Electronic Supplementary Information

Norborn-2-en-7-ones as Physiologically-Triggered Carbon Monoxide-Releasing Prodrugs

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Experimental

Experiments requiring anhydrous conditions were performed under a dry nitrogen or argon atmosphere using apparatus heated and dried under vacuum, unless stated otherwise.

Anhydrous dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), toluene, acetonitrile (CH_3CN) and methanol (CH_3OH) were dried using the PURE SOLV MD-6 solvent purification system. 6 M HCl in 1,4-dioxane was prepared from 36% aqueous HCl and 1,4-dioxane. All other reagents were purchased as analytical or reagent grade and used without further purification. Aqueous solutions of sodium chloride (NaCl), sodium bicarbonate ($NaHCO_3$) and ammonium chloride (NH_4Cl) were saturated. Reactions performed at room temperature (rt) were carried out at approximately 20 °C and reaction temperatures from -78 °C to 0 °C were obtained using the following cooling bath mixtures: acetone/dry ice, -78 °C; acetonitrile/dry ice, -40 °C; NaCl/ice, -15 °C; water/ice, 0 °C.

Reactions were monitored by thin layer chromatography (TLC) carried out on 0.2 mm Kieselgel F254 (Merck) silica gel plates using UV light as a visualising agent and then stained and developed with heat using either vanillin in ethanolic sulfuric acid, ammonium heptamolybdate and cerium sulfate in aqueous sulfuric acid, or potassium permanganate and potassium carbonate in aqueous sodium hydroxide. Separation of mixtures was performed by flash chromatography using 0.063–0.1 mm silica gel with the indicated eluent.

Infrared spectra were recorded on a Bruker Optics Alpha FT-IR spectrometer with a diamond Attenuated Total Reflectance (ATR) top plate. No sample preparation was required. Absorption peaks are reported as wavenumbers (ν, cm^{-1}).

NMR spectra were recorded on a Varian 400-MR spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei at 25 °C, or a Varian 500 MHz AR Premium Shielded Spectrometer at operating at 500 MHz for ^1H nuclei and 125 MHz for ^{13}C nuclei at 25 °C. ^1H

NMR chemical shifts are reported in parts per million (ppm) relative to the chloroform ($CDCl_3$, δ 7.26), or dimethyl sulfoxide (DMSO-*d6*, δ 2.50) peak. ^{1}H NMR values are reported as chemical shifts δ multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet), coupling constant (*J*, Hz) and relative integral. Coupling constants were taken directly from the spectra. ^{13}C NMR chemical shifts are reported in ppm relative to the chloroform ($CDCl_3$, δ 77.0), or dimethyl sulfoxide (DMSO-*d6*, δ 39.5) peak. ^{13}C NMR values are reported as chemical shifts δ and assignment. Decoupled ^{19}F NMR spectra were recorded on a Varian 400-MR spectrometer operating at 376 MHz at 25 °C and data are expressed in ppm. Assignments were made with the aid of DEPT, gCOSY, gHSQC, and gHMBC experiments. The term *inter alia* is used when reporting NMR data for the individual components of mixtures of endo and exo isomers.

Mass spectra were recorded on a Bruker micrOTOF-Q II mass spectrometer by electrospray ionisation in positive and negative mode. High-resolution mass spectra (HRMS) were obtained with a nominal resolution of 5,000 to 10,000.

Microanalyses were performed by Bob McAllister and Pauline Bandeen of the Campbell Microanalytical Laboratory, University of Otago.

HPLC analysis

HPLC grade acetonitrile (CH_3CN) was purchased from Merck Chemicals. MilliQ grade H_2O was obtained from a Millipore purification system. HPLC grade trifluoroacetic acid (TFA) was purchased from Scharlau. HPLC analyses were conducted on an analytical RP-HPLC (Shimadzu LC–20AD equipped with an SPD-20A UV detector [210 and 254 nm]) using a Phenomenex Prodigy column (C–18, 5 μm, 3.00 × 250 mm) at 0.5 mL min^{-1} and heated to 40 °C. Unless otherwise stated, the solvent system for all LC purposes was a mixture of

A (0.05% TFA in H_2O) and B (CH_3CN). A gradient of 10% to 100% B over 12.5 min, then 100% B for 2.5 min, with a flow rate of 0.5 mL min^{-1} was used unless otherwise stated.

3a-Bromo-3a,4,7,7a-tetrahydro-4,7-dimethyl-2,5,6-triphenyl-4,7-methano-1*H*-isoindole-1,3,8(2*H*)-trione (16)

The 2,5-dimethyl-3,4-diphenylcyclopentadien-1-one dimer (**15**)[1] (393 mg, 1.51 mmol) and 3-bromo-1-phenyl-1*H*-pyrrole-2,5-dione (**14**)[2, 3] (418 mg, 1.66 mmol) were refluxed in benzene (20 mL) for 6 h. The solution was concentrated *in vacuo* to a brown solid which was recrystallised from diethyl ether to afford the *title compound* **16** (551 mg, 71 %) as white crystals. m.p. 180 °C. ν_{max}/cm^{-1} 1781, 1719, 1367; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67 (s, 3H), 1.69 (s, 3H), 3.69 (s, 1H), 6.93-7.00 (m, 4H), 7.13-7.28 (m, 8H), 7.40-7.50 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 12.5, 56.8, 59.0, 60.3, 60.0,126.1, 128.2, 128.3, 128.35, 128.41, 129.2, 129.4, 129.5, 129.8, 131.2, 132.5, 132.6, 140.5, 144.6, 171.3, 171.9, 196.8; HRMS-ESI $[M + Na]^+$ Calcd for $C_{29}H_{22}{}^{81}BrNO_3Na^+$ 536.0655, found 536.0673.

4,7-Dimethyl-2,5,6-triphenyl-1*H*-isoindole-1,3(2*H*)-dione (17)

NEt_3 (0.33 mL, 2.38 mmol) was added to a solution of **16** (354 mg, 0.691 mmol) in dry THF (10 mL) and stirred for 3 h. The solution was washed with aqueous 1 M HCl, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford a white solid. The crude product was purified by column chromatography (2:1 CH_2Cl_2/Petrol) to afford the *title compound* **17** (258 mg, 93 %) as a white solid. m.p. 260 °C. ν_{max}/cm^{-1} 1706, 1375; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 6H), 6.90-6.94 (m, 4H), 7.11-7.21 (m, 6H), 7.38-7.48 (m, 3H), 7.49-7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 126.9, 127.0, 127.9, 128.0, 129.1, 129.6, 132.1, 135.0, 138.7, 148.9, 168.2;; HRMS-ESI $[M + Na]^+$ Calcd for $C_{28}H_{21}NO_2Na^+$

426.1446, found 426.1449; Anal. Calcd for $C_{28}H_{21}NO_2$: C, 83.35; H, 5.25; N, 3.47. Found: C, 83.20; H, 5.30; N, 3.46.

***tert*-Butyl (2-(3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)propanamido)ethyl)carbamate (19)**

A stirred solution of maleimide **18**[4] (1.51 g, 5.67 mmol) in anhydrous dichloromethane (35 mL) was cooled to 0 °C and a solution of *tert*-butyl (2-aminoethyl)carbamate (1.00 g, 6.24 mmol) in anhydrous dichloromethane (35 mL) added drop-wise. The reaction was stirred under nitrogen for 1 h at 0 °C then stirred overnight at rt. Upon consumption of the succinimidyl ester, the reaction was diluted with dichloromethane, washed with 5% $HCl_{(aq)}$, water and brine, then dried ($MgSO_4$) and filtered. After removal of the solvent the residue was purified by flash column chromatography (EtOAc) to give the *title compound* **19** (1.22 g, 69%) as a white solid. R_f 0.4 (EtOAc); m.p. 135–136 °C; IR: ν_{max}/cm^{-1} 3352, 3325, 2976, 2941, 1698 , 1679, 1642, 1544, 1525, 1445; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.49 (t, J = 7.1 Hz, 2H), 3.22 – 3.24 (m, 2H), 3.29–3.83 (m, 2H), 3.82 (t, J = 7.1 Hz, 2H), 5.03 (br s, 1H), 6.43 (br s, 1H), 6.69 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3, 34.3, 34.7, 40.1, 40.7, 79.6, 134.2, 156.9, 170.3, 170.5; HRMS-ESI: $[M + Na]^+$ Calcd for $C_{14}H_{21}N_3O_5Na$ 334.1373, found 334.1403; Anal. Calcd for $C_{14}H_{21}N_3O_5$: C, 54.01; H, 6.80; N, 13.50; Found: C, 53.83; H, 6.81; N, 13.33.

***tert*-Butyl (2-(3-(3-bromo-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)propanamido)ethyl)carbamate (20)**

Maleimide **19** (1.00 g, 3.21 mmol) was dissolved in carbon tetrachloride (12.5 mL) and treated with bromine (0.18 mL, 3.53 mmol) then heated at reflux for 1 h. Upon cooling, the precipitate was collected by vacuum filtration and re-dissolved in anhydrous THF (15 mL). The solution was cooled to 0 °C and anhydrous NEt_3 (0.45 mL, 3.21 mmol) added dropwise followed by stirring for 2 h. Volatiles were removed *in vacuo* and the residue partitioned between ethyl

acetate and water. The organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Removal of solvent under vacuum gave the crude bromomaleimide which was purified by flash column chromatography (EtOAc) to provide the *title compound* **20** (708 mg, 57%) as an off-white solid. R_f 0.5 (EtOAc); M.p. 156-158 °C (decomposition); IR: ν_{max}/cm^{-1} 3343, 3323, 3095, 2984, 2941, 1712, 1678, 1645; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.51 (t, *J* = 7.1 Hz, 2H), 3.22–3.25 (m, 2H), 3.31–3.34 (m, 2H), 3.87 (t, *J* = 7.1 Hz, 2H), 4.93 (s, 1H), 6.33 (s, 1H), 6.86 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.4, 34.5, 35.2, 40.1, 40.9, 79.8, 131.4, 132.0, 157.0, 165.1, 168.2, 169.9; HRMS-ESI: $[M + Na]^+$ Calcd for $C_{14}H_{20}{}^{79}BrN_3O_5Na^+$ 412.0479, found 412.0498; HPLC t_R = 9.1 min.

***tert*-Butyl (2-(3-(3a-bromo-4,7-dimethyl-1,3,8-trioxo-5,6-diphenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindol-2(2*H*)-yl)propanamido)ethyl)carbamate (21)**

Bromomaleimide **20** (200 mg, 0.51 mmol) and diene dimer **15** (140 mg, 0.54 mmol) were dissolved in toluene (5 mL) and heated at reflux for 4 h under nitrogen. The solvent was removed under vacuum and the crude residue purified by flash column chromatography (1:1 EtOAc/Petrol) to give the *title compound* **21** (310 mg, 93%) as a 3:1 mixture of *endo*- and *exo*-isomers in the form of a white solid. M.p. 97–100 °C; IR: ν_{max}/cm^{-1} 3325 (br), 3293 (br), 2978, 2935, 2873, 1782, 1709 (s), 1655, 1514 (br), 1443; HRMS-ESI: $[M + Na]^+$ Calcd for $C_{33}H_{36}{}^{79}BrN_3O_6Na$ 672.1680, found 672.1670; RP-HPLC t_R = 13.5 min.

NMR data for *endo*-**21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ *inter alia* 1.42 (s, 9H), 1.59 (s, 3H), 1.61 (s, 3H), 2.51 (td, *J* = 7.9, 2.2 Hz, 2H), 3.18 – 3.28 (m, 2H), 3.28 – 3.36 (m, 2H), 3.51 (s, 1H), 3.76 – 3.97 (m, 2H), 4.95 (br s, 1H), 6.32 (br s, 1H), 6.80 – 6.90 (m, 4H), 7.12 – 7.29 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ *inter alia* 11.5, 12.3, 28.3, 33.4, 36.1, 40.0, 40.9, 56.4, 57.1, 58.8, 59.0, 60.2, 60.7, 79.8, 126.8, 127.7, 128.0, 128.1, 128.2, 128.3, 128.4, 129.2, 129.2, 129.4, 129.6, 130.4, 132.3, 132.4, 140.3, 144.6, 156.9, 169.5, 172.1, 172.3, 196.8.

NMR data for *exo*-**21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ *inter alia* 1.35 (s, 3H), 1.43 (s, 9H), 1.46 (s, 3H), 2.44 (t, *J* = 6.9 Hz, 2H), 3.37 (s, 1H), 5.06 (br s, 1H,), 6.16 (br s, 1H,), 7.02 – 7.06 (m, 4H,); ^{13}C NMR (125 MHz, $CDCl_3$) δ *inter alia* 8.1, 9.3, 57.1, 58.8, 61.51, 132.6, 132.8, 144.9, 170.3, 170.6.

_N_-(2-Aminoethyl)-3-(3a-bromo-4,7-dimethyl-1,3,8-trioxo-5,6-diphenyl-3a,4,7,7a-tetrahydro-1_H_-4,7-methanoisoindol-2(2_H_)-yl)propanamide hydrochloride (oCOm-19.HCl)

Adduct **21** (230 mg, 0.35 mmol) was dissolved in anhydrous 1,4-dioxane (1 mL) and cooled to 0 °C under nitrogen. A solution of 6 M HCl in 1,4-dioxane (3 mL) was added dropwise and the reaction allowed to warm to rt and stirred overnight. Removal of volatiles under vacuum provided the amine hydrochloride salt which was lyophilized to provide the *title compound* **oCOm-19.HCl** (205 mg, 99%) as a 3:1 mixture of *endo*- and *exo*-isomers in the form of a white solid. M.p. 142 – 148 °C (decomposition); IR: ν_{max}/cm^{-1} 3378 (br), 2979, 2937, 2873, 1781, 1711, 1676, 1520 (br), 1444; HRMS-ESI: $[M - Cl]^+$ Calcd for $C_{28}H_{29}{}^{79}BrN_3O_4$ 550.1336, found 550.1355; Anal. Calcd for $C_{28}H_{29}BrClN_3O_4.H_2O$: C, 55.59; H, 5.17; N, 6.95; Found: C, 55.61; H, 5.19; N, 6.92; RP-HPLC t_R = 8.8 min.

NMR data for *endo*- **oCOm-19.HCl**: ^{1}H NMR (500 MHz, DMSO-d_6) δ *inter alia* 1.45 (s, 3H), 1.48 (s, 3H), 2.38 – 2.45 (m, 2H,), 2.84 (q, *J* = 6.1 Hz, 2H), 3.28 (q, *J* = 6.2 Hz, 2H), 3.75 (td, *J* = 13.5, 6.4 Hz, 2H), 4.00 (s, 1H), 6.91 – 6.82 (m, 4H), 7.19 – 7.26 (m, 6H), 8.03 (br s, 3H), 8.37 (t, *J* = 5.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ *inter alia* 11.2, 11.7, 32.7, 36.0, 36.4, 38.5, 55.7, 58.3, 58.9, 60.1, 128.0, 128.1, 128.3, 129.1, 129.4, 132.3, 132.4, 139.6, 144.6, 169.5, 171.8, 172.3, 196.7.

NMR data for *exo*- **oCOm-19.HCl**: ^{1}H NMR (500 MHz, DMSO-d_6) δ *inter alia* 1.18 (s, 3H), 1.32 (s, 3H), 2.34 (t, *J* = 7.5 Hz, 2H), 3.91 (s, 1H), 8.26 (t, *J* = 5.6 Hz,); ^{13}C NMR (125 MHz, DMSO-d_6) δ *inter alia* 169.4, 197.1.

***tert*-Butyl (2-(3-(4,7-dimethyl-1,3-dioxo-5,6-diphenylisoindolin-2-yl)propanamido)ethyl)carbamate (22)**

Adduct **21** (200 mg, 0.31 mmol) was dissolved in anhydrous THF (5 mL) and DBU (0.09 mL, 0.62 mmol) was added dropwise. The reaction was stirred and monitored by TLC until no starting material remained (1 h). Volatiles were removed under vacuum and the residue taken up in ethyl acetate and washed with 5% $HCl_{(aq)}$. After drying over $MgSO_4$ and filtering the organic extracts, removal of volatiles under vacuum gave the crude aromatized material. Purification by flash column chromatography (3:2 EtOAc/Petrol) provided the *title compound* **22** (147 mg, 88%) as a white solid. R_f 0.2 (1:1 EtOAc/petrol); m.p. 183 – 185 °C; IR: ν_{max}/cm^{-1} 3312 (br), 2974, 2932, 1761, 1700, 1646, 1523 (br), 1443; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.39 (s, 6H), 2.63 (t, *J* = 7.0 Hz, 2H), 3.20 – 3.32 (m, 2H), 3.32 – 3.43 (m, 2H), 4.01 (t, *J* = 7.0 Hz, 2H), 5.09 (br s, 1H), 6.44 (br s, 1H), 6.82 – 6.95 (m, 4H), 7.05 – 7.22 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6, 28.4, 34.1, 35.2, 40.2, 40.6, 79.6, 126.8, 127.7, 128.0, 129.5, 134.5, 138.6, 148.5, 156.7, 169.0, 170.6; HRMS-ESI: $[M + Na]^+$ Calcd for $C_{32}H_{35}N_3O_5Na$ 564.2469, found 564.2455.

***N*-(2-aminoethyl)-3-(4,7-dimethyl-1,3-dioxo-5,6-diphenylisoindolin-2-yl)propanamide hydrochloride (24) (BP-CO-19)**

6 M HCl in anhydrous 1,4-dioxane (3 mL) was added dropwise to a solution of Boc-protected amine **22** (139 mg, 0.26 mmol) in 1,4-dioxane (1 mL) at 0 °C under nitrogen . The reaction was allowed to warm to rt and stirred overnight. Removal of volatiles under vacuum followed by lyophilization provided the *title compound* **BP-CO-19** (117 mg, 95%) as its HCl salt in the form of a white solid. M.p. 185 – 187 °C; IR: ν_{max}/cm^{-1} 3274 (br), 3057, 3024, 2939 (br), 1760, 1695, 1645, 1549, 1495, 1441; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.30 (s, 6H), 2.49 (t, *J* = 5.0

Hz, 2H), 2.78 – 2.91 (m, 2H), 3.25 – 3.32 (m, 2H), 3.82 (t, *J* = 7.3 Hz, 2H), 6.90 – 7.04 (m, 4H), 7.07 – 7.17 (m, 2H), 7.17 – 7.27 (m, 4H), 7.99 (s, 3H), 8.30 (t, *J* = 5.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 15.2, 34.0, 34.0, 36.4, 38.5, 126.9, 127.7, 127.8, 129.3, 133.2, 138.3, 147.8, 168.1, 170.5; HRMS-ESI: $[M - Cl]^+$ Calcd for $C_{27}H_{28}N_3O_3$ 442.2125, found 442.2116. RP-HPLC: t_R = 9.2 min.

_N_-(2-Aminoethyl)-3-(3a-bromo-1_H_-4,7-dimethyl-1,3,8-trioxo-5,6-diphenyl-isoindolin-2(2_H_)-yl) propanamide 2,2,2-trifluoroacetate (oCOm-19.CF_3CO_2H)

6 M HCl in 1,4-dioxane (2 mL) was added to a solution of **21** (305 mg, 0.47 mmol) in 1,4-dioxane (1.4 mL) under a nitrogen atmosphere. The reaction mixture was allowed to warm to rt and monitored by RP-HPLC (10% to 100% B over 12.5 min, then 100% B for 2.5 min, 0.5 mL/min). Upon consumption of the starting material (4-5 h), the solvent was removed *in vacuo*. The residue was dissolved in a mixture of approximately 50% H_2O in 1,4-dioxane (50 mL) and then lyophilised. The off-white solid obtained was dissolved in approximately 20% CH_3CN in H_2O (2 x 5 mL) and then loaded onto a C-18 solid phase extraction cartridge (pre-wash procedure100% CH_3CN [2 x 10 mL], then 90%, then 50% CH_3CN in H_2O [1 x 10 mL each], 20% CH_3CN in H_2O [2 x 10 mL]). The compound was eluted from the C-18 cartridge (20% to 40% CH_3CN in H_2O [10% increments, 2 x 10 mL each], then 50% to 100% CH_3CN in H_2O [10% increments, 10 mL each]). The fractions collected were analysed by RP-HPLC (10% to 100% B over 12.5 min, then 100% B for 2.5 min, t_R = 8.99 min) and lyophilised to afford the *title compound* **oCOm-19.CF_3CO_2H** (106.9 mg, 34%, >97% purity, inseparable 10:1 mixture of *endo*:*exo* isomers) as a white powder M.p. 142–148 °C; IR (ATR) ν_{max}/cm^{-1} 3378 (br), 2979, 1937, 2873, 1781, 1711, 1676, 1520 (br), 1444; HRMS (ESI-TOF) *m/z*: $[M - {}^{-}O_2CCF_3]^+$ Calcd for $C_{28}H_{28}{}^{79}BrN_3O_4Na^+$ 572.1155, found 572.1141; RP-HPLC: t_R = 8.99 min, *endo*- and *exo*-isomers co-elute as a single peak.

Endo- **oCOm-19.CF_3CO_2H** NMR data: ^{1}H NMR (400 MHz, DMSO-*d6*) δ *inter alia* 1.45 (s, 3H), 1.49 (s, 3H), 2.41 (t, *J* = 8.0 Hz, 2H), 2.84 (q, *J* = 6.0 Hz, 2H), 3.25 (q, *J* = 6.0 Hz, 2H), 3.71–3.79 (m, 2H), 4.00 (s, 1H), 6.85–6.88 (m, 4H), 7.17–7.29 (m, 6H), 7.68 (br s, 3H), 8.21 (t, *J* = 6.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ *inter alia* 11.2, 11.7, 32.7, 36.0, 36.4, 38.7, 55.7, 58.3, 58.9, 60.0, 128.0, 128.1, 128.3, 129.1, 129.4, 132.3, 132.4, 139.5, 144.6, 169.8, 171.9, 172.3, 196.7; ^{19}F NMR (376 MHz, DMSO-*d6*) δ -73.74.

Exo-**oCOm-19.CF_3CO_2H** NMR data: ^{1}H NMR (400 MHz, DMSO-*d6*) δ *inter alia* 1.19 (s, 3H), 1.32 (s, 3H), 3.92 (s, 1H).

A further fraction containing mixture of **oCOm-19** and **22** (112.4 mg, 3:1) was also isolated.

***tert*-Butyl *N*-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethylcarbamate (24)**

To a solution of *tert*-butyl (2-ethylamino)carbamate (1.13 g, 7.1 mmol) in saturated $NaHCO_3$ (35 mL) at 0 ºC was added *N*-(ethoxycarbonyl)maleimide[5] (**23**) (1.1 g, 7.1 mmol). The reaction mixture was warmed to rt and stirred for 15 min. THF (55 mL) was then added and the reaction mixture stirred for a further 45 min. H_2O (50 mL) was added and the aqueous phase extracted with EtOAc (3 x 75 mL). The combined organic extracts were washed with saturated NaCl (100 mL) and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an off-white solid that was purified by flash chromatography (0%, then 5%, then 10% EtOAc in CH_2Cl_2) to afford the *title compound* **24** (1.1 g, 58%) as a white solid. M.p. 126–128 °C; R_f (10% EtOAc in CH_2Cl_2) 0.3; IR (ATR) ν_{max}/cm^{-1} 3350, 3089, 2977, 1701, 1678 , 1516, 1434, 1288, 1256, 1167, 944, 844, 692, 623; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.30–3.35 (m, 2H), 3.66 (t, *J* = 6.0 Hz, 2H), 4.74 (br s, 1H), 6.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 38.0, 39.4, 79.5, 131.1, 155.9, 170.8. The ^{1}H and ^{13}C NMR data obtained were in agreement with those reported from literature.[6]

***tert*-Butyl 3-(3-bromo-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethylcarbamate (26)**

A solution of **24** (2.0 g, 8.32 mmol) in CH_2Cl_2 (12 mL) was treated with bromine (470 μL, 9.13 mmol) and heated at reflux for 1 h. The reaction was cooled to rt and concentrated *in vacuo* to give the dibrominated intermediate as a thick orange oil which was then diluted in anhydrous THF (40 mL) and cooled to 0 °C. Anhydrous NEt_3 (1.16 mL, 8.32 mmol) was added drop-wise and the reaction mixture stirred for 2 h at 0 °C. The resulting thick off-white suspension was diluted in H_2O (20 mL) and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a dark brown oil that was purified by flash chromatography (0%, then 5%, then 10% EtOAc in CH_2Cl_2) to afford the *title compound* **26** (1.944 g, 73%) as a pale yellow solid. M.p. 90–93 °C; R_f (10% EtOAc in CH_2Cl_2) 0.3; IR (ATR) ν_{max}/cm^{-1} 3354, 2970, 1702, 1681, 1523, 1406, 1284, 1246, 1160; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.32 – 3.36 (m, 2H), 3.70 (t, J = 6.0 Hz, 2H), 4.70 (br s, 1H), 6.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 39.1, 39.2, 79.7, 131.4, 131.9, 156.0, 165.4, 168.6; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{11}H_{15}{}^{79}BrN_2O_4Na^+$ 341.0107, found 341.0102. Anal. Calcd for $C_{11}H_{15}BrN_2O_4$: C, 41.40; H, 4.74; N, 8.78; Br, 25.04. Found: C, 41.41; H, 4.51; N, 8.76; Br, 25.23.

***tert*-Butyl (2-(3a-bromo-4,7-dimethyl-1,3,8-trioxo-5,6-diphenyl-3a,4,7,7a-tetrahydro-2*H*-4,7-methanoisoindol-2-yl)ethyl)carbamate (28)**

Boc-bromomaleimide **26** (356 mg, 1.11 mmol) and **15** (305 mg, 0.59 mmol) were dissolved in anhydrous toluene (6.5 mL) and placed under argon. The mixture was then heated at reflux for 4 h. After cooling to rt, the solvent was removed *in vacuo* to afford a brown oil containing cycloadduct (**28**) as a 2.5:1 mixture of *endo*- and *exo*-isomers. Purification by flash chromatography (0%, then 2%, then 10% EtOAc in CH_2Cl_2) afforded the *title compound* **28** as a white foamy solid in two fractions: the pure *endo*-isomer (204 mg, 32%) and a ~1:1 mixture

of *endo*- and *exo*-isomers (333 mg, 52%). *Endo*-**28** data: M.p. 107–109 °C; R_f (2% EtOAc in CH_2Cl_2) 0.1; IR (ATR) ν_{max}/cm^{-1} 2984, 2937, 1790, 1713, 1390, 1366, 1248, 1201; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.61 (s, 3H), 1.62 (s, 3H), 3.37 – 3.39 (m, 2H), 3.52 (s, 1H), 3.73 (t, J = 5.8 Hz, 2H), 4.72 (br s, 1H), 6.83 – 6.88 (m, 4H), 7.15 – 7.19 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.5, 12.4, 28.4, 38.7, 40.0, 56.3, 58.7, 60.4, 60.8, 79.8, 128.1, 128.3, 128.3, 129.3, 129.6, 132.4, 132.5, 140.4, 144.5, 155.8, 172.4, 172.7, 196.9; HRMS (ESI-TOF) *m/z*: $[M - Boc + H]^+$ Calcd for $C_{25}H_{24}{}^{79}BrN_2O_3^+$ 479.0965; Found 479.0949. $[M + Na]^+$ Calcd for $C_{30}H_{31}{}^{79}BrN_2O_5Na^+$ 601.1309 found 601.1303; Anal. Calcd for $C_{30}H_{31}BrN_2O_5$: C, 62.18; H, 5.39; N, 4.83; Br, 13.79. Found: C, 62.16; H, 5.39; N, 4.89; Br, 13.89; RP-HPLC: t_R = 14.56 min.

Exo-**28** data: RP-HPLC: t_R = 14.97 min.

2-(3a-Bromo-4,7-dimethyl-1,3,8-trioxo-5,6-diphenyl-2*H*-4,7-methanoisoindolin-2-yl)ethan-1-aminium 2,2,2-trifluoroacetate (oCOm-21)

6 M HCl in 1,4-dioxane (6 mL) was added to a solution of *endo*-**28** (400 mg, 0.69 mmol) in 1,4-dioxane (2 mL) at 0 °C. The solution was warmed to rt and monitored by RP-HPLC. Upon consumption of the starting material (4-5 h), the solvent was removed *in vacuo*. The residue was dissolved in a mixture of approximately 75% H_2O in 1,4-dioxane (40 mL) and lyophilised. The crude off-white solid obtained was dissolved in approximately 16% CH_3CN in H_2O (12 mL) and loaded onto a C-18 solid phase extraction cartridge (pre-wash procedure as described for the preparation of **oCOm-19.TFA**). The product was eluted from the C-18 cartridge (20% to 40% CH_3CN in H_2O [10% increments, 2 x 10 mL each], then 50% to 100% CH_3CN in H_2O [10% increments, 10 mL each]). The fractions collected were analysed by RP-HPLC and lyophilised to afford the *title compound* **oCOm-21.TFA** (259 mg, 63%) as a white powder. IR (ATR) ν_{max}/cm^{-1} 2937, 1781, 1711 , 1664, 1648, 1443, 1388, 1203, 1180, 1134, 798, 723, 697; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.46 (s, 3H), 1.52 (s, 3H), 2.95 – 3.07 (m, 2H), 3.77 –

3.81 (m, 2H), 3.93 (s, 1H), 6.83 – 6.87 (m, 4H), 7.20 – 7.24 (m, 6H,), 7.90 (br s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 11.3, 11.8, 36.5, 37.0, 55.6, 58.5, 58.7, 60.5, 128.1, 128.2, 128.2, 128.3, 129.1, 129.3, 132.2, 132.3, 139.5, 144.5, 172.0, 172.6, 196.5; ^{19}F NMR (376 MHz, DMSO-*d6*) δ -73.97; HRMS (ESI-TOF) *m/z*: $[M - {}^{-}O_2CCF_3]^+$ Calcd for $C_{25}H_{24}{}^{79}BrN_2O_3{}^+$ 479.0965, found 479.0978; RP-HPLC: t_R = 9.00 min.

2-(3a-Bromo-4,7-dimethyl-1,3,8-trioxo-5,6-diphenyl-2H-4,7-methanoisoindolin-2-yl)ethan-1-aminium chloride (oCOm-21.HCl)

A solution of *endo*-**28** (200 mg, 0.35 mmol) in 1,4-dioxane (1 mL) was mixed with 6 M HCl in 1,4-dioxane (2 mL) at 0 ºC. The reaction mixture was allowed to warm to rt and monitored by RP-HPLC. Upon consumption of the starting material (4 h), the solvent was removed *in vacuo*. The residue was dissolved in a mixture of approximately 75% H_2O in 1,4-dioxane (40 mL) and lyophilised to give the *title compound* **oCOm-21.HCl** as a pale brown powder (175 mg, 98%). ^{1}H NMR (500 MHz, DMSO-*d6*) δ 1.45 (3H, s), 1.52 (s, 3H), 2.90 – 3.05 (m, 2H), 3.78 –3 .83 (m, 2H), 3.93 (s, 1H), 6.8 3– 6.87 (m, 4H), 7.20 – 7.24 (m, 6H), 8.18 (br s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 11.3, 11.8, 36.4, 36.9, 55.5, 58.6, 58.7, 60.5, 128.1, 128.1, 128.2, 128.3, 129.1, 129.3, 132.2, 132.3, 139.5, 144.5, 172.0, 172.6, 196.5; HRMS (ESI-TOF) *m/z*: $[M - {}^{-}O_2CCF_3]^+$ Calcd for $C_{25}H_{24}{}^{79}BrN_2O_3{}^+$ 479.0965, found 479.0932; RP-HPLC: t_R = 9.00 min.

***tert*-Butyl (2-(4,7-dimethyl-1,3-dioxo-5,6-diphenylisoindolin-2-yl)ethyl)carbamate (30)**

To a solution of **28** (414 mg, 0.71 mmol, *endo:exo* 2.5:1) in anhydrous THF (12 mL) at 0 ºC was added DBU (210 µL, 1.40 mmol) dropwise. The reaction mixture was allowed to warm to rt. Upon consumption of starting material by TLC (approximately 10 min), saturated NH_4Cl

(7 mL) was added and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford a brown crystalline solid. Purification by flash chromatography (0%, then 5%, then 10% EtOAc in CH_2Cl_2) afforded the *title compound* **30** (205 mg, 61%) as a white solid. M.p. 181–182 °C; R_f (10% EtOAc in CH_2Cl_2) 0.4; IR (ATR) ν_{max}/cm^{-1} 3431, 2981, 2944, 1758, 1725, 1698, 1504, 1431, 1401, 1391; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.41 (s, 6H), 3.42 – 3.47 (m, 2H), 3.85 (t, J = 5.6 Hz, 2H), 4.89 (br s, 1H), 6.87 – 6.89 (m, 4H), 7.10 – 7.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 28.3, 37.6, 39.9, 79.4, 126.8, 127.8, 128.1, 129.5, 134.4, 138.7, 148.4, 155.9, 169.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{29}H_{30}N_2NaO_4^+$ 493.2098, found 493.2097; Anal. Calcd for $C_{29}H_{30}N_2O_4$: C, 74.02; H, 6.43; N, 5.95. Found: C, 74.00; H, 6.52; N, 5.91; RP-HPLC: t_R = 15.21 min.

2-(4,7-Dimethyl-1,3-dioxo-5,6-diphenylisoindolin-2-yl)ethanaminium 2,2,2-trifluoroacetate (BP-CO-21)

A solution of **30** (204 mg, 0.43 mmol) in 1,4-dioxane (9 mL) and 6 M HCl in 1,4-dioxane (4 mL) at rt was monitored by RP-HPLC. Upon consumption of the starting material (4-5 h), the solvent was removed *in vacuo*. The residue was dissolved in a mixture of approximately 60% H_2O in 1,4-dioxane (20 mL) and lyophilised. The crude off-white solid obtained was dissolved in approximately 10% CH_3CN in H_2O (2 x 5 mL) and loaded onto a pre-washed C-18 solid phase extraction cartridge (100% CH_3CN [2 x 10 mL]), then 90%, then 50% CH_3CN in H_2O [1 x 10 mL each], 20% CH_3CN in H_2O [2 x 10 mL]). The product was eluted from the C-18 cartridge (20% to 40% CH_3CN in H_2O [10% increments, 2 x 10 mL each], then 50% to 100% CH_3CN in H_2O [10% increments, 10 mL each]). The fractions collected were analysed by RP-HPLC and lyophilised to afford the *title compound* **BP-CO-21** (163 mg, 78%) as a white powder. M.p.113 °C (decomposition); IR (ATR) ν_{max}/cm^{-1} 1763, 1697, 1664, 1430, 1403, 1364;

^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.32 (s, 6H), 3.11 (q, *J* = 6.0 Hz, 2H), 3.86 (t, *J* = 6.0 Hz, 2H), 6.95 – 6.97 (m, 4H), 7.13 – 7.17 (m, 2H), 7.20 – 7.24 (m, 4H), 7.85 (br s, 3H,); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 15.2, 35.1, 37.7, 126.9, 127.8, 128.0, 129.3, 133.3, 138.2, 147.8, 168.4; ^{19}F NMR (376 MHz, DMSO-*d6*) δ -73.78; HRMS (ESI-TOF) *m/z*: $[M - {}^{-}O_2CCF_3]^+$ Calcd for $C_{24}H_{23}N_2O_2^+$ 371.1754, found 371.1741; RP-HPLC: t_R = 9.22 min.

***tert*-Butyl (2-aminoethyl)(2-((tert-butoxycarbonyl)amino)ethyl)carbamate**

A solution of ethyl trifluoroacetate (4 mL, 33.6 mmol) in anhydrous CH_2Cl_2 (40 mL) was slowly added to a solution of diethyltriamine (3.6 mL, 33.6 mmol) in anhydrous CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then rt for a further 2 h. The solvent was removed *in vacuo* to obtain a yellow oil that was re-dissolved in anhydrous CH_2Cl_2 (66 mL) and cooled to 0 °C. A solution of Boc_2O (14.8 g, 68 mmol) in anhydrous CH_2Cl_2 (66 mL) was added over 1 h by dropping funnel and the reaction mixture was allowed to stir at rt for 48 h. Removal of the solvent *in vacuo* gave a thick yellow oil that was taken up in a solution of 5% H_2O in CH_3OH (75 mL). $K_2CO_{3\ (s)}$ (26 g, 188 mmol) was added and the suspension refluxed for 2.5 h. Upon cooling, the CH_3OH was removed *in vacuo* and the residue diluted in distilled H_2O (100 mL). The pH was adjusted to ~13 using 15% (w/v) aqueous NaOH and the aqueous phase extracted with $CHCl_3$ (3 x 100 mL). The solvent was removed *in vacuo* and purified by flash chromatography (0%, then 5% EtOAc in CH_2Cl_2 with 5% NEt_3, then 10% CH_3OH in $CHCl_3$ with 5% NEt_3) to yield the title compound (4.2 g, 41%) as a yellow oil that solidified upon cooling to form a waxy yellow solid.

M.p. 77–80 °C; R_f (10% EtOAc in CH_2Cl_2 and 5% NEt_3) 0.1; R_f (10% CH_3OH in $CHCl_3$ and 5% NEt_3) 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ *inter alia* 1.41 – 1.44 (m, 18H), 2.90 – 2.93 (m, 2H), 3.23 – 3.26 (m, 4H), 3.29 – 3.33 (m, 4H), 5.28 – 5.45 (m, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ *inter alia* 28.3, 28.4, 39.2, 39.6, 40.2, 40.4, 47.6, 48.2, 49.6, 50.3, 79.2, 80.3, 156.2. The ^1H and ^{13}C NMR data obtained were in agreement with those reported in literature.[7]

tert-Butyl (2-((_tert_-butoxycarbonyl)amino)ethyl)(2-(2,5-dioxo-2,5-dihydro-1_H_-pyrrol-1-yl)ethyl)carbamate (25)

To a suspension of crude *tert*-butyl (2-aminoethyl)-(2-((tert-butoxycarbonyl)amino)ethyl)carbamate (11.1 g, 36.6 mmol) in saturated $NaHCO_3$ (180 mL) at rt was added powdered *N*-(ethoxycarbonyl)maleimide (**23**)[5] (6.2 g, 36.7 mmol). After stirring the reaction mixture for 15 min, THF was added (280 mL) and the resulting biphasic suspension was stirred vigourously at rt for 2 h. H_2O (100 mL) was then added and the aqueous phase extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with saturated NaCl (150 mL), dried over $MgSO_4$ and then concentrated *in vacuo* to afford an orange oil. Purification by flash chromatography (0%, then 5%, then 10%, then 50% EtOAc in CH_2Cl_2) gave a 1:1 mixture of the *title compound* **25** and ethyl carbamate (3.7 g) as a yellow oil.

An analytically pure sample of **25** was obtain on re-purification by flash chromatography (0%, then 5%, then 20% EtOAc in CH_2Cl_2, then 100% EtOAc) to afford the *title compound* **25** as a pale yellow oil that forms colourless crystals upon cooling. M.p. 105–107 °C; R_f (20% EtOAc in CH_2Cl_2) 0.4; IR (ATR) ν_{max}/cm^{-1} 2976, 2929, 1708, 1671, 1508, 1404, 1364; ^1H NMR (500 MHz, $CDCl_3$) δ *inter alia* 1.37 – 1.40 (m, 18H), 3.21 – 3.29 (m, 4H), 3.38 – 3.40 (m, 2H), 3.62 – 3.67 (m, 2H), 5.07 (br s, 1H), 6.65 – 6.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ *inter alia* 28.2, 28.3, 35.9, 36.2, 39.4, 45.6, 45.9, 46.5, 47.7, 79.1, 80.1, 80.3, 134.1, 134.1, 134.2, 155.6, 155.8, 156.0, 170.3, 170.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{29}N_3O_6Na^+$ 406.1949 found 406.1968.

***tert*-Butyl (3-(4-bromo-1,3-dioxo-1,3-dihydro-1*H*-pyrrol-1-yl)ethyl)(4-((*tert*-butoxycarbonyl)amino)ethyl)carbamate (27)**

To a solution containing a 1:1 mixture of maleimide **25** and ethyl carbamate (1.81 g, 4.7 mmol) in CH_2Cl_2 (25 mL) was added bromine (270 µL, 5.2 mmol) at rt. The dark brown solution was heated to reflux for 1.5 h and then cooled to rt. Removal of the solvent *in vacuo* gave a thick orange gum that was dissolved in anhydrous THF (25 mL) and cooled to 0 °C under argon. Anhydrous NEt_3 (730 µL, 5.2 mmol) was added dropwise at 0 °C and the resulting orange suspension was stirred at 0 °C for 4 h. H_2O (30 mL) was then added at 0 °C and the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford a brown-yellow oil. Purification by flash chromatography (0%, then 5%, then 10%, then 20% EtOAc in CH_2Cl_2) gave the *title compound* **27** (550 mg, 25%) as a yellow oil and an approximate 1:1 mixture of **27** and ethyl carbamate (806 mg). R_f (20% EtOAc in CH_2Cl_2) 0.4; IR (ATR) ν_{max}/cm^{-1} 3370, 2976, 2933, 1716, 1677, 1508; ^{1}H NMR (500 MHz, $CDCl_3$) δ *inter alia* 1.39 – 1.46 (m, 18H), 3.24 – 3.32 (m, 4H), 3.40–3.43 (m, 2H), 3.69 – 3.73 (m, 2H), 5.06 – 5.10 (m, 1H), 6.85–6.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ *inter alia* 28.2, 28.4, 36.8, 37.3, 39.1, 39.4, 45.4, 45.9, 46.3, 47.8, 79.1, 79.3, 80.3, 80.5, 131.3, 131.5, 131.9, 131.9, 132.0, 155.8, 155.9, 156.1, 165.0, 165.5, 168.1, 168.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{28}{}^{79}BrN_3O_6Na^+$ 484.1054, found 484.1074.

***tert*-Butyl (2-(3a-bromo-4,7-dimethyl-1,3,8-trioxo-5,6-diphenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindol-2(2*H*)-yl)ethyl)(2-((tert-butoxycarbonyl)amino)ethyl)carbamate (29)**

A suspension of bromomaleimide **27** (275 mg, 0.60 mmol) and diene dimer **15** (163 mg, 0.31 mmol) in anhydrous toluene (5 mL) was placed under an argon atmosphere and then heated to reflux for 4 h. The reaction mixture was cooled to rt and the solvent removed *in vacuo* to afford a brown oil. Purification by flash chromatography (0%, then 5%, then 10% EtOAc in CH_2Cl_2) afforded the *endo*-isomer of the *title compound* **29** (261 mg, 60%) as a colourless foam and a 2:1 mixture of the *endo*:*exo*-isomers of **29** as a thick yellow oil (115 mg, 27%).

Data for *endo*-**29**: M.p. 73–78 °C (decomp.); R_f (10% EtOAc in CH_2Cl_2) 0.5; IR (ATR) ν_{max}/cm^{-1} 2976, 2922, 1791, 1716, 1685, 1391; ^{1}H NMR (500 MHz, $CDCl_3$) δ *inter alia* 1.41 – 1.48 (m, 18H), 1.60 (s, 3H), 1.61 (s, 3H), 3.25 – 3.32 (m, 4H), 3.45 – 3.51 (m, 3H), 3.74 – 3.75 (m, 2H), 4.94 (br s, 1H), 6.83 – 6.86 (m, 4H), 7.16 – 7.20 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ *inter alia* 11.5, 12.4, 28.4, 37.9, 38.5, 39.4, 44.6, 45.0, 45.0, 46.7, 47.8, 56.2, 56.4, 58.7, 60.4, 61.0, 79.3, 80.6, 80.8, 128.1, 128.1, 128.2, 128.3, 129.3, 129.6, 132.4, 132.4, 132.5, 140.4, 144.6, 155.7, 155.9, 172.2, 172.6, 196.8, 197.0; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{37}H_{44}{}^{79}BrN_3O_7Na^+$ 744.2255, found 744.2231; RP-HPLC: t_R = 15.61 min.

Exo-**29**: R_f (10% EtOAc in CH_2Cl_2) 0.37; RP-HPLC: t_R = 15.61 min.

2-(2-(2-Aminoethyl)aminoethyl)-3a-bromo-3a,4,7,7a-tetrahydro-4,7-dimethyl--5,6-diphenyl-4,7-methano-1*H*-isoindole-1,3,8(2*H*)-trione bis-trifluoroacetate salt (oCOm-23)

A solution of *endo*-**29** (261 mg, 0.36 mmol) in 1,4-dioxane (2 mL) and 6 M HCl in 1,4-dioxane (3 mL) at 0 °C was warmed to rt and monitored by RP-HPLC. Upon consumption of the starting material (4 h), the solvent was removed *in vacuo* to afford an off-white solid that was dissolved in distilled H_2O (40 mL) and then lyophilised to obtain a crude fluffy powder. The crude product was dissolved in 10% CH_3CN in H_2O (2 x 5 mL) and loaded onto a C-18 solid phase extraction cartridge (pre-wash procedure as for the preparation of **oCOm-19.TFA**). The

product was eluted from the C-18 cartridge (20% to 40% CH_3CN in H_2O [10% increments, 2 x 10 mL each], then 50% to 100% CH_3CN in H_2O [10% increments, 10 mL each]). The fractions collected were analysed by RP-HPLC and lyophilised to afford the *endo*-isomer of the *title compound* **oCOm-23** (171 mg, 63%) as a white fluffy powder. M.p. 111–114 °C (decomp.); IR (ATR) ν_{max}/cm^{-1} 2965, 1786, 1715, 1670; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.46 (s, 3H), 1.52 (s, 3H), 3.12 – 3.20 (m, 6H), 3.79 – 3.90 (m, 2H), 3.99 (s, 1H), 6.84 – 6.88 (m, 4H), 7.21 – 7.24 (m, 6H), 8.11 (br s, 3H), 9.26 – 9.31 (m, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 11.3, 11.8 , 35.2, 35.7, 43.7, 44.1, 55.6, 58.6, 60.5, 128.1, 128.2, 128.3, 128.3, 129.2, 129.3, 132.2, 132.3, 139.5, 144.6, 171.9, 172.5, 196.5; ^{19}F NMR (376 MHz, DMSO-*d6*) δ –73.67, –73.66; HRMS (ESI-TOF) *m/z*: $[M - [^-O_2CCF_3]_2 - H]^+$ Calcd for $C_{27}H_{29}{}^{79}BrN_3O_3{}^+$ 522.1387, found 522.1364; RP-HPLC (10% to 100% B over 12.5 min, then 100% B for 7.5 min, with a flow rate of 0.5 mL min^{-1}): t_R = 7.96 min.

tert-Butyl (3-((_tert_-butoxycarbonyl)amino)ethyl)(2-(4,7-dimethyl-1,3-dioxo-5,6-diphenylisoindolin-2-yl)ethyl)carbamate (31)

To a solution of adduct **29** (220 mg, 0.31 mmol, *endo:exo* ~1:1) in anhydrous THF (5 mL) at 0 ºC was added DBU (90 µL, 0.60 mmol) dropwise. The brown reaction mixture was then allowed to warm to rt. Upon consumption of the starting material by TLC (approximately 30 min), a brown precipitate had formed and saturated NH_4Cl (20 mL) was then added. The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford a brown crystalline solid. Purification by flash chromatography (0%, then 5%, then 10% EtOAc in CH_2Cl_2) furnished the *title compound* **31** (142 mg, 76%) as a white solid. M.p. 202–205 °C (decomp.); R_f (5% EtOAc in CH_2Cl_2) 0.17, R_f (10% EtOAc in CH_2Cl_2) 0.5; IR (ATR) ν_{max}/cm^{-1} 3345, 2976, 2922, 1702, 1677, 1518, 1402, 1381; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 – 1.35 (m, 9H), 1.44 (s, 9H), 2.39

(s, 6H), 3.31 – 3.41 (m, 4H), 3.51 – 3.55 (m, 2H), 3.83 – 3.86 (m, 2H), 5.17 – 5.30 (m, 1H), 6.86 – 6.88 (m, 4H), 7.09 – 7.17 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6, 15.6, 28.0, 28.0, 28.1, 28.4, 35.8, 36.2, 39.4, 39.5, 45.8, 46.3, 46.6, 48.1, 79.1, 79.9, 80.1, 126.7, 126.8, 127.7, 128.1, 128.2, 129.4, 134.1, 134.4, 138.6, 138.8, 148.1, 148.5, 155.7, 156.0, 168.9, 169.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{36}H_{43}N_3O_6Na^+$ 636.3044, found 636.3071; RP-HPLC (10% to 100% B over 12.5 min, then 100% B for 7.5 min, with a flow rate of 0.5 mL min^{-1}): t_R = 16.23 min.

2-(2-(2-Aminoethyl)aminoethyl)-4,7-dimethyl-5,6-diphenyl-1*H*-isoindole-1,3,8(2*H*)-dione bis-trifluoroacetate salt (BP-CO-23)

6 M HCl in 1,4-dioxane (1.7 mL) was added dropwise to a suspension of **31** (120 mg, 0.20 mmol) in 1,4-dioxane (2 mL) at rt. Additional quantities of 1,4-dioxane (7 mL) and distilled H_2O (5 mL) were added. The reaction mixture was monitored by RP-HPLC. After stirring for 6 h, the reaction mixture was heated to 30 °C for 14.5 h and then 50 °C for 7 h. The solvent was removed *in vacuo* to afford a white precipitate that was dissolved in 10% 1,4-dioxane in H_2O (22 mL) and lyophilised. The resulting white solid was then dissolved in 10% CH_3CN in H_2O (2 x 5 mL) and loaded onto a C-18 solid phase extraction cartridge (pre-wash procedure as for the preparation of **oCOm-19.TFA**). The product was eluted from the C-18 cartridge (20% to 40% CH_3CN in H_2O [10% increments, 2 x 10 mL each], then 50% to 100% CH_3CN in H_2O [10% increments, 10 mL each]). The fractions collected were analysed by RP-HPLC and lyophilised to afford the *title compound* **BP-CO-23** (102 mg, 82%) as a white powder. IR (ATR) ν_{max}/cm^{-1} 2976, 1765, 1700, 1671, 1429, 1404; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 2.32 (s, 6H), 3.13 (t, *J* = 7.5 Hz, 2H), 3.24 (t, *J* = 7.5 Hz, 2H), 3.33 – 3.34 (m, 2H), 3.92 (t, *J* = 5.0 Hz, 2H), 6.94 – 6.96 (m, 4H), 7.13 – 7.17 (m, 2H), 7.20 – 7.24 (m, 4H), 8.09 (br s, 3H), 9.07 (br s, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 15.2, 34.0, 35.1), 44.1, 45.4, 117.1 (q, $^1J_{C–}$

$_F$ = 1191.7), 126.9, 127.8, 127.9, 129.2, 133.4, 138.2, 147.8, 158.2 (q, $^1J_{C-F}$ = 125.0), 168.3; ^{19}F NMR (376 MHz, DMSO-*d6*) δ -73.75; HRMS (ESI-TOF) *m/z*: [M – [$^-$O$_2$CCF$_3$]$_2$ – H]$^+$ Calcd $C_{26}H_{28}N_3O_2^+$ for 414.2176, found 414.2169; RP-HPLC (10% to 100% B over 12.5 min, then 100% B for 7.5 min, with a flow rate of 0.5 mL min^{-1}): t_R = 8.09 min.

***tert*-Butyl (2-(3-(4,7-dimethyl-1,3,8-trioxo-5,6-diphenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindol-2(3*H*)-yl)propanamido)ethyl)carbamate (32)**

Maleimide (**19**) (90 mg, 0.29 mmol) and diene dimer (**15**) (75 mg, 0.29 mmol) were dissolved in toluene (3 mL) and heated at reflux for 4 h under nitrogen. Solvent was removed under vacuum and the crude residue purified by flash column chromatography (1:1 EtOAc / Petrol) to provide the *title compound* **32** as a white solid (163 mg, 99%) as an 11:1 mixture of *endo*- and *exo*-cycloadducts. R_f 0.1 (3:2 EtOAc / Petrol). IR (ATR) ν_{max}/cm^{-1} 3317 (br), 2973, 2930, 2869, 1787, 1772, 1699, 1652, 1516, 1443; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{33}H_{37}N_3O_6Na$ 594.2575, found 594.2604.

NMR data for *endo* **32**: ^{1}H NMR (500 MHz, $CDCl_3$) δ *inter alia* 1.42 (s, 9H), 1.56 (s, 6H), 2.45 (t, *J* = 7.3 Hz, 2H), 3.18 – 3.25 (m, 2H), 3.24 (s, 2H), 3.26 – 3.32 (m, 2H), 3.81 (t, *J* = 7.3 Hz, 2H), 4.96 (br s, 1H), 6.35 (br s, 1H) 6.82 – 6.95 (m, 4H), 7.11 – 7.22 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ *inter alia* 12.2, 28.3, 33.8, 35.5, 40.1, 40.9, 47.9, 56.5, 79.8, 127.7, 128.0, 128.2, 128.3, 129.0, 129.5, 133.0, 141.6, 169.9, 175.4, 199.5.

NMR data for *exo* **32**: ^{1}H NMR (500 MHz, $CDCl_3$) δ *inter alia* 1.15 (s, 3H), 1.20 (s, 3H), 1.38 (s, 9H), 2.40 (t, *J* = 6.8 Hz, 2H), 3.32 – 3.38 (m, 2H), 5.10 (br s, 1H), 6.18 (br s, 1H), 6.96 – 7.08 (m, 4H), 7.22 – 7.25 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ *inter alia* 9.1, 49.7, 55.5, 173.3, 197.1.

***N*-(2-Aminoethyl)-3-(4,7-dimethyl-1,3,8-trioxo-5,6-diphenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindol-2(3*H*)-yl)propanamide hydrochloride (14) (DB-CO-19)**

Boc-protected amine (**32**) (100 mg, 0.35 mmol) was dissolved in 1,4-dioxane (0.5 mL) with cooling to 0 °C under nitrogen and 6M HCl in 1,4-dioxane (2.5 mL) added dropwise. The reaction allowed to warm to rt and stirred overnight. Removal of volatiles under vacuum followed by lyophilization gave the amine HCl salt (**DB-CO-19**) as a white solid (53 mg, 85%) as a 13:1 mixture of *endo*- and *exo*-isomers. IR (ATR) ν_{max}/cm^{-1} 3317 (br), 2973, 2930, 2869, 1787, 1772, 1699, 1652, 1516, 1443 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M - Cl^-]^+$ Calcd for $C_{28}H_{30}N_3O_4$ 472.2231, found 472.2252. RP-HPLC: t_R = 8.4 min (100%).

NMR data for *endo*-**DB-CO-19**: ^{1}H NMR (500 MHz, DMSO-*d6*) δ *inter alia* 1.41 (s, 6H), 2.31- 2.36 (m, 2H), 2.83 (t, *J* = 6.1 Hz, 2H), 3.25 (q, *J* = 5.9 Hz, 2H), 3.47 (s, 2H), 3.60 – 3.65 (m, 2H), 6.86 – 6.88 (m, 4H), 7.14 – 7.30 (m, 6H), 7.77 (br s, 3H), 8.21 (t, *J* = 5.7 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ *inter alia* 11.9, 30.7, 32.9, 35.1, 36.3, 38.6, 38.6, 47.4, 55.7, 127.6, 128.1, 129.2, 133.1, 141.3, 170.0, 175.8, 199.1, 206.5.

***tert*-Butyl (2-(4,7-dimethyl-1,3,8-trioxo-5,6-diphenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindol-2(2*H*)-yl)ethyl)carbamate (33)**

Maleimide **24** (150 mg, 0.62 mmol) and diene dimer **15** (171 mg, 0.66 mmol) were dissolved in anhydrous toluene (3.6 mL) and placed under argon. The mixture was then heated to reflux for 4 h. After cooling to rt, the solvent was removed *in vacuo* to afford an orange oil that was purified by flash chromatography (0%, then 5%, then 7%, then 20% EtOAc in CH_2Cl_2) to afford an inseparable ~4.2:1 mixture (*endo:exo*) of the *title compound* **33** (300 mg, 52%) as a white foam. M.p. 81 °C (decomp.); IR (ATR) ν_{max}/cm^{-1} 3411, 2977, 2933, 1788, 1770, 1704, 1698, 1693, 1509, 1392; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{30}H_{32}N_2NaO_5^+$

523.2203, found 523.2173; RP-HPLC: t_R = 14.56 min, *endo*- and *exo*-isomers co-elute as a single peak.

Endo-**33** NMR data: ^{1}H NMR (500 MHz, $CDCl_3$) δ *inter alia* 1.40 (s, 9H), 1.57 (s, 6H), 3.23 (s, 2H), 3.32 – 3.35 (m, 2H), 3.64 (t, *J*= 5.0 Hz, 2H), 4.78 (br s, 1H), 6.87 – 6.91 (m, 4H), 7.15 – 7.17 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ *inter alia* 12.2, 28.3, 38.9, 39.6, 48.0, 56.5, 79.5, 127.7, 128.2, 129.5, 133.0, 141.6, 156.1, 175.7, 199.7.

Exo-**33** NMR data: ^{1}H NMR (500 MHz, $CDCl_3$) δ *inter alia* 1.40 (s, 6H), 1.45 (s, 9H), 3.20 – 3.22 (m, 2H), 3.23 (s, 2H), 3.68 (t, *J* = 5.0 Hz, 2H), 4.78 (br s, 1H), 7.03 – 7.05 (m, 4H), 7.23 – 7.25 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ *inter alia* 9.1, 28.3 , 38.1, 38.7, 49.8, 55.7, 79.4, 128.0, 128.3, 129.0, 133.0, 144.4, 155.8, 173.4, 204.7.

2-(4,7-Dimethyl-1,3,8-trioxo-5,6-diphenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindol-2(2*H*)-yl)ethanaminium 2,2,2-trifluoroacetate (DB-CO-21)

6 M HCl in 1,4-dioxane (9 mL) was added to a solution of **33** (513 mg, 1.02 mmol) in 1,4-dioxane (3 mL) at 0 °C. The reaction mixture was allowed to warm to rt and monitored by RP-HPLC. Upon consumption of the starting material (2-3 h) as indicated by the formation of a white precipitate, the solvent was removed *in vacuo* to afford an off-white solid that was dissolved in 16% CH_3CN in H_2O (15 mL) and loaded onto a C-18 solid phase extraction cartridge (pre-wash procedure as for the preparation of **oCOm-19.TFA**). The product was eluted from the C-18 cartridge (20% to 40% CH_3CN in H_2O [10% increments, 2 x 10 mL each], then 50% to 100% CH_3CN in H_2O [10% increments, 10 mL each]). The fractions collected were analysed by RP-HPLC and lyophilised to afford an inseparable ~4.1:1 mixture (*endo:exo*) of the *title compound* **DB-CO-21** (407 mg, 73%) as a pale yellow oil. IR (ATR) ν_{max}/cm^{-1} 2984, 2933, 1790, 1774, 1736, 1702, 1697, 1670, 1394; HRMS (ESI-TOF) *m/z*: [M – $^-$

$O_2CCF_3]^+$ Calcd for $C_{25}H_{25}N_2O_3^+$ 401.1860, found 401.1840; RP-HPLC: t_R = 8.60 min, *endo*- and *exo*-isomers co-elute as a single peak.

Endo-**DB-CO-21** NMR data: ^{1}H NMR (400 MHz, DMSO-*d6*) δ *inter alia* 1.43 (s, 6H), 2.93–2.97 (m, 2H), 3.51 (s, 2H), 3.67 (t, *J* = 8.0 Hz, 2H), 6.84 – 6.87 (m, 4H), 7.17 – 7.28 (m, 6H), 7.81 (br s, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ *inter alia* 11.8, 36.1, 36.7, 47.7, 55.8, 127.6, 128.1, 129.2, 133.1, 141.3, 176.1, 199.0; ^{19}F NMR (376 MHz, DMSO-*d6*) δ -73.77.

Exo-**DB-CO-21** NMR data: ^{1}H NMR (400 MHz, DMSO-*d6*) δ *inter alia* 1.19 (s, 6H).

tert-Butyl (2-((_tert_-butoxycarbonyl)amino)ethyl)(2-(4,7-dimethyl-1,3,8-trioxo-5,6-diphenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindol-2(2*H*)-yl)ethyl)carbamate (34)

A suspension of maleimide **25** (109 mg, 0.28 mmol) and diene dimer **15** (111 mg, 0.29 mmol) in anhydrous toluene (2 mL) was placed under an argon atmosphere. The mixture was heated to reflux for 4 h and then allowed to cool to rt. The solvent was removed under reduced pressure to afford a brown oil. Purification by flash chromatography (0%, then 10%, then 20% EtOAc in CH_2Cl_2) furnished the *title compound* **34** (80 mg, 43%) as an inseparable mixture of *endo*- and *exo*-isomers (11:1) as a colourless foam. R_f (20% EtOAc in CH_2Cl_2) 0.3; IR (ATR) ν_{max}/cm^{-1} 2980, 2936, 1790, 1702, 1677, 1392; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{37}H_{45}N_3O_7Na^+$ 666.3150, found 666.3169.

Endo-**34** NMR data: ^{1}H NMR (500 MHz, $CDCl_3$) δ *inter alia* 1.42–1.46 (18H, m), 1.56 (s, 6H,), 3.18 – 3.24 (m, 4H), 3.27 – 3.31 (m, 2H), 3.37 – 3.45 (m, 2H), 3.64 – 3.68 (m, 2H), 4.96–5.17 (m, 1H), 6.87 – 6.89 (m, 4H), 7.15 – 7.16 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ *inter alia* 12.2, 28.3, 28.4, 37.3, 37.9, 39.6, 44.8, 45.4, 48.1, 48.2, 56.4, 79.3, 79.4, 80.2, 127.6, 128.1, 129.6, 133.1, 141.7, 156.0, 156., 175.2, 175.9, 199.5, 200.0; RP-HPLC (10% to 100% B over 12.5 min, then 100% B for 7.5 min, with a flow rate of 0.5 mL min^{-1}): t_R = 14.97 min.

Exo-**34** NMR data: ^{1}H NMR (500 MHz, $CDCl_3$) δ *inter alia* 1.38 (s, 6H), 7.01-7.05 (m, 4H), 7.23–7.24 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ *inter alia* 9.1, 46.6, 128.3, 129.0; RP-HPLC: t_R = 15.19 min.

2-(2-(2-Aminoethyl)aminoethyl)-3a,4,7,7a-tetrahydro-4,7-dimethyl--5,6-diphenyl-4,7-methano-1*H*-isoindole-1,3,8(2*H*)-trione bis-trifluoroacetate salt (DB-CO-23)

6 M HCl in dioxane (1 mL) was added dropwise to a suspension of **34** (80 mg, 0.12 mmol) in 1,4-dioxane (1 mL) at rt. Additional 1,4-dioxane (1 mL) was added to allow for dissolution of the precipitate. The reaction mixture was stirred at rt and monitored by RP-HPLC. After stirring for 4 h the solvent was removed *in vacuo*. The resulting yellow precipitate was then dissolved in 10% CH_3CN in H_2O (2 x 5 mL) and loaded onto a pre-washed C-18 solid phase extraction cartridge (100% CH_3CN [2 x 10 mL]), then 90%, then 50% CH_3CN in H_2O [1 x 10 mL each], 10% CH_3CN in H_2O [2 x 10 mL]). The product was eluted from the C-18 cartridge (20% to 40% CH_3CN in H_2O [10% increments, 2 x 10 mL each], then 50% to 100% CH_3CN in H_2O [10% increments, 10 mL each]). The fractions collected were analysed by RP-HPLC. The initial fractions (20% CH_3CN in H_2O and the first 30% CH_3CN in H_2O collection) were found to contain unknown impurities that co-eluted with **DB-CO-23** and were kept separate. Pending RP-HPLC analysis, the later fractions were pooled and lyophilised to afford the title compound **DB-CO-23** (68 mg, 82%) as an approximate 15:1 mixture of *endo*- and *exo*-isomers in the form of a white powder). IR (ATR) ν_{max}/cm^{-1} 1773, 1707, 1670, 1396, 1199, 1132, 837, 799, 722, 698; HRMS (ESI-TOF) *m/z*: [M – [$^{-}O_2CCF_3$]$_2$ – H]$^{+}$ Calcd for $C_{27}H_{30}N_3O_3^{+}$ 444.2282, found 444.2291; RP-HPLC (10% to 100% B over 12.5 min, then 100% B for 7.5 min, 0.5 mL/min): t_R = 7.47 min.

Endo-**DB-oCOm-23** NMR data: ^{1}H NMR (400 MHz, DMSO-*d6*) δ *inter alia* 1.43 (s, 6H), 3.04 – 3.21 (m, 6H), 3.52 (s, 2H), 3.71 (t, *J* = 5.9 Hz, 2H), 6.85 – 6.88 (m, 4H), 7.18 – 7.22 (m, 6H),

7.93 (br s, 3H), 8.88 (br s, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ *inter alia* 11.8, 34.9, 35.1, 43.8, 44.3, 47.7, 55.8, 127.6, 128.2, 129.3, 133.0, 141.3, 158.5 (CF_3, q, $^2J_{CF}$ 125.0, $^-O_2C\underline{C}F_3$), 176.0, 198.9; ^{19}F NMR (376 MHz, DMSO-*d6*) –73.69, –73.66 (6F, $^-O_2CC\underline{F_3}$).

Exo-**DB-oCOm-23** NMR data: ^{1}H NMR (400 MHz, DMSO-*d6*) δ *inter alia* 1.20 (s, 6H), 3.44 (s, 2H), 7.13 – 7.16 (m, 4H), 7.27 – 7.32 (m, 6H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ *inter alia* 9.0.

General procedure for HPLC CO-release study

The CO compound was weighed out into a sample tube (**oCOm-21** [~0.5 mg], and for **oCOM-23** [~0.7-0.75 mg]). In separate vessels prior to mixing, the CO compound (**oCOm-21** or **oCOM-23**) and the TRIS-sucrose buffer (pH 7.4) were both allowed to equilibrate to the specified temperature (thermostat waterbath = 37 °C or cold room = 4-5 °C). TRIS-sucrose buffer (1 mL) was added to the CO compound at the specified temperature and mixed by gently swirling the HPLC vial (final concentration of **oCOm-21**, ~843 μM, final concentration of **oCOm-23**, ~930-999 μM). Prior to removing an aliquot for analysis, the sample was gently mixed by hand and then an aliquot was sampled (30 μL) and immediately added to a solution of 0.1 M aq. HCl (170 μL). The acidified aliquot was sonicated for approximately 10 seconds to ensure the entire sample was homogeneous. These aliquots were immediately analysed by RP-HPLC (3 replicate injections for each aliquot taken) using the specified HPLC method.

RP-HPLC method for **oCOm-21** CO release study: (30% to 60% B over 12.5 min, then 60% to 100% B over 2.5 min, 100% B for 2.0 min, 100% to 30% B over 2.0 min, 0.5 mL min^{-1}).
RP-HPLC method for **oCOm-23** CO release study: (35% to 50% B over 15.0 min, then 50% to 100% B over 1.0 min, 100% B for 2.0 min, 100% to 35% B over 2.0 min, 0.5 mL min^{-1}).

The area under the CO compound and the BP compound was integrated in the 254 nm spectrum and used to calculate the % conversion using the following formula:

$$\%\ \text{conversion of CO compound} = \frac{\text{peak area of CO compound}}{peak\ area\ of\ CO\ compound + peak\ area\ of\ BP\ compound}\ X\ 100$$

Table S1: CO-release study for oCOm-21 in TRIS-sucrose buffer (pH 7.4) at 37 ºC

Expt.[a]	Concentration (mg/mL)	Concentration (μM)	Approx. time for 50% conversion of **oCOm-21** to **BP-CO-21** (mins)
01	0.5	843	23
02	0.5	843	18
03	0.5	843	19
04	0.5	843	16
Average time at 37 °C			19

[a] Samples were hand mixed prior to taking an aliquot. Aliquots were mixed with 0.1 M HCl by sonication (~10 secs.)

Table S2: CO-release study for oCOm-21 in TRIS-sucrose buffer (pH 7.4) at 4-5 ºC

Expt.[a]	Concentration (mg/mL)	Concentration (μM)	Approx. time for 50% conversion of **oCOm-21** to **BP-CO-21** (mins)
01	0.5	843	1433 (~23.8 h)
02	0.5	843	2082 (~34.7 h)
03	0.5	843	1159 (~19.3 h)
04	0.5	843	2275 (~37.9 h)
05	0.5	843	2264 (~37.7 h)
Combined average time at 4-5 °C			1843 (30.7 h)

[a] Samples were hand mixed prior to taking an aliquot. Aliquots were mixed with 0.1 M HCl by sonication (~10 seconds).

Table S3: CO-release study for oCOm-23 in TRIS-sucrose buffer (pH 7.4) at 37 ºC

Expt.[a]	Concentration (mg/mL)	Concentration (μM)	Approx. time for 50% conversion of **oCOm-23** to **BP-CO-23** (mins)
01	0.7	930	95
02	0.7	930	63
03	0.7	930	65
04	0.74	986	75
05	0.74	986	77
Average time at 37 ºC			75

[a] Samples were hand mixed prior to taking an aliquot. Aliquots were mixed with 0.1 M HCl by sonication (10 secs.).

Table S4: CO-release study for oCOm-23 in TRIS-sucrose buffer (pH 7.4) at 4-5 ºC

Expt.[a]	Concentration (mg/mL)	Concentration (μM)	Approx. time for 50% conversion of **oCOm-23** to **BP-CO-23** (mins)
01	0.7	930	1570 (26.2 h)
02	0.75	999	2300 (38.3 h)
03	0.7	930	1920 (32 h)
04[b]	0.7	930	1960 (32.7 h)
Average time at 4-5 ºC			~1940 (~32.3 h)

[a] Samples were hand mixed prior to taking an aliquot. Aliquots were mixed with 0.1 M HCl by sonication (10 secs.).

Detection of Carbon Monoxide Release by amperiometric CO selective electrode

The rate of CO release from **oCOm-21** and **oCOm-23** was measured in Tris-sucrose buffer pH 7.4, 37ºC using an amperiometric CO selective electrode (ISO-COP-2, World Precision Instruments (WPI), Inc, Sarasota, USA). The amount of CO released was recorded as the magnitude of electrode current generated on CO diffusion through a selective gas permeable membrane and oxidised to CO_2 on the electrode. Current changes were recorded using a WPI TRB4100 4-channel free radical analyser with the poise potential set to 950mV. Solutions of **oCOm-21** and **oCOm-23** were freshly prepared in ultrapure water (nominally pH 6.9) and 10µL immediately injected into a water jacketed chamber containing 500µL of Tris-sucrose solutions at a physiological pH to give a final CO donor concentration of 75µM.

Measurement of CO binding to Myoglobin

CO released from **oCOm-19** and **oCOm-21** was measured using an established carboxymyoglobin spectrophotometric assay,[8] adapted to a 96 well plate format to enable the simultaneous correction at all absorbance wavelengths arising from any potential interference from the donor compounds.[9] Freshly prepared horse heart myoglobin (66µM) in a PBS solution (pH 7.4) was reduced with 10% w/v sodium dithionite and added to a 96 well plate. The CO donors, **oCOm-19** and **oCOm-21**, as well as the commercially available CO donor, **CORM-2** (Sigma-Aldrich, Castle Hill, NSW, Australia), were added to each well in triplicate to produce a final concentration range of 100-800µM and 50µL paraffin oil added to each well to prevent the diffusion of gases. Absorption spectra (λ 500 - 600nm) were run at ten minute intervals using a Spectramax 96-well spectrophotometer (Molecular Devices, Crawley, UK) at 37°C. CO gas saturated PBS (714µM), was employed as a positive control.

Cell Toxicity

The loss of cell adhesion for anchorage-dependent cell lines, such as Madin Darby Canine Kidney (MDCK) cells, represents a surrogate marker of cell death which can be measured by the crystal violet cell adhesion (CVCA) assay. MDCK cells plated at $1x10^6$ cells/mL in 24 well plates were grown to 60% confluency in DMEM supplemented with 4% donor calf serum and 1% antibiotic (Gibco Life Technologies, Auckland NZ). CO donor compounds, BP-compounds or non CO releasing, DB-derivatives were dissolved in either ultrapure water or for non-water soluble compounds, in DMSO and diluted to 20-100µM (to a final concentration of 1% DMSO where appropriate). **oCOm-19** was initially dissolved in 0.1% DMSO while oCOm-21, -23 and -24 were dissolved directly in deionised, distilled water. Cells were exposed to CO donor compounds or the respective vehicle control solution for 1 hour at 37°C prior to washing and incubating for a further 23 hours in fresh media. Cells were fixed in 96% ethanol and stained in 0.05% crystal violet solution in 20% ethanol, prior to washing and solubilising (24 hours) in 2mL 0.1% acetic acid in 50% ethanol. Sample solutes (100µL) from each well were transferred into a 96 well plate and absorbance measured at 585nm. Cell survival was reported as a percentage of the value obtained for cells exposed to vehicle only and used to plot a concentration-response curve for each compound from which an EC_{50} value was obtained.

General procedure for determining solubility of CO compounds by HPLC

The CO compound (4.2 mg, or 6.0 mg) was dissolved in CH_3CN (1 mL) and then passed through a syringe filter (0.45 µM, nylon membrane) to create **stock solution A** and **stock solution B** respectively. A series of solutions were created by dilution of the stock solution (Table 6 for **stock solution A**, Table 5 for **stock solution B**)

Table 5: Solutions created from stock solution A (4.2 mg/mL)

Entry	1	2	3	4	5
Concentration ($mg.mL^{-1}$)	2.9	2.1	1.03	0.51	0.26

Table 6: Solutions created from stock solution B (6.0 mg/mL)

Entry	1	2	3	4	5
Concentration ($mg.mL^{-1}$)	4.0	2.0	1.49	0.50	0.25

Each solution was analysed by three replicate injections using RP-HPLC. HPLC analyses were conducted on an analytical RP-HPLC using the method specified in the general experimental section for HPLC analysis. The average peak integration values obtained from the three replicate injections monitored at λ 254 nm were used to generate a standard curve of integrated peak area (y-axis) against concentration in $mg.mL^{-1}$ (x-axis).

In separate vessels, the CO compound to be investigated and tissue culture H_2O (Sigma Aldrich, W3500, Lot RNBB4164) was first allowed to equilibrate to the specified temperature (20 °C or 8 °C). Tissue culture H_2O was then added in small aliquots until most of the solid had dissolved to form a saturated solution of CO compound, which was then passed through a syringe filter (0.45 µM, nylon membrane) at the specified temperature (20 °C or 8 °C). The filtered solution of CO compound was diluted as necessary with tissue culture H_2O and then

analysed by RP-HPLC (three replicate injections). The solubility of the CO compound was calculated using **formula (2)** derived from the standard curve for that particular CO compound:

$$[y = mx] \qquad \textbf{formula (1)}$$

Where y = integrate area under peak (254 nm), m = gradient of standard curve, x = concentration in $mg.mL^{-1}$.

Rearrangement of formula (1) to determine x = concentration in $mg.mL^{-1}$

$$x = \left(\frac{y}{m}\right) \text{ X dilution factor} \qquad \textbf{formula (2)}$$

Formulas for calculating water solubility of CO compounds

For **oCOm-19** $x = \left(\frac{y}{2226006}\right)$ X dilution factor **formula (3)**

For **oCOm-21** $x = \left(\frac{y}{4444262}\right)$ X dilution factor **formula (4)**

For **DB-CO-21** $\left(x = \frac{y}{4261592}\right)$ X dilution factor **formula (5)**

For **oCOm-23** $x = \left(\frac{y}{4491248}\right)$ X dilution factor **formula (6)**

For **DB-CO-23** $x = \left(\frac{y}{4051904}\right)$ X dilution factor **formula (7)**

Table S7: Solubility of oCOm-19 in tissue culture water at 20 °C

Integration area (254 nm)	1211597	1563066	1440397
Average area under peak	1405020		
Dilution factor	5		
Concentration (mg.mL^{-1})	3.2		

Table S8: Solubility of oCOm-21 in tissue culture water at 20 °C

Integration area (254 nm)	9589947	9592734	9600962
Average area under peak	9594548		
Dilution factor	5		
Concentration (mg.mL^{-1})	10.8		

Table S9: Solubility of oCOm-21 in tissue culture water at 8 °C

Integration area (254 nm)	8625496	8645923	8648255
Average area under peak	8639891		
Dilution factor	2		
Concentration (mg.mL^{-1})	3.9		

Table S10: Solubility of DB-CO-21 in tissue culture water at 20 °C

Integration area (254 nm)	15874422	15916820	15896945
Average area under peak	15896062		
Dilution factor	2		

Concentration ($mg.mL^{-1}$)	7.5

Table S11: Solubility of oCOM-23 in tissue culture water at 20 °C

Integration area (254 nm)	16348778	16365832	16348778
Average area under peak	16354463		
Dilution factor	5		
Concentration (mg.mL^{-1})	18.2		

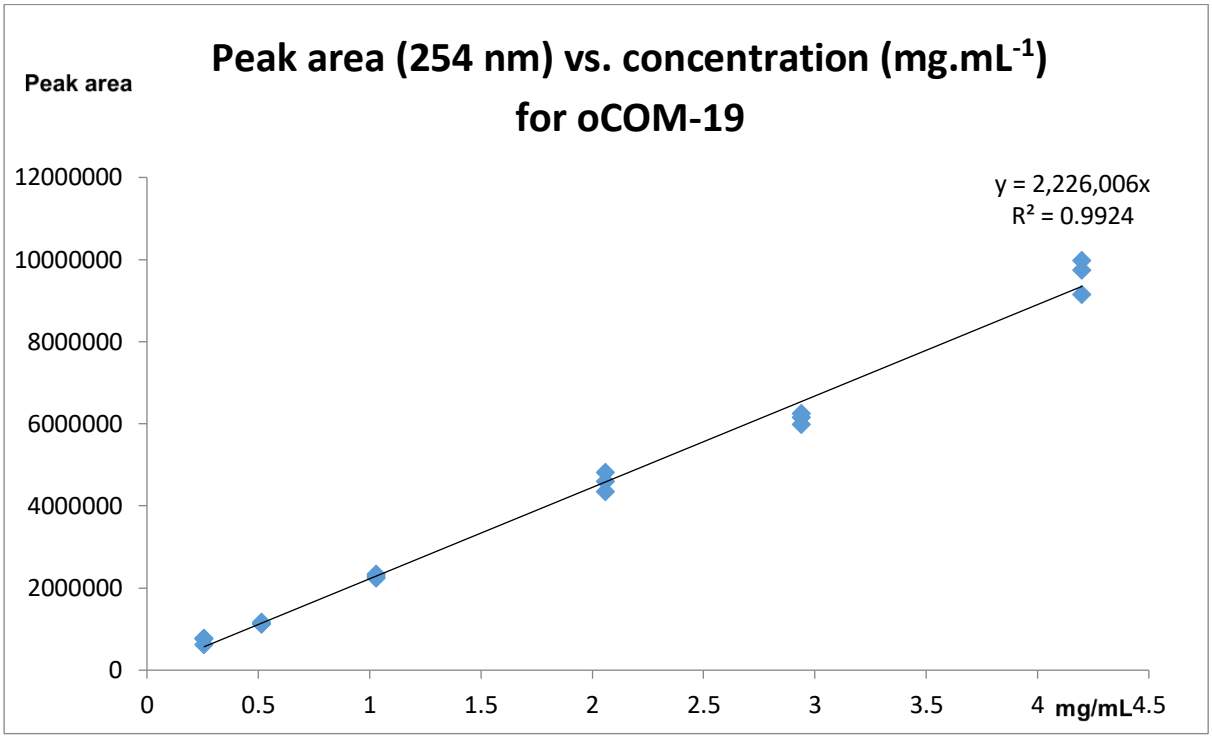
Table S12: Solubility of oCOM-23 in tissue culture water at 8 °C

Integration area (254 nm)	9858537	9887512	9907150
Average area under peak	9884400		
Dilution factor	8		
Concentration (mg.mL^{-1})	17.6		

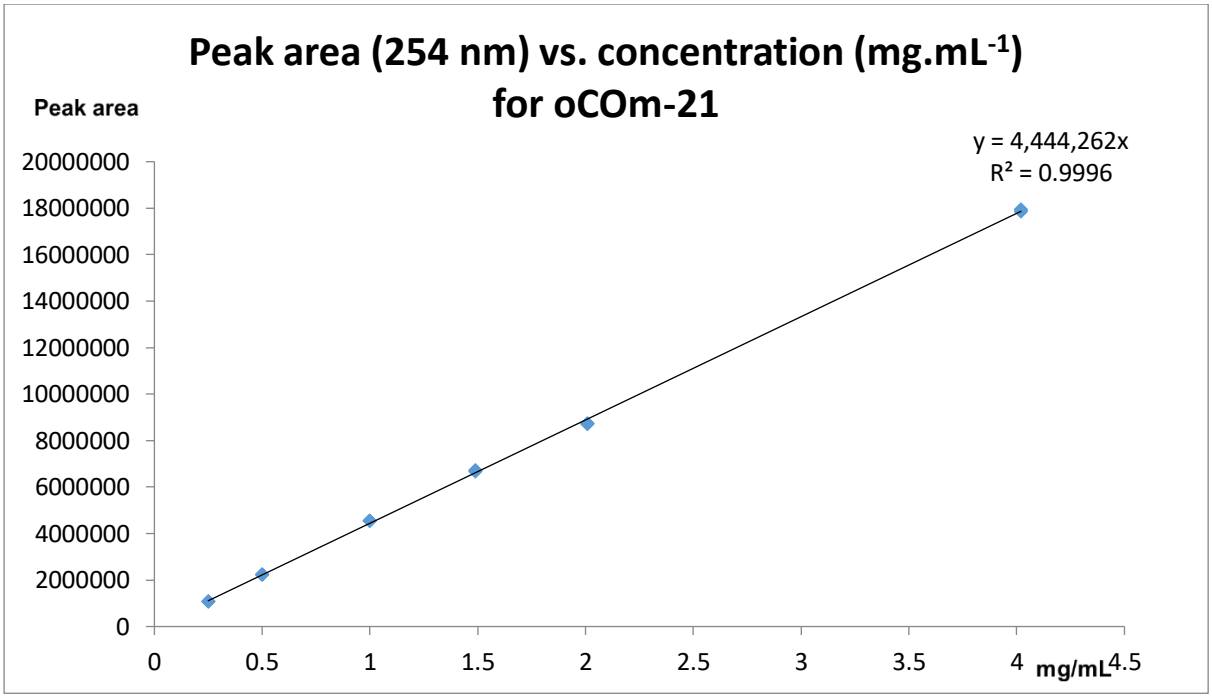
Table S13: Solubility of DB-CO-23 in tissue culture water at 20 °C

Integration area (254 nm)	10171940	10181776	10186914
Average area under peak	10180210		
Dilution factor	8		
Concentration (mg.mL^{-1})	20.1		

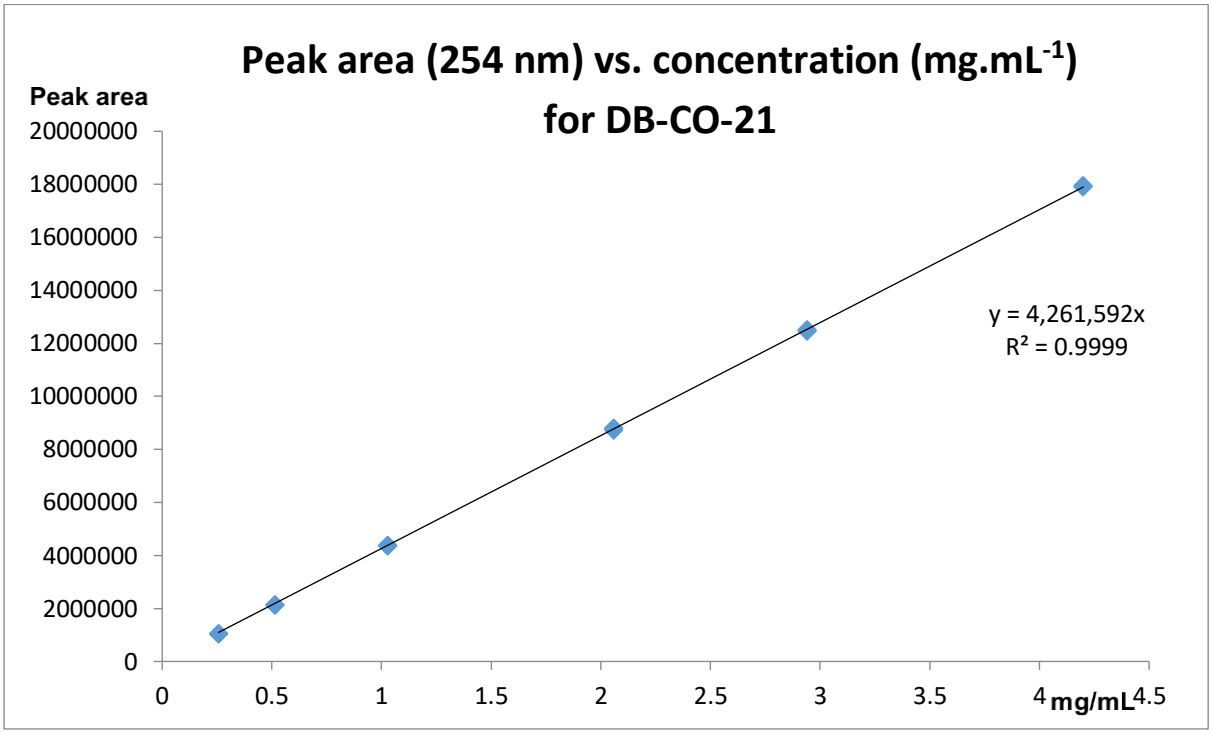
Standard curve for oCOm-19



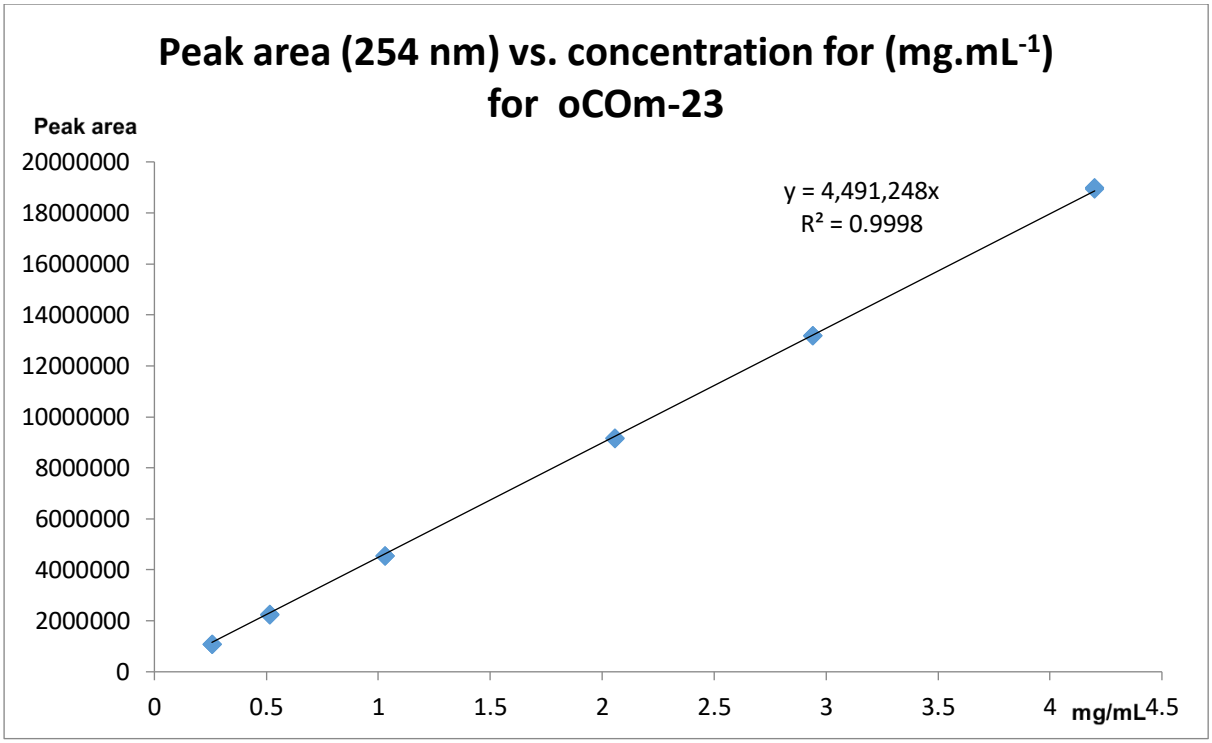
Standard curve for oCOm-21



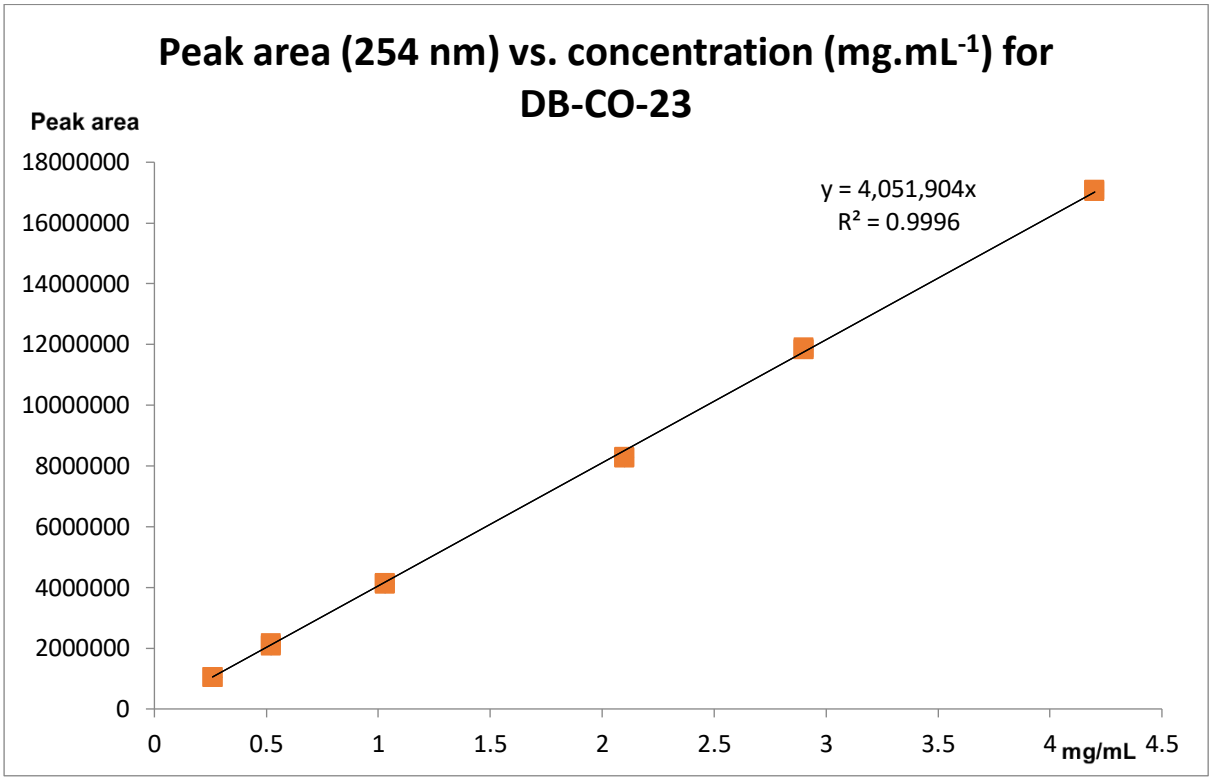
Standard curve for DB-CO-21



Standard curve for oCOm-23



Standard curve for DB-CO-23



Imaging of Carbon Monoxide in Living Cells

A palladium CO-responsive small-molecule fluorescent probe (**COP-1**)[10] was synthesised and carbonylation of the probe by CO confirmed as previously described.[10] The ability of the CO donors to increase intracellular levels of CO was tested in MDCK cells. 96 well black-walled tissue culture plates were seeded with MDCK cells at $1x10^6$ cells/mL in advanced Glutamax® DMEM containing 1% glutamine, and supplemented with 5% foetal bovine serum and 1% antibiotic (Gibco Life Technologies, Auckland NZ) and incubated at 37ºC, 65% relative humidity for 48 hours. The media was replaced with fresh media and **oCOm-21**, **oCOm-23, BP-CO-21** and **BP-CO-23** dissolved in sterile DPS were added in triplicate at 5 to 50µM final concentration. Cells were incubated for 1 hour at either 8 or 37ºC then 1µM **COP-1** in DPS added per well and cells incubated for a further 15 minutes. Cells were imaged on a fluorescent inverted microscope (Nikon Eclipse Ti-E).

Animals

All procedures were approved and conducted in accordance with the guidelines of the Animal Ethics Committee at the University of Otago and complied with the University of Otago "Code of Ethical Conduct for the Manipulation of Animals". Male Sprague Dawley rats (300 - 320 g) were obtained from the University of Otago Animal Resource Unit. Animals were housed on a 12 hour light/dark cycle at 22 °C with food and water *ad libitum* and left to acclimate for 5 days prior to experimentation.

Oral Bioavailability

Male Sprague Dawley rats (300 - 320g) were orally dosed with either **oCOm-19** (133.33 µmol/kg) or **oCOm-21** (33.33 µmol/kg) in ultra-pure water by oral gavage. Animals were observed every 15 minutes for any changes in behaviour or signs of distress. Tail vein

blood samples were collected in heparinised capillary tubes immediately prior to and at 1 - 3 hours post CO-donor administration. Blood gas analysis on each sample was performed using a Radiometer ABL800 Flex analyser.

Isolated Rat Aortic Ring Preparations

Transverse ring sections (2mm) of aorta were isolated from naïve untreated animals (*n*=5 per group) under halothane anaesthesia and suspended under a 1g tension in an organ bath containing 10mL of oxygenated (95% O_2/5% CO_2) Krebs Henseleit (KH) buffer containing 118mM NaCl, 4.7mM KCl, 1.2mM KH_2PO_4, 1.2mM $MgSO_4.7H_2O$, 22mM $NaHCO_3$, 11mM glucose, 0.03mM K^+EDTA, and 2.5mM $CaCl_2$ (37°C) as previously described.[11] Indomethacin (10µM; Sigma-Aldrich, Auckland, NZ) was present in the buffer to exclude endogenous prostaglandins as potential modulators of vascular tone. Relaxation responses to **oCOm-19** and **oCOm-21** (0.01 – 300µM) were assessed using individual dosing in tissues pre-contracted with a submaximal concentration (0.1µM) of phenylephrine (Sigma-Aldrich, Auckland, NZ). All results were subsequently expressed as a percentage of the maximal phenylephrine-induced contraction. Following repeat wash steps (x4) with Krebs Henseleit buffer to remove the pressor agent, smooth muscle function and viability was confirmed by repeating the contractile response to phenylephrine. Aortic responses to individual EC_{50} concentrations of **oCOm-19** in phenylephrine vasoconstricted rings were repeated separately, in the presence of the selective, irreversible inhibitor of sGC, 1H-(1,2,4)oxadiazolo[4,3-a]quinoxalin-1-one, (ODQ, 10µM), as previously described.[12]

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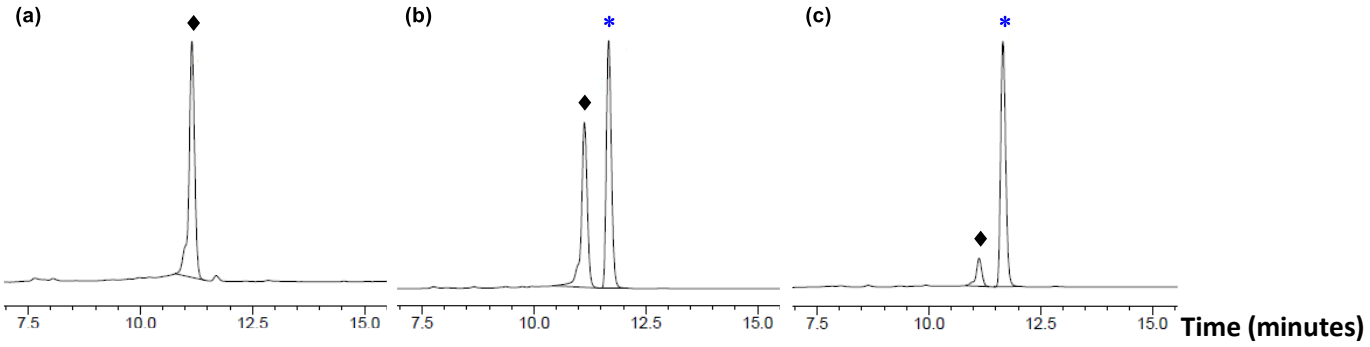
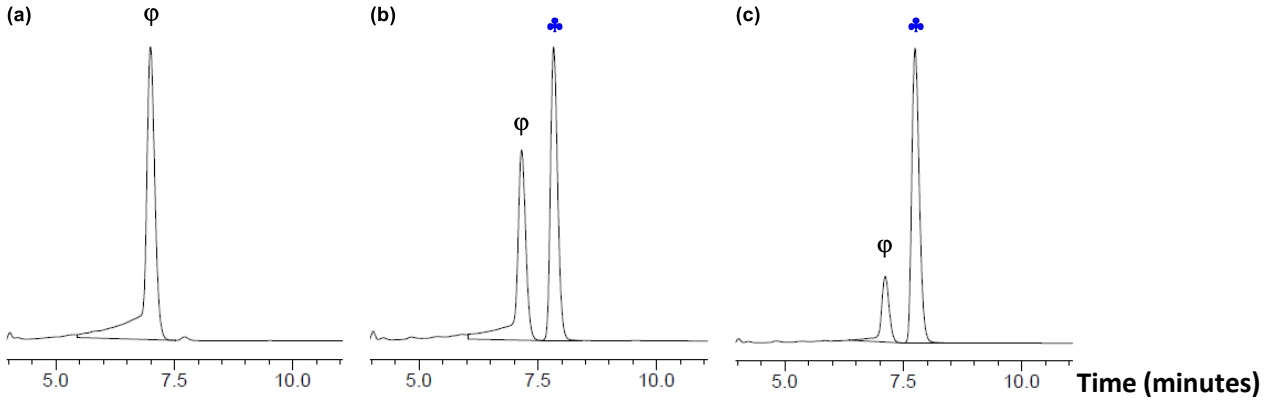
Figures for Supporting Information

Figure SI 1a



RP-HPLC chromatograms showing the conversion of **oCOM-21** to **BP-CO-21** in TRIS-sucrose buffer (pH 7.4) at 37 °C at specified time points: **(a)** 0 minutes **(b)** 20 minutes **(c)** 60 minutes. *Key* ♦ = **oCOM-21** * = **BP-CO-21**. *RP-HPLC method*: 30-60% B over 12.5 mins, 60%-100% B over 2.5 mins, 100% B for 2.5 mins, flowrate 0.5 mL.min^{-1}. Injection volume = 3 µL. Column: Phenomenex, C-18 Prodigy, 250 mm x 3 mm, 5 µM.

Figure SI 1b



RP-HPLC chromatograms showing the conversion of **oCOM-23** to **BP-CO-23** in TRIS-sucrose buffer (pH 7.4) at 37 °C at specified time points: **(a)** 0 minutes **(b)** 90 minutes **(c)** 180 minutes. *Key* φ = **oCOM-23** ♣ = **BP-CO-23**. *RP-HPLC method*: 35-50% B over 15.0 mins, 50%-100% B over 1.0 min, 100% B for 1.0 min, flowrate 0.5 mL.min^{-1}. Injection volume = 3 µL. Column: Phenomenex, C-18 Prodigy, 250 mm x 3 mm, 5 µM.

Figure S2a: Comparison of CO release from oCOm-21 (75uM) and oCOm-23 (75uM) at 37°C in Tris sucrose buffer (pH7.4) measured using a CO selective electrode.

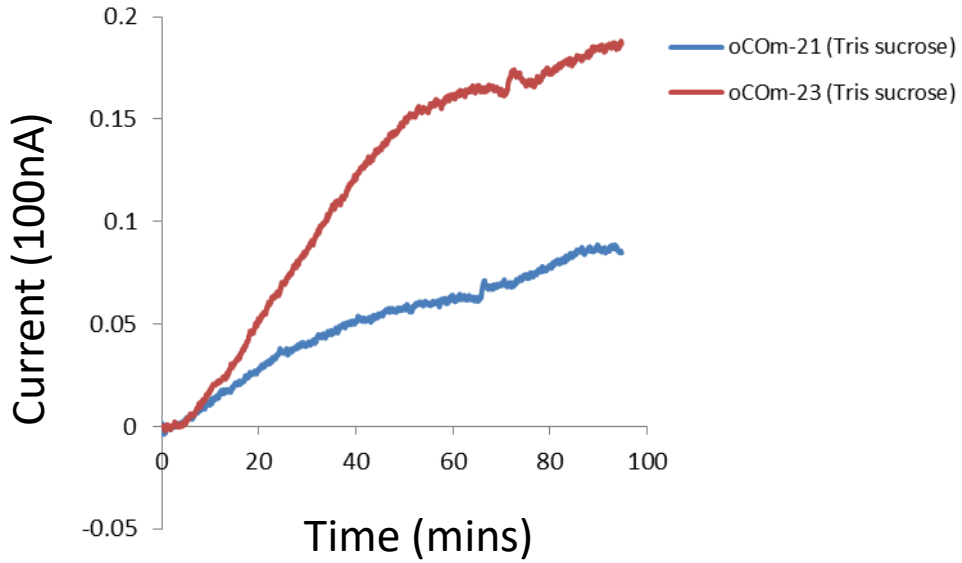


Figure S2b: The effect of pH on CO release from oCOm-19 in tris-sucrose buffer at 37 °C measured using a CO selective electrode

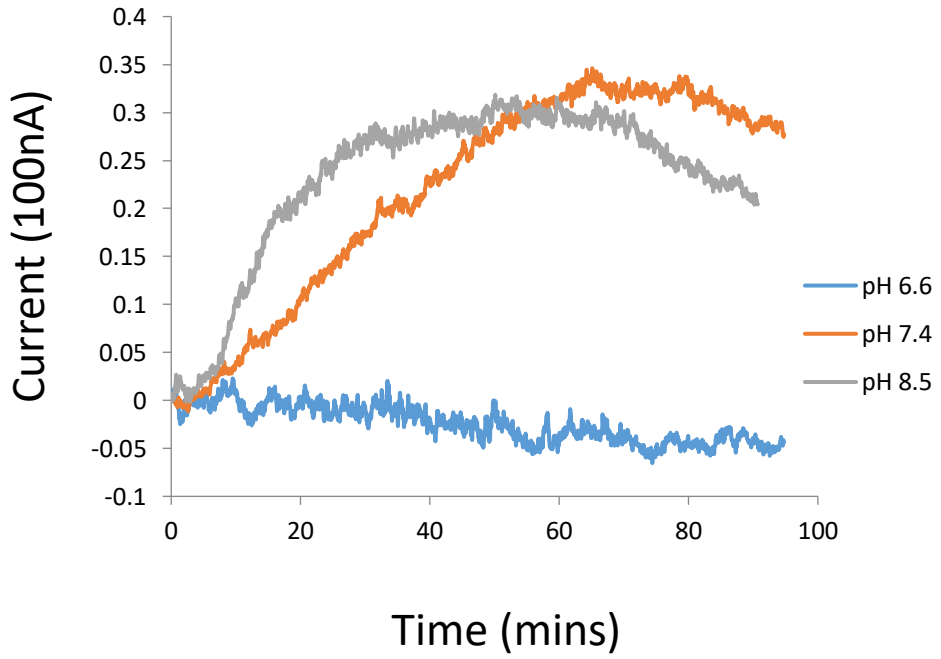


Figure S2c: The generation of physiologically active CO by the CO donor compounds was demonstrated by myoglobin binding studies, measured as a shift in the absorbance spectra peaks to 540nm

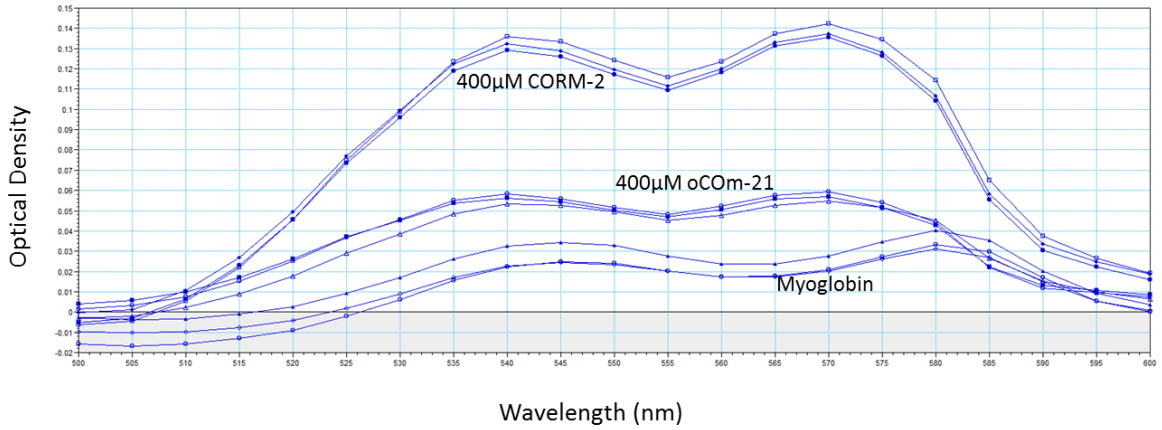
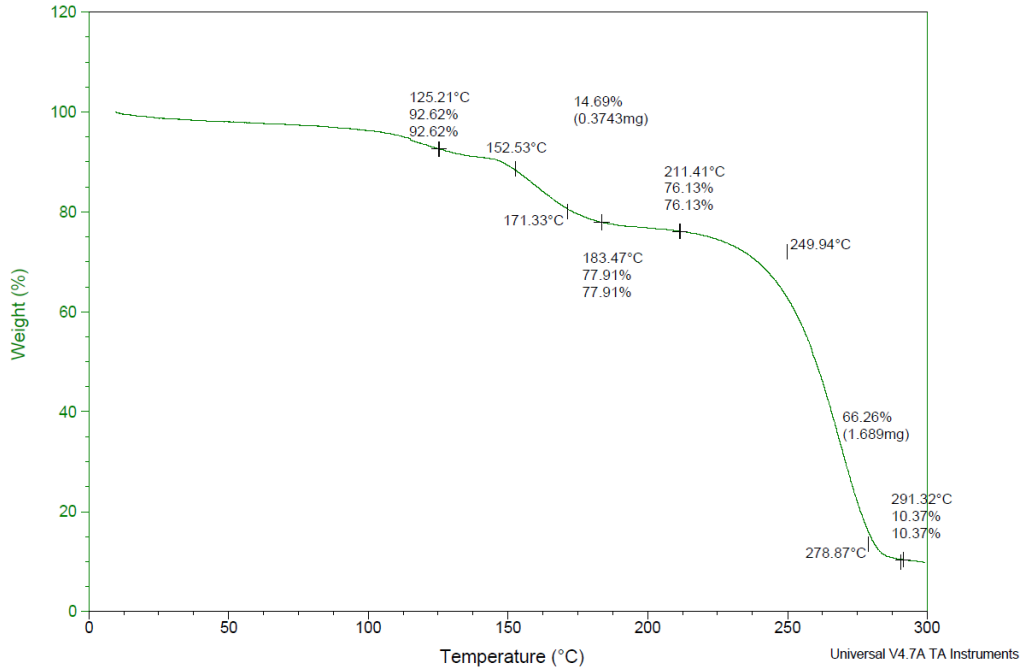


Figure S3a: TGA analysis of **oCOM-21** using Method A (heating rate of 2.00 °C/min from 20 °C to 300 °C).



A gradual loss in mass (~8% loss in mass) was observed up to the temperature of 125 ˚C. Between the temperatures of 153–183 ˚C, a sudden loss in mass (approximately 15% loss in mass) was detected indicating thermal instability at this temperature range.
A second and much larger loss in mass (67% loss) was observed between 211–291 ˚C.

Figure S3b: TGA analysis of oCOM-21 using Method B (heating rate of 2.00 °C/min from 20 °C to 90 °C and then isothermal at 90 °C for 30 mins).

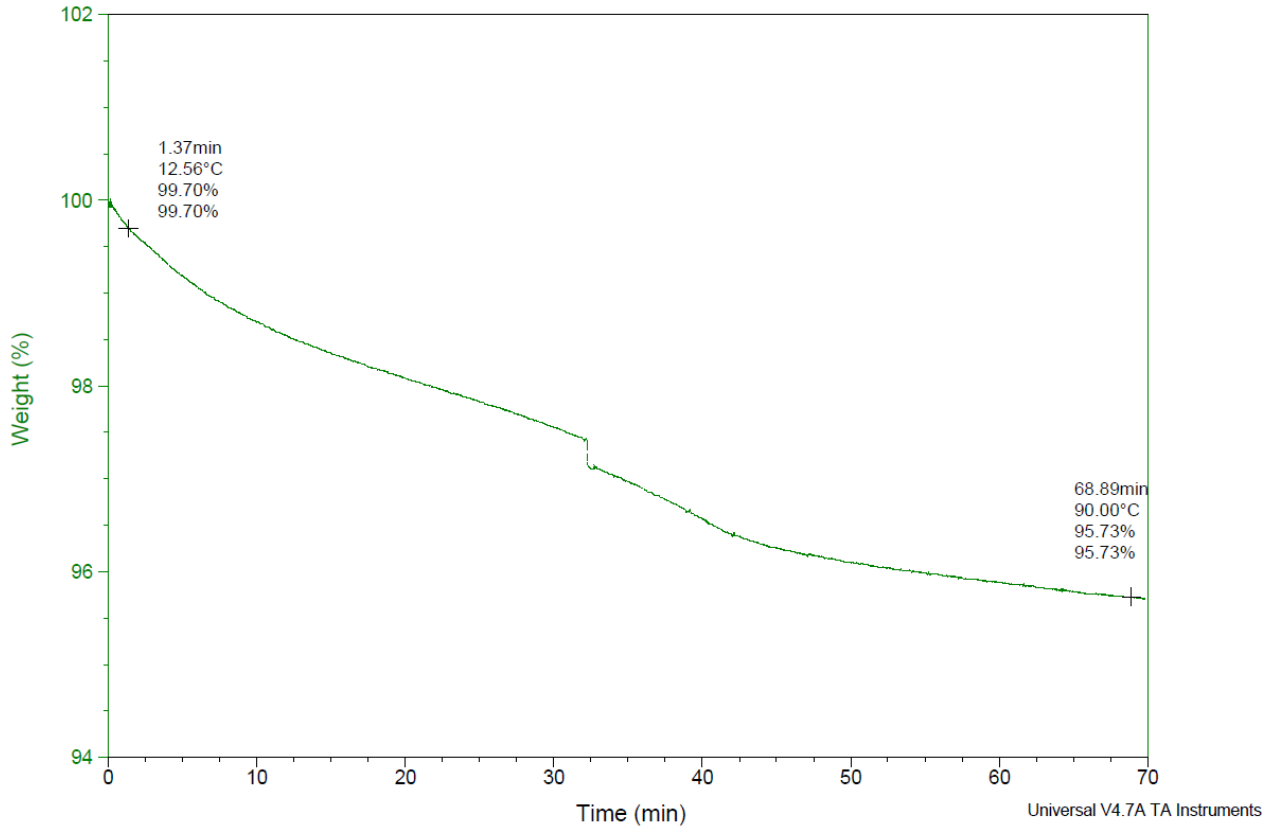


Figure S3c: HPLC chromatogram of **oCOM-21** sample heat treated at 90 ˚C for 30 mins (a), reference samples of **oCOM-21** and **BP-CO-21** included in entries (b) and (c).

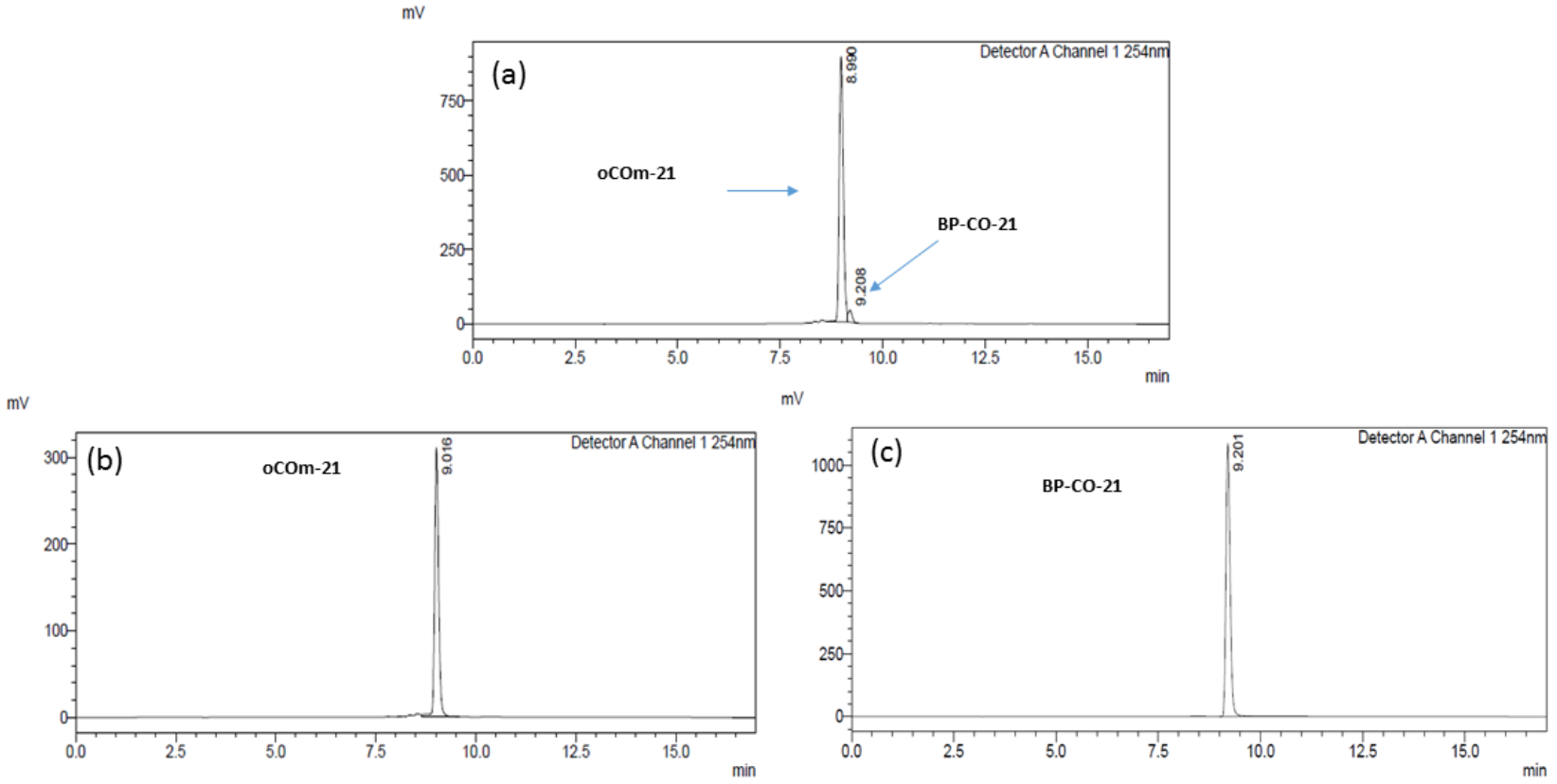


Figure S3c: Cell viability as a % of control 23 hrs following 1hr exposure to the CO donors **oCOm-19**, **-2**1 and **-23** or their inactive debromo (**DB-CO-23**) or CO expired (**BP-CO-19, -21**) analogues as assessed at 37°C in MDCK cells using the crystal violet assay as a marker of loss of cellular adhesion.

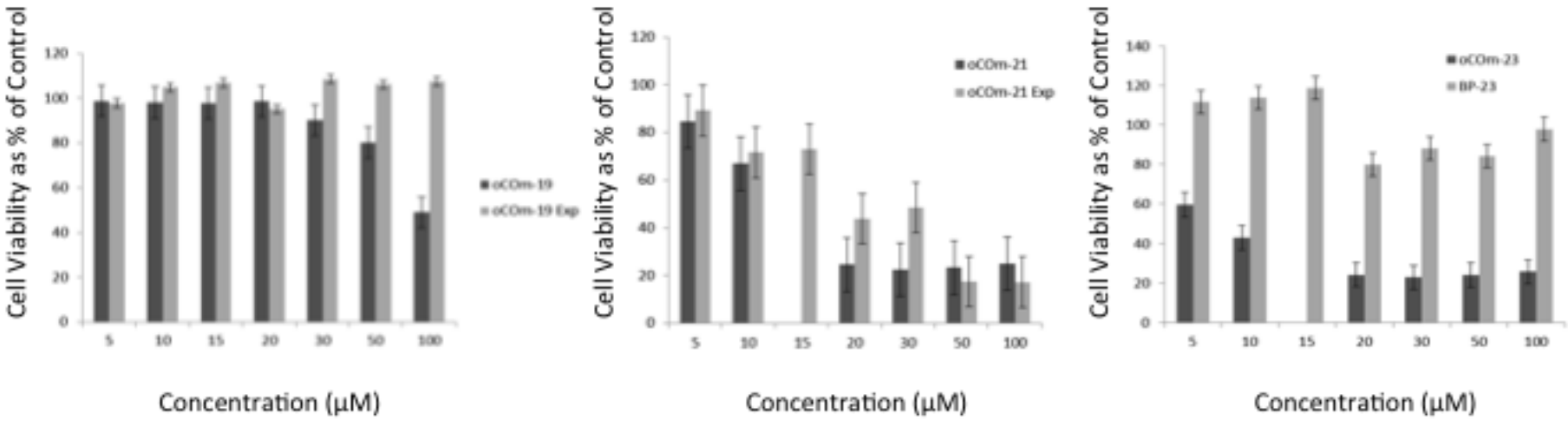
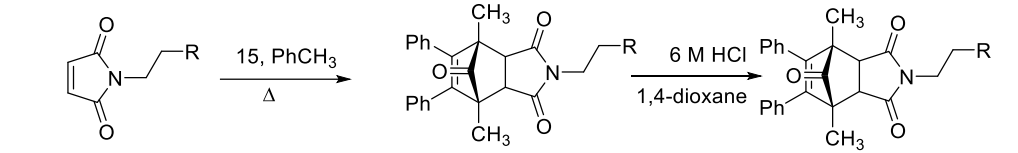


Table S1: Plasma carboxyhaemoglobin recorded at 1-3 hours following CO donor administration.

	% Carboxyhaemoglobin in blood			
	Pre-dosing	**1 hour post**	**2 hours post**	**3 hours post**
oCOm -19 133.3 µmol/kg	0.7 ± 0.28	0.9 ± 0	1.2 ± 0	1.3 ± 0.14*
oCOm -21 33.3 µmol/kg	0.54 ± 0.36	1.52 ± 0.44*	1.74 ± 0.45*	1.25 ± 0.42
BP-CO-19 133.3 µmol/kg	0.57 ± 0.25	0.63 ± 0.54	0.04 ± 0.65	0.63 ± 0.47

Effects on circulating carboxyhaemoglobin levels of oCOm-19 and oCOm-21 administered by oral gavage in Sprague Dawley rats (n=3). Data expressed as expressed as mean ± SEM.
* indicates P<0.05 compared to the pre-dosing level as determined by Student t test.

Scheme S1: Synthesis of DB-CO-19, -21 and -23



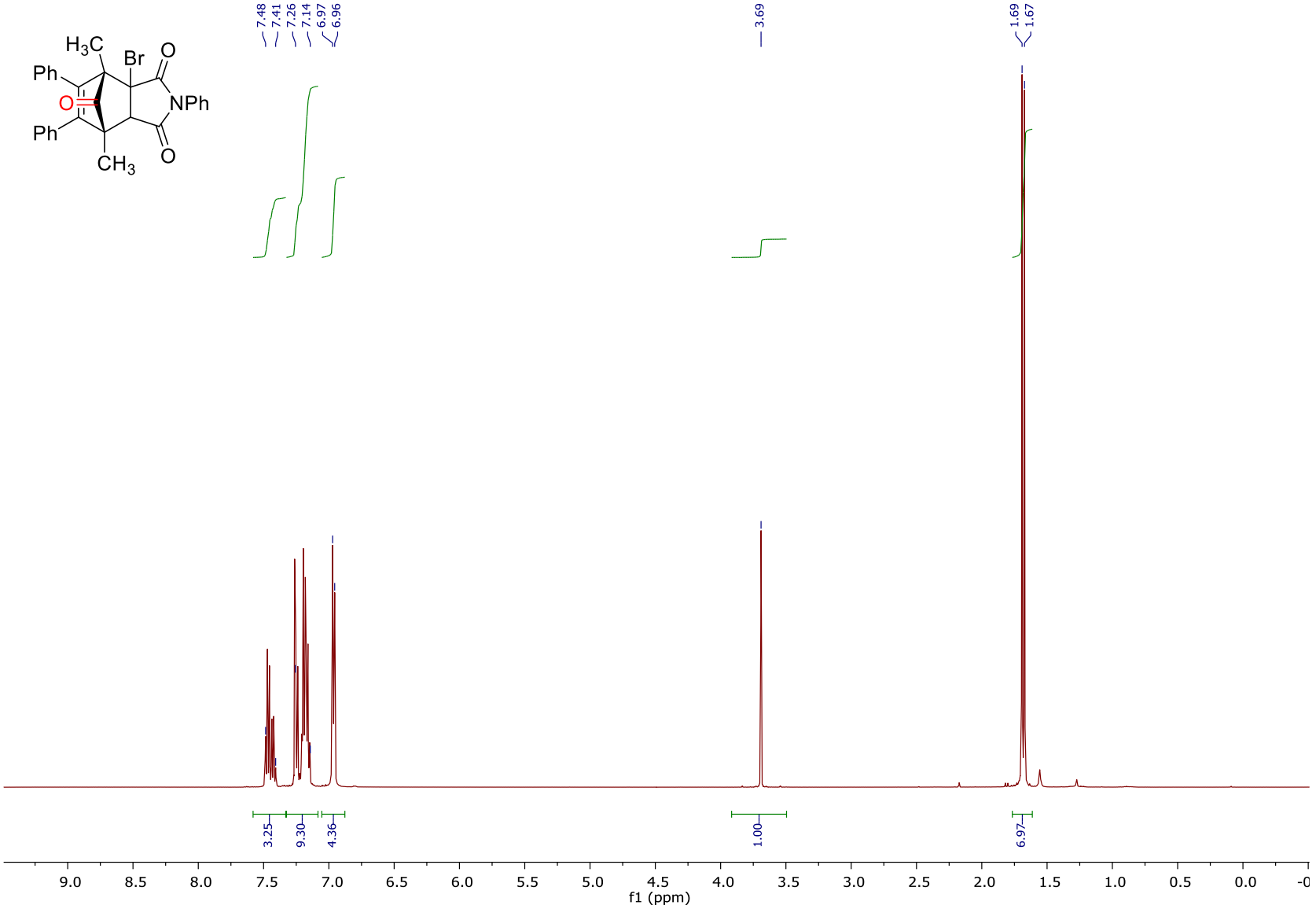
19 R = $CONH(CH_2)_2NHBoc$
24 R = NHBoc
25 R = $N(Boc)CH_2CH_2NHBoc$

32 R = $CONH(CH_2)_2NHBoc$
33 R = NHBoc
34 R = $N(Boc)CH_2CH_2NHBoc$

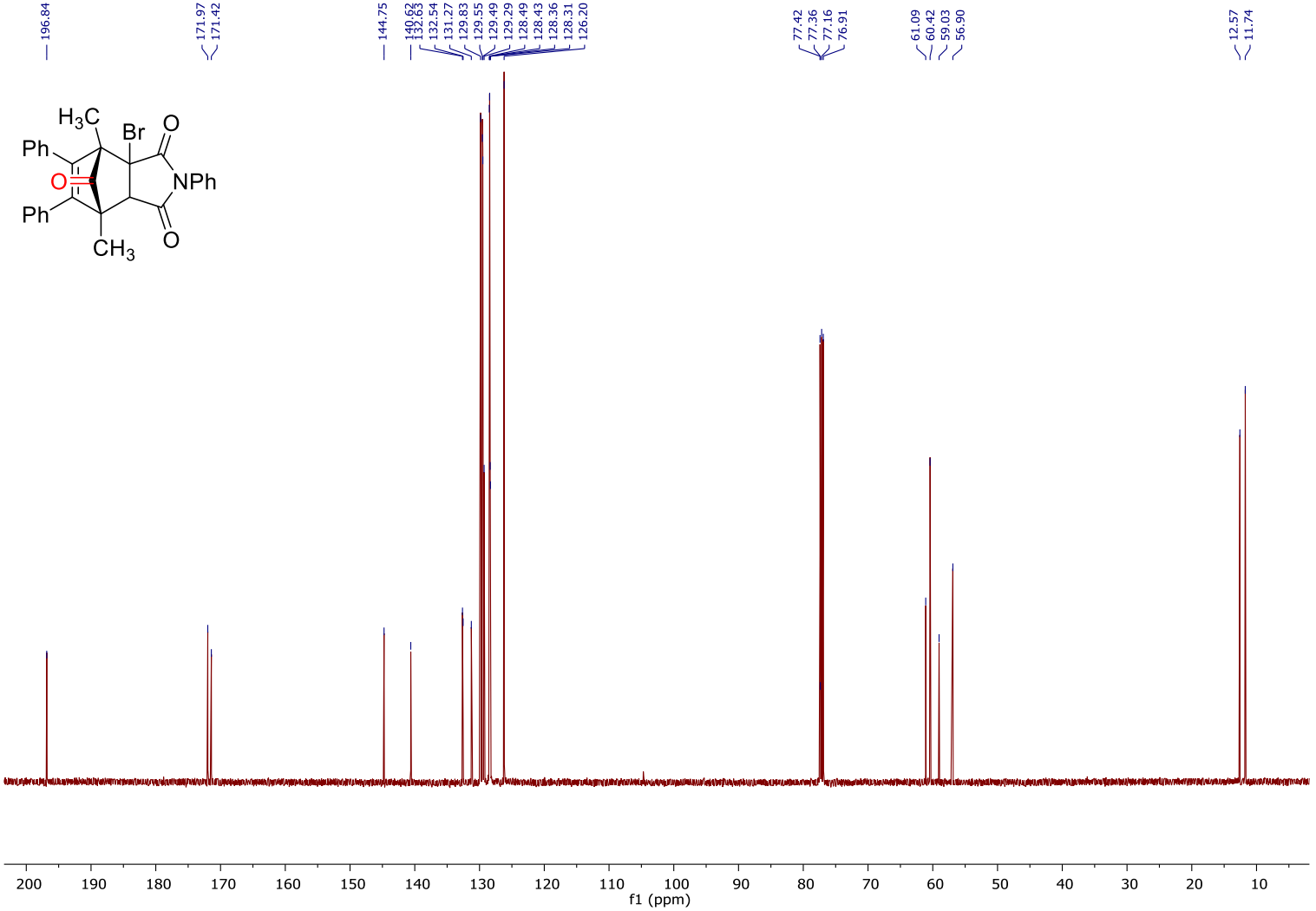
DB-CO-19 R = $CONH(CH_2)_2NH_2$ .TFA
DB-CO-21 R = NH_2 .TFA
DB-CO-23 R = $NHCH_2CH_2NH_2$ .2TFA

NMR Spectra

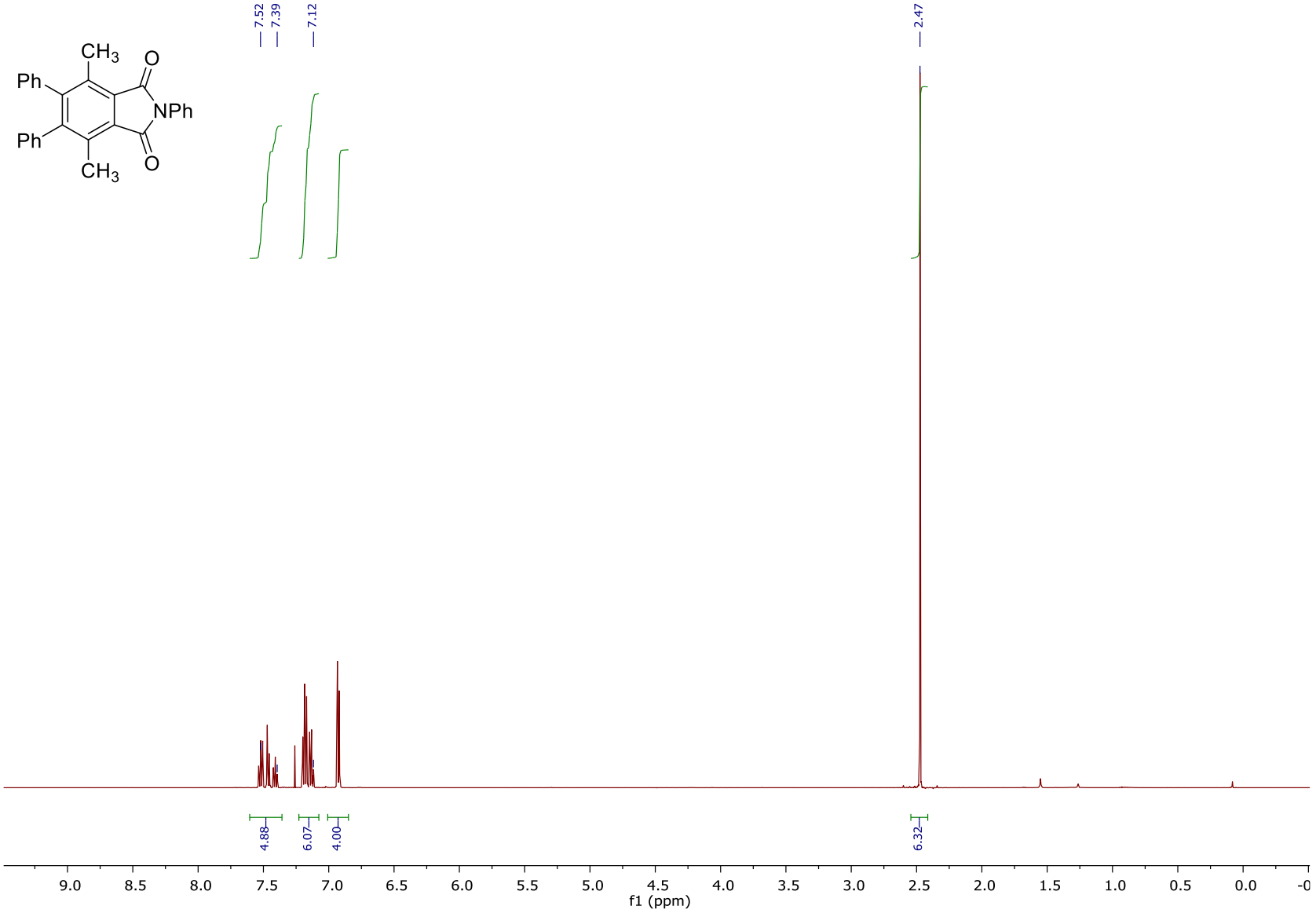
Compound **16**. ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



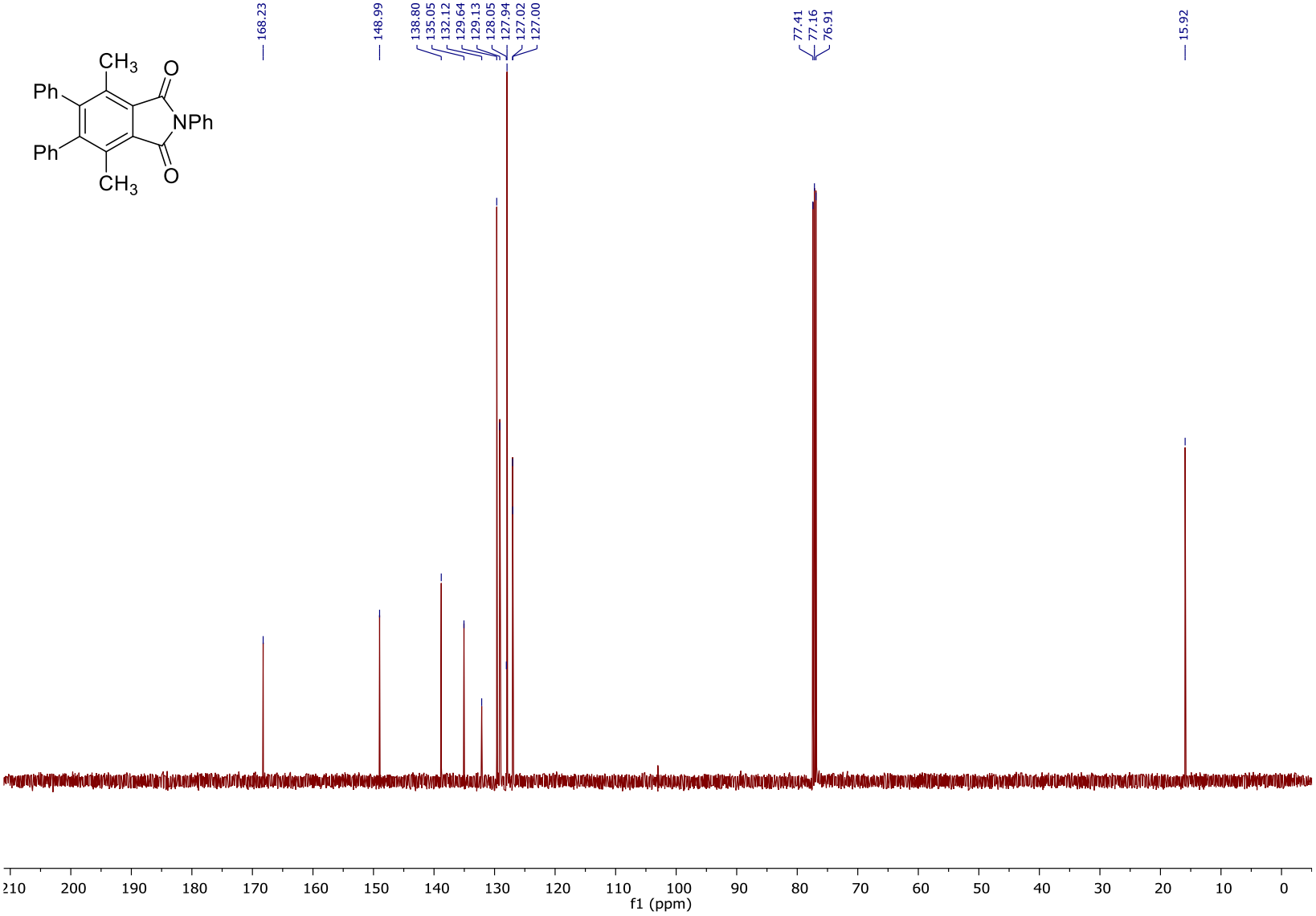
Compound **16** ^{13}C NMR spectrum (500 MHz, $CDCl_3$).



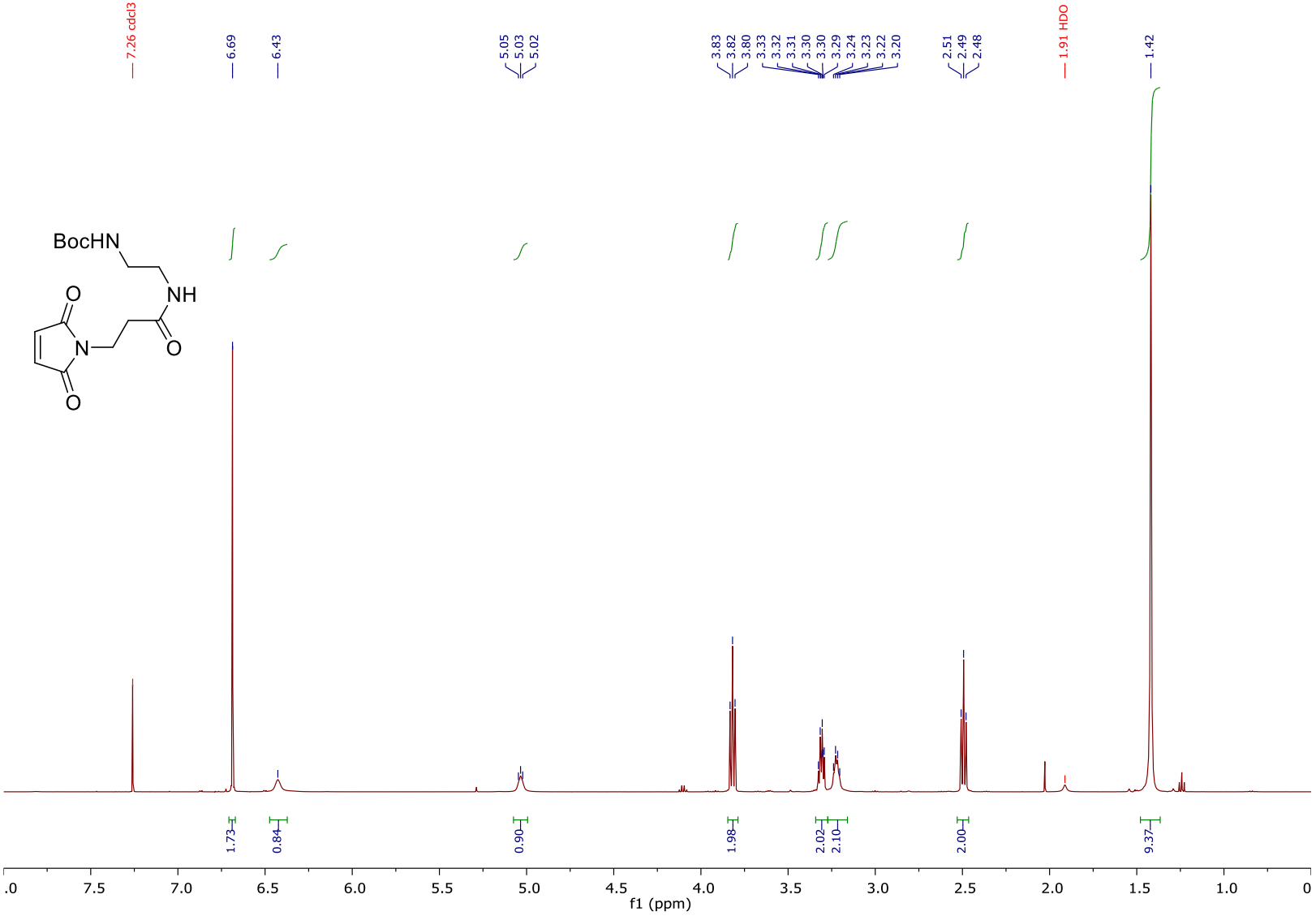
Compound **17**. ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



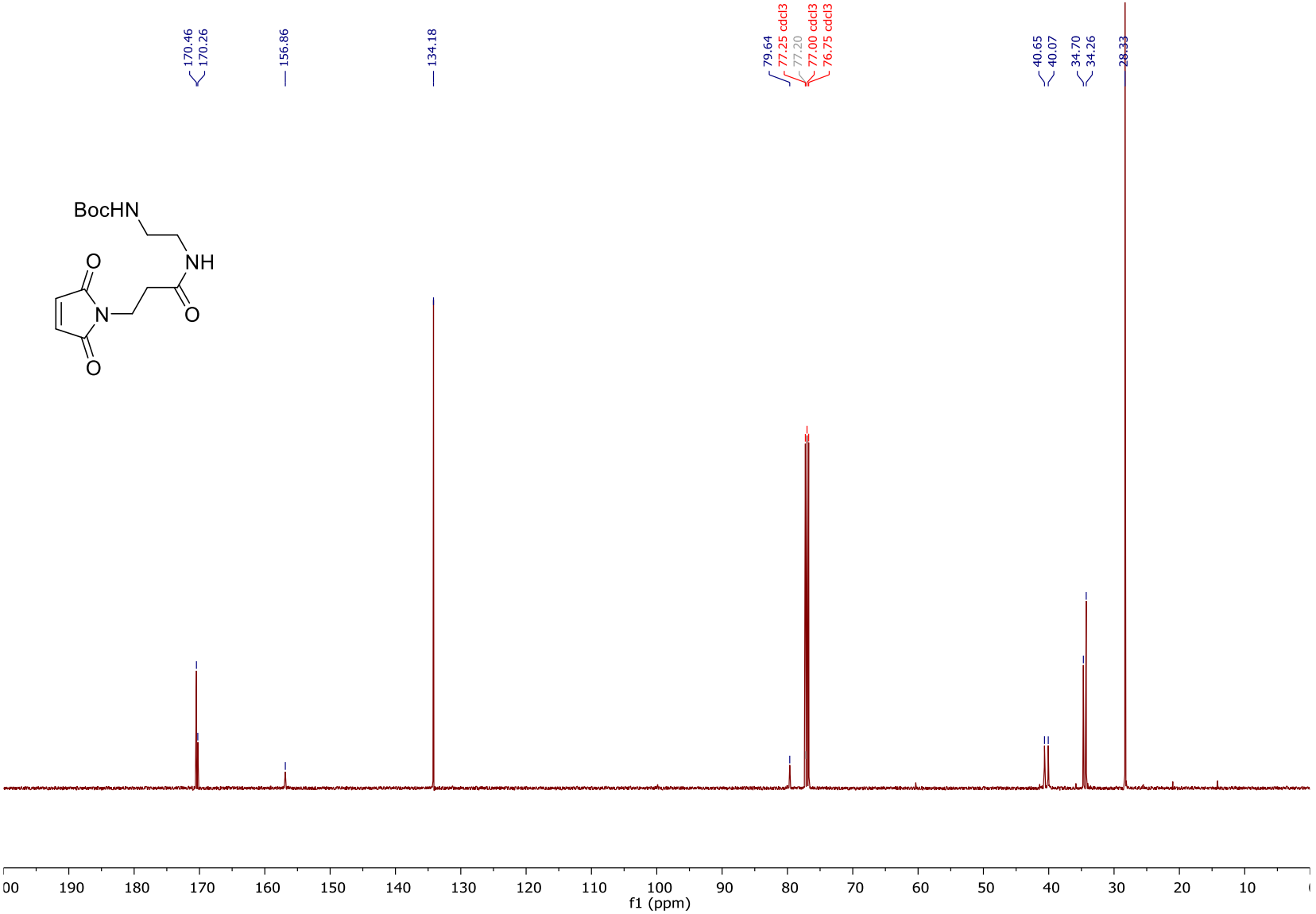
Compound **17** ^{13}C NMR spectrum (500 MHz, $CDCl_3$).



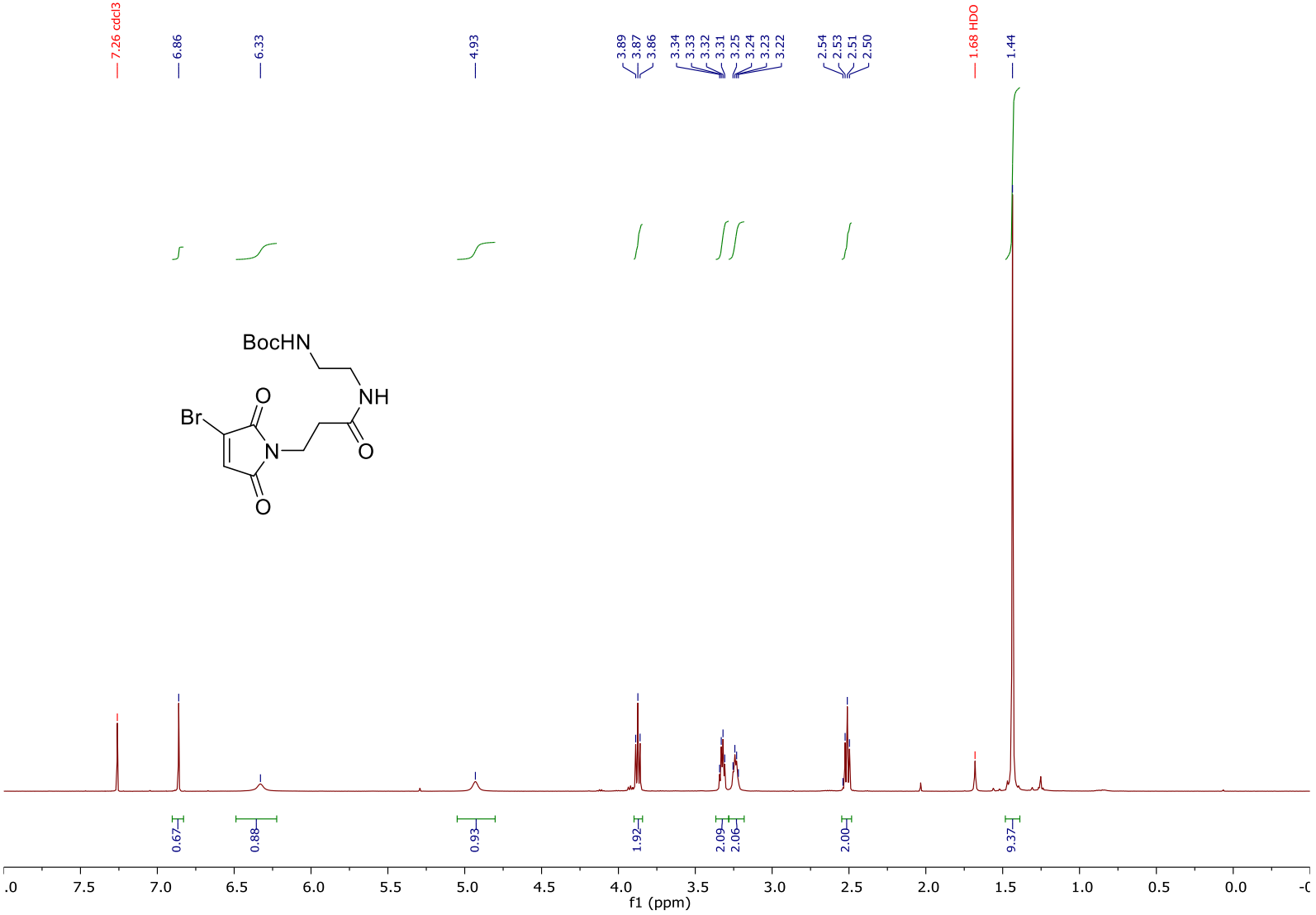
Compound **19**. ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



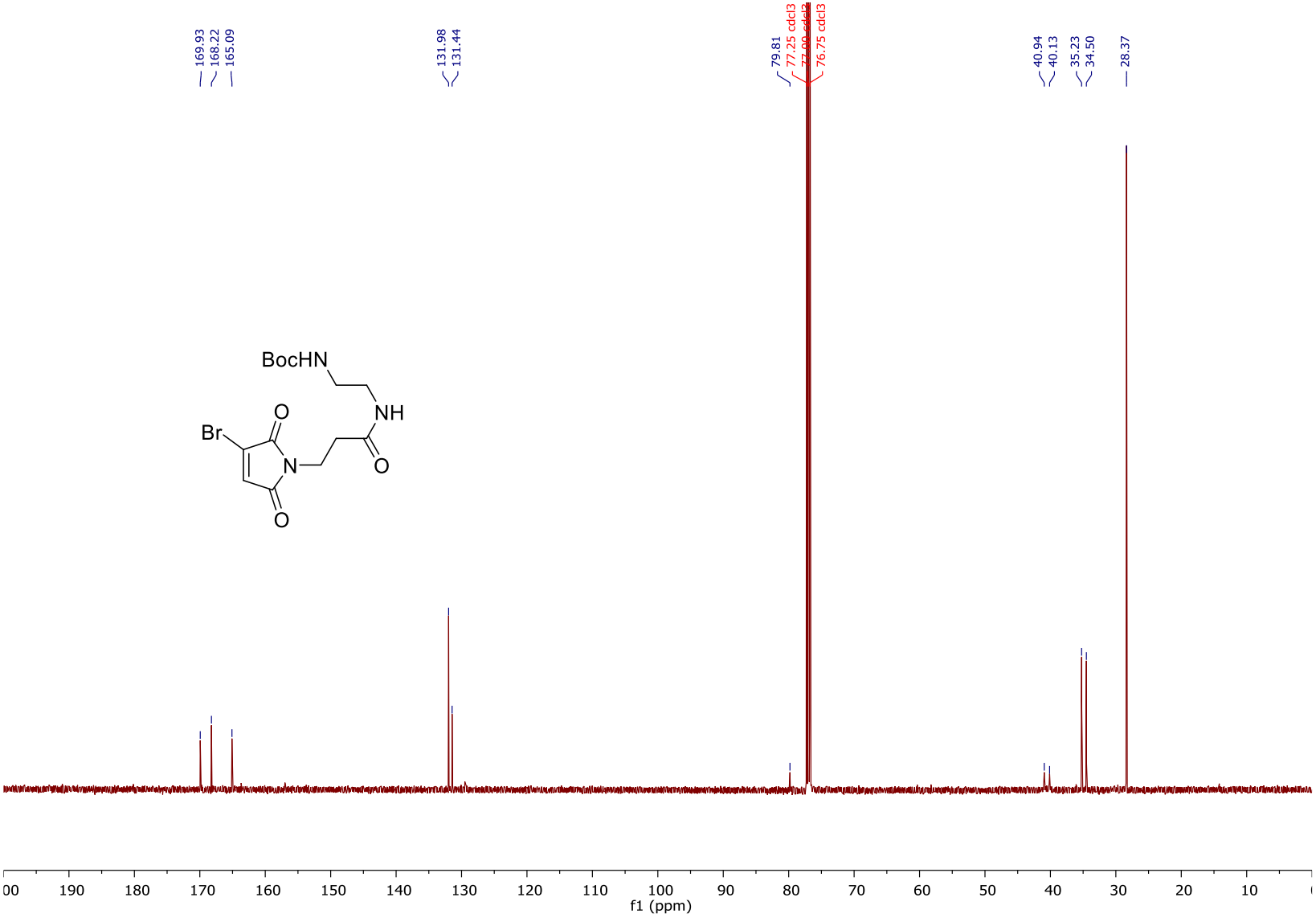
Compound **19** ^{13}C NMR spectrum (500 MHz, $CDCl_3$).



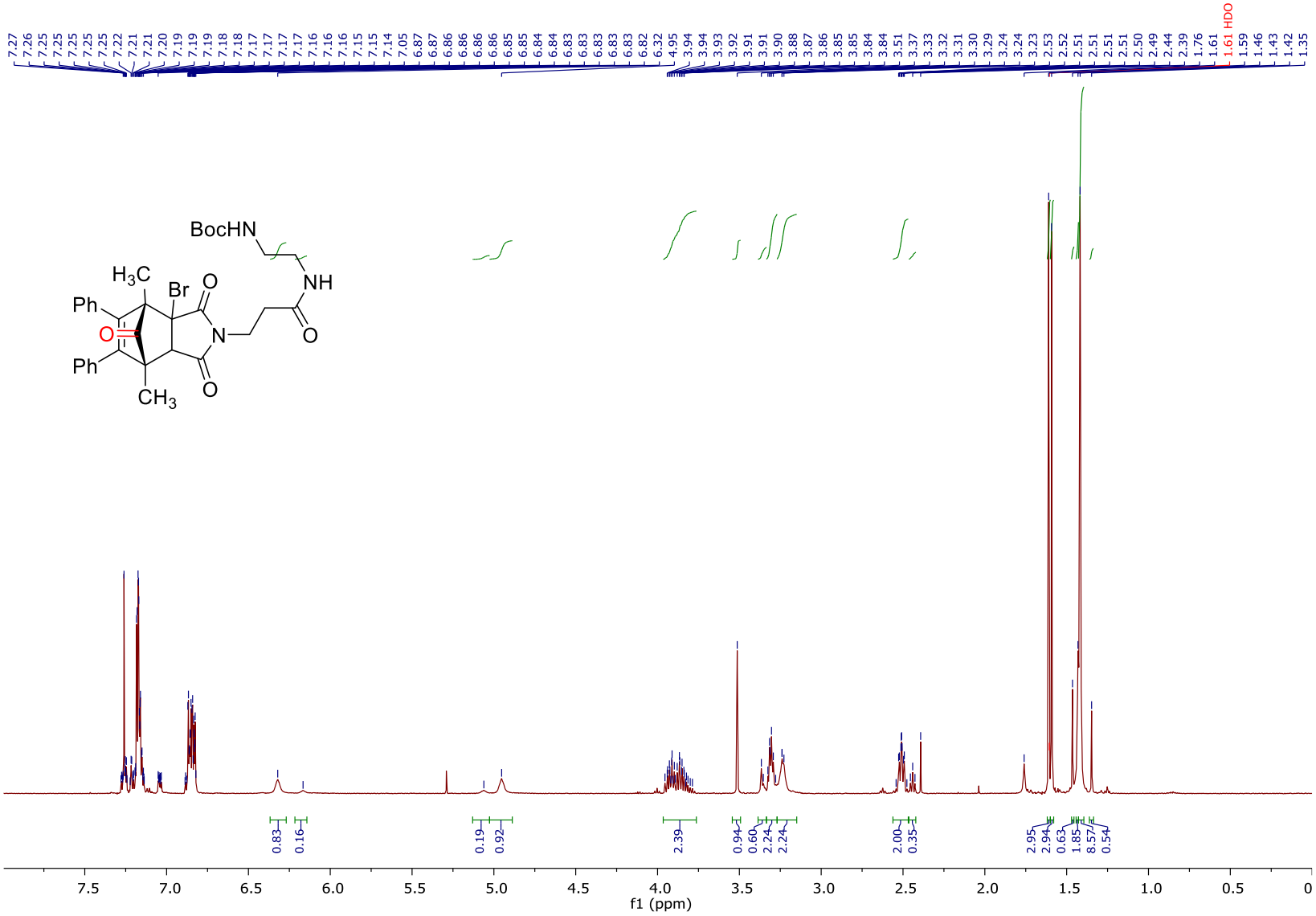
Compound **20** ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



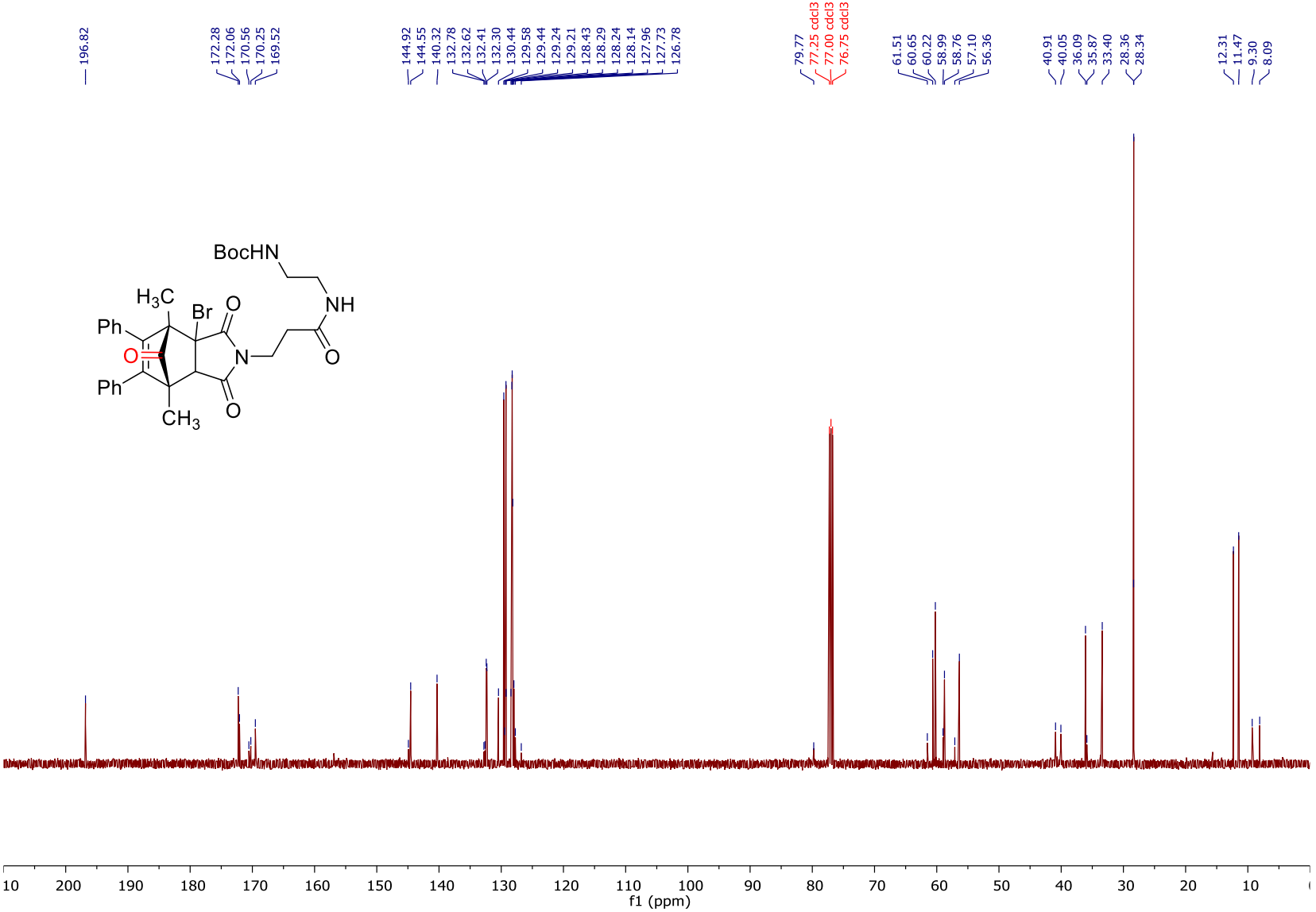
Compound **20** ^{13}C NMR spectrum (500 MHz, $CDCl_3$).



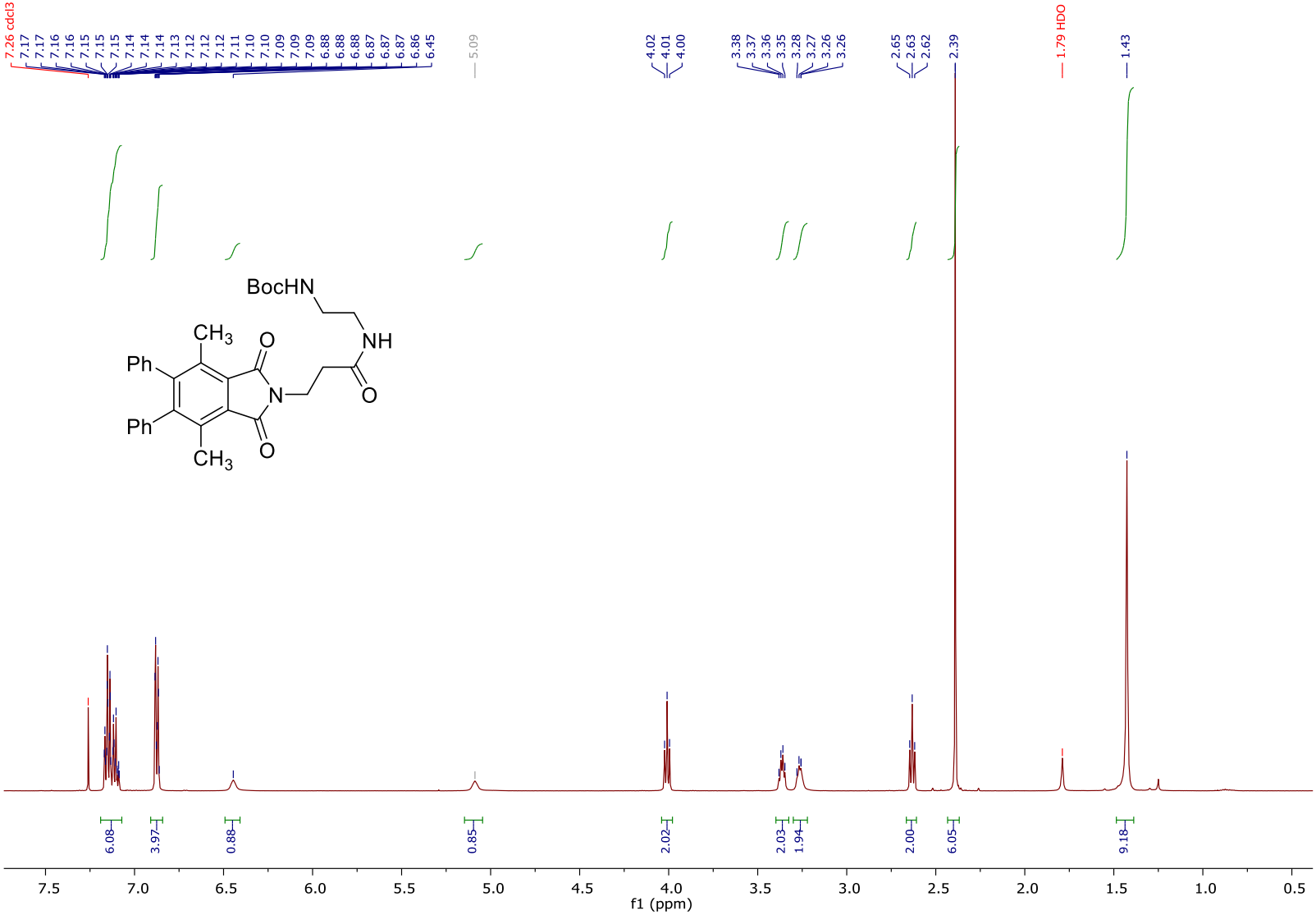
Compound **21**. ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



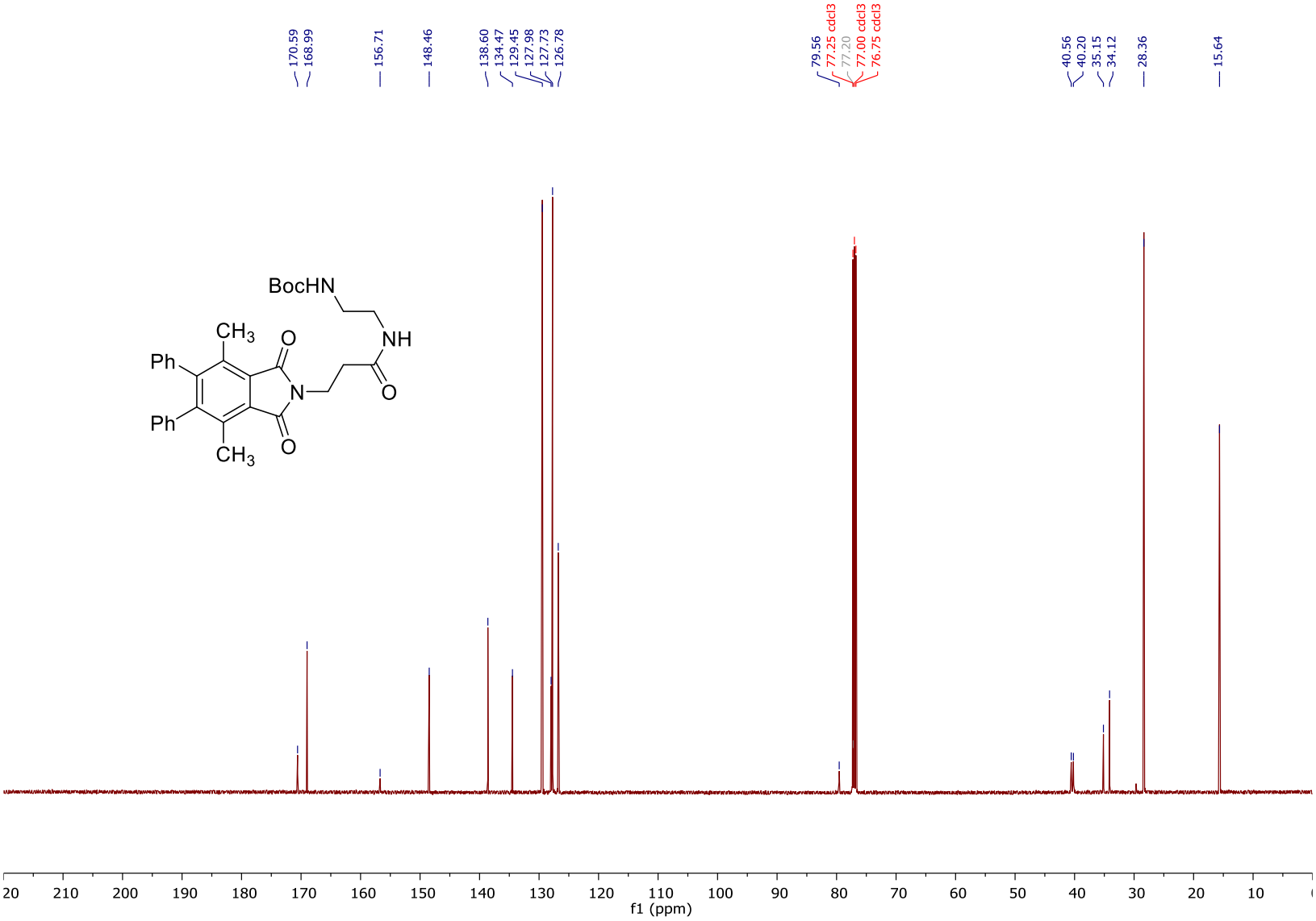
Compound **21** ^{13}C NMR spectrum (500 MHz, $CDCl_3$).



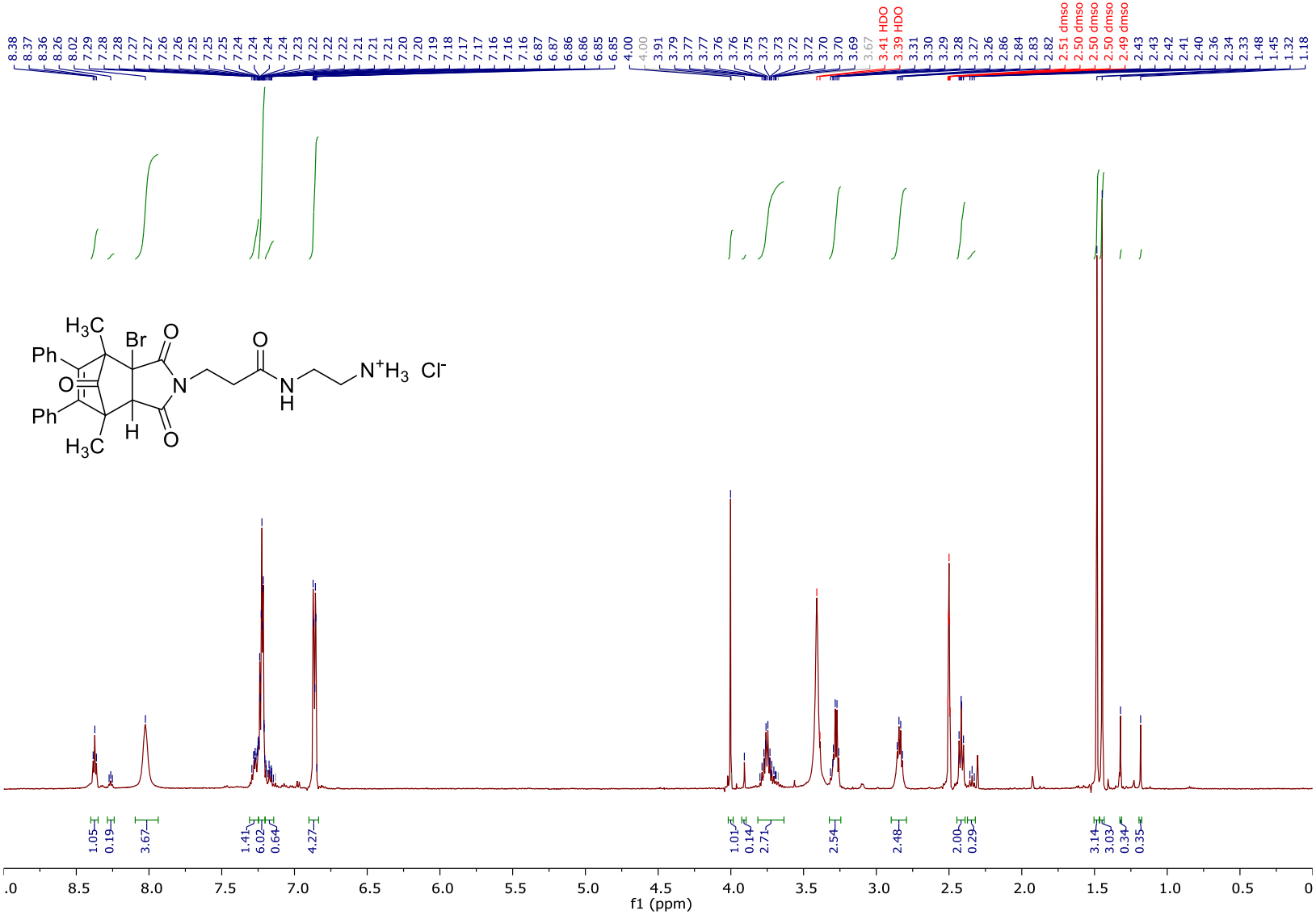
Compound **22**. ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



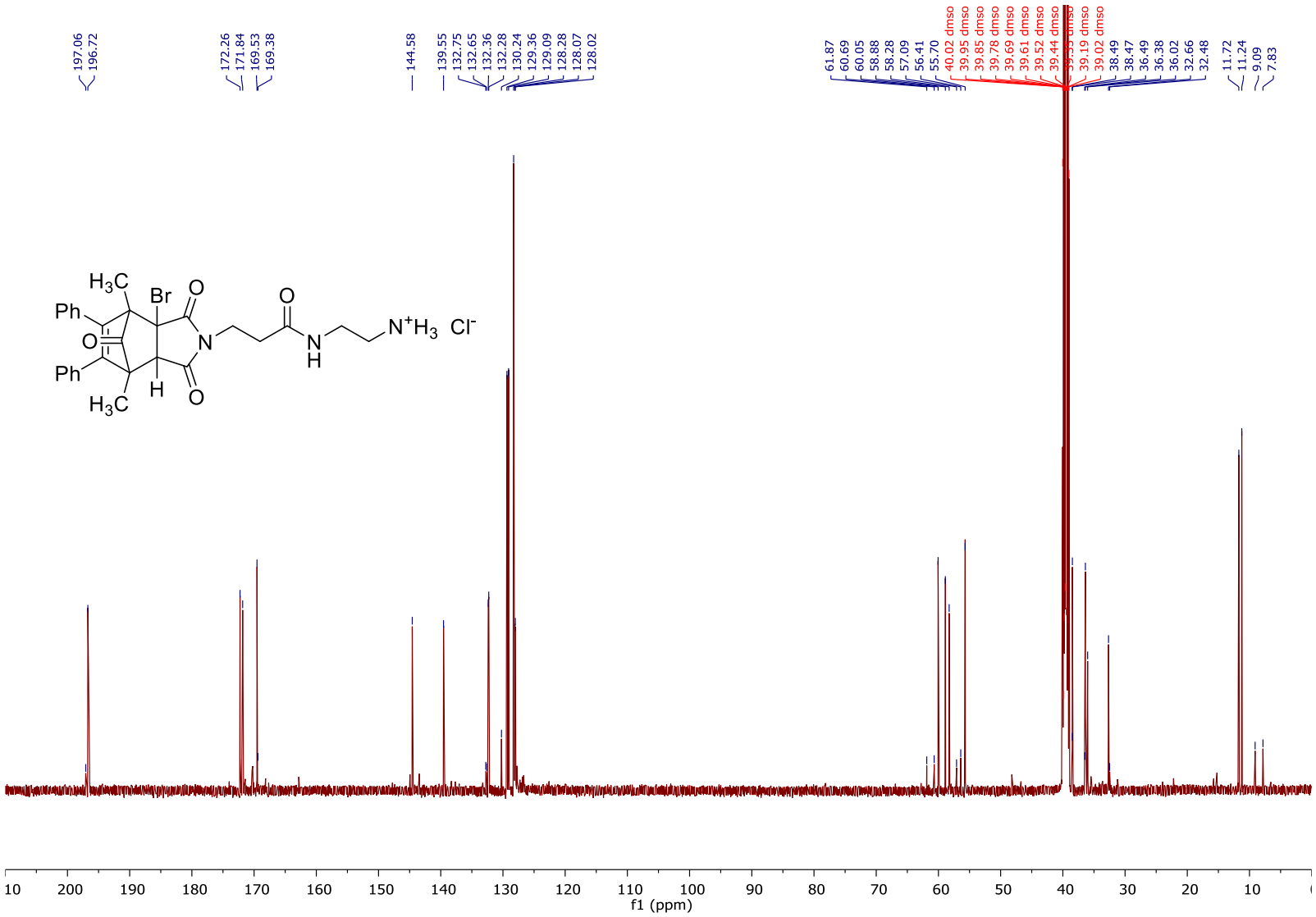
Compound **22** ^{13}C NMR spectrum (500 MHz, $CDCl_3$).



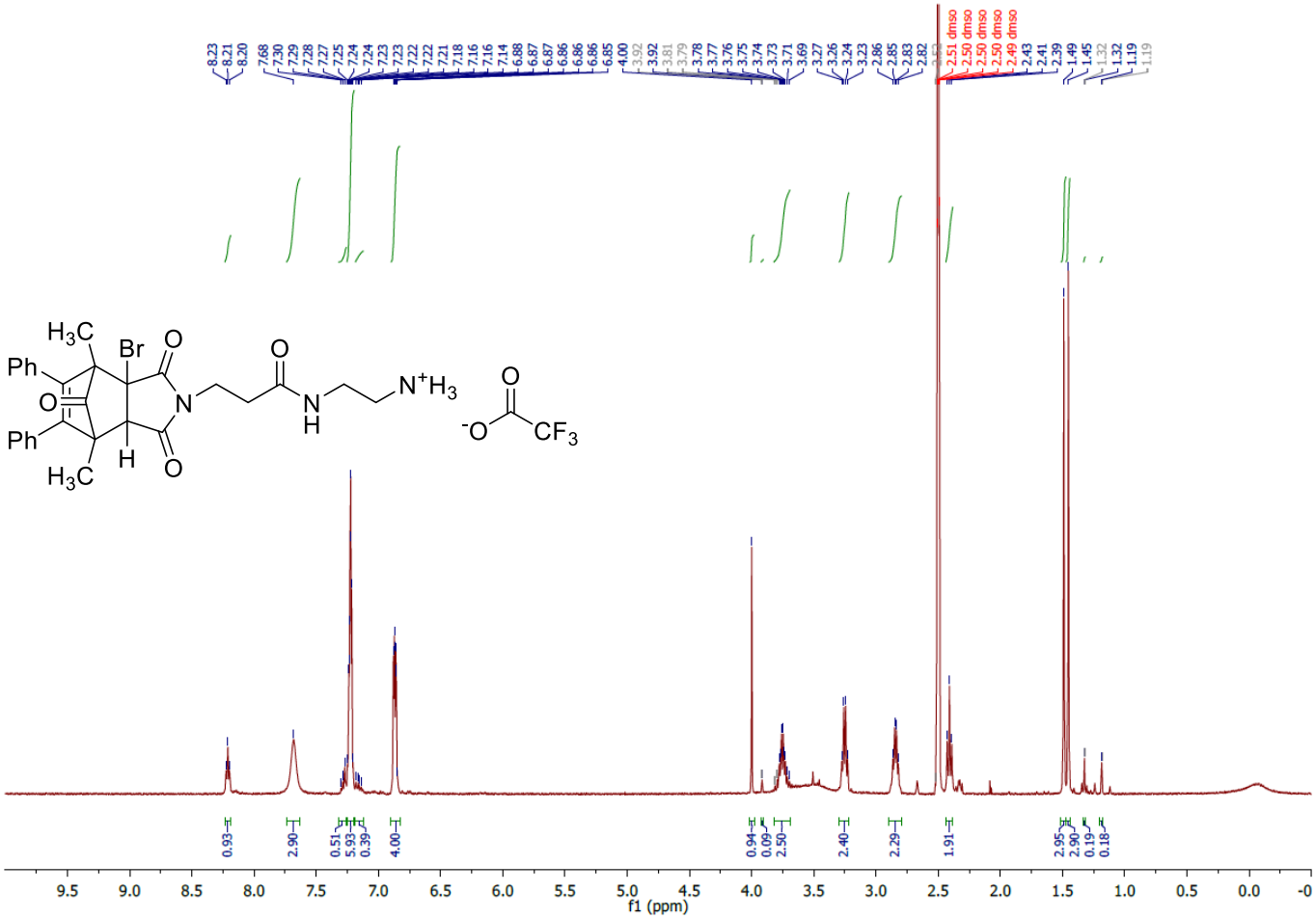
oCOm-19. HCl salt (3:1 mixture of *endo*- and *exo*-isomers). ^{1}H NMR spectrum (400 MHz, DMSO-*d6*).



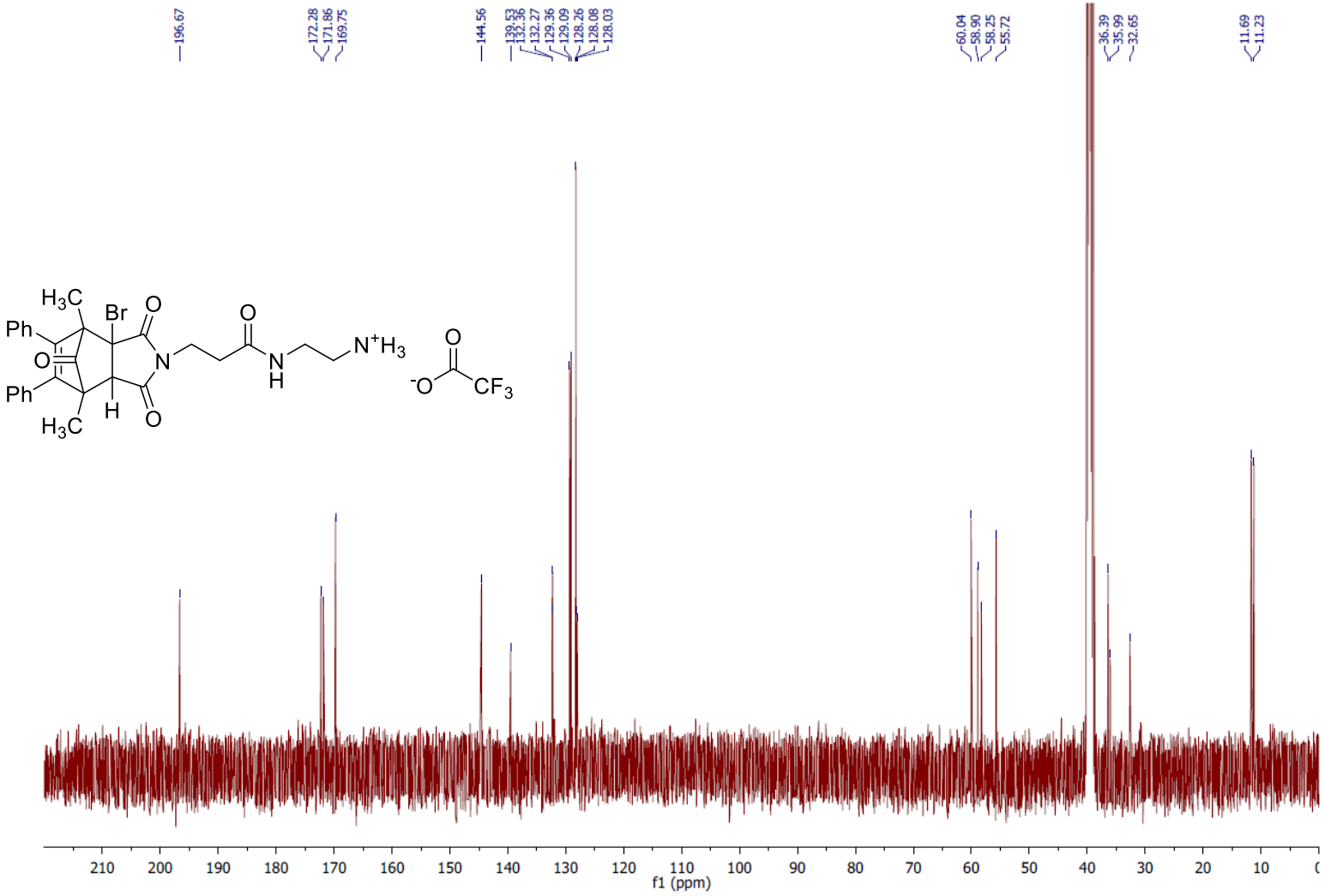
oCOm-19. HCl salt (3:1 mixture of *endo*- and *exo*-isomers)^{13C} NMR spectrum (125 MHz, DMSO-d6)



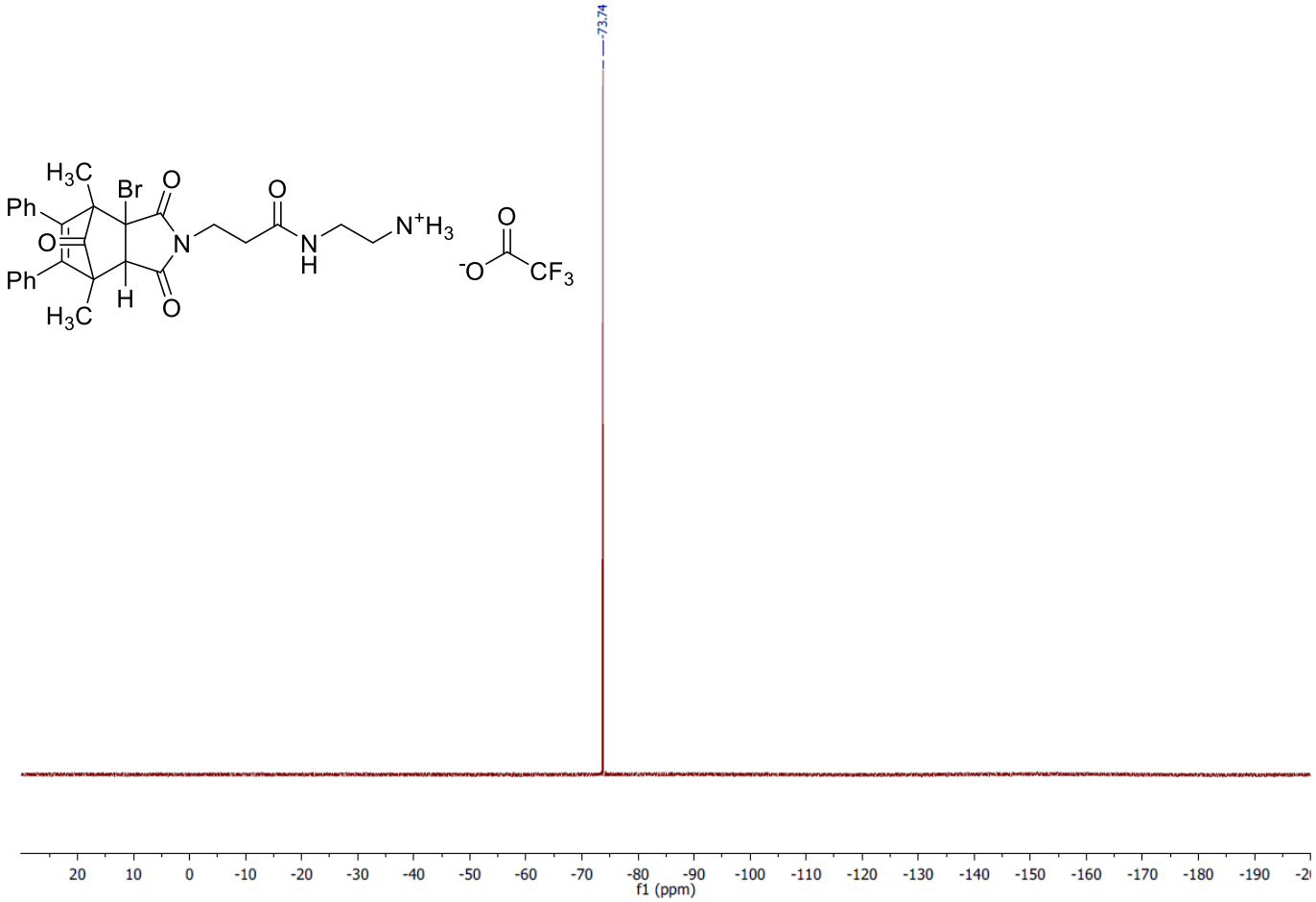
oCOm-19. TFA salt (10:1 mixture of *endo*- and *exo*-isomers). ^{1}H NMR spectrum (400 MHz, DMSO-*d6*).



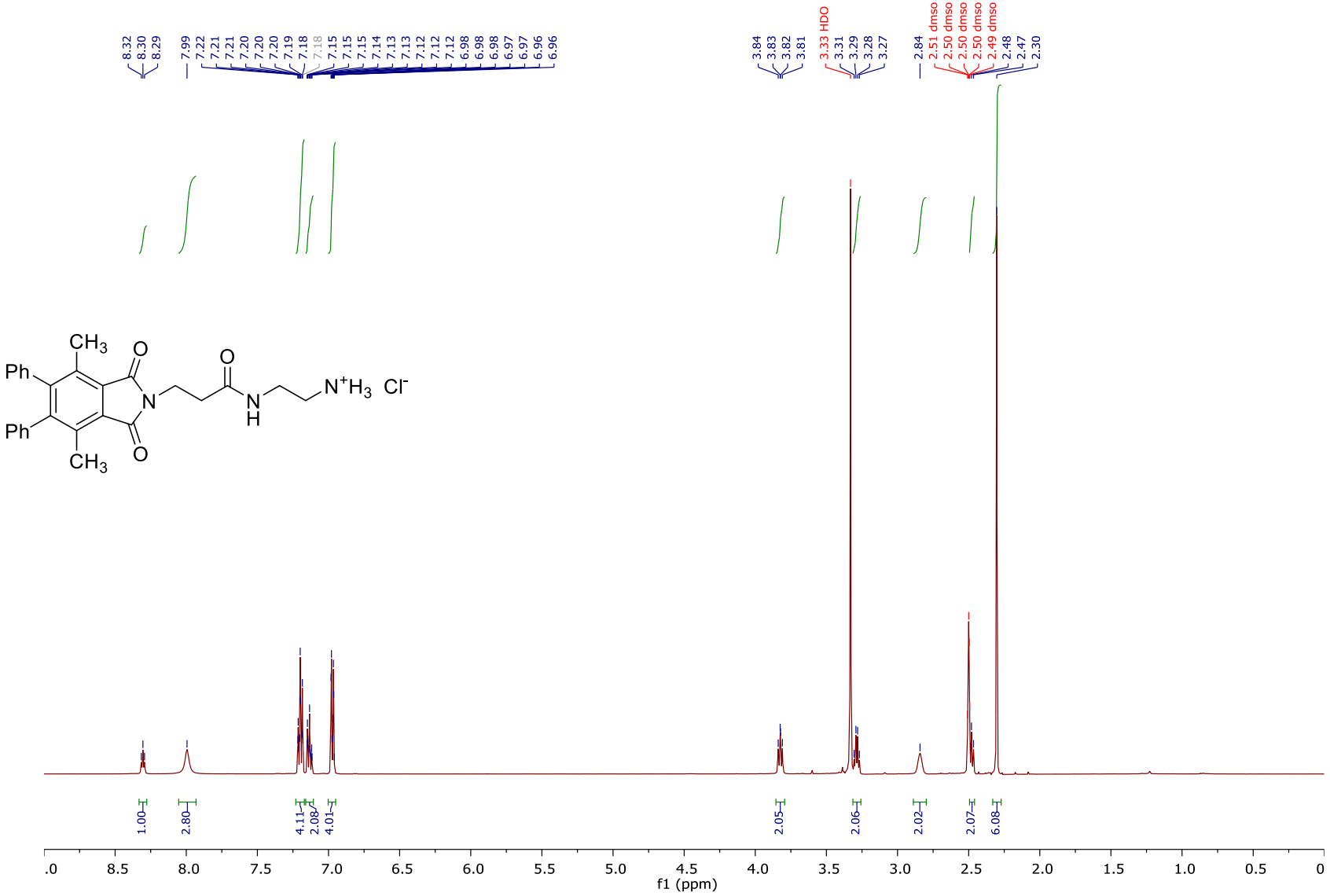
oCOm-19. TFA salt (10:1 mixture of *endo*- and *exo*-isomers). ^{13}C NMR spectrum (125 MHz, DMSO-*d6*).



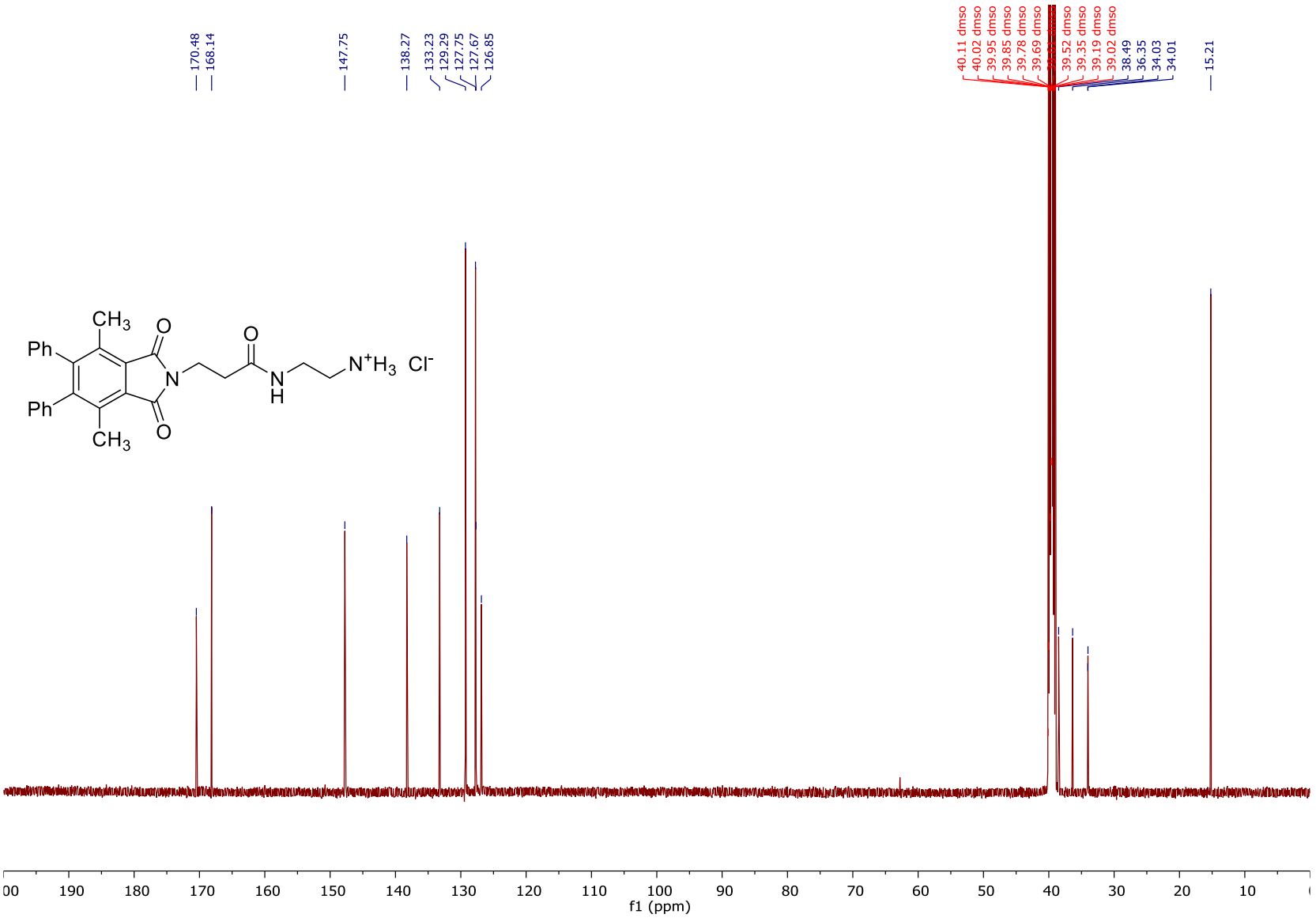
oCOm-19. TFA salt (10:1 mixture of endo- and exo-isomers). 19F NMR spectrum (376 MHz, DMSO-d6).



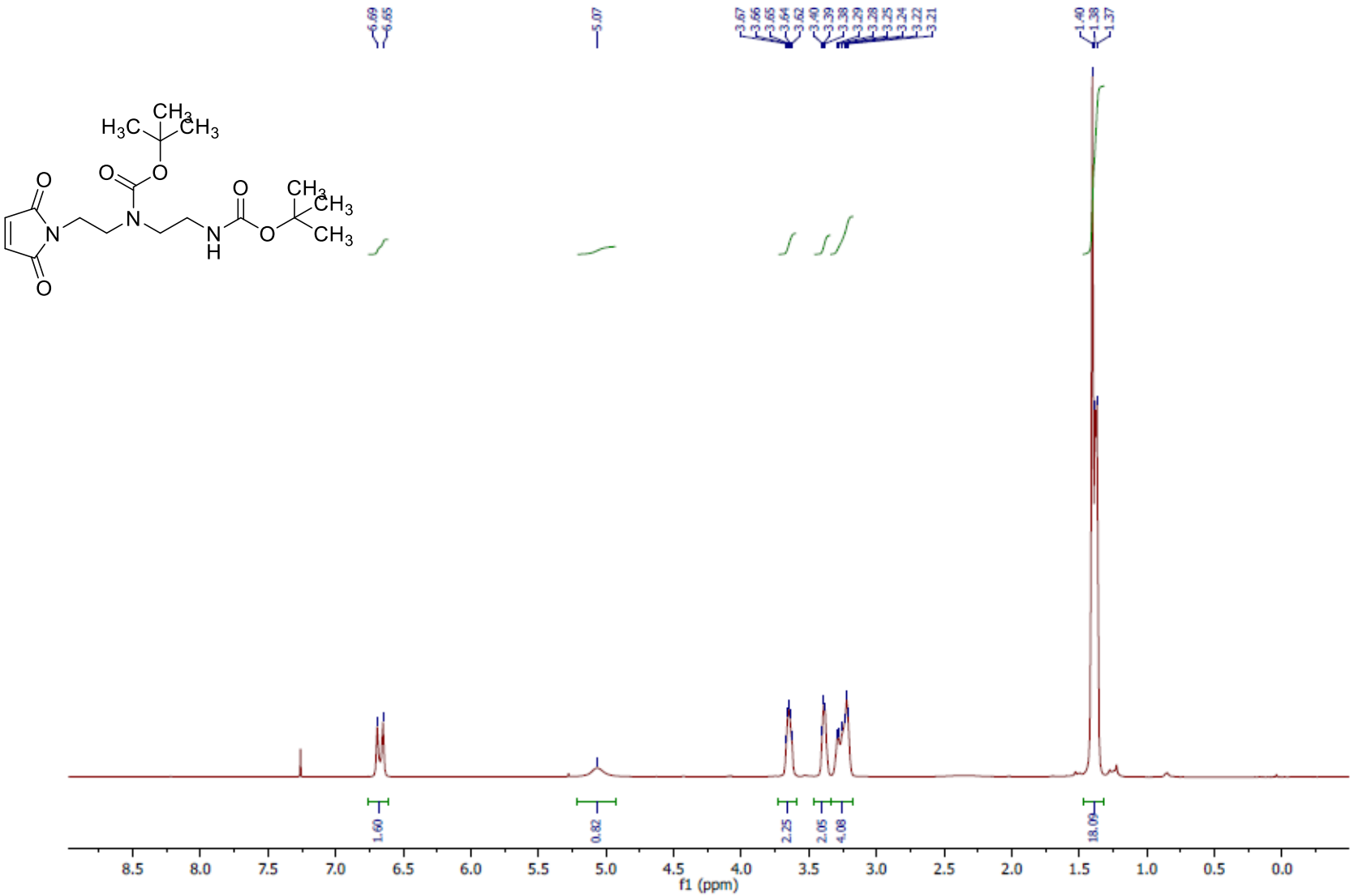
BP-CO-19. HCl salt (10:1 mixture of *endo*- and *exo*-isomers). ^{1}H NMR spectrum (500 MHz, DMSO-*d6*).



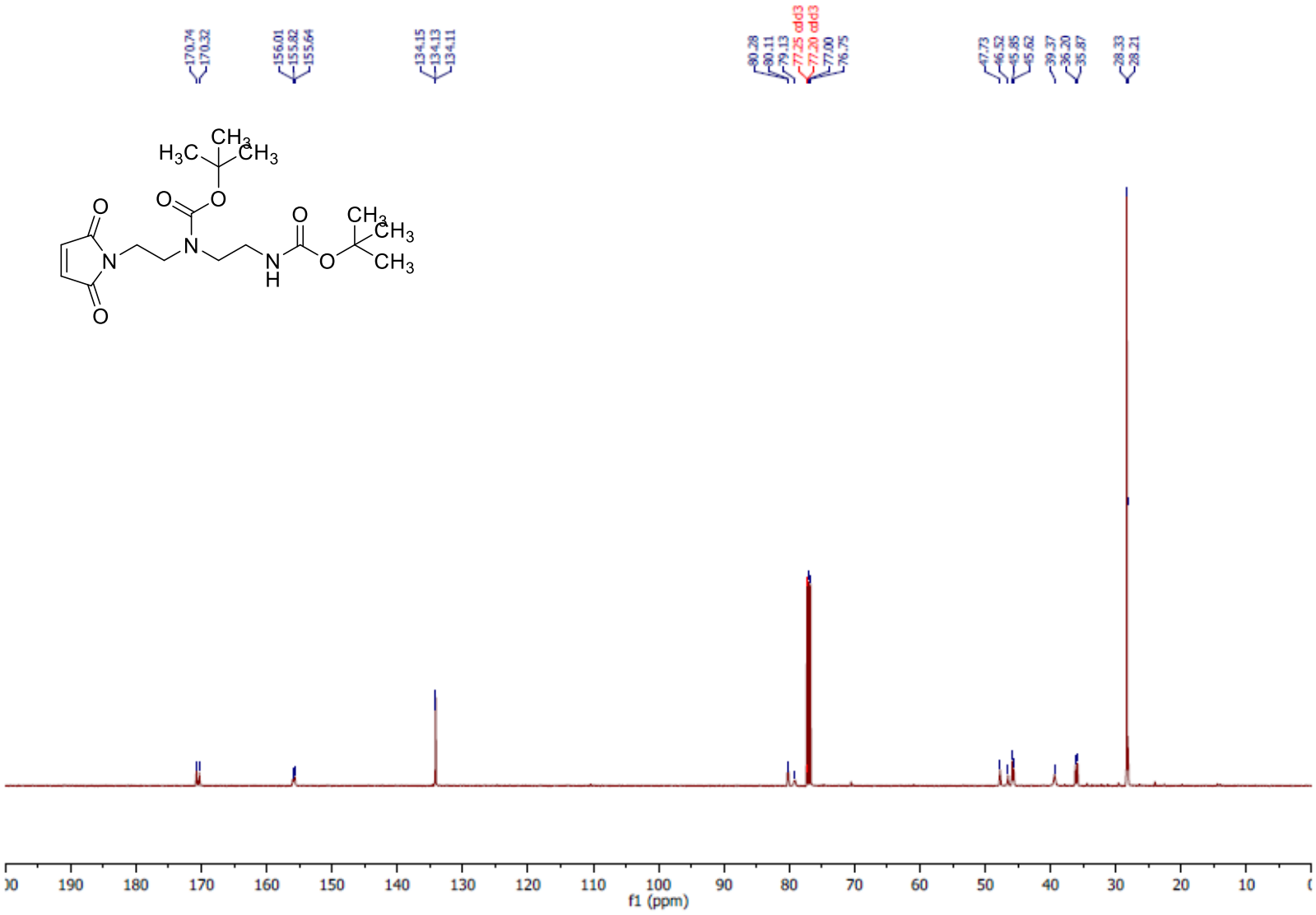
BP-CO-19. HCl salt (10:1 mixture of *endo*- and *exo*-isomers). ^{1}H NMR spectrum (500 MHz, DMSO-*d6*).



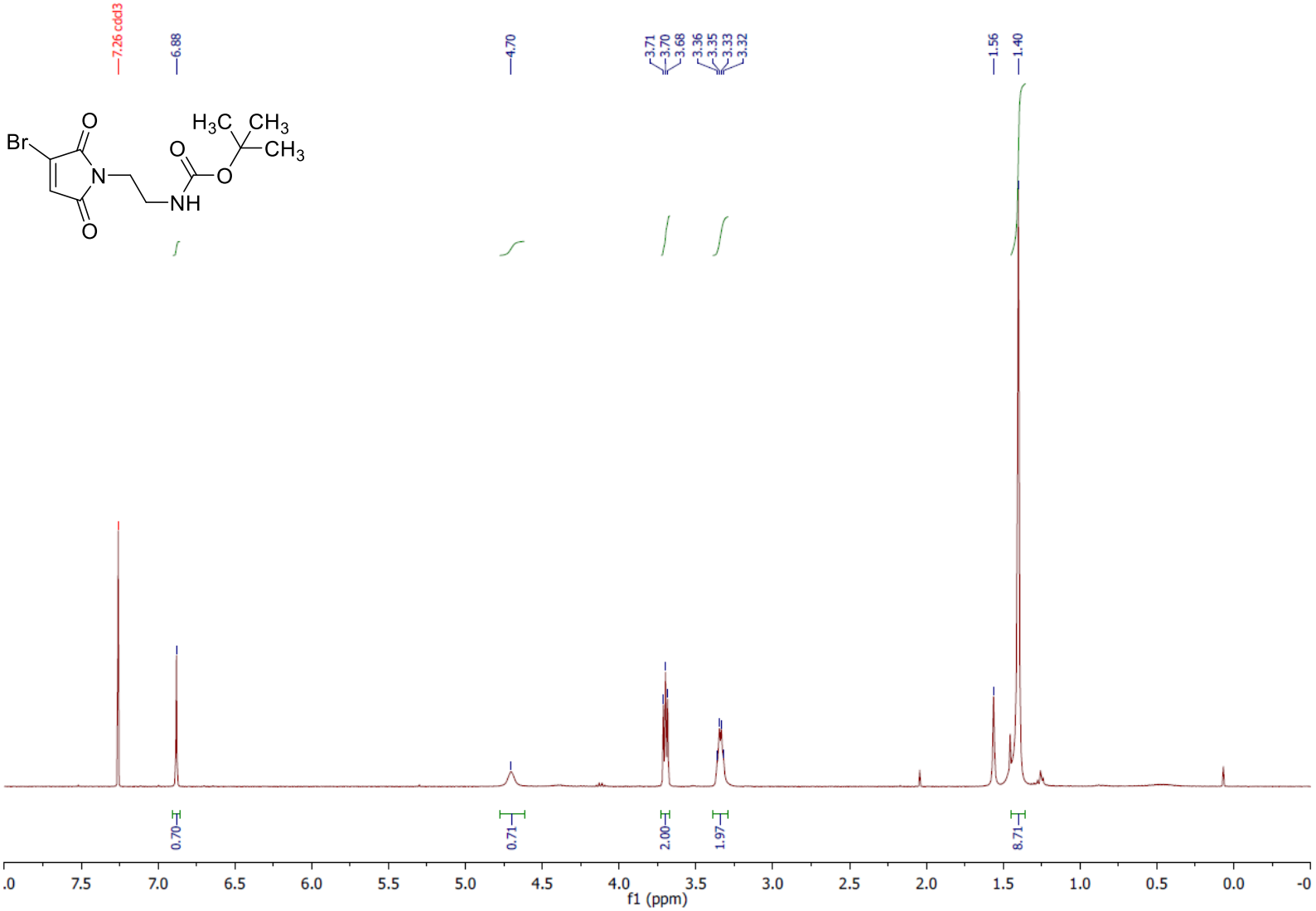
Compound **25**. ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



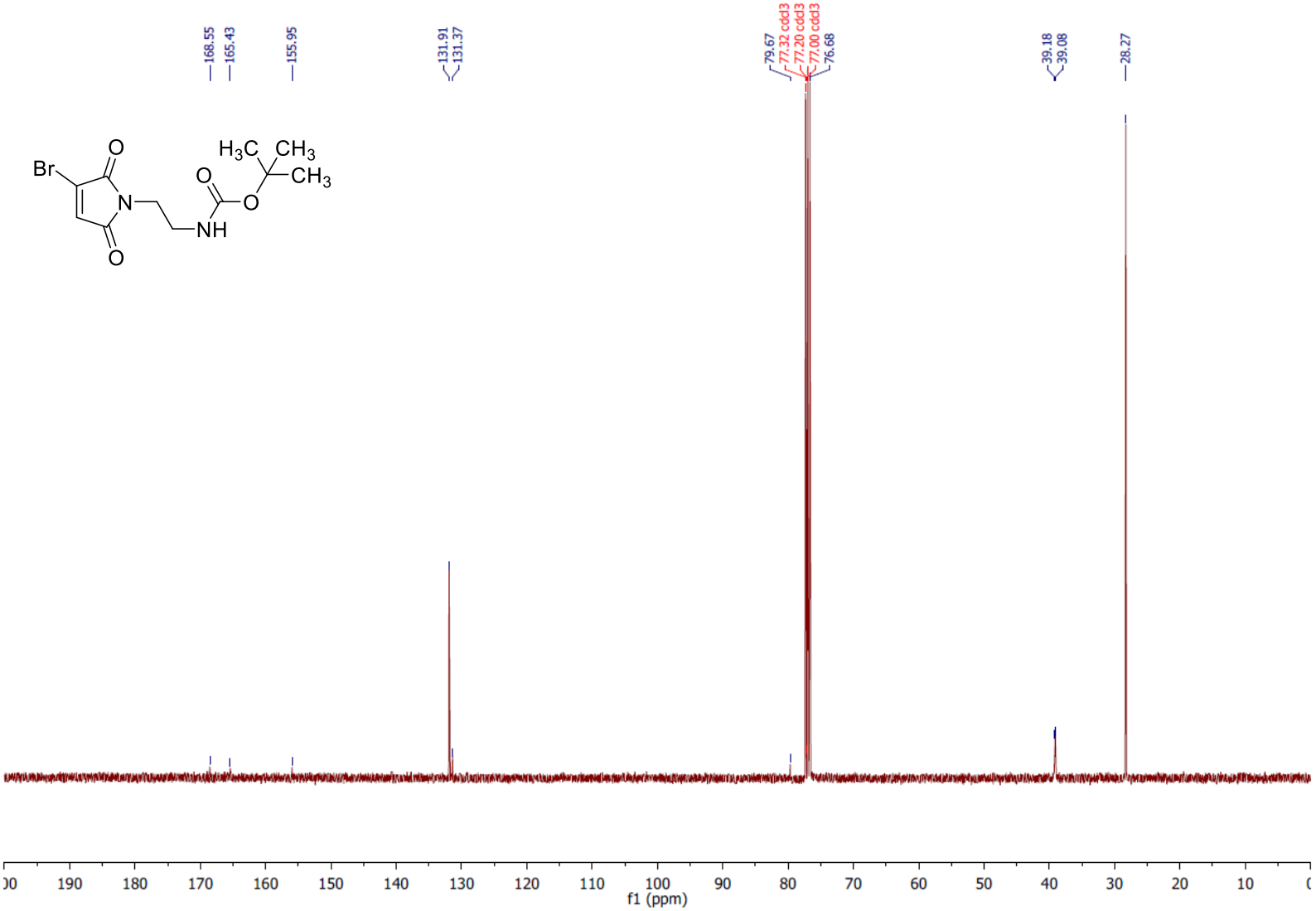
Compound **25**. ^{13}C NMR spectrum (125 MHz, $CDCl_3$).



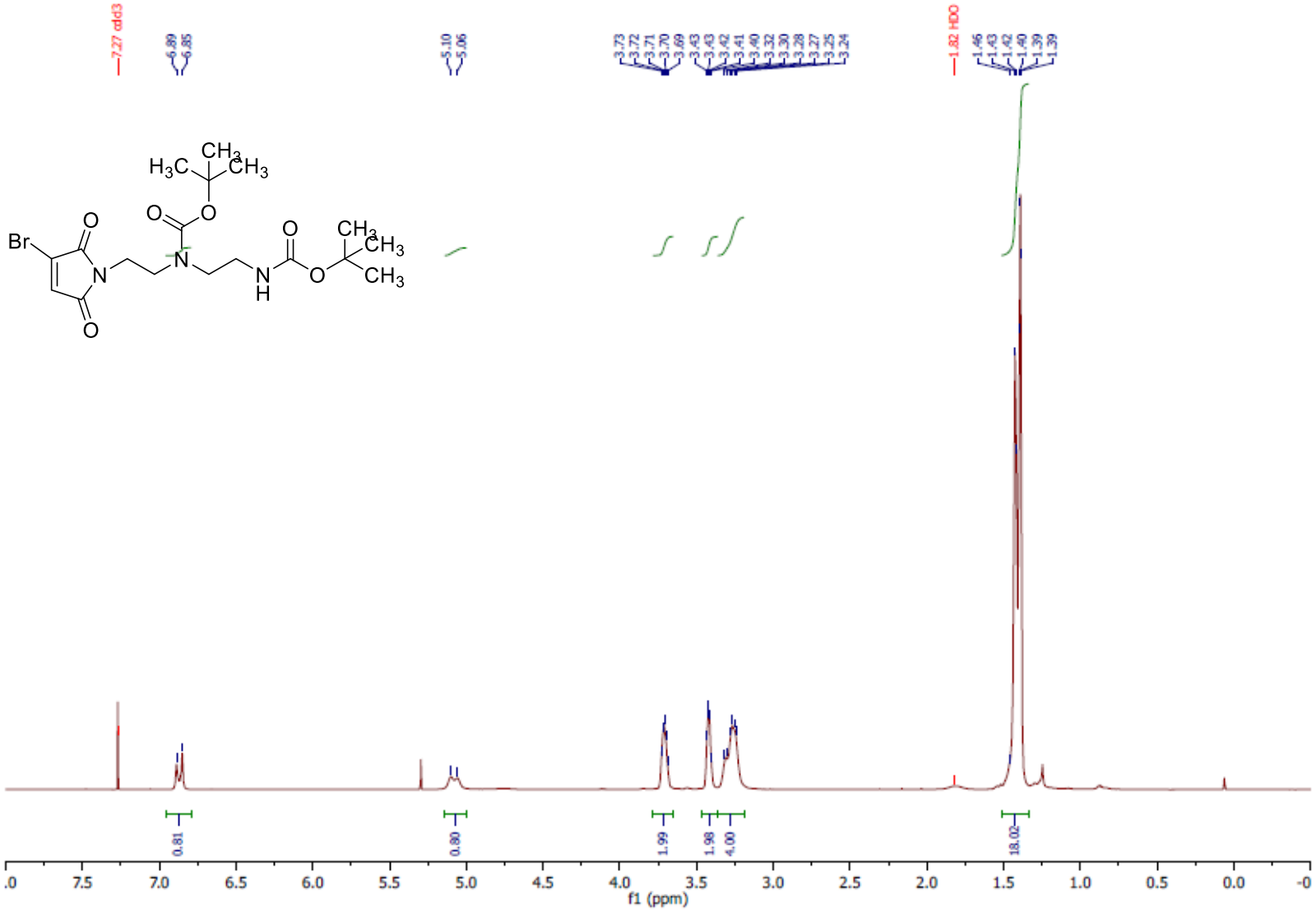
Compound **26**. ^{1}H NMR spectrum (400 MHz, $CDCl_3$).



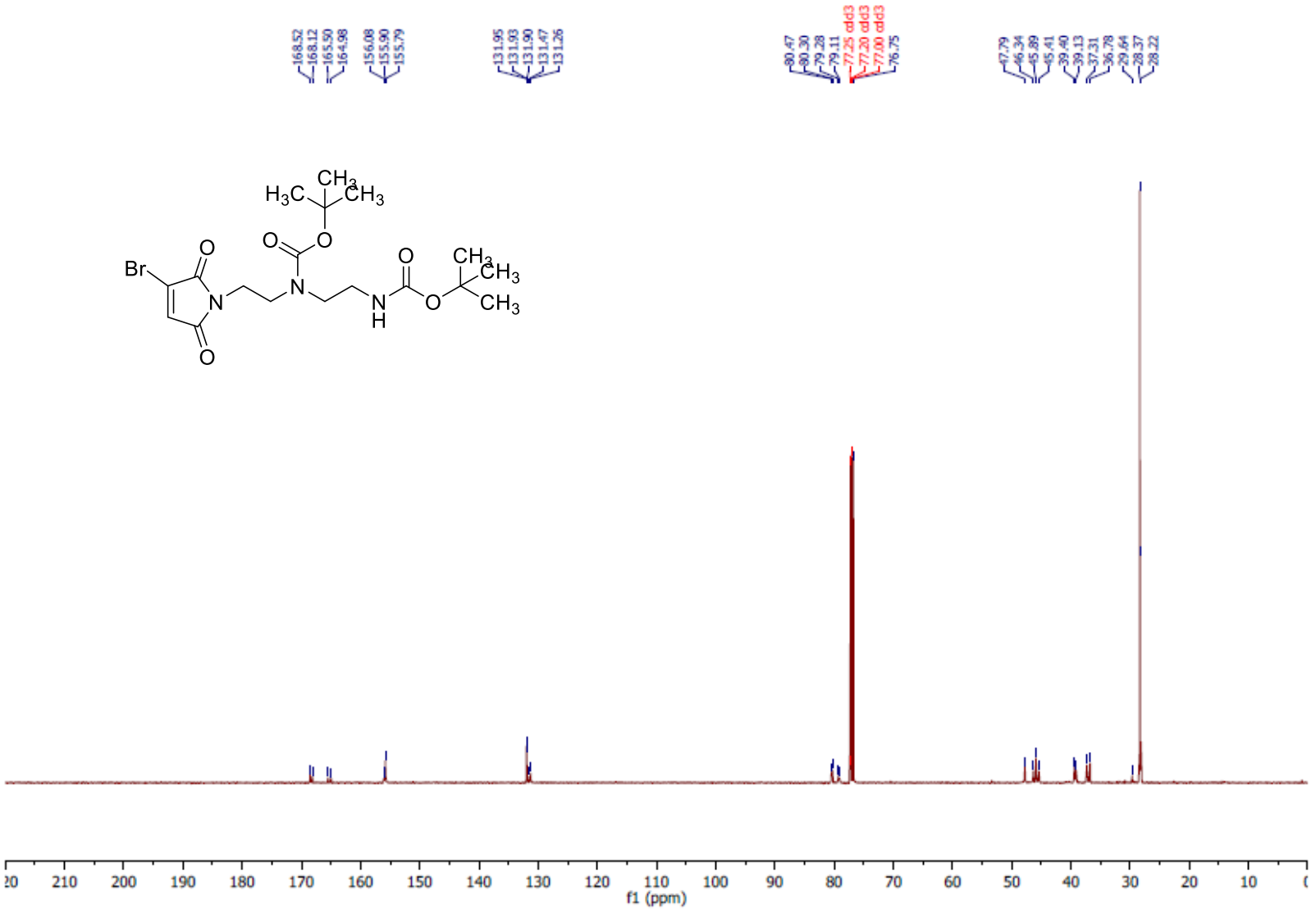
Compound **26**. ^{13}C NMR spectrum (100 MHz, $CDCl_3$).



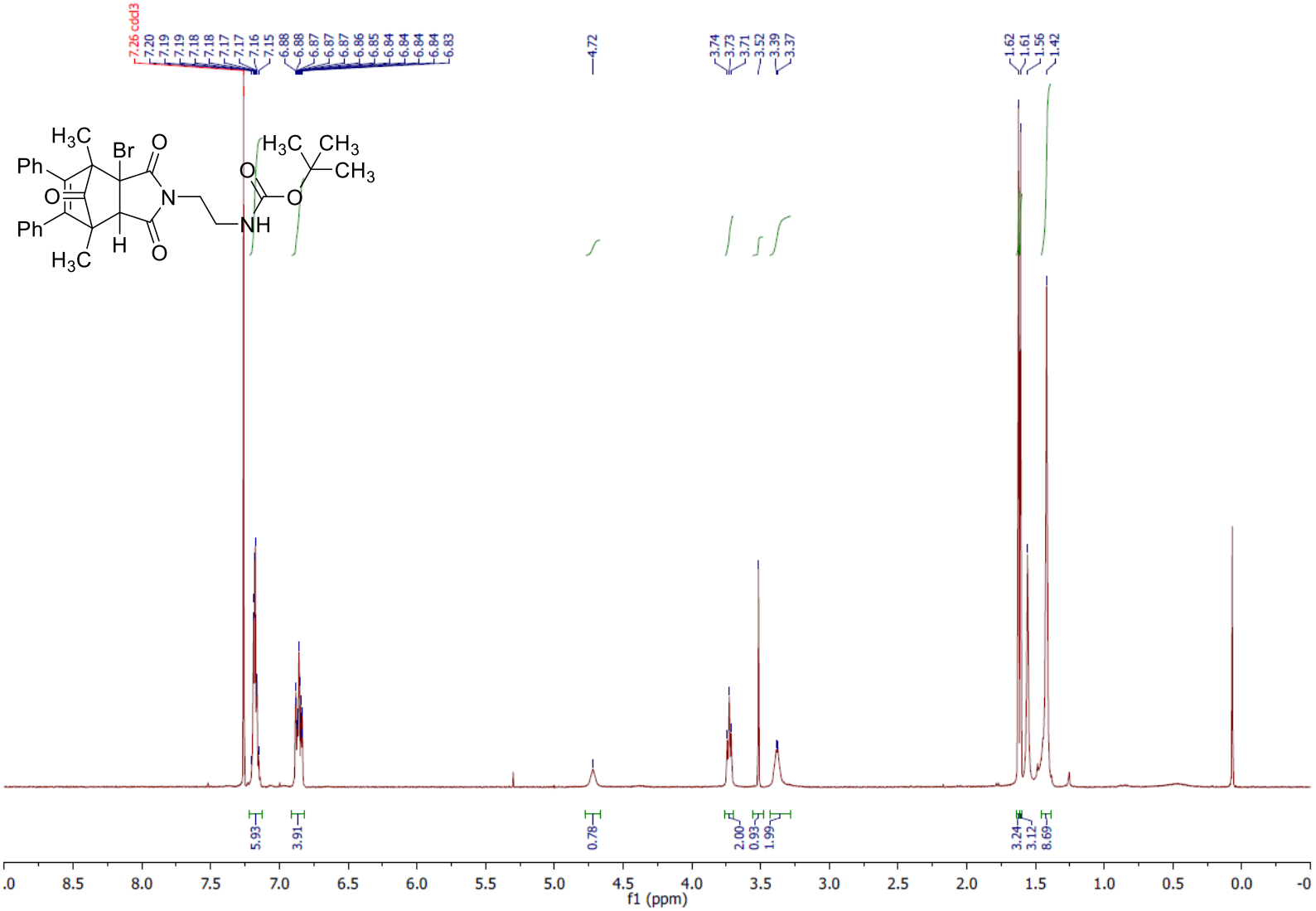
Compound **27**. ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



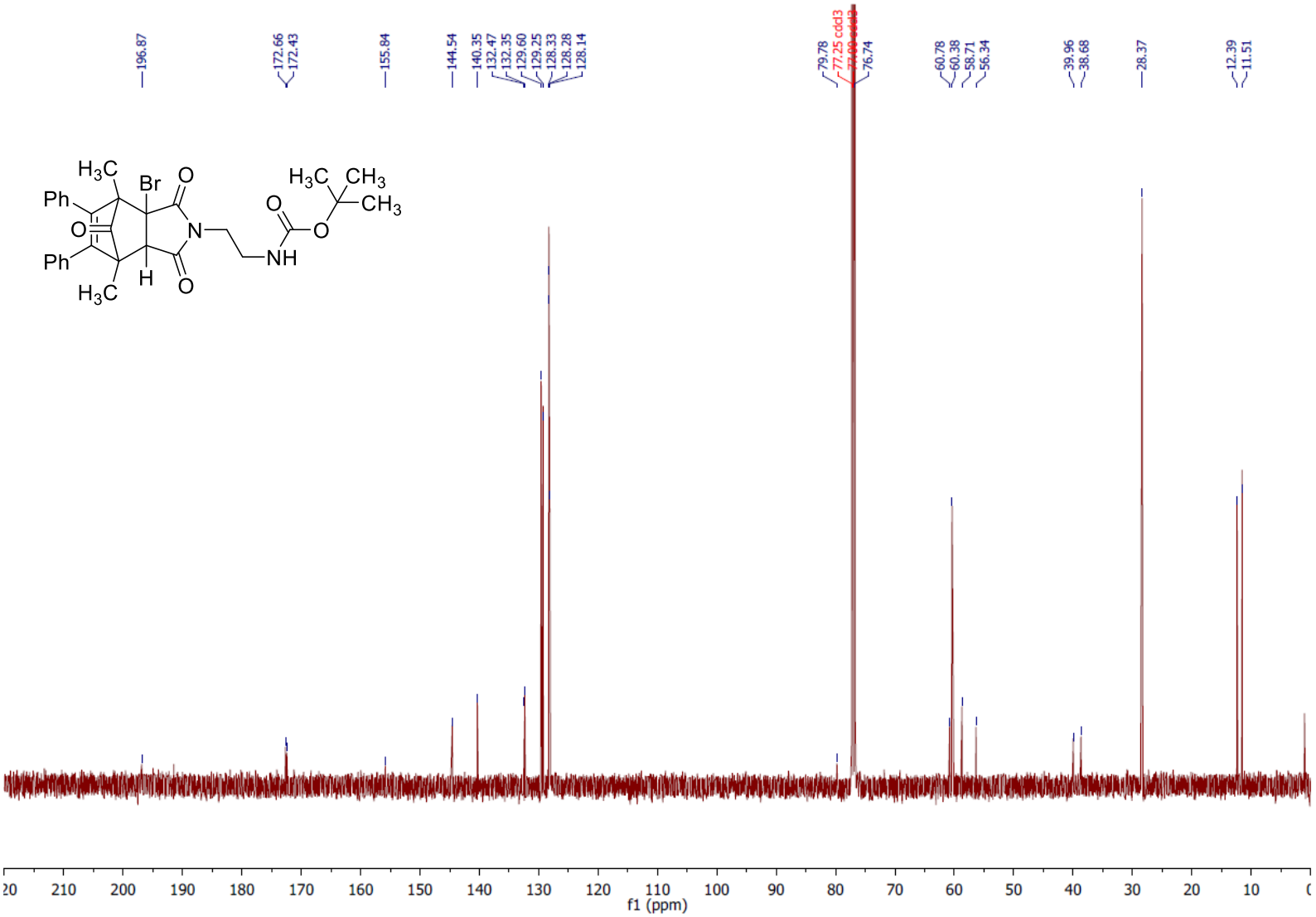
Compound **27**. ^{13}C NMR spectrum (125 MHz, $CDCl_3$).



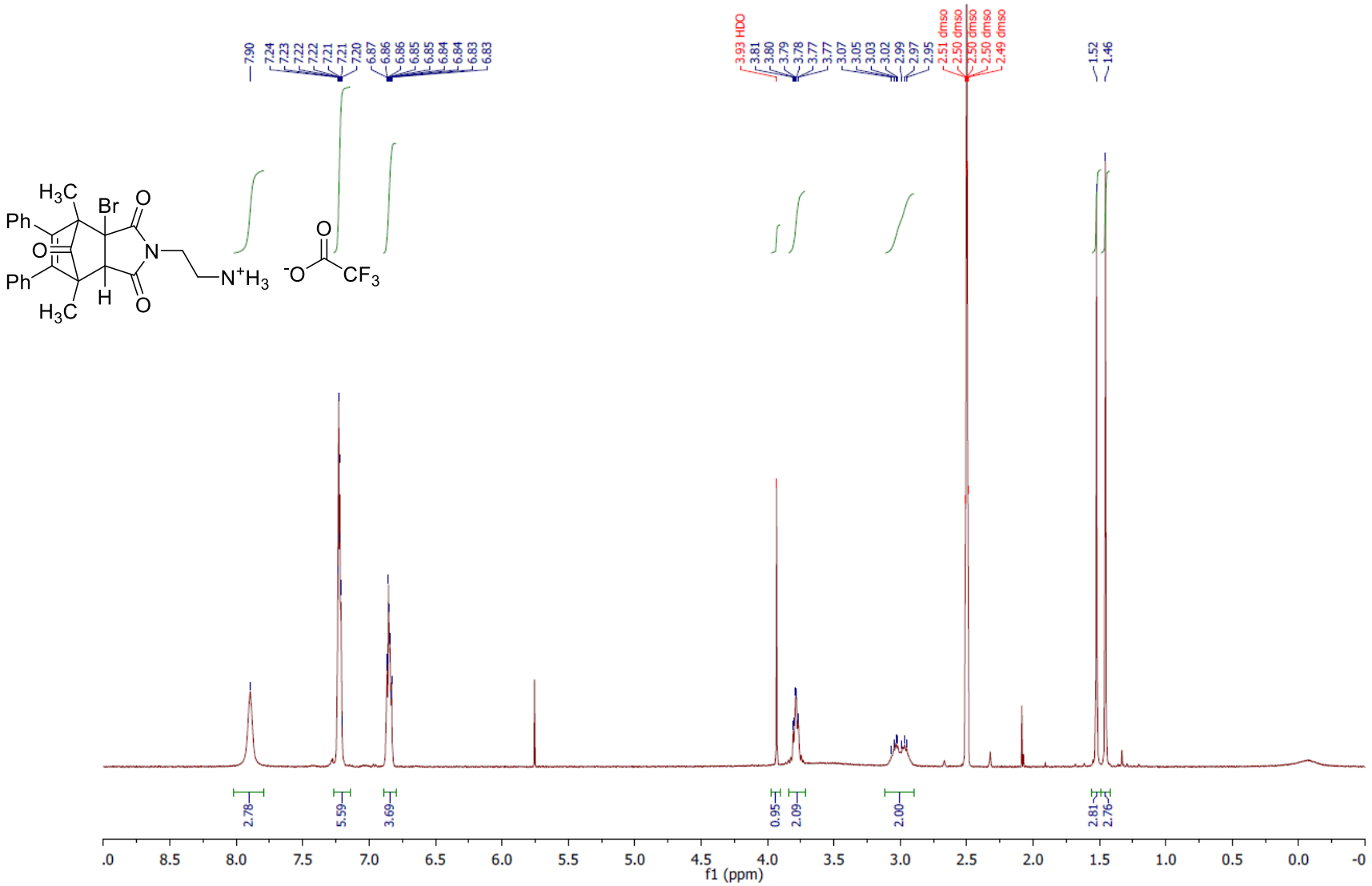
Compound **28** (*endo*-isomer). ^{1}H NMR spectrum (400 MHz, $CDCl_3$).



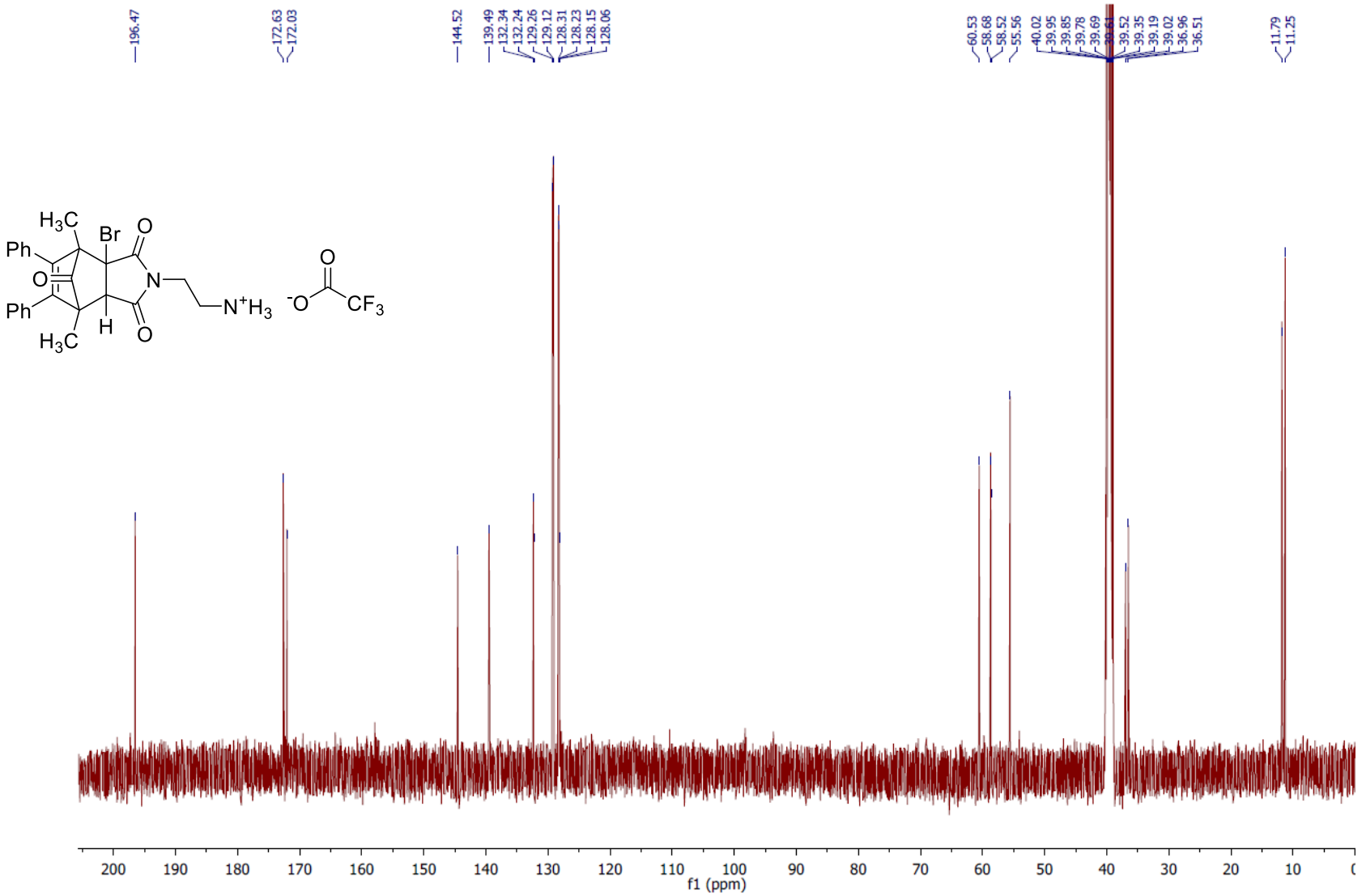
Compound **28** (*endo*-isomer). ^{13}C NMR spectrum (125 MHz, $CDCl_3$).



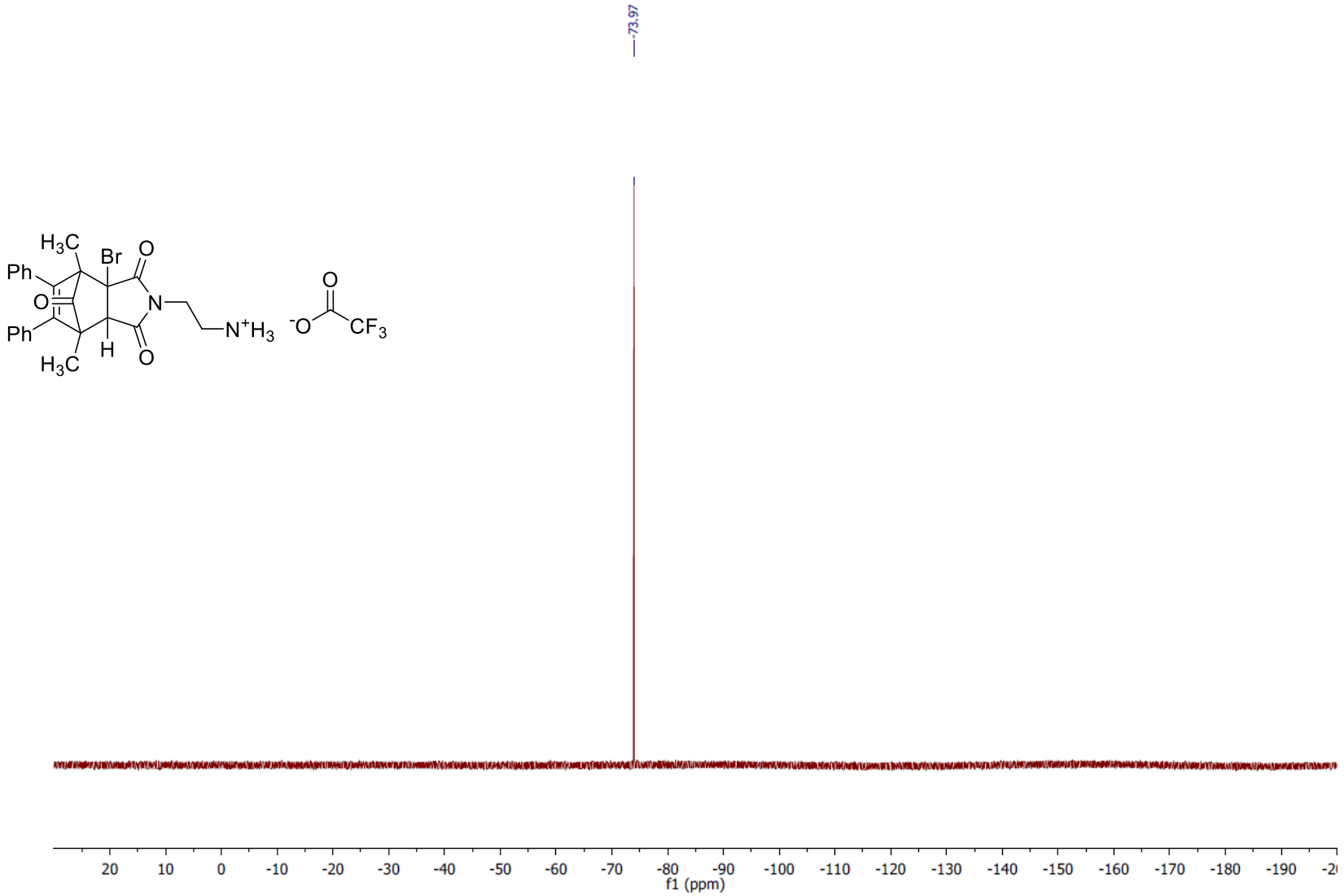
o**COm-21** (*endo*-isomer). ^{1}H NMR spectrum (400 MHz, DMSO-*d6*).



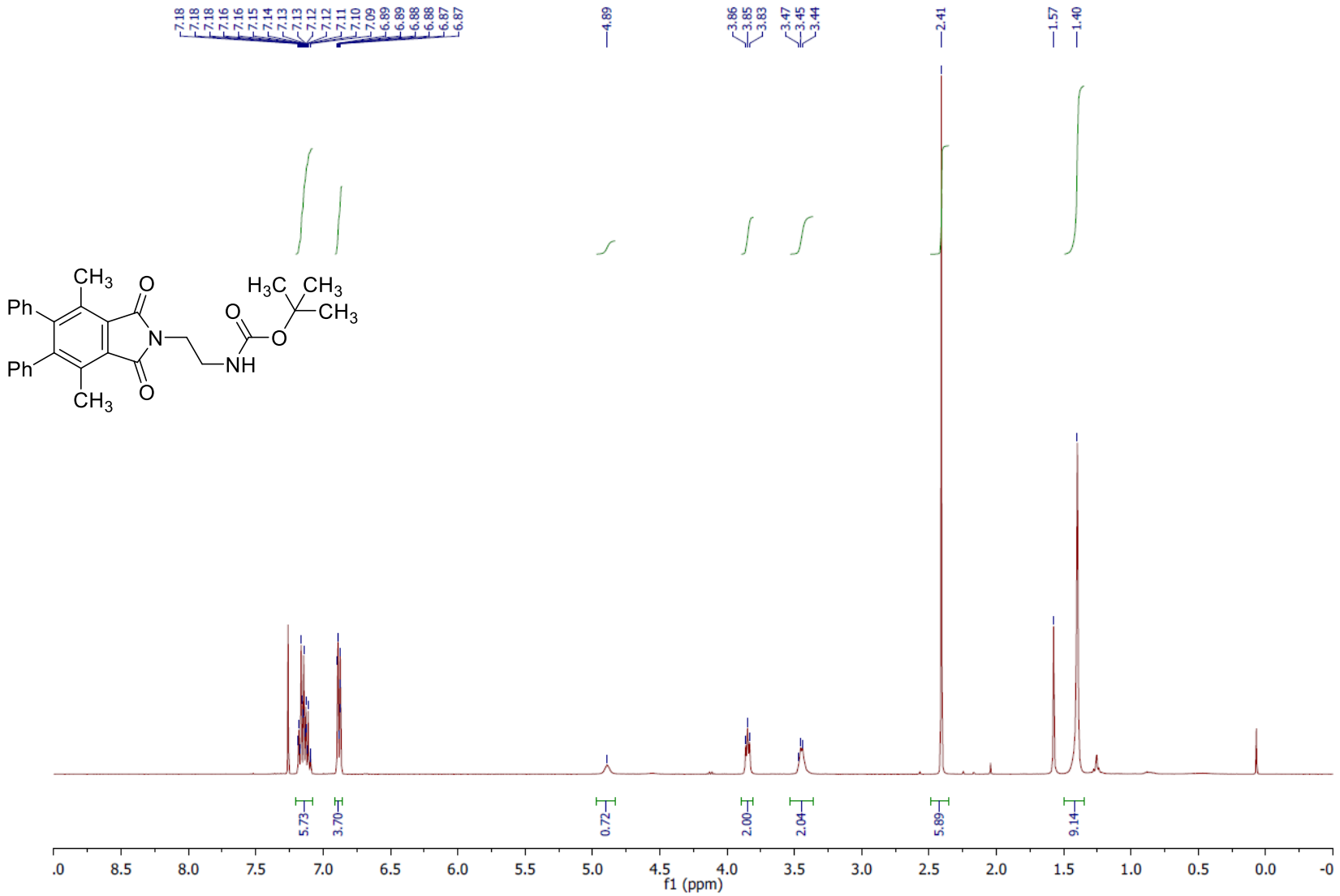
o**COm-21** (*endo*-isomer). ^{13}C NMR spectrum (125 MHz, DMSO-*d6*).



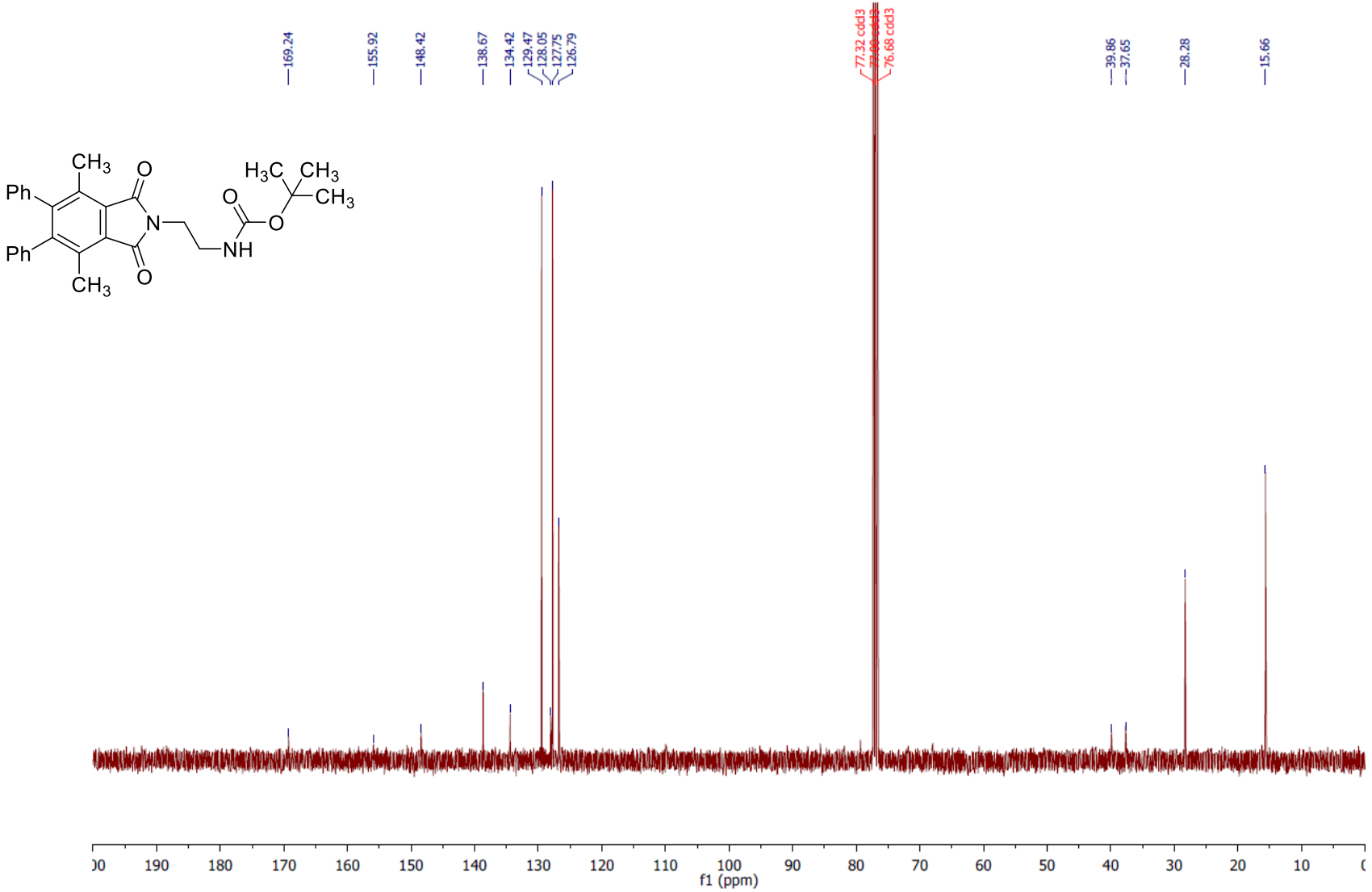
o**COm-21** (*endo*-isomer). ^{19}F NMR spectrum (376 MHz, DMSO-*d6*).



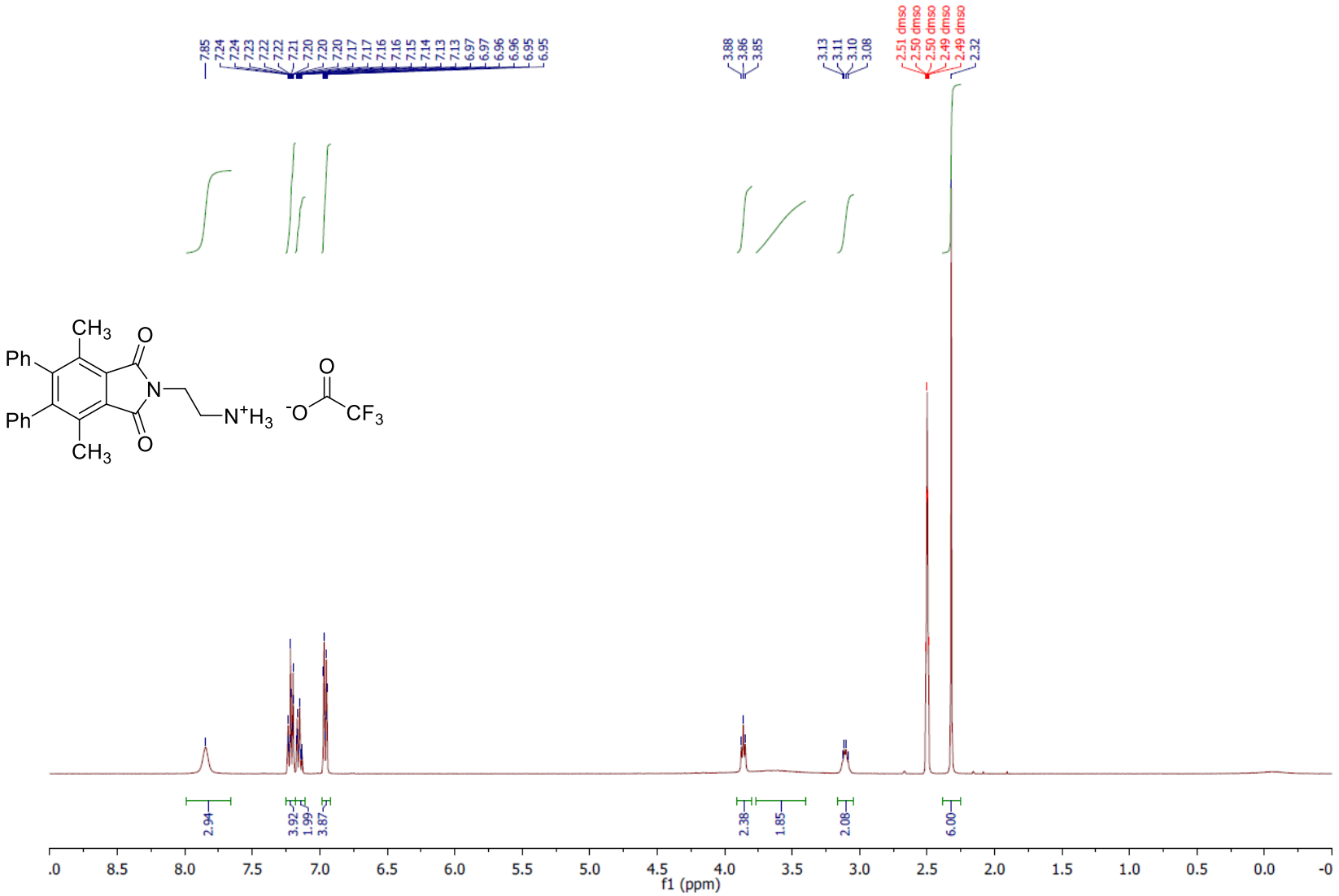
Compound **30**. ^{1}H NMR spectrum (400 MHz, $CDCl_3$).



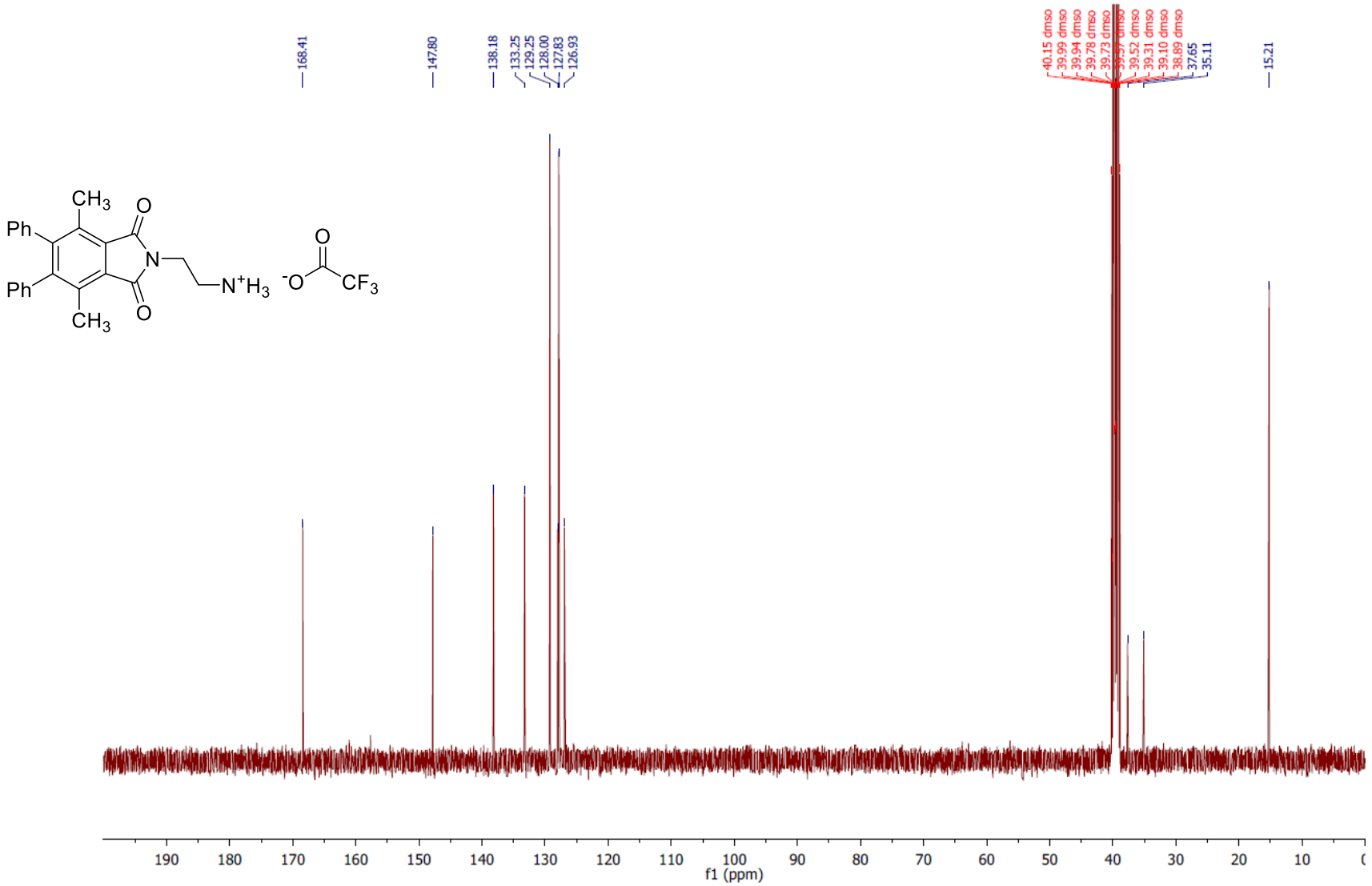
Compound **30**. ^{13}C NMR spectrum (100 MHz, $CDCl_3$).



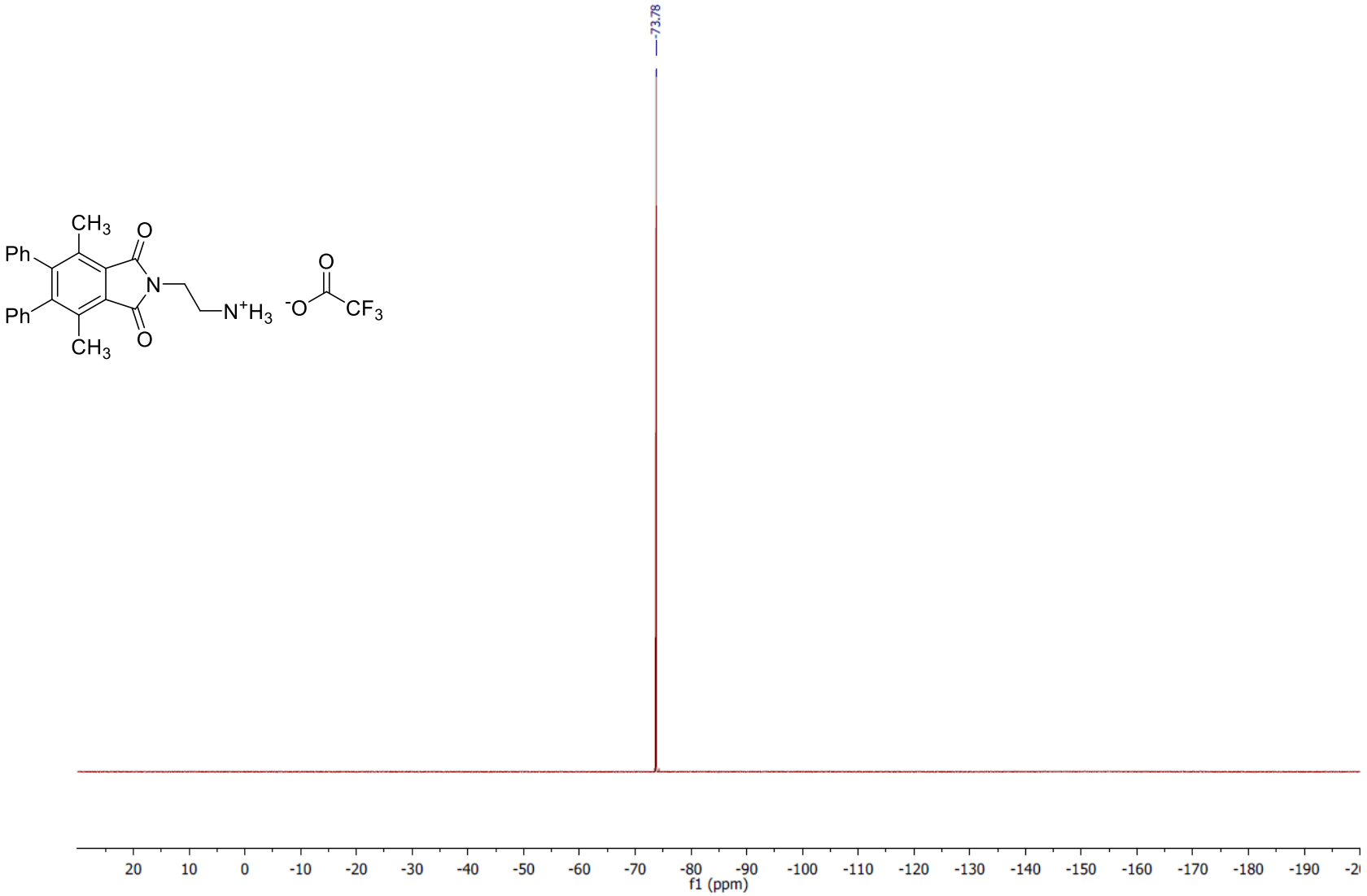
BP-CO-21. ^{1}H NMR spectrum (400 MHz, DMSO-*d6*).



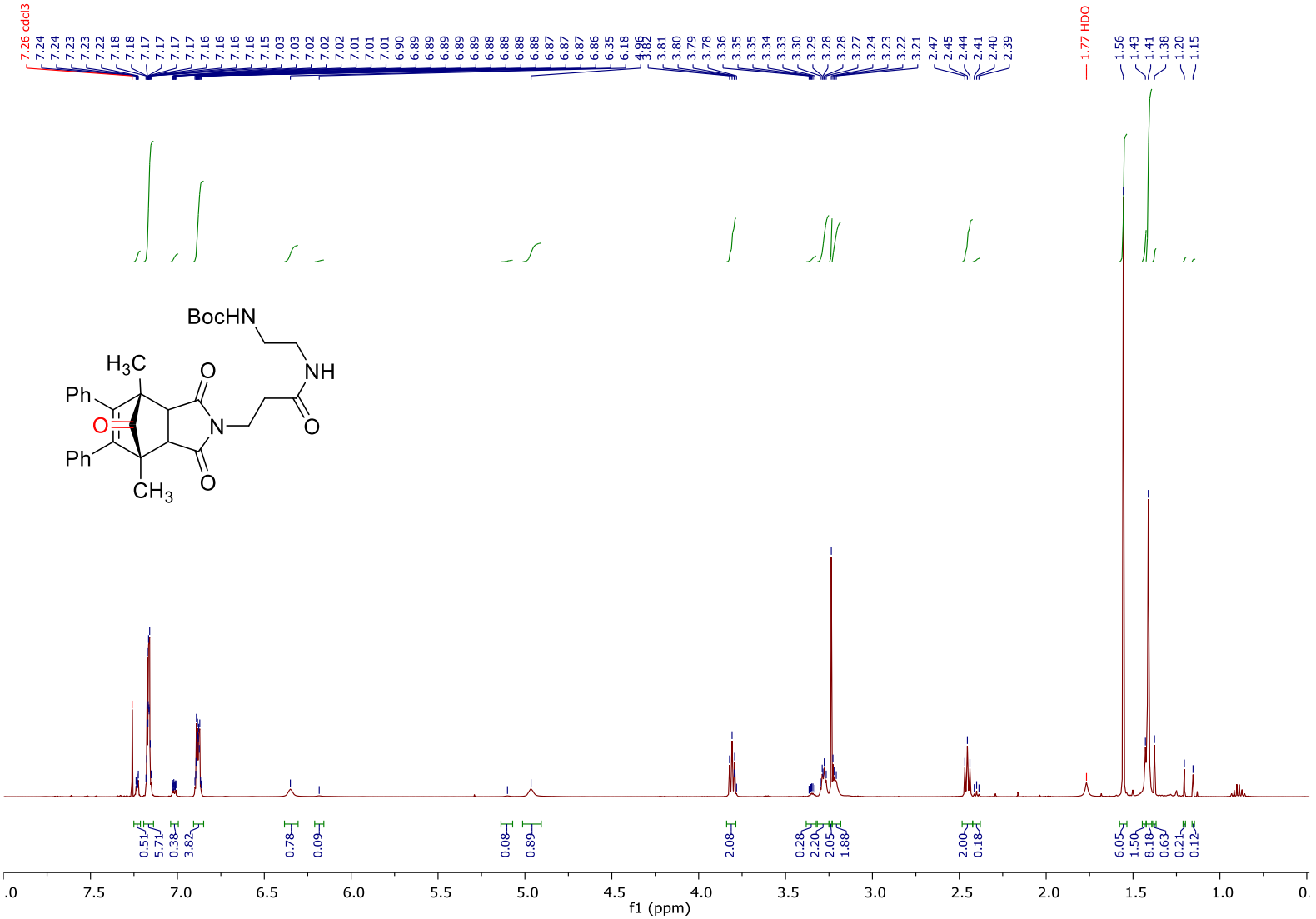
BP-CO-21. ^{13}C NMR spectrum (100 MHz, DMSO-*d6*).



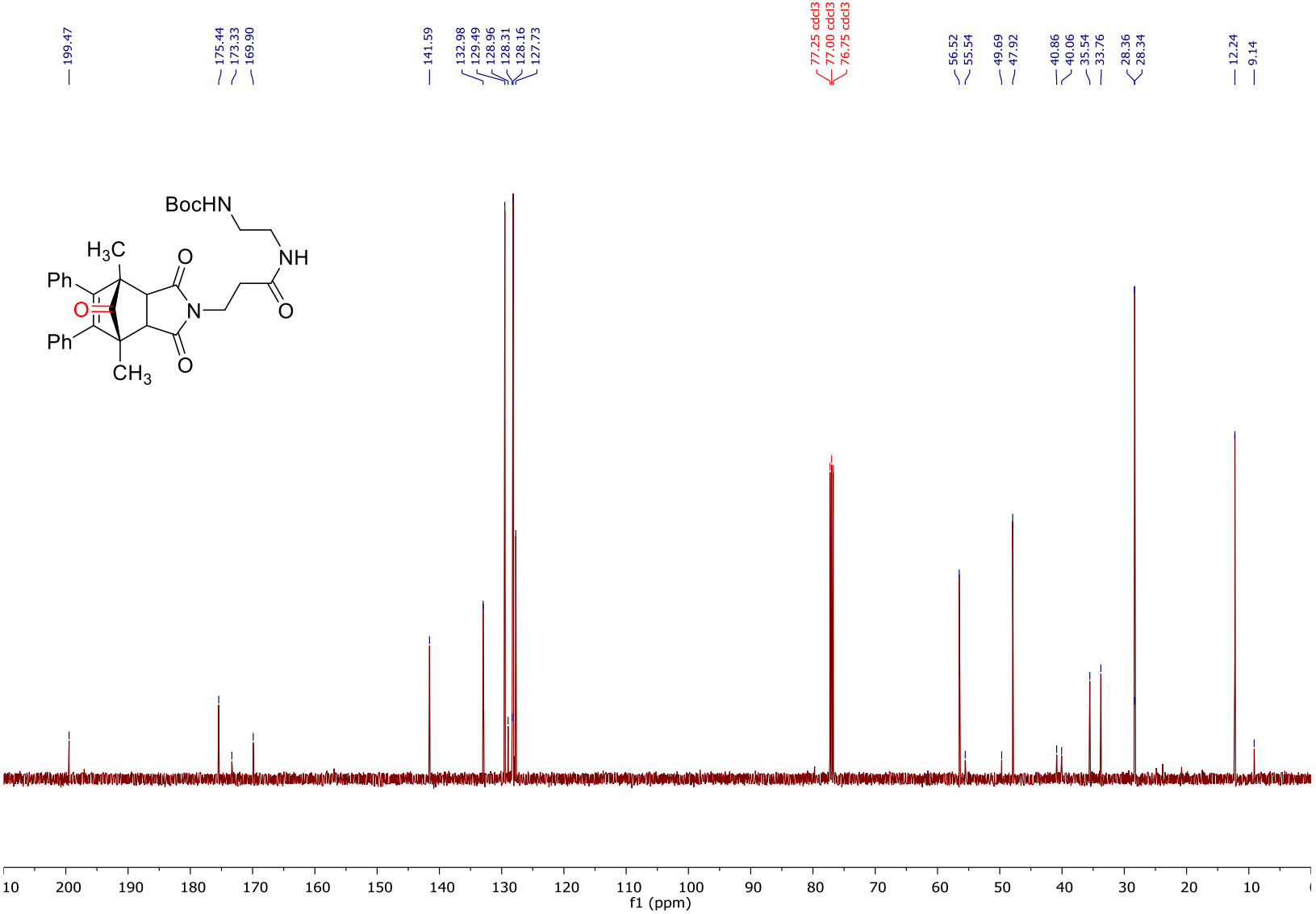
BP-CO-21. ^{19}F NMR spectrum (376 MHz, DMSO-*d6*).



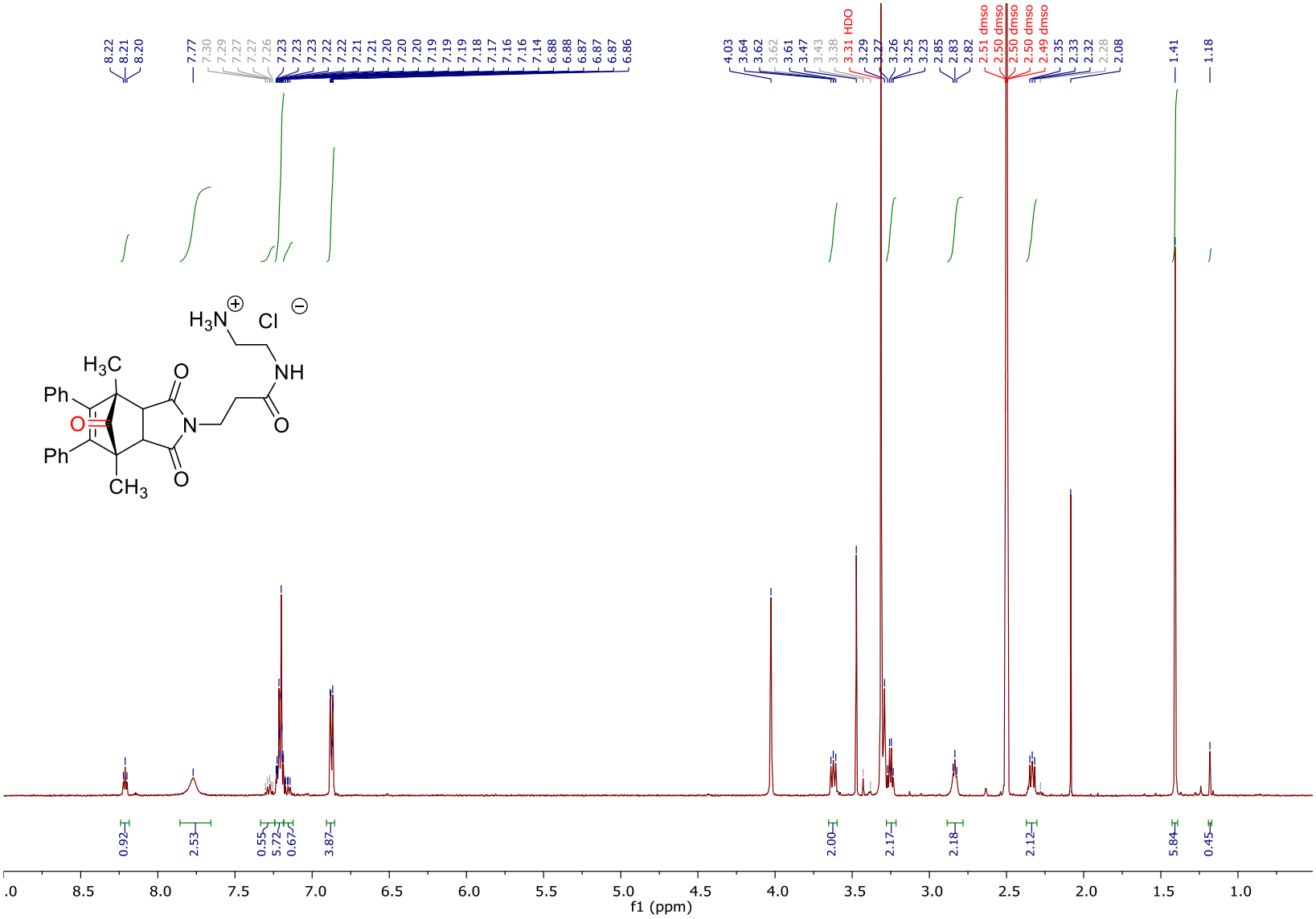
Compound **32** (11:1 mixture of *endo*- and *exo*-isomers). ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



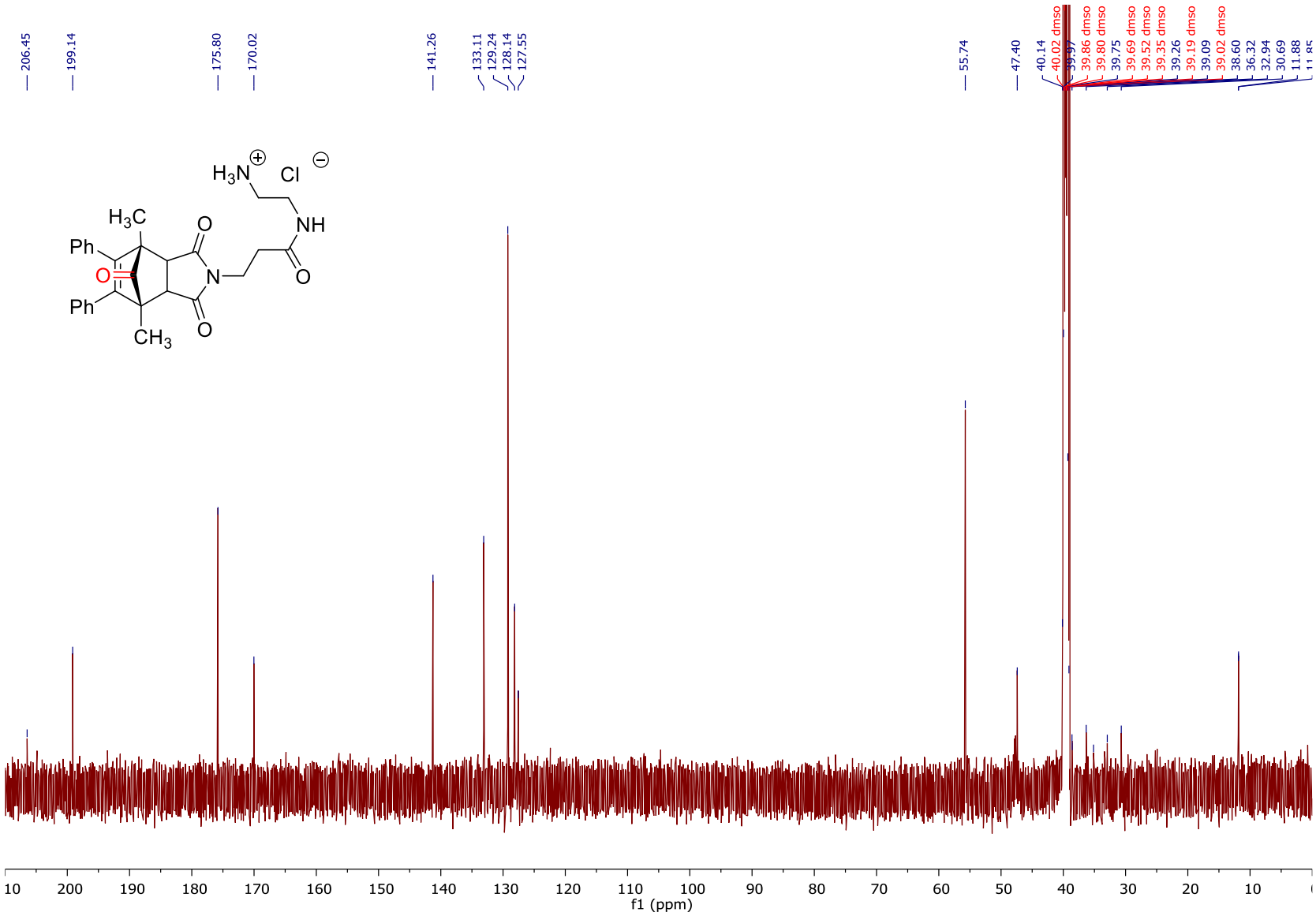
Compound **32** (11:1 mixture of *endo*- and *exo*-isomers). ^{13}C NMR spectrum (125 MHz, $CDCl_3$).



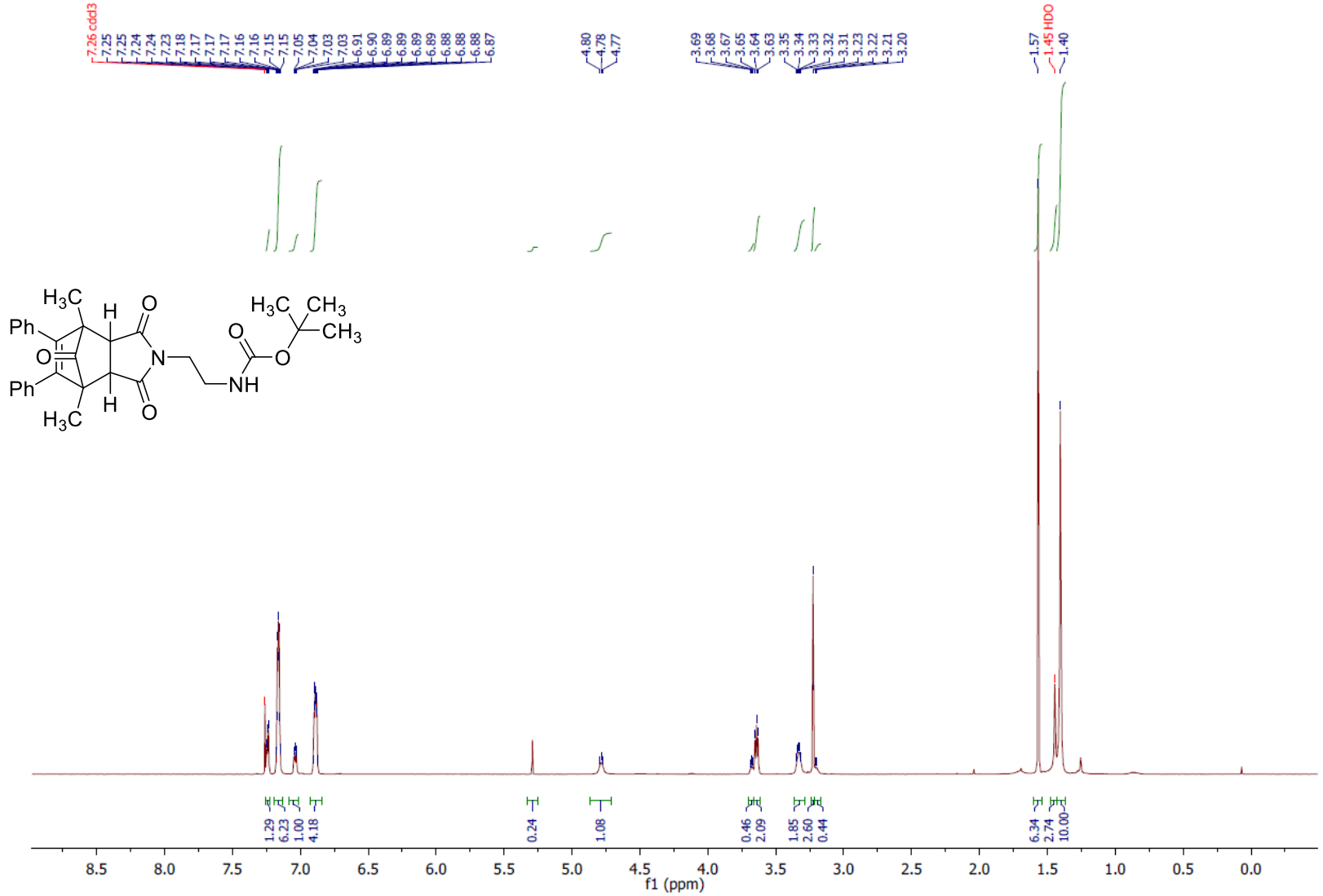
DB-CO-19 (13:1 mixture of *endo*- and *exo*-isomers). ^{1}H NMR spectrum (500 MHz, DMSO-*d6*).



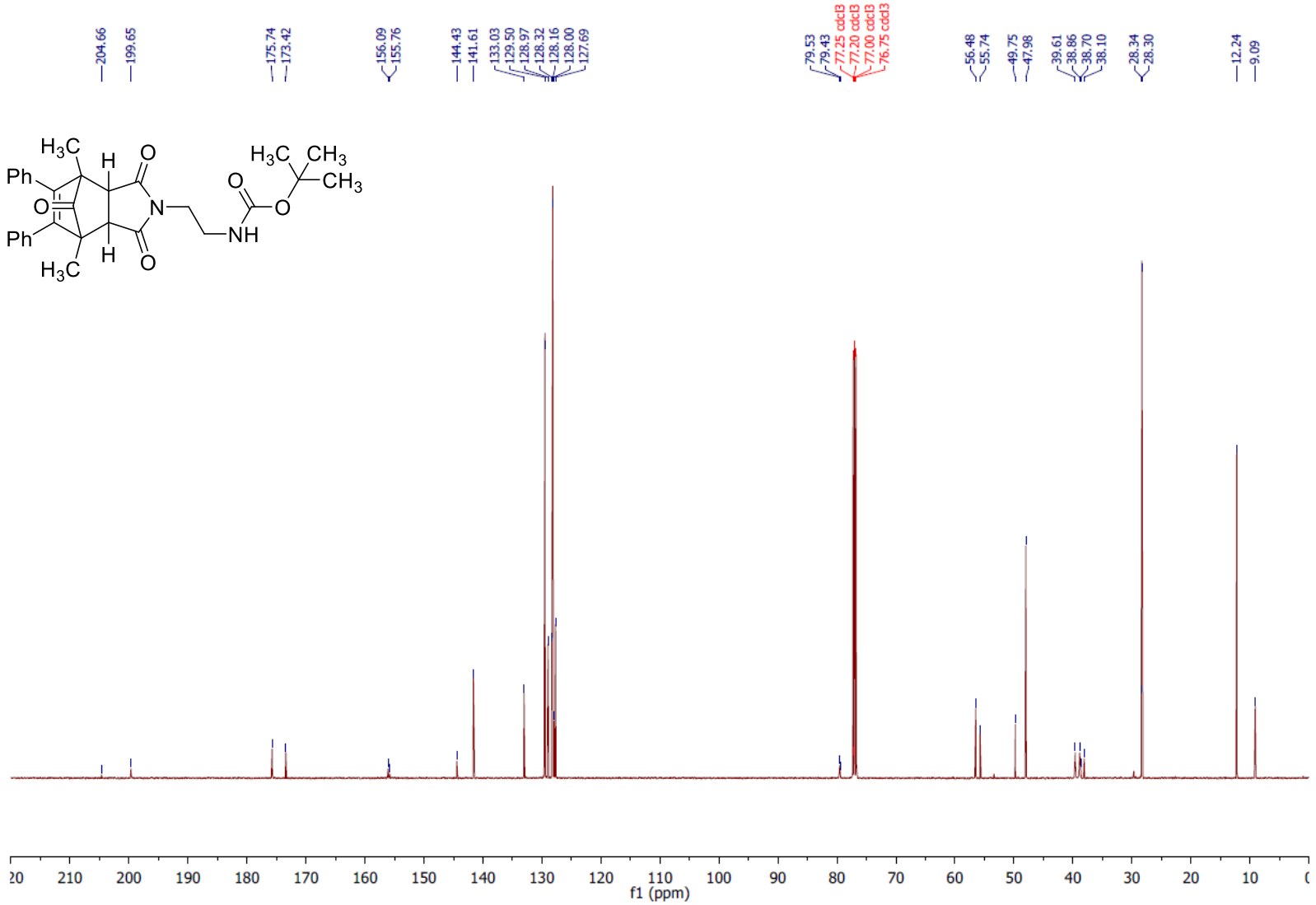
DB-CO-19 (13:1 mixture of *endo*- and *exo*-isomers). ^{13}C NMR spectrum (125 MHz, DMSO-*d6*).



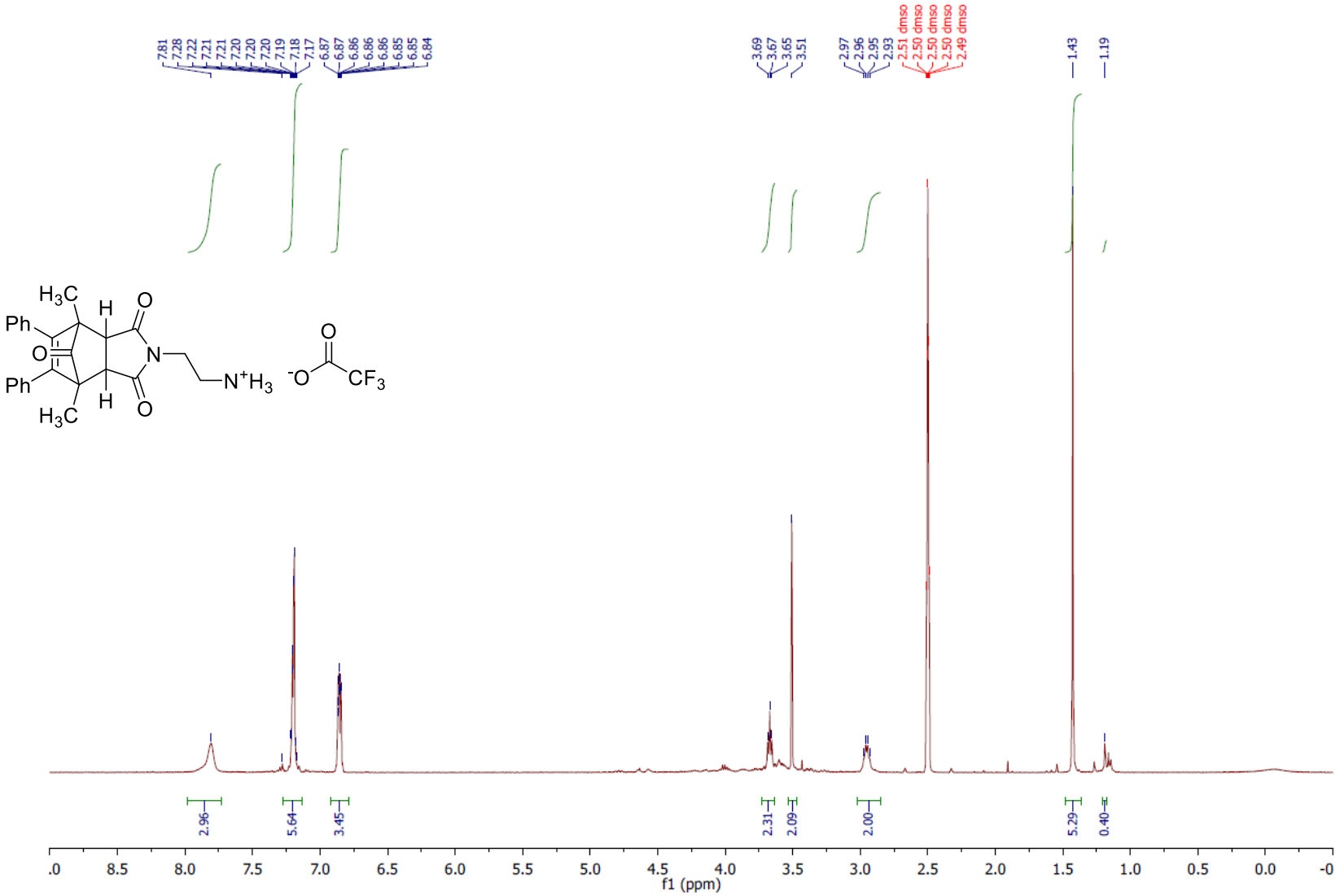
Compound **33** (4.2:1 mixture of *endo*- and *exo*-isomers). ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



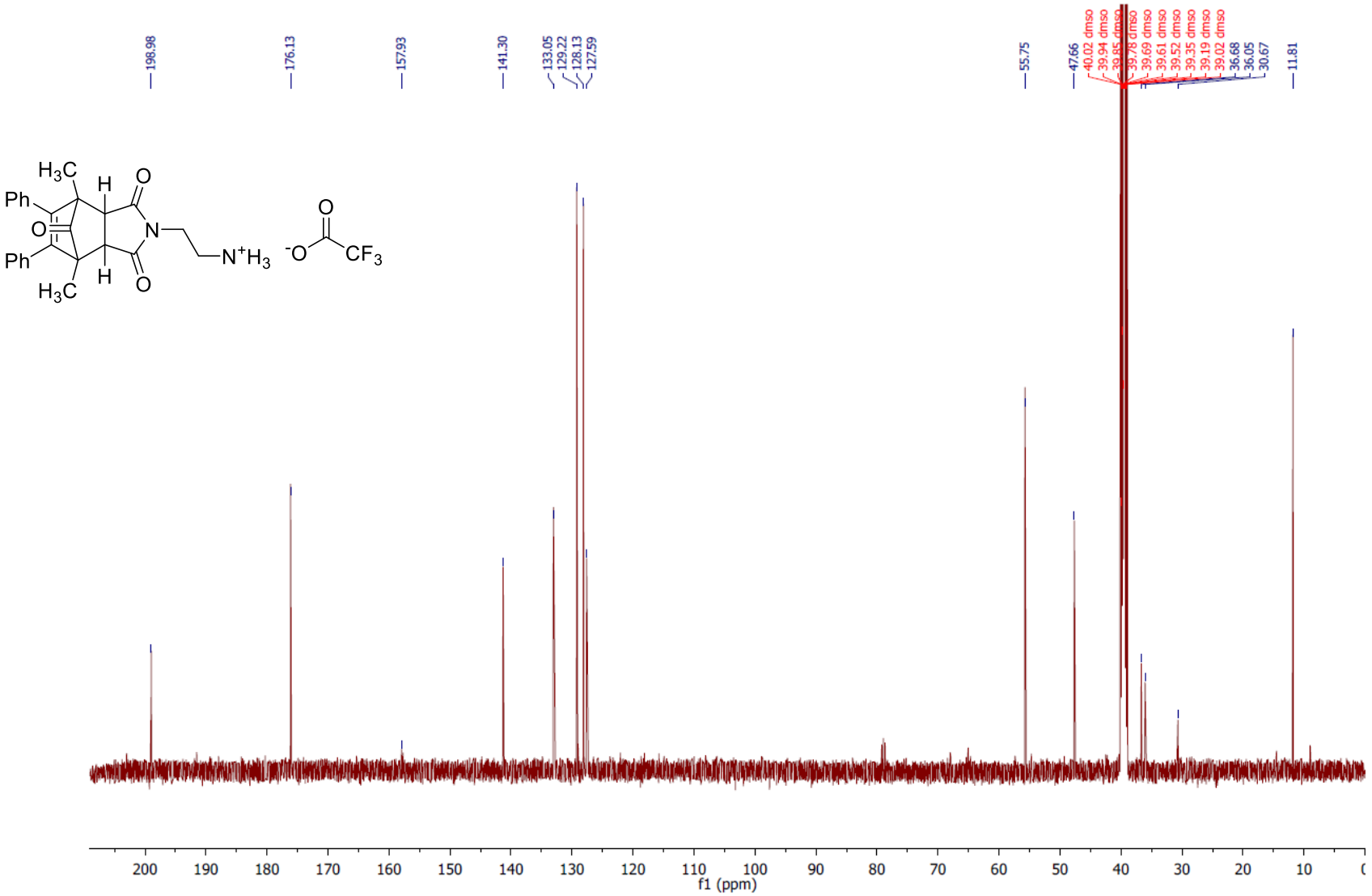
Compound **33** (4.2:1 mixture of *endo*- and *exo*-isomers). ^{13}C NMR spectrum (100 MHz, $CDCl_3$).



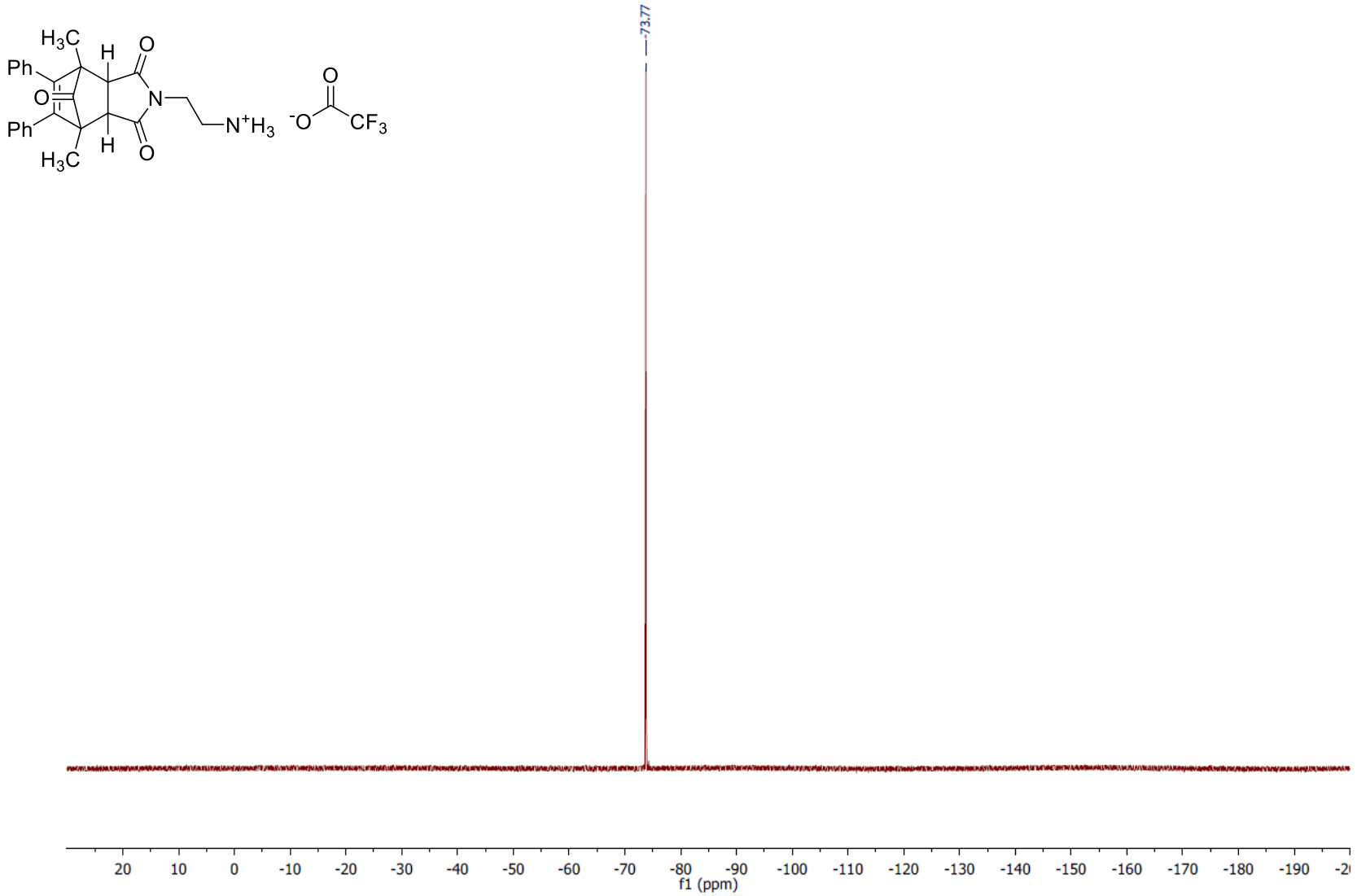
DB-CO-21 (4.1:1 mixture of *endo*- and *exo*-isomers). ^{1}H NMR spectrum (400 MHz, DMSO-*d6*).



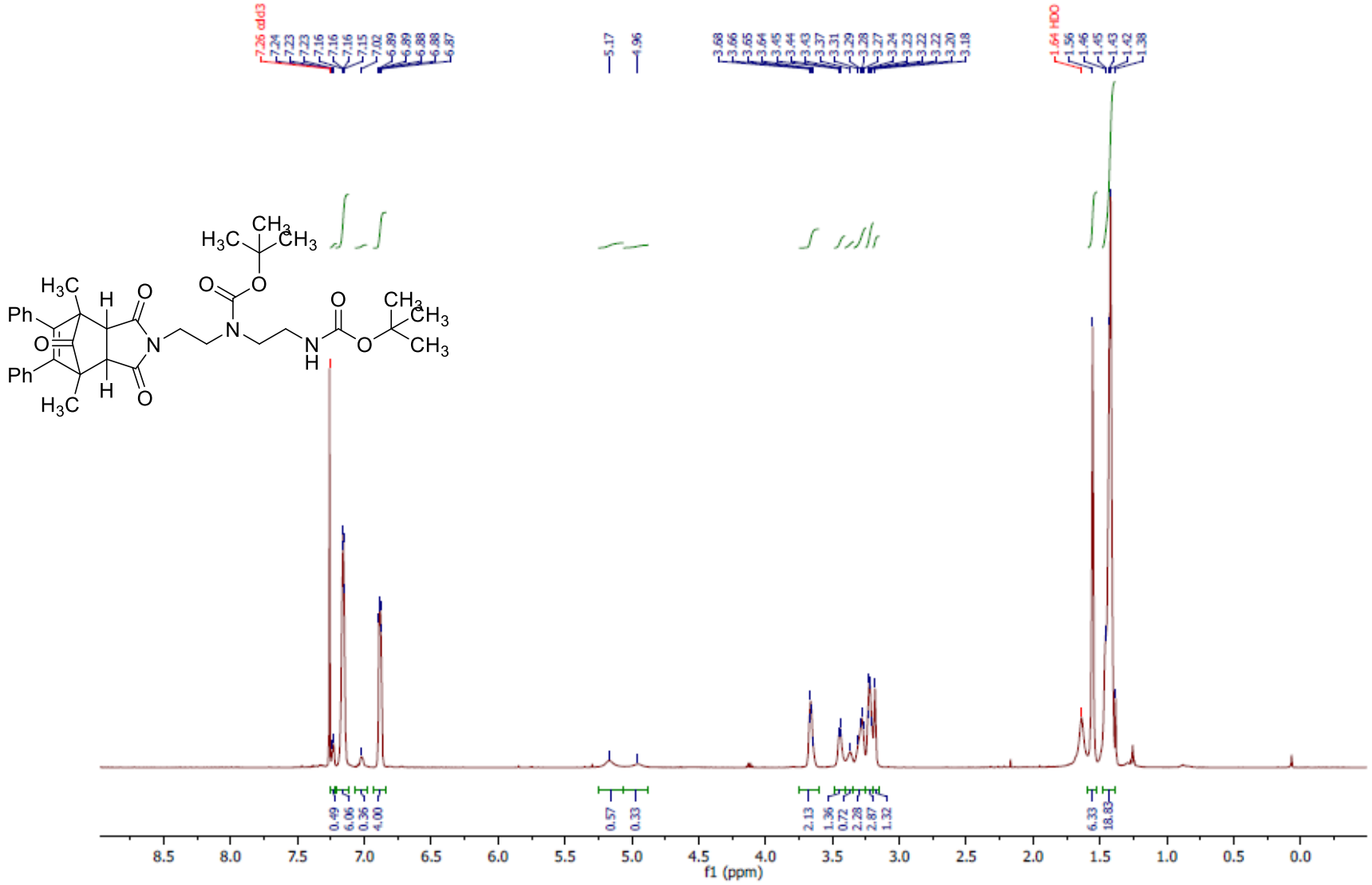
DB-**CO-21** (4.1:1 mixture of *endo*- and *exo*-isomers). ^{13}C NMR spectrum (125 MHz, DMSO-*d6*).



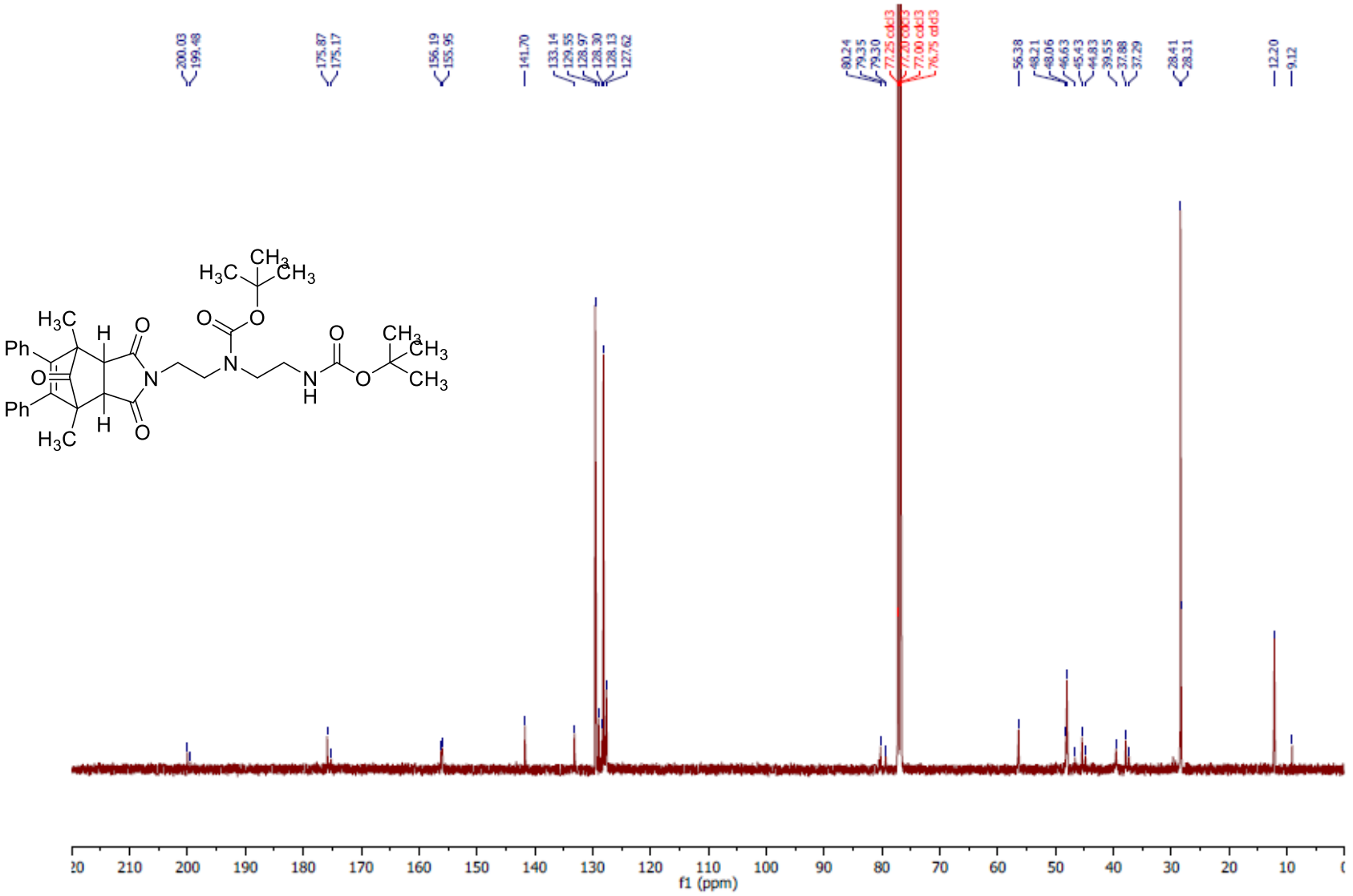
DB-CO-21 (4.1:1 mixture of *endo*- and *exo*-isomers). ^{19}F NMR spectrum (376 MHz, DMSO-*d6*).



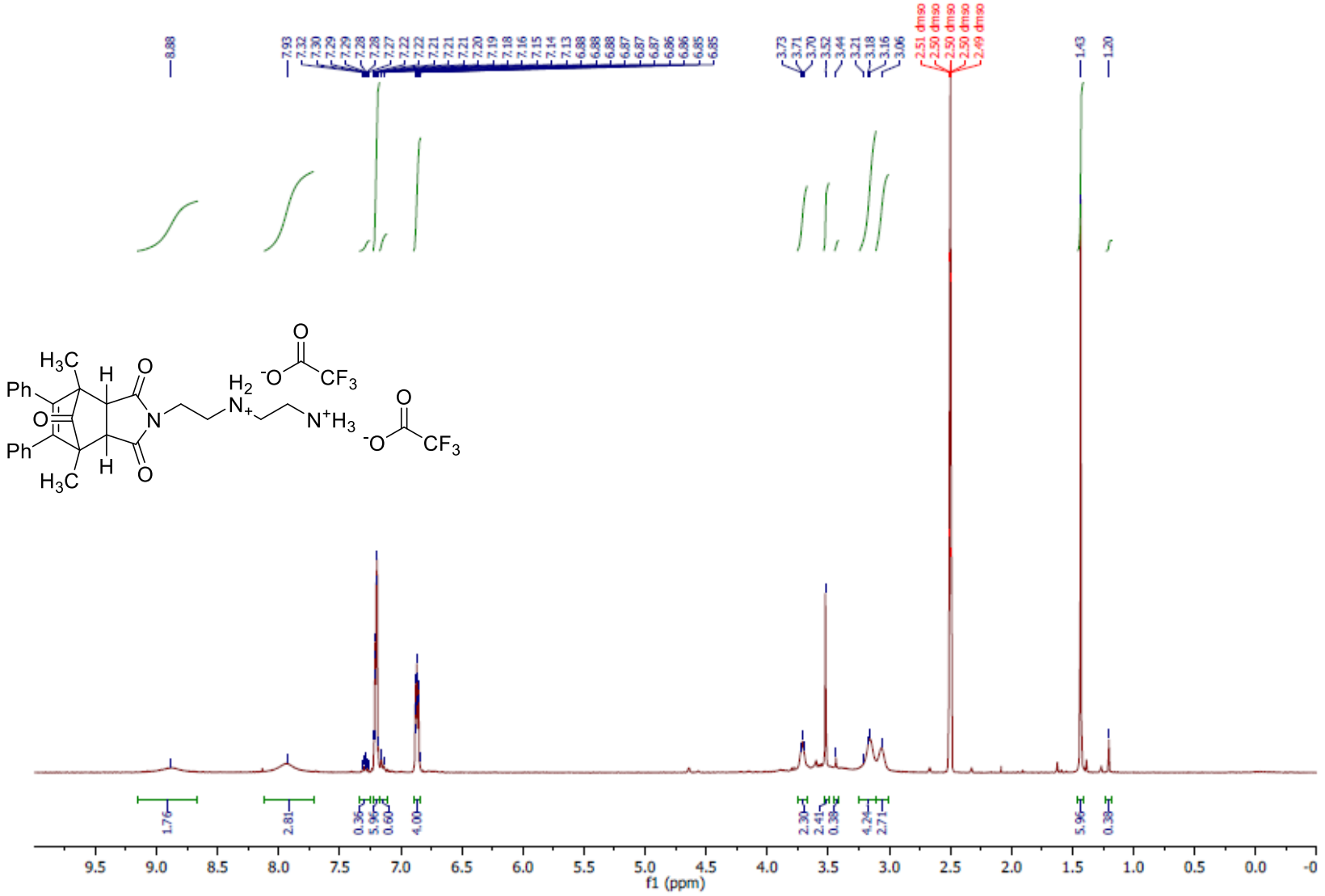
Compound **34** (11:1 mixture of *endo*- and *exo*-isomers). ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



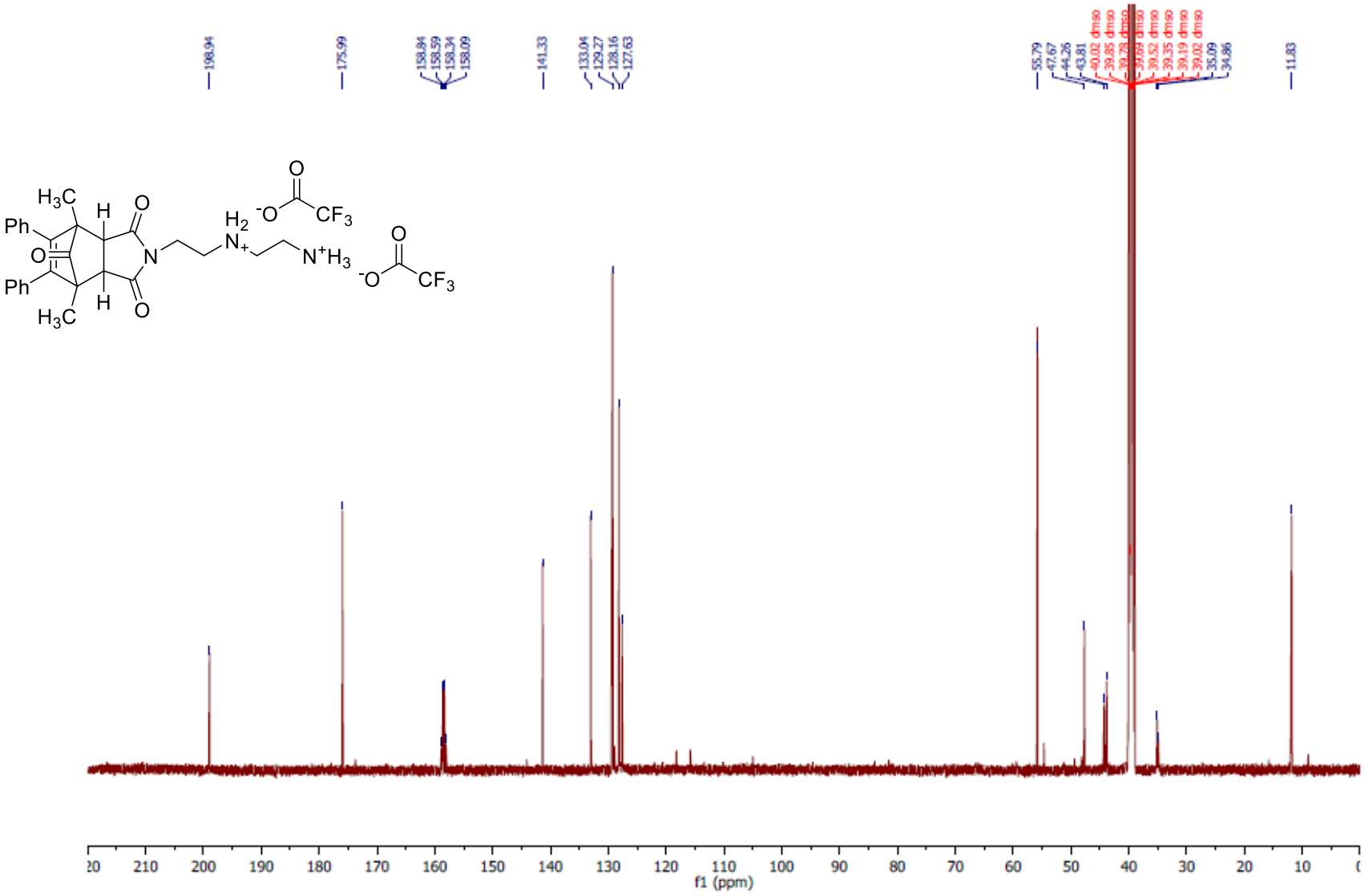
Compound **34** (11:1 mixture of *endo*- and *exo*-isomers). ^{13}C NMR spectrum (125 MHz, $CDCl_3$).



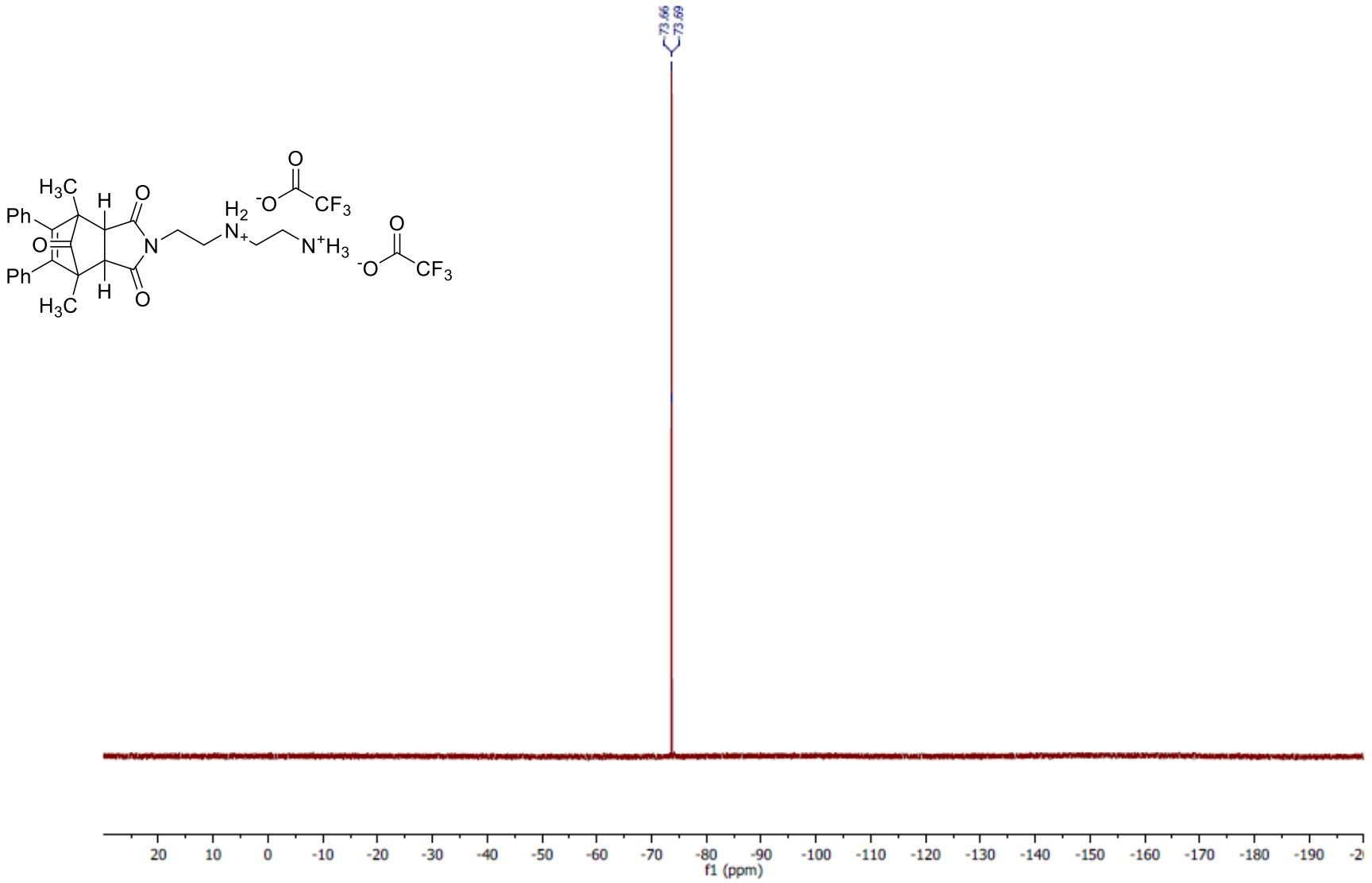
DB-CO-23 (15.7:1 mixture of *endo*- and *exo*-isomers). ^{1}H NMR spectrum (400 MHz, DMSO-*d6*).



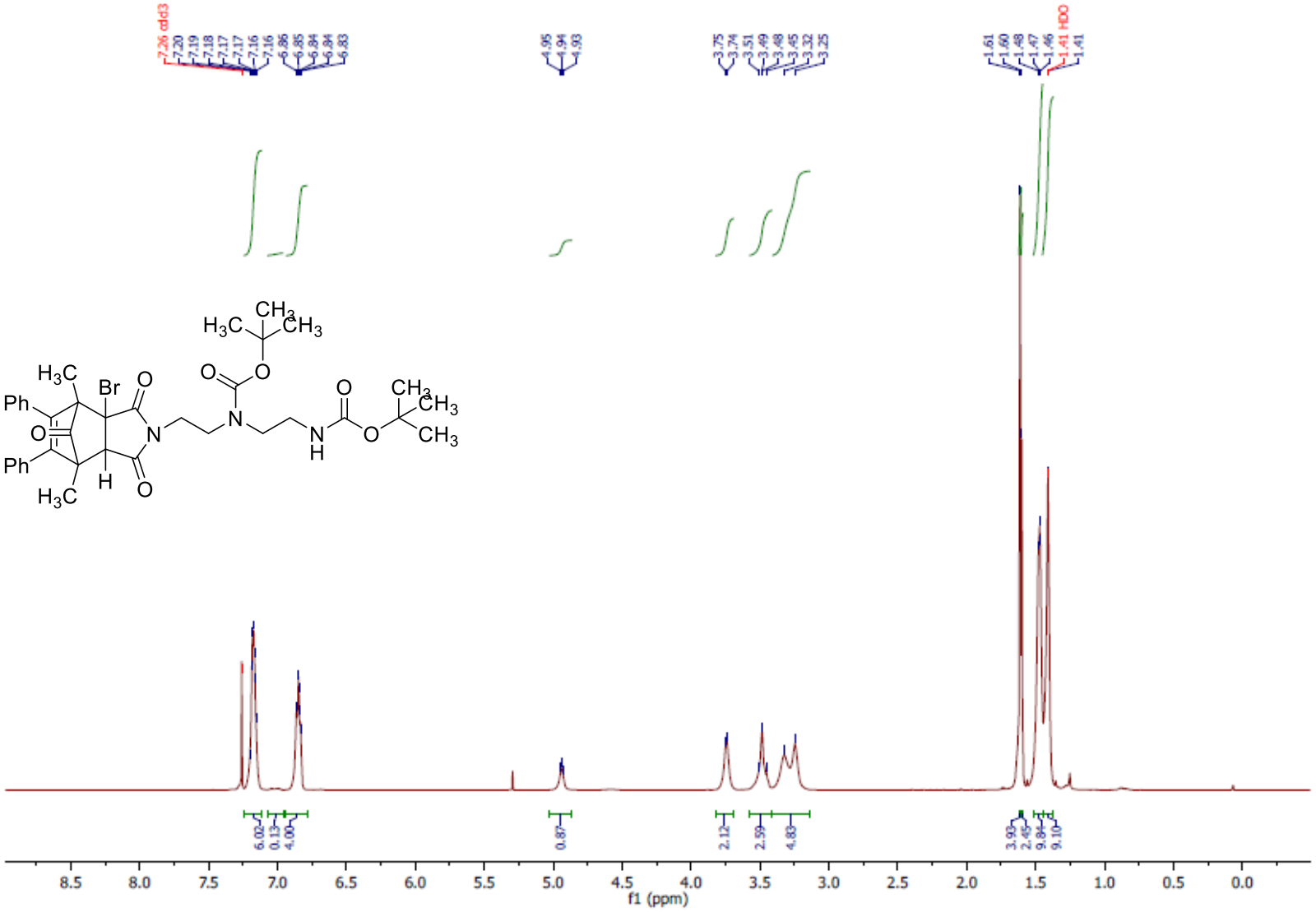
DB-CO-23 (15.7:1 mixture of *endo*- and *exo*-isomers). ^{13}C NMR spectrum (125 MHz, DMSO-*d6*).



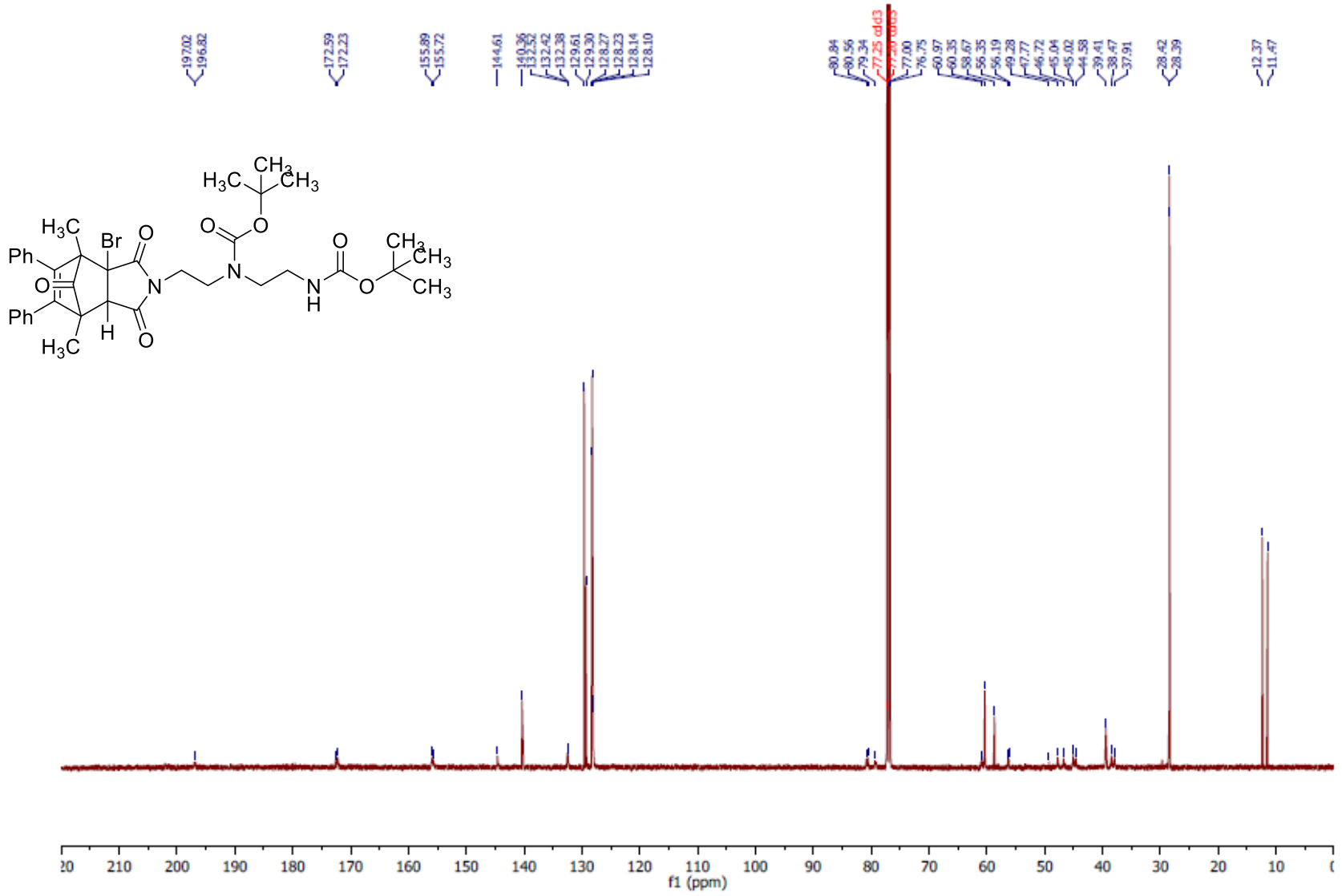
DB-CO-23 (15.7:1 mixture of *endo*- and *exo*-isomers). ^{19}F NMR spectrum (376 MHz, DMSO-*d6*).



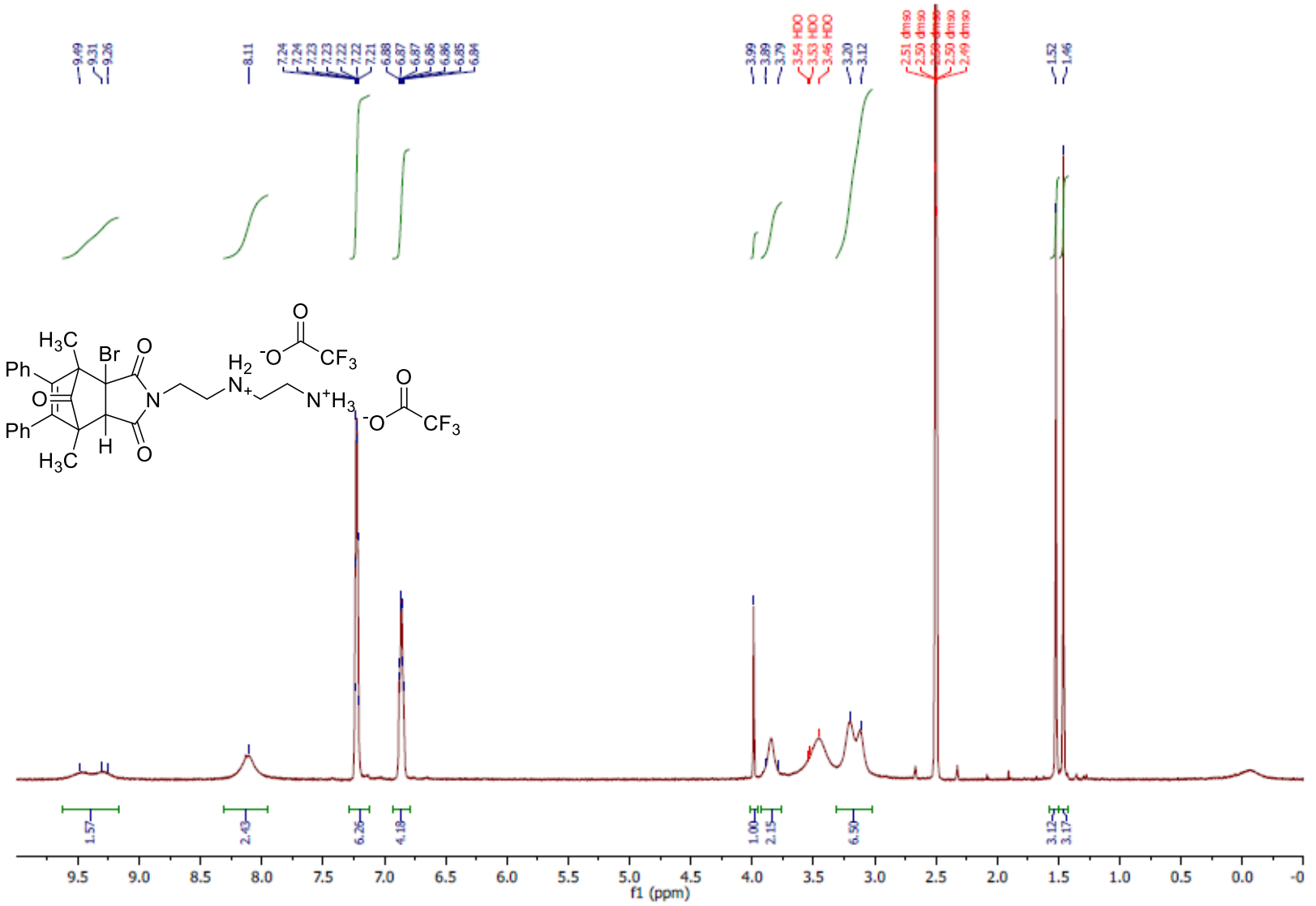
Compound **29** (*endo*-isomer). ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



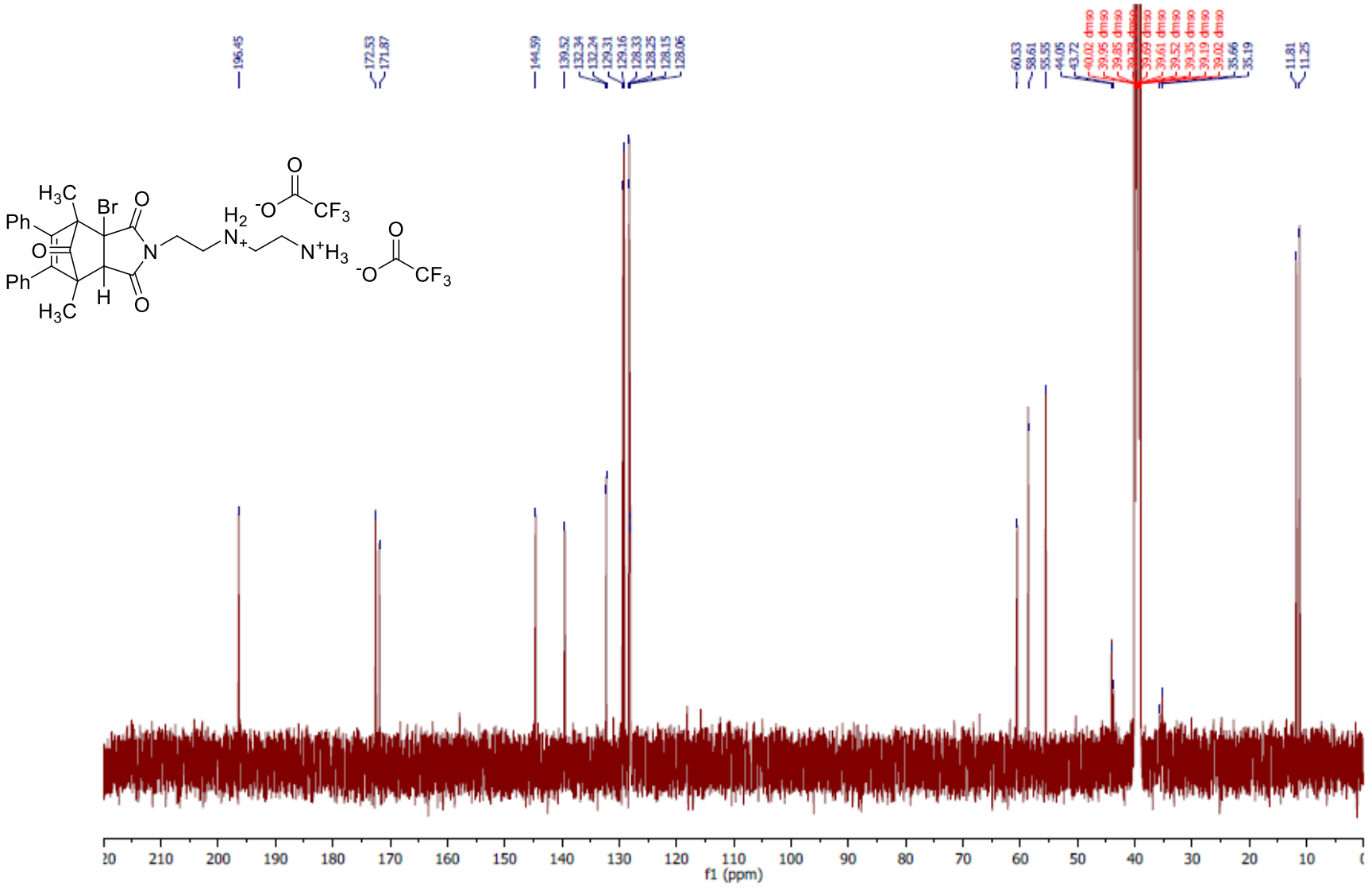
Compound **29** (*endo*-isomer). ^{13}C NMR spectrum (125 MHz, $CDCl_3$).



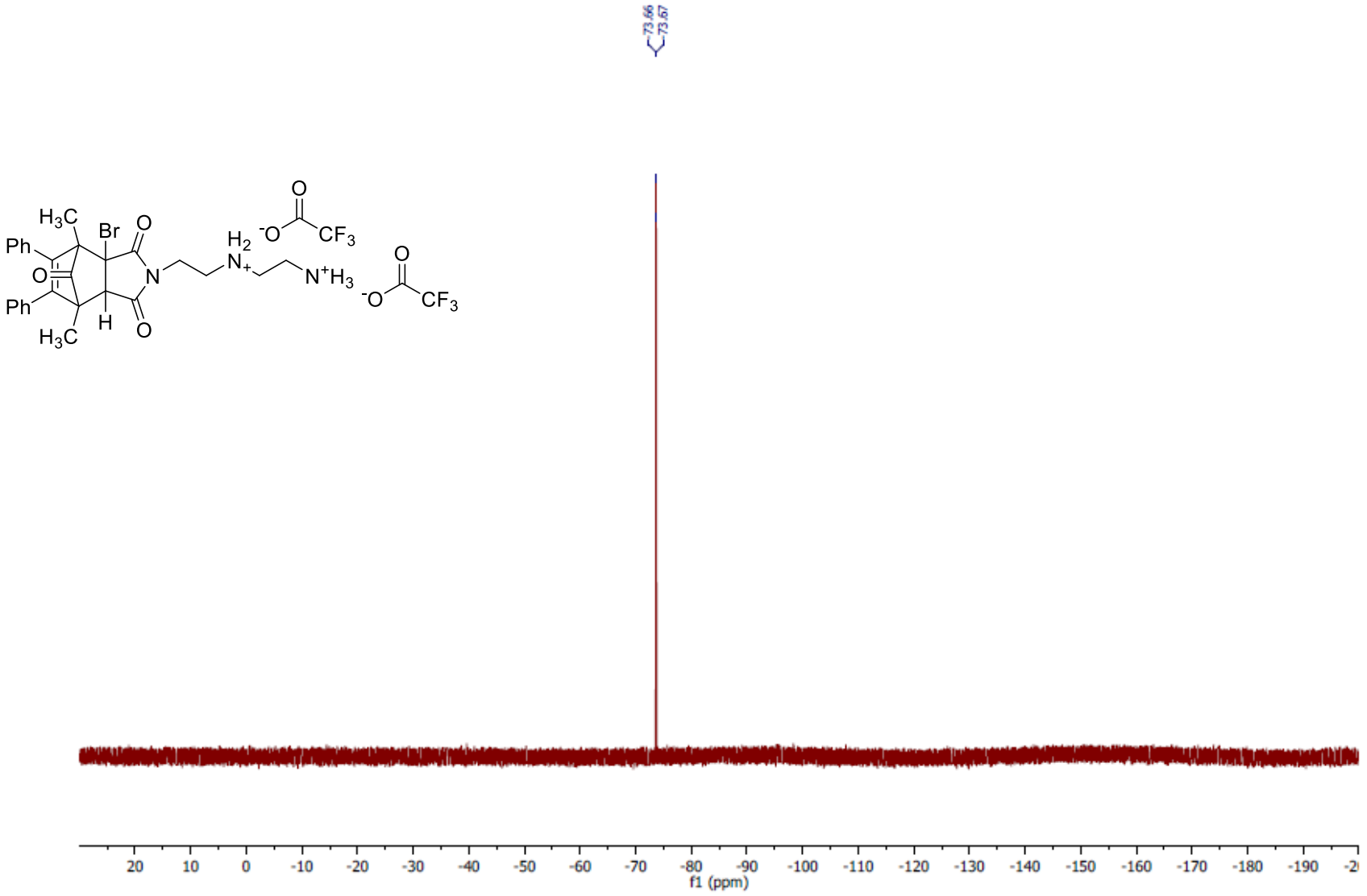
oCOm-23 (*endo*-isomer). ^{1}H NMR spectrum (400 MHz, DMSO-*d6*).



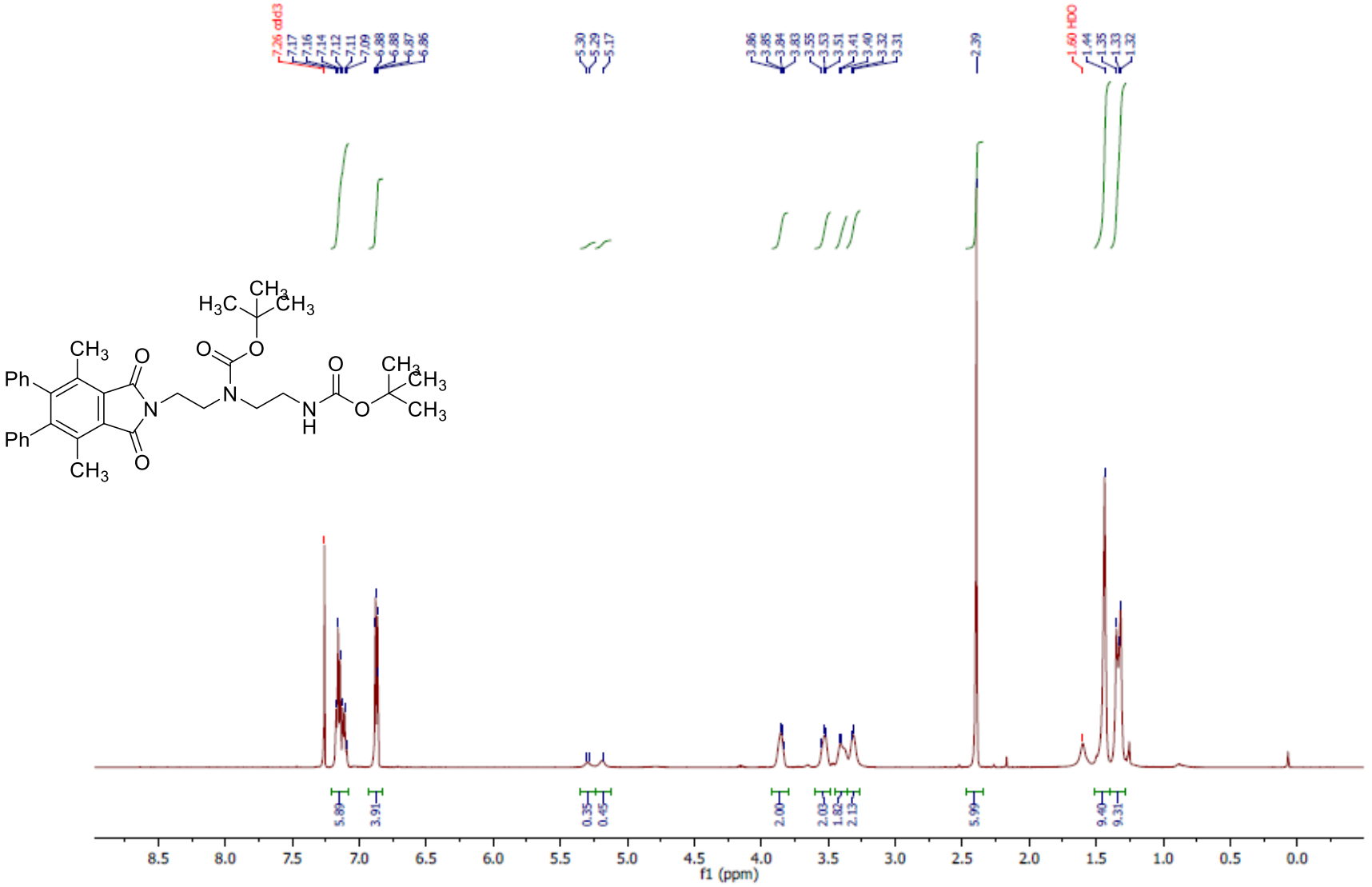
oCOm-23 (*endo*-isomer). ^{13}C NMR spectrum (125 MHz, DMSO-*d6*).



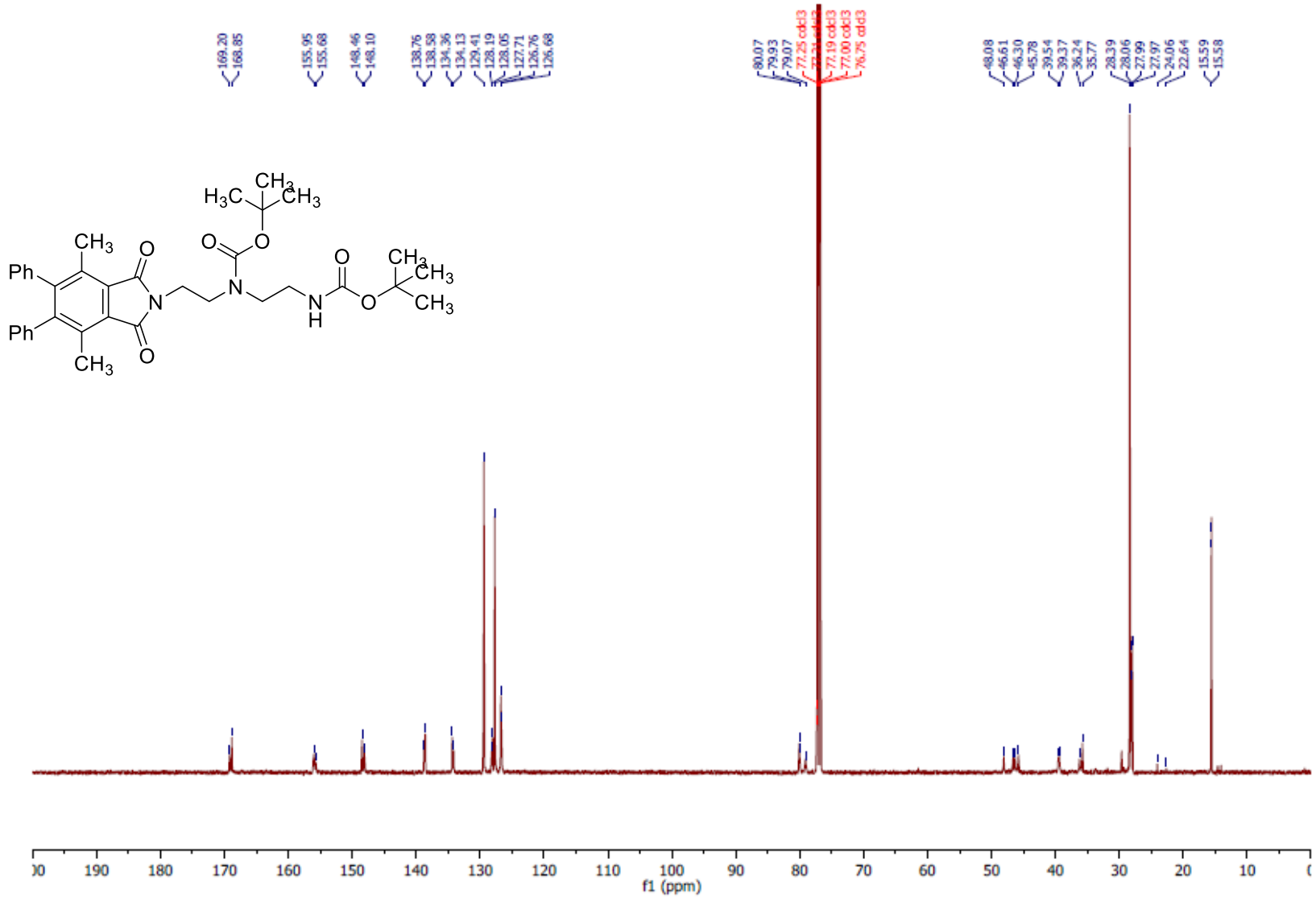
oCOm-23 (*endo*-isomer). ^{19}F NMR spectrum (376 MHz, DMSO-*d6*).



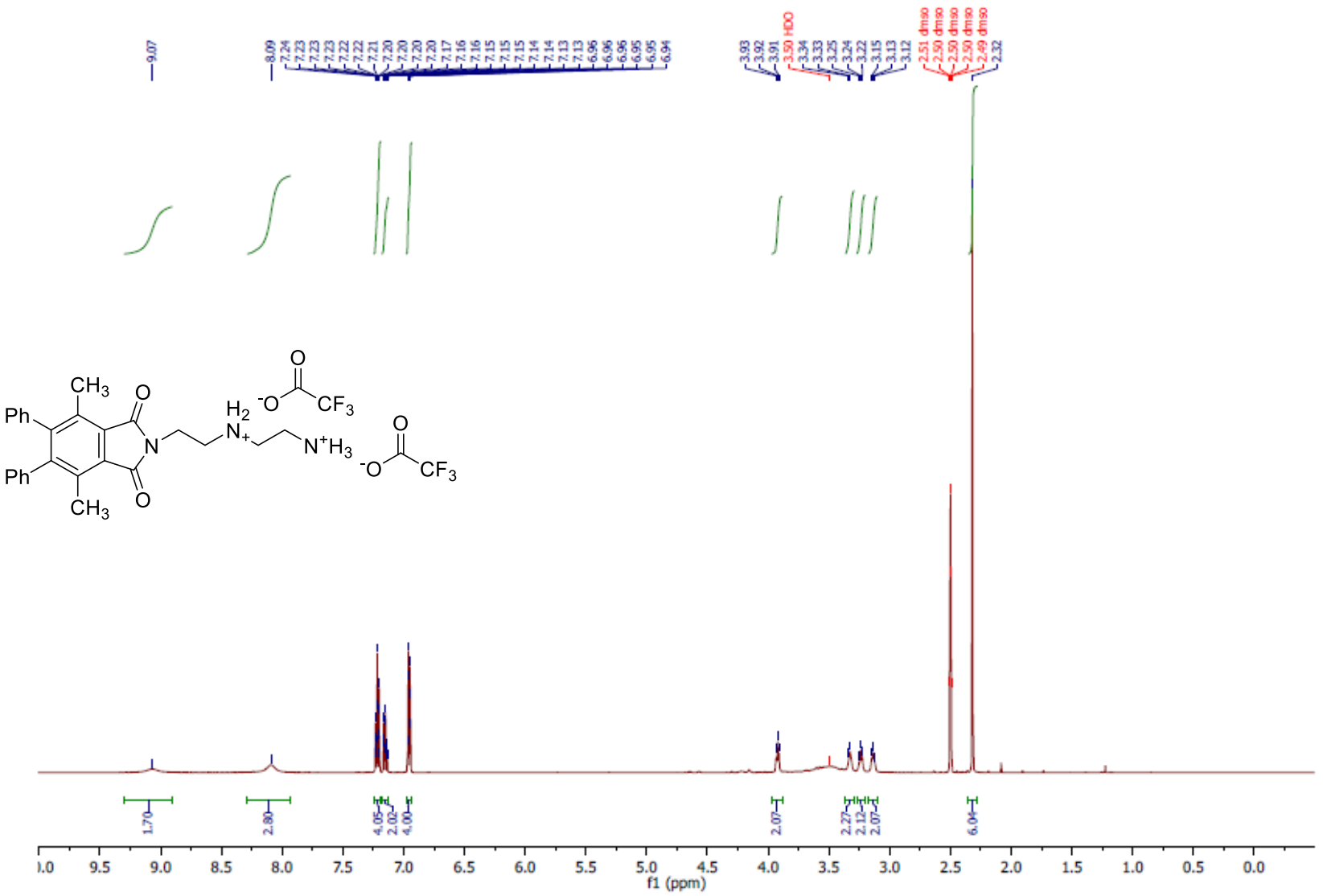
Compound **31**. ^{1}H NMR spectrum (500 MHz, $CDCl_3$).



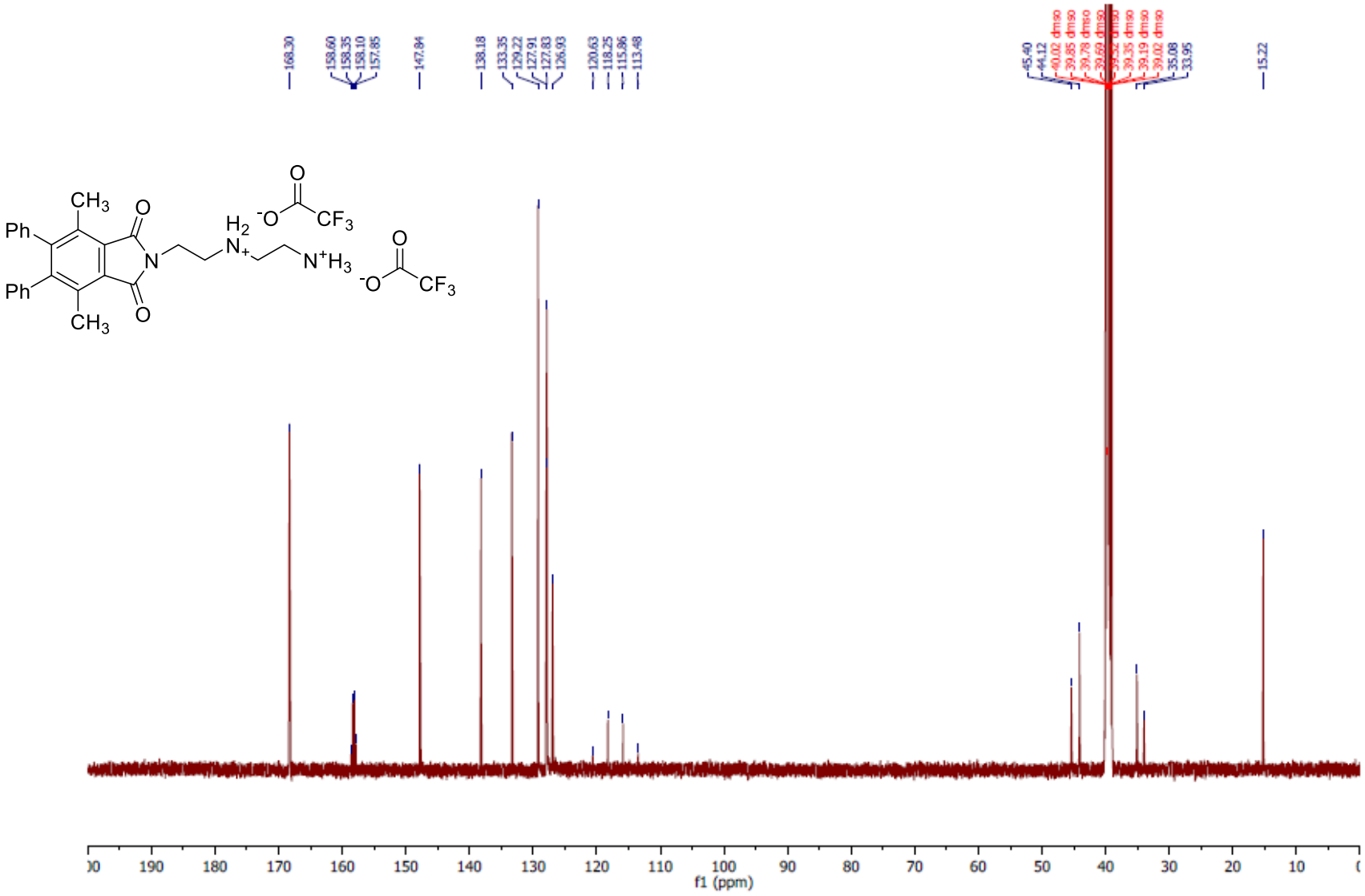
Compound **31**. ^{13}C NMR spectrum (125 MHz, $CDCl_3$).



BP-CO-23. ^{1}H NMR spectrum (500 MHz, DMSO-*d6*).



BP-CO-23. ^{13}C NMR spectrum (125 MHz, DMSO-*d6*).



BP-CO-23. ^{19}F NMR spectrum (376 MHz, DMSO-*d6*).