Supplementary Information (SI) for Organic & Biomolecular Chemistry.

Electronic Supplementary Information (ESI) for

Multigram-Scale Synthesis of an experimental antibiotic, Lolamicin and its intermediate

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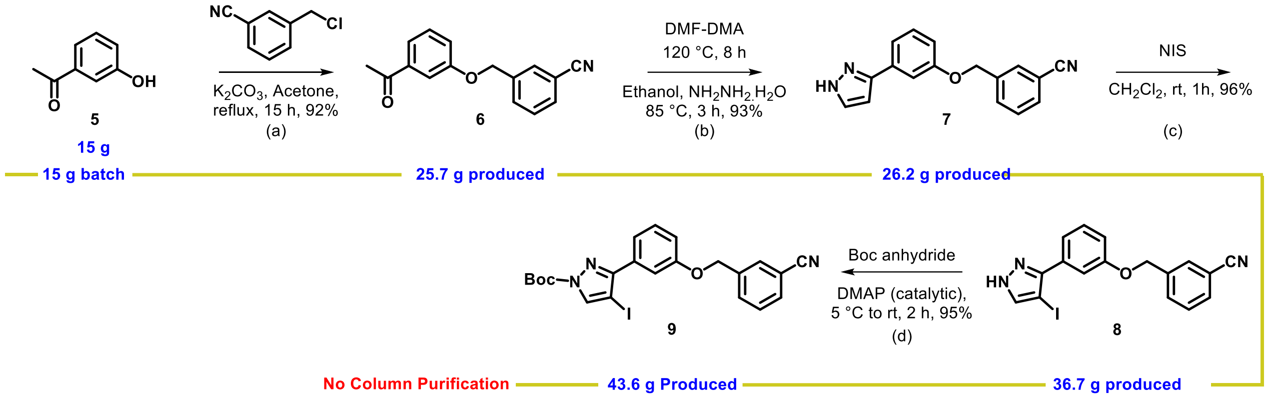
General Information:

All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen. Moisture-sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus through rubber septa. Reagents, starting materials, and solvents were received from available commercial suppliers and utilised with no further purification. All the reactions were monitored by thin-layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualisation was accomplished with the help of either UV light, iodine adsorbed on silica gel or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), panisaldehyde, $KMnO_4$, and ninhydrin solution, followed by heating with a heat gun for ~15 sec. Purification was carried out on column chromatography over silica gel (100-200 mesh size). Commercially received deuterated solvents were used as such for NMR spectroscopic analysis and ^{1}H NMR, ^{13}C NMR spectra were obtained using a 300 MHz, 400 MHz, 500 MHz or 600 MHz spectrometer. Coupling constants were mentioned in Hertz, and chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard ($CDCl_3$ = 7.27 ppm). abbreviations below were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. HRMS (ESI) were recorded on an ORBITRAP mass analyser (Thermo Scientific, Exploris 120). Mass spectra were measured with ESI ionisation in an LCMS (SHIMADZU) mass spectrometer. Infrared (IR) spectra were recorded on a Brucker FT-IR spectrometer as a thin film, and data were integrated by using OPUS (version 17.5) software. Chemical nomenclature was generated using Chembiodraw 23.0. The 3-mercaptopropyl silica gel was procured from TCI (M1979).

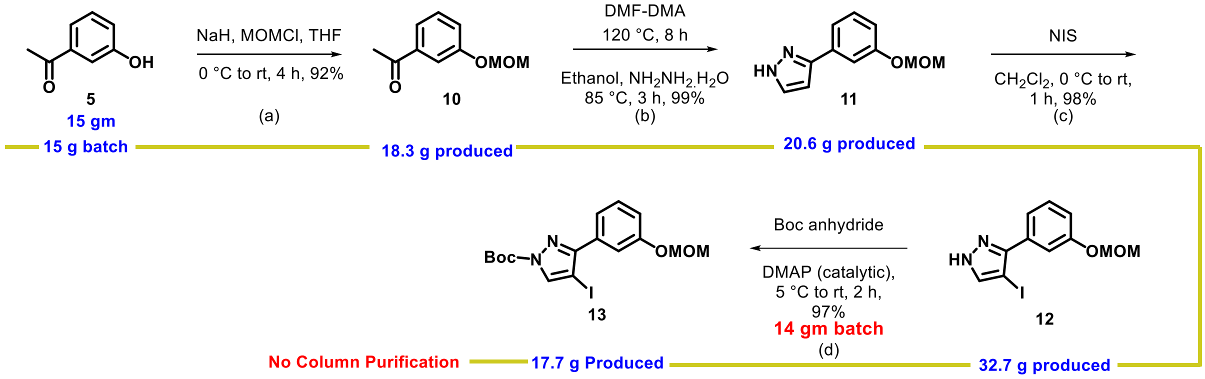
HPLC Method: The compound's purity was assessed using a Shimadzu SPD-M40 system with a C18 reverse column (220 mm × 4.6 mm, 5 µm). The mobile phase comprised water and acetonitrile, with a flow rate of 1.0 mL/min. UV detection was carried out using a photodiode array (PDA) detector. The injection volume ranged from 5 to 10 µL, and the column temperature was set at 30 °C. Purity was determined using the peak area normalization method.

Stepwise Synthesis of 9 [A]



[A]a) **5** (15 g, 110.17 mmol), 3-(Chloromethyl)benzonitrile (16.7 g, 110.17 mmol), K_2CO_3 (38 g, 275.43 mmol); b) **6** (25.7 g, 102.27 mmol), DMF-DMA (68.5 mL, 511.38 mmol), Hydrazine monohydrate (12.5 mL, 409.10 mmol); c) **7** (26.2 g, 95.16 mmol), NIS (23.6 g, 104.67 mmol); d) **8** (36.7 g, 91.47 mmol), DMAP (2.23 g, 18.29 mmol), Boc anhydride (24.8 mL, 104.67 mmol).

Stepwise Synthesis of the key intermediate 13[B]

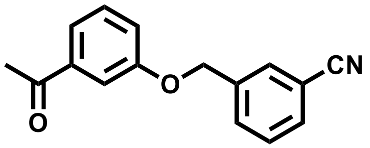


[B]a) **5** (15 g, 110.17 mmol), NaH (7.2 g, 165.25 mmol), MOMCl (10 mL, 132.20 mmol); b) **10** (18.3 g, 101.55 mmol), DMF-DMA (68 mL, 507.76 mmol), Hydrazine monohydrate (12.5 mL, 406.21 mmol); c) **11** (20.6 g, 100.87 mmol), NIS (25 g, 110.95 mmol); d) **12** (32.7 g, 99.05 mmol), DMAP (1 g, 19.81 mmol), Boc anhydride (11 mL, 108.96 mmol).

Note:

*The scheme above shows the stepwise syntheses of compound **9** and the key intermediate **13**. Following completion and workup of each reaction step, the organic layer was concentrated, characterized by NMR spectroscopy, and then used directly in the subsequent reaction without further purification.*

Synthesis and Characterization of Compounds:



6

3-((3-acetylphenoxy)methyl)benzonitrile (6): A 1000 mL, two-neck round-bottom flask equipped with magnetic stirring, a reflux condenser, and a nitrogen inlet was charged with 3-hydroxyacetophenone **5** (15 g, 110.17 mmol) and acetone (0.4 L). The mixture was stirred under a nitrogen atmosphere, and potassium carbonate (38.06 g, 275.43 mmol) was added in 3 portions. 3-(Chloromethyl)benzonitrile (16.70 g, 110.17 mmol) was added in five equal portions over 20 min, and the resulting mixture was heated to reflux and maintained for 15 h. After cooling to ambient temperature, the reaction mass was filtered through a sintered funnel, and the solids were washed with acetone (50 mL). The combined filtrate was concentrated under reduced pressure to give a crude oil, which was treated with n-hexane (0.2 L) at 10–15 °C. The resulting suspension was stirred, and the solid was collected by filtration, washed with n-hexane, and dried under reduced pressure to afford the product **6** as an **off-white solid (26.2 g, 94% yield).**

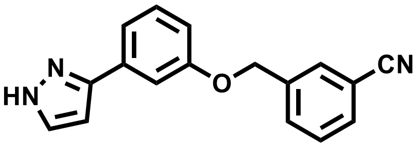
R*f* = 0.6 (hexane/EtOAc = 70:30);

IR υ_{max}(film): 3070, 2923, 2230, 1682, 1583, 1271, 1358, 1214 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.74 (m, 1H), 7.68 (bd, *J* = 7.8 Hz, 1H), 7.64 – 7.62 (m, 1H), 7.59 – 7.55 (m, 2H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.18 (ddd, *J* = 8.2, 2.7, 0.9 Hz, 1H), 5.14 (s, 2H), 2.60 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 158.5, 138.7, 138.3, 131.8, 131.6, 130.8, 129.9, 129.5, 122.0, 120.4, 118.7, 113.2, 112.9, 68.8, 26.8.

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}NO_2$ 252.1024; Found 252.1023.



7

3-((3-(1*H*-pyrazol-3-yl)phenoxy)methyl)benzonitrile (7): A 500 mL round-bottom flask equipped with magnetic stirring and a reflux condenser was charged with compound **6** (26.2 g, 104.34 mmol) and DMF-DMA (69.80 mL, 521.72 mmol). The mixture was heated at 120 °C for 8 h, cooled to room temperature, and concentrated under reduced pressure to afford a brown oil. The residue was diluted with ice–water and stirred for 20 min, followed by extraction with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with water (2 x 200 mL) and saturated brine (150 mL), dried, and concentrated to provide a thick brown oil. This material was dissolved in ethanol (150 mL), and hydrazine monohydrate (13.09 mL, 417.38 mmol) was added dropwise over 20 min at 10–15 °C. The reaction mixture was then heated to reflux for 3 h and concentrated under reduced pressure to afford a crude brown oil. The residue was taken up in ethyl acetate (400 mL), washed sequentially with water (2 x 150 mL) and saturated brine solution (150 mL) and passed over sodium sulphate, and concentrated under reduced pressure to Offord compound **7** as a **light-brown oil (27 g, 94% yield)**, which is directly forwarded to the next step.

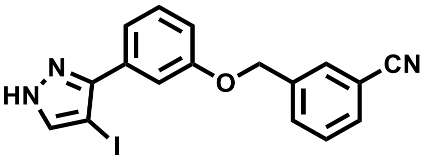
R*f* = 0.2 (hexane/EtOAc = 70:30);

IR ʋmax(film): 3174, 2925, 2231, 1583, 1608, 1214, 863, 753 cm^{-1};

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.68 (bs, 1H), 7.62 – 7.75 (m, 3H), 7.48 – 7.27 (m, 4H), 6.98 – 6.92 – 6.88 (m, 1H), 6.60 (s, 1H), 5.01 (s, 2H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 158.5, 148.7, 138.4, 133.5, 133.0, 131.4, 131.4, 130.5, 129.9, 129.2, 118.9, 118.7, 114.5, 112.3, 111.6, 102.7, 68.3.

HRMS (ESI) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{14}N_3O$ 276.1136; Found 276.1135.



8

3-((3-(4-iodo-1*H*-pyrazol-3-yl)phenoxy)methyl)benzonitrile (8): To a 1000-mL round-bottomed flask equipped with a magnetic stir bar was charged **7** (27 g, 98.07 mmol) in dichloromethane (500 mL). The solution was cooled to 0–5 °C, and N-iodosuccinimide (NIS, 24.27 g, 107.87 mmol) was added in small portions over 60 min. Upon complete addition, the mixture was stirred for 1 h at room temperature. The water was added (200 mL), and the layers were separated. The organic layer was washed successively with an aqueous sodium thiosulfate solution (3 x 200 mL), water (200 mL), and a saturated brine solution (200 mL). The combined organic extracts were passed over sodium sulphate and used directly in the next step without solvent evaporation.

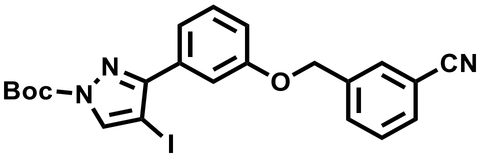
R*f* = 0.5 (hexane/EtOAc = 70:30);

IR ʋmax(film): 3156, 3019, 2923, 2231, 1606, 1582, 1215, 1044, 753 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.63 – 7.61 (m, 2H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.40 – 7.35 (m, 3H), 7.03 – 7.0 (m, 1H), 5.11 (s, 2H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 158.3, 147.5, 141.0, 138.6, 132.1, 131.8, 131.7, 130.9, 130.1, 129.6, 121.2, 118.8, 115.8, 114.2, 112.9, 68.9, 57.3.

HRMS (ESI) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{13}IN_3O$ 402.0103; Found 402.0096



9

tert-butyl 3-(3-((3-cyanobenzyl)oxy)phenyl)-4-iodo-1*H*-pyrazole-1-carboxylate (9): To a 1000-mL round-bottomed flask equipped with a magnetic stir bar was charged the above dichloromethane solution of compound **8** and cooled to 5 °C. 4-Dimethylaminopyridine (DMAP) 2.54 g, 20.86 mmol) was added, followed by the slow dropwise addition of di-tert-butyl dicarbonate (Boc_2O)(28.75 mL, 125.20 mmol) over 50 min at 5 °C. Upon complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with water (200 mL) at 10–15 °C, and the layers were separated. The organic phase was washed successively with water (150 mL) and saturated brine solution (150 mL). The combined organic and concentrated under reduced pressure to afford the crude Boc-protected intermediate **9** as a thick brown oil (**44.1 g, 89% yield after 2 steps**), which can be used directly in the subsequent step without further purification.

HPLC: 97.85% (t_R = 16.69 min.)

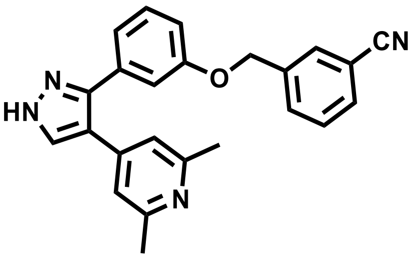
R*f* = 0.8 (hexane/EtOAc = 70:30);

IR υ_{max}(film): 3140, 2980, 2230, 1771, 1752, 1453, 1370, 1222, 1150, 841 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.77 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.05 – 7.01 (m, 1H), 5.15 (s, 2H), 1.66 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 155.2, 146.6, 138.7, 137.4, 132.9, 131.7, 131.6, 130.8, 129.7, 129.5, 121.9, 118.8, 116.4, 114.4, 112.8, 86.4, 68.9, 62.1, 28.0.

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{20}IN_3O_3Na$ 524.0447; Found 524.0460



1

3-((3-(4-(2,6-dimethylpyridin-4-yl)-1*H*-pyrazol-3-yl)phenoxy)methyl)benzonitrile (1): A solution of compound **9** (10.5 g, 20.95 mmol) in 1,4-dioxane (300 mL) and water (15 mL) was charged to a Parr reactor. The vessel was purged with nitrogen for 15 min. Cs_2CO_3 (13.6 g, 41.90 mmol), 2,6-dimethylpyridin-4-yl boronic acid (3.80 g, 25.15 mmol), and Pd(dppf)Cl_2

(0.76 g, 1.04 mmol) were added, and the reactor was sealed. The mixture was purged again with nitrogen for 5 min, then heated to 120 °C and stirred for 12 h. After cooling to room temperature, the reaction mixture was removed from the reactor and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford a crude product, which was purified by silica gel column chromatography, yielding compound **1** as an **off-white foam (6.3 g, 79%).**

Note: Based on one of the reviewer's suggestions, we have measured residual Pd content in the final product using ICP-MS analysis, and it was found to be 45 ppm levels. Subsequently, the residual palladium was removed using a known protocol. A solution of **1** (300 mg) in dichloromethane was passed through a small bed of commercially available 3-mercaptopropyl silica gel and resulted in pure material of **1**, which is free of Pd traces.

HPLC: 99.80% (t_R = 12.91 min.)

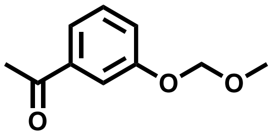
R_f = 0.2 (hexane/EtOAc = 50:50);

IR υ_{max}(film): 3127, 2922, 1606, 1448, 1377, 1215, 1025, 794 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.68 (s, 1H), 7.62 – 7.59 (m, 2H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 8.2 Hz, 1H), 7.10 – 7.08 (m, 2H), 7.01 – 6.98 (m, 1H), 6.92 (s, 2H), 5.01 (s, 2H), 2.48 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 158.0, 141.6, 138.5, 132.5, 131.8, 131.5, 130.8, 130.3, 130.2, 129.6, 121.5, 119.5, 118.7, 118.1, 115.6, 114.4, 112.9, 68.9, 24.6.

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{21}N_4O$ 381.1715; Found 381.1728



10

1-(3-(methoxymethoxy)phenyl)ethan-1-one (10): To a 2000-mL, two-necked, round-bottomed flask equipped with a magnetic stir bar and maintained under a nitrogen atmosphere was charged 3-hydroxyacetophenone **5** (50 g, 367.24 mmol) and dry tetrahydrofuran (800 mL). The solution was cooled to 0 °C, and sodium hydride (24.03 g, 550.86 mmol, 55% dispersion in mineral oil) was added portion-wise over 45 min. The reaction mixture was stirred for an additional 20 min at 0 °C, and chloromethyl methyl ether (33.47 mL, 440.68 mmol) was added dropwise over 30 min at the same temperature. After the addition was complete, the mixture was allowed to warm gradually to room temperature and stirred for 4 h. The reaction mass was cooled to 10 °C, and crushed ice (100 g) was added slowly with stirring. The mixture was extracted with ethyl acetate (400 mL × 3). The combined organic layers were washed successively with water (500 mL) and a saturated aqueous brine solution (400 mL), then dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to yield the crude oil product. The crude product was treated with n-hexane (150 mL × 2) and stirred for 20 min. The n-hexane layer was decanted, and the remaining residue was dried under reduced pressure to afford the MOM-protected intermediate **10** as a thick **brown oil (63 g, 95% yield)**, which was used directly in the next step without further purification.

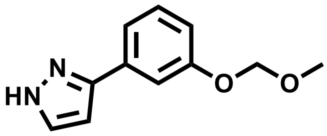
R*f* = 0.4 (hexane/EtOAc = 80:20);

IR υmax(film): 2923, 1682, 1583, 1484, 1357, 1268, 1152 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 2H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.24 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 5.22 (s, 2H), 3.49 (s, 3H), 2.59 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 157.5, 138.7, 129.8, 122.1, 121.3, 115.8, 94.6, 56.3, 26.9.

HRMS (ESI) *m/z*: [M+H]$^+$ Calcd for $C_{10}H_{13}O_3$ 181.0864; Found 181.0864.



11

3-(3-(methoxymethoxy)phenyl)-1*H*-pyrazole (11): A 1000 mL round-bottom flask equipped with a magnetic stirring bar and a reflux condenser was charged with compound **10** (63 g, 349.61 mmol) and DMF-DMA (208.3 mL, 1748.05 mmol). The mixture was heated at 120 °C for 8 h, cooled to room temperature, and concentrated under reduced pressure to afford a brown oil. The residue was diluted with ice–water (400 mL) and stirred for 20 min, followed by extraction with dichloromethane (2 x 600 mL). The combined organic extracts were washed with water (2 x 400 mL) and saturated brine (300 mL), dried, and concentrated to provide a thick brown oil. This material was dissolved in ethanol (500 mL), and hydrazine monohydrate (43.87 mL, 1398.44 mmol) was added dropwise over 40 min at 10–15 °C. The reaction mixture was then heated to reflux for 3 h and concentrated under reduced pressure to afford a crude brown oil. The residue was taken up in dichloromethane (1000 mL), washed sequentially with water (2 x 400 mL) and saturated brine (300 mL) and the combined organic extracts were passed over sodium sulphate and used directly in the next step without solvent evaporation.

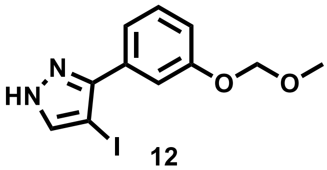
R*f* = 0.2 (hexane/EtOAc = 80:20);

IR υmax(film): 3174, 2956, 1585, 1477, 1152, 1014, 964 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.2 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.02 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 6.60 (d, *J* = 2.2 Hz, 1H), 5.22 (s, 2H), 3.50 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 148.9, 133.8, 133.1, 129.9, 119.6, 115.9, 113.7, 102.7, 94.4, 56.0.

HRMS (ESI) *m/z*: [M+H]$^+$ Calcd for $C_{11}H_{13}N_2O_2$ 205.0977; Found 205.0979



12

4-iodo-3-(3-(methoxymethoxy)phenyl)-1*H*-pyrazole (12): To a 2000-mL round-bottomed flask equipped with a magnetic stir bar was charged the above dichloromethane solution of **11**. The solution was cooled to 0–5 °C, and N-iodosuccinimide (NIS, 86 g, 382.41 mmol) was added in small portions over 60 min. Upon complete addition, the mixture was stirred for 1 h at room temperature. The water was added (400 mL), and the layers were separated. The organic layer was washed successively with a saturated aqueous sodium thiosulfate solution (3 x 300 mL), water (400 mL), and a saturated brine solution (300 mL). The combined organic extracts were passed over sodium sulphate and used directly in the next step without solvent evaporation.

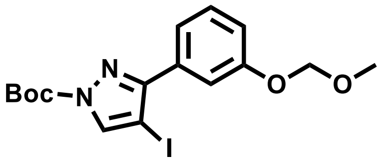
R*f* = 0.5 (hexane/EtOAc = 80:20);

IR υ_{max}(film): 3153, 2922, 1583, 1458, 1152, 978 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.44 (bs, 1H), 7.39 – 7.34 (m, 2H), 7.10 (dt, *J* = 7.0, 2.2 Hz, 1H), 5.22 (s, 2H), 3.51 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 147.1, 141.4, 131.8, 129.8, 121.6, 116.8, 115.8, 94.5, 57.1, 56.2.

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{12}IN_2O_2$ 330.9943; Found 330.9943



13

tert-butyl 4-iodo-3-(3-(methoxymethoxy)phenyl)-1*H*-pyrazole-1-carboxylate (13): To a 2000-mL round-bottomed flask equipped with a magnetic stir bar was charged the above dichloromethane solution of compound **12** and cooled to 5 °C. 4-Dimethylaminopyridine ((DMAP) 8.4 g, 69.06 mmol) was added, followed by the slow dropwise addition of di-tert-butyl dicarbonate (Boc_2O)(95.2 mL, 414.37 mmol) over 50 min at 5 °C. Upon complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with water (400 mL) at 10–15 °C, and the layers were separated. The organic phase was washed successively with water (400 mL) and saturated brine solution (300 mL), and concentrated under reduced pressure to afford the key intermediate **13** as a **thick brown oil (136.9 g, 91% yield after 3 steps)**

HPLC: 97.72% **(**t_R = 16.67 min.)

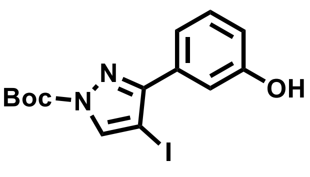
R*f* = 0.7 (hexane/EtOAc = 80:20);

IR υ_{max}(film): 3137, 2978, 1584, 1454, 1285, 1144, 1017, 922, 839 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.57 – 7.52 (m, 2H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.10 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 5.23 (s, 2H), 3.49 (s, 3H), 1.65 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 155.3, 146.6, 137.3, 132.7, 129.4, 122.3, 117.2, 116.5, 94.5, 86.2, 62.2, 56.1, 28.0.

HRMS (ESI) *m/z*: [M+H]$^+$ Calcd for $C_{16}H_{20}IN_2O_4$ 431.0467; Found 431.0451



14

tert-butyl 3-(3-hydroxyphenyl)-4-iodo-1H-pyrazole-1-carboxylate (14): To a round-bottomed flask equipped with a magnetic stir bar and maintained under a nitrogen atmosphere was charged compound **13** (1 g, 2.32 mmol) and dichloromethane (50 mL). The solution was cooled to 0 °C, and TBAB (3.74 g, 11.62 mmol) was added in four portions, followed by the slow addition of TMSCl (1.5 ml, 11.62 mmol). After the addition was complete, the mixture was allowed to warm gradually to room temperature and stirred for 8 h. The reaction mass was cooled to 0 °C, and water (100 mL) was added, and the mixture was extracted with dichloromethane (50 mL × 2). The combined organic layers were washed successively with a saturated aqueous brine solution (100 mL), then dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to yield the crude product, which was purified by silica gel column chromatography to yield compound **14** as **white foam (0.74 g, 82%).**

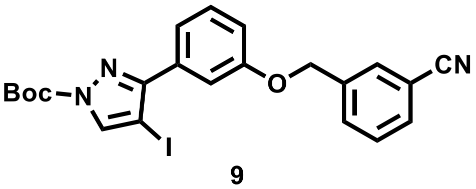
R*f* = 0.3 (hexane/EtOAc = 70:30);

IR υ_{max}(film): 3332, 2981, 2934, 1754, 1591, 1292, 1231, 1144, 867, cm^{-1};

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.68 (s, 1H), 8.52 (s, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.21 (dd, *J* = 9.4, 4.8 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 1.59 (s, 9H).

^{13}C NMR (125 MHz, DMSO-*d6*) δ 157.3, 154.6, 146.0, 137.9, 132.5, 129.5, 118.8, 116.2, 114.7, 85.6, 63.9, 27.4.

HRMS (ESI) *m/z*: [M+Na]$^+$ Calcd for $C_{14}H_{15}IN_2O_3Na$ 409.0025; Found 408.9998.



9

tert-butyl 3-(3-((3-cyanobenzyl)oxy)phenyl)-4-iodo-1H-pyrazole-1-carboxylate (9): To a round-bottomed flask equipped with a magnetic stir bar and maintained under a nitrogen atmosphere was charged compound **14** (0.1 g, 0.26 mmol) and DMF (3 mL). The solution was cooled to 0 °C, and K_2CO_3 (90 mg, 0.64 mmol) was added, followed by 3-(bromomethyl)benzonitrile (56 mg, 0.28 mmol). After the addition was complete, the mixture was allowed to warm gradually to room temperature and stirred for 2 h. Ice water was added, and the compound was extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed successively with a saturated aqueous brine solution (20 mL), then dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to yield the crude product, which was purified by silica gel column chromatography to yield compound **9** (94 mg, 72%). The spectroscopic data were identical to compound **9**.

Note: The above synthesized compound **9** (50 mg, 0.09 mmol) was then further converted to Lolamicin **1** by following the same procedure as shown on page No. S7.

X-ray Crystallography of compound 12 (VA 287)

X-ray Crystallography.

X-ray data for the compound was collected at room temperature on a Bruker D8 VENTURE instrument with an IμS Mo microsource (λ = 0.7107 Å) and a Bruker PHOTON III C14 detector. The raw data frames were reduced and corrected for absorption effects using the Bruker Apex 5 software suite programs.[1] The structure was solved using intrinsic phasing method[3] and further refined with the SHELXL[2] program and expanded using Fourier techniques. Anisotropic displacement parameters were included for all non-hydrogen atoms. The iodine atoms (I1A, I1B and I1C) were disordered over two positions and their site occupational factors were refined to 0.568(15)/0.432(15), 0.678(5)/0.322(5) and 0.575(17)/0.425(17), respectively. Further, the atoms O1B/C10B/O2B/C11B were also disordered over two positions and their site occupational factors were refined to 0.678(5)/0.322(5). The N bound H atoms were located in the difference Fourier maps and its positions and isotropic displacement parameters were refined. All C bound H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H = 0.93-0.97 Å, and $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl H or $1.2U_{eq}(C)$ for other H atoms].

Method of Crystallization: The crystal of compound **12** was obtained using a slow evaporation method in Dichloromethane at 20 °C.

Crystal structure determination of 12 (VA 287)

Crystal Data for $C_{11}H_{11}N_2O_2I$ (M =330.12 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 19.0900(17) Å, b = 9.6073(8) Å, c = 20.2257(18) Å, β = 95.037(3)°, V = 3695.1(6) Å^3, Z = 12, T = 294.15 K, μ(MoKα) = 2.587 mm^{-1}, $Dcalc$ = 1.780 g/cm^3, 42332 reflections measured (5.088° ≤ 2Θ ≤ 56.53°), 8926 unique (R_{int} = 0.0369, R_{sigma} = 0.0334) which were used in all calculations. The final R_1 was 0.0267 ($I > 2\sigma(I)$) and wR_2 was 0.0766 (all data). **CCDC 2497610** deposition number contains the supplementary crystallographic data for this paper which can be obtained free of charge at https://www.ccdc.cam.ac.uk/structures/

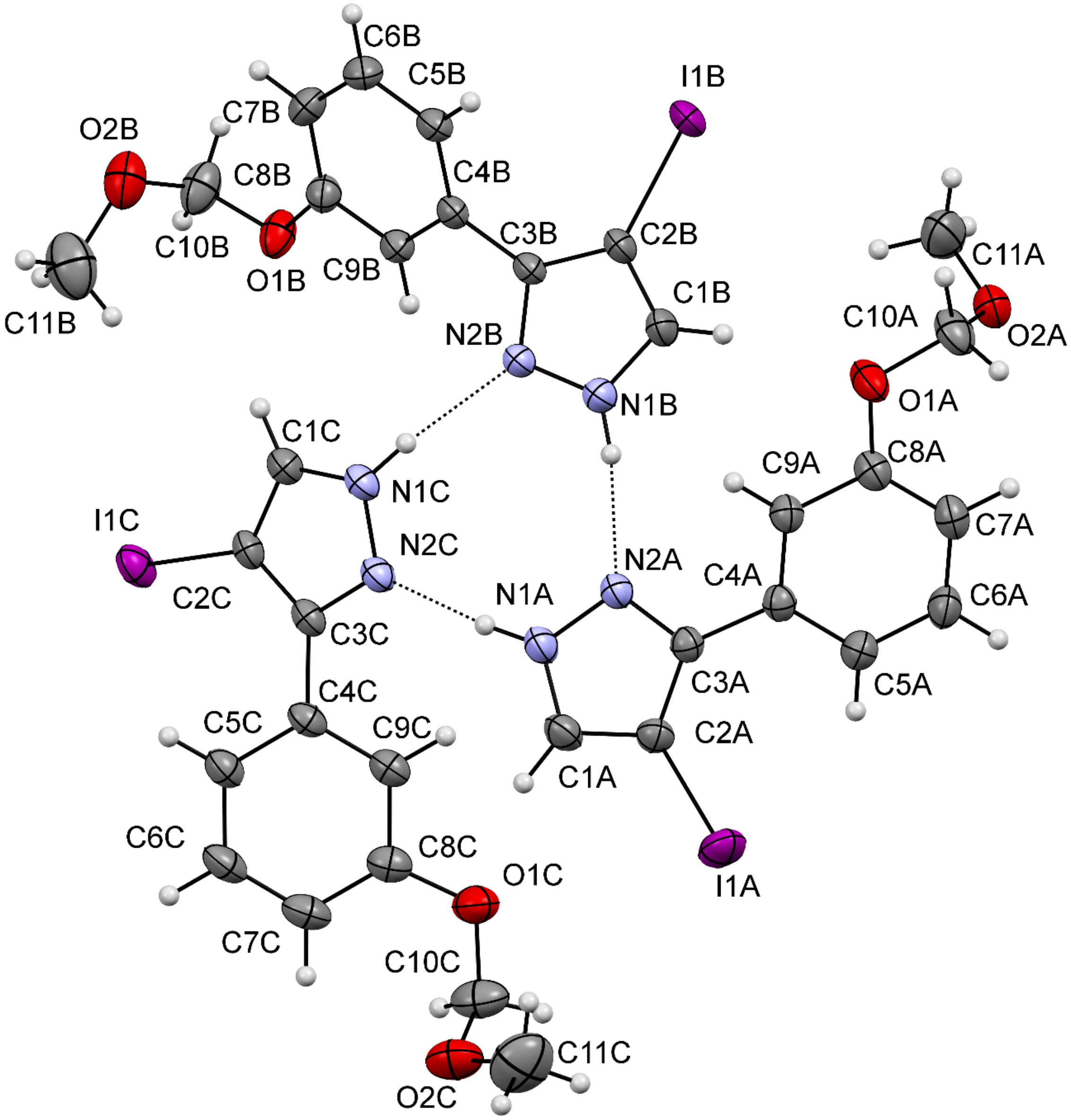


Figure caption: ORTEP diagram of **12 (VA 287)** with the atom-numbering. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius. The asymmetric unit contains three crystallographically independent molecules. The minor component of the disordered atoms was omitted for clarity.

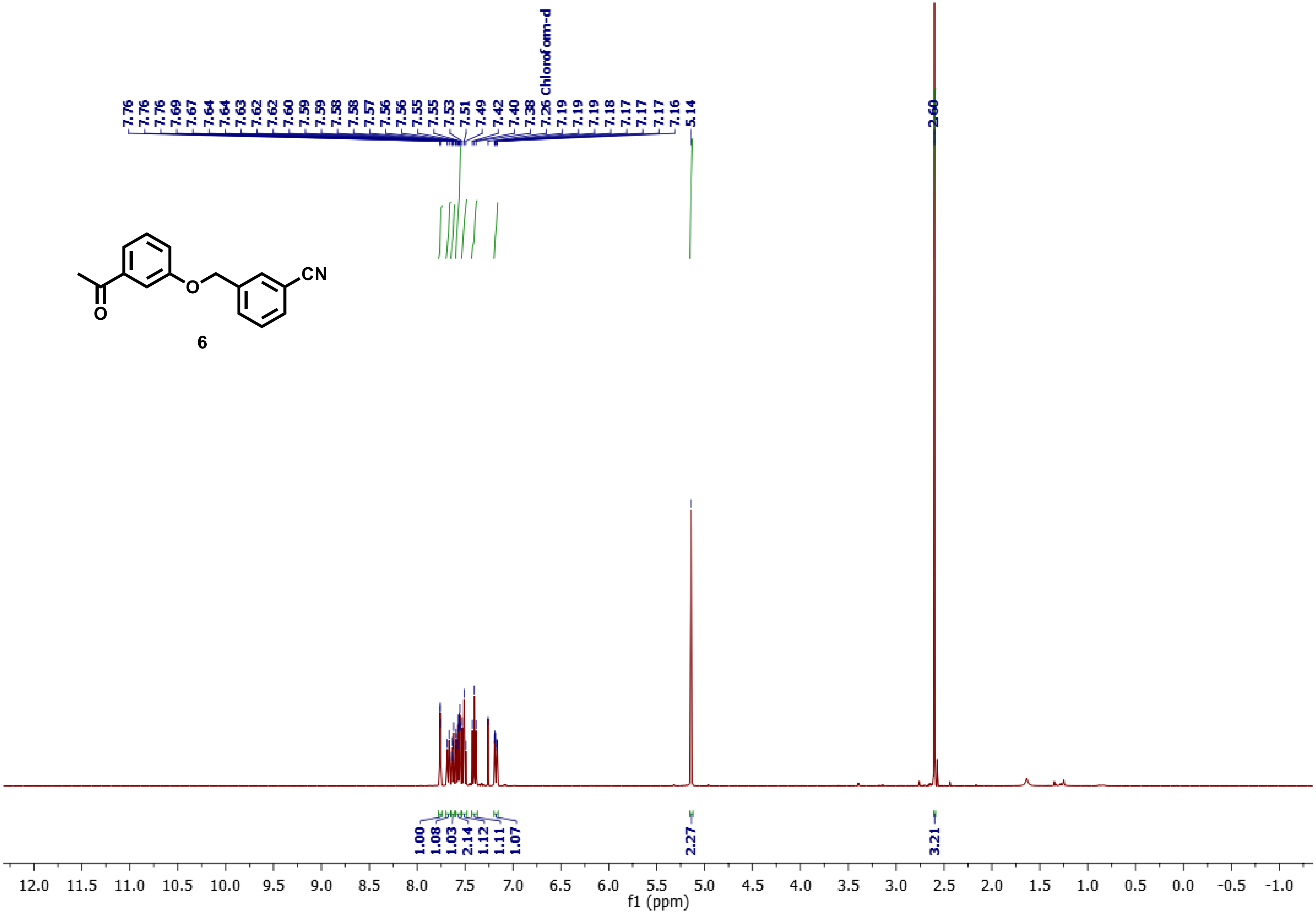
References:

1) Bruker, A.P.E.X. 2023. SAINT and SADABS. APEX5, SAINT and SADABS: Data Collection and Processing Software, Bruker AXS. Inc., Madison, Wisconsin, USA.

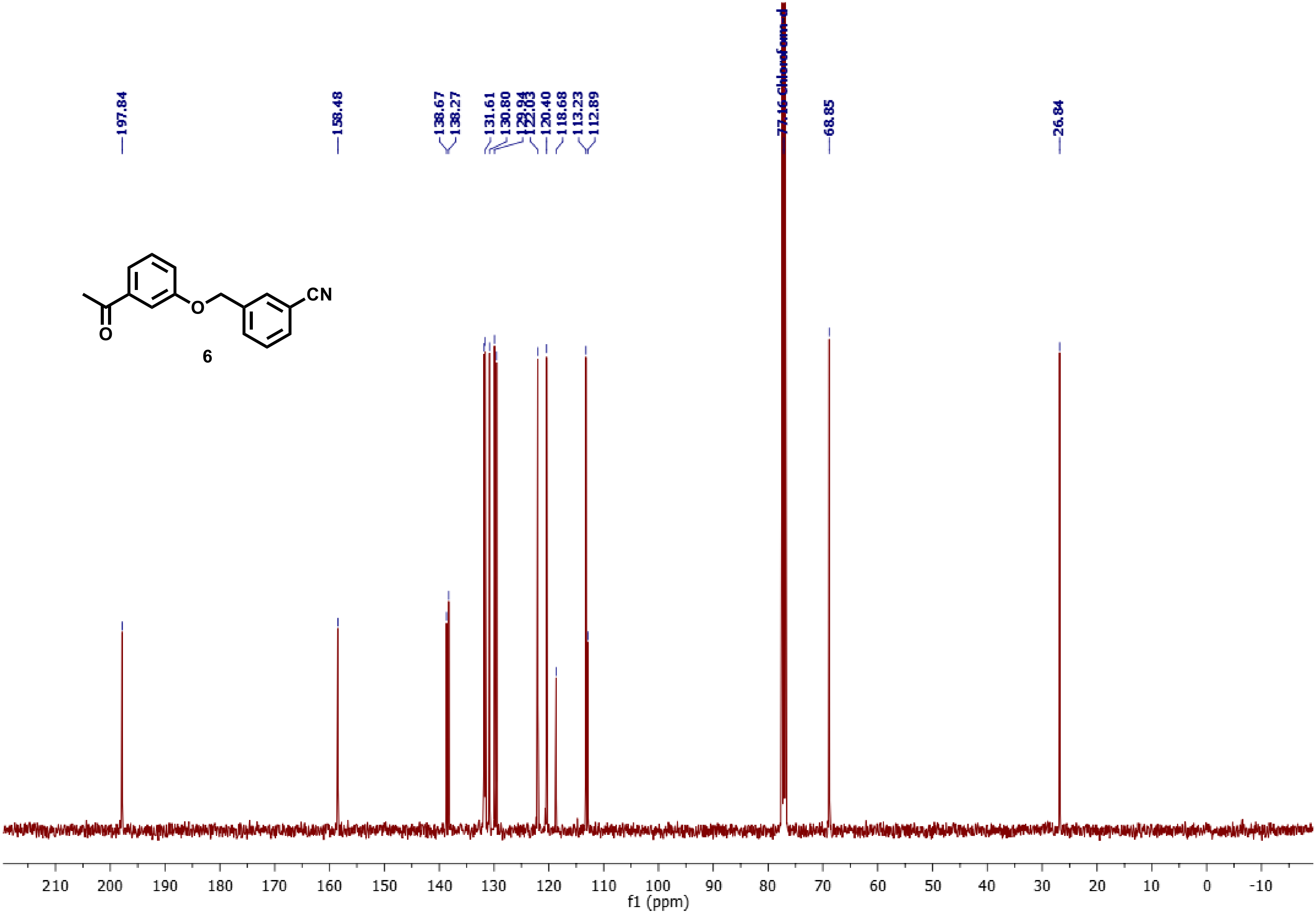
2) Sheldrick, G. M. *Acta Crystallographica.* 2015, **C71**, 3-8

Copies of ^{1}H, ^{13}C NMR and HPLC spectra

^{1}H NMR of 6 in CDCl$_3$ at 400 MHz

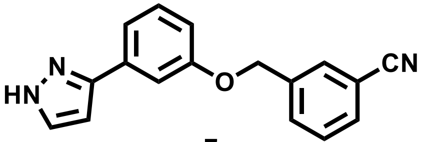


^{13}C NMR of 6 in $CDCl_3$ at 100 MHz

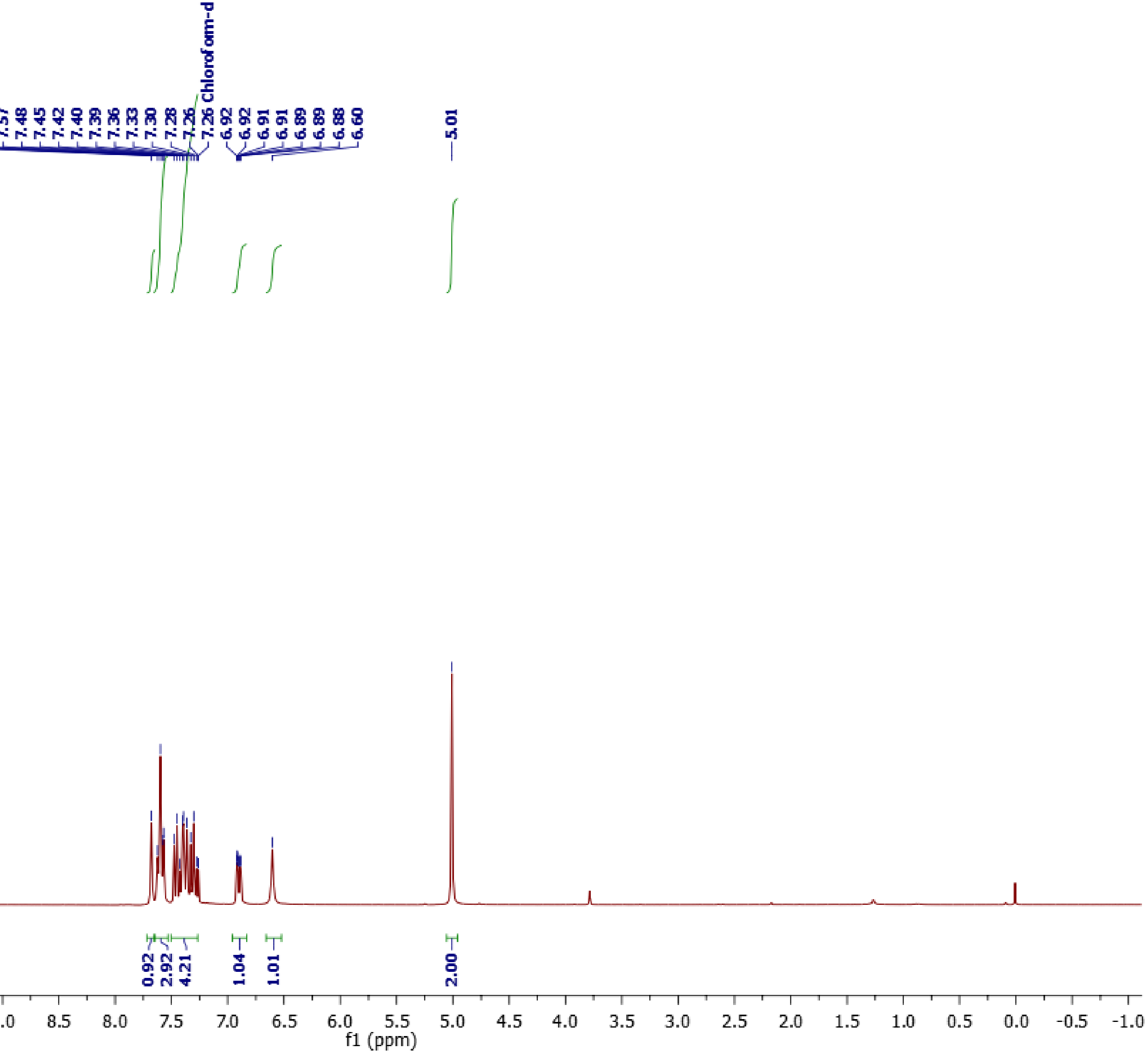


6

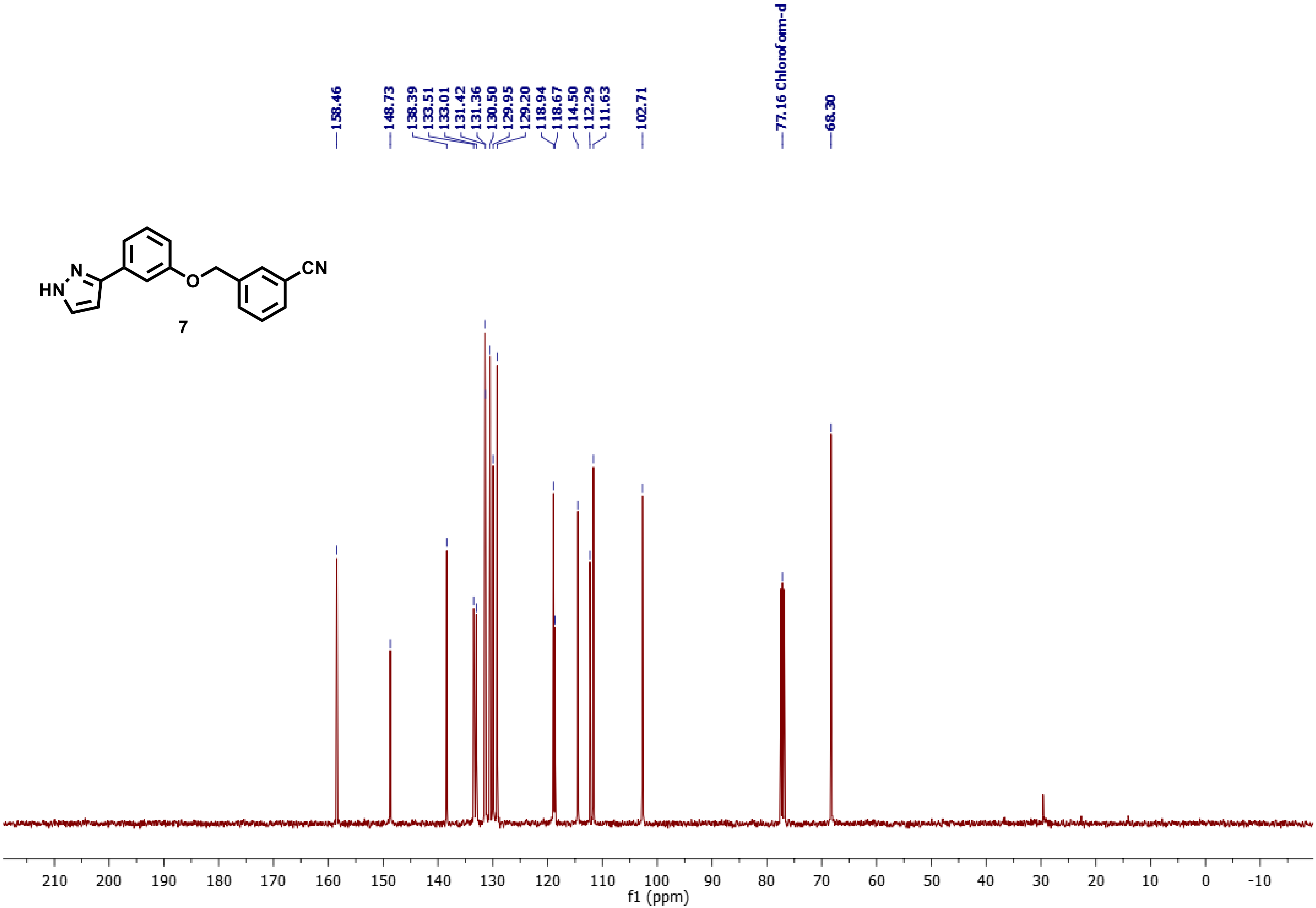
^{1}H NMR of 7 in $CDCl_3$ at 300 MHz



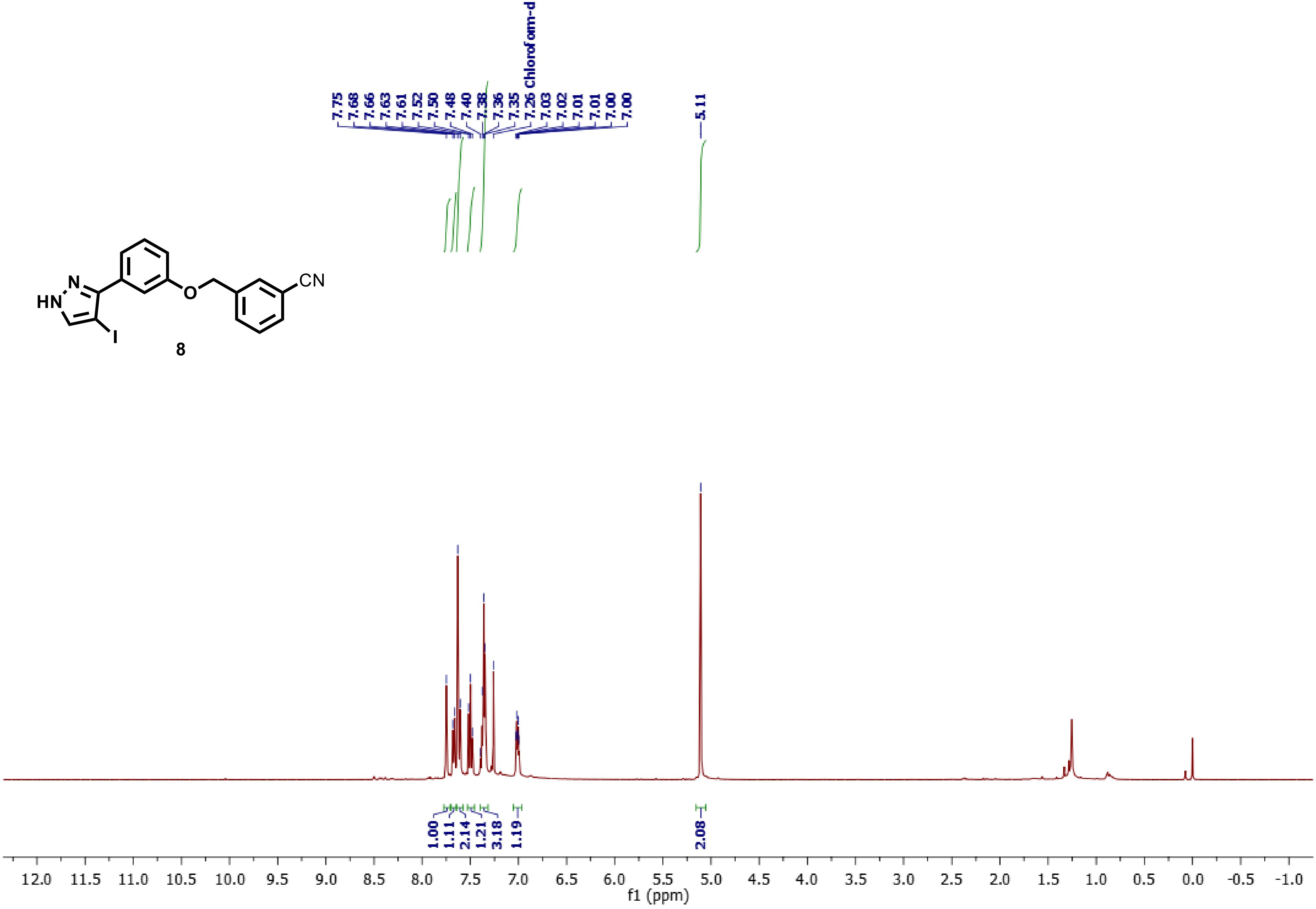
7



^{13}C NMR of 7 in $CDCl_3$ at 100 MHz

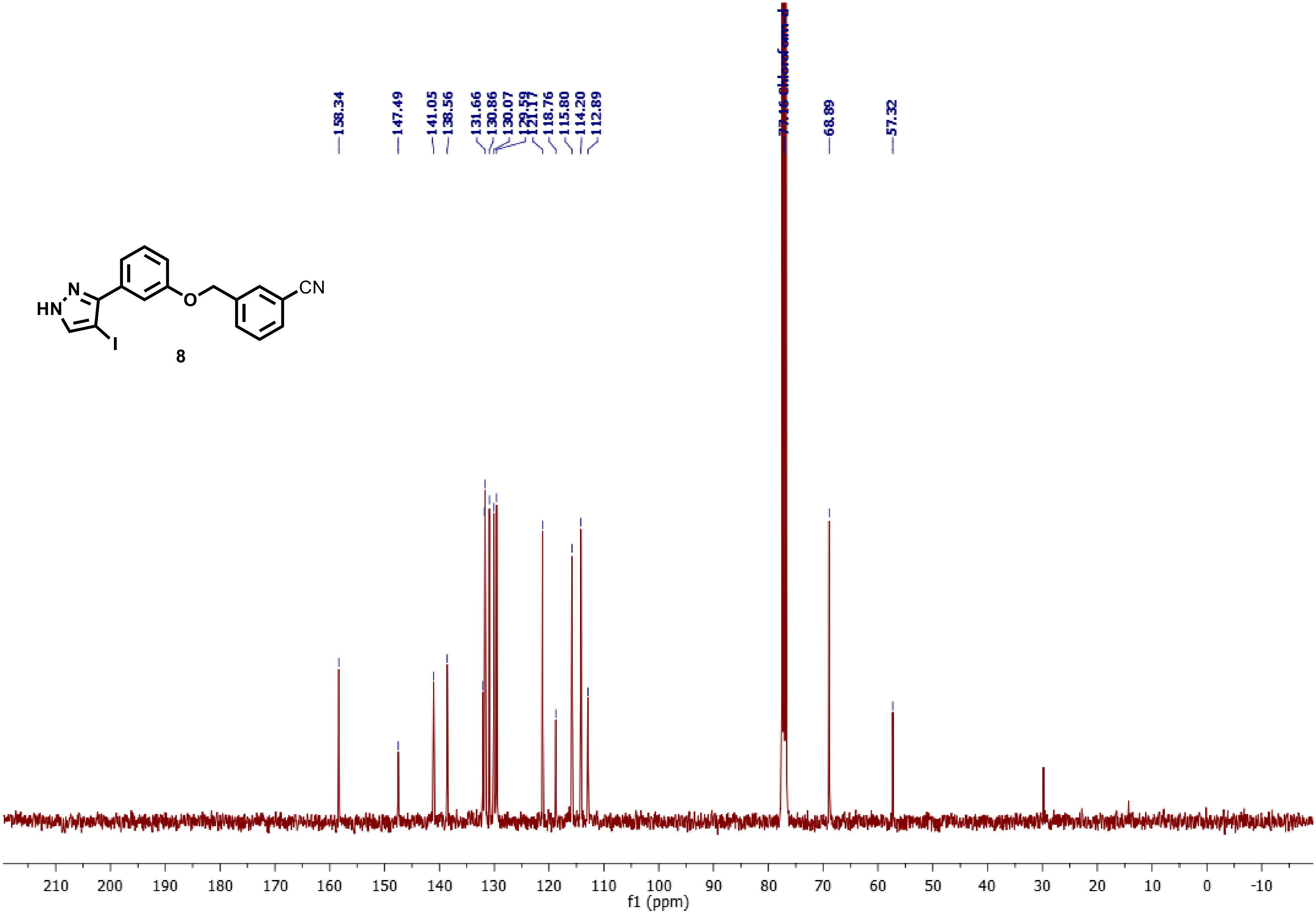


^{1}H NMR of 8 in $CDCl_3$ at 400 MHz

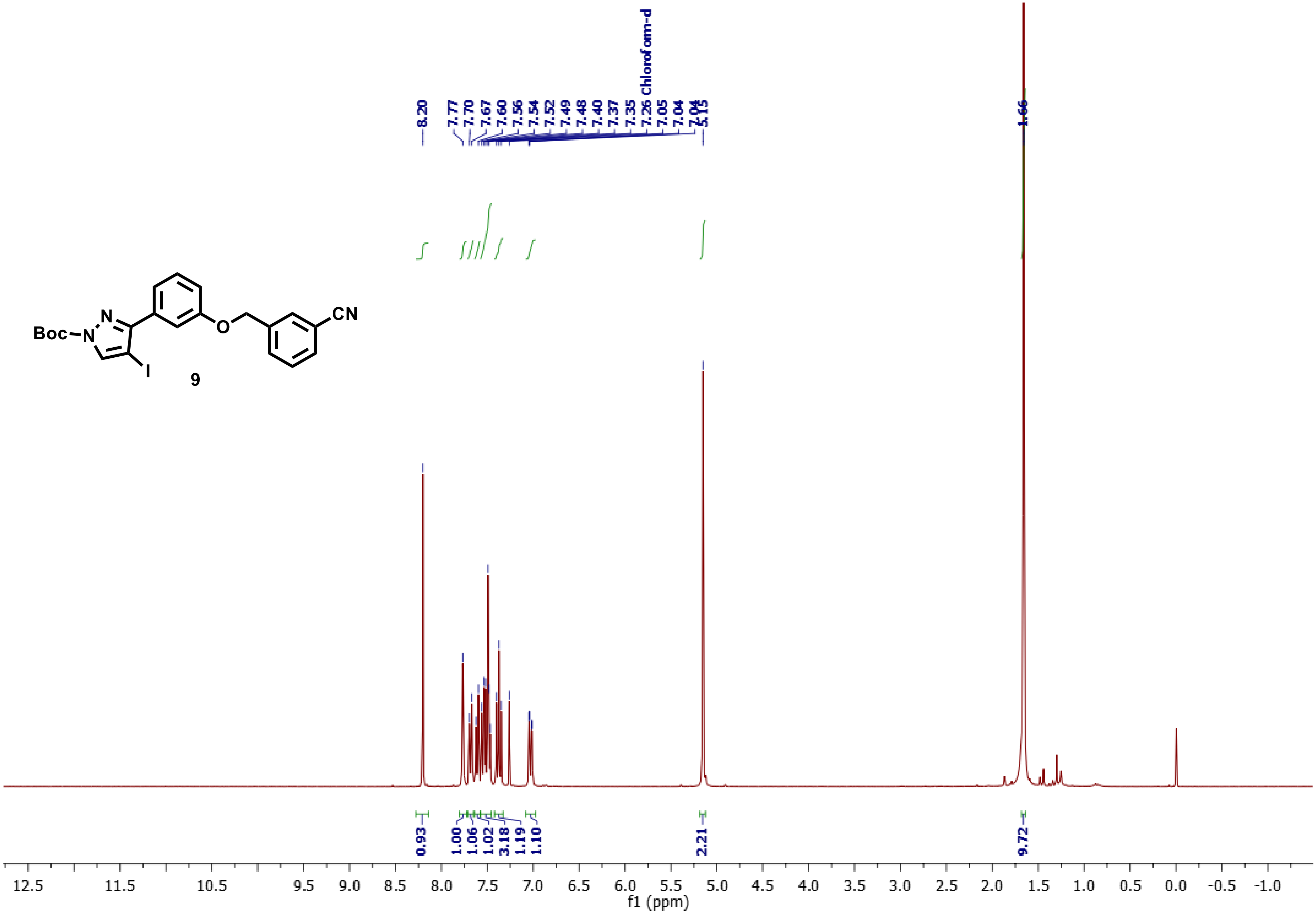


8

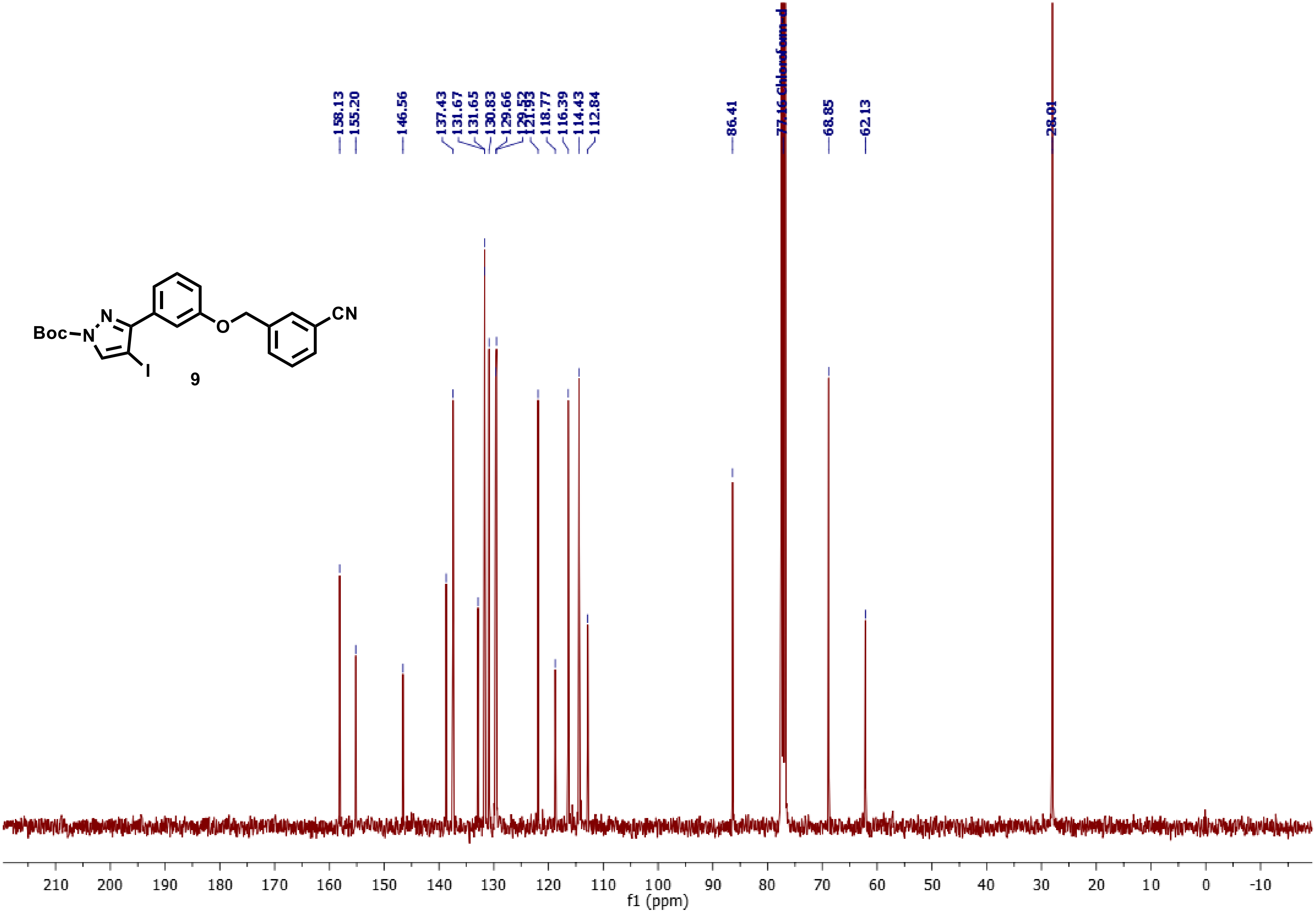
^{13}C NMR of 8 in $CDCl_3$ at 100 MHz



^{1}H NMR of 9 in $CDCl_3$ at 300 MHz



^{13}C NMR of 9 in $CDCl_3$ at 100 MHz



HPLC Chromatogram of 9

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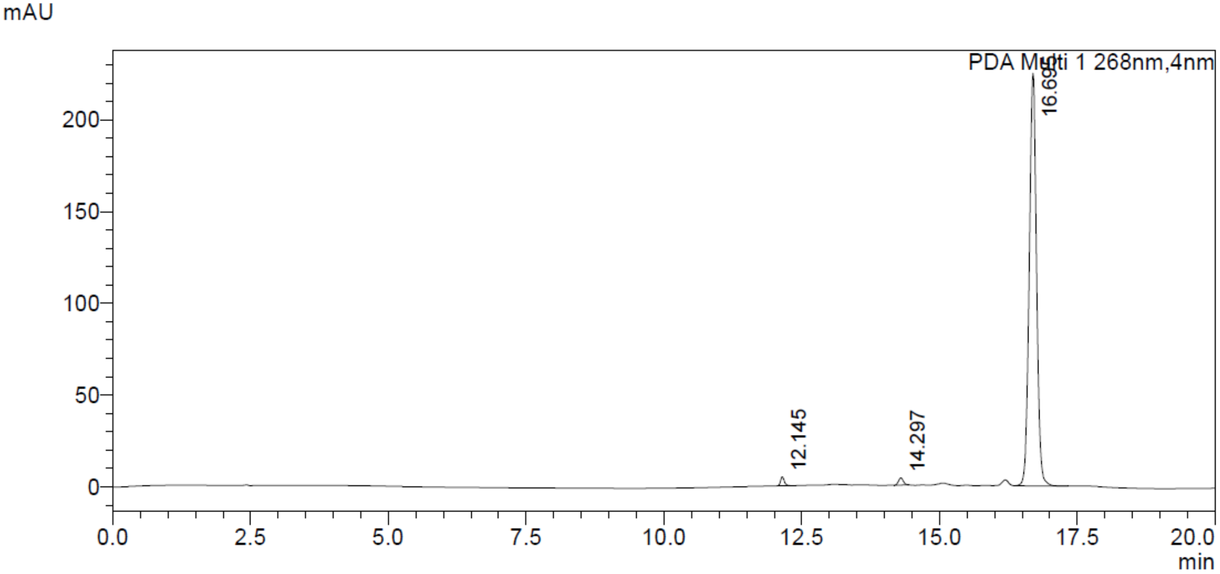

<Peak Table>

PDA Ch1 268nm

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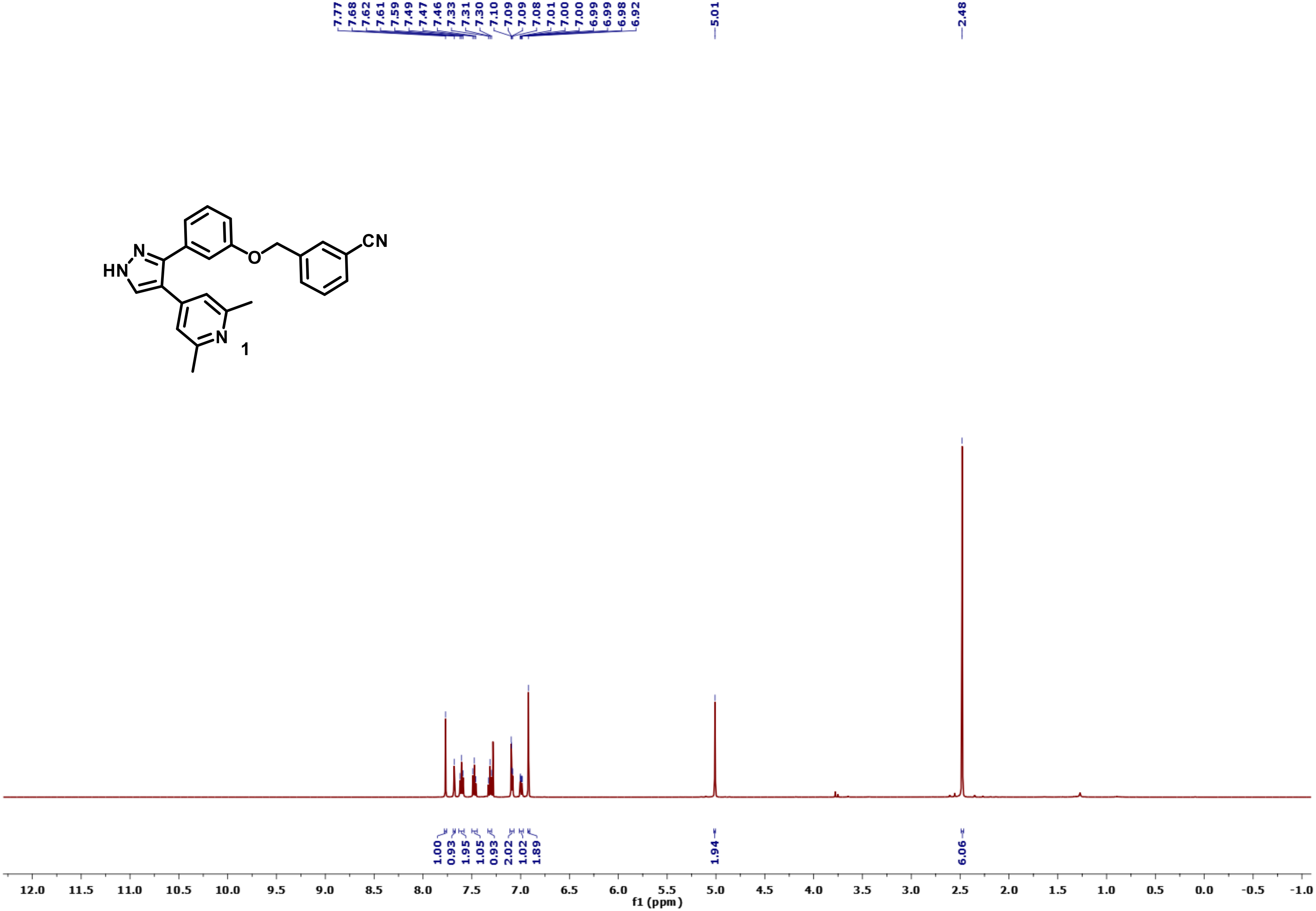
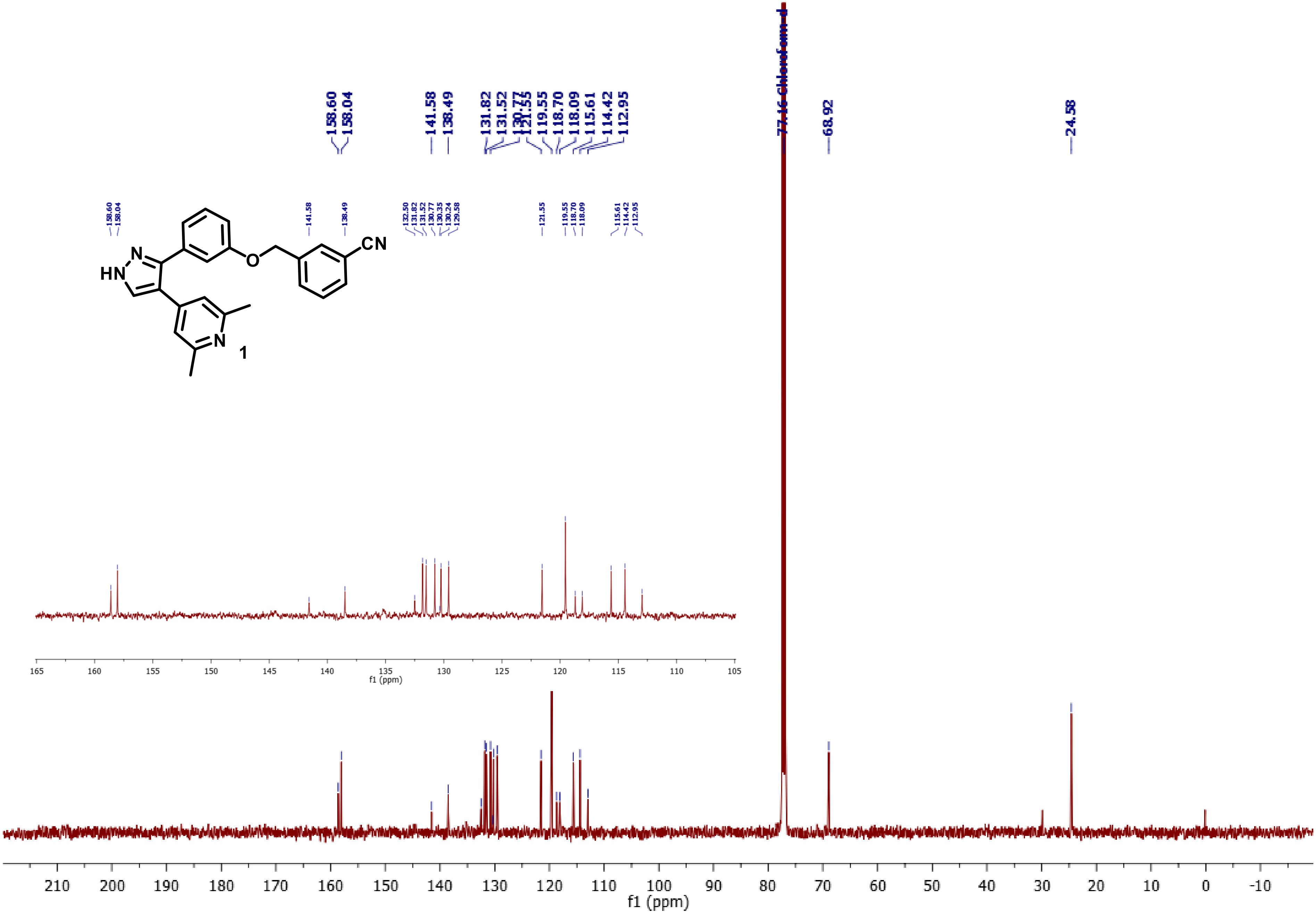
2	14.297	3874	23042	1.091
3	16.695	224779	2066607	97.850
Total		233450	2112008	100.000

^{1}H NMR of 1 in CDCl$_3$ at 500 MHz

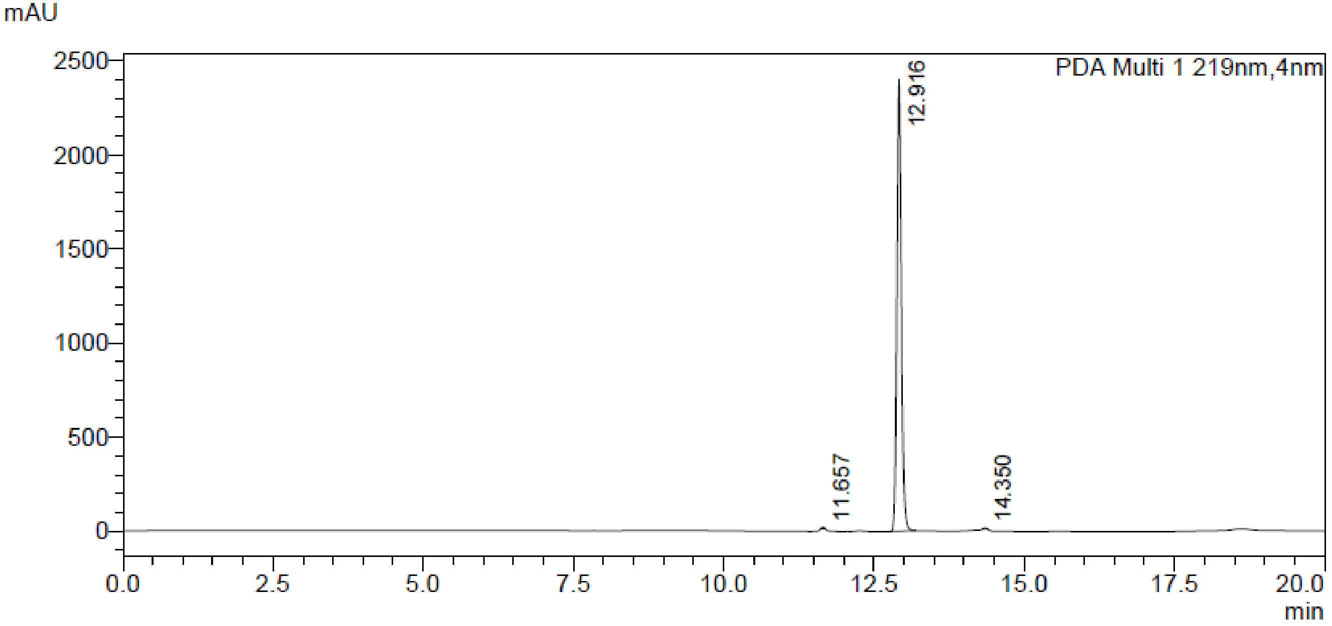


^{13}C NMR of 1 in $CDCl_3$ at 125 MHz



HPLC Chromatogram of 1

<Chromatogram>



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PDA Ch1 219nm

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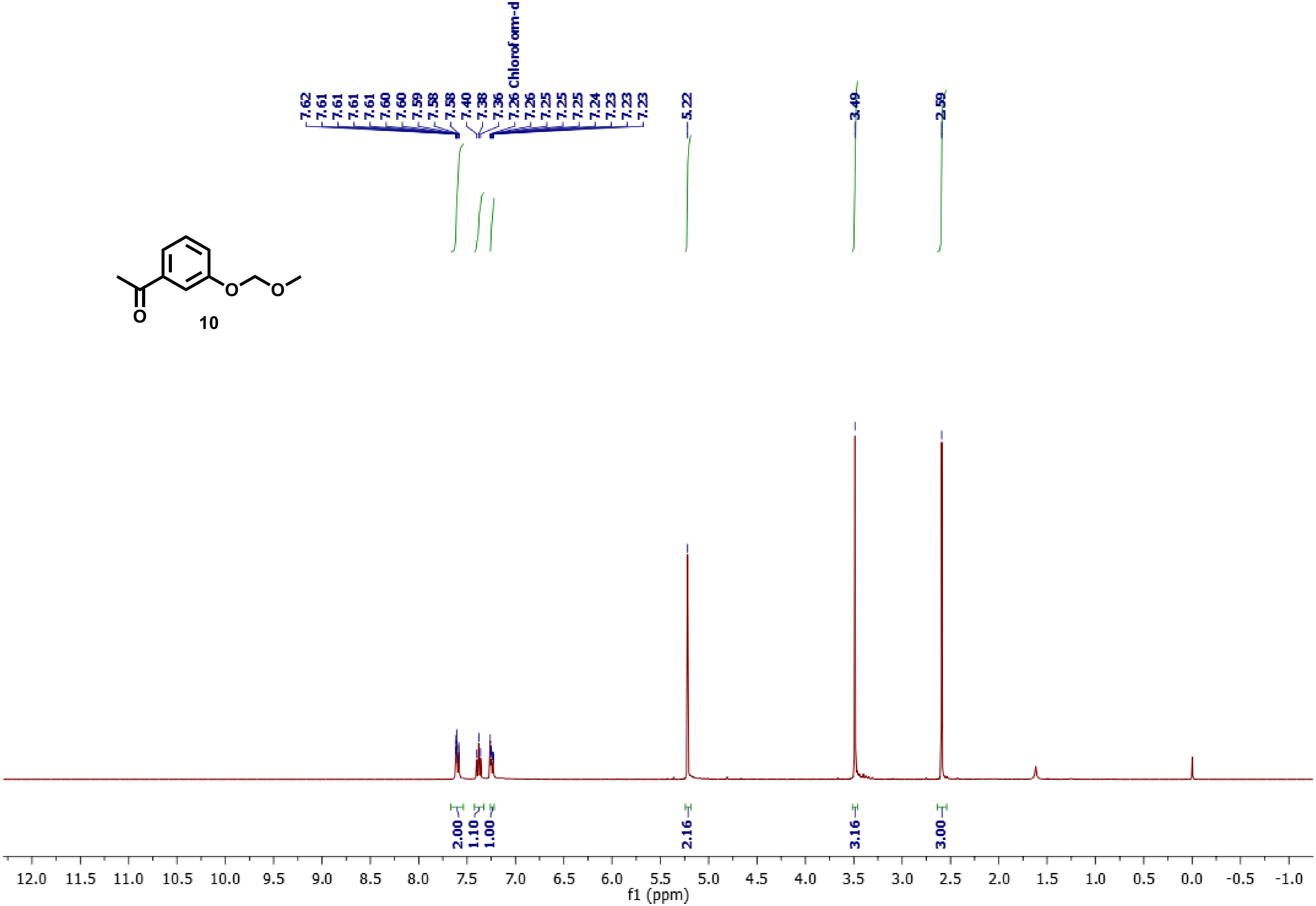
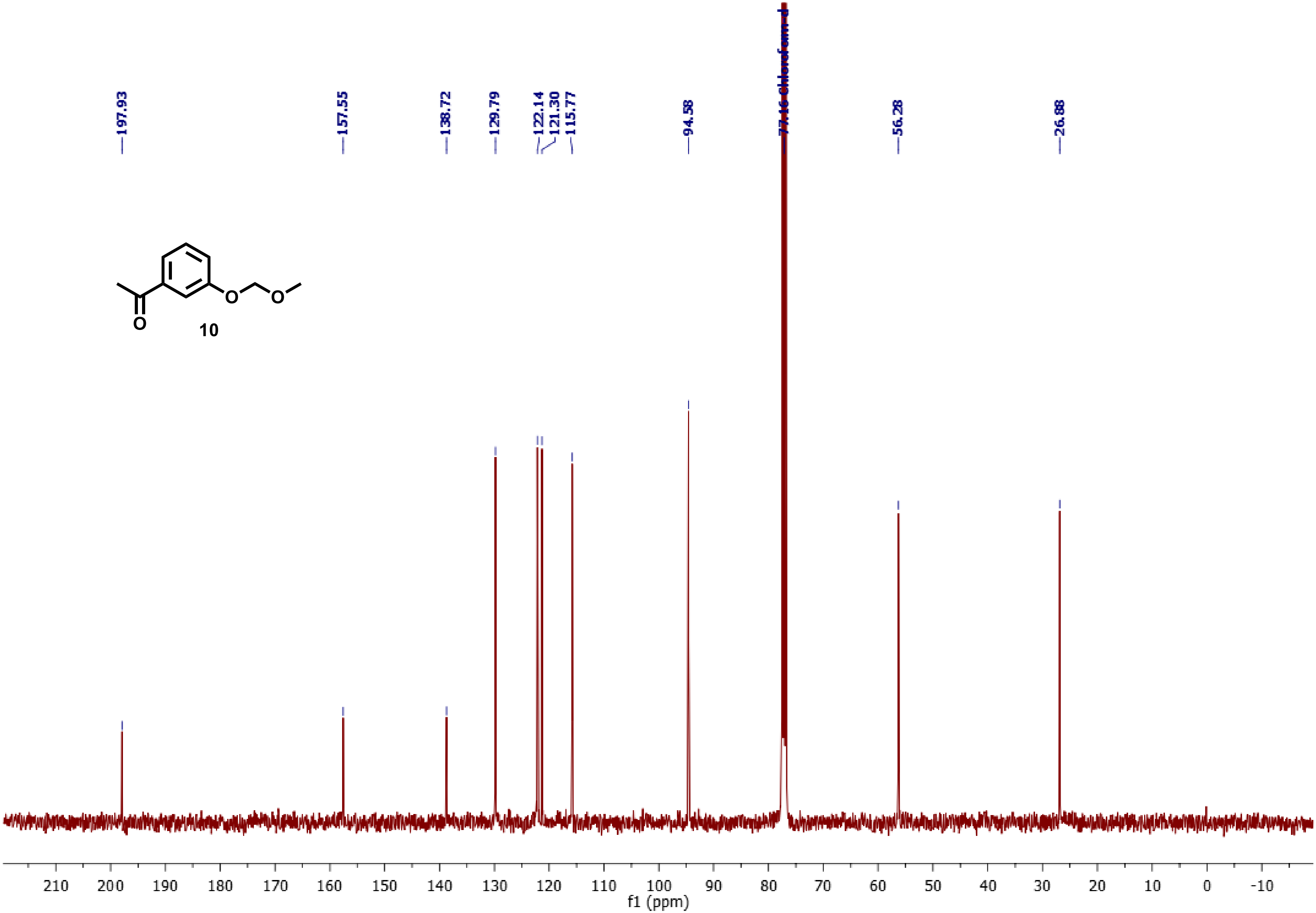
2	12.916	2405867	12519986	99.804
3	14.350	6009	19555	0.156
Total		2415312	12544623	100.000

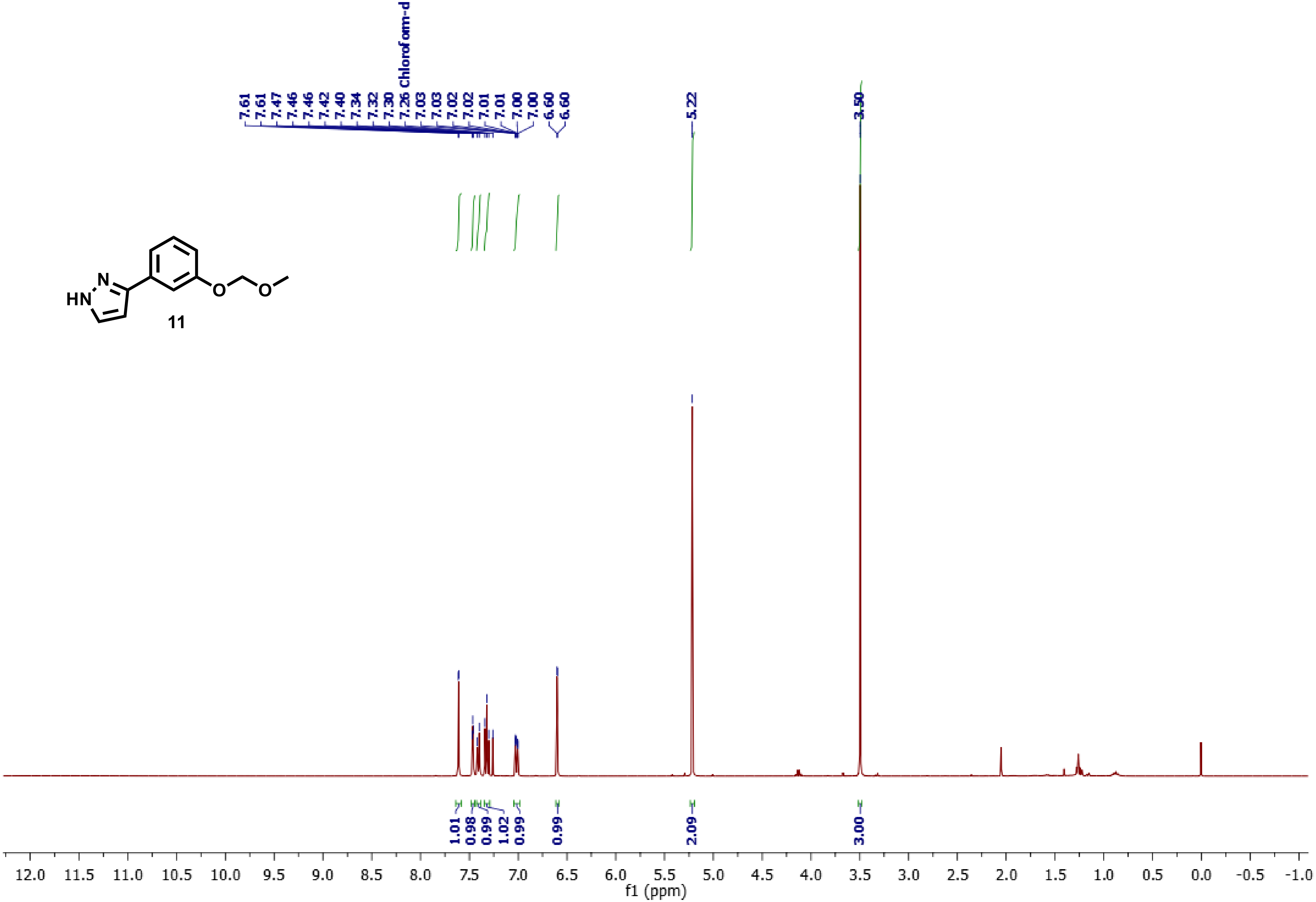
^{1}H NMR of 10 in $CDCl_3$ at 400 MHz



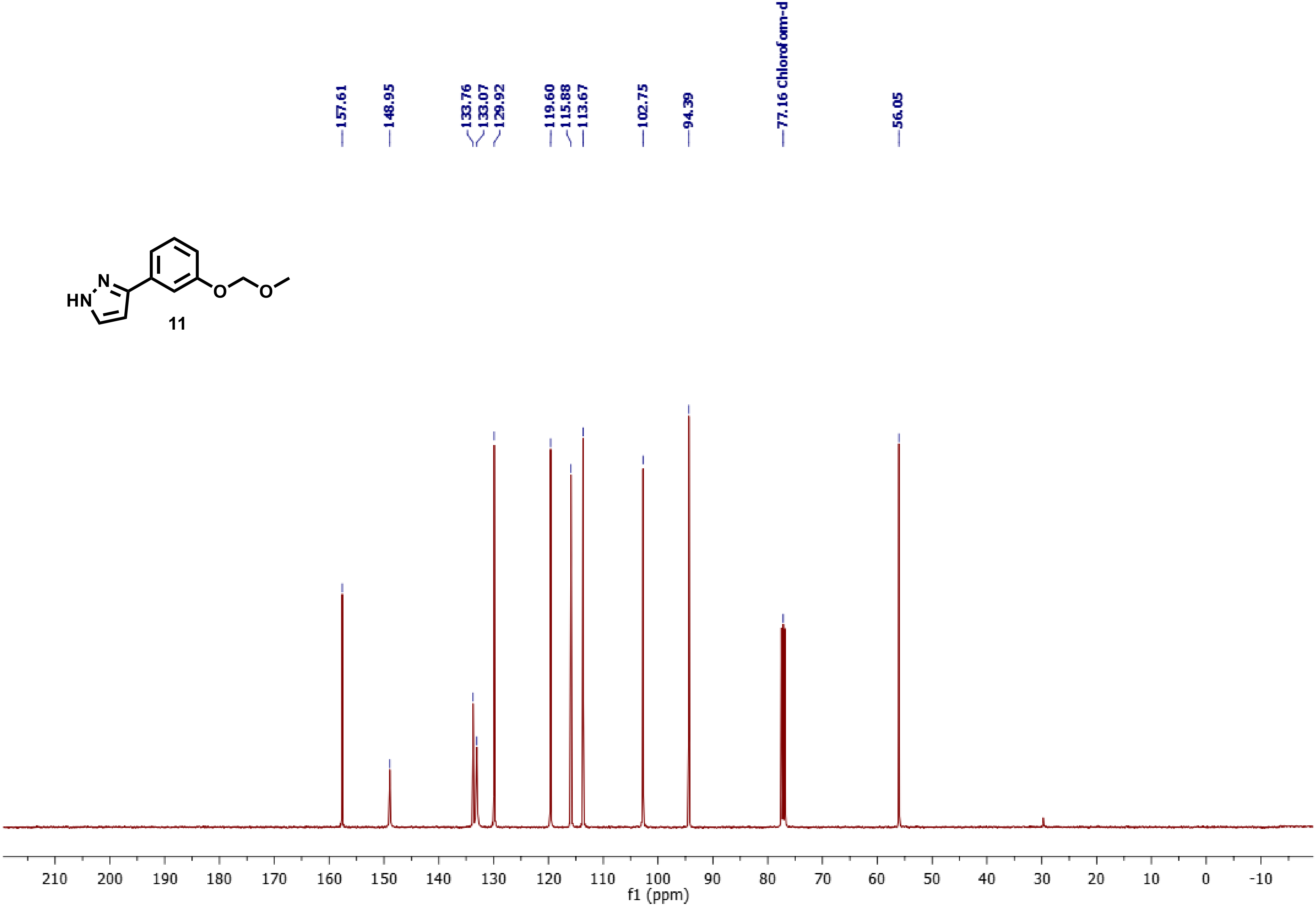
^{13}C NMR of 10 in $CDCl_3$ at 100 MHz



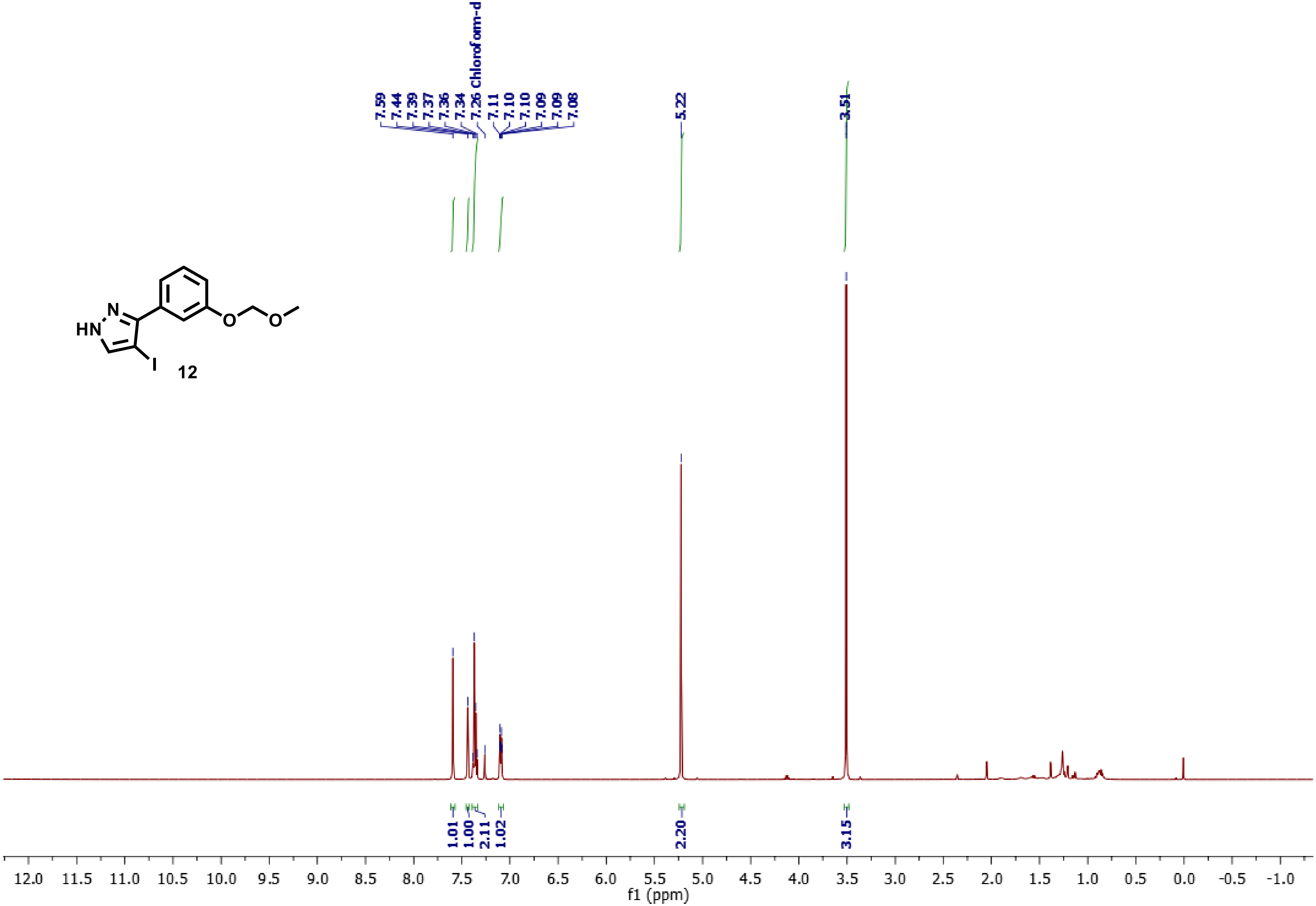
^{1}H NMR of 11 in CDCl$_3$ at 400 MHz



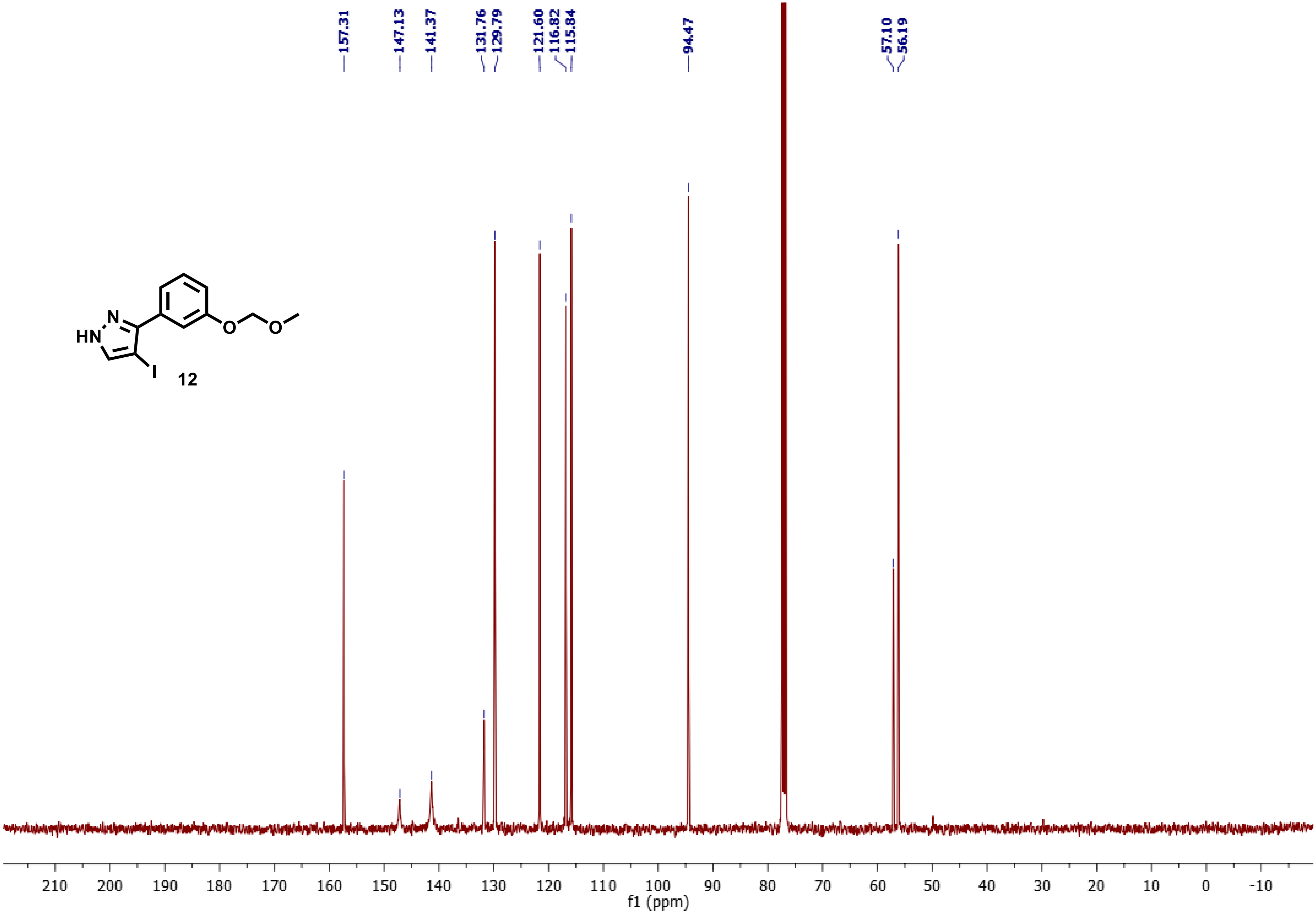
^{13}C NMR of 11 in CDCl$_3$ at 100 MHz



^{1}H NMR of 12 in $CDCl_3$ at 500 MHz

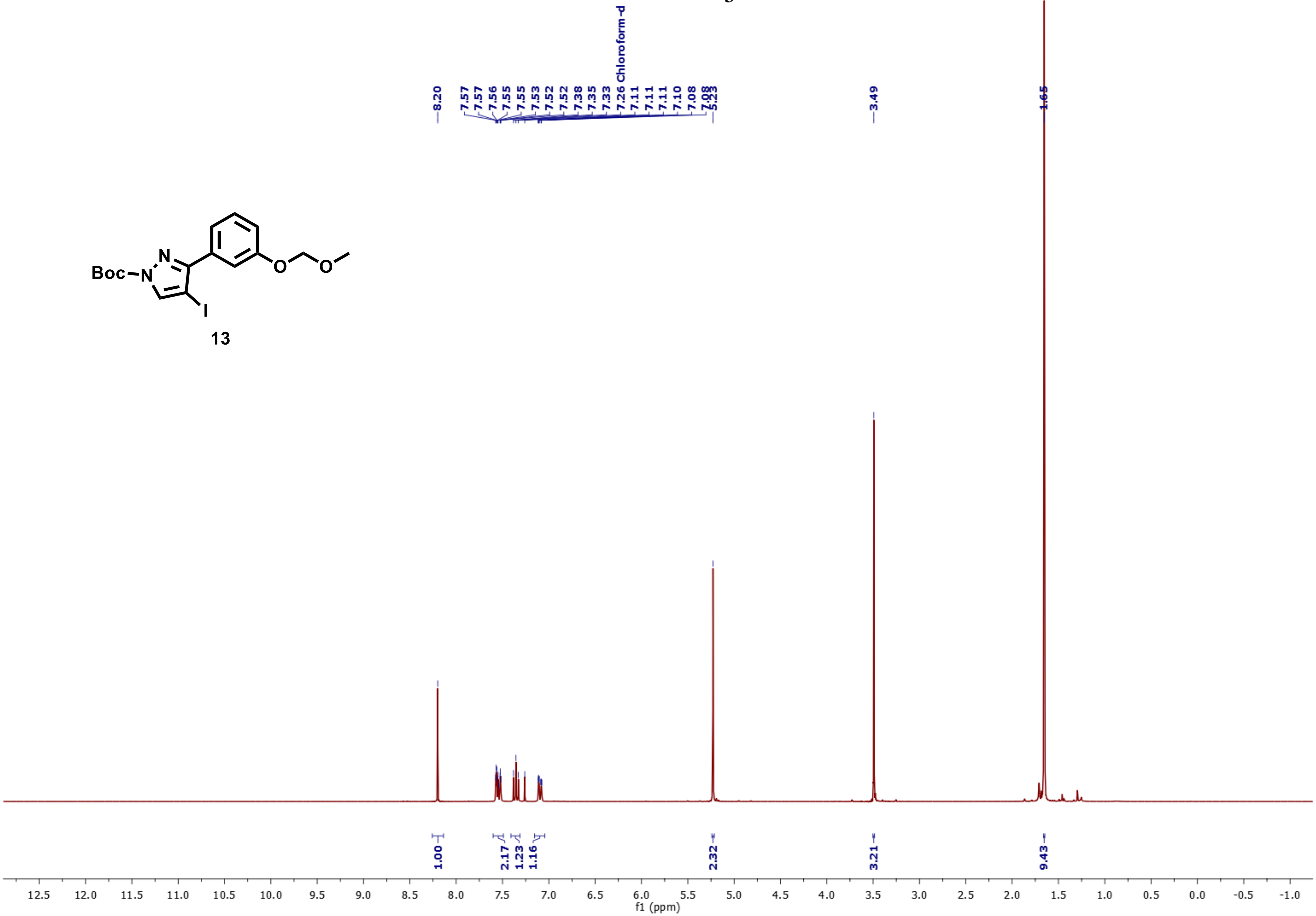


^{13}C NMR of 12 in $CDCl_3$ at 100 MHz

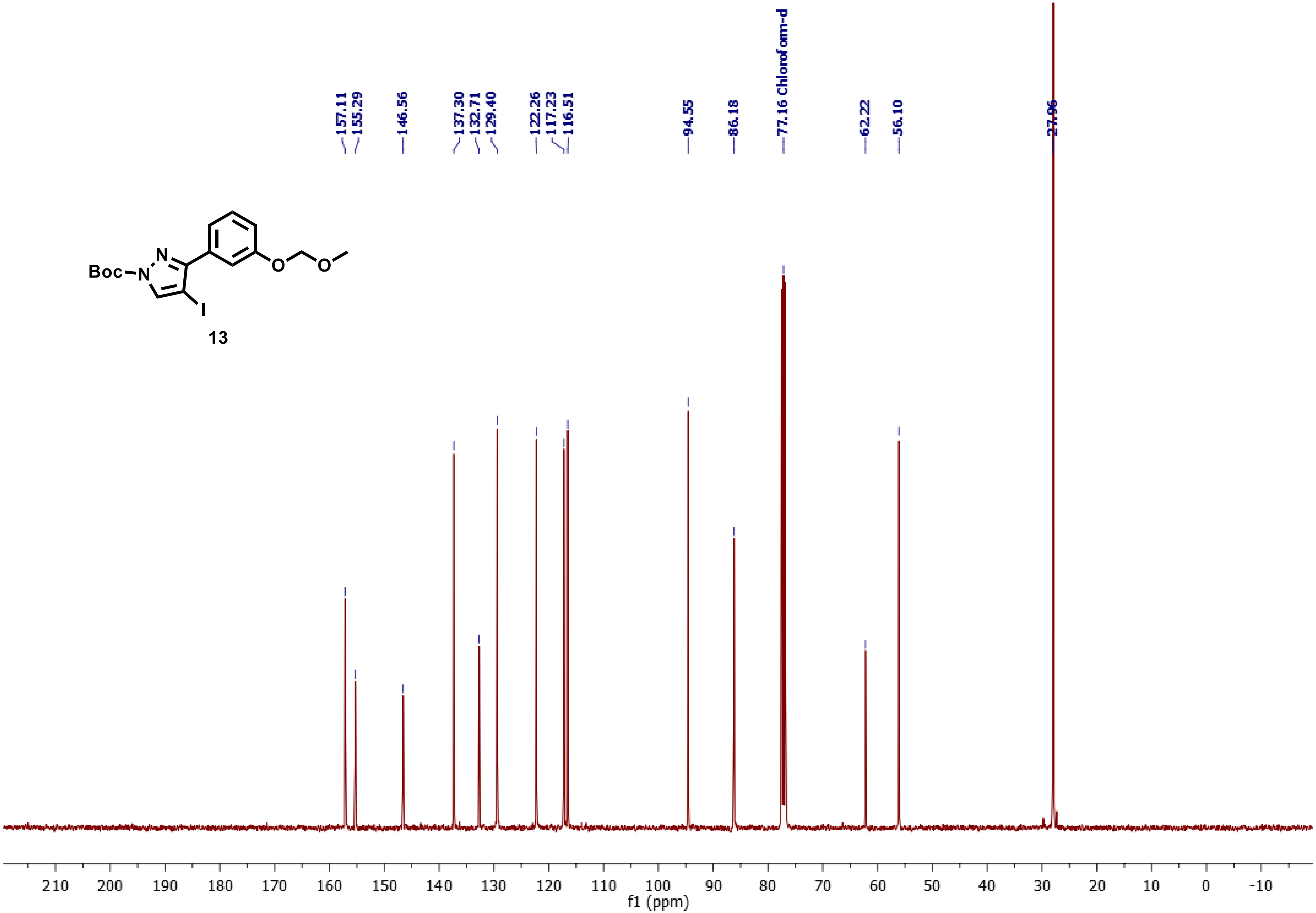


12

^{1}H NMR of 13 in CDCl$_3$ at 300 MHz



^{13}C NMR of 13 in $CDCl_3$ at 100 MHz



HPLC Chromatogram of 13

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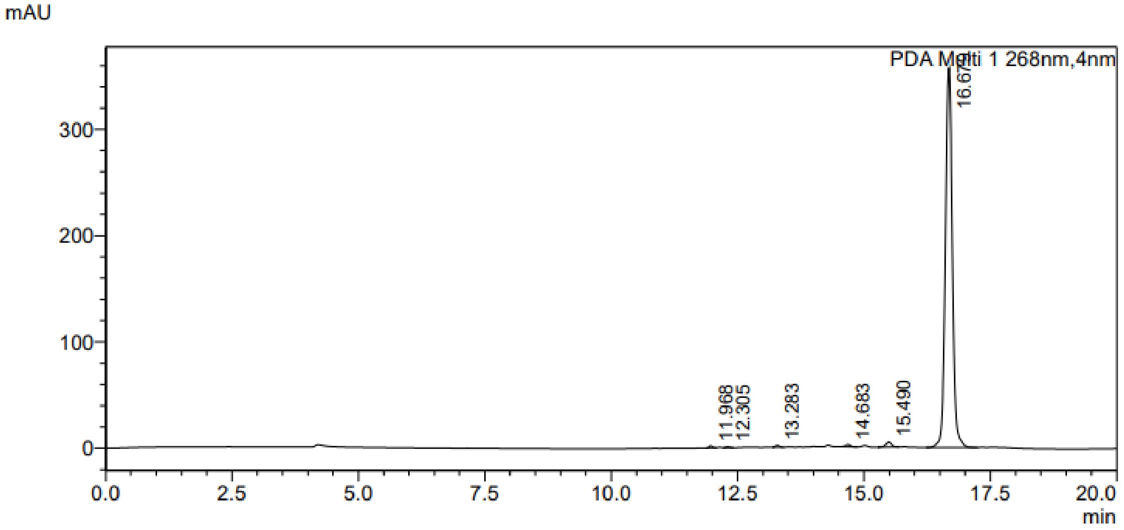

<Peak Table>

PDA Ch1 268nm

Peak#	Ret. Time	Height	Area	Area%
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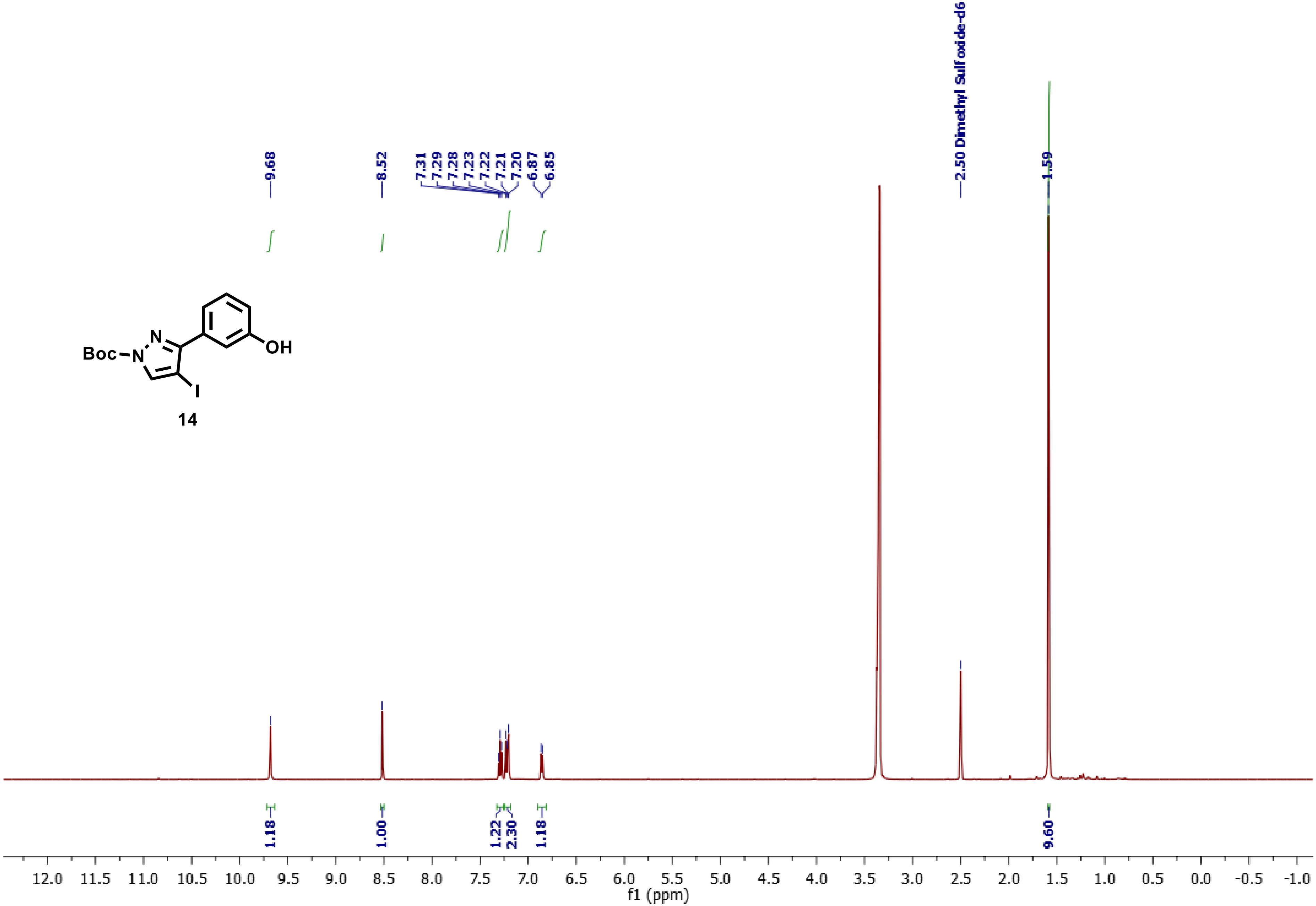
2	12.305	891	3993	0.118
3	13.283	1856	9070	0.268
4	14.683	2300	16382	0.483
5	15.490	4958	38738	1.143
6	16.679	356773	3311626	97.721
Total		368859	3388865	100.000

^{1}H NMR of 14 in DMSO-*d6* at 500 MHz



^{13}C NMR of 14 in DMSO-*d6* at 125 MHz