Cascade Palladium Catalysis: A Predictable and Selectable Regiocontrolled Synthesis of *N*-Arylbenzimidazoles

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Supporting Information

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I. General Information

I-A. General Reagent Information

All reactions were set up on the bench top and conducted under a nitrogen atmosphere. Flash chromatography was carried out using a Biotage Isolera 4 equipped with SNAP column cartridges packed with SiliaFlash® F60 silica gel obtained from Silicycle. Precatalyst **P1** was prepared according to a literature procedure.[S1] Amides and arylamines were purchased from Aldrich Chemical Co., Alfa Aesar, Acros Organics, or Oakwood Products and were used as received. 2,3-dichloropyridine and 3-bromo-4-chlorobenzotrifluoride were purchased from Aldrich Chemical Co. and were used as received. *O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (HBTU, 99%) and 4-bromo-3-chlorobenzoic acid were purchased from Oakwood Products and were used as received. 3-Bromo-4-chlorobenzoic acid was purchased from Matrix Scientific and was used as received. Anhydrous cesium carbonate (99% reagent grade) was purchased from Aldrich Chemical Co. and was stored in a nitrogen-filled glovebox. Prior to use, the base was finely ground using a mortar and pestle (inside the glovebox) and removed from the glovebox in ~10 g batches. When not in use, these vials of base were stored in a benchtop dessicator and their use in the described processes remained constant for up to one month. Anhydrous *tert*-butanol was purchased in Sure-Seal bottles from Aldrich Chemical Co. and was used as received.

I-B. General Analytical Information

Yields in table 1 refer to assay yields that were determined using gas chromatography with the exception of entry 8, where the isolated yield on a 1.0 mmol scale is also provided. Yields in tables 2 and 3 refer to isolated yields and reflect the average values of two independent runs on a 1.0 mmol scale. New compounds were characterized by NMR, IR spectroscopy, melting point, and elemental analysis or HRMS. NMR data were recorded on a Varian XL 500 MHz spectrometer and chemical shifts (δ) are internally referenced to residual protio solvent ($CDCl_3$: δ 7.26 ppm for ^1H NMR and 77.2 ppm). ^{13}C spectra were obtained with ^1H decoupling and copies of NMR spectra can be found at the end of the supporting information. Infrared (IR) spectra were obtained using a Thermo Scientific Nicolet iS5 FT-IR spectrometer equipped with an iD5 ATR Diamond plate. GC analyses were carried out on and Agilent 6890 gas chromatograph with

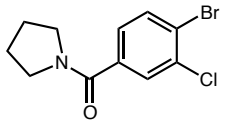
[S1] N. C. Bruno and S. L. Buchwald, *Org. Lett.*, **2013**, *15*, 2876–2879.

an FID detector using an Agilent J&W DB-200 column (30 m X 0.250 mm ID). Elemental analyses were carried out by Atlantic Microlabs Inc., Norcross, GA.

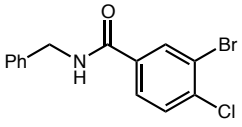
II. Experimental Procedures and Characterization Data

II-A. Starting Material Preparation:

Unless otherwise indicated, 2-Chloroaryl triflates were prepared according to literature procedures.[S2, S3]



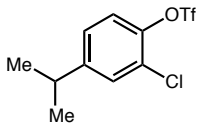
(4-bromo-3-chlorophenyl)(pyrrolidin-1-yl)methanone. A stirred solution of 4-bromo-3-chlorobenzoic acid (1.18 g, 5.0 mmol), *N,N*-diisopropylethylamine (1.30 mL, 7.5 mmol), HBTU (1.85 g, 5.0 mmol) and DMF (10 mL) was treated with pyrrolidine (0.50 mL, 6.0 mmol) and the resulting solution was stirred for 3 h at room temperature. The solution was diluted with EtOAc and washed sequentially with water, 1M HCl, 1M KOH, and brine and the organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 20-80% EtOAc/Hexanes) to afford the title compound as a white solid (1.1 g, 76%). Mp = 62–63 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 1H), 7.62 (s 1H), 7.3 (d, *J* = 8.2 Hz, 1H), 3.62 (t, *J* = 6.9 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 2H), 1.96 (p, *J* = 6.8 Hz, 2H), 1.89 (p, *J* = 6.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 137.7, 134.8, 133.8, 129.3, 126.7, 124.2, 49.7, 46.5, 26.5, 24.5. IR (neat, cm^{-1}): 1421, 1373, 1114, 1014, 926, 840, 750, 711. Anal Calcd. for $C_{11}H_{11}BrClNO$: C, 45.78; H, 3.84. Found: C, 45.53; H, 3.71.



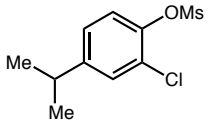
***N*-benzyl-3-bromo-4-chlorobenzamide.** A stirred solution of 3-bromo-4-chlorobenzoic acid (1.18 g, 5.0 mmol), *N,N*-diisopropylethylamine (1.30 mL, 7.5

[S2] J. Barluenga, A. Jiménez-Aquino, F. Aznar, C. Valdés, *J. Am. Chem. Soc.*, **2009**, *131*, 4031–4041.
[S3] W. Liu et. al., *J. Med. Chem.*, **2011**, *54*, 8541.

mmol), HBTU (1.85 g, 5.0 mmol) and DMF (10 mL) was treated with benzylamine (0.66 mL, 6.0 mmol) and the resulting solution was stirred for 3 h at room temperature. The solution was diluted with EtOAc and washed sequentially with water, 1M HCl, 1M KOH, and brine and the organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was recrystallized from EtOAc/hexanes to give the title compound as tan needles (990 mg, 61%). Mp = 120–121 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 2.1 Hz, 1H), 7.66 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.40-7.28 (m, 5H), 6.33 (bs, 1H), 4.63 (d, *J* = 5.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 138.2, 137.8, 134.3, 132.6, 130.7, 129.1, 128.2, 128.1, 127.0, 123.1, 44.6. IR (neat, cm^{-1}): 3260, 1629, 1589, 1541, 1495, 1454, 1368, 1023, 829. 742, 693, 656. Anal Calcd. for $C_{14}H_{11}BrClNO$: C, 51.80; H, 3.42. Found: C, 51.73; H, 3.30.



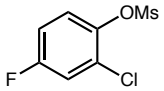
2-Chloro-4-isopropylphenyl triflate. To a solution of 2-chloro-4-isopropylphenol[S4] (640 mg, 3.75 mmol), pyridine (400 μL, 5.0 mmol), and CH_2Cl_2 (25 mL) at 0 °C was slowly added trifluoromethanesulfonic anhydride (670 μL, 4.0 mmol). The solution was allowed to warm to room temperature over the course of 1 h and quenched with 1M HCl (10 mL). The layers were separated, organic layer dried (Na_2SO_4), filtered, and concentrated using a rotary evaporator. The crude product was purified by passing the residue through a short plug of silica (hexanes eluent) to afford the title compound as a clear colorless oil (1.1 g, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 2.2 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.18 (dd, *J* = 8.5, 2.2 Hz, 1H), 2.93 (hept, *J* = 6.9 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8, 143.7, 129.3, 126.6, 122.9, 120.1, 117.5, 33.9, 23.9. IR (neat, cm^{-1}): 1485, 1426, 1205, 1134, 1048, 910, 829, 814, 618. Anal Calcd. for $C_{10}H_{10}ClF_3O_3S$: C, 39.68; H, 3.33. Found: C, 39.94; H, 3.88.



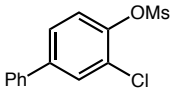
2-Chloro-4-isopropylphenyl mesylate. To a solution of 2-chloro-4-isopropylphenol[S4] (853 mg, 5.0 mmol), triethylamine (1.03 mL, 7.5 mmol), and CH_2Cl_2 (25 mL) at room temperature was slowly added methanesulfonyl chloride (430 μL, 5.5 mmol). The solution was stirred for 1 h and quenched with 1M HCl (10 mL). The layers were separated, organic layer dried (Na_2SO_4), filtered, and concentrated using a rotary evaporator. The crude product was purified using a

[S4] H. Koyama et. al., *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3347.

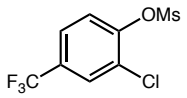
Biotage Isolera 4 (silica-packed 25 g SNAP column, 10% EtOAc/Hexanes) to afford the title compound as a clear colorless oil (1.1 g, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 2.2 Hz, 1H), 7.16 (dd, *J* = 8.5, 2.2 Hz, 1H), 3.23 (s, 3H), 2.90 (hept, *J* = 6.9 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.7, 143.3, 128.9, 127.6, 126.5, 124.5, 38.7, 33.8, 23.9. IR (neat, cm^{-1}): 1486, 1368, 1222, 1171, 1052, 968, 893, 806, 622. Anal Calcd. for $C_{10}H_{13}ClO_3S$: C, 48.29; H, 5.27. Found: C, 48.48; H, 5.27.



2-Chloro-4-fluorophenyl mesylate. To a solution of 2-chloro-4-fluorophenol (547 μL, 5.0 mmol), pyridine (533 μL, 6.0 mmol), and CH_2Cl_2 (25 mL) at room temperature was slowly added methanesulfonyl chloride (390 μL, 5.0 mmol). The solution was stirred for 1 h and quenched with 1M HCl (10 mL). The layers were separated, organic layer dried (Na_2SO_4), filtered, and concentrated using a rotary evaporator. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 10–30% EtOAc/Hexanes) to afford the title compound as a colorless solid (0.9 g, 81%). Mp = 45–46 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 9.1, 5.1 Hz, 1H), 7.24 (dd, *J* = 7.8, 3.0 Hz, 1H), 7.05 (ddd, *J* = 9.2, 7.5, 3.0 Hz, 2H), 3.25 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.8 (d, *J* = 250.7 Hz), 141.7 (d, *J* = 3.6 Hz), 128.1 (d, *J* = 10.8 Hz), 125.8 (d, *J* = 9.3 Hz), 118.3 (d, *J* = 26.3 Hz), 115.5 (d, *J* = 23.1 Hz), 38.8. IR (neat, cm^{-1}): 1479, 1458, 1359, 1338, 1192, 1158, 971, 843, 822, 777, 669. HRMS (DART) Calcd. for $C_7H_{10}ClFNO_3S$ $[M+NH_4]^+$ 242.0048. Found: 242.0041.



3-Chloro-[1,1'-biphenyl]-4-yl mesylate. To a solution of 3-chloro-[1,1'-biphenyl]-4-ol (1.8 g, 8.8 mmol), triethylamine (2.1 mL, 15.0 mmol), and CH_2Cl_2 (50 mL) was slowly added methanesulfonyl chloride (880 μL, 10.8 mmol). The solution was stirred for 1 h and quenched with 1M HCl (20 mL). The layers were separated, organic layer dried (Na_2SO_4), filtered, and concentrated using a rotary evaporator. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 10–20% EtOAc/Hexanes) to afford the title compound as a colorless solid (2.35 g, 94%). Mp = 86–88 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (ddd, *J* = 1.0, 0.4 Hz, 1H), 7.56- 7.51 (m, 4H), 7.49-7.44 (m, 2H), 7.42- 7.38 (m, 1H), 3.28 (d, *J* = 0.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) 144.5, 141.9, 138.7, 129.5, 129.2, 128.5, 127.3, 127.2, 127.0, 124.9, 38.9. IR (neat, cm^{-1}): 1478, 1350, 1332, 1220, 1171, 1056, 977, 857, 834, 809, 766, 701, 676. Anal Calcd. for $C_{13}H_{11}ClO_3S$: C, 55.22; H, 3.92. Found: C, 55.02; H, 3.89.



2-Chloro-4-(trifluoromethyl)phenyl methanesulfonate. 2-chloro-4-fluorophenol (669 μL, 5.0 mmol), triethylamine (1.0 mL, 7.5 mmol), and CH_2Cl_2 (25 mL) was slowly added methanesulfonyl chloride (430 μL, 5.5 mmol). The solution was stirred for 1 h and quenched with 1M HCl (10 mL). The layers were separated, organic layer dried (Na_2SO_4), filtered, and concentrated using a rotary evaporator. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 10% EtOAc/Hexanes) to afford the title compound as a clear colorless oil (1.26 g, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dt, J = 1.8, 0.9 Hz, 1H), 7.64-7.55 (m, 2H), 3.30 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8 (q, J = 1.4 Hz), 130.7 (q, J = 34.2 Hz), 128.4 (q, J = 3.8 Hz), 128.0 , 125.6 (q, J = 3.7 Hz), 125.21, 122.97 (q, J = 272.7 Hz), 39.29. IR (neat, cm^{-1}): 1376, 1318, 1173, 1126, 1079, 1060, 969, 878, 838, 810, 714, 680. Anal Calcd. for $C_8H_6ClF_3O_3S$: C, 34.99; H, 2.20. Found: C, 35.12; H, 2.08.

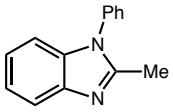
II-B. General Procedures for Benzimidazole Synthesis

General procedure A for benzimidazole synthesis. An oven-dried test tube equipped with a magnetic stir bar and a Teflon screw-cap was charged with tBuBrettPhos precatalyst (**P1**, 2–5 mol%, as indicated), arylamine (1.0 mmol, if solid), amide (1.3 mmol, if solid), 2-chloroaryl triflate or 2-chloroaryl bromide (1.0 mmol, if solid), and Cs_2CO_3 (2.4 mmol). The tube was evacuated and backfilled with nitrogen using standard Schlenk techniques and this process was conducted three times. The arylamine (1.0 mmol, if liquid), amide (1.3 mmol, if liquid) and 2-chloroaryl triflate or 2-chloroaryl bromide (1.0 mmol, if liquid) were added followed by *t*-BuOH (1.5 mL) via syringe and the punctured cap was replaced with a new one under a stream of nitrogen. The test tube was placed in a preheated oil bath at 110 °C and stirred for the indicated time. After cooling to room temperature, the mixture was diluted (3 mL CH_2Cl_2), filtered through Celite (CH_2Cl_2 rinse), and concentrated using a rotary evaporator. The residue was purified by silica gel chromatography using a Biotage Isolera 4 or by neutral alumina column chromatography to provide the title compound.

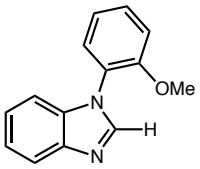
General procedure B for Benzimidazole synthesis (two-stage heating). The reaction was conducted exactly as in general procedure A with the following exception: after adding all of the reagents and replacing the screw cap, the test tube was placed in a preheated oil bath at 45 °C and stirred for 1 h before it was transferred to a second preheated oil bath at 110 °C where it was stirred for the indicated time. Upon completion, the reaction mixture was manipulated exactly as described in general procedure A.

II-C. Experimental Procedures and Characterization Data

Procedure for Table 1 (Ligand Screen). Ten separate reactions were set up according to general procedure A, wherein mixtures each containing 2-chlorophenyl triflate (87 μL, 0.5 mmol), aniline (46 μL, 0.5 mmol), acetamide (38 mg, 0.65 mmol), tetradecane (50 μL, internal standard), $(allylPdCl)_2$ (1.8 mg, 0.005 mmol), the indicated ligand (0.015 mmol), and Cs_2CO_3 (391 mg, 1.2 mmol) in *t*-BuOH (1.0 mmol) were stirred at 110 °C for 12 h. After cooling to room temperature, the crude mixtures were diluted (2 mL EtOAc each) and aliquots were filtered through silica and analyzed by GC.



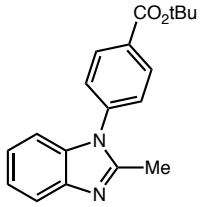
2-methyl-1-phenyl-1*H*-benzo[*d*]imidazole (Table 1, entry 8). According to general procedure A, a mixture of 2-chlorophenyl triflate (174 μL, 1.0 mmo), aniline (91 μL, 1.0 mmol), acetamide (77 mg, 1.3 mmol), **P1** (17 mg, 0.02 mmol), and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mmol) was stirred at 110 °C for 12 h. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 20-75% EtOAc/Hexanes) to afford the title compound as a tan solid (179 mg, 86%). The spectroscopic data for this compound were in complete accord with previously reported values.[S5]



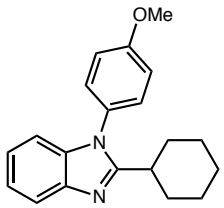
1-(2-Methoxyphenyl)-1*H*-benzo[*d*]imidazole (Table 2, 4a). According to general procedure B, a mixture of 2-chlorophenyl triflate (174 μL, 1.0 mmol), *o*-anisidine (113 μL, 1.0 mmol), formamide (53 μL, 1.3 mmol), **P1** (17 mg, 0.02 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 1 h at 45 °C then for 12 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 20-80% EtOAc/Hexanes) to afford the title compound as an amber oil (run 1: 161 mg (72%); run 2: 183 mg (82%); average yield: 77%). The spectroscopic data for this compound were in complete accord with previously reported values.[S6]

[S5] C. T. Brain and J. T. Steer, *J. Org. Chem.* 2003, **68**, 6814.

[S6] L. Liu, M. Frohn, N. Xi, C. Dominguez, R. Hungate and P. J. Reider, *J. Org. Chem.* 2005, **70**, 10135.

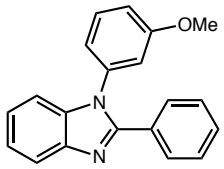


***Tert*-butyl 4-(2-methyl-1*H*-benzo[*d*]imidazol-1-yl)benzoate (Table 2, 4b).** According to general procedure A, a mixture of 2-chlorophenyl triflate (174 μL, 1.0 mmol), *tert*-butyl 4-aminobenzoate (193 mg, 1.0 mmol), acetamide (77 mg, 1.3 mmol), **P1** (17 mg, 0.02 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 12 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 20-80% EtOAc/Hexanes) to afford the title compound as a tan solid (run 1: 238 mg (77%); run 2: 220 mg (72%); average yield: 74%). Mp = 107–109 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.70 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.23 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.16 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.09 (ddd, *J* = 8.1, 1.3, 0.7 Hz, 1H), 2.48 (s, 3H), 1.61 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 151.1, 142.7, 139.6, 136.0, 132.2, 131.2, 126.7, 122.9, 122.7, 119.2, 109.8, 81.8, 28.2, 14.6. IR (neat, cm^{-1}): 1710, 1606, 1513, 1391, 1364, 1297, 1283, 1248, 1166, 1116, 1101, 1015, 765, 731, 704. Anal Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54. Found: C, 73.84; H, 6.58.

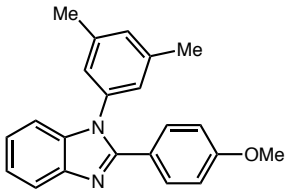


2-Cyclohexyl-1-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole (Table 2, 4c). According to general procedure A, a mixture of 2-chlorophenyl triflate (174 μL, 1.0 mmol), *p*-anisidine (123 mg, 1.0 mmol), cyclohexane carboxamide (165 mg, 1.3 mmol), **P1** (17 mg, 0.02 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 12 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 10-35% EtOAc/Hexanes) to afford the title compound as a white solid (run 1: 246 mg (80%); run 2: 233 mg (76%); average yield: 78%). Mp = 133–134 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1, 1H), 7.29-7.23 (m, 3H), 7.17 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 1H), 3.92 (s, 3H), 2.73-2.62 (m, 1H), 1.95-1.75 (m, 5H), 1.72-1.64 (m, 1H), 1.37-1.14 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 159.7, 142.6, 136.9, 128.9, 128.6, 122.4, 122.2, 119.2, 115.1, 110.1, 55.7,

36.3, 32.1, 26.3, 25.8. IR (neat, cm^{-1}): 1508, 1459, 1270, 1244, 1181, 1022, 844, 830, 750. Anal Calcd. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24. Found: C, 78.15; H, 7.16.

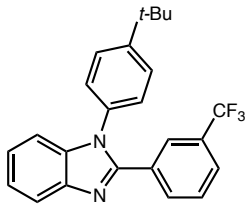


1-(3-Methoxyphenyl)-2-phenyl-1*H*-benzo[*d*]imidazole (Table 2, 4d). According to general procedure A, a mixture of 2-chlorophenyl triflate (174 μL, 1.0 mmol), *m*-anisidine (112 μL, 1.0 mmol), benzamide (157 mg, 1.3 mmol), **P1** (34 mg, 0.04 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 12 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 5-35% EtOAc/Hexanes) to afford the title compound as a white solid (run 1: 249 mg (83%); run 2: 246 mg (82%); average yield: 83%). Mp = 120–122 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.1 Hz, 1H), 7.63-7.60 (m, 2H), 7.42-7.25 (m, 7H), 7.00 (ddd, J = 8.4, 2.5, 0.9 Hz, 1H), 6.89 (ddd, J = 7.8, 2.0, 0.9 Hz, 1H), 6.86 (t, J = 2.2 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.7, 152.4, 143.1, 138.1, 137.3, 130.7, 130.1, 129.6, 129.5, 128.4, 123.5, 123.1, 120.0, 119.7, 114.4, 113.1, 110.7, 55.6. IR (neat, cm^{-1}): 1606, 1582, 1474, 1440, 1377, 1287, 1265, 1232, 1172, 1047, 861, 772, 742, 701. Anal Calcd. for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37. Found: C, 79.76; H, 5.41.

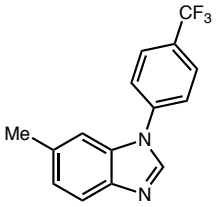


1-(3,5-Dimethylphenyl)-2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole (Table 2, 4e). According to general procedure A, a mixture of 2-chlorophenyl triflate (174 μL, 1.0 mmol), 3,5-dimethylaniline (125 μL, 1.0 mmol), 4-methoxybenzamide (197 mg, 1.3 mmol), **P1** (17 mg, 0.02 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 12 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 2-20% EtOAc/Hexanes) to afford the title compound as a tan solid (run 1: 282 mg (86%); run 2: 277 mg (84%); average yield: 85%). Mp = 161–162 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.9 Hz, 2H), 7.32 (t, J = 8.1 Hz, 1H), 7.24 (td, J = 7.5, 7.0, 1.1 Hz, 1H), 7.20 (d, J = 8.1 Hz, 1H), 7.11 (s, 1H), 6.94 (s, 2H), 6.84 (d, J = 8.9 Hz, 2H), 3.82 (s, 3H), 2.36 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 152.4, 143.1, 139.8, 137.6, 137.1, 130.9, 130.4, 125.2, 122.9, 122.8, 122.6, 119.5, 113.8, 110.6, 55.4, 21.4. IR (neat, cm^{-1}): 1606, 1474, 1455,

1440, 1415, 1353, 1250, 1173, 1028, 869, 839, 786, 723, 706. Anal Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14. Found: C, 80.42; H, 6.12.

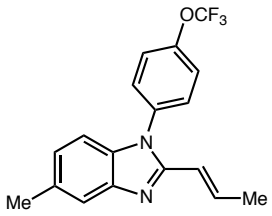


1-(4-(*Tert*-butyl)phenyl)-2-(3-(trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazole (Table 2, 4f). According to general procedure A, a mixture of 2-chlorophenyl triflate (174 μL, 1.0 mmol), 4-*tert*-butylaniline (159 μL, 1.0 mmol), 3-(trifluoromethyl)benzamide (246 mg, 1.3 mmol), **P1** (43 mg, 0.05 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 12 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 2-20% EtOAc/Hexanes) to afford the title compound as a white solid (run 1: 276 mg (70%); run 2: 302 mg (77%); average yield: 73%). Mp = 121–123 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.70 (s, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.54 (d, J = 8.3 Hz, 2H), 7.45 (t, J = 7.9 Hz, 1H), 7.36 (dt, J = 8.1, 4.2 Hz, 1H), 7.32-7.29 (m, 2H), 7.23 (d, J = 8.3 Hz, 2H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 151.4, 143.5, 138.1, 134.4, 133.3 (q, J = 1.1 Hz), 131.5, 131.3 (q, J = 32.5 Hz), 129.6, 127.7, 127.6, 126.8 (q, J = 4.0 Hz), 126.6 (q, J = 3.7 Hz), 126.4 (q, J = 272.7 Hz), 124.5, 123.9, 120.7, 111.5, 35.6, 32.0. IR (neat, cm^{-1}): 1411, 1393, 1337, 1277, 1163, 1122, 1112, 1072, 692. Anal Calcd. for $C_{24}H_{21}F_3N_2$: C, 73.08; H, 5.37. Found: C, 72.82; H, 5.41.

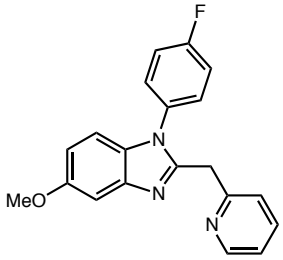


6-Methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazole (Table 2, 4g). According to general procedure B, a mixture of 2-chloro-5-methylphenyl triflate (196 μL, 1.0 mmol), 4-(trifluoromethyl)aniline (124 μL, 1.0 mmol), formamide (53 μL, 1.3 mmol), **P1** (17 mg, 0.02 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 1 h at 45 °C then for 12 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 20-80% EtOAc/Hexanes) to afford the title compound as a yellow solid (run 1: 215 mg (78%); run 2: 198 mg (72%); average yield: 75%). Mp = 95–97 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.35 (s, 1H), 7.19 (d, J = 8.1 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.0, 142.1, 140.2 (q, J = 1.3 Hz), 135.1,

134.1, 130.5 (q, J = 33.1 Hz), 128.1 (q, J = 3.7 Hz), 125.6, 125.4 (q, J = 272.7 Hz), 124.6, 121.1, 110.8, 22.6. IR (neat, cm^{-1}): 1615, 1498, 1323, 1295, 1241, 1197, 1162, 1107, 1066, 1017, 841, 805, 781. Anal Calcd. for $C_{15}H_{11}F_3N_2$: C, 65.21; H, 4.01. Found: C, 65.33; H, 4.11.

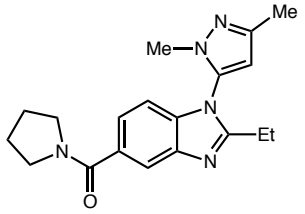


(*E*)-5-Methyl-2-(prop-1-en-1-yl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-benzo[*d*]imidazole (Table 2, 4h). According to general procedure A, a mixture of 2-chloro-4-methylphenyl triflate (196 μL, 1.0 mmol), 4-(trifluoromethoxy)aniline (134 μL, 1.0 mmol), crotonamide (111 mg, 1.3 mmol), **P1** (26 mg, 0.03 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 12 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 20-80% EtOAc/Hexanes) to afford the title compound as a white solid (run 1: 219 mg (66%); run 2: 220 mg (66%); average yield: 66%). Mp = 124–126 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.46-7.39 (m, 4H), 7.10 (dq, J = 15.5, 6.9 Hz, 1H), 7.05-6.98 (m, 2H), 6.17 (dq, J = 15.5, 1.7 Hz, 1H), 2.48 (s, 3H), 1.91 (dd, J = 6.9, 1.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8, 149.1, 143.4, 136.8, 134.5, 134.4, 133.0, 129.1, 124.6, 122.4 (2C), 119.3, 117.7, 109.4, 21.7, 19.0. IR (neat, cm^{-1}): 1509, 1247, 1219, 1162, 1132, 1018, 1031, 958, 861, 795. Anal Calcd. for $C_{18}H_{15}F_3N_2O$: C, 65.06; H, 4.55. Found: C, 65.09; H, 4.51.

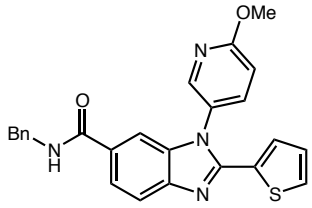


1-(4-Fluorophenyl)-5-methoxy-2-(pyridin-2-ylmethyl)-1*H*-benzo[*d*]imidazole (Table 2, 4i). According to general procedure B, a mixture of 2-chloro-4-methoxyphenyl triflate (291 mg, 1.0 mmol), 4-fluoroaniline (95 μL, 1.0 mmol), 2-pyridineacetamide (177 mg, 1.3 mmol), **P1** (34 mg, 0.04 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 1 h at 45 °C then for 12 h at 110 °C. The crude product was purified via column chromatography using neutral alumina as stationary phase (30-100% EtOAc/hexanes) to afford the title compound as a tan solid (run 1: 249 mg (75%); run 2: 254 mg (76%); average yield: 76%). Mp = 139–140 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (ddd, J = 4.8,

1.9, 0.9 Hz, 1H), 7.55 (td, *J* = 7.7, 1.9 Hz, 1H), 7.30-7.25 (m, 3H), 7.20 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.18-7.12 (m, 2H), 7.09 (ddd, *J* = 7.5, 5.0, 1.2 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.32 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5 (d, *J* = 249.3 Hz), 157.0, 156.5, 152.6, 149.5, 143.5, 136.7, 131.9 (d, *J* = 3.3 Hz), 131.5, 129.4 (d, *J* = 8.8 Hz), 123.3, 121.9, 116.8 (d, *J* = 22.9 Hz), 112.9, 110.5, 102.1, 56.0, 37.1. IR (neat, cm^{-1}): 1511, 1474, 1459, 1434, 1227, 1191, 1150, 1132, 1009, 842, 819, 796, 783, 753. Anal Calcd. for $C_{20}H_{16}FN_3O$: C, 72.06; H, 4.84. Found: C, 71.84; H, 4.74.

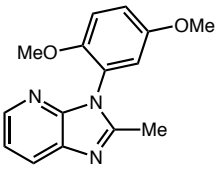


(1-(1,3-Dimethyl-1*H*-pyrazol-5-yl)-2-ethyl-1*H*-benzo[*d*]imidazol-5-yl)(pyrrolidin-1-yl)methanone (Table 2, 4j). According to general procedure A, a mixture of (4-bromo-3-chlorophenyl)(pyrrolidin-1-yl)methanone (289 mg, 1.0 mmol), 5-amino-1,3-dimethylpyrazole (111 mg, 1.0 mmol), propionamide (95 mg, 1.3 mmol), **P1** (43 mg, 0.05 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 12 h at 110 °C. The crude product was purified via column chromatography using neutral alumina as stationary phase (0-5% MeOH/EtOAc) to afford the title compound as a colorless solid (run 1: 190 mg (56%); run 2: 172 mg (51%); average yield: 54%). Mp = 142–144°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.49 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.04 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.17 (s, 1H), 3.67 (t, *J* = 7.0 Hz, 2H), 3.53-3.44 (m, 5H), 2.72 (qd, *J* = 7.5, 3.2 Hz, 2H), 2.35 (s, 3H), 1.97 (p, *J* = 7.0 Hz, 2H), 1.87 (p, *J* = 6.8 Hz, 2H), 1.36 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 158.7, 149.2, 142.6, 137.6, 134.1, 133.1, 124.1, 119.3, 110.4, 104.5, 50.6, 47.0, 35.9, 27.2, 25.2, 21.8, 14.8, 12.3. IR (neat, cm^{-1}): 1626, 1558, 1410, 1281, 1218, 1070, 1004, 818, 728. HRMS (ESI) Calcd. for $C_{19}H_{24}N_5O$ [M+H$^+$]: 338.1981. Found 338.1978.

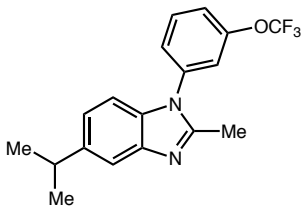


***N*-benzyl-1-(6-methoxypyridin-3-yl)-2-(thiophen-2-yl)-1*H*-benzo[*d*]imidazole-6-carboxamide (Table 2, 4k).** According to general procedure B, a mixture of *N*-benzyl-3-bromo-4-chlorobenzamide (325 mg, 1.0 mmol), 2-methoxy-5-aminopyridine (107 μL, 1.0 mmol), 2-thiophenecarboxamide (165 mg, 1.3 mmol), **P1** (17 mg, 0.02 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was

stirred for 1 h at 45 °C then for 12 h at 110 °C. The crude product was purified via column chromatography using neutral alumina as stationary phase (20-50% EtOAc/hexanes) to afford the title compound as a slightly pink solid (run 1: 294 mg (67%); run 2: 291 mg (66%); average yield: 66%). Mp = 229–230°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 2.7, 0.7 Hz, 1H), 7.78- 7.72 (m, 1H), 7.70-7.65 (m, 2H), 7.57 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.39 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.34-7.22 (m, 5H), 7.06 (dd, *J* = 3.7, 1.2 Hz, 1H), 6.97 (dd, *J* = 5.1, 3.8 Hz, 1H), 6.93 (dd, *J* = 8.7, 0.7 Hz, 1H), 6.79 (t, *J* = 5.6 Hz, 1H), 4.61 (d, *J* = 5.7 Hz, 2H), 4.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 164.8, 150.0, 146.7, 145.3, 138.6, 138.4, 138.1, 131.7, 129.8, 129.6, 129.3, 128.8, 128.1, 128.0, 127.7, 126.2, 121.8, 119.3, 112.5, 110.3, 54.3, 44.4. IR (neat, cm^{-1}): 1634, 1533, 1493, 1467, 1279, 1021, 831, 697. Anal Calcd. for $C_{25}H_{20}N_4O_2S$: C, 68.16; H, 4.58. Found: C, 68.03; H, 4.63.

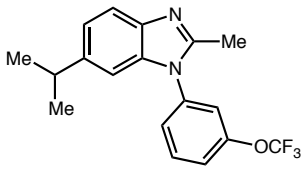


3-(2,5-Dimethoxyphenyl)-2-methyl-3*H*-imidazo[4,5-*b*]pyridine (Table 2, 4l). According to general procedure B, a mixture of 2,3-dichloropyridine (148 mg, 1.0 mmol), 2,5-dimethoxyaniline (153 mg, 1.0 mmol), acetamide (77 mg, 1.3 mmol), **P1** (26 mg, 0.03 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 1 h at 45 °C then for 12 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 40-100% EtOAc/Hexanes) to afford the title compound as a tan solid (run 1: 165 mg (61%); run 2: 165 mg (61%); average yield: 61%). Mp = 140–141 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.97 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.18 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.03-7.01 (m, 2H), 6.90 (dd, *J* = 2.2, 1.2 Hz, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 153.9, 149.5, 143.7, 135.1, 126.4, 123.6, 118.4, 116.0, 115.4, 113.6, 56.4, 55.9, 14.7. IR (neat, cm^{-1}): 1508, 1435, 1381, 1308, 1281, 1267, 1219, 1182, 1166, 1039, 815, 800, 776, 741. Anal Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61. Found: C, 66.65; H, 5.60.

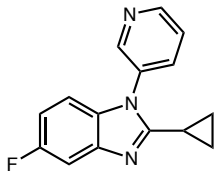


5-Isopropyl-2-methyl-1-(3-(trifluoromethoxy)phenyl)-1*H*-benzo[*d*]imidazole (Table 3, 5A). According to general procedure A, a mixture of 2-chloro-4-isopropylphenyl triflate (224 μL, 1.0 mmol), 3-trifluoromethoxyaniline (133 μL, 1.0

mmol), acetamide (77 mg, 1.3 mmol), **P1** (26 mg, 0.03 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for for 12 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 20-80% EtOAc/Hexanes) to afford the title compound as a tan solid (run 1: 251 mg (75%); run 2: 254 mg (76%); average yield: 76%). Mp = 100–102 °C.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65-7.58 (m, 2H), 7.38 (ddt, *J* = 8.3, 2.2, 1.1 Hz, 1H), 7.34 (ddd, *J* = 7.9, 2.0, 0.9 Hz, 1H), 7.27 (dt, *J* = 2.2, 1.1 Hz, 1H), 7.13 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.07 (dd, *J* = 8.4, 0.6 Hz, 1H), 3.05 (hept, *J* = 6.9 Hz, 1H), 2.52 (s, 3H), 1.32 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 150.1, 144.2, 143.0, 137.8, 134.5, 131.3, 125.4, 122.1, 121.1, 119.8, 116.6, 109.4, 34.4, 24.7, 14.6. IR (neat, cm^{-1}): 1494, 1248, 1180, 1088, 879, 835, 810, 794, 693, 700. Anal Calcd. for $C_{18}H_{17}F_3N_2O$: C, 64.66; H, 5.13. Found: C, 65.06; H, 5.26.

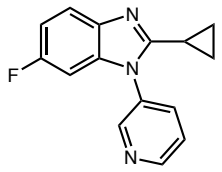


6-Isopropyl-2-methyl-1-(3-(trifluoromethoxy)phenyl)-1*H*-benzo[*d*]imidazole (Table 3, 5B). According to general procedure A, a mixture of 2-chloro-4-isopropylphenyl mesylate (198 μL, 1.0 mmol), 3-trifluoromethoxyaniline (133 μL, 1.0 mmol), acetamide (77 mg, 1.3 mmol), **P1** (51 mg, 0.06 mmol) and K_3PO_4 (636 mg, 3.0 mmol) in *t*-BuOH (1.5 mL) was stirred for for 24 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 20-80% EtOAc/Hexanes) to afford the title compound as a tan solid (run 1: 275 mg (82%); run 2: 269 mg (80%); average yield: 81%). Mp = 102–103 °C.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68-7.62 (m, 2H), 7.40 (ddt, *J* = 8.4, 2.3, 1.0 Hz, 0H), 7.37-7.34 (m, 1H), 7.29 (tt, *J* = 2.2, 1.0 Hz, 1H), 7.18 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.98-6.95 (m, 1H), 2.98 (hept, *J* = 6.9 Hz, 1H), 2.51 (s, 3H), 1.26 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4, 150.7, 145.1, 141.6, 138.3, 136.8, 131.9, 126.1, 122.5, 121.7, 120.5, 119.6, 107.6, 35.1, 25.2, 15.2. IR (neat, cm^{-1}): 1495, 1246, 1167, 852, 815, 729, 670, 650, 631. Anal Calcd. for $C_{18}H_{17}F_3N_2O$: C, 64.66; H, 5.13. Found: C, 64.96; H, 5.33.

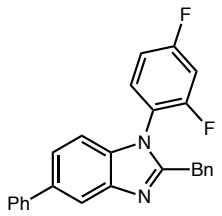


2-Cyclopropyl-5-fluoro-1-(pyridin-3-yl)-1*H*-benzo[*d*]imidazole (Table 3, 6A). According to general procedure B, a mixture of 2-chloro-4-fluorophenyl triflate (178 μL, 1.0 mmol), 3-aminopyridine (94 mg, 1.0 mmol), cyclopropanecarboxamide (111 mg, 1.3 mmol), **P1** (34 mg, 0.04 mmol) and

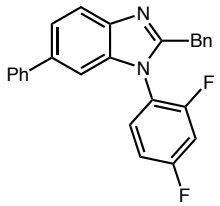
Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 1 h at 45 °C then for 12 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 30-90% EtOAc/Hexanes) to afford the title compound as a brown solid (run 1: 181 mg (72%); run 2: 192 mg (76%); average yield: 74%). Mp = 107–108 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 2.5, 0.7 Hz, 1H), 8.78 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.84 (ddd, *J* = 8.0, 2.5, 1.6 Hz, 1H), 7.57 (ddt, *J* = 8.1, 4.8, 0.7 Hz, 1H), 7.37 (dd, *J* = 9.3, 2.4 Hz, 1H), 7.01 (dd, *J* = 8.8, 4.6 Hz, 1H), 6.94 (dd, *J* = 9.0, 2.5 Hz, 1H), 1.75 (tt, *J* = 8.1, 4.8 Hz, 1H), 1.36-1.30 (m, 2H), 1.11-1.04 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9 (d, *J* = 237.8 Hz), 158.4 (d, *J* = 0.7 Hz), 150.1, 148.5, 143.3 (d, *J* = 12.7 Hz), 134.7, 132.9, 132.8, 124.6, 110.7 (d, *J* = 25.9 Hz), 109.6 (d, *J* = 10.3 Hz), 105.3 (d, *J* = 24.6 Hz), 9.9, 8.5. IR (neat, cm^{-1}): 1522, 1477, 1443, 1429, 1410, 1296, 1228, 1148, 1111, 1025, 958, 885, 858, 813, 804, 719, 711, 619. Anal Calcd. for $C_{15}H_{12}FN_3$: C, 71.13; H, 4.78. Found: C, 71.06; H, 4.81.



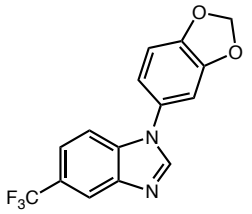
2-Cyclopropyl-6-fluoro-1-(pyridin-3-yl)-1*H*-benzo[*d*]imidazole (Table 3, 6B). According to general procedure A, a mixture of 2-chloro-4-fluorophenyl mesylate (225 mg, 1.0 mmol), 3-aminopyridine (94 mg, 1.0 mmol), cyclopropanecarboxamide (111 mg, 1.3 mmol), **P1** (51 mg, 0.06 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for for 24 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 30-90% EtOAc/Hexanes) to afford the title compound as a brown solid (run 1: 163 mg (64%); run 2: 159 mg (63%); average yield: 64%). Mp = 123–124 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87-8.75 (m, 2H), 7.84 (ddd, *J* = 8.1, 2.6, 1.5 Hz, 1H), 7.68-7.52 (m, 2H), 7.00 (ddd, *J* = 9.6, 8.8, 2.5 Hz, 1H), 6.81 (dd, *J* = 8.5, 2.4 Hz, 1H), 1.75 (tt, *J* = 8.2, 4.9 Hz, 1H), 1.38-1.26 (m, 2H), 1.11-0.97 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9 (d, *J* = 240.1 Hz), 157.4 (d, *J* = 2.9 Hz), 150.2, 148.5, 139.0, 136.4 (d, *J* = 12.9 Hz), 134.7, 132.7, 124.6, 119.9 (d, *J* = 10.0 Hz), 111.1 (d, *J* = 24.7 Hz), 96.5 (d, *J* = 28.1 Hz), 9.8, 8.4. IR (neat, cm^{-1}): 1478, 1423, 1049, 1235, 1189, 1140, 1028, 813, 800, 716, 709. Anal Calcd. for $C_{15}H_{12}FN_3$: C, 71.13; H, 4.78. Found: C, 70.66; H, 4.88.



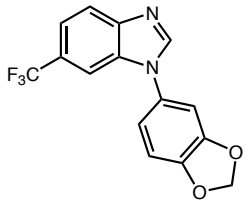
2-Benzyl-1-(2,4-difluorophenyl)-5-phenyl-1*H*-benzo[*d*]imidazole (Table 3, 7A). According to general procedure A, a mixture of 3-chloro-[1,1'-biphenyl]-4-yl triflate (234 μL, 1.0 mmol), 2,4-difluoroaniline (102 μL, 1.0 mmol), phenylacetamide (176 mg, 1.3 mmol), **P1** (26 mg, 0.03 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 12 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 10-35% EtOAc/Hexanes) to afford the title compound as a tan solid (run 1: 331 mg (83%); run 2: 320 mg (81%); average yield: 82%). Mp = 142.5–143.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07-8.04 (m, 1H), 7.68-7.62 (m, 2H), 7.50-7.43 (m, 4H), 7.38-7.33 (m, 1H), 7.20-7.15 (m, 2H), 7.12-7.07 (m, 1H), 7.07-6.99 (m, 5H), 6.96 (dddd, *J* = 8.9, 7.7, 2.7, 1.3 Hz, 1H), 4.29 (d, *J* = 15.6 Hz, 1H), 4.11 (d, *J* = 15.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2 (dd, *J* = 253.2, 11.0 Hz), 158.4 (dd, *J* = 255.6, 12.8 Hz), 154.5, 143.2, 141.7, 136.8, 136.3, 135.9, 131.0 (dd, *J* = 10.1, 1.3 Hz), 129.0, 128.7, 128.7, 127.6, 127.0 (2C), 123.2, 119.9 (d, *J* = 17.3, 4.4 Hz), 118.4, 112.5 (dd, *J* = 22.5, 4.1 Hz), 109.8, 105.7 (dd, *J* = 26.5, 23.4 Hz), 34.8. IR (neat, cm^{-1}): 1514, 1471, 1277, 1072, 962, 858, 756, 700. Anal Calcd. for $C_{26}H_{18}F_2N_2$: C, 78.77; H, 4.58. Found: C, 78.49; H, 4.76.



2-Benzyl-1-(2,4-difluorophenyl)-6-phenyl-1*H*-benzo[*d*]imidazole (Table 3, 7B). According to general procedure A, a mixture of 3-chloro-[1,1'-biphenyl]-4-yl mesylate (283 mg, 1.0 mmol), 2,4-difluoroaniline (102 μL, 1.0 mmol), phenylacetamide (176 mg, 1.3 mmol), **P1** (51 mg, 0.06 mmol) and Cs_2CO_3 (782 mg, 2.4 mmol) in *t*-BuOH (1.5 mL) was stirred for 24 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 10-35% EtOAc/Hexanes) to afford the title compound as an amber syrup (run 1: 310 mg (78%); run 2: 319 mg (81%); average yield: 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 1H), 7.58-7.54 (m, 3H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.34-7.28 (m, 1H), 7.22-7.14 (m, 4H), 7.11 (td, *J* = 8.6, 5.8 Hz, 1H), 7.05-6.99 (m, 3H), 6.95 (dddd, *J* = 8.9, 7.6, 2.8, 1.3 Hz, 1H), 4.29 (d, *J* = 15.6 Hz, 1H), 4.11 (d, *J* = 15.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2 (dd, *J* = 253.1, 10.8 Hz), 158.4 (dd, *J* = 255.7, 12.6 Hz), 154.4, 142.2, 141.7, 137.4, 137.3, 135.9, 131.1 (dd, *J* = 10.2, 1.2 Hz), 128.9, 128.7, 128.6, 127.9, 127.2, 127.0, 122.7, 120.0, 112.5 (dd, *J* = 22.5, 3.8 Hz), 108.2, 105.7 (dd, *J* = 26.4, 23.3 Hz), 34.8. IR (neat, cm^{-1}): 1513, 1469, 1436, 1270, 1143, 1103, 853, 821, 749, 722, 694. HRMS (DART) Calcd. for $C_{26}H_{19}F_2N_2$ $[M+H]^+$ 397.1516. Found: 397.1528.

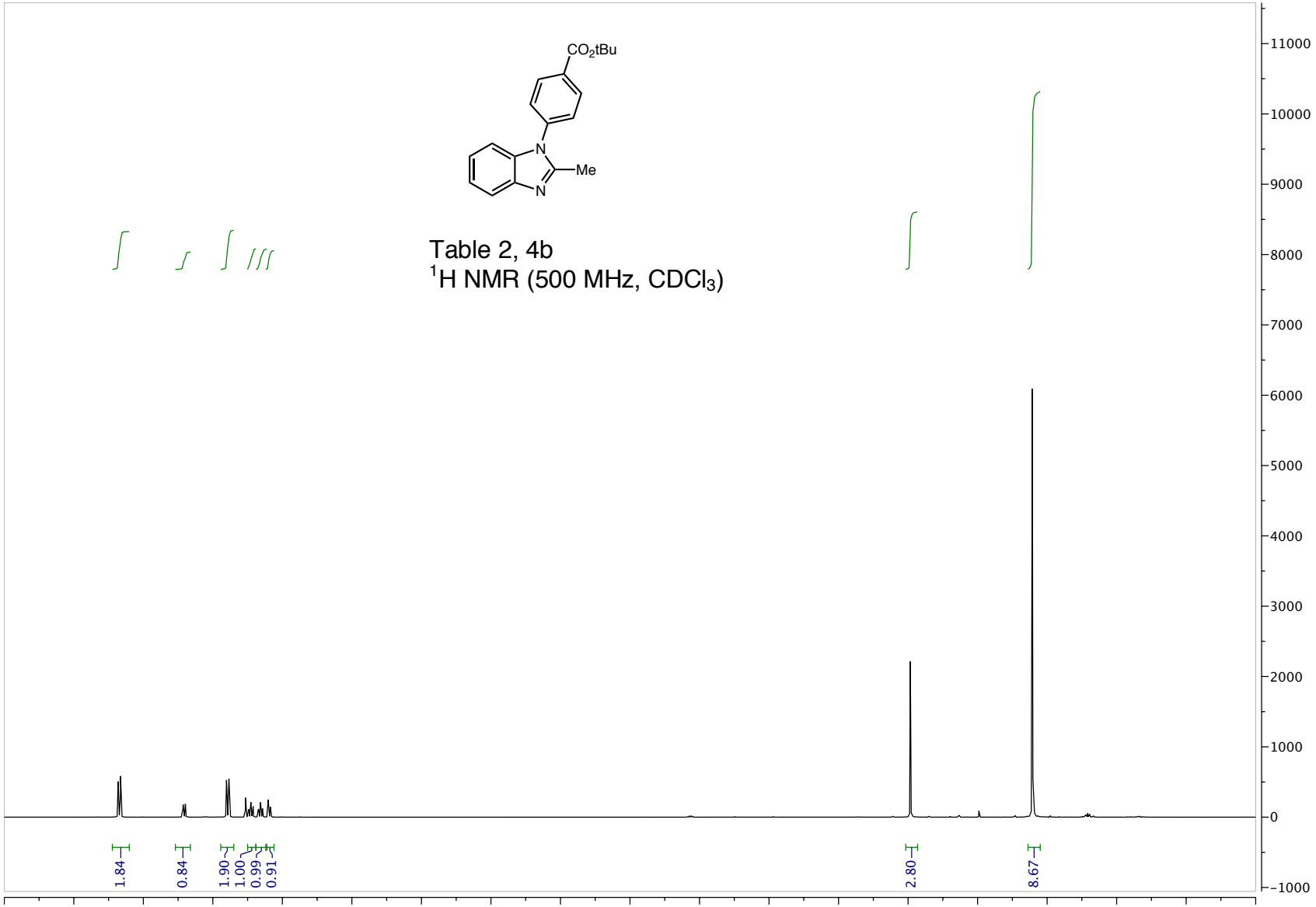


1-(Benzo[*d*][1,3]dioxol-5-yl)-5-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (Table 3, 8A). According to general procedure B, a mixture of 2-chloro-4-(trifluoromethyl)phenyl triflate (208 μL, 1.0 mmol), 3,4-(methylenedioxy)aniline (137 mg, 1.0 mmol), formamide (53 μL, 1.3 mmol), **P1** (51 mg, 0.06 mmol) and K_3PO_4 (636 mg, 3.0 mmol) in *t*-BuOH (1.5 mL) was stirred for 1 h at 45 °C then 12 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 10-65% EtOAc/Hexanes) to afford the title compound as a tan solid (run 1: 187 mg (61%); run 2: 192 mg (63%); average yield: 62%). Mp = 123–125 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25-8.03 (m, 2H), 7.57 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 6.98 (dt, *J* = 7.8, 0.5 Hz, 1H), 6.96-6.92 (m, 2H), 6.11 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 148.2, 144.5, 143.4, 136.2, 129.6, 125.5 (q, *J* = 32.4 Hz), 124.9 (q, *J* = 271.6 Hz), 120.8 (q, *J* = 3.6 Hz), 118.5 (q, *J* = 4.2 Hz). 118.3, 111.1, 109.2, 106.0, 102.4. IR (neat, cm^{-1}): 1501, 1327, 1218, 1109, 1033, 935, 920, 811. Anal Calcd. for $C_{15}H_9F_3N_2O_2$: C, 58.83; H, 2.96. Found: C, 58.77; H, 2.97.



1-(Benzo[*d*][1,3]dioxol-5-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (Table 3, 8B). According to general procedure B, a mixture of 2-chloro-4-(trifluoromethyl)phenyl mesylate (183 μL, 1.0 mmol), 3,4-(methylenedioxy)aniline (137 mg, 1.0 mmol), formamide (53 μL, 1.3 mmol), **P1** (51 mg, 0.06 mmol) and K_3PO_4 (636 mg, 3.0 mmol) in *t*-BuOH (1.5 mL) was stirred for 2 h at 23 °C then 24 h at 110 °C. The crude product was purified using a Biotage Isolera 4 (silica-packed 25 g SNAP column, 10-65% EtOAc/Hexanes) to afford the title compound as a white solid (run 1: 196 mg (64%); run 2: 214 mg (70%); average yield: 67%). Mp = 134–135 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.94 (dt, *J* = 8.5, 0.8 Hz, 1H), 7.72 (dt, *J* = 1.7, 0.8 Hz, 1H), 7.58 (ddd, *J* = 8.6, 1.7, 0.7 Hz, 1H), 7.01-6.97 (m, 1H), 6.96-6.91 (m, 2H), 6.11 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 148.3, 146.0, 145.0, 133.9, 129.4, 126.1 (q. *J* = 32.3 Hz), 124.8 (q, *J* = 272.0 Hz), 121.2, 119.8 (q, *J* = 3.6 Hz), 118.4, 109.2, 108.4 (*J* = 4.4 Hz), 106.1, 102.4. IR (neat, cm^{-1}): 1500, 1320, 1227, 1164, 1106, 1036, 851, 827, 817. Anal Calcd. for $C_{15}H_9F_3N_2O_2$: C, 58.83; H, 2.96. Found: C, 58.17; H, 2.85.

II. ^{1}H and ^{13}C NMR Spectra


CO2tBu
N
Me
N
Table 2, 4b
1H NMR (500 MHz, CDCl3)
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
1.84
0.84
1.90
1.00
0.99
0.91
2.80
8.67

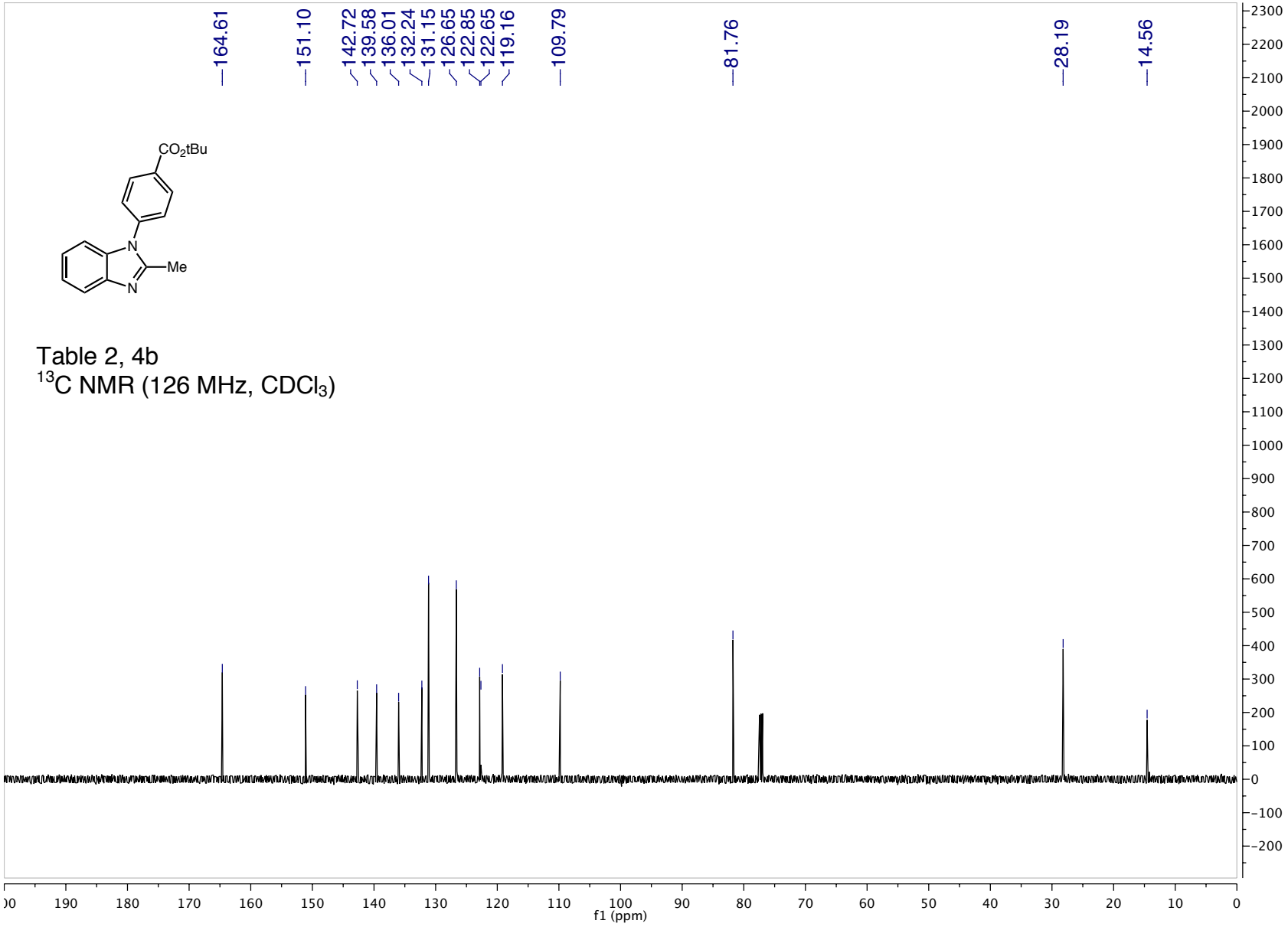
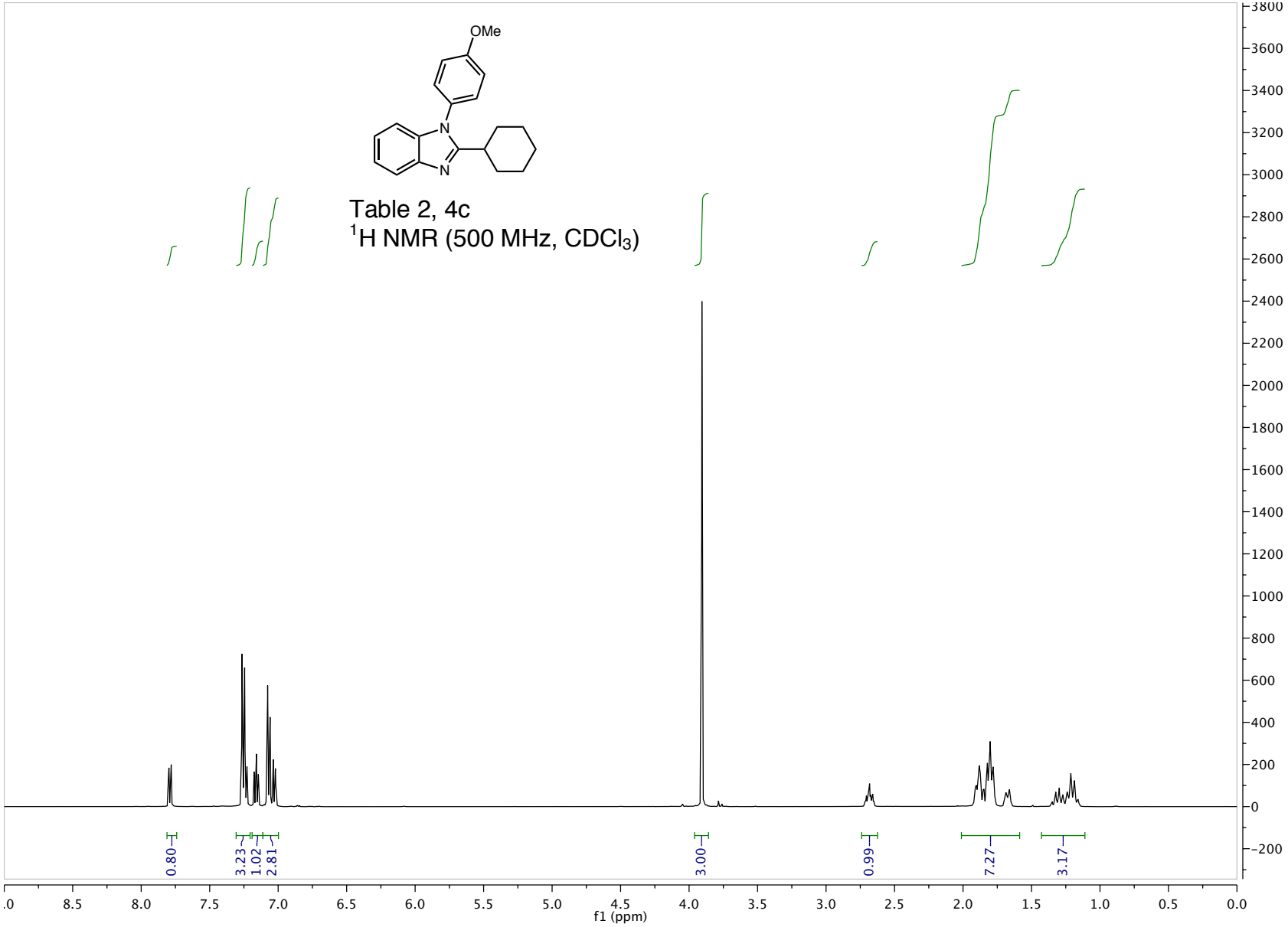
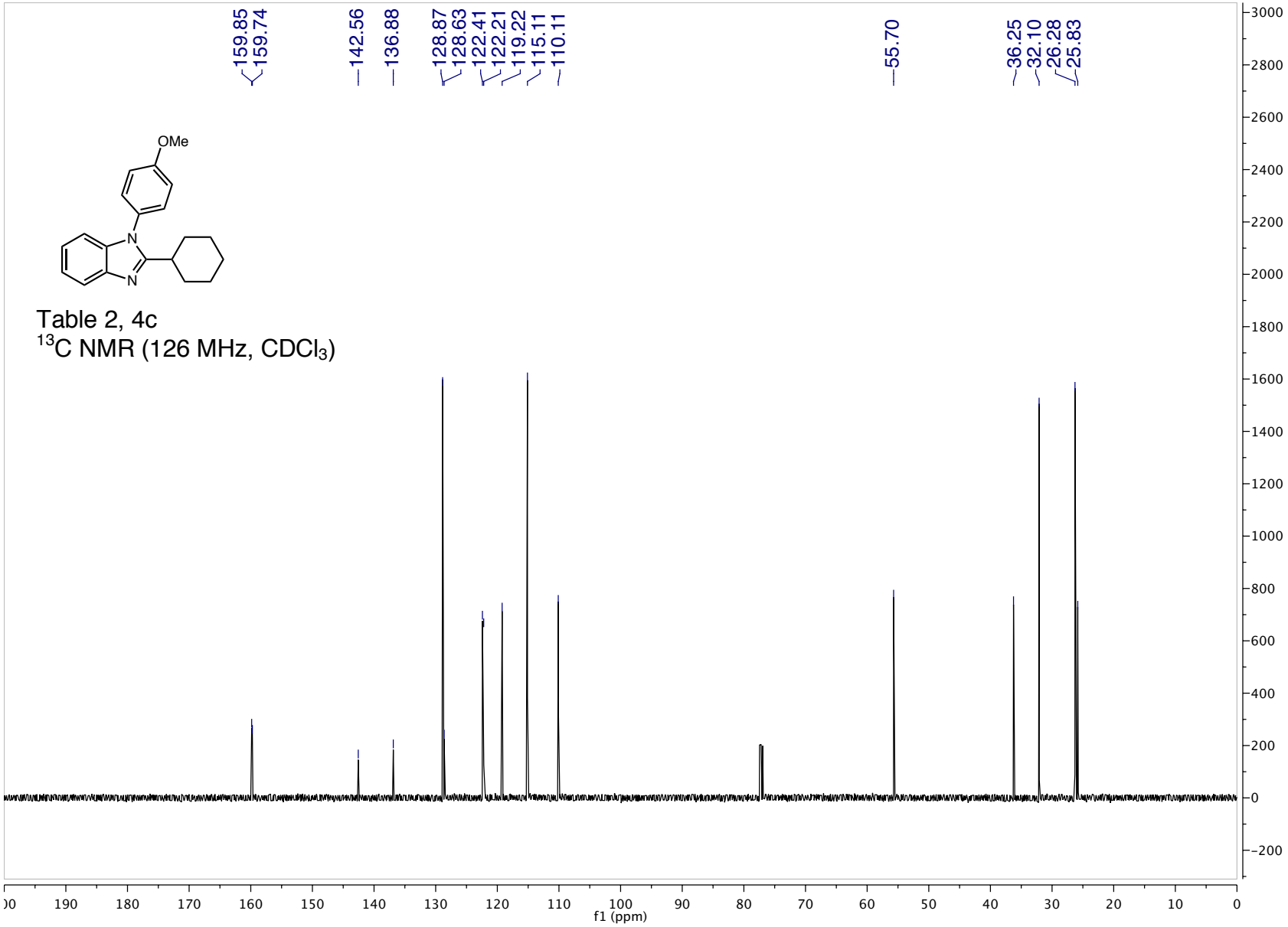
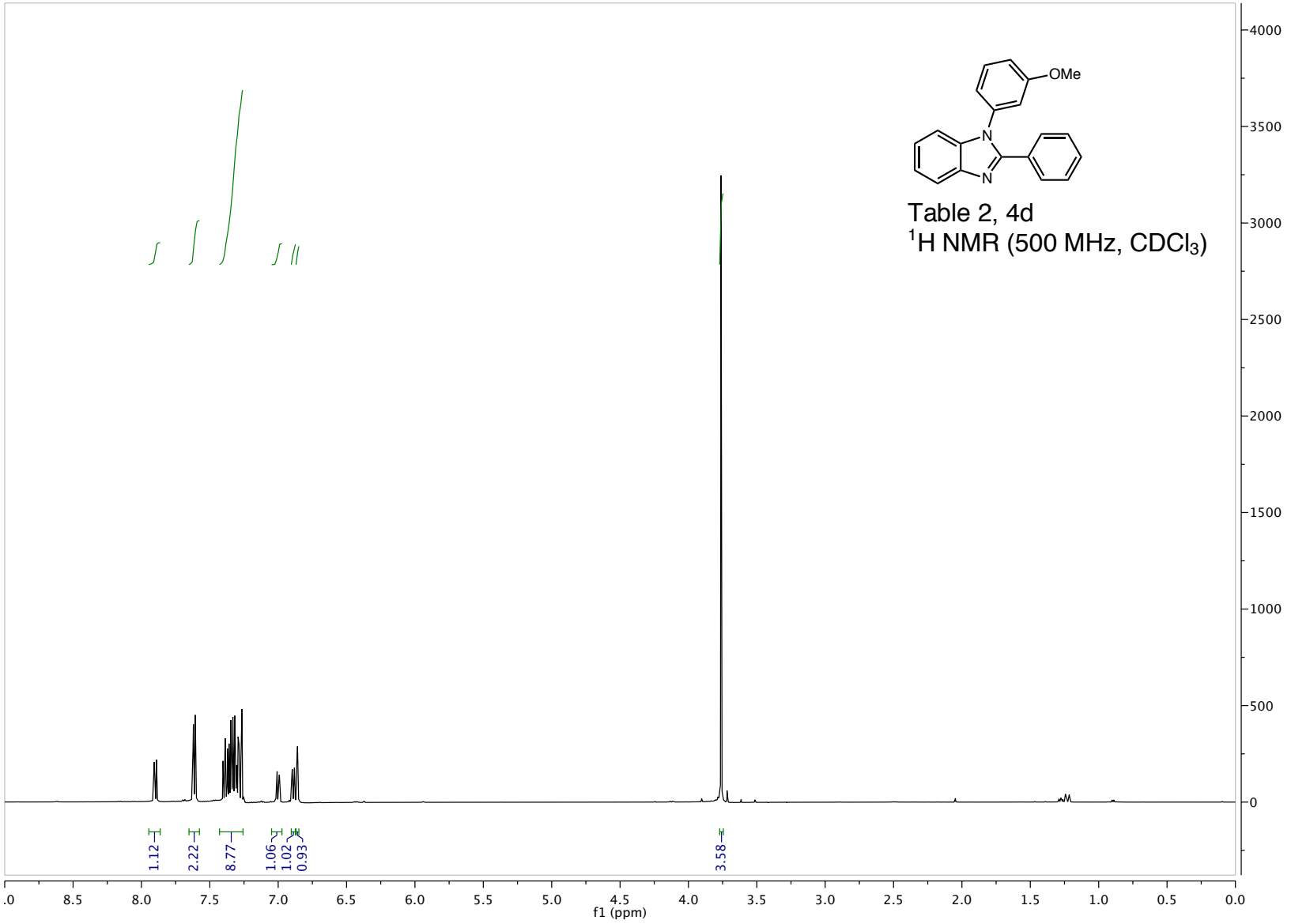


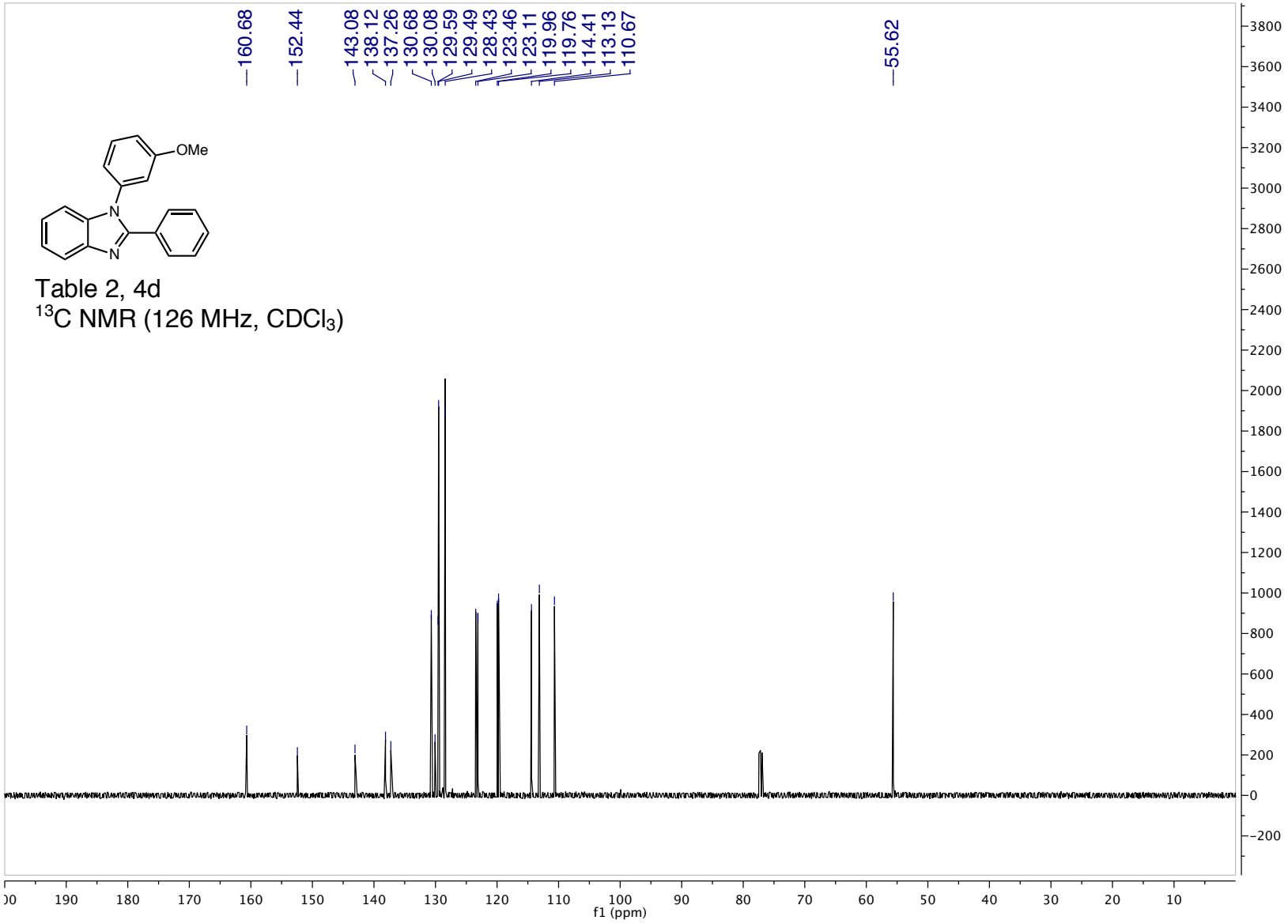
Table 2, 4b

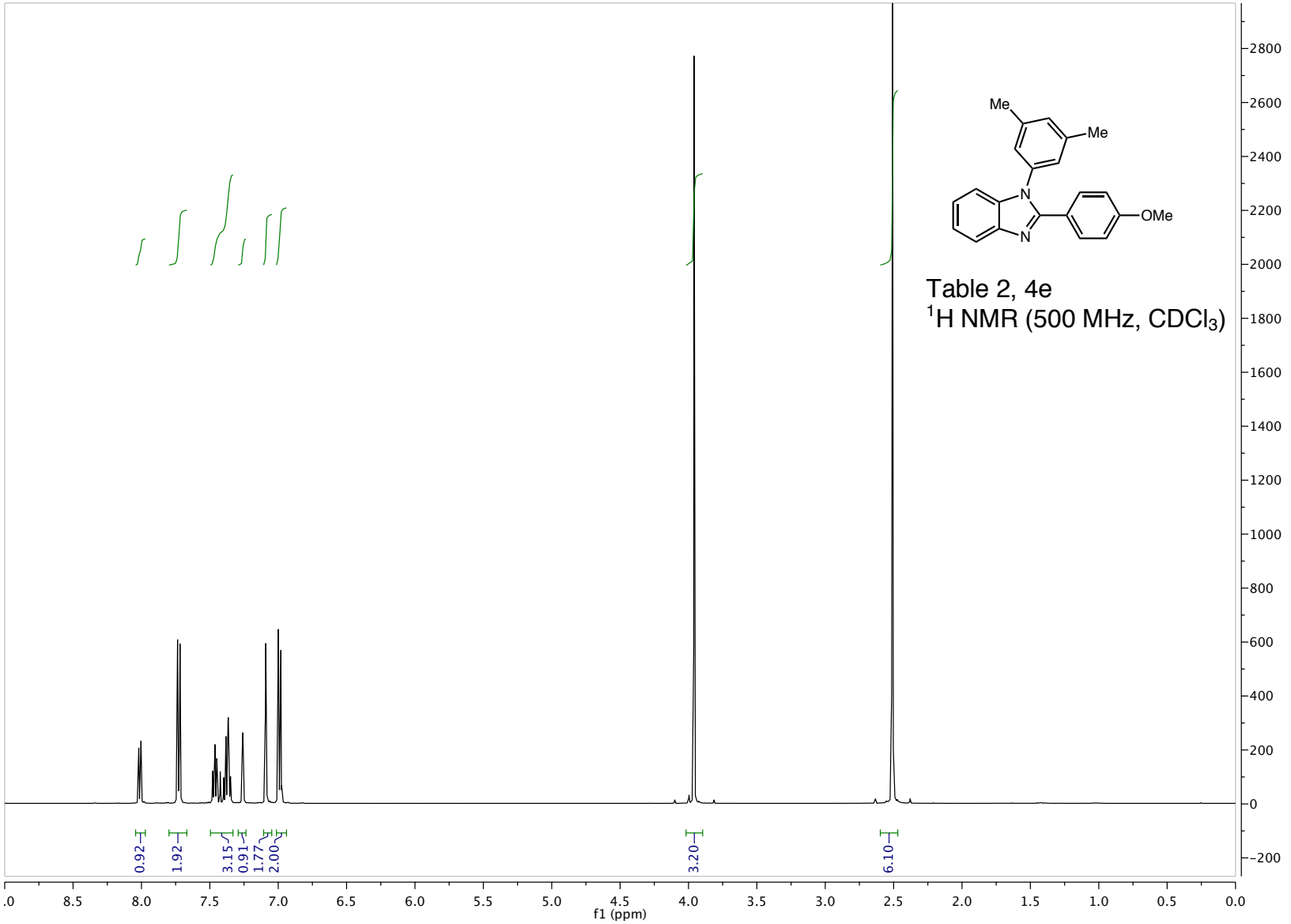
^{13}C NMR (126 MHz, $CDCl_3$)

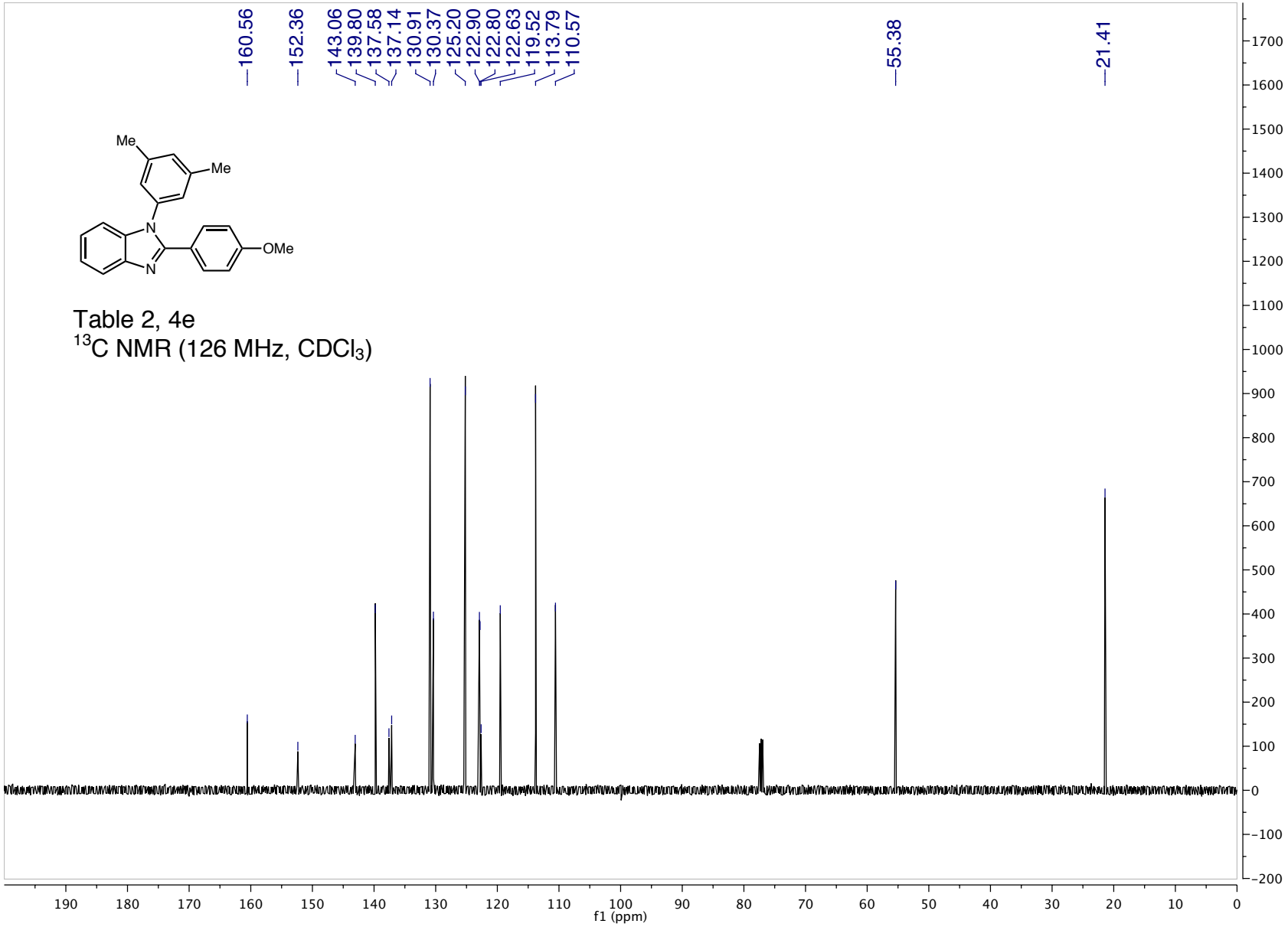

OMe
N
N
Table 2, 4c
^{1}H NMR (500 MHz, $CDCl_3$)
0.80
3.23
1.02
2.81
3.00
0.99
7.27
3.17
f1 (ppm)

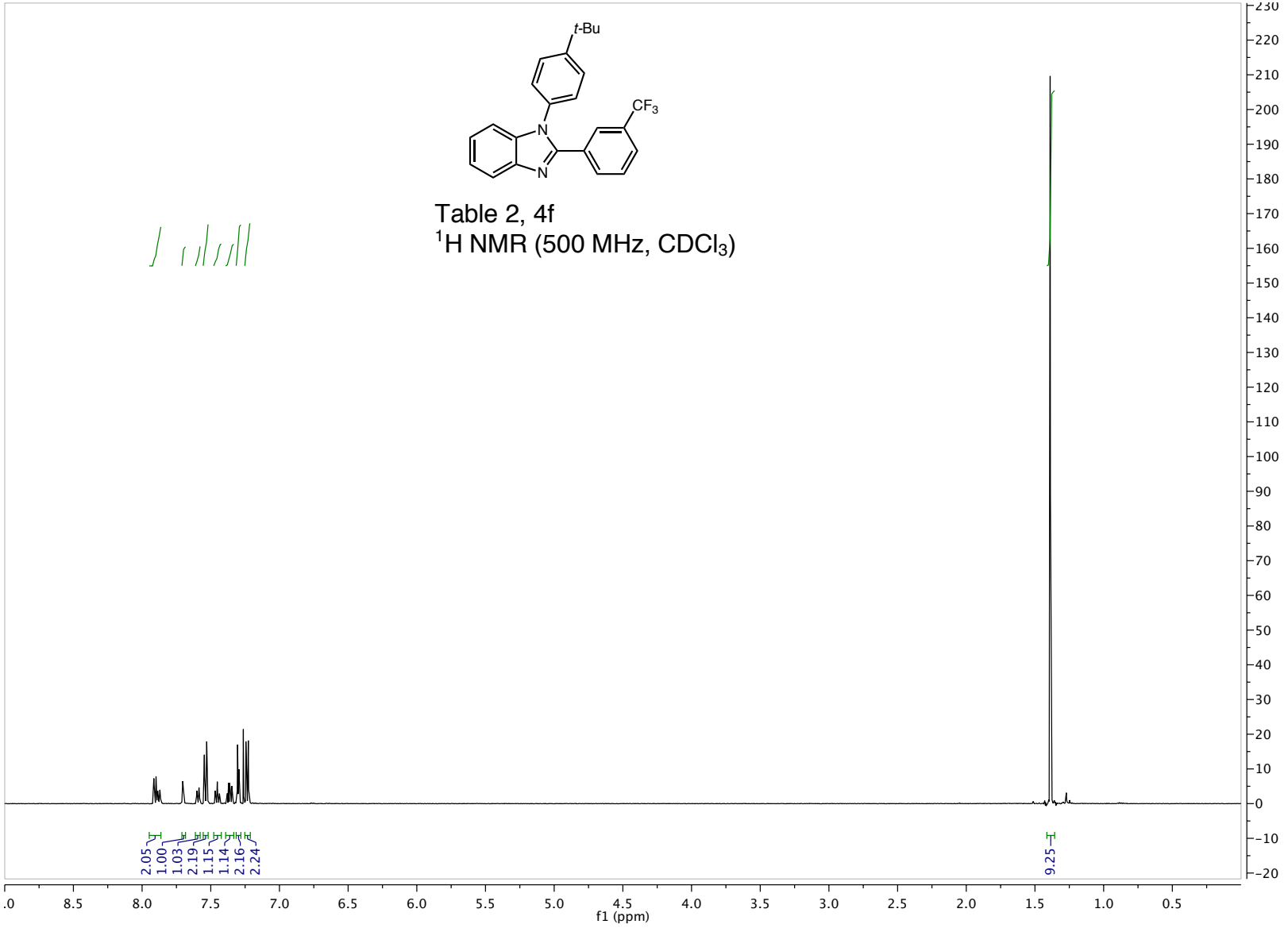

159.85
159.74
142.56
136.88
128.87
128.63
122.41
122.21
119.22
115.11
110.11
55.70
36.25
32.10
26.28
25.83
OMe
N
N
Table 2, 4c
13C NMR (126 MHz, CDCl3)
f1 (ppm)

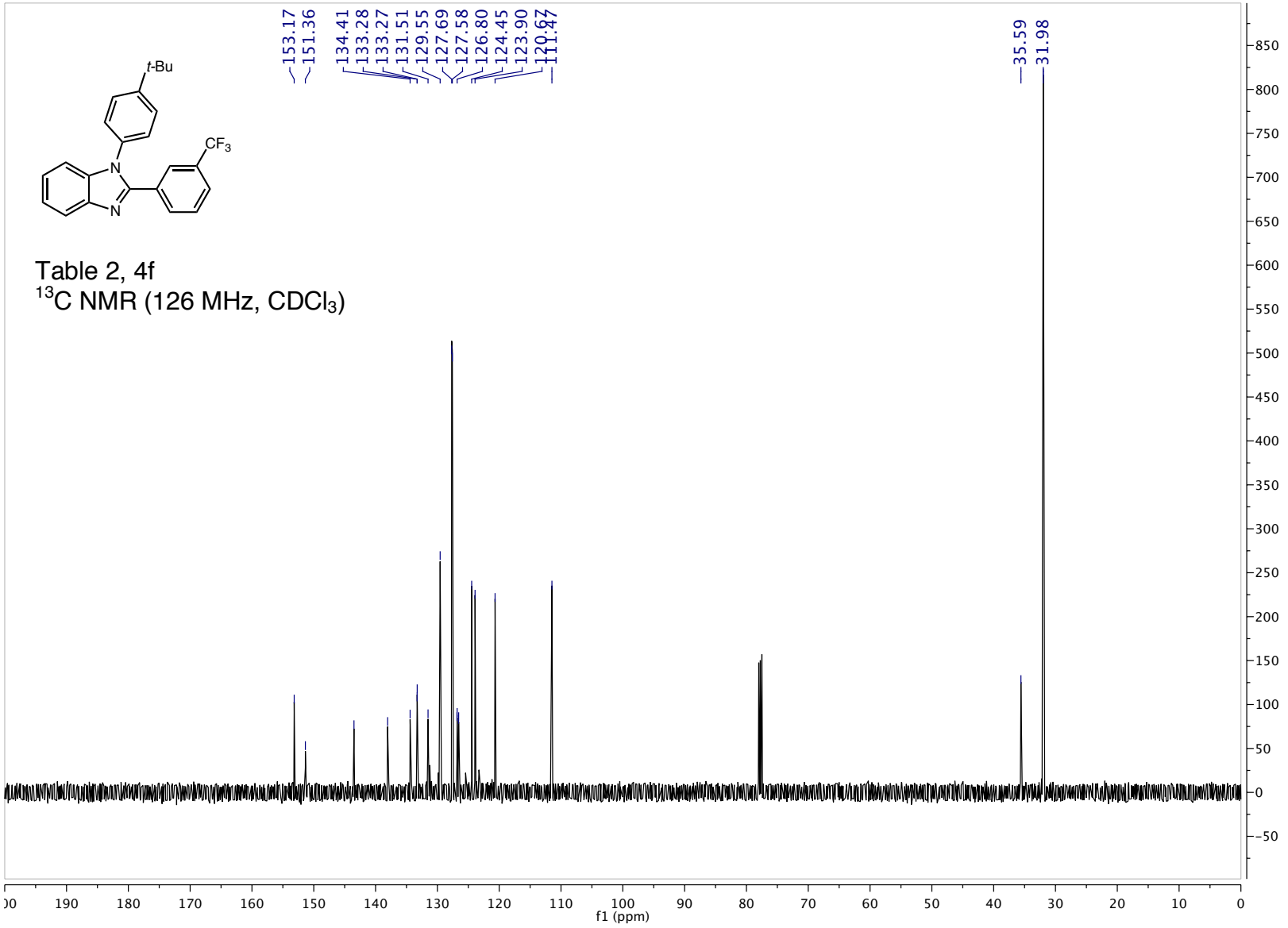

OMe
N
N
Table 2, 4d
^{1}H NMR (500 MHz, $CDCl_3$)
4000
3500
3000
2500
2000
1500
1000
500
0
1.12
2.22
8.77
1.06
1.02
0.93
3.58
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

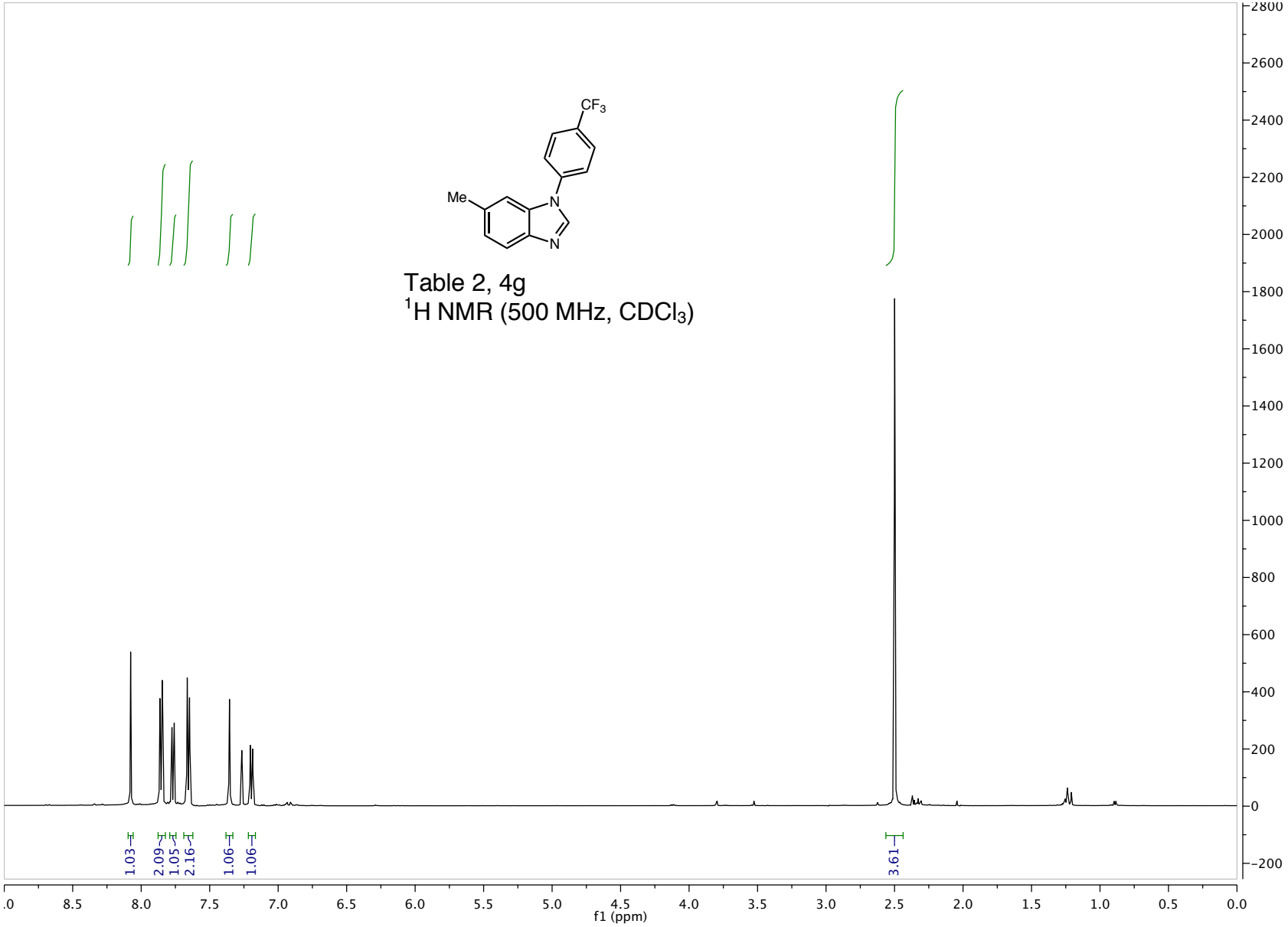

160.68
152.44
143.08
138.12
137.26
130.68
130.08
129.59
129.49
128.43
123.46
123.11
119.96
119.76
114.41
113.13
110.67
55.62
OMe
N
N
Table 2, 4d
13C NMR (126 MHz, CDCl3)
f1 (ppm)

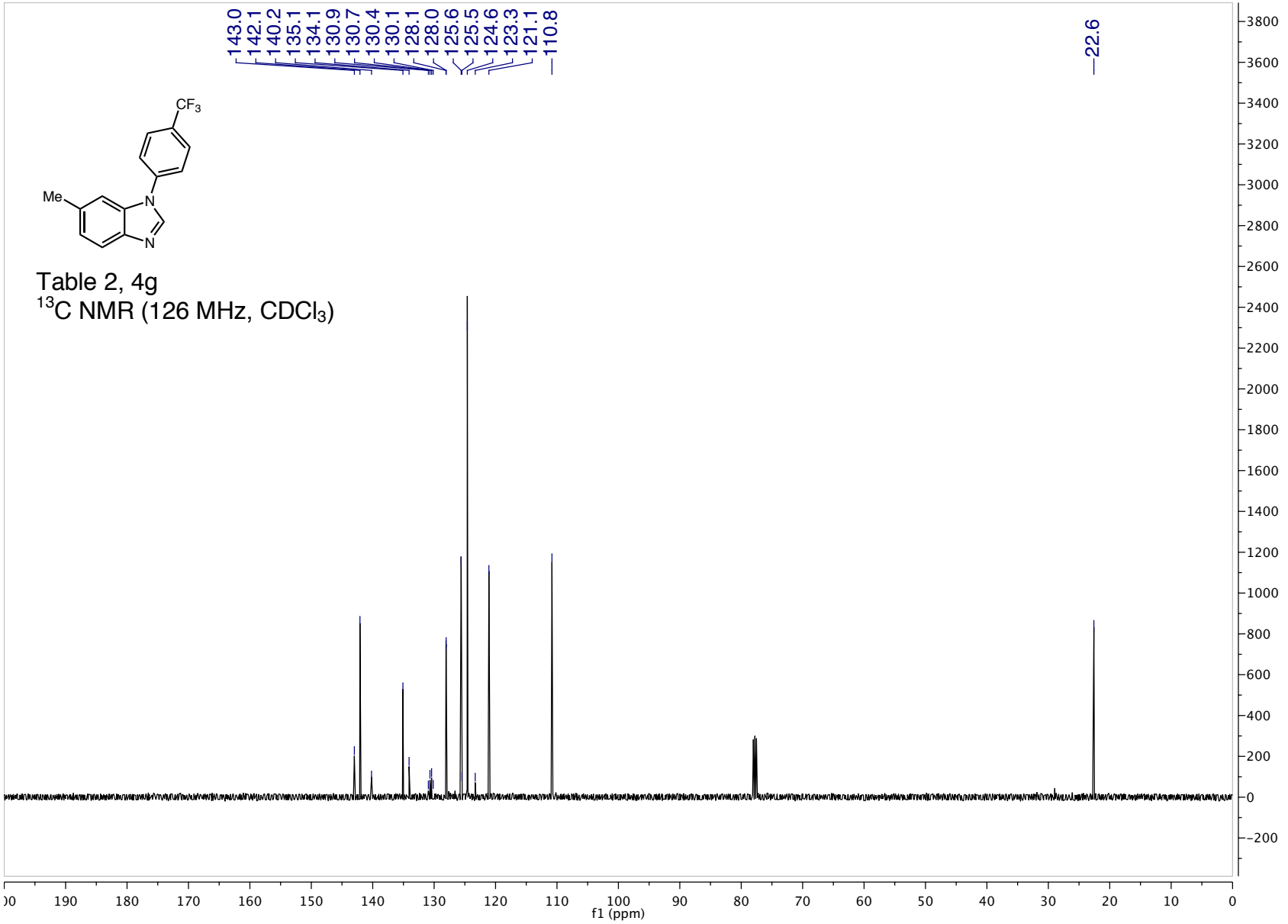

Me
Me
N
N
OMe
Table 2, 4e
^{1}H NMR (500 MHz, $CDCl_3$)
0.92
1.92
3.15
0.91
1.77
2.00
3.20
6.10
f1 (ppm)

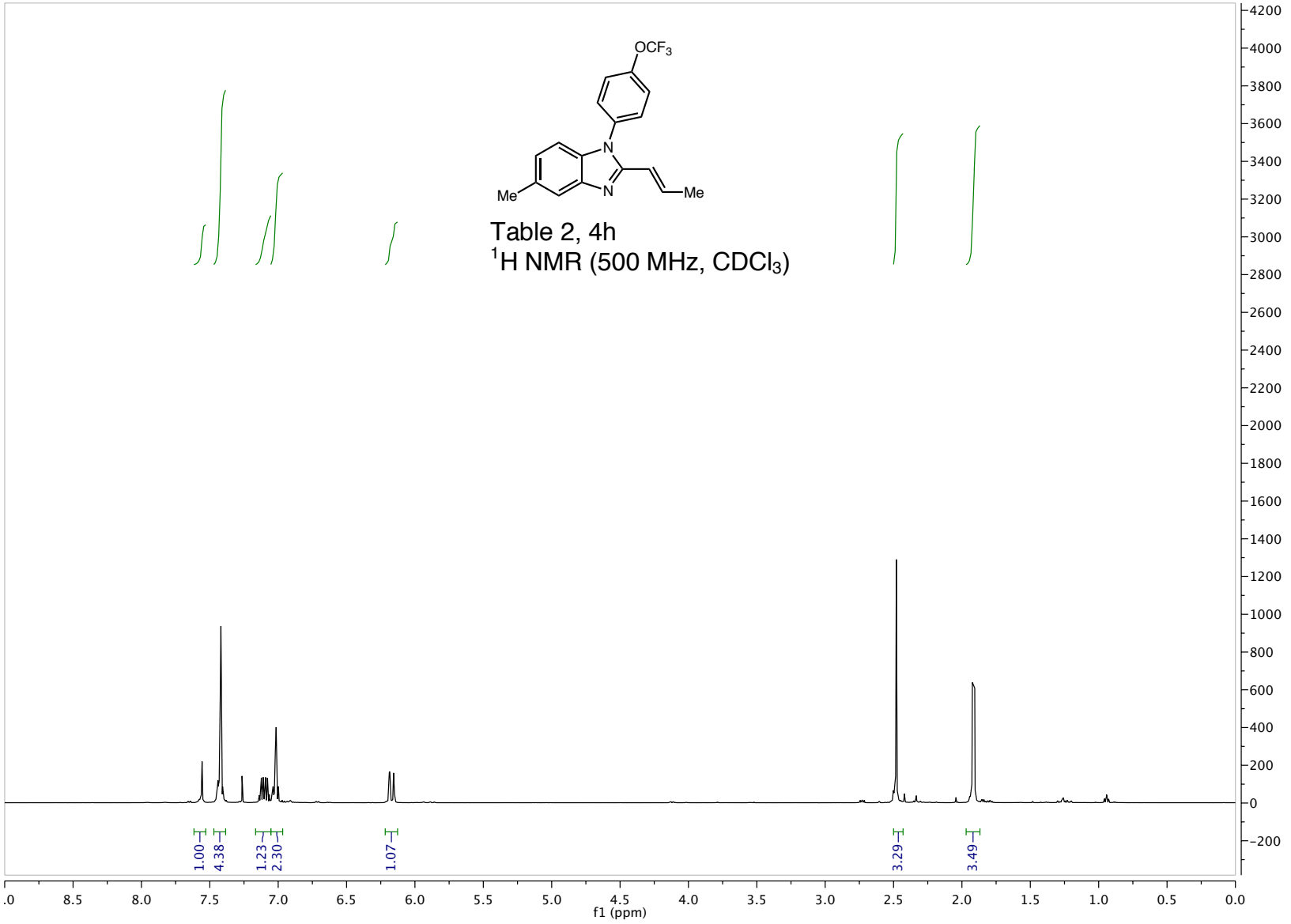

160.56
152.36
143.06
139.80
137.58
137.14
130.91
130.37
125.20
122.90
122.80
122.63
119.52
113.79
110.57
55.38
21.41
Me
Me
N
N
OMe
Table 2, 4e
13C NMR (126 MHz, CDCl3)
f1 (ppm)

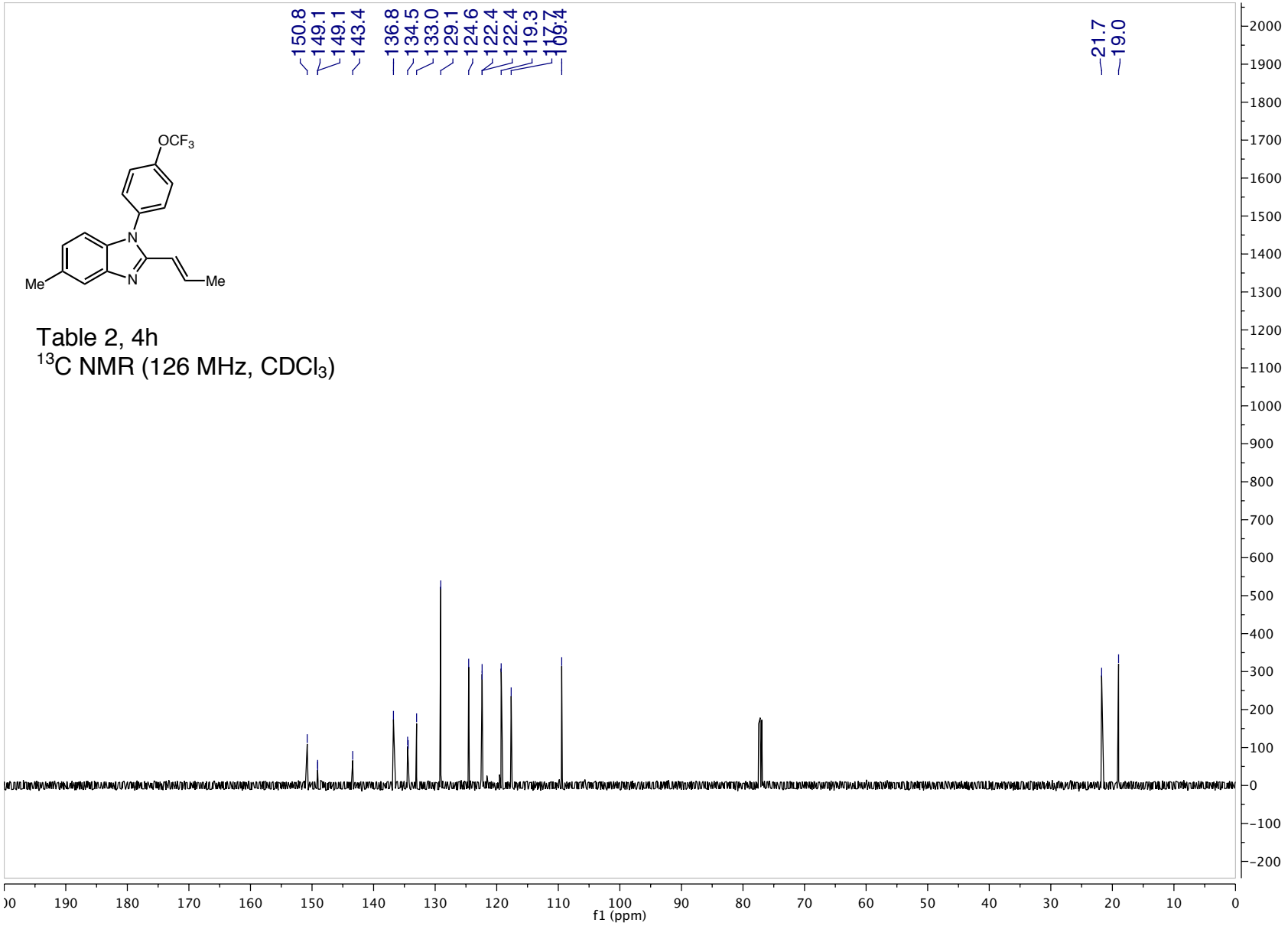

t-Bu
CF3
N
N
Table 2, 4f
1H NMR (500 MHz, CDCl3)
2.05
1.00
1.03
2.19
1.15
1.14
2.16
2.24
9.25
f1 (ppm)

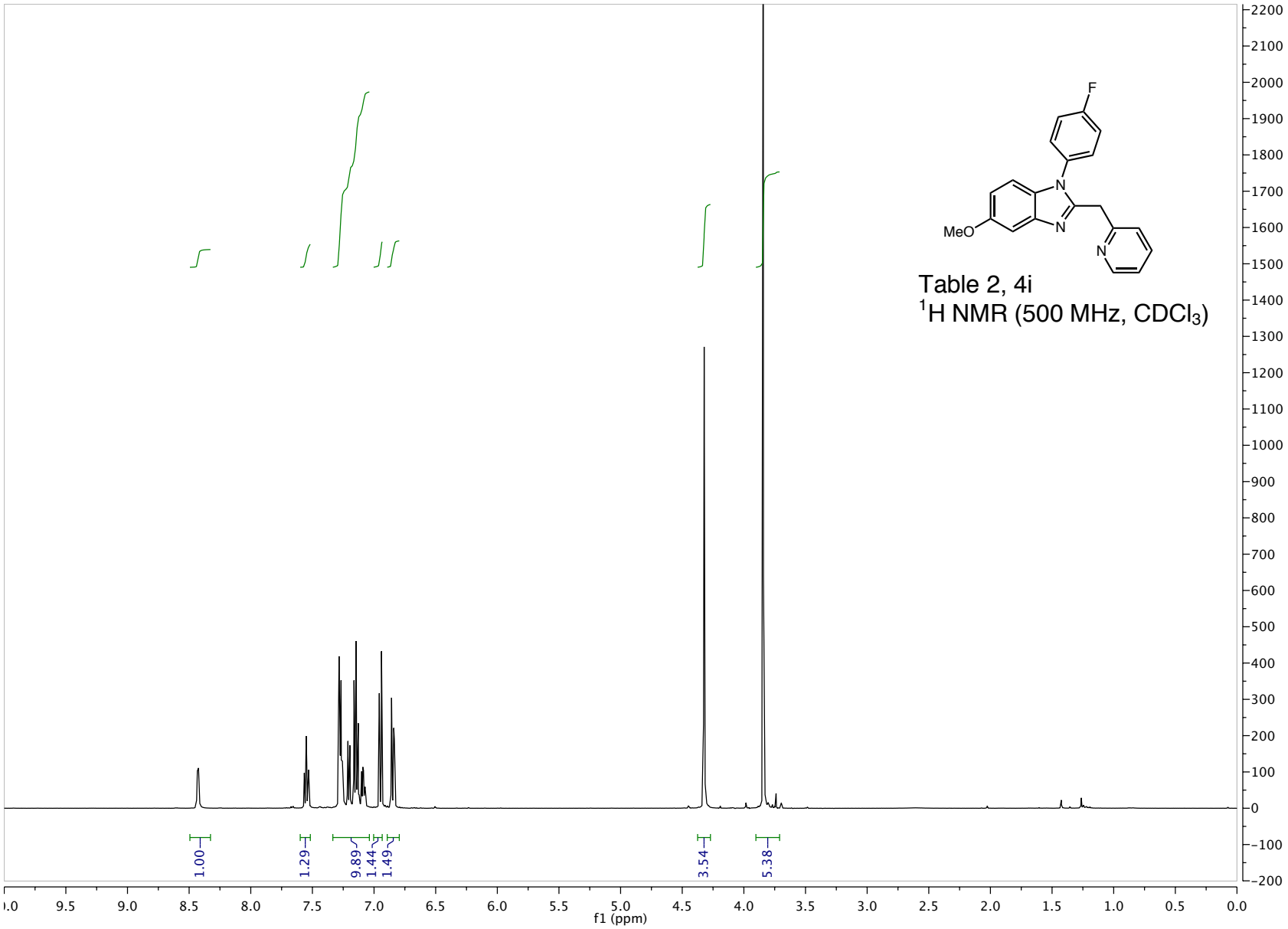

153.17
151.36
134.41
133.28
133.27
131.51
129.55
127.69
127.58
126.80
124.45
123.90
120.67
111.47
35.59
31.98
t-Bu
CF3
N
N
Table 2, 4f
13C NMR (126 MHz, CDCl3)
f1 (ppm)

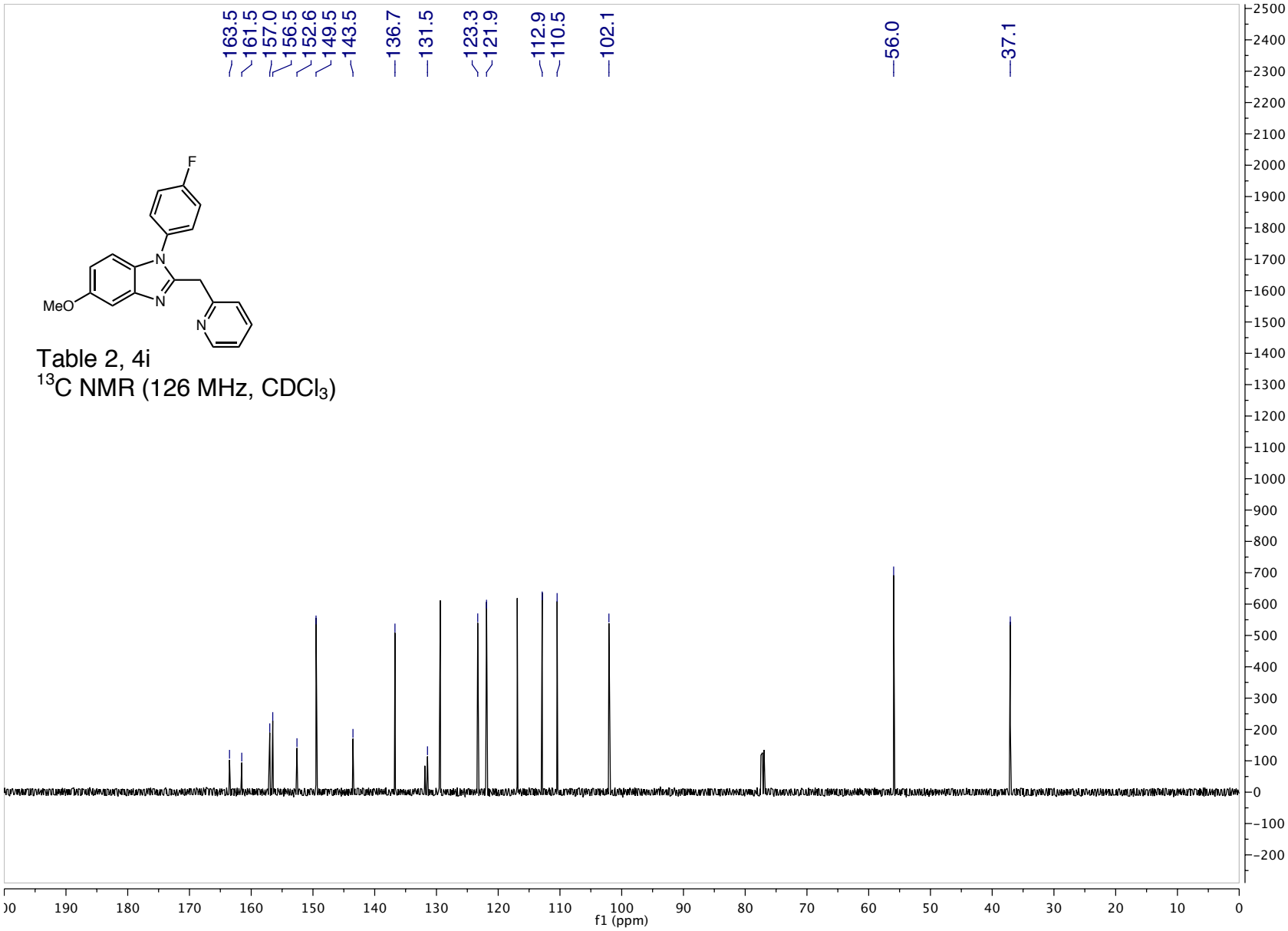

CF3
Me
N
N
Table 2, 4g
1H NMR (500 MHz, CDCl3)
1.03
2.09
1.05
2.16
1.06
1.06
3.61
f1 (ppm)


143.0
142.1
140.2
135.1
134.1
130.9
130.7
130.4
130.1
128.1
128.0
125.6
125.5
124.6
123.3
121.1
110.8
22.6
CF3
Me
N
N
Table 2, 4g
13C NMR (126 MHz, CDCl3)
f1 (ppm)


OCF3
N
N
Me
Me
Table 2, 4h
1H NMR (500 MHz, CDCl3)
1.00
4.38
1.23
2.30
1.07
3.29
3.49
f1 (ppm)


150.8
149.1
149.1
143.4
136.8
134.5
133.0
129.1
124.6
122.4
122.4
119.3
117.7
109.4
21.7
19.0
OCF3
N
N
Me
Me
Table 2, 4h
13C NMR (126 MHz, CDCl3)
f1 (ppm)


F
N
N
MeO
N
Table 2, 4i
1H NMR (500 MHz, CDCl3)
1.00
1.29
9.89
1.44
1.49
3.54
5.38
f1 (ppm)


163.5
161.5
157.0
156.5
152.6
149.5
143.5
136.7
131.5
123.3
121.9
112.9
110.5
102.1
56.0
37.1
F
N
N
MeO
N
Table 2, 4i
13C NMR (126 MHz, CDCl3)
f1 (ppm)

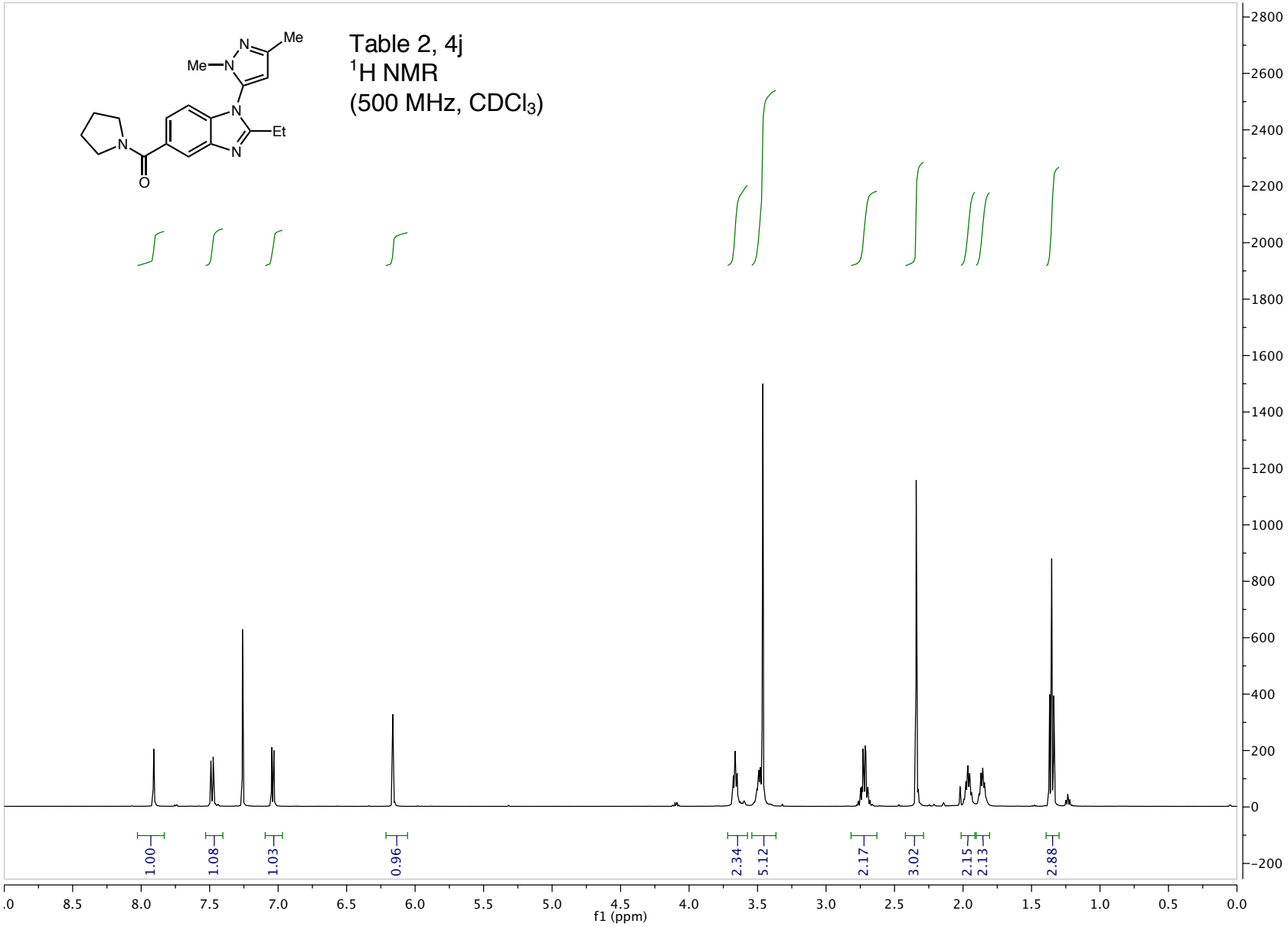


Table 2, 4j
1H NMR
(500 MHz, CDCl3)
Me
N
Me
N
N
Et
N
O
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
1.00
1.08
1.03
0.96
2.34
5.12
2.17
3.02
2.15
2.13
2.88
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

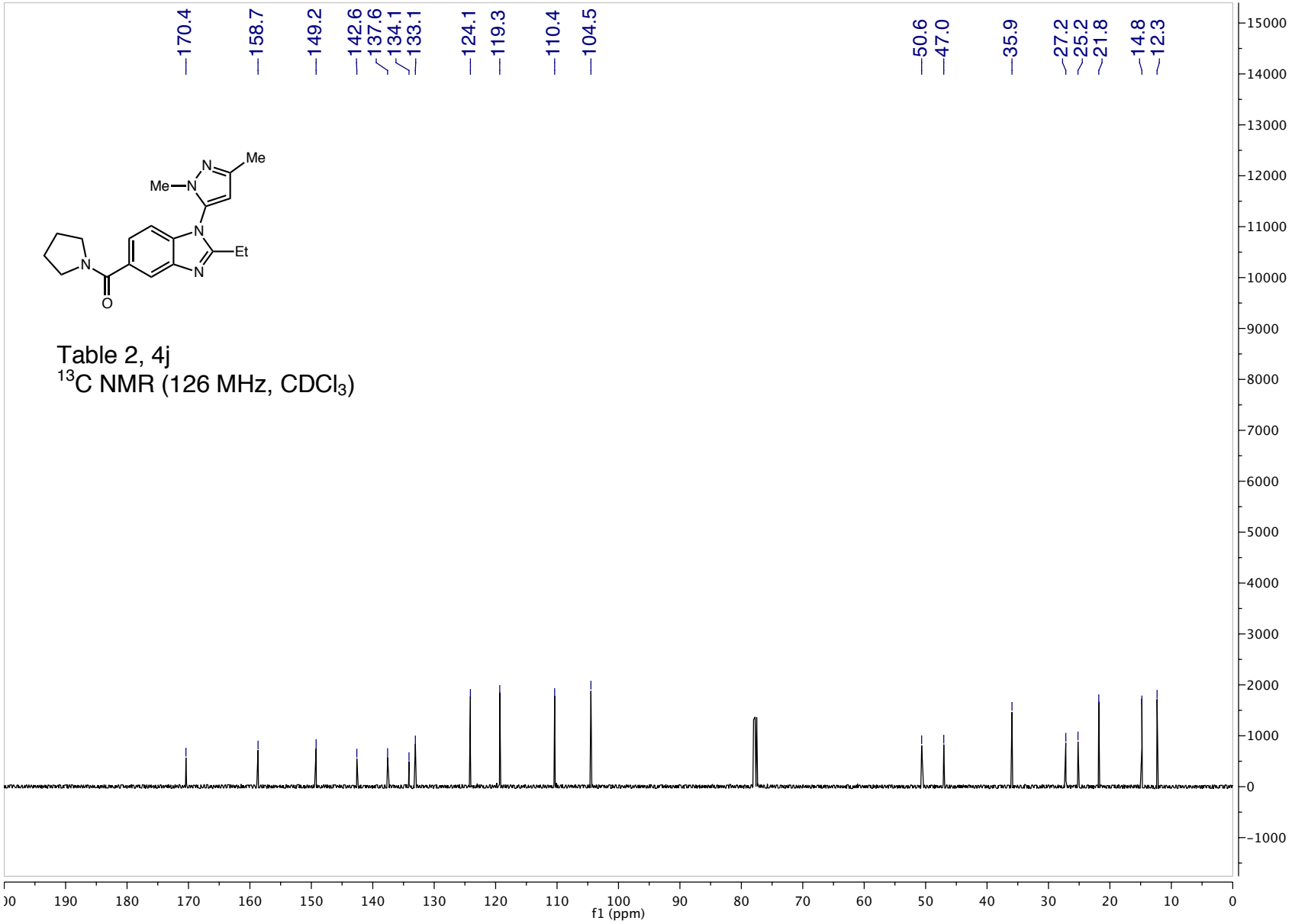
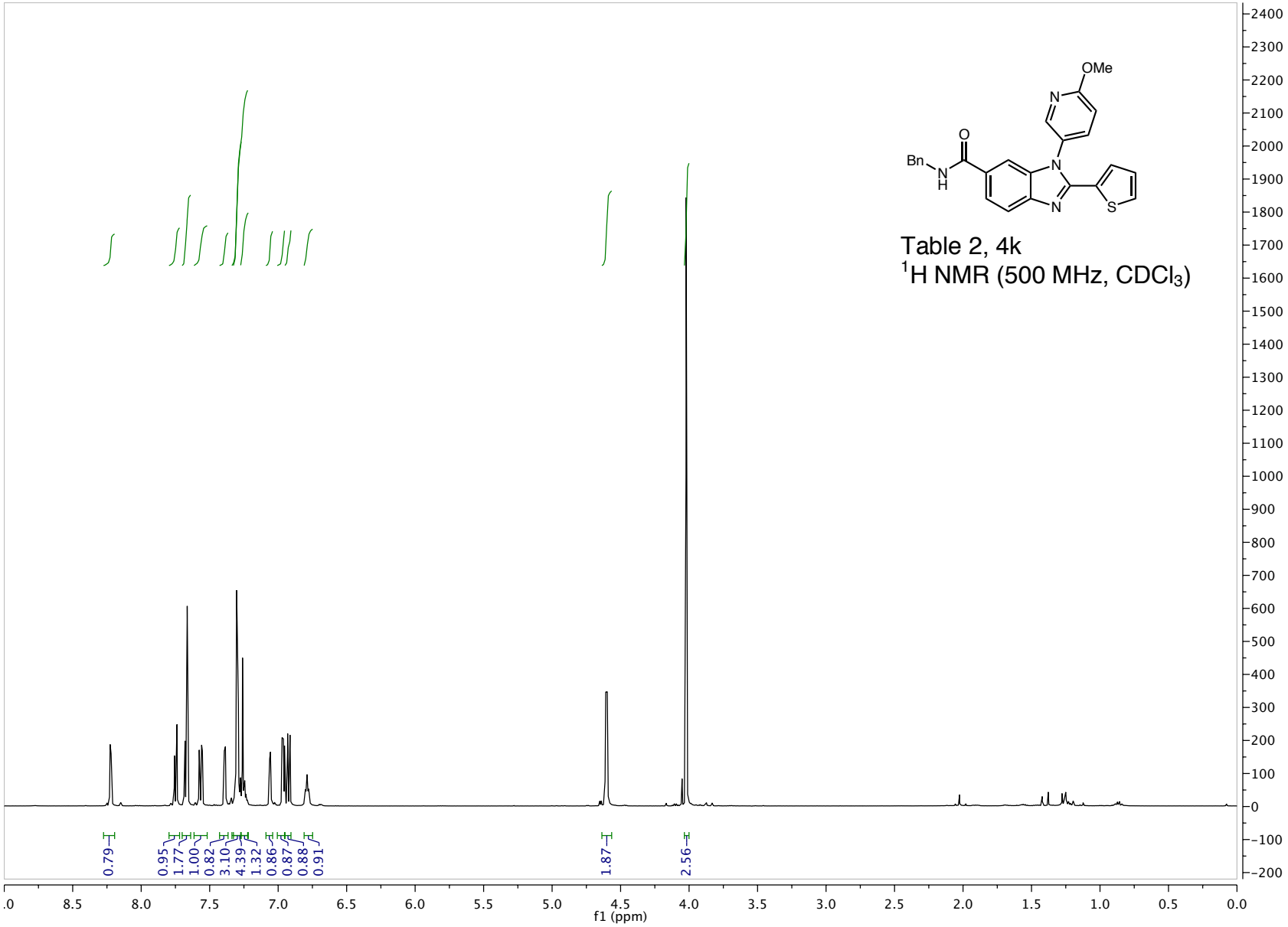


Table 2, 4j

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


OMe
N
O
Bn
N
H
N
N
S
Table 2, 4k
1H NMR (500 MHz, CDCl3)
0.79
0.95
1.77
1.00
0.82
3.10
4.39
1.32
0.86
0.87
0.88
0.91
1.87
2.56
f1 (ppm)

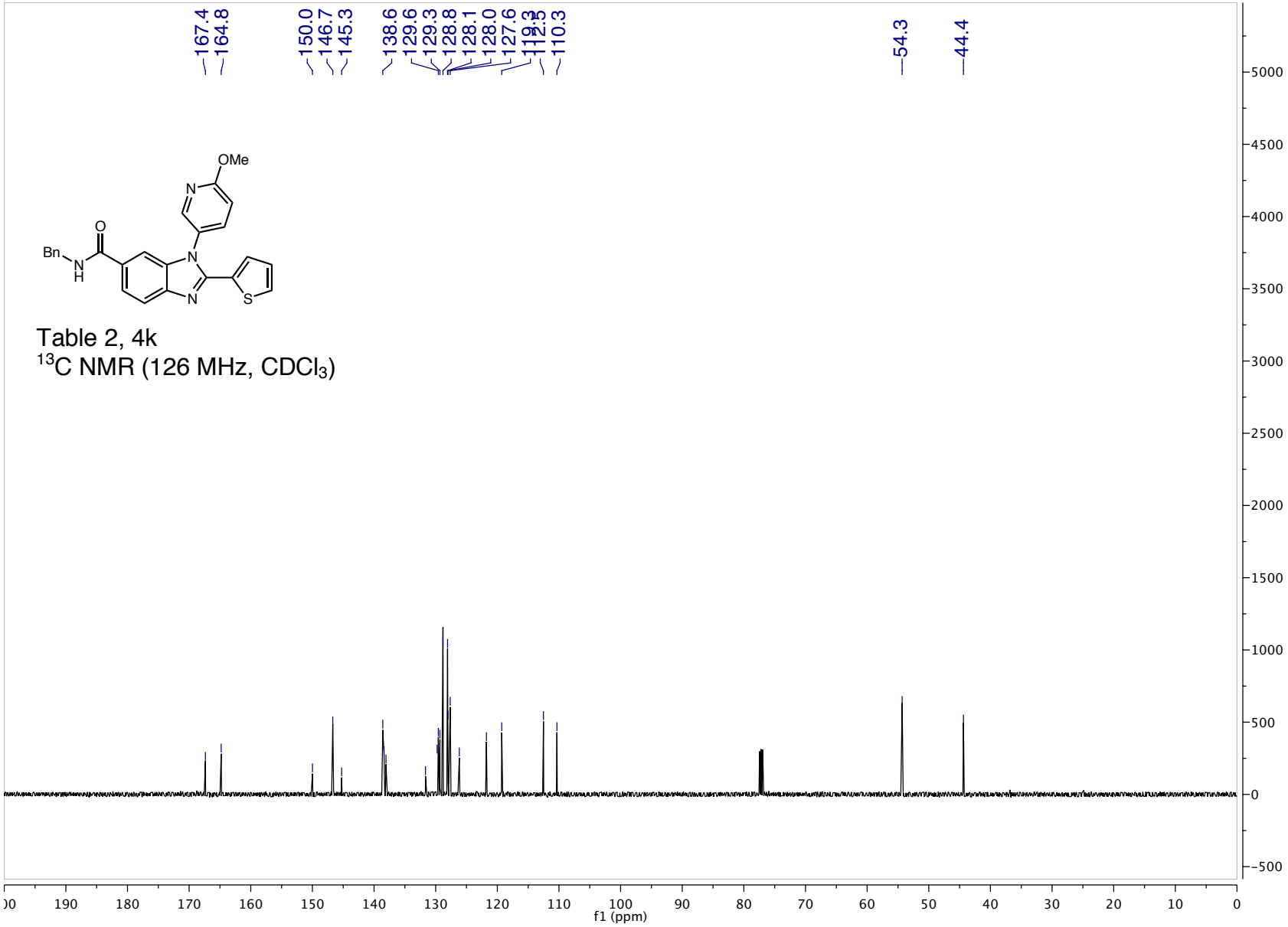
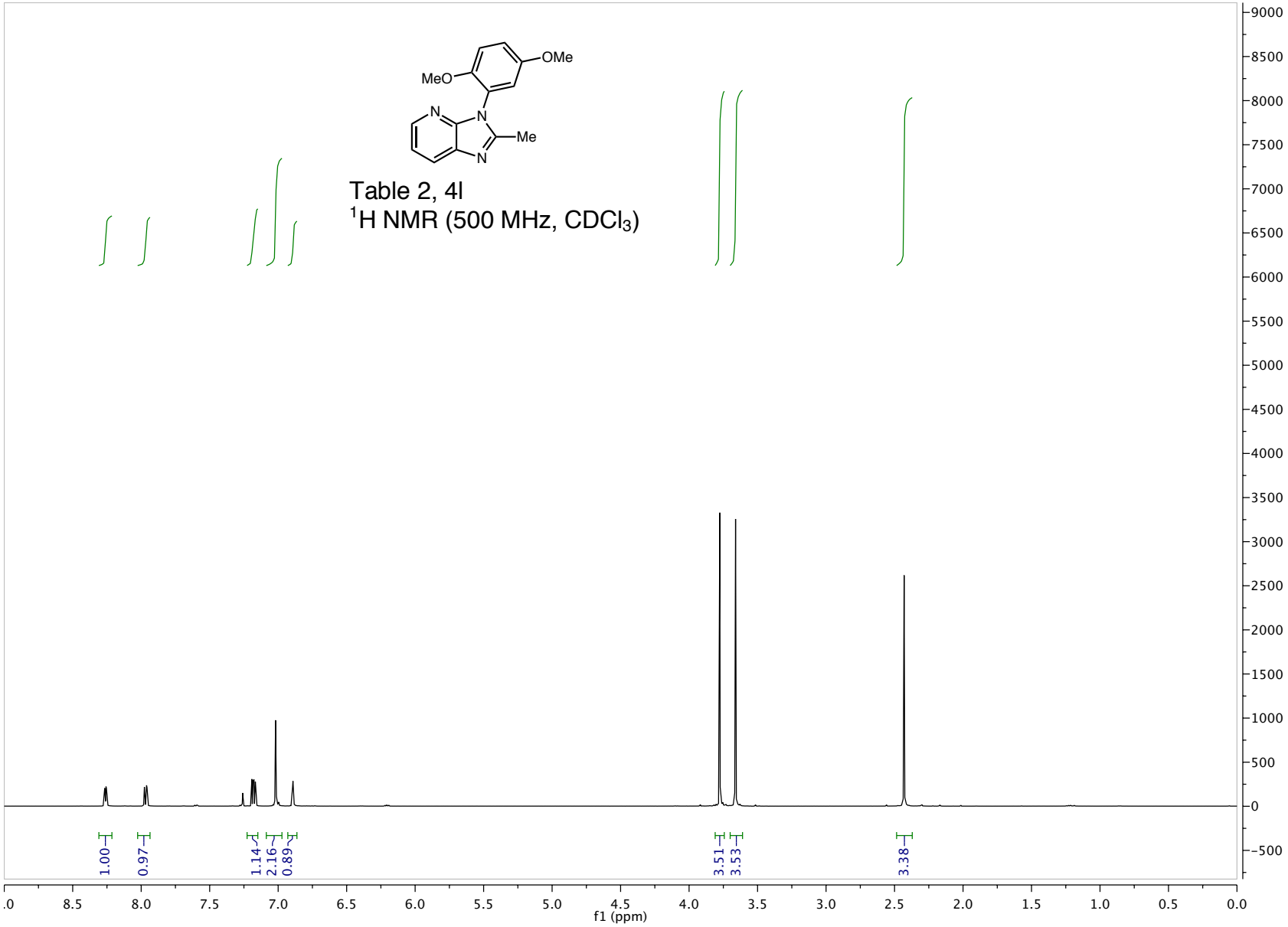
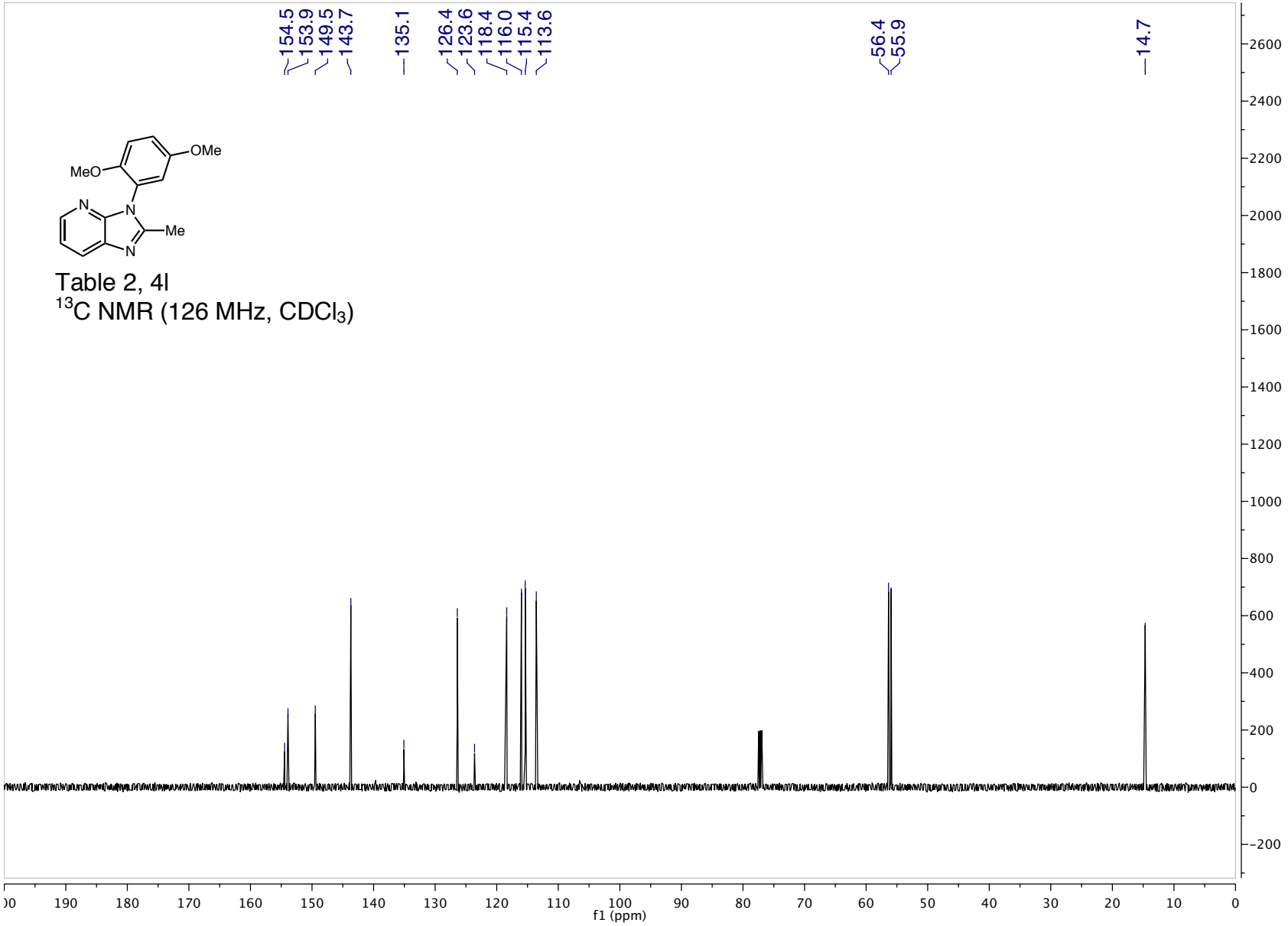
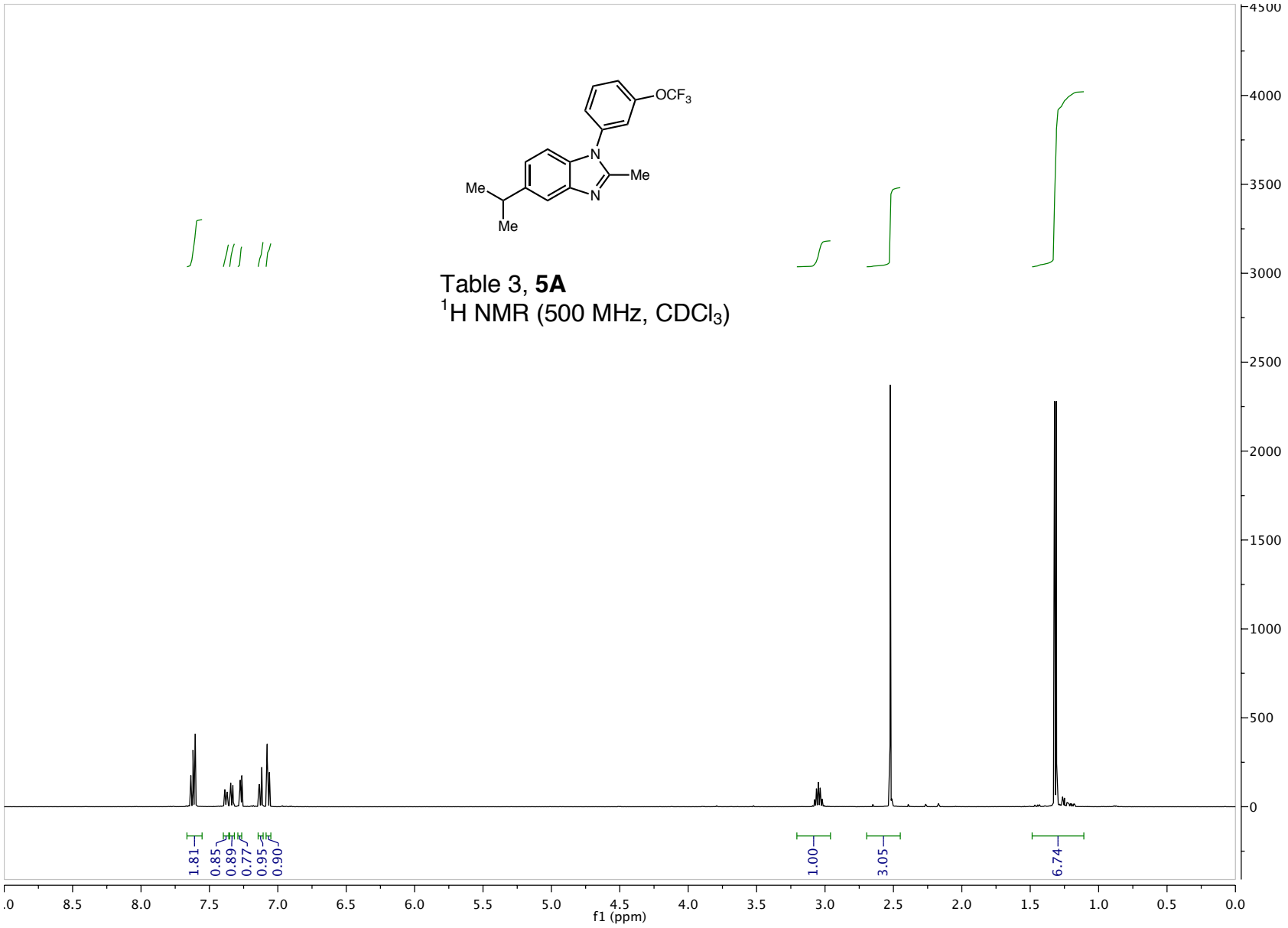


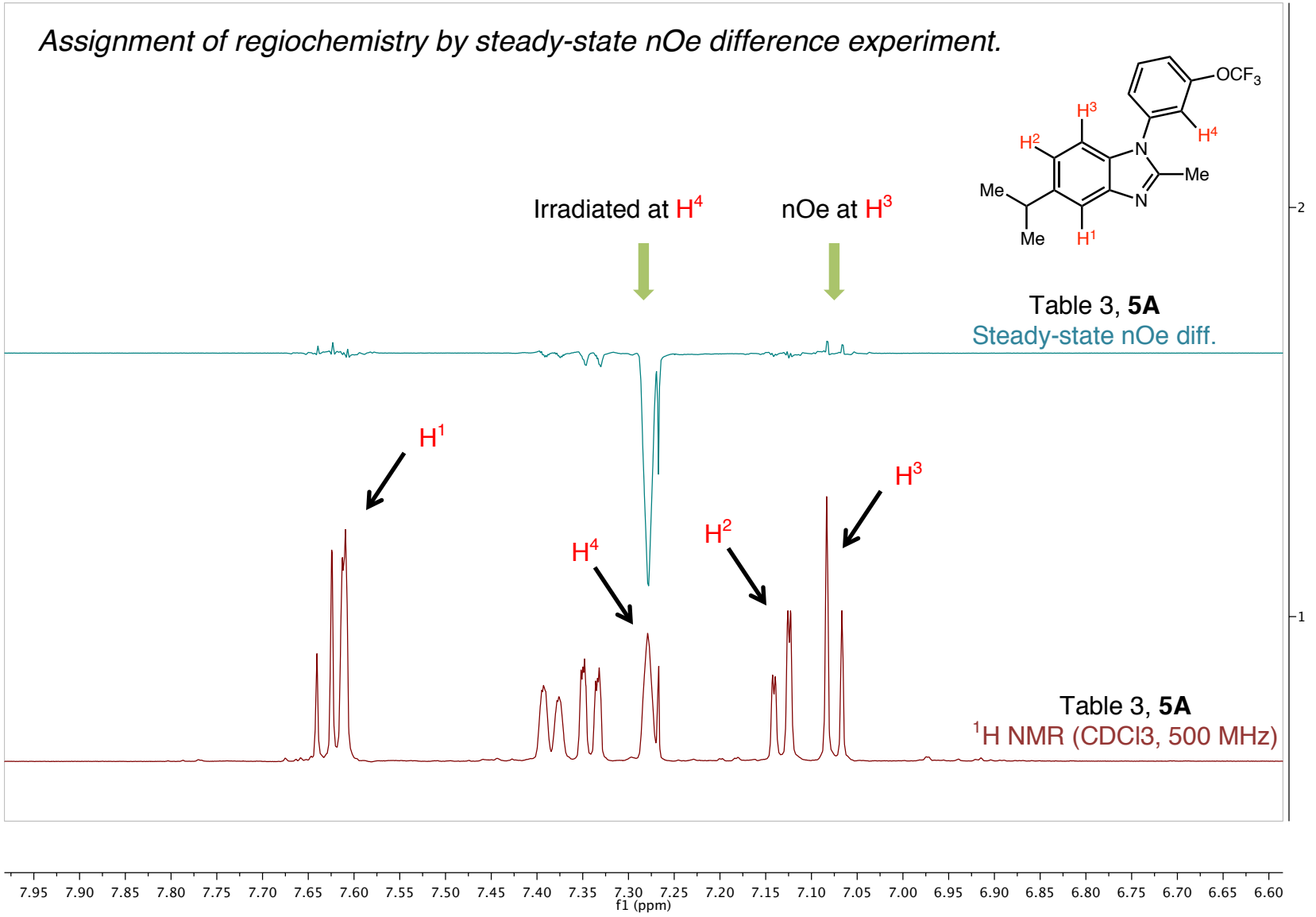
Table 2, 4k

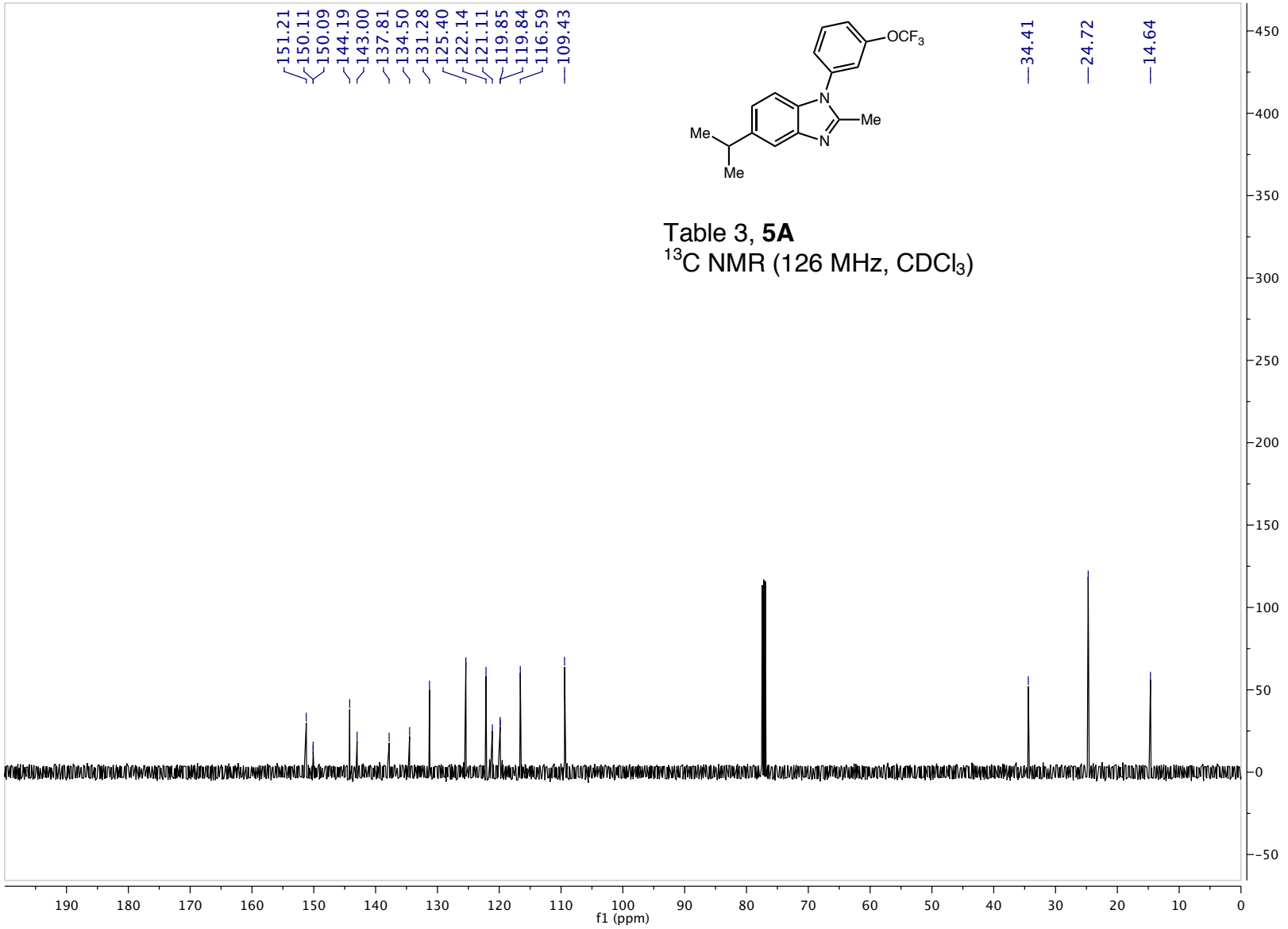
^{13}C NMR (126 MHz, $CDCl_3$)


OMe
MeO
N
N
Me
N
Table 2, 4l
^{1}H NMR (500 MHz, $CDCl_3$)
1.00
0.97
1.14
2.16
0.89
3.51
3.53
3.38
f1 (ppm)


154.5
153.9
149.5
143.7
135.1
126.4
123.6
118.4
116.0
115.4
113.6
56.4
55.9
14.7
MeO
OMe
N
N
Me
N
Table 2, 4l
13C NMR (126 MHz, CDCl3)
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OCF3
N
N
Me
Me
Me
Table 3, 5A
1H NMR (500 MHz, CDCl3)
1.81
0.85
0.89
0.77
0.95
0.90
1.00
3.05
6.74
f1 (ppm)


Assignment of regiochemistry by steady-state nOe difference experiment.
Irradiated at H4
nOe at H3
OCF3
H3
H2
H4
N
Me
Me
N
Me
H1
Table 3, 5A
Steady-state nOe diff.
H1
H4
H2
H3
Table 3, 5A
1H NMR (CDCl3, 500 MHz)
2
1
7.95 7.90 7.85 7.80 7.75 7.70 7.65 7.60 7.55 7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00 6.95 6.90 6.85 6.80 6.75 6.70 6.65 6.60
f1 (ppm)


151.21
150.11
150.09
144.19
143.00
137.81
134.50
131.28
125.40
122.14
121.11
119.85
119.84
116.59
109.43
34.41
24.72
14.64
OCF3
N
N
Me
Me
Me
Table 3, 5A
13C NMR (126 MHz, CDCl3)
f1 (ppm)

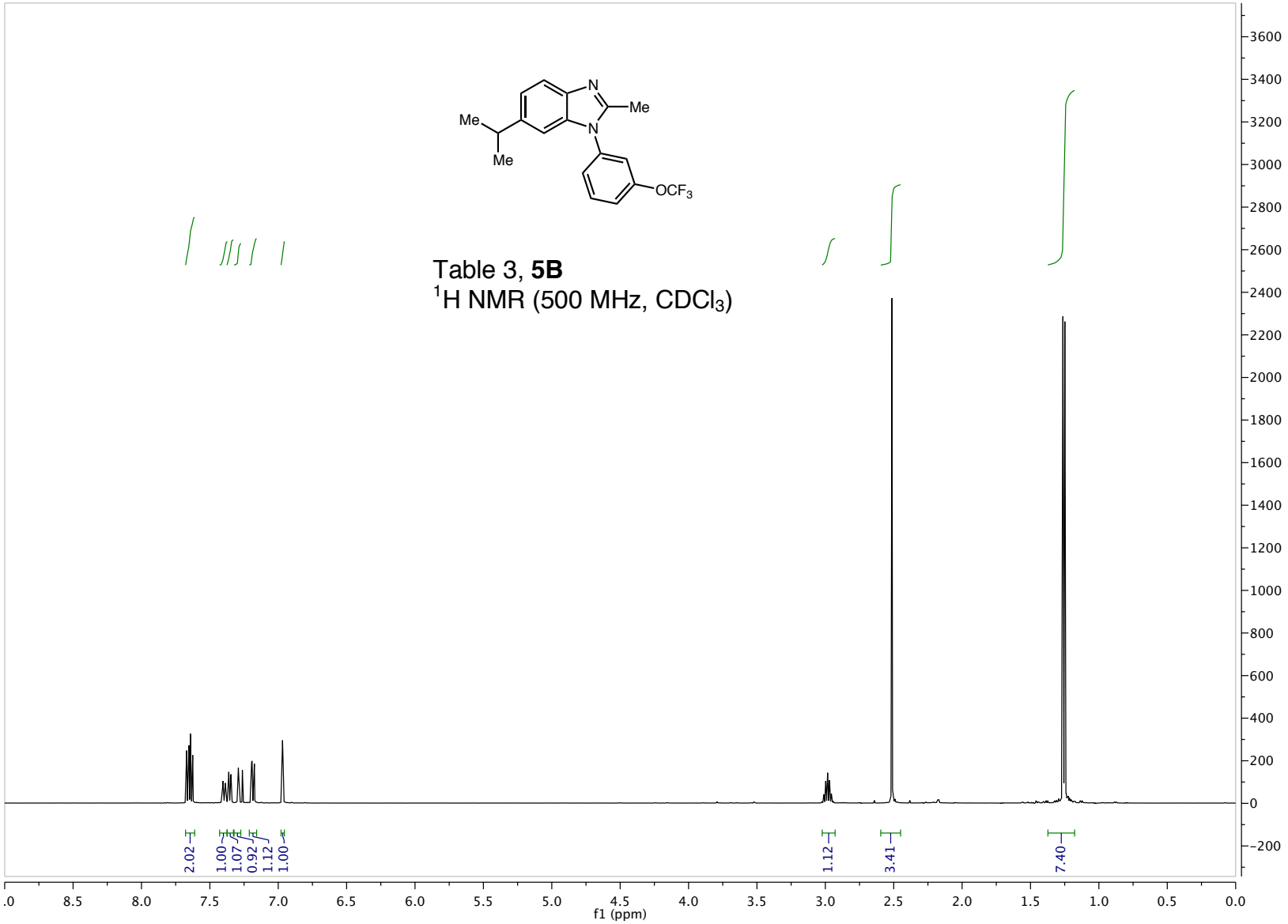
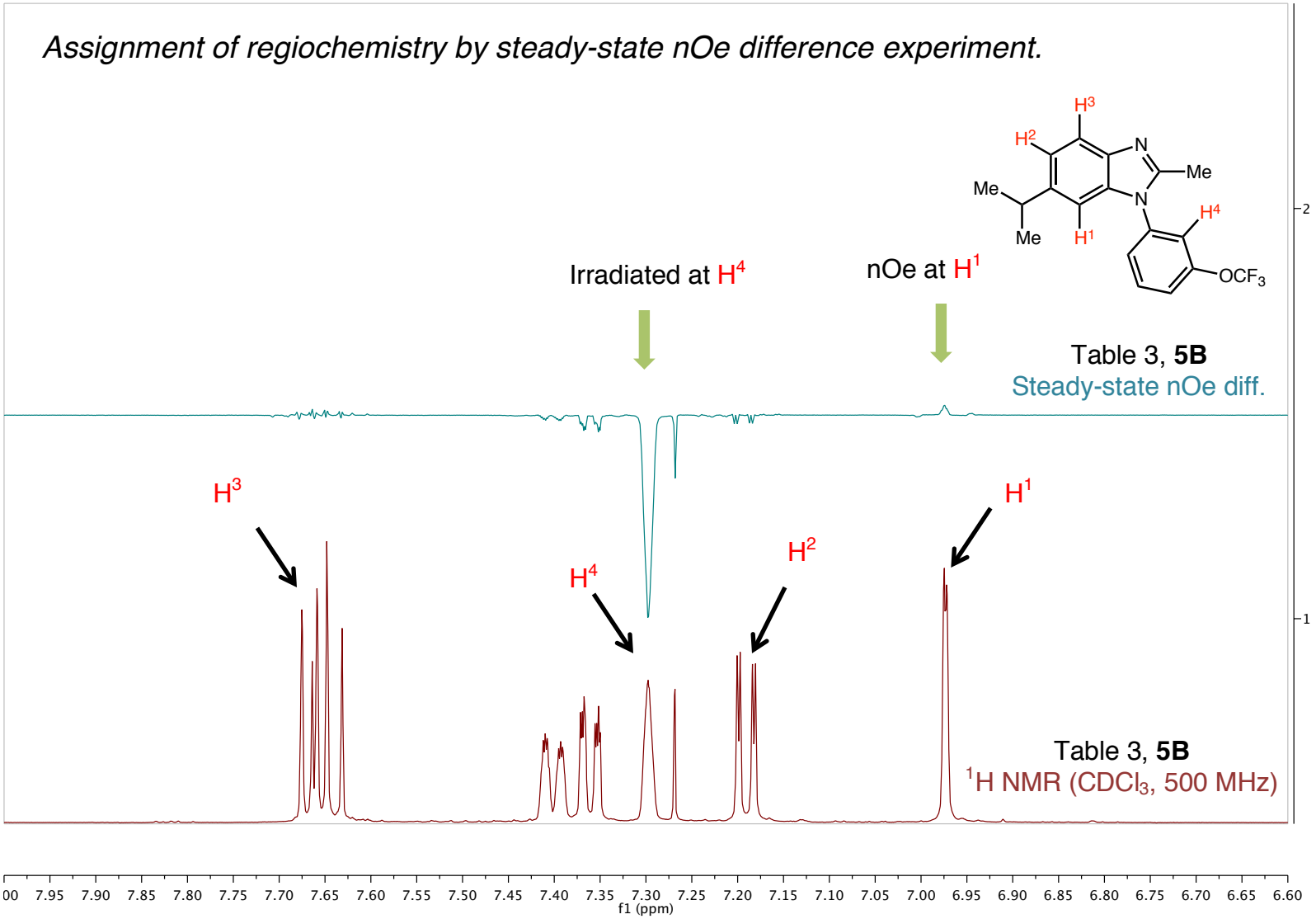


Table 3, **5B**
^{1}H NMR (500 MHz, $CDCl_3$)
Me
Me
N
N
Me
OCF_3
2.02
1.00
1.07
0.92
1.12
1.00
1.12
3.41
7.40
f1 (ppm)

Assignment of regiochemistry by steady-state nOe difference experiment.



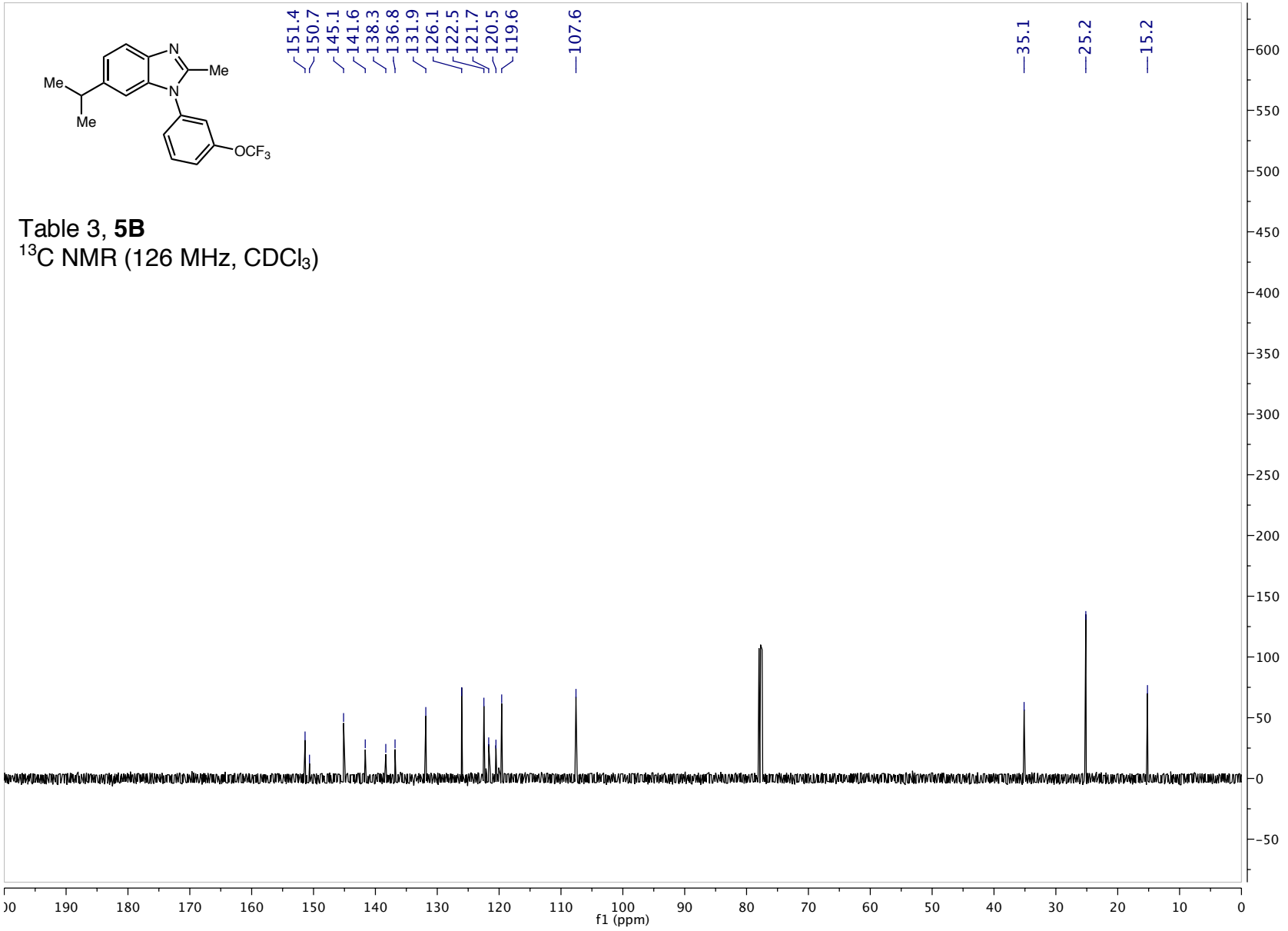


Table 3, **5B**
^{13}C NMR (126 MHz, $CDCl_3$)

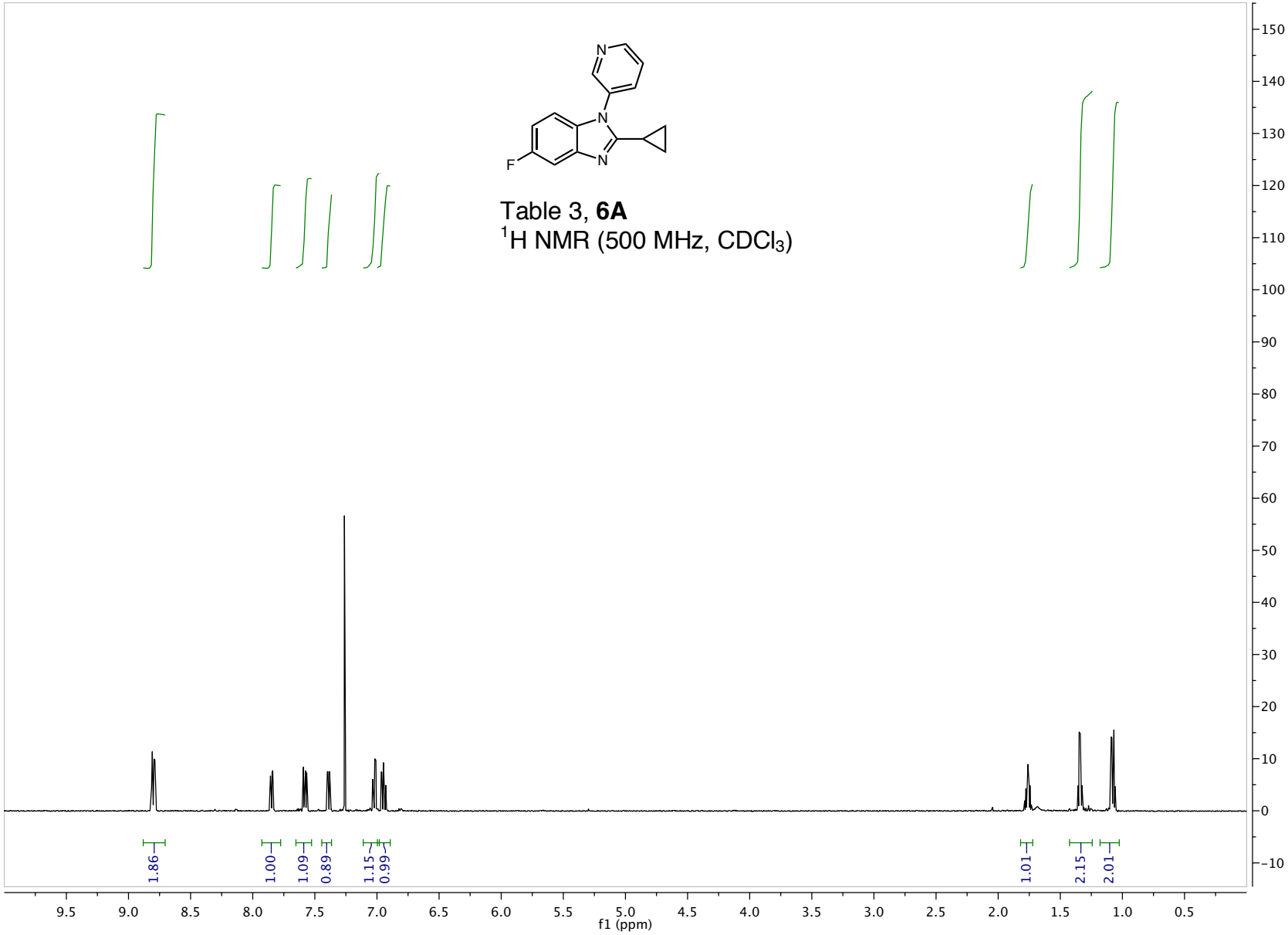
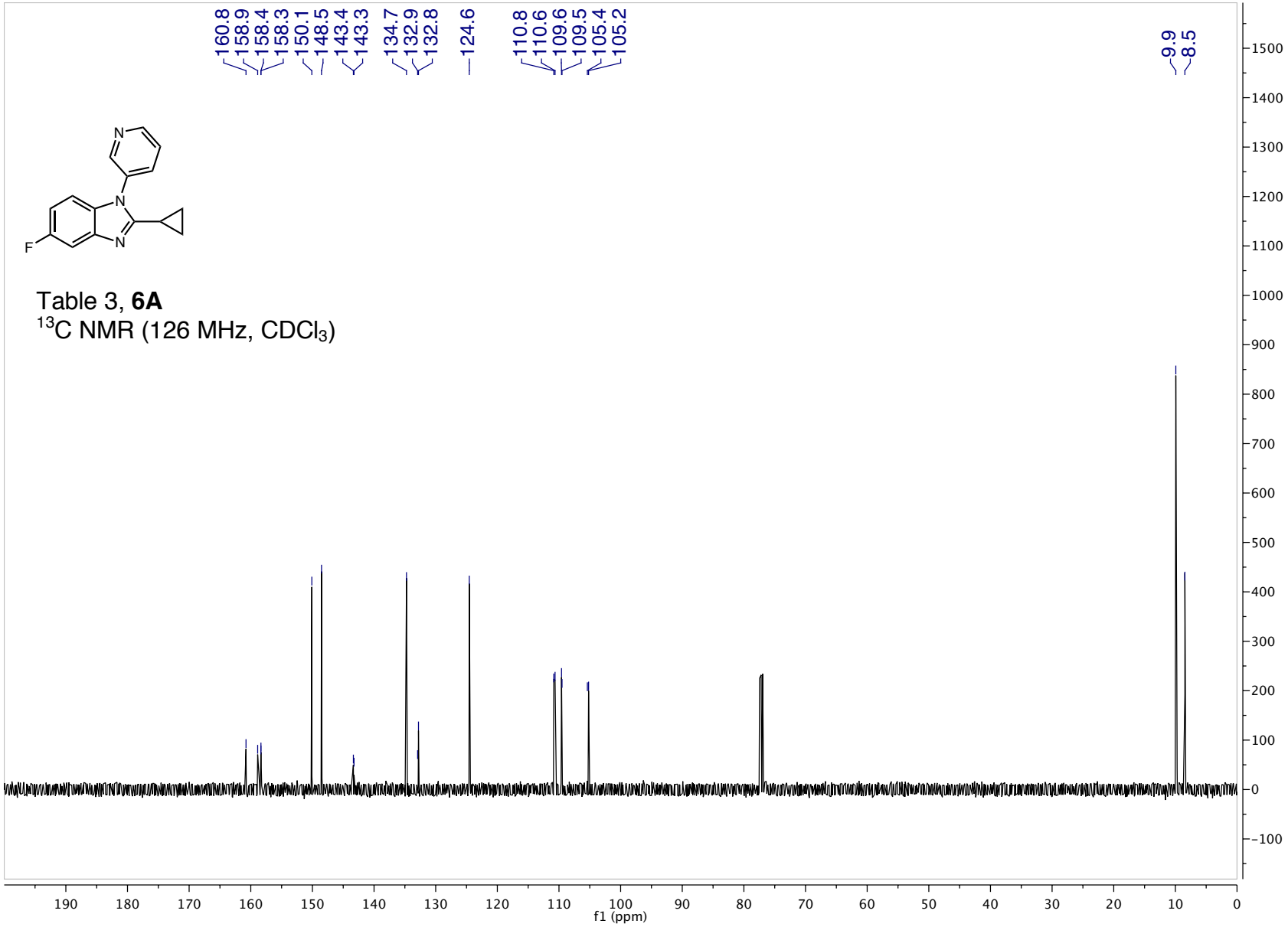
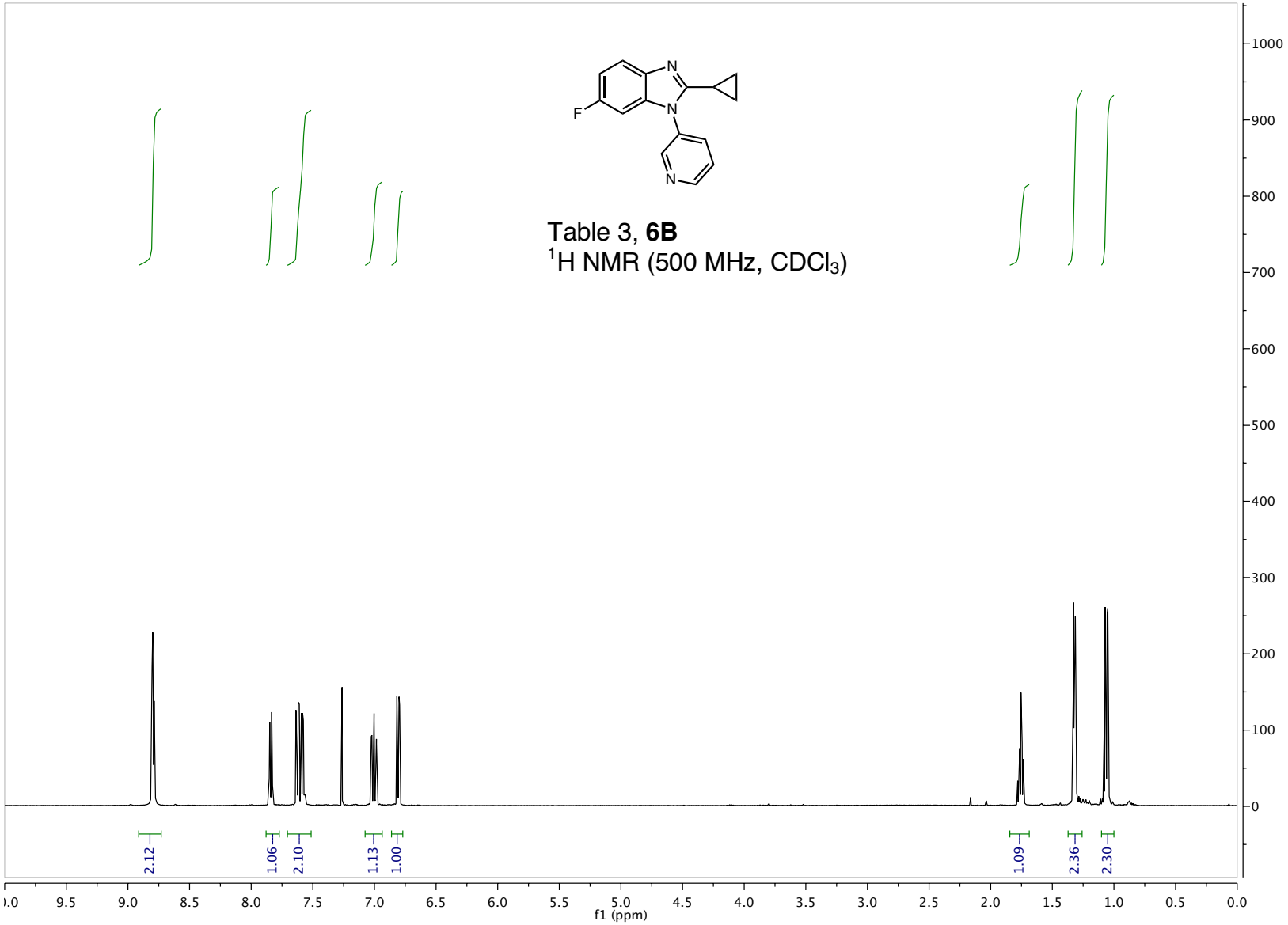
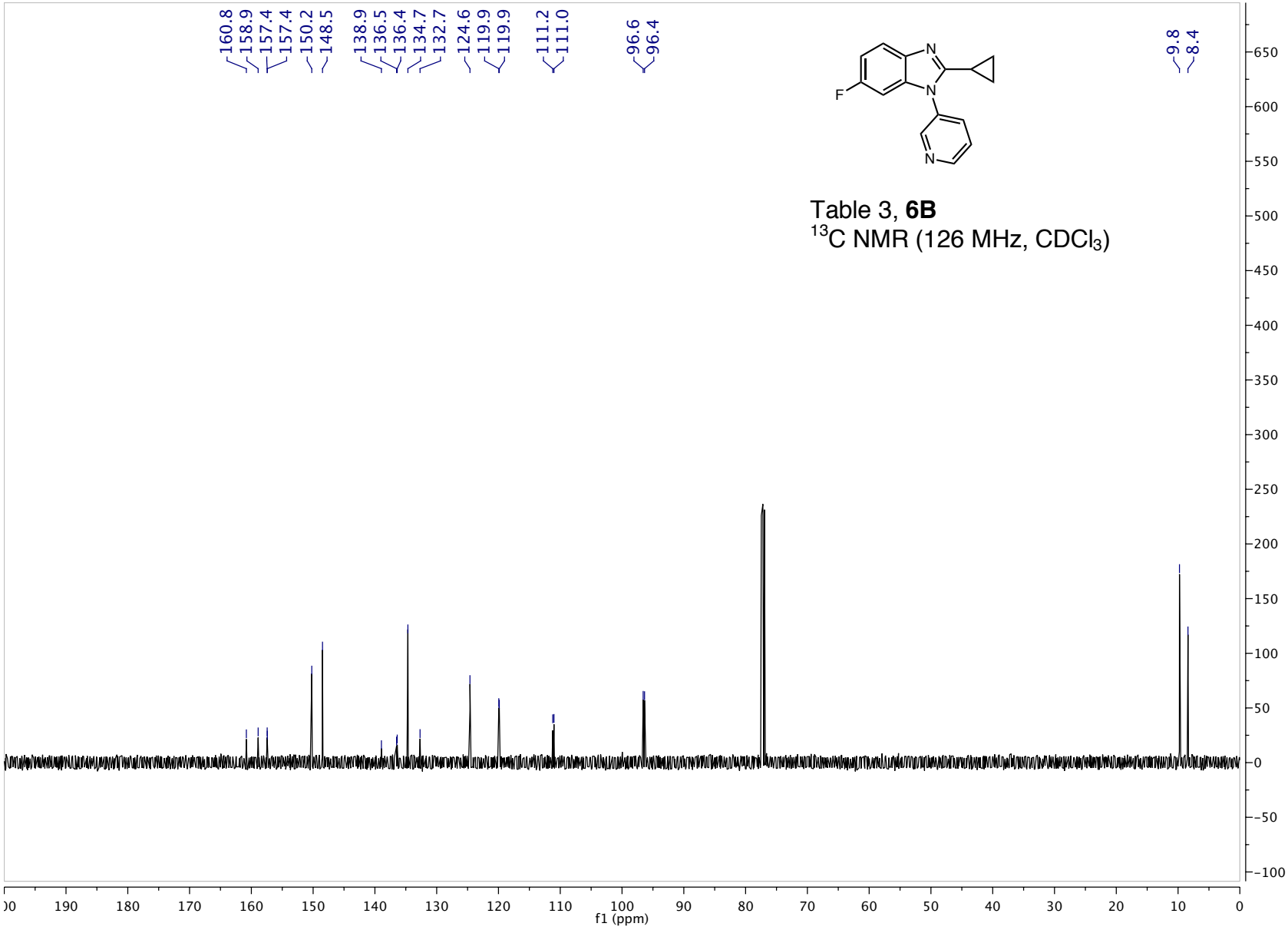
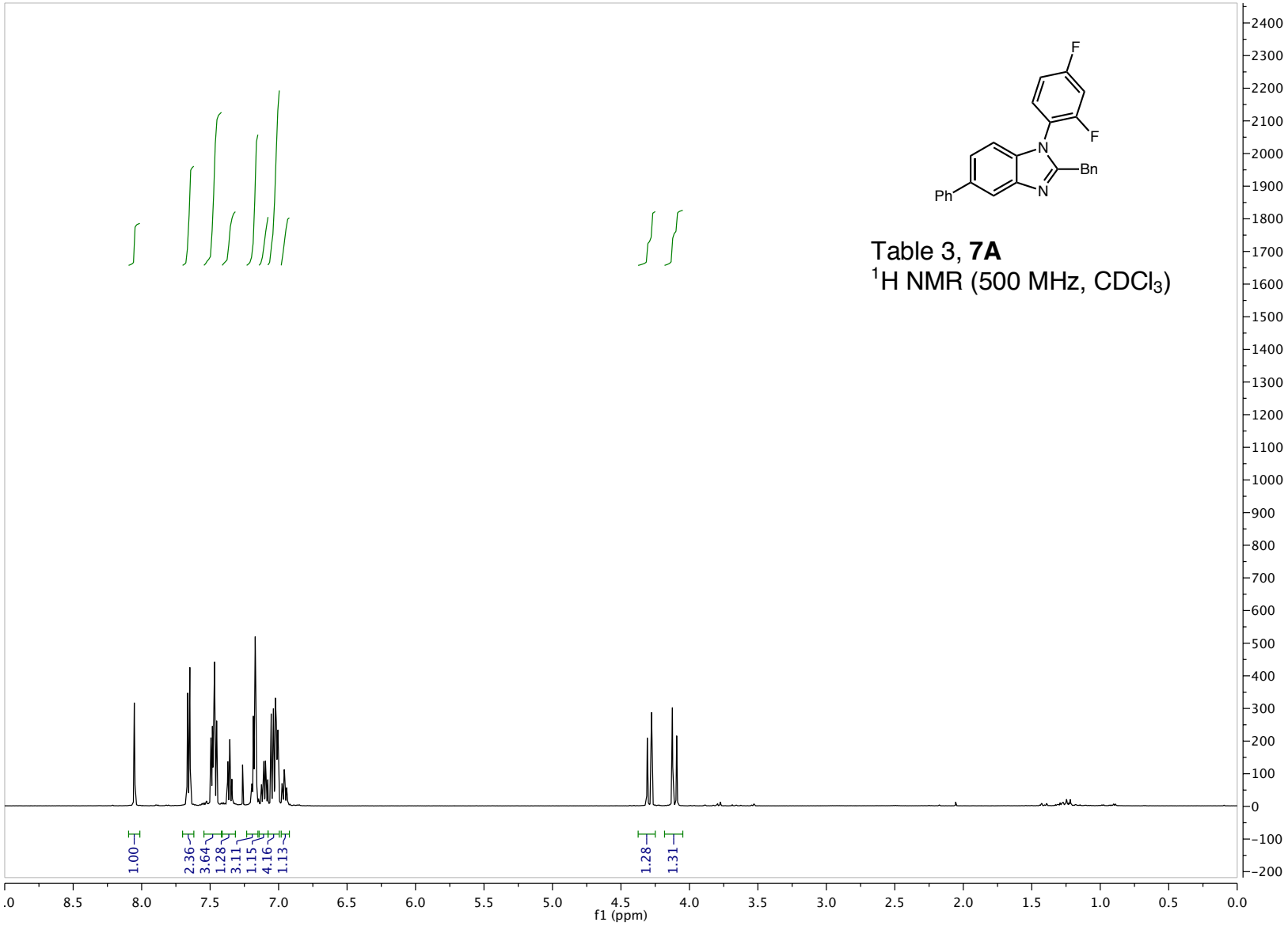


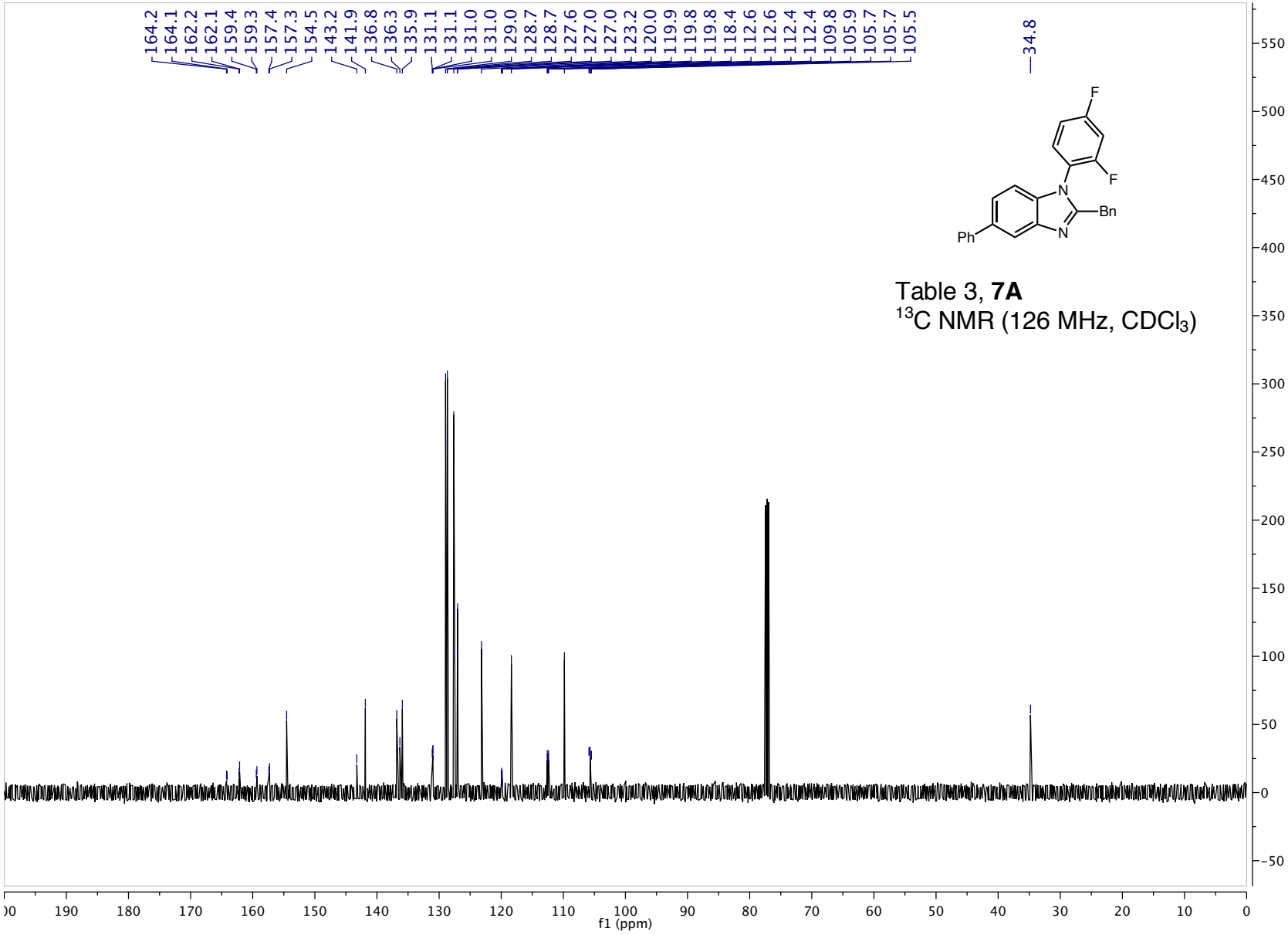
Table 3, **6A**
^{1}H NMR (500 MHz, $CDCl_3$)
f1 (ppm)
1.86
1.00
1.09
0.89
1.15
0.99
1.01
2.15
2.01


160.8
158.9
158.4
158.3
150.1
148.5
143.4
143.3
134.7
132.9
132.8
124.6
110.8
110.6
109.6
109.5
105.4
105.2
9.9
8.5
N
N
N
F
Table 3, **6A**
^{13}C NMR (126 MHz, $CDCl_3$)
f1 (ppm)


F
N
N
N
Table 3, 6B
1H NMR (500 MHz, CDCl3)
2.12
1.06
2.10
1.13
1.00
1.09
2.36
2.30
f1 (ppm)


160.8
158.9
157.4
157.4
150.2
148.5
138.9
136.5
136.4
134.7
132.7
124.6
119.9
119.9
111.2
111.0
96.6
96.4
9.8
8.4
F
N
N
N
Table 3, 6B
13C NMR (126 MHz, CDCl3)
f1 (ppm)


F
F
N
Bn
N
Ph
Table 3, 7A
1H NMR (500 MHz, CDCl3)
1.00
2.36
3.64
1.28
3.11
1.15
4.16
1.13
1.28
1.31
f1 (ppm)


164.2
164.1
162.2
162.1
159.4
159.3
157.4
157.3
154.5
143.2
141.9
136.8
136.3
135.9
131.1
131.1
131.0
131.0
129.0
128.7
128.7
127.6
127.0
127.0
123.2
120.0
119.9
119.8
119.8
118.4
112.6
112.6
112.4
112.4
109.8
105.9
105.7
105.7
105.5
34.8
F
F
N
Bn
N
Ph
Table 3, **7A**
^{13}C NMR (126 MHz, $CDCl_3$)
f1 (ppm)

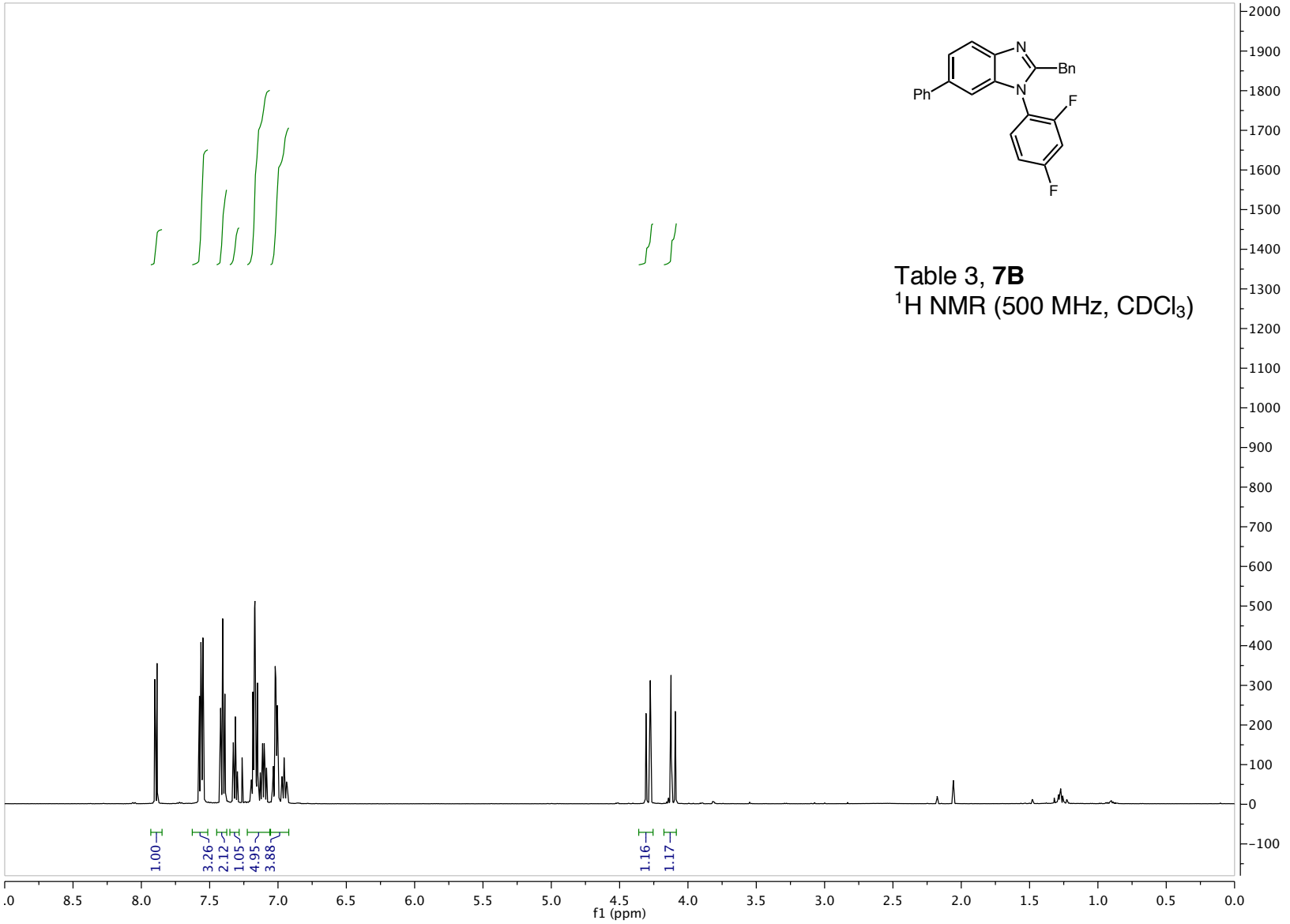
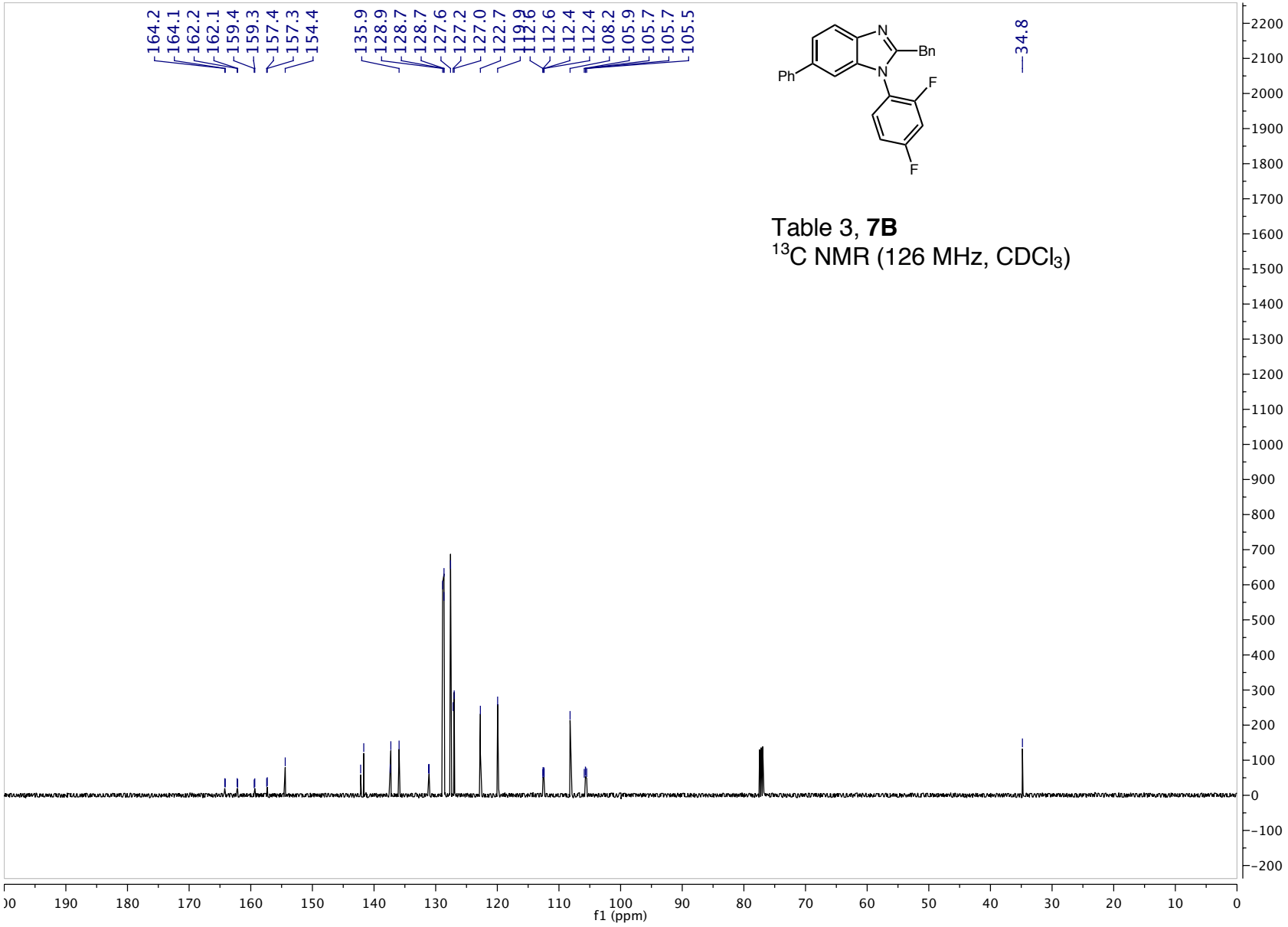


Table 3, 7B
1H NMR (500 MHz, CDCl3)
Ph
N
Bn
N
F
F
1.00
3.26
2.12
1.05
4.95
3.88
1.16
1.17
f1 (ppm)


164.2
164.1
162.2
162.1
159.4
159.3
157.4
157.3
154.4
135.9
128.9
128.7
128.7
127.6
127.2
127.0
122.7
112.6
112.4
112.4
108.2
105.9
105.7
105.7
105.5
34.8
N
Bn
Ph
N
F
F
Table 3, 7B
13C NMR (126 MHz, CDCl3)
f1 (ppm)

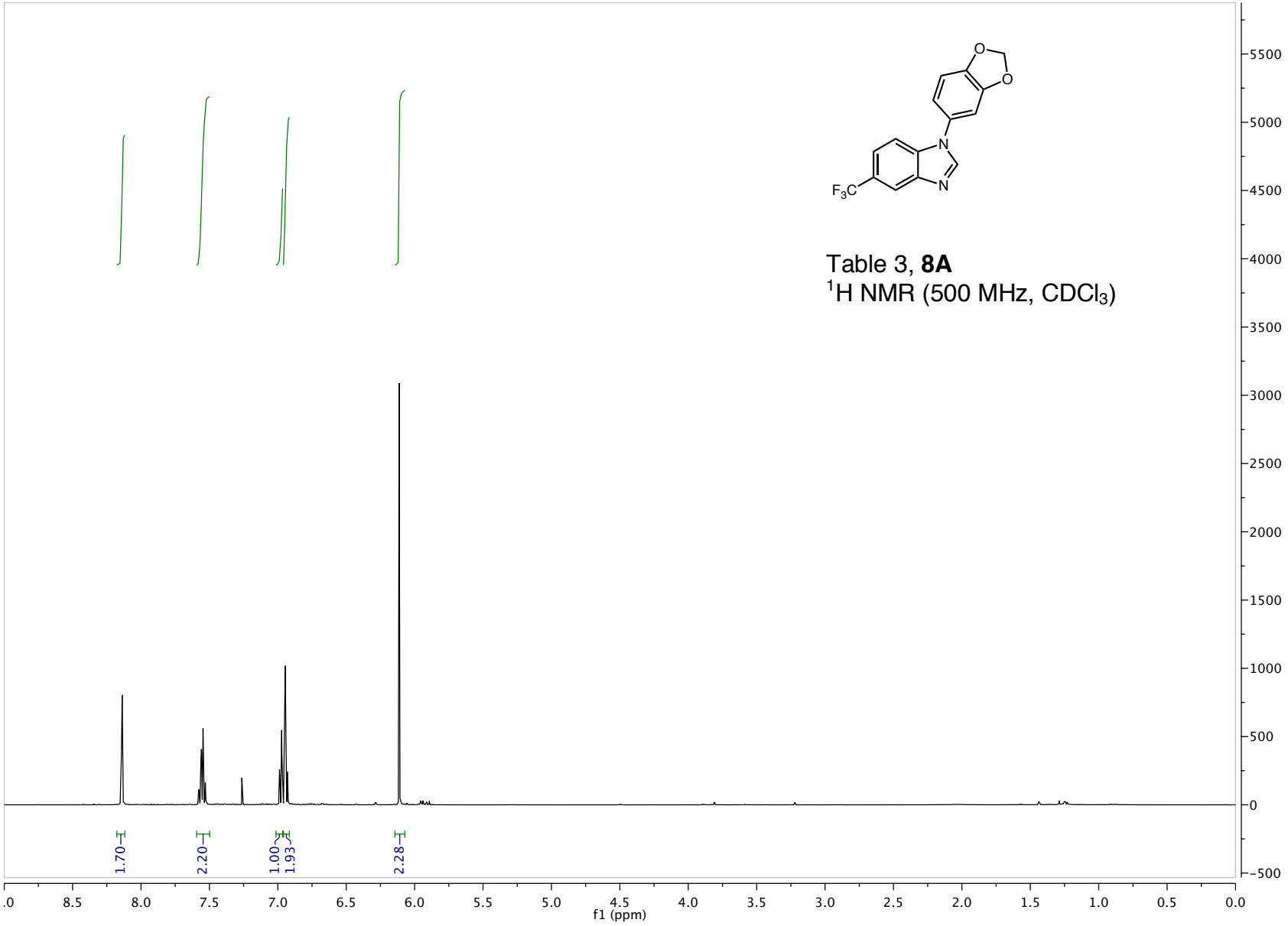
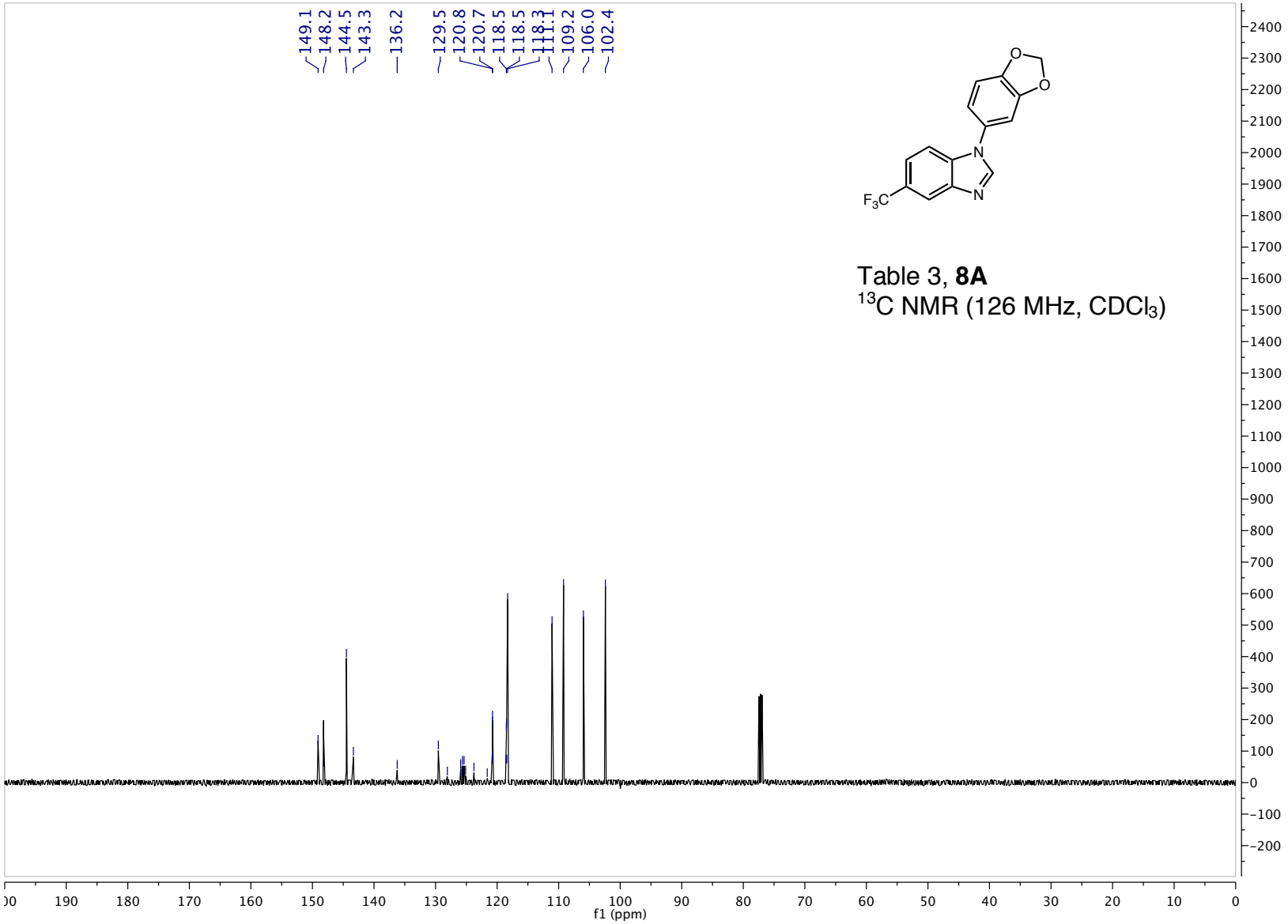
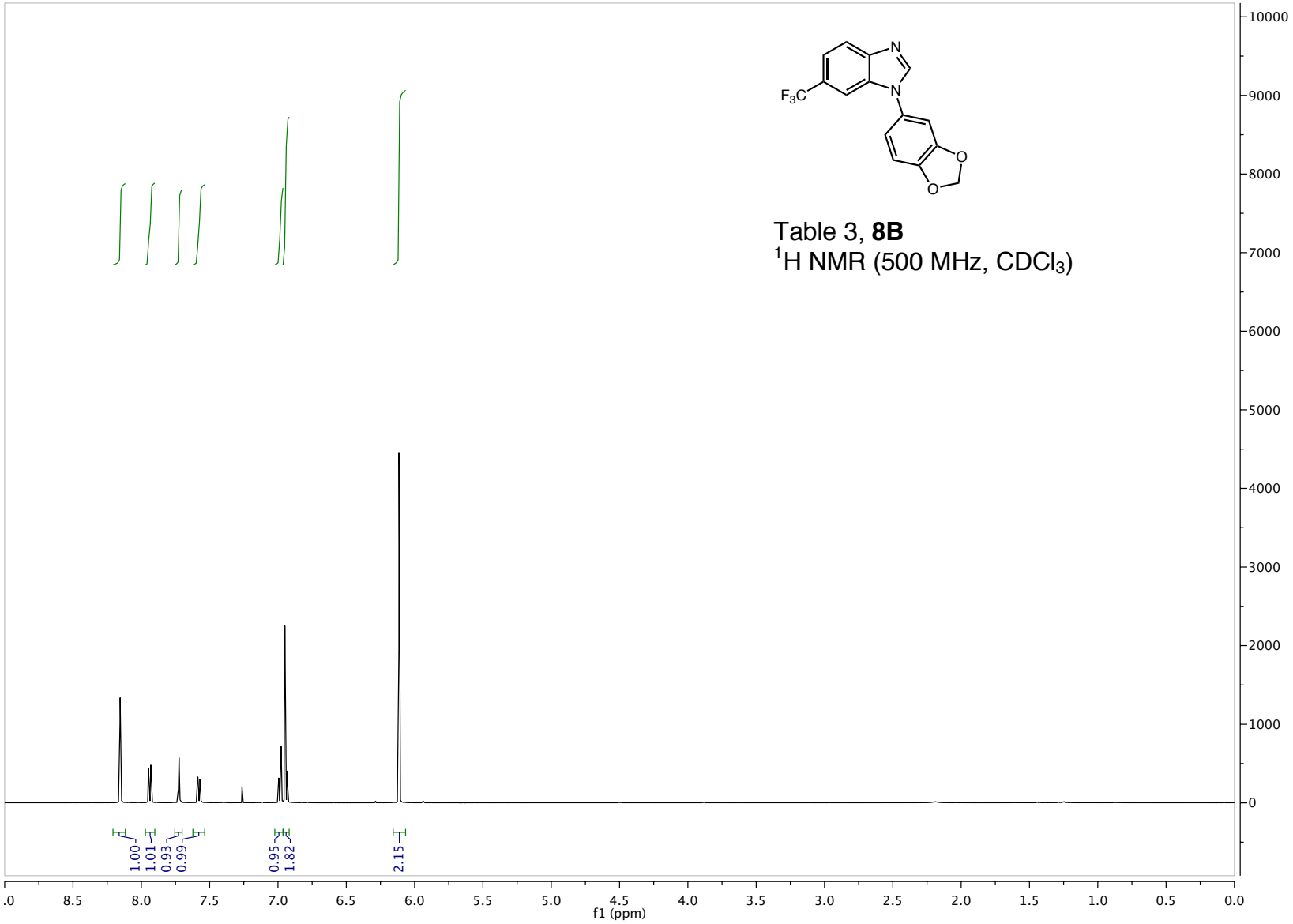


Table 3, 8A
1H NMR (500 MHz, CDCl3)
F3C
1.70
2.20
1.00
1.93
2.28
f1 (ppm)


149.1
148.2
144.5
143.3
136.2
129.5
120.8
120.7
118.5
118.5
118.3
111.1
109.2
106.0
102.4
O
O
N
N
F3C
Table 3, 8A
13C NMR (126 MHz, CDCl3)
f1 (ppm)


F3C
N
N
O
O
Table 3, 8B
1H NMR (500 MHz, CDCl3)
1.00
1.01
0.93
0.99
0.95
1.82
2.15
f1 (ppm)

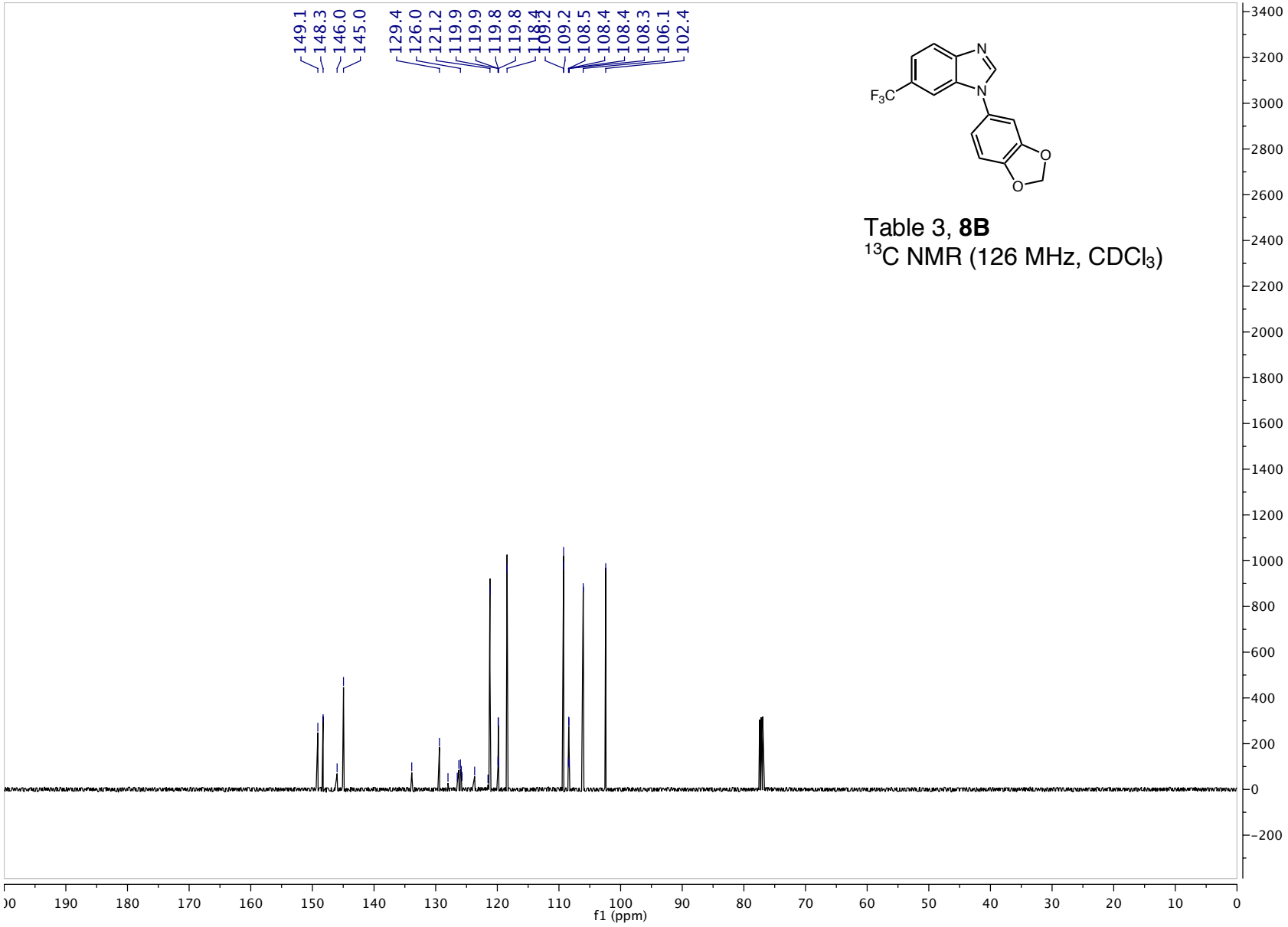


Table 3, **8B**
^{13}C NMR (126 MHz, $CDCl_3$)