Realisation of Small Molecule Libraries based on Frameworks Distantly Related to Natural Products

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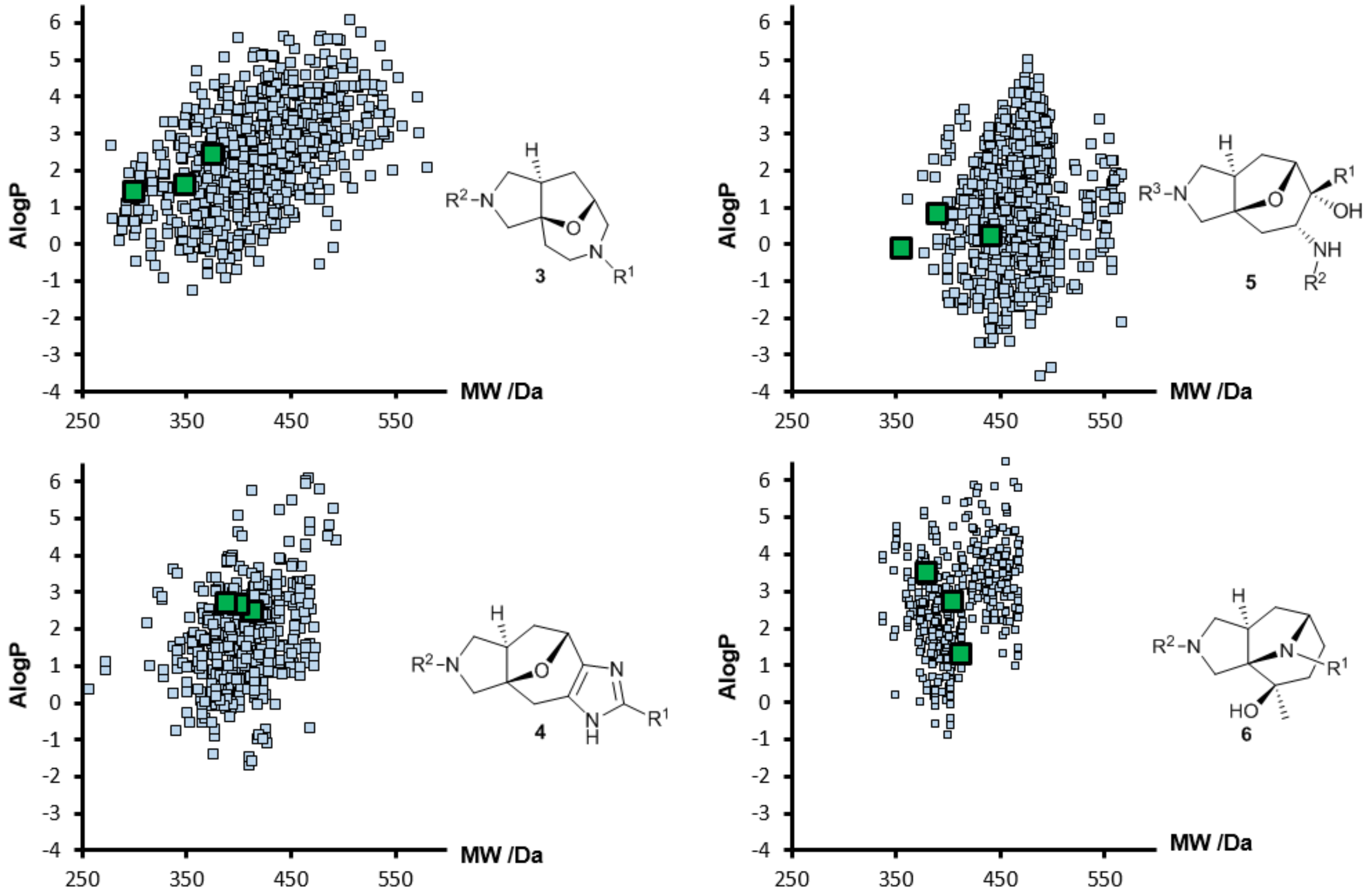
Supplementary Information

Contents:

1.0 Computational analysis of the compound libraries



Molecular properties analysis of the compound libraries produced (pale blue squares) and exemplar compounds described in this paper (large, green squares).

- Scaffold **3**: 751 compounds, 87% of attempted decorations were successful.
- Scaffold **4**: 594 compounds, 94% of attempted decorations were successful.
- Scaffold **5**: 1082 compounds, 88% of attempted decorations were successful.
- Scaffold **6**: 476 compounds, 76% of attempted decorations were successful.

The molecular properties for the library compounds were calculated using Datawarrior (open access: http://www.openmolecules.org/datawarrior). The molecular properties of the exemplar compounds prepared in this paper were calculated using the LLAMA webtool.[1]

1.0 Experimental

1.1 General experimental

All non-aqueous reactions were performed under an atmosphere of nitrogen unless otherwise stated. Water-sensitive reactions were performed in oven-dried glassware, cooled under nitrogen before use. THF, CH_2Cl_2, PhMe and MeCN were dried and purified by means of a Pure Solv MD solvent purification system (Innovative Technology Inc.). Anhydrous DMA and DMF were obtained in SureSeal bottles from Sigma-Aldrich. All other solvents used were of chromatography or analytical grade. Petrol refers to petroleum spirit (b.p. 40-60 °C). Commercially available starting materials were obtained from Sigma-Aldrich, Fluka, Acros, Alfa Aesar or Fluorochem and were used without purification.

Thin layer chromatography (TLC) was carried out on aluminium backed silica plates (Merck silica gel 60 F254). Visualisation of the plates was achieved using an ultraviolet lamp (λ_{max} = 254 nm) and $KMnO_4$. Flash chromatography was carried out using silica gel 60 (60-63 μm particles) supplied by Merck. Strong cation exchange solid phase extraction (SCX SPE) was carried out using pre-packed Discovery DSC-SCX cartridges supplied by Supelco, see the general procedure, below.

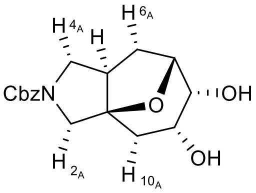
Melting points were measured on a Reichert hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Bruker Alpha Platinum-ATR, with absorption reported in wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were recorded on a Bruker MaXis Impact spectrometer with electrospray ionisation (ESI) source. Low resolution mass spectra (LRMS) were recorded by HP-LCMS, which was generally carried out on an Agilent 1200 series LC system comprising a Bruker HCT Ultra ion trap mass spectrometer. The solvent system used was CH_3CN/H_2O + 0.1% formic acid with a Phenomenex Luna C18 50 × 2 mm 5 micron column. Mass-directed HPLC purification was carried out using an Agilent 1260 Infinity HPLC system comprising an Agilent 6120 Quadrupole LC/MS and Agilent G1968D active splitter. A Genevac EZ-2 Elite centrifugal evaporator was used for the removal of MeOH–H_2O or MeCN–H_2O after mass-directed purification.

Proton (^1H) and carbon (^{13}C) NMR spectral data were collected on Bruker Advance 500, Bruker DPX500, Bruker Advance 400 and Bruker DPX300 spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the residual solvent peak. Coupling constants (*J*) are quoted in Hertz (Hz) and splitting patterns reported in an abbreviated manner: app. (apparent), br. (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). All fully characterised products were assigned with the aid of COSY, DEPT-135 and HMQC experiments. Where stated NOESY experiments were also used to aid assignments. Compounds are numbered with respect to their IUPAC names. Where necessary, coloured text was used to distinguish similar protons and carbons (e.g. for major and minor diastereomers). Diastereomeric ratios were calculated by integration of the

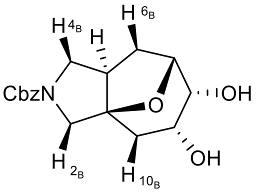
^{1}H NMR spectra. Diastereomers were assigned through the interpretation of coupling constants, NOESY spectra, and by small molecule crystallographic studies. Small molecule X-ray crystallography studies were performed by Dr Christopher Pask.

A note regarding NMR assignments

Where compounds have been assigned through analysis of the corresponding NOESY spectrum, protons labelled ‘A’ are on the ‘bottom’ face of the molecules (as drawn), while protons labelled ‘B’ are on the ‘top’ face of the molecules (as drawn), see compound **18** below as an example.



18
'A' protons



18
'B' protons

Where the polycyclic assemblies **were not** assigned using NOESY the ‘A’ and ‘B’ descriptors are reported through analysis of the coupling constants or otherwise arbitrarily.

1.2 General procedures

General procedure A: Strong cation exchange solid phase extraction (SCX SPE)

TfOH (0.5 M in MeOH, 10 mL / 5 g SCX SPE) was dripped through the SCX SPE cartridge prior to use. MeOH (20 mL) was then flushed through using pressurised air. The crude residue was loaded (3.5 mmol / 5 g SCX SPE silica) in the minimum amount of MeOH. The cartridge was flushed with MeOH and the fractions were collected and monitored by TLC. The cartridge was then flushed with sat. NH_3/MeOH and the fractions were collected and monitored by TLC. Fractions containing product were combined and concentrated.

General Procedure B: Hydrogenation using Pd/C

The substrate (1.0 eq.) was dissolved in MeOH or EtOH (~20 mL g^{-1}) and added *via* syringe to a round-bottomed flask containing 10 wt% Pd/C (% w/w as specified) which was pre-submerged in minimal EtOH under N_2. If required, conc. HCl (~12 M) was added as specified. The head-space of the flask was subjected to a sequence of vacuum/H_2 flushes (×3), then exposed to an atmosphere of H_2 (balloon). The reaction was monitored by TLC until complete (generally reactions were complete in ≤18 h). At this point the balloon was removed and the reaction mixture was purged with

N_2 (with a gas outlet) for 5 minutes. The reaction mixture was filtered through Celite® eluting with MeOH, then concentrated *in vacuo*. The product was typically used in the next step without further purification.

General Procedure C: Amide formation

TBTU (1.6 eq.) was added to a stirred solution of the appropriate carboxylic acid (1.5 eq.), amine (1.0 eq.) and DIPEA (2.5 eq.) in DMA (0.13 M). The reaction mixture was stirred at rt for 24 h, then H_2O (0.1 volumes) was added. Reaction mixtures were purified by mass-directed preparative HPLC.

General procedure D: Reductive amination

The appropriate aldehyde or ketone (2.5 eq.) was added to a stirred solution of amine (1.0 eq.) and AcOH (2.0 eq.) in DMA (0.13 M). $NaBH(OAc)_3$ (3.0 eq.) was added and the reaction mixture was heated to 60 ˚C and stirred for 24 h. The reaction mixture was cooled to rt then H_2O (0.1 volumes) was added. Reaction mixtures were purified by mass-directed preparative HPLC.

General procedure E: Sulfonamide formation

RSO_2Cl (3.0 eq.) was added to a mixture of amine (1.0 eq.) and $NaHCO_3$ (6.0 eq.) in DMA (0.13 M). The reaction mixture was stirred at rt for 2.5 h, then H_2O (0.1 volumes) was added. Reaction mixtures were purified by mass-directed preparative HPLC.

General procedure F: Urea formation

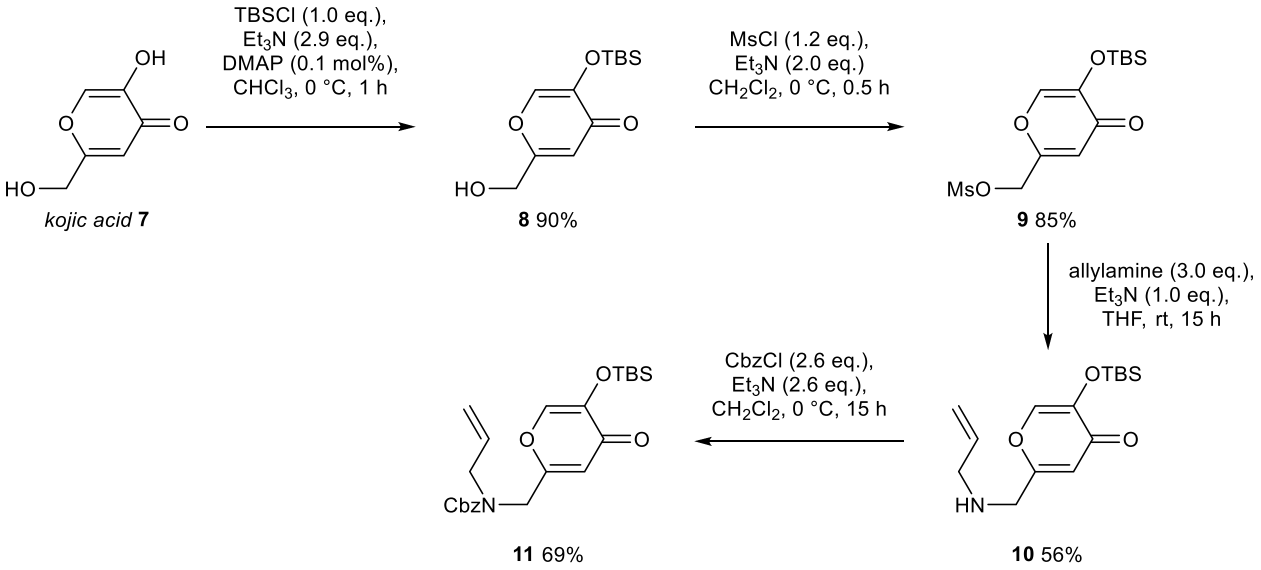
The appropriate isocyanate (2.0 eq.) was added to a mixture of amine (1.0 eq.) and $NaHCO_3$ (6.0 eq.) in DMA (0.13 M). The reaction mixture was stirred at rt for 16 h, then H_2O (0.1 volumes) was added. Reaction mixtures were purified by mass-directed preparative HPLC.

1.3 Compound data

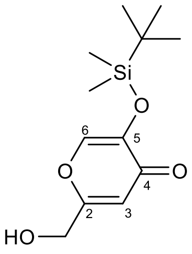
1.3.1 Preparation of cycloaddition precursors and cycloadducts

1.3.1.1 Preparation of *O*-bridged cycloadduct 1

1.3.1.1.1 Preparation of each intermediate in the synthesis of cycloaddition precursor 11



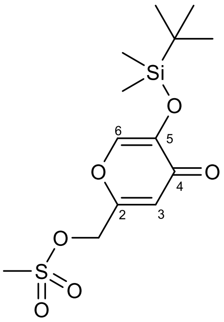
5-[(*tert*-Butyldimethylsilyl)oxy]-2-(hydroxymethyl)-4H-pyran-4-one 8



8

Following a procedure by Miyazaki,[2] TBSCl (5.3 g, 35 mmol, 1.0 eq.) was added to a stirred suspension of kojic acid **7** (5.0 g, 35 mmol, 1.0 eq.), Et_3N (7.4 mL, 100 mmol, 2.90 eq.) and DMAP (5 mg, 0.04 mmol, 0.001 eq.) in $CHCl_3$ (50 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1 h then aqueous $KHSO_4$ (5 wt%, 50 mL) was added. The phases were separated and the organic phase was washed with brine (50 mL), dried, filtered, and concentrated *in vacuo*. Flash chromatography eluting with 1:1 pentane–EtOAc gave the title compound **8** (8.1 g, 32 mmol, 90%) as a colourless amorphous solid.* **R_f** 0.57 (1:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.65 (1H, s, 6-H), 6.47 (1H, s, 3-H), 4.46 (2H, d, J 6.3, CH_2OH), 3.13 (1H, t, J 6.3, O*H*), 0.95 (9H, s, $SiC(CH_3)_3$), 0.21 (6H, s, 2 × $SiCH_3$). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.1 (4-C), 166.6 (2-C), 144.6 (5-C), 144.2 (6-C), 112.4 (3-C), 61.1 (CH_2OH), 25.8 ($SiC(CH_3)_3$), 18.7 (SiC_q), −4.4 (2 × $SiCH_3$). **IR** ν_{max}(film)/cm^{-1} 3358 (br., OH), 2954, 2857, 1651 (CO), 1629, 1268, 1211, 874. **LRMS** (HPLC-MS): $C_{12}H_{21}O_4Si$; found 257.1 $[M+H]^+$. Spectral data are consistent with the literature values.[S8]

{5-[(*tert*-Butyldimethylsilyl)oxy]-4-oxo-4H-pyran-2-yl}methyl methanesulfonate 9



9

Et_3N (3.30 mL, 23.4 mmol, 2.00 eq.) was added to a stirred solution of compound **8** (3.00 g, 11.7 mmol, 1.00 eq.) in CH_2Cl_2 (24 mL). The reaction mixture was cooled to 0 °C, then methanesulfonyl chloride (1.1 mL, 14 mmol, 1.2 eq.) was added dropwise. The reaction mixture was stirred at 0 °C for 0.5 h, then warmed to rt and partitioned with H_2O (25 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the title compound **9** (3.31 g, 9.89 mmol, 85% mass recovery) which was used subsequently without further purification. **R_f** 0.62 (1:1 petrol–EtOAc). **^{1}H NMR** (300 MHz, $CDCl_3$, characteristic peaks): δ 7.69 (1H, s, 6-H), 6.48 (1H, s, 3-H), 4.97 (2H, s, CH_2), 3.11 (3H, s, SO_2CH_3), 0.95 (9H, s, $SiC(CH_3)_3$), 0.23 (6H, s, 2 × $SiCH_3$).

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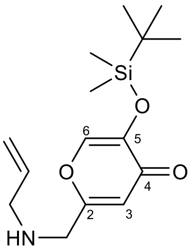
*Compound **8** and related silylated pyranone derivatives **9-11** slowly decomposed on standing in air or in mildly acidic solvents (e.g. $CDCl_3$). Compounds of this type should be stored in a freezer at −18 °C. N.b. derived cycloadduct **1** was bench stable at rt for several weeks.

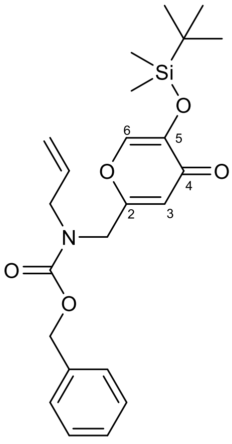
5-[(*tert*-Butyldimethylsilyl)oxy]-2-{[(prop-2-en-1-yl)amino]methyl}-4*H*-pyran-4-one 10



10

Et$_3$N (3.5 mL, 35 mmol, 1.0 eq.) was added to a stirred solution of compound **9** (11.8 g, 35 mmol, 1.0 eq.) in THF (120 mL). Allylamine (8.0 mL, 106 mmol, 3.0 eq.) was added and the reaction mixture was stirred for 15 h, then concentrated *in vacuo*. The resulting residue was diluted in EtOAc (50 mL) and washed with sat. aq. NaHCO$_3$ solution (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (50 mL). The combined organics were washed with brine (50 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was washed through a pad of silica with 9:1 EtOAc–MeOH to give the title compound **10** (5.9 g, 20 mmol, 56%) as a dark brown oil. **R$_f$** 0.57 (1:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, CDCl$_3$): δ 7.64 (1H, s, 6-H), 6.36 (1H, s, 3-H), 5.86 (1H, ddt, *J* 16.8, 10.3, 6.0, C*H*=CH$_2$), 5.20 (1H, app. dq, *J* 16.8, 1.4, CH=CH_AH$_B$), 5.14 (1H, ddd, *J* 10.3, 2.7, 1.4, C*H*=CH$_A$$H_B$), 3.62 (2H, s, C$_qCH_2$NH), 3.27 (2H, dt, *J* 6.0, 1.4, NHCH_2CH=CH$_2$), 0.96 (9H, s, SiC(CH$_3$)$_3$), 0.23 (6H, s, 2 × SiCH$_3$). **^{13}C NMR** (125 MHz, CDCl$_3$): δ 175.7 (4-C), 165.7 (2-C), 145.5 (5-C), 144.2 (6-C), 135.9 (*C*H=CH$_2$), 117.1 (CH=*C*H$_2$), 113.7 (3-C), 51.5 (*C*H$_2$CH=CH$_2$), 49.8 (C$_q$CH$_2$NH), 25.8 (SiC(*C*H$_3$)$_3$), 18.7 (SiC$_q$), −4.3 (2 × SiCH$_3$). **IR** ν_{max}(film)/cm^{-1} 2954, 2930, 2857, 1651 (CO), 1232, 919, 879, 786. **LRMS** (HPLC-MS): C$_{15}$H$_{25}$NO$_3$Si; found 296.1 [M+H]$^+$.

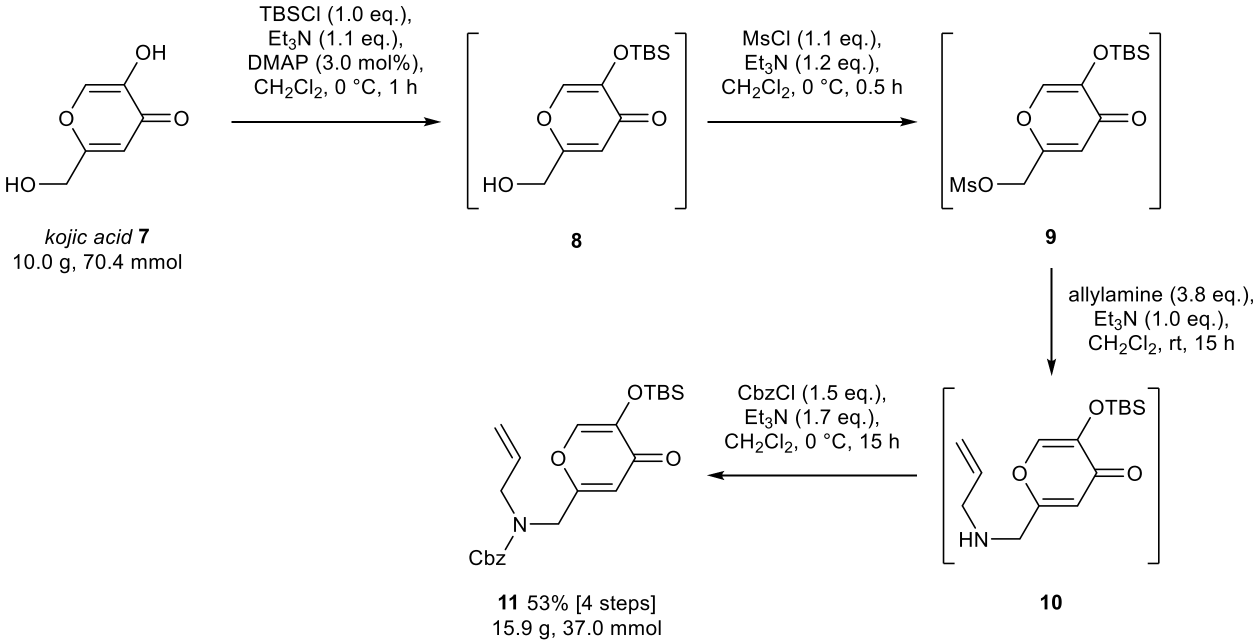
Benzyl *N*-({5-[(*tert*-butyldimethylsilyl)oxy]-4-oxo-4*H*-pyran-2-yl}methyl)-*N*- (prop-2-en-1-yl)carbamate 11



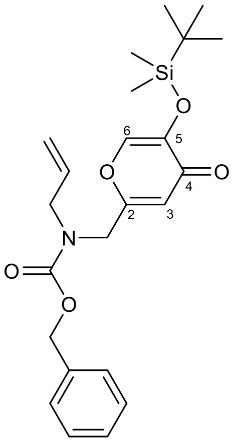
11

Benzyl chloroformate (180 µL, 1.28 mmol, 2.6 eq.) was added to a stirred solution of compound **10** (145 mg, 0.49 mmol, 1.0 eq.) and Et$_3$N (180 µL, 1.28 mmol, 2.6 eq.) in CH$_2$Cl$_2$ (5.0 mL) at 0 °C. The reaction mixture warmed to rt and stirred for 15 h, then concentrated *in vacuo*. Flash chromatography eluting with 9:1 EtOAc–MeOH gave the title compound **11** (145 mg, 0.34 mmol, 69%) as a pale yellow oil. **R$_f$** 0.82 (1:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, CDCl$_3$, 330 K): δ 7.56 (1H, s, 6-H), 7.39-7.27 (5H, m, Cbz Ar-H), 6.23 (1H, s, 3-H), 5.81-5.70 (1H, m, C*H*=CH$_2$), 5.21-5.10 (4H, m, CH=CH_2 and OCH_2Ph), 4.26 (2H, s, C$_q$CH$_2$N), 3.96 (2H, s, NCH_2CH=CH$_2$), 0.97 (9H, s, SiC(CH$_3$)$_3$), 0.24 (6H, s, 2 × SiCH$_3$). **^{13}C NMR** (125 MHz, CDCl$_3$, 330 K): δ 175.3 (4-C), 163.3 (2-C), 156.1 (N(CO)O), 145.8 (5-C), 144.0 (6-C), 136.5 (*C*H=CH$_2$), 132.9 (Ar-C$_q$), 128.7 (Ar-C), 128.4 (Ar-C), 128.2 (Ar-C), 118.2 (CH=*C*H$_2$), 113.7 (3-C), 65.6 (O*C*H$_2$Ph), 50.3 (*C*H$_2$CH=CH$_2$), 47.6 (C$_q$*C*H$_2$NH), 25.8 (SiC(*C*H$_3$)$_3$), 18.7 (SiC$_q$), −4.3 (2 × SiCH$_3$). **IR** ν_{max}(film)/cm^{-1} 2953, 2929, 2857, 1702 (CO), 1649, 1460, 1410, 1210. **HRMS** (ESI): C$_{23}$H$_{32}$NO$_5$Si [M+H]$^+$; calculated 430.2058, found 430.2044.

1.3.1.1.2 Telescoped synthesis of cycloaddition precursor 11



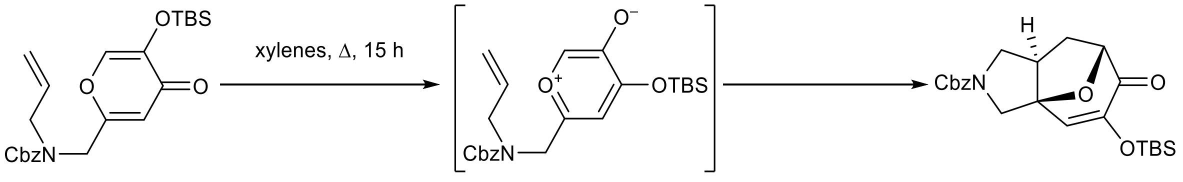
Benzyl *N*-({5-[(*tert*-butyldimethylsilyl)oxy]-4-oxo-4*H*-pyran-2-yl}methyl)-*N*- (prop-2-en-1-yl)carbamate 11



11

TBSCl (10.7 g, 71.0 mmol, 1.01 eq.) was added to a stirred solution of kojic acid **7** (10.0 g, 70.4 mmol, 1.00 eq.), Et_3N (10.8 mL, 77.9 mmol, 1.10 eq.) and DMAP (258 mg, 2.11 mmol, 0.03 eq.) in CH_2Cl_2 (150 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 45 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution (100 mL) and H_2O (100 mL). After separation, the aqueous phase was extracted with CH_2Cl_2 (2 × 150 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. To the residue **8** (70.4 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added Et_3N (12.0 mL, 86.5 mmol, 1.23 eq.) and methanesulfonyl chloride (6.0 mL, 78 mmol, 1.1 eq.) dropwise. The reaction mixture was warmed to rt and stirred for 0.5 h, then quenched with water (150 mL). After phase separation, the aqueous phase was extracted using CH_2Cl_2 (2 × 150 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. To the residue **9** (70.4 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added Et_3N (10.0 mL, 72.0 mmol, 1.02 eq.) and allylamine (3.80 eq.). The reaction mixture warmed to rt, stirred for 15 h, then quenched with H_2O (150 mL). After phase separation, the aqueous phase was extracted using CH_2Cl_2 (2 × 150 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. To the residue **10** (70.4 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added Et_3N (17.0 mL, 121 mmol, [1.72 eq.]) followed by the very slow addition (*gas outlet necessary!*) of benzyl chloroformate (15.0 mL, 106 mmol, 1.50 eq.). The reaction mixture warmed to rt and stirred 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (150 mL) and H_2O (150 mL). After phase separation, the aqueous phase was extracted with CH_2Cl_2 (2 × 150 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography eluting with 9:1 to 8:2 pentane–EtOAc gave the title compound **11** (15.9 g, 37.0 mmol, 53%, 4 steps) as a pale yellow oil (see above for spectral data).

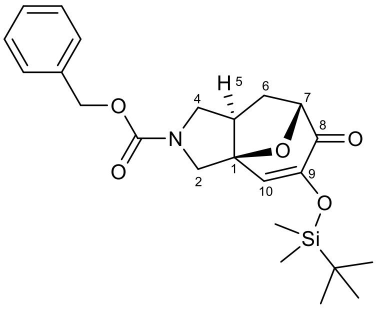
1.3.1.1.3 Preparation of *O*-bridged cycloadduct 1



11
[15.9 g, 37.0 mmol]

1 87%
[13.8 g, 32.1 mmol]

Benzyl (*1R,*5S**,*7S**)-9-[(tert-butyldimethylsilyl)oxy]-8-oxo-11-oxa-3-zatricyclo[5.3.1.$0^{1,5}$]undec-9-ene-3-carboxylate 1**



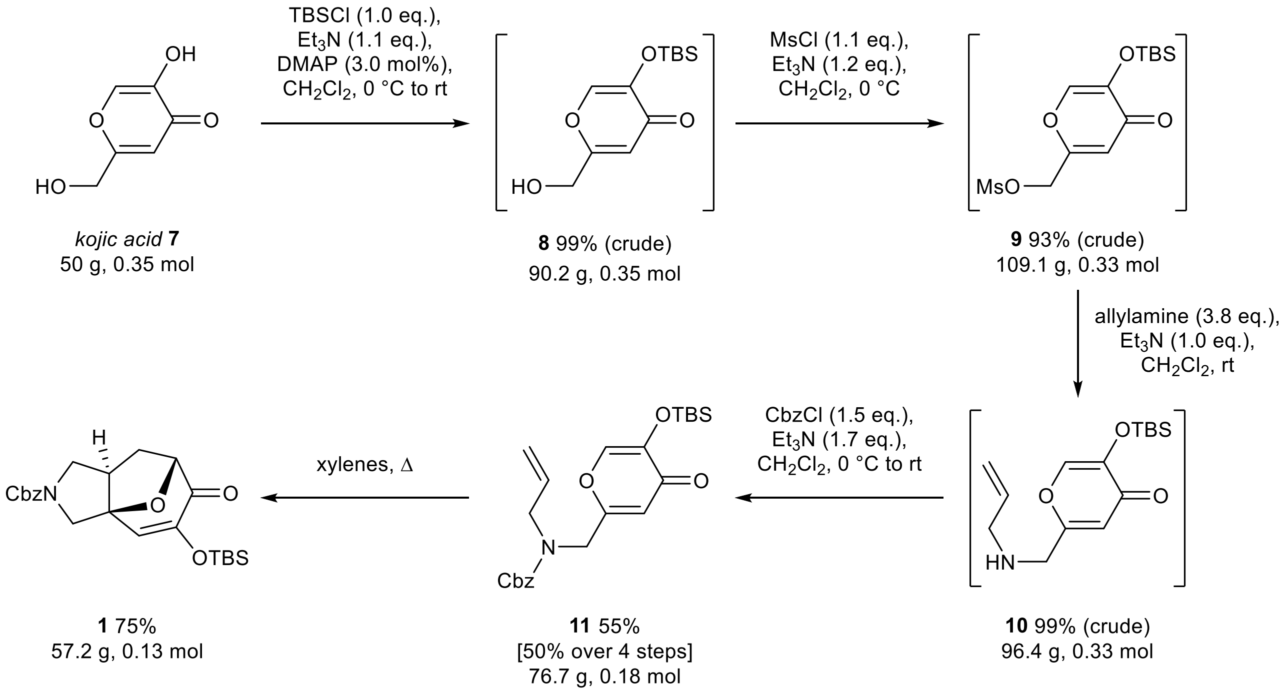
1

A stirred solution of compound **11** (15.9 g, 37.0 mmol) in xylenes (36 mL) was heated at reflux (155 °C) for 15 h. The reaction mixture was cooled to rt then concentrated *in vacuo*. Flash chromatography eluting with 9:1 to 8:2 pentane–EtOAc gave the title compound **1** (13.8 g, 32.1 mmol, 87%) as a colourless amorphous solid.[†] **M.p.** 96-98 °C, colourless plates, hexane–EtOAc. **R*f*** 0.18 (4:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$, 50:50 mixture of rotamers): δ 7.41-7.29 (5H, m, Cbz Ar-H), 6.29 (0.5H, s, 10-H), 6.26 (0.5H, s, 10-H), 5.15 (1H, app. d, *J* 12.0, $\mathrm{OC}\mathit{H}_{\mathrm{A}}\mathrm{H}_{\mathrm{B}}\mathrm{Ph}$), 5.12 (1H, app. d, *J* 12.0, $\mathrm{OCH}_{\mathrm{A}}\mathit{H}_{\mathrm{B}}\mathrm{Ph}$), 4.78 (1H, d, *J* 8.2, 7-H), 4.04-3.90 (2H, m, 2-H_B and 4-H_A), 3.68 (0.5H, d, *J* 12.8, 2-H_A), 3.64 (0.5H, d, *J* 12.8, 2-H_A), 3.22-3.13 (1H, m, 4-H_B), 2.84-2.74 (1H, m, 5-H), 2.34-2.21 (1H, m, 6-H_B), 1.89 (1H, app. td, *J* 13.2, 8.2, 6-H_A), 0.94 (4H, s, $SiC(CH_3)_3$), 0.93 (5H, s, $SiC(CH_3)_3$), 0.16 (6H, m, 2 × $SiCH_3$). **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of two rotamers): δ 193.7 (8-C), 154.5 (N(CO)O), 154.3 (N(CO)O), 148.1 (9-C), 136.8 (Ar-C_q), 138.7 (Ar 1-C), 128.7 (Ar-C), 128.3 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 127.3 (10-C), 127.2 (10-C), 90.6 (1-C), 89.8 (1-C), 83.4 (7-C), 67.2 ($\mathrm{O}\mathit{C}\mathrm{H_2Ph}$), 53.9 (2-C or 4-C), 53.5 (2-C or 4-C), 53.1 (2-C or 4-C), 52.7 (2-C or 4-C), 47.1 (5-C), 46.2 (5-C), 31.6 (6-C), 31.5 (6-C), 25.7 ($\mathrm{SiC(}\mathit{C}\mathrm{H_3)_3}$), 18.6 ($SiC_q$), −4.5 (2 × $SiCH_3$) [28 of 36 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1} 2954, 2953, 1703 (CO), 1652, 1419, 1347, 1163, 919. **HRMS** (ESI): $C_{23}H_{32}NO_5Si$ $[M+H]^+$; calculated 430.2044, found 430.2048. **X-ray crystallography**: CCDC 1526777 contains the supplementary crystallographic data for this compound. Crystals were grown by slow evaporation from diethyl ether.

[†] Compound **1** was stable for several months when stored in a freezer at −18 °C.

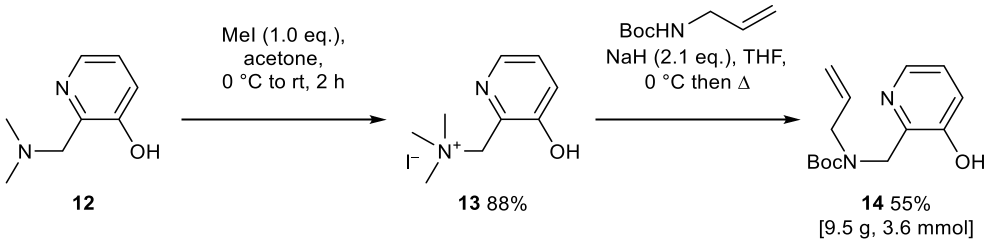
1.3.1.1.4 Scaled-up synthesis of *O*-bridged cycloadduct 1

The route to compound **1** outlined above in Sections 1.3.1.1.2 and 1.3.1.1.3 was followed starting with 50 g (0.35 mol) kojic acid **7** to prepare 57.2 g (0.13 mmol, 38% overall yield) cycloadduct **1**.

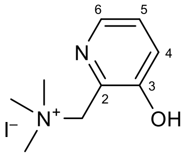


1.3.1.2 Preparation of *N*-bridged cycloadduct 2

1.3.1.2.1 Preparation of precursors to *N*-bridged cycloadduct 2



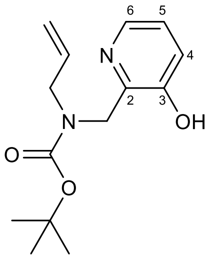
[(3-Hydroxypyridin-2-yl)methyl]trimethylazanium iodide 13



13

Methyl iodide (8.40 mL, 132 mmol, 1.00 eq.) was added to stirred solution of 2-(dimethylaminomethyl)-3-hydroxypyridine **12** (20.1 g, 132 mmol, 1.00 eq.) in acetone (66 mL) at 0 °C. The resulting mixture was warmed to rt and stirred for 2 h, during which time a pale yellow precipitate formed. The solid was collected by filtration to give the title compound **13** (34.1 g, 115.9, 88%) as a pale yellow solid. **M.p.** Decomposition observed above 164 °C. **^{1}H NMR** (D_2O, 400 MHz): 8.21 (1H, dd, *J* 3.9, 2.1, 5-H), 7.56-7.47 (2H, m, 4-H and 6-H), 4.61 (2H, s, CH_2Ar), 3.21 (9H, s, $N^+(CH_3)_3$). **^{13}C NMR** (D_2O, 100 MHz): 154.3, 141.1, 134.7, 127.6, 125.7, 64.5, 53.2. **IR** ν_{max}(film)/cm^{-1} 3381, 1629, 1583, 1484, 1462, 1300. **HRMS** (ESI): $C_9H_{15}N_2O$ $[M]^+$; calculated 167.1184, found 167.1186.

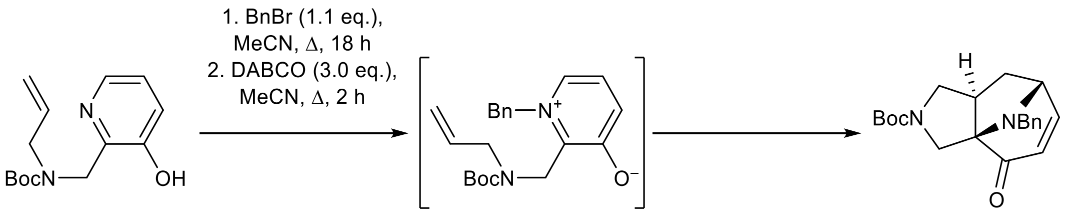
tert-Butyl *N*-[(3-hydroxypyridin-2-yl)methyl]-*N*-(prop-2-en-1-yl)carbamate 14



14

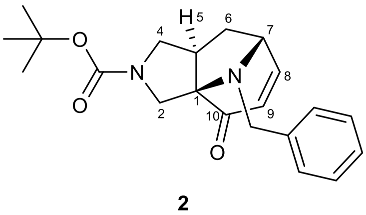
N-Boc-allylamine (10.2 g, 65.1 mmol, 1.00 eq.) was added to a stirred suspension of NaH (60% dispersion in mineral oil, 5.47 g, 137 mmol, 2.10 eq.) in THF (280 mL) at 0 °C. The resulting suspension was stirred at rt for 2 h. After this time, the suspension was cooled to 0 °C and compound **13** (21.1 g, 71.6 mmol, 1.10 eq.) was added in one portion. The suspension was stirred at reflux for 2 h, then cooled to rt and quenched with sat. aq. NH_4Cl solution (100 mL). EtOAc (100 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to deliver a crude brown oil. Flash chromatography eluting with (4:5:1 petrol–CH_2Cl_2–EtOAc) gave the title compound **14** (9.47 g, 35.8 mmol, 55%) as a colourless solid. **^{1}H NMR** (MeOD-d_4, 500 MHz, 333 K): 7.87 (1H, dd, *J* 4.4, 1.7, 6-H), 7.08 (1H, dd, *J* 8.1, 1.6, 4-H), 7.05 (1H, dd, *J* 8.1, 4.4, 5-H), 5.67 (1H, ddt, *J* 17.0, 10.4, 5.6, C*H*=CH_2), 4.98 (1H, app. dq, *J* 17.0, 1.7, CH=CH_AH_B), 4.96 (1H, app dq, *J* 10.4, 1.5, CH=CH_AH_B), 4.37 (2H, s, CH_2Ar), 3.80 (2H, d, *J* 5.6, NCH_2CH=CH_2), 1.33 (9H, s, $C_q(CH_3)_3$). **^{13}C NMR** (MeOD-d_4, 125 MHz, 333 K): 158.3, 153.7, 146.0, 140.6, 134.9, 124.9, 124.3, 116.7, 81.7, 50.9, 48.7, 28.7. **IR** ν_{max}(film)/cm^{-1} 3271, 1651, 1447, 1414, 1161. **HRMS** (ESI): $C_{14}H_{21}N_2O_3$ [MH]$^+$; calculated 265.1547, found 265.1551.

1.3.1.2.2 Preparation of *N*-bridged cycloadduct 2



14 **15** **2** 65%
[7.42 g, 20.9 mmol]

tert-Butyl (*1R**,*5R**,*7R**)-11-benzyl-10-oxo-3,11-diazatricyclo[5.3.1.0^{1,5}]undec-8-ene-3-carboxylate 2

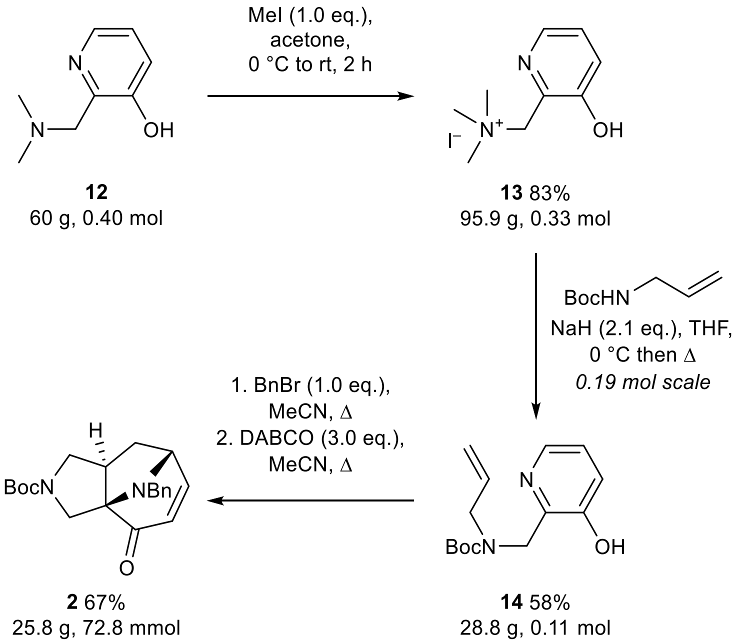


2

Benzyl bromide (4.2 mL, 35.6 mmol, 1.10 eq.) was added to a stirred solution of compound **14** (8.57 g, 32.4 mmol, 1.00 eq.) in MeCN (65 mL). The resulting solution was stirred at reflux for 18 h. After cooling to rt, DABCO (10.9 g, 97.2 mmol, 3.00 eq.) was added in one portion and the resulting suspension was stirred at reflux for 2 h, then cooled to rt. H_2O (200 mL) and CH_2Cl_2 (200 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (200 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography eluting with 4:5:1 petrol–CH_2Cl_2–EtOAc gave the title compound **2** (7.42 g, 20.9 mmol, 65%) as a yellow oil. **^{1}H NMR** (MeOD-d$_4$, 500 MHz, 333 K): 7.21-7.09 (5H, m, Bn Ar-H), 6.95 (1H, dd, *J* 9.8, 4.8, 8-H), 5.99 (1H, d, *J* 9.8, 9-H), 3.98 (1H, d, *J* 12.5, 2-H$_A$), 3.82 (1H, dd, *J* 10.9, 9.2, 4-H$_B$), 3.76-3.69 (1H, m, 7-H), 3.63 (1H, d, *J* 13.7, NC*H*$_A$H$_B$Ph), 3.56 (1H, d, *J* 13.7, NCH$_A$*H*$_B$Ph), 3.31 (1H, dd, *J* 10.9, 7.9, 4-H$_A$), 3.30-3.23 (1H, m, 2-H$_B$), 2.55 (1H, app. qd, *J* 8.5, 4.7, 5-H), 1.93 (1H, dd, *J* 12.1, 8.5, 6-H$_A$), 1.80-1.89 (1H, m, 6-H$_B$), 1.36 (9H, s, $C_q(CH_3)_3$). **^{13}C NMR** (MeOD-d$_4$, 125 MHz, 333 K): 197.3, 156.1, 152.1, 140.3, 129.4, 129.3, 128.2, 127.9, 82.7, 81.1, 61.4, 54.3, 50.4, 47.6, 45.8, 35.3, 28.7. **IR** ν_{max}(film)/cm^{-1} 1681, 1403, 1365, 1167, 1125, 882. **HRMS** (ESI): $C_{21}H_{27}N_2O_3$ [MH]$^+$; calculated 355.2016, found 355.2023.

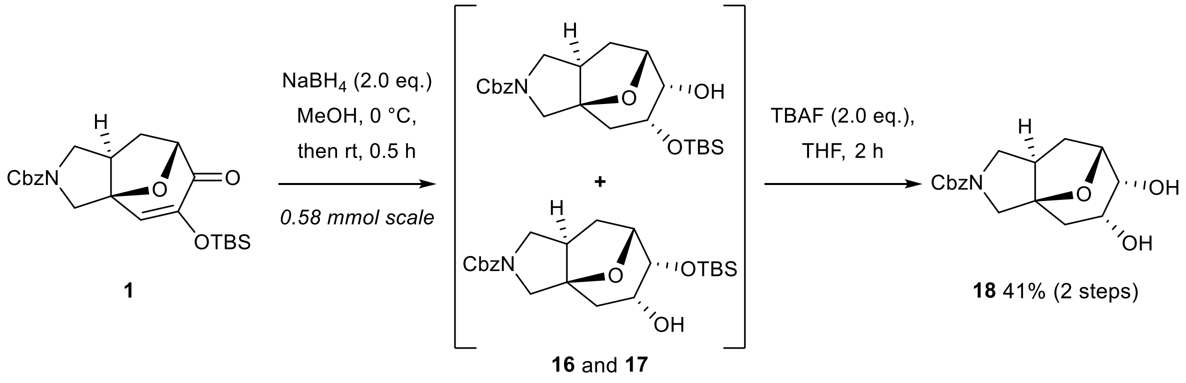
1.3.1.2.3 Scaled-up synthesis of *N*-bridged cycloadduct 2

The route to compound **2** outlined above in Sections 1.3.1.2.1 and 1.3.1.2.2 was followed starting with 60 g (0.35 mol) compound **12** to prepare 25.8 g (72.8 mmol, 32% overall yield) cycloadduct **2**.

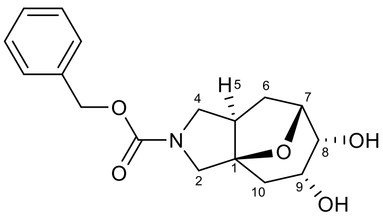


1.3.2 Preparation of scaffolds 3

1.3.2.1 Initial procedure to prepare diol 18



Benzyl (1R*,5R*,7R*,8R*,9R*)-8,9-dihydroxy-11-oxa-3-azatricyclo[5.3.1.$0^{1,5}$]undecane-3-carboxylate 18



18

$NaBH_4$ (44 mg, 1.2 mmol, 2.0 eq.) was added to a stirred solution of compound **1** (250 mg, 0.58 mmol, 1.00 eq.) in MeOH (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h, then H_2O (1.0 mL) was added. The reaction mixture was warmed to rt, then concentrated *in vacuo* to give a 2:3[‡] mixture of TBS-protected diols **16** and **17** as a colourless oil (characteristic ^1H NMR peaks given below). To a stirred solution of the residue in THF (10 mL) was added TBAF (1.0 M in THF, 1.2 mL, 1.2 mmol, 2.0 eq.). The reaction mixture was stirred for 2 h then concentrated *in vacuo*. Flash chromatography eluting with 0-10% MeOH in EtOAc gave a mixture of the title compound with TBAF. Further purification by SCX following general procedure A, eluting with MeOH, gave the title compound **18** (76 mg, 0.24 mmol, 41%) as a colourless oil. **R$_f$** 0.58 (9:1 EtOAc–MeOH). **^{1}H NMR** (500 MHz, $CDCl_3$, 50:50 mixture of rotamers): δ 7.41-7.27 (5H, m, Cbz Ar-H), 5.11 (2H, s, OCH_2Ph), 4.35 (1H, dd, *J* 7.2, 4.8, 7-H), 4.15-4.10 (1H, m, 9-H), 3.93-3.85 (1H, m, 4-H$_A$, includes at δ 3.91: 0.5H, d, *J*, 10.5; and at δ 3.87: 0.5H, d, *J*, 10.5), 3.86-3.80 (1H, m, 8-H), 3.79-3.71 (1H, m, 2-H$_A$, includes at δ 3.76: 0.5H, d, *J*, 12.6; and at δ 3.74: 0.5H, d, *J*, 12.6), 3.41 (0.5H, d, *J* 12.6, 2-H$_B$), 3.36 (0.5H, d, *J* 12.6, 2-H$_B$), 3.24-3.15 (1H, m, 4-H$_B$), 3.08-3.00 (1H, m, 5-H), 2.63 (1H, app. td, *J* 12.7, 8.5, 6-H$_A$), 2.49 (2H, br. s, 2 × OH), 2.19 (0.5H, dd, *J* 14.7, 4.3, 10-H$_B$), 2.13 (0.5H, dd, *J* 14.7, 4.3, 10-H$_B$), 1.97-1.90 (1H, m, 10-H$_A$, includes at δ 1.95: 0.5H, d, *J* 14.7; and at δ 1.93: 0.5H, d, *J* 14.7), 1.78-1.66 (1H, m, 6-H$_B$). **^{13}C NMR** (125 MHz, DMSO-d_6, mixture of two rotamers): δ 153.5 (N(CO)O), 153.4 (N(CO)O), 137.1 (Ar-C$_q$), 128.4 (Ar-C), 127.7 (Ar-C), 127.5 (Ar-C), 88.7 (1-C), 87.7 (1-C), 79.0 (7-C), 68.0 (8-C), 65.9 (9-C), 65.7 (OCH_2Ph), 54.8 (2-C or 4-C), 54.5 (2-C or 4-C), 54.2 (2-C or 4-C), 54.0 (2-C or 4-C), 44.2 (5-C), 43.2 (5-C), 38.0 (10-C), 37.9 (10-C), 32.7 (6-C), 32.6 (6-C) [22 of 30 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1} 3423 (OH), 2948, 2884, 1683 (CO), 1425, 1350, 1149, 1107. **HRMS** (ESI): $C_{17}H_{22}NO_5$ [M+H]$^+$; calculated 320.1495, found 320.1496.

Characteristic **^{1}H NMR** peaks for compounds **16** and **17** (500 MHz, $CDCl_3$, 40:60 mixture of regioisomers): δ 7.38-7.28 (major and minor, 5H, m, Cbz Ar-H), 5.15-5.07 (major and minor, 2H, m, OCH_2Ph), 4.36 (minor, 0.4H, dd, *J* 7.3, 4.6), 4.25-4.20 (major, 0.6H, dd, *J* 6.9, 5.2), 4.13-4.09 (minor, 0.4H, m), 3.98-3.93 (major, 0.6H, m), 3.93-3.86 (major and minor, 1H, m), 3.84-3.79 (major, 0.6H, m), 3.77-3.68 (major and minor, 1.4H, m), 3.44-3.32 (major and minor, 1H, m), 3.24-3.13 (major and minor, 1H, m), 3.09-3.01 (major, 0.6H, m), 2.95-2.86 (minor, 0.4H, m), 2.77 (major, 0.6H, d, *J* 4.5), 2.62 (major, 0.6H, td, *J* 13.2, 8.5), 2.57-2.50 (minor, 0.4H, m), 2.49 (minor, 0.4H, d, *J* 10.6),

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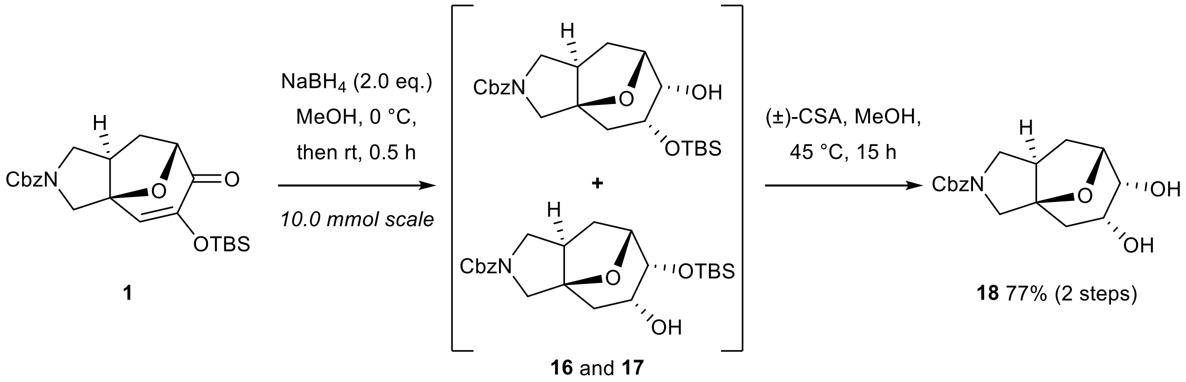
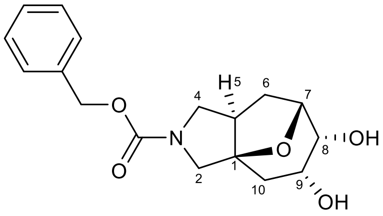
[‡] As judged by analysis of the crude reaction product by ^1H NMR spectroscopy (500 MHz, $CDCl_3$). Identity of the major regioisomer not determined.

2.24-2.10 (major, 0.6H, m), 2.07 (minor, 0.4H, dd, *J* 14.6, 3.7), 1.98 (major, 0.6H, dd, *J* 14.5, 7.9), 1.80 (minor, 0.4H, dd, *J* 14.6, 9.3), 1.76-1.56 (major and minor, 1H, m), 0.94 (minor, 3.6H, s, $SiC(CH_3)_3$), 0.91 (major, 5.4H, s, $SiC(CH_3)_3$), 0.13-0.10 (major and minor, 6H, m, $SiCH_3$)].

1.3.2.2 Optimised synthetic route to prepare diol 18



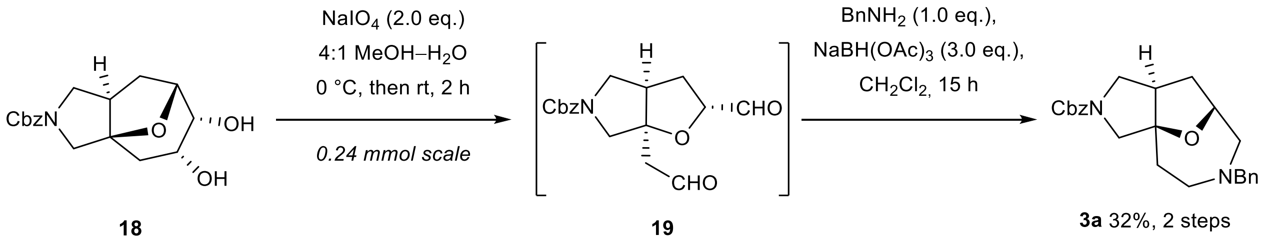
Benzyl (*1R**,*5R**,*7R**,*8R**,*9R**)-8,9-dihydroxy-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecane-3-carboxylate 18



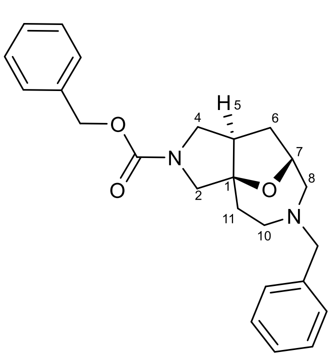
18

$NaBH_4$ (832 mg, 22.0 mmol, 2.20 eq.) was added to a stirred solution of compound **1** (4.30 g, 10.0 mmol, 1.0 eq.) in MeOH (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, warmed to rt, stirred for 0.5 h, then concentrated *in vacuo* to give a 2:3 mixture of TBS-protected diols **16** and **17** as a colourless oil (see above for characteristic ^1H NMR peaks). The residue containing **16** and **17** was diluted in CH_2Cl_2 (50 mL) and washed with 1.0 M HCl (50 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue (10.0 mmol) was dissolved in MeOH (60 mL) and (±)-camphorsulfonic acid (3.02 g, 13.0 mmol, 1.30 eq.) was added. The reaction mixture was heated at 45 °C for 15 h, then concentrated *in vacuo*. The residue was diluted in CH_2Cl_2 (50 mL). Sat. aq. $NaHCO_3$ (50 mL) and H_2O (50 mL) were added and the phases were separated. The aqueous phase was extracted using CH_2Cl_2 (2 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography eluting with 0-10% MeOH in EtOAc gave the title compound **18** (2.45 g, 7.67 mmol, 77%, 2 steps) as a colourless oil (see above for spectral data).

1.3.2.3 Initial route to prepare scaffold 3a



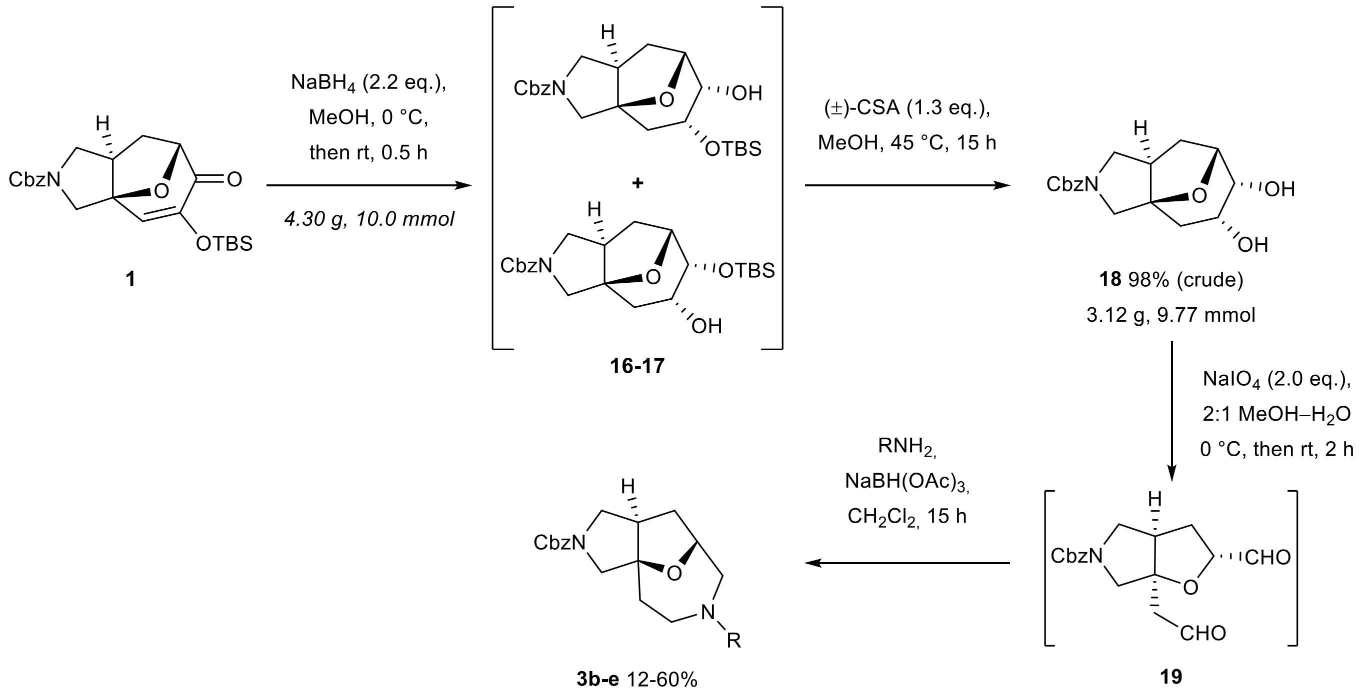
Benzyl (*1R**,*5R**,*7R**)-9-benzyl-12-oxa-3,9-diazatricyclo[5.4.1.$0^{1,5}$]dodecane-3-carboxylate 3a



3a

$NaIO_4$ (105 mg, 0.490 mmol, 2.00 eq.) was added to a stirred solution of compound **18** (78 mg, 0.24 mmol, 1.0 eq.) in 8:2 MeOH–H_2O (10 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for 2 h, then concentrated *in vacuo*. The residue was diluted in CH_2Cl_2 (10 mL) and washed with H_2O (10 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude dialdehyde was dissolved in CH_2Cl_2 (10 mL). $BnNH_2$ (26 µL, 0.25 mmol, 1.0 eq.), $NaBH(OAc)_3$ (153 mg, 0.72 mmol, 3.0 eq.) and 4 Å MS (10 mg) were added. The reaction mixture was stirred for 15 h, then filtered through Celite® and concentrated *in vacuo*. The resulting residue was diluted in EtOAc (25 mL) and washed with brine (25 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography eluting with 0-100% EtOAc in pentane gave the title compound **3a** (30 mg, 76 µmol, 32%, 2 steps) as a colourless oil. **R_f** 0.74 (1:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$, 50:50 mixture of rotamers): δ 7.39-7.21 (10H, m, Ar-H), 5.11 (2H, s, OCH_2Ph), 4.43-4.38 (1H, m, 7-H, includes at δ 4.41: 0.5H, d, *J* 8.1; and at δ 4.40: 0.5H, d, *J* 8.1), 3.89 (1H, d, *J* 12.3, 2-H_A), 3.64-3.53 (3H, includes: 1H, m, 4-H_A; at δ 3.61: 1H, d, *J* 13.3, NC$H_A$$H_B$Ph; and at δ 3.55: 1H, d, *J* 13.3, NC$H_A$$H_B$Ph), 3.52-3.33 (1H, m, 4-H_B), 3.22-3.06 (1H, m, 2-H_B), 2.90-2.80 (1H, m, 5-H), 2.77-2.68 (1H, m, 10-H_A), 2.58-2.44 (2H, includes: 1H, m, 10-H_B; and at δ 2.52: 1H, d, *J* 12.4, 8-H_A), 2.43-2.36 (1H, m, 8-H_B, includes at δ 2.40: 0.5H, d, *J* 12.4; and at δ 2.39: 0.5H, d, *J* 12.4), 2.28-2.21 (1H, m, 6-H_A), 1.92-1.74 (3H, m, 6-H_B and 11-H). **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of two rotamers): δ 155.1 (N(CO)O), 139.9 (Ar-C_q) 137.1 (Ar-C_q), 128.8 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.0 (2 peaks, 2 × Ar-C), 127.2 (Ar-C), 93.2 (1-C), 92.2 (1-C), 80.2 (7-C), 66.9 (OCH_2Ph), 64.3 (NCH_2Ph), 63.6 (8-C), 57.9 (2-C), 57.5 (2-C), 54.0 (4-C), 53.8 (4-C), 53.6 (10-C), 50.1 (5-C), 38.3 (11-C), 36.6 (6-C) [23 of 40 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1} 2930, 2865, 1702 (CO), 1451, 1419, 1360, 1217, 1143. **HRMS** (ESI): $C_{24}H_{29}N_2O_3$ $[M+H]^+$; calculated 393.2173, found 393.2185.

1.3.2.4 Telescoped synthesis of scaffolds 3b-e

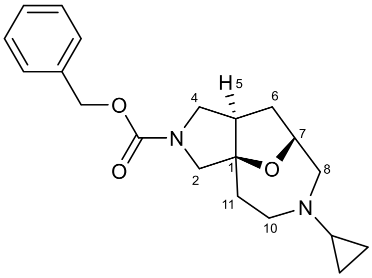


$NaBH_4$ (832 mg, 22.0 mmol, 2.20 eq.) was added to a stirred solution of compound **1** (4.30 g, 10.0 mmol, 1.0 eq.) in MeOH (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, warmed to rt, stirred for 0.5 h, then concentrated *in vacuo*. The residue was diluted in CH_2Cl_2 (50 mL) and washed with 1.0 M HCl (50 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue 10.0 mmol) was dissolved in MeOH (60 mL) and (±)-camphorsulfonic acid (3.02 g, 13.0 mmol, 1.30 eq.) was added. The reaction mixture was heated at 45 °C for 15 h, then concentrated *in vacuo*. The residue was diluted in CH_2Cl_2 (50 mL). Sat. aq. $NaHCO_3$ (50 mL) and H_2O (50 mL) were added and the phases were separated. The aqueous phase was extracted using CH_2Cl_2 (2 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue of compound **18** (3.12 g) was used directly in the next step. $NaIO_4$ (4.28 g, 20.0 mmol, 2.00 eq.) was added to a stirred solution of compound **18** (3.12 g) in MeOH–H_2O (150 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 1.5 h, then concentrated *in vacuo*. The residue was diluted in CH_2Cl_2 (100 mL) and washed with H_2O (100 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue **19** was not purified further and was divided into separate flasks to prepare compounds **3b**-**e** using General Procedure G (see below).

General procedure G: Double reductive amination to give amines 3b-e

The appropriate amine (1.2 eq.) was added to a stirred solution of crude dialdehyde **19** (1.0 eq.) in CH_2Cl_2 (0.1 M). The reaction mixture was stirred for 10 min, then $NaBH(OAc)_3$ (2.6 eq.) was added. The reaction mixture was stirred overnight, then H_2O (1 volume) was added. The phases separated and the aqueous phase was extracted using CH_2Cl_2 (2 × 1 volume). The organic extracts were combined, washed with brine (1 volume), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction products were purified by flash column chromatography.

Benzyl (*1R**,*5R**,*7S**)-9-cyclopropyl-12-oxa-3,9-diazatricyclo[5.4.1.0^{1,5}]dodecane-3-carboxylate 3b

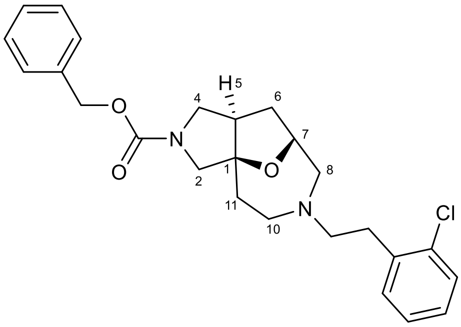


3b

General procedure **G** was followed using the crude dialdehyde **19** (9.19 mmol) and cyclopropylamine. Flash chromatography eluting with 7:3 hexane–EtOAc gave the *title compound* **3b** (1.90 g, 5.55 mmol, 60% over 4 steps) as a colourless oil. **R_f** 0.55 (1:1 petrol–EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$, 50:50 mixture of rotamers): δ 7.39-7.27 (5H, m, Cbz Ar-H), 5.11 (1H, s, OC*H*$_2$Ph), 5.10 (1H, s, OC*H*$_2$Ph), 4.41 (1H, app. d, *J* 6.5, 7-H), 3.86 (1H, d, *J* 12.3, 2-H$_A$), 3.60-3.49 (1H, m, 4-H$_A$), 3.45-3.23 (1H, m, 4-H$_B$), 3.23-3.05 (1H, m, 2-H$_B$), 2.94 (1H, dd, *J* 13.0, 6.4, 10-H$_A$), 2.74-2.54 (4H, m, 10-H$_B$, 5-H, and 8-H), 2.09 (1H, app. t, *J* 10.2, 6-H$_A$), 1.93-1.68 (4H, m, includes 6-H$_B$, 11-H, and cyclopropyl C*H*), 0.48-0.35 (3H, m, cyclopropyl (C*H*$_A$H$_B$)$_A$ and cyclopropyl (CH$_2$)$_B$), 0.31-0.19 (1H, m, cyclopropyl (CH$_A$*H*$_B$)$_A$). **^{13}C NMR** (100 MHz, $CDCl_3$, mixture of two rotamers, 1 C$_q$ not observed): δ 137.1 (Ar-C$_q$), 128.6 (Ar-C), 128.0 (Ar-C), 80.0 (7-C), 66.9 (O*C*H$_2$Ph), 63.9 (8-C), 63.8 (8-C), 57.5 (2-C), 57.4 (2-C), 53.9 (4-C and 10-C), 50.3[§] (5-C), 40.3 (cyclopropyl *C*H), 38.6 (11-C), 36.4 (6-C), 8.1 (cyclopropyl (*C*H$_2$)$_A$), 7.5 (cyclopropyl (*C*H$_2$)$_B$) [16 of 34 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1} 2821, 1705 (CO), 1449, 1419, 1364, 1351, 1236, 1127. **HRMS** (ESI): $C_{20}H_{27}N_2O_3$ [M+H]$^+$; calculated 343.2022, found 343.2015.

[§] Inferred by HMQC analysis.

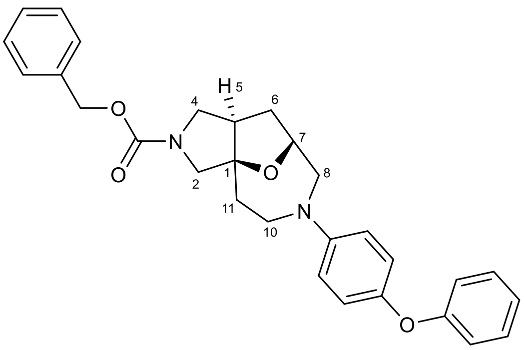
Benzyl (*1R**,*5R**,*7S**)-9-[2-(2-chlorophenyl)ethyl]-12-oxa-3,9-diazatricyclo[5.4.1.0^{1,5}]dodecane-3-carboxylate 3c



3c

General procedure **G** was followed using the crude dialdehyde **19** (0.27 mmol) and 2-(2-chlorophenyl)ethylamine. Flash chromatography eluting with 7:3 hexane–EtOAc gave the *title compound* **3c** (65 mg, 0.15 mmol, 56% over 4 steps) as a colourless oil. **^{1}H NMR** (400 MHz, CDCl$_3$, 50:50 mixture of rotamers): δ 7.46-7.03 (9H, m, Ar-H), 5.11 (2H, s, OC*H*$_2$Ph), 4.47-4.40 (1H, m, 7-H, includes at δ 4.44: 0.5H, d, *J* 8.1; and at δ 4.43: 0.5H, d, *J* 8.1), 3.87 (1H, d, *J* 12.3, 2-H$_A$), 3.65-3.52 (1H, m, 4-H$_A$, includes at δ 3.58: 0.5H, d, *J* 11.0; and at δ 3.57: 0.5H, d, *J* 11.0), 3.44-3.26 (1H, m, 4-H$_B$), 3.24-3.07 (1H, m, 2-H$_B$), 2.92-2.69 (4H, m, 8-H$_A$, 10-H$_A$ and NC*H*$_2$CH$_2$Ph), 2.69-2.47 (4H, m, 8-H$_B$, 10-H$_B$ and NCH$_2$C*H*$_2$Ph), 2.22-2.10 (1H, m, 6-H$_A$), 1.97-1.66 (4H, m, 11-H, 5-H and 6-H$_B$). **IR** ν$_{max}$(film)/cm^{-1} 2926, 1703 (CO), 1420, 1350, 1218, 1146, 1112, 1086. **HRMS** (ESI): C$_{25}$H$_{30}$ClN$_2$O$_3$ [M+H]$^+$; calculated 441.1945, found 441.1936.

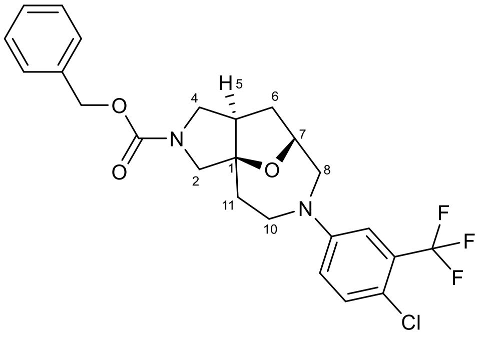
Benzyl (*1R**,*5R**,*7S**)-9-(4-phenoxyphenyl)-12-oxa-3,9-diazatricyclo[5.4.1.0^{1,5}]dodecane-3-carboxylate 3d



3d

General procedure **G** was followed using the crude dialdehyde **19** (0.27 mmol) and 4-phenoxyaniline. Flash chromatography eluting with 7:3 hexane–EtOAc gave the *title compound* **3d** (71 mg, 0.15 mmol, 56% over 4 steps) as a colourless oil. **^{1}H NMR** (400 MHz, CDCl$_3$, 50:50 mixture of rotamers): δ 7.39-7.23 (7H, m), 7.02 (1H, t, *J* 7.3, Ar-H), 6.93 (4H, dd, *J* 8.4, 4.1, Ar-H), 6.85-6.68 (2H, m, Ar-H), 5.19-5.04 (2H, m, OC*H*$_2$Ph), 4.56 (1H, d, *J* 7.7, 7-H), 3.97 (1H, d, *J* 12.7, 2-H$_A$), 3.75-3.59 (2H, m, includes 8-H$_A$ and 10-H$_A$), 3.54-3.31 (3H, m, 4-H and 10-H$_B$), 3.19 (2H, app. d, *J* 12.7, 2-H$_B$ and 8-H$_B$), 2.61-2.45 (1H, m, 5-H), 2.33-1.94 (3H, m, includes 6-H$_A$ and 11-H), 1.91-1.72 (1H, m, 6-H$_B$). **^{13}C NMR** (100 MHz, CDCl$_3$, 2 × Ar-C$_q$ not observed): δ 158.9 (Ar-C$_q$), 155.1 (N(CO)O), 137.0 (Ar-C$_q$), 129.7 (Ar-C), 128.6 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 122.4 (Ar-C), 121.3 (Ar-C), 117.5 (Ar-C), 113.4 (Ar-C), 92.6 (1-C), 81.2 (7-C), 67.0 (O*C*H$_2$Ph), 57.8 (2-C), 57.6 (2-C), 56.2 (8-C), 53.6 (4-C), 49.3 (5-C or 10-C), 48.9 (5-C or 10-C), 36.7 (6-C and 11-C) [21 of 46 expected peaks observed]. **IR** ν$_{max}$(film)/cm^{-1} 2924, 1701 (CO), 1510, 1488, 1420, 1231, 1091. **HRMS** (ESI): C$_{29}$H$_{31}$N$_2$O$_4$ [M+H]$^+$; calculated 471.2284, found 471.2278.

Benzyl (*1R**,*5R**,*7S**)-9-[4-chloro-3-(trifluoromethyl)phenyl]-12-oxa-3,9-diazatricyclo[5.4.1.0^{1,5}]dodecane-3-carboxylate 3e

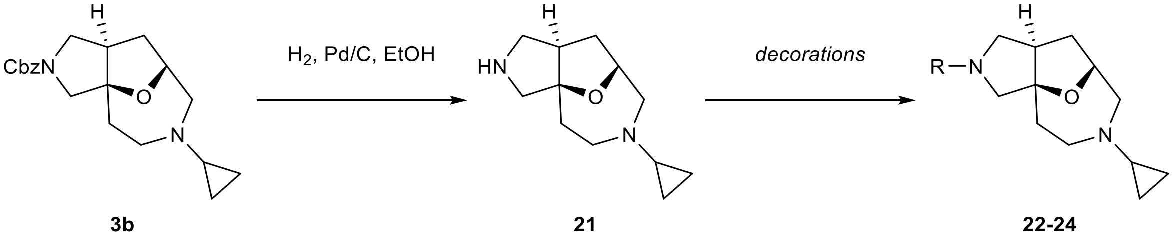


3e

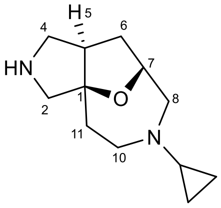
General procedure **G** was followed using the crude dialdehyde **19** (0.27 mmol) and 4-chloro-3-(trifluoromethyl)aniline. Flash chromatography eluting with 7:3 hexane–EtOAc gave the *title compound* **3e** (16 mg, 33.3 μmol, 12% over 4 steps) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$, 50:50 mixture of rotamers): δ 7.40-7.29 (5H, m, Cbz Ar-H), 7.29-7.21 (1H, m, Ar 5-H), 6.96 (1H, d, *J* 2.9, Ar 2-H), 6.76 (1H, dd, *J* 8.9, 2.9, Ar 6-H), 5.18-5.05 (2H, m, OCH_2Ph), 4.56 (1H, app. d, *J* 7.8, 7-H), 3.97 (1H, d, *J* 12.3, 2-H_A), 3.78 (1H, d, *J* 14.5, 8-H_A), 3.67 (1H, dd, *J* 15.4, 5.4, 10-H_A), 3.56-3.45 (1H, m, 10-H_B), 3.45-3.34 (2H, m, 4-H), 3.23 (1H, dd, *J* 14.5, 2.3, 8-H_B), 3.15 (1H, d, *J* 12.3, 2-H_B), 2.39-2.29 (1H, m, 5-H), 2.26-2.10 (1H, m, 11-H_A), 2.10-1.87 (2H, m, 6-H_A and 11-H_B), 1.87-1.72 (1H, m, 6-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$, mixture of two rotamers): δ 155.1 (N(CO)O), 147.4 (Ar 1-C), 136.9 (Cbz Ar 1-C), 132.5 (Ar 5-C), 129.1 (q, ^2J 31.0, Ar 3-C), 128.6 (Cbz Ar-C), 128.1 (Cbz Ar-C), 128.0 (Cbz Ar-C), 123.2 (q, ^1J 273, CF_3), 118.0 (Ar 4-C), 115.0 (Ar 6-C), 109.8 (q, ^3J 5.4, Ar 2-C), 81.2 (7-C), 67.1 (OCH_2Ph), 57.6 (2-C), 57.5 (2-C), 55.1 (8-C), 53.6 (4-C), 48.0 (5-C and 10-C)[**], 36.8 (6-C), 35.9 (11-C) [22 of 44 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1} 2934, 1703 (CO), 1606, 1500, 1432, 1315, 1236, 1218, 1126 **HRMS** (ESI): $C_{24}H_{25}ClF_3N_2O_3$ $[M+H]^+$; calculated 481.1506, found 481.1502.

[**] Inferred by HMQC analysis.

1.3.2.5 Exemplar decorations of scaffold 3b



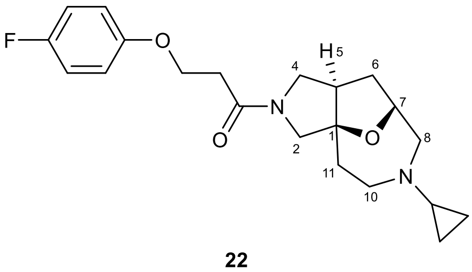
(*1R,*5R**,*7S**)-9-Cyclopropyl-12-oxa-3,9-diazatricyclo[5.4.1.0^{1,5}]dodecane 21**



21

Hydrogenation was carried out following general procedure **B**, using compound **3b** (1.75 g, 5.10 mmol, 1.00 eq.) to give the *title compound* **21** (1.05 g, 5.04 mmol, 99%) as a colourless oil. **^{1}H NMR** (500 MHz, CDCl$_3$): δ 4.31 (1H, d, *J* 8.1, 7-H), 3.08-3.02 (2H, m, includes 10-H$_A$ and at δ 3.06: 1H, d, *J* 12.3, 2-H$_A$), 2.83 (1H, dd, *J* 11.9, 6.9, 4-H$_A$), 2.77 (1H, d, H 11.9, 4-H$_B$), 2.72 (1H, app. dt, *J* 12.3 and 1.5, 8-H$_A$), 2.66-2.57 (2H, m, 5-H and 10-H$_B$), 2.55 (1H, dd, *J* 12.3, 2.8, 8-H$_B$), 2.41 (1H, d, *J* 12.3, 2-H$_B$), 2.02 (1H, dd, *J* 12.0, 9.8, 6-H$_B$), 1.90-1.86 (1H, m, cyclopropyl CH), 1.82 (1H, dd, *J* 13.4, 5.2, 11-H$_A$), 1.76-1.68 (2H, m, includes at δ 1.73: 1H, dd, J 13.4, 7.7, 11-H$_B$; and at δ 1.71: 1H, dd, *J* 13.5, 7.7, 6-H$_A$), 1.62 (1H, app. dt, J 12.2, 7.4, 6-H$_B$), 0.45-0.39 (3H, m, cyclopropyl (C*H*$_A$H$_B$)$_A$ and cyclopropyl (CH$_2$)$_B$), 0.28-0.24 (1H, cyclopropyl (C*H*$_A$H$_B$)$_A$). **^{13}C NMR** (125 MHz, CDCl$_3$): δ 94.3 (1-C), 80.2 (7-C), 64.9 (8-C), 59.6 (2-C), 55.8 (4-C), 54.5 (10-C), 51.9 (5-C), 40.4 (cyclopropyl CH), 39.2 (6-C), 37.8 (11-C), 8.1 (cyclopropyl CH$_2$), 7.5 (cyclopropyl CH$_2$). **IR** ν_{max}(film)/cm^{-1} 2912, 2818, 1460, 1451, 1366, 1186, 1043, 1014. **HRMS** (ESI): $C_{12}H_{21}N_2O$ [M+H]$^+$; calculated: 209.1654, found: 209.1643.

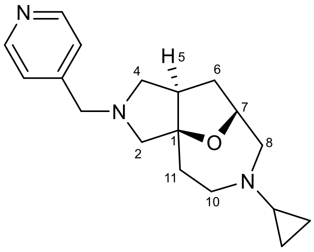
1-[(*1R**,*5R**,*7S**)-9-Cyclopropyl-12-oxa-3,9-diazatricyclo[5.4.1.$0^{1,5}$]dodecan-3-yl]-3-(4-fluorophenoxy)propan-1-one 22



22

TBTU (63 mg, 0.20 mmol, 1.30 eq.) was added to a solution of 3-(4-fluorophenoxy)propanoic acid (36 mg, 0.20 mmol, 1.30 eq.) and DIPEA (34 µL, 0.20 mmol, 1.30 eq.) in DMF (0.5 mL). The reaction mixture was stirred for 10 min at rt then a solution of compound **21** (32 mg, 0.15 mmol, 1.00 eq.) in DMF (0.5 mL) was added. The reaction mixture was stirred overnight at rt. The insolubles were removed by filtration, and the filtrate was purified by mass-directed preparative HPLC to give the *title compound* **22** (26 mg, 69 µmol, 46%). **^{1}H NMR** (500 MHz, $CDCl_3$, two stable conformations observed at the pyrrolidine ring): δ 6.99-6.91 (2H, m, Ar-H), 6.87-6.81 (2H, m, Ar-H), 4.46-4.36 (1H, m, includes at δ 4.43: 0.5H, dd, *J* 8.2, 2.4, 7-H; and at δ 4.40: 0.5H, *J* 8.2, 2.4, 7-H), 4.32-4.18 (2H, m, $\mathrm{OC}\mathit{H}_\mathrm{A}\mathrm{H}_\mathrm{B}\mathrm{CH}_2(\mathrm{CO})$ and $\mathrm{OCH}_2\mathrm{C}\mathit{H}_\mathrm{A}\mathrm{H}_\mathrm{B}(\mathrm{CO})$), 4.03 (0.5H, d, *J* 13.4, $2\text{-H}_{\text{A-conf1}}$), 3.83 (0.5H, d, *J* 11.8, $2\text{-H}_{\text{A-conf2}}$), 3.71 (0.5H, dd, *J* 10.7, 8.5, $4\text{-H}_{\text{A-conf1}}$), 3.62-3.51 (1H, m, $4\text{-H}_{\text{A-conf2}}$ and $4\text{-H}_{\text{B-conf2}}$), 3.33 (0.5H, dd, *J* 10.7, 5.9, $4\text{-H}_{\text{B-conf1}}$), 3.26 (0.5H, d, *J* 11.8, $2\text{-H}_{\text{B-conf2}}$), 3.19 (0.5H, d, *J* 13.4, $2\text{-H}_{\text{B-conf1}}$), 3.01-2.89 (1H, m, 10-H_A), 2.79-2.56 (6H, m, $\mathrm{OCH}_2\mathrm{C}\mathit{H}_2(\mathrm{CO})$, 5-H, 8-H, 10-H_B), 2.18-2.08 (1H, m, 11-H_A), 1.96-1.71 (4H, m, cyclopropyl CH, 6-H, 11-H_B), 0.52-0.37 (3H, m, cyclopropyl $(\mathrm{C}\mathit{H}_\mathrm{A}\mathrm{H}_\mathrm{B})_\mathrm{A}$ and cyclopropyl $(\mathrm{CH}_2)_\mathrm{B}$), 0.32-0.21 (1H, m, cyclopropyl $(\mathrm{CH}_\mathrm{A}\mathit{H}_\mathrm{B})_\mathrm{A}$). **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of two rotamers, unable to discern the ^{13}C – ^{19}F coupling constants): δ 168.9 (major, N(CO)), 168.7 (minor, N(CO)), 158.4 (Ar-C), 156.6 (Ar-C), 155.0 (Ar-C), 116.0 (Ar 2-C), 116.0 (Ar 2-C), 115.8 (4 peaks, Ar 3-C), 115.7 (Ar 3-C), 92.0 (major, 1-C), 90.4 (minor, 1-C), 80.1 (major, 7-C), 79.7 (minor, 7-C), 65.0 (minor, $\mathrm{O}\mathit{C}\mathrm{H}_2\mathrm{CH}_2(\mathrm{CO})$), 64.9 (major, $\mathrm{O}\mathit{C}\mathrm{H}_2\mathrm{CH}_2(\mathrm{CO})$), 63.8 (major, 8-C), 63.5 (minor, 8-C), 58.4 (major, 2-C), 57.1 (minor, 2-C), 54.5 (minor, 4-C), 53.9 (major, 4-C), 53.8 (minor, 10-C), 53.0 (major, 10-C), 50.9 (minor, 5-C), 49.5 (major, 5-C), 40.3 (major, cyclopropyl CH), 40.2 (minor, cyclopropyl CH), 38.8 (minor, 11-C), 38.5 (major, 11-C), 36.4 (major, 6-C), 35.3 (minor, 6-C), 34.5 (major, $\mathrm{OCH}_2\mathit{C}\mathrm{H}_2(\mathrm{CO})$), 34.3 (minor, $\mathrm{OCH}_2\mathit{C}\mathrm{H}_2(\mathrm{CO})$), 8.2 (major, cyclopropyl $(\mathrm{CH}_2)_\mathrm{A}$), 8.1 (minor, cyclopropyl $(\mathrm{CH}_2)_\mathrm{A}$), 7.5 (2 peaks, major and minor, cyclopropyl $(\mathrm{CH}_2)_\mathrm{B}$).

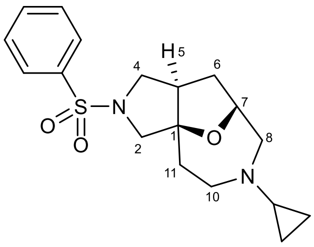
(*1R**,*5R**,*7S**)-9-Cyclopropyl-3-(pyridin-4-ylmethyl)-12-oxa-3,9-diazatricyclo[5.4.1.$0^{1,5}$]dodecane 23



23

Isonicotinaldehyde (40 mg, 0.38 mmol, 2.50 eq.) was added to a solution of compound **21** (32 mg, 0.15 mmol, 1.00 eq.) and AcOH (1.8 µL, 31.5 µmol, 0.2 eq.) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred for 10 min then $NaBH(OAc)_3$ (64 mg, 0.30 mmol, 2.0 eq.) was added. The reaction mixture was stirred overnight at rt. DMF (1.0 mL) was added, followed by 1.0 M NaOH (0.2 mL, 0.2 mmol, 1.3 eq.). The reaction mixture was partially concentrated *in vacuo*, the insolubles were removed by filtration, and the filtrate was purified by mass-directed preparative HPLC to give the *title compound* **23** (23 mg, 77 µmol, 51%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.51 (2H, dd, *J* 4.1 and 1.3, Py 3-H), 7.27 (2H, dd, *J* 4.1 and 1.3, Py 2-H), 4.37 (1H, d, *J* 7.3, 7-H), 3.67 (1H, d, *J* 14.2, 2-H_A), 3.40 (1H, d, *J* 14.2, 2-H_B), 3.04 (1H, d, *J* 9.7, $NC\mathit{H}_AH_BPy$), 3.03-2.97 (1H, m, 10-H_A), 2.72 (1H, d, *J* 12.2, 8-H_A), 2.68-2.58 (3H, m, 4-H_A, 5-H and 10-H_B), 2.55 (1H, d, *J* 12.2, 8-H_B), 2.12 (1H, dd, *J* 9.2 and 6.9, 4-H_B), 1.94 (1H, d, *J* 9.7, $NCH_A\mathit{H}_BPy$), 1.91-1.75 (4H, m, cyclopropyl CH, 6-H_A and 11-H), 1.70 (1H, m, 6-H_B), 0.46-0.37 (3H, m, cyclopropyl $(C\mathit{H}_AH_B)_A$ and cyclopropyl $(CH_2)_B$), 0.28-0.22 (1H, m, cyclopropyl $(CH_A\mathit{H}_B)_A$). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 149.8 (Py 3-C), 148.2 (Py 1-C), 123.8 (Py 2-C), 92.1 (1-C), 80.2 (7-C), 66.3 ($N\mathit{C}H_2Py$), 65.1 (8-C), 60.9 (4-C), 58.6 (2-C), 54.6 (10-C), 50.7 (5-C), 40.6 (cyclopropyl CH), 39.1 (6-C or 11-C), 38.7 (6-C or 11-C), 8.3 (cyclopropyl CH_2), 7.6 (cyclopropyl CH_2).

(*1R**,*5R**,*7S**)-3-(Benzenesulfonyl)-9-cyclopropyl-12-oxa-3,9-diazatricyclo[5.4.1.0^{1,5}]dodecane 24

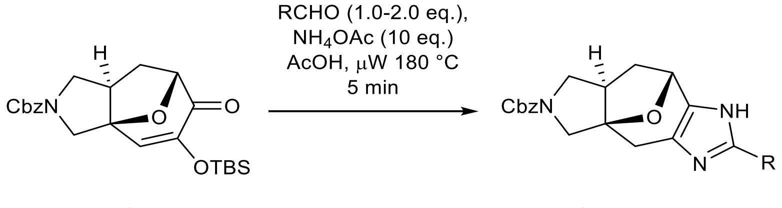


24

Benzenesulfonyl chloride (21 µL, 0.16 mmol, 1.10 eq.) was added to a solution of compound **21** (32 mg, 0.15 mmol, 1.00 eq.) and DIPEA (31 µL, 0.18 mmol, 1.20 eq.) in DMF (1.0 mL). The reaction mixture was stirred overnight at rt. The insolubles were removed by filtration and the filtrate was purified by mass-directed preparative HPLC to give the *title compound* **24** (21 mg, 60 µmol, 40%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.82-7.77 (2H, m, Ar-H), 7.63-7.56 (1H, m, Ar 3-H), 7.55-7.51 (2H, Ar-H), 4.29 (1H, d, *J* 7.5, 7-H), 3.58 (1H, d, *J* 10.7, 2-H_A), 3.19 (1H, dd *J* 9.8 and 2.2, 4-H_A), 2.95 (1H, ddt, *J* 13.3, 7.5, 1.5, 10-H_A), 2.87 (1H, dd, *J* 9.8 and 7.4, 4-H_B), 2.67 (1H, d, *J* 12.6, 8-H_A), 2.66-2.56 (2H, m, 5-H and 10-H_B), 2.55-2.50 (2H, m, includes 8-H_B, and at δ 2.52: 1H, d, *J* 10.7, 2-H_B), 1.94 (1H, dd, *J* 11.7 and 9.4, 6-H_A), 1.87-1.82 (1H, m, cyclopropyl CH), 1.80-1.70 (2H, m, 6-H_B and 11-H_A), 1.66-1.58 (1H, m, 11-H_B), 0.44-0.37 (2H, m, cyclopropyl $(CH_2)_A$), 0.34-0.30 (1H, cyclopropyl $(C\mathit{H}_AH_B)_B$), 0.23-0.18 (1H, cyclopropyl $(CH_A\mathit{H}_B)_B$). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 135.7 (Ar 1-C), 132.9 (Ar 3-C), 129.0 (Ar-C), 128.2 (Ar-C), 91.8 (1-C), 80.3 (7-C), 64.6 (8-C), 59.4 (2-C), 55.2 (4-C or 10-C), 54.2 (4-C or 10-C), 50.5 (5-C), 40.5 (cyclopropyl 1-C), 38.4 (6-C or 11-C), 38.1 (6-C or 11-C), 8.2 (cyclopropyl CH_2), 7.6 (cyclopropyl CH_2).

1.3.3 Preparation of scaffolds 4

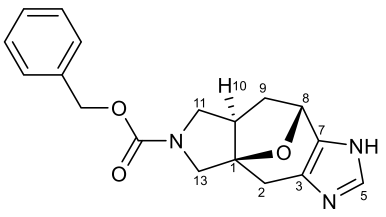
1.3.3.1 Initial procedure to prepare scaffolds 4a-b



1

4a R=H, 84%
4b R= Ph, 91%

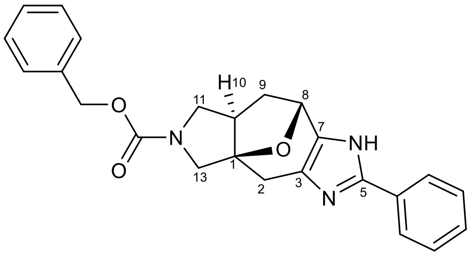
Benzyl (*1R**,*8R**,*10R**)-14-oxa-4,6,12-triazatetracyclo[6.5.1.$0^{1,10}$.$0^{3,7}$]tetradeca-3(7),4-diene-12-carboxylate 4a



4a

In two equally sized batches, p-formaldehyde (245 mg, 8.20 mmol, 2.00 eq.) and NH_4OAc (3.10 g, 41.0 mmol, 10.0 eq.) were added to a suspension of compound **1** (1.75 g, 4.10 mmol, 1.00 eq. [8.20 mmol over two batches]) in AcOH (5 mL). The reaction mixture was stirred at rt for 10 mins, then heated at heated at 180 °C under microwave irradiation for 5 min. The batches were combined and concentrated *in vacuo*. The residue was diluted in EtOAc (50 mL) and washed with sat. aq. $NaHCO_3$ (50 mL). The aqeuous layer was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with H_2O (2 × 25 mL) and brine (25 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by SCX SPE following general procedure **A**, eluting with MeOH, then sat. NH_3/MeOH, followed by flash chromatography eluting with 90:9:1 CH_2Cl_2–EtOH–NH_3/MeOH gave the title compound **4a** (2.24 g, 6.9 mmol, 84%) as a pale brown foam. **R*f*** 0.64 (50:8:1 CH_2Cl_2–EtOH–NH_3/MeOH). **^{1}H NMR** (400 MHz, $CDCl_3$, imidazole NH not observed): δ 7.43 (1H, s, 5-H), 7.40-7.28 (5H, m, Cbz Ar-H), 5.25 (1H, d, *J* 5.9, 8-H), 5.16 (1H, app. d, *J* 13.0, $OC\mathit{H}_AH_BPh$), 5.11 (1H, app. d, *J* 13.0, $OCH_A\mathit{H}_BPh$), 4.06 (1H, d, *J* 12.7, 13-H_A), 3.82-3.71 (1H, m, 11-H_A), 3.54-3.34 (2H, m, 11-H_B and 13-H_B), 3.26-3.10 (1H, m, 2-H_A), 2.70-2.61 (1H, m, 10-H), 2.58 (1H, d, *J* 15.4, 2-H_B), 2.53-2.42 (1H, m, 9-H_A), 2.15-2.03 (1H, m, 9-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$, mixture of two rotamers, 2 × imidazole C_q not observed): δ 154.9 (N(CO)O), 136.8 (Cbz Ar-C_q), 136.7 (Cbz Ar-C_q), 133.6 (2 peaks, Ar-C), 128.6 (Ar-C), 128.2 (Ar-C), 128.0 (Ar-C), 91.1 (1-C), 90.2 (1-C), 76.4 (8-C), 67.2 (OCH_2Ph), 55.4 (13-C), 55.0 (13-C), 53.6 (11-C), 47.1 (10-C), 46.1 (10-C), 45.8 (9-C), 45.7 (9-C), 32.7 (2-C) [20 of 32 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1} 2958, 1694 (CO), 1423, 1352, 1239, 1218, 1115, 732. **HRMS** (ESI): $C_{18}H_{20}N_3O_3$ $[M+H]^+$; calculated 326.1499, found 326.1500.

Benzyl (1R*,8R*)-5-phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.0^{1,10}.0^{3,7}]tetradeca-3(7),4-diene-12-carboxylate 4b

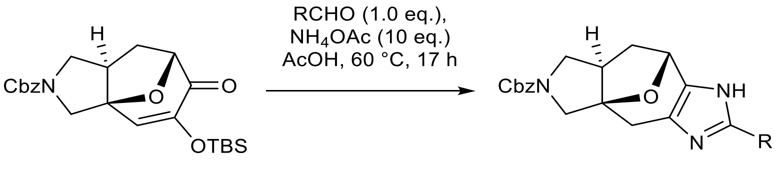


4b

PhCHO (18 µL, 0.17 mmol, 1.0 eq.) and NH$_4$OAc (135 mg, 1.70 mmol, 10.0 eq.) were added to a suspension of compound **1** (75 mg, 0.17 mmol, 1.0 eq.) in AcOH (1.0 mL). The resulting mixture was heated under microwave irradiation at 180 °C for 5 min. The reaction mixture was concentrated *in vacuo*, then partitioned between CH$_2$Cl$_2$ (25 mL) and NaHCO$_3$ (25 mL). The phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. Flash chromatography eluting with 0-100% EtOAc in pentane gave the title compound **4b** (64 mg, 0.16 mmol, 91%) as a pale brown oil. **R*f*** 0.12 (1:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, CDCl$_3$, imidazole NH not observed): δ 7.76 (2H, d, *J* 7.3, Ar-H), 7.43-7.28 (8H, m, Ar-H), 5.28 (1H, d, *J* 5.7, 8-H), 5.25-5.17 (2H, m, OC*H*$_2$Ph), 4.07 (1H, d, *J* 12.6, 13-H$_A$), 3.85-3.73 (1H, m, 11-H$_A$), 3.55-3.36 (2H, m, 11-H$_B$ and 13-H$_B$), 3.28-3.16 (1H, m, 2-H$_A$), 2.73-2.64 (1H, m, 10-H), 2.61 (1H, d, *J* 15.4, 2-H$_B$), 2.58-2.47 (1H, m, 9-H$_A$), 2.16-2.05 (1H, m, 9-H$_B$). **^{13}C NMR** (125 MHz, CDCl$_3$, mixture of two rotamers, 2 × imidazole C$_q$ not observed): δ 154.9 (N(CO)O), 145.6 (7-C), 136.7 (Ar-C$_q$), 130.4 (Ar-C$_q$), 129.1 (Ar-C), 128.6 (Ar-C), 128.2 (Ar-C), 128.0 (2 peaks, Ar-C), 125.1 (Ar-C), 91.1 (1-C), 90.1 (1-C), 77.4 (8-C), 67.2 (OCH$_2$Ph), 55.4 (13-C), 55.0 (13-C), 53.6 (11-C), 53.5 (11-C), 47.1 (10-C), 46.1 (10-C), 45.8 (9-C), 45.6 (9-C), 32.8 (2-C) [23 of 40 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1} 3274, 2241, 1682 (CO), 1448, 1418, 1348, 1116, 909. **HRMS** (ESI): C$_{24}$H$_{24}$N$_3$O$_3$ [M+H]$^+$; calculated 402.1812, found 402.1825.

1.3.3.2 Optimised synthetic route to scaffolds 4

The initial route (above) was adapted to enable preparation of imidazoles **4** using conventional thermal heating.



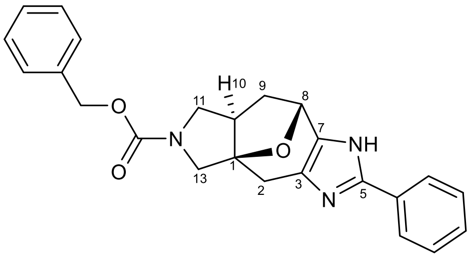
1

4b-e 23-65%

General procedure H: formation of imidazoles

NH_4OAc (10.0 eq.) was added to a stirred suspension of compound **1** (1.0 eq.) and aldehyde (1.0 eq.) in AcOH (0.5 M). The resulting mixture was heated at 60 °C for 17 h. The reaction was cooled to rt then slowly added to sat. aq. $NaHCO_3$ (until no further evolution of gas was observed). The mixture was extracted with EtOAc (4 × 1 volume) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction products were purified by flash column chromatography.

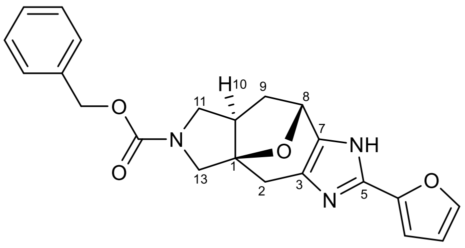
Benzyl (*1R**,*8R**)-5-phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.0^{1,10}.0^{3,7}]tetradeca-3(7),4-diene-12-carboxylate 4b



4b

General procedure **H** was followed using compound **1** (1.00 mmol) and PhCHO. Flash chromatography eluting with 50-100% EtOAc in pentane gave the title compound **4b** (225 mg, 0.56 mmol, 56%) as a brown amorphous solid. See above for spectral data.

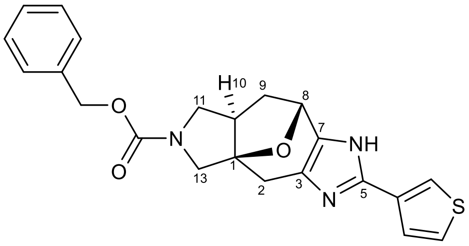
Benzyl (*1R**,*8R**,*10R**)-5-(furan-2-yl)-14-oxa-4,6,12-triazatetracyclo[6.5.1.0^{1,10}.0^{3,7}]tetradeca-3(7),4-diene-12-carboxylate 4c



4c

General procedure **H** was followed using compound **1** (1.00 mmol) and furfural. Flash chromatography eluting with 50-100% EtOAc in hexane gave the *title compound* **4c** (254 mg, 0.65 mmol, 65%) as a brown amorphous solid. **^{1}H NMR** (500 MHz, CDCl$_3$, imidazole NH not observed): 7.40-7.28 (6H, m, Ar-H and furan 5-H), 6.82 (1H, d, *J* 3.4, furan 3-H), 6.48 (1H, dd, *J* 3.5, 1.8, furan 4-H), 5.26 (1H, d, *J* 5.9, 8-H), 5.21-5.07 (2H, m, OCH_2Ph), 4.07 (1H, d, *J* 12.6, 13-H$_A$), 3.83-3.72 (1H, m, 11-H$_A$), 3.55-3.36 (2H, m, 11-H$_B$ and 13-H$_B$), 3.27-3.14 (1H, m, 2-H$_A$), 2.71-2.64 (1H, m, 10-H), 2.61 (1H, d, *J* 15.5, 2-H$_B$), 2.56-2.45 (1H, m, 9-H$_A$), 2.16-2.05 (1H, m, 9-H$_B$). **^{13}C NMR** (100 MHz, CDCl$_3$, 2 × Ar-C$_q$ not observed, mixture of two rotamers): 154.9 (N(CO)O), 146.1 (Ar-C$_q$), 142.1 (furan 5-C), 138.2 (Ar-C$_q$), 136.7 (Ar-C$_q$), 128.6 (Ph-C), 128.1 (Ph-C), 128.0 (Ph-C), 112.0 (furan 4-C), 106.7 (furan 3-C), 91.1 (1-C), 90.2 (1-C), 67.1 (OCH$_2$Ph), 55.0 (13-C), 53.3 (11-C), 53.5 (11-C), 47.1 (10-C), 46.1 (10-C), 45.7 (9-C), 45.6 (9-C), 32.8 (2-C) [21 of 40 expected peaks observed]. **IR** ν_{max}(neat)/cm^{-1} 3118, 3031, 2953, 2874, 1694, 1590. **HRMS** (ESI): $C_{22}H_{22}N_3O_4$ [M+H]$^+$ 392.1605, found 392.1608.

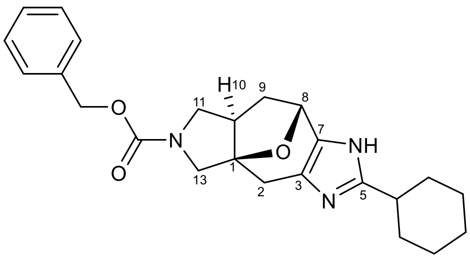
Benzyl (*1R**,*8R**,*10R**)-5-(thiophen-3-yl)-14-oxa-4,6,12-triazatetracyclo[6.5.1.0^{1,10}.0^{3,7}]tetradeca-3(7),4-diene-12-carboxylate 4d



4d

General procedure **H** was followed using compound **1** (1.00 mmol) and 3-thiophenecarboxaldehyde. Flash chromatography eluting with 50-100% EtOAc in hexane gave the *title compound* **4d** (244 mg, 0.60 mmol, 60%, imidazole NH not observed) as a brown amorphous solid. **^{1}H NMR** (500 MHz, CDCl$_3$): δ 7.61 (1H, s), 7.48 (1H, d, *J* 4.9), 7.43-7.25 (5H, m), 5.24-5.07 (3H, m), 4.06-3.97 (1H, m), 3.81-3.68 (1H, m), 3.50-3.38 (1H, m), 3.33 (1H, d, *J* 12.5), 3.07 (1H, d, *J* 15.4), 2.68-2.57 (1H, m), 2.54-2.39 (2H, m), 2.32-2.31 (1H, m), 2.04-1.97 (1H, m).

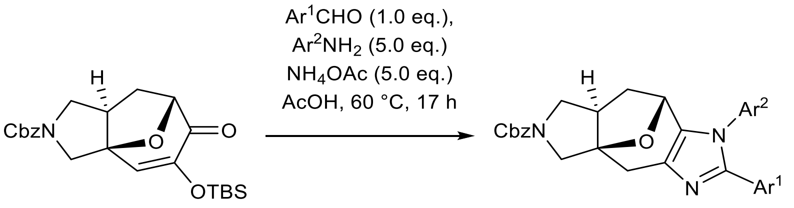
Benzyl (*1R**,*8R**,*10R**)-5-cyclohexyl-14-oxa-4,6,12-triazatetracyclo[$6.5.1.0^{1,10}.0^{3,7}$]tetradeca-3(7),4-diene-12-carboxylate 4e



4e

General procedure **H** was followed using compound **1** (1.00 mmol) and cyclohexane carboxaldehyde. Flash chromatography eluting with 50-100% EtOAc in hexane gave the *title compound* **4e** (94 mg, 0.23 mmol, 23%) as a brown amorphous solid. **^{1}H NMR** (400 MHz, CDCl$_3$, imidazole NH not observed): 7.36-7.28 (5H, m, Ar-H), 5.18-5.09 (3H, m, OC*H*$_2$Ph and 8-H), 4.01 (1H, dd, *J* 12.6, 2.4, 13-H$_A$), 3.80-3.70 (1H, m, 11-H$_A$), 3.48-3.31 (2H, m, 11-H$_B$ and 13-H$_B$), 3.14-3.03 (1H, m, 2-H$_A$), 2.68-2.59 (2H, m, Cy 1-H and 10-H), 2.48-2.35 (2H, m, includes 9-H$_A$ and at δ 2.44: 1H, d, *J* 15.3, 2-H$_B$), 2.04-1.88 (3H, m, 9-H$_B$, and Cy 2-H$_A$), 1.78-1.59 (3H, m, Cy-H), 1.47-1.08 (5H, m, Cy 2-H$_B$ and Cy-H). **^{13}C NMR** (125 MHz, CDCl$_3$, 2 × Ar-C$_q$ not observed, mixture of two rotamers): 154.7 (N(CO)O), 151.6 (Ar-C$_q$), 136.7 (Ar-C$_q$), 128.5 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 91.1 (1-C), 90.0 (1-C), 67.0 (O*C*H$_2$Ph), 55.0 (13-C), 53.5 (11-C), 47.0 (10-C), 46.0 (10-C), 45.7 (9-C), 45.5 (9-C), 37.9 (Cy 1-C), 32.7 (2-C), 32.2 (Cy 2-C), 32.1 (Cy 2-C), 26.0 (Cy 3-C or Cy 4-C), 25.8 (Cy 3-C or Cy 4-C) [21 of 40 expected peaks observed]. **IR** ν_{max}(neat)/cm^{-1} 3065, 2925, 2851, 1684, 1612, 1522. **HRMS** (ESI): $C_{24}H_{30}N_3O_3$ [M+H]$^+$ 408.2282, found 408.2283.

1.3.3.3 Preparation of disubstituted imidazoles 25



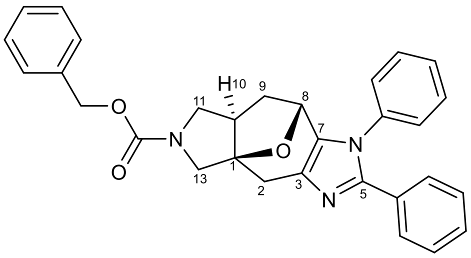
1

25a-c
55-62%

General procedure I: formation of disubstituted imidazoles

NH$_4$OAc (5.0 eq.) was added to a stirred suspension of the compound **1** (1.0 eq.), aldehyde (1.0 eq.), and aniline (5.0 eq.) in AcOH (0.5 M). The resulting mixture was heated at 60 °C for 17 h. The reaction was cooled to rt then slowly added to sat. aq. NaHCO$_3$ (until no further evolution of gas was observed). The mixture was extracted with EtOAc (4 × 1 volume) and the combined organic layers were dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude reaction products were purified by flash column chromatography.

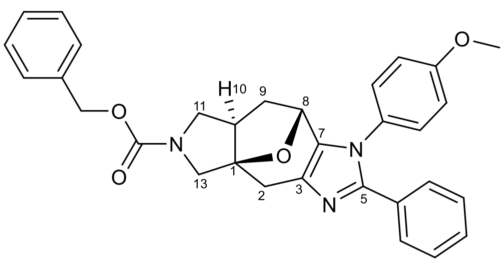
Benzyl (*1R**,*8R**,*10R**)-5,6-diphenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.0^{1,10}.0^{3,7}]tetradeca-3(7),4-diene-12-carboxylate 25a



25a

General procedure **I** was followed using compound **1** (1.00 mmol), benzaldehyde and 3,5-dimethyl aniline. Flash chromatography eluting with 50-100% EtOAc in hexane gave the *title compound* **25a** (296 mg, 0.62 mmol, 62%) as a pale yellow amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$,): 7.46-7.40 (3H, m, Ar-H), 7.38-7.29 (7H, m, Ar-H), 7.24-7.19 (3H, m, Ar-H), 7.19-7.14 (2H, m, Ar-H), 5.36 (1H, d, *J* 5.9, 8-H), 5.19-5.07 (2H, m, OCH_2Ph), 4.06 (1H, d, *J* 12.0, 13-H_A), 3.77 (1H, dd, *J* 11.5, 8.9, 11-H_A), 3.56-3.43 (1H, m, 13-H_B), 3.41-3.30 (1H, m, 11-H_B), 3.16-2.99 (1H, m, 9-H_A), 2.78-2.60 (2H, m, 2-H_A and 10-H), 2.39 (1H, d, *J* 15.7, 2-H_B), 2.20-2.10 (1H, m, 9-H_B). **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of two rotamers): δ 154.8 (N(CO)O), 145.8 (Ar-C), 141.4 (Ar-C), 136.9 (Ar-C), 136.8 (Ar-C), 130.2 (Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 128.8 (Ar-C), 128.6 (Ar-C), 128.4 (2 peaks, Ar-C), 128.3 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 126.9 (Ar-C), 124.9 (Ar-C), 90.9 (1-C), 89.9 (1-C), 73.8 (8-C), 67.1 (OCH_2Ph), 55.3 (13-C), 55.0 (13-C), 53.5 (2 × peaks, 11-C), 47.3 (10-C), 46.4 (10-C), 45.4 (9-C), 32.5 (2-C) [29 of 48 expected peaks observed]. **IR** ν_{max}(neat)/cm^{-1} 3062, 2953, 2874, 1696, 1597. **HRMS** (ESI): $C_{30}H_{28}N_3O_3$ [M+H]$^+$ 478.2125, found 478.2123.

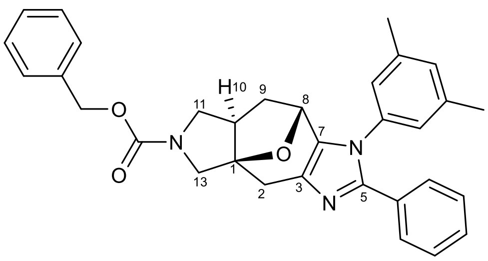
Benzyl (1R,8R,10R)-6-(4-methoxyphenyl)-5-phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.0^{1,10}.0^{3,7}]tetradeca-3(7),4-diene-12-carboxylate 25b



25b

General procedure **I** was followed using compound **1** (1.00 mmol), benzaldehyde and *p*-anisidine. Flash chromatography eluting with 50-100% EtOAc in hexane gave the *title compound* **25b** (294 mg, 0.58 mmol, 58%) as a dark brown amorphous solid. **^{1}H NMR** (500 MHz, $CDCl_3$): 7.39-7.28 (7H, m, Ar-H), 7.25-7.17 (3H, m, Ar-H), 7.08 (2H, d, *J* 8.8, PMP 2-H), 6.92 (2H, d, *J* 8.8, PMP 3-H), 5.35 (1H, d, *J* 5.9, 8-H), 5.18-5.08 (2H, m, OCH_2Ph), 4.10-3.99 (1H, m, 13-H_A), 3.84 (3H, s, OCH_3), 3.77 (1H, dd, *J* 11.6, 8.9, 11-H_A), 3.55-3.42 (1H, m, 13-H_B), 3.41-3.30 (1H, m, 11-H_B), 3.10-2.97 (1H, m, 2-H_A), 2.79-2.56 (2H, m, 9-H_A and 10-H), 2.38 (1H, d, *J* 15.6, 2-H_B), 2.21-2.09 (1H, m, 9-H_B). **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of two rotamers): 159.7 (PMP 4-C), 154.8 (N(CO)O), 145.9 (Ar-C_q), 141.4 (Ar-C_q), 136.9 (Ar-C_q), 130.6 (Ar-C_q), 129.8 (Ar-C_q), 128.6 (Ar-C), 128.3 (2 peaks, Ar-C), 128.2 (Ar-C), 128.1 (2 peaks, Ar-C), 128.0 (Ar-C), 125.1 (Ar-C), 115.0 (PMP 3-C), 90.9 (1-C), 90.0 (1-C), 77.5 (8-C), 67.1 (OCH_2Ph), 55.7 (OCH_3), 55.4 (13-C), 55.1 (11-C), 53.5 (11-C), 47.4 (10-C), 46.4 (10-C), 45.5 (9-C), 32.5 (2-C) [28 of 50 expected peaks observed]. **IR** ν_{max}(neat)/cm^{-1} 3060, 2953, 2837, 1698, 1608, 1584, 1511. **HRMS** (ESI): $C_{31}H_{30}N_3O_4$ $[M+H]^+$ 508.2231, found 508.2226.

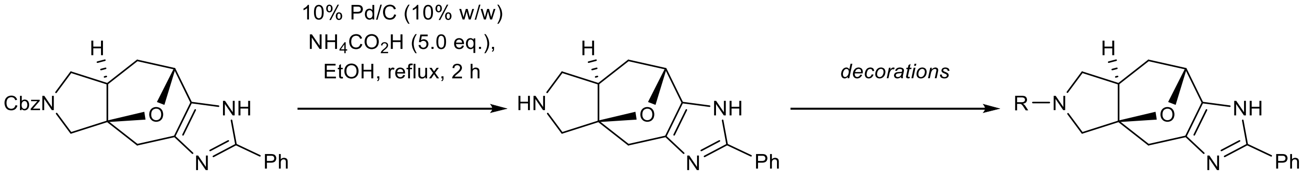
Benzyl (1R*,8R*,10R*)-6-(3,5-dimethylphenyl)-5-phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.$0^{1,10}$.$0^{3,7}$]tetradeca-3(7),4-diene-12-carboxylate 25c



25c

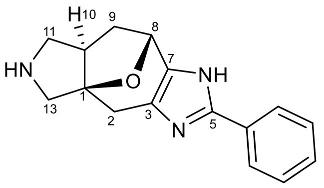
General procedure **I** was followed using compound **1** (1.00 mmol), benzaldehyde and 3,5-dimethylaniline. Flash chromatography eluting with 50-100% EtOAc in hexane gave the *title compound* **25c** (278 mg, 0.55 mmol, 55%) as a pale yellow amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45-7.27 (7H, m, Ar-H), 7.25-7.16 (3H, m, Ar-H), 7.10-7.00 (1H, m, Ar-H), 6.77 (2H, s, Ar-H), 5.34 (1H, d, *J* 5.9, 8-H), 5.20-5.05 (2H, m, OCH_2Ph), 4.15-3.99 (1H, m, 13-H_A), 3.77 (1H, dd, *J* 11.5, 8.8, 11-H_A), 3.55-3.31 (2H, m, 11-H_B and 13-H_B), 3.13-2.95 (1H, m, 2-H_A), 2.76-2.60 (2H, m, 10-H and 9-H_A), 2.38 (1H, d, *J* 15.8, 2-H_B), 2.30 (6H, s, CH_3), 2.20-2.09 (9-H_B). **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of two rotamers): δ 154.7 (N(CO)O), 145.6 (Ar-C), 141.3 (Ar-C), 139.7 (Ar-C), 139.6 (Ar-C), 136.9 (Ar-C), 136.8 (Ar-C), 130.2 (Ar-C), 130.3 (Ar-C), 128.5 (Ar-C), 128.2 (Ar-C), 128.1 (2 peaks, Ar-C), 128.0 (2 peaks, Ar-C), 124.8 (Ar-C), 124.4 (Ar-C), 90.8 (1-C), 89.9 (1-C), 73.8 (8-C), 67.0 (OCH_2Ph), 55.3 (13-C), 55.0 (13-C), 53.5 (11-C), 47.3 (10-C), 46.3 (10-C), 45.4 (9-C), 32.4 (2-C), 21.2 (CH_3) [29 of 50 expected peaks observed]. **IR** ν_{max}(neat)/cm^{-1} 3058, 3018, 2973, 2944, 2877, 1701, 1612, 1597, 1510. **HRMS** (ESI): $C_{32}H_{32}N_3O_3$ $[M+H]^+$ 506.2438, found 506.2432.

1.3.3.4 Exemplar decorations of scaffold 4b



4b **26** **27-29**

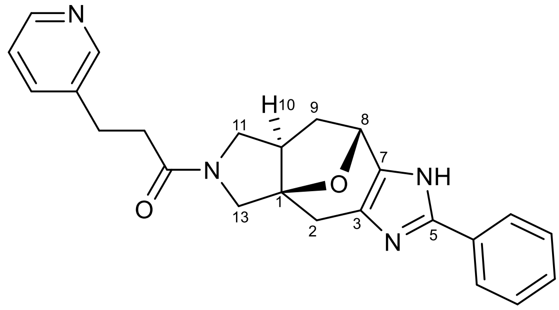
(*1R**,*8R**,*10R**)-5-Phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.0^{1,10}.0^{3,7}]tetradeca-3(7),4-diene 26



26

Pd/C (0.46 g, 10 wt%, 10% w/w) was added to a stirred solution of compound **4b** (4.63 g, 11.5 mmol, 1.00 eq.) and NH_4CO_2H (3.64 g, 57.7 mmol, 5.00 eq.) in EtOH (115 mL, 0.10 M). The mixture was stirred at reflux for 2 h. The reaction mixture was allowed to cool to rt, filtered through a pad of Celite®, flushed through with EtOH, and concentrated. The crude product was filtered through a pad of silica, eluting with a 1:9 NH_3(sat)/MeOH:CH_2Cl_2 to afford the *title compound* **26** (3.05 g, 11.2 mmol, 98%) as a yellow solid. **^{1}H NMR** (500 MHz; MeOD, 2 × NH not observed): δ 7.73 (2H, dd, *J* 8.4, 1.2, Ar-H), 7.34 (2H, t, *J* 7.5, Ar-H), 7.26 (1H, app. tt, *J* 7.5, 1.2, Ar-H), 5.08 (1H, d, *J* 5.7, 8-H), 3.27 (1H, d, *J*, 12.6, 13-H_A), 3.12-3.03 (2H, m, includes 11-H_B; and at δ 3.08: 1H, d, *J*, 15.5, 2-H_A), 2.87 (1H, d, *J* 12.0, 11-H_A), 2.77 (1H, d, *J* 12.6, 13-H_B), 2.63-2.53 (2H, m, includes 10-H; and at δ 2.60: 1H, d, *J* 15.5, 2-H_B), 2.45 (1H, dd, *J* 11.9, 8.8, 9-H_A), 1.95 (1H, dt, *J* 11.9, 6.2, 9-H_B).

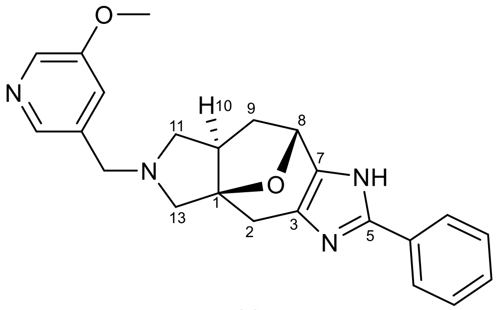
1-[(*1R**,*8R**,*10R**)-5-Phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.$0^{1,10}$.$0^{3,7}$]tetradeca-3(7),4-dien-12-yl]-3-(pyridin-3-yl)propan-1-one 27



27

TBTU (59 mg, 0.19 mmol, 1.5 eq.) was added to a solution of 3-(pyridin-3-yl)propanoic acid (28 mg, 0.19 mmol, 1.5 eq.) and DIPEA (32 µL, 0.19 mmol, 1.5 eq.) in DMF (0.5 mL). The reaction mixture was stirred for 10 min at rt, then a solution of amine **26** (33 mg, 0.12 mmol, 1.0 eq.) in DMF (0.5 mL) was added. The reaction mixture was stirred overnight at rt. The insolubles were removed by filtration, and the filtrate was purified by mass-directed preparative HPLC to give the *title compound* **27** (25 mg, 62 µmol, 52%). **^{1}H NMR** (500 MHz, $CDCl_3$, 1:1 mixture of rotamers, two stable conformations observed at the pyrrolidine ring): δ 8.49 (1H, s, Py 2-H), 8.46 (1H, dd, *J* 4.8, 1.5, Py 4-H), 7.79 (2H, d, *J* 7.5, Ar-H), 7.58 (1H, app. t, *J* 7.5, Py 5-H), 7.40 (2H, t, *J* 7.5, Ar-H), 7.33 (1H, app. td, *J* 7.5, 1.5, Ar-H), 7.26-7.19 (1H, m, Py 6-H), 5.26-5.24 (1H, m, 8-H), 4.17 (0.5H, d, *J* 13.6, 13-$H_{\text{A-conf1}}$), 3.94 (0.5H, d, *J* 12.0, 13-$H_{\text{A-conf2}}$), 3.82-3.63 (1.5H, m, 11-$H_{\text{A-conf1+2}}$ and 11-$H_{\text{B-conf1}}$), 3.45 (0.5H, d, *J* 13.6, 13-$H_{\text{B-conf1}}$), 3.37 (0.5H, d, *J* 12.0, 13-$H_{\text{B-conf2}}$), 3.31 (0.5H, dd, *J* 11.0, 5.4, 11-$H_{\text{B-conf2}}$), 3.23 (0.5H, dd, *J* 15.5, 2-H_A), 3.18 (0.5H, dd, *J* 15.5, 2-H_A), 3.11-2.92 (2H, m, CH_2CH_2Py), 2.79-2.46 (5H, m, CH_2CH_2Py, 2-H_B, 9-H_A, 10-H), 2.10-1.97 (1H, m, 9-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$, 2 × Ar-C_q not observed, mixture of rotamers): δ 170.3 (N(CO)), 170.2 (N(CO)), 149.9 (Py 2-C), 149.8 (Py 2-C), 147.6 (2 peaks, Py 4-C), 145.6 (Ar-C_q), 139.7 (Ar-C_q), 136.9 (Ar-C_q), 136.6 (Py 5-C), 130.3 (2 peaks, Ar-C), 129.1 (Ar-C), 128.7 (2 peaks, Ar-C), 125.1 (Ar-C), 123.7 (Py 6-C), 91.1 (1-C), 89.5 (1-C), 77.4 (8-C), 55.7 (13-C), 54.7 (13-C), 54.5 (11-C), 52.8 (11-C), 47.3 (10-C), 46.0 (10-C), 45.6 (9-C), 45.5 (9-C), 35.9 (CH_2CH_2Py), 35.7 (CH_2CH_2Py), 32.9 (2-C), 28.2 (CH_2CH_2Py).

(*1R**,*8R**,*10R**)-12-[(5-Methoxypyridin-3-yl)methyl]-5-phenyl-14-oxa-4,6,12-triazatetracyclo[6.5.1.$0^{1,10}$.$0^{3,7}$]tetradeca-3(7),4-diene 28

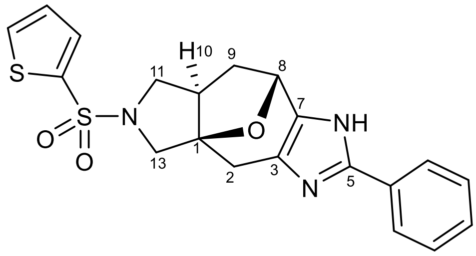


28

5-Methoxynicotinaldehyde (25 mg, 0.19 mmol, 1.50 eq.) was added to a stirred solution of compound 26 (33 mg, 0.12 mmol, 1.00 eq.) and AcOH (1.4 µL, 0.025 mmol, 0.20 eq.) in DMF (0.5 mL). The reaction mixture was stirred for 0.5 h then a solution of tetramethylammonium triacetoxyborohydride (49 mg, 0.19 mmol, 1.5 eq.) in DMF (0.5 mL) was added. The reaction mixture was stirred overnight at rt, then 30% NH_3OH solution (0.2 mL) was added. The insolubles were removed by filtration. The filtrate was purified by mass-directed preparative HPLC gave the *title compound* **28** (23 mg, 59 µmol, 49%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.20 (1H, d, *J* 2.9, Py 4-H), 8.15 (1H, s, Py 2-H), 7.80 (2H, d, *J* 8.6, Ar-H), 7.37 (2H, td, *J* 7.7, 1.9, Ar-H), 7.32-7.24 (2H, m, Ar-H, including Py 6-H), 5.28-5.16 (1H, m, 8-H), 3.86 (3H, s, OCH_3), 3.75 (1H, d, *J* 13.6, 13-H_A), 3.55 (1H, d, *J* 13.6, 13-H_B), 3.24-3.08 (2H, m, NCH_AH_BPy and 2-H_A), 2.70-2.62 (1H, m, 11-H_A), 2.56-2.41 (3H, m, 2-H_B, 9-H_A, 10-H and 11-H_B), 2.37 (1H, app. dd, *J* 10.3, 3.3, NCH_AH_BPy), 2.12-1.93 (1H, m, 9-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$, 2 × Ar-C_q not observed): δ 156.0 (Py 5-C), 145.2 (Ar-C), 142.3 (Py 2-C), 136.5 (Py 4-C), 134.8 (Ar-C), 130.6 (Ar-C), 129.0 (Ar-C), 128.4 (Ar-C), 125.0 (Ar-C), 121.3 (Py 6-C), 90.5 (1-C), 77.4 (8-C), 63.0 (NCH_2Py), 59.5 (11-C), 57.0 (13-C), 55.8 (OCH_3), 46.8 (10-C), 44.2 (9-C), 32.9[††] (2-C).

[††] Inferred by HMQC analysis.

(*1R**,*8R**,*10R**)-5-Phenyl-12-(thiophene-2-sulfonyl)-14-oxa-4,6,12-triazatetracyclo[6.5.1.0^{1,10}.0^{3,7}]tetradeca-3(7),4-diene 29

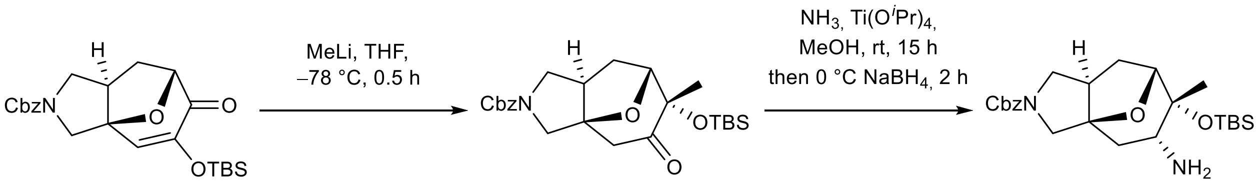


29

Thiophene-2-sulfonyl chloride (24 mg, 0.14 mmol, 1.1 eq.) was added to a solution of amine **26** (33 mg, 0.12 mmol, 1.0 eq.) and DIPEA (26 µL, 0.15 mmol, 1.2 eq.) in DMF (1.0 mL). The reaction mixture was stirred overnight at rt. The insolubles were removed by filtration. The filtrate was purified by mass-directed preparative HPLC to give the *title compound* **29** (24 mg, 58 µmol, 48%). **^{1}H NMR** (500 MHz, DMSO-d$_6$): δ 8.08 (1H, dd, *J* 5.0, 1.3, Ar-H), 7.82 (2H, d, *J* 7.0, Ar-H), 7.69 (1H, dd, *J* 3.7, 1.4, Ar-H), 7.38 (2H, t, *J* 7.7, Ar-H), 7.32 (1H, dd, *J* 5.0, 3.7, Ar-H), 7.27 (1H, t, *J* 7.4, Ar-H), 5.07 (1H, app. s, 8-H), 3.60 (1H, d, *J* 10.9, 13-H$_A$), 3.22-3.11 (11-H), 3.08-2.99 (1H, m, 2-H$_A$), 2.96 (1H, d, *J* 10.9, 13-H$_B$), 2.68-2.54 (2H, m, 2-H$_B$ and 10-H), 2.34 (1H, dd, *J* 11.9, 8.5, 9-H$_A$), 1.93 (1H, dt, *J* 11.9, 6.2, 9-H$_B$). **^{13}C NMR** (100 MHz, DMSO-d$_6$): δ 143.8 (Ar-C), 141.0 (Ar-C), 134.4 (Ar-C), 134.0 (Ar-C), 133.4 (Ar-C), 130.9 (Ar-C), 128.7 (Ar-C), 128.4 (Ar-C), 127.6 (Ar-C), 124.3 (Ar-C), 122.2 (Ar-C), 89.5 (1-C), 79.2 (8-C), 56.3 (13-C), 54.2 (11-C), 45.9 (10-C), 44.4 (9-C), 30.9 (2-C).

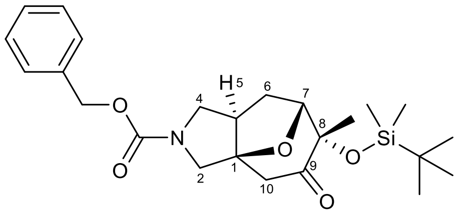
1.3.4 Preparation of scaffolds 5

1.3.4.1 Initial procedure to prepare compound 31



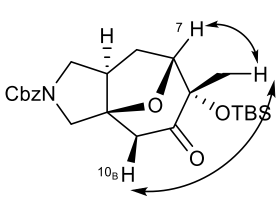
1   **30a** 91%   **31** 77%

Benzyl (*1R*,5R*,7R*,8S**)-8-[(*tert*-butyldimethylsilyl)oxy]-8-methyl-9-oxo-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecane-3-carboxylate 30a

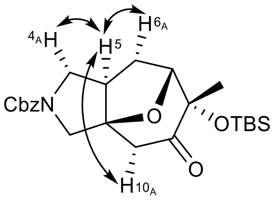


30a

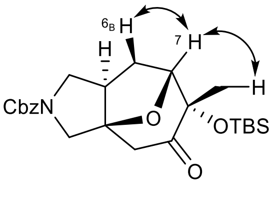
MeLi (1.6 M in Et_2O, 0.37 mL, 0.60 mmol, 1.30 eq.) was added to a stirred solution of compound **1** (200 mg, 0.46 mmol, 1.00 eq.) in THF (15 mL) at −78 °C. The reaction mixture was stirred at this temperature for 0.5 h, then sat. aq. brine (1.0 mL) was added. The reaction mixture was warmed to rt, then partitioned between EtOAc (25 mL) and brine (25 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. Flash chromatography eluting with 95:5 pentane–EtOAc gave the title compound **30a** (187 mg, 0.42 mmol, 91%) as a yellow oil. **R*f*** 0.30 (3:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$, 50:50 mixture of rotamers): δ 7.39-7.28 (5H, m, Cbz Ar-H), 5.12 (2H, s, OCH_2Ph), 4.21-4.15 (1H, m, 7-H), 3.95-3.83 (2H, m, 2-H_B and 4-H_A), 3.43 (0.5H, d, *J* 12.6, 2-H_A), 3.38 (0.5H, d, *J* 12.6, 2-H_A), 3.20-3.09 (1H, m, 4-H_B), 2.92 (0.5H, d, *J* 15.3, 10-H_B), 2.86 (0.5H, d, *J* 15.3, 10-H_B), 2.55-2.46 (1H, m, 5-H), 2.37 (0.5H, d, *J* 3.3, 10-H_A), 2.34 (0.5H, d, *J* 3.3, 10-H_A), 2.27-2.14 (1H, m, 6-H_A), 1.91-1.76 (1H, m, 6-H_B), 1.46 (1.5H, s, C_qCH_3), 1.45 (1.5H, s, C_qCH_3), 0.85 (9H, s, $SiC(CH_3)_3$), 0.17 (3H, s, $SiCH_3$), 0.13 (3H, s, $SiCH_3$). **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of two rotamers): δ 208.0 (9-C), 207.9 (9-C), 154.4 (N(CO)O), 136.8 (Ar-C_q), 128.6 (Ar-C), 128.2 (Ar-C), 128.12 (Ar-C), 91.5 (1-C), 90.7 (1-C), 85.4 (7-C), 81.4 (8-C), 67.1 (OCH_2Ph), 54.2 (2-C or 4-C), 53.8 (2-C or 4-C), 53.7 (2-C or 4-C), 47.3 (10-C), 45.7 (5-C), 44.8 (5-C), 31.7 (6-C), 31.4 (6-C), 26.0 ($SiC(CH_3)_3$), 24.4 (C_qCH_3), 18.5 (SiC_q), −2.3 ($SiCH_3$), −2.6 ($SiCH_3$) [25 of 38 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1} 2954, 2953, 2930, 2887, 1702 (CO), 1629,1593, 1419 **HRMS** (ESI): $C_{24}H_{36}NO_5Si$ $[M+H]^+$; calculated 446.2357, found 446.2360.



C_qCH_3



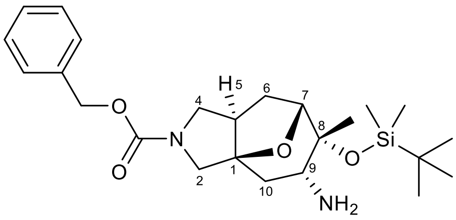
5-H



7-H

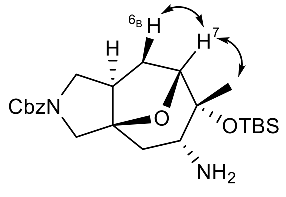
30a NOESY correlations:
C_qCH_3: 7-H; 10-H_B
5-H: 4-H_A; 6-H_A; 10-H_A
7-H: C_qCH_3; 6-H_B

Benzyl (_1R*,5R*,7R*,8R*,9R*_)-9-amino-8-[(_tert_-butyldimethylsilyl)oxy]-8-methyl-11-oxa-3-azatricyclo[5.3.1.$0^{1,5}$]undecane-3-carboxylate 31

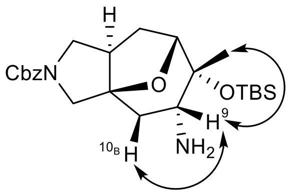


31

Ti(O^{i}Pr)$_4$ (4.30 mL, 14.4 mmol, 2.00 eq.) was added to a stirred solution of compound **30a** (3.21 g, 7.20 mmol, 1.00 eq.) in sat. NH$_3$/MeOH (100 mL). The reaction mixture was stirred for 15 h then NaBH$_4$ (409 mg, 10.8 mmol, 1.5 eq.) was added at 0 °C. The reaction mixture was warmed to rt, stirred for 2 h then concentrated *in vacuo*. The residue was diluted in EtOAc (50 mL) and sat. aq. brine (50 mL) and stirred vigorously. The phases were separated and the aqueous phase was extracted with EtOAc (2 × 25 mL). The combined organic phase was dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Flash chromatography eluting with EtOAc, then 9:1 EtOAc–MeOH, gave the title compound **31** (2.46 g, 5.51 mmol, 77%) as a colourless oil. **^{1}H NMR** (500 MHz, CDCl$_3$, 50:50 mixture of rotamers, NH$_2$ not observed): δ 7.38-7.27 (5H, m, Cbz Ar-H), 5.10 (2H, s, OCH_2Ph), 4.00 (1H, d, *J* 7.5, 7-H), 3.92-3.82 (1H, m, 4-H$_A$), 3.75-3.68 (1H, m, 2-H$_B$, includes at δ 3.72: 0.5H, d, *J* 12.5; and at δ 3.71: 0.5H, d, *J* 12.5), 3.38 (0.5H, d, *J* 12.5, 2-H$_A$), 3.33 (0.5H, d, *J* 12.5, 2-H$_A$), 3.23-3.12 (2H, m, 4-H$_B$ and 9-H), 3.11-3.03 (1H, m, 5-H), 2.96-2.87 (1H, m, 6-H$_A$), 2.16 (0.5H, dd, *J* 14.2, 5.4, 10-H$_B$), 2.11 (0.5H, dd, *J* 14.2, 5.4, 10-H$_B$), 1.72-1.60 (1H, m, 6-H$_B$), 1.57-1.50 (1H, m, 10-H$_A$, includes at δ 1.54: 0.5H, d, *J* 14.2; and at δ 1.53: 0.5H, d, *J* 14.2), 1.37 (1.5H, s, C$_q$CH_3), 1.36 (1.5H, s, C$_q$CH_3), 0.91 (9H, s, SiC(CH$_3$)$_3$), 0.13 (3H, s, SiCH$_3$), 0.12-0.10 (3H, m, SiCH$_3$). **^{13}C NMR** (125 MHz, DMSO-d$_6$, mixture of two rotamers): δ 153.6 (N(CO)O), 153.4 (N(CO)O), 137.1 (Ar-C$_q$), 128.4 (Ar-C), 127.7 (Ar-C), 127.5 (Ar-C), 89.3 (1-C), 88.4 (1-C), 83.2 (7-C), 73.1 (8-C), 65.7 (OCH$_2$Ph), 54.7 (2-C or 4-C), 54.6 (2-C or 4-C), 54.1 (2-C or 4-C), 54.0 (2-C or 4-C), 53.8 (9-C), 44.4 (5-C), 43.4 (5-C), 36.7 (10-C), 36.6 (10-C), 32.9 (6-C), 32.8 (6-C), 27.5 (C$_q$$CH_3$), 25.8 (SiC($CH_3$)$_3$), 18.0 (SiC$_q$), −2.0 (SiCH$_3$), −2.2 (SiCH$_3$) [27 of 38 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1} 2952, 2931, 2882, 2856, 1704 (CO), 1419, 1362, 1346. **HRMS** (ESI): $C_{24}H_{39}N_2O_4Si$ [M+H]$^+$; calculated 447.2674, found 447.2679.



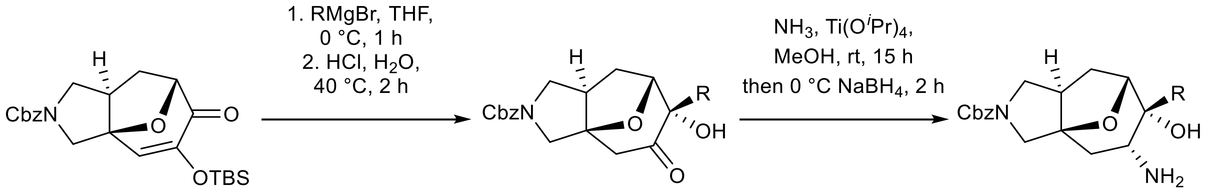
7-H



9-H

31 NOESY correlations:
Me: 7-H; 9-H
7-H: Me; 6-H$_B$
9-H: Me; 10-H$_B$

1.3.4.2 Optimised synthetic route to prepare scaffolds 5a-b

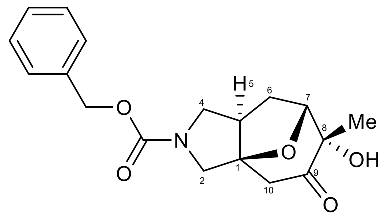


1

33a R= Me; 69%
33b R= Ph; 78%

5a R= Me; 71%
5b R= Ph; 67%

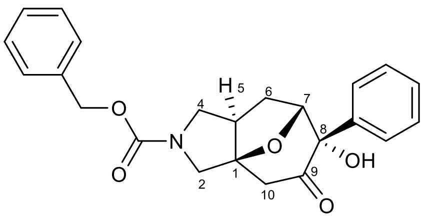
Benzyl (1R*,5R*,7R*,8S*)-8-hydroxy-8-methyl-9-oxo-11-oxa-3-azatricyclo[5.3.1.$0^{1,5}$]undecane-3-carboxylate 33a



33a

MeMgBr (3.0 M in Et_2O, 2.3 mL, 6.9 mmol, 1.5 eq.) was added to a stirred solution of compound **1** (2.0 g, 4.6 mmol, 1.0 eq.) in THF (4.6 mL) at 0 °C. The reaction was stirred at 0 ˚C for 10 min, then warmed to rt and stirred for 1 h. The reaction was cooled to 0 ˚C, H_2O (1.0 mL) was added dropwise, followed by HCl (2.0 M, 10 mL). The reaction mixture was warmed to 40 ˚C and stirred for 2 h. The reaction mixture was cooled, transferred to a separatory funnel and extracted with EtOAc (3 × 50 mL). The combined organics were concentrated *in vacuo*. Flash chromatography eluting with EtOAc–hexanes (20:80) gave the *title compound* **33a** (1.05 g, 3.17 mmol, 69%) as a colourless foam. **^{1}H NMR** (500 MHz, $CDCl_3$, 50:50 mixture of rotamers): δ 7.39-7.28 (5H, m, Cbz Ar-H), 5.12 (2H, s, OCH_2Ph), 4.39 (1H, d, *J* 7.4, 7-H), 3.99-3.92 (1H, m, includes at δ 3.96: 0.5H, d, *J* 12.8; and at δ 3.94: 0.5H, d, *J* 12.8, 2-H_A), 3.92-3.84 (1H, m, 4-H_A), 3.72 (1H, s, O*H*), 3.45 (0.5H, d, *J* 12.8, 2-H_B), 3.40 (0.5H, d, *J* 12.8, 2-H_B), 3.21-3.10 (1H, m, 4-H_B), 3.05 (0.5H, d, *J* 15.0, 10-H_A), 2.99 (0.5H, d, *J* 15.0, 10-H_A), 2.54-2.42 (2H, m, 5-H and 10-H_B), 2.15 (1H, td, *J* 14.5, 8.7, 6-H_A), 1.91-1.78 (1H, m, 6-H_B), 1.48 (1.5H, s, CH_3), 1.47 (1.5H, s, CH_3). **^{13}C NMR** (125 MHz, $CDCl_3$, 329 K, mixture of two rotamers): δ 210.0 (9-C), 154.4 (N(CO)O), 137.0 (Ar-C_q), 128.7 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 91.5 (1-C), 91.4 (1-C), 84.7 (7-C), 78.5 (8-C), 67.2 (OCH_2Ph), 54.1 (2-C and 4-C), 46.5 (10-C), 45.9 (5-C), 45.0 (5-C), 31.5 (6-C), 24.5 (CH_3) [17 of 34 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1} 2954, 2887, 1703 (CO), 1454, 1422, 1350, 1108, 771. **HRMS** (ESI): $C_{18}H_{22}NO_5$ $[M+H]^+$; calculated 332.1492, found 332.1491.

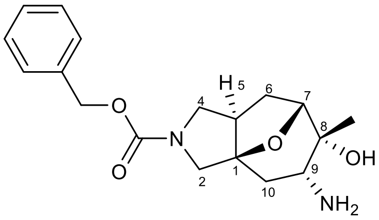
Benzyl (1R*,5R*,7R*,8S*)-8-hydroxy-9-oxo-8-phenyl-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecane-3-carboxylate 33b



33b

PhMgBr (1.0 M in THF, 6.9 mL, 6.9 mmol, 1.5 eq.) was added to a stirred solution of compound **1** (2.0 g, 4.6 mmol, 1.0 eq.) in THF (4.6 mL) at 0 °C. The reaction was stirred at 0 ˚C for 10 min, then warmed to rt and stirred for 1 h. The reaction was cooled to 0 ˚C, H_2O (1.0 mL) was added dropwise, followed by HCl (2.0 M, 10 mL). The reaction mixture was warmed to 40 ˚C and stirred for 2 h. The reaction mixture was cooled, transferred to a separatory funnel and extracted with EtOAc (3 × 50 mL). The combined organics were concentrated *in vacuo*. Flash chromatography eluting with EtOAc–hexanes (20:80) gave the *title compound* **33a** (1.41 g, 3.59 mmol, 78%) as a colourless foam. **^{1}H NMR** (500 MHz, $CDCl_3$, 1:1 mixture of rotamers): δ 7.52-7.46 (2H, m, Ar-H), 7.40-7.27 (8H, m, Ar-H), 5.15-5.06 (3H, m, OCH_2Ph and 7-H), 4.39 (1H, s, OH), 3.97-3.87 (2H, m, includes 4-H_A; and at δ 3.94: 1H, d, *J* 12.7, 2-H_A), 3.41 (0.5H, d, *J* 12.7, 2-H_B), 3.37 (0.5H, d, *J* 12.7, 2-H_B), 3.25-3.15 (1H, m, 4-H_B), 3.01 (0.5H, d, *J* 14.8, 10-H_A), 2.96 (0.5H, d, *J* 14.8, 10-H_A), 2.64-2.55 (1H, m, 5-H), 2.52 (1H, d, *J* 14.8, 10-H_B), 2.41-2.30 (1H, m, 6-H_B), 2.08-1.95 (1H, m, 6-H_A). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 207.8 (9-C), 154.3 (N(CO)O), 154.2 (N(CO)O), 139.6 (Ar-C_q), 136.7 (Ar-C_q), 136.7 (Ar-C_q), 128.9 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 126.9 (Ar-C), 92.3 (1-C), 91.5 (1-C), 82.3 (7-C), 81.1 (8-C), 67.1 (OCH_2Ph), 54.2 (2-C), 54.1 (2-C), 53.8 (4-C), 53.7 (4-C), 47.2 (5-C), 46.0 (10-C), 45.1 (10-C), 31.9 (6-C), 31.7 (6-C) [26 of 38 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1}: 3420 (OH), 2956, 2884, 1695 (CO), 1418, 1178, 1097, 935. **HRMS** (ESI): $C_{23}H_{24}NO_5$ [M+H]$^+$; calculated: 394.1654, found: 394.1663.

Benzyl (*1R**,*5R**,*7R**,*8R**,*9R**)-9-amino-8-hydroxy-8-methyl-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecane-3-carboxylate 5a

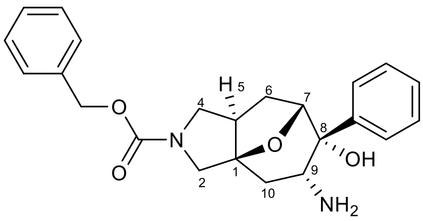


5a

Compound **33a** (1.0 g, 3.1 mmol, 1.0 eq.) was dissolved in sat. NH_3/MeOH (6.1 mL) and the reaction mixture was stirred at rt for 10 min. $Ti(O^iPr)_4$ (1.36 mL, 4.6 mmol, 1.5 eq.) was added and the reaction mixture was stirred at rt for 4 h. The reaction mixture was then cooled to 0 °C and $NaBH_4$ (243 mg, 6.2 mmol, 2.0 eq.) was added. After 1 h at 0 °C, the reaction mixture was warmed to rt and stirred for 1 h. NH_4OH (aq. 35%, 5 mL) was added and the reaction mixture was concentrated *in vacuo*. The residue was diluted with NH_4OH (aq. 35%, 5 mL) and EtOAc (20 mL), and the resulting suspesion was stirred for 5 min. The suspension was dried with $MgSO_4$ (*caution – exotherm!*)[‡‡] then filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* to give the *title compound* **5a** (715 mg, 2.2 mmol, 71%), which was not purified further. **^{1}H NMR** (500 MHz, $CDCl_3$, 1:1 mixture of rotamers, NH_2 and OH not observed): δ 7.39-7.28 (5H, m, Cbz Ar-H), 5.10 (2H, s, OCH_2Ph), 4.06 (1H, d, *J* 7.7, 7-H), 3.97-3.87 (1H, m, 4-H_A), 3.75-3.68 (1H, d, *J* 12.5, 2-H_A), 3.41 (0.5H, d, *J* 12.5, 2-H_B), 3.35 (0.5H, d, *J* 12.5, 2-H_B), 3.23-3.14 (1H, m, 4-H_B), 2.96 (1H, br. s, 9-H), 2.81-2.72 (1H, m, 5-H), 2.68-2.58 (1H, m, 6-H_A), 2.41 (0.5H, dd, *J* 14.8, 6.2, 10-H_A), 2.35 (0.5H, dd, *J* 14.8, 6.2, 10-H_A), 1.80-1.63 (2H, m, 6-H_B and 10-H_B), 1.33 (1.5H, s, CH_3), 1.32 (1.5H, s, CH_3). **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of two rotamers): δ 154.4 (N(CO)O), 136.9 (Ar-C_q), 128.6 (Ar-C), 128.1 (Ar-C), 128.0 (2 × peaks, Ar-C), 89.6 (1-C), 88.7 (1-C), 84.4 (7-C), 68.1 (8-C), 67.0 (OCH_2Ph), 55.1 (2-C or 4-C), 55.0 (2-C or 4-C), 54.7 (2-C or 4-C), 54.6 (2-C or 4-C), 52.8 (9-C), 45.2 (5-C), 44.2 (5-C), 38.4 (10-C), 31.4 (6-C), 31.0 (6-C), 26.9 (CH_3) [22 of 32 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1}: 2946, 1691 (CO), 1424, 1349, 1164, 1122. **HRMS** (ESI): $C_{18}H_{25}N_2O_4$ $[M+H]^+$; calculated: 333.1814, found: 333.1805.

[‡‡] Recommend cooling to 0 °C for large scale reactions.

(*1R**,*5R**,*7R**,*8R**,*9R**)-9-Amino-8-hydroxy-8-phenyl-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecane-3-carboxylate 5b

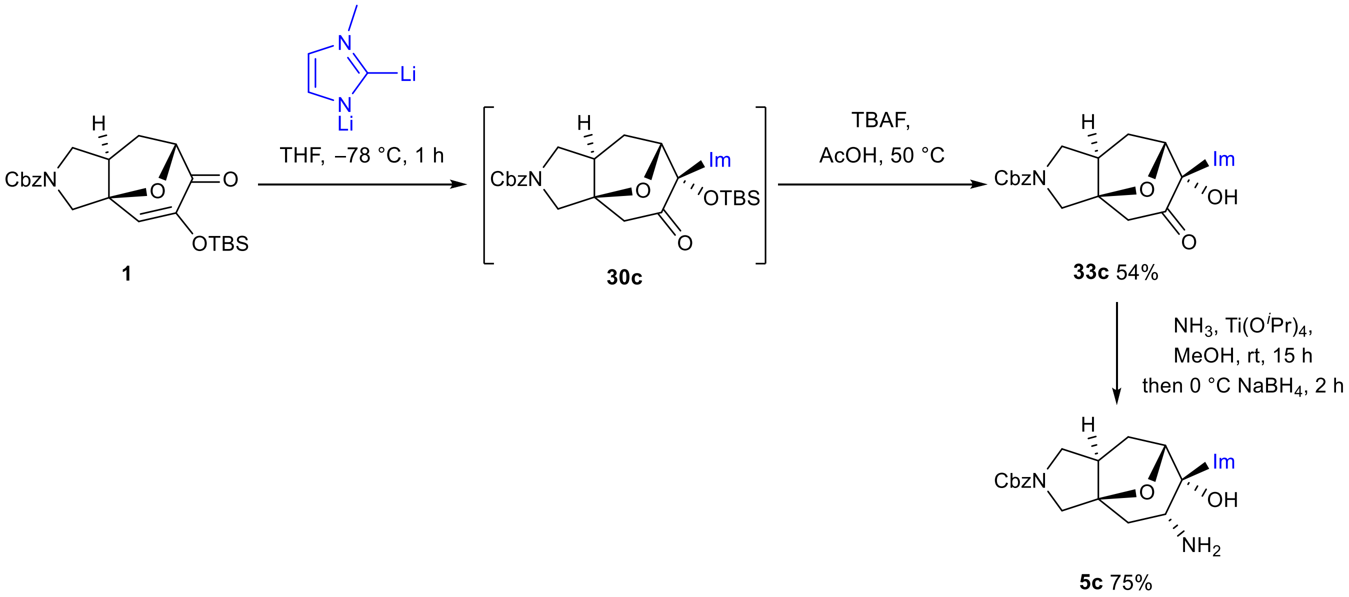


5b

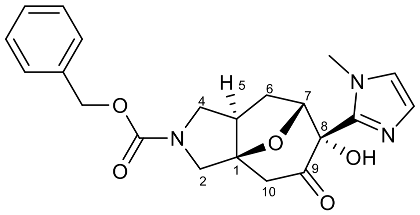
Compound **33b** (1.0 g, 2.5 mmol, 1.0 eq.) was dissolved in sat. NH_3/MeOH (5.0 mL) and the reaction mixture was stirred at rt for 10 min. $Ti(O^iPr)_4$ (1.12 mL, 3.8 mmol, 1.5 eq.) was added and the reaction mixture was stirred at rt for 4 h. The reaction mixture was then cooled to 0 °C and $NaBH_4$ (190 mg, 5.0 mmol, 2.0 eq.) was added. After 1 hour at 0 °C, the reaction mixture was warmed to rt and stirred for 1 h. NH_4OH (aq. 35%, 5 mL) was added and the reaction mixture was concentrated *in vacuo*. The residue was diluted with NH_4OH (aq. 35%, 5 mL) and EtOAc (20 mL), and the resulting suspesion was stirred for 5 min. The suspension was dried with $MgSO_4$ (*caution – exotherm!*)[§§] then filtered through a pad of Celite®. Flash chromatography eluting with CH_2Cl_2-EtOH-NH_4OH (50:8:1) gave the *title compound* **5b** (656 mg, 1.66 mmol, 67%). **^{1}H NMR** (500 MHz, $CDCl_3$, 1:1 mixture of rotamers, NH_2 and OH not observed): δ 7.64 (2H, d, *J* 7.6, Ph-H), 7.37-7.28 (7H, m, Ar-H), 7.26-7.20 (1H, m, Ar-H), 5.19-5.05 (2H, m, OCH_2Ph), 4.61 (1H, d, *J* 7.5, 7-H), 3.97-3.84 (2H, m, 2-H_A and 4-H_A), 3.45-3.30 (2H, m, 2-H_B and 9-H), 3.29-3.16 (1H, m, 4-H_B), 2.87-2.75 (1H, m, 6-H_A), 2.75-2.64 (1H, m, 5-H), 2.42-2.29 (1H, m, 10-H_B), 1.82-1.69 (1H, m, 6-H_B), 1.66 (1H, dd, *J* 14.2, 5.5, 10-H_A). **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of two rotamers): δ 154.6 (N(CO)O), 154.5 (N(CO)O), 147.9 (2 peaks, Ar-C_q), 137.0 (Ar-C_q), 128.6 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.1 (Ar-C), 126.0 (Ar-C), 89.0 (1-C), 88.1 (1-C), 85.4 (7-C), 71.2 (8-C), 67.0 (OCH_2Ph), 55.6 (2-C or 4-C), 55.2 (2-C or 4-C), 54.9 (2-C or 4-C), 54.6 (2-C or 4-C), 52.6 (9-C), 47.5 (5-C), 46.5 (5-C), 37.7 (10-C), 37.6 (10-C), 32.3 (6-C), 32.0 (6-C) [27 of 38 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1}: 3399 (OH), 2945, 1691 (CO), 1418, 1347, 1100, 730, 698. **HRMS** (ESI): $C_{23}H_{27}N_2O_4$ $[M+H]^+$; calculated: 395.1971, found: 395.1976.

[§§] Recommend cooling to 0 °C for large scale reactions.

1.3.4.3 Preparation of scaffold 5c



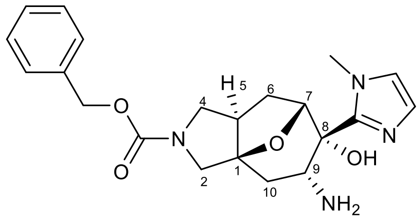
Benzyl (*1R**,*5R**,*7R**,*8S*)-8-hydroxy-8-(1-methyl-1*H*-imidazol-2-yl)-9-oxo-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecane-3-carboxylate 33c



33c

Part 1: Addition of the 1-methyl-1H-imidazol-2-yl lithium carbanion to compound **1***:* To a stirred solution of methylimidazole (5.84 g, 71.2 mmol, 2.20 eq.) in THF (110 mL) at −78 °C was added dropwise BuLi (2.5 M in hexane, 25.9 mL, 64.7 mmol, 2.00 eq.). The reaction mixture was stirred at this temperature for 0.5 h, then a solution of compound **1** (13.9 g, 32.4 mmol) in THF (130 mL) was added dropwise. The solution was stirred at −78 °C for 1 h. The reaction mixture was warmed to 0 °C and used directly in the next step. *Part 2: Deprotection of silyl-protected alcohol* **30c***:* TBAF (1.0 M in THF, 35 mL, 35 mmol, 1.1 eq.) and AcOH (2.0 mL) were added to the stirring reaction mixture at 0 °C. The reaction mixture was warmed to rt and then heated at 35 °C overnight. Additional TBAF (1.0 M in THF, 10 mL, 10 mmol, 0.3 eq.) was added and the reaction mixture was heated at 50 °C for 8 h. The reaction mixture was concentrated *in vacuo*. The crude reaction mixture was diluted in EtOAc–Et_2O (2:1, 1 volume) and washed with sat. aq. NH_4Cl solution (5 × 1 volumes) and brine (1 volume). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by dry column vacuum chromatography (DCVC, 200 g silica) eluting with 30-100% EtOAc in *c*-hexane to give the *title compound* **33c** as a yellow oil (7.0 g, 17.6 mmol, 54%). **R*f*** 0.32 (3:7 *c*-hexane–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$, 1:1 mixture of rotamers): δ 7.38-7.27 (5H, m, Cbz Ar-H), 6.89 (1H, d, *J* 8.7, imidazole H), 6.83 (1H, app. s, imidazole H), 5.14-5.06 (2H, m, OCH_2Ph), 4.97 (1H, d, *J* 7.3, 7-H), 4.30 (1H, s, OH), 3.98-3.84 (3H, m, 2-H_A and 4-H), 3.81 (3H, s, NCH_3), 3.45 (0.5H, d, *J* 12.8, 2-H_B), 3.40 (0.5H, d, *J* 12.8, 2-H_B), 3.21-3.09 (1H, m, 10-H_A), 2.72-2.66 (1H, m, 10-H_B; includes at δ 2.70: 0.5H, d, *J* 14.7; and at δ 2.68: 0.5H, d, *J* 14.7), 2.63-2.54 (1H, m, 5-H), 2.28-2.19 (1H, m, 6-H_A), 2.06-1.92 (1H, m, 6-H_B). **LRMS** (LCMS): $C_{21}H_{24}N_3O_5$ $[M+H]^+$; found 398.3.

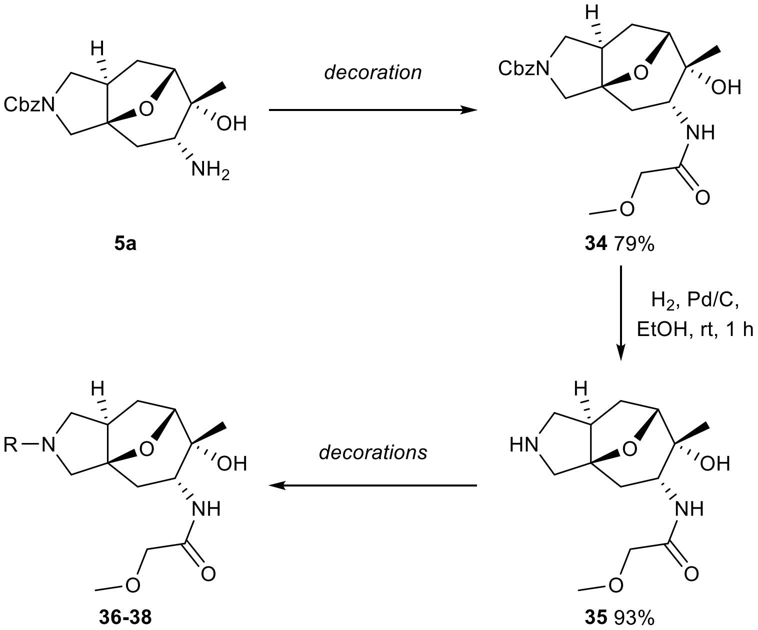
(*1R**,*5R**,*7R**,*8R**,*9R**)-9-Amino-8-hydroxy-8-(1-methyl-1*H*-imidazol-2-yl)-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecane-3-carboxylate 5c



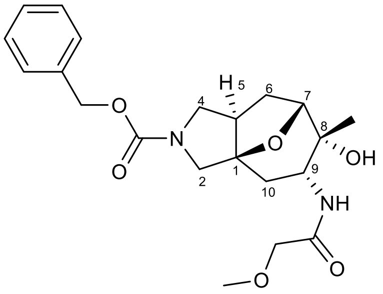
5c

Ti(O^{i}Pr)$_4$ (671 µL, 2.26 mmol, 1.50 eq.) was added to a stirred solution of compound **33c** (600 mg, 1.51 mmol, 1.00 eq.) in sat. NH_3/MeOH (4.0 mL). The reaction mixture was stirred for 4 h then $NaBH_4$ (115 mg, 3.02 mmol, 2.0 eq.) was added at 0 °C. The reaction mixture was warmed to rt, stirred overnight. Additional $NaBH_4$ (58 mg, 1.51 mmol, 1.0 eq.) was added at the reaction mixture was heated at 50 °C for 4 h. The reaction mixture was cooled to rt. NH_4OH (aq. 35%, 4 mL) and EtOAc (10 mL) were added and the reaction mixture was stirred for 5 min then filtered through a short Celite® pad and washing with EtOAc. The filtrate was separated and the aqueous phase was extracted with EtOAc (3 × 1 volume). The combined organics were concentrated *in vacuo* to give the *title compound* **5c** (450 mg, 1.13 mmol, 75%) as a colourless solid. **^{1}H NMR** (500 MHz, $CDCl_3$, 1:1 mixture of rotamers, NH_2 not observed): δ 7.38-7.27 (5H, m, Cbz Ar-H), 6.89 (1H, app. s, imidazole H), 6.84-6.79 (1H, m, imidazole H), 5.14-5.05 (2H, m, OCH_2Ph), 4.60 (1H, d, *J* 7.5, 7-H), 3.94 (1H, dd, *J* 6.9, 3.9, 9-H), 3.86-3.79 (5H, m, includes 2-H$_A$, 4-H$_A$ and at δ 3.81: 3H, s, NCH_3), 3.40 (0.5H, d, *J* 12.6, 2-H$_B$), 3.34 (0.5H, d, *J* 12.6, 2-H$_B$), 3.24-3.13 (1H, m, 4-H$_B$), 2.85 (1H, dd, *J* 14.3, 6.9, 10-H$_A$), 2.78-2.64 (2H, m, 5-H and 6-H$_A$), 1.88-1.73 (2H, m, includes 6-H$_B$ and at δ 1.76: 1H, dd, *J* 14.3, 3.9, 10-H$_B$). **LRMS** (LCMS): $C_{21}H_{27}N_4O_4$ $[M+H]^+$; found 399.4.

1.3.4.4 Exemplar decorations of scaffold 5a



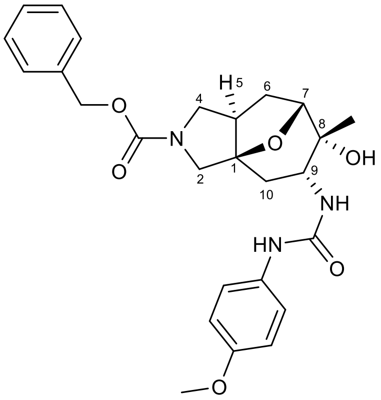
Benzyl (*1R**,*5R**,*7R**,*8R**,*9R**)-8-hydroxy-9-(2-methoxyacetamido)-8-methyl-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecane-3-carboxylate 34



34

Methoxyacetyl chloride (166 µL, 1.81 mmol, 1.20 eq.) was added to a stirred solution of compound **5a** (500 mg, 1.51 mmol, 1.0 eq.) and DIPEA (522 µL, 3.00 mmol, 2.0 eq.) in CH_2Cl_2 (3.0 mL). The reaction mixture was stirred for 4 h, then concentrated *in vacuo*. Flash chromatography eluting with EtOAc gave the *title compound* **34** (478 mg, 1.18 mmol, 79%). **^{1}H NMR** (300 MHz, $CDCl_3$, 1:1 mixture of rotamers, OH not observed): δ 7.40-7.28 (5H, m, Cbz Ar-H), 7.10 (1H, s, NH), 4.08 (1H, d, *J* 7.6, 7-H), 4.02-3.85 (4H, m, includes 4-H$_A$ and 9-H and at δ 3.91: 2H, s, NH(CO)C*H*$_2$), 3.80-3.71 (1H, m, 2-H$_A$, includes at δ 3.76: 0.5H, d, *J* 12.5; and at δ 3.75: 0.5H, d, *J* 12.5), 3.49-3.31 (4H, m, includes 2-H$_B$; and at δ 3.45: 3H, s, OCH_3), 3.26-3.13 (1H, m, 4-H$_B$), 2.75-2.62 (1H, m, 5-H), 2.62-2.47 (1H, m, 6-H$_A$), 2.43-2.22 (1H, m, 10-H$_A$), 1.98-1.75 (2H, m, 6-H$_B$ and 10-H$_B$), 1.47 (3H, s, C_qCH_3). **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of two rotamers): δ 171.2 (NH(CO)), 154.4 (N(CO)O), 136.9 (2 peaks, Ar-C$_q$), 128.6 (Ar-C), 128.1 (2 peaks, Ar-C), 89.8 (1-C), 88.9 (1-C), 83.6 (7-C), 83.5 (7-C), 72.0 (NH(CO)*C*H$_2$), 70.0 (8-C), 67.0 (OCH_2Ph), 59.5 (OCH_3), 55.1 (2-C or 4-C), 54.8 (2-C or 4-C), 54.7 (2-C or 4-C), 54.4 (2-C or 4-C), 52.0 (2 peaks, 9-C), 44.8 (5-C), 43.8 (5-C), 34.8 (10-C), 34.7 (10-C), 31.9 (6-C), 31.6 (6-C), 28.5 (C_qCH_3) [28 of 38 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1}: 3393, 2939, 1701 (CO), 1677 (CO), 1422, 1350, 1116. **HRMS** (ESI): $C_{21}H_{28}N_2NaO_6$ [M+Na]$^+$; calculated: 427.1845, found: 427.1838.

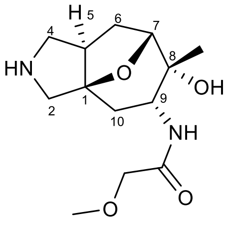
Benzyl (*1R**,*5R**,*7R**,*8R**,*9R**)-8-hydroxy-9-{[(4-methoxyphenyl)carbamoyl]amino}-8-methyl-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecane-3-carboxylate S-34



S-34

4-methoxyphenyl isocyanate (52 mg, 0.35 mmol, 1.1 eq.) was added to a stirred solution of compound **5a** (106 mg, 0.32 mmol, 1.0 eq.) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred for 1 h, then concentrated *in vacuo*. Flash chromatography eluting with EtOAc gave the *title compound* **S-34** (141 mg, 0.29 mmol, 92%) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$, 1:1 mixture of rotamers): δ 7.39-7.29 (5H, m, Cbz Ar-H), 7.18 (2H, d, *J* 9.1, PMP 2-H), 6.89 (2H, d, *J* 9.1, PMP 3-H), 6.43 (0.5H, s, NH), 6.34 (0.5H, s, NH), 5.26 (0.5H, d, *J* 3.2, CHNH), 5.21 (0.5H, d, *J* 3.2, CHNH), 5.10 (2H, s, OCH_2Ph), 4.02 (1H, d, *J* 7.6, 7-H), 3.93-3.77 (5H, m, includes 4-H_A, 9-H, and at δ 3.80: 3H, s, OCH_3), 3.76-3.68 (1H, m, 2-H_A, includes at δ 3.73: 0.5H, d, *J* 12.7; and at δ 3.71: 0.5H, d, *J* 12.7), 3.33 (1H, app. t, *J* 12.5, 2-H_B), 3.22-3.07 (1H, m, 4-H_B), 2.89 (0.5H, s, OH), 2.81 (0.5H, s, OH), 2.57-2.17 (3H, m, 5-H, 6-H_A and 10-H_A), 1.86 (1H, d, *J* 15.1, 10-H_B), 1.78-1.63 (1H, m, 6-H_B), 1.43 (3H, s, C_qCH_3). **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of two rotamers, 1 × CO not observed): δ 158.3 (PMP 4-C), 158.2 (PMP 4-C), 154.5 (CO), 136.8 (Ar-C_q), 130.3 (2 peaks, Ar-C), 128.6 (Ar-C), 128.2 (Ar-C), 128.0 (Ar-C), 125.4 (PMP 2-C), 115.0 (PMP 3-C), 89.5 (1-C), 88.9 (1-C), 83.6 (2 peaks, 7-C), 69.9 (2 peaks, 8-C), 67.5 (OCH_2Ph), 67.1 (OCH_2Ph), 55.7 (OCH_3), 55.0 (2-C or 4-C), 54.8 (2-C or 4-C), 54.7 (2-C or 4-C), 54.5 (2-C or 4-C), 53.2 (9-C), 53.1 (9-C), 44.5 (5-C), 43.6 (5-C), 35.3 (10-C), 31.9 (6-C), 31.7 (6-C), 28.5 (C_qCH_3) [32 of 44 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1}: 3357 (OH), 1678 (CO), 1551, 1510, 1456, 1429, 1172. **HRMS** (ESI): $C_{26}H_{31}N_3NaO_6$ $[M+Na]^+$; calculated: 504.2111, found: 504.2099.

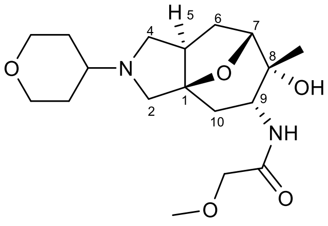
N-[(*1R**,*5R**,*7R**,*8R**,*9R**)-8-hydroxy-8-methyl-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecan-9-yl]-2-methoxyacetamide 35



35

Hydrogenation was carried out following general procedure **B**, using compound **34** (478 mg, 1.18 mmol) to give the *title compound* **35** as a colourless oil (296 mg, 1.09 mmol, 93%). **^{1}H NMR** (500 MHz, 333 K, MeOD, NH and OH not observed): δ 4.09-4.05 (1H, m, 7-H), 3.93 (1H, d, *J* 15.3, $C\mathit{H}_AH_BOCH_3$), 3.85 (1H, d, *J* 15.3, $CH_A\mathit{H}_BOCH_3$), 3.81-3.75 (1H, m, 9-H), 3.43-3.32 (5H, m, includes 2-H$_A$, 4-H$_A$; and at δ 3.35: 3H, s, OCH_3), 2.98 (2H, app. d, *J* 12.3, 2-H$_B$ and 4-H$_B$), 2.90-2.82 (1H, m, 5-H), 2.68 (1H, dd, *J* 13.7, 8.9, 6-H$_A$), 2.21-2.17 (1H, m, 10-H), 1.85-1.78 (1H, m, 6-H$_B$), 1.42 (3H, s, C_qCH_3). **^{13}C NMR** (125 MHz, MeOD): δ 172.5 (NH(CO)), 91.0 (1-C), 85.2 (7-C), 73.0 (CH_2OCH_3), 69.1 (8-C), 59.8 (OCH_3), 55.1 (2-C or 4-C), 54.8 (2-C or 4-C), 53.3 (9-C), 45.0 (5-C), 34.7 (6-C), 33.2 (10-C), 28.0 (C_qCH_3). **IR** ν_{max}(film)/cm^{-1}: 3391 (OH), 2936, 1658 (CO), 1520, 1453, 1113. **HRMS** (ESI): $C_{13}H_{23}N_2O_4$ [M+H]$^+$; calculated: 271.1658, found: 271.1647.

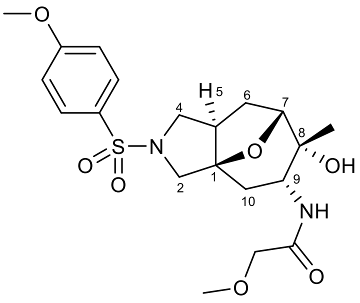
N-[(*1R**,*5R**,*7R**,*8R**,*9R**)-8-hydroxy-8-methyl-3-(oxan-4-yl)-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecan-9-yl]-2-methoxyacetamide 36



36

General procedure **D** was followed using compound **35** (26 mg, 95 μmol) and tetrahydro-4*H*-pyran-4-one. Purification by mass directed preparative HPLC gave the *title compound* **36** (14 mg, 40 μmol, 42%) as an amorphous solid. **^{1}H NMR** (500 MHz, $CDCl_3$, OH not observed): δ 7.14 (1H, d, *J* 5.3, NH), 4.06 (1H, d, *J* 7.4, 7-H), 4.00-3.93 (4H, m, 9-H, THP 2-H$_A$, and THP 4-H), 3.90 (2H, d, *J* 5.2, $C\mathit{H}_2OCH_3$), 3.45 (3H, s, OCH_3), 3.40-3.33 (2H, m, THP 2-H$_B$), 3.12 (1H, app. t, *J* 8.3, 4-H$_A$), 2.88 (1H, d, *J* 10.8, 2-H$_A$), 2.75 (1H, d, *J* 10.8, 2-H$_B$), 2.71-2.63 (1H, m, 5-H), 2.47 (1H, dd, *J* 13.6, 8.7, 6-H$_A$), 2.39-2.27 (2H, m, 4-H$_B$ and 10-H$_A$), 1.96 (1H, d, *J* 14.6, 10-H$_B$), 1.80-1.70 (3H, m, 6-H$_B$ and THP 3-H$_A$), 1.62-1.51 (2H, m, THP 3-H$_B$), 1.46 (3H, s, $C_qC\mathit{H}_3$). **^{13}C NMR** (125 MHz, MeOD): δ 171.5 (NH(CO)), 89.3 (1-C), 83.9 (7-C), 72.0 ($\mathit{C}H_2OCH_3$), 70.3 (8-C), 66.8 (THP 2-C), 60.8 (THP 4-C), 60.2 (2-C), 59.5 (OCH_3), 58.6 (4-C), 52.4 (9-C), 44.8 (5-C), 35.8 (10-C), 31.9 (6-C or THP 3-C), 30.2 (6-C or THP 3-C), 27.3 (C_qCH_3). **IR** ν_{max}(film)/cm^{-1}: 3328 (OH), 2946, 2834, 1648, 1450, 1410, 1114, 1018. **HRMS** (ESI): $C_{18}H_{31}N_2O_5$ [M+H]$^+$; calculated: 355.2233, found: 355.2224.

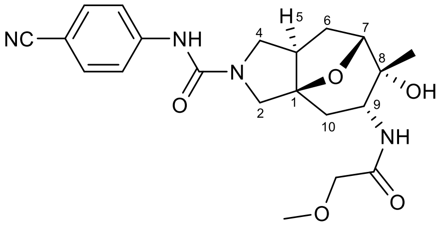
***N*-[(*1R**,*5R**,*7R**,*8R**,*9R**)-8-hydroxy-3-(4-methoxybenzenesulfonyl)-8-methyl-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecan-9-yl]-2-methoxyacetamide 37**



37

General procedure **F** was followed using compound **35** (26 mg, 95 μmol) and 4-methoxyphenylsulfonyl chloride. Purification by mass directed preparative HPLC gave the *title compound* **37** (29 mg, 66 mmol, 70%) as an amorphous solid. **^{1}H NMR** (500 MHz, MeOD, NH and OH not observed): δ 7.77 (2H, d, *J* 9.0, Ar 2-H), 7.12 (2H, d, *J* 9.0, Ar 3-H), 3.96-3.88 (4H, m, includes 7-H; and at δ 3.90: 3H, s, Ar-OCH$_3$), 3.87 (1H, d, *J* 15.3, C*H*$_A$H$_B$OCH$_3$), 3.79 (1H, d, *J* 15.3, CH$_A$*H*$_B$OCH$_3$), 3.68-3.58 (2H, m, 4-H$_A$ and 9-H), 3.43 (3H, s, CH$_2$OC*H*$_3$), 3.38 (1H, d, *J* 12.2, 2-H$_A$), 3.20 (1H, d, *J* 12.2, 2-H$_B$), 2.87, (1H, dd, *J* 10.2 and 8.2, 4-H$_B$), 2.53-2.44 (1H, m, 5-H), 2.35 (1H, dd, *J* 13.8, 8.5, 6-H$_B$), 2.07 (1H, dd *J*, 14.6 and 5.6, 10-H$_A$), 1.95 (1H, d, *J* 14.6, 10-H$_B$), 1.70-1.62 (1H, m, 6-H$_A$), 1.35 (3H, s, C$_q$C*H*$_3$). **^{13}C NMR** (125 MHz, MeOD): δ 172.3 (NH(CO)), 164.9 (Ar 4-C), 131.0 (Ar 1-C), 128.9 (Ar 2-C), 115.5 (Ar 3-C), 91.1 (1-C), 85.5 (7-C), 72.7 (*C*H$_2$OCH$_3$), 68.5 (8-C), 59.7 (CH$_2$O*C*H$_3$), 57.6 (2-C or 4-C), 57.1 (2-C or 4-C), 56.2 (Ar-O*C*H$_3$), 53.3 (9-C), 45.4 (5-C), 35.1 (10-C), 32.1 (6-C), 27.9 (C$_q$*C*H$_3$). **HRMS** (ESI): $C_{20}H_{28}N_2NaO_7S$ [M+Na]$^+$; calculated: 463.1514, found: 463.1507.

(*1R,*5R**,*7R**,*8R**,*9R**)-*N*-(4-cyanophenyl)-8-hydroxy-9-(2-methoxyacetamido)-8-methyl-11-oxa-3-azatricyclo[5.3.1.0^{1,5}]undecane-3-carboxamide 38**

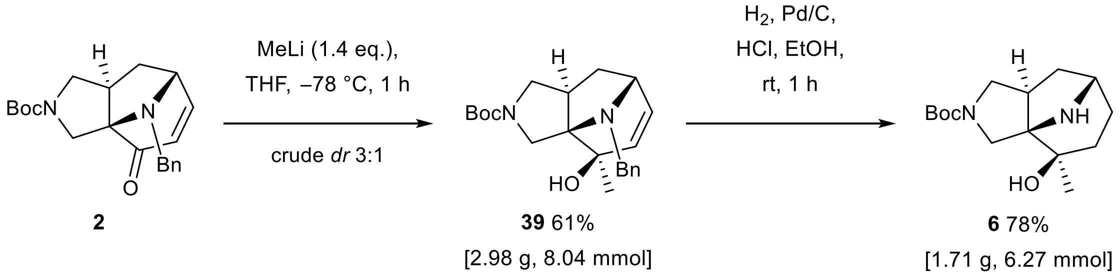


38

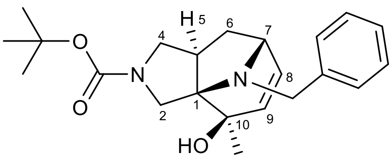
General procedure **F** was followed using compound **35** (26 mg, 95 μmol) and 4-cyanophenylisocyanate. Purification by mass directed preparative HPLC gave the *title compound* **38** (20 mg, 48 μmol, 50%) as an amorphous solid. **^{1}H NMR** (500 MHz, MeOD, NH and OH not observed): δ 7.69- 7.57 (4H, m, Ar-H), 4.10 (1H, d, *J* 7.8, 7-H), 4.01-3.93 (2H, m, includes 4-H$_A$; and at δ 3.97: 1H, d, *J* 15.1, C*H*$_A$H$_B$OCH$_3$), 3.88 (1H, d, *J* 15.1, CH$_A$*H*$_B$OCH$_3$), 3.82-3.75 (2H, m, 2-H$_A$ and 9-H), 3.50-3.43 (4H, m, includes 2-H$_B$; and at δ 3.49: 3H, s, OCH$_3$), 3.28 (1H, dd, *J* 10.7, 7.8, 4-H$_B$), 2.94-2.84 (1H, m, 5-H), 2.60 (1H, dd, *J* 14.2 and 8.6, 6-H$_B$), 2.26 (1H, dd, *J* 14.8, 1.7, 10-H$_B$), 2.20 (1H, dd, *J* 14.8, 5.5, 10-H$_A$), 1.94-1.85 (1H, m, 6-H$_A$), 1.44 (3H, s, C$_q$CH$_3$). **^{13}C NMR** (125 MHz, MeOD): δ 172.5 (NH(*C*O)CH$_2$), 155.5 (NH(*C*O)NH), 145.8 (Ar-C$_q$), 133.9 (Ar-C$_q$), 120.9 (Ar-C), 120.1 (Ar-C), 105.9 (CN), 90.6 (1-C), 85.2 (7-C), 72.8 (*C*H$_2$OCH$_3$), 68.8 (8-C), 59.7 (OCH$_3$), 56.1 (2-C or 4-C), 55.6 (2-C or 4-C), 53.3 (9-C), 44.7 (5-C), 34.7 (10-C), 33.6 (6-C), 27.9 (C$_q$*C*H$_3$). **IR** ν_{max}(film)/cm^{-1}: 3400 (OH), 2938, 2222 (CN), 1652 (CO), 1515, 1441, 1414. **HRMS** (ESI): $C_{21}H_{26}N_4NaO_5$ [M+Na]$^+$; calculated: 437.1800, found: 437.1795.

1.3.5 Preparation of scaffold 6

1.3.5.1 Initial procedure to prepare scaffold 6



tert-Butyl (*1R**,*5R**,*7R**,*10R**)-11-benzyl-10-hydroxy-10-methyl-3,11-diazatricyclo[5.3.1.0^{1,5}]undec-8-ene-3-carboxylate 39

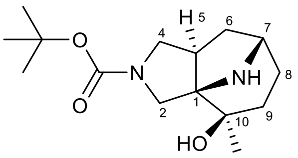


39

MeLi (11.5 mL, 18.4 mmol, 1.4 eq.) was added dropwise to a stirred solution of compound **2** (4.64 g, 13.1 mmol, 1.0 eq.) in THF (65 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h, then quenched at that temperature with sat. aq. NH_4Cl solution (20 mL). The reaction mixture was warmed to rt, then EtOAc (70 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 70 mL). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography eluting with 85:15 hexane–EtOAc gave *title compound* **39** (2.98 g, 8.04 mmol, 61%) as a single diastereomer.[***] **^{1}H NMR** (500 MHz, MeOH-*d*$_4$, 40:60 mixture of rotamers, OH not observed): δ 7.33-7.27 (4H, m, Ar-H), 7.23-7.19 (1H, m, Ar-H), 5.92-5.87 (1H, m, 8-H), 5.67 (1H, d, *J* 9.7, 9-H), 4.03 (1H, d, *J* 14.7, 2-H$_A$), 3.91-3.84 (2H, m, includes 4-H$_A$; and at d 3.90: 1H, d, *J* 14.7, 2-H$_B$), 3.72-3.63 (2H, m, NC*H*$_2$Ph), 3.47-3.42 (1H, m, 7-H), 3.36-3.34 (1H, m, 4-H$_B$), 2.71-2.65 (1H, m, 5-H), 1.84-1.75 (1H, m, 6-H$_A$), 1.71-1.65 (1H, m, 6-H$_B$), 1.55 (3.6H, s, N(CO)C(CH_3)$_3$), 1.51 (5.4H, s, N(CO)C(CH_3)$_3$), 1.34 (3H, s, C$_q$CH$_3$). **^{13}C NMR** (100 MHz, MeOD, mixture of two rotamers): δ 156.3 (N(CO)O), 142.8 (Ar-C$_q$), 132.5 (8-C or 9-C), 132.4 (8-C or 9-C), 131.9 (8-C or 9-C), 131.8 (8-C or 9-C), 129.1 (Ar-C), 129.0 (Ar-C), 127.5 (Ar-C), 80.8 (2 peaks, O*C*$_q$(CH_3)$_3$), 78.9 (1-C), 78.1 (1-C), 70.0 (10-C), 69.9 (10-C), 58.8 (7-C), 58.4 (7-C), 56.0 (4-C), 55.6 (4-C), 51.4 (NCH$_2$Ph or 2-C), 50.0 (NCH$_2$Ph or 2-C), 49.9 (NCH$_2$Ph or 2-C), 49.7 (NCH$_2$Ph or 2-C), 44.4 (5-C), 43.6 (5-C), 37.5 (6-C), 37.4 (6-C), 28.9 (OC$_q$(*C*H$_3$)$_3$), 25.7 (C$_q$*C*H$_3$) [29 of 36 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1} 3374, 2483, 2072, 1671. **HRMS** (ESI): $C_{22}H_{31}N_2O_3$ [M+H]$^+$; calculated 371.2335, Found: 371.2326.

[***] N.b. the crude reaction product was a 3:1 mixture of diastereomers (as judged by analysis of the crude reaction product by ^{1}H NMR spectroscopy at 500 MHz).

tert-Butyl (*1R**,*5R**,*7S**,*10R**)-10-hydroxy-10-methyl-3,11-diazatricyclo[5.3.1.$0^{1,5}$]undecane-3-carboxylate 6

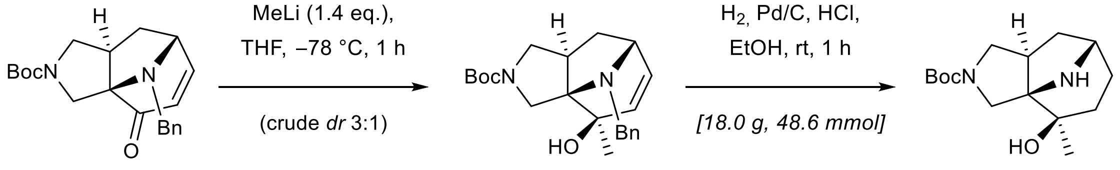


6

Hydrogenation was carried out following general procedure **B**, using compound **39** (2.98 g, 8.05 mmol) and conc. HCl (600 μL, 51.5 mmol, 6.4 eq.). Following completion of the reaction, the reaction mixture was filtered through a pad of Celite® and washed through with EtOAc. The resulting solution was then concentrated *in vacuo*. The residue was diluted in CH_2Cl_2 (30 mL) and sat. aq. K_2CO_3 was added with stirring until the solution reached basic pH. The solution was stirred for 20 min, then the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the *title compound* **6** as a colourless oil (1.71 g, 6.05 mmol, 75%). **^{1}H NMR** (400 MHz, MeOD): δ 3.86-3.80 (1H, app. t, *J* 10.4, 4-H_A), 3.65 (1H, d, *J* 12.0, 2-H_A), 3.61-3.53 (1H, m, 7-H), 3.30-3.20 (1H, m, 2-H_B, includes at δ 3.25: 0.5H, d, *J* 12.0; and at δ 3.24: 0.5H, d, *J* 12.0), 3.10 (1H, app. t, *J* 9.2, 4-H_B), 2.67-2.54 (1H, m, 5-H), 1.95-1.78 (3H, m, 6-H_A and 9-H), 1.75-1.64 (1H, m, 8-H_A), 1.58-1.33 (11H, m, includes 6-H_B, 8-H_B, and at δ 1.46: 9H, s, $C(CH_3)_3$), 1.25 (3H, s, C_qCH_3). **^{13}C NMR** (100 MHz, MeOD, mixture of two rotamers): δ 156.1 (N(CO)O), 156.0 (N(CO)O), 80.9 ($OC_q(CH_3)_3$), 78.5 (1-C), 77.6 (1-C), 71.8 (10-C), 57.8 (2 peaks, 7-C), 55.9 (4-C), 55.4 (4-C), 52.4 (2-C), 52.1 (2-C), 43.9 (5-C), 43.1 (5-C), 36.1 (9-C), 35.9 (9-C), 33.9 (8-C), 30.5 (6-C), 28.8 ($OC(CH_3)_3$), 25.3 (C_qCH_3) [20 of 26 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1} 3374, 2935, 2482, 2071, 1670. **HRMS** (ESI): $C_{15}H_{27}N_2O_3$ $[M+H]^+$; calculated 283.2022, found 283.2016.

1.3.5.2 Scaled-up synthesis of scaffold 6

The route to compound **6** outlined above was followed starting with 25.7 g (72.6 mmol) of compound **2** to prepare 15.7 g (42.5 mmol, 58%) of compound **39**, which was isolated from the crude reaction mixture as a single diasteriomer. Hydrogenation of 18.0 g (48.6 mmol) of compound **39** gave 13.1 g (46.4 mmol, 95%) scaffold **6**.

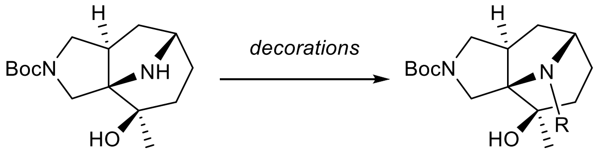


2
[25.7 g, 72.6 mmol]

39 58%
[15.7 g, 42.5 mmol]

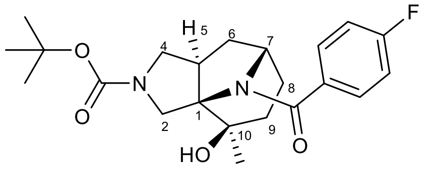
6 95%
[13.1 g, 46.4 mmol]

1.3.5.3 Exemplar decorations of scaffold 6



6 **40-42**

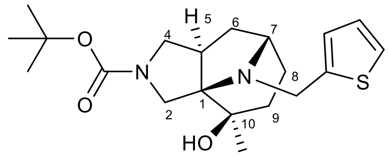
tert-Butyl (*1R**,*5R**,*7S**,*10R**)-11-(4-fluorobenzoyl)-10-hydroxy-10-methyl-3,11-diazatricyclo[5.3.1.0^{1,5}]undecane-3-carboxylate 40



40

4-Fluorobenzoyl chloride (113 µL, 0.96 mmol, 2.0 eq.) was added to a stirred solution of compound **6** (135 mg, 0.48 mmol, 1.0 eq.) and DIPEA (242 µL, 1.44 mmol, 3.0 eq.) in CH_2Cl_2 (4 mL). After 16 h the reaction was quenched with sat. aq. NH_4Cl solution (10 mL) and transferred to a separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), then the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography eluting with 90:10 CH_2Cl_2–MeOH gave the *title compound* **40** (160 mg, 0.40 mmol, 83%) as a colourless amorphous solid. **^{1}H NMR** (500 MHz, DMSO-*d*$_6$, 333 K): δ 7.54 (2H, dd, *J* 8.3, 5.6, Ar 2-H), 7.24 (2H, app. t, *J* 8.7, Ar 3-H), 4.33-4.14 (2H, m, 2-H$_A$ and 7-H), 3.83 (1H, dd, *J* 10.7, 9.0, 4-H$_A$), 3.70 (1H, d, *J* 13.1, 2-H$_B$), 3.01 (1H, dd, *J* 10.7, 9.3, 4-H$_B$), 2.76 (1H, qd, *J* 8.8, 3.8, 5-H), 1.94-1.85 (1H, m, 8-H$_A$), 1.83-1.66 (3H, m, 6-H$_A$, 8-H$_B$, 9-H$_A$), 1.54-1.46 (1H, m, 9-H$_B$), 1.39 (9H, s, $C(CH_3)_3$), 1.32-1.24 (1H, m, 6-H$_B$), 1.18 (3H, s, C_qCH_3). **^{13}C NMR** (125 MHz, DMSO-*d*$_6$, 333 K): δ 169.9 (N(CO)Ar), 162.6 (d, *J* 247.5, Ar 4-C), 152.8 (N(CO)O), 133.3 (Ar 1-C), 129.2 (d, *J* 8.7, Ar 2-C), 114.9 (d, *J* 21.7, Ar 3-C), 78.7 (1-C), 78.1 ($\mathit{C}_q(CH_3)_3$), 73.4 (10-C), 61.0 (7-C), 52.1 (4-C), 46.3 (2-C), 44.4 (5-C), 32.5 (9-C), 30.4 (8-C), 28.6 (6-C), 27.8 ($C(\mathit{C}H_3)_3$), 25.1 ($C_q\mathit{C}H_3$). **IR** ν_{max}(film)/cm^{-1} 3375, 2975, 2933, 2486, 2072, 1692, 1605. **HRMS** (ESI): $C_{22}H_{29}FN_2NaO_4$ [M+Na]$^+$; calculated 427.2009, found 427.1997.

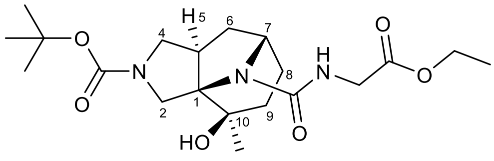
***tert*-Butyl (*1R**,*5R**,*7S**,*10R**)-10-hydroxy-10-methyl-11-(thiophen-2-ylmethyl)-3,11-diazatricyclo[5.3.1.0^{1,5}]undecane-3-carboxylate 41**



41

2-Thiophene carboxaldehyde (110 µL, 1.18 mmol, 2.18 eq.) was added to a solution of compound **6** (0.54 mmol) in CH_2Cl_2 (5.0 mL). The reaction mixture was stirred for 10 min, then $NaBH(OAc)_3$ (286 mg, 1.35 mmol, 2.5 eq.) was added. The reaction mixture was stirred at rt for 48 h, then further 2-thiophene carboxaldehyde (1.0 eq.) was added. Following 48 h stirring, the reaction was quenched with sat. aq. NH_4Cl solution (10 mL) and transferred to a separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography eluting with 60:40 to 50:50 hexane–EtOAc gave the *title compound* **41** (86 mg, 0.23 mmol, 43%). **^{1}H NMR** (500 MHz, MeOD, 40:60 mixture of rotamers): δ 7.23-7.19 (1H, m, Ar-H), 6.93-6.87 (2H, m, Ar-H), 4.28-4.22 (1H, m, 2-H$_A$; included at δ 4.26: 0.5H, d, *J* 15.3; and at δ 4.25: 0.5H, d, *J* 15.3), 3.99 (1H, d, *J* 15.3, 2-H$_B$), 3.85-3.77 (1H, m, 4-H$_A$), 3.59 (1H, dd, *J* 13.1, 2.9, NC*H*$_A$H$_B$Ar), 3.55 (1H, dd, *J* 13.1, 2.9, NCH$_A$*H*$_B$Ar), 3.47-3.42 (1H, m, 7-H), 3.18-3.12 (1H, m, 4-H$_B$), 2.75-2.64 (1H, m, 5-H), 2.13-2.01 (1H, m, 8-H$_A$), 1.93-1.78 (2H, m, 6-H), 1.76 (1H, td, *J* 13.8 and 6.0, 9-H$_A$), 1.56-1.40 (10H, m, includes 9-H$_B$; and at d 1.47: 3.6H, s, $OC(CH_3)_3$; and at δ 1.43: 5.4H, s, $OC(CH_3)_3$), 1.22 (3H, s, C_qCH_3), 1.20-1.12 (1H, m, 8-H$_B$). **^{13}C NMR** (125 MHz, MeOD, mixture of two rotamers): δ 156.1 (N(CO)O), 156.0 (N(CO)O), 149.0 (2 peaks, Ar-C$_q$), 127.5 (Ar-C), 124.9 (Ar-C), 124.2 (Ar-C), 81.0 (O*C*$_q$(CH_3)$_3$), 80.3 (1-C), 79.4 (1-C), 73.2 (10-C), 60.9 (7-C), 60.4 (7-C), 56.3 (4-C), 55.9 (4-C), 47.6 (N*C*H$_2$Ar), 47.4 (N*C*H$_2$Ar), 45.7 (5-C), 44.9 (5-C), 34.6 (6-C or 9-C), 34.4 (6-C or 9-C), 28.8 (OC$_q$(*C*H$_3$)$_3$), 26.1 (C$_q$*C*H$_3$), 26.0 (C$_q$*C*H$_3$), 25.3 (8-C), 25.1 (8-C) [26 of 36 expected peaks observed]. **IR** ν_{max}(film)/cm^{-1} 3374, 2933, 2484, 2071, 1672. **HRMS** (ESI): $C_{20}H_{31}N_2O_3S$ [M+H]$^+$; calculated 283.2022, found 283.2016.

tert-Butyl (*1R**,*5R**,*7S**,*10R**)-11-[(2-ethoxy-2-oxoethyl)carbamoyl]-10-hydroxy-10-methyl-3,11-diazatricyclo[5.3.1.0^{1,5}]undecane-3-carboxylate 42

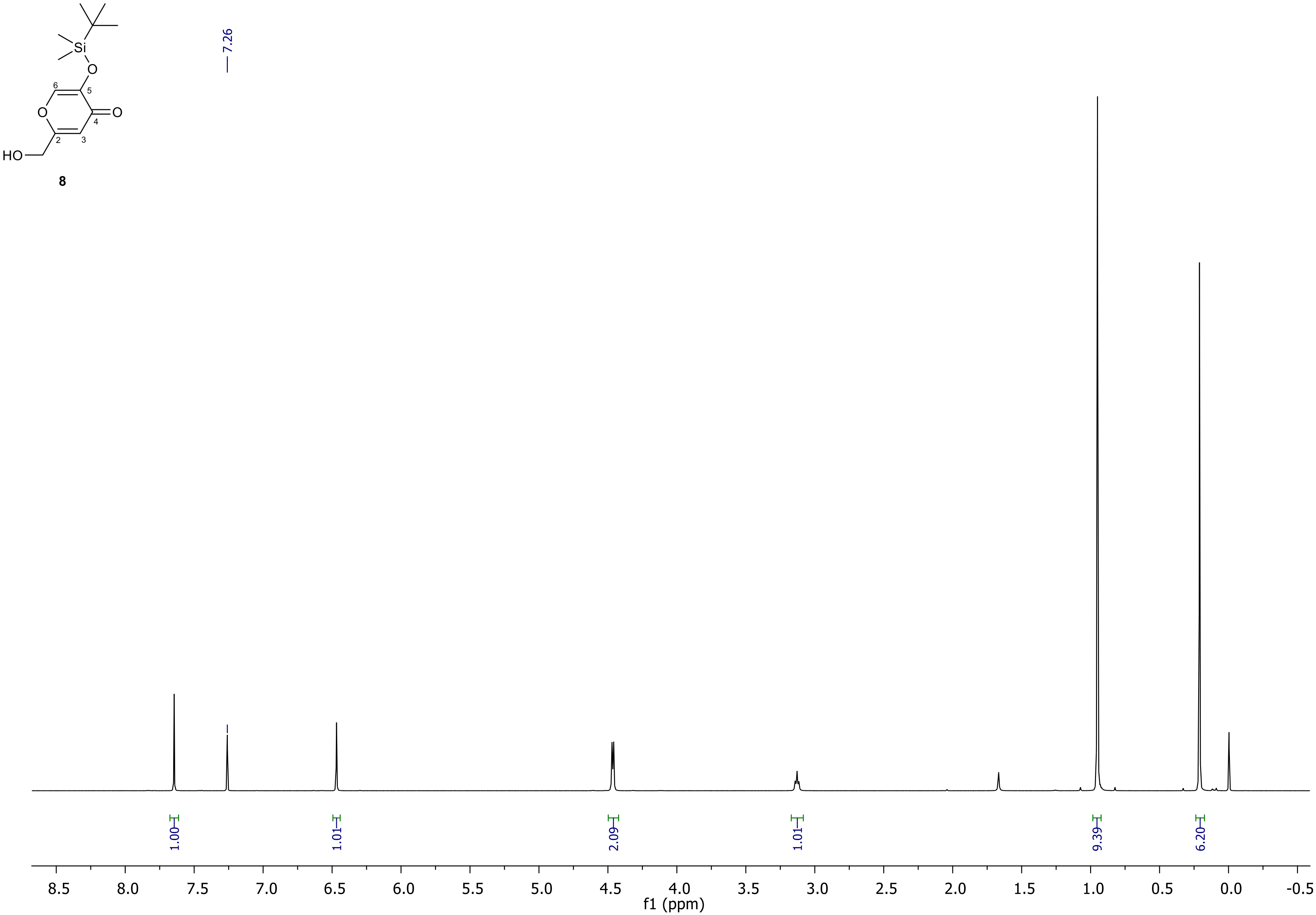


42

Ethyl isocyanatoacetate (160 µL, 1.43 mmol, 1.24 eq.) was added to a stirred solution of compound **6** (325 mg, 1.15 mmol, 1.0 eq.) and DIPEA (320 mL, 1.83 mmol, 1.6 eq.) in CH_2Cl_2 (10 mL) and the reaction mixture was stirred overnight at rt. The reaction was quenched with sat. aq. NH_4Cl solution (10 mL) and transferred to a separating funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography eluting with CH_2Cl_2 then 9:1 CH_2Cl_2–MeOH gave the *title compound* **42** (425 mg, 1.03 mmol, 89%) as a colourless amorphous solid. **^{1}H NMR** (500 MHz, MeOD, OH not observed): δ 4.56-4.48 (1H, m, 7-H), 4.22 (2H, q, *J* 7.3, OCH_2CH_3), 3.94-3.89 (3H, m, $NHCH_2CO$ and 4-H_A), 2.93 (1H, app. t, *J* 10.3, 4-H_B), 2.80 (1H, m, 5-H), 2.20-2.12 (1H, m, 8-H_A), 1.95-1.82 (3H, m, 6-H and 9-H_A), 1.64 (1H, dd, *J* 14.9 and 5.4, 9-H_B), 1.49 (9H, s, $C(CH_3)_3$), 1.46-1.40 (1H, m, 8-H_B), 1.31 (3H, t, OCH_2CH_3), 1.27 (3H, s, C_qCH_3). **IR** ν_{max}(film)/cm^{-1} 3360, 2976, 2934, 2487, 1741, 1693, 1613. **HRMS** (ESI): $C_{20}H_{34}N_3O_6$ $[M+H]^+$; calculated 412.2448, Found: 412.2441.

2.0 Processed NMR Spectra

Compounds are listed in order of appearance within in the Supplementary Information. NOESY Spectra (where relevant) are also included in this Section.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5
O
4
O
2
3
HO
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1.00
1.01
2.09
1.01
9.39
6.20
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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f1 (ppm)

8

Si
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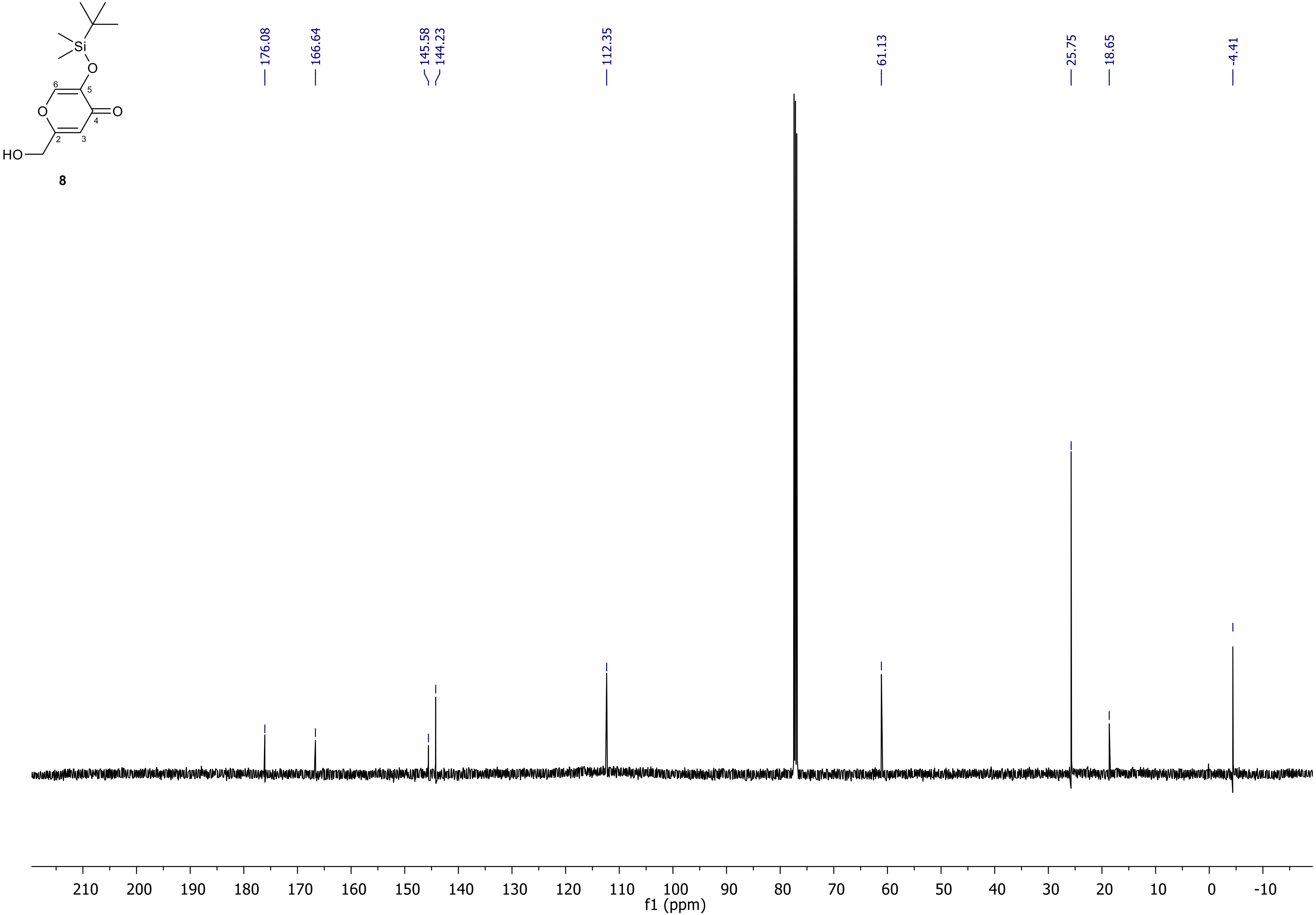
O
O
HO
6
5
4
3
2

8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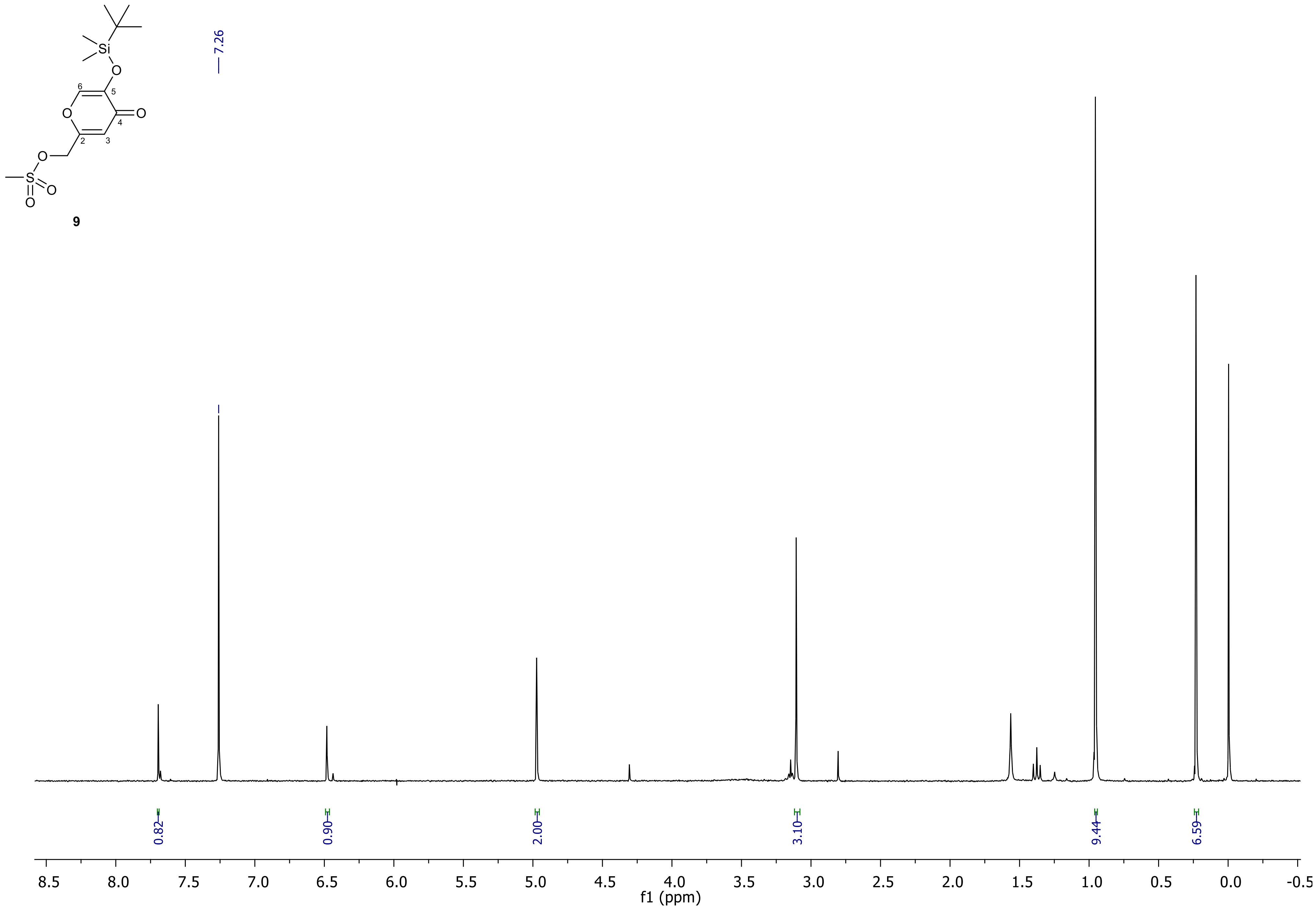
f1 (ppm)



9

6
5
4
3
2
O
O
O
Si
O
S
O
O
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3.10
9.44
6.59
8.5
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7.0
6.5
6.0
5.5
5.0
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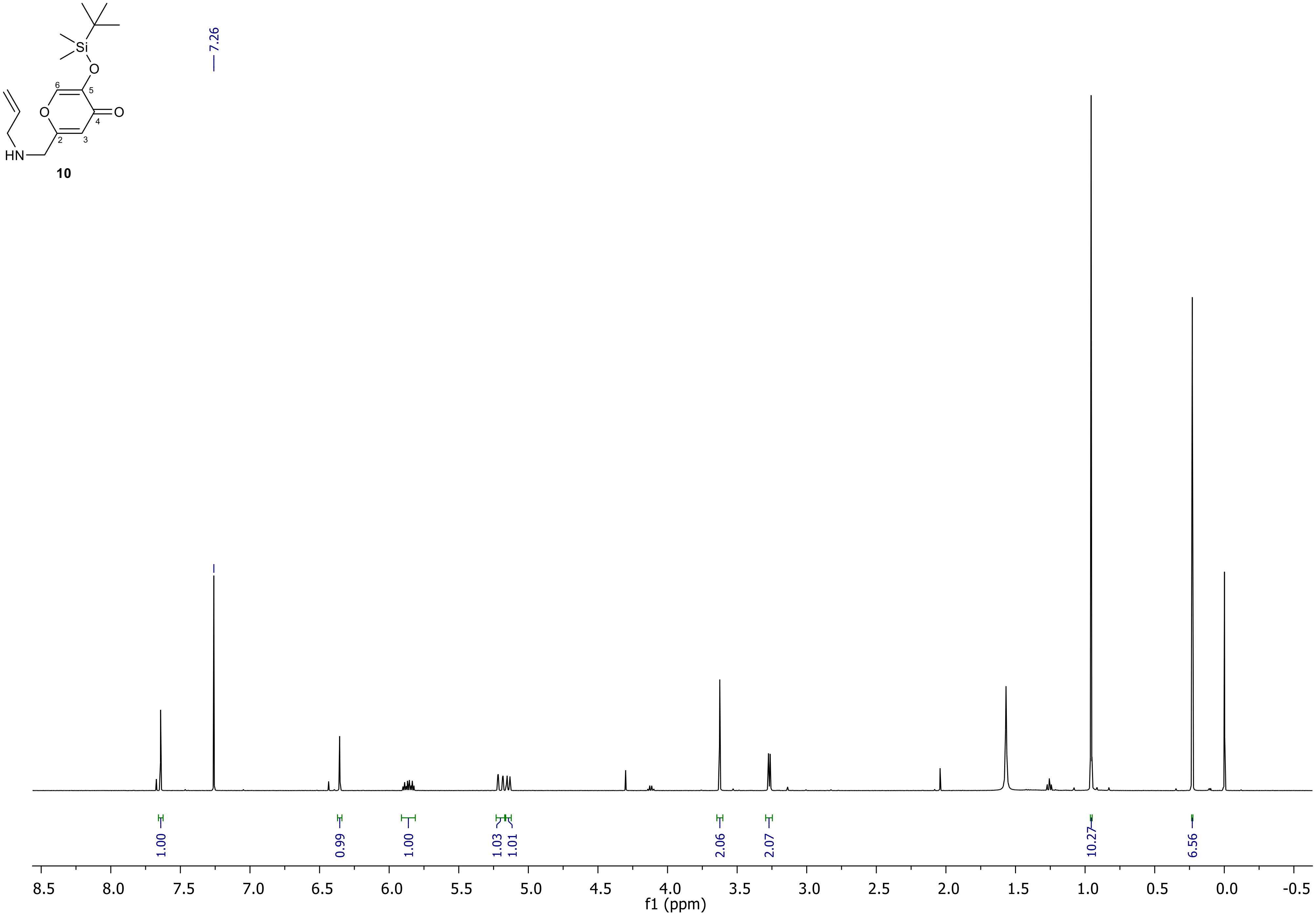
f1 (ppm)



10

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O
6
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O
4
O
2
3
HN
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1.01
2.06
2.07
10.27
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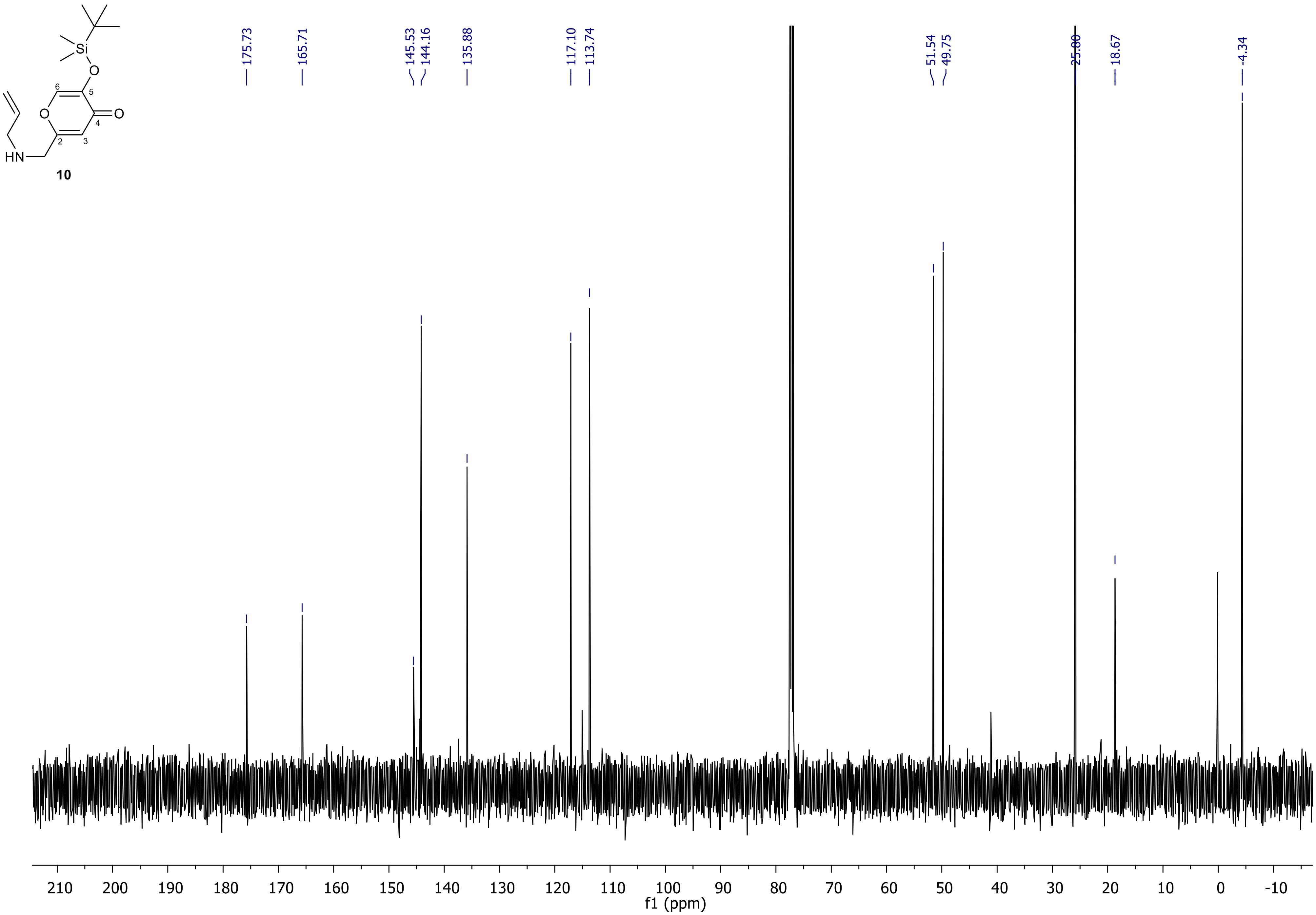
f1 (ppm)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O
HN
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4
3
2
10
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117.10
113.74
51.54
49.75
25.80
18.67
-4.34
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190
180
170
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110
100
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80
70
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40
30
20
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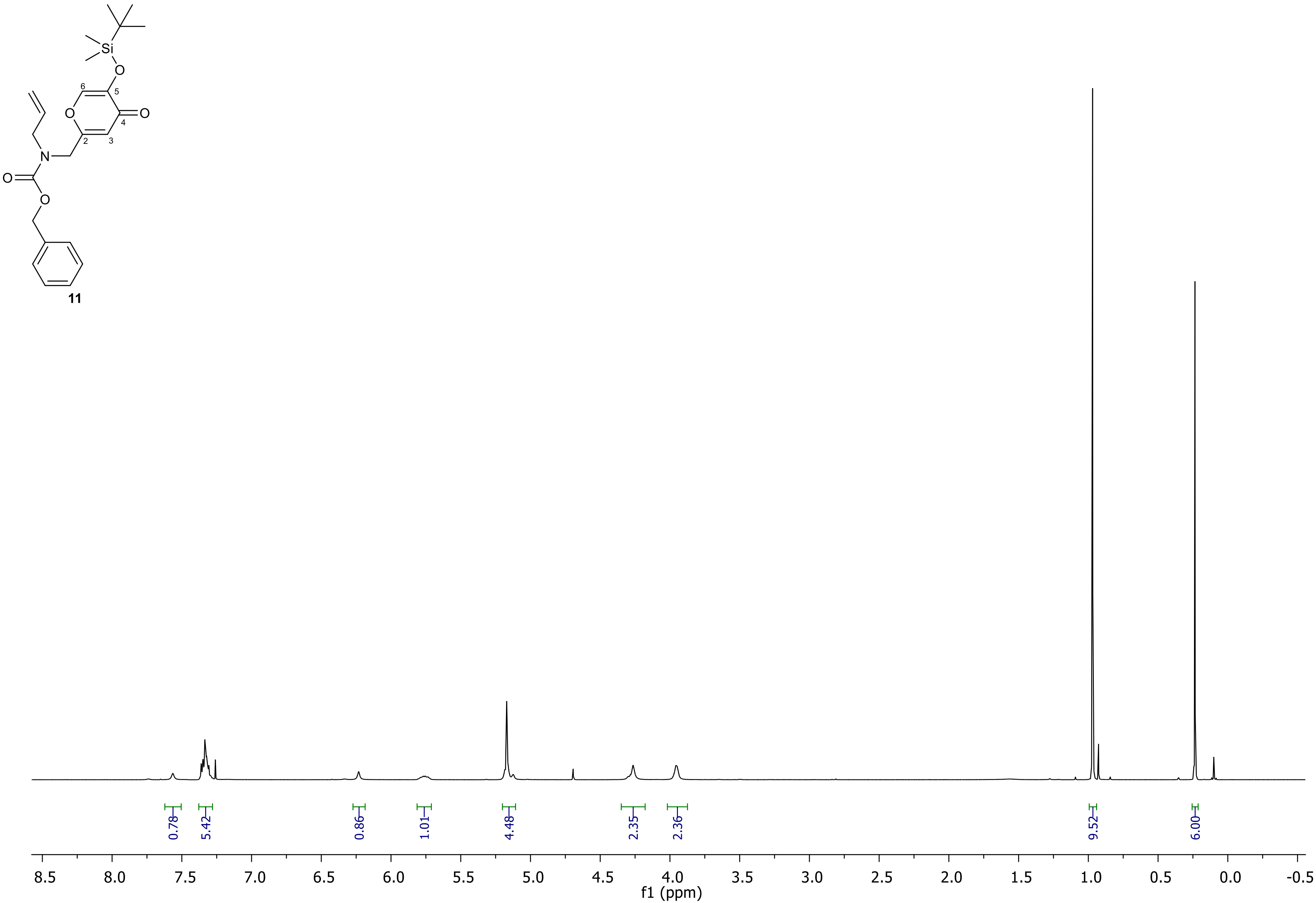
-10
f1 (ppm)



11

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O
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8.5
8.0
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7.0
6.5
6.0
5.5
5.0
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4.0
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3.0
2.5
2.0
1.5
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0.5
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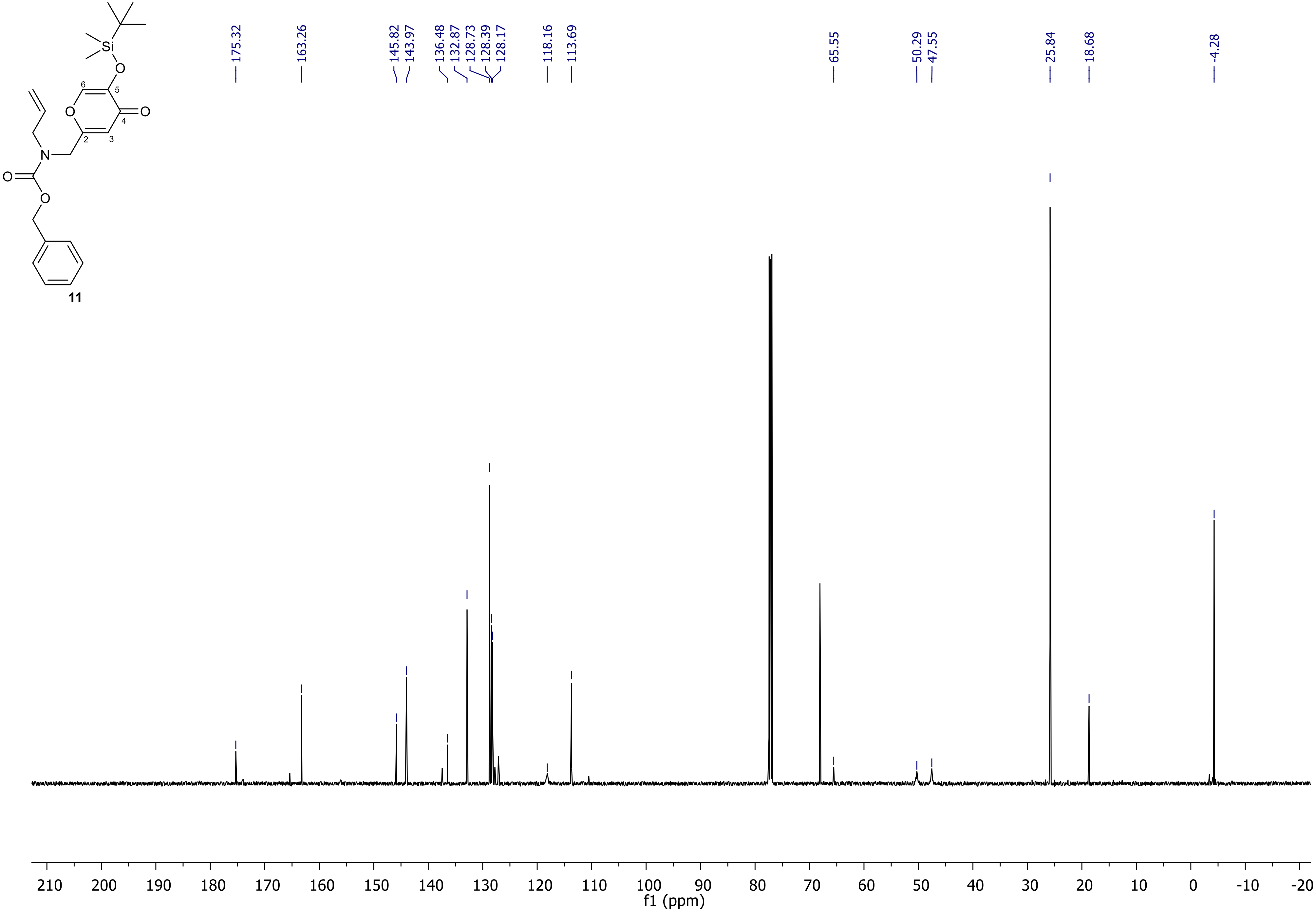
f1 (ppm)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O
6
5
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2
N
O
O
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132.87
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128.39
128.17
118.16
113.69
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50.29
47.55
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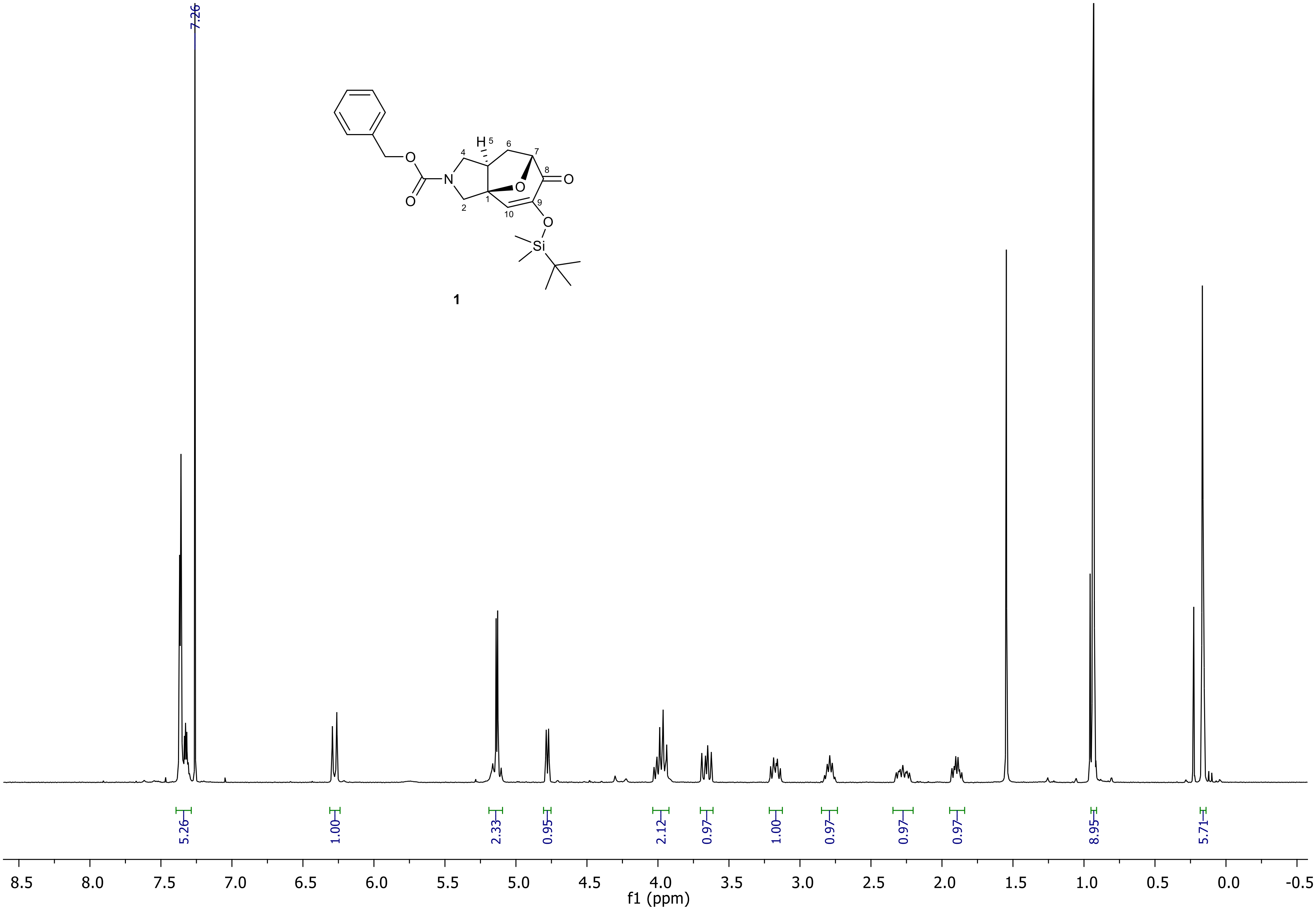
-20
f1 (ppm)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O
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0.97
1.00
0.97
0.97
0.97
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7.0
6.5
6.0
5.5
5.0
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2.5
2.0
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0.5
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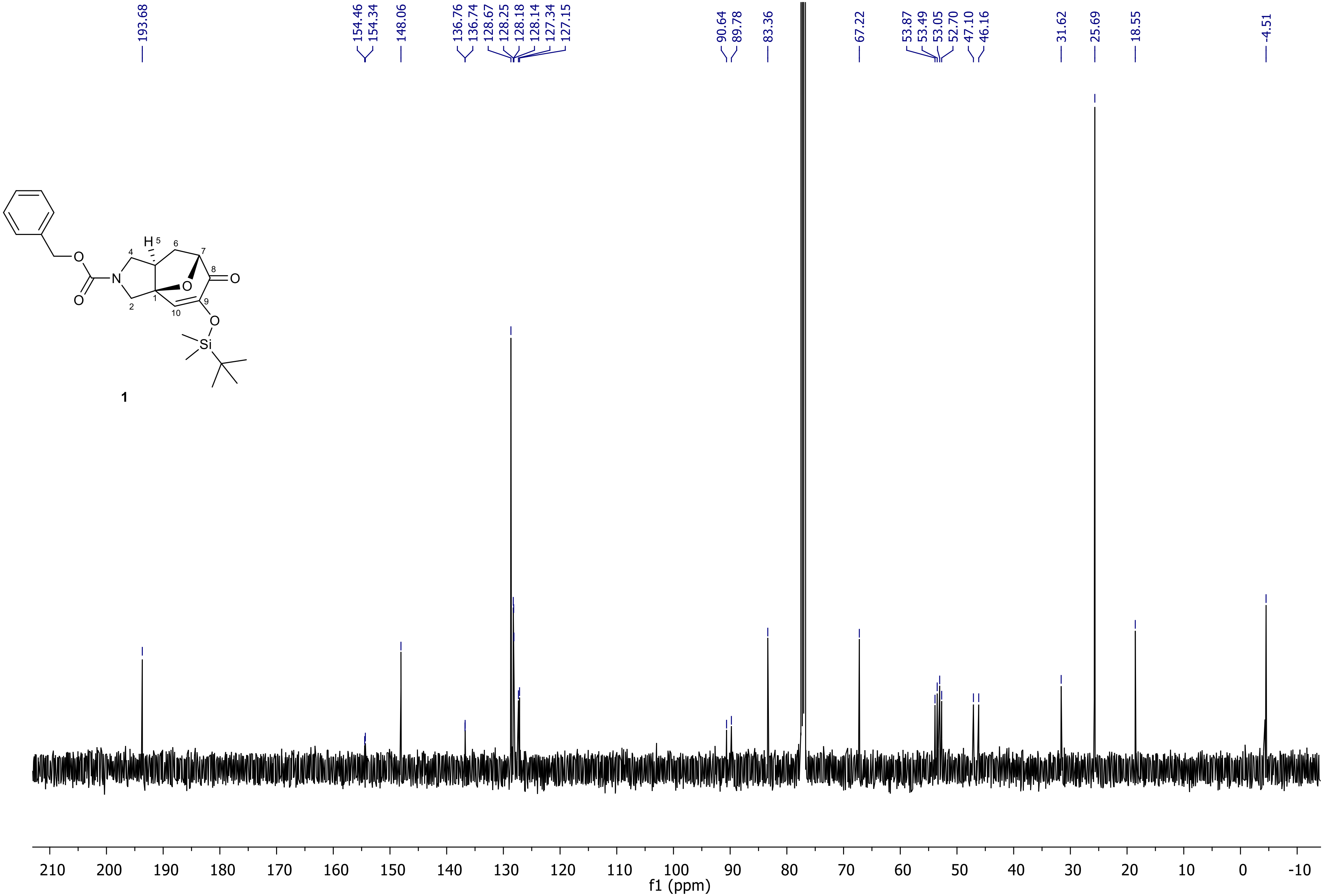
f1 (ppm)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128.14
127.34
127.15
90.64
89.78
83.36
67.22
53.87
53.49
53.05
52.70
47.10
46.16
31.62
25.69
18.55
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200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
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0
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f1 (ppm)
H
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6
7
4
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N
O
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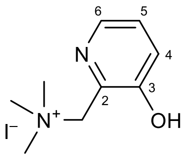
2
10
9
Si

1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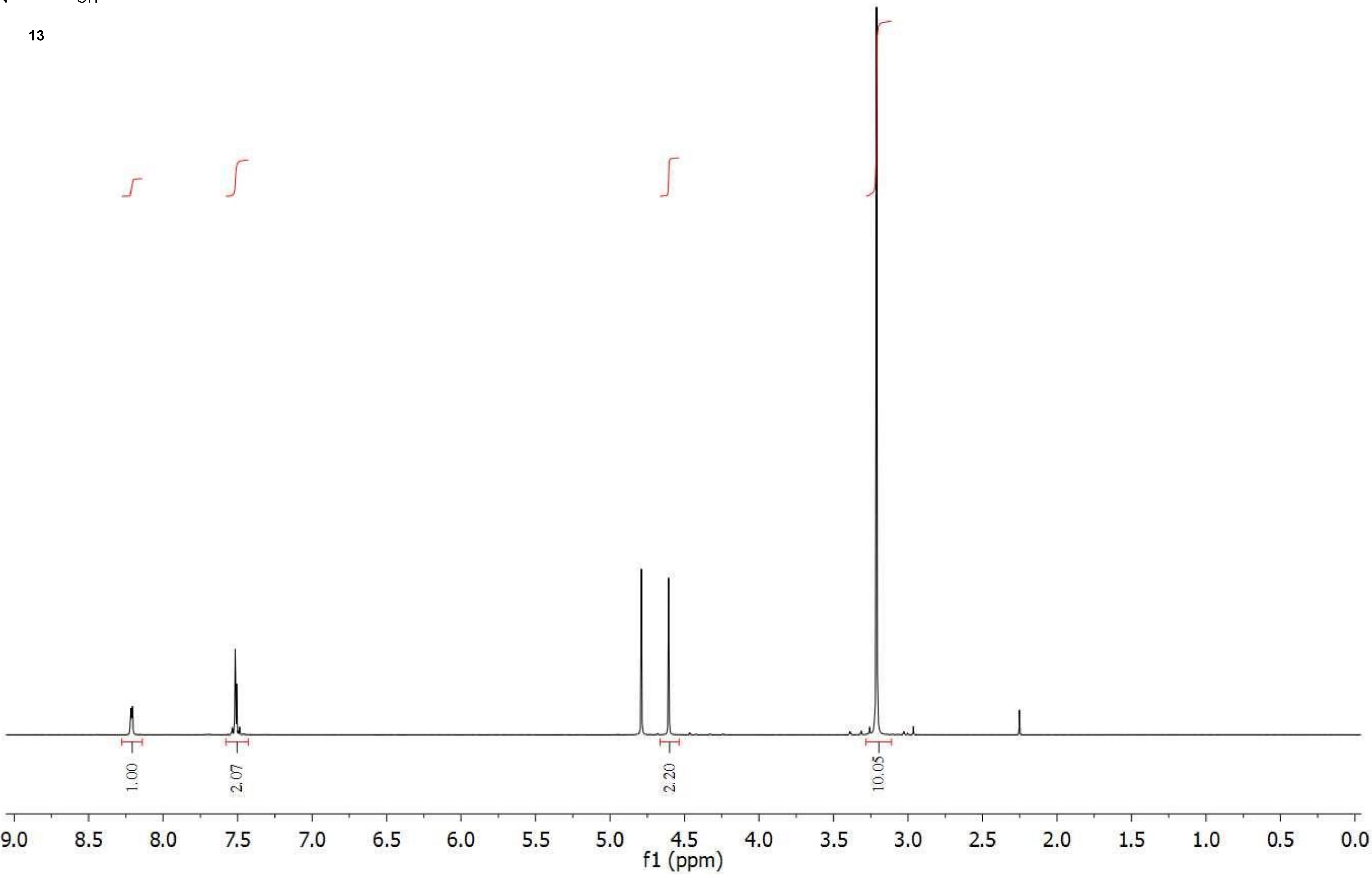
2
I⁻
N⁺
OH

13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3.5
3.0
2.5
2.0
1.5
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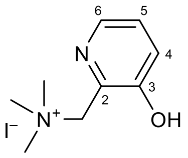
0.0
f1 (ppm)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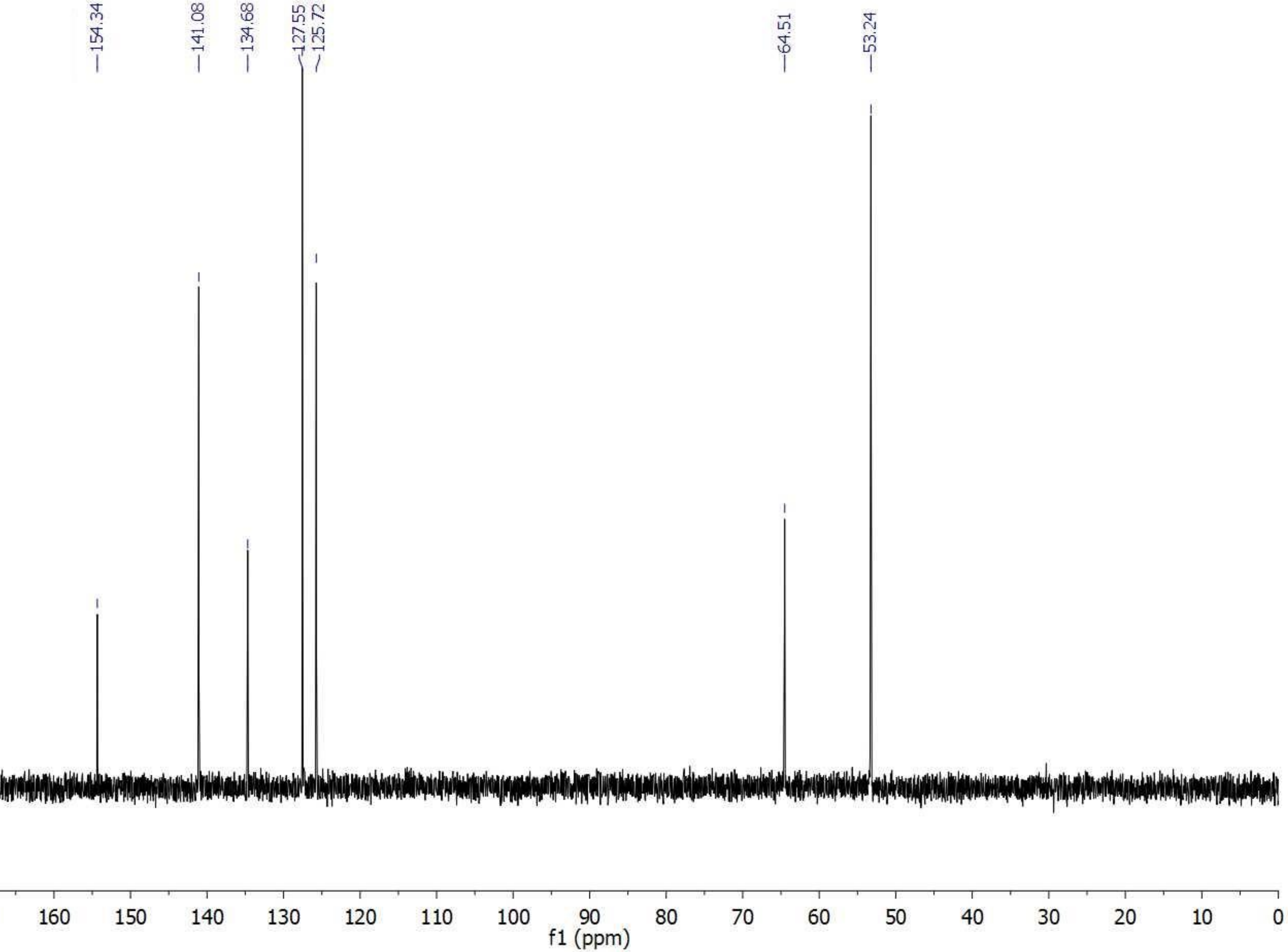
2
3
OH
N+
I−

13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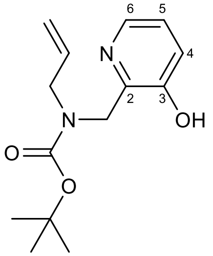
f1 (ppm)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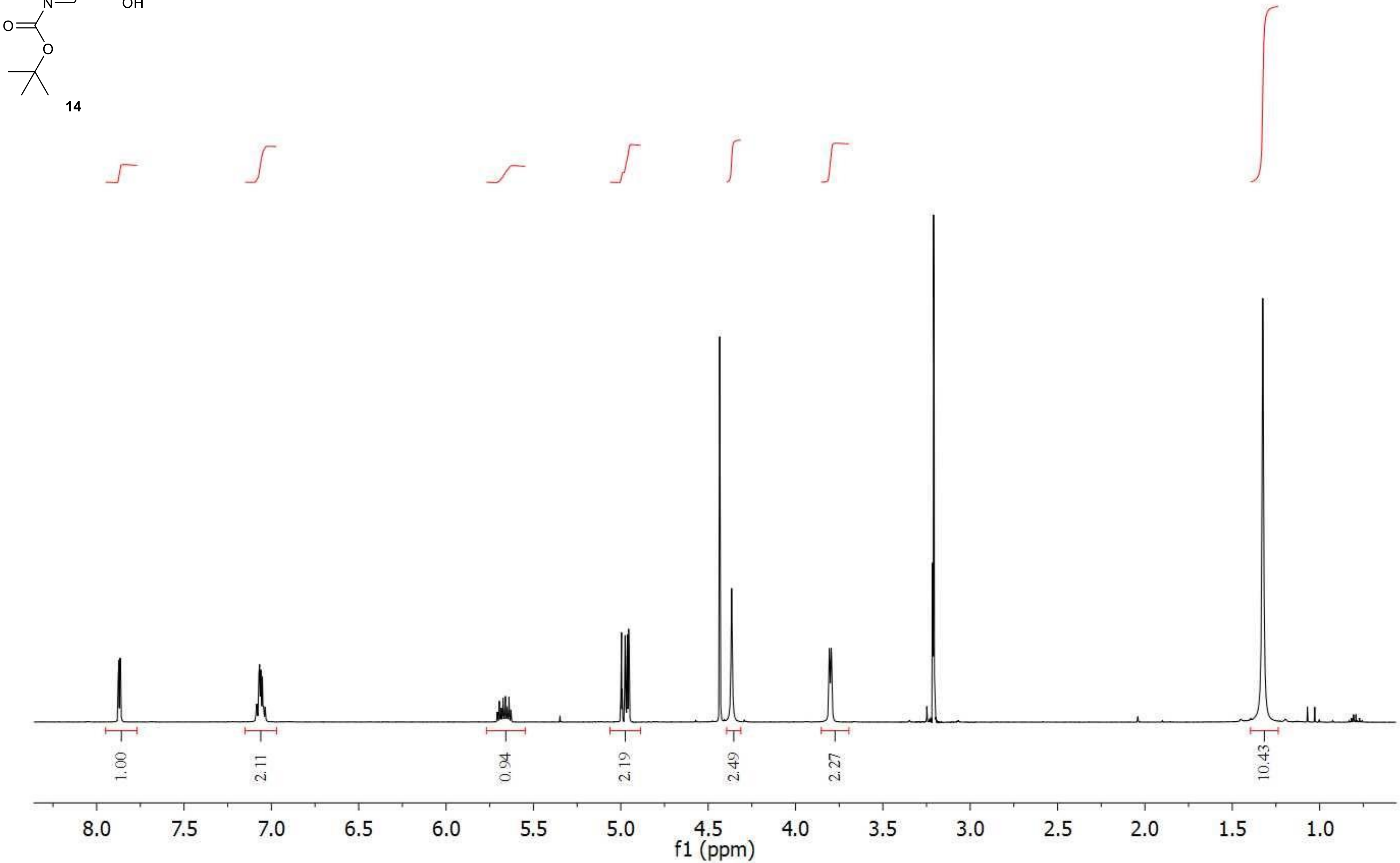
OH
N
O
O

14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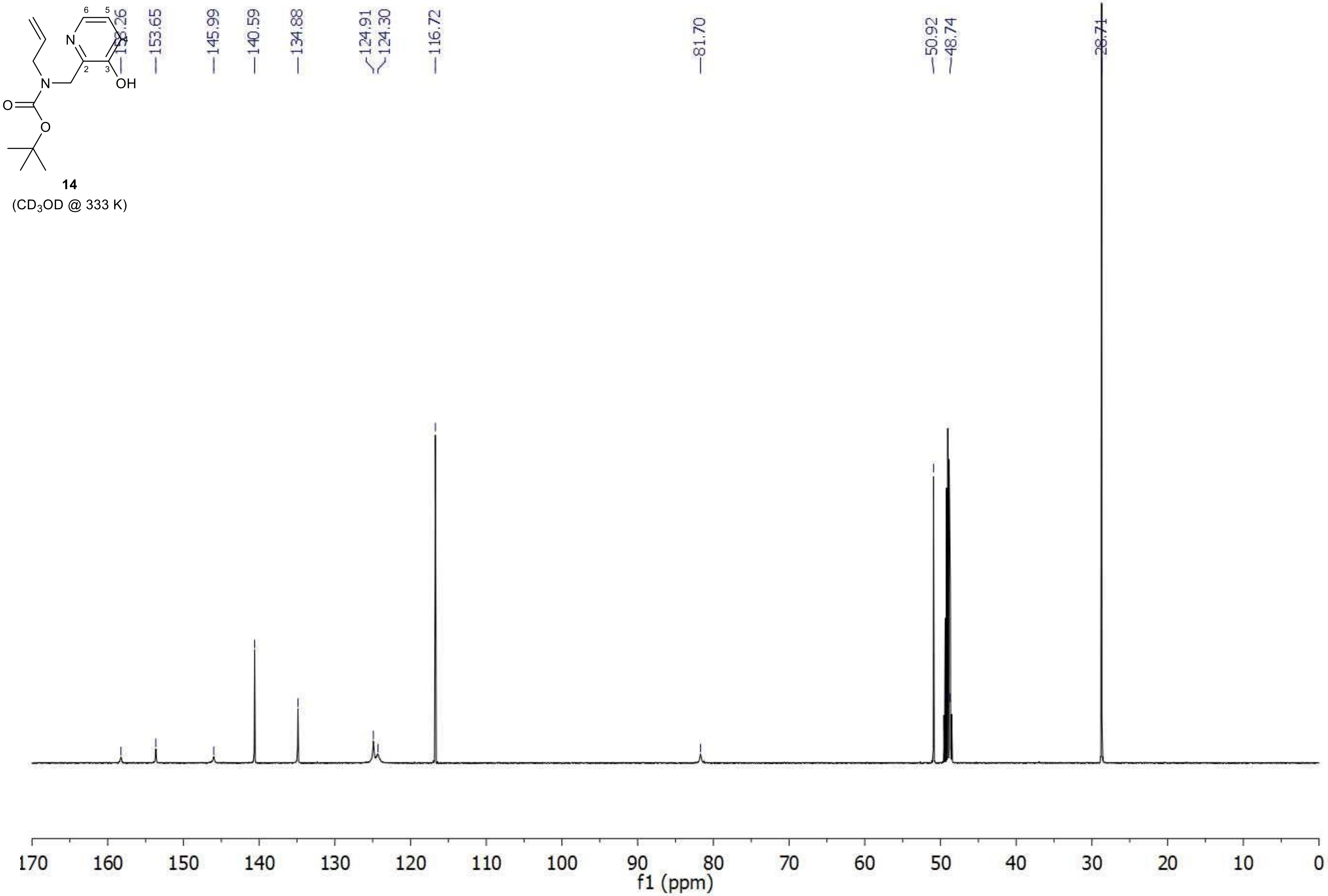
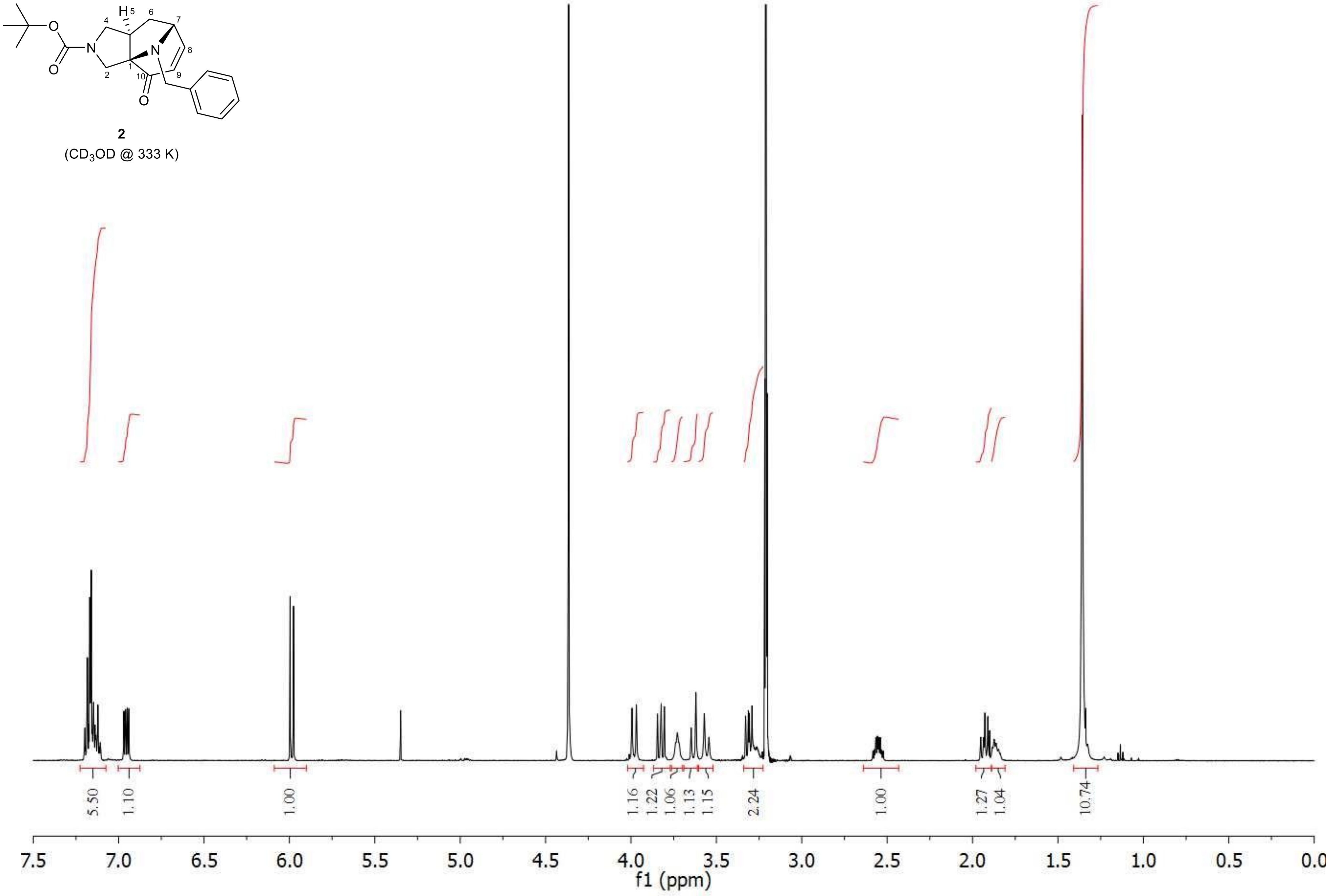


14

(CD_3OD @ 333 K)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7
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8
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9
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1.27
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6.5
6.0
5.5
5.0
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4.0
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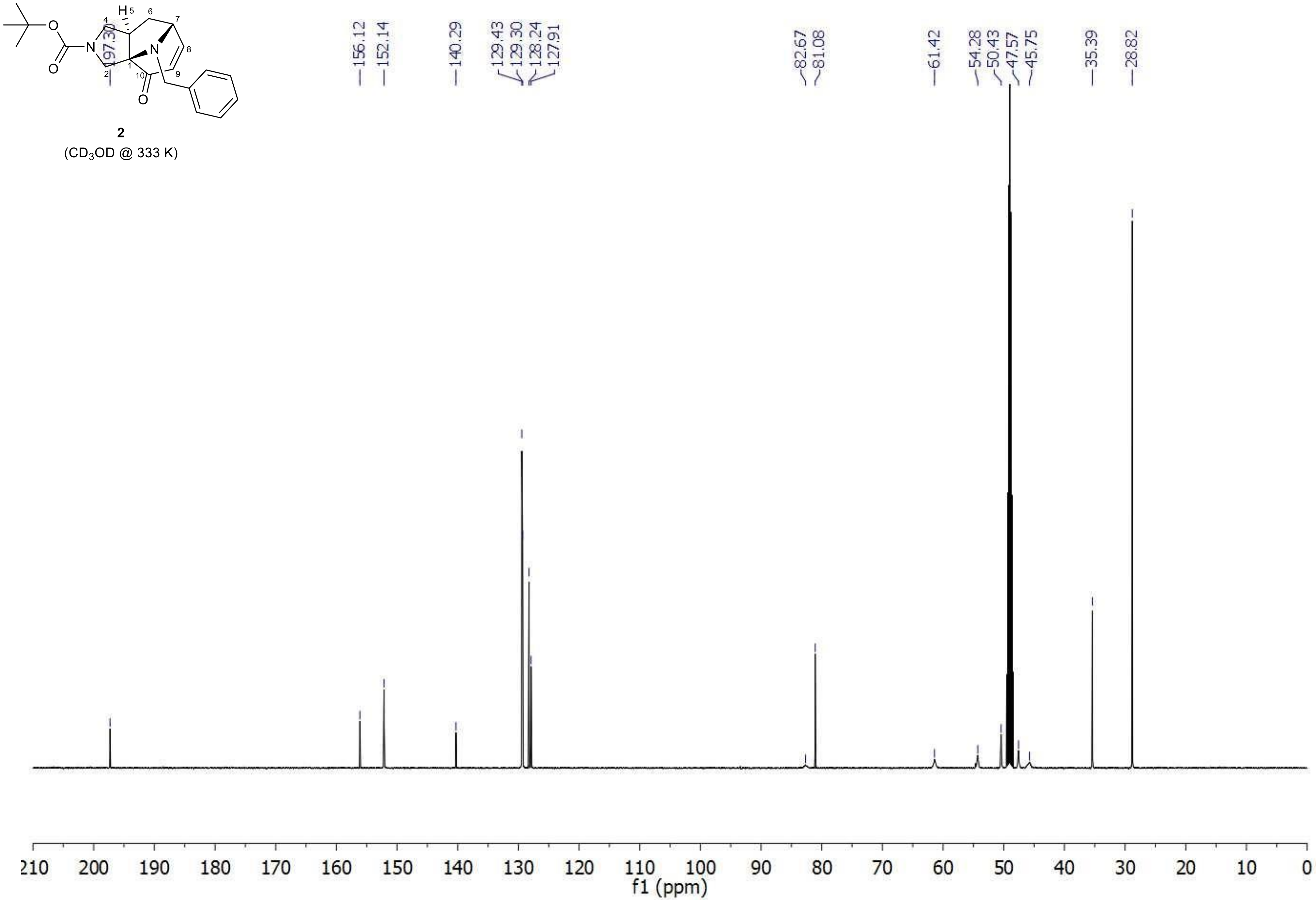
1.0
0.5
0.0
f1 (ppm)

2
(CD$_3$OD @ 333 K)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9
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O
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129.43
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128.24
127.91
82.67
81.08
61.42
54.28
50.43
47.57
45.75
35.39
28.82
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200
190
180
170
160
150
140
130
120
110
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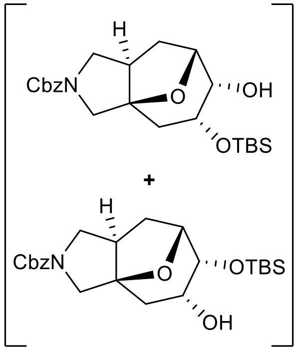
80
70
60
50
40
30
20
10
0
f1 (ppm)

2
(CD_3OD @ 333 K)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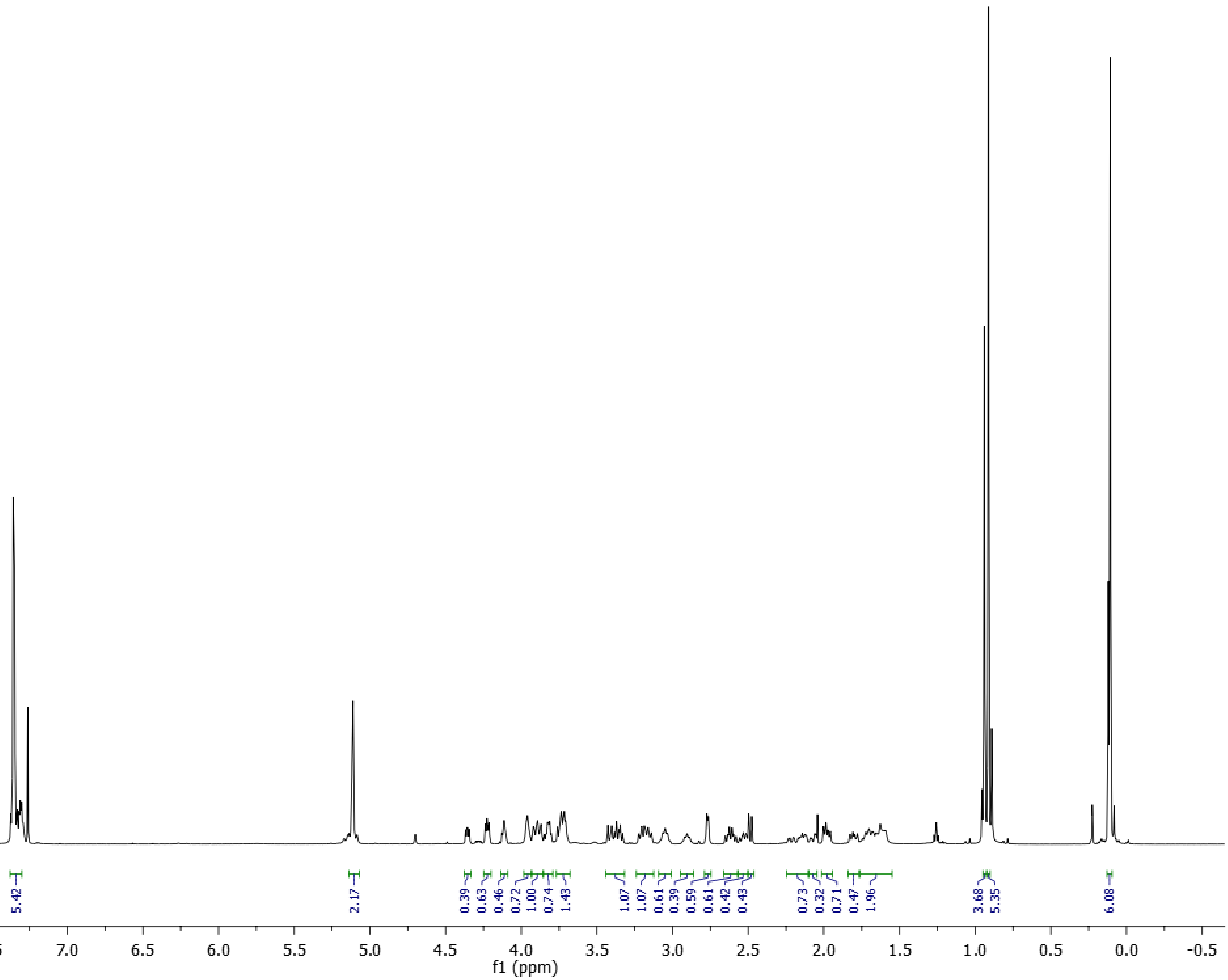
O
OH
OTBS
+
H
CbzN
O
OTBS
OH

16 and **17**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0.43
0.73
0.32
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0.47
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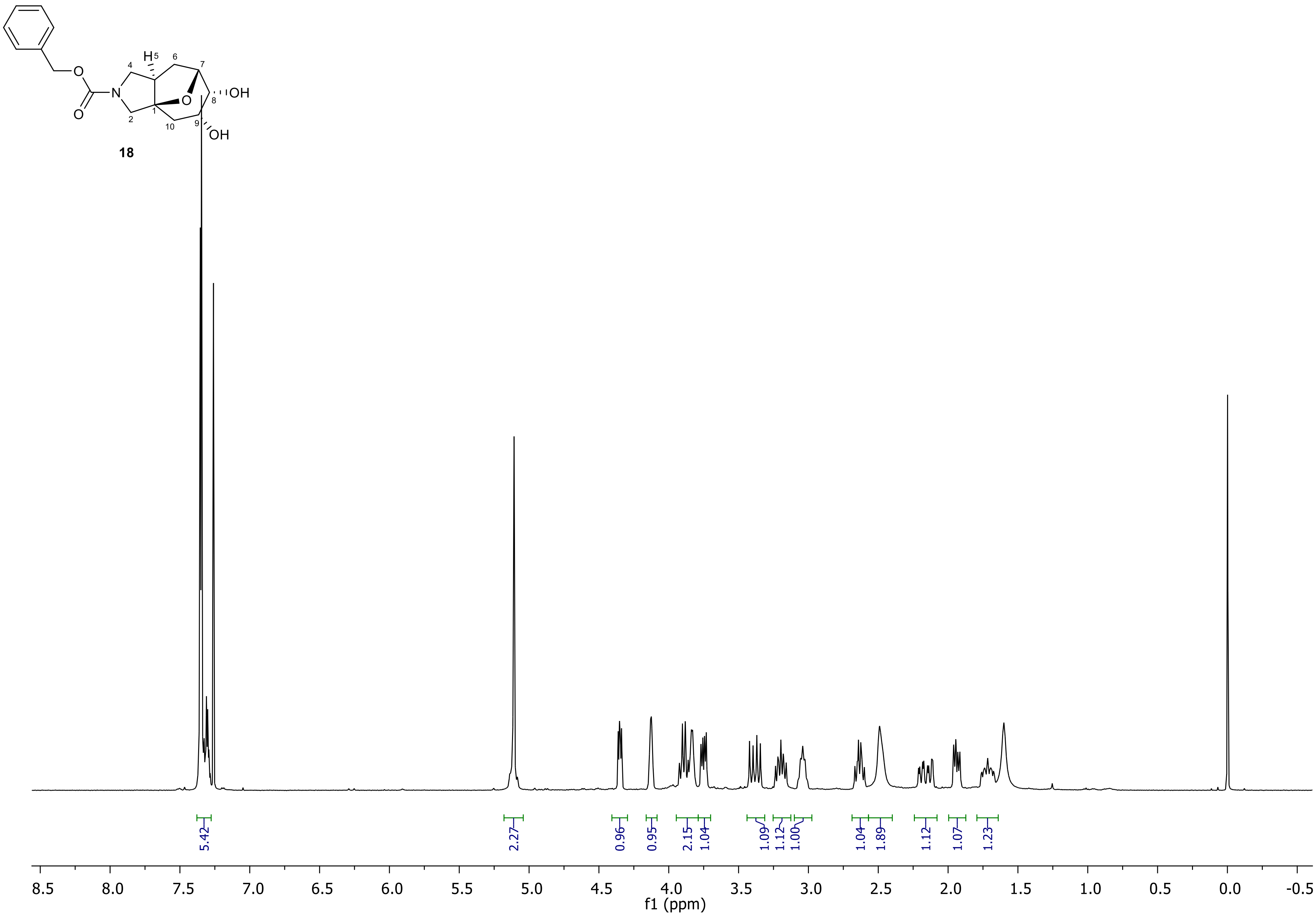
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8
OH
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OH
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0.95
2.15
1.04
1.09
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1.04
1.89
1.12
1.07
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8.5
8.0
7.5
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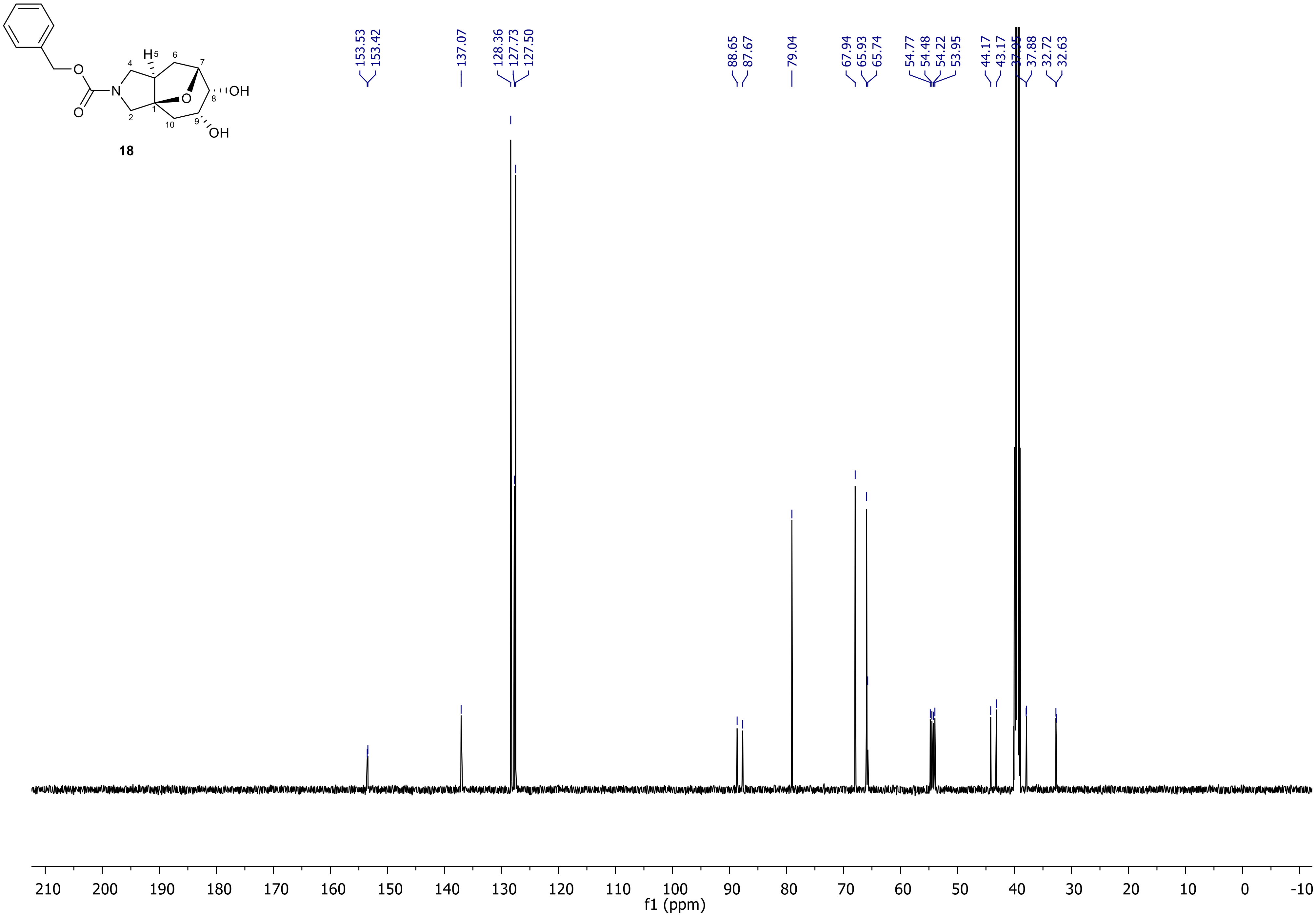
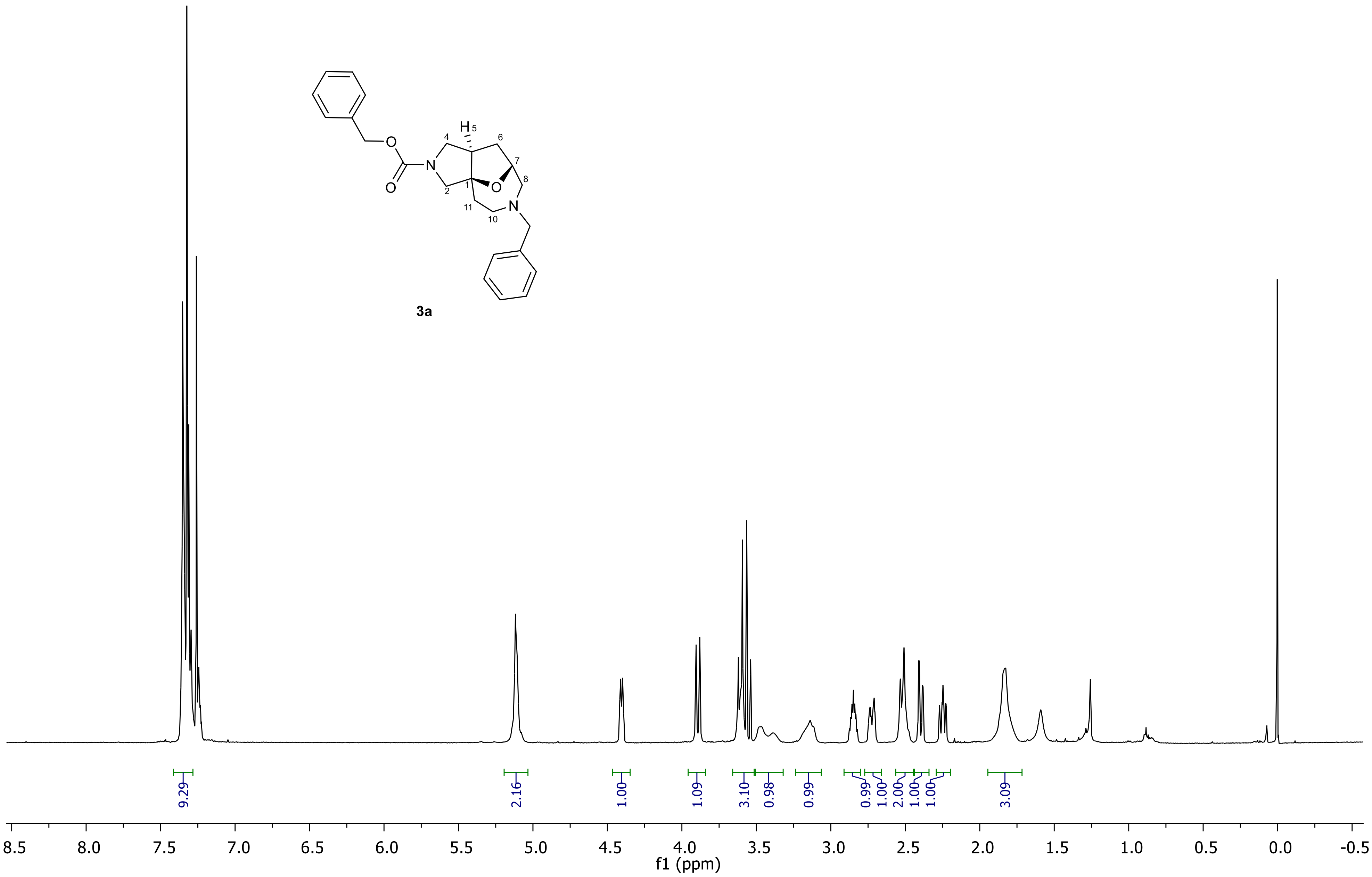
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

18

H
5
4
6
7
O
N
O
O
8
OH
2
1
10
9
OH

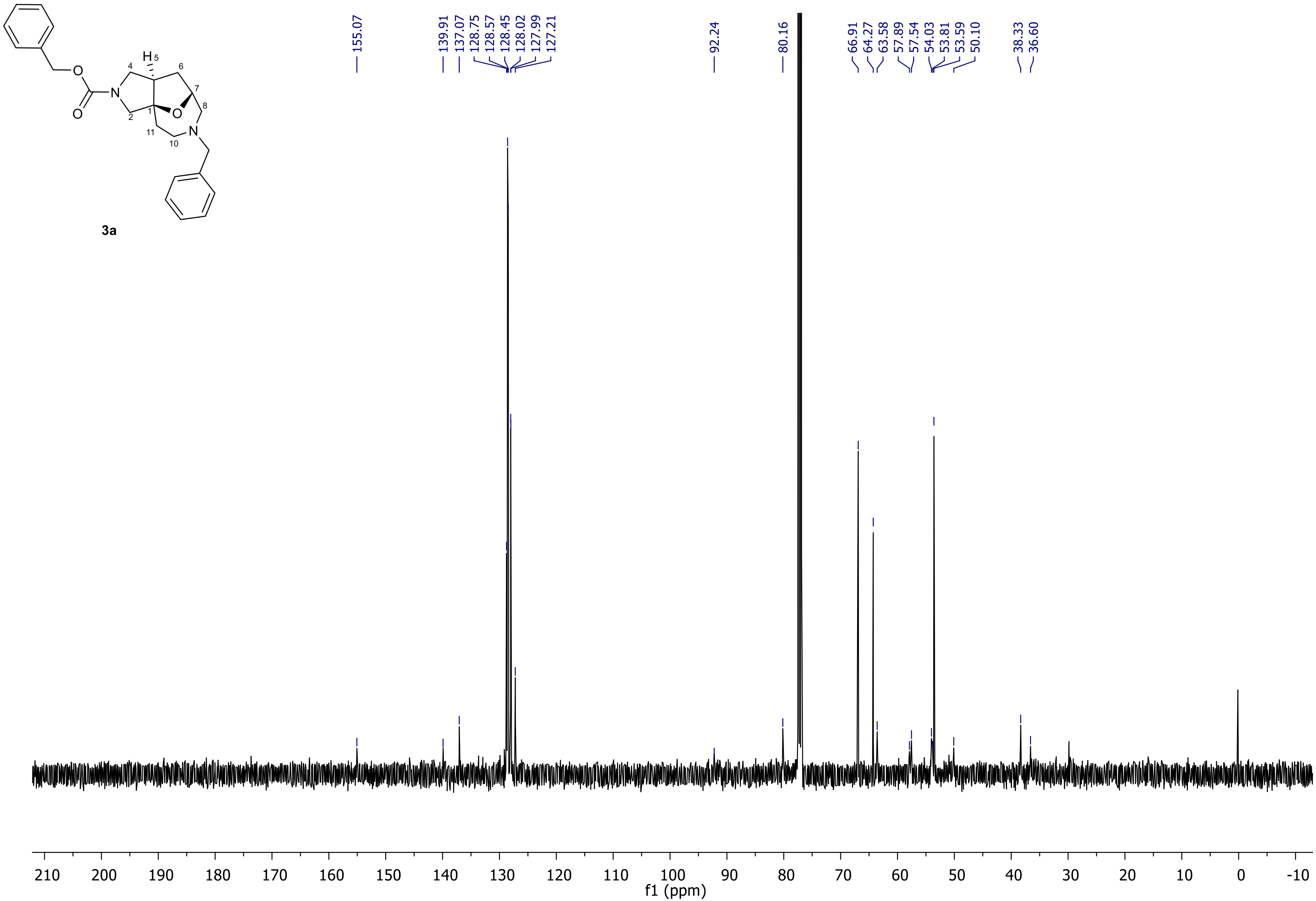
18


153.53
153.42
137.07
128.36
127.73
127.50
88.65
87.67
79.04
67.94
65.93
65.74
54.77
54.48
54.22
53.95
44.17
43.17
37.95
37.88
32.72
32.63
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

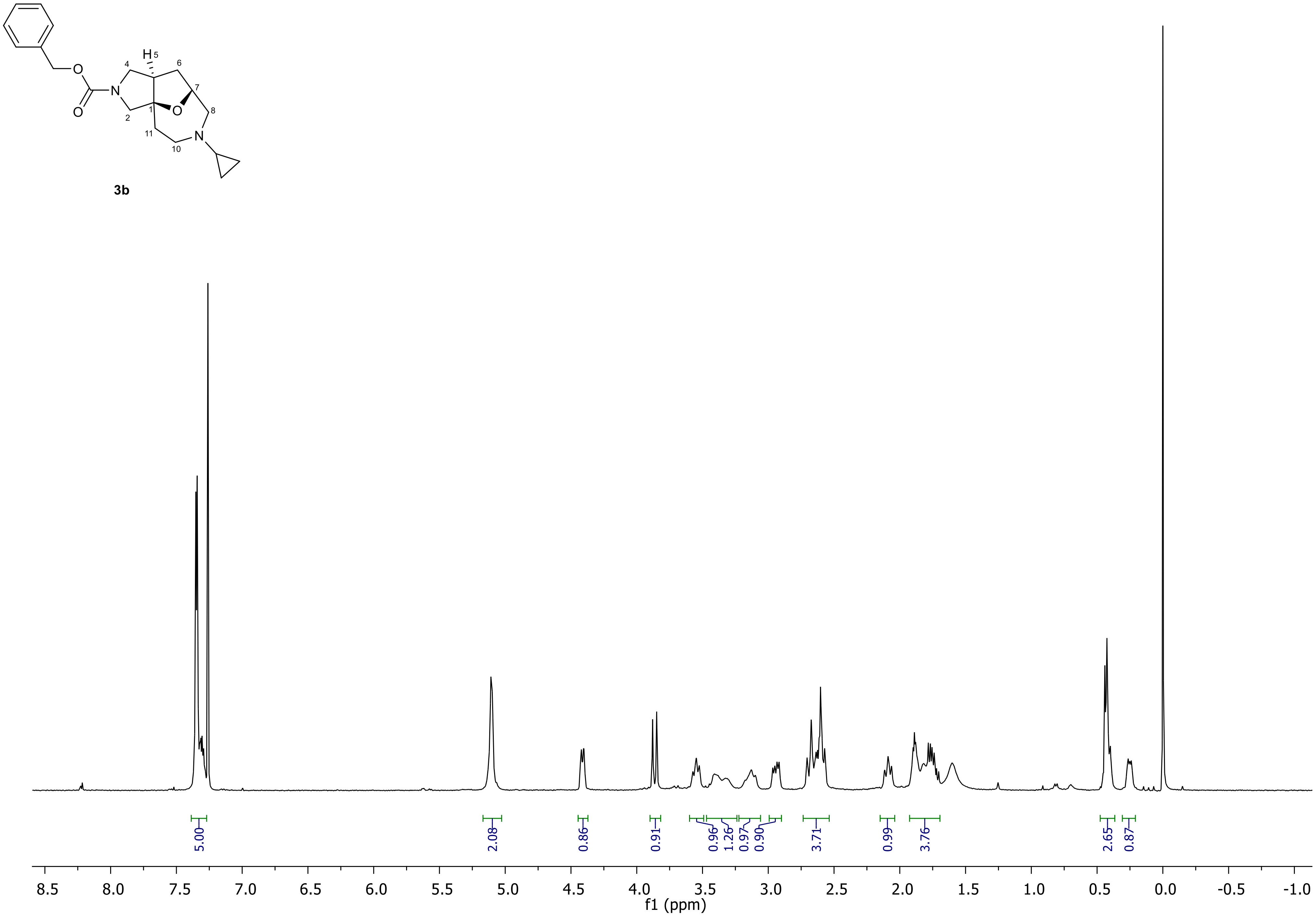


3a

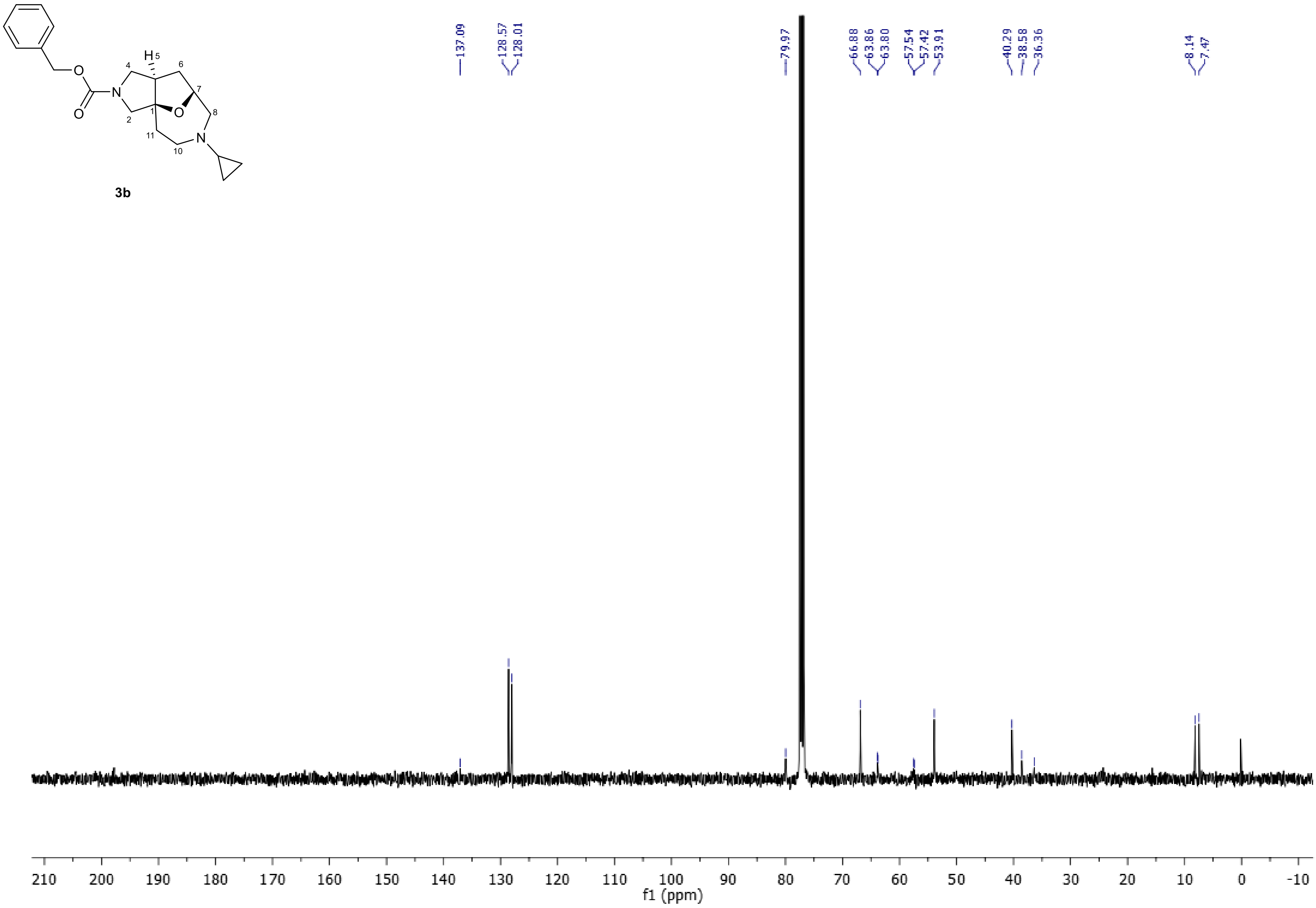
H 5
4
6
7
8
2
1
O
N
N
11
10
O
O
9.29
2.16
1.00
1.09
3.10
0.98
0.99
0.99
1.00
2.00
1.00
1.00
3.09
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


155.07
139.91
137.07
128.75
128.57
128.45
128.02
127.99
127.21
92.24
80.16
66.91
64.27
63.58
57.89
57.54
54.03
53.81
53.59
50.10
38.33
36.60
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
H
5
4
6
7
8
1
2
11
10
O
N

3a

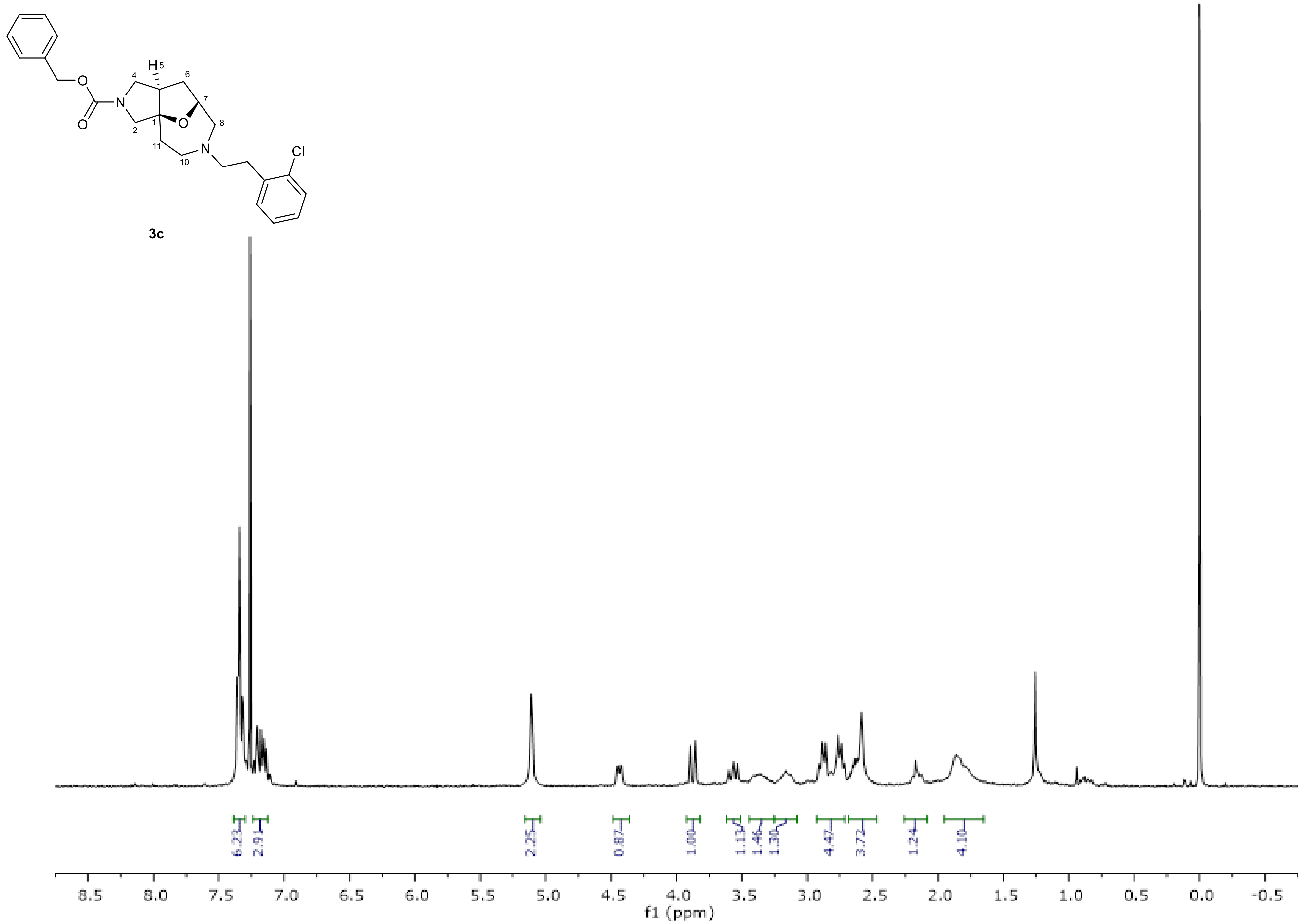

H 5
4
6
7
8
1
2
11
10
O
N
5.00
2.08
0.86
0.91
0.96
1.26
0.97
0.90
3.71
0.99
3.76
2.65
0.87
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

3b


H
5
4
6
7
1
2
8
11
10
O
N
N
O
O

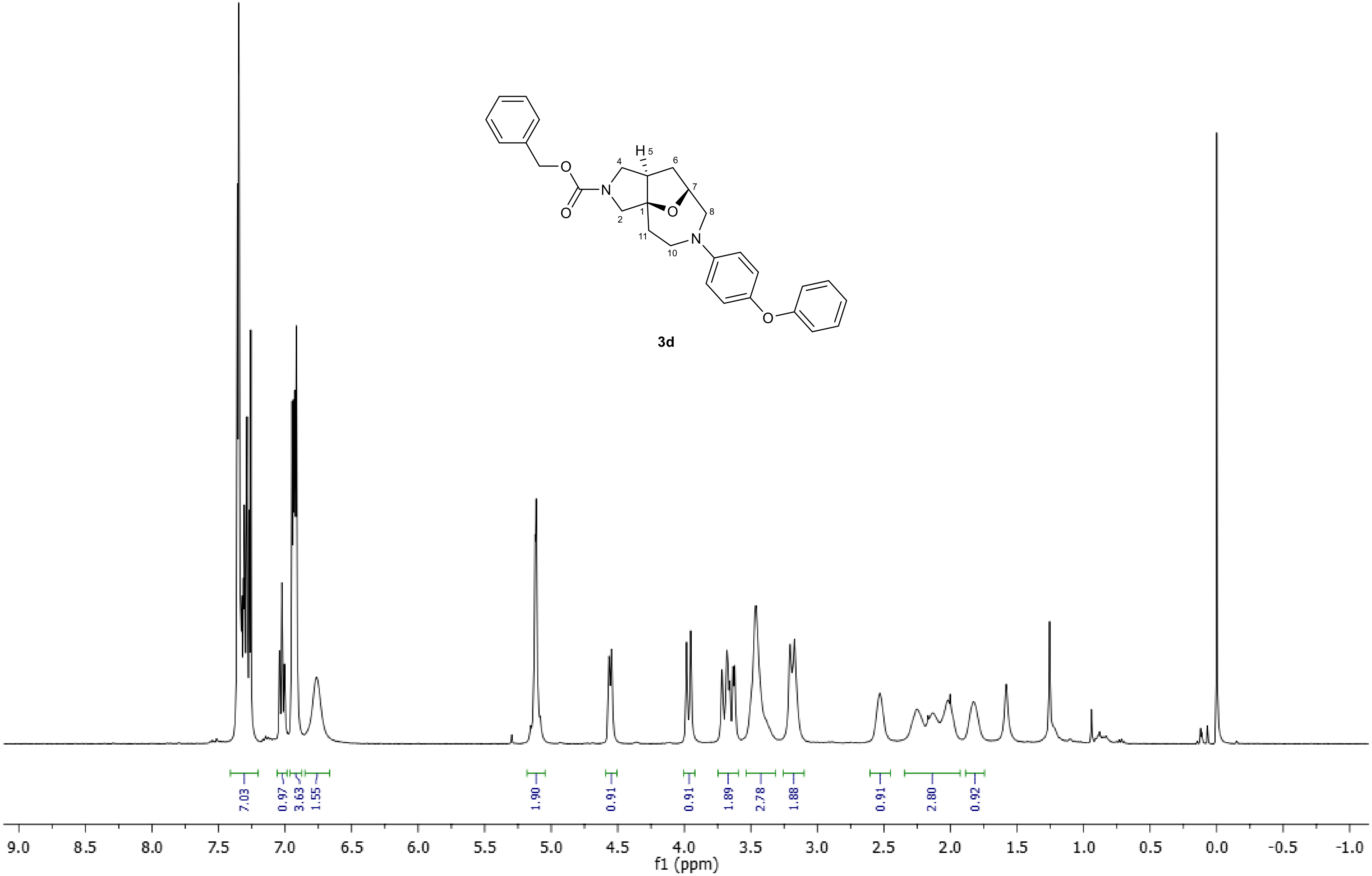
3b

137.09
128.57
128.01
79.97
66.88
63.86
63.80
57.54
57.42
53.91
40.29
38.58
36.36
8.14
7.47
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



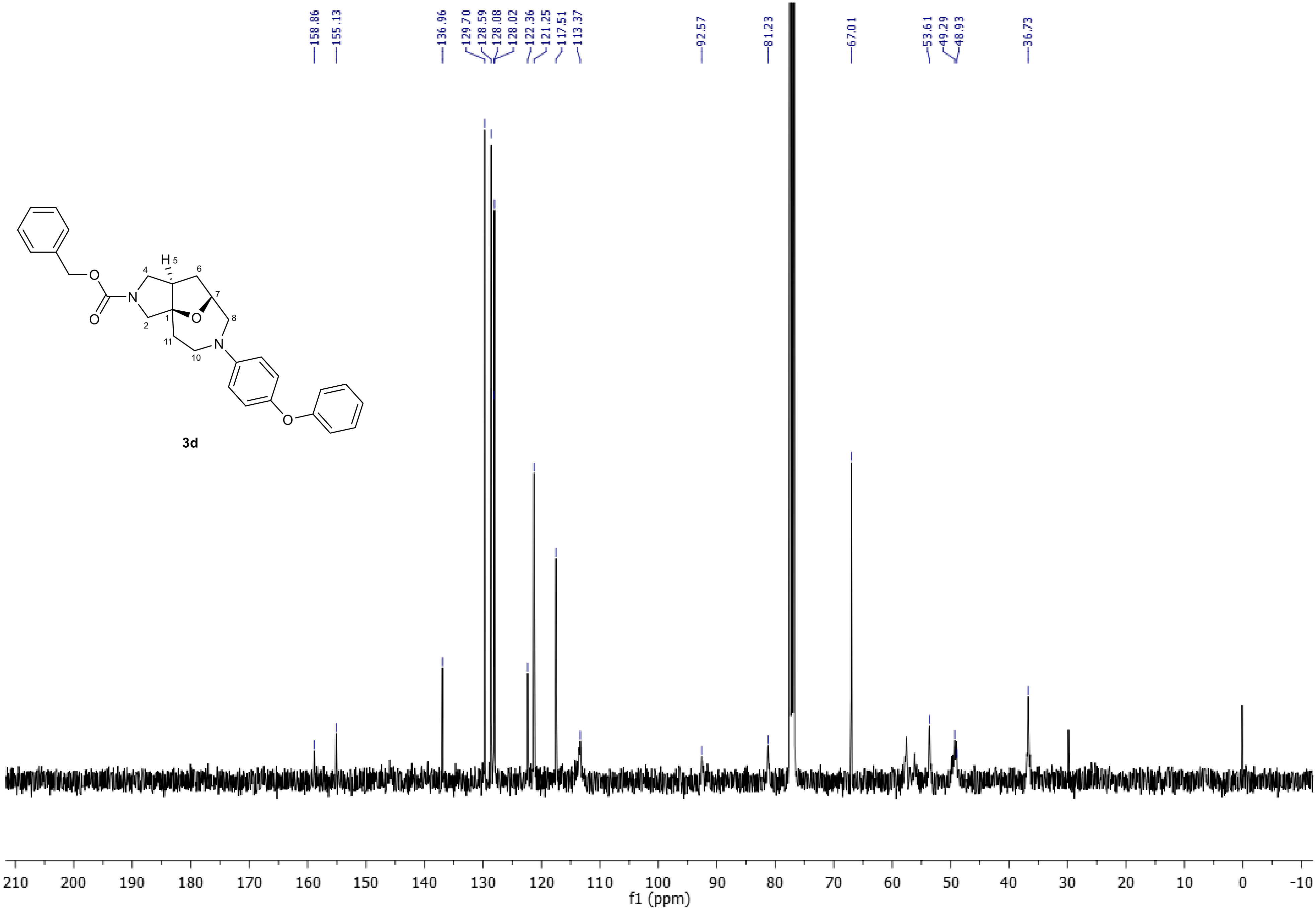
3c

O
O
O
N
H
5
4
6
7
8
2
1
11
10
N
Cl
6.23
2.91
2.25
0.87
1.00
1.13
1.46
1.30
4.47
3.72
1.24
4.10
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

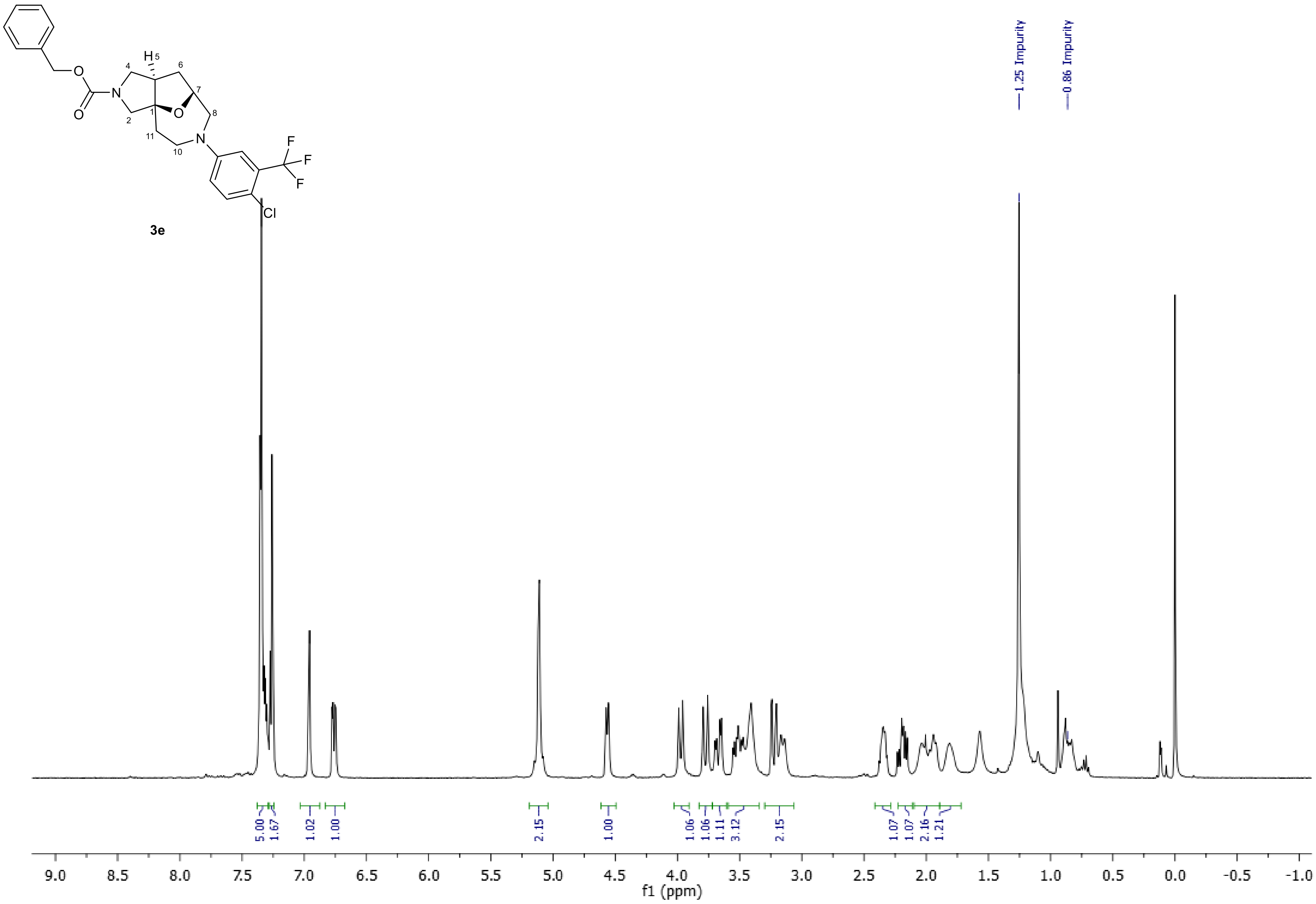


H 5
4
6
7
O
N
O
O
1
2
8
11
10
N
O
7.03
0.97
3.63
1.55
1.90
0.91
0.91
1.89
2.78
1.88
0.91
2.80
0.92
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

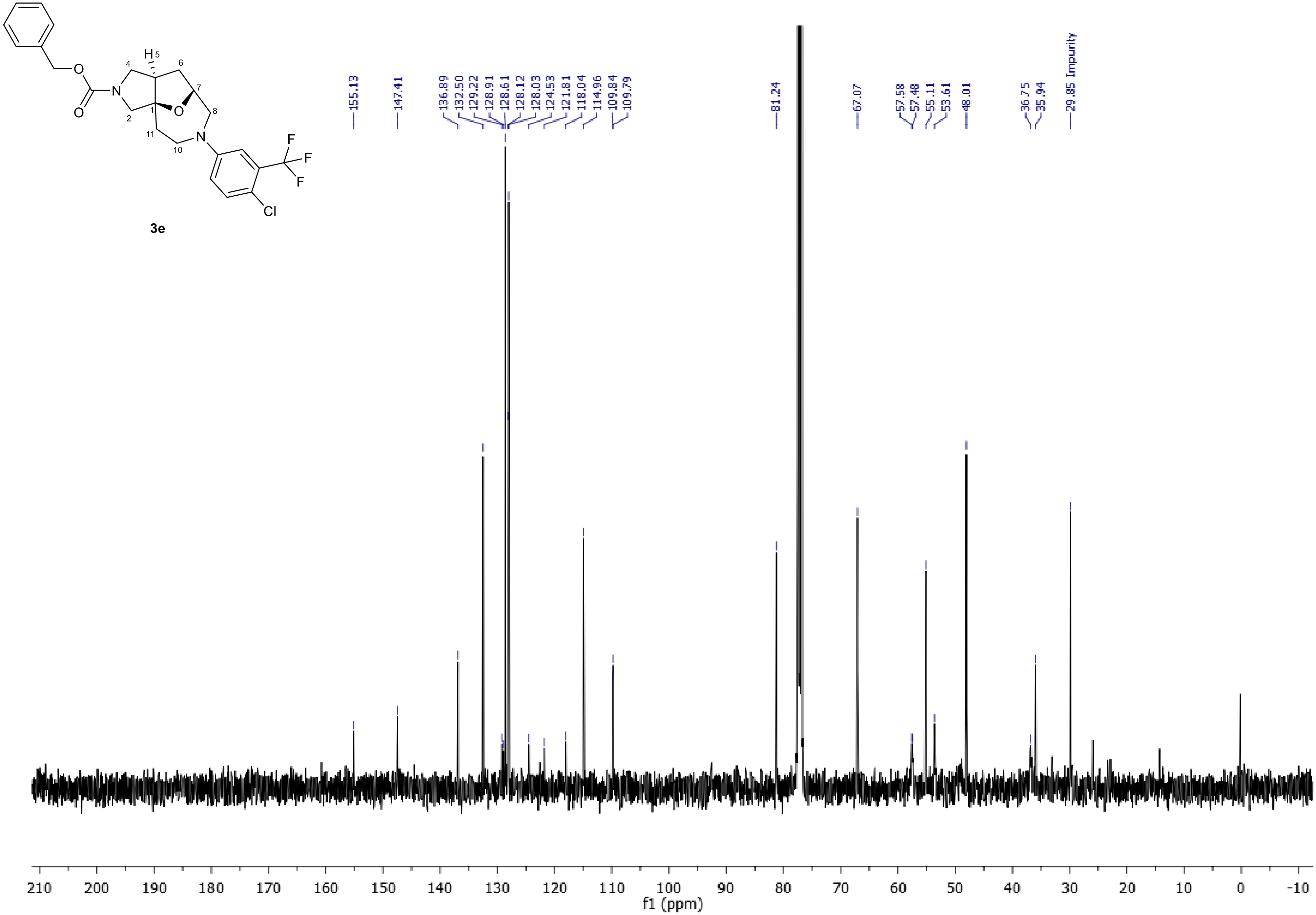
3d


158.86
155.13
136.96
129.70
128.59
128.08
128.02
122.36
121.25
117.51
113.37
92.57
81.23
67.01
53.61
49.29
48.93
36.73
H
5
4
6
7
8
1
2
11
10
N
O
O
O
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

3d

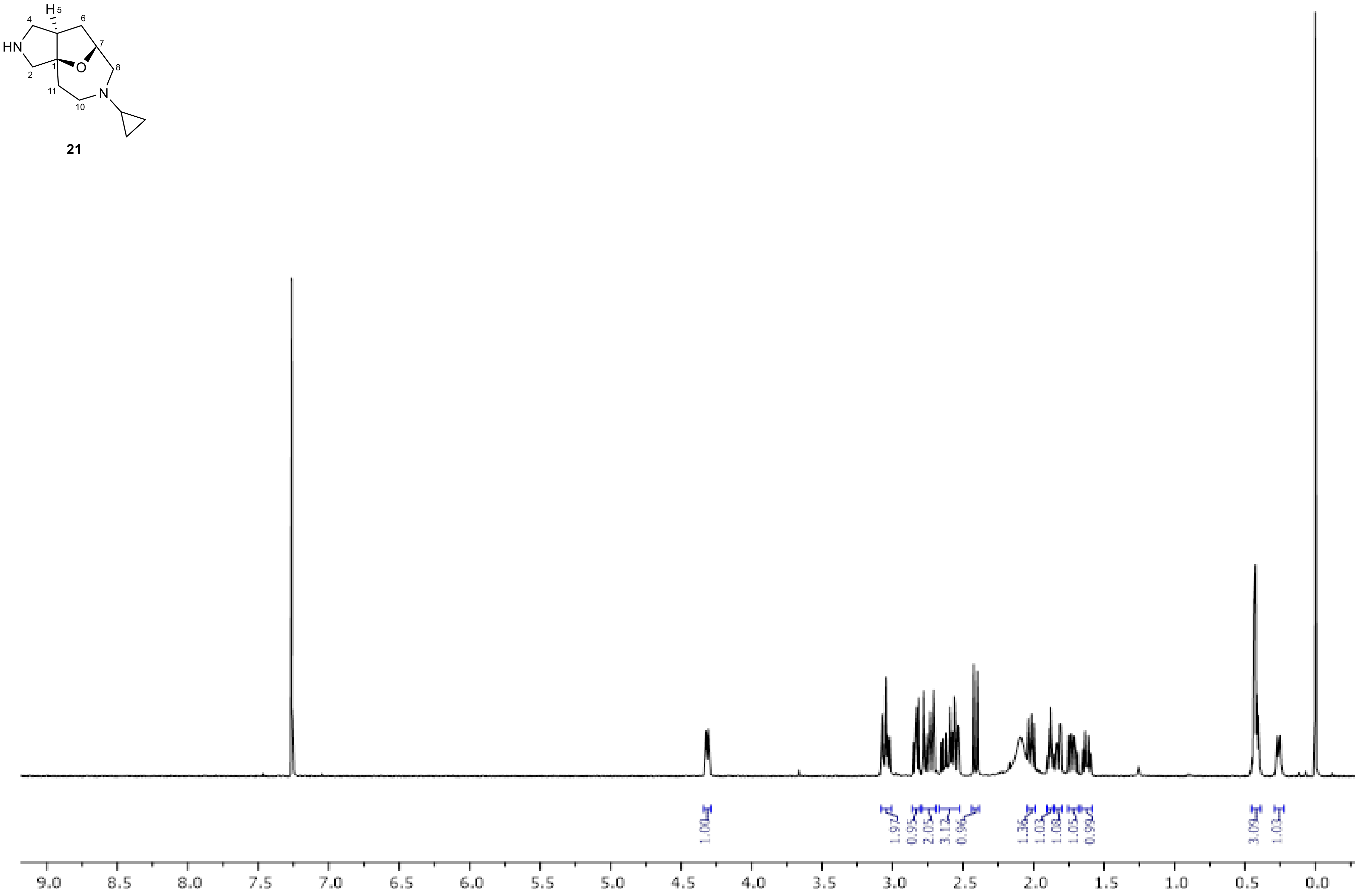

H
5
4
6
7
1
2
8
11
10
O
O
O
N
N
F
F
F
Cl
1.25 Impurity
0.86 Impurity
5.00
1.67
1.02
1.00
2.15
1.00
1.06
1.06
1.11
3.12
2.15
1.07
1.07
2.16
1.21
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

3e


O
N
O
H
5
6
4
7
2
1
O
8
11
N
10
F
F
F
Cl

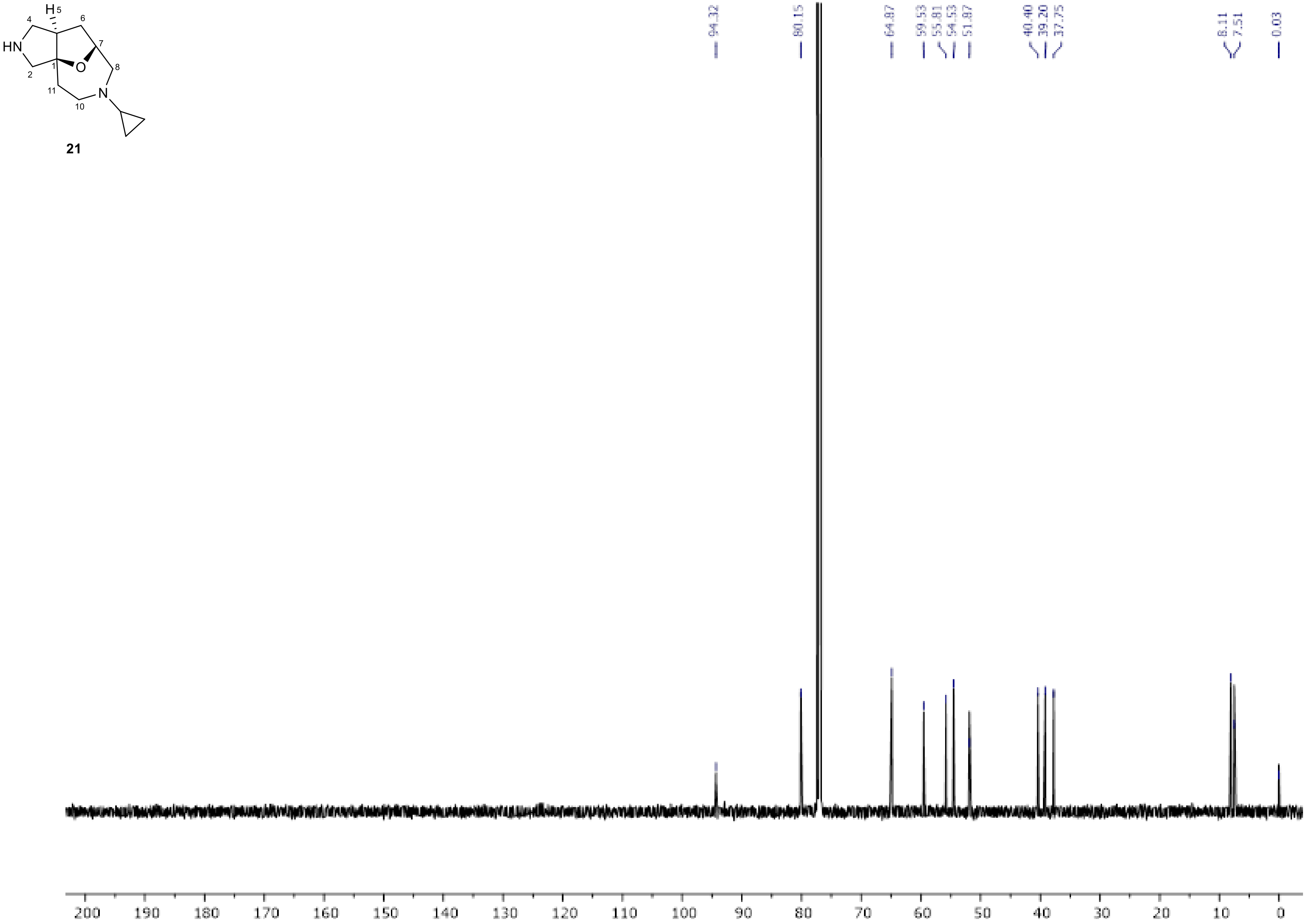
3e

155.13
147.41
136.89
132.50
129.22
128.91
128.61
128.12
128.03
124.53
121.81
118.04
114.96
109.84
109.79
81.24
67.07
57.58
57.48
55.11
53.61
48.01
36.75
35.94
29.85 Impurity
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



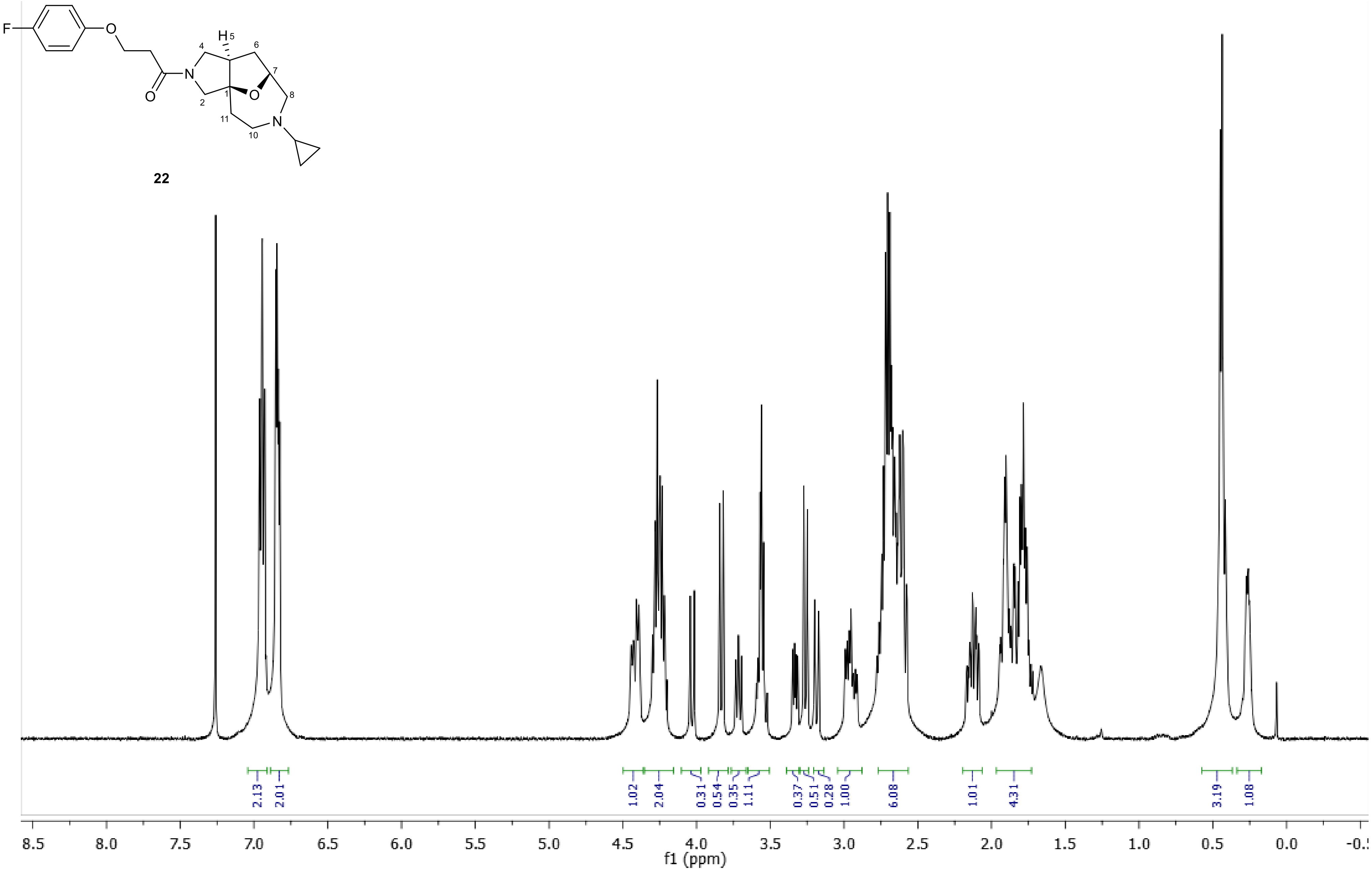
21

H
5
4
6
HN
7
1
O
2
8
11
N
10
1.00
1.97
0.95
2.05
3.12
0.96
1.36
1.03
1.08
1.05
0.99
3.09
1.03
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



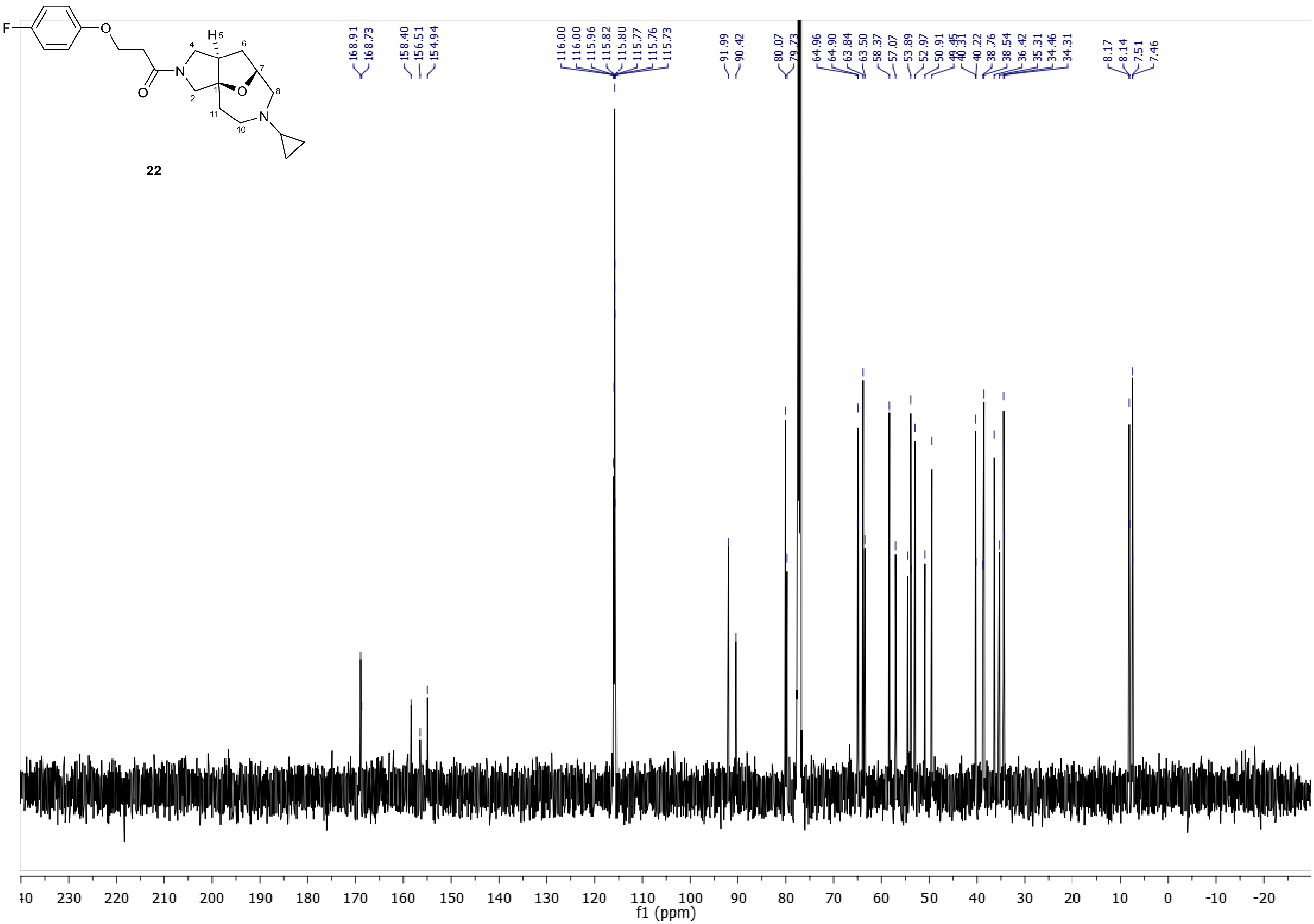
21

H
5
4
6
HN
7
O
8
2
1
11
N
10
94.32
80.15
64.87
59.53
55.81
54.53
51.87
40.40
39.20
37.75
8.11
7.51
0.03
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



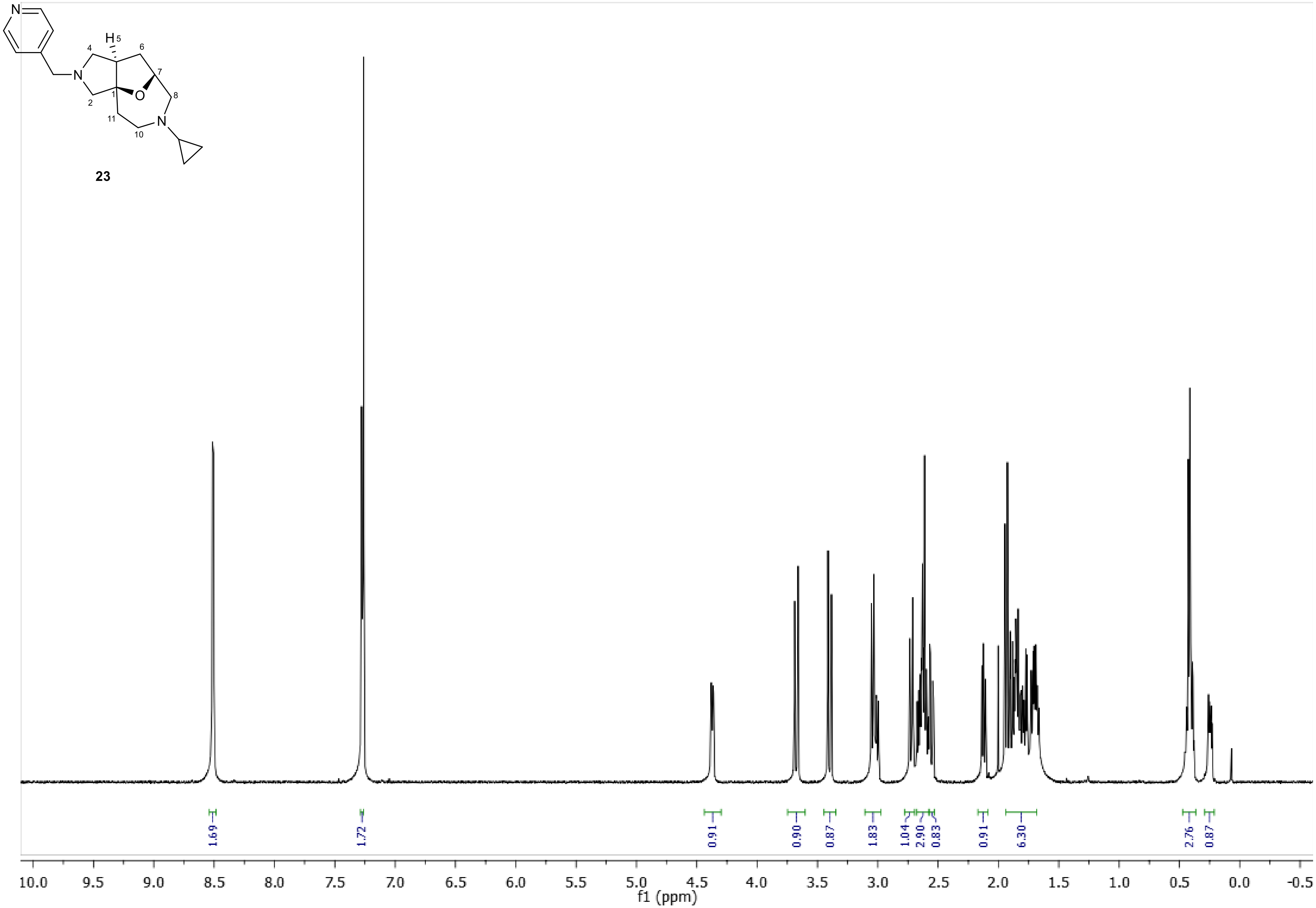
22

F
O
O
N
H
5
4
6
7
8
2
1
11
10
N
2.13
2.01
1.02
2.04
0.31
0.54
0.35
1.11
0.37
0.51
0.28
1.00
6.08
1.01
4.31
3.19
1.08
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

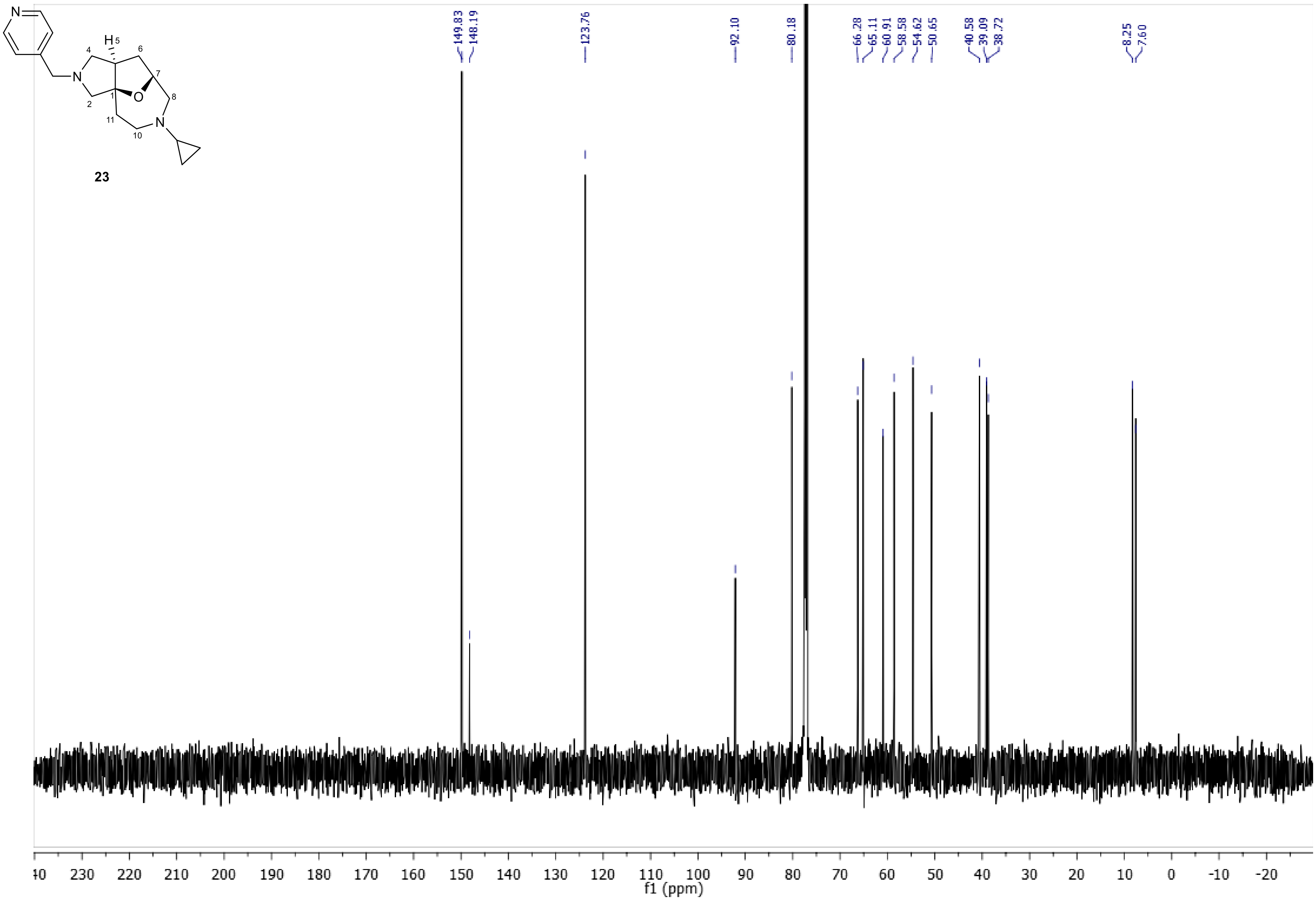


22

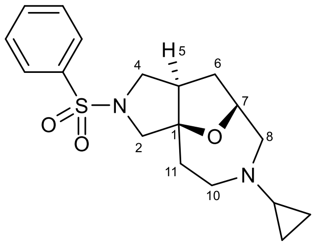
F
O
O
N
H5
4
6
7
1
O
2
8
11
N
10
168.91
168.73
158.40
156.51
154.94
116.00
116.00
115.96
115.82
115.80
115.77
115.76
115.73
91.99
90.42
80.07
79.73
64.96
64.90
63.84
63.50
58.37
57.07
53.89
52.97
50.91
49.45
40.31
40.22
38.76
38.54
36.42
35.31
34.46
34.31
8.17
8.14
7.51
7.46
40
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


N
H
5
4
6
7
O
1
2
8
11
10
N
1.69
1.72
0.91
0.90
0.87
1.83
1.04
2.90
0.83
0.91
6.30
2.76
0.87
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

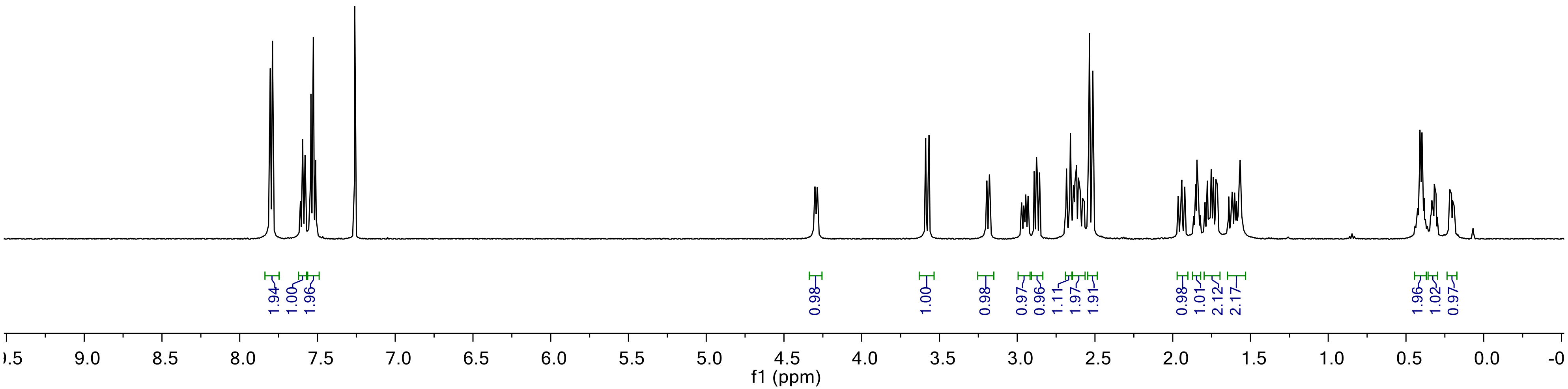
23

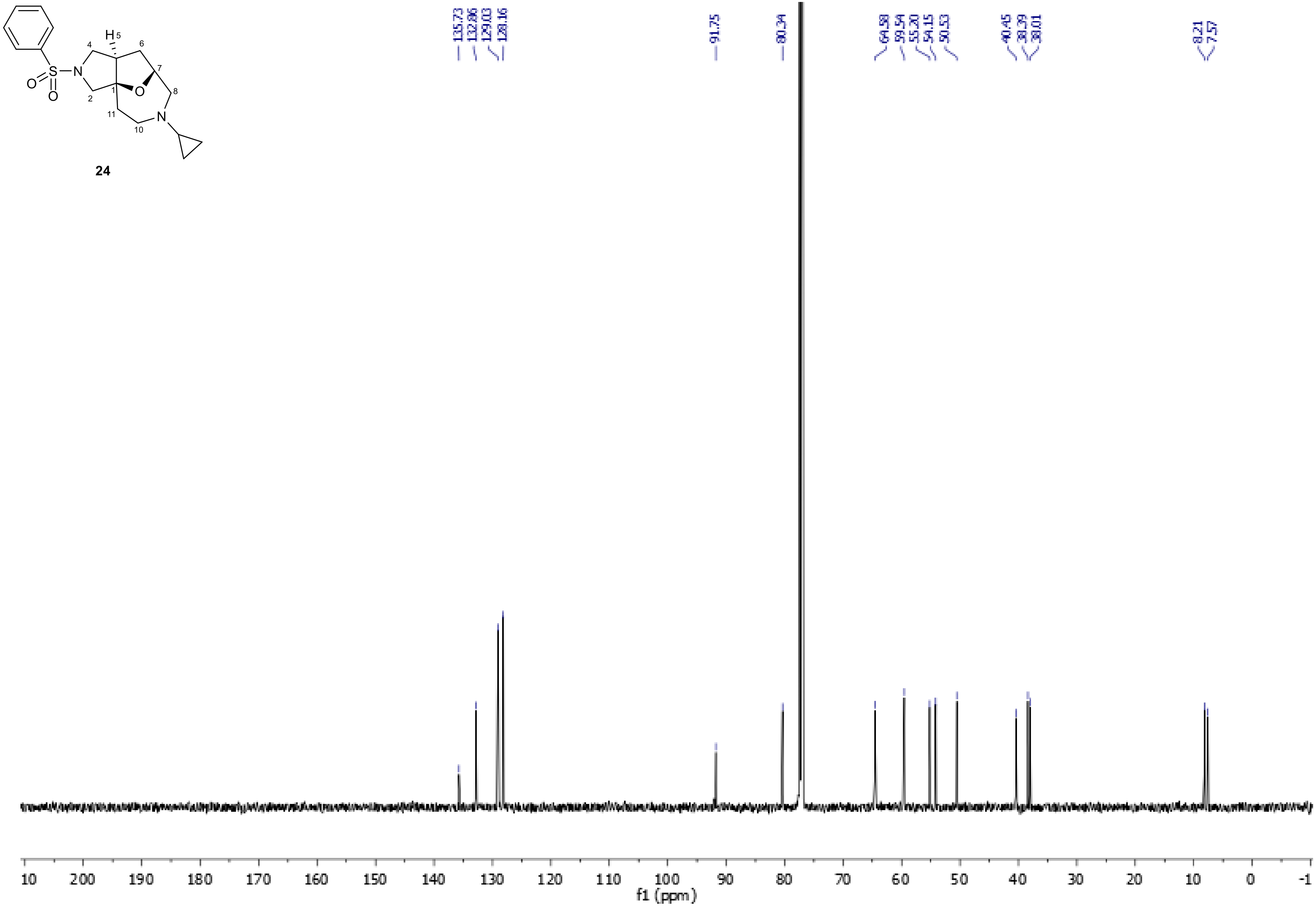

23

N
H
5
4
6
7
1
8
2
O
11
N
10
149.83
148.19
123.76
92.10
80.18
66.28
65.11
60.91
58.58
54.62
50.65
40.58
39.09
38.72
8.25
7.60
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

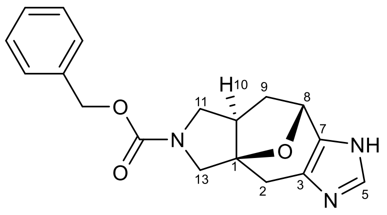

O
S
O
N
4
H
5
6
7
1
O
8
2
11
10
N

24

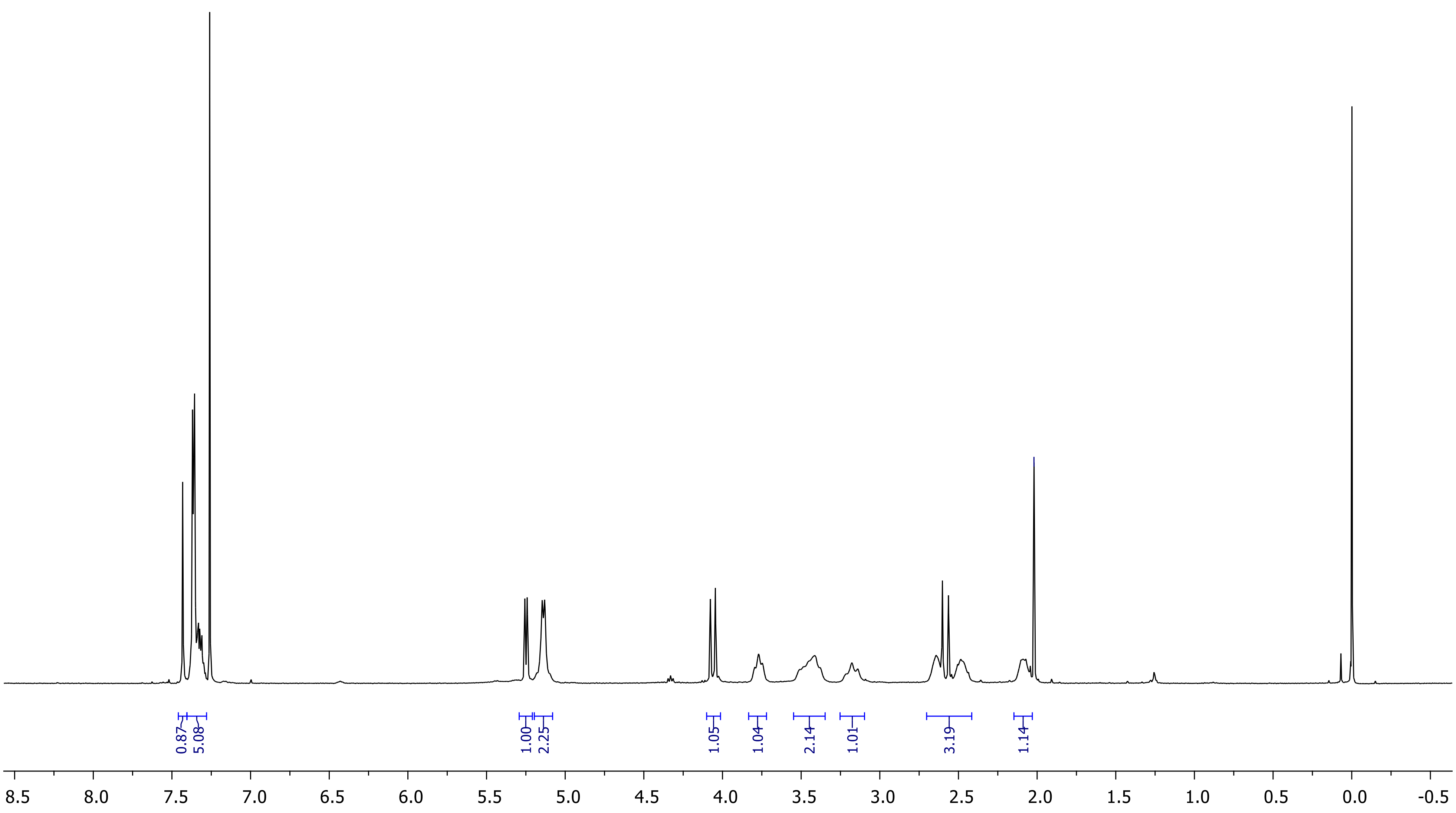

1.94
1.00
1.96
0.98
1.00
0.98
0.97
0.96
1.11
1.97
1.91
0.98
1.01
2.12
2.17
1.96
1.02
0.97
.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

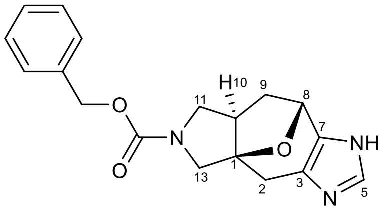

H 5
4
6
7
8
1
2
11
10
N
S
O
O
O
N
135.73
132.86
129.03
128.16
91.75
80.34
64.58
59.54
55.20
54.15
50.53
40.45
38.39
38.01
8.21
7.57
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

24

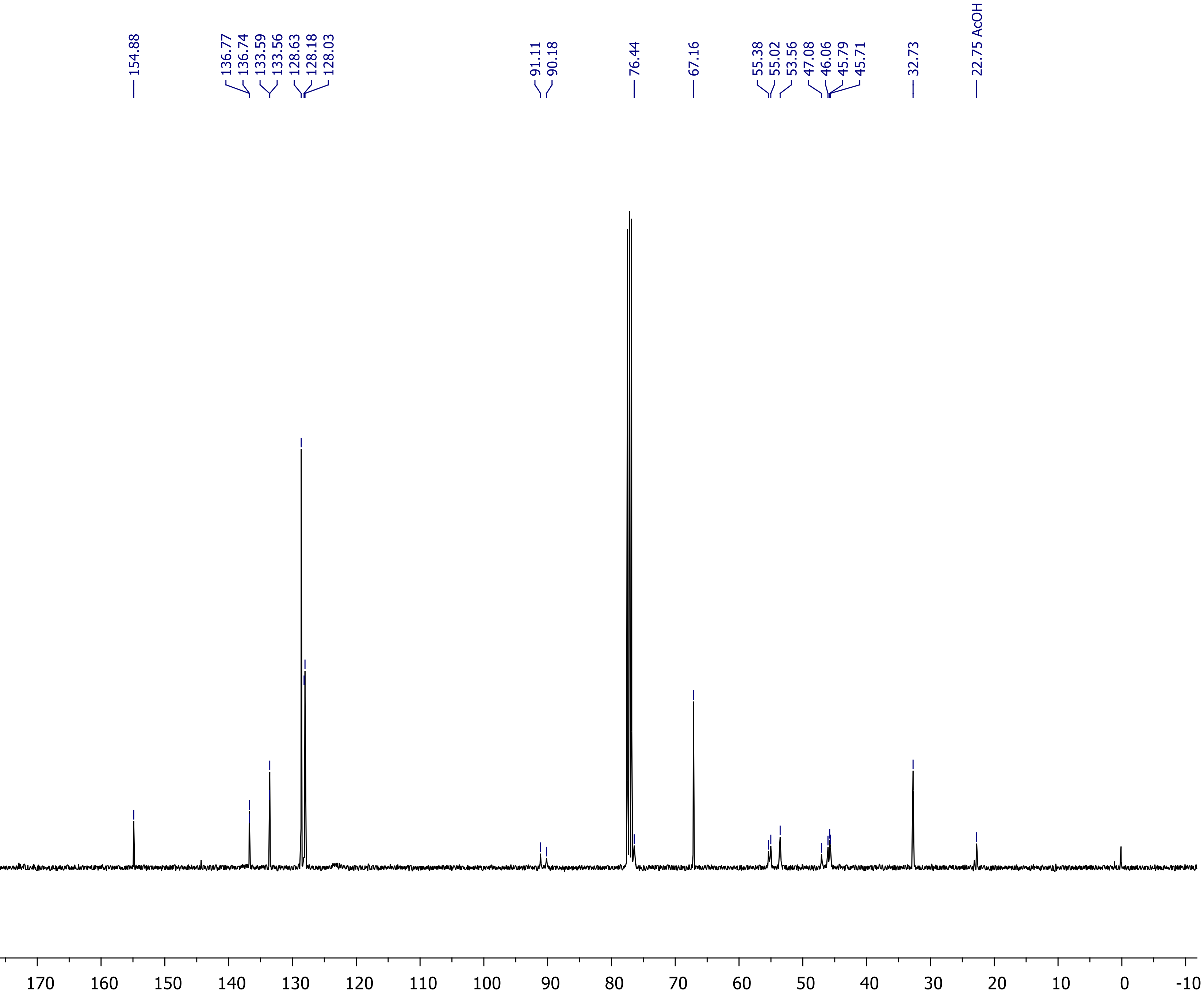

H
10
9
8
11
7
NH
O
N
O
O
13
1
2
3
N
5

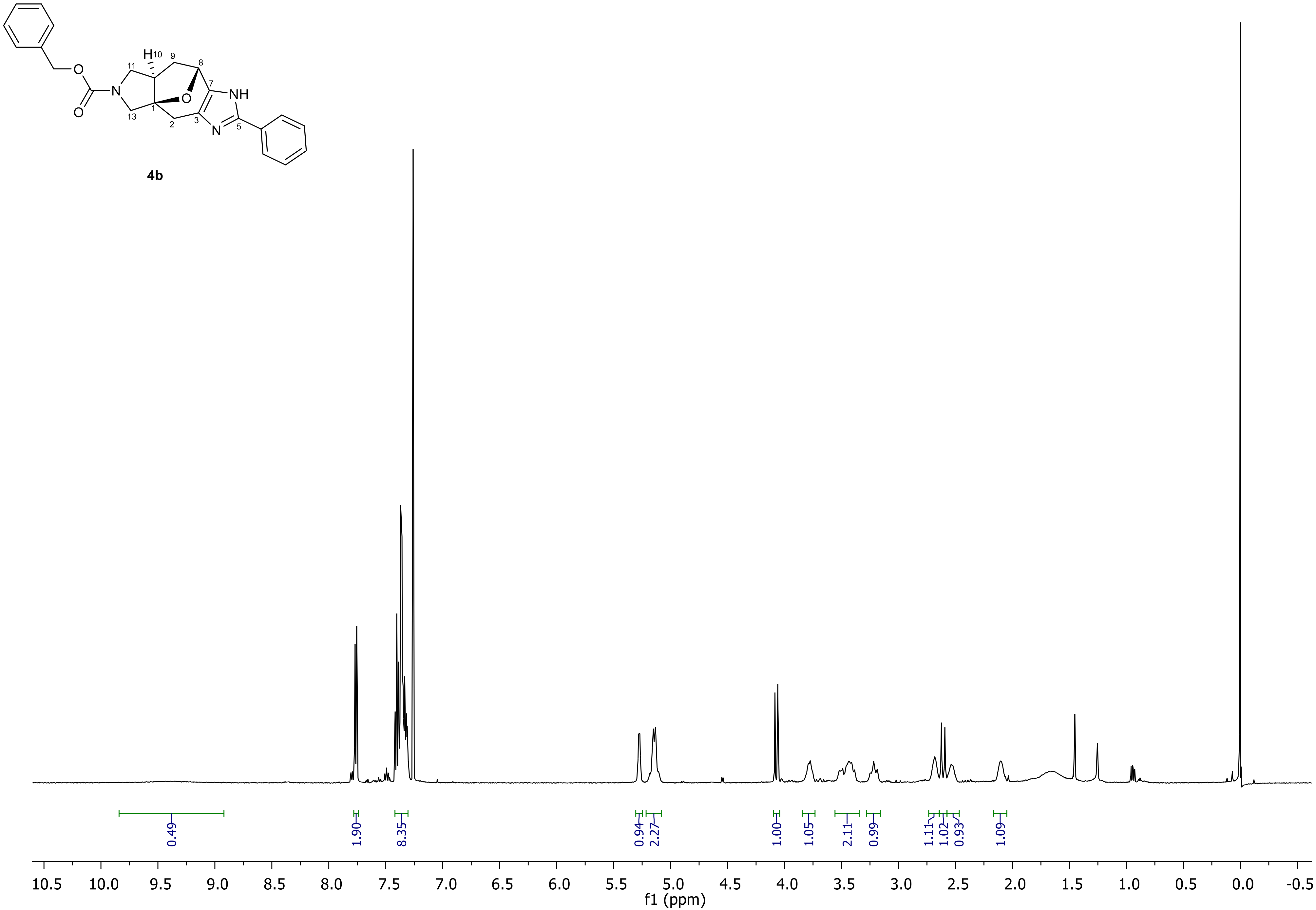
4a


2.02 AcOH
0.87
5.08
1.00
2.25
1.05
1.04
2.14
1.01
3.19
1.14
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


H10
9
8
11
7
NH
O
N
O
O
1
13
2
3
N
5

4a


154.88
136.77
136.74
133.59
133.56
128.63
128.18
128.03
91.11
90.18
76.44
67.16
55.38
55.02
53.56
47.08
46.06
45.79
45.71
32.73
22.75 AcOH
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

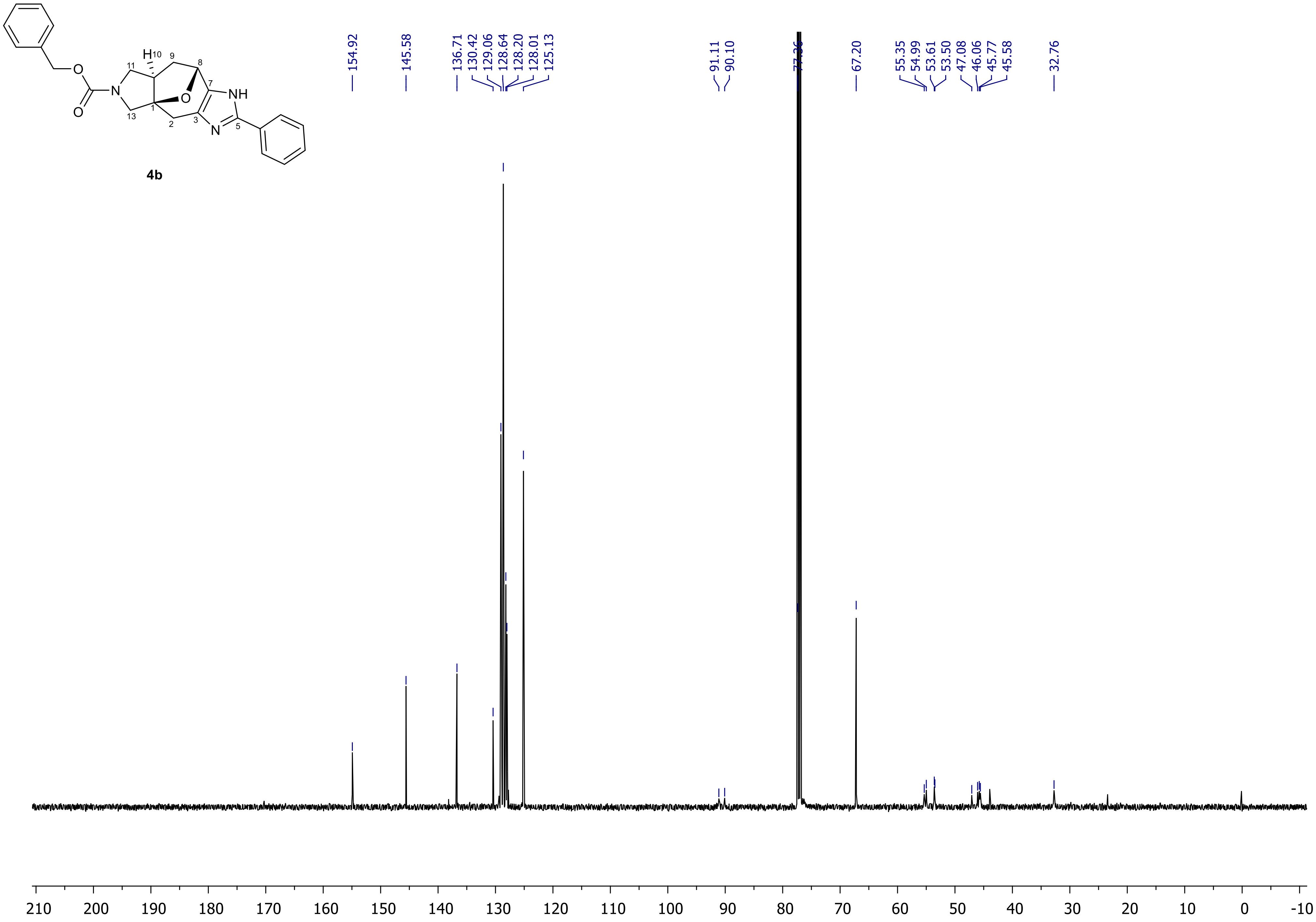

H10
9
8
11
O
N
O
7
NH
1
O
13
2
3
N
5

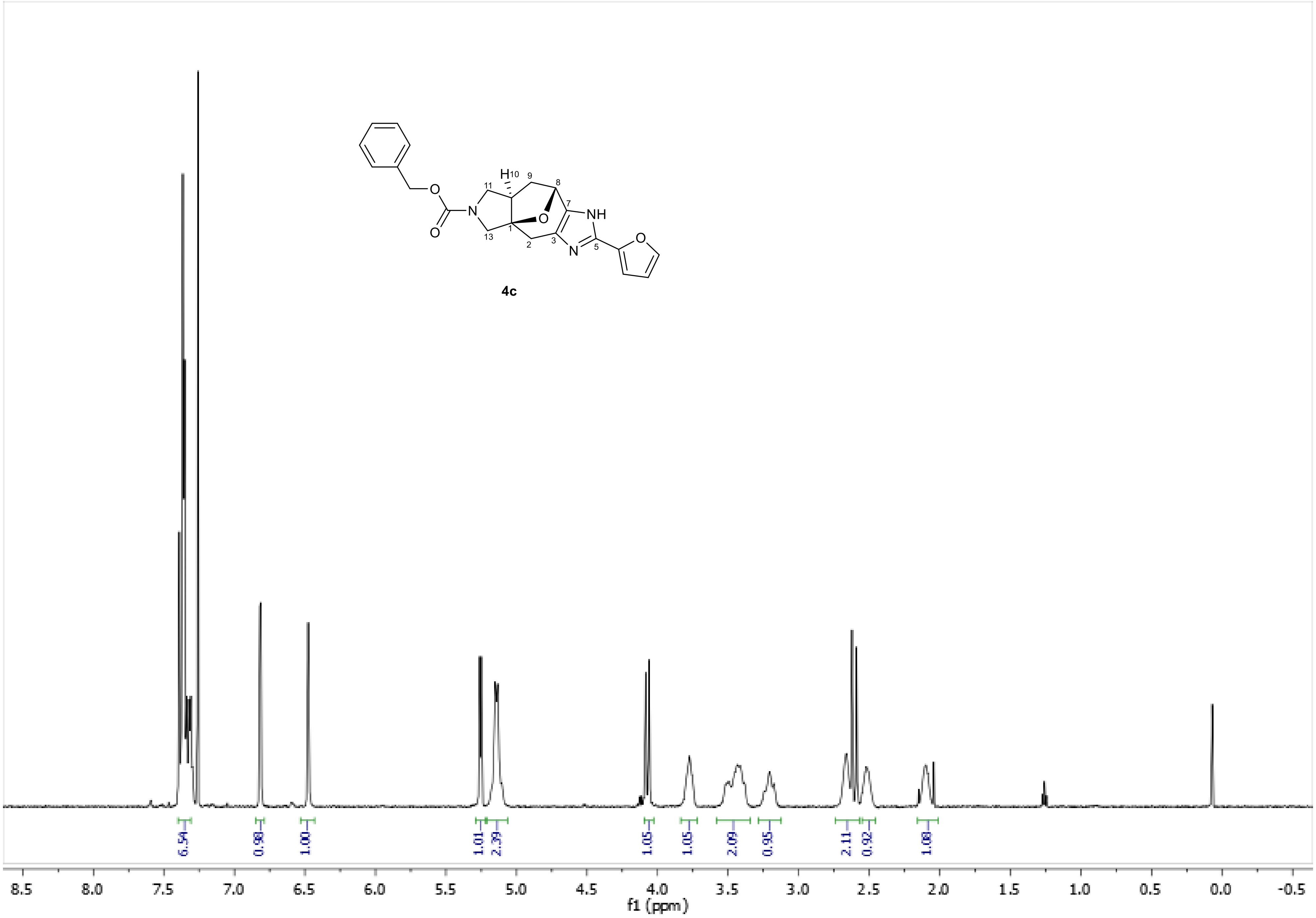
4b

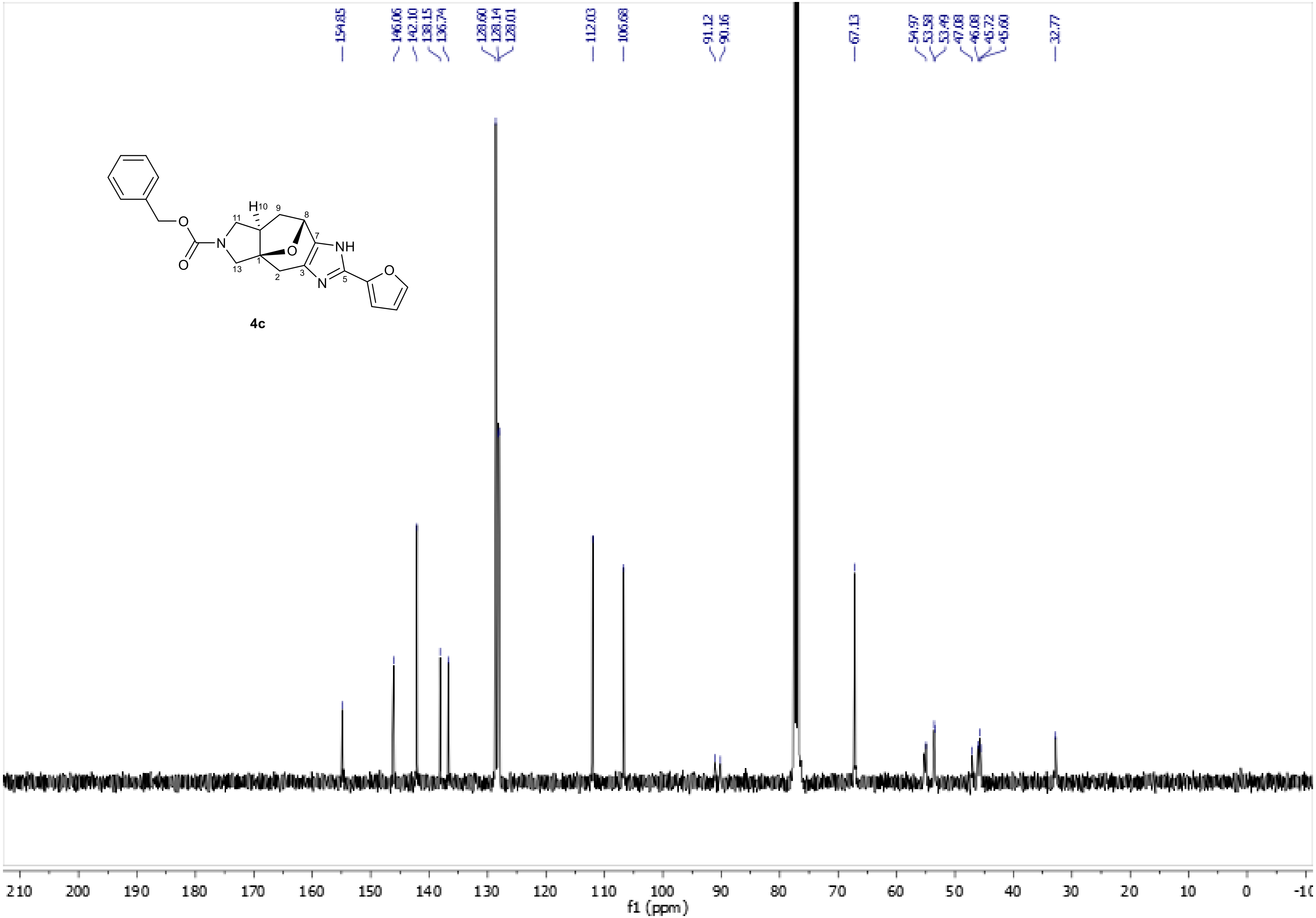
0.49
1.90
8.35
0.94
2.27
1.00
1.05
2.11
0.99
1.11
1.02
0.93
1.09
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

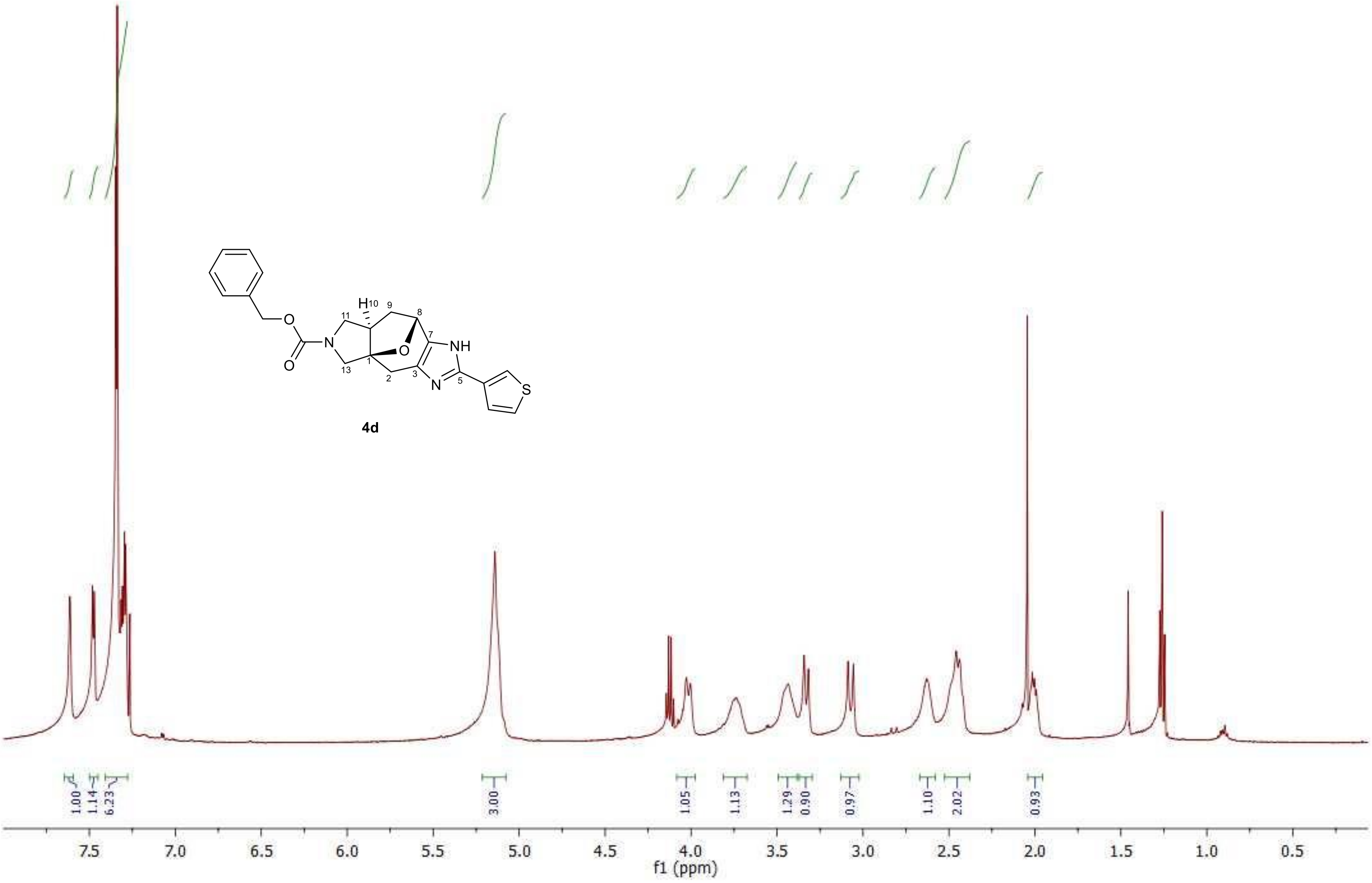
H
10
9
8
11
O
O
7
NH
N
13
1
2
3
N
5
O

4b


154.92
145.58
136.71
130.42
129.06
128.64
128.20
128.01
125.13
91.11
90.10
77.36
67.20
55.35
54.99
53.61
53.50
47.08
46.06
45.77
45.58
32.76
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

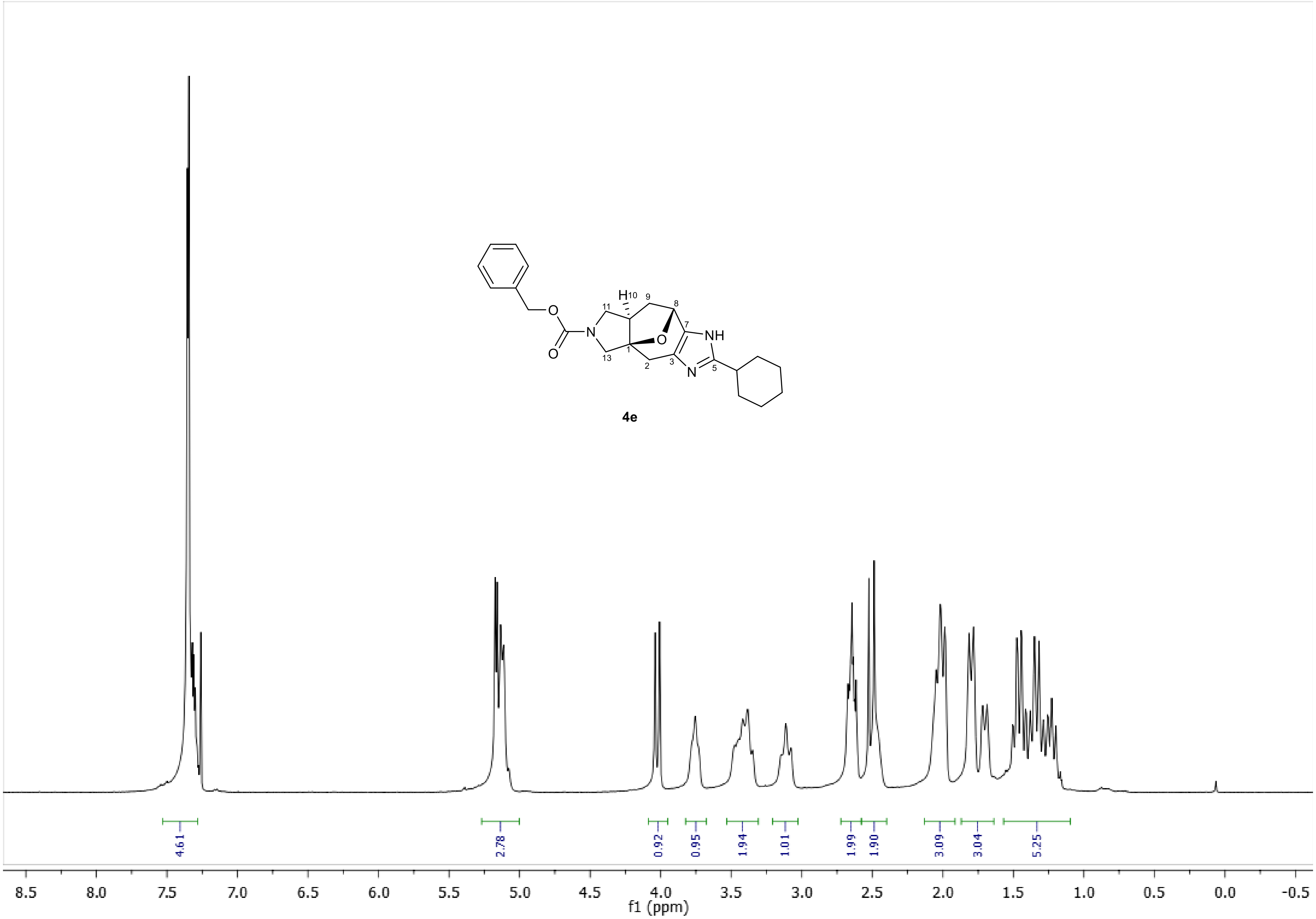

H10
9
8
11
7
NH
O
N
O
O
13
1
2
3
N
5
O
4c
6.54
0.98
1.00
1.01
2.39
1.05
1.05
2.09
0.95
2.11
0.92
1.08
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


154.85
146.06
142.10
138.15
136.74
128.60
128.14
128.01
112.03
106.68
91.12
90.16
67.13
54.97
53.58
53.49
47.08
46.08
45.72
45.60
32.77
H
10
9
8
11
O
7
NH
N
O
O
1
13
2
3
N
5
O
4c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

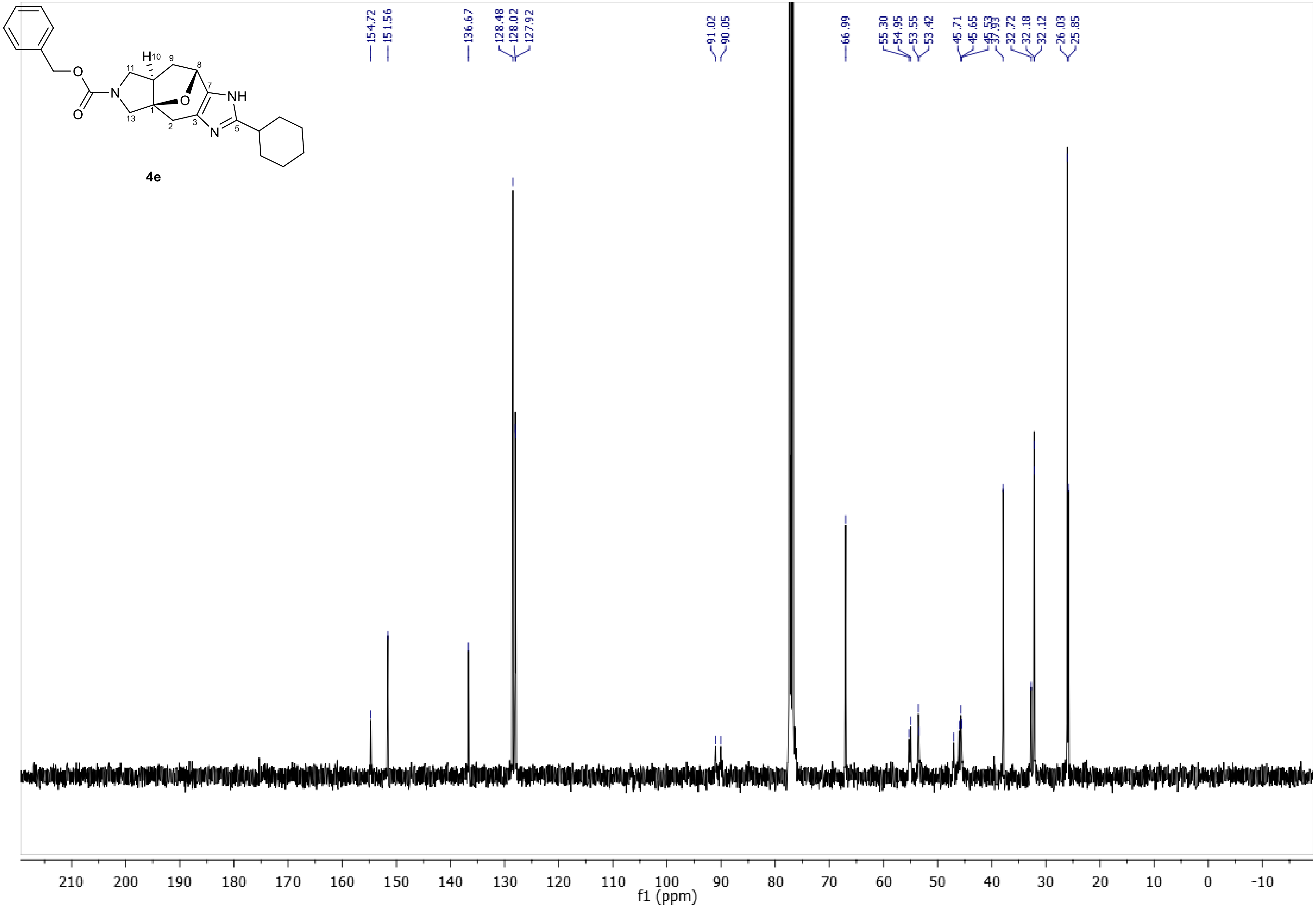


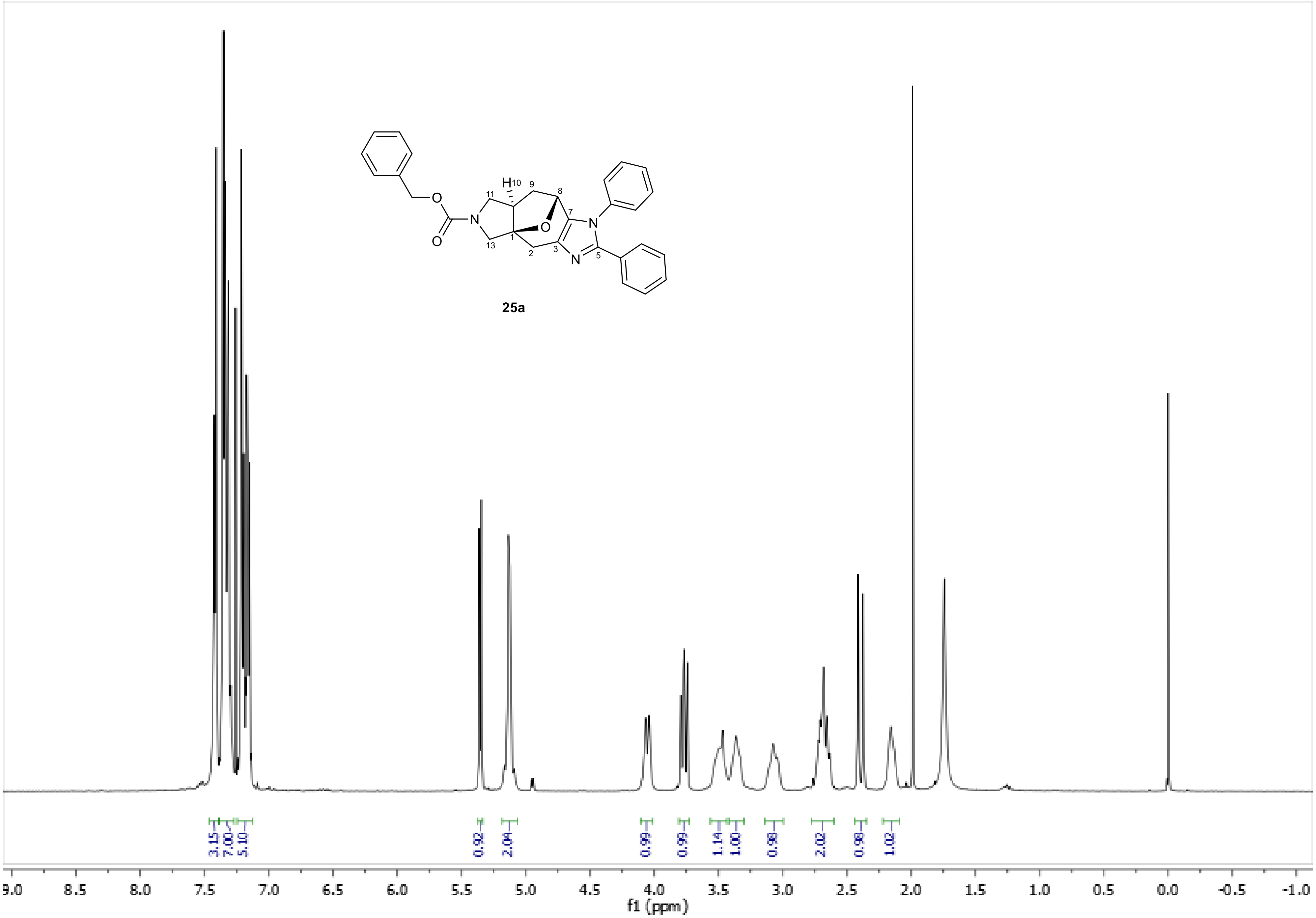
4d

H
10
9
8
7
11
NH
O
N
O
O
13
1
2
3
5
N
S
1.00
1.14
6.23
3.00
1.05
1.13
1.29
0.90
0.97
1.10
2.02
0.93
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

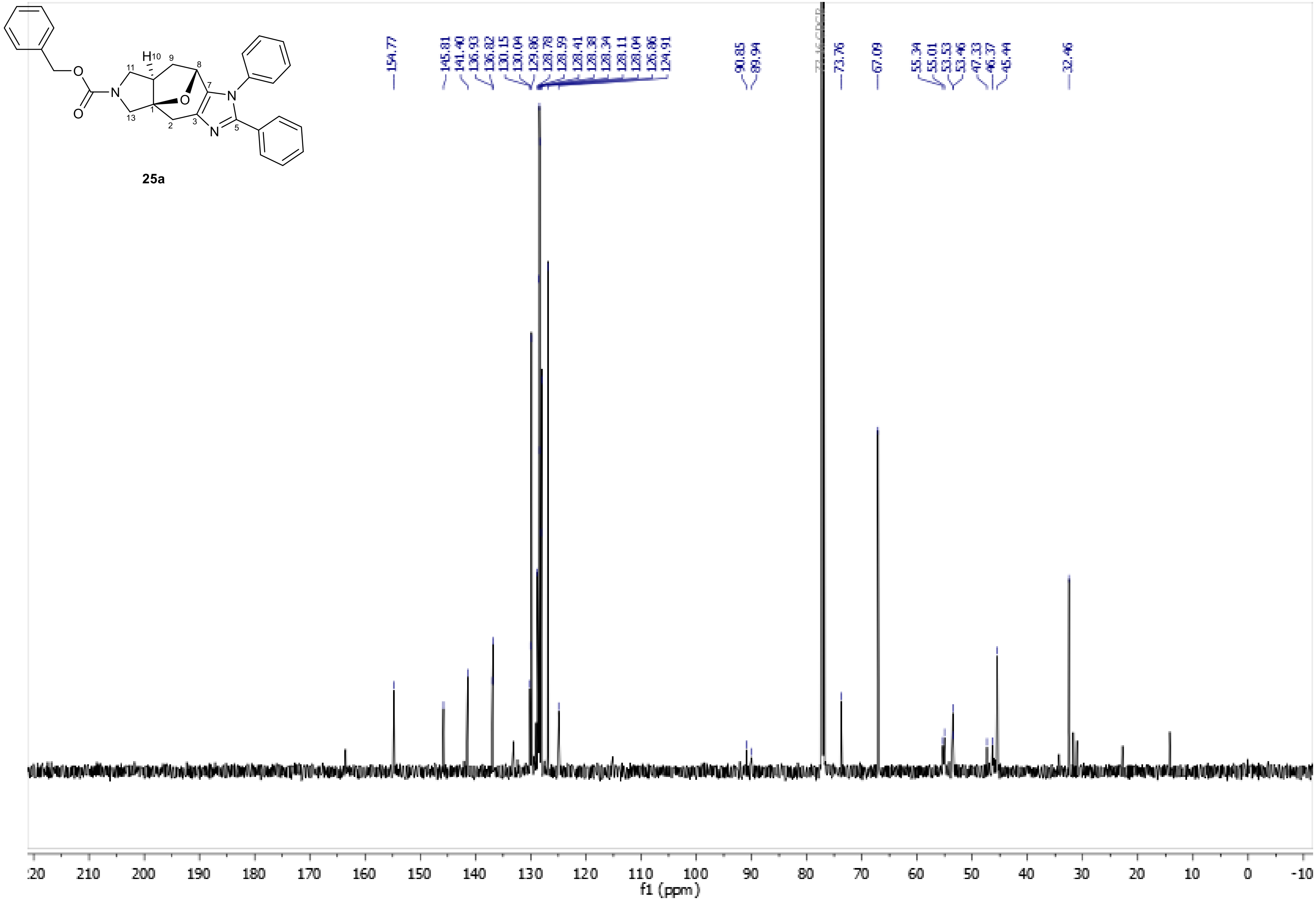

H
10
11
9
8
7
NH
O
N
O
O
1
13
2
3
N
5
4.61
2.78
0.92
0.95
1.94
1.01
1.99
1.90
3.09
3.04
5.25
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

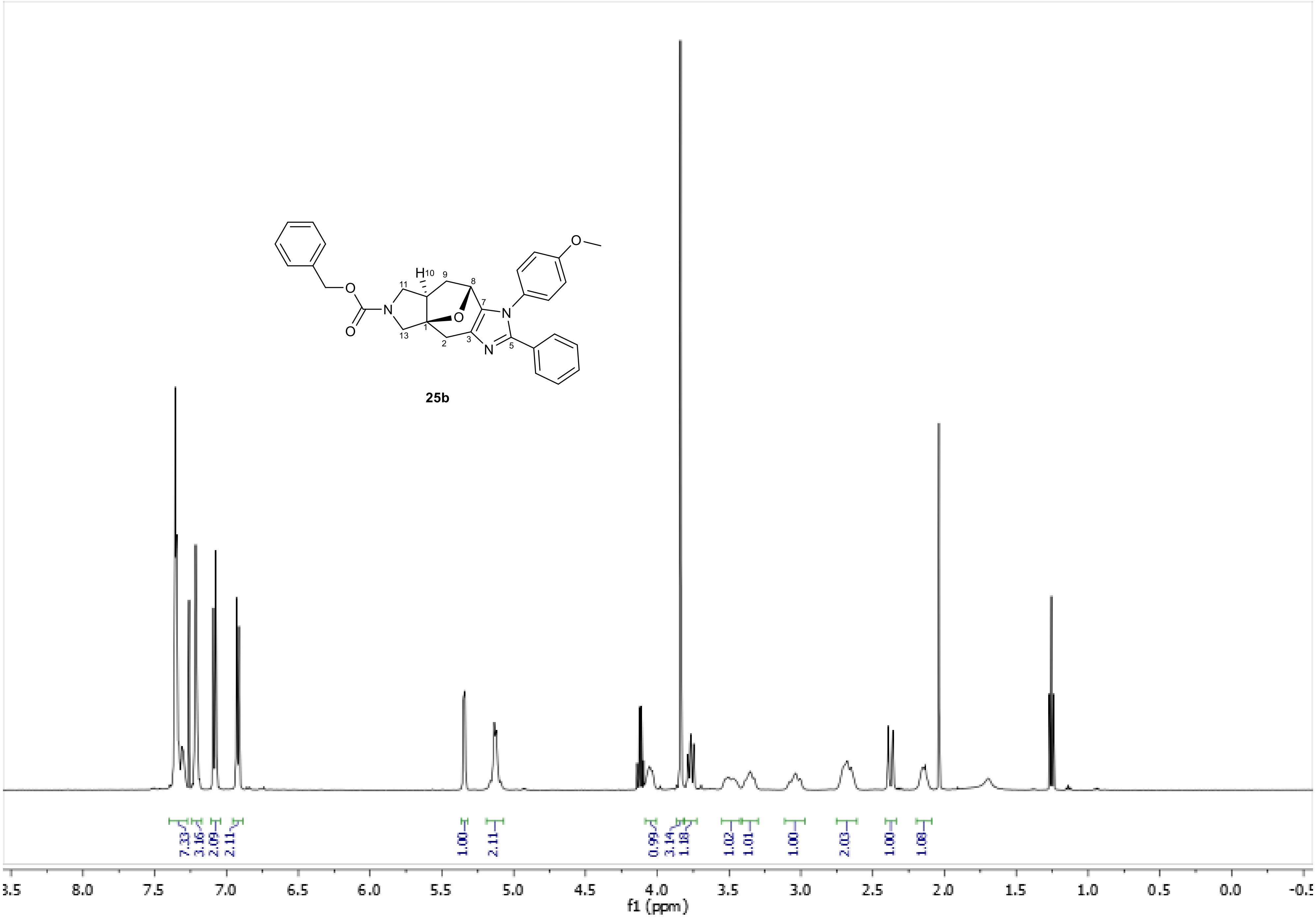
4e

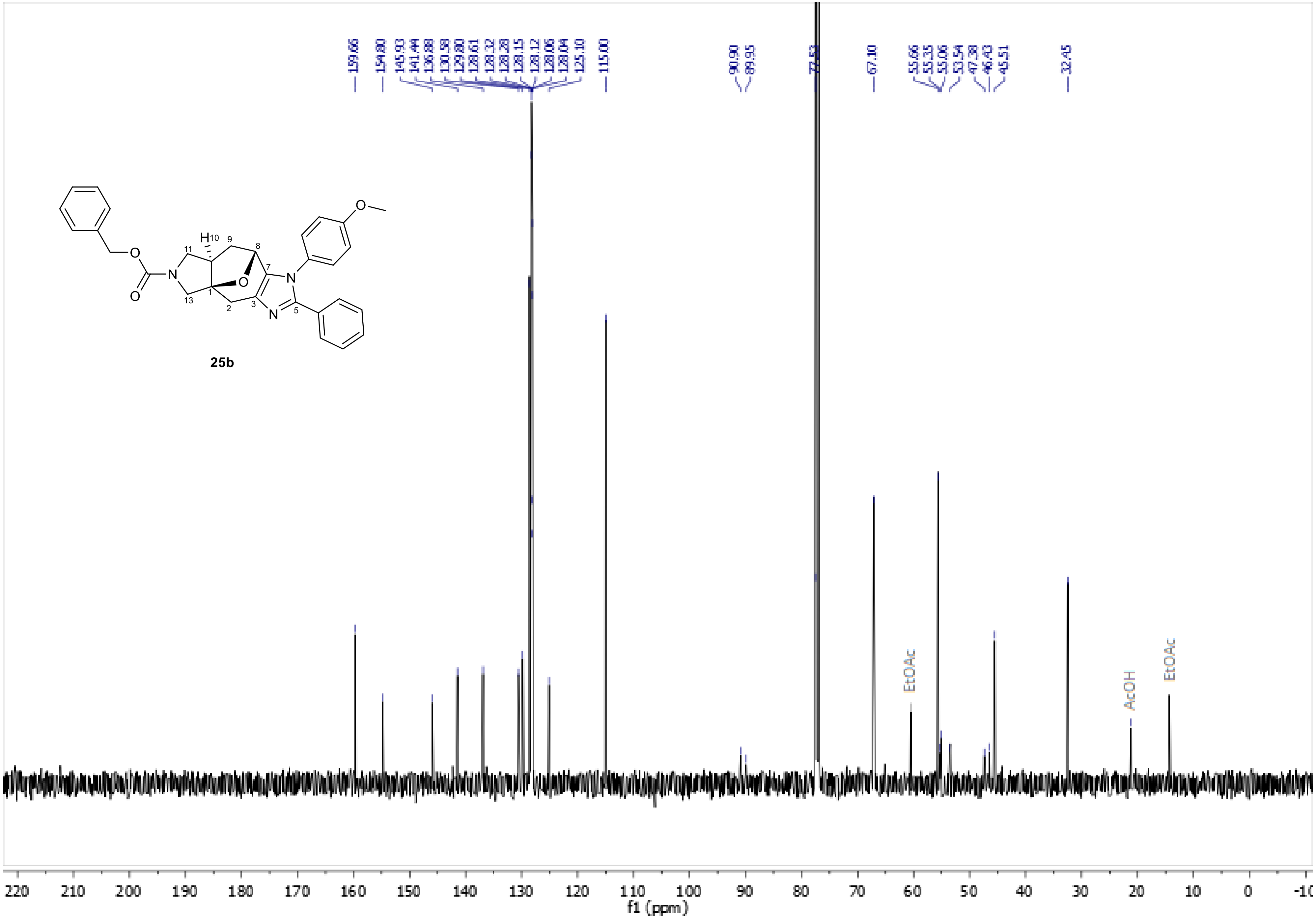

4e
H10
9
8
11
7
NH
N
O
O
O
13
1
2
3
N
5
154.72
151.56
136.67
128.48
128.02
127.92
91.02
90.05
66.99
55.30
54.95
53.55
53.42
45.71
45.65
45.53
37.93
32.72
32.18
32.12
26.03
25.85
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



H
10
9
8
7
11
N
O
O
O
N
N
1
13
2
3
5
25a
3.15
7.00
5.10
0.92
2.04
0.99
0.99
1.14
1.00
0.98
2.02
0.98
1.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

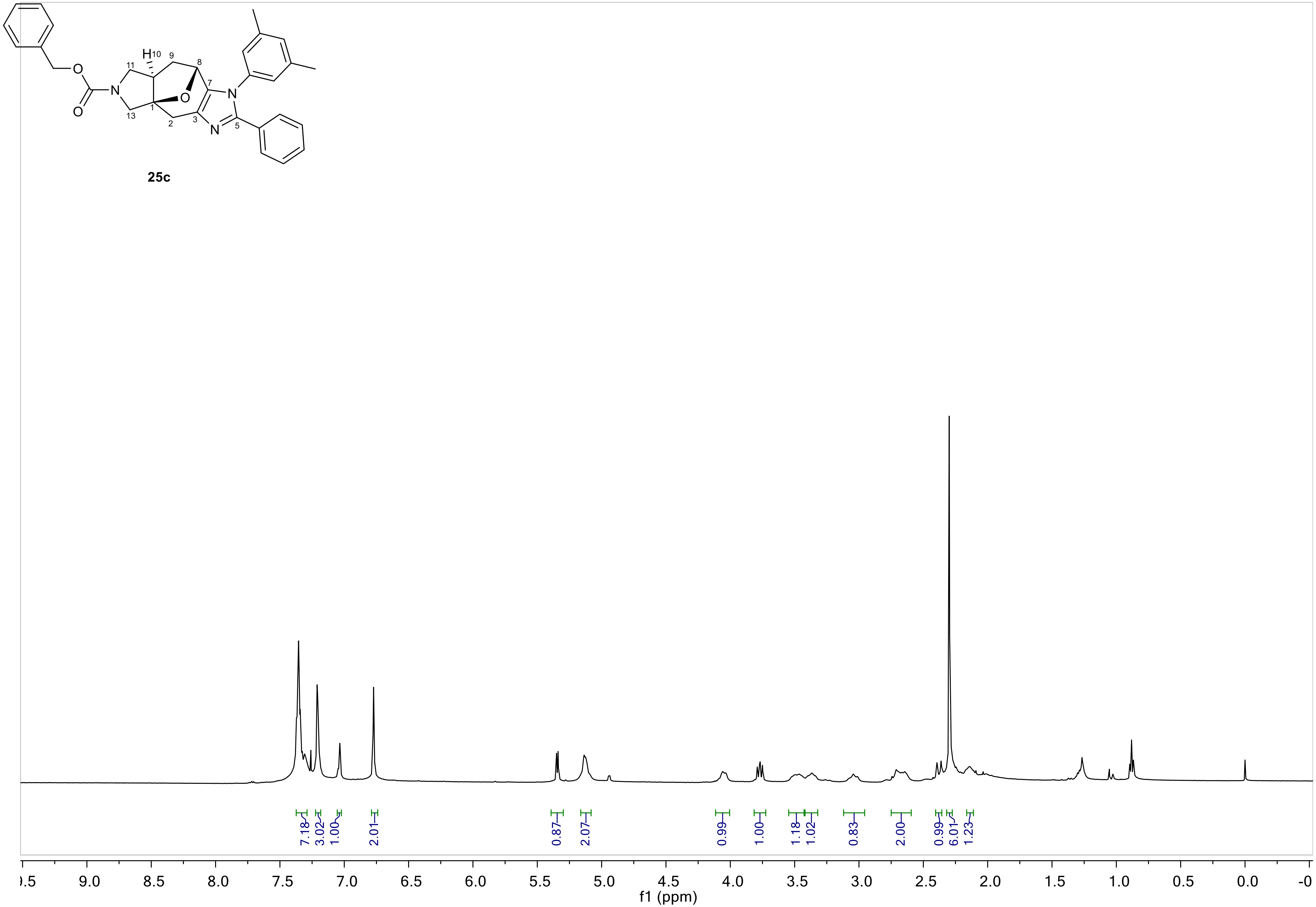

25a
O
N
O
H10
9
8
11
7
N
1
O
13
2
3
N
5
154.77
145.81
141.40
136.93
136.82
130.15
130.04
129.86
128.78
128.59
128.41
128.38
128.34
128.11
128.04
126.86
124.91
90.85
89.94
77.16 CDCl3
73.76
67.09
55.34
55.01
53.53
53.46
47.33
46.37
45.44
32.46
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

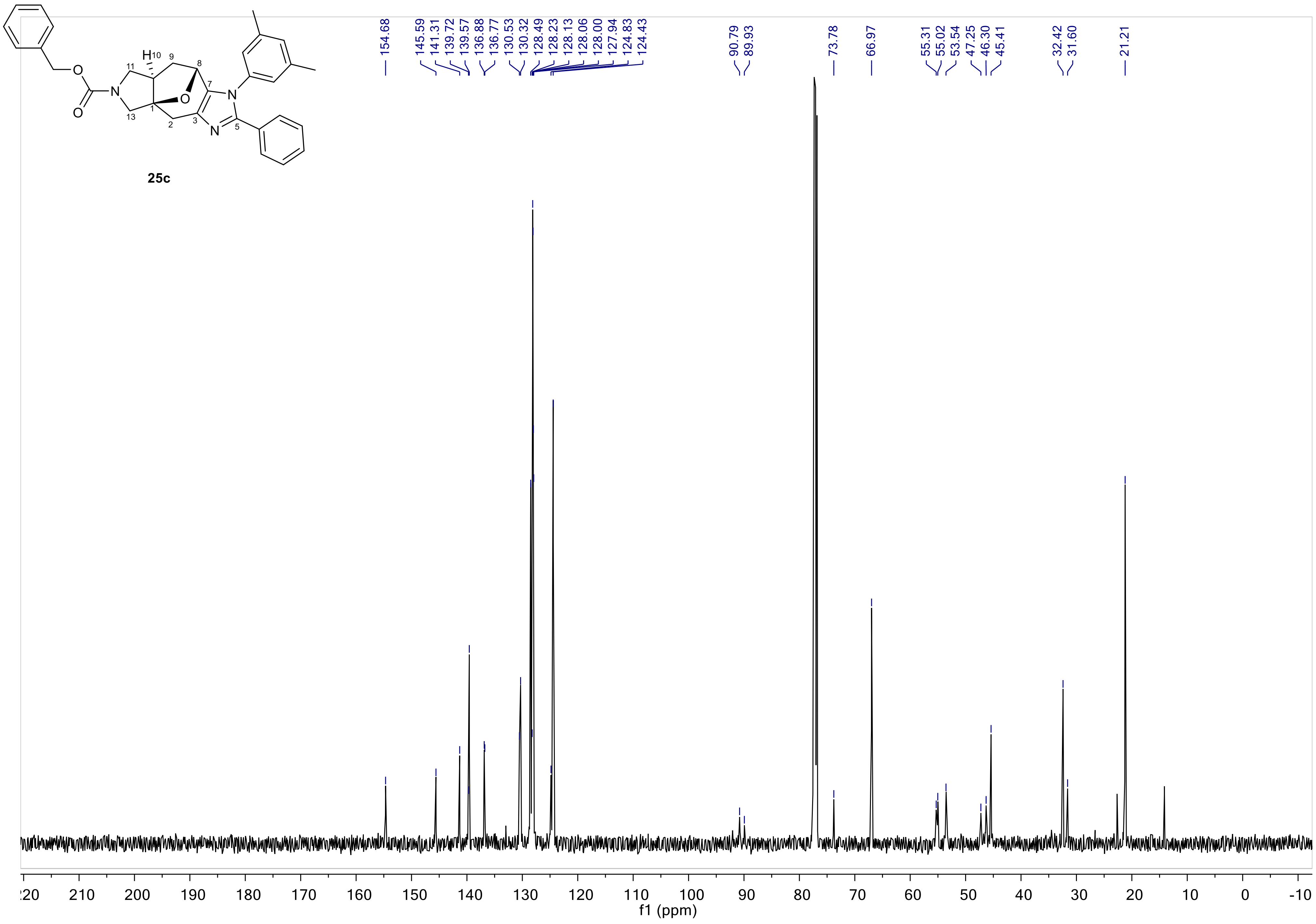

25b
H
10
9
8
11
7
N
O
N
O
1
O
13
2
3
5
N
O
O
7.33
3.16
2.09
2.11
1.00
2.11
0.99
3.14
1.18
1.02
1.01
1.00
2.03
1.00
1.08
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



25b

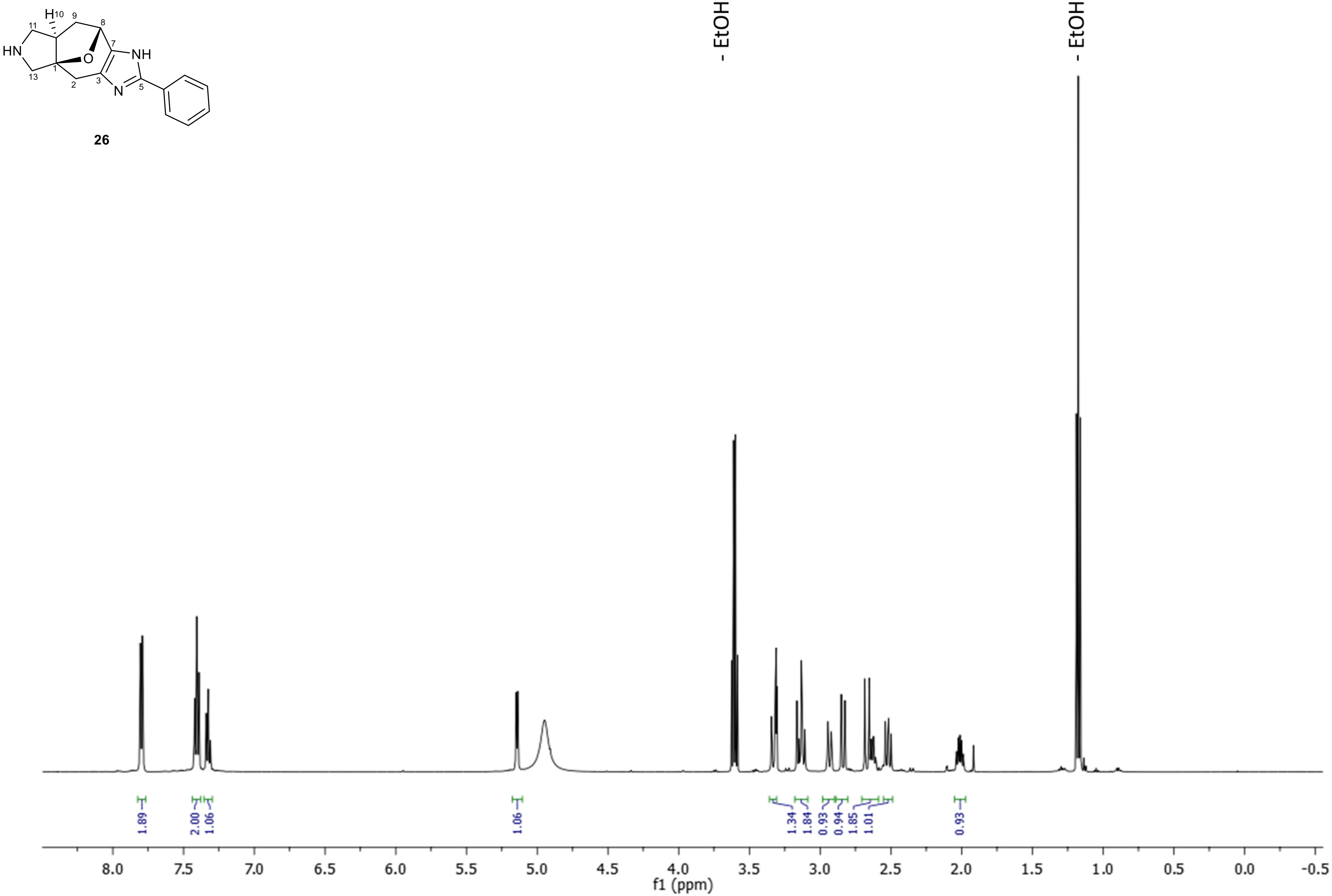
159.66
154.80
145.93
141.44
136.88
130.58
129.80
128.61
128.32
128.28
128.15
128.12
128.06
128.04
125.10
115.00
90.90
89.95
77.53
67.10
55.66
55.35
55.06
53.54
47.38
46.43
45.51
32.45
EtOAc
AcOH
EtOAc
H
10
9
8
7
11
O
N
O
N
O
13
1
2
3
N
5
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


H
10
9
8
11
7
N
N
O
O
O
13
1
2
3
N
5
25c
7.18
3.02
1.00
2.01
0.87
2.07
0.99
1.00
1.18
1.02
0.83
2.00
0.99
6.01
1.23
.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)



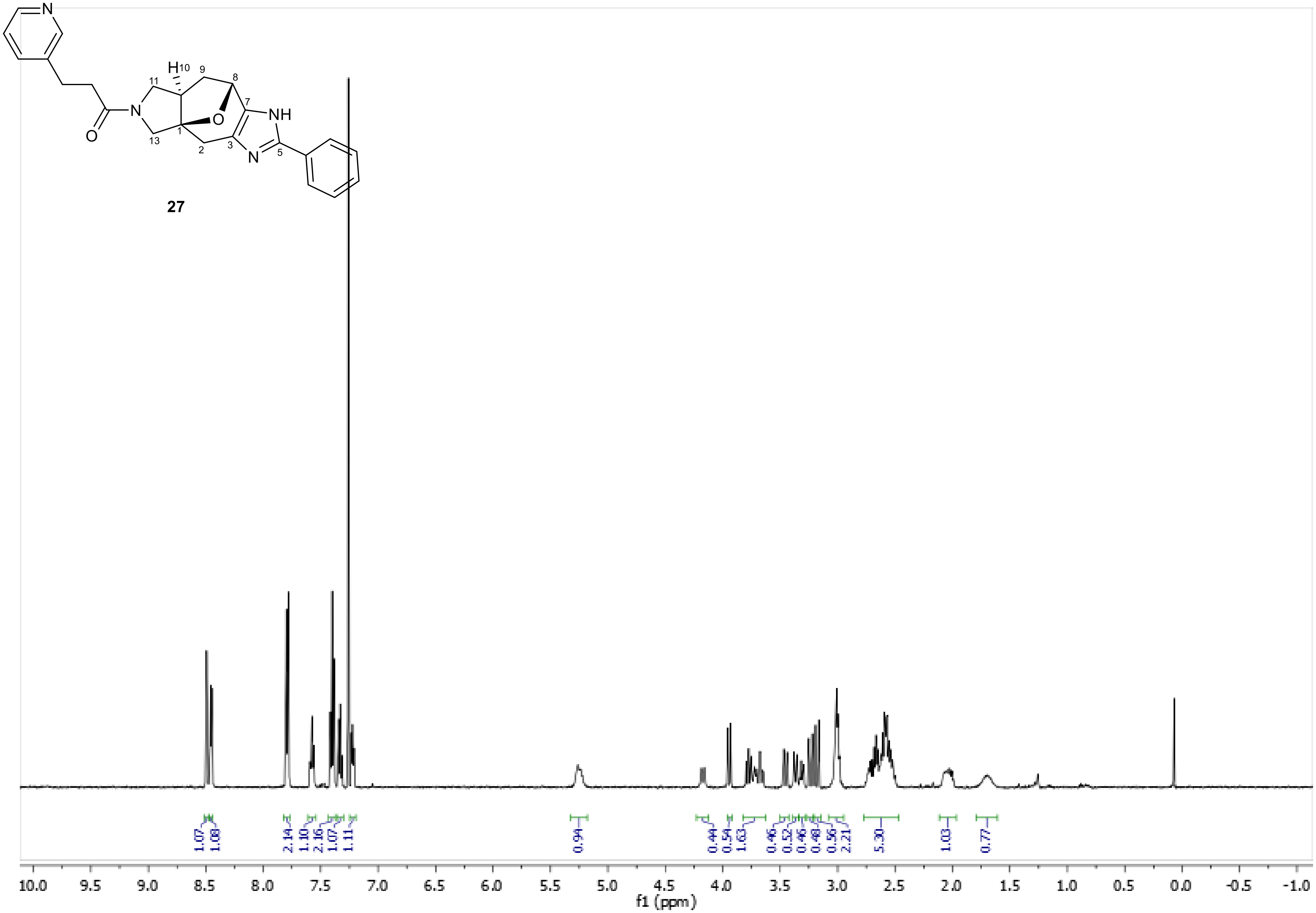
25c

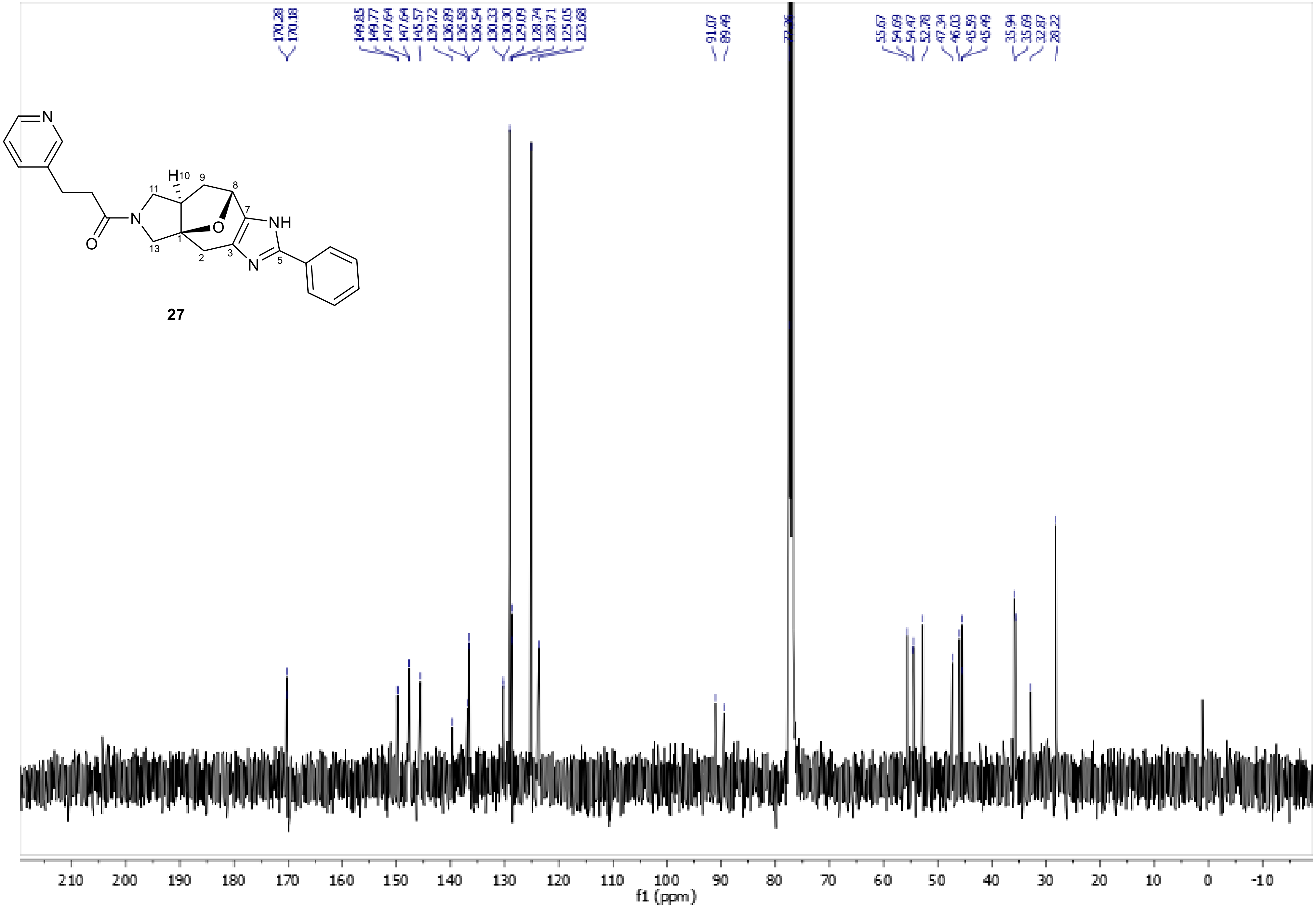
H
1
2
3
5
7
8
9
10
11
13
O
N
154.68
145.59
141.31
139.72
139.57
136.88
136.77
130.53
130.32
128.49
128.23
128.13
128.06
128.00
127.94
124.83
124.43
90.79
89.93
73.78
66.97
55.31
55.02
53.54
47.25
46.30
45.41
32.42
31.60
21.21
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



26

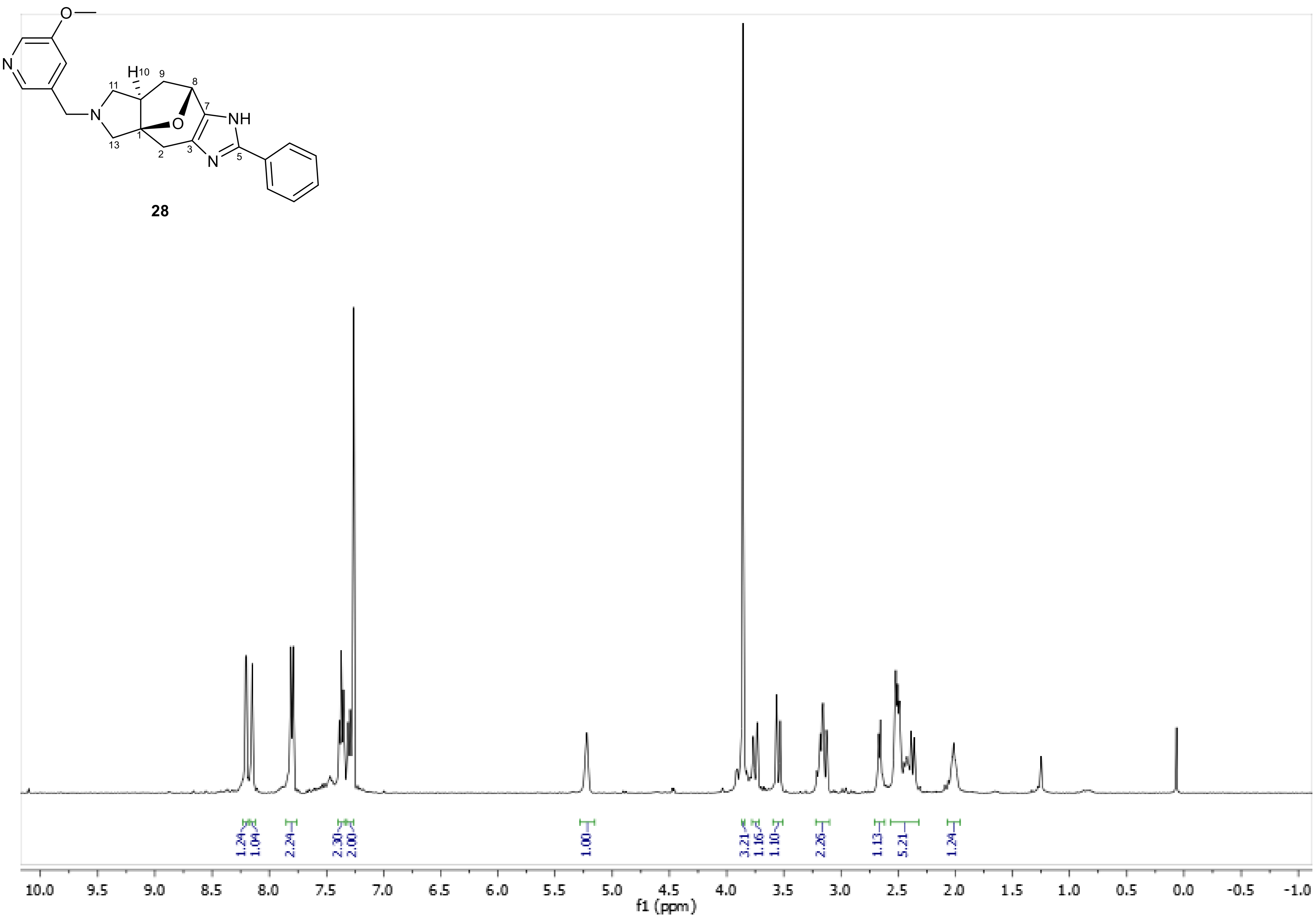
H
10
9
8
11
7
HN
O
NH
1
13
3
2
N
5
- EtOH
- EtOH
1.89
2.00
1.06
1.06
1.34
1.84
0.93
0.94
1.85
1.01
0.93
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


N
H
10
9
8
11
7
NH
N
O
O
1
13
2
3
N
5
27
1.07
1.08
2.14
1.10
2.16
1.07
1.11
0.94
0.44
0.54
1.63
0.46
0.52
0.46
0.48
0.56
2.21
5.30
1.03
0.77
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

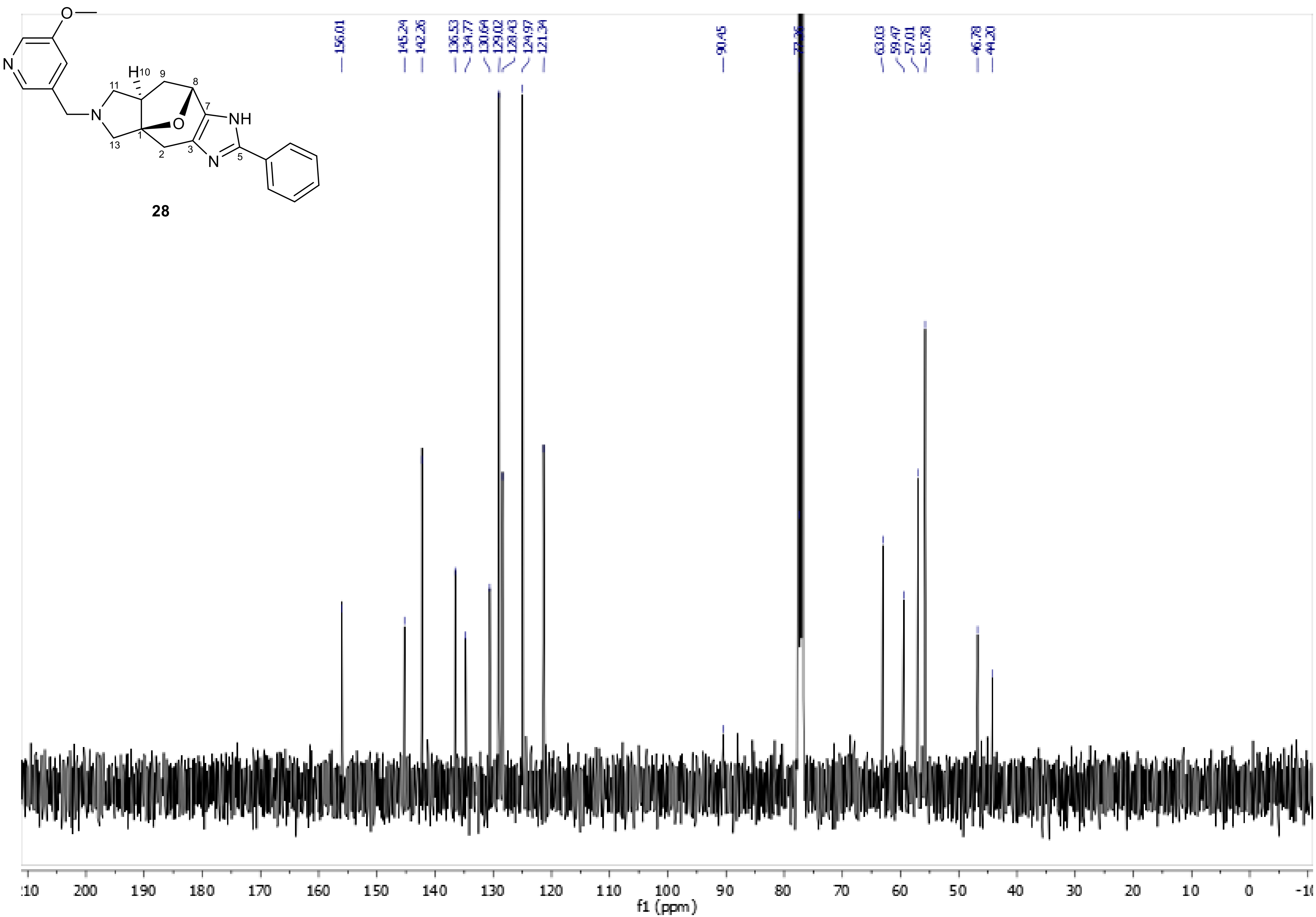

N
H
10
9
8
11
7
NH
N
O
O
1
13
2
3
5
N

27

170.28
170.18
149.85
149.77
147.64
147.64
145.57
139.72
136.89
136.58
136.54
130.33
130.30
129.09
128.74
128.71
125.05
123.88
91.07
89.49
77.36
55.67
54.69
54.47
52.78
47.34
46.03
45.59
45.49
35.94
35.69
32.87
28.22
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

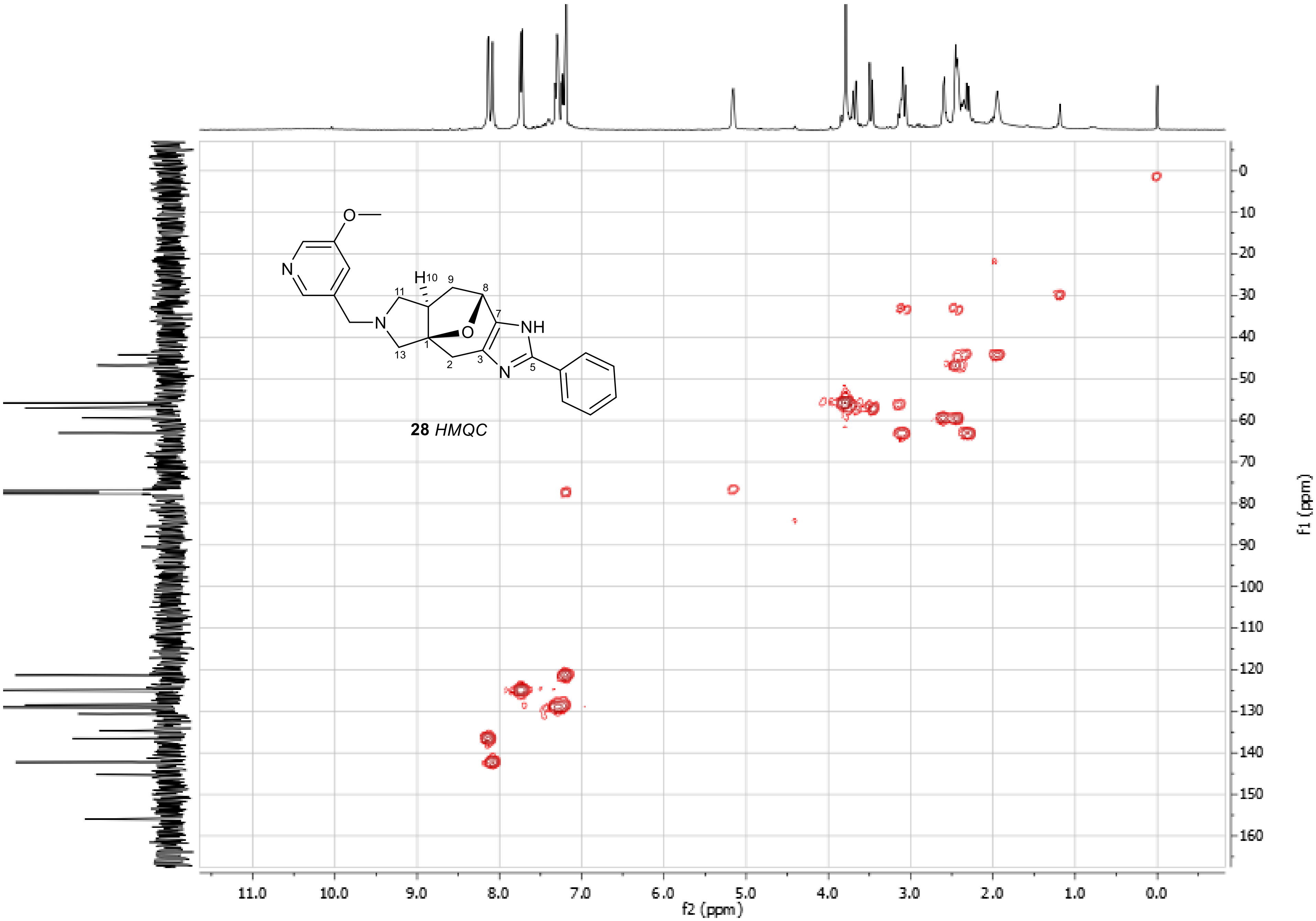

O
N
H10
9
8
11
N
7
NH
O
1
13
2
3
N
5
1.24
1.04
2.24
2.30
2.00
1.00
3.21
1.16
1.10
2.26
1.13
5.21
1.24
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

28

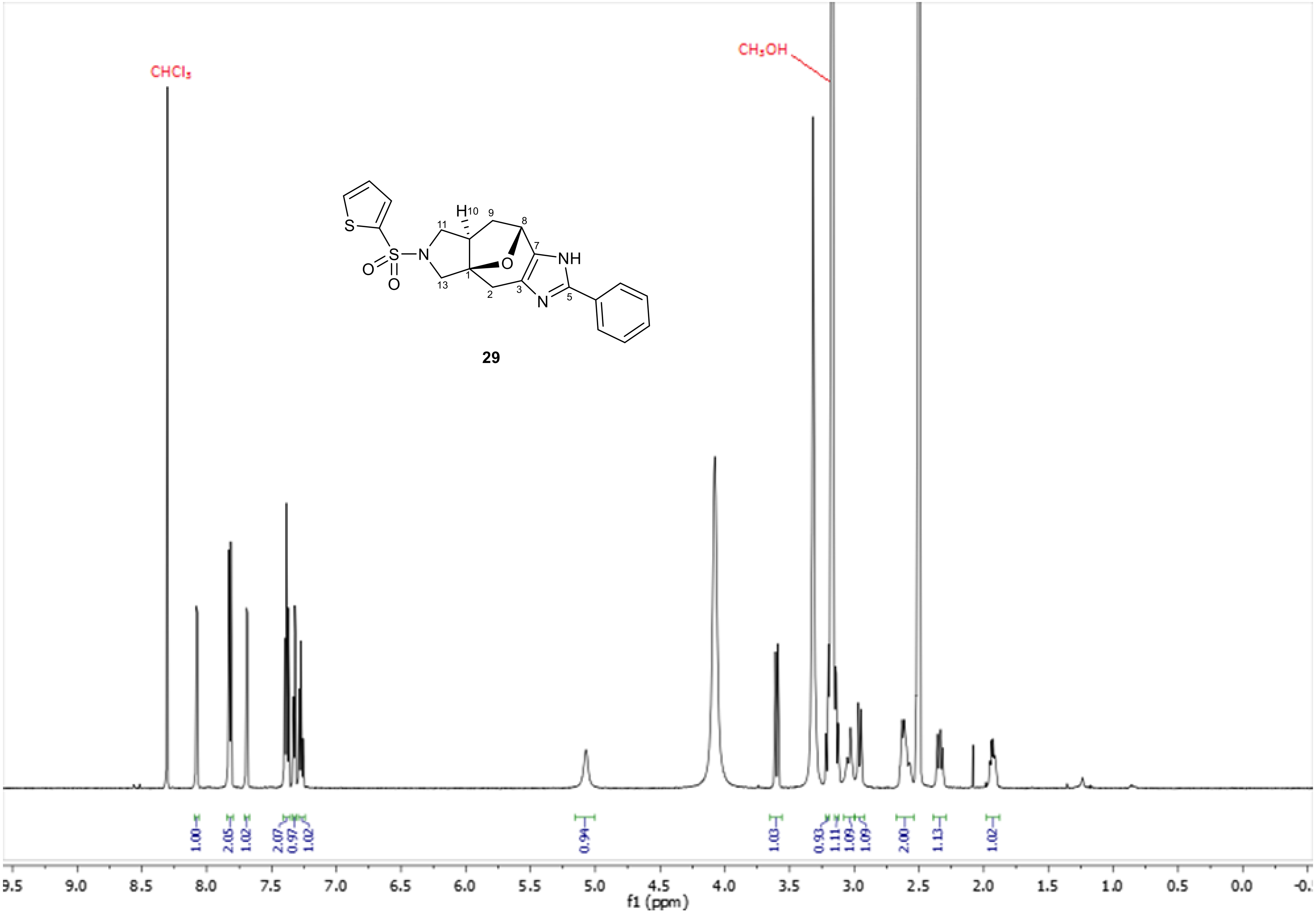


28

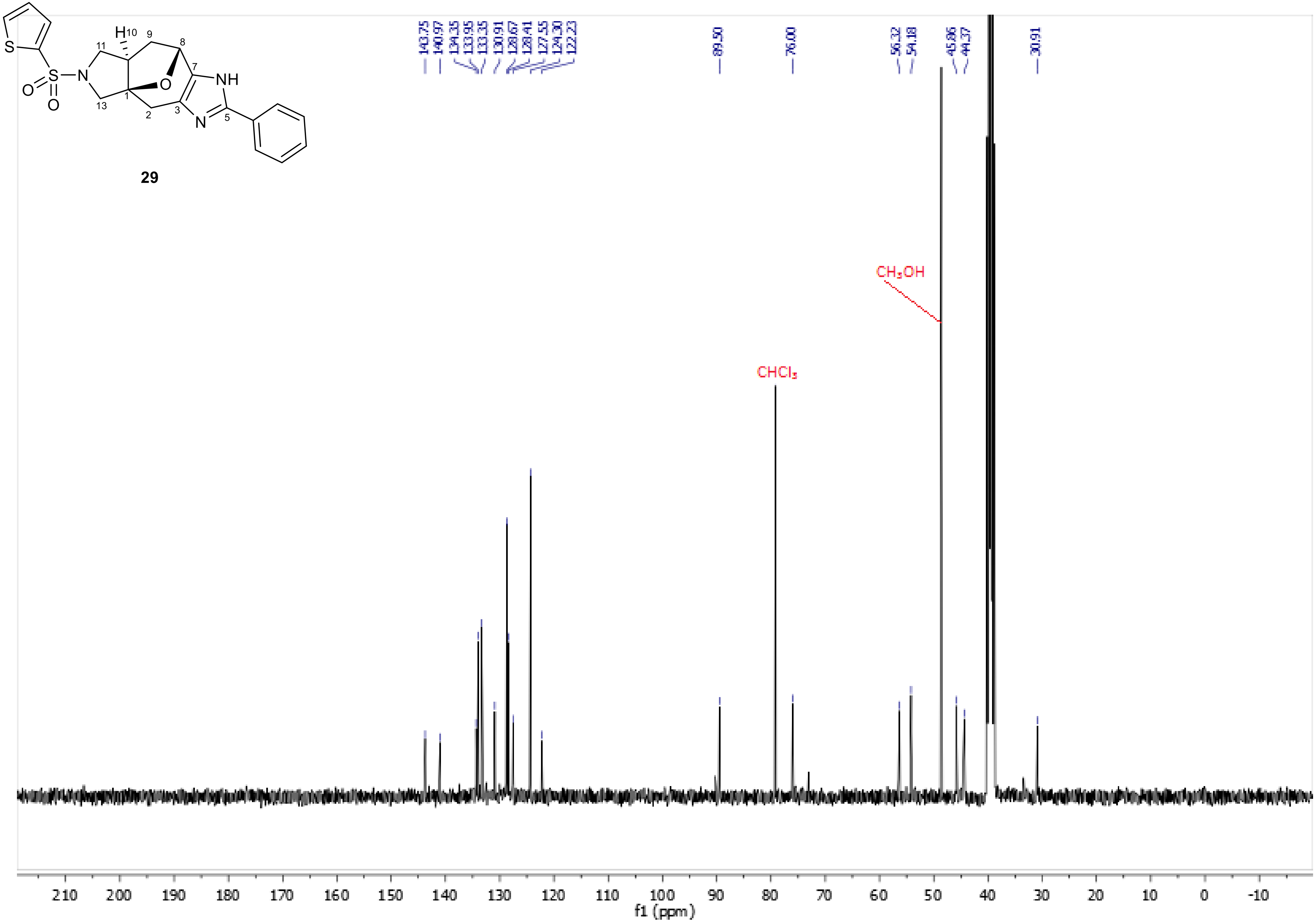
N
O
H
10
9
8
11
N
O
7
NH
1
13
2
3
N
5
156.01
145.24
142.26
136.53
134.77
130.64
129.02
128.43
124.97
121.34
90.45
77.36
63.03
59.47
57.01
55.78
46.78
44.20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

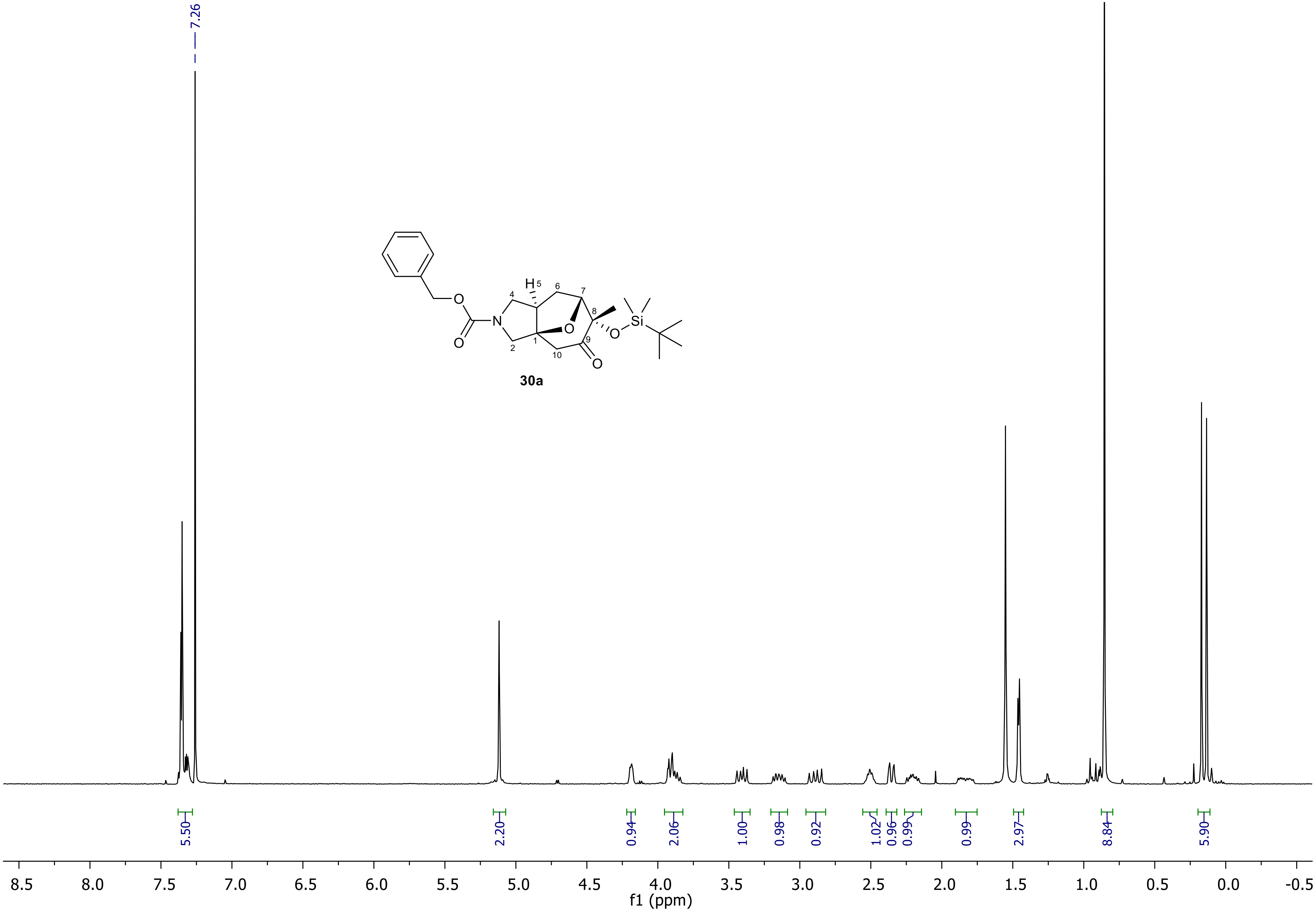

O
N
H10
9
8
11
7
NH
N
O
13
1
2
3
5
N
f2 (ppm)
f1 (ppm)
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160

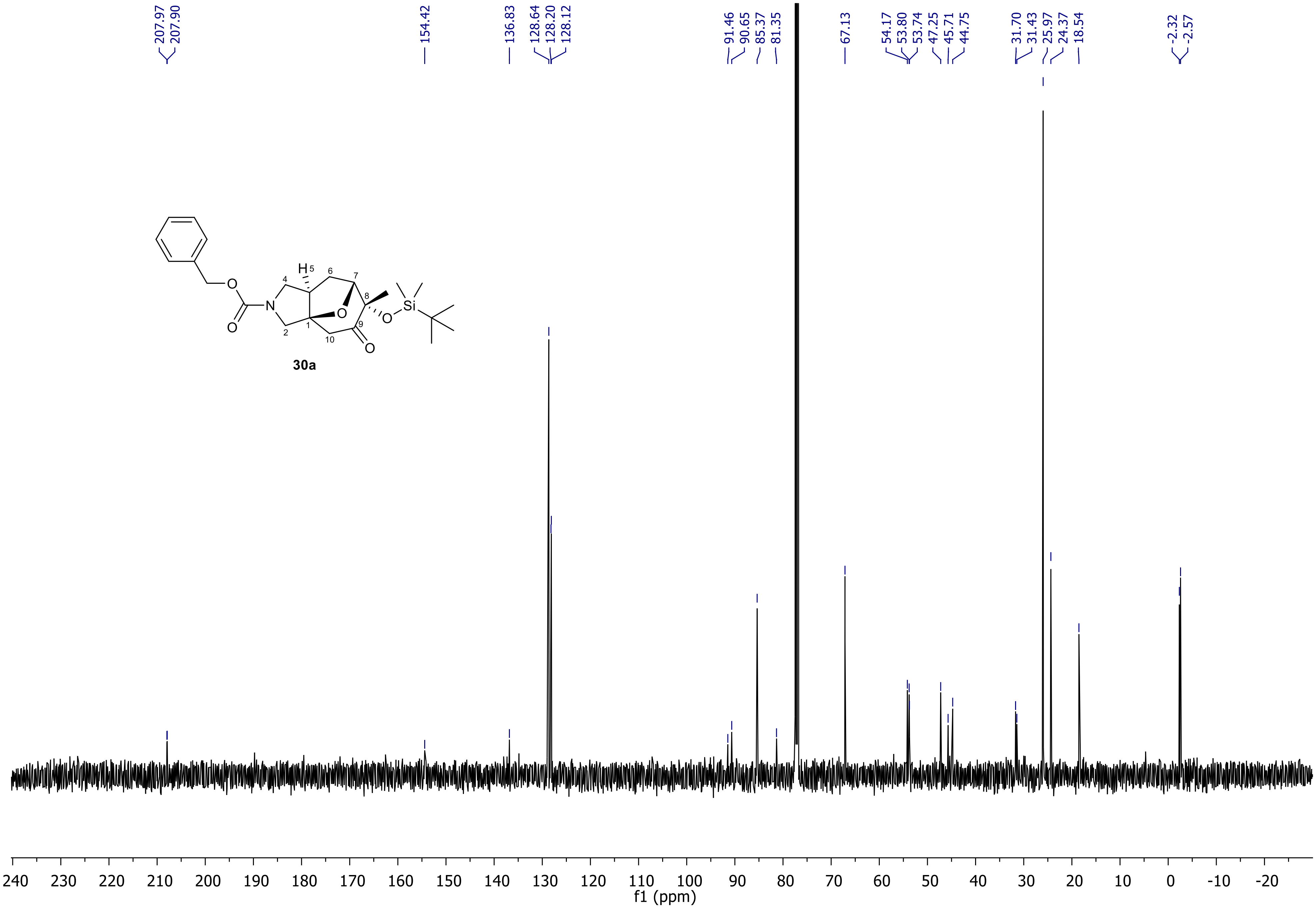
28 *HMQC*

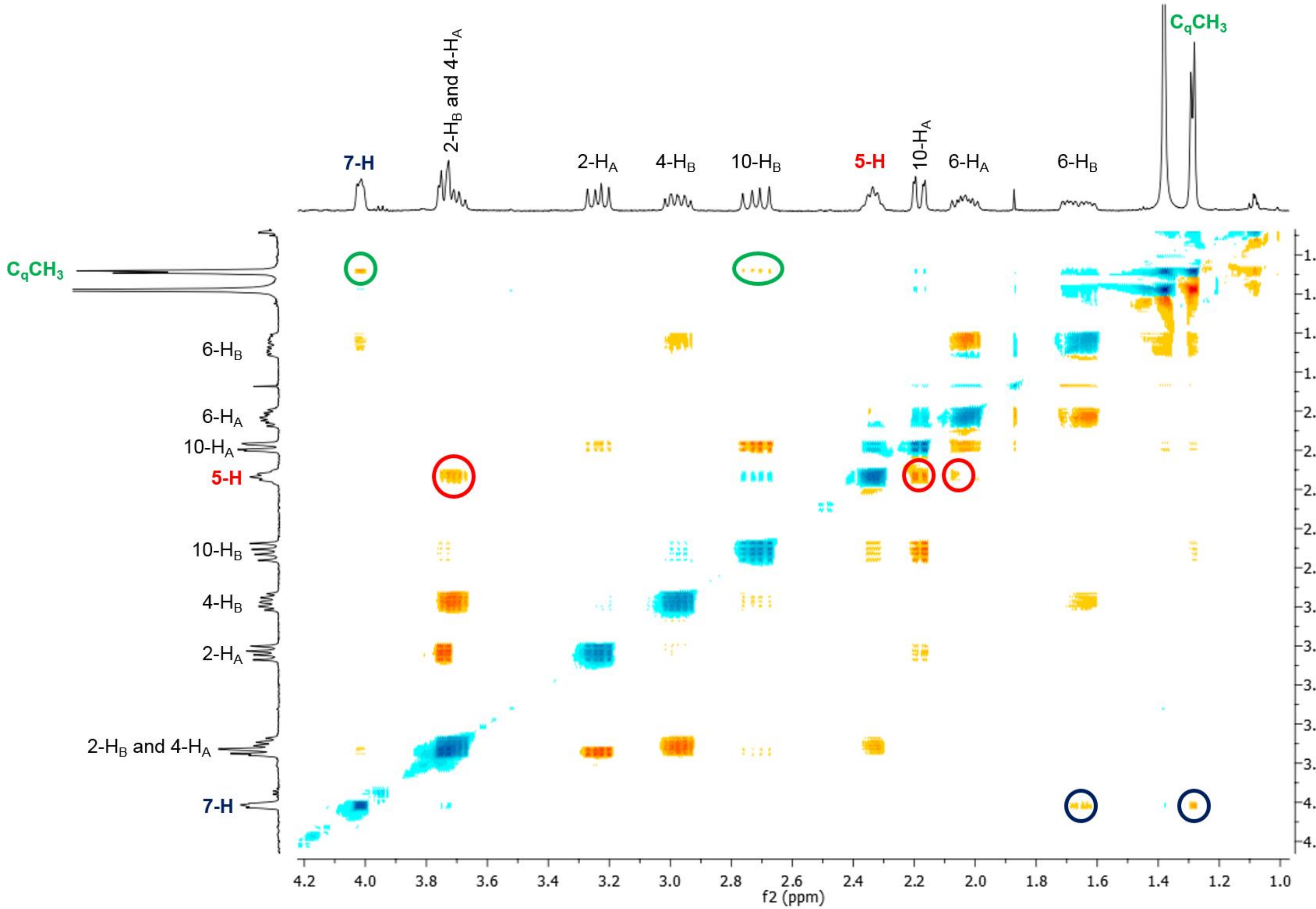

CHCl₃
CH₃OH
H
10
9
8
11
7
NH
S
O
S
N
O
O
13
1
2
3
N
5
1.00
2.05
1.02
2.07
0.97
1.02
0.94
1.03
0.93
1.11
1.09
1.09
2.00
1.13
1.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.
f1 (ppm)

29


S
O
O
N
H10
9
8
11
7
NH
O
1
13
2
3
N
5
29
143.75
140.97
134.15
133.95
133.35
130.91
128.67
128.41
127.55
124.30
122.23
89.50
76.00
56.32
54.18
45.86
44.37
30.91
CH₃OH
CHCl₃
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.26
30a
H
1
2
4
5
6
7
8
9
10
N
O
Si
5.50
2.20
0.94
2.06
1.00
0.98
0.92
1.02
0.96
0.99
0.99
2.97
8.84
5.90
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


207.97
207.90
154.42
136.83
128.64
128.20
128.12
91.46
90.65
85.37
81.35
67.13
54.17
53.80
53.74
47.25
45.71
44.75
31.70
31.43
25.97
24.37
18.54
-2.32
-2.57
H
5
4
6
7
8
9
10
1
2
N
O
O
O
O
O
Si
30a
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

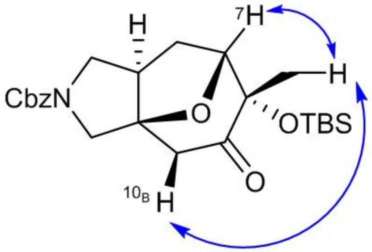


30a NOESY correlations:

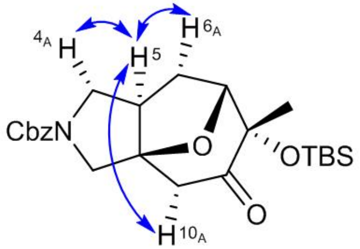
C_qCH_3: 7-H; 10-H_B

5-H: 4-H_A; 6-H_A; 10-H_A

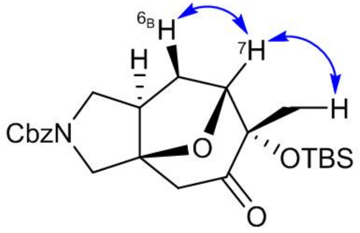
7-H: C_qCH_3; 6-H_B



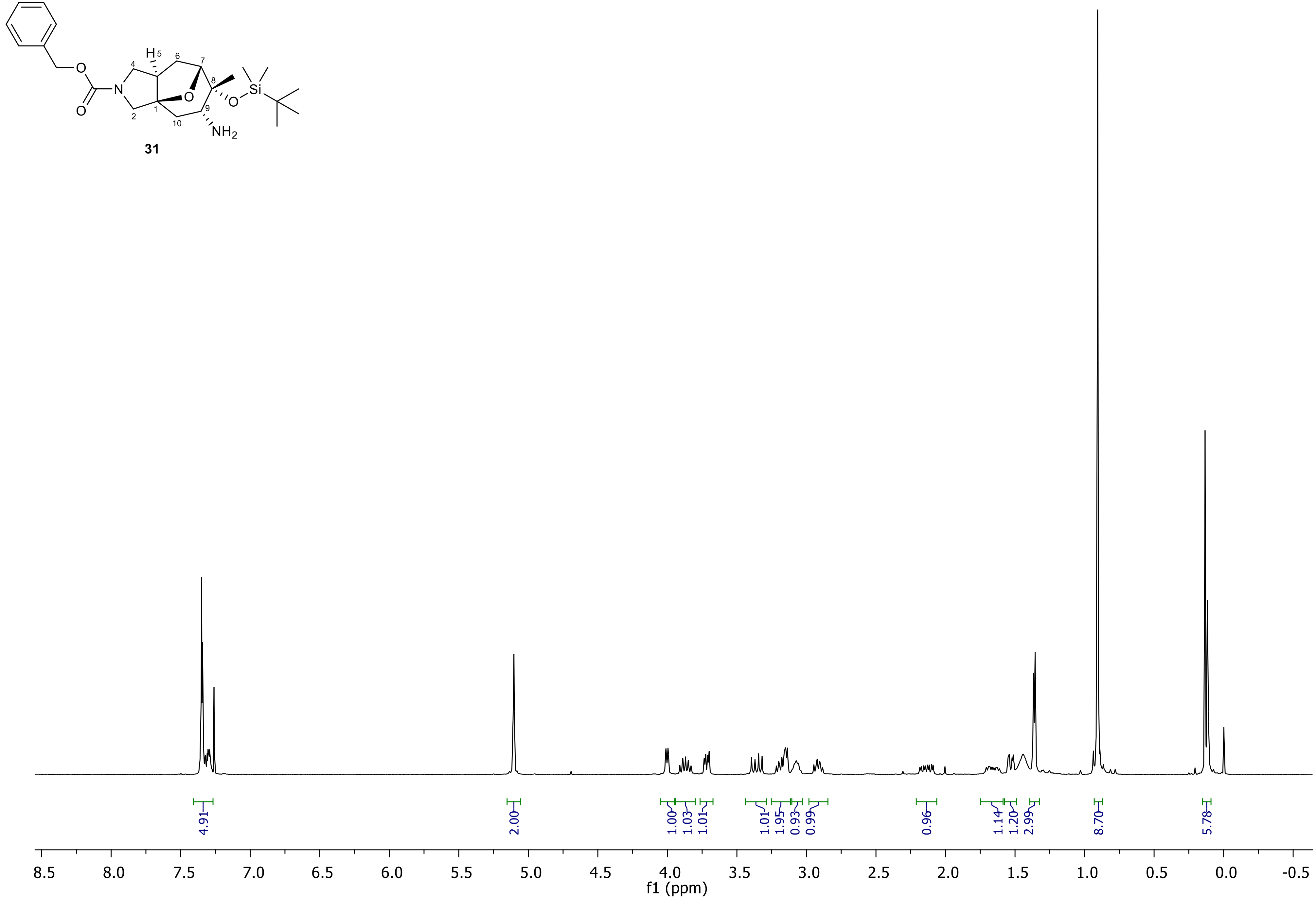
C_qCH_3

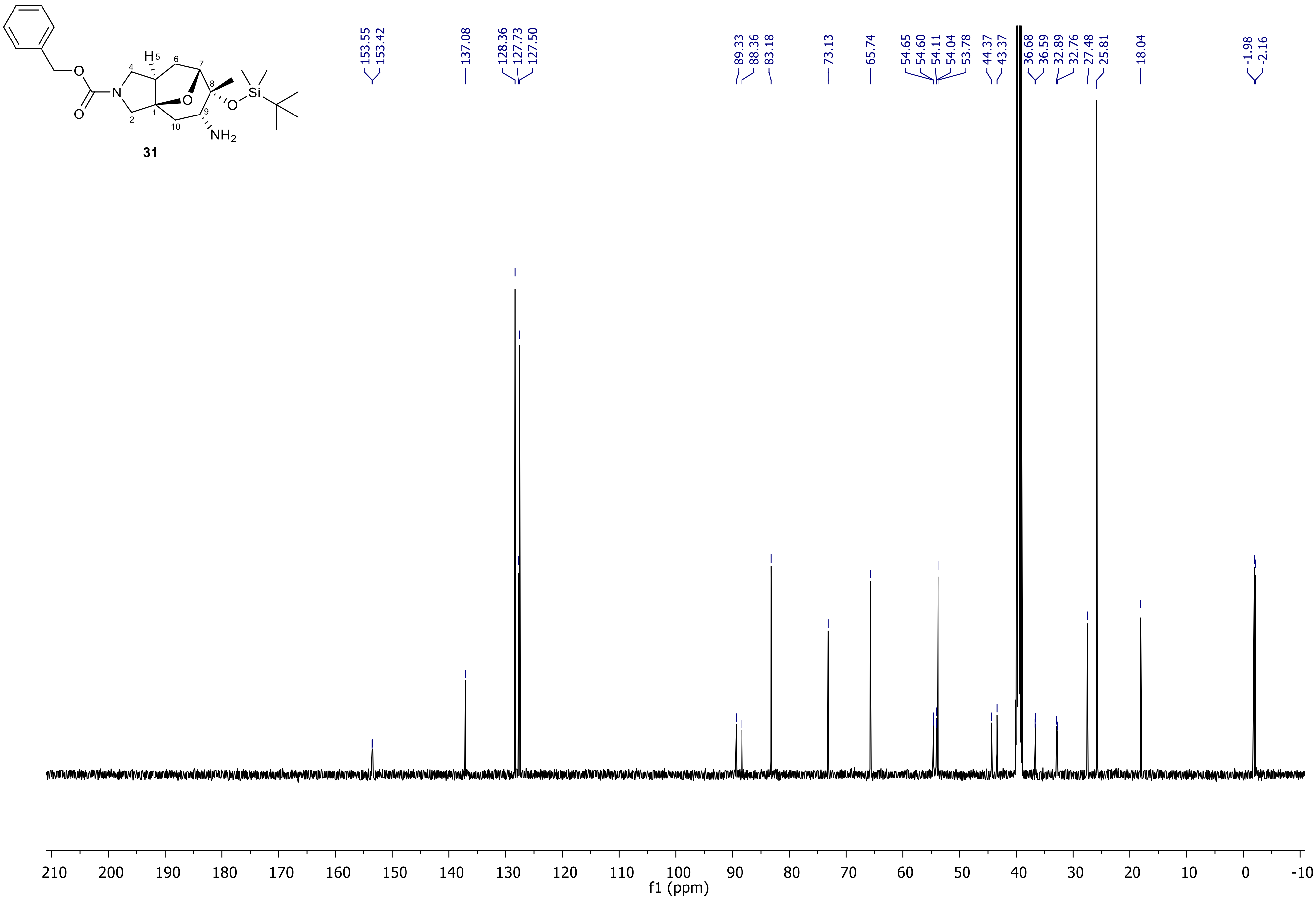


5-H



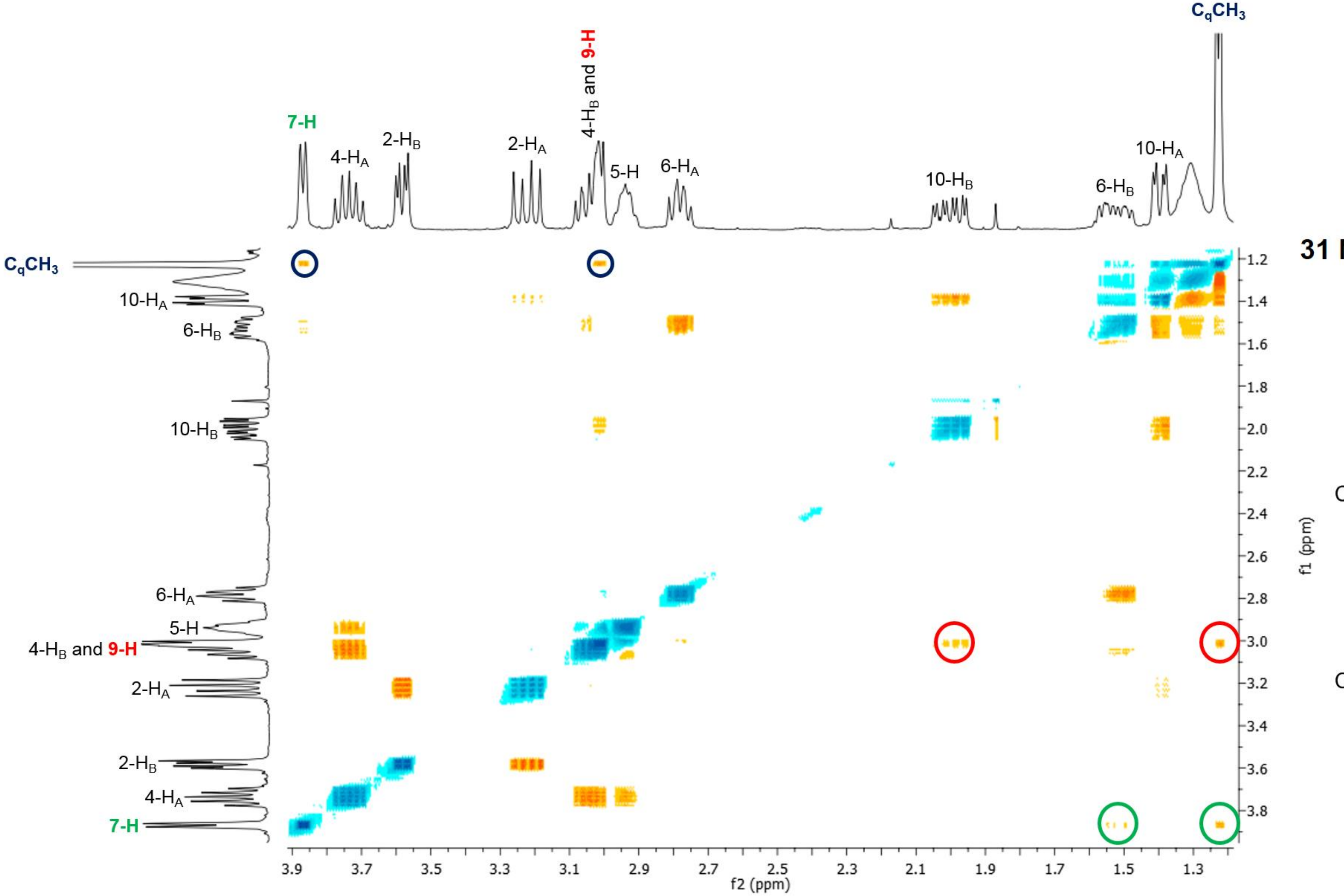
7-H


O
N
O
H 5
4
6
7
8
O
Si
O
1
2
10
9
NH$_2$
31
4.91
2.00
1.00
1.03
1.01
1.01
1.95
0.93
0.99
0.96
1.14
1.20
2.99
8.70
5.78
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



31

H 5
4
6
7
8
9
10
2
1
O
N
O
O
O
Si
NH2
153.55
153.42
137.08
128.36
127.73
127.50
89.33
88.36
83.18
73.13
65.74
54.65
54.60
54.11
54.04
53.78
44.37
43.37
36.68
36.59
32.89
32.76
27.48
25.81
18.04
-1.98
-2.16
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

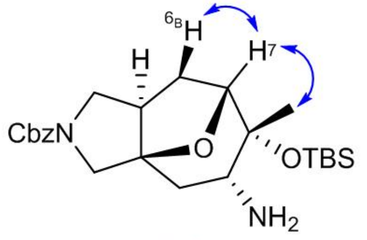


31 NOESY correlations:

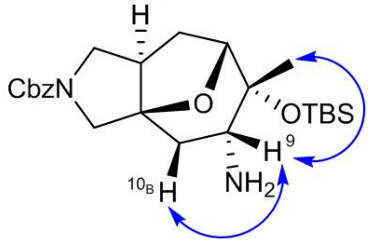
Me: 7-H; 9-H

7-H: Me; 6-H$_B$

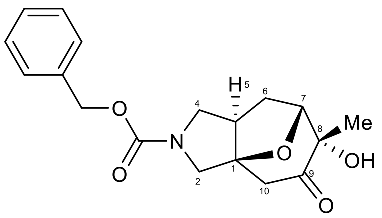
9-H: Me; 10-H$_B$



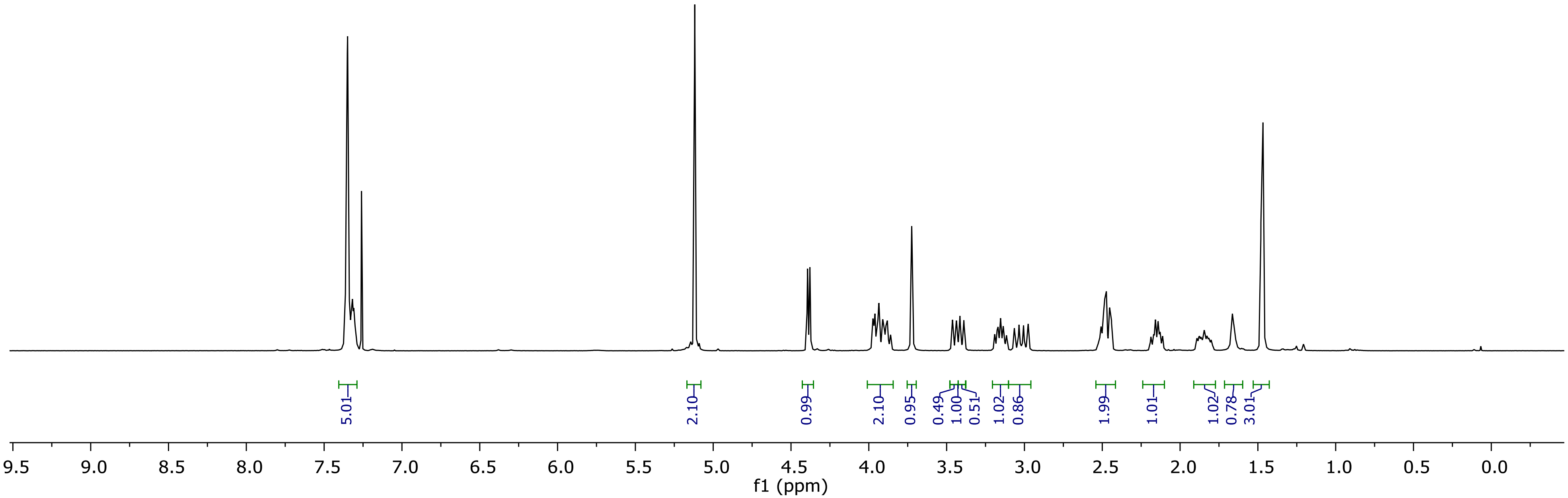
7-H

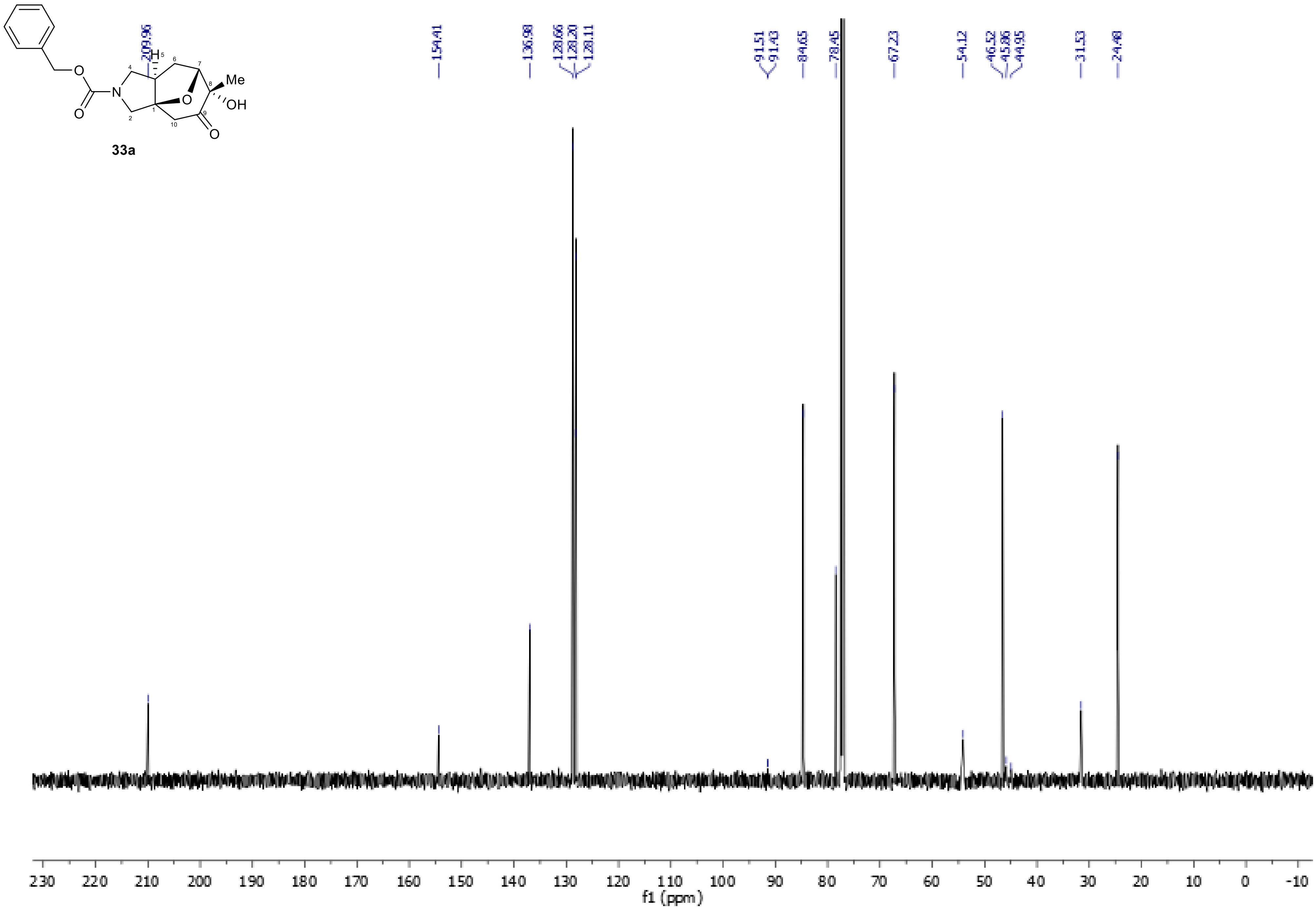


9-H

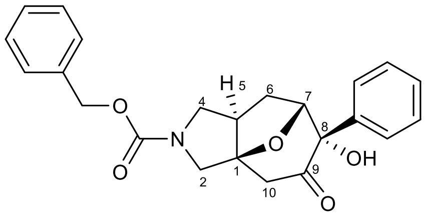

H5
4
6
7
8
Me
OH
N
O
O
O
1
2
10
9
O

33a


5.01
2.10
0.99
2.10
0.95
0.49
1.00
0.51
1.02
0.86
1.99
1.01
1.02
0.78
3.01
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

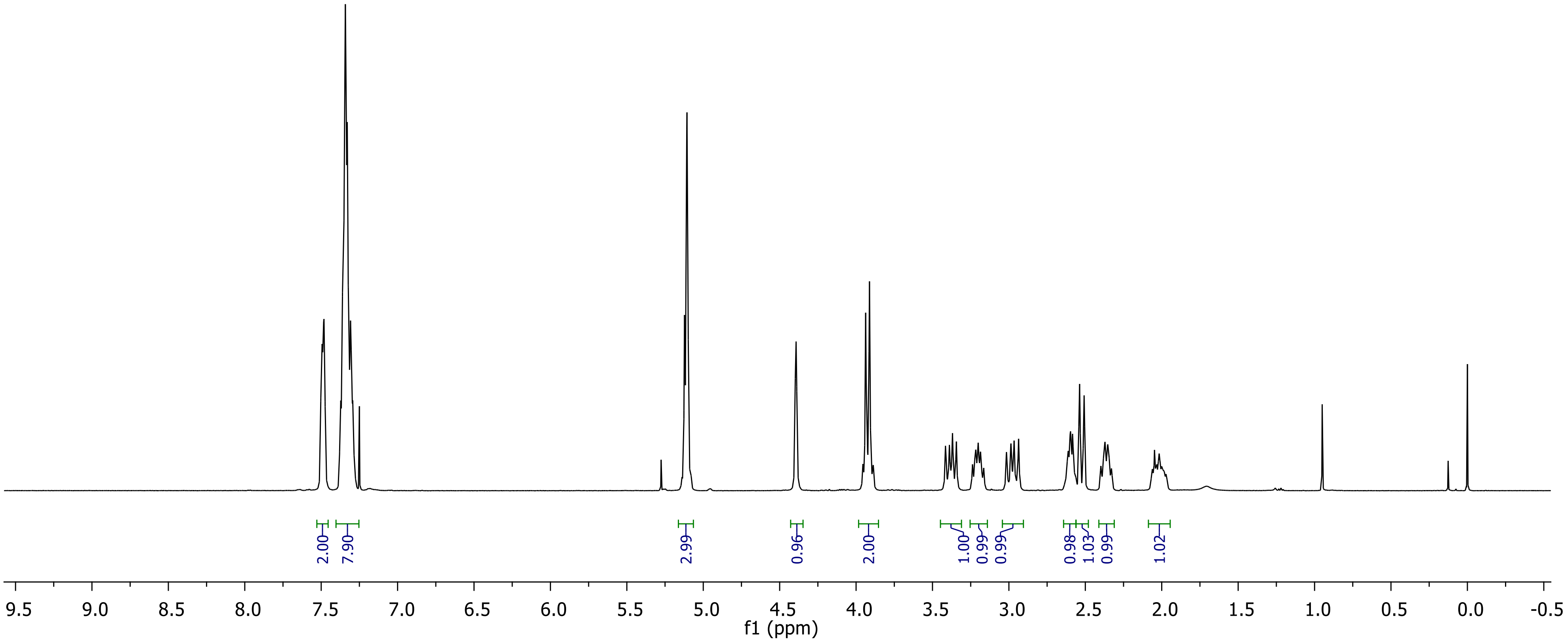

O
N
O
H
5
4
6
7
8
Me
OH
O
1
2
10
9
O
209.96
154.41
136.98
128.66
128.20
128.11
91.51
91.43
84.65
78.45
67.23
54.12
46.52
45.86
44.95
31.53
24.48
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

33a

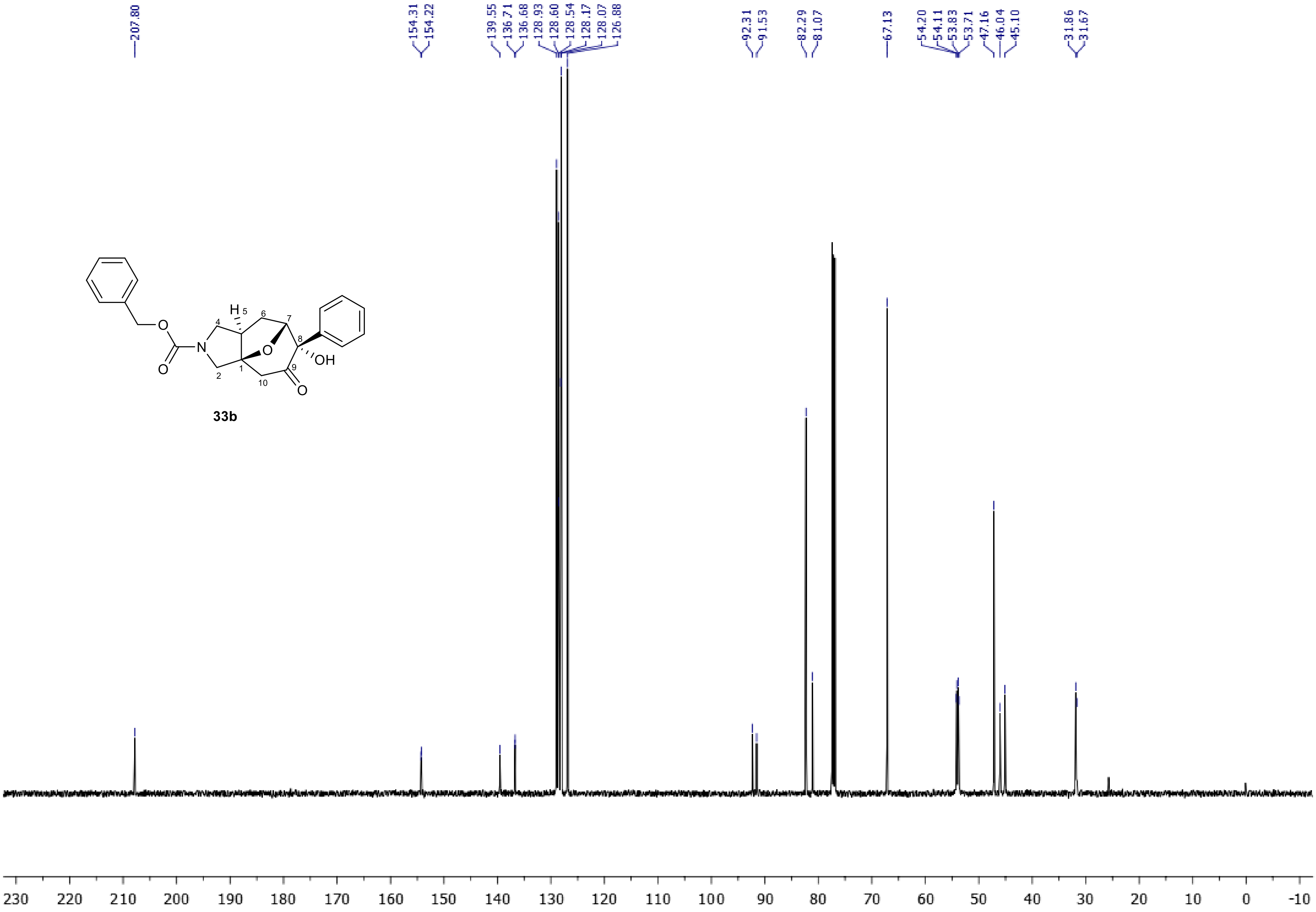


H
5
6
7
4
O
8
N
O
OH
O
1
9
2
10
O

33b

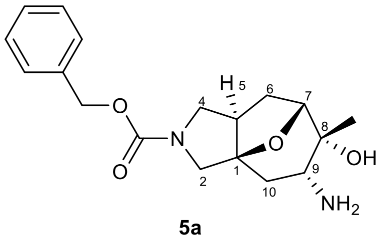


2.00
7.90
2.99
0.96
2.00
1.00
0.99
0.99
0.98
1.03
0.99
1.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

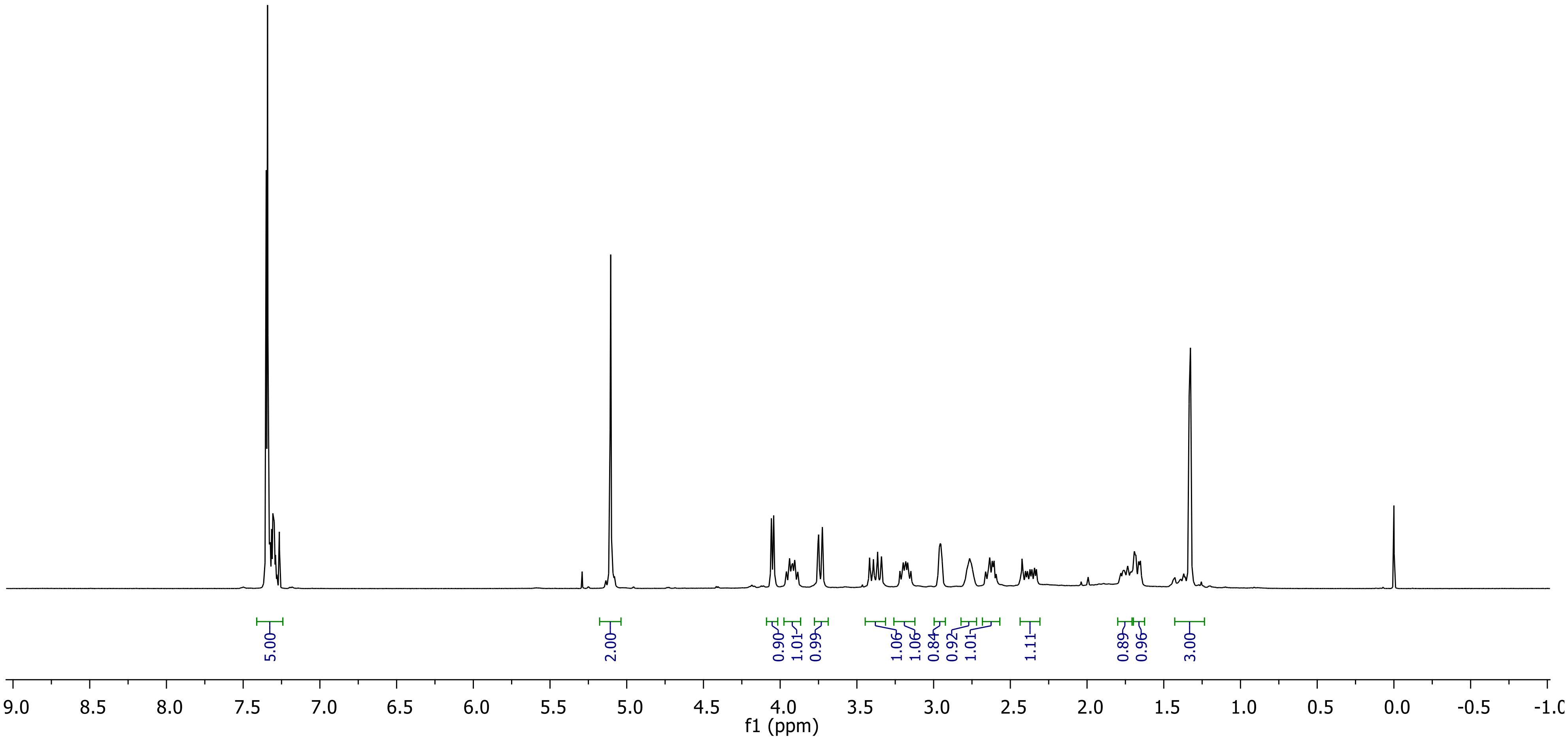


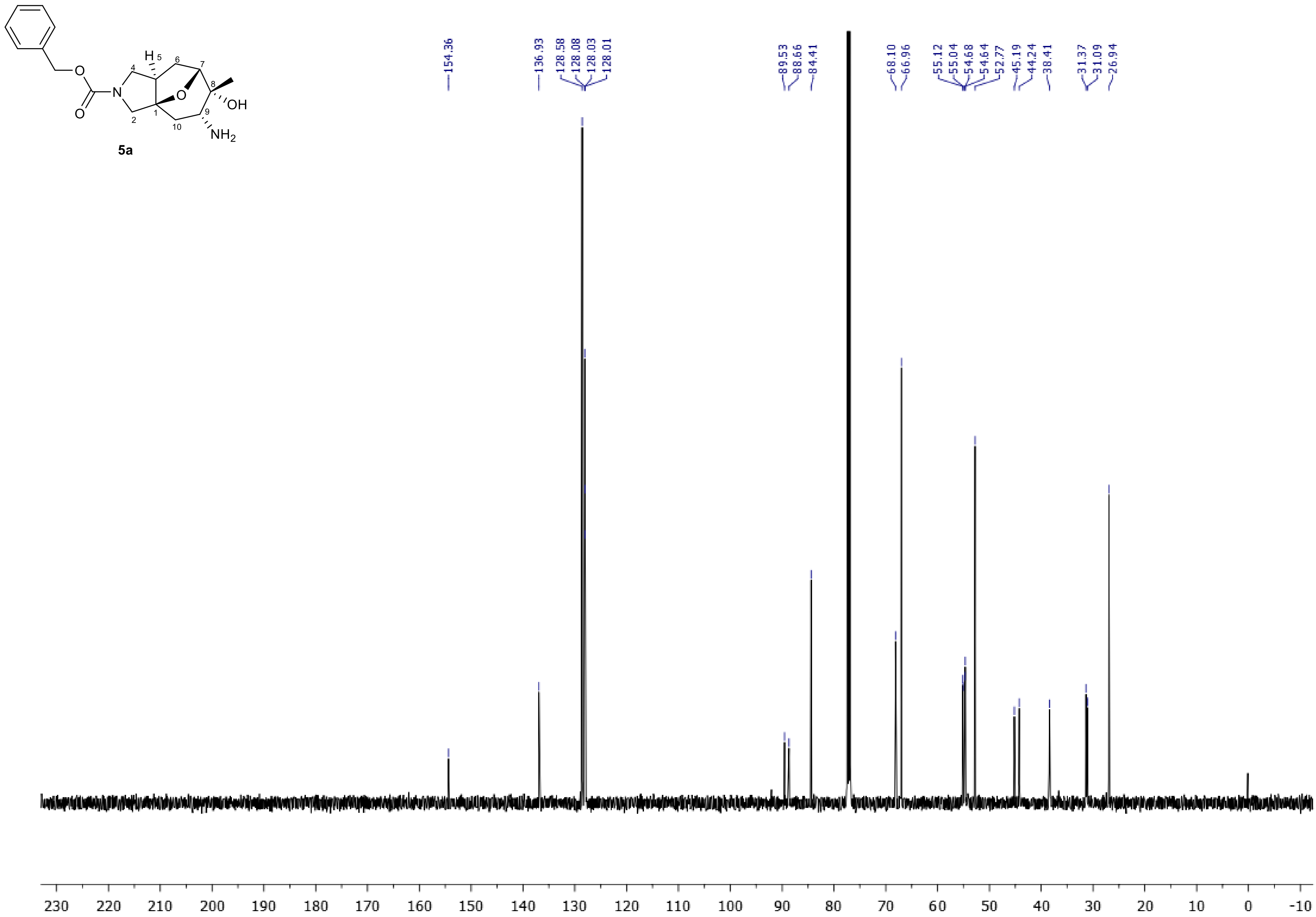
33b

207.80
154.31
154.22
139.55
136.71
136.68
128.93
128.60
128.54
128.17
128.07
126.88
92.31
91.53
82.29
81.07
67.13
54.20
54.11
53.83
53.71
47.16
46.04
45.10
31.86
31.67
H
5
6
7
8
4
O
N
O
O
OH
9
2
1
10
O
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


H
5
6
7
4
O
N
O
8
OH
1
9
2
10
NH2

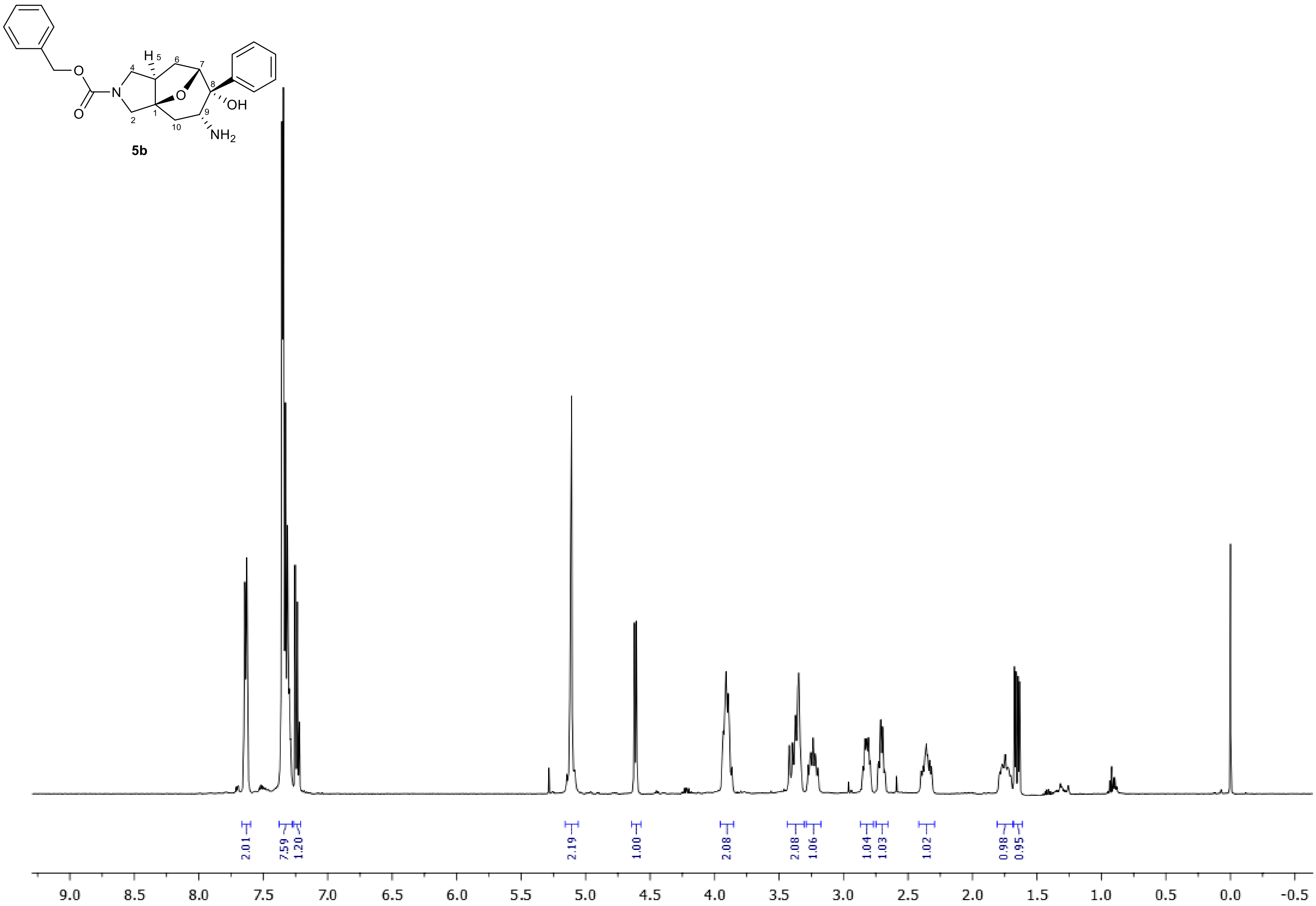
5a

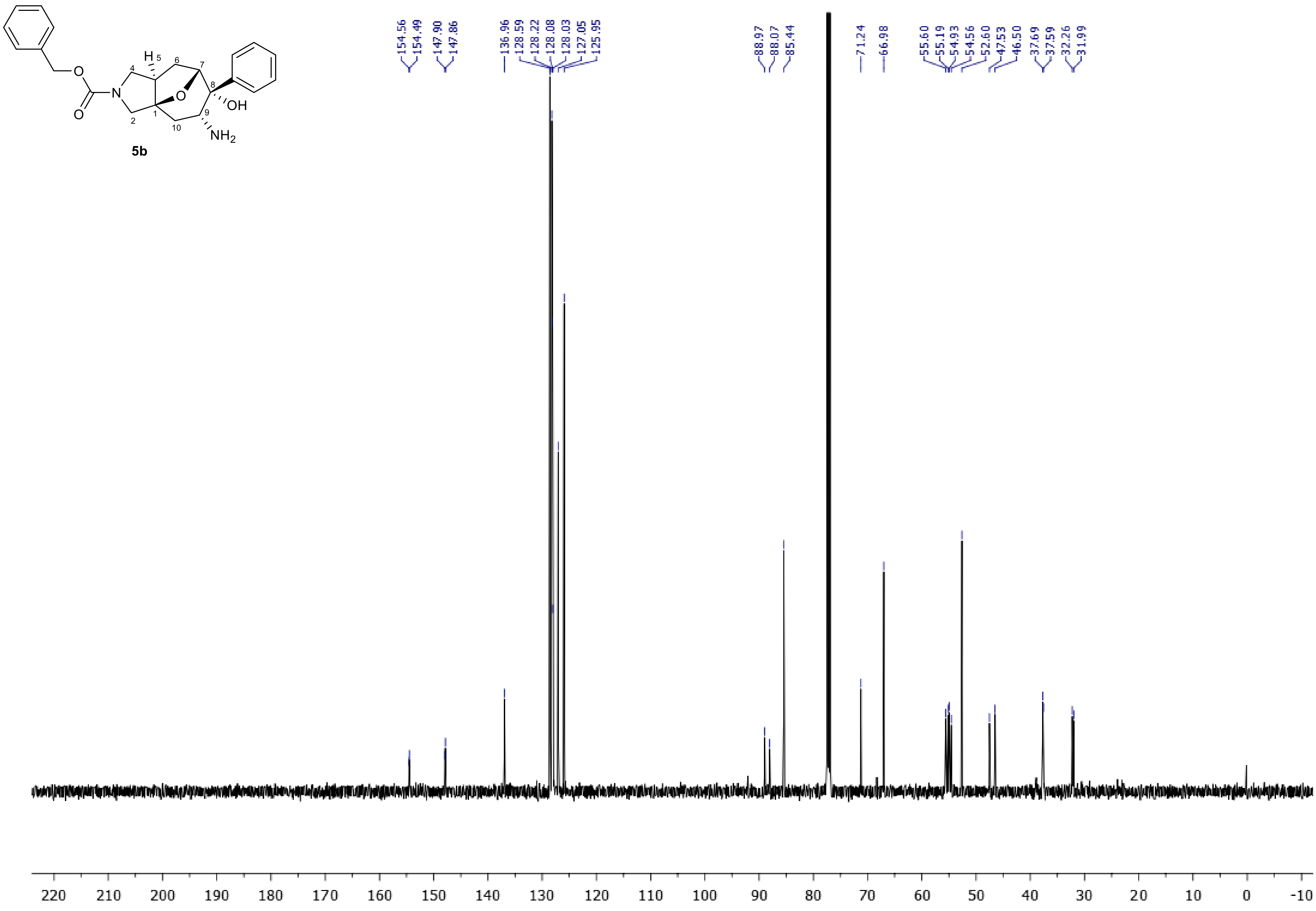

5.00
2.00
0.90
1.01
0.99
1.06
1.06
0.84
0.92
1.01
1.11
0.89
0.96
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


H
5
4
6
7
8
O
N
O
O
OH
2
1
9
10
NH$_2$

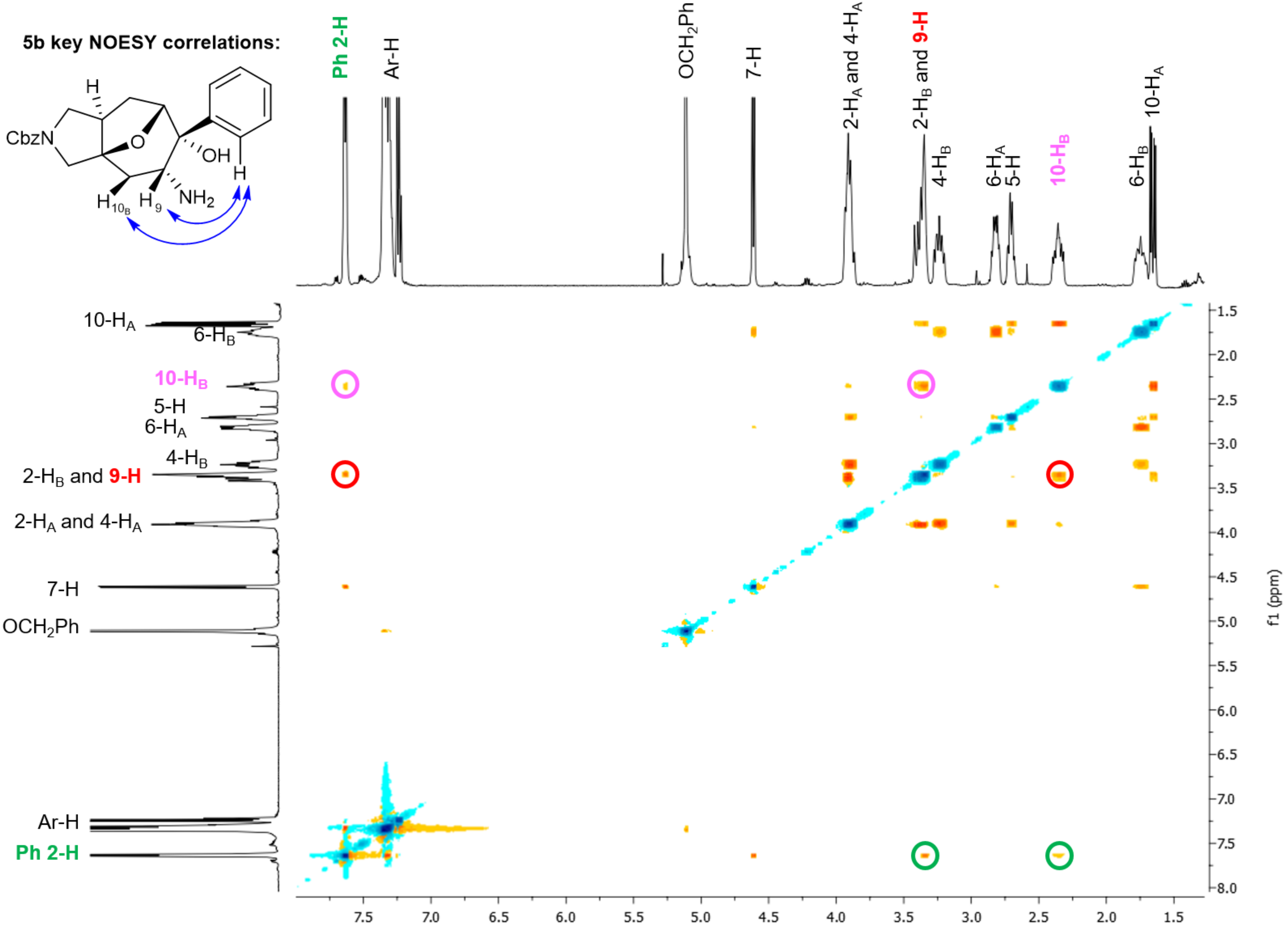
5a

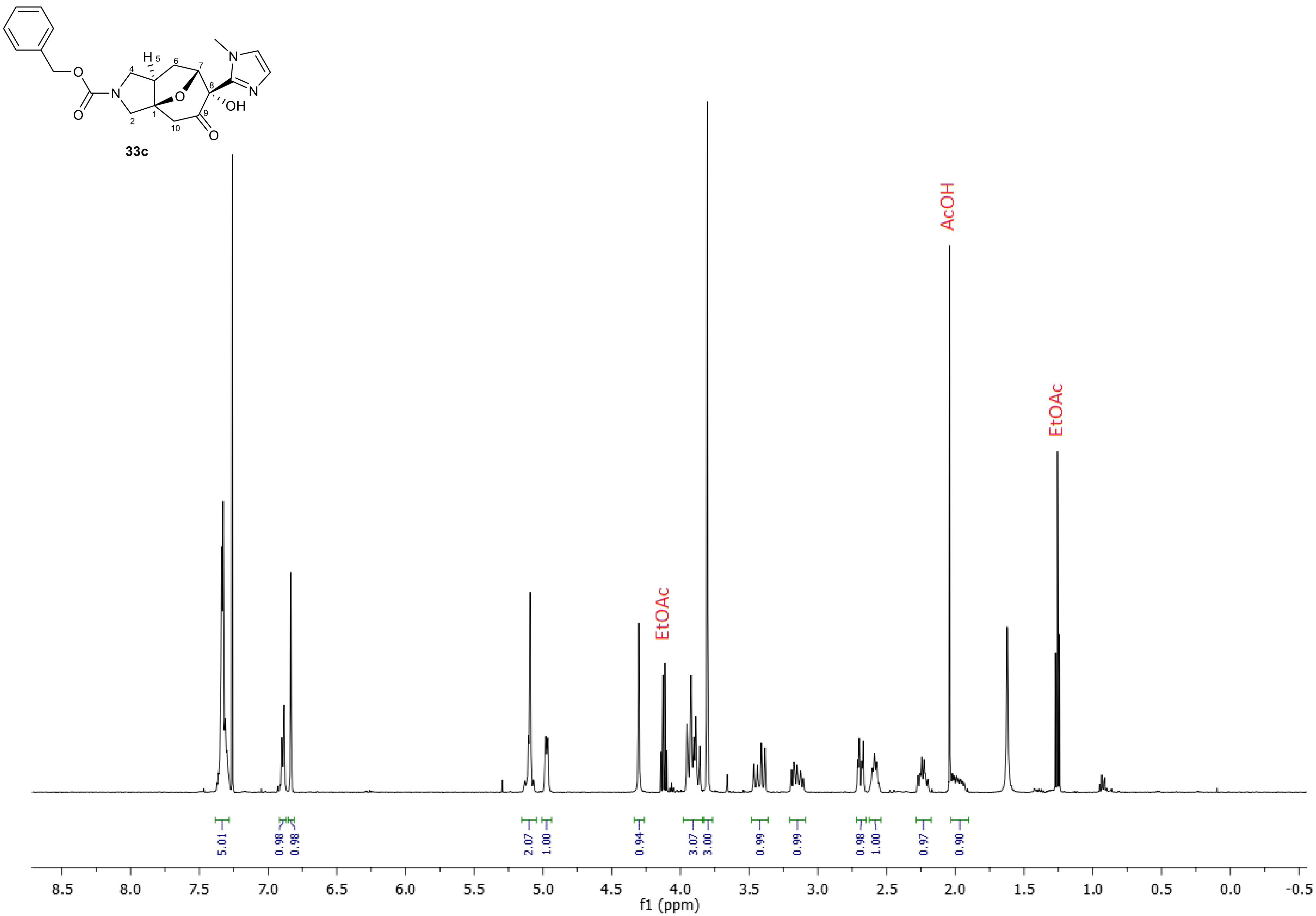
154.36
136.93
128.58
128.08
128.03
128.01
89.53
88.66
84.41
68.10
66.96
55.12
55.04
54.68
54.64
52.77
45.19
44.24
38.41
31.37
31.09
26.94
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


5b
O
O
N
H
OH
NH2
O
1
2
4
5
6
7
8
9
10
2.01
7.59
1.20
2.19
1.00
2.08
2.08
1.06
1.04
1.03
1.02
0.98
0.95
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

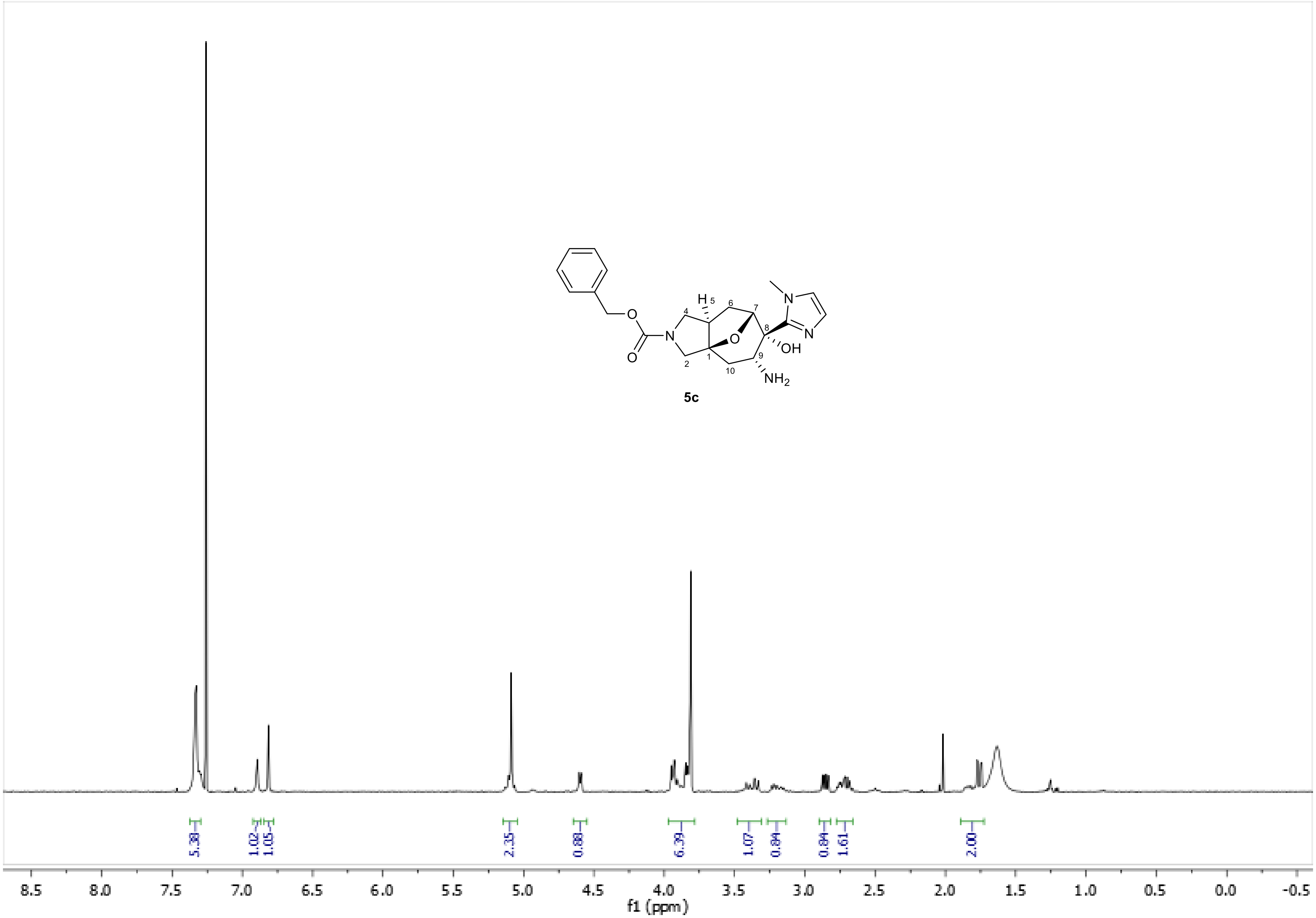

5b
H
O
N
O
O
OH
NH2
1
2
4
5
6
7
8
9
10
154.56
154.49
147.90
147.86
136.96
128.59
128.22
128.08
128.03
127.05
125.95
88.97
88.07
85.44
71.24
66.98
55.60
55.19
54.93
54.56
52.60
47.53
46.50
37.69
37.59
32.26
31.99
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

5b key NOESY correlations:



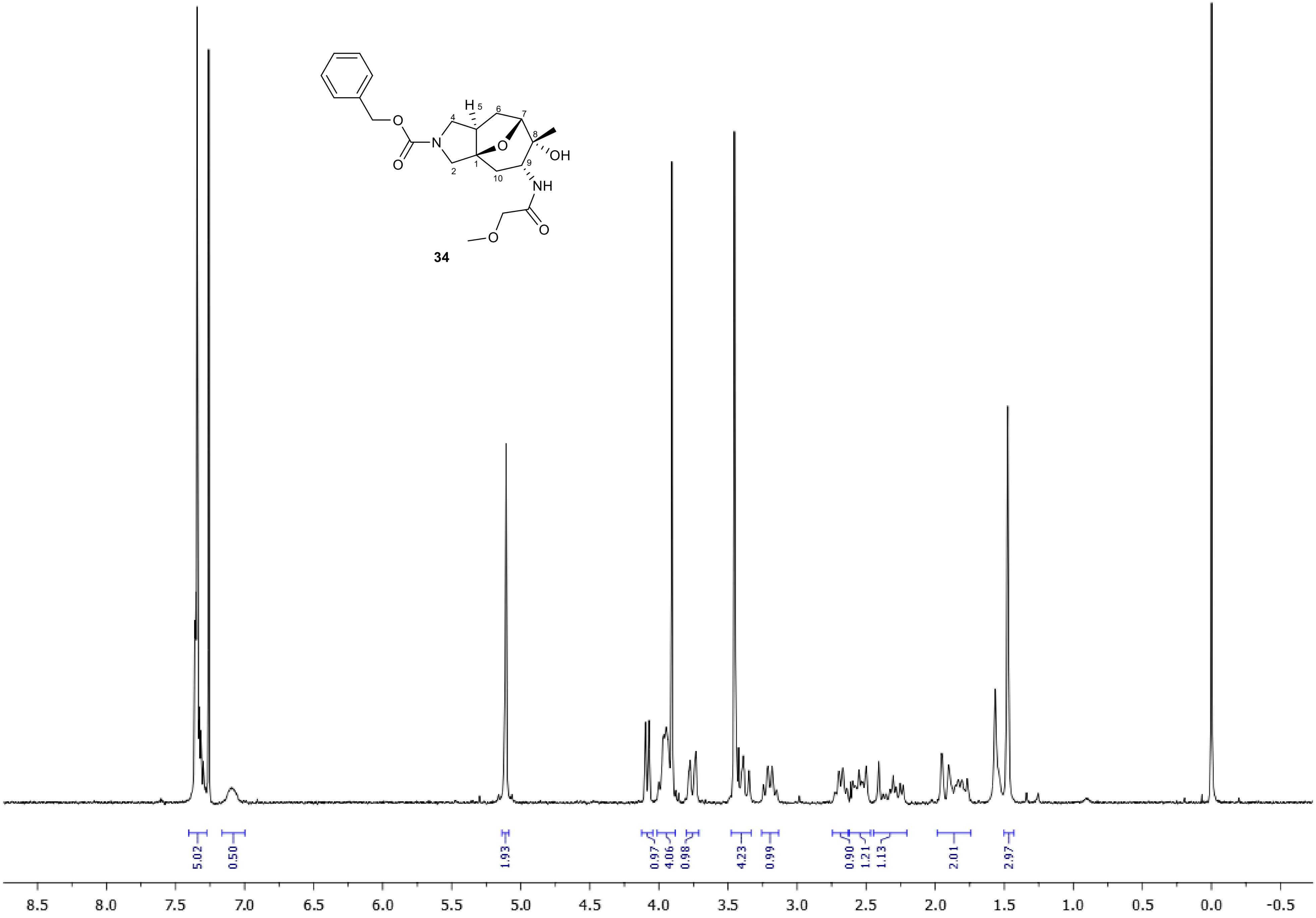

33c

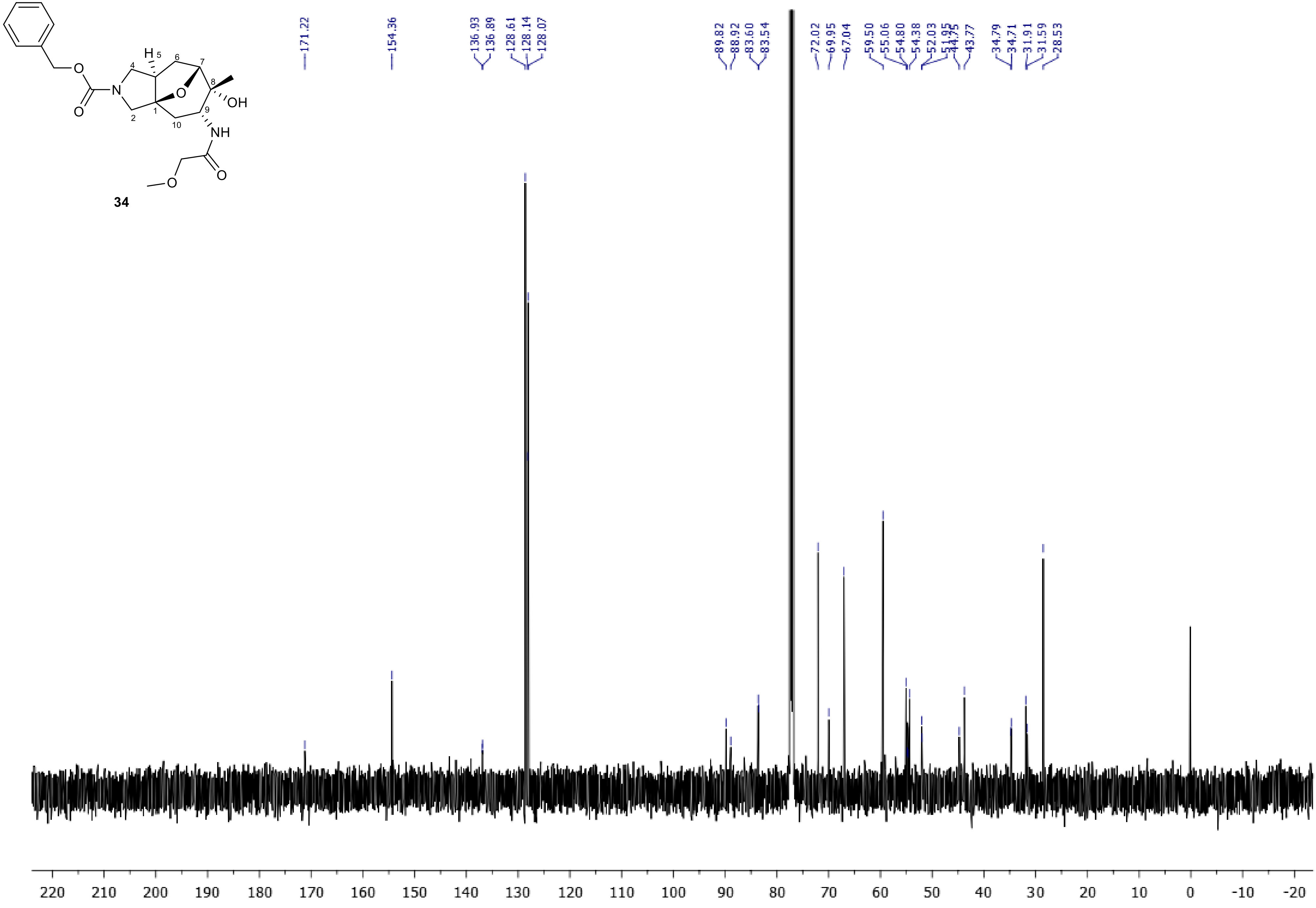
H
5
4
6
7
8
9
10
1
2
N
O
O
O
O
N
N
OH
O
EtOAc
AcOH
EtOAc
5.01
0.98
0.98
2.07
1.00
0.94
3.07
3.00
0.99
0.99
0.98
1.00
0.97
0.90
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

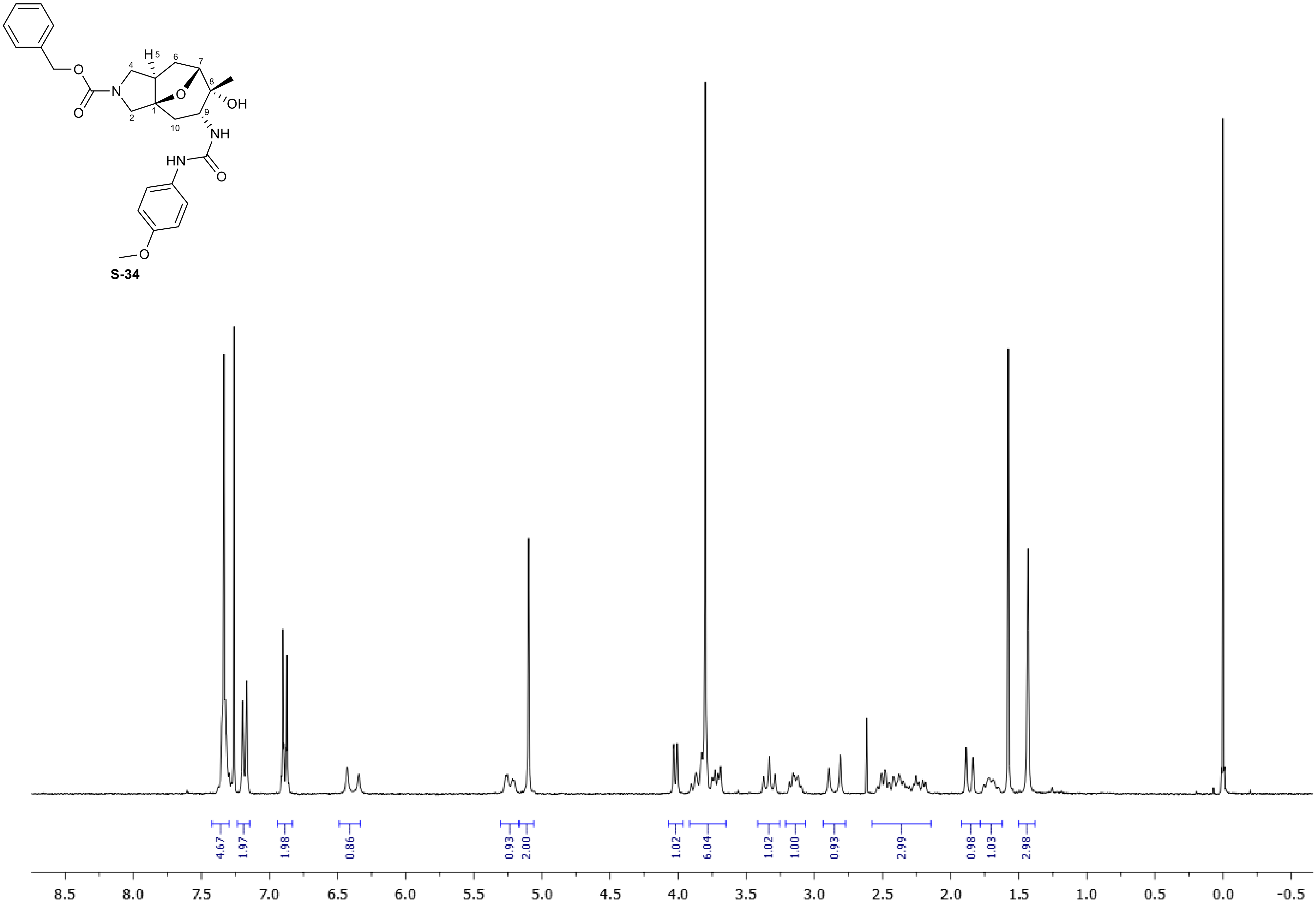


5c

H 5
4
6
7
8
1
2
9
10
N
O
OH
NH2
5.38
1.02
1.05
2.35
0.88
6.39
1.07
0.84
0.84
1.61
2.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

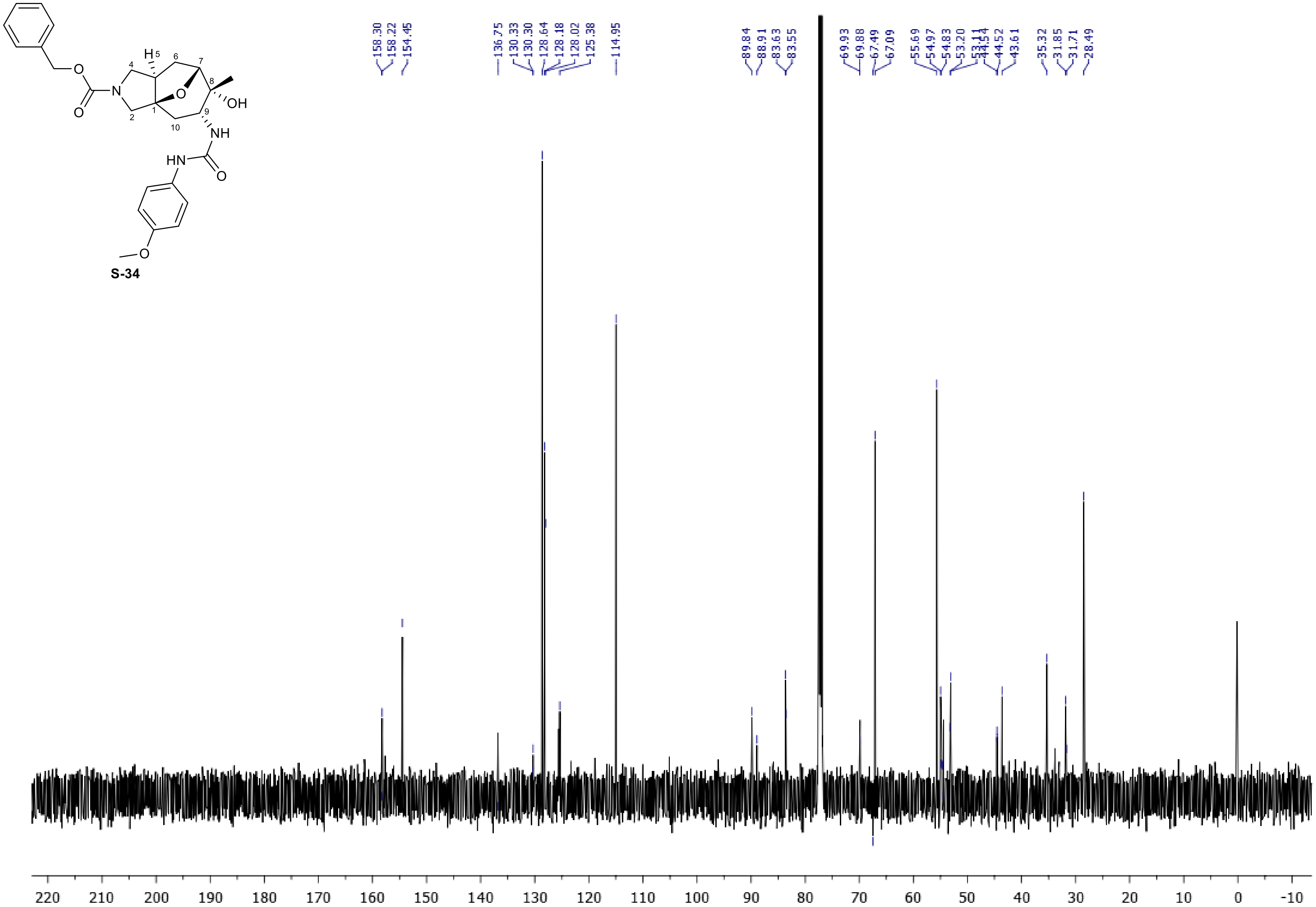

H
5
6
7
8
4
2
1
10
9
N
O
O
O
OH
NH
O
O
34
5.02
0.50
1.93
0.97
4.06
0.98
4.23
0.99
0.90
1.21
1.13
2.01
2.97
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


H
1
2
4
5
6
7
8
9
10
N
O
O
O
OH
NH
O
O
34
171.22
154.36
136.93
136.89
128.61
128.14
128.07
89.82
88.92
83.60
83.54
72.02
69.95
67.04
59.50
55.06
54.80
54.38
52.03
51.95
44.75
43.77
34.79
34.71
31.91
31.59
28.53
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

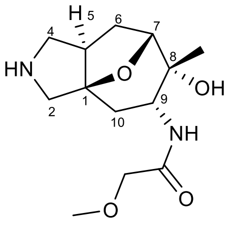

H
5
6
7
8
4
O
N
O
O
OH
2
1
9
10
NH
HN
O
O

S-34

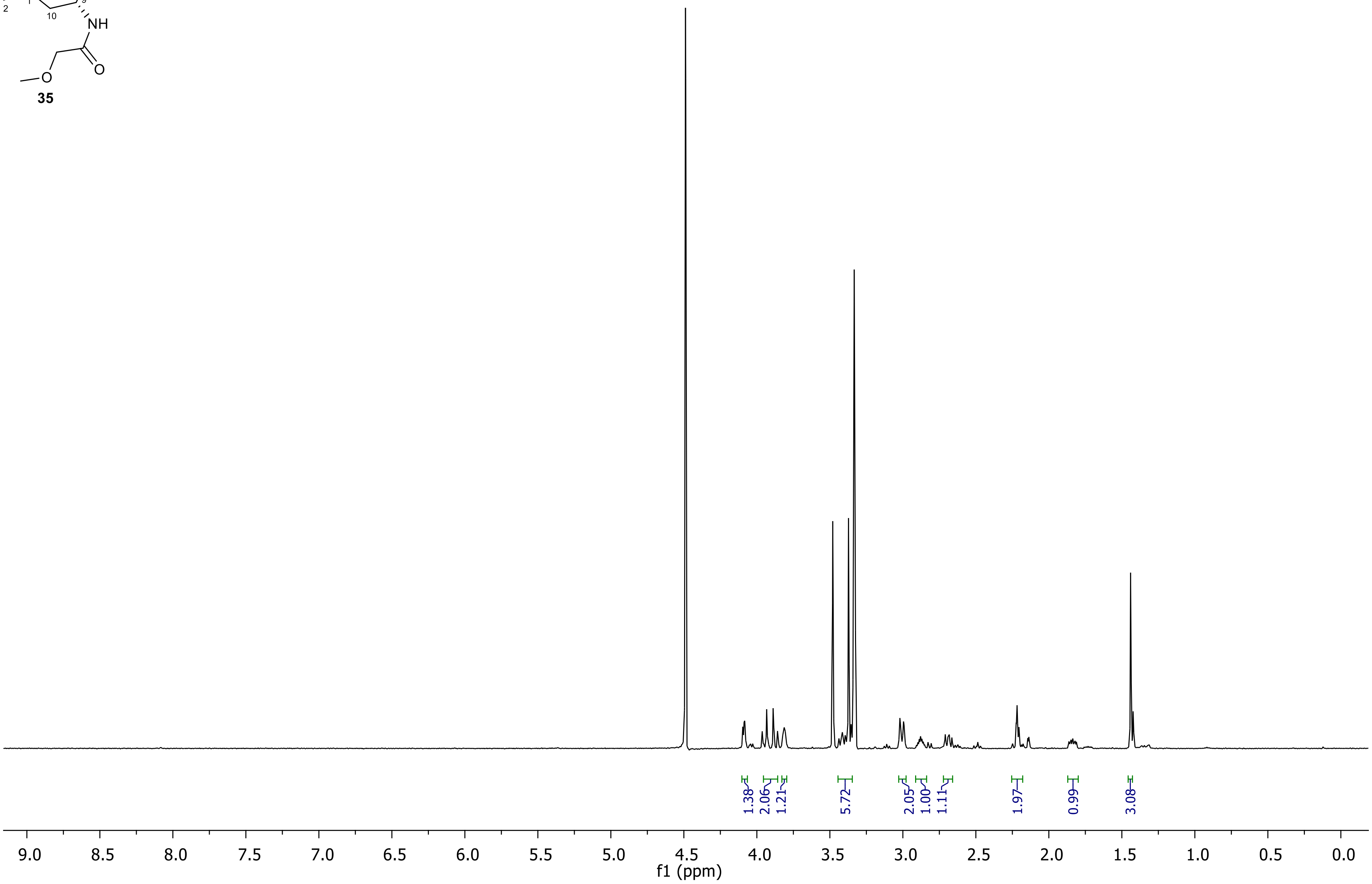
4.67
1.97
1.98
0.86
0.93
2.00
1.02
6.04
1.02
1.00
0.93
2.99
0.98
1.03
2.98
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

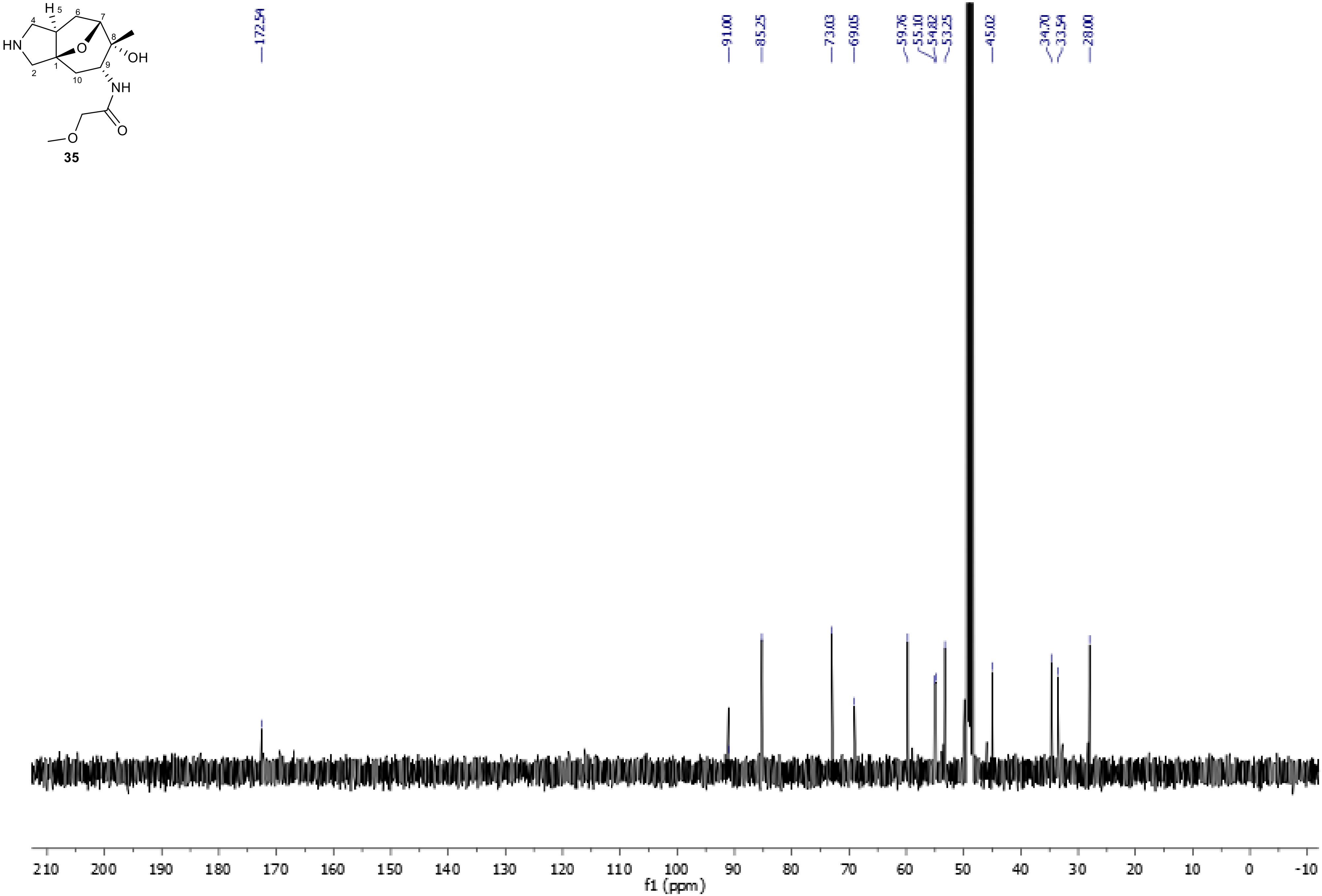

H
5
6
7
4
8
N
O
OH
2
1
9
10
NH
HN
O
O
O
158.30
158.22
154.45
136.75
130.33
130.30
128.64
128.18
128.02
125.38
114.95
89.84
88.91
83.63
83.55
69.93
69.88
67.49
67.09
55.69
54.97
54.83
53.20
53.11
44.54
44.52
43.61
35.32
31.85
31.71
28.49
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

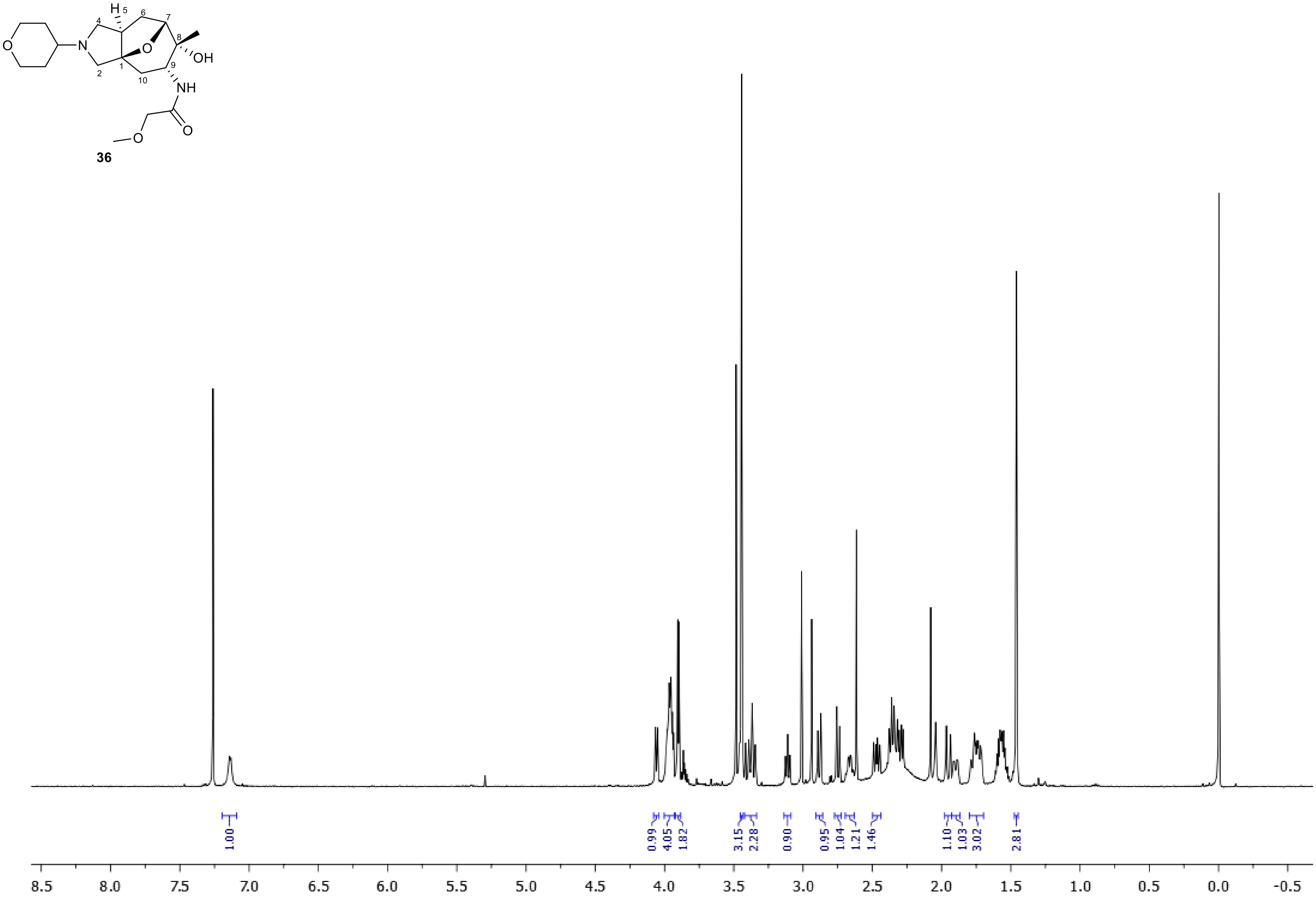
S-34


H
5
4
6
7
8
HN
O
OH
1
9
2
10
NH
O
O

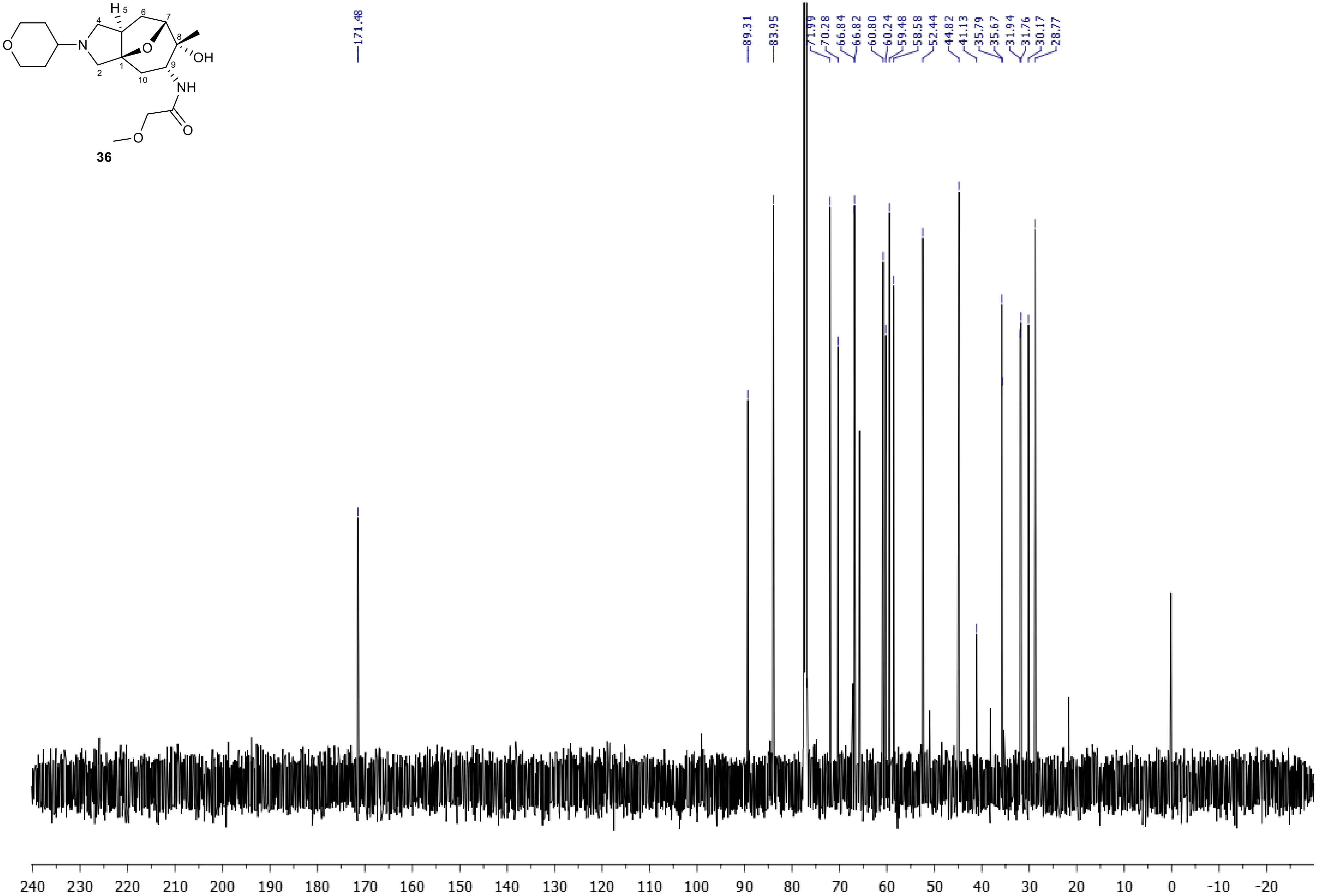
35

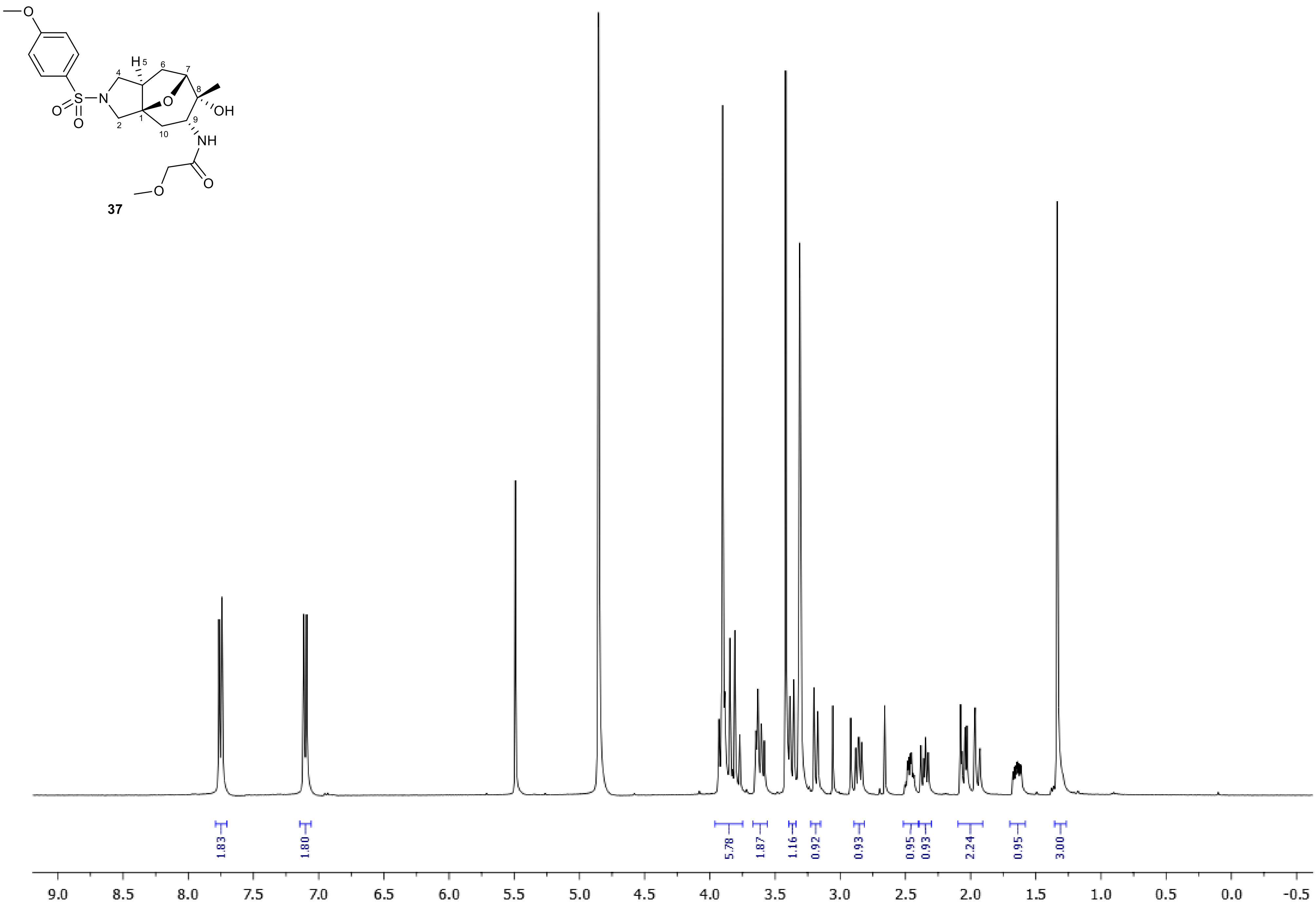

1.38
2.06
1.21
5.72
2.05
1.00
1.11
1.97
0.99
3.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


H
5
6
7
4
8
HN
O
OH
2
1
9
10
NH
O
O
35
172.54
91.00
85.25
73.03
69.05
59.76
55.10
54.82
53.25
45.02
34.70
33.54
28.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
N
H
5
4
6
7
8
O
OH
2
1
10
9
NH
O
O
1.00
0.99
4.05
1.82
3.15
2.28
0.90
0.95
1.04
1.21
1.46
1.10
1.03
3.02
2.81
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

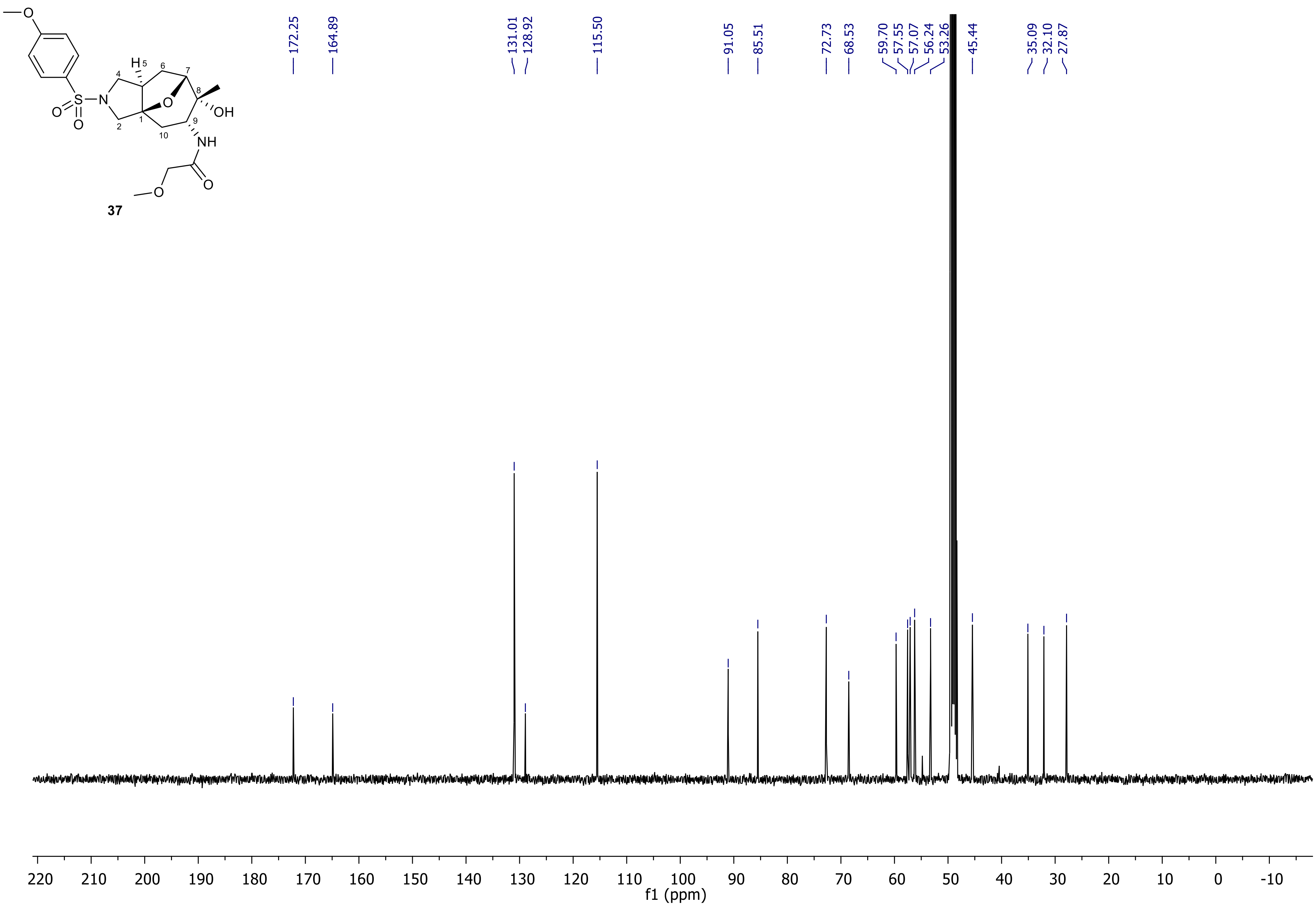
36


O
N
H
5
4
6
7
8
OH
O
2
1
10
9
NH
O
O
36
171.48
89.31
83.95
71.99
70.28
66.84
66.82
60.80
60.24
59.48
58.58
52.44
44.82
41.13
35.79
35.67
31.94
31.76
30.17
28.77
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

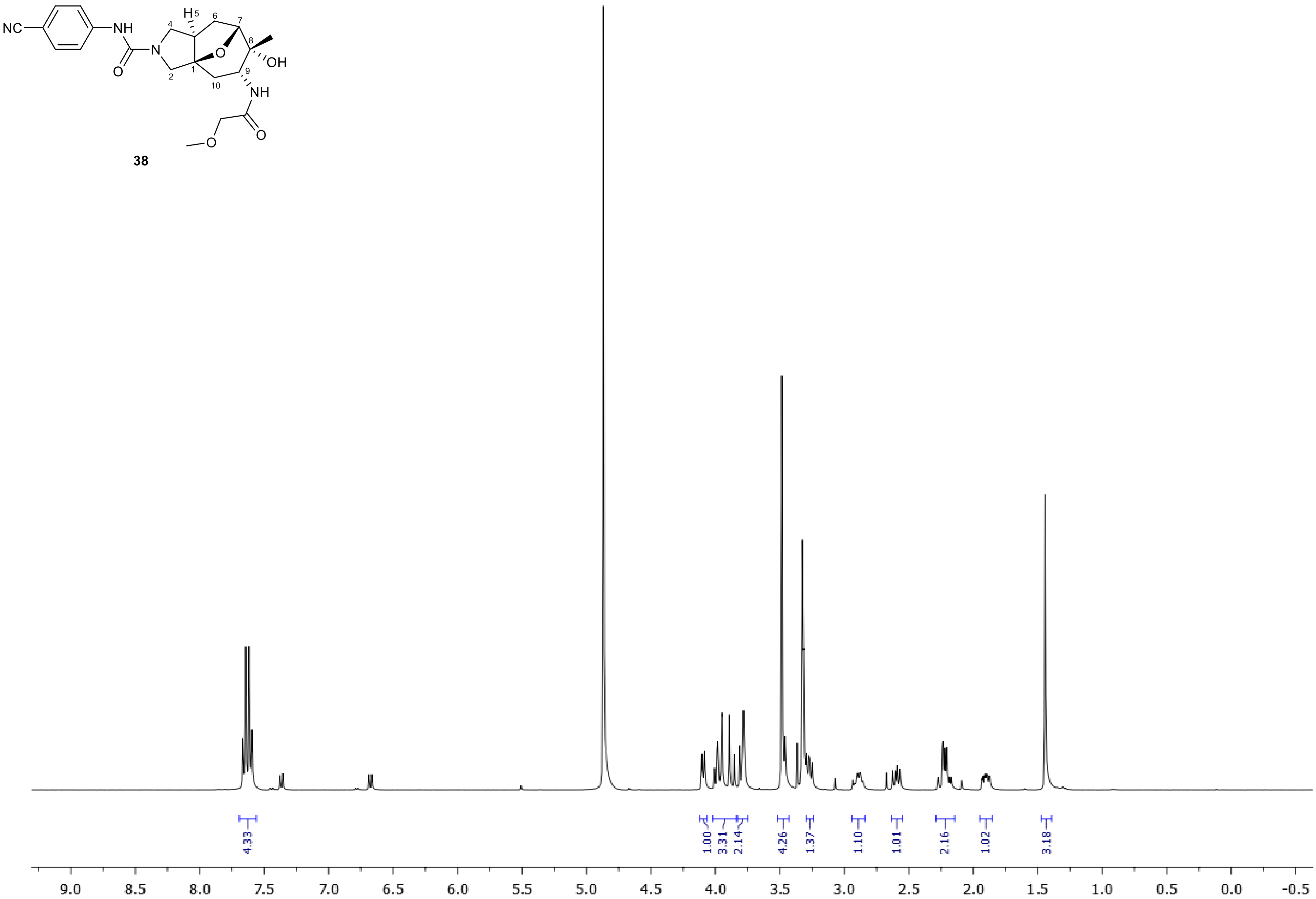


37

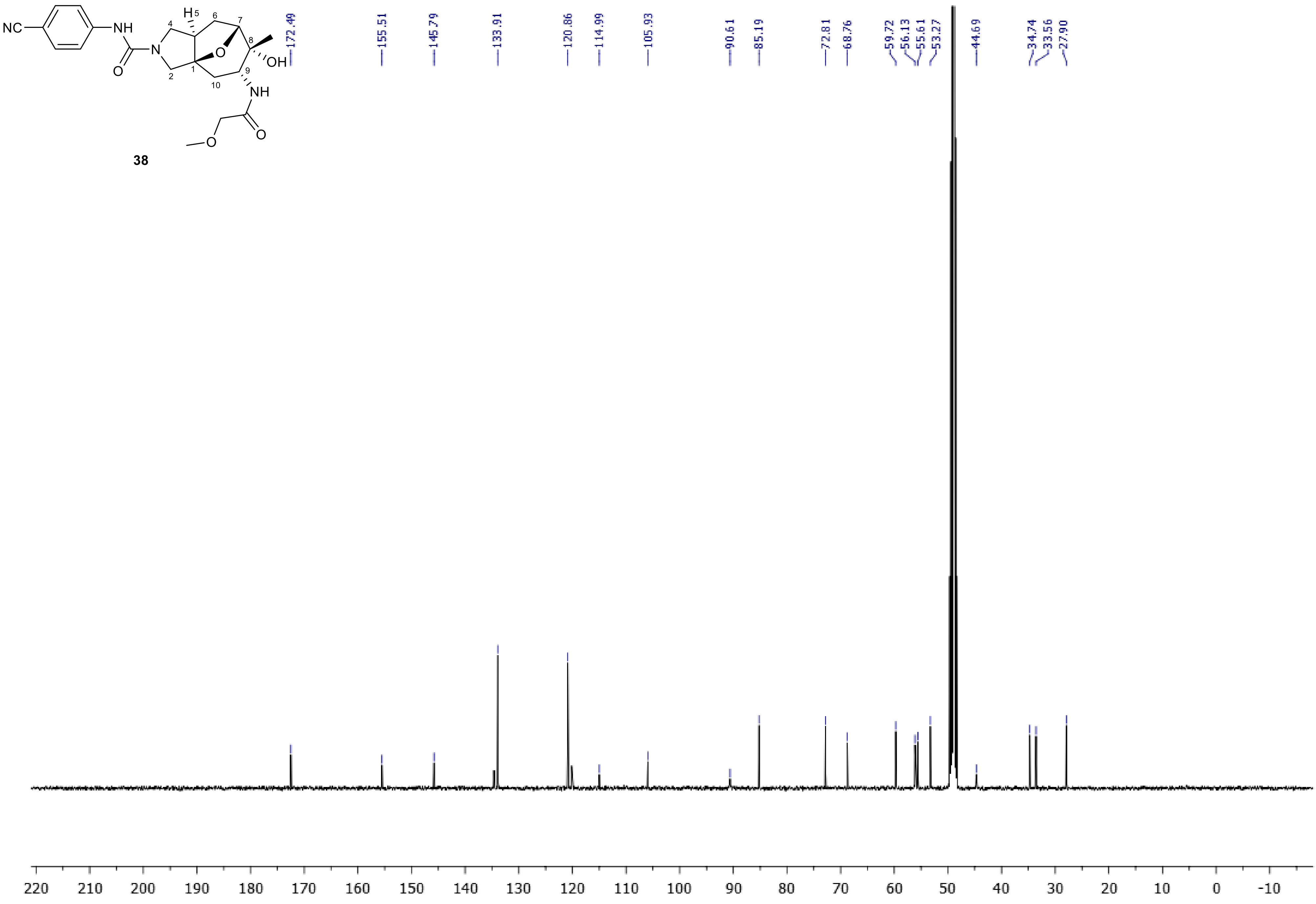
O
S
N
O
O
H
5
4
6
7
8
OH
1
2
10
9
NH
O
O
1.83
1.80
5.78
1.87
1.16
0.92
0.93
0.95
0.93
2.24
0.95
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


37

O
S
O
O
N
H 5
4
6
7
8
OH
2
1
10
9
NH
O
O
172.25
164.89
131.01
128.92
115.50
91.05
85.51
72.73
68.53
59.70
57.55
57.07
56.24
53.26
45.44
35.09
32.10
27.87
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

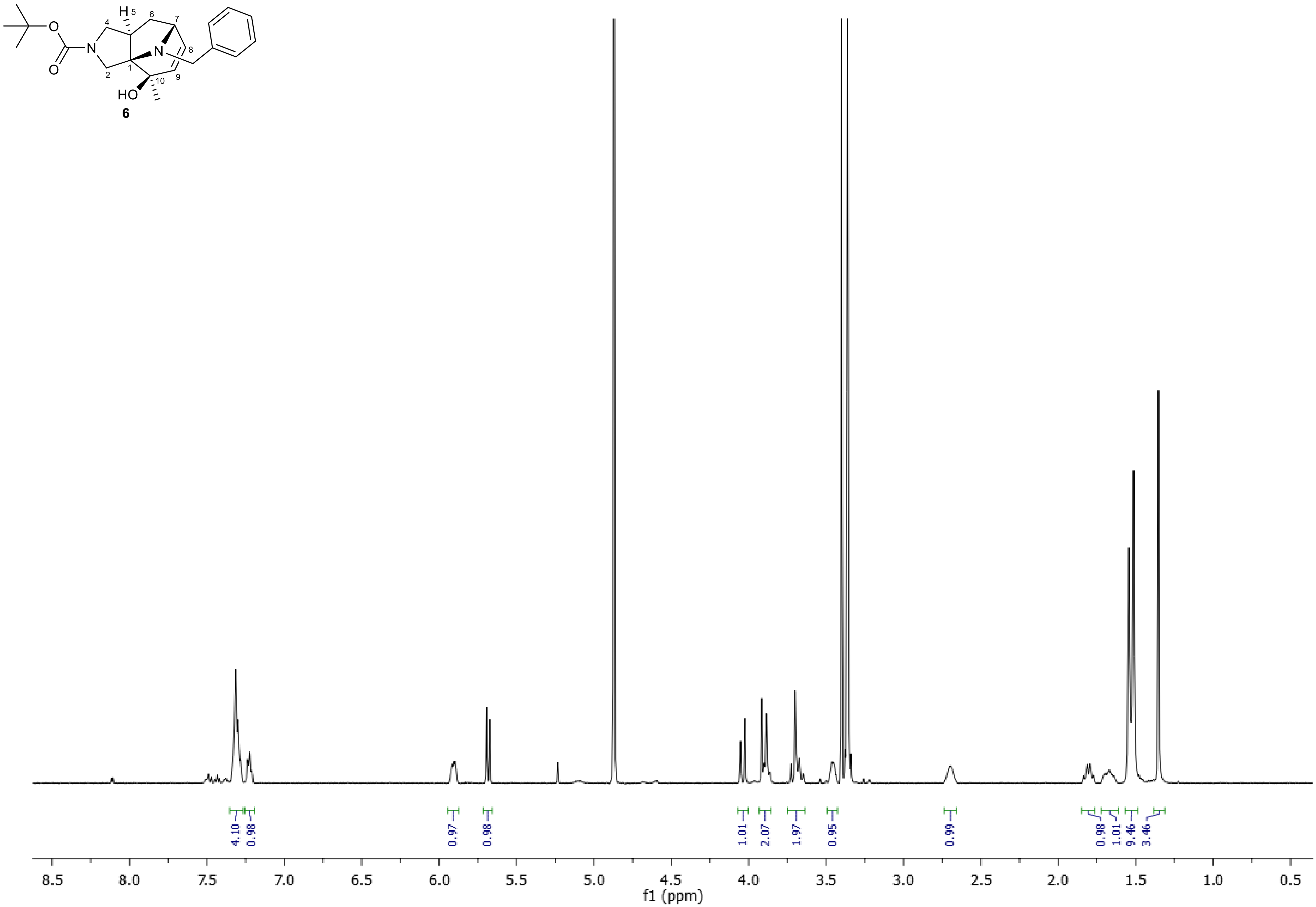

NC
NH
N
O
H5
4
6
7
8
OH
1
2
9
10
NH
O
O
O
4.33
1.00
3.31
2.14
4.26
1.37
1.10
1.01
2.16
1.02
3.18
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

38

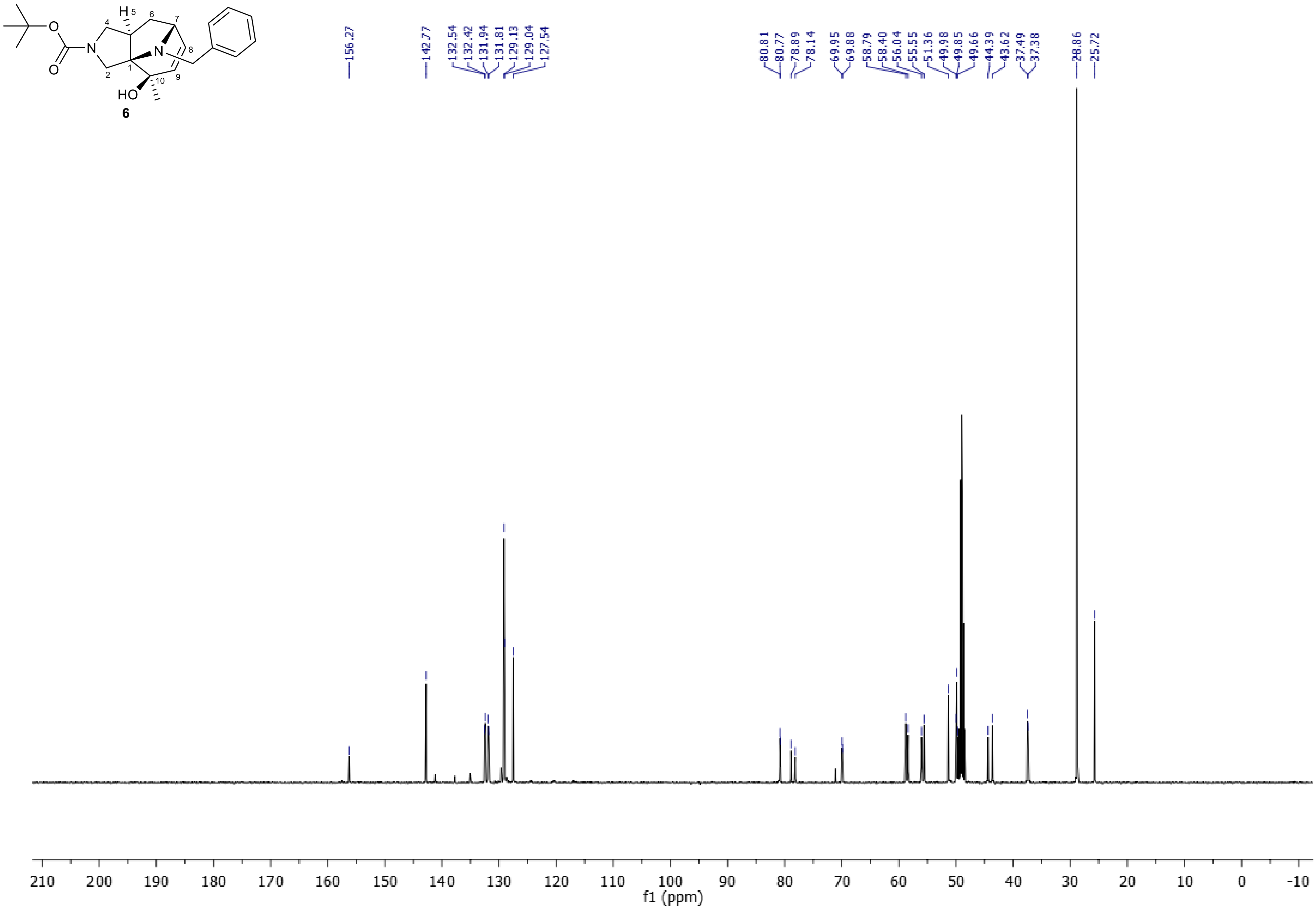


38

NC
NH
O
N
H5
4
6
7
8
O
OH
1
2
10
9
NH
O
O
172.49
155.51
145.79
133.91
120.86
114.99
105.93
90.61
85.19
72.81
68.76
59.72
56.13
55.61
53.27
44.69
34.74
33.56
27.90
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

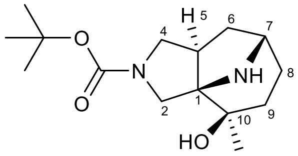

H 5
6
7
4
O
N
N
8
1
2
10
9
HO
O
4.10
0.98
0.97
0.98
1.01
2.07
1.97
0.95
0.99
0.98
1.01
9.46
3.46
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

6

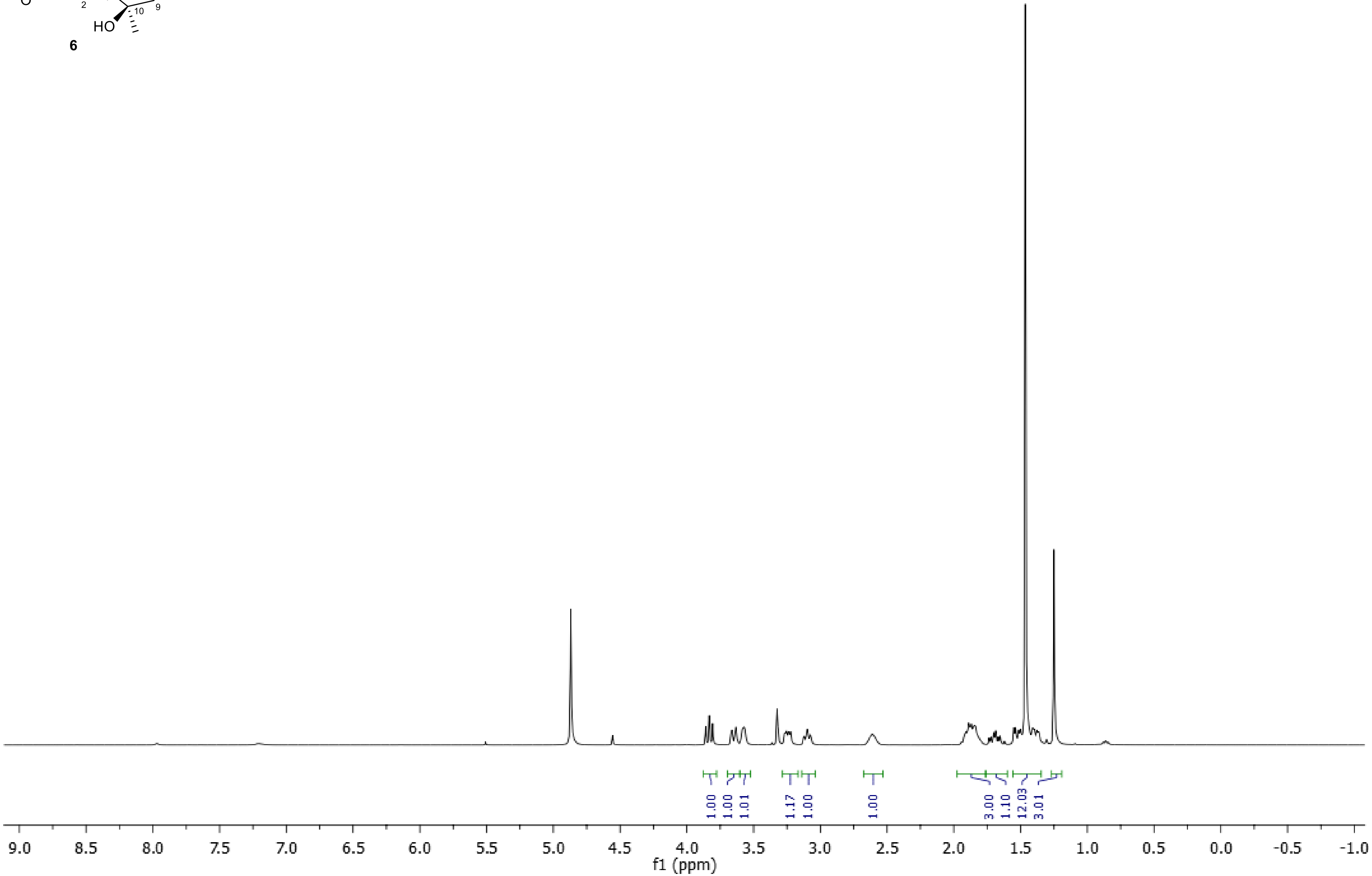


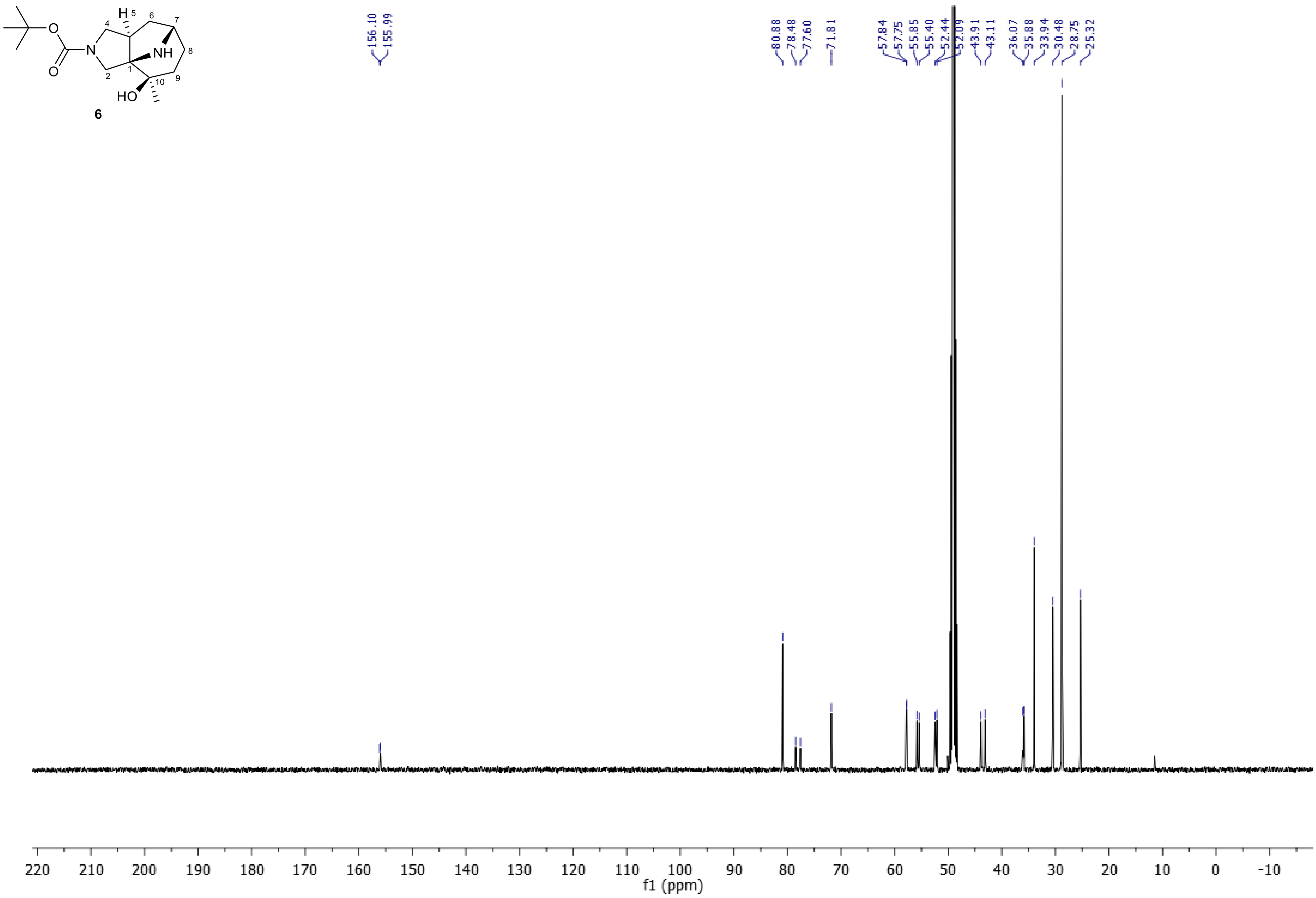
6

O
N
O
H 5
4
6
7
N
8
1
2
10
9
HO
156.27
142.77
132.54
132.42
131.94
131.81
129.13
129.04
127.54
80.81
80.77
78.89
78.14
69.95
69.88
58.79
58.40
56.04
55.55
51.36
49.98
49.85
49.66
44.39
43.62
37.49
37.38
28.86
25.72
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
N
H 5
4
6
7
NH
8
1
2
10
9
HO

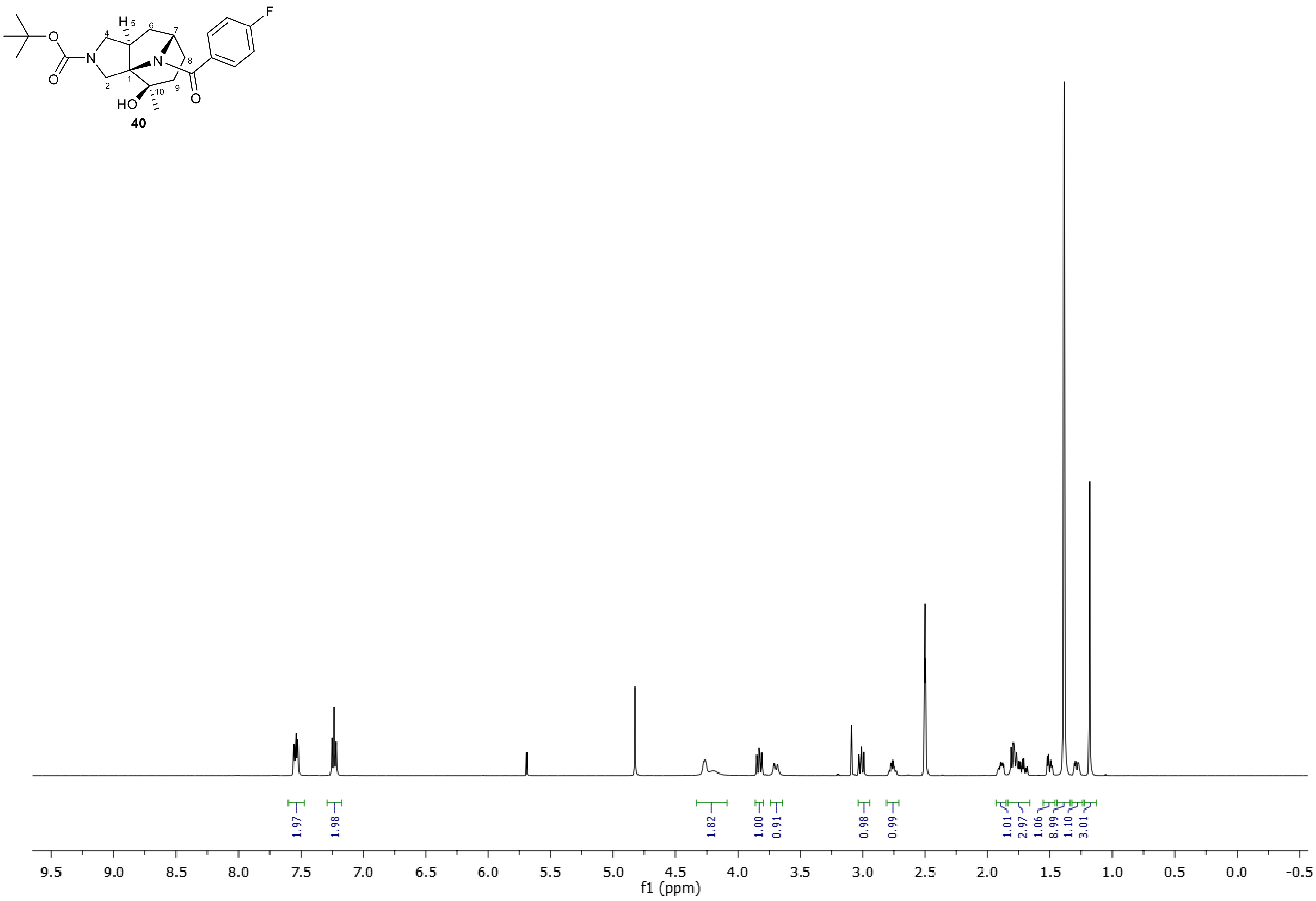
6


1.00
1.00
1.01
1.17
1.00
1.00
3.00
1.10
12.03
3.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

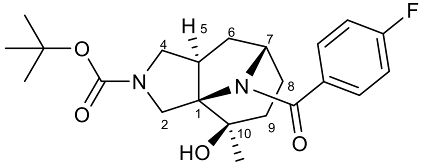


H
5
6
7
4
O
N
NH
8
O
2
1
10
9
HO
156.10
155.99
80.88
78.48
77.60
71.81
57.84
57.75
55.85
55.40
52.44
52.09
43.91
43.11
36.07
35.88
33.94
30.48
28.75
25.32
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

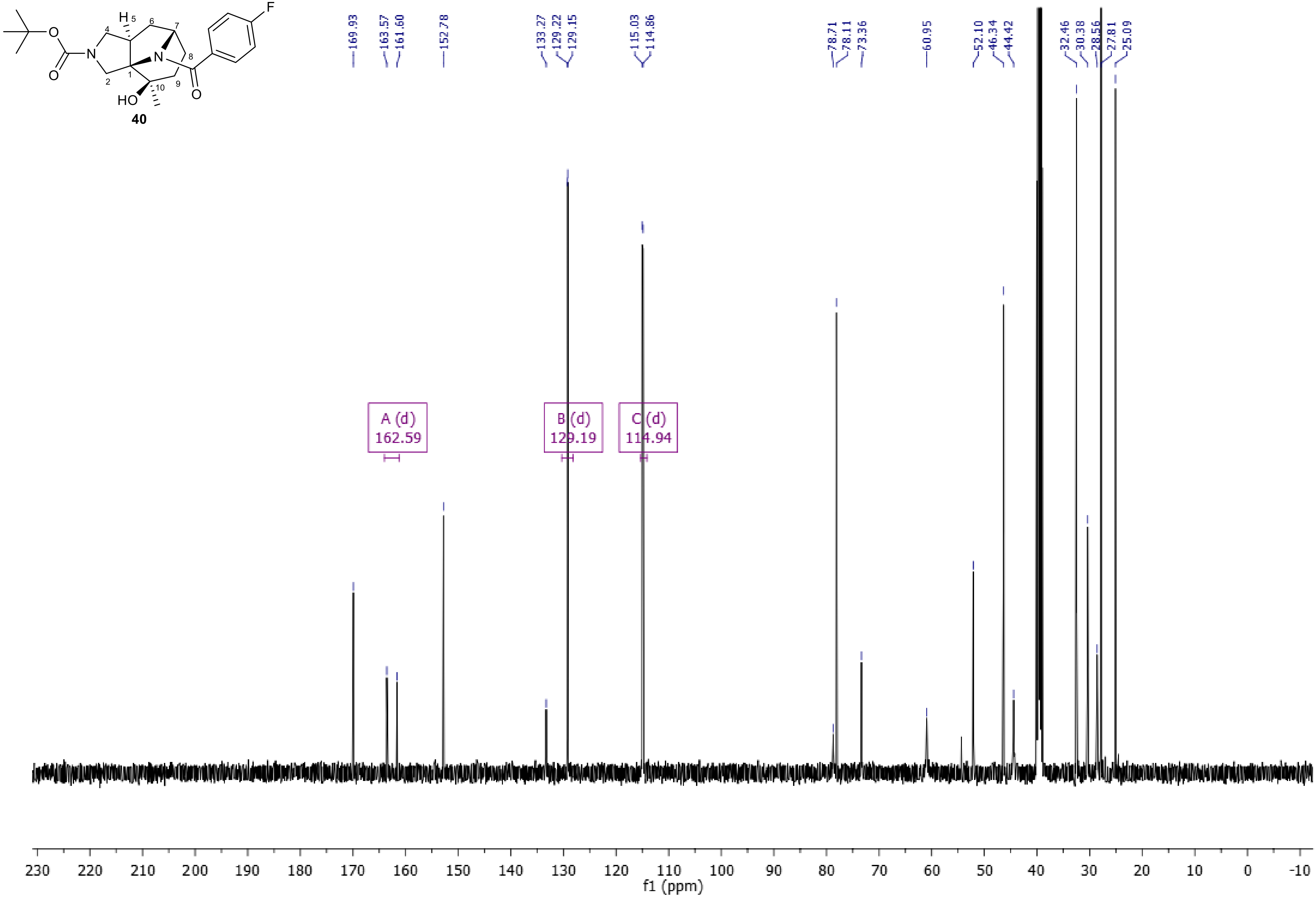
6

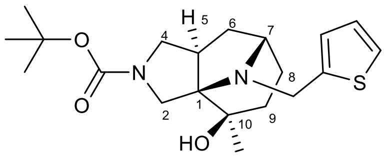

F
H
5
4
6
7
N
N
O
8
O
1
2
10
9
HO
O
1.97
1.98
1.82
1.00
0.91
0.98
0.99
1.01
2.97
1.06
8.99
1.10
3.01
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

40

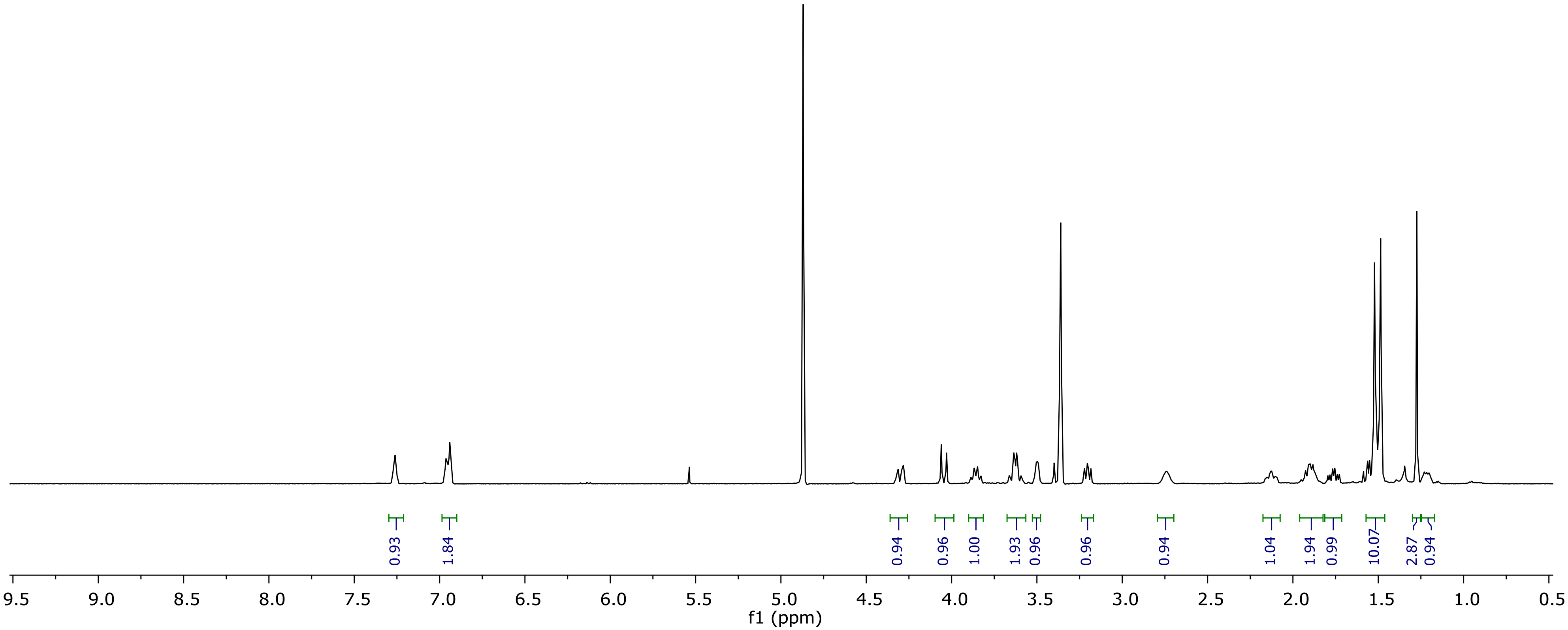

F
H
5
6
7
4
O
N
N
8
1
2
9
10
O
O
HO

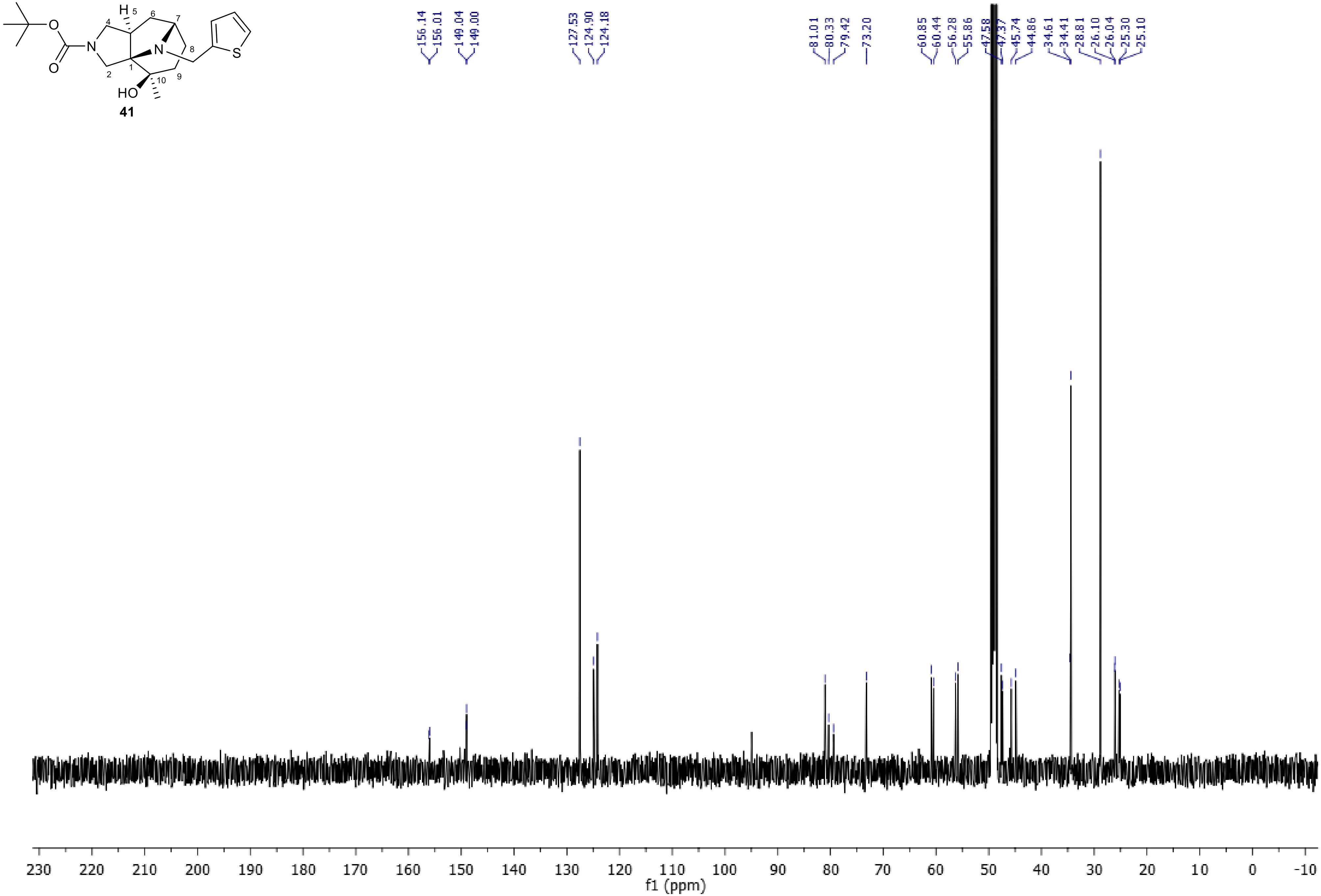
40


169.93
163.57
161.60
152.78
133.27
129.22
129.15
115.03
114.86
78.71
78.11
73.36
60.95
52.10
46.34
44.42
32.46
30.38
28.56
27.81
25.09
A (d)
162.59
B (d)
129.19
C (d)
114.94
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

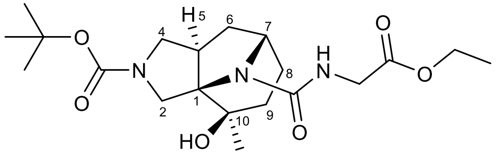

O
N
O
H
5
4
6
7
8
N
S
2
1
10
9
HO

41

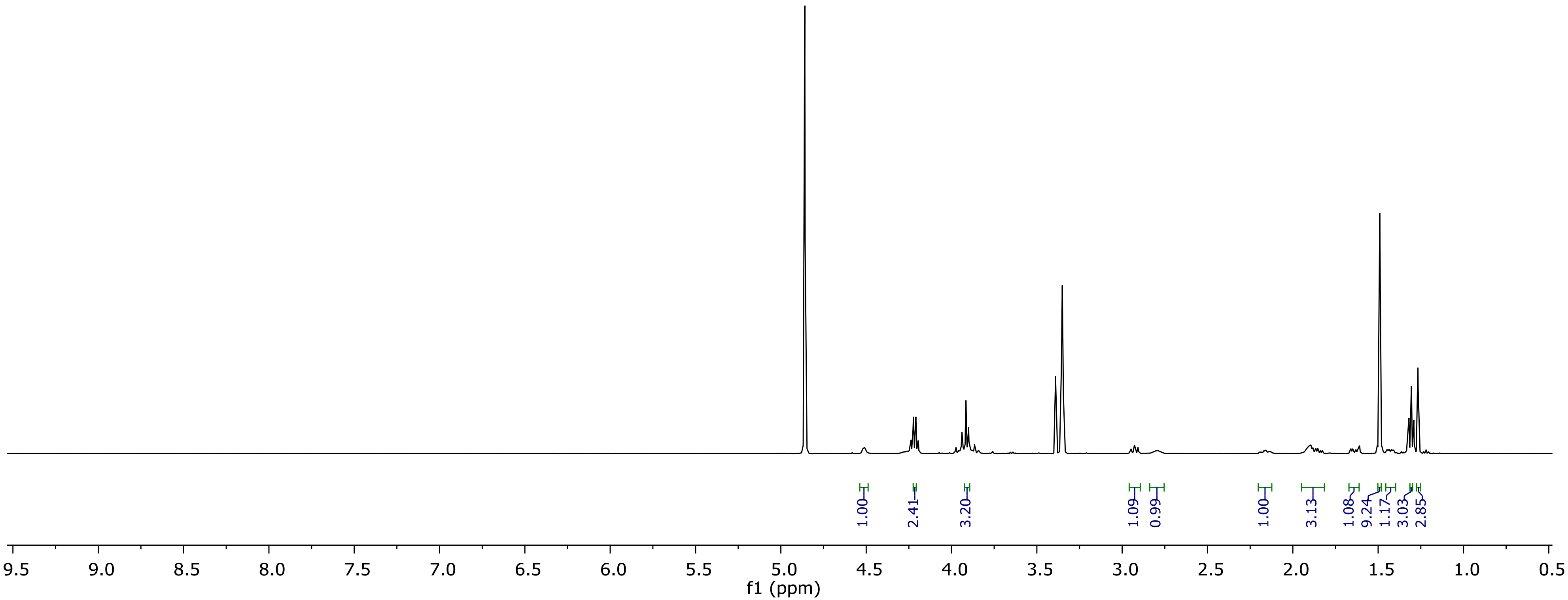

0.93
1.84
0.94
0.96
1.00
1.93
0.96
0.96
0.94
1.04
1.94
0.99
10.07
2.87
0.94
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


H
5
6
7
4
O
N
O
N
8
S
2
1
10
9
HO
156.14
156.01
149.04
149.00
127.53
124.90
124.18
81.01
80.33
79.42
73.20
60.85
60.44
56.28
55.86
47.58
47.37
45.74
44.86
34.61
34.41
28.81
26.10
26.04
25.30
25.10
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

41


1
2
4
5
6
7
8
9
10
H
N
O
HO

42


1.00
2.41
3.20
1.09
0.99
1.00
3.13
1.08
9.24
1.17
3.03
2.85
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

3.0 References

1 I. Colomer, C. J. Empson, P. Craven, Z. Owen, R. G. Doveston, I. Churcher, S. P. Marsden and A. Nelson, *Chem. Commun.*, 2016, **52**, 7209.

2 S. Miyazaki, S. Katoh, K. Adachi, H. Isoshima, S. Kobayashi, Y. Matsuzaki, W. Watanabe, K. Yamataka, S. Kiyonari and S. Wamaki, *US 2005/54645 A1*, 2005.