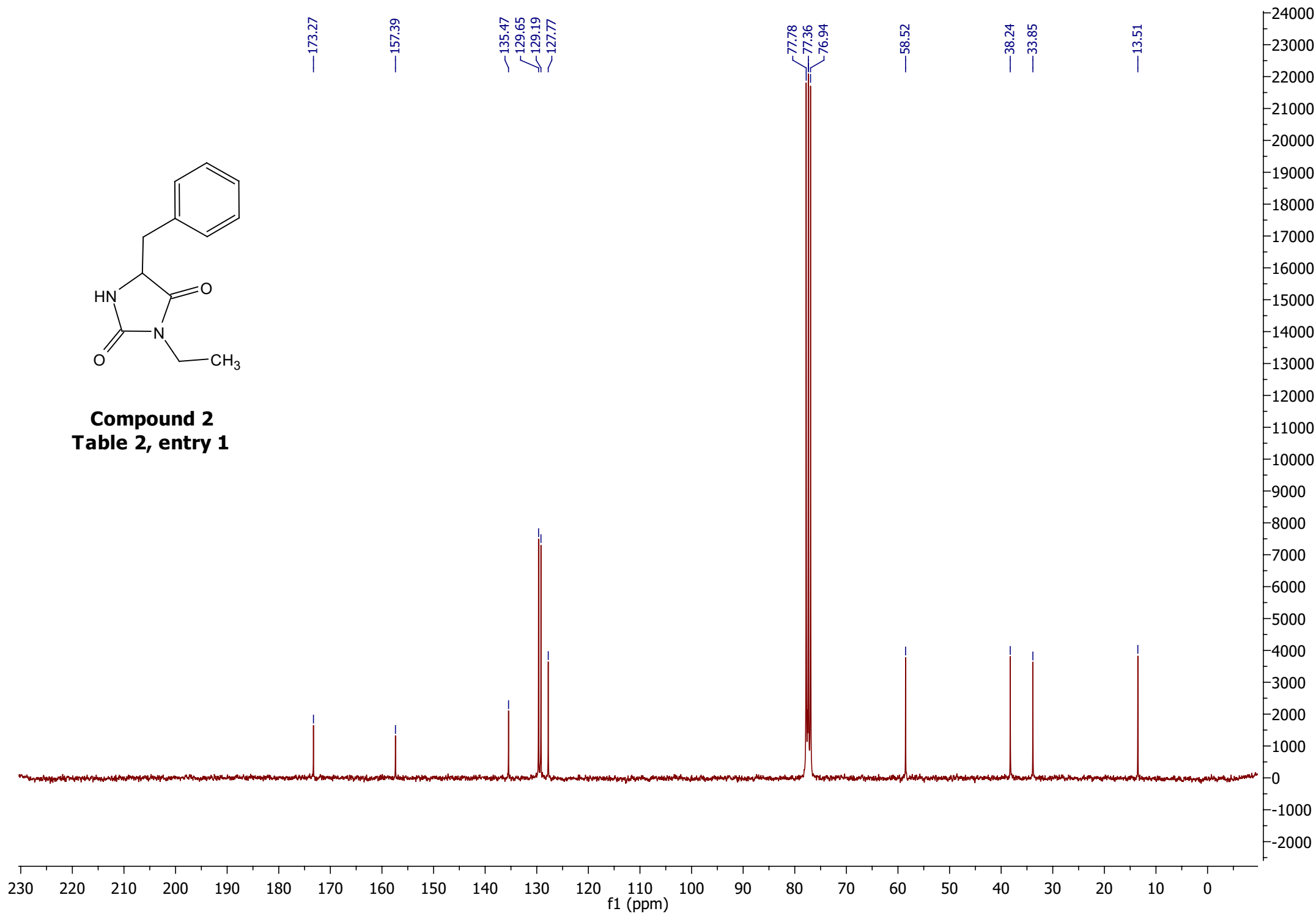


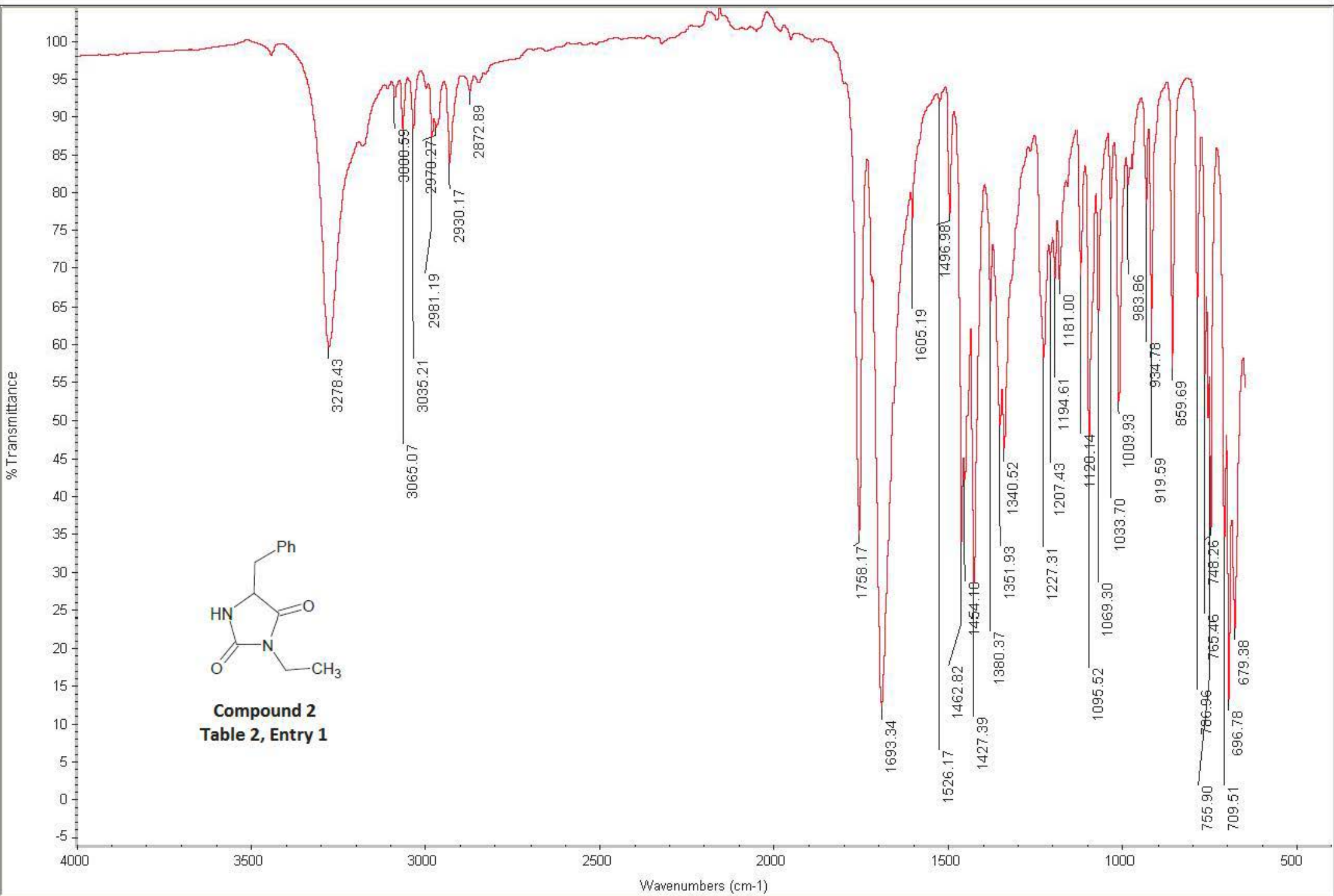
Compound 2
Table 2, entry 1

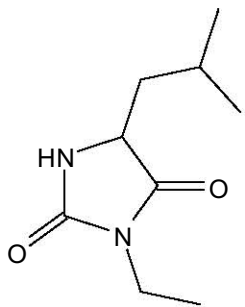




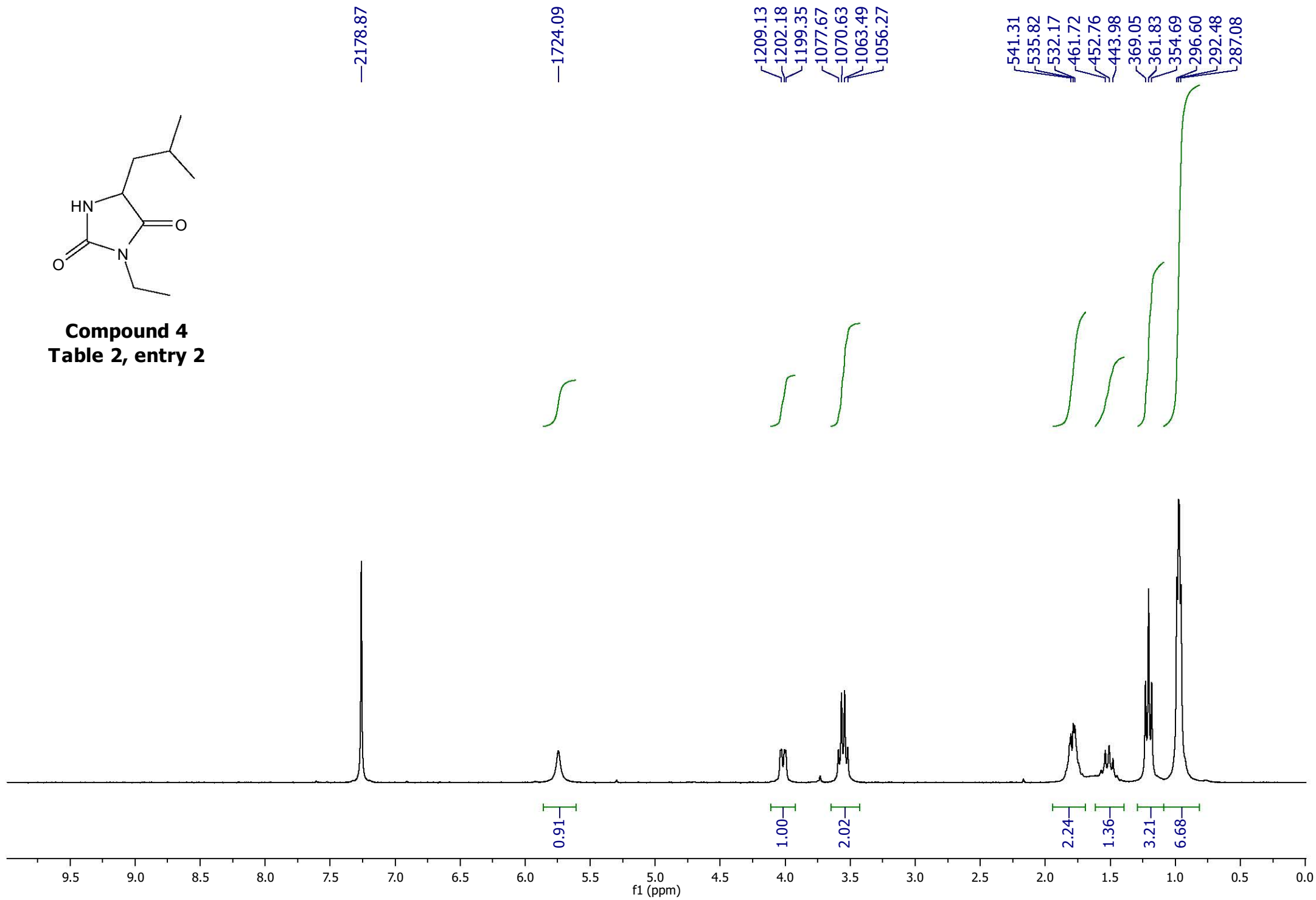
Compound 2
Table 2, entry 1

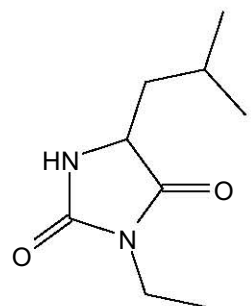




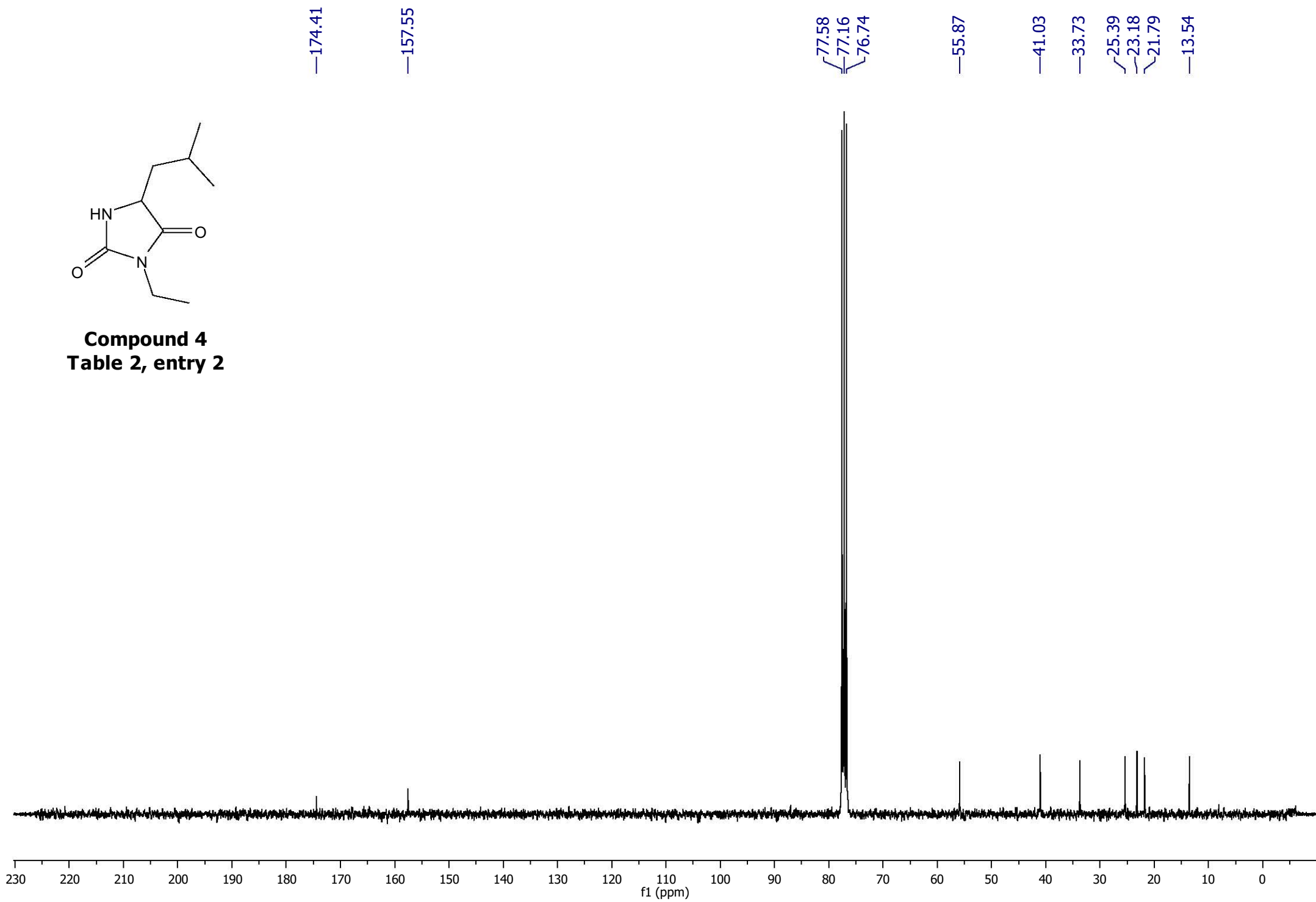


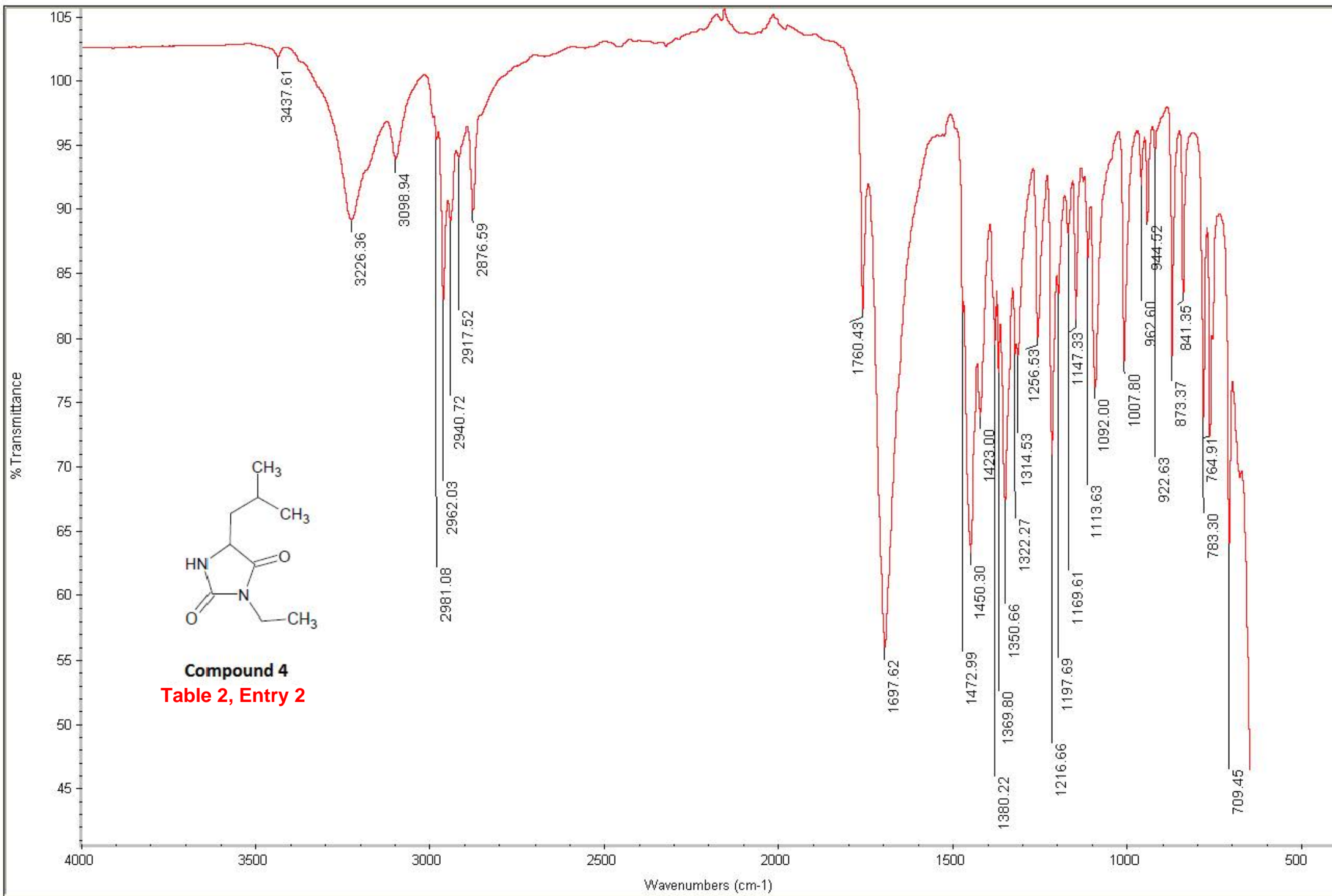
Compound 4
Table 2, entry 2

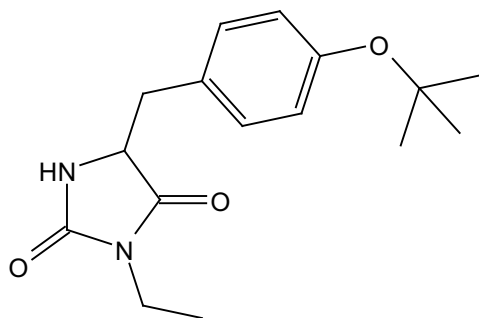




Compound 4
Table 2, entry 2







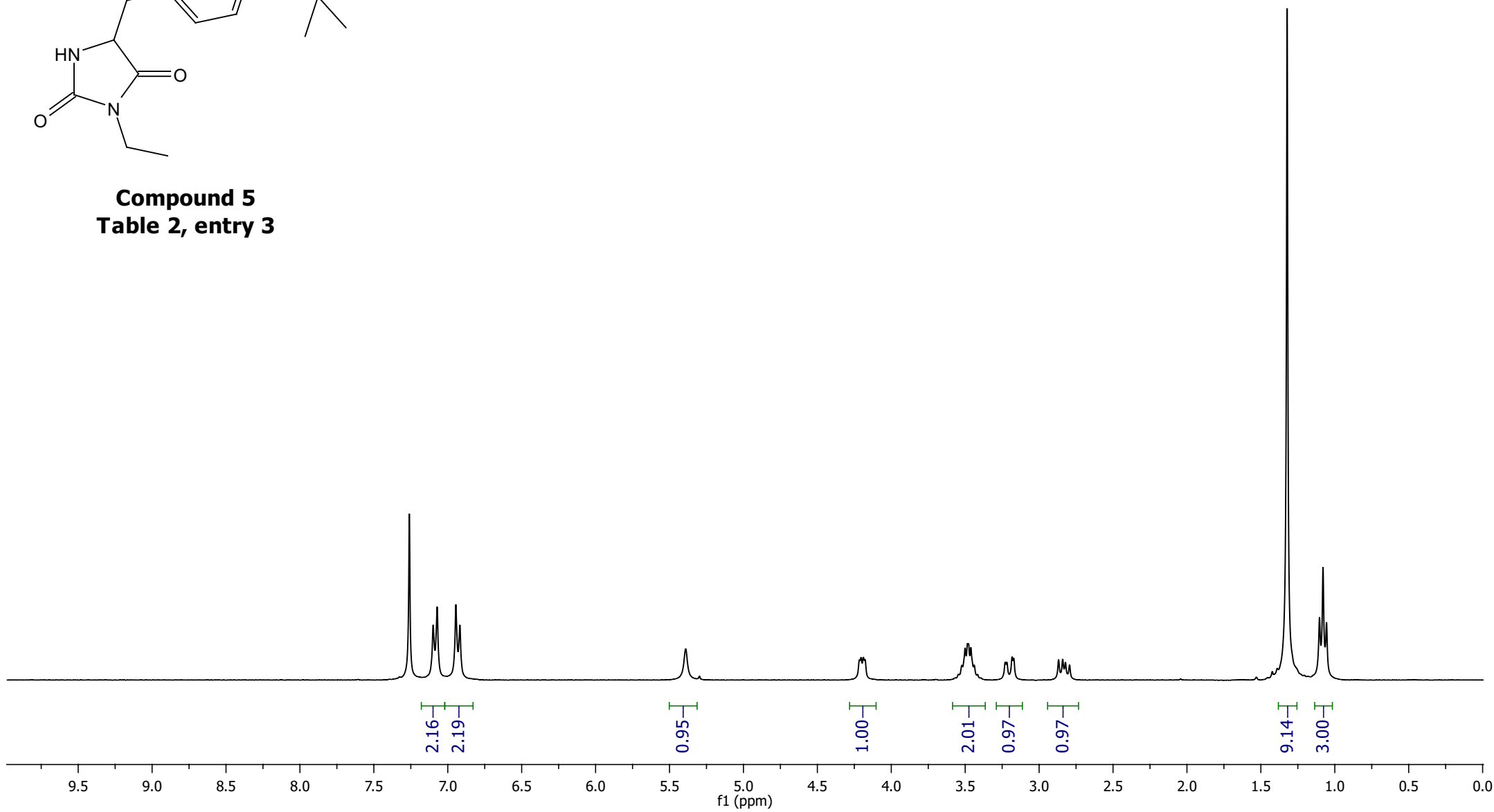
Compound 5
Table 2, entry 3

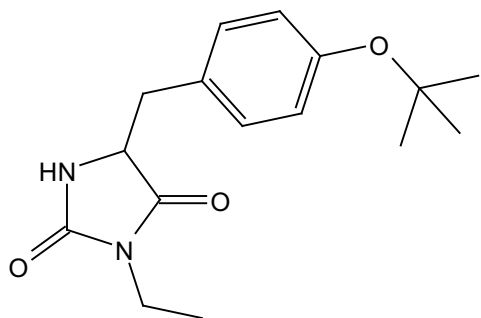
2178.85
2130.64
2122.40
2084.44
2076.20

1617.88

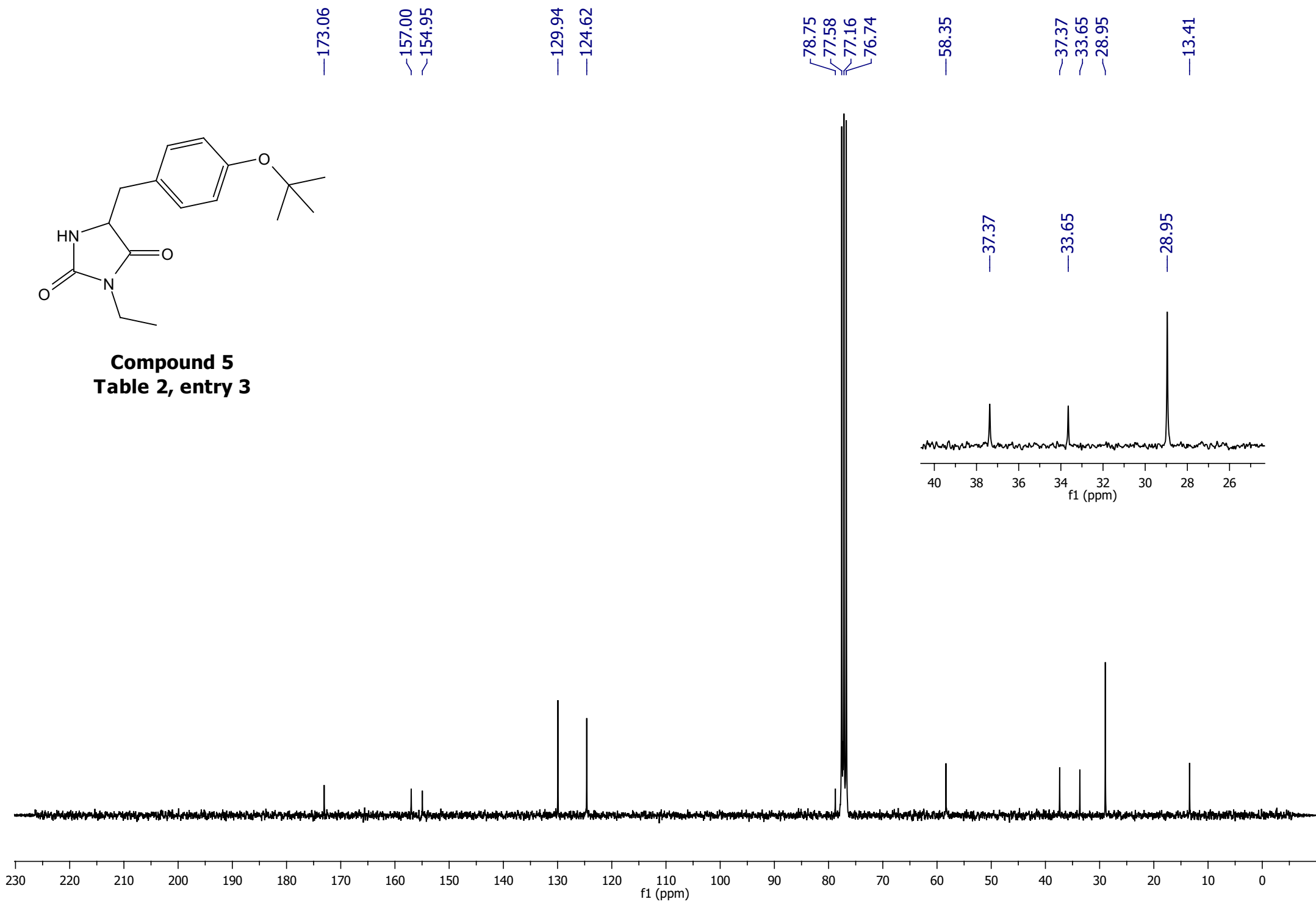
1262.01
1257.16
1253.96
1057.27
1050.69
1045.75
1038.89
1032.12
969.18
965.88
955.27
951.79
860.77
852.54
846.96
838.54

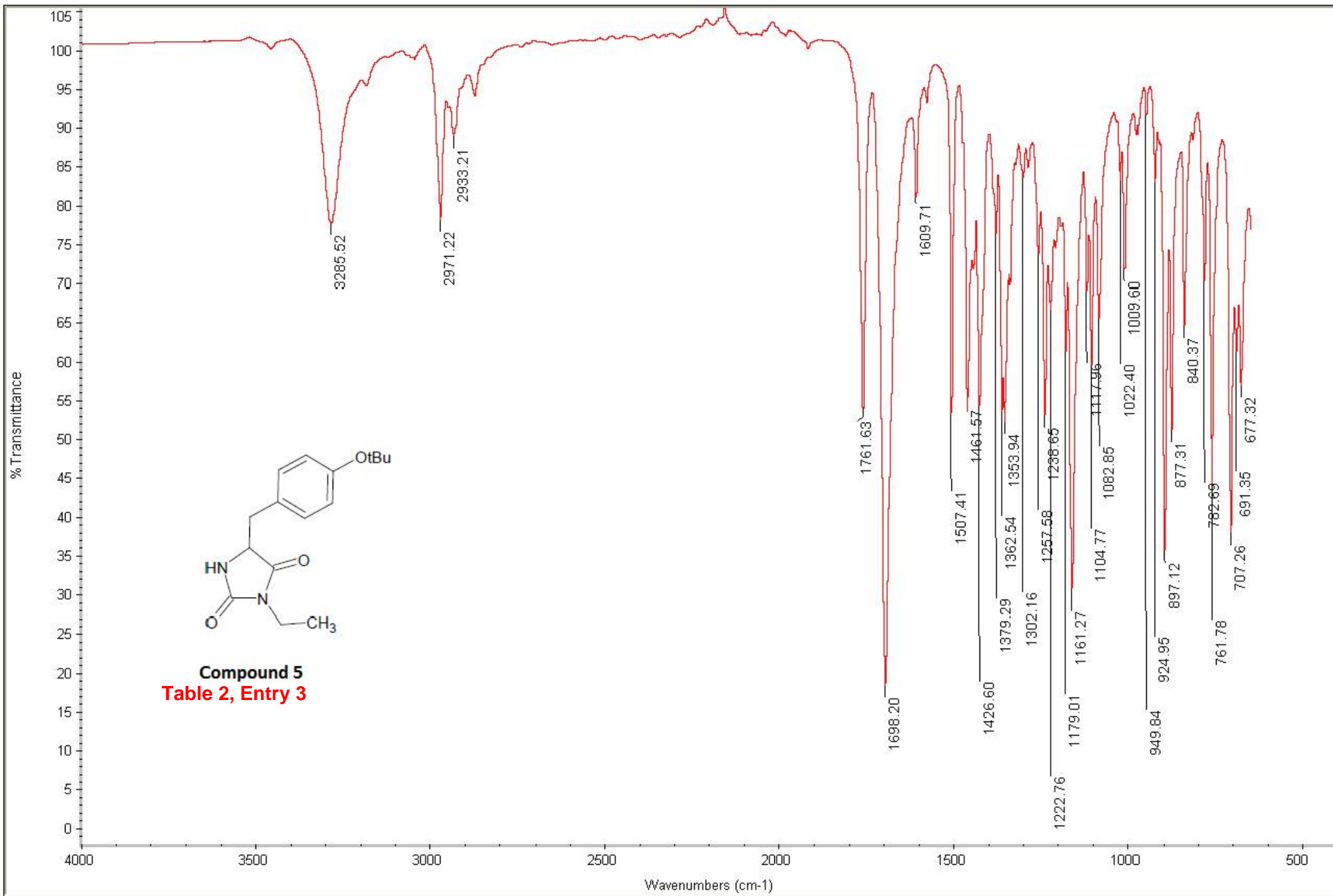
396.86
331.18
324.04
316.91

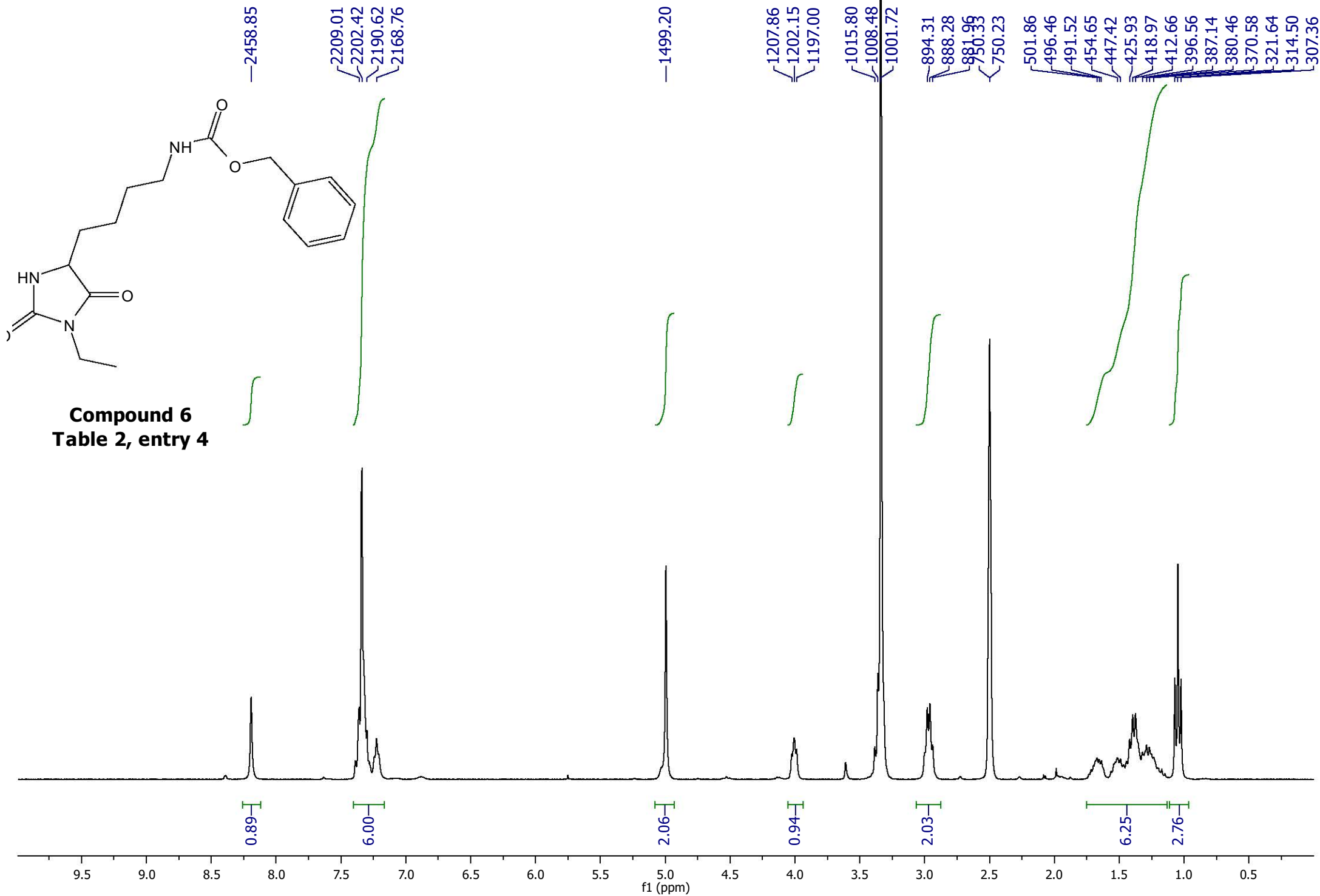


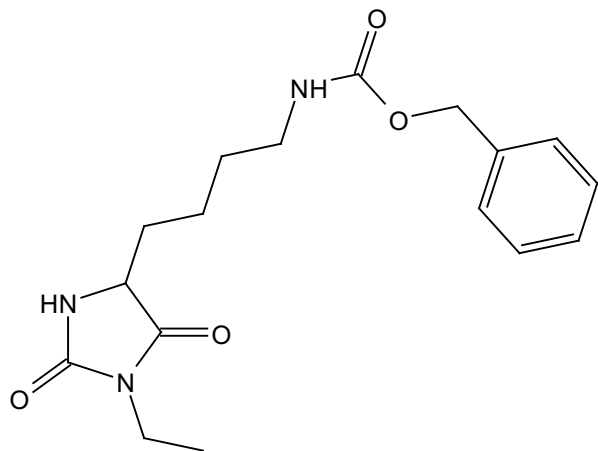


Compound 5
Table 2, entry 3

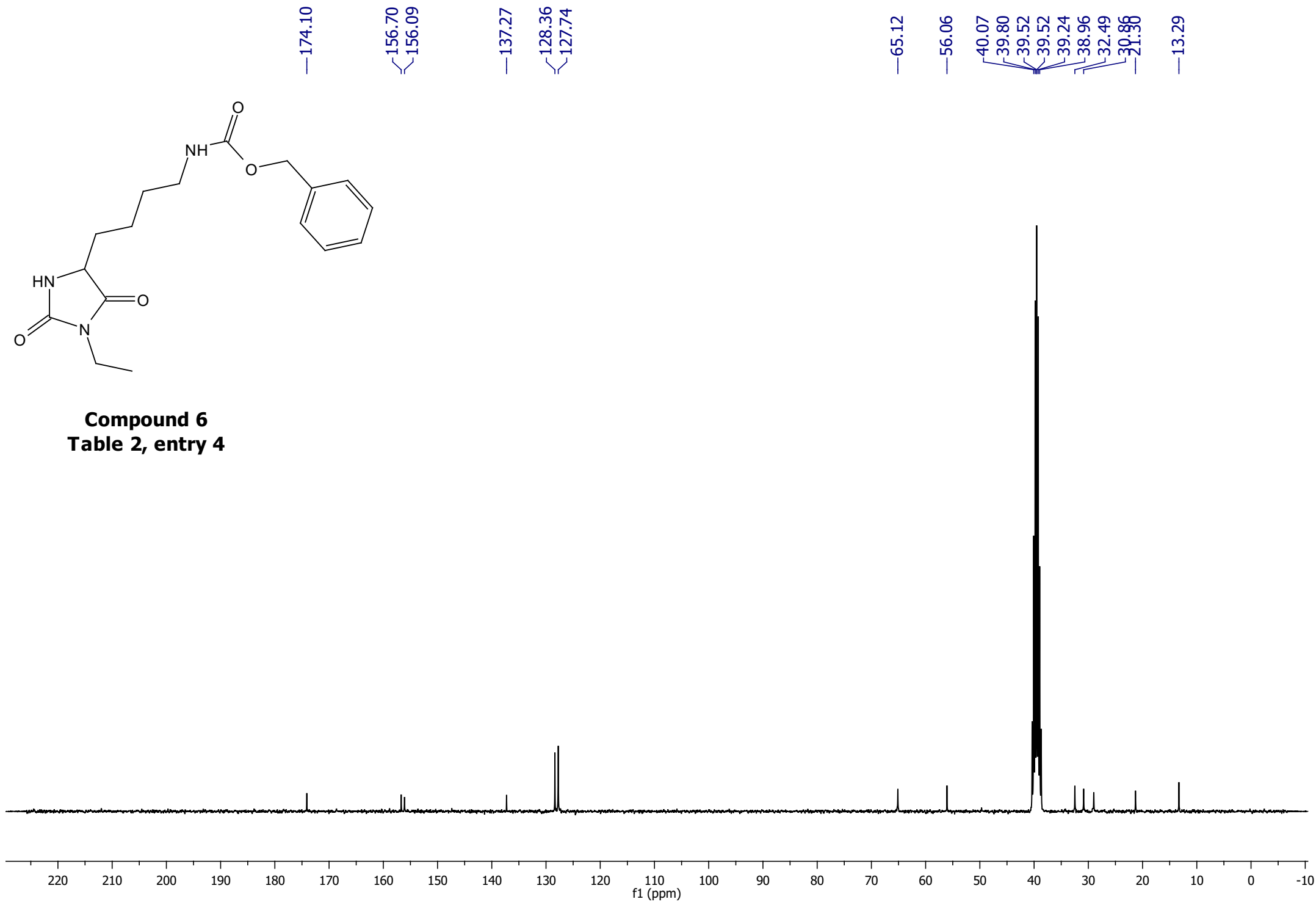


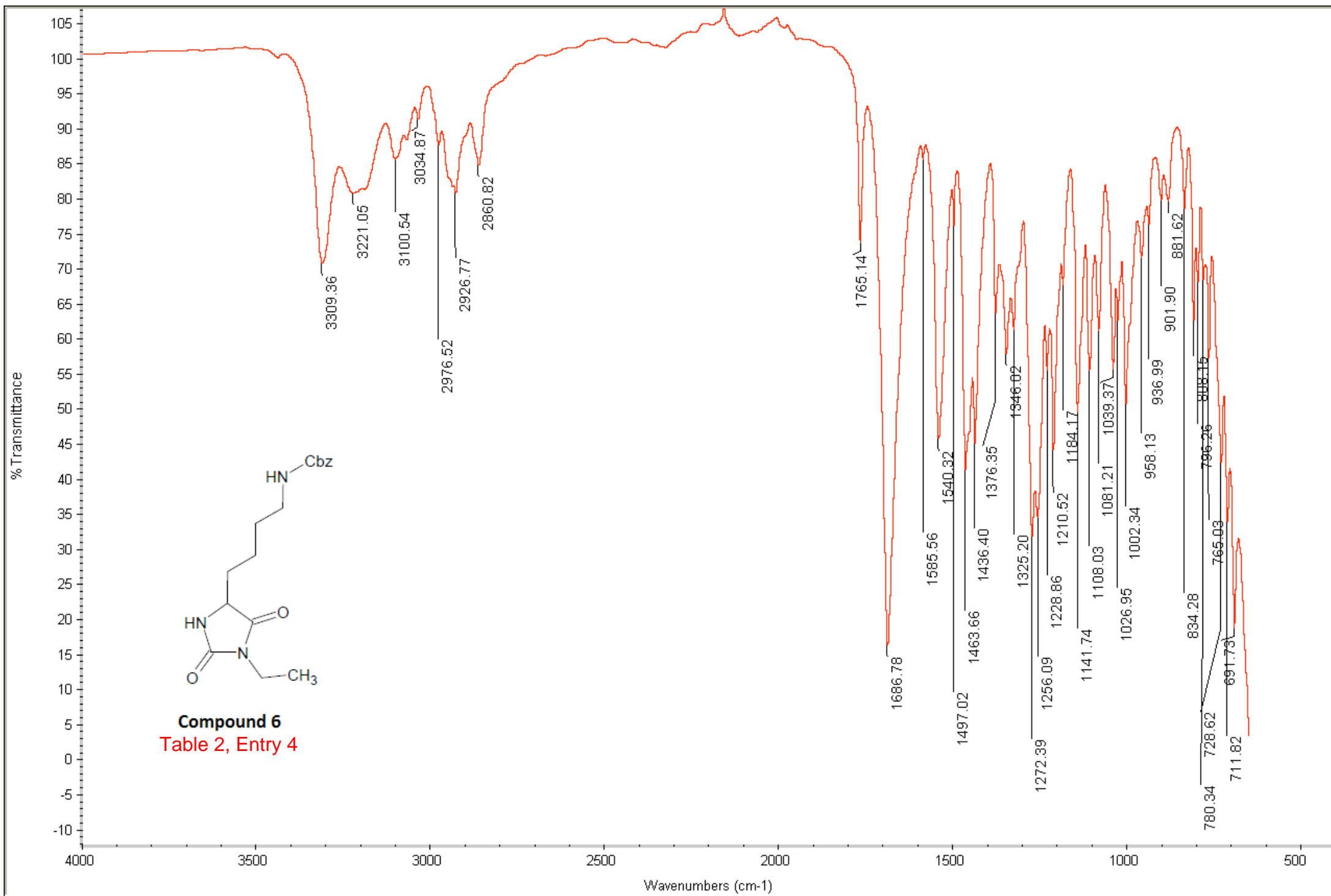


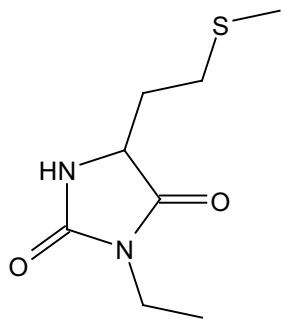




Compound 6
Table 2, entry 4







Compound 7
Table 2, entry 5

—2178.94

—1876.86

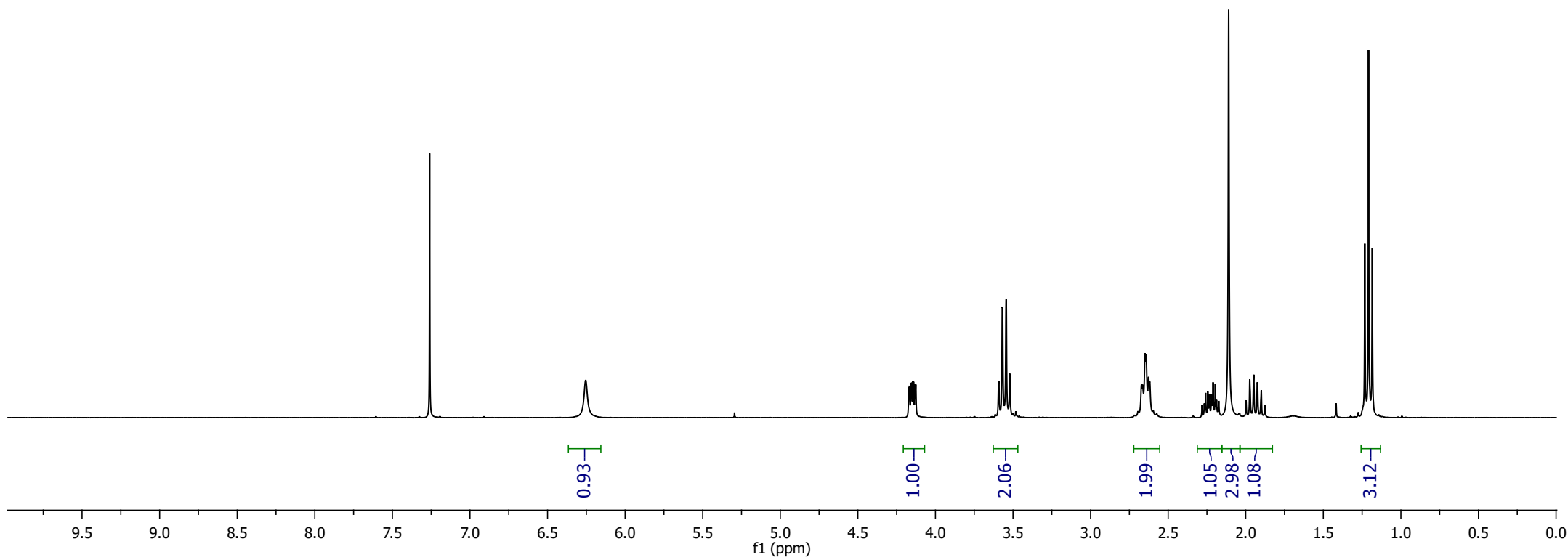
1252.04
1250.76
1247.83
1246.46
1244.08
1242.71
1239.78
1238.50

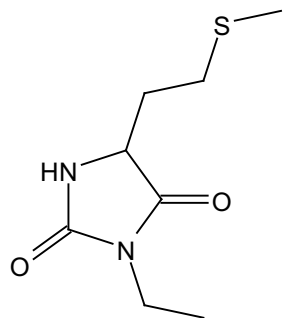
1077.86
1070.63
1063.59
1056.54

795.09
792.80
788.22
785.94

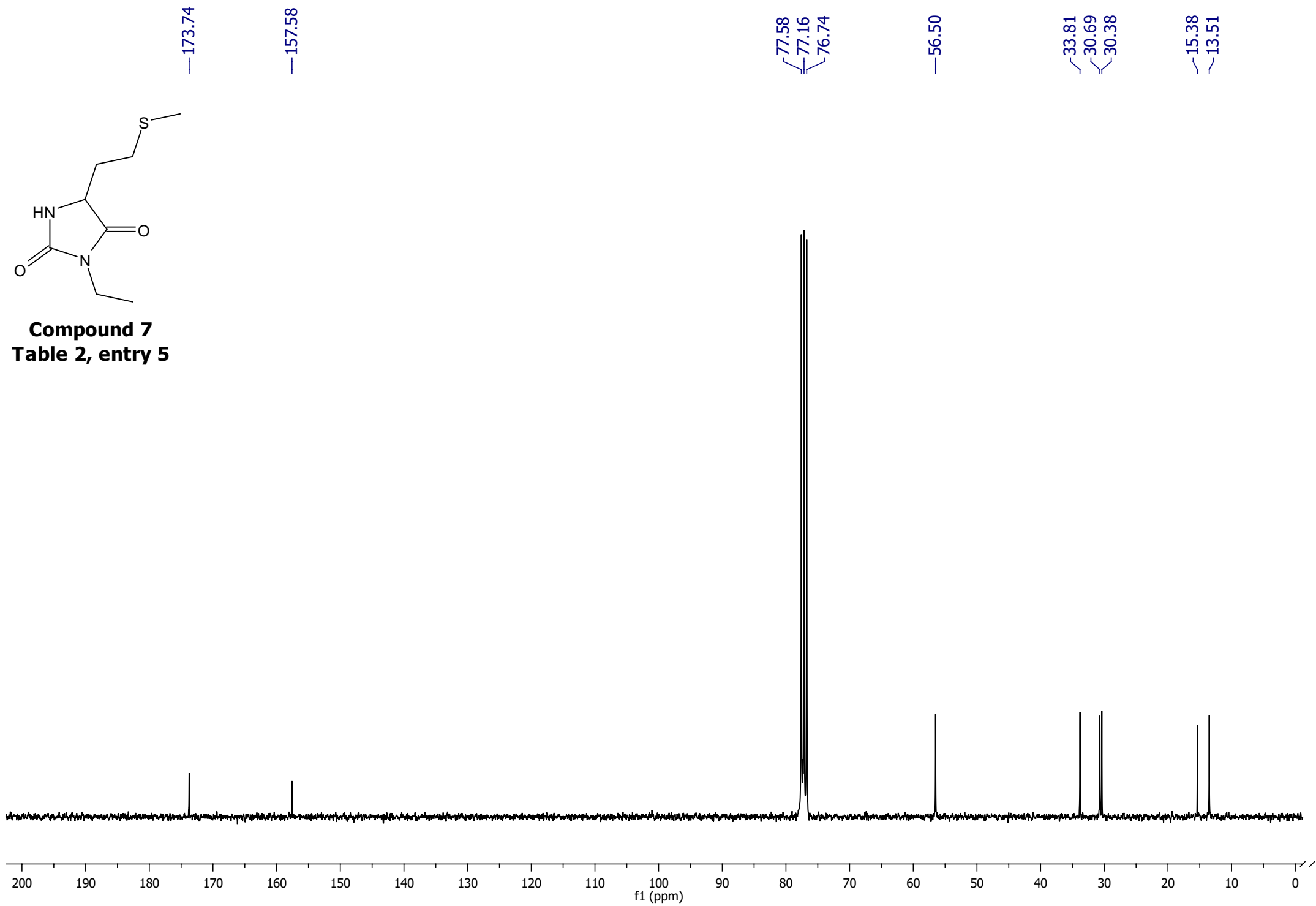
663.44
659.14
633.25
592.45

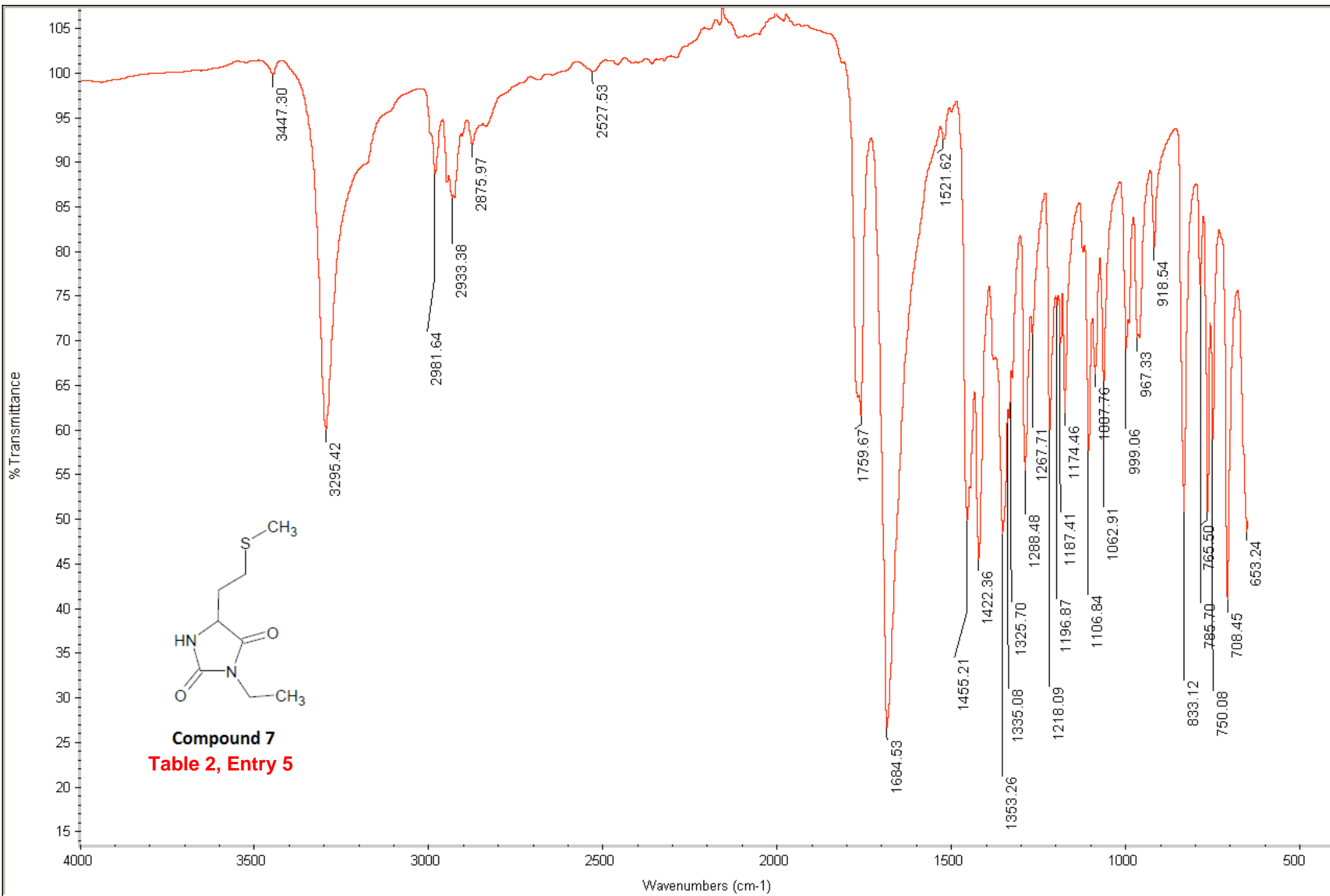
584.58
577.45
569.88
362.74
355.51

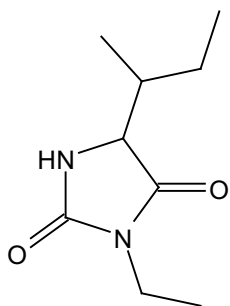




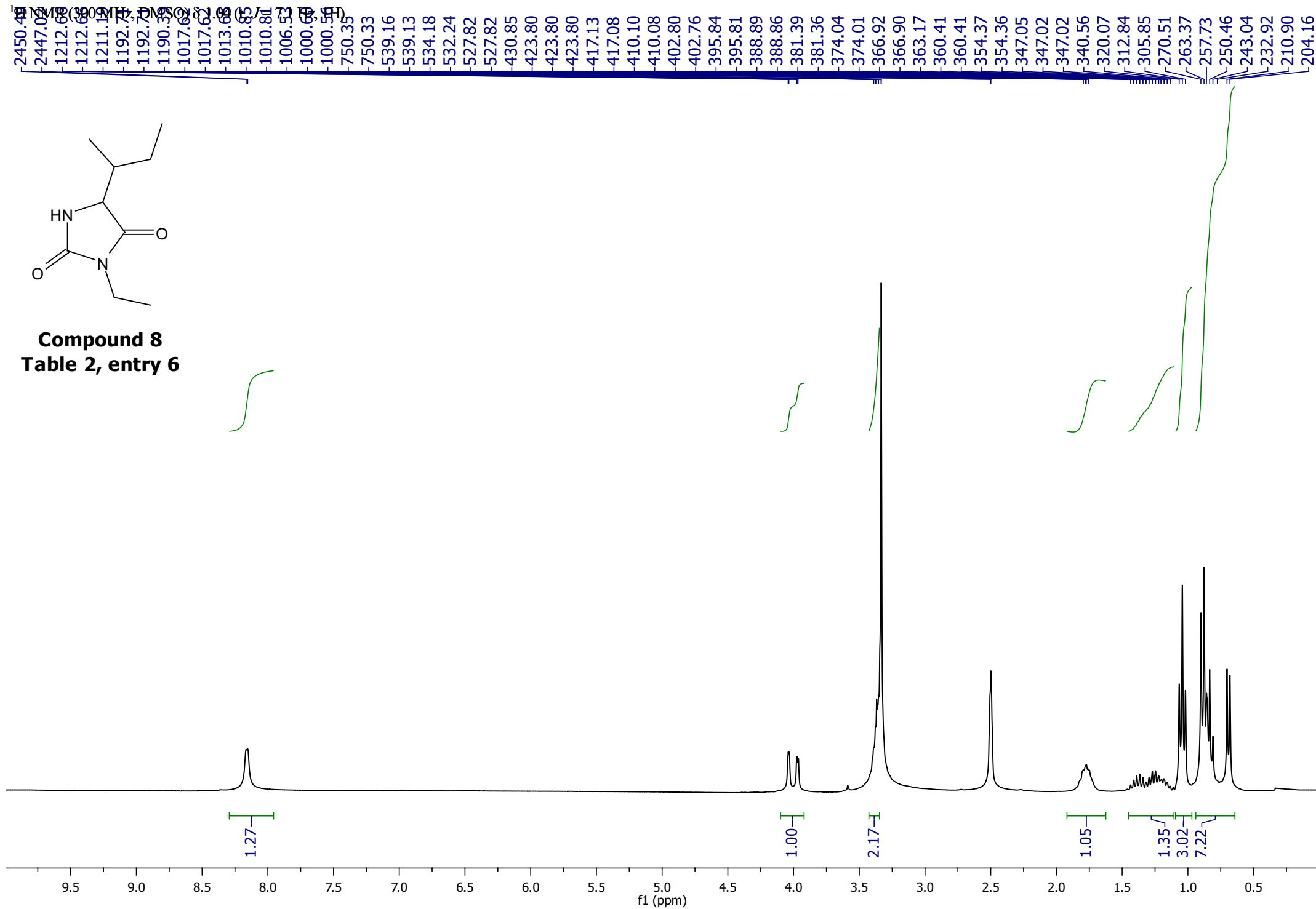
Compound 7
Table 2, entry 5

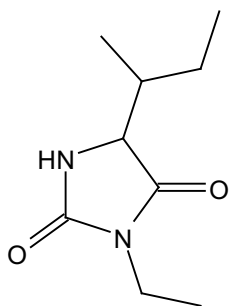






Compound 8
Table 2, entry 6



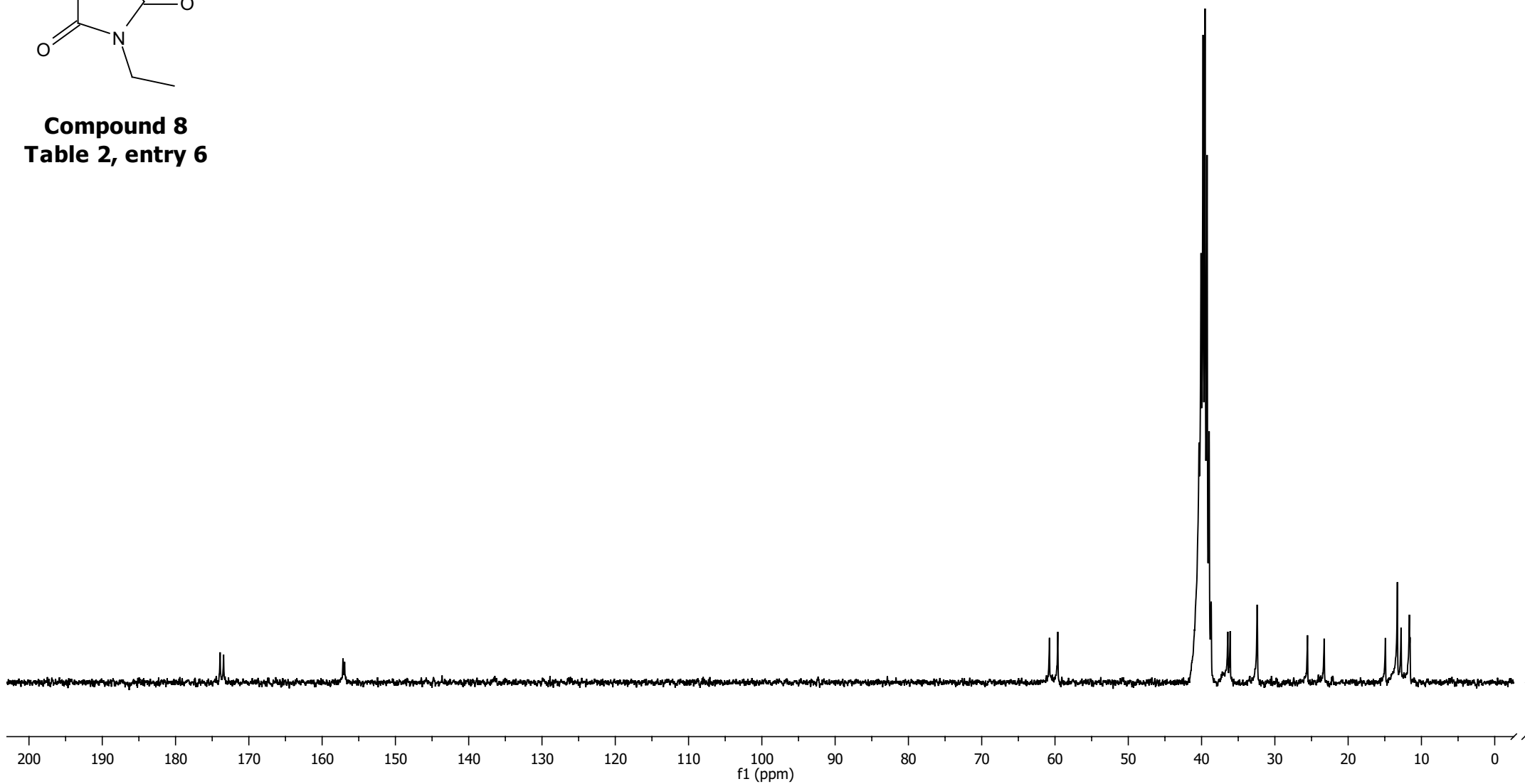


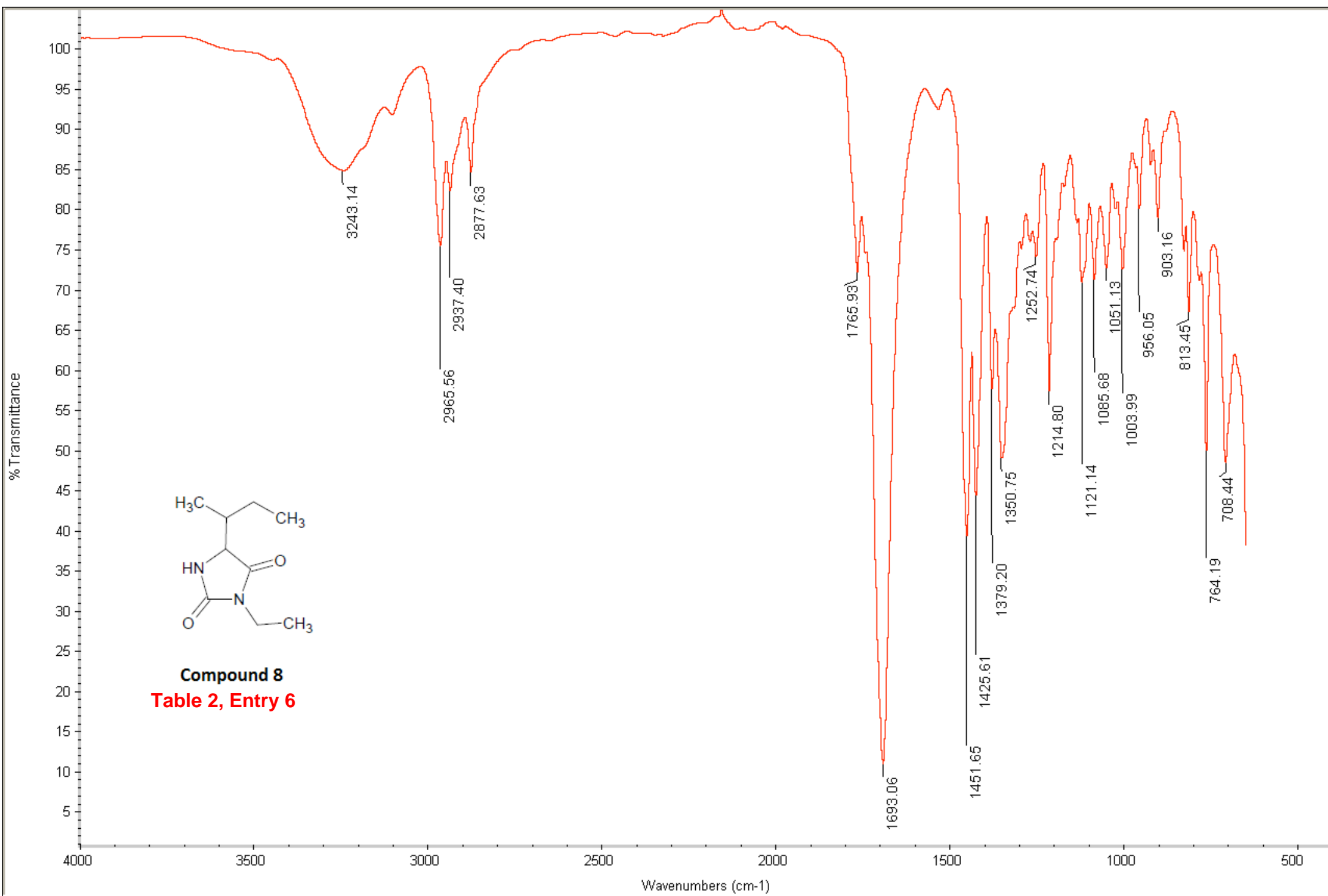
Compound 8
Table 2, entry 6

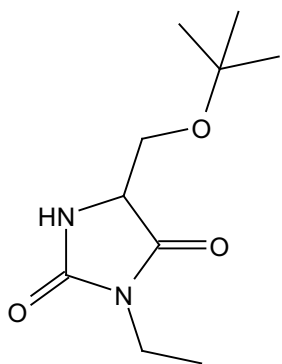
173.92
173.45

157.15
156.93

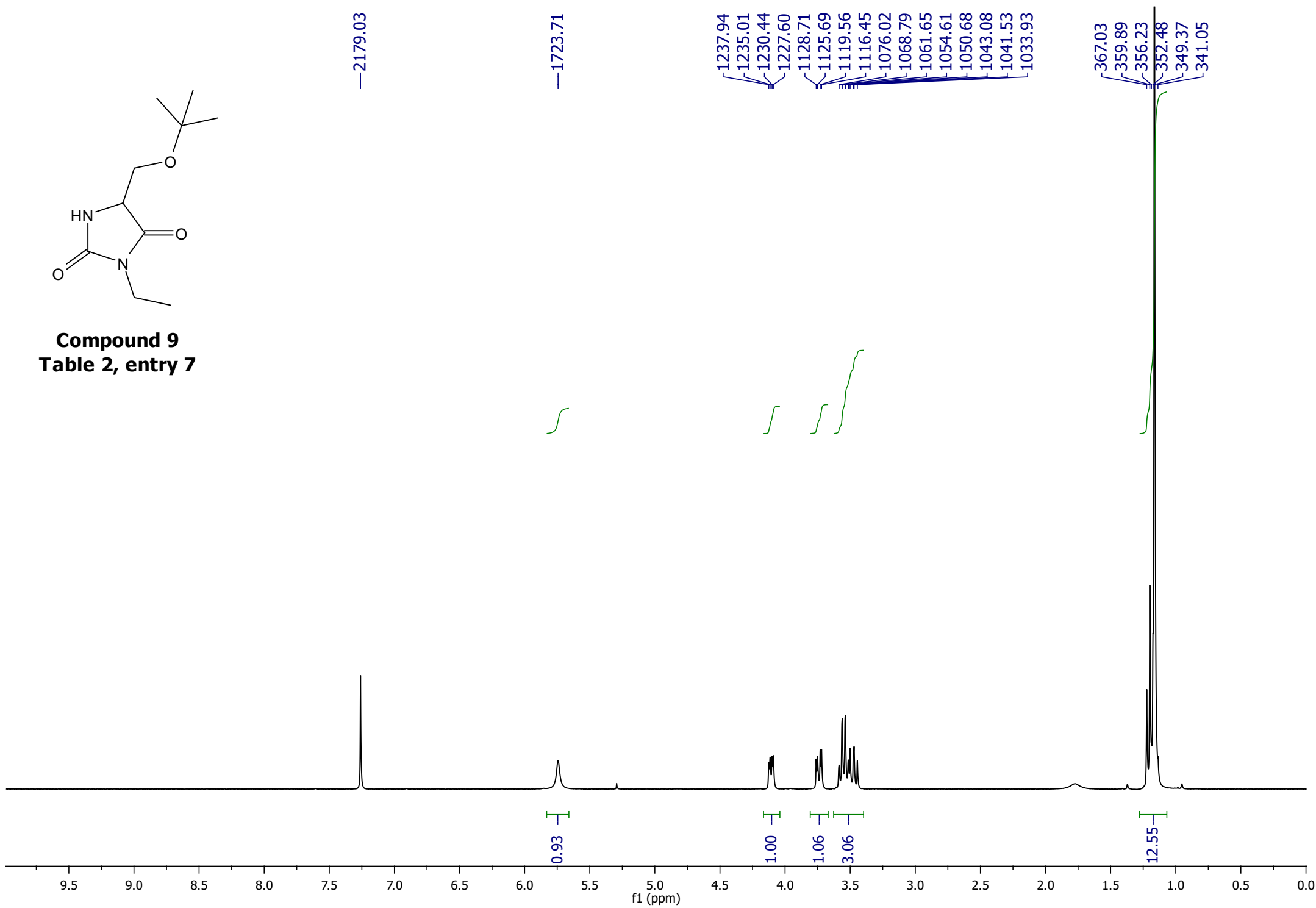
60.76
59.62
40.34
40.07
39.80
39.52
39.24
38.96
38.69
36.10
32.41
25.54
23.27
14.92
13.28
12.78
11.64

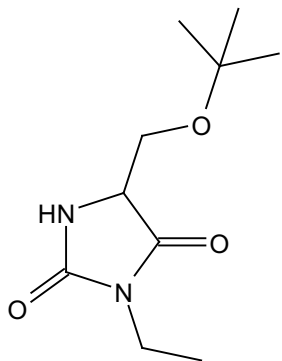




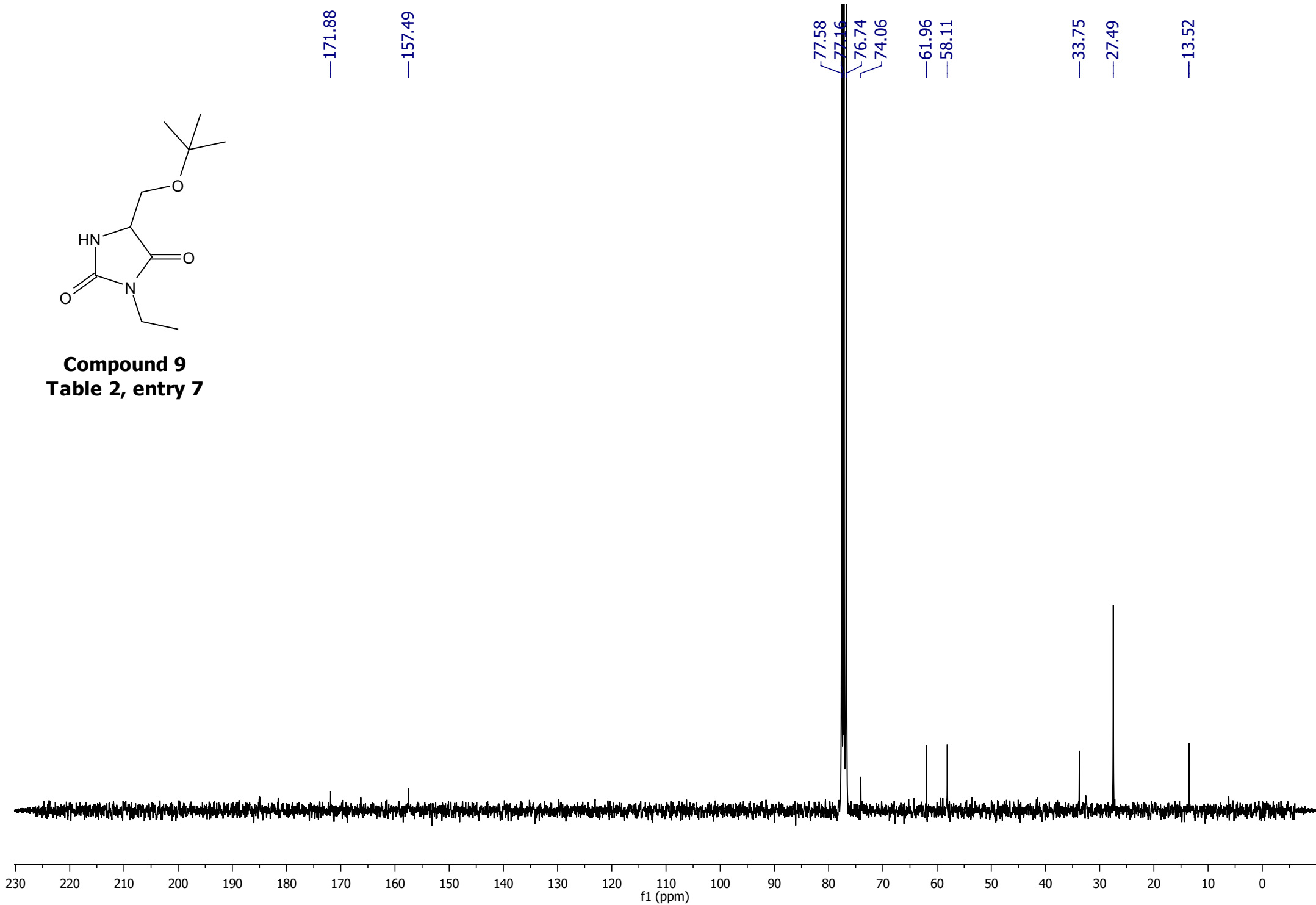


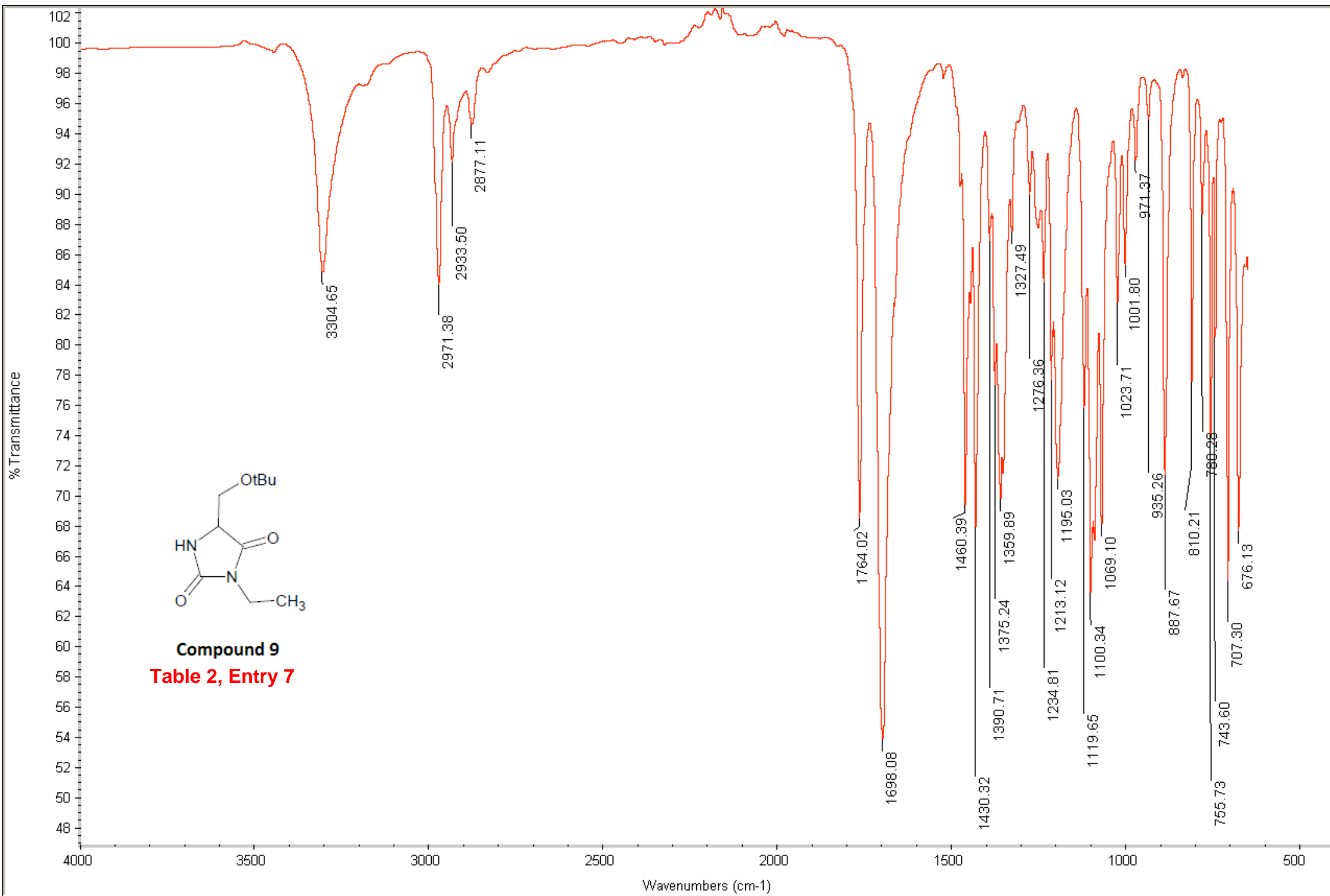
Compound 9
Table 2, entry 7

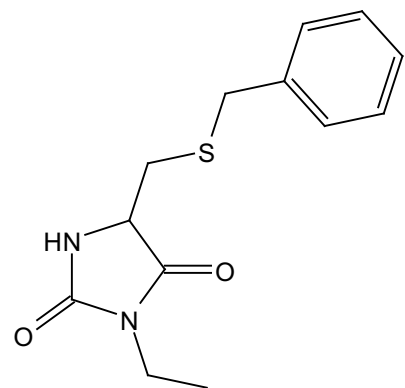




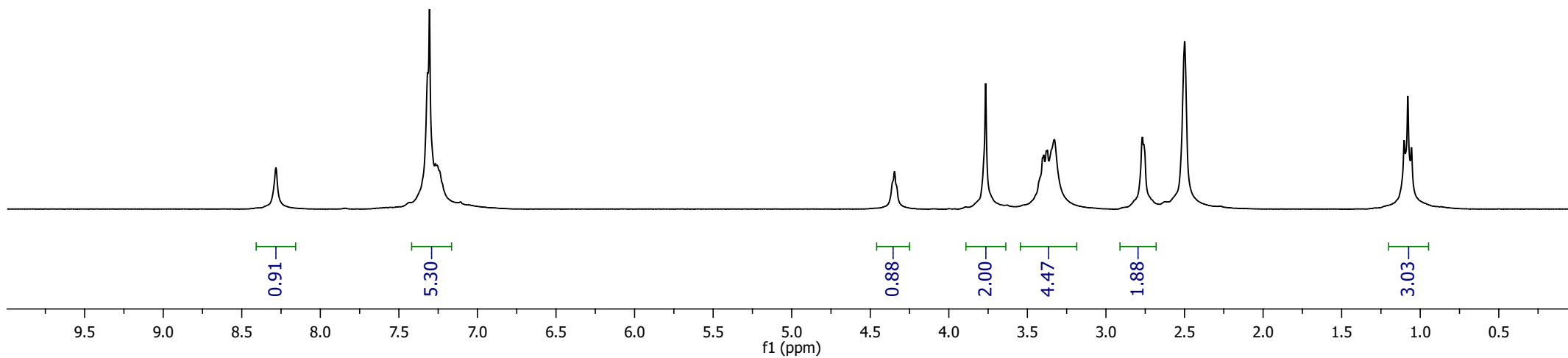
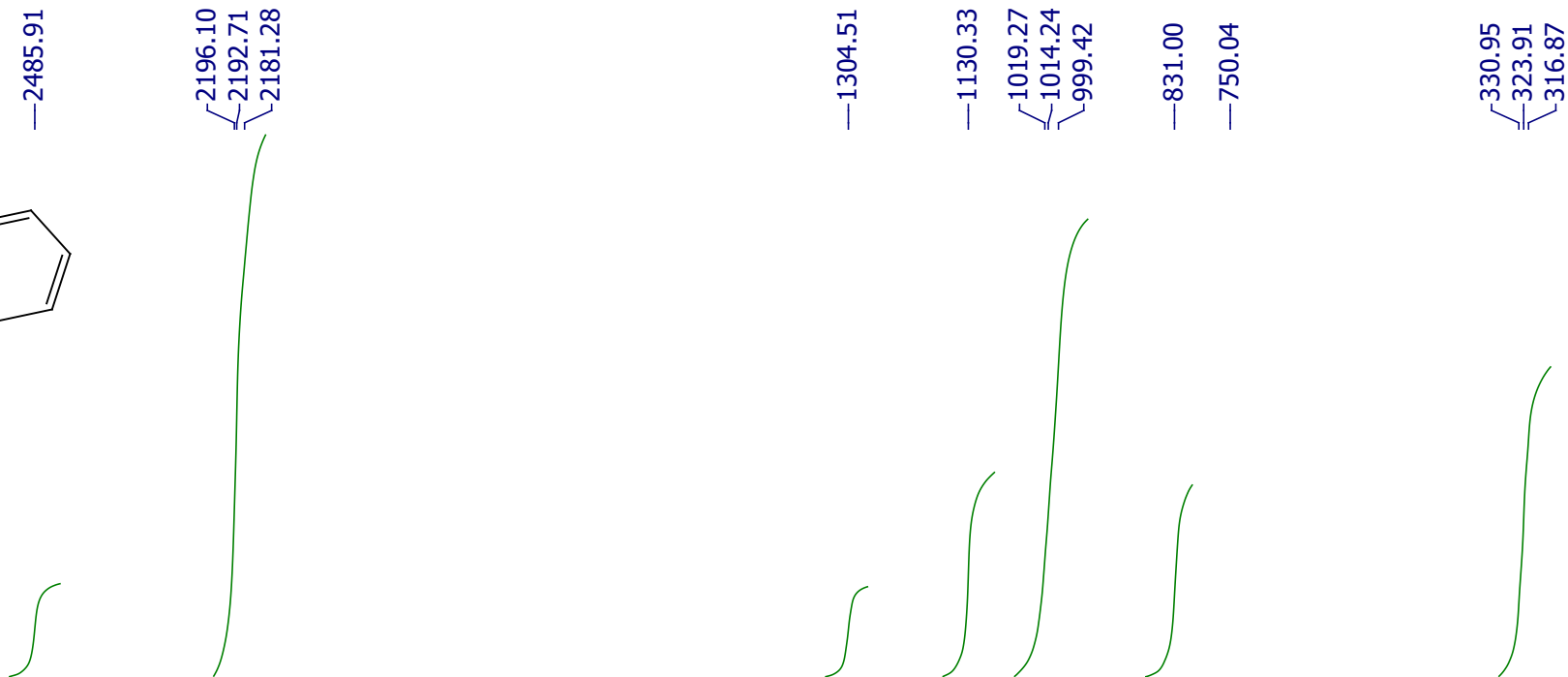
Compound 9
Table 2, entry 7

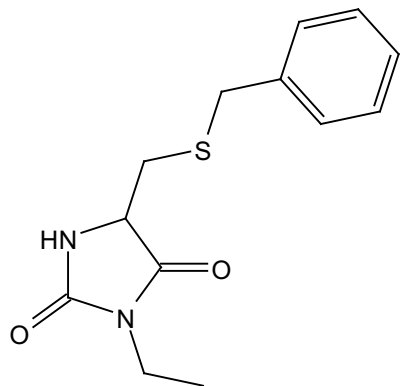




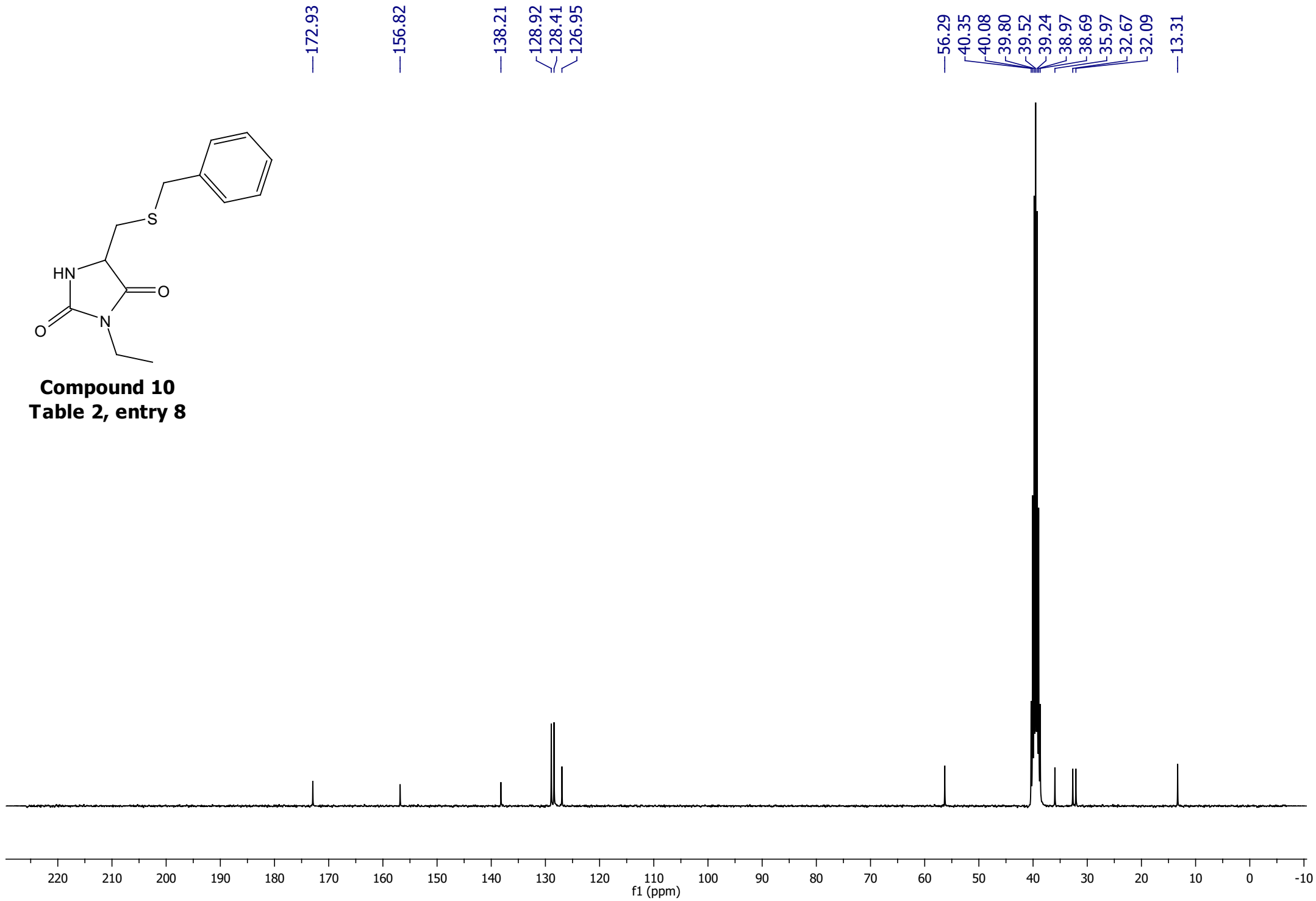


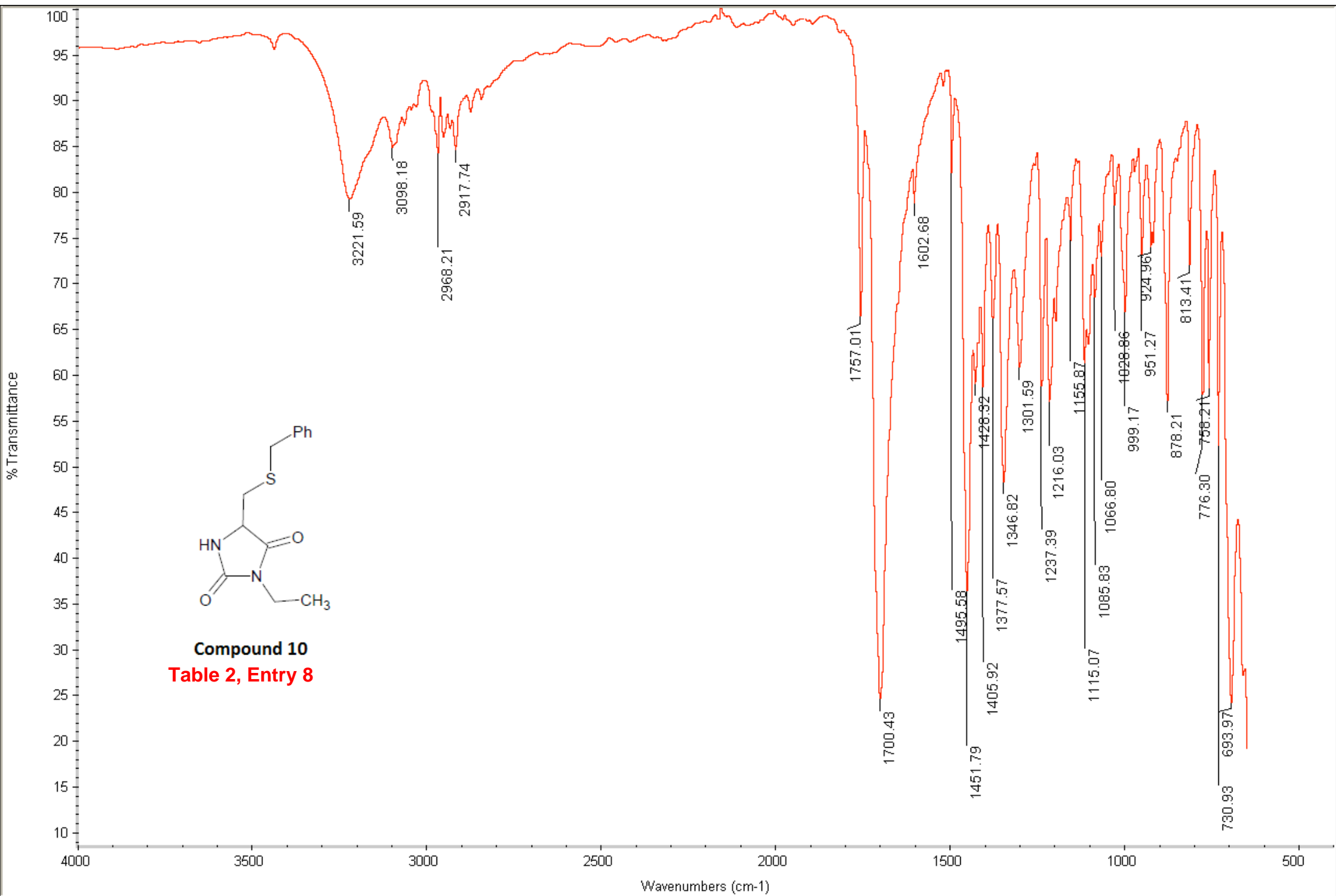
Compound 10
Table 2, entry 8

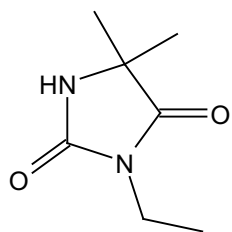




Compound 10
Table 2, entry 8







Compound 11
Table 2, entry 9

—2468.20



0.83

1016.92
1009.79
1002.56
997.07



2.24

752.08
750.43
750.33



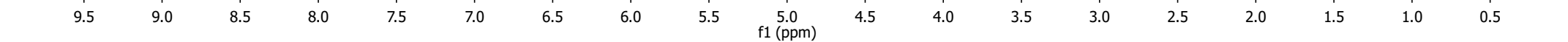
377.74
324.77
317.63
310.50



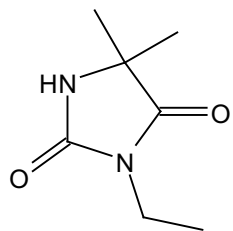
6.21



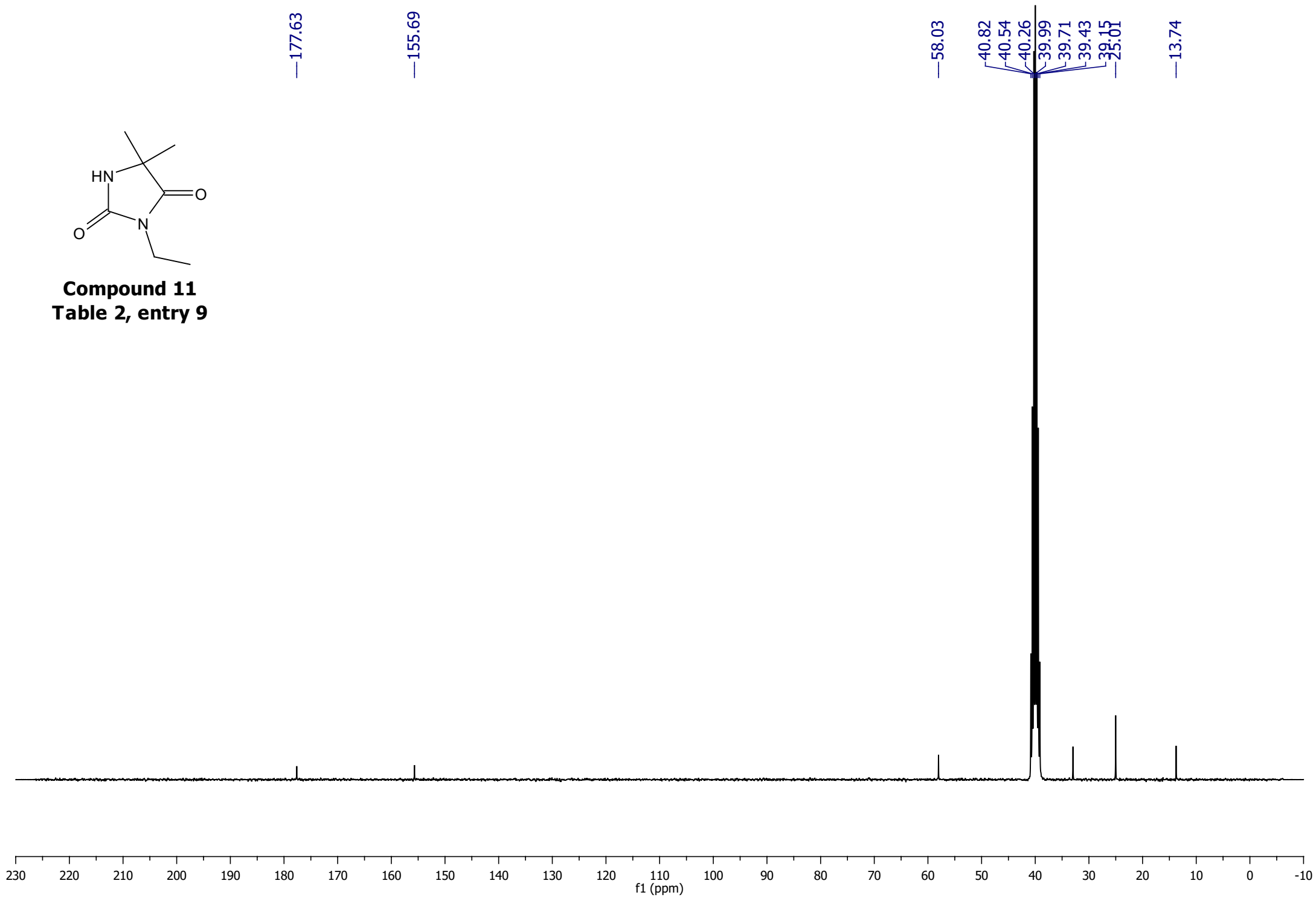
3.00

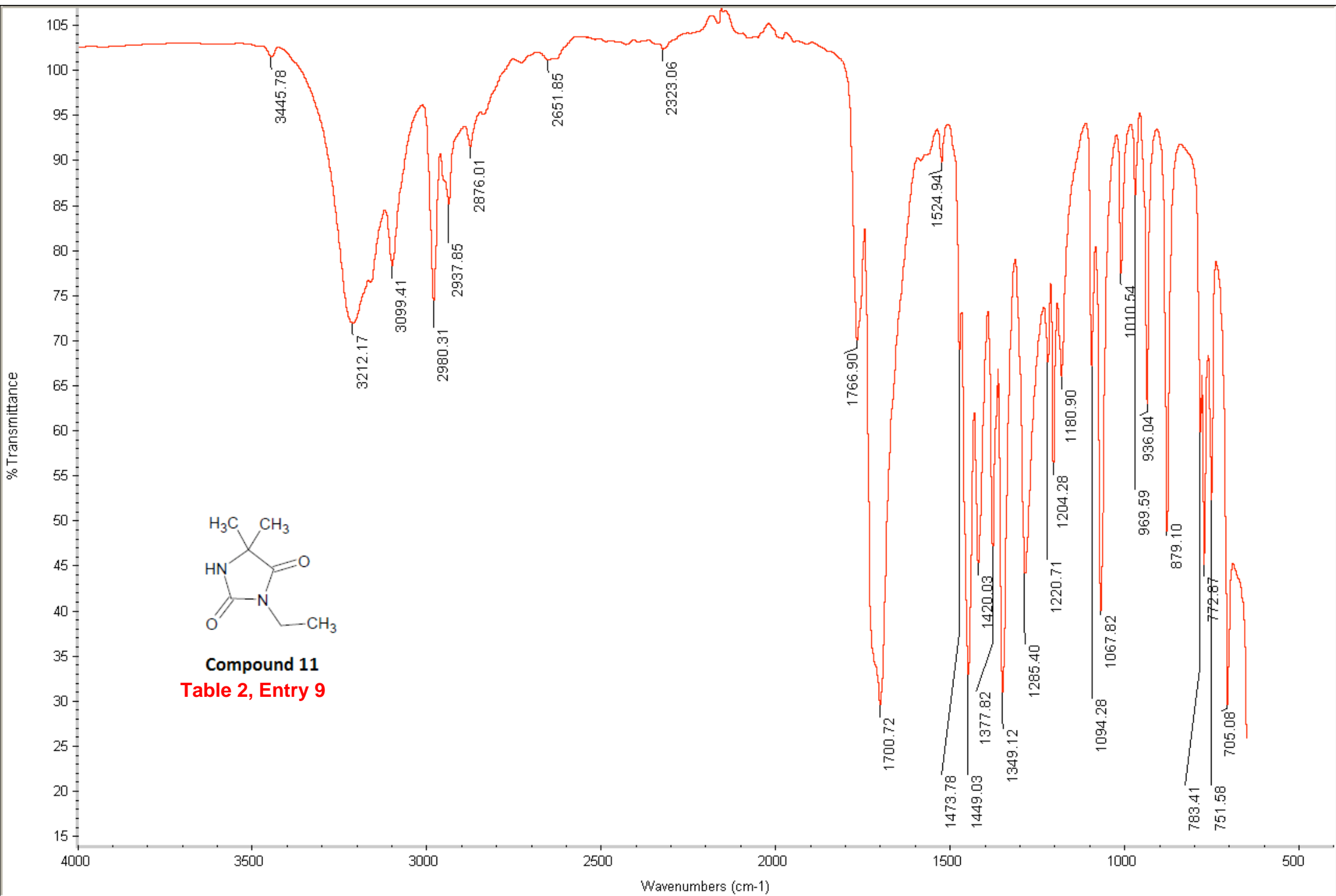


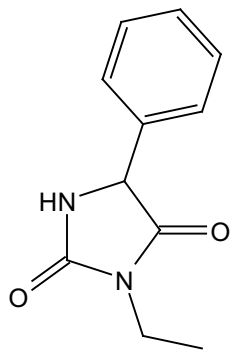
f1 (ppm)



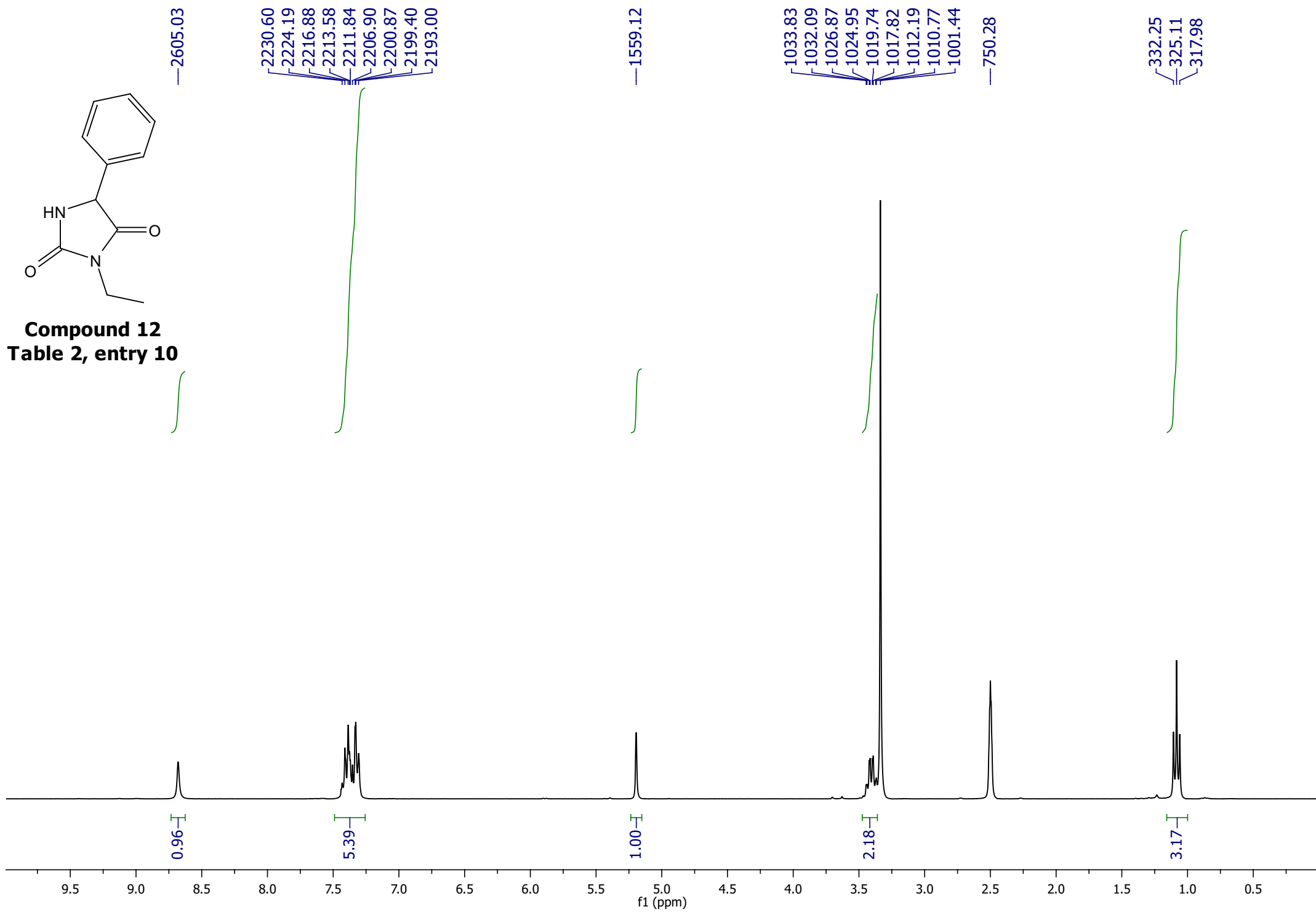
Compound 11
Table 2, entry 9

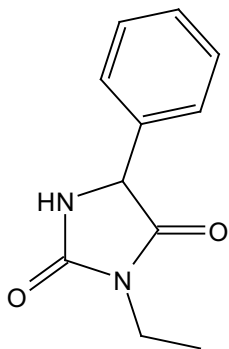




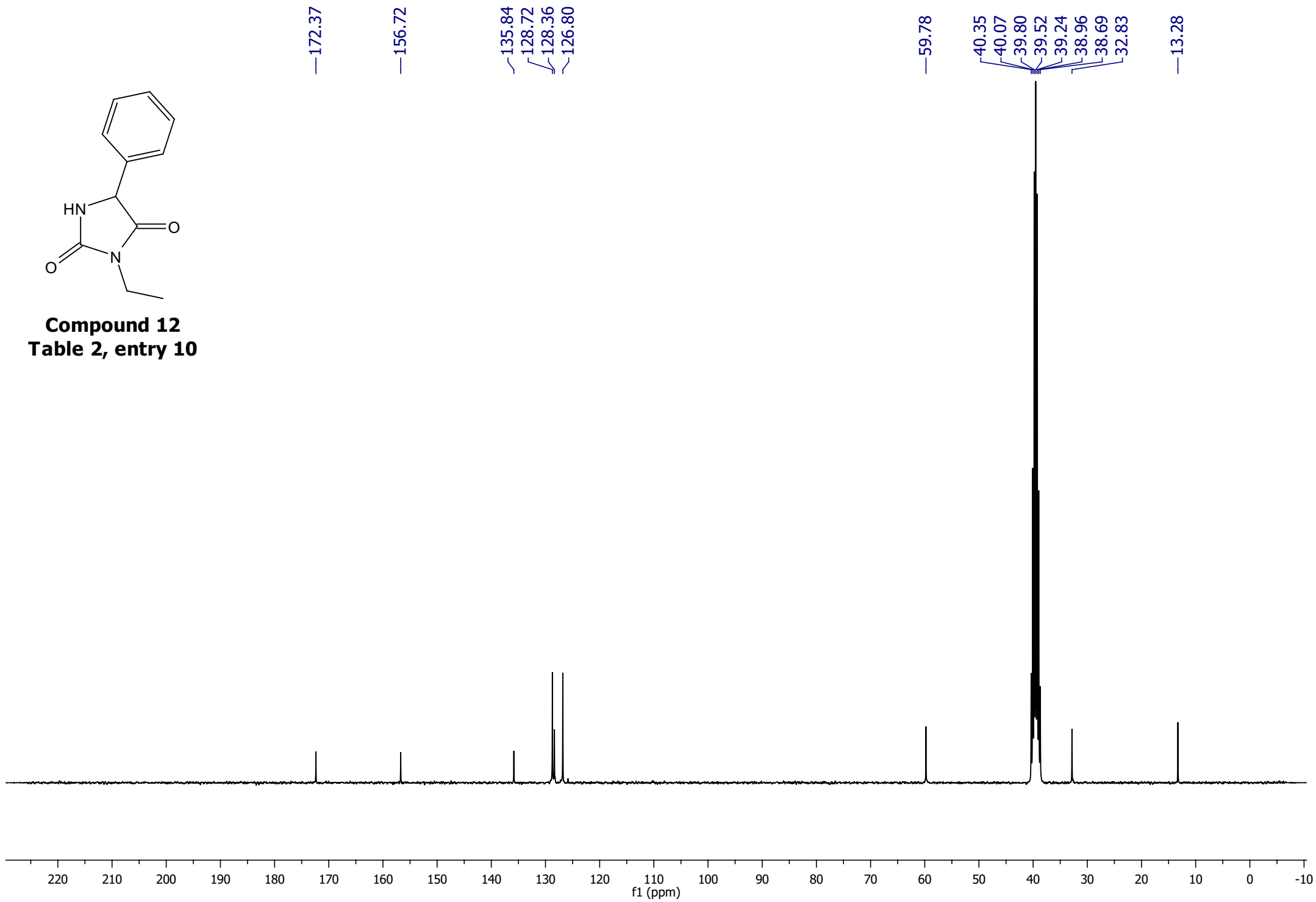


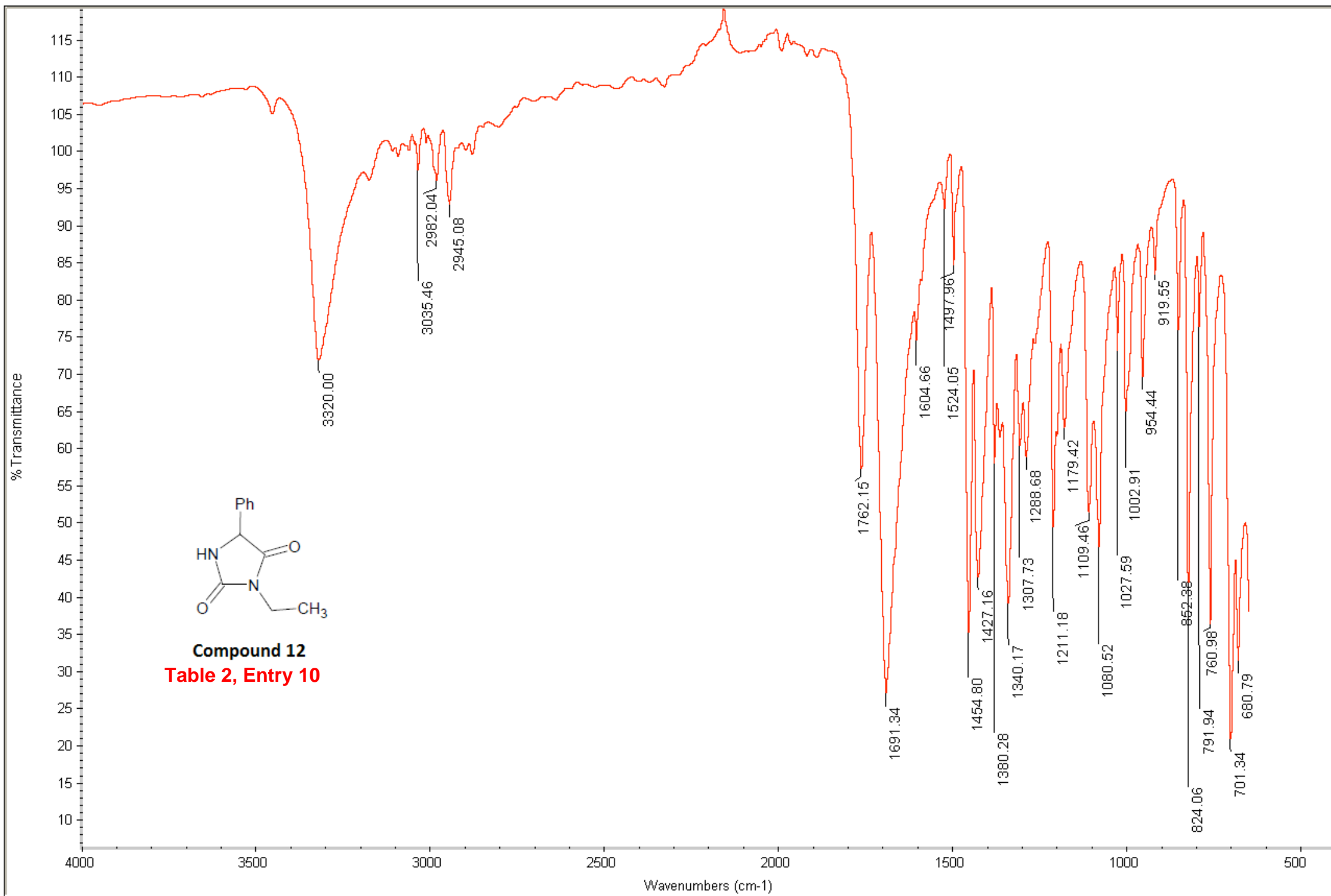
Compound 12
Table 2, entry 10

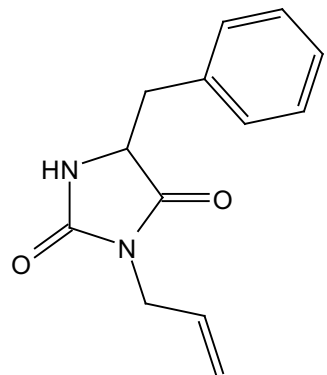




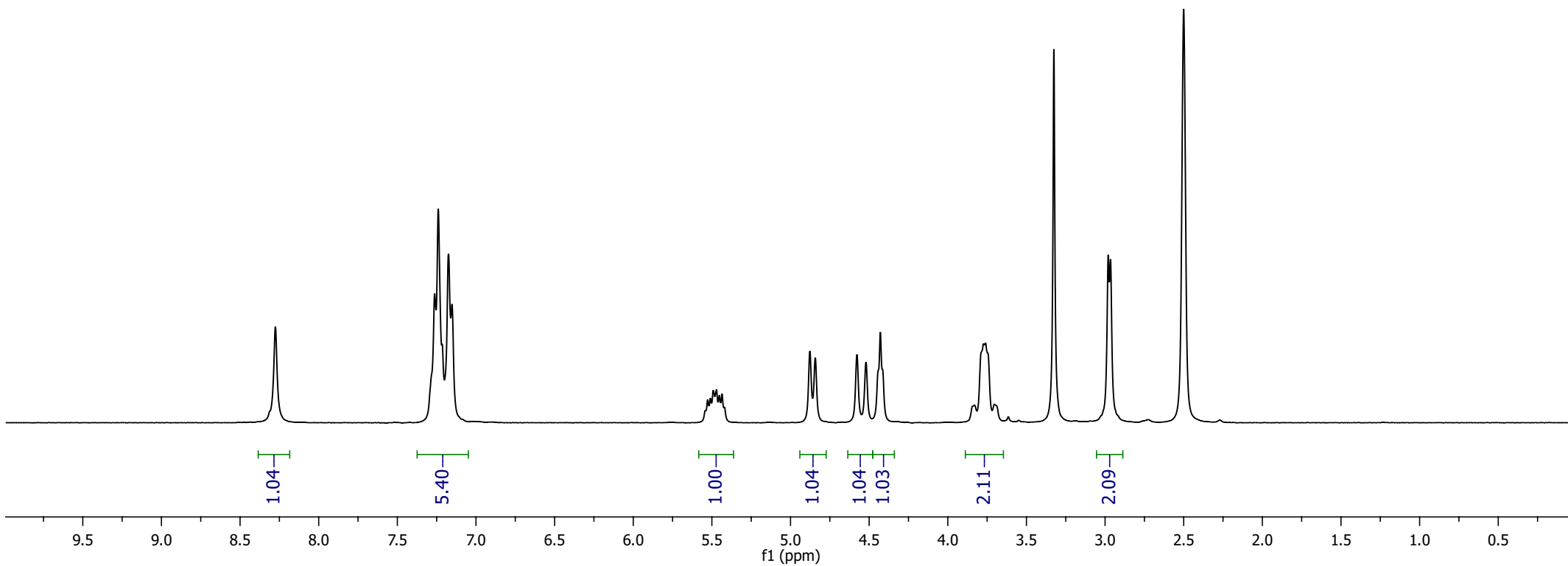
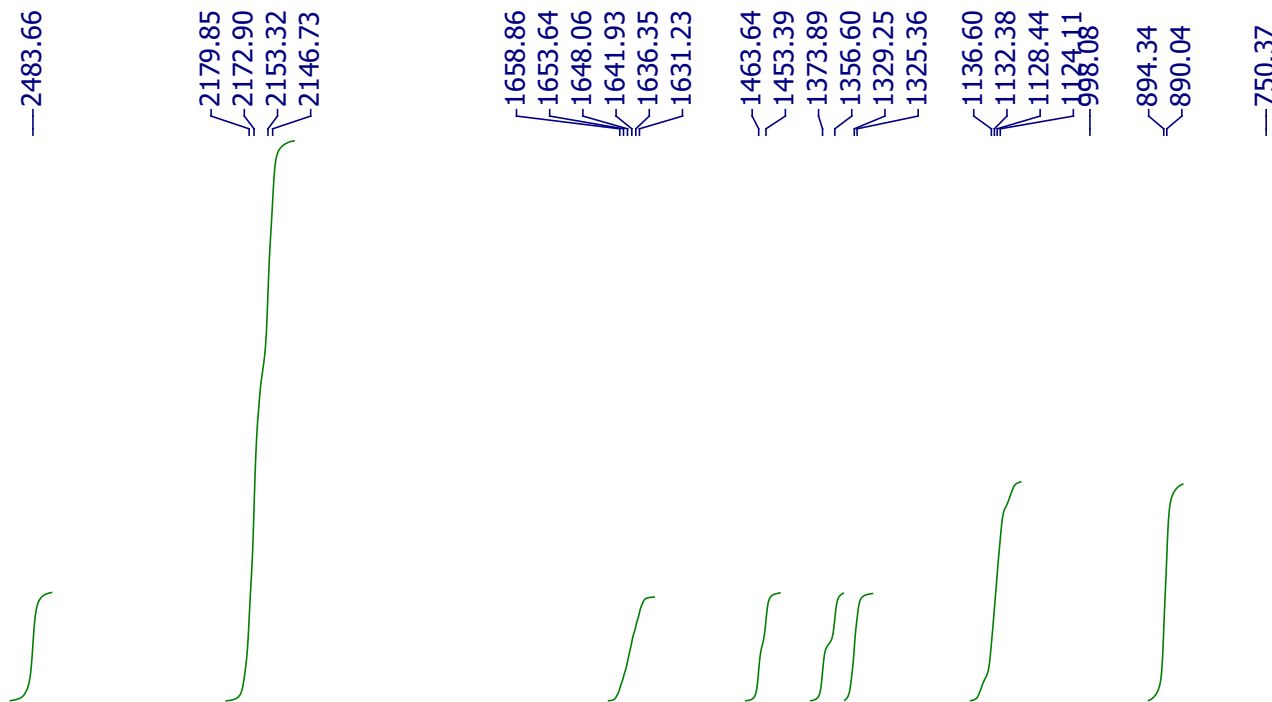
Compound 12
Table 2, entry 10

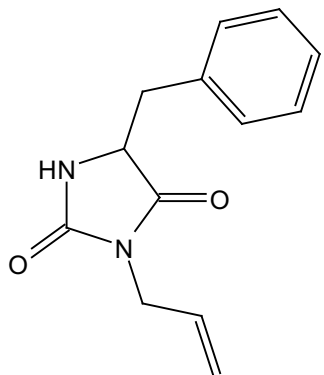






Compound 13
Table 2, entry 11





Compound 13
Table 2, entry 11

—173.04

—156.09

—135.17

—131.80

—129.82

—128.06

—126.73

—115.56

—57.12

—40.35

—40.08

—39.80

—39.52

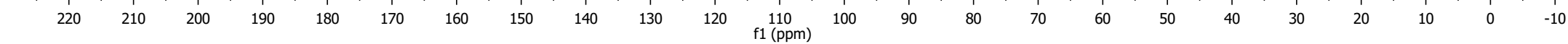
—39.35

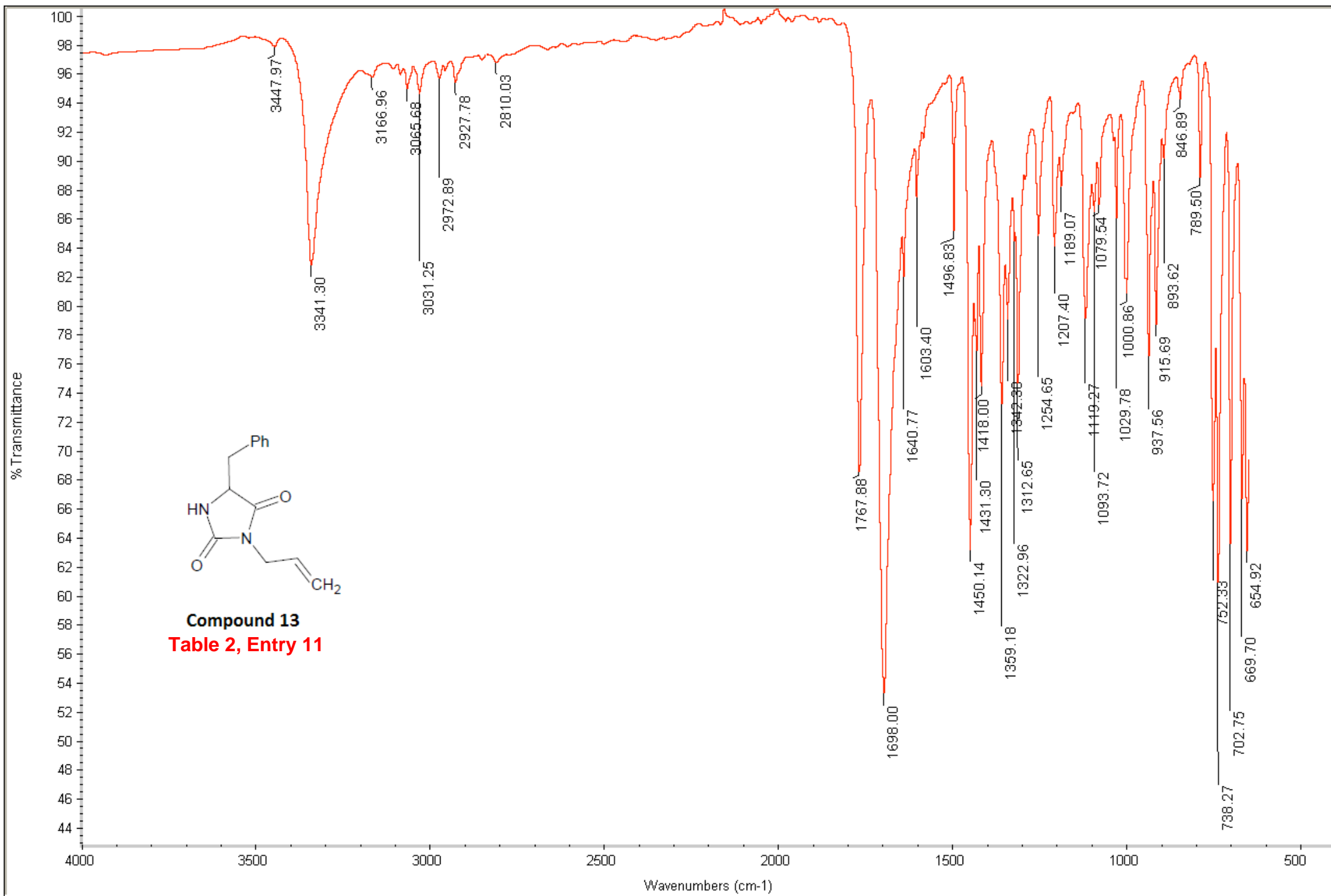
—39.24

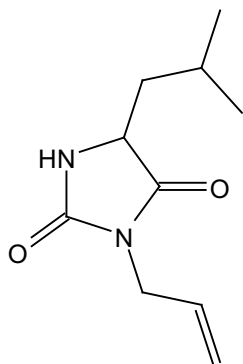
—38.97

—38.69

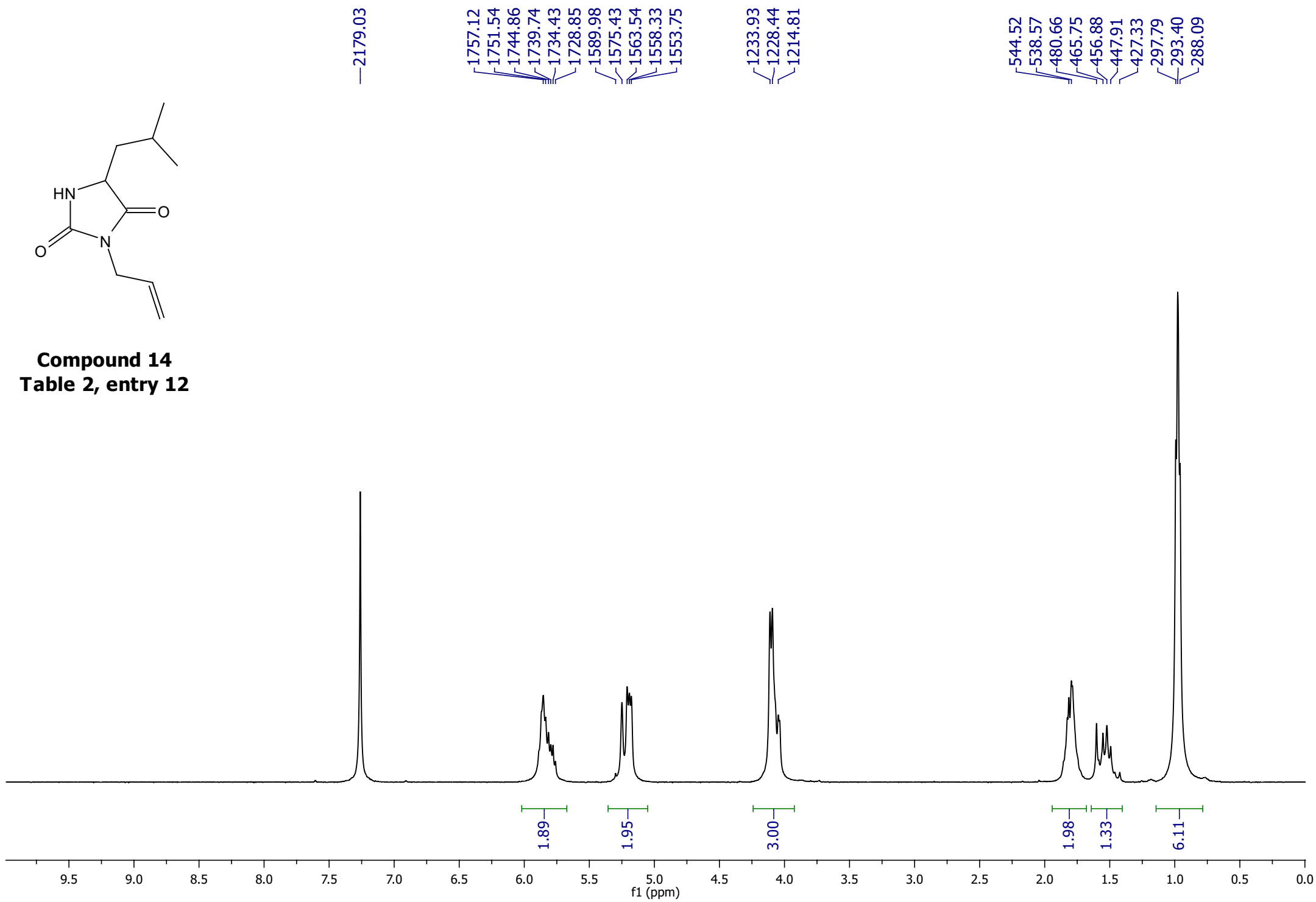
—36.29

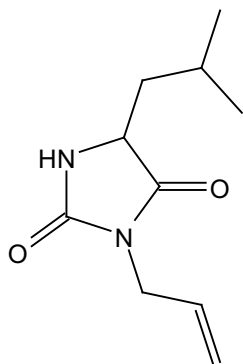




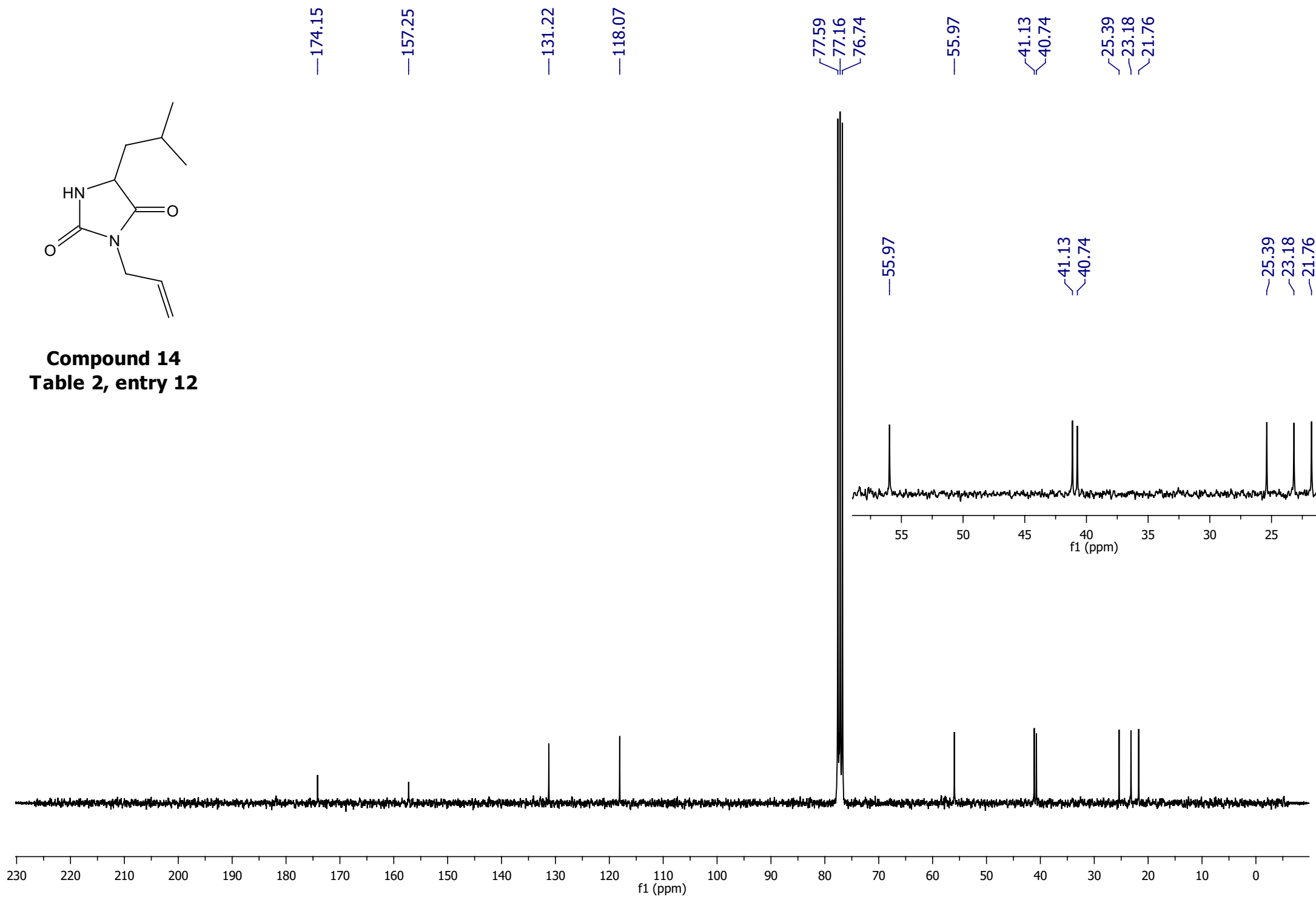


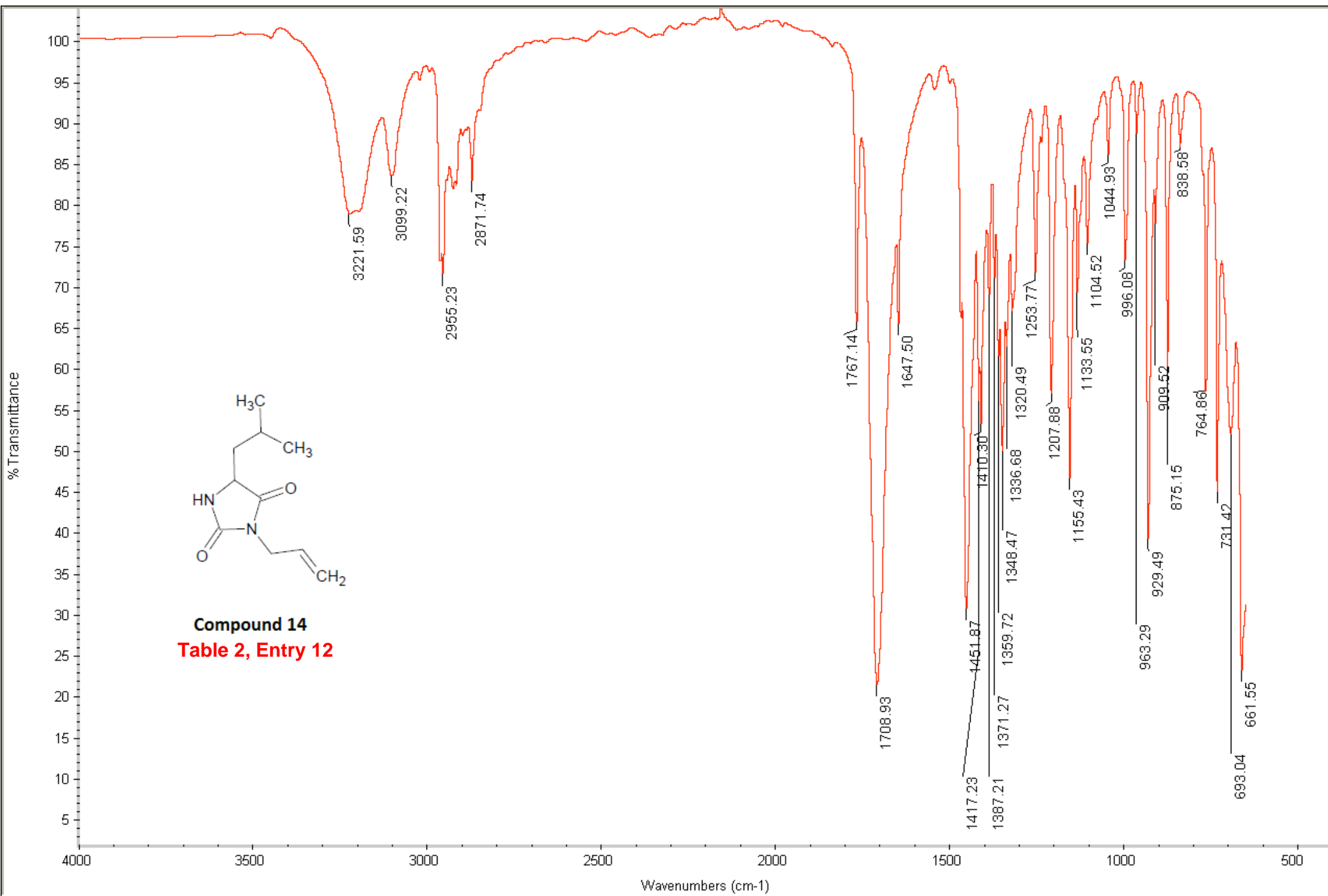
Compound 14
Table 2, entry 12

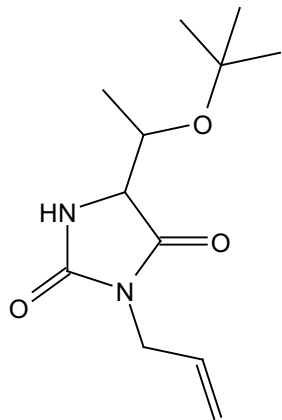




Compound 14
Table 2, entry 12







Compound 15
Table 2, entry 13

2471.87
2439.58

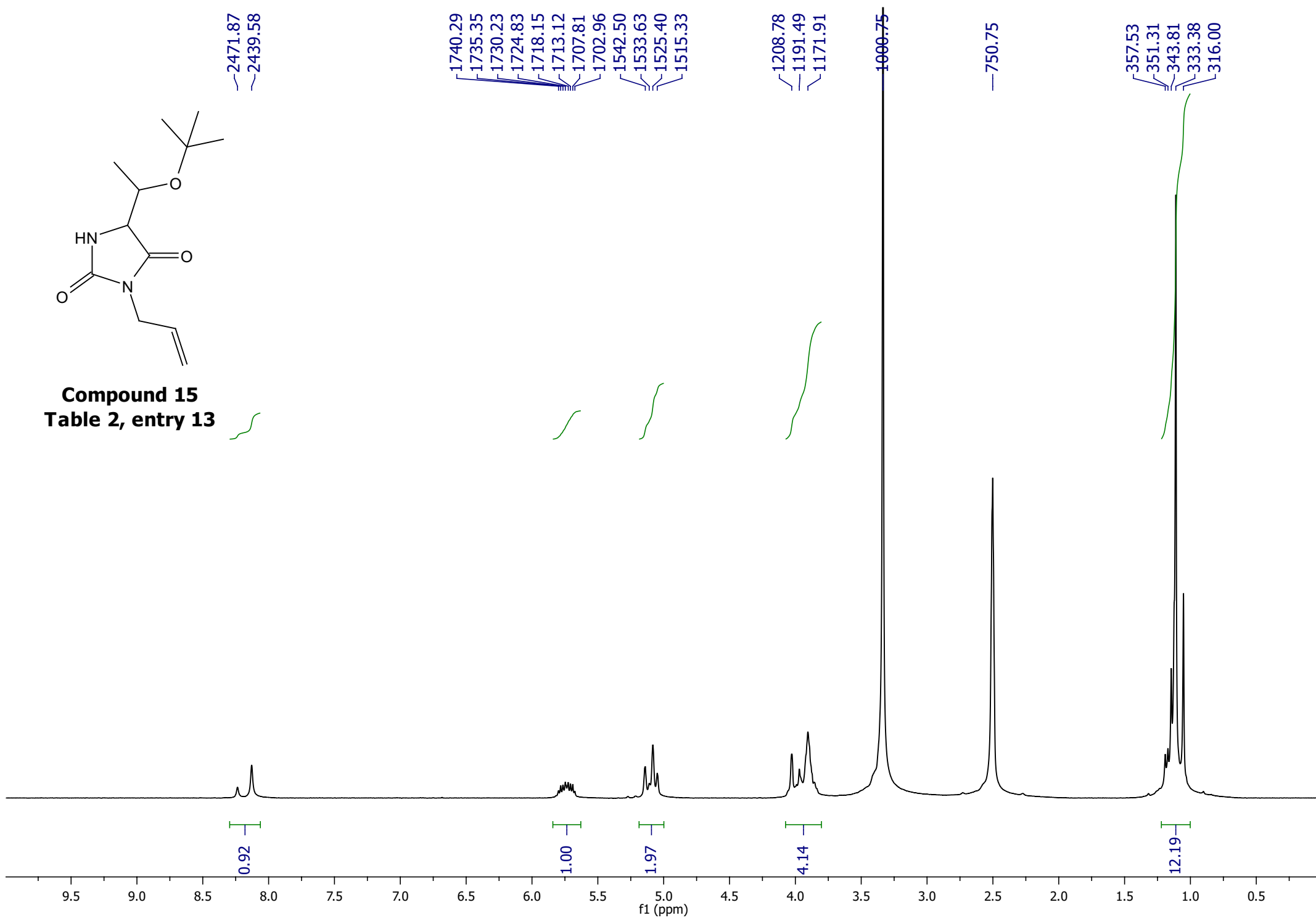
1740.29
1735.35
1730.23
1724.83
1718.15
1713.12
1707.81
1702.96
1542.50
1533.63
1525.40
1515.33

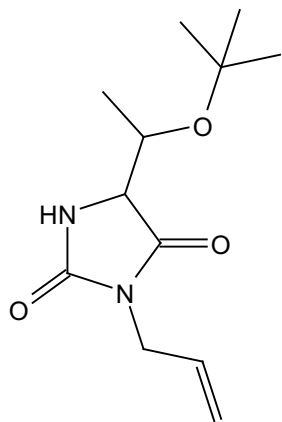
1208.78
1191.49
1171.91

1000.75

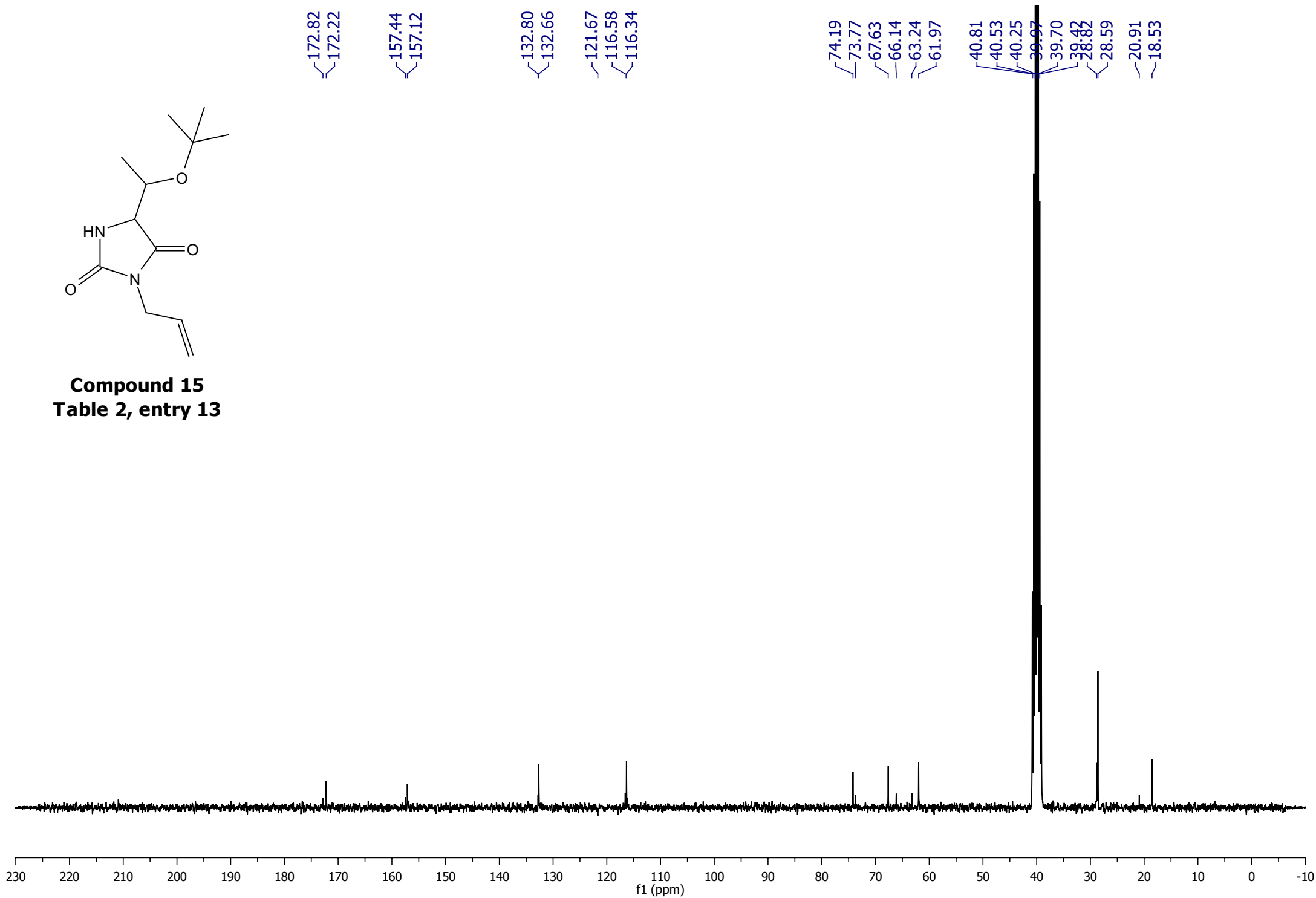
750.75

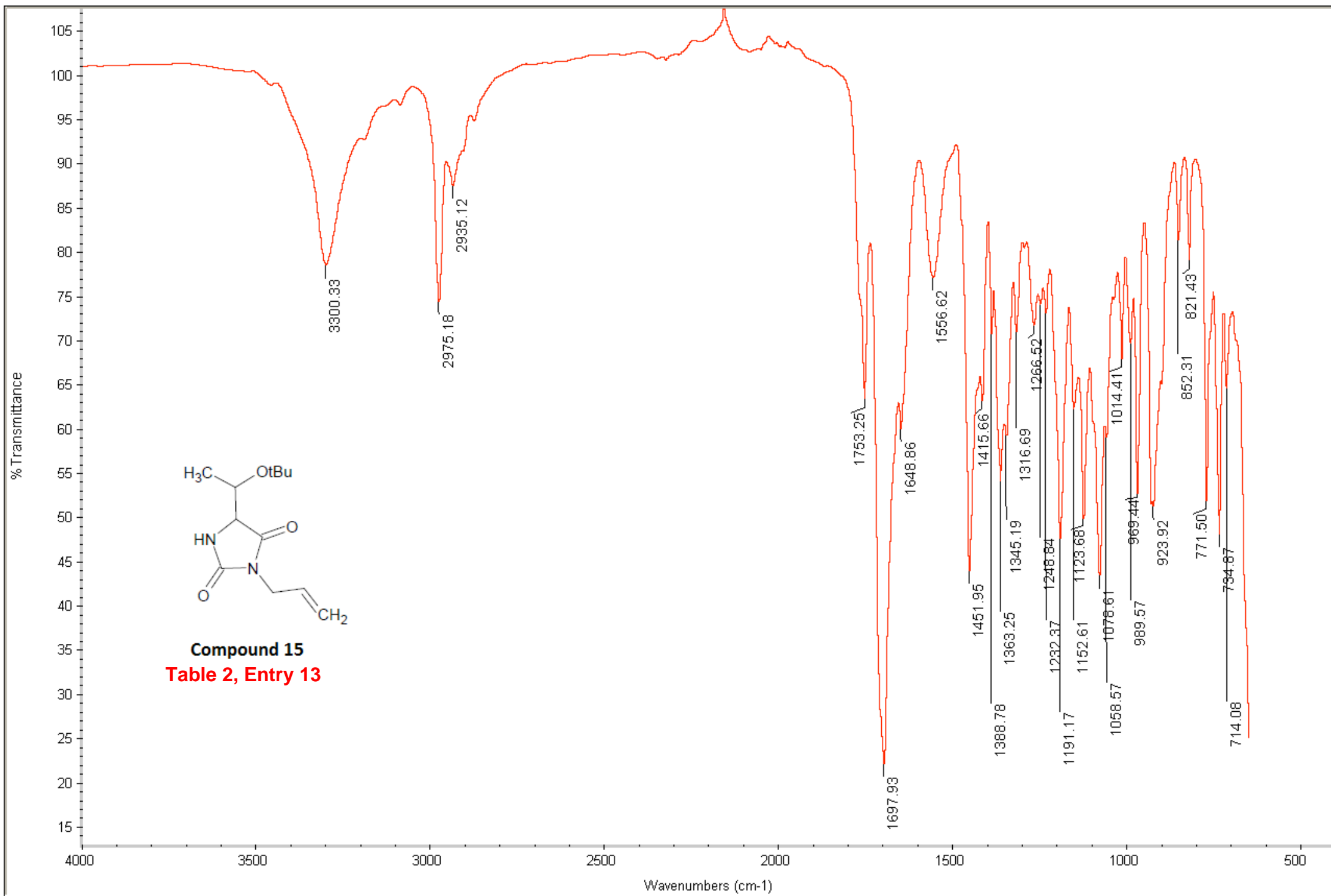
357.53
351.31
343.81
333.38
316.00

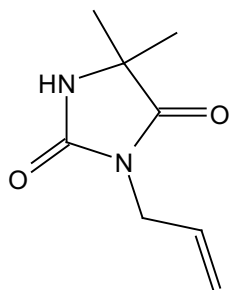




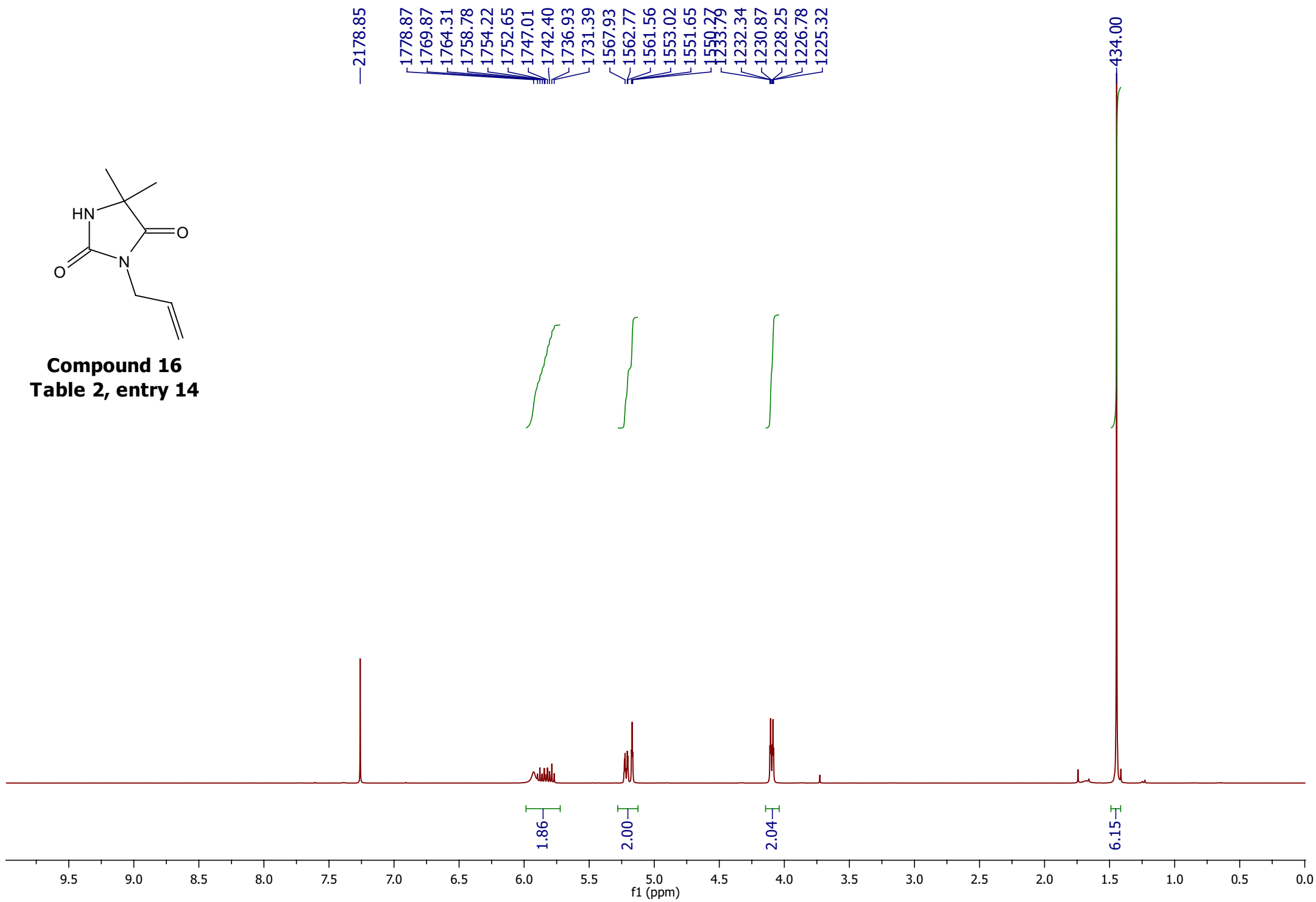
Compound 15
Table 2, entry 13

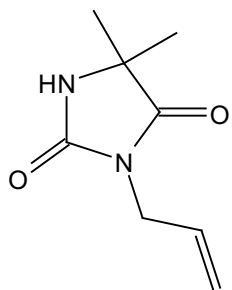




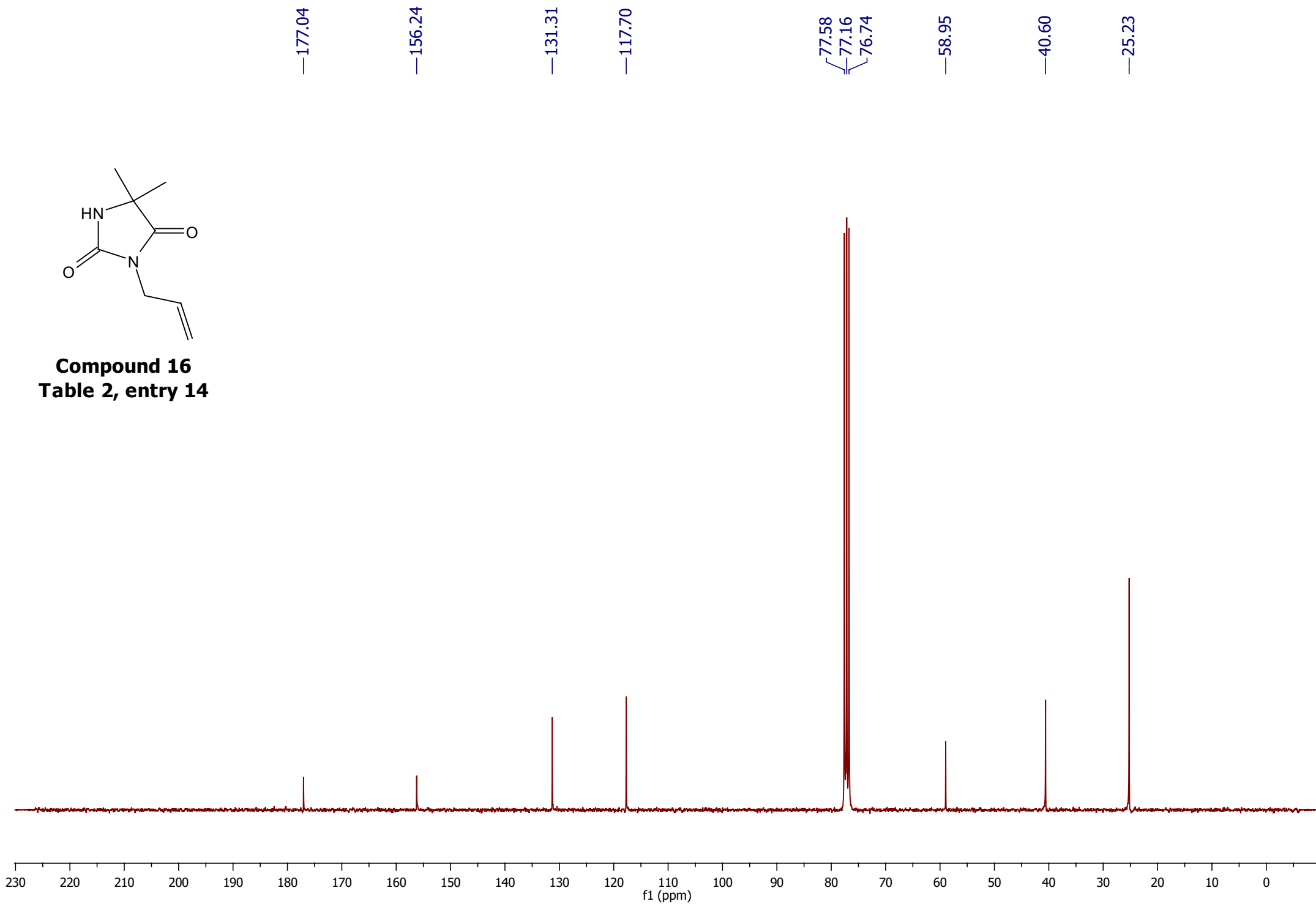


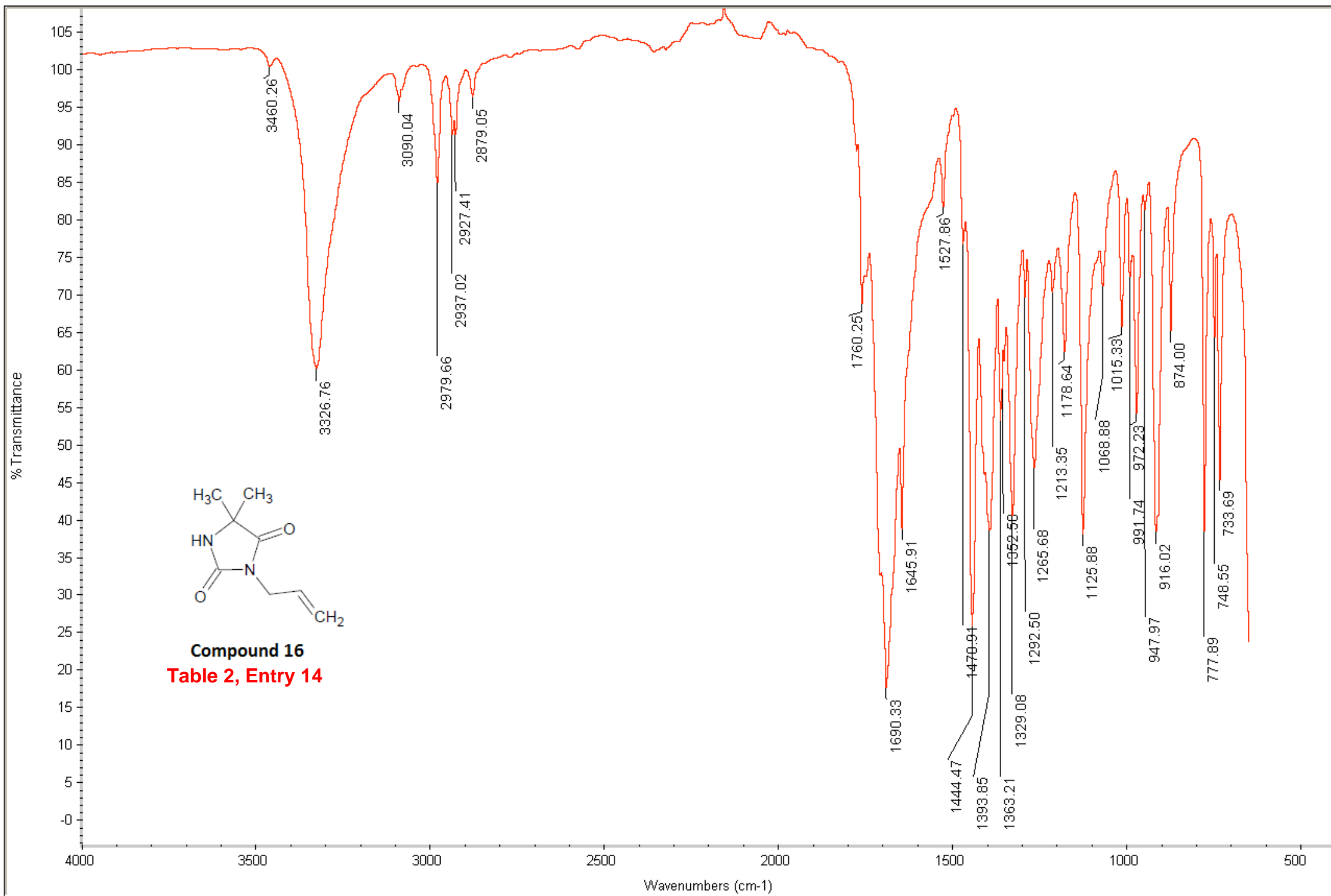
Compound 16
Table 2, entry 14

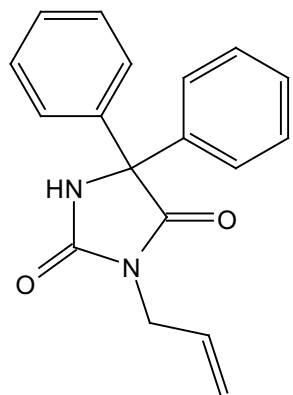




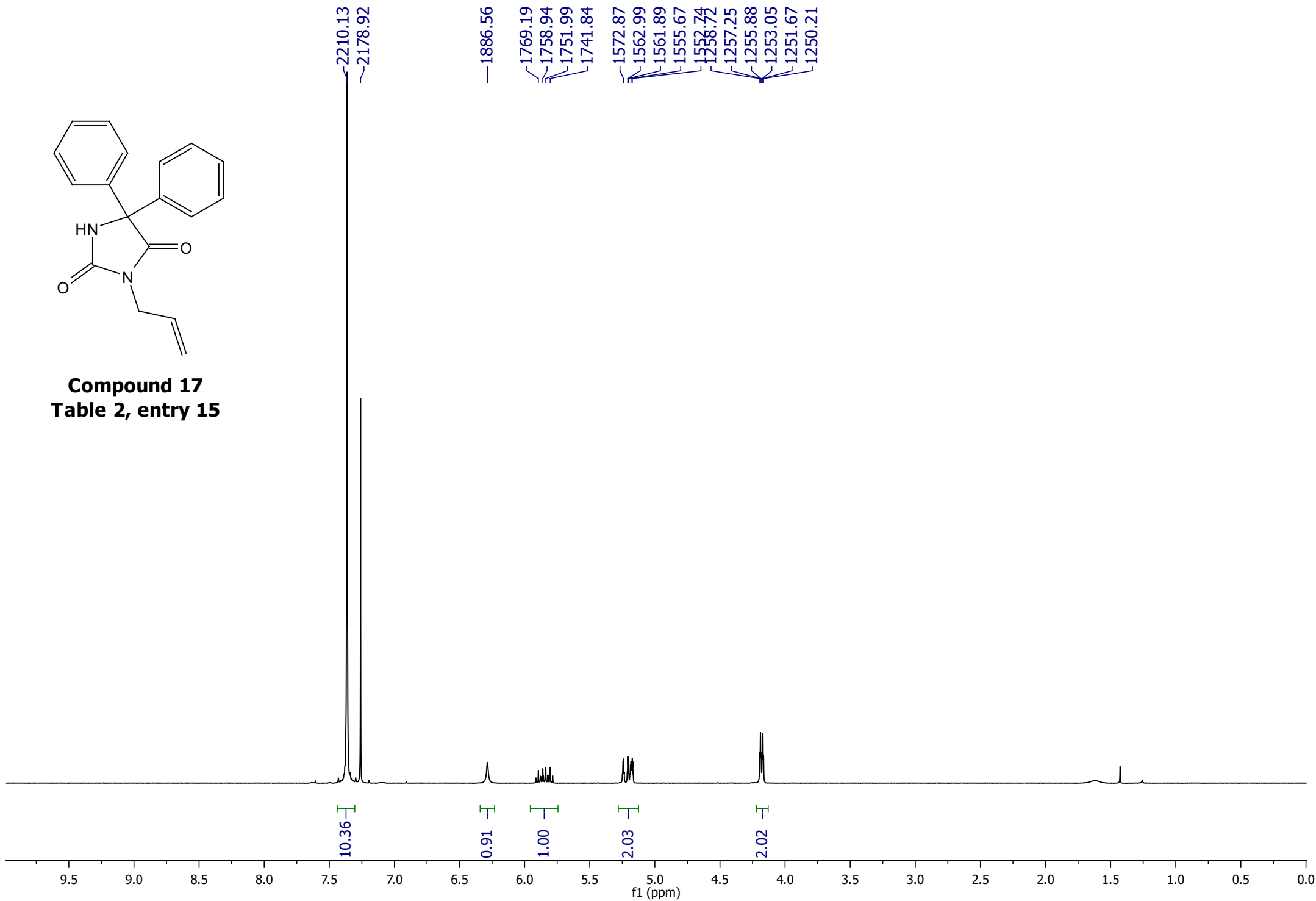
Compound 16
Table 2, entry 14

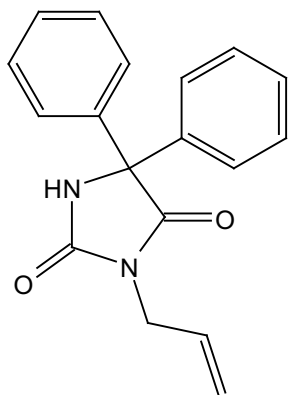




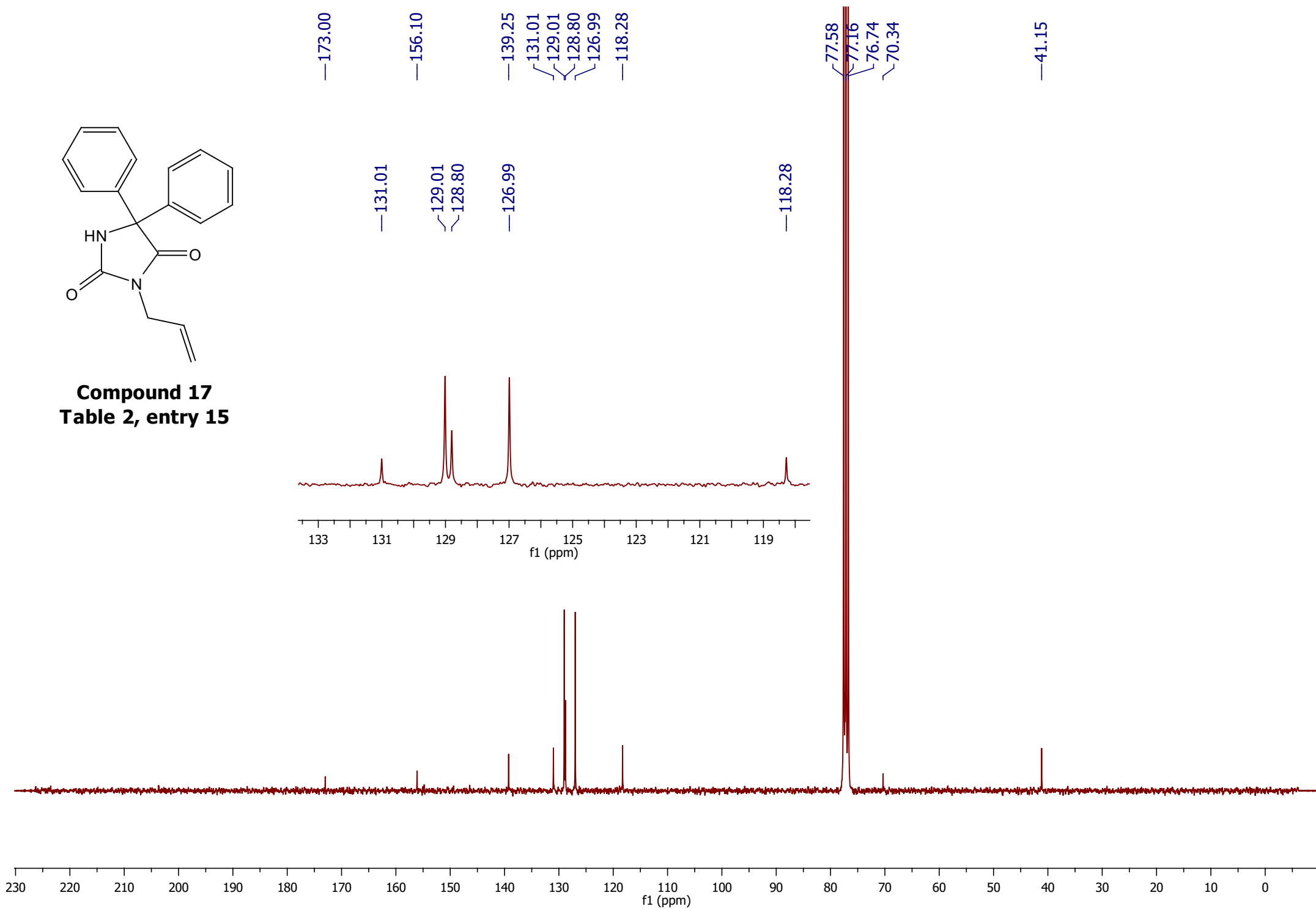


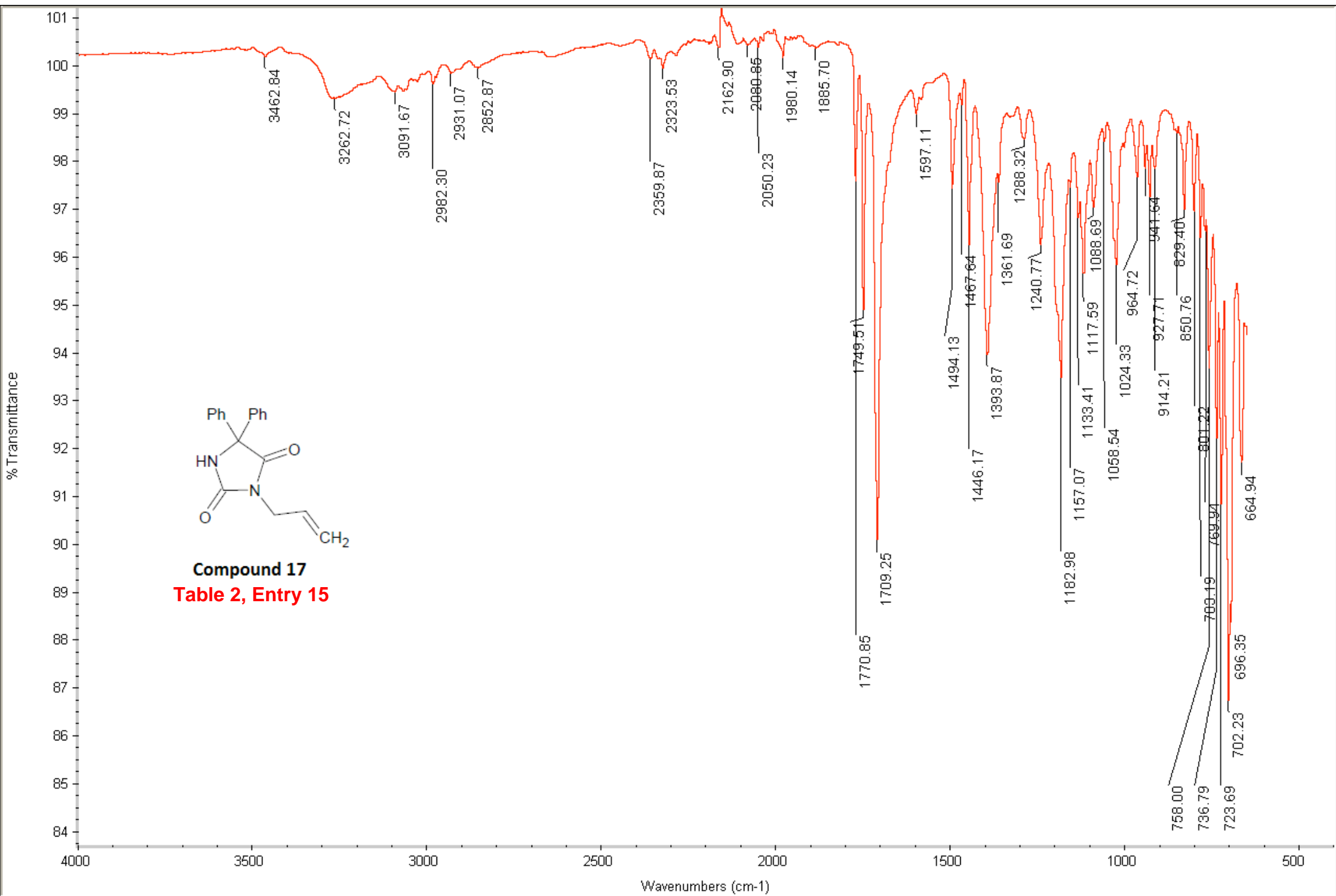
Compound 17
Table 2, entry 15

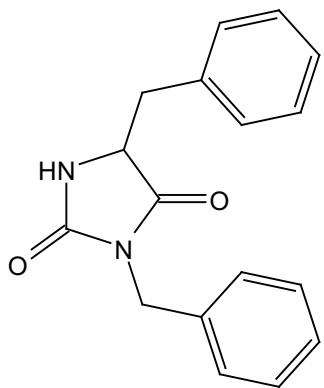




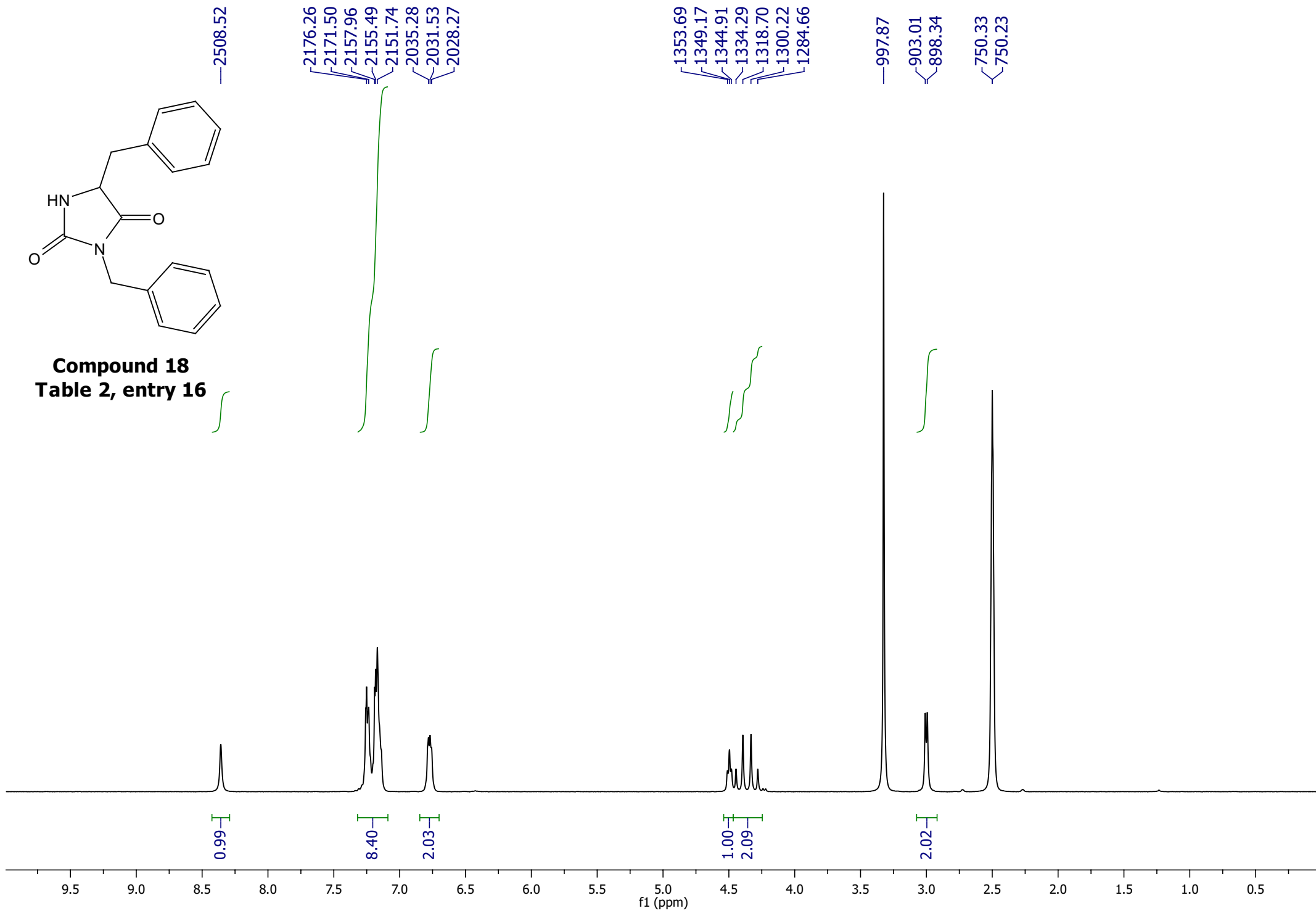
Compound 17
Table 2, entry 15

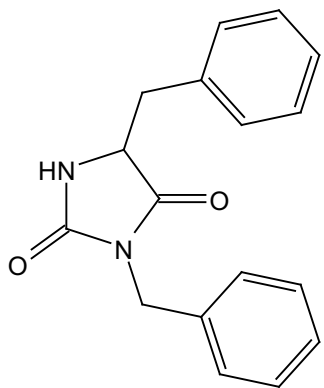




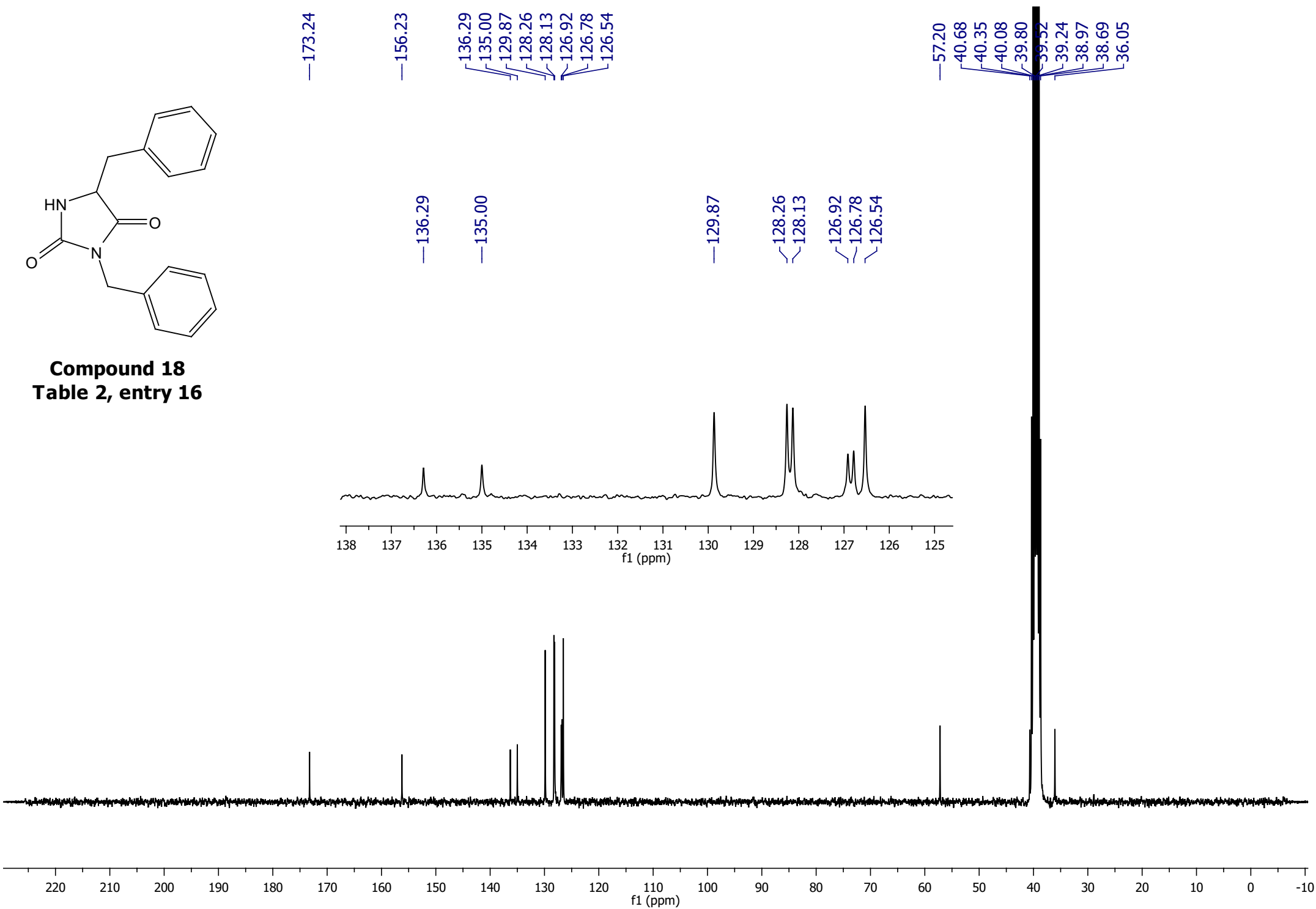


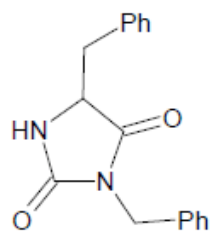
Compound 18
Table 2, entry 16





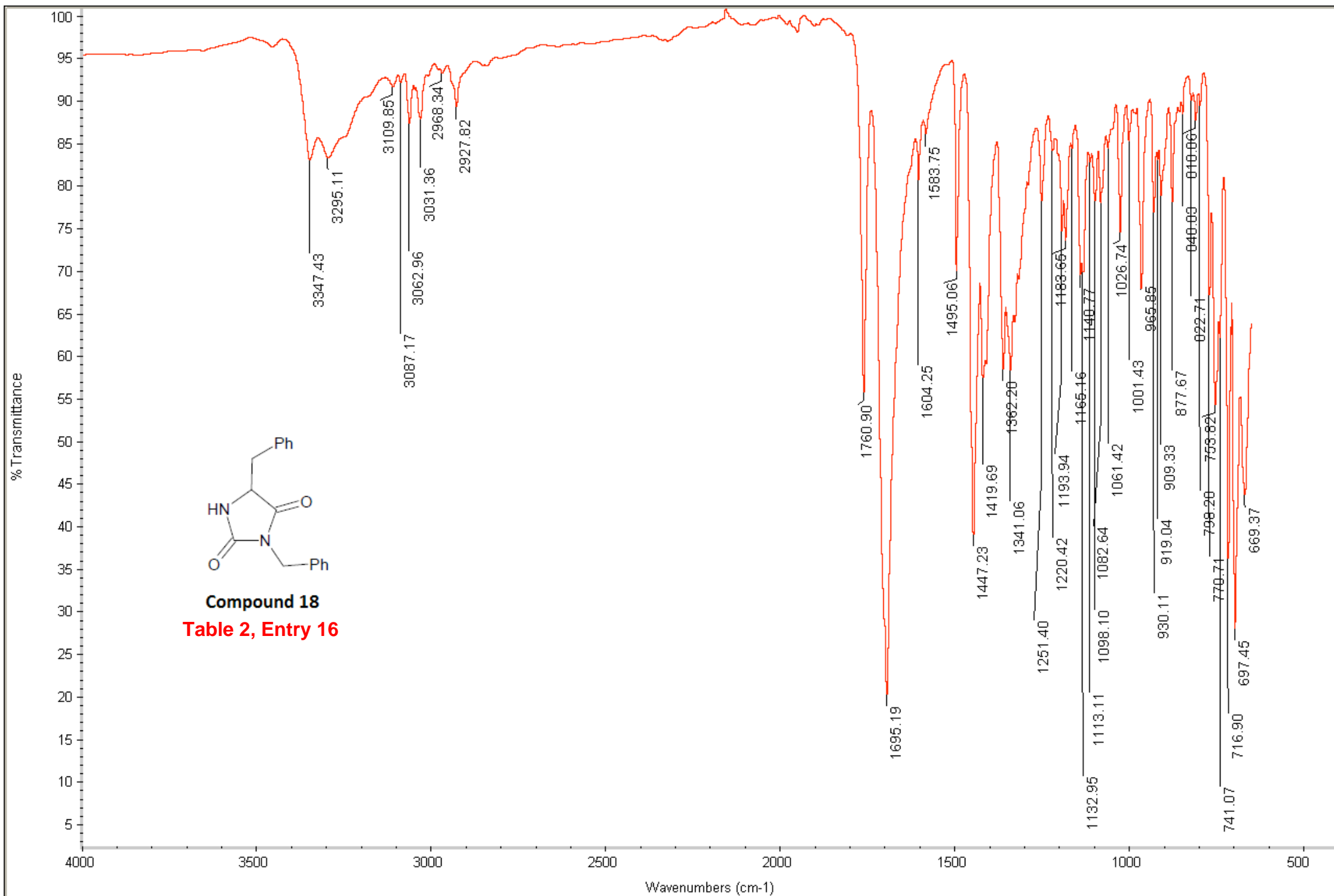
Compound 18
Table 2, entry 16

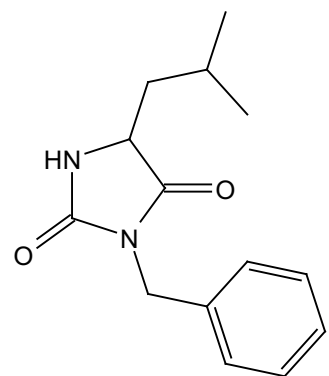




Compound 18

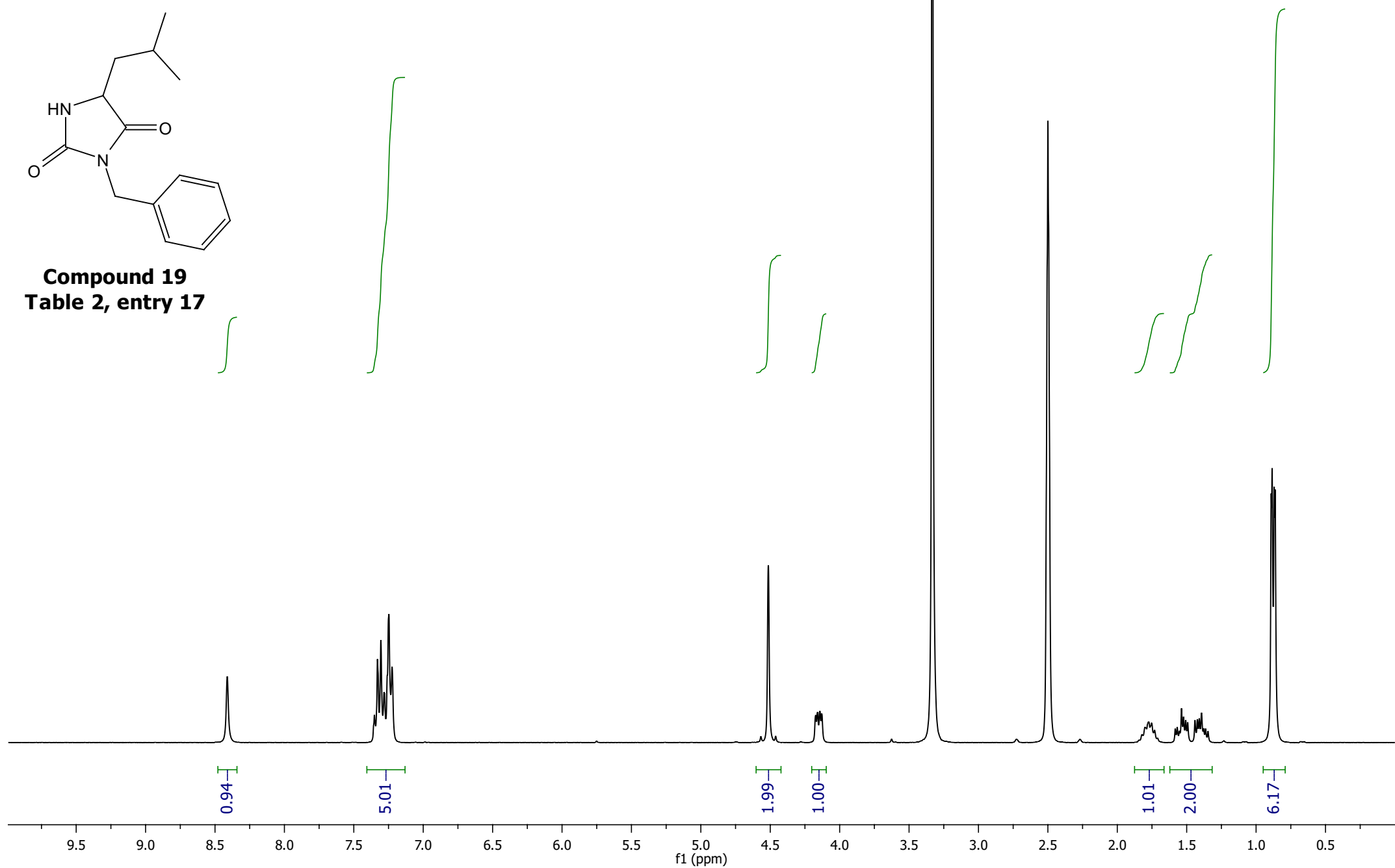
Table 2, Entry 16

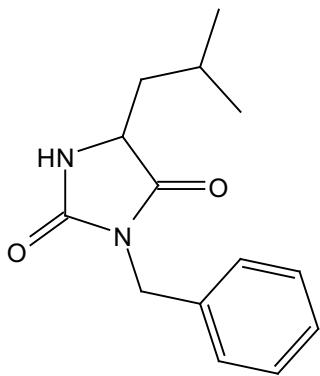




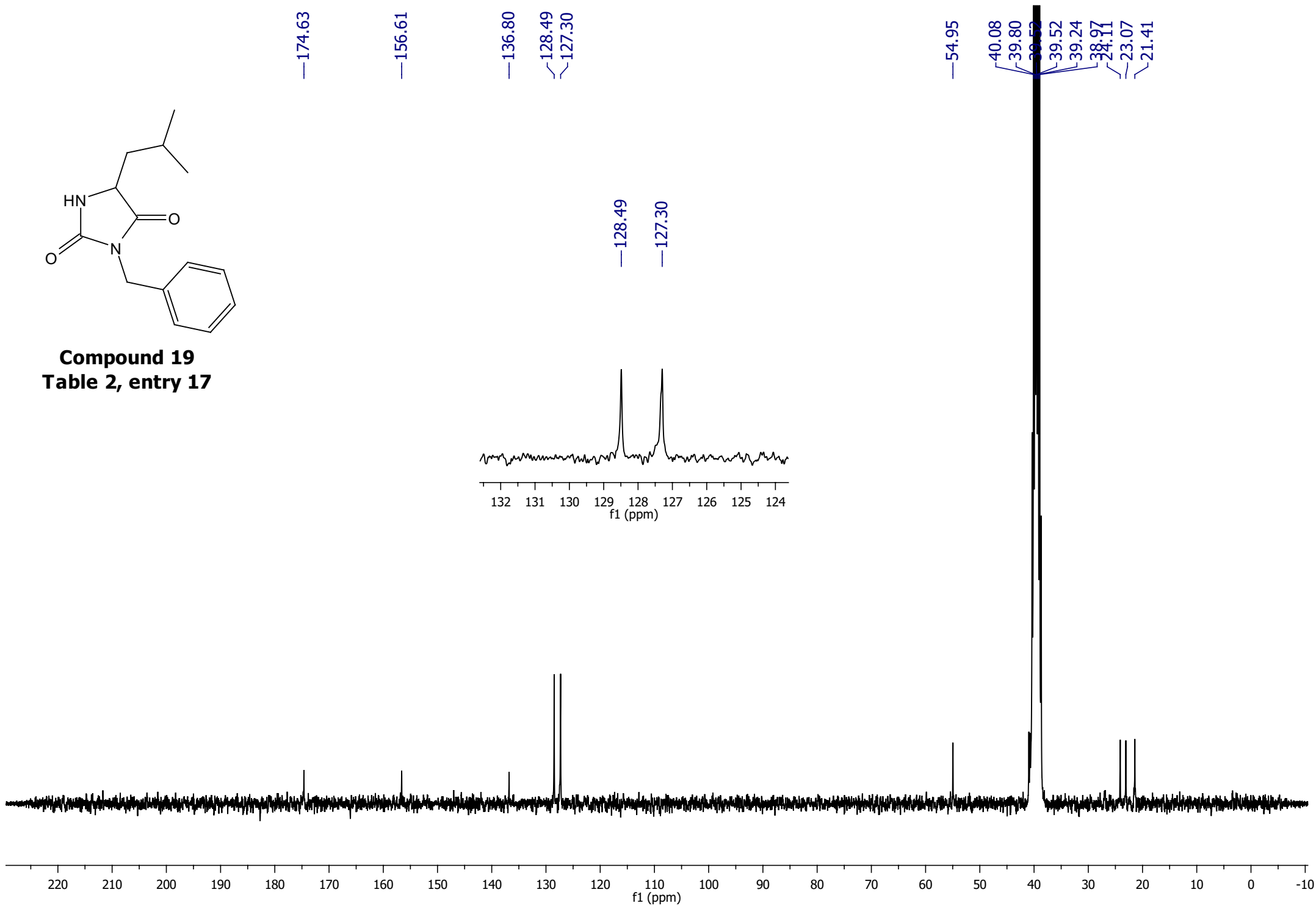
Compound 19
Table 2, entry 17

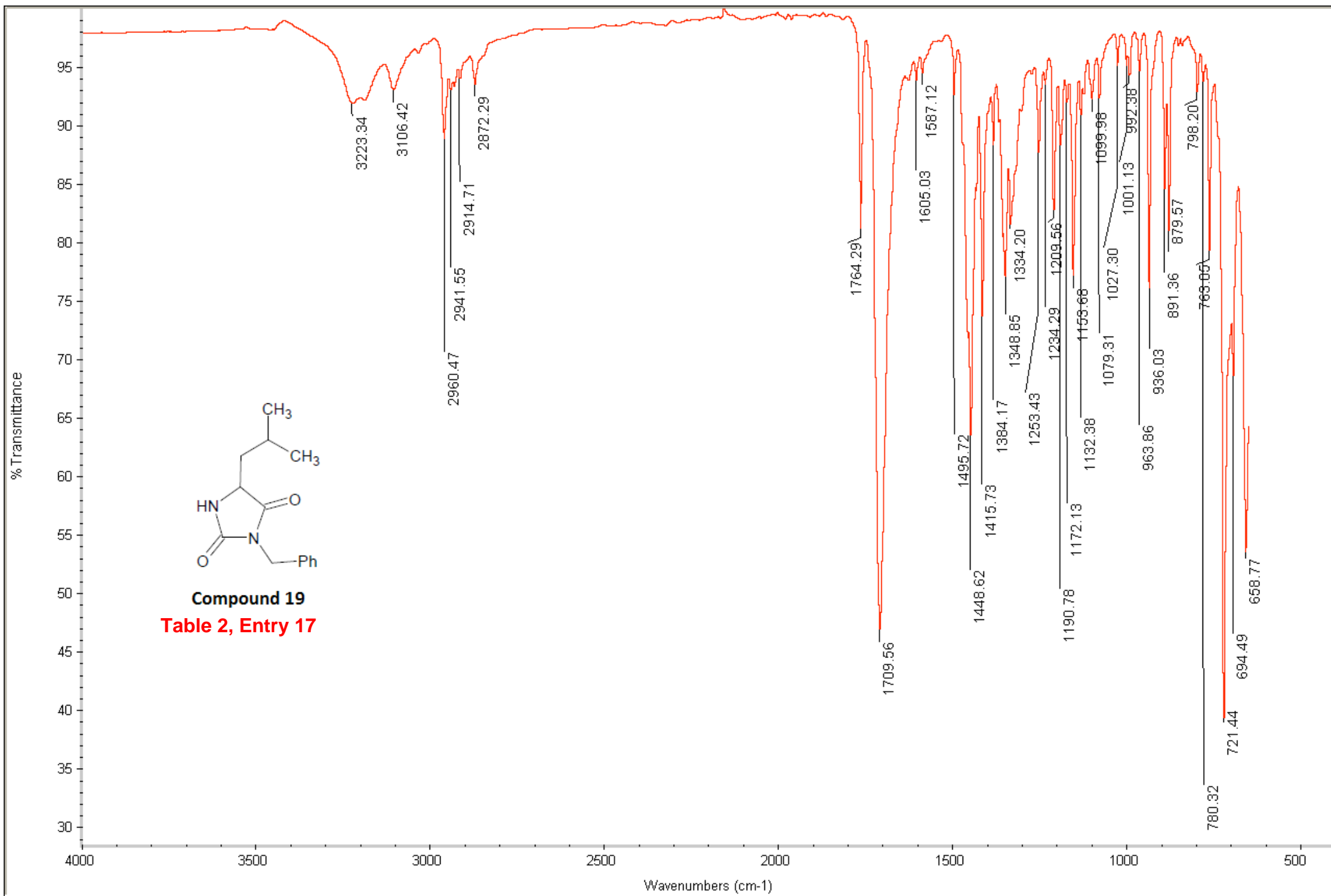
—2524.71
2199.86
2192.54
2185.50
2175.16
2168.21
—1354.65
1252.29
1248.17
1243.05
1239.29
1000.34
750.33
750.23
461.42
457.03
452.36
432.24
427.11
423.00
417.97
267.48
265.47
260.98
258.88

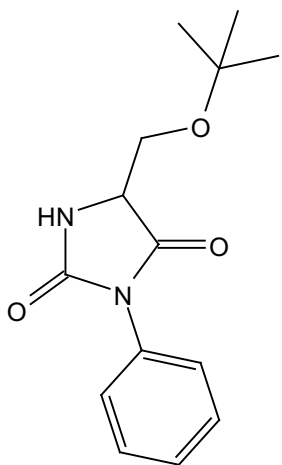




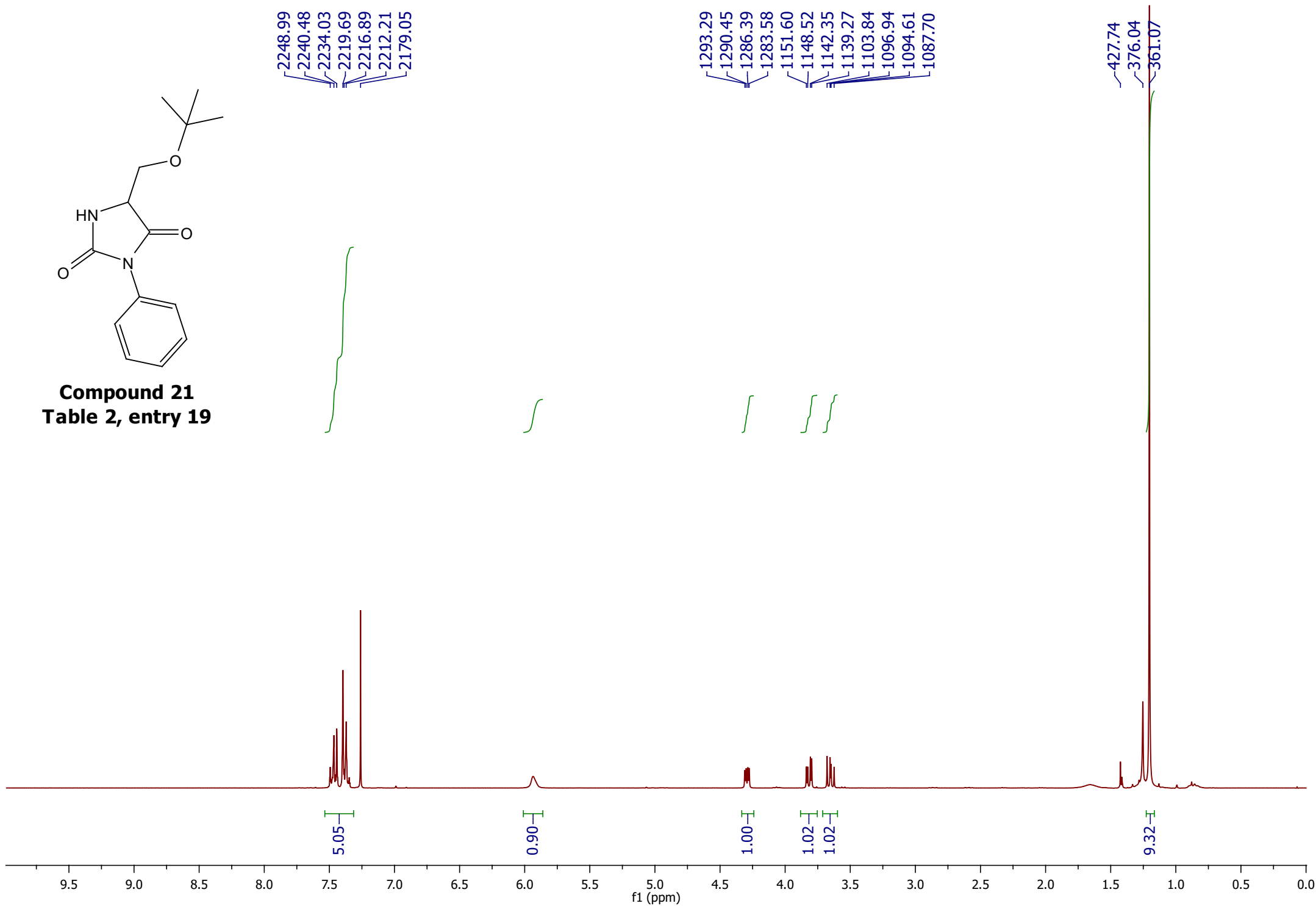
Compound 19
Table 2, entry 17

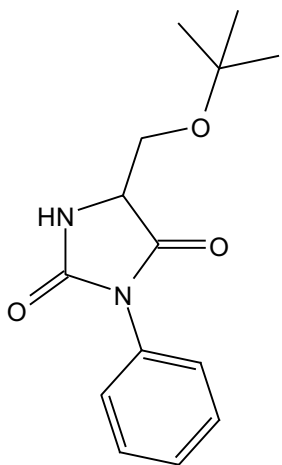




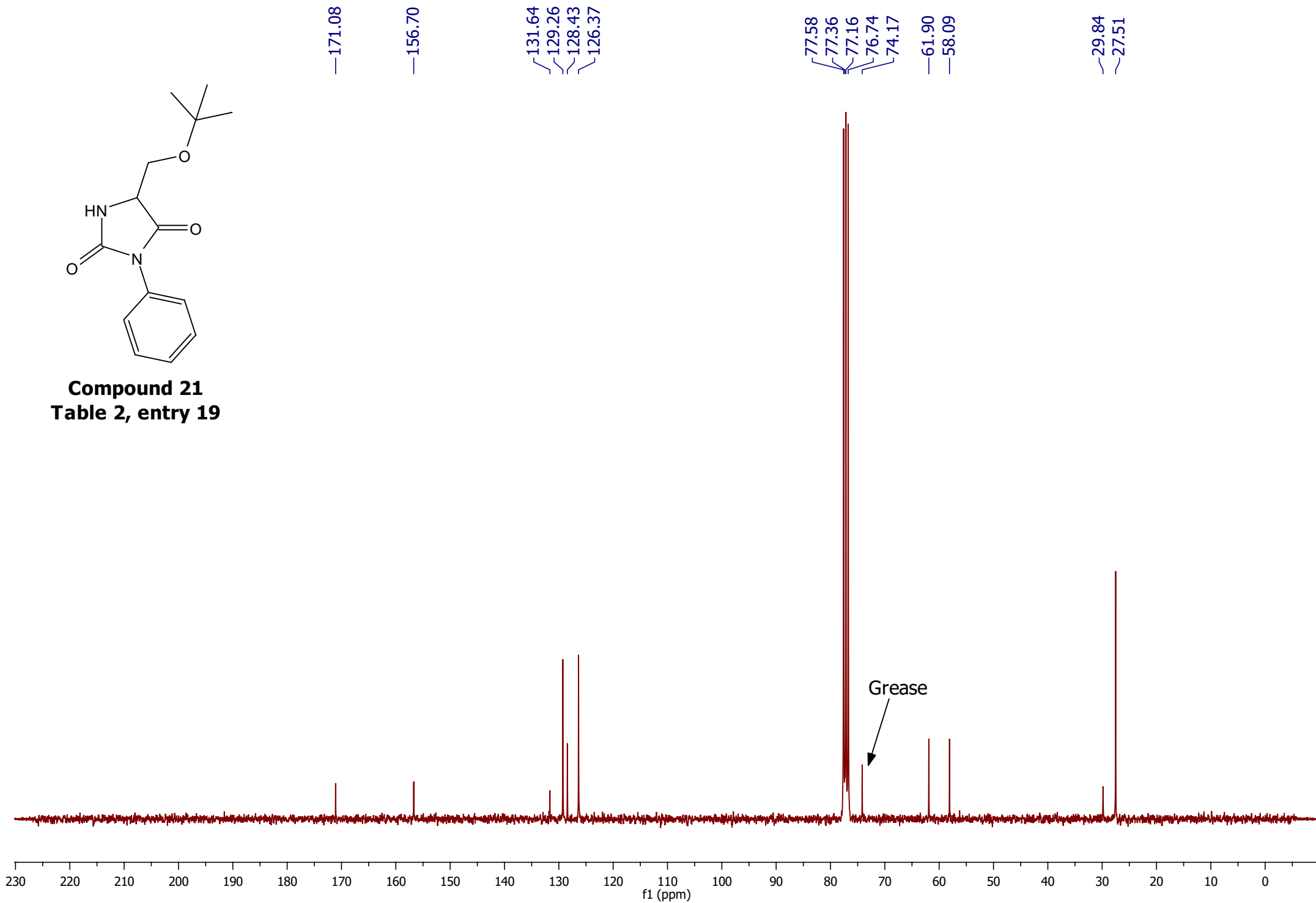


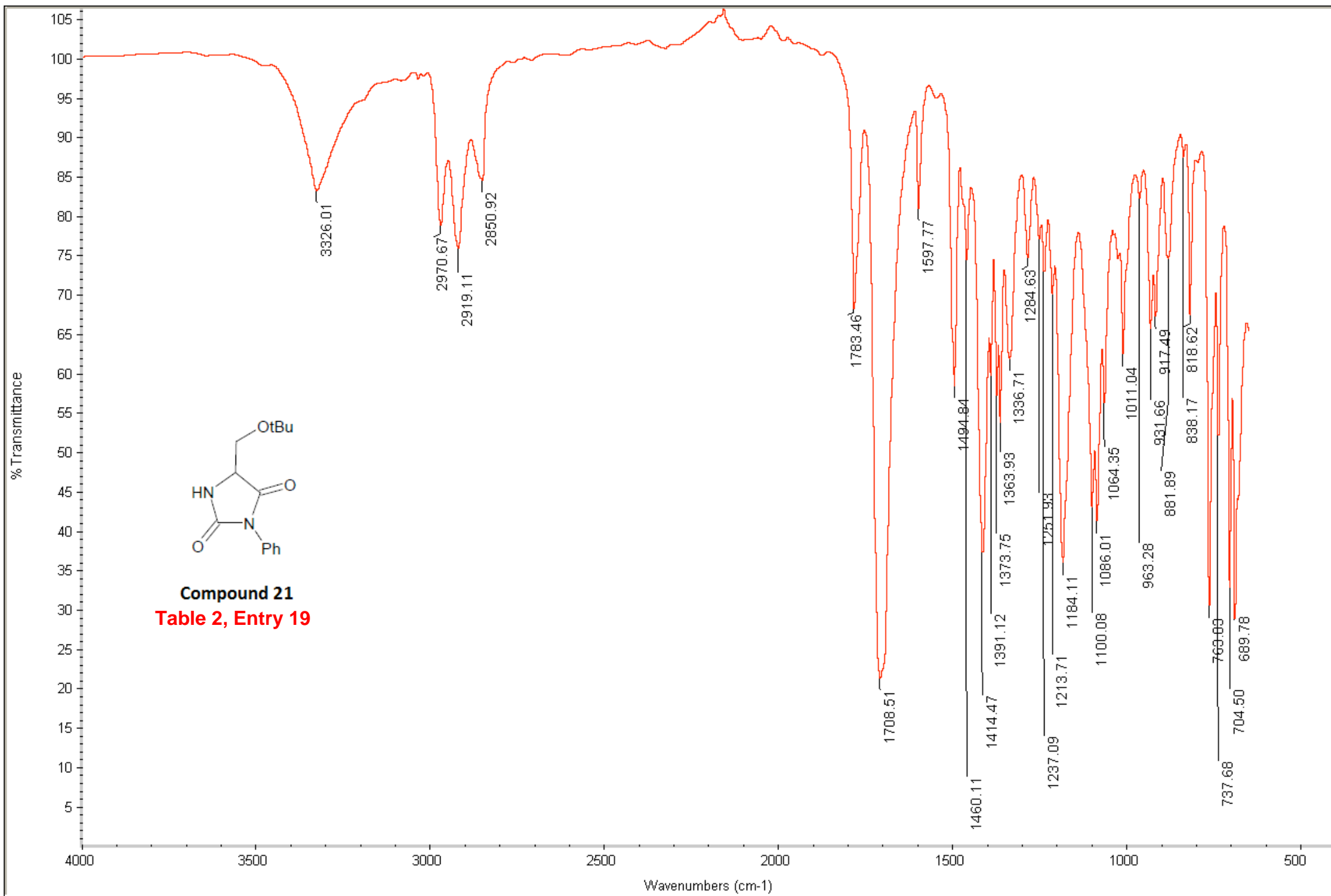
Compound 21
Table 2, entry 19



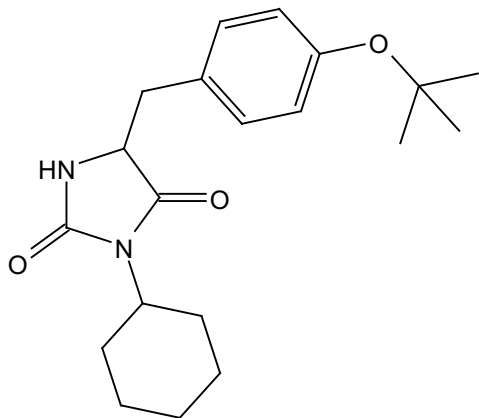


Compound 21
Table 2, entry 19

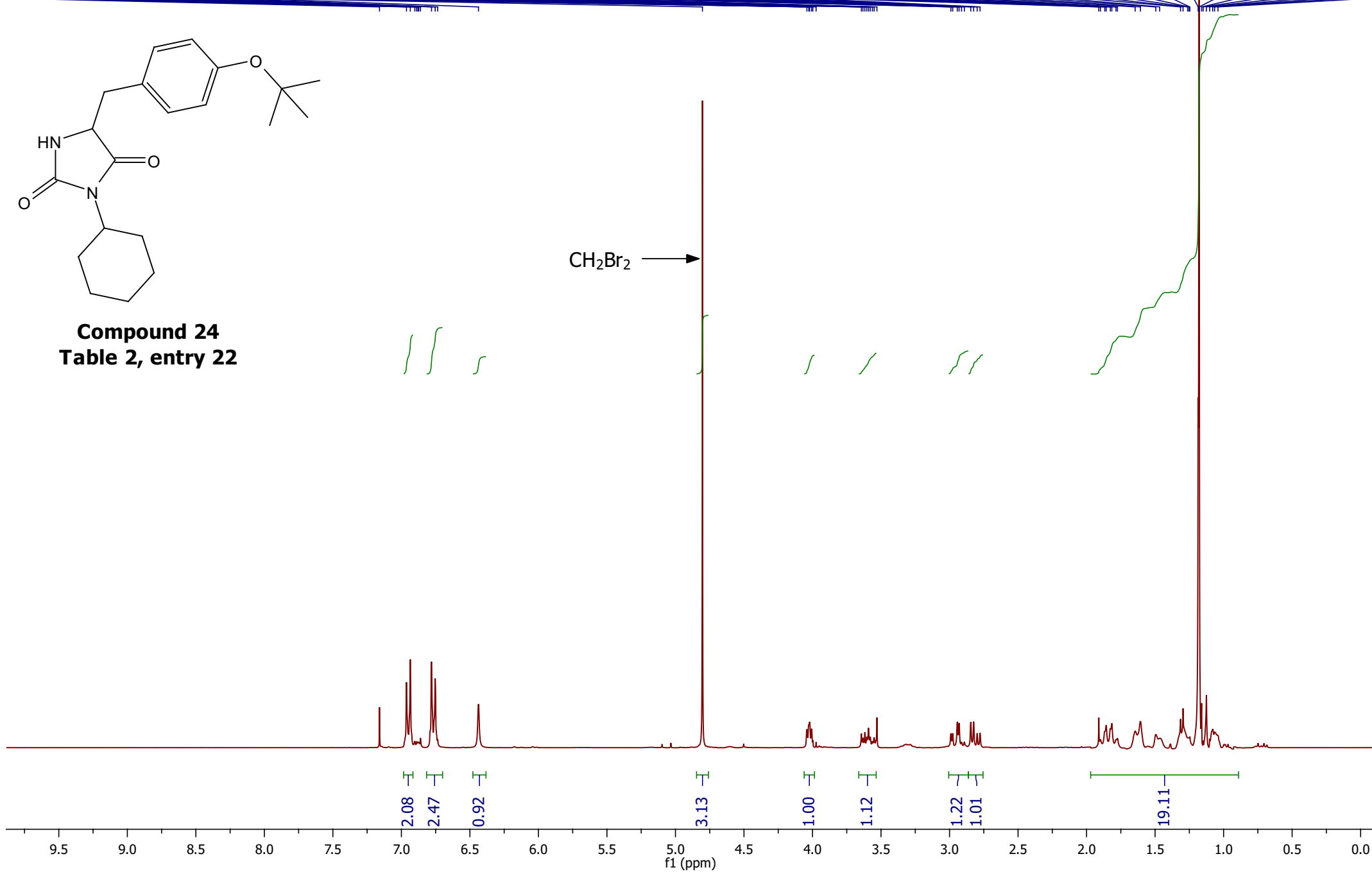


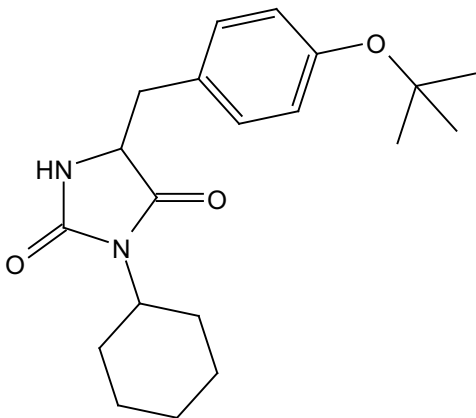


2148.85
2089.74
2081.39
2071.50
2067.51
2064.58
2062.87
2059.00
2034.85
2026.87
2021.48
1932.08
1441.57
1212.76
1208.56
1206.90
1202.59
1199.83
1192.64
1093.42
1090.10
1085.86
1081.62
1077.80
1073.97
1069.34
1065.51
1059.39
897.41
893.45
883.40
879.49
874.06
867.97
853.87
847.53
839.87
833.49
573.44
569.78
560.43
557.35
548.14
544.94
535.83
532.57
493.80
482.18
448.71
440.06
394.47
388.94
378.99
376.01
374.07
355.86
353.83
348.34
344.95
337.82
330.62
323.97
319.82
312.46

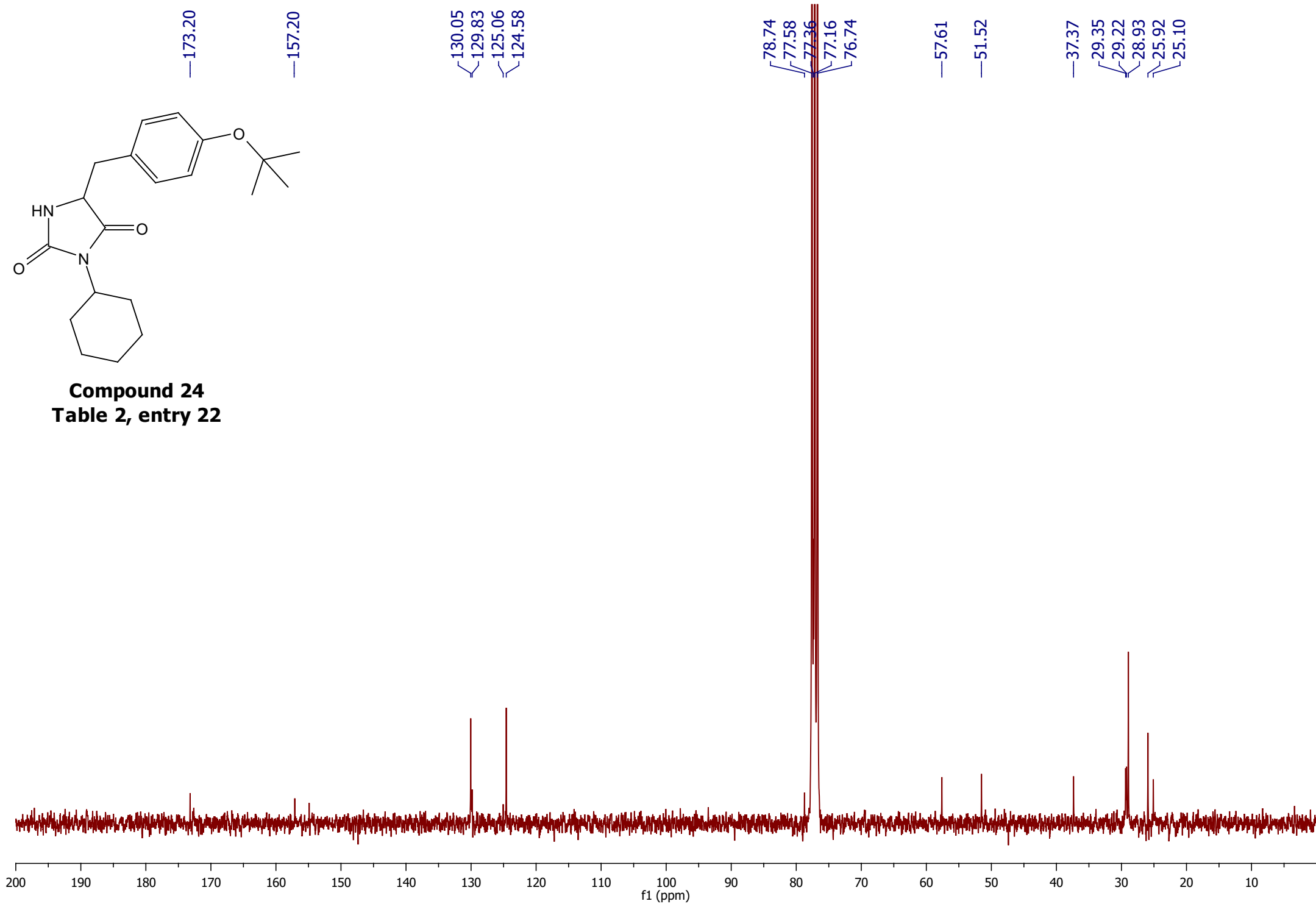


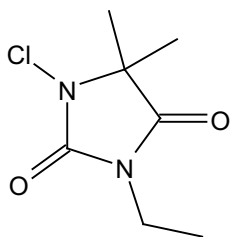
Compound 24
Table 2, entry 22





Compound 24
Table 2, entry 22



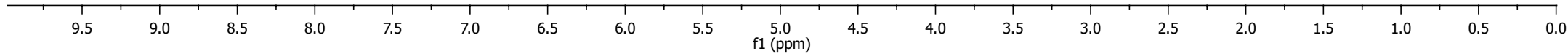


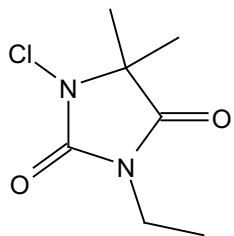
Compound 25
Scheme 2

—2179.08

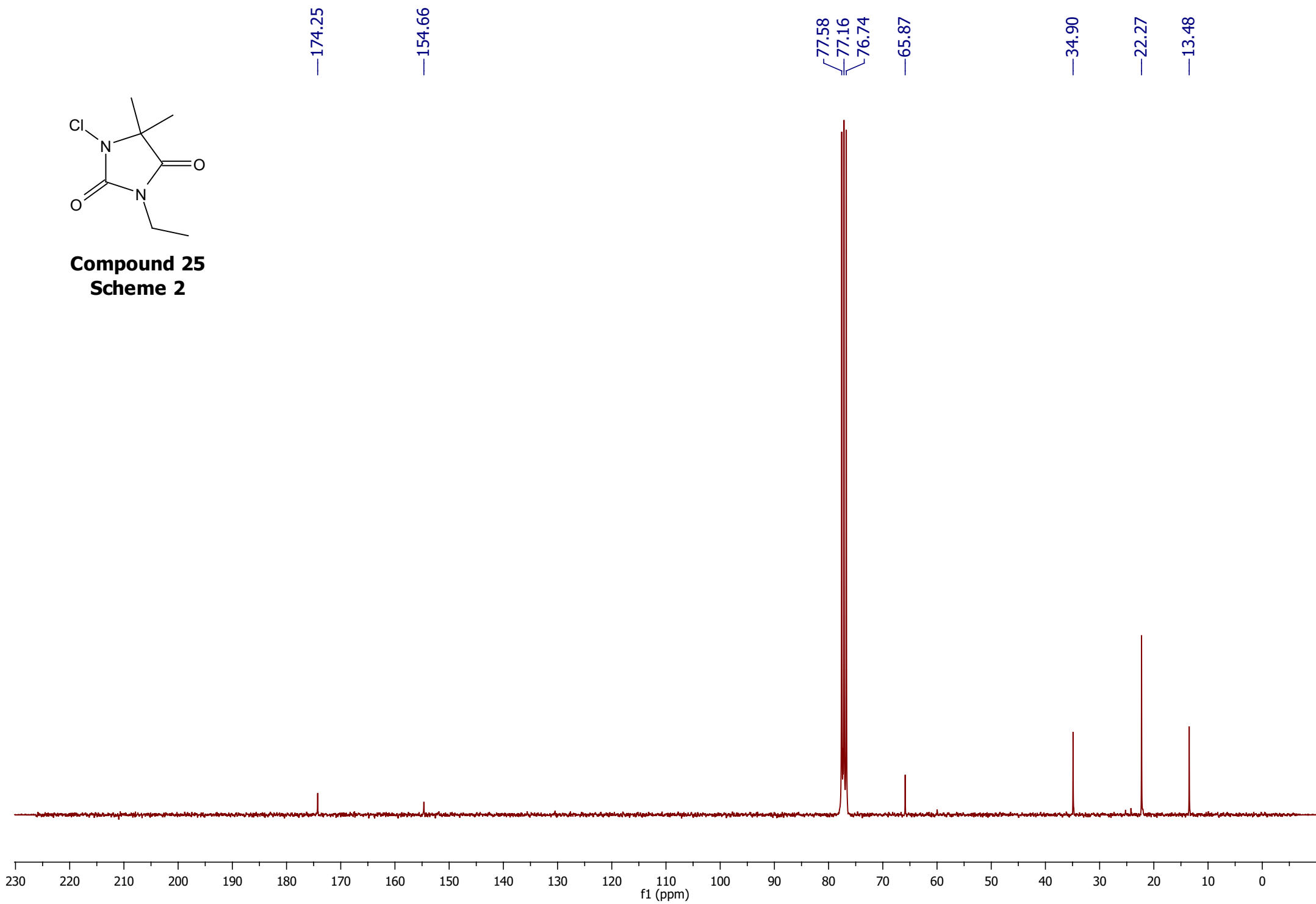
1095.96
1088.76
1081.56
1074.37

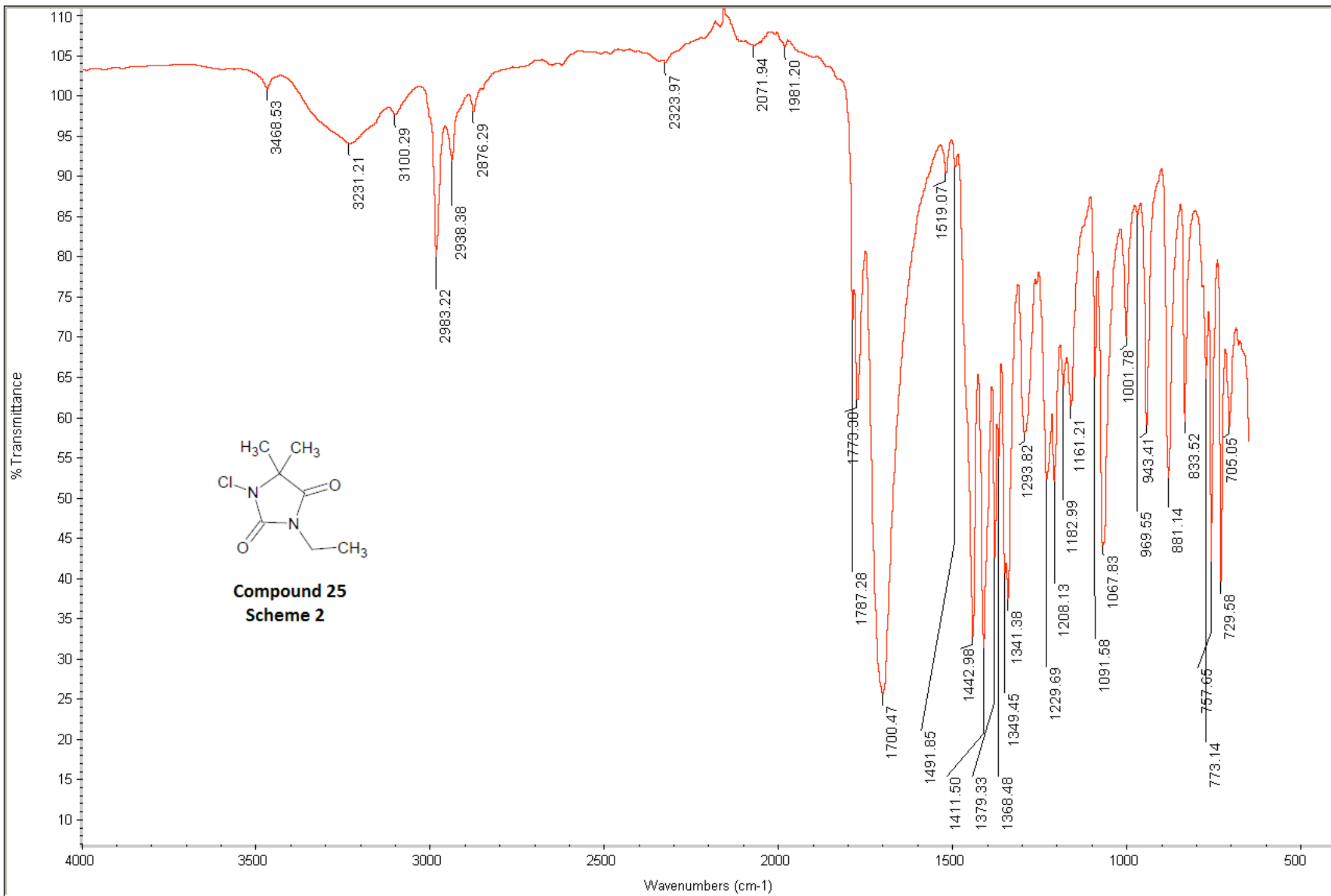
475.70
436.57
374.47
367.28
360.08

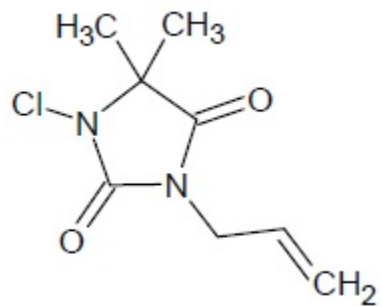




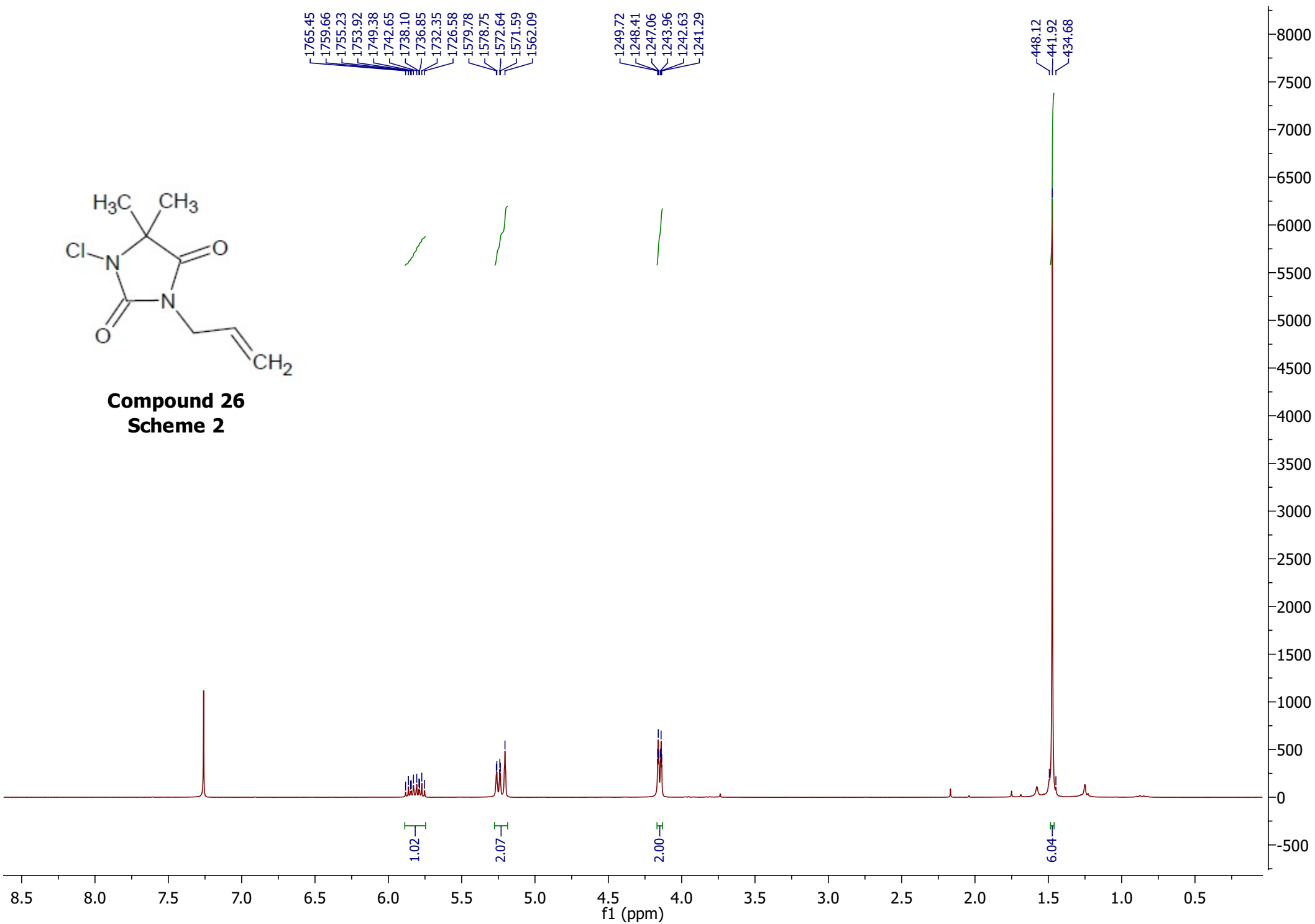
Compound 25
Scheme 2

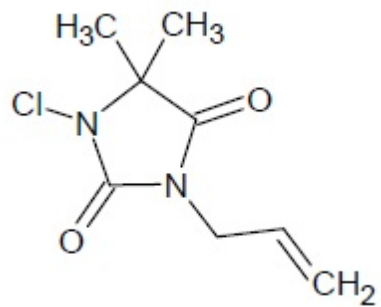






Compound 26
Scheme 2





Compound 26
Scheme 2

