

Concise Syntheses of Meridianins and Meriolins Using A Catalytic Domino Amino-Palladation Reaction

Scott R. Walker,[†] Milena L. Czyz,[‡] and Jonathan C. Morris^{‡,*}

School of Chemistry and Physics, University of Adelaide, Adelaide, SA, Australia and School of Chemistry, University of New South Wales, Sydney, NSW, Australia

jonathan.morris@unsw.edu.au

General Experimental

Unless otherwise stated, all experiments were performed in flame-dried glassware under an atmosphere of nitrogen or argon. When stated, reaction mixtures were degassed using a standard freeze-pump-thaw technique.¹ Reaction temperatures refer to the external bath temperatures. Solvents were removed under reduced pressure on a rotary evaporator and the residual solvent was removed under high vacuum.

Chromatography - Analytical Thin Layer Chromatography (TLC) was carried out using aluminium-backed Merck KieselgelKG60F₂₅₄ silica plates. The plates were visualised by irradiation with short-wave ultraviolet light and stained with one of the following TLC dips (potassium permanganate, vanillin, PMA or ninhydrin) when required. The flash chromatography was performed on Scharlau Silica Gel 60 0.04 – 0.06 mm (230 – 400 mesh ASTM). Deactivated silica gel was prepared by mixing silica gel with 5% volume per weight of triethylamine.

Reagents and solvents - Unless otherwise stated, reagents were purchased from commercial sources and used without further purification. Solvents were purified according to well-established procedures.² Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl under an atmosphere of argon directly before use. Triethylamine and pyridine were distilled from calcium hydride. Dichloromethane were obtained from a Pure Solv dry solvent system (Innovative Technology, Inc. model #PS-MD-7). Pd(PPh₃)₄ was prepared according to the literature procedure.³

¹ Errington, R. J. *Advanced Practical Inorganic and Metalorganic Chemistry*, Blackie Academic & Professional, 1997.

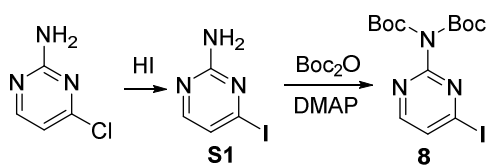
² Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*, 2nd ed.; Blackie Academic & Professional, 1995.

³ Coulson, D. R.; Satek, L.C.; Grim, S. O. In *Inorg. Synth.*; John Wiley & Sons, Inc.; 2007, p 107

Instrumental conditions

Infrared (IR) spectra were obtained on a ThermoNicolet Avatar 370 FT-IR spectrometer and are reported as wavenumbers (cm^{-1}). Spectra were recorded from thin films using NaCl plates. The samples were prepared by dissolving in CDCl_3 , CHCl_3 or CH_2Cl_2 . HRMS was performed at the Bioanalytical Mass Spectrometry Facility within the Mark Wainwright Analytical Centre of the University of New South Wales, Australia. Melting points were obtained on OptiMelt Automated Melting Point System with Digital Image Processing Technology and are uncorrected. Spectra were recorded on Varian Gemini 200 MHz and Varian Gemini 300 MHz spectrometers running vNMR 6.1c software at the University of Adelaide. At the University of New South Wales, spectra were recorded on a Bruker Avance III 300 (300 MHz), Bruker Avance IV (400 MHz), Bruker Avance V (500 MHz), Bruker Avance VI (600 MHz), with data acquired and processed using TopSpin 3.0 software. Chemical shifts are expressed in parts per million (PPM) and are referenced to the internal solvent peaks.

Bis-*tert*-butyl (4-iodopyrimidin-2-yl)carbamate (**8**)



(a) 4-Iodo-2-aminopyrimidine (**S1**)

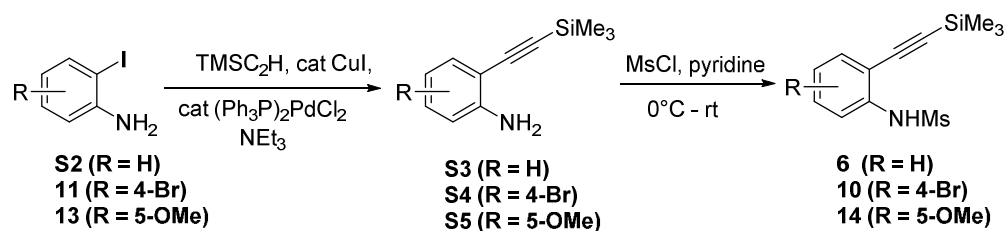
A mixture of 4-chloro-2-aminopyrimidine (2.64 g, 20.4 mmol), sodium iodide (8.69 g, 58.0 mmol) and 40% aqueous hydriodic acid (60 mL) was vigorously stirred at room temperature for 3.5 h. The heterogenous mixture was quenched with saturated sodium bicarbonate solution (150 mL), and the mixture neutralised with additional solid sodium bicarbonate. The obtained slurry was extracted with dichloromethane (500 mL), the aqueous phase was separated and washed with additional dichloromethane (2x 300 mL). The dichloromethane extracts were combined, dried over sodium sulfate and evaporated to give 4-iodo-2-aminopyrimidine (**S1**) as an off-white solid (3.85 g, 86% yield), containing less than 2% of the chloropyrimidine starting material by NMR mp: 143-145°C (decomp.);

IR (neat) 3330, 3298, 3118, 1646, 1485 cm^{-1} ; ^1H NMR (300 MHz, d_6 -DMSO) δ ppm 7.77 (d, J = 5.0 Hz, 1H), 7.00 (br s, 2H), 6.99 (d, J = 5.0 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ 162.6, 157.9, 130.9, 120.1. HRMS: calculated for $\text{C}_4\text{H}_5\text{IN}_3$ ($\text{M}+\text{H}$) $^+$ 221.9528, found: 221.9527.

(b) *Bis-tert-butyl (4-iodopyrimidin-2-yl)carbamate (8)*

4-Iodo-2-aminopyrimidine (**S1**) (3.661 g, 16.6 mmol) was added to a stirred mixture of di-*tert*-butyl dicarbonate (8.52 g, 39.0 mmol) in dry THF (30 mL) and the mixture was cooled in an ice bath. DMAP (0.2076 g, 1.70 mmol) was added, and the mixture was allowed to stir at room temperature overnight. After evaporation of the solvent, the residue was purified by flash chromatography on silica, eluting with 20% ethyl acetate/*n*-hexane, to give pyrimidine **8** as a white solid (6.355 g, 91% yield). mp: 90-91°C; IR (cm^{-1} , *nujol* mull) 3092, 3053, 1744, 1709. ^1H NMR (300 MHz, CDCl_3) δ 8.25 (d, J = 5.1 Hz, 1H), 7.64 (d, J = 5.1 Hz, 1H), 1.46 (s, 18H). ^{13}C NMR (75 MHz, CDCl_3) δ 157.4, 150.3, 130.2, 129.3, 84.0, 28.0. HRMS: calculated for $\text{C}_{14}\text{H}_{21}\text{IN}_3\text{O}_4$ ($\text{M}+\text{H}$) $^+$ 422.0577, found: 422.0571.

General procedure for preparation of alkynylmethanesulfonamides (6, 10 and 14)



(a) *Sonogashira Coupling*

A suspension of aryl iodide (**S2**, **11** or **13**) (1 eq), bis(triphenylphosphine)palladium(II) chloride (3 mol%) and copper(I) iodide (3 mol %) in dry triethylamine (5 mL/ mmol iodide) was degassed by bubbling argon through the mixture for ten minutes, then trimethylsilylacetylene (1.1 eq) was added, and the mixture stirred overnight at room temperature. The mixture was poured into diethyl ether (two volumes), and the resulting suspension filtered through Celite and evaporated. The residue was separated by flash chromatography on silica to give the alkynylanilines (**S3**, **S4** or **S5**).

(b) *Mesylation*

The alkynylaniline (**S3**, **S4** or **S5**) (1 eq) was dissolved in dry pyridine (3 mL/mmol alkyne), cooled to 0

°C under nitrogen, and methanesulfonyl chloride (2 eq) added. After stirring at room temperature for 2 h, the reaction progress was determined by TLC. If required, additional methanesulfonyl chloride (2 eq) was added, and upon reaction completion the reaction was poured into saturated aqueous copper(II) sulfate solution, and extracted with 3 portions of ethyl acetate. The combined organic phases were washed with additional aqueous copper(II) sulphate solution, water, brine and then dried over sodium sulfate and evaporated. Purification of the residue by flash chromatography on silica gave the sulfonamides (**6**, **10** or **14**).

N-(2-((Trimethylsilyl)ethynyl)phenyl)methanesulfonamide (6**)⁴**

(a) Treatment of aryl iodide **S2** (2.068 g, 9.44 mmol) with trimethylsilylacetylene by the general procedure, followed by purification by flash chromatography on silica, using 10% ethyl acetate/*n*-hexane as the eluent, gave alkynylaniline **S3** as a pale brown oil (1.690 g, 95% yield), with spectroscopic data consistent with that previously reported.⁵ ¹H NMR (300 MHz, CDCl₃) δ 7.36 – 7.27 (m, 2H), 7.15 – 7.07 (m, 1H), 6.71 – 6.62 (m, 2H), 4.23 (br s, 2H), 0.27 (s, 9H).

(b) Treatment of alkynylaniline **S3** (820 mg, 4.33 mmol) with mesyl chloride by the general procedure followed by flash chromatography on silica (10% ethyl acetate/ hexanes) gave sulfonamide **6** as an off-white solid (783 mg, 68% yield). The spectroscopic data was consistent with that previously reported.⁴ mp: 140-141°C; IR (nujol mull, cm⁻¹) 3239, 2165, 2086 (br), 1329; ¹H NMR (300 MHz, CDCl₃) δ 7.57 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.46 (ddd, *J* = 7.7, 1.6, 0.5 Hz, 1H), 7.35 (ddd, *J* = 7.3, 1.6, 0.4 Hz, 1H), 7.12 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.00 (br s, 1H), 3.00 (s, 3H), 0.29 (s, 9H); ¹³C NMR (75.5 MHz, CDCl₃) δ 138.0, 132.3, 130.1, 124.6, 119.6, 114.2, 102.8, 99.5, 39.5, -0.1; HRMS calculated for C₁₂H₁₈NO₂SSi (M+H)⁺ 268.0828, found 268.0822; calculated for C₁₂H₂₁N₂O₂SSi (M+NH₄)⁺ 285.1093, found 285.1087.

⁴ Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1*: **1999**, 4, 529.

⁵ Alayrac, C.; Witulski, B., *Angew. Chem. Int. Ed.*, **2002**, 41, 3281.

N-(4-Bromo-2-((trimethylsilyl)ethynyl)phenyl)methanesulfonamide (**10**)

(a) Aryl iodide **11**⁶ (2.504 g, 8.40 mmol) was treated with trimethylsilylacetylene by the general procedure and purified by flash chromatography on silica (5% ethyl acetate/ hexanes) to give alkynylaniline **S4** as a pale brown solid (1.809 g, 80%). Mp 65-66°C; IR (neat): 3488, 3388, 2960 2150, 1608, 1484 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.40 (d, *J* = 2.3 Hz, 1H), 7.18 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.55 (d, *J* = 8.6 Hz, 1H), 4.24 (br s, 2H), 0.26 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 139.0, 138.2, 137.6, 134.8, 131.9, 129.1, 120.1, 119.6, 27.6; HRMS: calculated for C₁₁H₁₅⁷⁹BrNSi (M+H)⁺ 268.0152, found: 268.0156.

(b) Treatment of alkynylaniline **S4** (1.762 g, 6.57 mmol) with mesyl chloride by the general procedure followed by flash chromatography on silica (10% ethyl acetate/ hexanes) gave sulfonamide **10** as a white solid (1.560 g, 69% yield). mp: 100-102°C; IR (nujol mull, cm⁻¹) 3224, 2160, 2090 (br); ¹H NMR (300 MHz, CDCl₃) δ 7.59 (t, *J* = 1.3 Hz, 1H), 7.46 (d, *J* = 1.4 Hz, 2H), 6.94 (br s, 1H), 3.00 (s, 1H), 0.28 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 137.1, 134.7, 133.1, 121.0, 117.3, 116.0, 104.4, 97.9, 39.7, -0.2; HRMS: calculated for C₁₂H₂₀⁷⁹BrN₂O₂SSi (M+NH₄)⁺ 363.0193, found 363.0189, calculated for C₁₂H₂₀⁸¹BrN₂O₂SSi (M+NH₄)⁺ 365.0178, found 365.0174.

N-(5-Methoxy-2-((trimethylsilyl)ethynyl)phenyl)methanesulfonamide (**14**)

(a) Unstable aryl iodide **13** was prepared by the method of Cook and coworkers⁷ and used without further purification. Reaction of iodide **13** (1.757 g, 7.06 mmol) with trimethylsilylacetylene by the general procedure followed by flash chromatography (20% diethyl ether/ hexanes) to give alkynylaniline **S5** as a yellow oil (927 mg, 60% yield). The spectroscopic data was consistent with that previously reported.⁸ ¹H NMR (300 MHz, CDCl₃) δ 7.21 (d, *J* = 8.4 Hz, 1H), 6.24 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.21 (d, *J* = 2.3 Hz, 1H), 4.25 (s, 2H), 3.75 (s, 3H), 0.25 (s, 9H).

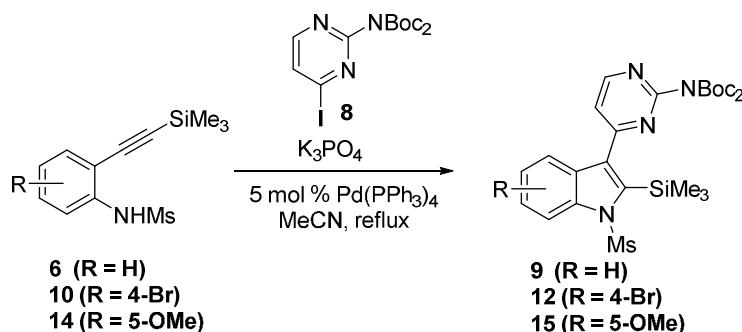
⁶ Callaghan, P. D.; Gibson, M. S. *J. Chem. Soc. (C)*, **1970**, 2106.

⁷ Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, 66, 4525

⁸ Gimeno, A.; Medio-Simon, M.; De Arellano, C. R.; Asensio, G.; Cuenca, A. B. *Organic Lett.* **2010**, 12, 1900.

(b) Treatment of alkynylaniline **S5** (927 mg, 4.22 mmol) with mesyl chloride by the general procedure and purification by flash chromatography on silica (10 to 20% ethyl acetate/ hexanes) gave sulfonamide **14** as an off-white solid (840 mg, 67% yield). mp: 143-144°C; IR (nujol mull, cm⁻¹) 3242, 2154, 2079 (br), 1335; ¹H NMR (300 MHz, CDCl₃) δ 7.37 (d, *J* = 8.6 Hz, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 6.98 (br s, 1H), 6.65 (dd, *J* = 8.6, 2.5 Hz, 1H), 3.82 (s, 3H), 3.00 (s, 3H), 0.27 (s, 9H); ¹³C NMR (75.5 MHz, CDCl₃) δ 160.9, 139.5, 133.3, 110.9, 106.3, 105.0, 101.1, 99.7, 55.5, 39.4, 0.0; HRMS Calculated for C₁₃H₂₀NO₃SSi (M+H)⁺ 298.0933, found 298.0929.

General procedure for pyrimidyl indole formation



The sulfonamide (**6**, **10** or **14**) (1 eq), aryl iodide **8** (1.5 eq), finely ground tripotassium phosphate (1.5 eq) and tetrakis(triphenylphosphine)palladium(0) (5 mol %) were loaded into a Schlenk tube, and flushed with nitrogen. Dry acetonitrile (16 mL/mmol) was added, the mixture was degassed with three cycles of vacuum/nitrogen flushing then lowered into a preheated oil bath. The progress of the reaction was monitored by TLC, and once the reaction was judged complete the deeply coloured mixture was cooled and quenched with 2 volumes of water, and extracted with three portions of ethyl acetate. The combined organic phases were washed with brine, dried with sodium sulfate and evaporated. The residue was purified by flash chromatography to give the desired pyrimidyl indoles (**9**, **12**, or **15**).

Bis-tert-butyl 4-(1-(methylsulfonyl)-2-(trimethylsilyl)-1H-indol-3-yl)pyrimidin-2-yl)carbamate (**9**)

Reaction of sulfonamide **6** (136 mg, 0.510 mmol) and pyrimidyl iodide **8** (316 mg, 0.750 mmol) by the general procedure gave indole **9** as a white solid (240 mg, 84% yield). mp: 70-73°C; IR (film cast from

CH₂Cl₂, cm⁻¹): 3336, 2981, 2933, 1793, 1758, 1579, 1369; ¹H NMR (300 MHz, CDCl₃) δ 8.85 (d, *J* = 5.0 Hz, 1H), 8.01 (td, *J* = 8.4, 0.8, 0.8 Hz, 1H), 7.47 (ddd, *J* = 7.9, 1.3, 0.8 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.38 (d, *J* = 5.0 Hz, 1H), 7.28 (ddd, *J* = 8.0, 7.2, 0.9 Hz, 1H), 3.05 (s, 3H), 1.46 (s, 18H), 0.25 (s, 9H); ¹³C NMR (75.5 MHz, CDCl₃) δ 164.4, 158.6, 158.4, 150.4, 141.3, 138.4, 133.3, 130.5, 126.3, 124.1, 121.2, 120.0, 117.2, 114.1, 83.4, 40.0, 27.9, 2.0; HRMS: calculated for C₂₆H₃₇N₄O₆SSi (M+H)⁺ 561.2203, found 561.2196.

Bis-*tert*-butyl (4-(5-bromo-1-(methylsulfonyl)-2-(trimethylsilyl)-1H-indol-3-yl)pyrimidin-2-yl)-carbamate (12)

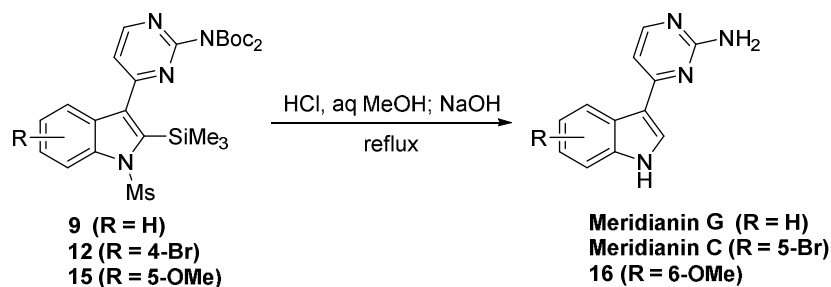
Reaction of sulfonamide **10** (174 mg, 0.502 mmol) and pyrimidyl iodide **8** (317 mg, 0.752 mmol) by the general procedure gave indole **12** as a white solid (200 mg, 64% yield). NMR indicated a 82:18 mixture of indole *N*-Ms: N-H products. IR (film cast from CH₂Cl₂, cm⁻¹): 3355 (br), 2981, 2928, 1795, 1760, 1581, 1370; ¹H NMR (300 MHz, CDCl₃) δ peaks for the major indole *N*-Ms compound: 8.86 (d, *J* = 5.0 Hz, 1H), 7.88 (dd, *J* = 8.9, 0.5 Hz, 1H), 7.61 (dd, *J* = 2.0, 0.5 Hz, 1H), 7.50 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.35 (d, *J* = 5.0 Hz, 1H), 3.06 (s, 3H), 1.46 (s, 18H), 0.24 (s, 9H); distinct peaks for the minor indole NH compound 8.74 (d, *J* = 5.4 Hz, 2H minor), 8.12-8.11 (m, 1H), 1.41 (s, 18H minor), 0.42 (s, 9H minor); ¹³C NMR (75.5 MHz, CDCl₃) δ peaks for the major indole *N*-Ms compound 163.8, 158.6, 150.3, 142.7, 137.0, 132.3, 132.2, 129.1, 122.6, 121.3, 117.9, 115.4, 83.6, 40.4, 27.9, 1.9; distinct peaks for the minor indole NH compound 125.8, 122.1, 113.1, 83.1, 27.8, -0.6; HRMS: calculated for C₂₆H₃₆⁸¹BrN₄O₆SSi, (M+H)⁺ 641.1288, found 641.1285; calculated for C₂₅H₃₄⁸¹BrN₄O₄Si (M+H)⁺ 563.1512, found 563.1504.

Bis-*tert*-butyl (4-(6-methoxy-1-(methylsulfonyl)-2-(trimethylsilyl)-1H-indol-3-yl)pyrimidin-2-yl)-carbamate (15)

Reaction of sulfonamide **14** (149 mg, 0.502 mmol) and pyrimidyl iodide **8** (322 mg, 0.764 mmol) by the general procedure gave indole **15** as a oil that set to a white solid on standing (225 mg, 76% yield). mp:

105-109°C; IR (film cast from CH₂Cl₂, cm⁻¹): 3348, 2927, 2853, 1791, 1760, 1575, 1372; ¹H NMR (300 MHz, CDCl₃) δ 8.83 (d, *J* = 5.0 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.41-7.30 (m, 2H), 6.90 (dd, *J* = 8.8, 2.3 Hz, 1H), 3.88 (s, 3H), 2.98 (s, 3H), 1.45 (s, 18H), 0.22 (s, 9H); ¹³C NMR (75.5 MHz, CDCl₃) δ 164.4, 159.3, 158.5, 158.4, 150.4, 139.9, 139.8, 133.9, 124.5, 121.1, 120.7, 113.6, 98.1, 83.4, 55.8, 39.5, 27.8, 2.0; HRMS: calculated for C₂₇H₃₉N₄O₇SSi (M+H)⁺ 591.2309, found 591.2302.

General Procedure for meridianin deprotection



4M Aqueous hydrochloric acid solution was added to a vigorously stirred solution of protected indole (**9**, **12** or **15**) in methanol. The resulting yellow suspension was refluxed overnight, then cooled to room temperature. The reaction mixture was basified with sodium hydroxide to pH 14 and heated at reflux for the time indicated, then cooled and the methanol removed on a rotary evaporator. The resulting suspension was extracted with dichloromethane (5x 50 mL), and the organic phases dried over sodium sulfate and evaporated to give the meridianin cleanly without further purification.

Meridianin G

The protected indole **9** (210 mg, 0.374 mmol) was heated at reflux overnight with 4M aqueous hydrochloric acid (4 mL) and methanol (8 mL), then after the addition of solid sodium hydroxide until the pH was 14, the mixture was heated at reflux for 4.5 h. After workup, as described in the general procedure, meridianin G was obtained as a white solid (66 mg, 83%). mp (CH₂Cl₂): 186-188°C, lit m.p.⁹ (CHCl₃): 183-185°C; IR (nujol mull, cm⁻¹): 3408, 1661, 1568, 1520, 1245; ¹H NMR (300 MHz, d₆-

⁹ Corbel, B.; Michaud, F.; Meijer, L.; Simon, G.; Couthon-Gourves, H.; Haelters, J-P.; Kervarec, N. *J. Heterocyclic Chem.* **2007**, *44*, 793.

DMSO) δ 11.66 (s, 1H), 8.58 (dm, J = 7.5 Hz, 1H), 8.19 (s, 1H), 8.09 (d, J = 5.3 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.14 (app dt, J = 7.2, 1.4 Hz, 2H), 7.01 (d, J = 5.4 Hz, 1H), 6.40 (s, 2H); ^{13}C NMR (75.5 MHz, d_6 -DMSO) δ 163.4, 162.6, 156.9, 136.9, 128.1, 125.2, 122.3, 121.8, 120.1, 113.5, 111.7, 105.2; HRMS: calculated for $\text{C}_{12}\text{H}_{11}\text{N}_4$ ($\text{M}+\text{H}$) $^+$ 211.0984, found 211.0978.

Meridianin C

The protected indole **12** (157 mg, 0.252 mmol) was heated at reflux overnight with 4M aqueous hydrochloric acid (4 mL) and methanol (8 mL), then after the addition of solid sodium hydroxide until the pH was 14 the mixture was heated at reflux for 4 h. After workup, as described in the general procedure, meridianin C was obtained as a yellow solid (64 mg, 88%). mp (dichloromethane): 235-236°C, lit. mp¹⁰ (pentane) 238-240°C; ^1H NMR (300 MHz, d_6 -DMSO) δ 11.88 (br s, 1H), 8.76 (d, J = 1.9 Hz, 1H), 8.26 (s, 1H), 8.10 (d, J = 5.3 Hz, 1H), 7.41 (dd, J = 8.6, 0.3 Hz, 1H), 7.28 (dd, J = 8.6, 2.0 Hz, 1H), 7.00 (d, J = 5.3 Hz, 1H), 6.51 (br s, 2H); ^{13}C NMR (75.5 MHz, d_6 -DMSO) δ 163.5, 162.2, 157.1, 135.7, 129.5, 127.0, 124.5, 124.5, 113.7, 113.3, 113.2, 105.1; FTIR (nujol mull, cm^{-1}) 3475, 3370, 1576, 1526, HRMS: calculated for $\text{C}_{12}\text{H}_{10}^{79}\text{BrN}_4$ ($\text{M}+\text{H}$) $^+$ 289.0089, found 289.0081, calculated for $\text{C}_{12}\text{H}_{10}^{81}\text{BrN}_4$ ($\text{M}+\text{H}$) $^+$ 291.0068, found 291.0063.

6-Methoxymmeridianin G (16)

The protected indole **15** (203 mg, 0.344 mmol) was heated at reflux overnight with 4M aqueous hydrochloric acid (10 mL) and methanol (5 mL), then after the addition of solid sodium hydroxide until the pH was 14 the mixture was heated at reflux for 6 h. A fine suspension was formed and this was collected by vacuum filtration. The precipitate was azeotropically dried by evaporating from toluene, then stirred in dichloromethane (150 mL) with sodium sulfate, the mixture filtered and the filtrate evaporated to give 6-methoxymmeridianin G (**16**) as a yellow solid (63 mg, 76%). mp (CH_2Cl_2) 230-232 °C, IR (nujol mull, cm^{-1}): 3456, 3305, 1613 1574, 1556; ^1H NMR (300 MHz, d_6 -DMSO) δ 11.5 (br s, 1H, indole NH), 8.44 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 5.4 Hz, 1H), 8.05 (s, 1H), 6.97 (d, J = 5.4 Hz, 1H), 6.92

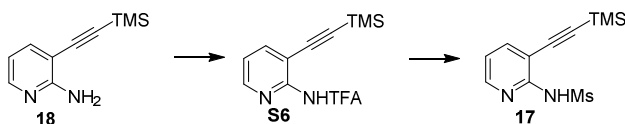
¹⁰ Karpov, A. S.; Merkul, E.; Rominger, F.; Müller, T. J. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6951.

(s, 1H), 6.75 (dd, J = 8.8, 2.3 Hz, 1H), 6.38 (s, 1H), 3.78 (s, 1H); ^{13}C NMR (75.5 MHz, d_6 -DMSO) δ 163.4, 162.5, 156.7, 155.7, 137.7, 126.9, 123.0, 119.4, 113.6, 110.2, 105.0, 94.4, 55.0; HRMS: calculated for $\text{C}_{13}\text{H}_{13}\text{N}_4\text{O}$ ($\text{M}+\text{H}$) $^+$ 241.1089, found 241.1083

3-((Trimethylsilyl)ethynyl)pyridin-2-amine (**18**)¹¹

A suspension of 3-iodopyridin-2-amine (**19**) (700 mg, 3.20 mmol), ethynyltrimethylsilane (0.5 mL, 3.50 mmol), copper(I) iodide (0.024 g, 0.095 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.09 g, 0.095 mmol) in freshly distilled triethylamine (13 mL) was freeze-pump-thaw degassed and stirred at r.t. for 12 h. The reaction mixture was filtered through a plug of Celite with dichloromethane. The solvent was removed under reduced pressure to give a yellow solid. Purification by flash chromatography on deactivated silica, eluting with 20% ethyl acetate/*n*-hexane, gave the title compound as a beige solid (570 mg, 94% yield). The data obtained matched that reported in the literature.¹¹ m.p. = 80 - 81°C; ^1H NMR (CDCl_3 , 300 MHz): δ 0.25 (s, 9H), 5.02 (br s, 2H) 6.58 (dd, J = 7.5, 5.0 Hz, 1H), 7.52 (dd, J = 7.5, 1.9 Hz, 1H), 8.01 (dd, J = 5.0, 1.9 Hz).

N-(3-((Trimethylsilyl)ethynyl)pyridin-2-yl)methanesulfonamide (**17**)



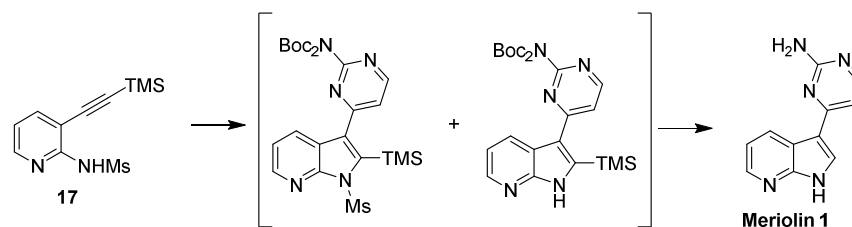
(a) Trifluoroacetic anhydride (0.73 mL, 5.25 mmol) was added dropwise to a solution of 3-((trimethylsilyl)ethynyl)pyridin-2-amine (**18**) (0.5 g, 2.62 mmol) in dry THF (12 mL) at 0°C and the reaction mixture was stirred at r.t. for 5 h. It was quenched with saturated aqueous sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (3 $\times$). The combined organic extracts were washed with water (2 $\times$) and brine (3 $\times$) and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield a pale orange solid (0.69 g, 92% yield). The product **S6** was used without any further purification. m.p. = 85 - 86°C; IR (neat): 3434, 2151, 1651, 1459 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ

¹¹ Nair, R. N.; Lee, P. J.; Rheingold, A. L.; Grotjahn, D. B. *Chem. Eur. J.* **2010**, *16*, 7992.

0.28 (s, 9H), 7.16 (dd, $J = 7.7, 4.9$ Hz, 1H), 7.80 (dd, $J = 7.7, 1.7$ Hz, 1H), 8.48 (m, 1H) 8.92 (br s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ -0.37, 97.3, 106.4, 115.7 (q, $^1J_{\text{C-F}} = 288$ Hz), 120.9, 140.6, 144.8, 148.3, 150.0, 153.7 (q, $^2J_{\text{C-F}} = 37$ Hz); HRMS (EI) calcd for $\text{C}_{12}\text{H}_{14}\text{F}_3\text{N}_2\text{OSi}$ ($\text{M}+\text{H}$) $^+$ 287.0827, found 287.0821.

(b) Mesyl chloride (0.17 mL, 2.20 mmol) was added dropwise to a solution of 2,2,2-trifluoro-*N*-(3-((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide **S6** (0.6 g, 2.10 mmol) and triethylamine (0.31 mL, 2.20 mmol) in dry THF (15 mL) at 0°C. Saturated, aqueous sodium bicarbonate solution (15 mL) was added and the mixture stirred vigorously for 30 min. It was extracted with ethyl acetate (4 $\times$) and the combined organic extracts washed with brine (3 $\times$) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give an orange solid. Purification by flash chromatography, eluting with 5% *n*-hexane/dichloromethane, gave the title compound **17** as a pale yellow oil (0.43 g, 77% yield). IR (neat): 3479, 2979, 2145, 1760, 1538 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 0.27 (s, 9H), 3.48 (s, 3H), 6.94 (dd, $J = 7.7, 5.0$ Hz, 1H), 7.68 (dd, $J = 7.7, 1.8$ Hz, 1H), 8.26 (dd, $J = 5.0, 1.7$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ -0.18, 42.4, 97.7, 105.0, 106.9, 117.9, 140.7, 147.6, 152.0; HRMS (EI) calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{NaO}_2\text{SSi}$ ($\text{M}+\text{Na}$) $^+$ 291.0594, found 291.0595.

Synthesis of Meriolin 1



A suspension of *N*-(3-((trimethylsilyl)ethynyl)pyridin-2-yl)methanesulfonamide (**17**) (120 mg, 0.45 mmol), bis-*tert*-butyl(4-iodopyrimidin-2-yl)carbamate (**8**) (280 mg, 0.67 mmol), potassium phosphate (140 mg, 0.67 mol) and tetrakis(triphenylphosphine)palladium(0) (26 mg, 0.022 mmol) in dry acetonitrile (7 mL) was freeze-pump-thaw degassed and heated at reflux in a sealed tube for 18 h. The bright red reaction mixture was filtered through a plug of Celite with dichloromethane. The solvent was removed under reduced pressure to give a red solid, which was taken up in methanol (30 mL) and 4M aqueous

hydrochloric acid solution (10 mL) and heated at reflux for 5 h. The reaction mixture was basified with saturated aqueous sodium hydroxide solution to pH 10 and heated at reflux for 14 h. The yellow reaction mixture was extracted with dichloromethane (5×) and the combined organic extracts washed with brine (1×) and dried (Na₂SO₄). The solvent was removed under reduced pressure to give a yellow solid (67 mg). Purification by flash chromatography on deactivated silica (9:1 EtOH/NH₃), eluting with 1% ethanol/ethyl acetate, gave the title compound as a pale yellow solid (48 mg, 51% yield over 2 steps); m.p. = 273 - 274°C, lit mp¹² = 258 - 271°C, lit. mp¹³ = 286 - 289°C; IR (film): 3442, 2958, 2922, 1644 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 6.47 (br s, 2H), 7.05 (d, *J* = 5.3 Hz, 1H), 7.18 (dd, *J* = 7.9, 4.7 Hz, 1H), 8.13 (d, *J* = 5.3 Hz, 1H), 8.29 (dd, *J* = 4.7 Hz, 1.7 Hz, 1H), 8.34 (d, *J* = 2.9 Hz, 1H), 8.92 (dd, *J* = 7.9, 1.7 Hz, 1H), 12.2 (br s, 1H); ¹³C NMR (DMSO-d₆, 75 MHz): δ 105.0, 112.5, 116.7, 117.8, 128.4, 130.8, 143.5, 149.2, 157.3, 162.1, 163.6; HRMS (EI) calcd for C₁₁H₁₀N₅ (M+H)⁺ 212.0931, found 212.0930.

5-Bromo-3-iodopyridin-2-amine (20)¹⁴

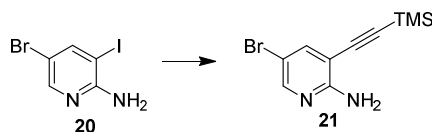
N-Bromosuccinimide (0.58 g, 3.26 mmol) was added, in one portion, to a solution of 3-iodopyridin-2-amine (0.7 g, 3.18 mmol) in dry dichloromethane (14 mL) and the reaction mixture was stirred at r.t. for 3 h. It was washed with water (1×) and the aqueous layer re-extracted with dichloromethane (3×). The combined organic extracts were washed with brine (3×) and dried (Na₂SO₄). The solvent was removed under reduced pressure to give crude 5-bromo-3-iodopyridin-2-amine as a brown solid. Purification by flash chromatography, eluting with 20% ethyl acetate/*n*-hexane, gave the title compound as an orange solid (0.87 g, 91% yield). m.p. = 113 - 114°C; IR (film): 3447, 1629 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 5.01 (br s, 2H), 7.95 - 7.94 (m, 1H), 8.06 - 8.05 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 77.6, 107.3, 148.3, 156.3; HRMS (EI) calcd for C₅H₅⁷⁹BrIN₂ (M+H)⁺ 298.8681, found 298.8675.

¹² Merkul, E.; Schäfer, E.; Müller, T. J. J. *Org. Biomol. Chem.* **2011**, 9, 3139.

¹³ Fresneda, P. M.; Molina, P.; Bleda, J. A. *Tetrahedron*, **2001**, 57, 2355.

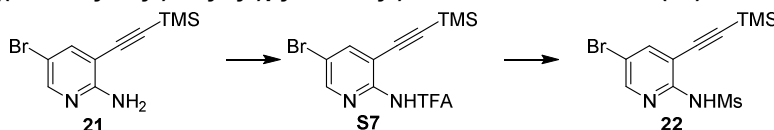
¹⁴ Rossy, C; Fouquet, E.; Felpin, F-X. *Beilstein J. Org. Chem.* **2013**, 9, 1426.

5-Bromo-3-((trimethylsilyl)ethynyl)pyridin-2-amine (**21**)¹⁵



A suspension of 5-bromo-3-iodopyridin-2-amine (**20**) (0.7 g, 2.35 mmol), ethynyltrimethylsilane (0.37 mL, 2.59 mmol), copper(I) iodide (0.018 g, 0.071 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.066 g, 0.071 mmol) in freshly distilled triethylamine (13 mL) was freeze-pump-thaw degassed and stirred at r.t. for 12 h. The reaction mixture was filtered through a plug of Celite with dichloromethane. The solvent was removed under reduced pressure to give a yellow solid. Purification by flash chromatography on deactivated silica eluting with 20% ethyl acetate/*n*-hexane gave the title compound as a beige solid (0.50 g, 82% yield). m.p. = 131 - 132°C; IR (neat): 3456, 2150, 1629 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 0.26 (s, 9H), 5.10 (br s, 2H), 7.63 (d, *J* = 2.4 Hz, 1H), 8.04 (d, *J* = 2.4 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ -0.002, 98.8, 103.0, 105.0, 106.9, 142.1, 148.6, 157.8; HRMS (EI) calcd for C₁₀H₁₄⁷⁹BrN₂Si (M+H)⁺ 269.0104, found 269.0110.

N-(5-Bromo-3-((trimethylsilyl)ethynyl)pyridin-2-yl)methanesulfonamide (**22**)



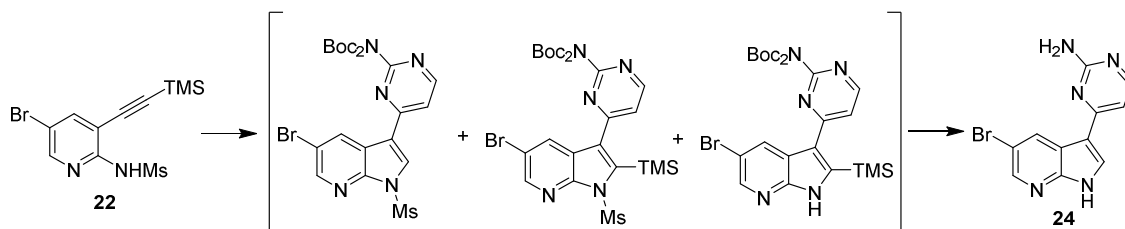
(a) Trifluoroacetic anhydride (0.53 mL, 3.83 mmol) was added dropwise to a solution of 5-bromo-3-((trimethylsilyl)ethynyl)pyridin-2-amine (0.5 g, 1.91 mmol) in dry THF (12 mL) at 0°C. The reaction mixture was stirred at r.t. for 5 h. It was quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (3×). The combined organic extracts were washed with brine (3×) and dried (Na₂SO₄). The solvent was removed under reduced pressure to give an orange solid (0.62 g, 89% yield), which was used without any further purification. m.p. = 79 - 80°C; IR (neat): 3444, 2152, 1629 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 0.29 (s, 9H) 7.94 (d, *J* = 2.3 Hz, 1H), 8.51 - 8.50 (m, 1H), 8.83 (br s,

¹⁵ Zhao, S.-B.; Cui, Q.; Wang, S. *Organometallics*, **2010**, 29, 998.

1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ -0.45, 95.9, 112.4, 115.6 (q, $^1J_{\text{C-F}} = 288$ Hz), 116.4, 142.6, 148.5, 149.3, 153.5; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{12}^{79}\text{BrF}_3\text{N}_2\text{NaOSi}$ 386.9747, found 386.9752.

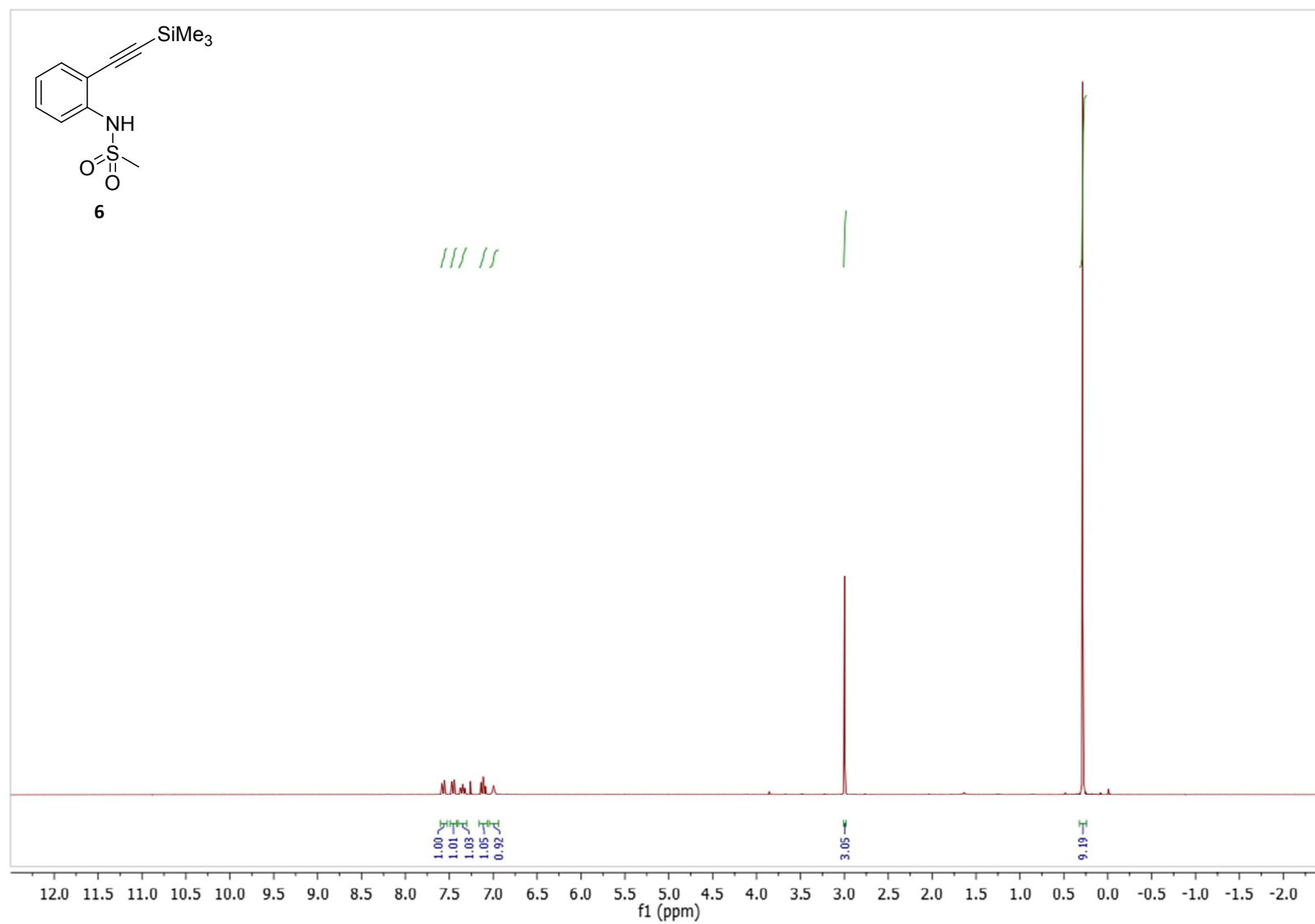
(b) Mesityl chloride (0.13 mL, 1.73 mmol) was added dropwise to a solution of *N*-(5-bromo-3-((trimethylsilyl)ethynyl)pyridin-2-yl)-2,2,2-trifluoroacetamide (0.6 g, 1.64 mmol) and triethylamine (0.24 mL, 1.73 mmol) in dry THF (15 mL) at 0°C. The reaction mixture was stirred at r.t. for 13 h. Saturated aqueous sodium bicarbonate solution (15 mL) was added and the mixture stirred vigorously for 30 min. It was extracted with ethyl acetate (4×) and the combined organic extracts washed with brine (3×) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give an orange solid. Purification by flash chromatography, eluting with 15% ethyl acetate/*n*-hexane, gave the title compound **22** as a colourless gum (0.43 g, 77% yield). IR (neat): 3423, 2927, 2069, 1643, 1560 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 0.29 (s, 9H), 3.47 (s, 3H), 7.50 (br s, 1H), 7.83 (d, $J = 2.3$ Hz, 1H), 8.33 (d, $J = 2.3$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ -0.22, 42.5, 96.3, 106.7, 108.6, 113.1, 142.7, 148.6, 150.7; HRMS (EI) calcd for $\text{C}_{11}\text{H}_{16}^{79}\text{BrN}_2\text{O}_2\text{SSi}$ ($\text{M}+\text{H}$) $^+$ 346., found 9880346.9885.

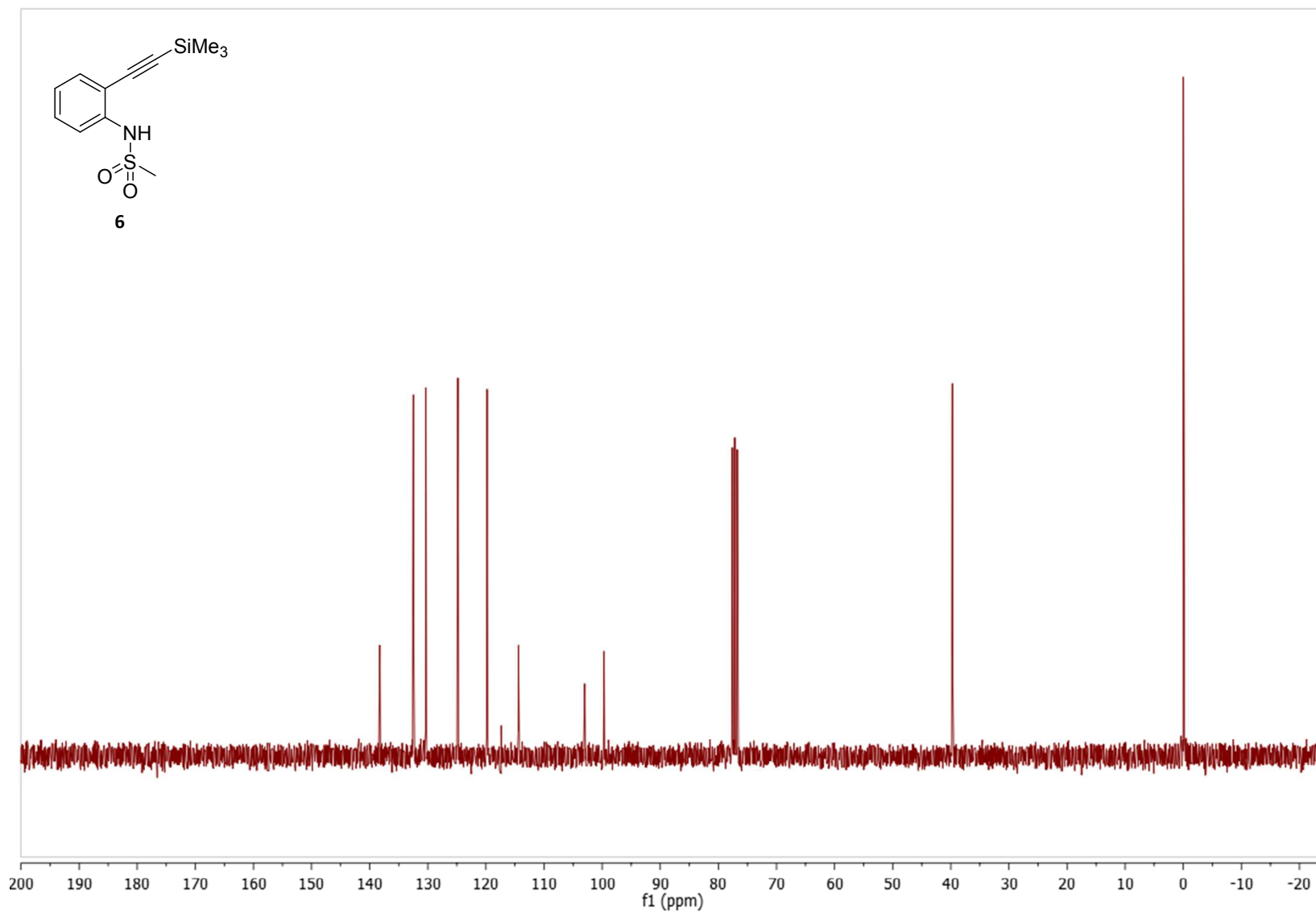
Synthesis of 24

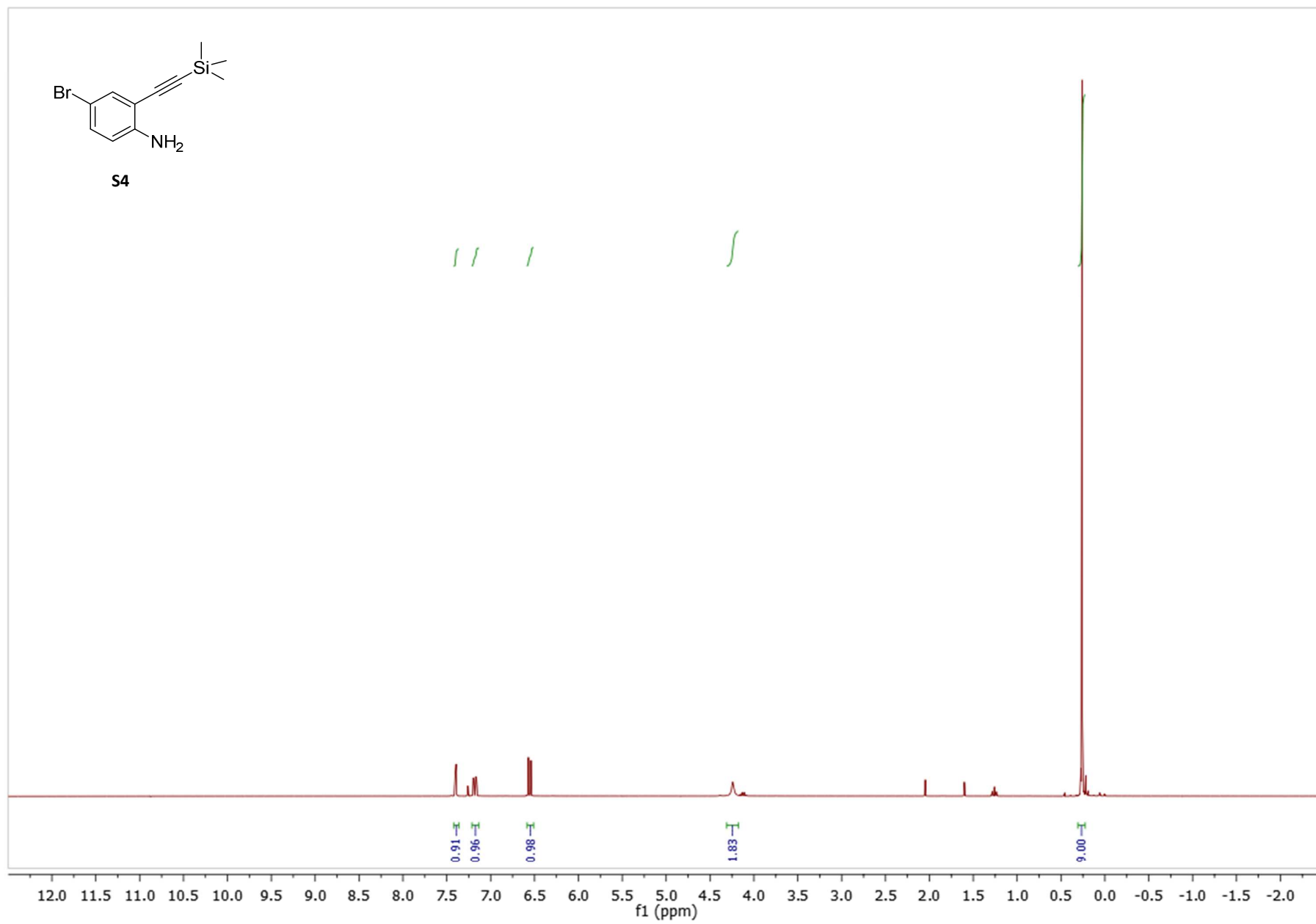


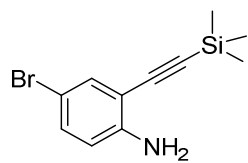
A suspension of *N*-(5-bromo-3-((trimethylsilyl)ethynyl)pyridin-2-yl)methanesulfonamide (**22**) (0.16 g, 0.47 mmol), bis-*tert*-butyl(4-iodopyrimidin-2-yl)carbamate (**8**) (0.29g, 0.70 mmol), potassium phosphate (0.15 g, 0.71 mol) and tetrakis(triphenylphosphine)palladium(0) (0.027 g, 0.024 mmol) in dry acetonitrile (10 mL) was freeze-pump-thaw degassed and heated at reflux in a sealed tube for 18 h. The bright orange reaction mixture was filtered through a plug of Celite with dichloromethane. The solvent was removed under reduced pressure to give an orange solid, which was taken up in methanol (30 mL) and 4M aqueous hydrochloric acid solution (10 mL) was heated at reflux for 4 h. The reaction mixture was

basified with saturated aqueous sodium hydroxide solution to pH 10 and heated at reflux for 18 h. The yellow reaction mixture was extracted with chloroform (5×) and the combined organic extracts washed with brine (1×) and dried (Na₂SO₄). The solvent was removed under reduced pressure to give a yellow solid. Purification by flash chromatography on deactivated silica (9:1 EtOH/NH₃), eluting with 95% ethyl acetate/*n*-hexane gave the title compound as a pale yellow solid (0.075 g, 55% yield over three steps); m.p. = 248 - 250°C; IR (film): 3424, 1650, 1556 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 6.59 (br s, 2H), 7.06 (d, *J* = 5.3 Hz, 1H), 8.14 (d, *J* = 5.3 Hz, 1H), 8.35 (d, *J* = 2.3 Hz, 1H), 8.43 - 8.42 (m, 1H), 9.11 (d, *J* = 2.3 Hz, 1H); ¹³C NMR (DMSO-d₆, 75 MHz): δ 104.8, 112.2, 112.3, 119.5, 130.1, 132.6, 143.6, 147.6, 157.5, 161.6, 163.6; HRMS (EI) calcd for C₁₁H₉⁷⁹BrN₅ (M+H)⁺ 290.0036, found 290.0041.

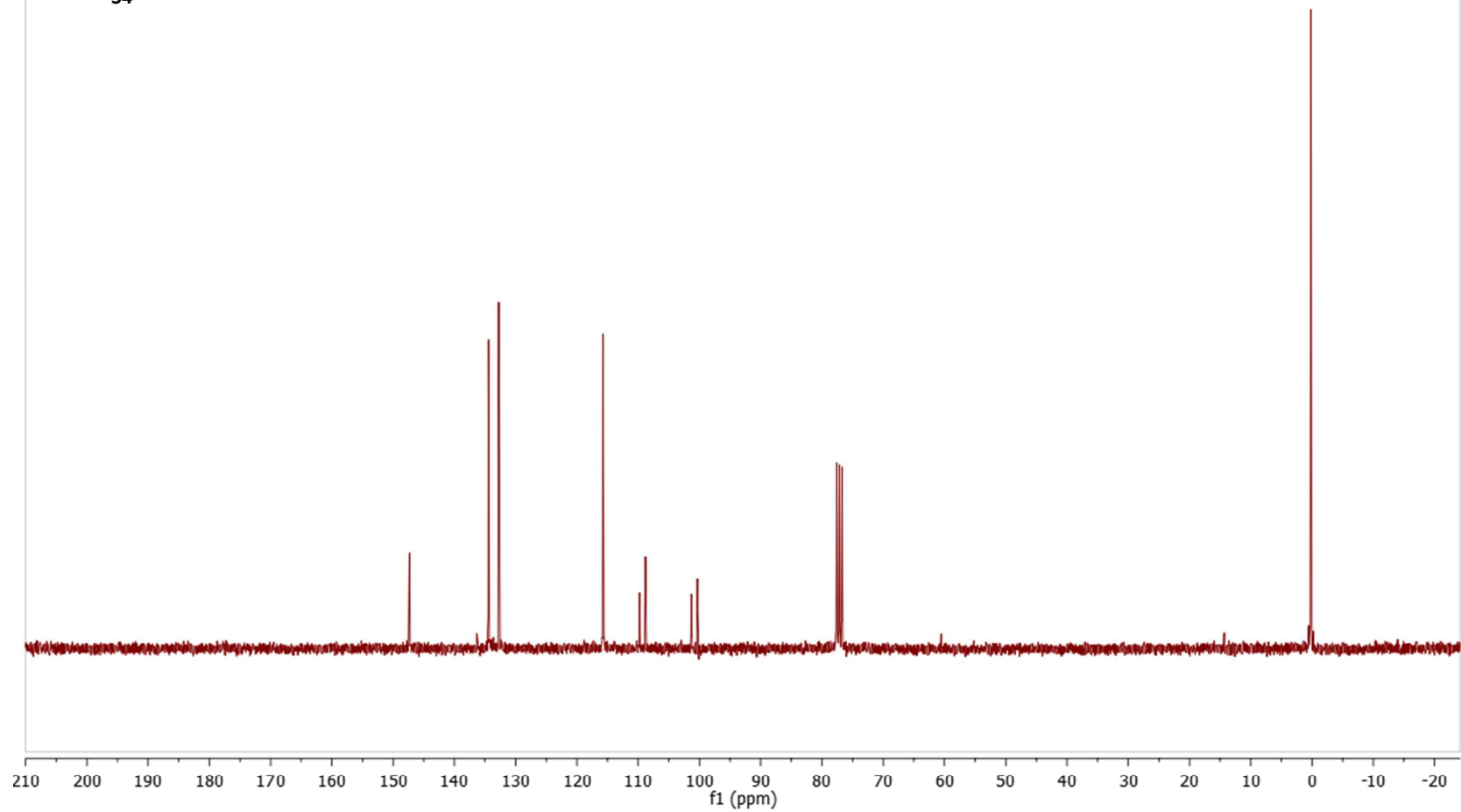


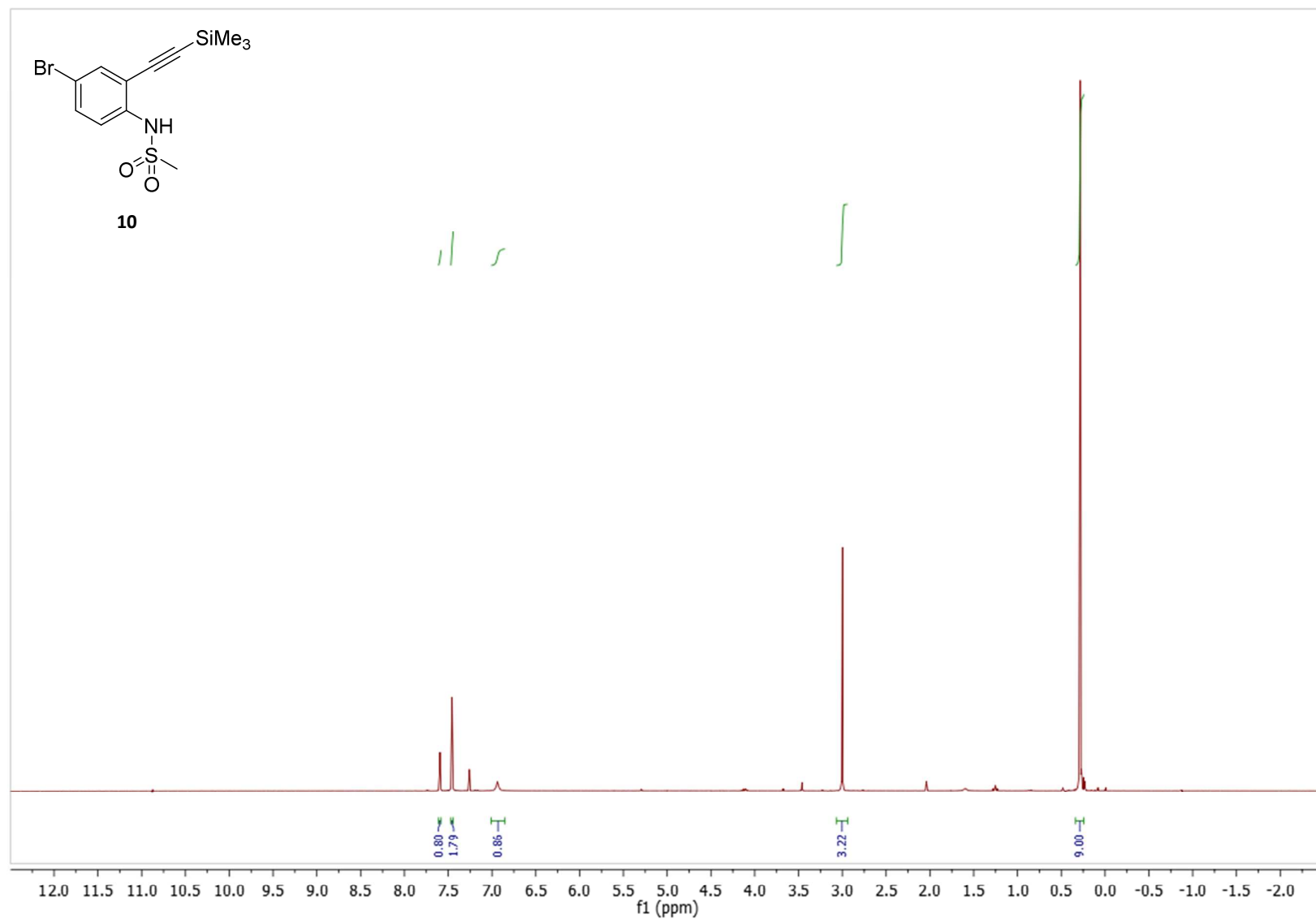


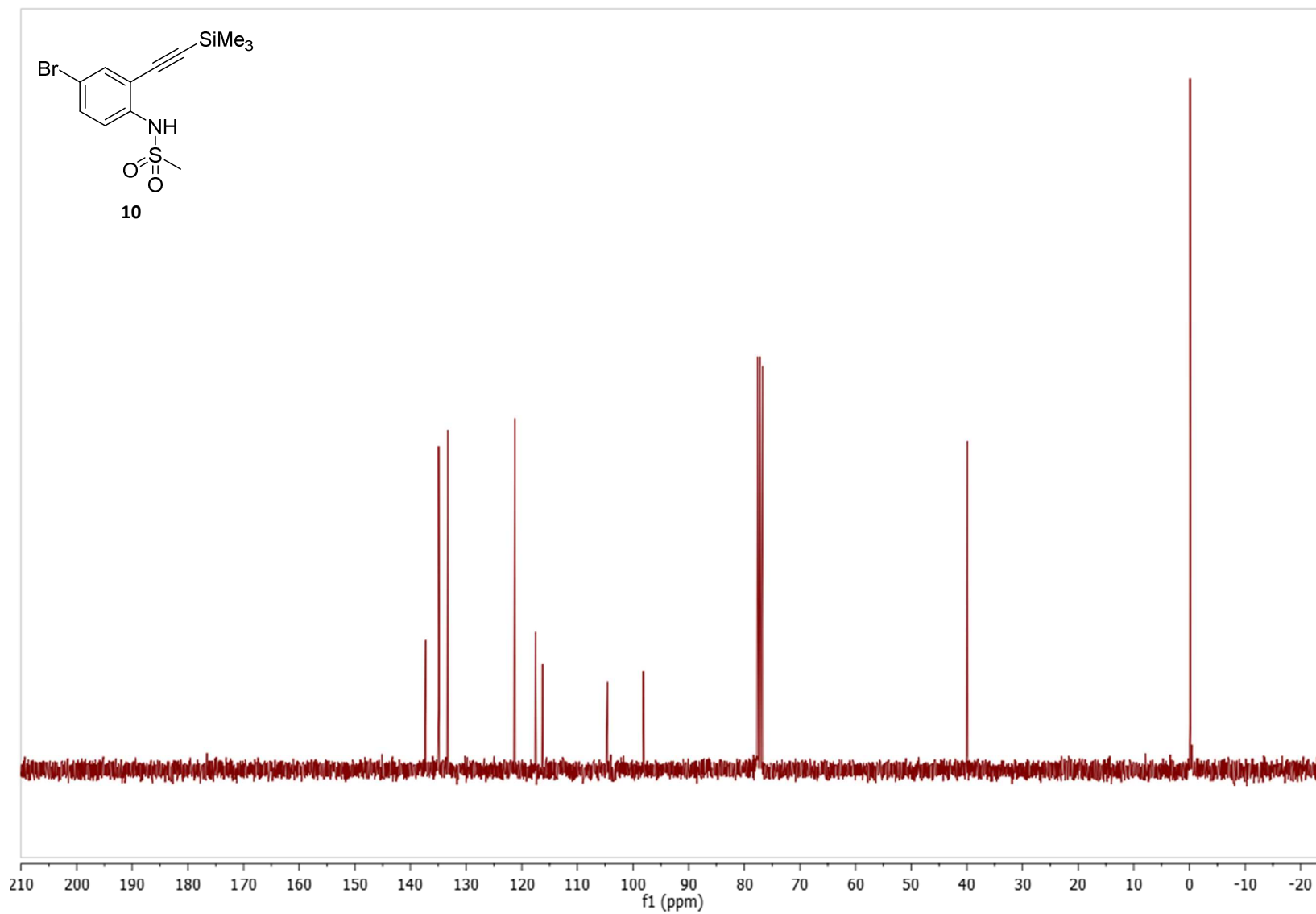


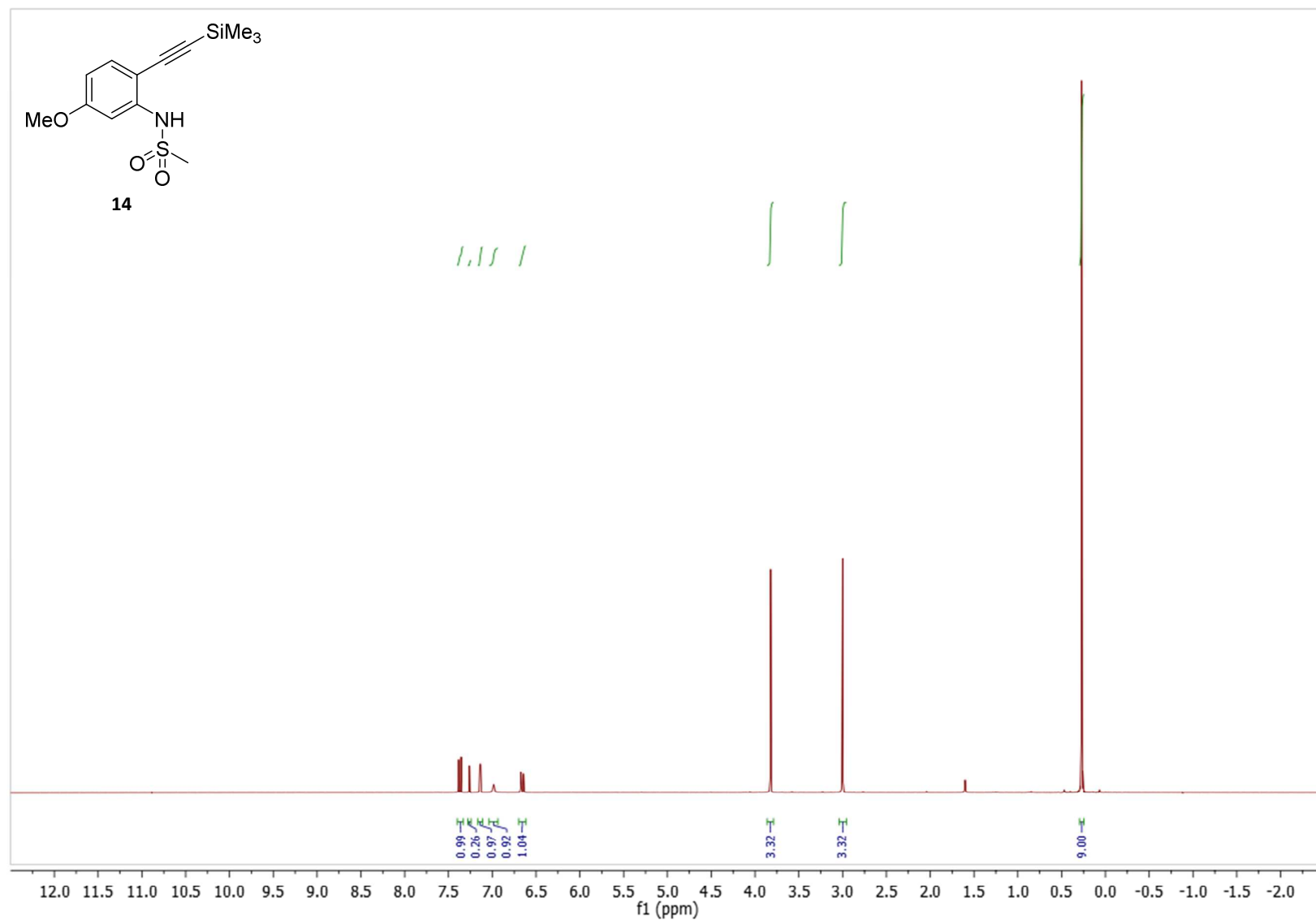


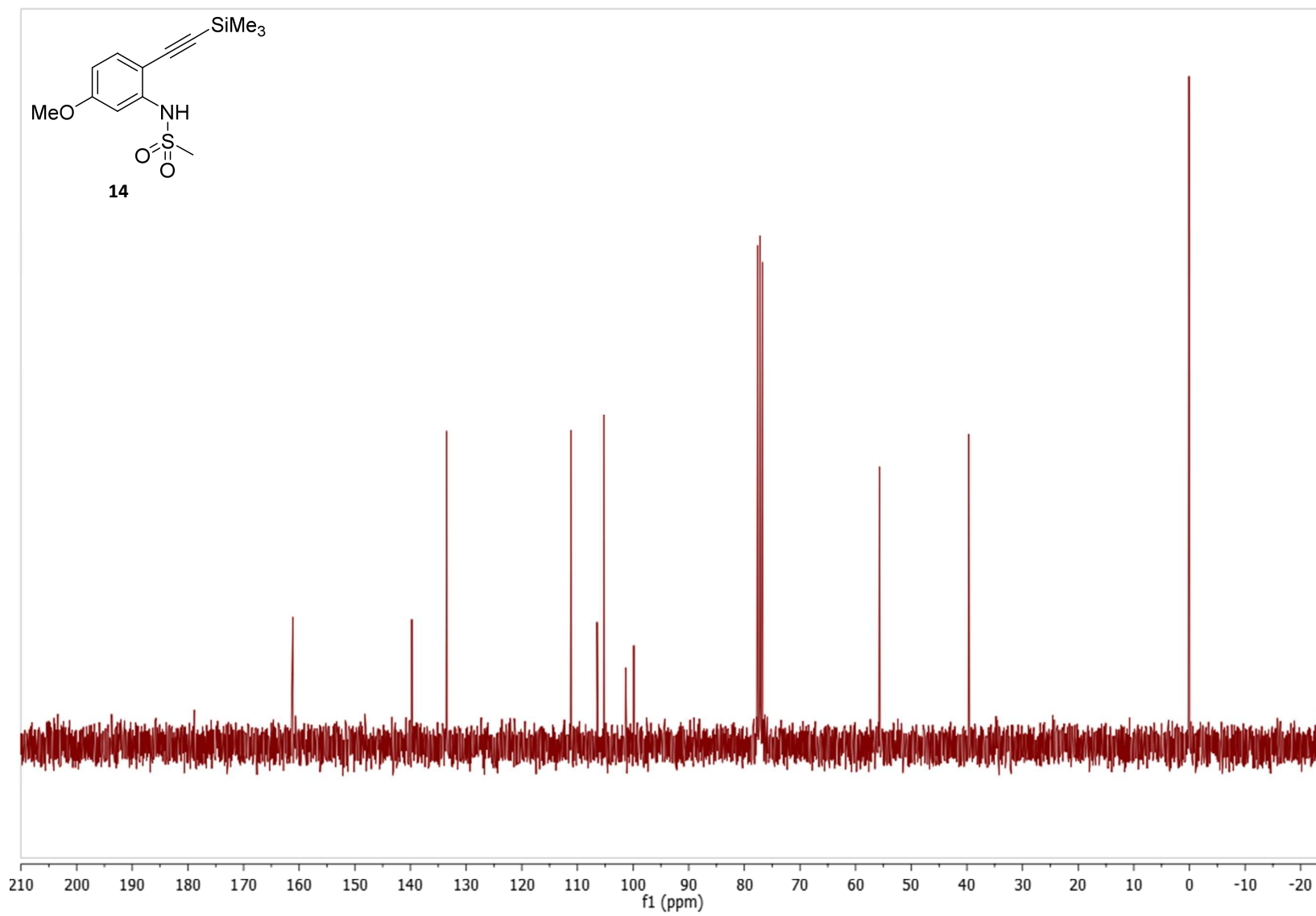
S4

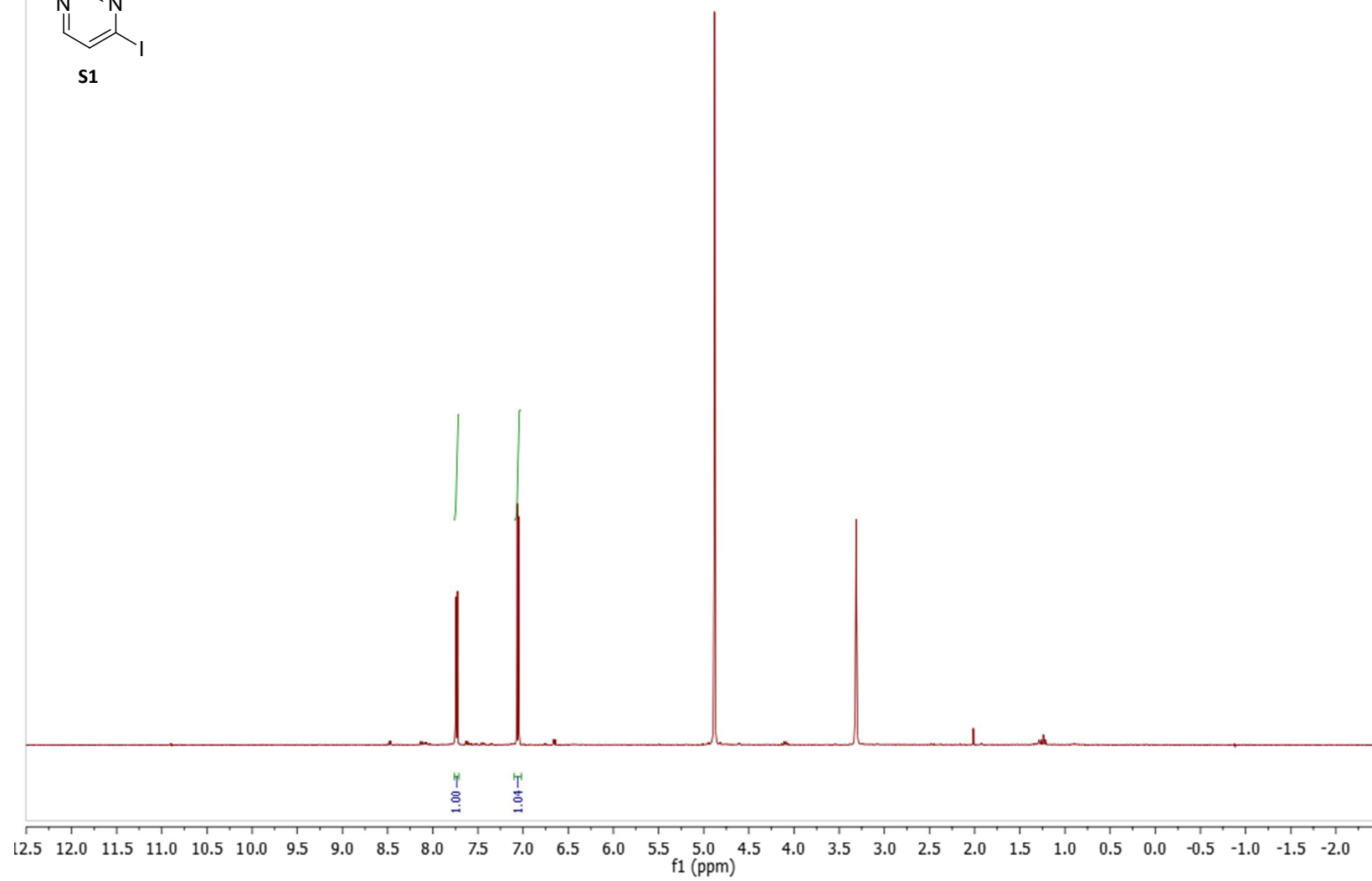
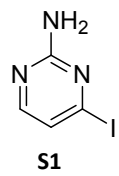


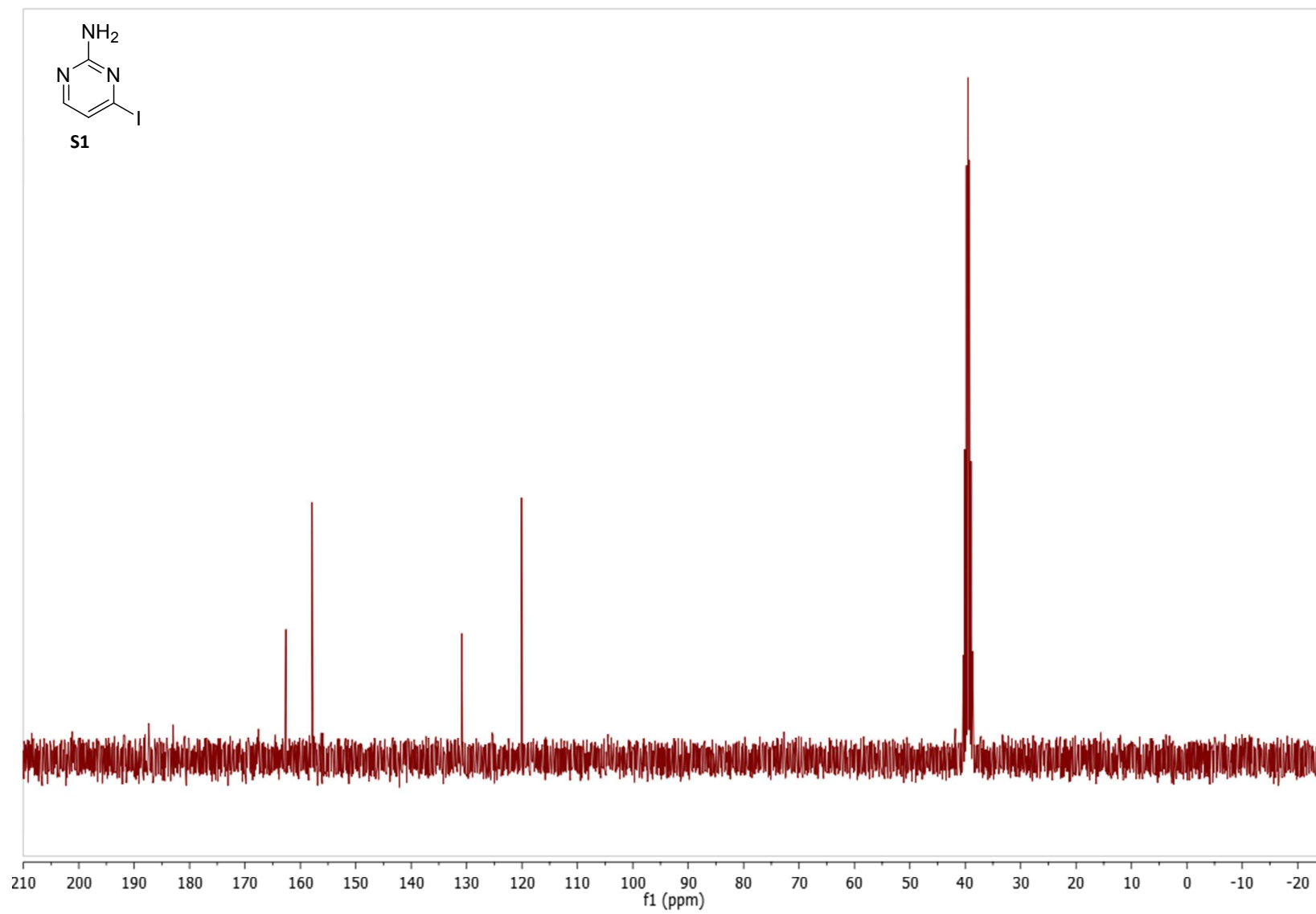
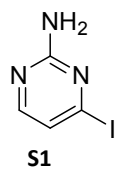


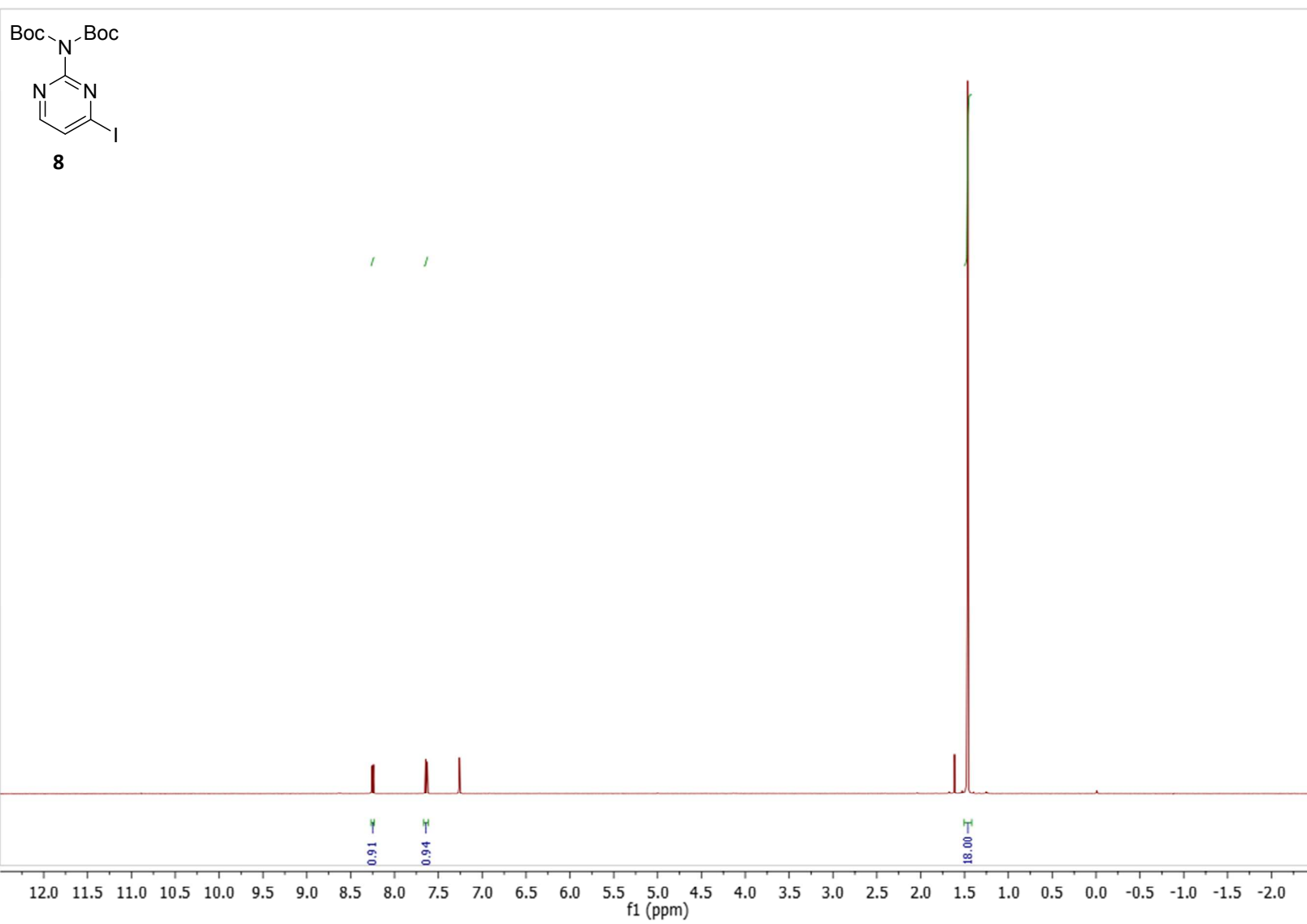


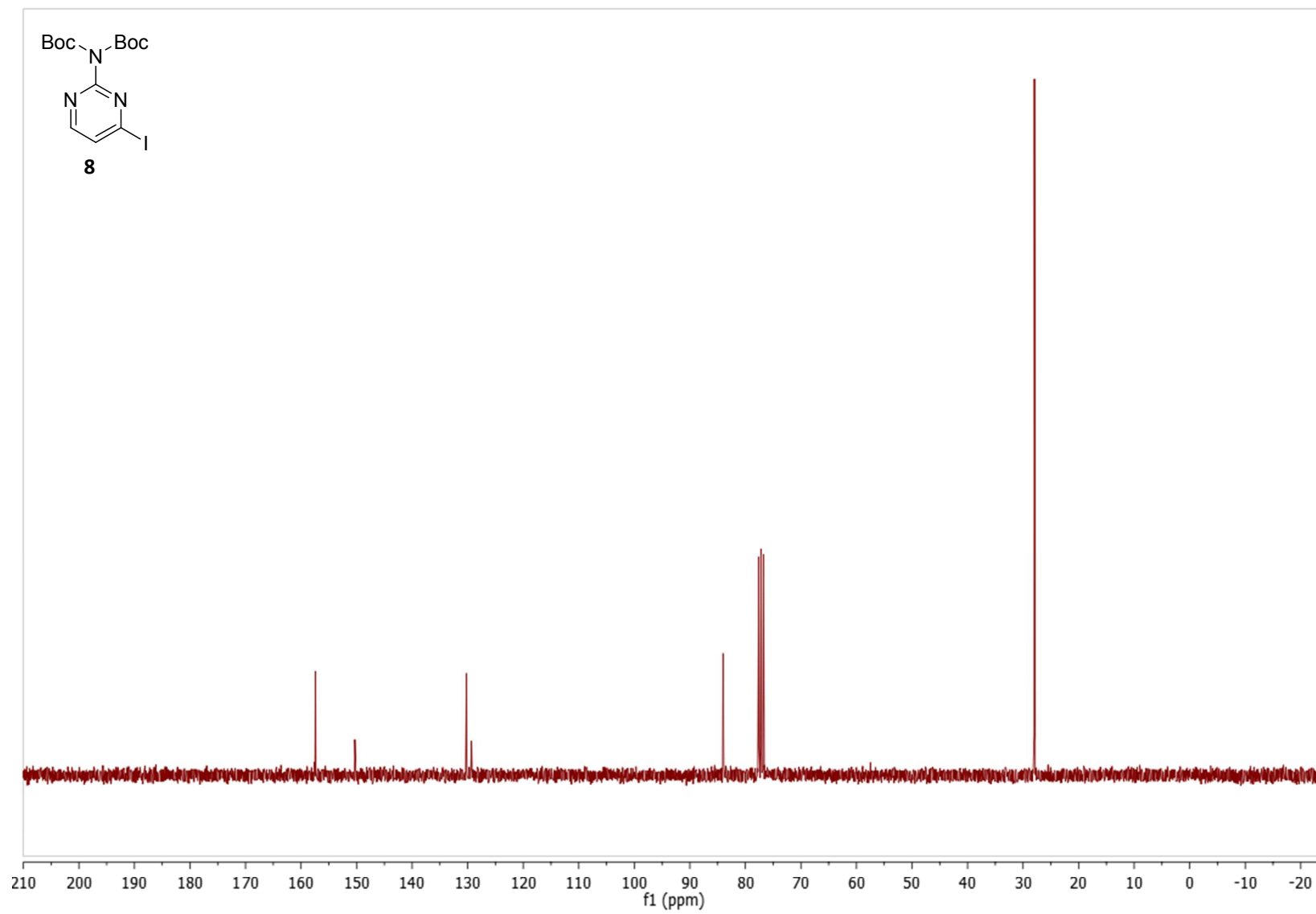


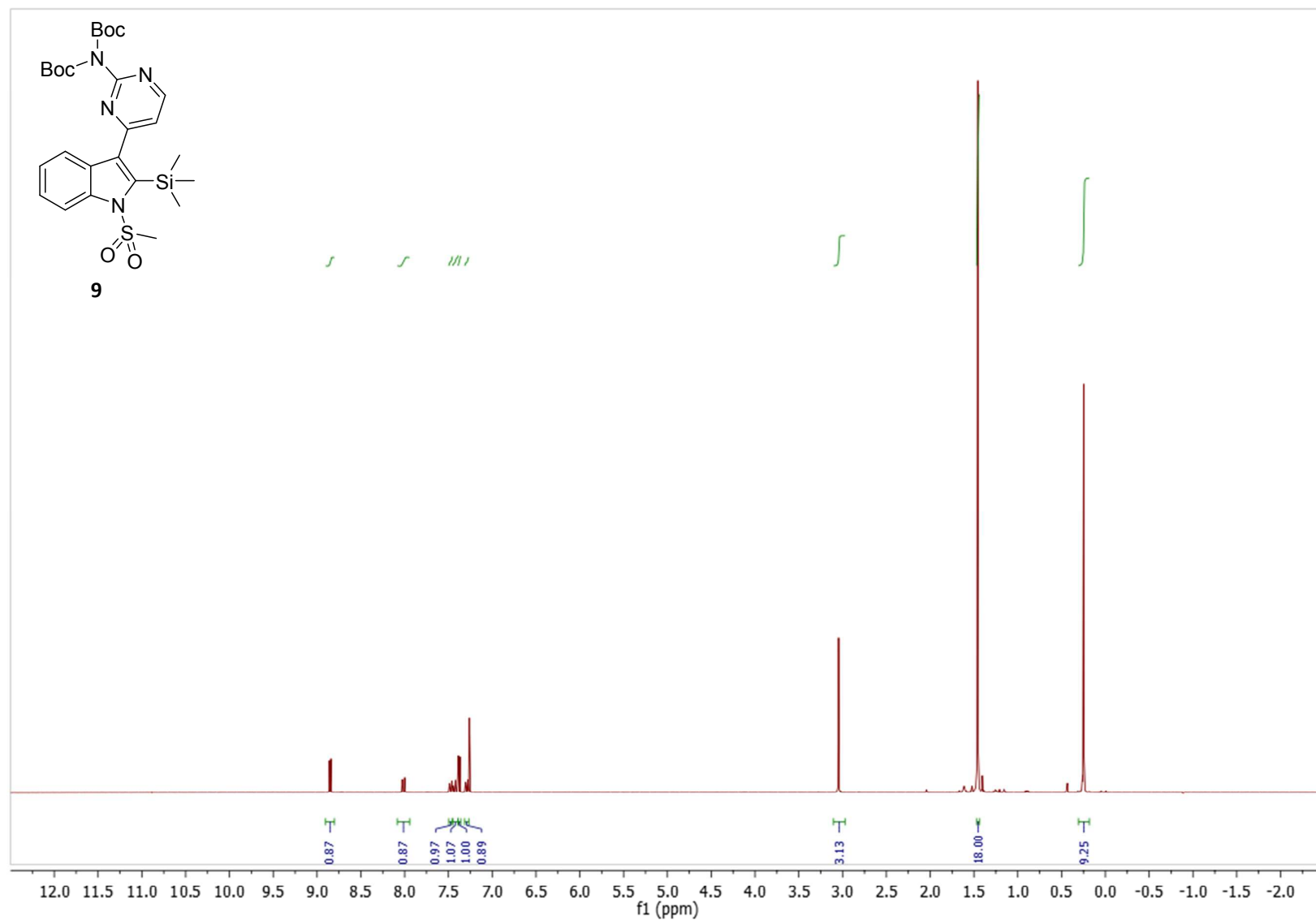


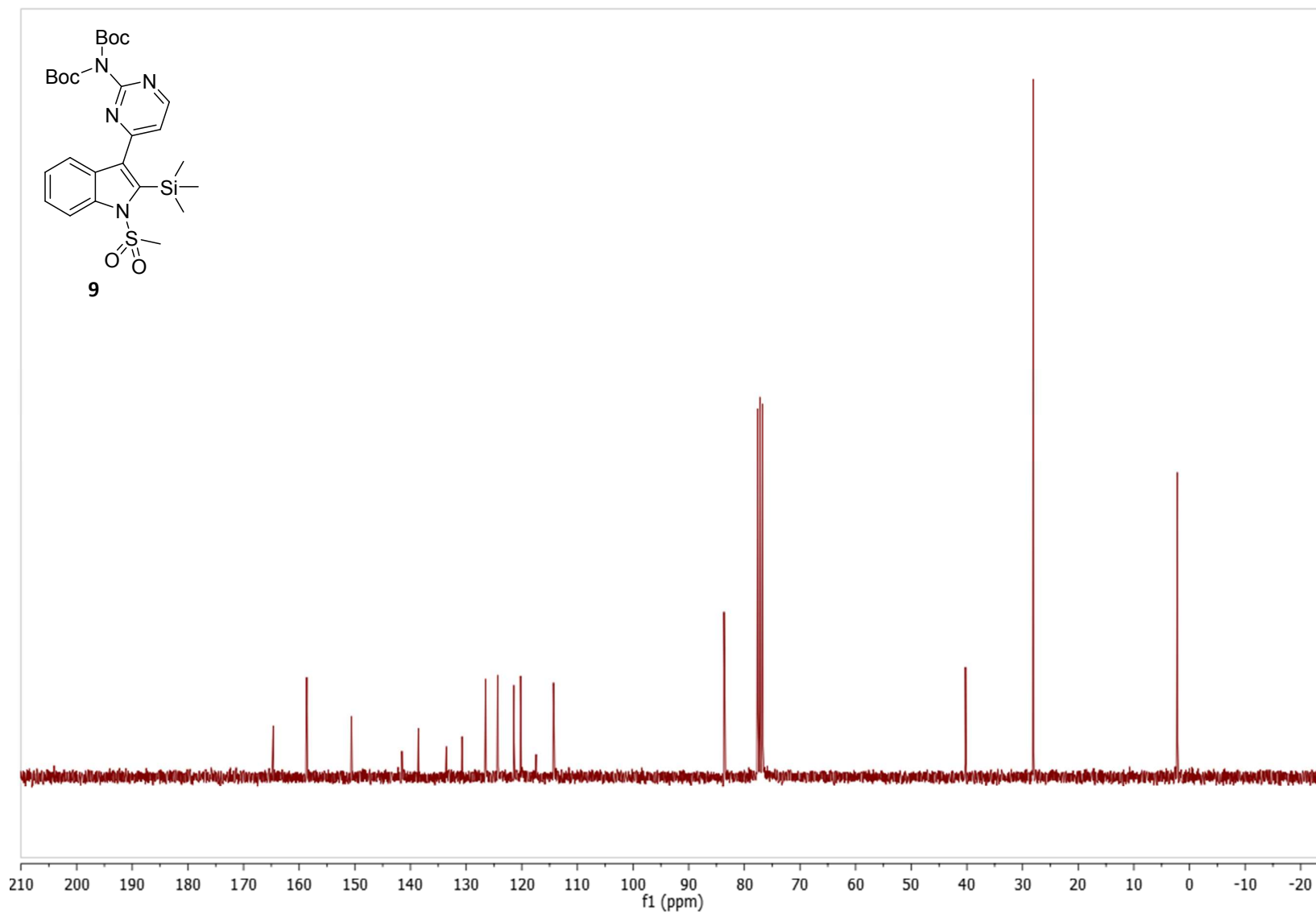


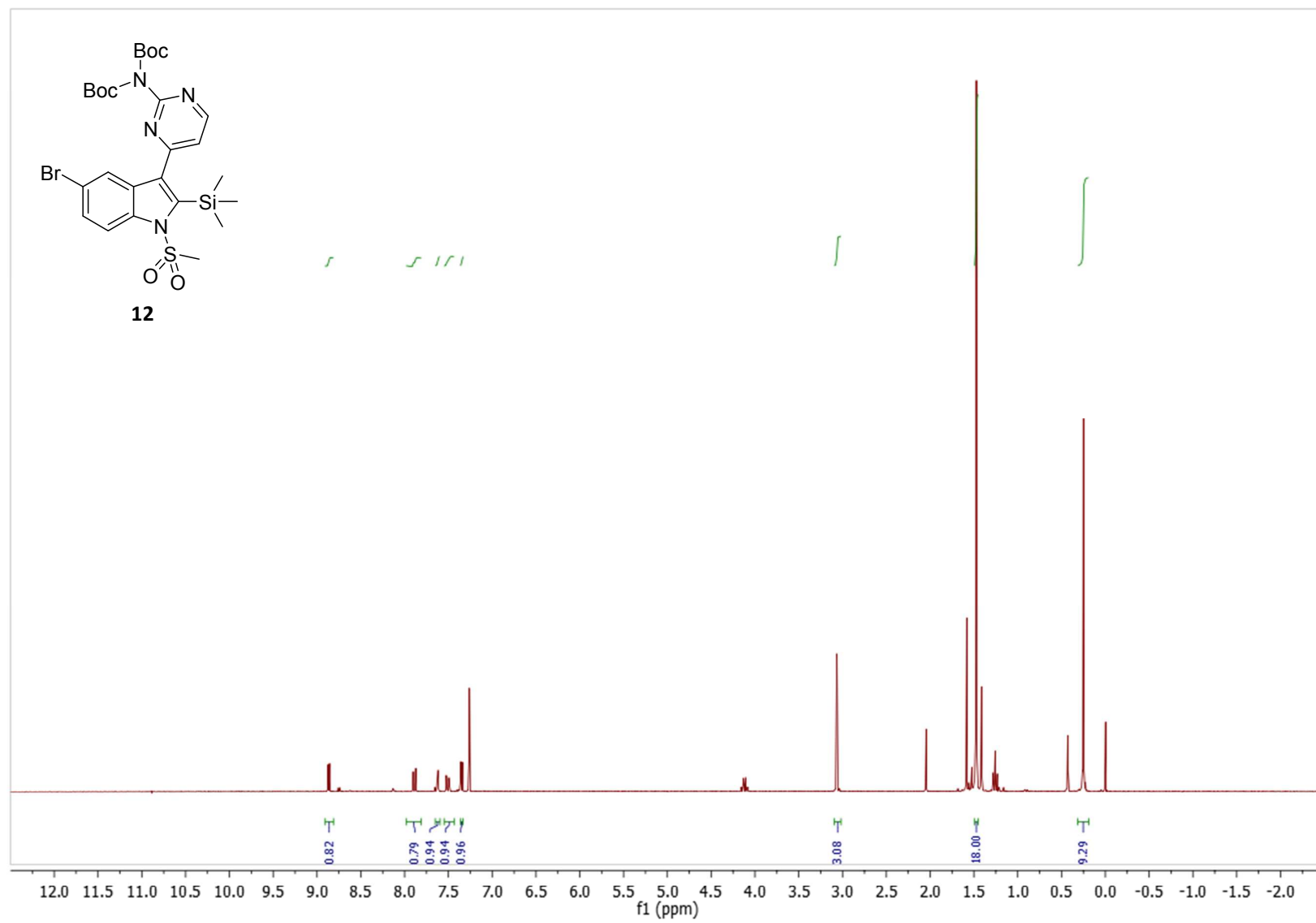


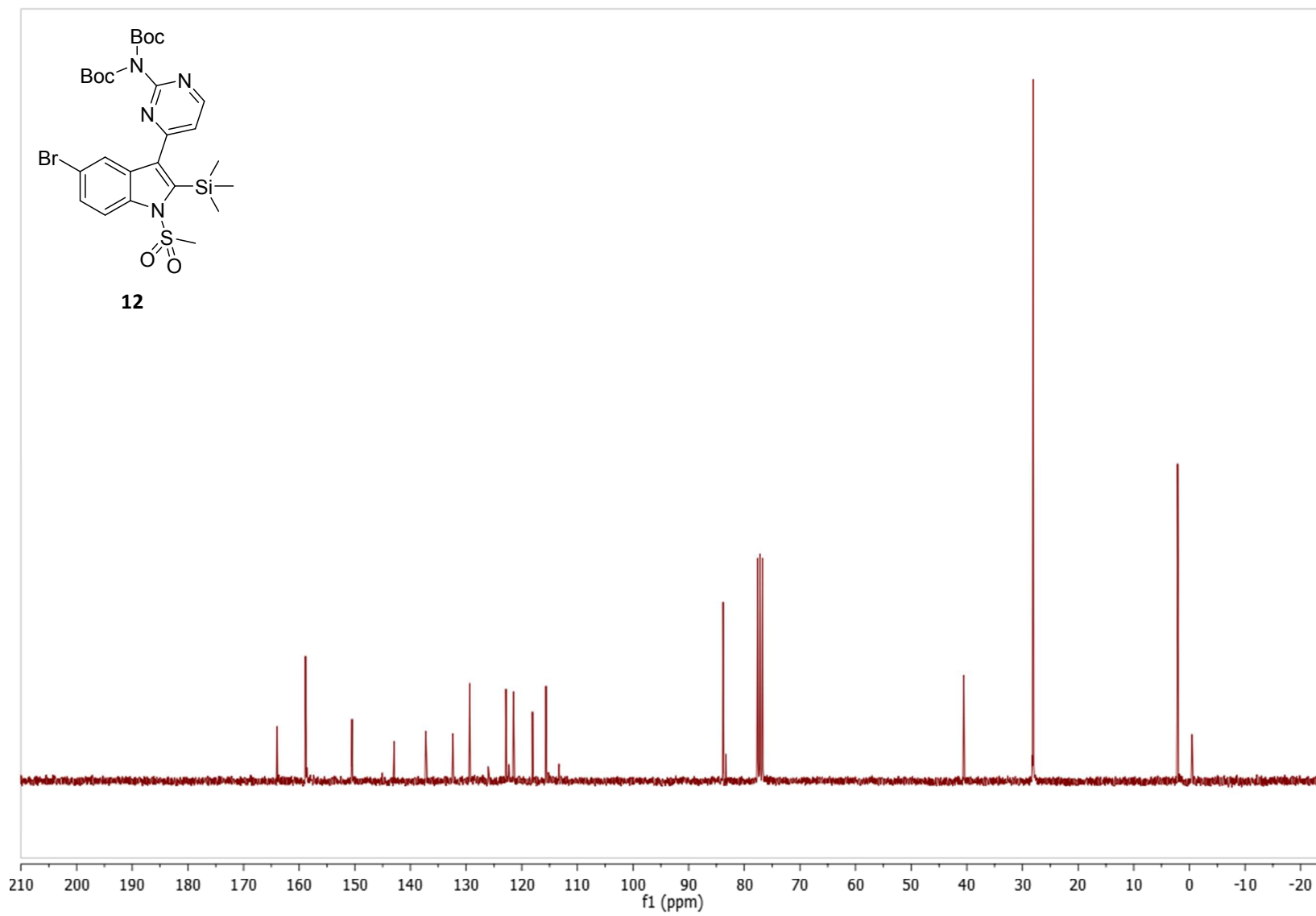


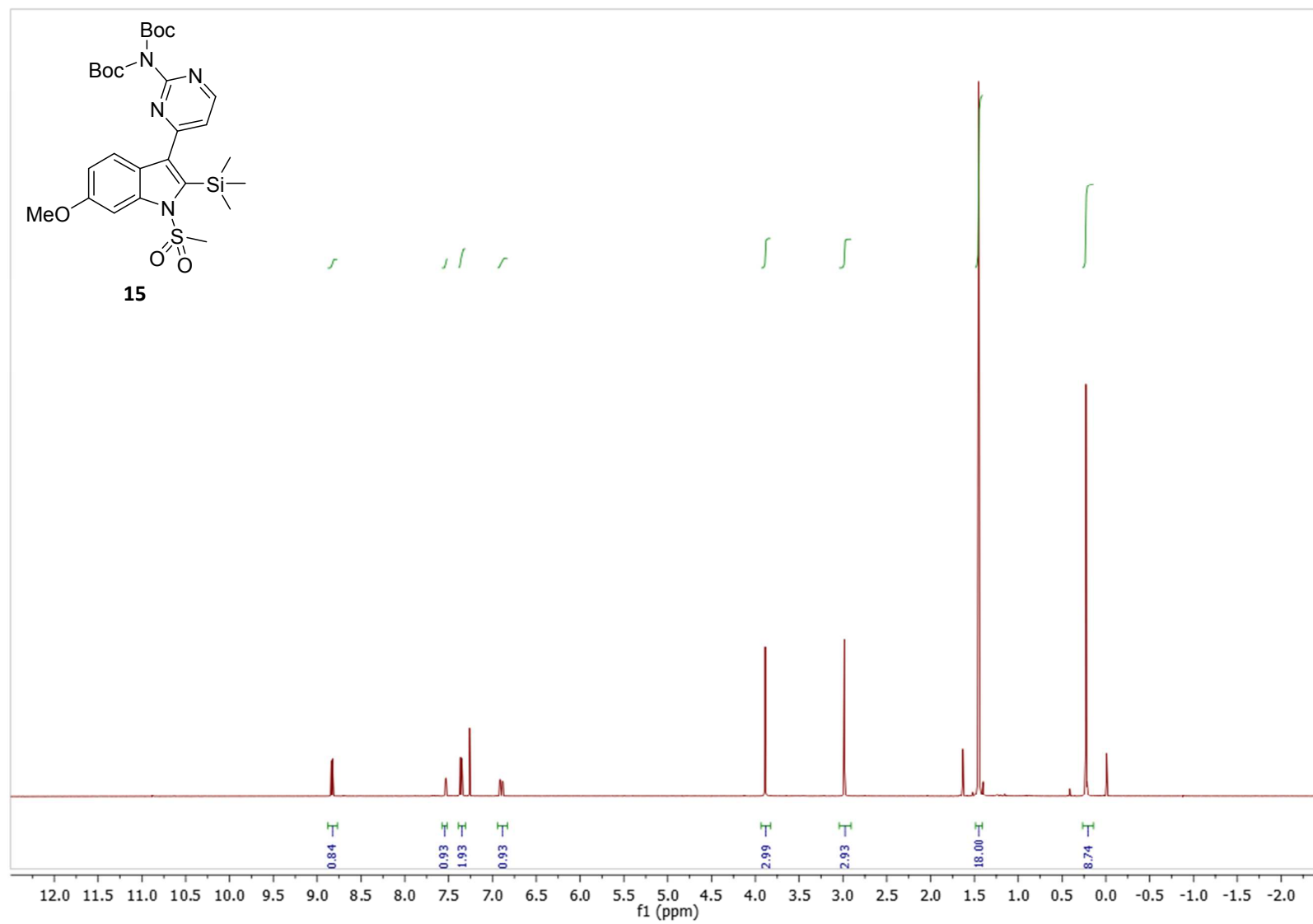


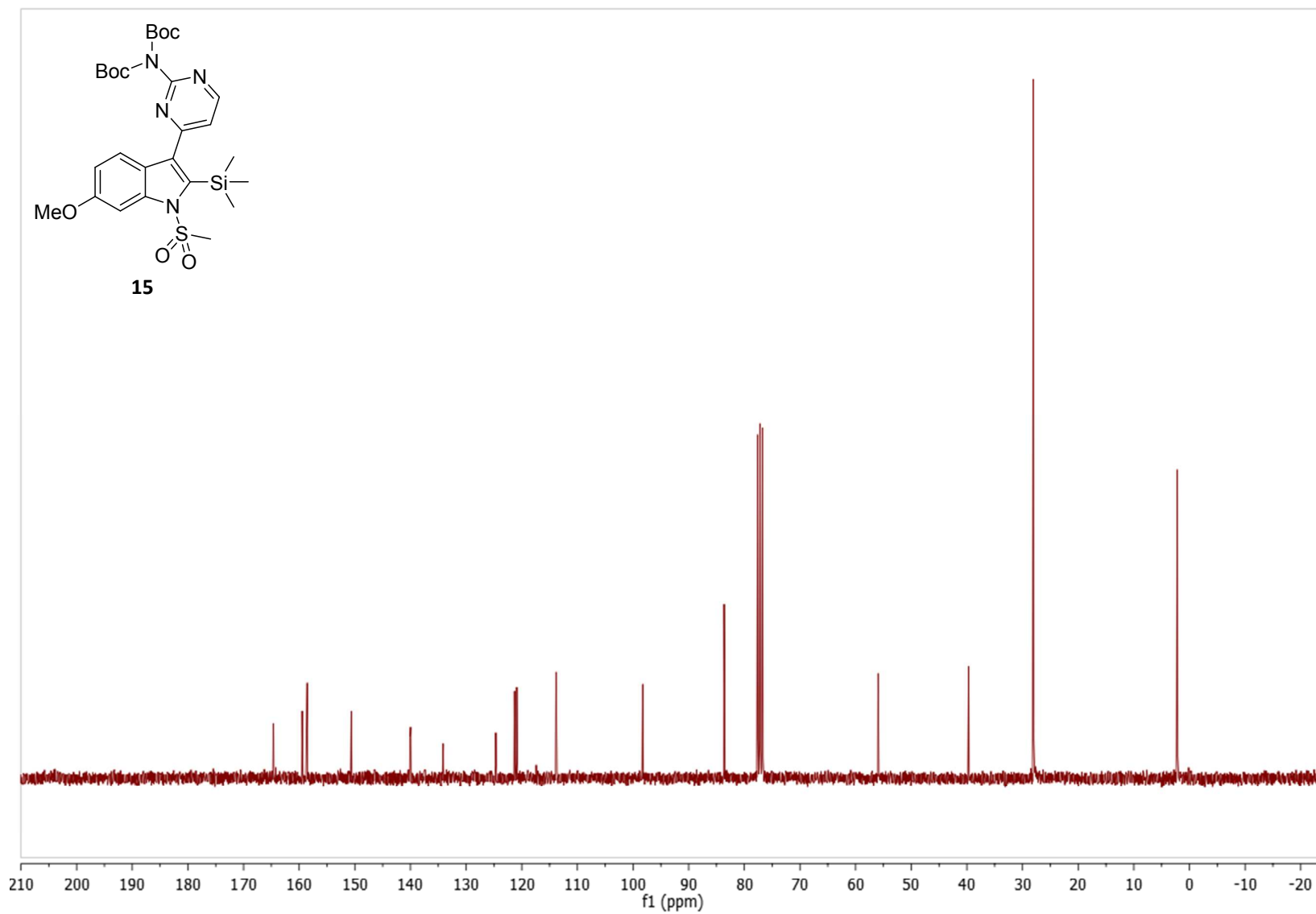


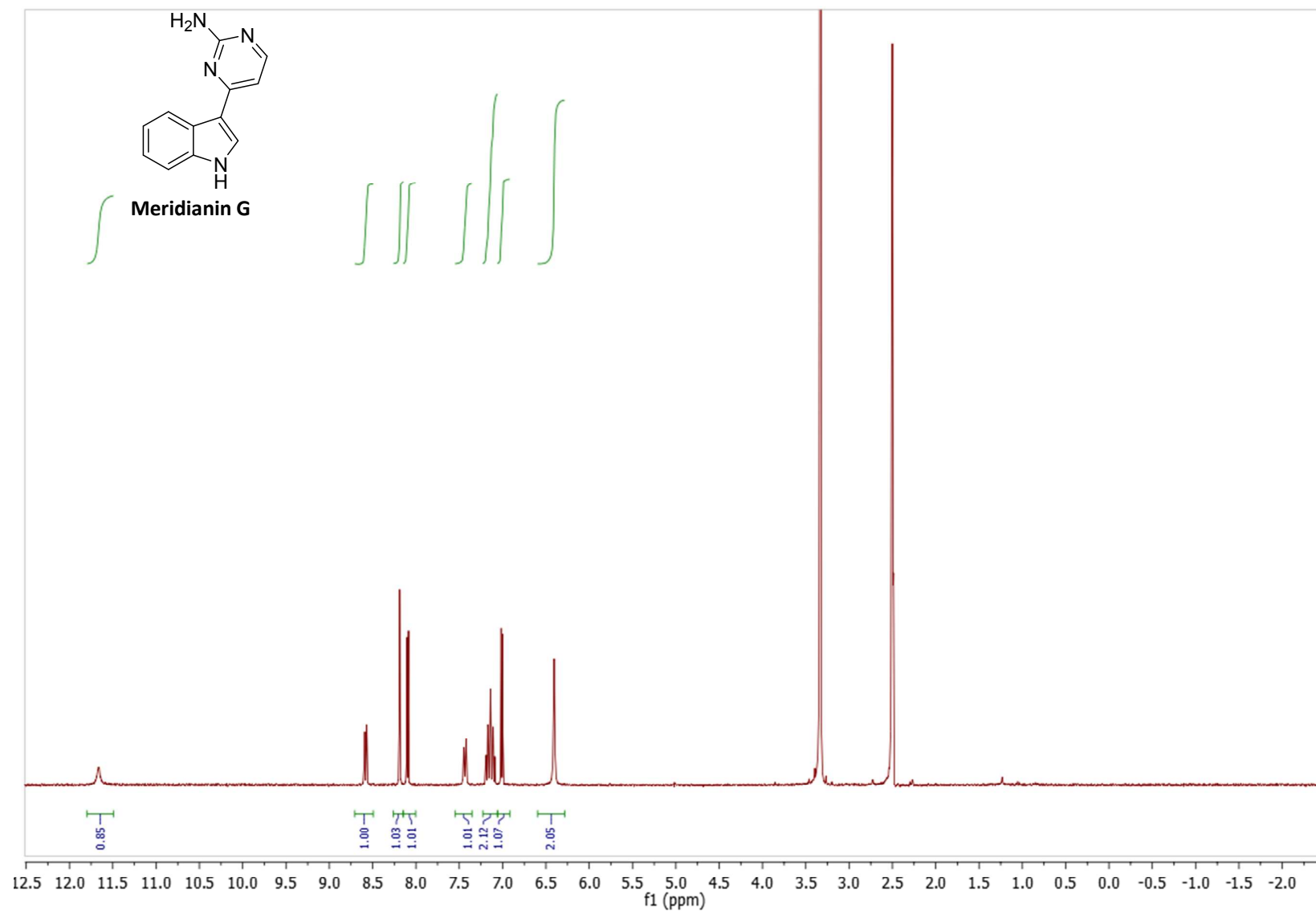


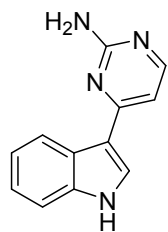




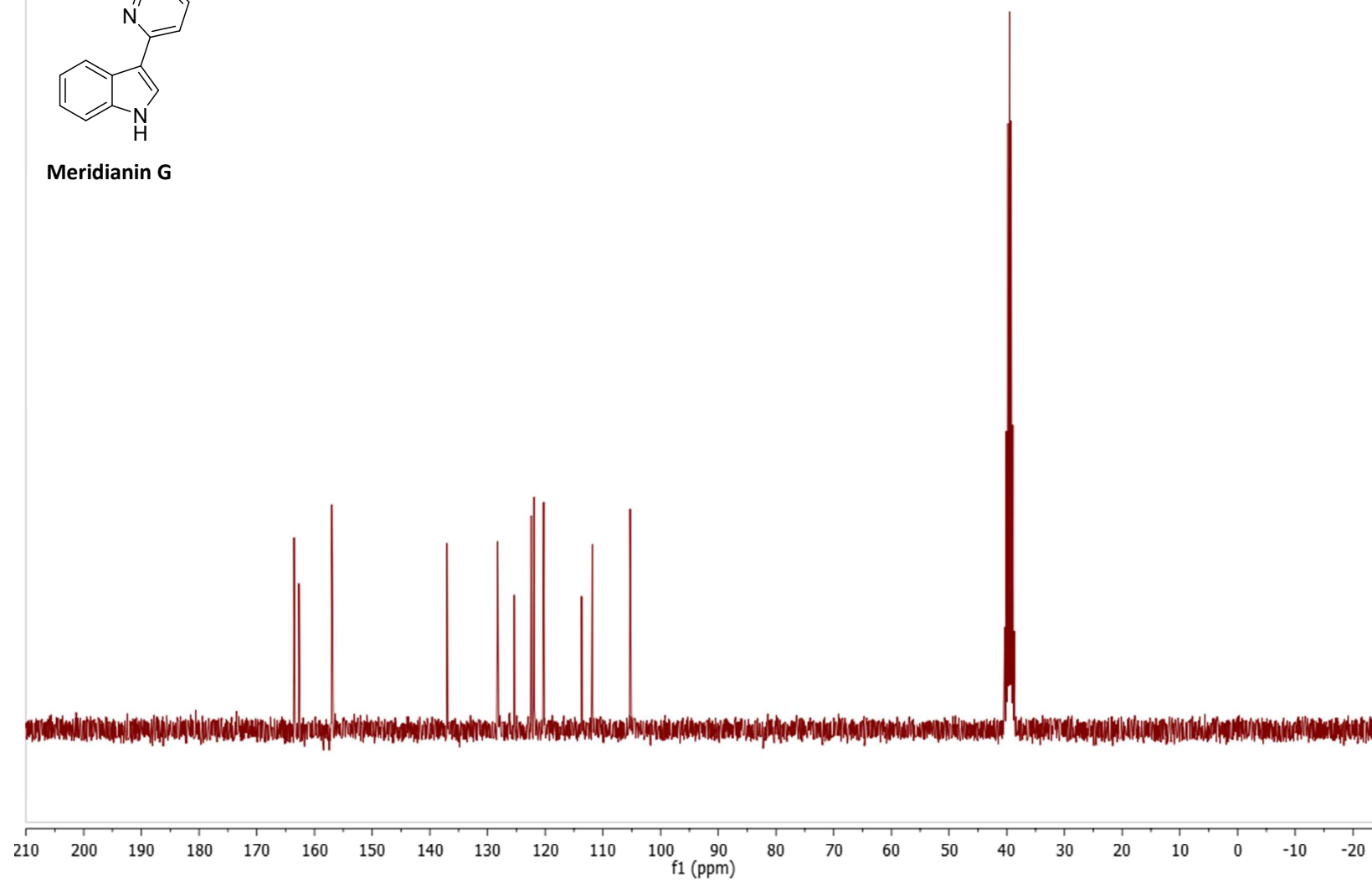


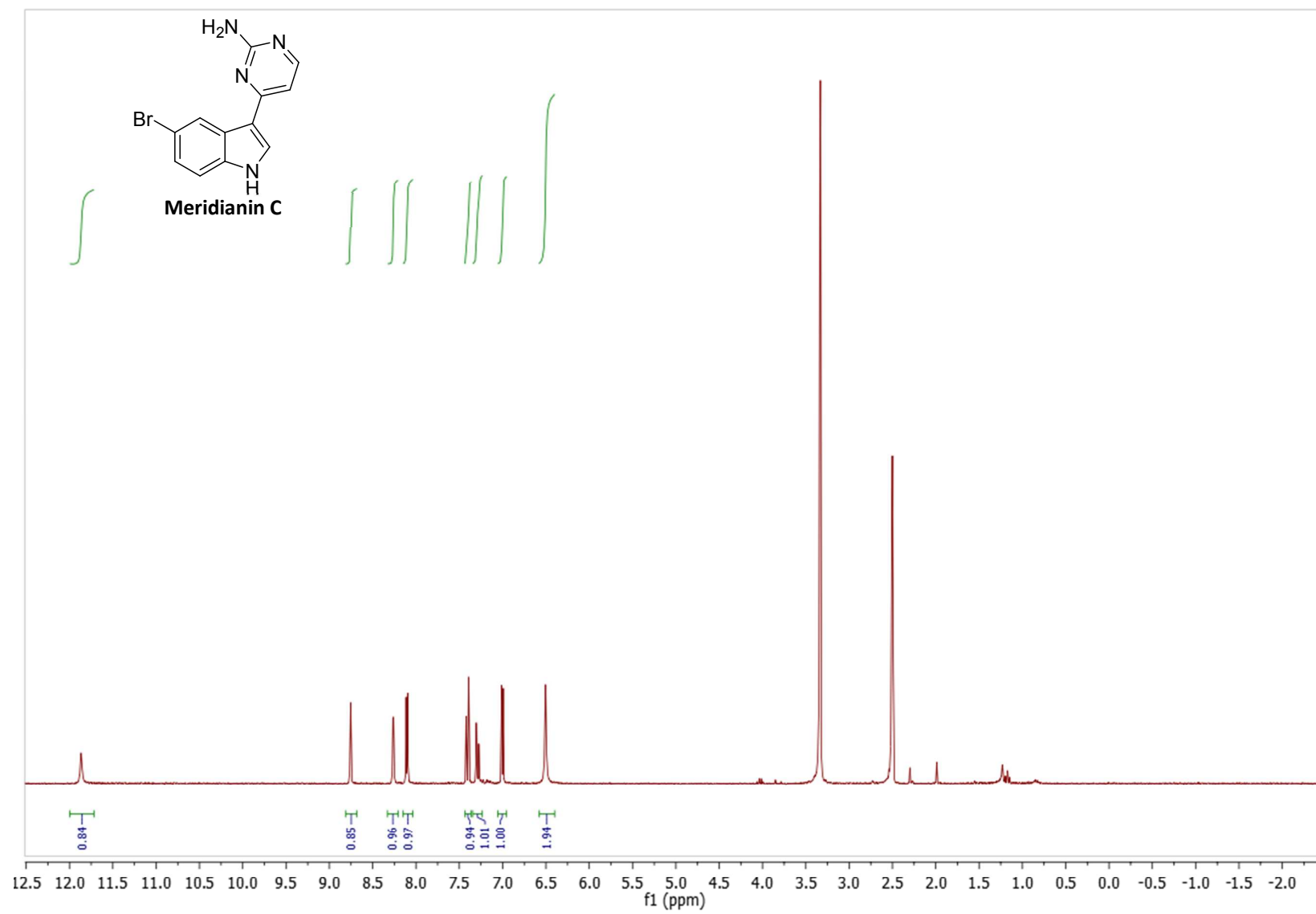


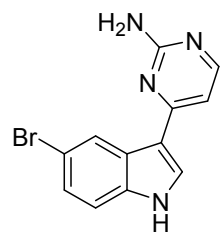




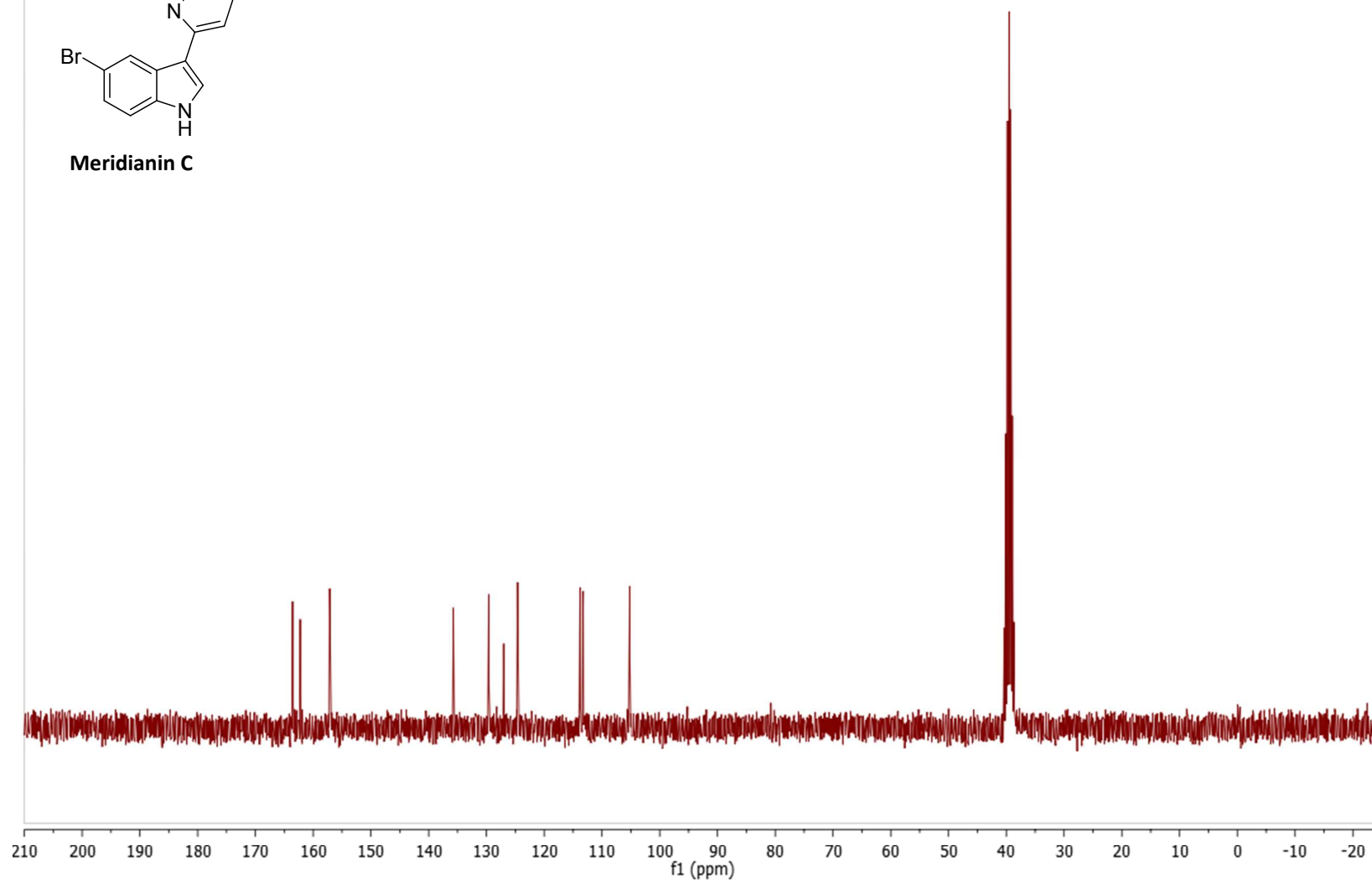
Meridianin G

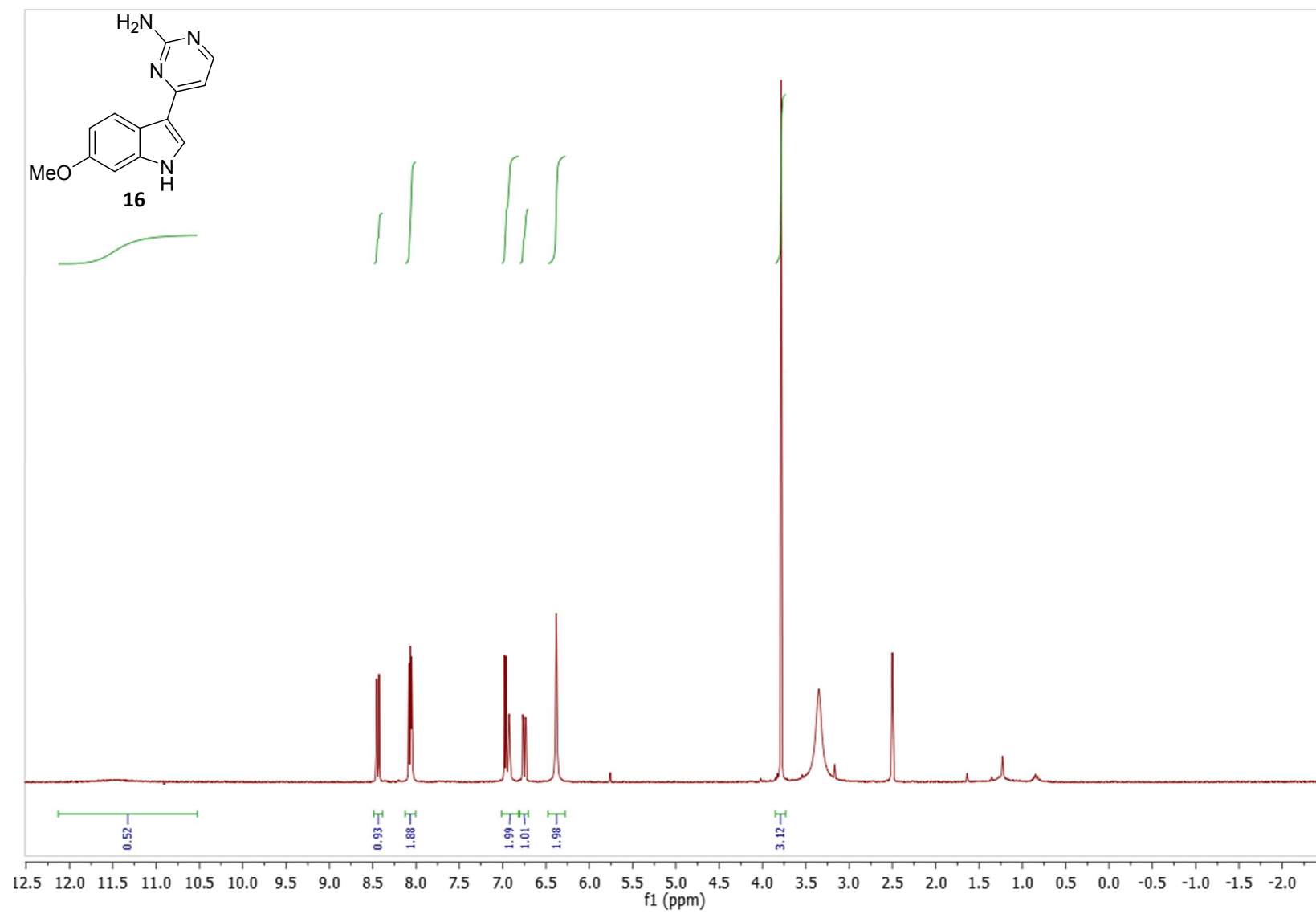


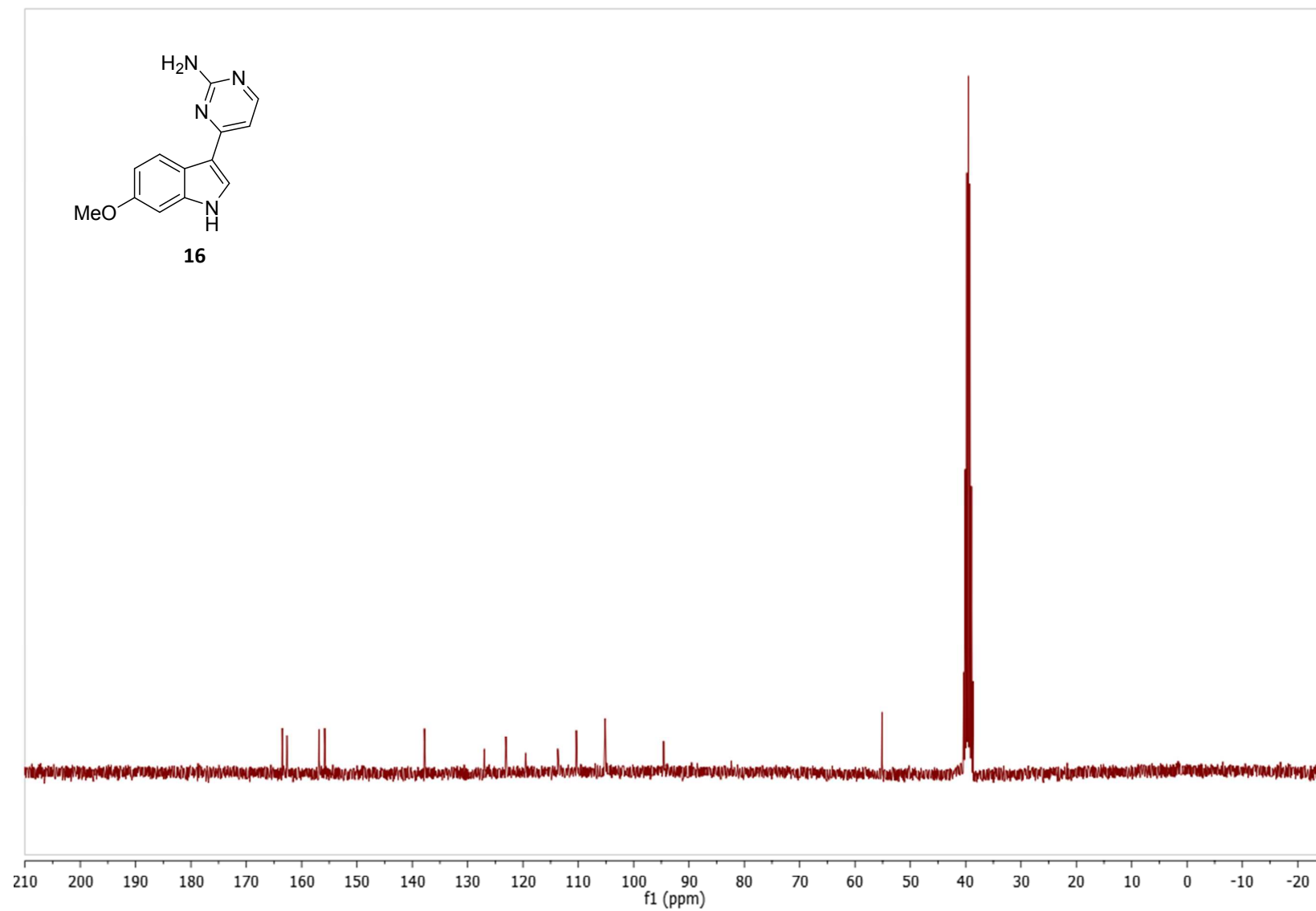
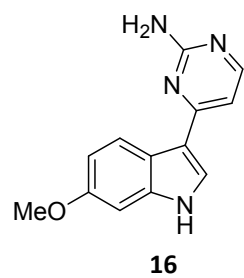




Meridianin C

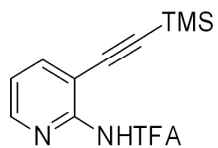






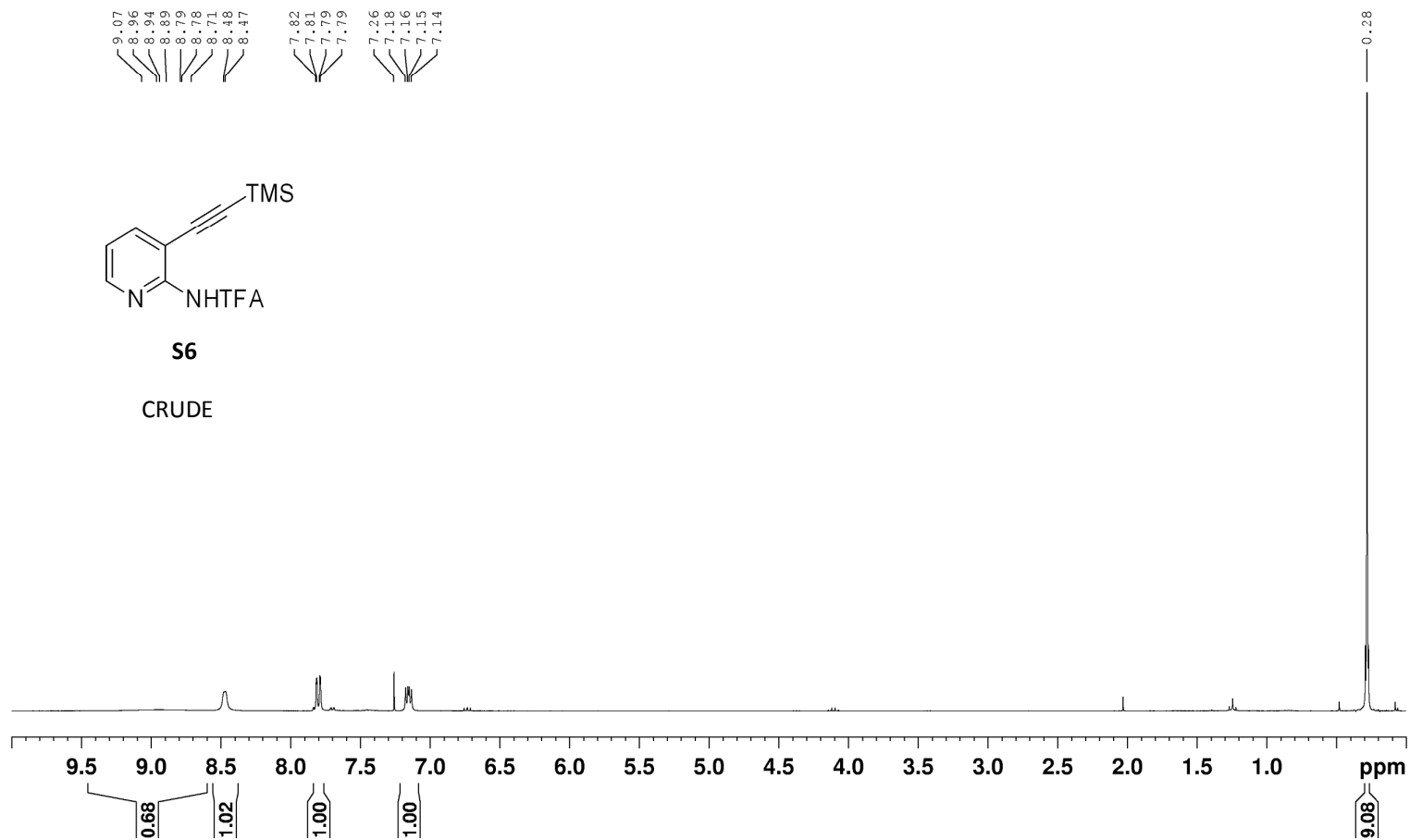
Supervisor Morris
 MC E43 CDC13 300MHz
 1H CDC13 F:\ mlc 38

9.07
8.96
8.94
8.89
8.79
8.78
8.71
8.48
8.47
 7.82
7.81
7.79
7.79
 7.26
7.18
7.16
7.15
7.14

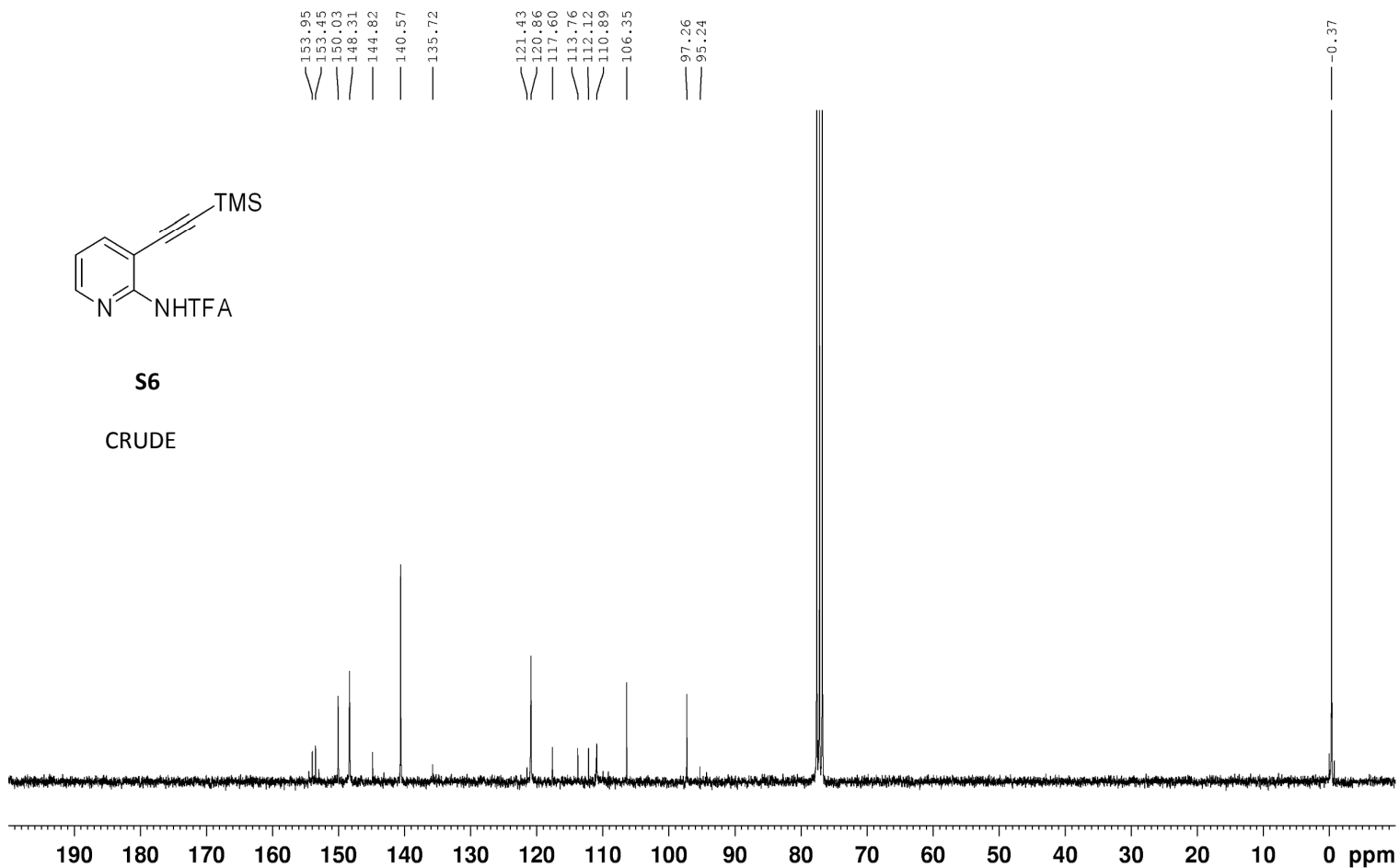


S6

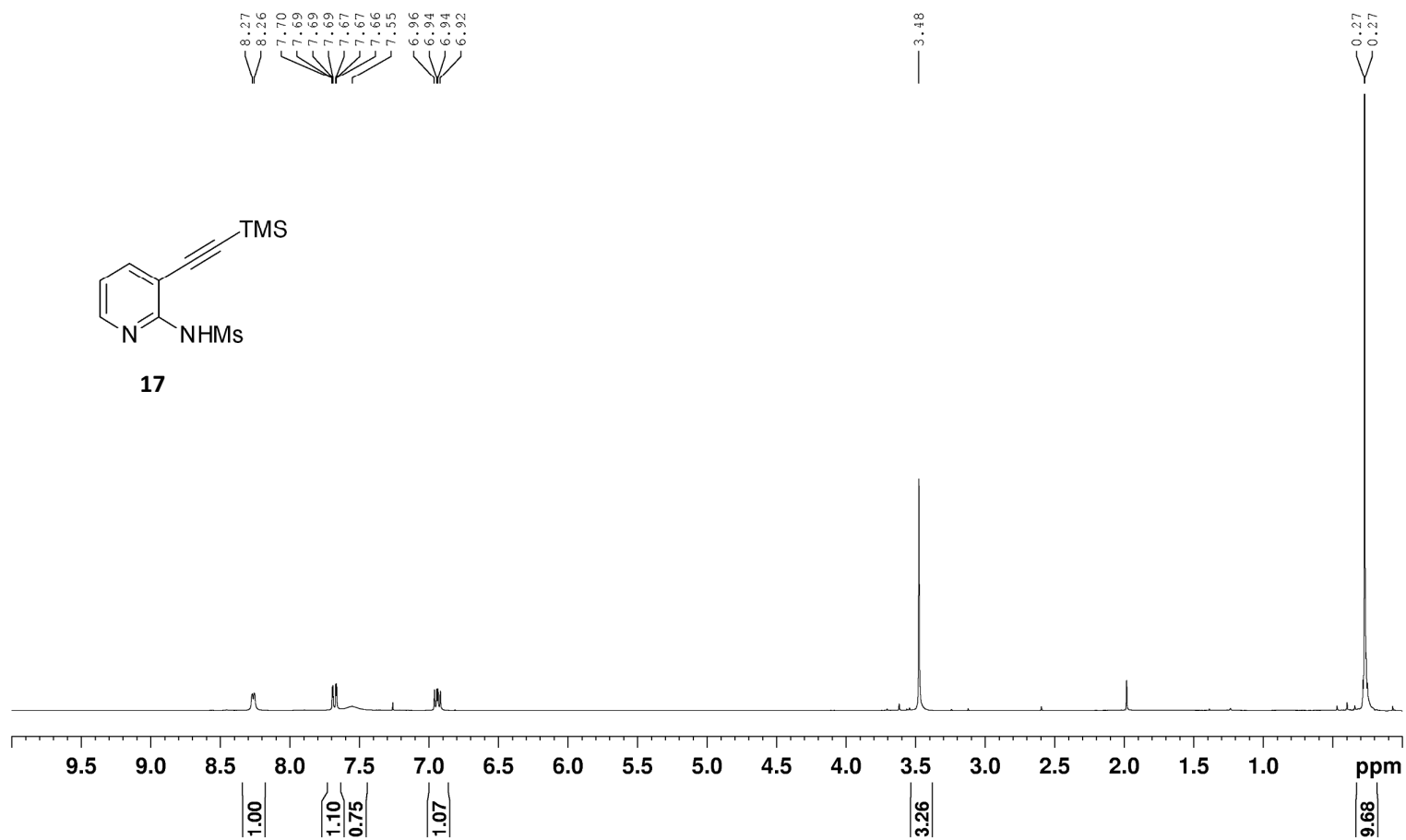
CRUDE



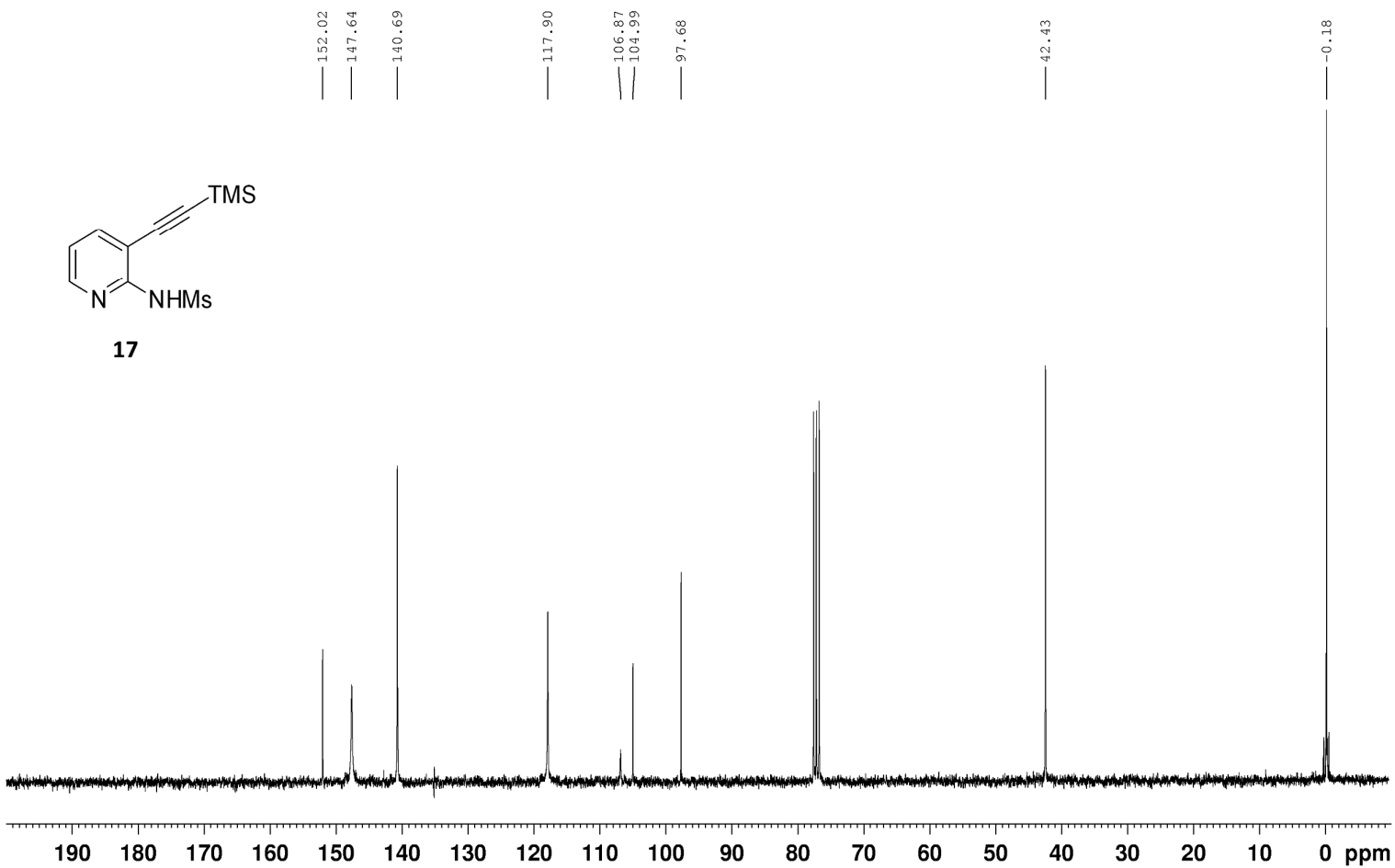
Supervisor Morris
MC E43 CDCl3 300MHz
13C.day CDCl3 F:\ mlc 38



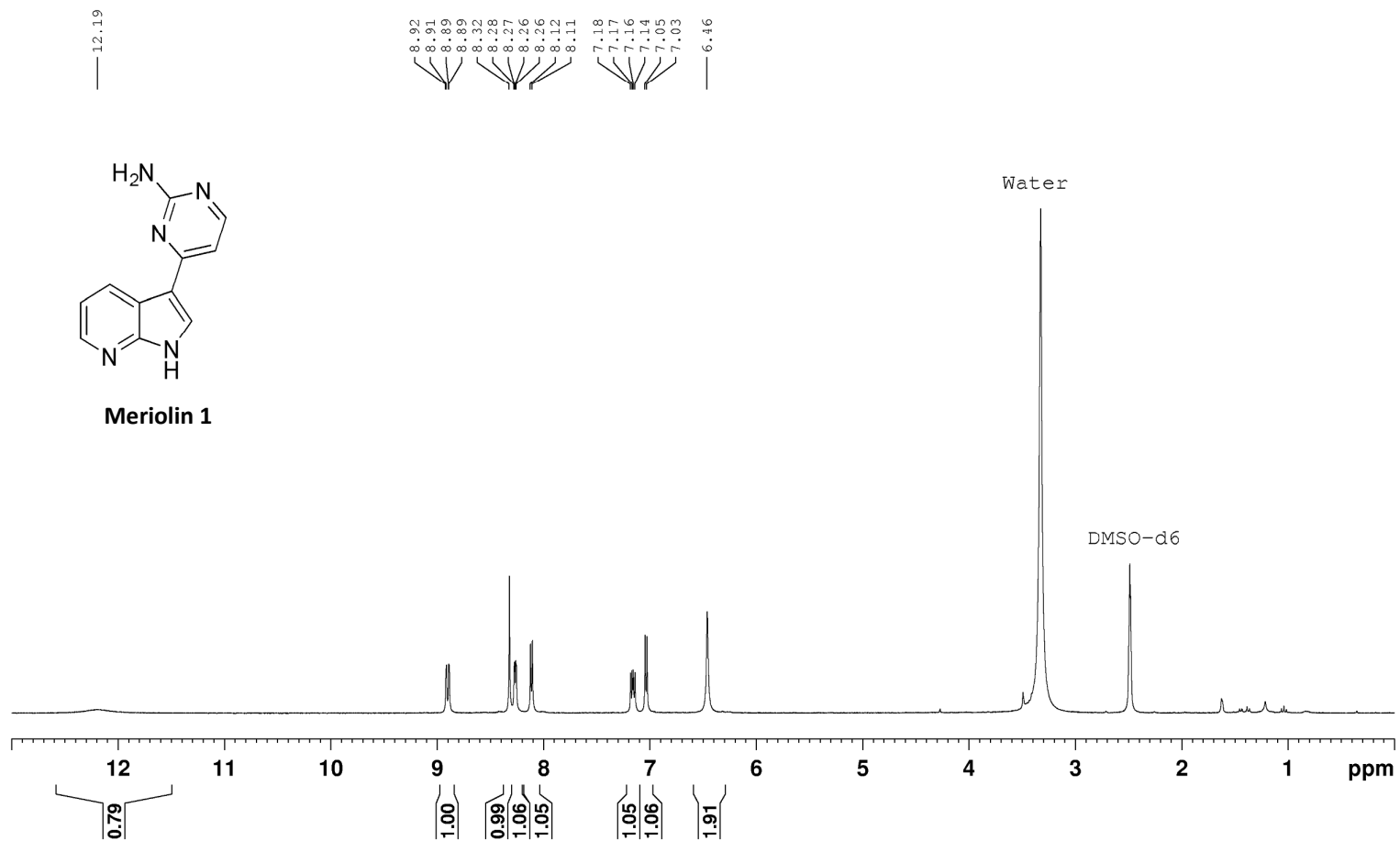
MC E45 CDCl3 300MHz



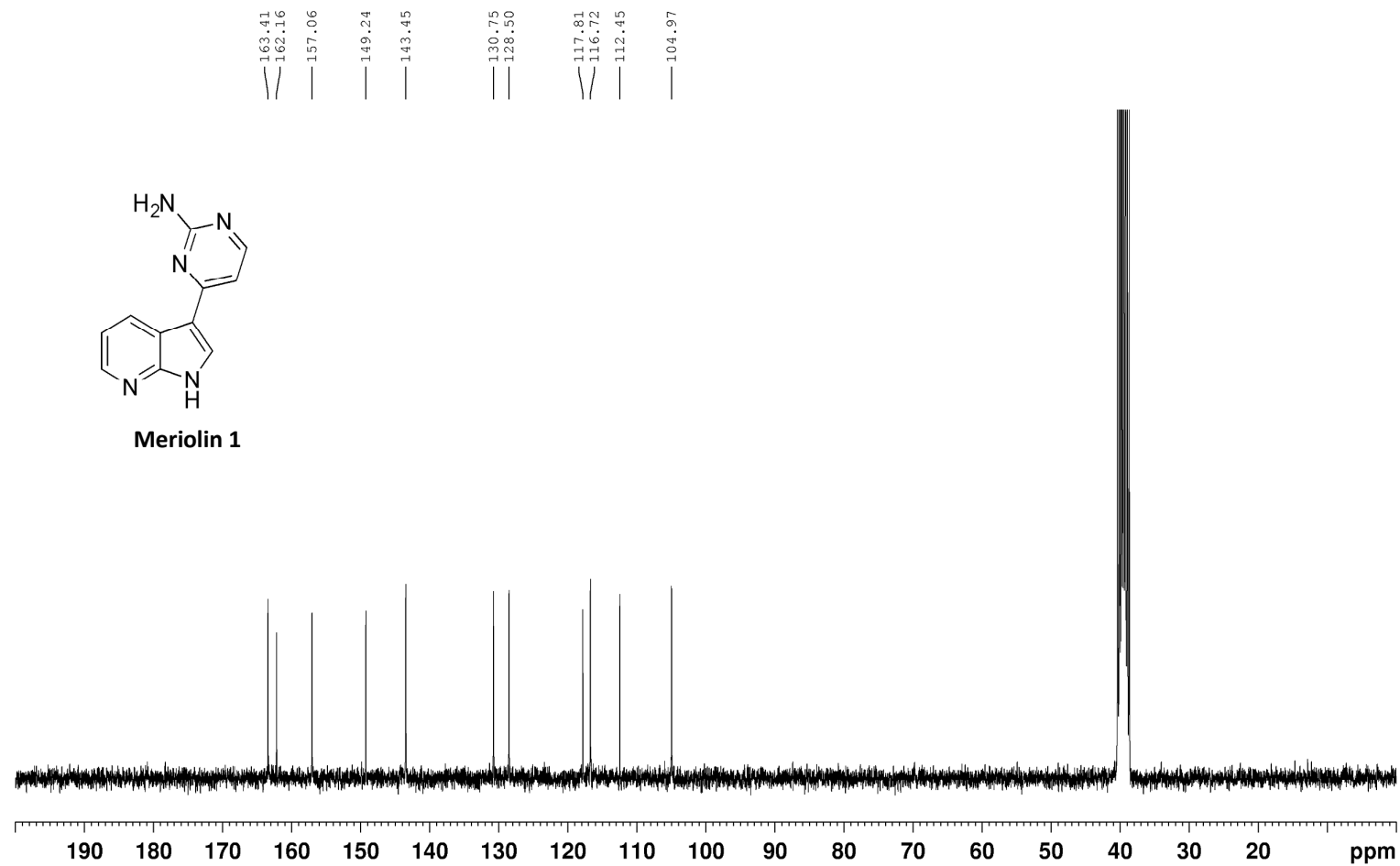
MC E45 CDCl3 300MHz



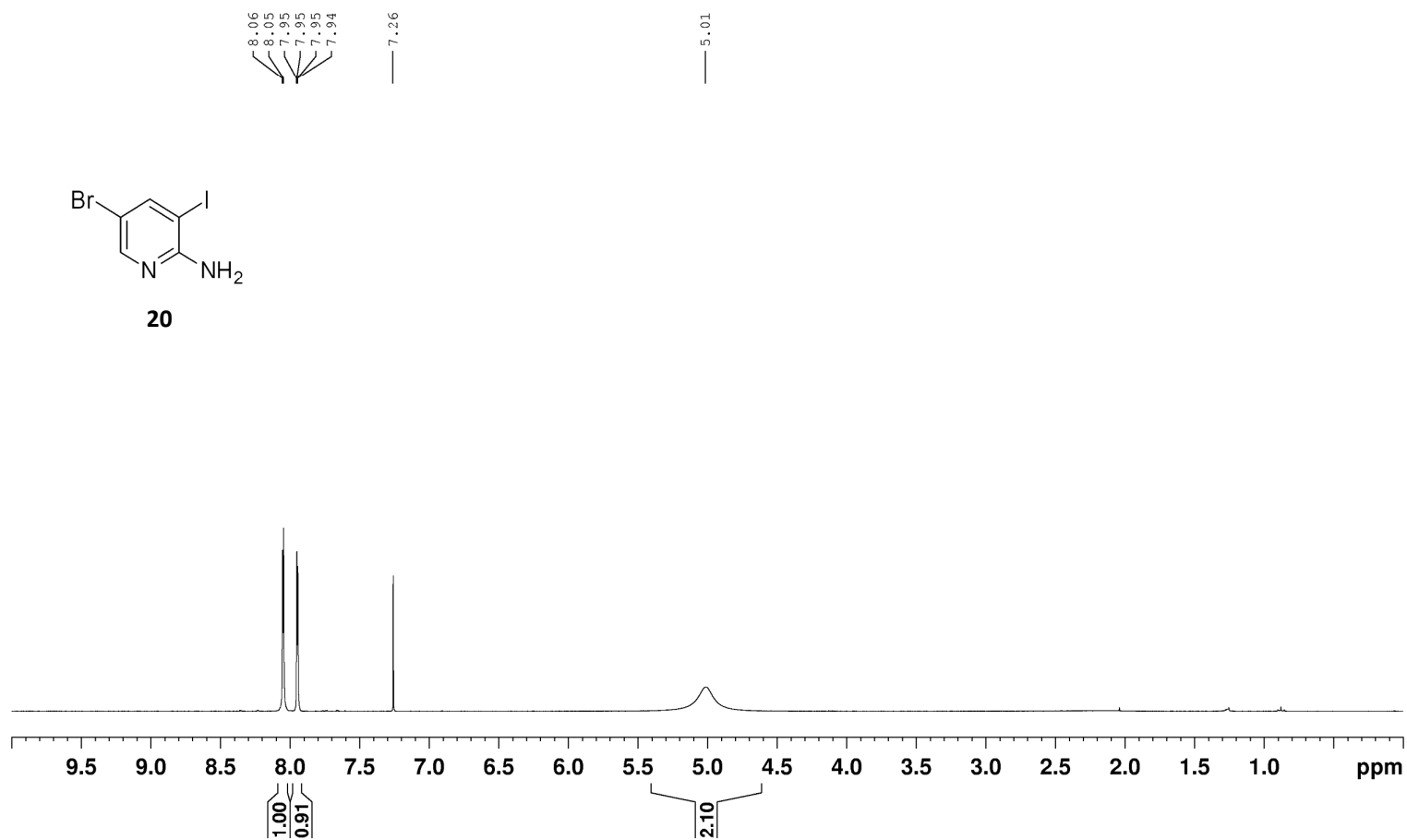
MC E52 (2) DMSO d6 300MHz



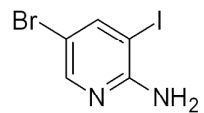
Supervisor Morris
MC E52 DMSO-d6 300MHz
13C.day DMSO F:\ mlc 27



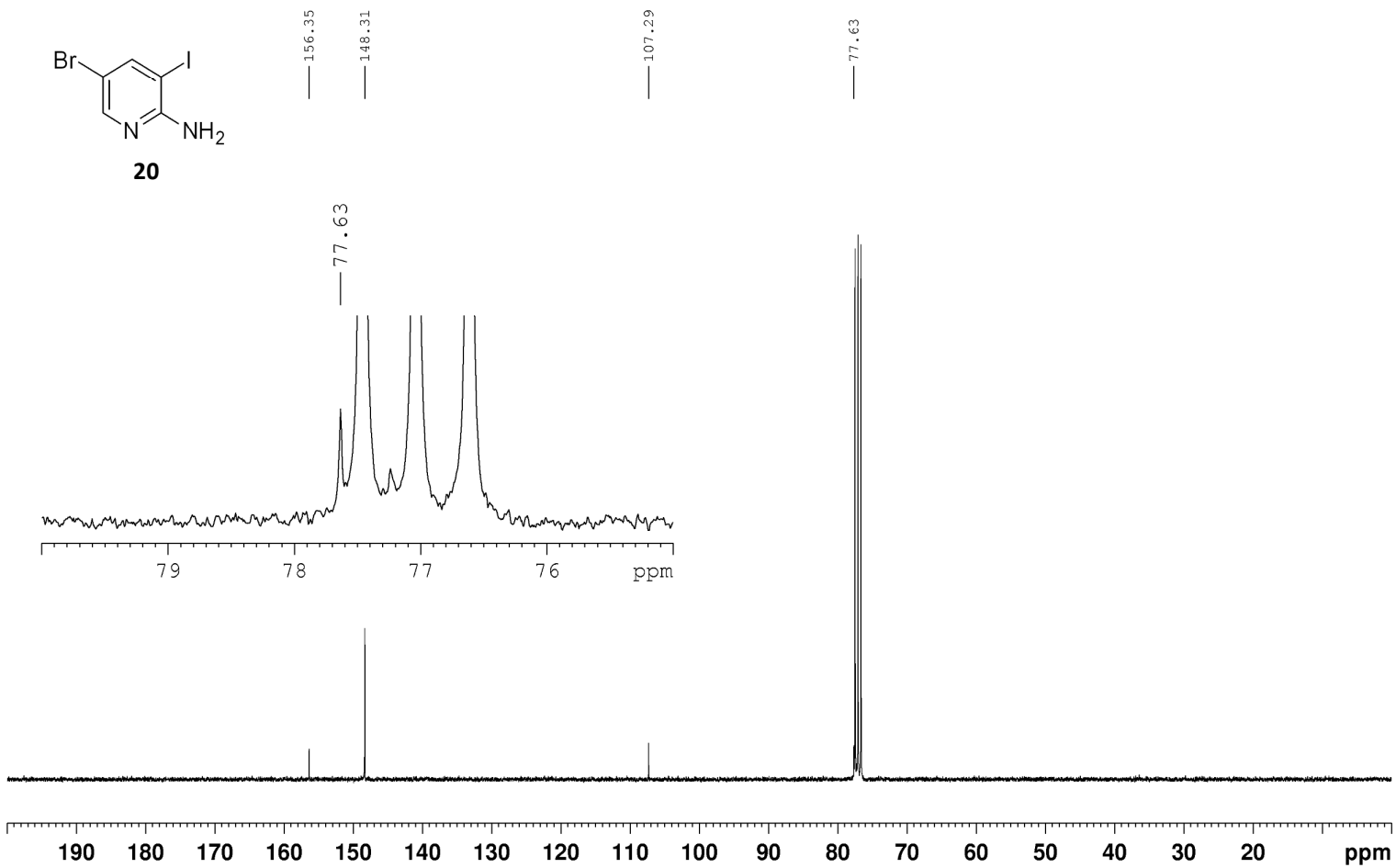
Supervisor Morris
MC E26 CDCl3 300MHz
1H CDCl3 F:\ mlc 11



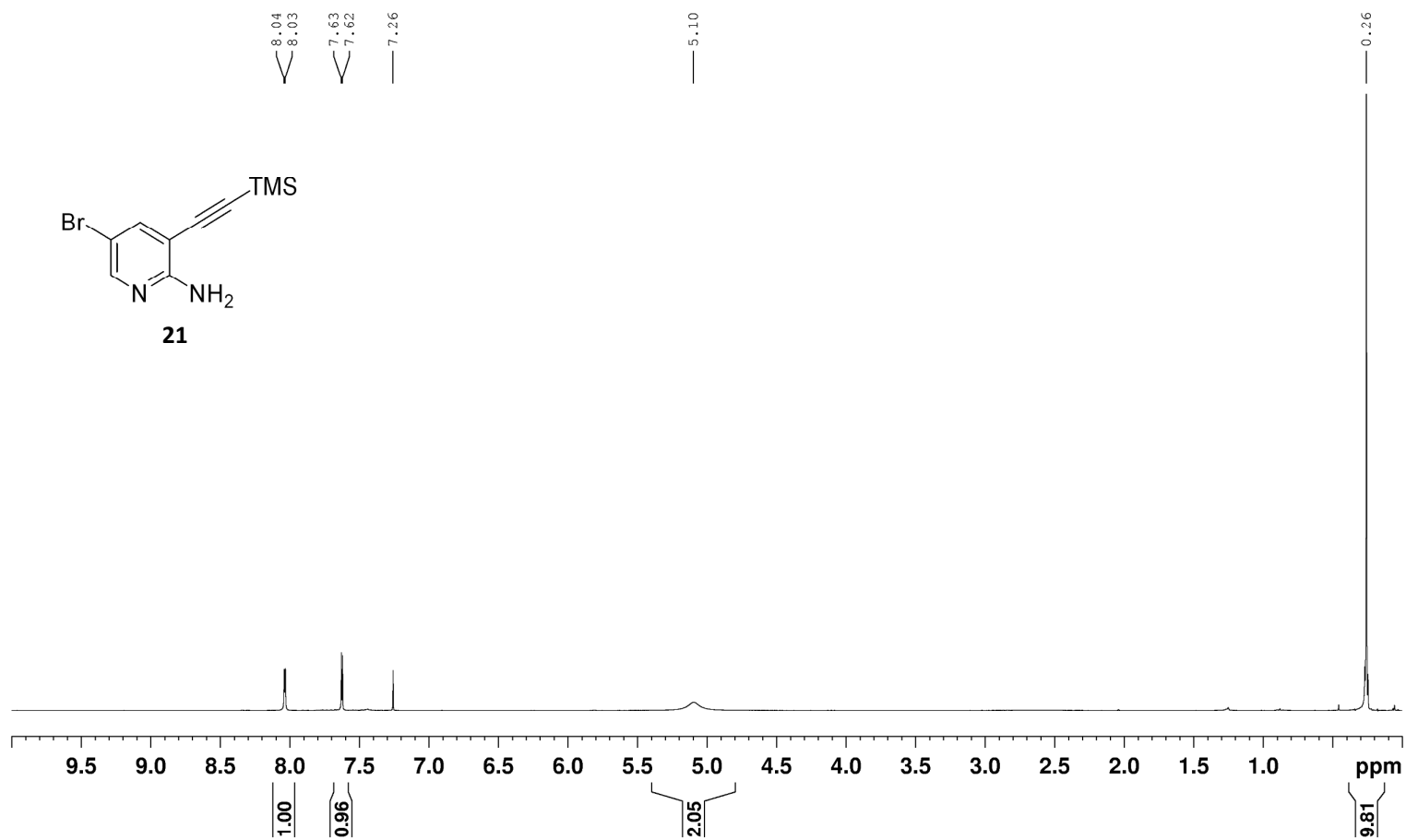
Supervisor Morris
MC E40 CDCl3 300MHz
13C.day CDCl3 F:\ mlc 37



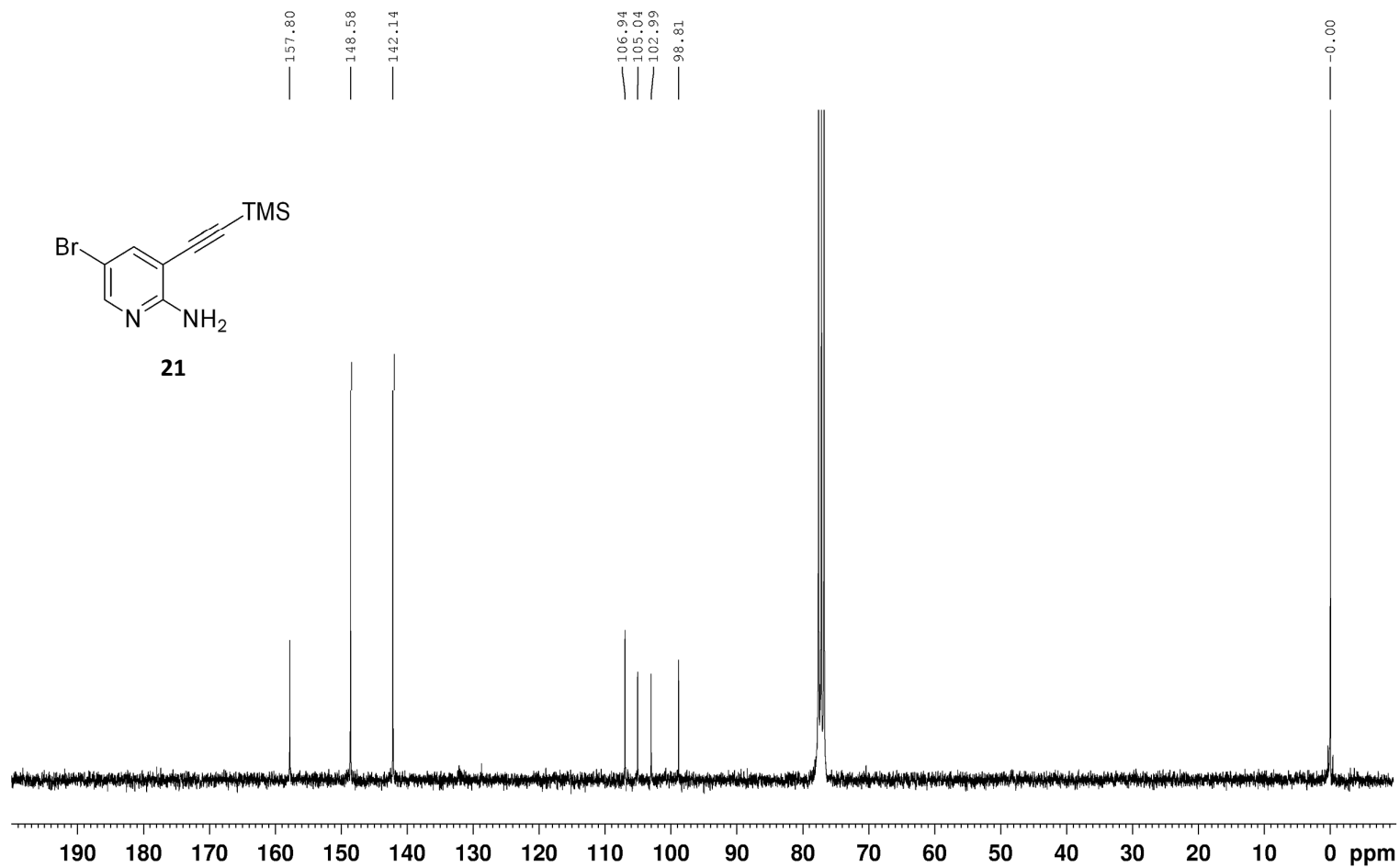
20



Supervisor Morris
MC E28 CDCl3 300MHz
1H CDCl3 F:\ mlc 4

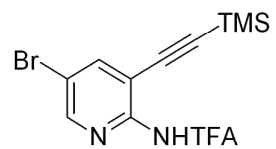


Supervisor Morris
 MC E28 CDCl3 300MHz
 13C{1H} CDCl3 F:\ mlc 3



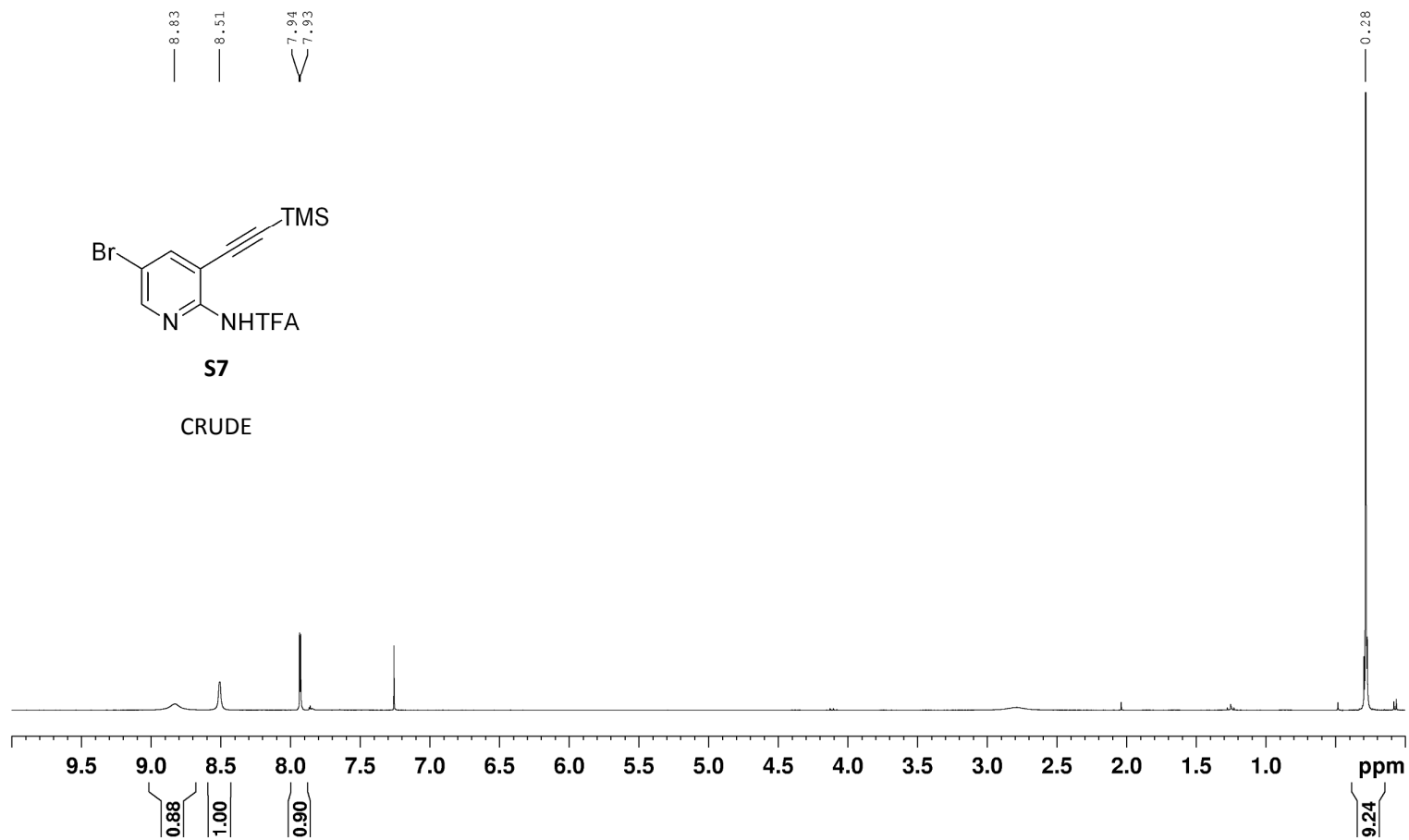
Supervisor Morris
MC E44 CDCl3 300MHz
1H CDCl3 F:\ mlc 39

8.83
8.51
7.94
7.93

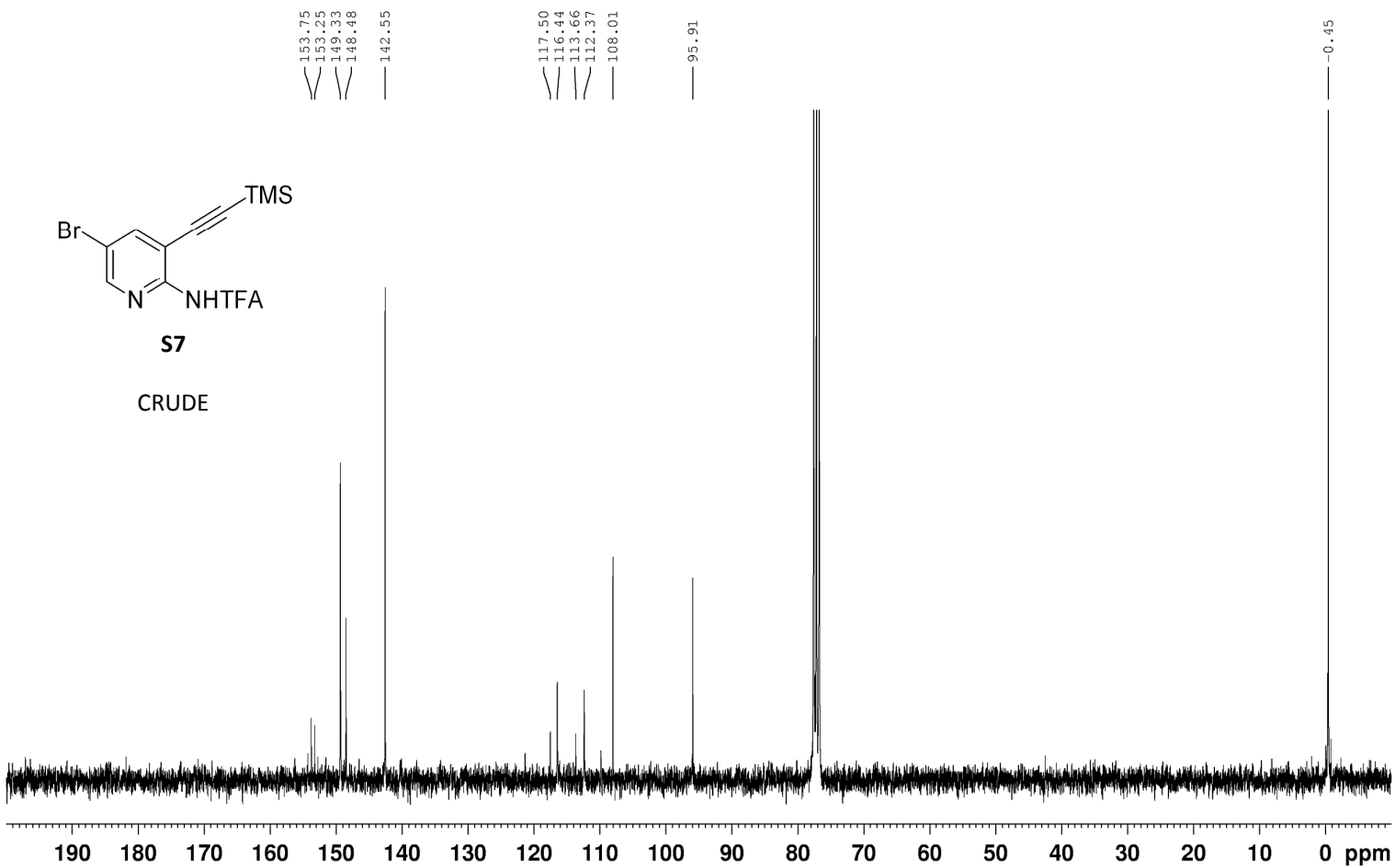


S7

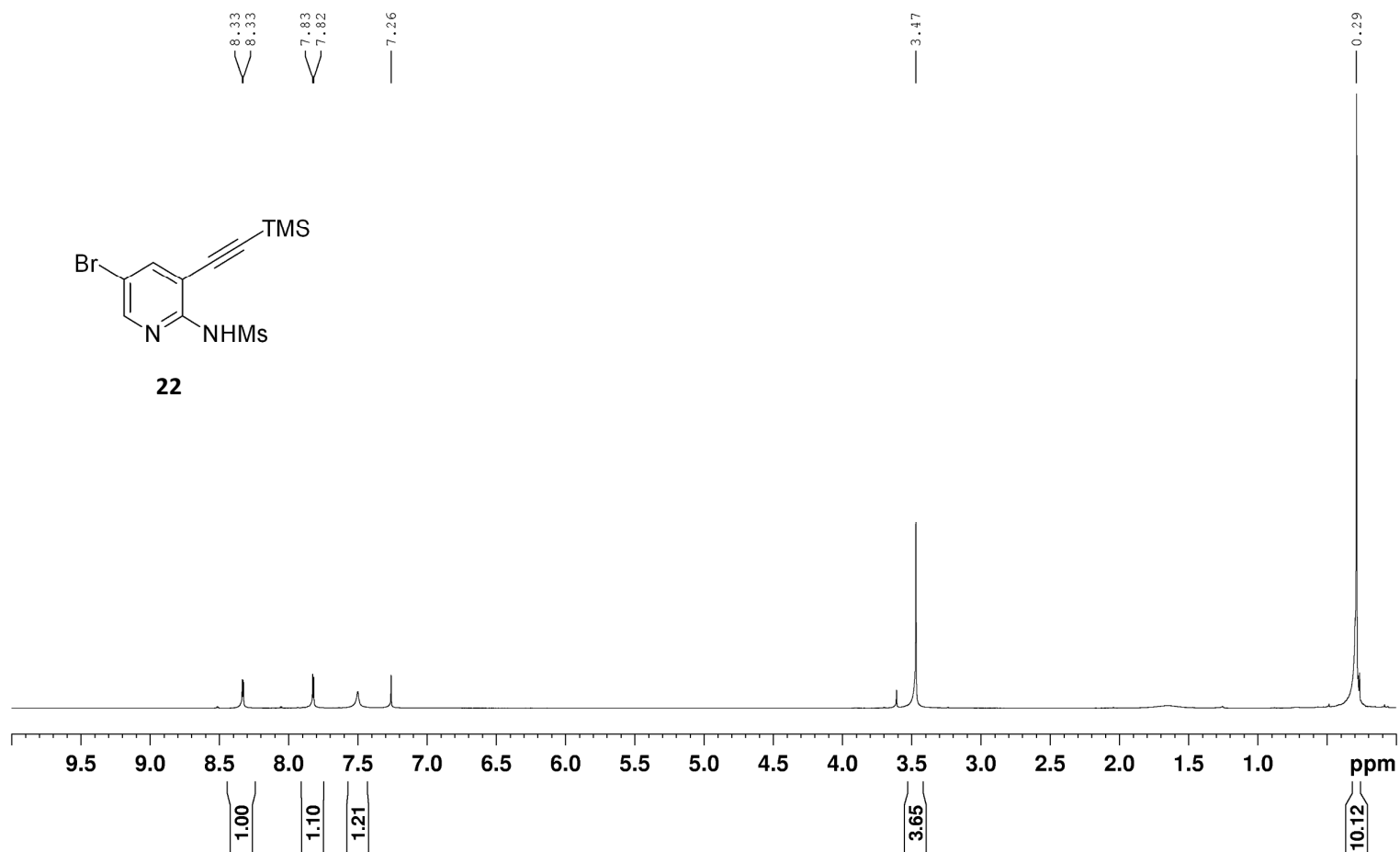
CRUDE



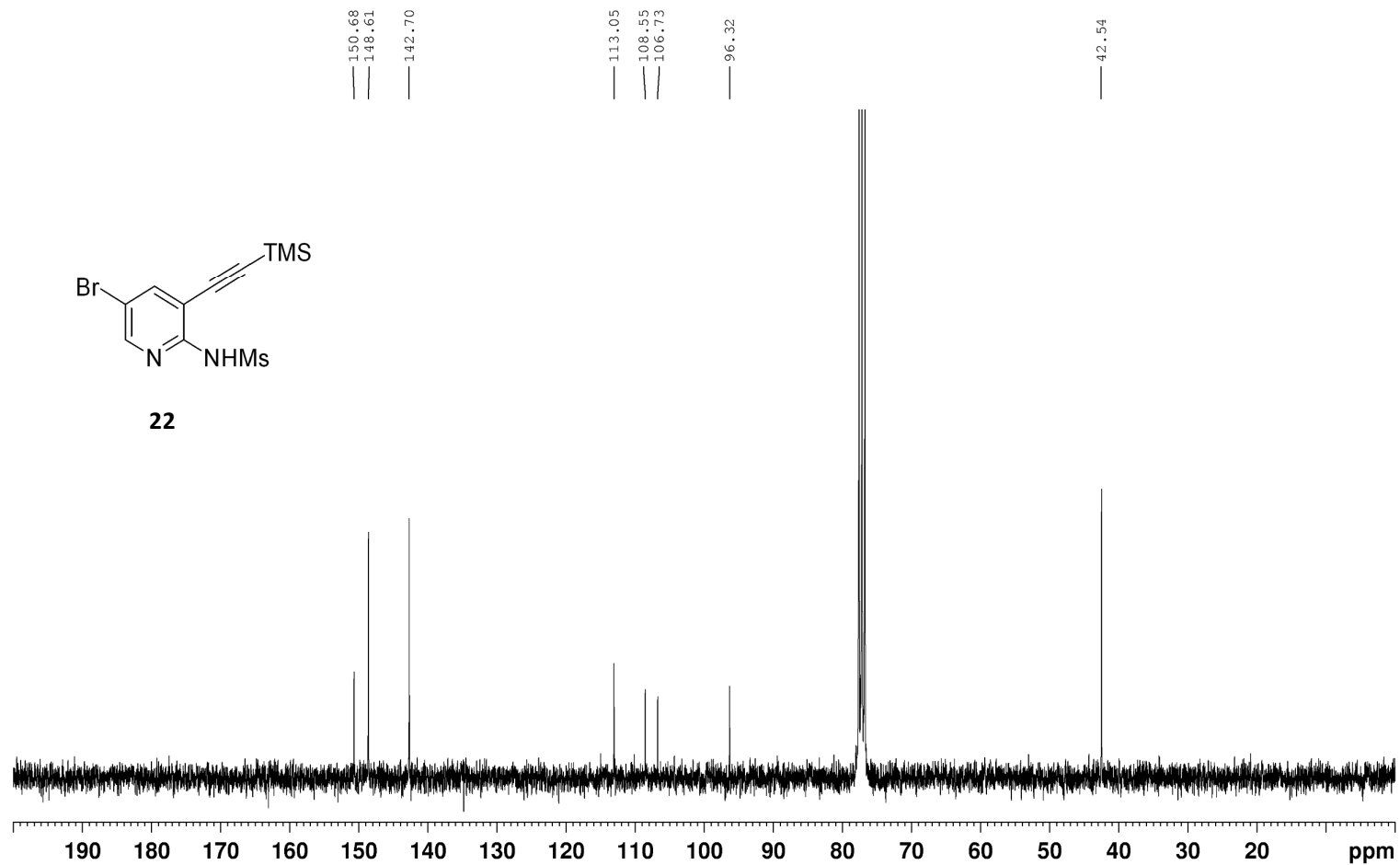
Supervisor Morris
MC E44 CDCl3 300MHz
13C.day CDCl3 F:\ mlc 39



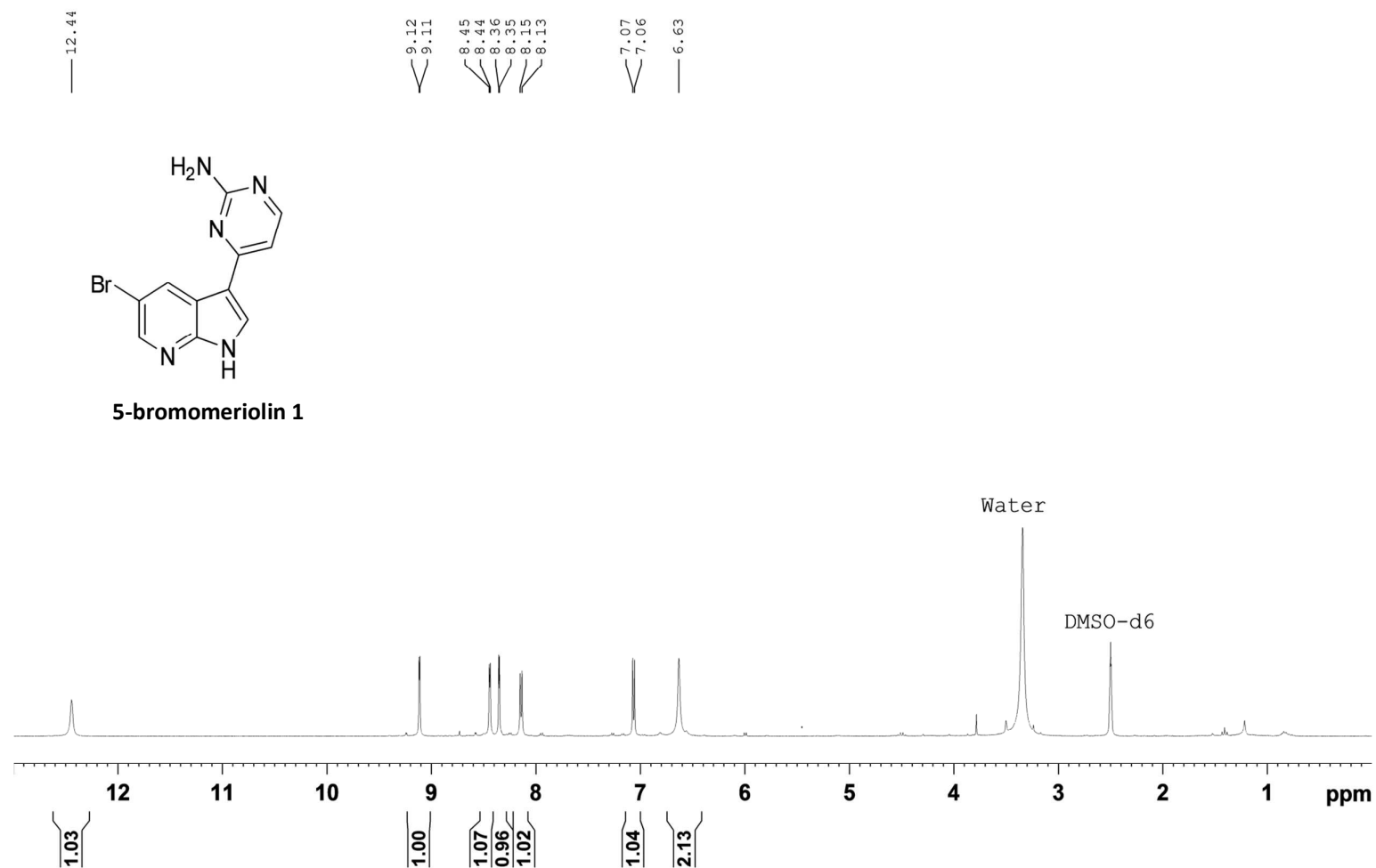
Supervisor Morris
 MC E30 CDC13 300MHz
 1H CDC13 F:\ mlc 5



Supervisor Morris
MC E30 CDCl3 300MHz
13C{1H} CDCl3 F:\ mlc 5



MC E53 DMSO-d6 300MHz



Supervisor Morris
MC E53 DMSO-d6 300MHz
13C.day DMSO F:\\ mlc 28

