Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Low-Cost Instant CO Generation at Room Temperature from Formic Acid, Mesyl Chloride and Triethylamine

*Cedrick Veryser,[a] Seger Van Mileghem,[a] Brecht Egle, Philippe Gilles and Wim M. De Borggraeve**

(a) Authors contributed equally

Department of Chemistry, Molecular Design and Synthesis, KU Leuven, Celestijnenlaan 200F box 2404, 3001 Leuven, Belgium.

Wim.DeBorggraeve@chem.kuleuven.be

Supporting Information

Table of Contents

1. General Information

^{1}H NMR spectra

^{1}H-NMR spectra were recorded on Bruker Avance 300 (300 MHz), Bruker Avance 400 (400 MHz) and Bruker Avance II^{+} 600 (600 MHz) spectrometers. Samples were dissolved in $CDCl_3$ or DMSO-d_6 and tetramethylsilane was used as internal standard. The δ-values are expressed in ppm.

^{13}C NMR spectra

^{13}C-NMR spectra were recorded on Bruker Avance 300 (working at 75 MHz), Bruker Avance 400 (working at 100 MHz) and Bruker Avance II^{+} 600 (working at 150 MHz) spectrometers. The deuterated solvents were used as internal standard ($CDCl_3$: 77.16 ppm, triplet; DMSO-d_6: 39.52 ppm, quintet). The δ-values are expressed in ppm.

Chromatography

TLC plates: pre-coated TLC-plates SIL G-25 (with fluorescence-indicator 254 nm): layer thickness 0.25 mm; average pore diameter 60 Å; 20x20 cm glass plates

Silica gel for column chromatography: MP Silica 32-63, average pore diameter 60 Å, Ecochron

MPLC apparatus: Büchi SepacoreTM flash apparatus, consisting of a C-660 Büchi fraction collector,C-615 Pump manager, C-635 UV-photometer, two C-605 pump modules and a Linseis D120S plotter.

Materials

All reagents were obtained from commercially available sources and were used as purchased without further purification. All moisture-sensitive reactions were carried out under argon atmosphere and in flame-dried glassware. Reactions were magnetically stirred and monitored by using pre-coated silica gel 60 F254 (250 µm) glass-supported TLC plates. Compounds were visualized by UV irradiation (254 nm). Flash column chromatography was performed on pre-packed silica gel (40-63 µm) columns. Solvents were evaporated with a rotavapor at a temperature of 40°C. Yields refer to isolated compounds after chromatography.

2. ^{13}C-NMR study of the CO generating system

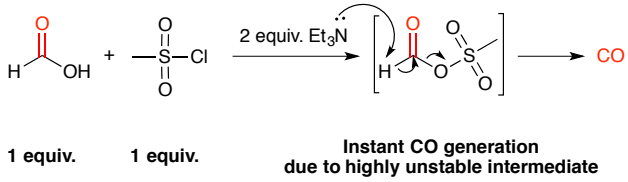
To gain insight in the steps involved in the decomposition mechanism of formic acid to carbon monoxide in presence of mesyl chloride and triethylamine, a ^{13}C-NMR study was conducted at room temperature (Scheme S2). The recorded spectra were measured in acetonitrile-d_3.

- Spectrum [A] 0.5 mmol HCOOH in 600 µL CD_3CN.
- Spectrum [B] 0.5 mmol MsCl in 600 µL CD_3CN.
- Spectrum [C] 0.5 mmol HCOOH and 0.5 mmol MsCl in 600 µL CD_3CN.
- Spectrum [D] 0.5 mmol HCOOH, 0.5 mmol MsCl and 1.0 mmol Et_3N in 600 µL CD_3CN.
- Spectrum [E] 0.5 mmol MsOH and 1.0 mmol Et_3N in 600 µL CD_3CN.

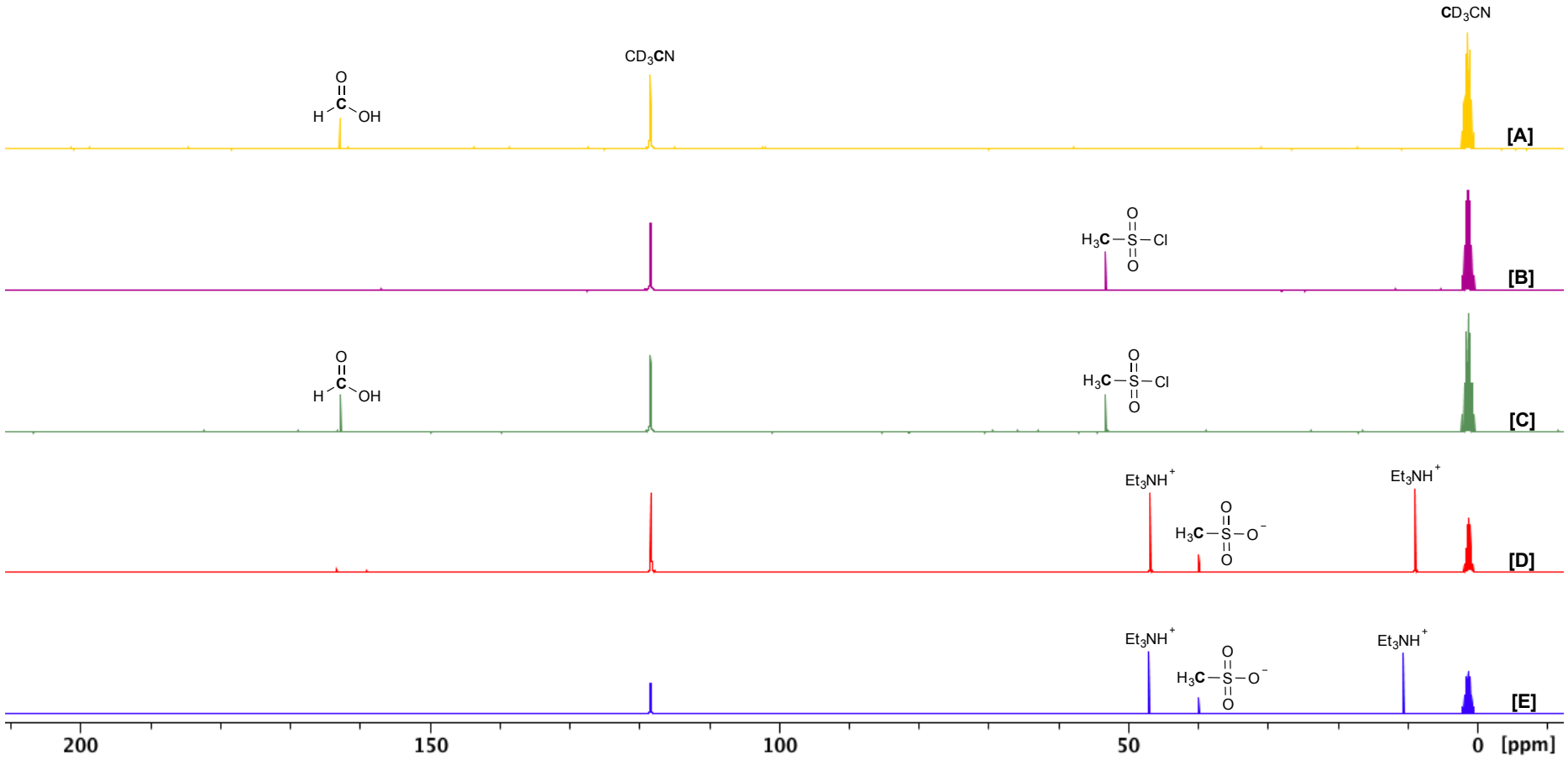
Spectra [A], [B], [E] show the reference ppm-values of formic acid (HCOOH = 162.7 ppm), mesyl chloride (MsCl = 53.3 ppm) and methanesulfonate (MsO^- = 39.6 pppm). Upon addition of mesyl chloride to formic acid, no gas formation is observed in the tube. This is confirmed by NMR where no shifts in peaks were observed (spectrum [C] is the sum of spectra [A] and [B]). Apparently no reaction occurs between these reagents in the absence of base.

Upon dropwise addition of 1.0 mmol Et_3N to 0.5 mmol HCOOH and 0.5 mmol MsCl, vigorous gas development occurs for several seconds. Afterwards a ^{13}C-NMR spectrum was recorded (spectrum [D]) and complete decomposition of HCOOH was observed as the corresponding peak disappeared. The peak of mesyl chloride shifted to lower ppm-values (from 53.3 to 39.6 ppm), indicating the formation of triethyl ammonium methanesulfonate salt.

These results indicate that once the formic acid is deprotonated, it most probably reacts with mesyl chloride and forms a highly unstable mixed anhydride intermediate. A second deprotonation leads to instant CO formation, as the methanesulfonate is an excellent leaving group (Scheme S1).



Scheme S1. Proposed decomposition mechanism of formic acid in presence of 1 equiv. mesyl chloride and 2 equiv. triethylamine leading to instant CO generation.



Scheme S2. ^{13}C-NMR study of the CO precursor at room temperature. [A] 0.5 mmol HCOOH in 600 µL CD_3CN. [B] 0.5 mmol MsCl in 600 µL CD_3CN. [C] 0.5 mmol HCOOH and 0.5 mmol MsCl in 600 µL CD_3CN. [D] 0.5 mmol HCOOH, 0.5 mmol MsCl and 1.0 mmol Et_3N in 600 µL CD_3CN. [E] 0.5 mmol MsOH and 1.0 mmol Et_3N in 600 µL CD_3CN.

3. Influence of Mesyl Chloride and Acetic Anhydride on the decomposition rate of Formic Acid – A Visual Experiment

Recently the Wu group reported that formic acid releases carbon monoxide in presence of acetic anhydride under basic conditions.[1,2] Unfortunately this decomposition is slow, while instant carbon monoxide generation is desired as it directly stabilises the catalytic system and shortens the reaction time.[3]

We have discovered that formic acid can be instantly decomposed to carbon monoxide in presence of mesyl chloride and triethylamine.

A visual experiment was conducted to compare the influence of mesyl chloride and acetic anhydride on the decomposition rate of formic acid in presence of triethylamine (Figure S1). Two 10 mL screw-capped vials were filled with 0.5 mmol formic acid and 2 mL dry degassed toluene. Next 0.5 mmol of mesyl chloride and 0.5 mmol acetic anhydride were added to respectively the left and right tube. Then two syringes were connected to the head-space through the sealed cap. One syringe contained 1.0 mmol triethylamine and the other syringe (12 mL) was empty (Figure S1 [A]). After the addition of triethylamine instant expansion of the left syringe was observed. After 10 seconds, the left syringe already contained 7 mL of CO (Figure S1 [C]). On the other hand the expansion of the right syringe (containing acetic anhydride) only started after 70 seconds. Using acetic anhydride as additive results in a much slower CO generation, as the corresponding syringe only contained 4 mL of CO after three minutes (Figure S1 [F]).

Remark: A video of this visual experiment is available in Supporting Info (MsCl_versus_AcOAc.mp4).

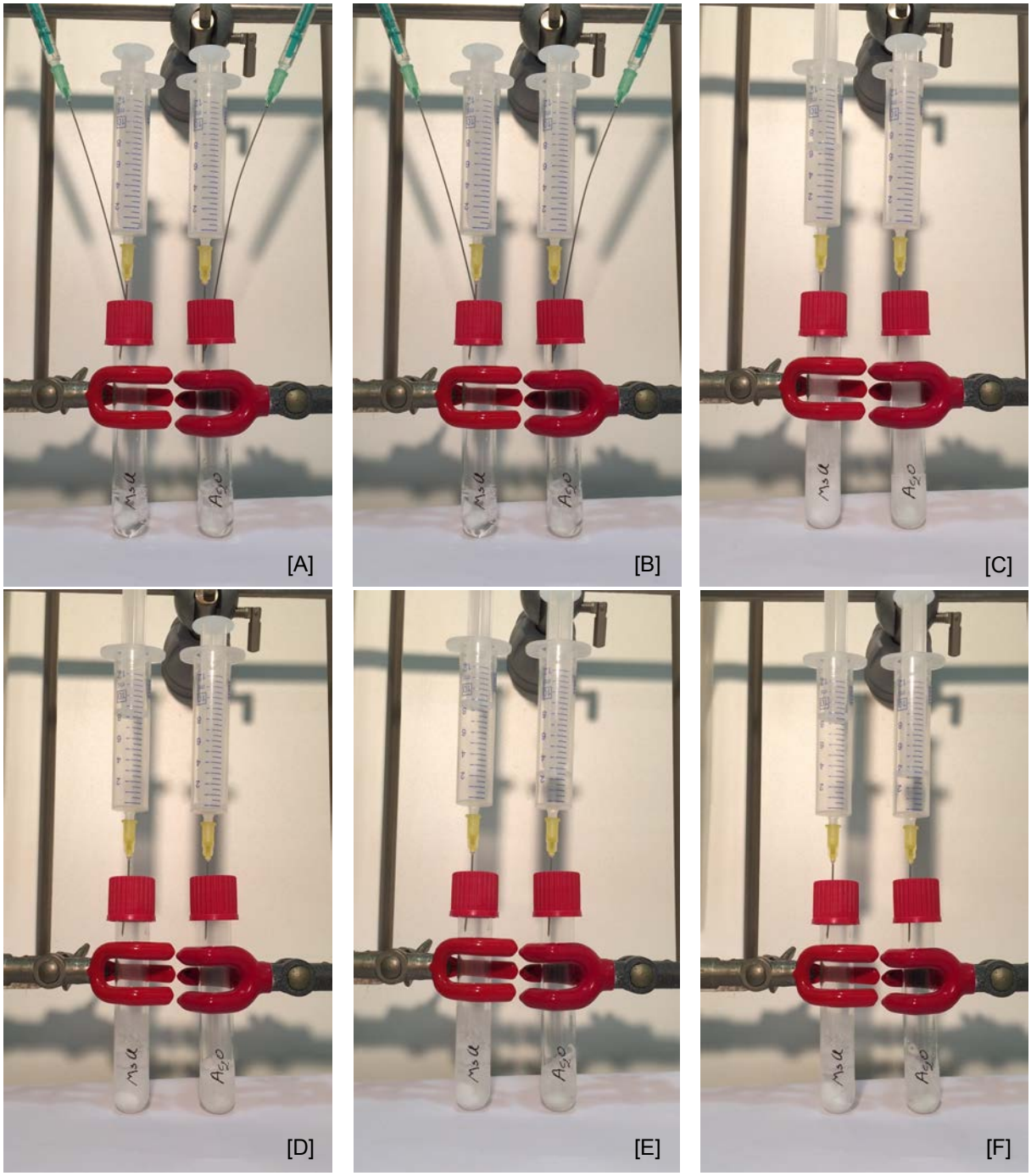


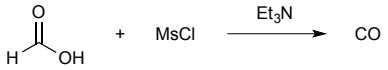
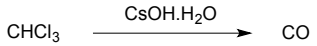
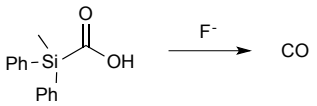
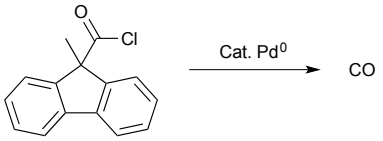
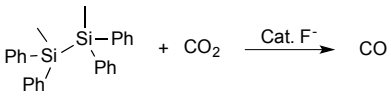
Figure S1. Visual experiment about the influence of mesyl chloride (left tube) and acetic anhydride (right tube) on the decomposition rate of formic acid to carbon monoxide in presence of triethylamine. Each tube contains 0.5 mmol HCOOH and 0.5 mmol additive in 2 mL dry degassed toluene. 1.0 mmol triethylamine was added to decompose the formic acid. [A] Before addition of triethylamine. [B] Addition of triethylamine. [C] 10 seconds after the addition of Et_3N. [D] 1 minute after the addition of Et_3N. [E] 2 minutes after the addition of Et_3N. [F] 3 minutes after the addition of Et_3N.

4. Price comparison of recently published CO generating systems

Recently a few new excellent CO generating systems were reported.[4-7] However some of these CO-precursors and/or additives are non-trivial chemicals and require one or more synthetic steps to produce.[5,6] In addition, the use of an expensive heterogeneous base or a transition metal is sometimes necessary to decompose the precursor.[4,7] Therefore it is advantageous if inexpensive commodities can be used to release carbon monoxide.

In this paper we report a state-of-the-art low-cost CO generation system based on the instant decomposition of formic acid by addition of mesyl chloride and triethylamine at room temperature. As shown in Table S1, this system is 30 to 140 times more cost efficient than the other reported precursors. The details of these price calculations are reported in Table S2 - Table S8. Note that no costs of solvent, work-up, purification and carbon dioxide were taken into account for these calculations. Also note that these price calculations are only indicative, as they will change over time. However the price difference is significant (factor 30 – 140).

Table S1. Price comparison of recently published CO generating systems. [a]Detailed information see Table S2 - Table S8. [b]The actual and relative price are even higher as no costs of work-up, purification and carbon dioxide were taken into account.

Method	CO generating system	Price[a]	Relative price compared to method 1
1		0.03 euro	1
2		3.45 euro	115
3		0.96 euro[b]	32[b]
4		4.24 euro	140
5		1.12 euro[b]	37[b]

4.1. Low-Cost Instant CO Generation at Room Temperature from Formic Acid, Mesyl Chloride and Triethylamine

Our reported CO generating systems consists of 1.3 equiv. formic acid, 1.3 equiv. mesyl chloride and 2.6 equiv. triethylamine.

Table S2. Price of our reported CO generating system. [a]Equivalents reported in the article. [b]Compared to 0.5 mmol aryl bromide as limiting reagent. [c]Commercial price based on the online catalogues of Sigma-Aldrich (date of consultation: the 19th of December 2015).

Chemicals	Equivalents[a]	mmol[b]	Commercial price[c]	Commercial price per mmol	Price
Formic acid	1.3	0.65	43.50 euro per 1 L	0.002 euro	0.001 euro
Mesyl chloride	1.3	0.65	24.10 euro per 100 mL	0.019 euro	0.01 euro
Triethylamine	2.6	1.30	107.00 euro per 1 L	0.015 euro	0.02 euro
				Total Price	0.03 euro

4.2. Chloroform as a Carbon Monoxide Precursor: In or Ex Situ Generation.[4]

The CO generating system in this article consists of 3.0 equiv. chloroform and 10.0 equiv. of cesiumhydroxide monohydrate.

Table S3. Price of the reported CO generating system. [a]Equivalents reported in the article. [b]Compared to 0.5 mmol aryl bromide as limiting reagent. [c]Commercial price based on the online catalogues of Sigma-Aldrich (date of consultation: the 19th of December 2015).

Chemicals	Equivalents[a]	mmol[b]	Commercial price[c]	Commercial price per mmol	Price
$CHCl_3$	3.0	1.5	72.20 euro per 1 L	0.003 euro	0.01 euro
$CsOH.H_2O$	10.0	5.0	40.90 euro per 10 G	0.688 euro	3.44 euro
				Total Price	3.45 euro

4.3. Silacarboxylic Acids as Efficient Carbon Monoxide Releasing Molecules: Synthesis and Application in Palladium-Catalyzed Carbonylation Reactions.[5]

The CO generating system in this article consists of 1.5 equiv. methyldiphenylsilacarboxylic acid and 1.7 equiv. potassium fluoride. However the methyldiphenylsilacarboxylic acid is not commercially available, but can be prepared via one extra synthesis step.

Table S4. Price of the methyldiphenylsilacarboxylic acid synthesis. [a]Equivalents reported in the article. [b]Compared to 0.5 mmol methyldiphenylsilacarboxylic acid as limiting reagent. [c]Commercial price based on the online catalogues of Sigma-Aldrich (date of consultation: the 19th of December 2015).

Chemicals	Equivalents[a]	mmol[b]	Commercial price[c]	Commercial price per mmol	Price
Lithium	4.5	2.25	83.90 euro per 25 G	0.023 euro	0.05 euro
Chlorodiphenyl (methyl)silane	1.0	0.5	91.50 euro per 25 G	0.855 euro	0.43 euro
Carbon dioxide	-	-	-	-	-
				Total Price	0.48 euro

Taken into account a reported yield of 77%, the total price to synthesise 0.5 mmol methyldiphenylsilacarboxylic acid is 0.62 euro. However the actual price is higher as no costs of work-up, purification and carbon dioxide were considered.

Table S5. Price of the reported CO generating system. [a]Equivalents reported in the article. [b]Compared to 0.5 mmol aryl bromide as limiting reagent. [c]Commercial price based on the online catalogues of Sigma-Aldrich (date of consultation: the 19th of December 2015).

Chemicals	Equivalents[a]	mmol[b]	Commercial price[c]	Commercial price per mmol	Price
Methyldiphenyl silacarboxylic acid	1.5	0.75	-	-	0.93 euro
Potassium fluoride	1.7	0.85	64.50 euro per 100 G	0.03 euro	0.03 euro
				Total Price	0.96 euro

4.4. Ex Situ Generation of Stoichiometric and Substoichiometric ^{12}CO and ^{13}CO and Its Efficient Incorporation in Palladium Catalyzed Aminocarbonylations.[7]

The CO generating system in this article consists of 1.0 equiv. 9-methyl-9*H*-fluorene-9-carbonyl chloride, 5 mol% $Pd(dba)_2$, 5 mol% P(*t*Bu)$_3$ and 1.5 equiv. DIPEA.

Table S6. Price of the reported CO generating system. [a]Equivalents reported in the article. [b]Compared to 0.5 mmol aryl bromide as limiting reagent. [c]Commercial price based on the online catalogues of Sigma-Aldrich (date of consultation: the 19th of December 2015).

Chemicals	Equivalents[a]	mmol[b]	Commercial price[c]	Commercial price per mmol	Price
9-methyl-9*H*-fluorene-9-carbonyl chloride	1.0	0.50	128.50 euro per 5 G	6.24 euro	3.12 euro
$Pd(dba)_2$	0.05	0.025	93.00 euro per 2 G	26.72 euro	0.67 euro
$P(tBu)_3$	0.05	0.025	79.50 euro per 1 G	16.09 euro	0.40 euro
DIPEA	1.5	0.75	371 euro per 1 L	0.065 euro	0.05 euro
				Total Price	4.24 euro

4.5. Efficient Fluoride-Catalyzed Conversion of CO_2 to CO at Room Temperature.[6]

The CO generating system in this article consists of 1.5 equiv. tetraphenyldimethyldisilane, 2.0 equiv. carbon dioxide and 0.1 equiv. of cesium fluoride. However the tetraphenyldimethyldisilane additive is not commercially available, but can be prepared via one extra synthesis step.

Table S7. Price of the tetraphenyldimethyldisilane synthesis. [a]Equivalents reported in the article. [b]Compared to 0.5 mmol tetraphenyldimethyldisilane as limiting reagent. [c]Commercial price based on the online catalogues of Sigma-Aldrich (date of consultation: the 19th of December 2015).

Chemicals	Equivalents[a]	mmol[b]	Commercial price[c]	Commercial price per mmol	Price
Lithium	0.7	0.35	83.90 euro per 25 G	0.023 euro	0.01 euro
Chlorodiphenyl (methyl)silane	1.0	0.50	91.50 euro per 25 G	0.855 euro	0.43 euro
				Total Price	0.44 euro

Taken into account a reported yield of 60%, the total price to synthesise 0.5 mmol tetraphenyldimethyldisilane acid is 0.73 euro. However the actual price is higher as no costs of work-up and purification were considered.

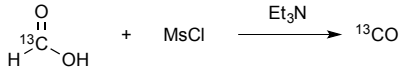
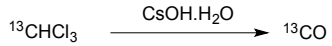
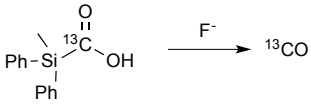
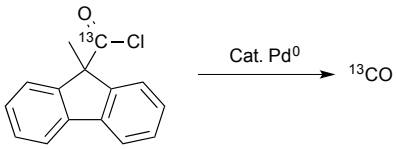
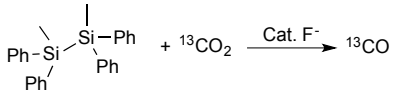
Table S8. Price of the reported CO generating system. [a]Equivalents reported in the article. [b]Compared to 0.5 mmol aryl bromide as limiting reagent. [c]Commercial price based on the online catalogues of Sigma-Aldrich (date of consultation: the 19th of December 2015).

Chemicals	Equivalents[a]	mmol[b]	Commercial price[c]	Commercial price per mmol	Price
Tetraphenyldimethyl-disilane	1.5	0.75	-	-	1.10 euro
Cesium fluoride	0.1	0.05	63.00 euro per 25 G	0.38 euro	0.02 euro
Carbon dioxide	2.0	1.00	-	-	-
				Total Price	1.12 euro

5. Price comparison of commercially available ^{13}CO precursors

Since ^{13}C-formic acid is commercially available, our reported procedure also provides an obvious source of ^{13}CO. Note that this enriched precursor is at least 9 times less expensive per mmol ^{13}CO than any other reported commercial ^{13}CO precursor (Table S9). Also note that these price calculations are only indicative, as they will change over time. However the price difference is significant (factor 9 – 11).

Table S9. Price comparison of the commercial available ^{13}CO precursors. [a]Commercial price is based on the online catalogues of Sigma-Aldrich (date of consultation: the 19th of December 2015). [b]Methyldiphenylsilacarboxylic acid and tetraphenyldimethyldisilane are not commercially available.

Method	CO generating system	Commercial price per gram[a]	Commercial price per mmol ^{13}CO	Relative price compared to method 1
1		307 euro	14 euro	1
2		1056 euro	126 euro	9
3		-[b]	-	-
4		653 euro	158 euro	11
5		-[b]	-	-

6. Palladium-catalysed Aminocarbonylation

6.1. General procedure

Aminocarbonylation

Chamber A of a flame-dried two-chamber reactor (Figure S2) was filled with 1 mg Palladium(II) acetate (5.00 µmol, 1 mol%), 3 mg Xantphos (5.00 µmol, 1 mol%) and 159 mg sodium carbonate (1.50 mmol, 3 equiv.). The reactor was brought under argon atmosphere by two consecutive vacuum-argon cycles. Next, chamber B was filled with 2 mL dry degassed toluene, 51 µL mesyl chloride (0.65 mmol, 1.3 equiv.) and 25 µL formic acid (0.65 mmol, 1.3 equiv.). In chamber A, 1 mL dry degassed toluene was added, followed by 0.5 mmol aryl bromide (1 equiv.) and 0.75 mmol amine (1.5 equiv.). Finally, 181 µL triethylamine (1.3 mmol, 2.6 equiv.) was added by injection through the septum in chamber B at room temperature and instant gas formation was observed. After 2 minutes, the reactor was immersed in an oil-bath at 100 °C.

A video of the last step is available in Supporting Info (General_Procedure.mp4)

Remark: when the aryl bromide and/or the amine are solids at room temperature, they were added to Chamber A after the addition of Palladium(II) acetate and Xantphos.

Remark: for the C-13 labelled compounds, 25 µL of ^{13}C-HCOOH (95 wt. % in H_2O) was used.

Purification

After 2 hours, the reactor was brought to room temperature and excess CO was released by removing one of the caps. As carbon monoxide is a highly toxic gas, the reaction was left stirring at room temperature for another 15 minutes to ensure that all carbon monoxide gas was extracted out of the fume hood. Next, the content of chamber A was transferred to a 100 mL round-bottomed flask. This chamber was washed 5 times with 2 mL of EtOAc, these fractions were added to the same flask. After the addition of 1 gram Celite®535, the solvent was removed under reduced pressure. The crude product was purified by solid-phase flash column chromatography on silica gel.

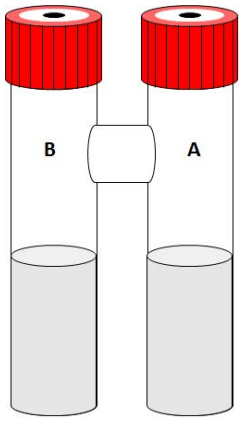
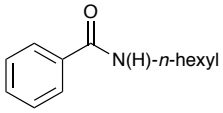


Figure S2. Representation of the two-chamber reactor. Inner volume = 20 mL.

6.2. Synthesis of Benzamides

***N*-hexylbenzamide (compound 3a)**



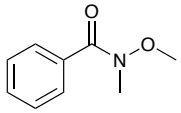
The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv.) and 99 µL *n*-hexylamine (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (85:15 heptane/ethyl acetate). The title compound was obtained as a colourless oil (101 mg, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) 7.85 – 7.30 (5 H, m), 6.65 (1 H, brd), 3.39 (2 H, td, *J* 7.2, 5.9), 1.65 – 1.50 (2 H, m), 1.42 – 1.16 (6 H, m), 0.86 (3H, t, *J* 6.7).

^{13}C NMR (75 MHz, $CDCl_3$) 167.68, 134.89, 131.25, 128.48, 126.97, 40.19, 31.56, 29.65, 26.73, 22.61, 14.07.

These data are in agreement with literature data.[8]

***N*-methoxy-*N*-methylbenzamide (compound 3b)**



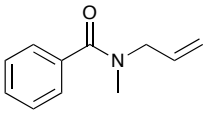
The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv.) and 73 mg *N,O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a colourless oil (73 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) 7.69 – 7.34 (5 H, m), 3.54 (3 H, s), 3.35 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$) 170.06, 134.22, 130.65, 128.22, 128.11, 61.12, 33.88.

These data are in agreement with literature data.[9]

***N*-allyl-*N*-methylbenzamide (compound 3c)**



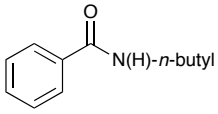
The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv.) and 71 µL *N*-methylprop-2-en-1-amine (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a colourless oil (71 mg, 81%).

^{1}H NMR (600 MHz, DMSO-d_6) 7.47 – 7.35 (5 H, m), 5.89 – 5.75 (1 H, m), 5.24 – 5.15 (2 H, m), 3.94 (2 H, s), 2.90 (3 H, s).

^{13}C NMR (151 MHz, DMSO-d_6) 169.99, 136.28, 133.06, 128.76, 127.76, 126.09, 116.50, 50.78, 34.04.

These data are in agreement with literature data.[10]

_N_-butylbenzamide (compound 3d)



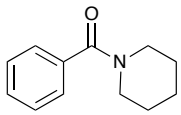
The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv.) and 74 µL *N*-butylamine (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (85:15 heptane/ethyl acetate). The title compound was obtained as a colourless oil (79 mg, 89%).

^{1}H NMR (400 MHz, DMSO-d_6) 8.42 (1 H, brd), 7.48 (5 H, m), 3.26 (2 H, dd, *J* 12.8, 6.9), 1.57 – 1.45 (2 H, m), 1.39 – 1.27 (2 H, m), 0.90 (3 H, t, *J* 7.3).

^{13}C NMR (101 MHz, DMSO-d_6) 166.07, 134.75, 130.90, 128.16, 127.09, 38.85, 31.25, 19.65, 13.69.

These data are in agreement with literature data.[4]

Phenyl(piperidin-1-yl)methanone (compound 3e)



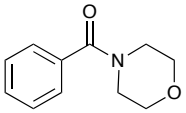
The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv.) and 74 µL piperidine (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a colourless oil (88 mg, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) 7.36 (5 H, s), 3.68 (2 H, s), 3.31 (2 H, s), 1.64 (4 H, s), 1.49 (2 H, s).

^{13}C NMR (75 MHz, $CDCl_3$) 170.29, 136.49, 129.33, 128.38, 126.76, 48.73, 43.10, 26.53, 25.66, 24.58.

These data are in agreement with literature data.[11]

Morpholino(phenyl)methanone (compound 3f)



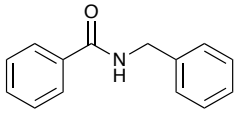
The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv.) and 66 µL morpholine (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (50:50 heptane/ethyl acetate). The title compound was obtained as a colourless oil (91 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) 7.38 (5 H, s), 3.63 (8 H, brd).

^{13}C NMR (101 MHz, $CDCl_3$) 170.52, 135.67, 129.90, 128.62, 127.21, 67.00, 46.88 (brd).

These data are in agreement with literature data.[4]

_N_-benzylbenzamide (compound 3g)



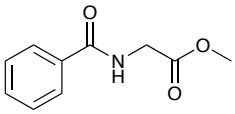
The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv.) and 82 µL phenylmethanamine (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (85:15 heptane/ethyl acetate). The title compound was obtained as a white solid (96 mg, 91%).

^{1}H NMR (400 MHz, DMSO-d_6) 9.04 (1 H, brd), 7.95 – 7.86 (2 H, m), 7.58 – 7.43 (3 H, m), 7.33 (4 H, d, *J* 4.3), 7.24 (1 H, dd, *J* 8.6, 4.4), 4.49 (2 H, d, *J* 6.0).

^{13}C NMR (101 MHz, DMSO-d_6) 166.19, 139.68, 134.34, 131.20, 128.29, 128.25, 127.22, 127.17, 126.70, 42.59, 39.52.

These data are in agreement with literature data.[4]

Methyl 2-benzamidoacetate (compound 3h)



The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv.) and 94 mg methyl glycinate hydrochloride (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a white solid (93 mg, 96%).

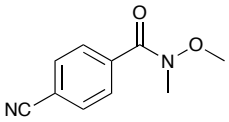
^{1}H NMR (300 MHz, $CDCl_3$) 7.82 – 7.75 (2 H, m), 7.52 – 7.34 (3 H, m), 7.06 (1 H, brd), 4.18 (2 H, d, *J* 5.3), 3.73 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$) 170.18, 167.28, 133.18, 131.39, 128.15, 126.72, 52.01, 41.29.

These data are in agreement with literature data.[12]

6.3 Synthesis of Weinreb Amides

4-isocyano-*N*-methoxy-*N*-methylbenzamide (compound 4a)



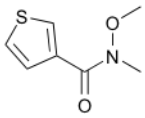
The general procedure was followed using 91 mg 4-bromobenzonitrile (0.5 mmol, 1 equiv.) and 73 mg *N,O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (60:40 heptane/ethyl acetate). The title compound was obtained as a light yellow oil (87 mg, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) 7.72 (4 H, dd, *J* 20.6, 8.5), 3.50 (3 H, s), 3.35 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$) 167.95, 138.33, 131.92, 128.88, 118.24, 114.15, 61.40, 33.26.

These data are in agreement with literature data.[13]

***N*-methoxy-*N*-methylthiophene-3-carboxamide (compound 4b)**



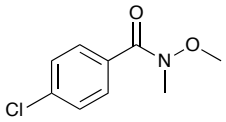
The general procedure was followed using 47 µL 3-bromothiophene (0.5 mmol, 1 equiv.) and 73 mg *N,O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a light yellow oil (77 mg, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) 8.06 (1 H, dd, *J* 3.0, 1.2), 7.56 (1 H, dd, *J* 5.1, 1.2), 7.27 (1 H, dd, *J* 5.1, 3.0), 3.64 (3 H, s), 3.35 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$) 163.41, 134.11, 130.54, 128.69, 124.46, 60.86, 32.94.

These data are in agreement with literature data.[14]

4-chloro-*N*-methoxy-*N*-methylbenzamide (compound 4c)



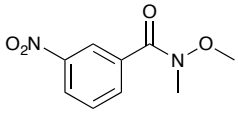
The general procedure was followed using 144 mg 1-bromo-4-chlorobenzene (0.75 mmol, 1.5 equiv.) and 49 mg *N,O*-dimethylhydroxylamine hydrochloride (0.50 mmol, 1.0 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a colourless oil (83 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) 7.64 (2 H, d, *J* 8.7), 7.36 (2 H, d, *J* 8.7), 3.52 (3 H, s), 3.34 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$) 168.73, 136.81, 132.34, 129.94, 128.35, 77.16, 61.19, 33.59.

These data are in agreement with literature data.[14]

***N*-methoxy-*N*-methyl-3-nitrobenzamide (compound 4d)**



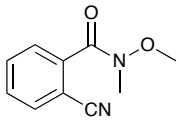
The general procedure was followed using 101 mg 1-bromo-3-nitrobenzene (0.5 mmol, 1 equiv.) and 73 mg *N,O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (75:25 heptane/ethyl acetate). The title compound was obtained as a light yellow oil (90 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) 8.57 – 8.53 (1 H, m), 8.34 – 8.27 (1 H, m), 8.05 – 7.99 (1 H, m), 7.60 (1 H, t, *J* 8.0), 3.54 (3 H, s), 3.38 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$) 167.26, 147.85, 135.58, 134.44, 129.30, 125.36, 123.61, 61.45, 33.33.

These data are in agreement with literature data.[14]

2-cyano-*N*-methoxy-*N*-methylbenzamide (compound 4e)



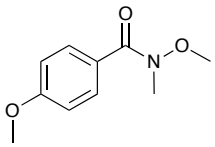
The general procedure was followed using 92 mg 2-bromobenzonitrile (0.5 mmol, 1 equiv.) and 73 mg *N,O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (70:30 heptane/ethyl acetate). The title compound was obtained as a colourless oil (85 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) 7.74 – 7.45 (4 H, m), 3.52 (3 H, s), 3.36 (3 H, s).

^{13}C NMR (101 MHz, $CDCl_3$) 166.92, 139.14, 132.85, 132.49, 129.92, 127.95, 116.94, 110.93, 61.46,

These data are in agreement with literature data.[14]

***N*,4-dimethoxy-*N*-methylbenzamide (compound 4f)**



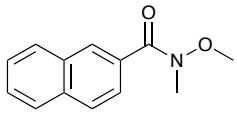
The general procedure was followed using 63 µL 1-bromo-4-methoxybenzene (0.5 mmol, 1 equiv.) and 73 mg *N,O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a colourless oil (85 mg, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) 7.70 (2 H, d, *J* 8.9), 6.87 (2 H, d, *J* 8.9), 3.81 (3 H, s), 3.53 (3 H, s), 3.32 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$) 168.98, 161.12, 130.14, 125.57, 112.84, 60.49, 54.92, 33.49.

These data are in agreement with literature data.[13]

***N*-methoxy-*N*-methyl-2-naphthamide (compound 4g)**



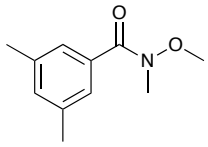
The general procedure was followed using 104 mg 2-bromonaphtalene (0.5 mmol, 1 equiv.) and 73 mg *N,O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (85:15 heptane/ethyl acetate). The title compound was obtained as a colourless oil (94 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) 8.22 (1 H, s), 7.92 – 7.73 (4 H, m), 7.58 – 7.47 (2 H, m), 3.55 (3 H, s), 3.40 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$) 169.91, 134.23, 132.50, 131.42, 128.86, 128.69, 127.73, 127.66, 127.43, 126.52, 125.08, 61.15, 33.89.

These data are in agreement with literature data.[15]

***N*-methoxy-*N*,3,5-trimethylbenzamide (compound 4h)**



The general procedure was followed using 68 µL 1-bromo-3,5-dimethylbenzene (0.5 mmol, 1 equiv.) and 73 mg *N,O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (70:30 heptane/ethyl acetate). The title compound was obtained as a colourless oil (86 mg, 89%).

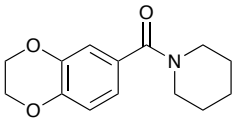
^{1}H NMR (300 MHz, $CDCl_3$) 7.22 (2 H, s), 7.06 (1 H, s), 3.56 (3 H, s), 3.31 (3 H, s), 2.32 (6 H, s).

^{13}C NMR (75 MHz, $CDCl_3$) 170.53, 137.66, 134.24, 132.16, 125.64, 77.16, 61.04, 34.10, 21.29.

These data are in agreement with literature data.[16]

6.4 Synthesis of C-12 and C-13 Pharmaceutical Compounds

(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)(piperidin-1-yl)methanone or CX-546 (compound 5a)



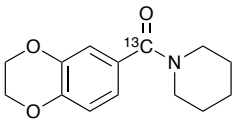
The general procedure was followed using 67 µL 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine (0.5 mmol, 1 equiv.) and 74 µL piperidine (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). Compound **5a** was obtained as a white solid (111 mg, 90%).

^{1}H NMR (600 MHz, $CDCl_3$) 6.95 – 6.82 (3 H, m), 4.25 (4 H, m), 3.52 (4 H, m), 1.68 – 1.64 (2 H, m), 1.57 (4 H, m).

^{13}C NMR (151 MHz, $CDCl_3$) 169.99, 144.91, 143.56, 130.03, 120.65, 117.26, 116.70, 64.65, 64.52, 45.98 (brd), 26.29, 24.85.

These data are in agreement with literature data.[4]

Carbon-13 labelled (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)(piperidin-1-yl)methanone or CX-546 (compound 5b)



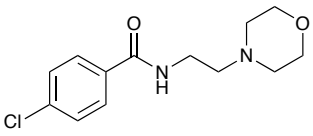
The general procedure was followed using 67 µL 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine (0.5 mmol, 1 equiv.) and 74 µL piperidine (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). Compound **5b** was obtained as a white solid (124 mg, 94%).

Remark: for the C-13 labelled CX-546, 25 µL of ^{13}C-HCOOH (95 wt. % in H_2O) was used.

^{1}H NMR (600 MHz, $CDCl_3$) 6.94 – 6.81 (3 H, m), 4.26 – 4.20 (4 H, m), 3.66 – 3.38 (4 H, m), 1.68 – 1.62 (2 H, m), 1.61 – 1.52 (4 H, m).

^{13}C NMR (151 MHz, $CDCl_3$) 169.94 (s), 144.87 (s), 143.51 (s), 129.95 (d, *J* 67.7), 120.59 (s), 117.20 (d, *J* 4.9), 116.64 (d, *J* 2.3), 64.60 (s), 64.48 (s), 46.23 (brd), 26.24 (s), 24.80 (s).

4-chloro-*N*-(2-morpholinoethyl)benzamide or Moclobemide (compound 6a)



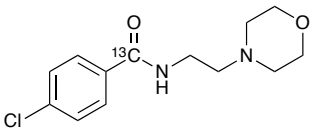
The general procedure was followed using 98 mg 1-bromo-4-chlorobenzene (0.5 mmol, 1 equiv.) and 99 µL 2-morpholinoethan-1-amine (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (96:4 dichloromethane/methanol). Compound **6a** was obtained as a white solid (130 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) 7.75 – 7.68 (2 H, m), 7.45 – 7.37 (2 H, m), 6.76 (1 H, brd), 3.77 – 3.68 (4 H, m), 3.57 – 3.48 (2 H, m), 2.63 – 2.56 (2 H, m), 2.54 – 2.43 (4 H, m).

^{13}C NMR (75 MHz, $CDCl_3$) 166.44, 137.75, 133.08, 128.95, 128.47, 67.11, 56.90, 53.43, 36.18.

These data are in agreement with literature data.[6]

Carbon-13 labelled 4-chloro-*N*-(2-morpholinoethyl)benzamide or Moclobemide (compound 6b)



The general procedure was followed using 98 mg 1-bromo-4-chlorobenzene (0.5 mmol, 1 equiv.) and 99 µL 2-morpholinoethan-1-amine (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (96:4 dichloromethane/methanol). Compound **6b** was obtained as a white solid (126 mg, 94%).

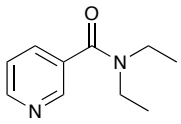
Remark: for the C-13 labelled Moclobemide, 25 µL of ^{13}C-HCOOH (95 wt. % in H_2O) was used.

^{1}H NMR (300 MHz, $CDCl_3$) 7.70 (2 H, m), 7.39 (2 H, m), 6.80 (1 H, brd), 3.78 – 3.64 (4 H, m), 3.59 – 3.48 (2 H, m), 2.58 (2 H, m), 2.54 – 2.41 (4 H, m).

^{13}C NMR (75 MHz, $CDCl_3$) 166.43 (s), 137.70 (s), 133.04 (d, *J* 65.2), 128.91 (d, *J* 4.4), 128.45 (d, *J* 2.5), 67.08 (s), 56.89 (s), 53.41 (s), 36.18 (s).

These data are in agreement with literature data.[6]

***N*,*N*-diethylnicotinamide or Nikethamide (compound 7a)**



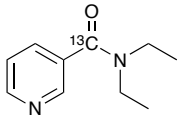
The general procedure was followed using 49 µL 3-bromopyridine (0.5 mmol, 1 equiv.) and 78 µL diethylamine (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (97:3 dichloromethane/methanol). Compound **7a** was obtained as a yellow oil (68 mg, 76%).

^{1}H NMR (300 MHz, $CDCl_3$) 8.58 (2 H, m), 7.71 – 7.62 (1 H, m), 7.34 – 7.26 (1 H, m), 3.36 (4 H, m), 1.14 (6 H, m).

^{13}C NMR (75 MHz, $CDCl_3$) 168.59, 150.29, 147.19, 134.28, 133.00, 123.43, 43.45, 39.57, 14.30, 12.87.

These data are in agreement with literature data.[4]

Carbon-13 labelled *N*,*N*-diethylnicotinamide or Nikethamide (compound 7b)



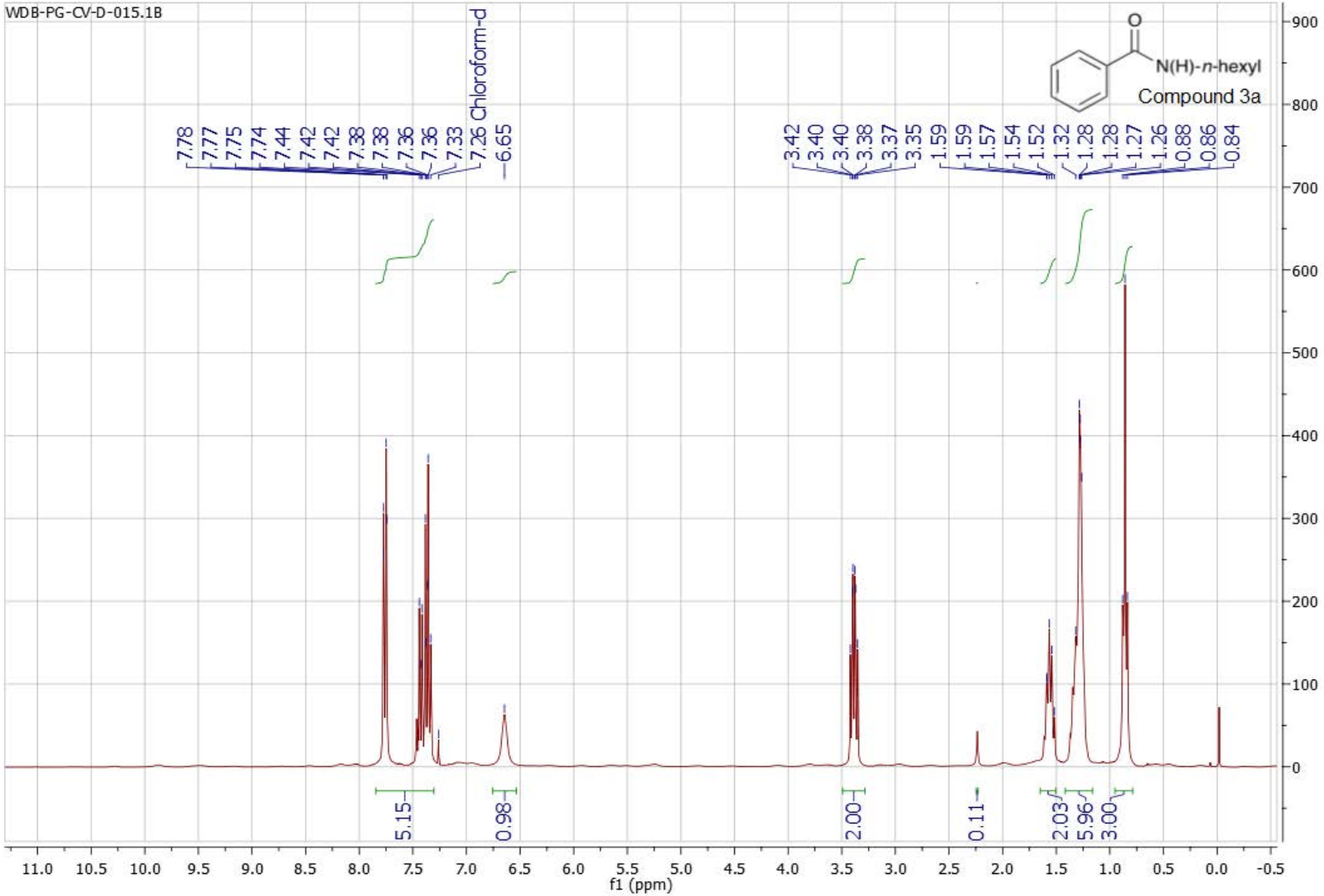
The general procedure was followed using 49 µL 3-bromopyridine (0.5 mmol, 1 equiv.) and 78 µL diethylamine (0.75 mmol, 1.5 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (97:3 dichloromethane/methanol). Compound **7b** was obtained as a yellow oil (73 mg, 82%).

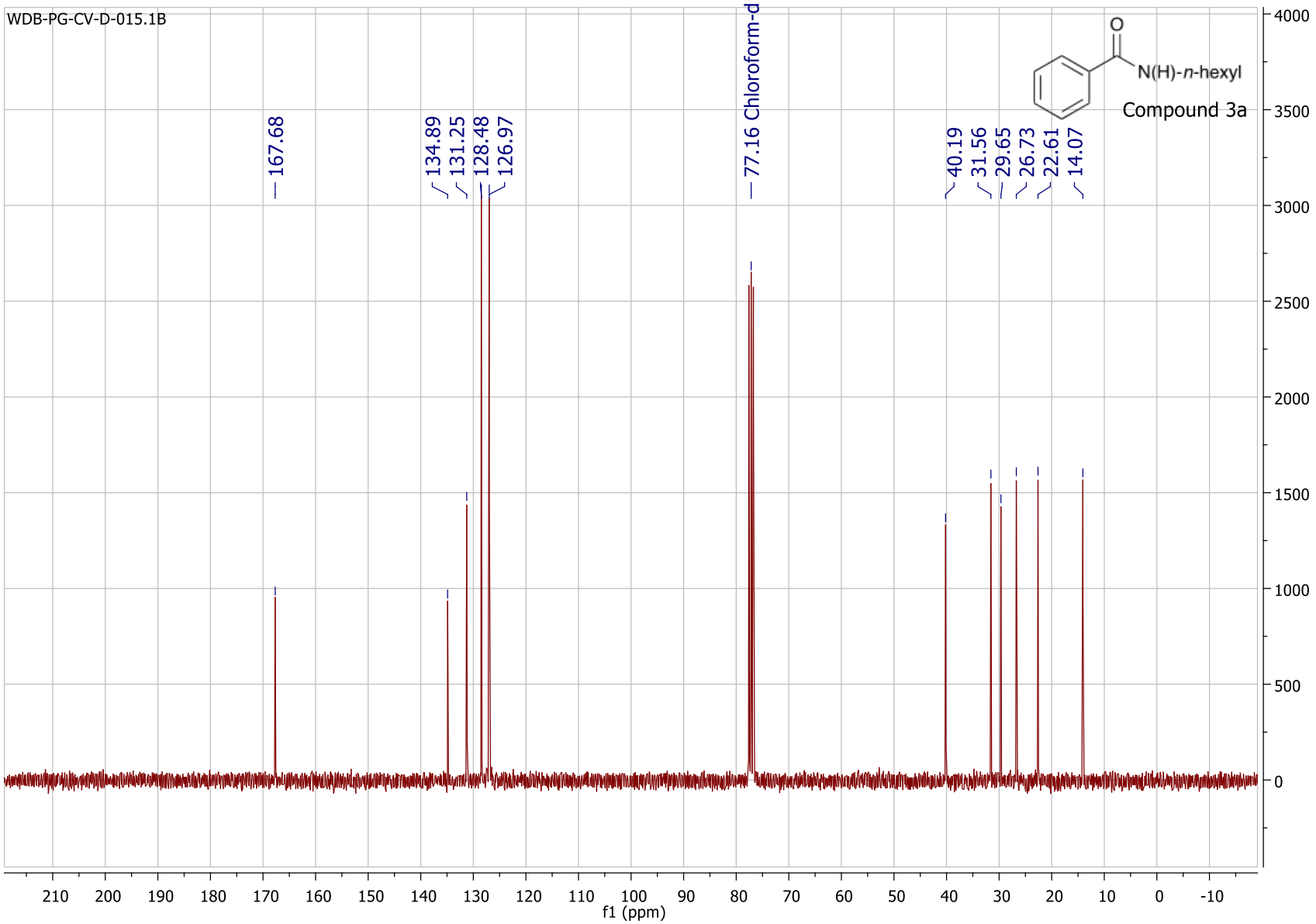
Remark: for the C-13 labelled Nikethamide, 25 µL of ^{13}C-HCOOH (95 wt. % in H_2O) was used.

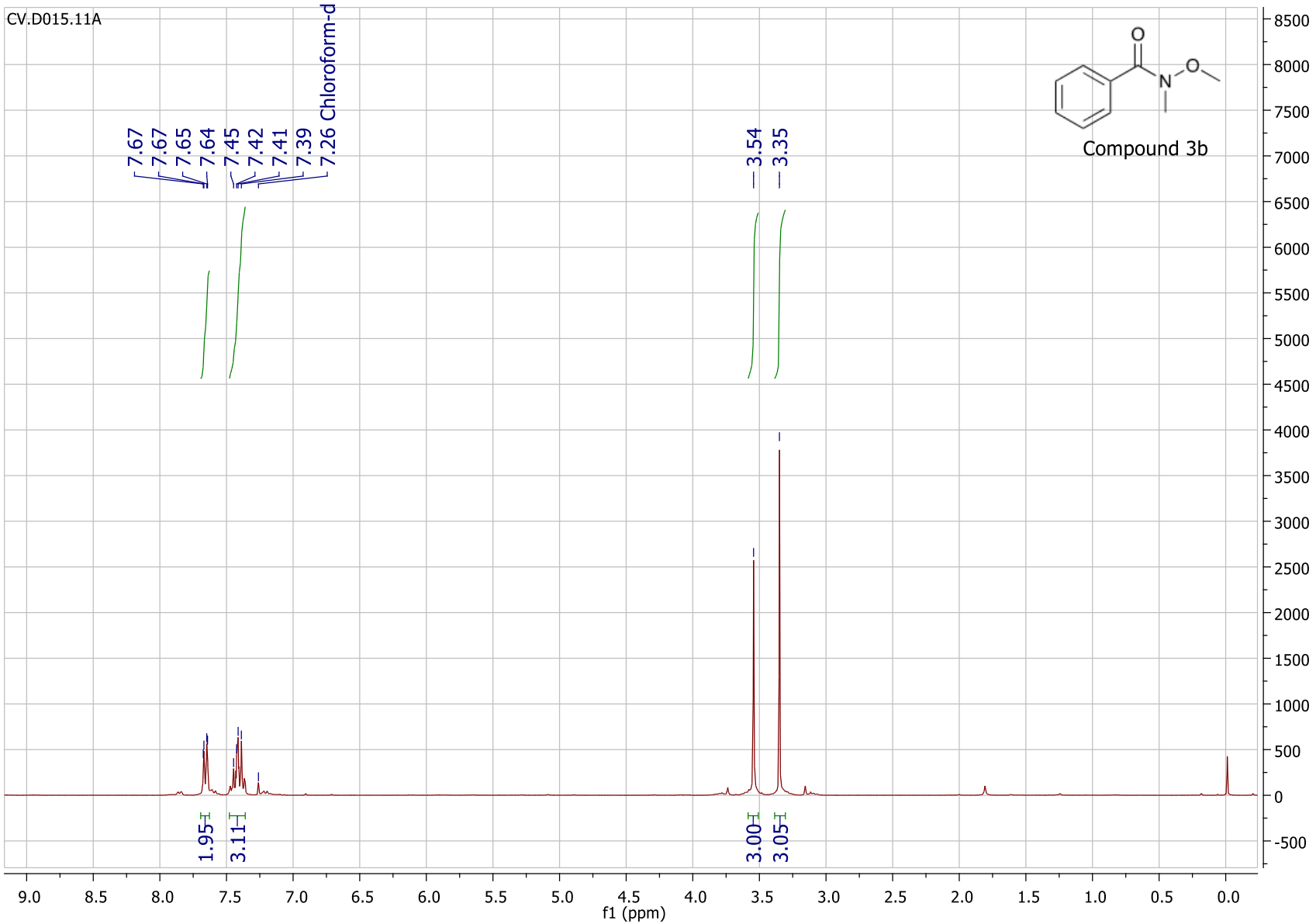
^{1}H NMR (300 MHz, $CDCl_3$) 8.60 (2 H, m), 7.78 – 7.57 (1 H, m), 7.38 – 7.26 (1 H, m), 3.37 (4 H, m), 1.15 (6 H, m).

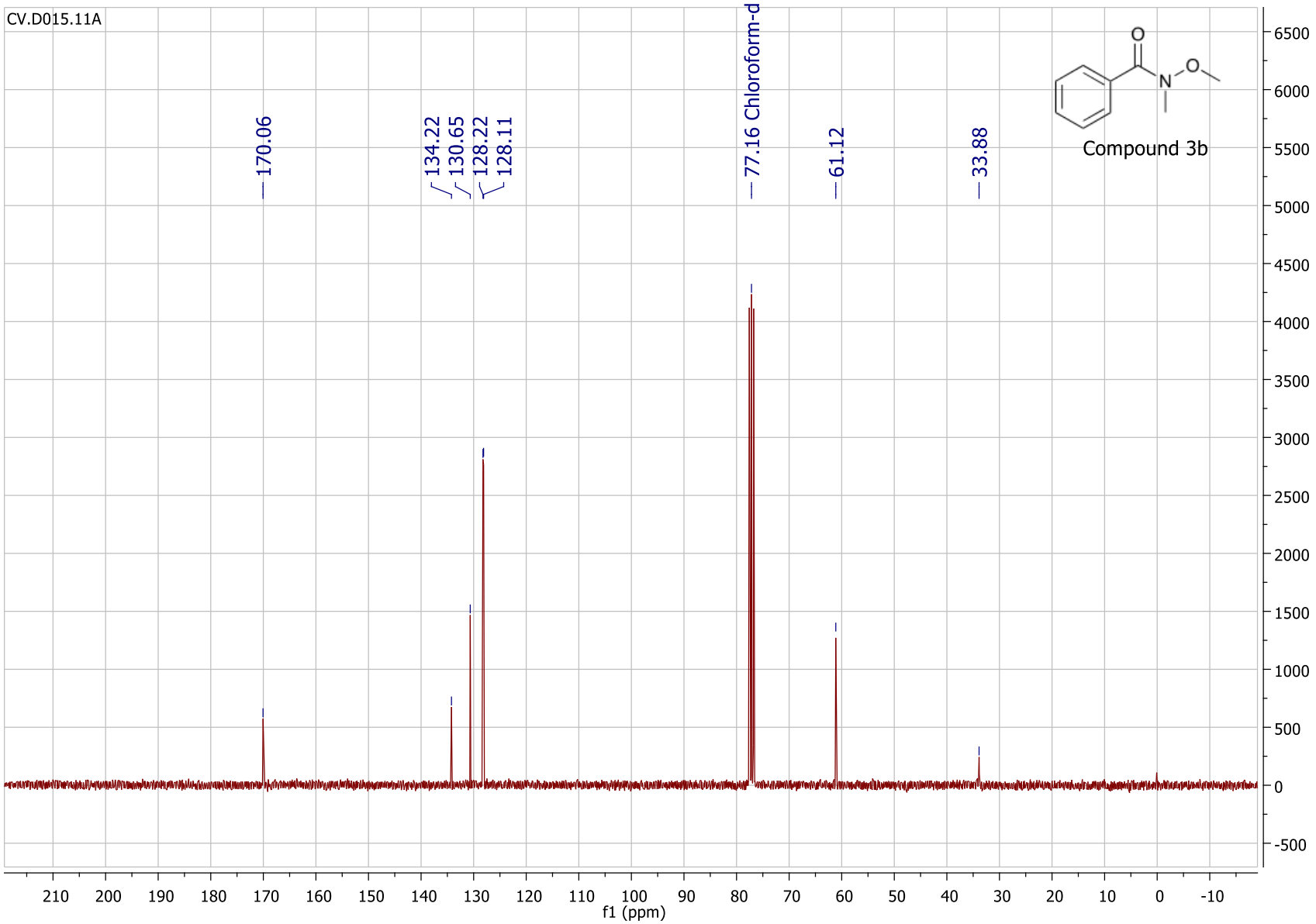
^{13}C NMR (75 MHz, $CDCl_3$) 168.63 (s), 150.34 (s), 147.23 (d, *J* 3.0), 134.30 (d, *J* 1.6), 133.03 (d, *J* 66.7), 123.48 (s), 43.47 (s), 39.60 (s), 14.32 (s), 12.91 (s).

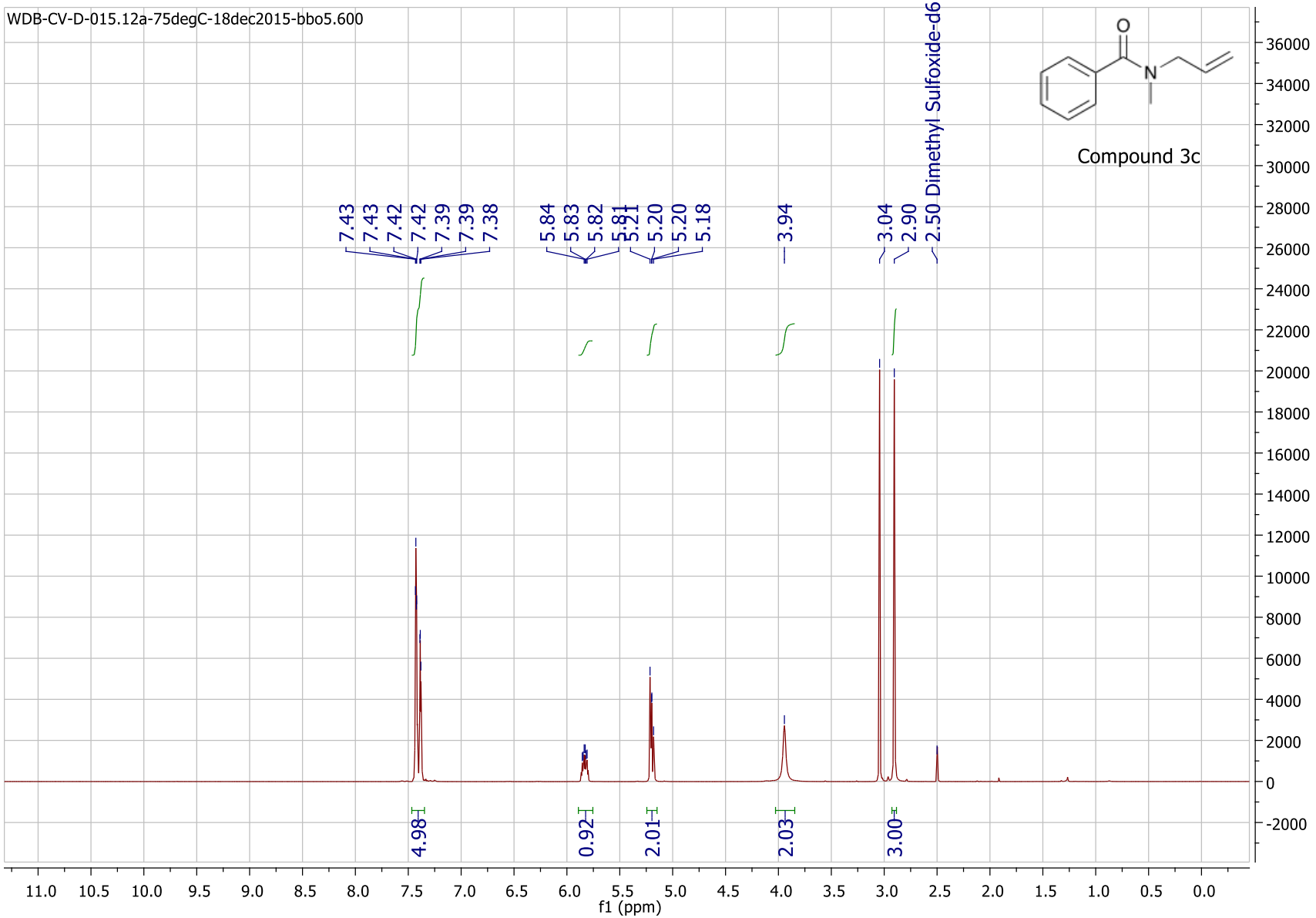
6.5 NMR spectra of the synthesised compounds

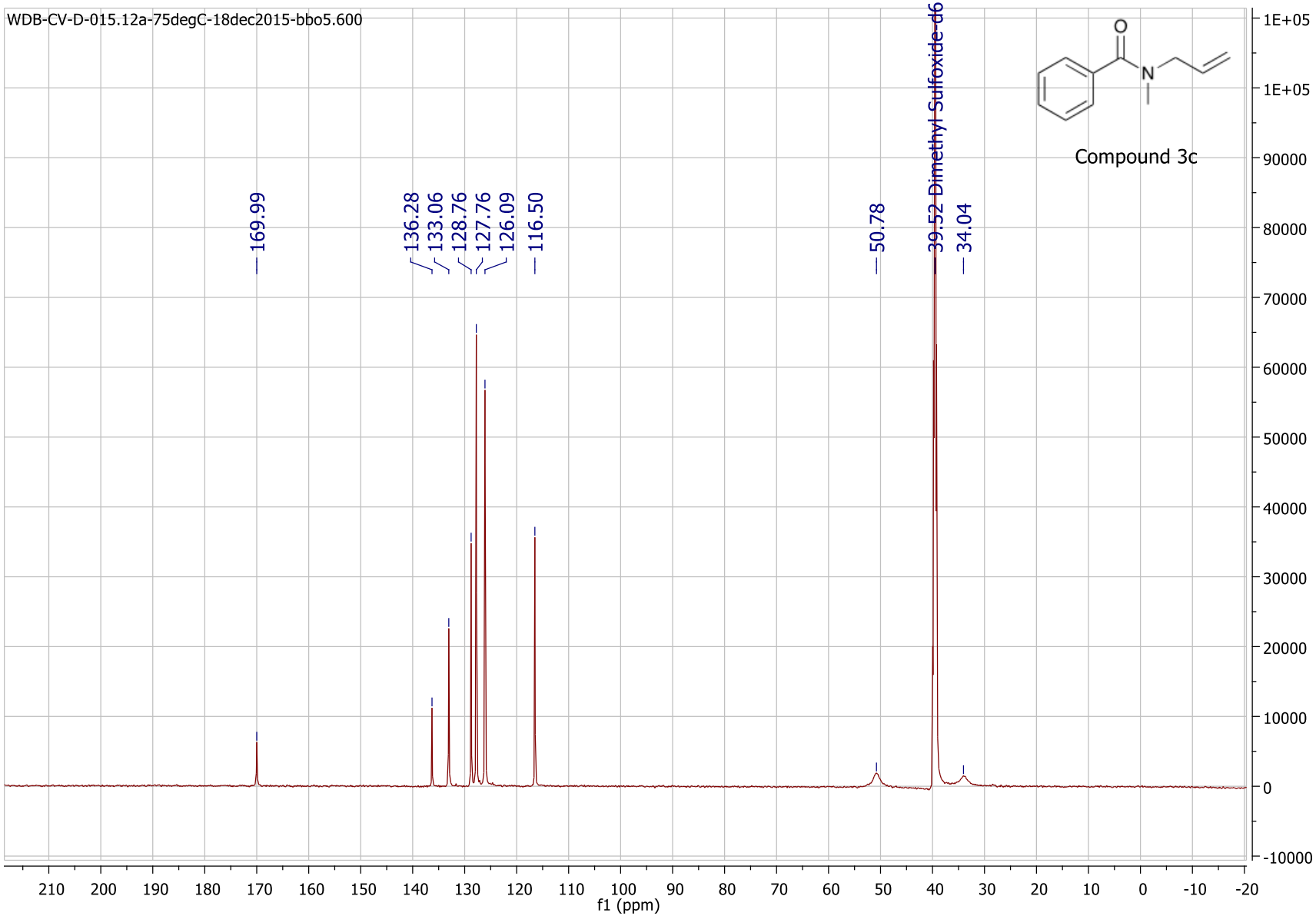


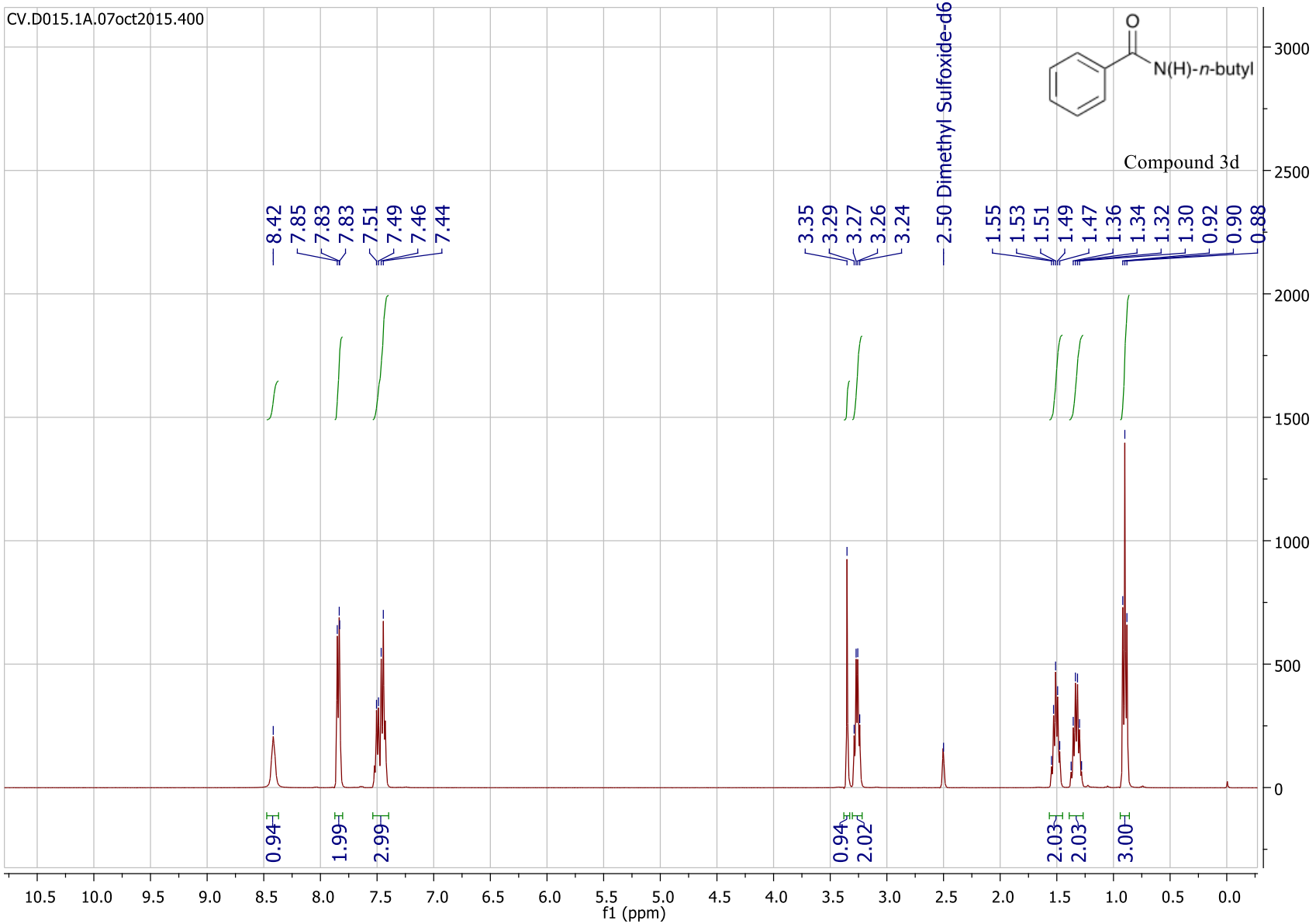

WDB-PG-CV-D-015.1B
167.68
134.89
131.25
128.48
126.97
77.16 Chloroform-d
40.19
31.56
29.65
26.73
22.61
14.07
N(H)-n-hexyl
Compound 3a
f1 (ppm)

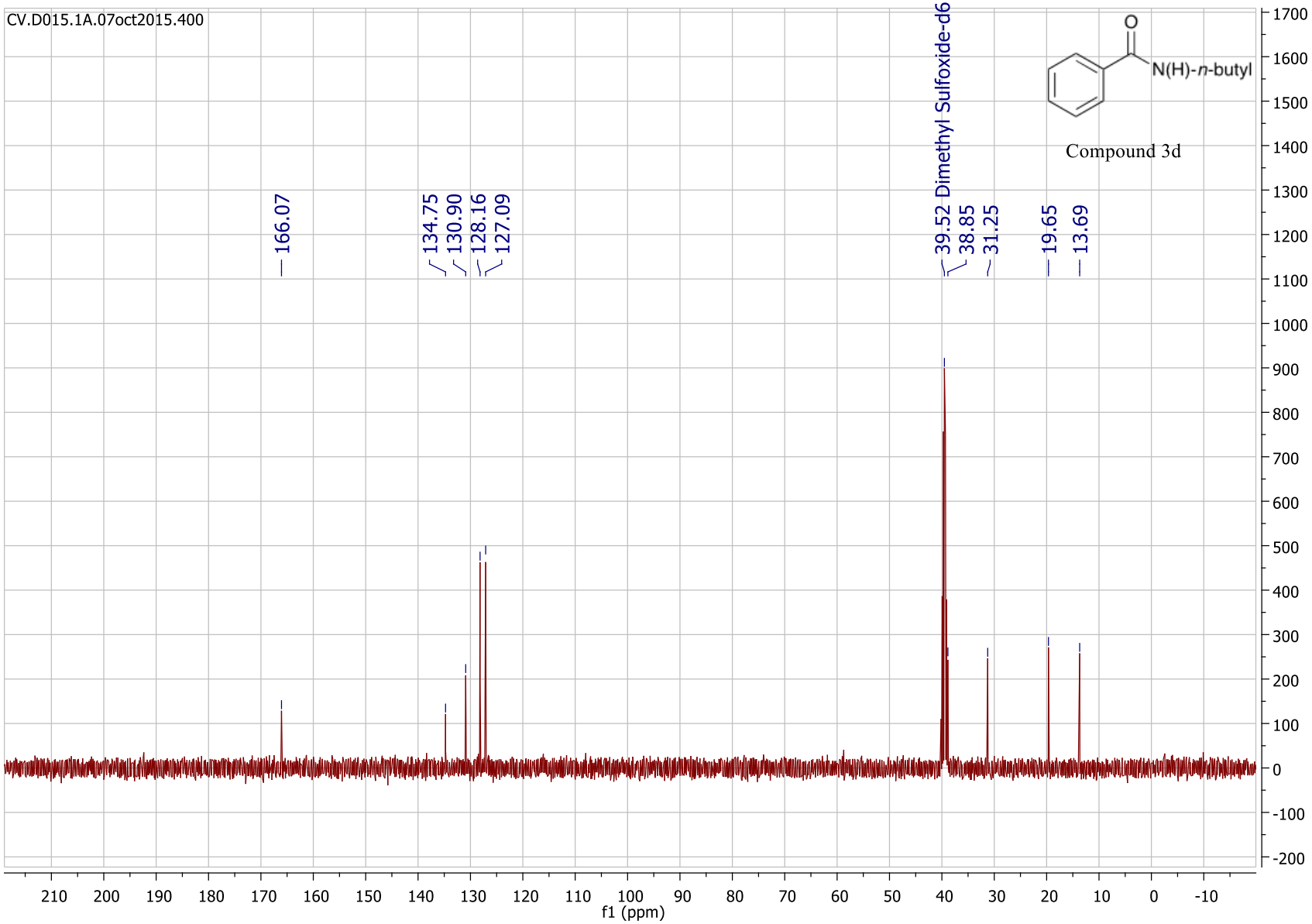

CV.D015.11A
7.67
7.67
7.65
7.64
7.45
7.42
7.41
7.39
7.26 Chloroform-d
3.54
3.35
Compound 3b
1.95
3.11
3.00
3.05
f1 (ppm)

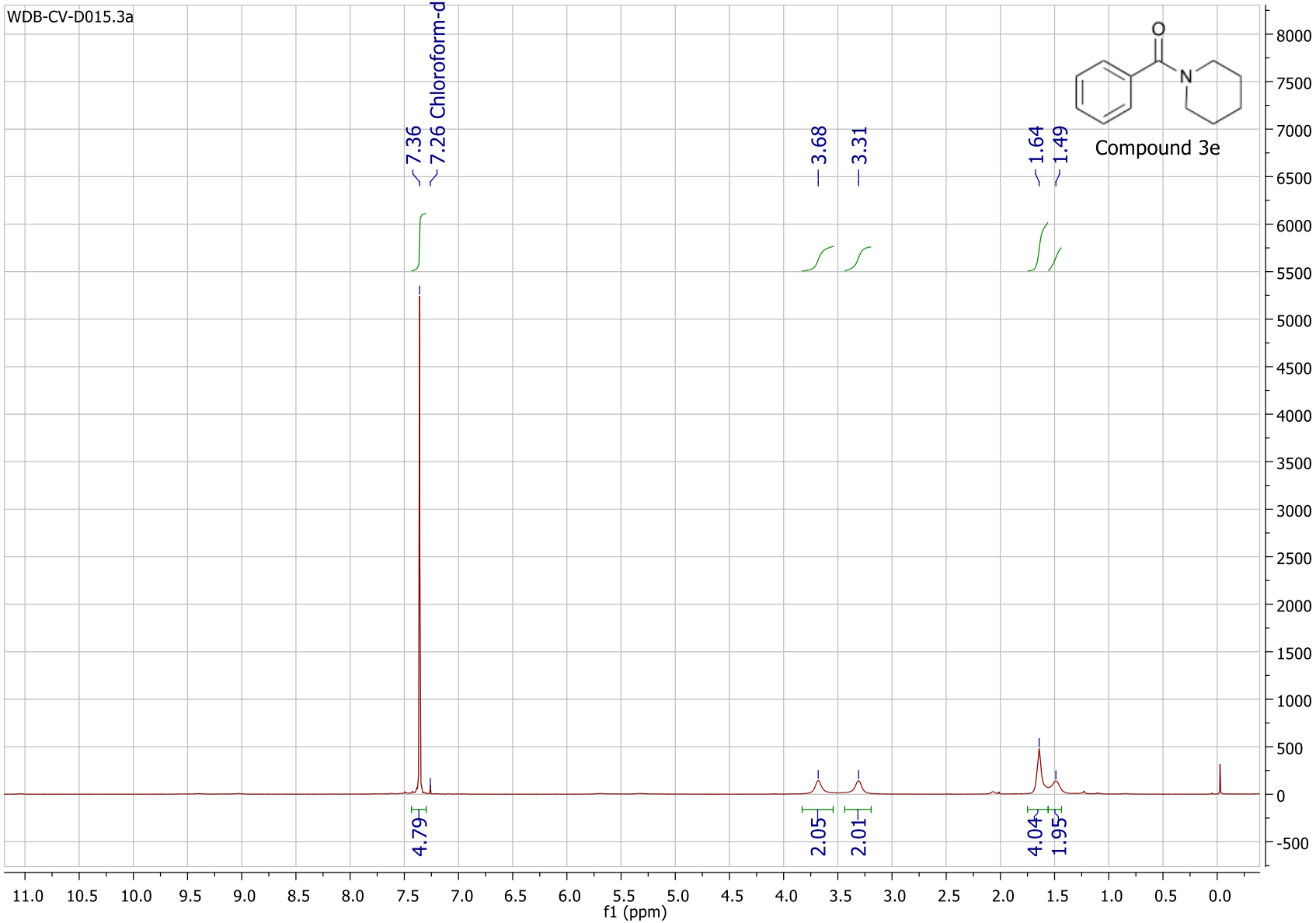

CV.D015.11A
170.06
134.22
130.65
128.22
128.11
77.16 Chloroform-d
61.12
33.88
Compound 3b
f1 (ppm)

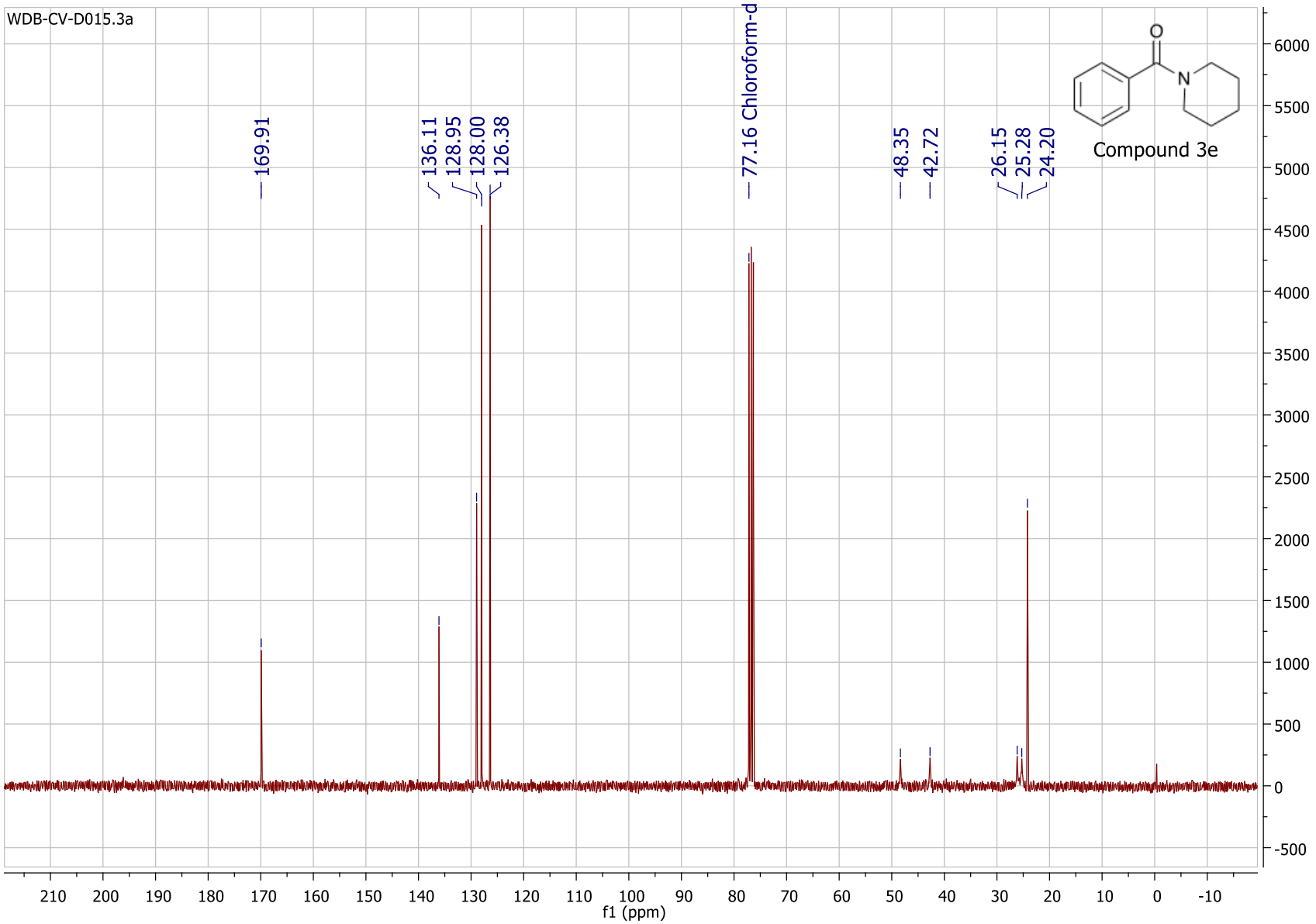

WDB-CV-D-015.12a-75degC-18dec2015-bbo5.600
Compound 3c
Dimethyl Sulfoxide-d6
7.43
7.43
7.42
7.42
7.39
7.39
7.38
5.84
5.83
5.82
5.81
5.21
5.20
5.20
5.18
3.94
3.04
2.90
2.50
4.98
0.92
2.01
2.03
3.00
f1 (ppm)

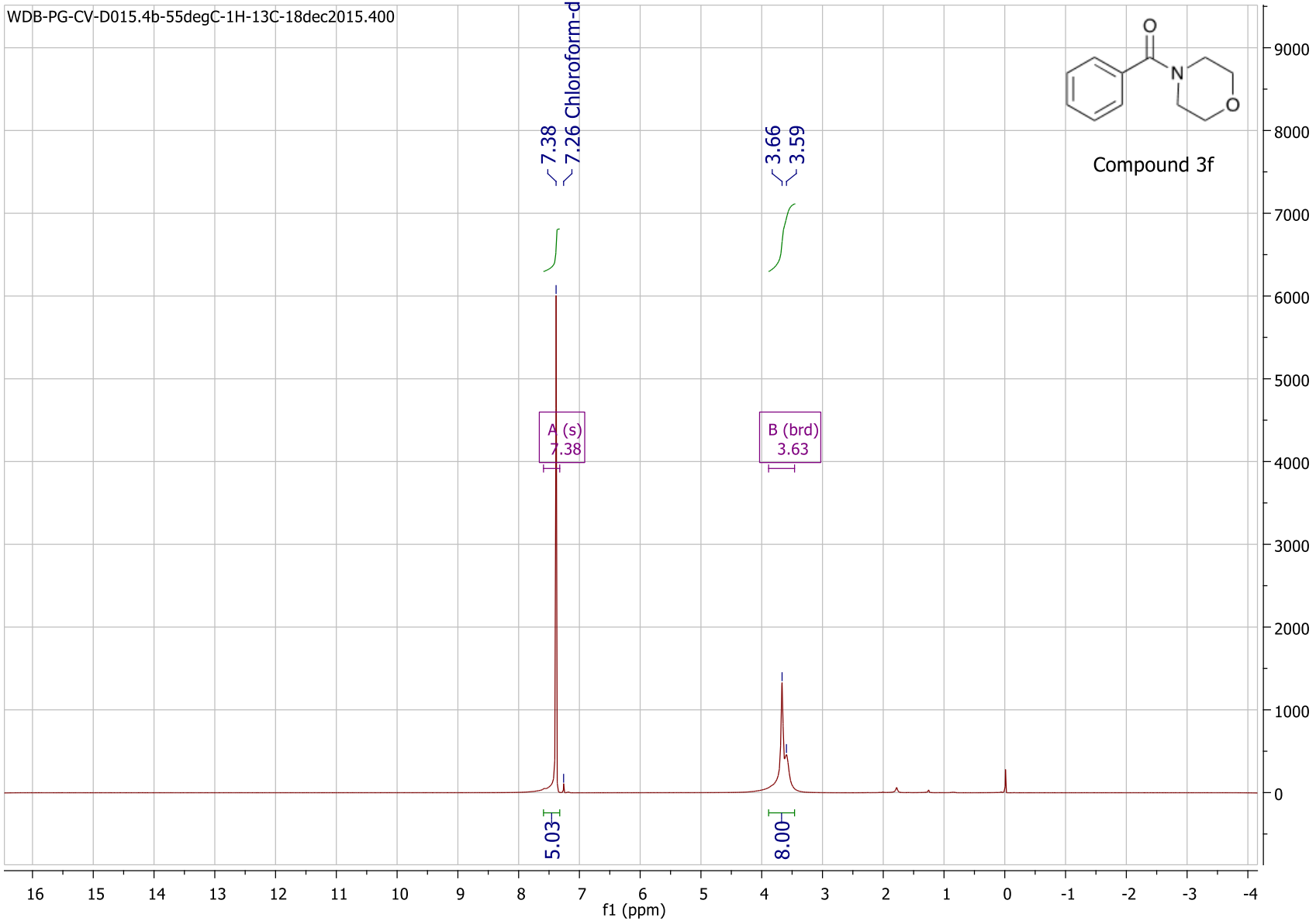

WDB-CV-D-015.12a-75degC-18dec2015-bbo5.600
169.99
136.28
133.06
128.76
127.76
126.09
116.50
50.78
39.52 Dimethyl Sulfoxide-d6
34.04
Compound 3c
f1 (ppm)

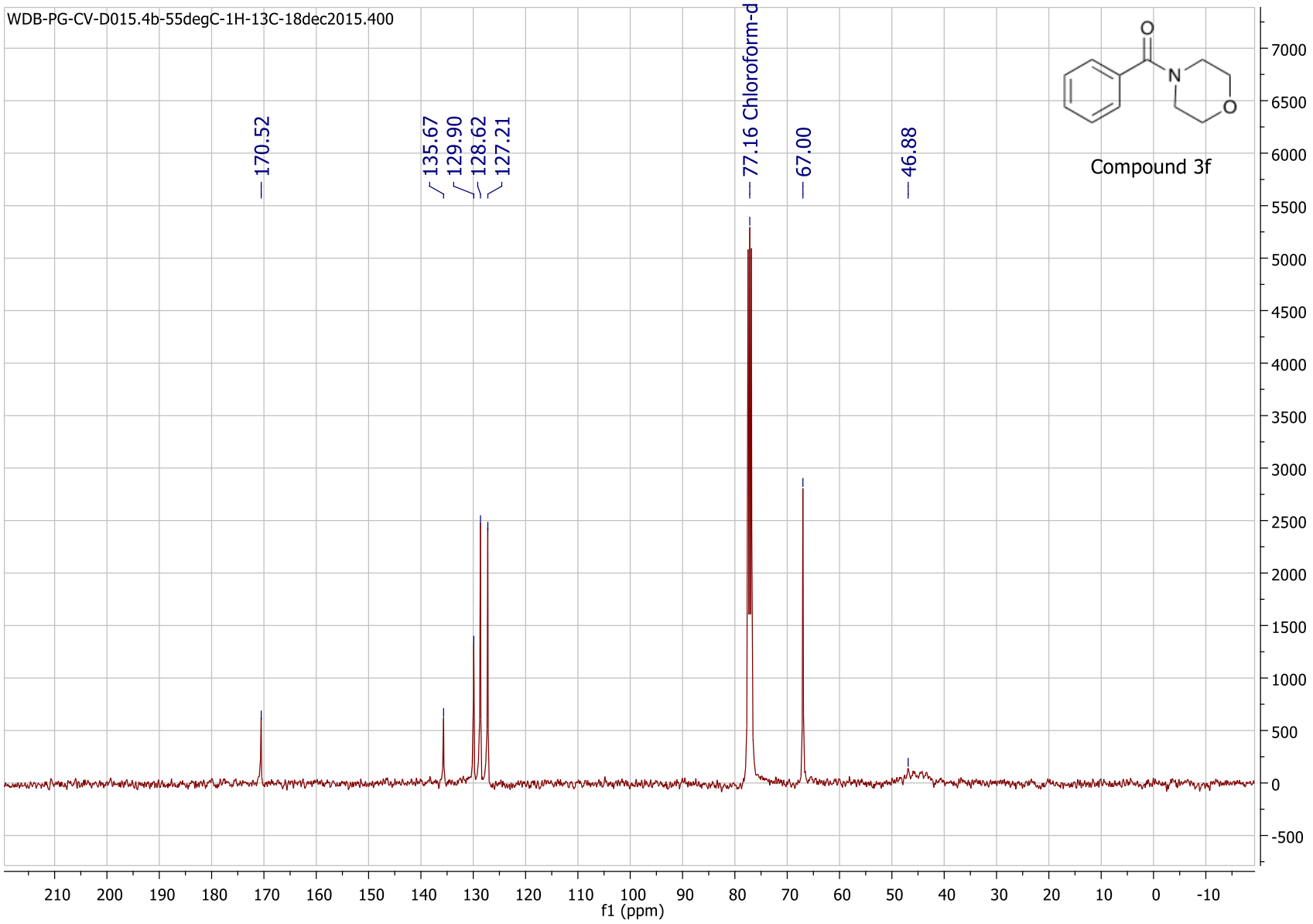

CV.D015.1A.07oct2015.400
O
N(H)-n-butyl
Compound 3d
2.50 Dimethyl Sulfoxide-d6
8.42
7.85
7.83
7.83
7.51
7.49
7.46
7.44
3.35
3.29
3.27
3.26
3.24
1.55
1.53
1.51
1.49
1.47
1.36
1.34
1.32
1.30
0.92
0.90
0.88
0.94
1.99
2.99
0.94
2.02
2.03
2.03
3.00
f1 (ppm)

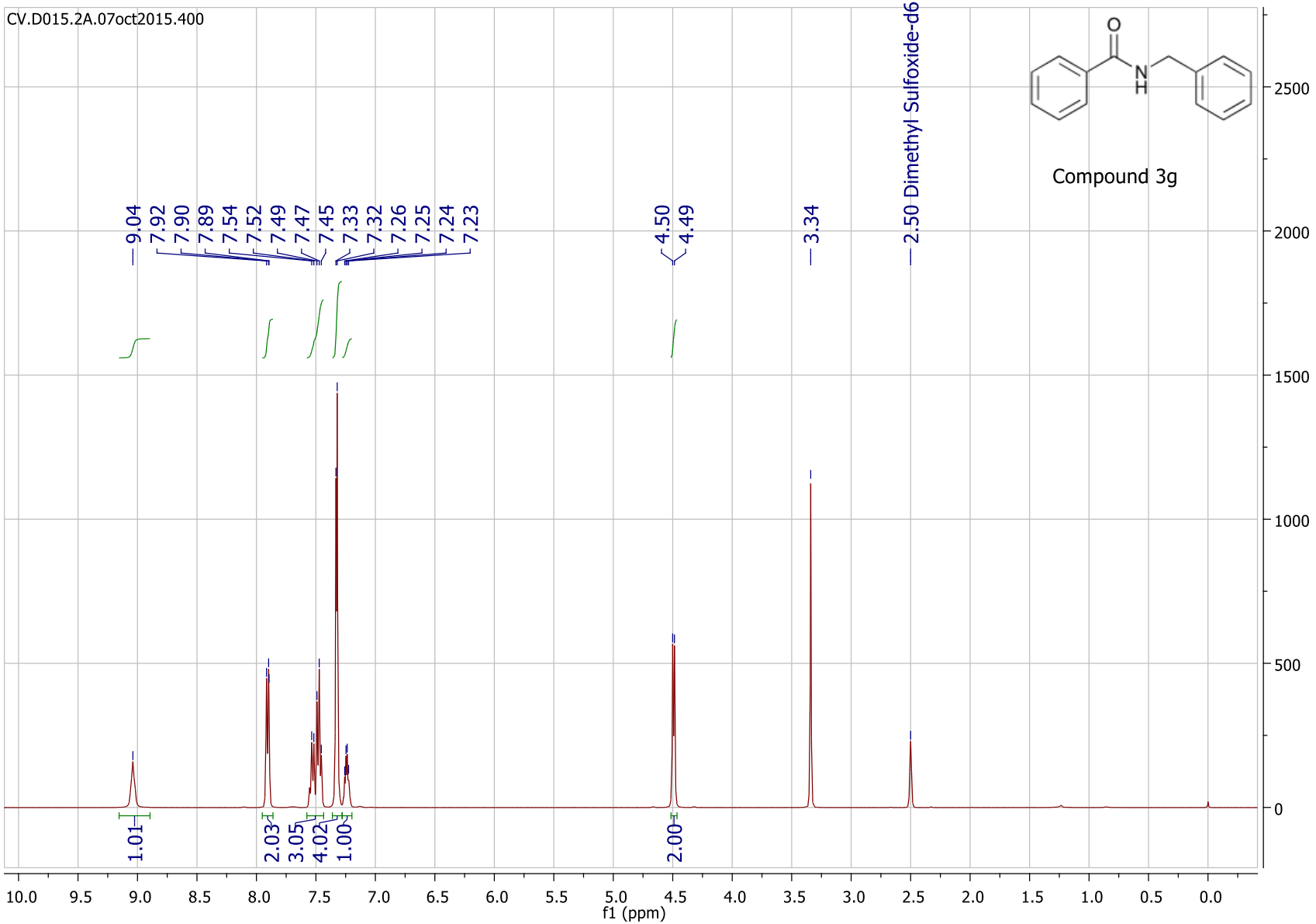

CV.D015.1A.07oct2015.400
166.07
134.75
130.90
128.16
127.09
39.52 Dimethyl Sulfoxide-d6
38.85
31.25
19.65
13.69
O
N(H)-n-butyl
Compound 3d
f1 (ppm)

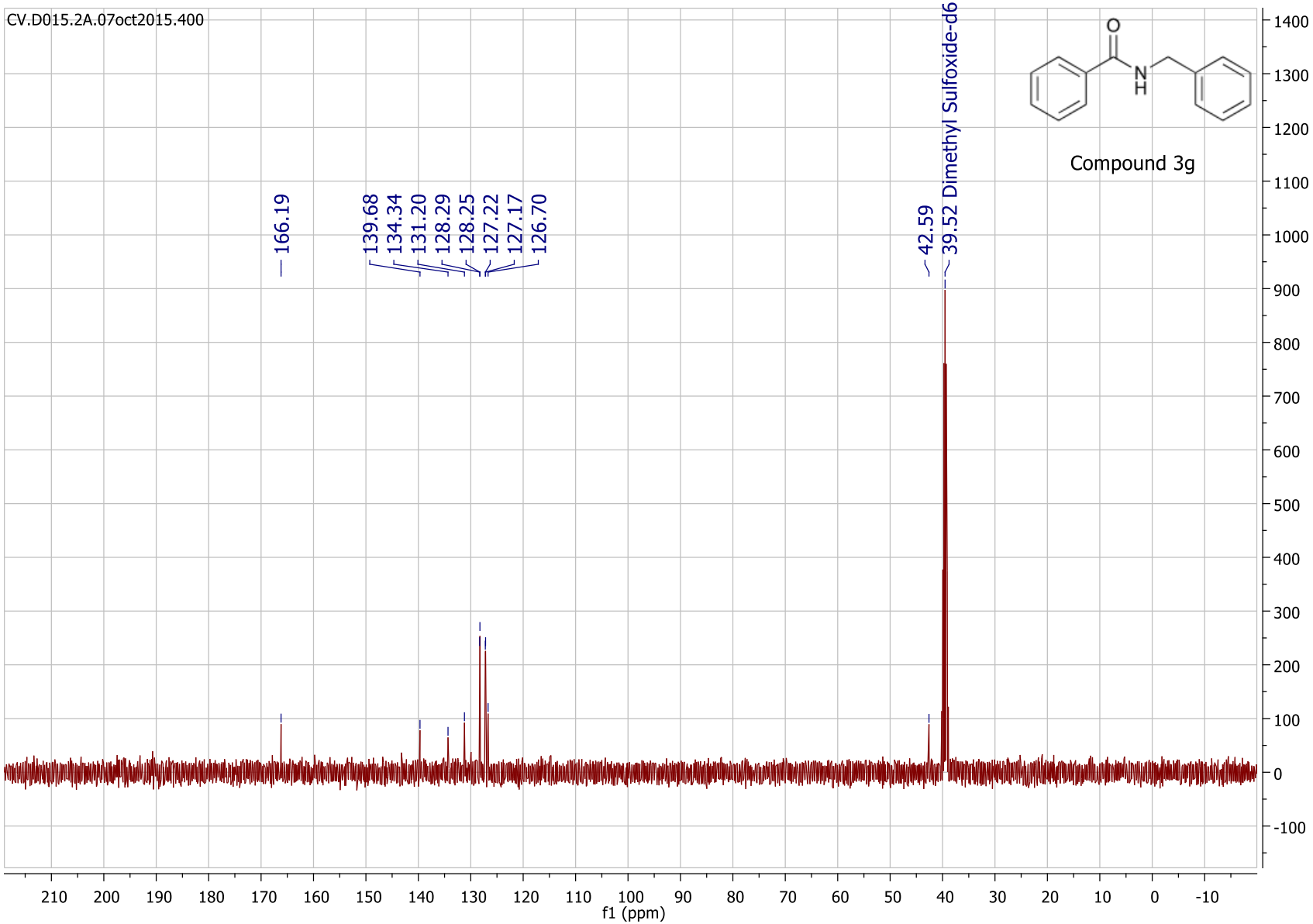

WDB-CV-D015.3a
7.36
7.26 Chloroform-d
3.68
3.31
1.64
1.49
Compound 3e
4.79
2.05
2.01
4.04
1.95
f1 (ppm)

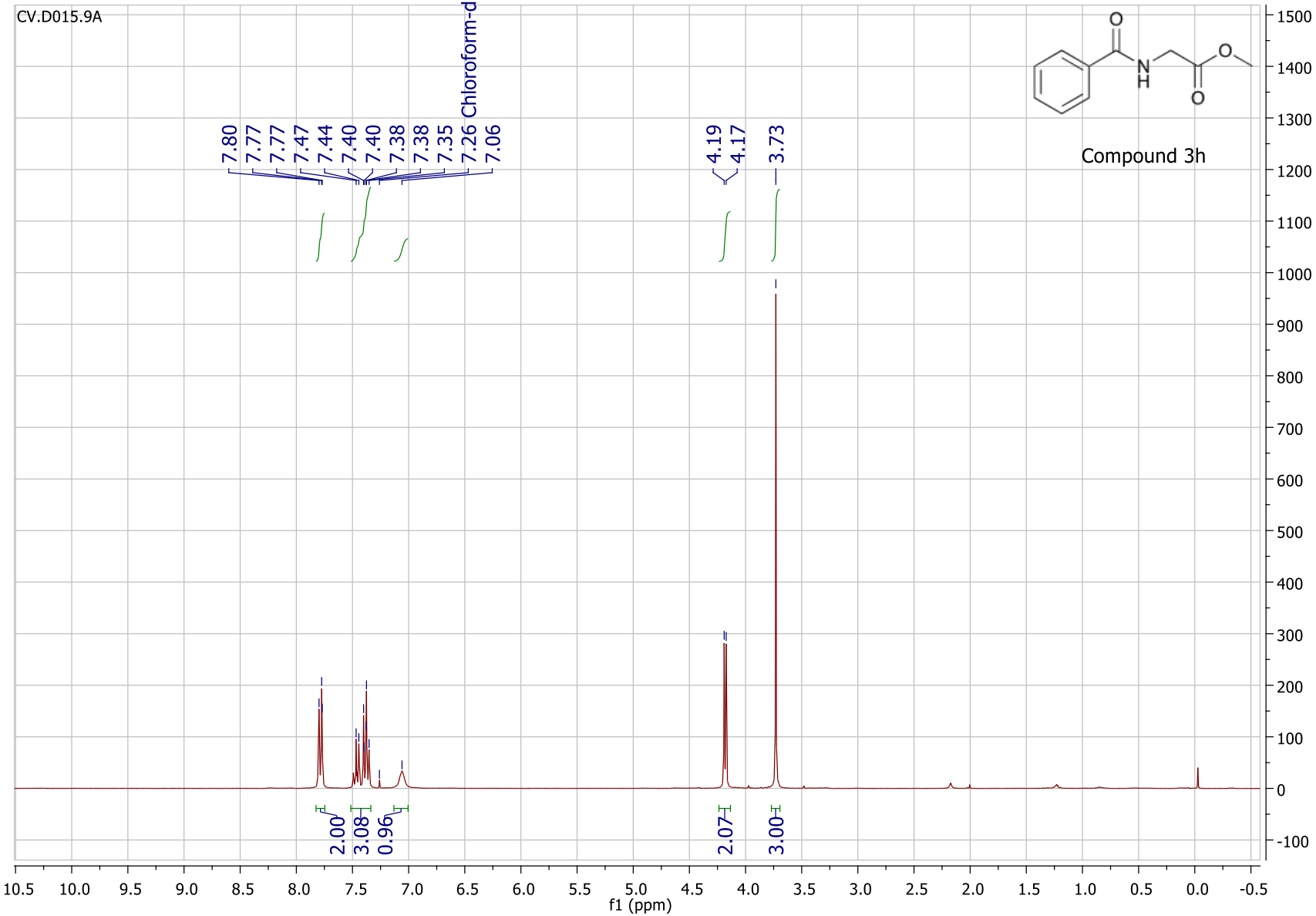

WDB-CV-D015.3a
169.91
136.11
128.95
128.00
126.38
77.16 Chloroform-d
48.35
42.72
26.15
25.28
24.20
O
N
Compound 3e
f1 (ppm)

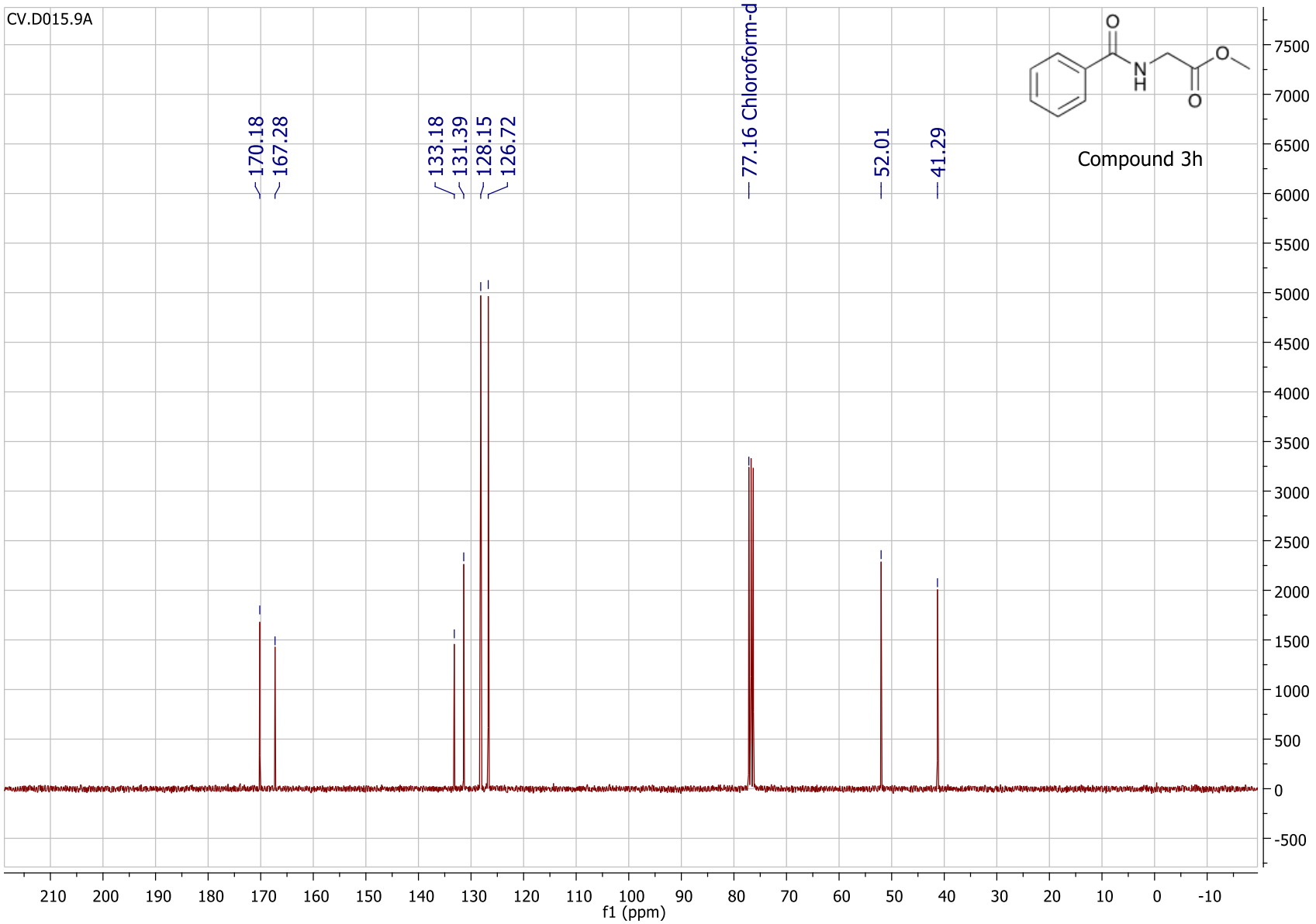

WDB-PG-CV-D015.4b-55degC-1H-13C-18dec2015.400
7.38
7.26 Chloroform-d
3.66
3.59
A (s)
7.38
B (brd)
3.63
5.03
8.00
Compound 3f
f1 (ppm)

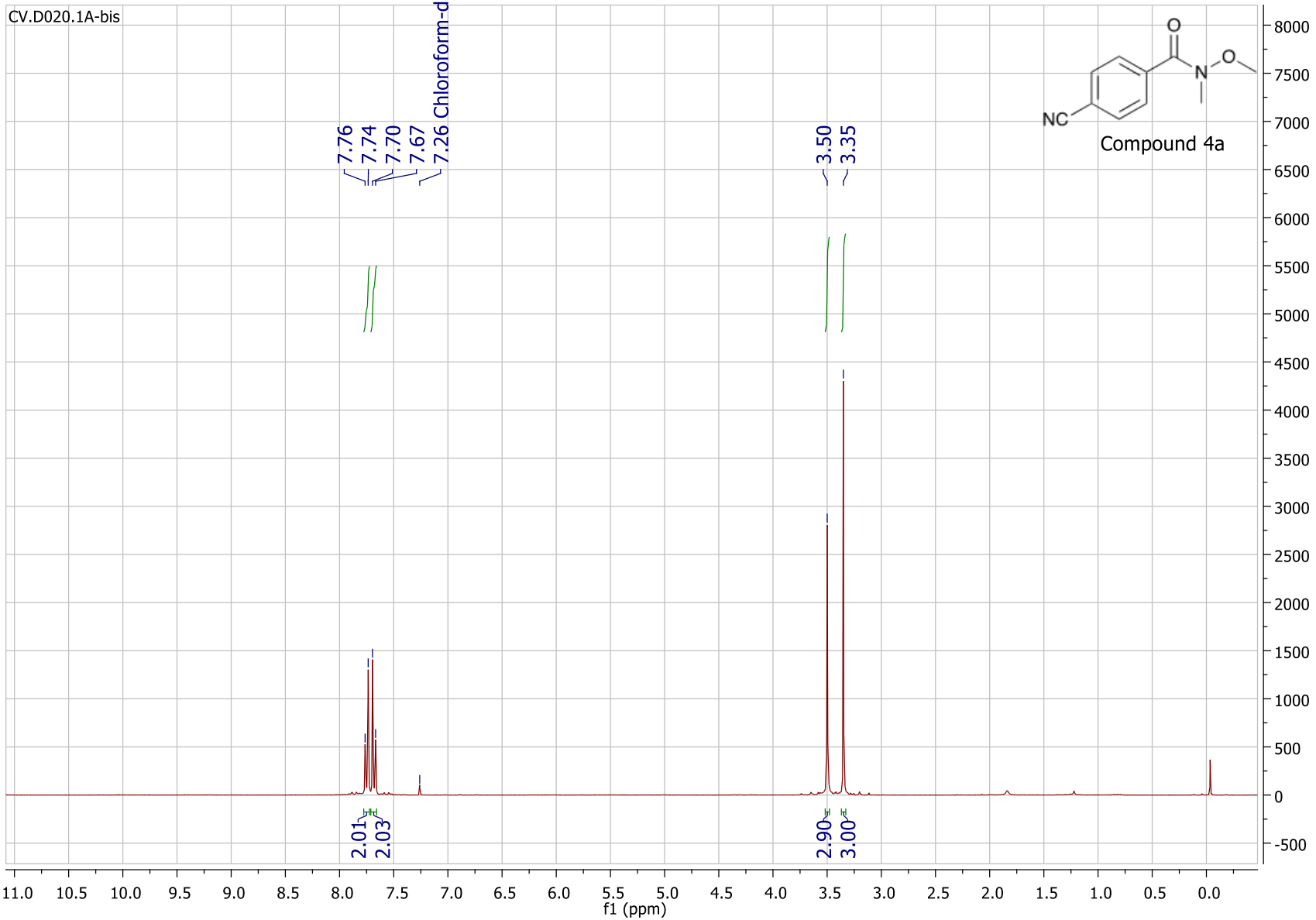

WDB-PG-CV-D015.4b-55degC-1H-13C-18dec2015.400
170.52
135.67
129.90
128.62
127.21
77.16 Chloroform-d
67.00
46.88
Compound 3f
f1 (ppm)

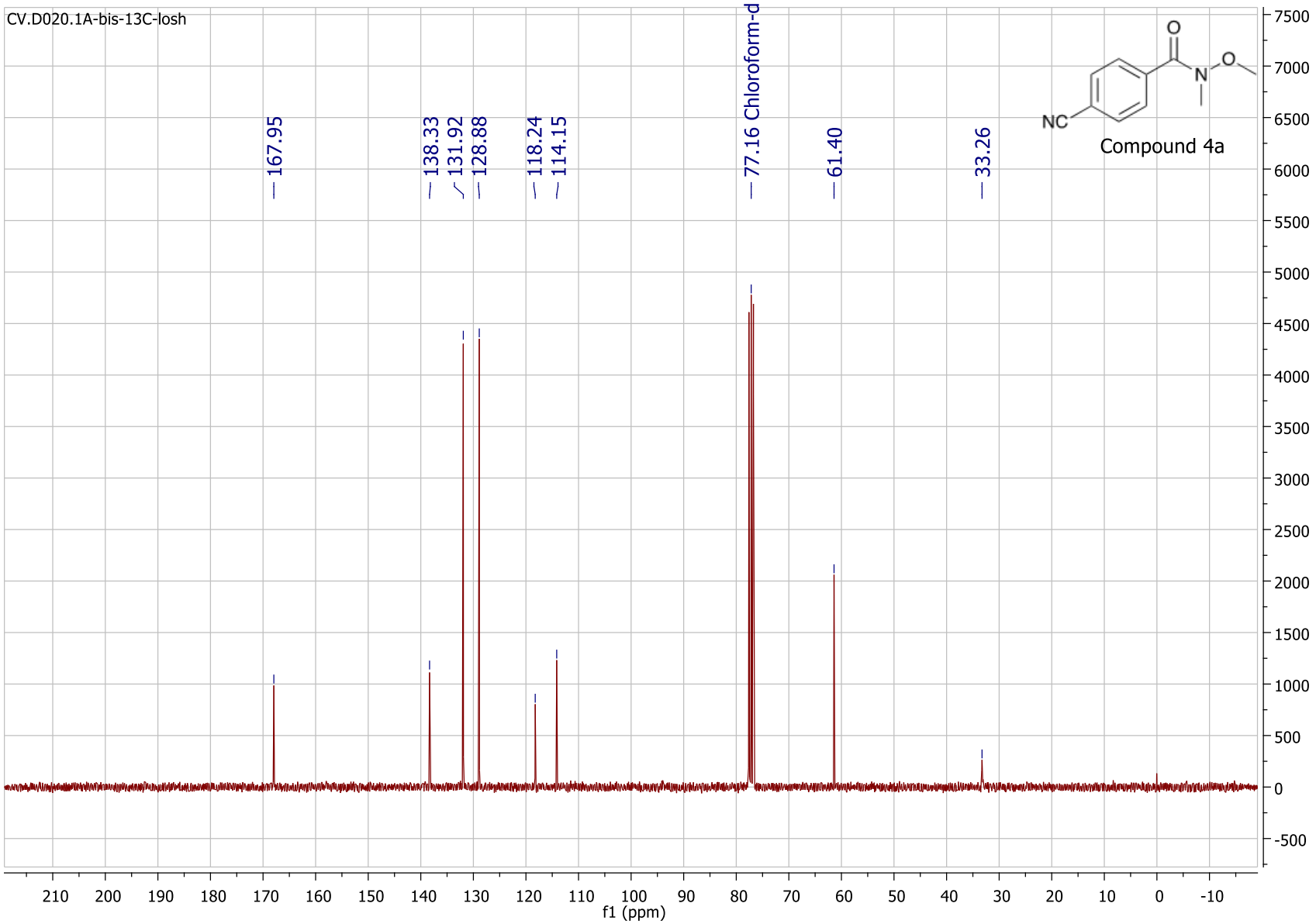

CV.D015.2A.07oct2015.400
9.04
7.92
7.90
7.89
7.54
7.52
7.49
7.47
7.45
7.33
7.32
7.26
7.25
7.24
7.23
4.50
4.49
3.34
2.50 Dimethyl Sulfoxide-d6
Compound 3g
1.01
2.03
3.05
4.02
1.00
2.00
f1 (ppm)

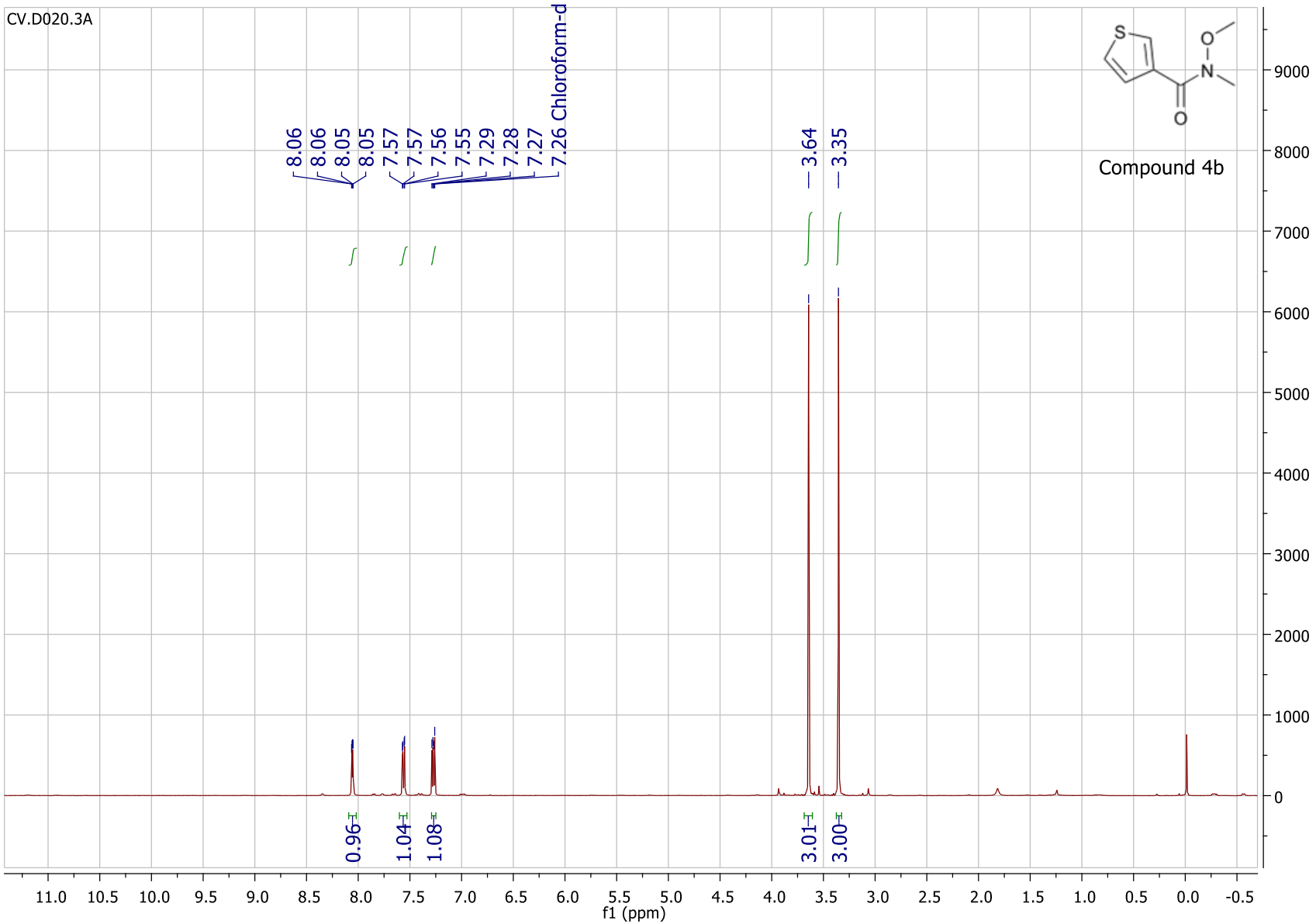

CV.D015.2A.07oct2015.400
166.19
139.68
134.34
131.20
128.29
128.25
127.22
127.17
126.70
42.59
39.52 Dimethyl Sulfoxide-d6
Compound 3g
f1 (ppm)

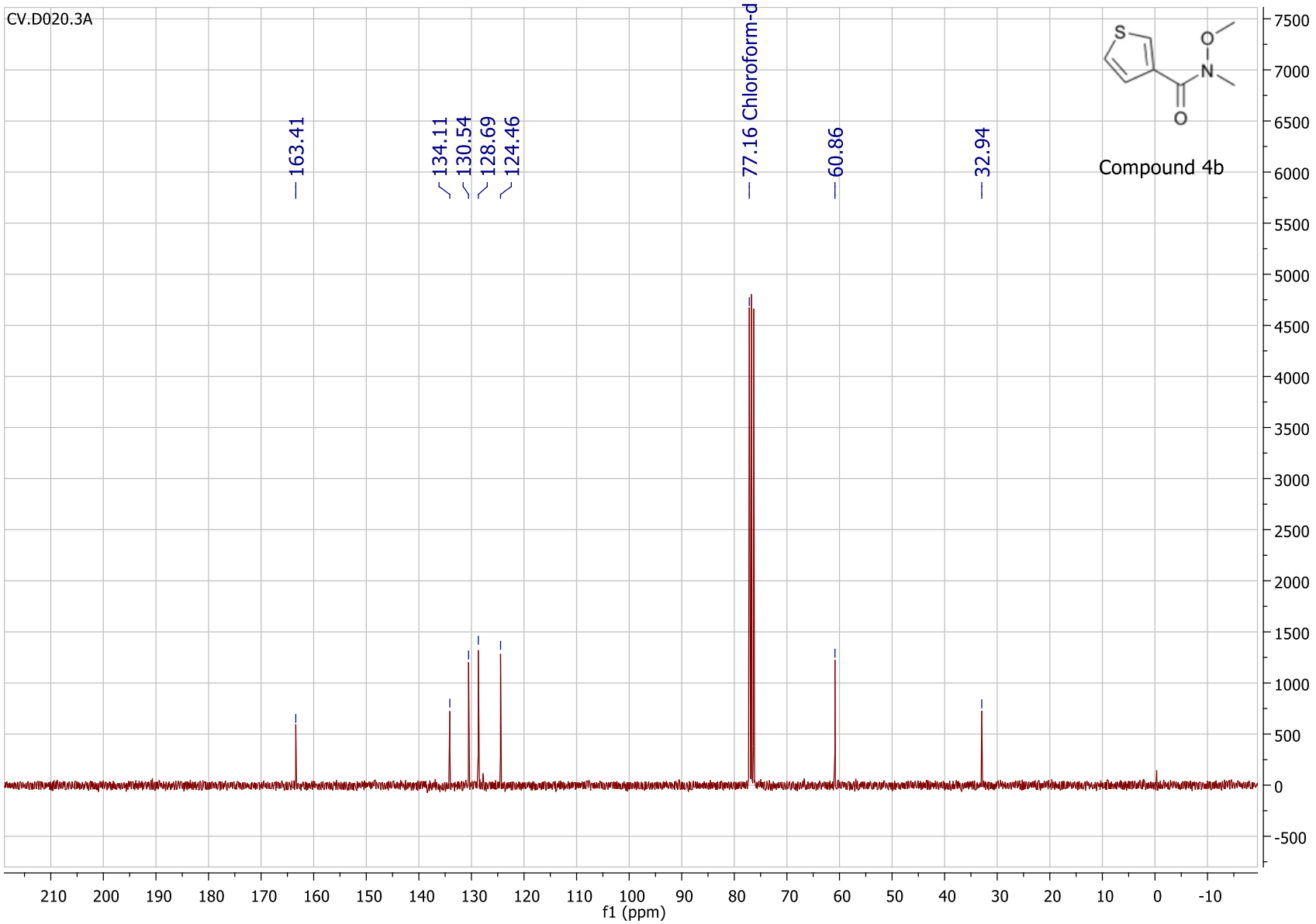

CV.D015.9A
7.80
7.77
7.77
7.47
7.44
7.40
7.40
7.38
7.38
7.35
7.26 Chloroform-d
7.06
4.19
4.17
3.73
2.00
3.08
0.96
2.07
3.00
Compound 3h
f1 (ppm)

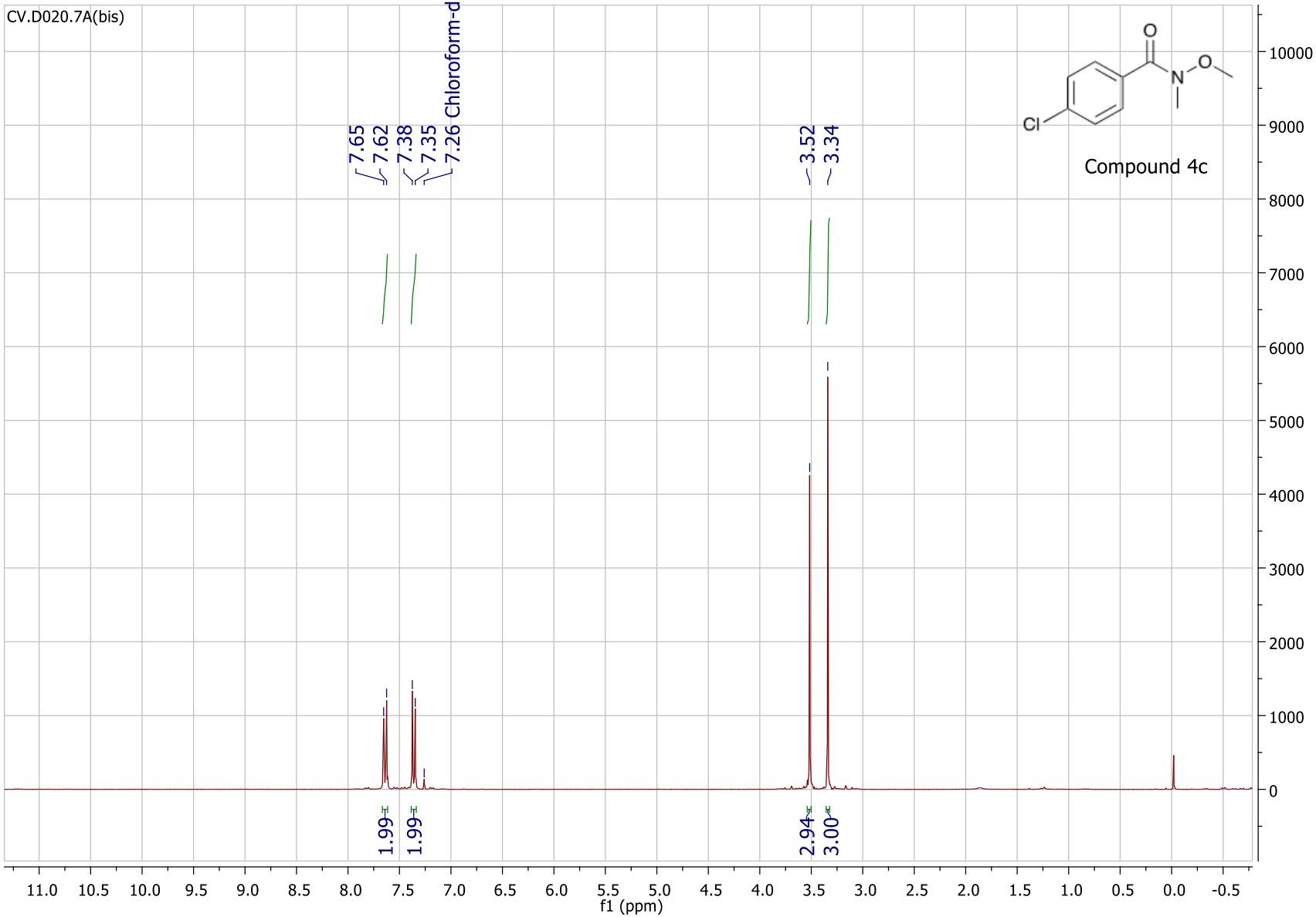

CV.D015.9A
170.18
167.28
133.18
131.39
128.15
126.72
77.16 Chloroform-d
52.01
41.29
Compound 3h
f1 (ppm)

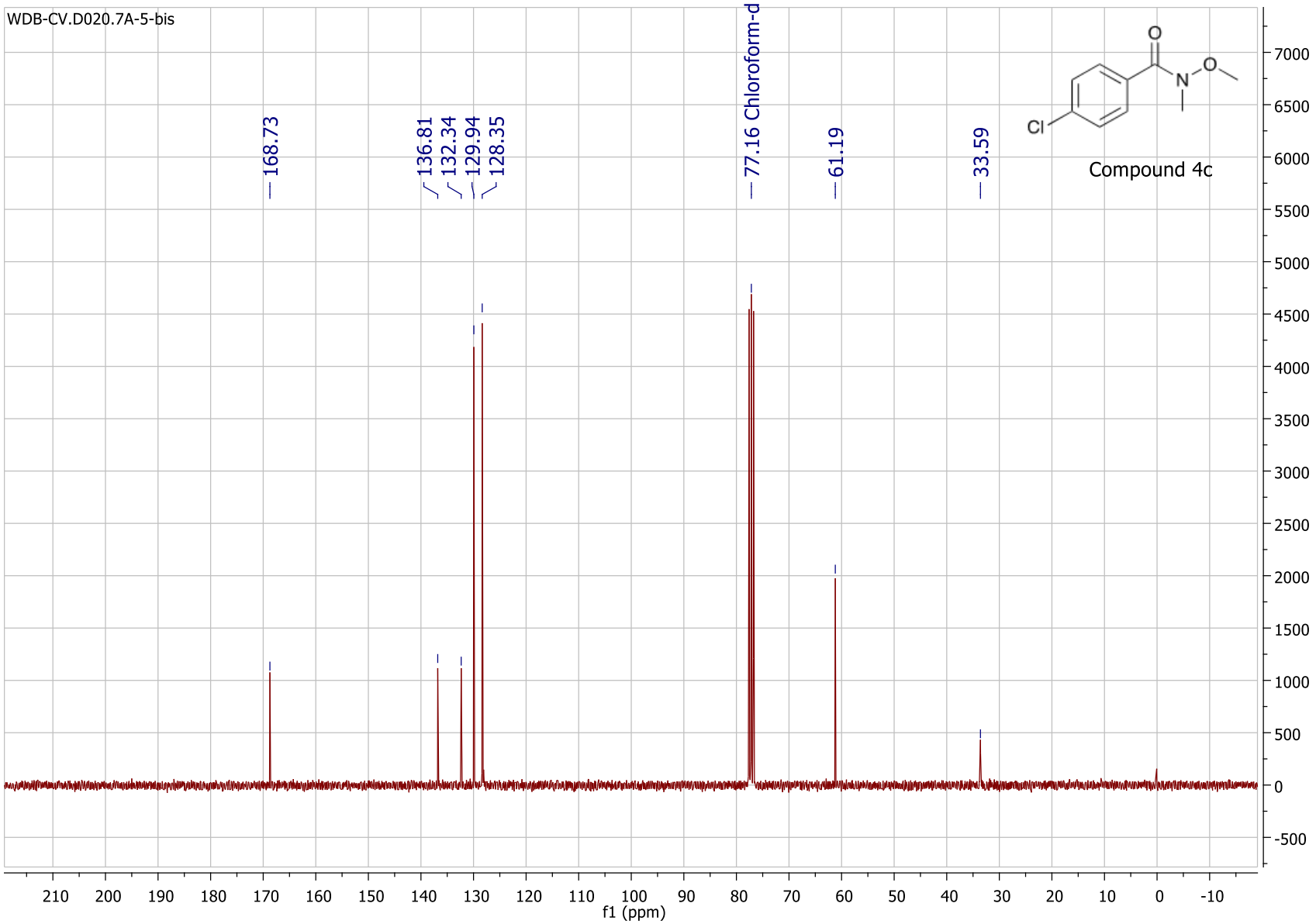

CV.D020.1A-bis
7.76
7.74
7.70
7.67
7.26 Chloroform-d
3.50
3.35
2.01
2.03
2.90
3.00
f1 (ppm)
Compound 4a

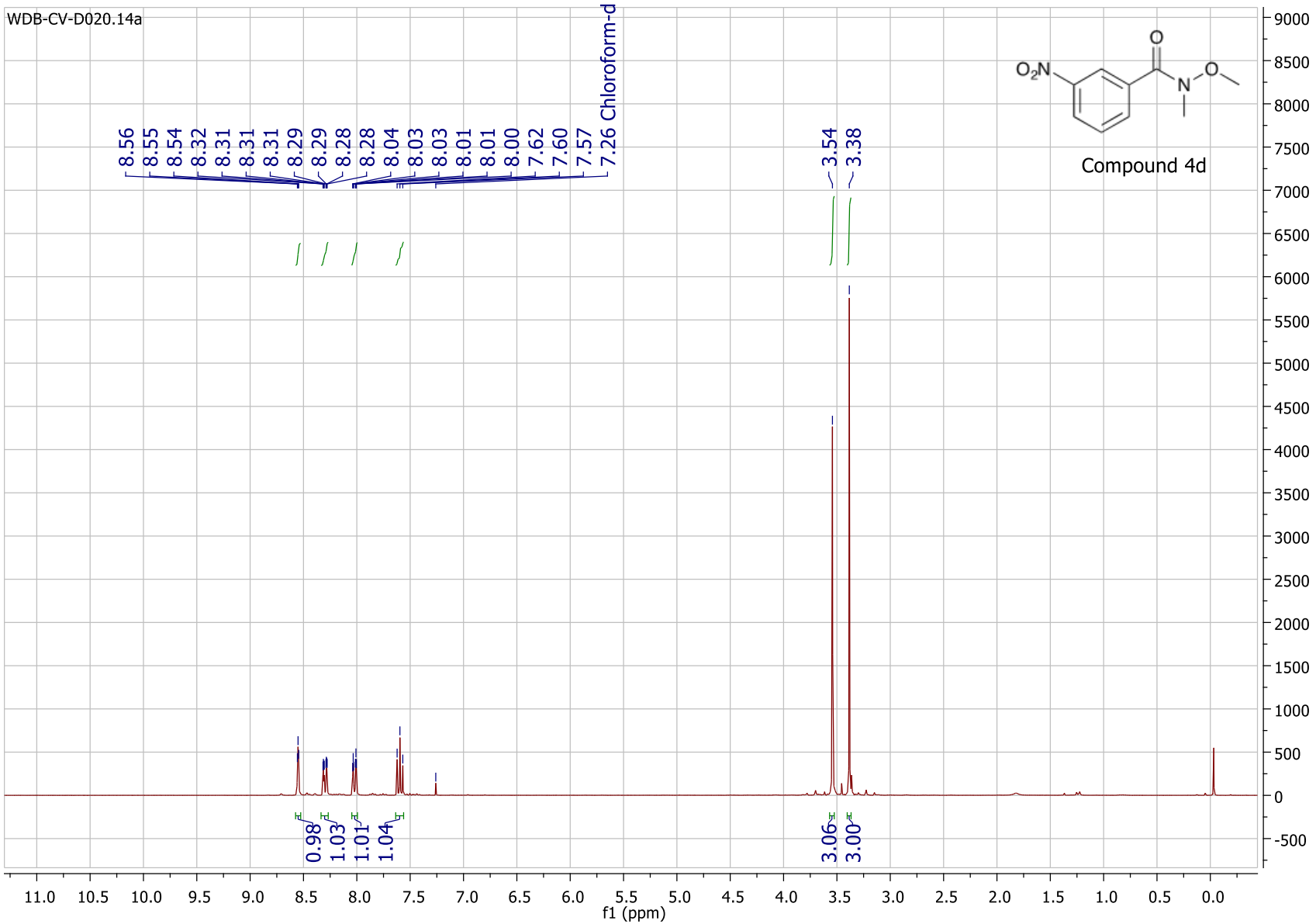

CV.D020.1A-bis-13C-losh
167.95
138.33
131.92
128.88
118.24
114.15
77.16 Chloroform-d
61.40
33.26
NC
O
N
O
Compound 4a
f1 (ppm)

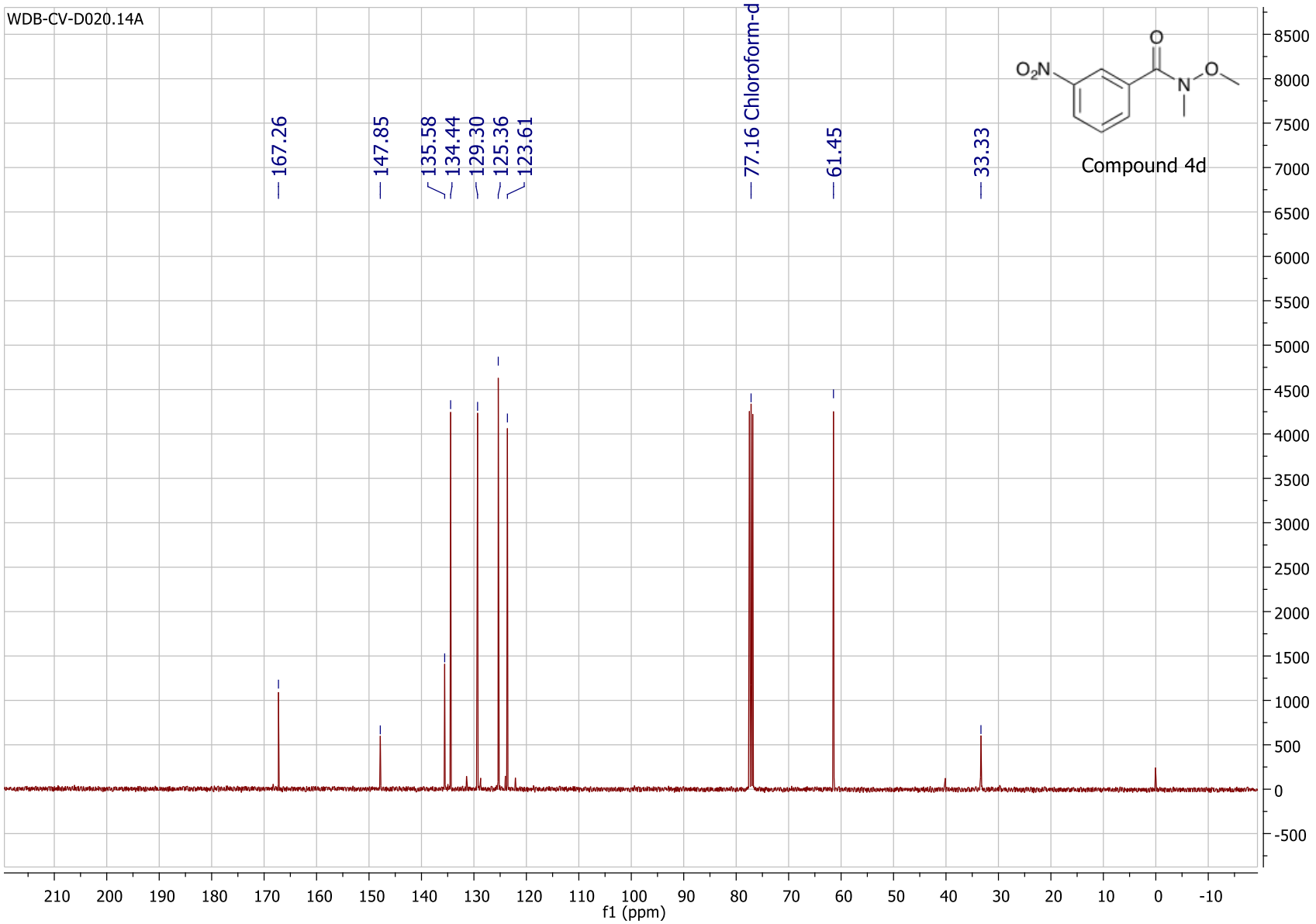

CV.D020.3A
8.06
8.06
8.05
8.05
7.57
7.57
7.56
7.55
7.29
7.28
7.27
7.26 Chloroform-d
3.64
3.35
Compound 4b
0.96
1.04
1.08
3.01
3.00
f1 (ppm)

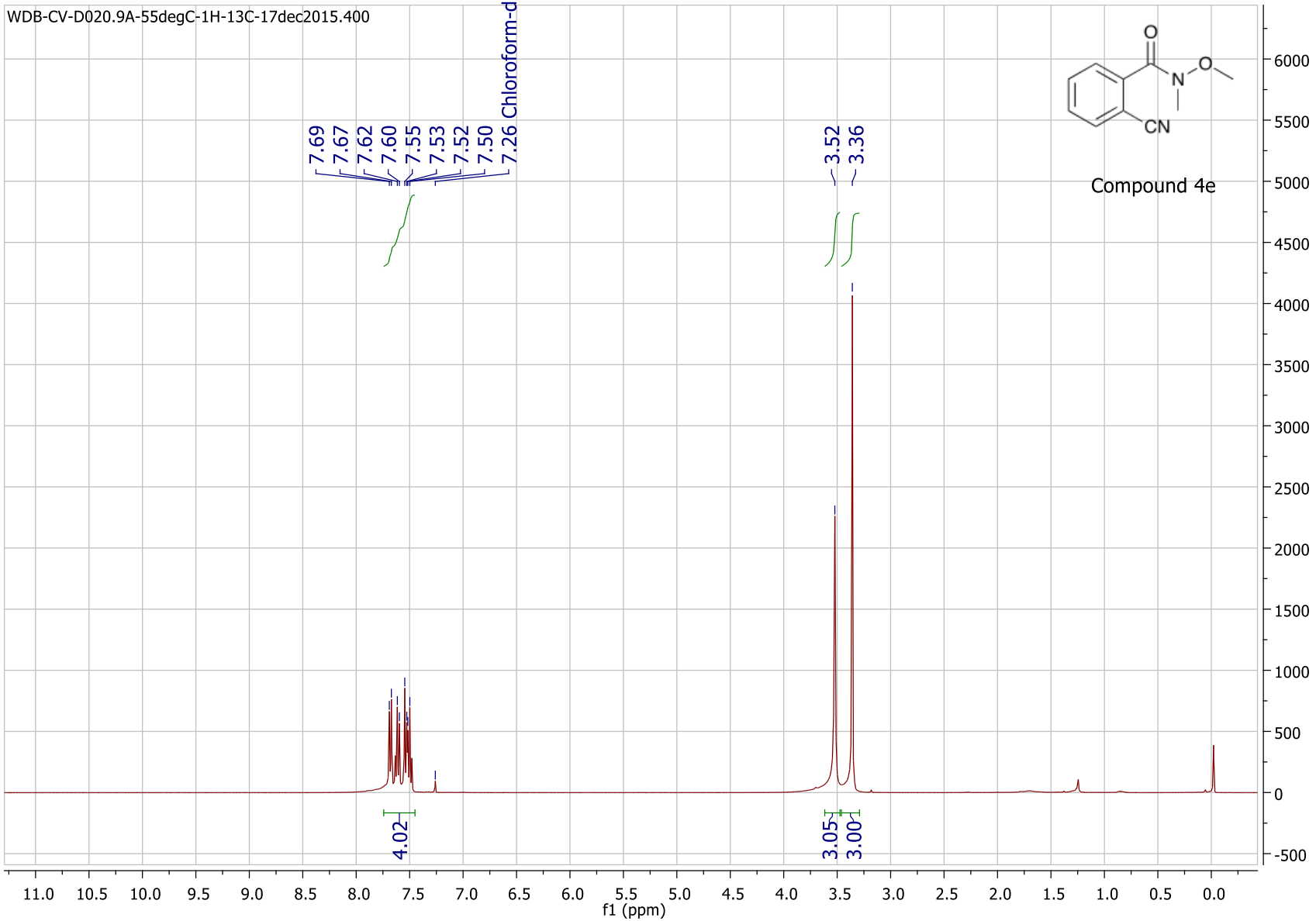

CV.D020.3A
163.41
134.11
130.54
128.69
124.46
77.16 Chloroform-d
60.86
32.94
Compound 4b
f1 (ppm)

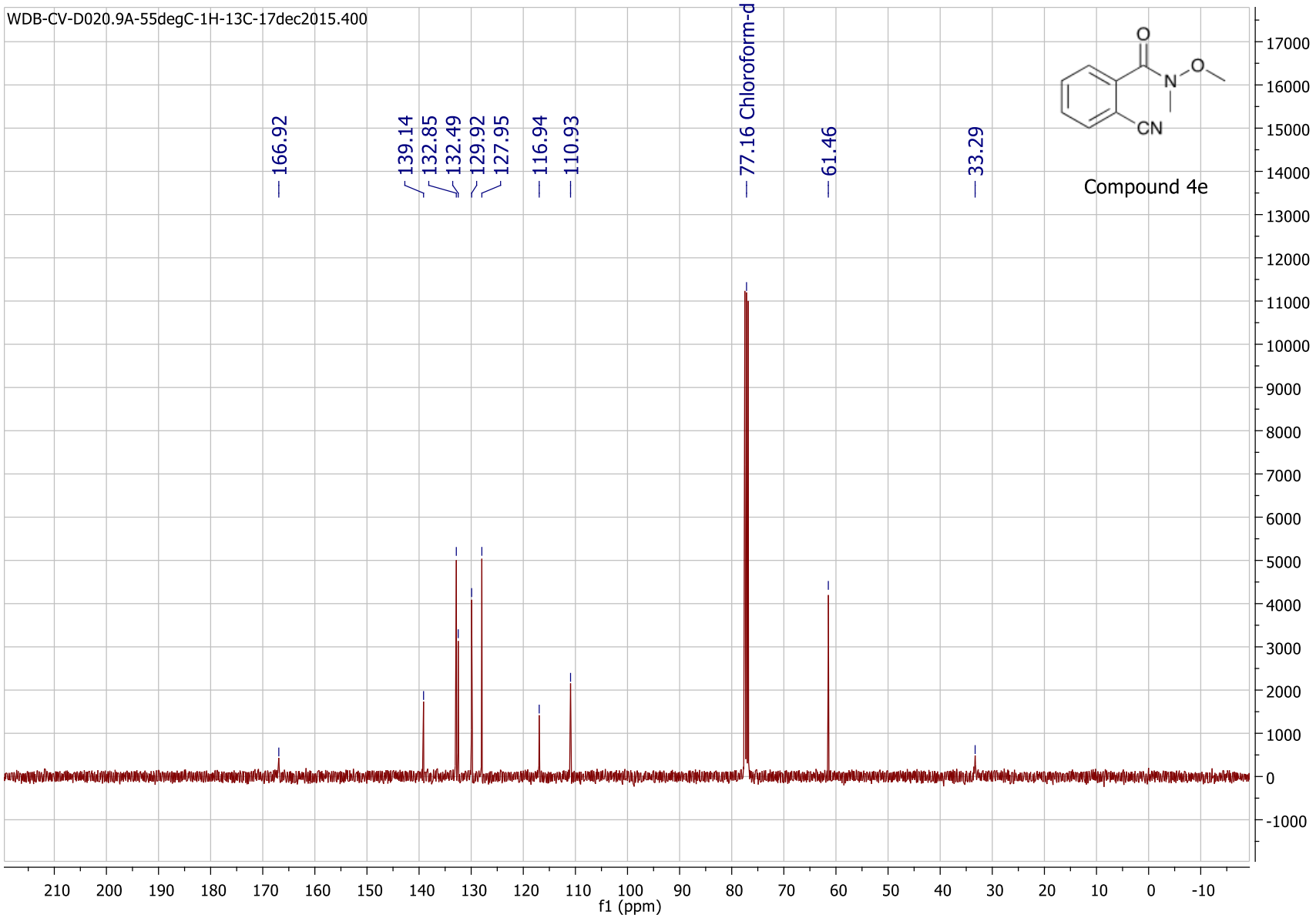

CV.D020.7A(bis)
7.65
7.62
7.38
7.35
7.26 Chloroform-d
3.52
3.34
Cl
O
N
O
Compound 4c
1.99
1.99
2.94
3.00
f1 (ppm)

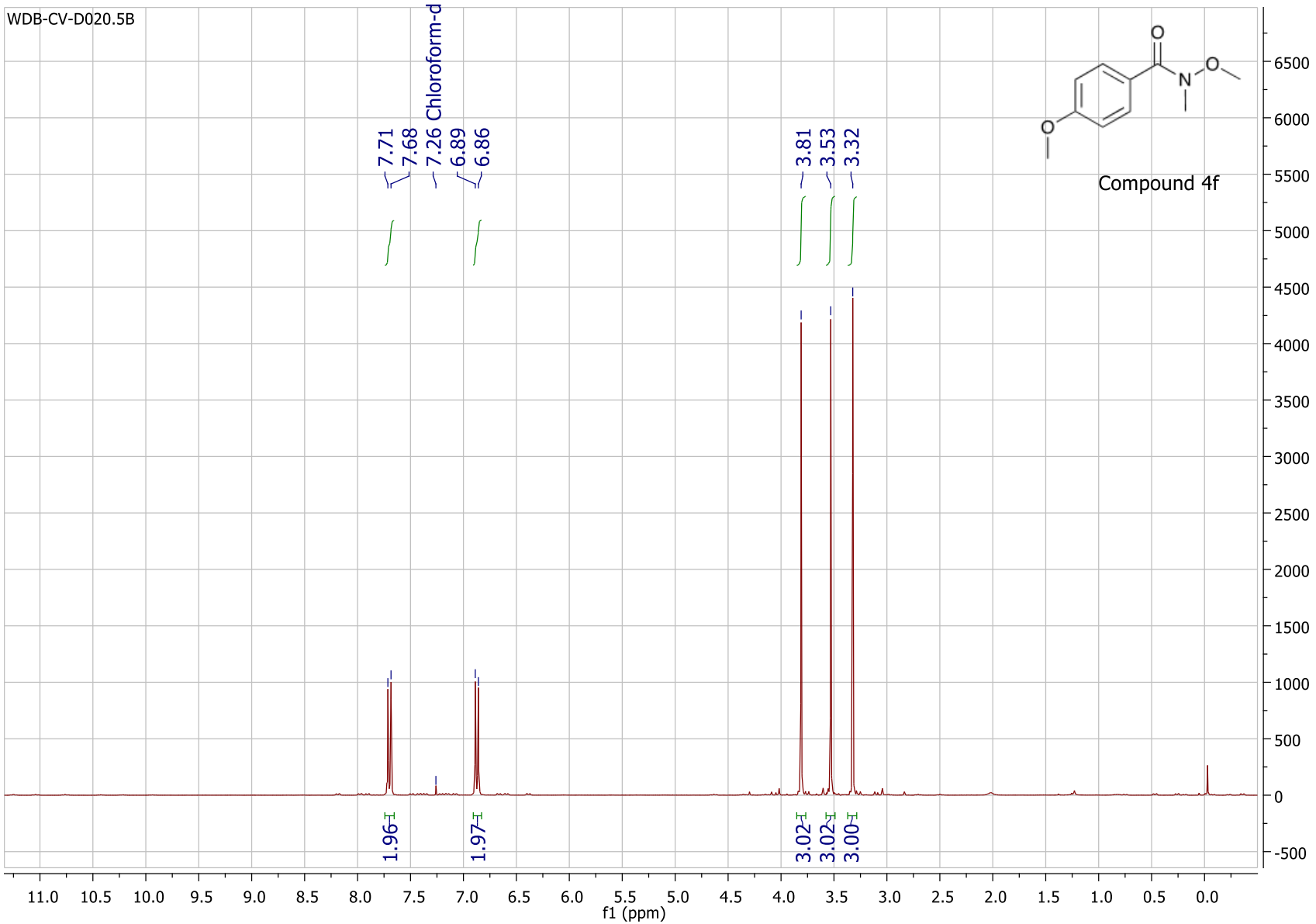

WDB-CV.D020.7A-5-bis
168.73
136.81
132.34
129.94
128.35
77.16 Chloroform-d
61.19
33.59
Cl
O
N
O
Compound 4c
f1 (ppm)

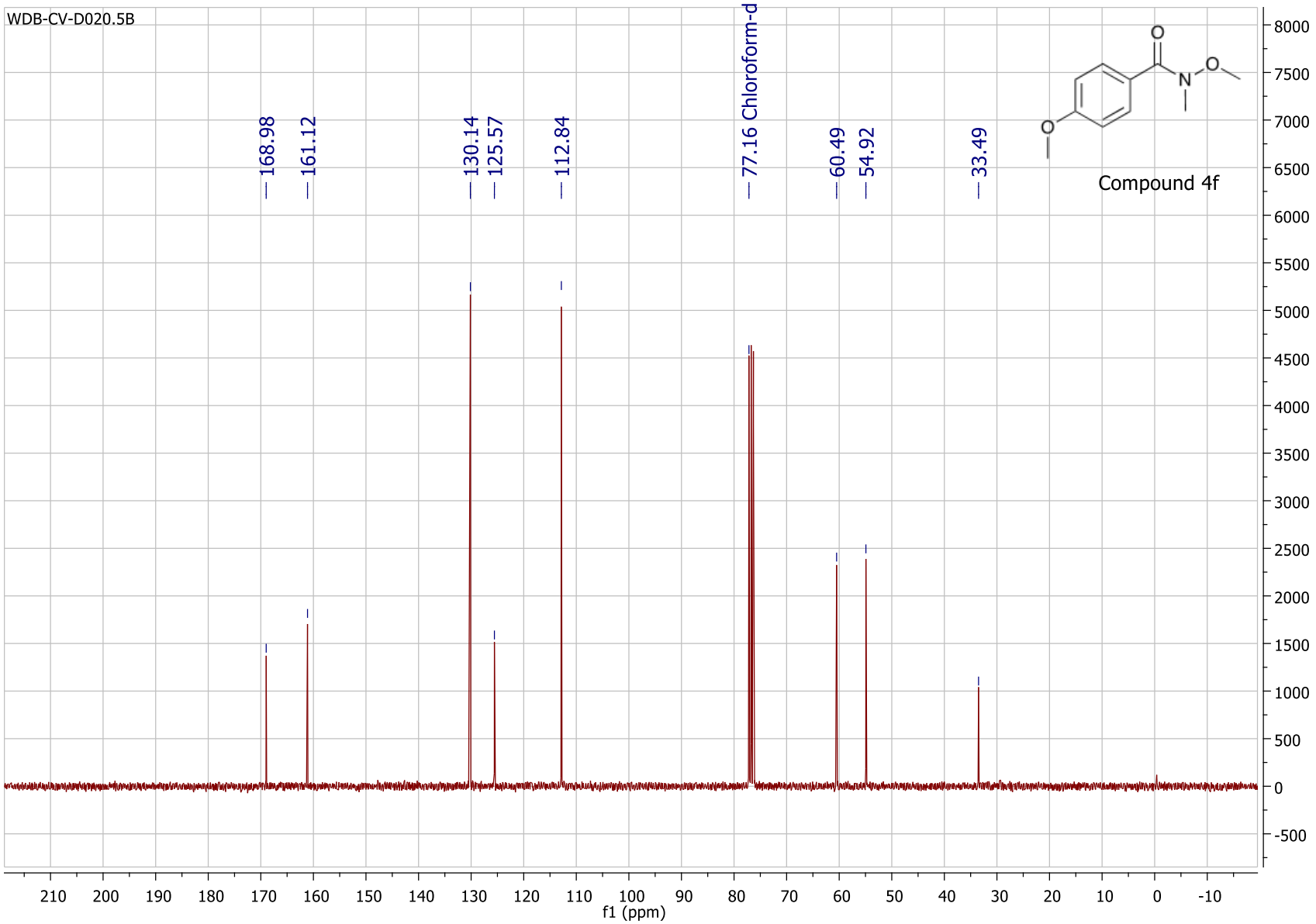

WDB-CV-D020.14a
8.56
8.55
8.54
8.32
8.31
8.31
8.31
8.29
8.29
8.28
8.28
8.04
8.03
8.03
8.01
8.01
8.00
7.62
7.60
7.57
7.26 Chloroform-d
3.54
3.38
Compound 4d
0.98
1.03
1.01
1.04
3.06
3.00
f1 (ppm)

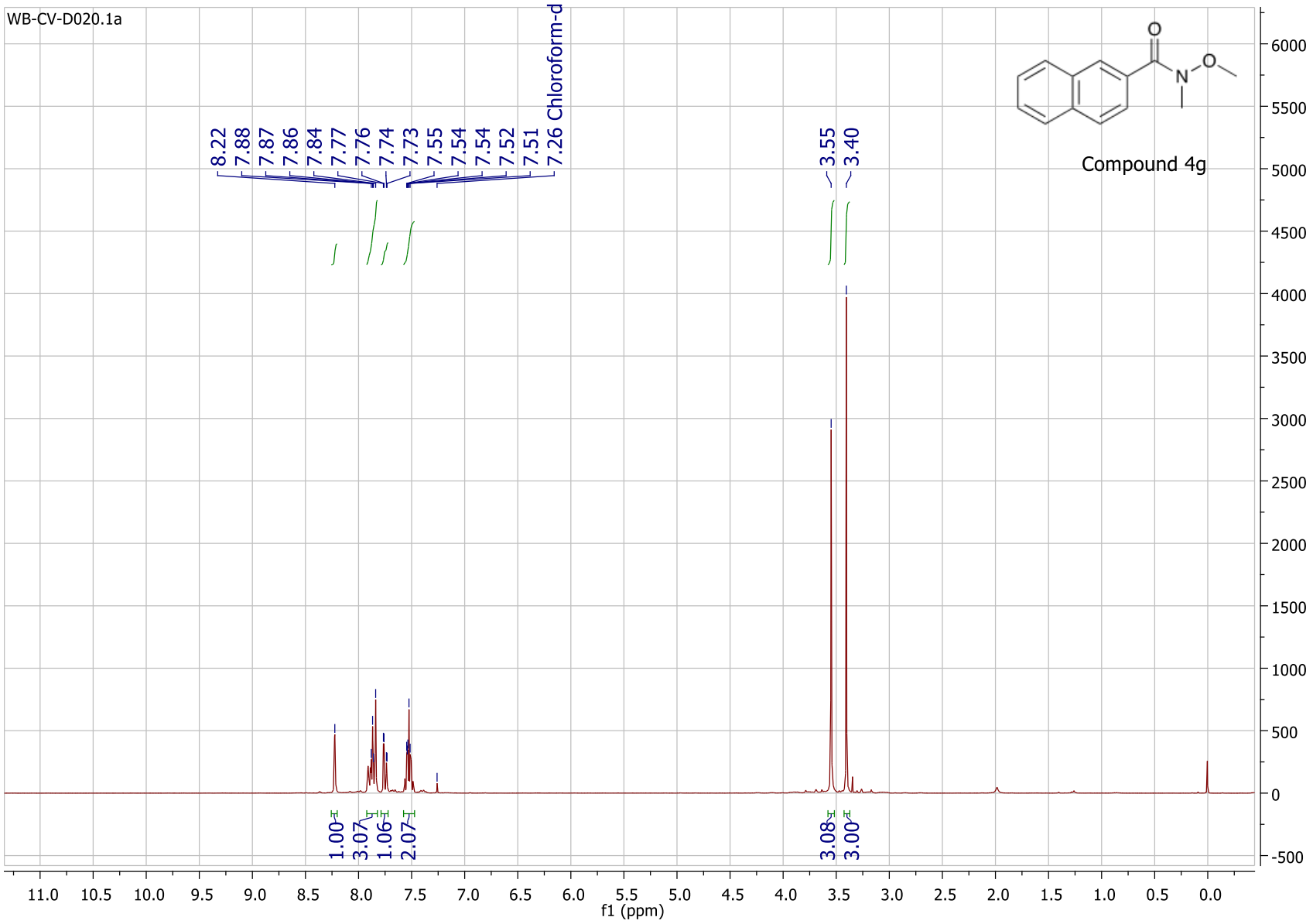

WDB-CV-D020.14A
167.26
147.85
135.58
134.44
129.30
125.36
123.61
77.16 Chloroform-d
61.45
33.33
Compound 4d
f1 (ppm)

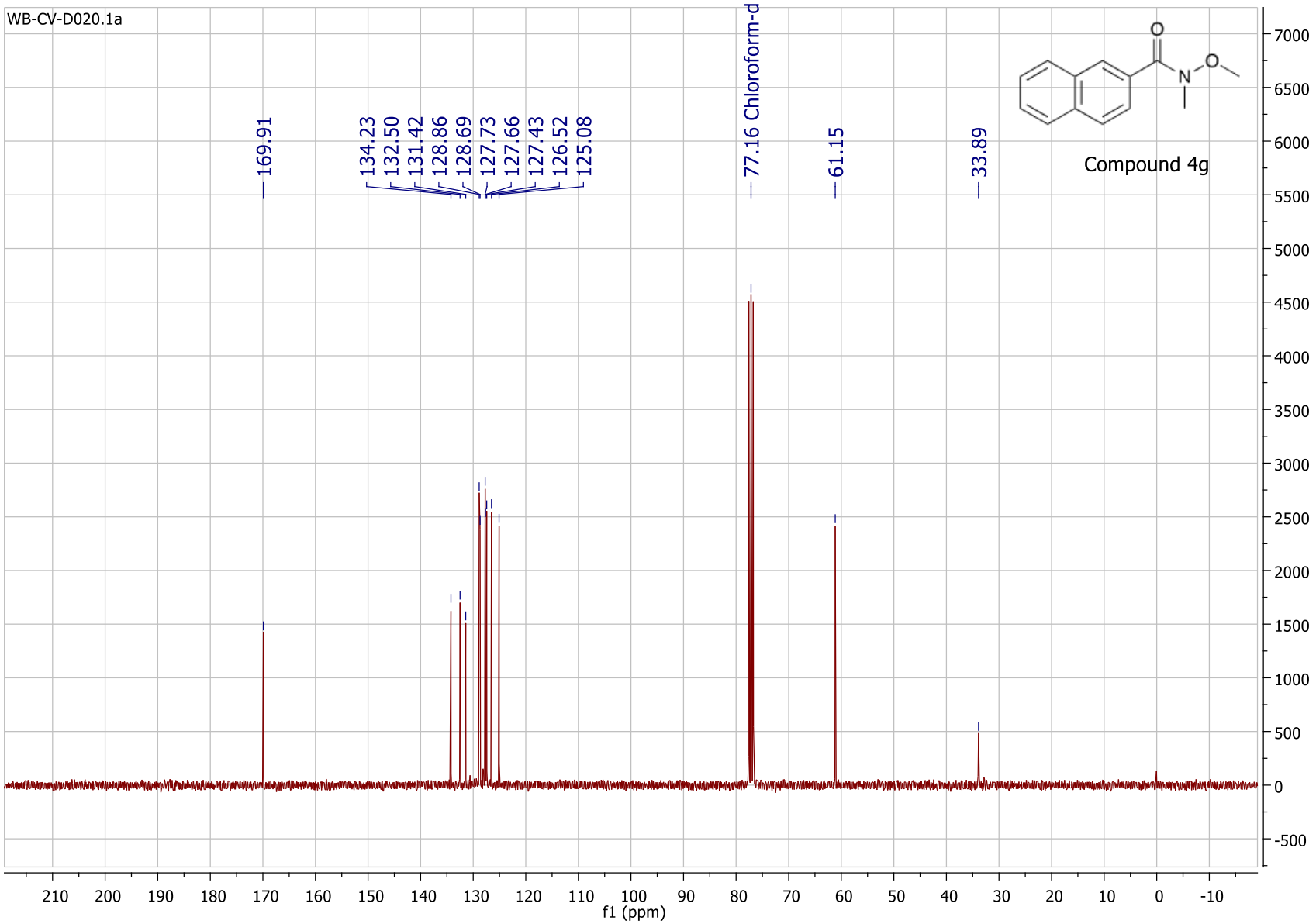

WDB-CV-D020.9A-55degC-1H-13C-17dec2015.400
7.69
7.67
7.62
7.60
7.55
7.53
7.52
7.50
7.26 Chloroform-d
3.52
3.36
4.02
3.05
3.00
Compound 4e
f1 (ppm)

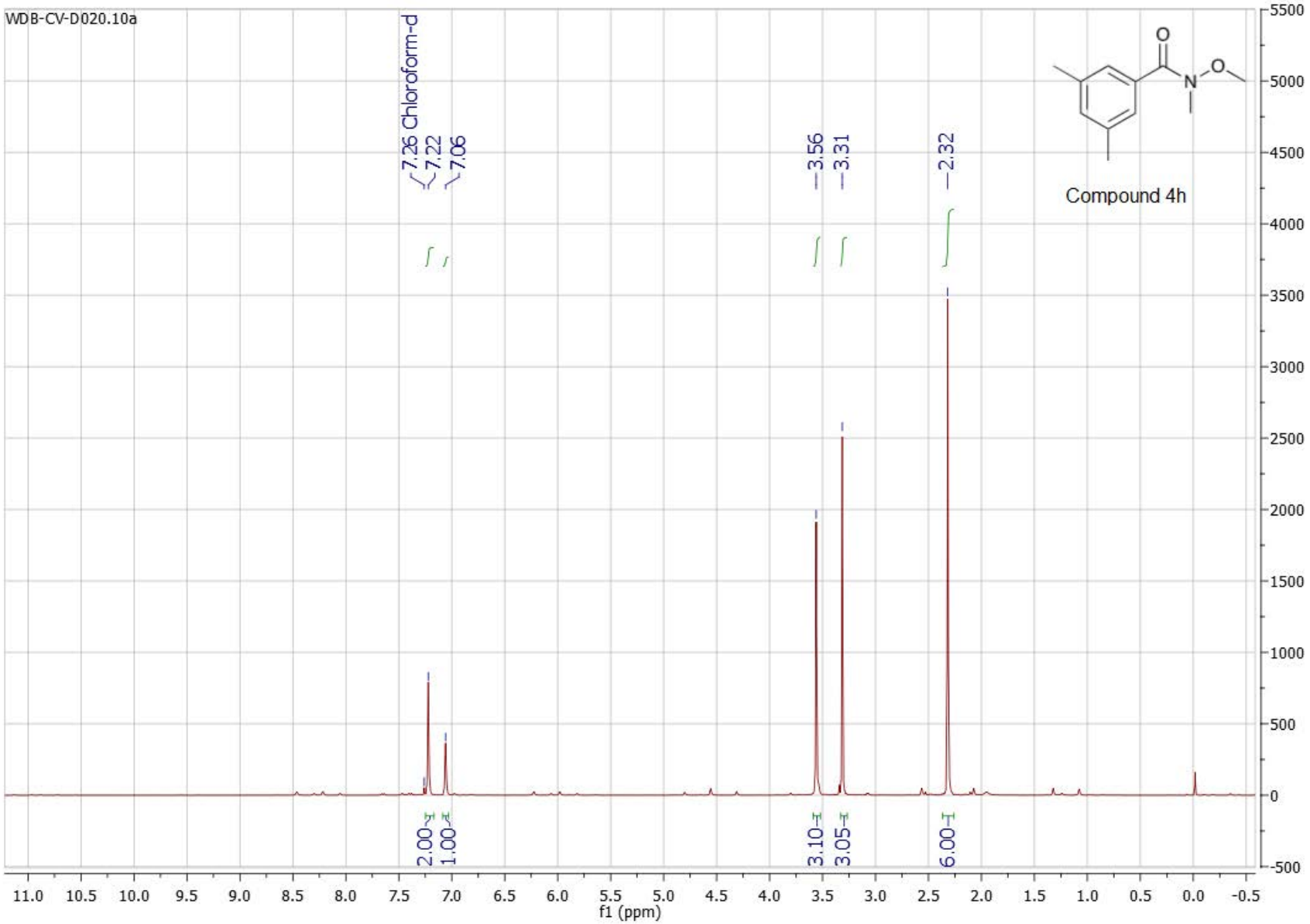

WDB-CV-D020.9A-55degC-1H-13C-17dec2015.400
166.92
139.14
132.85
132.49
129.92
127.95
116.94
110.93
77.16 Chloroform-d
61.46
33.29
O
N
O
CN
Compound 4e
f1 (ppm)

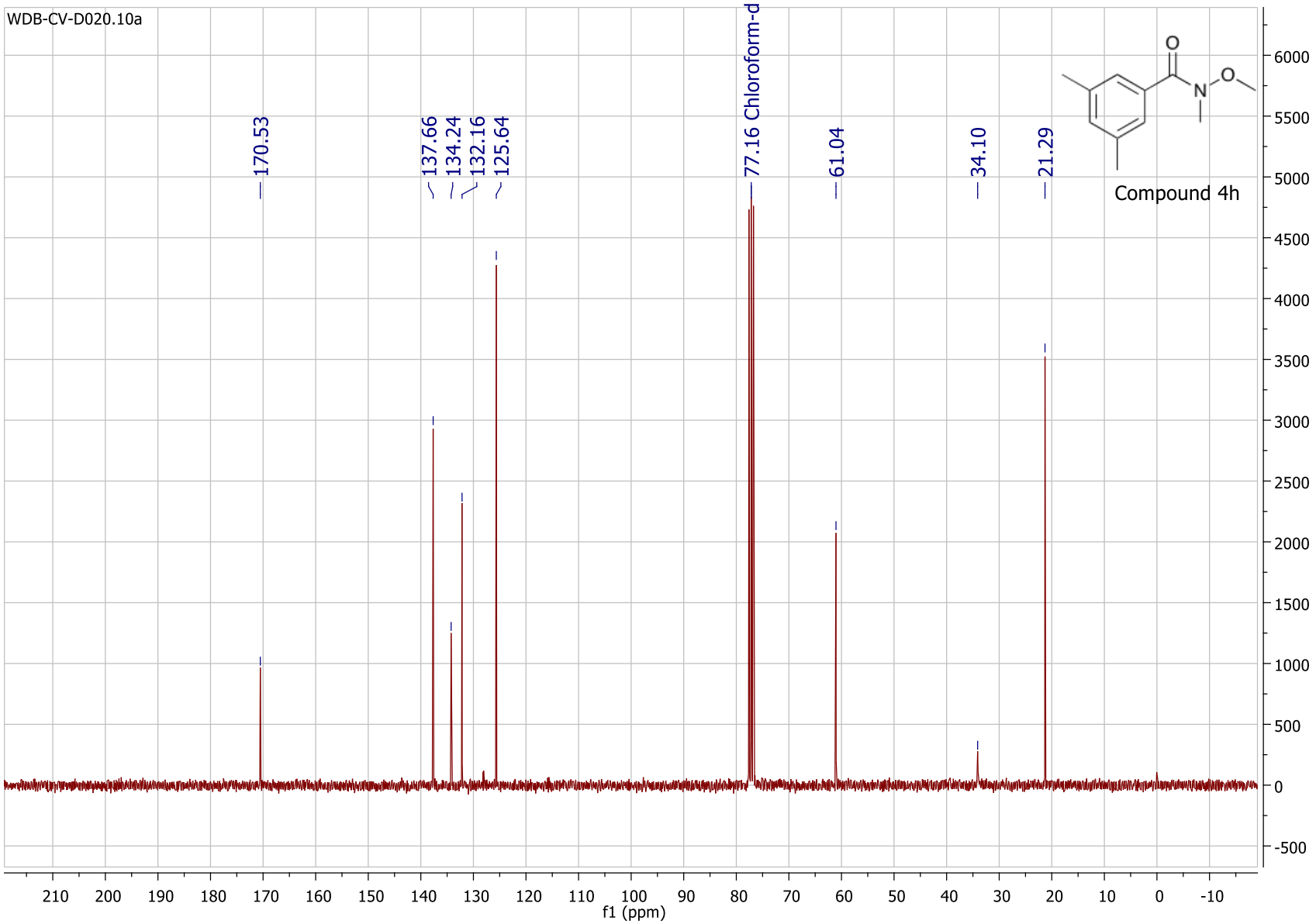

WDB-CV-D020.5B
7.71
7.68
7.26 Chloroform-d
6.89
6.86
3.81
3.53
3.32
Compound 4f
1.96
1.97
3.02
3.02
3.00
f1 (ppm)

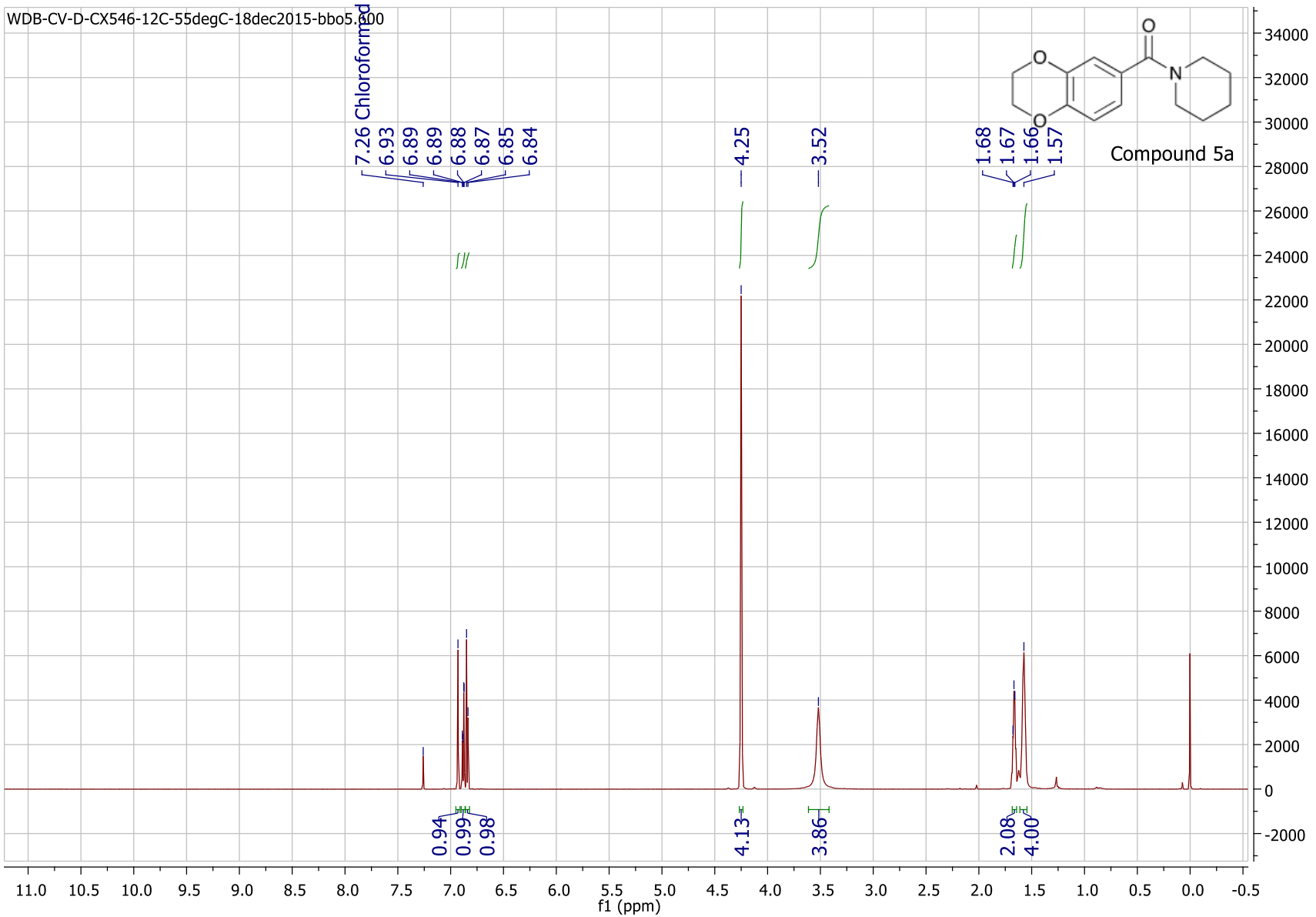

WDB-CV-D020.5B
168.98
161.12
130.14
125.57
112.84
77.16 Chloroform-d
60.49
54.92
33.49
Compound 4f
f1 (ppm)

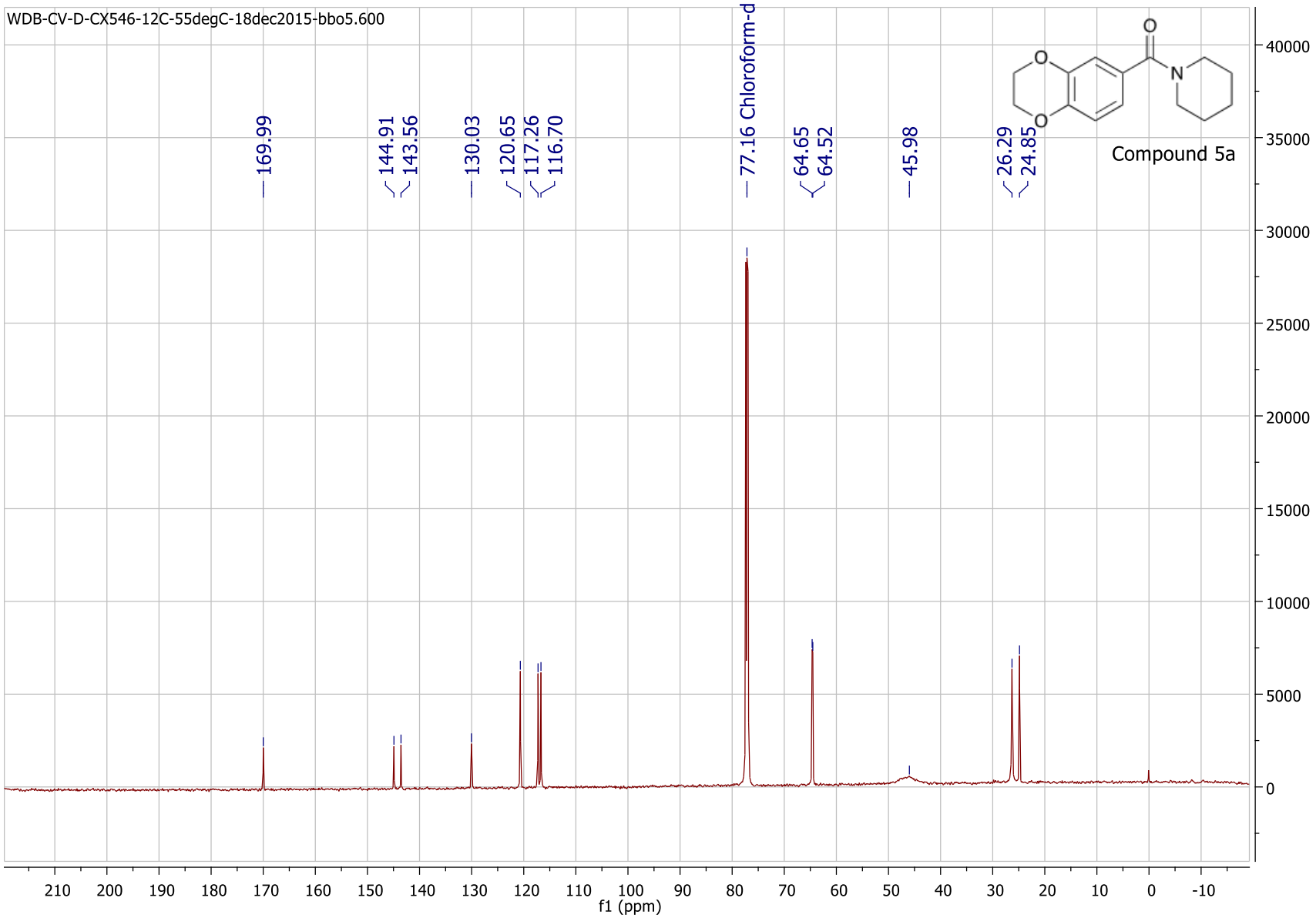

WB-CV-D020.1a
8.22
7.88
7.87
7.86
7.84
7.77
7.76
7.74
7.73
7.55
7.54
7.54
7.52
7.51
7.26 Chloroform-d
3.55
3.40
1.00
3.07
1.06
2.07
3.08
3.00
Compound 4g
f1 (ppm)

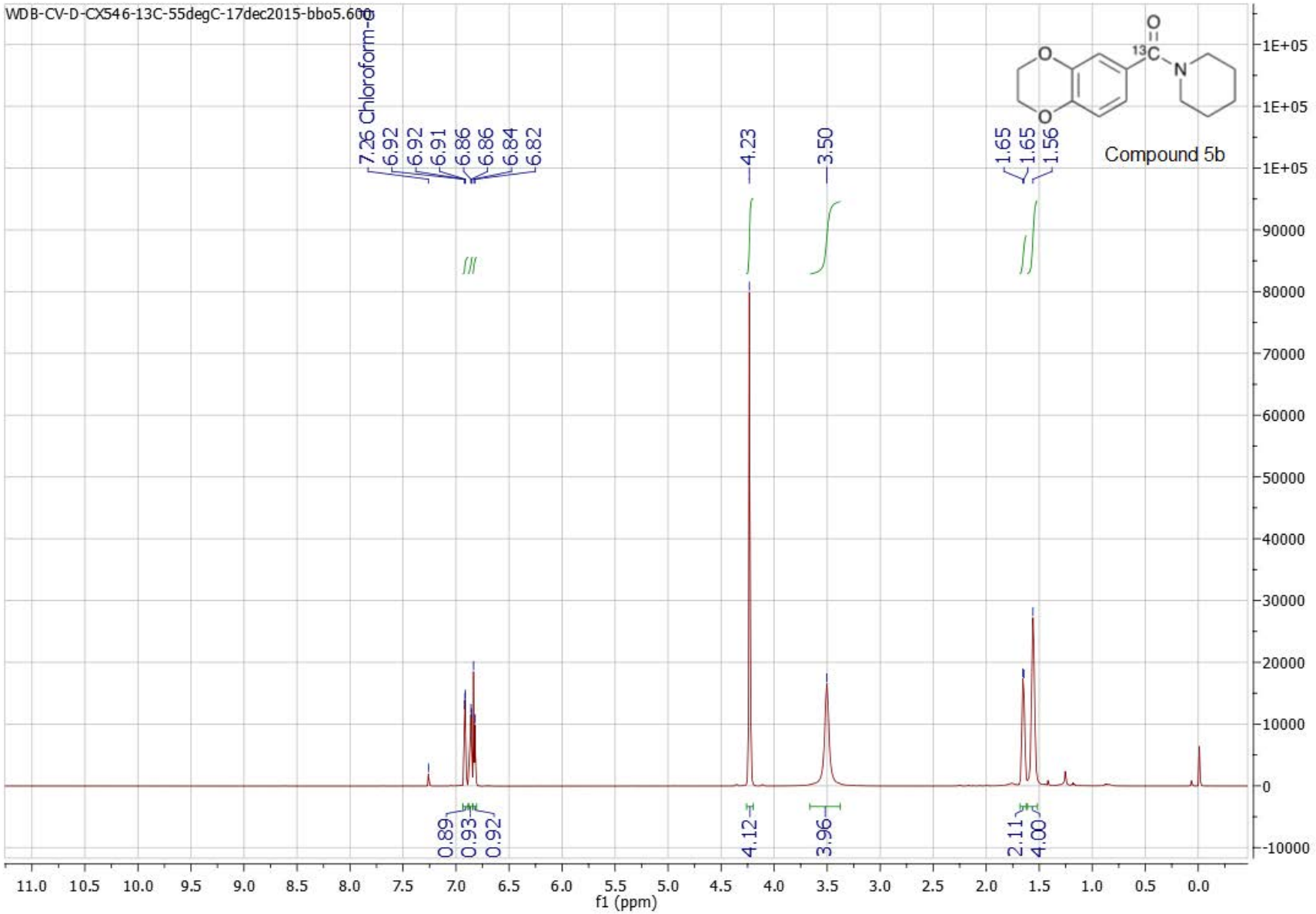

WB-CV-D020.1a
169.91
134.23
132.50
131.42
128.86
128.69
127.73
127.66
127.43
126.52
125.08
77.16 Chloroform-d
61.15
33.89
Compound 4g
f1 (ppm)

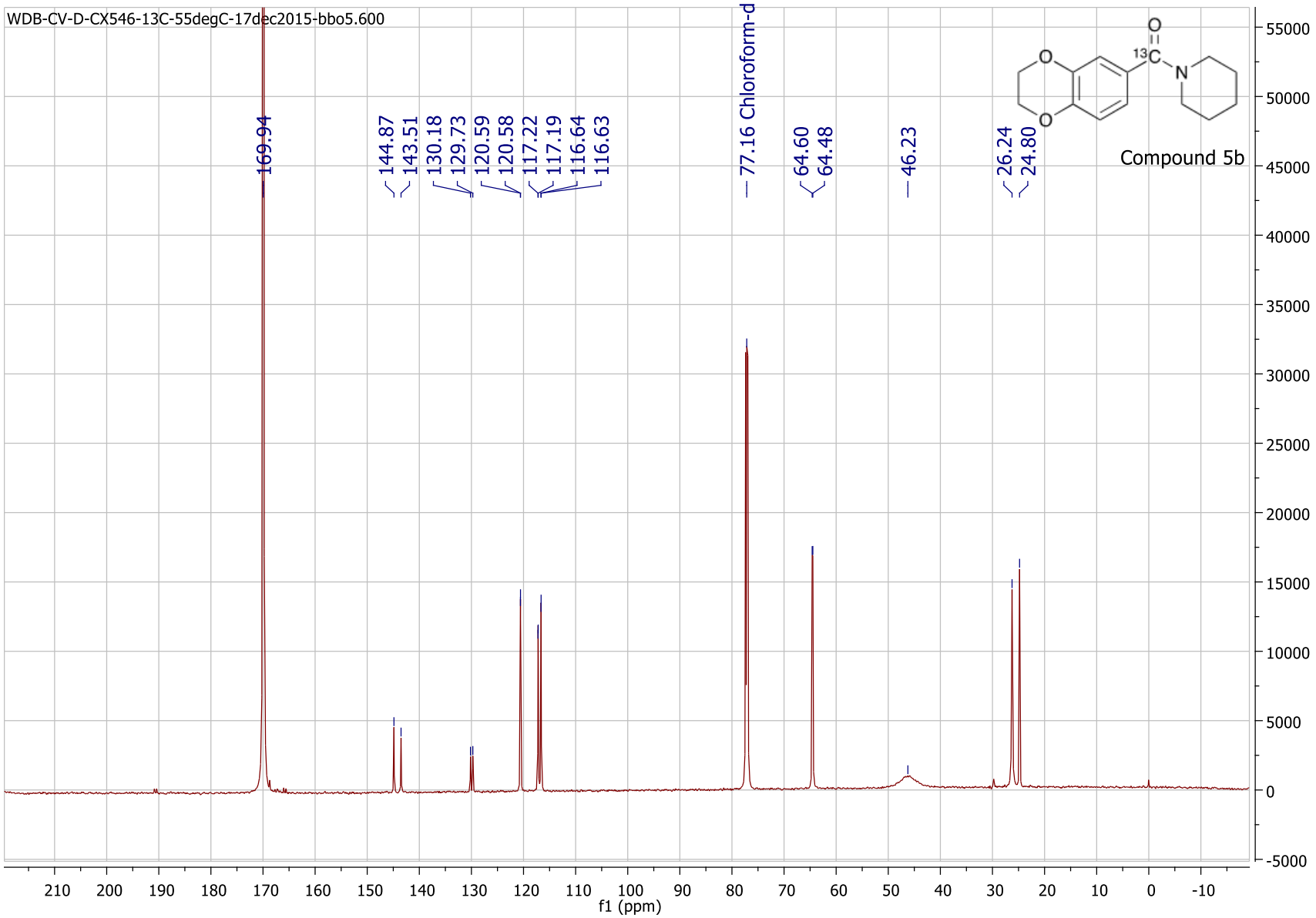

WDB-CV-D020.10a
7.26 Chloroform-d
7.22
7.06
3.56
3.31
2.32
Compound 4h
2.00
1.00
3.10
3.05
6.00
f1 (ppm)

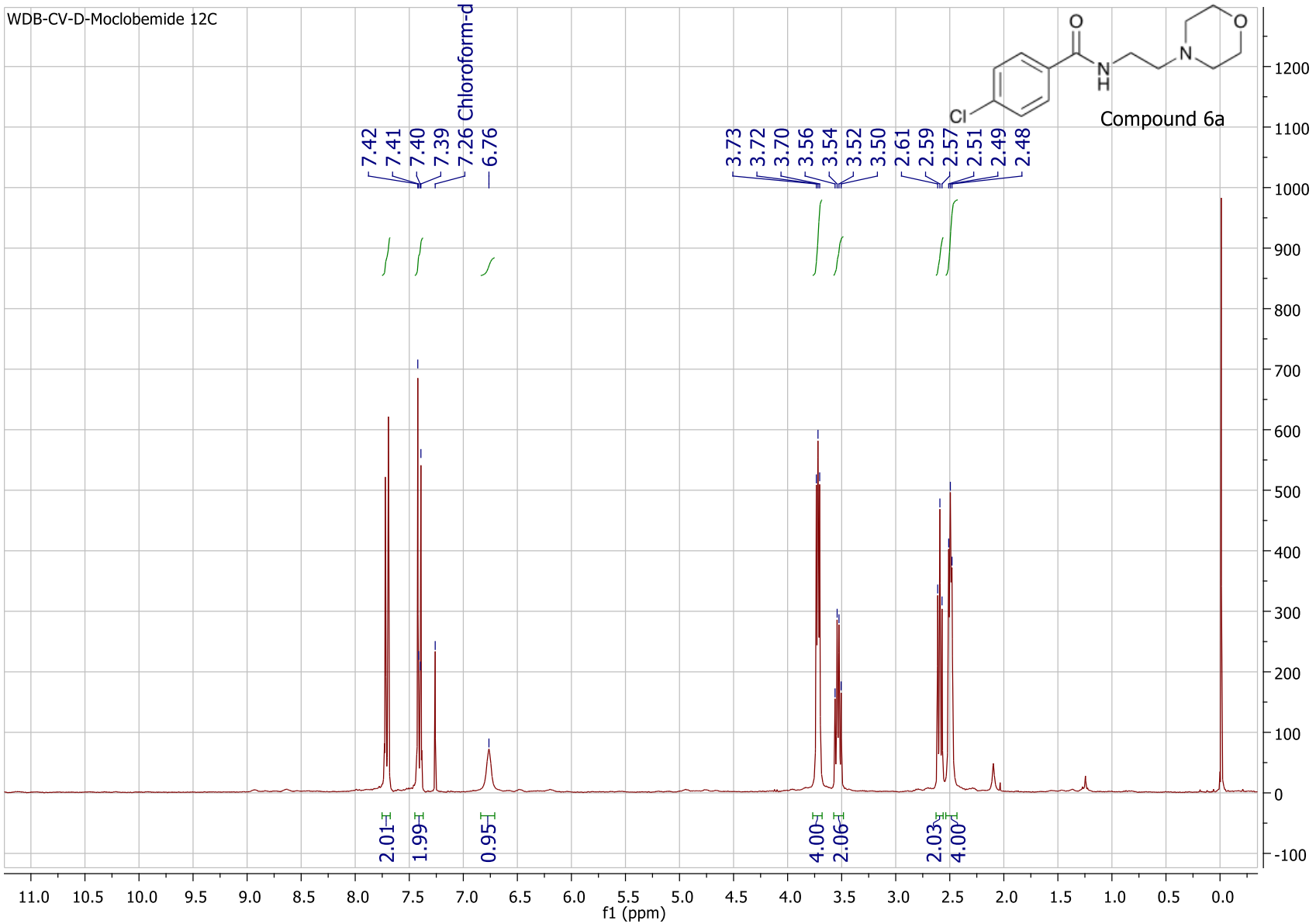

WDB-CV-D020.10a
170.53
137.66
134.24
132.16
125.64
77.16 Chloroform-d
61.04
34.10
21.29
Compound 4h
f1 (ppm)

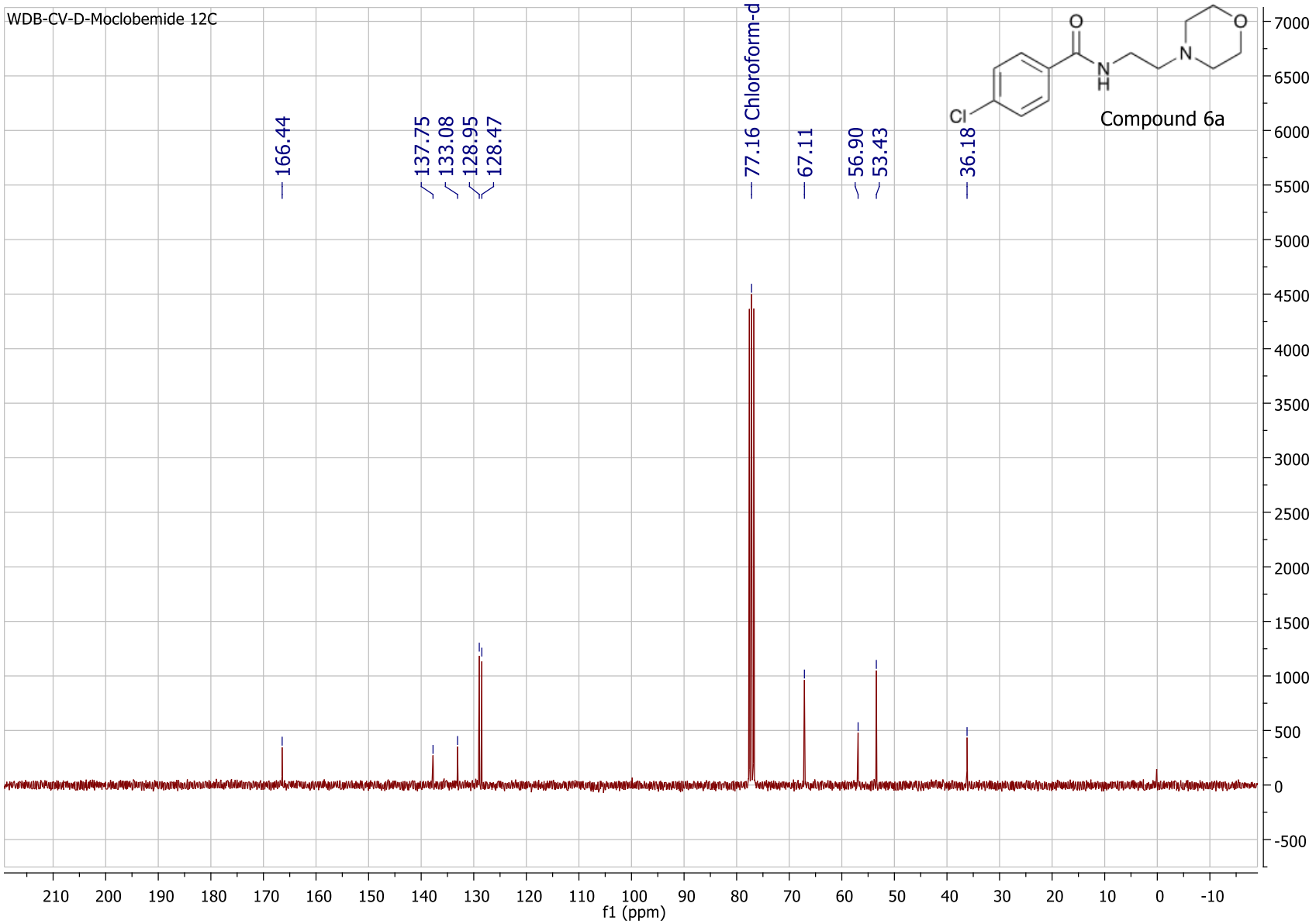

WDB-CV-D-CX546-12C-55degC-18dec2015-bbo5.600
7.26 Chloroform-d
6.93
6.89
6.89
6.88
6.87
6.85
6.84
4.25
3.52
1.68
1.67
1.66
1.57
Compound 5a
0.94
0.99
0.98
4.13
3.86
2.08
4.00
f1 (ppm)

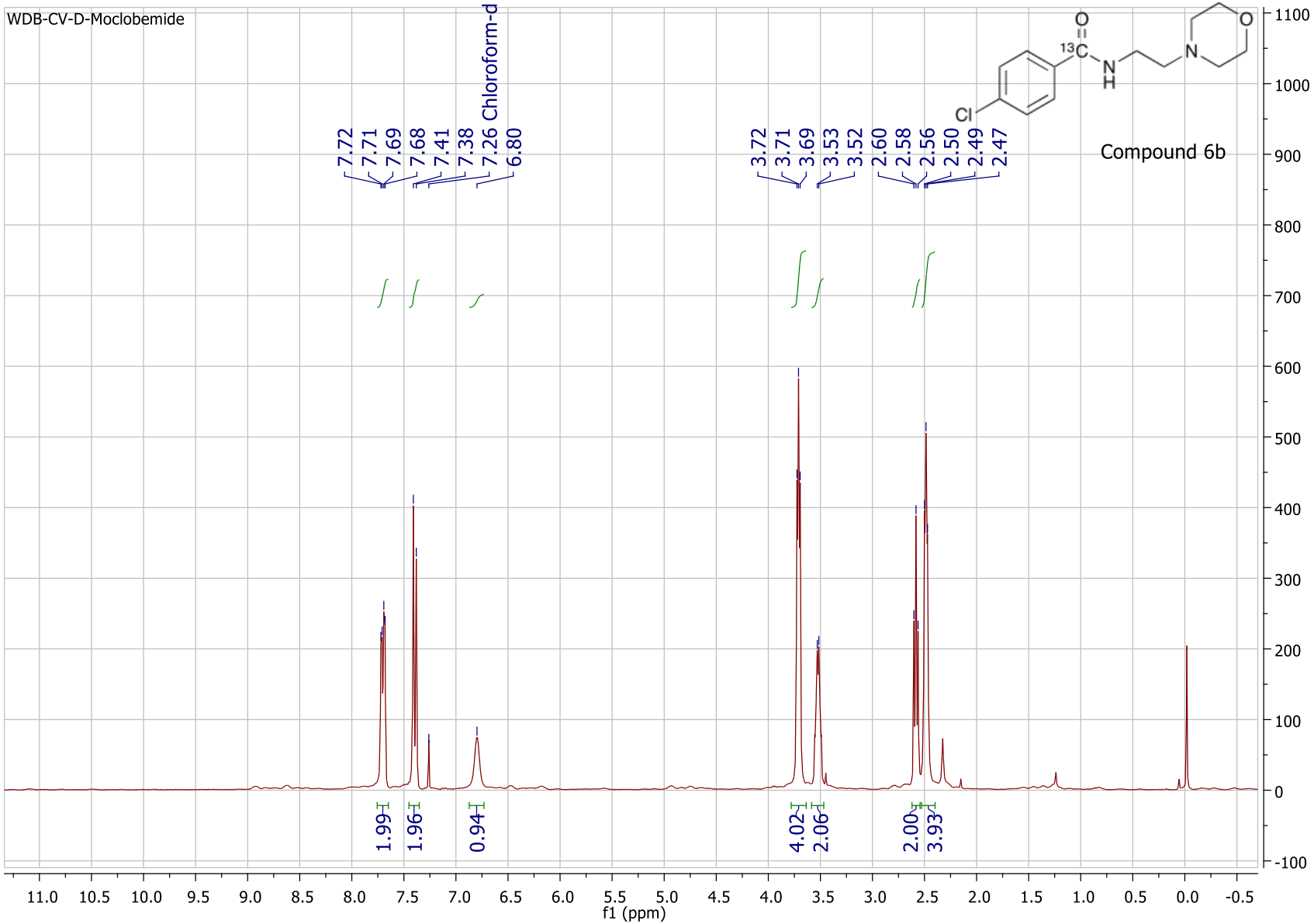

WDB-CV-D-CX546-12C-55degC-18dec2015-bbo5.600
169.99
144.91
143.56
130.03
120.65
117.26
116.70
77.16 Chloroform-d
64.65
64.52
45.98
26.29
24.85
Compound 5a
f1 (ppm)

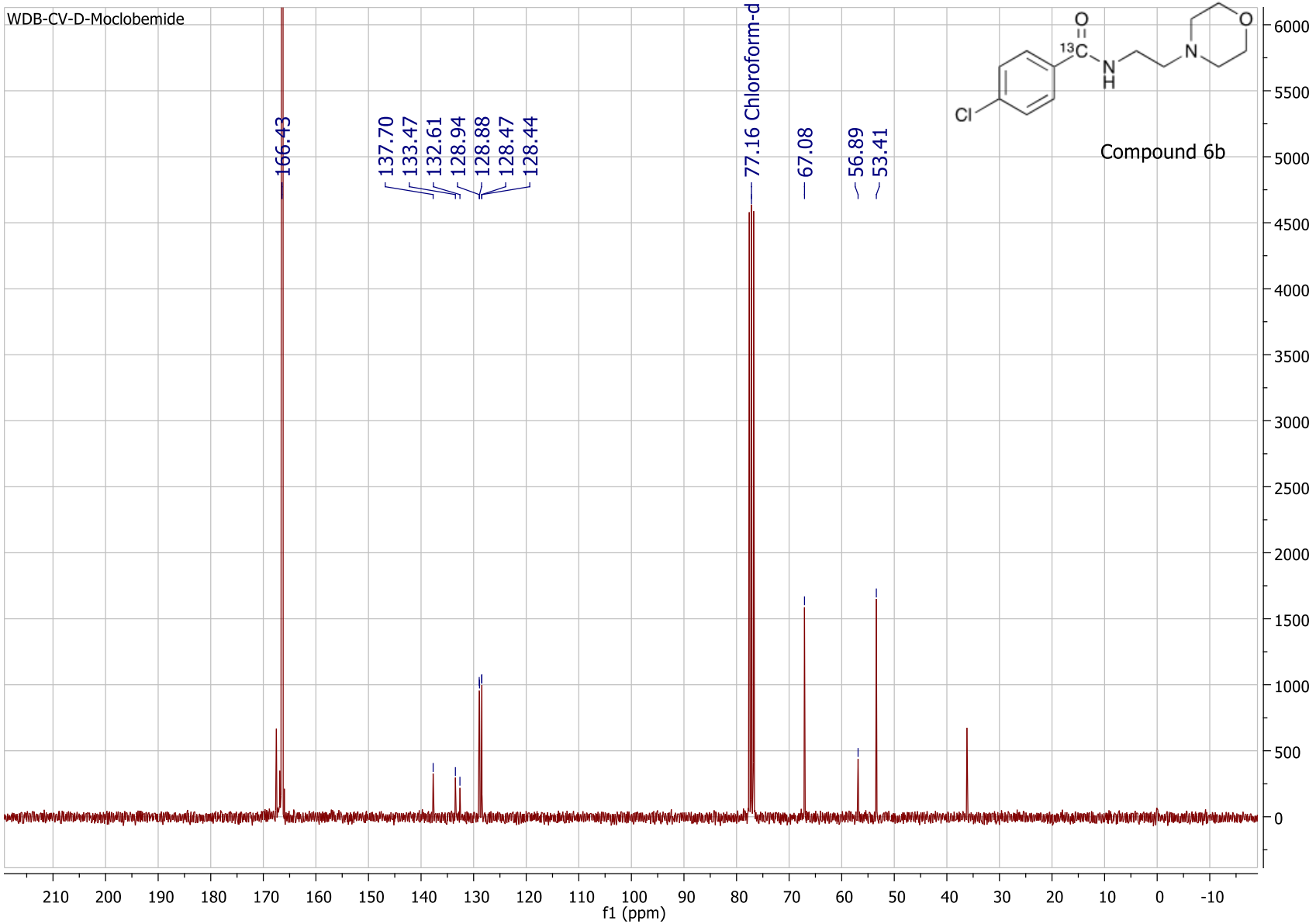

WDB-CV-D-CX546-13C-55degC-17dec2015-bbo5.600
7.26 Chloroform-d
6.92
6.92
6.91
6.86
6.86
6.84
6.82
4.23
3.50
1.65
1.65
1.56
Compound 5b
0.89
0.93
0.92
4.12
3.96
2.11
4.00
f1 (ppm)

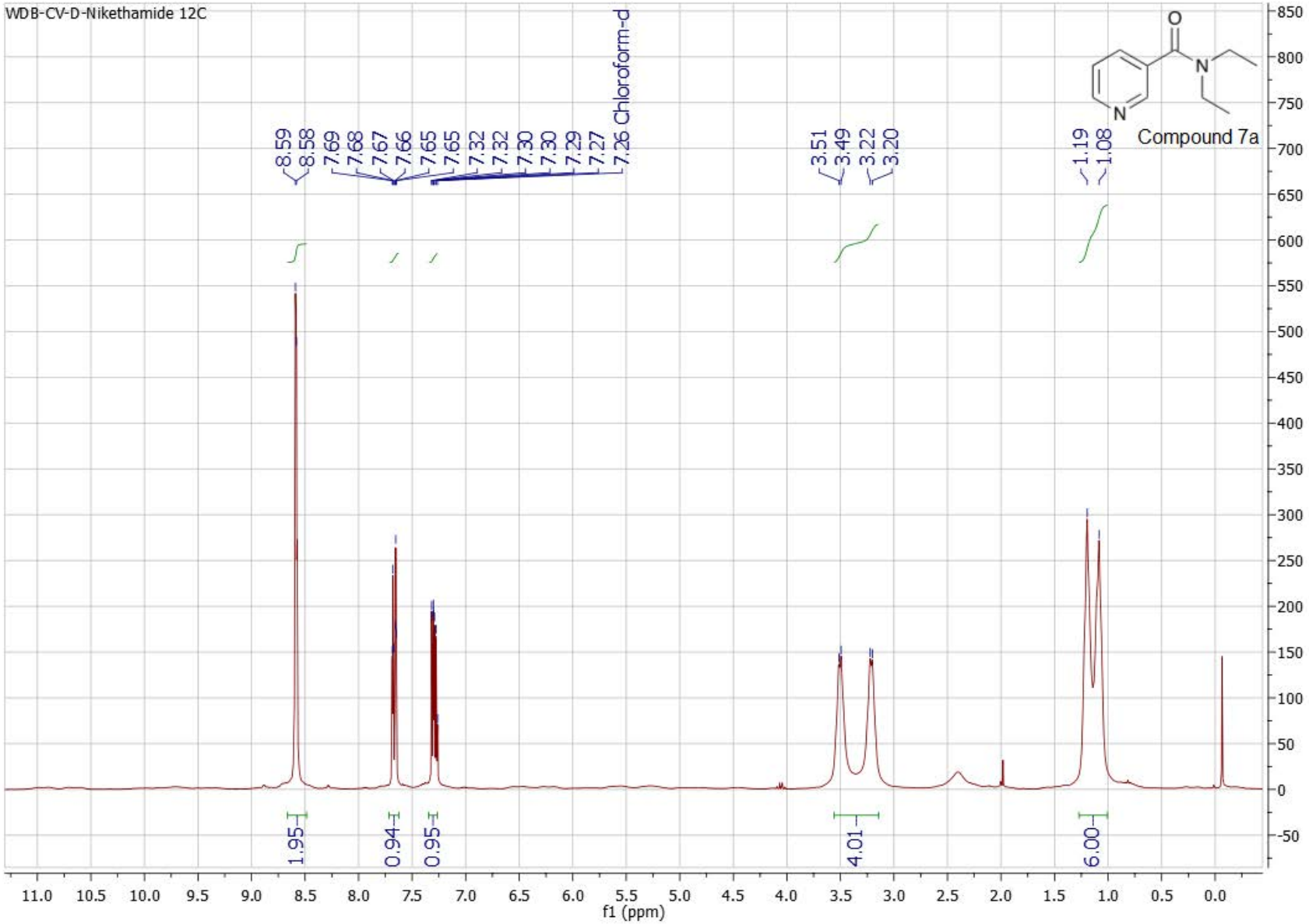

WDB-CV-D-CX546-13C-55degC-17dec2015-bbo5.600
169.94
144.87
143.51
130.18
129.73
120.59
120.58
117.22
117.19
116.64
116.63
77.16 Chloroform-d
64.60
64.48
46.23
26.24
24.80
Compound 5b
f1 (ppm)

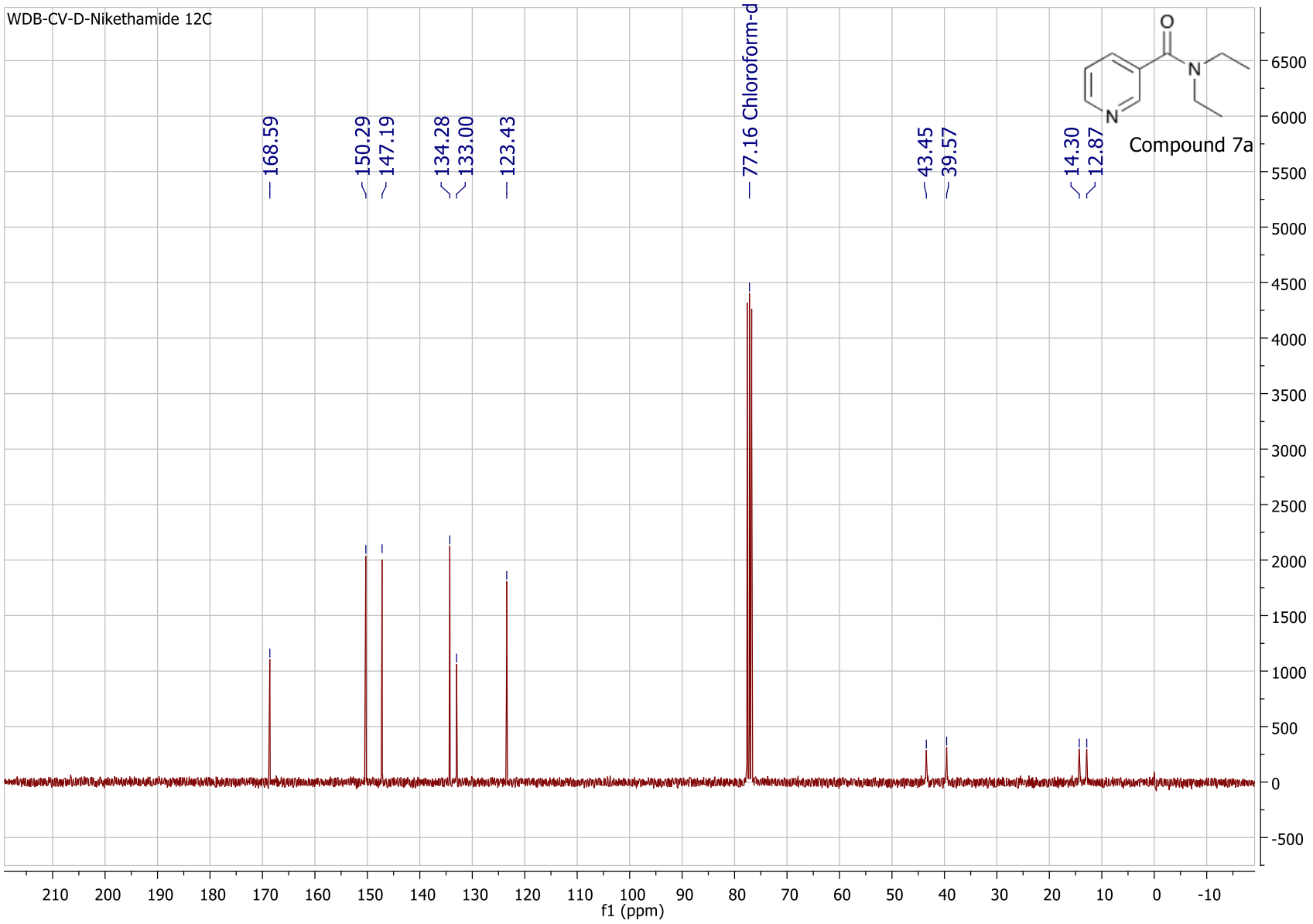

WDB-CV-D-Moclobemide 12C
Chloroform-d
7.42
7.41
7.40
7.39
7.26
6.76
3.73
3.72
3.70
3.56
3.54
3.52
3.50
2.61
2.59
2.57
2.51
2.49
2.48
Compound 6a
2.01
1.99
0.95
4.00
2.06
2.03
4.00
f1 (ppm)

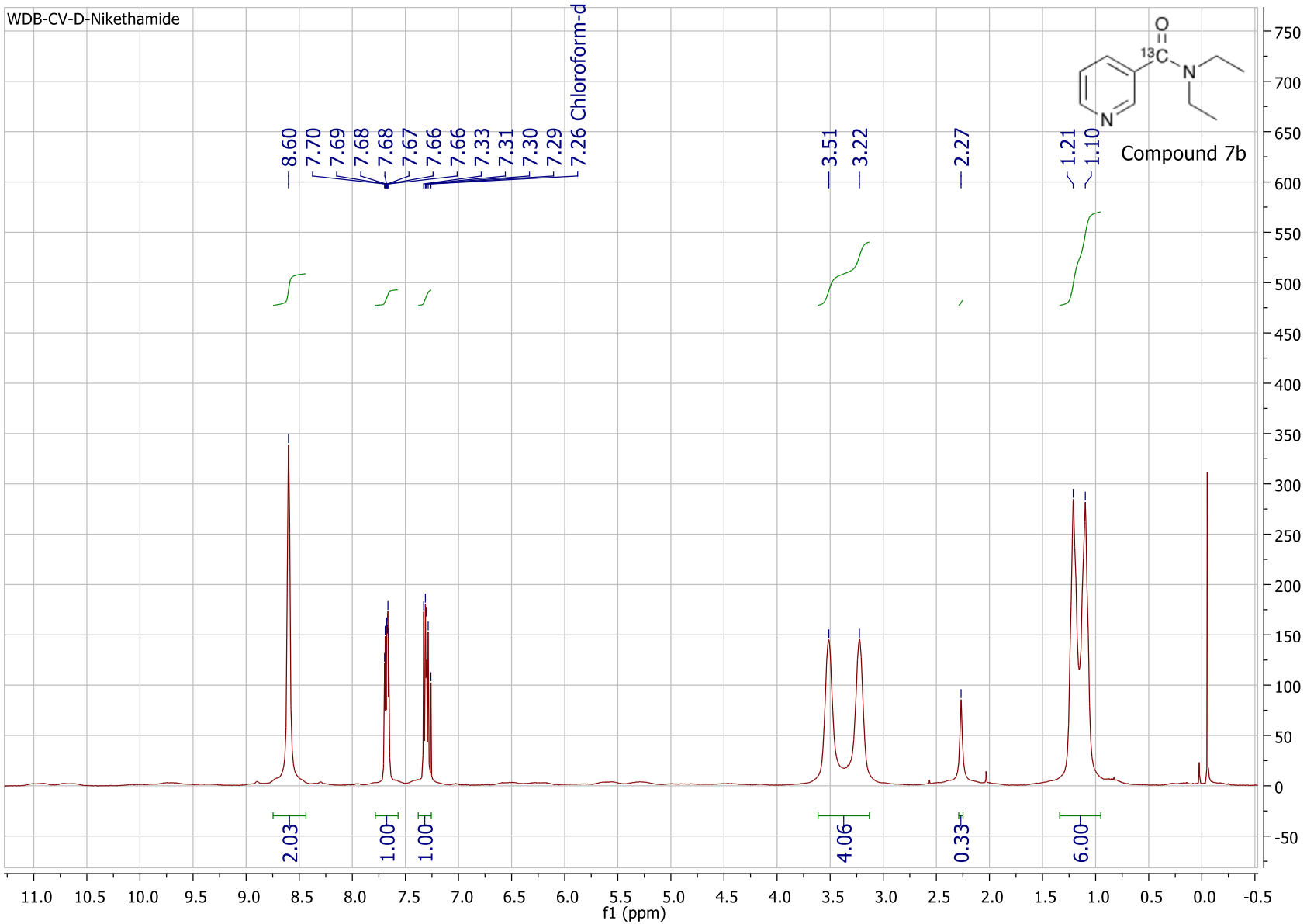

WDB-CV-D-Moclobemide 12C
166.44
137.75
133.08
128.95
128.47
77.16 Chloroform-d
67.11
56.90
53.43
36.18
Compound 6a
f1 (ppm)

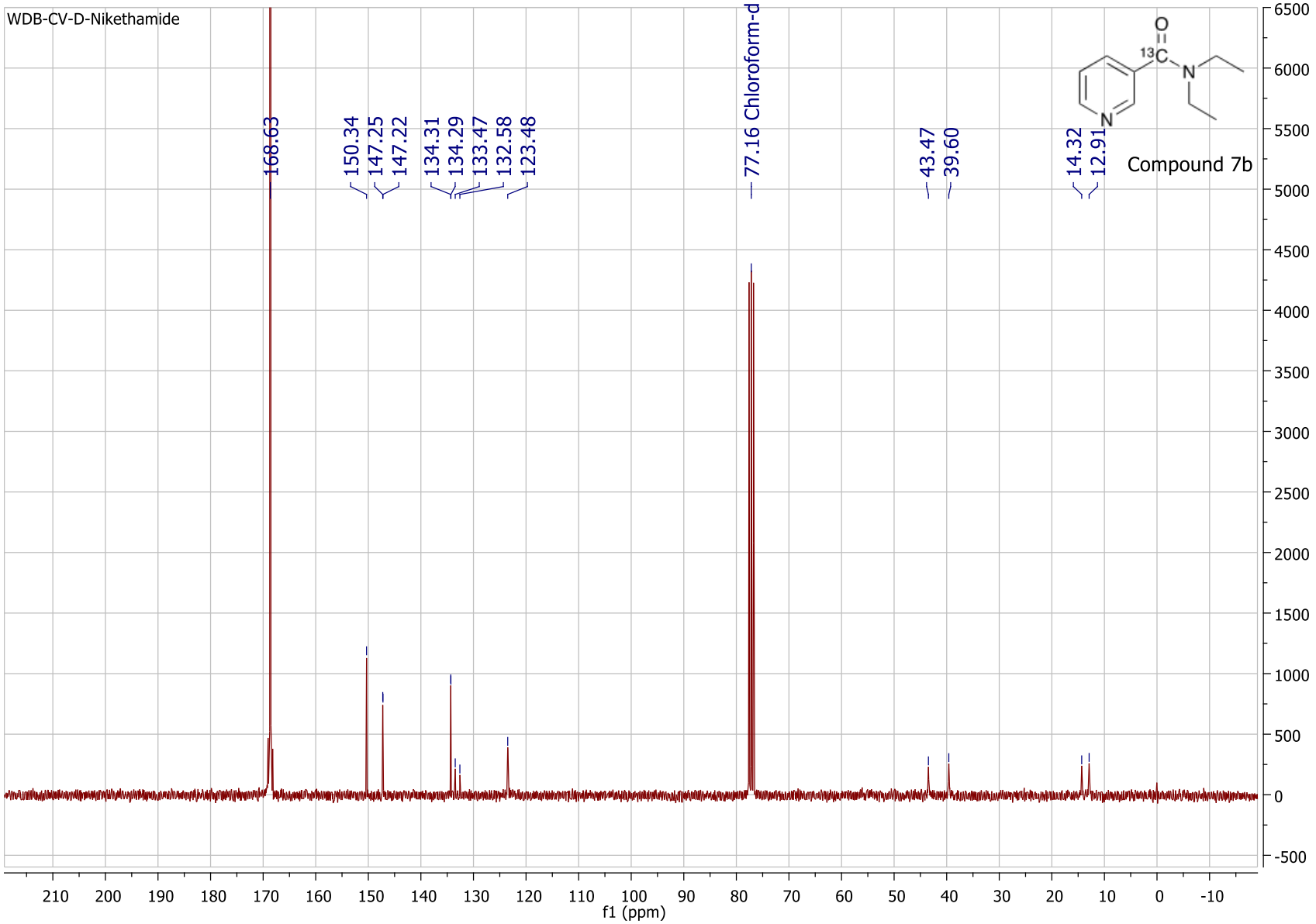

WDB-CV-D-Moclobemide
7.72
7.71
7.69
7.68
7.41
7.38
7.26 Chloroform-d
6.80
3.72
3.71
3.69
3.53
3.52
2.60
2.58
2.56
2.50
2.49
2.47
Compound 6b
1.99
1.96
0.94
4.02
2.06
2.00
3.93
f1 (ppm)


WDB-CV-D-Moclobemide
166.43
137.70
133.47
132.61
128.94
128.88
128.47
128.44
77.16 Chloroform-d
67.08
56.89
53.41
Compound 6b
f1 (ppm)


WDB-CV-D-Nikethamide 12C
Chloroform-d
8.59
8.58
7.69
7.68
7.67
7.66
7.65
7.65
7.32
7.32
7.30
7.30
7.29
7.27
7.26
3.51
3.49
3.22
3.20
1.19
1.08
Compound 7a
1.95
0.94
0.95
4.01
6.00
f1 (ppm)


WDB-CV-D-Niketamide 12C
168.59
150.29
147.19
134.28
133.00
123.43
77.16 Chloroform-d
43.45
39.57
14.30
12.87
Compound 7a
f1 (ppm)


WDB-CV-D-Nikethamide
8.60
7.70
7.69
7.68
7.68
7.67
7.66
7.66
7.33
7.31
7.30
7.29
7.26 Chloroform-d
3.51
3.22
2.27
1.21
1.10
Compound 7b
2.03
1.00
1.00
4.06
0.33
6.00
f1 (ppm)


WDB-CV-D-Nikethamide
168.63
150.34
147.25
147.22
134.31
134.29
133.47
132.58
123.48
77.16 Chloroform-d
43.47
39.60
14.32
12.91
Compound 7b
f1 (ppm)

7. References

1. X. X. Qi, L. B. Jiang, C. L. Li, R. Li and X. F. Wu, *Chem-Asian J*, 2015, **10**, 1870-1873.
2. L.-B. J. Xinxin Qi, Hao-Peng Li, Xiao-Feng Wu, *Chemistry A European Journal*, 2015, **21**, 17650-17656.
3. F. Aubke and C. Wang, *Coord. Chem. Rev.*, 1994, **137**, 483-524.
4. S. N. Gockel and K. L. Hull, *Org. Lett.*, 2015, **17**, 3236-3239.
5. S. D. Friis, R. H. Taaning, A. T. Lindhardt and T. Skrydstrup, *J. Am. Chem. Soc.*, 2011, **133**, 18114-18117.
6. C. Lescot, D. U. Nielsen, I. S. Makarov, A. T. Lindhardt, K. Daasbjerg and T. Skrydstrup, *J. Am. Chem. Soc.*, 2014, **136**, 6142-6147.
7. P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp and T. Skrydstrup, *J. Am. Chem. Soc.*, 2011, **133**, 6061-6071.
8. T. Ohshima, Y. Hayashi, K. Agura, Y. Fujii, A. Yoshiyama and K. Mashima, *Chem. Commun.*, 2012, **48**, 5434-5436.
9. T. Ueda, H. Konishi and K. Manabe, *Org. Lett.*, 2013, **15**, 5370-5373.
10. N. Ohmura, A. Nakamura, A. Hamasaki and M. Tokunaga, *Eur. J. Org. Chem.*, 2008, DOI: 10.1002/ejoc.200800771, 5042-5045.
11. N. Caldwell, C. Jamieson, I. Simpson and A. J. B. Watson, *Chem. Commun.*, 2015, **51**, 9495-9498.
12. F. Xu, J. Y. L. Chung, J. C. Moore, Z. Q. Liu, N. Yoshikawa, R. S. Hoerrner, J. Lee, M. Royzen, E. Cleator, A. G. Gibson, R. Dunn, K. M. Maloney, M. Alam, A. Goodyear, J. Lynch, N. Yasuda and P. N. Devine, *Org. Lett.*, 2013, **15**, 1342-1345.
13. T. Niu, K. H. Wang, D. F. Huang, C. M. Xu, Y. P. Su, Y. L. Hu and Y. Fu, *Synthesis*, 2014, **46**, 320-330.
14. J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder and S. L. Buchwald, *J. Org. Chem.*, 2008, **73**, 7102-7107.
15. S. T. Gadge and B. M. Bhanage, *Org. Biomol. Chem.*, 2014, **12**, 5727-5732.
16. L. Z. Zhang, J. Guo, X. Liu, H. Q. Liu, E. De Clercq, C. Pannecouque and X. Y. Liu, *Chem Biol Drug Des*, 2015, **86**, 333-343.