

Supporting Information

Sulfonamide Synthesis via Calcium Triflimide Activation of Sulfonyl Fluorides

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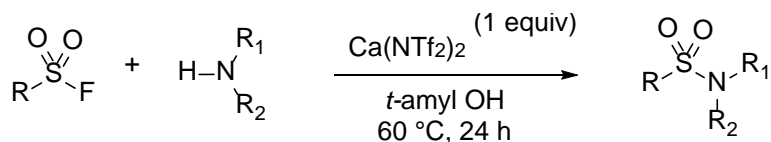
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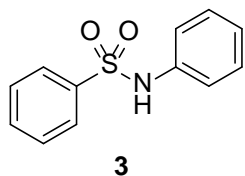
General Methods:

All commercially available chemicals, reagents and solvents were used as received. Calcium(II) bis(trifluoromethanesulfonimide) (CAS# 165324-09-4) was purchased from TCI America and MilliporeSigma. Reactions were monitored by thin layer chromatography (TLC) performed on Analtech, Inc. silica gel GF 250 μm plates or Merck silica gel plates (60 F₂₅₄) and were visualized with ultraviolet (UV) light (254 nm) and/or KMnO₄ staining or by UPLC-MS (Waters Acquity, ESI (ESI +/-, APCI +/-)). Proton nuclear magnetic resonance (¹H NMR) spectra, carbon nuclear magnetic resonance (¹³C NMR) spectra and fluorine nuclear magnetic resonance (¹⁹F NMR) spectra were recorded on a Bruker 400 (400, 101 and 376 MHz, respectively) or a Bruker 500 (500, 126 and 470 MHz, respectively) equipped with cryoprobes. Chemical shifts are reported in ppm relative to chloroform (¹H, δ = 7.26 and ¹³C NMR δ = 77.00), methanol (¹H, δ = 3.31, ¹³C NMR δ = 49.15) or dimethyl sulfoxide (¹H, δ = 2.50 ppm, ¹³C NMR δ = 39.51). The NMR peak multiplicities are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, pentate; sext, sextet; m, multiplet; br s, broad singlet. Infrared (IR) spectra were recorded with a Thermo-Nicolet Avatar 360 FT-IR or a Perkin-Elmer Spectrum RXI FT-IR spectrometer using a MIRacle ATR attachment. High-resolution mass spectra (HRMS) were acquired on an Agilent model 6220 MS(TOF) or were conducted at the California Institute of Technology Mass Spectroscopy Center using a JMS-60H (JEOL) double-focusing magnetic sector mass spectrometer. Melting points were recorded on a Sanford Research Systems OptiMelt or on a Mettler Toledo MP50 Melting Point System and are uncorrected. UPLC-MS (Waters Acquity), Column: Waters Acquity HSS T3, 2.1 mm x 50 mm, C18, 1.7 μm ; Column Temperature 60 °C, Mobile Phase: A: 0.1% formic acid in water (v/v); Mobile phase B: 0.1% formic acid in acetonitrile (v/v), Gradient Profiles: Flow - 1.25 mL/min, 1.5 min Run: Initial conditions: A-95%:B-5%; hold at initial from 0.0-0.1 min; Linear Ramp to A-5%:B-95% over 0.1-1.0 min; hold at A-5%:B-95% from 1.0-1.1 min; return to initial conditions 1.1-1.5 min, 3.0 min run: Initial conditions: A-95%:B-5%; hold at initial from 0.0-0.1 min; Linear Ramp to A-5%:B-95% over 0.1-2.6 min; hold at A-5%:B-95% from 2.6-2.95 min; return to initial conditions 2.95-3.0 min. Detectors: Waters Acquity PDA ; 200-450 nm scan; 1.2 nm interval, Waters Acquity ELS detector; drift tube 65 °C, Waters SQ MS(single quad) Tune: ESI- 3.5kV Capillary/APCI (in ESI mode)-0.3 μA Corona Pin, 30 V Cone, Source 150 °C , Desolvation 475 °C, Desolvation Gas N₂ 400 L/hr, MS Methods: ESI (ESI+/-, APCI+/-), 100-2000 m/z scan, 0.4 sec scan time, Centroid, Injection Volume: 5 μL , System Components: Waters Acquity UPLC (Acquity Binary Solvent Manager, 2777C-Autosampler, Acquity PDA, Acquity ELS and Acquity Column Manager) and Waters Acquity SQ systems from Waters Corporation, Milford, MA. Column chromatography was performed on an ISCO Combiflash Rf⁺ system using a pre-packed column with a gradient of hexanes or heptane and ethyl acetate.



General procedure for the synthesis of sulfonamides: To a two-dram vial containing sulfonyl fluoride (1 equiv), amine substrate (2 equiv) and Ca(NTf₂)₂ (1 equiv), *t*-amyl alcohol (0.2 M) was added. The reaction mixture was stirred at 60 °C for 24 h, cooled to room temperature and partitioned between ethyl acetate and either 0.5 N HCl (1x) and brine (1x), or brine (1x). The brine layer was washed with ethyl acetate (1x), and the combined organic fraction was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified by column chromatography. An average of two independent experiments was used to calculate the yield reported in the manuscript. Reactions were performed on 0.40 mmol scale unless otherwise noted.

A control reaction was performed without Ca(NTf₂)₂ following the general procedure.



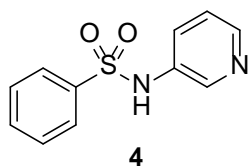
***N*-Phenylbenzenesulfonamide (3):** Compound **3** was prepared following the general procedure using benzenesulfonyl fluoride and aniline. Yield = 83 mg, 89% and 80 mg, 86%, average: 88%. Without Ca = No reaction. The NMR spectra are consistent with those previously reported.¹

Physical State: Brown solid

¹H NMR: (400 MHz, CDCl₃) δ 7.79 (d, *J* = 7.3 Hz, 2 H), 7.53 (t, *J* = 7.4 Hz, 1 H), 7.43 (t, *J* = 7.7 Hz, 2 H), 7.23 (t, *J* = 7.8 Hz, 2 H), 7.15 – 7.04 (m, 3 H), 6.92 (s, 1 H).

¹³C NMR: (101 MHz, CDCl₃) δ 139.0, 136.3, 133.0, 129.3, 129.0, 127.2, 125.6, 121.8.

HRMS: Calculated for C₁₂H₁₁NO₂S [M]⁺ 233.0510, found 233.0507.



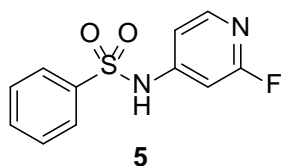
***N*-(Pyridin-3-yl)benzenesulfonamide (4):** Compound **4** was prepared following the general procedure using benzenesulfonyl fluoride and 3-aminopyridine. Yield = 20 mg, 85 % (0.10 mmol scale) and 20 mg, 85% (0.10 mmol scale); average: 85%. Without Ca = No reaction (0.10 mmol scale). The NMR spectra are consistent with those previously reported.²

Physical State: White solid

¹H NMR: (400 MHz, DMSO-*d*₆) δ 10.6 (br s, 1 H), 8.27-8.23 (multiple peaks, 2 H), 7.77 - 7.75 (multiple peaks, 2 H), 7.62 (m, 1 H), 7.58 – 7.54 (multiple peaks, 2 H), 7.50 (m, 1 H), 7.28 (dd, *J* = 5.0, 8.0 Hz, 1 H).

¹³C NMR: (101 MHz, DMSO-*d*₆) δ 145.4, 141.8, 139.0, 134.4, 133.3, 129.5, 127.4, 126.7, 124.0.

HRMS: Calculated for C₁₁H₁₀N₂O₂S [M+H]⁺ 235.0541, found 235.0548.



***N*-(2-fluoropyridin-4-yl)benzenesulfonamide (5):** Compound **5** was prepared following the general procedure using benzenesulfonyl fluoride and 5-amino-2-fluoropyridine. Yield = 40 mg; 40% and 40 mg; 40% average: 40%. Without Ca = No reaction.

Physical State: White solid

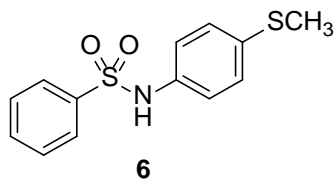
¹H NMR: (400 MHz, DMSO-*d*₆) δ 10.50 (br s, 1 H), 7.63 (br s, 1 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.68-7.63 (m, 2 H), 7.59-7.55 (m, 2 H), 7.11 (dd, *J* = 3.0, 9.0 Hz, 1 H).

¹³C NMR: (101 MHz, DMSO-*d*₆) δ 159.8 (d, ¹*J*_{CF} = 234.0 Hz), 139.7 (d, ³*J*_{CF} = 16.0 Hz), 138.7, 135.0 (d, ⁴*J*_{CF} = 9.0 Hz), 133.3, 132.6 (d, ⁵*J*_{CF} = 5.0 Hz), 129.5, 126.7, 110.1 (d, ²*J*_{CF} = 40.0 Hz).

¹⁹F NMR: (376 MHz, DMSO-*d*₆) δ -73.2.

IR: (neat, ν cm⁻¹) 3110, 1606, 1497, 1479, 1446, 1386, 1331, 1302, 1252, 1165, 1090, 1025.

HRMS: Calculated for C₁₁H₁₀FN₂O₂S [M+H]⁺ 253.0447, found 253.0442.



***N*-(4-(methylthio)phenyl)benzenesulfonamide (6):** Compound **6** was prepared following the general procedure using benzenesulfonyl fluoride and 4-methylthioaniline. Yield = 85 mg; 76% and 95 mg; 85%, average: 81%. Without Ca = No reaction.

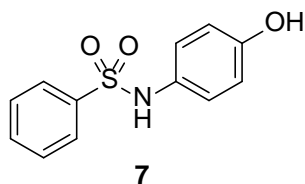
Physical State: Purple crystalline solid, melting point = 88 – 90 °C.

¹H NMR: (400 MHz, DMSO-*d*₆) δ 10.30 (br s, 1 H), 7.76 (br m, 2 H), 7.62 - 7.55 (m, 3 H), 7.14 - 7.13 (m, 2 H), 7.06 (br m, 2 H), 2.37 (s, 3 H).

¹³C NMR: (101 MHz, DMSO-*d*₆) δ 139.4, 134.8, 133.5, 132.9, 129.3, 127.1, 126.7, 121.3, 15.1.

IR: (neat, ν cm⁻¹) 3310, 3294, 2912, 2854, 2356, 2331, 1597, 1493, 1452, 1435, 1385, 1332, 1315, 1290, 1215, 1153, 1086, 1012, 995, 929, 900.

HRMS: Calculated for C₁₃H₁₃N₂O₂S₂ [M]⁺ 279.0388, found 279.0375.



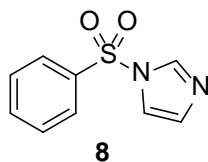
N-(4-Hydroxyphenyl)benzenesulfonamide (7): Compound **7** was prepared following the general procedure using benzenesulfonyl fluoride and 4-aminophenol. Yield = 17 mg; 68% (0.10 mmol scale) and 15.6 mg; 64% (0.10 mmol scale), average: 66%. Without Ca = No reaction (0.10 mmol scale). The NMR spectra are consistent with those previously reported.³

Physical State: Yellow oil

¹H NMR: (400 MHz, DMSO-*d*₆) δ 9.73 (br s, 1 H), 9.31 (br s, 1 H), 7.66–7.64 (multiple peaks, 2 H), 7.61–7.56 (multiple peaks, 1 H), 7.54–7.49 (multiple peaks, 2H), 6.84–6.80 (m, 2 H), 6.61–6.57 (m, 2 H).

¹³C NMR: (101 MHz, DMSO-*d*₆) δ 154.9, 139.5, 132.6, 129.1, 128.4, 126.7, 124.1, 115.5.

HRMS: Calculated for C₁₂H₁₁NO₃S [M]⁺ 249.0460, found 249.0456.



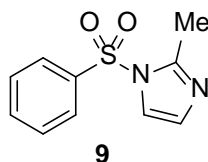
1-(Phenylsulfonyl)-1H-imidazole (8): Compound **8** was prepared following the general procedure using benzenesulfonyl fluoride and imidazole. Yield = 16 mg; 77% (0.10 mmol scale) and 17 mg; 82% (0.10 mmol scale), average: 80%. Without Ca = No reaction (0.10 mmol scale).⁴

Physical State: White solid

¹H NMR: (400 MHz, CDCl₃) δ 8.02 (br m, 1 H), 7.95 - 7.93 (m, 2 H), 7.70 – 7.66 (m, 1 H), 7.59 - 7.55 (m, 2 H), 7.30 (t, *J* = 2.0 Hz, 1 H), 7.09 – 7.08 (m, 1 H).

¹³C NMR: (101 MHz, CDCl₃) δ 137.9, 136.7, 134.9, 131.5, 129.8, 127.3, 117.5.

HRMS: Calculated for C₉H₈N₂O₂S [M+H]⁺ 209.0385, found 209.0389.



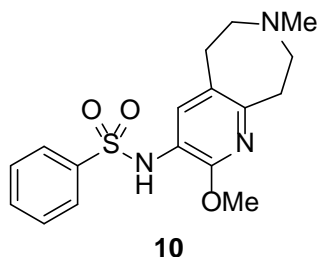
2-Methyl-1-(phenylsulfonyl)-1H-imidazole (9): Compound **9** was prepared following the general procedure using benzenesulfonyl fluoride and 2-methylimidazole. Yield = 68 mg; 77% and 65 mg; 73%, average: 75%. Without Ca = no reaction. The NMR spectra are consistent with those previously reported.⁵

Physical State: White solid

¹H NMR: (400 MHz, CDCl₃) δ 7.89 – 7.87 (m, 2 H), 7.68 – 7.65 (m, 1 H), 7.58 – 7.54 (m, 2 H), 7.42 (d, *J* = 2 Hz, 1 H), 6.89 (d, *J* = 2 Hz, 1 H), 2.51 (s, 1 H).

¹³C NMR: (101 MHz, CDCl₃) δ 145.8, 137.9, 134.7, 129.7, 128.0, 127.3, 119.4, 15.07.

HRMS: Calculated for C₁₀H₁₁N₂O₂S [M+H]⁺ 223.0541, found 223.0542.



***N*-(2-methoxy-7-methyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*d*]azepin-3-yl)benzenesulfonamide (10):** Compound **10** was prepared following the general procedure using benzenesulfonyl fluoride and 2-methoxy-7-methyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*d*]azepin-3-amine. Yield = 85 mg; 61% and 89 mg; 64%, average: 63%. Without Ca = No reaction.

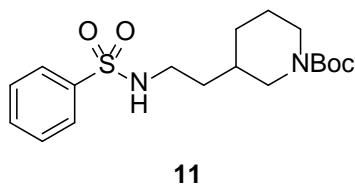
Physical State: Off-white solid

¹H NMR: (400 MHz, CDCl₃) δ 7.75 – 7.73 (m, 2 H), 7.55 – 7.50 (m, 2 H), 7.44 – 7.41 (m, 2 H), 3.69 (s, 3 H), 2.98 – 2.95 (m, 2 H), 2.82 – 2.79 (m, 2 H), 2.53 – 2.51 (m, 4 H), 2.36 (s, 3 H).

¹³C NMR: (101 MHz, CDCl₃) δ 155.1, 152.5, 139.2, 133.0, 130.8, 129.7, 128.8, 127.1, 117.7, 57.2, 55.8, 53.3, 47.6, 38.5, 33.9.

IR: (neat, ν cm⁻¹) 2947, 2797, 1586, 1473, 1446, 1418, 1338, 1263, 1169, 1154, 1091, 1019, 949, 753, 722.

HRMS: Calculated for C₁₇H₂₂N₃O₃S [M+H]⁺ 348.1382, found 348.1370.



***tert*-Butyl 3-(2-(phenylsulfonamido)ethyl)piperidine-1-carboxylate (11):** Compound **11** was prepared following the general procedure using benzenesulfonyl fluoride and 3-(2-aminoethyl)-1-Boc-piperidine. Yield = 110 mg; 75%, 94 mg; 64% and 90 mg; 61%, average: 67%. Without Ca = 16 mg; 11%.

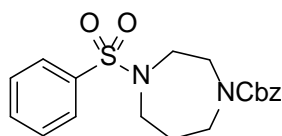
Physical State: Colorless oil.

¹H NMR: (500 MHz, DMSO-*d*₆, 348 K) δ 7.82 – 7.78 (m, 2 H), 7.65 – 7.56 (m, 3 H), 7.38 (s, 1 H), 3.67 – 3.60 (m, 2 H), 2.86 – 2.77 (m, 3 H), 2.57 – 2.51 (m, 1 H), 1.69 – 1.62 (m, 1 H), 1.56 – 1.49 (m, 1 H), 1.43 (ddd, *J* = 3.5, 8.6, 9.7 Hz, 1 H), 1.39 (s, 9 H), 1.32 (ddd, *J* = 5.0, 6.9, 9.2 Hz, 1 H), 1.29 – 1.21 (m, 2 H), 1.03 (ddd, *J* = 3.8, 10.7, 13.5 Hz, 1 H).

¹³C NMR: (126 MHz, DMSO-*d*₆, 348 K) δ 153.6, 140.6, 131.8, 128.7, 126.0, 78.0, 48.4, 43.6, 39.9, 32.3, 32.2, 29.4, 27.8, 23.6.

IR: (neat, ν cm⁻¹) 3267, 2931, 2856, 1663, 1427, 1366, 1328, 1270, 1242, 1153.

HRMS: Calculated for C₁₈H₂₉N₂O₄S [M+H]⁺ 369.1843, found 369.1834.



12

Benzyl 4-(phenylsulfonyl)-1,4-diazepane-1-carboxylate (12): Compound **12** was prepared following the general procedure using benzenesulfonyl fluoride and benzyl 1,4-diazepine-1-carboxylate. Yield = 131 mg; 87% and 121 mg; 81%, average: 84%. Without Ca = trace product observed by LC/MS, could not be isolated.

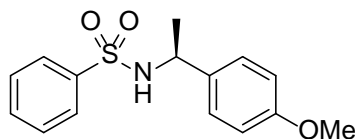
Physical State: Colorless oil.

¹H NMR: (500 MHz, DMSO-*d*₆, 348 K) δ 7.80 – 7.76 (m, 2 H), 7.69 – 7.64 (m, 1 H), 7.60 (dd, *J* = 4.7, 10.4 Hz, 2 H), 7.38 – 7.28 (m, 5 H), 5.07 (s, 2 H), 3.54 (t, *J* = 10.0 Hz, 2 H), 3.44 (t, *J* = 10.0 Hz, 2 H), 3.34 (t, *J* = 5.0 Hz, 2 H), 3.26 (t, *J* = 5.0 Hz, 2 H), 1.79 – 1.72 (m, 2 H).

¹³C NMR: (126 MHz, DMSO-*d*₆, 348 K) δ 154.6, 138.9, 136.6, 132.3, 129.0, 128.0, 127.3, 127.0, 126.2, 66.0, 48.0, 47.0, 46.8, 45.0, 28.2.

IR: (neat, ν cm⁻¹) 2949, 1693, 1476, 1445, 1420, 1331, 1224, 1155.

HRMS: Calculated for C₁₉H₂₃N₂O₄S [M+H]⁺ 375.1373, found 375.1364.



13

(S)-N-(1-(4-Methoxyphenyl)ethyl)benzenesulfonamide (13): Compound **13** was prepared following the general procedure using benzenesulfonyl fluoride and (S)-1-(4-methoxyphenyl)ethylamine. Yield = 85 mg; 73% and 85 mg; 73%, average: 73%. Without Ca = trace product observed by LC/MS, could not be isolated.

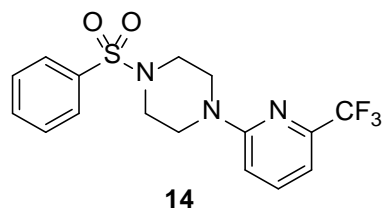
Physical State: White solid.

¹H NMR: (400 MHz, CDCl₃) δ 7.73 (d, *J* = 8.0 Hz, 2 H), 7.49 (t, *J* = 7.4 Hz, 1 H), 7.39 (t, *J* = 7.7 Hz, 2 H), 7.00 (d, *J* = 8.7 Hz, 2 H), 6.70 (d, *J* = 8.7 Hz, 2 H), 4.90 (d, *J* = 6.7 Hz, 1 H), 4.45 (p, *J* = 6.8 Hz, 1 H), 3.75 (s, 3 H), 1.42 (d, *J* = 6.8 Hz, 3 H).

¹³C NMR: (101 MHz, CDCl₃) δ 158.9, 140.7, 133.9, 132.3, 128.8, 127.3, 127.0, 113.9, 55.3, 53.2, 23.4.

IR: (neat, ν cm⁻¹) 3272, 2973, 2836, 1612, 1513, 1447, 1307, 1244, 1156.

HRMS: Calculated for C₁₅H₁₆NO₃S [M-H]⁻ 290.0857, found 290.0856.



1-(Phenylsulfonyl)-4-(6-(trifluoromethyl)pyridin-2-yl)piperazine (14): Compound **14** was prepared following the general procedure using benzenesulfonyl fluoride and 1-[6-(trifluoromethyl)pyridine-2-yl]piperazine. Yield = 143 mg; 96% and 138 mg; 93%, average: 95%. Without Ca = 1.5 mg; 1%. Yield = 1.6 g; 70% (1g, 6.24 mmol scale).

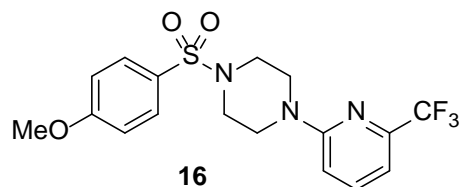
Physical State: White solid.

¹H NMR: (400 MHz, CDCl₃) δ 7.78 (d, *J* = 7.3 Hz, 2 H), 7.65 – 7.49 (m, 4 H), 6.95 (d, *J* = 7.3 Hz, 1 H), 6.72 (d, *J* = 8.6 Hz, 1 H), 3.71 (t, *J* = 4.0 Hz, 4 H), 3.12 (t, *J* = 4.0 Hz, 4 H).

¹³C NMR: (101 MHz, CDCl₃) δ 158.0, 146.4 (q, ²*J*_{CF} = 34.3 Hz), 138.6, 135.4, 133.1, 129.1, 127.8, 121.4 (q, ¹*J*_{CF} = 275.7 Hz), 109.6 (q, ³*J*_{CF} = 3.0 Hz), 109.5 (q, ⁴*J*_{CF} = 1.0 Hz), 45.7, 44.2.

IR: (neat, ν cm⁻¹) 2854, 1602, 1479, 1447, 1331, 1255, 1167, 1113 cm⁻¹.

HRMS: Calculated for C₁₆H₁₇F₃NO₂S [M+H]⁺ 372.0988, found 372.0980.



1-((4-Methoxyphenyl)sulfonyl)-4-(6-(trifluoromethyl)pyridin-2-yl)piperazine (16):

Compound **16** was prepared following the general procedure using 4-methoxybenzenesulfonyl fluoride and 1-[6-(trifluoromethyl)pyridine-2-yl]piperazine. Yield = 142 mg; 88% and 132 mg, 82%, average: 85%. Without Ca = 2 mg, 1%.

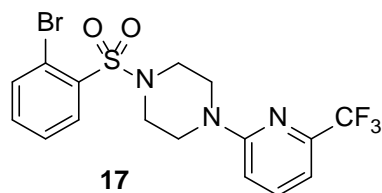
Physical State: White solid.

¹H NMR: (400 MHz, CDCl₃) δ 7.71 (d, *J* = 8.9 Hz, 2 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 7.03 – 6.97 (m, 2 H), 6.95 (d, *J* = 7.3 Hz, 1 H), 6.72 (d, *J* = 8.7 Hz, 1 H), 3.86 (s, 3 H), 3.71 (t, *J* = 5.1 Hz, 4 H), 3.10 (t, *J* = 5.1 Hz, 4 H).

¹³C NMR: (101 MHz, CDCl₃) δ 163.2, 158.0, 146.4 (q, ²J_{CF} = 34.3 Hz), 138.6, 130.0, 126.9, 121.5 (q, ¹J_{CF} = 274.7 Hz), 114.3, 109.6 (q, ³J_{CF} = 3 Hz), 109.5 (q, ⁴J_{CF} = 1 Hz), 55.6, 45.8, 44.2.

IR: (neat, ν cm⁻¹) 2849, 1596, 1576, 1496, 1452, 1331, 1255, 1159, 1112.

HRMS: Calculated for C₁₇H₁₉F₃N₃O₃S [M+H]⁺ 402.1094, found 402.1085.



1-((2-bromophenyl)sulfonyl)-4-(6-(trifluoromethyl)pyridin-2-yl)piperazine (17): Compound **17** was prepared following the general procedure using 2-bromobenzenesulfonyl fluoride and 1-[6-(trifluoromethyl)pyridine-2-yl]piperazine. Yield = 128 mg; 71% and 144 mg; 80%, average: 76%. Without Ca = 3 mg; 2%. The amorphous physical state of the product made it challenging to obtain an IR spectrum.

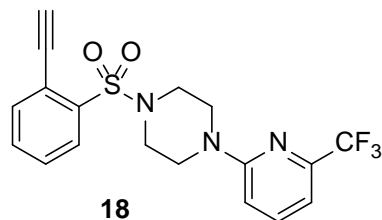
Physical State: Amorphous white solid.

¹H NMR: (400 MHz, DMSO-*d*₆) δ 8.04 – 8.03 (m, 1 H), 7.88 – 7.87 (m, 1 H), 7.75 – 7.74 (m, 1 H), 7.62 – 7.57 (m, 2 H), 7.12 (br m, 1 H), 7.05 (br m, 1 H), 3.64 (br m, 4 H), 3.30 (br m, 4 H).

¹⁹F NMR: (376 MHz, DMSO-*d*₆) δ -67.3 (s, 3 H).

¹³C NMR: (101 MHz, DMSO-*d*₆) δ 158.1, 144.6 (q, ²J_{CF} = 33.0 Hz), 139.3, 136.9, 136.0, 134.6, 131.8, 128.4, 121.6 (q, ¹J_{CF} = 274.0 Hz), 119.6, 111.1, 109.3 (q, ³J_{CF} = 3.0 Hz), 45.1, 44.1.

HRMS: Calculated for C₁₆H₁₆F₃N₃O₂SBr [M+H]⁺ 450.0099; found 450.0100.



1-((2-Ethynylphenyl)sulfonyl)-4-(6-(trifluoromethyl)pyridin-2-yl)piperazine (18): Compound **18** was prepared following the general procedure using 2-ethynylbenzenesulfonyl fluoride and 1-[6-(trifluoromethyl)pyridine-2-yl]piperazine. Yield = 131 mg; 83% and 128 mg; 81%, average: 82%. Without Ca = No reaction.

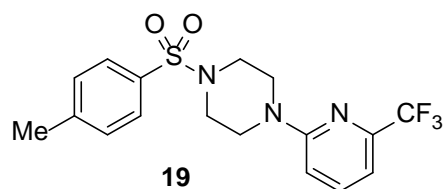
Physical State: White solid.

¹H NMR: (400 MHz, CDCl₃) δ 7.98 (dd, *J* = 1.2, 7.7 Hz, 1 H), 7.73 – 7.68 (m, 1 H), 7.62 – 7.56 (m, 1 H), 7.56 – 7.47 (m, 2 H), 6.97 (d, *J* = 7.3 Hz, 1 H), 6.76 (d, *J* = 8.7 Hz, 1 H), 3.70 (t, *J* = 4.0 Hz, 4 H), 3.54 (s, 1 H), 3.36 (t, *J* = 4.0 Hz, 4 H).

¹³C NMR: (101 MHz, CDCl₃) δ 158.2, 146.4 (q, ²*J*_{CF} = 34.0 Hz), 138.7, 138.6, 136.2, 132.4, 130.2, 128.9, 121.5 (q, ¹*J*_{CF} = 276.0 Hz), 121.0, 109.6, 109.6 (q, ³*J*_{CF} = 3.0 Hz), 85.1, 80.7, 45.6, 44.5.

IR: (neat, ν cm⁻¹) 3271, 2865, 1602, 1477, 1452, 1351, 1329, 1260, 1169, 1127, 1115, 952, 735, 588.

HRMS: Calculated for C₁₈H₁₇F₃N₃O₂S [M+H]⁺ 396.0988, found 396.0980.



1-Tosyl-4-(6-(trifluoromethyl)pyridin-2-yl)piperazine (19): Compound **19** was prepared following the general procedure using 4-methylbenzenesulfonyl fluoride and 1-[6-(trifluoromethyl)pyridine-2-yl]piperazine. Yield = 138 mg; 90% and 129 mg; 84%, average: 87%. Without Ca = No reaction.

Physical State: White solid.

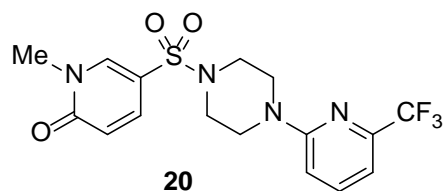
¹H NMR: (400 MHz, DMSO-*d*₆) δ 7.73 (t, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 8.0 Hz, 2 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.09 (d, *J* = 9.0 Hz, 1 H), 7.04 (d, *J* = 7.0 Hz, 1 H), 3.66 – 3.63 (m, 4 H), 2.95 – 2.93 (m, 4 H), 2.38 (s, 3 H).

¹⁹F NMR: (376 MHz, DMSO-*d*₆) δ -67.3 (s, 3 H).

¹³C NMR: (101 MHz, DMSO-*d*₆) δ 157.9, 144.3 (q, ²*J*_{CF} = 33.0 Hz), 143.9, 139.3, 131.7, 129.9, 127.7, 121.6 (q, ¹*J*_{CF} = 273.0 Hz), 111.0, 109.2 (q, ³*J*_{CF} = 3.0 Hz), 45.5, 43.5, 21.0.

IR: (neat, ν cm⁻¹) 2954, 2921, 2855, 1606, 1568, 1477, 1451, 1385, 1327, 1269, 1253, 1177, 1157, 1111, 1086, 1062, 979, 954, 932.

HRMS: Calculated for C₁₇H₁₉F₃N₃O₂S [M+H]⁺ 386.1150; found 386.1161.



1-methyl-5-((4-(6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyridin-2(1H)-one (20): Compound **20** was prepared following the general procedure using 1-methyl-6-oxo-1,6-dihydropyridine-3-sulfonyl fluoride and 1-[6-(trifluoromethyl)pyridine-2-yl]piperazine. Yield = 114 mg; 83% (0.343 mmol scale) and 58 mg, 92% (0.16 mmol scale), average: 88%. Without Ca = 17 mg; 12% (0.343 mmol scale).

Physical State: Off-white solid.

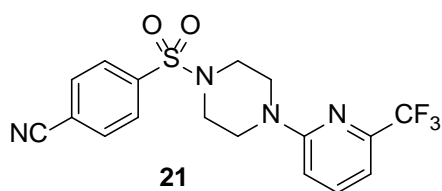
¹H NMR: (400 MHz, CDCl₃) δ 7.94 (d, *J* = 2.5 Hz, 1 H), 7.60 (t, *J* = 8.0 Hz, 1 H), 7.52 (dd, *J* = 2.6, 9.6 Hz, 1 H), 6.99 (d, *J* = 7.3 Hz, 1 H), 6.76 (d, *J* = 8.6 Hz, 1 H), 6.58 (d, *J* = 9.6 Hz, 1 H), 3.74 (t, *J* = 4.0 Hz, 4 H), 3.59 (s, 3 H), 3.19 (t, *J* = 4.0 Hz, 4 H).

¹³C NMR: (101 MHz, CDCl₃) δ 161.9, 157.9, 146.5 (q, ²*J*_{CF} = 34 Hz), 142.1, 138.8, 136.3, 121.4 (q, ¹*J*_{CF} = 276 Hz), 120.6, 114.7, 109.9 (q, ³*J*_{CF} = 3.0 Hz), 109.6 (q, ⁴*J*_{CF} = 1.0 Hz), 45.5, 44.2, 38.4.

IR: (neat, ν cm⁻¹) 2850, 1662, 1603, 1491, 1336, 1259, 1158, 1117, 950, 924, 744, 572.

MS: (ESI) 403.0 [M+H]⁺

HRMS: Calculated for C₁₆H₁₈F₃N₄O₃S [M+H]⁺ 403.1046, found 403.1038.



4-((4-(6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)benzonitrile (21): Compound **21** was prepared following the general procedure using 4-cyanobenzenesulfonyl fluoride and 1-[6-(trifluoromethyl)pyridine-2-yl]piperazine. Yield = 126 mg; 79% and 134 mg; 85%, average: 82%. Without Ca = 150 mg; 95%.

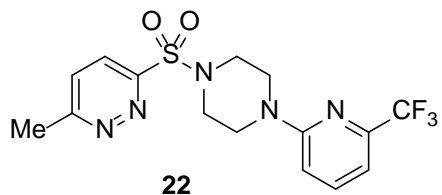
Physical State: White solid.

¹H NMR: (400 MHz, CDCl₃) δ 7.89 (d, *J* = 8.5 Hz, 2 H), 7.84 (d, *J* = 8.5 Hz, 2 H), 7.59 (t, *J* = 8.0 Hz, 1 H), 6.98 (d, *J* = 7.4 Hz, 1 H), 6.73 (d, *J* = 8.6 Hz, 1 H), 3.77 – 3.69 (m, 4 H), 3.16 (t, *J* = 5.1 Hz, 4 H).

¹³C NMR: (101 MHz, CDCl₃) δ 157.8, 146.5 (q, ²*J*_{CF} = 34.0 Hz), 140.1, 138.8, 133.0, 128.3, 121.4 (q, ¹*J*_{CF} = 274.0 Hz), 117.1, 116.9, 109.9 (q, ³*J*_{CF} = 3.1 Hz), 109.6, 45.6, 44.2.

IR: (neat, ν cm⁻¹) 2918, 2854, 2233, 1604, 1481, 1451, 1354, 1332, 1255, 1164, 1114.

HRMS: Calculated for C₁₇H₁₆F₃N₄O₂S [M+H]⁺ 397.0941, found 397.0934.



3-Methyl-6-((4-(6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)pyridazine (22):

Compound **22** was prepared following the general procedure using 6-methylpyridazine-3-sulfonyl fluoride and 1-[6-(trifluoromethyl)pyridine-2-yl]piperazine. Yield = 117 mg; 92% (0.33 mmol scale) and 117 mg; 88% (0.343 mmol scale), average: 90%. Without Ca = 101 mg; 81% (0.32 mmol scale).

Physical State: White solid

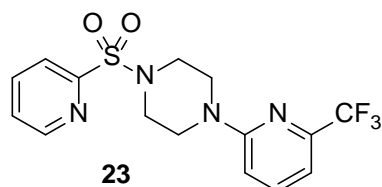
¹H NMR: (400 MHz, CDCl₃) δ 7.94 (d, *J* = 8.6 Hz, 1 H), 7.59 (t, *J* = 8.0 Hz, 1 H), 7.54 (d, *J* = 8.7 Hz, 1 H), 6.97 (d, *J* = 7.3 Hz, 1 H), 6.77 (d, *J* = 8.6 Hz, 1 H), 3.76 (t, *J* = 4.0 Hz, 4 H), 3.58 (t, *J* = 4.0 Hz, 4 H), 2.80 (s, 3 H).

¹³C NMR: (101 MHz, CDCl₃) δ 162.8, 159.6, 158.0, 146.4 (q, ²*J*_{CF} = 34.0 Hz), 138.6, 128.3, 125.7, 121.4 (q, ¹*J*_{CF} = 275.0 Hz), 109.7 (q, ⁴*J*_{CF} = 1.0 Hz), 109.6 (q, ³*J*_{CF} = 3.0 Hz), 46.3, 44.6, 22.3.

IR: (neat, ν cm⁻¹) 2863, 1610, 1492, 1403, 1348, 1332, 1256, 1127, 1116, 953, 726, 572.

MS: (ESI) 388.0 [M+H]⁺

HRMS: Calculated for C₁₅H₁₇F₃N₅O₂S [M+H]⁺ 388.1050, found 388.1042.



1-(Pyridin-2-ylsulfonyl)-4-(6-(trifluoromethyl)pyridin-2-yl)piperazine (23): Compound **23** was prepared following the general procedure using pyridine-2-sulfonyl fluoride and 1-[6-(trifluoromethyl)pyridine-2-yl]piperazine. Yield = 143 mg; 96% (0.4 mmol scale) and 143 mg; 94% (0.41 mmol scale), average: 95%. Without Ca = 138 mg; 90% (0.41 mmol scale).

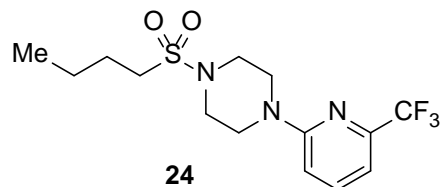
Physical State: White solid.

¹H NMR: (400 MHz, CDCl₃) δ 8.69 (d, *J* = 4.5 Hz, 1 H), 7.97 (d, *J* = 7.7 Hz, 1 H), 7.95 – 7.90 (m, 1 H), 7.59 (t, *J* = 8.0 Hz, 1 H), 7.50 (ddd, *J* = 1.3, 4.7, 7.2 Hz, 1 H), 6.96 (d, *J* = 7.3 Hz, 1 H), 6.76 (d, *J* = 8.7 Hz, 1 H), 3.71 (t, *J* = 4.0 Hz, 4 H), 3.45 (t, *J* = 4.0 Hz, 4 H).

¹³C NMR: (101 MHz, CDCl₃) δ 158.2, 156.2, 150.1, 146.4 (q, ²*J*_{CF} = 34.0 Hz), 138.7, 138.1, 126.8, 123.1, 121.5 (q, ¹*J*_{CF} = 275.0 Hz), 109.6 (q, ⁴*J*_{CF} = 2.0 Hz), 109.6 (q, ³*J*_{CF} = 3.0 Hz), 46.2, 44.6.

IR: (neat, ν cm⁻¹) 2848, 1602, 1479, 1345, 1328, 1253, 1171, 1114, 954, 748, 708, 564.

HRMS: Calculated for C₁₅H₁₆F₃N₄O₂S [M+H]⁺ 373.0941, found 373.0932.



1-(Butylsulfonyl)-4-(6-(trifluoromethyl)pyridin-2-yl)piperazine (24): Compound **24** was prepared following the general procedure using butanesulfonyl fluoride and 1-[6-(trifluoromethyl)pyridine-2-yl]piperazine. Yield = 126 mg; 90% and 114 mg; 81%, average: 86%. Without Ca = 25 mg; 18%.

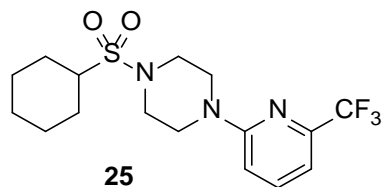
Physical State: Off-white solid

¹H NMR: (400 MHz, CDCl₃) δ 7.62 (t, *J* = 8.0 Hz, 1 H), 7.00 (d, *J* = 7.3 Hz, 1 H), 6.80 (d, *J* = 8.6 Hz, 1 H), 3.72 (t, *J* = 4.0 Hz, 4 H), 3.39 (t, *J* = 4.0 Hz, 4 H), 2.97 – 2.89 (m, 2 H), 1.87 – 1.76 (m, 2 H), 1.46 (sext, *J* = 7.4 Hz, 2 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

¹³C NMR: (101 MHz, CDCl₃) δ 158.3, 146.4 (q, ²*J*_{CF} = 34.0 Hz), 138.7, 121.5 (q, ¹*J*_{CF} = 276.0 Hz), 109.8 (q, ³*J*_{CF} = 3.0 Hz), 109.8, 49.2, 45.4, 45.0, 25.0, 21.8, 13.6.

IR: (neat, ν cm⁻¹) 2963, 2873, 1611, 1483, 1452, 1324, 1257, 1132, 1116, 1067, 956, 815, 574.

HRMS: Calculated for C₁₅H₂₁F₃N₃O₂S [M+H]⁺ 352.1301, found 352.1294.



1-(Cyclohexylsulfonyl)-4-(6-(trifluoromethyl)pyridin-2-yl)piperazine (25): Compound **25** was prepared following the general procedure using cyclohexanesulfonyl fluoride and 1-[6-(trifluoromethyl)pyridine-2-yl]piperazine. Yield = 127 mg; 84% and 137 mg; 91%, average: 88%. Without Ca = No reaction.

Physical State: White solid.

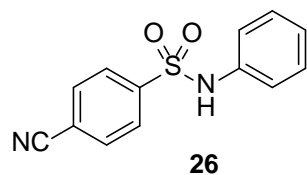
¹H NMR: (400 MHz, CDCl₃) δ 7.63 – 7.59 (m, 1 H), 6.99 (d, *J* = 7.3 Hz, 1 H), 6.79 (d, *J* = 8.6 Hz, 1 H), 3.68 (t, *J* = 4.0 Hz, 4 H), 3.45 (t, *J* = 4.0 Hz, 4 H), 2.93 (tt, *J* = 3.4, 12.1 Hz, 1 H), 2.16 – 2.09 (m, 2 H), 1.93 – 1.83 (m, 2 H), 1.73 – 1.67 (m, 1 H), 1.52 (qd, *J* = 3.1, 12.3 Hz, 2 H), 1.34 – 1.12 (m, 3 H).

¹³C NMR: (101 MHz, CDCl₃) δ 158.4, 146.4 (q, ²*J*_{CF} = 34.0 Hz), 138.6, 121.5 (q, ¹*J*_{CF} = 276.0 Hz), 109.8 (q, ⁴*J*_{CF} = 1.0 Hz), 109.6 (q, ³*J*_{CF} = 3.0 Hz), 61.6, 45.8, 45.4, 26.6, 25.2, 25.1.

IR: (neat, ν cm⁻¹) 2941, 2861, 1607, 1492, 1329, 1312, 1266, 1136, 1117, 959, 793.

MS: (ESI) 378.0 [M+H]⁺

HRMS: Calculated for C₁₆H₂₃F₃N₃O₂S [M+H]⁺ 378.1458, found 378.1450.



4-Cyano-N-phenylbenzenesulfonamide (26): Compound **26** was prepared following the general procedure using 4-cyanobenzenesulfonyl fluoride and aniline. Yield = 85 mg; 82% and 91 mg; 88%, average: 85%. Without Ca = No reaction. The NMR spectra are consistent with those previously reported.⁶

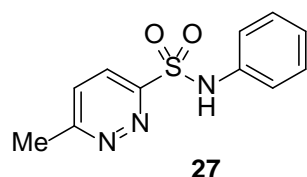
Physical State: White solid

¹H NMR: (400 MHz, CDCl₃) δ 7.85 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.28 (t, *J* = 8.0 Hz, 2 H), 7.18 (t, *J* = 8.0 Hz, 1 H), 7.08 – 7.04 (m, 2 H), 6.72 (br s, 1 H).

¹³C NMR: (101 MHz, CDCl₃) δ 143.1, 135.4, 132.8, 129.7, 127.9, 126.5, 122.4, 117.2, 116.8.

IR: (neat, ν cm⁻¹) 3254, 2235, 1598, 1494, 1410, 1347, 1282, 1219, 1160.

HRMS: Calculated for C₁₃H₁₁N₂O₂S [M+H]⁺ 259.0536, found 259.1693.



6-Methyl-*N*-phenylpyridazine-3-sulfonamide (27): Compound **27** was prepared following the general procedure using 6-methylpyridazine-3-sulfonyl fluoride and aniline. Yield = 90 mg; 90% and 85 mg; 85%, average: 88%. Without Ca = trace product observed by LC/MS, could not be isolated (0.2 mmol scale).

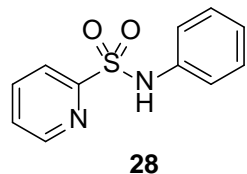
Physical State: White solid

¹H NMR: (400 MHz, CDCl₃) δ 7.89 (d, *J* = 8.7 Hz, 2 H), 7.47 (d, *J* = 8.6 Hz, 1 H), 7.31 – 7.23 (m, 4 H), 7.18 – 7.12 (m, 1 H), 2.82 (s, 3 H).

¹³C NMR: (101 MHz, CDCl₃) δ 162.9, 159.0, 135.5, 129.3, 128.2, 126.2, 125.8, 123.4, 22.3.

IR: (neat, ν cm⁻¹) 3126, 2900, 1496, 1336, 1324, 1200, 1134, 1056, 932, 799, 743, 571.

HRMS: Calculated for C₁₁H₁₂N₃O₂S [M+H]⁺ 250.0645, found 250.0641.



***N*-Phenylpyridine-2-sulfonamide (28):** Compound **28** was prepared following the general procedure using pyridine-2-sulfonyl fluoride and aniline. Yield = 90 mg; 96% and 97 mg; 98% (0.42 mmol scale), average: 97%. Without Ca = trace product observed by LC/MS, could not be isolated. The NMR spectra are consistent with those previously reported.⁶

Physical State: White solid.

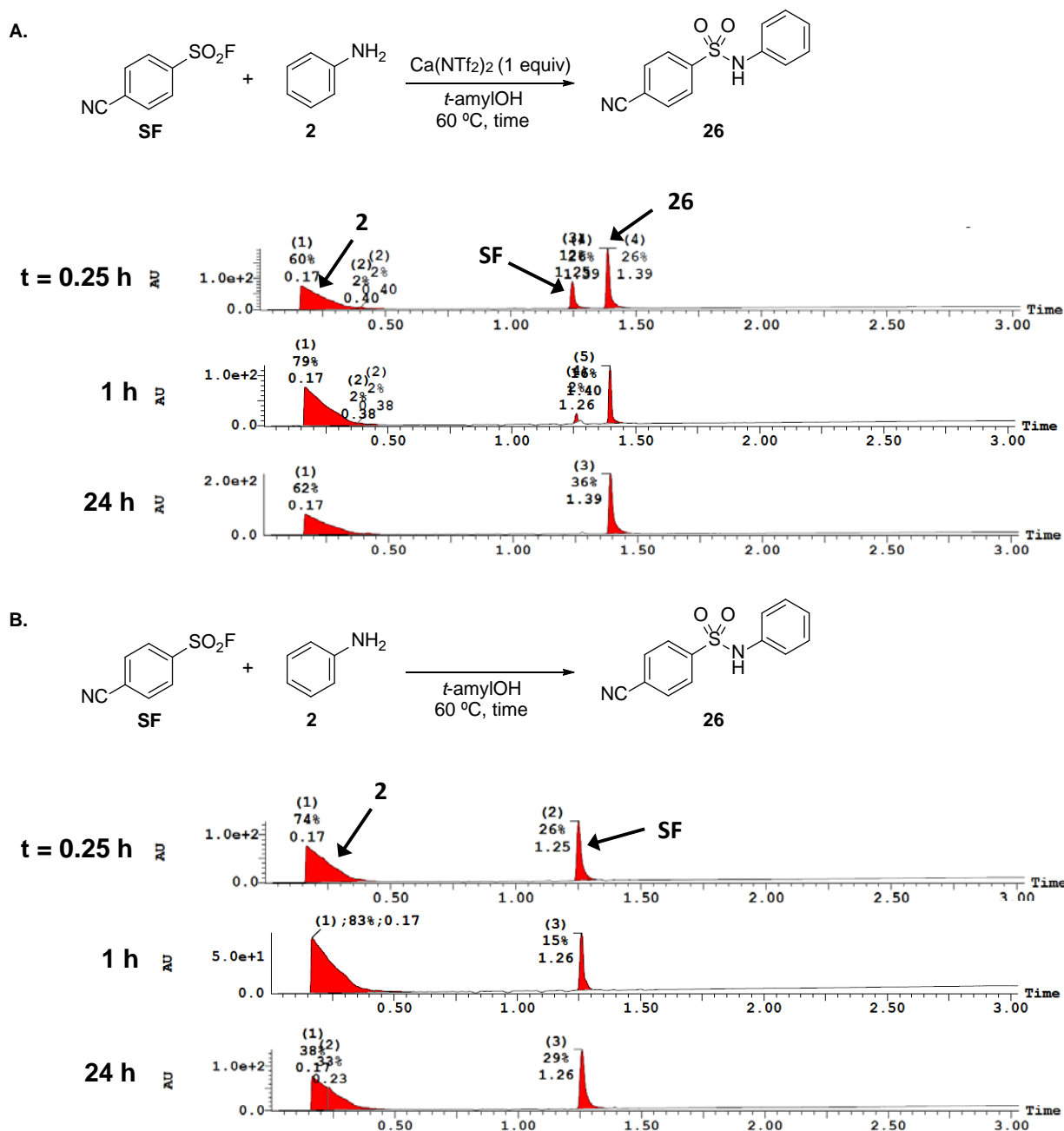
¹H NMR: (400 MHz, CDCl₃) δ 8.74 (d, *J* = 4.6 Hz, 1 H), 8.01 (s, 1 H), 7.90 (d, *J* = 7.8 Hz, 1 H), 7.81 (td, *J* = 1.6, 7.7 Hz, 1 H), 7.48 – 7.43 (m, 1 H), 7.23 – 7.18 (m, 4 H), 7.08 (p, *J* = 4.4 Hz, 1 H).

¹³C NMR: (101 MHz, CDCl₃) δ 156.1, 150.1, 138.0, 136.1, 129.2, 127.0, 125.7, 123.1, 122.7.

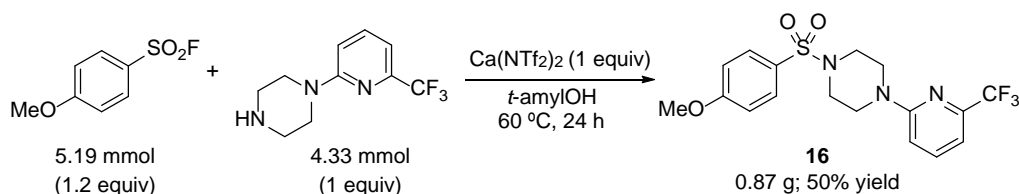
HRMS: Calculated for C₁₁H₁₁N₂O₂S [M+H]⁺ 235.0536, found 235.0532.

LC-MS Monitoring of Reaction of 4-Cyanobenzenesulfonyl Fluoride with Aniline in Presence and Absence of $\text{Ca}(\text{NTf}_2)_2$

The reaction was conducted using the conditions outlined in general procedure for the synthesis of sulfonamides.

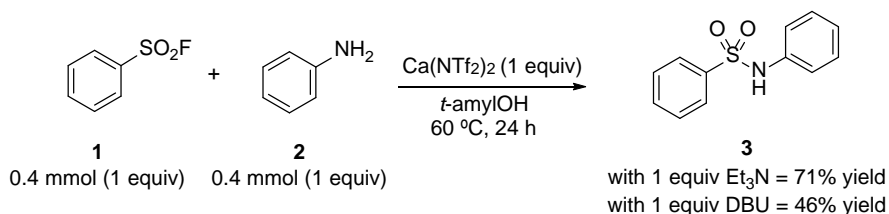


Procedure for the synthesis of sulfonamide 4a with amine as the limiting reagent



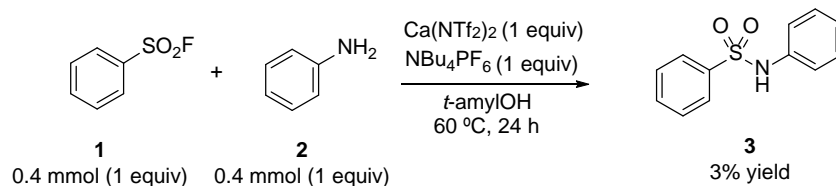
Compound **16** was prepared following the general procedure using 4-methoxybenzenesulfonyl fluoride (990 mg, 5.19 mmol, 1.2 equiv), 1-[6-(trifluoromethyl)pyridine-2-yl]piperazine (1 g, 4.33 mmol, 1 equiv) and calcium triflimide (2.6 g, 4.33 mmol, 1 equiv). Yield = 0.87 g, 50%.

Procedure for the synthesis of sulfonamide 3 with triethylamine or DBU as added base



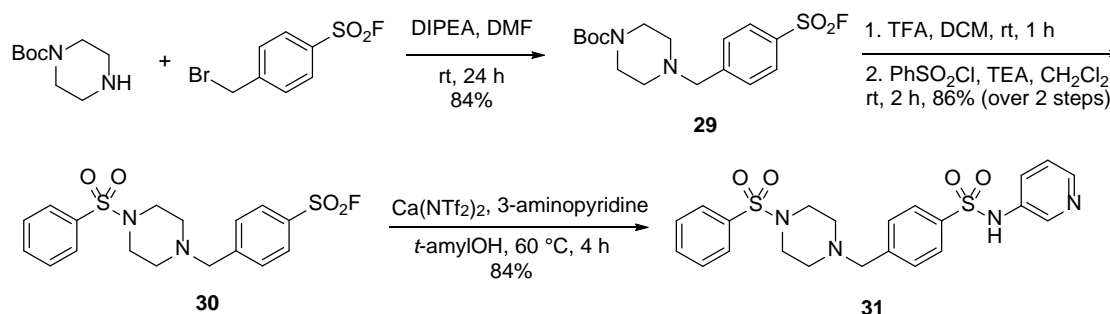
Compound **3** was prepared following the general procedure using benzenesulfonyl fluoride (64.1 mg, 0.4 mmol, 1 equiv), aniline (37.3 mg, 0.4 mmol, 1 equiv) and triethylamine (40.5 mg, 0.4 mmol, 1 equiv). Yield = 63 mg; 68% and 68 mg; 73%, average: 71%. In addition, **3** was prepared using benzenesulfonyl fluoride (64.1 mg, 0.4 mmol, 1 equiv), aniline (37.3 mg, 0.4 mmol, 1 equiv) and DBU (60.9 mg, 0.4 mmol, 1 equiv). Yield = 45 mg; 48% and 41 mg; 44%, average: 46%.

Procedure for the synthesis of sulfonamide 3 with NBu_4PF_6



Compound **3** was prepared following the general procedure using benzenesulfonyl fluoride (64.1 mg, 0.4 mmol, 1 equiv), aniline (37.3 mg, 0.4 mmol, 1 equiv) and tetrabutylammonium hexafluorophosphate (155 mg, 0.4 mmol, 1 equiv). Yield = 2.1 mg; 2.3% and 3.6 mg; 3.9%, average: 3%.

Sulfonyl Fluoride as a Latent Electrophile



***tert*-Butyl 4-(4-(fluorosulfonyl)benzyl)piperazine-1-carboxylate (29).** To a stirred solution of 4-(bromomethyl)benzenesulfonyl fluoride (300 mg, 1.19 mmol, 1 equiv) and *tert*-butyl piperazine-1-carboxylate (317 mg, 1.42 mmol, 1.2 equiv) in DMF (10 mL), DIPEA (460 mg, 3.56 mmol, 3 equiv) was added. The reaction was stirred at room temperature for 24 h. The resulting mixture was partitioned between water and ethyl acetate, and layers separated. The aqueous layer was extracted with ethyl acetate (2x), and the combined organic fractions were washed with brine (1x), dried with anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by column chromatography to obtain **29** as a white solid (356 mg, 84%).

¹H NMR: (400 MHz, CDCl₃) δ 7.96 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 8.1 Hz, 2 H), 3.61 (s, 2 H), 3.44 (t, *J* = 4.0 Hz, 4 H), 2.40 (t, *J* = 4.0 Hz, 4 H), 1.46 (s, 9 H).

¹³C NMR: (101 MHz, CDCl₃) δ 154.6, 147.3, 131.5 (d, ³*J*_{CF} = 24.2 Hz), 129.7, 128.4, 79.7, 62.1, 52.9, 43.8 (br), 43.1 (br), 28.3.

MS: (ESI) 302.9 [M-(Me)₂CH=CH₂+H]⁺

4-((4-(phenylsulfonyl)piperazin-1-yl)methyl)benzenesulfonyl fluoride (30). Compound **29** (100 mg, 0.28 mmol) was dissolved in dichloromethane (2 mL), and trifluoroacetic acid (0.28 mL) added. The reaction was stirred at room temperature for 1 h, upon which TLC indicated complete consumption of compound **30** to form a more polar compound. The reaction was concentrated under reduced pressure and dichloromethane was added and then concentrated again. This was repeated two times. The amine was used directly in the next step without further purification. The crude amine was re-dissolved in dichloromethane (2 mL), treated with triethylamine (0.23 mL, 1.67 mmol) and stirred. To this, benzenesulfonyl chloride (74 mg, 53 μL, 0.42 mmol) was added, and the reaction stirred at room temperature for 2 h. LCMS and TLC indicated consumption of the amine. The reaction mixture was partitioned between 50% sodium bicarbonate and dichloromethane, and separated. The aqueous layer was extracted once more with dichloromethane, the combined organics were washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography to obtain **30** as a white solid (96 mg, 86%, 2 steps).

¹H NMR: (400 MHz, CDCl₃) δ 7.92 (d, *J* = 8.3 Hz, 2 H), 7.78 – 7.73 (m, 2 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 7.56 (d, *J* = 7.8 Hz, 2 H), 7.53 (d, *J* = 8.1 Hz, 2 H), 3.60 (s, 2 H), 3.06 (s, 4 H), 2.59 – 2.51 (m, 4 H).

¹³C NMR: (101 MHz, CDCl₃) δ 146.7, 135.5, 132.9, 131.8 (d, *J* = 24 Hz), 129.7, 129.1, 128.5, 127.8, 61.7, 52.2, 46.0.

IR: (neat, ν cm⁻¹) 2854, 1594, 1445, 1411, 1346, 1326, 1217.

HRMS: Calculated for C₁₇H₂₀FN₂O₄S₂ [M+H]⁺ 399.0843, found 399.0838.

4-((4-(phenylsulfonyl)piperazin-1-yl)methyl)-*N*-(pyridin-3-yl)benzenesulfonamide (31). To a two-dram vial containing compound **30** (65.4 mg, 0.164 mmol), 3-aminopyridine (30.9 mg, 0.328 mmol, 2 equiv) and Ca(NTf₂)₂ (98.5 mg, 0.164 mmol, 1 equiv), *t*-amylOH (0.8 mL) was added. The reaction was stirred at 60 °C for 4 h, cooled to room temperature and partitioned between ethyl acetate and brine (1x). The brine layer was washed with ethyl acetate (1x), and the combined organic fraction was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified by column chromatography to give **31** as a white solid (64.7 mg, 84%).

¹H NMR: (400 MHz, MeOD) δ 8.21 (d, *J* = 4.1 Hz, 1 H), 8.19 (d, *J* = 2.2 Hz, 1 H), 7.79 – 7.73 (m, 2 H), 7.72 – 7.66 (m, 3 H), 7.64 – 7.58 (m, 3 H), 7.42 (d, *J* = 8.3 Hz, 2 H), 7.30 (dd, *J* = 8.2, 4.8 Hz, 1 H), 3.54 (s, 2 H), 2.99 (s, 4 H), 2.47 (t, *J* = 4.0 Hz, 4 H).

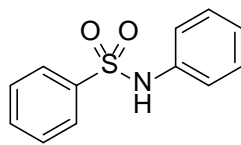
¹³C NMR: (101 MHz, MeOD) δ 146.2, 145.2, 143.0, 139.7, 137.0, 136.7, 134.4, 130.9, 130.5, 130.3, 129.1, 128.4, 125.7, 62.6, 53.4, 47.4.

IR: (neat, ν cm⁻¹) 2816, 1583, 1447, 1416, 1356, 1312, 1159.

HRMS: Calculated for C₂₂H₂₅N₄O₄S₂ [M+H]⁺ 473.1312, found 473.1307.

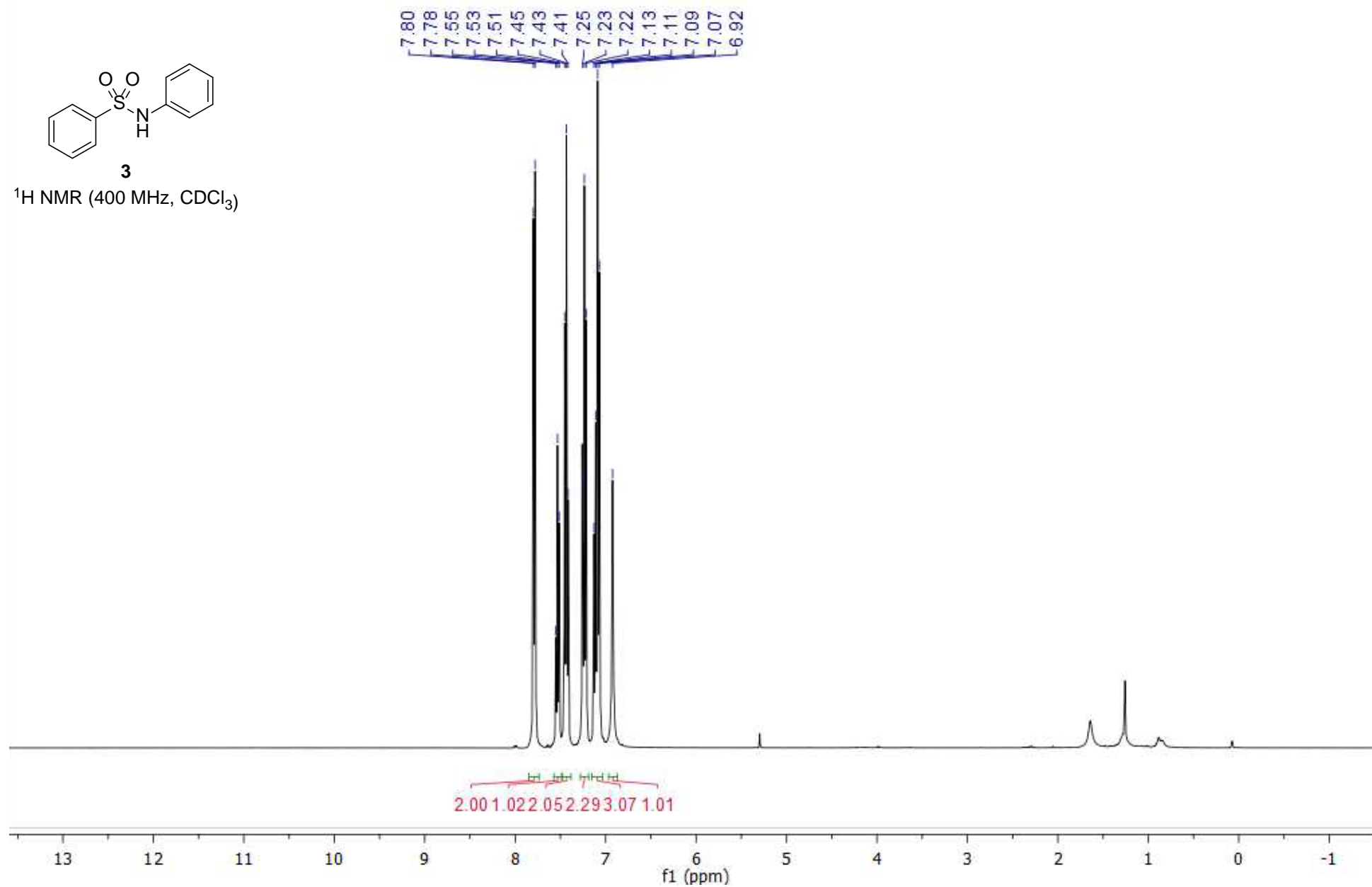
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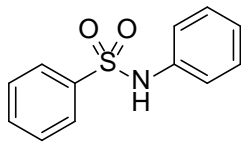
- (1) Zhang, W.; Xie, J.; Rao, B.; Luo, M. *J. Org. Chem.* **2015**, *80*, 3504.
- (2) Santanilla, A. B.; Regalado, E. L.; Pereira, T.; Shevlin, M.; Bateman, K.; Campeau, L.-C.; Schneeweis, J.; Berritt, S.; Shi, Z.-C.; Nantermet, P.; Liu, Y.; Helmy, R.; Welch, C. J.; Vachal, P.; Davies, I. W.; Cernak, T.; Dreher, S. D. *Science* **2015**, *347*, 49.
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- (4) Parumala, S. K. R.; Peddinti, R. K. *Tet. Lett.* **2016**, *57*, 1232.
- (5) Mohamady, S.; Desoky, A.; Taylor, S. D. *Org. Lett.* **2012**, *14*, 402.
- (6) Holden, C. M.; Sohel, S. M. A.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2016**, *55*, 2450.



3

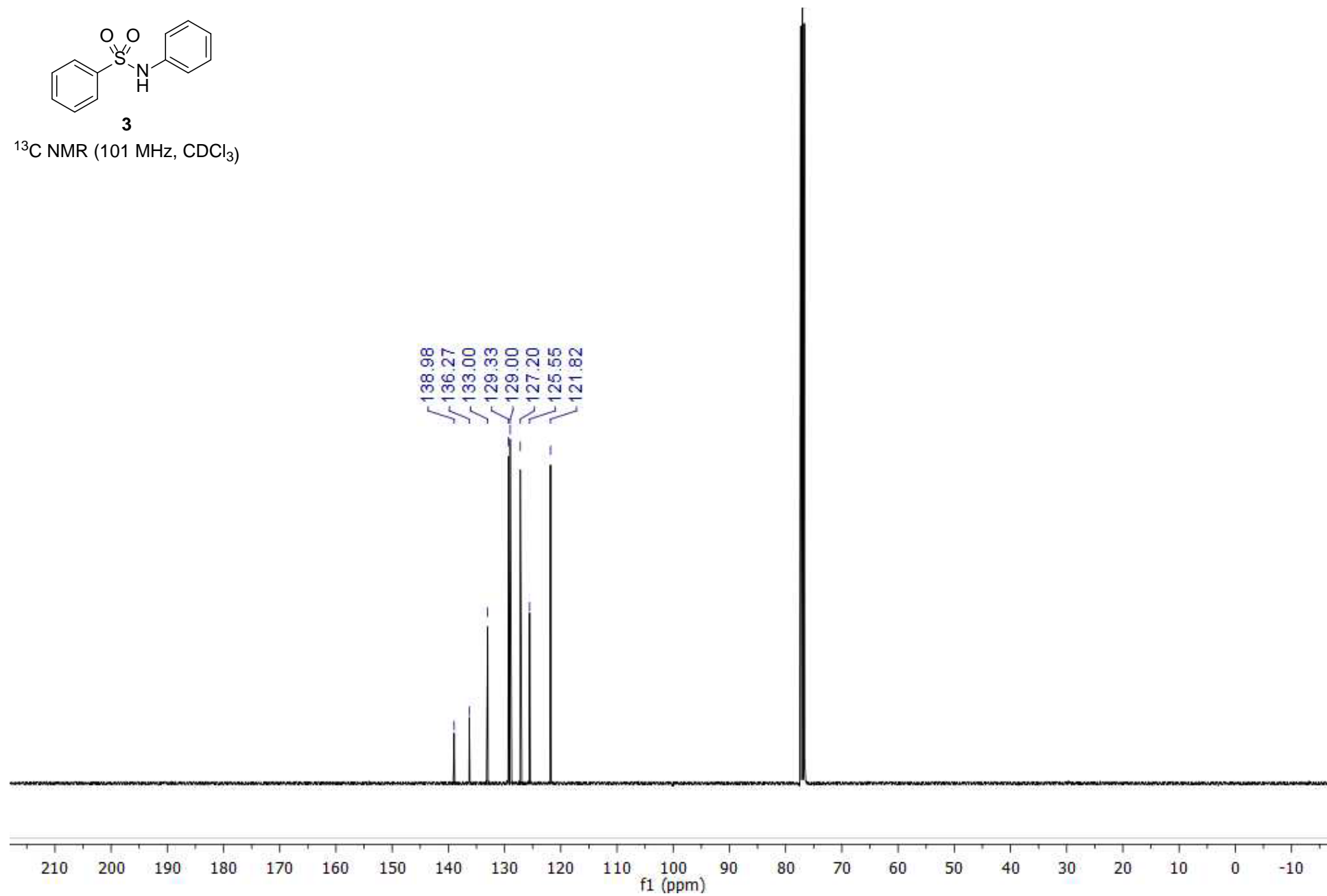
^1H NMR (400 MHz, CDCl_3)

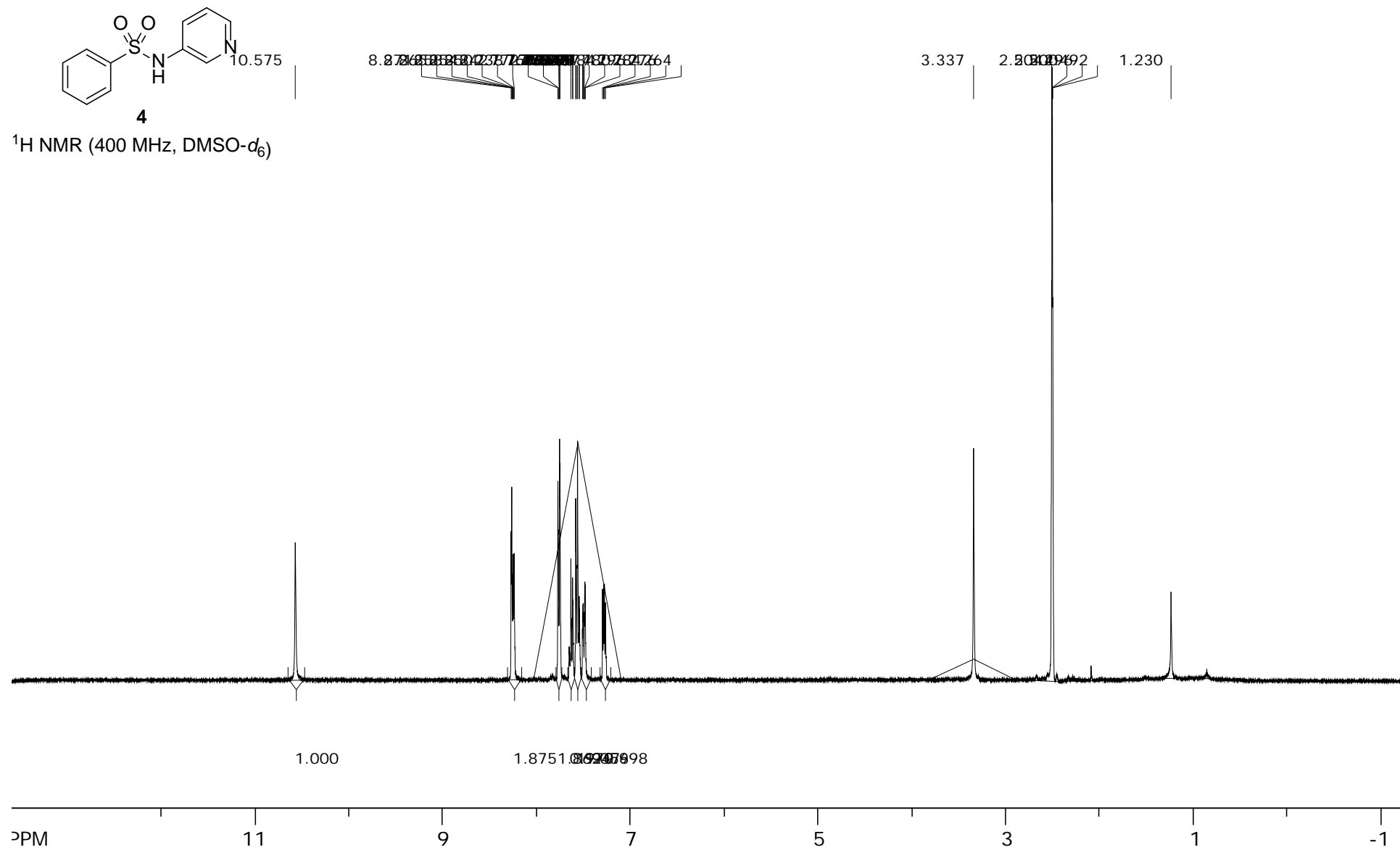


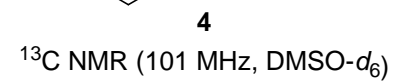


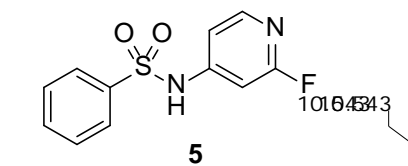
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^{13}C NMR (101 MHz, CDCl_3)

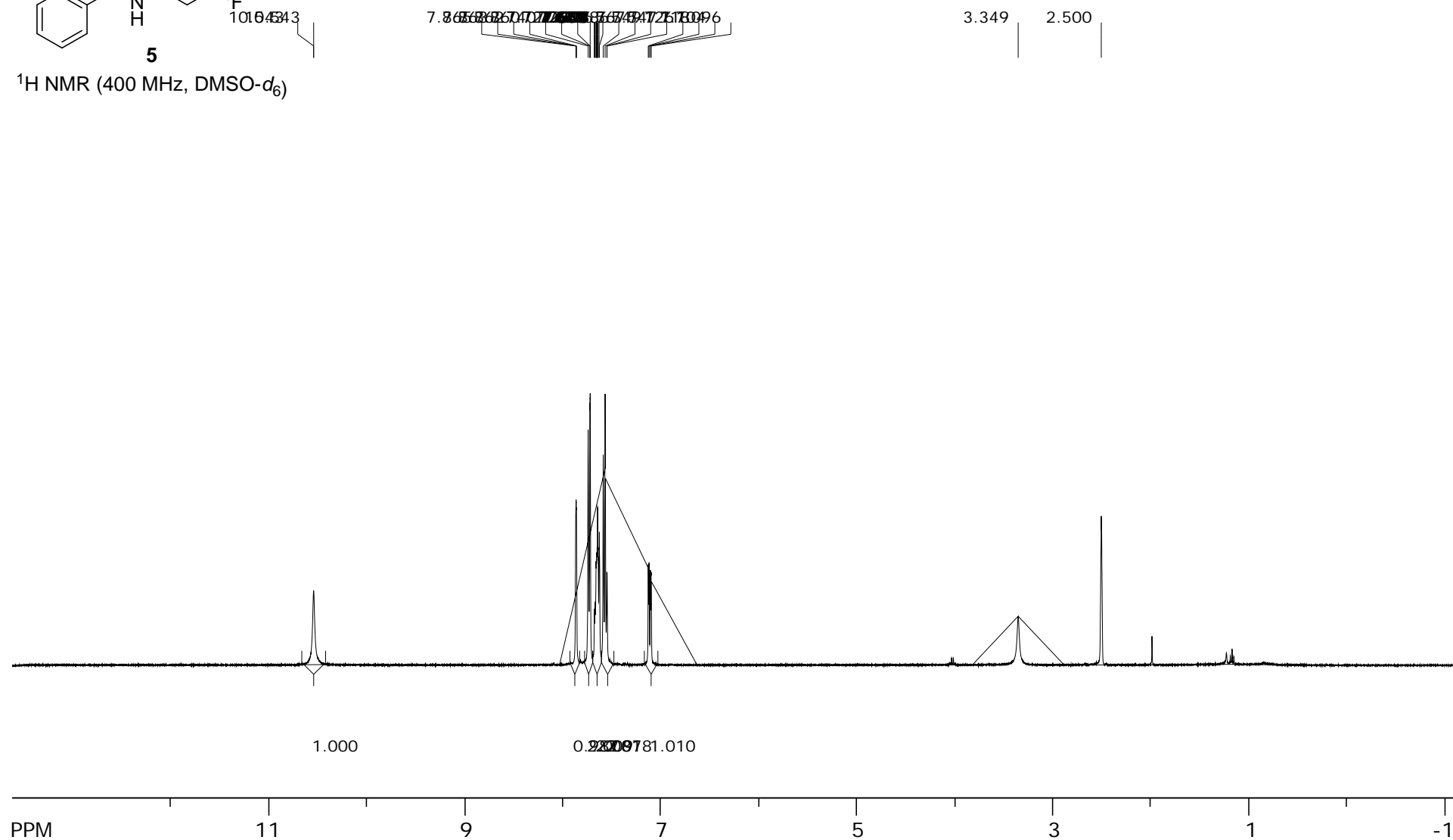


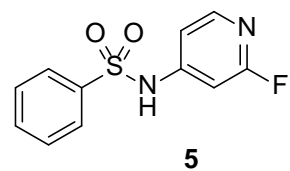




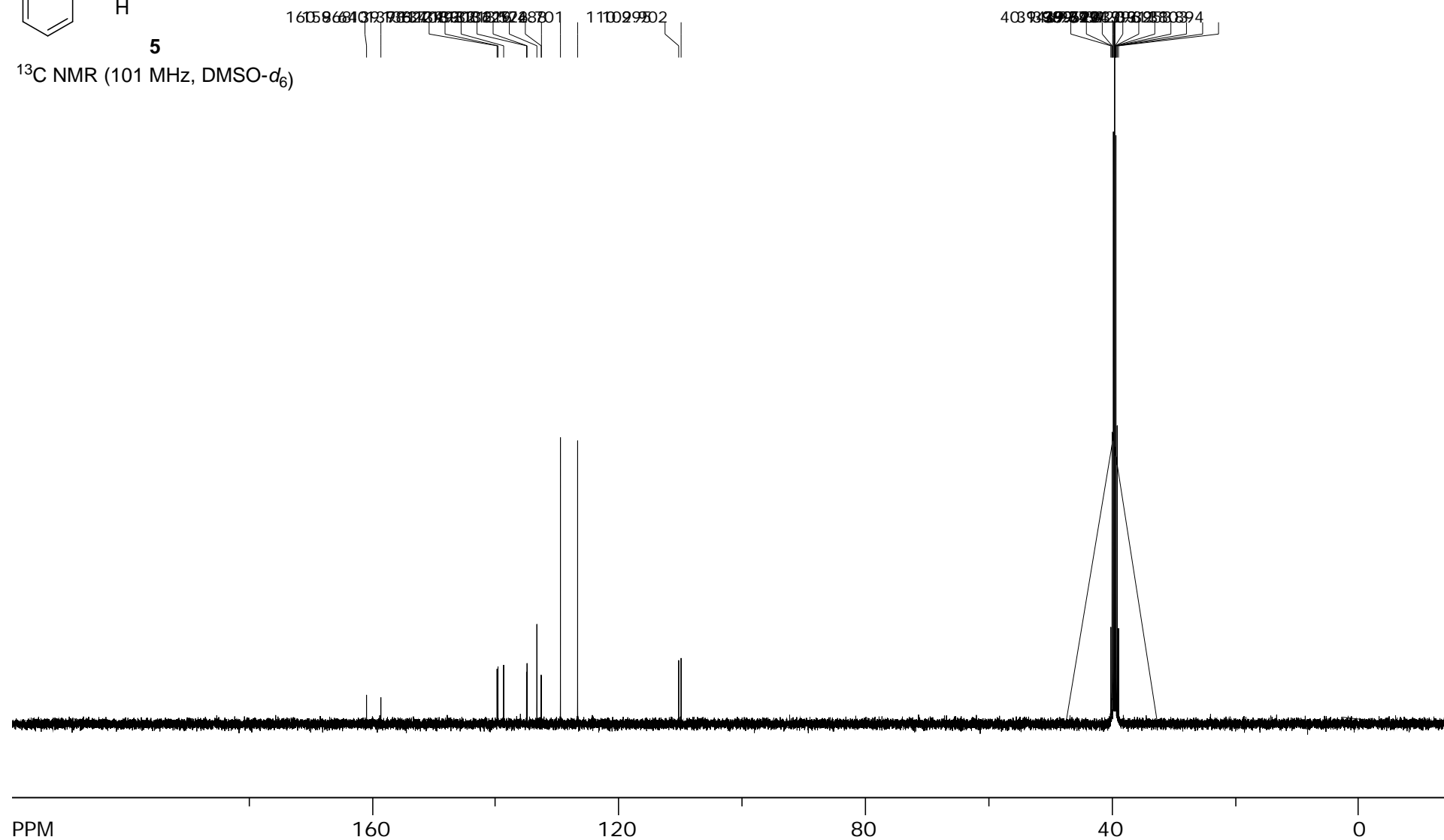


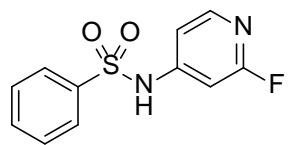
¹H NMR (400 MHz, DMSO-*d*₆)





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

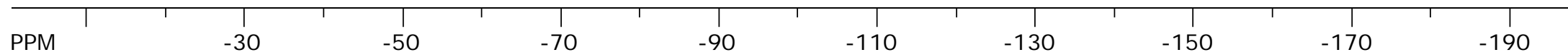


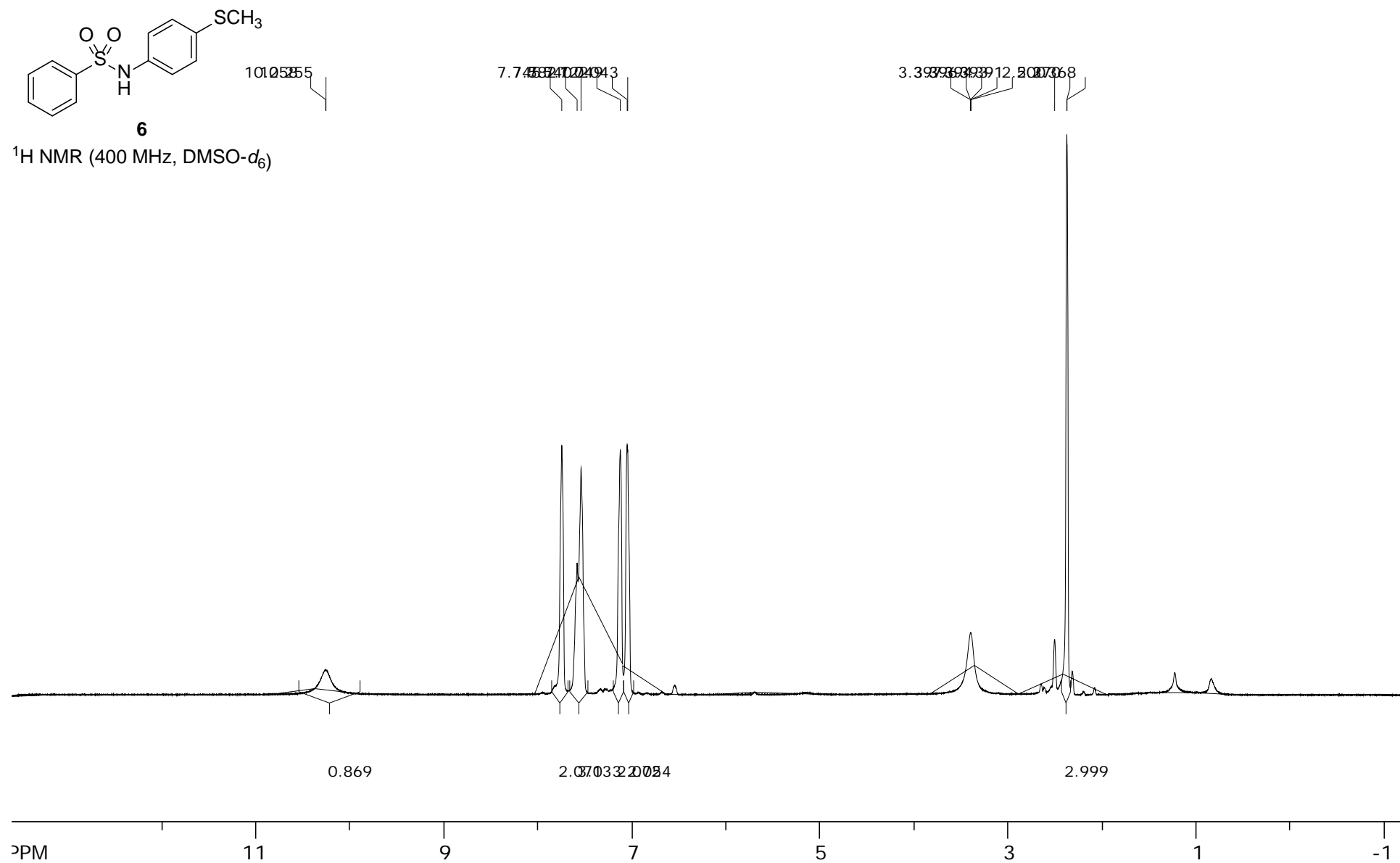


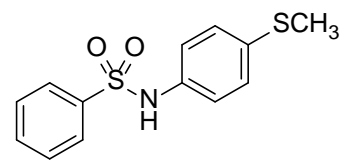
5

^{19}F NMR (376 MHz, $\text{DMSO}-d_6$)

-73.213

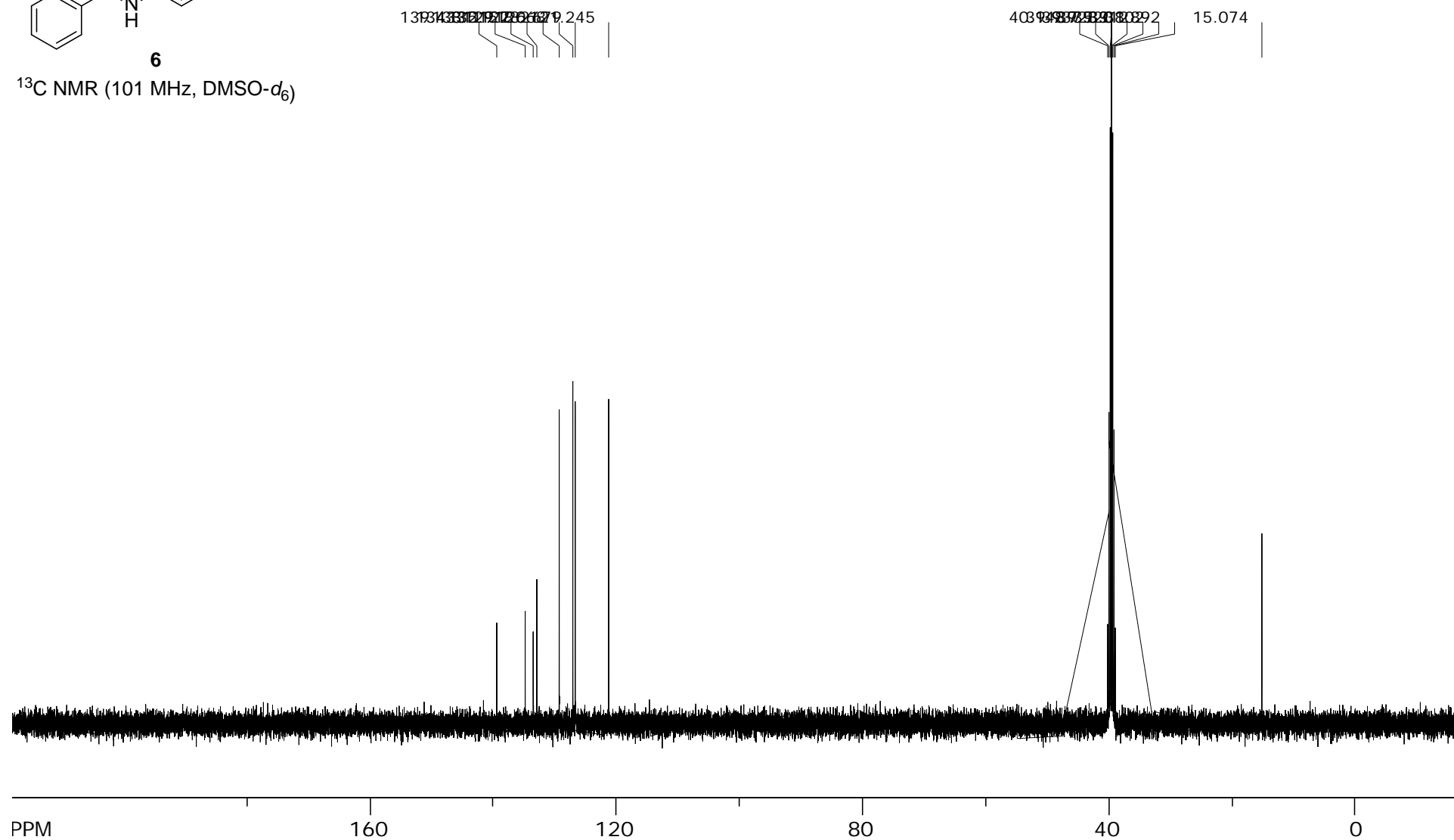


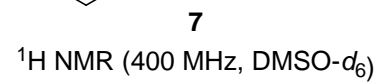


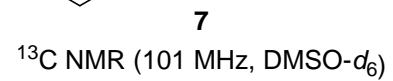


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^{13}C NMR (101 MHz, $\text{DMSO}-d_6$)

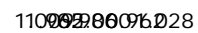








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77.338203

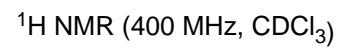


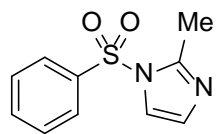
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80

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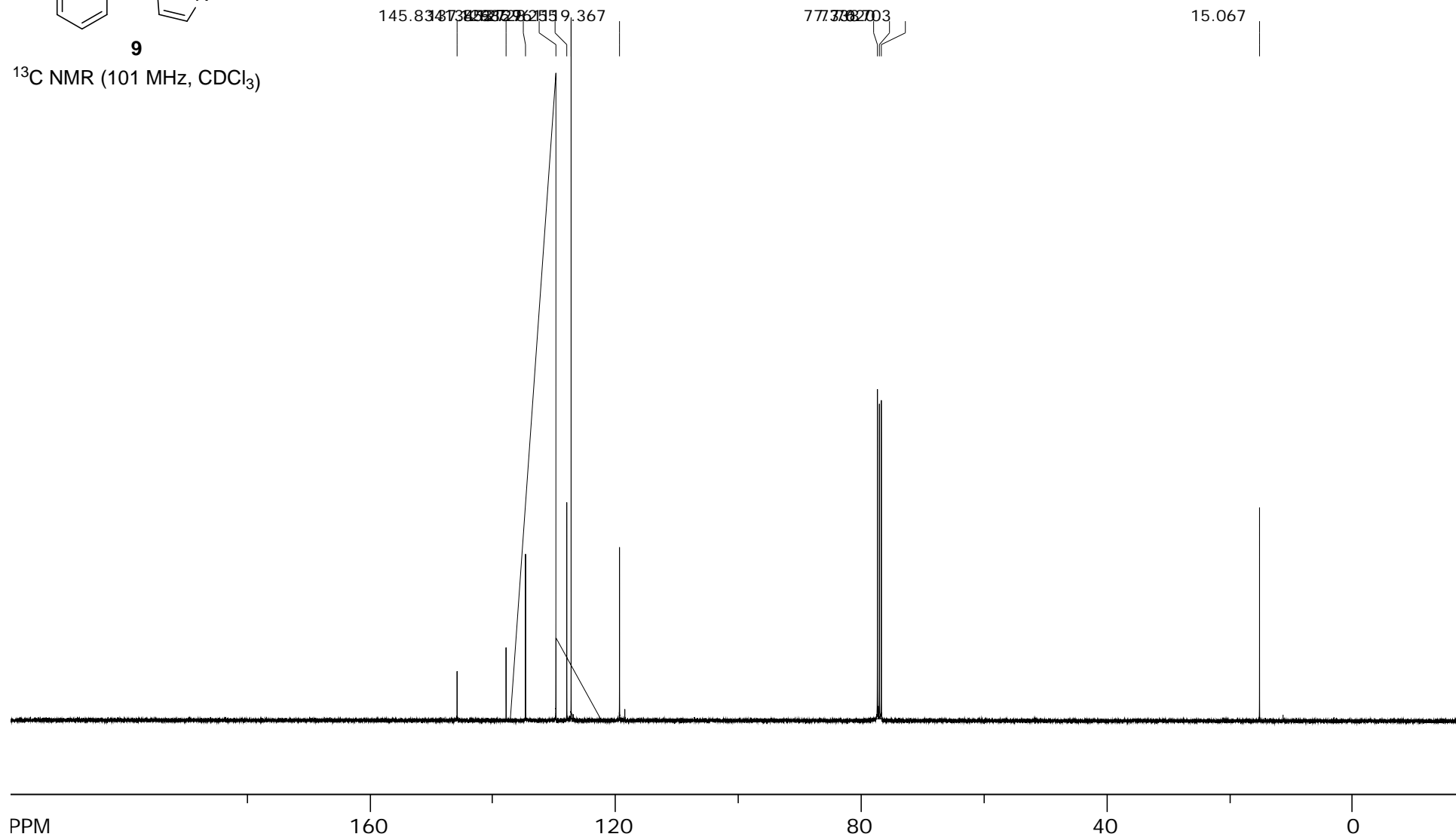
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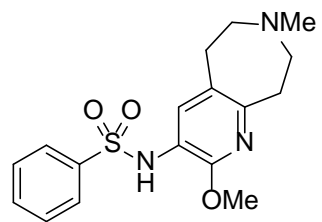




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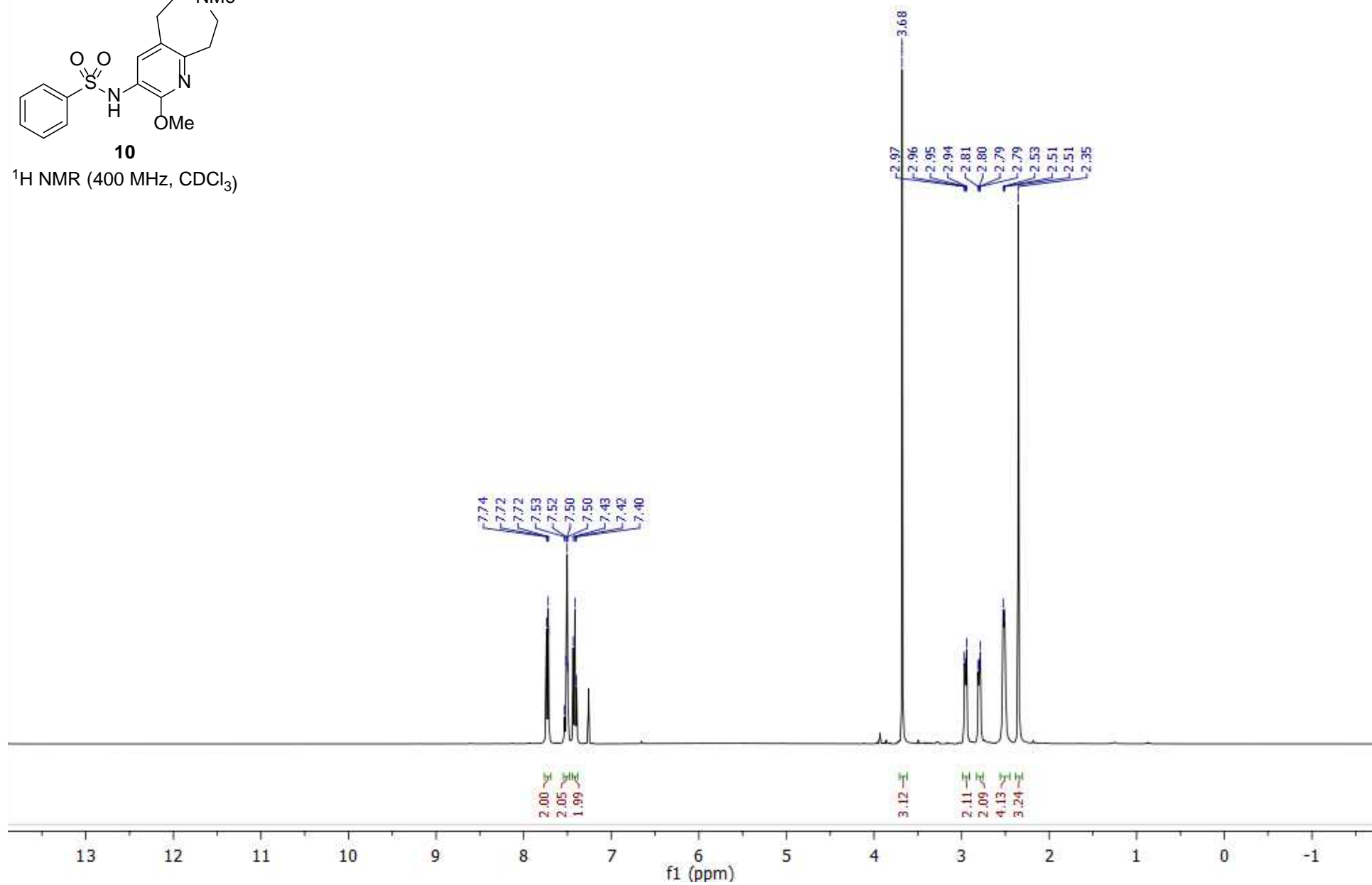
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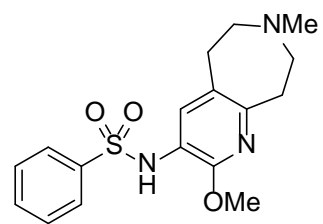




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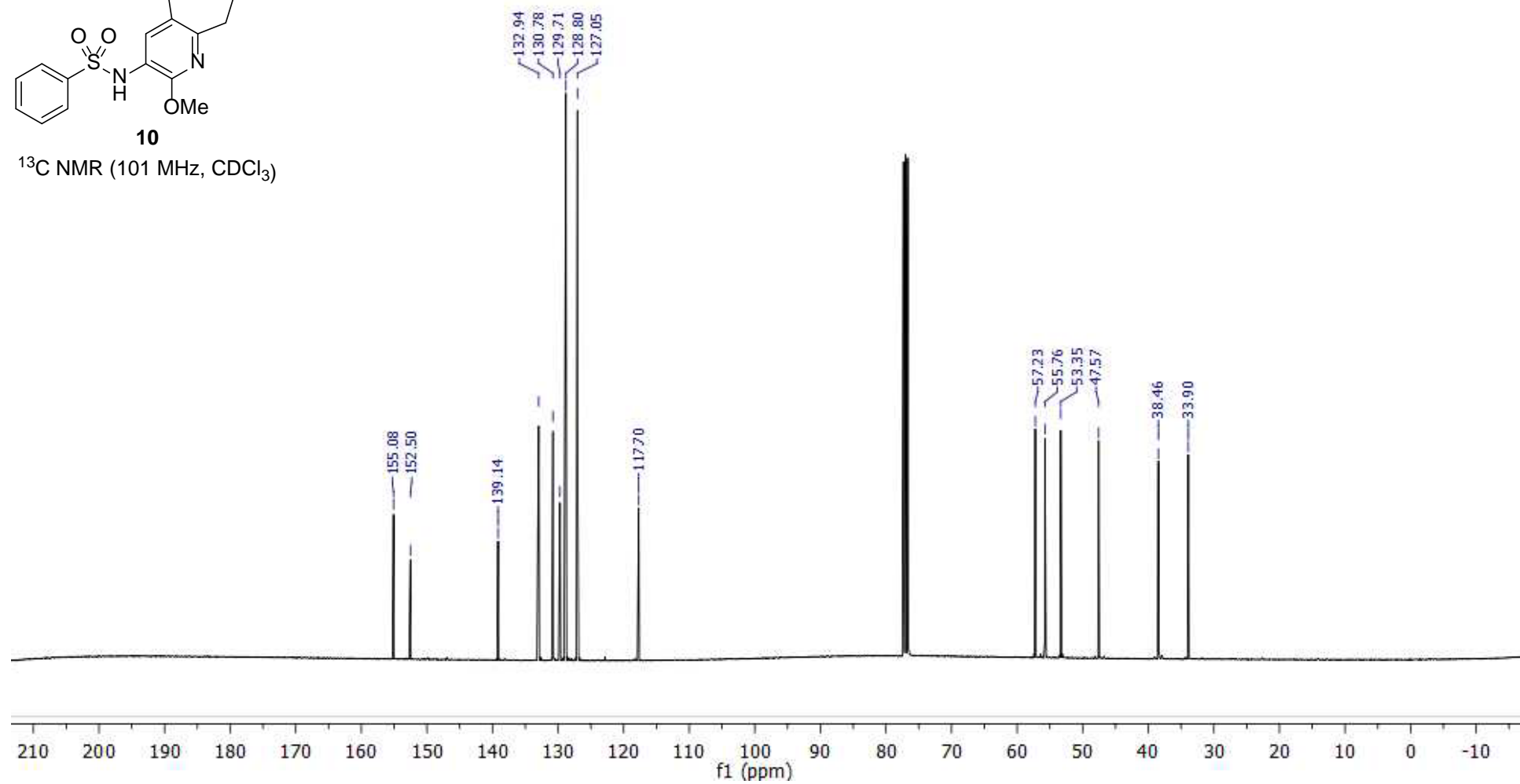
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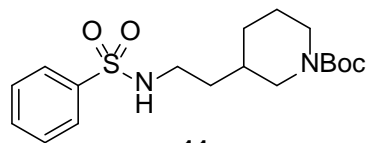




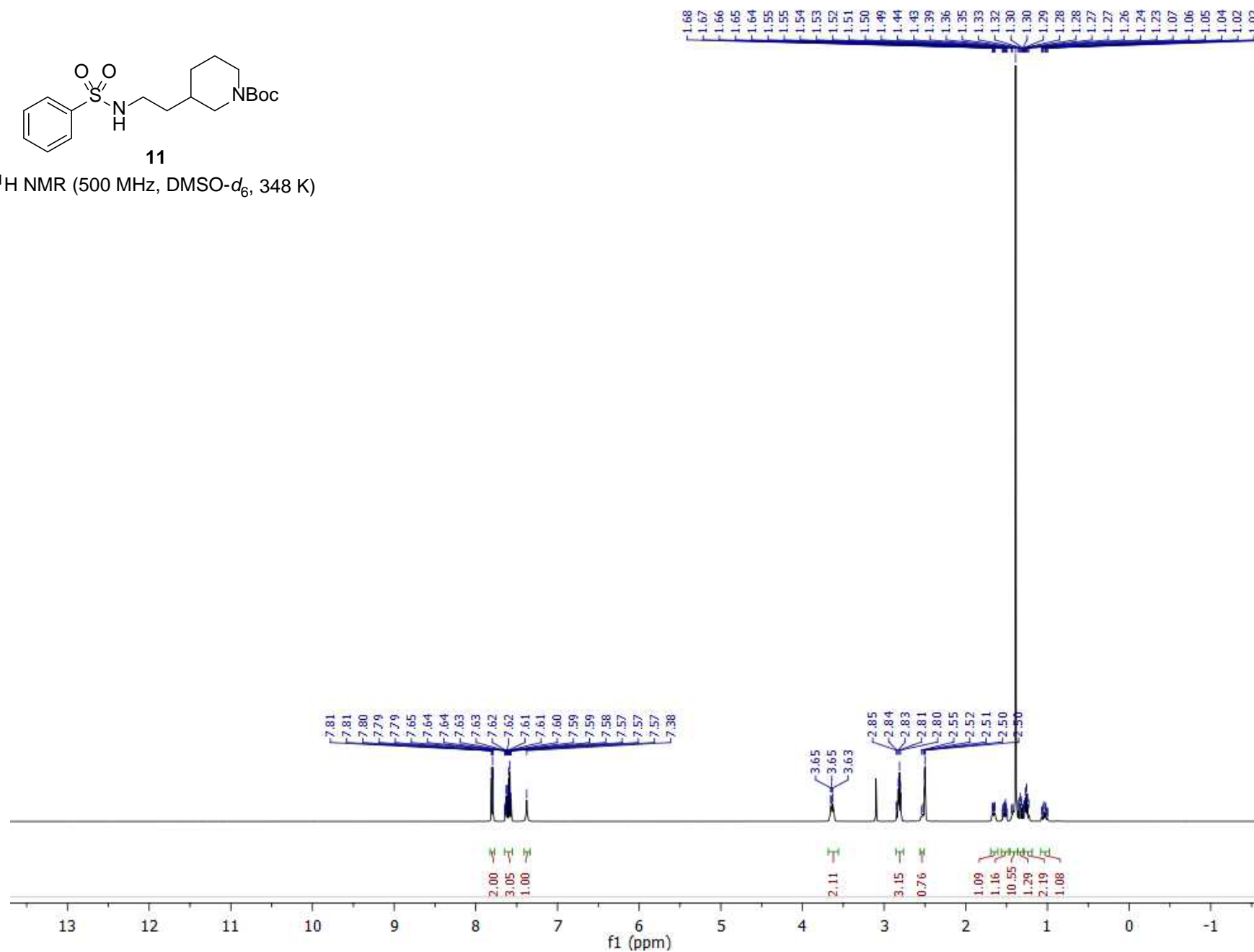
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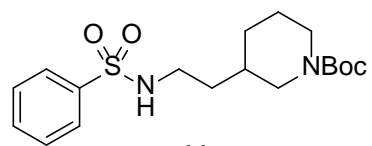
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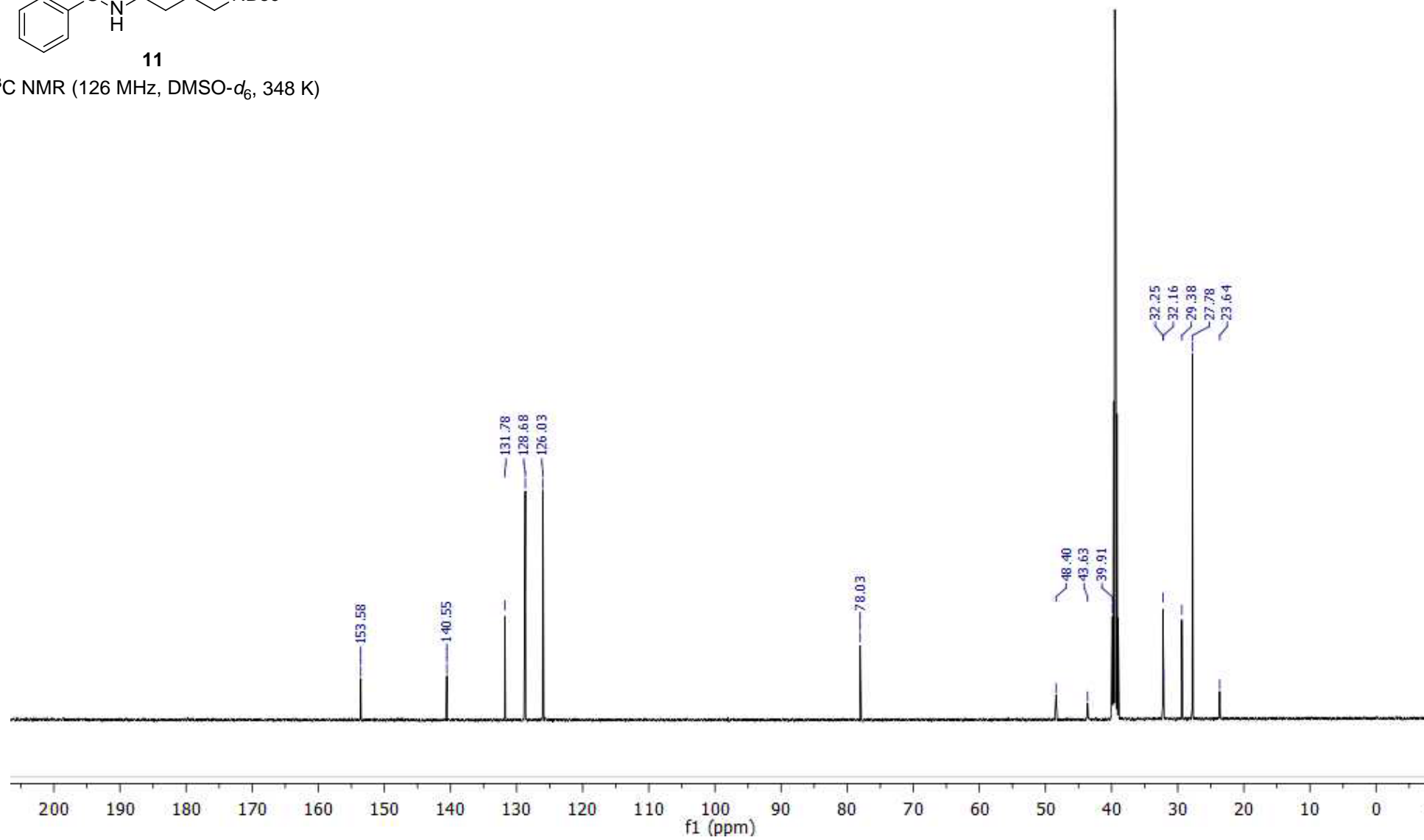
^1H NMR (500 MHz, $\text{DMSO}-d_6$, 348 K)

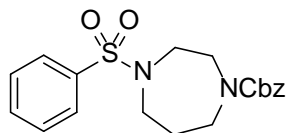




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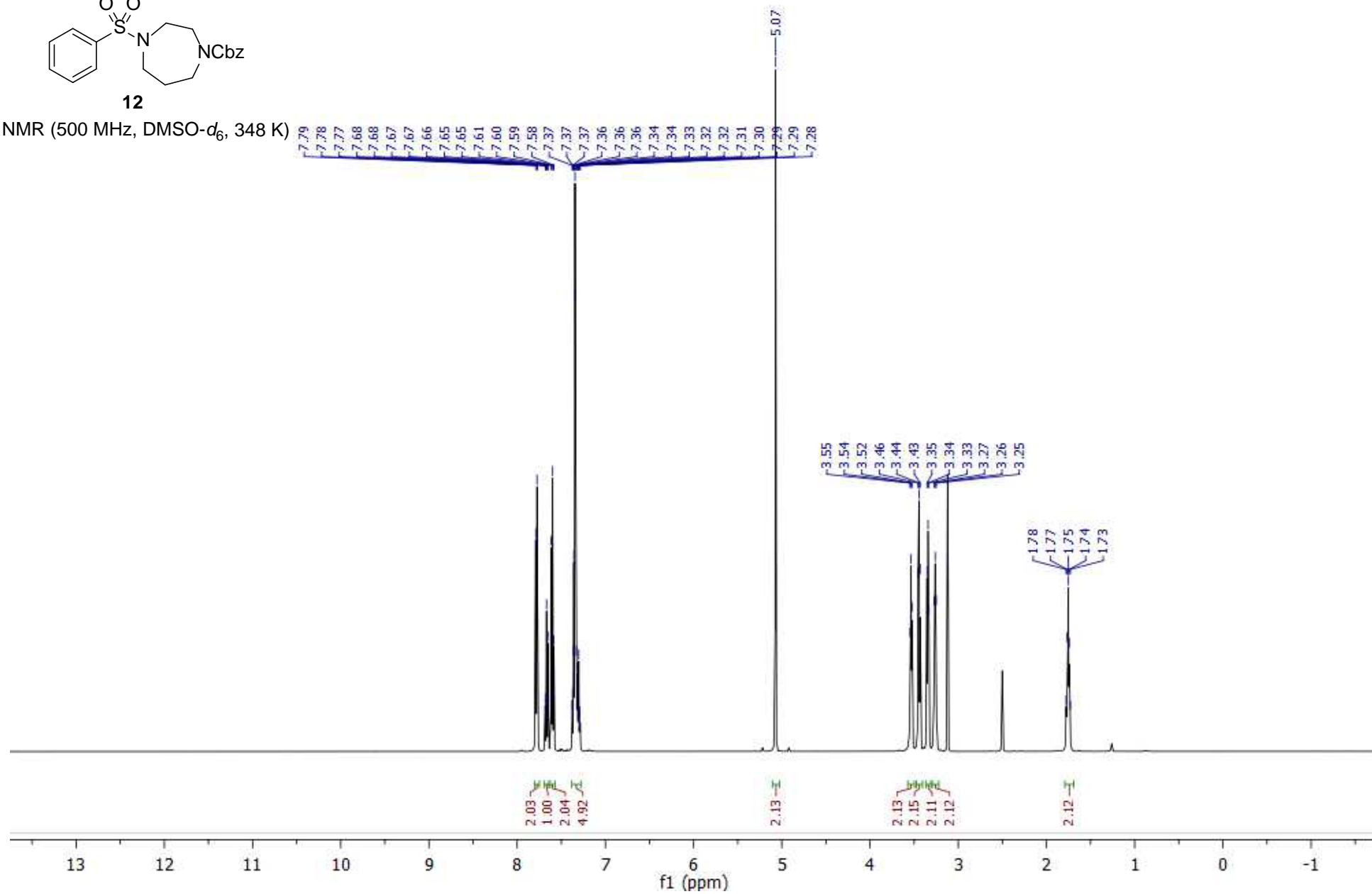
^{13}C NMR (126 MHz, $\text{DMSO-}d_6$, 348 K)

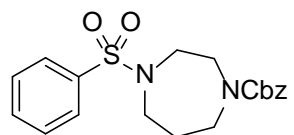




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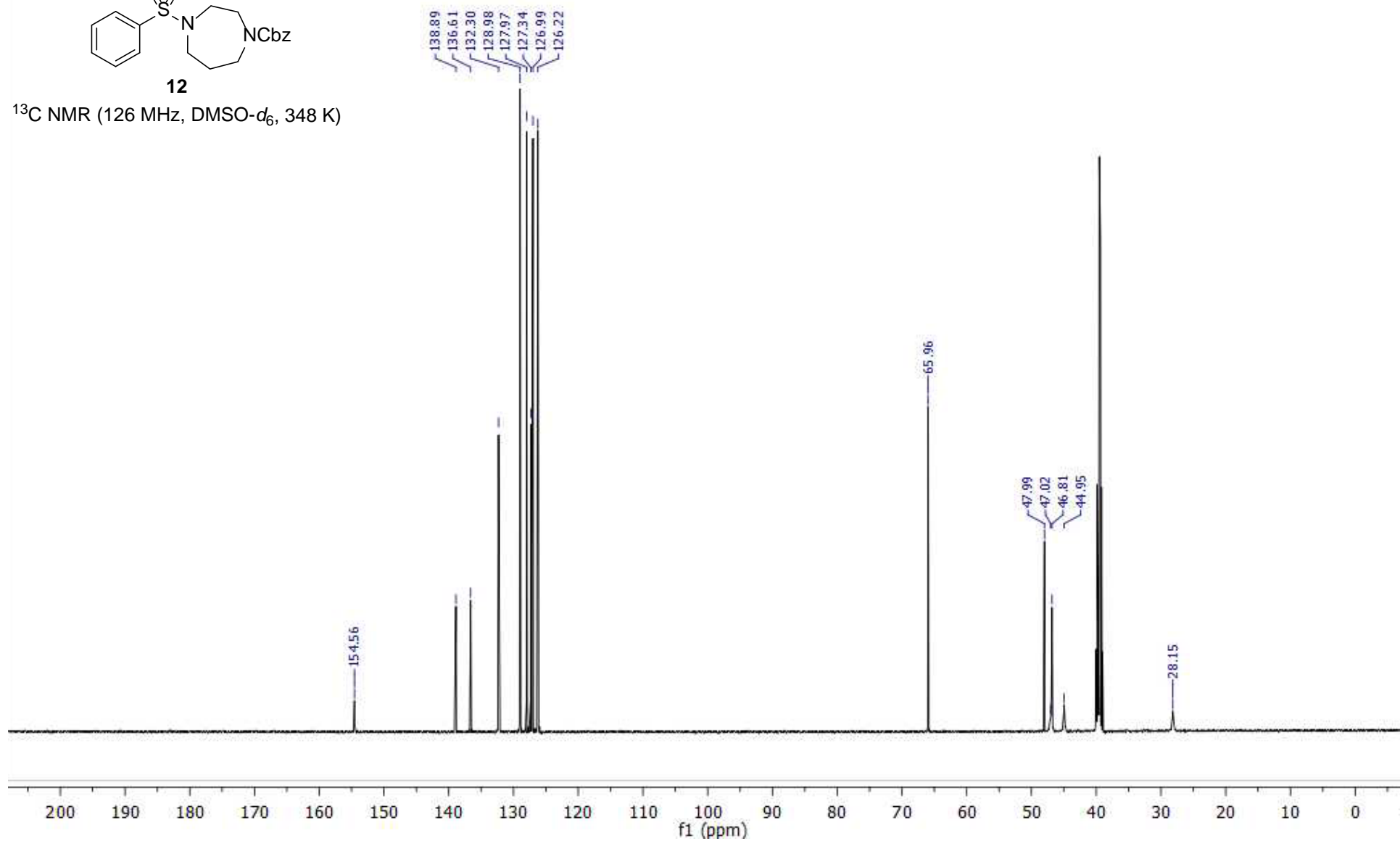
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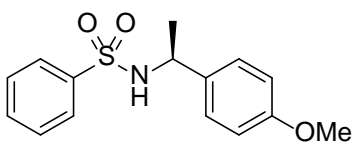




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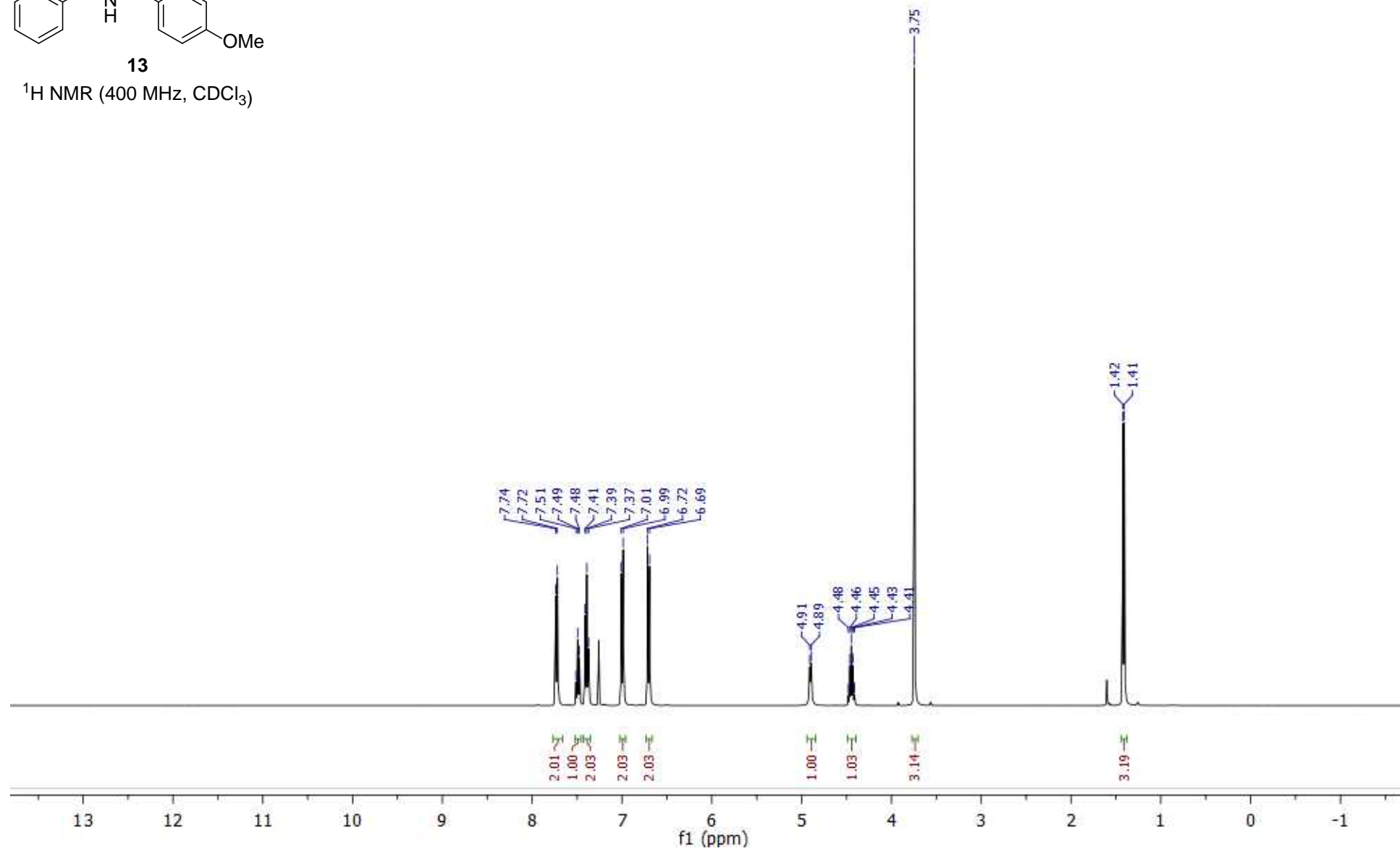
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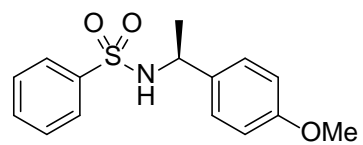




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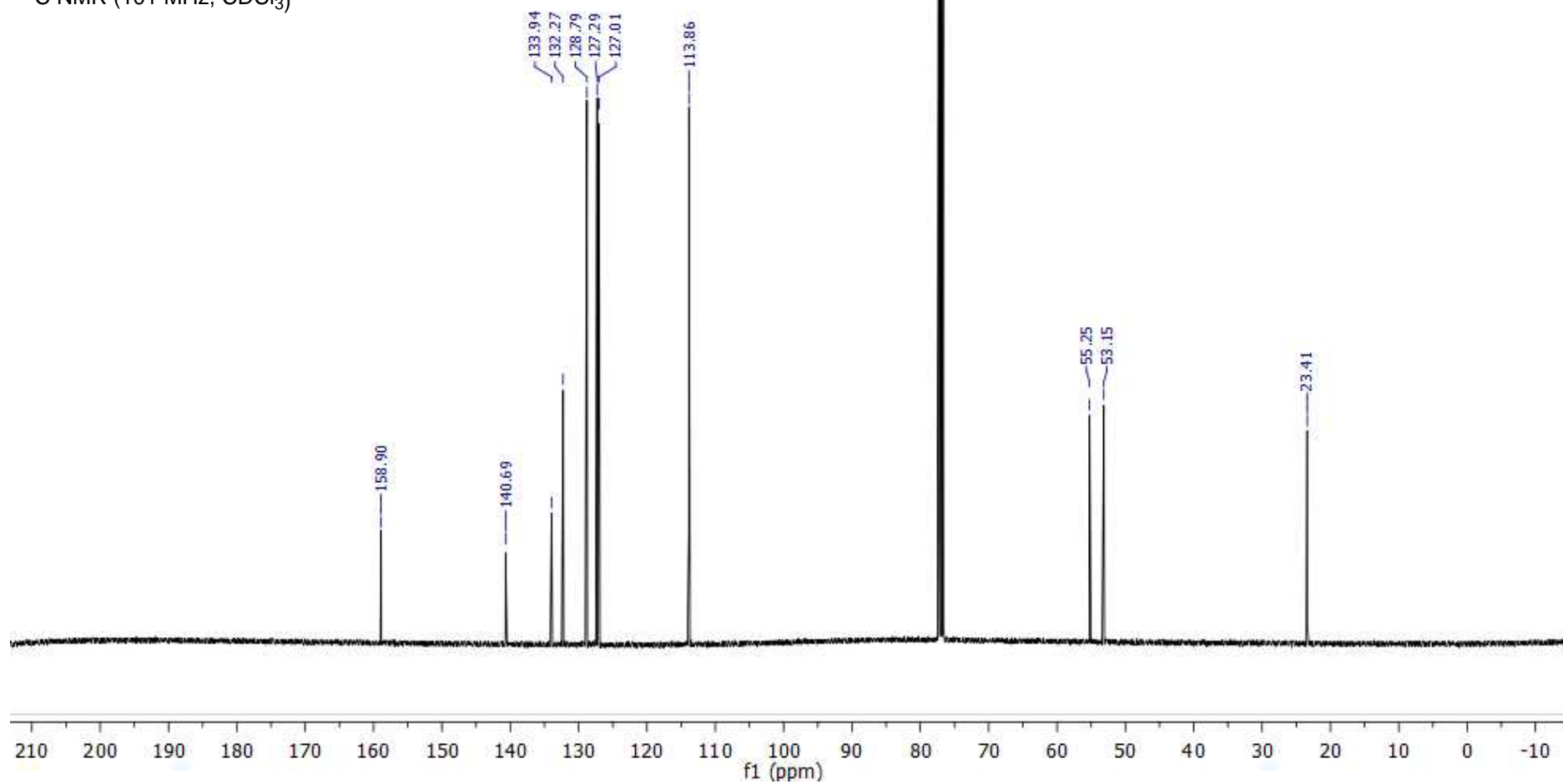
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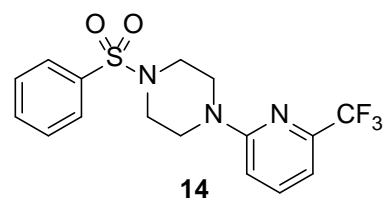




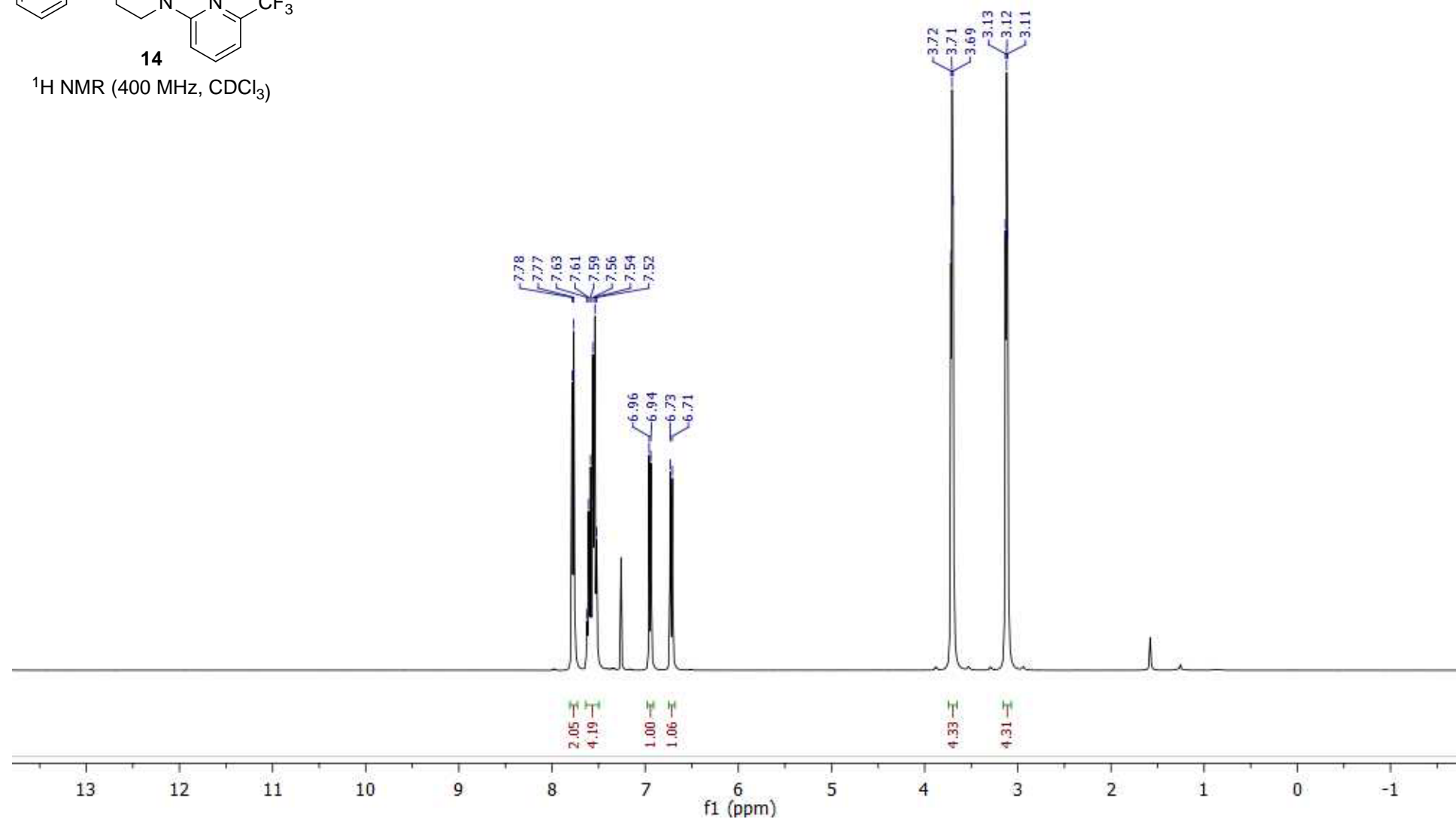
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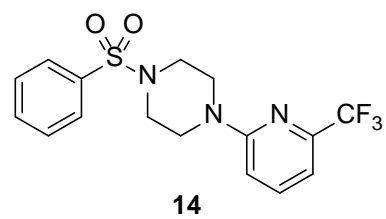
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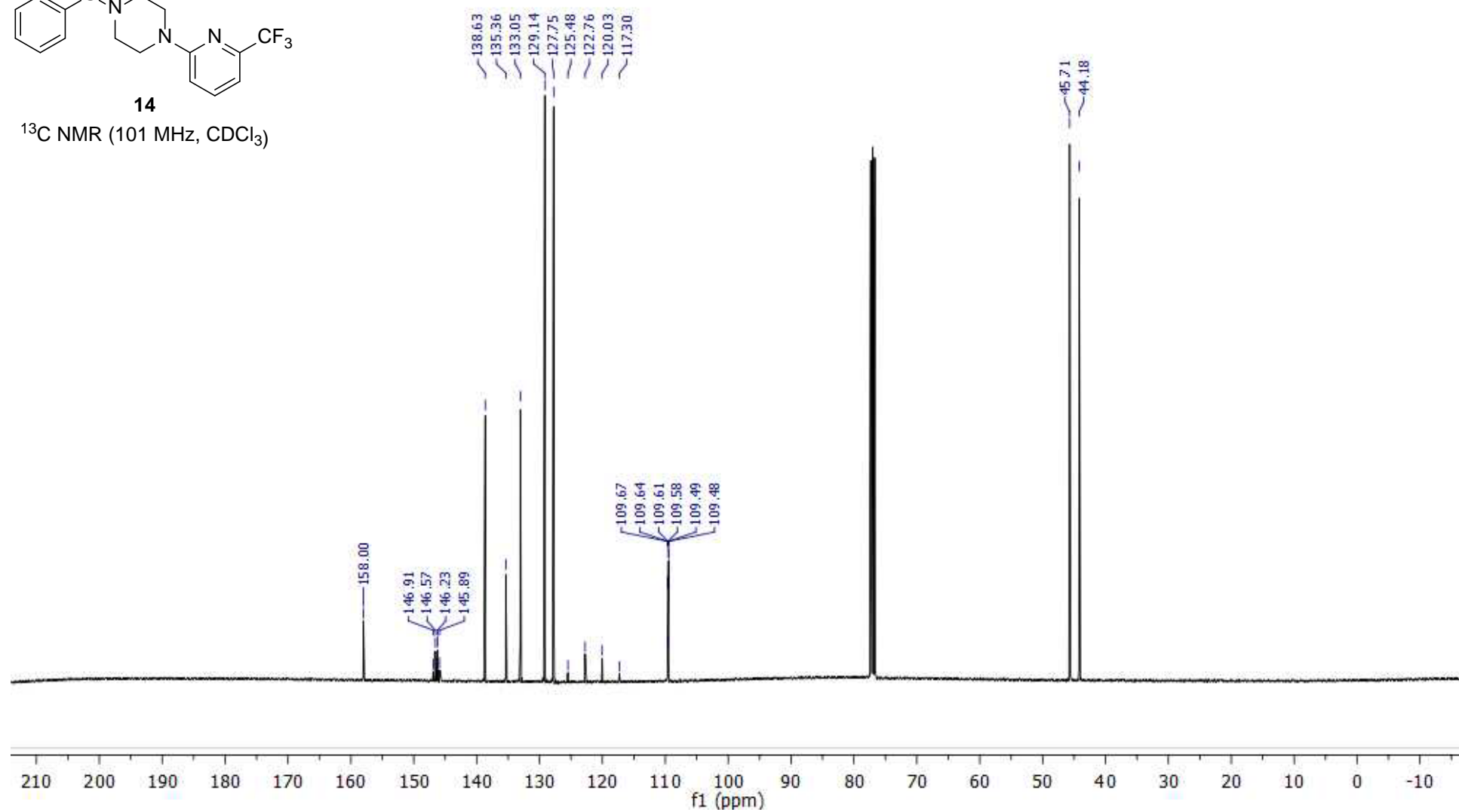


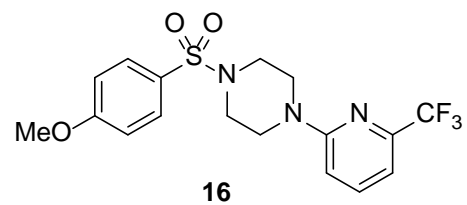
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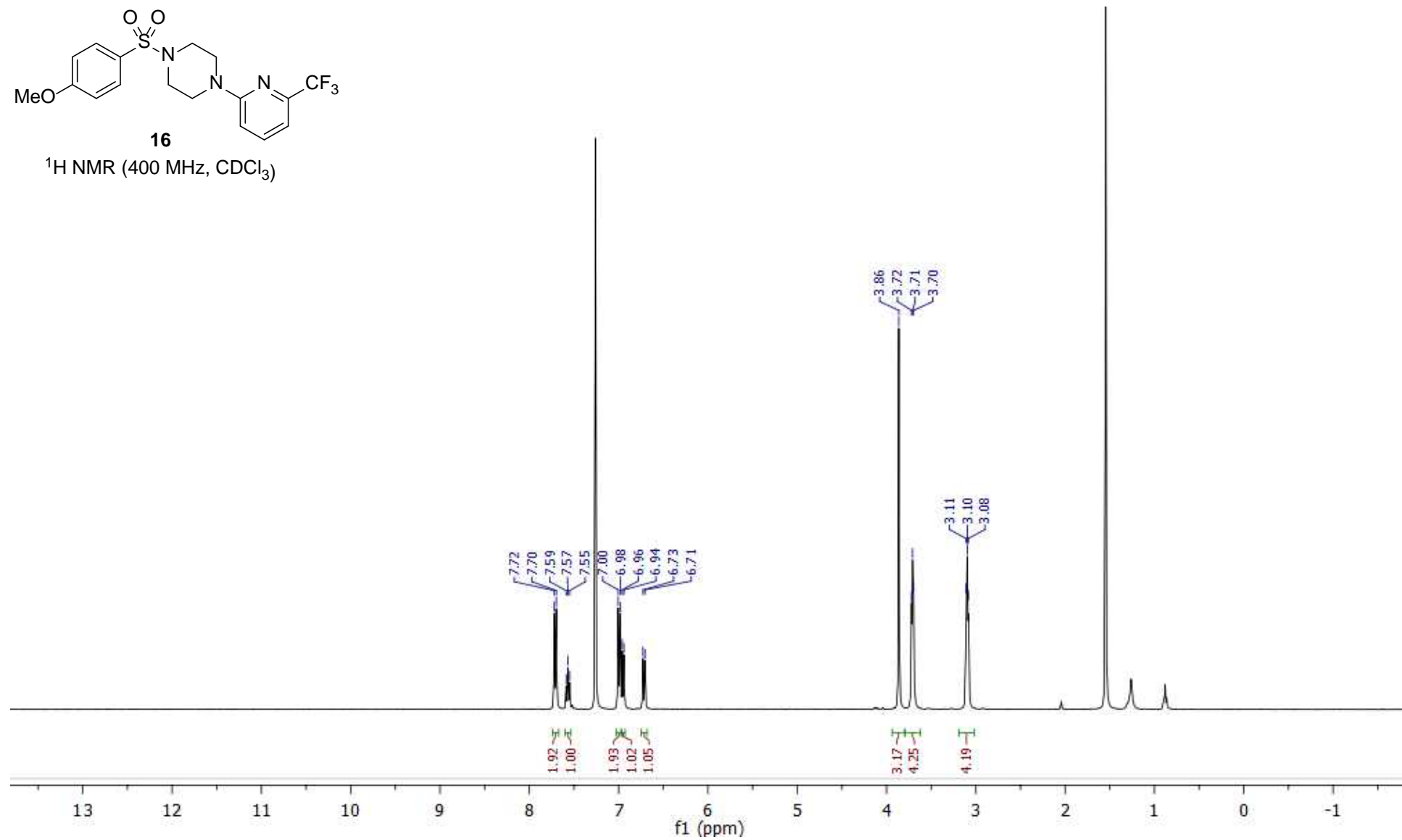


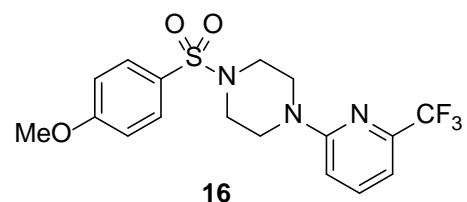
^{13}C NMR (101 MHz, CDCl_3)



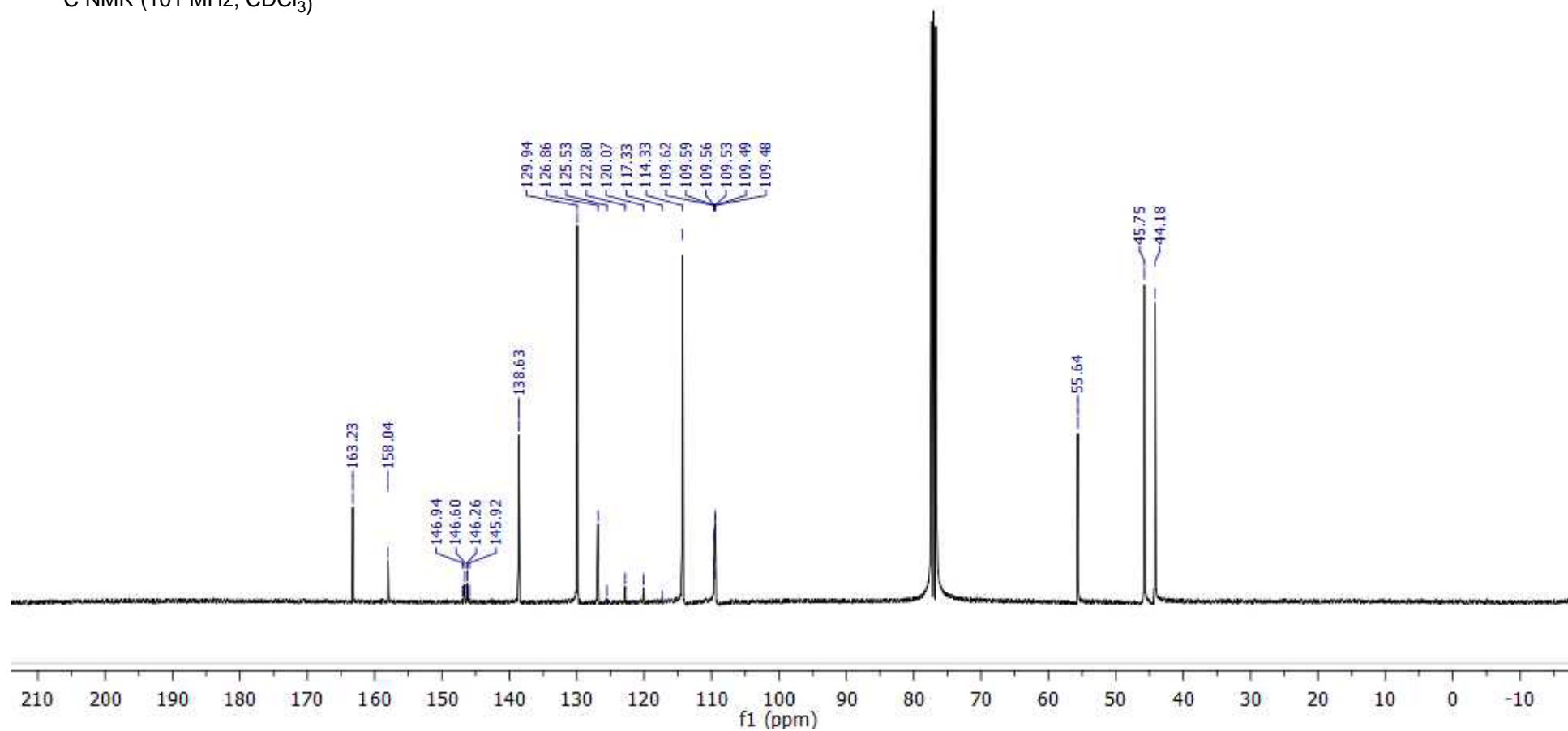


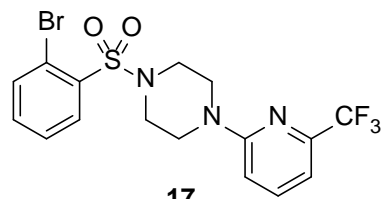
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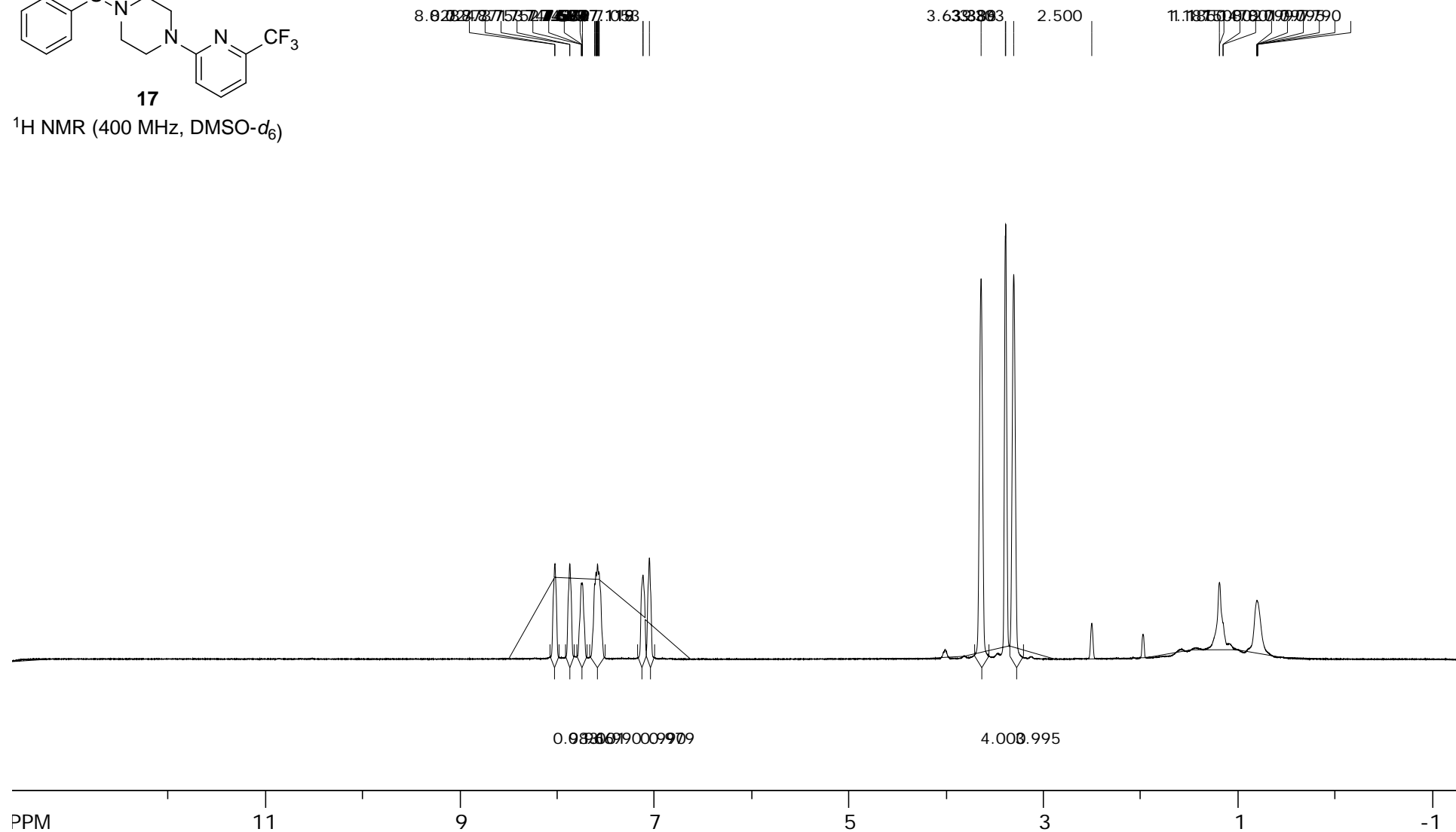


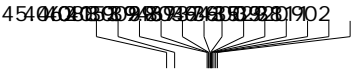
^{13}C NMR (101 MHz, CDCl_3)



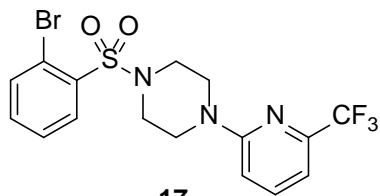


¹H NMR (400 MHz, DMSO-*d*₆)





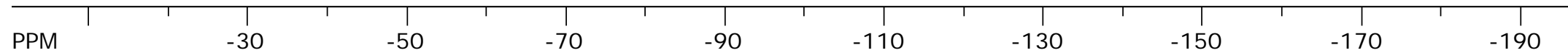
The image displays a ^{13}C NMR spectrum of 1,2-dichloroethane. The horizontal axis represents the chemical shift in PPM, ranging from 0 to 160. The spectrum features two main signal regions: a triplet at approximately 40 ppm and a multiplet between 120 and 140 ppm. The triplet is the most intense signal, while the multiplet is significantly less intense. The baseline is relatively flat with some noise.

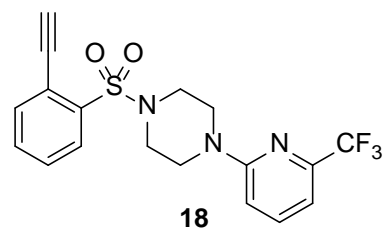


17

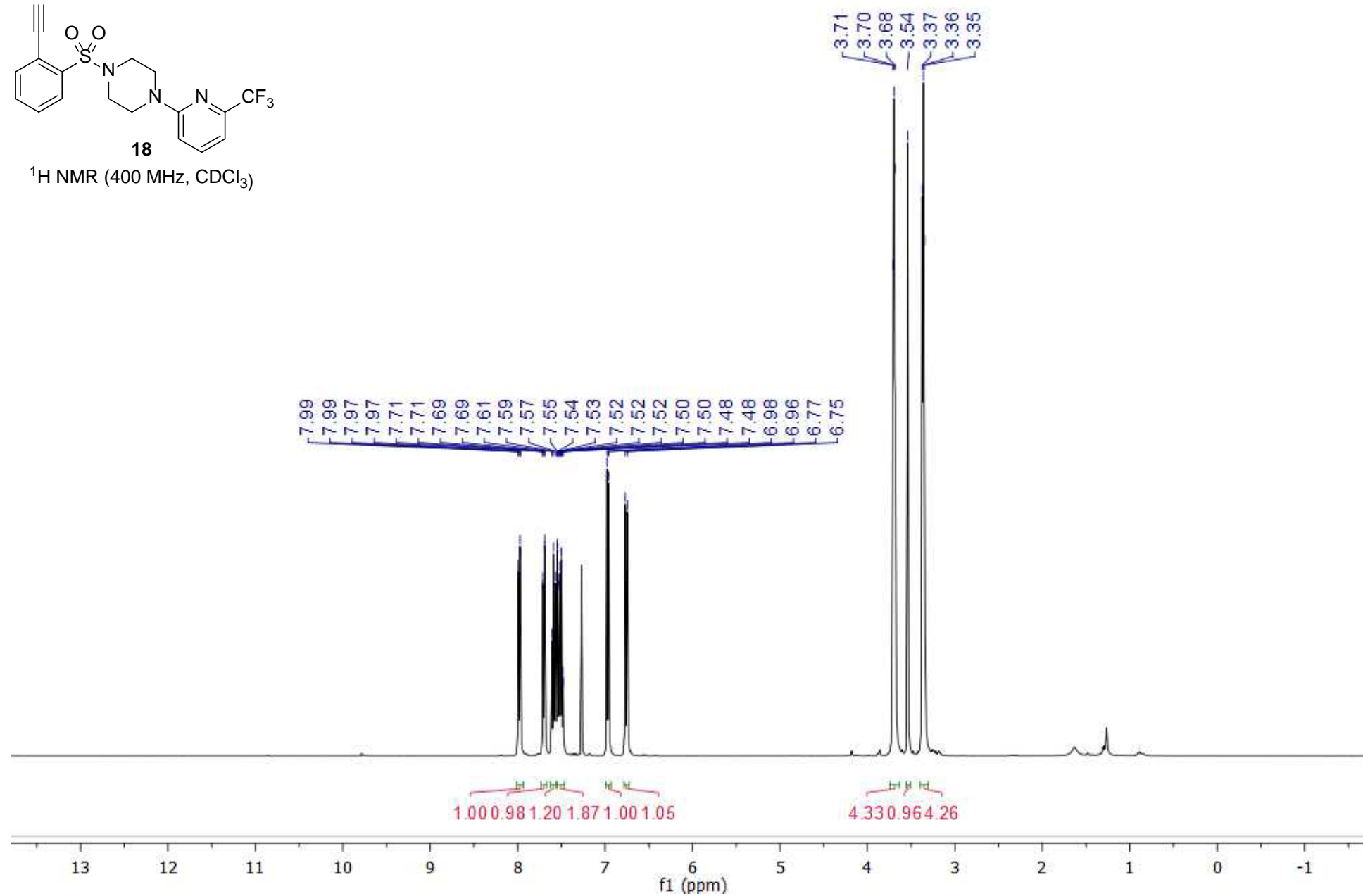
^{13}C NMR (376 MHz, $\text{DMSO}-d_6$)

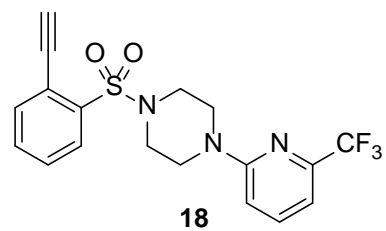
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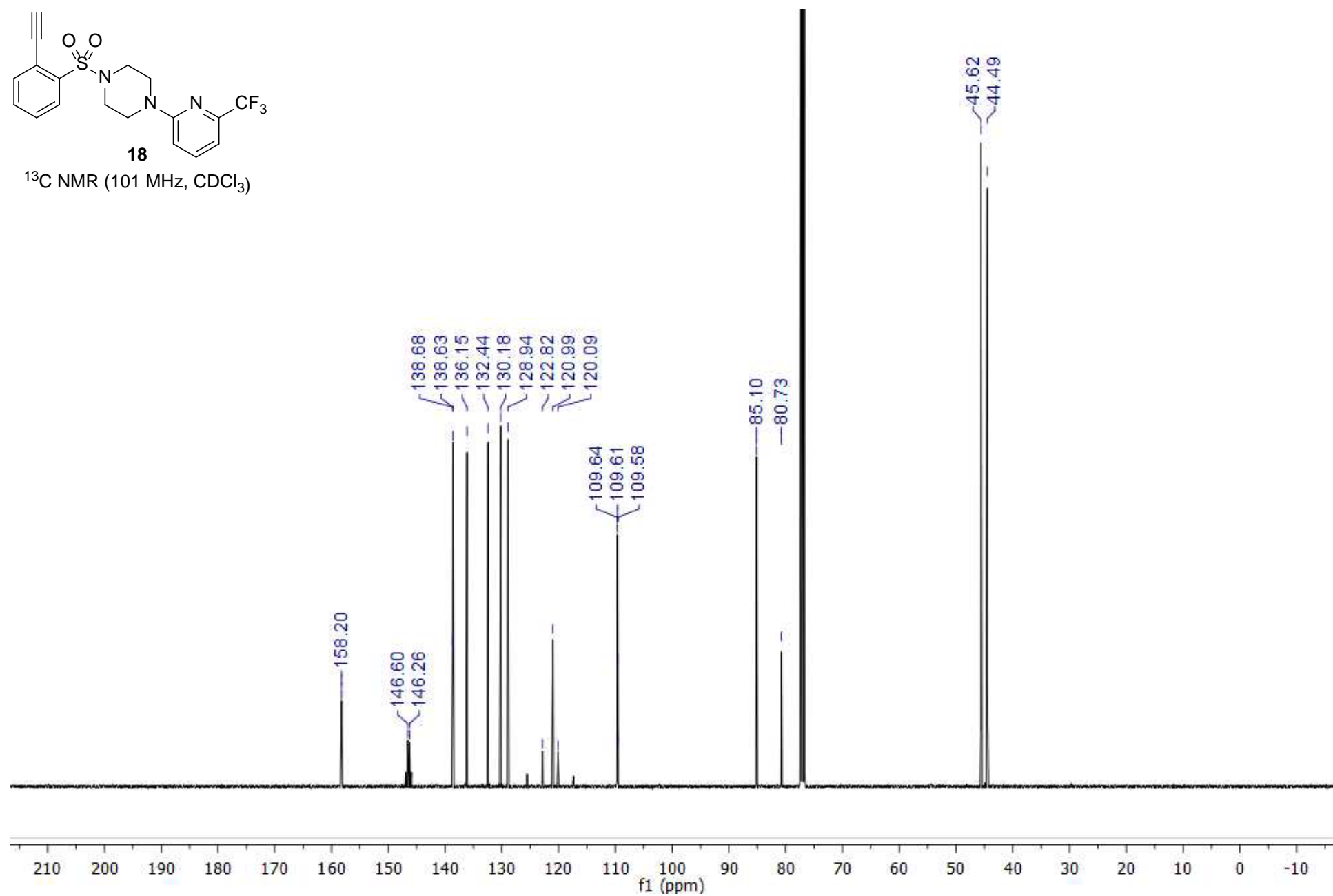


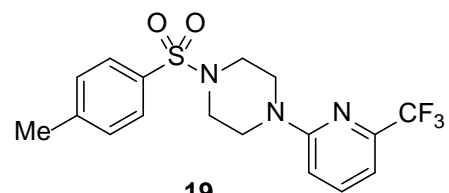
^1H NMR (400 MHz, CDCl_3)



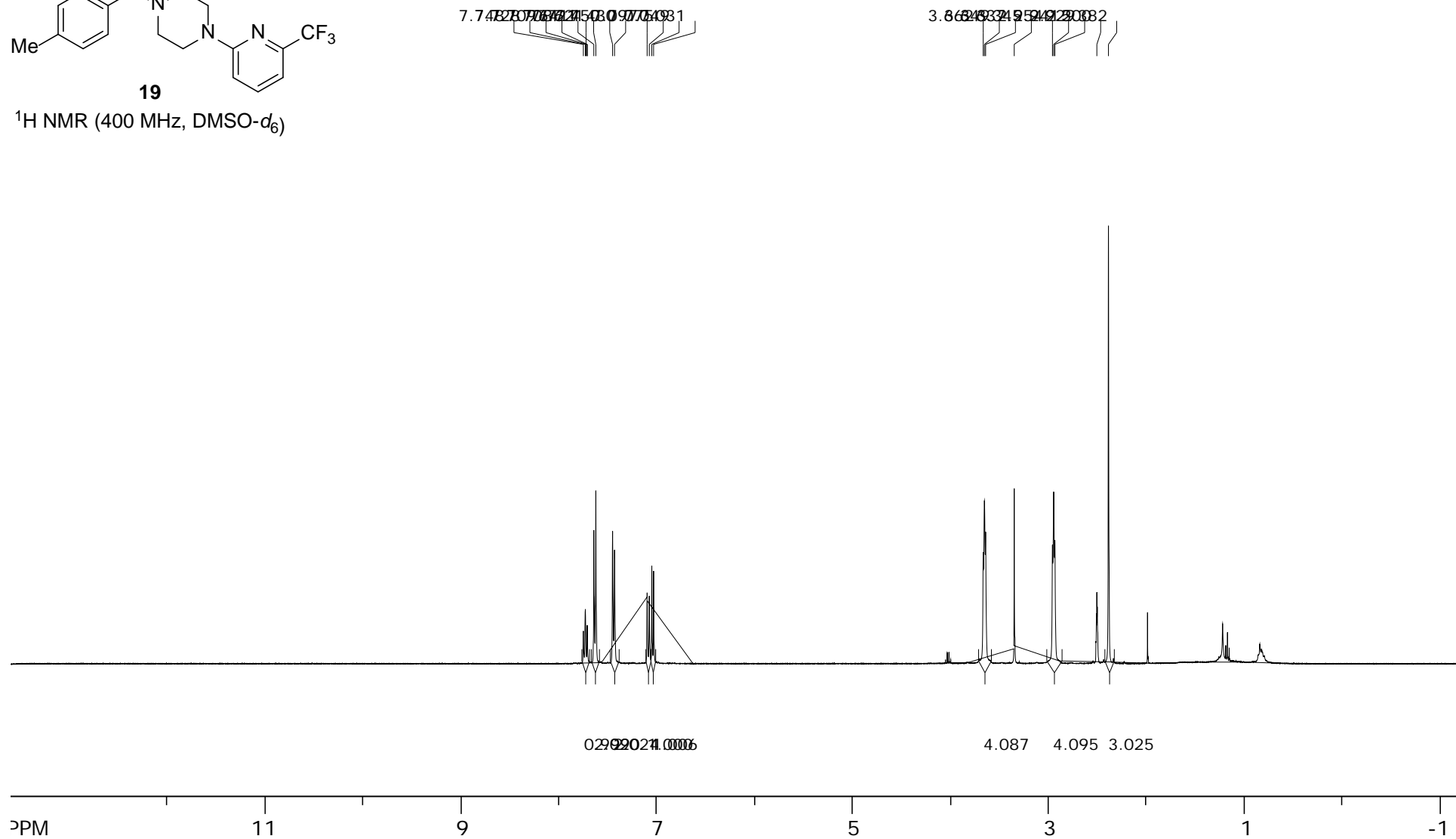


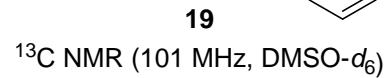
^{13}C NMR (101 MHz, CDCl_3)

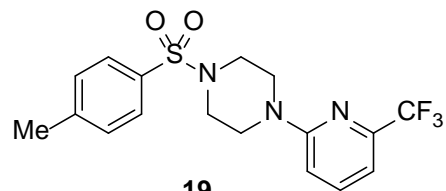




¹H NMR (400 MHz, DMSO-*d*₆)

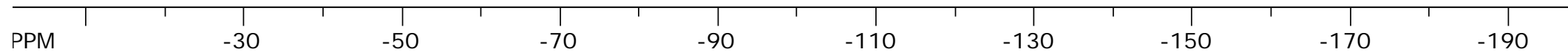


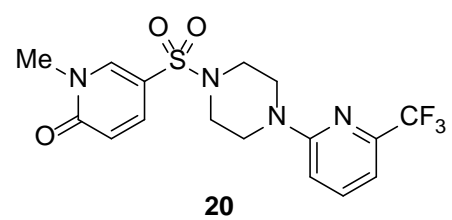




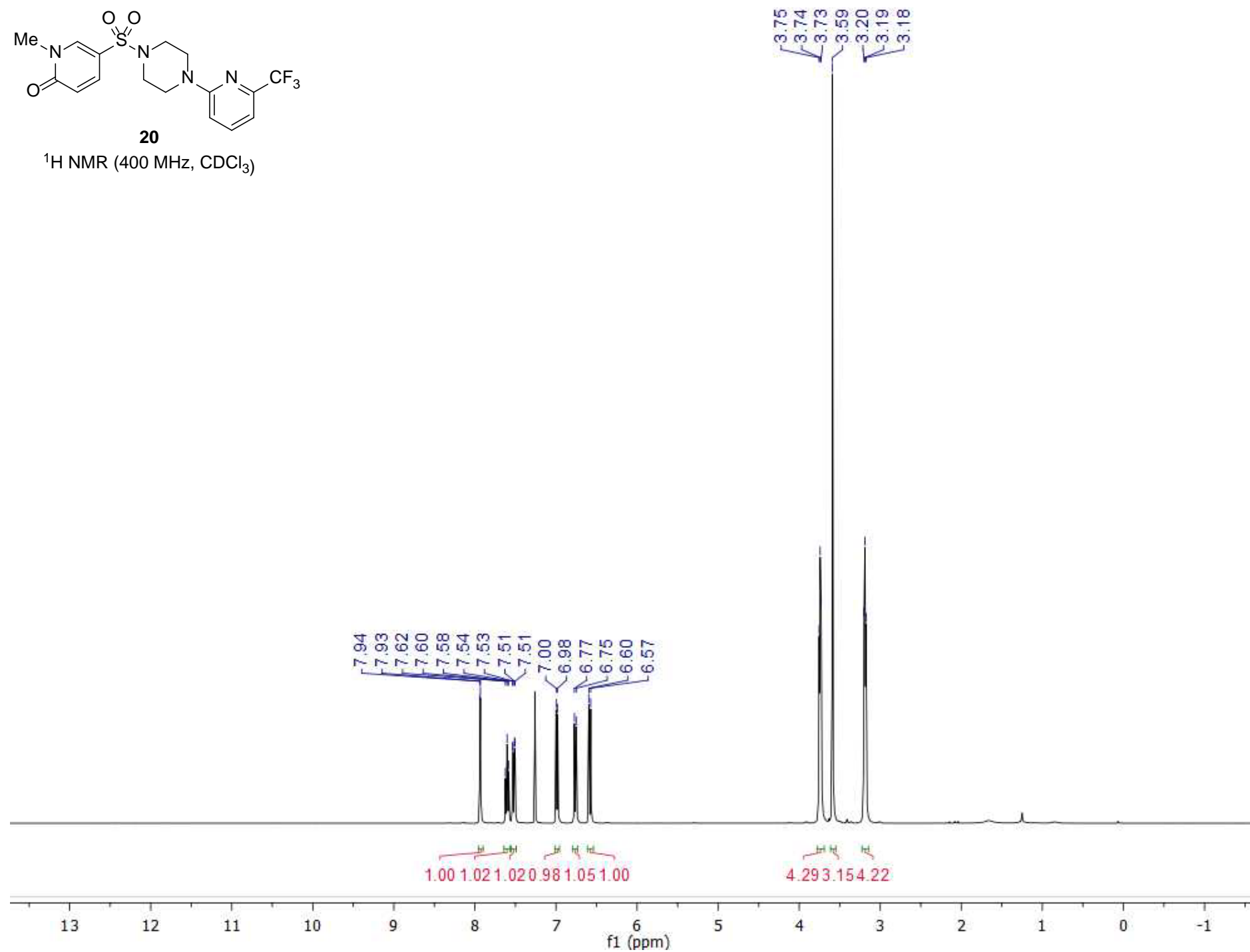
^{19}F NMR (376 MHz, $\text{DMSO-}d_6$)

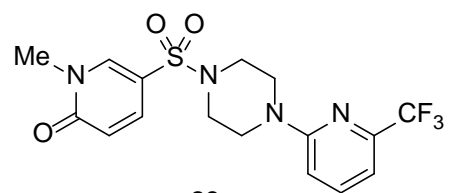
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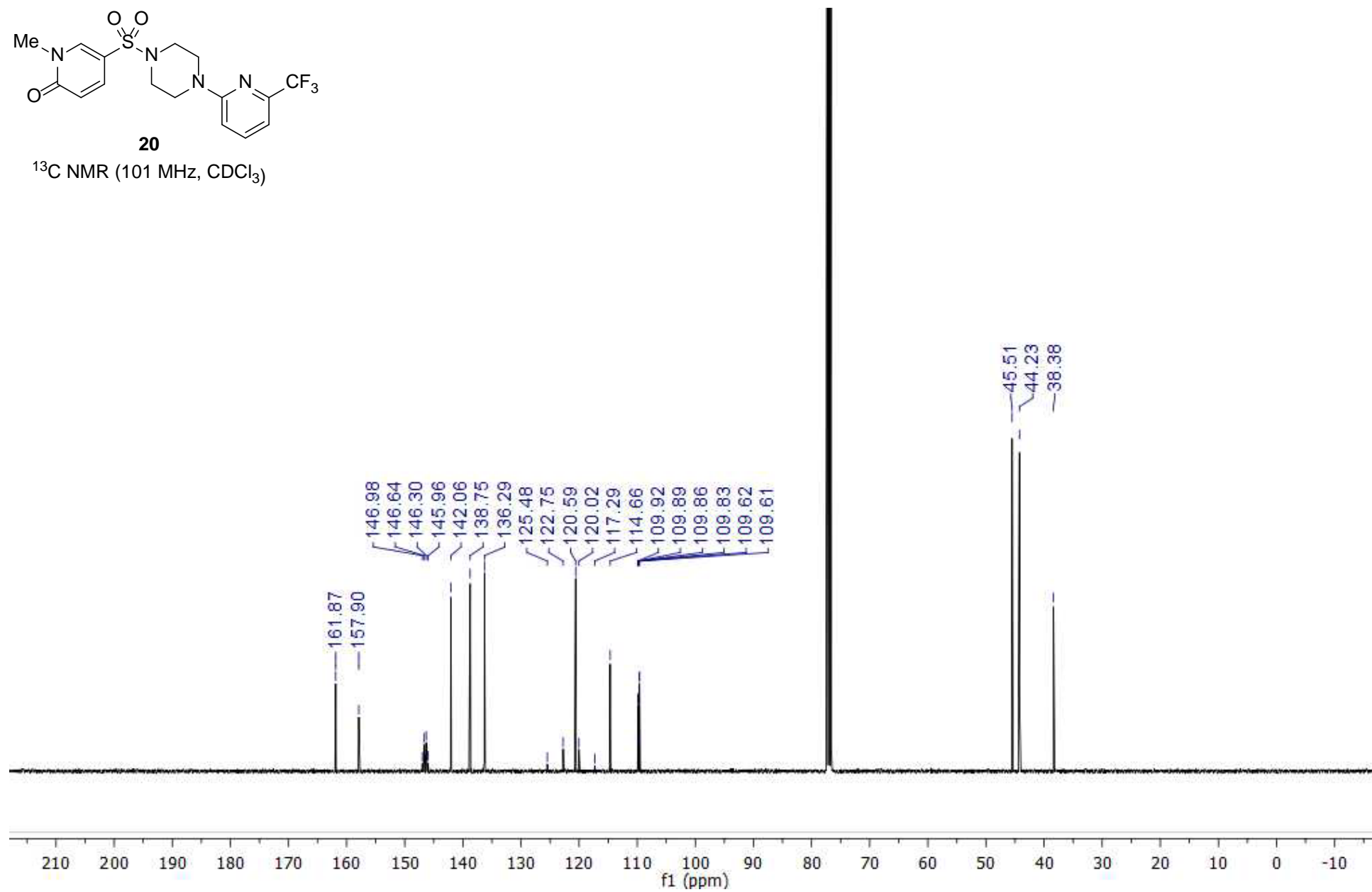
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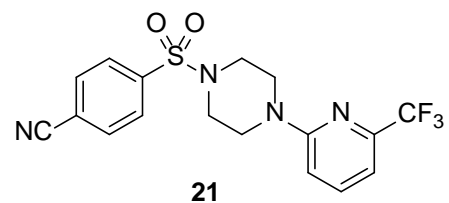




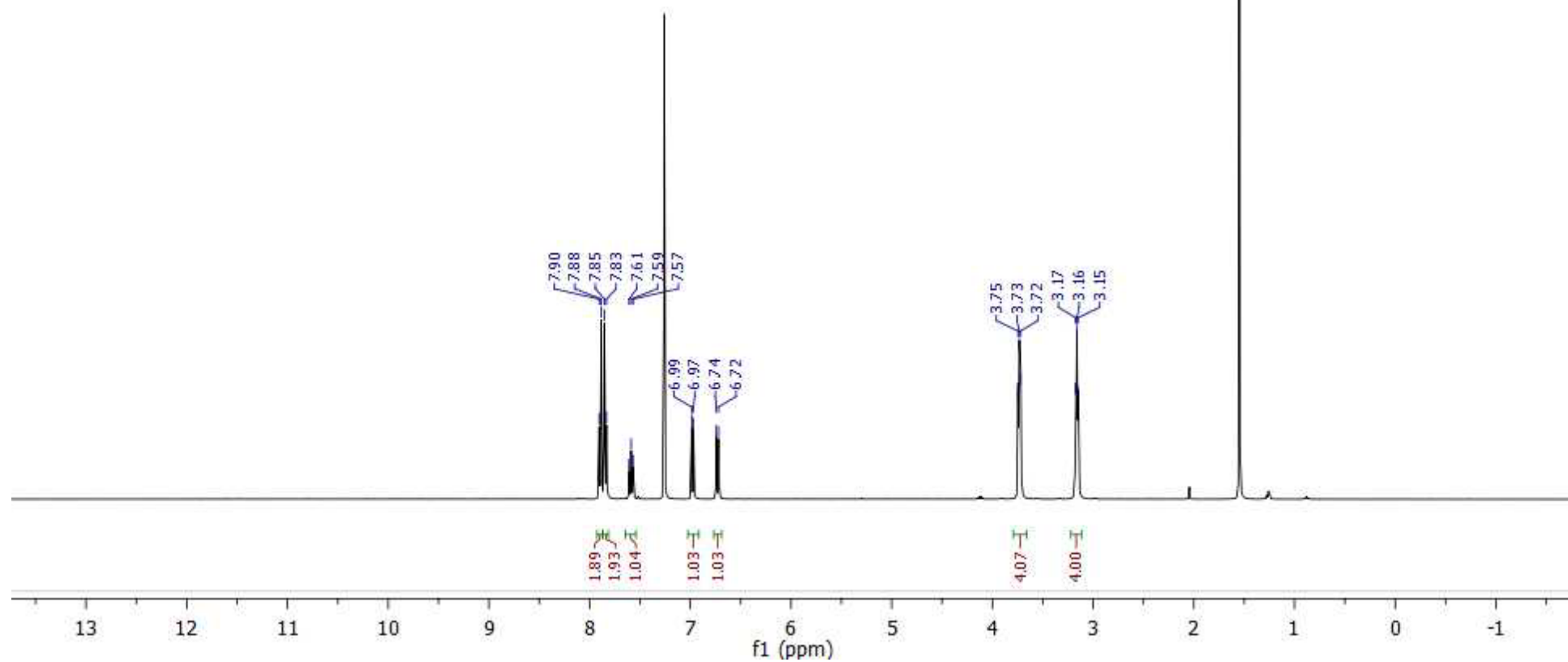
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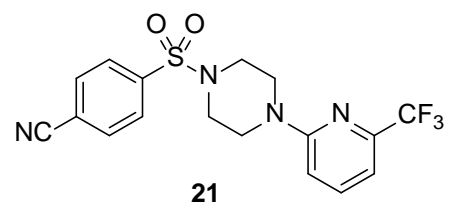
¹³C NMR (101 MHz, CDCl₃)



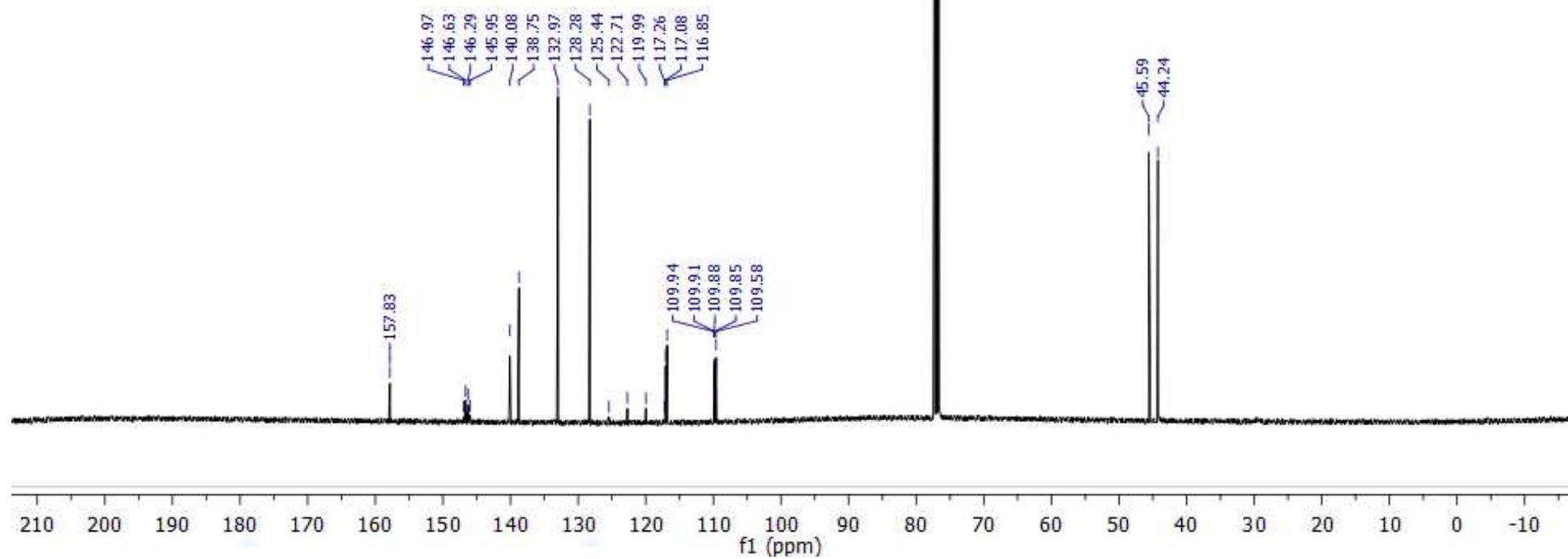


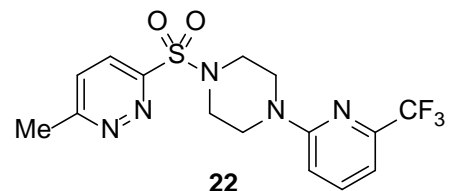
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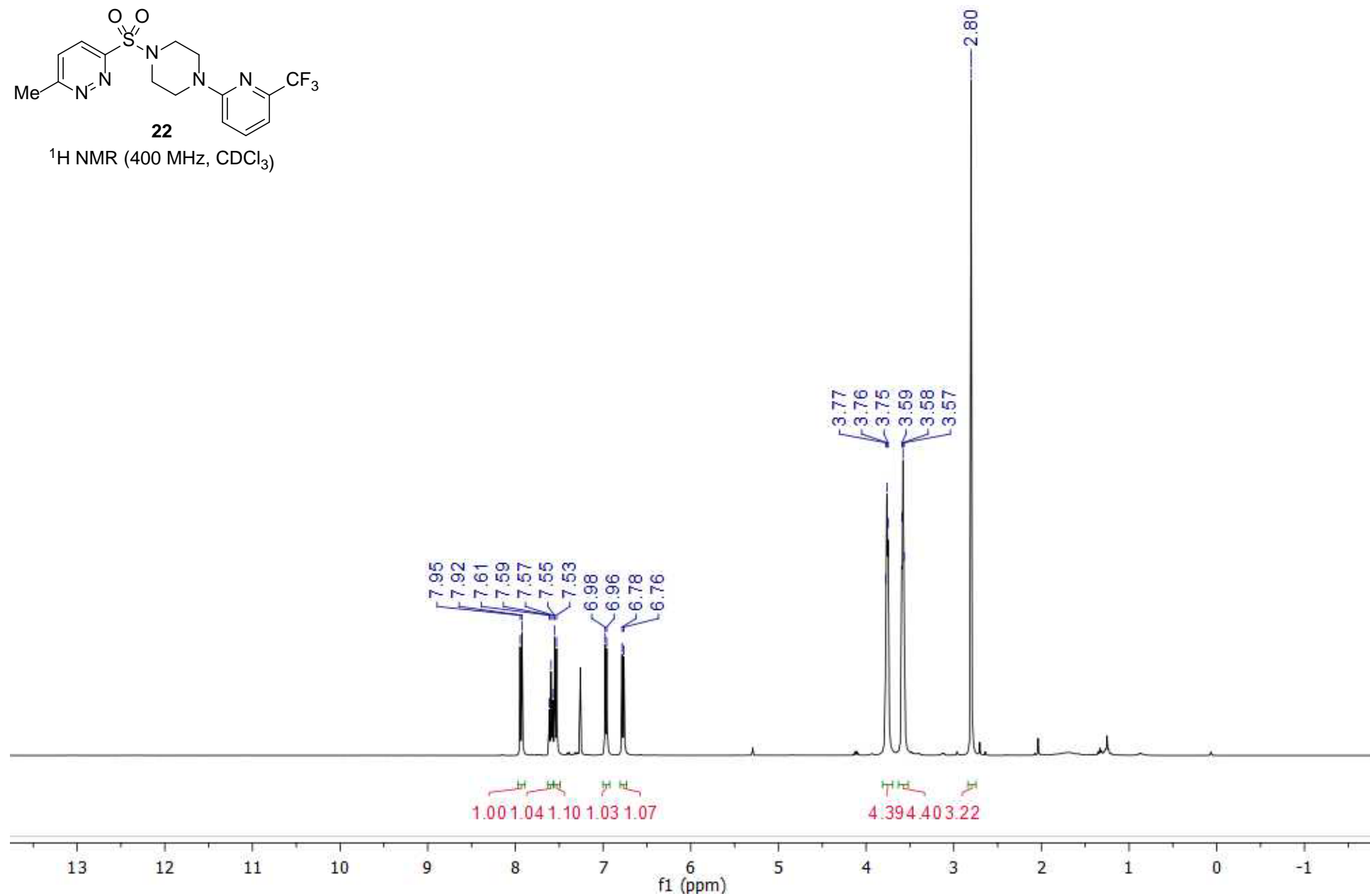


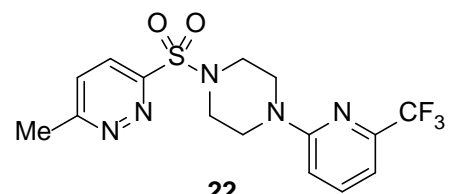
^{13}C NMR (101 MHz, CDCl_3)



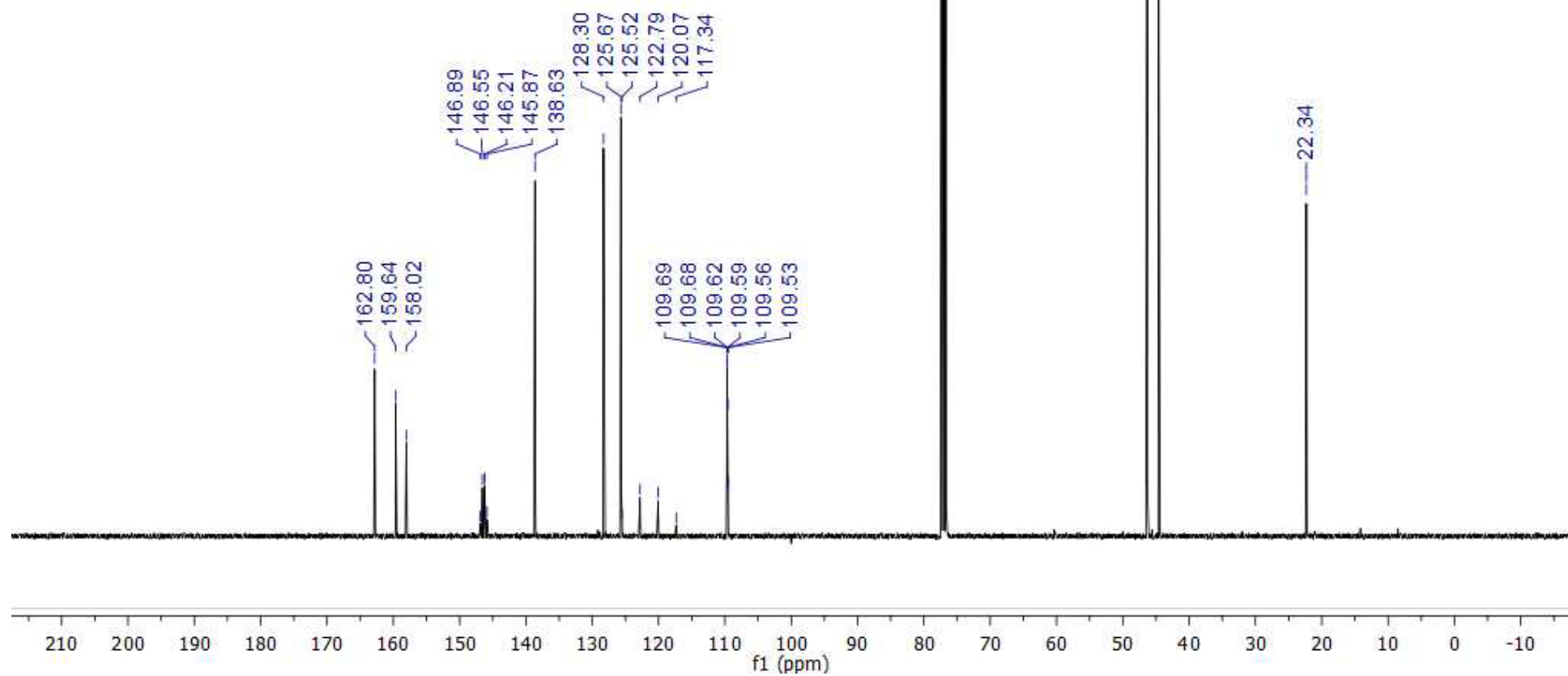


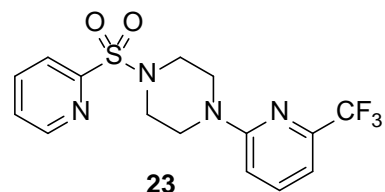
¹H NMR (400 MHz, CDCl₃)



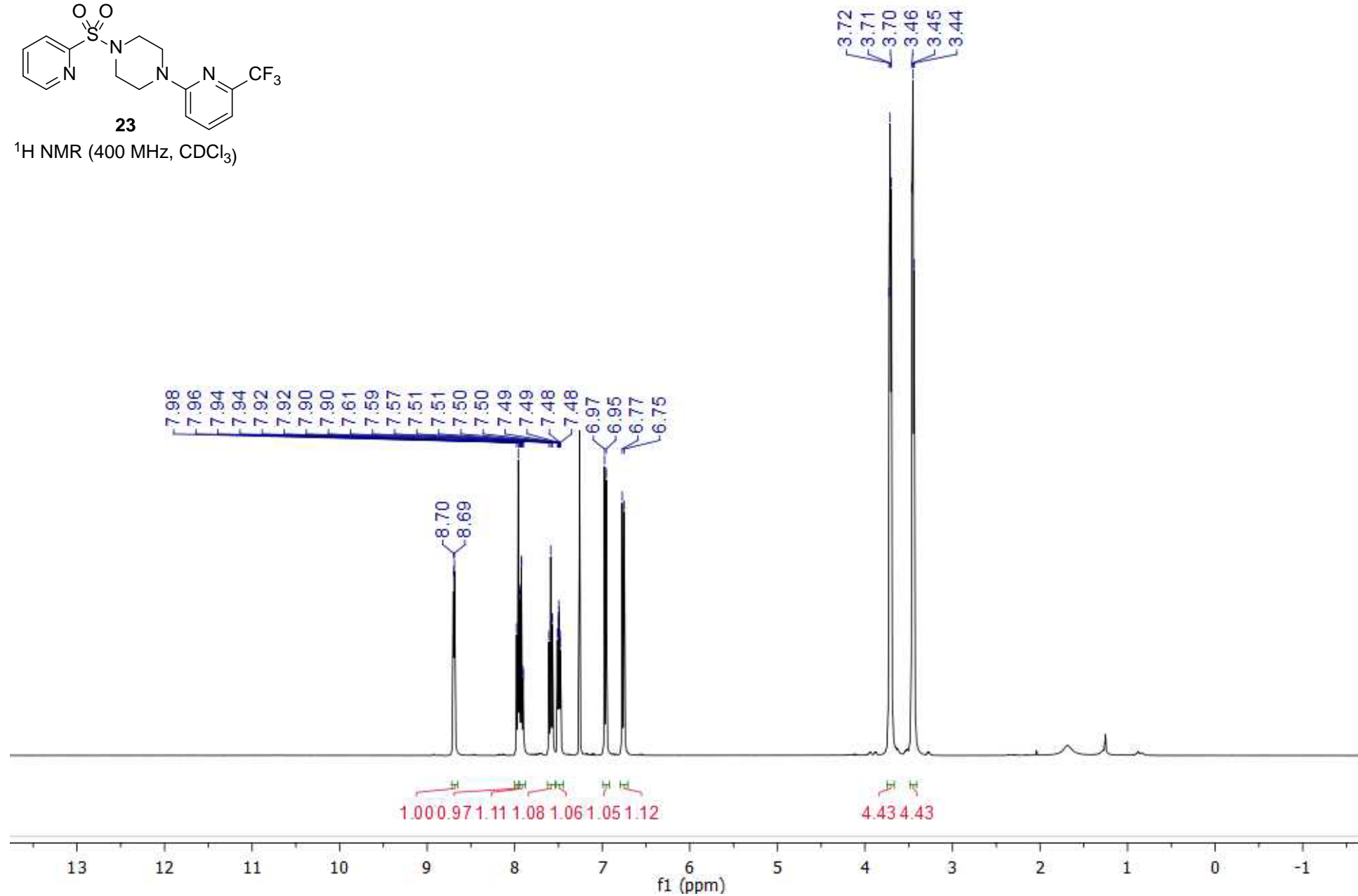


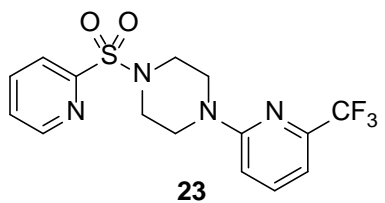
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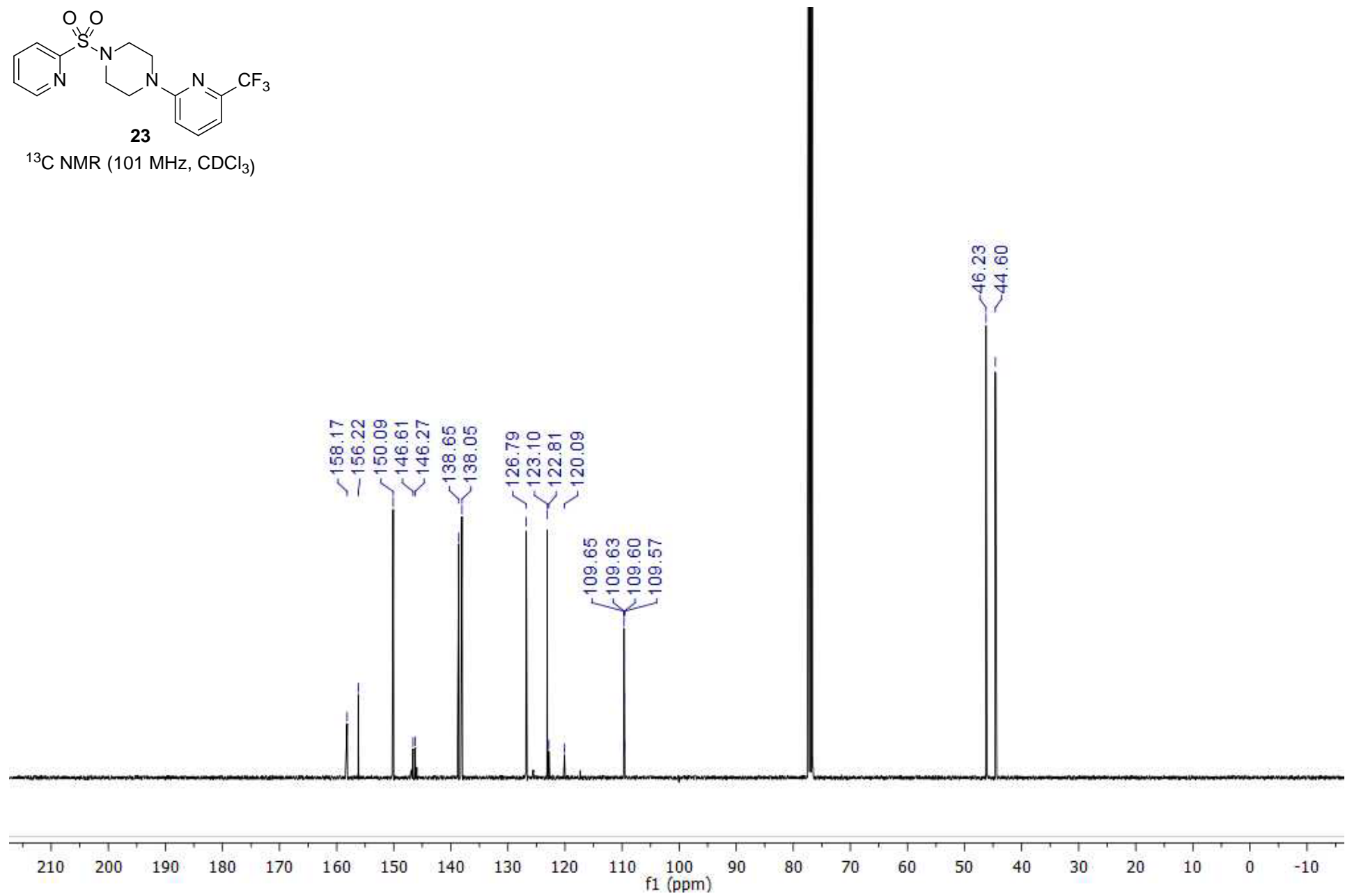


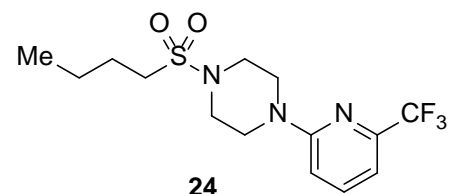
^1H NMR (400 MHz, CDCl_3)



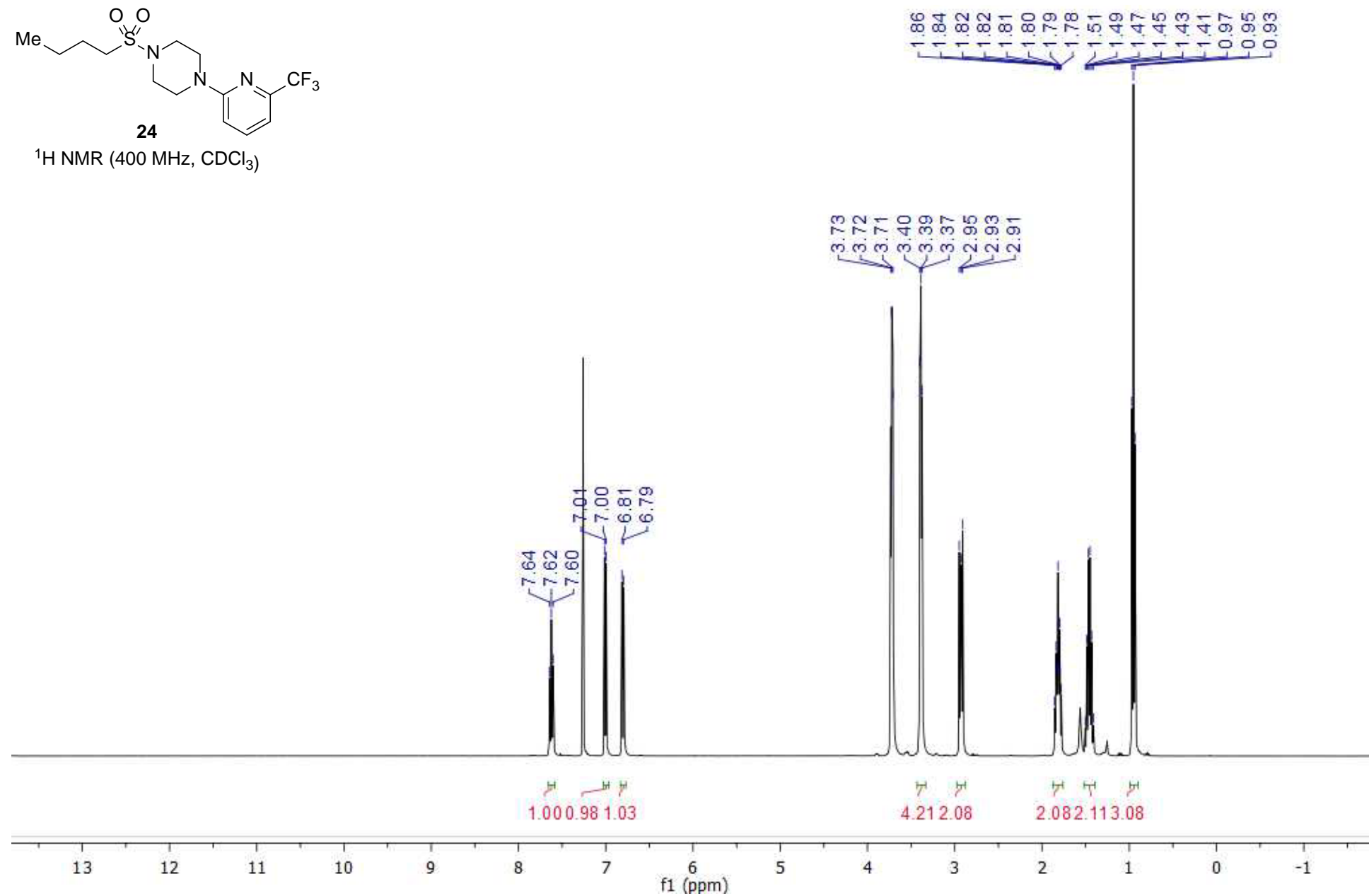


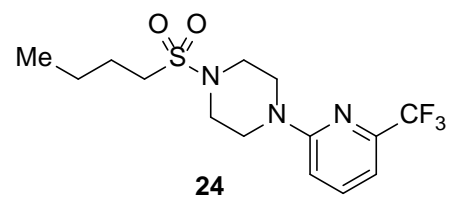
^{13}C NMR (101 MHz, CDCl_3)



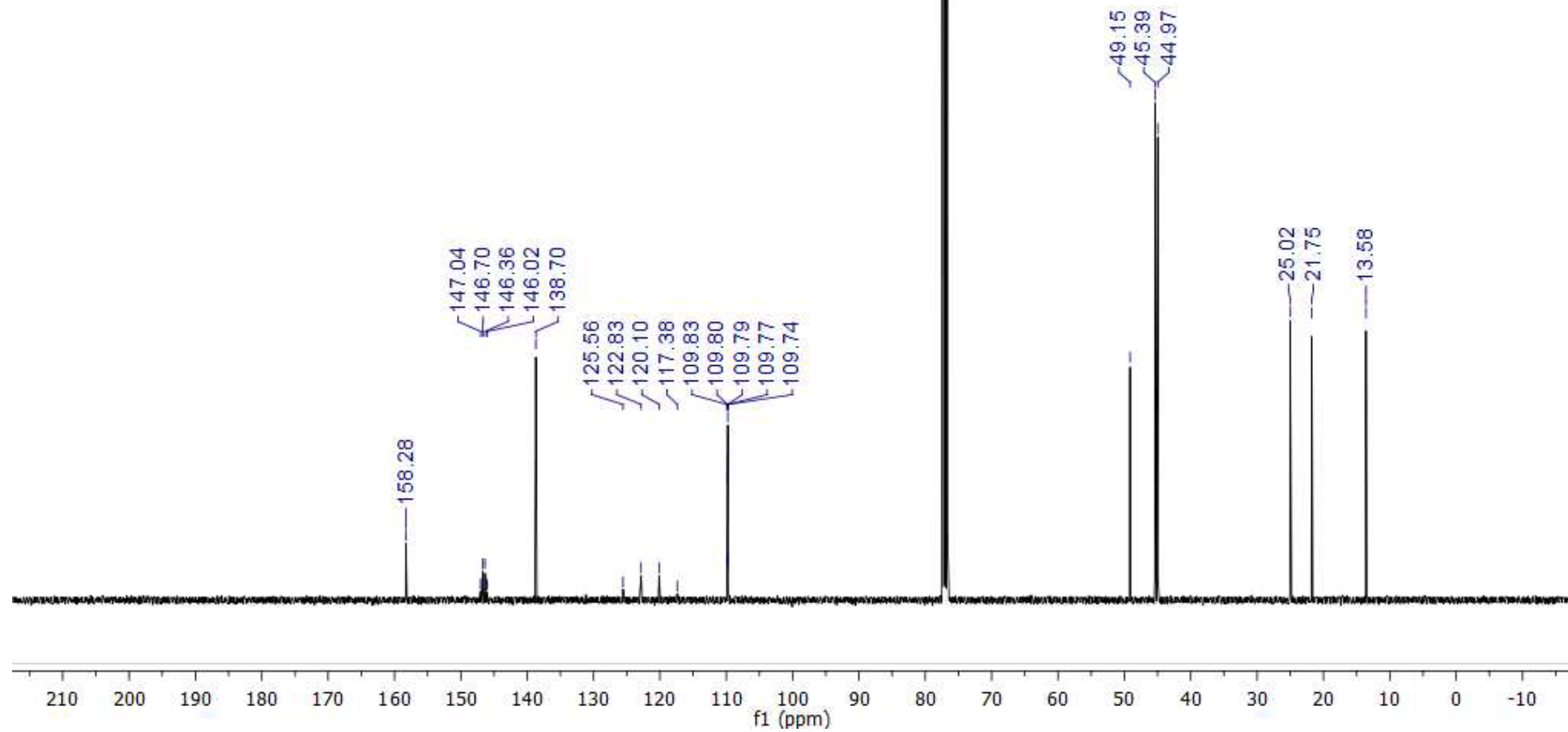


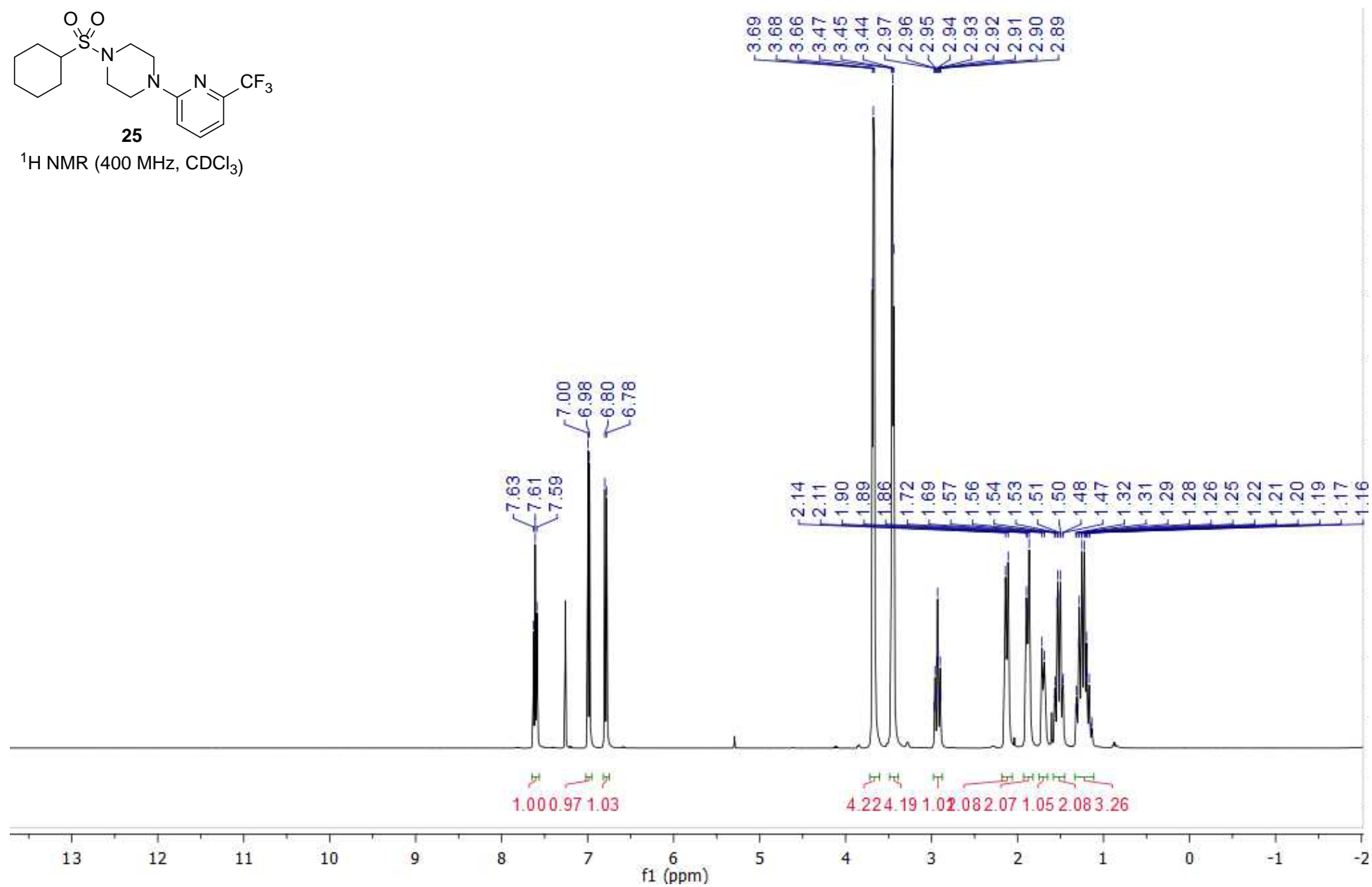
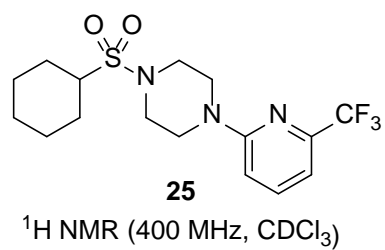
^1H NMR (400 MHz, CDCl_3)

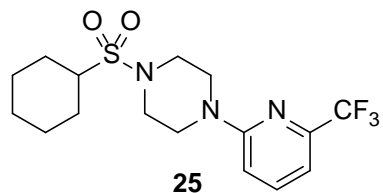




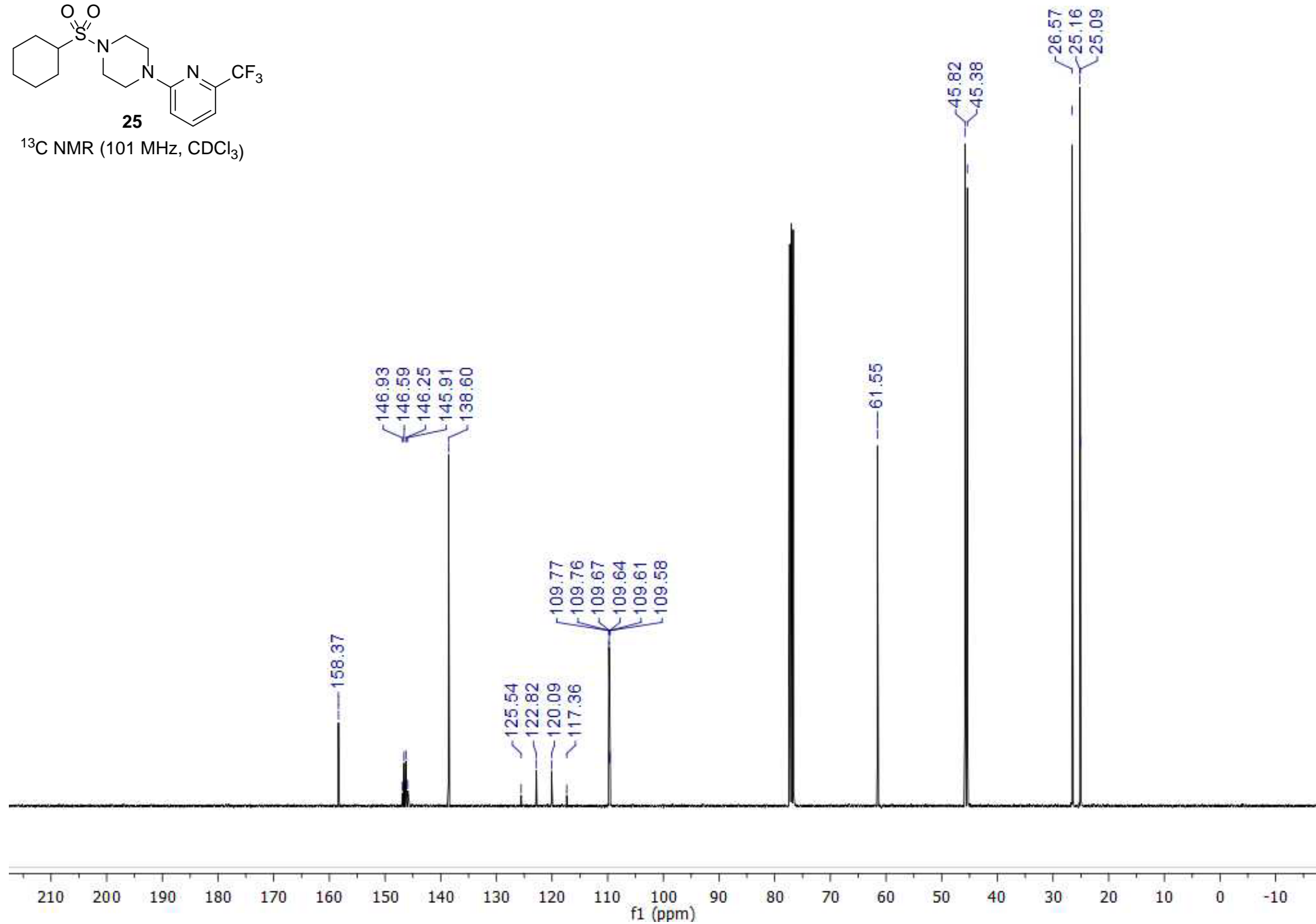
^{13}C NMR (101 MHz, CDCl_3)

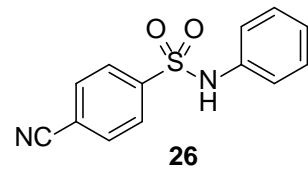




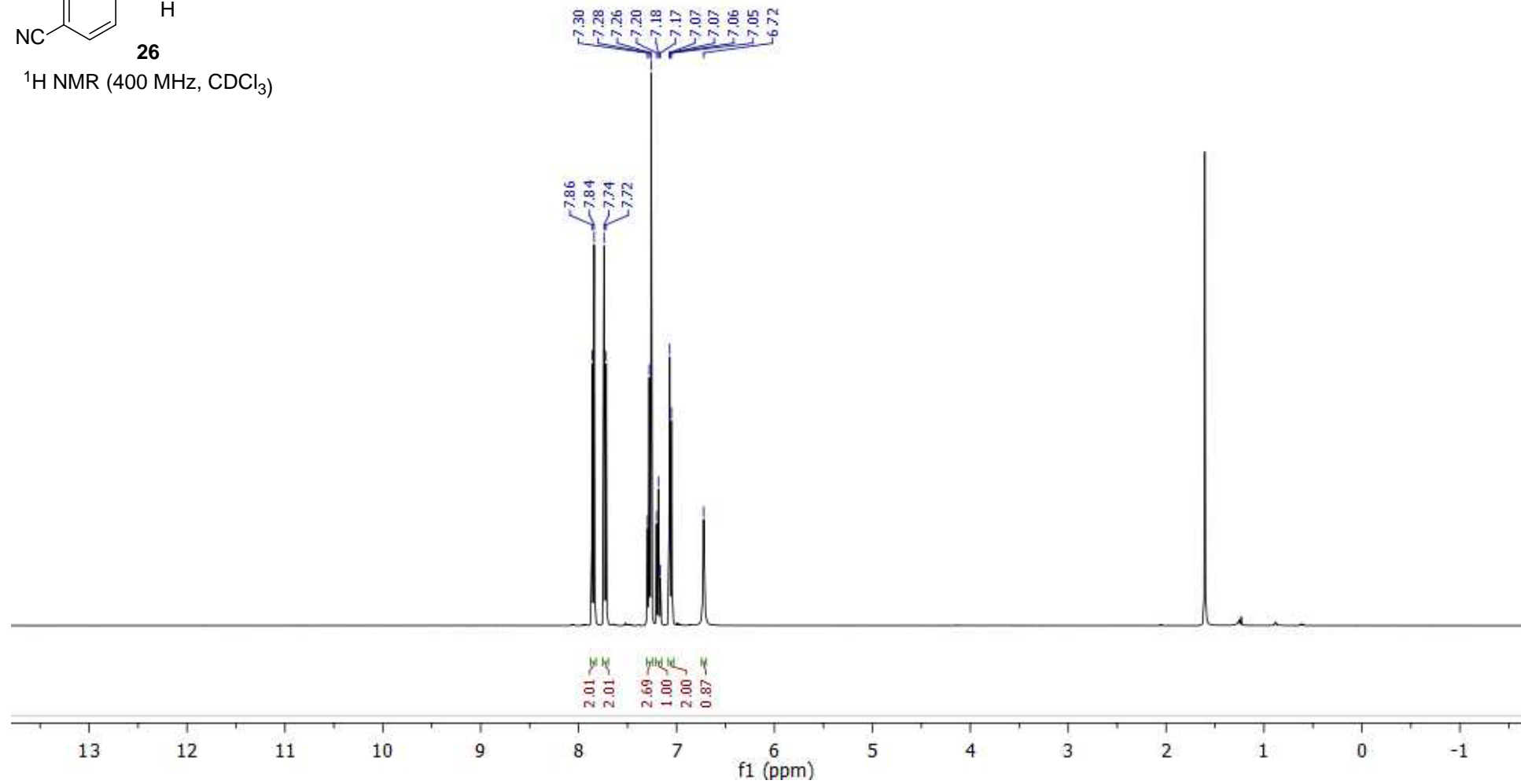


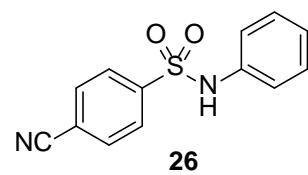
^{13}C NMR (101 MHz, CDCl_3)



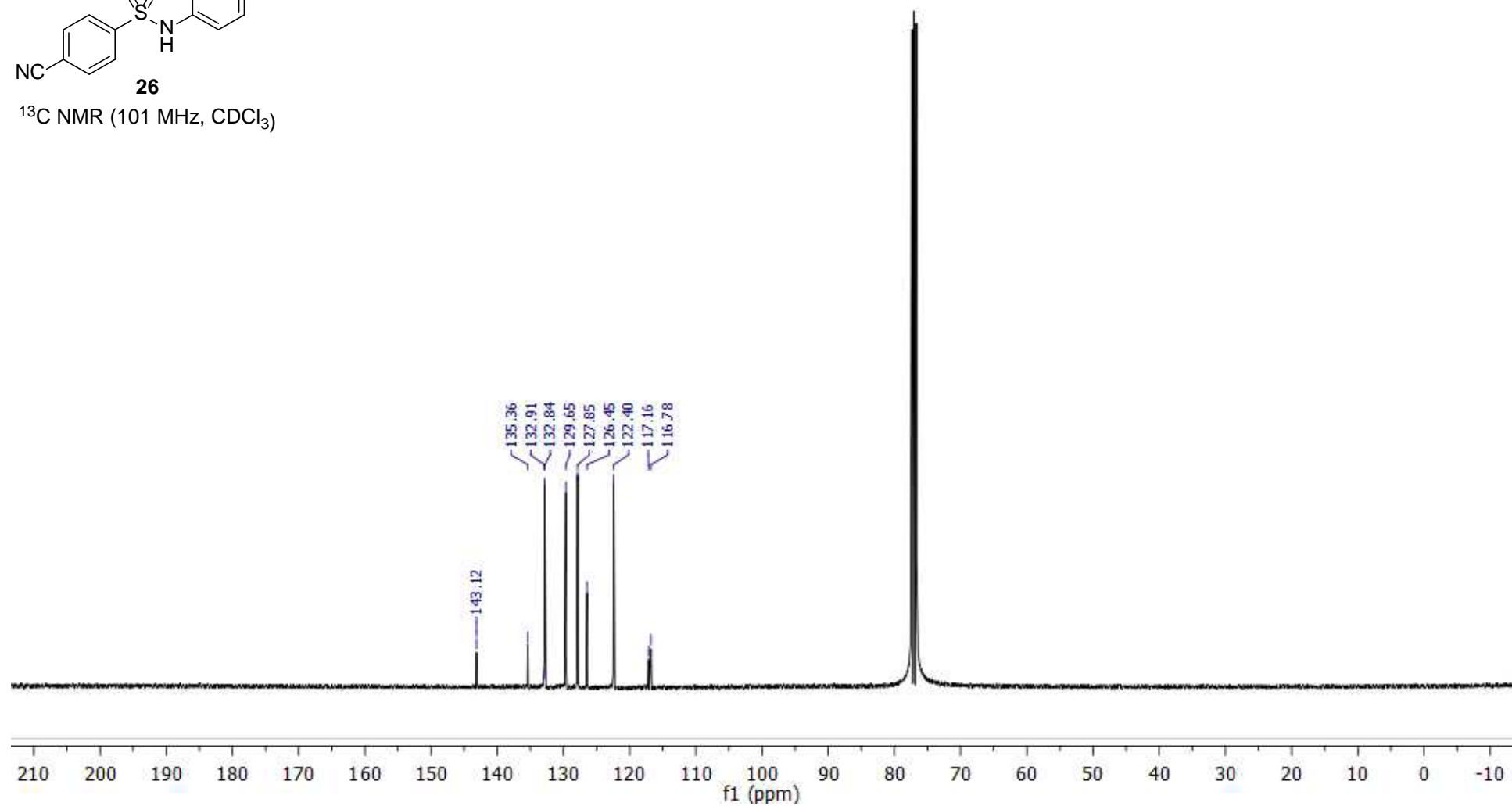


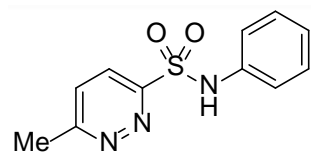
¹H NMR (400 MHz, CDCl₃)





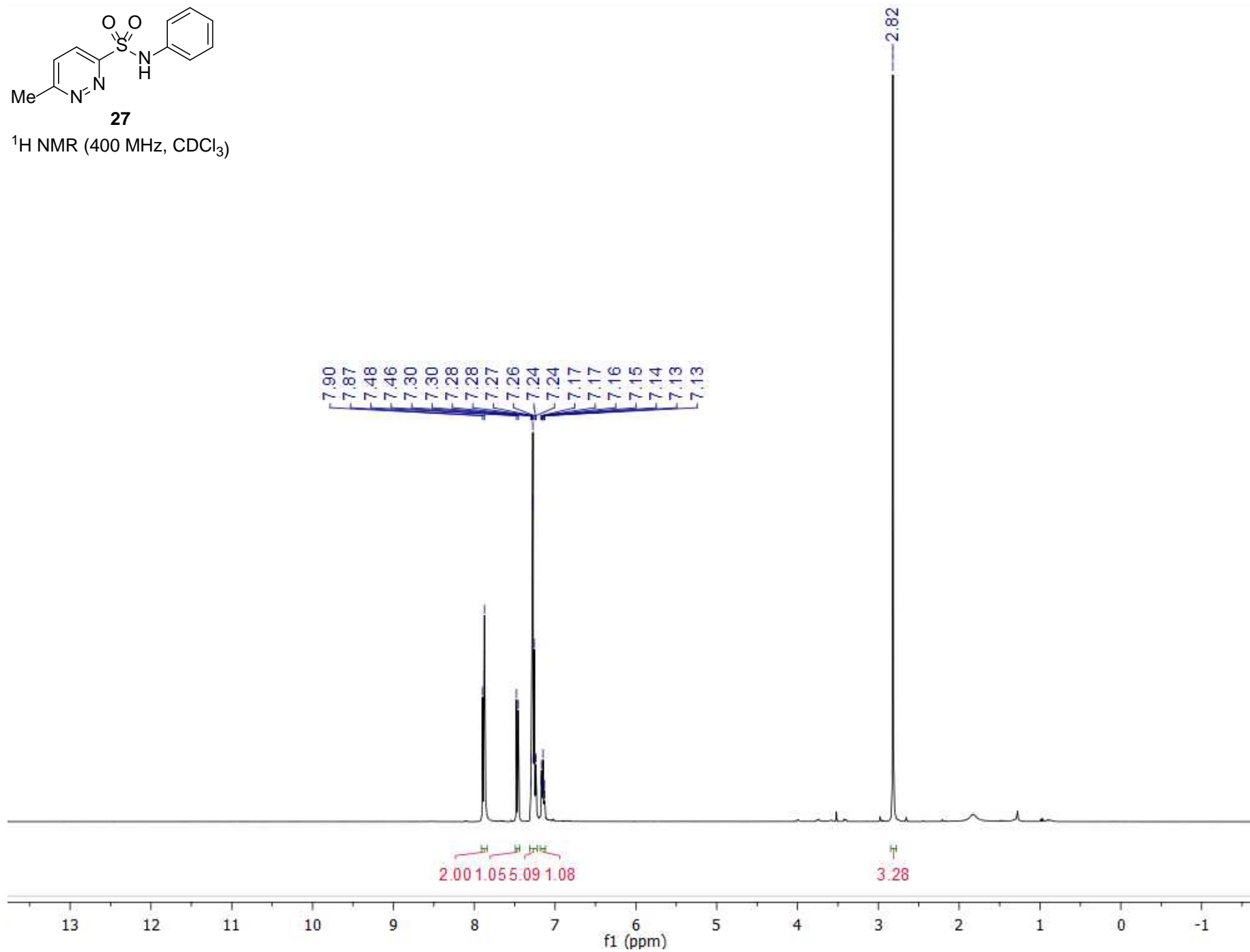
^{13}C NMR (101 MHz, CDCl_3)

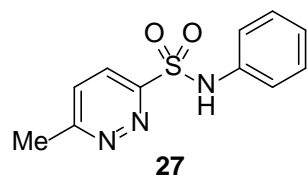




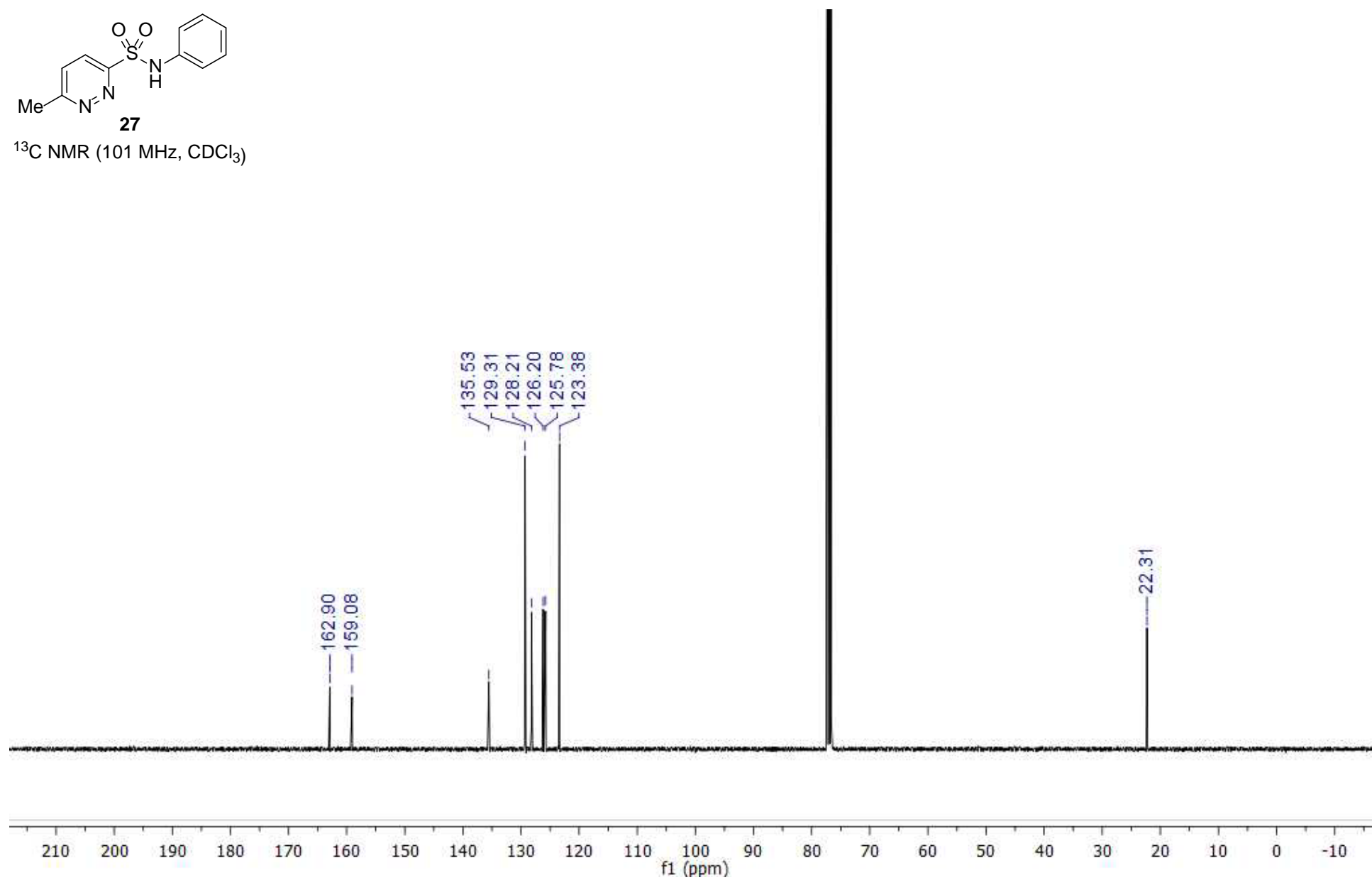
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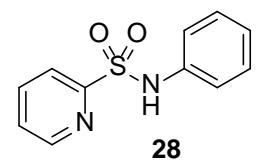
^1H NMR (400 MHz, CDCl_3)



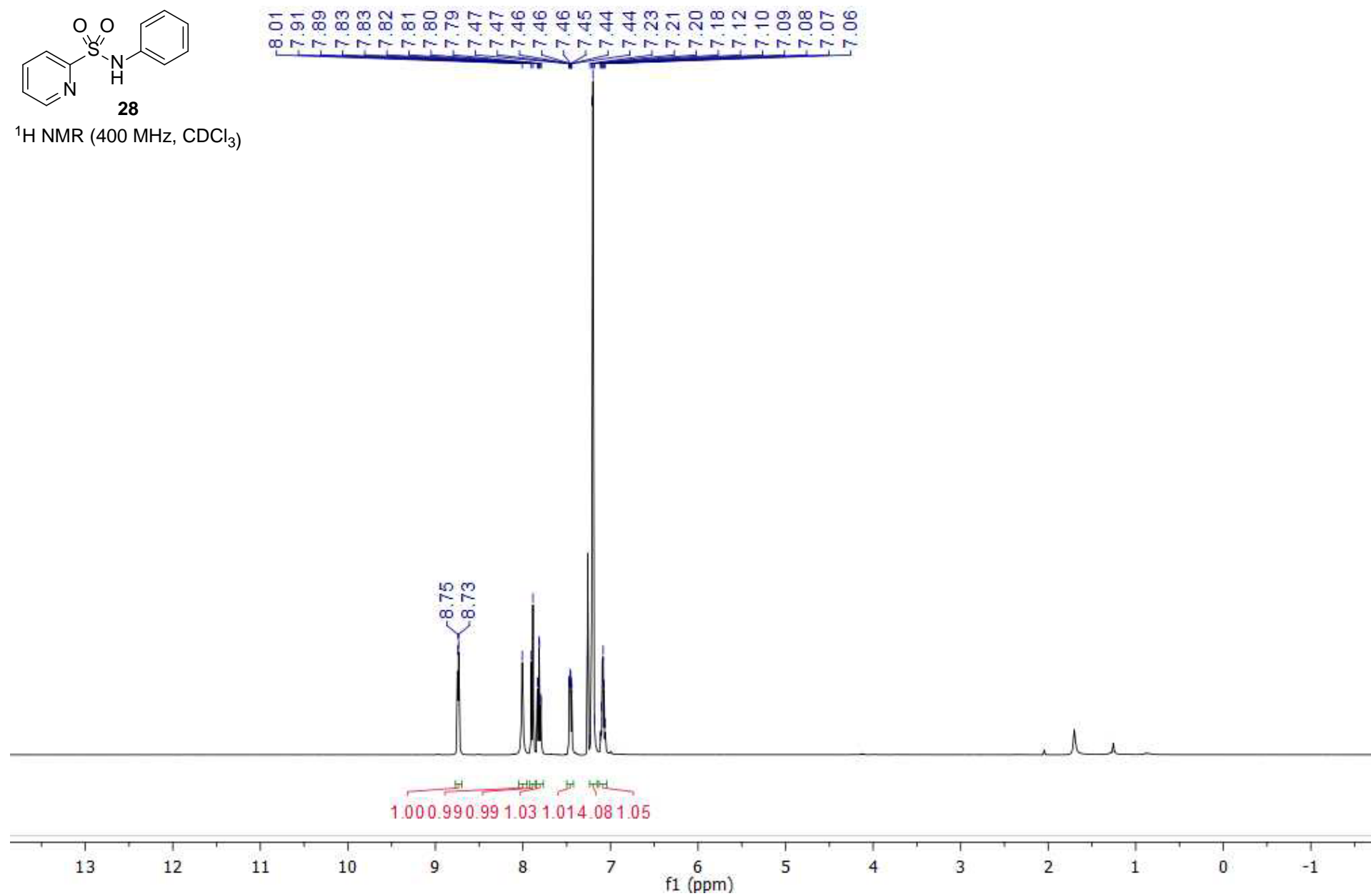


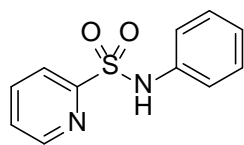
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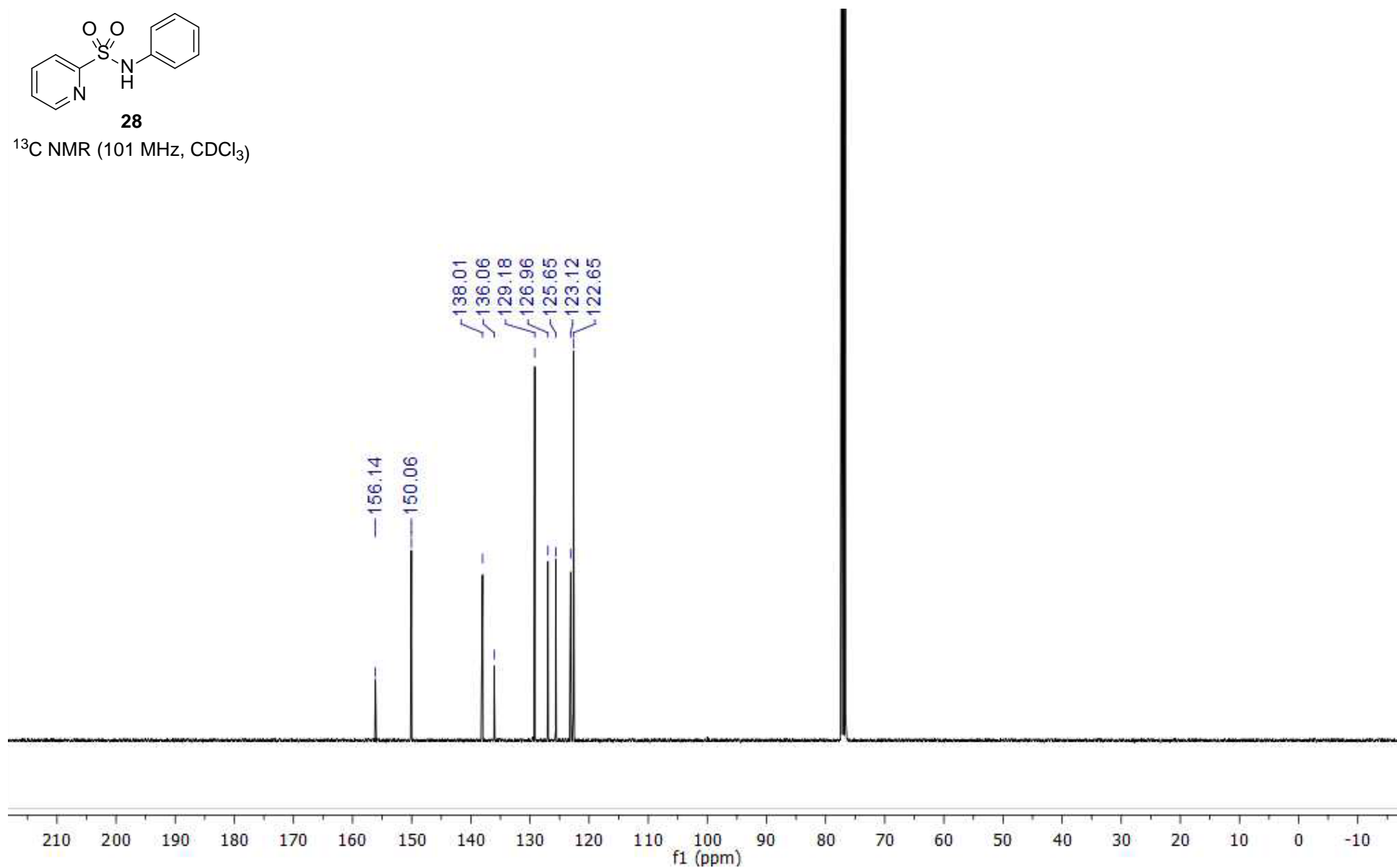
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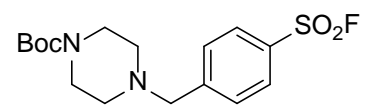




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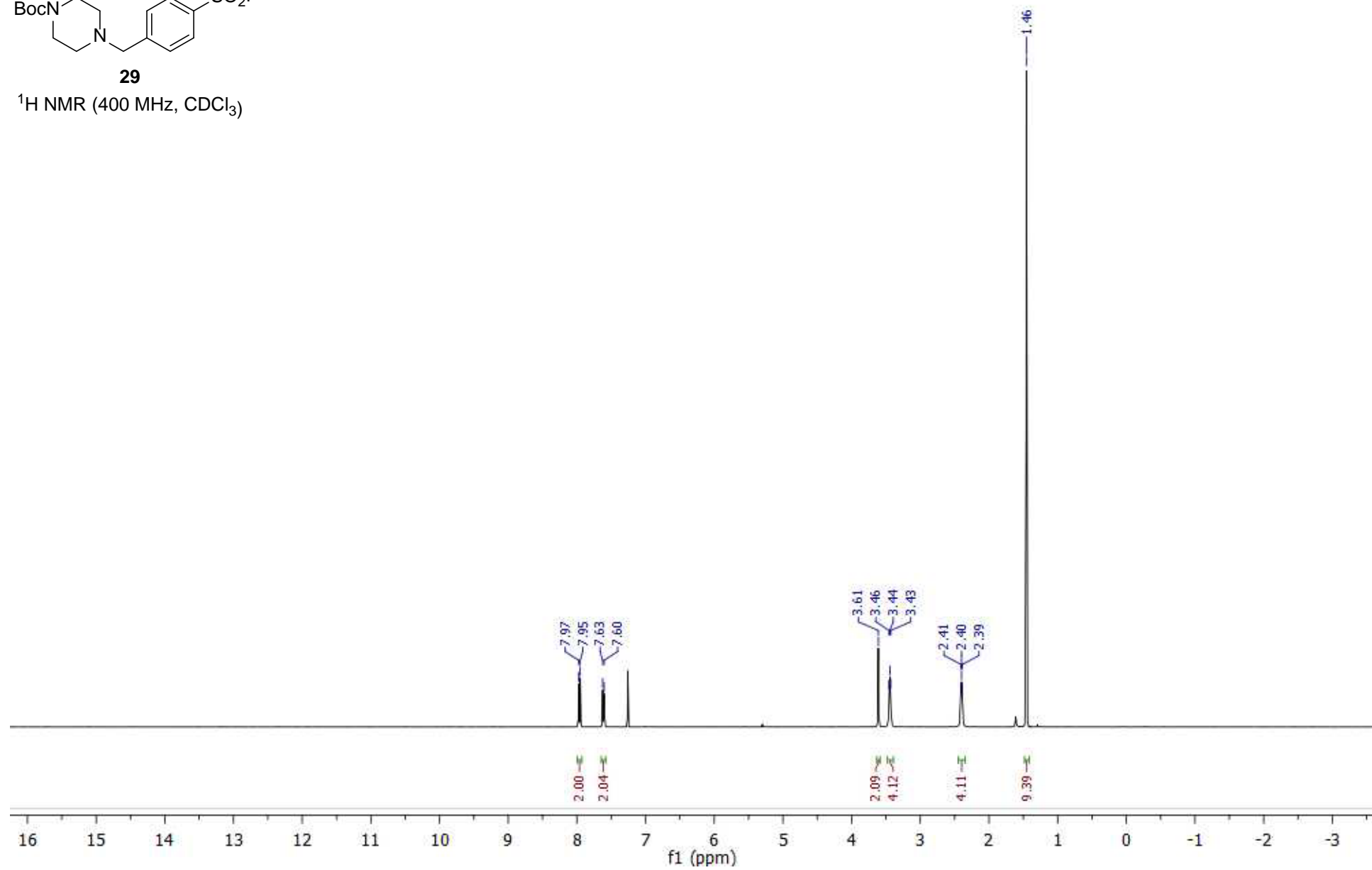
^{13}C NMR (101 MHz, CDCl_3)

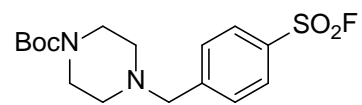
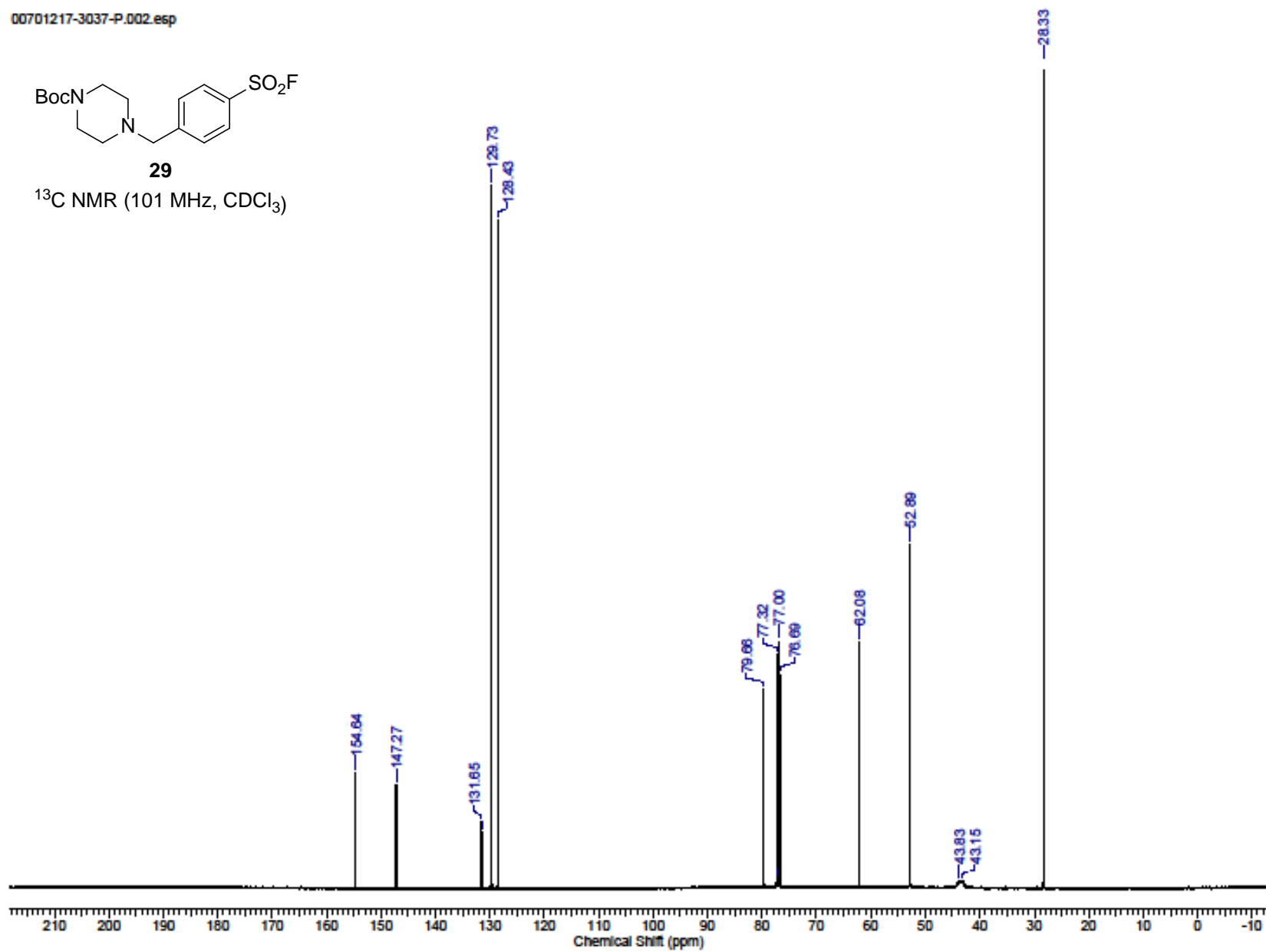


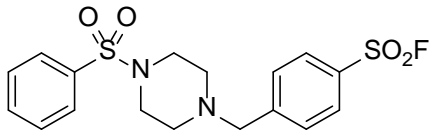


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^1H NMR (400 MHz, CDCl_3)

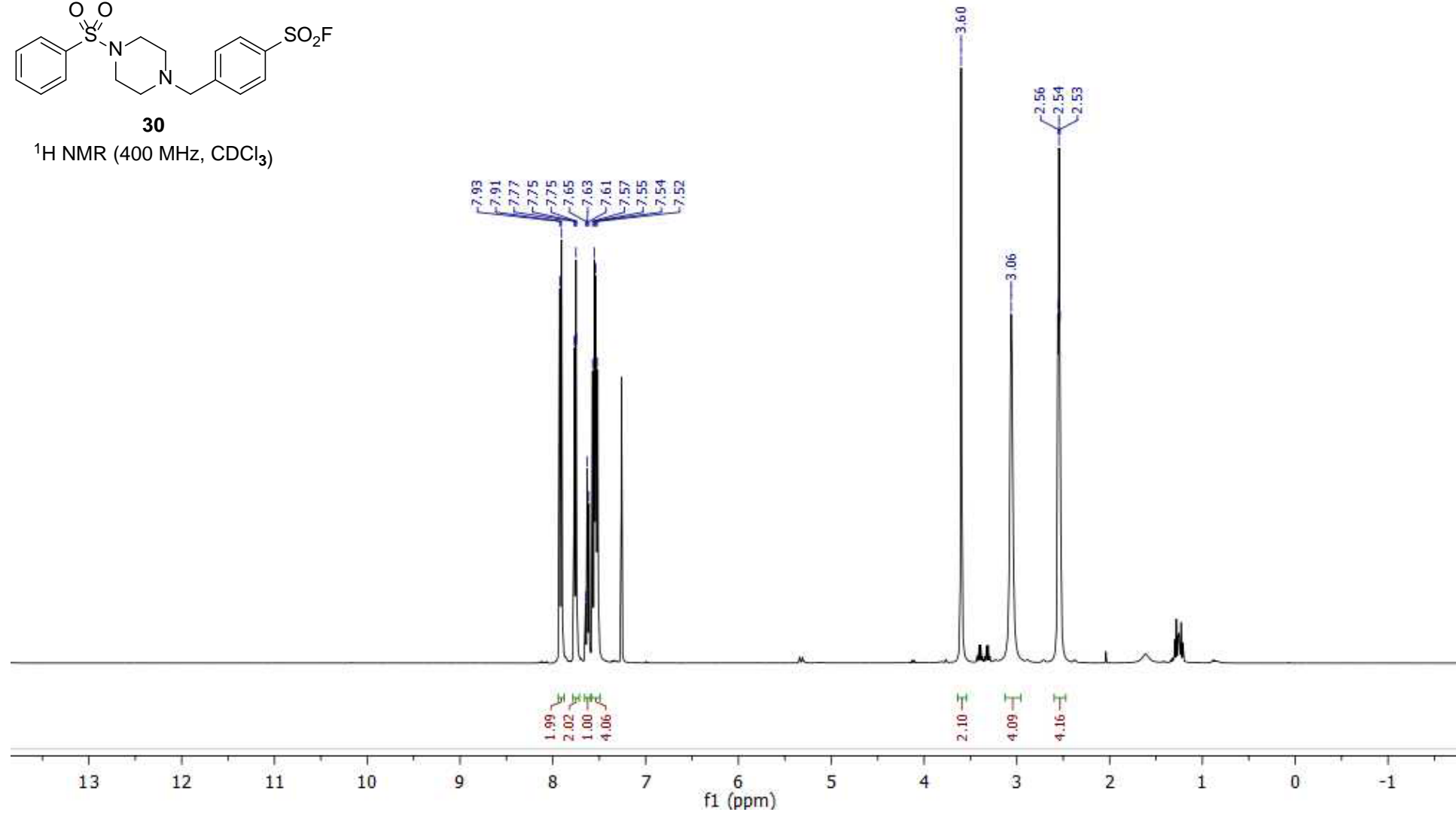


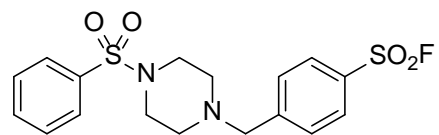
**29** ^{13}C NMR (101 MHz, CDCl_3)



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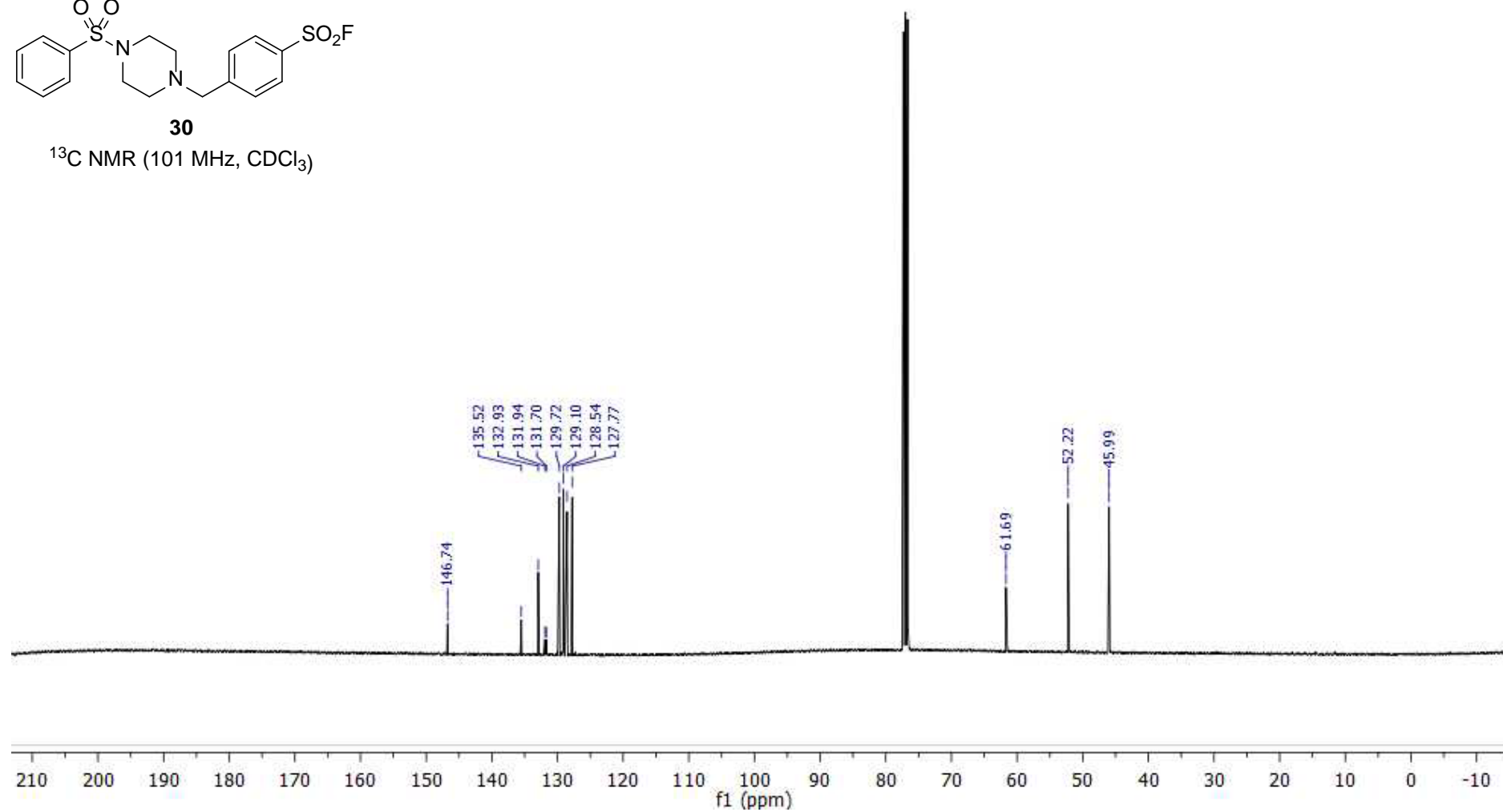
^1H NMR (400 MHz, CDCl_3)

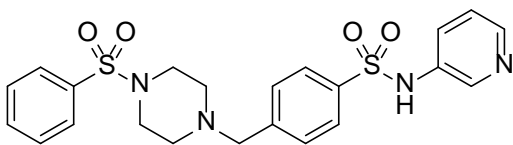




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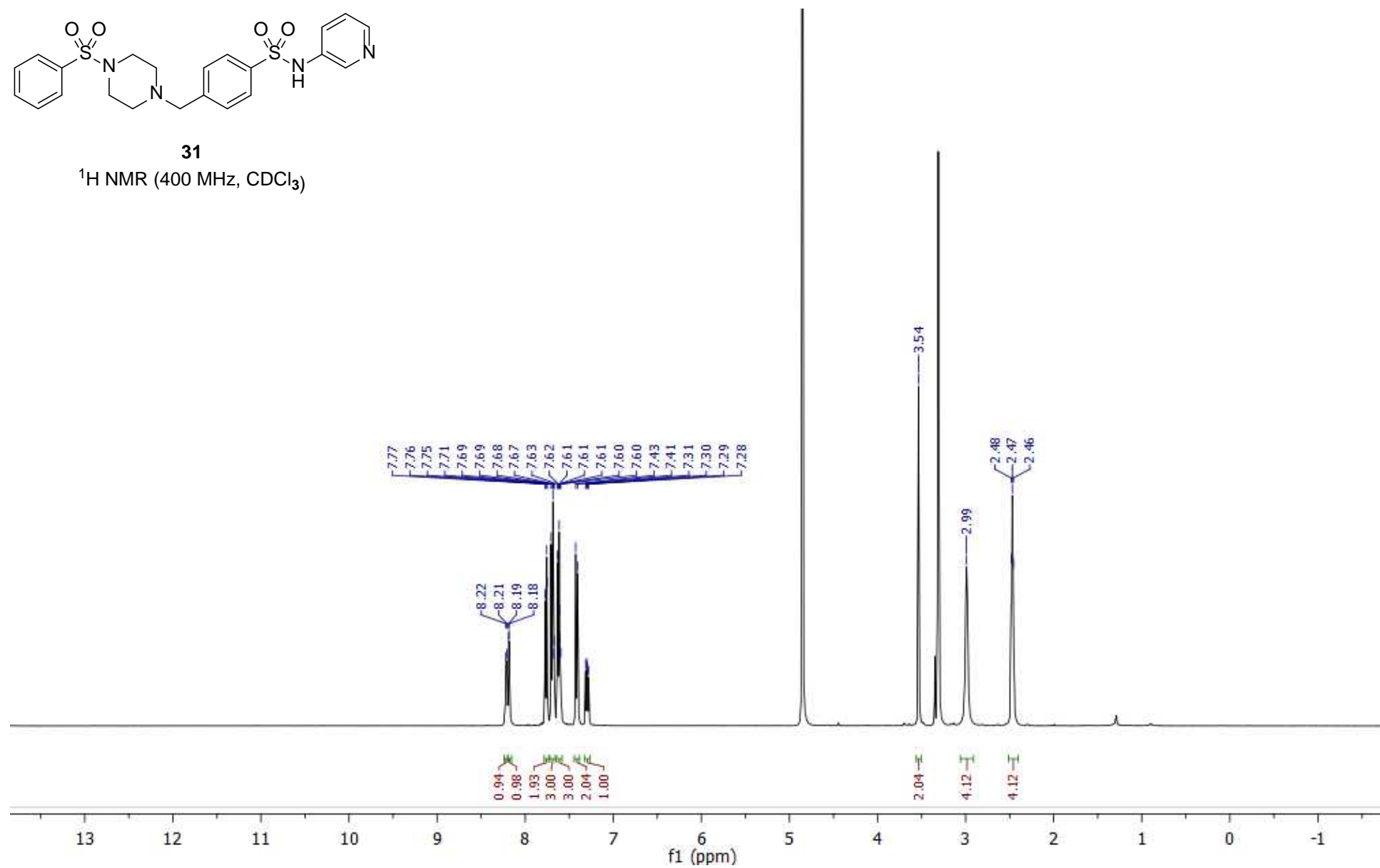
^{13}C NMR (101 MHz, CDCl_3)

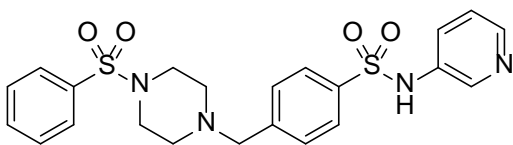




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^1H NMR (400 MHz, CDCl_3)





31

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

