Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supplementary Information

Bifunctional building blocks in Ugi-azide condensation: A general strategy toward lactam-tetrazoles scenarios

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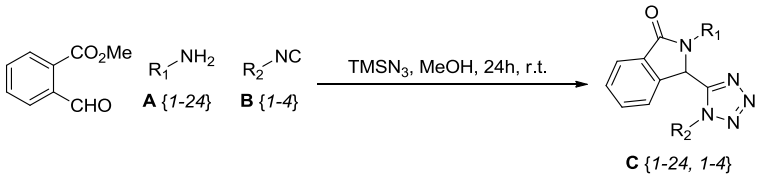
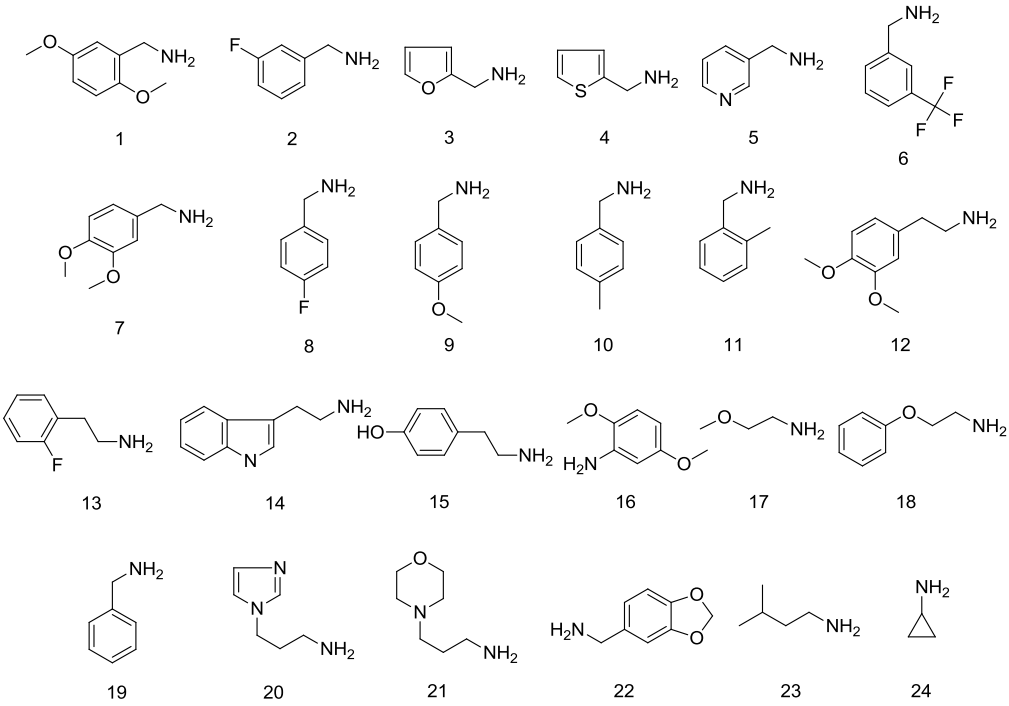
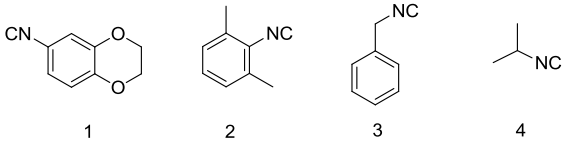
Reagents diversity for the four 24-well plate production of tetrazolyl-indolinones 10



*Primary amines (**A**)*



*Isocyanides (**B**)*



Yield and purity (%) of the 96-well plate production of **C** {*1-24*, *1-4*}

R_1NH_2 (A)	R_2NC (B)								R_1NH_2 (A)	R_2NC (B)							
	1		***2***		***3***		***4***			***1***		***2***		***3***		***4***	
	Y	P	Y	P	Y	P	Y	P		Y	P	Y	P	Y	P	Y	P
1	29	100	3	100	31	100	34	100	***13***	22	100	9	100	23	98	18	100
2	27	100	nr	-	21	100	27	100	***14***	34	100	nr	-	30	100	30	100
3	26	100	nr	-	21	100	8	100	***15***	20	100	26	100	21	100	34	99*
4	36	100	2	100	31	100	8	91	***16***	6	100	4	100*	nr	-	nr	-
5	38	100	nr	-	8	100	8	100	***17***	22	100	5	100	16	100	17	100
6	32	100	1	100	24	100	5	100	***18***	44	100	28	100	26	98	34	100
7	32	100	22	100	22	100	34	95	***19***	39	98	84	100	4	100	33	100
8	24	100	nr	-	28	100	34	100	***20***	39	100	42	100*	27	100	39	100
9	24	100	nr	-	14	98	25	100	***21***	15	100	11	100	24	100	32	100
10	33	100	30	100*	nr	-	19	100	***22***	26	100	1	100	13	100	5	100
11	31	100	nr	-	7	100	30	100	***23***	16	100	24	96	28	100	28	100
12	26	100	44	100	26	100	31	100	***24***	25	100	32	100	25	93	27	100

Y = Yield (%); P = Purity (%) based on UV 214 nm; nr = not recovered/lost during purification; * purity based on ELS

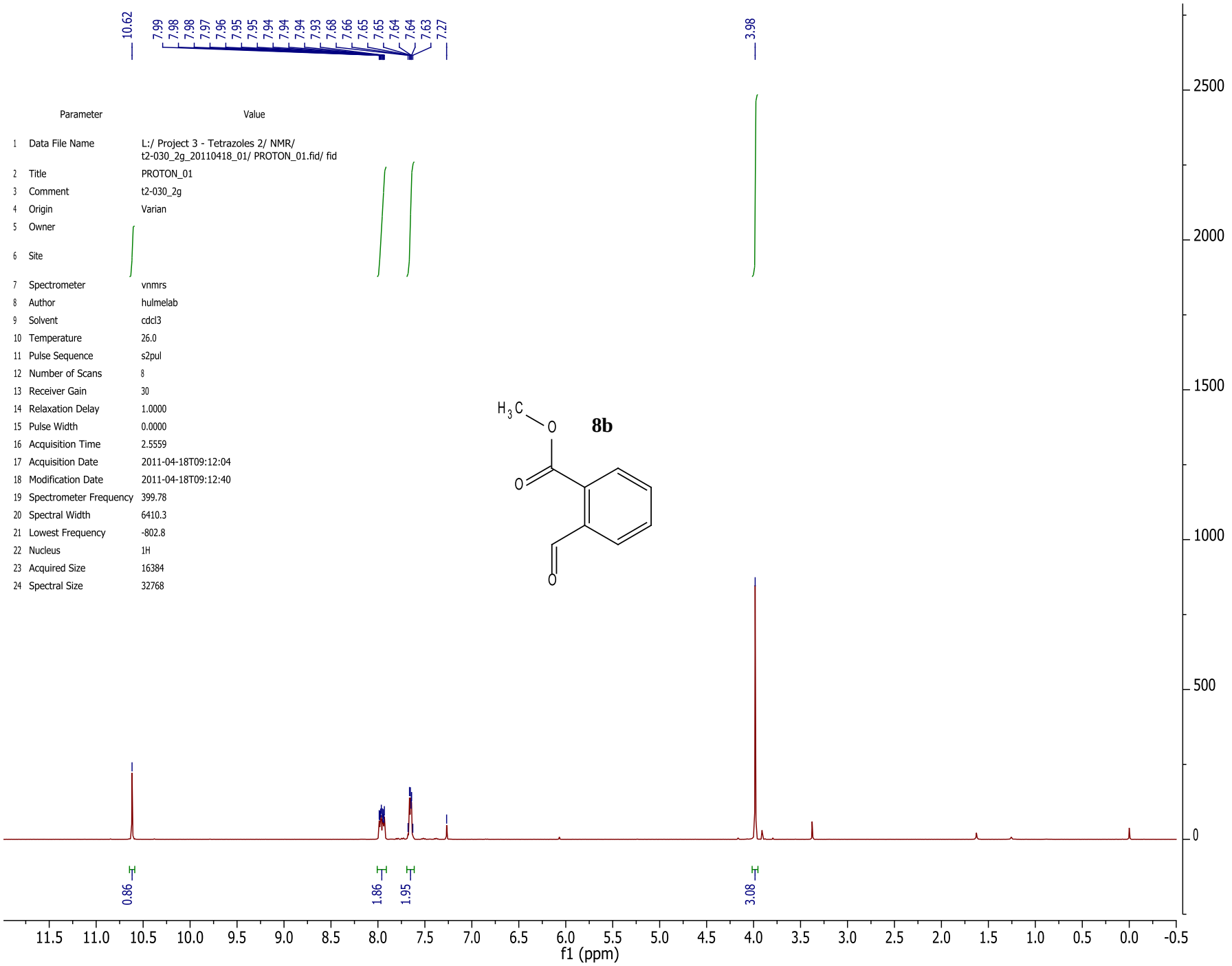
General experimental procedure for synthesis of methyl 2-formylbenzoate (8b)
To a stirred 2-carboxybenzaldehyde (2.108 g, 14.04 mmol) in MeOH (3.00 ml)-hexanes (38.00 ml) was added 2M $TMSCHN_2$ in hexanes (12.00 ml) via syringe dropwise at room temperatue. The mixture was stirred for 2 h and upon completion was concentrated *in vacuo* to afford the methyl 2-formylbenzoate **3c** (2.108 g, 12.84 mmol, 91%) as a clear oil. $[M+H]^+$ = 165. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 10.62 (s, 1H), 8.01 – 7.91 (m, 2H), 7.69 – 7.61 (m, 2H), 3.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 192.0, 166.7, 137.0, 132.9, 132.4, 131.9, 130.3, 128.4, 52.7.

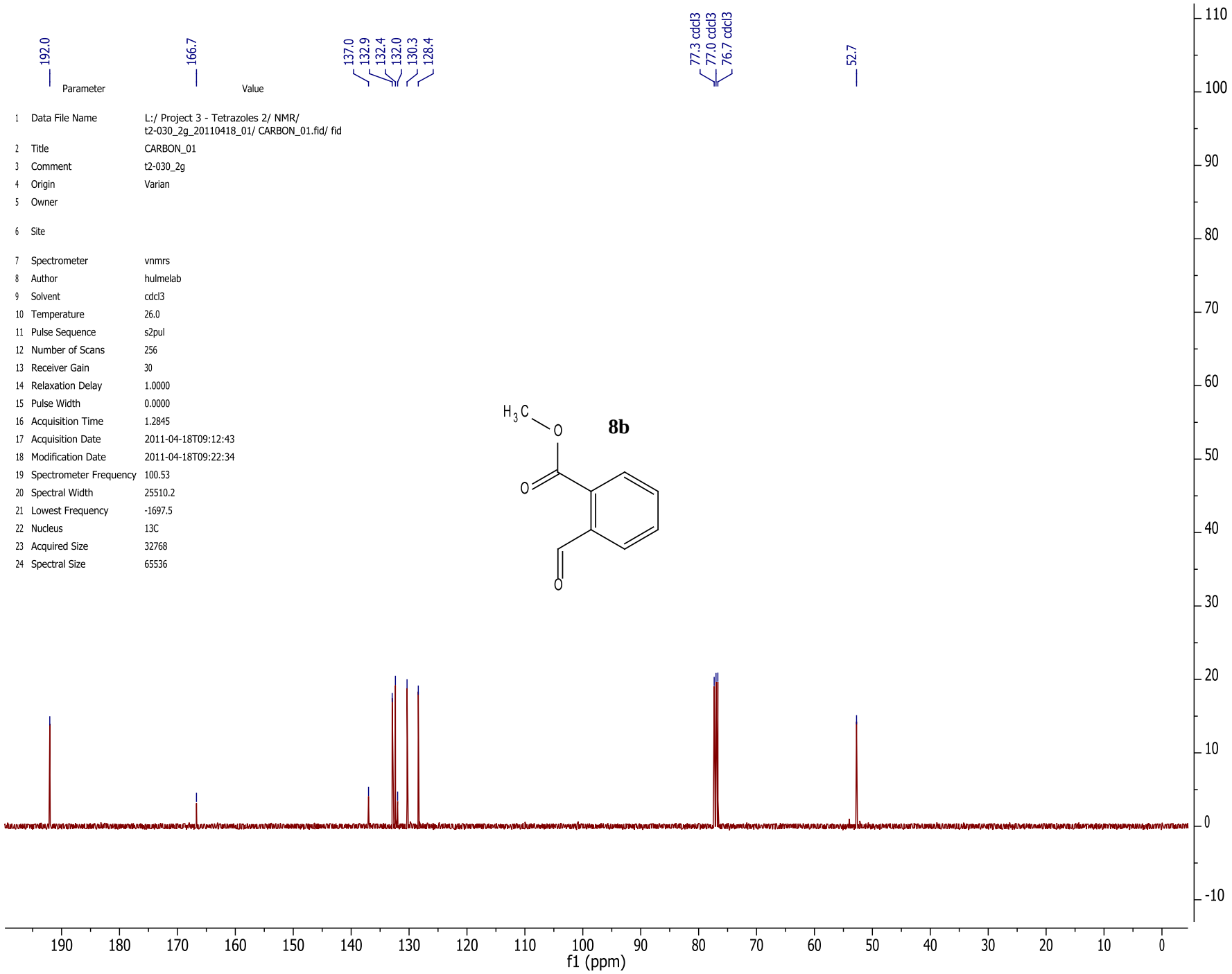
General experimental procedure for synthesis of methyl 2-((2-oxopropyl)thio)acetate (19b)
Methyl 2-mercaptoacetate (1.967 ml, 22.00 mmol) and triethylamine (5.58 ml, 40.00 mmol) were stirred in anhydrous DCM (50 ml) at 0 °C. Chloroacetone (1.609 ml, 20.00 mmol) was added and the reaction was stirred for 4h. Upon completion, the mixture was diluted in EtOAc (50ml), washed with saturated $NaHCO_3$ solution (2 x 75 ml) and brine solution (75 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford methyl 2-((2-oxopropyl)thio)acetate **17b** (2.90 g, 17.88 mmol, 89%) as a yellow oil. $[M+H]^+$ = 163. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.73 (s, 3H), 3.42 (s, 2H), 3.27 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 202.8, 170.1, 52.4, 42.1, 33.1, 28.2.

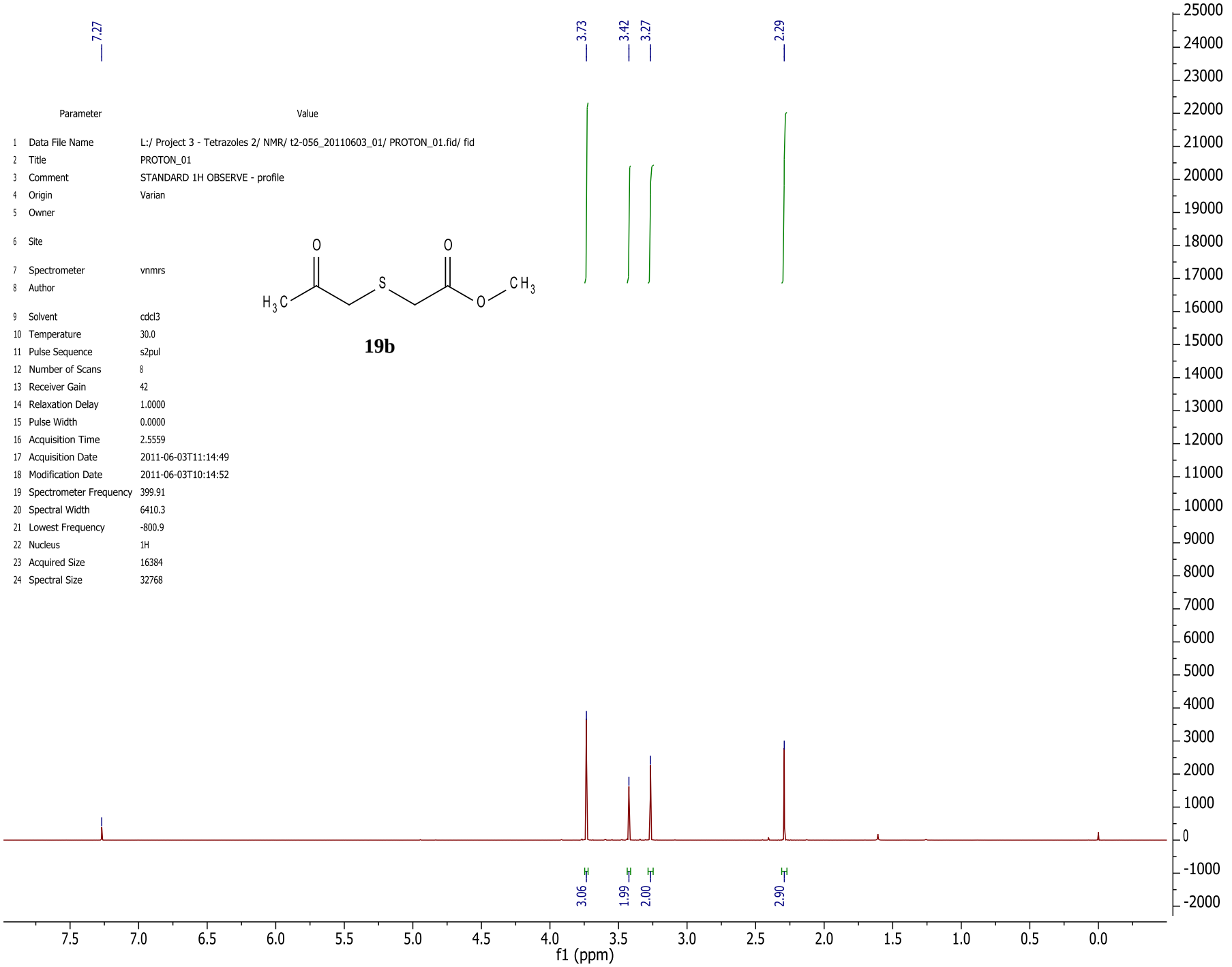
General experimental procedure for synthesis of methyl 2-((3-oxobutyl)thio)acetate (28)
Methyl 2-mercaptoacetate (1.967 ml, 22.00 mmol) and triethylamine (5.58 ml, 40.00 mmol) were stirred in anhydrous DCM (20 ml) at 0 °C. 4-chlorobutan-2-one (2.131 g, 20.00 mmol) dissolved in DCM (40 ml) was then added dropwise and the reaction was stirred for 4h. Upon completion, the mixture was diluted in EtOAc (50ml), washed with saturated $NaHCO_3$ solution (2 x 75 ml) and brine solution (75 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford methyl 2-((3-oxobutyl)thio)acetate **26** (1.95 g, 11.06 mmol, 55%) of a yellow oil. $[M+H]^+$ = 177. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.74 (s, 3H), 3.26 (s, 2H), 2.87 (t, J = 7.1 Hz, 2H), 2.78 (t, J = 6.9 Hz, 2H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 206.34, 170.80, 77.32, 77.00, 76.69, 52.41, 43.14, 33.84, 29.98, 26.43.

General experimental procedure for synthesis of methyl 2-(2-formylphenoxy)acetate (30)
A stirred 2-(2-formylphenoxy)acetic acid (6.000 g, 33.3 mmol) in MeOH (40 ml) was treated with a 37% solution of hydrochloric acid (5.06 ml) and refluxed for 12 hours. The solution was cooled to room temperature and concentrated *in vacuo*. EtOAc was added and the organic layer was washed with 5% aqueous solution of $NaHCO_3$ followed by brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford methyl 2-(2-formylphenoxy)acetate **28** (5.89 g, 30.3 mmol, 91%) of a light brown solid. $[M+H]^+$ = 195. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 10.57 (s, 1H), 7.87 (dd, J = 7.7, 1.8 Hz, 1H), 7.58 – 7.50 (m, 1H), 7.10 (td, J = 7.6, 0.5 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 4.78 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 189.5, 168.6, 160.0, 135.7, 128.7, 125.4, 121.9, 112.5, 65.5, 52.4.

Note: **8b**, **19b**, **28**, and **30** were used immediately in the Ugi-azide MCR without purification







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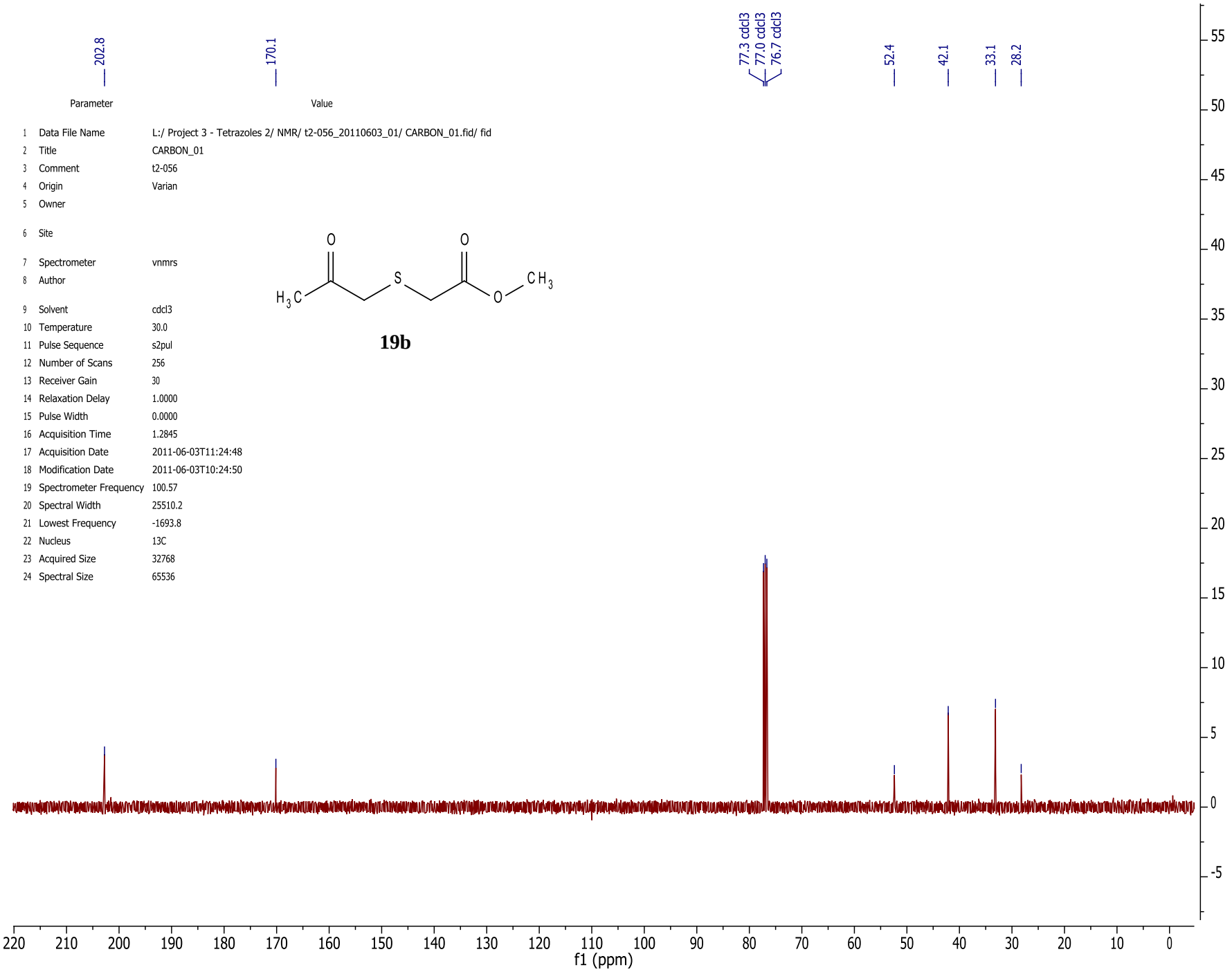
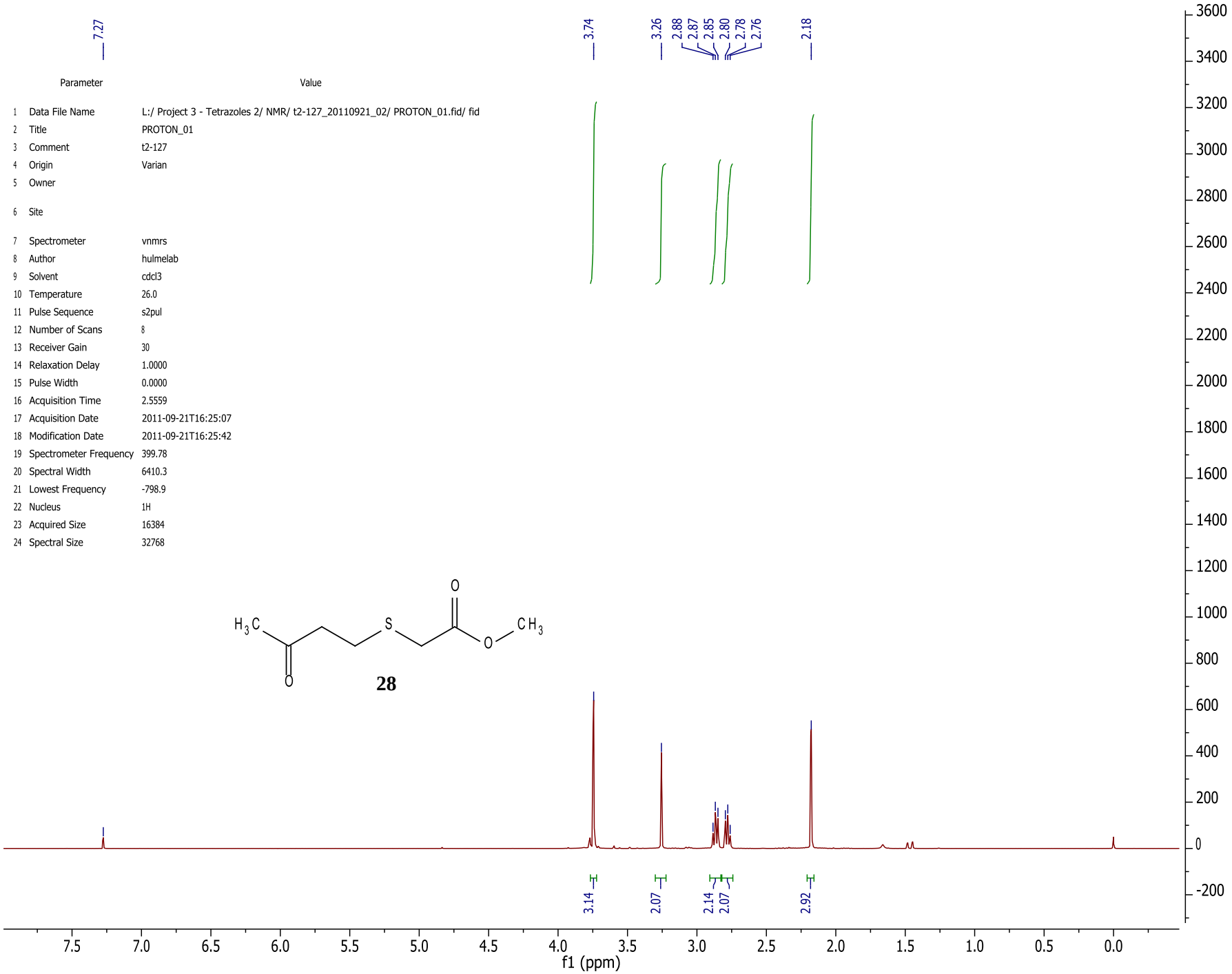
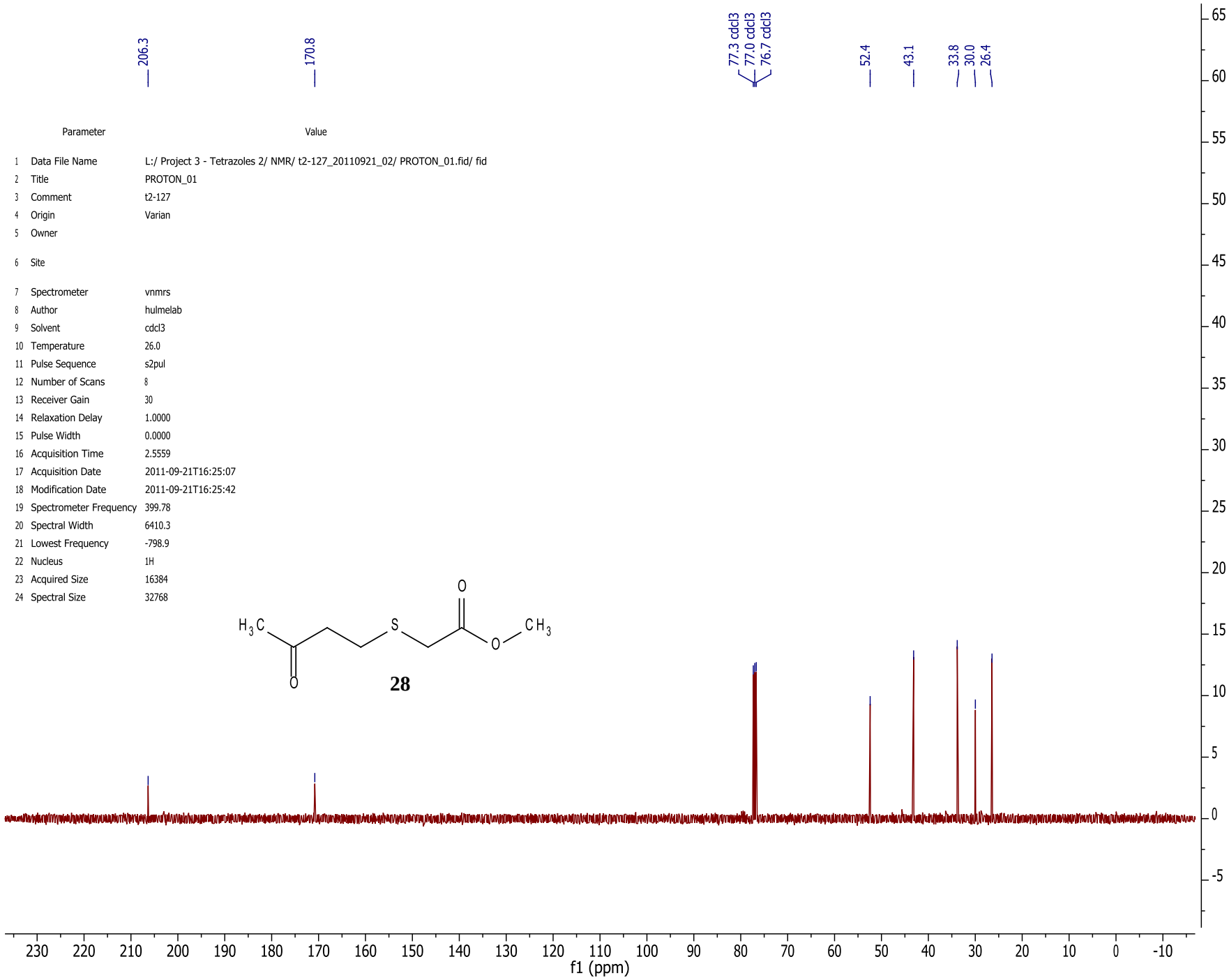
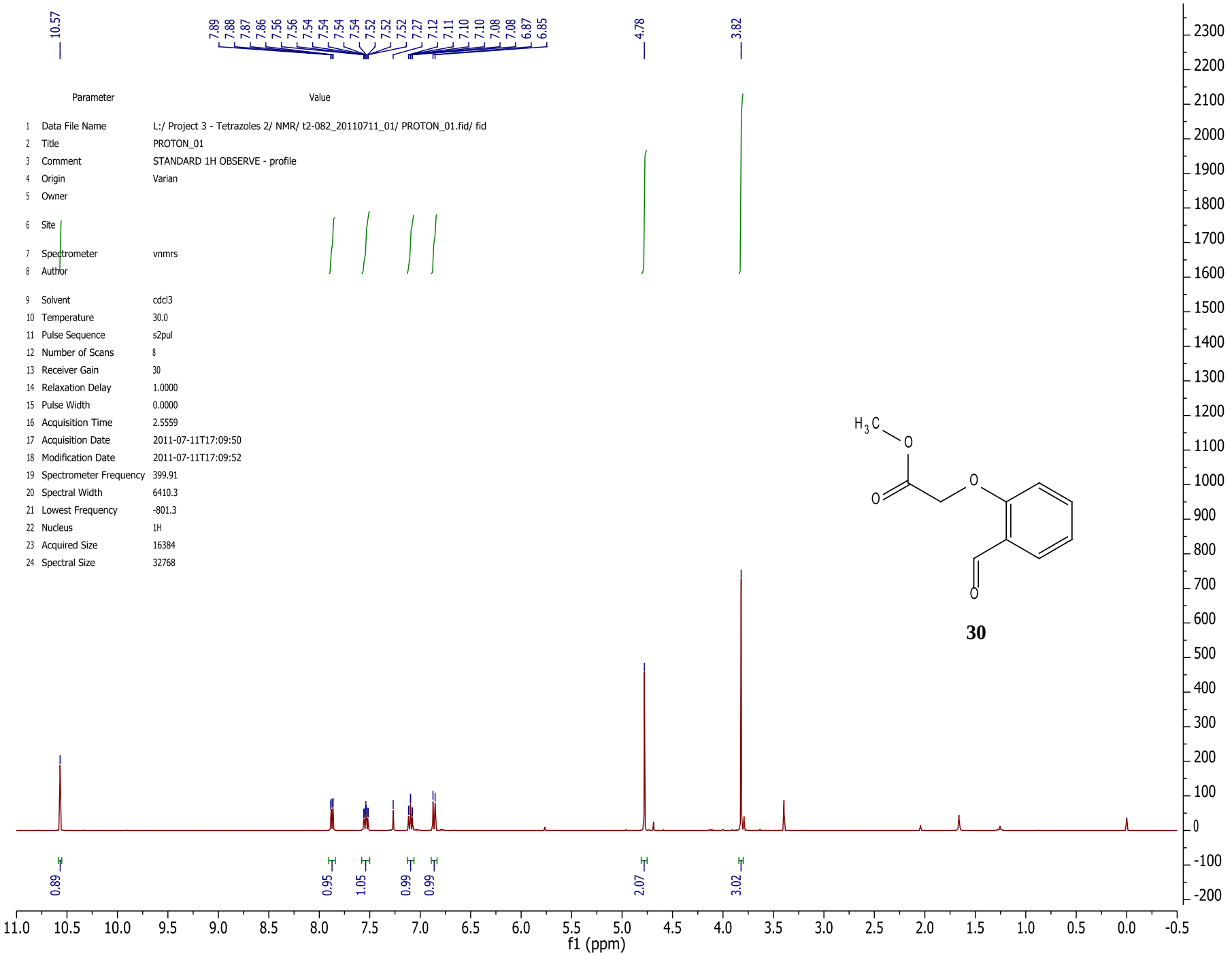
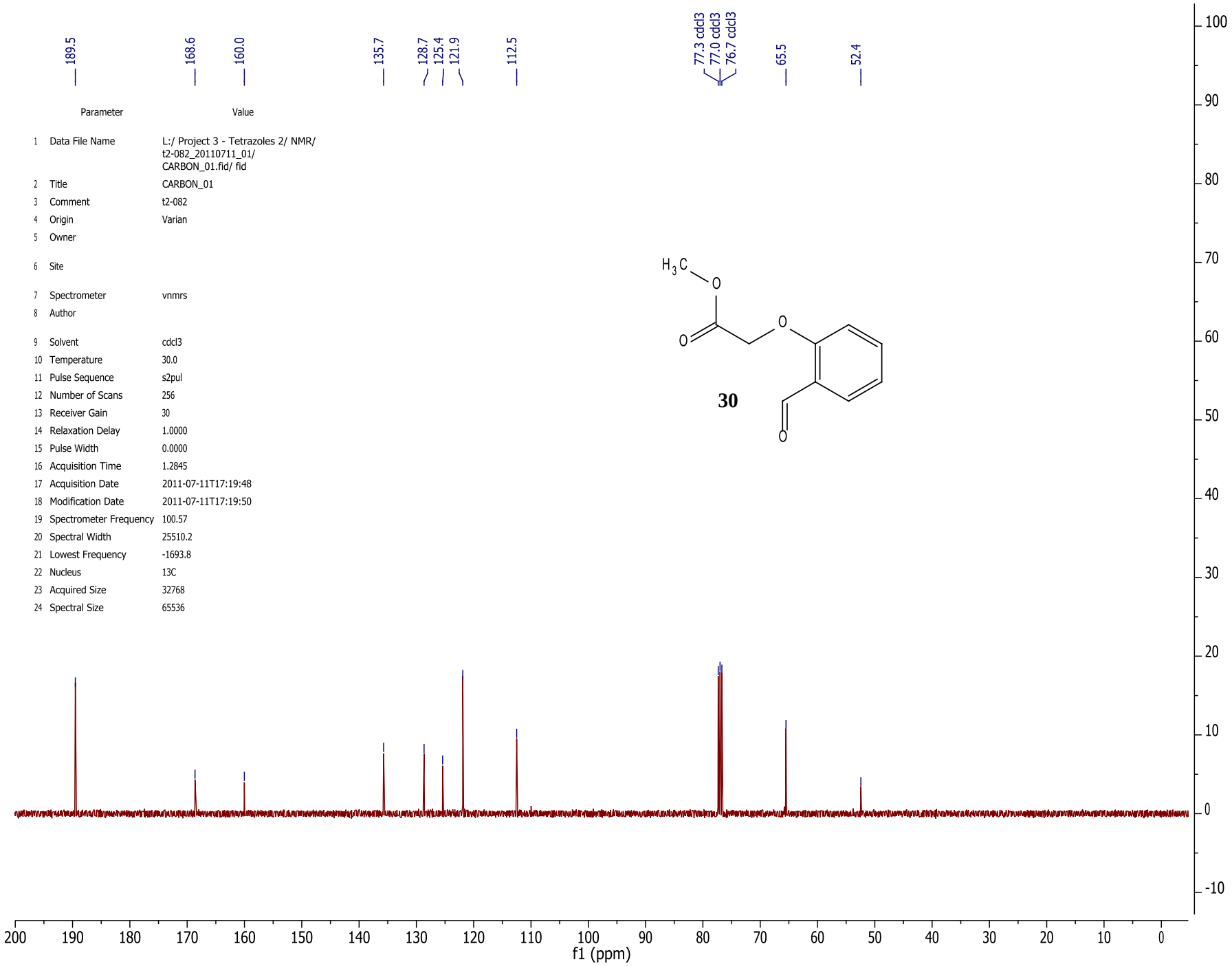
19b

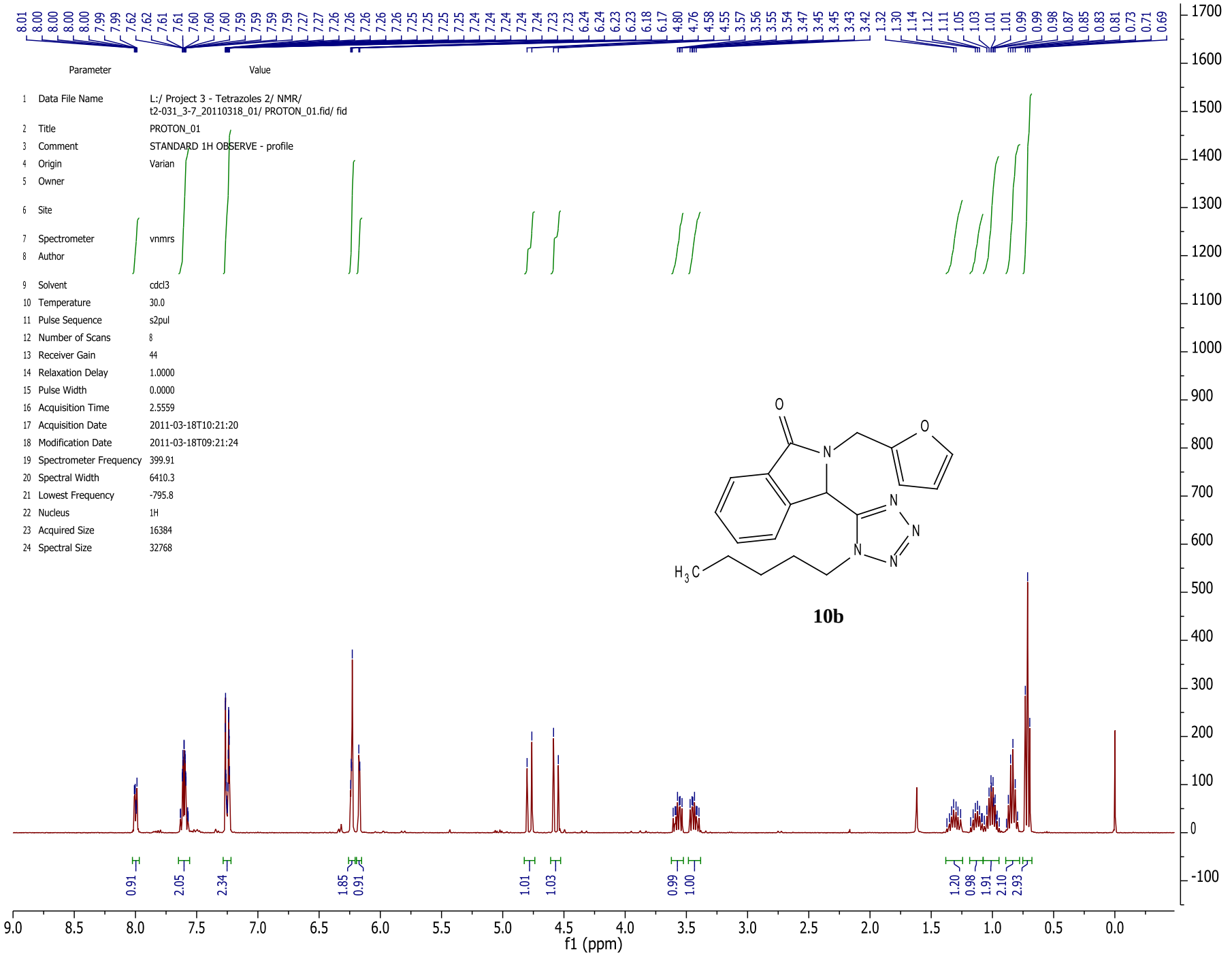


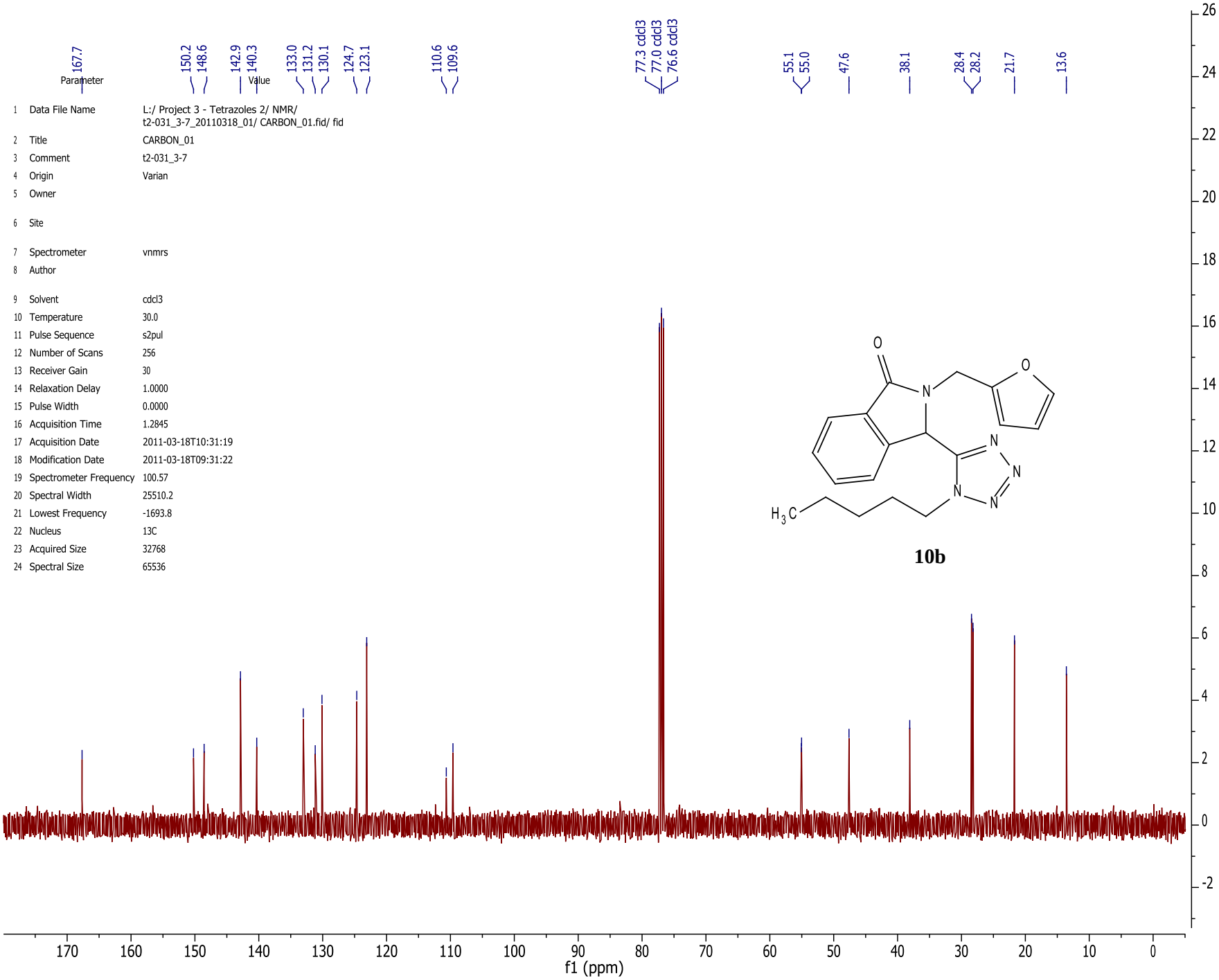


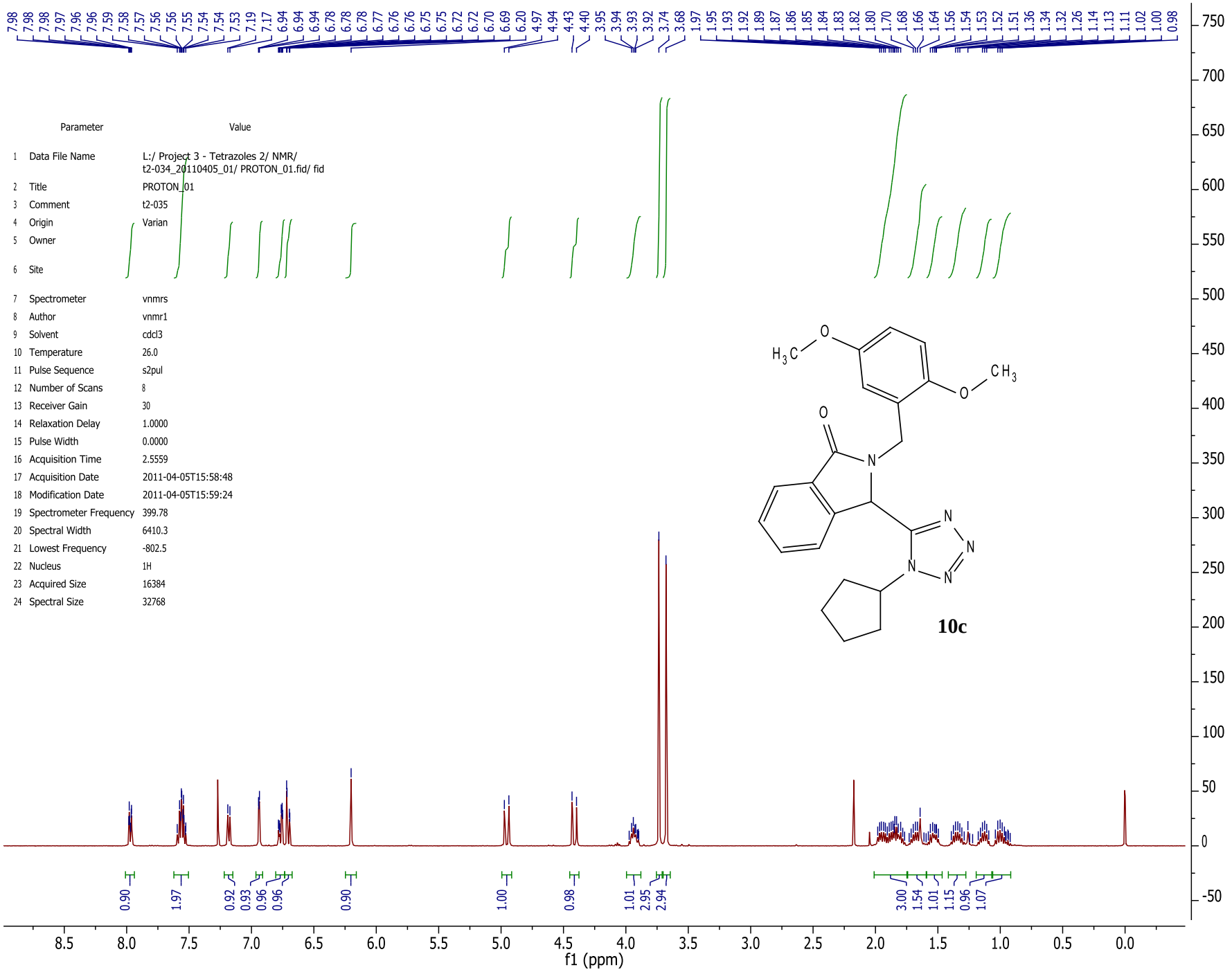


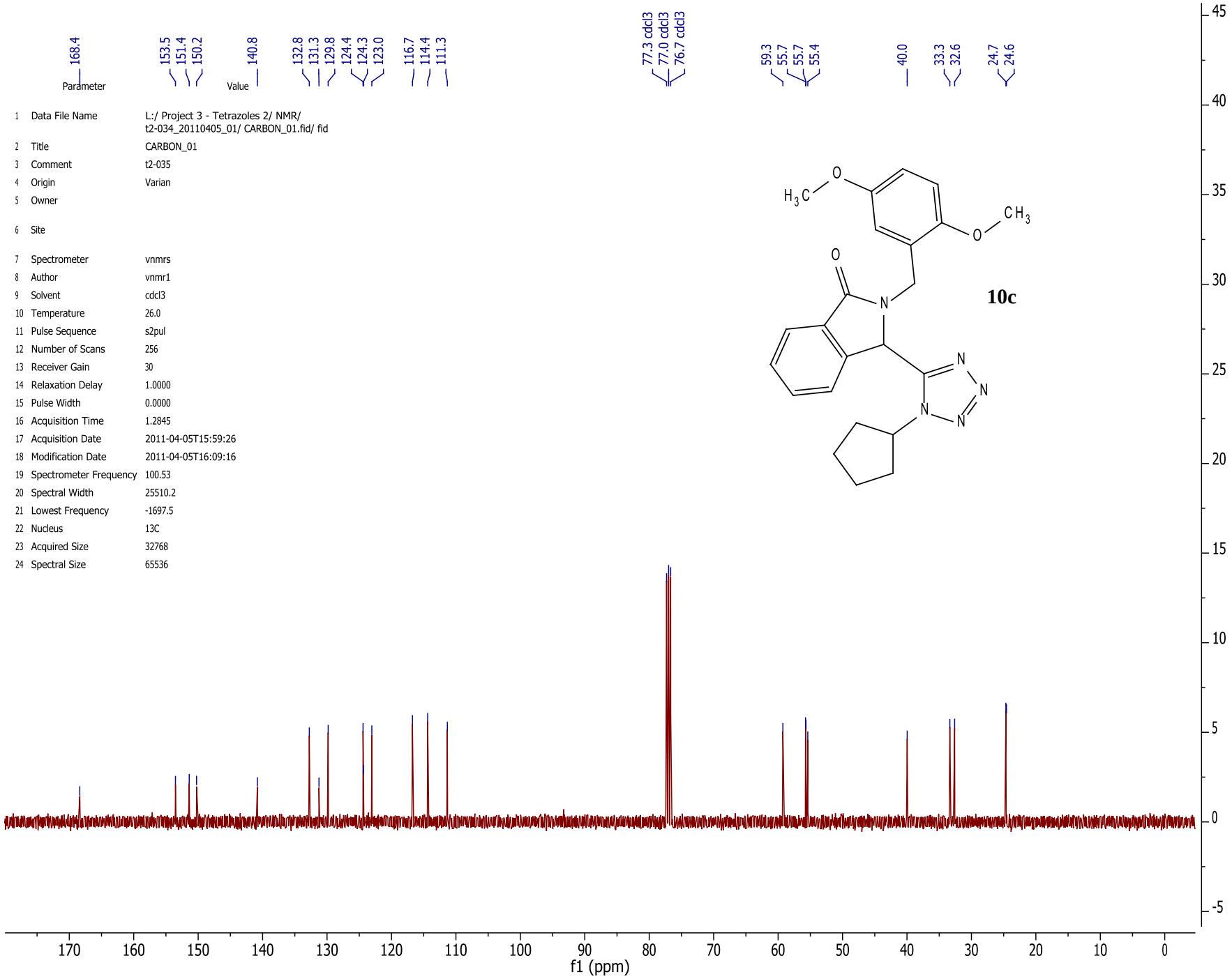


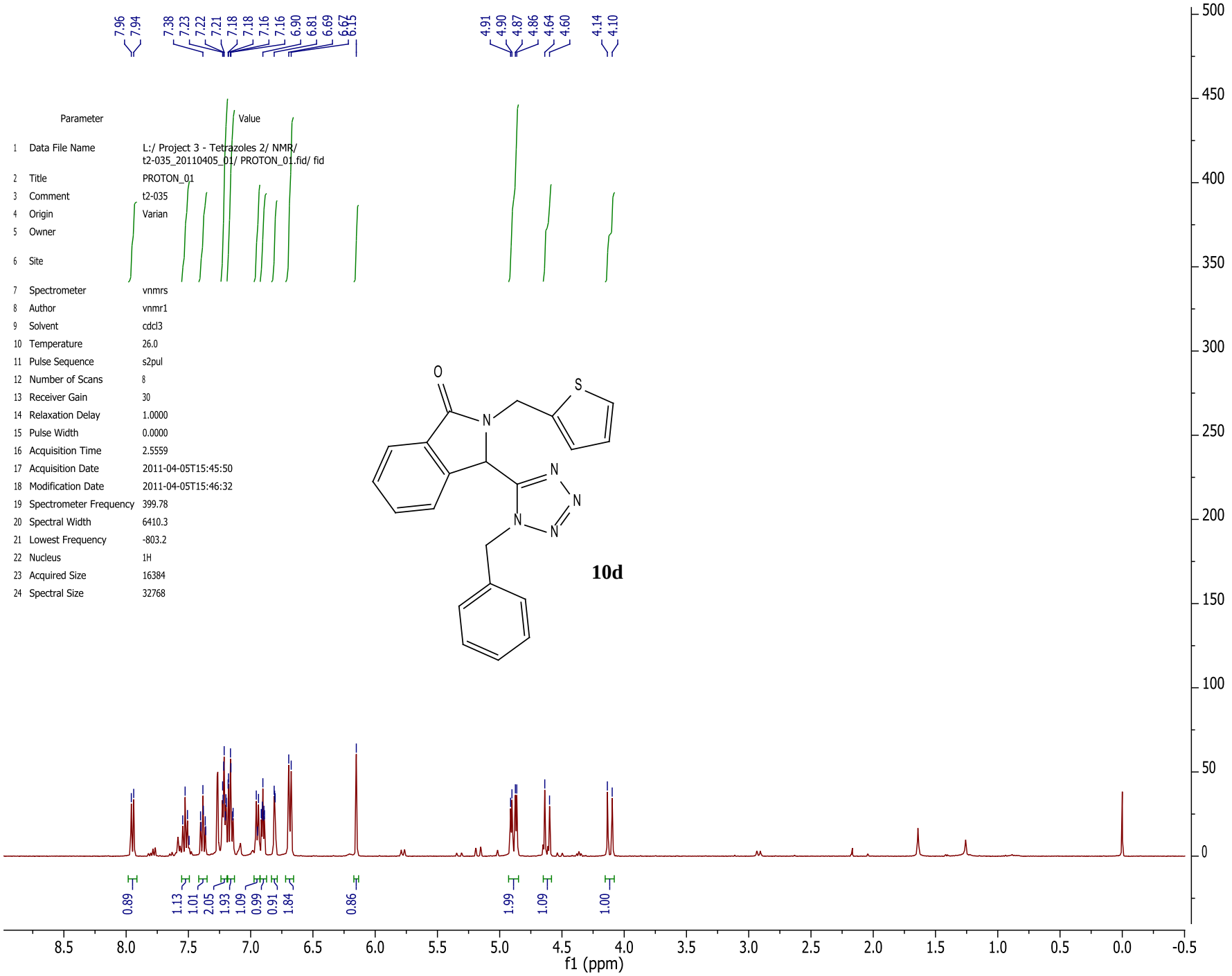


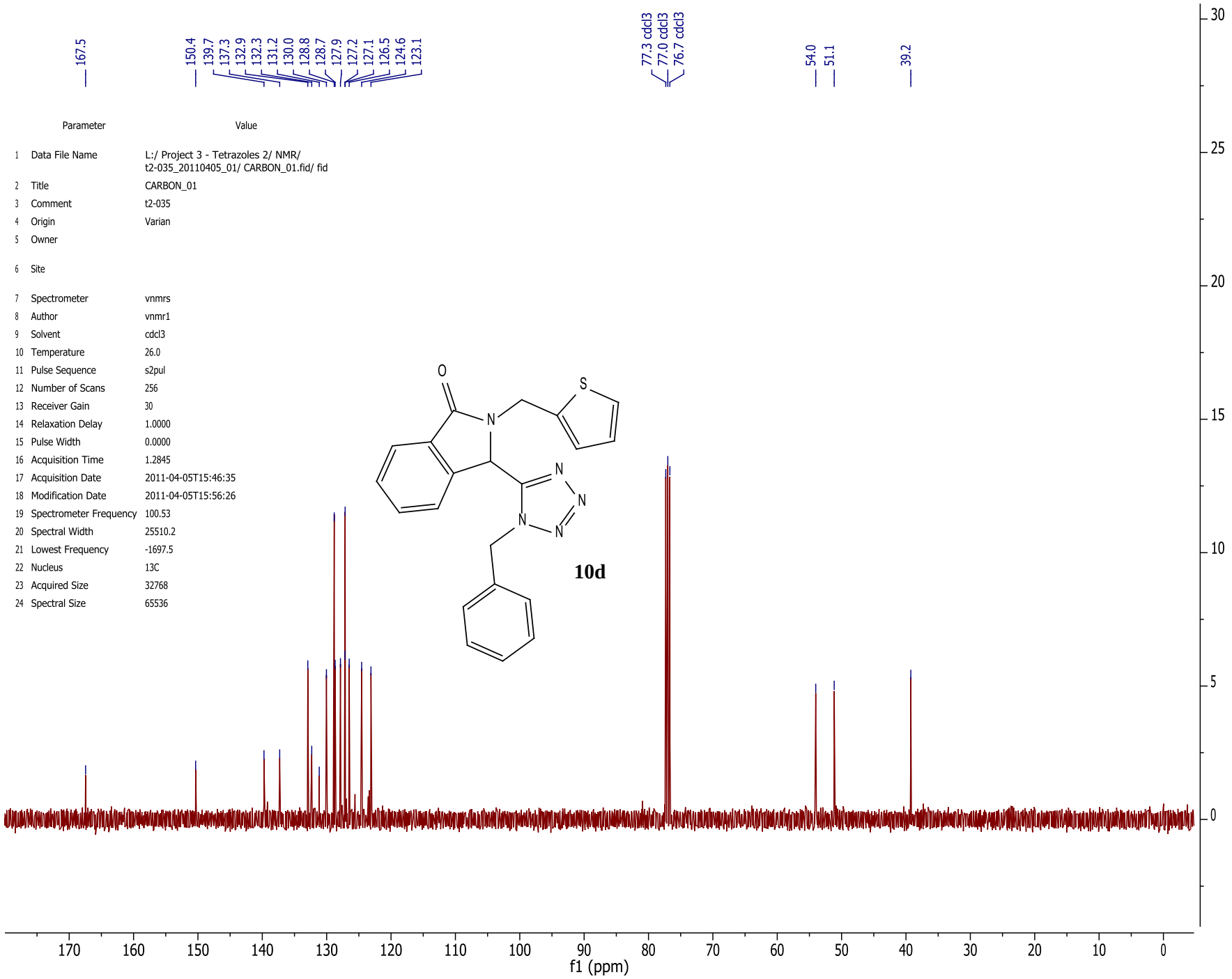


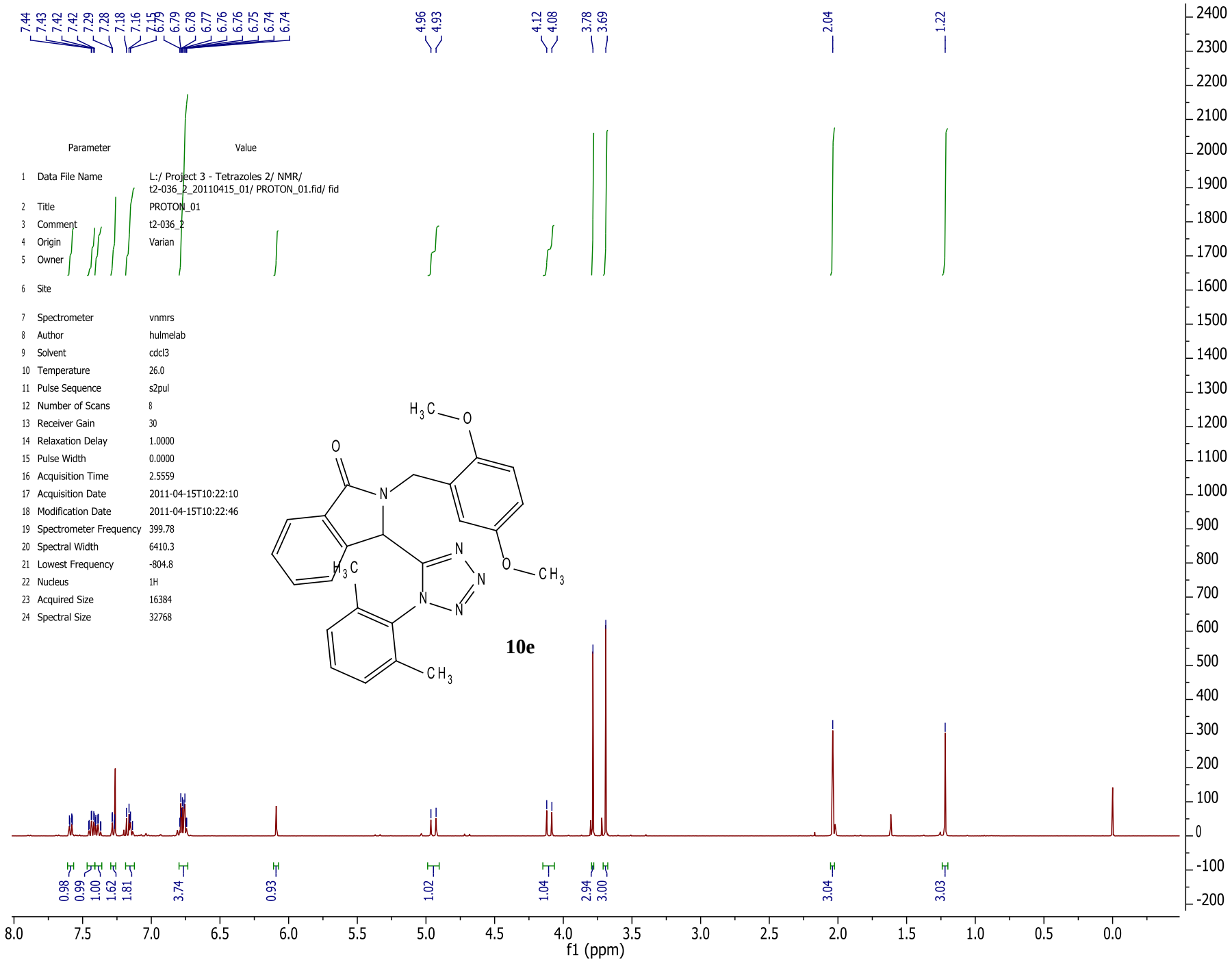


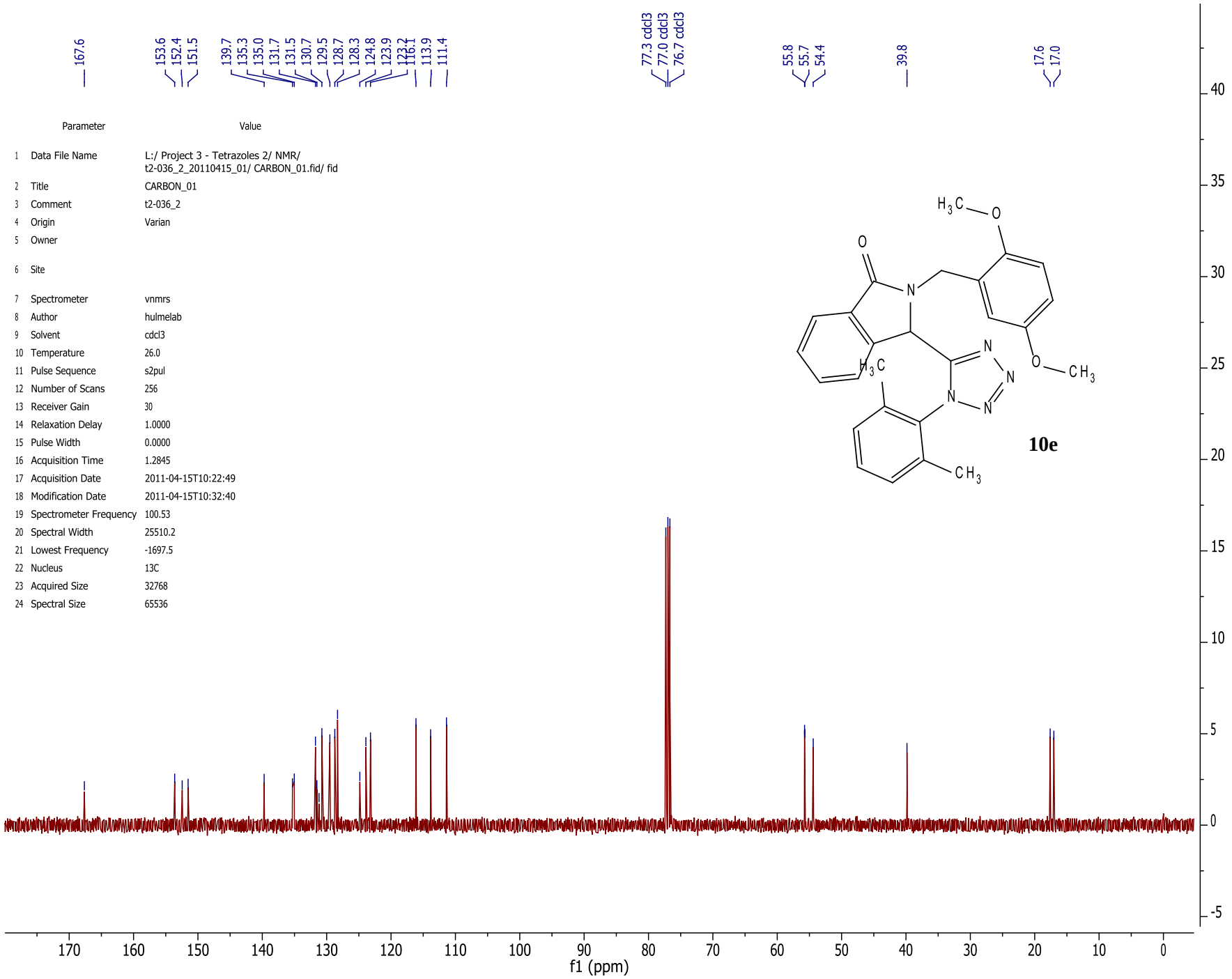


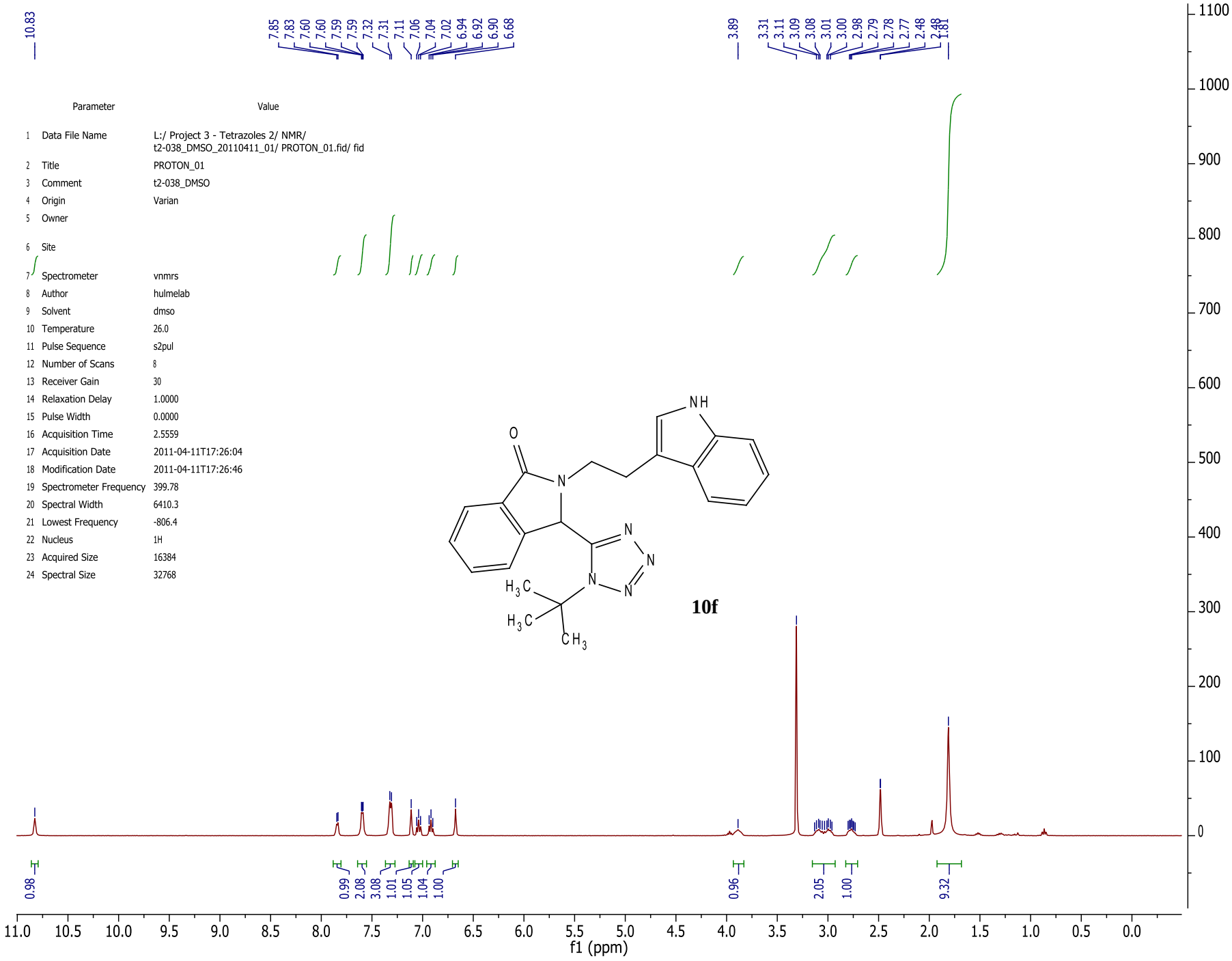


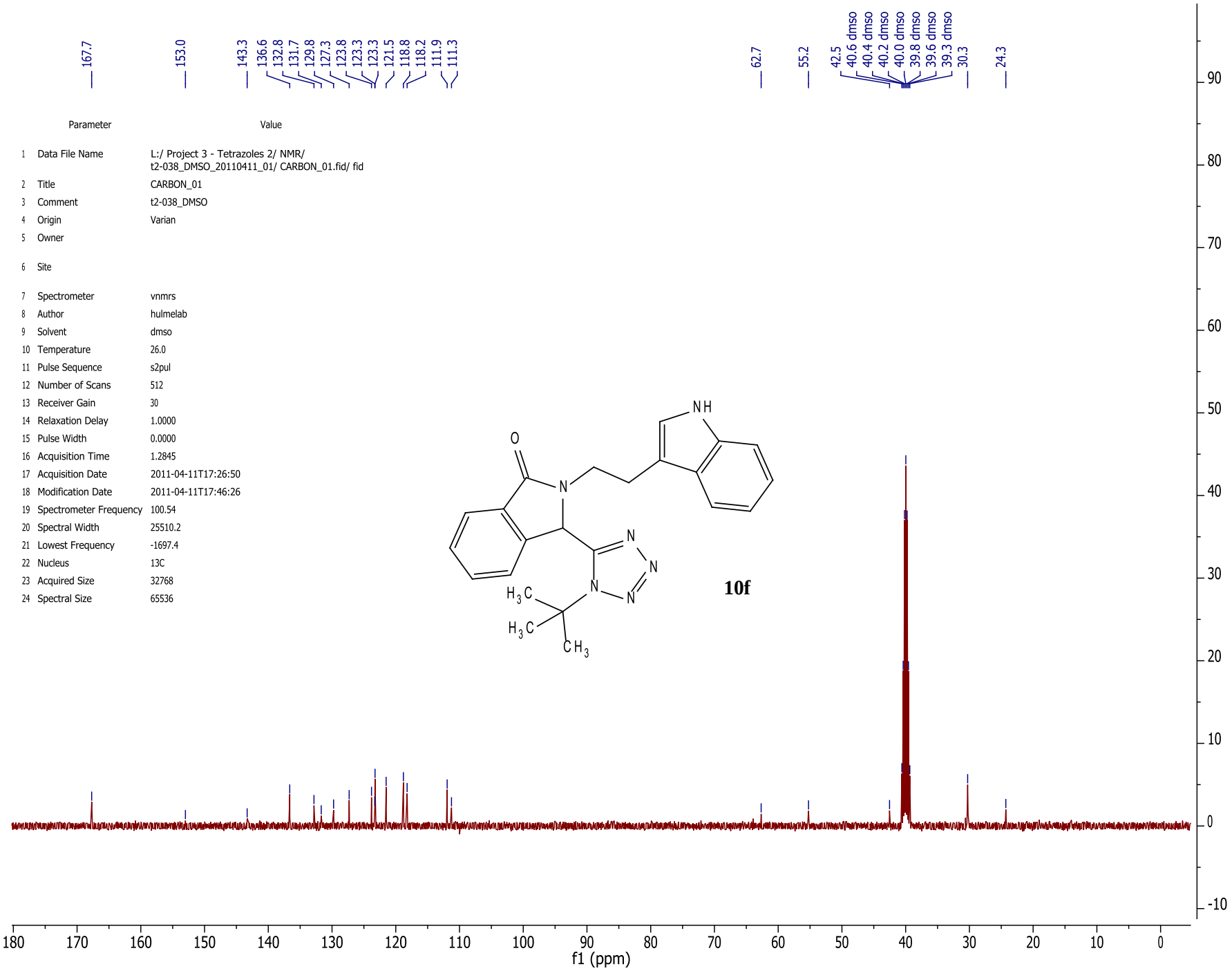


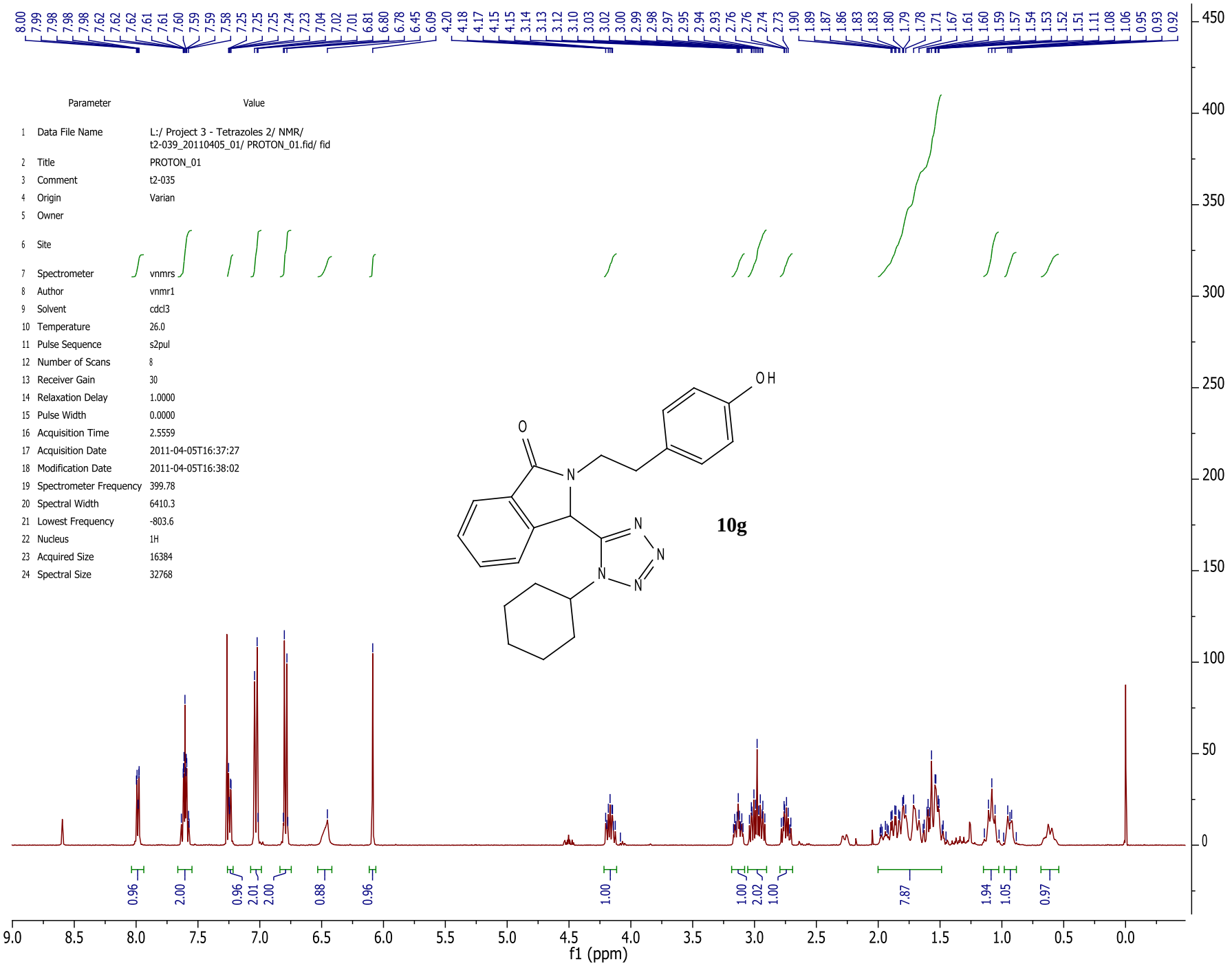


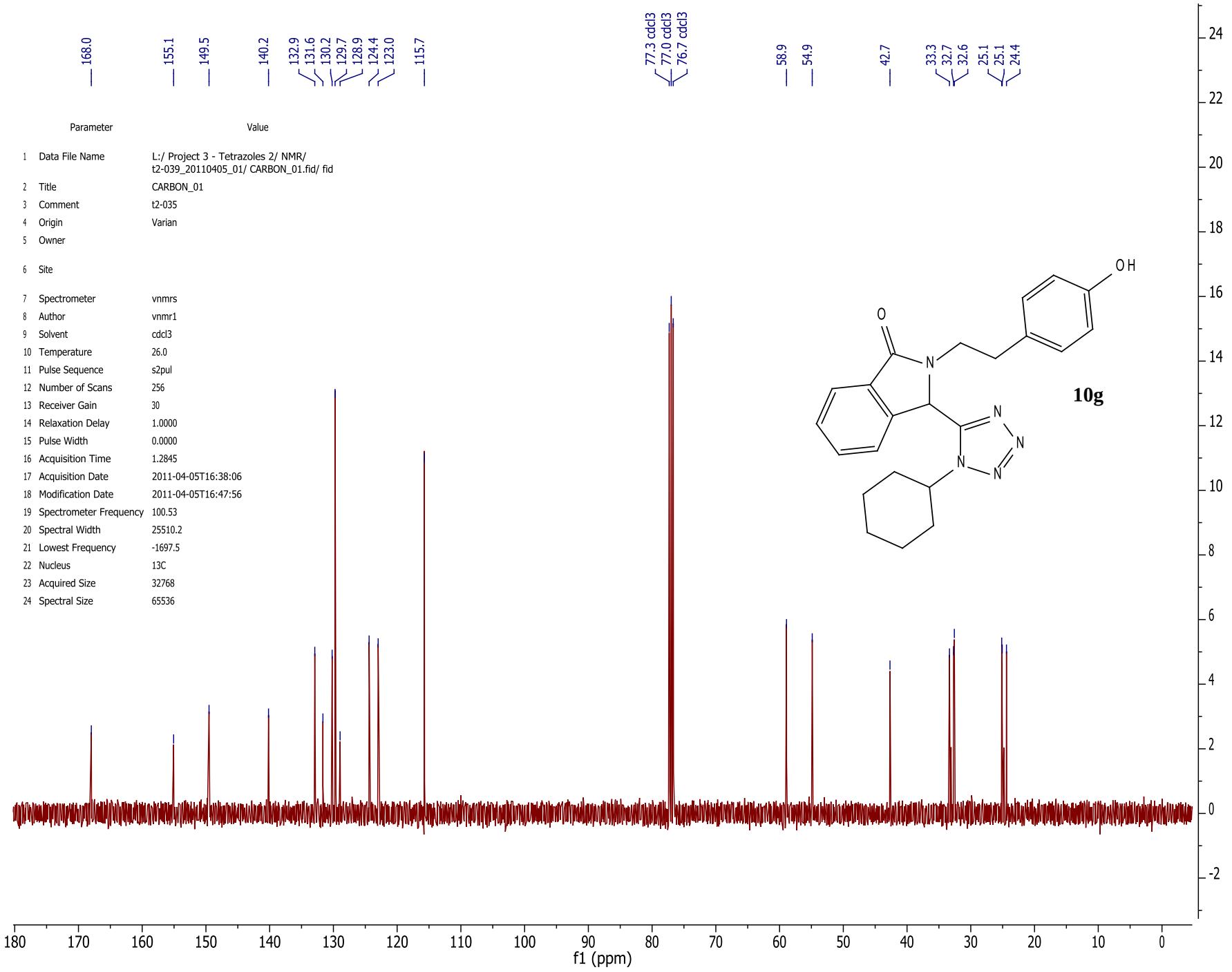


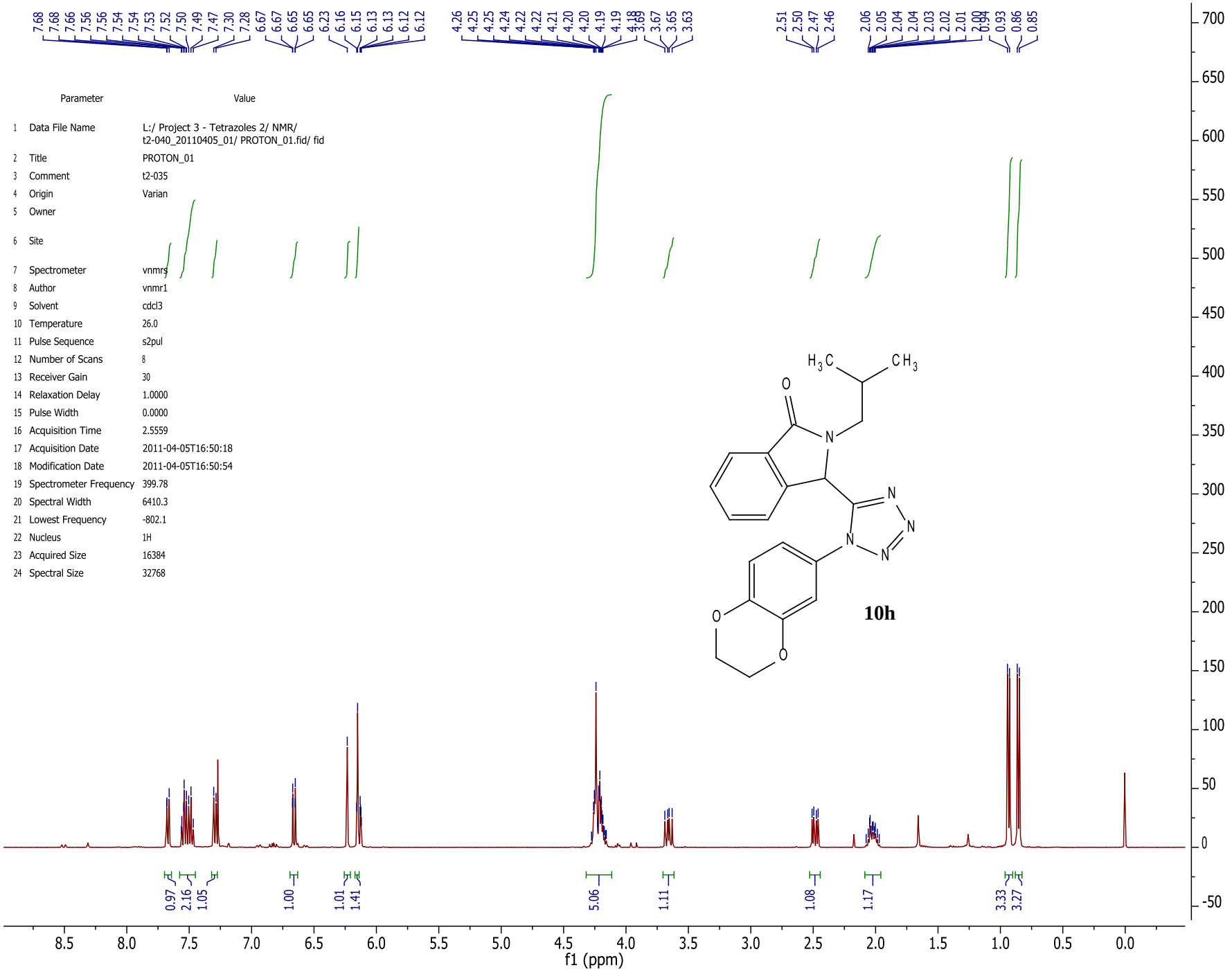


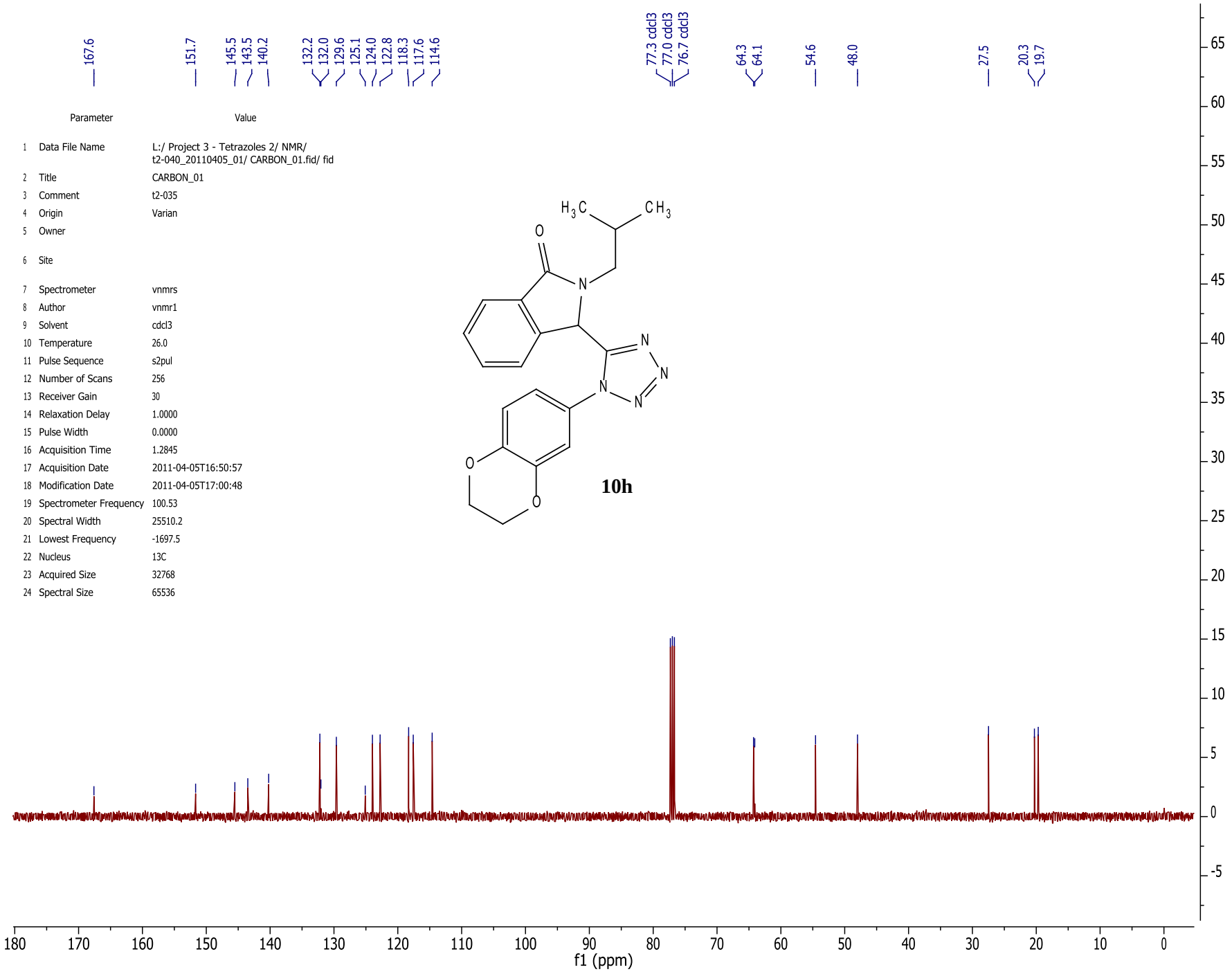


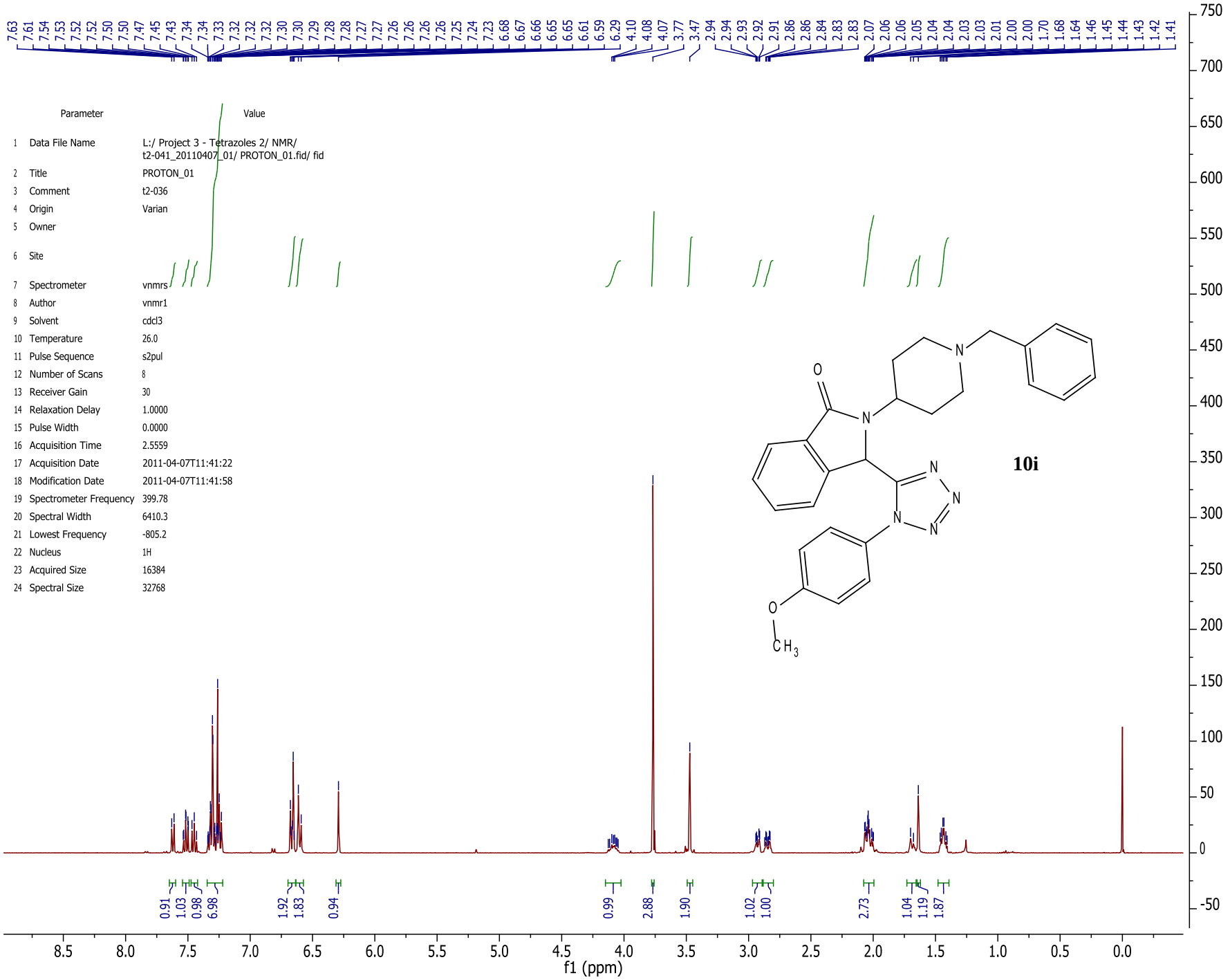


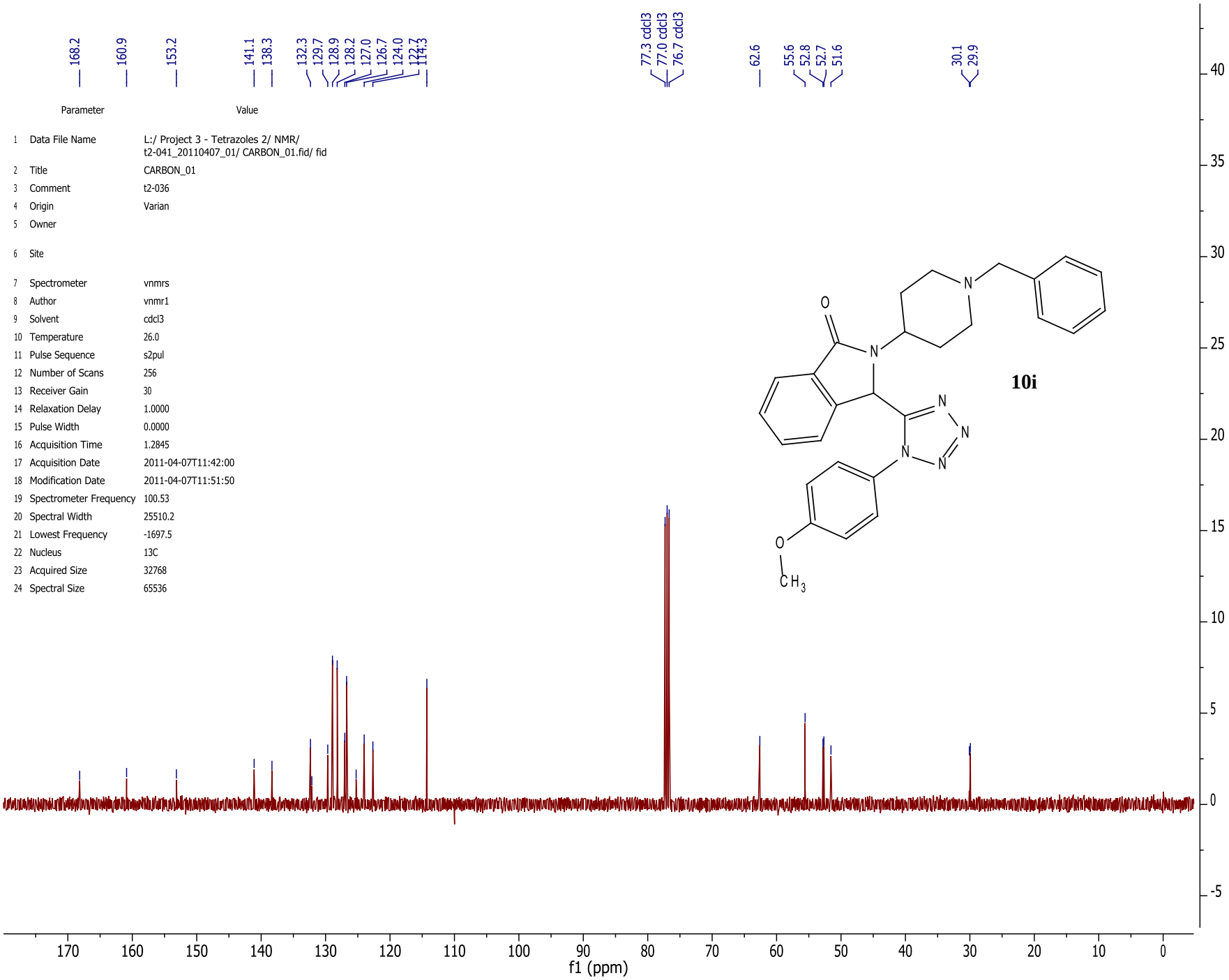


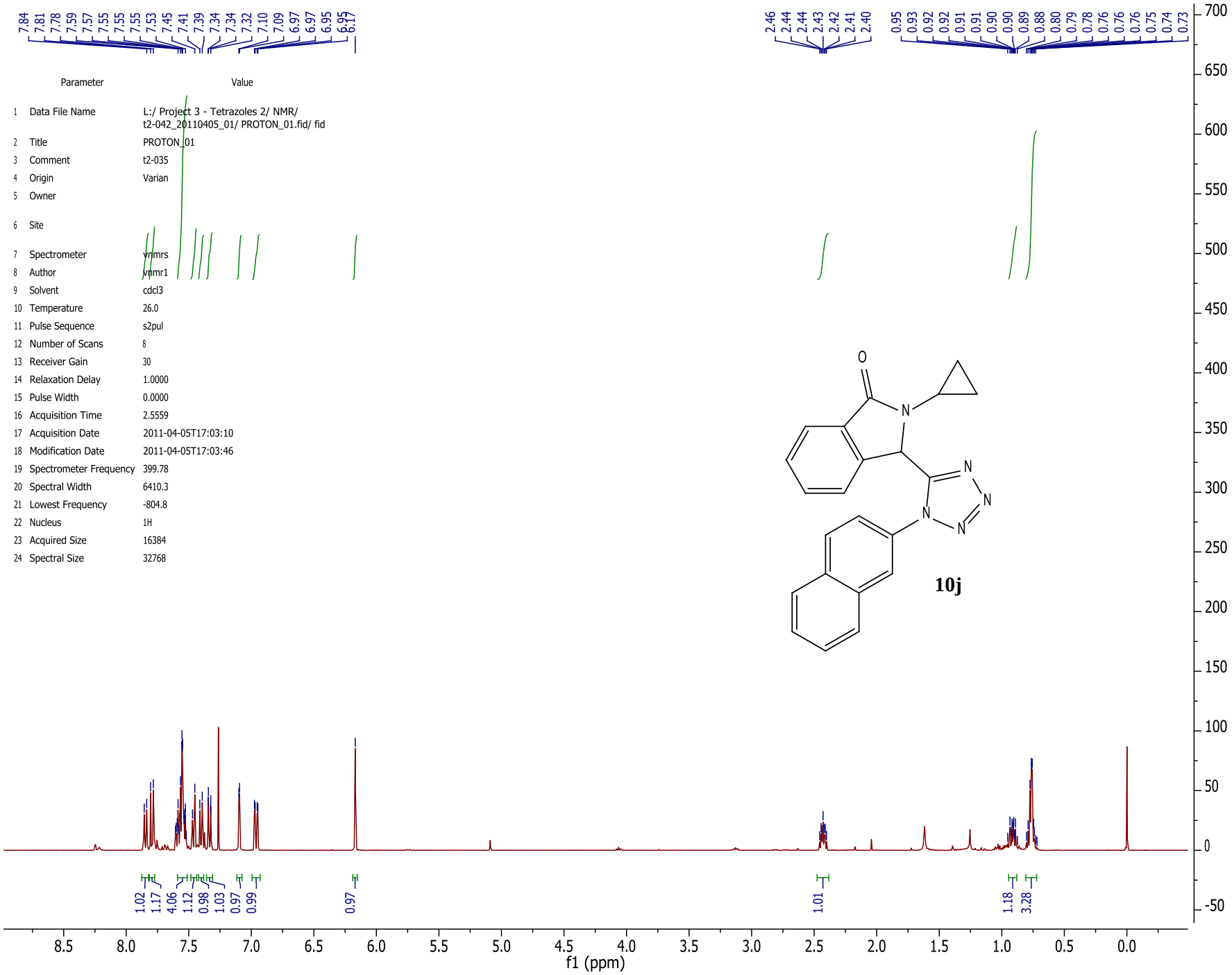


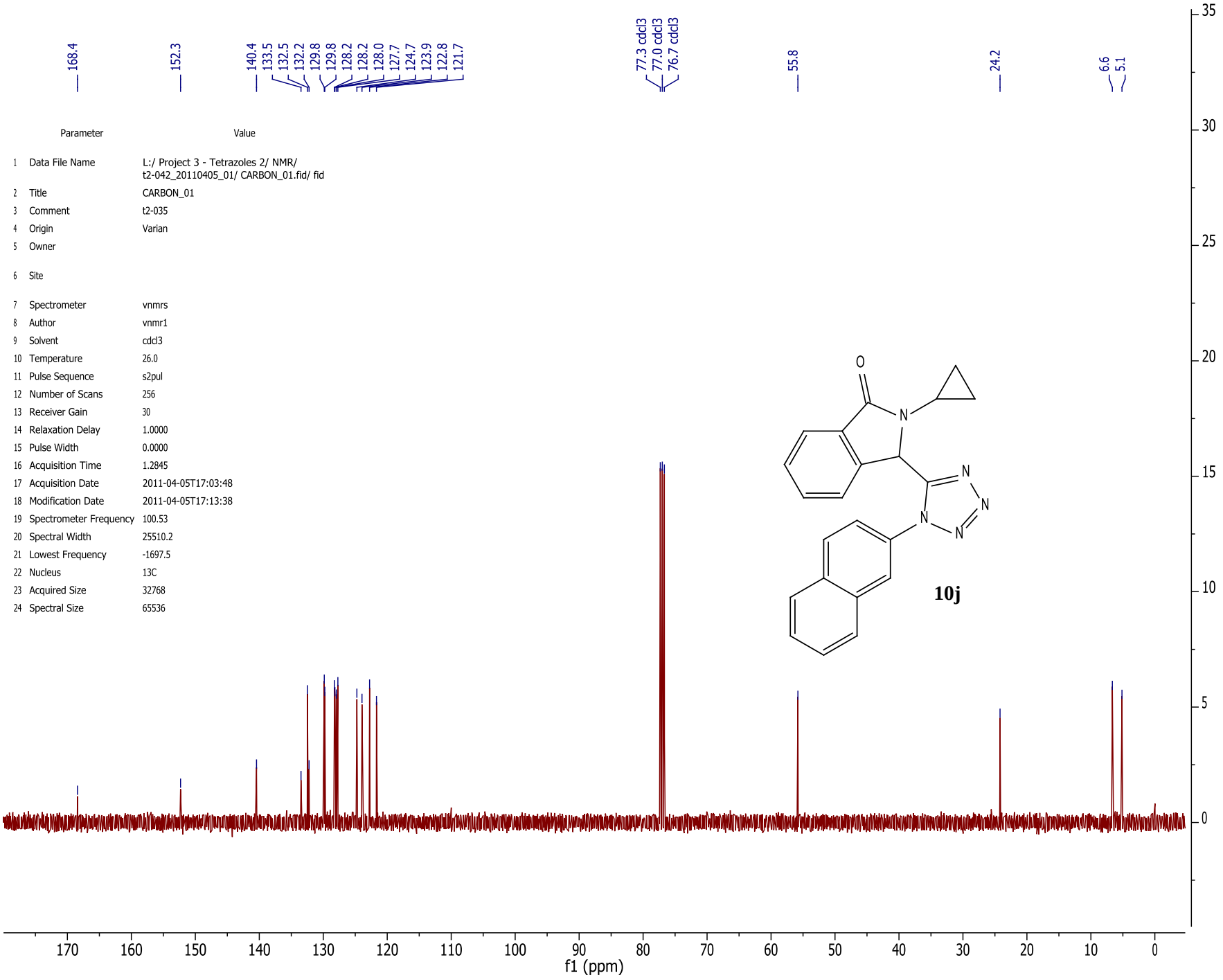


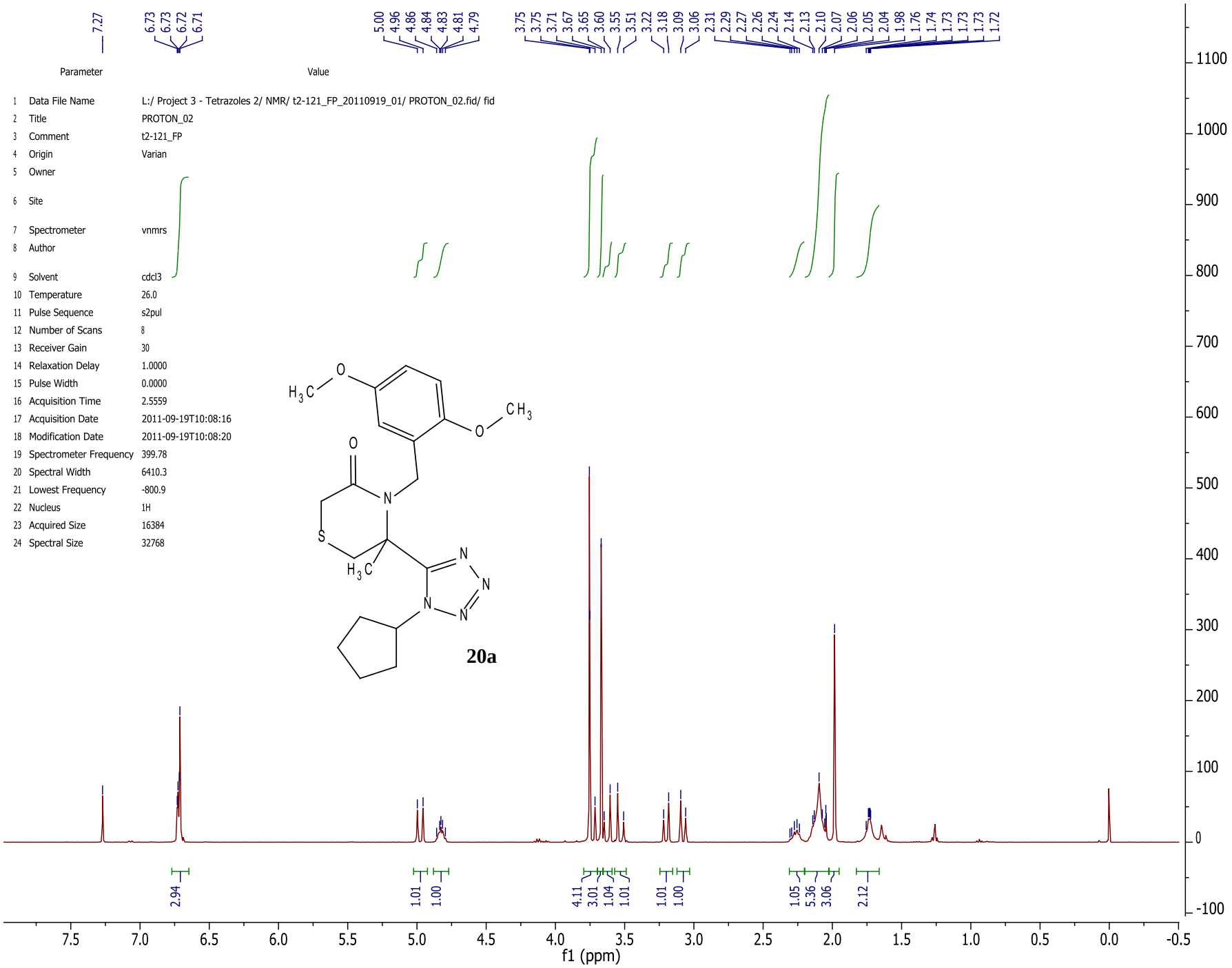


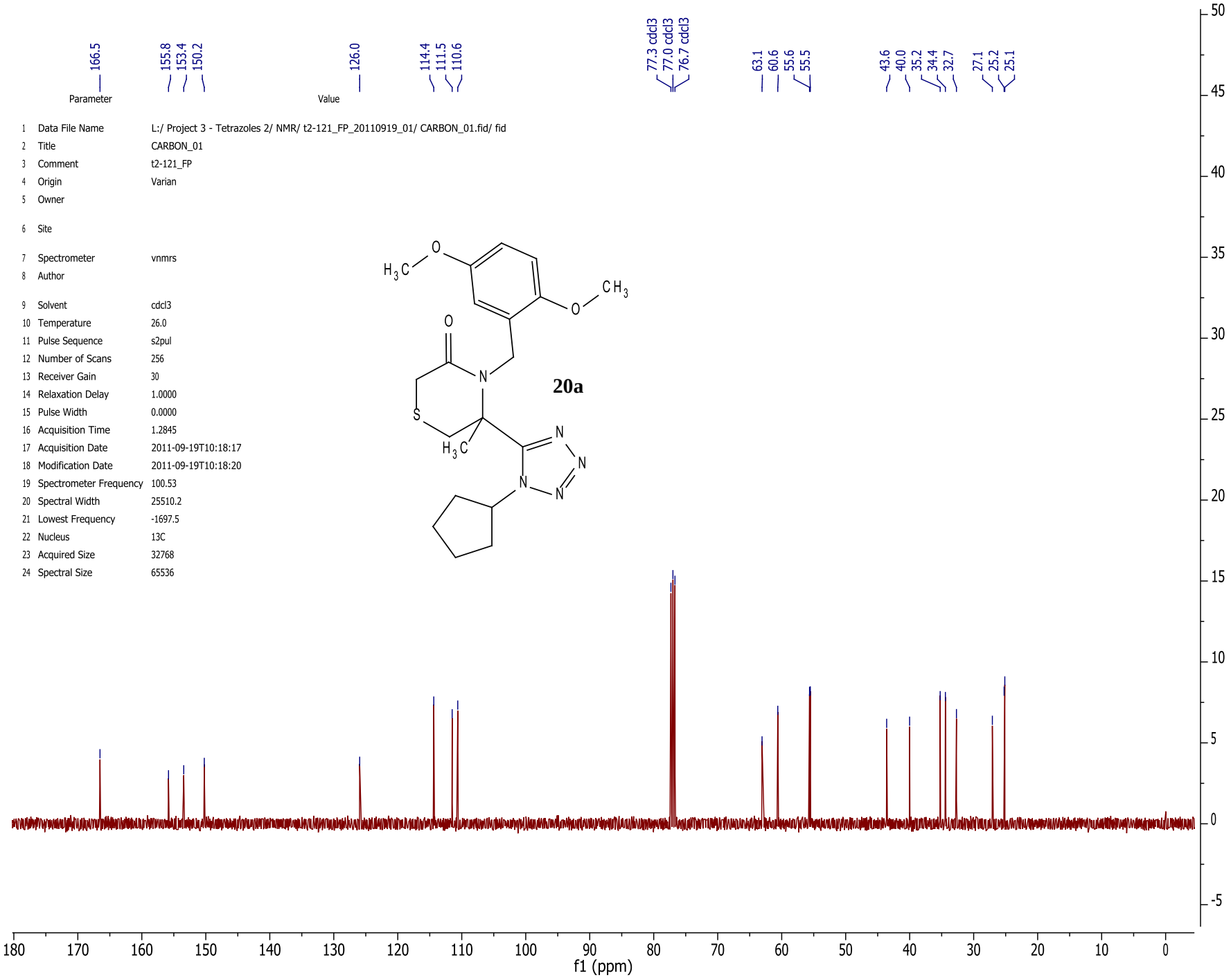


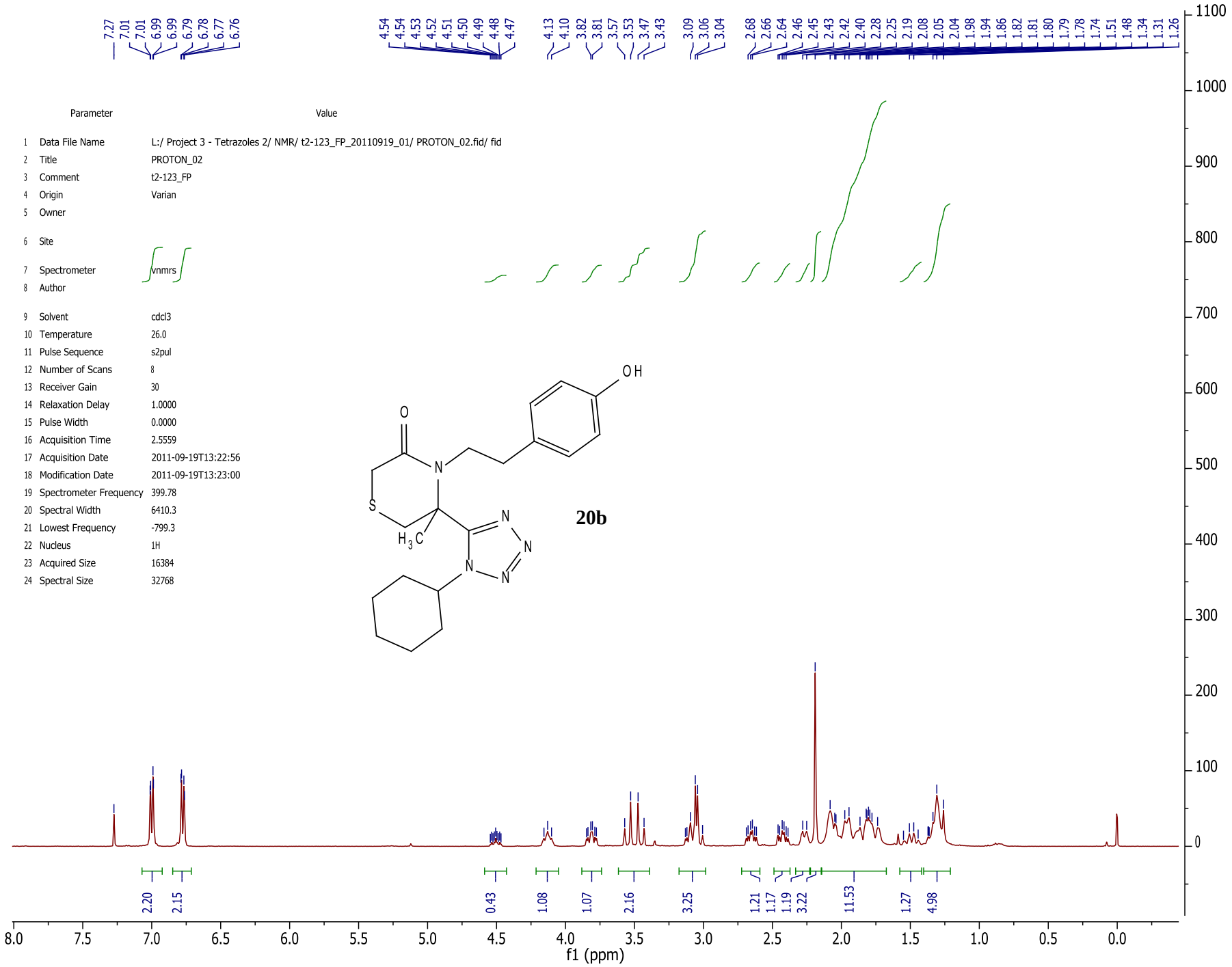


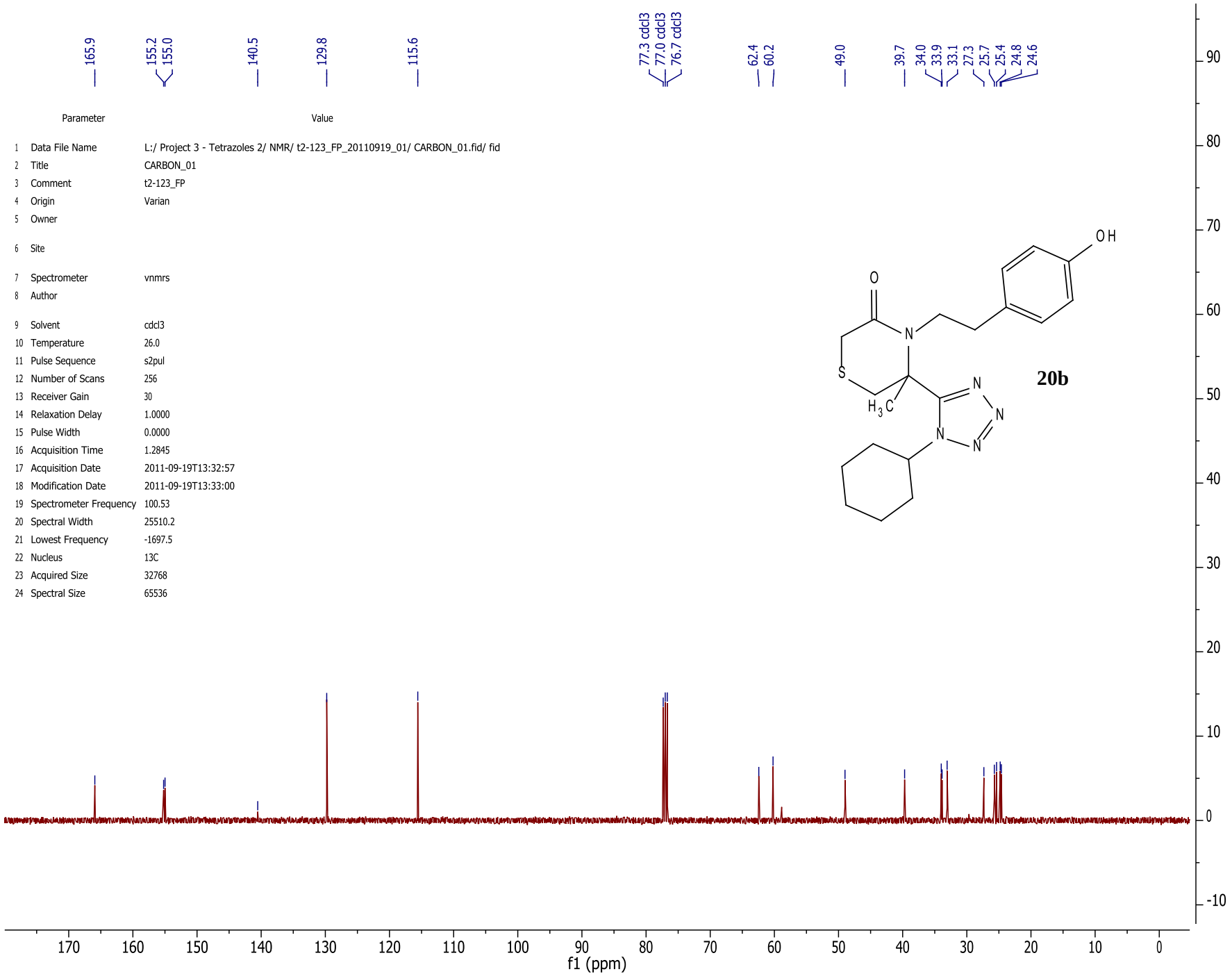


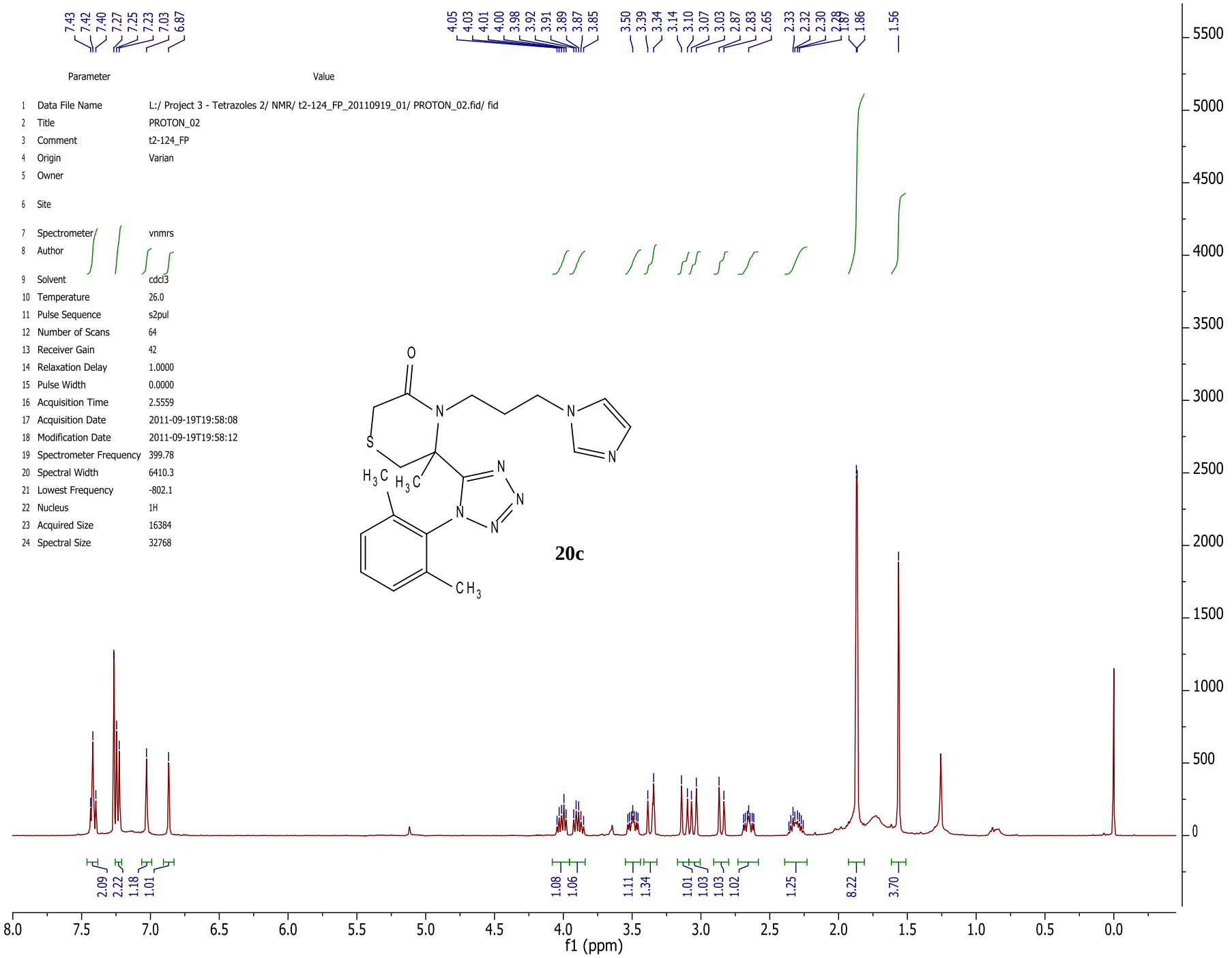


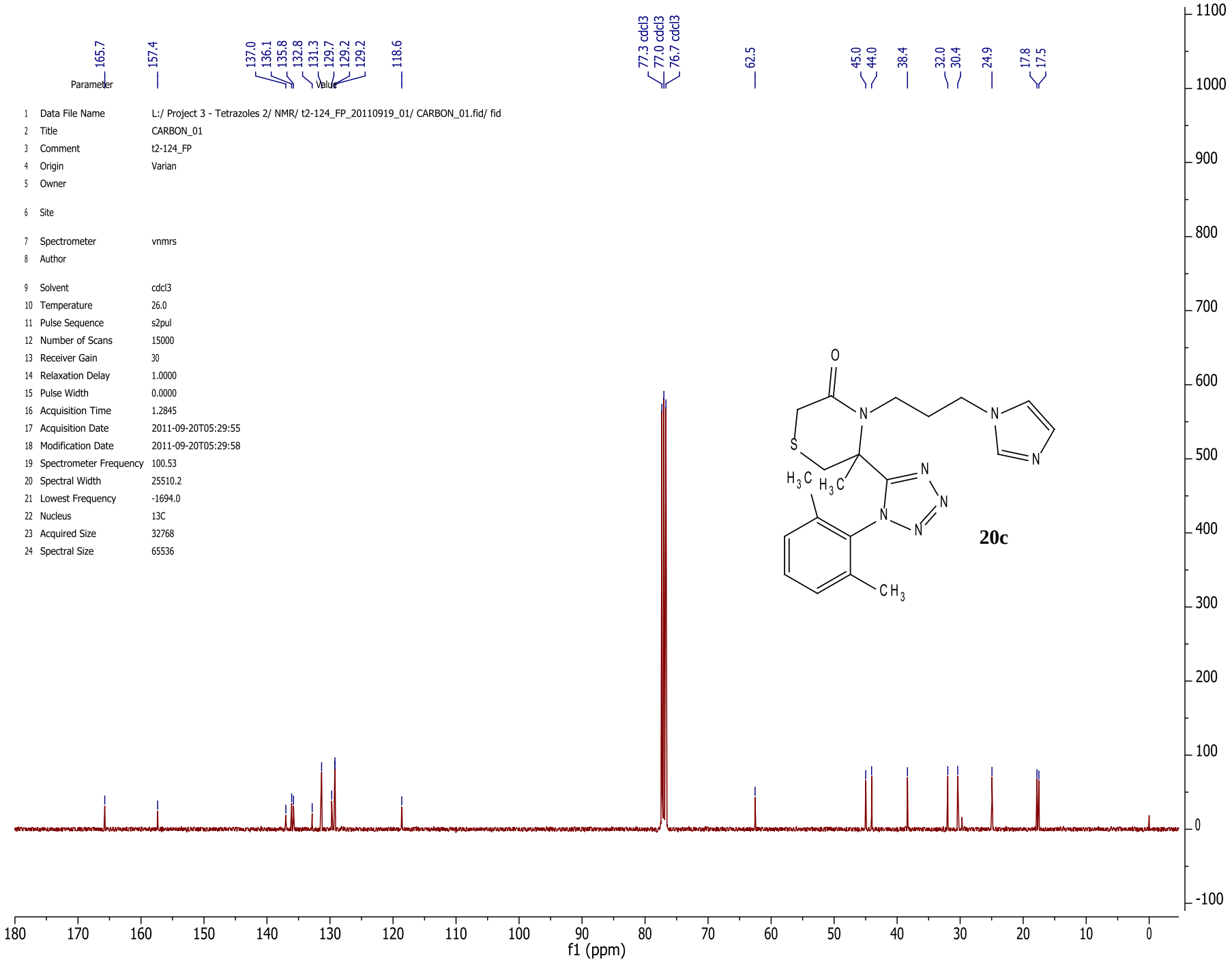


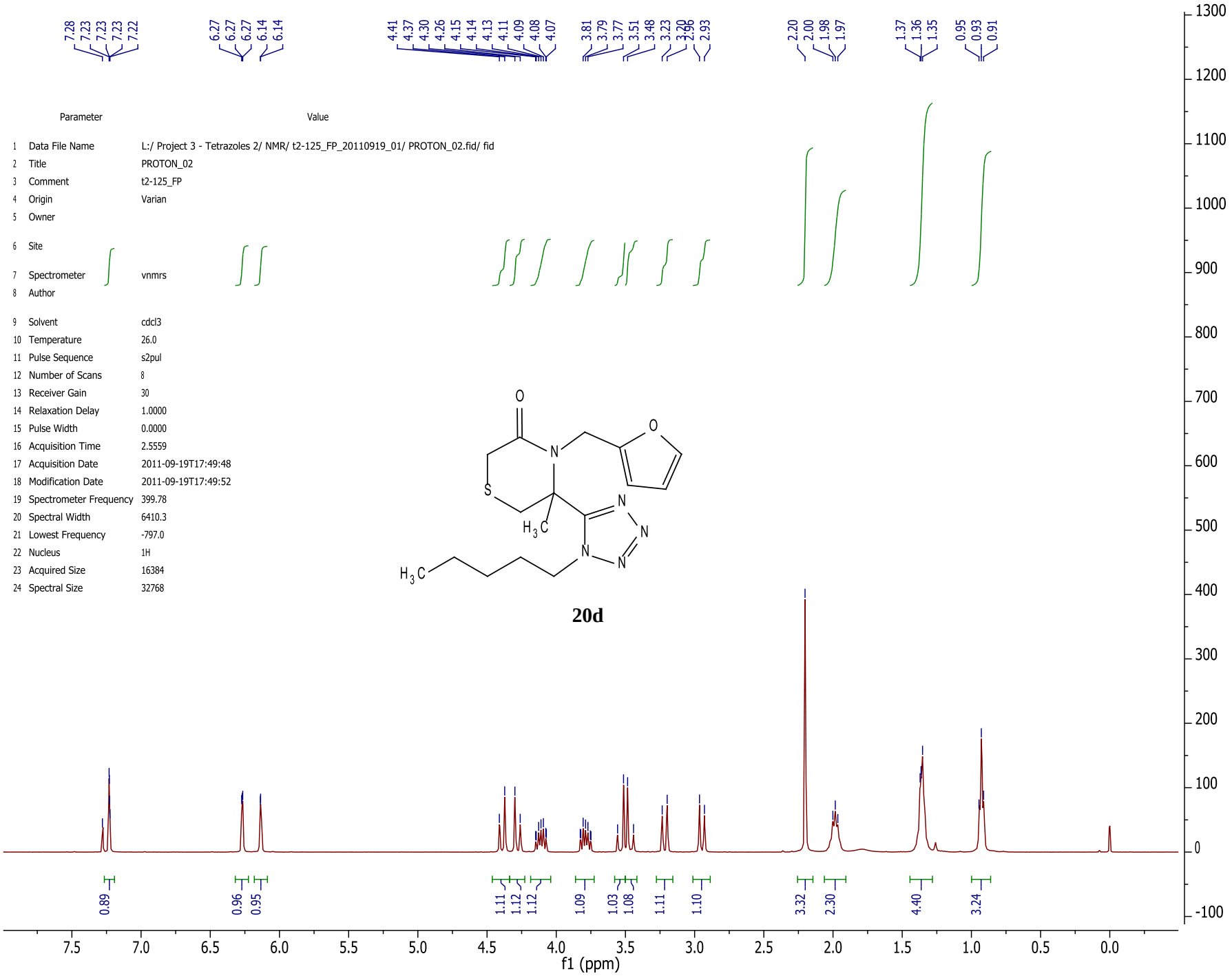












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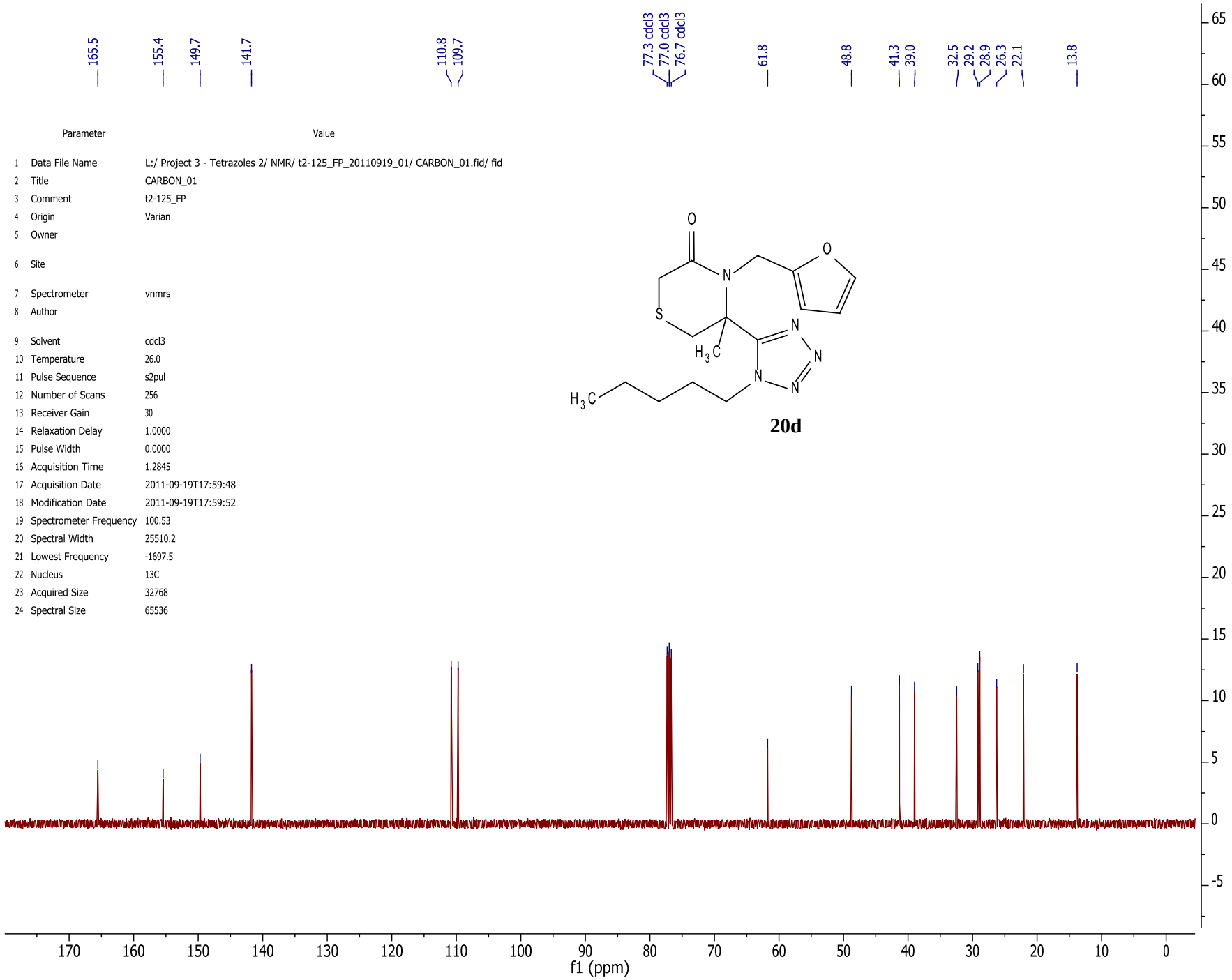

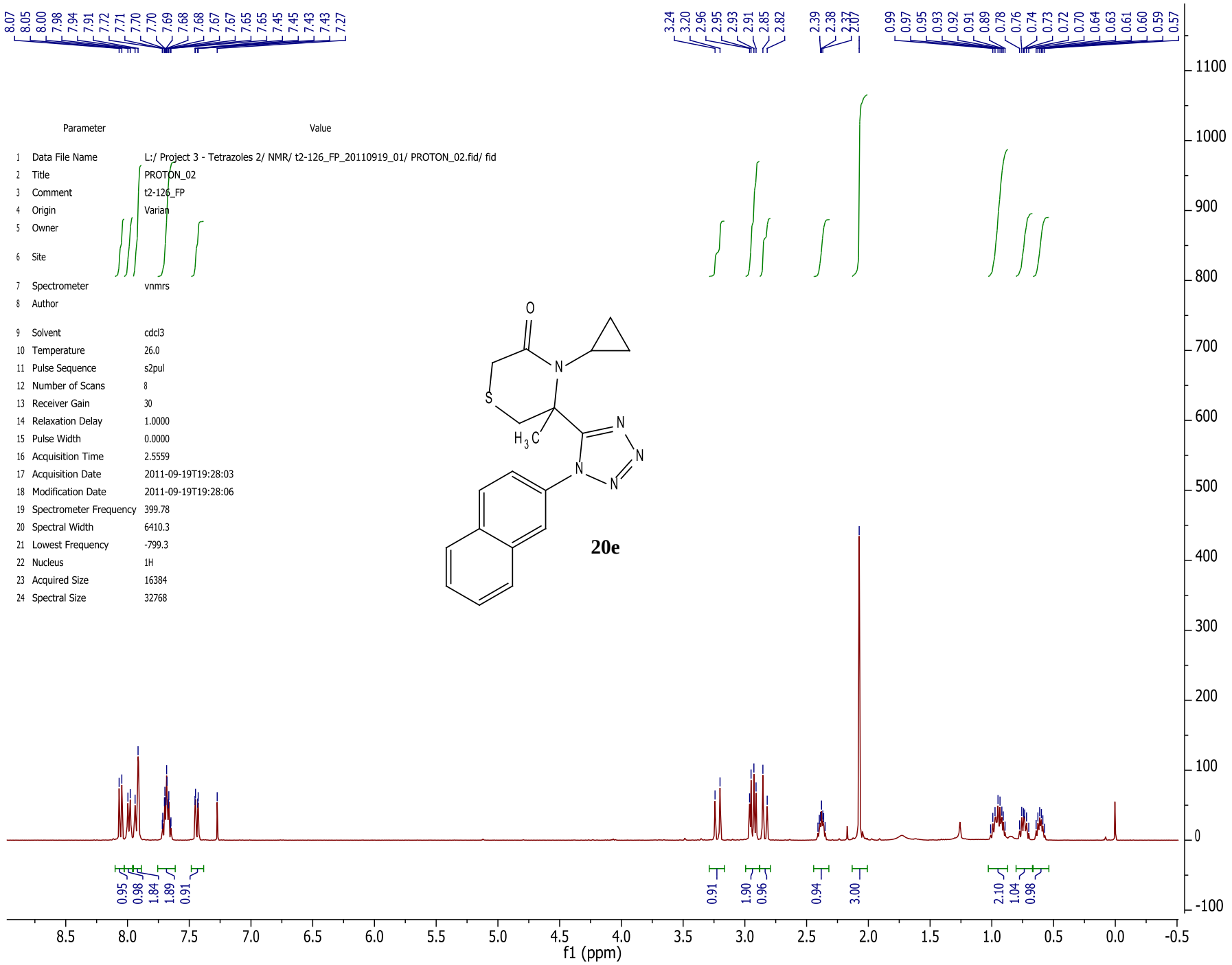

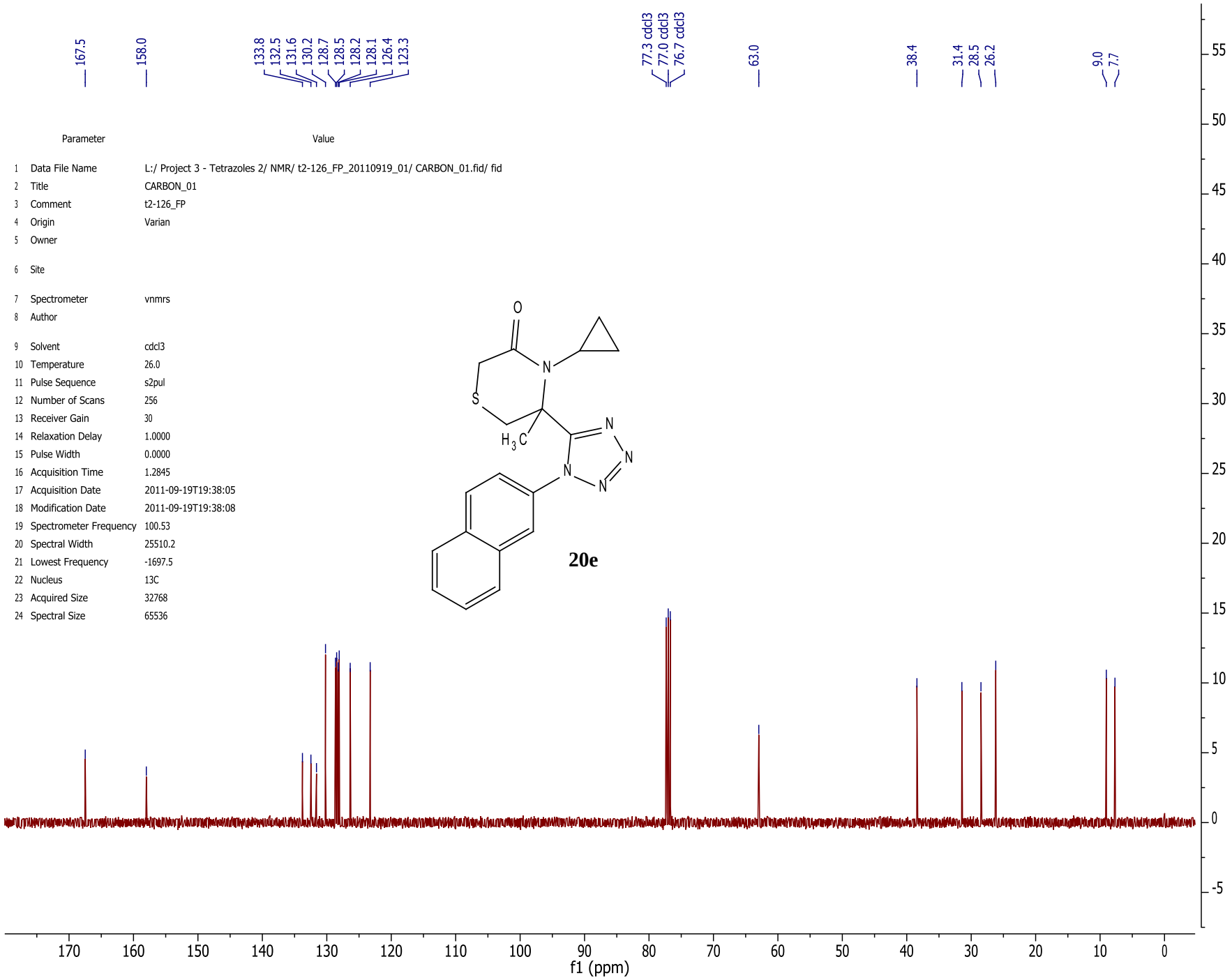

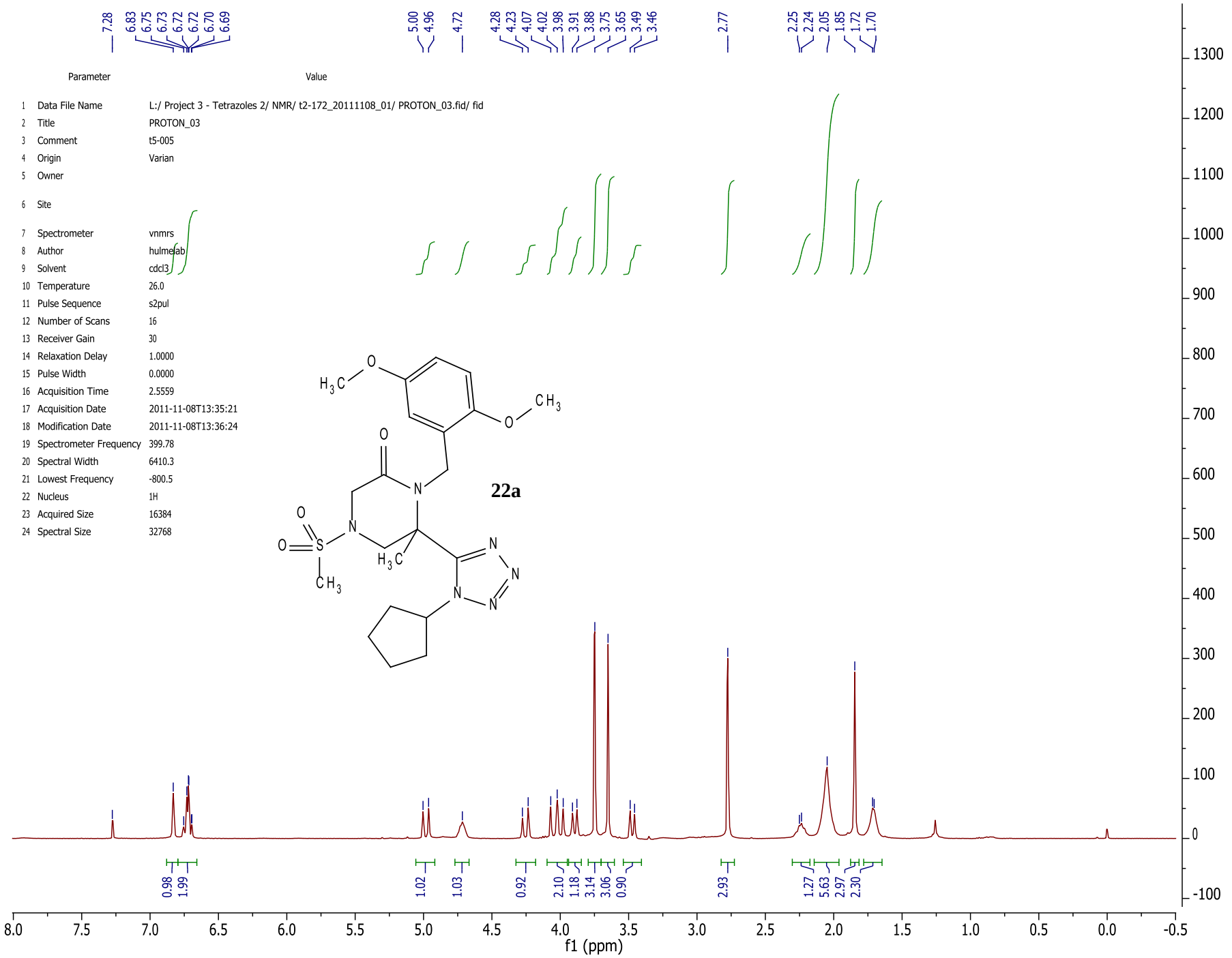

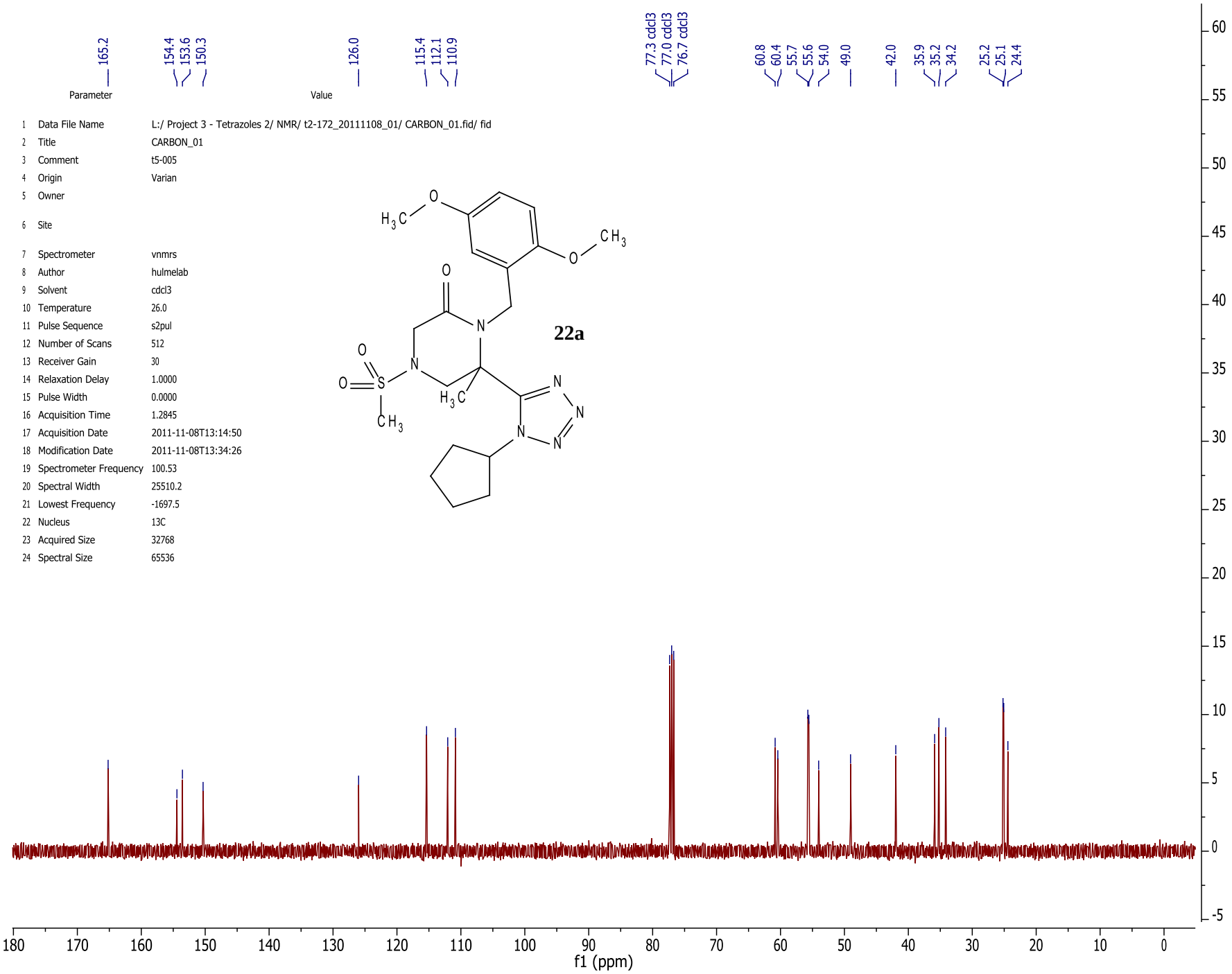

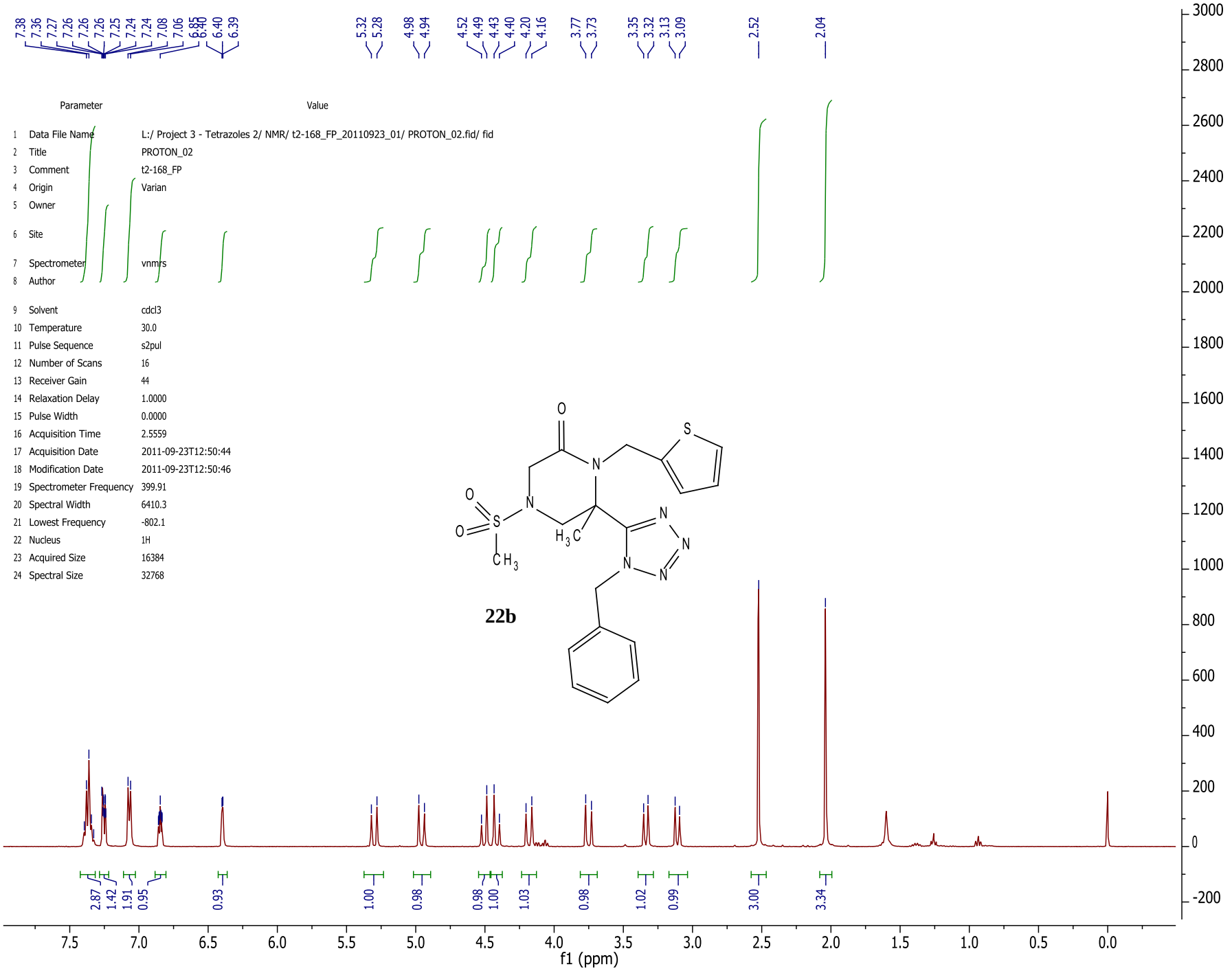
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8 Author
9 Solvent cdcl3
10 Temperature 30.0
11 Pulse Sequence s2pul
12 Number of Scans 16
13 Receiver Gain 44
14 Relaxation Delay 1.0000
15 Pulse Width 0.0000
16 Acquisition Time 2.5559
17 Acquisition Date 2011-09-23T12:50:44
18 Modification Date 2011-09-23T12:50:46
19 Spectrometer Frequency 399.91
20 Spectral Width 6410.3
21 Lowest Frequency -802.1
22 Nucleus 1H
23 Acquired Size 16384
24 Spectral Size 32768
22b
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1.91
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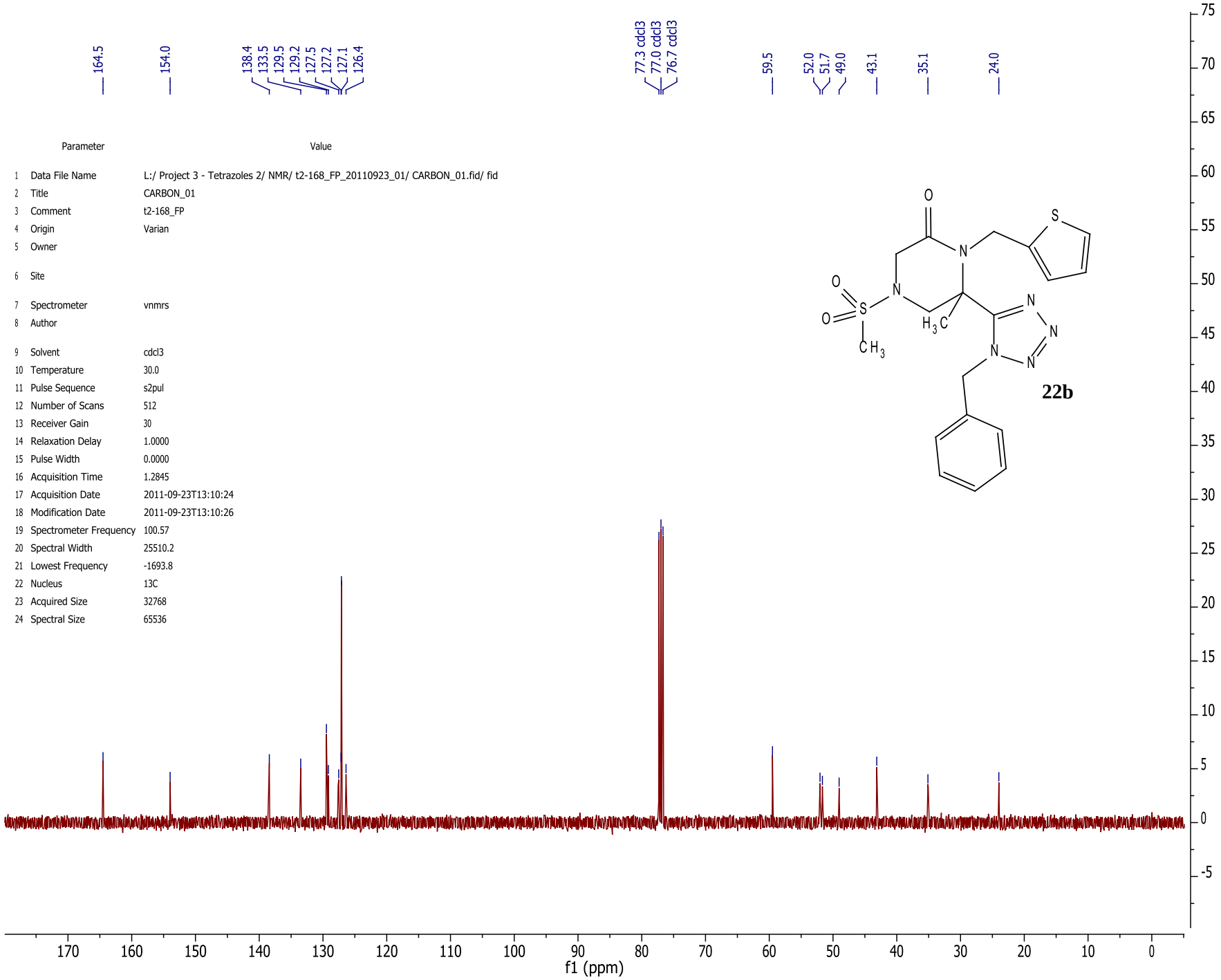
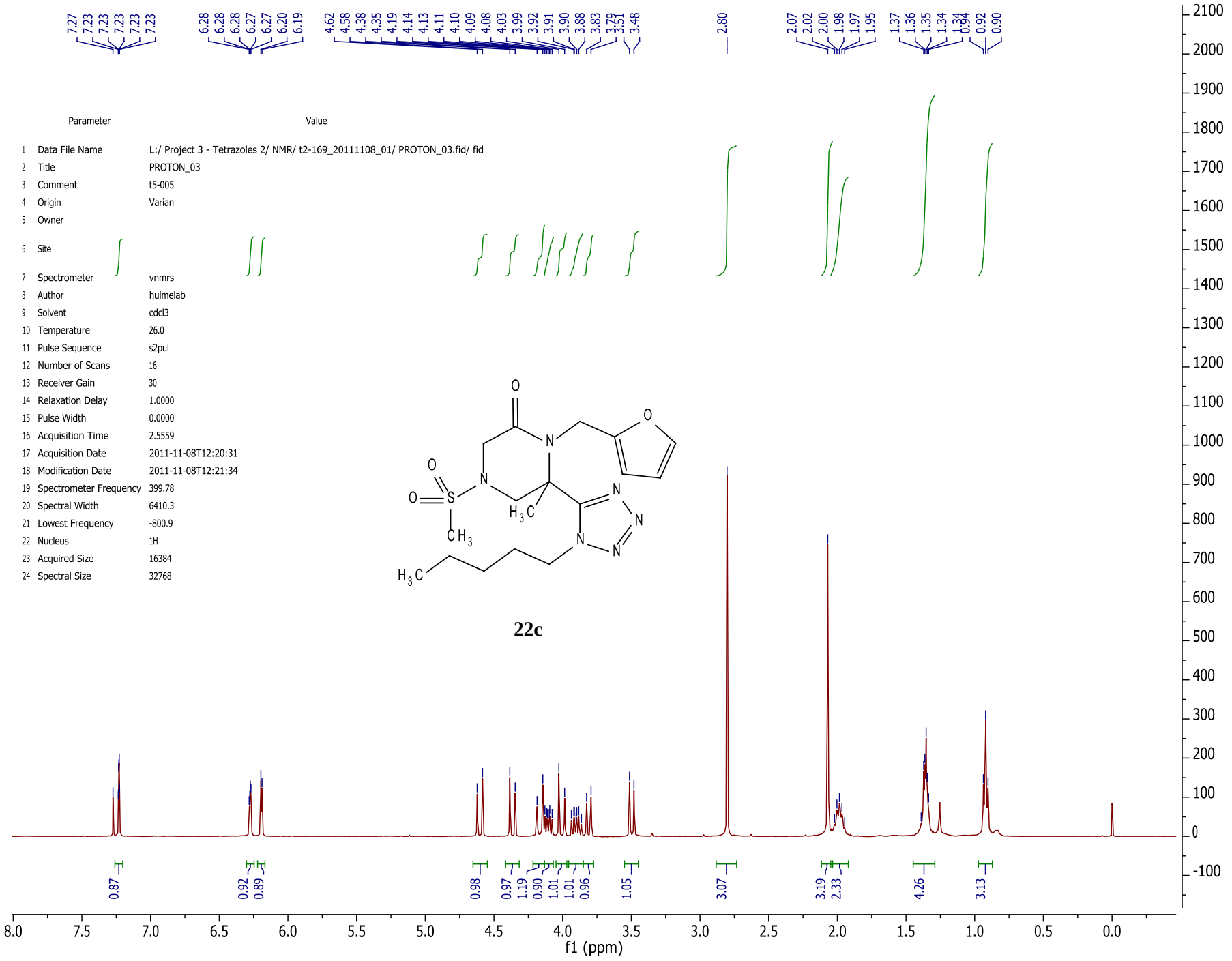
f1 (ppm)





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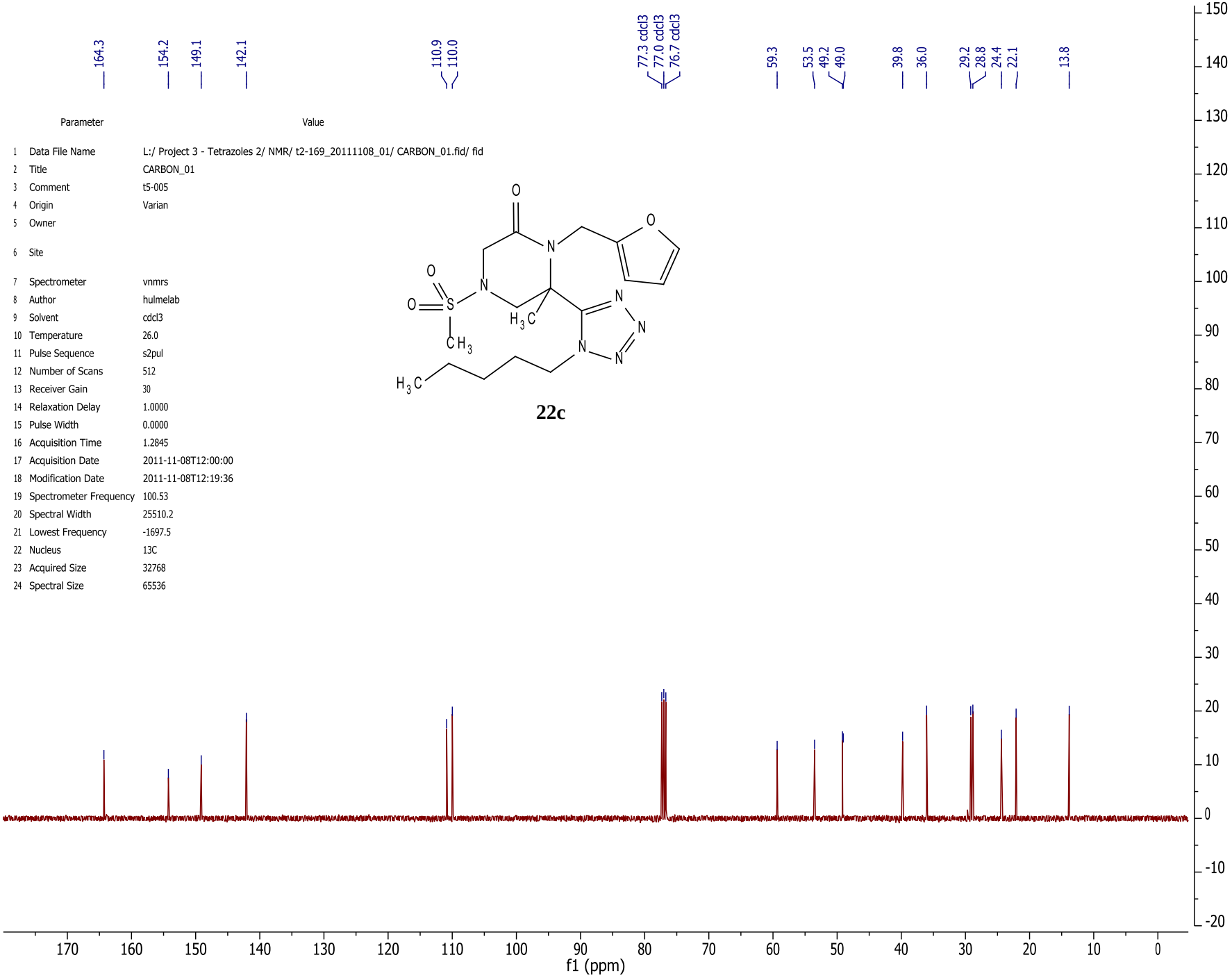

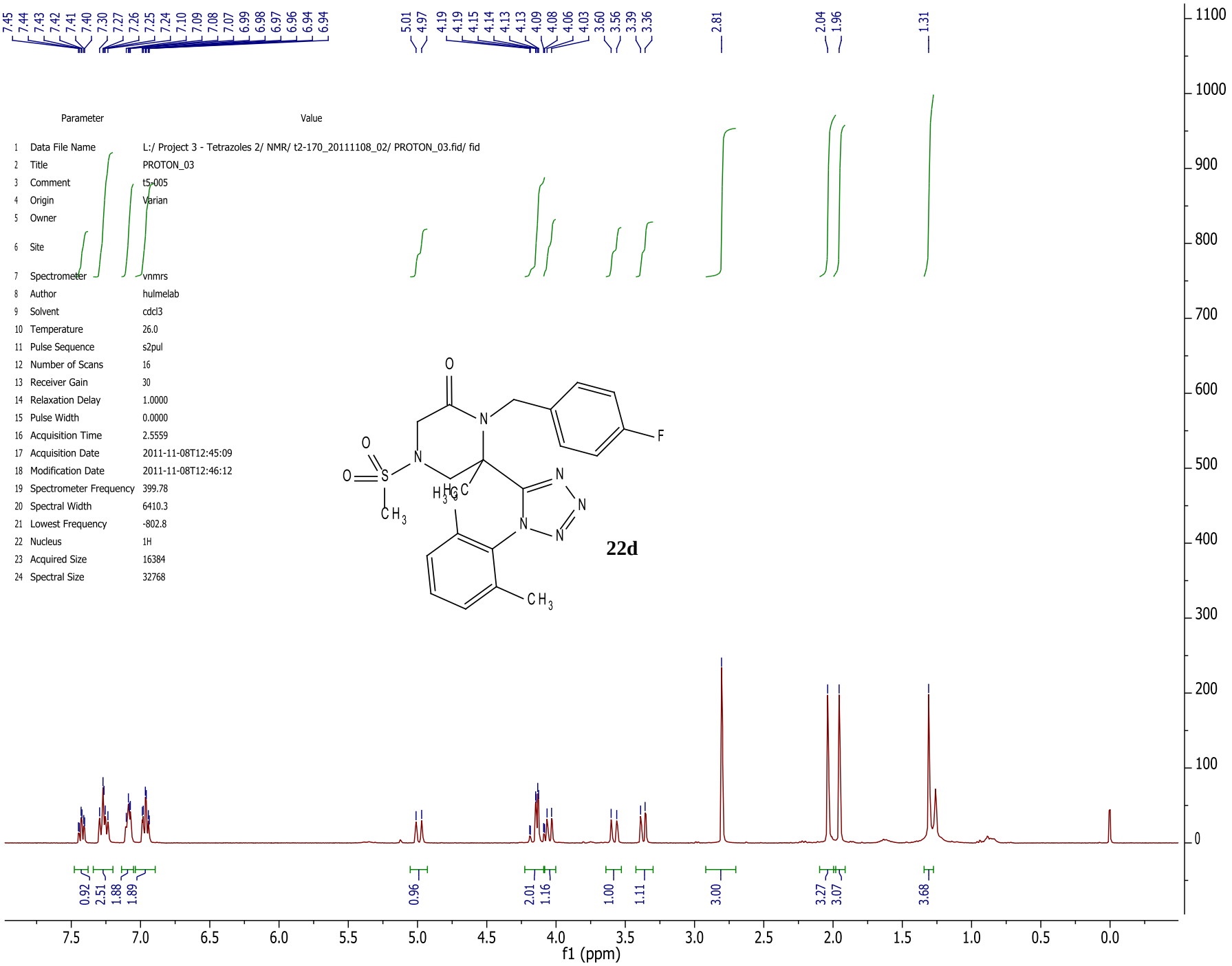

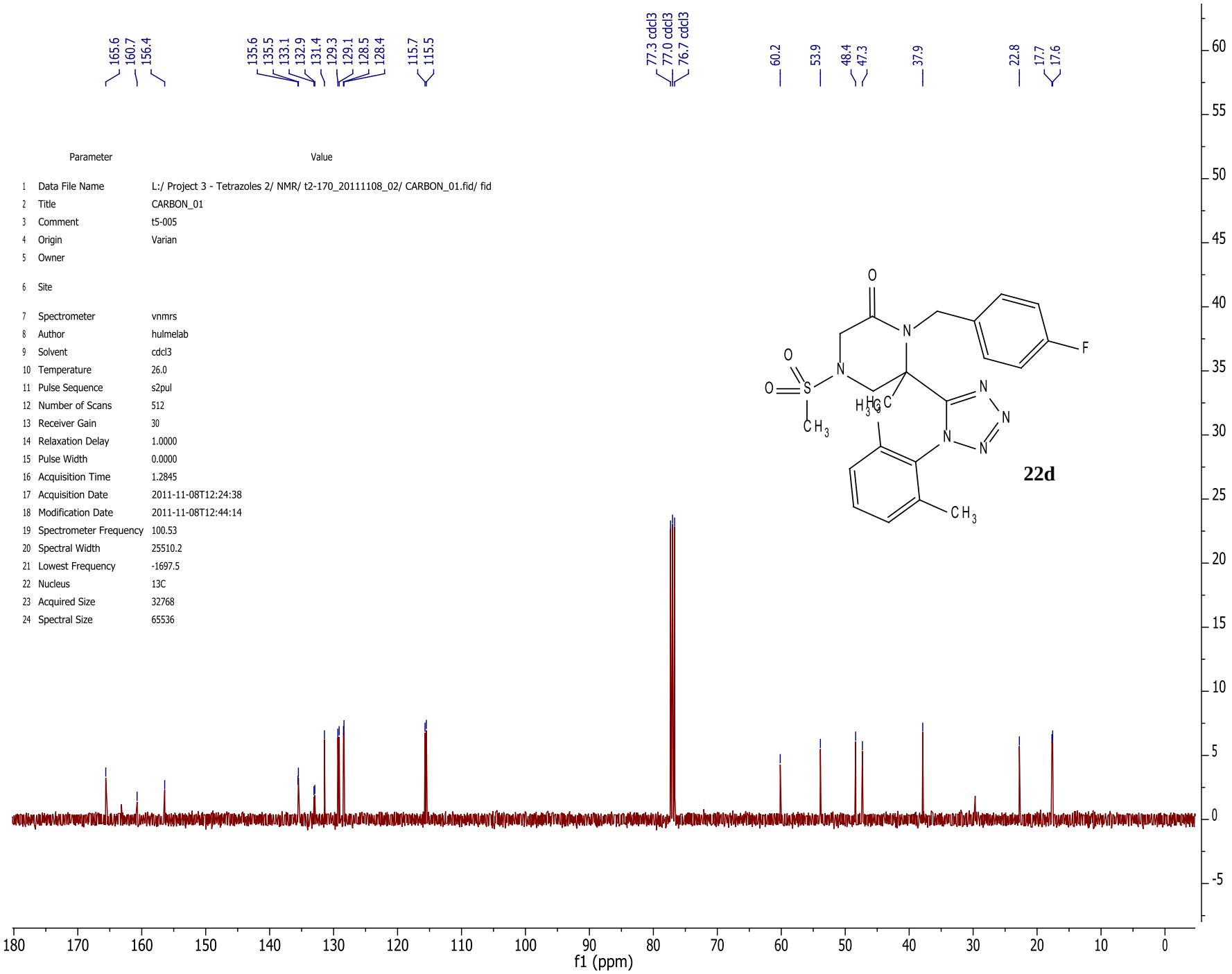

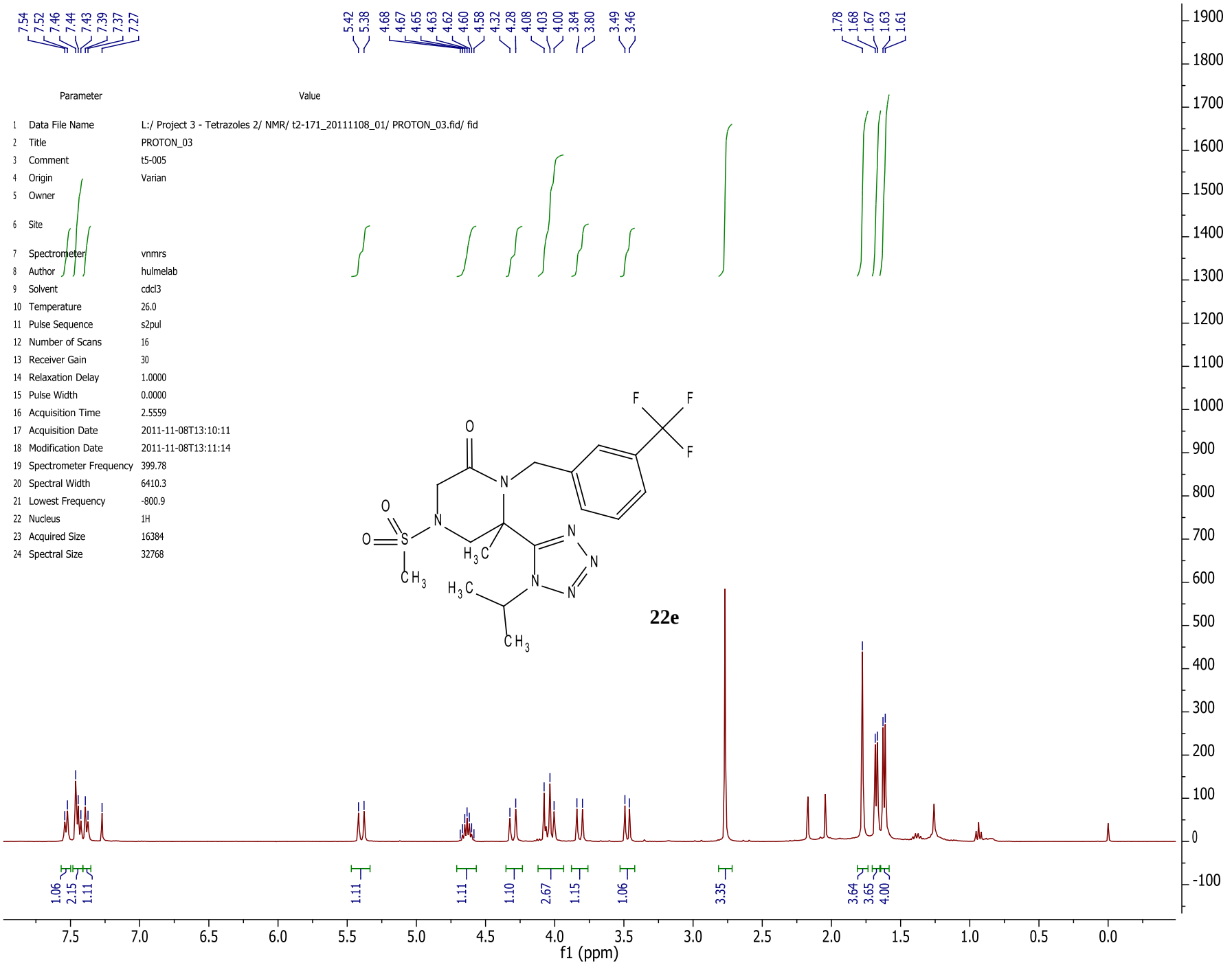
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1.78 1.68 1.67 1.63 1.61
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2 Title PROTON_03
3 Comment t5-005
4 Origin Varian
5 Owner
6 Site
7 Spectrometer vnmrs
8 Author hulmelab
9 Solvent cdcl3
10 Temperature 26.0
11 Pulse Sequence s2pul
12 Number of Scans 16
13 Receiver Gain 30
14 Relaxation Delay 1.0000
15 Pulse Width 0.0000
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18 Modification Date 2011-11-08T13:11:14
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20 Spectral Width 6410.3
21 Lowest Frequency -800.9
22 Nucleus 1H
23 Acquired Size 16384
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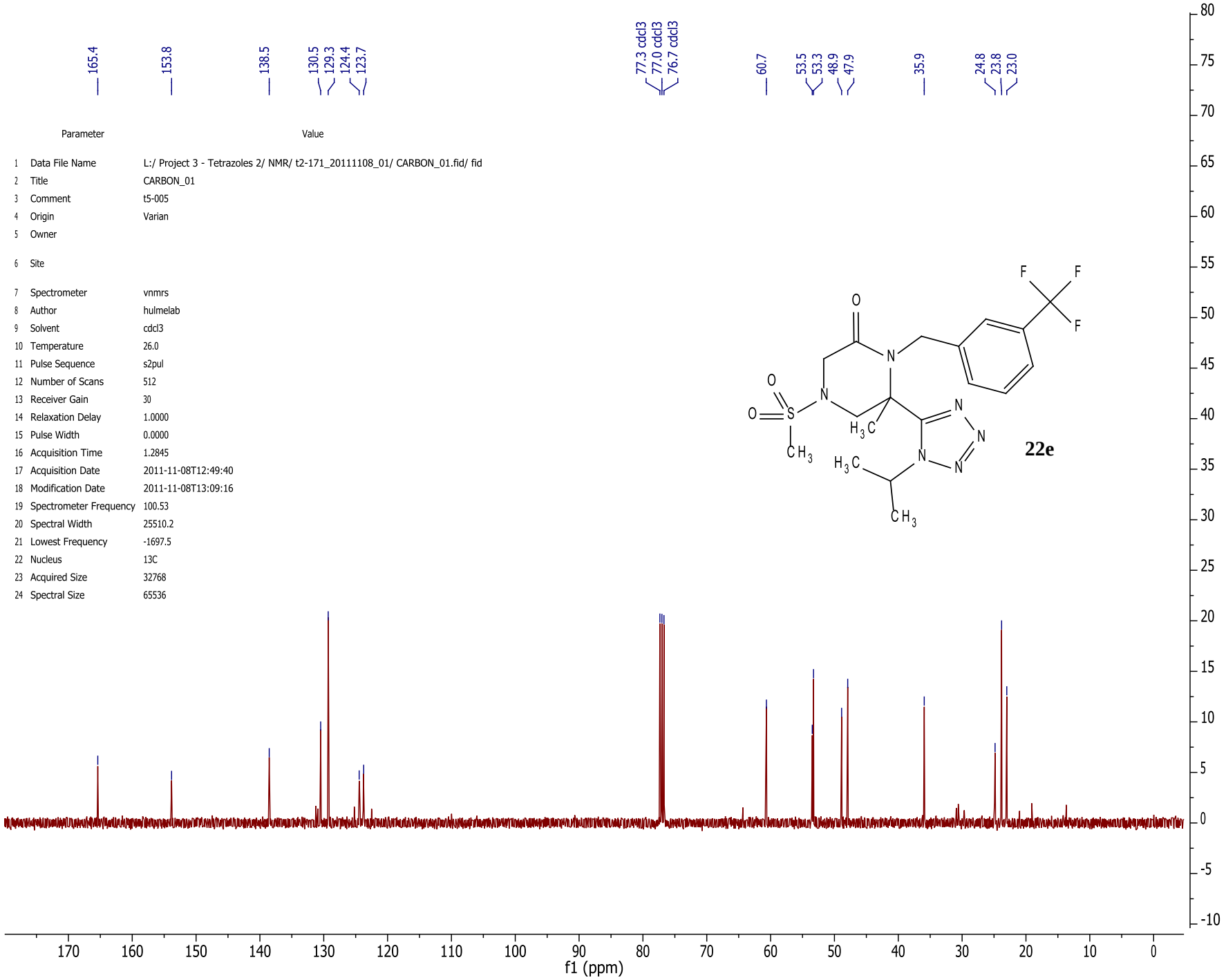
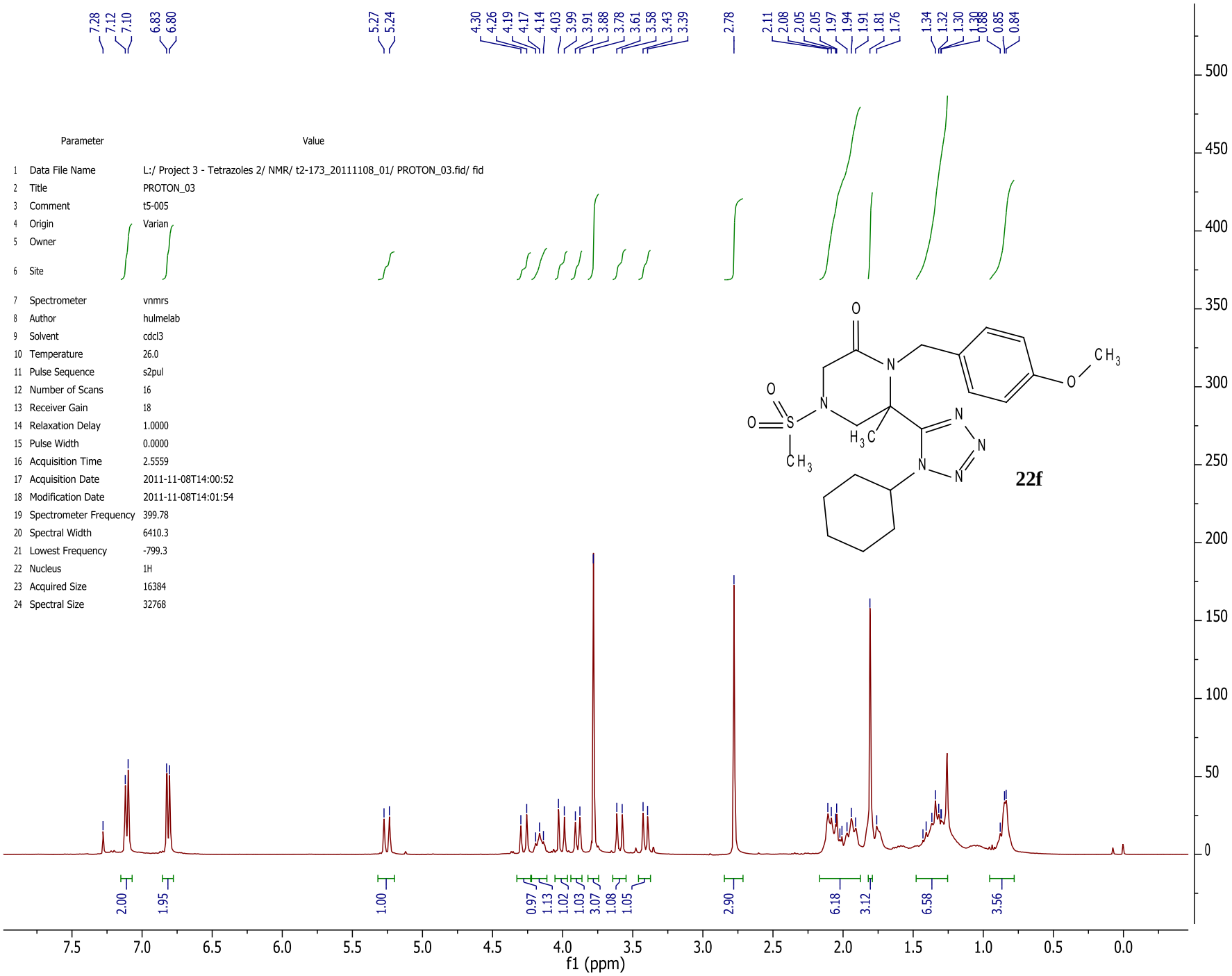
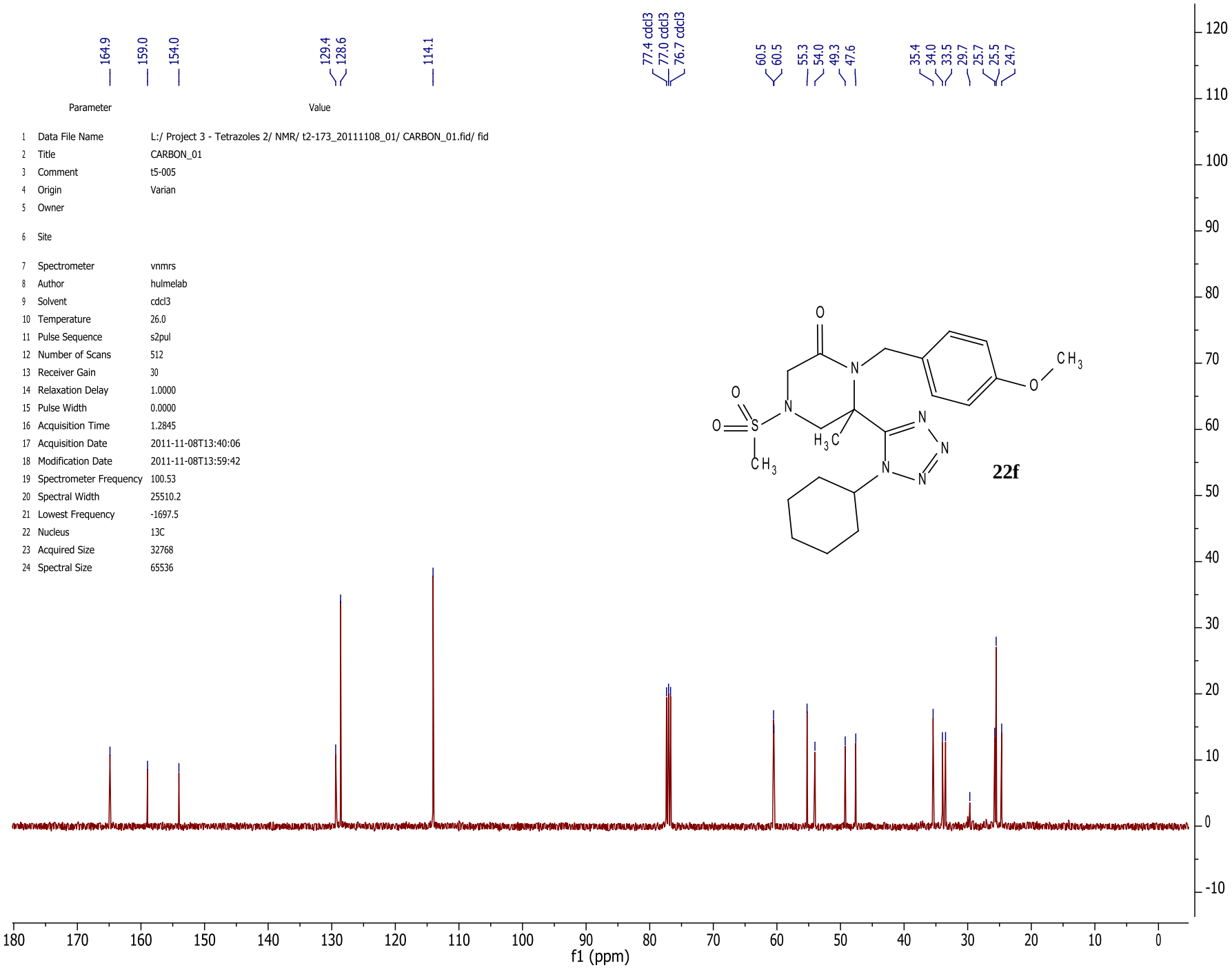
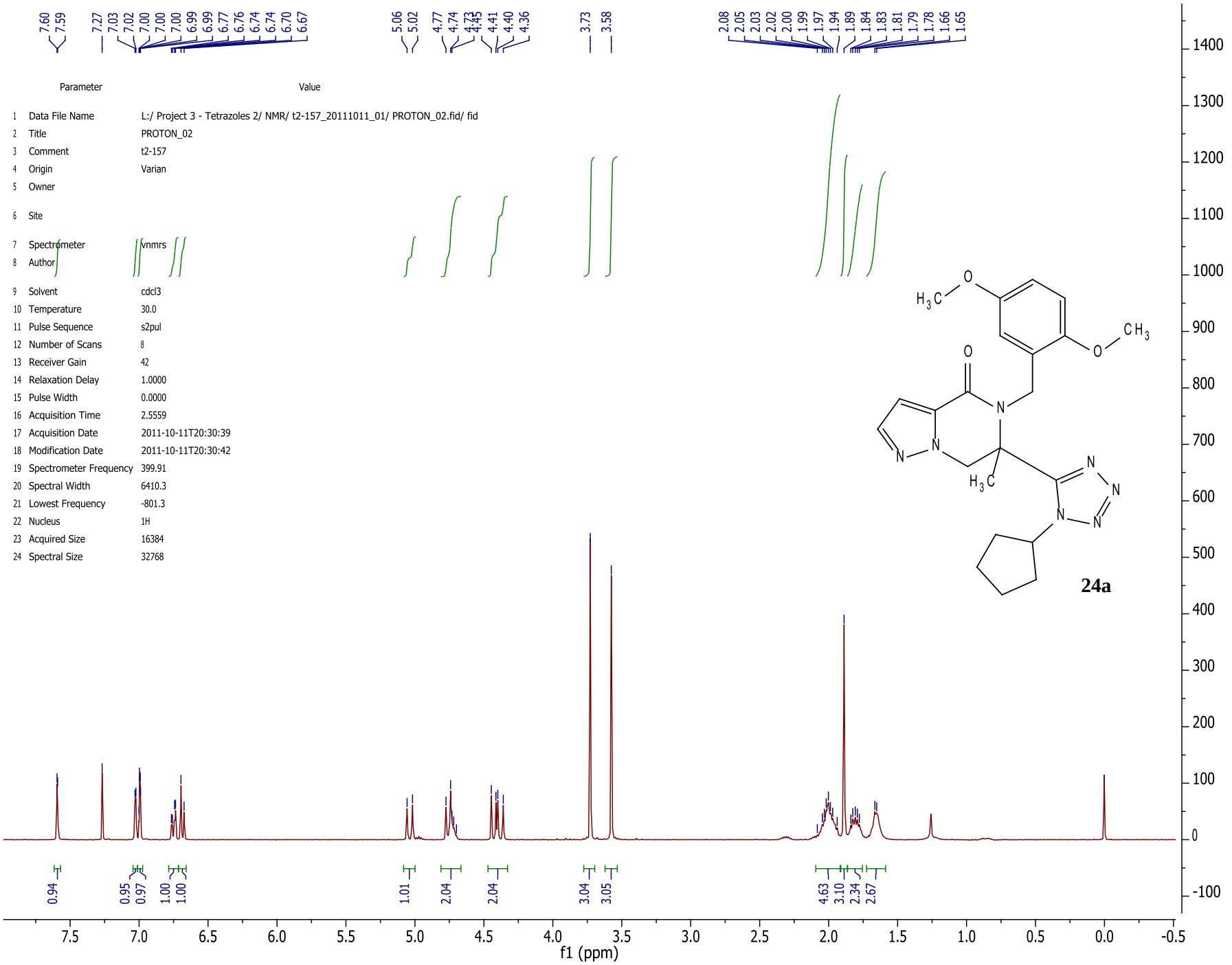
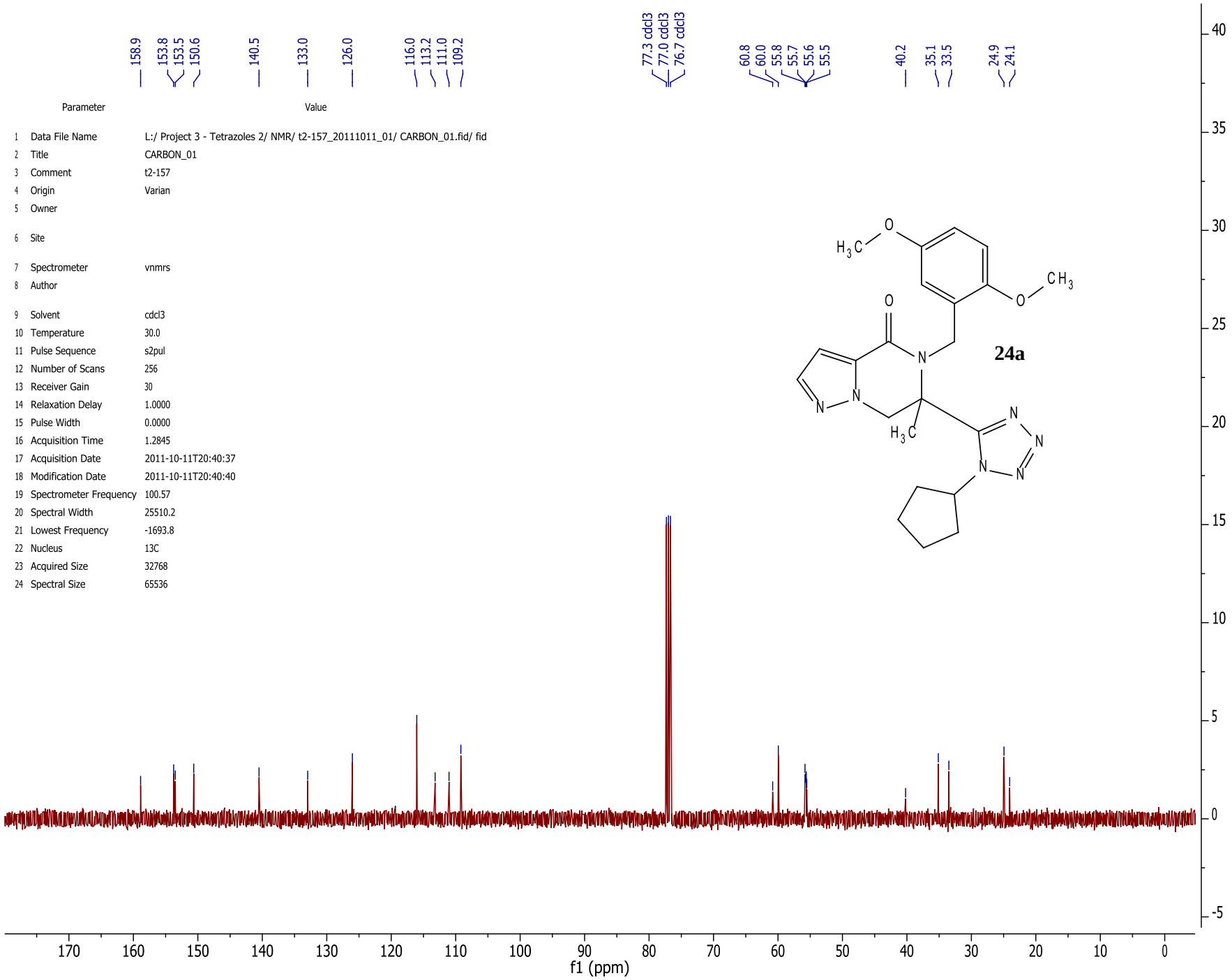
f1 (ppm)

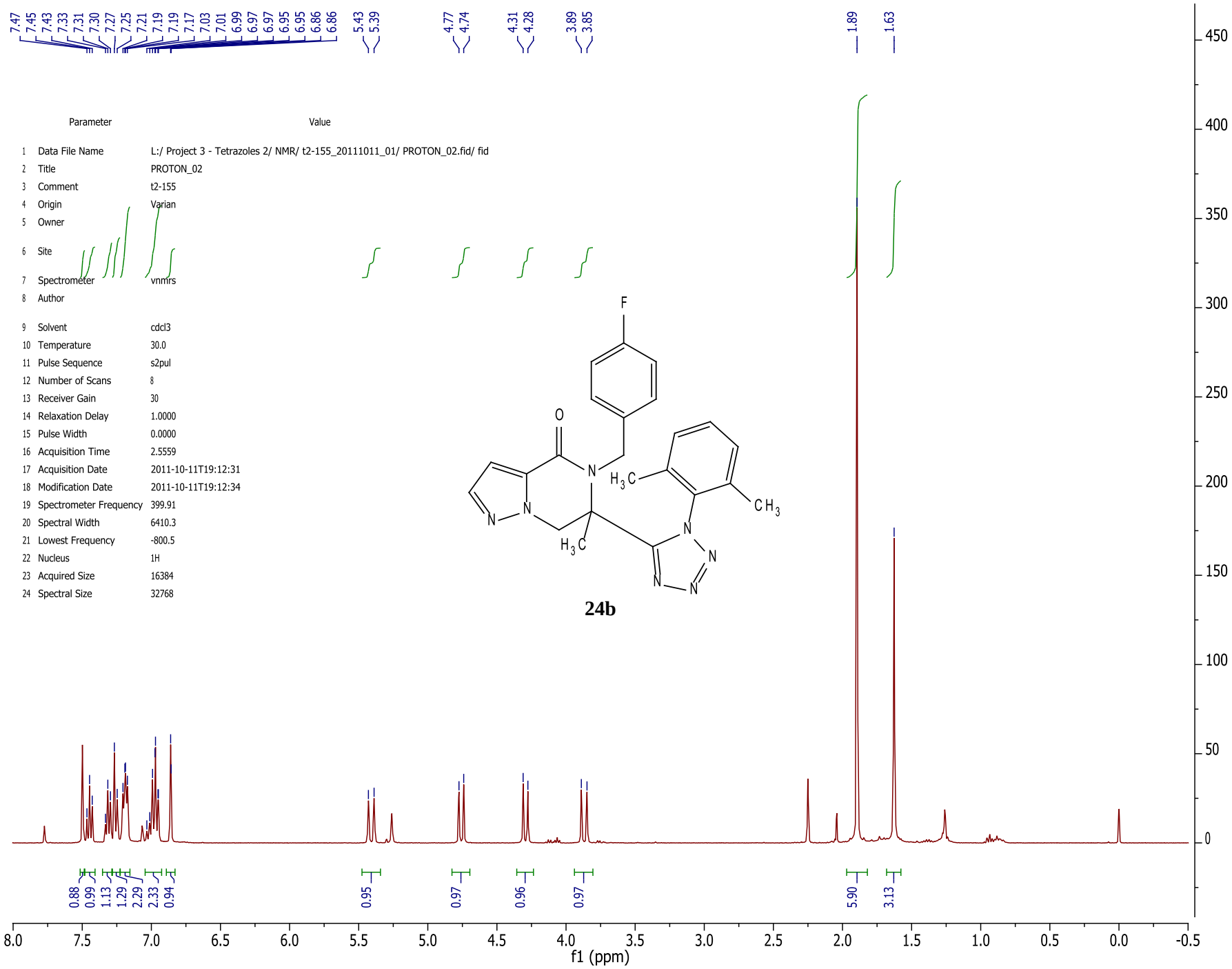


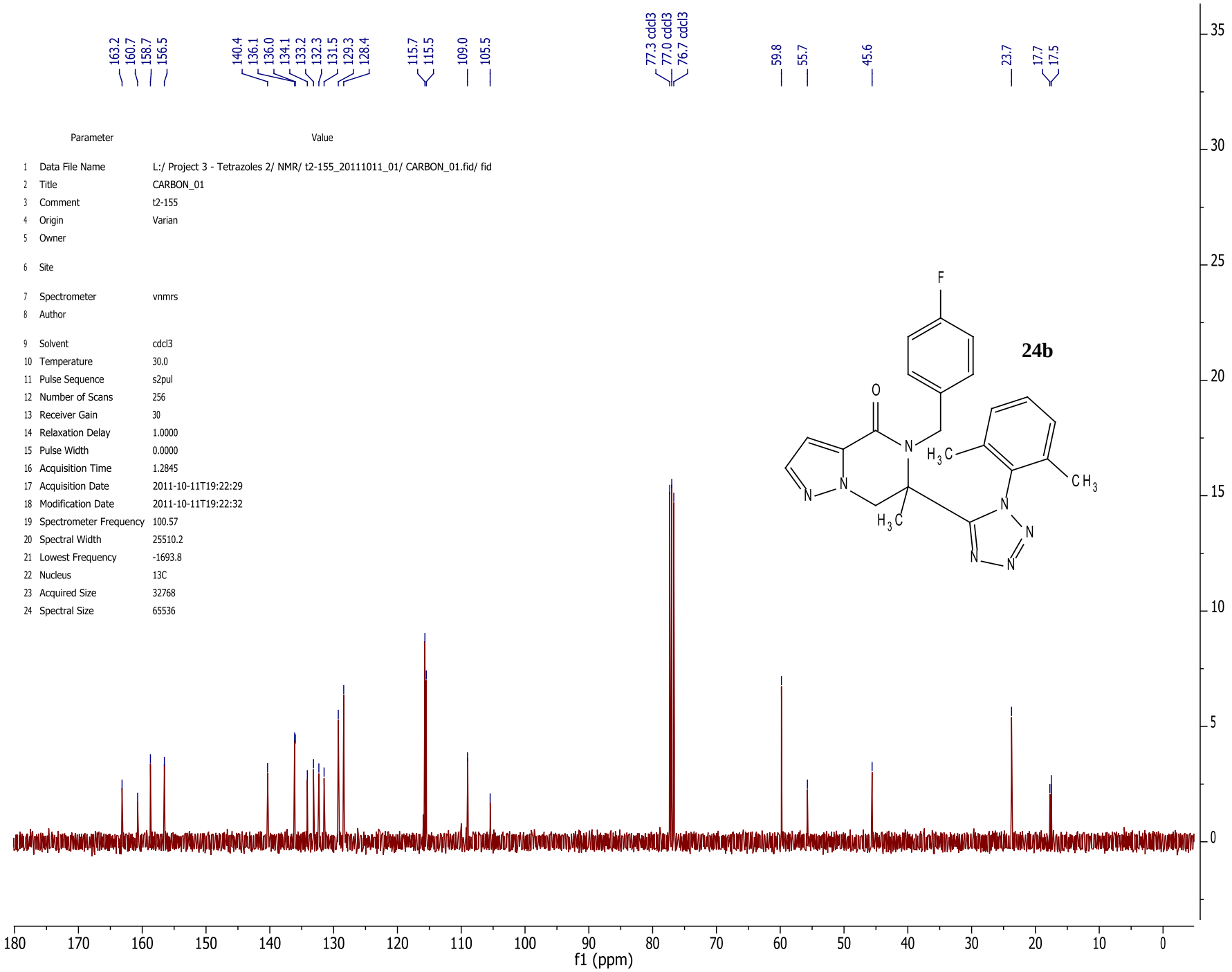


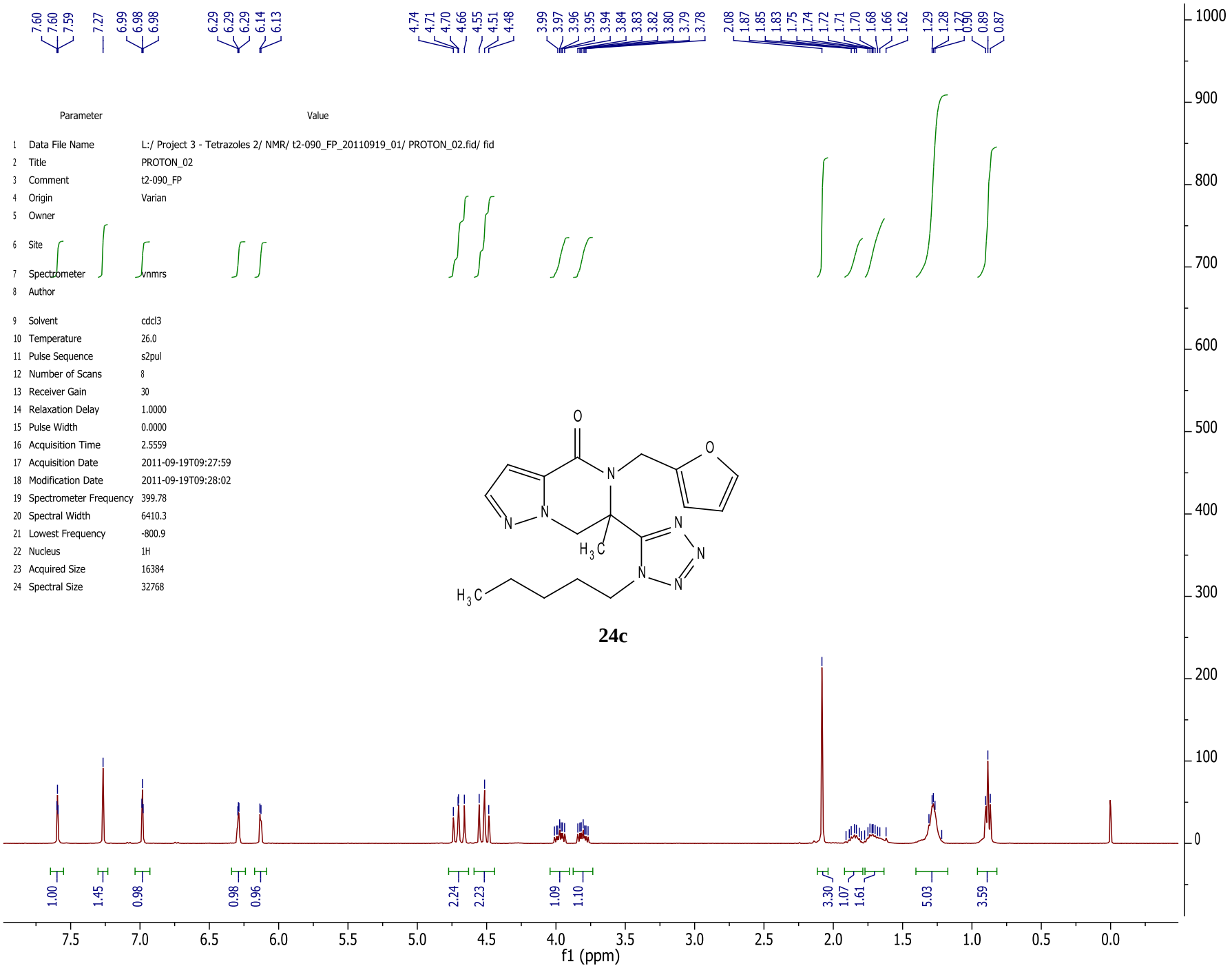












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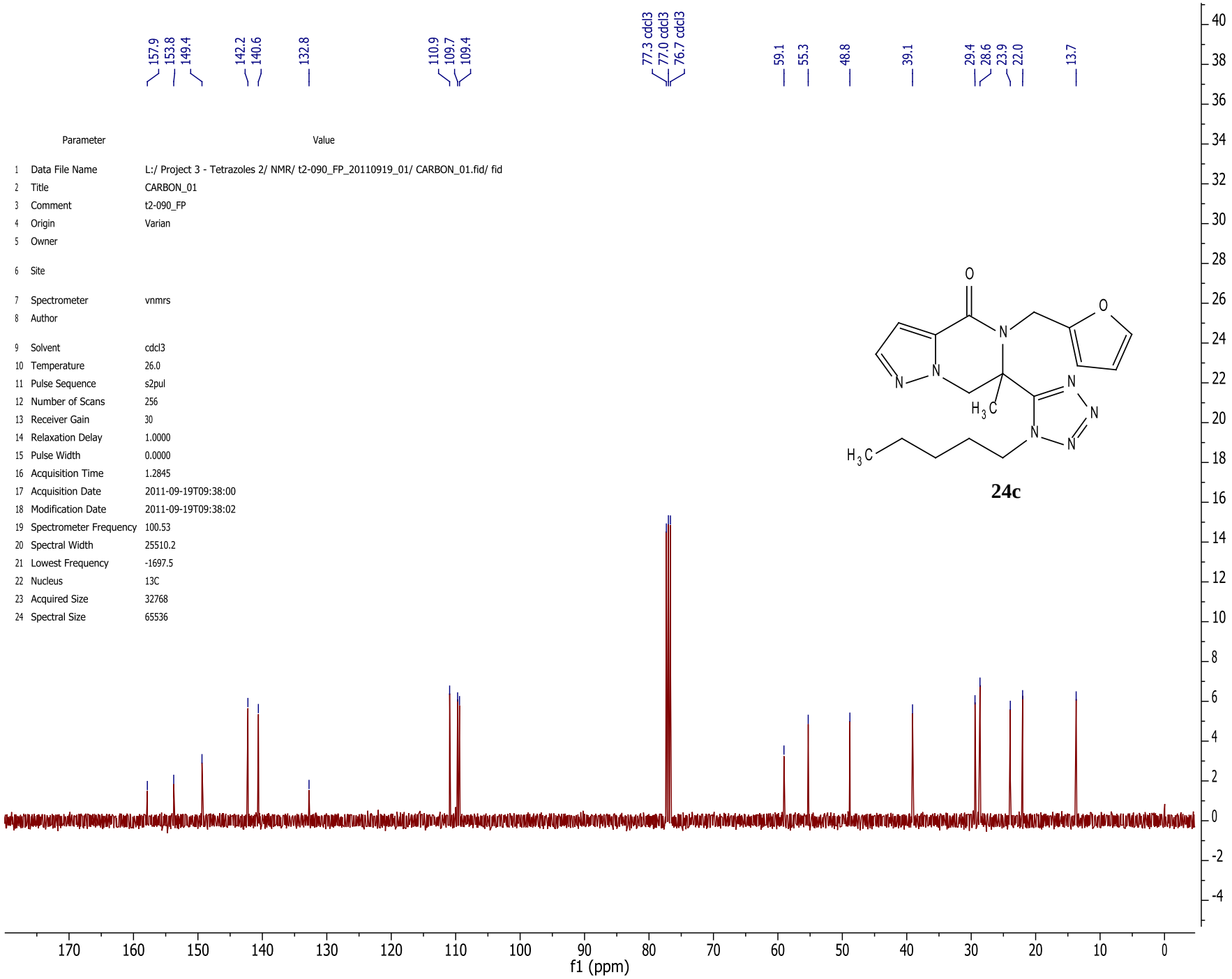
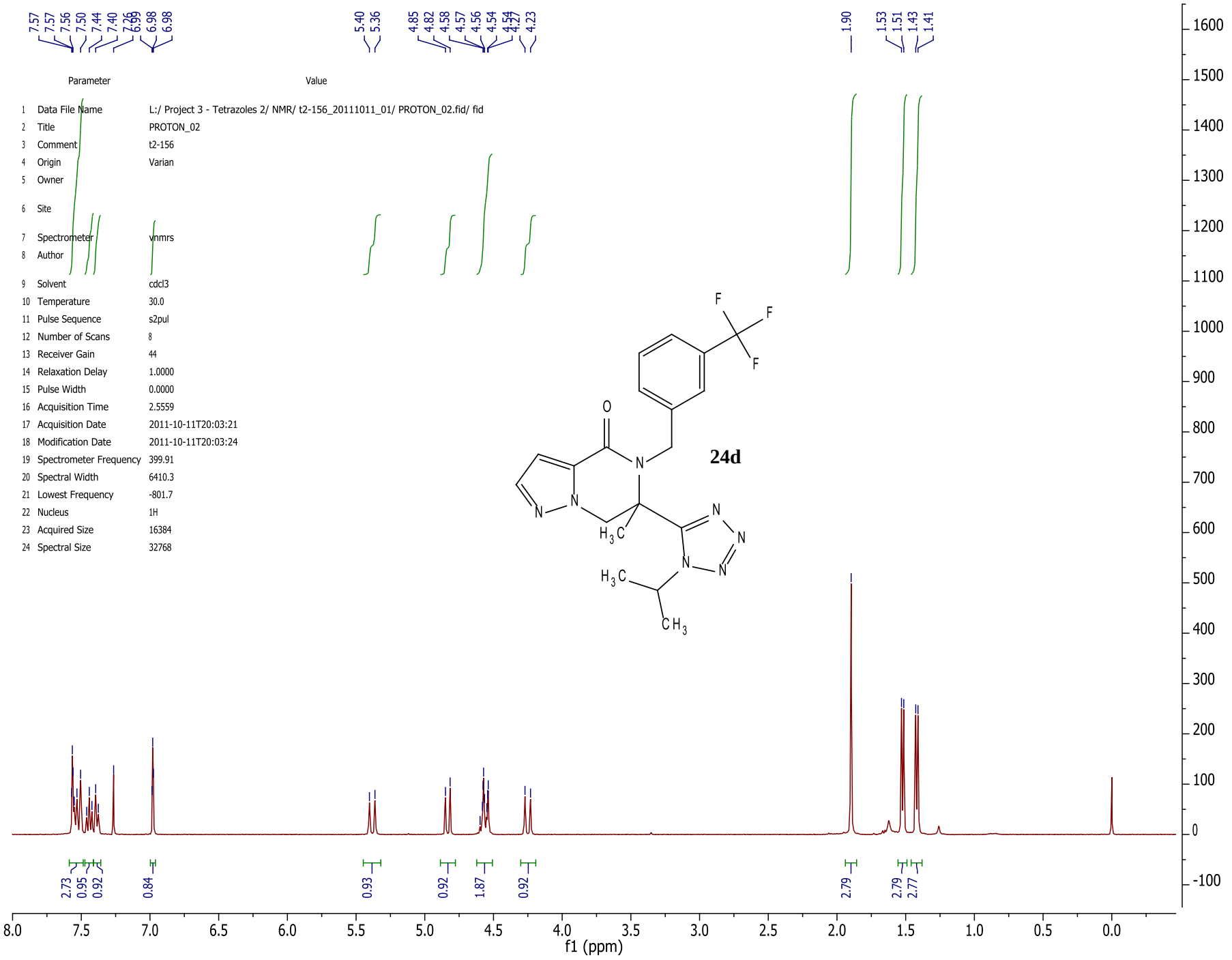
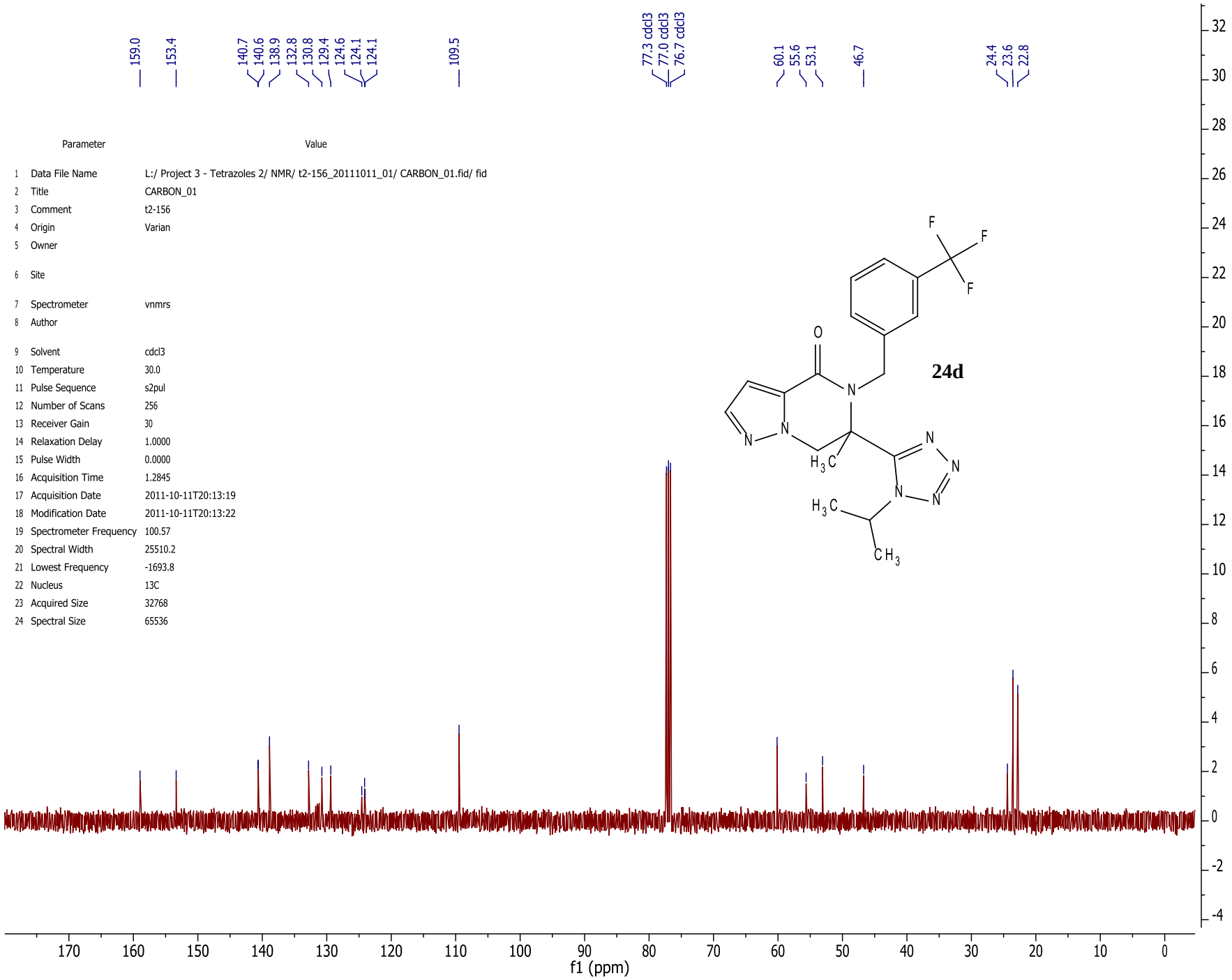
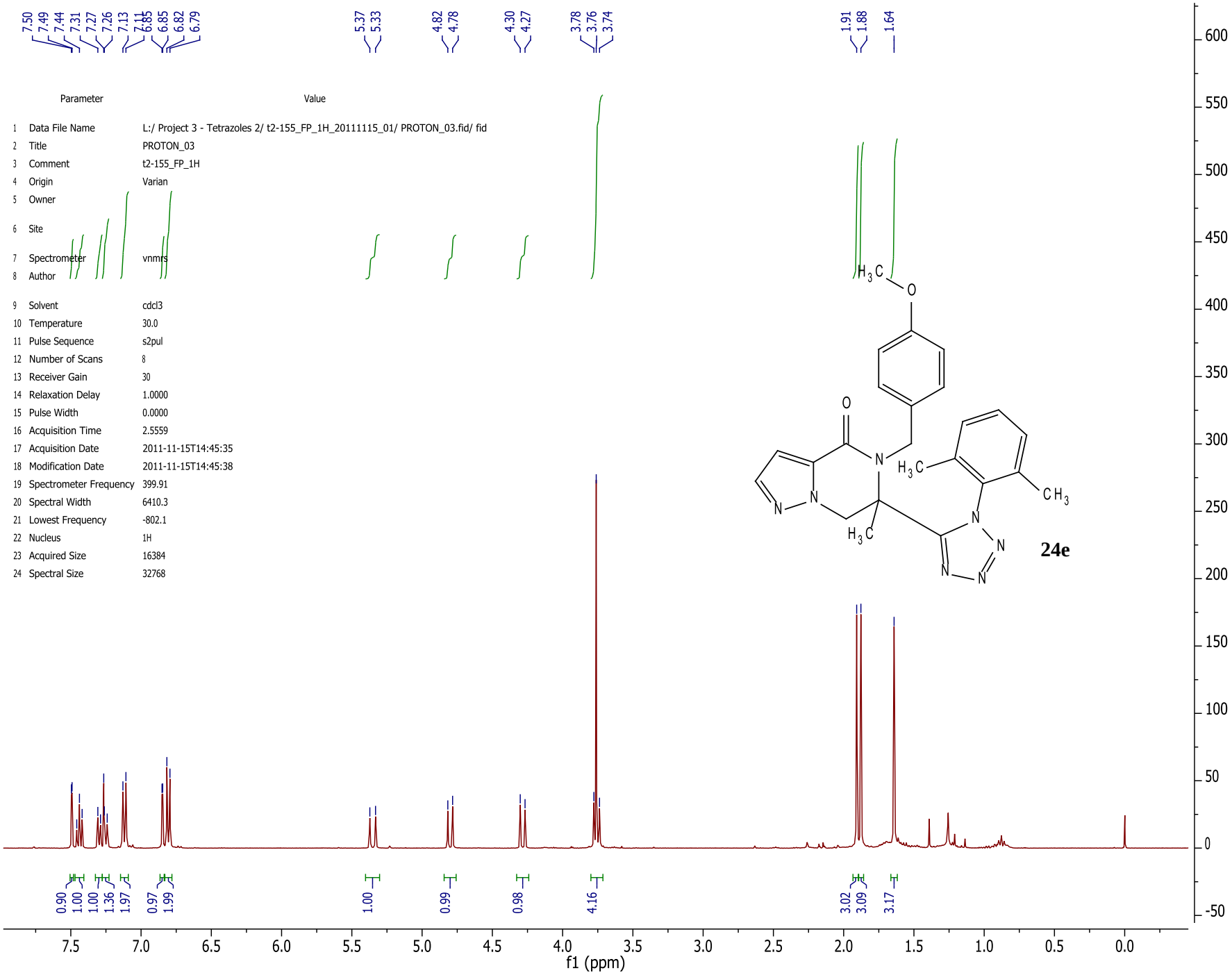
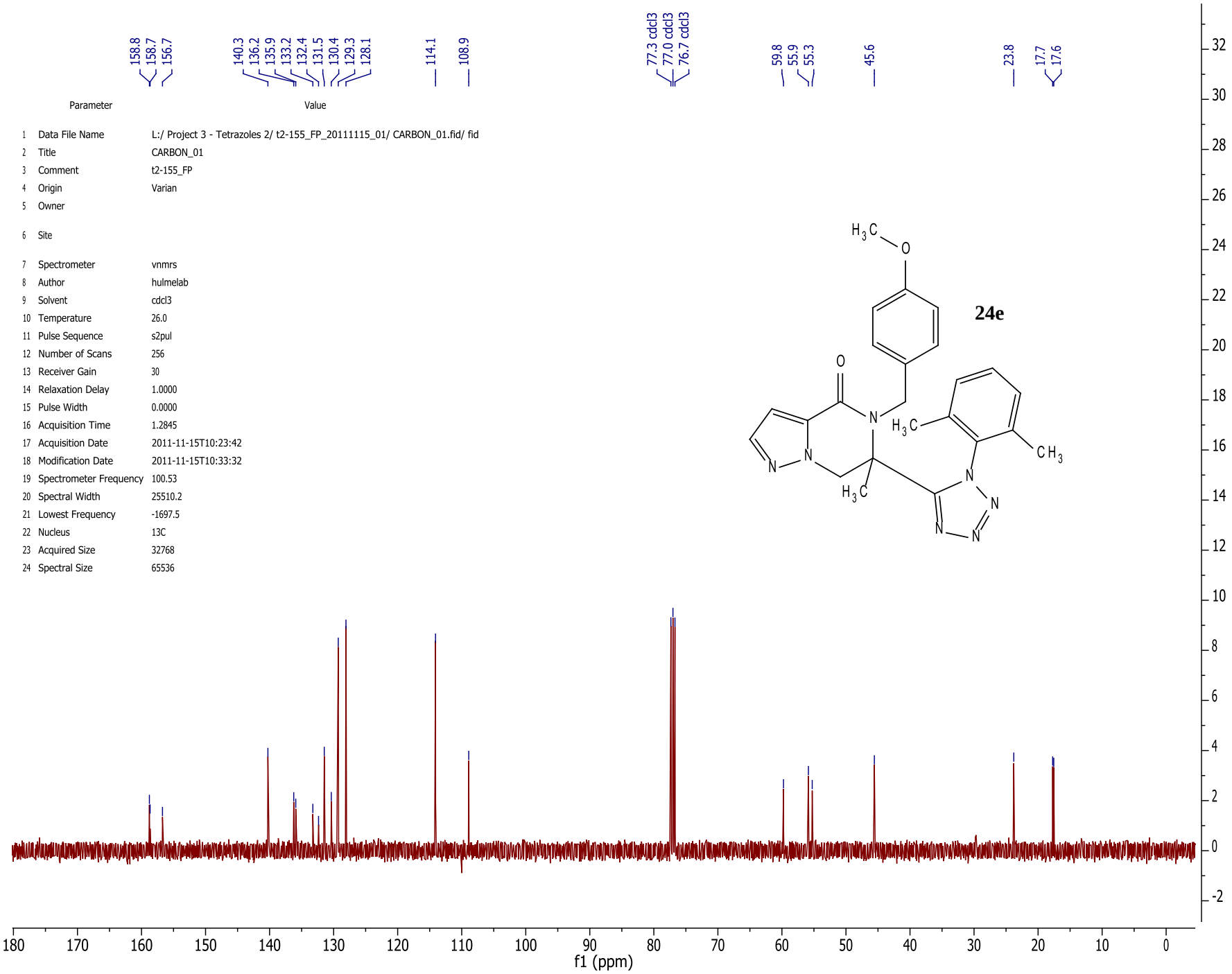
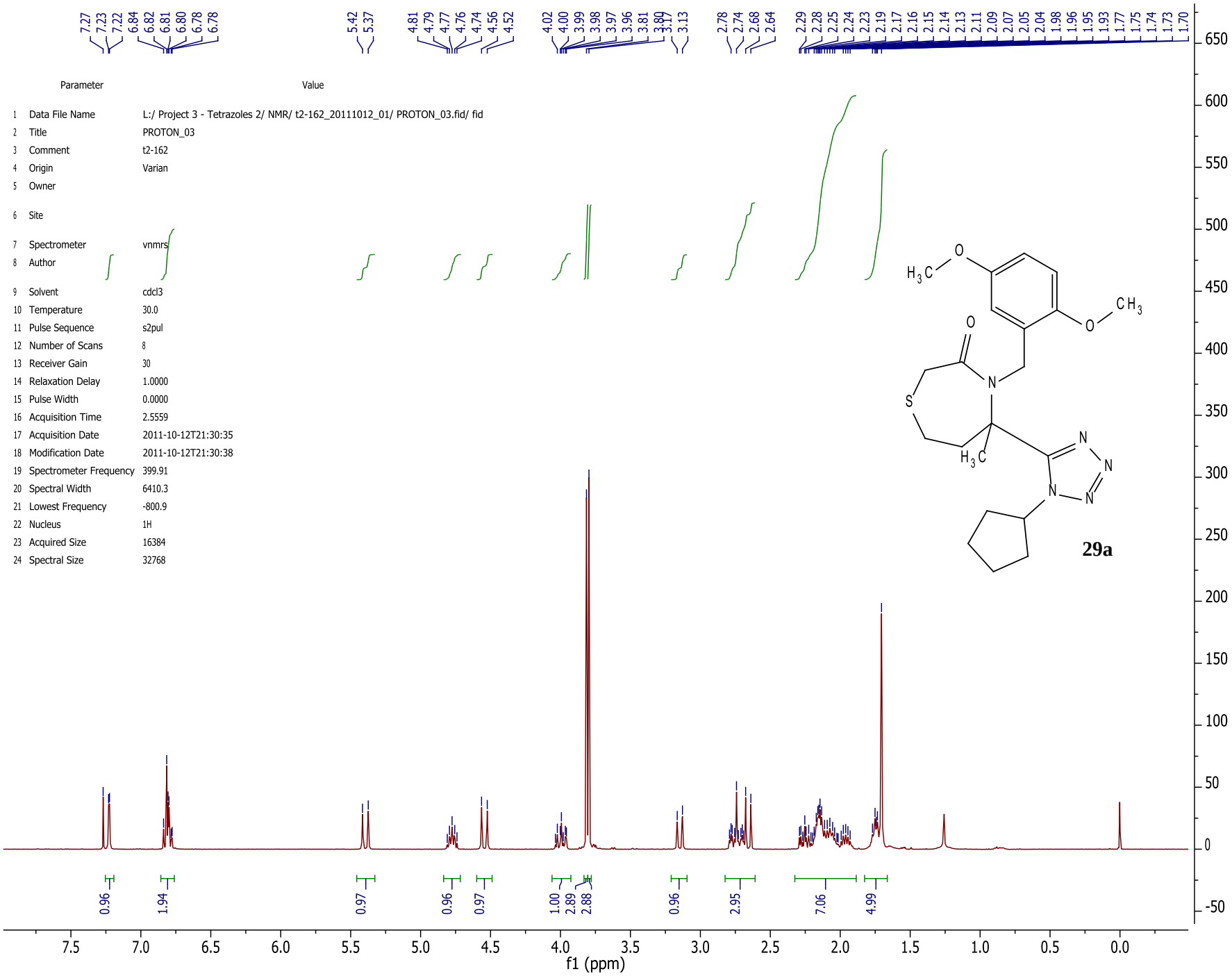


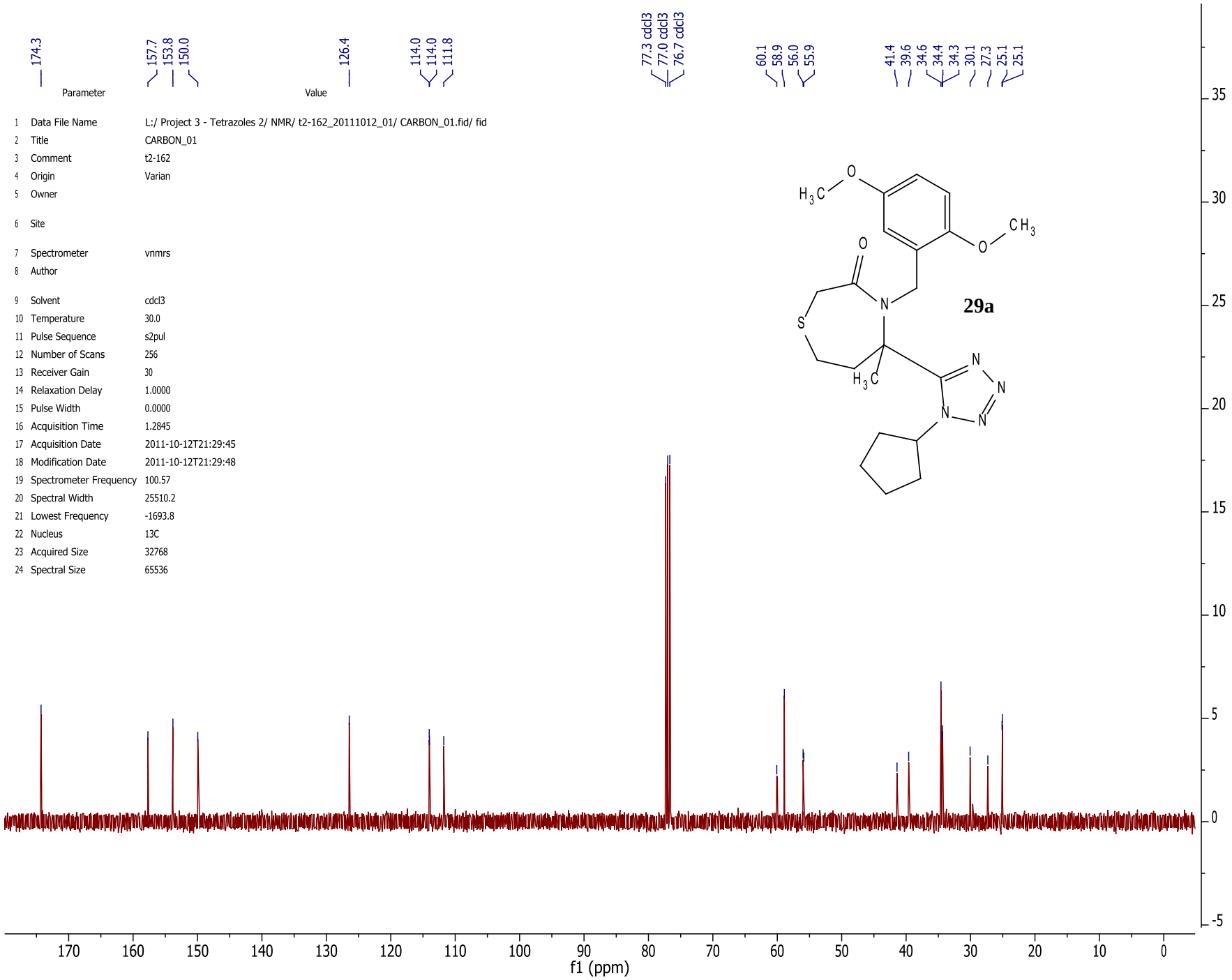


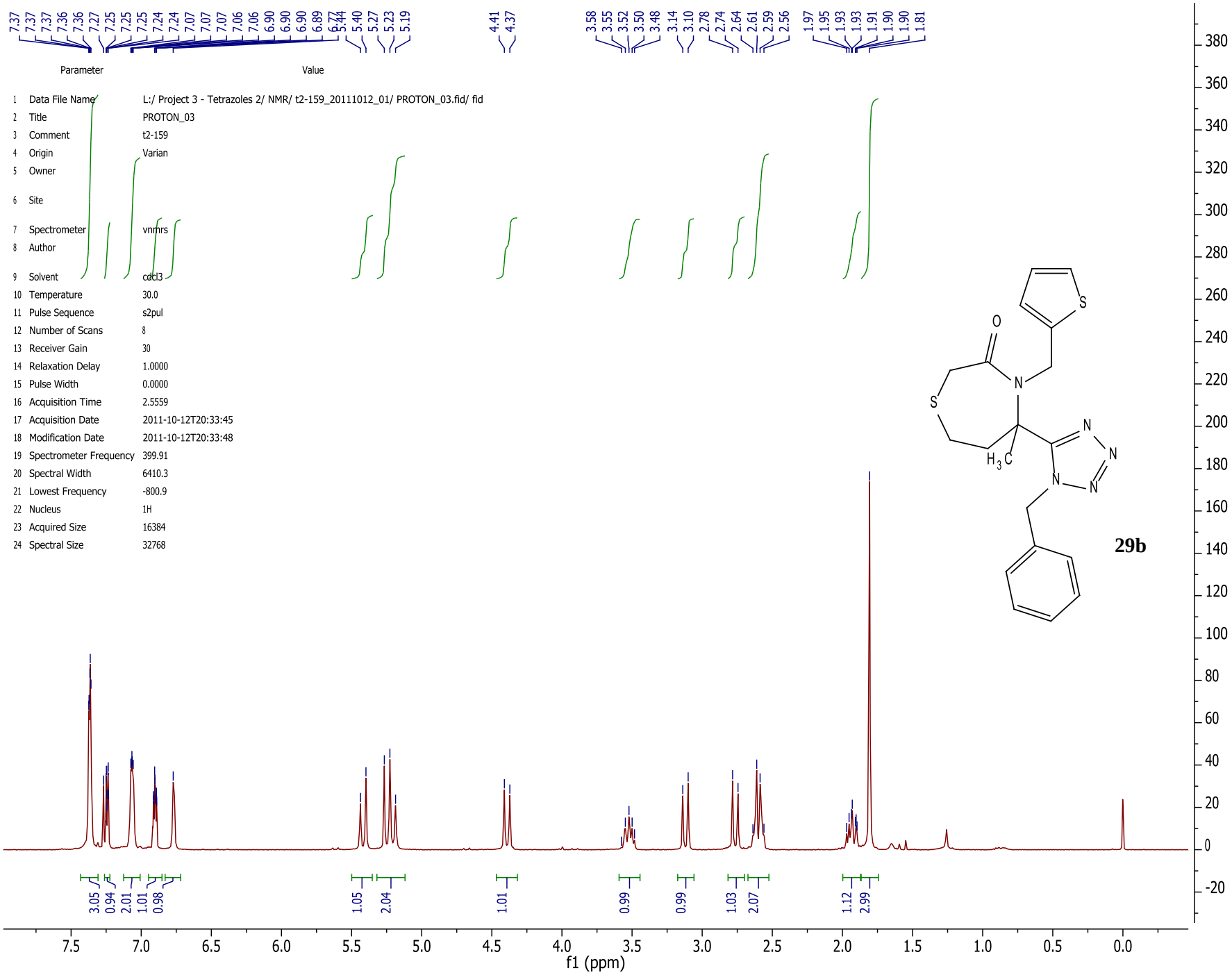


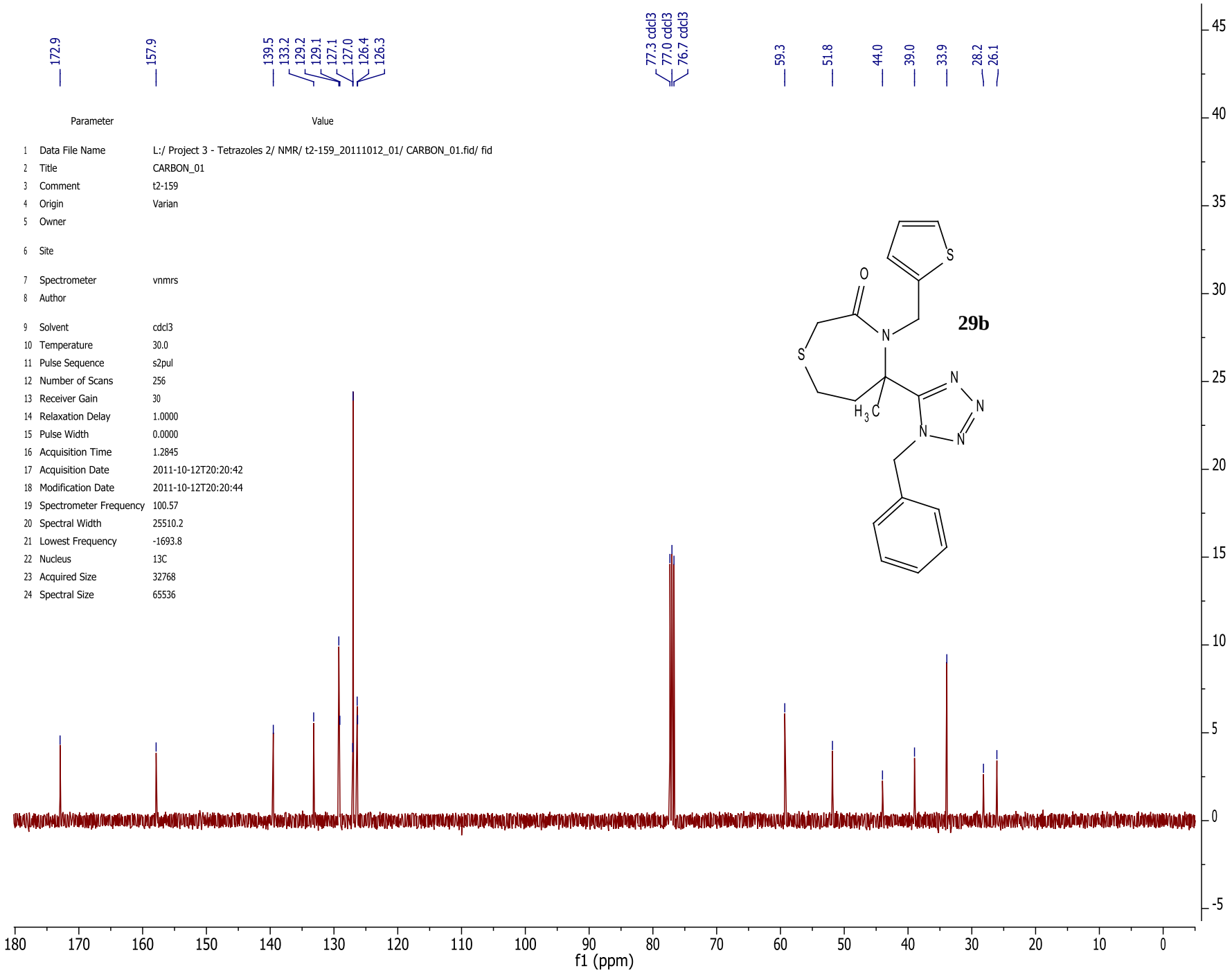


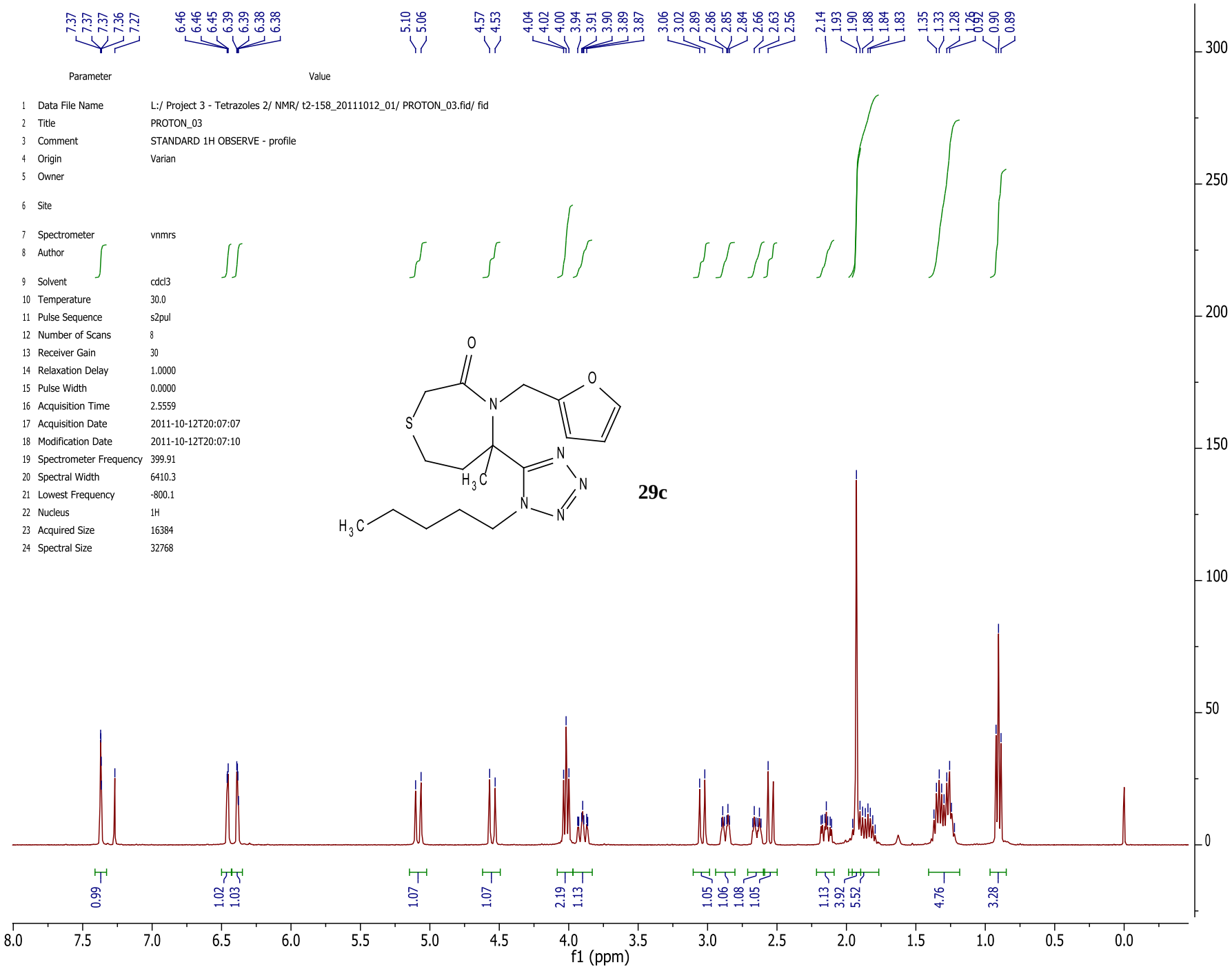


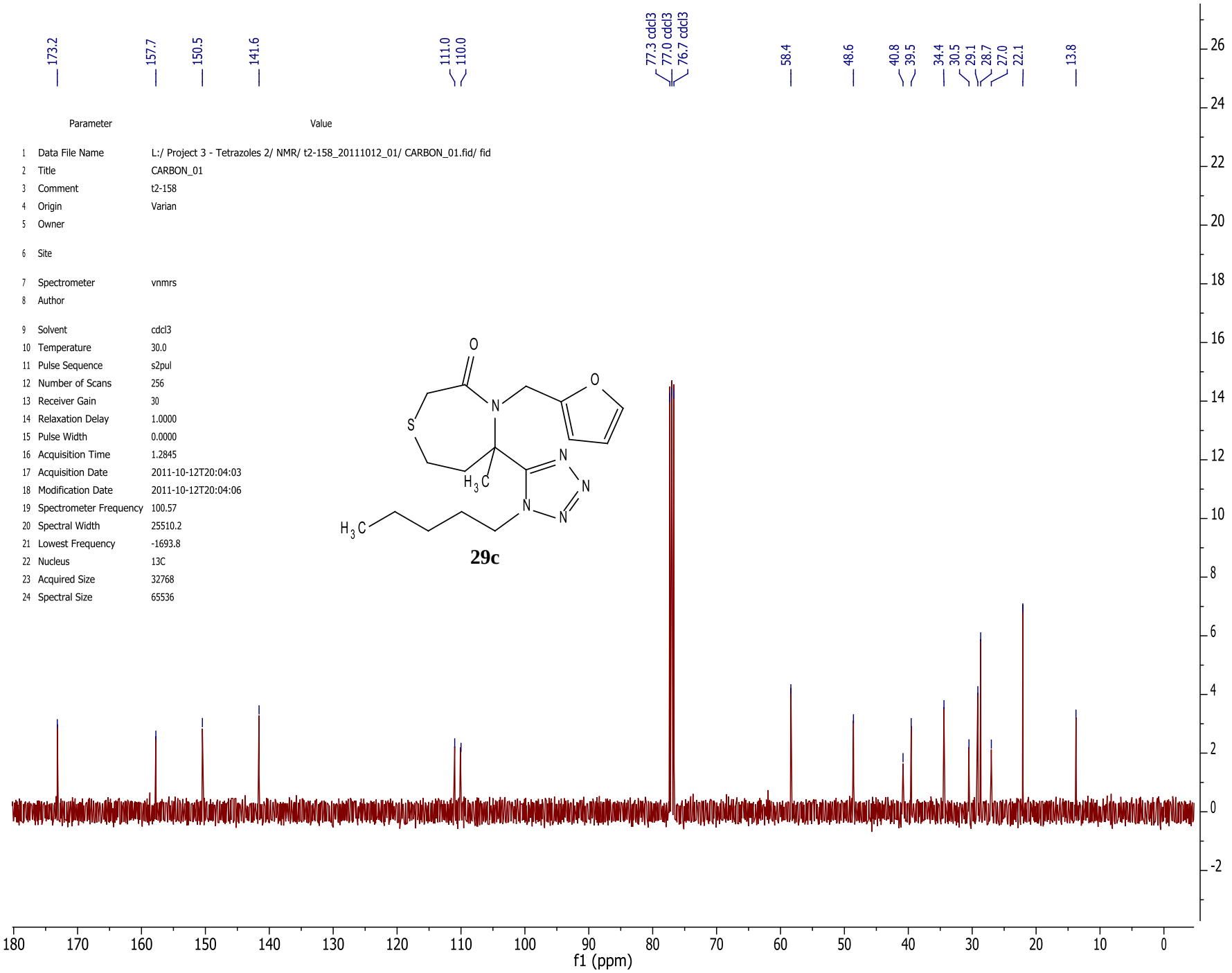


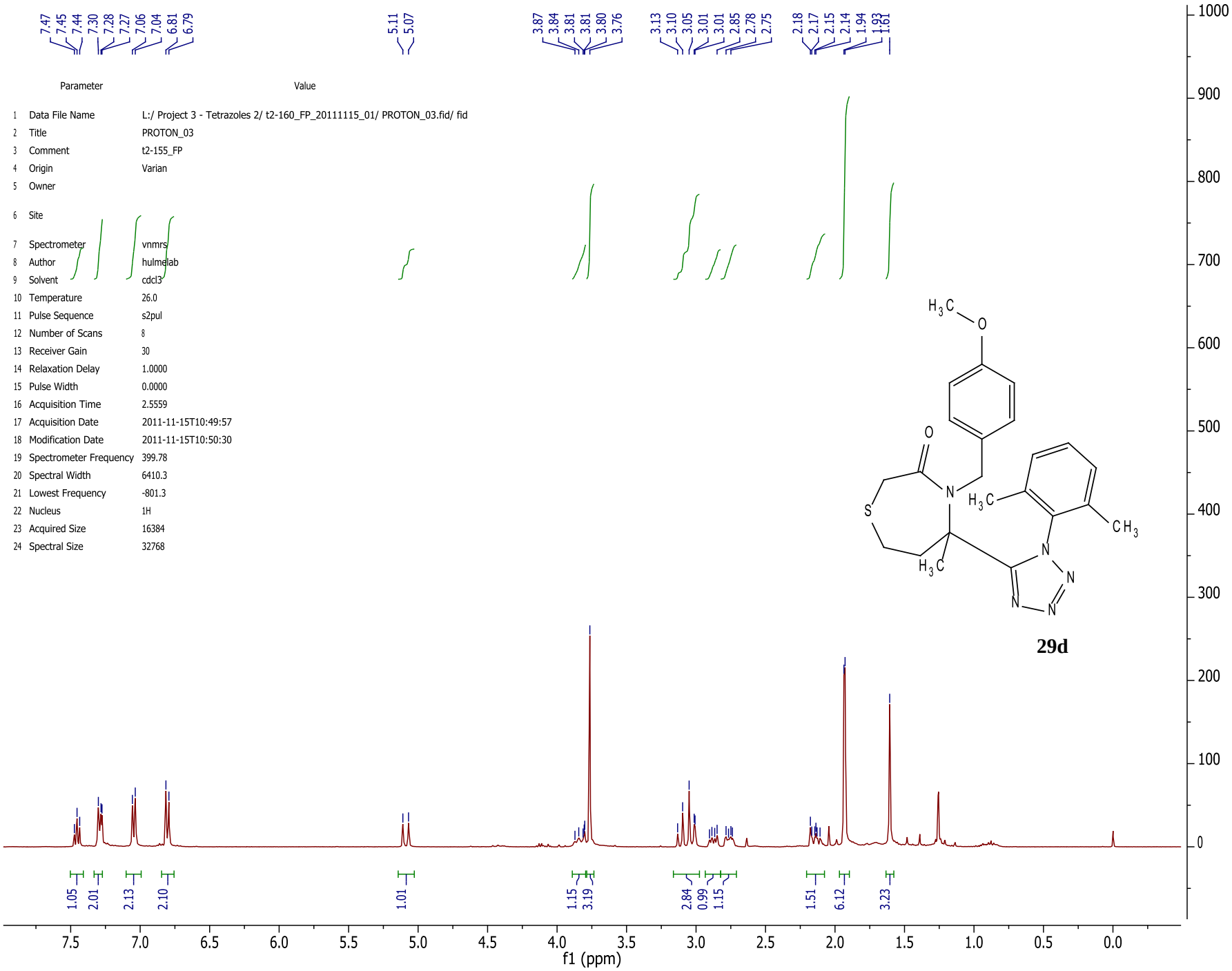




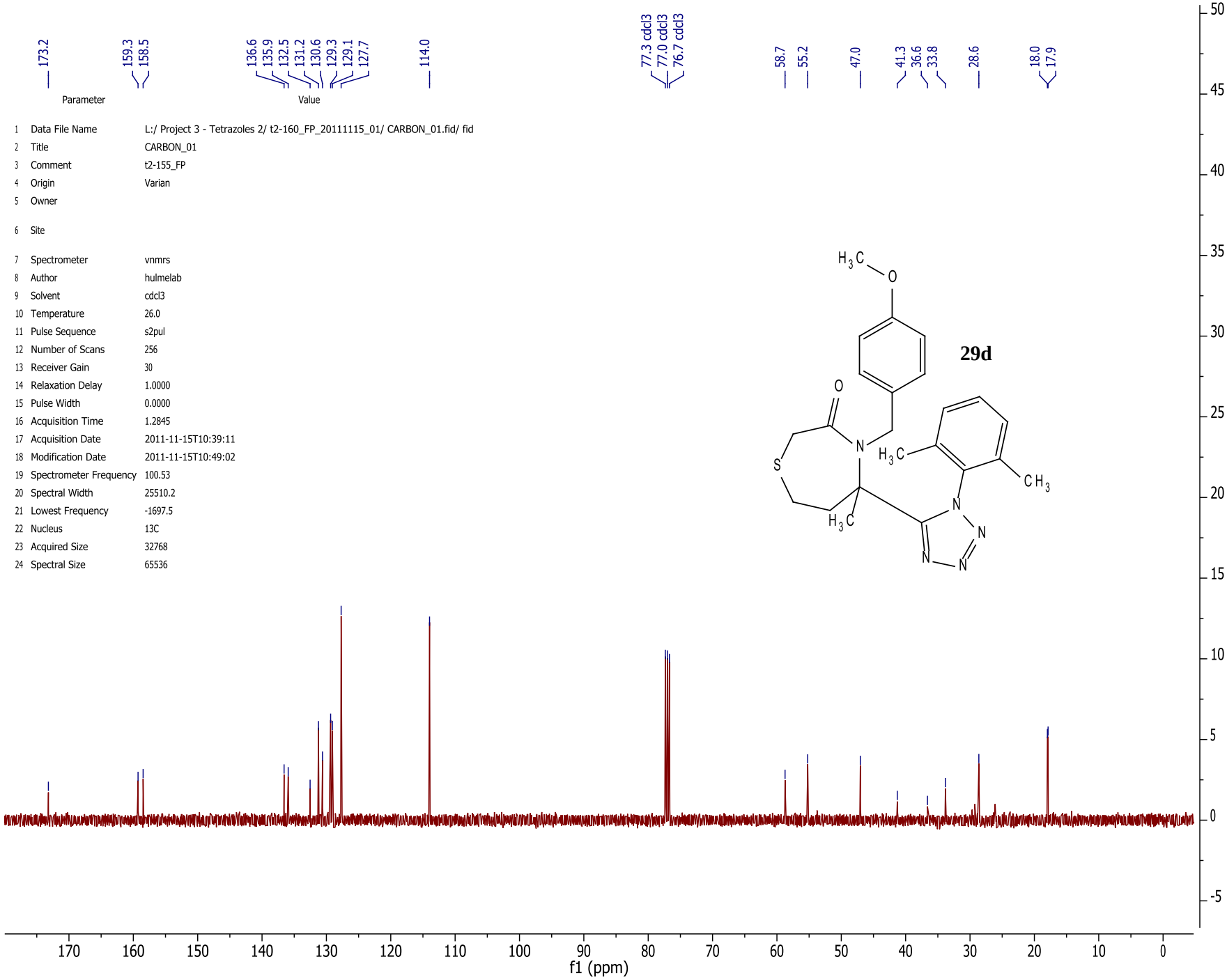


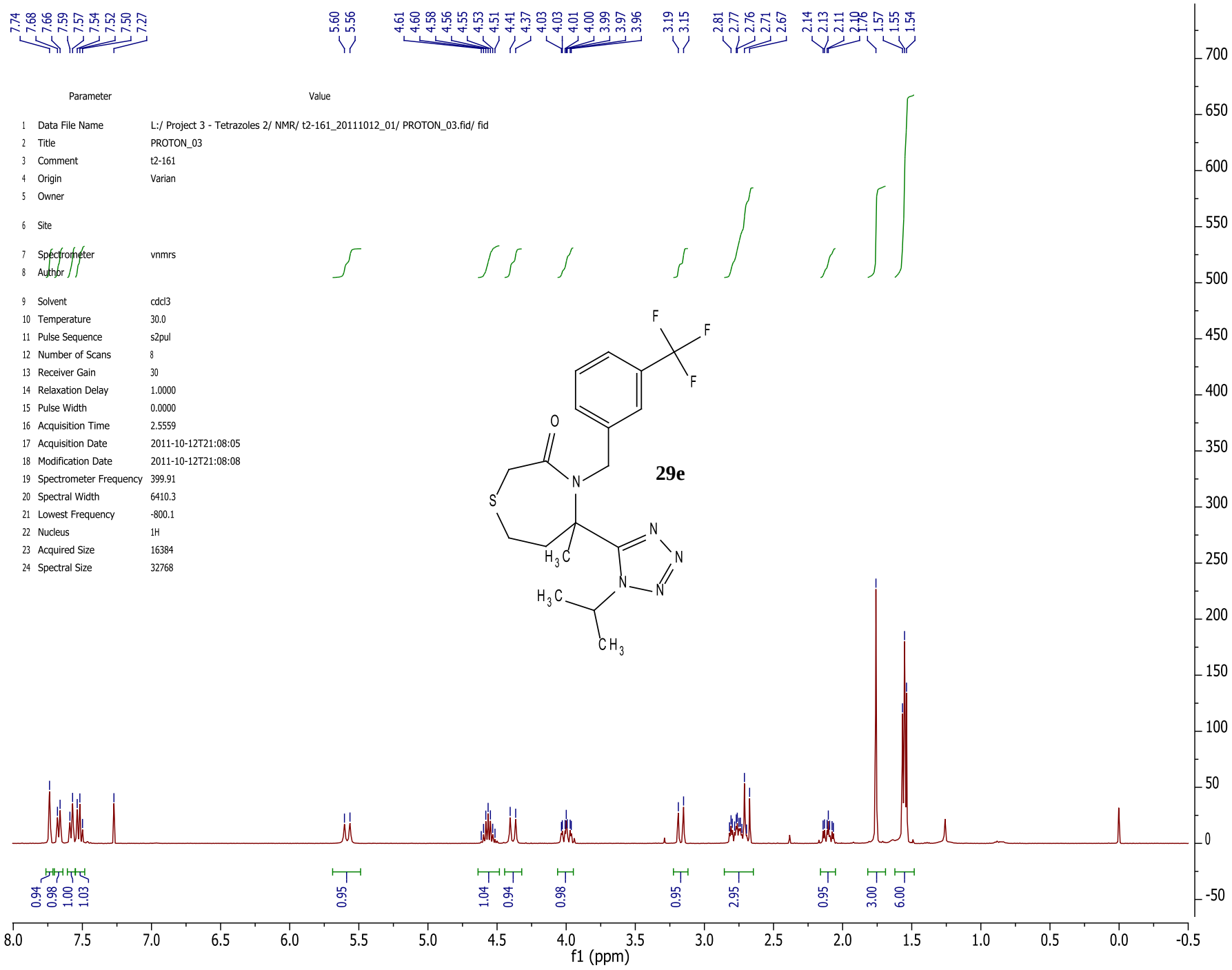


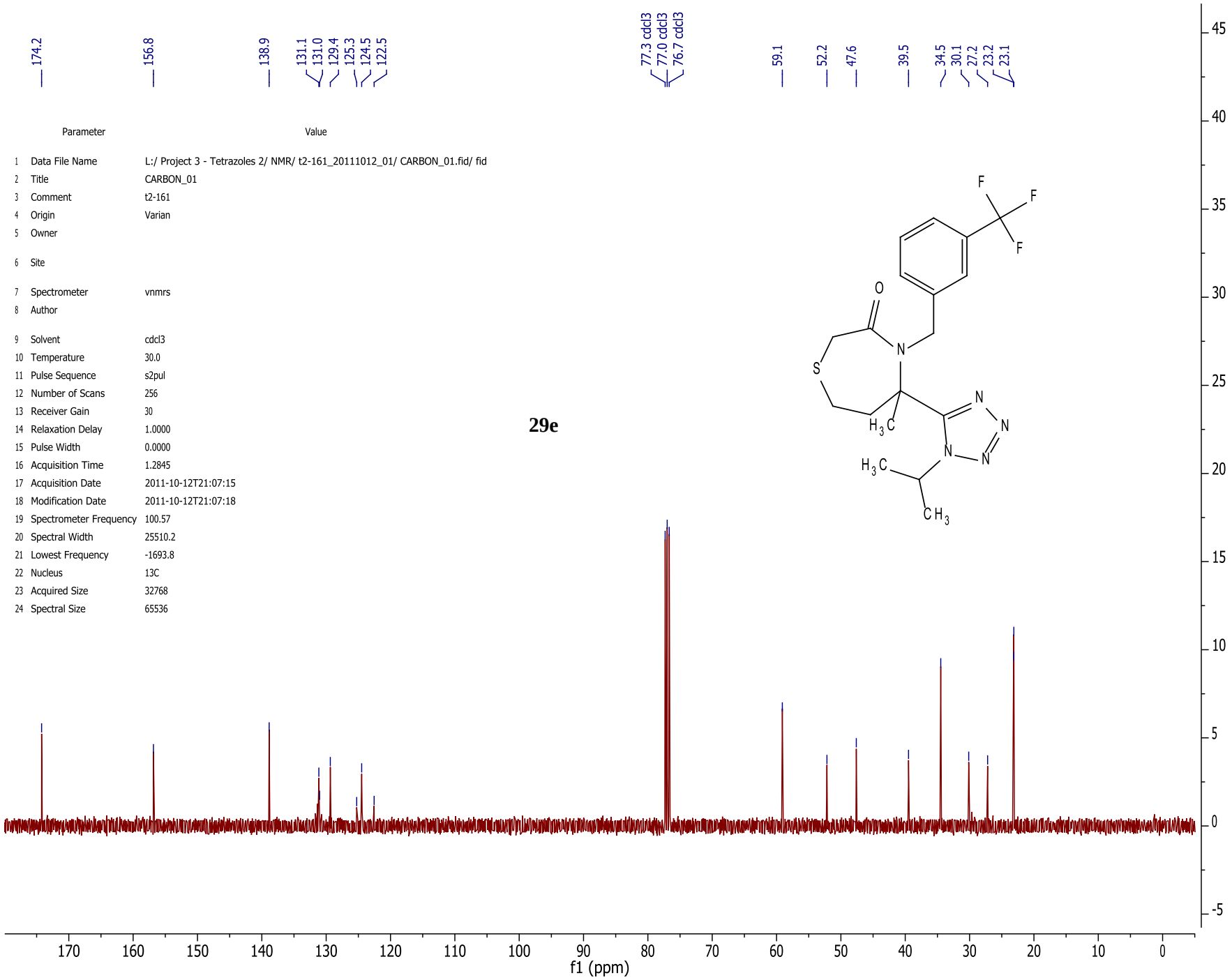


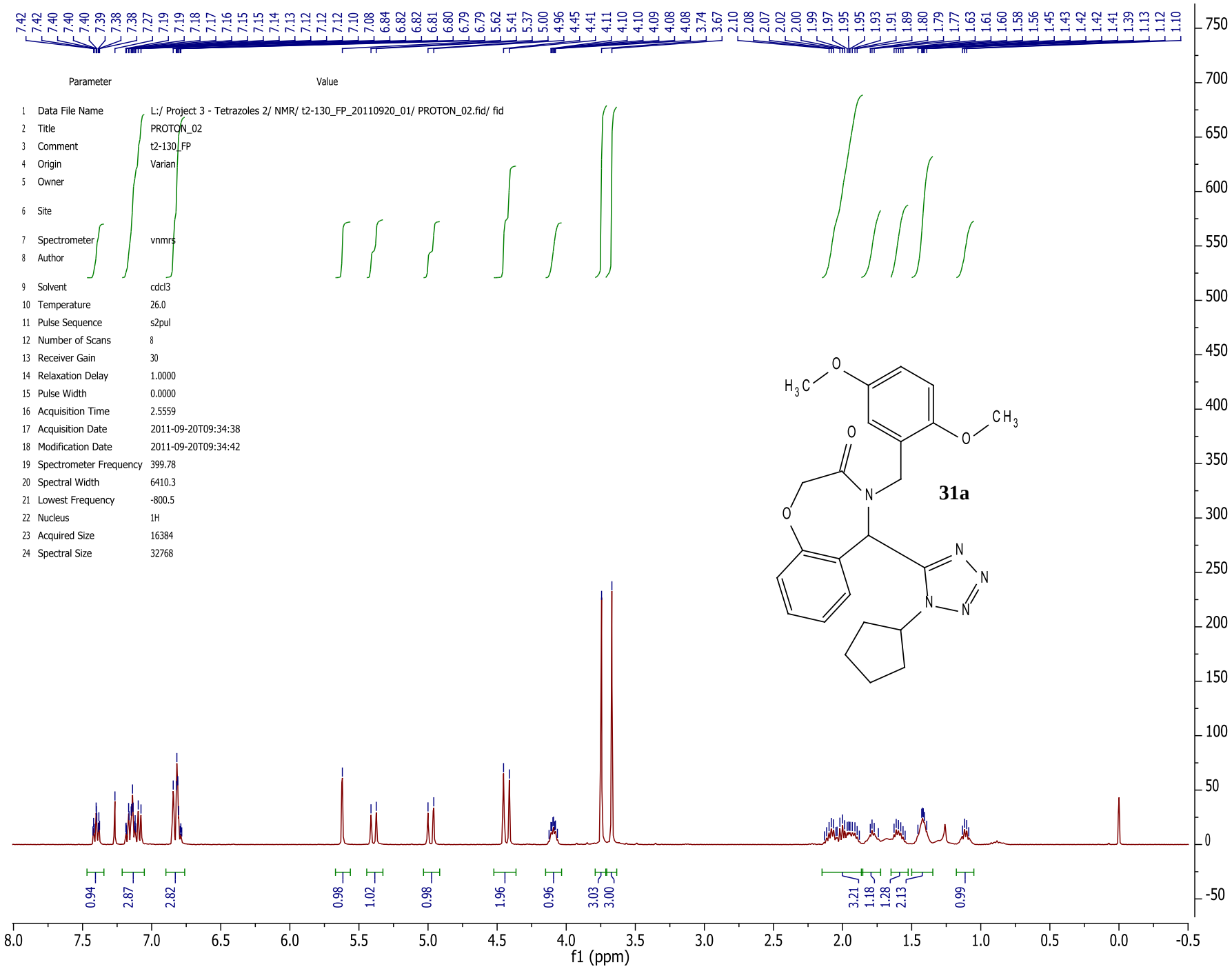


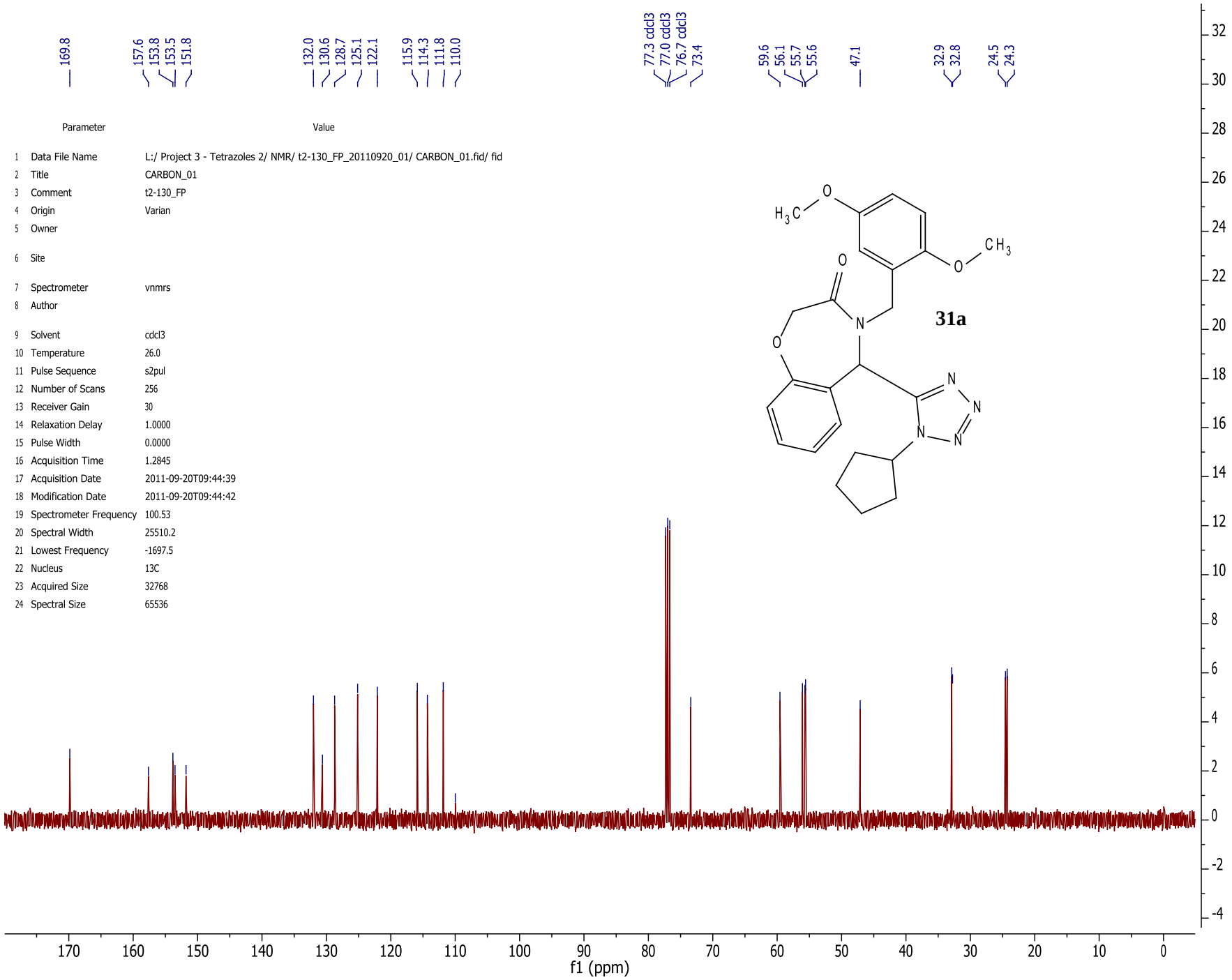
29d

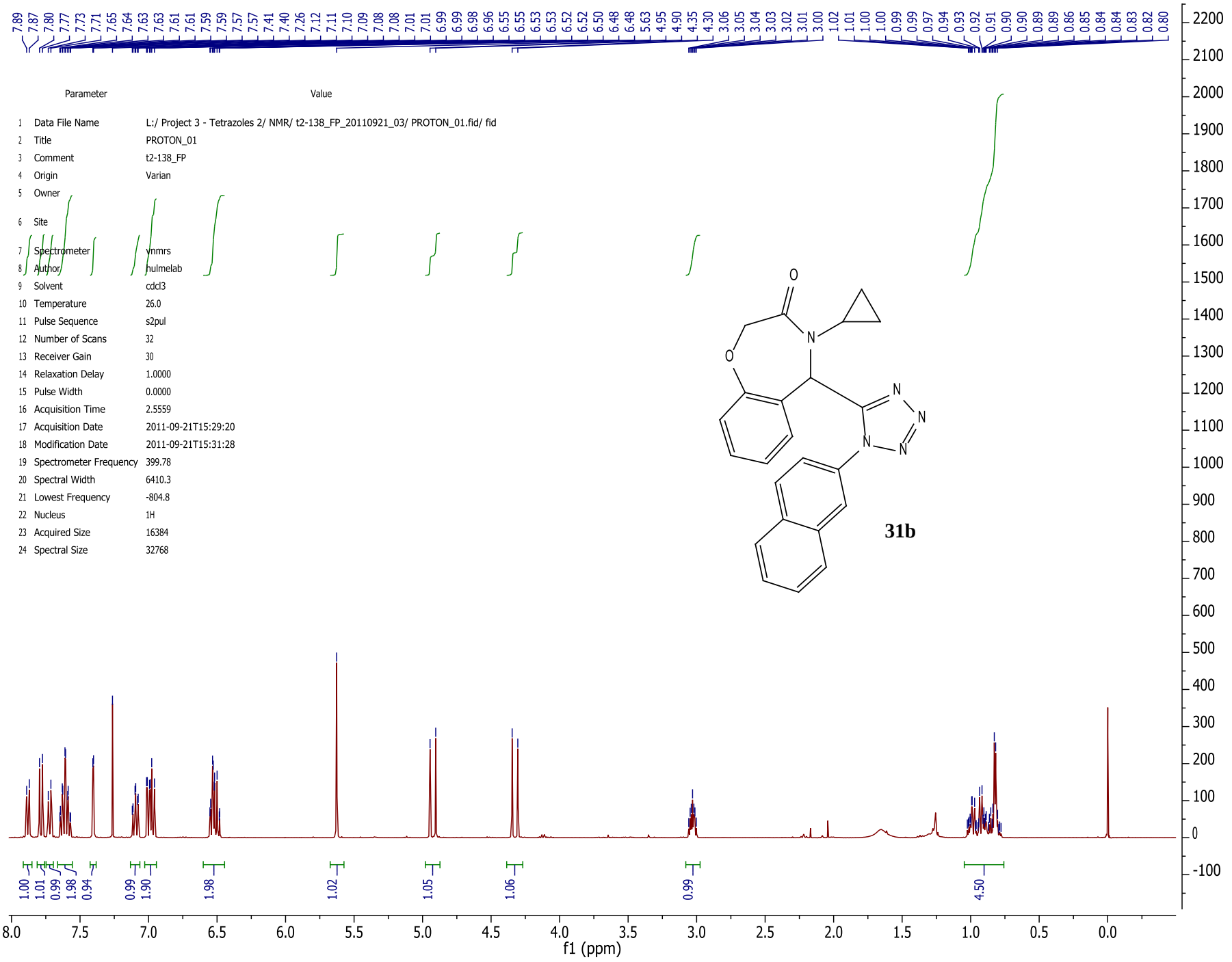


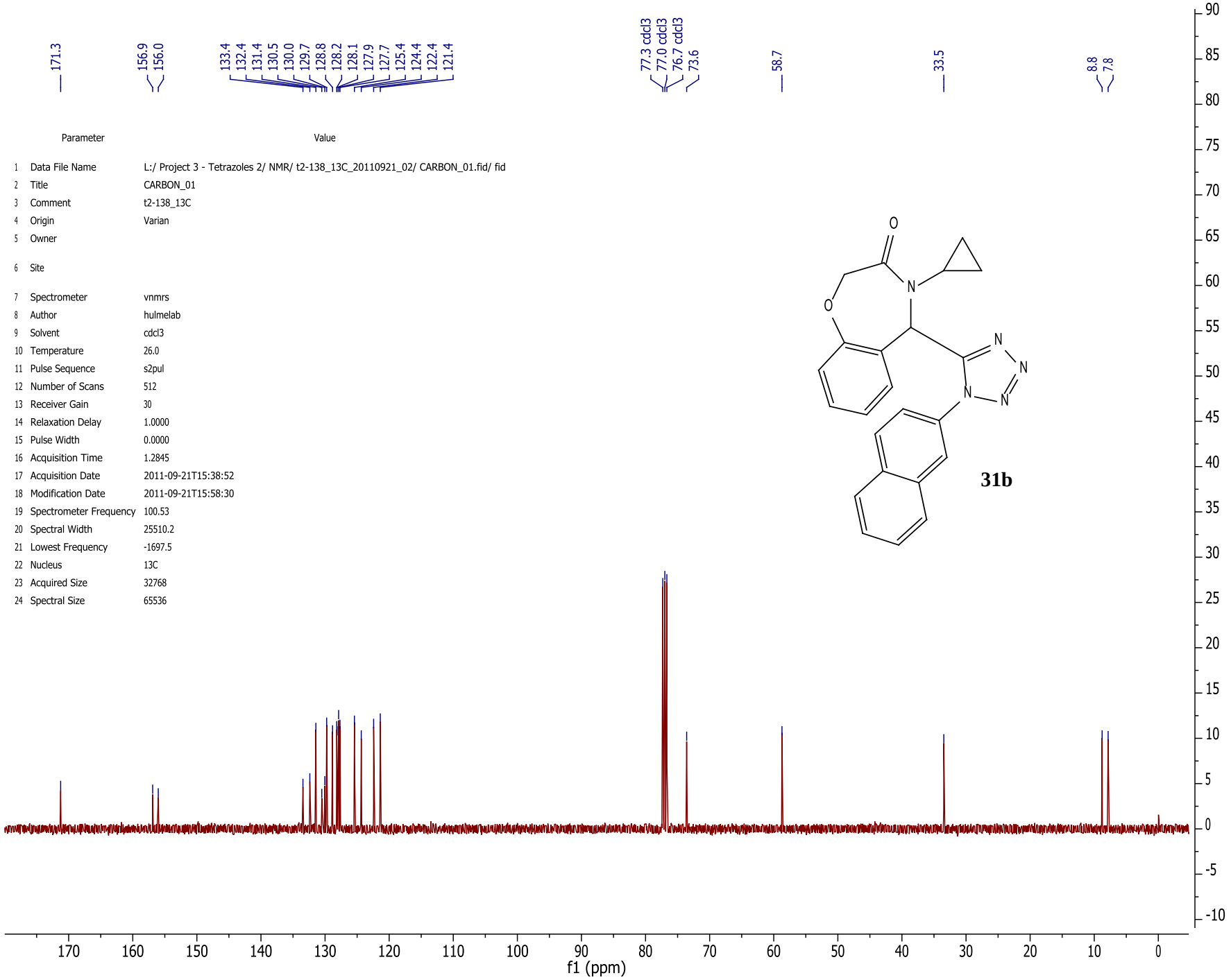


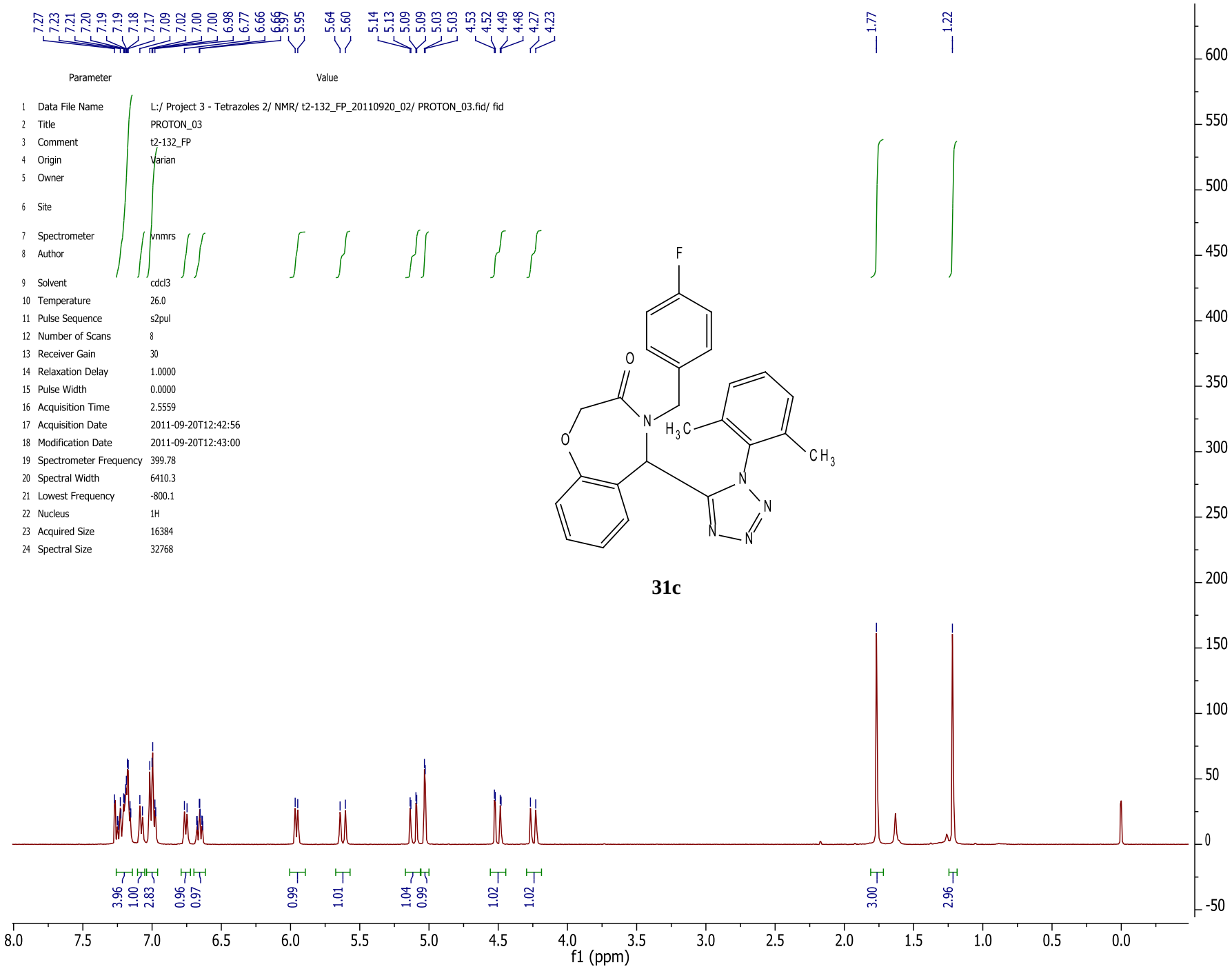








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4 Origin Varian
5 Owner
6 Site
7 Spectrometer vnmrs
8 Author
9 Solvent cdcl3
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11 Pulse Sequence s2pul
12 Number of Scans 8
13 Receiver Gain 30
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15 Pulse Width 0.0000
16 Acquisition Time 2.5559
17 Acquisition Date 2011-09-20T12:42:56
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19 Spectrometer Frequency 399.78
20 Spectral Width 6410.3
21 Lowest Frequency -800.1
22 Nucleus 1H
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24 Spectral Size 32768
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CH3
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N
N
N
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31c