Supporting Information

Cyclooctadiene-Derived Cage-Divergent Synthesis of Heteroadamantanes and Alternative Polycyclic Systems

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General information and materials

The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. Melting points were measured on an automated melting point system. ^{1}H, and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 500 MHz for Protons and 126 MHz for Carbon-13) and Varian Unity Plus 400 spectrometer (at 400 MHz for protons, 101 MHz for Carbon-13). Tetramethyl silane (^{1}H, ^{13}C) was used as standard. HPLC analyses were done on the Agilent 1200 instrument. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)). Column chromatography was performed using silica gel (200-300 mesh). The high-resolution mass spectrometric analyses (HRMS) were conducted using an Agilent instrument, specifically a hybrid system comprising the 6200 Series Time-of-Flight (TOF) and the 6500 Series Quadrupole Time-of-Flight (Q-TOF). This system was operated with software version B.08.00 (B8058.0). Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine, their results were found to be in good agreement (±0.4%) with the calculated values.

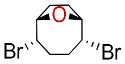
All crystallographic measurements for this publication were performed at 173K on a Bruker Smart Apex II diffractometer operating in the ϕ and ω scans mode. The intensity data were collected using Mo-K$_{\alpha}$ radiation (λ = 0.71078 Å). The crystals were mounted on a glass fibre and mounted on the diffractometer. The structures were solved by direct methods and refined by the full-matrix least-squares technique using the Bruker SHELXTL program package [1].

Non-hydrogen atoms were refined anisotropically. All CH hydrogen atoms were placed at calculated positions and refined as 'riding' model, with $U_{iso}(H)=1.2U_{eq}(CH_2)$ and $U_{iso}(H)=1.5U_{eq}(CH_3)$.

The NH hydrogen atoms in structures **7*HBr** and **11** were found in difference Fourier syntheses and refined isotropically. The absolute configuration of 8 is not determined because no heavy atoms are present in the molecule. The X-ray crystallographic data for all compounds are listed in Table S3.

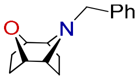
Crystallographic data for the structures in this paper have been deposited at Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 2454936-2454943. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Experimental procedures



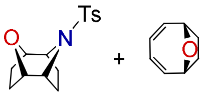
(1R,2R,5S,6S)-2,5-Dibromo-9-oxabicyclo[4.2.1]nonane (3).

Cycloocta-1,5-diene **1** (120 g, 1.109 mol) was dissolved in 2 L of methanol in a 4-L reactor under constant stirring. To this solution, a catalytic amount of concentrated sulfuric acid (5.35 g, 0.0546 mol) was added. The solution was cooled to 0–5 °C using an ice–salt bath, and at this temperature, N-bromosuccinimide (388.72 g, 2.184 mol) was added in portions of 10–15 g. The ice bath was then removed, and the mixture was allowed to warm to room temperature. After 14 hours at room temperature, the reaction mixture was evaporated under reduced pressure and dissolved in 2 L of hexane, to which 800 mL of a 10% aqueous $Na_2S_2O_3$ solution was added. Following extraction, the aqueous and organic layers were separated; the organic phase was further further extracted with 500 mL of saturated $NaHCO_3$ solution and washed with brine. The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was dissolved in 600 mL of ethanol with heating until complete dissolution. Upon cooling to 0 °C, a precipitate formed, which was filtered. The precipitate was then re-dissolved in 600 mL of hexane with heating, and after cooling to 0 °C, a precipitate was again obtained, filtered, washed with 100 mL of hexane, and dried. The mother liquor was evaporated under reduced pressure and recrystallized from hexane. Product **3** was obtained as white crystals (230 g, 73%).



(1R,2S,5R,6S)-10-benzyl-9-oxa-10-azatricyclo[4.2.1.12,5]decane (4).

The compound **3** (1 g, 3.52 mmol, 1 eq.) was transferred to a 50-mL reactor equipped with a stirring bar and dissolved in 20 mL of DMF. After that, benzyl amine (1.89 g, 1.92 mL, 17.6 mmol, 5 eq.) was added, and the reaction was left stirring at 100 °C overnight. The next day, the reaction mixture was allowed to cool down to room temperature, and an aliquot was taken and analyzed with LC/MS, only traces of product were found in the reaction mixture.

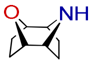


(1R,2S,5R,6S)-10-tosyl-9-oxa-10-azatricyclo[4.2.1.12,5]decane + (1R,6S)-9-oxabicyclo[4.2.1]nona-2,4-diene (5 + 6).

The compound **3** (1 g, 3.52 mmol, 1 eq.) was transferred to a 50-mL reactor equipped with a stirring bar and dissolved in 20 mL of DMF (a separate trial in THF was also attempted). After that, NaH (60% suspension in mineral oil, 0.42 g, 10.56 mmol, 3 eq.) was added, followed by 4-toluenesulfonamide (0.72 g, 4.22 mmol, 1.2 eq.) and the reaction was left stirring at 100 °C (60 °C for THF and 60 °C and 80°C for DMF were also attempted) overnight. The next day, the reaction mixture was allowed to cool down to room temperature, and an aliquot was taken and analyzed with LC/MS, only traces of product were found in the reaction mixture.

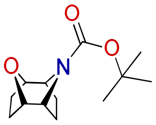
Table S1. Screening the conditions for the transformation **3** => **5** + **6**. None of the conditions yielded the product.

#	Reagents	Solvent	t, °C	Time, h
1	3 eq. NaH, 1.2 eq. $TsNH_2$	DMF	100	18
2	3 eq. NaH, 1.2 eq. $TsNH_2$	DMF	80	18
3	3 eq. NaH, 1.2 eq. $TsNH_2$	DMF	60	18
4	3 eq. NaH, 1.2 eq. $TsNH_2$	THF	60	18



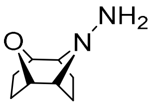
(1R,2S,5R,6S)-9-oxa-10-azatricyclo[4.2.1.$1^{2,5}$]decane (7) as a hydrobromide.

In a 2-L autoclave, 600 mL of THF, 300 mL of a 20% NH_3 solution in methanol (3.52 mol), and compound **3** (100 g, 0.352 mol) were charged. The autoclave was sealed and placed in a heating jacket. The mixture was heated to 160 °C (with pressure reaching 15 atm above 110 °C due to ammonia expansion) and stirred for 8 hours. After cooling, the autoclave was opened and the solvents evaporated under reduced pressure. The residue was triturated in 500 mL of acetonitrile, filtered, and washed with 100 mL of acetonitrile. The precipitate was then transferred to a 1-L flask, treated with 300 mL of methanol and 100 mL of triethylamine, and evaporated under reduced pressure. Subsequently, 500 mL of acetonitrile was added, the solution was heated to boiling and filtered hot. The precipitate was washed with 200 mL of acetonitrile and dried. Product **7** was obtained as a light brown hydrobromide powder (27.88 g, 36%).



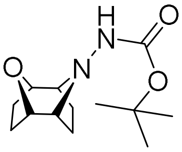
tert-butyl (1R,2S,5R,6S)-9-oxa-10-azatricyclo[4.2.1.1^{2,5}]decane-10-carboxylate (8).

The compound **7** (1 g, 7.184 mmol, 1 eq.) was transferred to a 100-mL reactor equipped with a stirring bar and was suspended in 30 mL of DCM. Triethylamine (2.91 g, 4.00 mL, 28.74 mmol, 4 eq.) was added, and the solution was cooled to 5–10 °C. At this temperature, a solution of Boc$_2$O (1.57 g, 7.184 mmol) in 5 mL of DCM was added dropwise. After stirring for 18 hours at room temperature, the reaction mixture was transferred to a separatory funnel, and 30 mL of a 10% NaHSO$_4$ solution was added. The organic layer was separated, washed with water (30 mL), brine (30 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure to obtain compound **8** as white crystals (1.51 g, 88% yield).



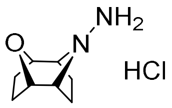
(1R,2S,5R,6S)-9-oxa-10-azatricyclo[4.2.1.1^{2}, ^{5}]decane-10-amine (9).

In a 1-L autoclave, 350 mL of THF, 150 mL of methanol, a 60% hydrazine hydrate solution (58.73 g, 0.704 mol), and compound **3** (40 g, 0.1408 mol) were charged. The autoclave was sealed and heated to 120 °C, where the mixture was stirred for 8 hours. After cooling and evaporation of the solvents under reduced pressure, the crude product was processed further. Product **9** (base form) was characterized by ^{1}H NMR (400 MHz, DMSO): δ 4.47 (m, 2H), 3.24 (m, 2H), 1.71 (m, 2H), 1.44 (m, 6H); GCMS: [M$^+$] = 154.



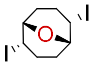
tert-Butyl ((1R,2S,5R,6S)-9-oxa-10-azatricyclo[4.2.1.1^{2}, ^{5}]decane-10-yl)carbamate (11).

The unpurified amine **9** was dissolved in 200 mL of methanol, and triethylamine was added. The mixture was evaporated under reduced pressure to remove residual hydrazine. The residue was transferred to a 1-L reactor and diluted with 500 mL of CH$_2$Cl$_2$. Triethylamine (17.07 g, 0.169 mol) was added, and the solution was cooled to 5–10 °C. At this temperature, a solution of Boc$_2$O (36.87 g, 0.169 mol) in 50 mL of CH$_2$Cl$_2$ was added dropwise. After stirring for 14 hours at room temperature, the reaction mixture was transferred to a separatory funnel and 300 mL of a 10% NaHSO$_4$ solution was added. The organic layer was separated, washed with 100 mL of brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was dissolved in 100 mL of MTBE, triturated, cooled to 5 °C, filtered, washed with 20 mL of MTBE, and dried. Product **11** was obtained as white crystals (13.96 g, 39% over two steps).



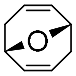
(1R,2S,5R,6S)-9-oxa-10-azatricyclo[4.2.1.1^{2,5}]decane-10-amine (9) as Hydrochloride.

In a 250 mL flask, compound **11** (10 g, 39.37 mmol) was dissolved in 100 mL of dioxane and cooled to 12 °C. Then, 100 mL of a 2 M HCl solution in dioxane was added dropwise at this temperature. After 14 hours at room temperature, the mixture was filtered and the precipitate washed twice with 50 mL of MTBE. The product, obtained as hydrochloride salt, weighed 6.76 g (90%).



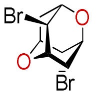
(1S,2S,5S,6S)-2,6-Diiodo-9-oxabicyclo[3.3.1]nonane (13).

Cycloocta-1,5-diene **1** (170 g, 1.571 mol) was dissolved in 2.5 L of methanol in a 6-L reactor, then, under constant stirring, catalytic amount of concentrated sulfuric acid (7.71 g, 0.079 mol) was added. The solution was cooled to 0–5 °C using an ice–water bath, and *N*-iodosuccinimide (714.09 g, 3.174 mol) was added in portions of 50 g, over 0.5 h, while maintaining the temperature. The ice bath was then removed, and the mixture was warmed up to room temperature. After 14 hours at room temperature, the precipitate was filtered, washed with 0.5 L of methanol and dried on air to obtain product **13**, as white crystals (500.1 g, 84% yield, 98% purity (GC/MS)). **Note:** the 2% impurity of the regioisomeric **(*1R,2R,5S,6S*)-2,5-diiodo-9-oxabicyclo[4.2.1]nonane** (compound **12** in the manuscript) was detected via GC/MS analysis, and this 98:2 mixture of compounds **13:12** was taken for further operations without additional purification.



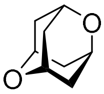
(1S,5S)-9-oxabicyclo[3.3.1]non-3,7-diene (14).

In a round-bottom flask, rac-(1R,2R,5R,6R)-2,6-diiodo-9-oxabicyclo[3.3.1]nonane **13** (250 g, 0.661 mol) was dissolved in toluene (1.25 L) and DBU (692.2 ml, 4.63 mol) was added. The solution was refluxed vigorously at 130 °C for 16 hours. After cooling to room temperature, 2 L of water was added, and the mixture was extracted with MTBE (2 L). The organic layer was washed with 10% $NaHSO_4$ (2 × 1.5 L), water (1 L), and brine (0.5 L), dried over Na_2SO_4, and evaporated to obtain the product **14**, as yellowish liquid (55 g, 68%).



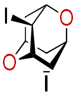
4,8-Dibromo-2,6-dioxaadamantane (17).

rac-(1R,5R)-9-oxabicyclo[3.3.1]nona-2,6-diene **14** (12 g, 0.098 mol) was dissolved in 144 mL of methanol in a round-bottom flask, then, under constant stirring, catalytic amount of concentrated sulfuric acid (0.48 g, 4.9 mmol) was added. The solution was cooled to 0–5 °C using an ice–water bath, and N-bromosuccinimide (34.96 g, 0.196 mol) was added in portions of 5 g, over 0.5 h, while maintaining the temperature. The ice bath was then removed, and the mixture was warmed up to room temperature. After 14 hours at room temperature, the mixture was cooled with ice-water bath and the precipitate was filtered, washed with 50 mL of methanol and dried on air to obtain product **17**, as white crystals (25 g, 85%).



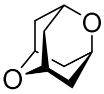
2,6-Dioxaadamantane via reduction of 17 with $LiAlH_4$ (literature approach)[2] (16).

In a round-bottom flask, 4,8-dibromo-2,6-dioxadamantane (34 g, 0.114 mol) was dissolved in THF (500 mL), and $LiAlH_4$ (17.33 g, 0.456 mol) was carefully added portionwise. The reaction mixture was refluxed at 75°C for 16 hours and then cooled to 0°C. Excess lithium aluminum hydride was cautiously quenched by sequential addition of 4 equiv. of water in THF followed by 4 equiv. of aqueous sodium hydroxide solution, with cooling in an ice bath over 1 hour. The resulting amorphous precipitate was filtered through sodium sulfate and washed with EtOAc (2 × 200 mL). The filtrate was concentrated to yield 11.2 g (70%) of **16** as white crystals.



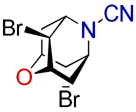
4,8-Diiodo-2,6-dioxaadamantane (15).

rac-(1R,5R)-9-oxabicyclo[3.3.1]nona-2,6-diene **14** (110 g, 0.9 mol) was dissolved in 1.5 L of methanol in a 4-L reactor, then, under constant stirring, catalytic amount of concentrated sulfuric acid (4.42 g, 0.045 mol) was added. The solution was cooled to 0–5 °C using an ice–water bath, and N-iodosuccinimide (405.07 g, 1.8 mol) was added in portions of 50 g, over 0.5 h, while maintaining the temperature. The ice bath was then removed, and the mixture was warmed up to room temperature. After 14 hours at room temperature, the precipitate was filtered, washed with 1 L of methanol and dried on air to obtain product **15**, as white crystals (295 g, 84%).



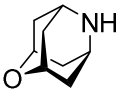
2,6-Dioxaadamantane (16).

4,8-diiodo-2,6-dioxaadamantane **15** (150 g, 0.383 mol) was suspended in 1.8 L of methanol in a 4-L round-bottom flask, then TEA (112 ml, 0.803 mol) and 10% Pd/C (40 g) were added. The mixture was degassed 5 times and stirred for 3 d at room temperature under 1 atm of hydrogen. Then Pd/C was filtered on SiO_2, filtrate was evaporated, quenched with MTBE, dried with Na_2SO_4, filtered on SiO_2, filtrate evaporated to obtain product **16**, as white crystals (47 g, 88%).



(1R,3R,4S,5R,7R,8S)-4,8-dibromo-2-oxa-6-azaadamantane-6-carbonitrile (18).

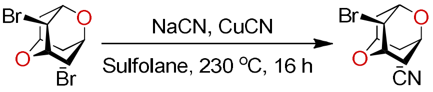
NBS (87.43 g, 0.49 mol, 2 eq.) was added portion-wise to a stirred solution of (1R,5R)-9-oxabicyclo[3.3.1]nona-2,6-diene (**14**) (30 g, 0.246 mol, 1eq.) and cyanamide (10.84 g, 0.258 mol, 1.05 eq.) in DCM (800 mL) at 5°C, after the addition was complete the reaction was left stirring overnight, allowing it to warm up to room temperature. The next day, the solvent was evaporated, and the residue was diluted with water (400 mL) and extracted with EtOAc (2 × 500 mL). The organic layers were combined and washed with 5% sodium thiosulfate solution (400 mL), saturated $NaHCO_3$ solution (300 mL), water (200 mL), and brine (100 mL), dried under Na_2SO_4, and concentrated in vacuo. The resulting mixture was triturated with MeOH (120 mL) to form a precipitate, which was washed with MeOH (40 mL) and dried to give the compound **18** (42.5 g, 54% yield) as a white powder.



(1r,3r,5r,7r)-2-oxa-6-azaadamantane (19) as hydrochloride.

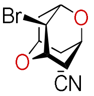
A solution of (1*R*,3*R*,4*S*,5*R*,7*R*,8*S*)-4,8-dibromo-2-oxa-6-azaadamantane-6-carbonitrile (**18**) (39.25 g, 0.12 mol, 1eq.) in THF (200 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (18.51 g, 0.49 mol, 4 eq.) in THF (400 mL) at 0-5°C. After the addition was complete, the reaction remained stirring overnight, allowing it to warm to room temperature. The next day, the reaction mixture was cooled to 0-5°C, and water (18 mL), then 10% solution of NaOH in water (36 mL), and then water (54 mL) again were added dropwise while keeping the temperature below 15°C. The resulting mixture was filtered, and the precipitate was washed with EtOAc (3 × 200 ml), dried under Na_2SO_4, and concentrated in vacuo. The residue was then diluted with MeOH (200 mL), followed by the addition of 4M HCl in dioxane (30.5 mL, 3 eq.). The resulting mixture was concentrated in vacuo, and MeCN was added to form a precipitate, which was filtered, washed with MTBE (2 × 100 mL), and dried to give the HCl salt of compound **19** (15.5 g, 88% yield) as a white powder.

Note: *The compounds* ***2*** *and* ***12*** *were never purified, so we have no spectral data for them, but the methods we used for making the compounds are based on the literature*[3] *(Reference 16 in the manuscript). Compounds* ***2*** *and* ***12*** *are characterized there, too.*



17 **1S**, 36% (GC/MS)

SchemeS1. Attempts to derivatize/dissymmetrize 2,6-dioxadamantane.



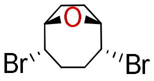
(1R,3R,4R,5R,7R,8R)-8-bromo-2,6-dioxaadamantane-4-carbonitrile (1S).

4,8-dibromo-2,6-dioxaadamantane **17** (0.3 g, 1.01 mmol), NaCN (0.25 g, 5.05 mmol) and CuCN (0.45 g, 5.05 mmol) were heated in dry sulfolane (3 ml) at 230 °C overnight and then evaporated in vacuo to obtain inseparable mixture containing product **1S** (36% according to GC/MS analysis).

Table S2. Screening the conditions for halogen substitution in 2,6-bis-oxaadamantane.

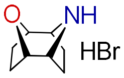
#	**Reagents**	**Solvent**	**t, °C**	**Time, h**	**Results**
1	5 eq. NaN_3	DMF	120	16	Starting material
2	5 eq. NaN_3	DMF	155	24	Starting material
3	5 eq. NaCN	DMF	155	24	Starting material
4	5 eq. CuCN	Pyridine	90	16	Starting material
5	5 eq. CuCN	DMF	155	24	Starting material
6	5 eq. NaCN; 0.2 eq. NaI	DMSO	180	16	Starting material
7	5 eq. NaCN; 0.2 eq. NaI	MeOH	120	16	Starting material
8	5 eq. NaCN; 0.2 eq. NaI	DMF	180	16	Starting material
9	3 eq. $TMSN_3$; 3 eq. $SnCl_4$	$CHCl_3$	65	16	Starting material
10	3 eq. TMSCN; 3 eq. $SnCl_4$	DCE	90	16	Starting material
11	3 eq $Zn(CN)_2$; 0.1 eq. $Pd(PPh_3)_4$	DMF	120	24	Starting material
12	3 eq. $Zn(CN)_2$; 0.1 eq. $Pd(PPh_3)_4$	DMF	180	24	Starting material
13	80 atm. CO, 3 eq. TEA; 0.1 eq. $PdCl_2(dppf)_2$	MeOH	80	16	Complex mixture, no desired product
14	80 atm. CO, 5 eq. $NaBH_4$; 0.2 eq AIBN	MeCN	80	16	Complex mixture, no desired product
15	5% $Ni(acac)_2$, 5% XantPhos; 0.4 eq Zn, 2 eq. DMAP; 0.8 eq. $Zn(CN)_2$; 0.5 eq. $n\text{-}Bu_4NCl$	MeCN	120	8	Starting material
16	4 eq. Zn 0.1 eq. DBE, 5% TMSCl	THF	65	3	Starting material
17	5 eq. CuCN, 5 eq. NaCN	Sulfolane	230	20	36% 1S + 11% starting material (by GCMS)

Analytical data



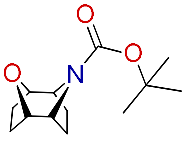
(1R,2R,5S,6S)-2,5-Dibromo-9-oxabicyclo[4.2.1]nonane (3).

White crystalline powder. M.p. 51°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.63 – 4.61 (m, 2H), 4.34 – 4.31 (m, 2H), 2.45 – 2.37 (m, 2H), 2.26 – 2.17 (m, 4H), 2.11 – 1.95 (m, 2H). ^{13}C NMR (151 MHz, Chloroform-d) δ 82.2, 53.7, 32.7, 28.3. GSMS, 70eV, m/z (rel. int.): 284 [M]$^+$ (5); 205 (28); 203 (28); 123 (29); 106 (11); 105 (28); 97 (30); 95 (50); 93 (12); 91 (10); 81 (19); 79 (93); 77 (29); 69 (44); 68 (14); 67 (68); 66 (12); 65 (23); 55 (34); 54 (12); 53 (44); 49 (16); 41 (100); 40 (14); 39 (99). HRMS (ESI): not informative. Anal. calcd. for $C_8H_{12}Br_2O$: C, 33.83; H, 4.26; Br, 56.27. Found: C, 33.53; H, 4.18; Br, 56.07.



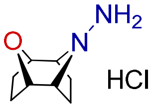
(1R,2S,5R,6S)-9-oxa-10-azatricyclo[4.2.1.1^{2,5}]decane hydrobromide (7*HBr).

Beige powder. M.p. 203-281°C (with decomposition). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.35 (br.s, 2H), 4.58 – 4.56 (m, 2H), 4.09 – 4.07 (m, 2H), 1.92 – 1.89 (m, 4H), 1.67 – 1.55 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 72.8, 56.0, 23.8, 21.9. LCMS, positive mode, m/z: 140.2 [M+H]$^+$ (compound as hydrobromide salt). HRMS (ESI): calcd. for $C_8H_{14}NO$ [M+H]$^+$: 140.1075; found: 140.1067.



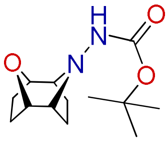
tert-butyl (1R,2S,5R,6S)-9-oxa-10-azatricyclo[4.2.1.1^{2,5}]decane-10-carboxylate (8).

White crystals. ^{1}H NMR (400 MHz, Chloroform-d): δ 4.51 – 4.42 (m, 2H), 4.32 – 4.15 (m, 2H), 1.85 – 1.79 (m, 2H), 1.72 – 1.59 (m, 6H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, APT, Chloroform-d) δ: 79.7, 75.5, 74.7, 58.2, 57.7, 28.7, 25.3, 25.0, 24.4. EIMS, 70eV, m/z (rel. int.): 239 [M]$^+$ (2); 120 (10); 96 (78); 94 (25); 82 (21); 70 (37); 68 (28); 67 (29); 57 (100); 56 (31); 55 (18); 44 (36); 41 (88); 39 (41). HRMS (ESI): calcd. for $C_{13}H_{22}NO_3$ [M+H]$^+$: 240.1600; found: 240.1590.



(1R,2S,5R,6S)-9-oxa-10-azatricyclo[4.2.1.1^{2},^{5}]decane-10-amine hydrochloride (9*HCl).

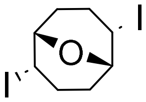
^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (br.s, 1H), 5.10 (br.s, 2H), 4.68 – 4.64 (m, 2H), 3.96 – 3.96 (m, 2H), 2.04 – 1.78 (m, 6H), 1.61 – 1.58 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 97.1, 74.0, 65.6, 24.6, 20.0. HRMS (ESI): calcd. for $C_8H_{15}N_2O$ [M+H]$^+$: 155.1184; found: 155.1176.



tert-Butyl ((1R,2S,5R,6S)-9-oxa-10-azatricyclo[4.2.1.1^{2},^{5}]decane-10-yl)carbamate (11).

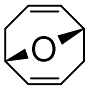
White crystals. ^{1}H NMR (400 MHz, Chloroform-d): δ 7.59 (s, 1H), 4.57 – 4.54 (m, 2H), 3.55 – 3.52 (m, 2H), 1.81 – 1.76 (m, 4H), 1.72 – 1.64 (m, 4H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, APT, Chloroform-d) δ 79.6, 76.2, 61.1, 28.5, 25.4, 23.4. EIMS, 70eV, m/z (rel. int.): 254 [M]$^+$ (1.4); 155

(26); 111 (12); 95 (10); 78 (10); 67 (19); 57 (48); 56 (44); 54 (24); 52 (11); 44 (56); 42 (10); 41 (100); 40 (15); 39 (55). HRMS (ESI): calcd. for $C_{13}H_{23}N_2O_3$ $[M+H]^+$: 255.1709; found: 255.1705.



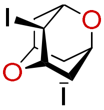
(1S,2S,5S,6S)-2,6-Diiodo-9-oxabicyclo[3.3.1]nonane (13).

White crystals. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.60 (s, 2H), 4.03 (dd, *J* = 5.6 Hz, 2H), 2.69 – 2.48 (m, 4H), 2.33 – 2.24 (m, 2H), 2.24 – 2.12 (m, 2H). ^{13}C NMR APT (101 MHz, $CDCl_3$) δ 70.4, 33.0, 29.6, 28.7. EIMS, 70eV, m/z (rel. int.): 251 (32); 128 (12); 127 (41); 124 (12); 123 (15); 105 (26); 93 (12); 91 (12); 80 (43); 79 (10); 77 (15); 77 (24); 69 (20); 68 (73); 67 (19); 66 (18); 65 (26); 63 (18); 57 (54); 54 (21); 54 (13); 53 (14); 41 (101); 39 (26); 39 (34). HRMS (ESI): not informative. Anal. calcd. for $C_8H_{12}I_2O$: C, 25.42; H, 3.20. Found: C, 25.23; H, 3.08.



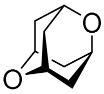
(1S,5S)-9-oxabicyclo[3.3.1]non-3,7-diene (14).

Yellowish liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.96 – 5.56 (m, 4H), 4.52 – 4.42 (m, 2H), 2.53 (dd, *J* = 17.7, 6.4 Hz, 2H), 1.77 (dd, *J* = 17.4, 5.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.1, 122.1, 65.9, 27.7. EIMS, 70eV, m/z (rel. int.): 122 $[M]^+$ (28); 104 (22); 94 (26); 93 (51); 92 (27); 91 (93); 81 (17); 79 (57); 78 (15); 77 (89); 67 (14); 65 (22); 65 (49); 63 (33); 62 (11); 61 (10); 56 (10); 53 (19); 52 (20); 52 (13); 50 (36); 49 (20); 41 (15); 40 (12); 39 (100). HRMS (ESI): not informative. Anal. calcd. for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.68; H, 7.88.



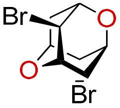
4,8-Diiodo-2,6-dioxaadamantane (15).

White crystals. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.62 (d, *J* = 4.0 Hz, 2H), 4.30 (s, 2H), 4.21 (d, *J* = 5.1 Hz, 2H), 3.14 (dd, *J* = 13.7, 5.1 Hz, 2H), 2.21 (dd, *J* = 13.8, 4.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.2, 69.9, 32.1, 29.2. EIMS, 70eV, m/z (rel. int.): 391 $[M]^+$ (10); 265 (100); 139 (28); 137 (37); 128 (26); 121 (11); 110 (26); 108 (10); 96 (13); 95 (17); 93 (11); 92 (31); 81 (44); 79 (38); 78 (12); 68 (26); 67 (25); 66 (14); 56 (15); 54 (14); 44 (11); 42 (25); 39 (27). HRMS (ESI): calcd. for $C_8H_{11}I_2O_2$ $[M+H]^+$: 392.8843; found: 392.8837.



2,6-Dioxaadamantane (16).

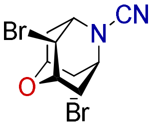
White crystals. M.p. 171-173ºC. ^{1}H NMR (400 MHz, Chloroform-d) δ: 4.21 (s, 4H), 1.99 (s, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 66.5, 35.1. EIMS, 70eV, m/z (rel. int.): 140 $[M]^+$ (100); 96 (25); 95 (28); 83 (12); 82 (18); 81 (94); 79 (16); 71 (13); 70 (10); 69 (28); 68 (34); 67 (75); 55 (14); 53 (21); 43 (32); 42 (12); 41 (59); 39 (31). HRMS (ESI): calcd. for $C_8H_{13}O_2$ $[M+H]^+$: 141.0916; found: 141.0908.



4,8-Dibromo-2,6-dioxaadamantane (17).

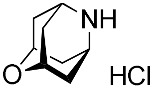
White crystals. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.40 (d, *J* = 4.1 Hz, 2H), 4.33 – 4.09 (m, 4H), 3.03 (dd, *J* = 13.8, 5.2 Hz, 2H), 2.03 (dd, *J* = 13.8, 4.4 Hz, 2H). ^{13}C NMR APT (126 MHz, $CDCl_3$) δ 70.3, 68.5, 48.7, 30.1. EIMS, 70eV, m/z (rel. int.): 300 (37); 298 $[M]^+$ (75); 296 (39); 219 (31); 217

(32); 205 (94); 203 (97); 161 (54); 159 (53); 147 (18); 145 (19); 137 (13); 123 (60); 121 (27); 119 (23); 109 (16); 107 (17); 95 (101); 94 (12); 93 (15); 91 (24); 81 (51); 79 (41); 77 (23); 71 (15); 69 (13); 68 (18); 67 (82); 66 (51); 65 (82); 55 (20); 53 (29); 51 (17); 43 (28); 42 (11); 41 (58); 40 (13); 39 (69). HRMS (ESI): calcd. for $C_8H_{11}Br_2O_2$ $[M+H]^+$: 296.9120; found: 296.9118.



(1R,3R,4S,5R,7R,8S)-4,8-dibromo-2-oxa-6-azaadamantane-6-carbonitrile (18).

White powder ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.43 (d, *J* = 3.8 Hz, 2H), 4.20 (d, *J* = 5.0 Hz, 2H), 3.88 (d, *J* = 4.3 Hz, 2H), 3.05 (ddd, *J* = 14.1, 5.1, 2.1 Hz, 2H), 2.10 (dd, *J* = 14.0, 3.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 114.1, 69.7, 54.5, 46.3, 28.6. EIMS, 70eV, m/z (rel. int.): 323 (36); 322 $[M]^+$ (74); 319 (37); 243 (50); 241 (54); 228 (31); 227 (31); 201 (10); 199 (11); 187 (20); 184 (63); 182 (46); 161 (47); 159 (39); 149 (13); 147 (28); 145 (11); 134 (13); 133 (34); 132 (13); 121 (29); 120 (17); 119 (82); 118 (23); 107 (14); 106 (23); 105 (41); 95 (100); 94 (23); 93 (43); 92 (35); 91 (58); 82 (12); 80 (46); 80 (25); 79 (38); 77 (25); 77 (39); 69 (10); 68 (22); 67 (59); 66 (51); 65 (78); 62 (12); 55 (22); 54 (15); 53 (55); 52 (17); 51 (29); 50 (11); 43 (11); 42 (14); 41 (56); 40 (18); 39 (84). HRMS (ESI): calcd. for $C_9H_{11}Br_2N_2O$ $[M+H]^+$: 320.9233; found: 320.9226.



(1r,3r,5r,7r)-2-oxa-6-azaadamantane (19*HCl).

White powder. M.p. 250-347°C (with decomposition). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (br.s, HCl), 4.05 (br.s, 2H), 3.75 (br.s, 2H), 2.18 – 1.85 (m, 8H) (one peak from the NH-group is overlapped with the peak of the solvent at 3.33 ppm). ^{13}C NMR (101 MHz, APT, DMSO-d_6) δ 63.6, 45.3, 31.4. HRMS (ESI): calcd. for $C_8H_{14}NO$ $[M+H]^+$: 140.1075; found: 140.1067.

X-ray structure determination

Table S3. X-Ray crystallographic data for compounds.

	3	**7*HBr**	**8**	**11**	**13**	**15**	**17**	**18**
Sum formula	$C_8H_{12}Br_2O$	$C_8H_{14}BrNO$	$C_{13}H_{21}NO_3$	$C_{13}H_{22}N_2O_3$	$C_8H_{12}I_2O$	$C_8H_{10}I_2O_2$	$C_8H_{10}Br_2O_2$	$C_9H_{10}Br_2N_2O$
Formula weight	284.00	220.11	239.31	254.32	377.98	391.96	297.98	322.01
Crystal system,	triclinic	orthorhombic	orthorhombic	monoclinic	monoclinic	monoclinic	monoclinic	triclinic
Space group	$P\,\text{-}1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1/c$	$C2/c$	$P2_1/c$	$P2_1/c$	$P\,\text{-}1$
a (Å)	*7.6076(3)*	*6.7405(2)*	9.4913(7)	11.3355(3)	*19.1580(8)*	*7.6576(4)*	7.3278(3)	6.5973(2)
b (Å)	7.7166(3)	7.1349(2)	11.0265(8)	11.1067(2)	5.3842(2)	7.0320(3)	18.7355(7)	7.1306(2)
c (Å)	8.4813(3)	17.6338(5)	12.1046(9)	12.0599(3)	13.0363(6)	18.5903(9)	6.6727(4)	11.5989(3)
α (°)	111.879(3)	90	90	90	90	90	90	105.496(2)
β(°)	99.742(3)	90	90	117.2665(15)	128.734(4)	94.643(2)	96.904(3)	95.839(2)
γ(°)	90.024(3)	90	90	90	90	90	90	91.827(2)
V (Å^3)	454.27(3)	848.06(4)	1266.82(16)	1349.63(6)	1048.95(9)	997.77(8)	909.45(7)	522.09(3)
Z	2	4	4	4	4	4	4	2
Dx (g/ cm^3)	2.076	1.724	1.255	1.252	2.393	2.609	2.176	2.048
μ(mm^{-1})	8.863	4.789	0.088	0.089	5.946	6.263	8.868	7.731
F(000)	276	448	520	552	696	720	576	312
Crystal size (mm)	0.17 × 0.22 × 0.24	0.17 × 0.17 × 0.26	0.08 × 0.09 × 0.46	0.15 × 0.22 × 0.44	0.06 × 0.07 × 0.21	0.17 × 0.20 × 0.26	0.15 × 0.17 × 0.29	0.23 × 0.24 × 0.35
Crystal colour	colourless	yellow	colourless	colourless	colourless	colourless	colourless	colourless
Temperature (K)	173(2)	173(2)	173(2)	173(2)	173(2)	173(2)	173(2)	173(2)
θ_{max}(°)	25.0	25.9	26.4	26.7	25.0	25.5	26.4	26.7
Refl. collected/ with $I>2\sigma(I)$)	5991/1334	7211/1457	12828/ 1630	20493/2122	7025 / 828	8869/ 1757	8470/1573	8343/1841
R_{int}	0.0557	0.0514	0.0760	0.0459	0.0254	0.0276	0.0439	0.0419
Completeness	1.000	0.991	0.999	0.991	1.000	0.997	0.998	0.990
R1 ($I>2\sigma(I)$)	0.0297	0.0283	0.0495	0.0463	0.0291	0.0192	0.0425	0.0233
wR(on F^2) ($I>2\sigma(I)$)	0.0691	0.0506	0.0778	0.1150	0.0570	0.0459	0.0921	0.0529
R1(all data)	0.0394	0.0352	0.0858	0.0646	0.0337	0.0210	0.0561	0.0327
wR(on F^2) (all data)	0.0734	0.0525	0.0840	0.1280	0.0605	0.0469	0.0977	0.0560
GOF(on F^2)	1.064	1.008	0.960	1.018	1.060	1.008	1.047	1.042
Flack parameter	-	0.003(12)	0.5(10)	-	-	-	-	-
Data/restraints/ parameters	1591/0/100	1630/0/108	2597/0/136	2808/0/167	924/0/51	1854/0/109	1874/0/109	2187/0/127
Δρ min/max(e/Å^3)	0.52/-0.92	0.63/-0.32	0.16/-0.16	0.20/-0.21	1.60/-1.34	0.38/-0.93	0.80/-0.87	0.36/-0.58
CCDC Number	2454936	2454939	2454937	2454942	2454943	2454938	2454941	2454940

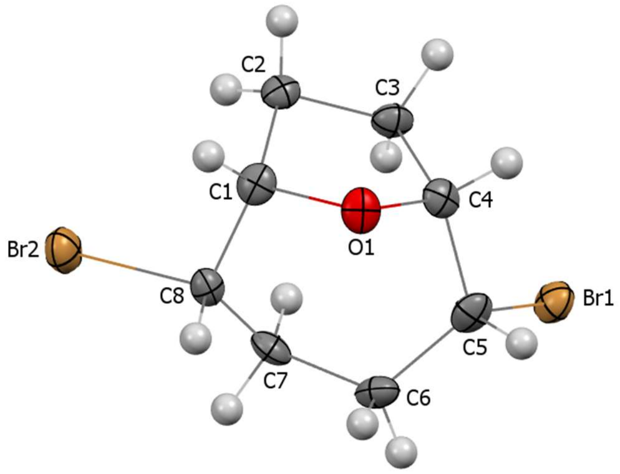


Figure 1. The molecular structure compound 3. The principal ellipses are drawn at 50% probability.

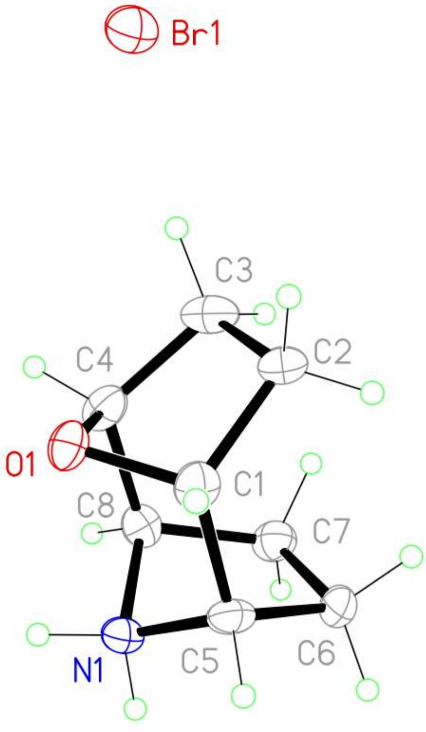


Figure 2. The molecular structure compound 7*HBr. The principal ellipses are drawn at 50% probability.

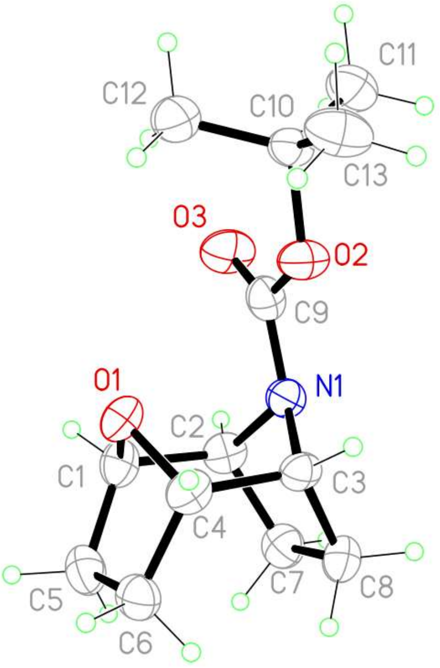


Figure 3. The molecular structure compound 8. The principal ellipses are drawn at 50% probability.

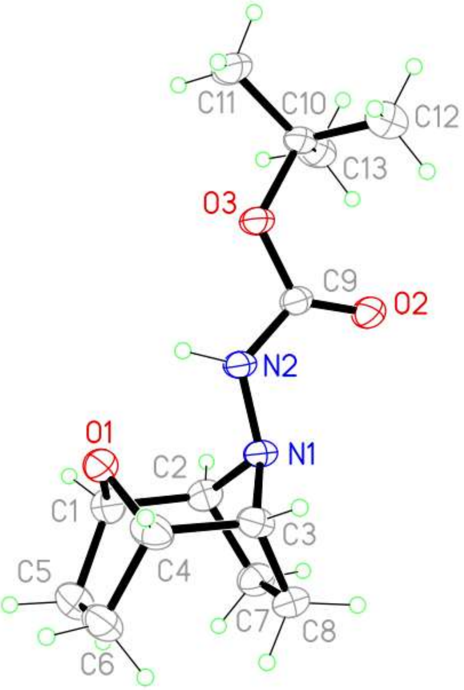


Figure 4. The molecular structure compound 11. The principal ellipses are drawn at 50% probability.

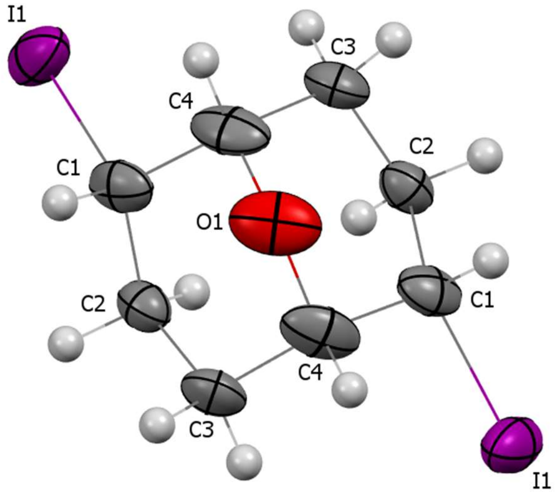


Figure 5. The molecular structure compound 13. The principal ellipses are drawn at 50% probability.

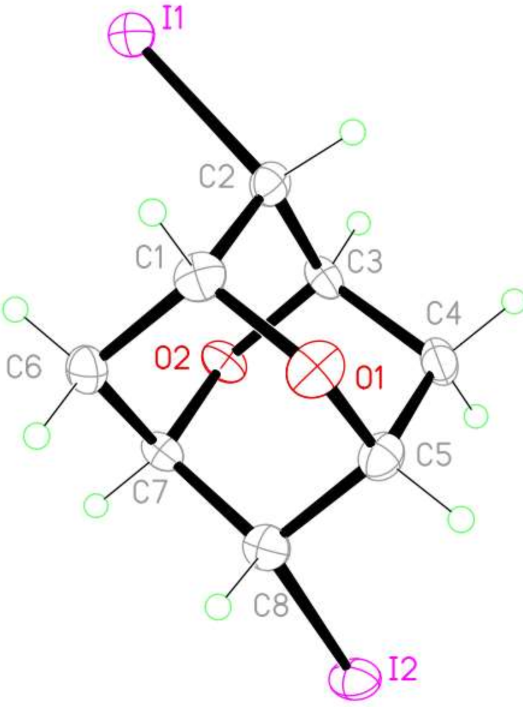


Figure 6. The molecular structure compound 15. The principal ellipses are drawn at 50% probability.

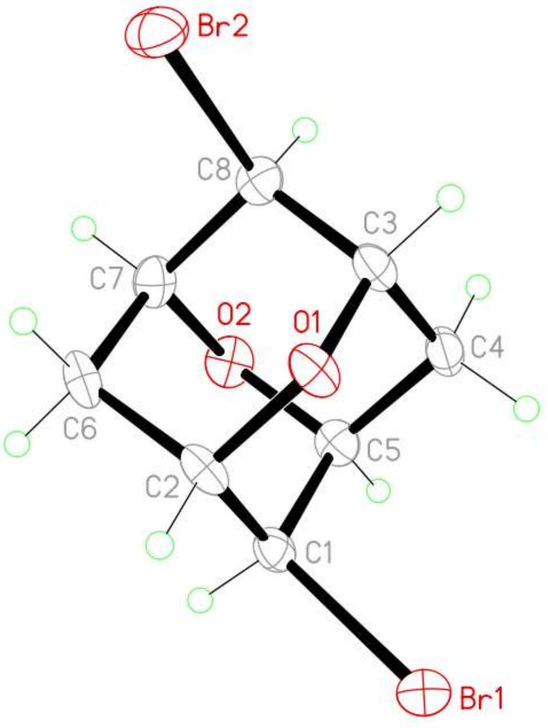


Figure7. The molecular structure compound 17. The principal ellipses are drawn at 50% probability.

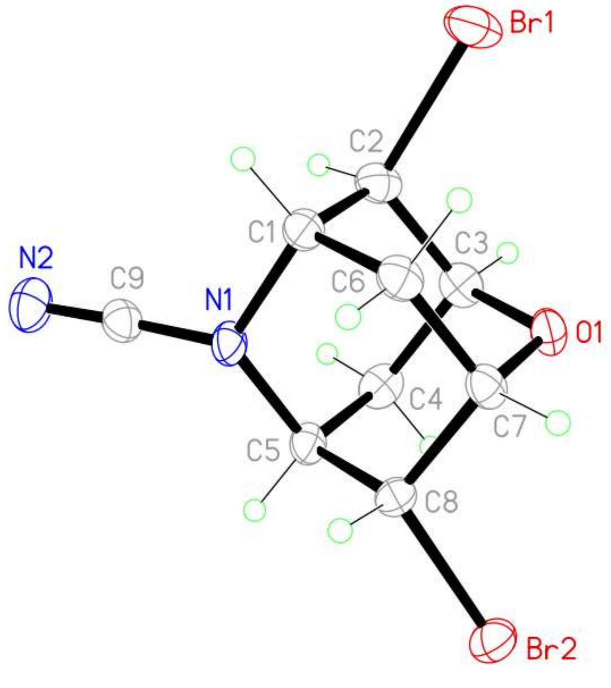
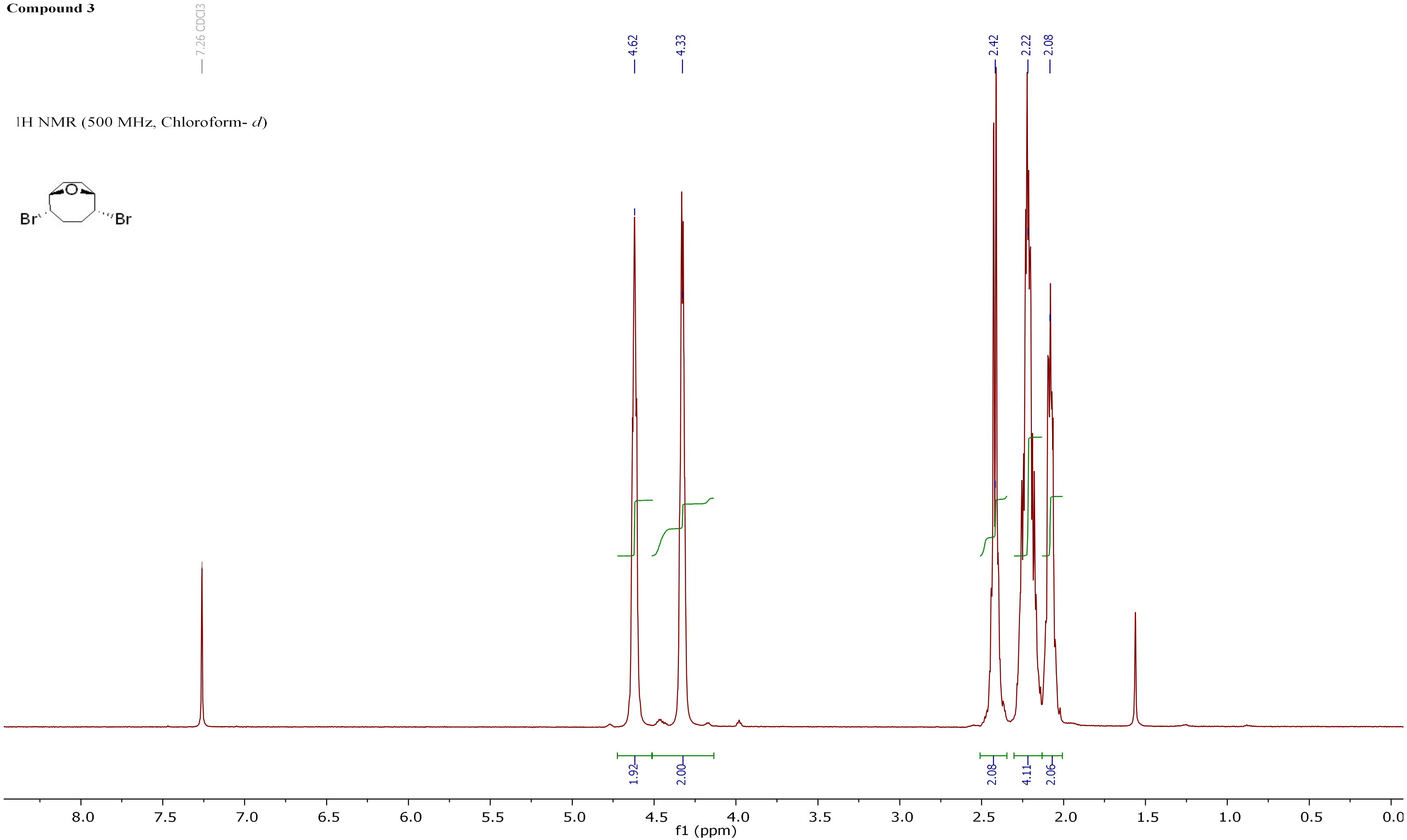


Figure 8. The molecular structure compound 18. The principal ellipses are drawn at 50% probability.

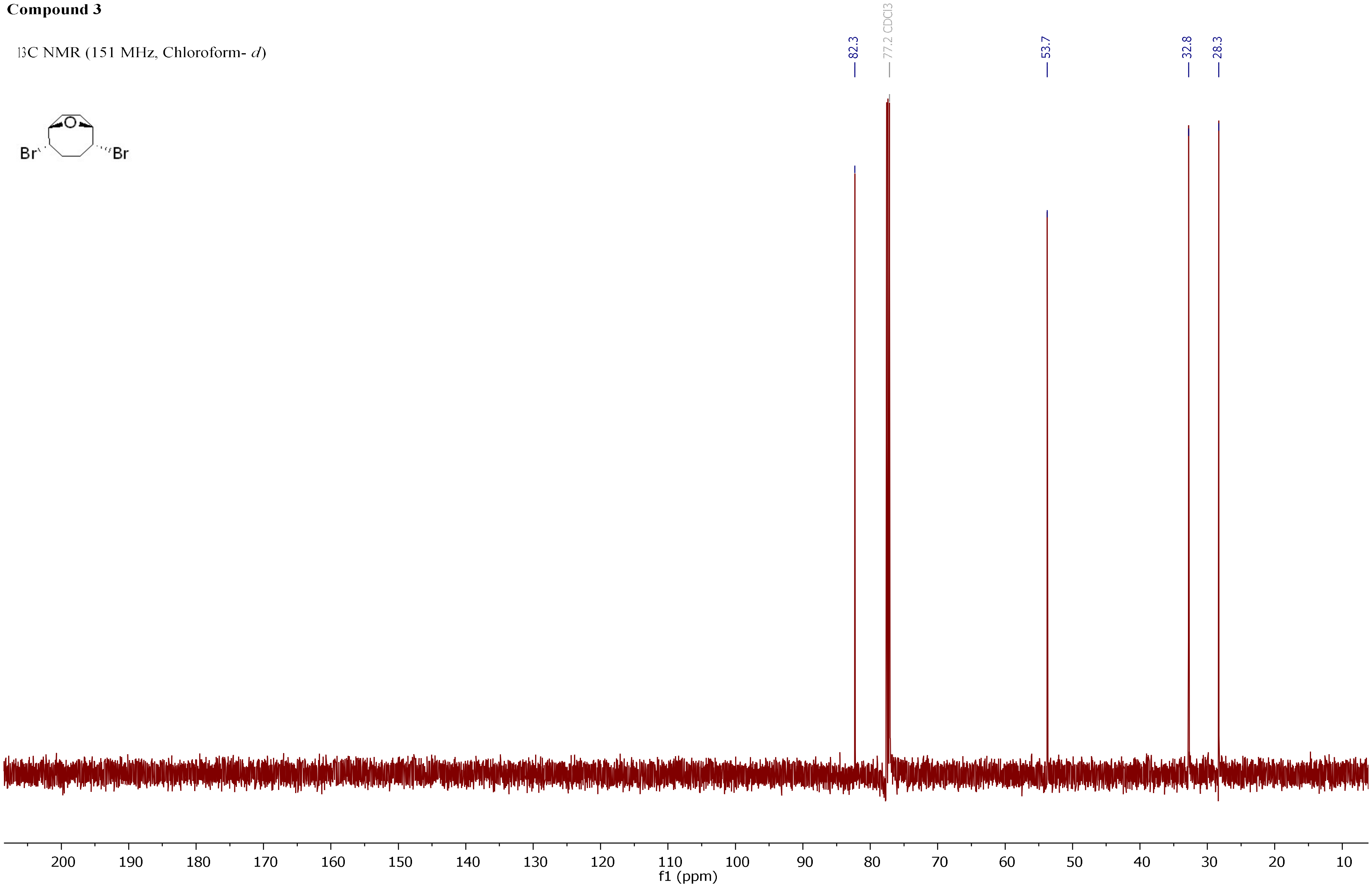
Copies of NMR spectra

Compound 3

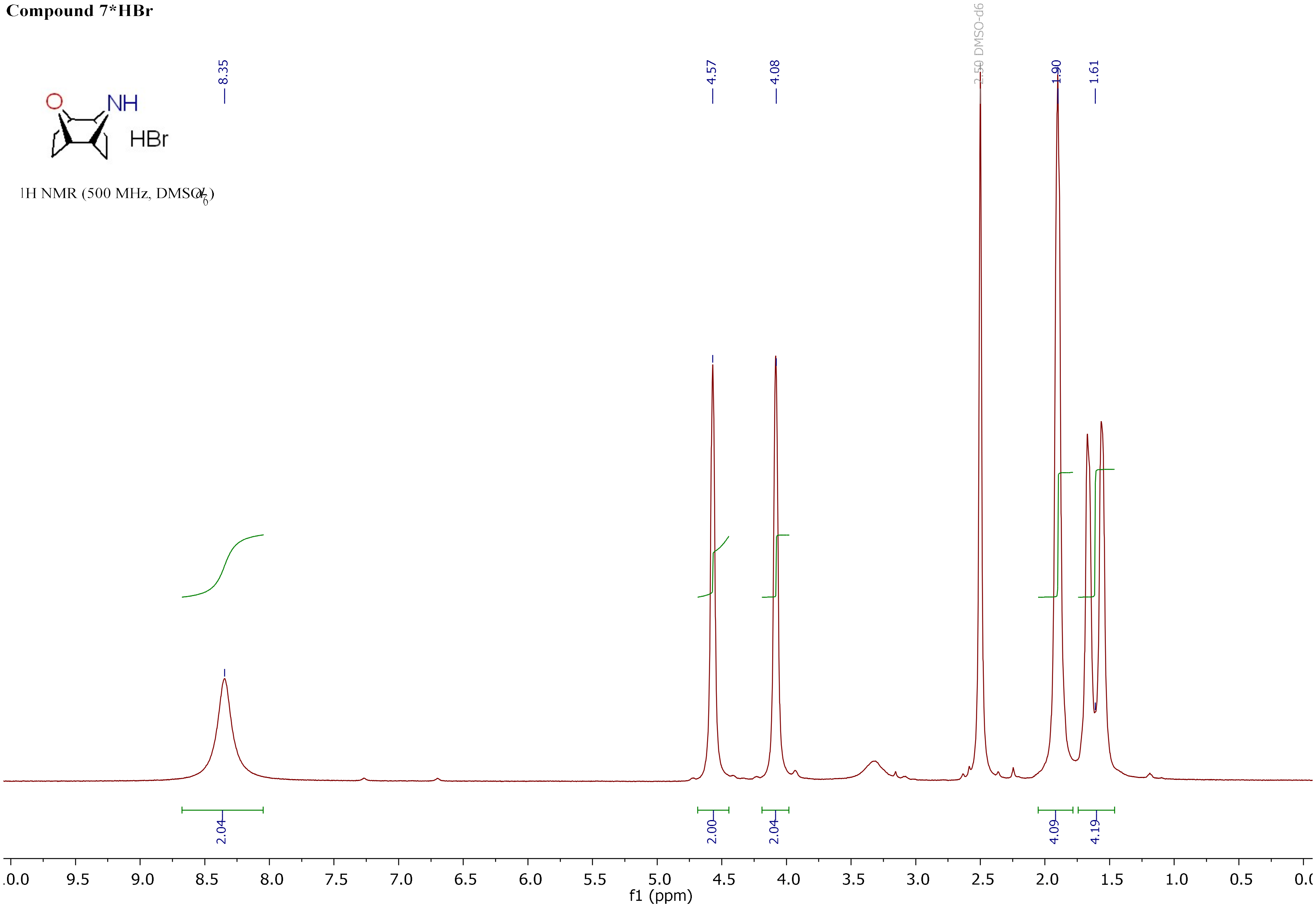


Compound 3

^{13}C NMR (151 MHz, Chloroform- *d*)



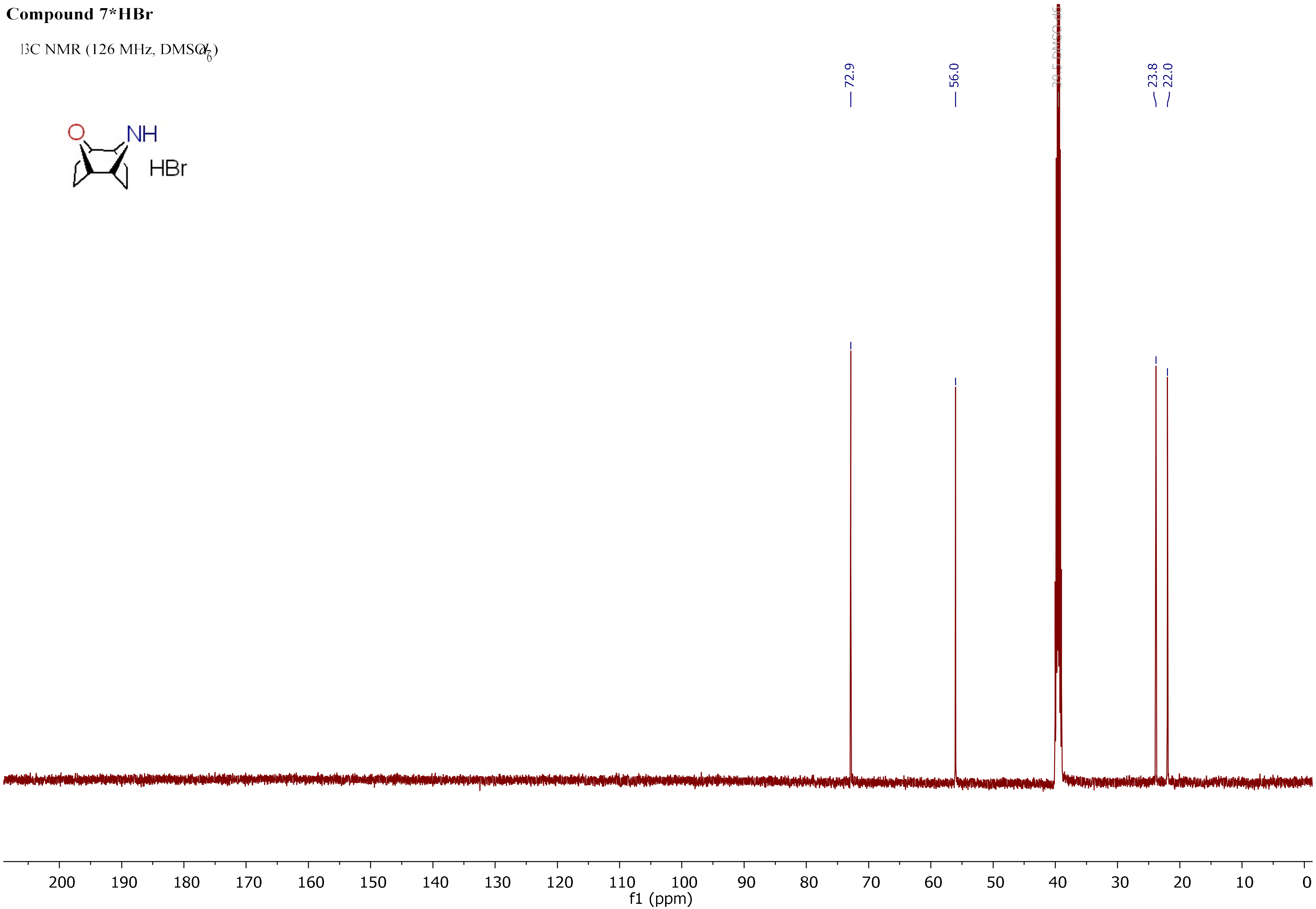
Compound 7*HBr



1H NMR (500 MHz, DMSO-d_6)

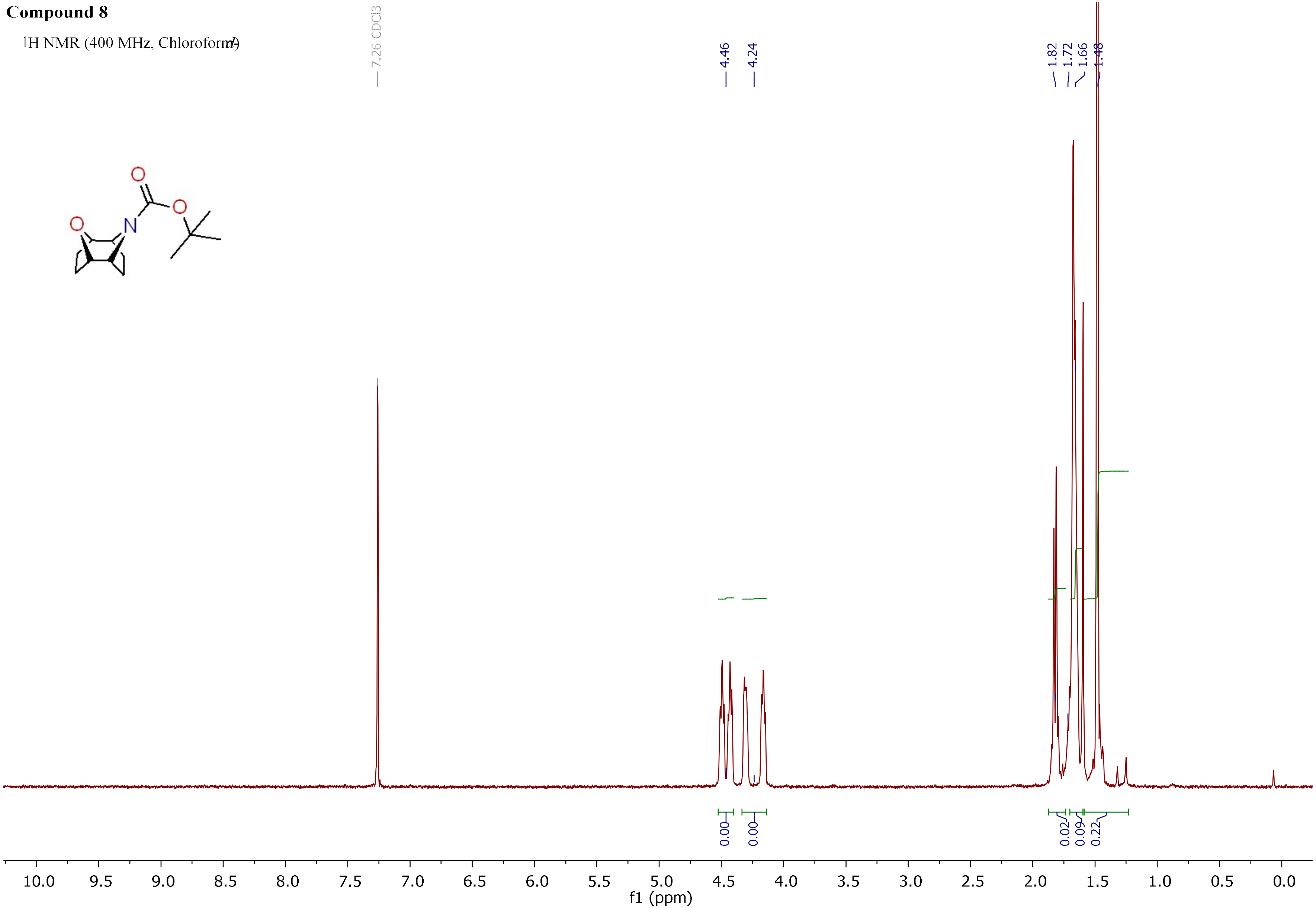
Compound 7*HBr

13C NMR (126 MHz, DMSO-d_6)



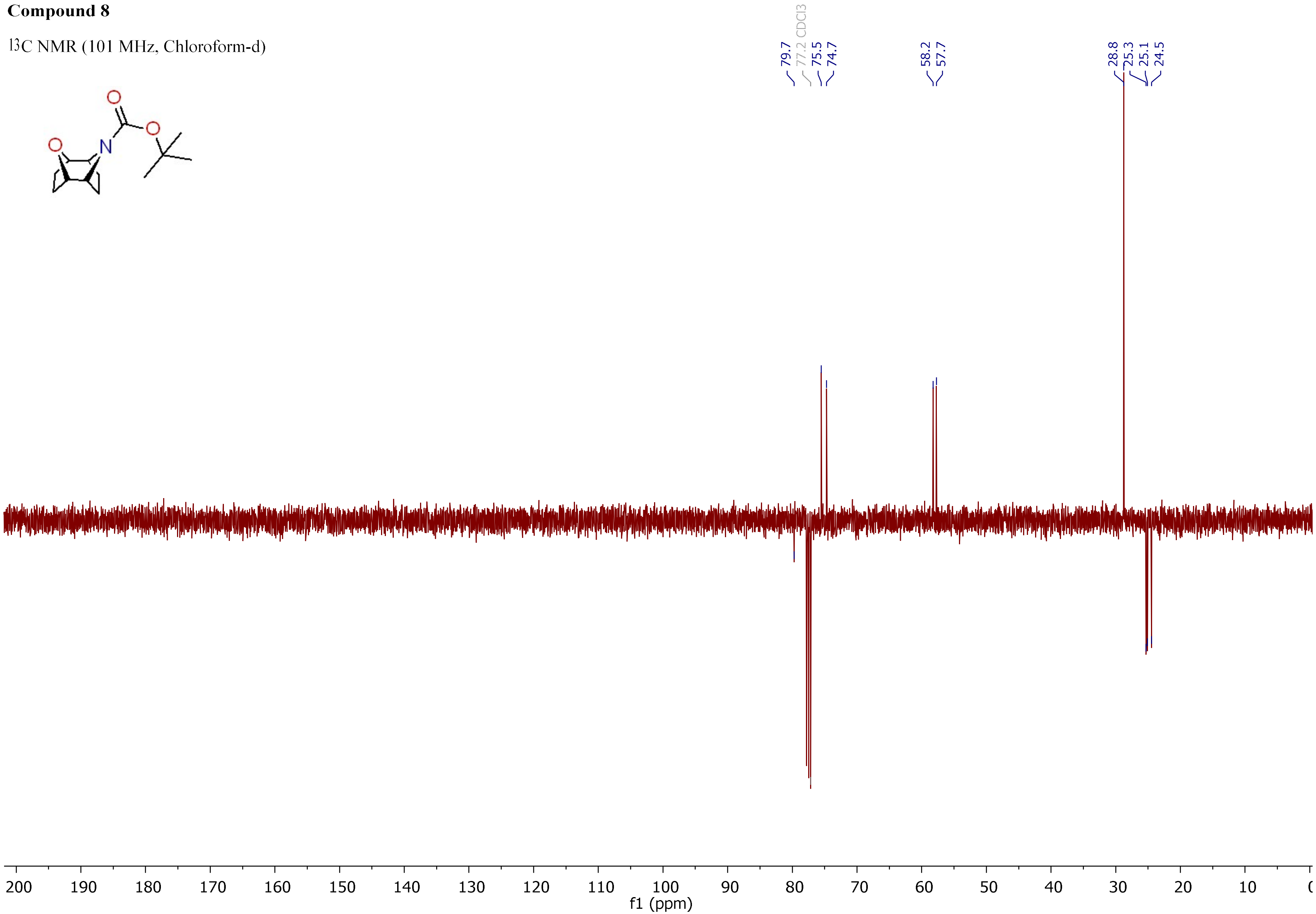
Compound 8

1H NMR (400 MHz, Chloroform-d)

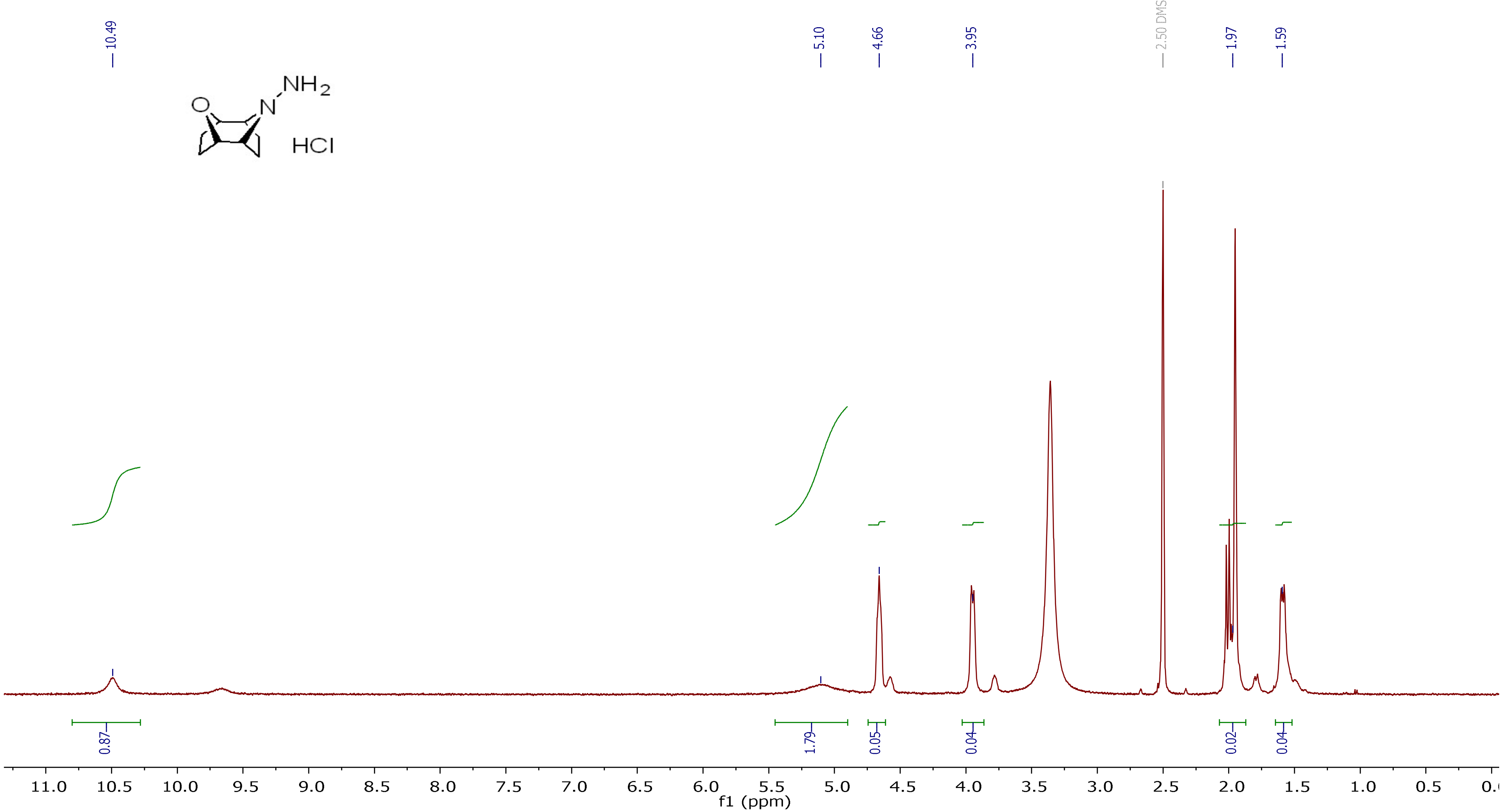


Compound 8

^{13}C NMR (101 MHz, Chloroform-d)

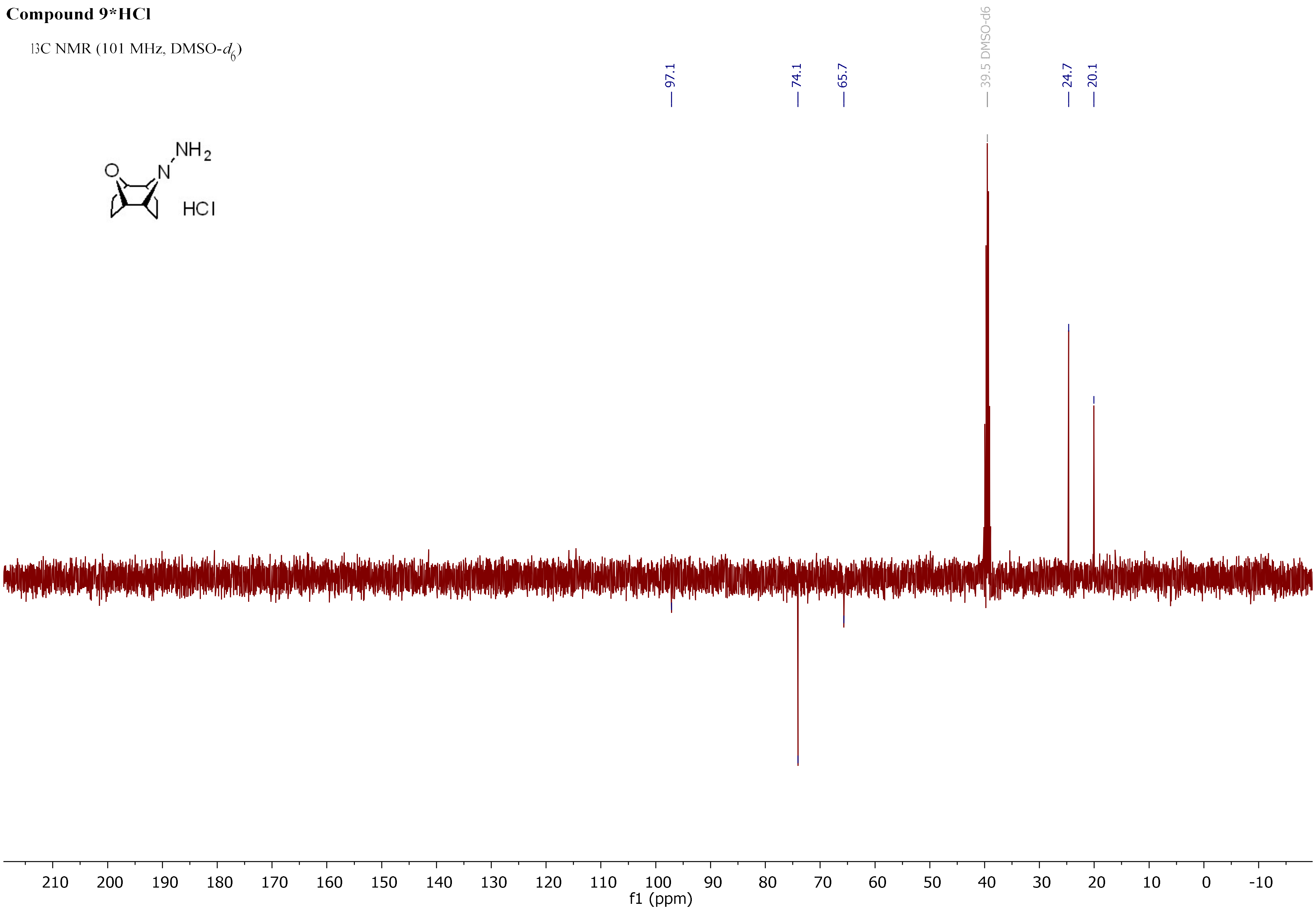


Compound 9*HCl 1H NMR (400 MHz, DMSO-d_6)



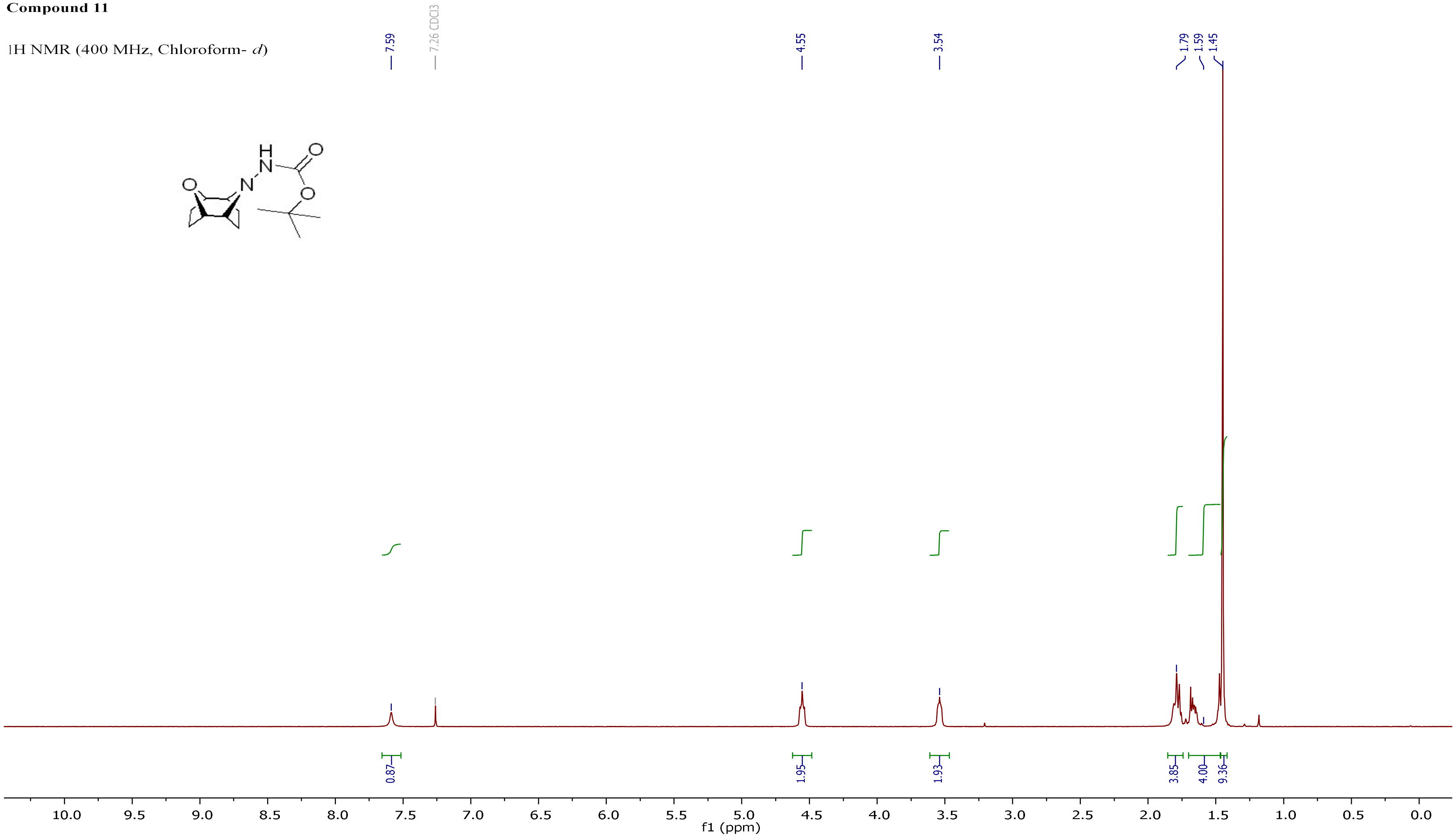
Compound 9*HCl

13C NMR (101 MHz, DMSO-d_6)



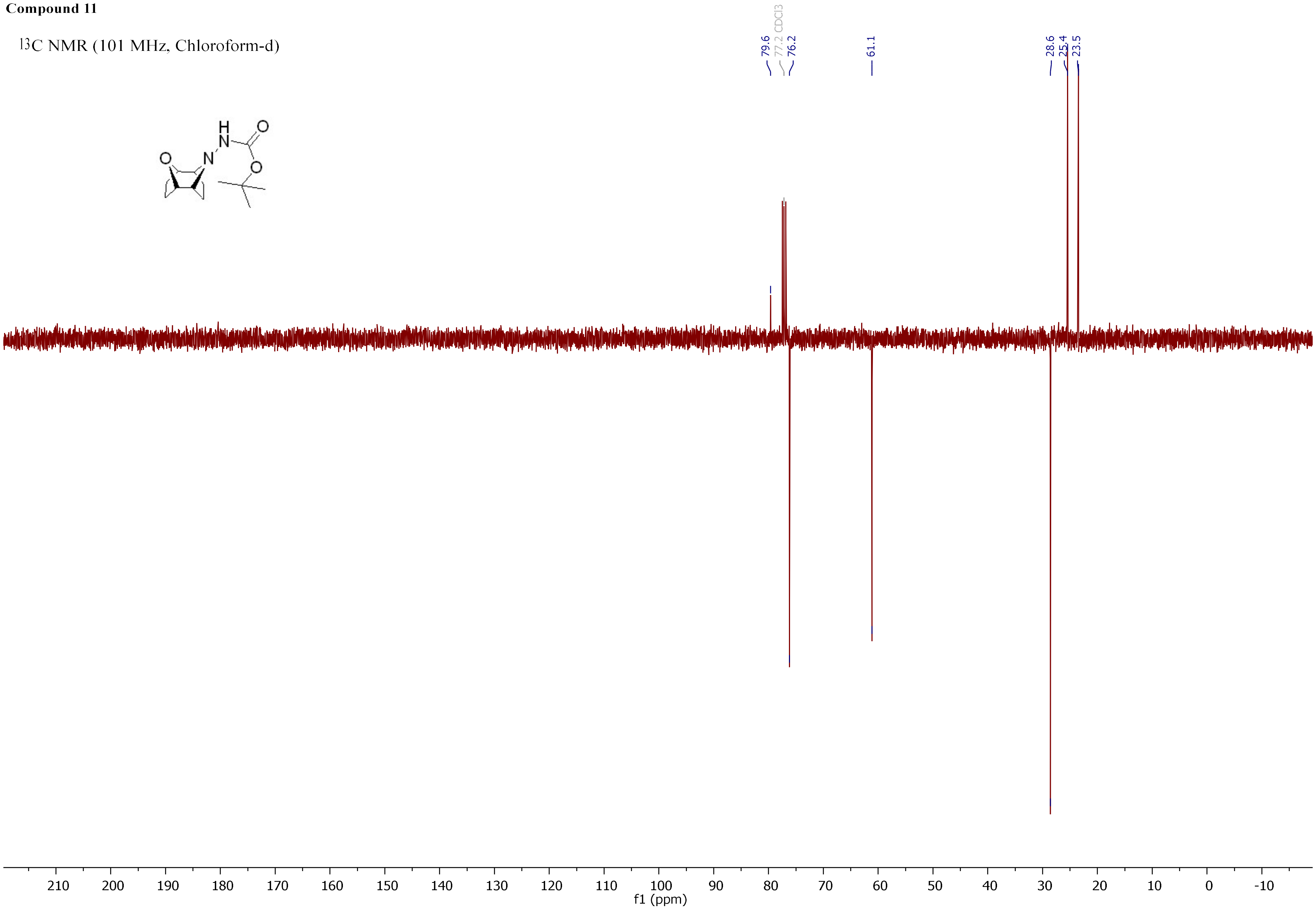
Compound 11

1H NMR (400 MHz, Chloroform- *d*)



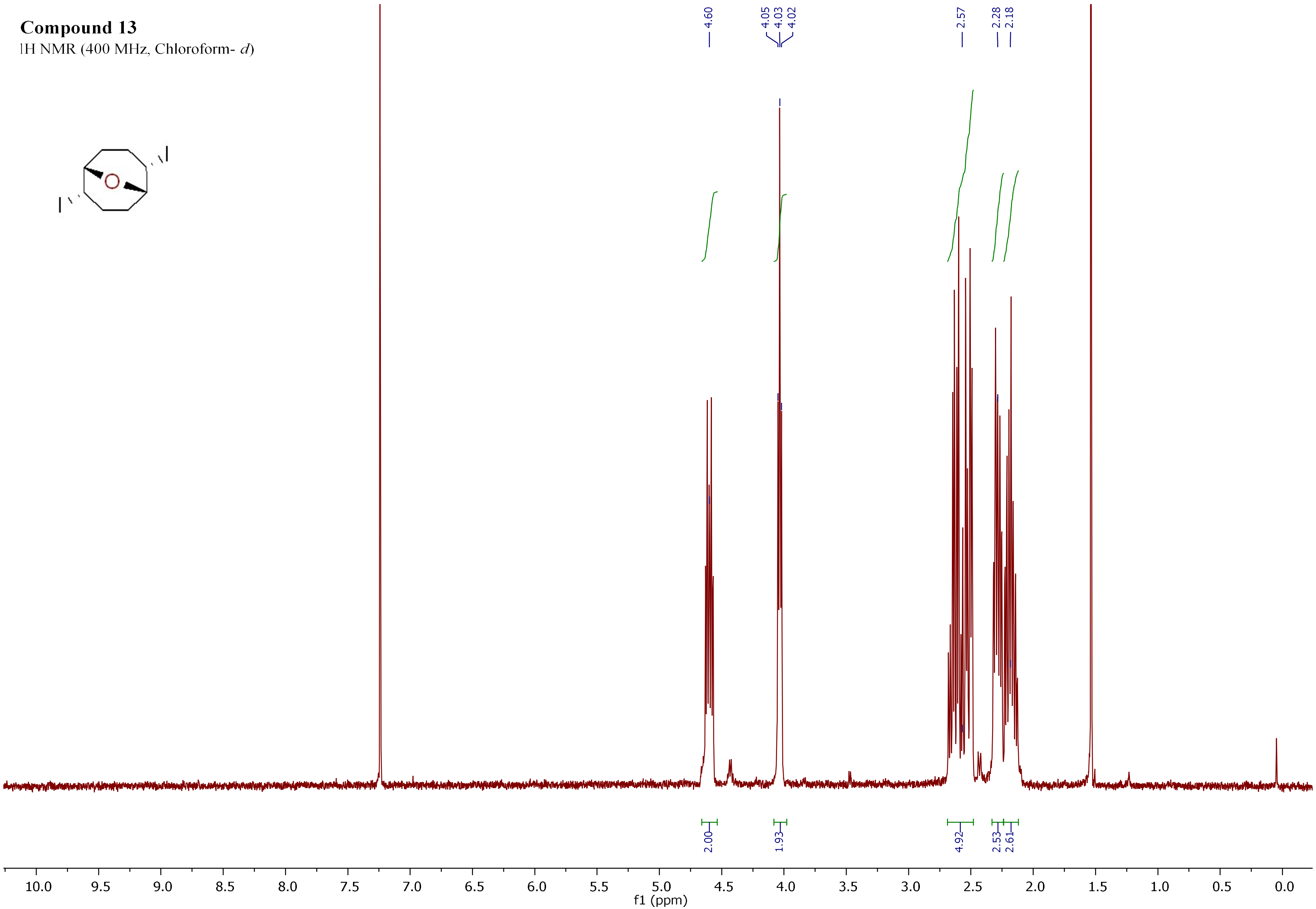
Compound 11

^{13}C NMR (101 MHz, Chloroform-d)



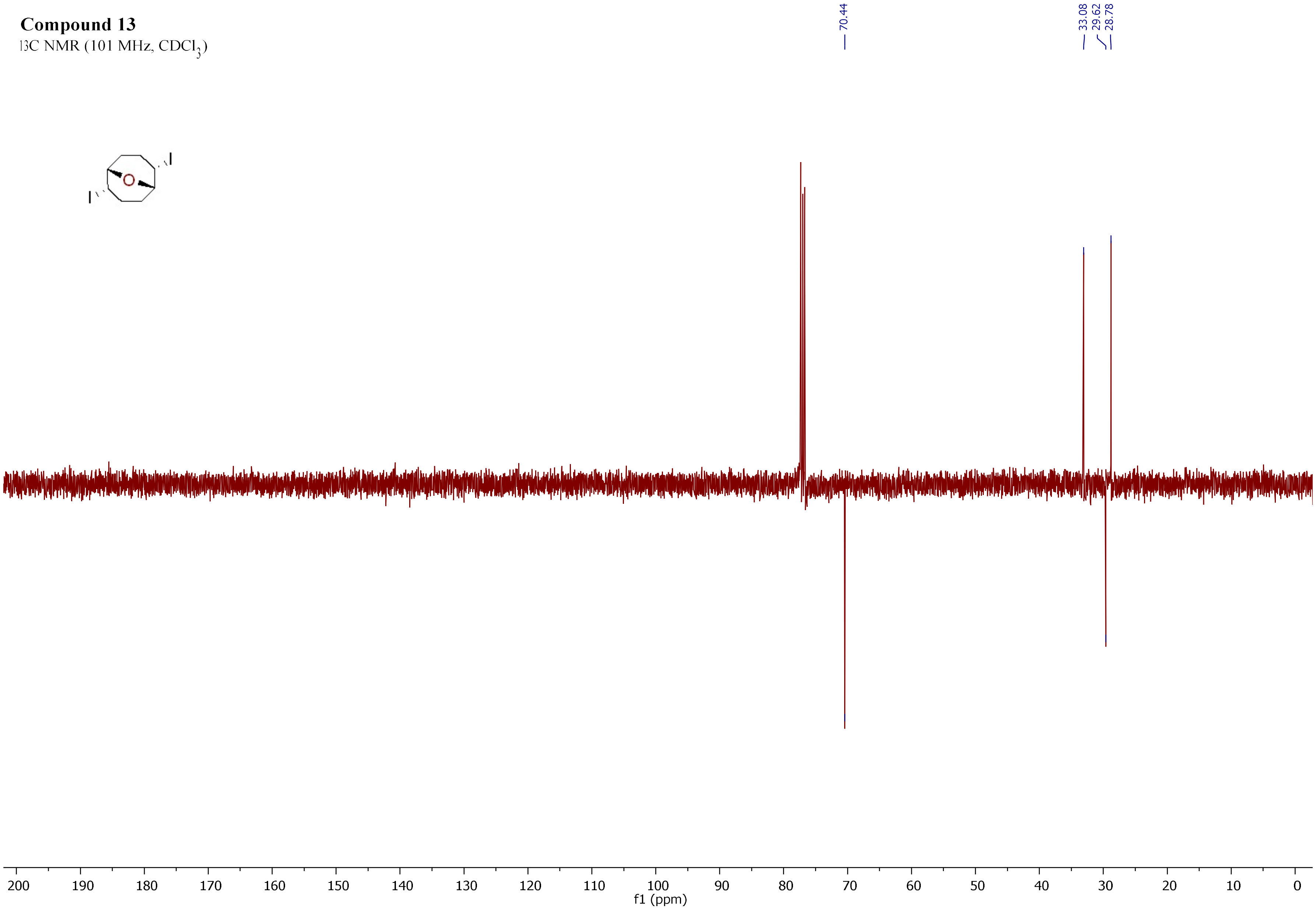
Compound 13

1H NMR (400 MHz, Chloroform- *d*)



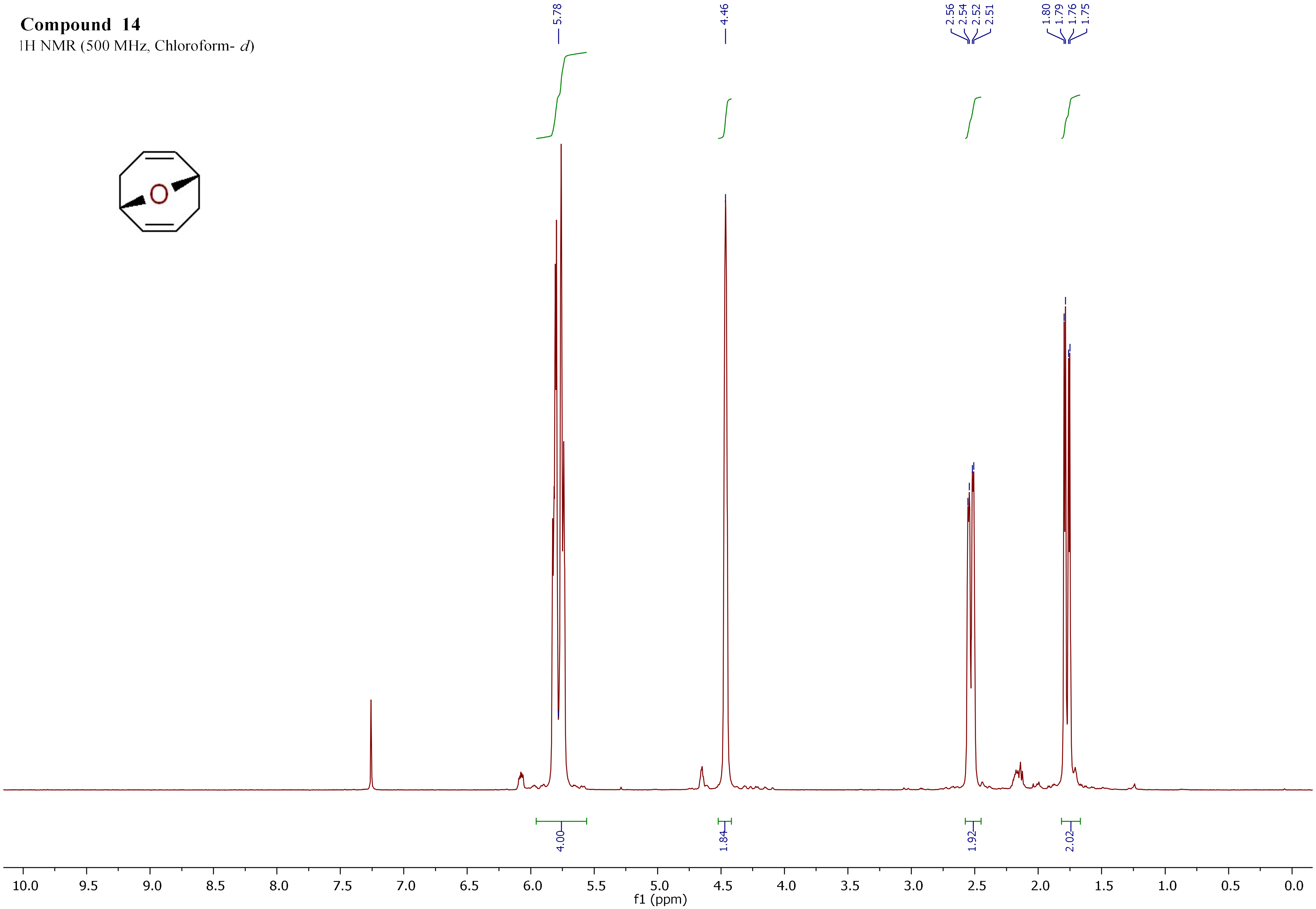
Compound 13

^{13}C NMR (101 MHz, $CDCl_3$)



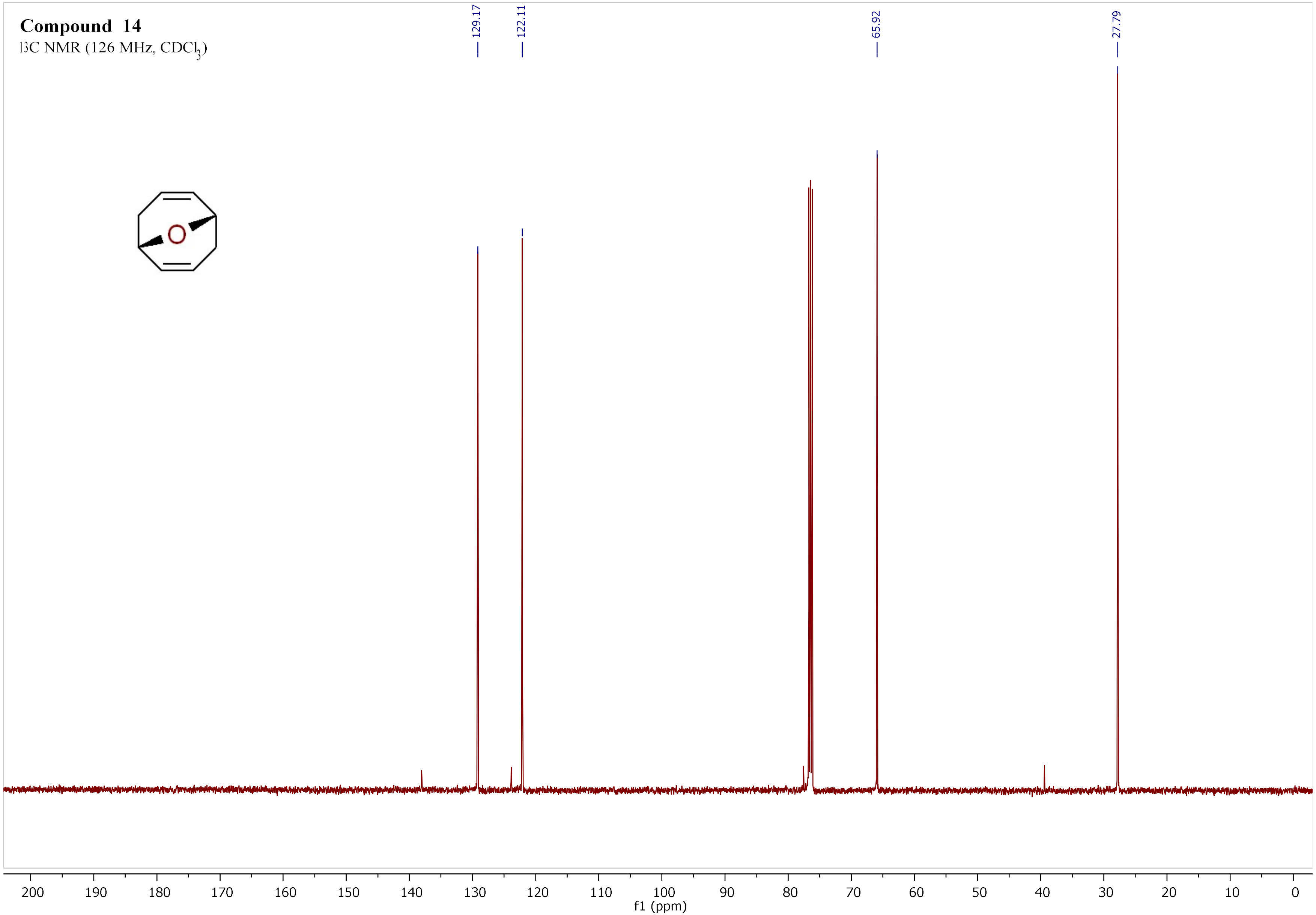
Compound 14

1H NMR (500 MHz, Chloroform- *d*)



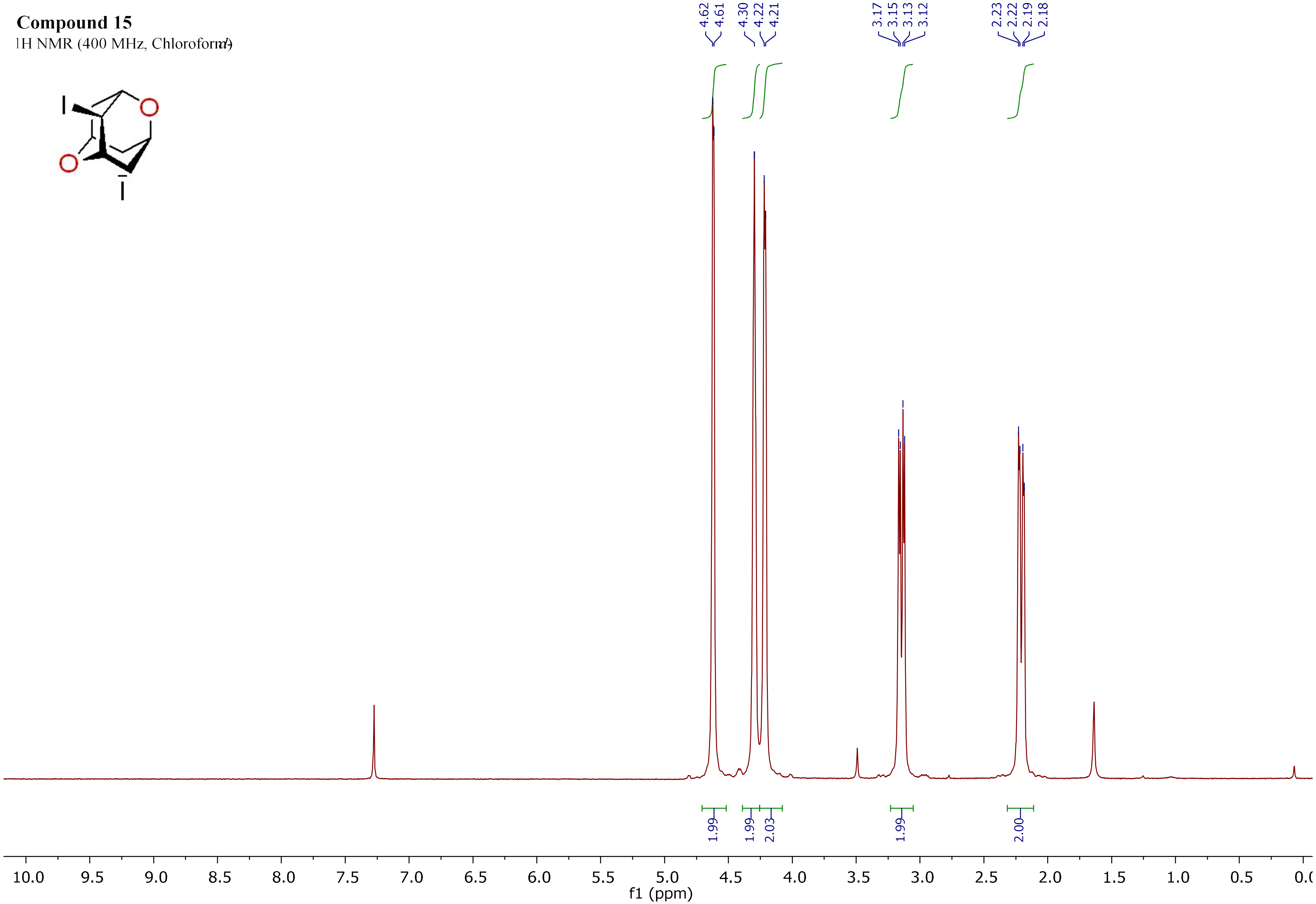
Compound 14

^{13}C NMR (126 MHz, $CDCl_3$)



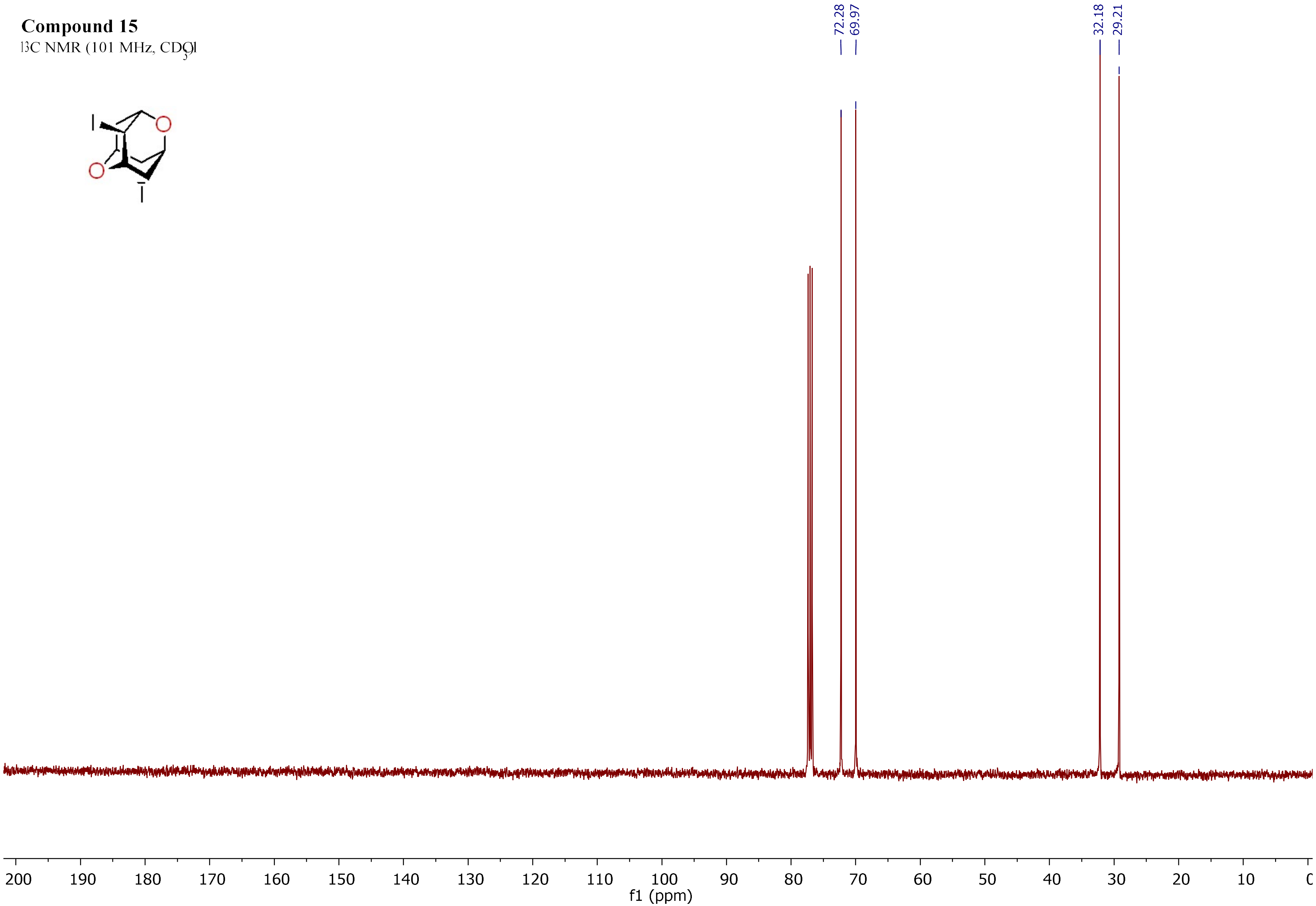
Compound 15

1H NMR (400 MHz, Chloroform-*d*)



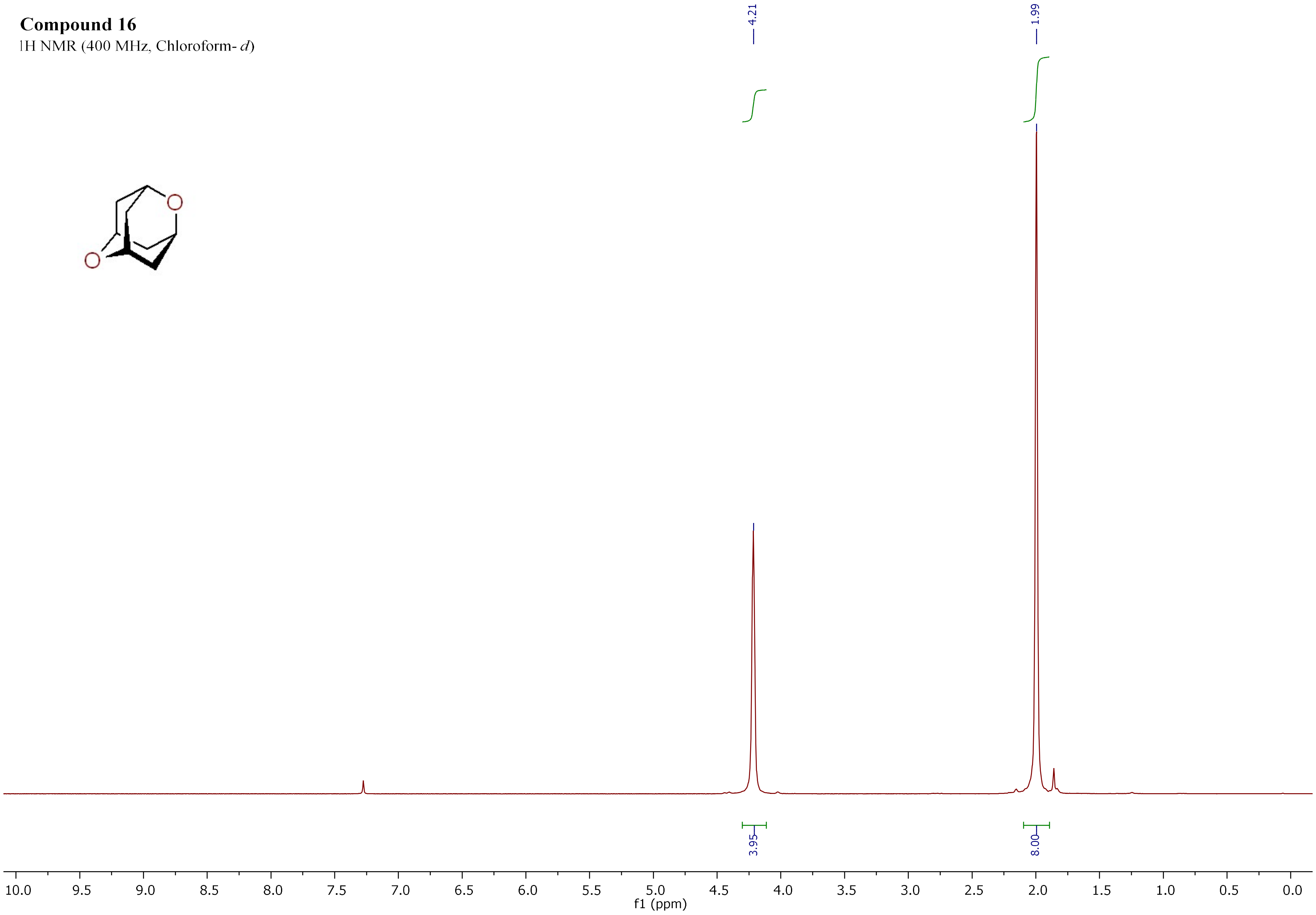
Compound 15

^{13}C NMR (101 MHz, CDCl$_3$)



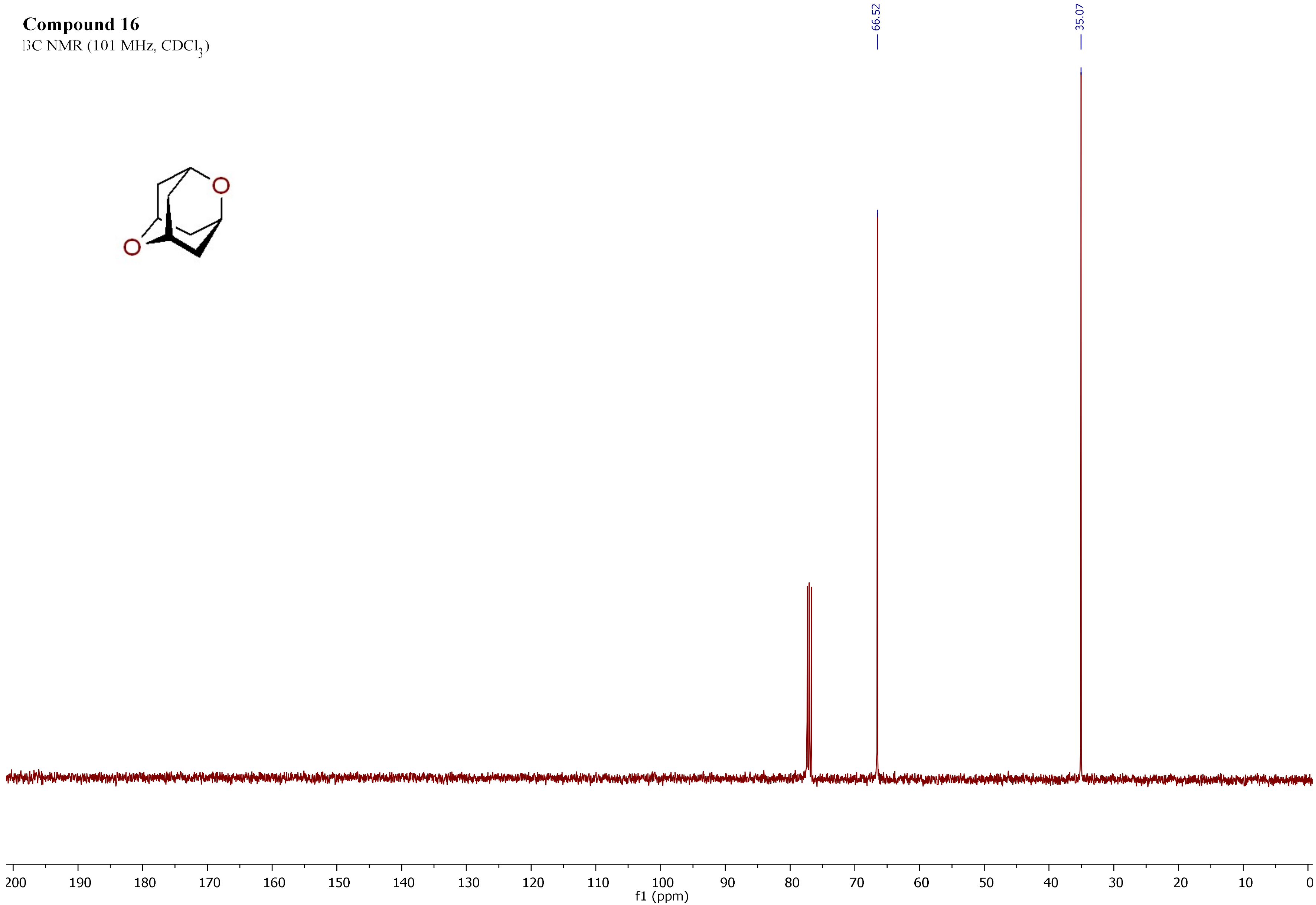
Compound 16

1H NMR (400 MHz, Chloroform- *d*)



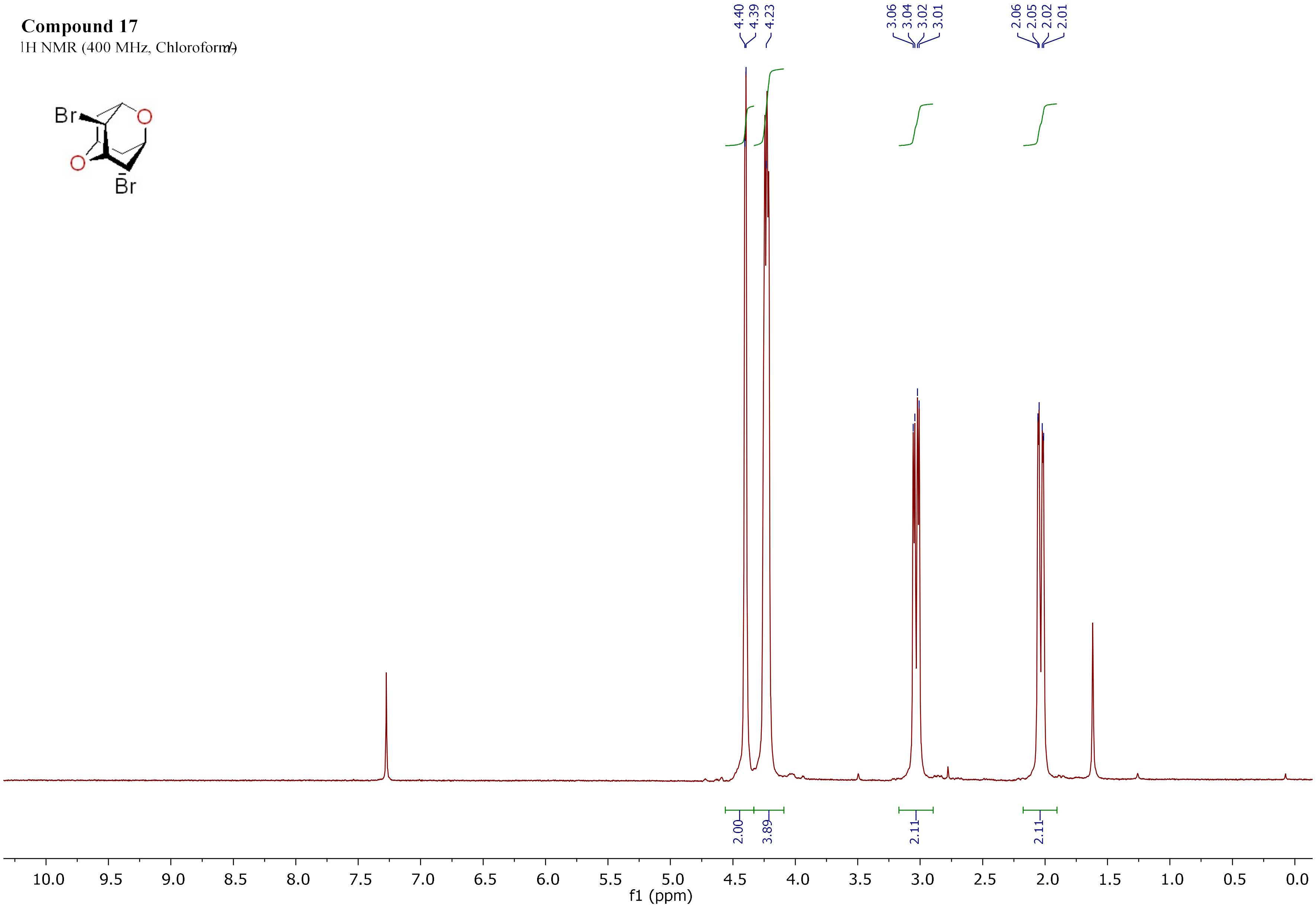
Compound 16

13C NMR (101 MHz, CDCl$_3$)



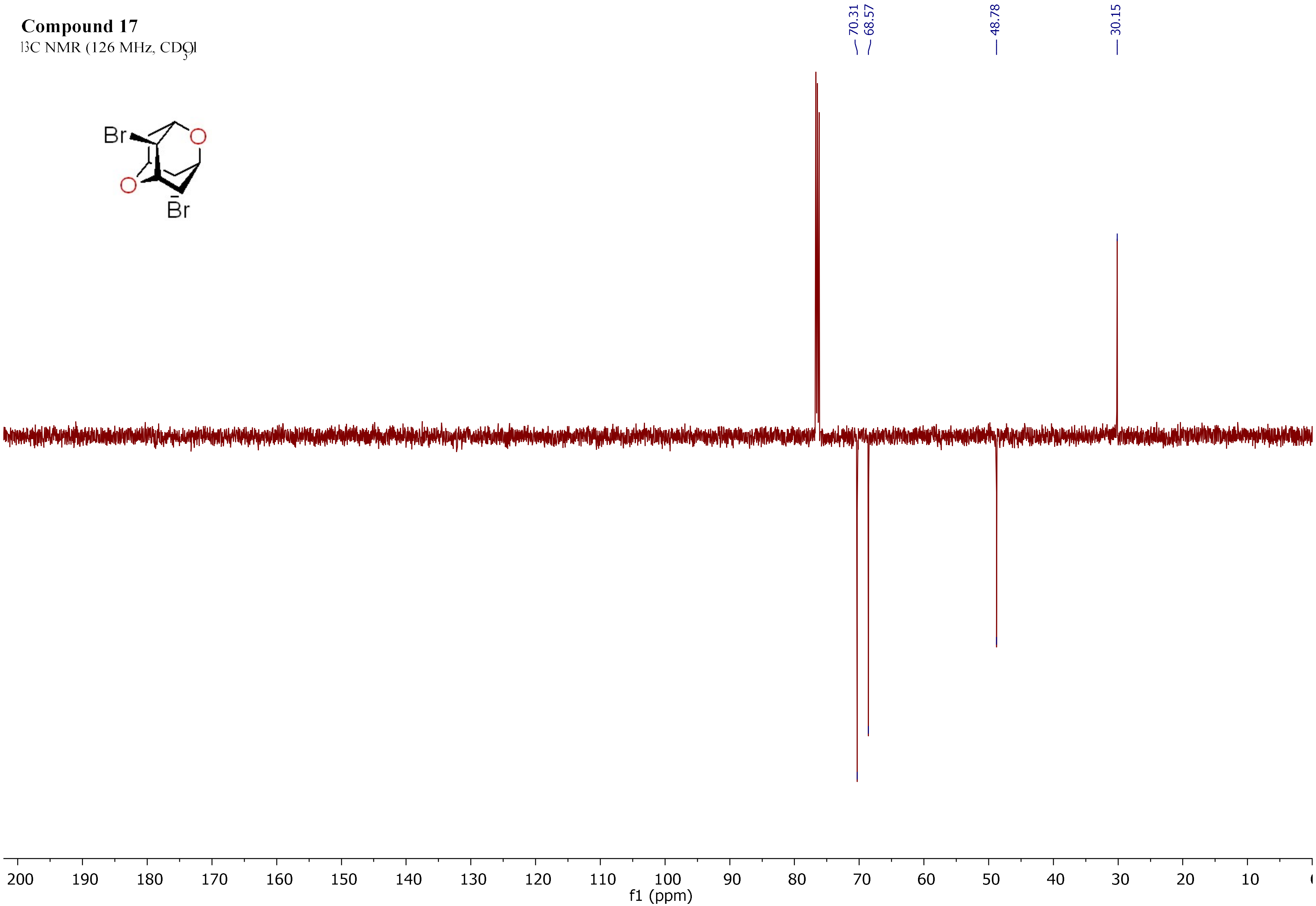
Compound 17

1H NMR (400 MHz, Chloroform-*d*)



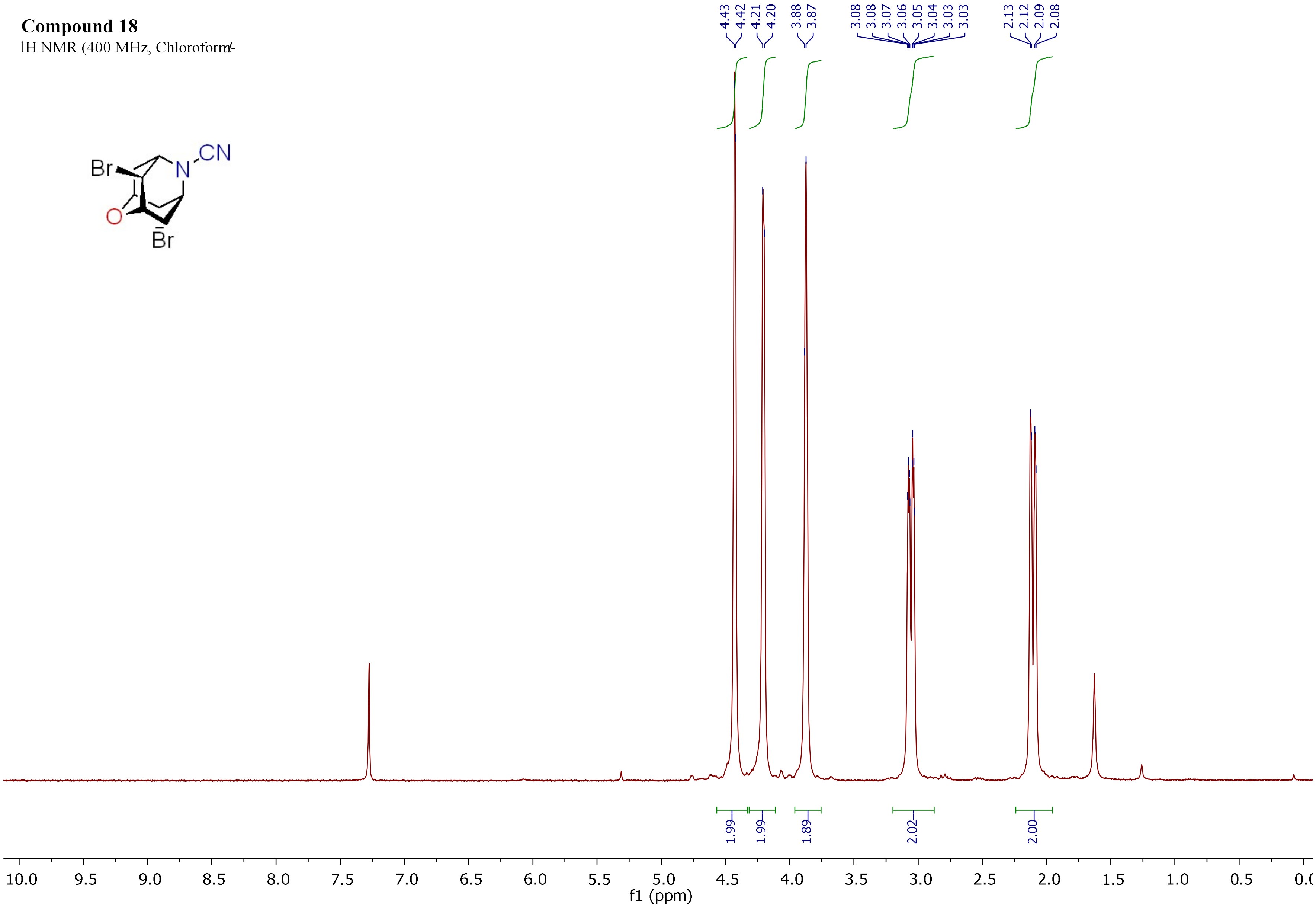
Compound 17

^{13}C NMR (126 MHz, CDCl$_3$)



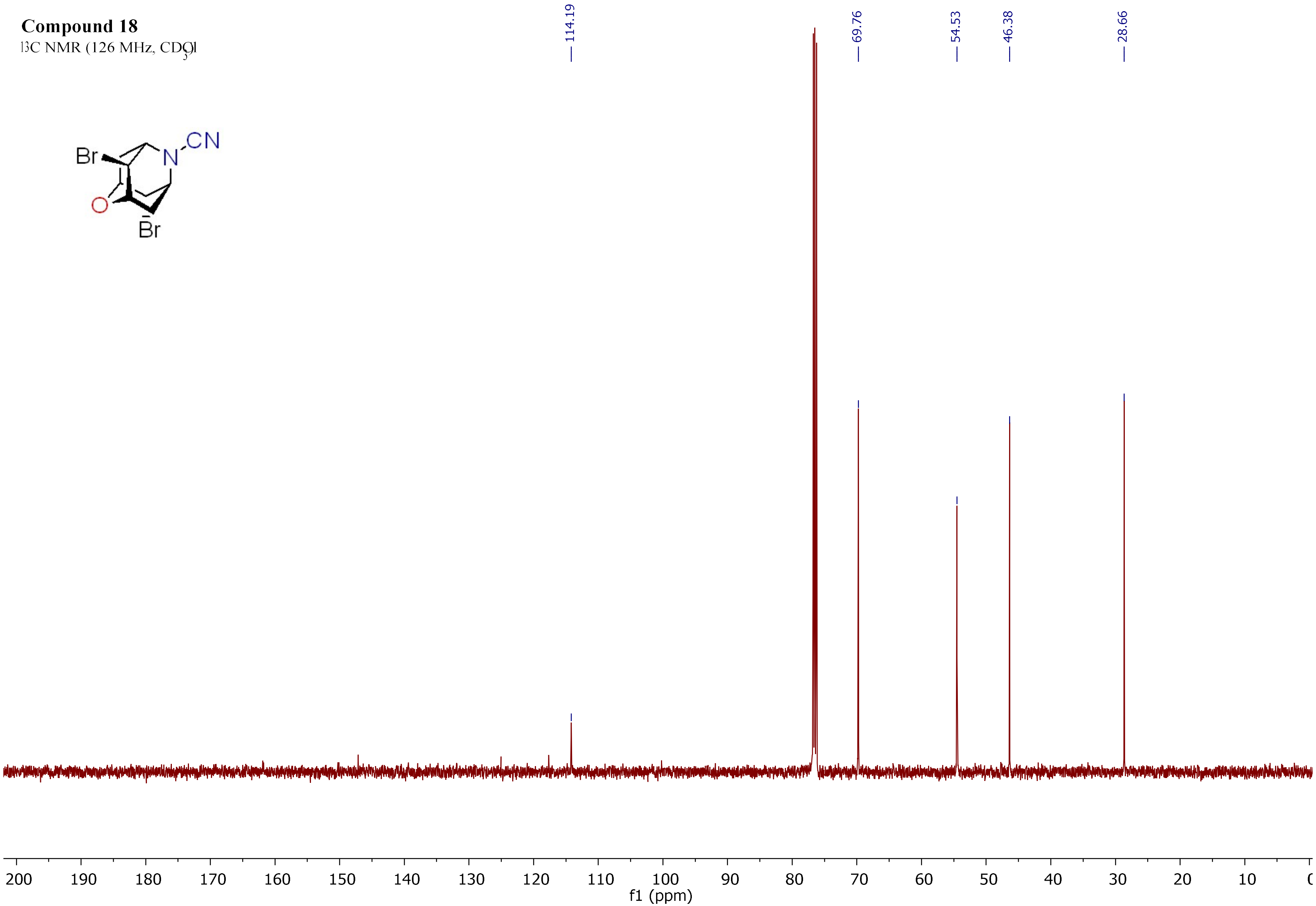
Compound 18

1H NMR (400 MHz, Chloroform-



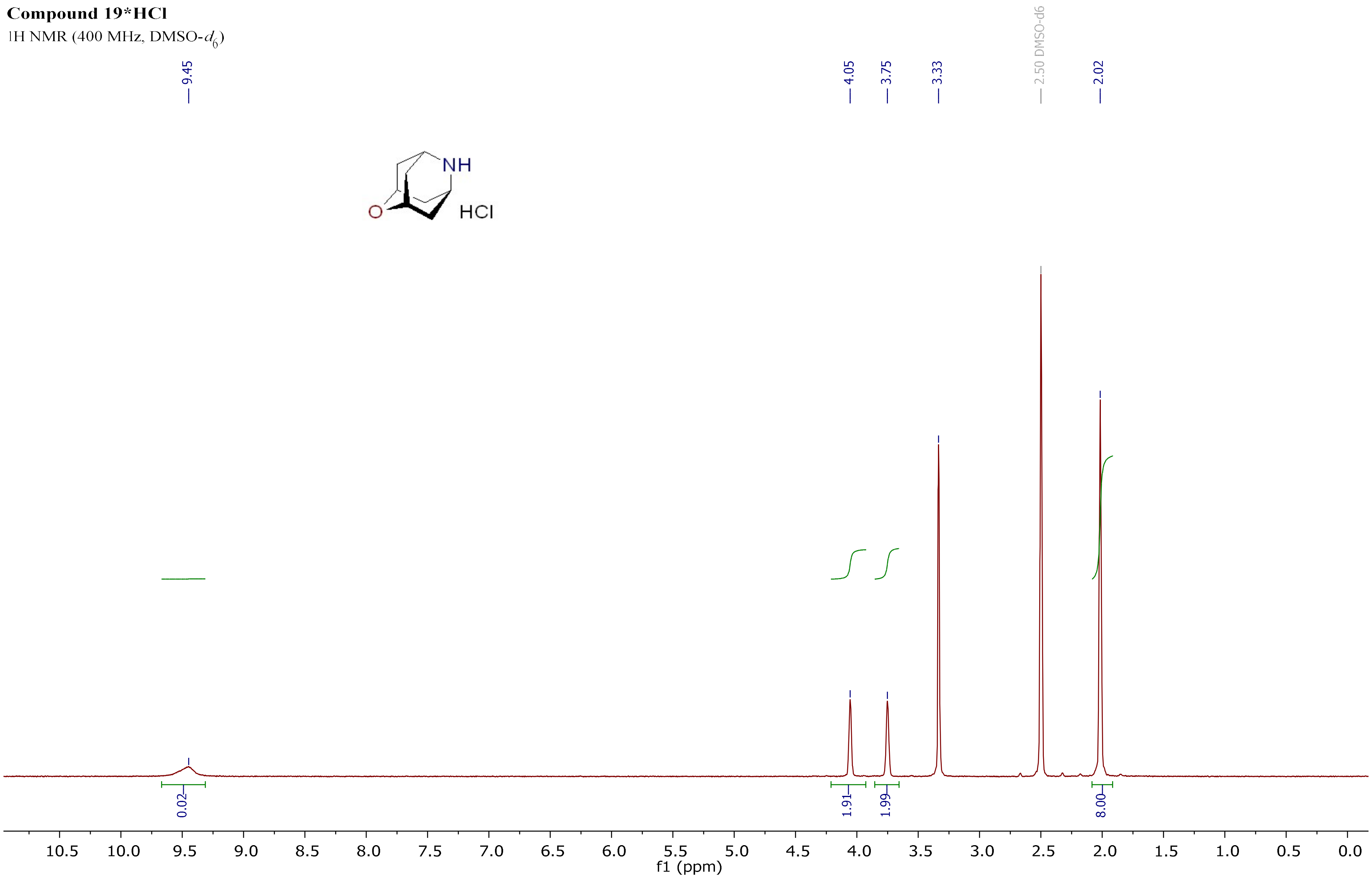
Compound 18

^{13}C NMR (126 MHz, $CDCl_3$)



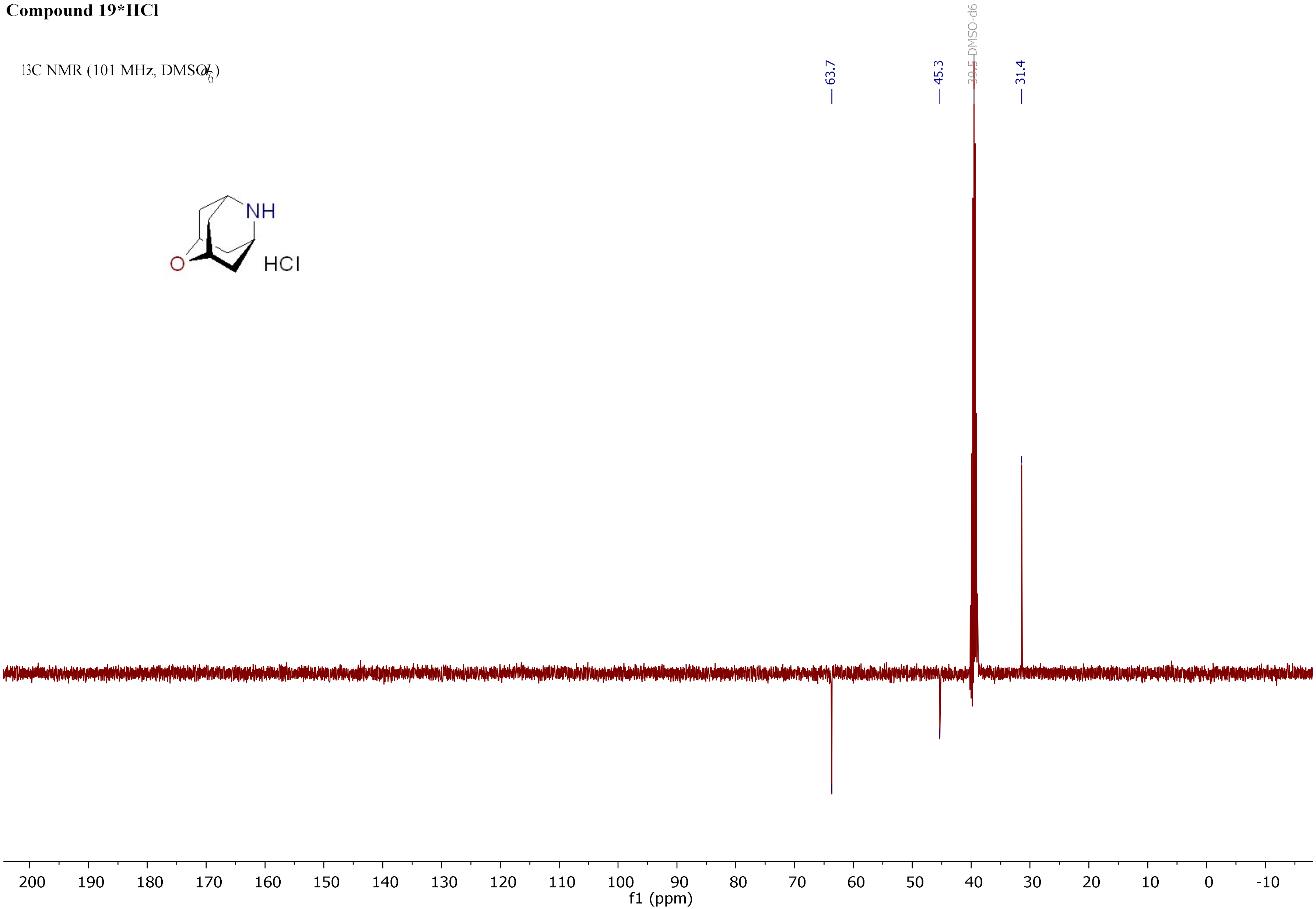
Compound 19*HCl

1H NMR (400 MHz, DMSO-d_6)



Compound 19*HCl

^{13}C NMR (101 MHz, DMSO-d_6)



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2. Cuthbertson, E.; MacNicol, D. D. Novel formation of the 2,6-dioxaadamantane nucleus. *Tetrahedron Lett.* **1974**, *15* (27), 2367-2368.
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