Supporting information

Carbon Dioxide as the C1 Source for Direct C—H Functionalization of Aromatic Heterocycles

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Experimental Section

Chemicals and Reagents

Loading of reagents for carboxylation was carried out under an inert N_2(g) atmosphere using glovebox techniques. Solvents were purified using a two-column solid-state purification system (Innovative Technology, NJ, USA) and transferred to the glove box without exposure to air. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., and were degassed and stored over activated 3 Å molecular sieves. Unless noted, all other reagents were purchased from commercial sources and used without further purification. Liquid compounds were degassed by standard freeze-pump-thaw procedures prior to use in the glovebox. Oxazole substrates were prepared according to a general procedure.[1]

Physical methods

The ^{1}H and ^{13}C NMR spectra were recorded at 293 K on a Bruker Avance 400 spectrometer. ^{1}H NMR chemical shifts were referenced to residual solvent as determined relative to Me_4Si ($\delta = 0$ ppm). The $^{13}C\{^{1}H\}$ chemical shifts were reported in ppm relative to the carbon resonance of $CDCl_3$ (77.00 ppm). GC-MS measurements were conducted on a Perkin-Elmer Clarus 600 GC equipped with Clarus 600T MS. GC measurement was conducted on a Perkin-Elmer Clarus 400 GC with a FID detector. HRESI-MS measurements were conducted at the EPFL ISIC Mass Spectrometry Service at Micro Mass QTOF Ultima. Elemental analyses were performed on a Carlo Erba EA 1110 CHN instrument at EPFL. Melting point measurements were conducted on Buchi Melting Point B-540.

[1] F. Besselievre, F. Mahuteau-Betzer, D. Grierson, S. Pigue, *J. Org. Chem.* **2008**, 73, 3278-3280.

General procedure for optimization of reaction conditions

(a). Optimized conditions

Benzothiazole (135 mg, 1 mmol) and the base (1.2 mmol) were placed in a 25 mL Schlenk flask. 2 mL of DMF was added. The reaction flask was degassed and flushed with CO_2 twice. After this, the mixture was heated at 125 ^{0}C for 16 h under a 400 mbar of overpressure of CO_2. Then the reaction mixture was cooled to room temperature, and the solvent was evaporated under vacuum. The products were analyzed by NMR.

(b). With other bases. The same conditions as in (a) were employed, except that other bases ($LiOBu^t$, NaOMe, NaOH, KOH, K_2CO_3, K_3PO_4) were used in the place of Cs_2CO_3.

(c). With CuI and $LiOBu^t$. The same conditions as in (a) were employed, except that 5 mol% of CuI was added to the initial mixture, and $LiOBu^t$ was used in the place of Cs_2CO_3.

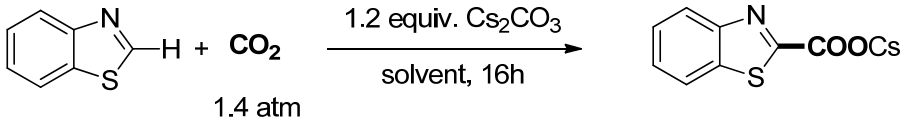
(d). With other solvents. For reactions in dioxane and toluene, the same conditions as in (a) were employed, except that dioxane and toluene were used in the place of DMF. For reactions in THF and acetonitrile, the same conditions as in (a) were employed, except that THF and acetonitrile were used in the place of DMF, and the reaction temperature was set to 90 ^{o}C.

(e) Without CO_2. The same conditions as in (a) were employed, except that no CO_2 was used.

Investigation and confirmation of Cs_2CO_3 as the valid base for the direct carboxylation

To confirm that the carboxylation reaction was mediated by Cs_2CO_3, rather than catalyzed by some metal impurities in Cs_2CO_3, we performed the carboxylation reactions using Cs_2CO_3 from different suppliers and with different purities (metal-based). The results are shown in Table S1.

Table S1. Investigation of different commercial Cs_2CO_3 for direct carboxylation



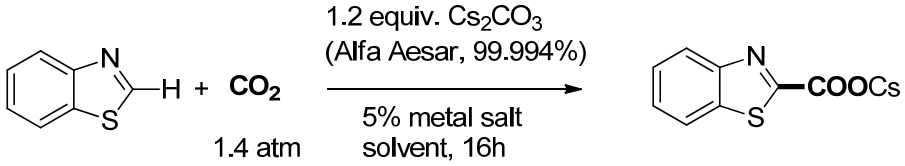
Entry	Supplier	Purity / % (metal-based)	Conversion[a]
1	Aldrich	98	100
2	Aldrich	99.995	100
3	Acros	99.5	100
4	VWR	Extra-pure	100
5	Chem-Impex	99.9	100
6	Alfa Aesar	99	100
7	Alfa Aesar	99.994 (Puratronic$^{(R)}$)	0

[a] Benzothiazolecarboxylate is the only detectable product.

According to table S1, six (6) of seven (7) commercial Cs_2CO_3 were effective for the direct carboxylation. Furthermore, 99.995% pure Cs_2CO_3 (Aldrich) could be used, suggesting that the possibility of carboxylation catalyzed by trace metal contaminants is low. Still, we were intrigued by the fact that 99.994% Cs_2CO_3 from Alfa Aesar was not effective.

First, we wanted to see if adding catalytic amount of metal salts together with this particular Cs_2CO_3 could mediate the carboxylation. The results are shown in Table S2.

Table S2. Examination of metal salts in combination with Alfa Aesar's 99.994% Cs_2CO_3 for direct carboxylation



Entry	Metal salt	Conversion
1	CuI	0
2	Cu_2O	0
3	$FeCl_3$	0
4	$NiCl_2$	0
5	$Pd(OAc)_2$	0
6	$LiOBu^t$	0

Thus, addition of common metal salts together with Alfa Aesar's 99.994% Cs_2CO_3 did not give any conversion for the carboxylation. These results again suggest that carboxylation is not likely catalyzed by trace metal contaminants in other commercial Cs_2CO_3.

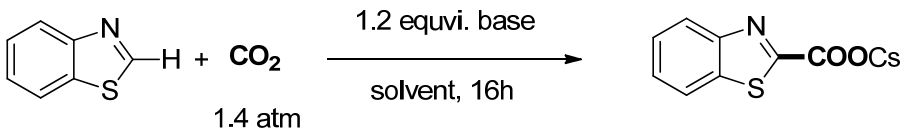
We then sent various commercial Cs_2CO_3 samples for chemical analysis. The main difference between Alfa Aesar's 99.994% Cs_2CO_3 and sources of Cs_2CO_3 is that the former contains more hydrogen. It has 0.66% of H, which would correspond to about 1 molecule of H_2O per Cs_2CO_3. Other sources of Cs_2CO_3 contain 0.1 to 0.3% of H. We suspected that water might be the origin for the abnormal behavior of Alfa Aesar's 99.994% Cs_2CO_3 for our reaction. The influence of hydration on the activity of Cs_2CO_3 in cross coupling reactions has been reported by Denmark et al. (e.g., Scott E. Denmark and Michael H. Ober, Organic Letters, 2003, 5, 1357-1360).

To confirm this hypothesis, we manually added H_2O to the reaction mixture using Cs_2CO_3 that gave 100% conversion (Chem-Impex, 99.9%). The results are shown in Table S3. The reaction was inhibited by water. Adding 0.5 equivalent of water lowered the conversion to 73% (entry 2, table S3); adding 1 equivalent of water completely shut down the reaction (entry 3, table S3). Thus, the inability of Alfa Aesar's 99.994% Cs_2CO_3 to mediate direct carboxylation could originate from its high water content. A mixture of Cs_2CO_3 (Chem-Impex, 99.9%) and Cs_2CO_3 (Alfa Aesar, 99.994%) gave reduced yields (entries 5 and 6, Table S3).

We also examined the morphologies of different Cs_2CO_3 under microscopy. Cs_2CO_3 (Alfa Aesar, 99.994%) appears to be less crystalline than all other samples of Cs_2CO_3. The latter samples also seem to be more uniform in terms of particle sizes. We tried to dry samples of Cs_2CO_3 (Alfa Aesar, 99.994%) under vacuum and with heating. However, the samples melted to form a rocky chunk which stuck onto the glassware.

In summary, most commercial Cs_2CO_3 can mediate direct carboxylation. Alfa Aesar's 99.994% Cs_2CO_3 did not mediate the carboxylation, probably due to its high water content. It is unlikely that the is catalyzed by trace metal contaminations in Cs_2CO_3.

Table S3. Examination of the influence of hydration of Cs_2CO_3 for direct carboxylation



Entry	Base and hydration	Conversion
1	Cs_2CO_3 (Chem-Impex, 99.9%) + no H_2O	100
2	Cs_2CO_3 (Chem-Impex, 99.9%) + 0.5 equiv. of water	73
3	Cs_2CO_3 (Chem-Impex, 99.9%) + 1 equiv. of water	0
4	Cs_2CO_3 (Chem-Impex, 99.9%) + 4 equiv. of water	0
5	0.6 equiv of Cs_2CO_3 (Chem-Impex, 99.9%) + 0.6 equiv. of Cs_2CO_3 (Alfa Aesar, 99.994%)	65
6	0.3 equiv of Cs_2CO_3 (Chem-Impex, 99.9%) + 0.9 equiv. of Cs_2CO_3 (Alfa Aesar, 99.994%)	0

General procedure for carboxylation to form acids

The heterocycle (2 mmol) and Cs_2CO_3 (782mg, 2.4 mmol, Chem-Impex, 99.9%) were placed in a 25 mL Schlenk flask. 3 mL of DMF was then added. The reaction flask was degassed and flushed with CO_2 twice. After this, the reaction mixture was heated at 125 ^{0}C for 16 h under a 400 mbar of overpressure of CO_2. It was then cooled to room temperature and the solvent was

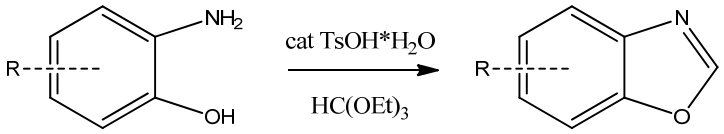
evaporated. Water is added to dissolve the solid residue, and the solution was then filtered. 3 mL of 25% aqueous solution of HCl was added slowly to the filtrate. The resulting precipitate was collected by filtration and dried under vacuum.

General procedure for carboxylation and then esterification

The heterocycle (2 mmol) and Cs_2CO_3 (782mg, 2.4 mmol, Chem-Impex, 99.9%) were placed in a 25 mL Schlenk flask. 3 mL of DMF was then added. The reaction flask was degassed and flushed with CO_2 twice. After this, the reaction mixture was heated at 125 ^{0}C for 16 h under a 400 mbar of overpressure of CO_2. It then cooled to 35 ^{0}C or 65 ^{0}C, and MeI (375 μL, 6 mmol) was added with a syringe. The reaction mixture was stirred for 2 more hours. Then the reaction mixture was cooled to room temperature and the solvent was evaporated. Water was added to make a suspension, and the organic product was extracted with CH_2Cl_2 (3 times, 20 mL each). The organic phase was dried with Na_2SO_4, filtered and the solvent was evaporated under vacuum. In the case that the product was not yet pure, it was purified by a flash chromatography, using hexane/ethyl acetate as a solvent.

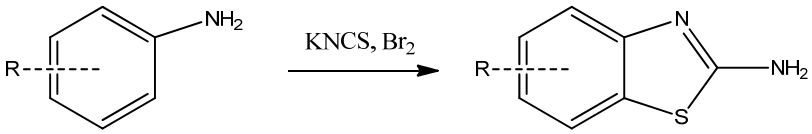
Synthesis of substrates

Synthesis of benzo[d]oxazole type substrates:

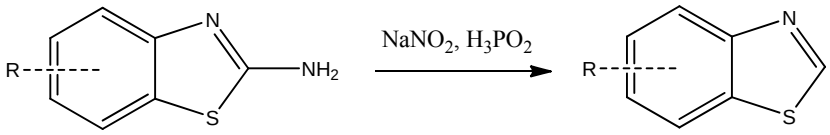


60 mL of triethyl orthoformate was added to a mixture of 2-aminophenol (33 mmol) and p-toluenesulfonic acid monohydrate (3 mol%, 1 mmol, 190 mg). The resulting mixture was heated overnight at 140 ^{0}C. After this, the solvent was evaporated under vacuum and 50 mL of water was added. The organic product was extracted by ethyl acetate (3 times, 40 mL each). The organic phase was dried with Na_2SO_4. Evaporation of solvent under vacuum gave the product in a pure form.

Synthesis of benzo[d]thiazole type substrates:

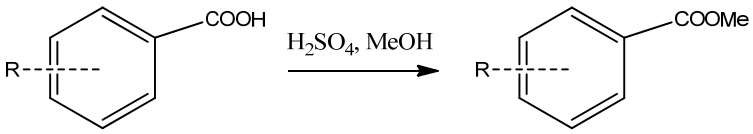


Substituted aniline (22 mmol) and KNCS (3.5 eq, 77mmol, 7.5 g) were dissolved in glacial acetic acid (it takes about 20 min). The solution was cooled with ice bath. Bromine (1.1 eq, 24 mmol, 3.9 g) in 4 ml of glacial acetic acid was then added dropwise, maintaining a reaction temperature below 25 ^{0}C. After addition, the reaction mixture was stirred overnight. Then the reaction mixture was neutralized with 25% solution of ammonia under cooling. The product was collected on the filter, washed with water and small quantity of cold ethyl acetate, and dried under vacuum. The resulting solid product was used without further purification.

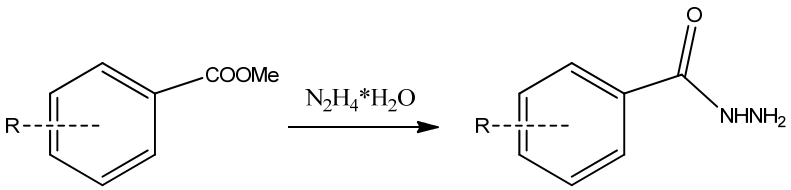


Substituted benzo[d]thiazol-2-amine (12.5 mmol) was dissolved in hot 85% H_3PO_4 (approximately 130 ^{0}C) and the solution was cooled to -8 ^{0}C. A solution of $NaNO_2$ (75 mmol, 5.2 g) in 20 mL of water was added slowly, maintaining a temperature below -4 ^{0}C. Then 30 mL of 50% H_3PO_2 was added slowly and the reaction mixture was stirred overnight. After this time, cold water was added to dissolve all the solid residues of the suspension. The reaction mixture was then neutralized with 25% ammonia solution under cooling. The organic product was extracted with ethyl acetate and purified with a flash chromatography. *Caution:* N_2 formed during the reaction, and the volume of the reaction mixture increases considerably. A sufficiently large size of flask should be used.

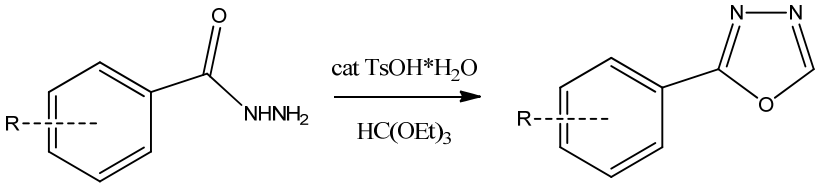
Synthesis of 1,3,4-oxadiazole type substrates:



A mixture of substituted benzoic acid (33 mmol) and catalytic quantity of concentrated H_2SO_4 in methanol was heated at 80 ^{0}C for 4 hours. Then methanol was evaporated under vacuum and 50 mL of water was added. The product was extracted with ethyl acetate (3 times, 40 mL each). The organic phase was dried with Na_2SO_4, and the solvent was evaporated under vacuum, giving the product in a pure form.

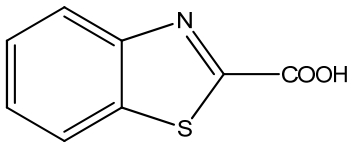


The ester was heated in 20 mL of hydrazine monohydrate at 80 ^{0}C during 2 h until the reaction mixture became homogeneous. Then the reaction mixture was cooled to room temperature, and 50 mL of water was added. The organic product was extracted with ethyl acetate (3 times, 40 mL each). The organic phase was dried with Na_2SO_4 and the solvent was evaporated under vacuum, giving the product in a pure form.



60 mL of triethyl orthoformate was added to a mixture of substituted benzohydrazide (33 mmol) and p-toluenesulfonic acid monohydrate (3 mol%, 1 mmol, 190 mg). The resulting mixture was heated overnight at 140 ^{0}C. After this, the solvent was evaporated under vacuum and 50 mL of water was added. The organic product was extracted by ethyl acetate (3 times, 40 mL each). The organic phase was dried with Na_2SO_4. Evaporation of solvent under vacuum gave the product in a pure form.

Detail descriptions for products



benzo[d]thiazole-2-carboxylic acid (1):

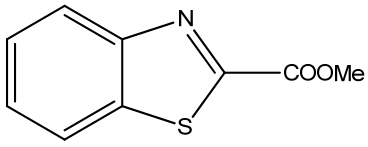
Obtained in 98% yield as a solid:

^{1}H NMR (400MHz, DMSO-D6): 14 - 15 (br., 1H), 8.21 (m, 2H), 7.62 (m, 2H).

^{13}C NMR (100 MHz, DMSO-D6): 161.4, 160.0, 152.9, 136.3, 127.5, 127.2, 124.8, 123.0.

HRESI-MS: calculated for ($C_8H_6NO_2S$, M+H), 180.0119; found, 180.0125.

Elemental analysis: Anal. Calcd for $C_8H_5NO_2S$: C, 53.62; H, 2.81; N, 7.82. Found: C, 53.35; H, 2.66; N, 7.76.



methyl benzo[d]thiazole-2-carboxylate (1b):

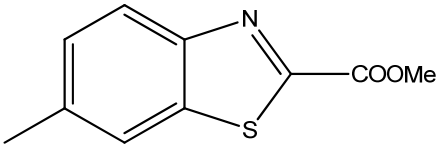
Obtained in 95% yield as a solid. Melting point: 95 ^{0}C (lit. value: 90 ^{0}C[2]).

^{1}H NMR (400MHz, $CDCl_3$): 8.24 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.56 (m, 2H), 4.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 161.1, 158.0, 153.1, 136.7, 127.6, 127.1, 125.5, 122.1, 53.6.

HRESC-MS: calculated for ($C_9H_8NO_2S$, M+H), 194.0276; found, 194.0276.

[2] O. Prakash, V. Sharma, and A. Sadana, *Journal of Chemical Research, Synopses,***1996**, 100-101.



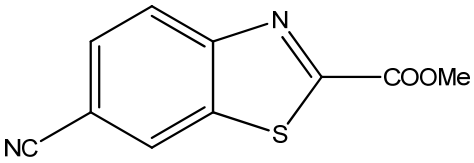
methyl 6-methylbenzo[d]thiazole-2-carboxylate (table 2, entry 1, labeled 2-1):

Obtained in 91% yield as a solid.

^{1}H NMR (400MHz, $CDCl_3$): 8.05 (d, J = 8.5 Hz, 1H), 7.69 (s, 1H), 7.33 (d, J = 8.5 Hz, 1H), 4.03 (s, 3H), 2.47 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 161.1, 156.7, 151.2, 138.1, 136.9, 128.9, 124.8, 121.4, 53.4, 21.6.

HRESI-MS: calculated for ($C_{10}H_{10}NO_2S$, M+H), 208.0432; found, 208.0428.



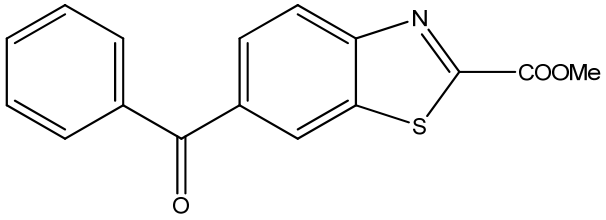
methyl 6-cyanobenzo[d]thiazole-2-carboxylate (table 2, entry 2, labeled 2-2):

Eluated from the column with hexane - ethyl acetate (2:1) in 90% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.35 (dd, J_1 = 1.5 Hz, J_2 = 0.6 Hz, 1H), 8.33 (dd, J_1 = 8.5 Hz, J_2 = 0.6 Hz, 1H), 7.83 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 4.12 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 162.1, 160.3, 155.2, 137.0, 129.9, 127.3, 126.4, 118.0, 111.3, 54.1.

HRESI-MS: calculated for ($C_{10}H_7N_2O_2S$, M+H), 219.0228; found, 219.0233.



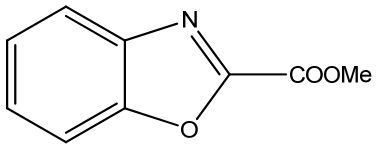
methyl 6-benzoylbenzo[d]thiazole-2-carboxylate (table 2, entry 3, labeled 2-3):

Eluated from the column with hexane - ethyl acetate (2:1) in 68% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.42 (m, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.01 (dd, J_1 = 8.5 Hz, J_2 = 1.8 Hz, 1H), 7.82 (dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz, 2H), 7.62 (m, 1H), 7.51 (m, 2H), 4.10 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 195.4, 161.1, 160.6, 155.2, 137.1, 136.6, 132.8, 130.0, 128.6, 128.5, 125.2, 124.7, 53.9.

HRESI-MS: calculated for ($C_{16}H_{12}NO_3S$, M+H), 298.0538; found, 298.0518.



methyl benzo[d]oxazole-2-carboxylate (table 2, entry 4, labeled 2-4):

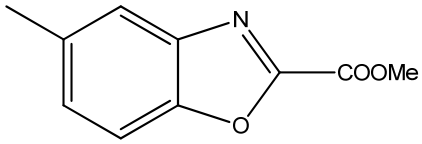
Obtained in 91% yield as a solid. Melting point: 99 ^{0}C (lit. value: 100 ^{0}C[3]).

^{1}H NMR (400MHz, $CDCl_3$): 7.87 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.51 (td, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 1H), 7.44 (m, 1H), 4.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.8, 152.4, 150.8, 140.4, 128.2, 125.8, 122.1, 111.7, 53.6.

HRESI-MS: calculated for ($C_9H_8NO_3$, M+H), 178.0504; found, 178.0506.

[3] H. Moeller, *ustus Liebigs Annalen der Chemie*,**1971**, 1-11.



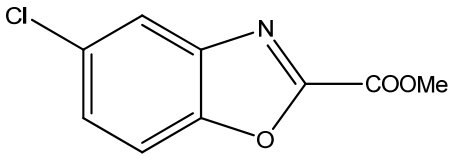
methyl 5-methylbenzo[d]oxazole-2-carboxylate (table 2, entry 5, labeled 2-5):

Obtained in 83% yield as a solid. Melting point: 97^{0}C (lit. value: 98 ^{0}C[3]).

^{1}H NMR (400MHz, $CDCl_3$): 7.61 (s, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.29 (dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz, 1H), 4.05 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.8, 152.4, 149.1, 140.6, 135.8, 129.6, 121.6, 111.0, 53.5, 21.4.

HRESI-MS: calculated for ($C_{10}H_{10}NO_3$, M+H), 192.0661; found, 192.0660.



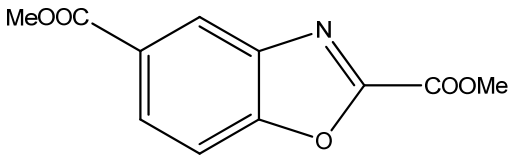
methyl 5-chlorobenzo[d]oxazole-2-carboxylate (table 2, entry 6, labeled 2-6):

Obtained in 92% yield as a solid. Melting point: 124 ^{0}C (lit. value: 122 ^{0}C[3]).

^{1}H NMR (400MHz, $CDCl_3$): 7.83 (d, J = 2.1 Hz, 1H), 7.57 (m, 1H), 7.47 (dd, J_1 = 8.8 Hz, J_2 = 2.1 Hz, 1H), 4.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.5, 153.6, 149.4, 141.4, 131.5, 128.8, 121.9, 112.6, 53.9.

HRESI-MS: calculated for ($C_9H_7NO_3Cl$, M+H), 212.0114; found, 212.0116.



dimethyl benzo[d]oxazole-2,5-dicarboxylate (table 2, entry 7, labeled 2-7):

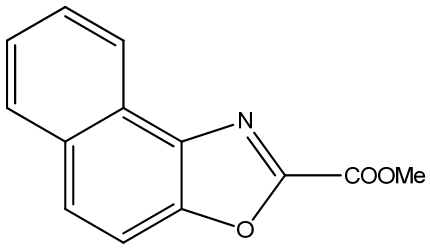
Eluated from the column with hexane - ethyl acetate (1:1) in 92% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.56 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 4.11 (s, 3H), 3.97 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.0, 156.5, 153.7, 153.5, 140.5, 129.8, 128.4, 124.2, 111.7, 53.9, 52.5.

HRESI-MS: calculated for ($C_{11}H_{10}NO_5$, M+H), 236.0559; found, 236.0565.

Elemental analysis: Anal. Calcd for $C_{11}H_9NO_5$: C, 56.17; H, 3.86; N, 5.96. Found: C, 55.73; H, 4.02; N, 5.72.



methyl naphtho[1,2-d]oxazole-2-carboxylate (table 2, entry 8, labeled 2-8):

Obtained in 97% yield as a solid. Melting point: 155 ^{0}C (lit. value: 146 ^{0}C[4]).

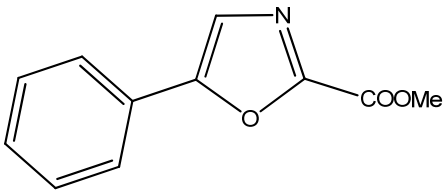
.

^{1}H NMR (400MHz, $CDCl_3$): 8.63 (d, *J* = 8.2 Hz, 1H), 7.97 (m, 2H), 7.73 (m, 2H), 7.61 (m, 1H), 4.13 (s, 3H).

[4] H. Barjesteh et al, *Journal of Chemical Research, Miniprint,***1995**, 2701 - 2720.

^{13}C NMR (100 MHz, $CDCl_3$): 156.8, 151.6, 148.9, 136.5, 131.5, 129.9, 128.8, 128.0, 126.9, 126.4, 122.3, 111.1, 53.7.

HRESI-MS: calculated for ($C_{13}H_{10}NO_3$, M+H), 228.0661; found, 228.0654.



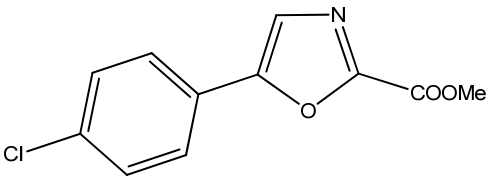
methyl 5-phenyloxazole-2-carboxylate (table 2, entry 9, labeled 2-9):

Eluated from the column with hexane - ethyl acetate (2:1) in 65% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 7.72 (m, 2H), 7.50 (s, 1H), 7.41 (m, 3H), 3.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.0, 154.3, 151.3, 129.8, 129.0, 126.5, 125.0, 123.8, 53.0.

HRESI-MS: calculated for ($C_{11}H_{10}NO_3$, M+H), 204.0661; found, 204.0666.



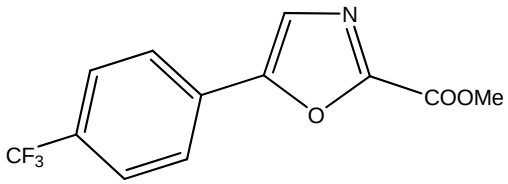
methyl 5-(4-chlorophenyl)oxazole-2-carboxylate (table 2, entry 10, labeled 2-10):

Eluated from the column with hexane - ethyl acetate (3:1) in 55% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 7.69 (d, J = 8.2 Hz, 2H), 7.52 (s, 1H), 7.43 (d, J = 8.5 Hz, 2H), 4.02 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.0, 153.3, 151.5, 135.9, 129.4, 126.3, 125.1, 124.2, 53.2.

HRESI-MS: calculated for ($C_{11}H_9NO_3Cl$, M+H), 238.0271; found, 238.0271.



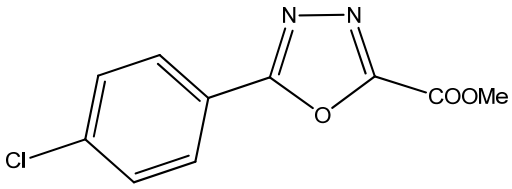
methyl 5-(4-(trifluoromethyl)phenyl)oxazole-2-carboxylate (table 2, entry 11, labeled 2-11):

Eluated from the column with hexane - ethyl acetate (3:1) in 61% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 7.88 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.64 (s, 1H), 4.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 155.9, 152.8, 152.1, 131.5 (q, *J* = 33 Hz), 129.8 (q, *J* = 1.4 Hz), 126.1 (q, *J* = 3.8 Hz), 125.4, 125.3, 123.7 (q, *J* = 272.3 Hz), 53.3.

HRESI-MS: calculated for ($C_{12}H_9NO_3F_3$, M+H), 272.0535; found, 272.0524.



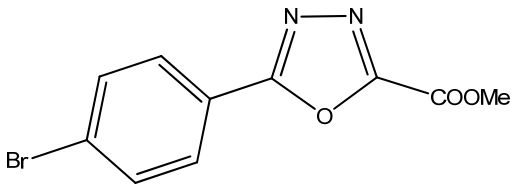
methyl 5-(4-chlorophenyl)-1,3,4-oxadiazole-2-carboxylate (table 2, entry 12, labeled 2-12):

Obtained in 88% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.11 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 4.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 156.3, 154.6, 139.3, 129.7, 128.8, 121.1, 53.8.

HRESI-MS: calculated for ($C_{10}H_8N_2O_3Cl$, M+H), 239.0223; found, 239.0212.



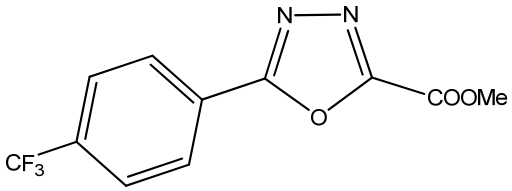
methyl 5-(4-bromophenyl)-1,3,4-oxadiazole-2-carboxylate (table 2, entry 13, labeled 2-13):

Obtained in 83% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.02 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 4.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 165.8, 156.3, 154.7, 132.7, 129.0, 127.9, 121.5, 53.9.

HRESI-MS: calculated for ($C_{10}H_8N_2O_3Br$, M+H), 282.9718 and 284.9699; found, 282.9726 and 284.9717.



methyl 5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole-2-carboxylate (table 2, entry 14, labeled 2-14):

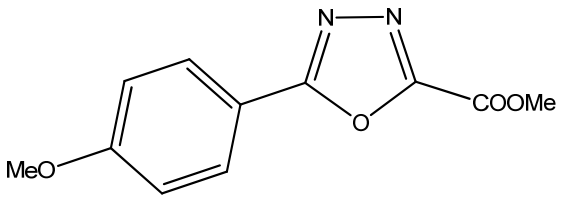
Obtained in 71% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.29 (d, *J* = 8.2 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 4.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 165.2, 156.6, 154.6, 134.4 (q, *J* = 33.1 Hz), 128.0, 126.0 (q, *J* = 268.2 Hz), 126.3 (q, *J* = 3.8 Hz), 125.9 (q, *J* = 1.5 Hz), 53.9.

HRESI-MS: calculated for ($C_{11}H_8N_2O_3F_3$, M+H), 273.0487; found, 273.0489.

Elemental analysis: Anal. Calcd for $C_{11}H_7N_2O_3F_3$: C, 48.54; H, 2.59; N, 10.29. Found: C, 48.25; H, 2.85; N, 9.95.



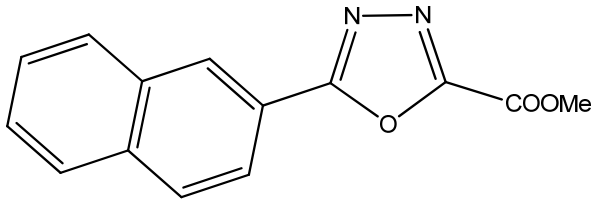
methyl 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2-carboxylate (table 2, entry 15, labeled 2-15):

Obtained in 96% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.07 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 9.1 Hz, 2H), 4.06 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.5, 163.2, 155.8, 154.9, 129.5, 115.0, 114.7, 55.5, 53.7.

HRESI-MS: calculated for ($C_{11}H_{11}N_2O_4$, M+H), 235.0719; found, 235.0710.



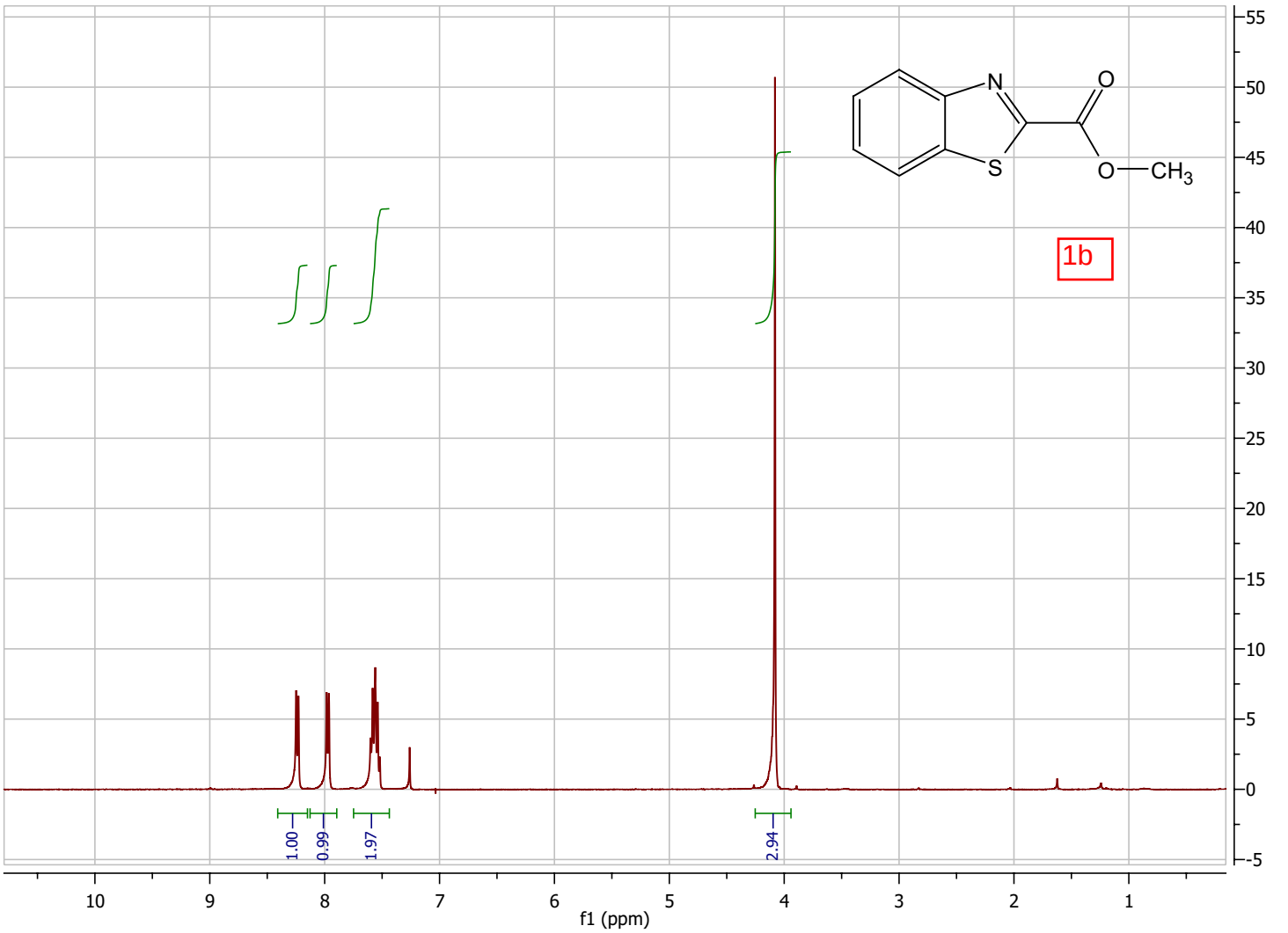
methyl 5-(naphthalen-2-yl)-1,3,4-oxadiazole-2-carboxylate (table 2, entry 16, labeled 2-16):

Eluated from the column with hexane - ethyl acetate (3:1) in 64% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.61 (s, 1H), 8.13 (dd, J_1 = 8.8 Hz, J_2 = 1.8 Hz, 1H), 7.93 (m, 2H), 7.85 (d, J = 8.2 Hz, 1H), 7.56 (m, 2H), 4.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.6, 156.2, 154.8, 135.0, 132.6, 129.2, 128.9, 128.5, 128.5, 127.9, 127.3, 123.1, 119.7, 53.7.

HRESI-MS: calculated for ($C_{14}H_{11}N_2O_3$, M+H), 255.0770; found, 255.0764.


1b
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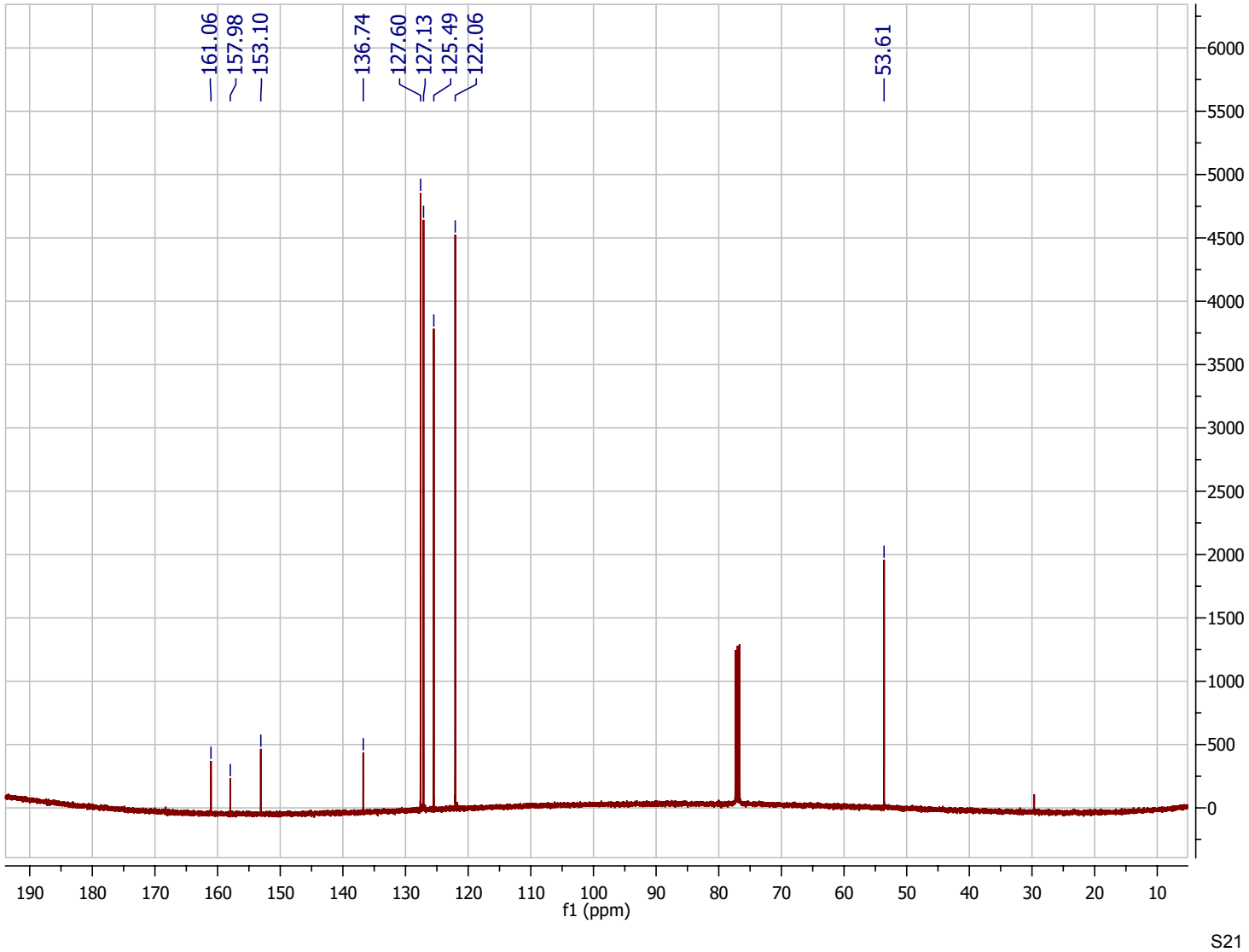
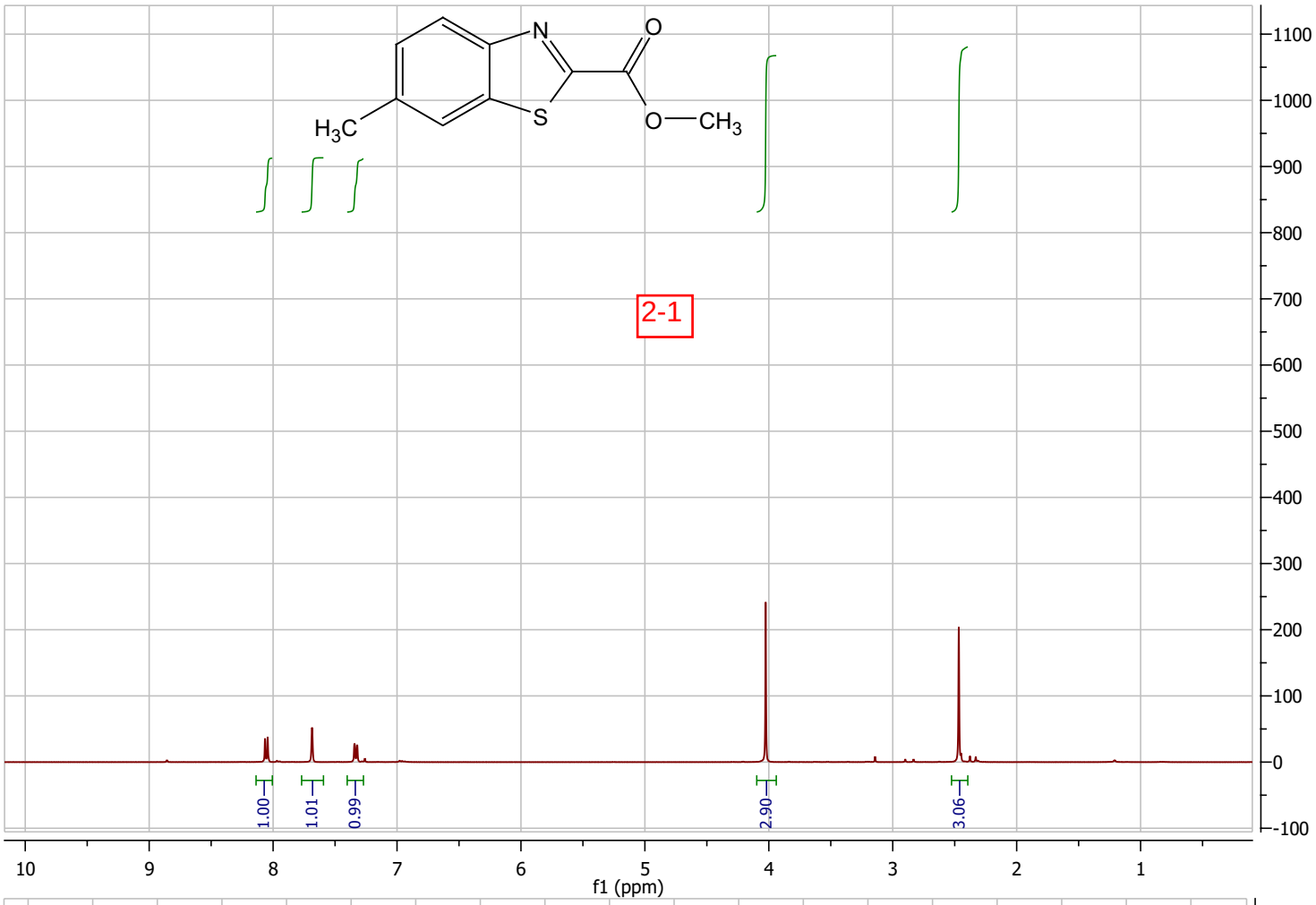
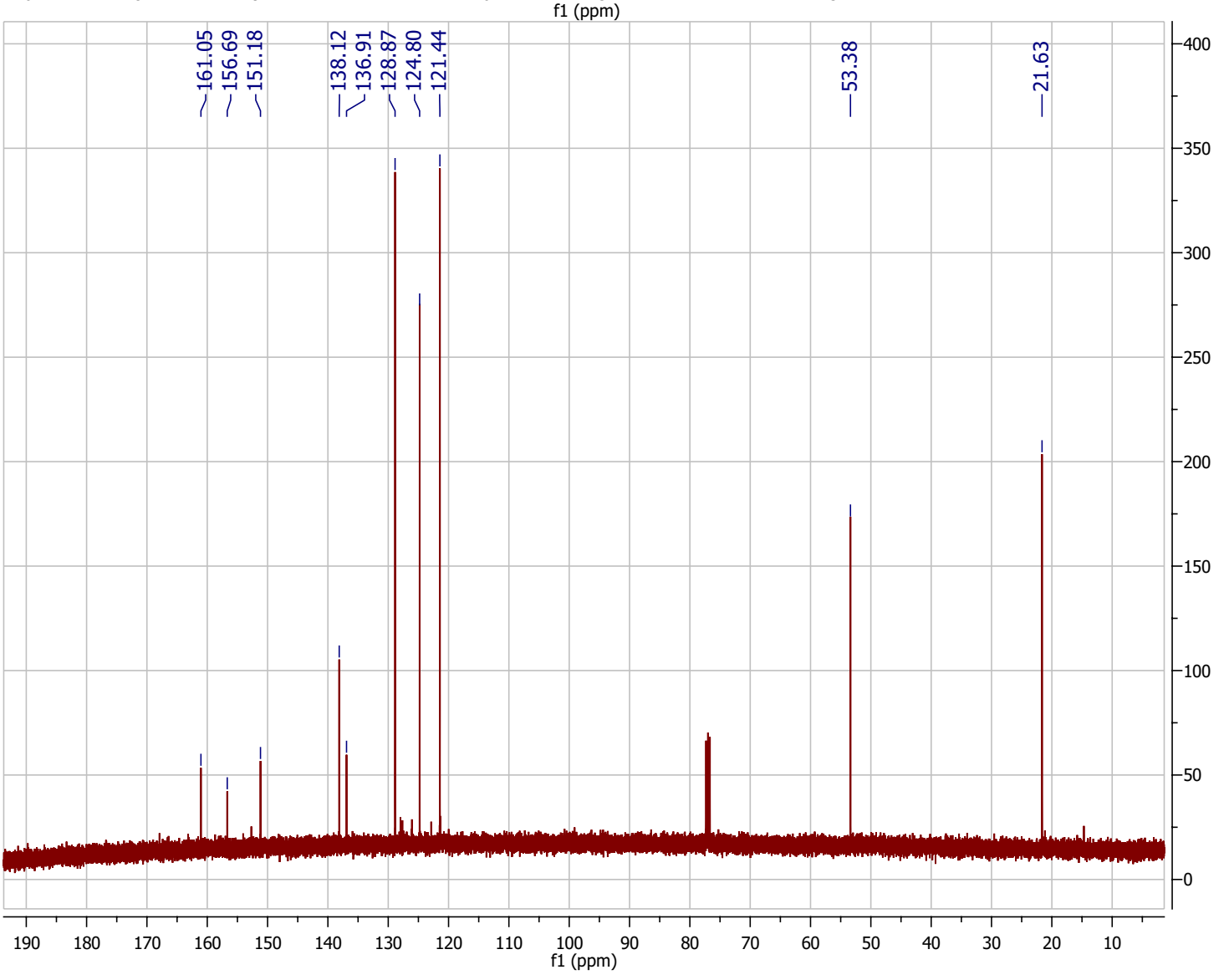
0.99
1.97
2.94
f1 (ppm)


161.06
157.98
153.10
136.74
127.60
127.13
125.49
122.06
53.61
f1 (ppm)


N
O
S
O—CH3
H3C
2-1
1.00
1.01
0.99
2.90
3.06
f1 (ppm)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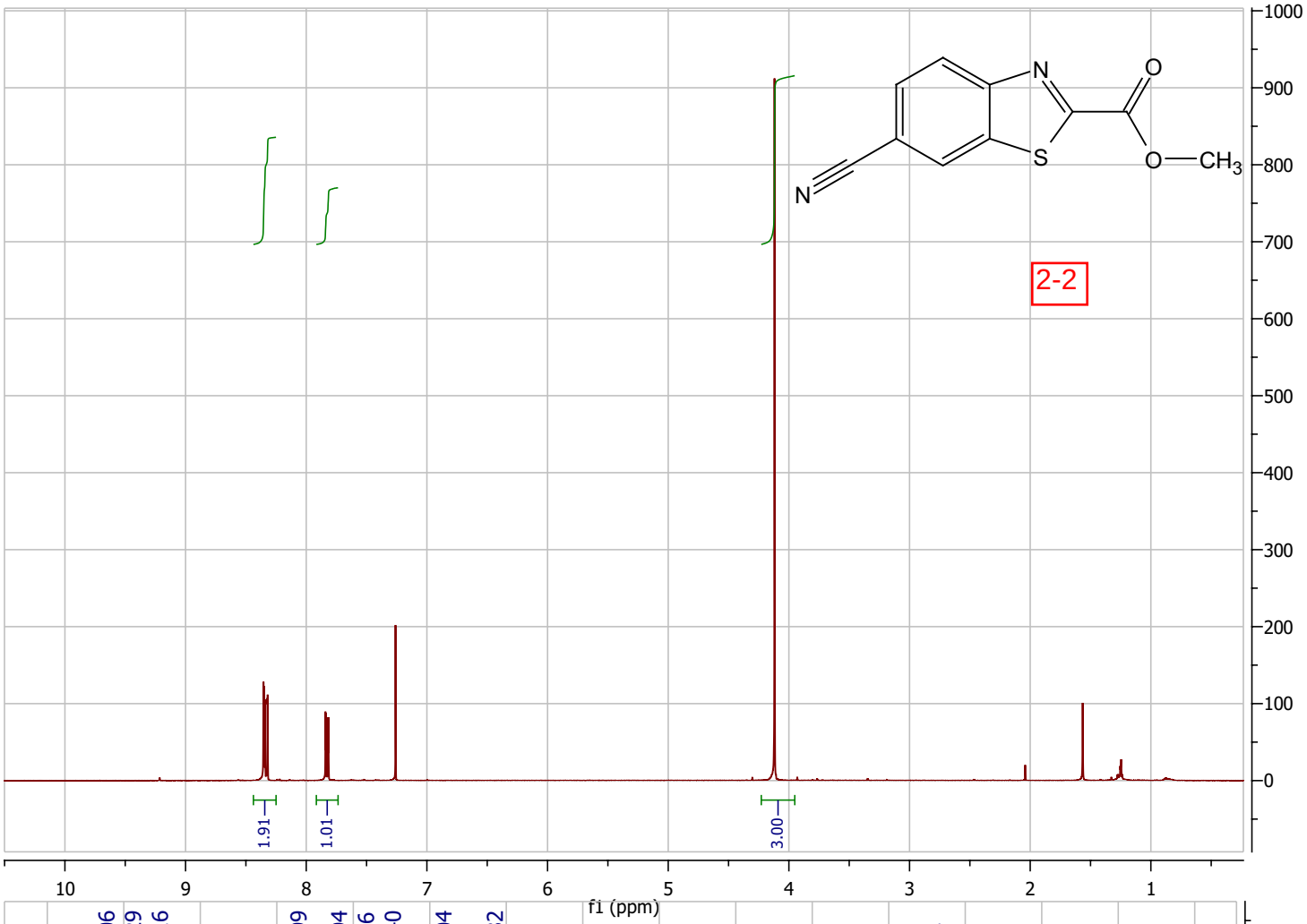
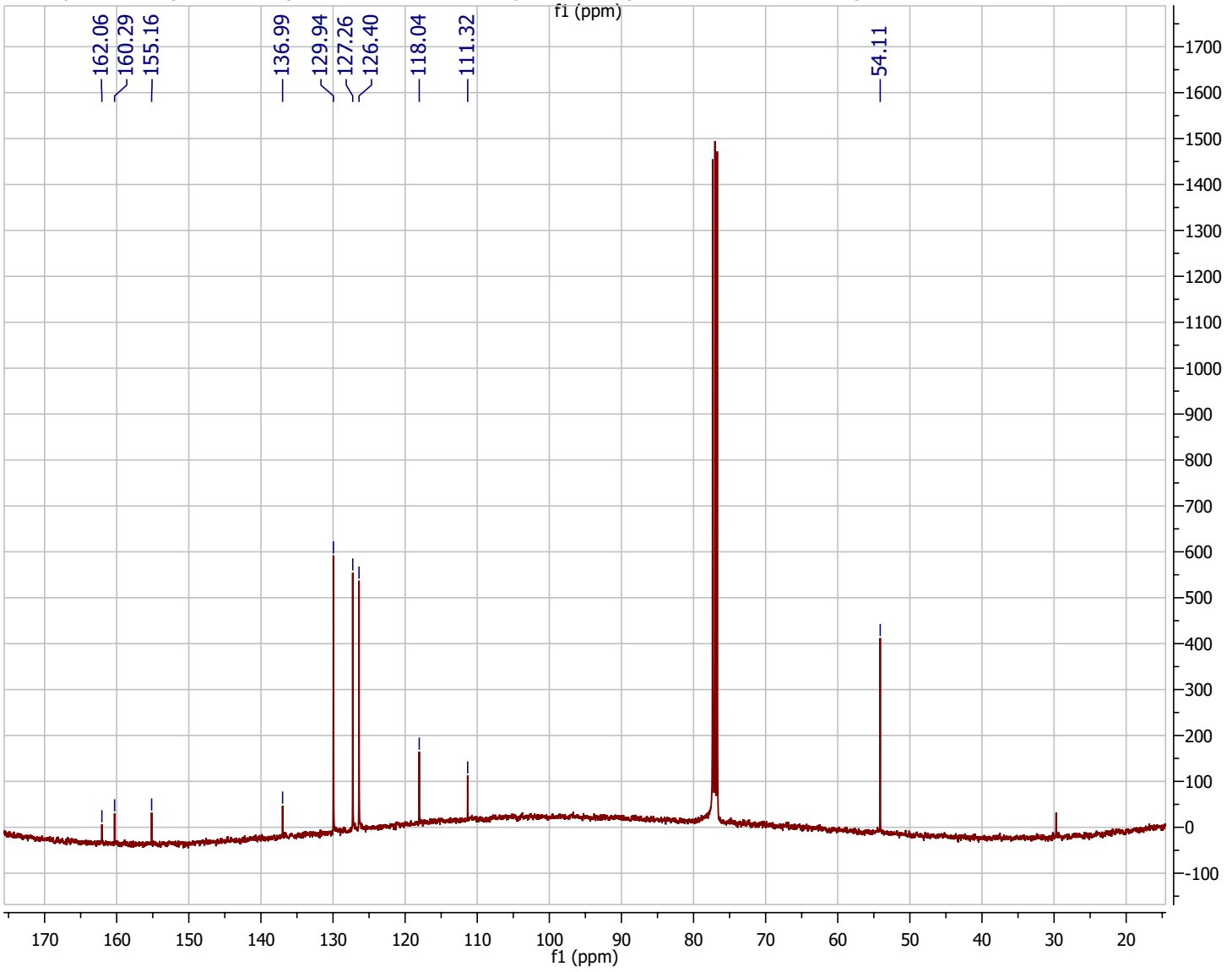
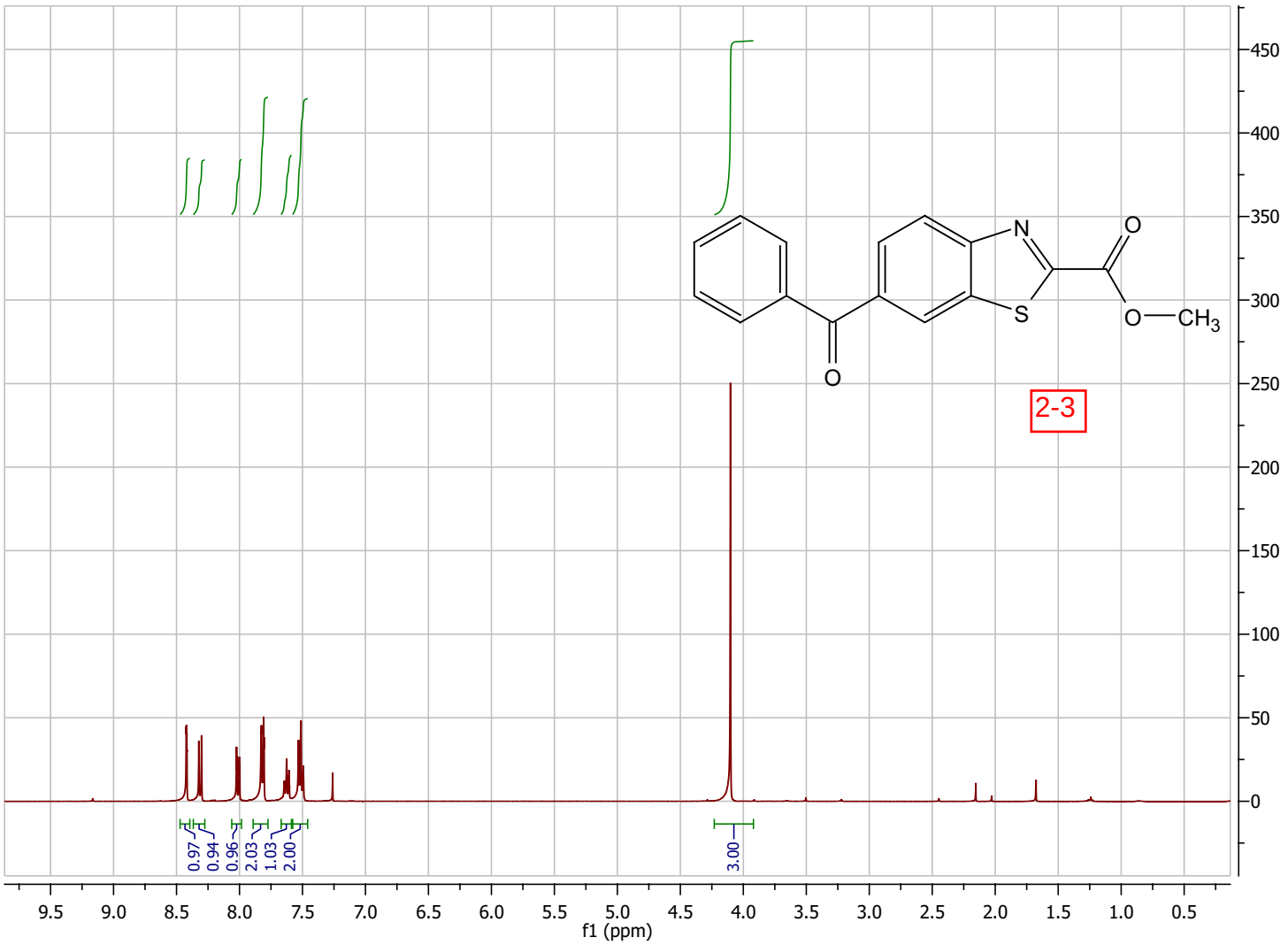
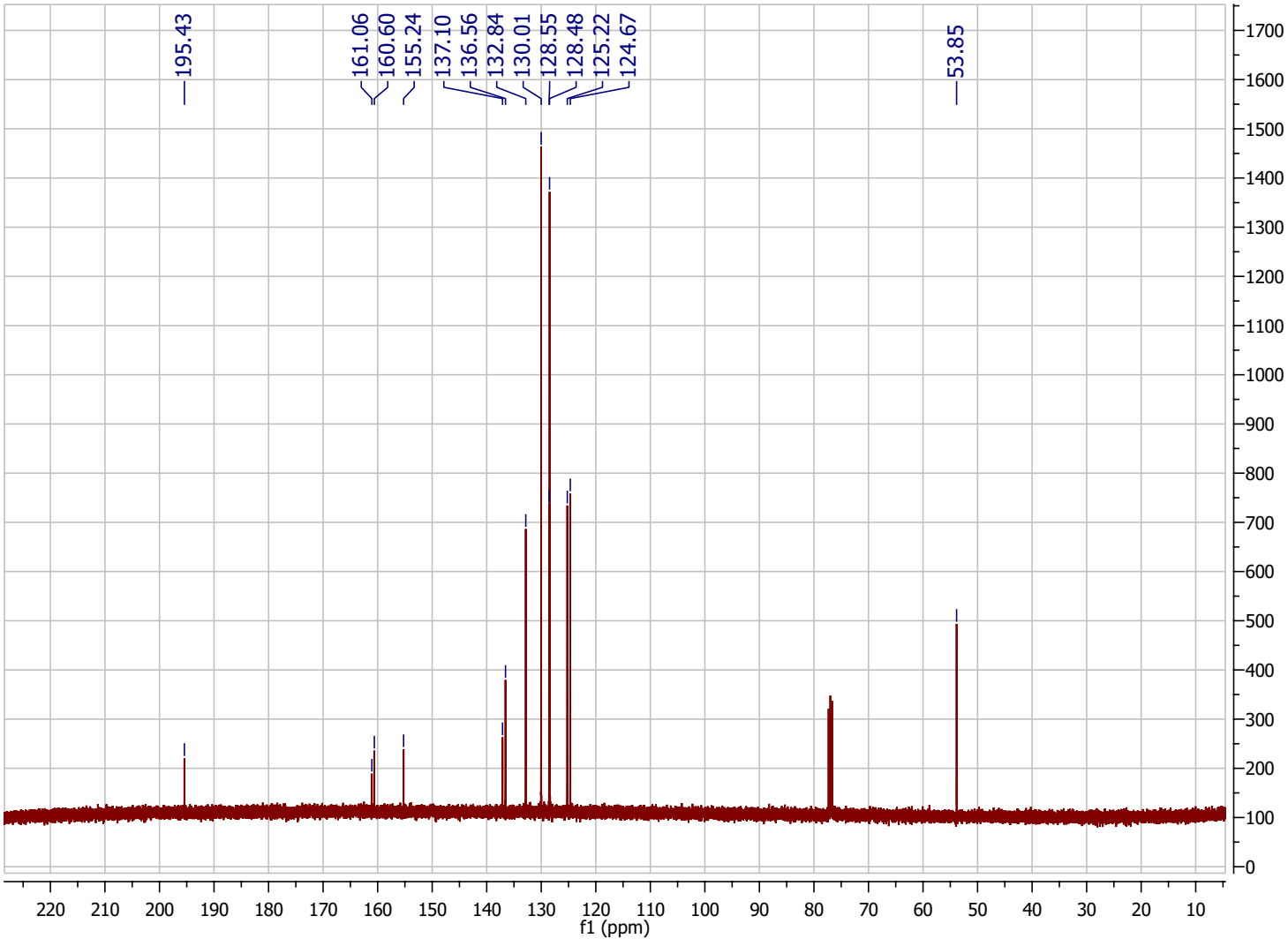
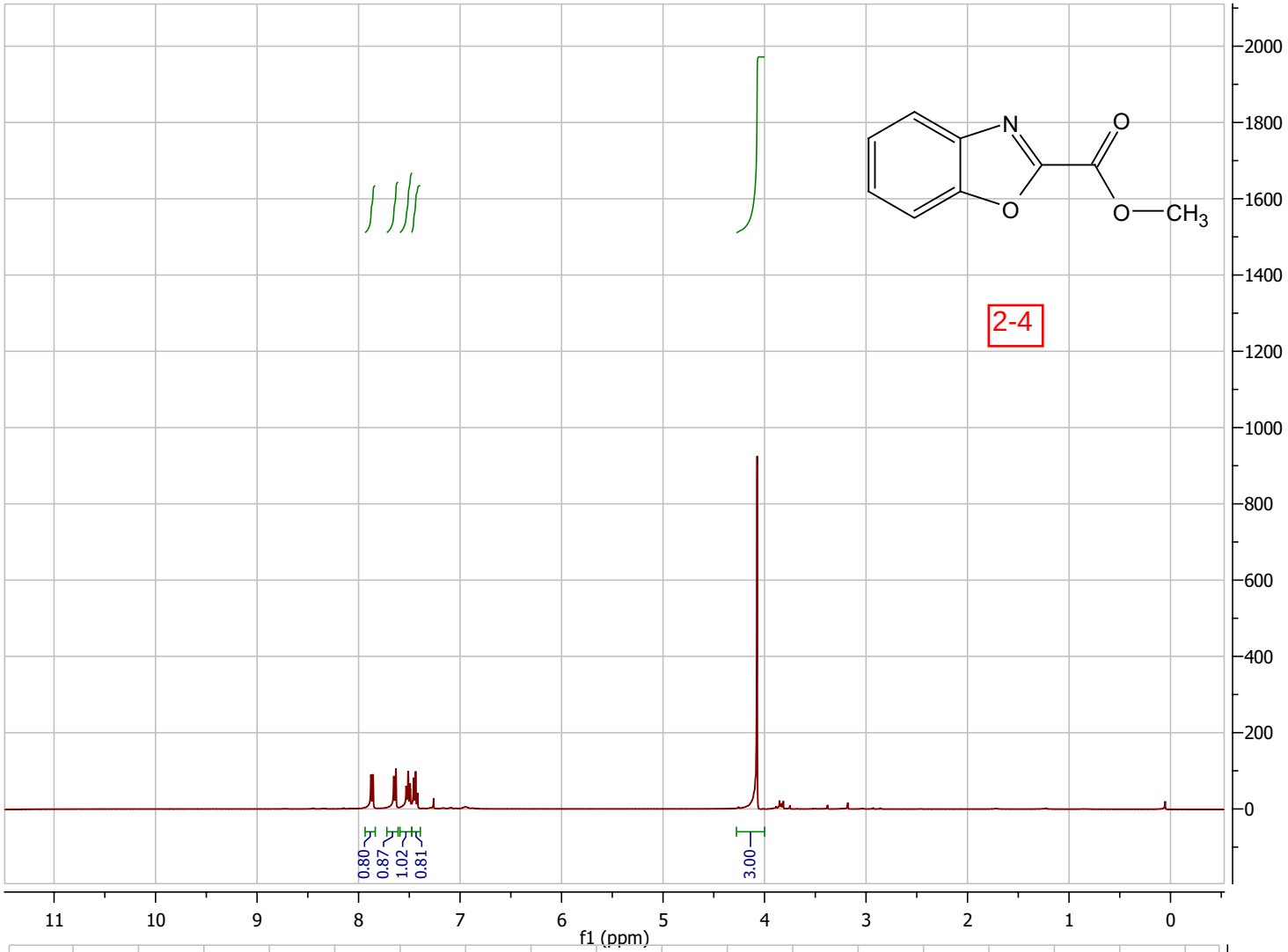
156.69
151.18
138.12
136.91
128.87
124.80
121.44
53.38
21.63
f1 (ppm)

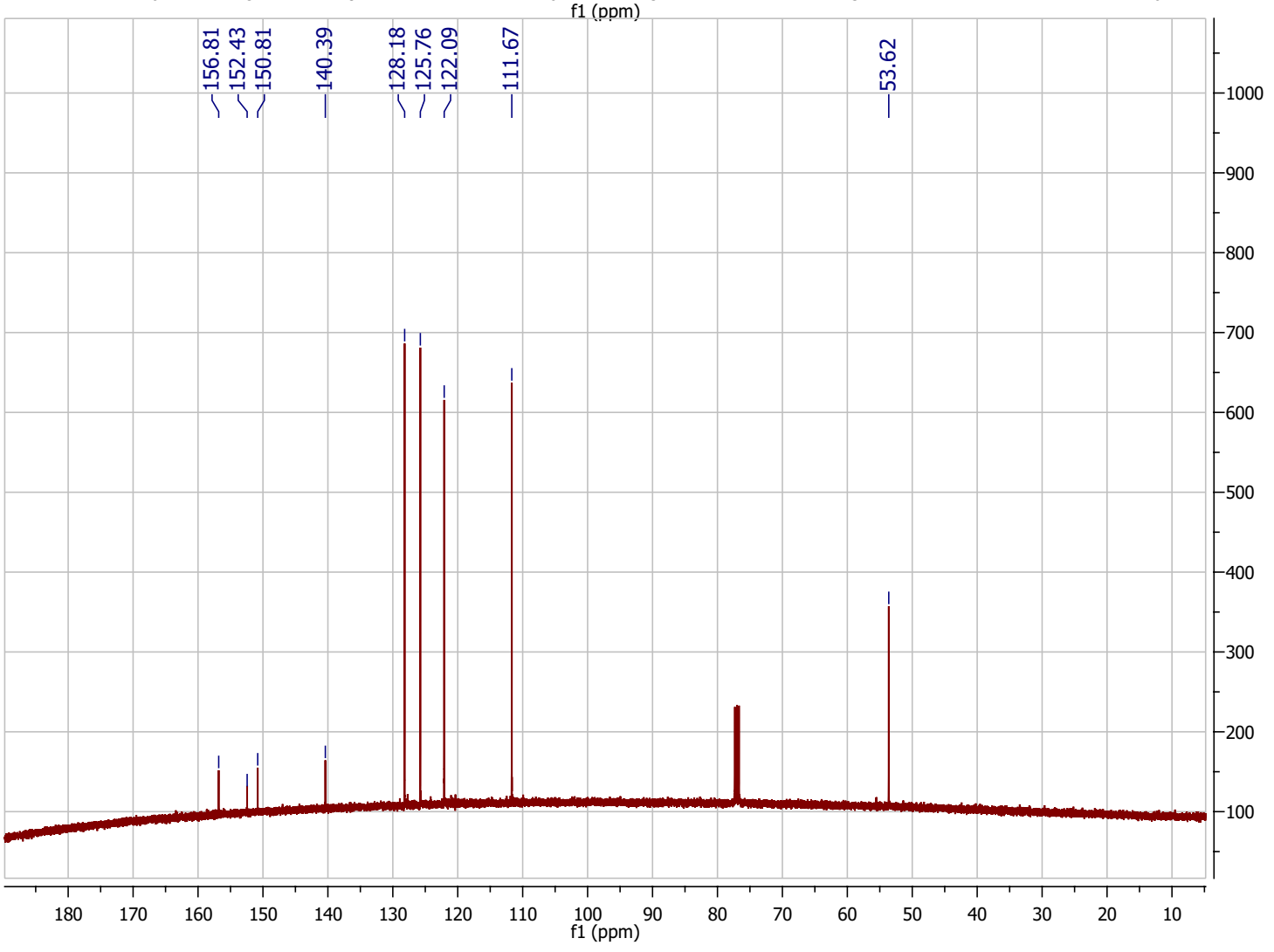

N
O
S
O
O—CH3
N
2-2
1.91
1.01
3.00
f1 (ppm)


162.06
160.29
155.16
136.99
129.94
127.26
126.40
118.04
111.32
54.11
f1 (ppm)


N
O
S
O
O—CH3
O
2-3
0.97
0.94
0.96
2.03
1.03
2.00
3.00
f1 (ppm)


195.43
161.06
160.60
155.24
137.10
136.56
132.84
130.01
128.55
128.48
125.22
124.67
53.85
f1 (ppm)


N
O
O
O
O—CH3
2-4
0.80
0.87
1.02
0.81
3.00
f1 (ppm)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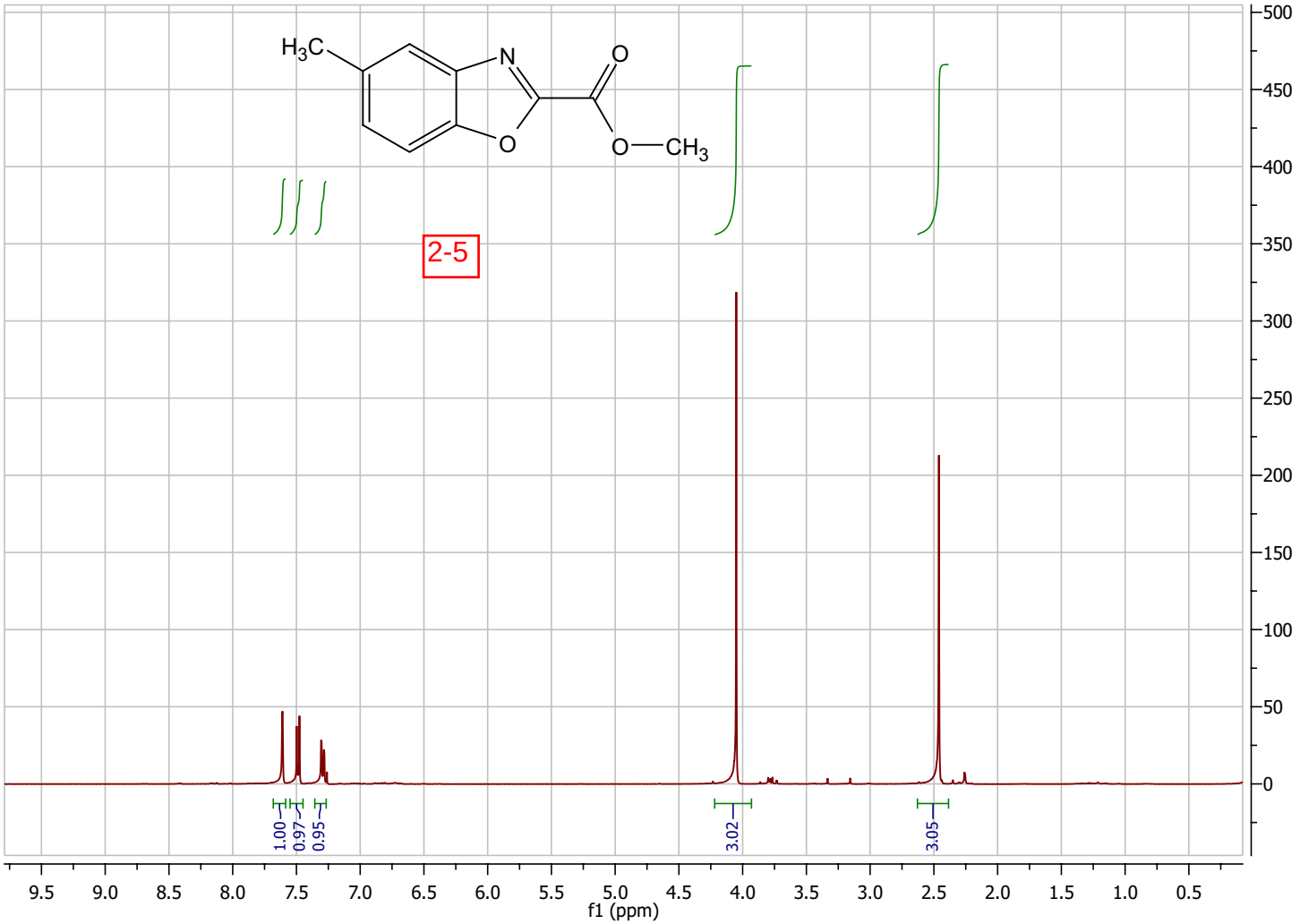
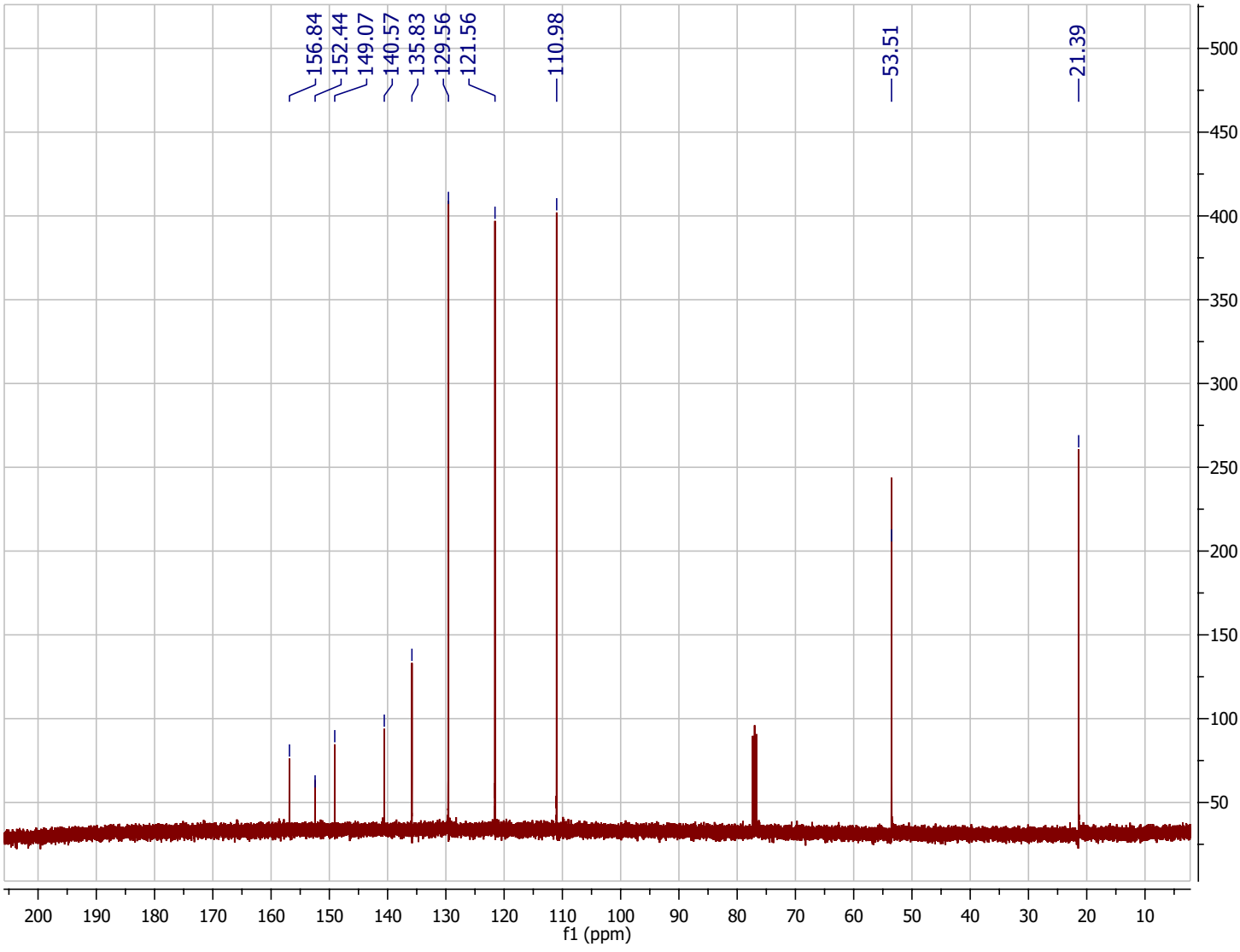
150.81
140.39
128.18
125.76
122.09
111.67
53.62
f1 (ppm)


2-5
1.00
0.97
0.95
3.02
3.05
f1 (ppm)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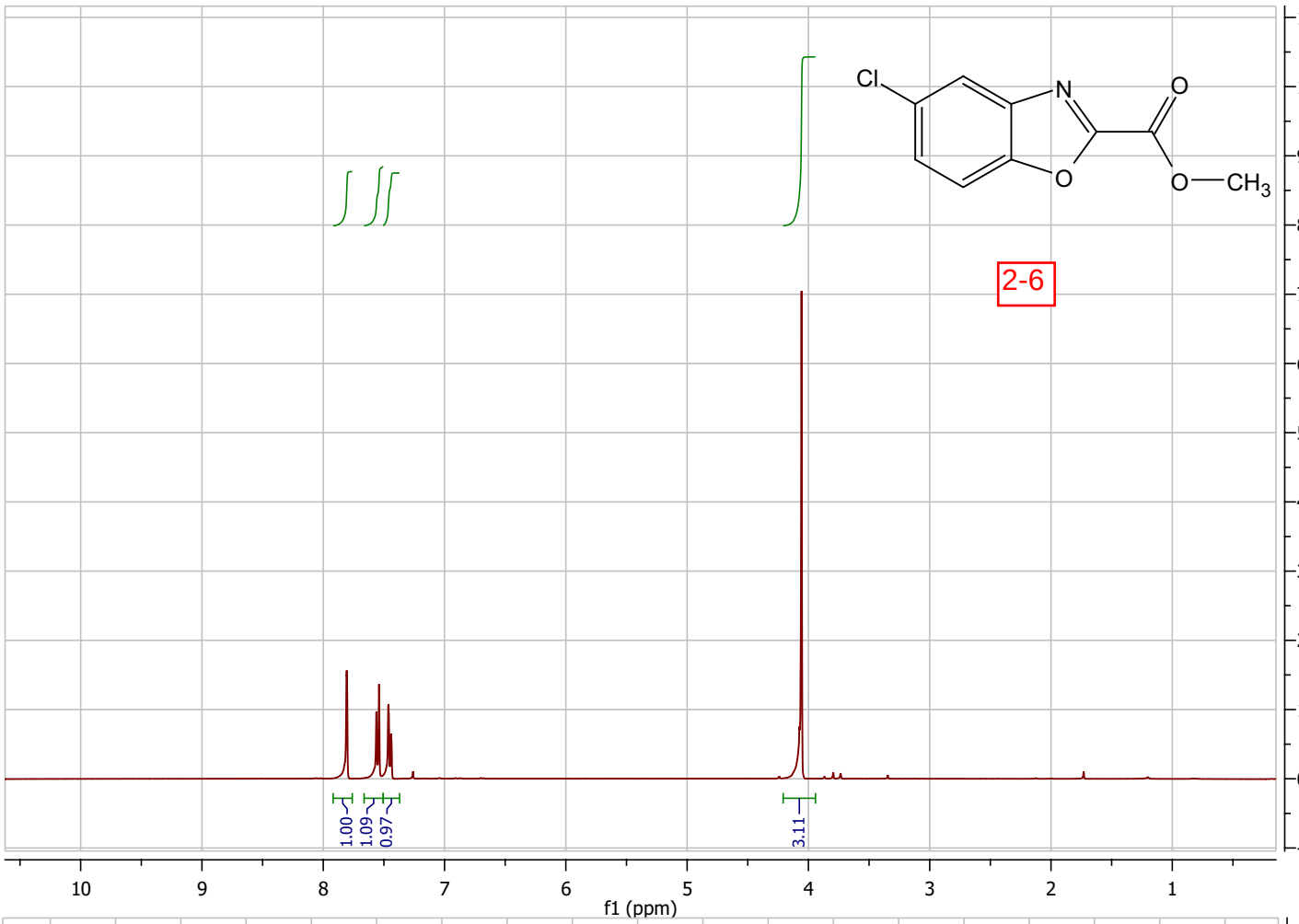
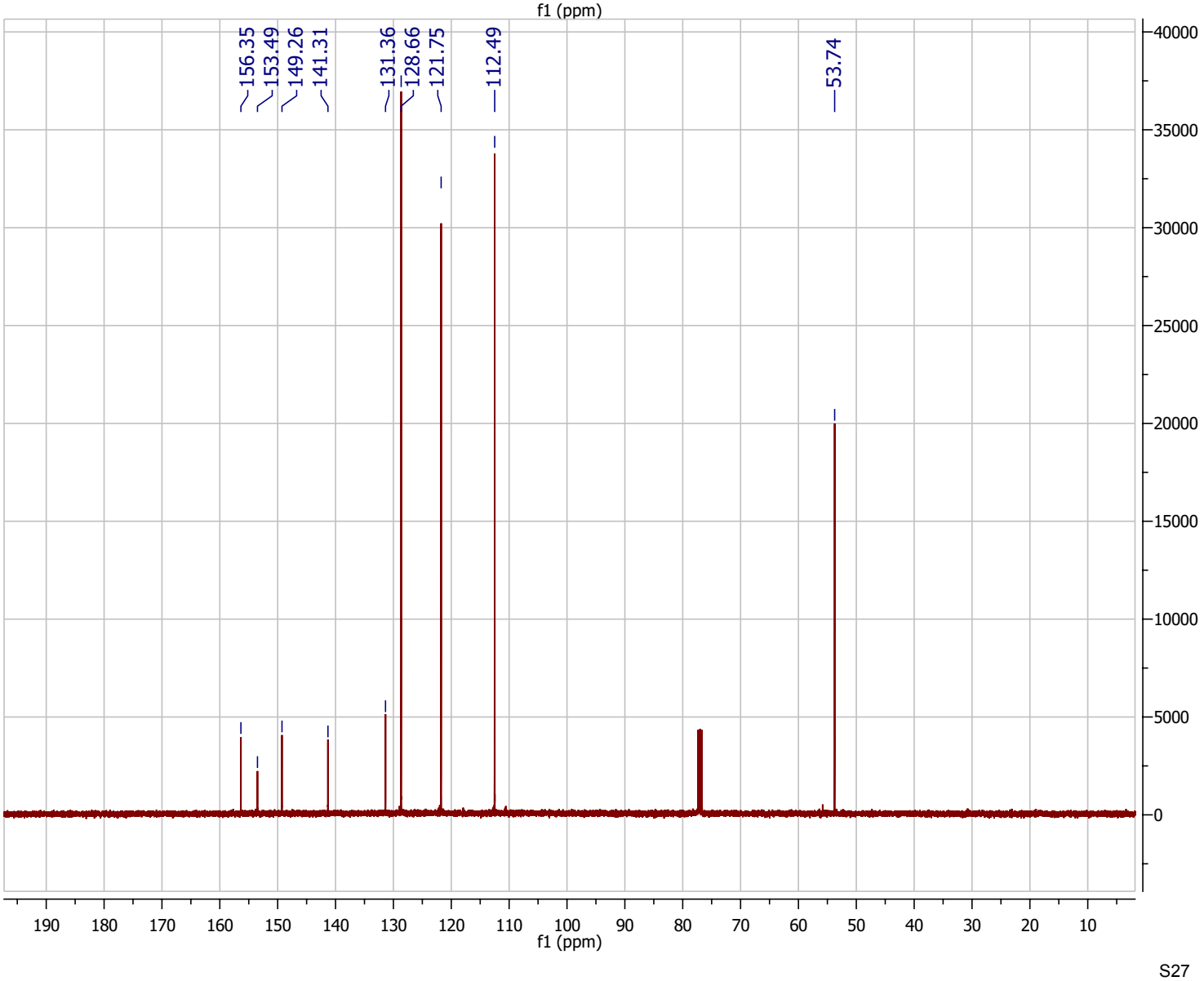
152.44
149.07
140.57
135.83
129.56
121.56
110.98
53.51
21.39
f1 (ppm)


Cl
N
O
O
O
O—CH3
2-6
1.00
1.09
0.97
3.11
f1 (ppm)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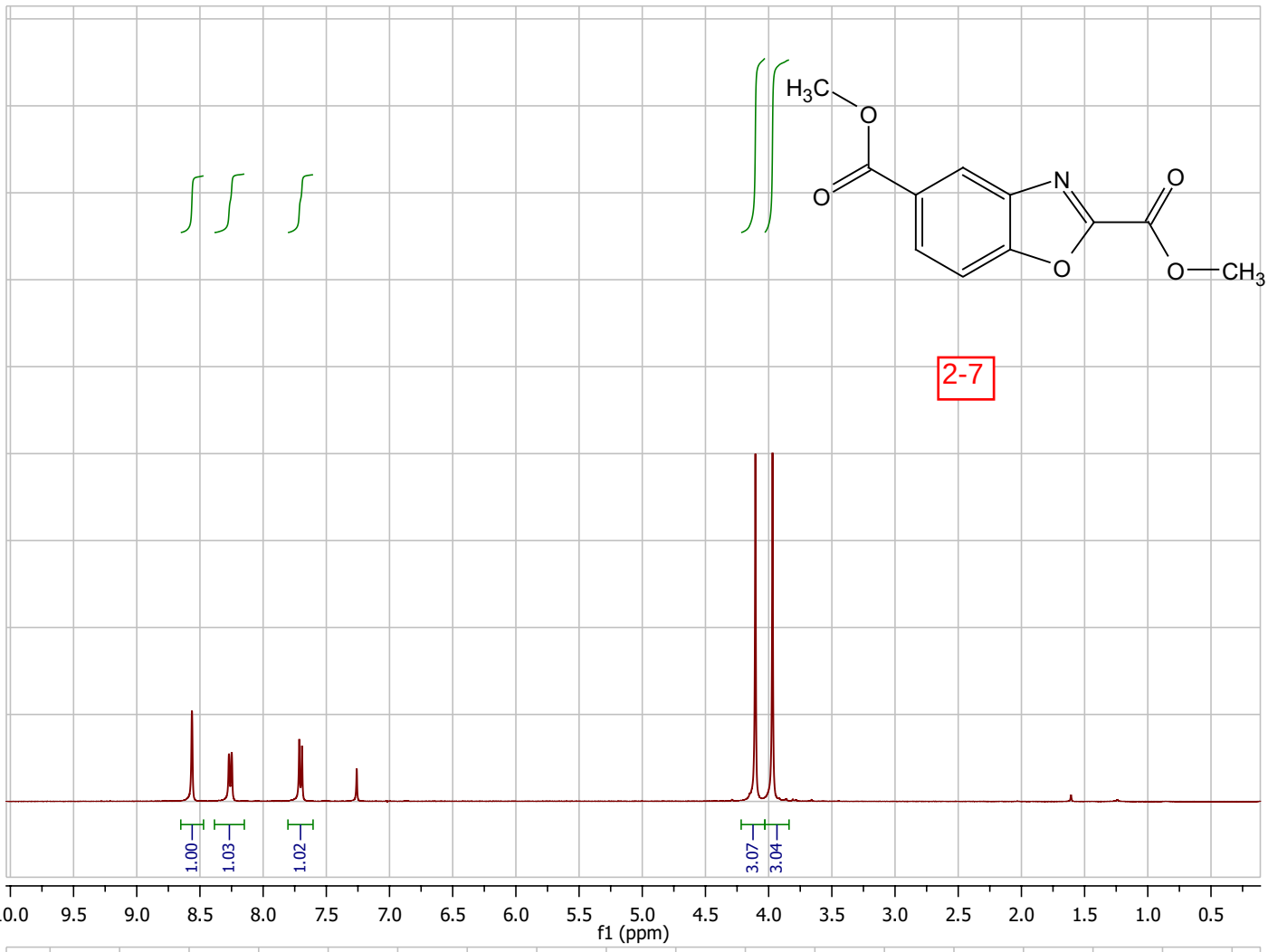
141.31
131.36
128.66
121.75
112.49
53.74
f1 (ppm)


2-7
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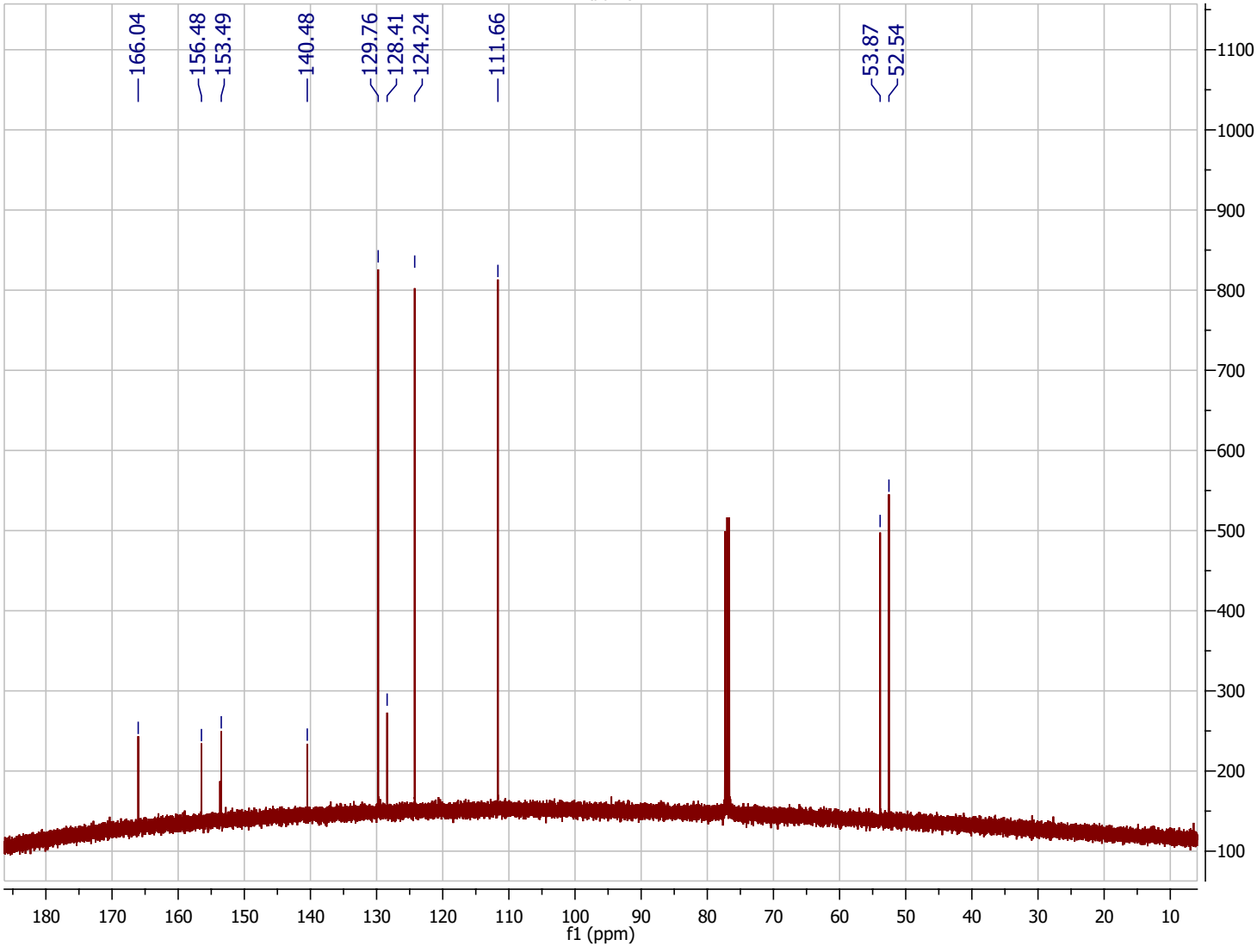
1.03
1.02
3.07
3.04
f1 (ppm)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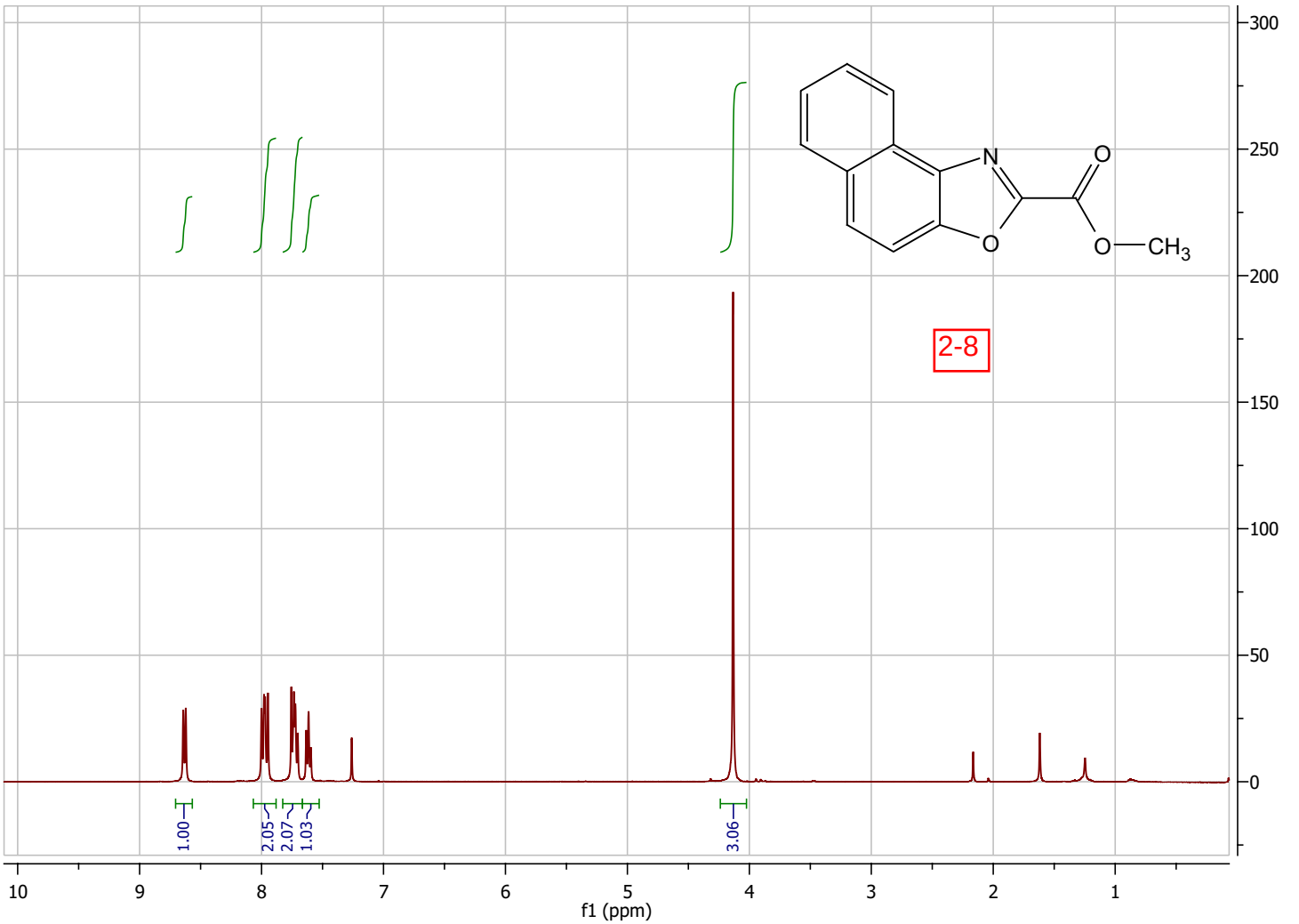
156.48
153.49
140.48
129.76
128.41
124.24
111.66
53.87
52.54
f1 (ppm)


2-8
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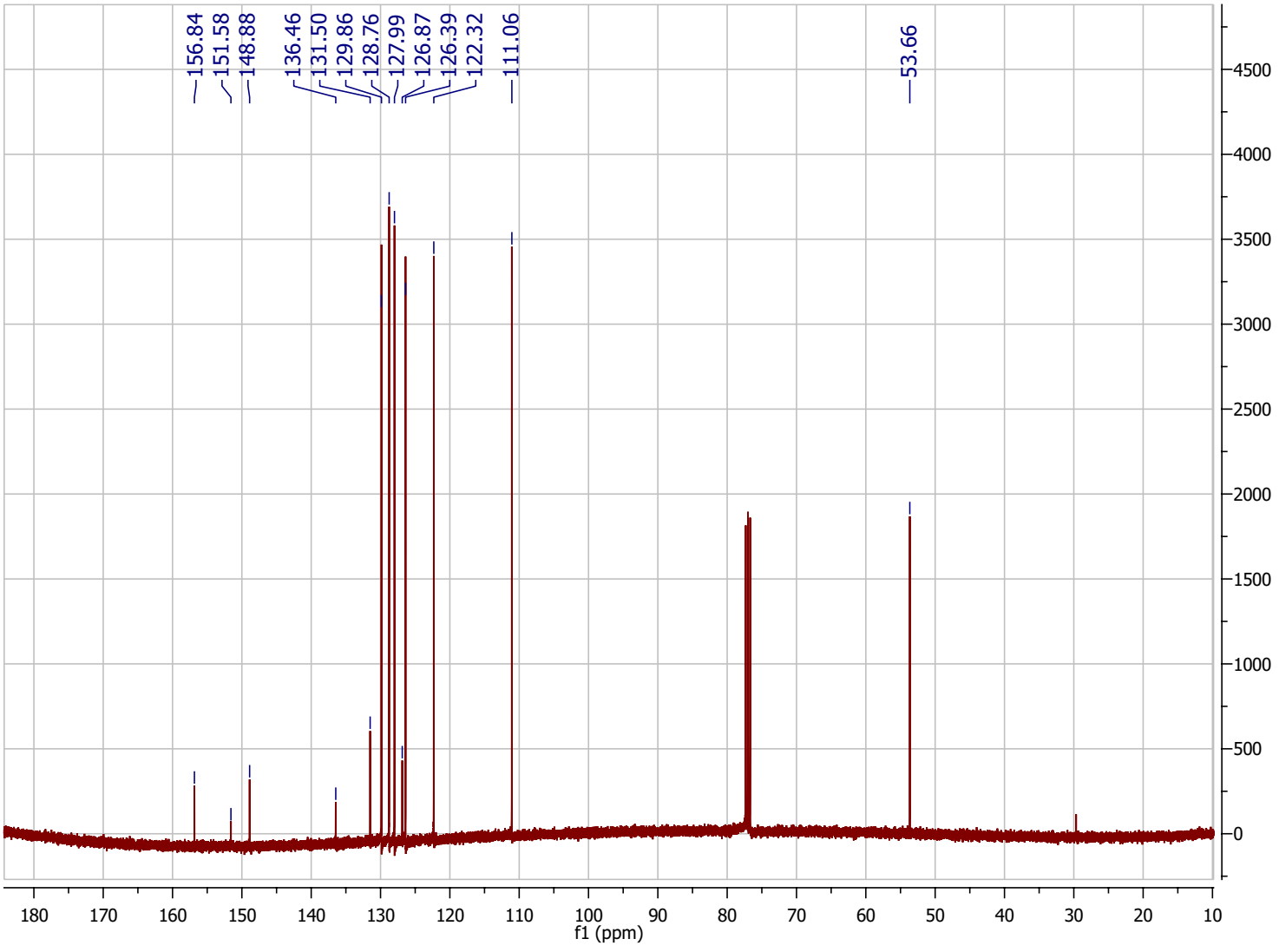
2.05
2.07
1.03
3.06
f1 (ppm)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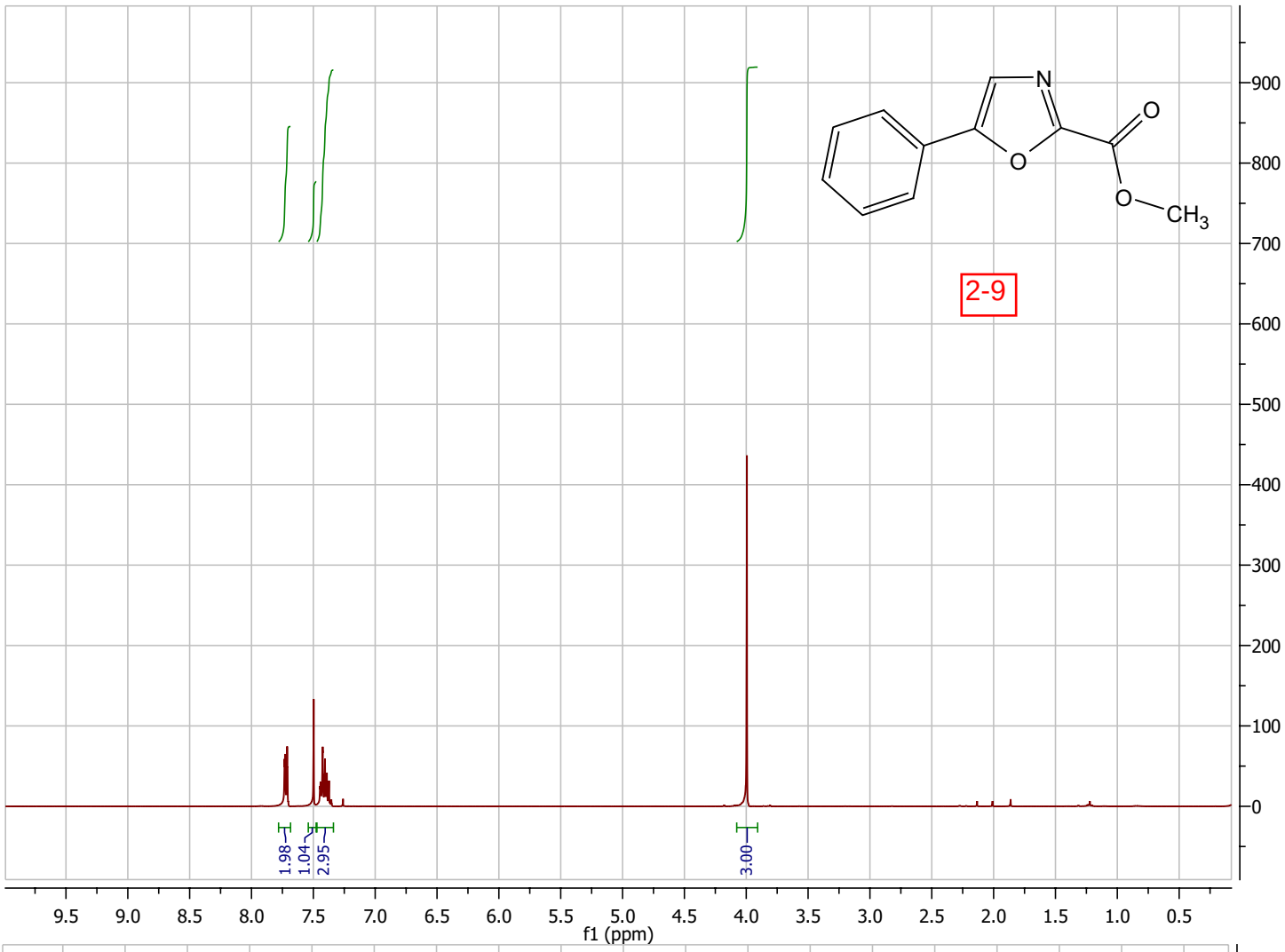
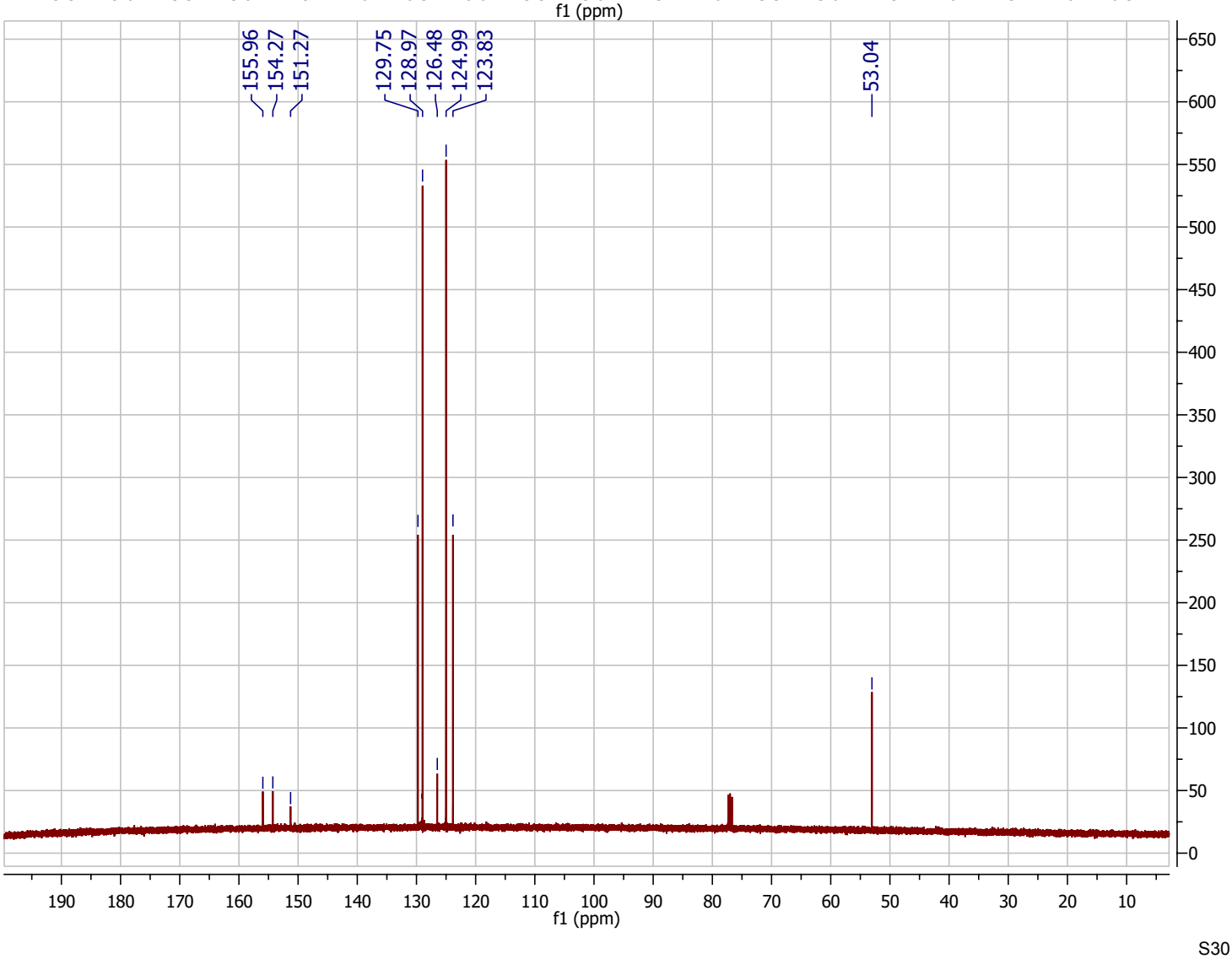
151.58
148.88
136.46
131.50
129.86
128.76
127.99
126.87
126.39
122.32
111.06
53.66
f1 (ppm)


N
O
O
O
CH3
2-9
1.98
1.04
2.95
3.00
f1 (ppm)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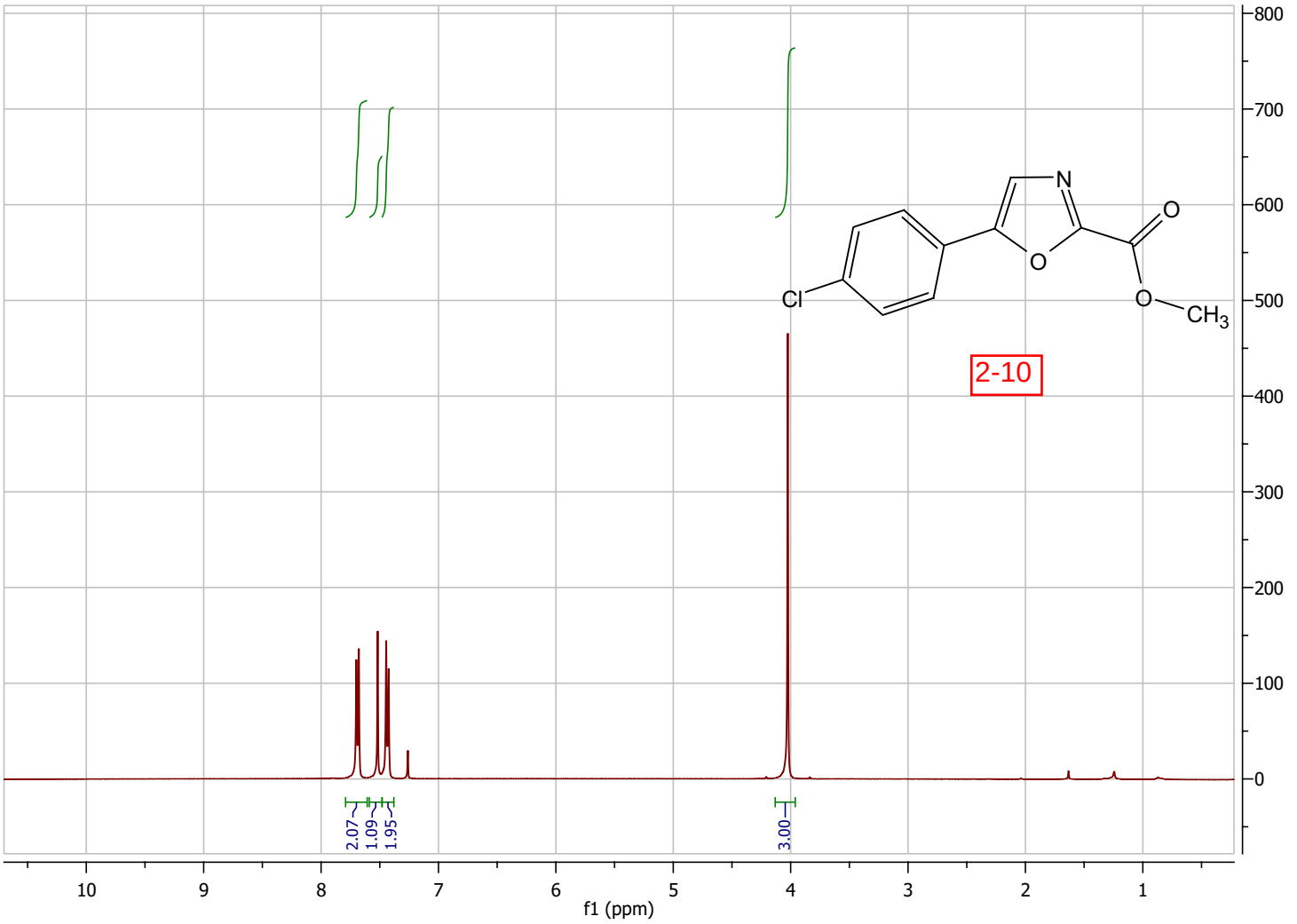
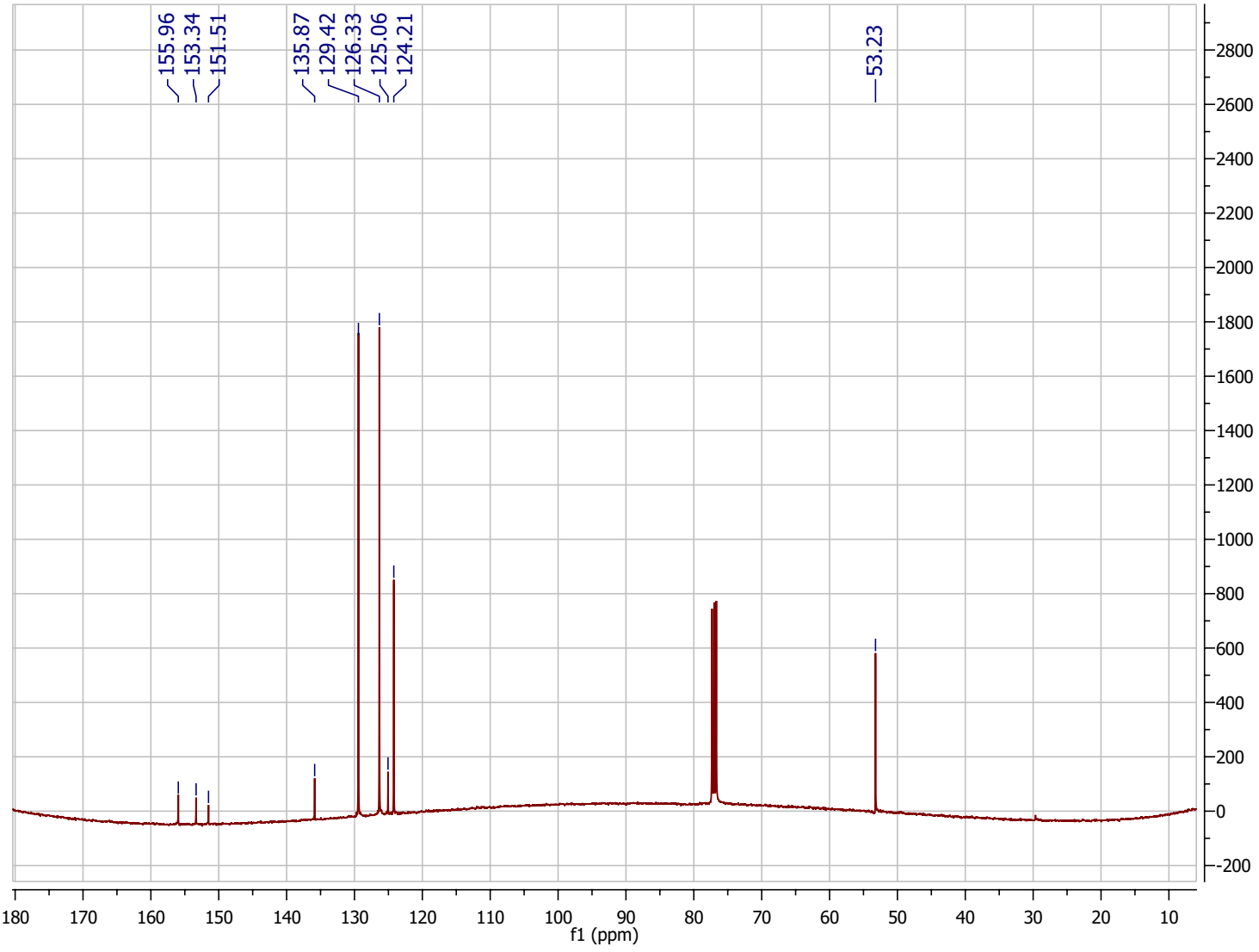
154.27
151.27
129.75
128.97
126.48
124.99
123.83
53.04
f1 (ppm)


N
O
O
O
Cl
CH3
2-10
2.07
1.09
1.95
3.00
f1 (ppm)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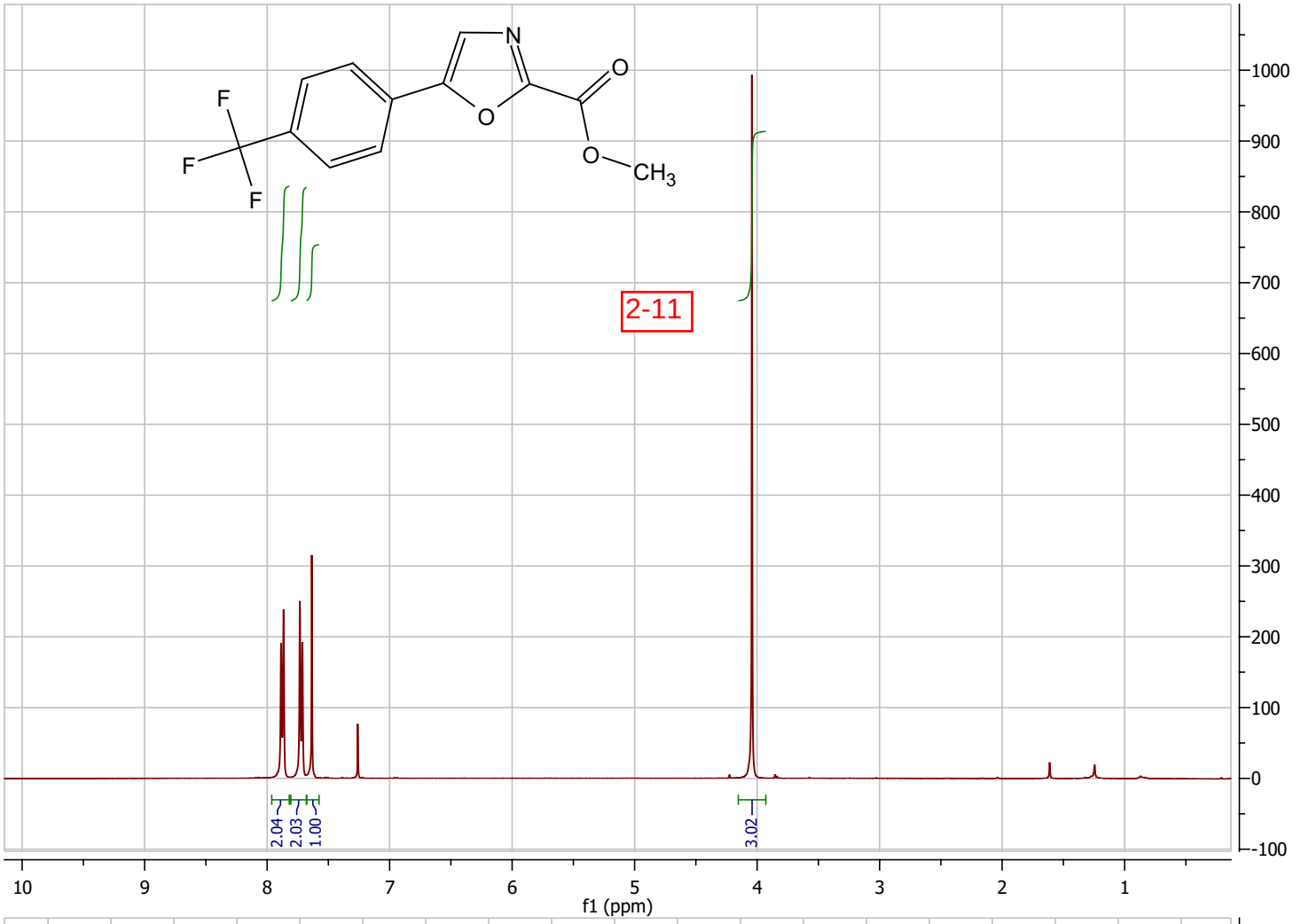
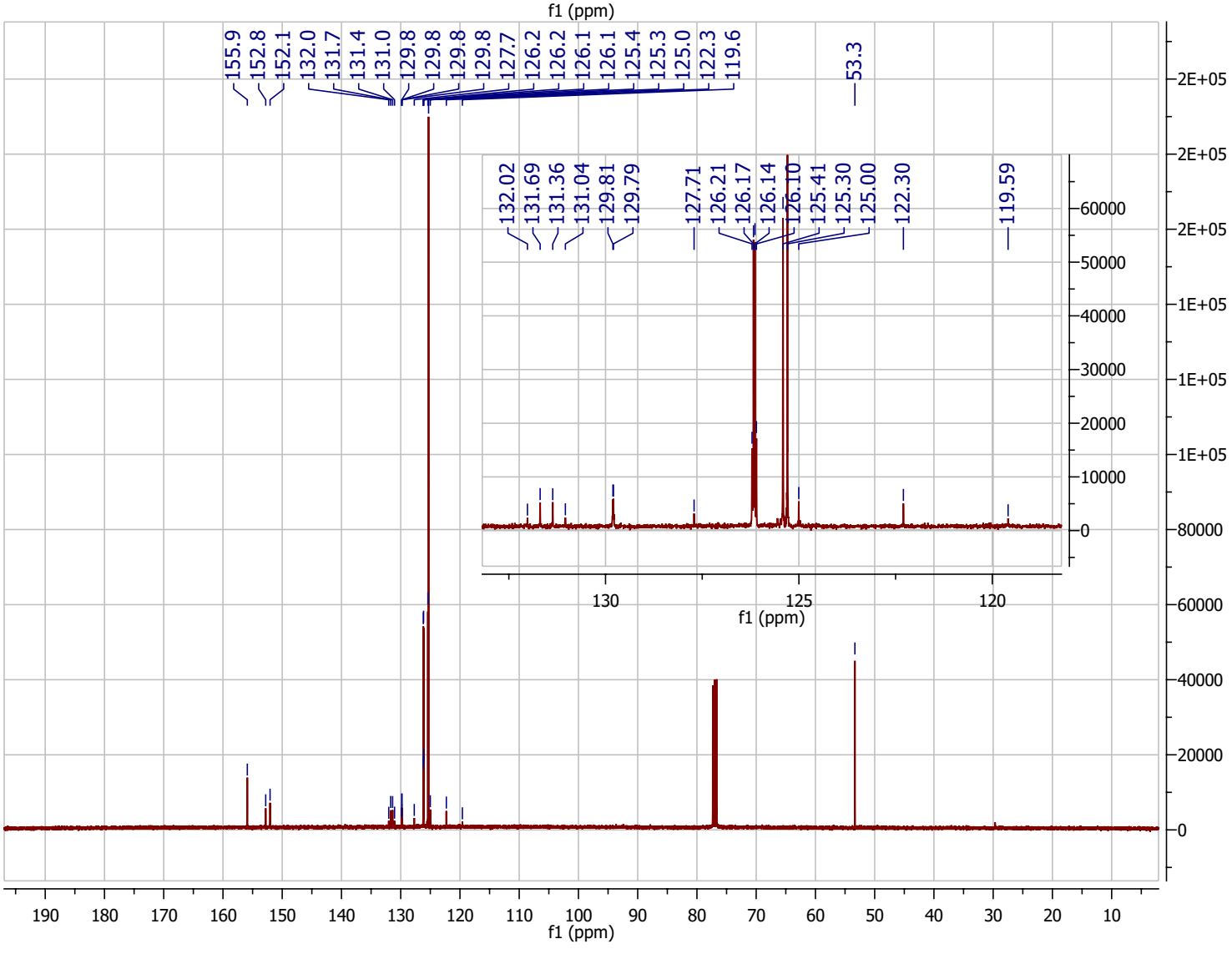
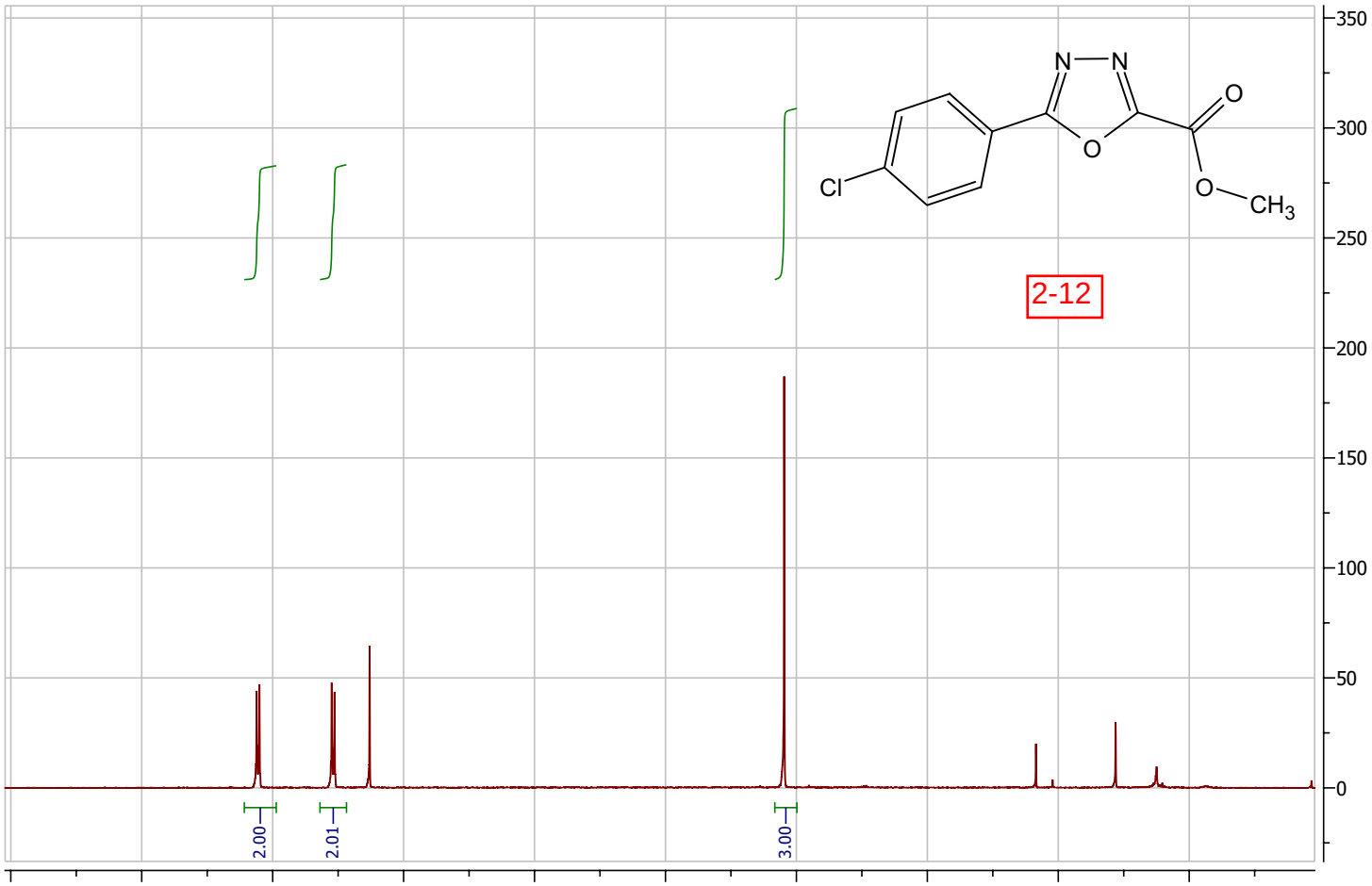
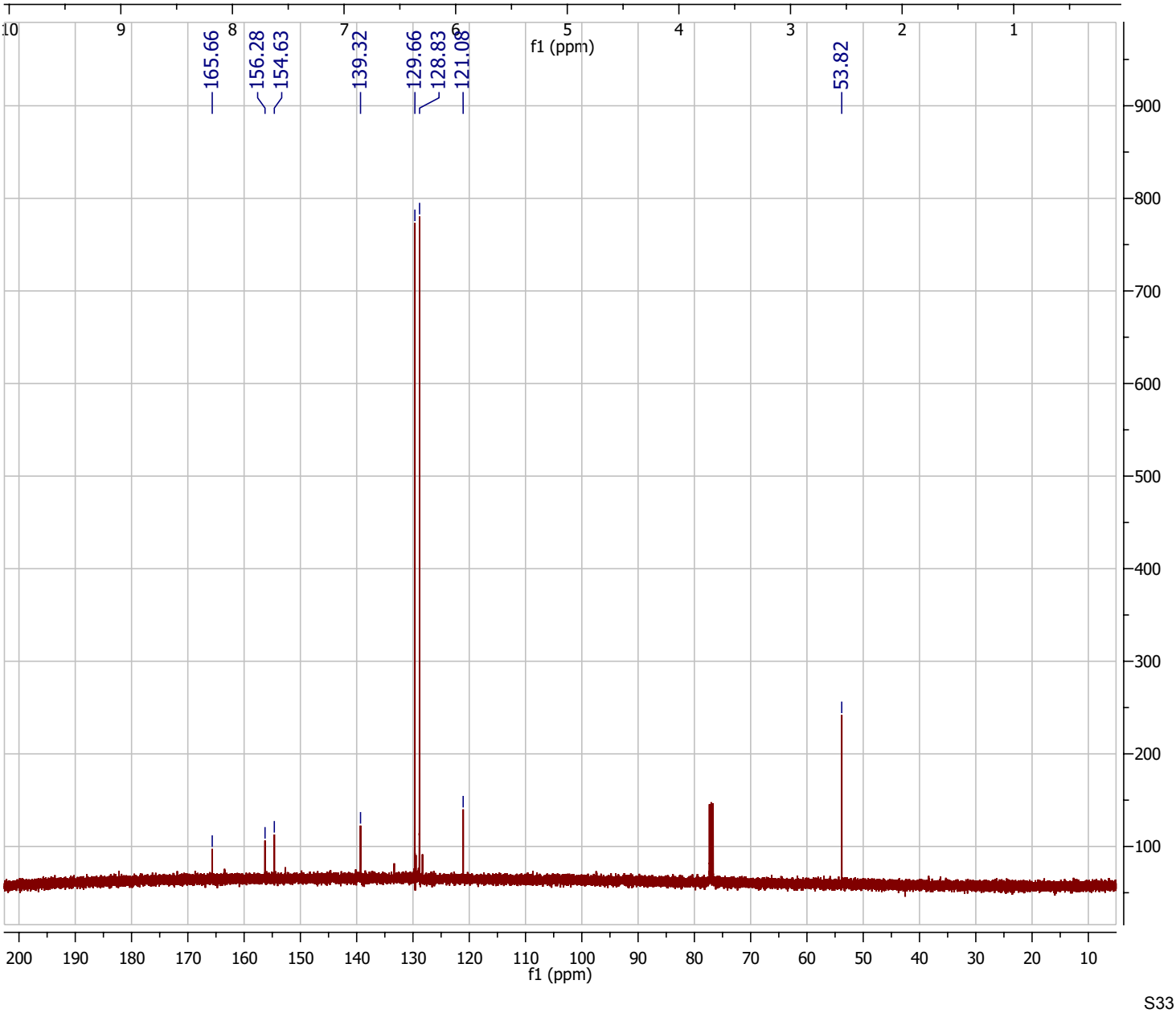
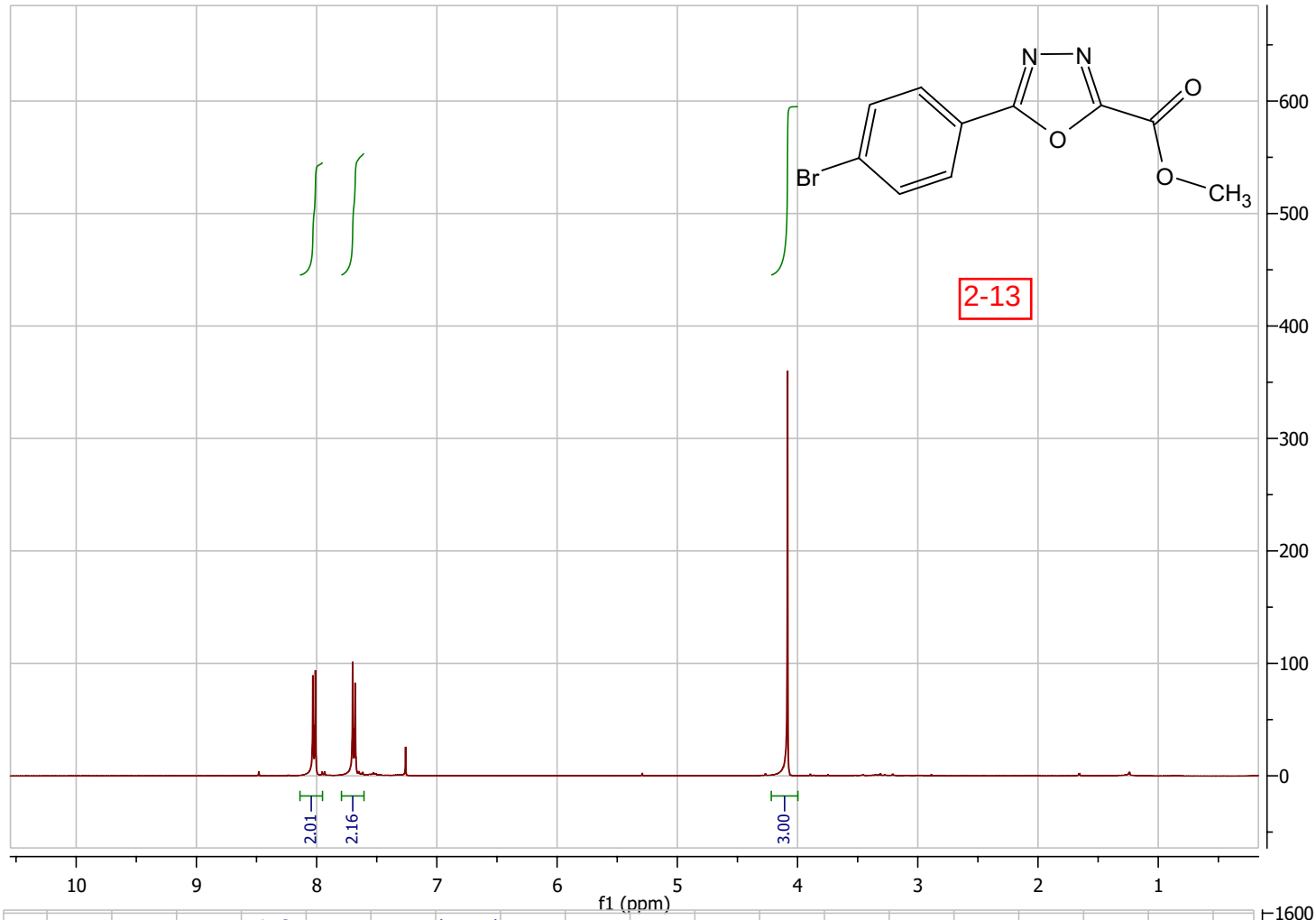
151.51
135.87
129.42
126.33
125.06
124.21
53.23
f1 (ppm)

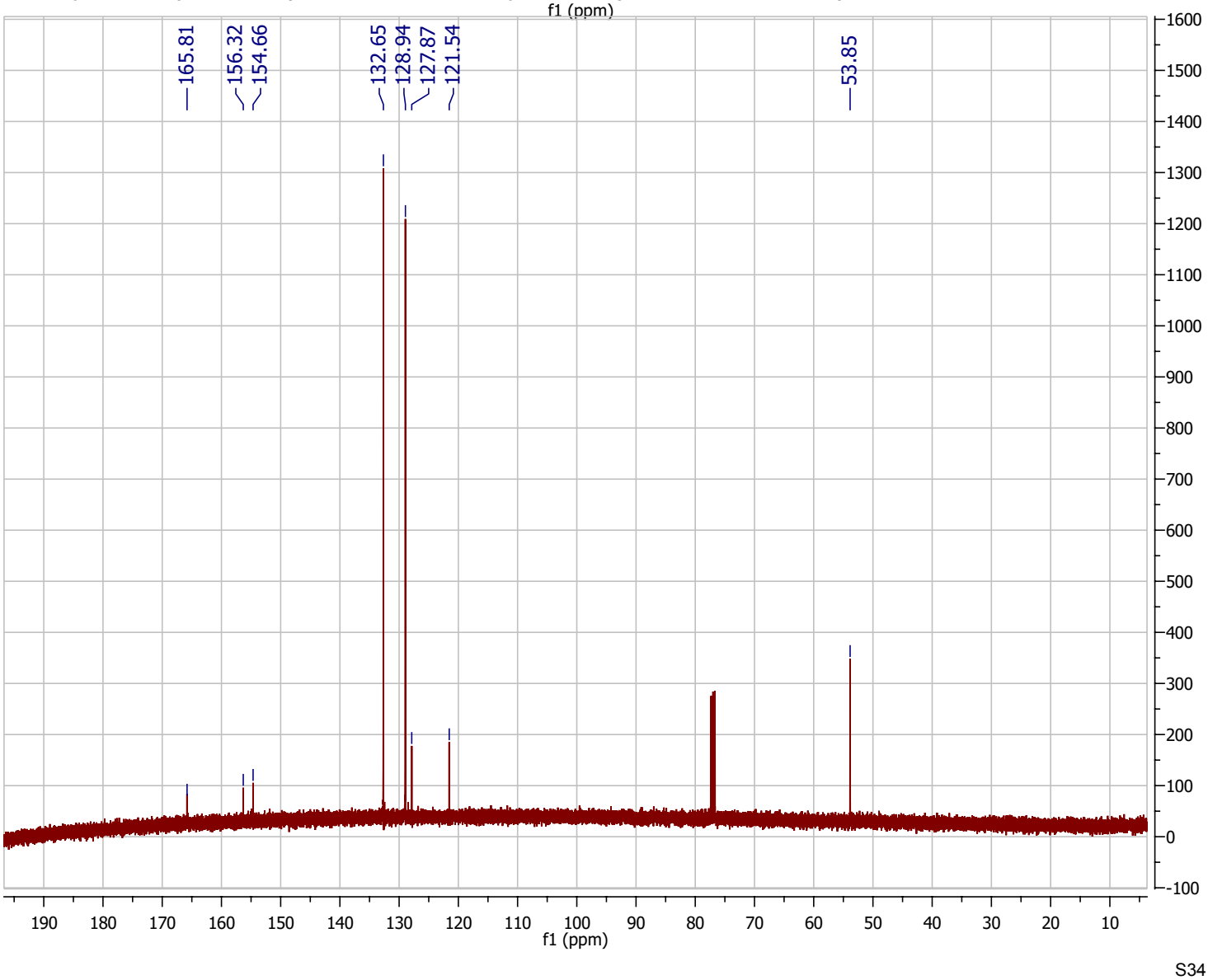

F
F
F
N
O
O
O
CH3
2-11
2.04
2.03
1.00
3.02
f1 (ppm)

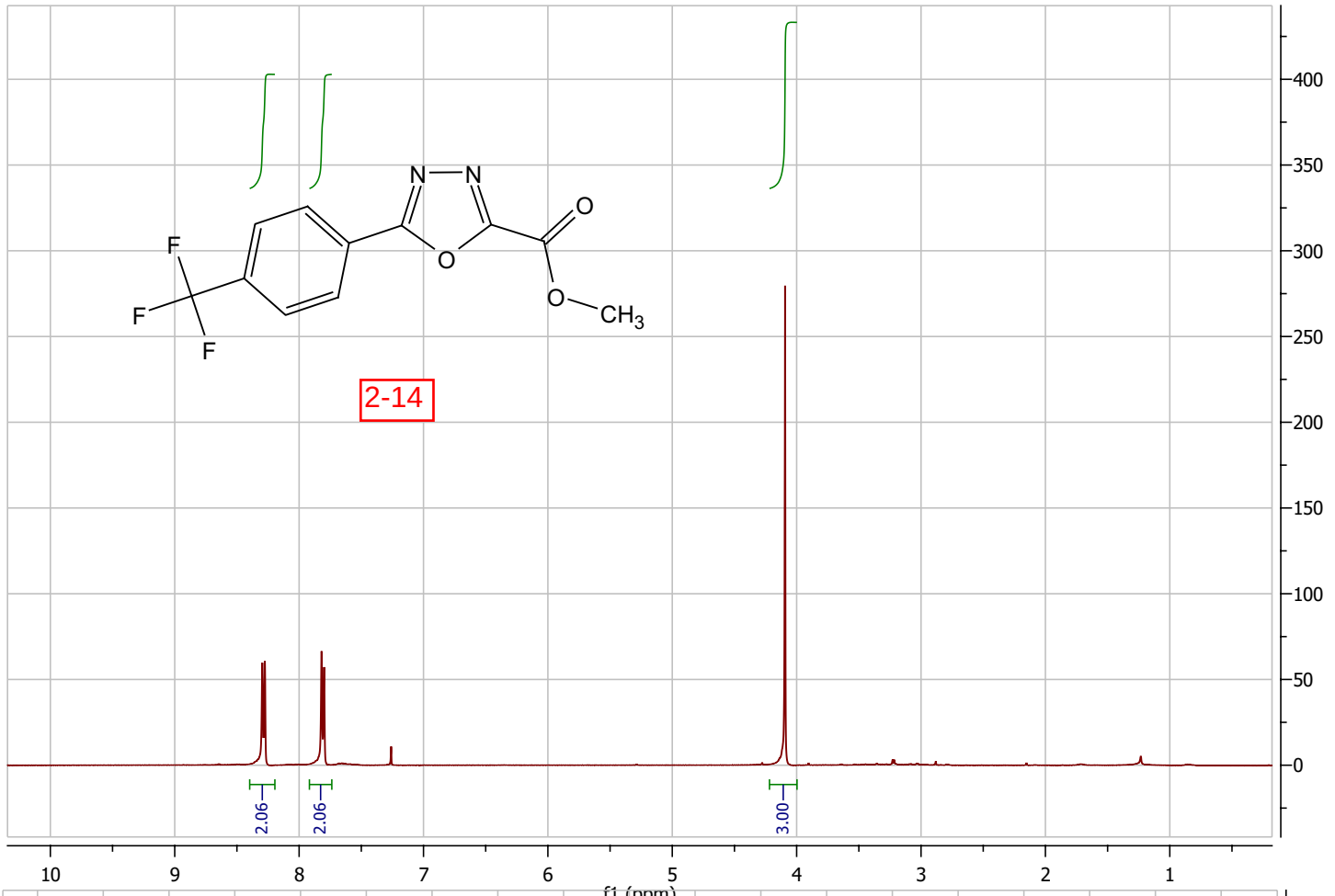

155.9
152.8
152.1
132.0
131.7
131.4
131.0
129.8
129.8
129.8
129.8
127.7
126.2
126.2
126.1
126.1
125.4
125.3
125.0
122.3
119.6
53.3
132.02
131.69
131.36
131.04
129.81
129.79
127.71
126.21
126.17
126.14
126.10
125.41
125.30
125.00
122.30
119.59
f1 (ppm)
f1 (ppm)

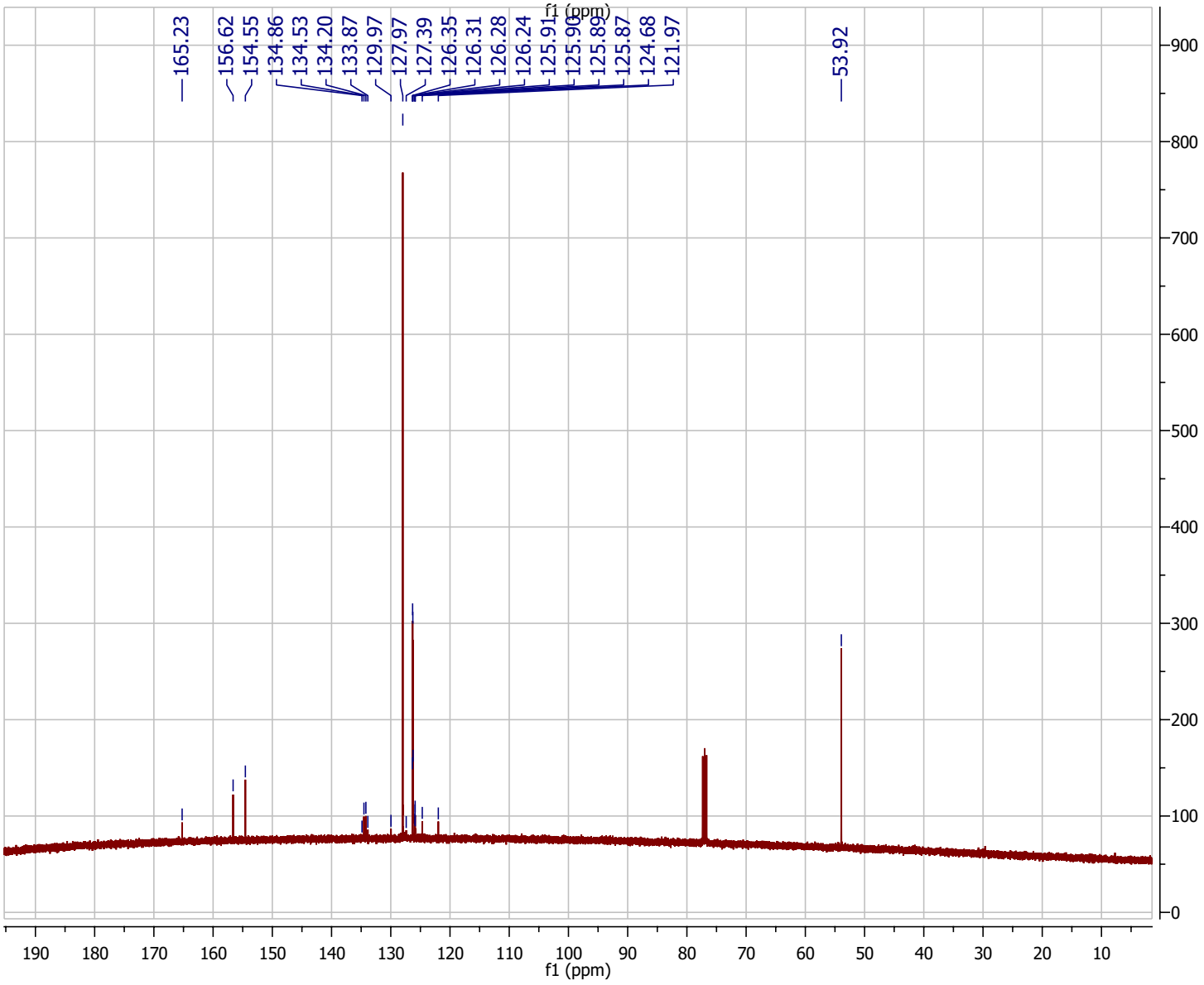

N
N
O
O
O
Cl
O
CH3
2-12
2.00
2.01
3.00
10
9
8
7
6
5
4
3
2
1
f1 (ppm)
350
300
250
200
150
100
50
0

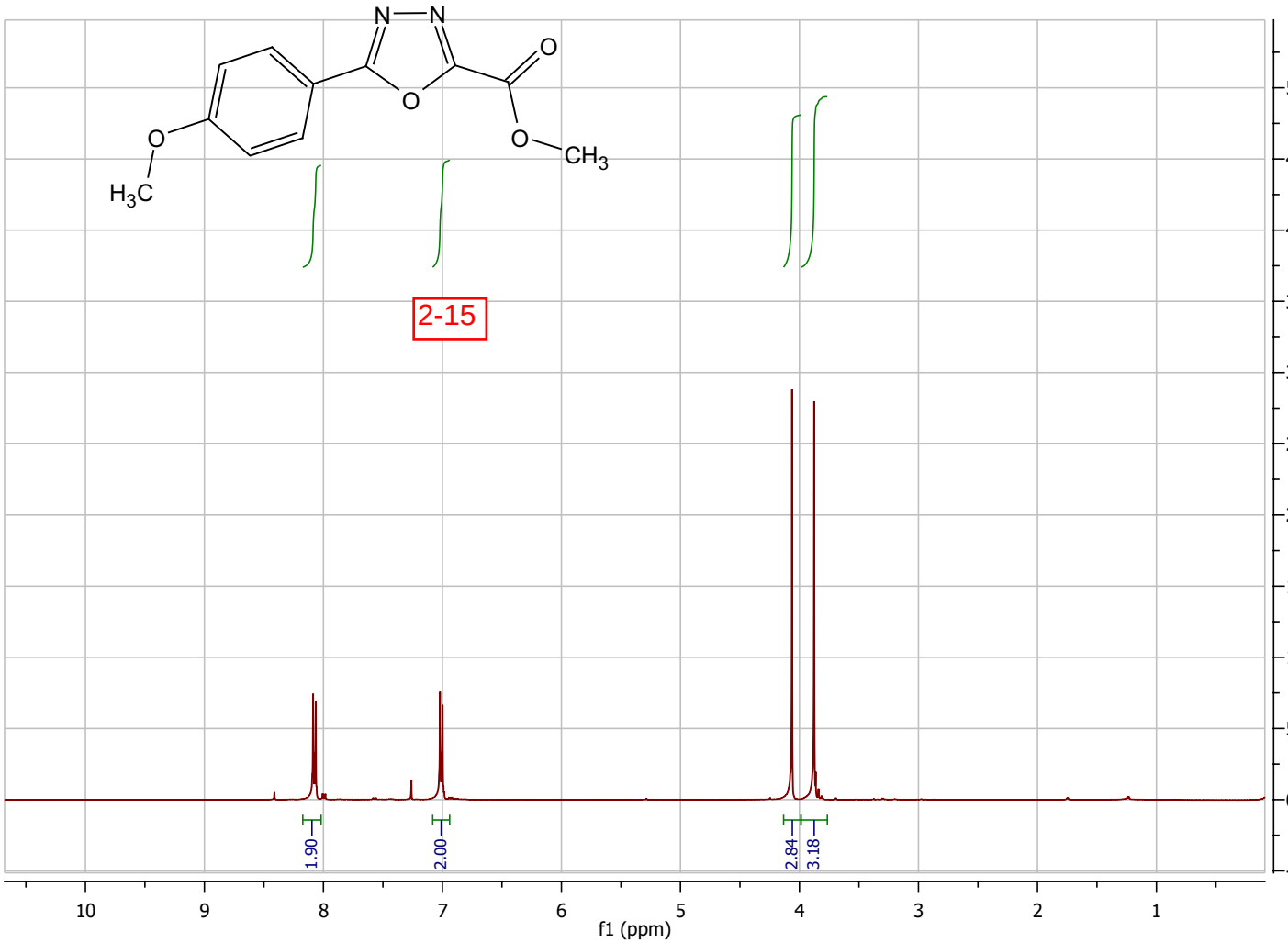

165.66
156.28
154.63
139.32
129.66
128.83
121.08
53.82
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)
900
800
700
600
500
400
300
200
100

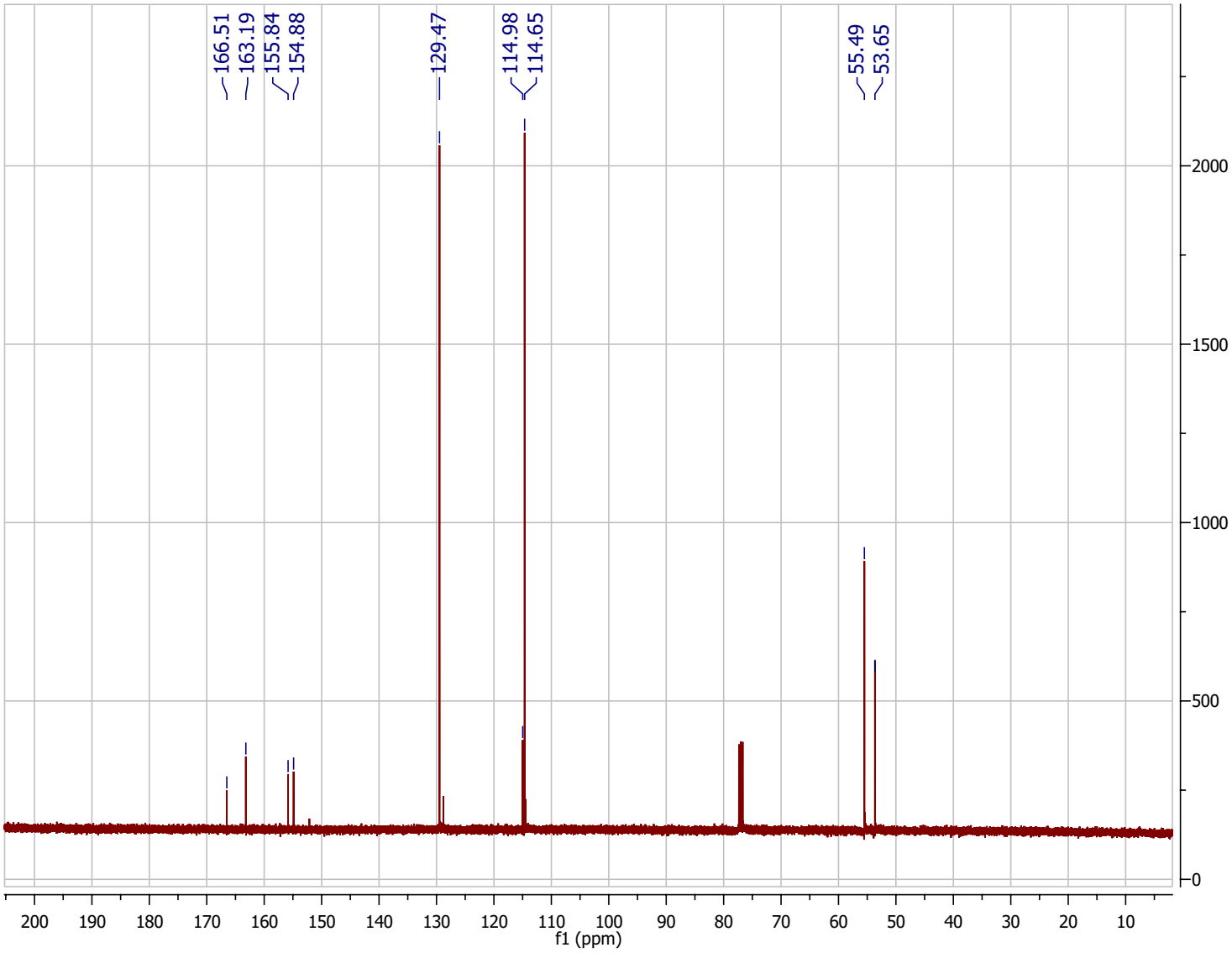

Br
N
N
O
O
O
CH3
2-13
2.01
2.16
3.00
f1 (ppm)

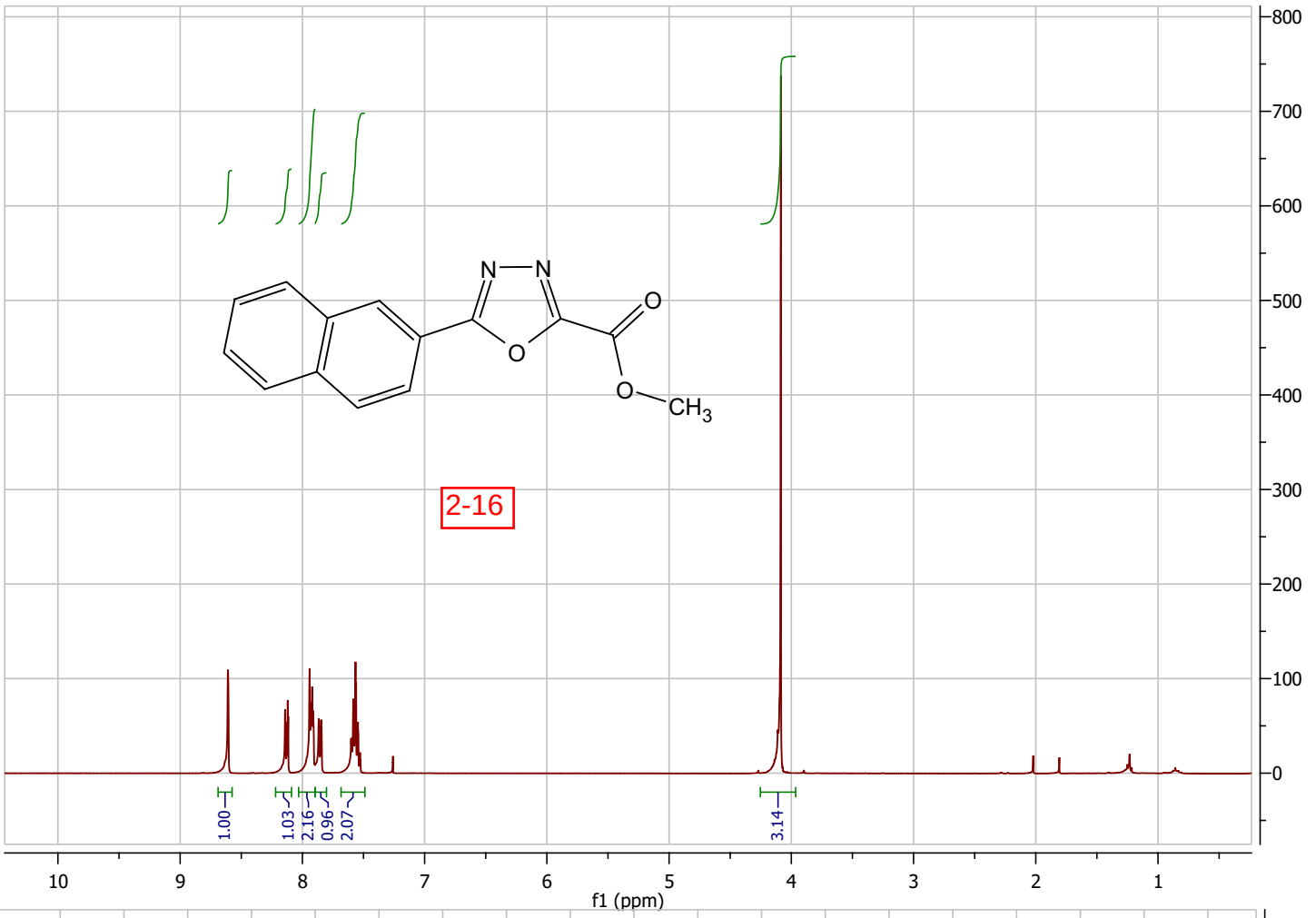

165.81
156.32
154.66
132.65
128.94
127.87
121.54
53.85
f1 (ppm)

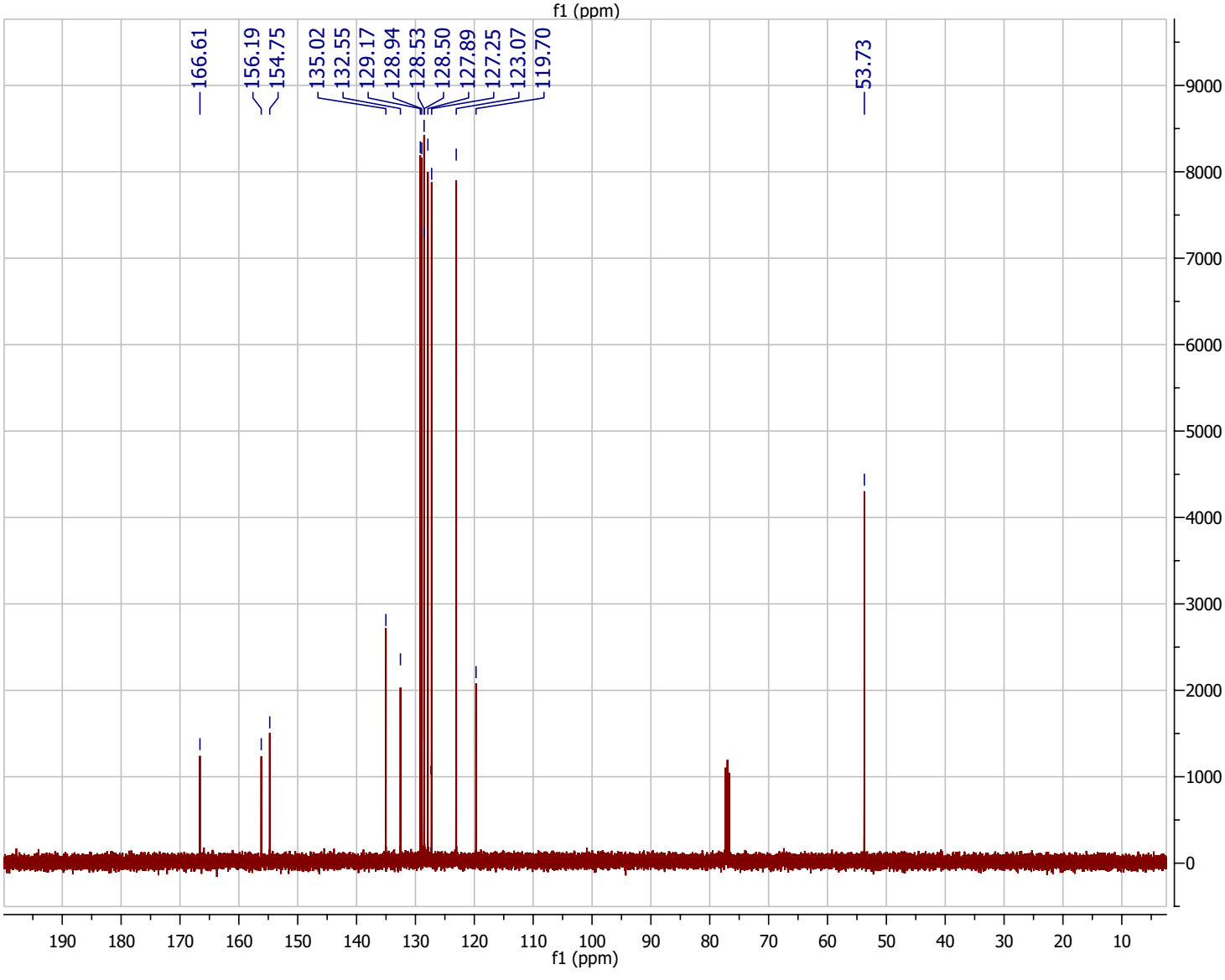

F
F
F
N
N
O
O
O
CH3
2-14
2.06
2.06
3.00
400
350
300
250
200
150
100
50
0
10
9
8
7
6
5
4
3
2
1
f1 (ppm)

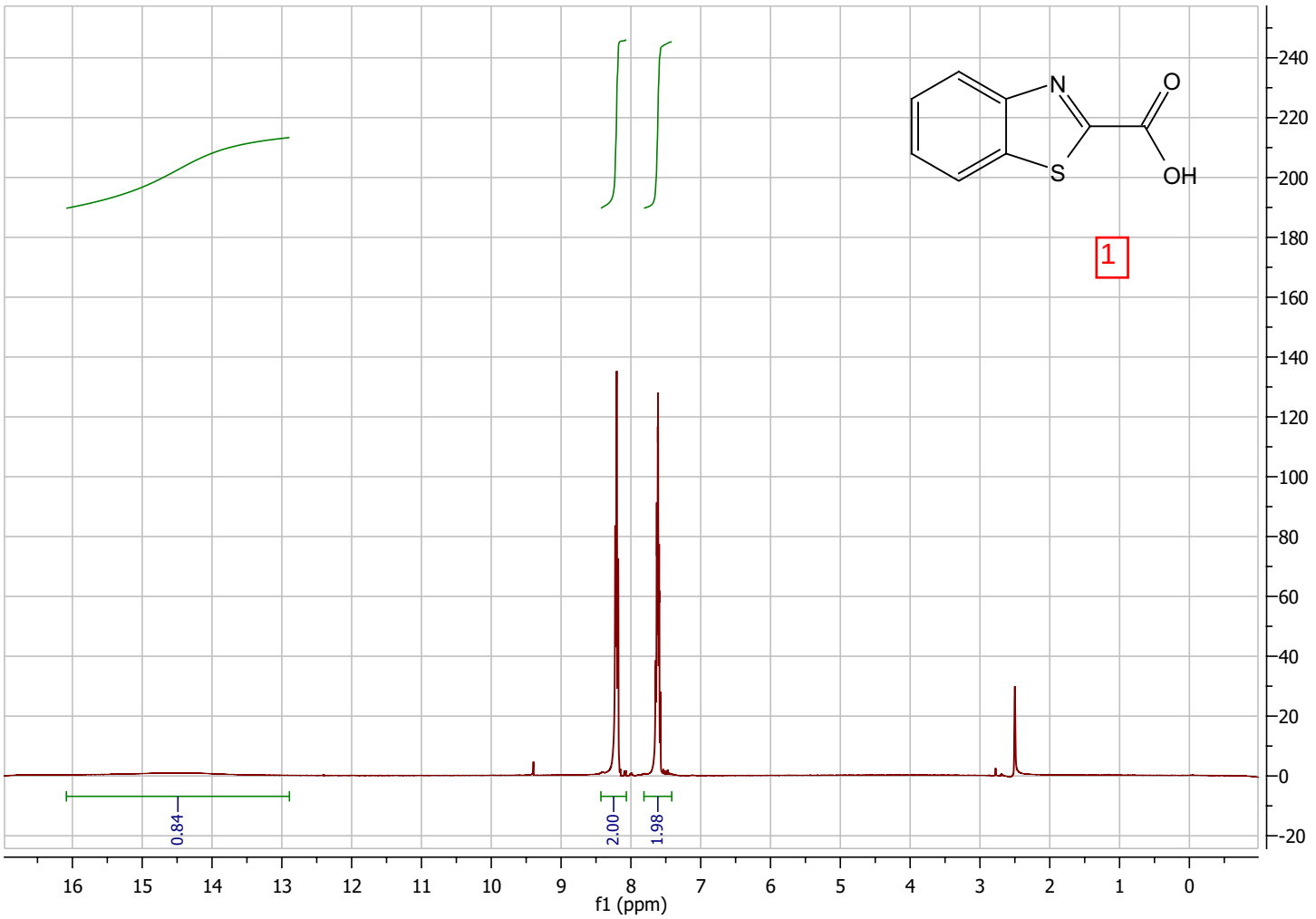

165.23
156.62
154.55
134.86
134.53
134.20
133.87
129.97
127.97
127.39
126.35
126.31
126.28
126.24
125.91
125.90
125.89
125.87
124.68
121.97
53.92
900
800
700
600
500
400
300
200
100
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

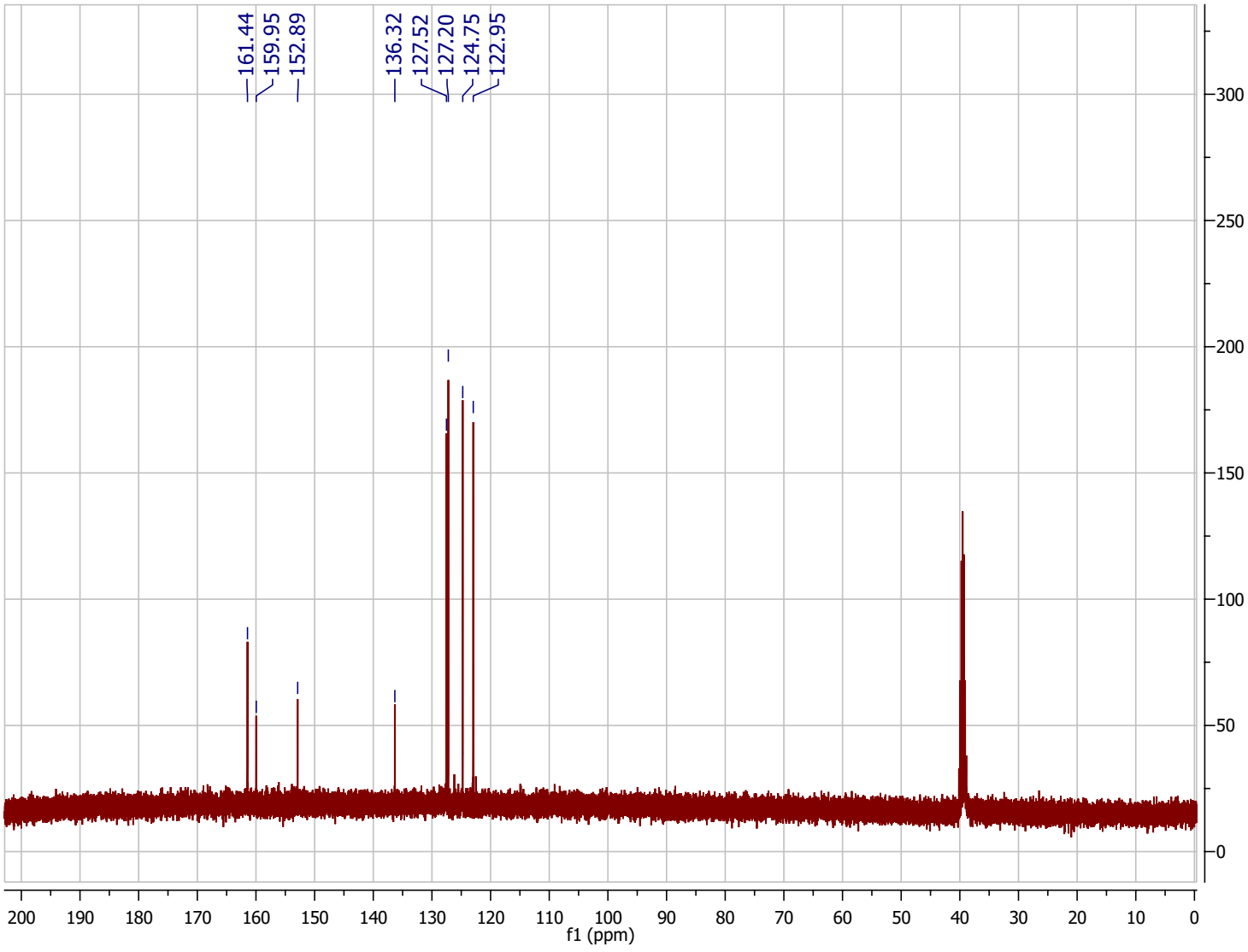

2-15
1.90
2.00
2.84
3.18
f1 (ppm)


166.51
163.19
155.84
154.88
129.47
114.98
114.65
55.49
53.65
f1 (ppm)


N
N
O
O
O
CH3
2-16
1.00
1.03
2.16
0.96
2.07
3.14
f1 (ppm)


166.61
156.19
154.75
135.02
132.55
129.17
128.94
128.53
128.50
127.89
127.25
123.07
119.70
53.73
f1 (ppm)


N
O
S
OH
1
0.84
2.00
1.98
f1 (ppm)


161.44
159.95
152.89
136.32
127.52
127.20
124.75
122.95
f1 (ppm)