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A convenient synthesis of a chlorobenzothiophenyl-indole-based inhibitor of bacterial cystathionine γ-lyase

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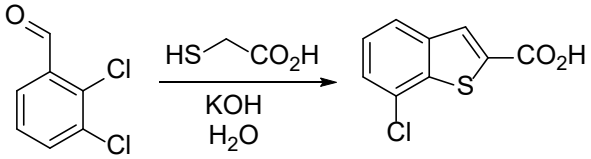
SUPPORTING INFORMATION

1. Materials and Methods

General Experimental Details

All reagents and catalysts were purchased from Sigma-Aldrich, Acros, J&K Scientific, TCI Europe, Macklin and used without further purification unless otherwise mentioned. TLC analysis was performed on Silufol chromatographic plates. For preparative chromatography, silica gel 60 (0.040–0.063 mm) was used. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AVANCE II 300 MHz (300.1, 75.5 MHz and 282.4 MHz, respectively) and a Bruker AMX III 400 MHz (400.1, 100.6 MHz and 376.5 MHz, respectively) spectrometers in $CDCl_3$, containing 0.05% Me_4Si as the internal standard. Determination and verification of structures of obtained compounds and assignments of ^{1}H and ^{13}C signals were made using 1D and 2D DEPT, COSY, HSQC and HMBC spectra. High-resolution mass spectra were recorded on a Bruker Daltonics micrOTOF-Q II device (electrospray ionization).

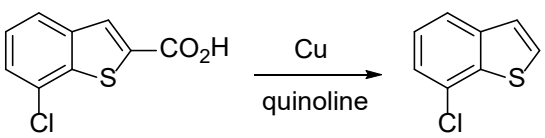


7-Chlorobenzo[*b*]thiophene-2-carboxylic acid

Thioglycolic acid (868 mg, 9.43 mmol) was added dropwise to a solution of KOH (1.16 g, 20.74 mmol) in water (10 ml) in glass ampoule. Then 2,3-dichlorobenzaldehyde (1.65 g, 9.43 mmol) was added to this solution. The ampoule was sealed, after that the mixture was heated to 125°C and stirred for 2 h. The mixture was cooled and solid was dissolved in water. Aqueous layer was washed with Et_2O и treated with 10% HCl. The resulting solid was collected, washed with water and dried under high vacuum. Colourless powder, 1.62 g, 81% yield.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (s, 1H), 8.01 (dd, J = 7.8, 1.0 Hz, 1H), 7.64 (dd, J = 7.8, 1.0 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 163.56, 140.69, 140.43, 136.20, 131.48, 127.29, 125.33.

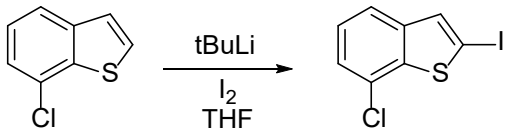


7-Chlorobenzo[*b*]thiophene

Copper powder (164 mg, 2.58 mmol) was added to a solution of 7-chlorobenzo[*b*]thiophene-2-carboxylic acid (500 mg, 2.35 mmol) in quinoline (5 ml). The resulting suspension was heated to 190°C and stirred at this temperature for 3 h. The mixture was cooled, diluted with 20 ml of CH_2Cl_2 and washed with 20 ml of 10% HCl. The organic layer was dried over Na_2SO_4 and concentrated. The compound was purified by column chromatography on silica gel (eluent: 100% hexane). Colorless liquid, 385 mg, 93% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.2, 1.7 Hz, 1H), 7.45 (d, *J* = 5.5 Hz, 1H), 7.38 – 7.18 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.07, 139.13, 127.98, 127.43, 125.43, 124.63, 123.91, 122.07.

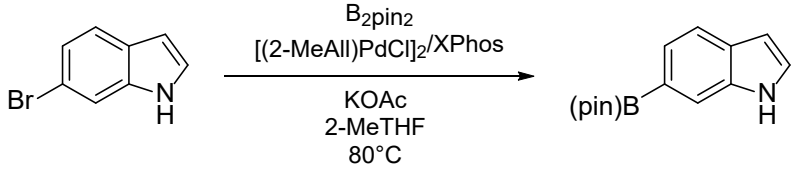


7-Chloro-2-iodobenzo[*b*]thiophene (3)

tert-Butyllithium (1.6 M in hexane, 4.5 ml, 7.20 mmol) was added dropwise to a solution of 7-chlorobenzo[*b*]thiophene (820 mg, 4.86 mmol) in 15 ml of THF at -78°C. The mixture was stirred at this temperature for 5 h and then was treated with the solution of I_2 (1.85 g, 7.29 mmol) in THF (7 ml). The resulting solution was quenched with 10% aq. $Na_2S_2O_3$ and extracted with EtOAc (3×20 ml). The organic layer was dried over Na_2SO_4 and concentrated. The compound was purified by column chromatography on silica gel (eluent: 100% hexane). Yellow liquid, 1.32 g, 92% yield. Purity approximately 70%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 6.3, 2.6 Hz, 1H), 7.52 (s, 1H), 7.28 – 7.17 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.47, 142.06, 134.40, 125.72, 123.99, 120.54, 79.71.



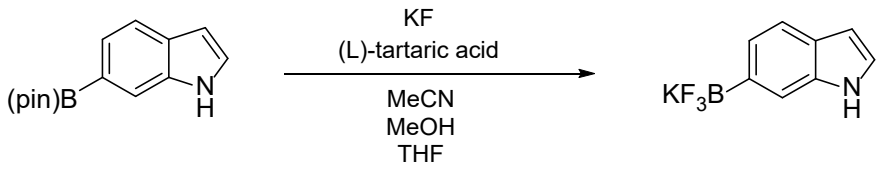
6-(4,4,5,5-Tetramethyl-1,3,2-dioxoborolan-2-yl)-1*H*-indole (2)

A Schlenk flask containing 6-bromo-1*H*-indole (992.4 mg, 5.1 mmol), B_2pin_2 (1.412 g, 5.6 mmol), $[(2\text{-MeAll})PdCl)]_2$ (20.0 mg, 0.051 mmol, 2 mol.% Pd) and XPhos (98.5 mg, 0.21 mmol, 4 mol %) was filled with argon. Absolute 2-MeTHF (50 ml) was added to this mixture, followed by KOAc (1.486 g, 15.1 mmol). The reaction mixture was stirred while heating in an oil bath at 80°C for 6 hours, and then evaporated on a rotary evaporator. The residue was purified by column chromatography on silica gel, eluting with a mixture of benzene/EtOAc 95/5 (R_f = 0.28). Colorless powder, 1.089 g, 88% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (br. s, 1H), 7.91 – 7.88 (m, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.56 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.25 (t, *J* = 2.8 Hz, 1H), 6.55 (ddd, *J* = 3.1, 2.0, 1.0 Hz, 1H), 1.37 (s, 12H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 130.5, 125.7, 125.6, 120.1, 118.1, 102.7, 83.6, 25.0.

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.4.



6-(Trifluoro-λ⁴-boranyl)-1*H*-indole, potassium salt (4)

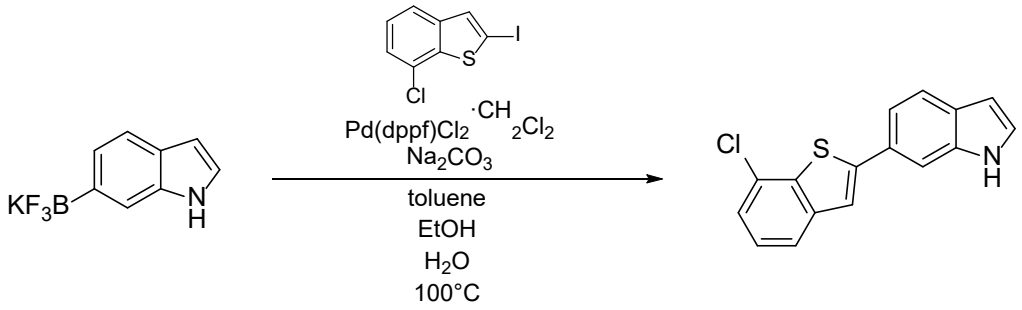
6-(4,4,5,5-Tetramethyl-1,3,2-dioxoborolan-2-yl)-1*H*-indole (762.9 mg 3.1 mmol) was dissolved in MeCN and MeOH (8 ml each). Then a solution of KF (732.1 mg, 12.6 mmol) in water (2.4 ml) was added in this mixture. A solution of tartaric acid (966.9 mg, 6.4 mmol) in THF (6.0 ml) was added dropwise to the resulting two-phase system with active stirring. A white precipitate immediately began to form. This mixture was stirred for 5 min and then MeCN (10 ml) was added. After another 5 min the second portion of MeCN (6 ml) was added, and the reaction mixture was stirred again for another 5 min. The precipitate that formed was filtered off and washed with MeCN (4 x 20 ml). The filtrate was evaporated. The residue was dried in a high vacuum. The resulting almost colorless solid was washed 3 times with Et_2O and dried under high vacuum. Colourless solid, 676.0 mg, 97% yield.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.55 (br. s, 1H), 7.36 (s, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.10 (t, J = 2.7 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 6.24 (ddd, J = 3.0, 1.9, 0.9 Hz, 1H).

^{19}F NMR (282 MHz, DMSO-d_6) δ –137.6.

^{11}B NMR (96 MHz, DMSO-d_6) δ 3.8.

^{13}C NMR (75 MHz, DMSO-d_6) δ 136.1, 125.5, 123.2 (q, J = 1.4 Hz), 122.8, 117.6, 113.8 (q, J = 2.0 Hz), 100.3.



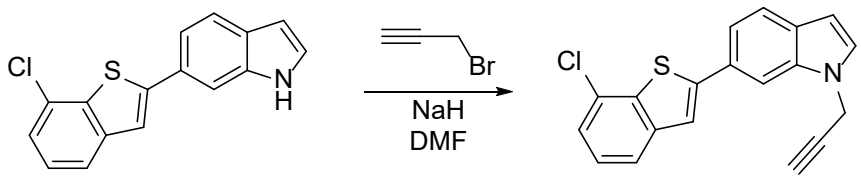
6-(7-Chlorobenzo[*b*]thiophen-2-yl)-1*H*-indole (5)

Potassium (1*H*-indol-6-yl)trifluoroborate (166.0 mg, 0.74 mmol), 7-chloro-2-iodobenzo[*b*]thiophene (146.1 mg, 0.35 mmol, purity approximately 70%), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (14.3 mg, 0.018 mmol, 5 mol %) and Na_2CO_3 (111.3 mg, 1.05 mmol) were placed in Schlenk flask and filled with argon. In a flow of argon, toluene, EtOH (1.3 ml each) and water (2.5 ml) were added. Then mixture was degassed, carefully evacuating while stirring and filling with argon 3 times. The mixture was stirred in an oil bath at 100°C for 4 hours. After cooling, the mixture was extracted 3 times with CH_2Cl_2; the extracts were dried over Na_2SO_4 and evaporated on a rotary evaporator. The residue was purified by column chromatography on silica gel, eluting first with a hexane/EtOAc (10:1) mixture, then with a hexane/benzene/EtOAc (7:3:1) mixture (R_f = 0.24). Colorless powder, 81.9 mg, 83% yield.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.32 (br. s, 1H), 7.88 (s, 1H), 7.85 – 7.77 (m, 2H), 7.65 (d, J = 8.3 Hz, 1H), 7.51 – 7.35 (m, 4H), 6.52 – 6.47 (m, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 146.3, 142.4, 136.8, 136.1, 128.4, 127.4, 126.4, 126.1, 125.8, 123.6, 122.3, 120.8, 119.2, 117.6, 109.2, 101.4.

HRMS (ESI), *m/z*: $[M+H]^+$, Calcd. for $C_{16}H_{11}ClNS^+$ 284.0295; Found 284.0301.

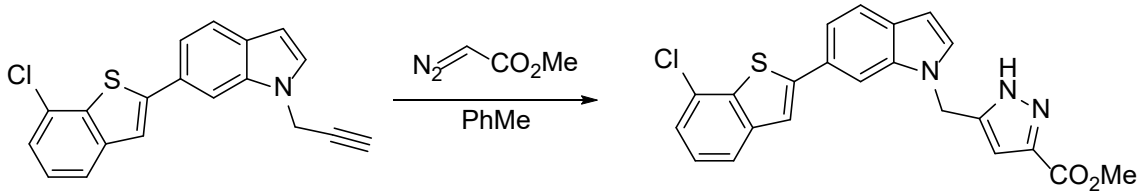


6-(7-Chlorobenzo[*b*]thiophen-2-yl)-1-(prop-2-yn-1-yl)-1*H*-indole (6)

6-(7-Chlorobenzo[*b*]thiophen-2-yl)-1*H*-indole (114 mg, 0.4017 mmol) was added to a suspension of NaH pre-washed with petroleum ether (60% in oil, 21 mg, 0.5225 mmol) in absolute DMSO (1.5 ml) and was kept stirring until the gas release stopped (2 hours). Propargyl bromide (62 mg, 0.5225 mmol) was added dropwise to the resulting solution under thermal control with a water bath for heat dissipation. The mixture was stirred for 3 h. Water (40 ml) was added dropwise to the resulting mixture and pre-cooled in an ice bath. The mixture was extracted with EtOAc (3 × 40 ml). The combined organic layers were washed with H_2O, with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by column chromatography on silica gel in the system benzene/hexane = 2:1. Colorless powder, 70 mg, 54% yield.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.76 (s, 1H), 7.75 – 7.64 (m, 2H), 7.61 (s, 1H), 7.58 (dd, J = 8.3, 1.4 Hz, 1H), 7.37 – 7.24 (m, 3H), 6.60 (d, J = 3.1 Hz, 1H), 4.94 (d, J = 2.5 Hz, 2H), 2.49 (t, J = 2.5 Hz, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 146.92, 142.30, 138.42, 136.05, 129.44, 128.81, 127.87, 127.47, 125.67, 123.54, 121.63, 119.15, 119.05, 107.63, 102.44, 74.05, 35.97.



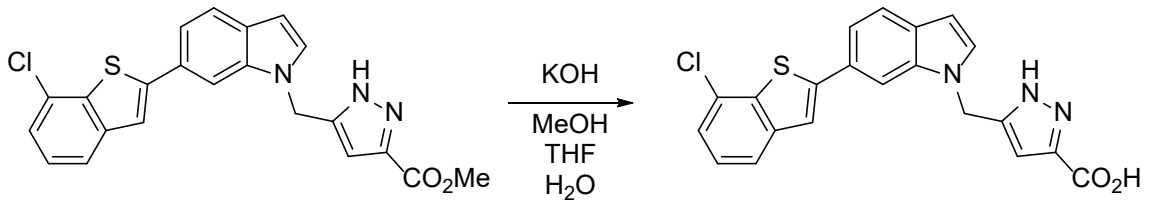
Methyl 5-{[6-(7-chlorobenzo[*b*]thiophen-2-yl)-1*H*-indol-1-yl]methyl}-1*H*-pyrazole-3-carboxylate (7)

Methyl diazoacetate (248 mg, 2.4776 mmol) was added to a solution of 6-(7-chlorobenzo[*b*]thiophen-2-yl)-1-(prop-2-yn-1-yl)-1*H*-indole (290 mg, 1.2388 mmol) in toluene (5 ml) and pyridine (1 ml). The resulting solution was stirred at 100°C for 8 h. The reaction mass was evaporated to dryness. The compound was purified by column chromatography on silica gel (eluent: benzene / EtOAc = 3:1). Colorless powder, 178 mg, 34% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.43 (br.s, 1H), 7.74 (br.s, 1H), 7.64 (dt, J = 8.4, 6.1 Hz, 2H), 7.56 – 7.49 (m, 2H), 7.30 (d, J = 0.8 Hz, 1H), 7.23 (d, J = 3.2 Hz, 1H), 6.62 (s, 1H), 6.57 (d, J = 2.9 Hz, 1H), 5.45 (s, 2H), 3.86 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.05, 146.92, 142.25, 138.36, 136.33, 129.33, 129.29, 127.81, 127.42, 125.61, 123.47, 121.56, 119.04, 118.88, 107.71, 107.49, 102.47, 52.26, 43.61.

HRMS (ESI), *m/z*: $[M+H]^+$, Calcd. for $C_{23}H_{16}ClN_3O_2S^+$ 422.0725; Found 422.0726



5-{[6-(7-Chlorobenzo[*b*]thiophen-2-yl)-1*H*-indol-1-yl]methyl}-1*H*-pyrazole-3-carboxylic acid (8)

Potassium hydroxide (236 mg, 4.198 mmol) in H_2O (2 ml) was added to a solution of methyl 5-{[6-(7-chlorobenzo[*b*]thiophen-2-yl)-1*H*-indol-1-yl]methyl}-1*H*-pyrazole-3-carboxylate (178 mg, 0.419 mmol) in MeOH (4 ml) and THF (2 ml). The resulting mixture was heated to 50°C and stirred for 8 h. The reaction mass was evaporated to dryness, diluted with H_2O (1 ml) and treated with 10% HCl. The solid was collected, washed with water and dried under high vacuum. Yellow powder, 120 mg, 70% yield.

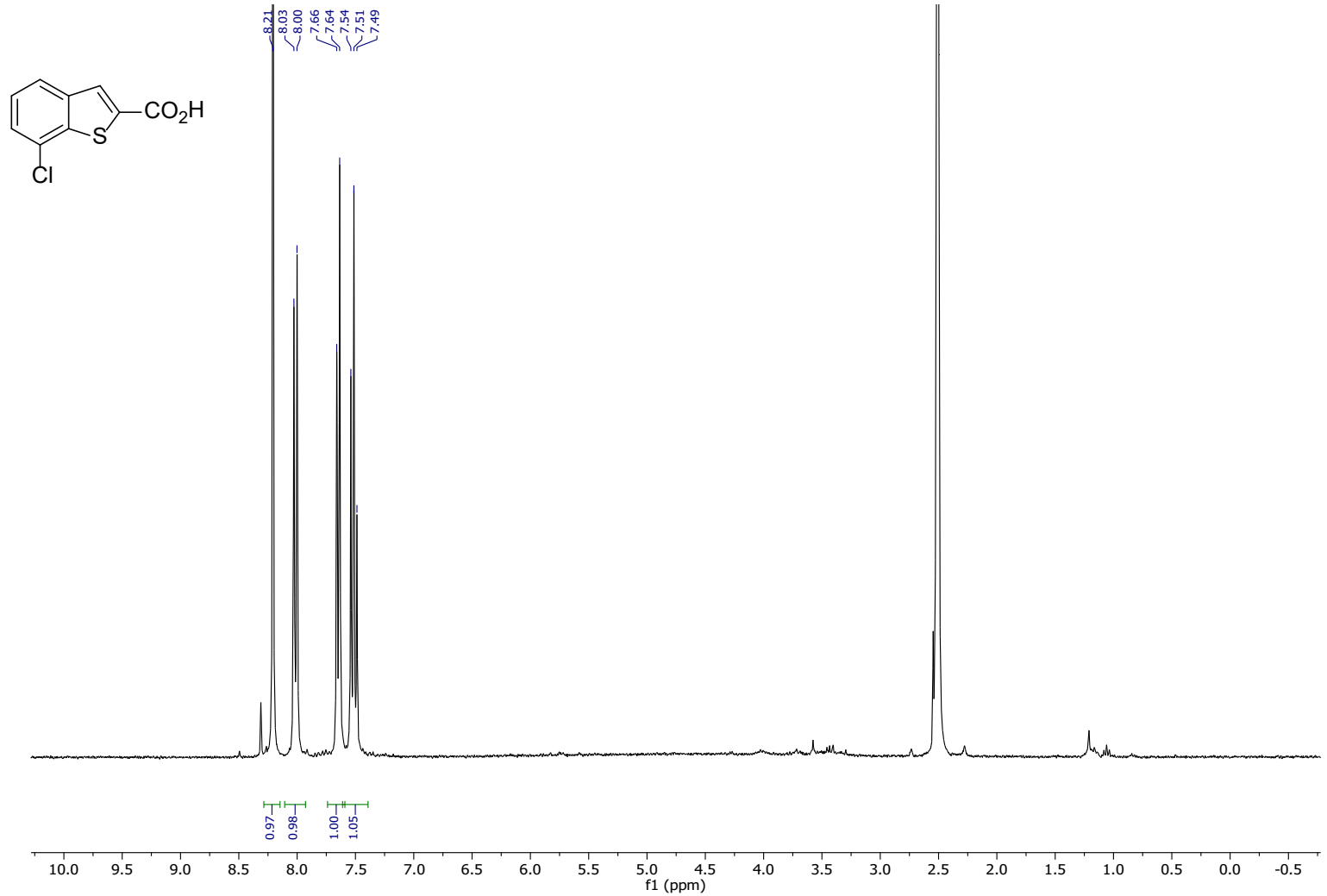
^{1}H NMR (300 MHz, DMSO-d_6), δ: 8.03 (s, 1H), 7.91 (dd, J = 7.8, 1.1 Hz, 1H), 7.81 (s, 1H), 7.52–7.37 (m, 5H), 7.15 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.54 (s, 1H), 6.48 (d, *J* = 3.1 Hz, 1H), 5.39 (s, 2H).

^{13}C NMR (75 MHz, DMSO-d_6), δ: 142.58, 141.74, 136.98, 133.92, 130.28, 127.71, 126.99, 126.24, 124.90, 123.57, 122.60, 122.48, 114.52, 113.35, 107.43, 101.84.

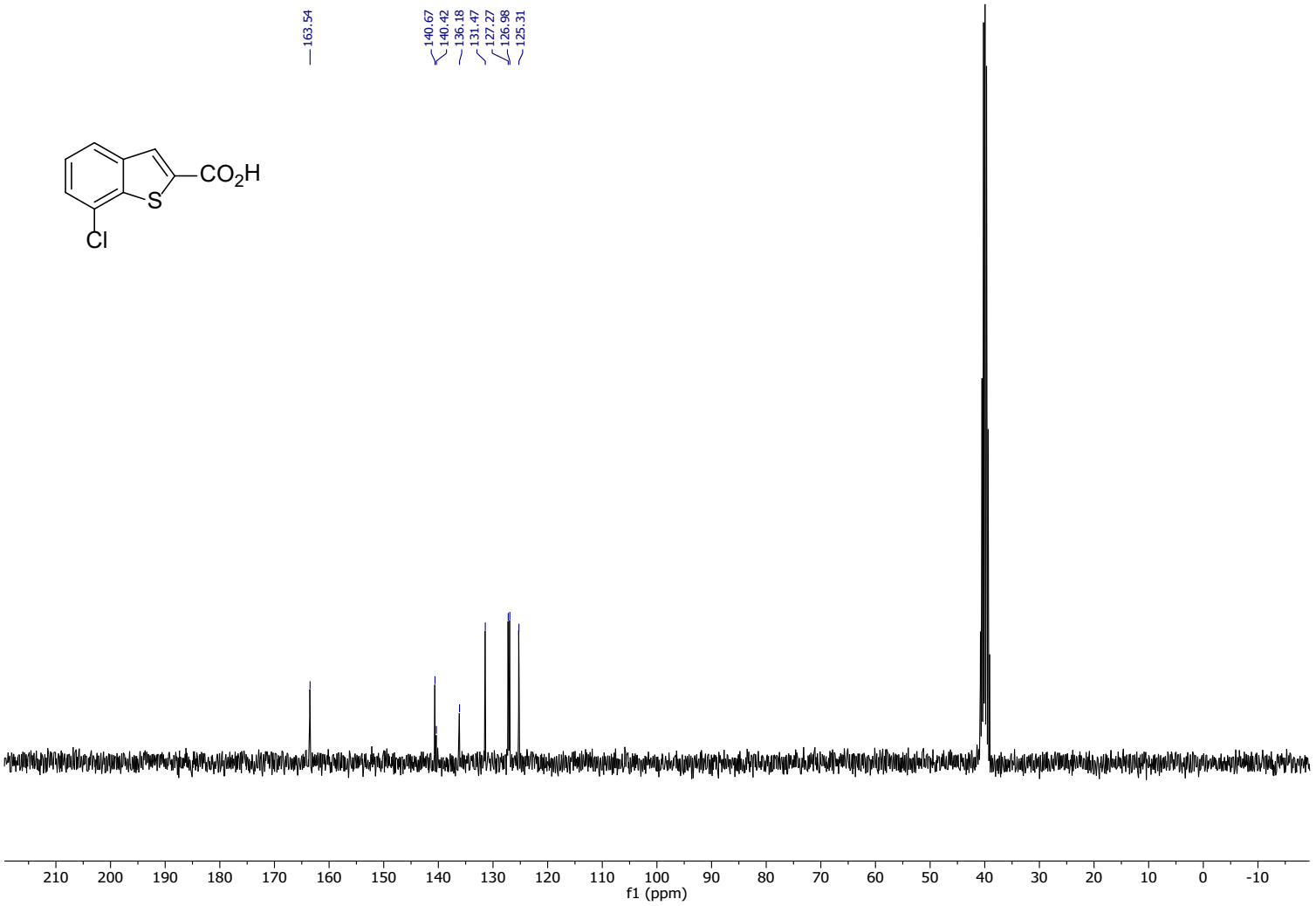
HRMS (ESI), *m/z*: $[M+H]^+$, Calcd. for $C_{22}H_{14}ClN_3O_2S^+$ 408.0561; Found 408.0568

2. NMR Spectra

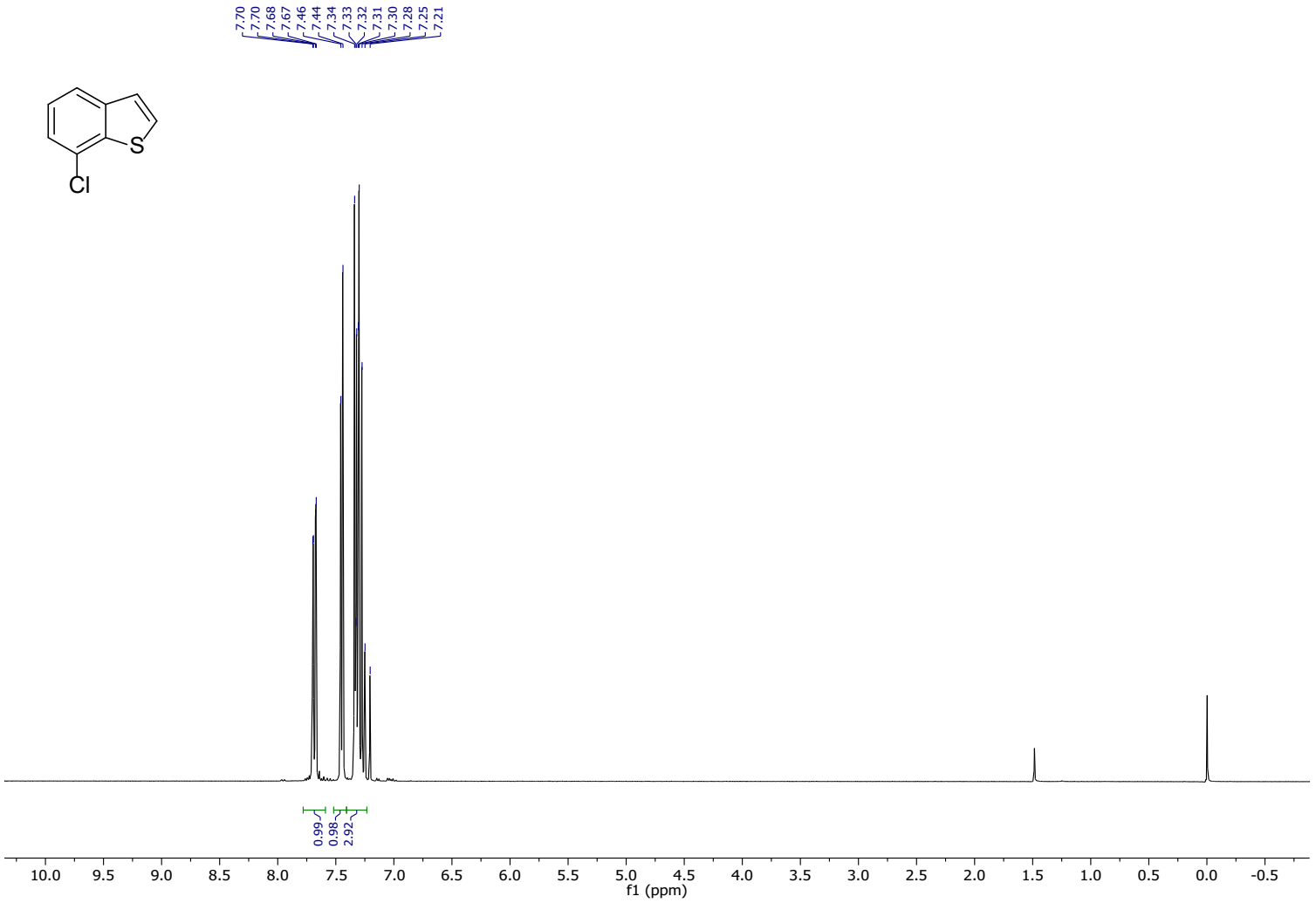
^{1}H NMR (300 MHz) in $CDCl_3$



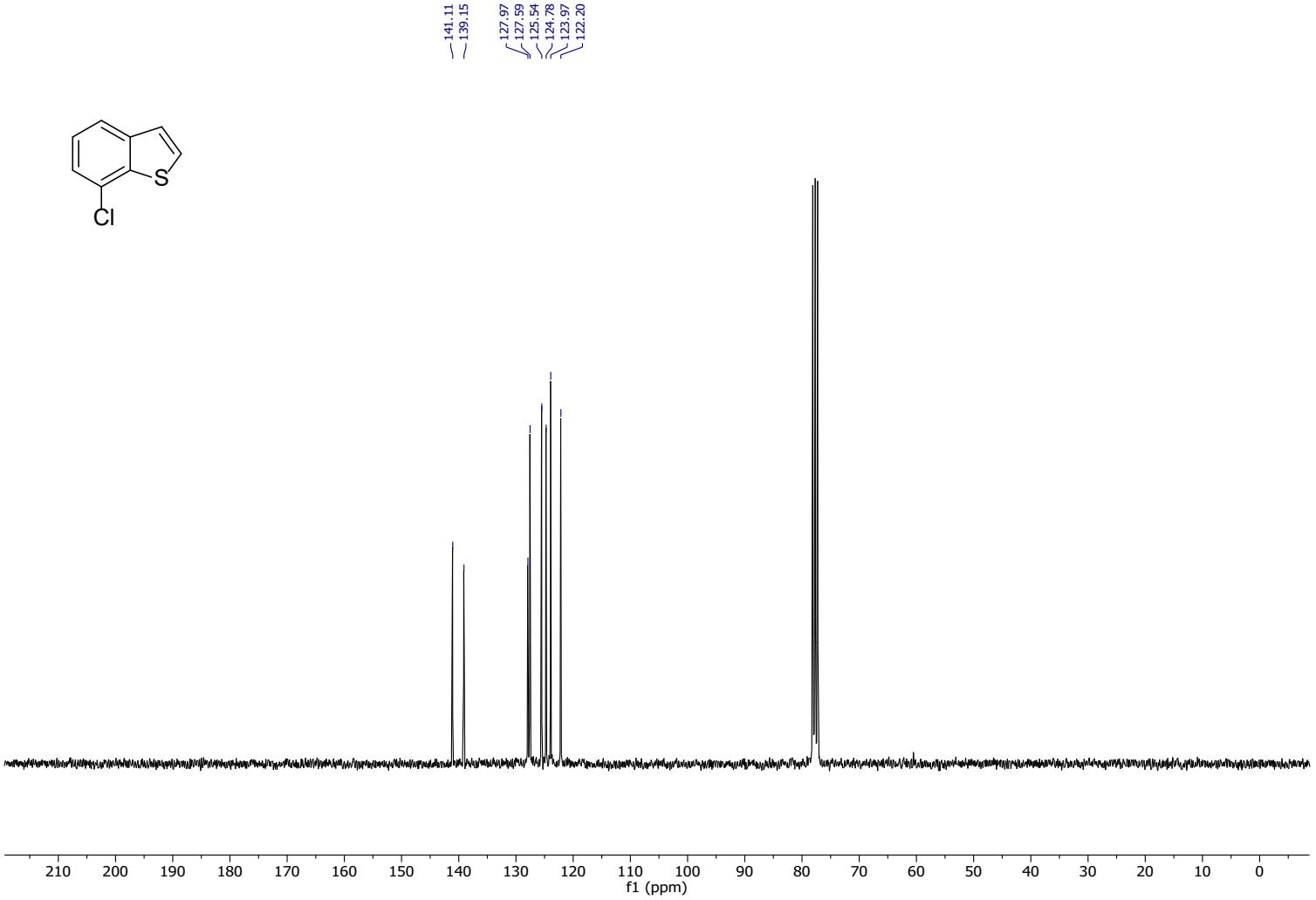
^{13}C NMR (76 MHz) in $CDCl_3$



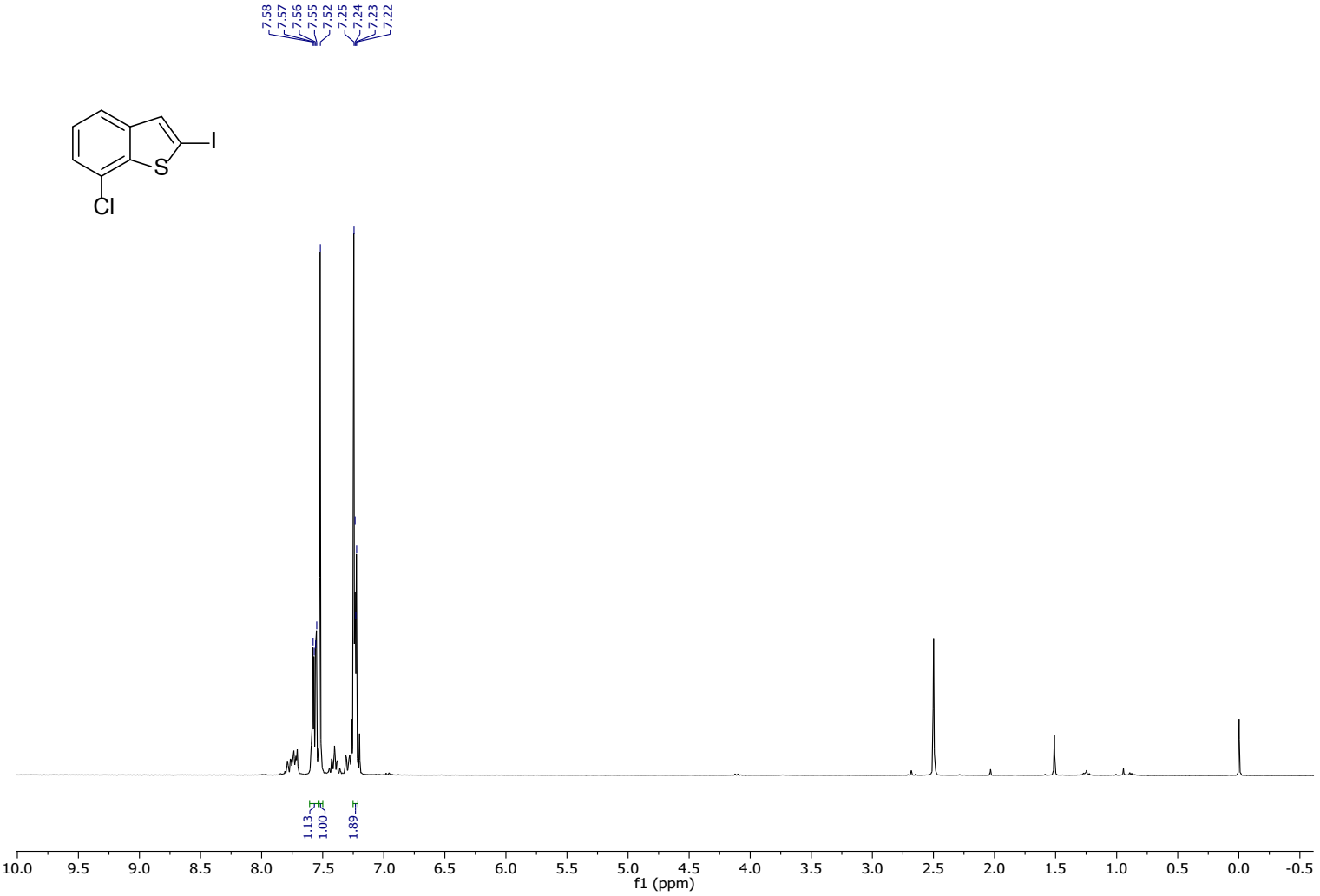
^{1}H NMR (300 MHz) in $CDCl_3$



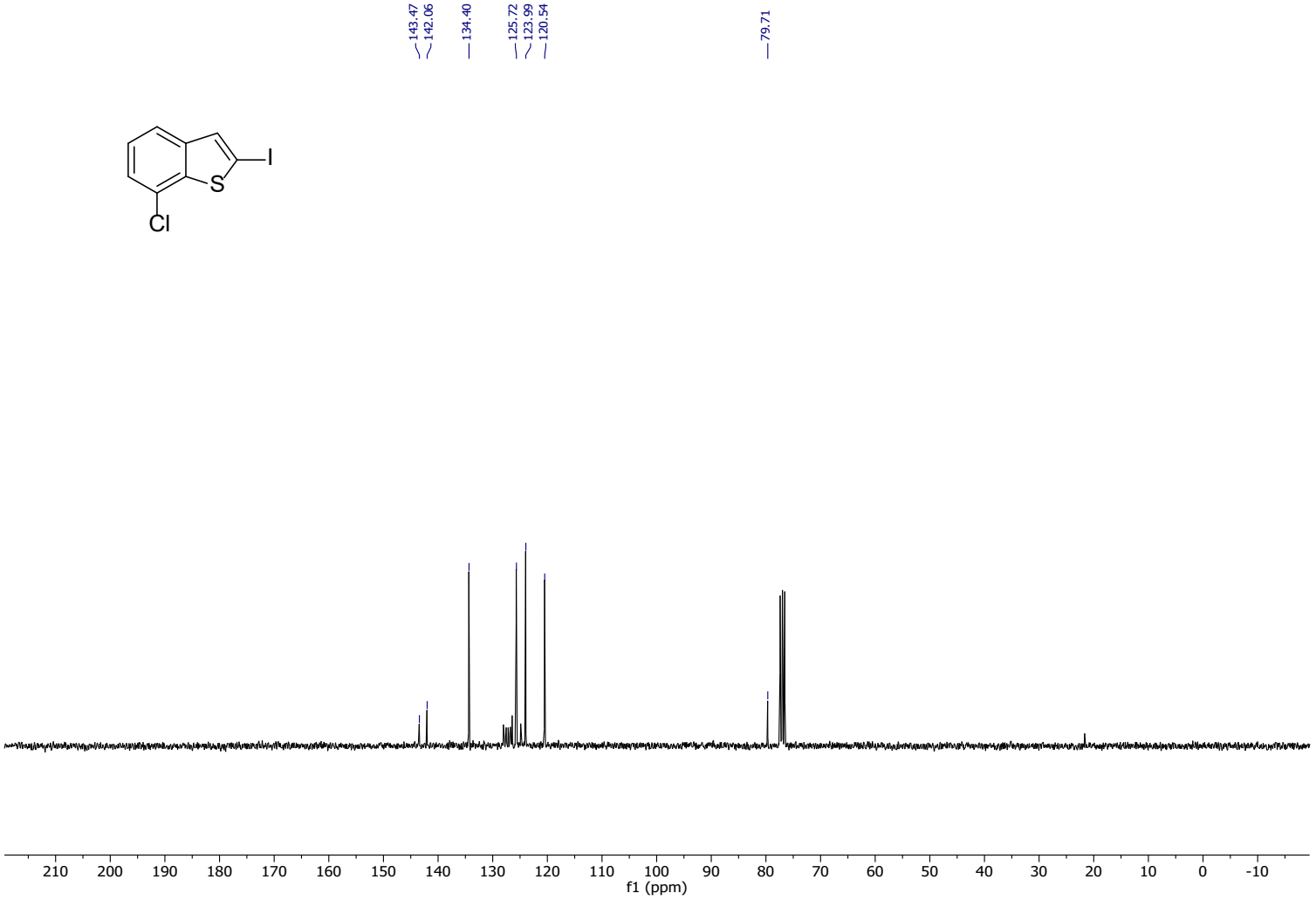
^{13}C NMR (76 MHz) in $CDCl_3$



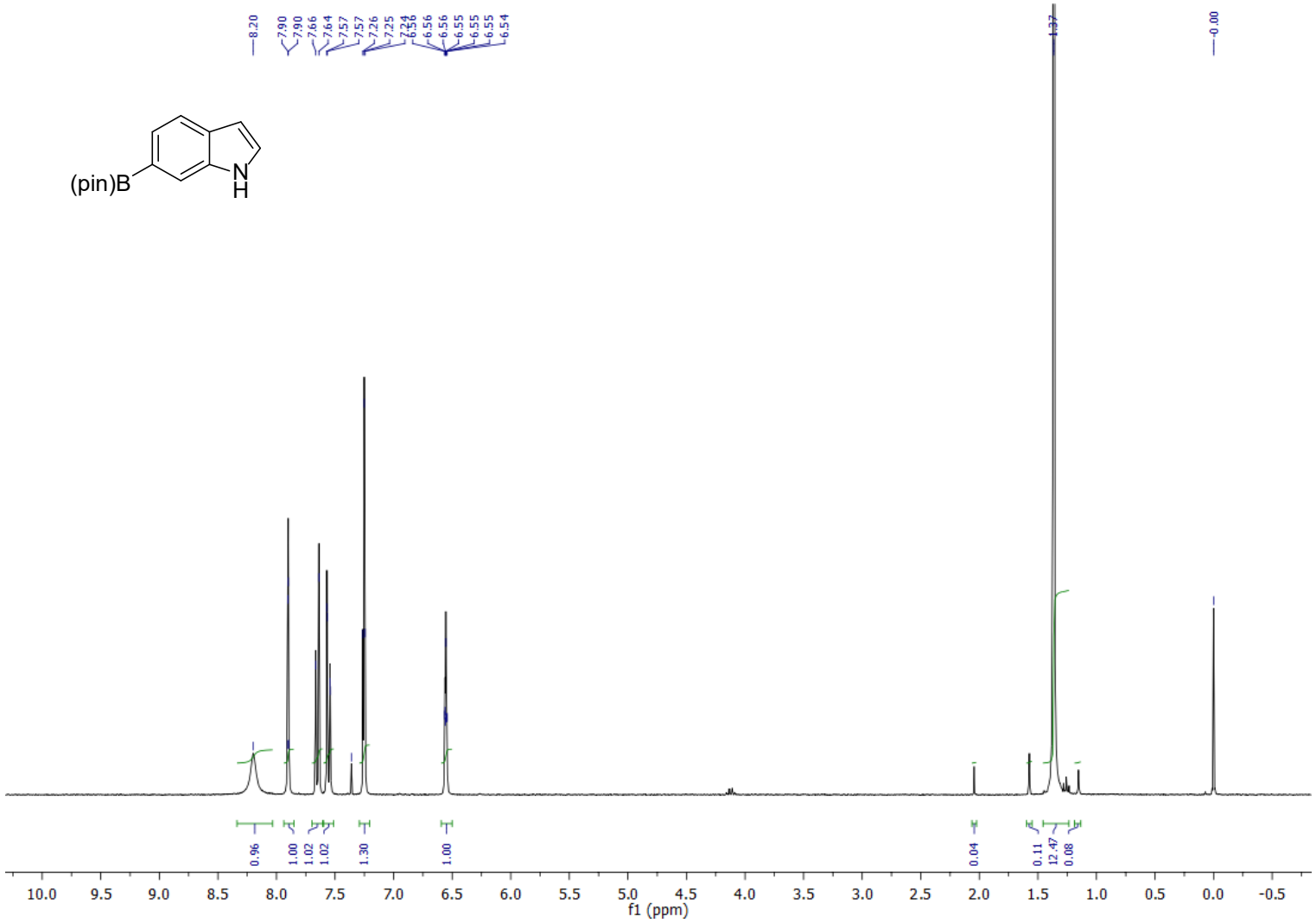
^{1}H NMR (300 MHz) in $CDCl_3$



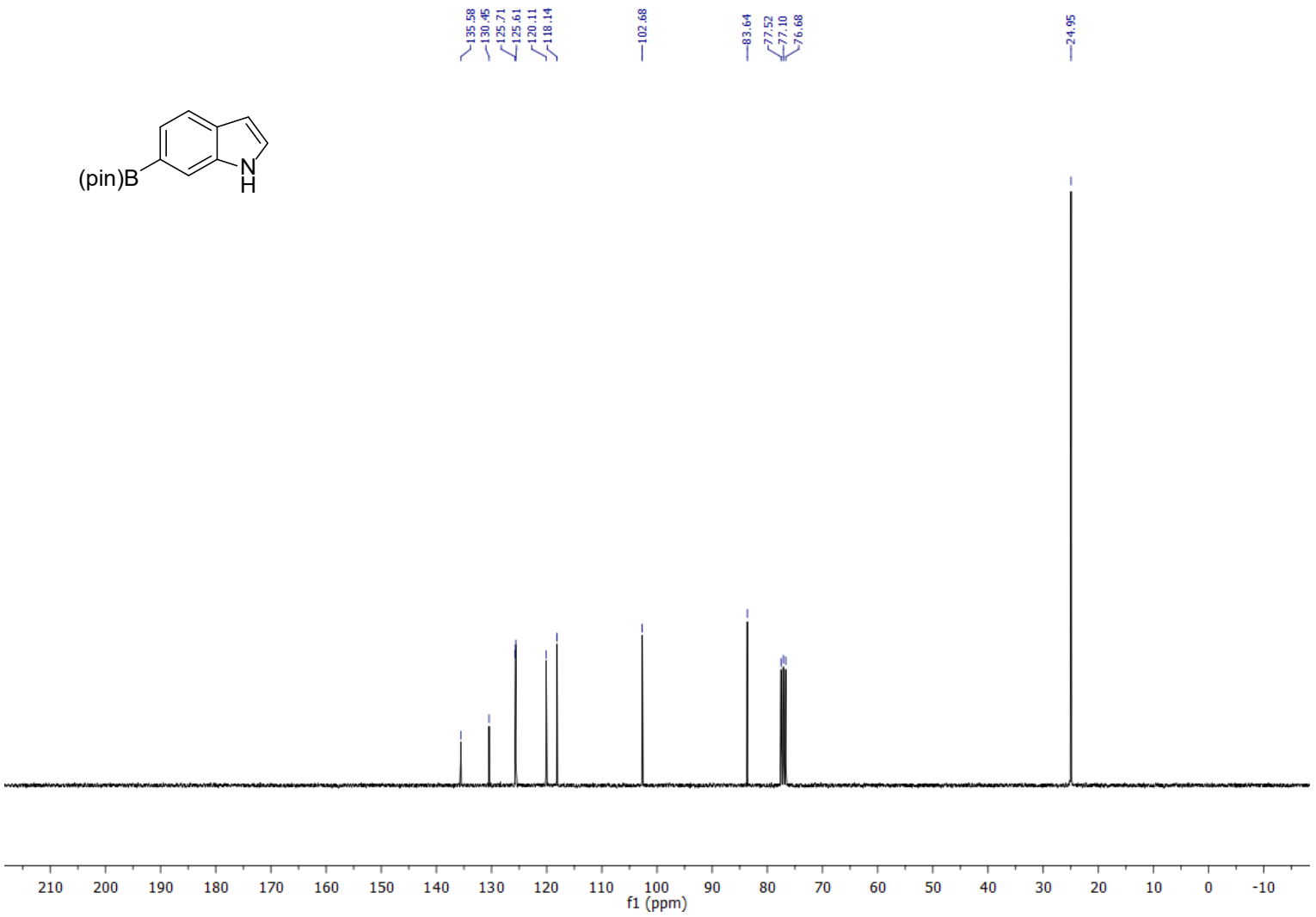
^{13}C NMR (76 MHz) in $CDCl_3$



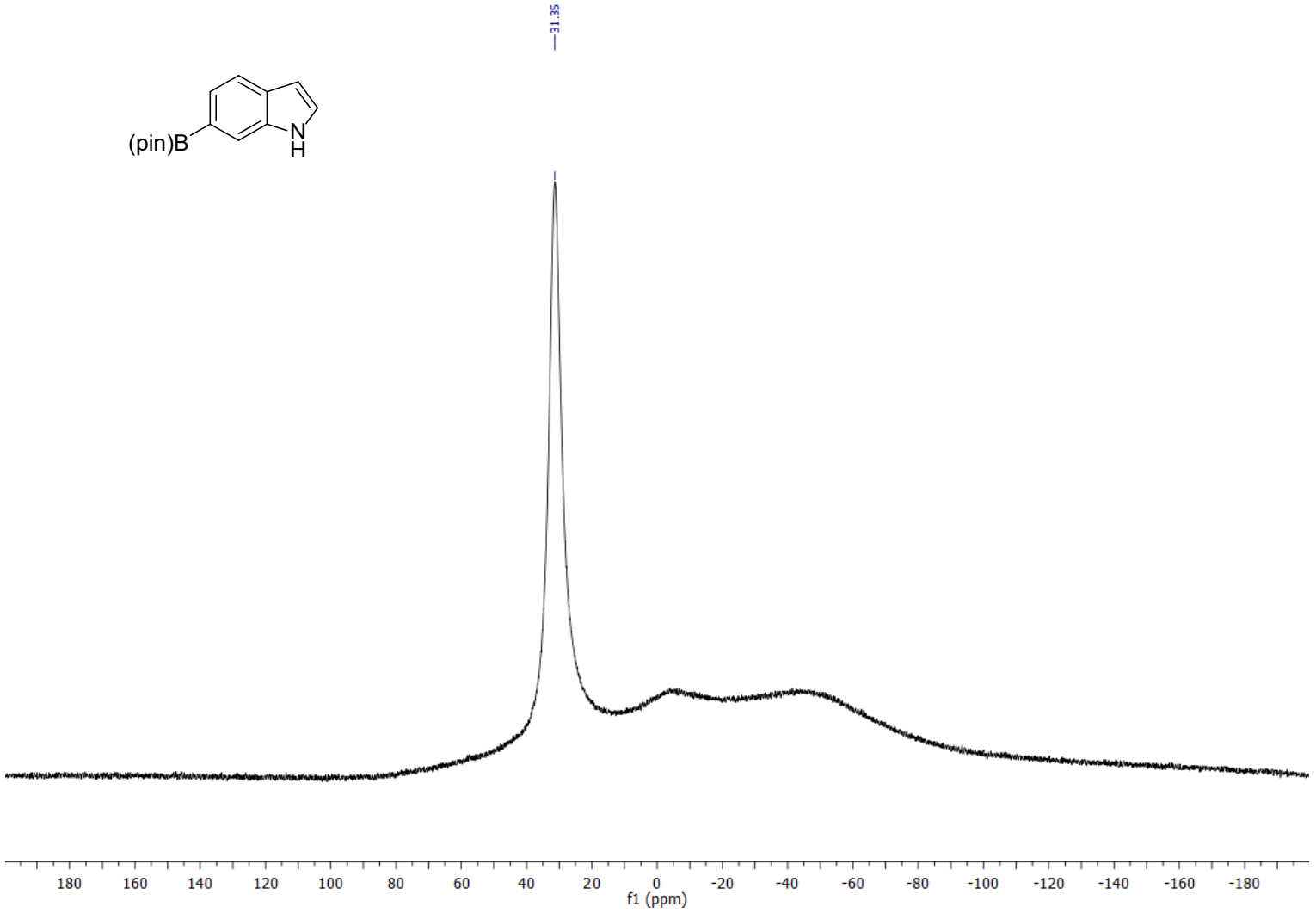
^{1}H NMR (300 MHz) in $CDCl_3$



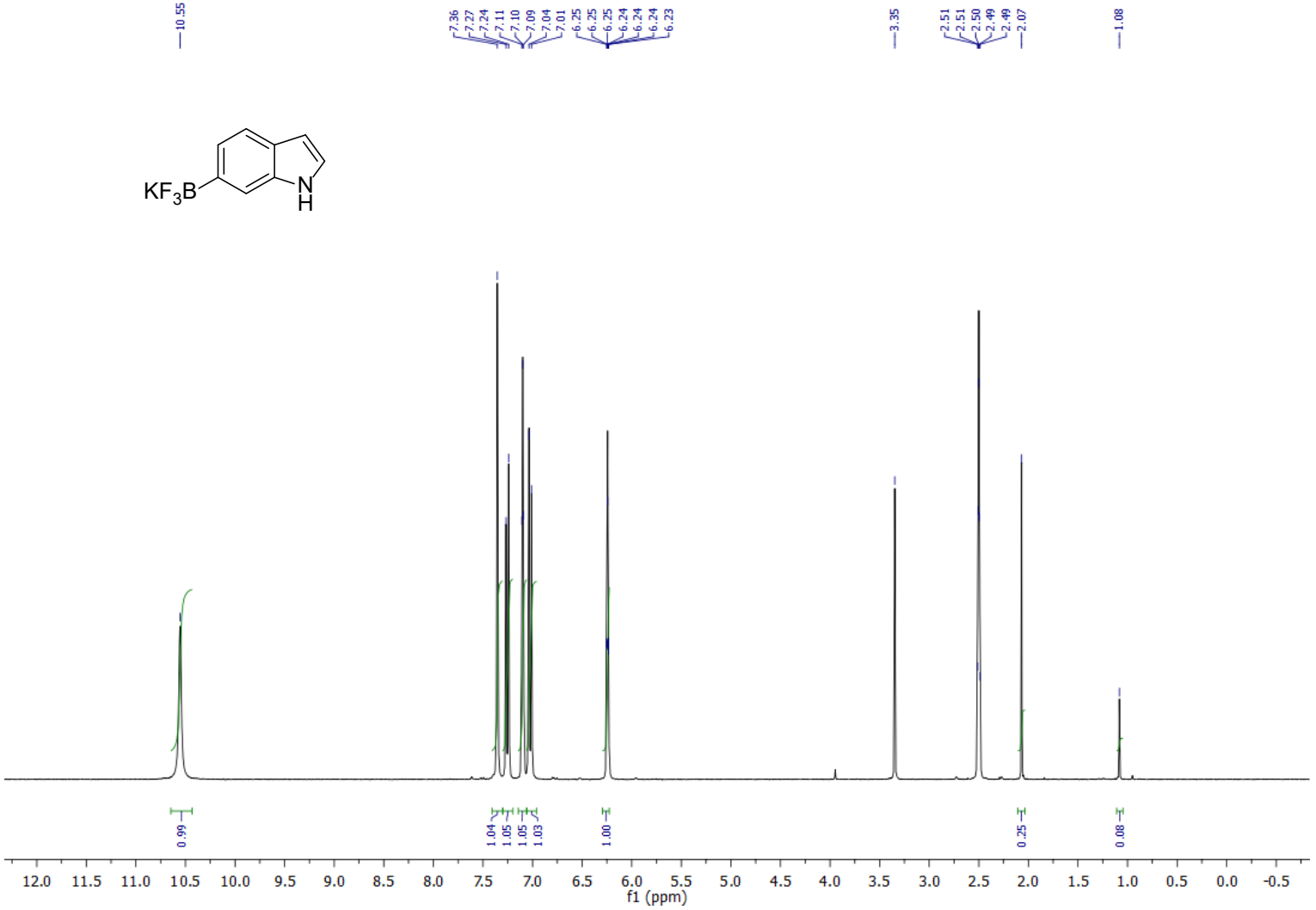
^{13}C NMR (76 MHz) in $CDCl_3$



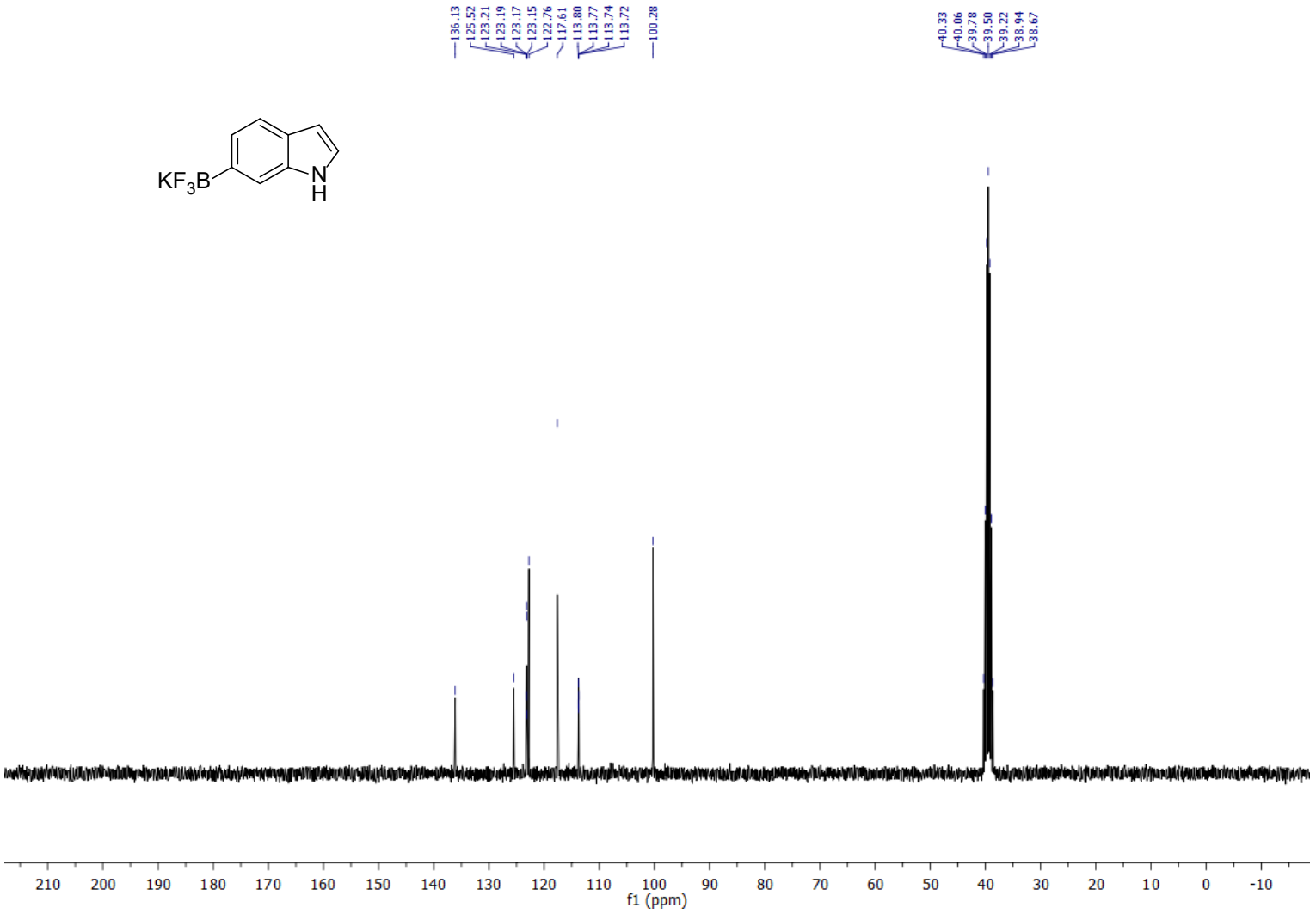
^{11}B NMR (96 MHz) in DMSO-d_6



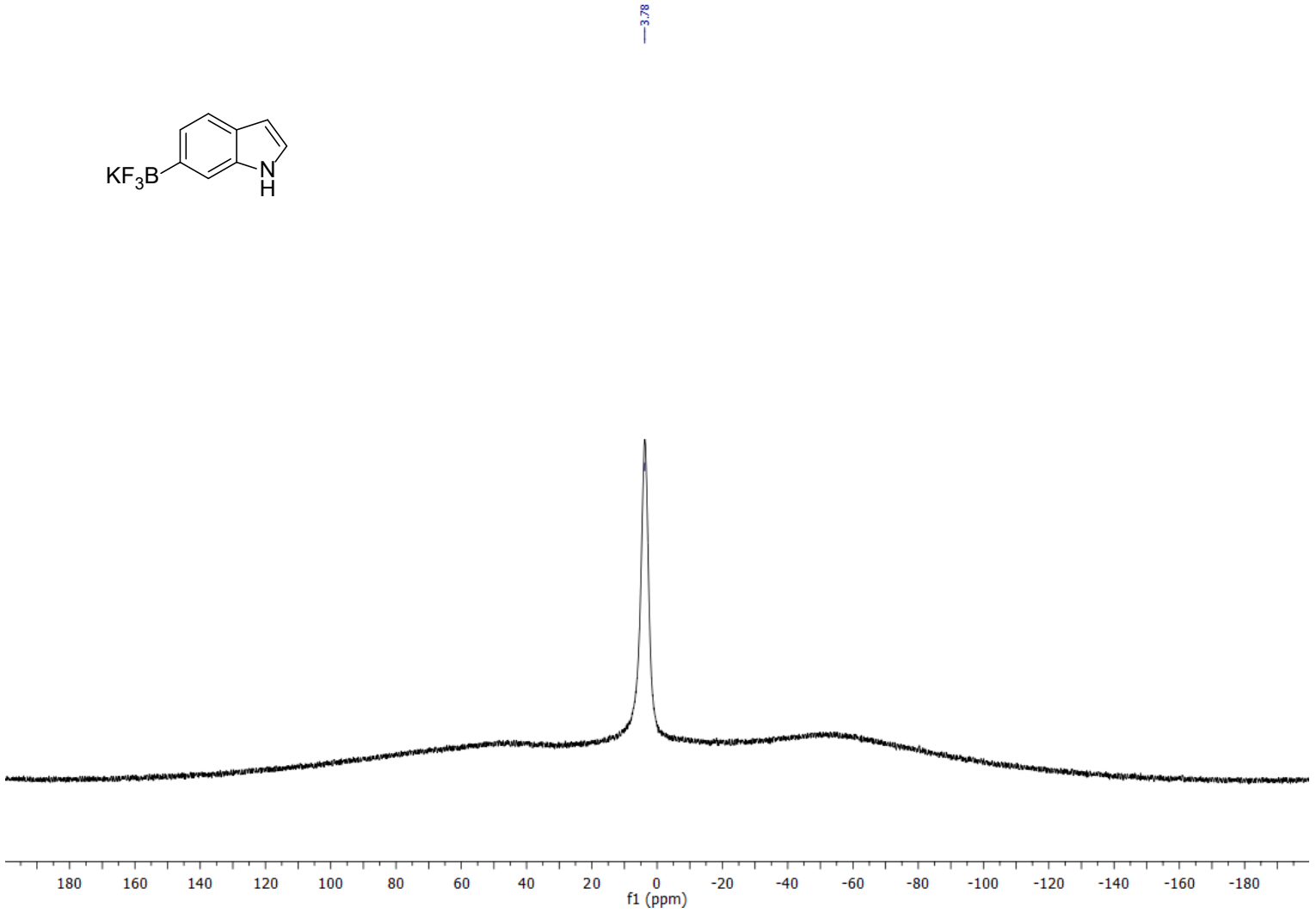
^{1}H NMR (300 MHz) in DMSO-d_6



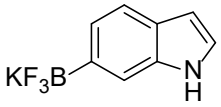
^{13}C NMR (76 MHz) in DMSO-d_6



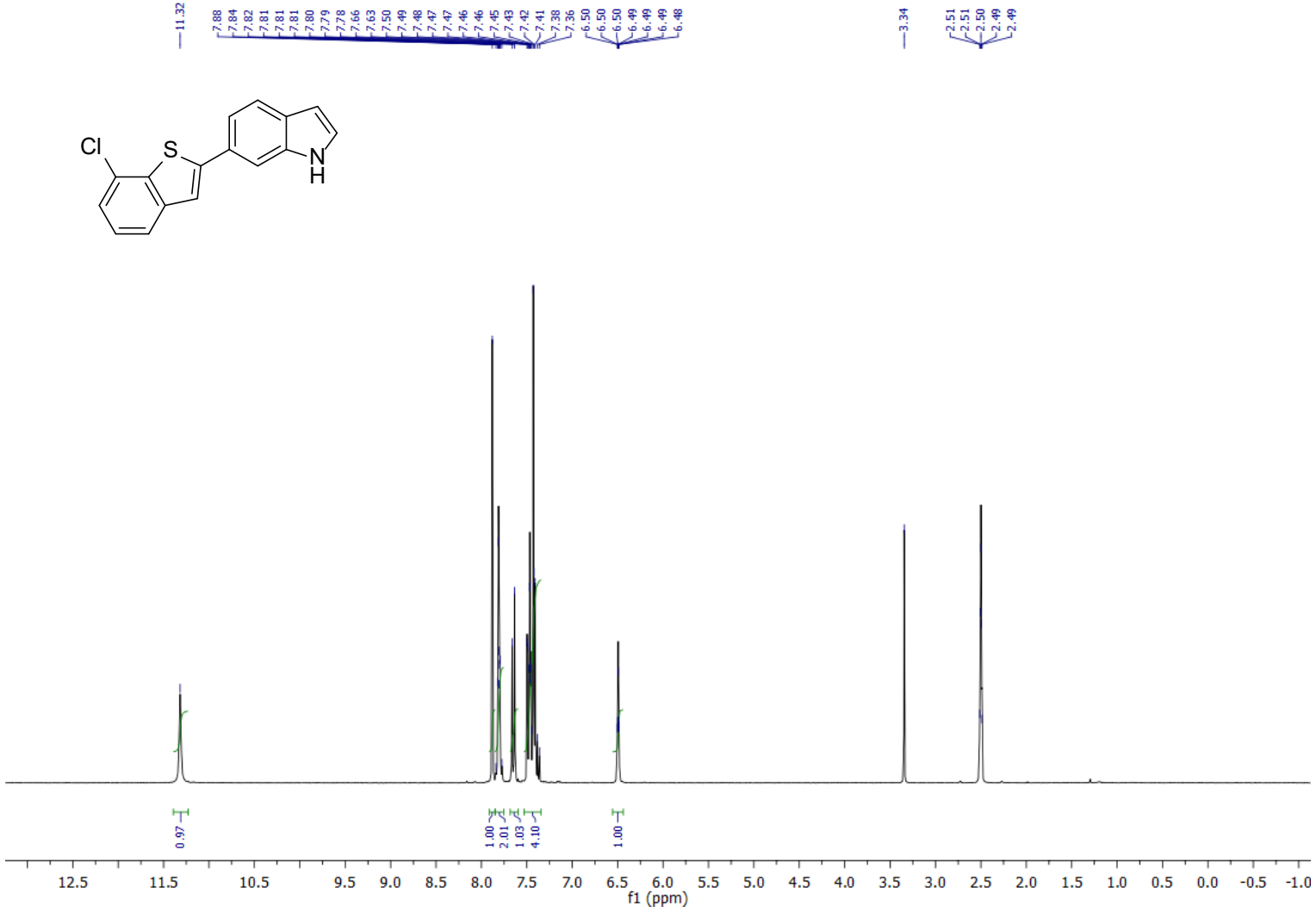
^{11}B NMR (96 MHz) in DMSO-d_6



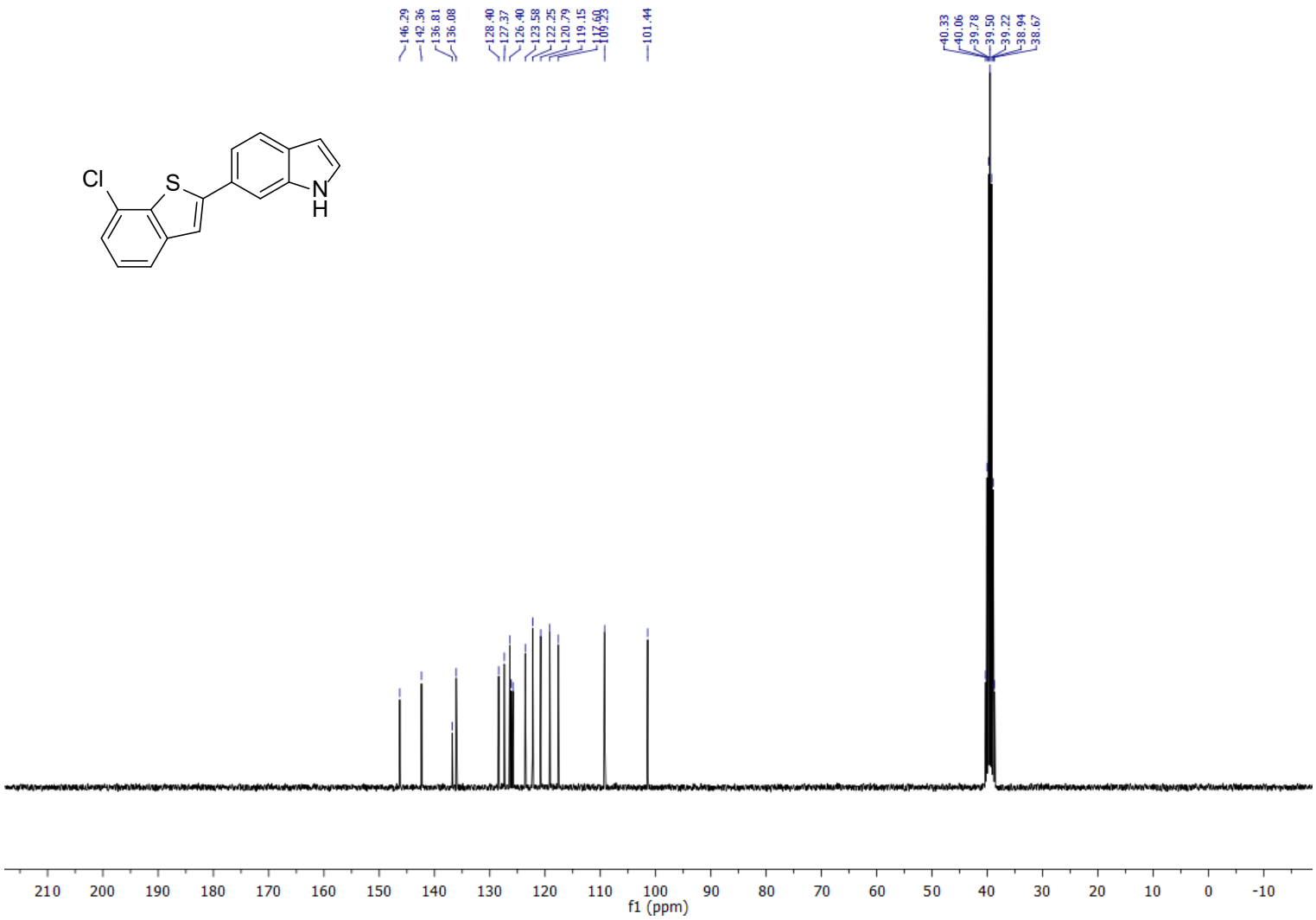
^{19}F NMR (282 MHz) in DMSO-d_6



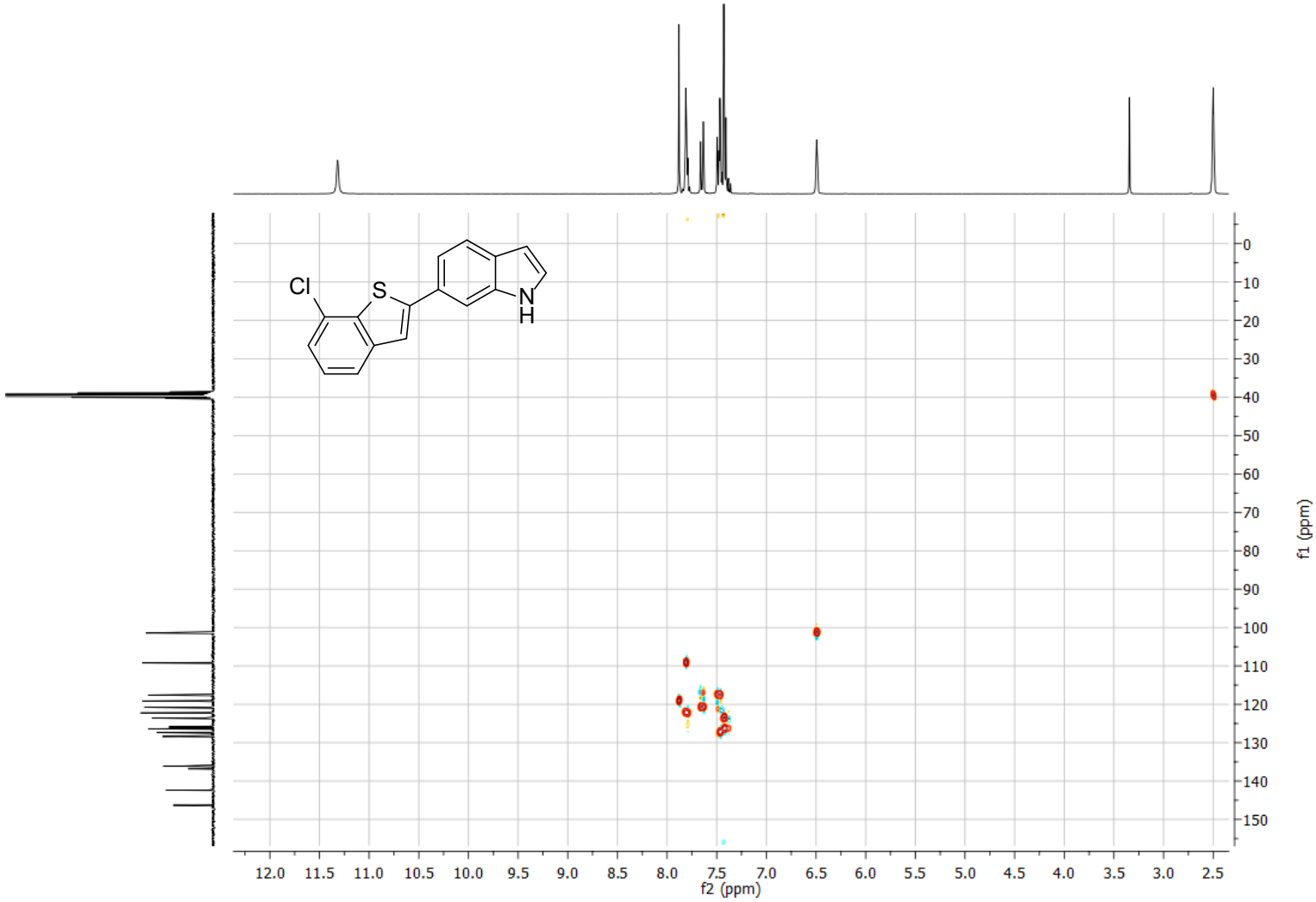
^{1}H NMR (300 MHz) in DMSO-d_6



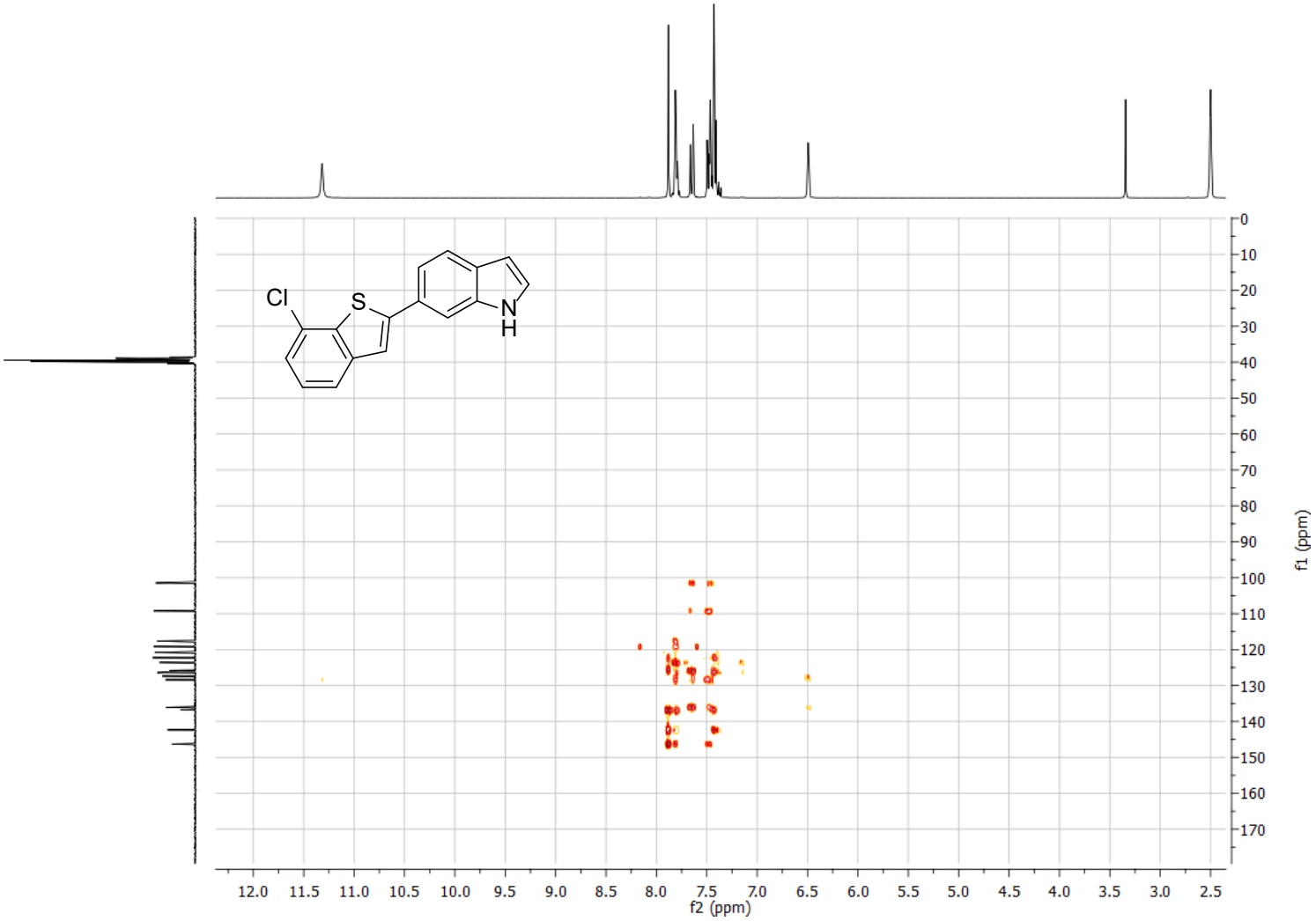
^{13}C NMR (76 MHz) in DMSO-d_6



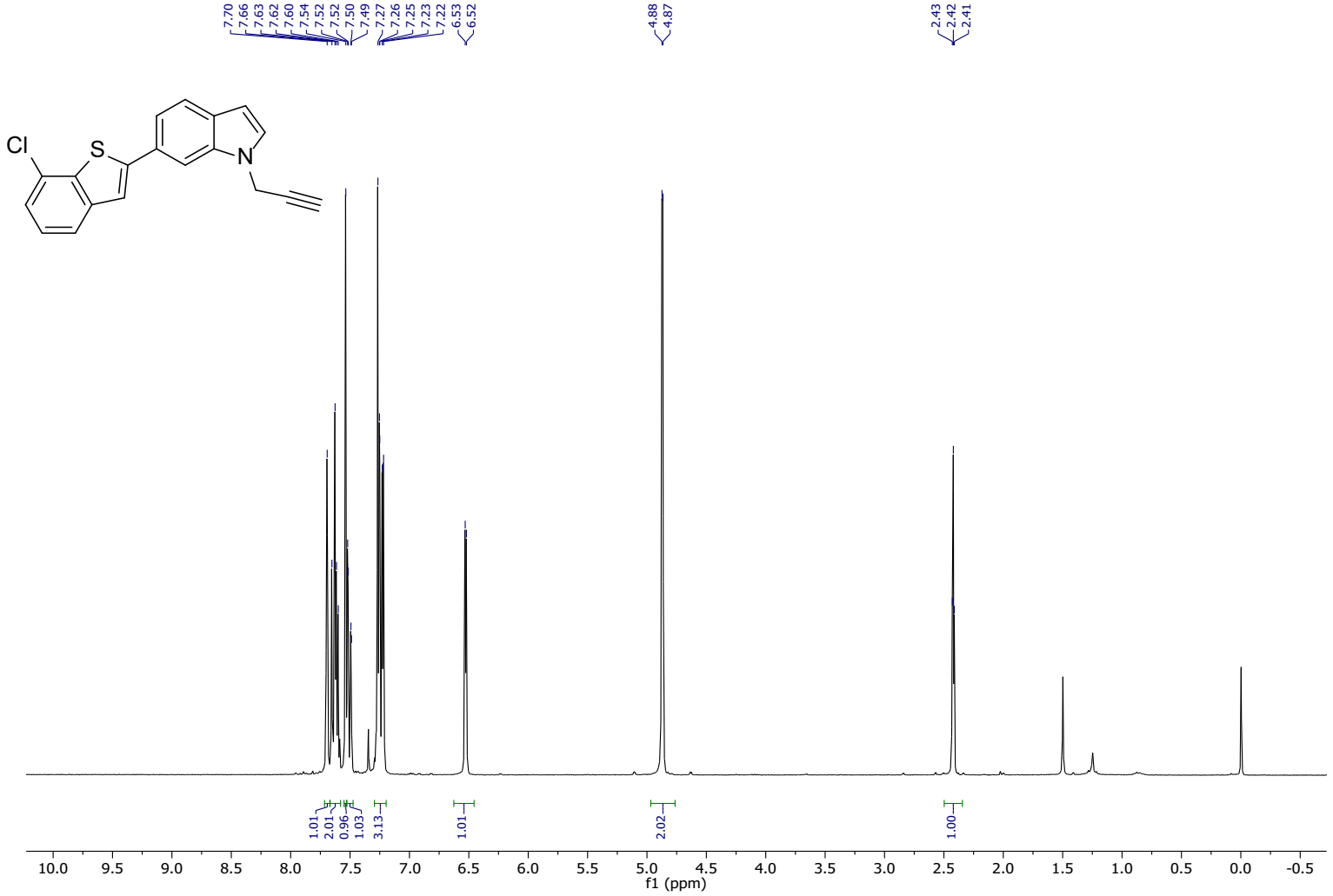
$^{1}H,^{13}C$-HSQC (300 & 76 MHz) in DMSO-d_6



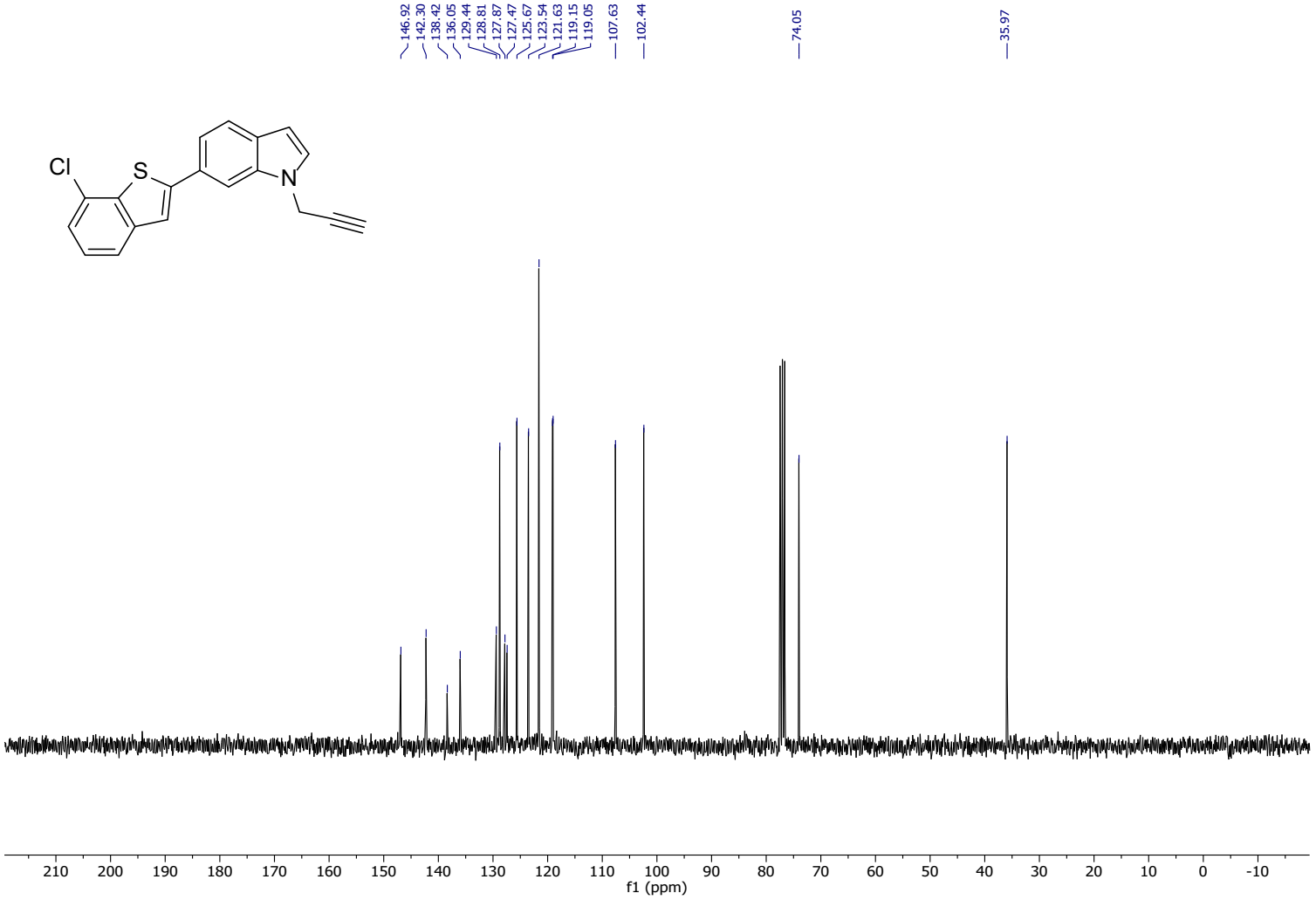
$^{1}H,^{13}C$-HMBC (300 & 76 MHz) in DMSO-d_6



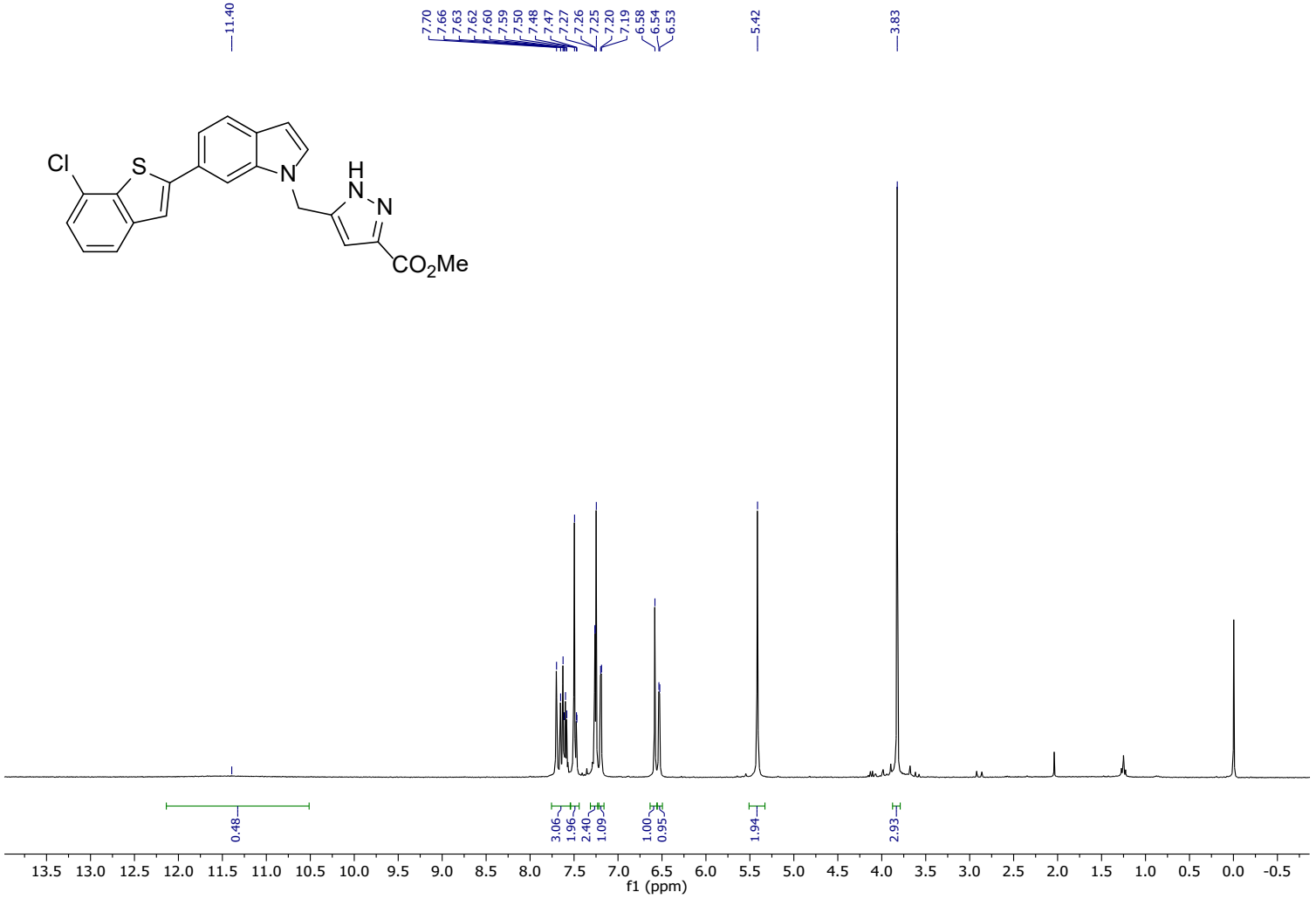
^{1}H NMR (300 MHz) in $CDCl_3$



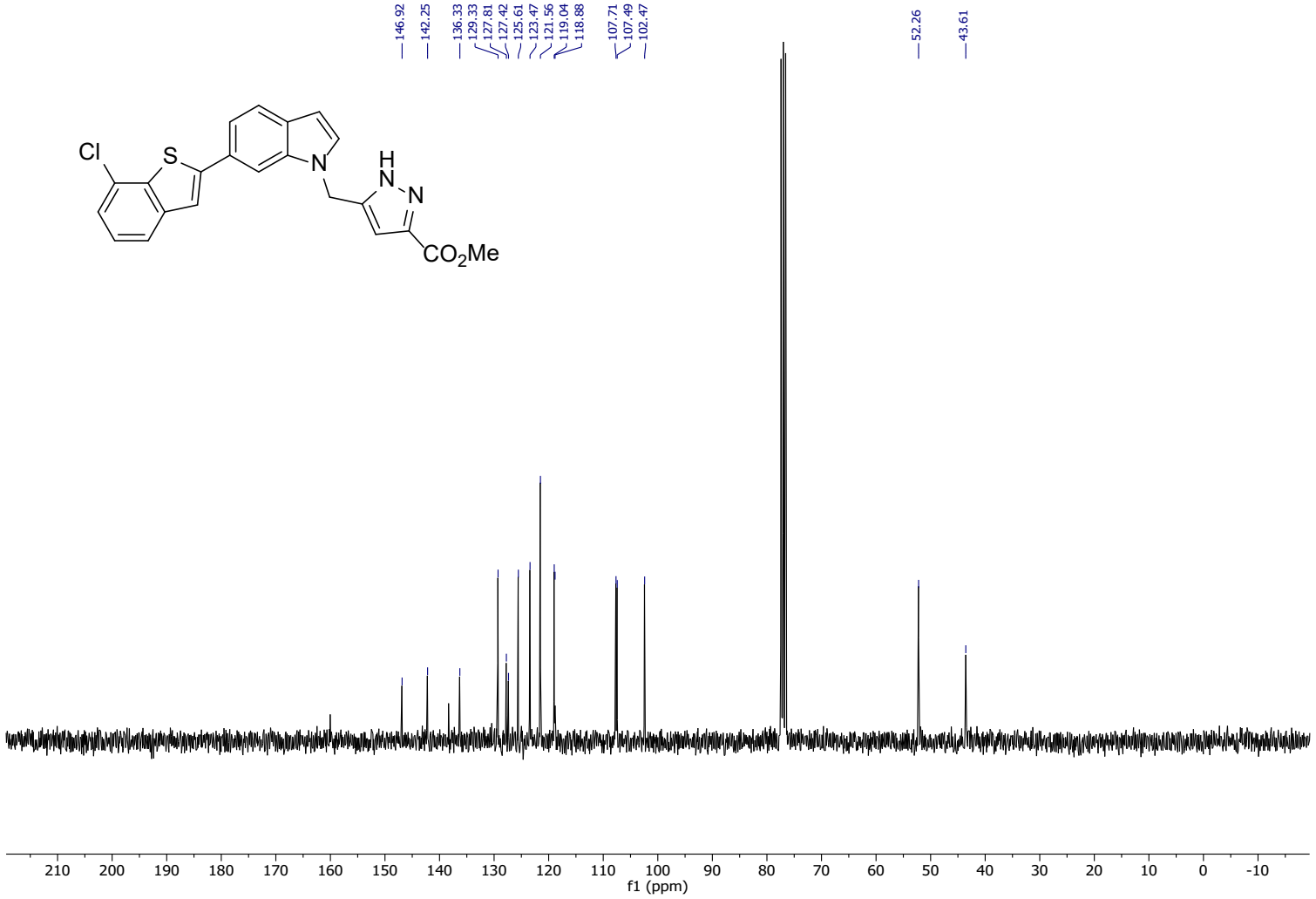
^{13}C NMR (76 MHz) in $CDCl_3$



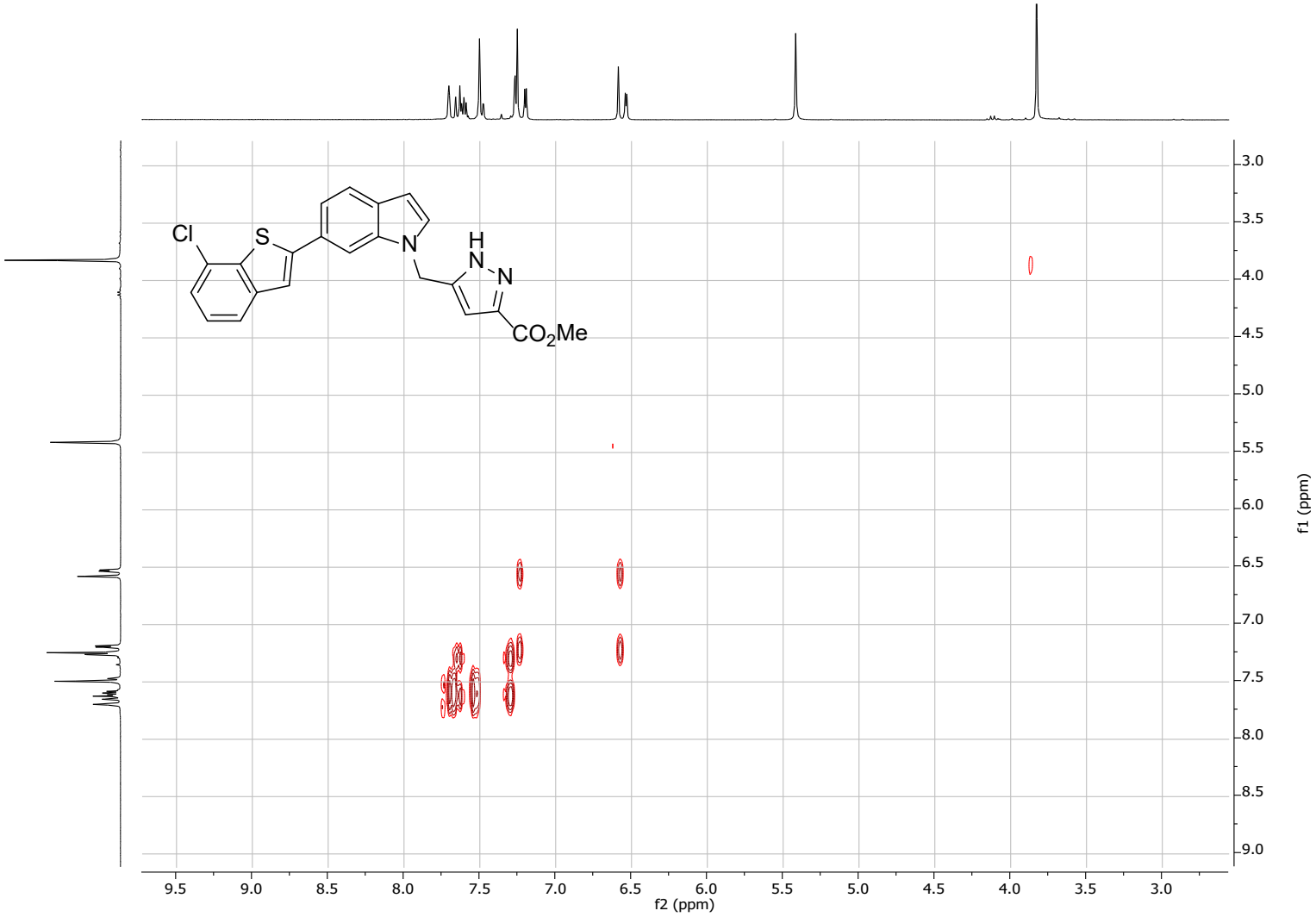
^{1}H NMR (300 MHz) in $CDCl_3$



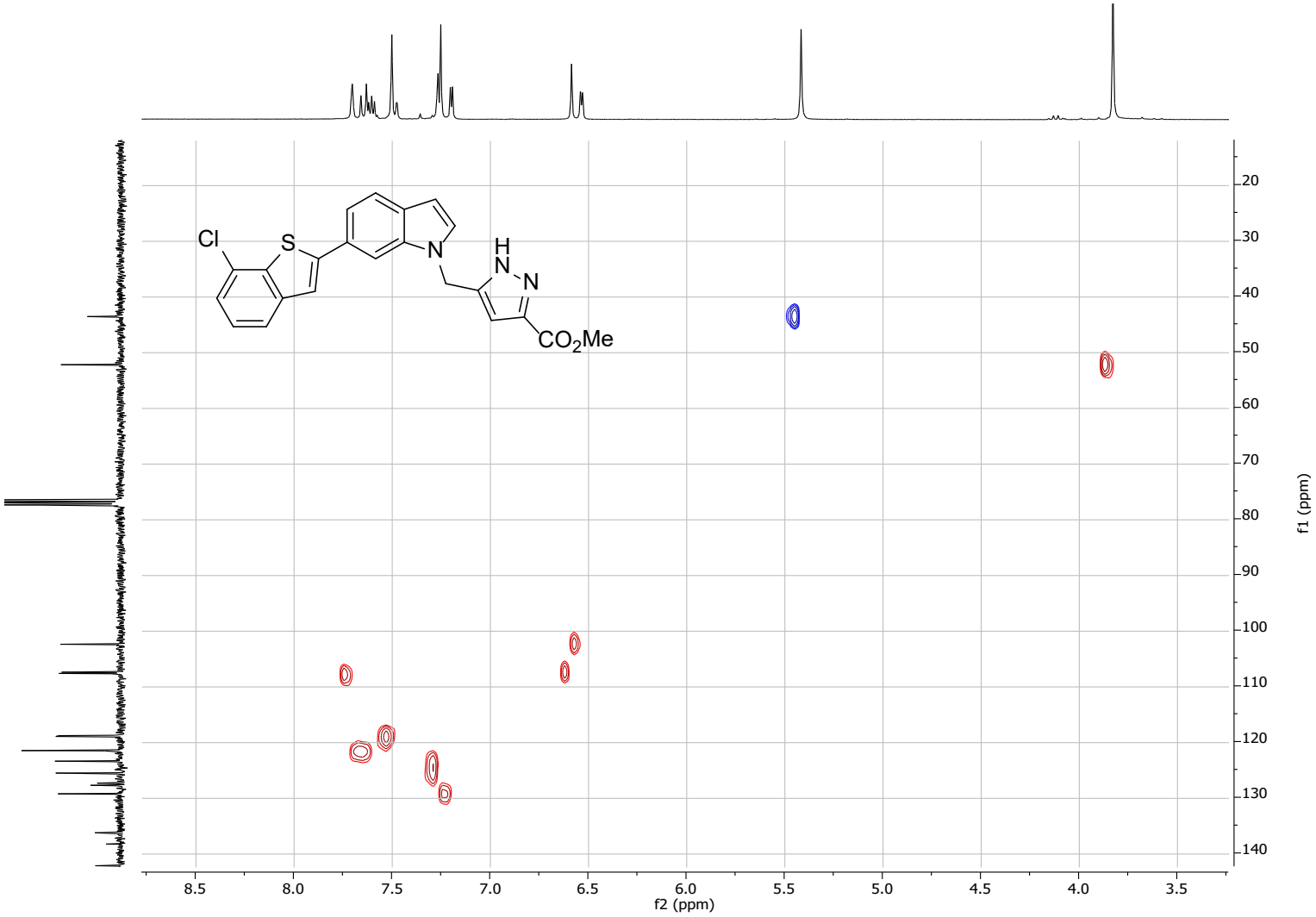
^{13}C NMR (76 MHz) in $CDCl_3$



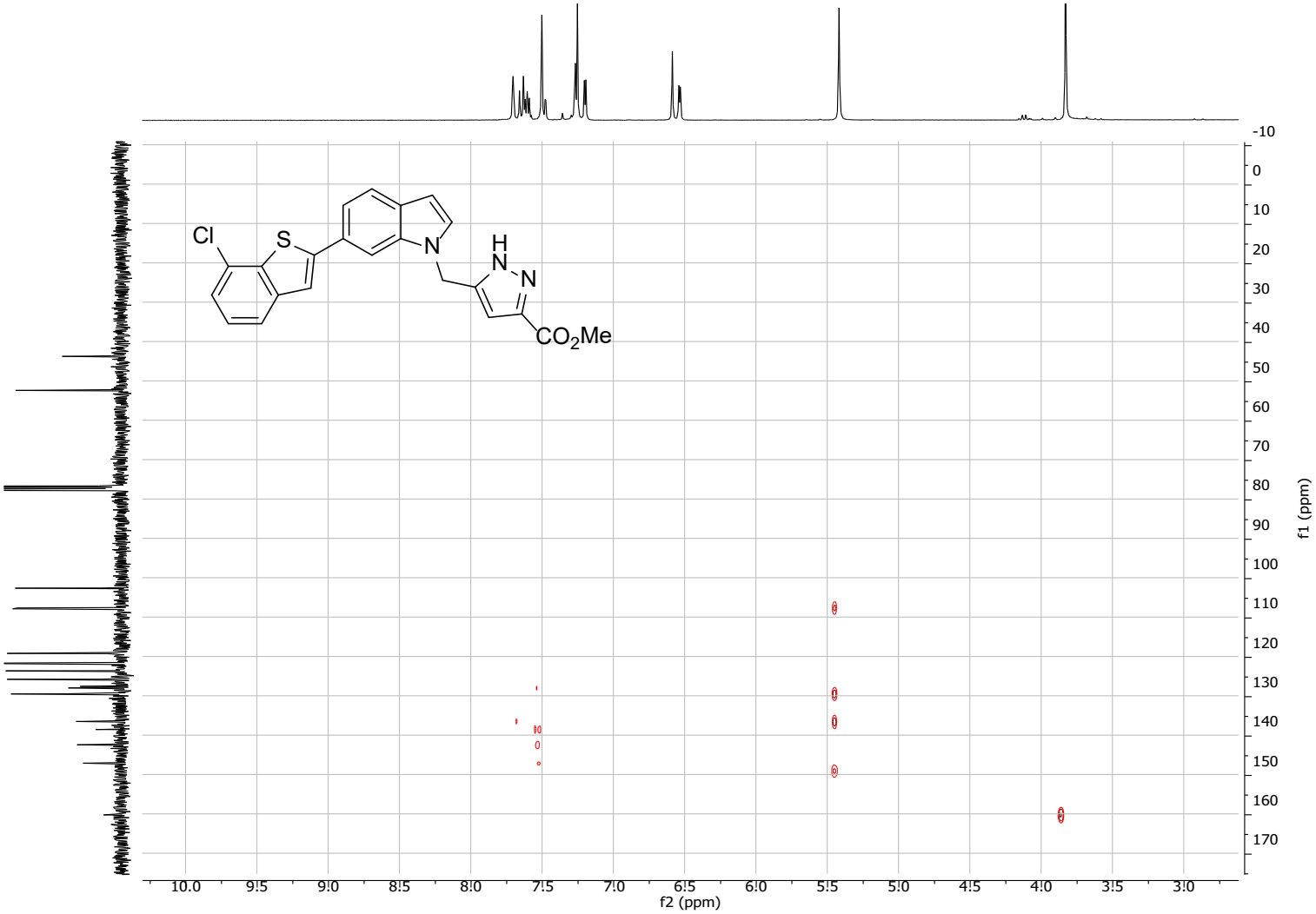
$^{1}H,^{1}H$-COSY (400 MHz) in $CDCl_3$



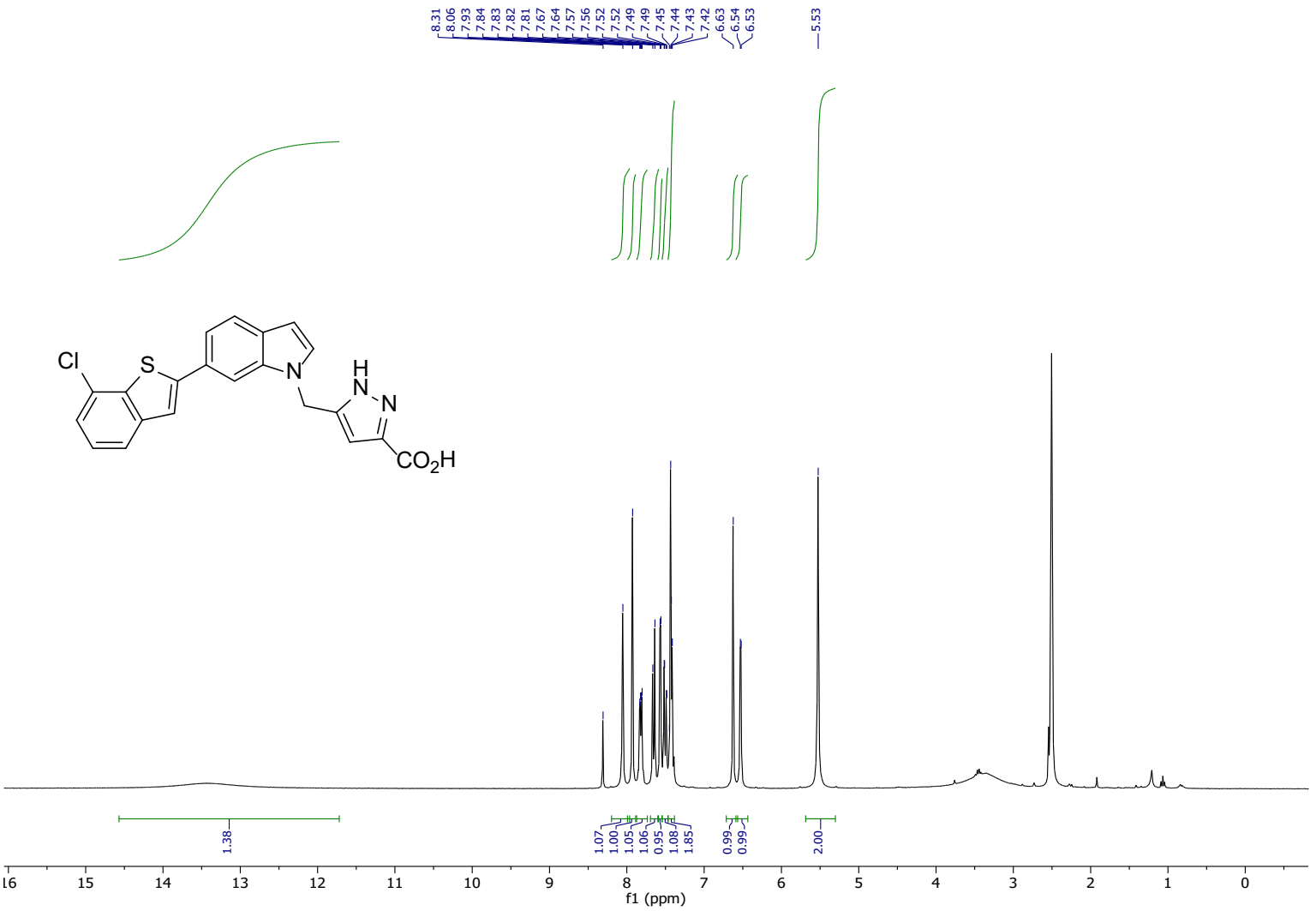
$^{1}H,^{13}C$-HSQC (300 & 76 MHz) in $CDCl_3$



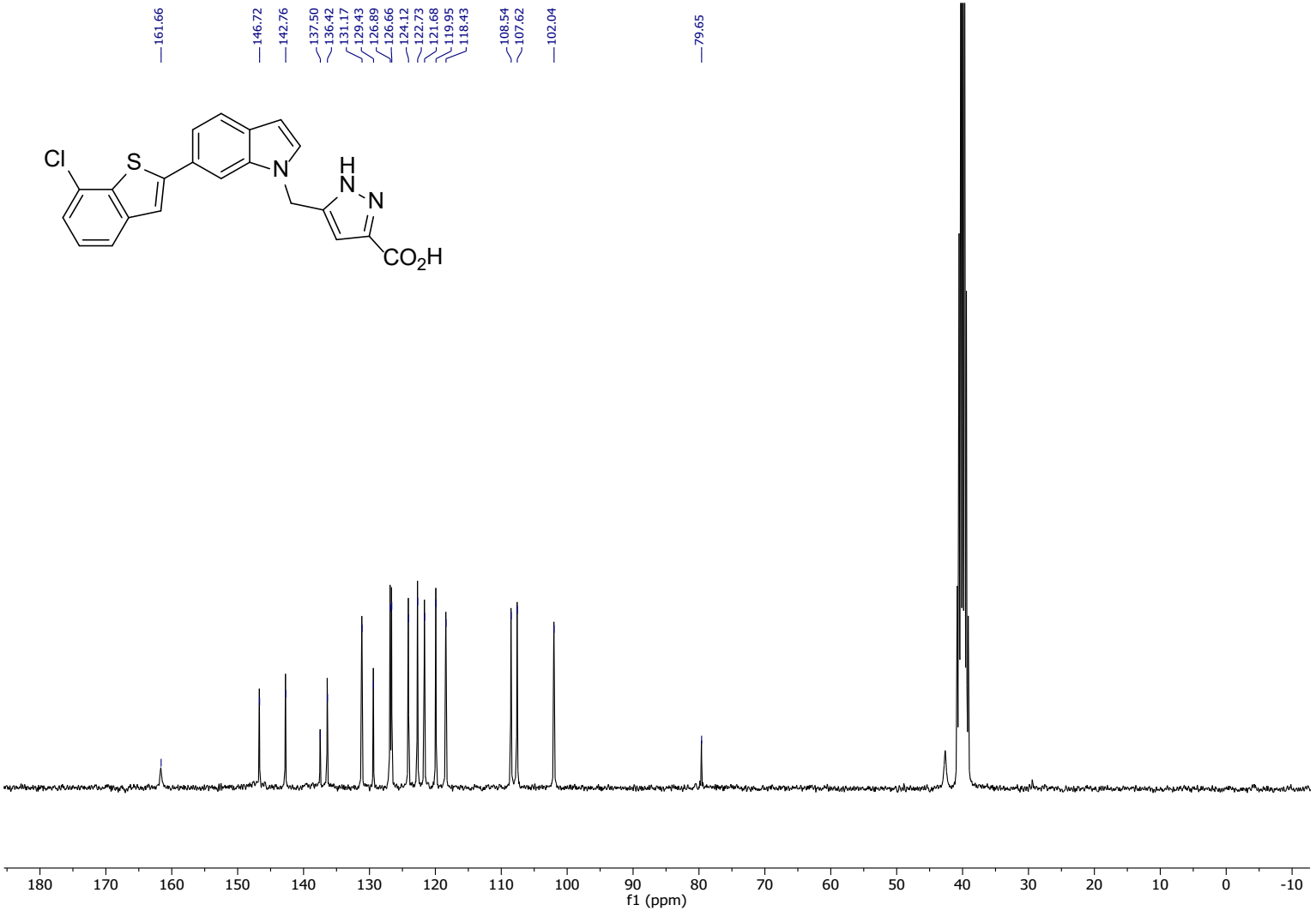
$^{1}H,^{13}C$-HMBC (300 & 76 MHz) in $CHCl_3$



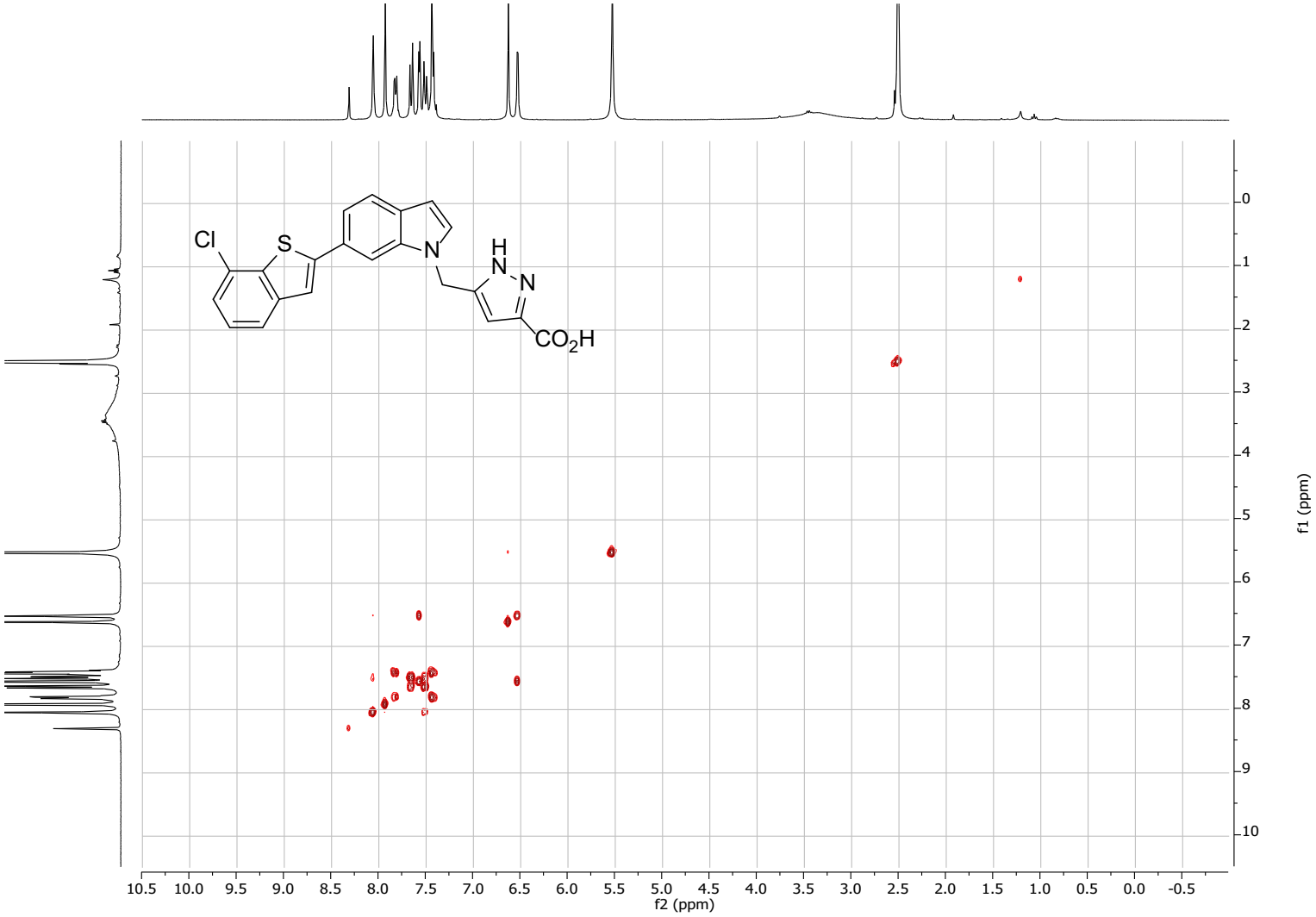
^{1}H NMR (300 MHz) in DMSO-d_6



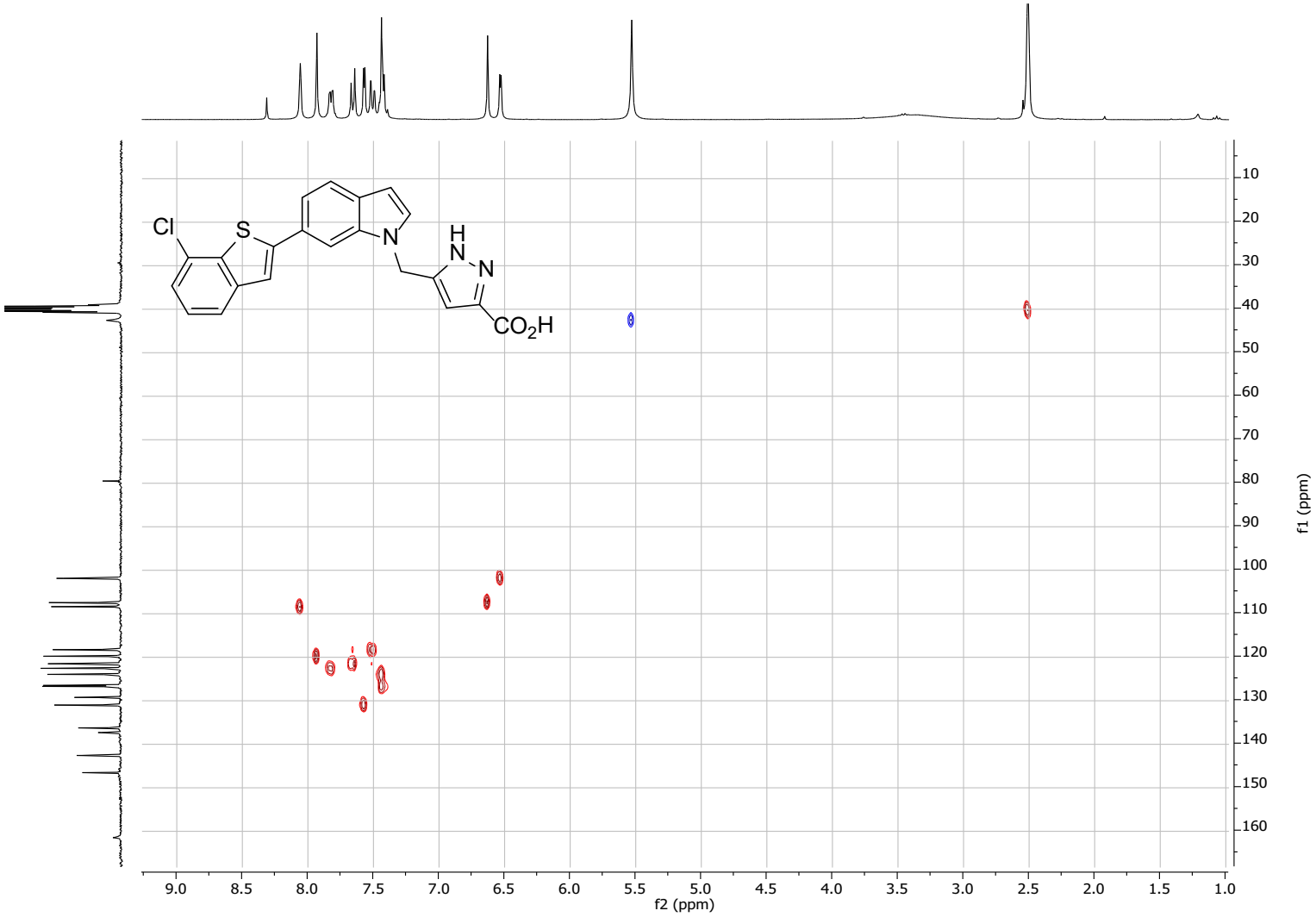
^{13}C NMR (76 MHz) in DMSO-d_6



^{1}H,^{1}H-COSY (300 MHz) in DMSO-d_6



$^{1}H,^{13}C$-HSQC (300 & 76 MHz) in DMSO-d_6



$^{1}H,^{13}C$-HMBC (300 & 76 MHz) in DMSO-d_6