Catalytic, Enantioselective Synthesis of Stilbene *cis*-Diamines: A Concise Preparation of (-)-Nutlin 3, a Potent p53-MDM2 Inhibitor

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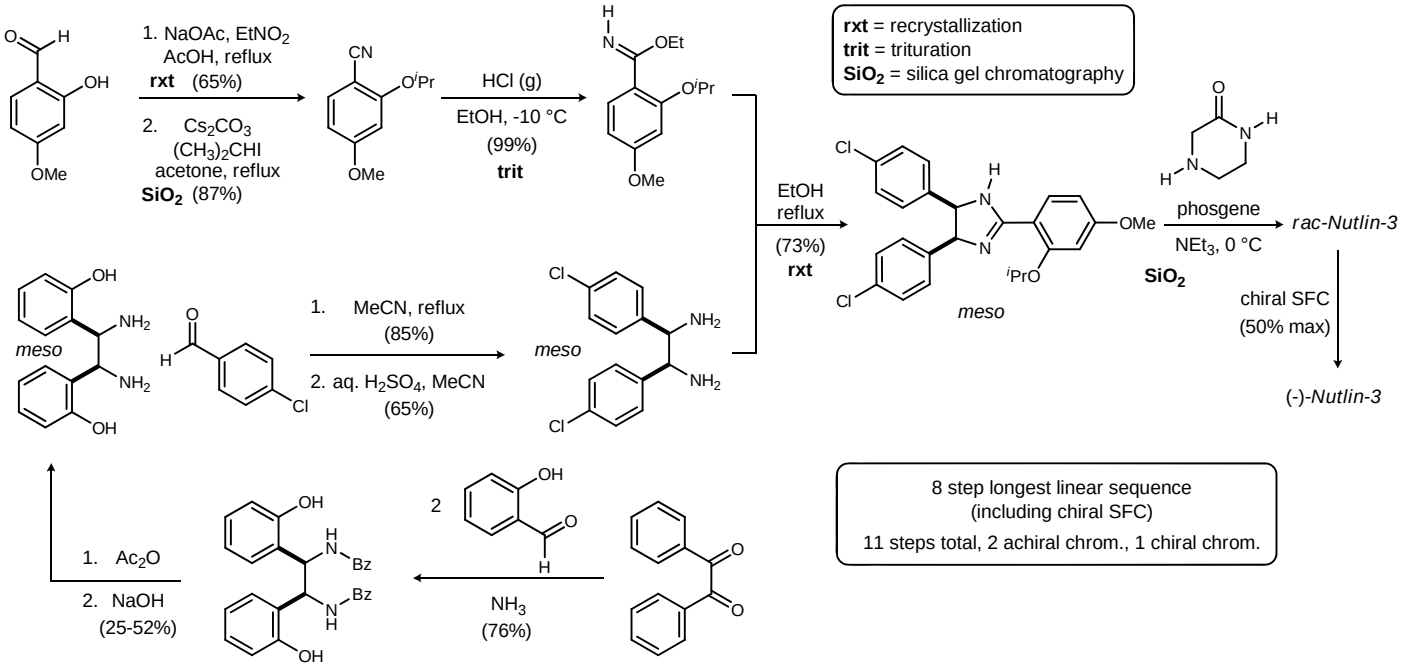
Hoffmann-La Roche Patent Synthesis



Vogtle, F.; Goldschmitt, E. *Chem. Ber*. **1976**, *109*, 1-40

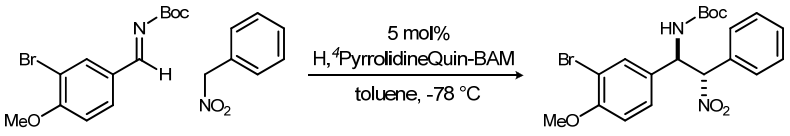
Experimental Section

All reagents and solvents were commercial grade and purified prior to use when necessary. The following reagents were used as supplied by Sigma-Aldrich without further purification except when noted otherwise. Aldimines were prepared as reported in the literature.[1] 2,4-Dichloro-6,7-dimethoxyquinoline was prepared with a procedure similar to that of **S5** and **S7**. Toluene was dried by passage through a column of activated alumina as described by Grubbs.[2] Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μm) plates and flash chromatography utilized 230–400 mesh silica gel from Sorbent Technologies. UV light, and/or the use of potassium iodoplatinate and potassium permanganate solutions were used to visualize products. IRA-900-NO_2 resin was prepared by washing IRA900-Cl resin with aq $NaNO_2$ until the wash no longer tested positive for chloride by a $AgNO_3$ test.

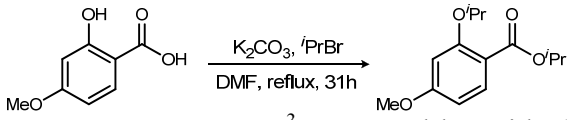
Nuclear magnetic resonance spectra (NMR) were acquired on a Bruker DRX-500 (500 MHz), Bruker AV-400 (400 MHz) or Bruker AV II-600 (600 MHz) instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 ($CDCl_3$). IR spectra were recorded on a Thermo Nicolet IR100 spectrophotometer and are reported in wavenumbers (cm^{-1}). Compounds were analyzed as neat films on a NaCl plate (transmission). Mass spectra were recorded on a Waters LCT spectrometer by use of the ionization method noted.

Absolute and relative configuration of **1a** was assigned by analogy to **S1**, for which a crystal structure was obtained (*see SI-2*).

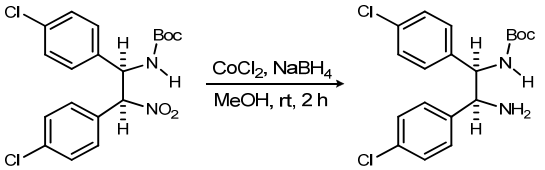
[1] Kanazawa, A. M.; Denis, J.; Greene, A. E. *J. Org. Chem*. **1994**, *59*, 1238-1240.
[2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.



***tert*-Butyl (1*R*,2*S*)-1-(3-bromo-4-methoxyphenyl)-2-nitro-2-phenylethylcarbamate (S1).** *tert*-Butyl 3-bromo-4-methoxybenzylidenecarbamate (62.8 mg, 200 μmol) and H,^{4}PyrrolidineQuin-BAM (5.1 mg, 10 μmol) were dissolved in toluene (2 mL) at room temperature. The solution was chilled to -78 °C before addition of nitromethylbenzene (41.1 mg, 300 μmol). The reaction was then stirred at -78 °C for 20 h. The reaction was kept at the reaction temperature until filtering through a pad of silica with CH_2Cl_2 and EtOAc. The filtrate was concentrated and then purified by column chromatography (5-40% ethyl acetate in hexanes) to afford a white solid (67.1 mg, 74%) that was found to be 73% ee by chiral HPLC; (Chiralcel IA, 5% iPrOH/hexanes, 1 mL/min, t_r(*anti*, major) = 61.8 min, t_r(*anti*, minor) = 29.2 min, t_r(*syn*, major) = 26.8 min, t_r(*syn*, minor) = 49.6 min); Mp 157.0-159.0 °C; R_f = 0.19 (20% EtOAc/hexanes); IR (film) 3387, 2979, 1685, 1553 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.2, 2.0 Hz, 2H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.46-7.38 (m, 3H), 7.30-7.25 (dd, *J* = 8.4, 2.0Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 5.72 (d, *J* = 10.0 Hz, 1H), 5.58 (dd, *J* = 9.2, 9.2 Hz, 1H), 4.77 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 156.1, 154.1, 131.9, 131.3, 131.1, 130.3, 128.9 (2C), 128.7 (2C), 127.7, 112.1, 112.0, 94.1, 80.5, 56.2, 55.8, 28.0; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}BrN_2NaO_5$ $[M+Na]^+$ 473.0688, found 473.0711.



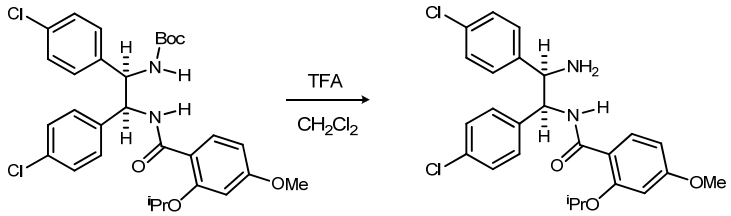
Isopropyl 2-isopropoxy-4-methoxybenzoate (S2).[3] Isopropyl bromide (2.926 g, 23.79 mmol) was added to a stirred mixture of 4-methoxysalicylic acid (1.000 g, 5.947 mmol), K_2CO_3 (3.286 g, 23.79 mmol), and dry DMF (30 mL) at room temperature. The mixture was allowed to stir for 20 min before heating to reflux for 31 h. The reaction mixture was cooled to room temperature, treated with KI (98.7 mg, 595 μmol) and stirred for 17 h. The reaction was quenched with 1 M aq HCl then extracted with diethyl ether. The combined organic layers were washed with 1 M aq Na_2CO_3, water, then brine before drying over $MgSO_4$. Concentration of the dried organic layers resulted in a bronze oil (1.0549 g, 70%) that was pure by ^{1}H NMR. R_f = 0.16 (5% EtOAc/hexanes); IR (film) 2979, 2936, 1721, 1694, 1608, 1575 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.2 Hz, 1H), 6.49-6.43 (m, 2H), 5.20 (heptet, *J* = 6.4 Hz, 1H), 4.55 (heptet, *J* = 6.0 Hz, 1H), 3.81 (s, 3H), 1.36 (d, *J* = 6.0 Hz, 6H), 1.33 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.8, 163.5, 159.3, 133.4, 114.9, 104.9, 101.8, 71.5, 67.5, 55.4, 22.0 (2C); HRMS (CI): Exact mass calcd for $C_{14}H_{21}O_4$ $[M+H]^+$ 253.1434, found 253.1431.



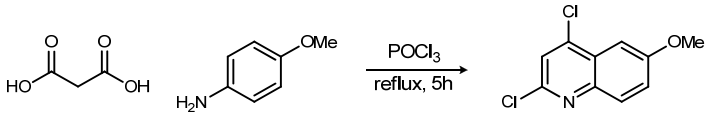
***tert*-Butyl (1*R*,2*S*)-2-amino-1,2-bis(4-chlorophenyl)ethylcarbamate (S3).** The nitroalkane (411.3 mg, 1.000 mmol) was dissolved in MeOH (4.0 mL) at room temperature. $CoCl_2$ (129.8 mg, 1.000 mmol) was added and the reaction mixture was chilled to 0 °C before $NaBH_4$ (567.6 mg, 15.00 mmol) was added in three portions over 40 min. The reaction mixture was stirred at 0 °C for an additional 30 min before the mixture was quenched with sat. aq. NH_4Cl. The reaction mixture was adjusted to pH 10 with conc. aq. NH_4OH. The mixture was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. Column chromatography (25-45% ethyl acetate in hexanes) of the residue afforded the product as a white solid (251.7 mg, 66%). Mp 149.0-150.0 °C;

[3]Adapted from: Hattori, T.; Shimazumi, Y.; Goto, H.; Yamabe, O.; Morohashi, N.; Kawai, W.; Miyano, S. *J. Org. Chem.* **2003**, *68*, 2099-2108.

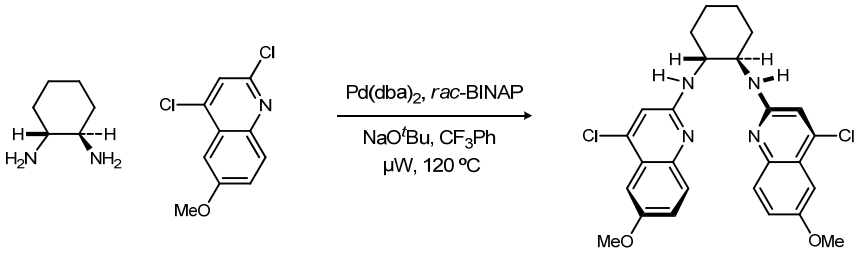
$[\alpha]_D^{20}$ +67 (*c* 0.12, $CHCl_3$); R_f = 0.12 (50% EtOAc/hexanes); IR (film) 3377, 2981, 1683, 1523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 5.49 (d, *J* = 7.6 Hz, 1H), 4.79 (br s, 1H), 4.23 (br s, 1H), 1.50 (s, 2H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.0, 140.3 (2C), 133.3, 133.2, 128.7, 128.4, 128.2 (2C), 79.8, 59.5, 59.1, 28.2; HRMS (ESI): Exact mass calcd for $C_{19}H_{23}Cl_2N_2O_2$ $[M+H]^+$ 381.1137, found 381.1147.



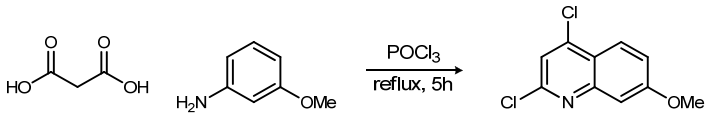
***N*-((1*S*,2*R*)-2-Amino-1,2-bis(4-chlorophenyl)ethyl)-2-isopropoxy-4-methoxybenzamide (S4).** Amide (180.0 mg, 313.9 μmol) was dissolved in CH_2Cl_2 (3.1 mL). TFA (932 μL, 12.6 mmol) was added and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured into satd. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to a light brown foam (130.3 mg, 88%). $[\alpha]_D^{20}$ -140 (*c* 0.11, $CHCl_3$); R_f = 0.46 (10% MeOH/CH_2Cl_2); IR (film) 3376, 2925, 2853, 1644, 1605, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.56 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.49 (d, *J* = 2.0 Hz, 1H), 5.43 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.75 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.41 (d, *J* = 4.8 Hz, 1H), 3.83 (s, 3H), 1.45 (d, *J* = 5.6 Hz, 3H), 1.44 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 164.7, 163.3, 157.2, 140.7, 136.8, 134.1, 133.2, 133.1, 129.1, 128.4, 128.3, 128.2, 115.0, 105.1, 100.3, 71.5, 59.0, 58.6, 55.5, 22.2, 22.0; HRMS (ESI): Exact mass calcd for $C_{25}H_{27}Cl_2N_2O_3$ $[M+H]^+$ 473.1399, found 473.1400.



2,4-Dichloro-6-methoxyquinoline (S5). Phosphorus(V) oxychloride (40 mL, 1.5 M) was added through a condenser into a 3-neck round bottom flask containing malonic acid (6.244 g, 60.00 mmol) and a stir bar at room temperature. While stirring, *p*-anisidine (9.236 g, 75.00 mmol) was added in small portions over a period of 15 minutes through an open neck of the round bottom flask. The reaction mixture was heated and stirred at reflux for 5 hours. The reaction mixture was allowed to cool to room temperature before it was poured over crushed ice (~700 mL). The pH of the resulting aqueous solution was then adjusted to 10 with concentrated ammonium hydroxide (~85 mL). The aqueous suspension was extracted with dichloromethane. The combined organic layers were then dried over $MgSO_4$ before concentration. Purification by column chromatography (0-5% ethyl acetate in hexanes) yielded the title compound as a slightly yellow solid (4.7812 g, 35%). Mp 170.5-171.5 °C; R_f = 0.27 (2% EtOAc/hexanes); IR (film) 3084, 3013, 2982, 1623, 1562, 1499 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 9.0 Hz, 1H), 7.45 (s, 1H), 7.40 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.36 (d, *J* = 3.0 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 158.9, 147.0, 144.0, 142.6, 130.4 126.3, 124.1, 122.0, 101.9, 55.7; HRMS (CI): Exact mass calcd for $C_{10}H_8Cl_2NO$ $[M+H]^+$ 227.9977, found 227.9974.

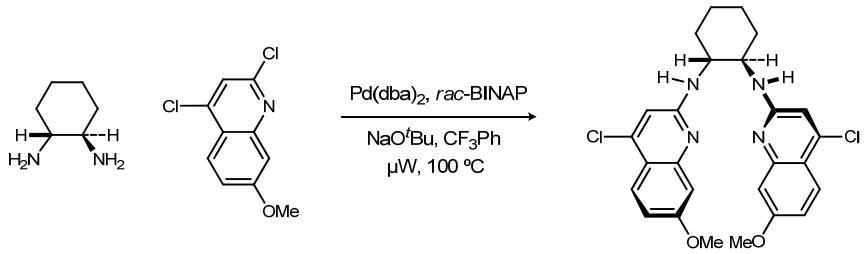


H,^{4}Cl^{6}MeOQuin-BAM (S6). A 2-5 mL μW vial was charged with (*R,R*)-diaminocyclohexane (125.2 mg, 1.096 mmol), 2,4-dichloro-6-methoxyquinoline (500 mg, 2.190 mmol), $Pd(dba)_2$ (12.6 mg, 22.0 μmol), *rac*-BINAP (13.6 mg, 22.0 μmol), and sodium *tert*-butoxide (316.2 mg, 3.290 mmol).[4] Trifluoromethylbenzene (3.8 mL) was added and the resulting suspension was heated at 120 °C and stirred in the microwave for 10 min. The reaction mixture was triturated with CH_2Cl_2 and filtered. The filtrate was concentrated and purified by column chromatography (10-20% ethyl acetate in hexanes) to provide a yellow solid (420.3 mg, 77%) that was pure by ^{1}H NMR; $[\alpha]_D^{20}$ +610 (*c* 0.18, $CHCl_3$); R_f = 0.18 (20% EtOAc/hexanes); IR (film) 3218, 2925, 1605, 1495 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 325 K) δ 7.64 (d, *J* = 9.0 Hz, 2H), 7.30 (d, *J* = 3.0 Hz, 2H), 7.25 (dd, *J* = 9.0, 3.0 Hz, 2H), 6.38 (br s, 2H), 5.72 (br s, 2H), 4.05-3.90 (m, 2H), 3.91 (s, 6H), 2.39-2.25 (m, 2H), 1.90-1.80 (m, 2H), 1.55-1.35 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$, 325 K) ppm 155.5, 155.4, 144.0, 141.4, 127.6, 121.9, 121.8, 111.8, 103.7, 56.1, 55.6, 33.0, 24.9; HRMS (ESI): Exact mass calcd for $C_{26}H_{27}Cl_2N_4O_2$ $[M+H]^+$ 497.1511, found 497.1500.

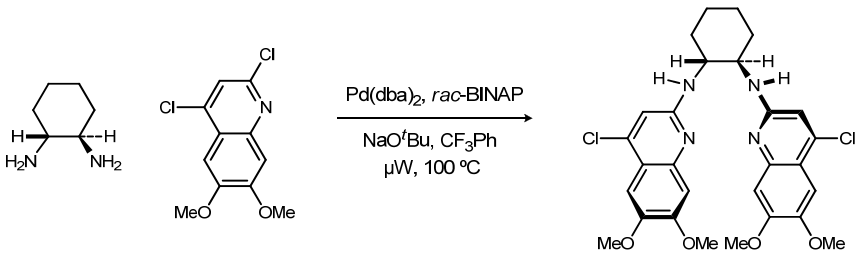


2,4-Dichloro-7-methoxyquinoline (S7). Phosphorus(V) oxychloride (20 mL, 1.3 M) was added through a running condenser into a 3-neck round bottom flask equipped with a stir bar containing malonic acid (2.710 g, 26.00 mmol) at room temperature. While stirring, *m*-anisidine (4.000 g, 32.48 mmol) was added in small portions over a period of 15 minutes through an open neck of the round bottom flask. The reaction mixture was heated and stirred at reflux for 5 hours. The reaction mixture was allowed to cool to room temperature before it was poured over crushed ice (~350 mL). The pH of the resulting aqueous solution was adjusted to 10 with concentrated ammonium hydroxide. The aqueous suspension was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and filtered before concentration to provide a 2.2:1 mixture (^{1}H NMR) of the 7-methoxy and 5-methoxy regioisomers. Purification by column chromatography (0-8% ethyl acetate in hexanes) yielded a white solid (3.181 g, 54%) that was recrystallized from ethyl acetate and hexanes to provide the 7-methoxy isomer. Mp 131.5-132.5 °C; R_f = 0.18 (5% EtOAc/hexanes); IR (film) 3092, 2982, 1623, 1572, 1559 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.2 Hz, 1H), 7.32 (s, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.23 (dd, *J* = 9.2 ,2.4 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 162.2, 150.2, 150.0, 143.9, 125.2, 120.7, 120.1, 119.5, 107.1, 55.7; HRMS (ESI): Exact mass calcd for $C_{10}H_8Cl_2NO$ $[M+H]^+$ 227.9977, found 227.9973.

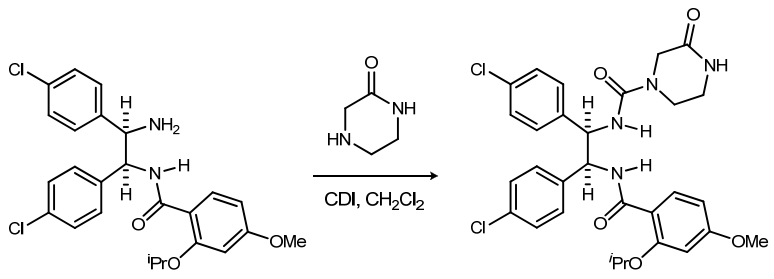
[4] Adapted from Wagaw, S.; Rennels, R.; Buchwald, S. *J Am. Chem. Soc*. **1997**, *119*, 8451-8458.



H,^{4}Cl^{7}MeOQuin-BAM (S8). A 2-5 mL μW vial was charged with (*R,R*)-diaminocyclohexane (125.2 mg, 1.096 mmol), 2,4-dichloro-7-methoxyquinoline (500 mg, 2.190 mmol), $Pd(dba)_2$ (12.6 mg, 22.0 μmol), *rac*-BINAP (13.6 mg, 22.0 μmol), and sodium *tert*-butoxide (316.2 mg, 3.290 mmol).[4] Trifluoromethylbenzene (3.8 mL) was added and the resulting suspension was heated at 100 °C and stirred in the microwave for 10 min. The reaction mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was concentrated and washed with CH_2Cl_2 then hexanes to provide a light brown powder (412.9 mg, 76%) that was pure by ^{1}H NMR; $[\alpha]_D^{20}$ +580 (*c* 0.19, $CHCl_3$); R_f = 0.25 (50% EtOAc/hexanes); IR (film) 3220, 2933, 1610, 1510 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 325 K) δ 7.82 (d, *J* = 9.0 Hz, 2H), 7.08 (s, 2H), 6.91 (dd, *J* = 9.0, 2.5 Hz, 2H), 6.31 (br s, 2H), 5.64 (br s, 2H), 4.09 (br s, 2H), 3.94 (s, 6H), 2.41-2.32 (m, 2H), 1.90-1.80 (m, 2H), 1.55-1.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 325 K) ppm 162.0, 157.3, 150.5, 142.3, 125.3, 116.3, 114.4, 109.5, 106.0, 56.1, 55.5, 32.9, 24.9; HRMS (ESI): Exact mass calcd for $C_{26}H_{27}Cl_2N_4O_2$ $[M+H]^+$ 497.1511, found 497.1501.

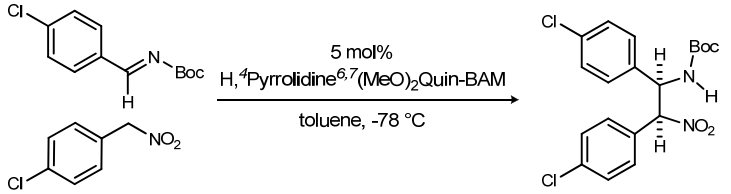


H,^{4}Cl^{6,7}(MeO)$_2$Quin-BAM (S9). A 10-20 mL μW vial was charged with (*R,R*)-diaminocyclohexane (442.4 mg, 3.874 mmol), 2,4-dichloro-6,7-dimethoxyquinoline (2.000 g, 7.749 mmol), $Pd(dba)_2$ (44.5 mg, 77.48 μmol), *rac*-BINAP (48.2 mg, 77.48 μmol), and sodium *tert*-butoxide (1.117 g, 11.62 mmol).[4] Trifluoromethylbenzene (13.4 mL) was added and the resulting suspension was heated at 100 °C and stirred in the microwave for 10 min. The reaction mixture was filtered through celite with CH_2Cl_2 and concentrated. The residue was triturated with ethyl acetate and hexanes to provide a light brown powder (1.4612 g, 68%) that was sufficiently pure by ^{1}H NMR; $[\alpha]_D^{20}$ +410 (*c* 0.10, $CHCl_3$); R_f = 0.15 (50% EtOAc/hexanes); IR (film) 3223, 2930, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 330 K) δ 7.24 (s, 2H), 7.09 (s, 2H), 6.32 (br s, 2H), 5.50 (br s, 2H), 4.02 (s, 6H), 4.00 (br s, 2H), 3.97 (s, 6H), 2.38-2.28 (m, 2H), 1.90-1.80 (m, 2H), 1.55-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 330 K) ppm 156.2, 153.2, 147.1, 145.3, 141.0, 115.7, 109.2, 106.6, 103.6, 56.2 (2C), 56.1, 33.0, 24.9; HRMS (CI): Exact mass calcd for $C_{28}H_{31}Cl_2N_4O_4$ $[M+H]^+$ 557.1717, found 557.1717.



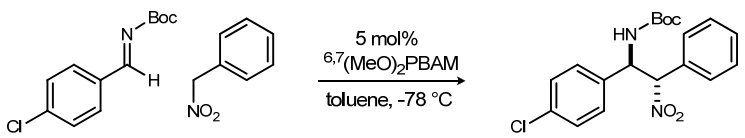
***N*-((1*R*,2*S*)-1,2-Bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)-3-oxopiperazine-1-carbox-amide (S10).** Amine (100.0 mg, 211.2 μmol) was dissolved in CH_2Cl_2 (1.0 mL) and stirred at room

temperature. CDI (41.1 mg, 253.5 μmol) was added and the reaction was stirred for 1 h. 2-Oxo-piperazine (42.3 mg, 422.4 μmol) was added, and the reaction mixture was stirred for an additional 4 hours. The reaction mixture was concentrated and purified by column chromatography (0-2-5% methanol in dichloromethane) to provide a white solid (119.6 mg, 94%). $[\alpha]_D^{20}$ +110 (*c* 0.14, $CHCl_3$); R_f = 0.34 (10% MeOH/CH_2Cl_2); IR (film) 3369, 2978, 2932, 2243, 1634, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.0 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 4.8 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.62 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 6.15 (br s, 1H), 5.77 (dd, *J* = 7.6, 2.0 Hz, 1H), 5.10 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.66 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.15 (d, *J* = 2.4 Hz, 2H), 3.86 (s, 3H), 3.73 (ddd, *J* = 13.2, 5.6, 4.4 Hz, 1H), 3.60 (ddd, *J* = 13.2, 6.4, 4.4 Hz, 1H), 3.46-3.35 (m, 2H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.14 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 168.0, 167.0, 163.0, 157.2, 155.9, 136.7, 136.6, 134.3, 133.8, 133.2, 129.4, 128.6, 128.4, 128.0, 113.5, 105.4, 100.3, 71.4, 61.6, 57.5, 55.5, 47.4, 40.9, 39.9, 21.9, 21.5; HRMS (CI): Exact mass calcd for $C_{30}H_{33}Cl_2N_4O_5$ $[M+H]^+$ 599.1823, found 599.1814.



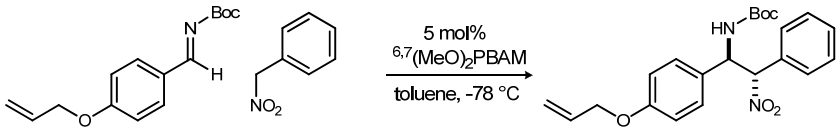
***tert*-Butyl (1*R*,2*S*)-1,2-bis(4-chlorophenyl)-2-nitroethylcarbamate (1a).** Imine (1.5000 g, 6.2580 mmol) and H,^{4}Pyrrolidine^{6,7}(MeO)$_2$Quin-BAM (196.1 mg, 312.9 μmol) were dispensed into a 100 mL round bottom flask equipped with stir bar. Toluene (63 mL) was added and the mixture was chilled to -78 °C before addition of the nitroalkane **9** (1.1810 g, 6.8840 mmol). The reaction was stirred at -78 °C for 24 h. The reaction was kept at the reaction temperature and filtered directly through a pad of silica gel with CH_2Cl_2. The filtrate was concentrated to give 2.2772 g of a white solid that was 6:1 *anti*:*syn*. A portion (1.1000 g) of this material was recrystallized from toluene to provide colorless crystals. The crystalline material (586.8 mg) was separated from the mother liquor and found to be >200:1 dr, 97% ee by chiral HPLC; (Chiralcel AD-H, 12% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) = 30.5 min, t_r(*anti*, minor) = 12.8 min, t_r(*syn*, major) = 14.9 min, t_r(*syn*, minor) = 45.6 min). Mp 172.0-174.0 °C; $[\alpha]_D^{20}$ -150 (*c* 0.13, $CHCl_3$); R_f = 0.24 (20% EtOAc/hexanes); IR (film) 3381, 2982, 1682, 1551, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 5.76 (d, *J* = 9.6 Hz, 1H), 5.58 (dd, *J* = 9.6, 9.6 Hz, 1H), 4.78 (d, *J* = 9.6 Hz, 1H), 1.28 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.2, 136.6, 135.6, 134.9, 130.1, 129.7, 129.3, 129.1, 128.6, 93.2, 80.8, 56.1, 28.0; HRMS (CI): Exact mass calcd for $C_{19}H_{21}Cl_2N_2O_4$ $[M+H]^+$ 411.0873, found 411.0865.

General Procedure for the Synthesis of Adducts 1b-m. Imine (100 μmol) and ^{6,7}(MeO)$_2$PBAM (**8d)** (3.1 mg, 5.0 μmol) were dispensed into a vial with a stir bar. Toluene (1.0 mL) was added, and the reaction was stirred at room temperature until homogenous. The reaction mixture was chilled to -78 °C before nitroalkane (110 μmol) was added. The reaction mixture was stirred for 18-26 h. The chilled mixture was diluted with CH_2Cl_2 and quickly filtered through a pad of silica. The silica pad was flushed with EtOAc. The filtrate was concentrated and purified by column chromatography.

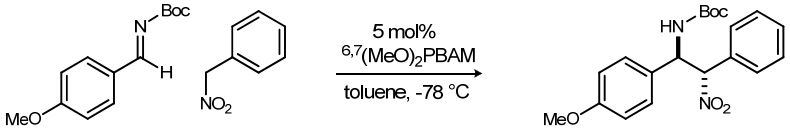


***tert*-Butyl (1*R*,2*S*)-1-(4-chlorophenyl)-2-nitro-2-phenylethylcarbamate (1b).** Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (35.0 mg, 93%) that was found to be 90% ee and 19:1 dr

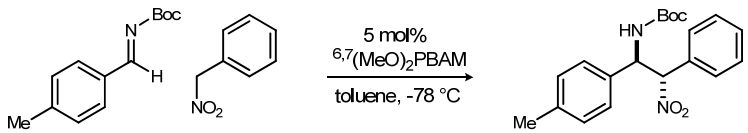
by chiral HPLC; (Chiralcel IA, 5% ^{i}PrOH/hexanes, 1 mL/min, 230 nm, t_r(*anti*, major) = 20.4 min, t_r(*anti*, minor) = 27.7 min, t_r(*syn*, major) = 24.3 min, t_r(*syn*, minor) = 46.1 min); mp 177.5-178.5 °C; $[\alpha]_D^{20}$ -28.2 (*c* 0.11, $CHCl_3$); R_f = 0.29 (20% EtOAc/hexanes); IR (film) 3386, 2984, 2924, 1683, 1549, 1520 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 6.6 Hz, 2H), 7.42 (m, 1H), 7.42 (d, *J* = 6.6 Hz, 2H), 7.34 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 5.76 (br s, 1H), 5.62 (br s, 1H), 4.84 (br s, 1H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.2, 130.4, 129.2, 128.9, 128.6, 128.6, 94.0, 80.6, 56.1, 28.2. HRMS (ESI): Exact mass calcd for $C_{19}H_{21}ClN_2NaO_4$ $[M+Na]^+$ 399.1088, found 399.1070.



***tert*-Butyl (1*R*,2*S*)-1-(4-(allyloxy)phenyl)-2-nitro-2-phenylethylcarbamate (1c).** Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (28.0 mg, 79%) that was found to be 87% ee and 131:1 dr by chiral HPLC; (Chiralcel IA, 12% EtOH/hexanes, 0.5 mL/min, t_r(*anti*, major) 14.9 min, t_r(*anti*, minor) = 13.1 min, t_r(*syn*, major) = 13.8 min, t_r(*syn*, minor) = 22.3 min); Mp 174.5-176.0 °C; $[\alpha]_D^{20}$ -42 (*c* 0.16, $CHCl_3$); R_f = 0.21 (20% EtOAc/hexanes); IR (film) 3394, 2981, 2930, 1683, 1549, 1514 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 2H), 7.45-7.37 (m, 3H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.04 (dddd, *J* = 16.8, 10.2, 4.8, 4.8 Hz, 1H), 5.74 (br s, 1H), 5.61 (br s, 1H), 5.41 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.29 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.80 (d, *J* = 7.8 Hz, 1H), 4.52 (d, *J* = 4.8 Hz, 2H) 1.25 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 158.8, 154.2, 133.0, 131.6, 130.1, 129.7, 128.8 (2C), 128.4, 117.8, 115.1, 94.4, 80.3, 68.8, 56.1, 28.0; HRMS (ESI): Exact mass calcd for $C_{22}H_{26}N_2NaO_5$ $[M+Na]^+$ 421.1739, found 421.1730.

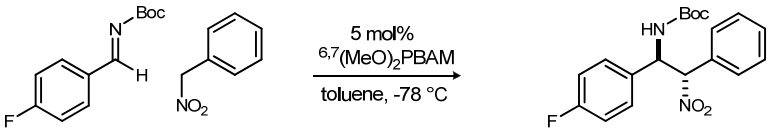


***tert*-Butyl (1*R*,2*S*)-1-(4-methoxyphenyl)-2-nitro-2-phenylethylcarbamate (1d).** Product was made according to the general procedure with the exception that reaction warmed to -20 °C and stirred for 1h before filtration. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (31.0 mg, 83%) that was found to be 85% ee and 81:1 dr by chiral HPLC; (Chiralcel IA, 12% ^{i}PrOH/hexanes, 0.5 mL/min, t_r(*anti*, major) 21.3 min, t_r(*anti*, minor) = 23.6 min, t_r(*syn*, major) = 19.8 min, t_r(*syn*, minor) = 37.0 min); Mp 161.0-162.5 °C; $[\alpha]_D^{20}$ -43 (*c* 0.14, $CHCl_3$); R_f = 0.18 (20% EtOAc/hexanes); IR (film) 3390, 2980, 1683, 1548, 1515 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.53 (m, 2H), 7.44-7.37 (m, 3H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.75 (d, *J* = 10.0 Hz, 1H), 5.61 (dd, *J* = 9.2, 9.2 Hz, 1H), 4.80 (d, *J* = 8.8 Hz, 1H), 3.80 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.7, 154.2, 131.6, 130.1, 129.5, 128.8 (2C), 128.4, 114.3, 94.4, 80.3, 56.2, 55.3, 28.0; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}N_2NaO_4$ $[M+Na]^+$ 395.1583, found 395.1567.

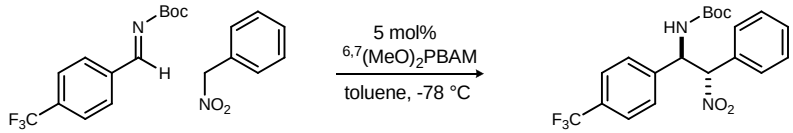


***tert*-Butyl (1*R*,2*S*)-2-nitro-2-phenyl-1-p-tolylethylcarbamate (1e).** Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (33.0 mg, 93%) that was found to be 91% ee and 38:1 dr by chiral HPLC; (Chiralcel IA, 12% ^{i}PrOH/hexanes, 0.7 mL/min, t_r(*anti*, major) 12.1 min, t_r(*anti*, minor) = 13.1 min, t_r(*syn*, major) = 11.2 min, t_r(*syn*, minor) = 20.7 min); Mp 181.0-183.0 °C; $[\alpha]_D^{20}$ -46

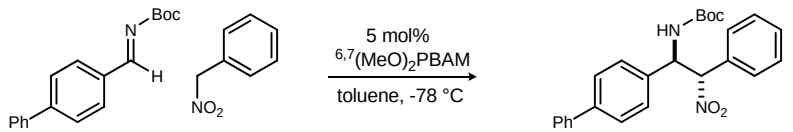
(*c* 0.11, $CHCl_3$); R_f = 0.36 (20% EtOAc/hexanes); IR (film) 3393, 2979, 1685, 1549, 1517 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2 Hz, 2H), 7.45-7.37 (m, 3H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 5.75 (br s, 1H), 5.64 (br s, 1H), 4.78 (d, *J* = 9.0 Hz, 1H), 2.34 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.2, 138.6, 134.5, 131.6, 130.1, 129.7, 128.78, 128.76, 127.0, 94.4, 80.2, 56.3, 28.0, 21.1; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}N_2NaO_4$ $[M+Na]^+$ 379.1634, found 379.1626.



***tert*-Butyl (1*R*,2*S*)-1-(4-fluorophenyl)-2-nitro-2-phenylethylcarbamate (1f).** Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (35.0 mg, 97%) that was found to be 87% ee and 15:1 dr by chiral HPLC; (Chiralcel IA, 5% EtOH/hexanes, 0.5 mL/min, t_r(*anti*, major) 19.1 min, t_r(*anti*, minor) = 20.5 min, t_r(*syn*, major) = 22.8 min, t_r(*syn*, minor) = 39.9 min); Mp 178.5-180.0 °C; $[\alpha]_D^{20}$ -18 (*c* 0.15, $CHCl_3$); R_f = 0.34 (20% EtOAc/hexanes); IR (film) 3391, 2986, 2925, 1683 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.46-7.39 (m, 3H), 7.34 (dd, *J* = 8.4, 4.8 Hz, 2H), 7.05 (dd, *J* = 8.4, 8.4 Hz, 2H), 5.75 (br s, 1H), 5.64 (br s, 1H), 4.81 (d, *J* = 9.0 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 162.7 (d, $^1J_{CF}$ = 246 Hz), 154.2, 133.4, 131.3, 130.3, 129.0 (d, $^3J_{CF}$ = 9.0 Hz), 128.9, 128.7, 116.0 (d, $^2J_{CF}$ = 23 Hz), 94.2, 80.6, 56.2, 28.0; ^{19}F NMR (376 MHz, $CDCl_3$) ppm -112.7; HRMS (ESI): Exact mass calcd for $C_{19}H_{21}FN_2NaO_4$ $[M+Na]^+$ 383.1383, found 383.1392.

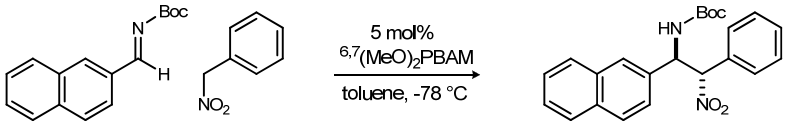


***tert*-Butyl (1*R*,2*S*)-2-nitro-2-phenyl-1-(4-(trifluoromethyl)phenyl)ethylcarbamate (1g).** Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (40.8 mg, 99%) that was found to be 84% ee and 14:1 dr by chiral HPLC; (Chiralcel IA, 8% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 9.2 min, t_r(*anti*, minor) = 13.9 min, t_r(*syn*, major) = 12.6 min, t_r(*syn*, minor) = 20.0 min); Mp 193.5-194.5 °C; $[\alpha]_D^{20}$ -21 (*c* 0.14, $CHCl_3$); R_f = 0.33 (20% EtOAc/hexanes); IR (film) 3390, 2985, 1683, 1548, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.58-7.53 (m, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.43-7.40 (m, 3H), 5.80 (br s, 1H), 5.71 (br s, 1H), 4.89 (br s, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 141.5, 131.0, 130.9 (q, $^2J_{CF}$ = 32 Hz), 130.5, 129.0, 128.6, 127.7, 126.0 (q, $^3J_{CF}$ = 4.0 Hz), 123.8 (q, $^1J_{CF}$ = 271 Hz), 93.7, 80.8, 56.3, 28.0; ^{19}F NMR (282 MHz, $CDCl_3$) ppm -61.1; HRMS (ESI): Exact mass calcd for $C_{20}H_{21}F_3N_2NaO_4$ $[M+Na]^+$ 433.1351, found 433.1364.

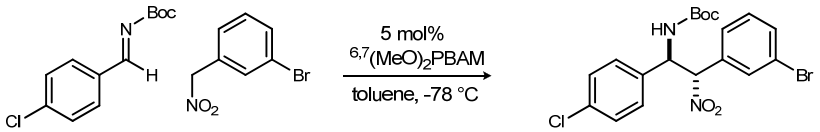


***tert*-Butyl (1*R*,2*S*)-1-(biphenyl-4-yl)-2-nitro-2-phenylethylcarbamate (1h).** Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (41.5 mg, 99%) that was found to be 93% ee and 44:1 dr by chiral HPLC; (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 32.6 min, t_r(*anti*, minor) = 23.9 min, t_r(*syn*, major) = 26.1 min, t_r(*syn*, minor) = 28.7 min); Mp 194.0-196.0 °C; $[\alpha]_D^{20}$ -56 (*c* 0.15, $CHCl_3$); R_f = 0.29 (20% EtOAc/hexanes); IR (film) 3398, 2978, 2922, 1686, 1548, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.55 (m, 6H), 7.47-7.40 (m, 7H), 7.39-7.33 (m, 1H), 5.82 (br s,

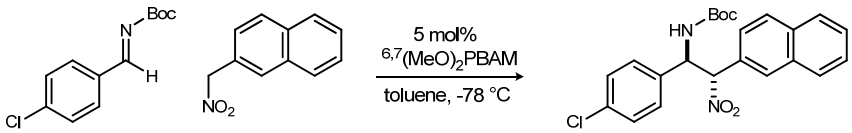
1H), 5.73 (br s, 1H), 4.90 (br s, 1H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 141.6, 140.3, 136.4, 131.5, 130.2, 128.83, 128.80, 128.76, 127.7, 127.59, 127.56, 127.1, 94.2, 80.4, 56.5, 28.0; HRMS (ESI): Exact mass calcd for $C_{25}H_{26}N_2NaO_4$ $[M+Na]^+$ 441.1790, found 471.1776.



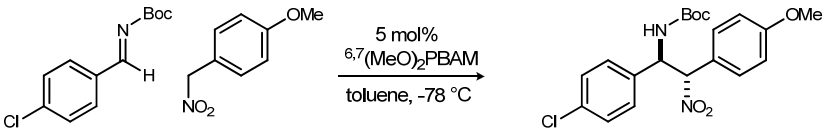
***tert*-Butyl (1*R*,2*S*)-1-(naphthalen-2-yl)-2-nitro-2-phenylethylcarbamate (1i).** Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (38.9 mg, 99%) that was found to be 91% ee and 25:1 dr by chiral HPLC; (Chiralcel IA, 12% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 10.6 min, t_r(*anti*, minor) = 13.2 min, t_r(*syn*, major) = 9.2 min, t_r(*syn*, minor) = 17.5 min); Mp 183.0-184.5 °C; $[\alpha]_D^{20}$ -39 (*c* 0.11, $CHCl_3$); R_f = 0.29 (20% EtOAc/hexanes); IR (film) 3403, 2977, 1688, 1547, 1519 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.80 (m, 4H), 7.65-7.58 (m, 2H), 7.54-7.48 (m, 2H), 7.48-7.40 (m, 4H), 5.97-5.80 (m, 2H), 4.90 (d, *J* = 8.4 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 134.8, 133.23, 133.16, 131.5, 130.2, 129.1, 128.9, 128.8, 128.1, 127.7, 126.7, 126.6 (2C), 124.4, 94.2, 80.3, 56.7, 28.0; HRMS (ESI): Exact mass calcd for $C_{23}H_{24}N_2NaO_4$ $[M+Na]^+$ 415.1634, found 415.1635.



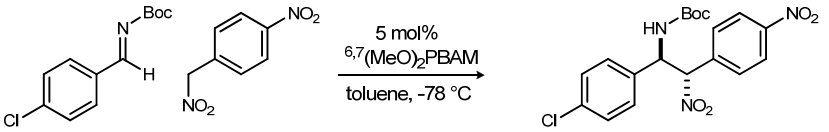
***tert*-Butyl (1*R*,2*S*)-2-(3-bromophenyl)-1-(4-chlorophenyl)-2-nitroethylcarbamate (1j).** Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (41.5 mg, 91%) that was found to be 89% ee and 13:1 dr by chiral HPLC; (Chiralcel AD-H, 15% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 29.7 min, t_r(*anti*, minor) = 14.6 min, t_r(*syn*, major) = 13.4 min, t_r(*syn*, minor) = 17.2 min); Mp 178.0-179.0 °C; $[\alpha]_D^{20}$ -39 (*c* 0.15, $CHCl_3$); R_f = 0.40 (20% EtOAc/hexanes); IR (film) 3388, 2982, 1681, 1549, 1519 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (br s, 1H), 7.58 (ddd, *J* = 8.0, 1.6, 0.8 Hz, 1H), 7.52 (br d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.29 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 5.75 (br s, 1H), 5.56 (br m, 1H), 4.87 (br s, 1H), 1.29 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$) ppm 154.2, 135.6, 134.9, 133.5, 133.3, 131.8, 130.4, 129.3, 128.6, 127.2, 122.8, 93.1, 80.8, 56.3, 28.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}BrClN_2NaO_4$ $[M+Na]^+$ 477.0193, found 477.0197.



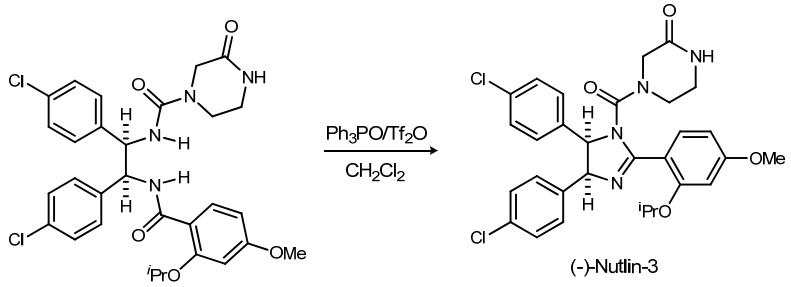
***tert*-Butyl (1*R*,2*S*)-1-(4-chlorophenyl)-2-(naphthalen-2-yl)-2-nitroethylcarbamate (1k).** Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (42.1 mg, 99%) that was found to be 80% ee and 10:1 dr by chiral HPLC; (Chiralcel AD-H, 15% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 53.9 min, t_r(*anti*, minor) = 18.0 min, t_r(*syn*, major) = 16.7 min, t_r(*syn*, minor) = 26.3 min); Mp 185.5-187.0 °C; $[\alpha]_D^{20}$ -27 (*c* 0.15, $CHCl_3$); R_f = 0.32 (20% EtOAc/hexanes); IR (film) 3388, 2980, 1683, 1550, 1520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.92-7.85 (m, 3H), 7.65 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.59-7.52 (m, 2H), 7.38-7.32 (m, 4H), 5.95 (br d, *J* = 8.8 Hz, 1H), 5.72 (br dd, *J* = 9.2, 9.2 Hz, 1H), 4.86 (d, *J* = 8.8 Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 136.1, 134.7, 134.0, 132.8, 129.3, 129.2, 129.0, 128.7, 128.6, 128.3, 127.7, 127.4, 126.9, 124.6, 94.2, 80.7, 56.0, 28.0; HRMS (ESI): Exact mass calcd for $C_{23}H_{23}ClN_2NaO_4$ $[M+Na]^+$ 449.1244, found 449.1256.



***tert*-Butyl (1*R*,2*S*)-1-(4-chlorophenyl)-2-(4-methoxyphenyl)-2-nitroethylcarbamate (1l).** Product was made according to the general procedure with the exception that reaction warmed to -20 °C and stirred for 1h before filtration. Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (36.5 mg, 90%) that was found to be 86% ee and 17:1 dr by chiral HPLC; (Chiralcel AD-H, 15% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 27.6 min, t_r(*anti*, minor) = 14.3 min, t_r(*syn*, major) = 16.7 min, t_r(*syn*, minor) = 37.9 min); Mp 165.0-166.0 °C; $[\alpha]_D^{20}$ -9.1 (*c* 0.11, $CHCl_3$); R_f = 0.27 (20% EtOAc/hexanes); IR (film) 3385, 2981, 1683, 1552, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 5.68 (br s, 1H), 5.58 (br s, 1H), 4.85 (br s, 1H), 3.82 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 161.1, 154.3, 136.2, 134.6, 130.1, 129.1, 128.6, 123.2, 114.3, 93.6, 80.6, 56.1, 55.4, 28.1.



***tert*-Butyl (1*R*,2*S*)-1-(4-chlorophenyl)-2-nitro-2-(4-nitrophenyl)ethylcarbamate (1m).** Column chromatography (15-30% ethyl acetate in hexanes) afforded a white solid (41.5 mg, 99%) that was found to be 76% ee and 2:1 dr by chiral HPLC; (Chiralcel IA, 10% EtOH/hexanes, 1 mL/min, t_r(d_1, major) 9.8 min, t_r(d_1, minor) = 12.6 min, t_r(d_2, major) = 21.5 min, t_r(d_2, minor) = 52.8 min); Mp 165.5-166.0 °C; R_f = 0.07 (10% EtOAc/hexanes); IR (film) 3405, 2981, 2926, 1681, 1551, 1522 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) ***d*$_1$** δ 8.35 (d, *J* = 8.8 Hz, 2H), 7.97 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 6.16 (d, *J* = 11.2 Hz, 1H), 5.57 (dd, *J* = 10.8, 10.8 Hz, 1H), 1.14 (s, 9H); ***d*$_2$** δ 8.13 (d, *J* = 8.8 Hz, 2H), 8.13-8.07 (1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.20 (d, *J* = 11.2 Hz, 1H), 5.69 (dd, *J* = 10.4, 10.4 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm 154.5, 154.2, 148.5, 148.3, 138.3, 137.9, 136.9, 136.1, 133.2, 132.6, 130.3, 130.2, 129.8, 129.6, 128.8, 128.5, 123.9, 123.7, 92.2, 91.9, 78.9 (2C), 56.3, 55.6, 28.0, 27.7.



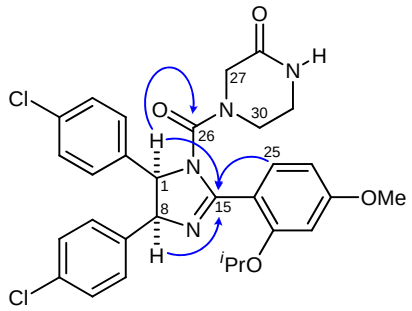
(-)-Nutlin-3 (2).[5] Tf_2O (28.1 μL, 166.8 μmol) was added to a stirred solution of Ph_3PO (92.8 mg, 333.6 μmol) in CH_2Cl_2 (500 μL) at 0 °C. The mixture was stirred for 10 min before urea (50.0 mg, 83.4 μmol) was added as a solution in CH_2Cl_2 (600 μL), and the reaction was stirred for 1 h at 0 °C. The reaction mixture was allowed to warm to room temperature before addition of aq. $NaHCO_3$. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. Column chromatography (0-4% methanol in dichloromethane) of the residue provided the compound as a white solid (42.5 mg, 88%). Mp 127.0-129.0 °C; $[\alpha]_D^{20}$ -150 (*c* 0.13, $CHCl_3$); R_f = 0.24 (5%

[5] Adapted from Pemberton, N.; Pinkner, J. S.; Edvinsson, S.; Hultgren, S. J.; Almqvist, F. *Tetrahedron* **2008**, *64*, 9368-9376.

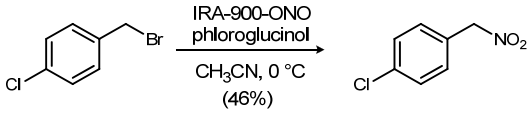
MeOH/CH_2Cl_2); IR (film) 3229, 2980, 2935, 2247, 1678, 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.66 (s, 1H), 6.54 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.47 (br s, 1H), 5.55 (d, *J* = 9.6 Hz, 1H), 5.47 (d, *J* = 9.6 Hz, 1H), 4.60 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.83 (s, 3H), 3.75 (d, *J* = 18.0 Hz, 1H), 3.62 (d, *J* = 18.0 Hz, 1H), 3.40-3.31 (m, 1H), 3.23-3.13 (m, 1H), 2.97 (br s, 2H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.9, 163.0, 160.2, 157.0, 154.7, 136.0, 135.0, 133.1, 132.8, 132.1, 129.2, 128.4, 128.1, 127.9, 113.4, 104.6, 100.1, 71.7, 70.9, 69.1, 55.5, 49.4, 41.8, 40.3, 20.03, 20.01; HRMS (CI): Exact mass calcd for $C_{30}H_{31}Cl_2N_4O_4$ $[M+H]^+$ 581.1717, found 581.1705.

This enantiomer corresponded to "enantiomer-a" using the HPLC conditions as described previously.[6] The compound was found to be 99% ee; (Chiralcel OD, 30% iPrOH/hexanes, 1 mL/min, t_r(major) = 8.6 min, t_r(minor) = *not observed*). Additionally, the (+)-enantiomer was prepared using an identical procedure with (*S*,*S*)-H,[4]PyrrolidineQuin-BAM to form compound **7** (84% ee), which was converted to (+)-Nutlin-3. This compound correlated with "enantiomer-b". and was found to be 85% ee; (Chiralcel OD, 30% iPrOH/hexanes, 1 mL/min, t_r(major) = 10.5 min, t_r(minor) = 8.6 min).

Figure 1. ***Nutlin-3 HMBC Correlations (600 MHz)***

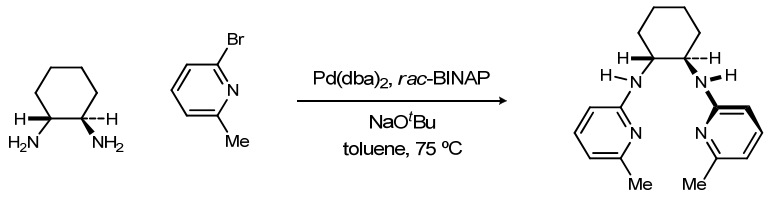


Further evidence supporting the structural assignment includes an HMBC (Figure 1), which clearly showed the anticipated couplings for Nutlin-3. C26 (155 ppm) Showed correlations to H27/H27` and H30/H30' and to H1 (but not H8). C15 (160 ppm) Showed correlations to both of the imidazoline methines (H1 and H8) and also to the H25. *See SI-2 for HMBC spectrum.*



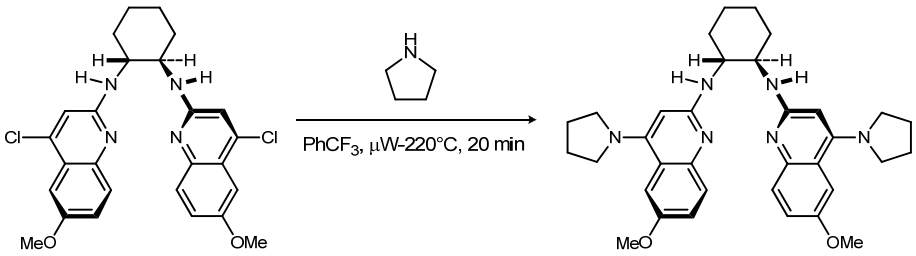
1-Chloro-4-(nitromethyl)benzene (4). 4-Chlorobenzyl bromide (3.000 g, 14.60 mmol) and phloroglucinol (1.841 g, 14.60 mmol) were dissolved in CH_3CN (32.3 mL) in a round bottom flask at room temperature. The reaction mixture was then chilled to 0 °C before IRA900-ONO (12.4 g, 2.4 equiv.) resin was added. The suspension was then stirred at 0 °C for 70 min and filtered. The resin was rinsed thoroughly with diethyl ether. The filtrate and rinsate were combined and concentrated. Column chromatography of the residue (0-3% ethyl acetate in hexanes) afforded a crystalline solid (1.1642 g, 46%). Mp 28.0-29.0 °C; R_f = 0.45 (20% EtOAc/hexanes); IR (film) 3095, 3036, 2916, 1555 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.35 (m, 4H), 5.41 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 136.3, 131.4, 129.4, 128.0, 79.1; HRMS (CI): Exact mass calcd for $C_7H_7ClNO_2$ $[M+H]^+$ 172.0160, found 172.0157.

[6] Wang, Z.; Jonca, M.; Lambros, T.; Ferguson, S.; Goodnow, R. *J. Pharm. Biomed. Anal.* **2007**, *45*, 720-729.

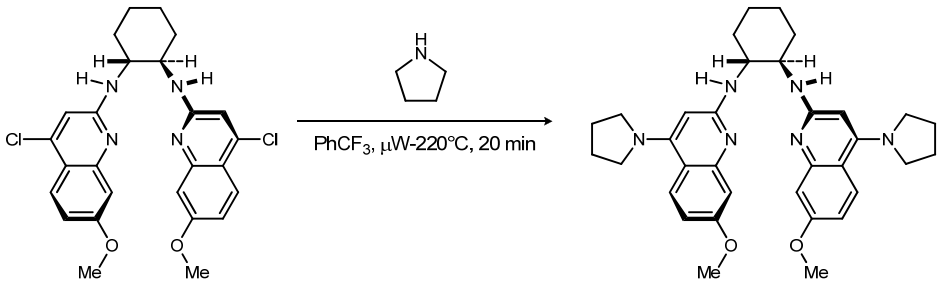


H,^{6}Me-BAM (7). $Pd(dba)_2$ (10.1 mg, 17.5 μmol), *rac*-BINAP (21.8 mg, 35.0 μmol), and sodium *tert*-butoxide (286.4 mg, 2.98 mmol) were loaded into a round bottom flask in a glove box. Toluene (10 mL, 0.10M) was added to the mixture, followed by (*R*,*R*)-diaminocyclohexane (100.0 mg, 876.0 μmol). 2-Bromo-6-methylpyridine (301.5 mg, 1.75 mmol) was added as a solution in toluene. The reaction was allowed to stir at 80 °C and monitored by TLC. The reaction was then cooled to room temperature, concentrated, and purified by flash column chromatography on silica gel (5% triethylamine, 10% ethyl acetate in hexanes) affording a white solid (200 mg, 77%). $[\alpha]_D^{20}$ +110 (*c* 0.10, $CHCl_3$); mp 126-128 °C; R_f = 0.17 (5% Et_3N, 10% EtOAc/hexanes); IR (neat) 3256, 3051, 2927, 2855, 1559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 8.0, 8.0 Hz, 2H), 6.35 (d, *J* = 7.2 Hz, 2H), 6.11 (d, *J* = 8.4 Hz, 2H), 5.16 (br s, 2H), 3.73-3.64 (m, 2H), 2.37 (s, 6H), 2.27-2.18 (m, 2H), 1.78-1.65 (m, 2H), 1.50-1.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 158.2, 156.5, 137.3, 111.3, 104.2, 55.0, 32.1, 24.4, 24.3; HRMS (EI) Exact mass calcd for $C_{18}H_{24}N_4$ $[M]^+$ 296.2001, found 296.1994.

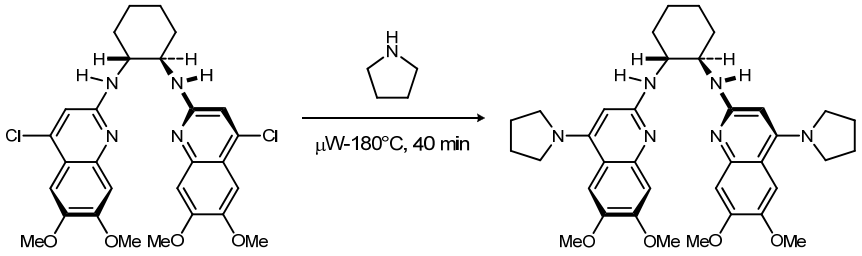
H,^{4}PyrrolidineQuin-BAM·HOTf (8a·HOTf). To a flame-dried vial with stir bar was added H,^{4}PyrrolidineQuin-BAM (**8a**) (286.3 mg, 565.1 μmol) and dichloromethane (2 mL). Trifluoromethanesulfonic acid (50.0 μL, 565 μmol) was added dropwise to the stirring solution at room temperature. The reaction mixture was allowed to stir an additional 10 minutes before concentration to a light brown solid that was used without further purification. *Other catalyst acid salts were made in a similar fashion.*



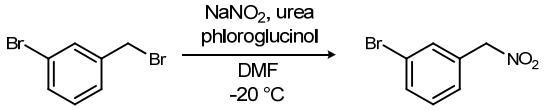
H,^{4}Pyrrolidine^{6}MeOQuin-BAM (8b). A 2-5 mL microwave vial was charged with H,^{4}Cl^{6}OMeQuin-BAM (200 mg, 402 μmol), pyrrolidine (660 μL, 8.041 mmol), and trifluoromethylbenzene (2 mL). This suspension was heated at 220 °C and stirred in the microwave for 20 min. The reaction was then concentrated and purified by column chromatography (5-10% methanol in dichloromethane) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (174.4 mg, 77%); $[\alpha]_D^{20}$ +350 (*c* 0.14, $CHCl_3$); R_f = 0.29 (10% MeOH/CH_2Cl_2); IR (film) 3261, 2930, 2856, 1595, 1531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 9.2 Hz, 2H), 7.27 (d, *J* = 2.8 Hz, 2H), 7.11 (dd, *J* = 8.8, 2.8 Hz, 2H), 5.57 (br s, 2H), 5.35 (s, 2H), 4.03 (br s, 2H), 3.82 (s, 6H), 3.32-3.20 (m, 4H), 3.15-3.05 (m, 4H), 2.32-2.25 (m, 2H), 1.90-1.75 (m, 10H), 1.50-1.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 157.3, 153.0, 152.8, 144.8, 127.5, 118.9, 118.4, 106.0, 94.0, 56.4, 55.6, 51.4, 33.4, 25.4, 25.1; HRMS (ESI): Exact mass calcd for $C_{34}H_{43}N_6O_2$ $[M+H]^+$ 567.3448, found 567.3442.



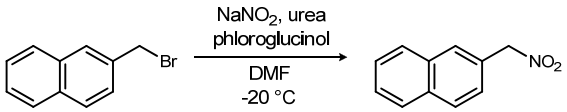
H,^{4}Pyrrolidine^{7}MeOQuin-BAM (8c). A 2-5 mL microwave vial was charged with H,^{4}Cl^{7}MeOQuin-BAM (200 mg, 402 μmol), pyrrolidine (660 μL, 8.041 mmol), and trifluoromethylbenzene (2 mL). This suspension was heated at 220 °C and stirred in the microwave for 20 min. The reaction was then concentrated and purified by column chromatography (5-10% methanol in dichloromethane) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (123.5 mg, 54%); $[\alpha]_D^{20}$ +480 (*c* 0.13, $CHCl_3$); R_f = 0.39 (10% MeOH/CH_2Cl_2); IR (film) 3253, 2930, 2855, 1616, 1589, 1526 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 9.0 Hz, 2H), 7.09 (s, 2H), 6.65 (dd, *J* = 9.5, 2.5 Hz, 2H), 5.77 (br s, 2H), 5.23 (s, 2H), 4.04 (br s, 2H), 3.88 (s, 6H), 3.35-3.25 (m, 4H), 3.20-3.10 (m, 4H), 2.33-2.25 (m, 2H), 1.90-1.78 (m, 10H), 1.55-1.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 159.9, 158.6, 153.2, 151.5, 125.9, 112.7, 110.4, 105.8, 90.7, 56.3, 55.2, 51.5, 33.3, 25.6, 25.0; HRMS (ESI): Exact mass calcd for $C_{34}H_{43}N_6O_2$ $[M+H]^+$ 567.3447, found 567.3467.



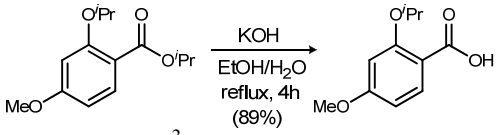
H,^{4}Pyrrolidine^{6,7}(MeO)$_2$Quin-BAM (8d). A 2-5 mL microwave vial was charged with ^{4}Cl^{6,7}(MeO)$_2$Quin-BAM (1.000 g, 1.794 mmol) and pyrrolidine (2.9 mL, 36 mmol). This suspension was heated at 180 °C and stirred in the microwave for 40 min. The reaction was then concentrated and purified by column chromatography (2-5-10% methanol in dichloromethane with 1% AcOH) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated. The material was then triturated with hexanes to afford a light brown viscous foam (351.1 mg, 31%); $[\alpha]_D^{20}$ +340 (*c* 0.11, $CHCl_3$); R_f = 0.22 (10% MeOH/1% AcOH/CH_2Cl_2); IR (film) 3391, 2931, 2855, 1593 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 2H), 7.10 (s, 2H), 5.51 (br s, 2H), 5.37 (s, 2H), 3.99 (br s, 2H), 3.99 (s, 6H), 3.89 (s, 6H), 3.37-3.26 (m, 4H), 3.23-3.13 (m, 4H), 2.35-2.25 (m, 2H), 1.91-1.79 (m, 10H), 1.52-1.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 157.6, 152.8, 150.7, 146.0, 143.5, 111.7, 106.5, 105.2, 91.9, 56.3, 55.8, 55.5, 51.2, 33.3, 25.3, 25.0; HRMS (CI): Exact mass calcd for $C_{36}H_{47}N_6O_4$ $[M+H]^+$ 627.3653, found 627.3658.



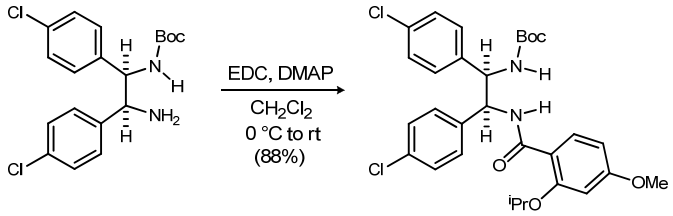
1-Bromo-3-(nitromethyl)benzene (17). $NaNO_2$ (414.0 mg, 6.000 mmol), urea (721.2 mg, 12.00 mmol), and phloroglucinol (756.7 mg, 6.000 mmol) were stirred with DMF (9.1 mL) at room temperature until homogenous. The reaction mixture was chilled to -20 °C before the addition of bromide (1.4996 g, 6.000 mmol). The mixture was stirred at -20 °C for 5.5 h before pouring into ice water. The mixture was extracted with ether. The combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (0-10% EtOAc/hexanes) provided a clear, slightly green oil (379.9 mg, 29%). R_f = 0.23 (10% EtOAc/hexanes); IR (film) 3064, 2914, 1553 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.64-7.61 (m, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.32 (dd, *J* = 7.8, 7.8 Hz), 5.40 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 133.2, 133.0, 131.4, 130.6, 128.6, 122.9, 79.1; HRMS (CI): Exact mass calcd for $C_7H_6BrNO_2$ $[M]^+$ 214.9576, found 214.9575.



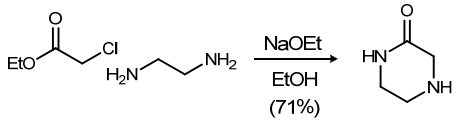
2-(Nitromethyl)naphthalene (18). $NaNO_2$ (1.035 g, 15.00 mmol), urea (1.202 g, 20.00 mmol), phloroglucinol (1.261 g, 10.00 mmol), and bromide (2.211 g, 10.00 mmol) were reacted according to the aforementioned procedure but with a reaction time of 5 h. Column chromatography (0-3% EtOAc/hexanes) provided a yellow solid (358.4 mg, 19%). Mp 81.5-82.5 °C. R_f = 0.30 (10% EtOAc/hexanes); IR (film) 3060, 2910, 1550 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.94-7.85 (m, 4H), 7.59-7.52 (m, 3H), 5.60 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 133.6, 133.0, 130.0, 129.0, 128.2, 127.8, 127.2, 127.0, 126.8, 126.4, 80.2; HRMS (CI): Exact mass calcd for $C_{11}H_9NO_2$ $[M]^+$ 187.0628, found 187.0634.



2-Isopropoxy-4-methoxybenzoic acid (21).[3] Ester (985.0 mg, 3.904 mmol) was boiled with KOH (703.8 mg, 12.54 mmol) in a mixture of ethanol (11.7 mL) and water (2.3 mL) for 4 h. EtOH was then removed by evaporation. The remaining material was diluted with water and treated with 3 M HCl until precipitation occurred. The suspension was then extracted with diethyl ether. The combined organic layers were washed with brine before drying over MgSO4. The solution was concentrated to a red oil (733.2 mg, 89%) that was pure by ^1H NMR. R_f = 0.33 (50% EtOAc/hexanes); IR (film) 3261, 2981, 1730, 1608 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.91 (br s, 1H), 8.12 (d, *J* = 9.0 Hz, 1H), 6.62 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 4.81 (heptet, *J* = 6.5 Hz, 1H), 3.86 (s, 3H), 1.47 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.5, 164.9, 157.8, 135.4, 111.4, 106.8, 100.7, 73.9, 55.7, 21.9; HRMS (ESI): Exact mass calcd for $C_{11}H_{14}NaO_4$ $[M+Na]^+$ 233.0790, found 233.0795.



***tert*-Butyl (1*R*,2*S*)-1,2-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethylcarbamate (22).** The amine (170.0 mg, 445.8 μmol) and carboxylic acid (93.7 mg, 445.8 μmol) were dissolved in CH_2Cl_2 (2.2 mL) at room temperature. The solution was chilled to 0 °C and EDC (111.1 mg, 579.6 μmol) and DMAP (5.4 mg, 44.6 μmol) were added. The reaction mixture was stirred and allowed to gradually warm to room temperature. After 16 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed once with water, dried over $MgSO_4$, and concentrated. The resulting white solid was washed with CH_2Cl_2 and hexanes, leaving a white solid (224.5 mg, 88%) that was pure by NMR. Mp 239.0-241.0 °C (decomp.); $[\alpha]_D^{20}$ -29 (*c* 0.13, $CHCl_3$); R_f = 0.13 (20% EtOAc/hexanes); IR (film) 3355, 2976, 1680, 1629, 1607, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 7.2 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 6.8 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.59 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.46 (d, *J* = 1.6 Hz, 1H), 5.91 (br s, 1H), 5.78 (br s, 1H), 5.07 (br s, 1H), 4.75-4.60 (m, 1H), 3.84 (s, 3H), 1.38 (s, 9H), 1.30-1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.6, 163.6, 157.2, 155.0, 136.9, 136.7, 134.2, 133.6, 133.3, 128.6 (2C), 128.5, 128.3, 114.1, 105.2, 100.2, 79.9, 71.4, 59.5, 56.6, 55.5, 28.3, 22.0, 21.6; HRMS (ESI): Exact mass calcd for $C_{30}H_{34}Cl_2N_2NaO_5$ $[M+Na]^+$ 595.1742, found 595.1743.



2-Oxo-piperazine (23).[7] The resulting orange oil was purified by column chromatography (10% MeOH in CH_2Cl_2 w/ 1% NH_4OH). A yellow solid (2.8634 g, 71%) was obtained that was sufficiently pure by ^1H NMR. R_f = 0.07 (10% MeOH/CH_2Cl_2 w/ 1% NH_4OH); IR (film) 3400, 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (br s, 1H), 3.46 (s, 2H), 3.35-3.28 (m, 2H), 2.98 (t, *J* = 5.5 Hz, 2H), 1.89 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.4, 49.6, 42.7, 42.2; HRMS (CI): Exact mass calcd for $C_4H_9N_2O$ $[M+H]^+$ 101.0709, found 101.0714.

[7] Elmaleh, D. R.; Choi, S.-W. Diagnostic and therapeutic piperazine and piperidine compounds and process. U.S. Patent 6,835,371, December 28, 2004.

Catalytic, Enantioselective Synthesis of Stilbene *cis*-Diamines: A Concise Preparation of (-)-Nutlin 3, a Potent p53-MDM2 Inhibitor

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S-II-X

Figure 1. ^{1}H NMR (400 MHz, $CDCl_3$) of **S1.**

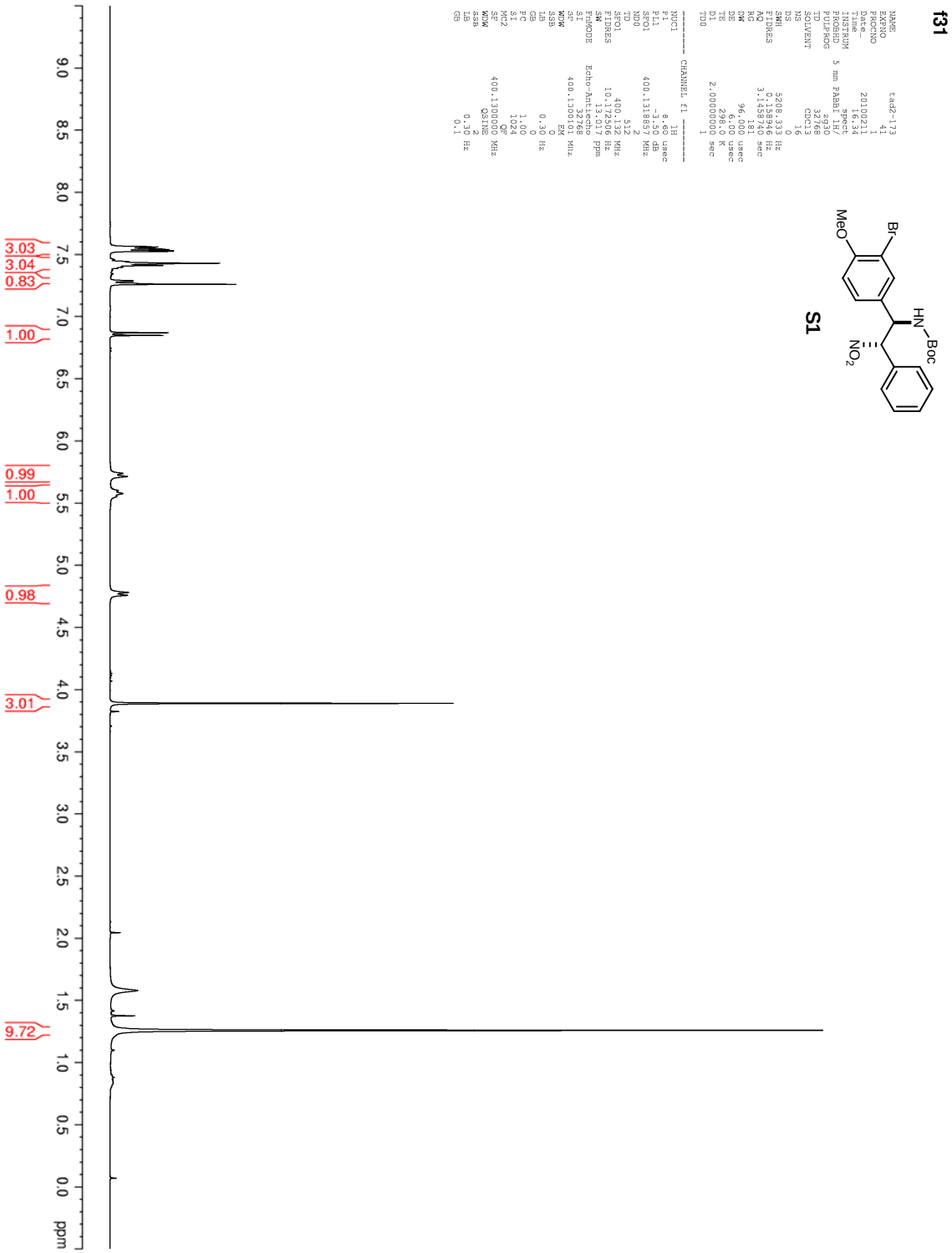


Figure 2. ^{13}C NMR (150 MHz, $CDCl_3$) of **S1**

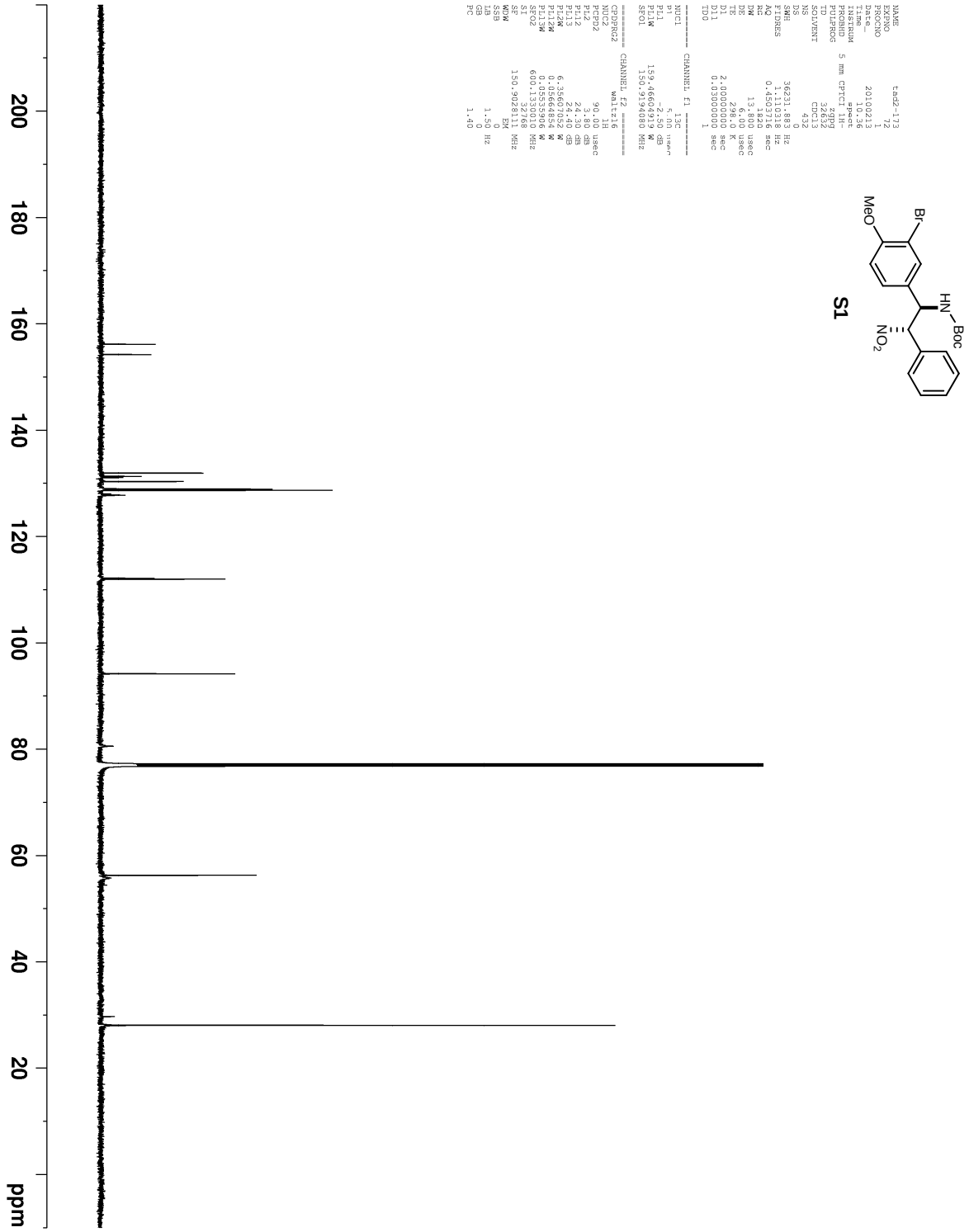
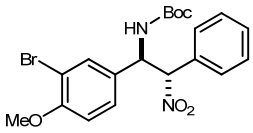


Figure 3. Crystal Structure of **S1**



S1

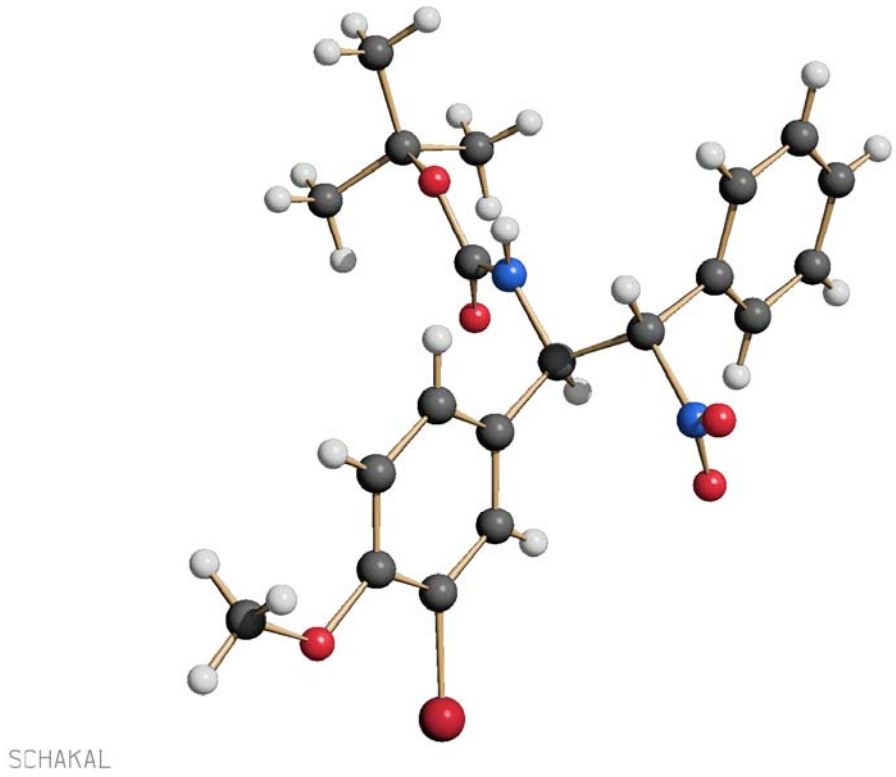


Figure 4. ^{1}H NMR (400 MHz, $CDCl_3$) of **S2**

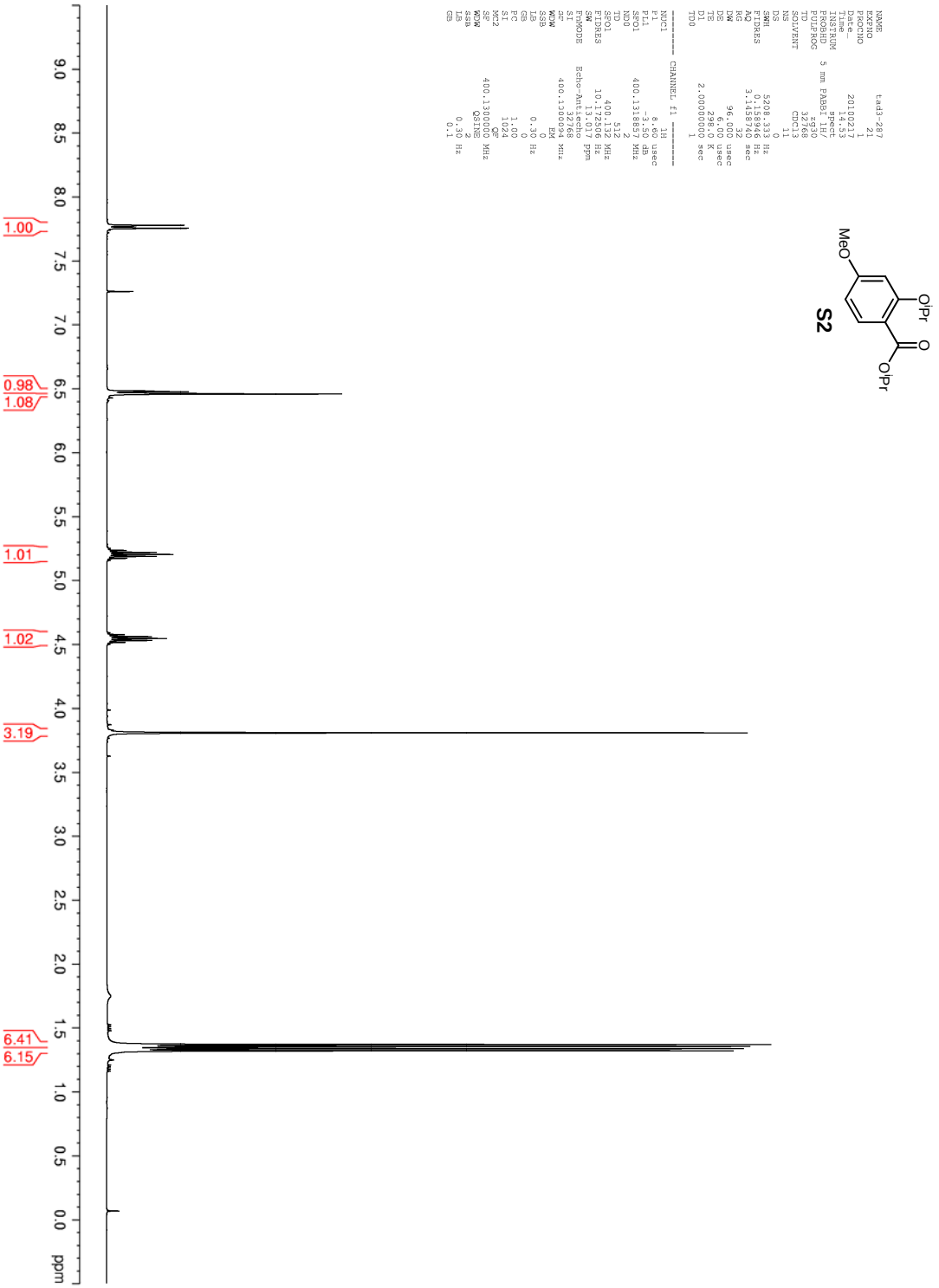


Figure 5. ^{13}C NMR (100 MHz, $CDCl_3$) of S2

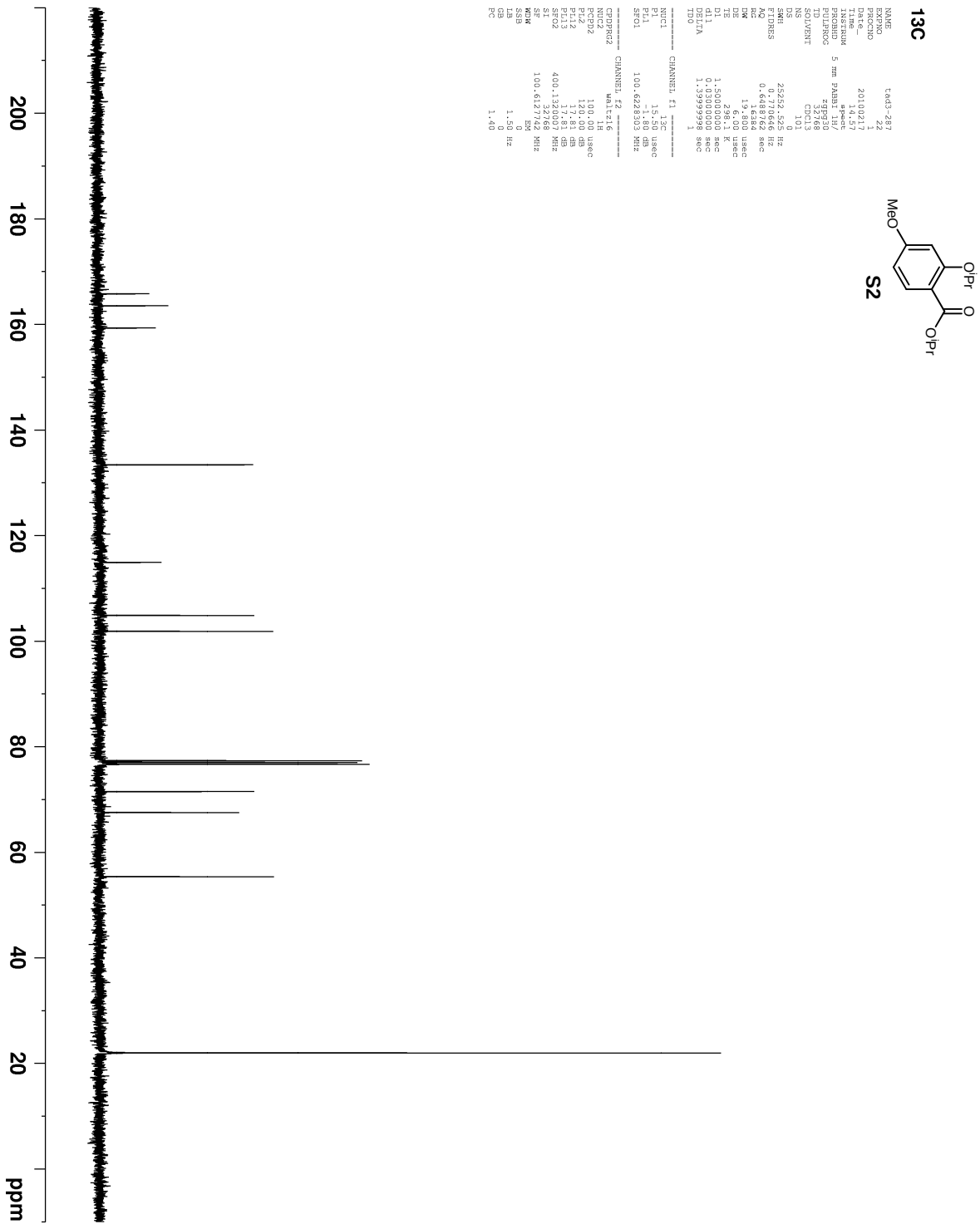


Figure 6. ^{1}H NMR (400 MHz, $CDCl_3$) of **S3**

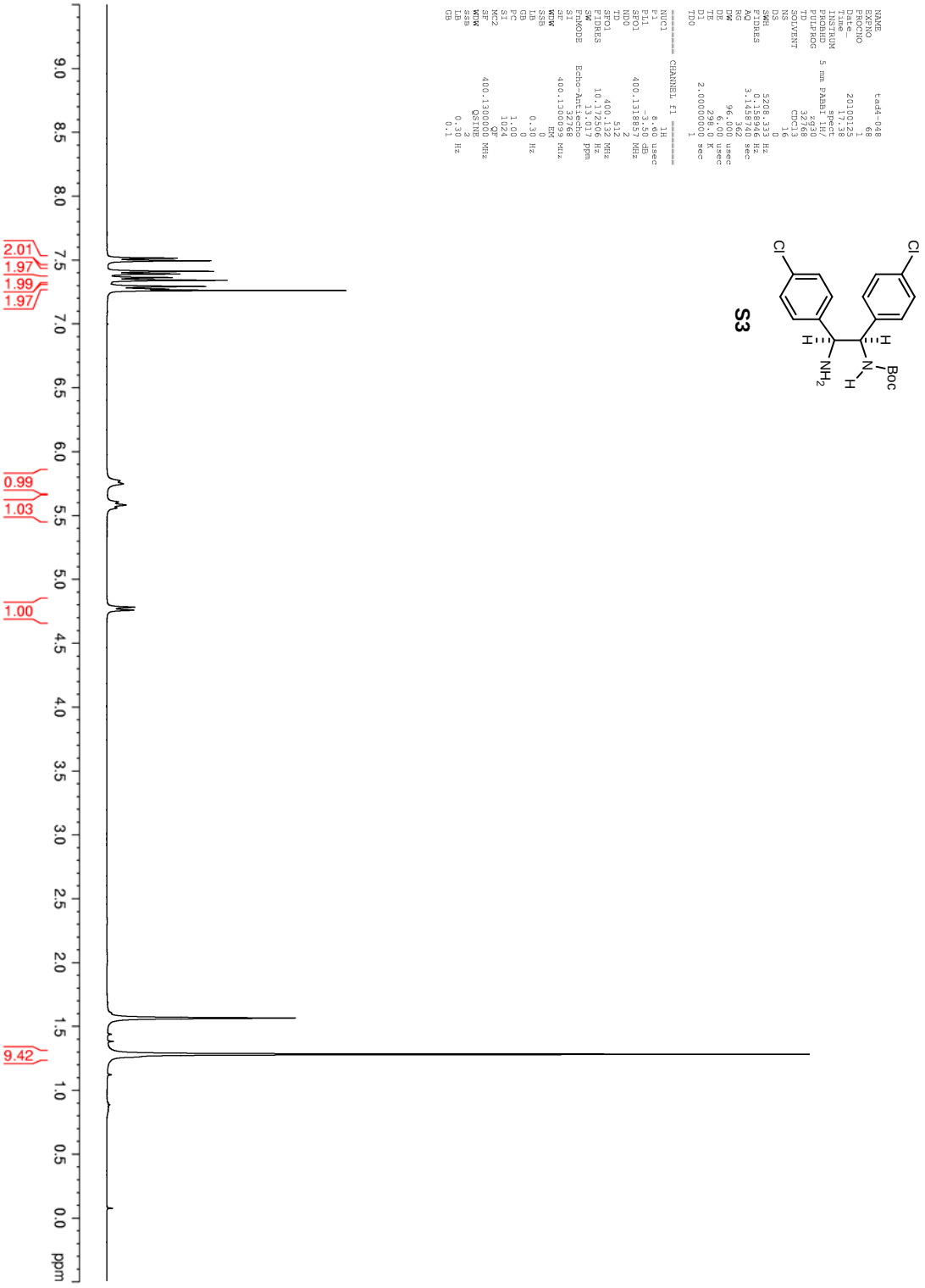


Figure 7. ^{13}C NMR (100 MHz, $CDCl_3$) of **S3**

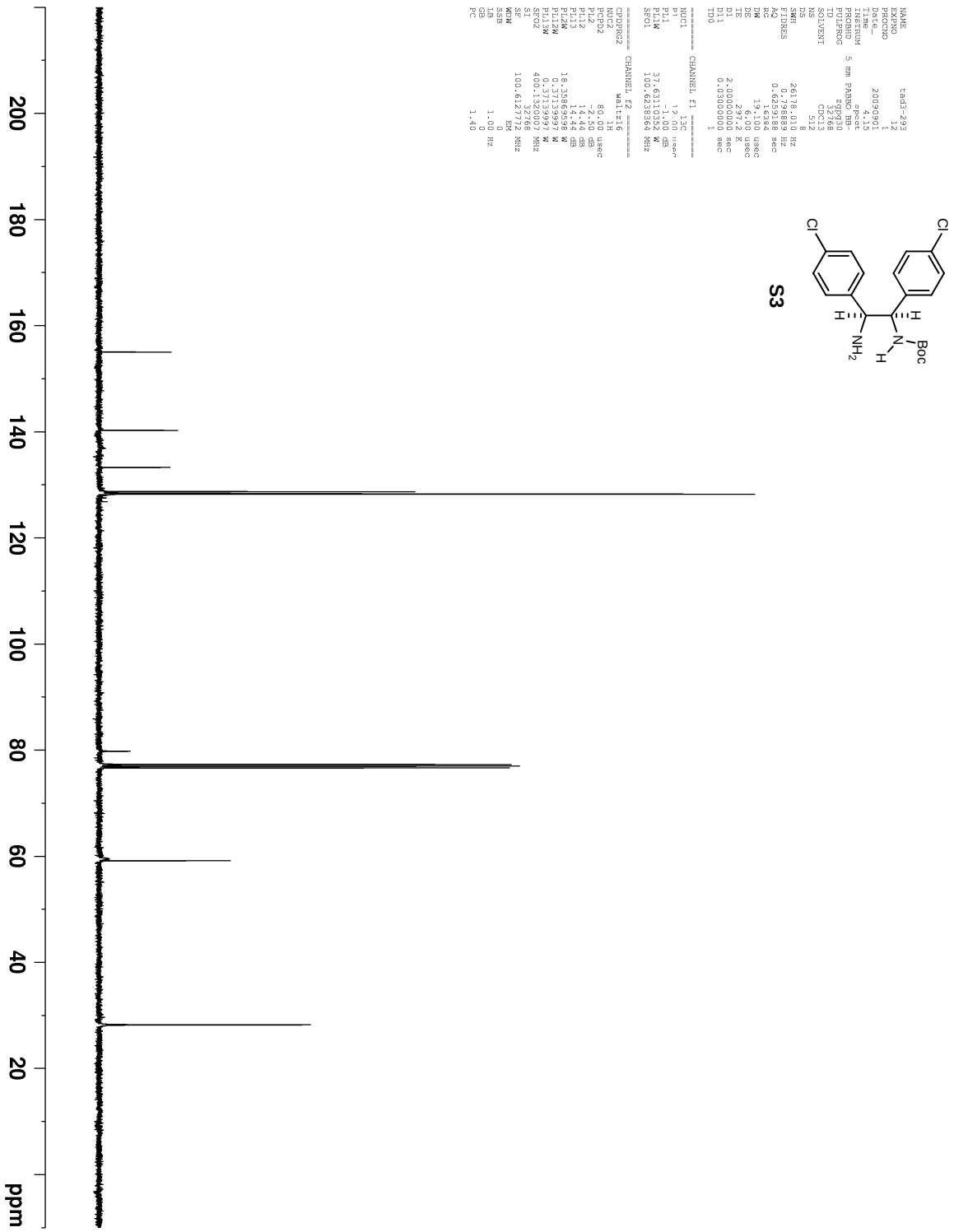


Figure 8. ^{1}H NMR (400 MHz, $CDCl_3$) of **S4**

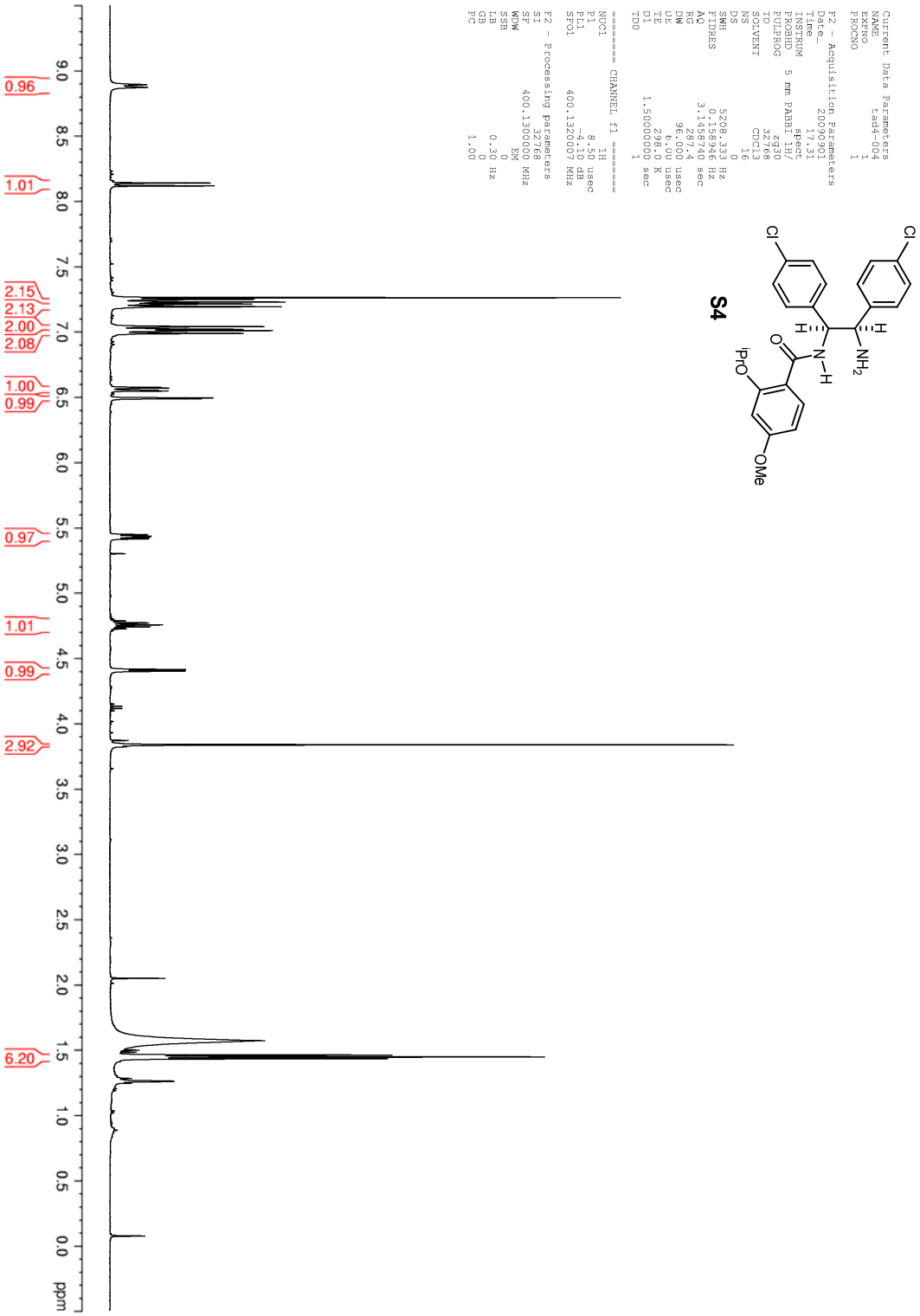


Figure 9. ^{13}C NMR (100 MHz, $CDCl_3$) of **S4**

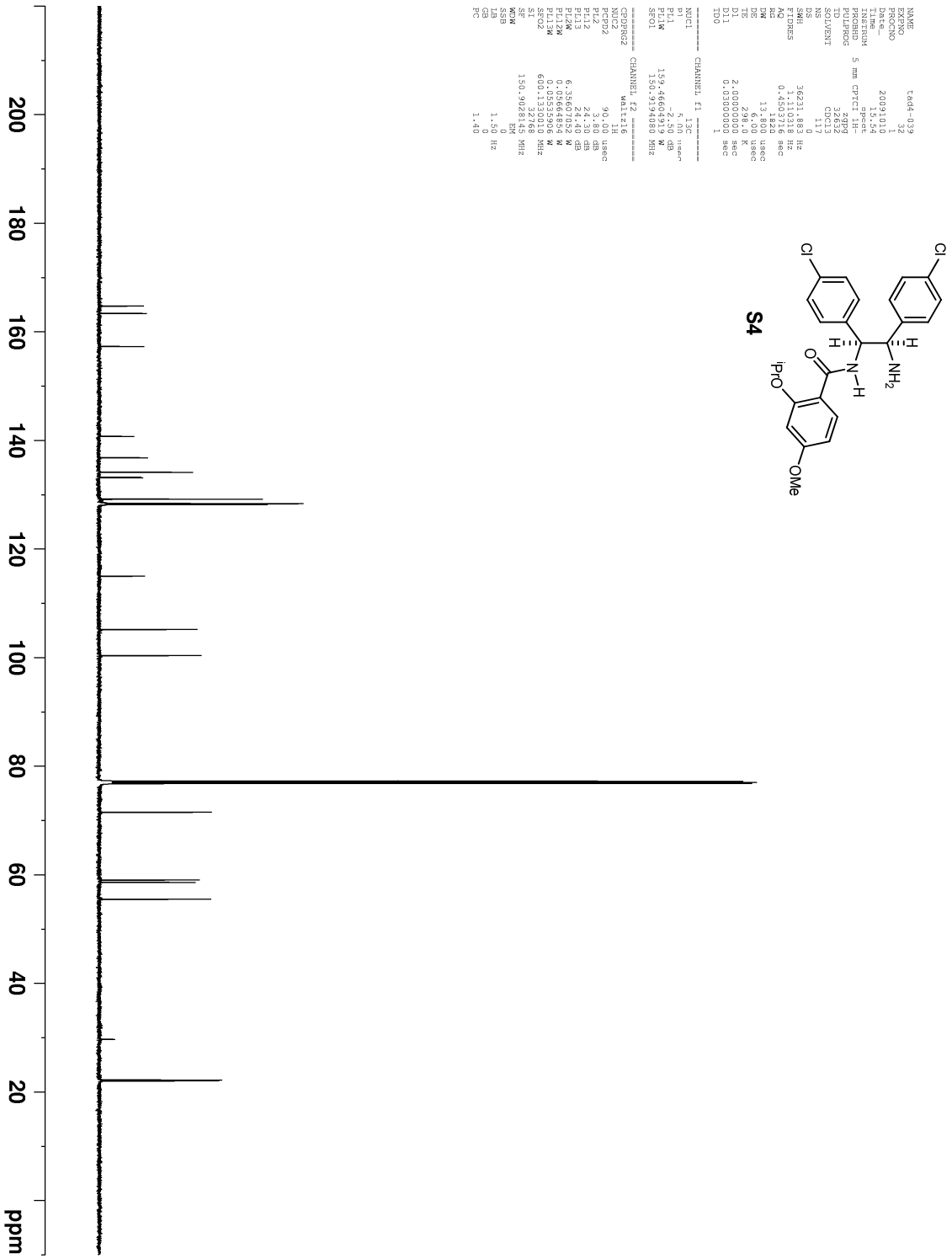


Figure 10. ^{1}H NMR (500 MHz, $CDCl_3$) of **S5**

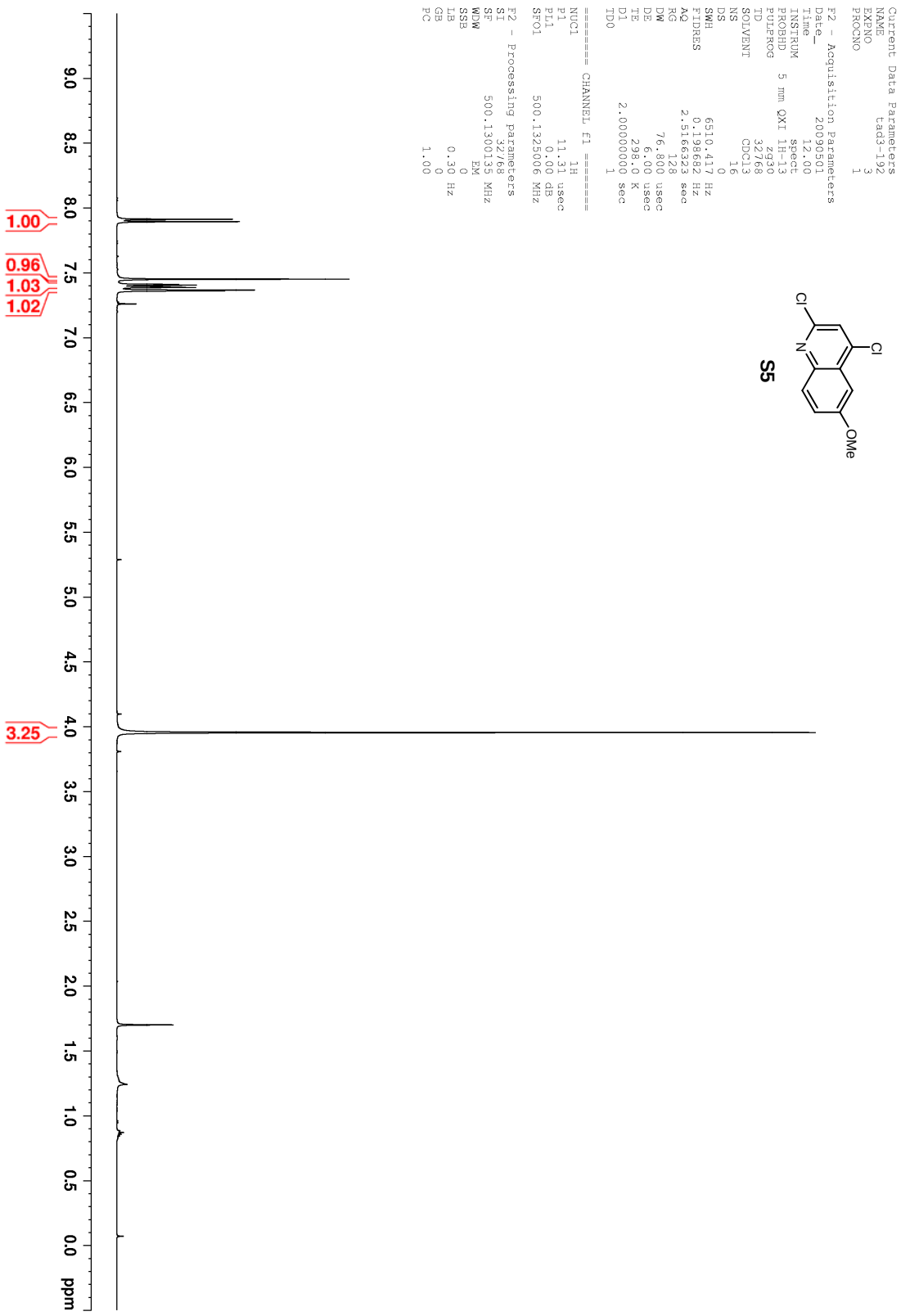


Figure 11. ^{13}C NMR (125 MHz, $CDCl_3$) of **S5**

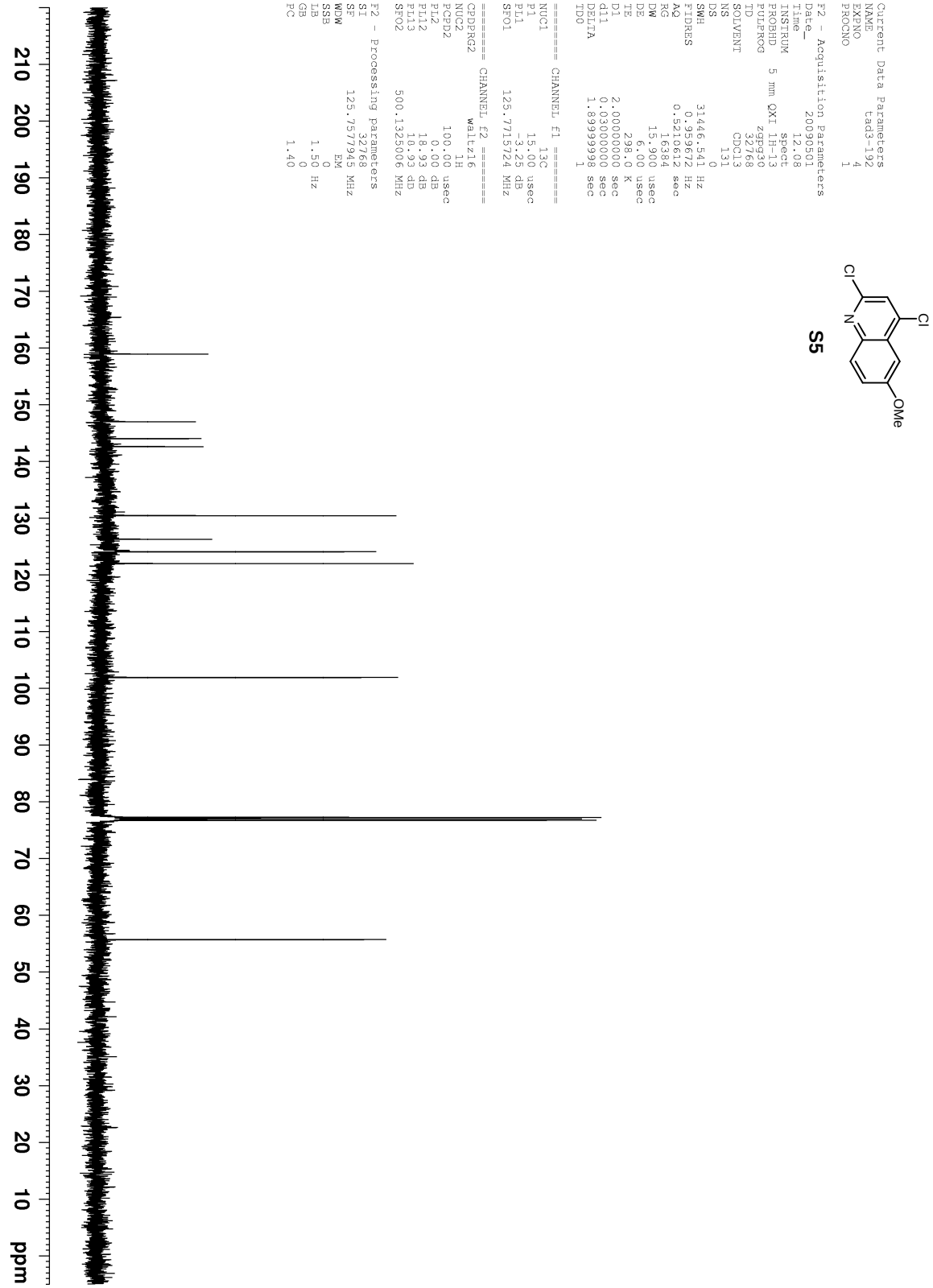


Figure 12. ^{1}H NMR (600 MHz, $CDCl_3$, 325 K) of **S6**

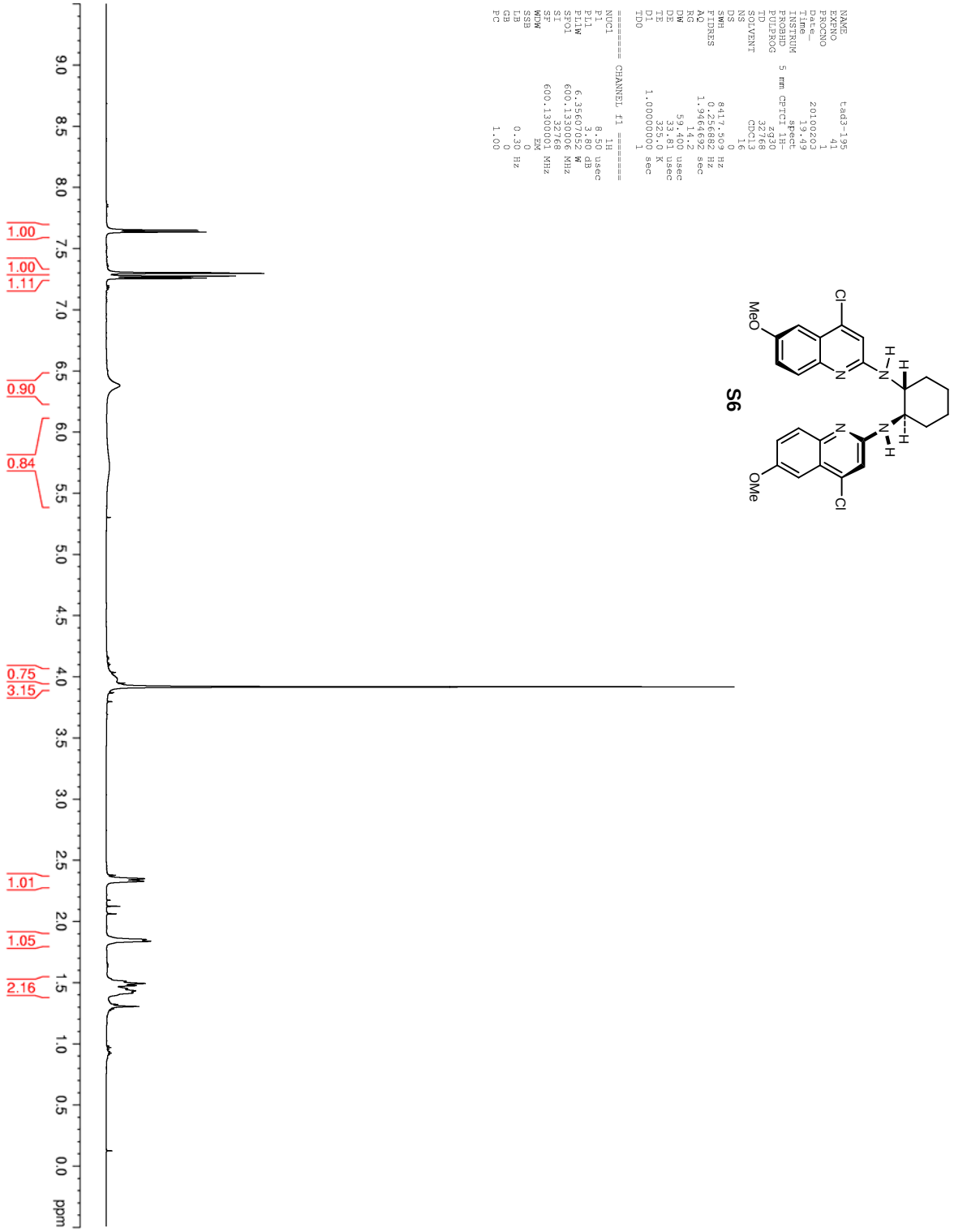


Figure 13. ^{13}C NMR (150 MHz, $CDCl_3$, 325 K) of **S6**

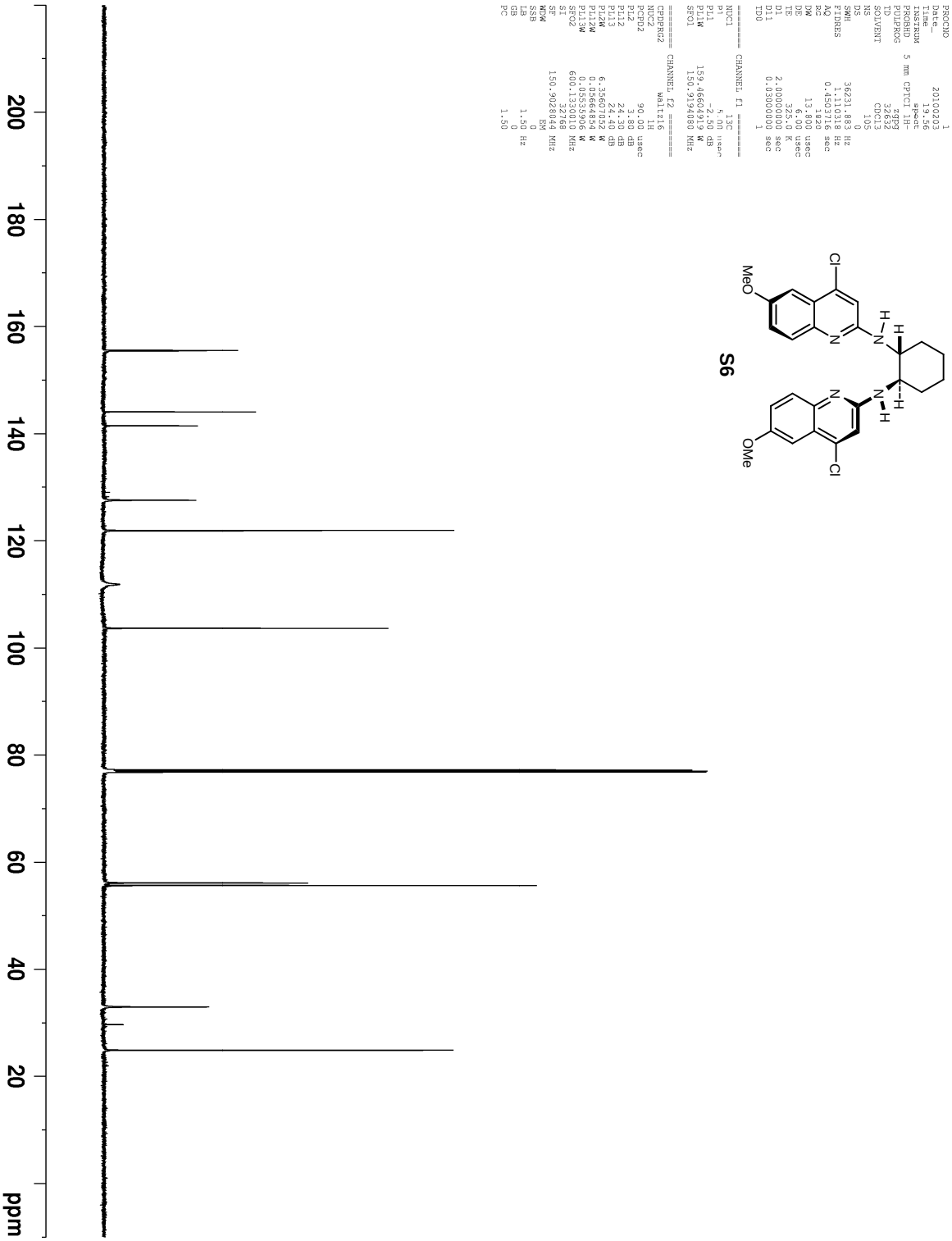


Figure 14. ^{1}H NMR (400 MHz, $CDCl_3$) of **S7**

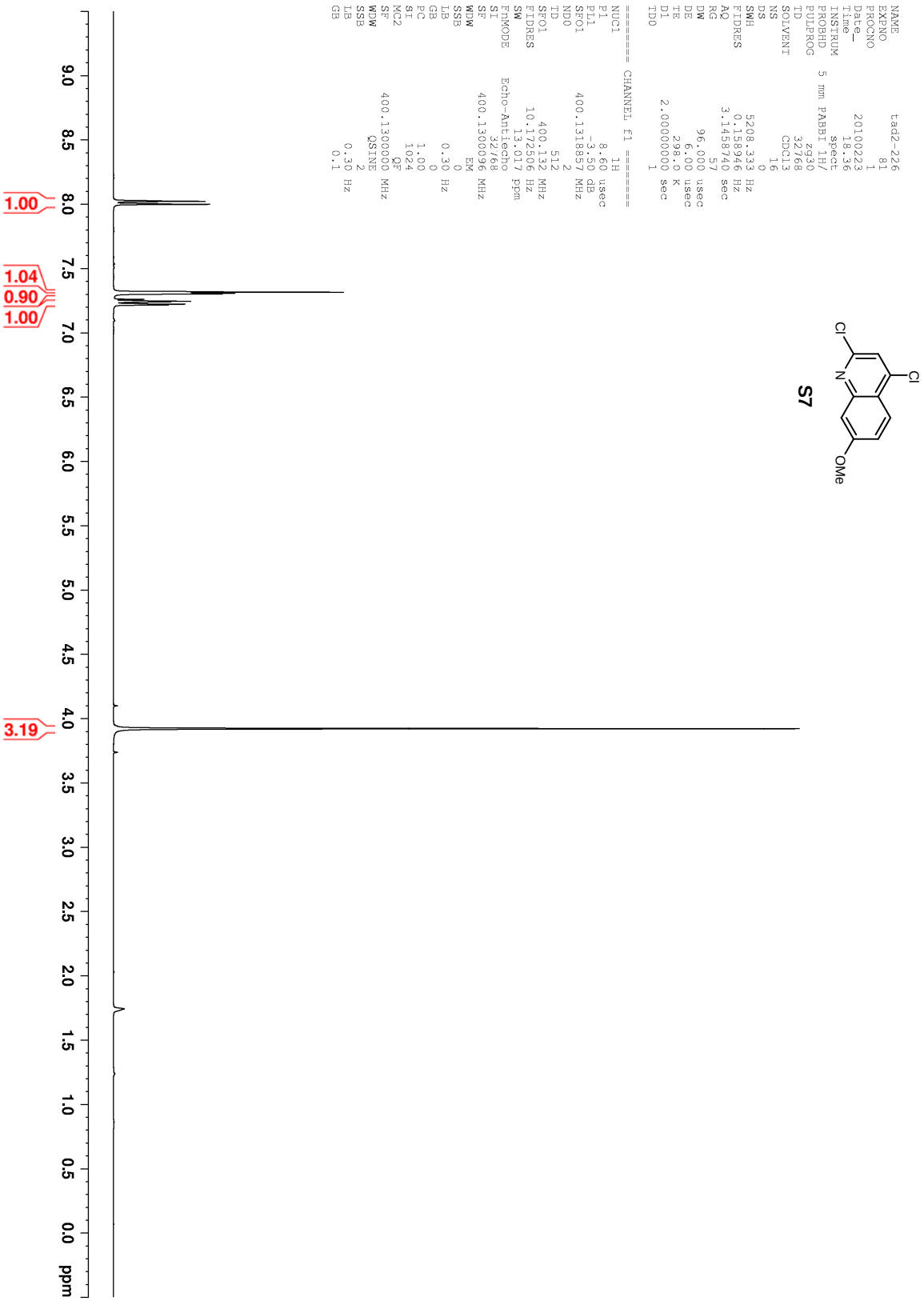


Figure 15. ^{13}C NMR (100 MHz, $CDCl_3$) of **S7**

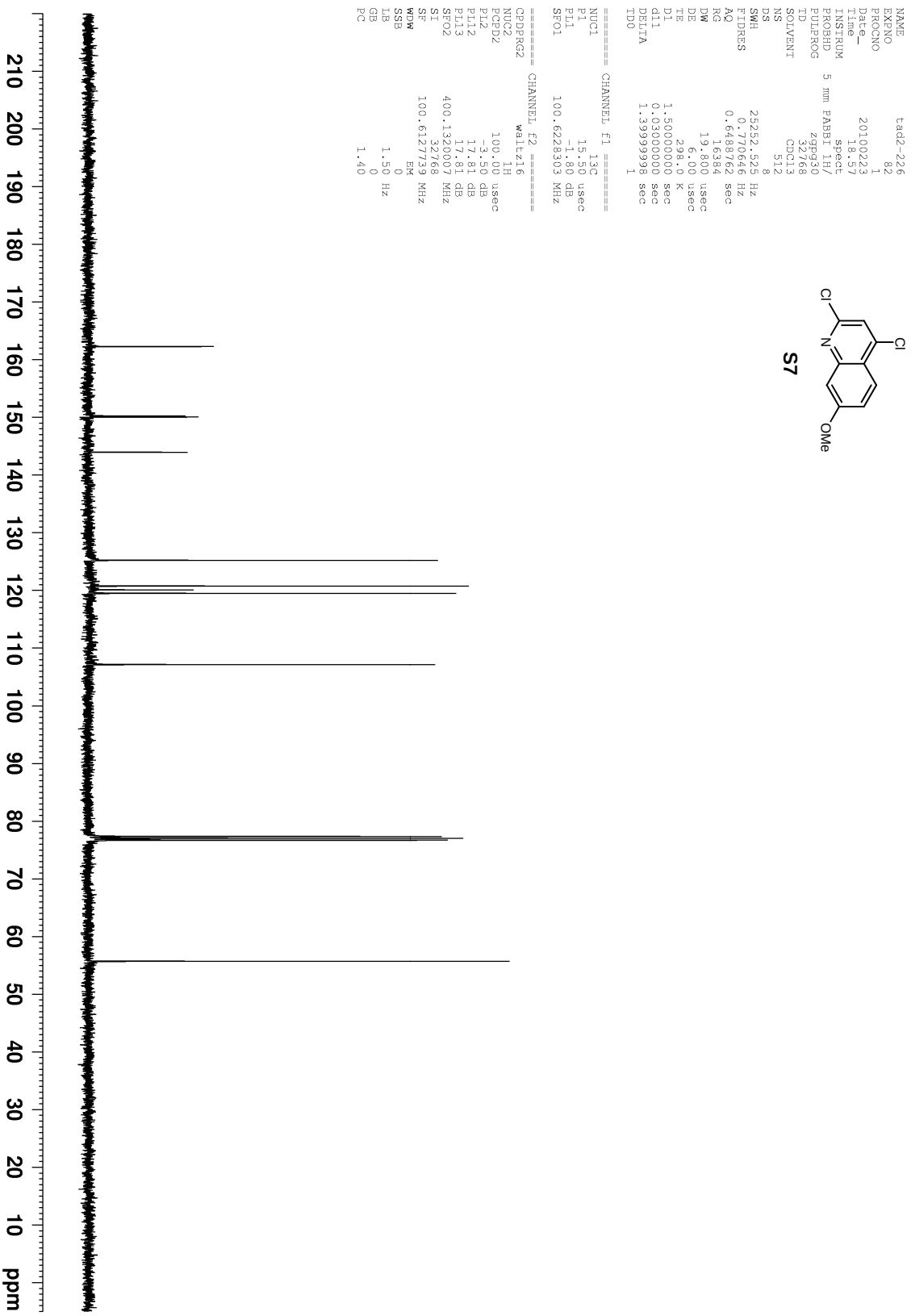


Figure 16. ^{1}H NMR (500 MHz, $CDCl_3$, 325 K) of **S8**

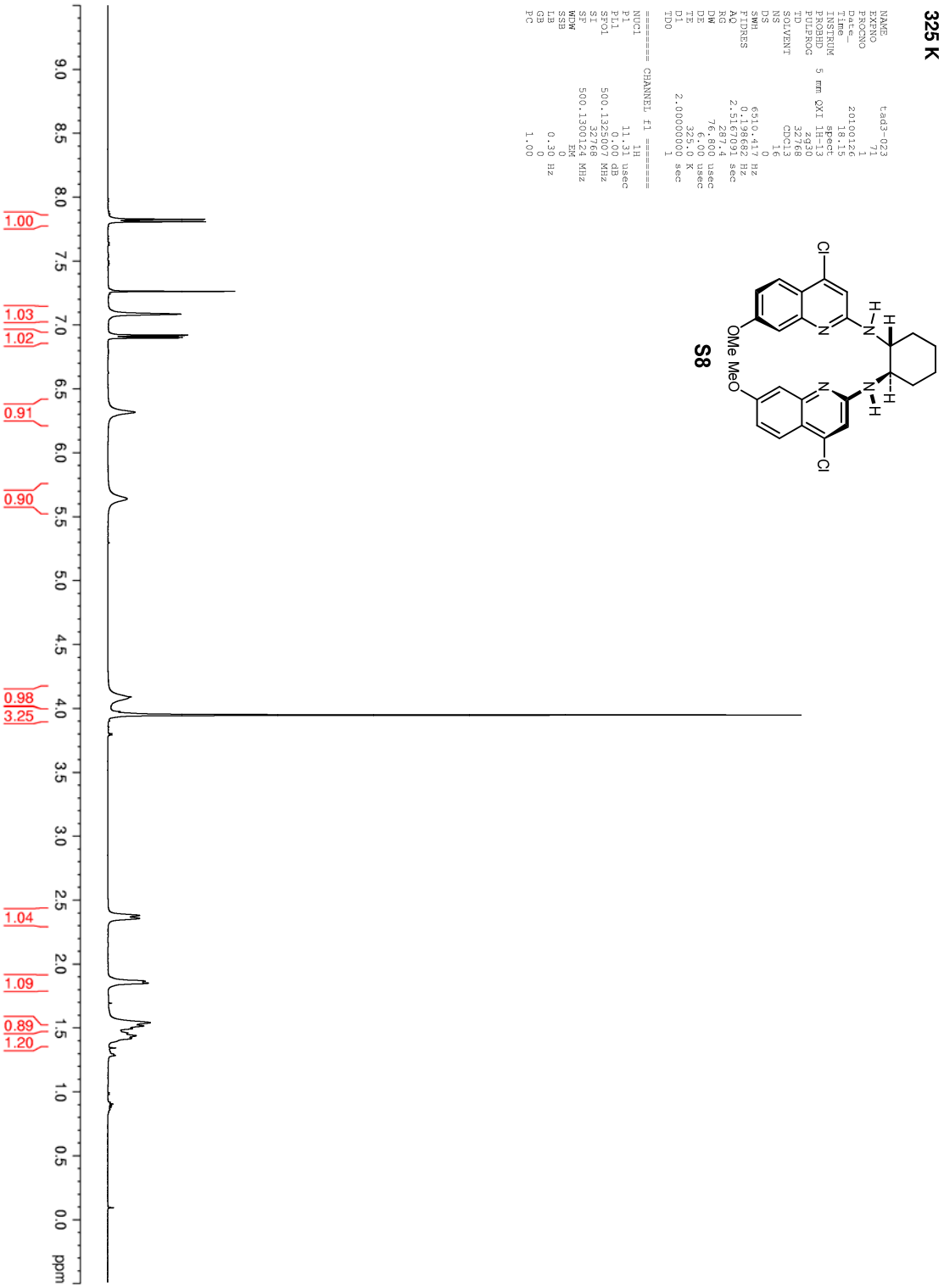


Figure 17. ^{13}C NMR (100 MHz, $CDCl_3$, 325 K) of **S8**

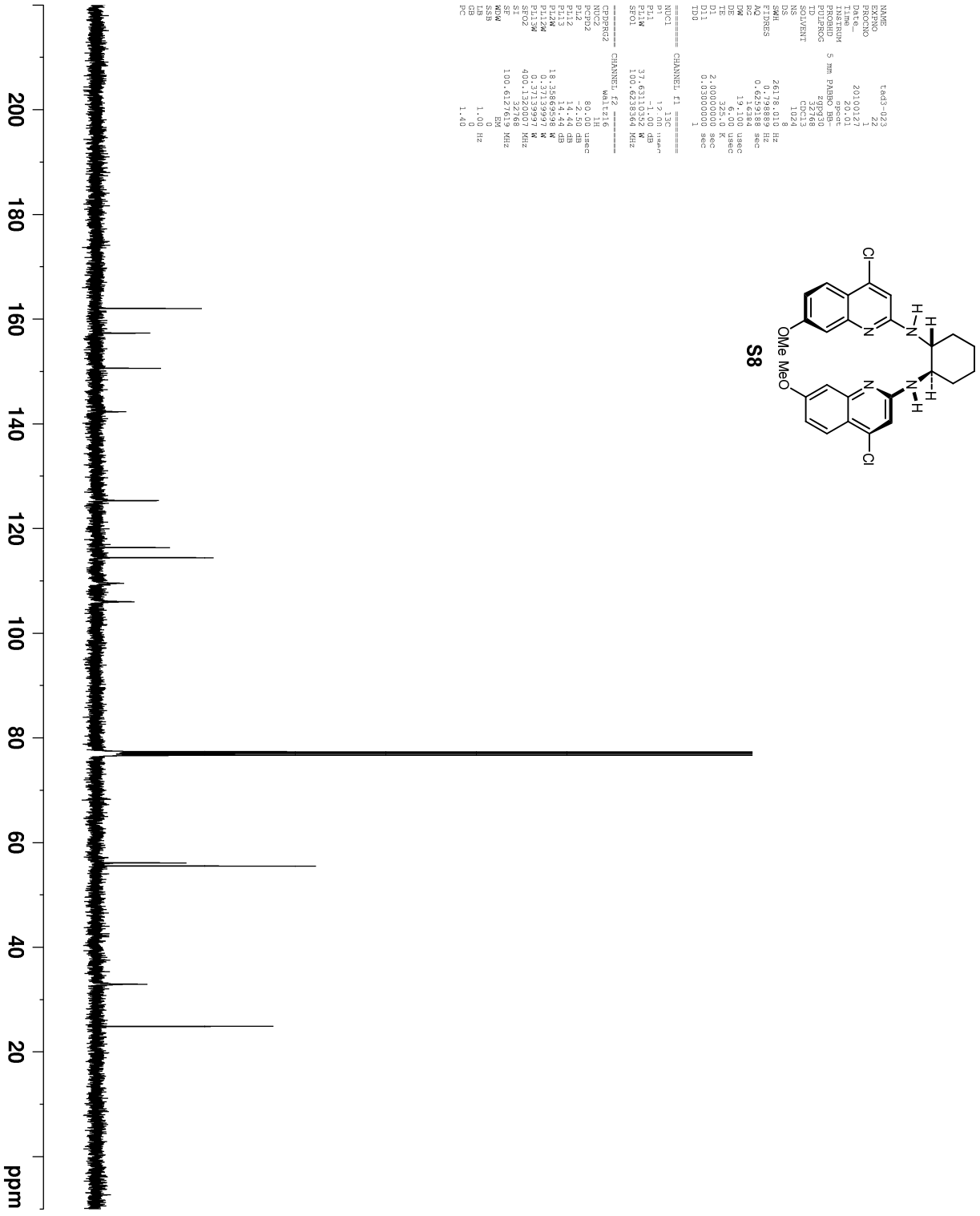


Figure 18. ^{1}H NMR (400 MHz, $CDCl_3$, 330 K) of **S9**

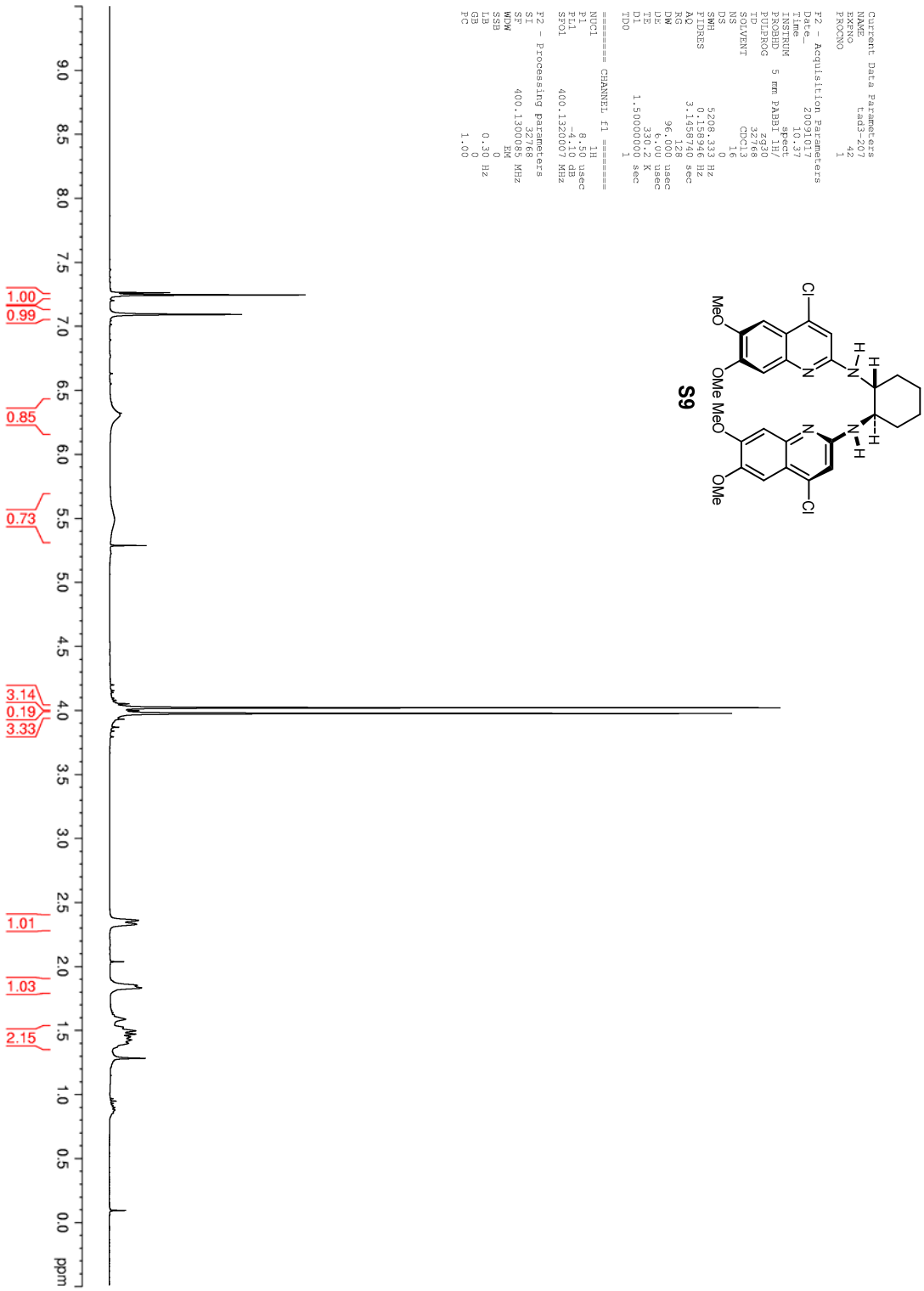


Figure 19. ^{13}C NMR (100 MHz, $CDCl_3$, 330 K) of **S9**

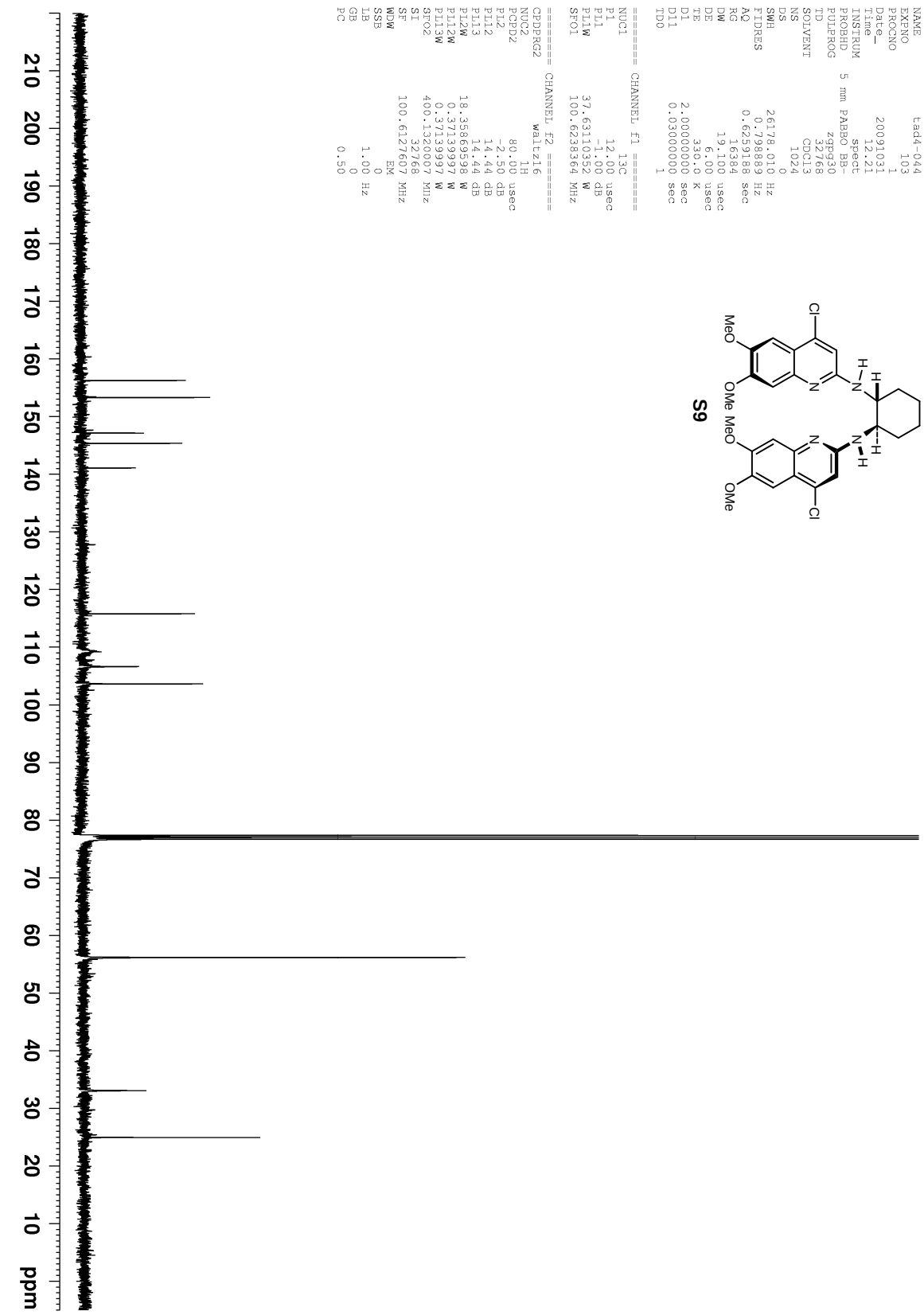


Figure 20. ^{1}H NMR (400 MHz, $CDCl_3$) of **S10**

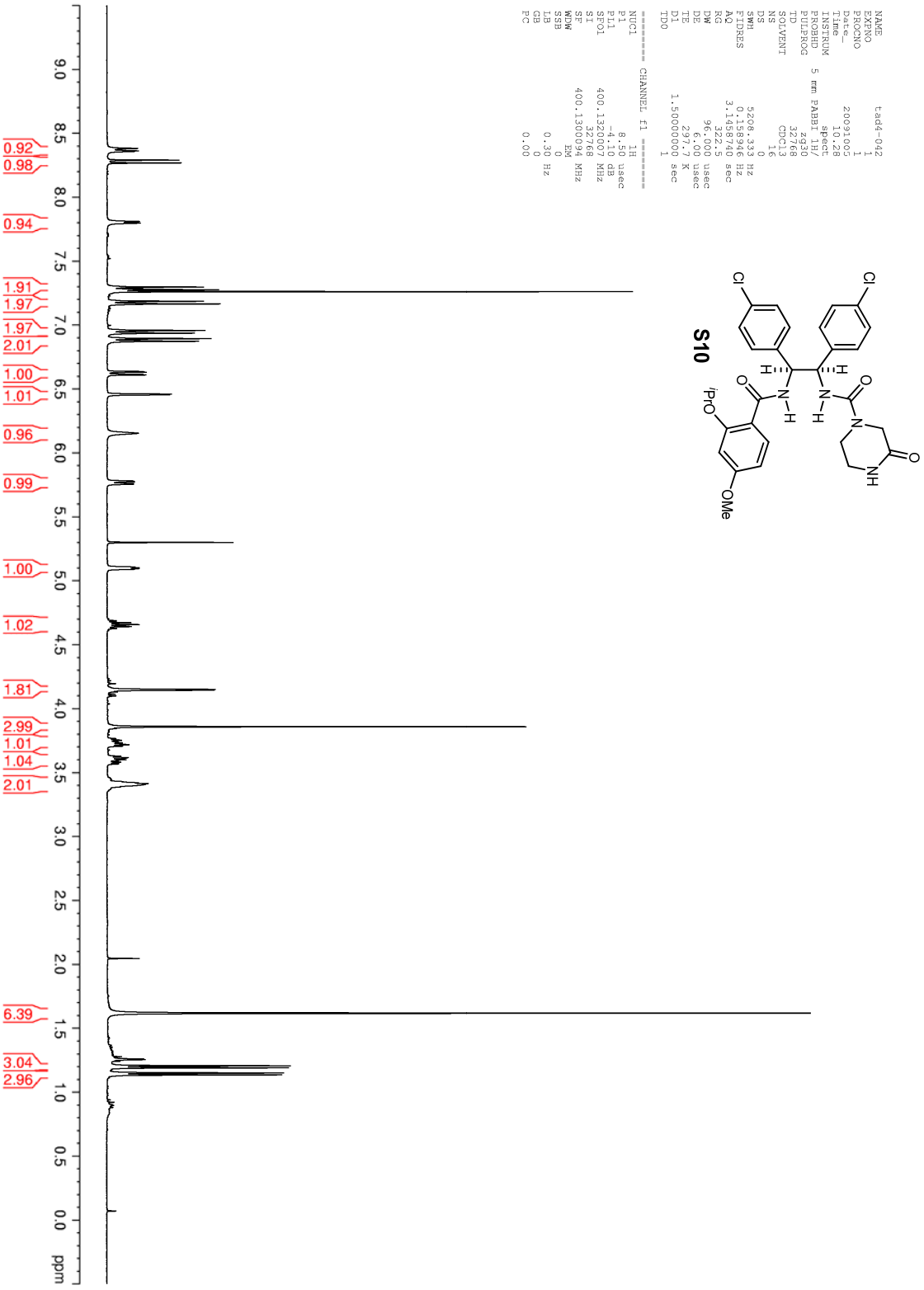


Figure 21. ^{13}C NMR (100 MHz, $CDCl_3$) of **S10**

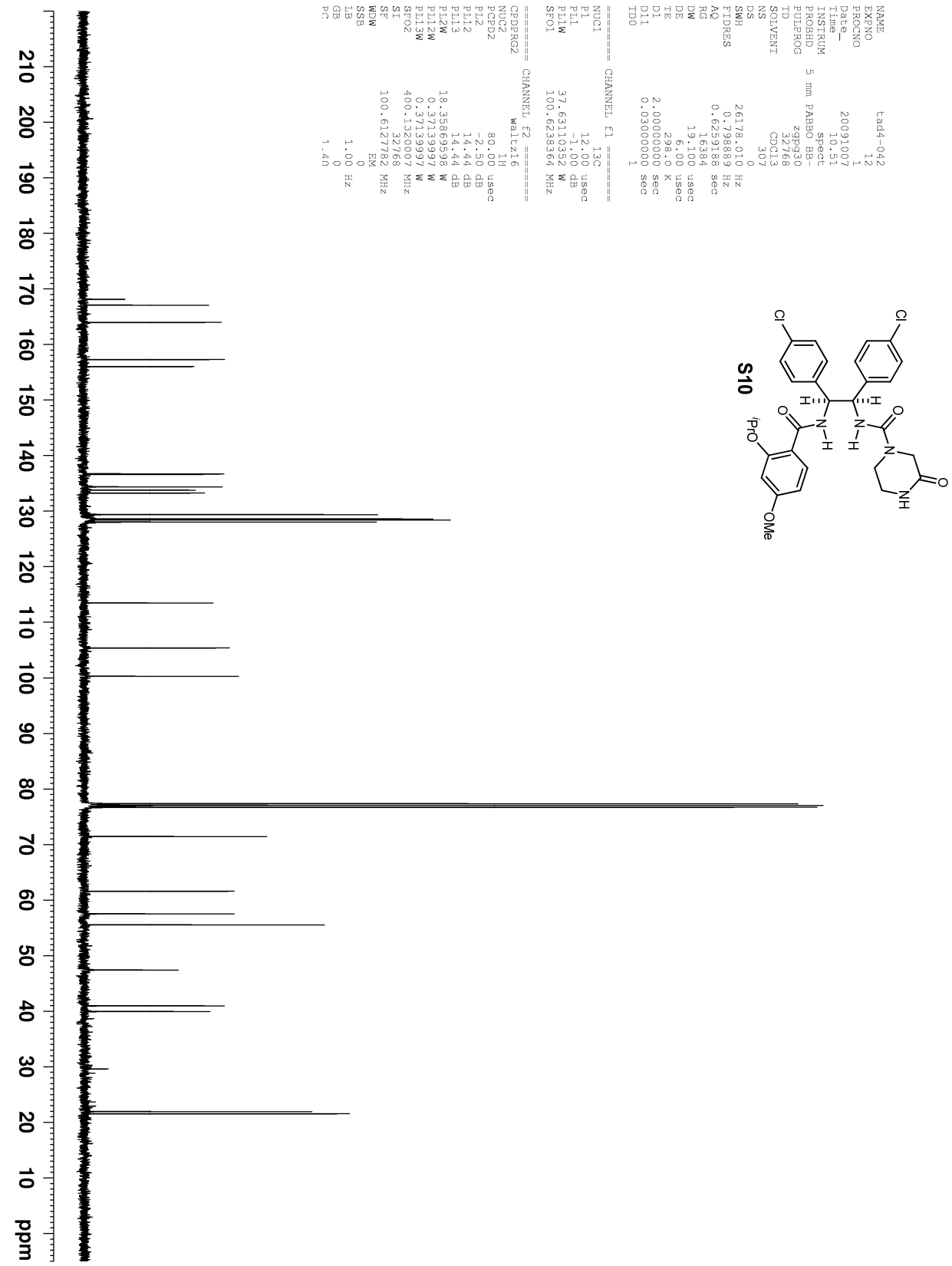


Figure 22. ^{1}H NMR (400 MHz, $CDCl_3$) of **1a**

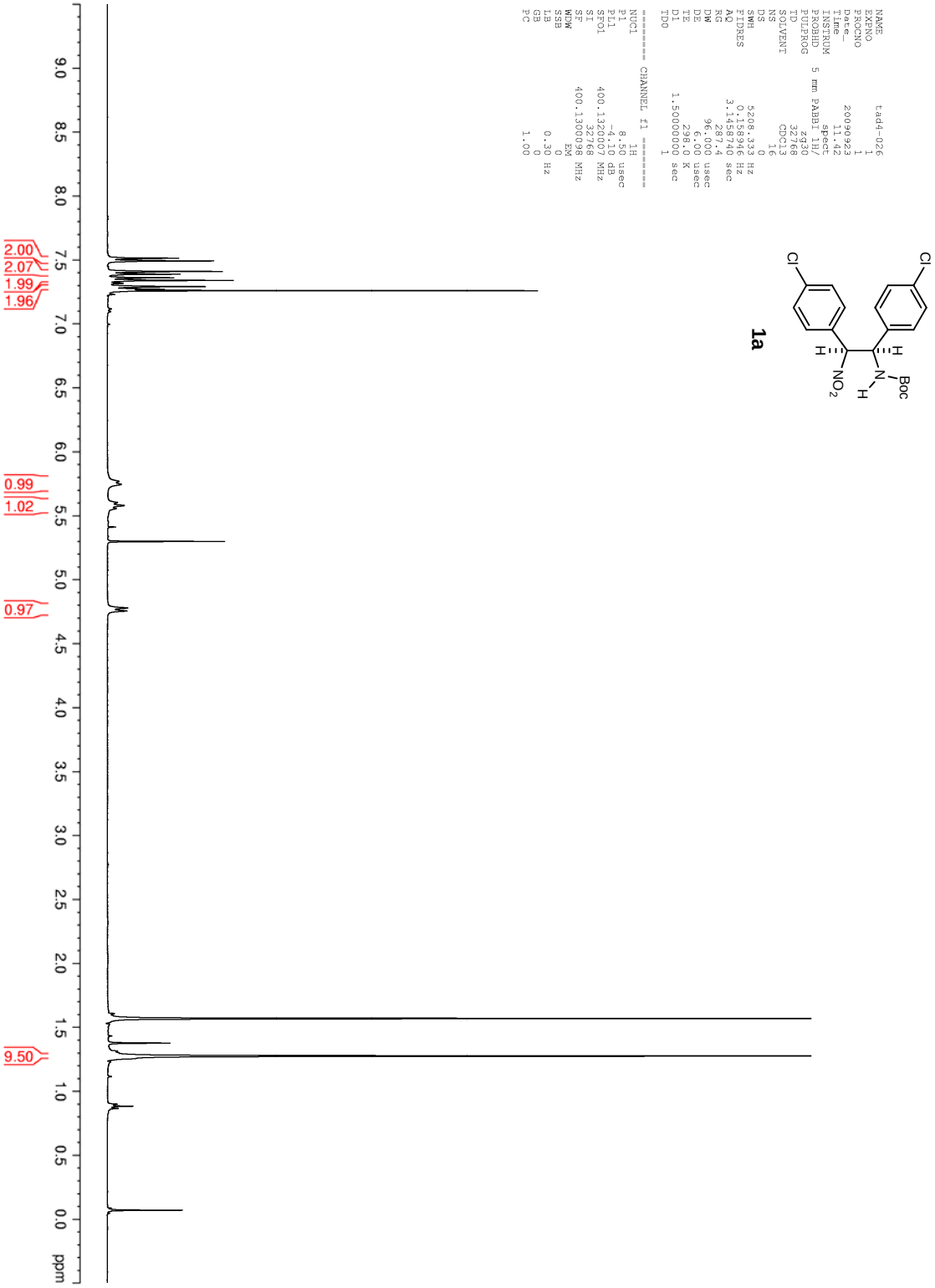


Figure 23. ^{13}C NMR (150 MHz, $CDCl_3$) of **1a**

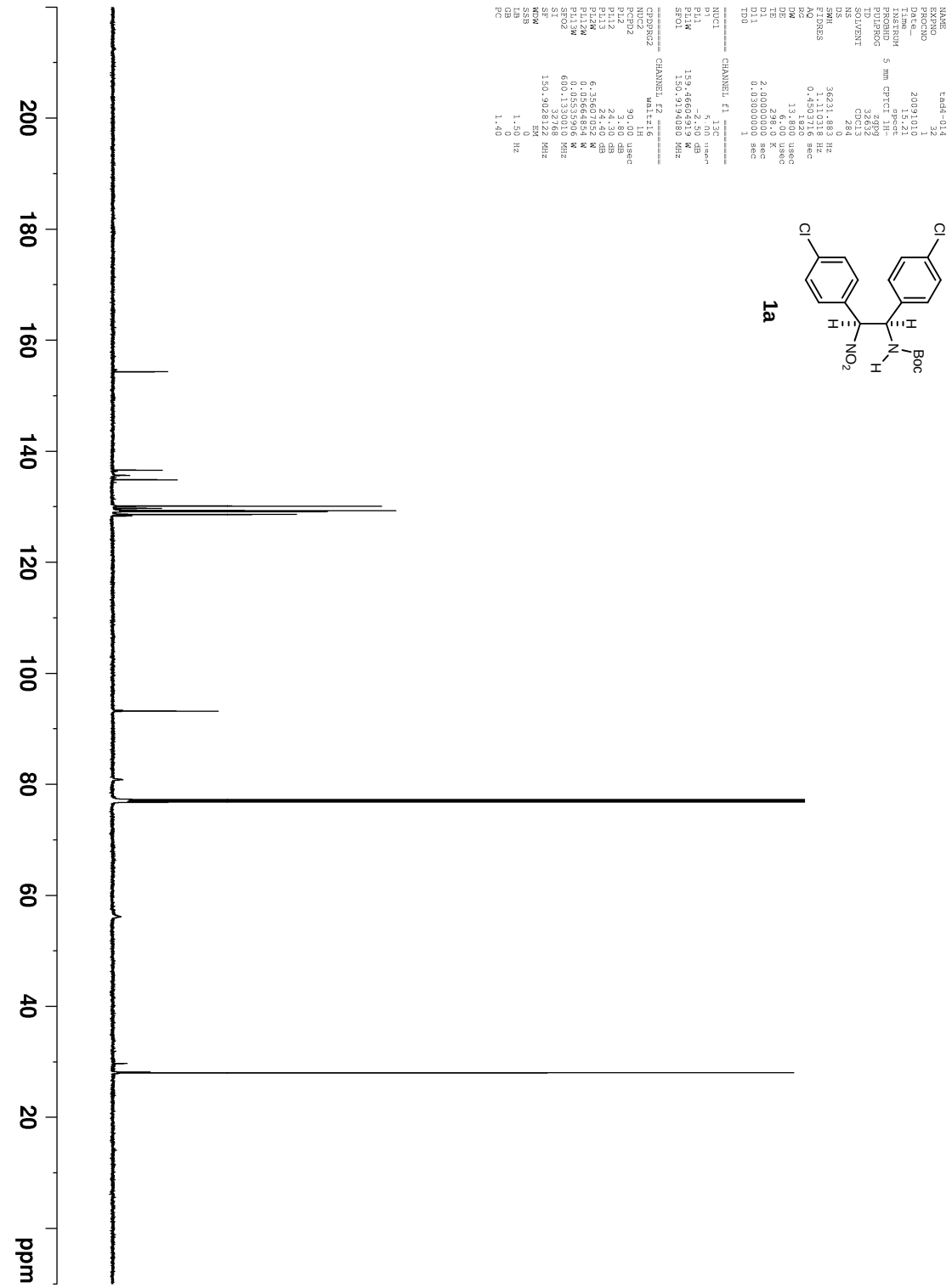


Figure 24. ^{1}H NMR (600 MHz, $CDCl_3$) of **1b**

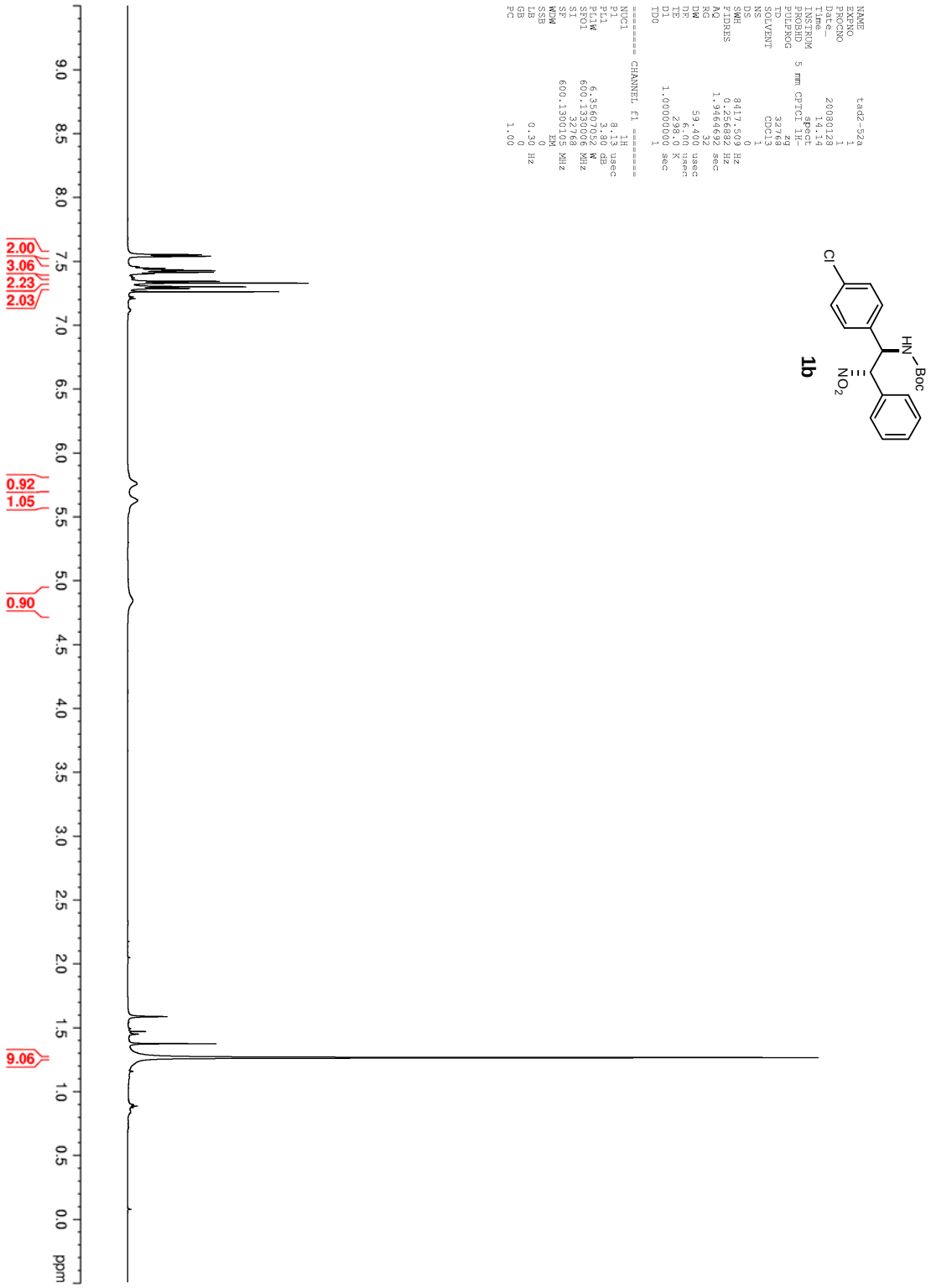


Figure 25. ^{13}C NMR (150 MHz, $CDCl_3$) of **1b**

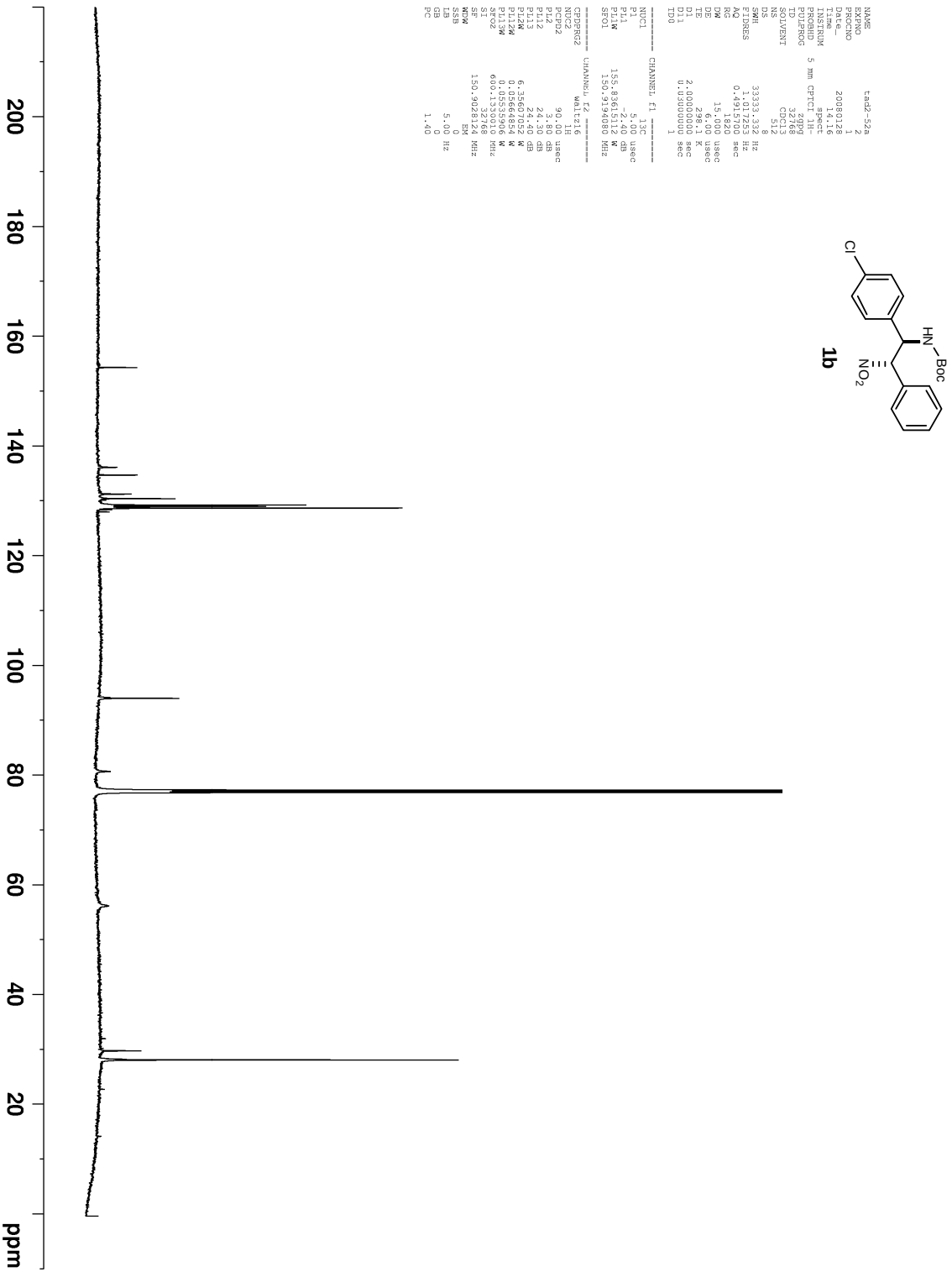


Figure 26. ^{1}H NMR (600 MHz, $CDCl_3$) of **1c**

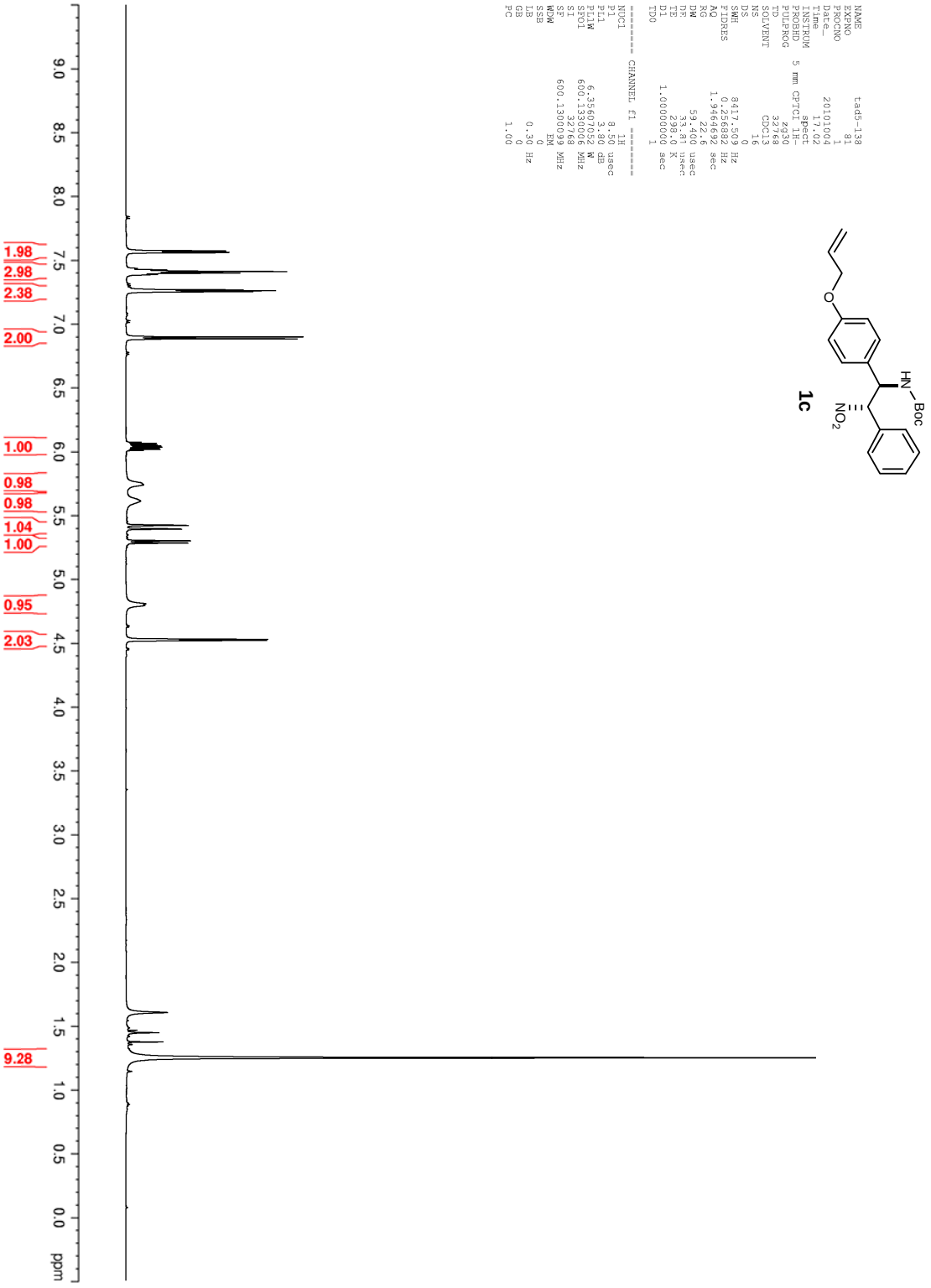


Figure 27. ^{13}C NMR (150 MHz, $CDCl_3$) of **1c**

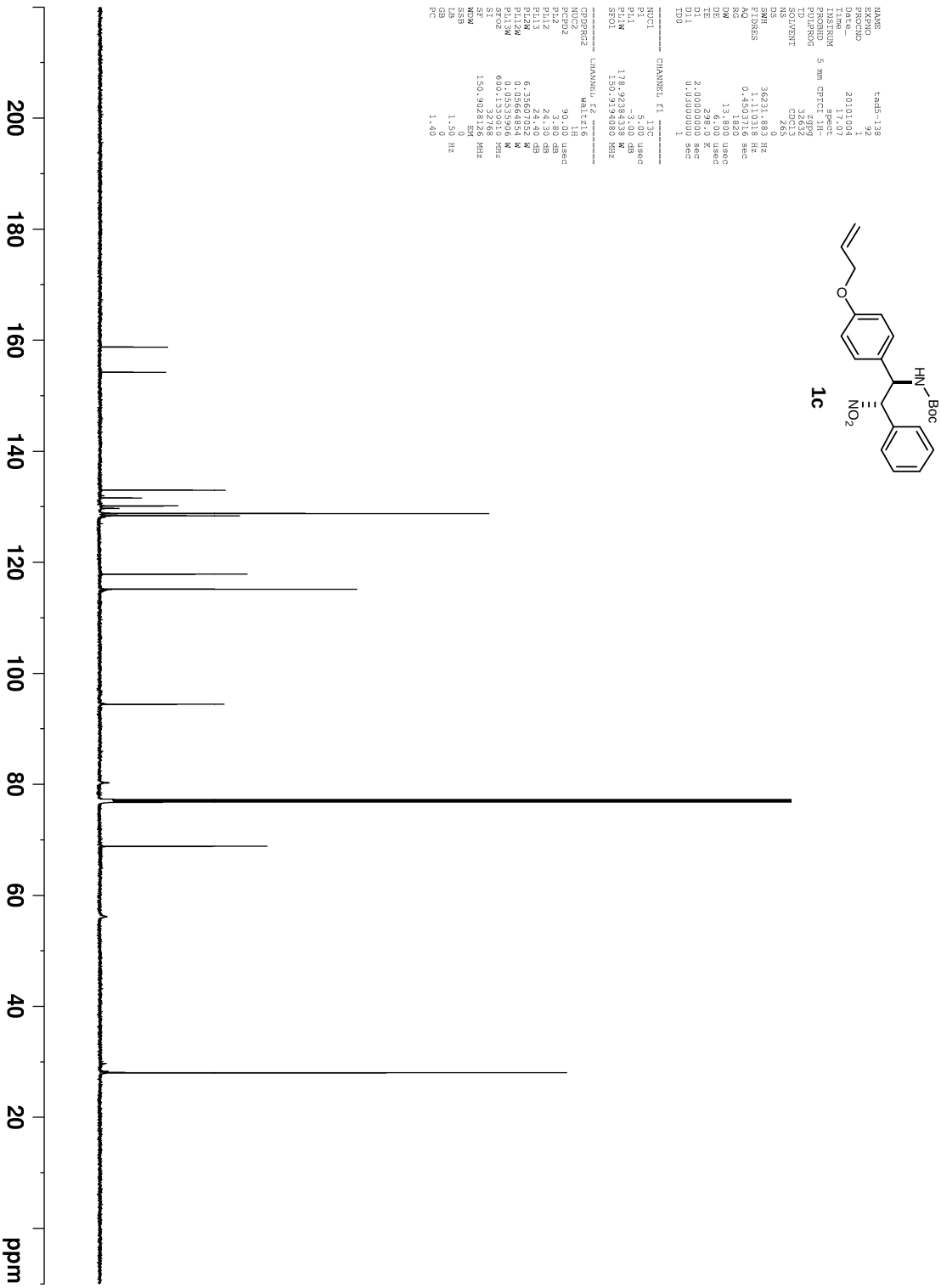


Figure 28. ^{1}H NMR (400 MHz, $CDCl_3$) of **1d**

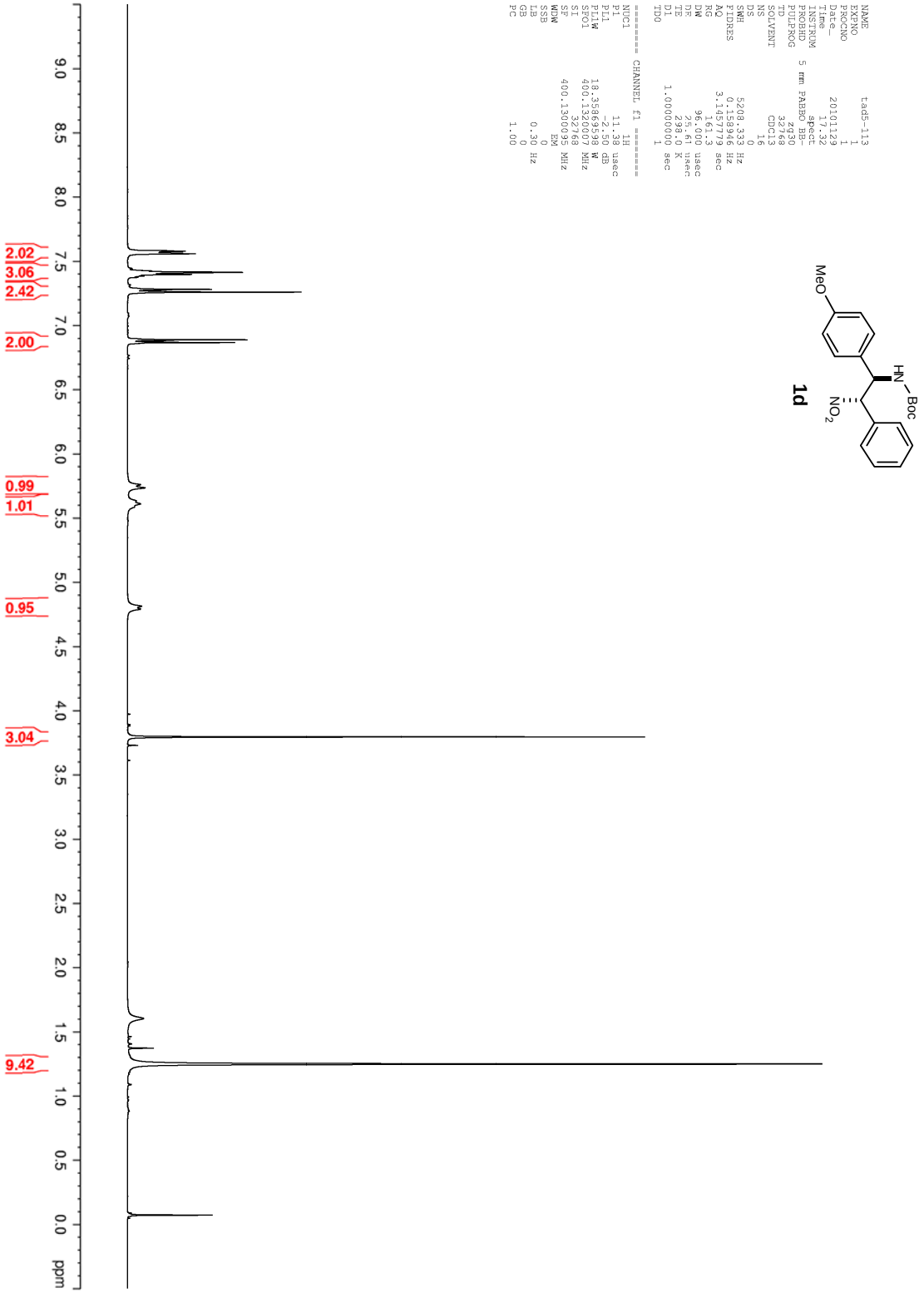


Figure 29. ^{13}C NMR (100 MHz, $CDCl_3$) of **1d**

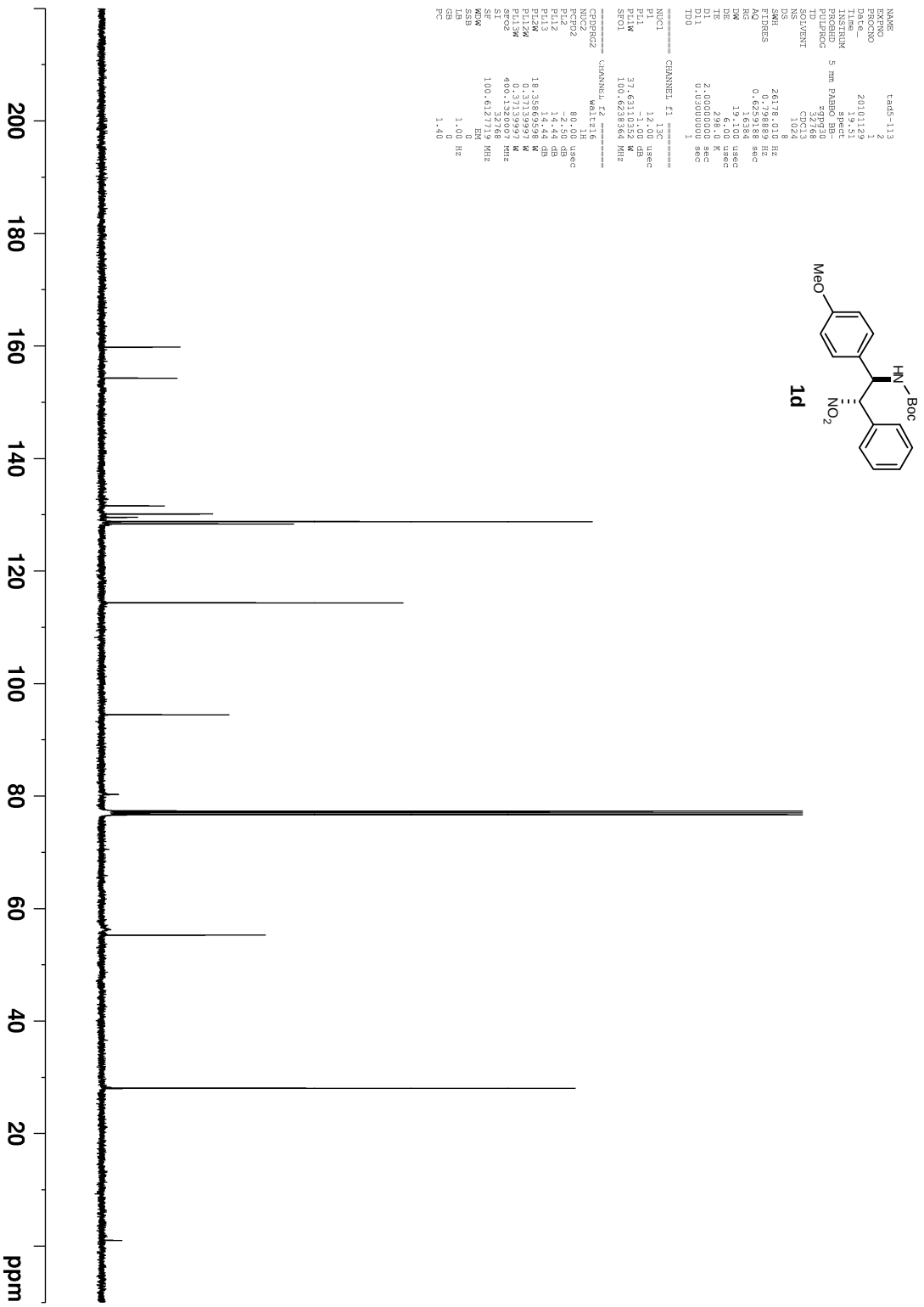


Figure 30. ^{1}H NMR (600 MHz, $CDCl_3$) of **1e**

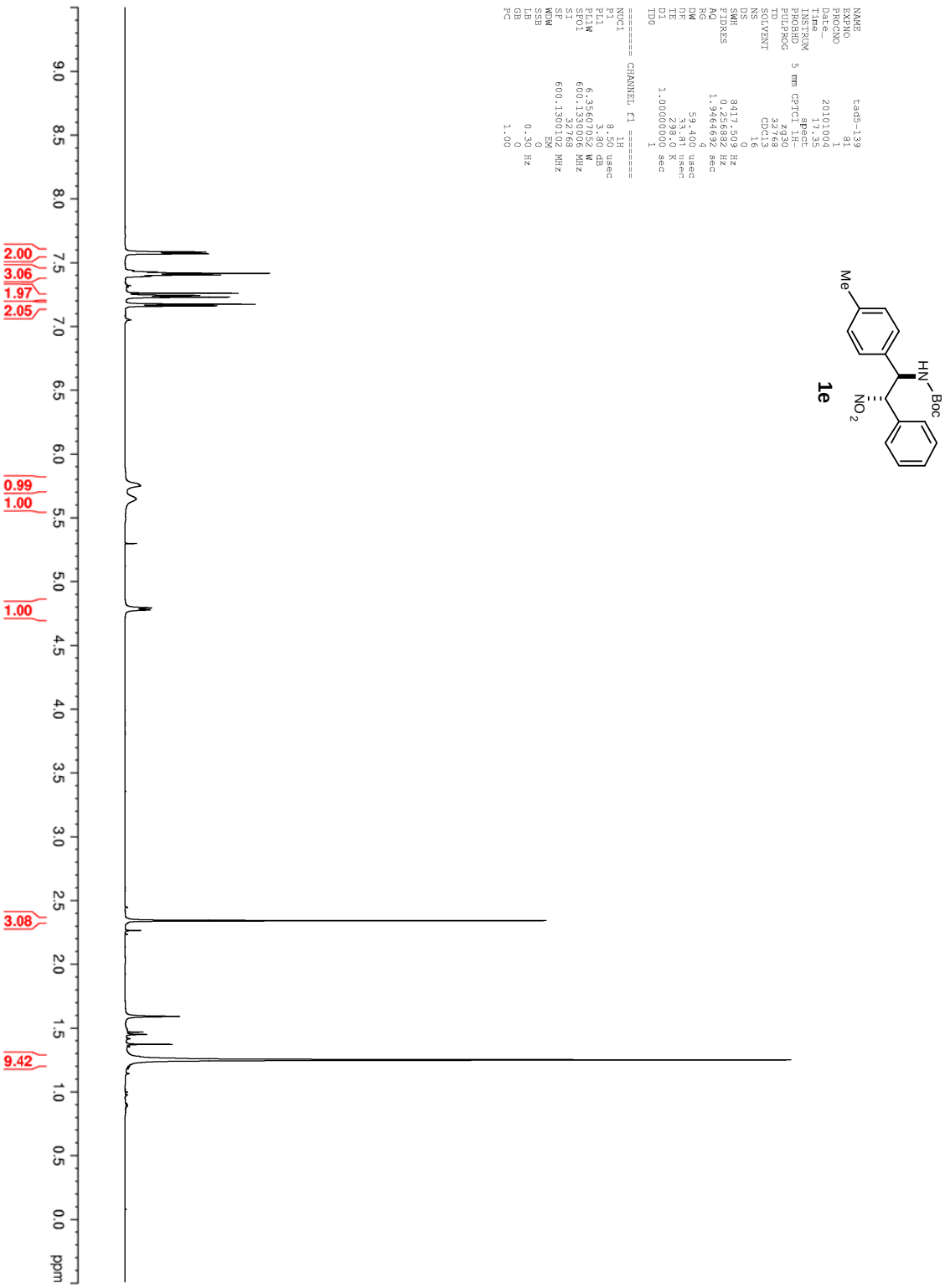


Figure 31. ^{13}C NMR (150 MHz, $CDCl_3$) of **1e**

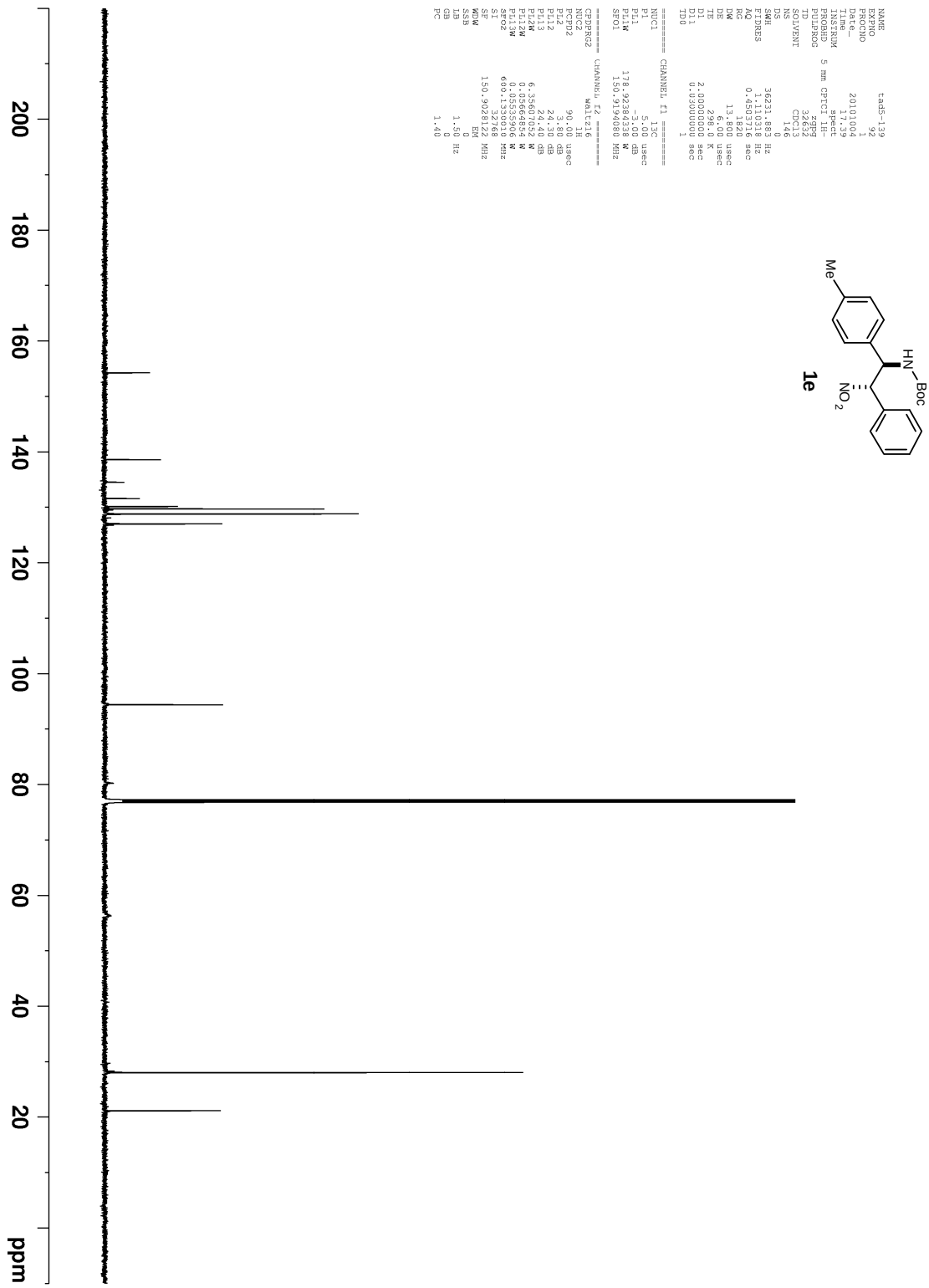


Figure 32. ^{1}H NMR (600 MHz, $CDCl_3$) of **1f**

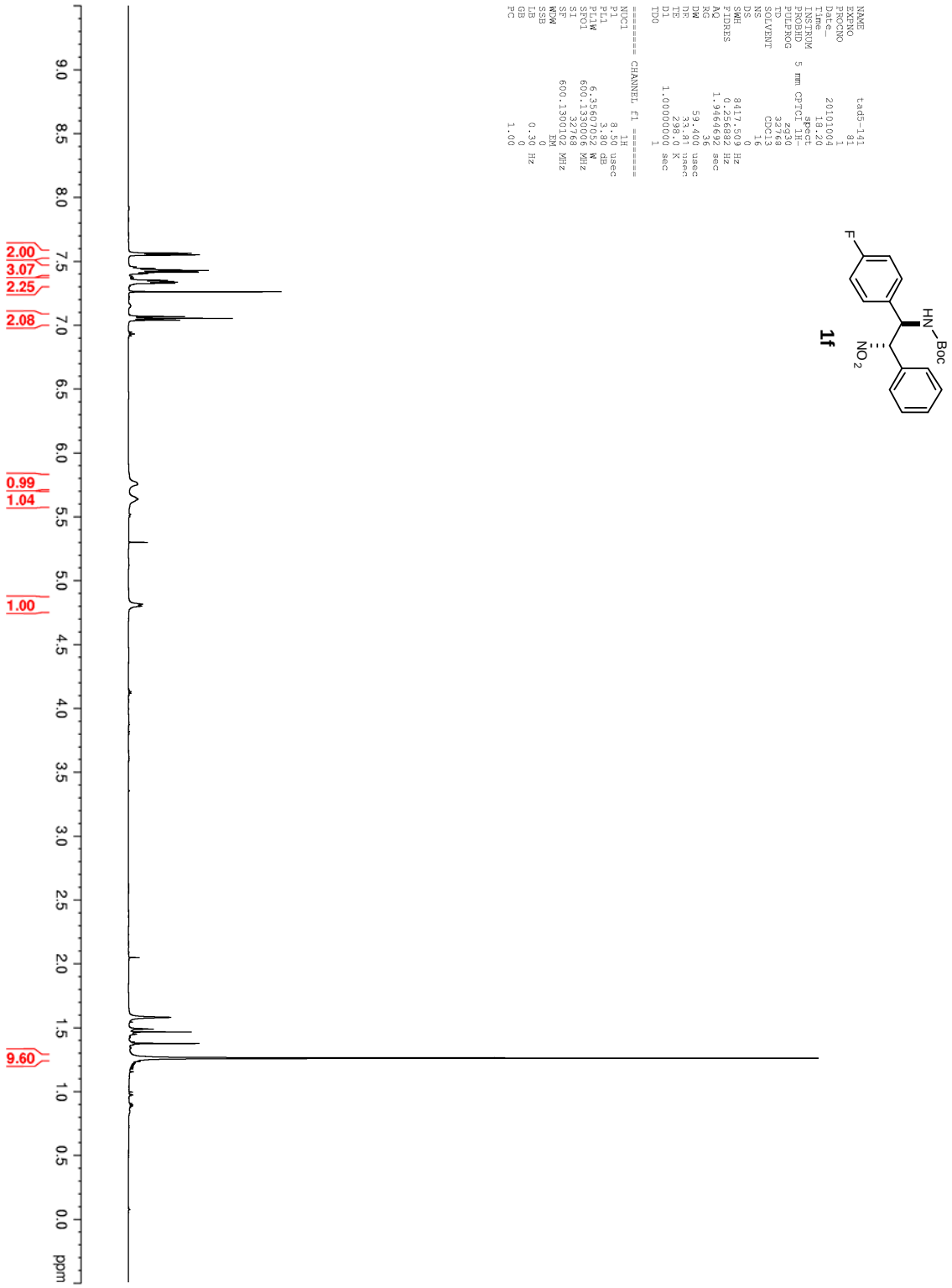


Figure 33. ^{13}C NMR (150 MHz, $CDCl_3$) of **1f**

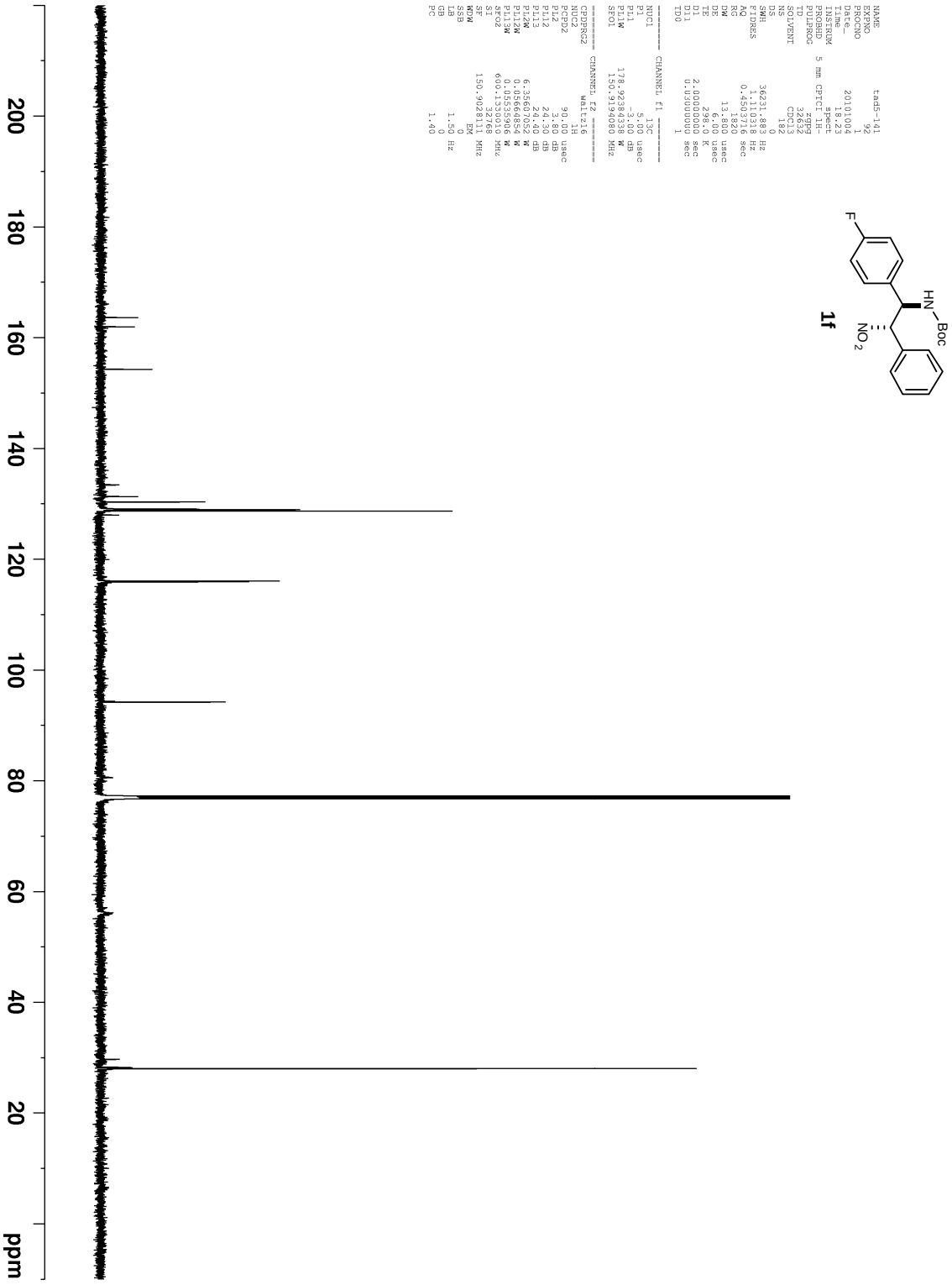


Figure 34. ^{1}H NMR (400 MHz, $CDCl_3$) of **1g**

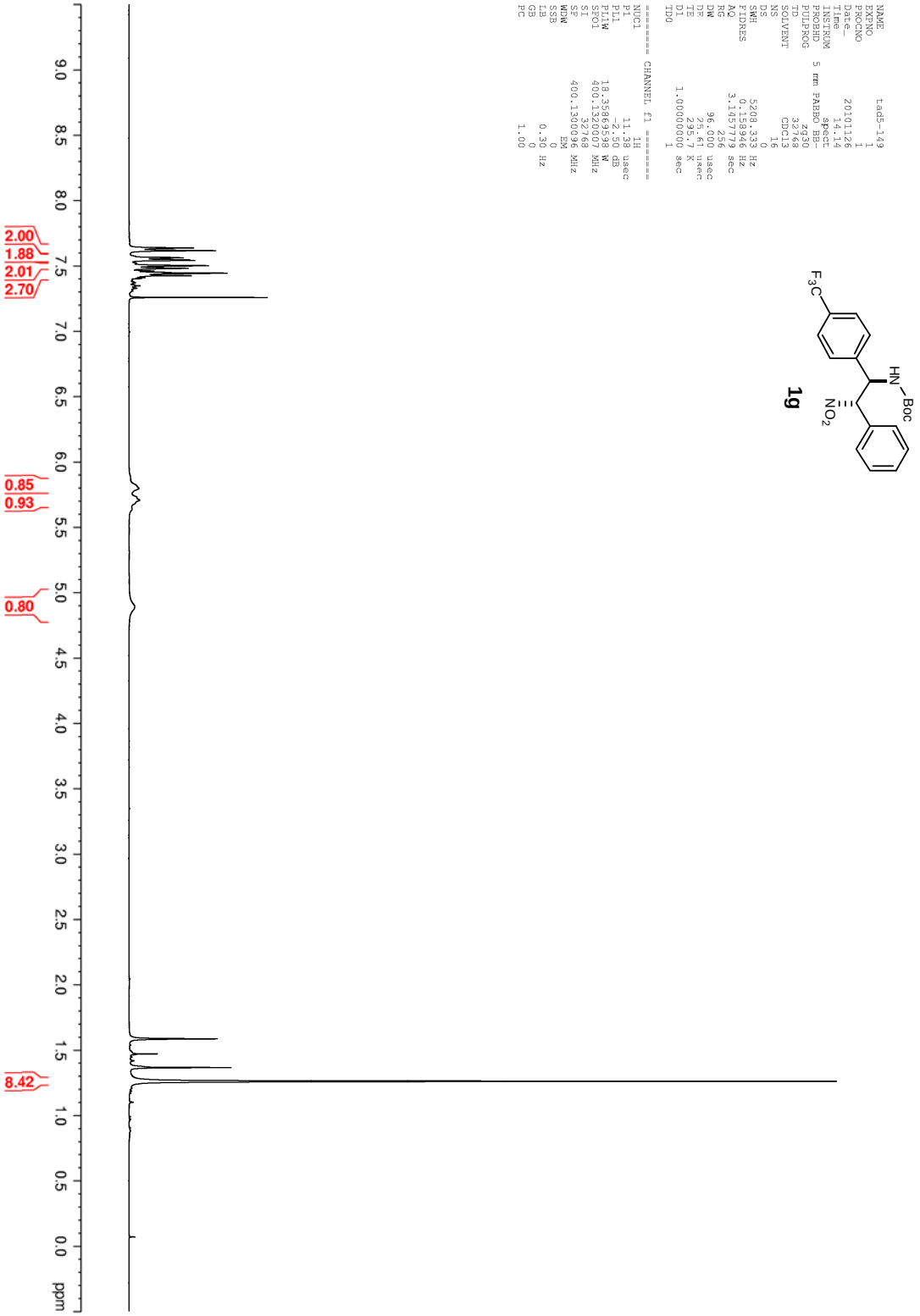


Figure 35. ^{13}C NMR (100 MHz, $CDCl_3$) of **1g**

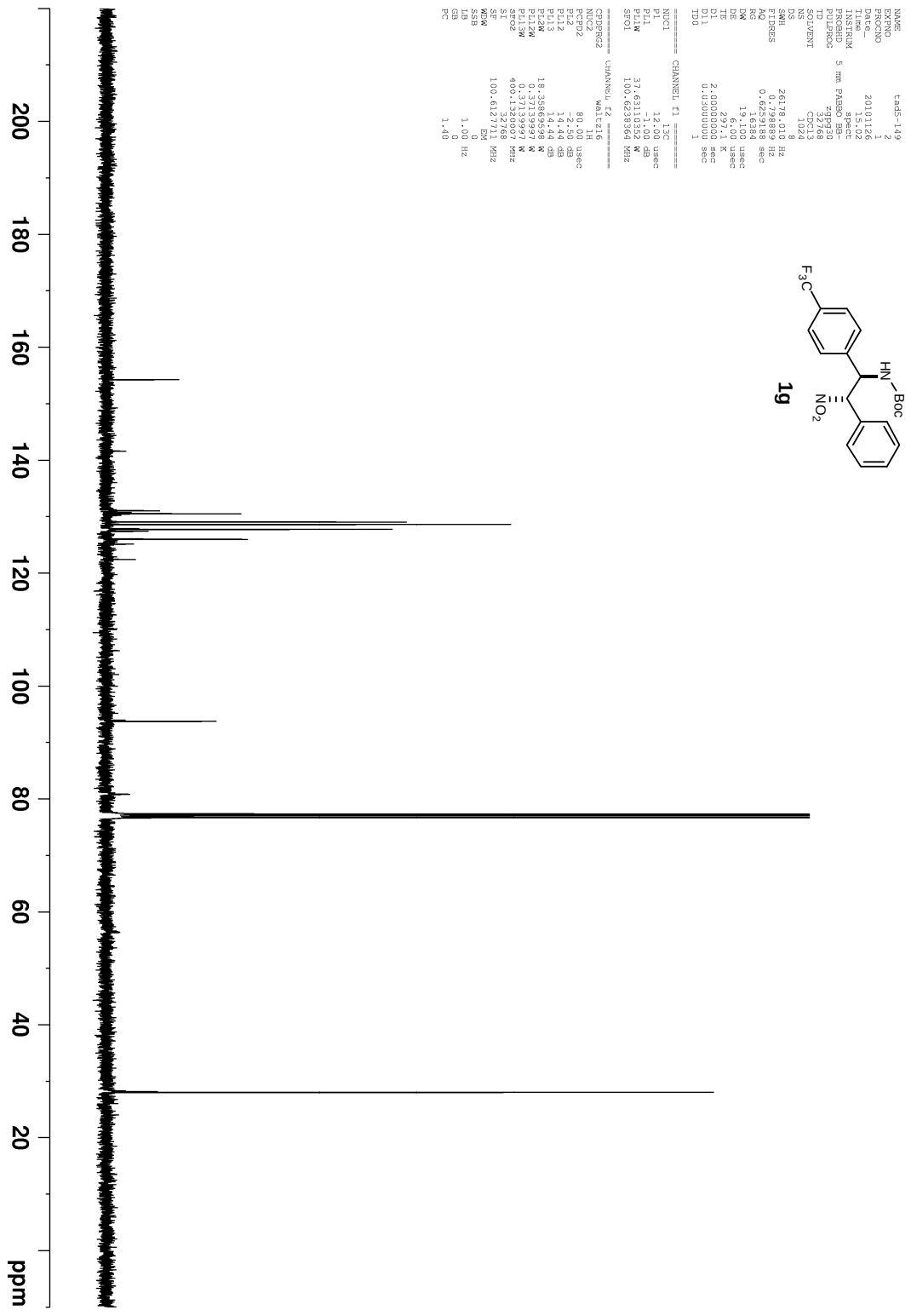


Figure 36. ^{1}H NMR (400 MHz, $CDCl_3$) of **1h**

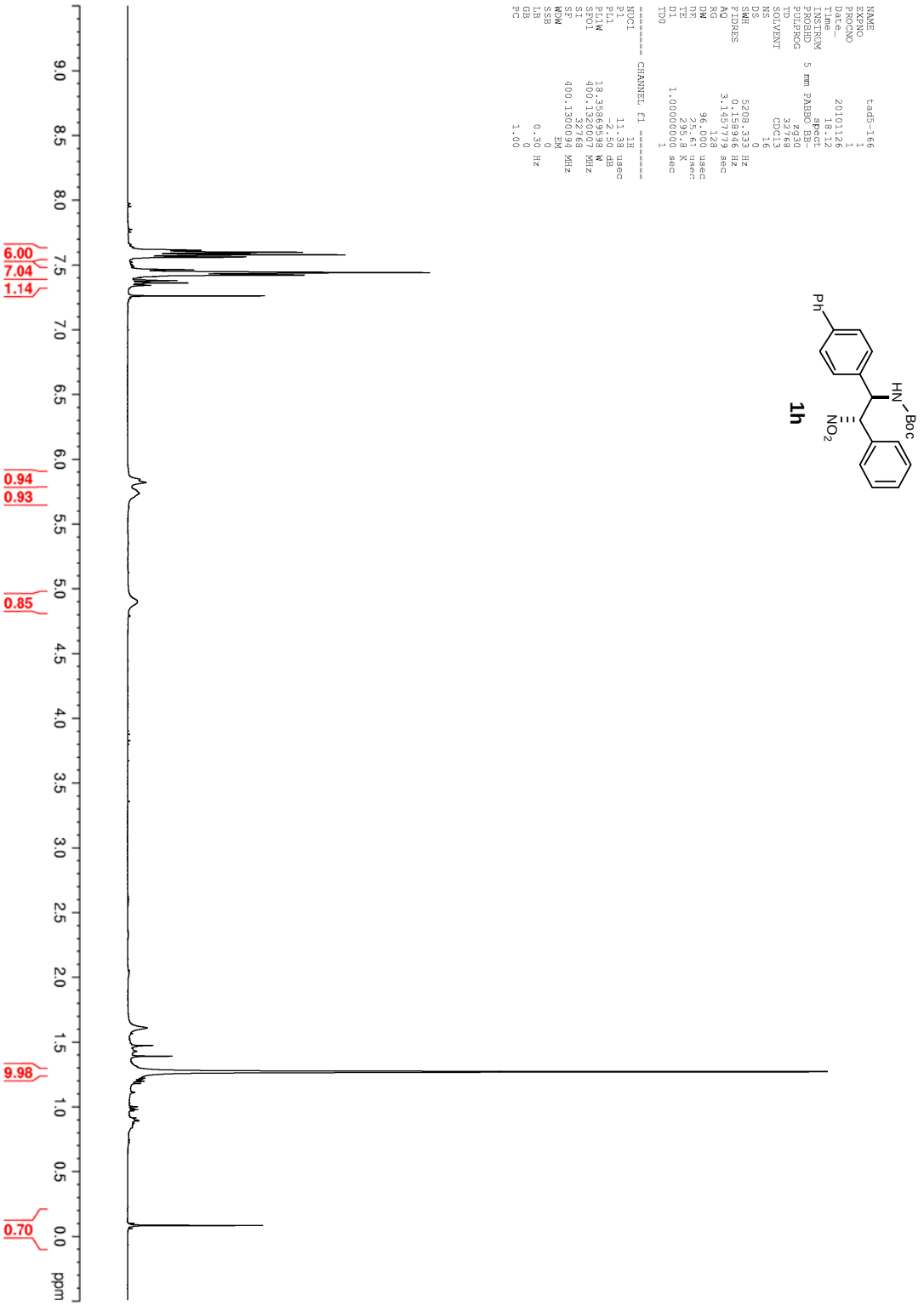


Figure 37. ^{13}C NMR (100 MHz, $CDCl_3$) of **1h**

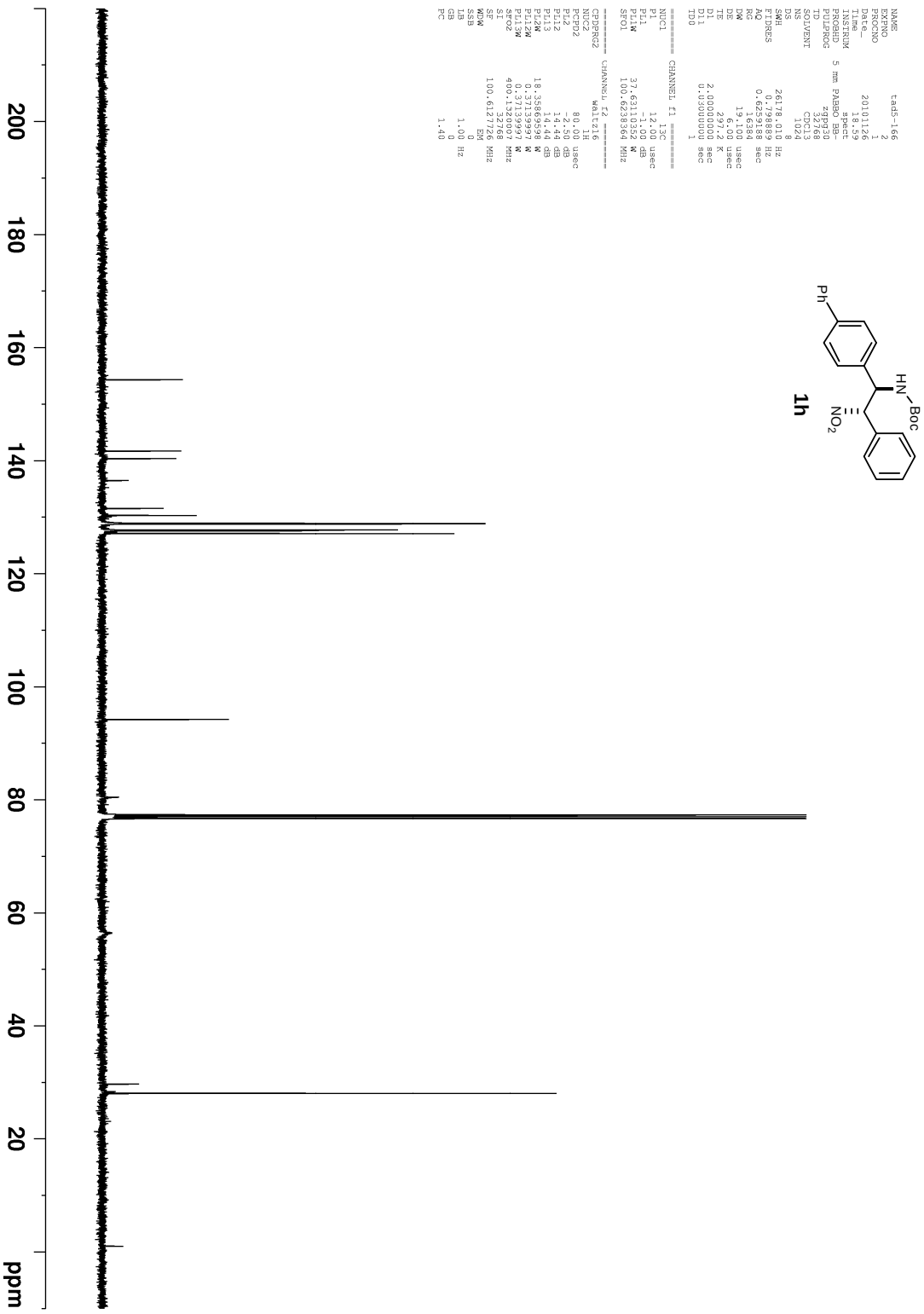


Figure 38. ^{1}H NMR (400 MHz, $CDCl_3$) of **1i**

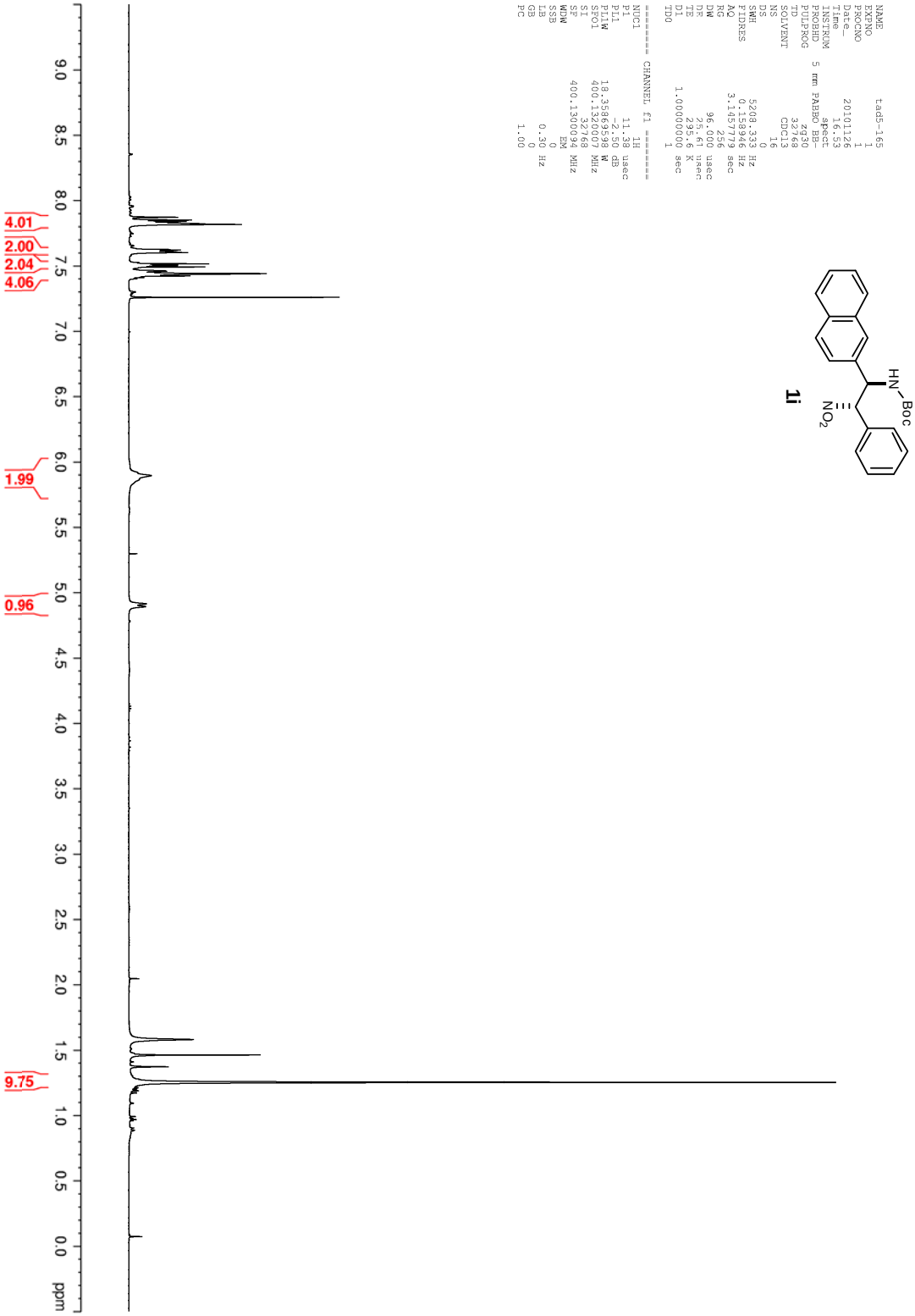


Figure 39. ^{13}C NMR (100 MHz, $CDCl_3$) of **1i**

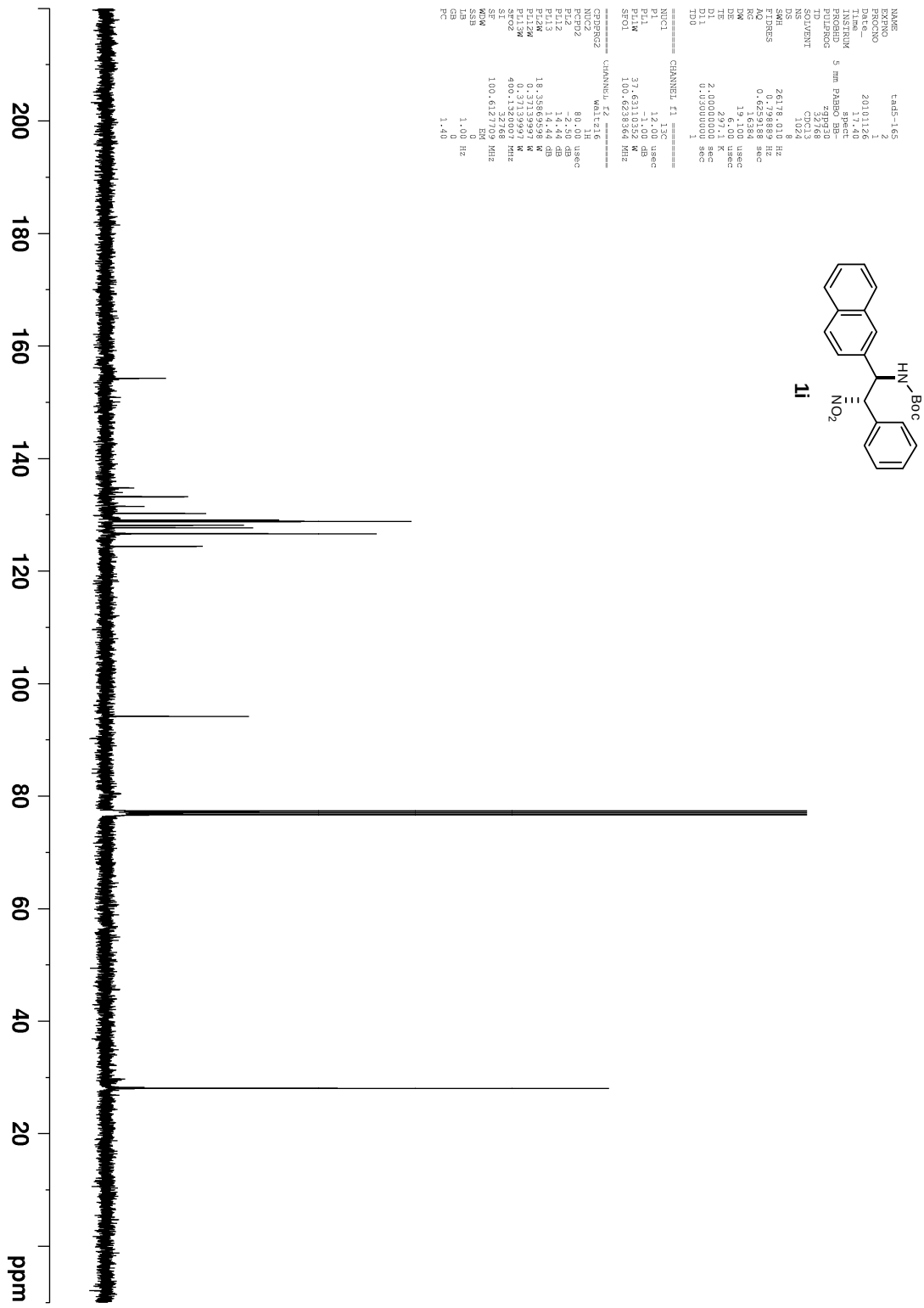


Figure 40. ^{1}H NMR (400 MHz, $CDCl_3$) of **1j**

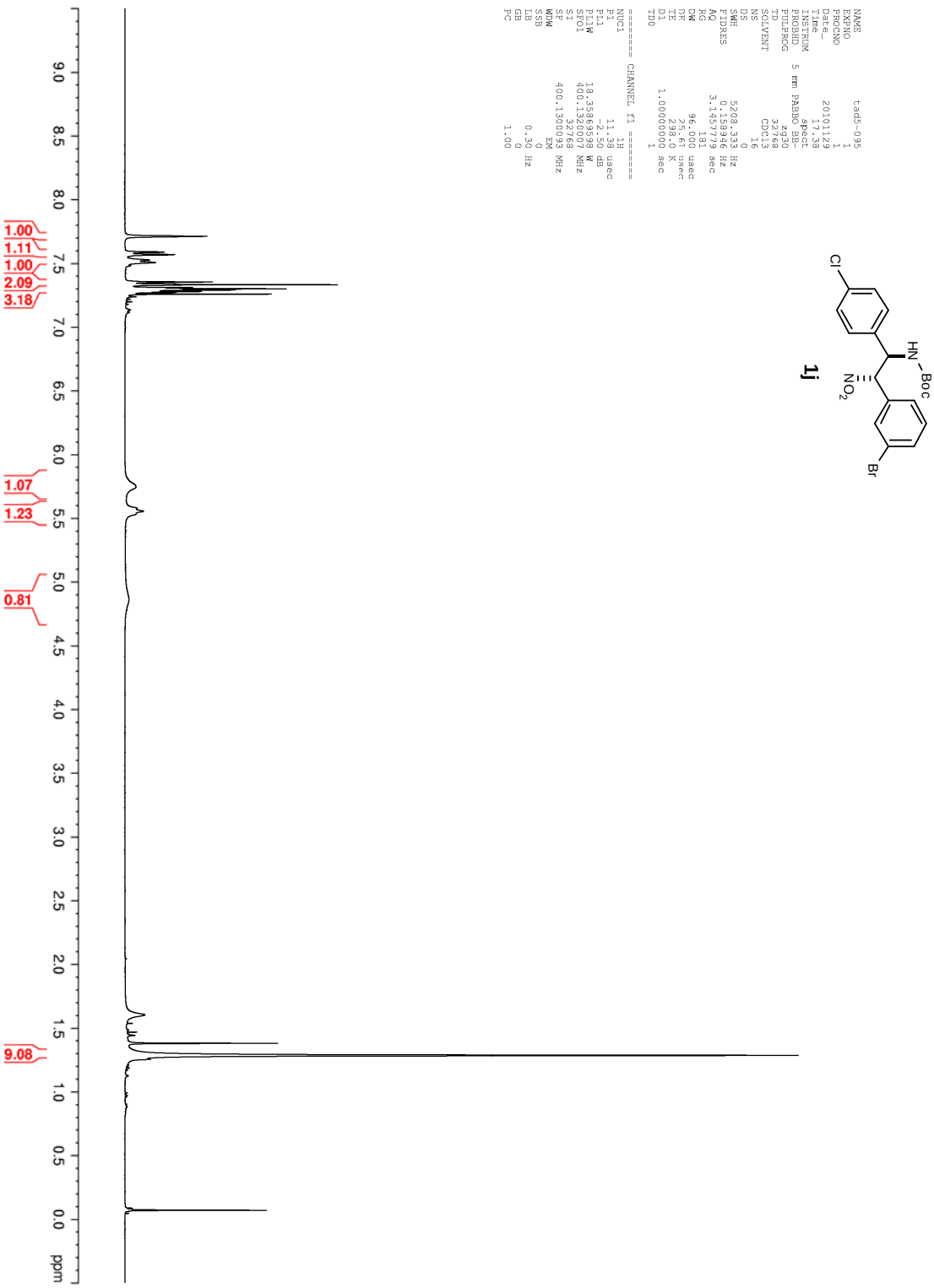


Figure 41. ^{13}C NMR (100 MHz, $CDCl_3$) of **1j**

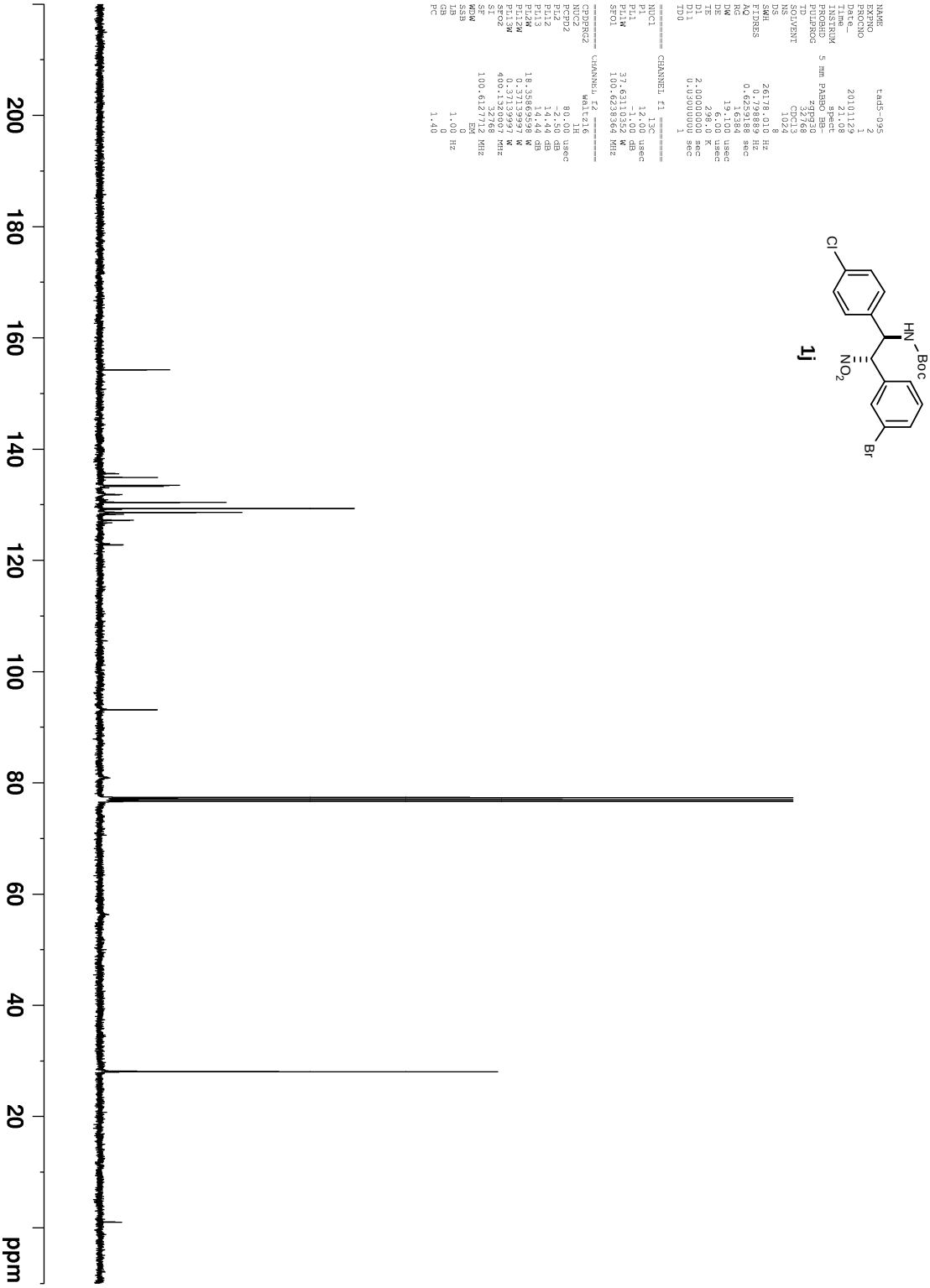


Figure 42. ^{1}H NMR (400 MHz, $CDCl_3$) of **1k**

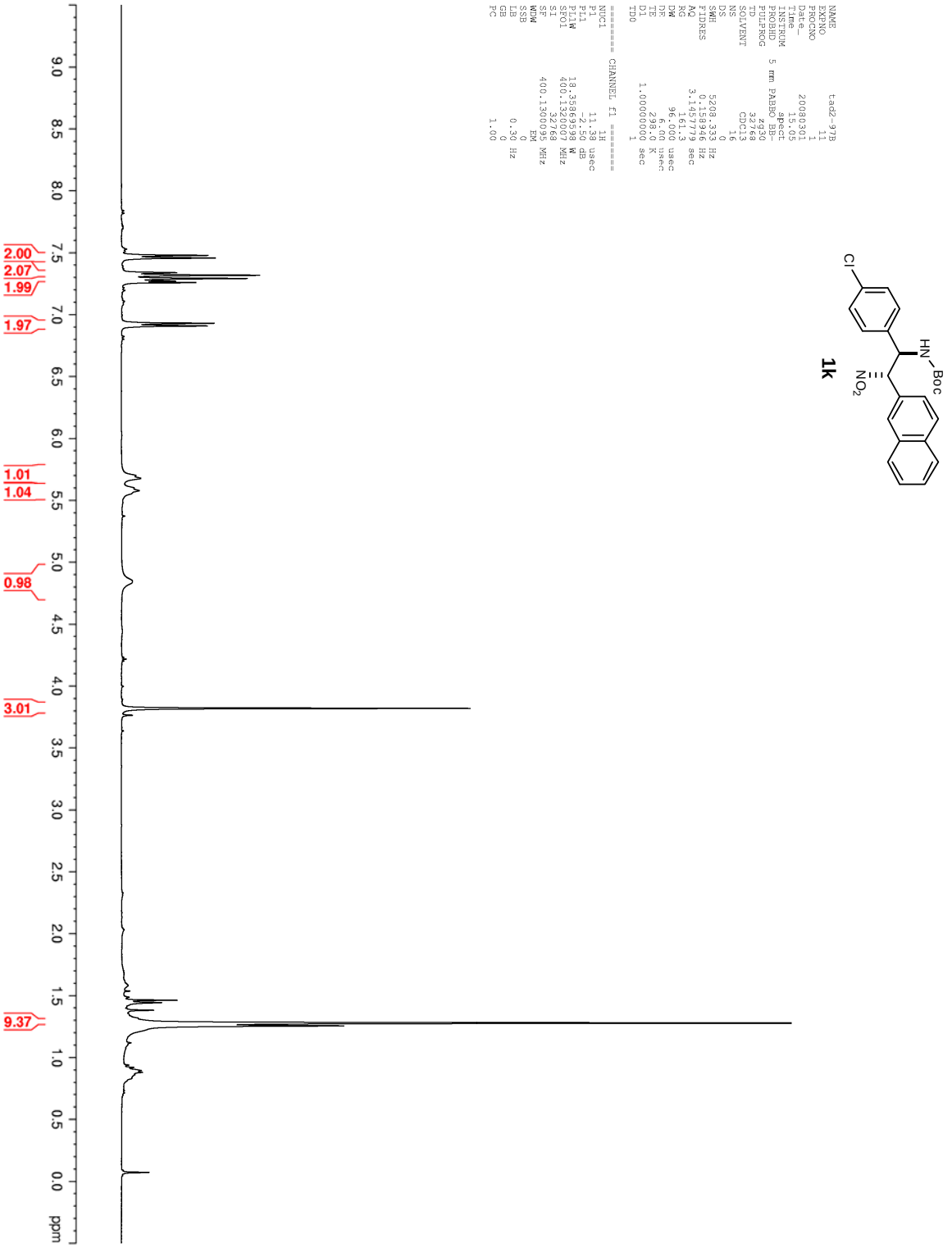


Figure 43. ^{13}C NMR (100 MHz, $CDCl_3$) of **1k**

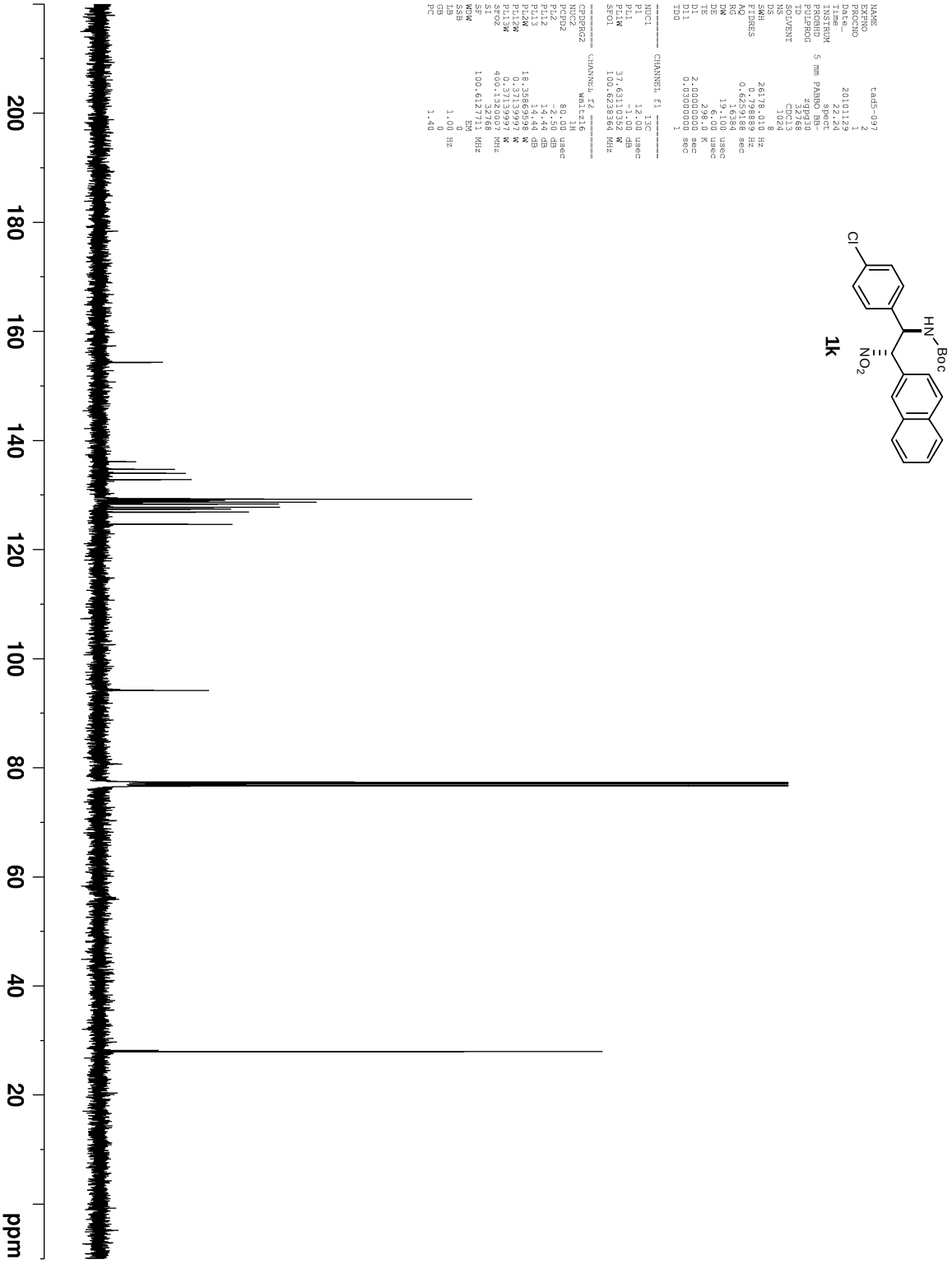


Figure 44. ^{1}H NMR (400 MHz, $CDCl_3$) of **1l**

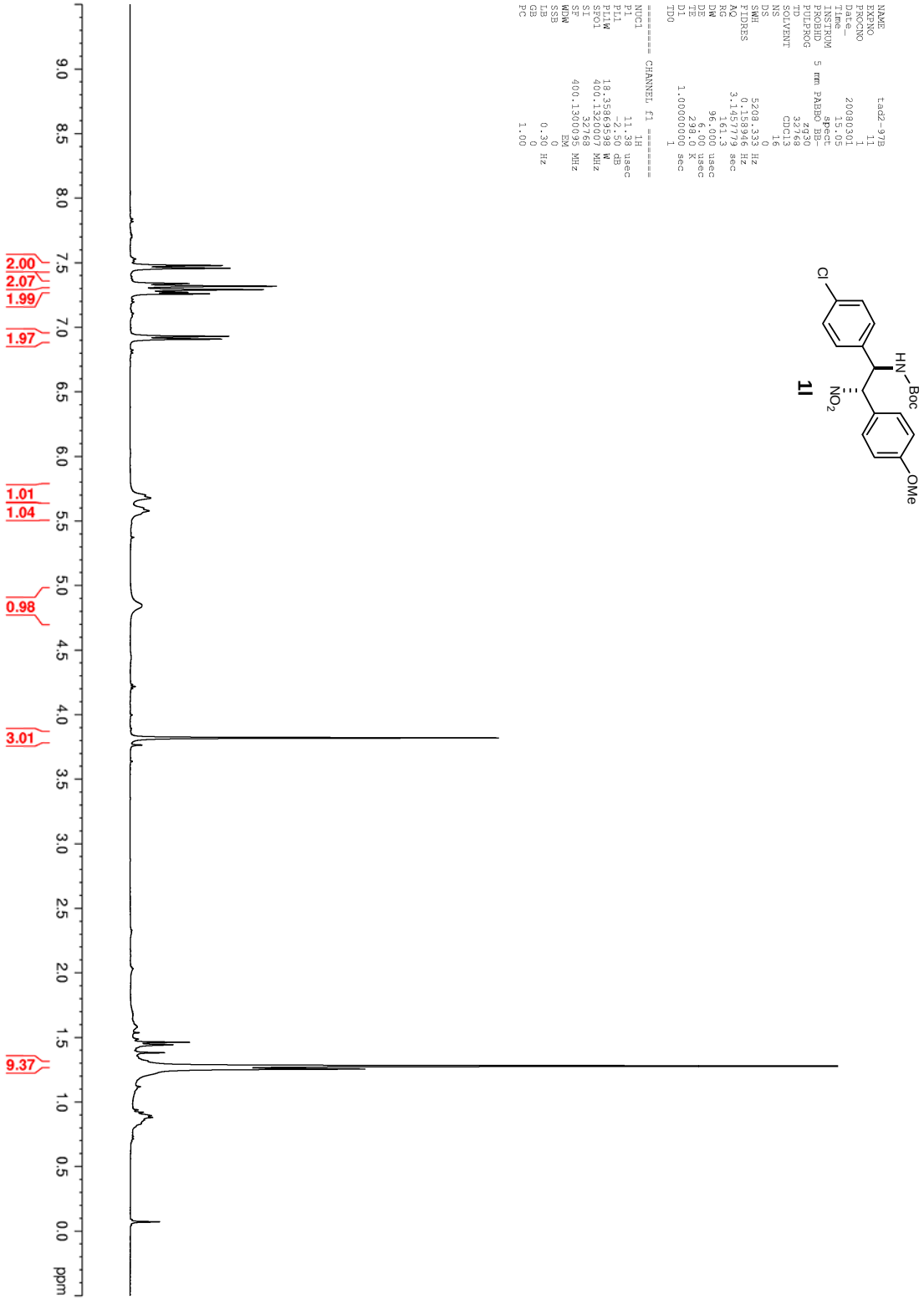


Figure 45. ^{13}C NMR (100 MHz, $CDCl_3$) of **1l**

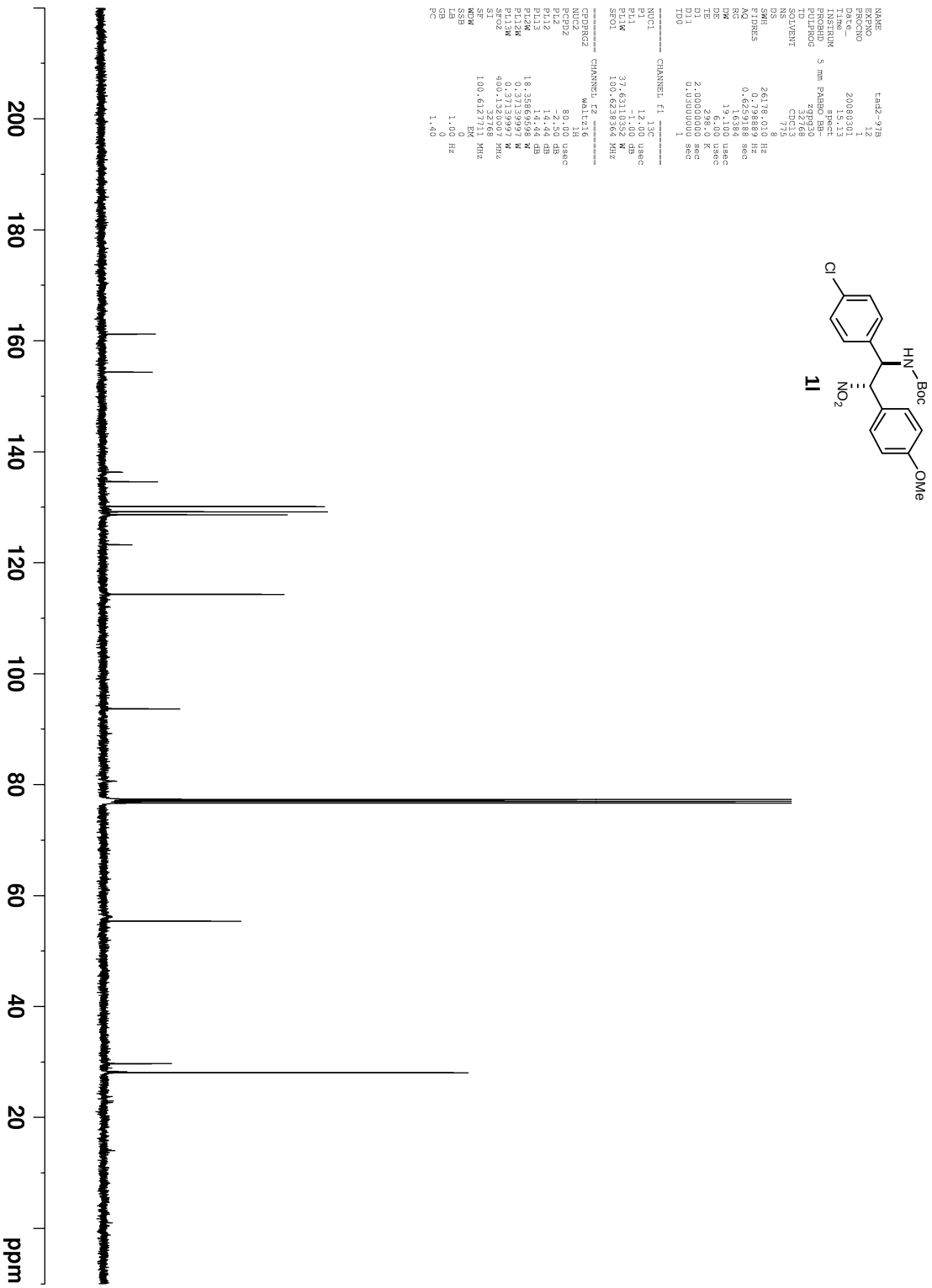


Figure 46. ^{1}H NMR (400 MHz, DMSO-d_6) of **1m**

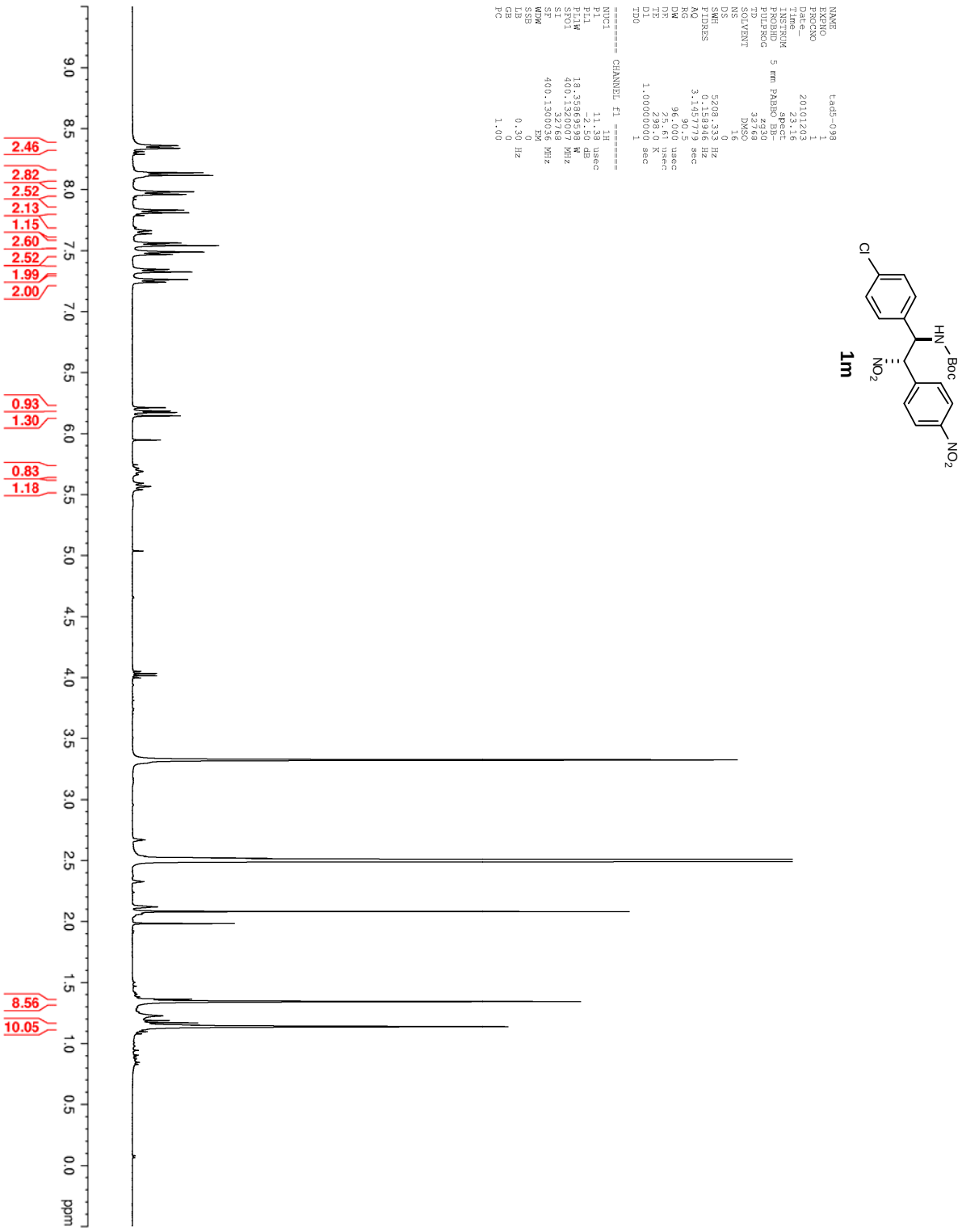


Figure 47. ^{13}C NMR (100 MHz, DMSO-d_6) of **1m**

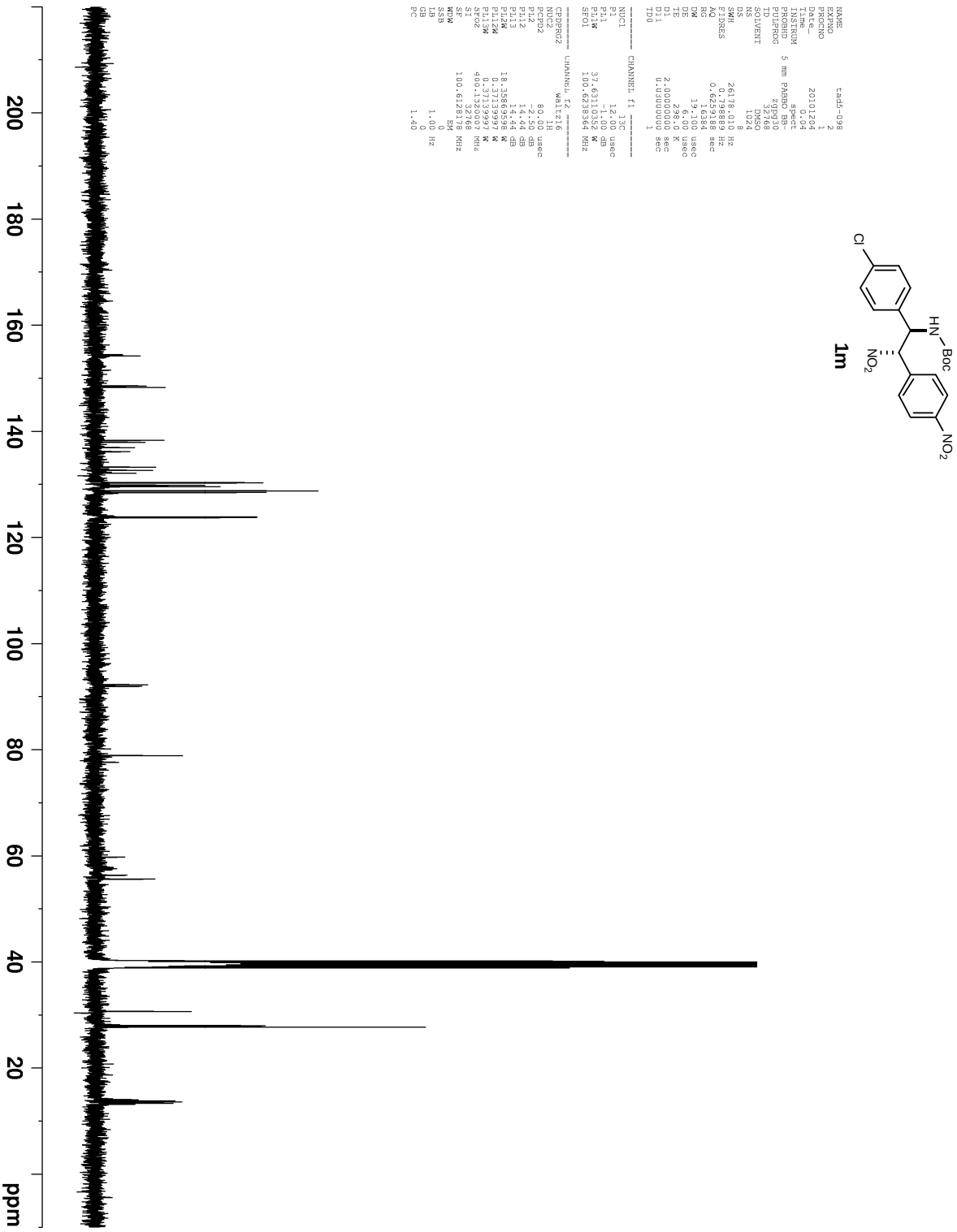


Figure 48. ^{1}H NMR (400 MHz, $CDCl_3$) of **2**

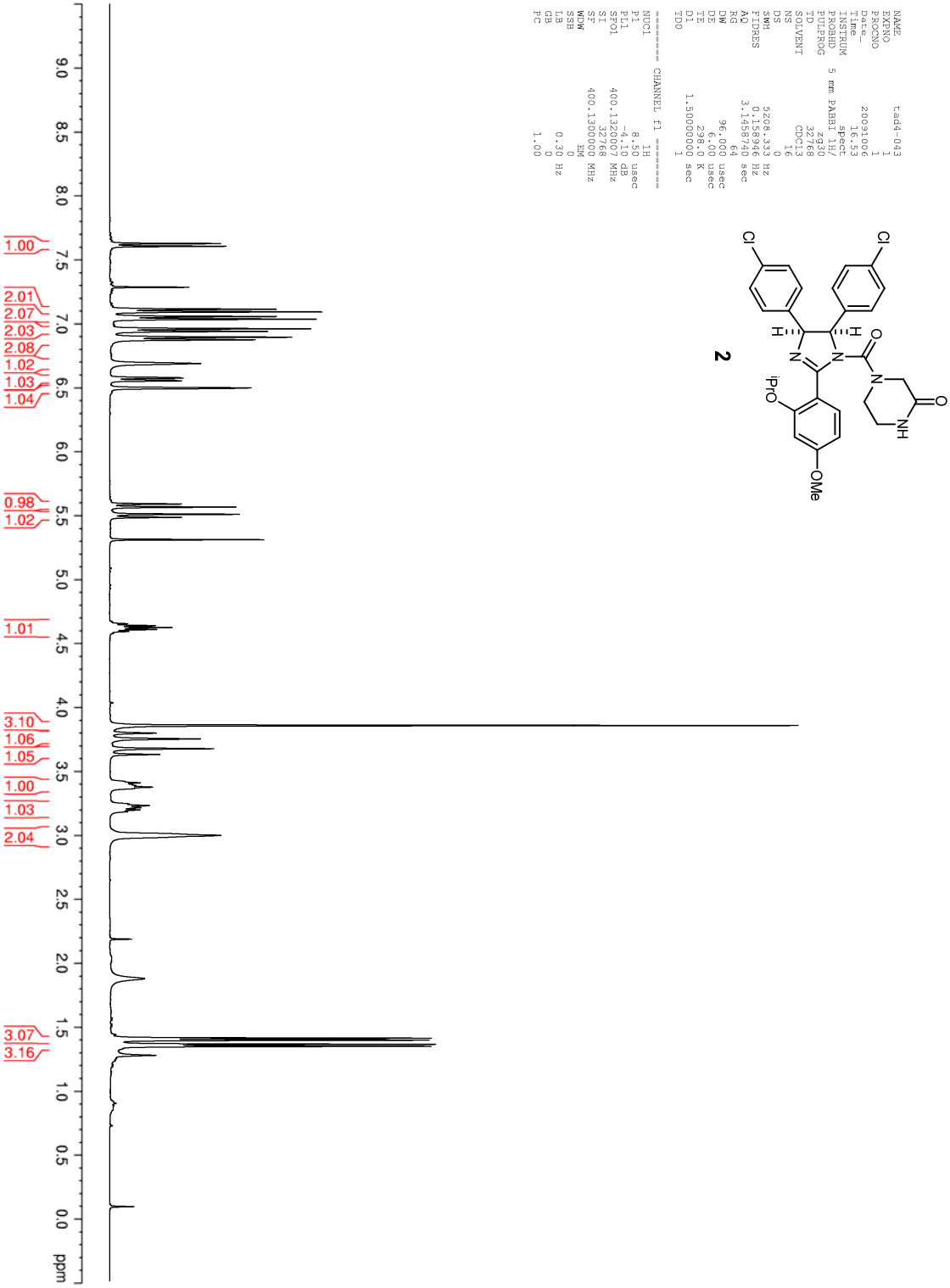


Figure 49. ^{13}C NMR (100 MHz, $CDCl_3$) of **2**

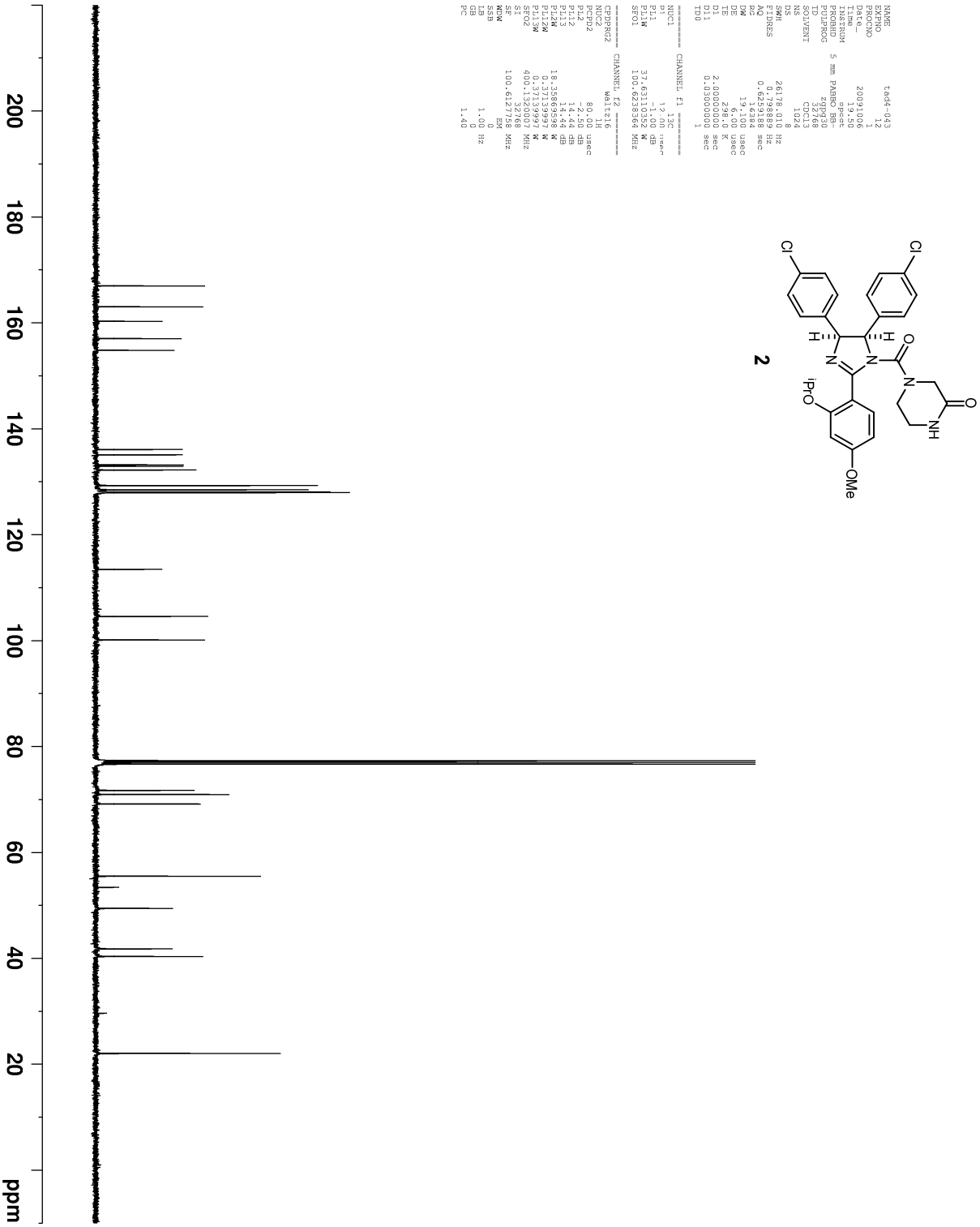


Figure 50. HMBC (600 MHz, $CDCl_3$) of **2**

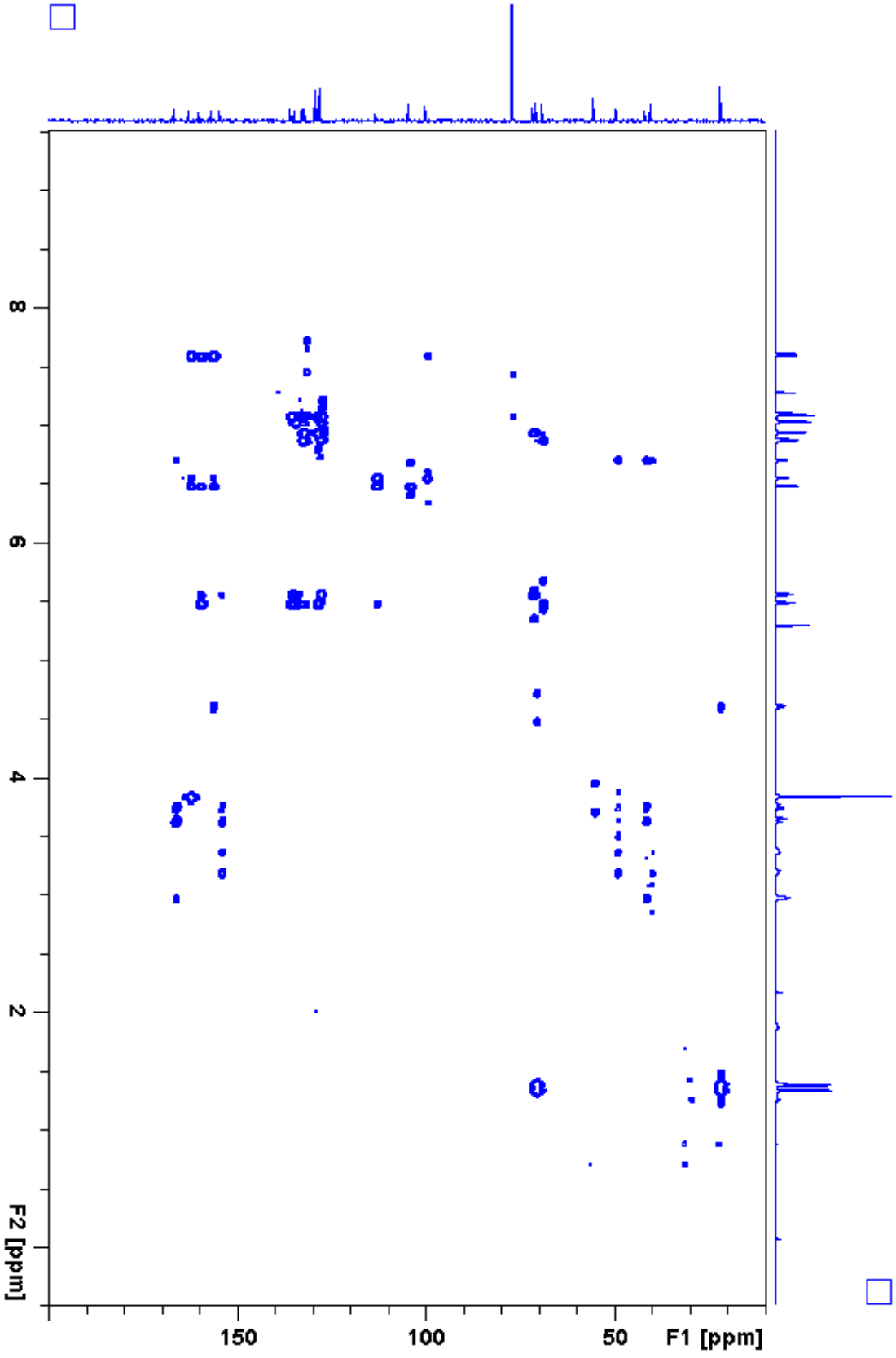
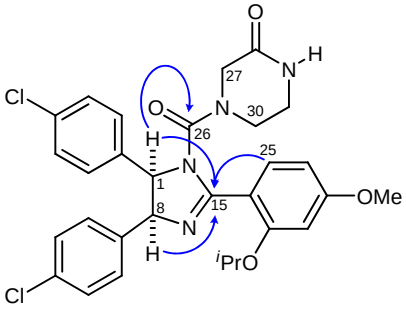


Figure 51. HMBC (600 MHz, $CDCl_3$) of **2**



C26 (155 ppm) Showed correlations to H27/H27` and H30/H30’ and to H1 (but not H8). C15 (160 ppm) Showed correlations to both of the imidazoline methines (H1 and H8) and also to the H25.

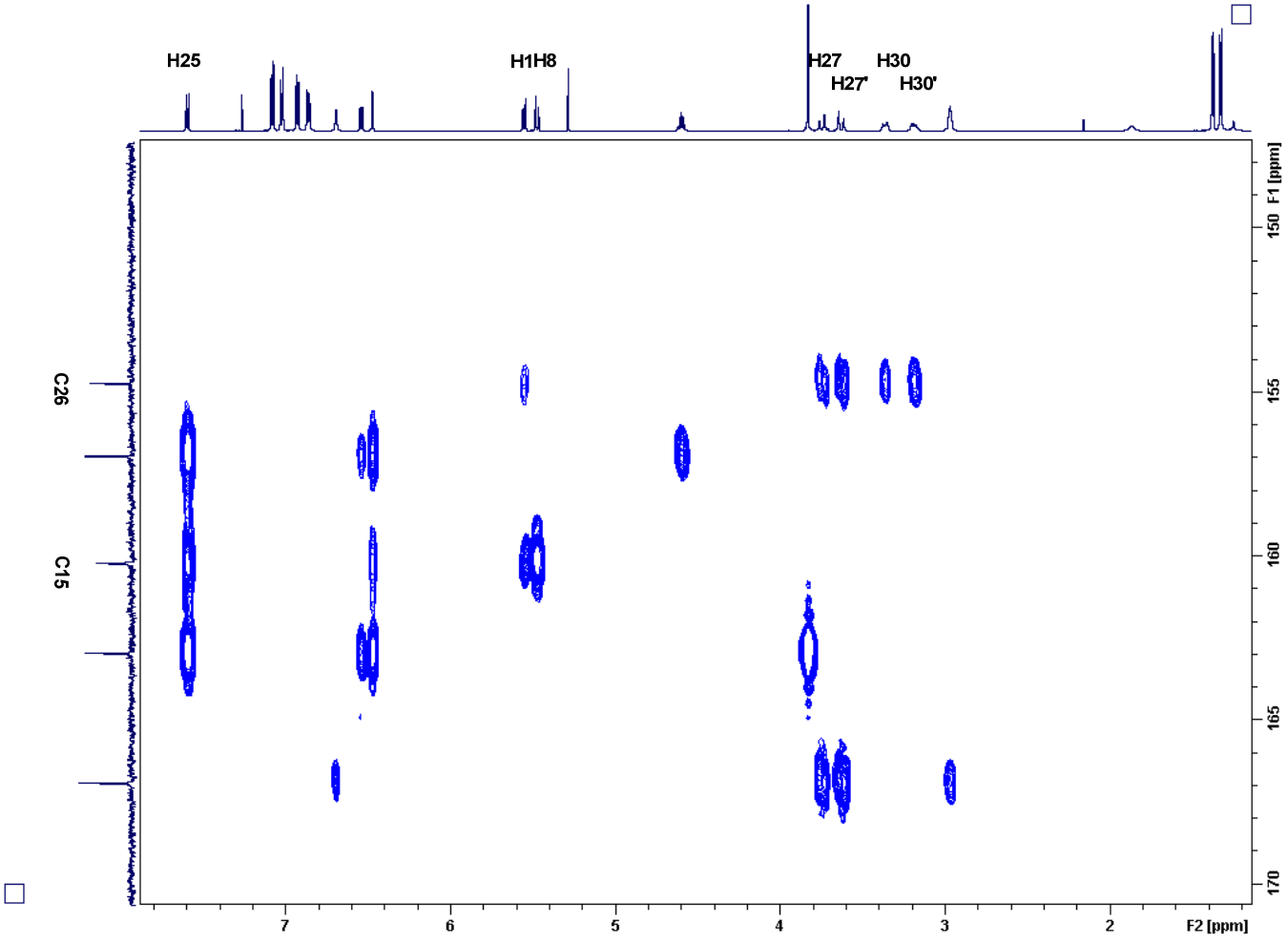


Figure 52. ^{1}H NMR (400 MHz, $CDCl_3$) of **4**

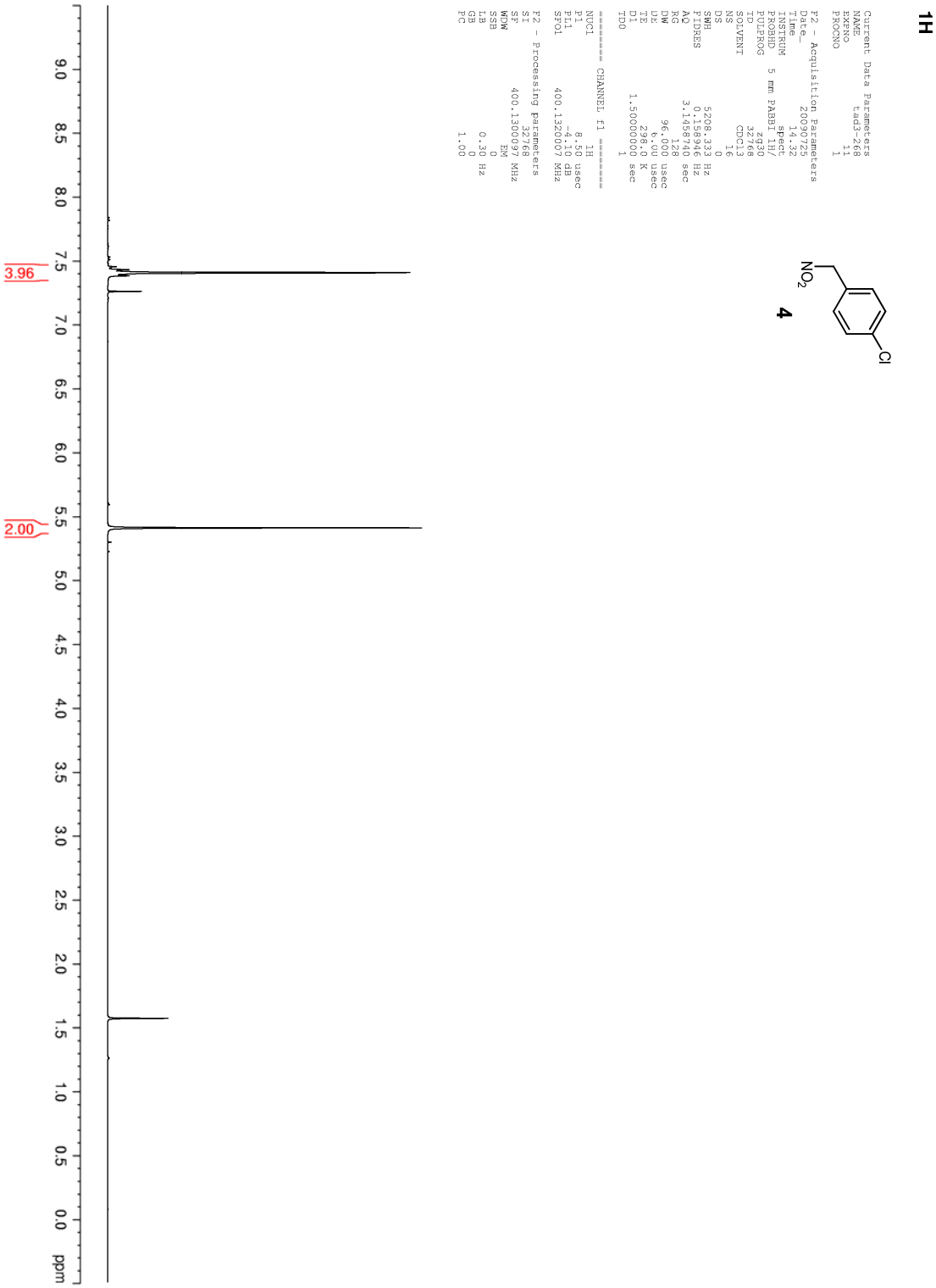


Figure 53. ^{13}C NMR (100 MHz, $CDCl_3$) of **4**

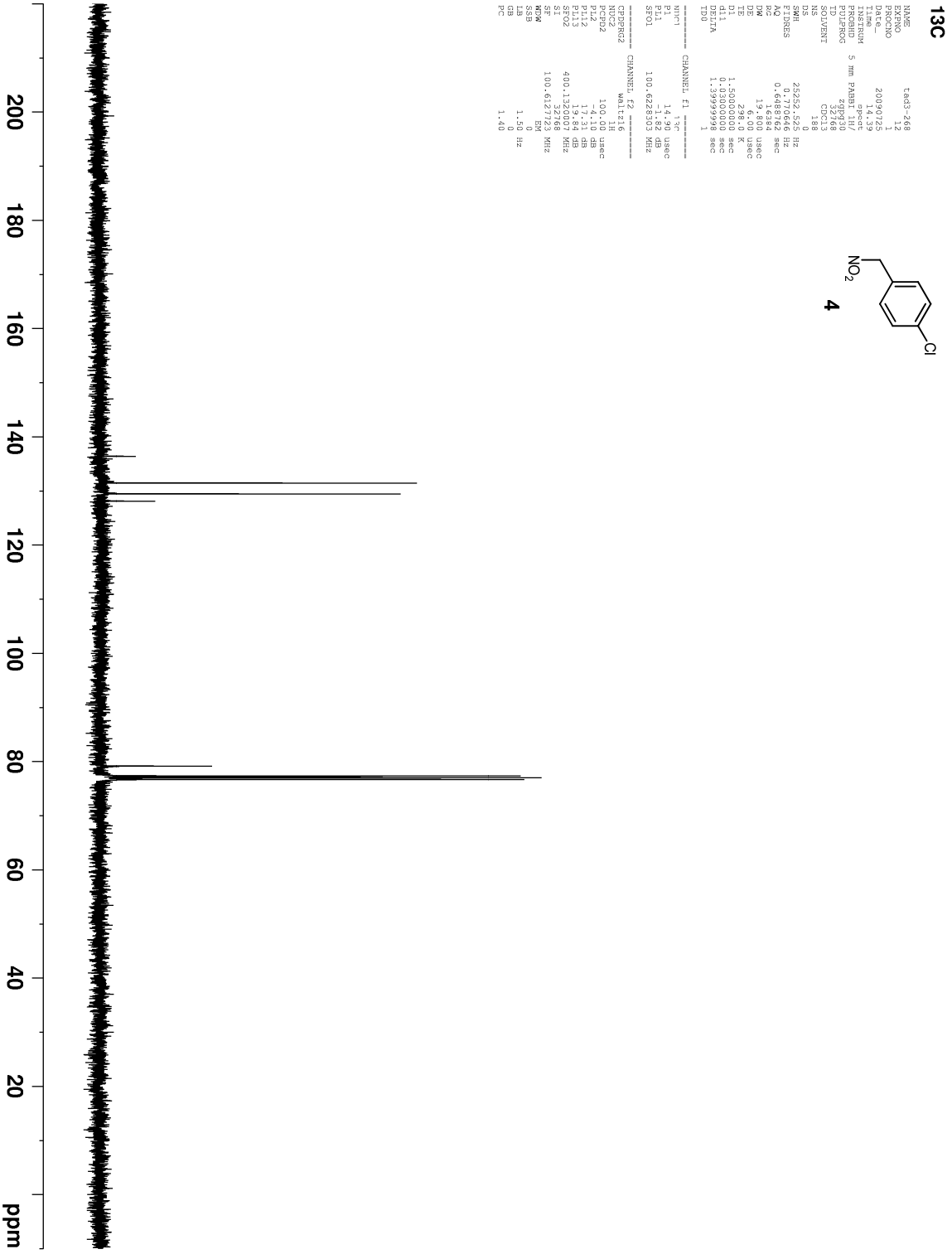


Figure 54. ^{1}H NMR (400 MHz, $CDCl_3$) of **7**

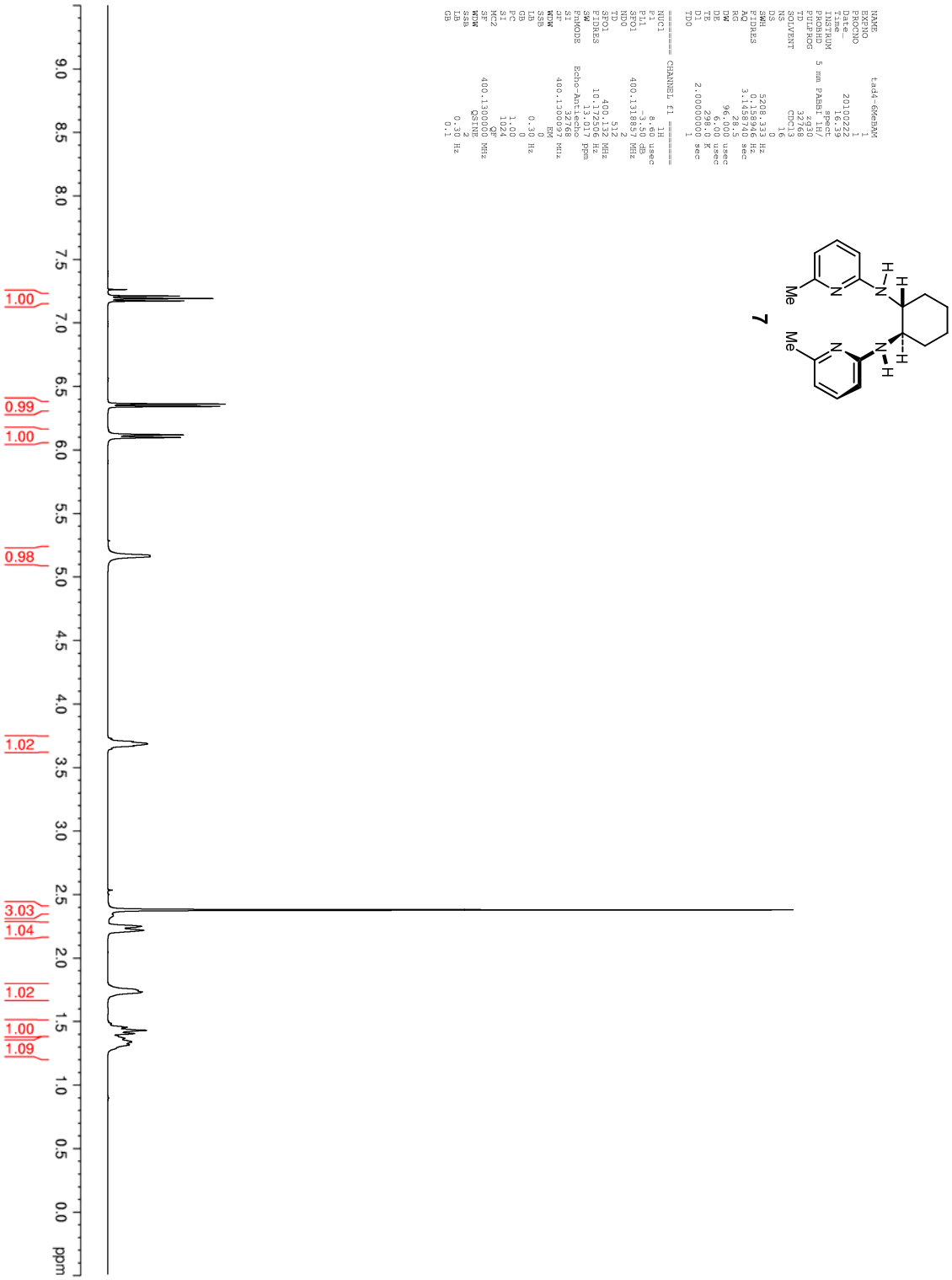


Figure 55. ^{13}C NMR (100 MHz, $CDCl_3$) of **7**

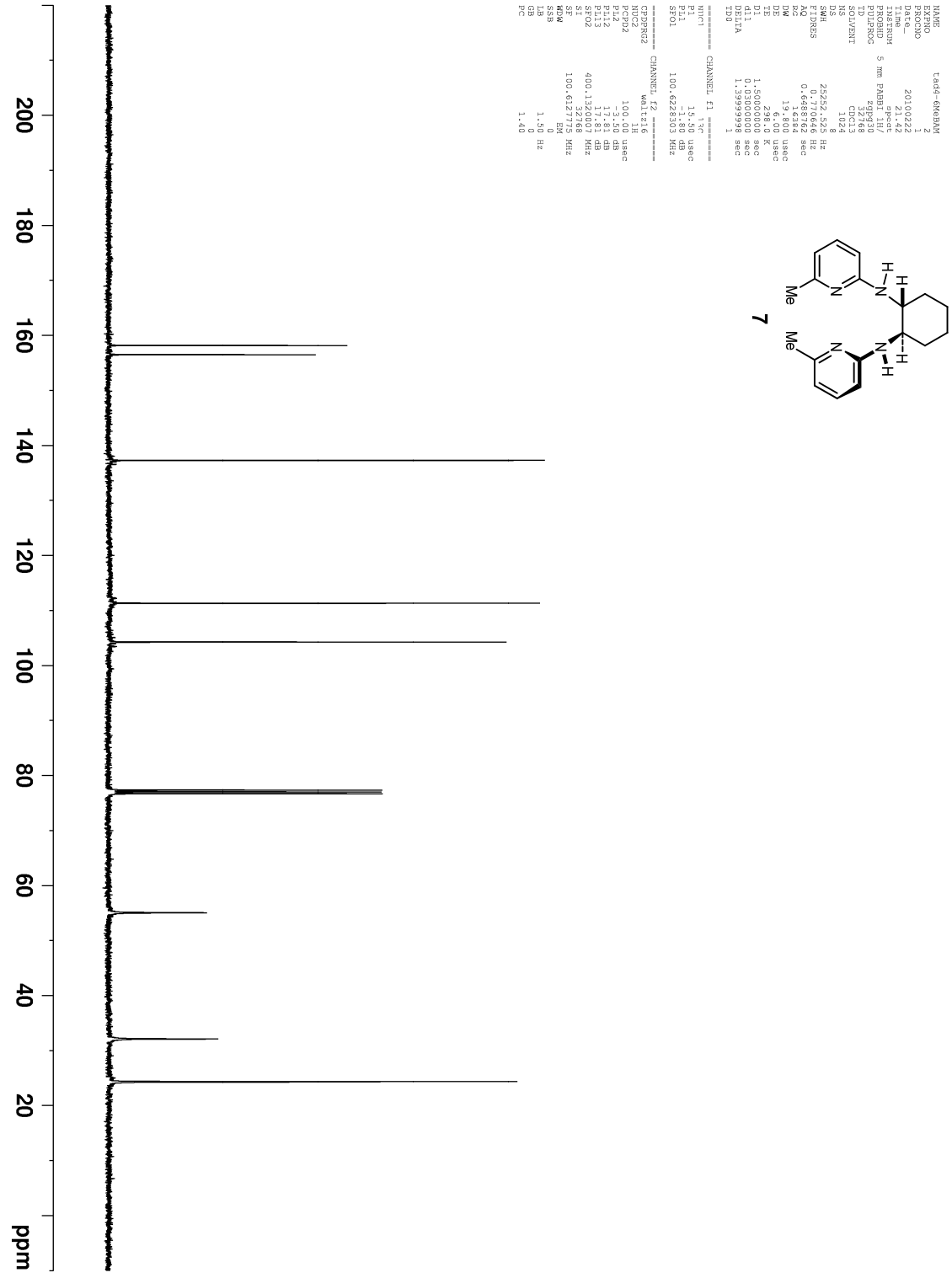


Figure 56. ^{1}H NMR (400 MHz, $CDCl_3$) of **8b**

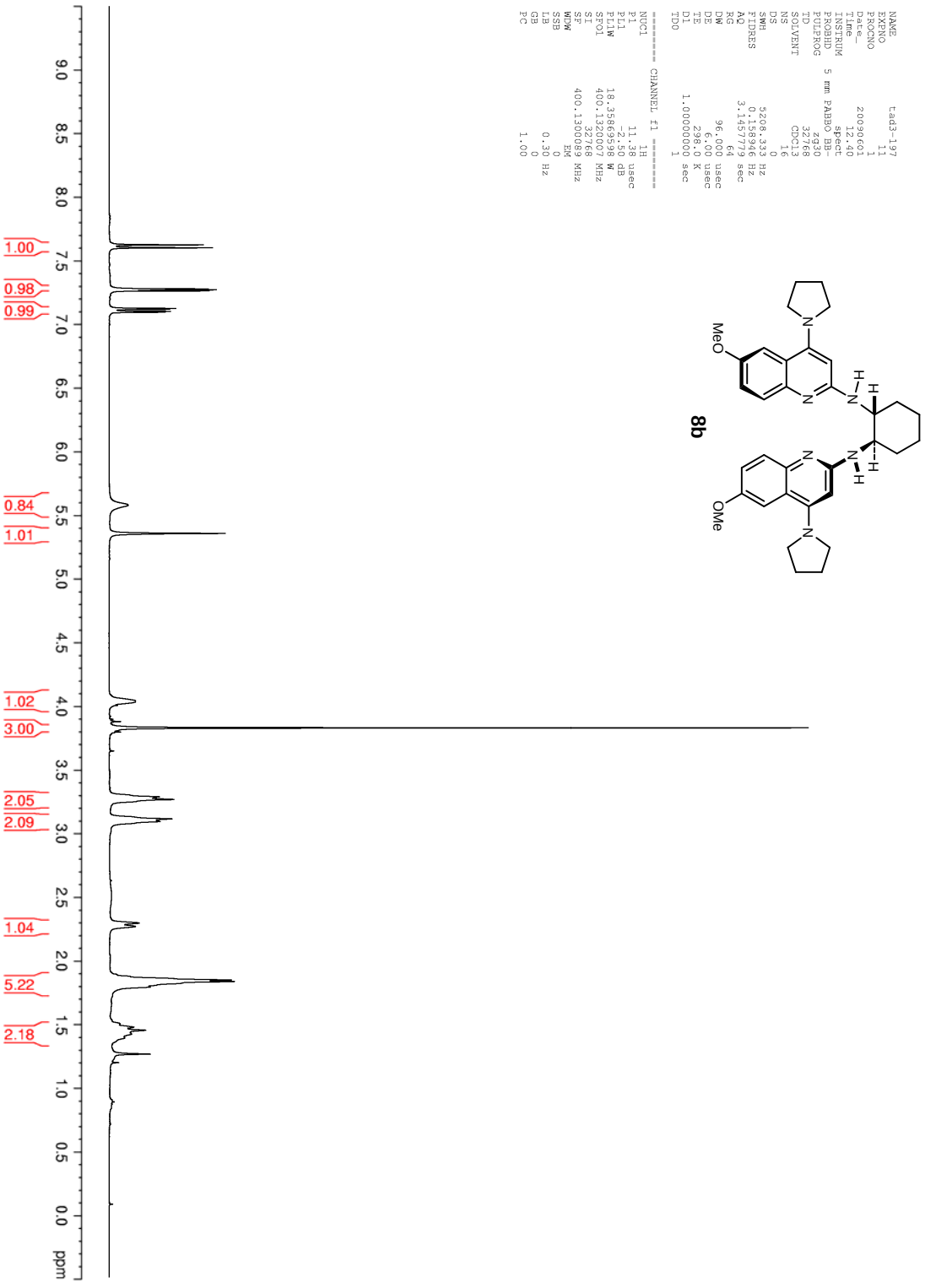


Figure 57. ^{13}C NMR (100 MHz, $CDCl_3$) of **8b**

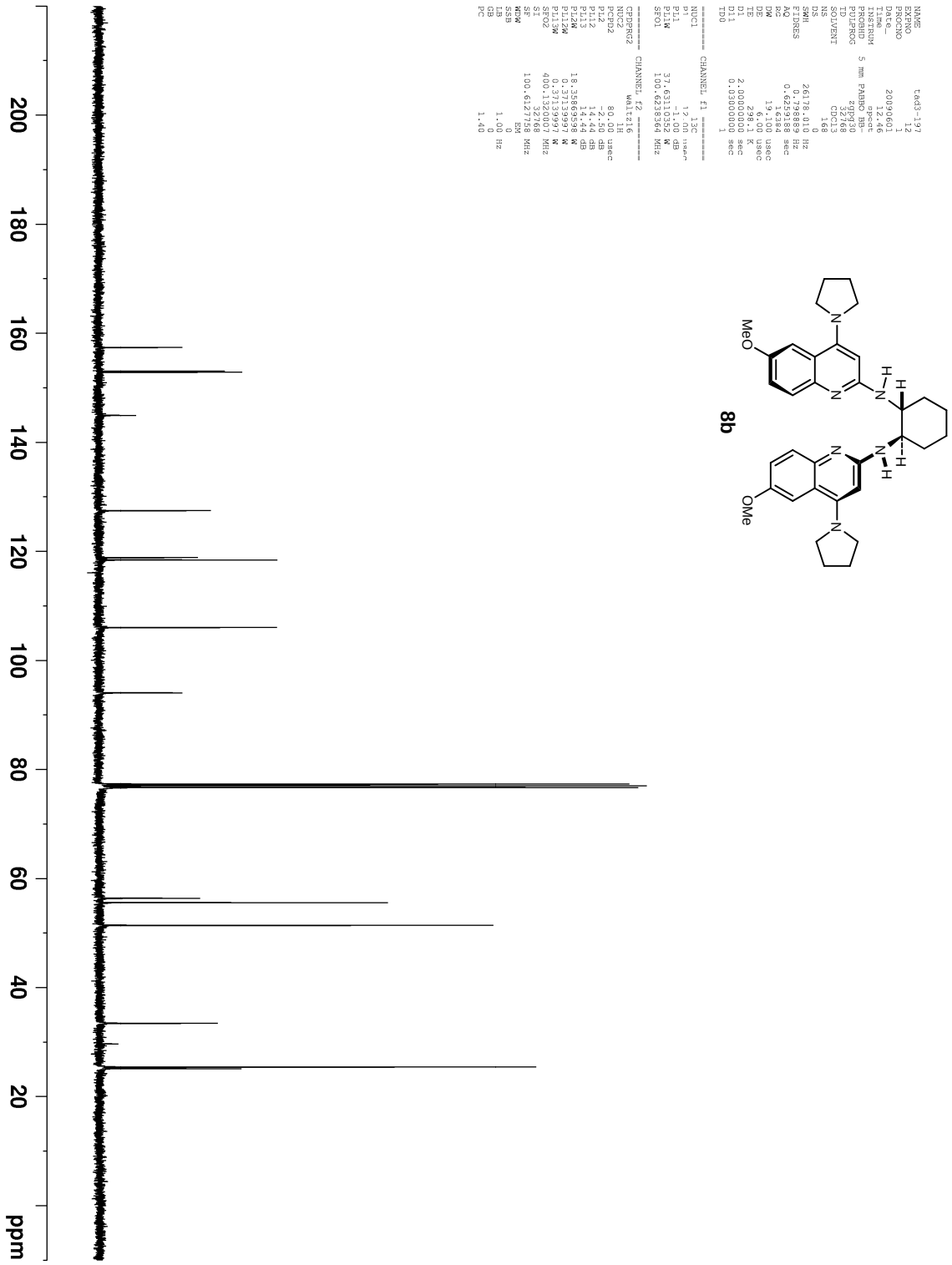


Figure 58. ^{1}H NMR (500 MHz, $CDCl_3$) of **8c**

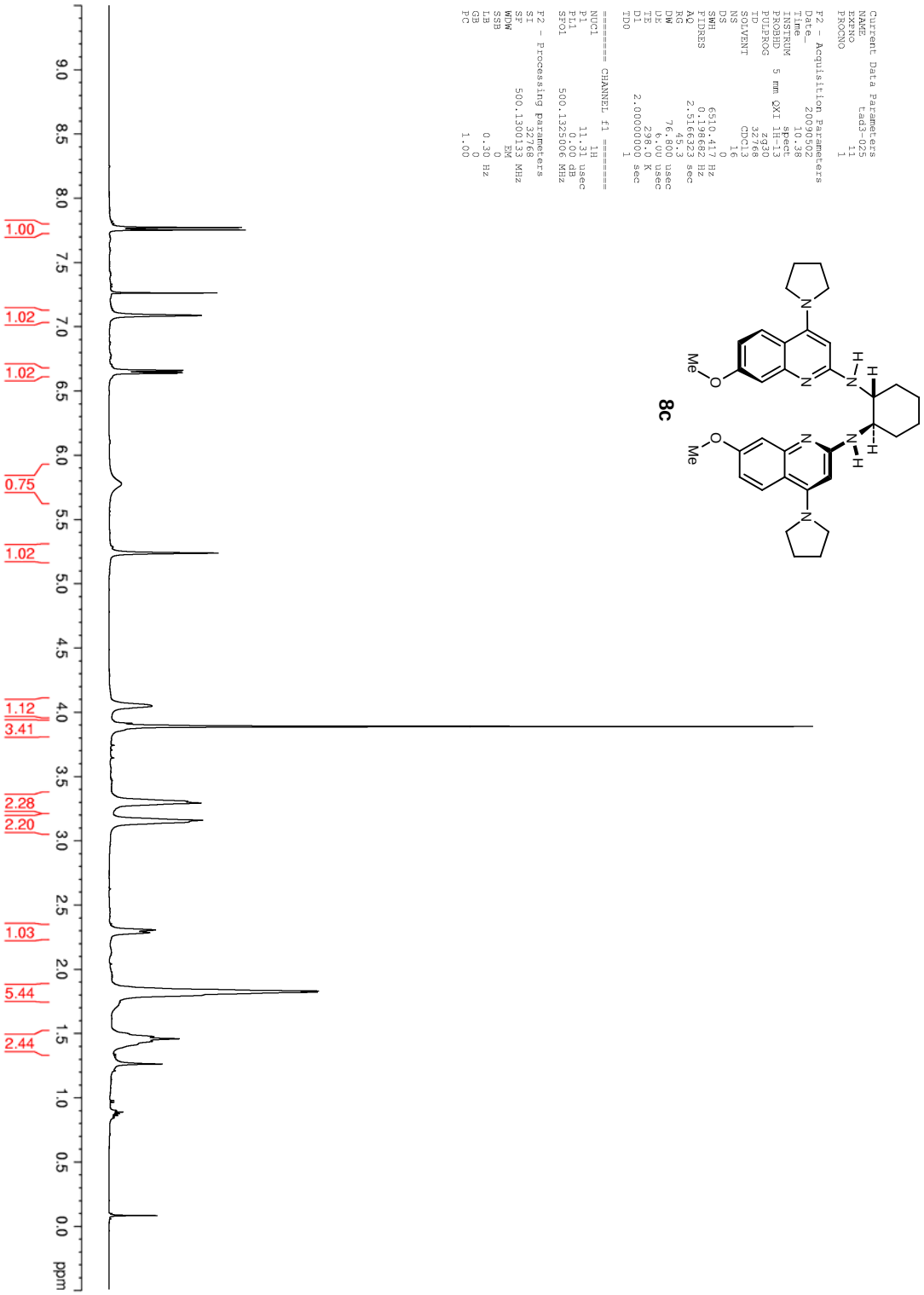


Figure 59. ^{13}C NMR (125 MHz, $CDCl_3$) of **8c**

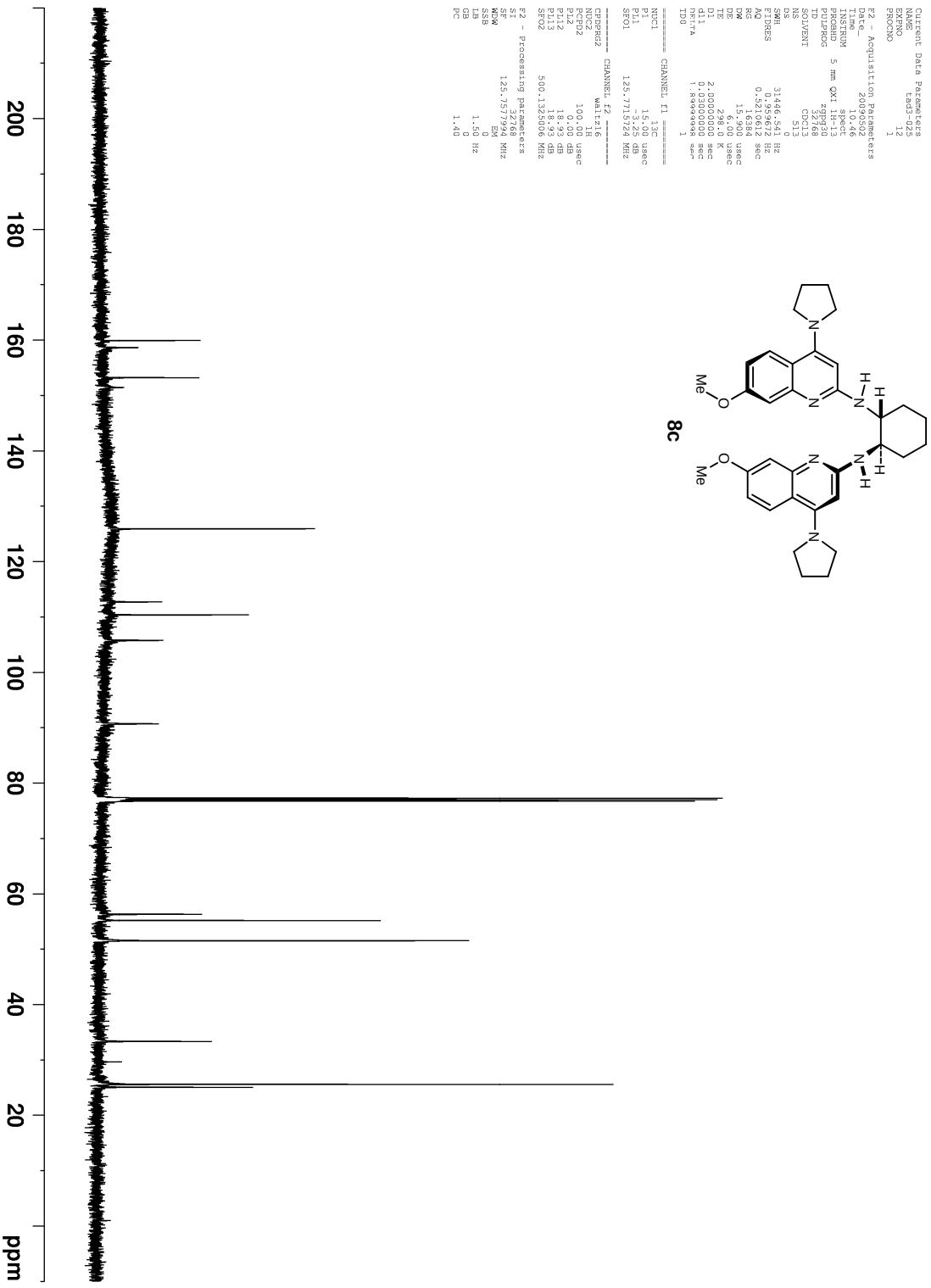


Figure 60. ^{1}H NMR (400 MHz, $CDCl_{3,}$) of **8d**

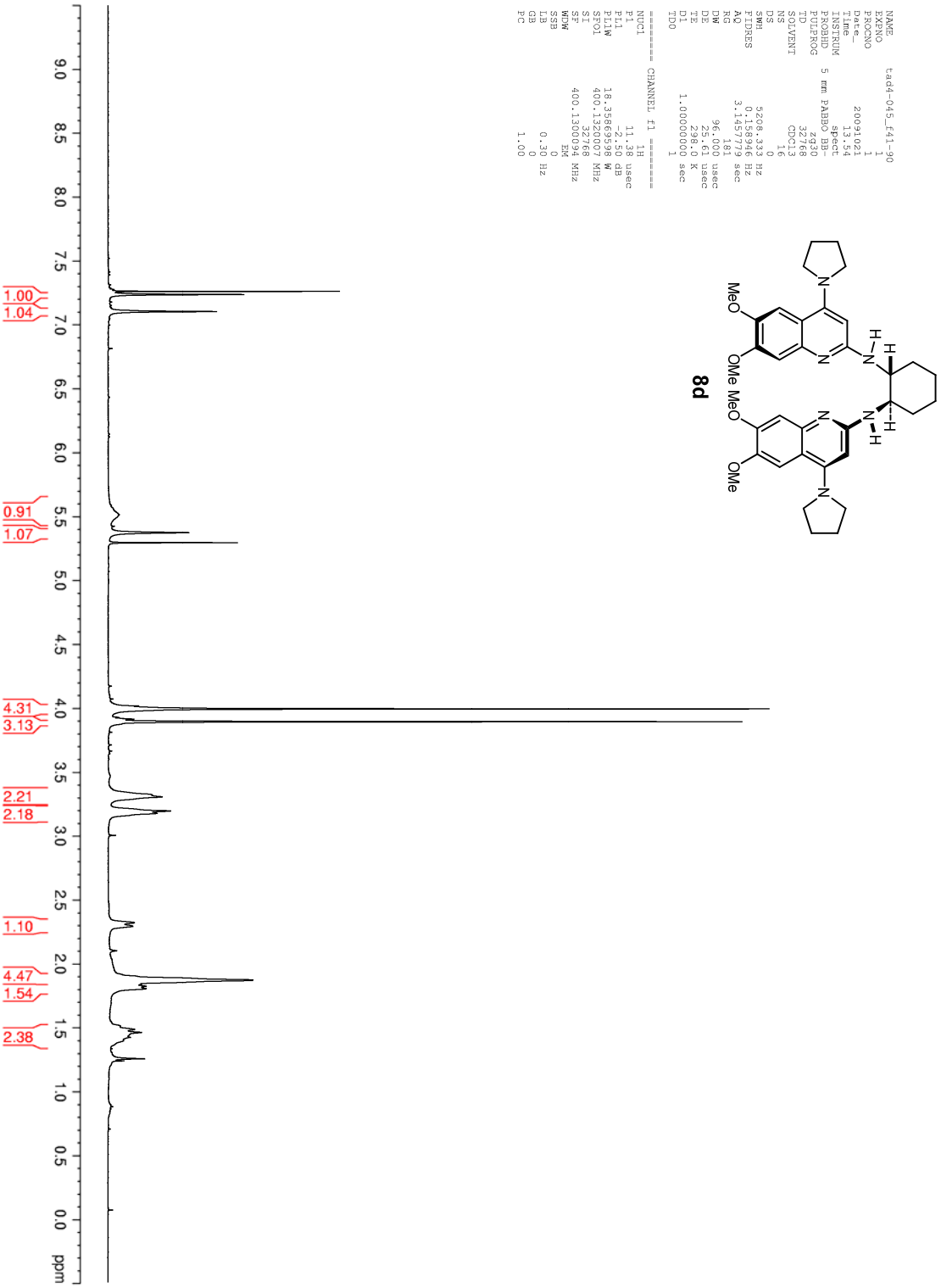


Figure 61. ^{13}C NMR (100 MHz, $CDCl_{3,}$) of **8d**

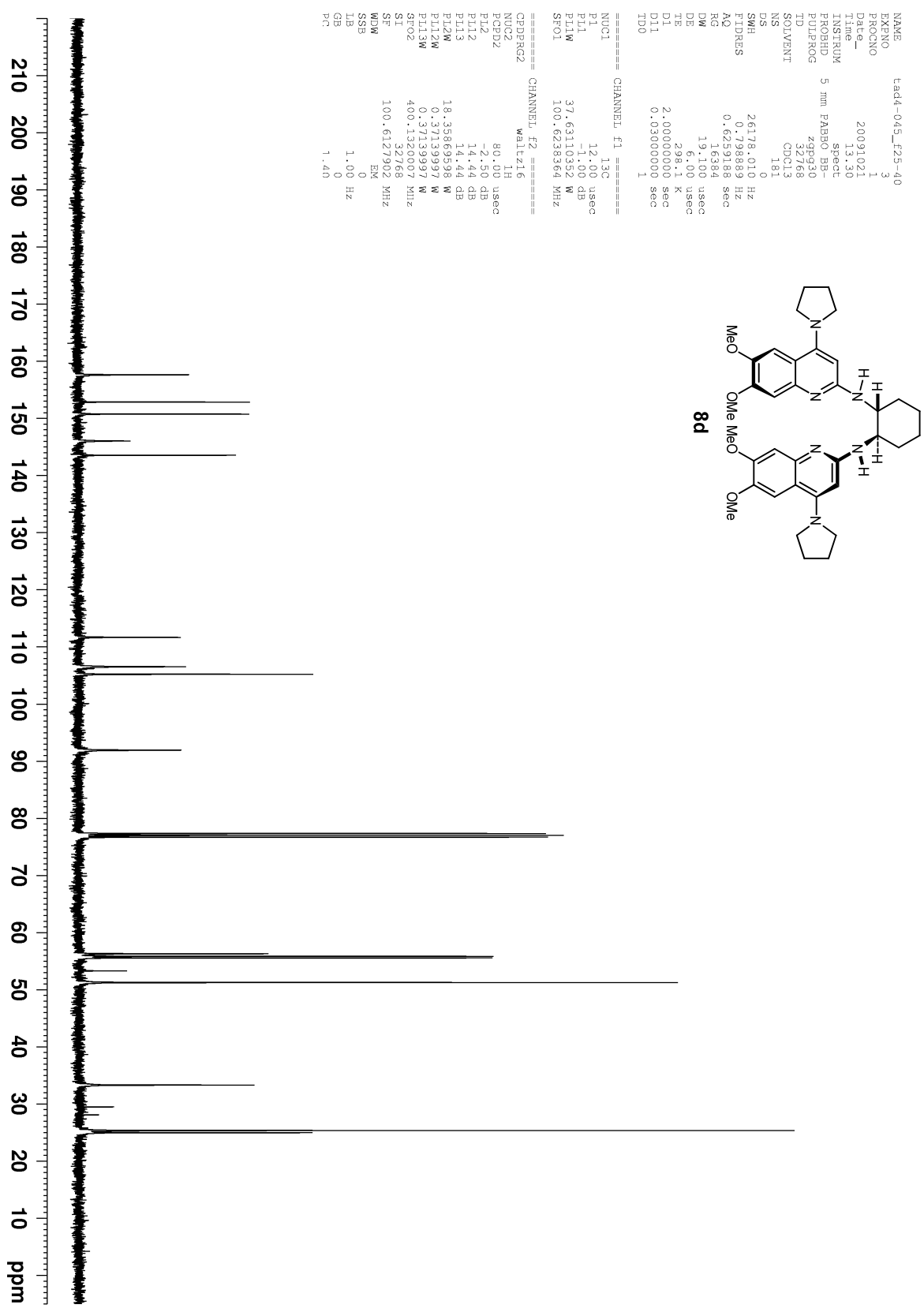


Figure 62. ^{1}H NMR (600 MHz, $CDCl_3$) of **17**

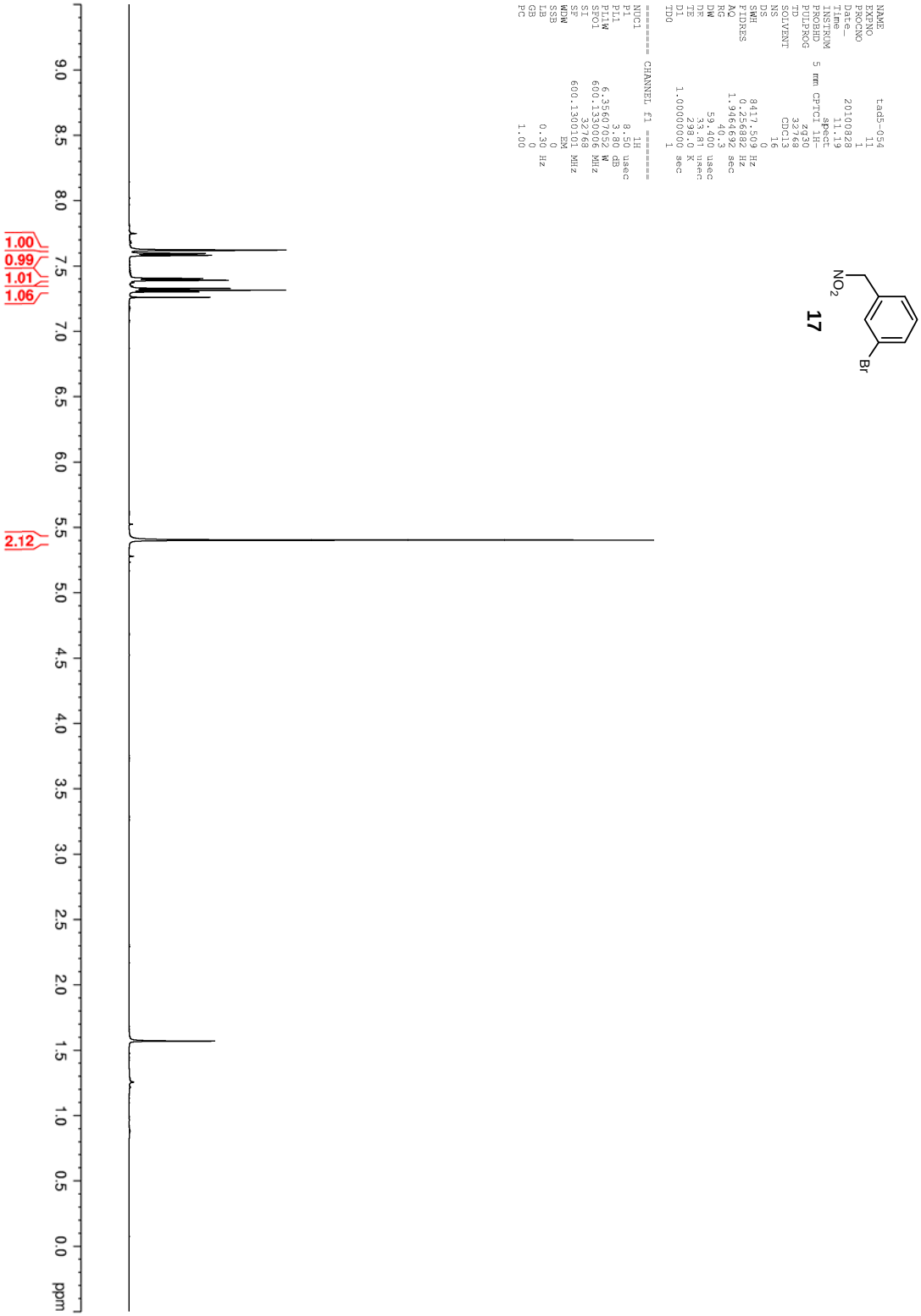


Figure 63. ^{13}C NMR (150 MHz, $CDCl_3$) of **17**

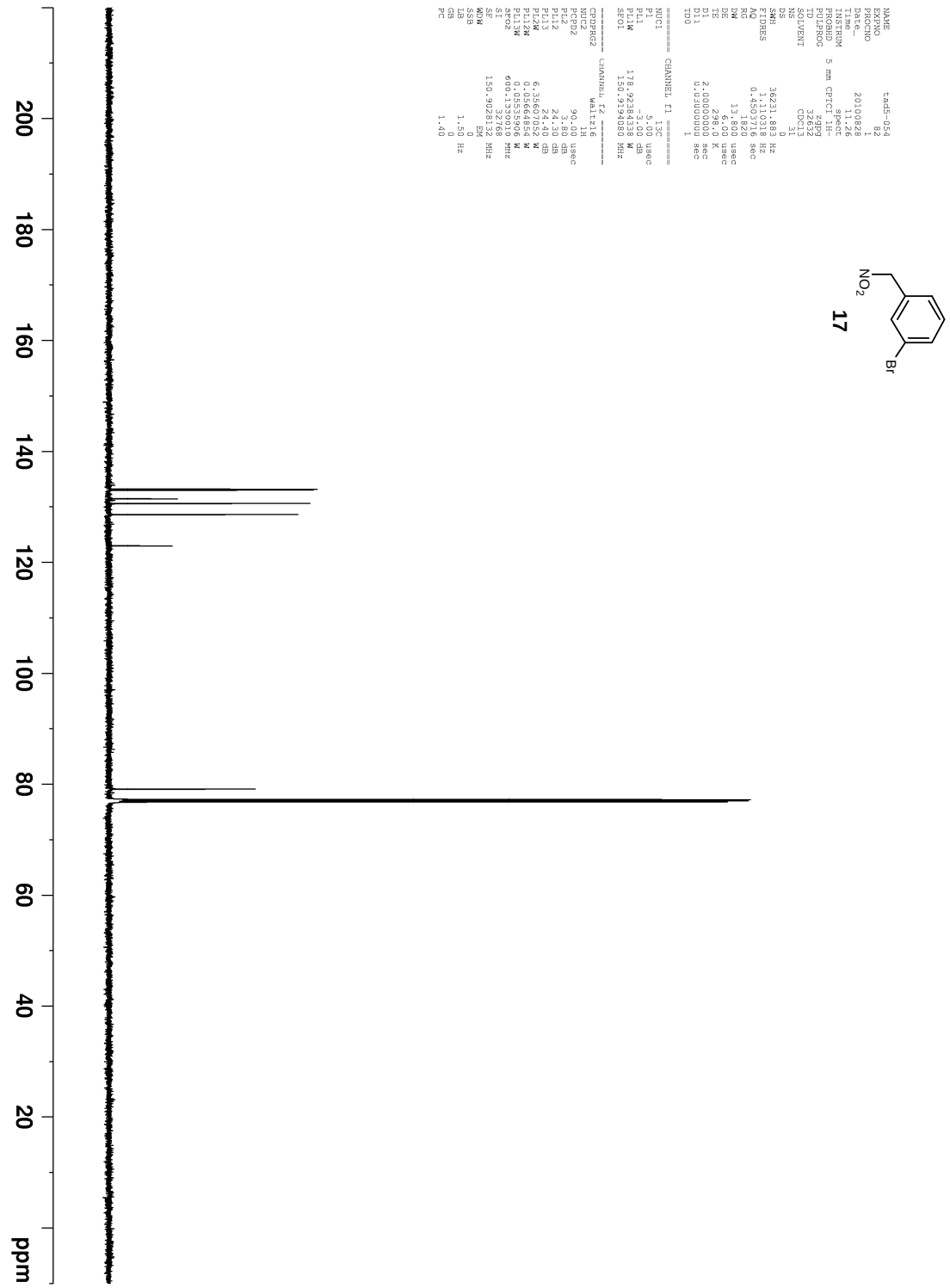


Figure 64. ^{1}H NMR (600 MHz, $CDCl_3$) of **18**

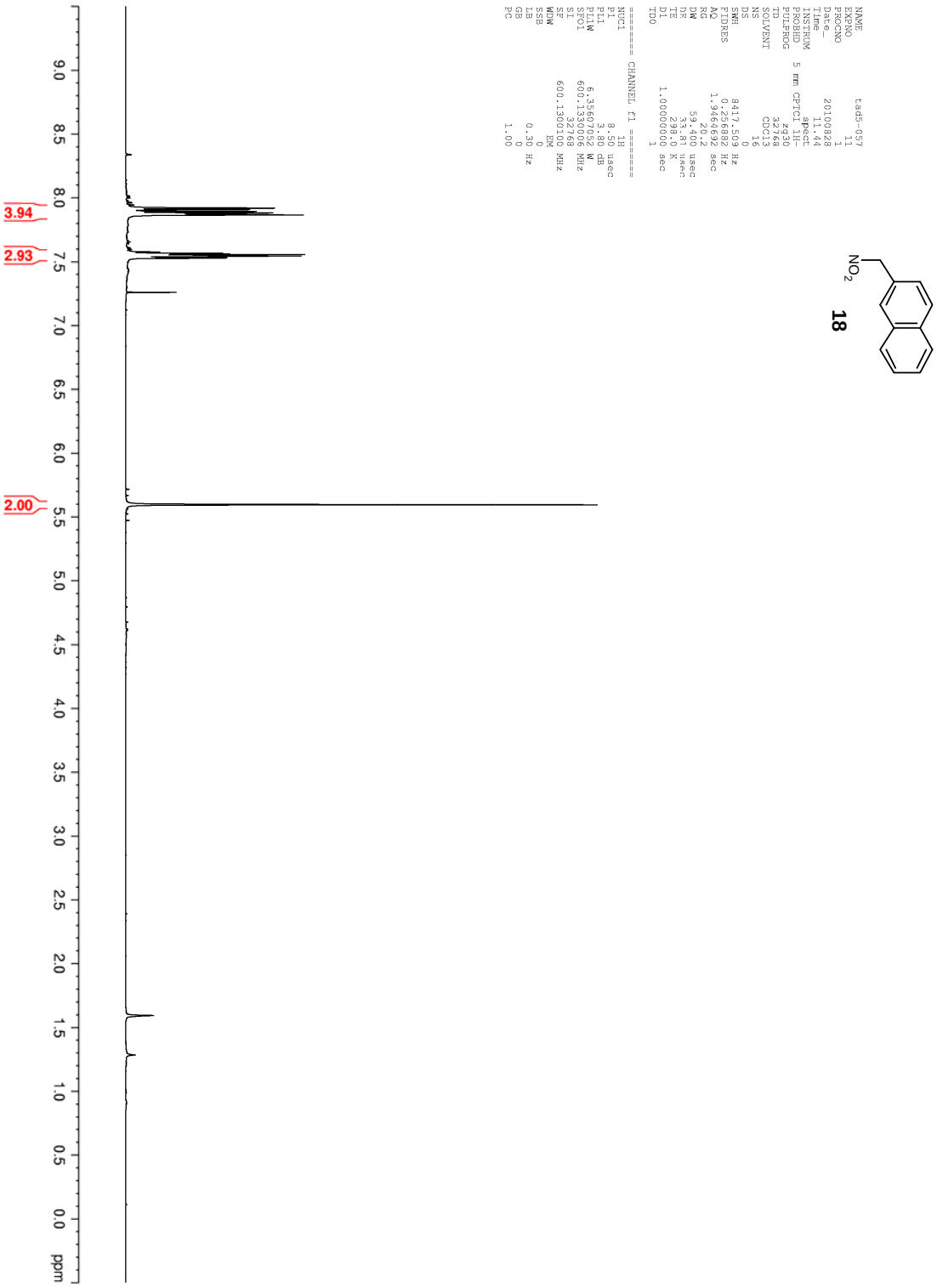


Figure 65. ^{13}C NMR (150 MHz, $CDCl_3$) of **18**

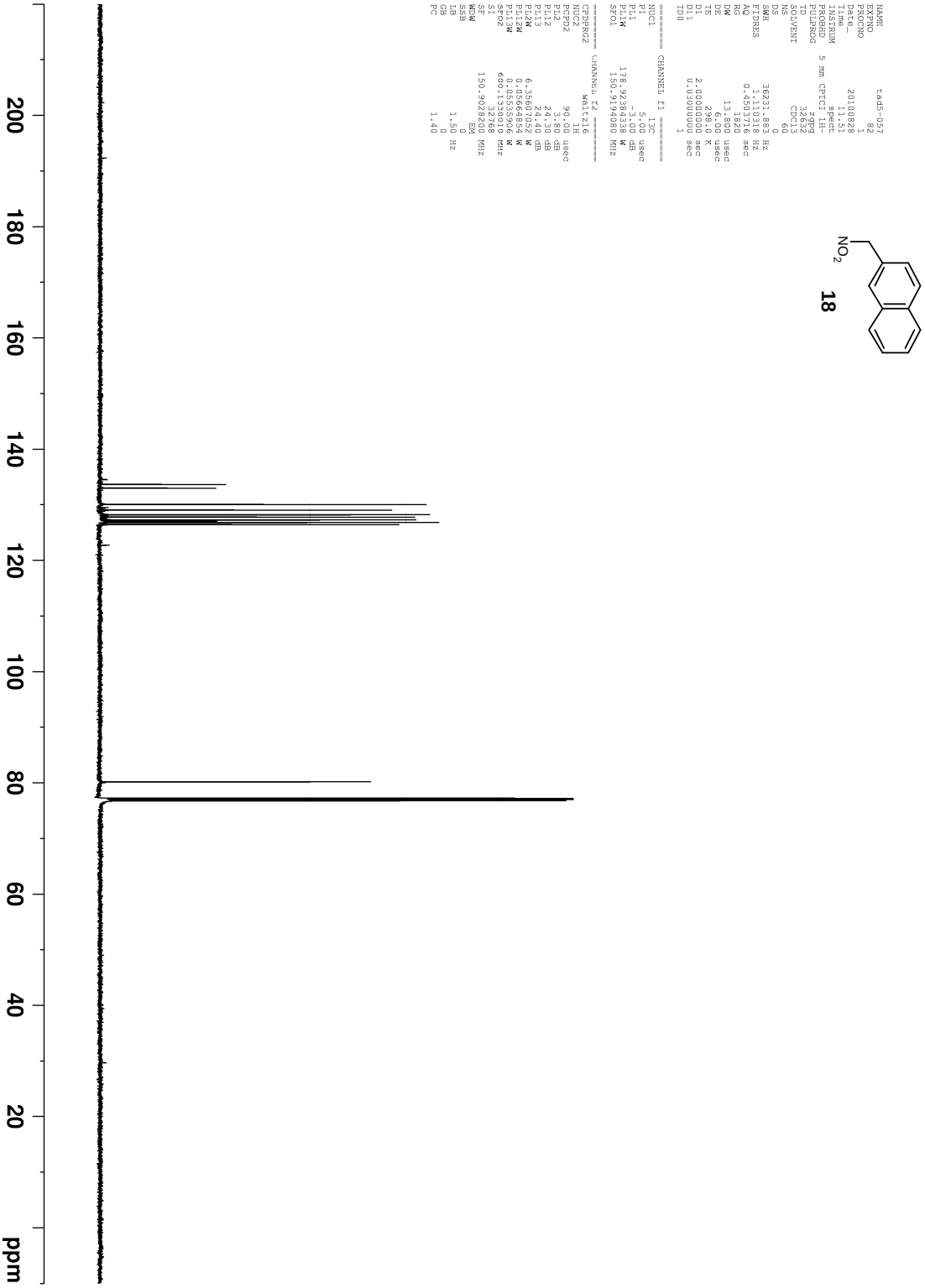


Figure 66. ^{1}H NMR (500 MHz, $CDCl_3$) of **21**

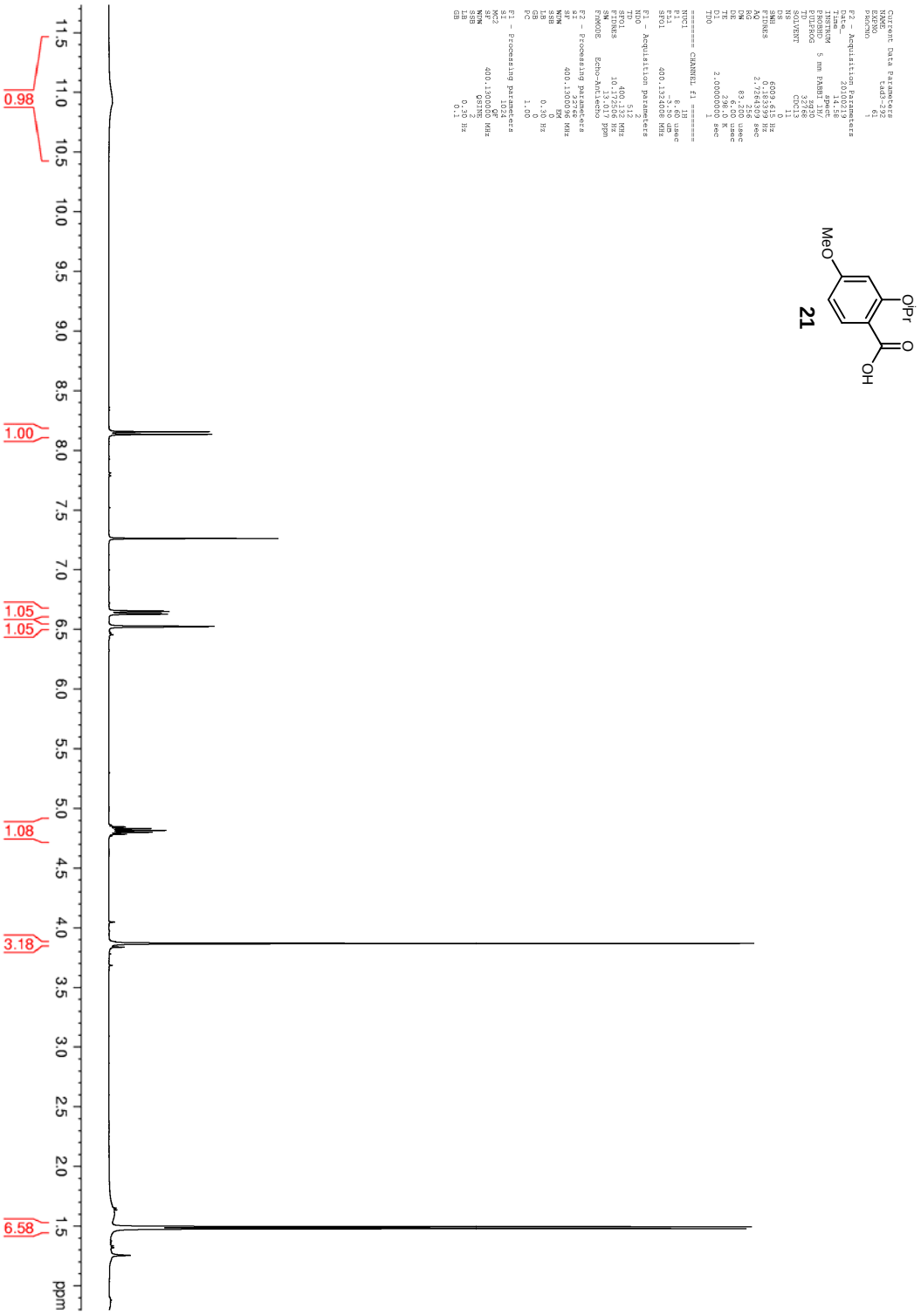


Figure 67. ^{13}C NMR (100 MHz, $CDCl_3$) of **21**

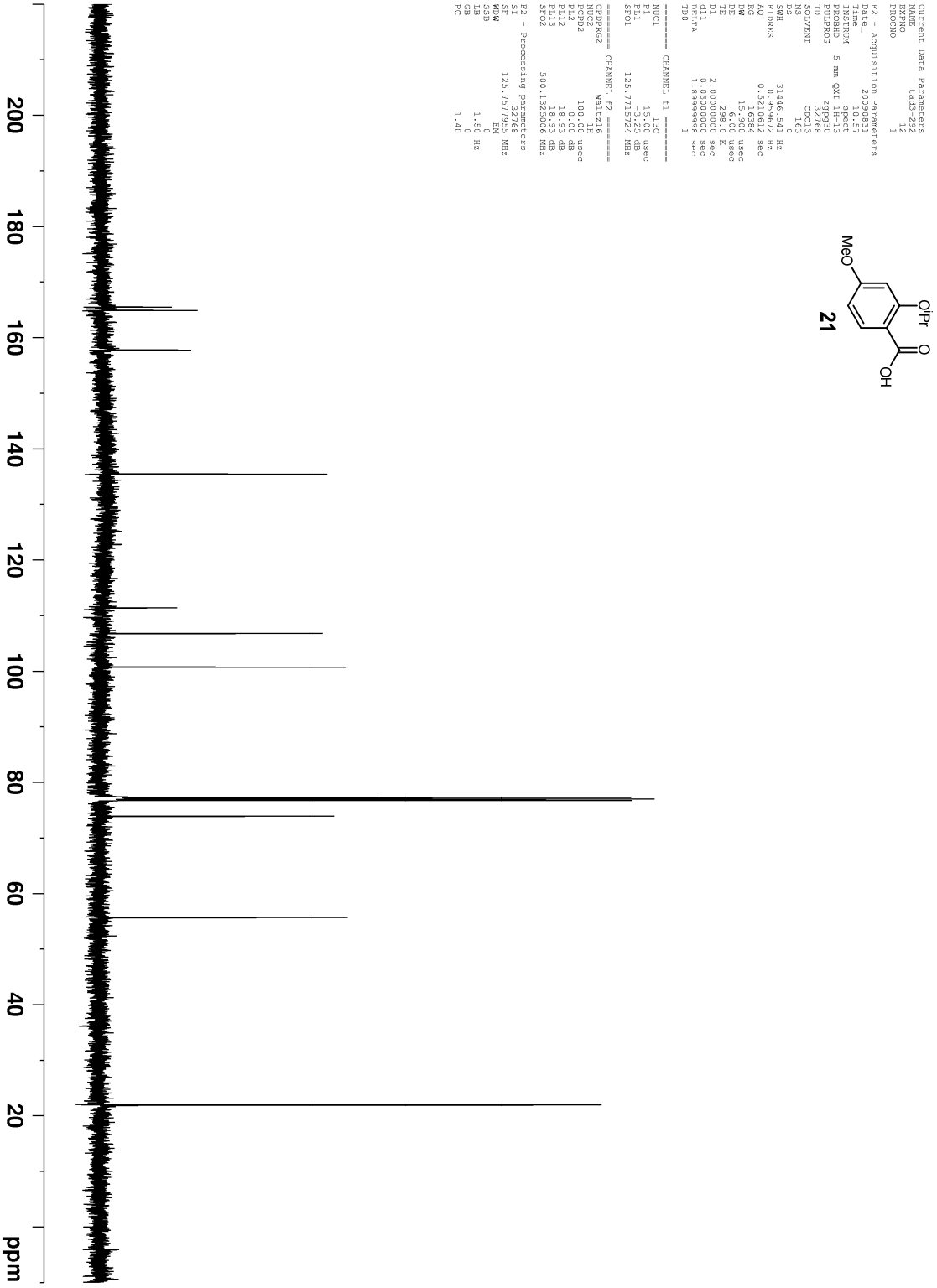


Figure 68. ^{1}H NMR (400 MHz, $CDCl_3$) of **22**

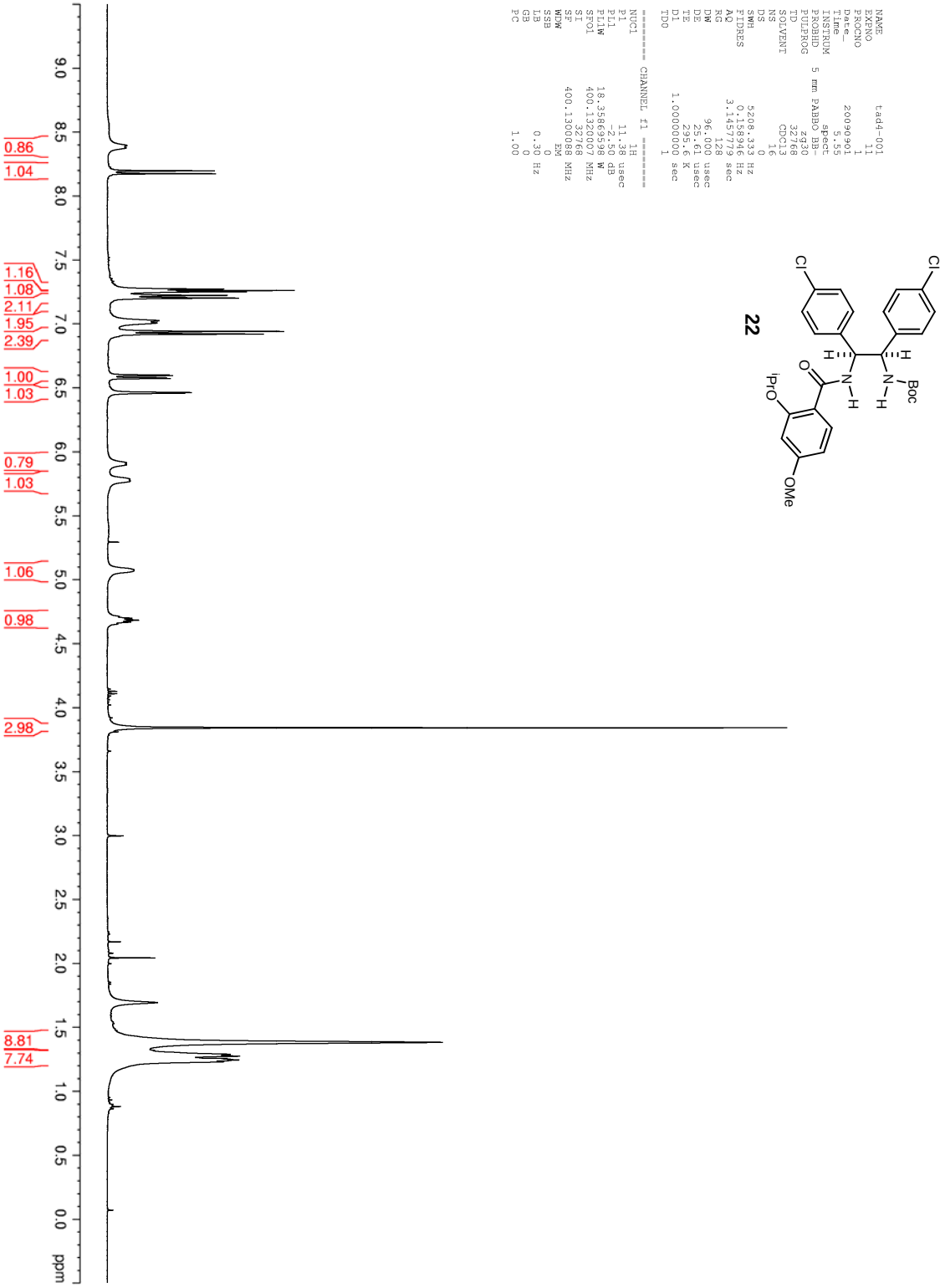


Figure 69. ^{13}C NMR (100 MHz, $CDCl_3$) of **22**

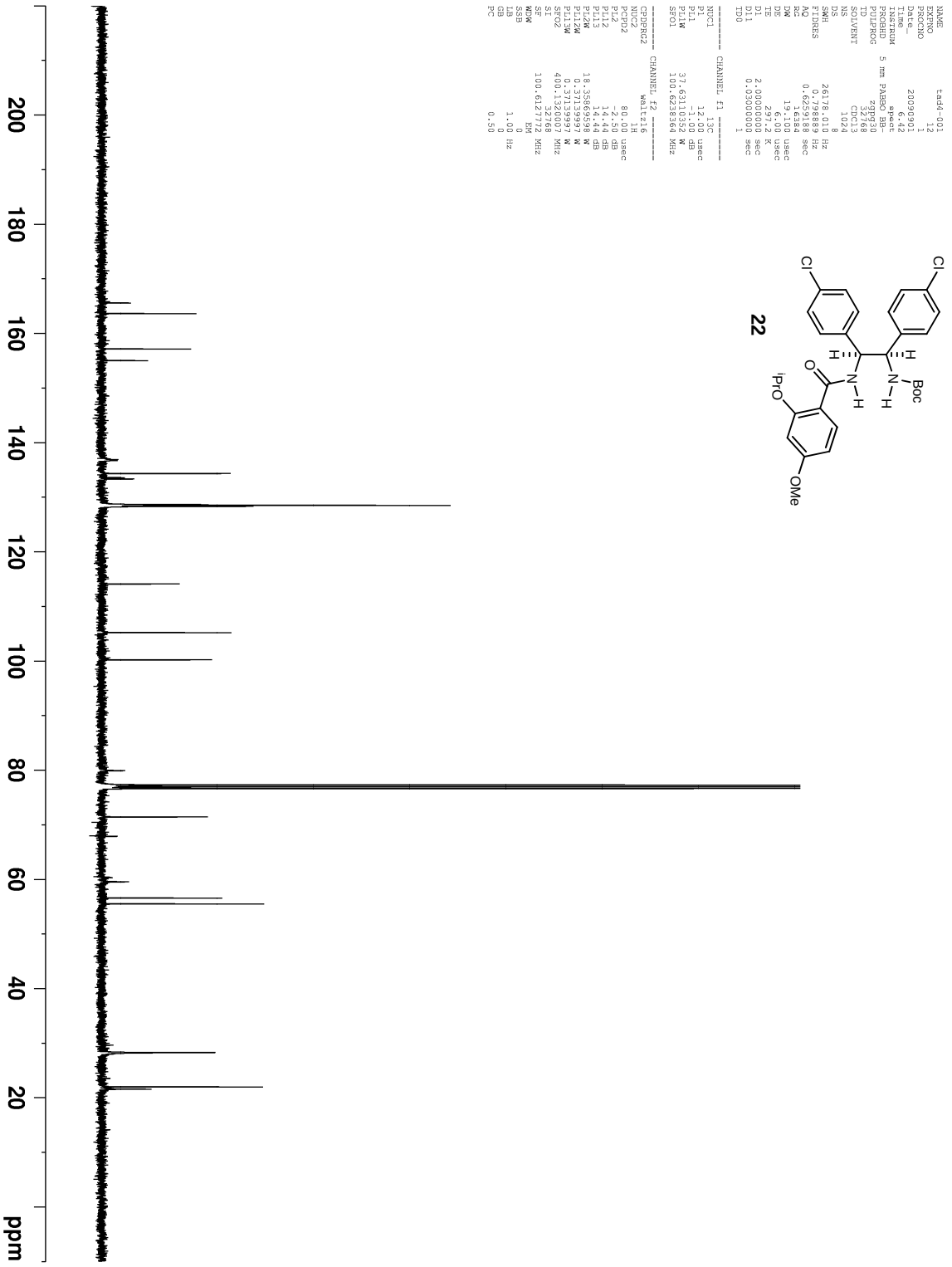


Figure 70. ^{1}H NMR (500 MHz, $CDCl_3$) of **23**

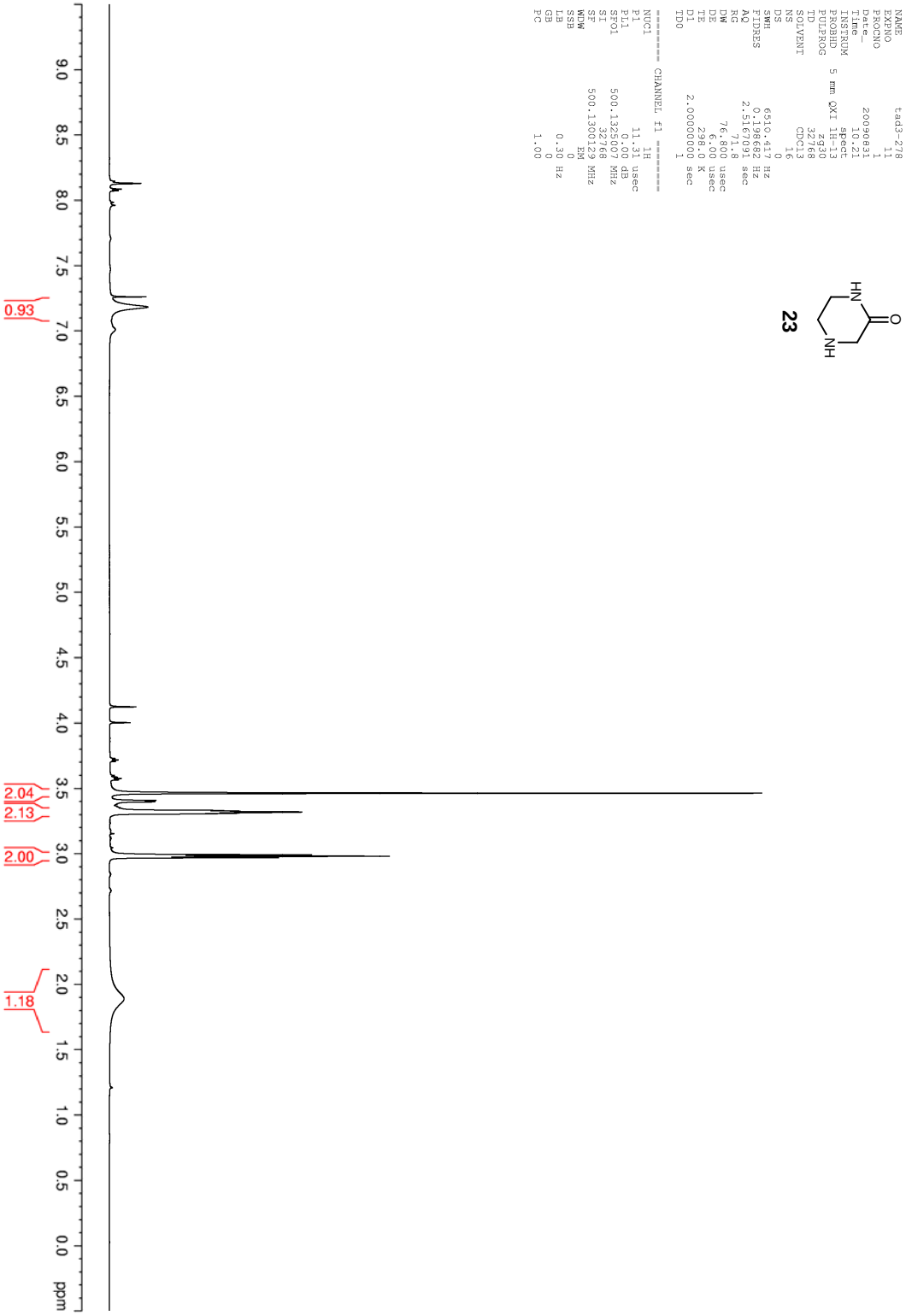


Figure 71. ^{13}C NMR (125 MHz, $CDCl_3$) of **23**