Supplementary Information (SI) for Organic Chemistry Frontiers.

Late Stage Defluorinative Functionalization: Synthesis of Thioamides and Heterocycles from Trifluoromethylarenes

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Methanethiol quench setup

Since toxic and nauseating methanethiol gas can be released, the thioamide synthesis should be performed inside fume-hood. Although only small amounts of methanethiol is released, we recommend quenching of the headspace into H_2O_2 before workup. Quenching method used in this work can be seen below. After reaction is completed, the headspace of the reaction vessel is connected to solution of aqueous H_2O_2 via syringe and tubing. A nitrogen stream is applied to the reaction vessel via syringe and the headspace is bubbled into the H_2O_2 solution before workup.

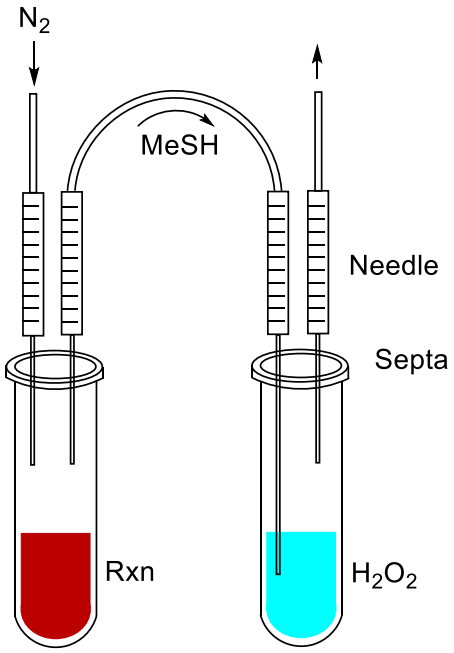


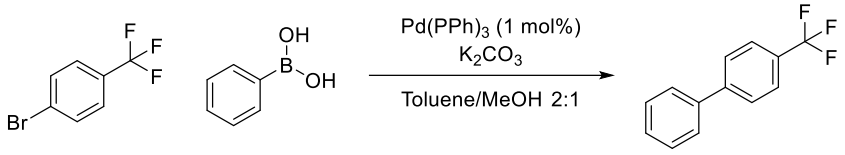
Figure S1. Methanethiol quenching method.

Experimental

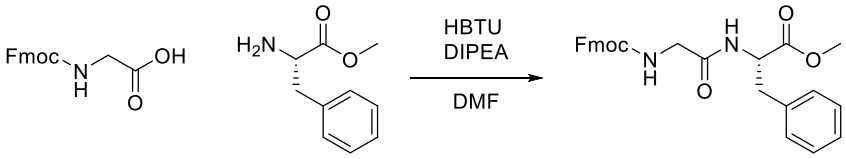
General Methods

Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F-254 plates and visualized with UV light. Flash column chromatography was performed using silica gel 60 (40–63 µm). Microwave reactions were carried out in an Biotage Initiator single-mode reactor, or in an Anton Paar Monowave 400, both producing controlled radiation at 2.45 GHz, with temperature monitored via the built-in online IR sensor. ^{1}H NMR spectra were recorded at 400 or 500 MHz. ^{13}C{^{1}H} NMR spectra were recorded at 101 or 126 MHz. ^{19}F NMR spectra were recorded at 376 or 565 MHz. The chemical shifts for ^{1}H NMR and ^{13}C{^{1}H} NMR are referenced to TMS via residual solvent signals (^{1}H: $CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm; ^{13}C{^{1}H}: $CDCl_3$ at 77.16 ppm, DMSO- d_6 at 39.52 ppm). Analytical HPLC/ESI-MS was performed using electrospray ionization (ESI) and a C18 column (50×3.0 mm, 2.6 µm particle size, 100 Å pore size) with CH_3CN/H_2O in 0.05% aqueous HCOOH as mobile phase at a flow rate of 1.5 ml/min. High-resolution molecular masses (HRMS) were determined on a mass spectrometer equipped with an ESI source and a time-of-flight (TOF) mass analyzer or a matrix-assisted laser-desorption ionization source with a Fourier transform ion cyclotron resonance mass analyzer as indicated. Optical rotations were recorded on a Rudolph Autopol II polarimeter. All chemicals purchased from commercial sources with exception of **14a** and **Fmoc-Gly-Phe-OMe**.

Synthesis of Starting Material **14a** and **Fmoc-Gly-Phe-OMe**



4-(trifluoromethyl)-1,1'-biphenyl (**14a**): 4-bromobenzotrifuoride (2.0 mmol, 450 mg) and phenylboronic acid (2.2 mmol, 268 mg) was dissolved in 4 mL toluene and 2 mL MeOH. K_2CO_3 (4.4 mmol, 608 mg) and PdTetrakis (1 mol%, 23.1 mg) was added and the mixture was degassed and purged 3 times with N_2. The mixture was heated to 110 ºC for 16 h under N_2 atmosphere. The mixture was cooled to ambient temperature and diluted with 50 mL EtOAc and washed with 3x20 mL water and 20 mL brine. The organic was dried over $MgSO_4$, filtered over celite and concentrated under reduced pressure. The crude material was purified over silica using *i*-hexane resulting in 269.9 mg (61%) isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 4H), 7.63 – 7.59 (m, 2H), 7.51 – 7.46 (m, 2H), 7.44 – 7.39 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.9, 139.9, 129.5 (q, *J* = 32.5 Hz), 129.1, 128.3, 127.6, 127.4, 125.9 (q, *J* = 3.8 Hz), 123.1. Data in accordance with reported literature.[1]



Methyl (((9H-fluoren-9-yl)methoxy)carbonyl)glycyl-L-phenylalaninate (**Fmoc-Gly-Phe-OMe**): Fmoc-Gly (2.0 mmol, 595 mg) was dissolved in 10 mL dry DMF. The mixture was cooled to 0 ºC and. DIPEA (3.0 mmol, 0.52 mL) was added followed by portion-wise addition of HBTU (3.0 mmol, 1138 mg). The mixture was allowed to reach ambient temperatures and was stirred for 30 min. A mixture of *L*-Phenylalanine methyl ester HCl (2.0 mmol, 431 mg) and 4 mmol DIPEA in 5 mL dry DMF was added drop-wise under stirring, and the resulting mixture was stirred at 25 ºC for 60 min. The mixture was quenched with 20 mL water and extracted with 2x100 mL EtOAc. The combined organics were pooled, washed with 3x100 mL brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude was purified over silica using 0-50% EtOAc in c-Hexane (rf = 0.36) resulting in 663.6 mg (72%) isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dt, *J* = 7.6, 0.9 Hz, 2H), 7.61 (d, *J* = 7.5 Hz, 2H), 7.43 (td, *J* = 7.5, 1.2 Hz, 2H), 7.33 (td, *J* = 7.5, 1.2 Hz, 2H), 7.30 – 7.19 (m, 3H), 7.13 – 7.07 (m, 2H), 6.51 (d, *J* = 7.9 Hz, 1H), 5.49 (d, *J* = 5.7 Hz, 1H), 4.92 (dt, *J* = 8.0, 5.9 Hz, 1H), 4.42 (dd, *J* = 7.3, 2.3 Hz, 2H), 4.24 (t, *J* = 7.1 Hz, 1H), 3.98 – 3.82 (m, 2H), 3.74 (s, 3H), 3.14 (qd, *J* = 13.9, 5.9 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.8, 168.6, 156.6, 143.9, 141.4, 135.6, 129.3, 128.8, 127.9, 127.4, 127.2, 125.2, 120.1, 67.4, 53.3, 52.6, 47.2, 44.5, 38.0. Data in accordance with reported literature.[2] Optical rotation: $[\alpha]_D^{25}$ = +47.98 (c = 0.1, $CHCl_3$).

General Procedure

An oven dried vial was charged with trifluoromethyl substrate (0.5 mmol) and 1 mL dry DCE. $BF_3{\cdot}SMe_2$ (3 mmol, 0.32 mL) was added under nitrogen and the vial was sealed and heated under microwave irradiation at 140 ºC for 10-120 min. The mixture was cooled to 0 ºC, followed by addition of the appropriate nucleophile (3 mmol) through septa via syringe. The mixture was allowed to reach 25 ºC and monitored by TLC. After consumption of methyl-dithioester the headspace was purged with nitrogen into hydrogen peroxide solution for 10 min (figure S1). The mixture was then diluted with 10 mL DCM and carefully poured into 10 mL sat. aq. Na_2CO_3. The phases were shaken, separated, and the aqueous phase was extracted with 2x10 mL DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude was purified over silica to afford the pure thioamide.

Unsuccessful Transformations

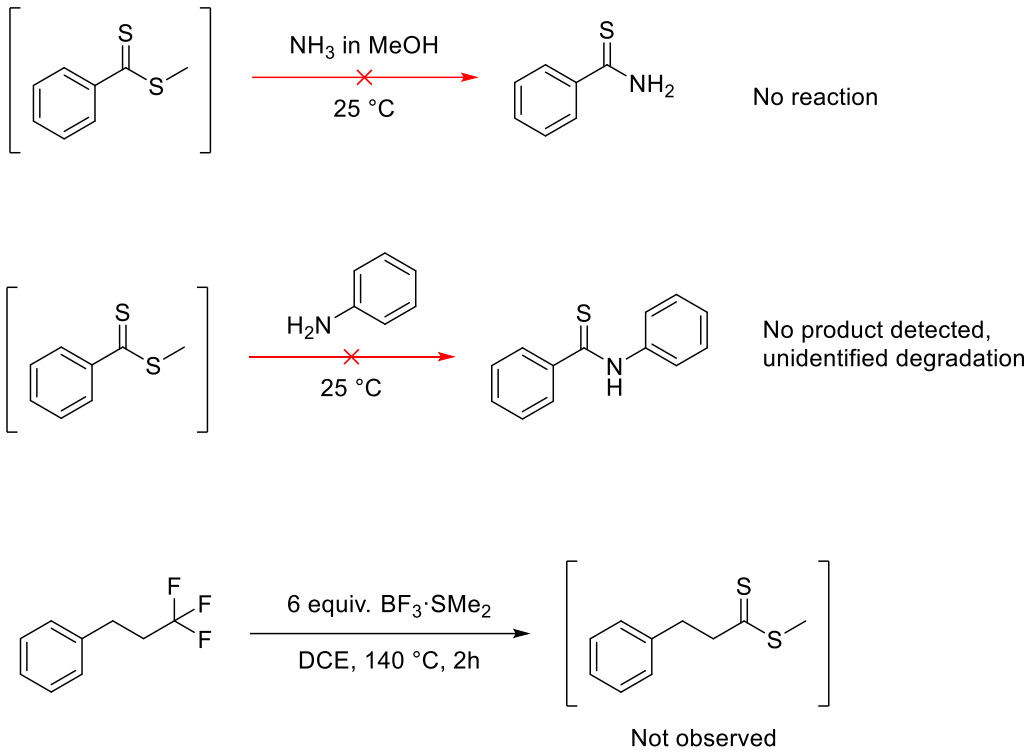
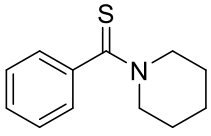


Figure S2. Unsuccessful Transformations.

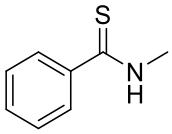
Detailed Procedures for Compounds **1b**-**21b**



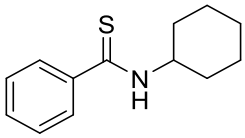
Phenyl*(piperidin-1-yl)methanethione* (**1b**): Synthesized according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and piperidine (3 mmol, 0.30 mL, 6 equiv.). Heated in MW for 30 min

in step 1. Stirred for 60 min in step 2. Purified over silica using 0-10% EtOAc in *i*-hexane gradient (rf = 0.32), affording 88.4 mg (86%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H), 4.35 (t, *J* = 5.4 Hz, 2H), 3.51 (t, *J* = 5.6 Hz, 2H), 1.86 – 1.76 (m, 2H), 1.79 – 1.69 (m, 2H), 1.61 – 1.50 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.4, 143.4, 128.3, 128.3, 125.4, 53.1, 50.6, 26.8, 25.5, 24.1. Data in accordance with reported literature.[3]

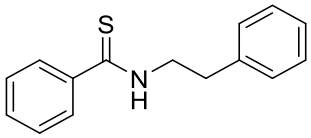
5 mmol scale: trifluorotoluene (5 mmol, 731 mg) was dissolved in 10 mL dry DCE in an oven dried vial. $BF_3{\cdot}SMe_2$ (30 mmol, 3.2 mL) was added and the mixture was heated in microwave at 140ºC for 30 min. (**Caution!** High initial pressure, 20 bar). The mixture was cooled to 0 ºC, followed by addition of piperidine (30 mmol, 3.0 mL) through septa and the mixture was allowed to reach 25ºC. After stirring for 60 min the mixture was diluted with 50 mL DCM and carefully poured into 50 mL sat. aq. Na_2CO_3. The phases were shaken, separated, and the aqueous phase was extracted with 2x50 mL DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude was purified over silica using 0-10% EtOAc in *c*-hexane gradient (rf = 0.36) affording 897.0 mg (87%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H), 4.40 – 4.33 (m, 2H), 3.55 – 3.48 (m, 2H), 1.87 – 1.79 (m, 2H), 1.75 (dtd, *J* = 11.4, 5.6, 2.1 Hz, 2H), 1.57 (ddt, *J* = 11.5, 8.0, 4.4 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.7, 143.5, 128.5, 128.4, 125.5, 53.2, 50.7, 27.0, 25.6, 24.2. Data in accordance with reported literature.[3]



N-methylbenzothioamide (**2b**): Synthesized according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and methaneamine (33 wt% in absolute ethanol, 3 mmol, 0.38 mL, 6 equiv.). Heated in MW for 30 min in step 1. Stirred for 30 min in step 2. Purified over silica using 0-25% EtOAc in *i*-hexane gradient (rf = 0.39), affording 65.3 mg (86%) as a pale-yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.74 – 7.69 (m, 2H), 7.46 – 7.42 (m, 1H), 7.38 – 7.33 (m, 2H), 3.32 (d, *J* = 4.9 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 200.3, 141.7, 131.2, 128.6, 126.7, 33.8. Data in accordance with reported literature.[4]

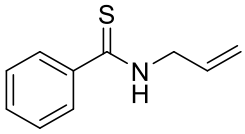


N-cyclohexylbenzenecarbothioamide (**3b**): Synthesized according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and cyclohexanamine (3 mmol, 0.35 mL, 6 equiv.). Heated in MW for 30 min in step 1. Stirred for 4 h in step 2. Purified over silica using 0-10% EtOAc in *i*-hexane gradient (rf = 0.36), affording 79.1 mg (72%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 2H), 7.47 – 7.42 (m, 1H), 7.40 – 7.35 (m, 2H), 4.59 – 4.48 (m, 1H), 2.23 – 2.15 (m, 2H), 1.83 – 1.73 (m, 2H), 1.73 – 1.65 (m, 1H), 1.53 – 1.41 (m, 2H), 1.38 – 1.19 (m, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 197.8, 142.5, 131.0, 128.6, 126.7, 55.0, 31.7, 25.6, 24.8. Data in accordance with reported literature.[3]

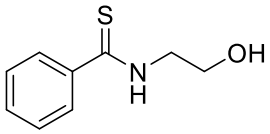


N-phenethylbenzothioamide (**4b**): Synthesized according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and phenethylamine (3 mmol, 0.38 mL, 6 equiv.). Heated in MW for 30 min in step 1. Stirred for 60 min in step 2. Purified over silica using 0-10% EtOAc in *i*-hexane gradient (rf = 0.21), affording 98.5 mg (82%) as a pale-yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 2H), 7.56 (s, 1H), 7.46 – 7.41 (m, 1H), 7.38 – 7.32 (m, 4H), 7.30 – 7.25 (m, 3H), 4.11 (td, *J* = 6.9, 5.5 Hz, 2H), 3.09 (t, *J* = 6.9 Hz,

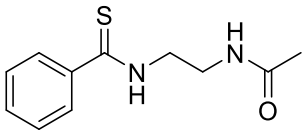
2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 199.4, 142.0, 138.3, 131.2, 129.0, 128.9, 128.6, 127.0, 126.6, 47.6, 33.9. Data in accordance with reported literature.[3]



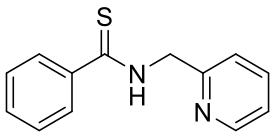
N-allylbenzenecarbothioamide (**5b**): Synthesized according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and allylamine (3 mmol, 0.23 mL, 6 equiv.). Heated in MW for 30 min in step 1. Stirred for 60 min in step 2. Purified over silica using 0-10% EtOAc in *i*-hexane gradient (rf = 0.20), affording 75.4 mg (85%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.72 (m, 2H), 7.62 (s, 1H), 7.49 – 7.43 (m, 1H), 7.42 – 7.35 (m, 2H), 6.07 – 5.95 (m, 1H), 5.36 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.30 (dq, *J* = 10.2, 1.3 Hz, 1H), 4.47 (tt, *J* = 5.7, 1.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 199.5, 141.9, 132.0, 131.3, 128.7, 126.8, 118.9, 49.2. Data in accordance with reported literature.[5]



N-(2-hydroxyethyl)benzothioamide (**6b**): Synthesized according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and ethanolamine (3 mmol, 0.18 mL, 6 equiv.). Heated in MW for 30 min in step 1. Stirred for 60 min in step 2. Purified over silica using 0-25% EtOAc in toluene gradient (rf = 0.34), affording 69.2 mg (76%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.79 – 7.74 (m, 2H), 7.50 – 7.44 (m, 1H), 7.42 – 7.36 (m, 2H), 4.06 – 4.00 (m, 2H), 3.99 – 3.94 (m, 2H), 1.98 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.0, 141.8, 131.4, 128.7, 126.9, 60.7, 48.6. Data in accordance with reported literature.[5]

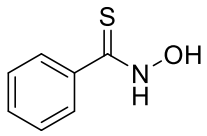


N-(2-phenylthioamidoethyl)acetamide (**7b**): Synthesized according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and ethylenediamine (3 mmol, 0.20 mL, 6 equiv.). Heated in MW for 30 min in step 1. Stirred for 30 min in step 2. After step 2, the mixture was cooled to 0 ºC and acetic anhydride (5 mmol, 0.47 mL, 10 equiv.) was added, followed by stirring at 25 ºC for 30 min. Purified over silica using 0-20% MeCN in DCM gradient (rf = 0.23), affording 52.0 mg (47%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.24 (t, *J* = 5.5 Hz, 1H), 8.07 (t, *J* = 5.7 Hz, 1H), 7.79 – 7.74 (m, 2H), 7.52 – 7.46 (m, 1H), 7.45 – 7.38 (m, 2H), 3.74 (q, *J* = 6.2 Hz, 2H), 3.37 (q, *J* = 6.2 Hz, 2H), 1.82 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 197.6, 169.9, 141.1, 130.6, 128.0, 127.2, 46.3, 36.7, 22.6. HRMS (ES+) calculated for $C_{11}H_{15}N_2OS$ $[M+H]^+$: 223.0905; Found: 223.0903.

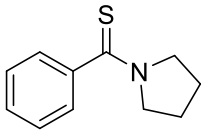


N-(pyridin-2-ylmethyl)benzothioamide. (**8b**): Synthesized according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and 2-picolylamine (1 mmol, 108 mg, 2 equiv., in 1 mL EtOH). Et_3N (2 mmol, 0.28 mL, 4 equiv.) added in step 2 before addition of 2-picolylamine. Heated in MW for 30 min in step 1. Stirred for 60 min in step 2. Purified over silica using 0-25% EtOAc in *i*-hexane gradient (rf = 0.26),

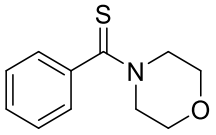
affording 93.9 mg (82%) as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.59 – 8.54 (m, 1H), 7.94 – 7.88 (m, 2H), 7.77 – 7.69 (m, 1H), 7.52 – 7.46 (m, 1H), 7.46 – 7.39 (m, 2H), 7.37 – 7.32 (m, 1H), 7.29 – 7.23 (m, 1H), 5.07 (d, *J* = 4.2 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 198.1, 154.2, 149.0, 141.4, 137.2, 131.2, 128.6, 127.0, 122.9, 122.4, 50.7. Data in accordance with reported literature.[6]



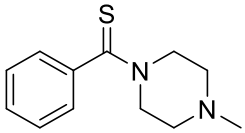
N-hydroxybenzothioamide (**9b**): Synthesised according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and hydroxylamine hydrochloride (1 mmol, 69 mg, 2 equiv.). Et_3N (3 mmol, 0.42 mL, 6 equiv.) and EtOH (1 mL) added in step 2 before addition of hydroxylamine hydrochloride. Heated in MW for 30 min in step 1. Stirred for 30 min in step 2. The aqueous phase was acidified to pH = 2 with 5M HCl before extraction. Purified over silica using 4% MeOH in DCM with 1% formic acid modifier (rf = 0.42) affording 20 mg (26%) as a green solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 2H), 7.68 (m, 2H), 7.48 (m, 1H), 7.41 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.5, 135.2, 131.4, 129.0, 126.9. Data in accordance with reported literature.[7]



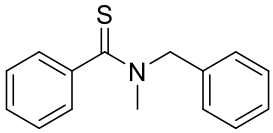
Phenyl(pyrrolidin-1-yl)methanethione (**10b**): Synthesized according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and pyrrolidine (3 mmol, 0.25 mL, 6 equiv.). Heated in MW for 30 min in step 1. Stirred for 30 min in step 2. Purified over silica using 0-10% EtOAc in *i*-hexane gradient (rf = 0.23), affording 78.1 mg (82%) as pale yellow solid ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 5H), 3.97 (t, *J* = 7.1 Hz, 2H), 3.46 (t, *J* = 6.8 Hz, 2H), 2.08 (p, *J* = 6.9 Hz, 2H), 1.96 (p, *J* = 6.8 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 197.4, 144.1, 128.8, 128.4, 125.7, 53.9, 53.5, 26.6, 24.8. Data in accordance with reported literature.[8]



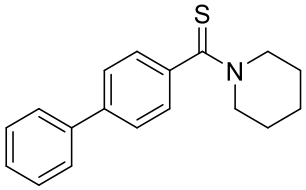
Morpholino(phenyl)methanethione (**11b**): Synthesized according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and morpholine (3 mmol, 0.26 mL, 6 equiv.). Heated in MW for 30 min in step 1. Stirred for 60 min in step 2. Purified over silica using 0-25% EtOAc in *i*-hexane gradient (rf = 0.38), affording 88.2 mg (85%) as a pale-yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 3H), 7.30 – 7.25 (m, 2H), 4.44 (t, *J* = 4.9 Hz, 2H), 3.88 (t, *J* = 4.9 Hz, 2H), 3.67 – 3.62 (m, 2H), 3.62 – 3.57 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 201.1, 142.6, 129.0, 128.7, 126.0, 66.9, 66.6, 52.6, 49.6. Data in accordance with reported literature.[3]



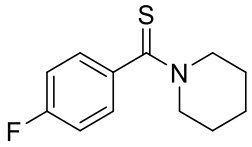
(4-methylpiperazin-1-yl)-phenyl-methanethione (**12b**): Synthesized according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and *N*-methyl piperazine (3 mmol, 0.34 mL, 6 equiv.). Heated in MW for 30 min in step 1. Stirred for 30 min in step 2. Purified over silica using EtOAc eluent (rf = 0.18), affording 99.6 mg (90%) as a pale-yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 3H), 7.25 – 7.21 (m, 2H), 4.40 (t, *J* = 5.1 Hz, 2H), 3.55 (t, *J* = 5.1 Hz, 2H), 2.58 (t, *J* = 5.1 Hz, 2H), 2.35 (t, *J* = 5.1 Hz, 2H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 200.7, 143.0, 128.8, 128.6, 125.9, 55.3, 54.4, 51.9, 49.2, 45.7. Data in accordance with reported literature.[9]



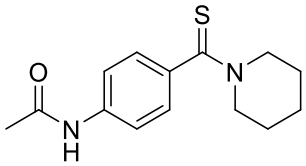
N-benzyl-N-methyl-benzenecarbothioamide (**13b**): Synthesized according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and N-methyl-1-phenyl-methanamine (3 mmol, 0.39 mL, 6 equiv.). Heated in MW for 30 min in step 1. Stirred for 4 h in step 2. Purified over silica using 0-10% EtOAc in *i*-hexane gradient (rf = 0.30), affording 83.5 mg (69%) as a yellow solid. NMR analysis showed a mixture of two rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.28 (m, 9H), 7.14 – 7.10 (m, 1H), 5.45 (s, 2H, minor), 4.72 (s, 2H, major), 3.48 (s, 3H, major), 3.01 (s, 3H, minor). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 202.5 (major), 202.5 (minor), 143.5 (minor), 143.4 (major), 135.5 (minor), 135.4 (major), 129.1 (major), 129.0 (minor), 128.7 (major), 128.7 (minor), 128.6 (major), 128.5 (minor), 128.2 (minor), 128.2 (major), 128.1 (minor), 127.1 (major), 125.8 (major), 125.6 (minor), 59.6 (major), 57.5 (minor), 41.3 (minor), 41.1 (major). Data in accordance with reported literature.[10]



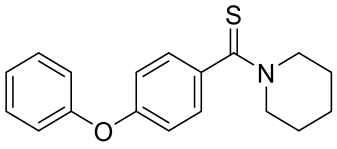
(4-phenylphenyl)-(1-piperidyl)methanethione (**14b**): Synthesized according to General Procedure from 1-phenyl-4-(trifluoromethyl)benzene (0.5 mmol, 111.1 mg) and piperidine (3 mmol, 0.30 mL, 6 equiv.). Heated in MW for 30 min in step 1. Stirred for 60 min in step 2. Purified over silica using 0-2% EtOAc in toluene gradient (rf = 0.23), affording 105.0 mg (75%) as a pale-yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.55 (m, 4H), 7.47 – 7.42 (m, 2H), 7.39 – 7.34 (m, 3H), 4.40 – 4.36 (m, 2H), 3.62 – 3.58 (m, 2H), 1.87 – 1.81 (m, 2H), 1.80 – 1.74 (m, 2H), 1.64 – 1.58 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 199.5, 142.3, 141.5, 140.5, 129.0, 127.7, 127.3, 127.2, 126.2, 53.4, 50.8, 27.1, 25.7, 24.3. Data in accordance with reported literature.[11]



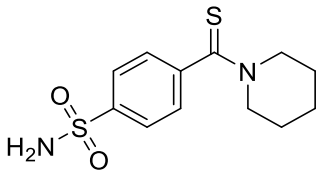
(4-fluorophenyl)-(1-piperidyl)methanethione (**15b**): Synthesized according to General Procedure from 4-fluorobenzotrifluoride (0.5 mmol, 82.1 mg) and piperidine (3 mmol, 0.30 mL, 6 equiv.). Heated in MW for 30 min in step 1. Stirred for 60 min in step 2. Purified over silica using 0-10% EtOAc in *i*-hexane gradient (rf = 0.35), affording 92.8 mg (83%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.07 – 7.01 (m, 2H), 4.37 – 4.33 (m, 2H), 3.56 – 3.51 (m, 2H), 1.86 – 1.79 (m, 2H), 1.79 – 1.73 (m, 2H), 1.61 – 1.55 (m, 2H). ^{19}F NMR (565 MHz, $CDCl_3$) δ -112.6. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 198.6, 162.66 (d, J = 248.6 Hz), 139.55 (d, J = 3.6 Hz), 127.73 (d, J = 8.2 Hz), 115.51 (d, J = 21.9 Hz), 53.4, 51.0, 27.0, 25.6, 24.2. Data in accordance with reported literature.[12]



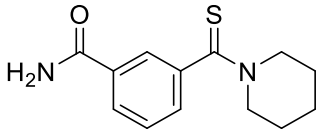
N-[4-(piperidine-1-carbothioyl)phenyl]acetamide (**16b**): Synthesized according to General Procedure from *N*-[4-(trifluoromethyl)phenyl]acetamide (0.5 mmol, 101.6 mg) and piperidine (3 mmol, 0.30 mL, 6 equiv.). Heated in MW for 10 min in step 1. Stirred for 60 min in step 2. Purified over silica using 0-10% MeCN in DCM gradient (rf = 0.14), affording 91.7 mg (70%) as yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.37 – 7.32 (m, 2H), 7.16 – 7.12 (m, 2H), 4.36 – 4.30 (m, 2H), 3.56 – 3.49 (m, 2H), 2.15 (s, 3H), 1.85 – 1.77 (m, 2H), 1.77 – 1.70 (m, 2H), 1.58 – 1.52 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 199.2, 168.9, 138.7, 138.4, 126.4, 120.0, 53.5, 51.1, 27.0, 25.7, 24.6, 24.2. HRMS (ESI) calculated for $C_{14}H_{19}N_2OS$ $[M+H]^+$: 263.1218; Found: 263.1210.



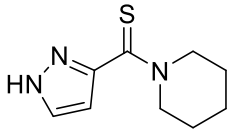
(4-phenoxyphenyl)-(1-piperidyl)methanethione (**17b**): Synthesized according to General Procedure from 1-phenoxy-4-(trifluoromethyl)benzene (0.5 mmol, 101.6 mg) and piperidine (3 mmol, 0.30 mL, 6 equiv.). Heated in MW for 10 min in step 1. Stirred for 60 min in step 2. Purified over silica using 0-10% EtOAc in *i*-hexane gradient (rf = 0.20), affording 124.1 mg (84%) as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 2H), 7.31 – 7.23 (m, 2H), 7.17 – 7.11 (m, 1H), 7.07 – 7.02 (m, 2H), 6.97 – 6.92 (m, 2H), 4.35 (t, *J* = 5.5 Hz, 2H), 3.61 – 3.54 (m, 2H), 1.86 – 1.71 (m, 4H), 1.63 – 1.54 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.4, 158.0, 156.5, 138.2, 130.0, 127.6, 124.0, 119.7, 118.1, 53.5, 51.1, 27.1, 25.6, 24.3. HRMS (ESI) calculated for $C_{18}H_{20}NOS$ $[M+H]^+$: 298.1266; Found: 298.1252.



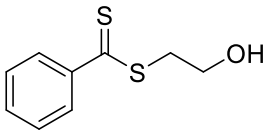
4-(piperidine-1-carbothioyl)benzenesulfonamide (**18b**): Synthesized according to General Procedure from 4-(trifluoromethyl)benzenesulfonamide (0.5 mmol, 112.6 mg) and piperidine (3 mmol, 0.30 mL, 6 equiv.). Heated in MW for 60 min in step 1. Stirred for 60 min in step 2. Purified over silica using 0-10% MeCN in DCM gradient (rf = 0.33), affording 64.0 mg (45%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.84 – 7.78 (m, 2H), 7.45 – 7.39 (m, 4H), 4.28 (t, *J* = 5.2 Hz, 2H), 3.44 (t, *J* = 5.5 Hz, 2H), 1.75 – 1.63 (m, 4H), 1.56 – 1.48 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 195.5, 146.0, 143.3, 125.8, 125.7, 52.7, 49.7, 26.3, 25.2, 23.4. HRMS (ESI) calculated for $C_{12}H_{15}N_2O_2S_2$ $[M-H]^-$: 283.0580; Found: 283.0580.



3-(piperidine-1-carbothioyl)benzamide (**19b**): Synthesized according to General Procedure from 3-(trifluoromethyl)benzamide (0.5 mmol, 112.6 mg) and piperidine (3 mmol, 0.30 mL, 6 equiv.). Heated in MW for 60 min in step 1. Stirred for 60 min in step 2. Purified over silica using 0-20% MeCN in DCM gradient (rf = 0.17), affording 47.9 mg (39%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.74 (m, 1H), 7.71 – 7.68 (m, 1H), 7.44 – 7.38 (m, 2H), 6.33 (s, 1H), 5.95 (s, 1H), 4.34 (t, *J* = 5.5 Hz, 2H), 3.49 (t, *J* = 5.6 Hz, 2H), 1.82 (p, *J* = 5.5 Hz, 2H), 1.75 (p, *J* = 5.8 Hz, 2H), 1.57 (p, *J* = 5.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 198.1, 168.8, 143.7, 133.9, 129.0, 128.9, 127.5, 124.5, 53.5, 50.8, 27.0, 25.6, 24.2. HRMS (ESI) calculated for $C_{13}H_{17}N_2OS$ $[M+H]^+$: 249.1062; Found: 249.1057.

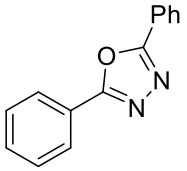


Piperidin-1-yl(1H-pyrazol-3-yl)methanethione (**20b**): Synthesized according to General Procedure from (trifluoromethyl)pyrazole (0.5 mmol, 68.0 mg) and piperidine (3 mmol, 0.30 mL, 6 equiv.). Heated in MW for 120 min in step 1. Stirred for 30 min in step 2. Purified over silica using 40-60% EtOAc in *i*-Hexane gradient (rf = 0.35), affording 46.0 mg (47%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 2.2 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H), 4.33 (t, *J* = 5.3 Hz, 2H), 3.84 (t, *J* = 5.5 Hz, 2H), 1.86 – 1.73 (m, 4H), 1.72 – 1.62 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 187.7, 147.8, 133.1, 105.6, 53.7, 51.5, 27.1, 25.6, 24.3. HRMS (MALDI) calculated for $C_9H_{13}N_3S$ $[M+H]^+$: 196.0903; Found: 196.0903.

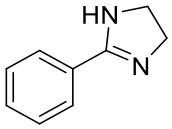


2-hydroxyethyl benzodithioate (**21b**): Synthesized according to General Procedure from trifluorotoluene (0.5 mmol, 73.1 mg) and 2-mercaptoethanol (1.0 mmol, 0.07 mL). Et_3N (3 mmol, 0.42 mL, 6 equiv.) added in step 2 before addition of 2-mercaptoethanol. Heated in MW for 30 min in step 1. Stirred for 6 h under a gentle N_2 stream (see figure S1) in step 2. Purified over silica using 0-25% EtOAc in *i*-Hexane gradient (rf = 0.37), affording 30.0 mg (30%) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H), 7.57 – 7.50 (m, 1H), 7.43 – 7.35 (m, 2H), 3.96 (t, *J* = 6.1 Hz, 2H), 3.65 (t, *J* = 6.1 Hz, 2H), 1.90 – 1.83 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 228.4, 145.0, 132.6, 128.4, 127.0, 60.3, 39.4. Data in accordance with reported literature.[13]

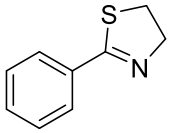
Detailed Procedures for Compounds **1c-6c**



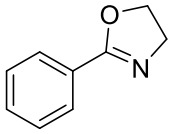
2,5-diphenyl-1,3,4-oxadiazole (**1c**): An oven dried vial was charged with trifluorotoluene (0.5 mmol, 73.1 mg) and 1 mL dry DCE. $BF_3 \cdot SMe_2$ (3 mmol, 0.32 mL) was added under nitrogen, the vial was sealed and the mixture was heated under microwave irradiation at 140 ºC for 30 min. The reaction mixture was cooled to 0 ºC, followed by careful addition of Et_3N (2 mmol, 0.28 mL, 4 equiv.). benzhydrazide (1 mmol, 139.1 mg, 2 equiv.) was added, followed by 1 mL EtOH, and the mixture was heated at 80 ºC for 18 h. The reaction mixture was cooled to ambient and diluted with 10 mL DCM, and carefully poured into 10 mL sat. aq. Na_2CO_3. The phases were shaken, separated, and the aqueous phase was extracted with 2x10 mL DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude was purified over silica using 0-10% EtOAc in *i*-hexane gradient (rf = 0.24), affording 65.5 mg (59%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 – 8.12 (m, 4H), 7.59 – 7.50 (m, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 164.7, 131.9, 129.2, 127.1, 124.1. Data in accordance with reported literature.[14]



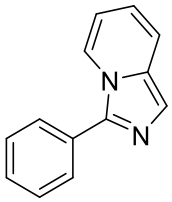
2-phenyl-4,5-dihydro-1H-imidazole (**2c**): An oven dried vial was charged with trifluorotoluene (0.5 mmol, 73.1 mg) and 1 mL dry DCE. $BF_3 \cdot SMe_2$ (3 mmol, 0.32 mL) was added under nitrogen, the vial was sealed and the mixture was heated under microwave irradiation at 140 ºC for 30 min. The reaction mixture was cooled to 0 ºC, followed by careful addition of ethylenediamine (3 mmol, 0.2 mL, 6 equiv.) The resulting mixture was stirred at 25 ºC until consumption of the dithioester (30 min), followed by heating at 80 ºC for 18h. The reaction mixture was cooled to ambient and diluted with 10 mL DCM, and carefully poured into 10 mL sat. aq. Na_2CO_3. The phases were shaken, separated, and the aqueous phase was extracted with 2x10 mL DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude was purified over silica using 50% acetone and 5% Et_3N in EtOAc eluent (rf = 0.33), affording 39.2 mg (54%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.75 (m, 2H), 7.46 – 7.35 (m, 3H), 4.54 (s, 1H), 3.77 (s, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.9, 130.8, 130.5, 128.6, 127.1, 50.4. Data in accordance with reported literature.[15]



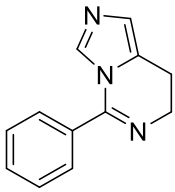
2-phenyl-4,5-dihydrothiazole (**3c**): An oven dried vial was charged with trifluorotoluene (0.5 mmol, 73.1 mg) and 1 mL dry DCE. $BF_3{\cdot}SMe_2$ (3 mmol, 0.32 mL) was added under nitrogen, the vial was sealed and the mixture was heated under microwave irradiation at 140 ºC for 30 min. The reaction mixture was cooled to 0 ºC, followed by careful addition of cysteamine (3 mmol, 231 mg, 6 equiv.) and 1 mL EtOH. The resulting mixture was stirred at 25 ºC until consumption of the dithioester (30 min), followed by heating at 80 ºC for 18h. The reaction mixture was cooled to ambient and diluted with 10 mL DCM, and carefully poured into 10 mL sat. aq. Na_2CO_3. The phases were shaken, separated, and the aqueous phase was extracted with 2x10 mL DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude was purified over silica using 0-10% EtOAc in *i*-hexane gradient (rf = 0.25), affording 65.5 mg (80%) as a pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.81 (m, 2H), 7.48 – 7.38 (m, 3H), 4.46 (t, *J* = 8.3 Hz, 2H), 3.41 (t, *J* = 8.3 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.6, 133.3, 131.2, 128.6, 128.5, 65.3, 33.8. Data in accordance with reported literature.[16]



2-phenyloxazole (**4c**): An oven dried vial was charged with trifluorotoluene (0.5 mmol, 73.1 mg) and 1 mL dry DCE. $BF_3{\cdot}SMe_2$ (3 mmol, 0.32 mL) was added under nitrogen, the vial was sealed and the mixture was heated under microwave irradiation at 140 ºC for 30 min. The reaction mixture was cooled to 0 ºC, followed by careful addition of ethanolamine (3 mmol, 0.18 mL, 6 equiv.). The resulting mixture was stirred at 25 ºC until consumption of the dithioester (60 min). The resulting reaction mixture was cooled to 0 ºC followed by addition of I_2 (1.5 mmol, 381 mg, 3 equiv.) and was then allowed to reach ambient temperatures over 15 min. The resulting mixture was diluted with 10 mL DCM, and carefully poured into 10 mL sat. aq. Na_2CO_3. The phases were shaken, separated, and the aqueous phase was extracted with 2x10 mL DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude was purified over silica using 0-25% EtOAc in *i*-hexane gradient (rf = 0.21), affording 31.4 mg (43%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.91 (m, 2H), 7.49 – 7.44 (m, 1H), 7.43 – 7.37 (m, 2H), 4.42 (t, *J* = 9.6 Hz, 2H), 4.04 (t, *J* = 9.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.7, 131.4, 128.4, 128.3, 127.8, 67.7, 55.0. Data in accordance with reported literature.[17]

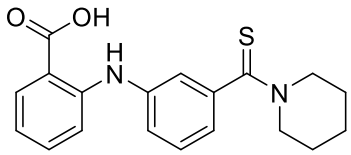


3-phenylimidazo[1,5-α]pyridine (**5c**): An oven dried vial was charged with trifluorotoluene (0.5 mmol, 73.1 mg) and 1 mL dry DCE. $BF_3{\cdot}SMe_2$ (3 mmol, 0.32 mL) was added under nitrogen, the vial was sealed and the mixture was heated under microwave irradiation at 140 ºC for 30 min. The reaction mixture was cooled to 0 ºC, followed by careful addition of Et_3N (2 mmol, 0.28 mL, 4 equiv.) and a solution of 2-picolylamine (1 mmol, 108 mg, 2 equiv.) in 1 mL EtOH. The resulting mixture was stirred at 25 ºC until consumption of the dithioester (60 min). The resulting reaction mixture was cooled to 0 ºC followed by addition of I_2 (1.5 mmol, 381 mg, 3 equiv.) and was then allowed to reach ambient temperatures over 15 min. The resulting mixture was diluted with 10 mL DCM, and carefully poured into 10 mL sat. aq. Na_2CO_3. The phases were shaken, separated, and the aqueous phase was extracted with 2x10 mL DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude was purified over silica using 0-25% EtOAc in *i*-hexane gradient (rf = 0.39), affording 39.2 mg (40%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.21 (m, 1H), 7.82 – 7.73 (m, 2H), 7.57 – 7.38 (m, 5H), 6.74 – 6.65 (m, 1H), 6.57 – 6.49 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.3, 131.7, 130.5, 129.1, 128.7, 128.0, 121.5, 120.7, 118.9, 118.8, 113.1. Data in accordance with reported literature.[6]

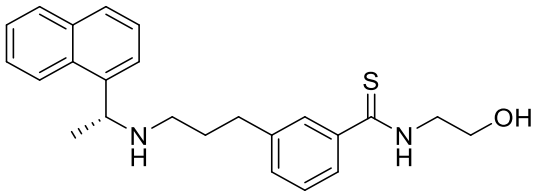


5-phenyl-7,8-dihydroimidazo[1,5-c]pyrimidine (**6c**): An oven dried vial was charged with trifluorotoluene (0.5 mmol, 73.1 mg) and 1 mL dry DCE. $BF_3{\cdot}SMe_2$ (3 mmol, 0.32 mL) was added under nitrogen, the vial was sealed and the mixture was heated under microwave irradiation at 140 ºC for 30 min. The reaction mixture was cooled to 0 ºC, followed by careful addition of Et_3N (4 mmol, 0.56 mL, 8 equiv.), histamine dihydrochloride (2 mmol, 184 mg, 2 equiv.) and 1 mL EtOH. The resulting mixture was stirred at 25ºC until consumption of the dithioester (4 h). The resulting reaction mixture was cooled to 0 ºC followed by addition of I_2 (1.5 mmol, 381 mg, 3 equiv.) and was then allowed to reach ambient temperatures over 15 min. The resulting mixture was diluted with 10 mL DCM, and carefully poured into 10 mL sat. aq. Na_2CO_3. The phases were shaken, separated, and the aqueous phase was extracted with 2x10 mL DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude was purified over silica using 0-100% EtOAc in *i*-hexane gradient (rf = 0.29), affording 54.2 mg (55%) as a thick yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.67 (m, 2H), 7.58 (s, 1H), 7.57 – 7.46 (m, 3H), 6.90 (d, J = 1.1 Hz, 1H), 3.80 (t, J = 6.7 Hz, 2H), 2.92 (td, J = 6.8, 1.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.7, 134.4, 133.0, 131.4, 128.9, 128.8, 127.4, 124.6, 45.2, 19.2. HRMS (ES+) calculated for $C_{12}H_{12}N_3$ $[M+H]^+$: 198.1031; Found: 198.1037.

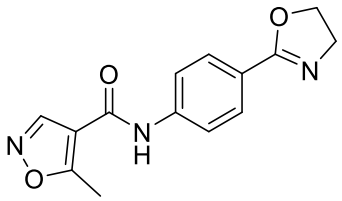
Detailed Procedures for Compounds **1d-6d**



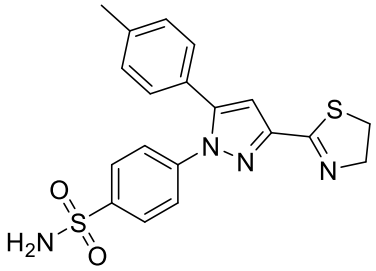
2-((3-(piperidine-1-carbonothioyl)phenyl)amino)benzoic acid (**1d**): Synthesized according to General procedure from flufenamic acid (0.5 mmol, 141.6 mg) and piperidine (3 mmol, 0.30 mL, 6 equiv.). Heated conventionally at 80 ºC for 18h in step 1. Stirred for 60 min in step 2. Purified over silica using *i*-hexane to 25% EtOAc in *i*-hexane with 1% formic acid modifier (rf = 0.32), affording 99.4 mg (58%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (s, 1H), 9.65 (s, 1H), 7.94 – 7.88 (m, 1H), 7.45 – 7.39 (m, 1H), 7.37 – 7.31 (m, 1H), 7.28 – 7.24 (m, 1H), 7.23 – 7.19 (m, 1H), 7.10 – 7.05 (m, 1H), 6.92 – 6.86 (m, 1H), 6.85 – 6.79 (m, 1H), 4.26 (t, *J* = 5.0 Hz, 2H), 3.55 (t, *J* = 5.6 Hz, 2H), 1.71 – 1.64 (m, 4H), 1.53 (t, *J* = 5.8 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO d_6) δ 196.9, 169.8, 146.3, 144.3, 140.6, 134.2, 131.9, 129.5, 120.3, 119.4, 118.0, 117.5, 114.2, 113.3, 52.7, 49.8, 26.4, 25.1, 23.5. HRMS (ESI) calculated for $C_{15}H_{14}NO_2S_2$ $[M+H]^+$: 304.0466; Found: 304.0466.



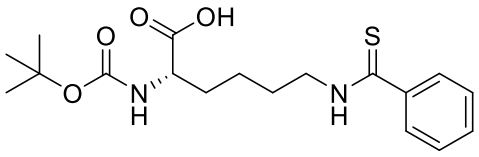
N-(2-hydroxyethyl)-3-(3-((1-(naphthalen-1-yl)ethyl)amino)propyl)benzothioamide (**2d**): Synthesized according to General Procedure from cinacalcet hydrochloride (0.5 mmol, 196.9 mg) and ethanolamine (5 mmol, 0.30 mL, 10 equiv.). Heated in MW for 10 min in step 1. Stirred for 60 min in step 2. Purified over silica using 0-5% MeOH in DCM gradient with 1% Et_3N modifier (rf = 0.33), affording 110.0 mg (56%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.14 (m, 1H), 8.08 – 8.03 (m, 1H), 7.90 – 7.83 (m, 1H), 7.77 – 7.71 (m, 1H), 7.66 – 7.61 (m, 1H), 7.60 – 7.54 (m, 2H), 7.54 – 7.44 (m, 3H), 7.27 – 7.19 (m, 2H), 4.64 (q, *J* = 6.6 Hz, 1H), 4.02 (td, *J* = 5.6, 4.1 Hz, 2H), 3.98 – 3.93 (m, 2H), 2.76 – 2.54 (m, 4H), 2.03 (s, 2H), 1.85 (p, *J* = 7.4 Hz, 2H), 1.50 (d, *J* = 6.5 Hz, 3H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.7, 141.9, 141.3, 134.1, 131.4, 131.1, 129.3, 128.6, 128.4, 126.6, 125.9, 125.9, 123.4, 122.4, 60.4, 53.6, 49.2, 46.6, 32.9, 29.8, 22.5. HRMS (ES+) calculated for $C_{24}H_{29}N_2OS$ $[M+H]^+$: 393.2001; Found: 393.2001. Optical rotation: $[\alpha]_D^{25}$ = +4.33 (c = 0.1, $CHCl_3$).



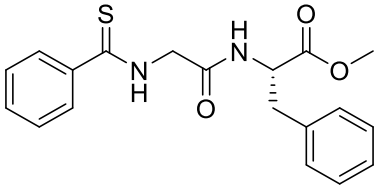
N-(4-(4,5-dihydrooxazol-2-yl)phenyl)-5-methylisoxazole-4-carboxamide (**3d**): An oven dried vial was charged with leflunomide (0.5 mmol, 135.1 mg) and 1 mL dry DCE. $BF_3{\cdot}SMe_2$ (3 mmol, 0.32 mL) was added under nitrogen, the vial was sealed and the mixture was heated under microwave irradiation at 140 ºC for 5 min. The reaction mixture was cooled to 0 ºC, followed by careful addition of ethanolamine (3 mmol, 0.18 mL) and 1 mL EtOH. The resulting mixture was stirred at 25 ºC until consumption of the dithioester (60 min). The resulting reaction mixture was cooled to 0 ºC followed by addition of I_2 (1.5 mmol, 381 mg, 3 equiv.) and was then allowed to reach ambient temperatures over 15 min. The resulting mixture was diluted with 10 mL DCM, and carefully poured into 10 mL sat. aq. Na_2CO_3. The phases were shaken, separated, and the aqueous phase was extracted with 2x10 mL DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude was purified over silica using 0-50% MeCN in DCM gradient. (rf = 0.33) affording 38.1 mg (28%) as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 9.08 (s, 1H), 7.89 – 7.83 (m, 2H), 7.83 – 7.77 (m, 2H), 4.39 (t, J = 9.4 Hz, 2H), 3.94 (t, J = 9.4 Hz, 2H), 2.69 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 173.1, 162.6, 159.4, 149.0, 141.3, 128.5, 122.6, 119.6, 111.9, 67.3, 54.3, 12.2. HRMS (ES+) calculated for $C_{14}H_{14}N_3O_3$ $[M+H]^+$: 272.1035; Found: 272.1032.



4-(3-(4,5-dihydrothiazol-2-yl)-5-(p-tolyl)-1H-pyrazol-1-yl)benzenesulfonamide (**4d**): An oven dried vial was charged with celecoxib (0.5 mmol, 190.7mg) and 1 mL dry DCE. $BF_3{\cdot}SMe_2$ (3 mmol, 0.32 mL) was added under nitrogen, the vial was sealed and the mixture was heated under microwave irradiation at 140 ºC for 120 min. The reaction mixture was cooled to 0 ºC, followed by careful addition of cysteamine (3 mmol, 0.18 mL) and 1 mL EtOH. The resulting mixture was stirred at 25 ºC until consumption of the dithioester (30 min), followed by heating at 80 ºC for 60 min. The reaction mixture was cooled to ambient and diluted with 10 mL DCM, and carefully poured into 10 mL sat. aq. Na_2CO_3. The phases were shaken, separated, and the aqueous phase was extracted with 2x10 mL DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude was purified over silica using 0-20% MeCN in toluene gradient (rf = 0.18) affording 83.6 mg (42%) as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 – 7.84 (m, 2H), 7.52 – 7.47 (m, 4H), 7.23 – 7.16 (m, 4H), 7.02 (s, 1H), 4.39 (t, J = 8.4 Hz, 2H), 3.40 (t, J = 8.4 Hz, 2H), 2.31 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.4, 147.3, 144.8, 143.4, 141.5, 138.7, 129.4, 128.6, 126.8, 126.1, 125.6, 106.9, 64.7, 32.3, 20.8. HRMS (ES+) calculated for $C_{19}H_{19}N_4O_2S_2$ $[M+H]^+$: 399.0949; Found: 399.0945.



N²-(tert-butoxycarbonyl)-N⁶-(phenylcarbonothioyl)lysine (**5d**): An oven dried vial was charged with trifluorotoluene (0.5 mmol, 73.1 mg) and 1 mL dry DCE. $BF_3{\cdot}SMe_2$ (3 mmol, 0.32 mL) was added under nitrogen, the vial was sealed and the mixture was heated under microwave irradiation at 140 ºC for 30 min. The reaction mixture was cooled to 0 ºC, followed by careful addition of Et_3N (3 mmol, 0.42 mL), L-lysine (0.25 mmol, 61.6 mg) and 1 mL EtOH. The resulting mixture was stirred at 25 ºC for 24h. The mixture was diluted with 10 mL DCM and poured into 10 mL brine. The aqueous phase was adjusted to pH 5 by addition of 1M HCl (aq.). The phases were shaken, separated, and the aqueous phase was extracted with 2x10 mL DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude was purified over silica using 0-25% EtOAc in *i*-hexane gradient, followed by 25% EtOAc and 5% AcOH in *i*-hexane (rf = 0.18) affording 71.1 mg (78%) as a pale-yellow waxy solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (s, 1H), 10.23 (t, *J* = 5.5 Hz, 1H), 7.74 – 7.69 (m, 2H), 7.48 – 7.44 (m, 1H), 7.43 – 7.37 (m, 2H), 7.10 – 6.99 (m, 1H), 3.86 (td, *J* = 8.8, 4.7 Hz, 1H), 3.72 – 3.62 (m, 2H), 1.76 – 1.50 (m, 4H), 1.37 (d, *J* = 3.3 Hz, 11H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 197.1, 174.3, 155.6, 141.5, 130.5, 127.9, 127.2, 78.0, 53.4, 45.9, 30.5, 28.2, 26.8, 23.3. HRMS (ES+) calculated for $C_{18}H_{27}N_2O_4S$ $[M+H]^+$: 367.1692; Found: 367.1706. Optical rotation: $[\alpha]_D^{25}$ = -21.66 (c = 0.1, $CHCl_3$).



Methyl (phenylcarbonothioyl)glycyl-L-phenylalaninate (**6d**): An oven dried vial was charged with trifluorotoluene (0.5 mmol, 73.1 mg) and 1 mL dry DCE. $BF_3{\cdot}SMe_2$ (3 mmol, 0.32 mL) was added under nitrogen, the vial was sealed and the mixture was heated under microwave irradiation at 140 ºC for 30 min. The reaction mixture was cooled to 0 ºC, followed by careful addition of Et_3N (3 mmol, 0.42 mL).

A vial was charged with 0.25 mmol Fmoc-Gly-Phe-OMe. To this was added 1 mL of a 20% (v/v) diethylamine in MeCN solution. The mixture was stirred at room temperature for 60 min. The mixture was evaporated to dryness, and the resulting residue was reconstituted in 3 mL of a 1:1 MeOH/DCM mixture. This mixture was added to the dithioester reaction mixture.

This mixture was stirred at 25 ºC for 24h. The mixture was diluted with 10 mL DCM and poured into 10 mL sat. aq. Na_2CO_3. The resulting phases were shaken, separated, and the aqueous phase was extracted with 2x10 mL DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude was purified over silica using 0-50% EtOAc in *c*-hexane gradient (rf = 0.44) affording 31.9 mg (36%) as a yellow resin. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 4.4 Hz, 1H), 7.30 – 7.23 (m, 2H), 6.96 – 6.90 (m, 1H), 6.87 – 6.81 (m, 2H), 6.76 – 6.68 (m, 3H), 6.58 – 6.54 (m, 2H), 6.12 (d, *J* = 7.9 Hz, 1H), 4.37 (dt, *J* = 7.8, 5.9 Hz, 1H), 3.89 (d, *J* = 4.6 Hz, 2H), 3.20 (s, 3H), 2.63 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.55 (dd, *J* = 13.9, 6.3 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 198.8, 171.7, 167.3, 140.7, 135.5, 131.6, 129.3, 128.9, 128.6, 127.5, 127.0, 53.6, 52.7, 49.4, 38.0. HRMS (ES+) calculated for $C_{19}H_{21}N_2O_3S$ $[M+H]^+$: 357.1273; Found: 357.1264. Optical rotation: $[\alpha]_D^{25}$ = +42.32 (c = 0.1, $CHCl_3$).

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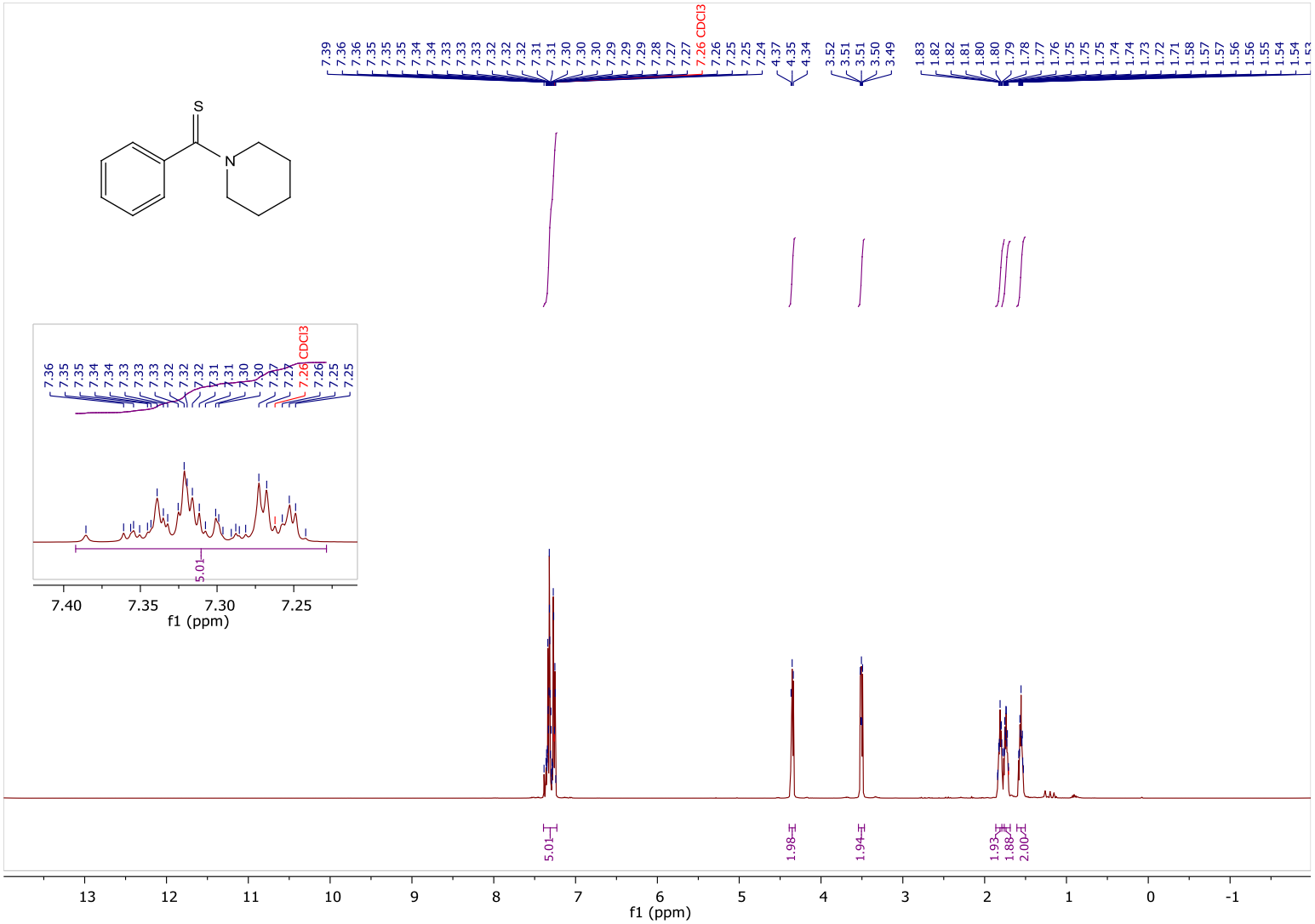
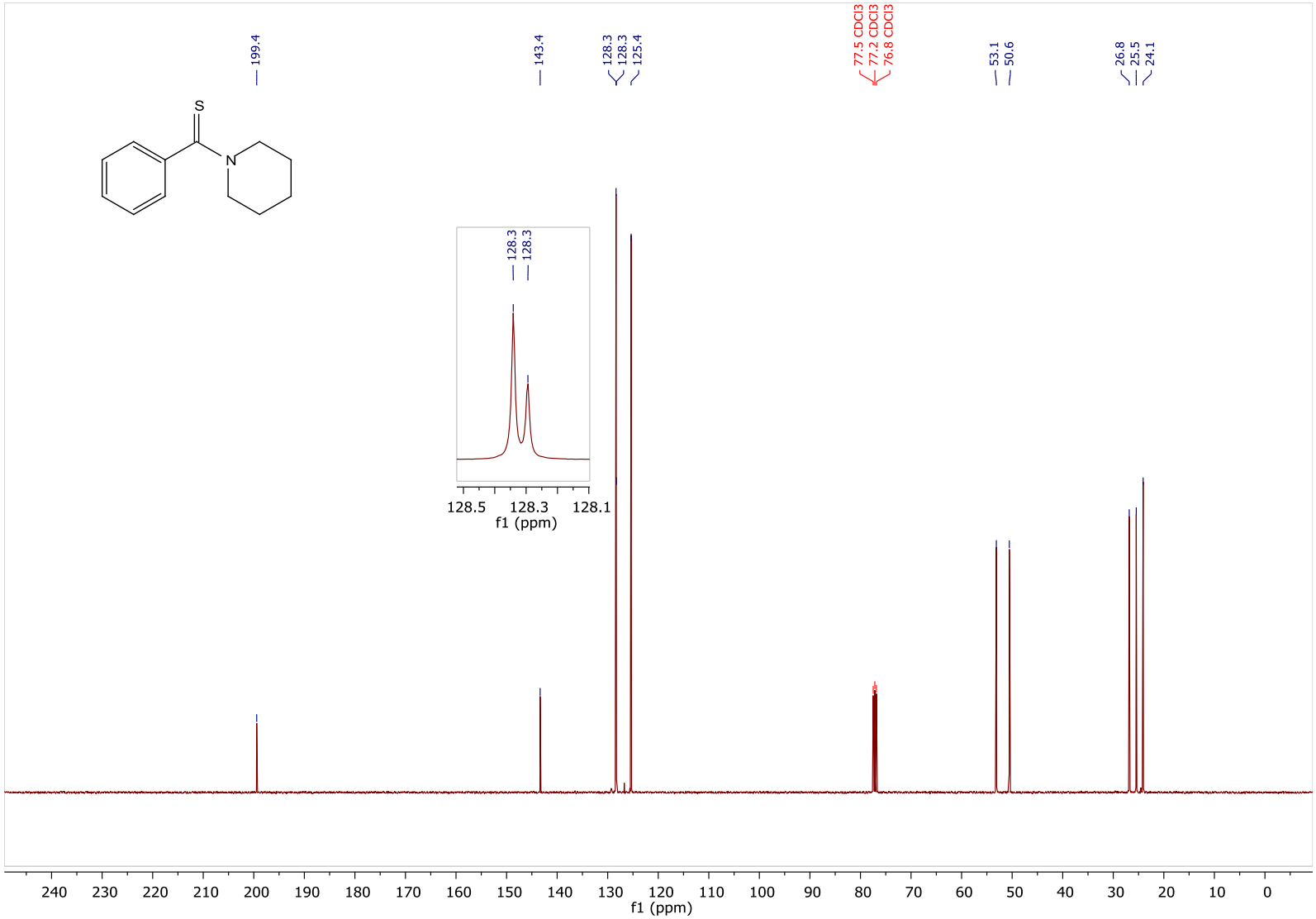
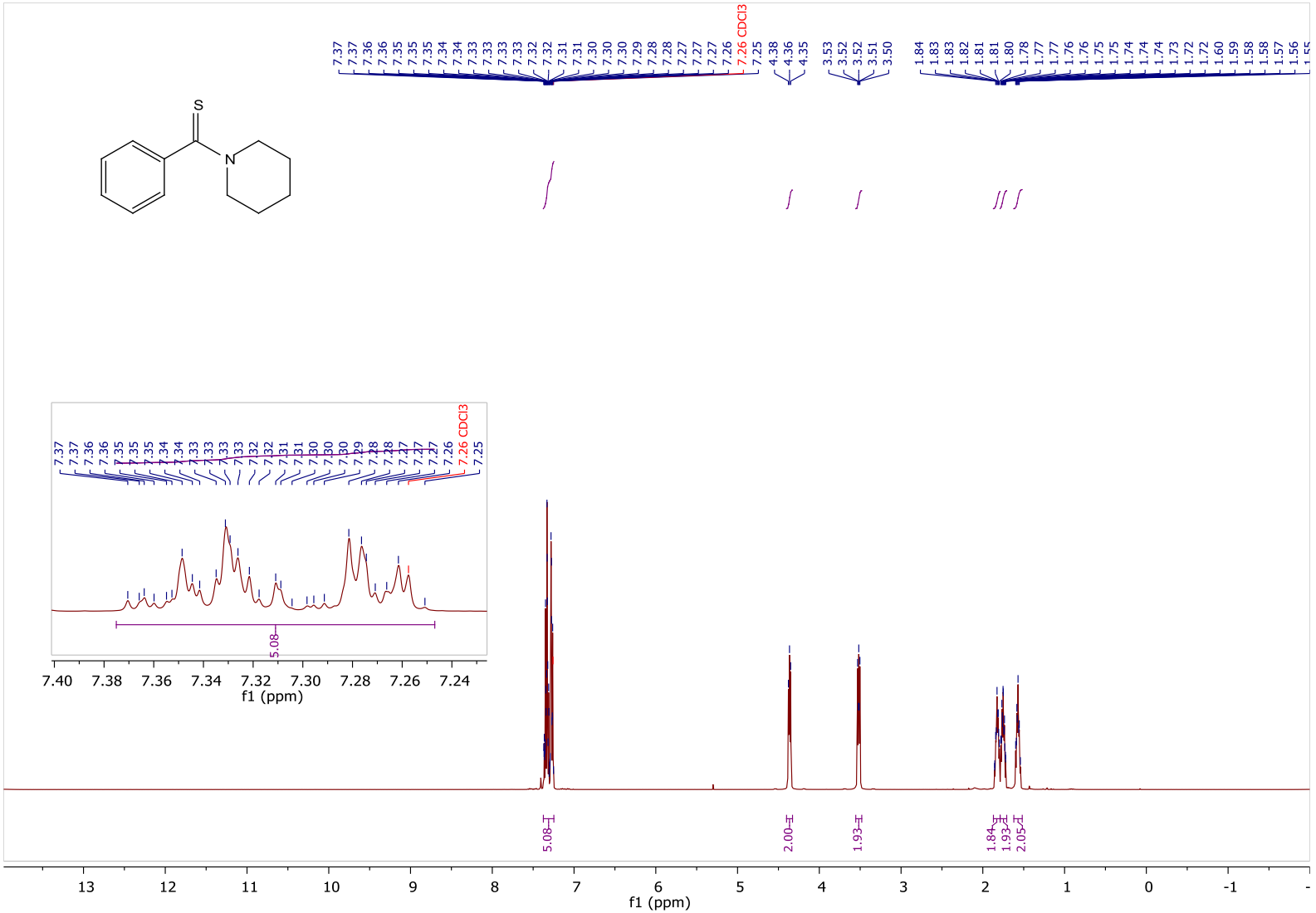
NMR Spectra of **1b-21b**



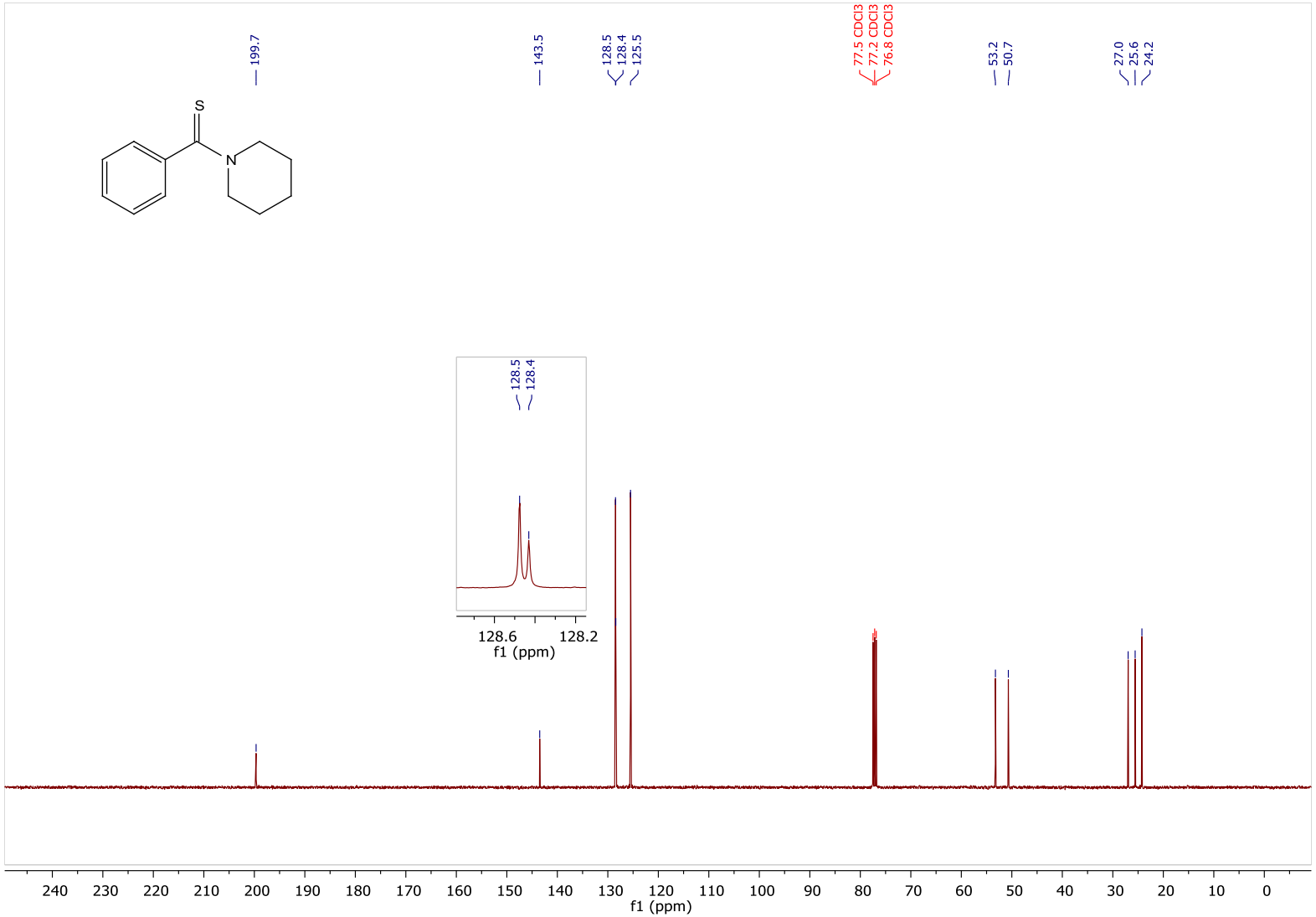
^{1}H-NMR (400 MHz, $CDCl_3$) of **1b.**



$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **1b.**



^{1}H-NMR (400 MHz, $CDCl_3$) of **1b (5 mmol scale).**



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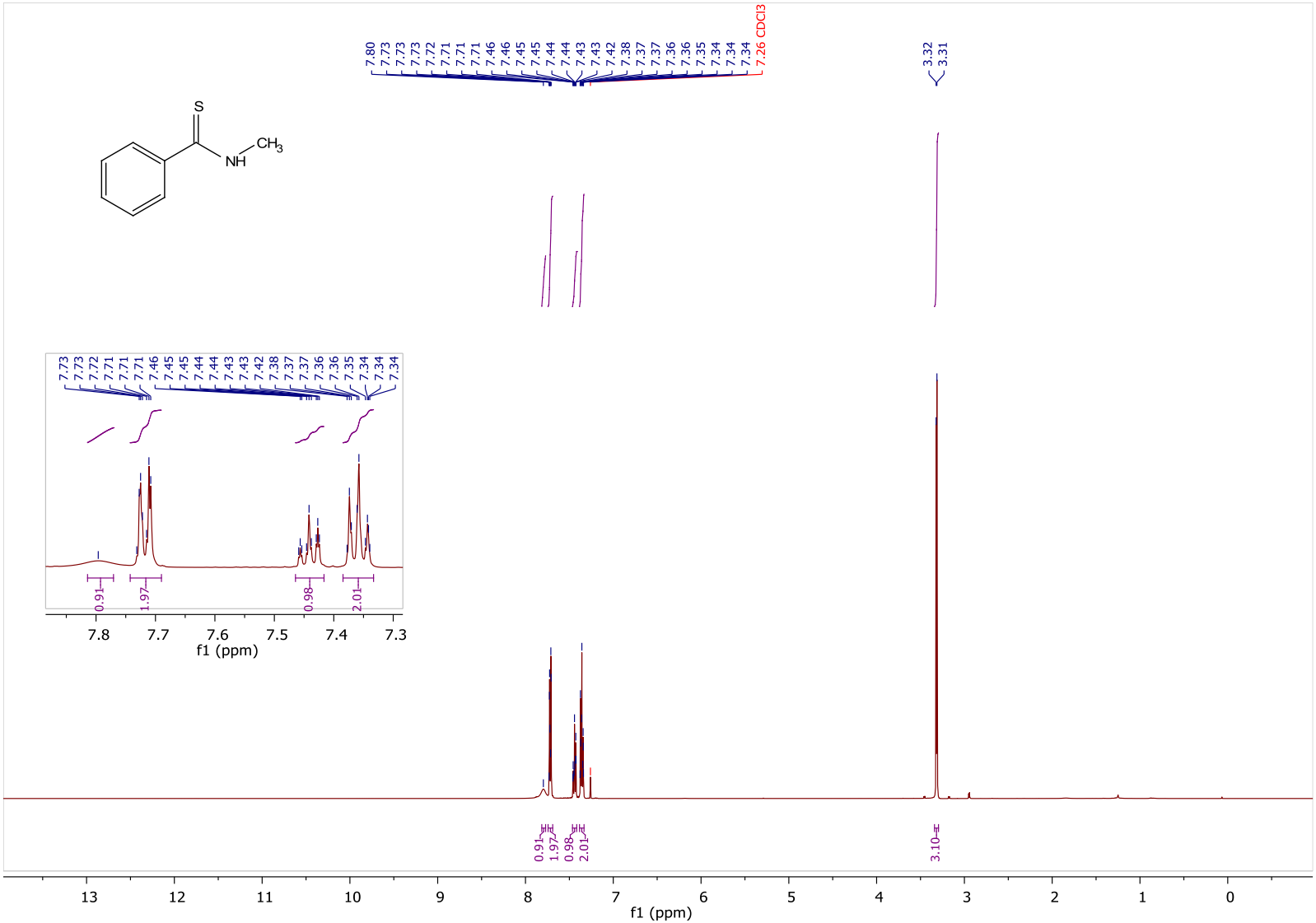
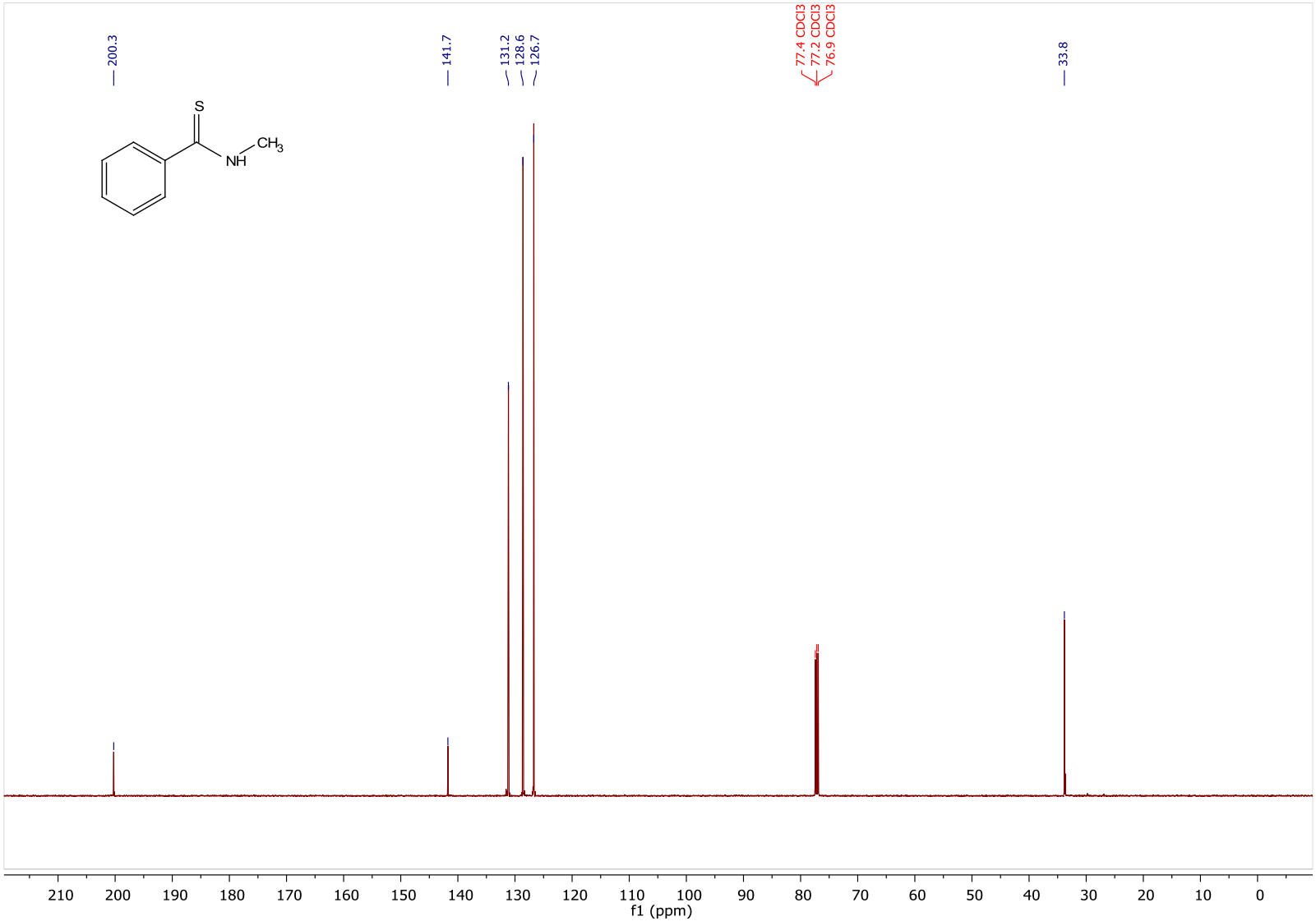


^{1}H-NMR (500 MHz, $CDCl_3$) of **2b**.



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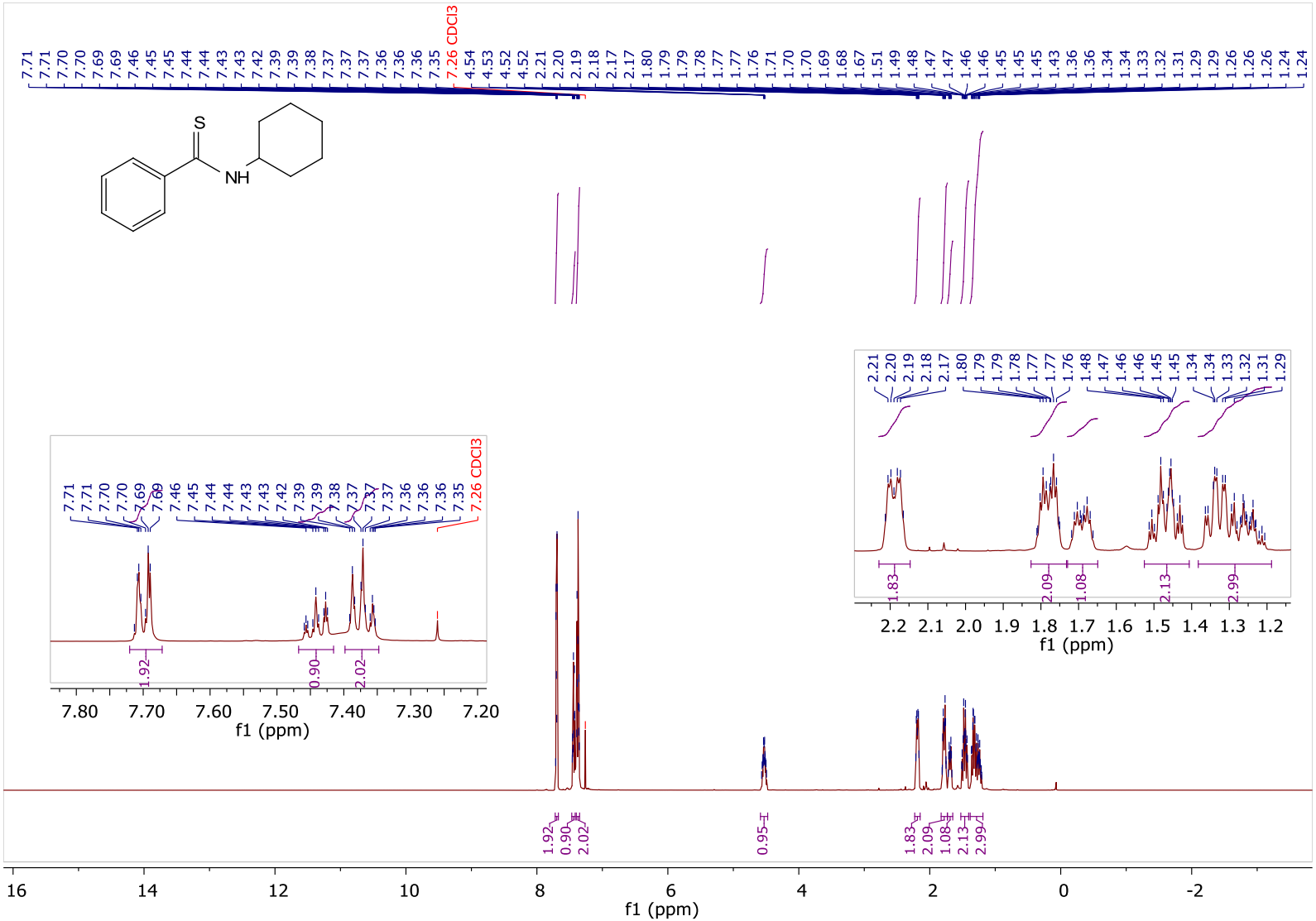
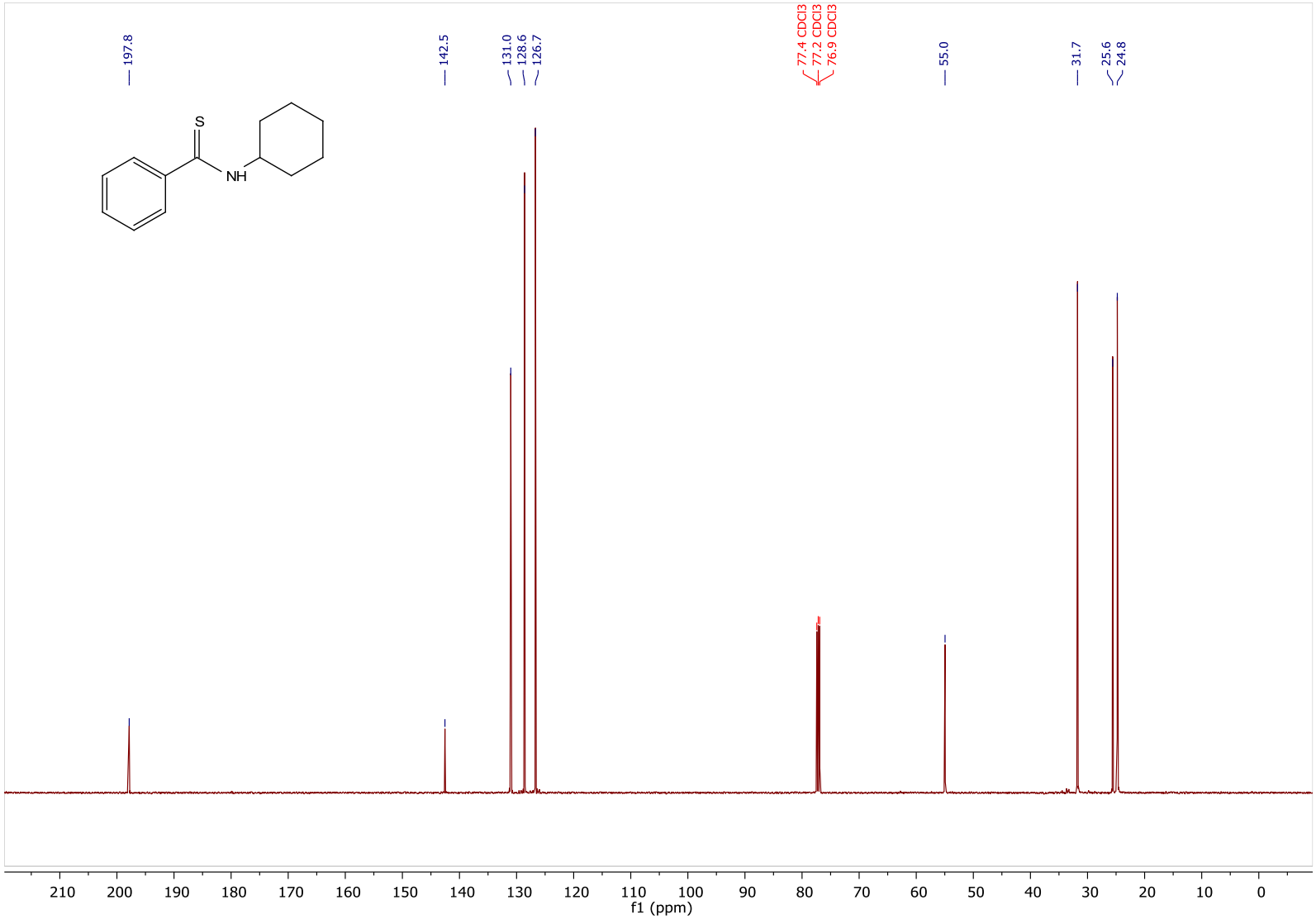
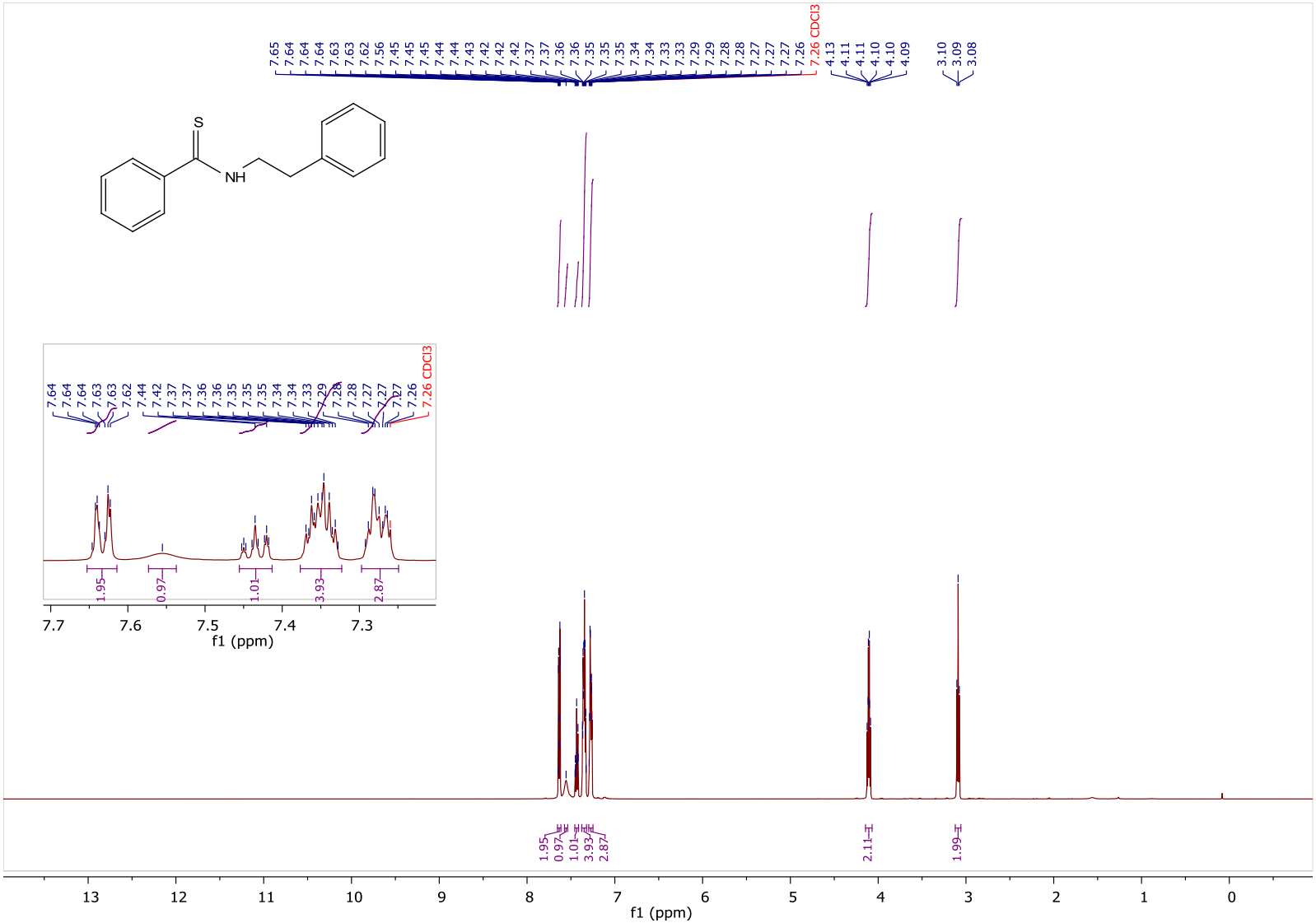


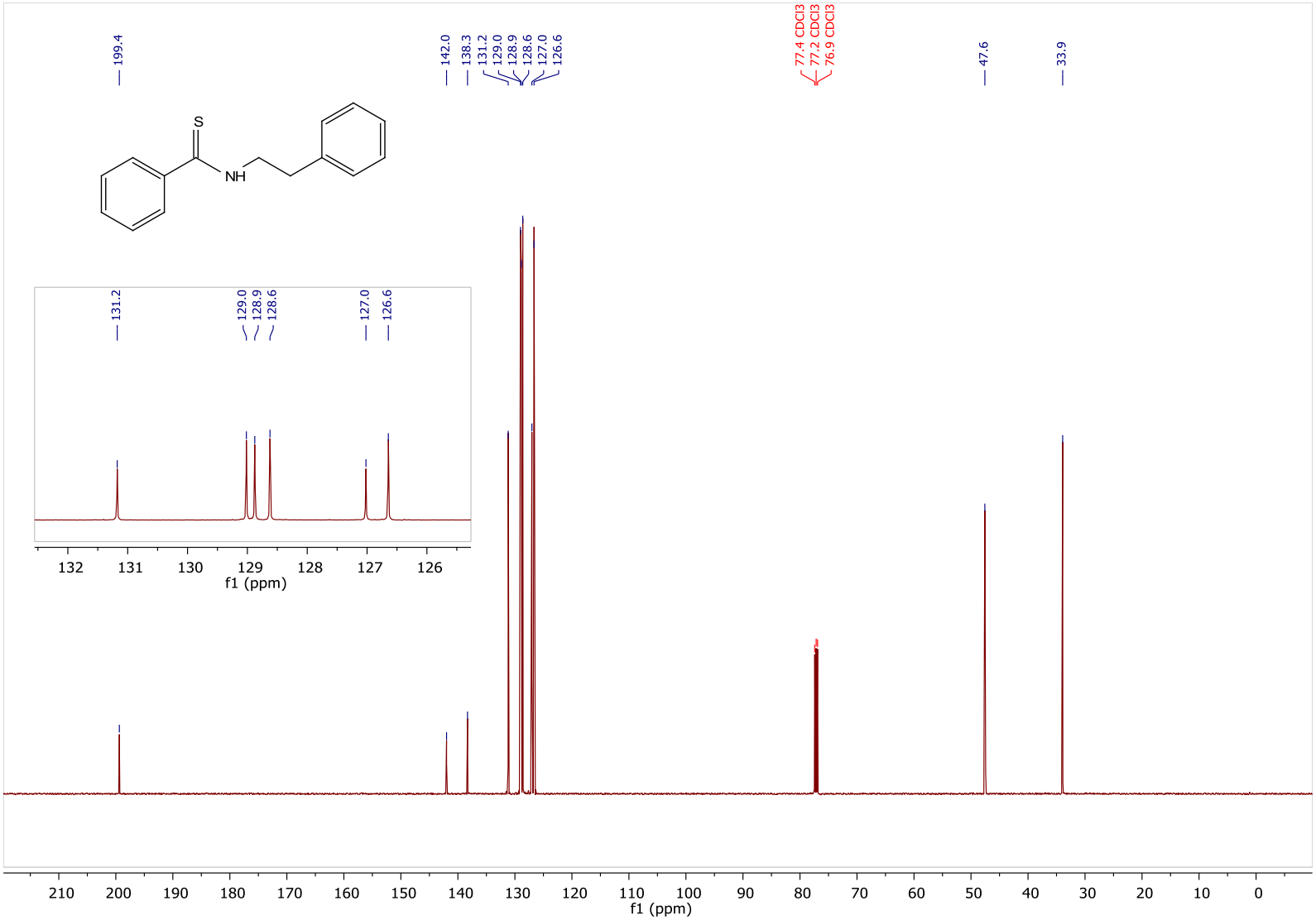
^{1}H-NMR (500 MHz, $CDCl_3$) of **3b.**



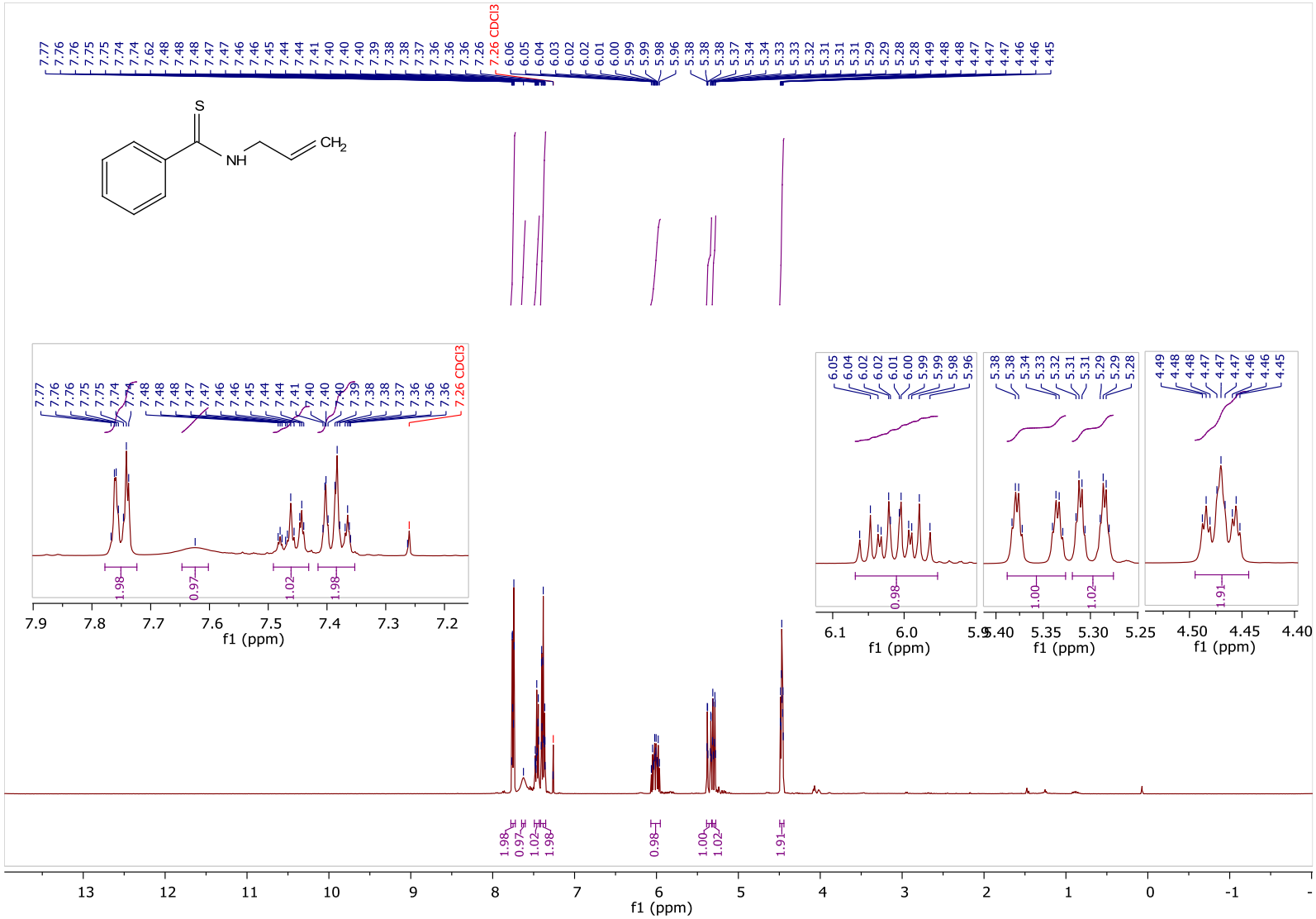
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) of **3b.**



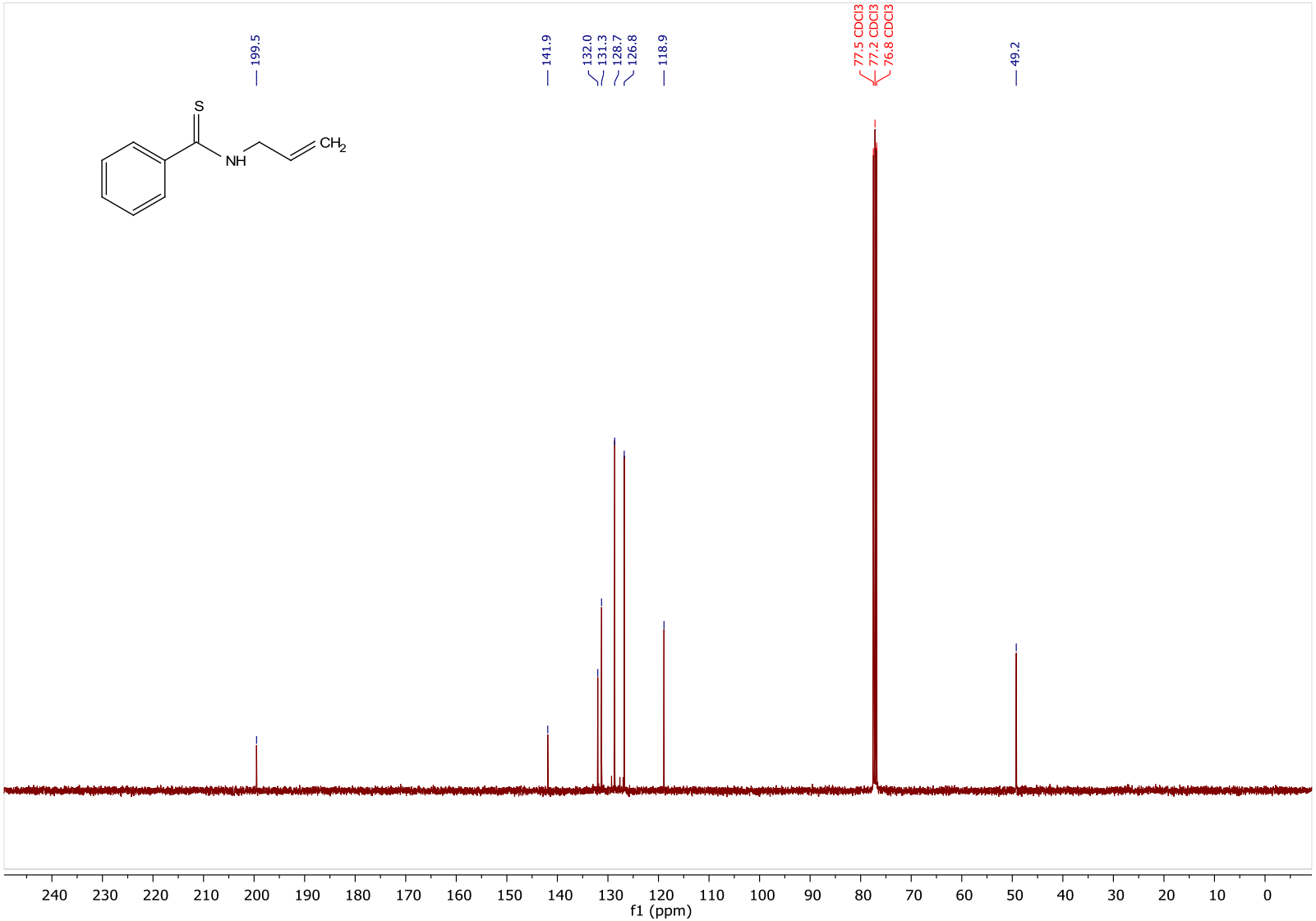
^{1}H-NMR (500 MHz, $CDCl_3$) of **4b.**



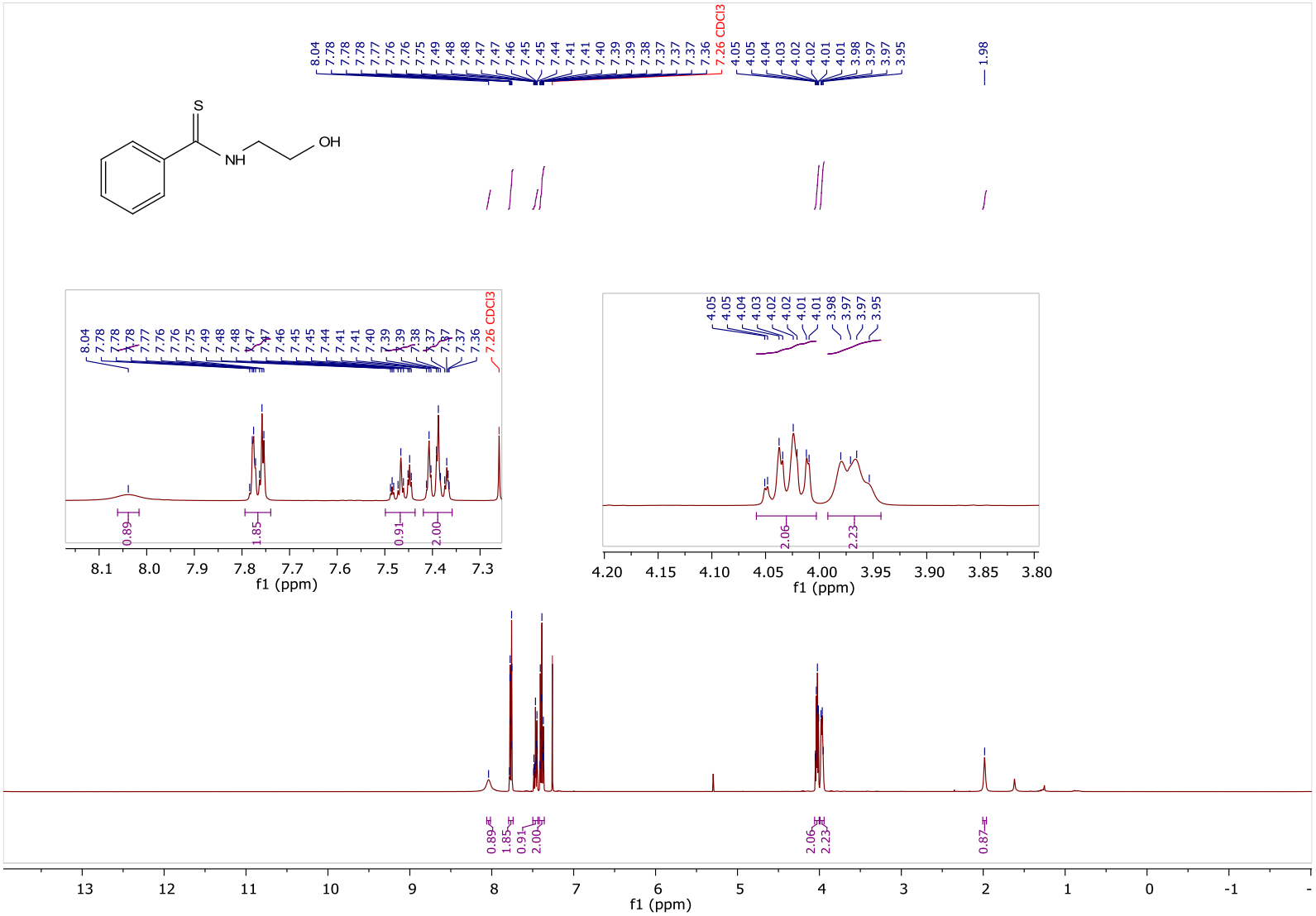
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) of **4b.**



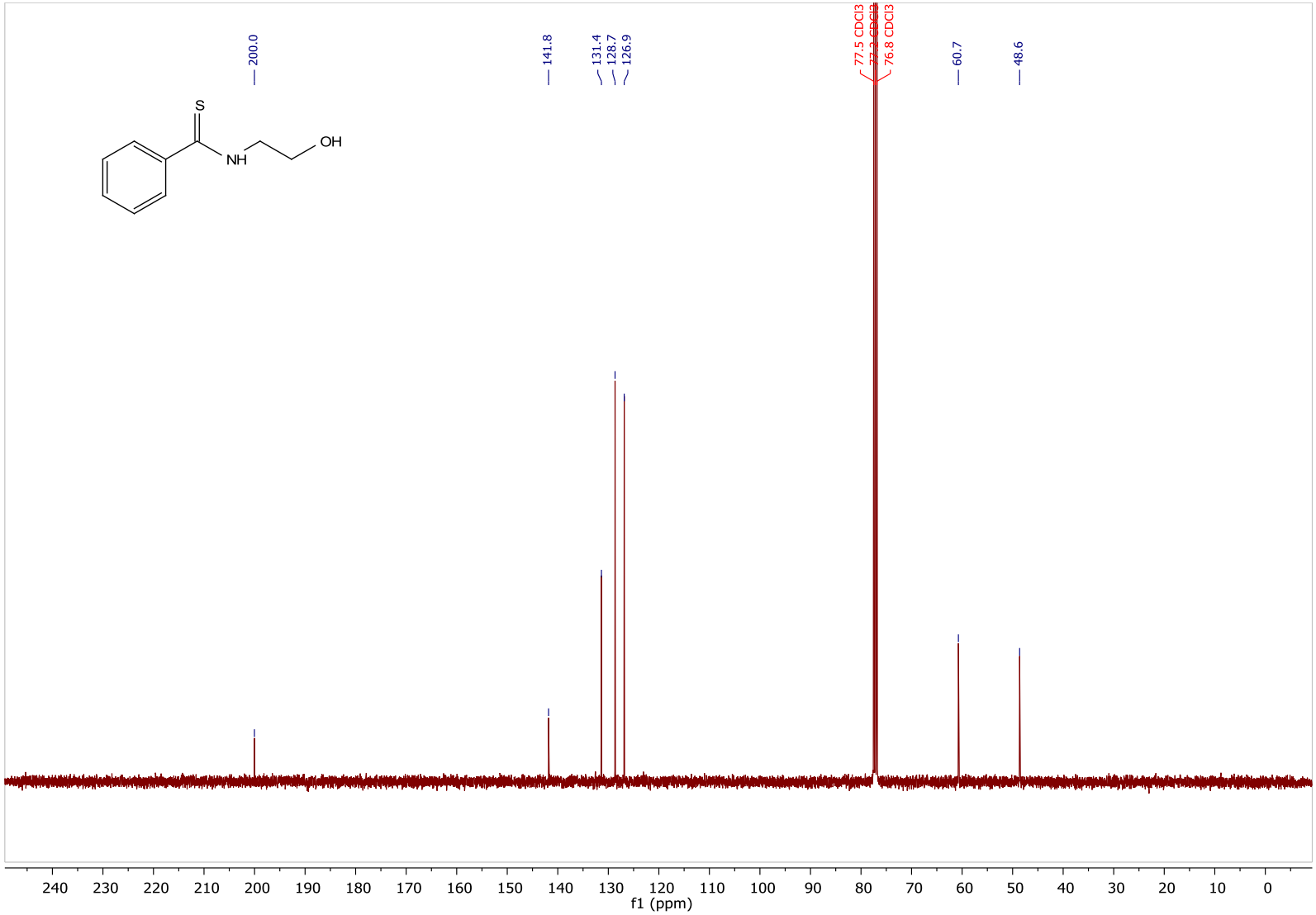
^{1}H-NMR (400 MHz, $CDCl_3$) of **5b.**



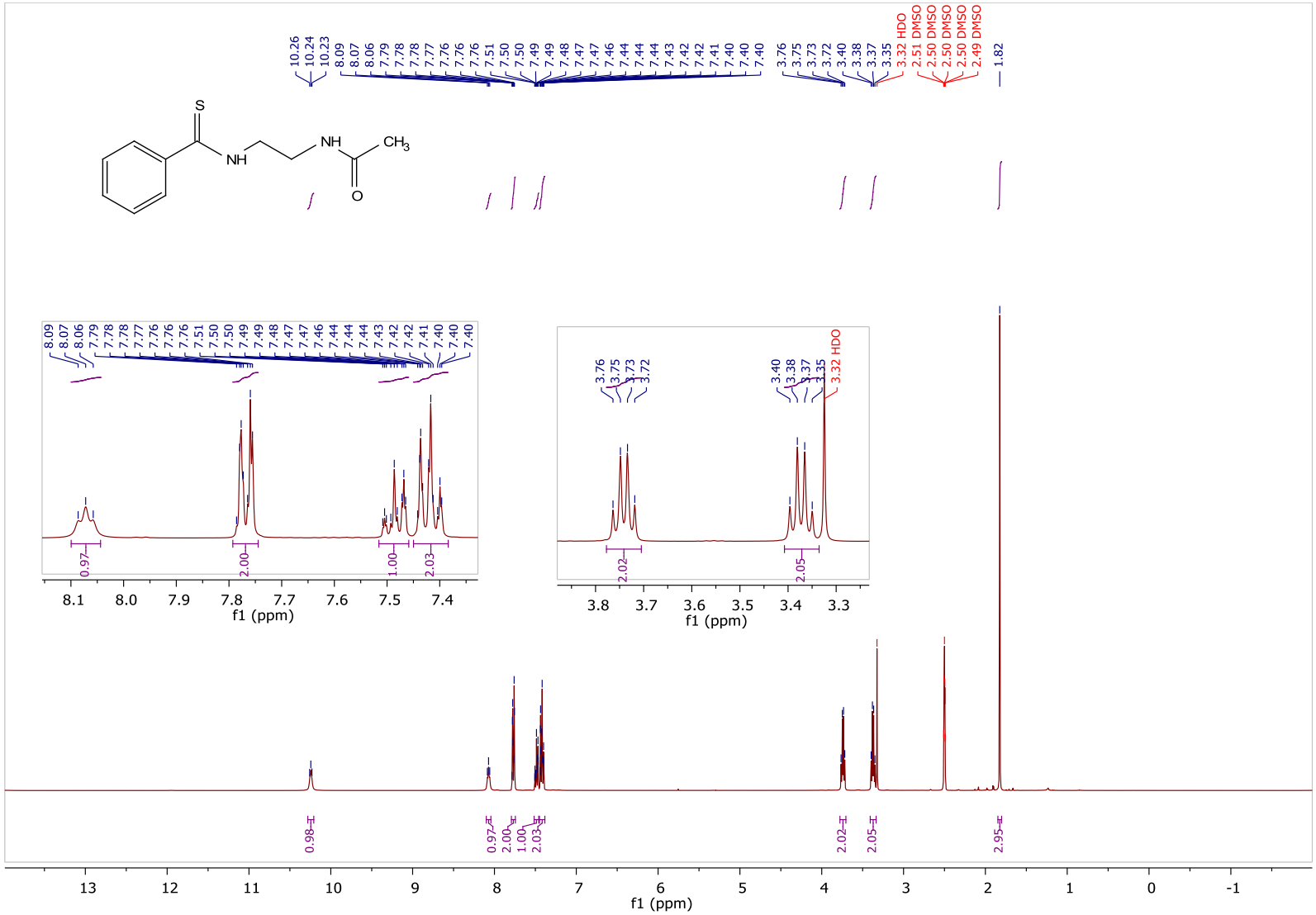
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **5b.**



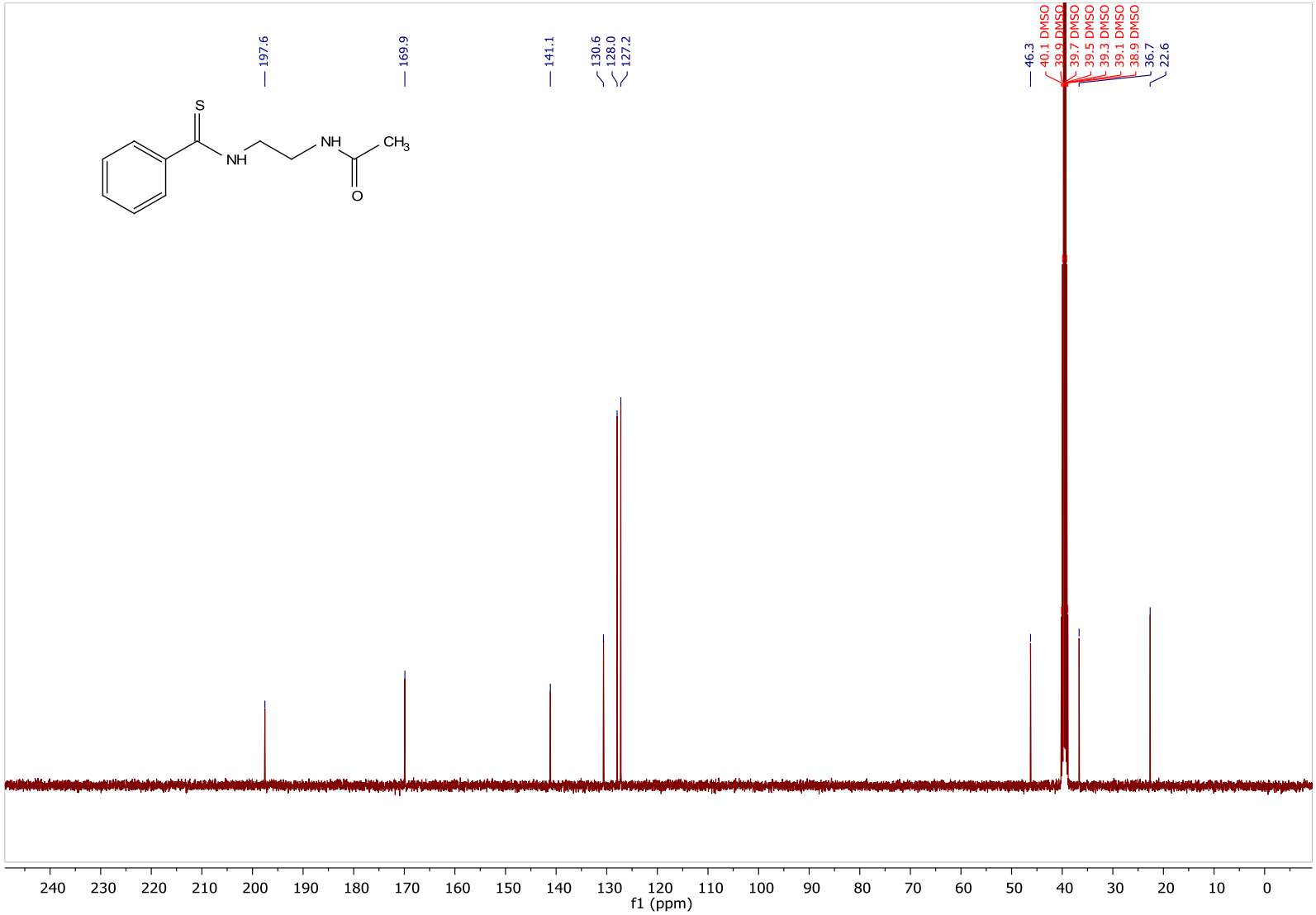
^{1}H-NMR (400 MHz, $CDCl_3$) of **6b.**



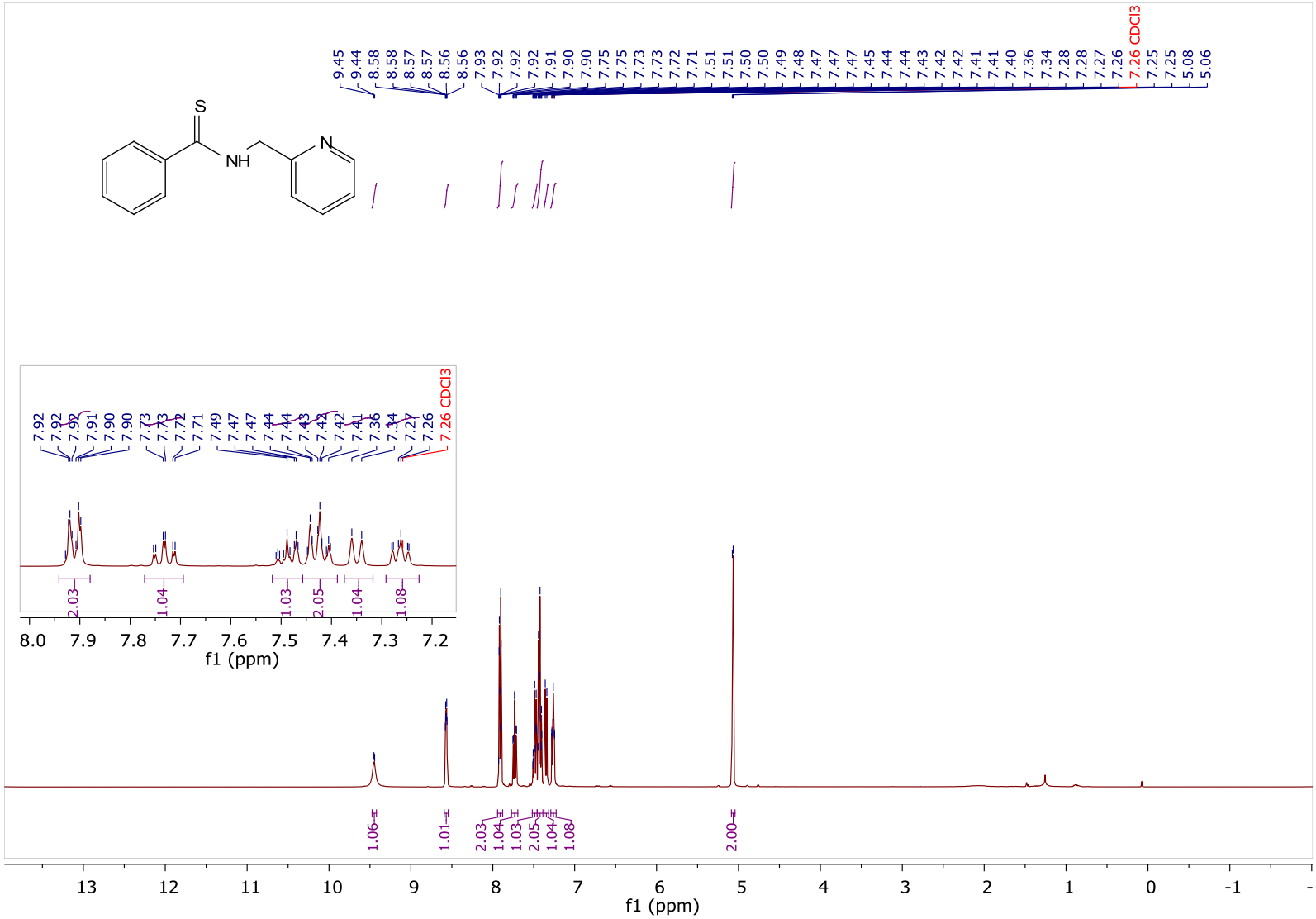
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **6b.**



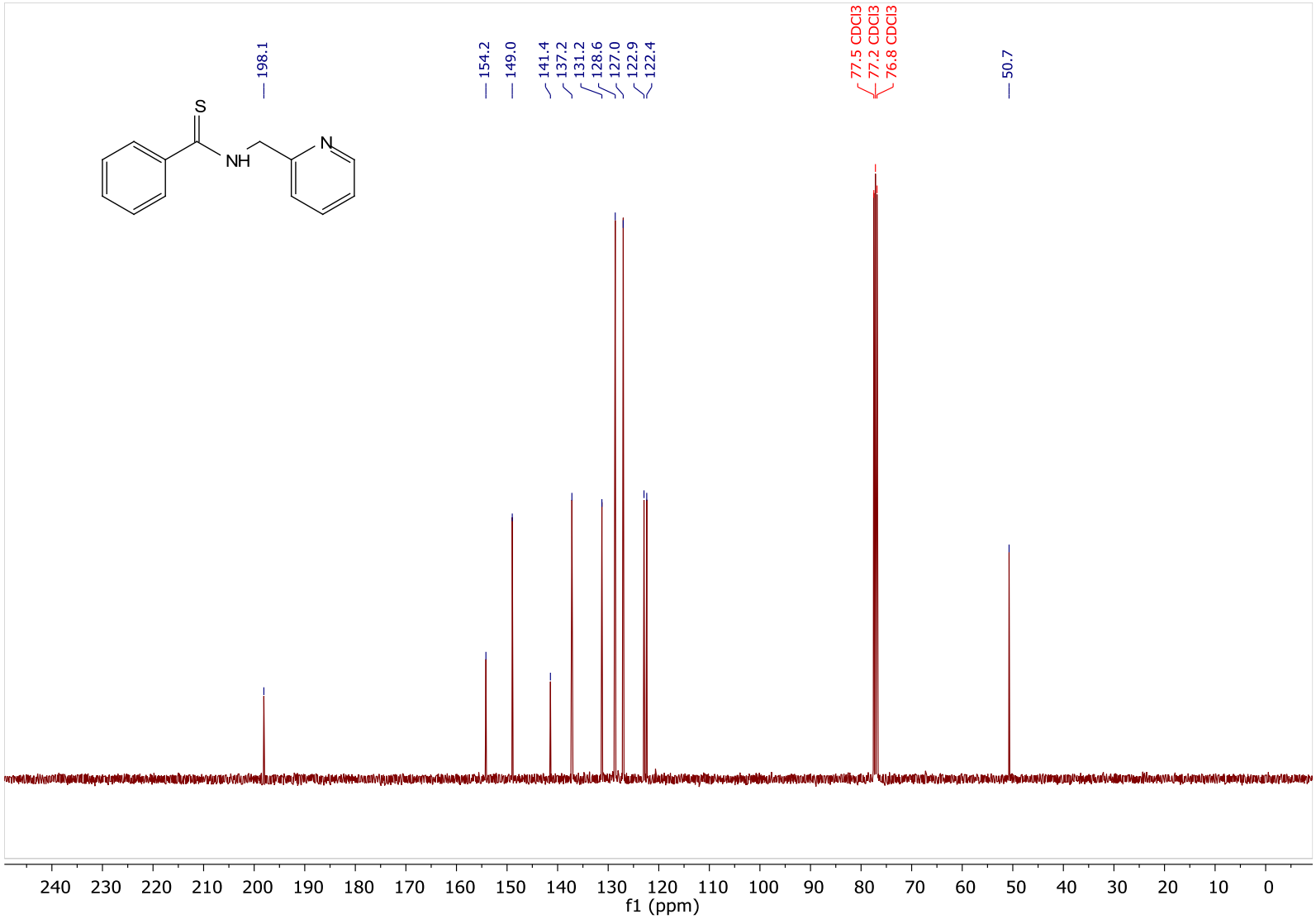
^{1}H-NMR (400 MHz, $CDCl_3$) of **7b.**



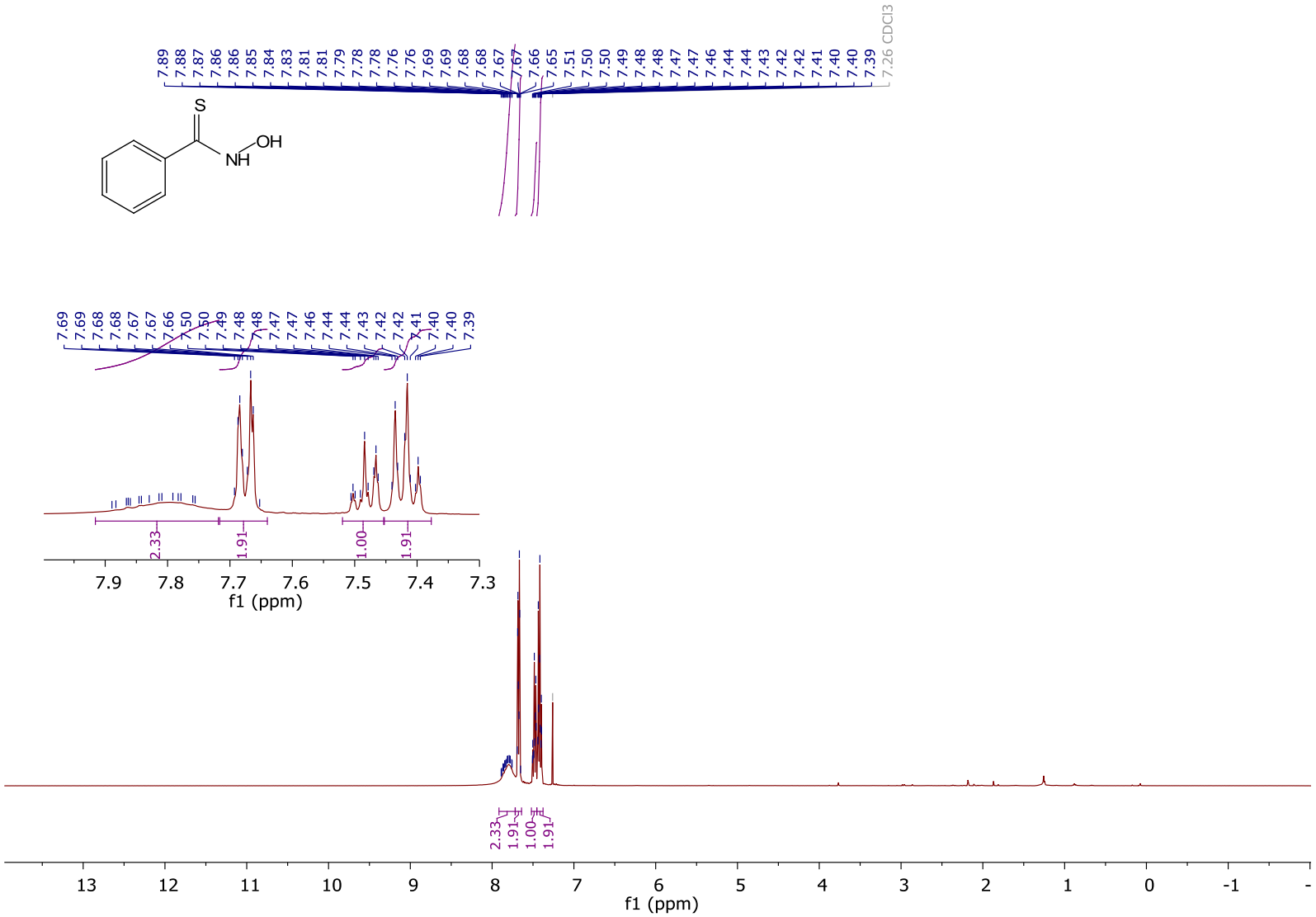
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **7b.**



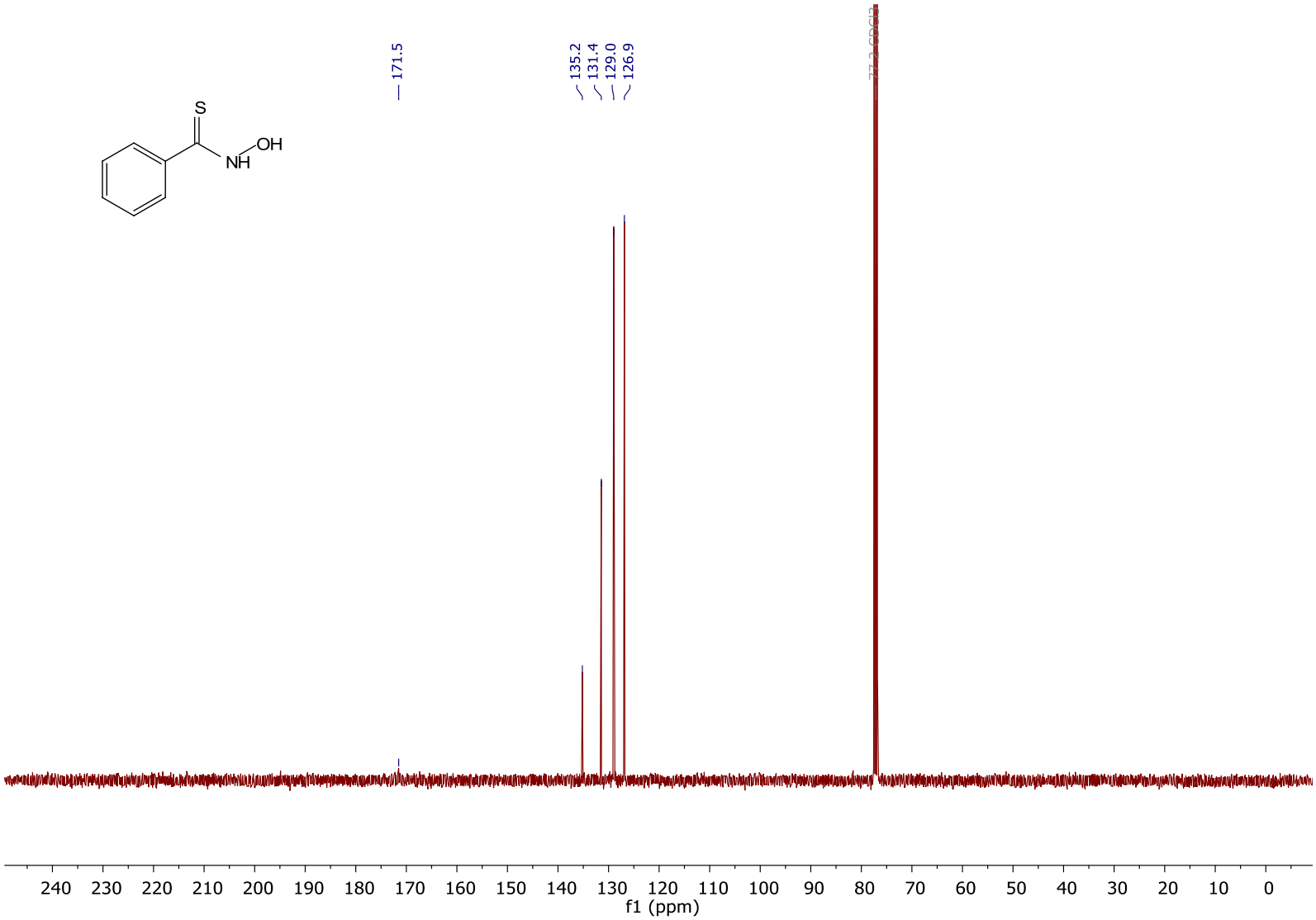
^{1}H-NMR (400 MHz, $CDCl_3$) of **8b.**



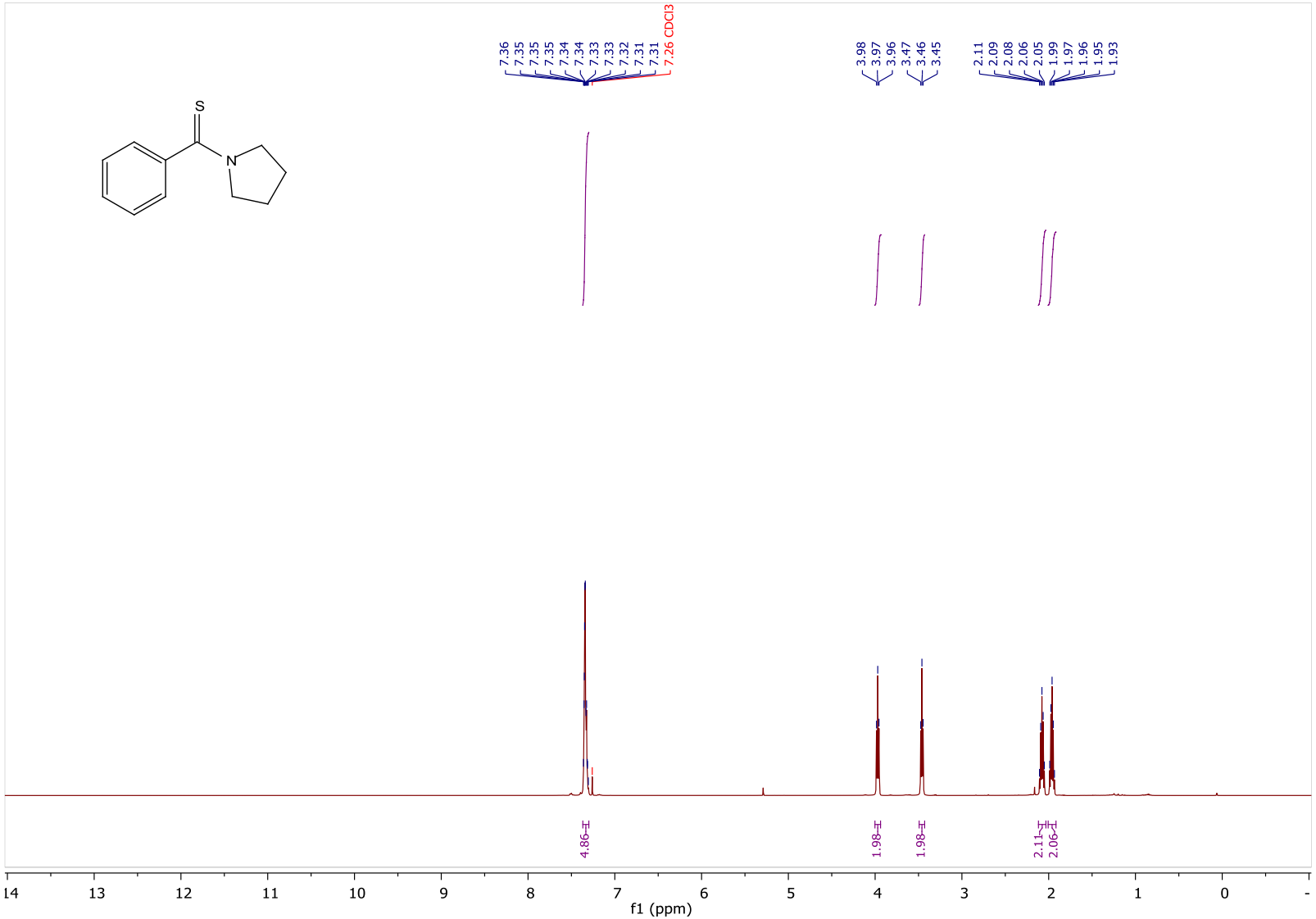
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **8b.**



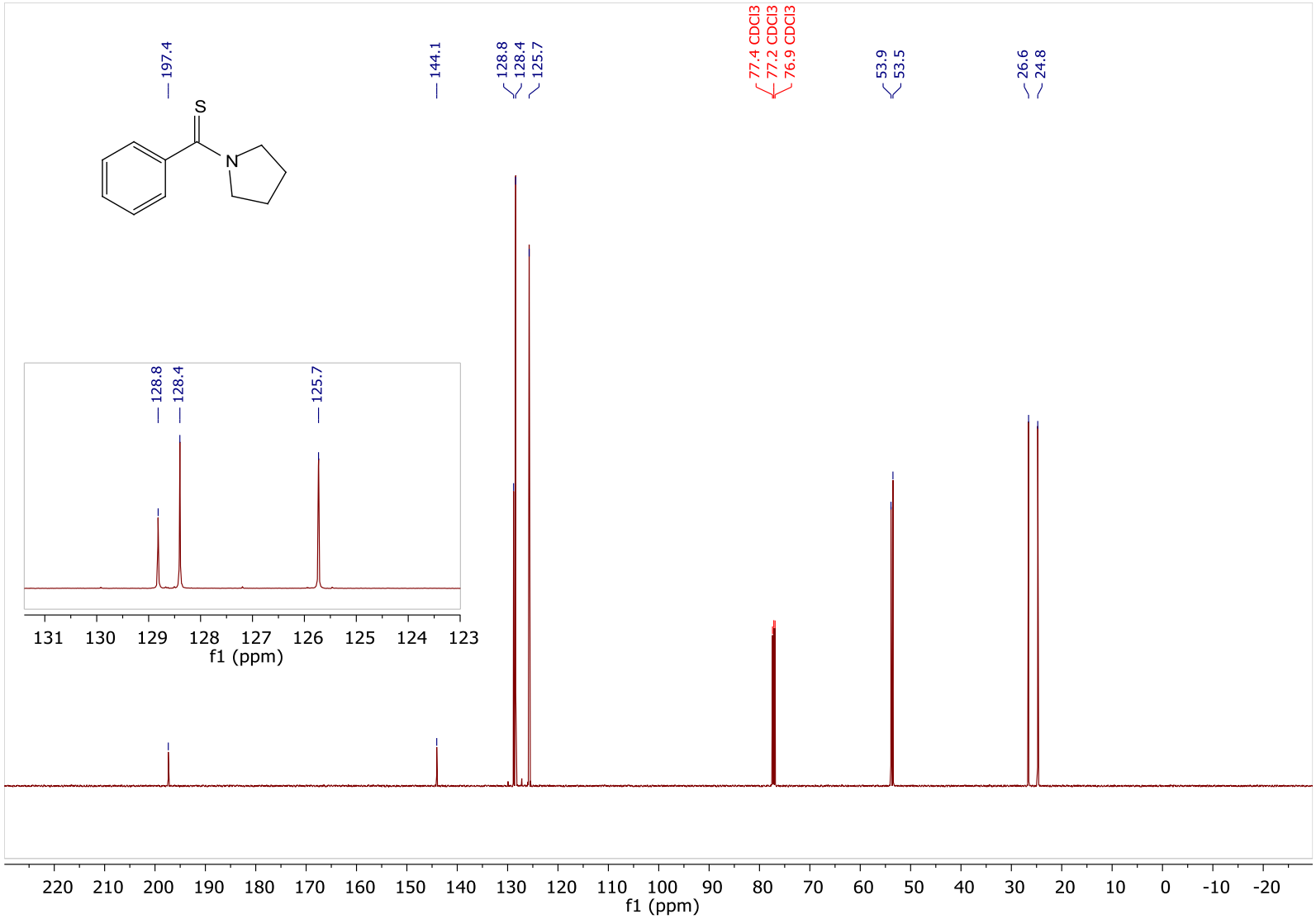
^{1}H-NMR (400 MHz, $CDCl_3$) of **9b.**



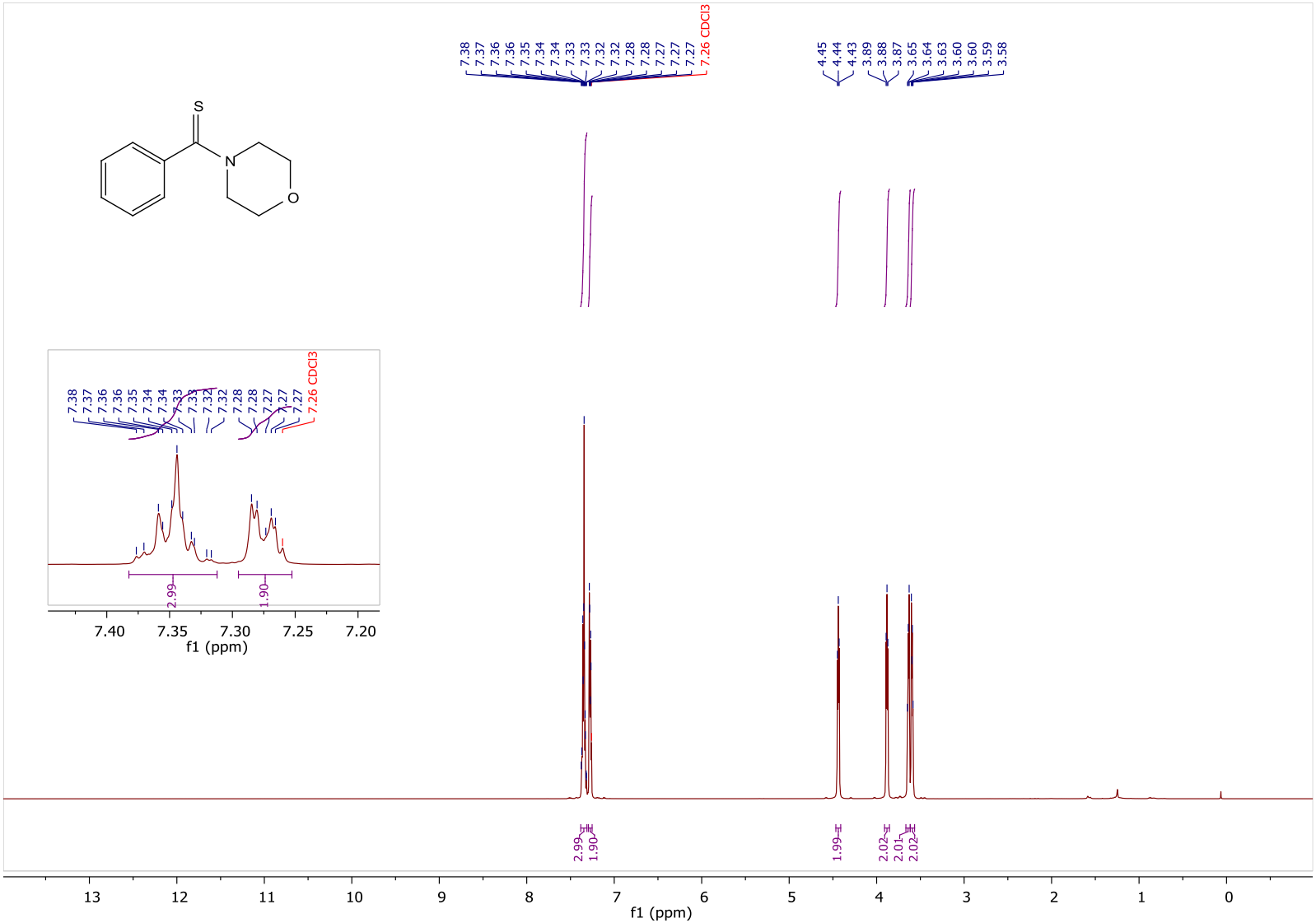
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **9b.**



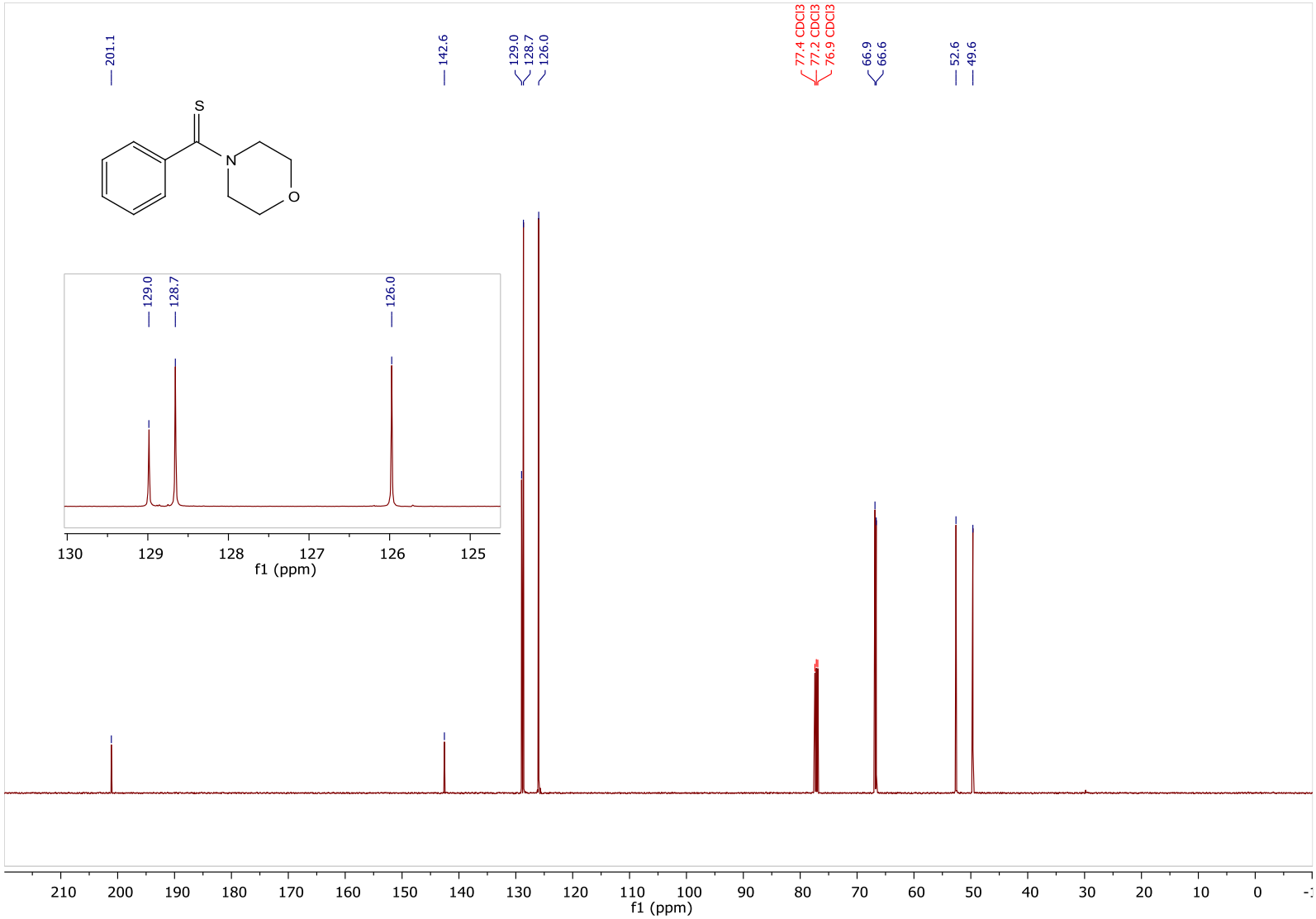
^{1}H-NMR (500 MHz, $CDCl_3$) of **10b.**



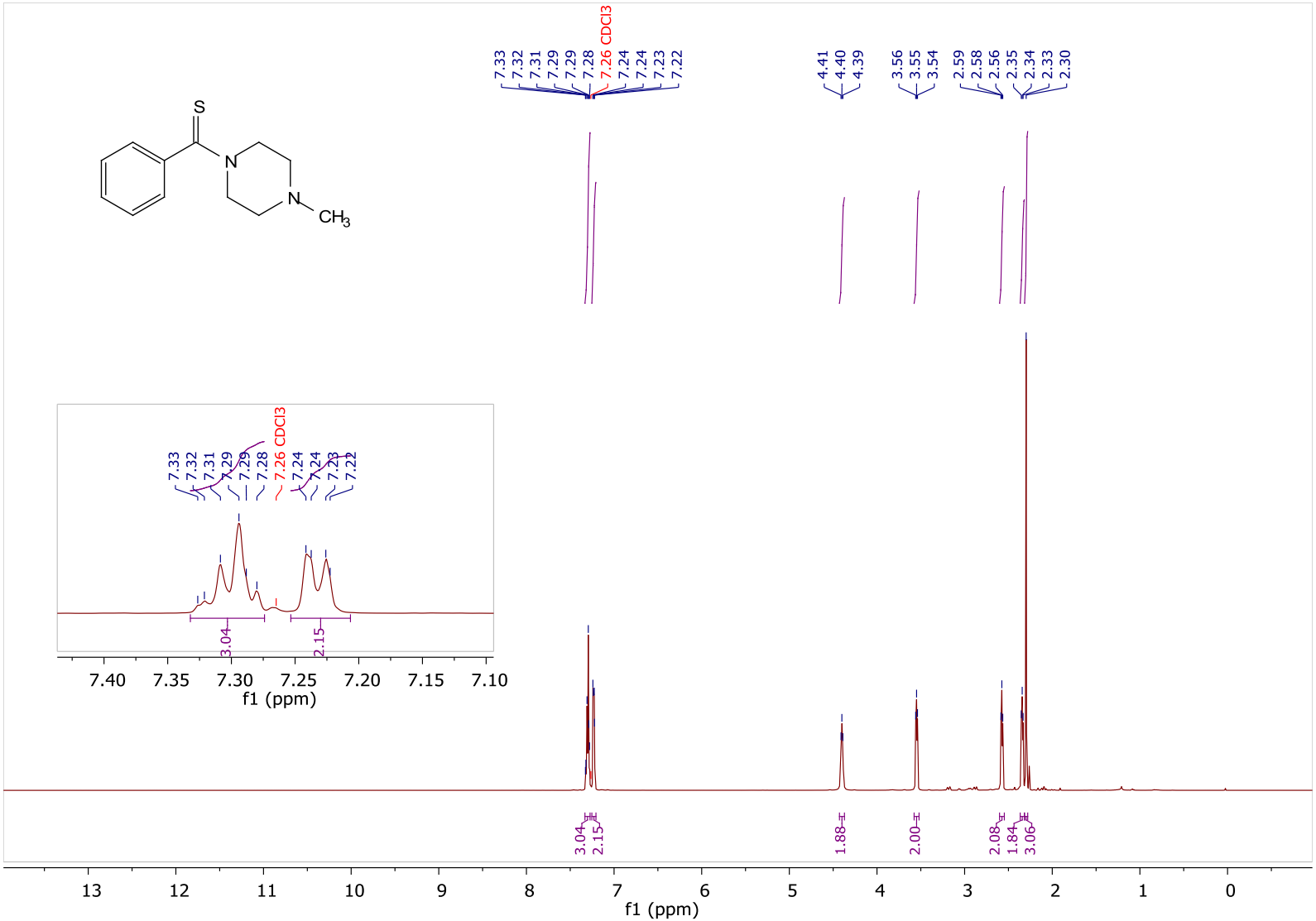
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) of **10b.**



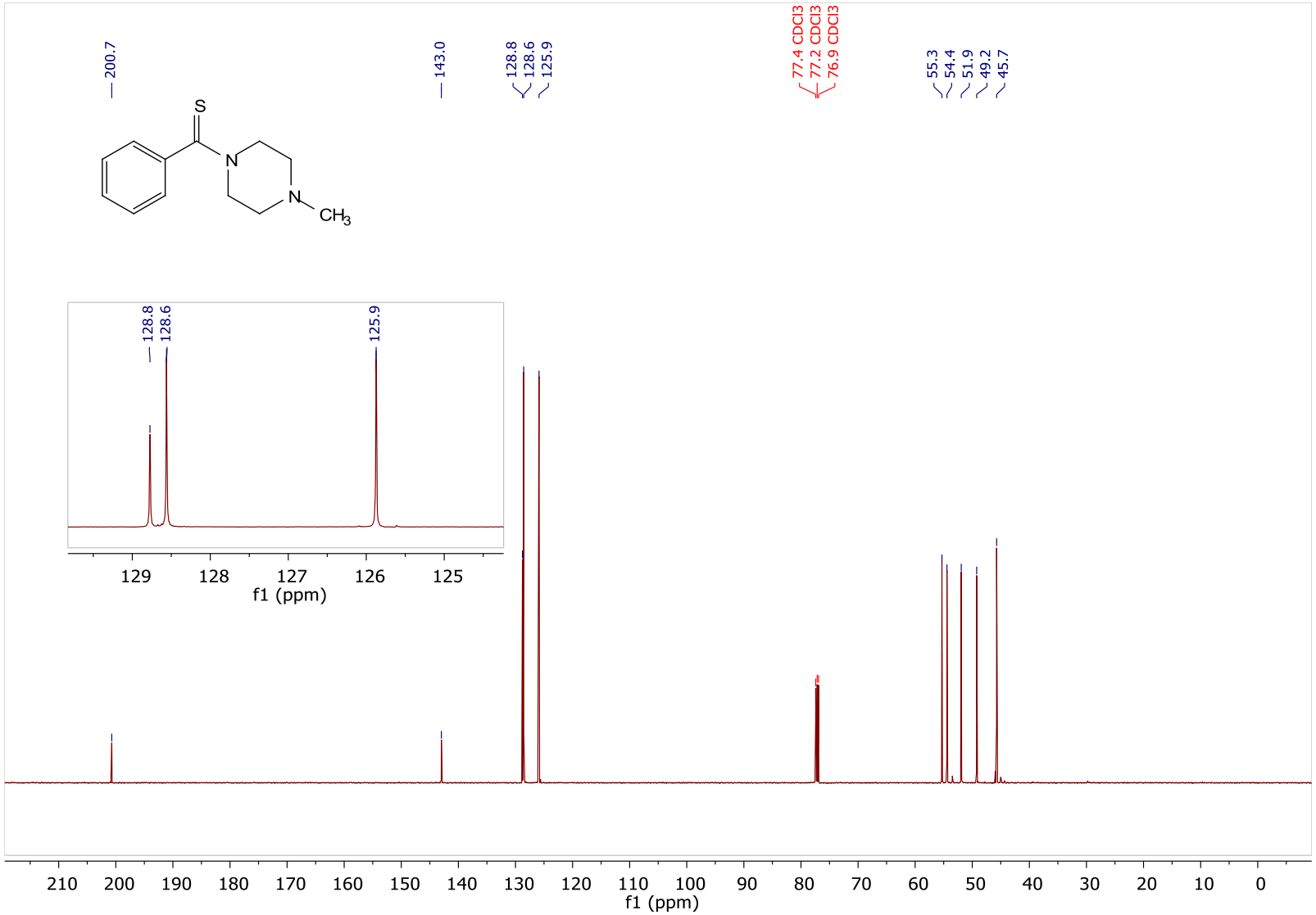
^{1}H-NMR (500 MHz, $CDCl_3$) of **11b.**



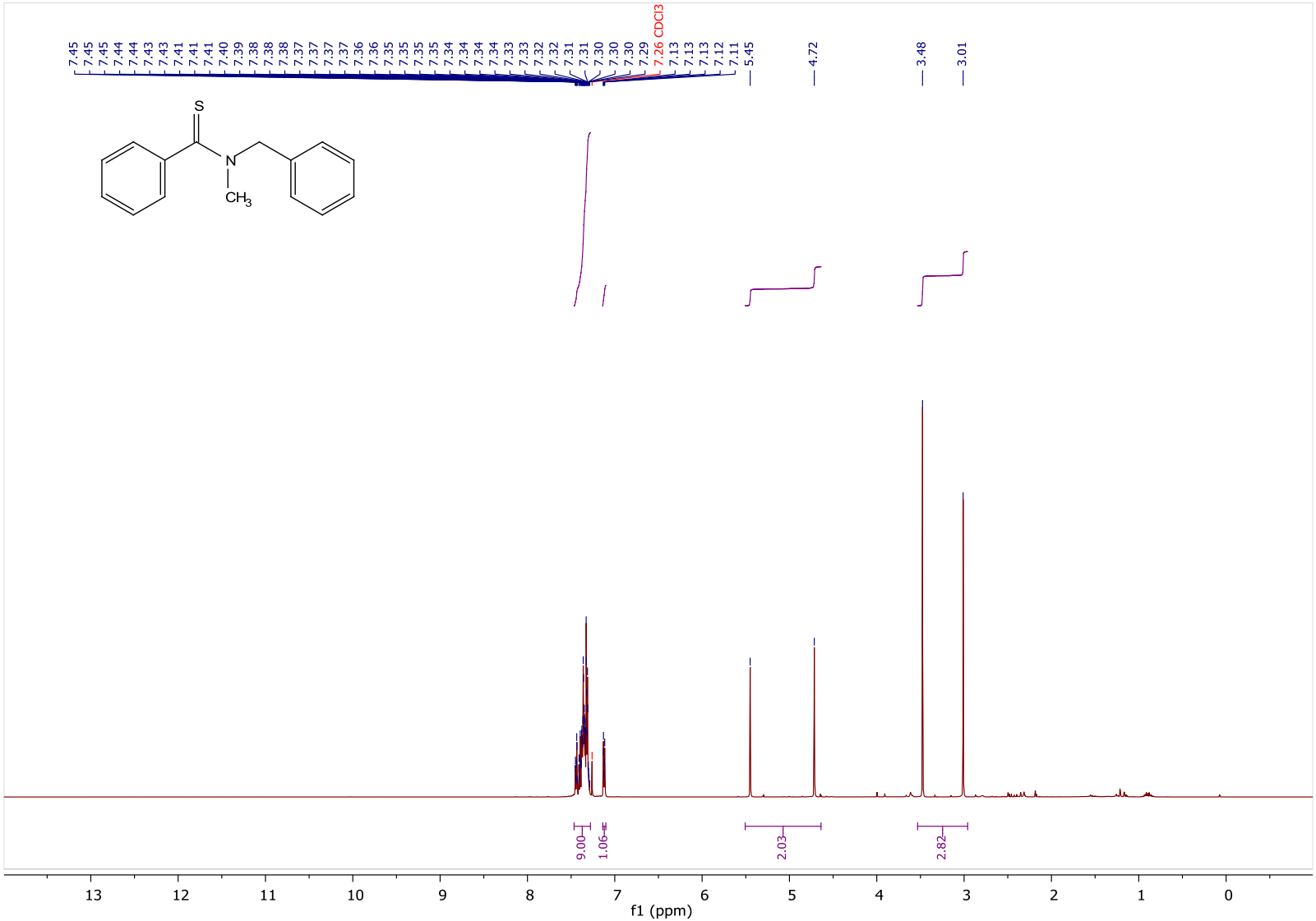
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) of **11b.**



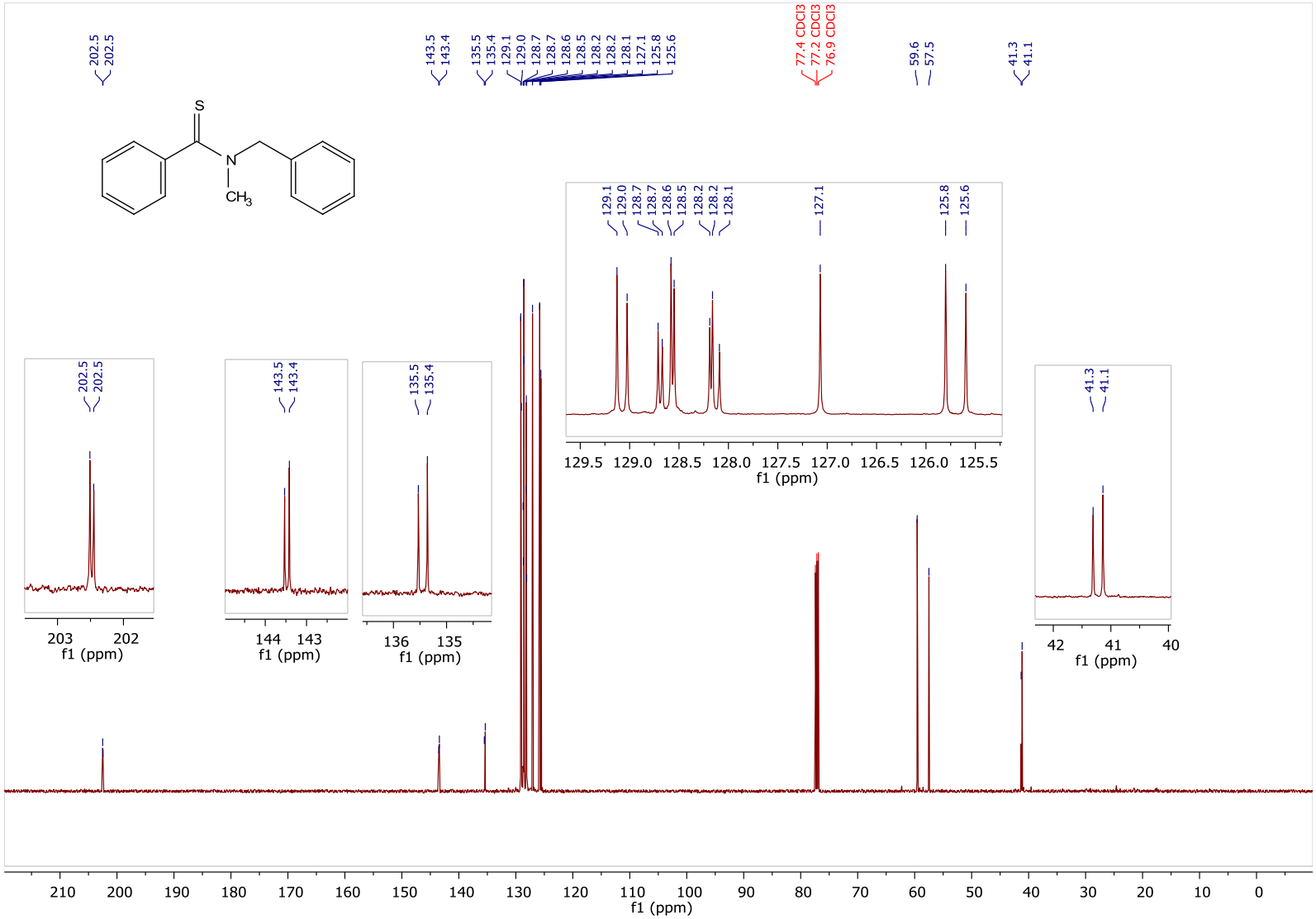
^{1}H-NMR (500 MHz, $CDCl_3$) of **12b.**



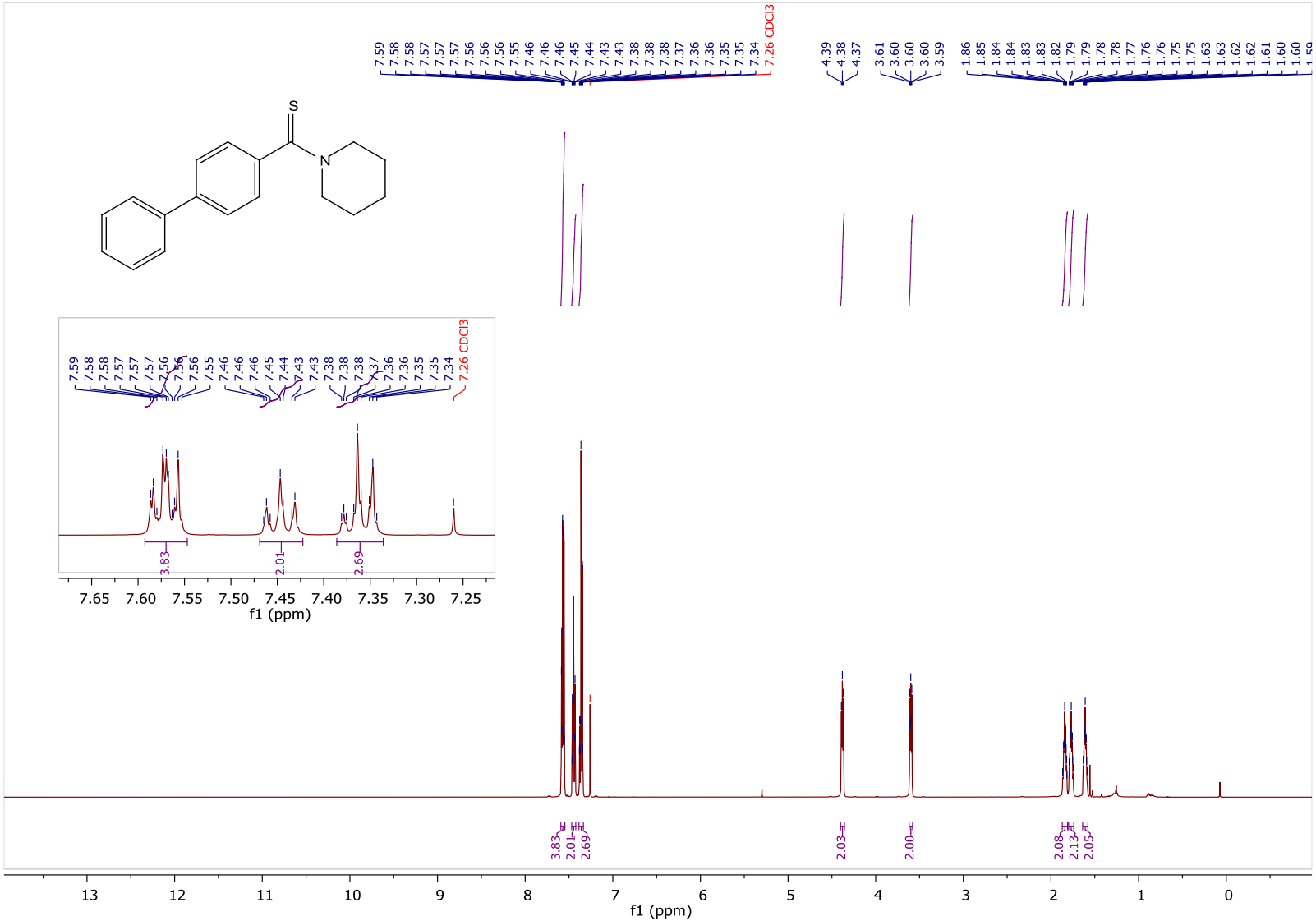
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) of **12b.**



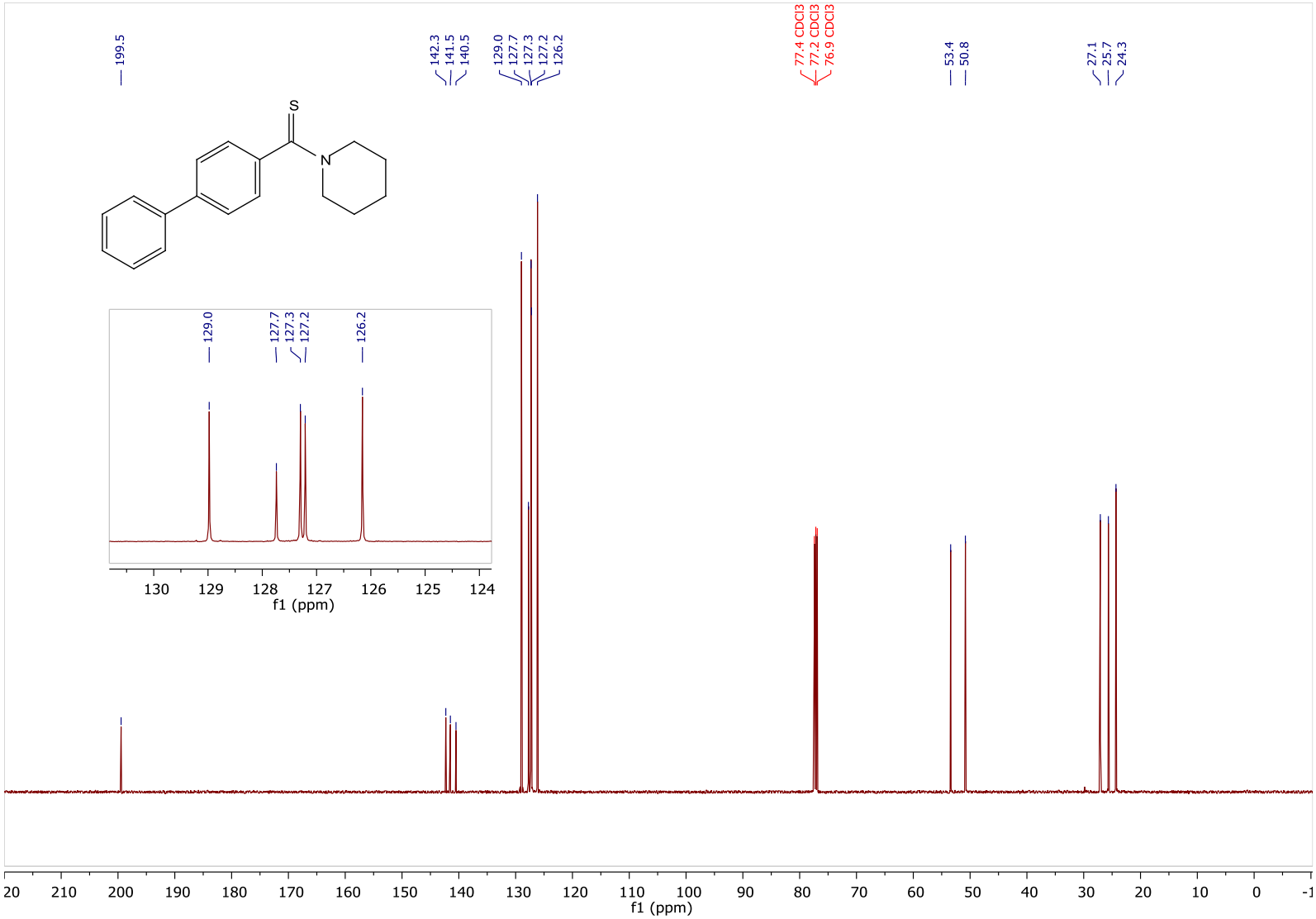
^{1}H-NMR (500 MHz, $CDCl_3$) of **13b.**



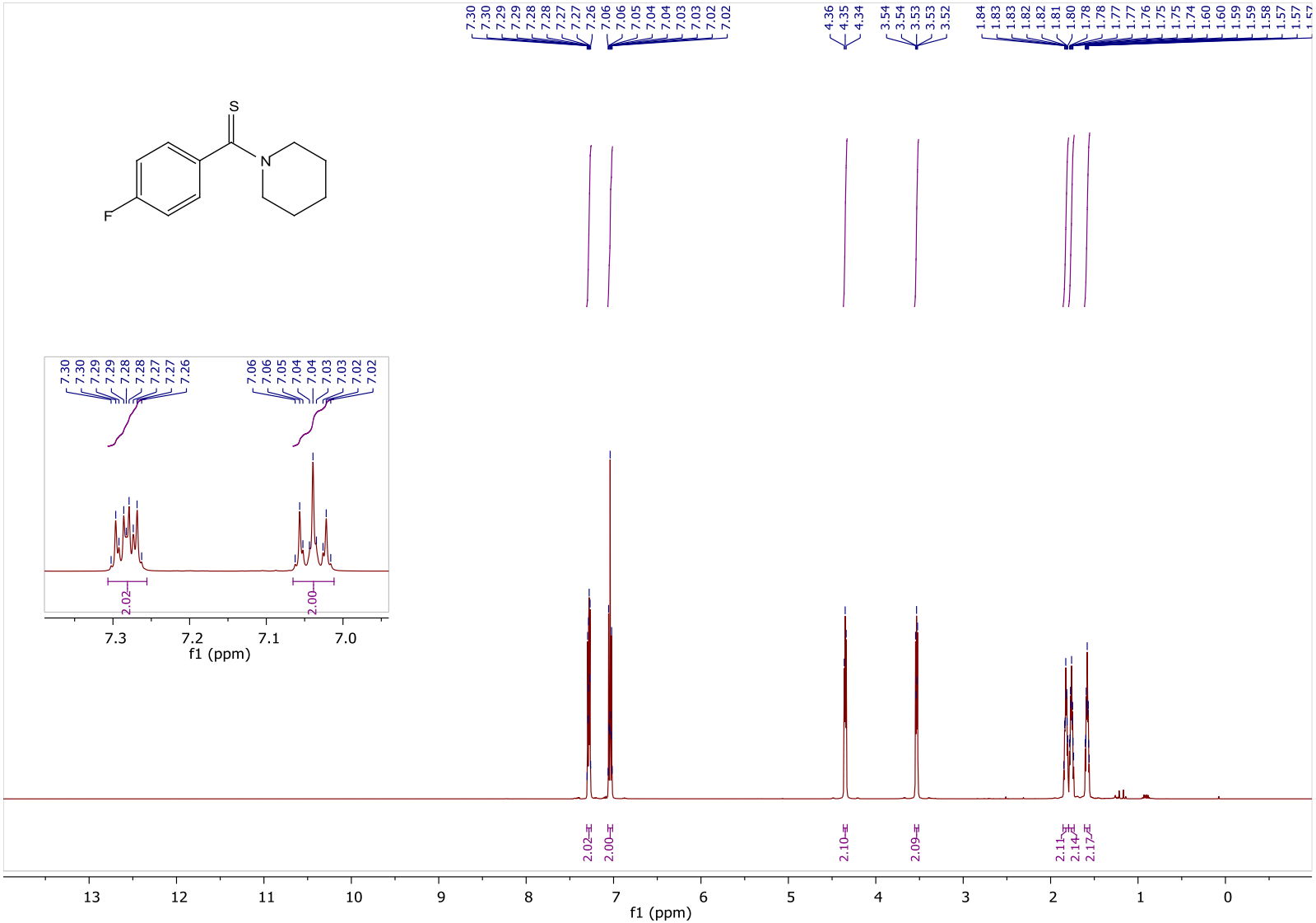
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) of **13b.**



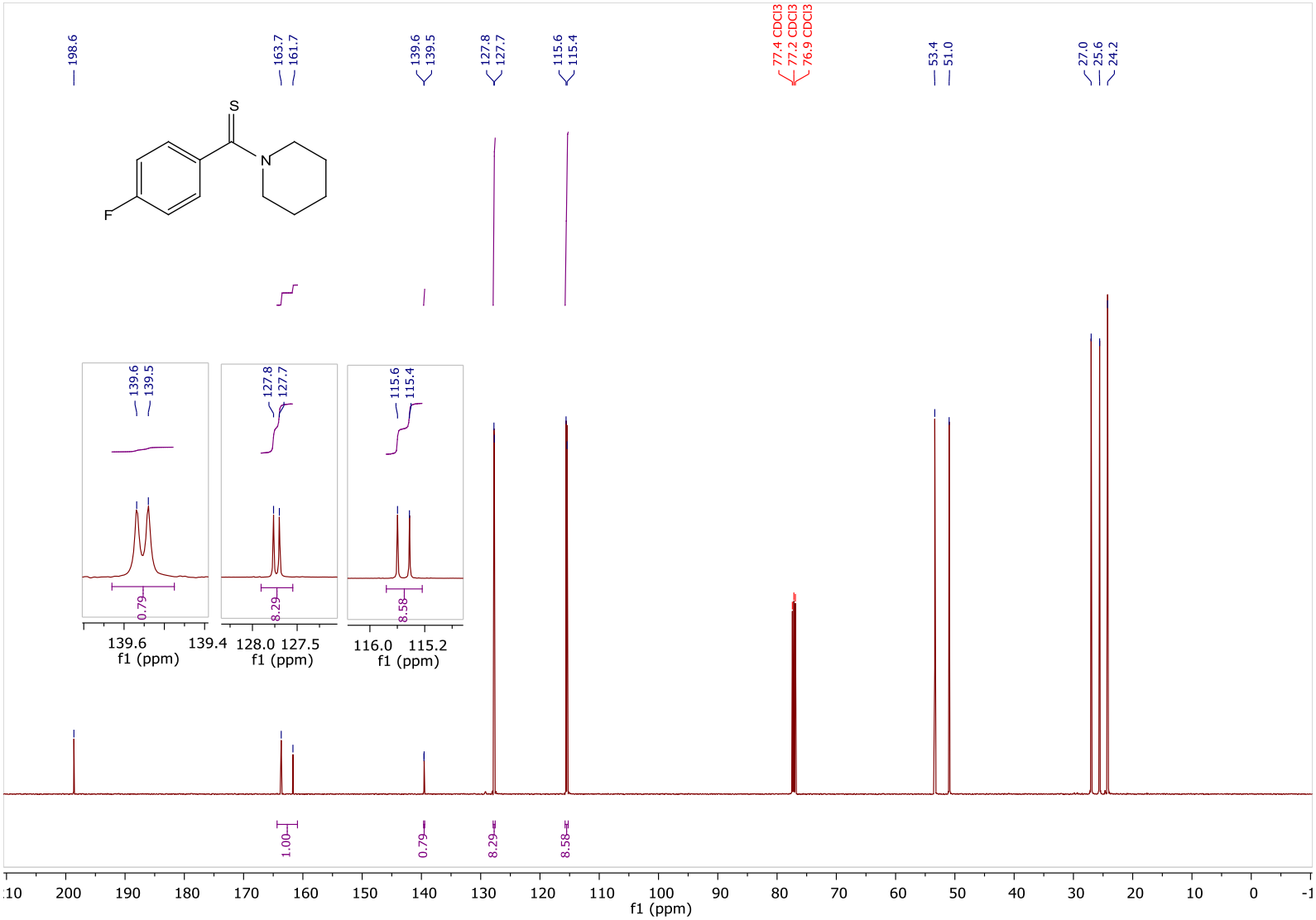
^{1}H-NMR (500 MHz, $CDCl_3$) of **14b.**



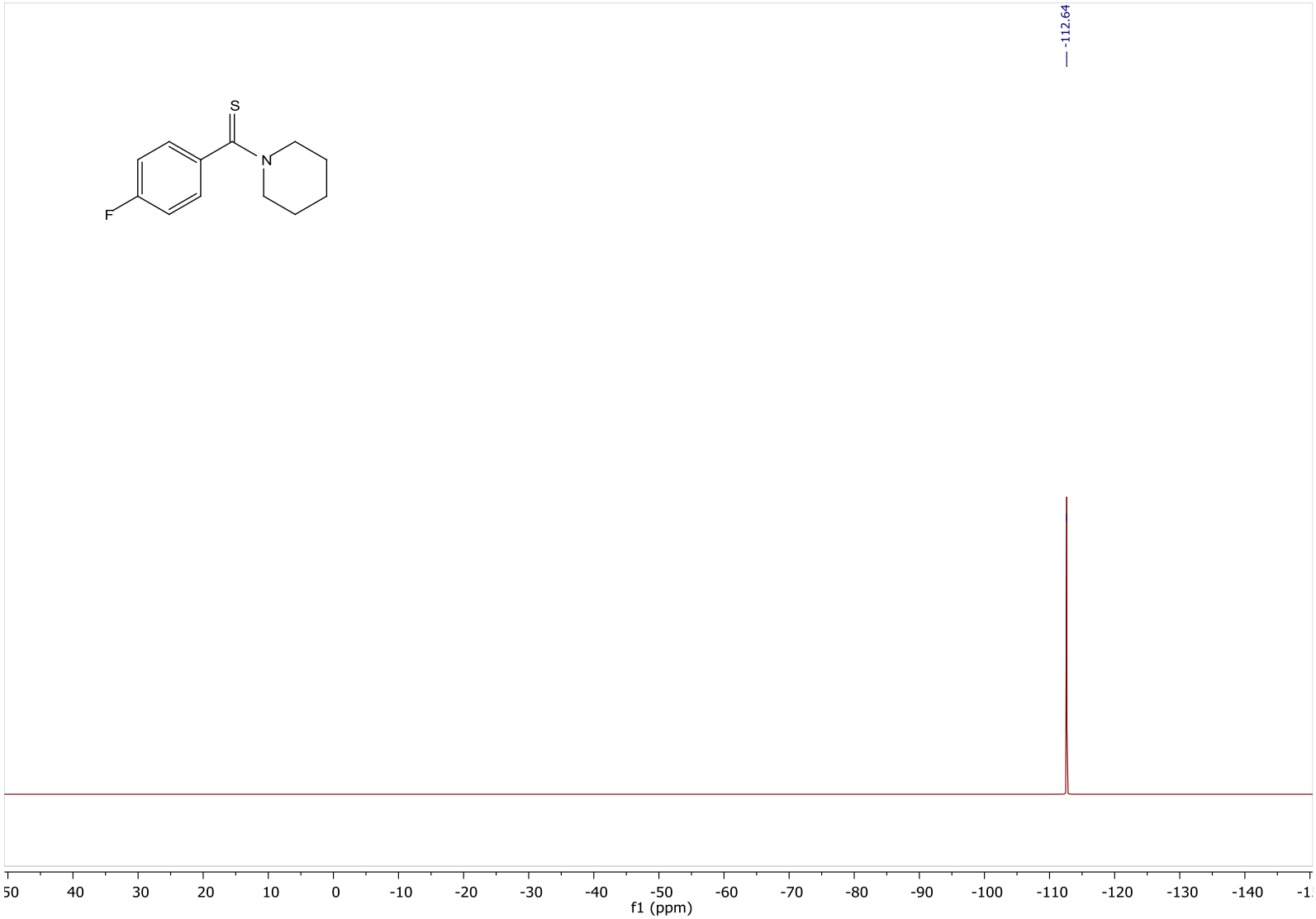
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) of **14b.**



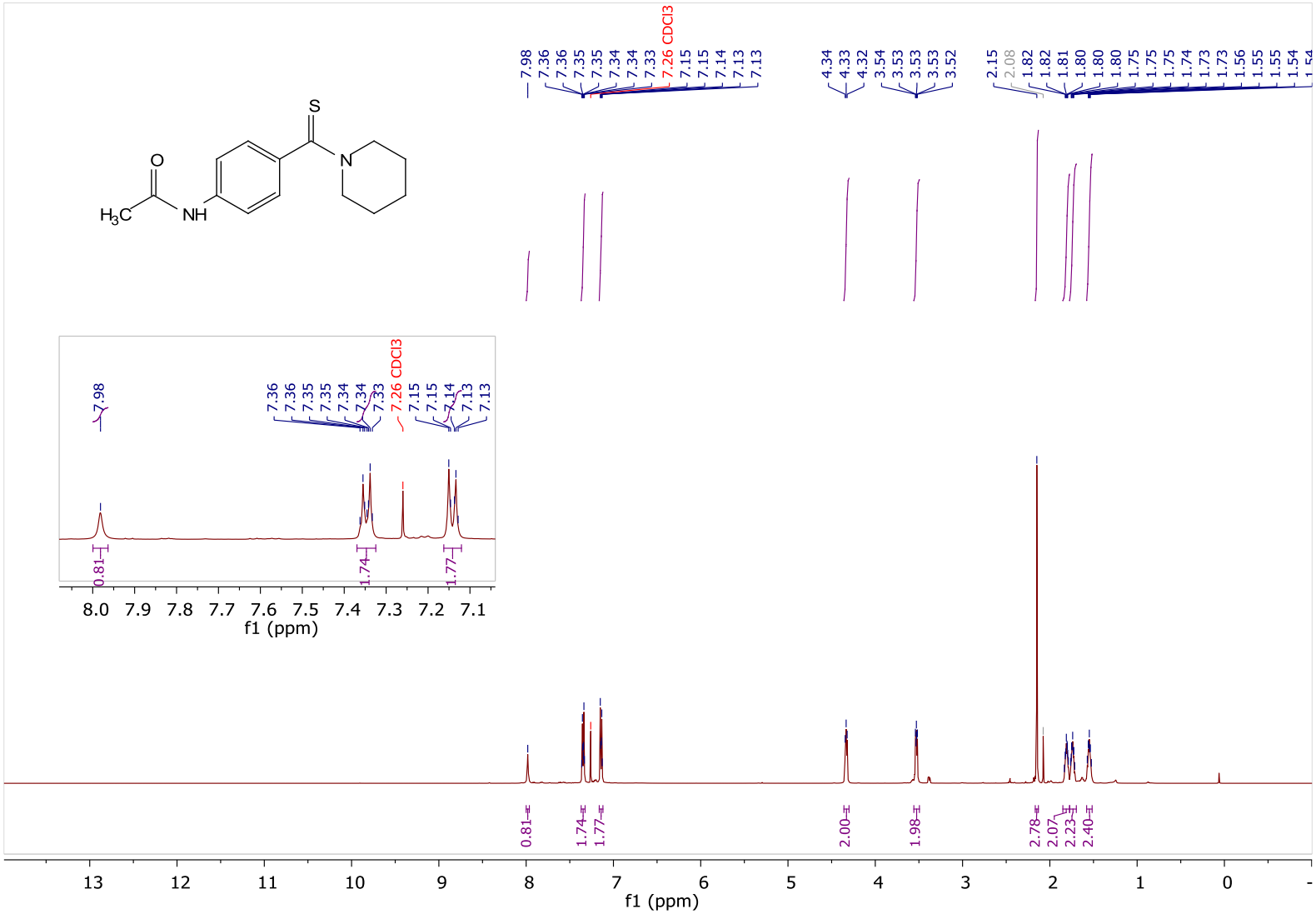
^{1}H-NMR (500 MHz, $CDCl_3$) of **15b.**



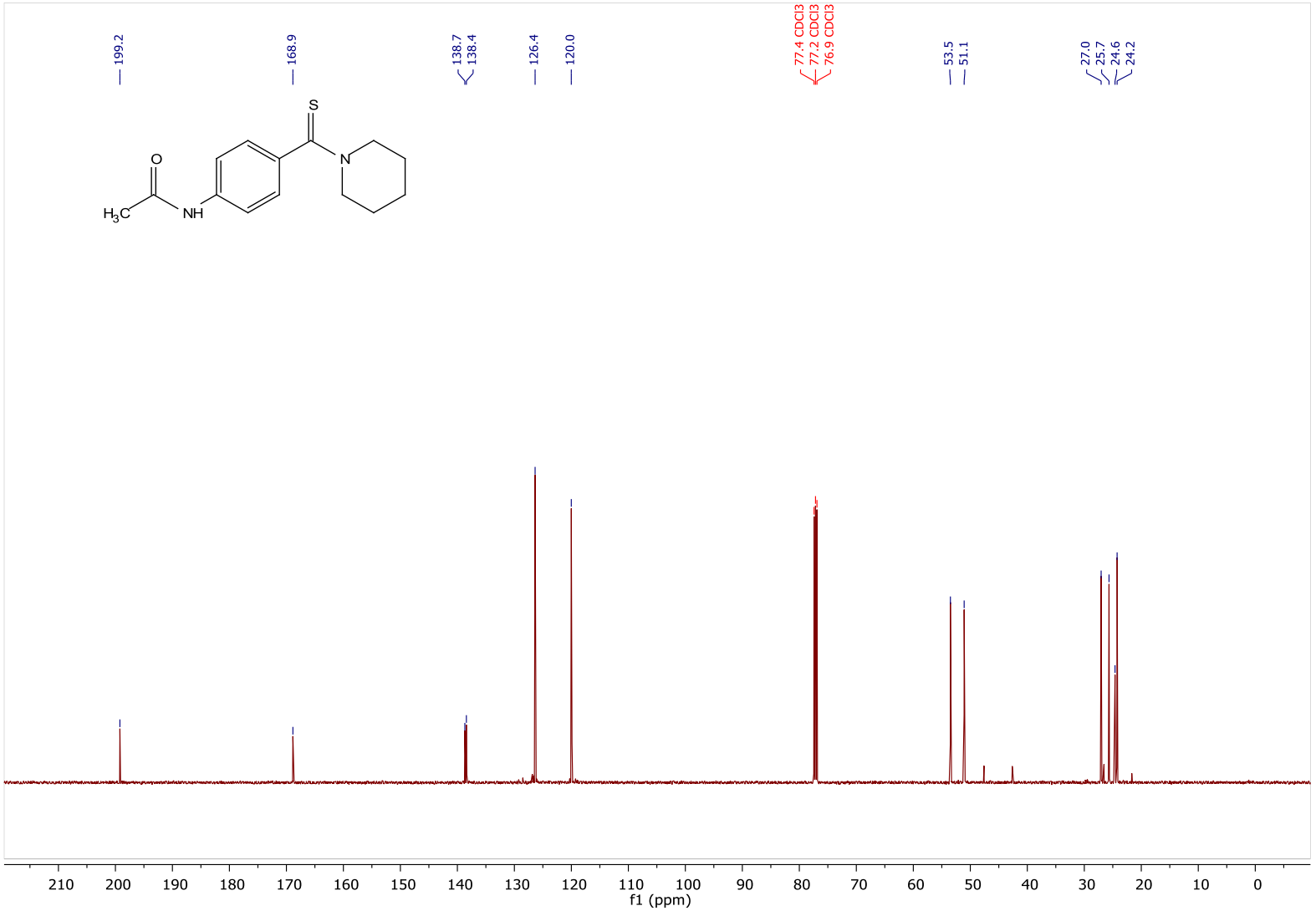
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) of **15b.**



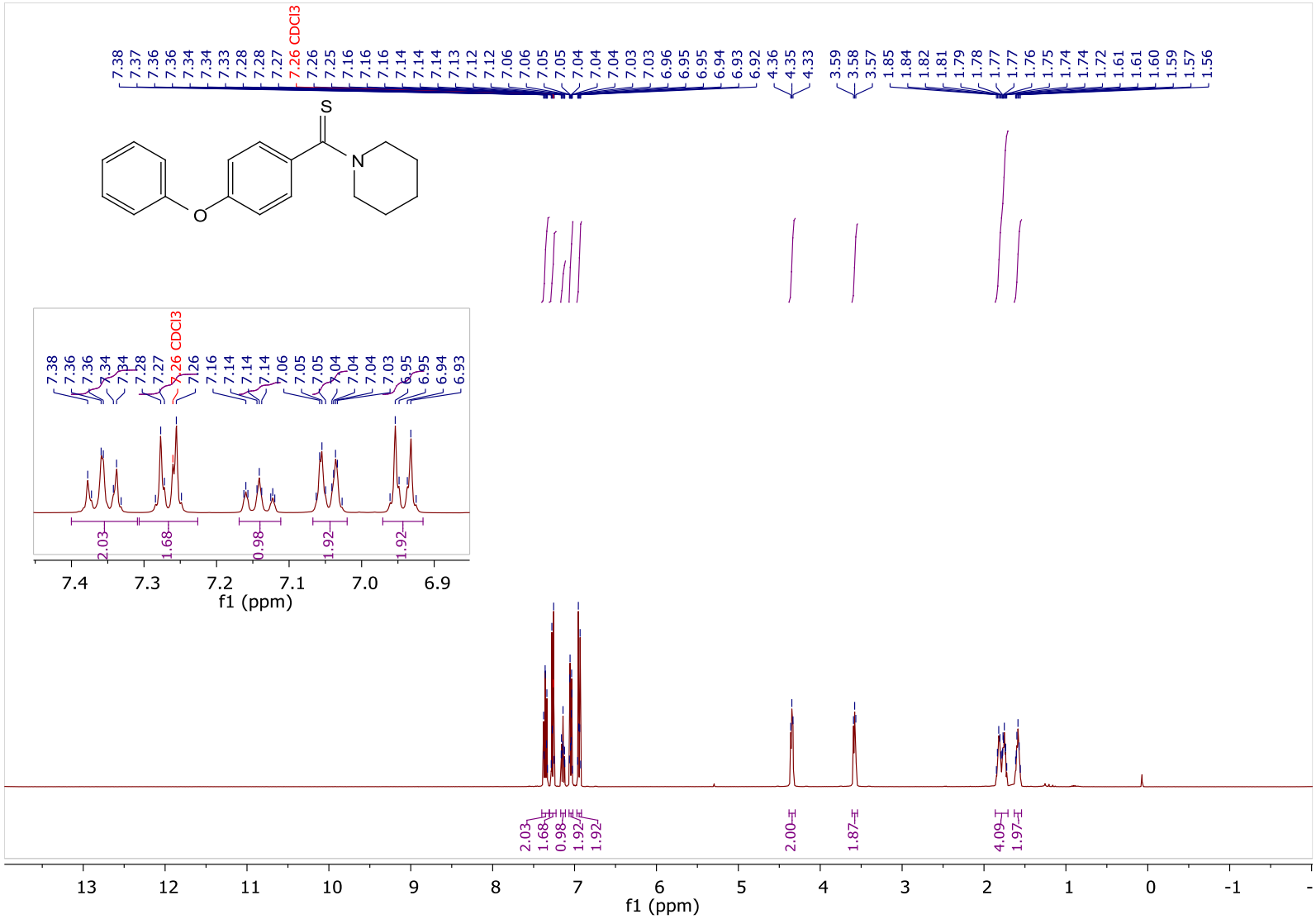
^{19}F NMR (565 MHz, $CDCl_3$) of **15b.**



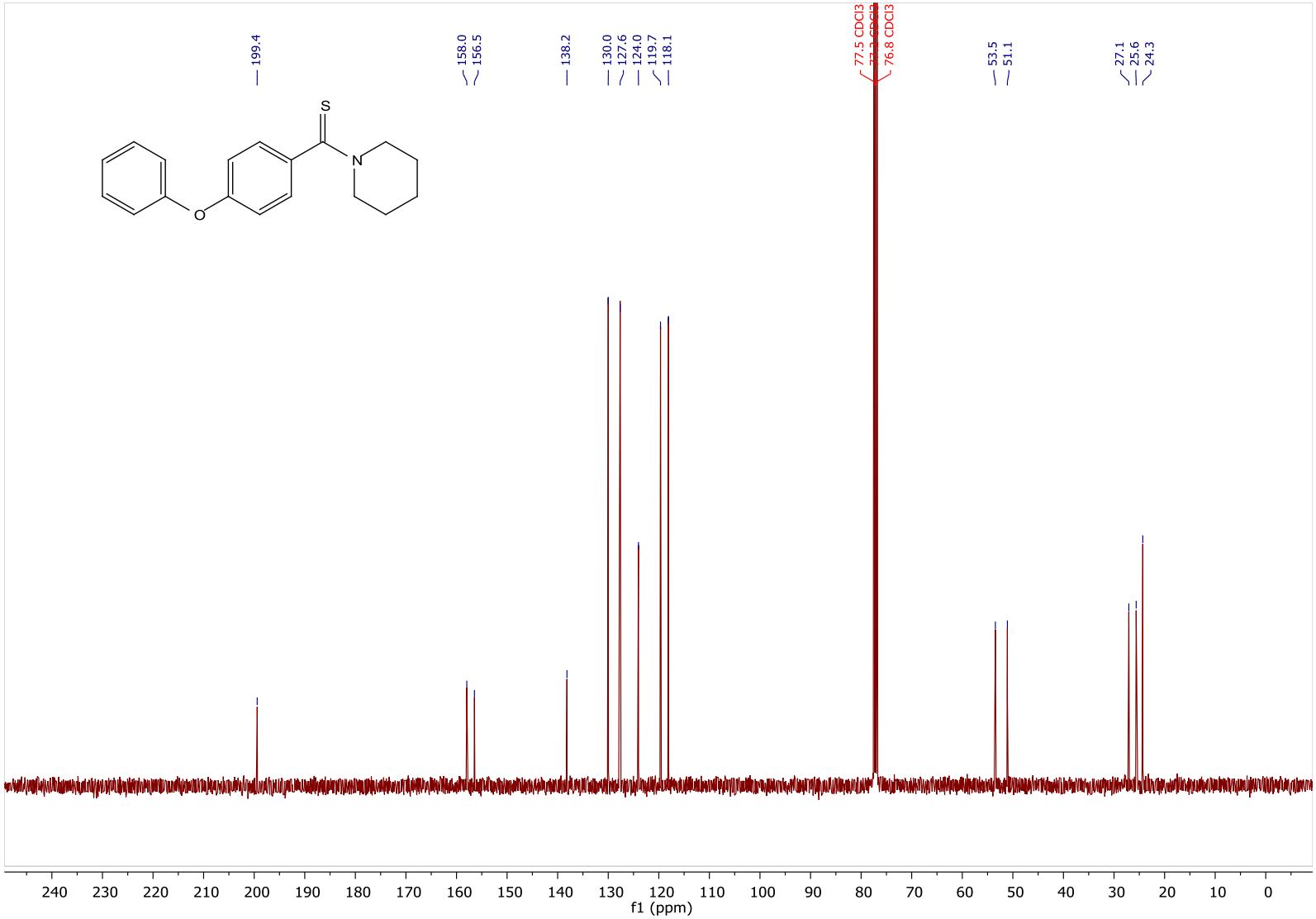
^{1}H-NMR (500 MHz, $CDCl_3$) of **16b.**



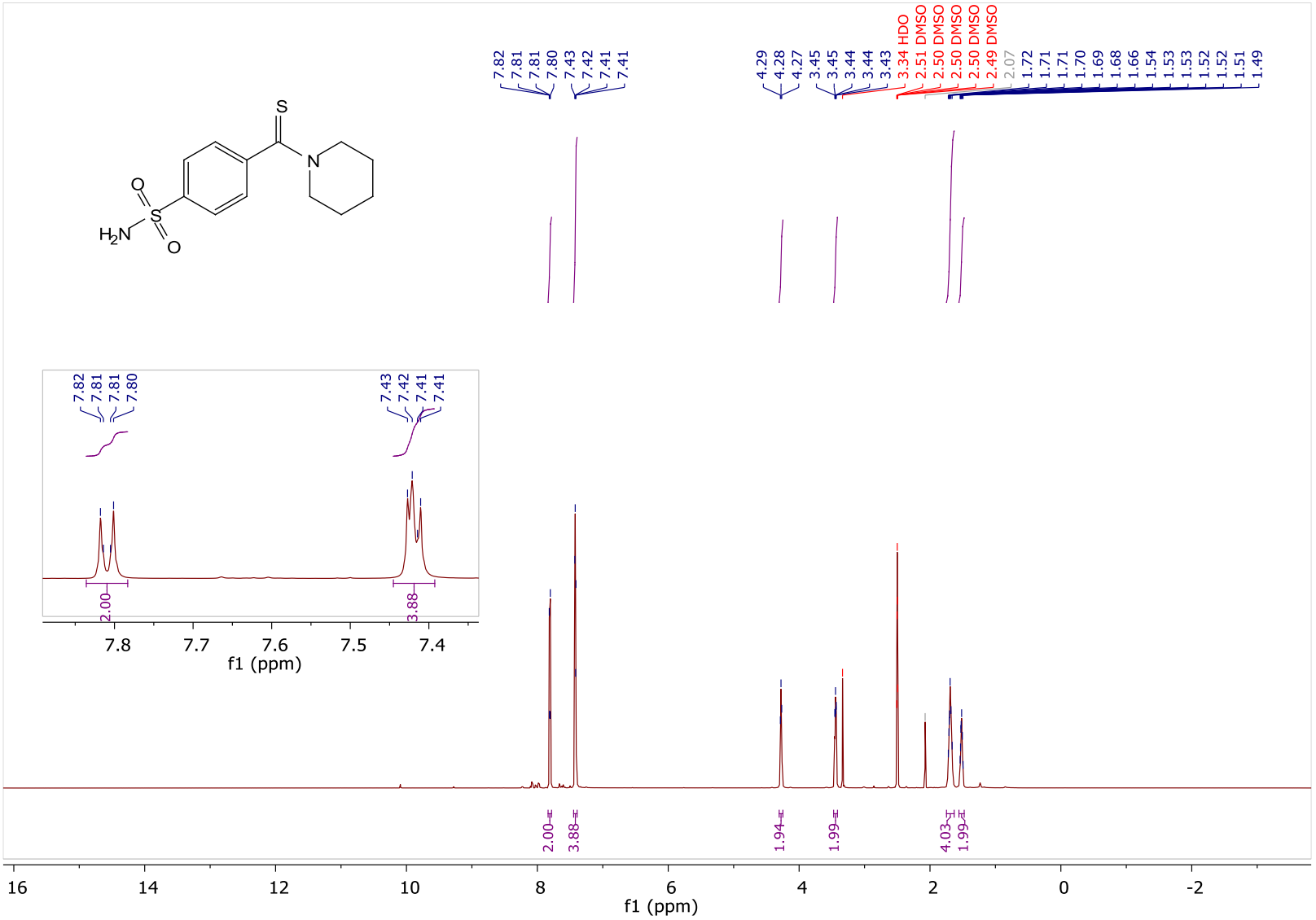
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) of **16b.**



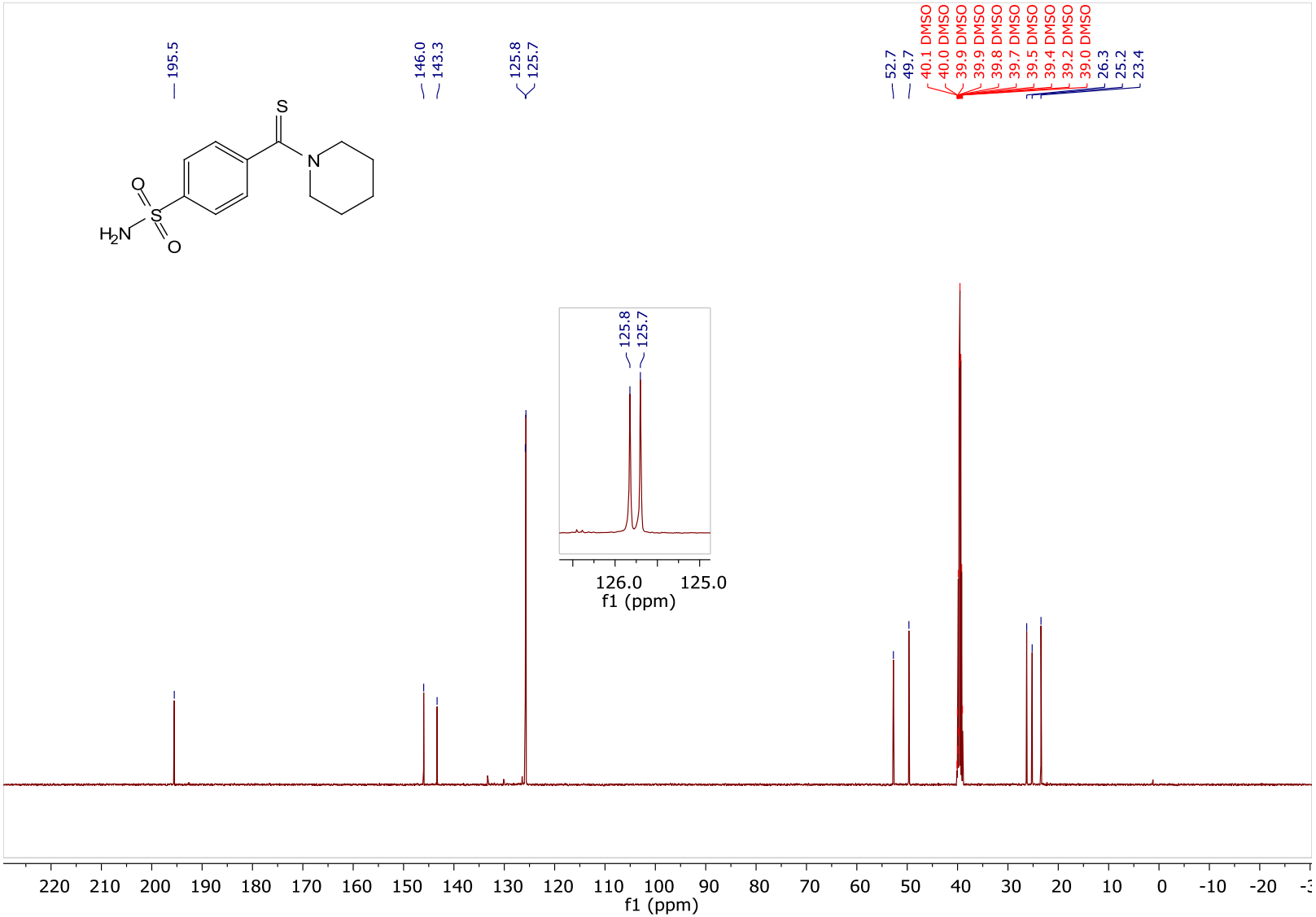
^{1}H-NMR (400 MHz, $CDCl_3$) of **17b.**



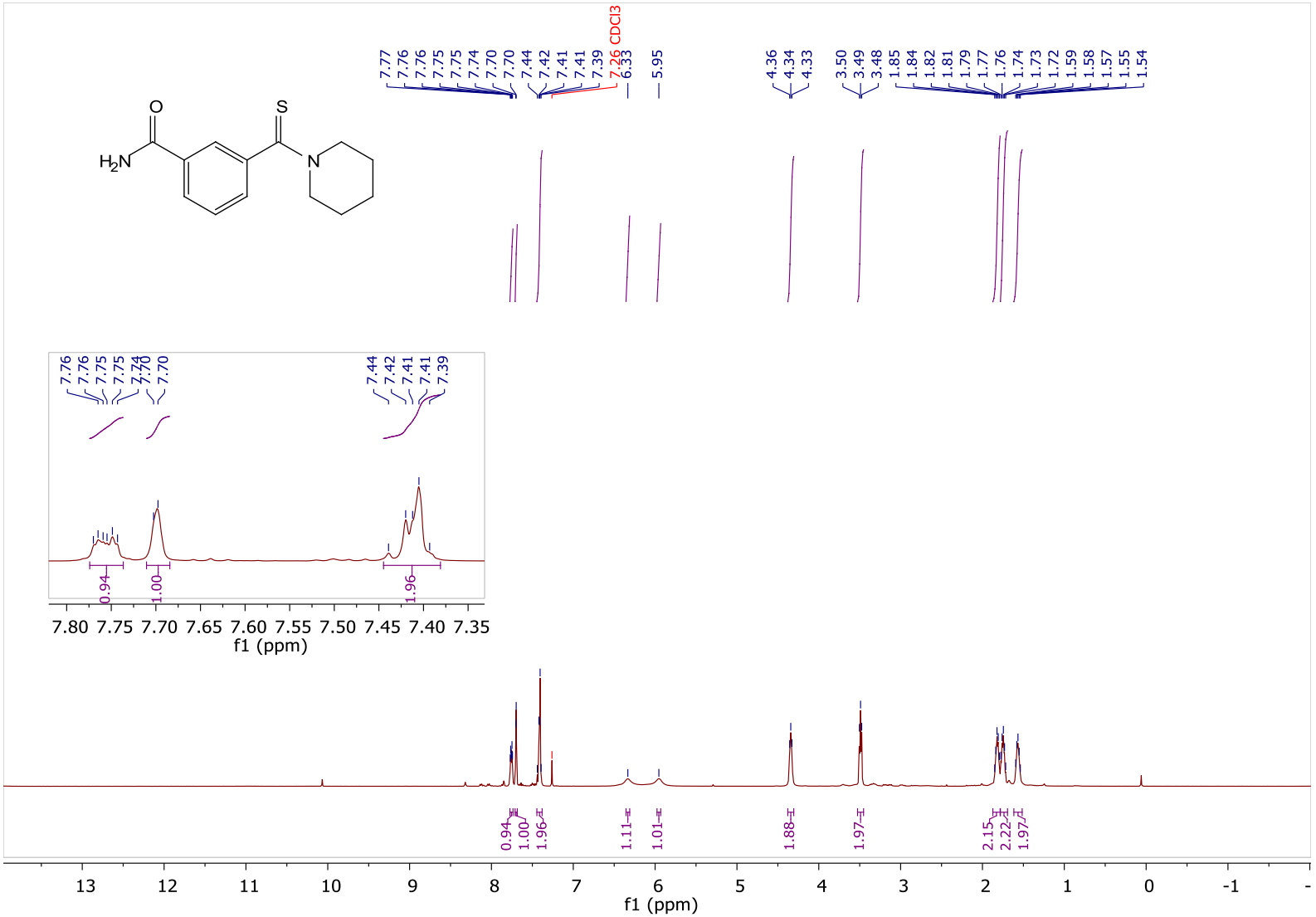
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **17b.**



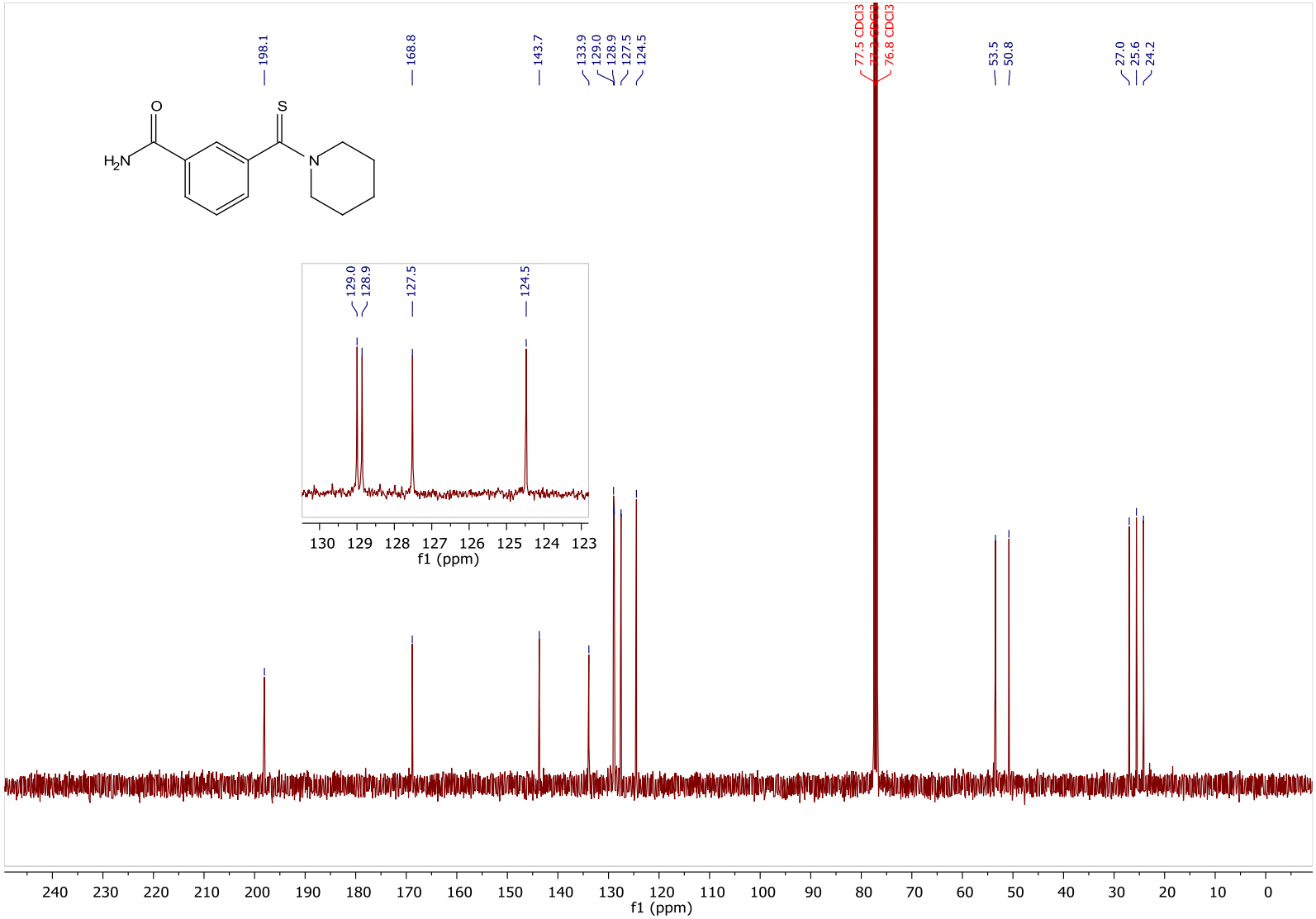
^{1}H-NMR (500 MHz, $CDCl_3$) of **18b.**



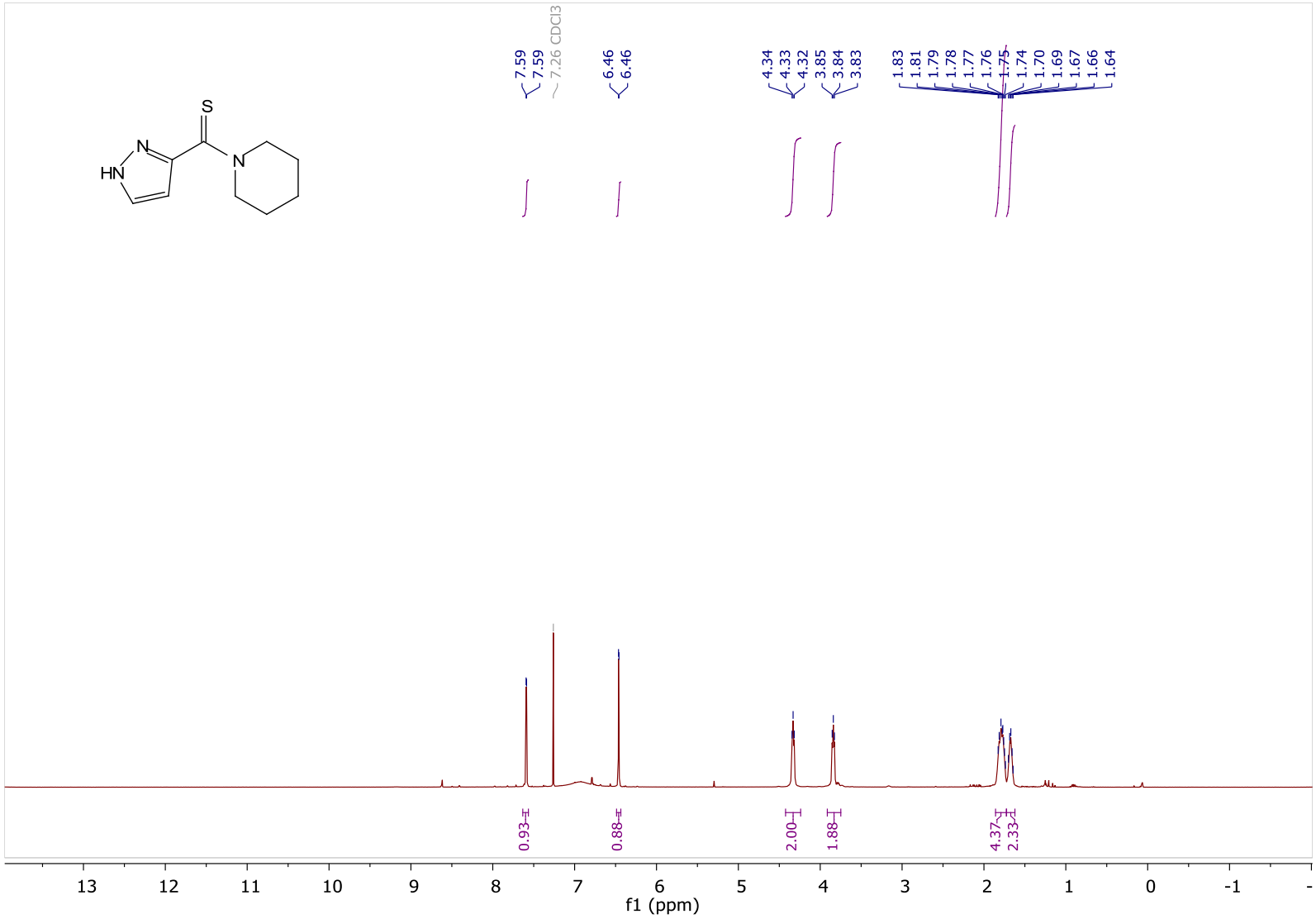
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) of **18b.**



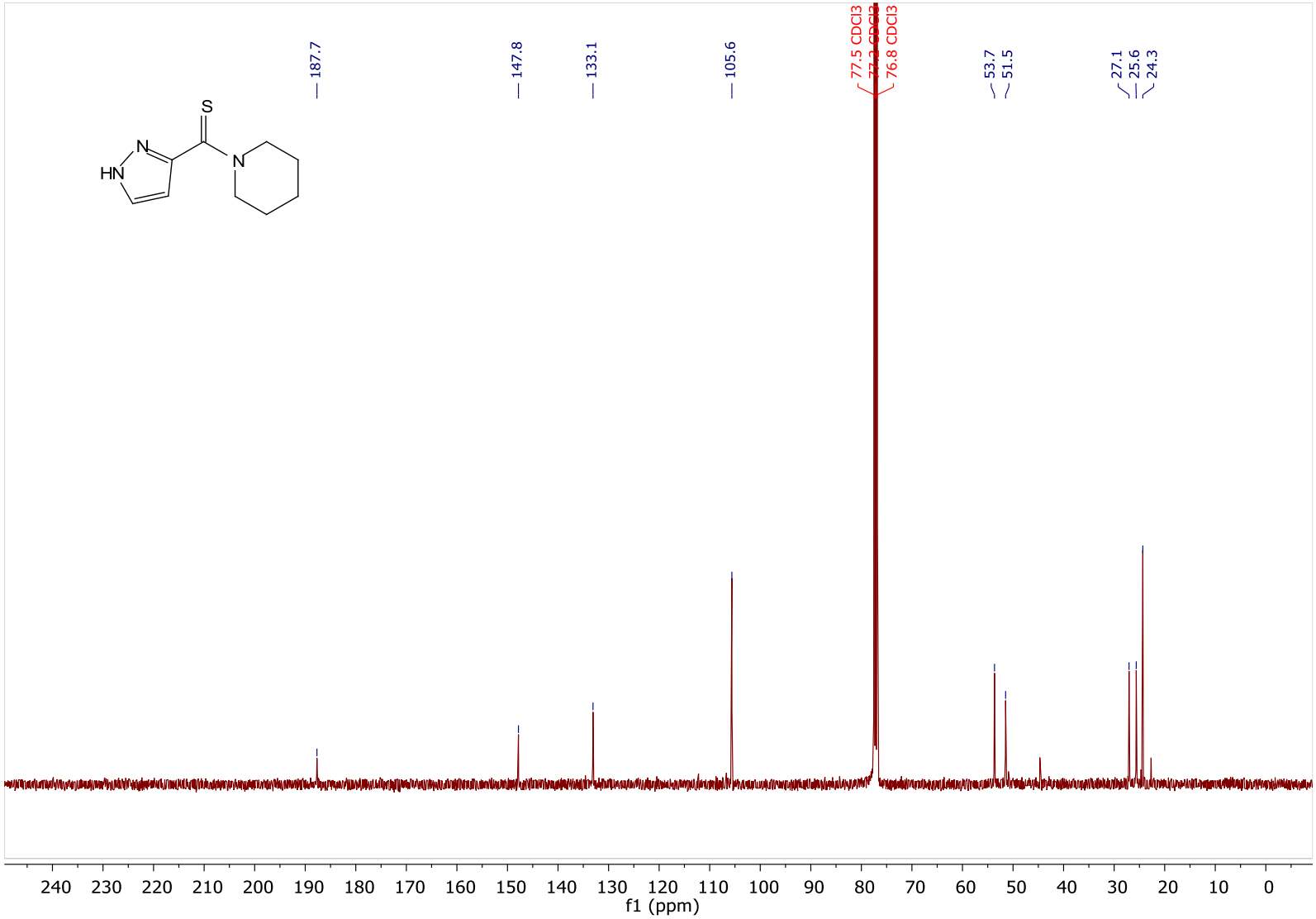
^{1}H-NMR (400 MHz, $CDCl_3$) of **19b.**



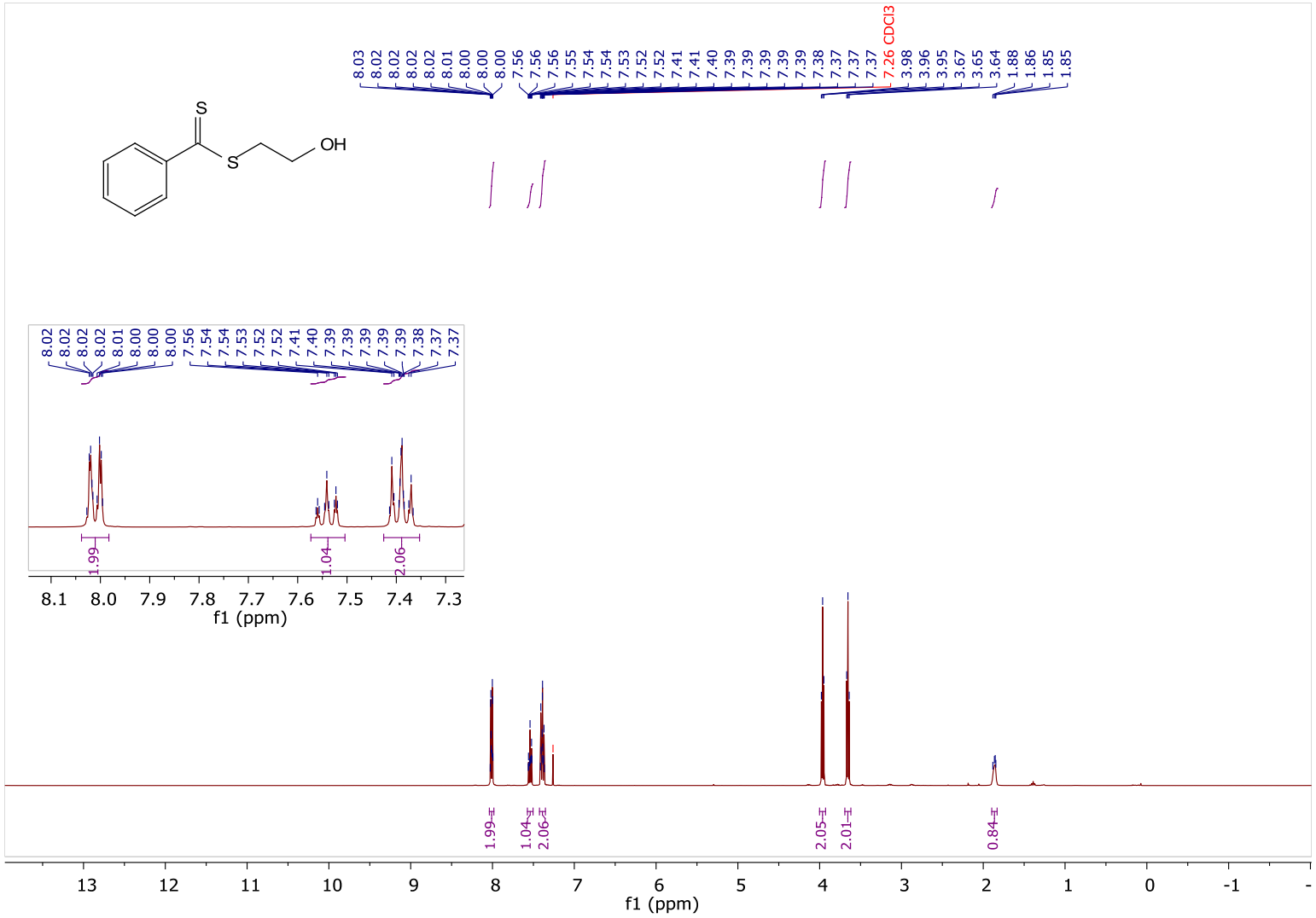
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **19b.**



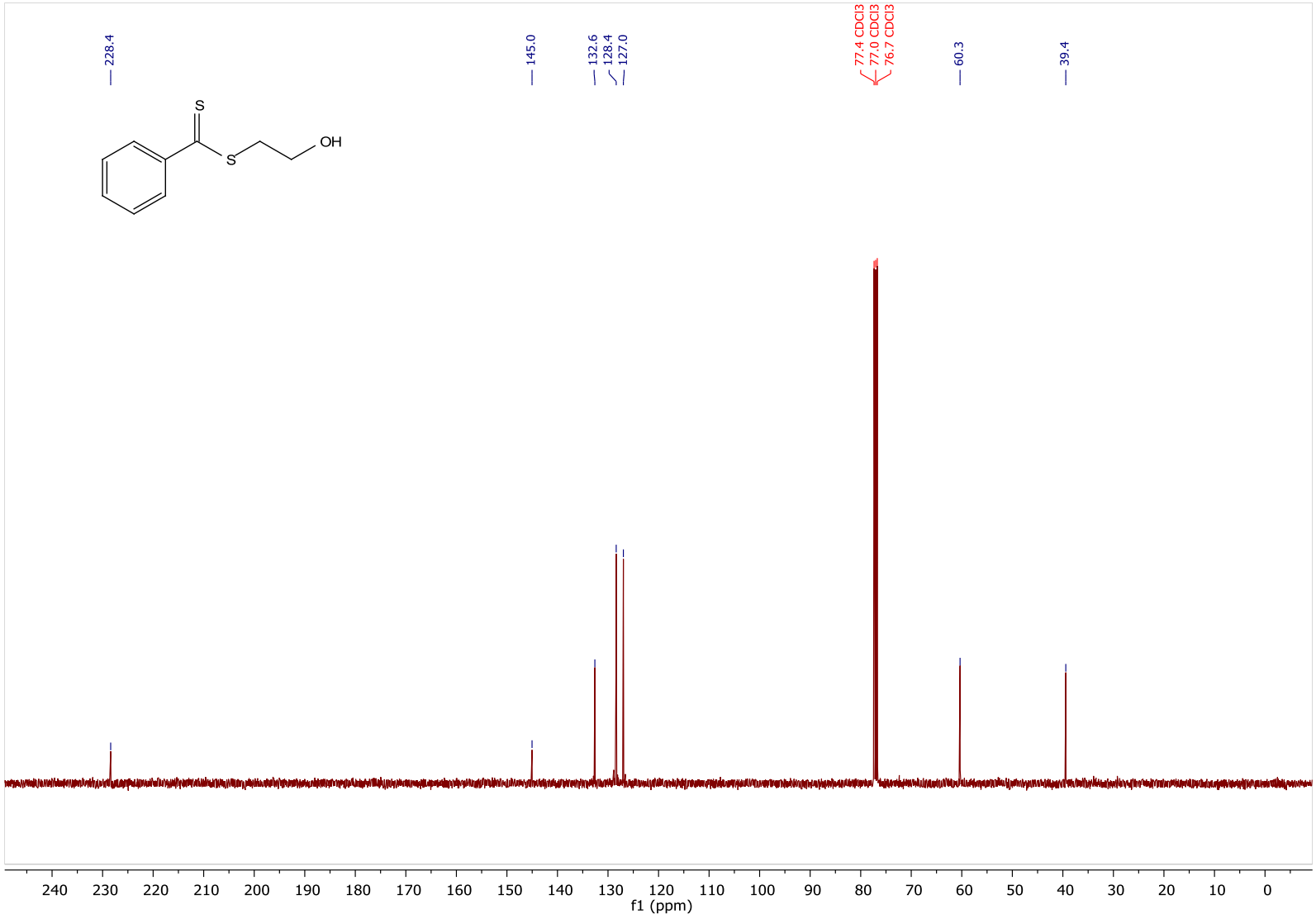
^{1}H-NMR (400 MHz, $CDCl_3$) of **20b.**



$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **20b.**

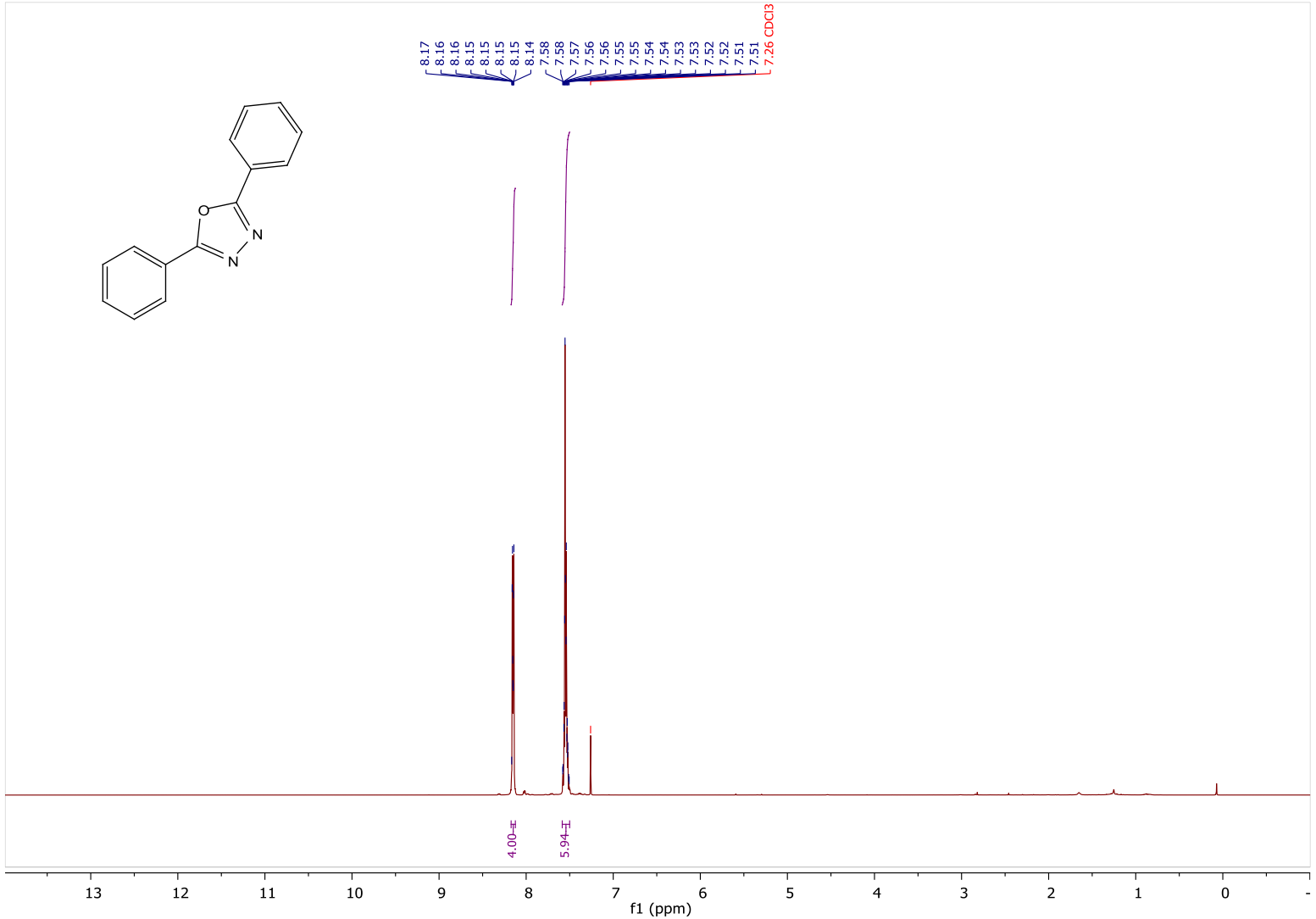


^{1}H-NMR (400 MHz, $CDCl_3$) of **21b.**

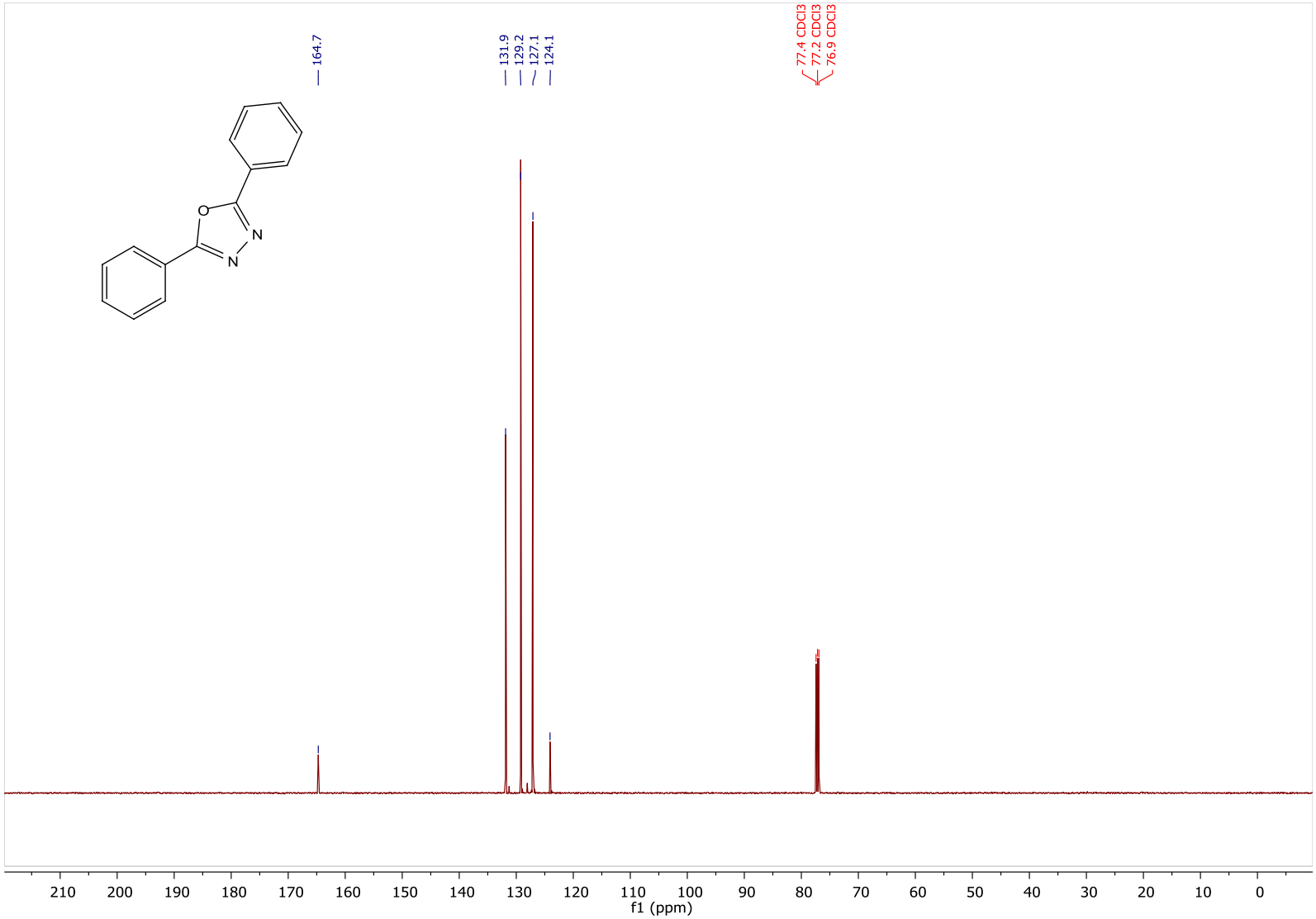


$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **21b.**

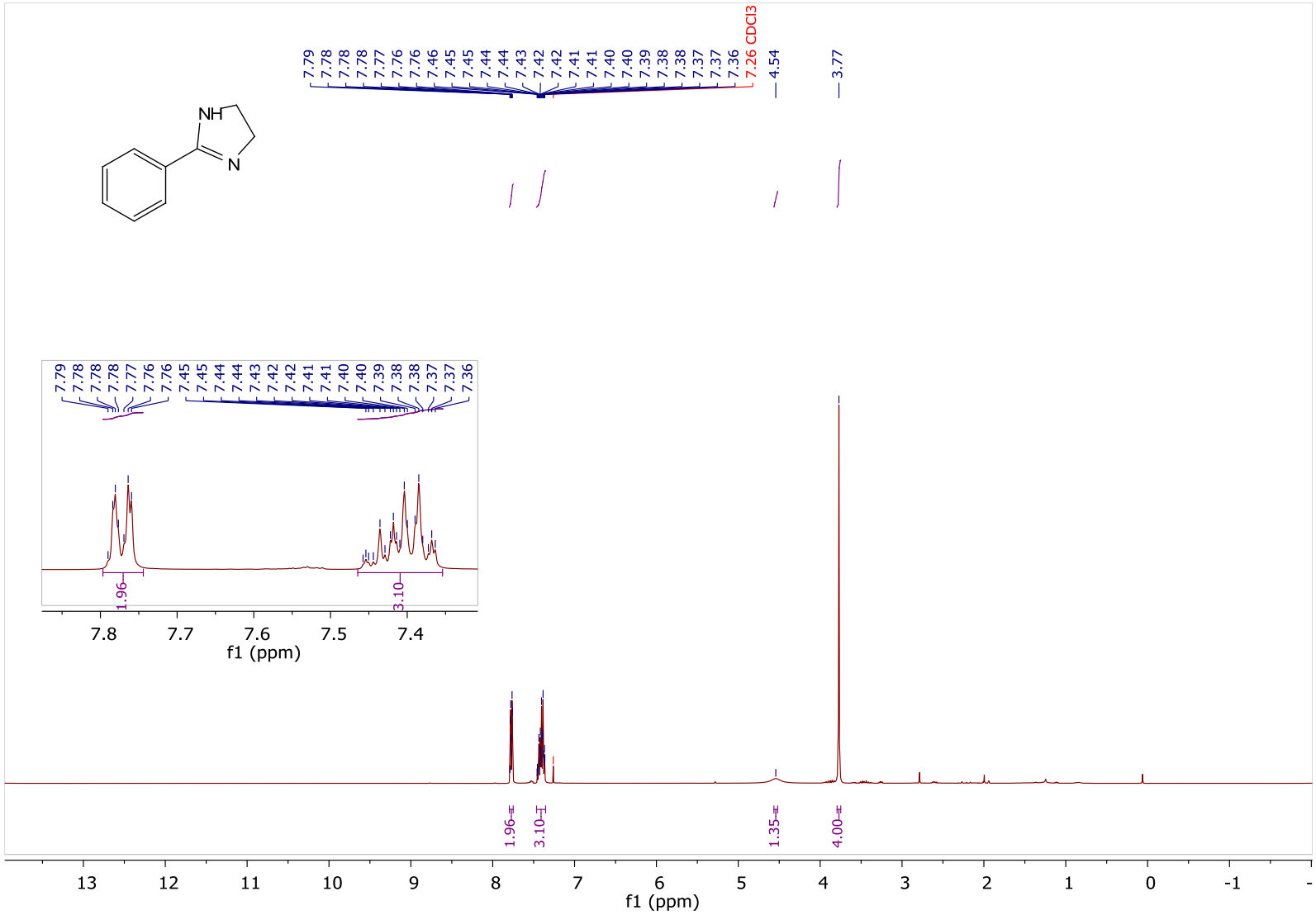
NMR Spectra of **1c**-**6c**



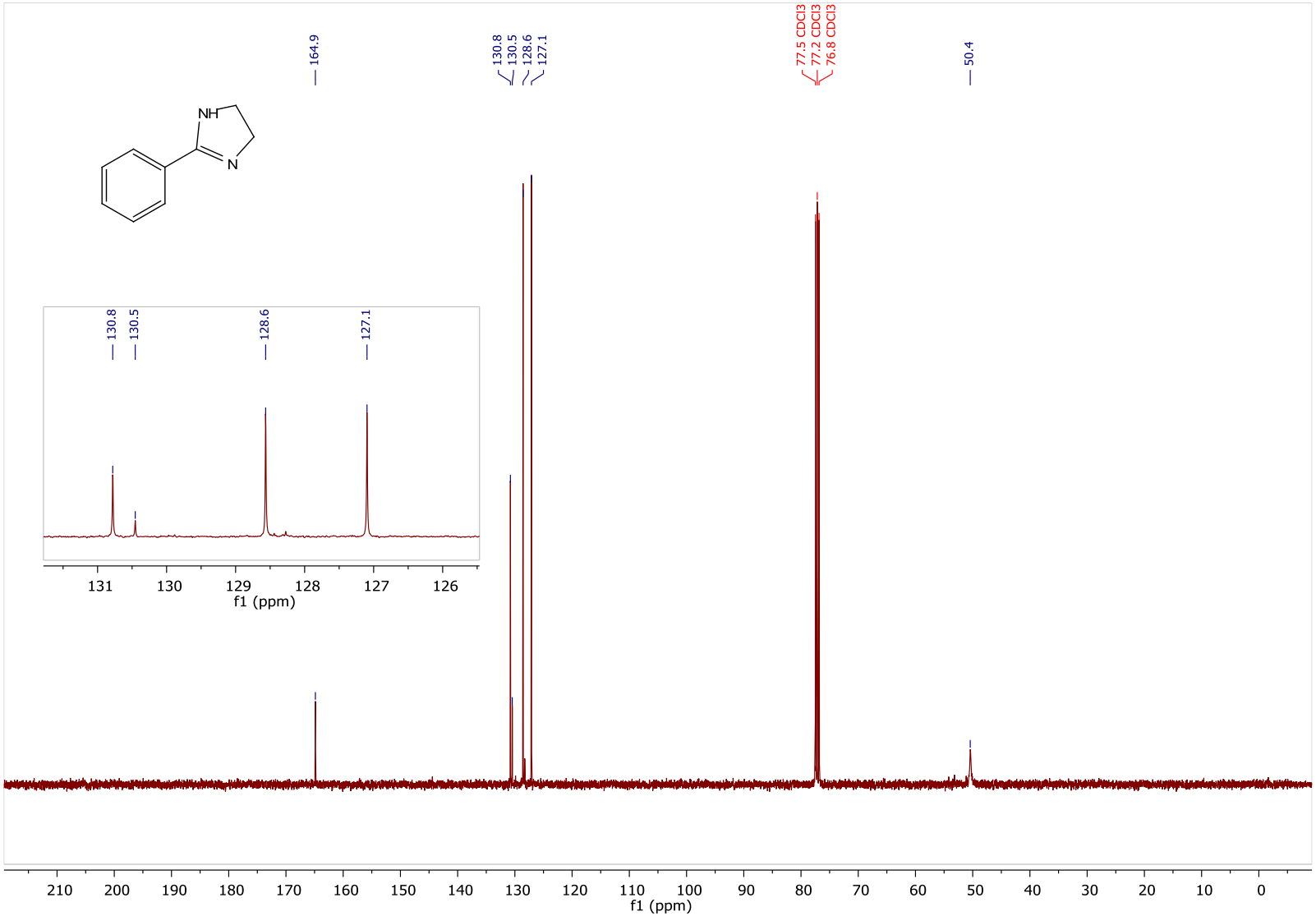
^{1}H-NMR (500 MHz, $CDCl_3$) of **1c.**



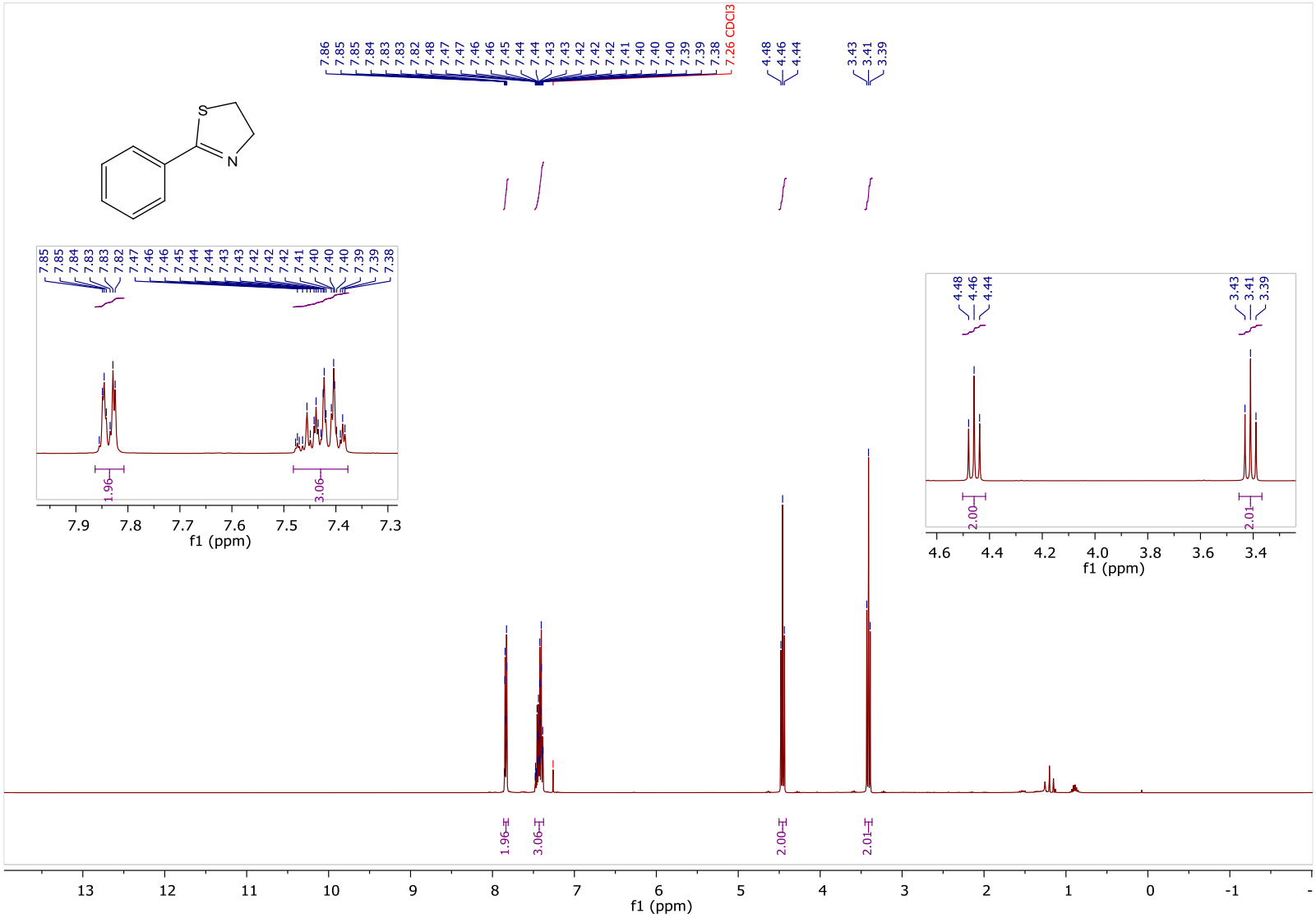
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) of **1c.**



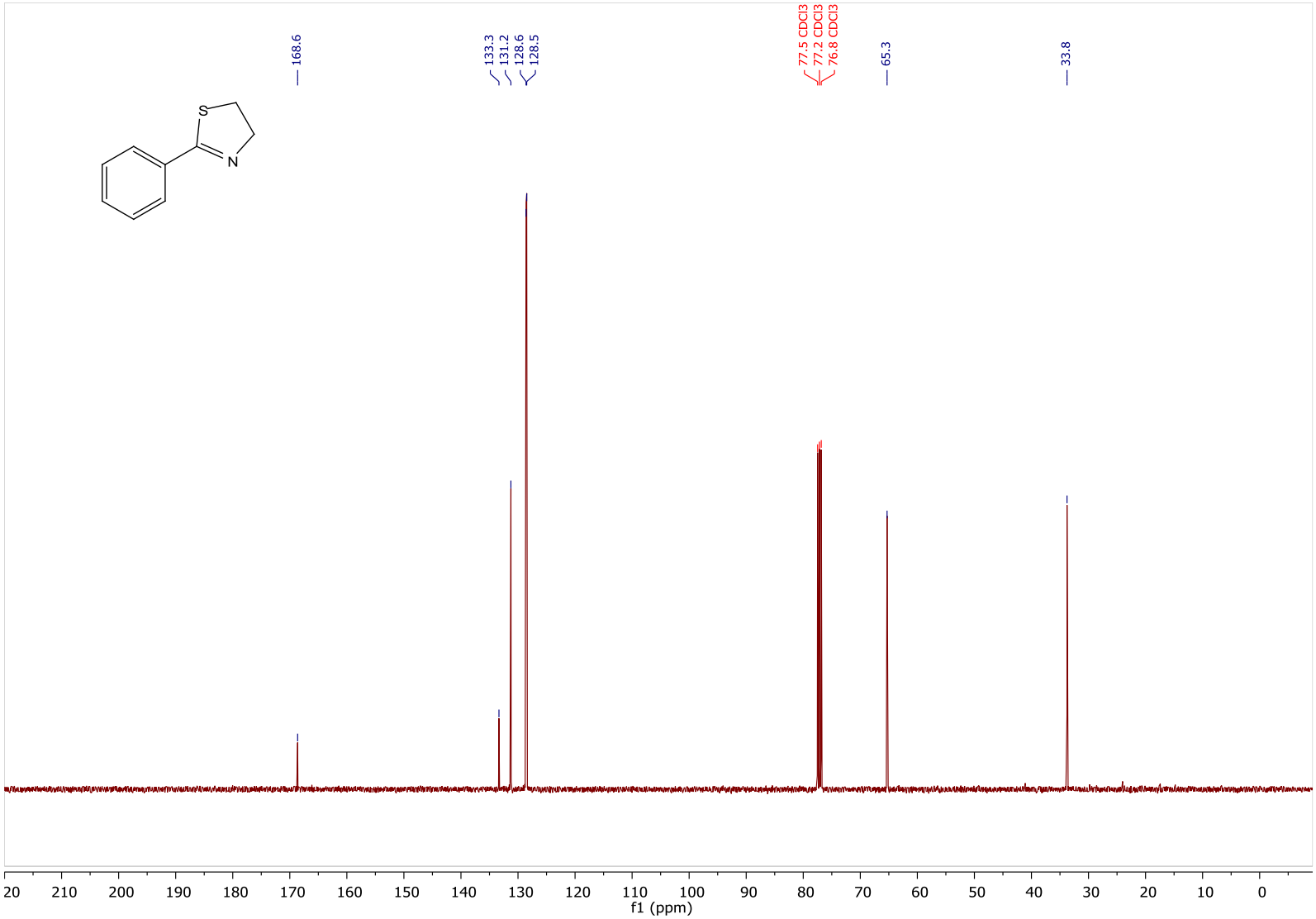
^{1}H-NMR (400 MHz, $CDCl_3$) of **2c.**



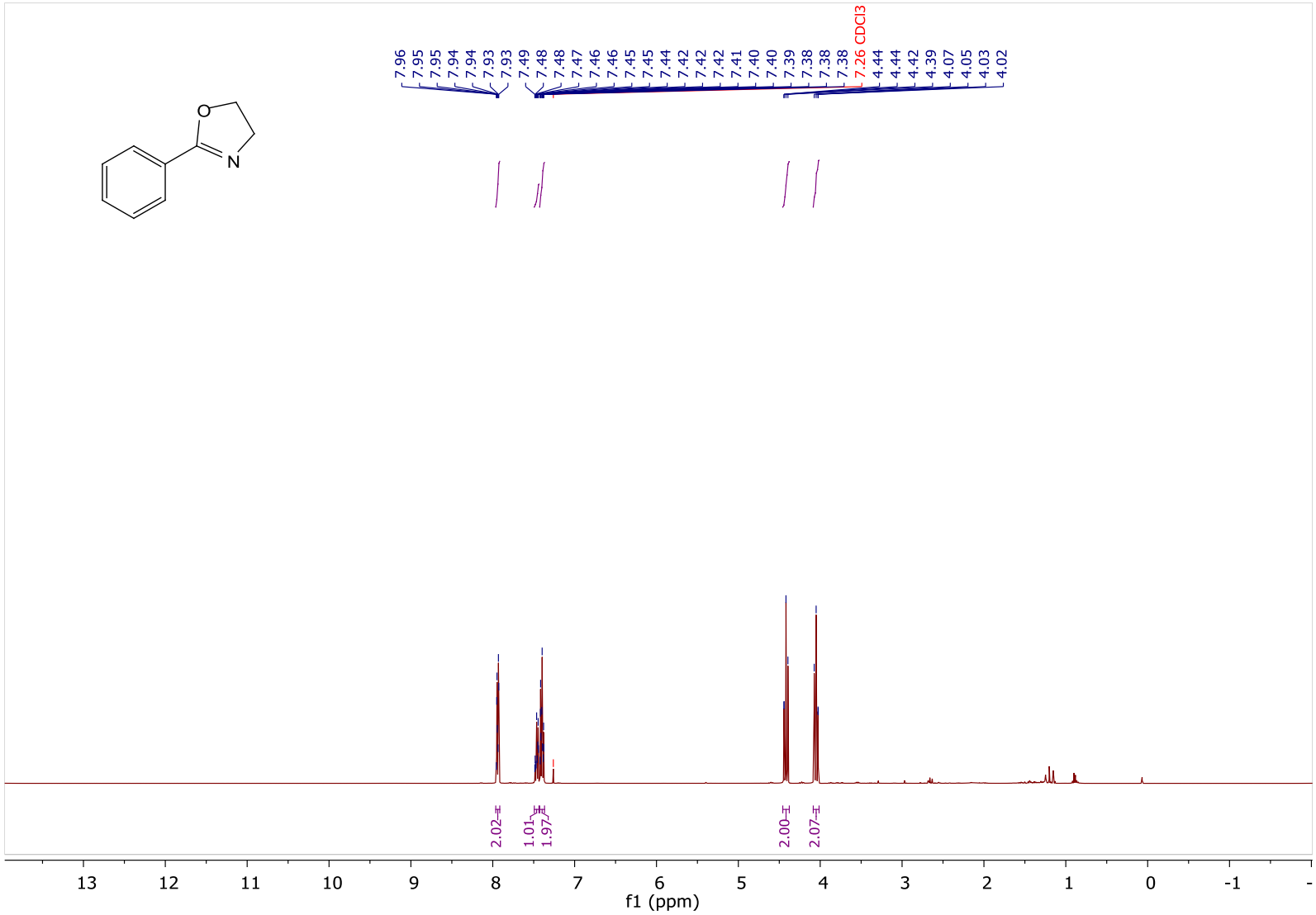
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **2c.**



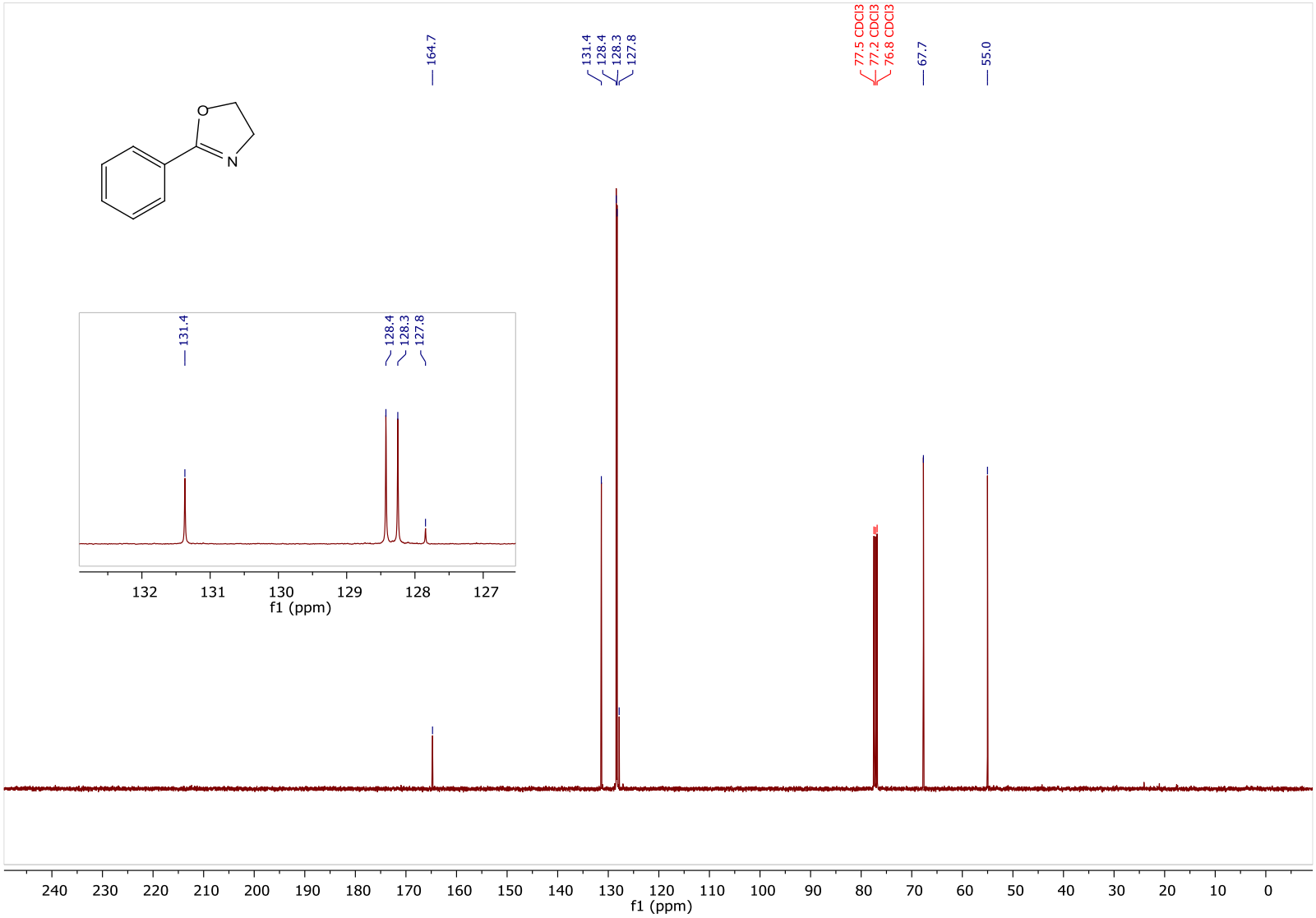
^{1}H-NMR (400 MHz, $CDCl_3$) of **3c.**



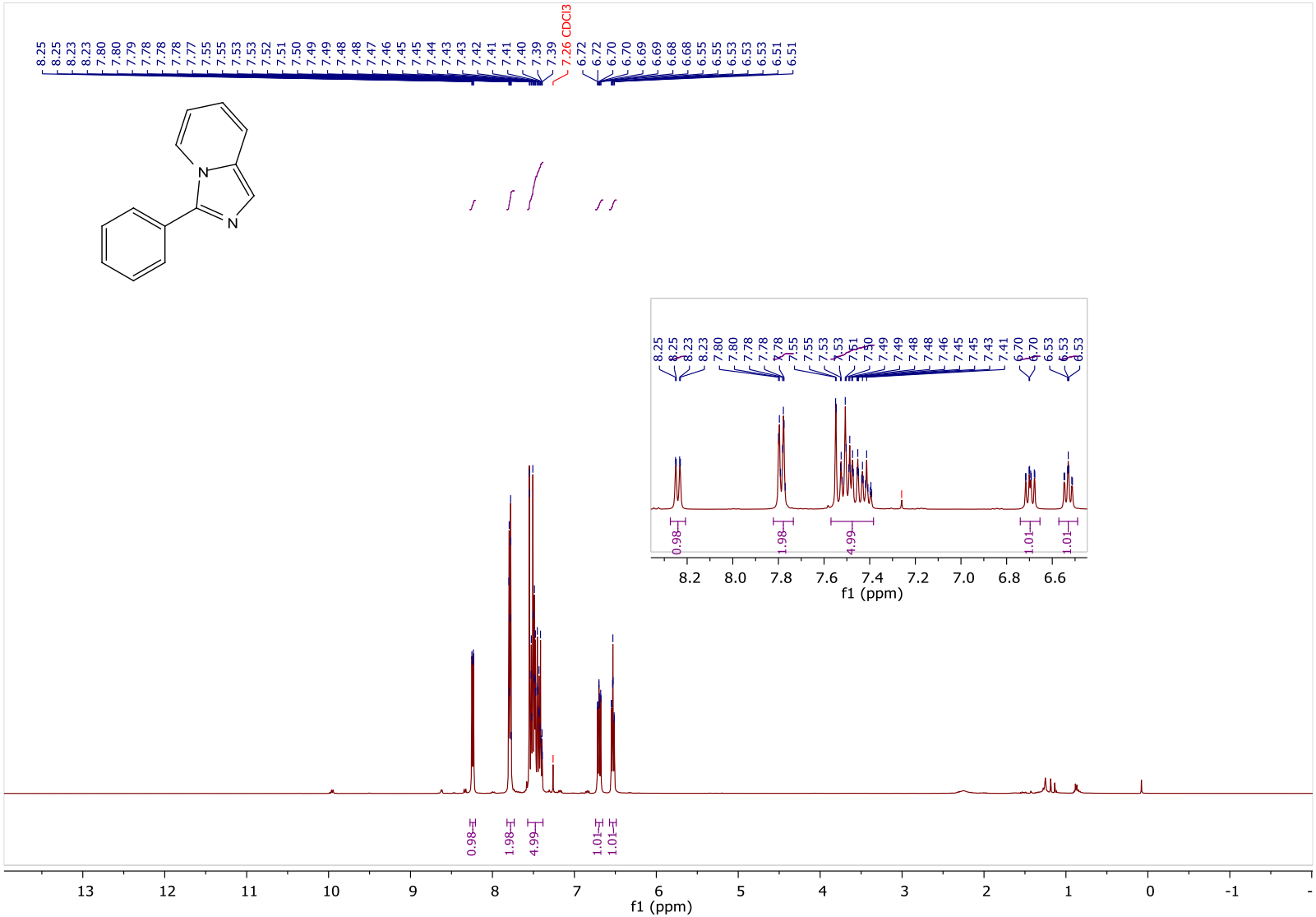
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **3c.**



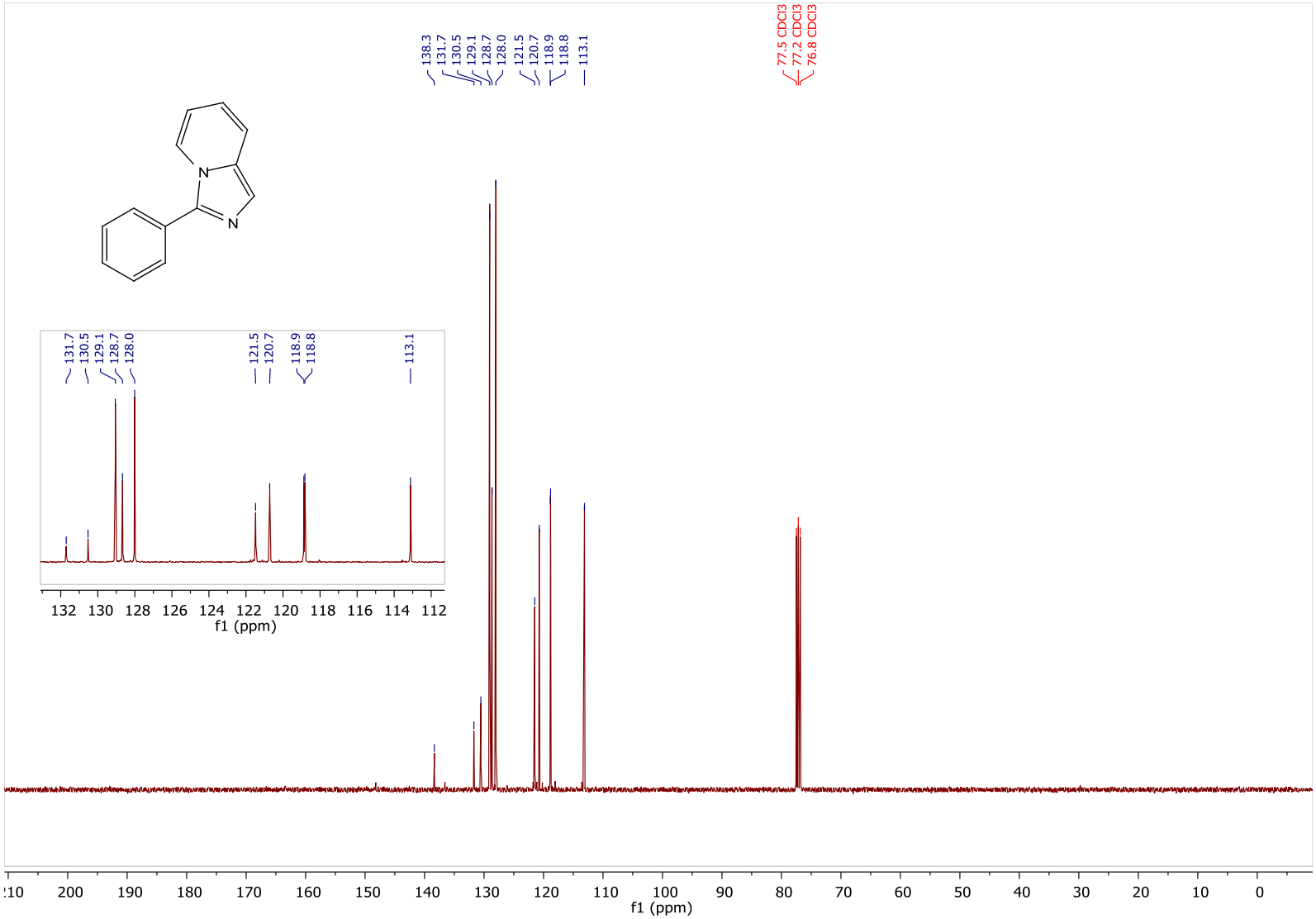
^{1}H-NMR (400 MHz, $CDCl_3$) of **4c.**



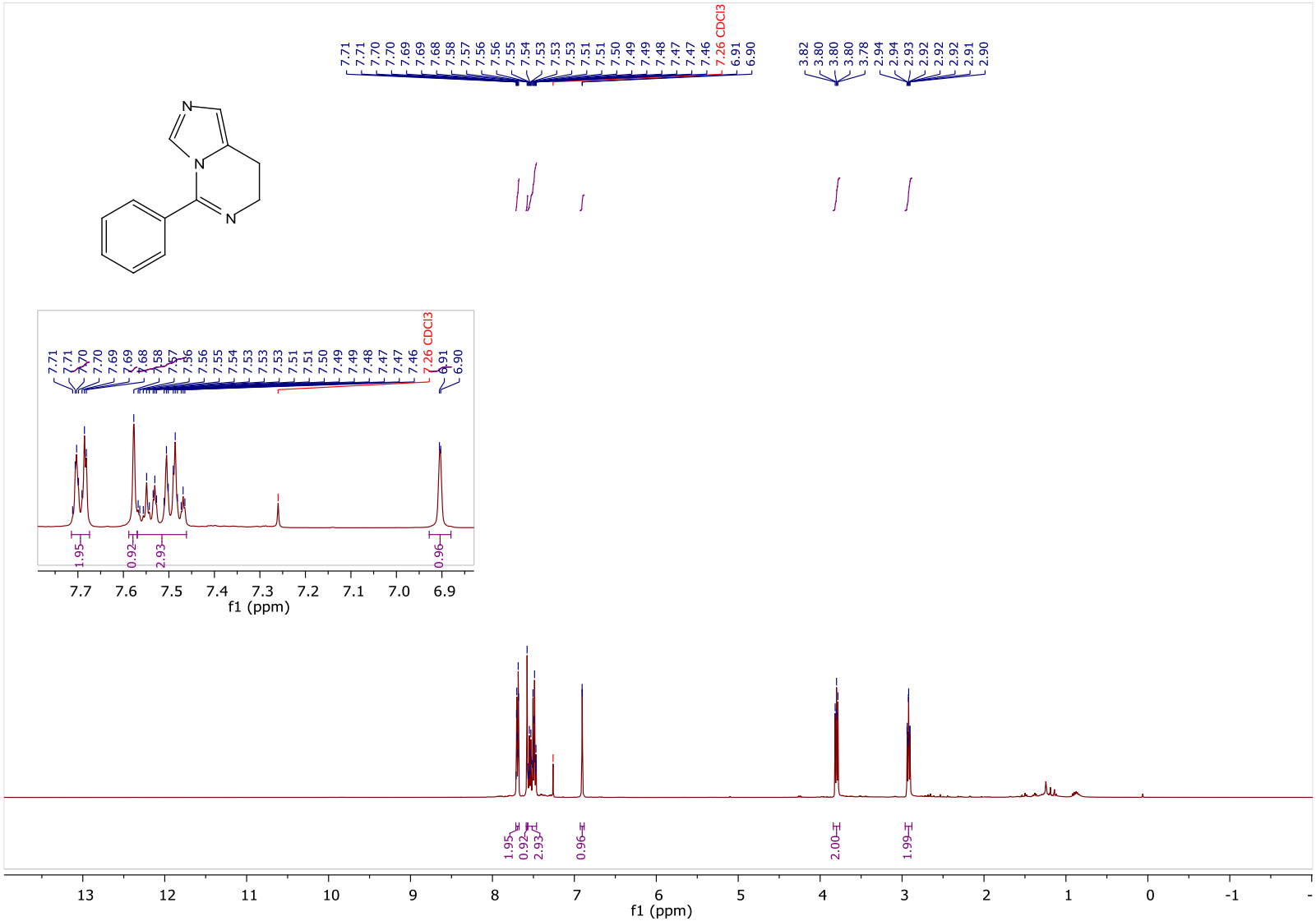
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **4c.**



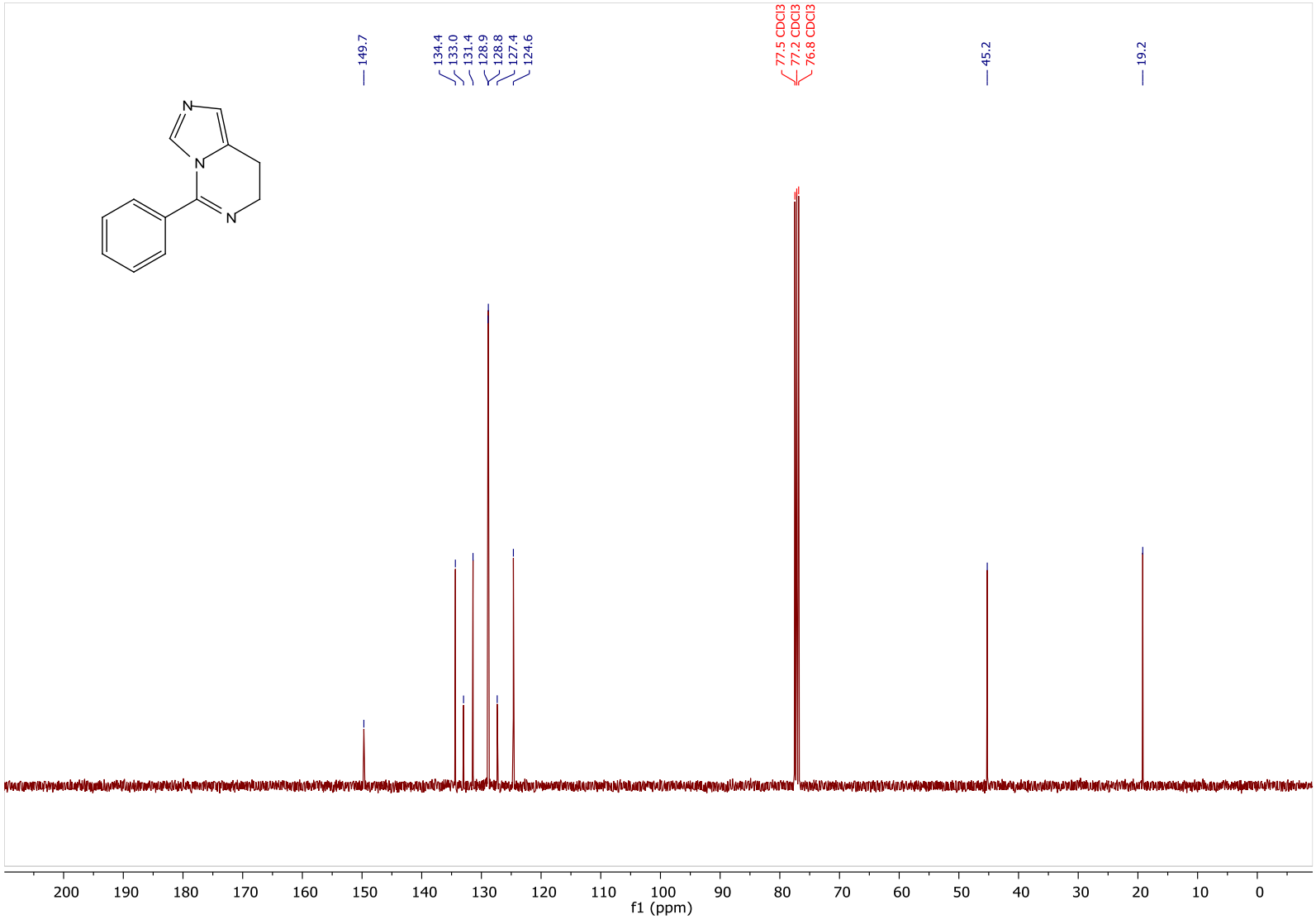
^{1}H-NMR (400 MHz, $CDCl_3$) of **5c.**



$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **5c.**

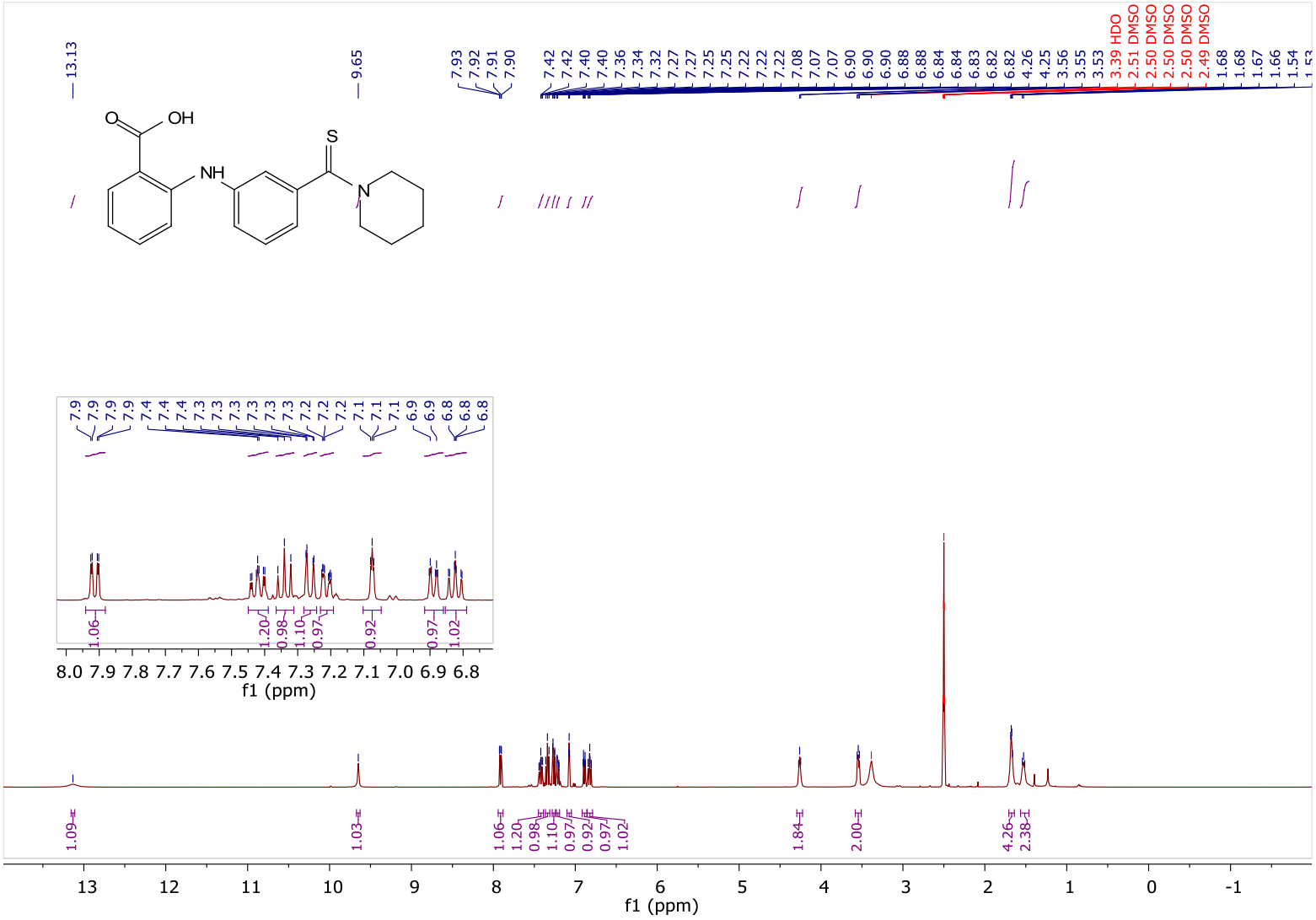


^{1}H-NMR (400 MHz, $CDCl_3$) of **6c.**

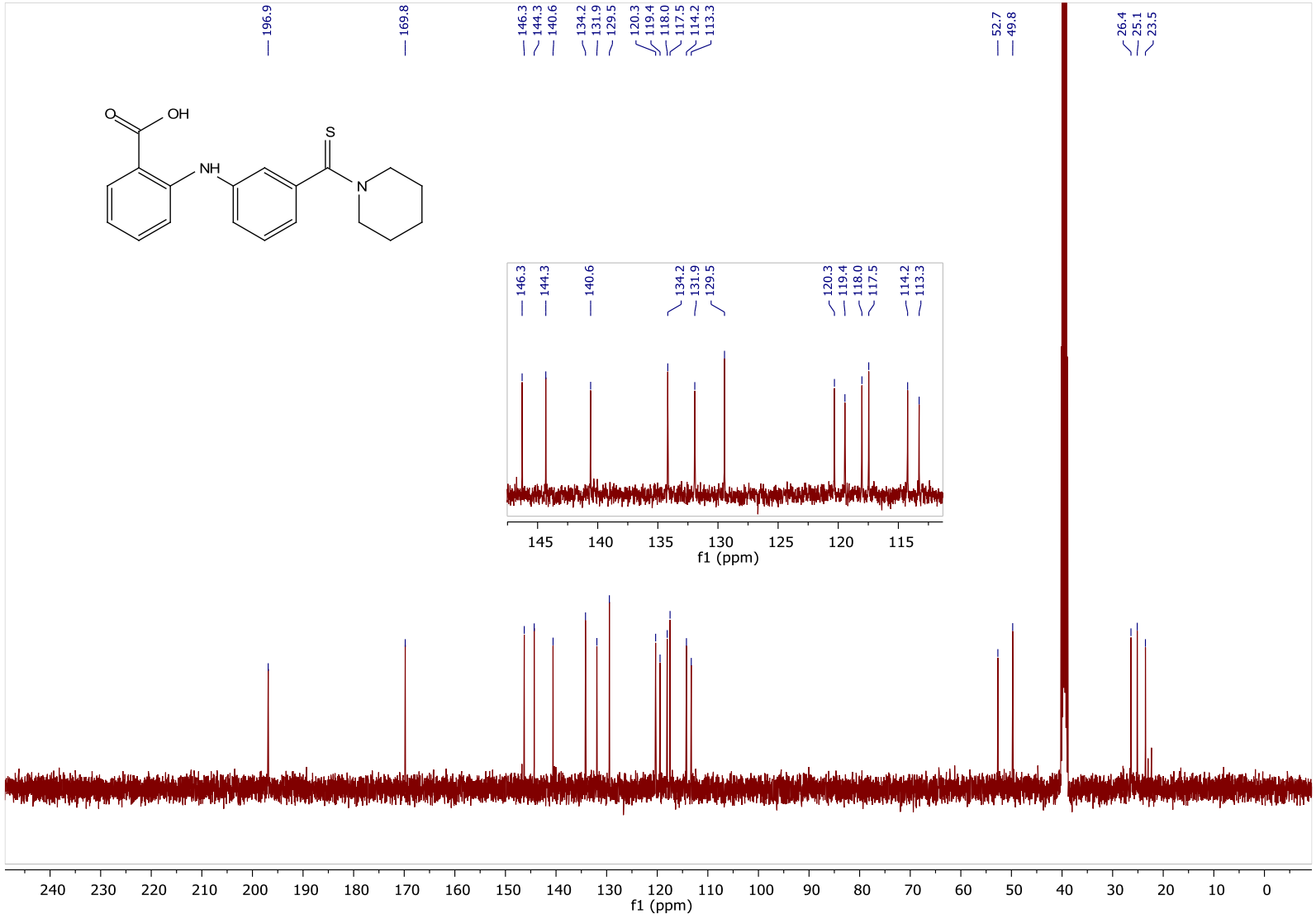


$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **6c.**

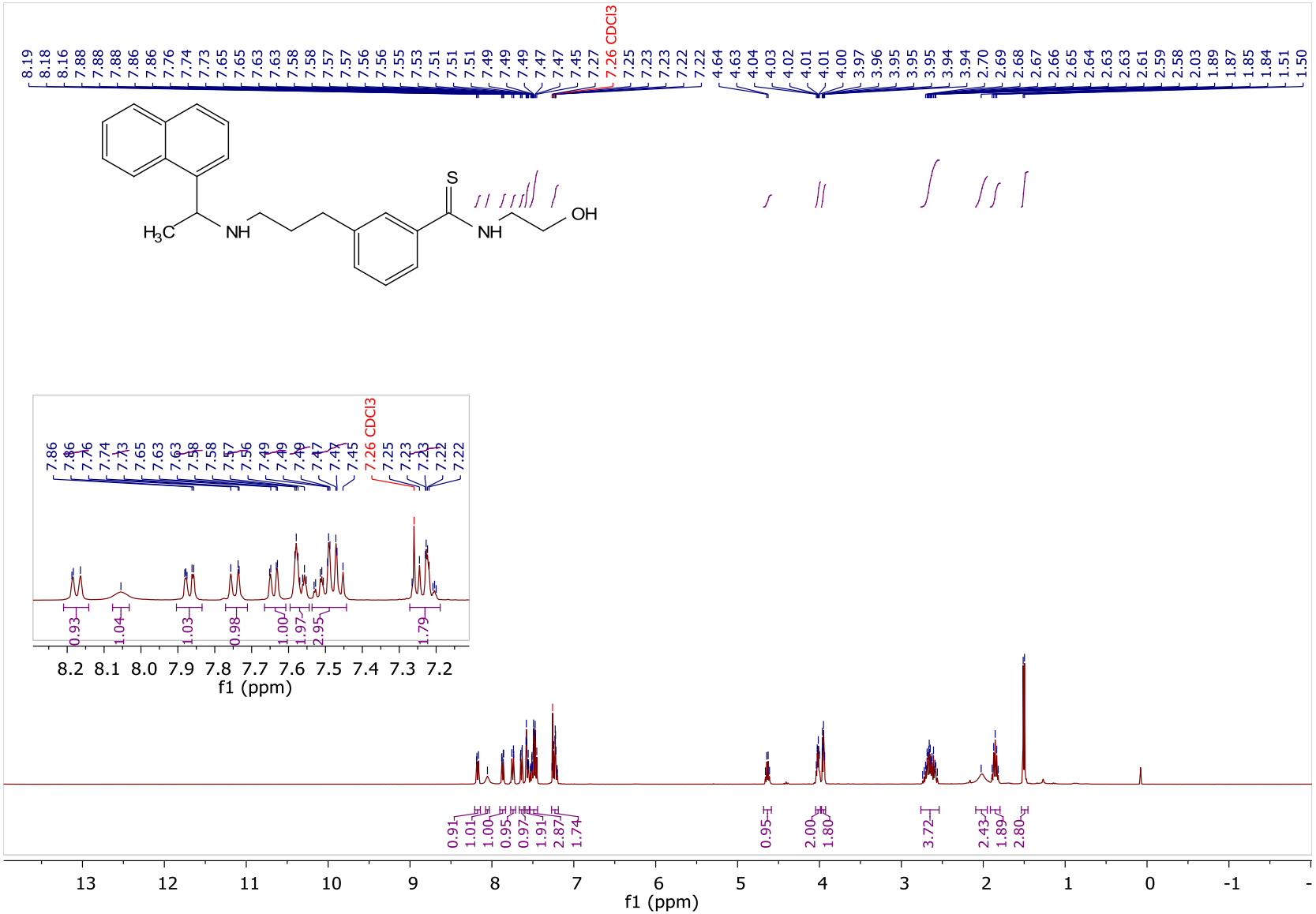
NMR Spectra of **1d**-**6d**



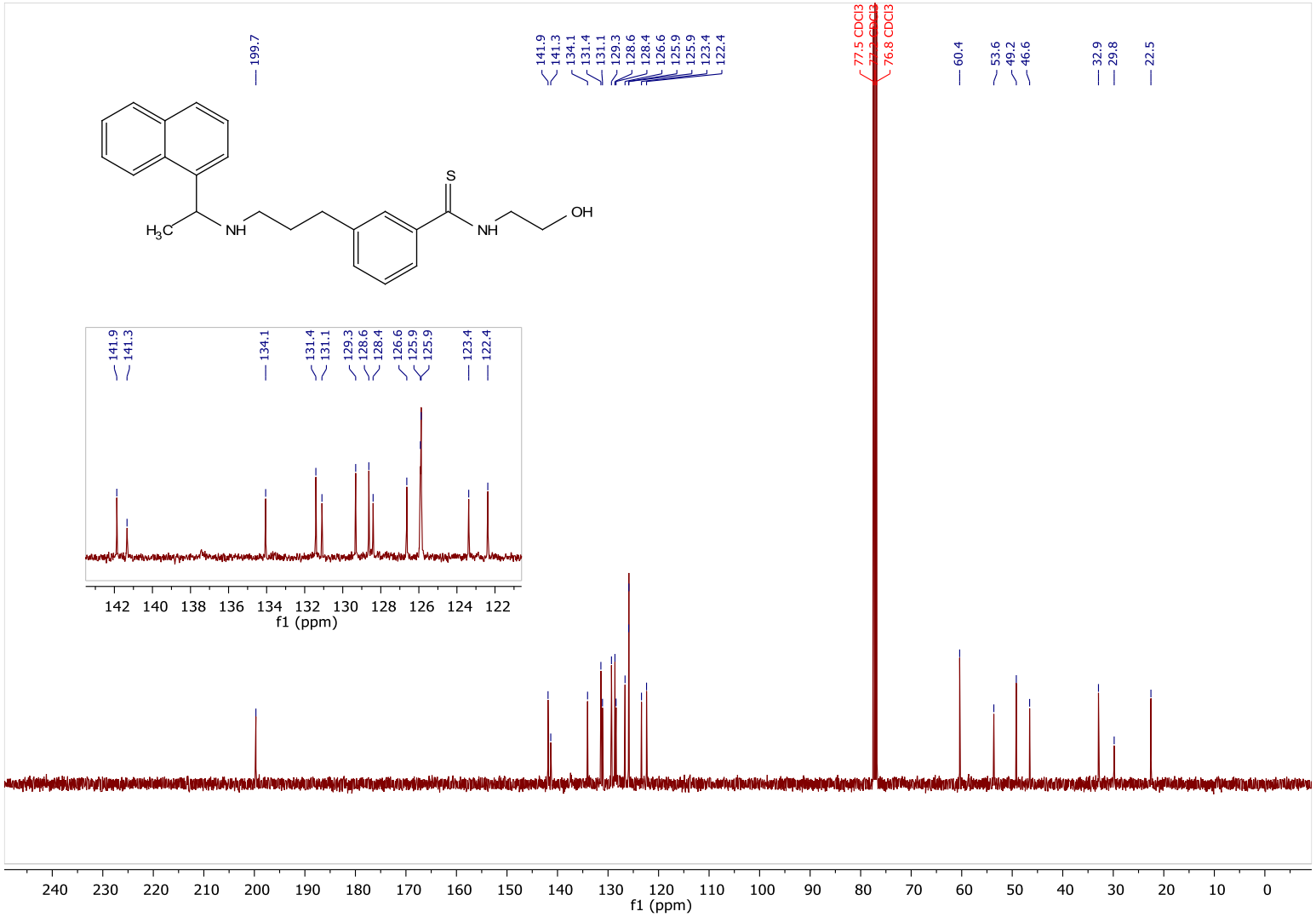
^{1}H-NMR (400 MHz, $CDCl_3$) of **1d.**



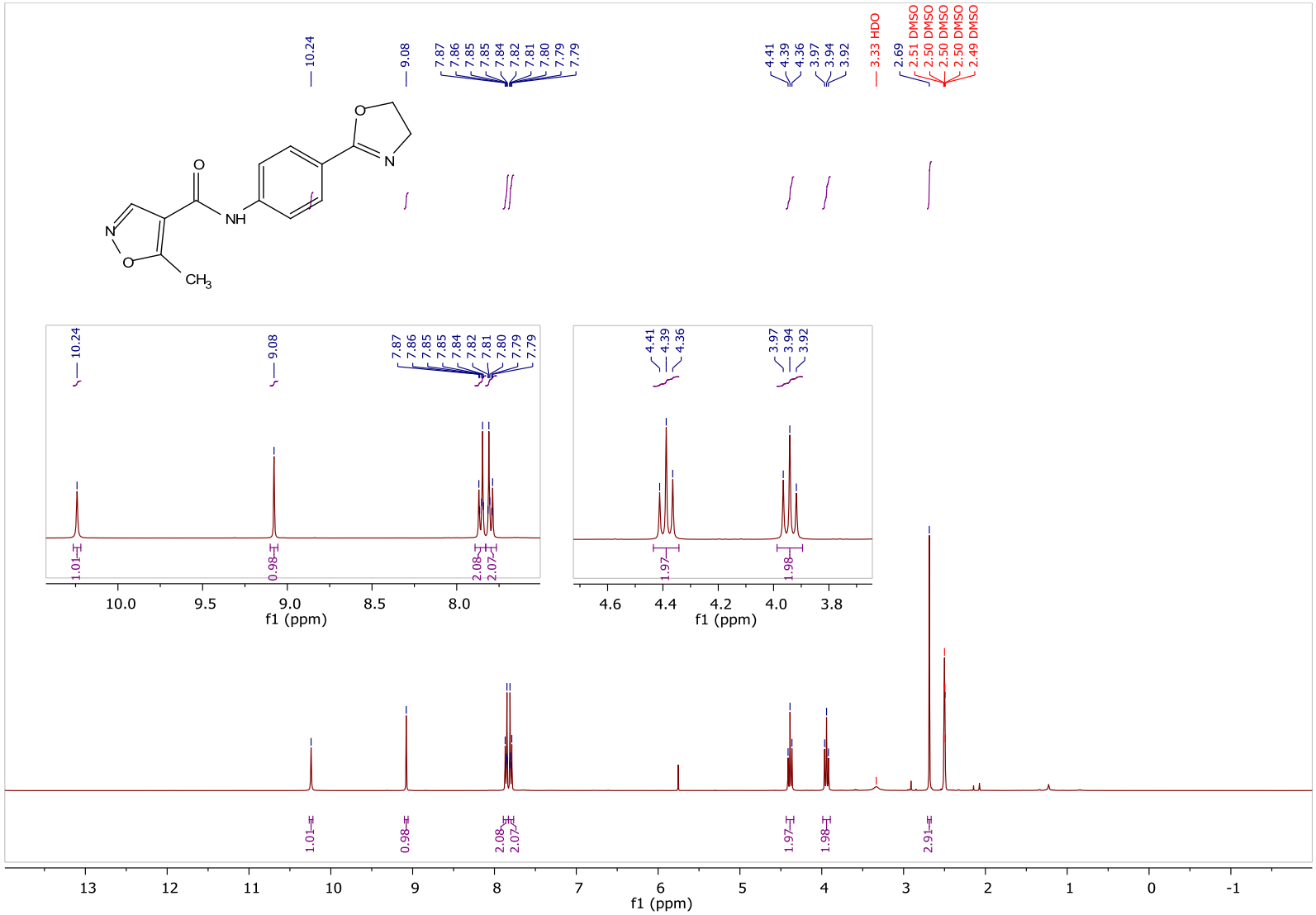
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **1d.**



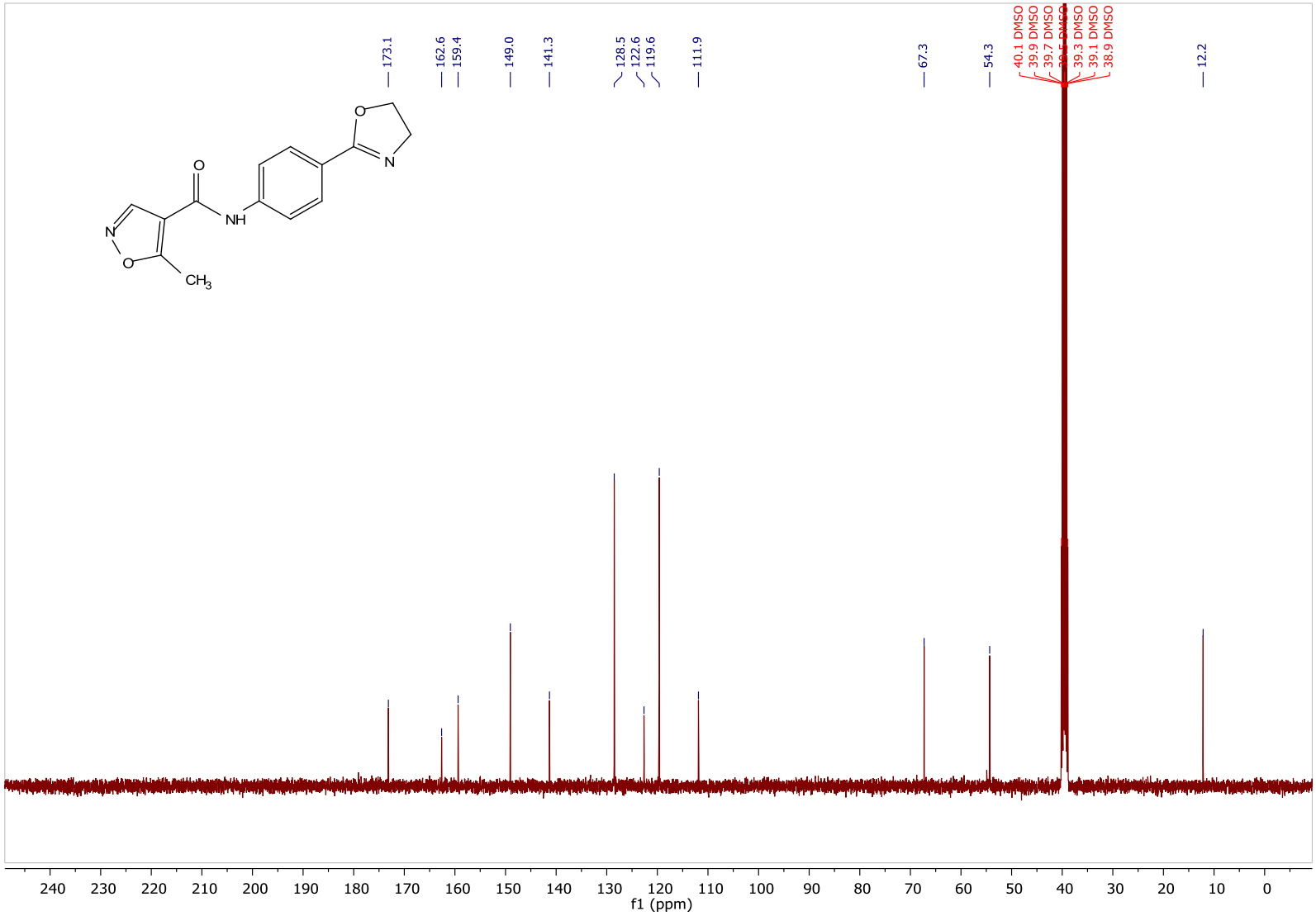
^{1}H-NMR (400 MHz, $CDCl_3$) of **2d.**



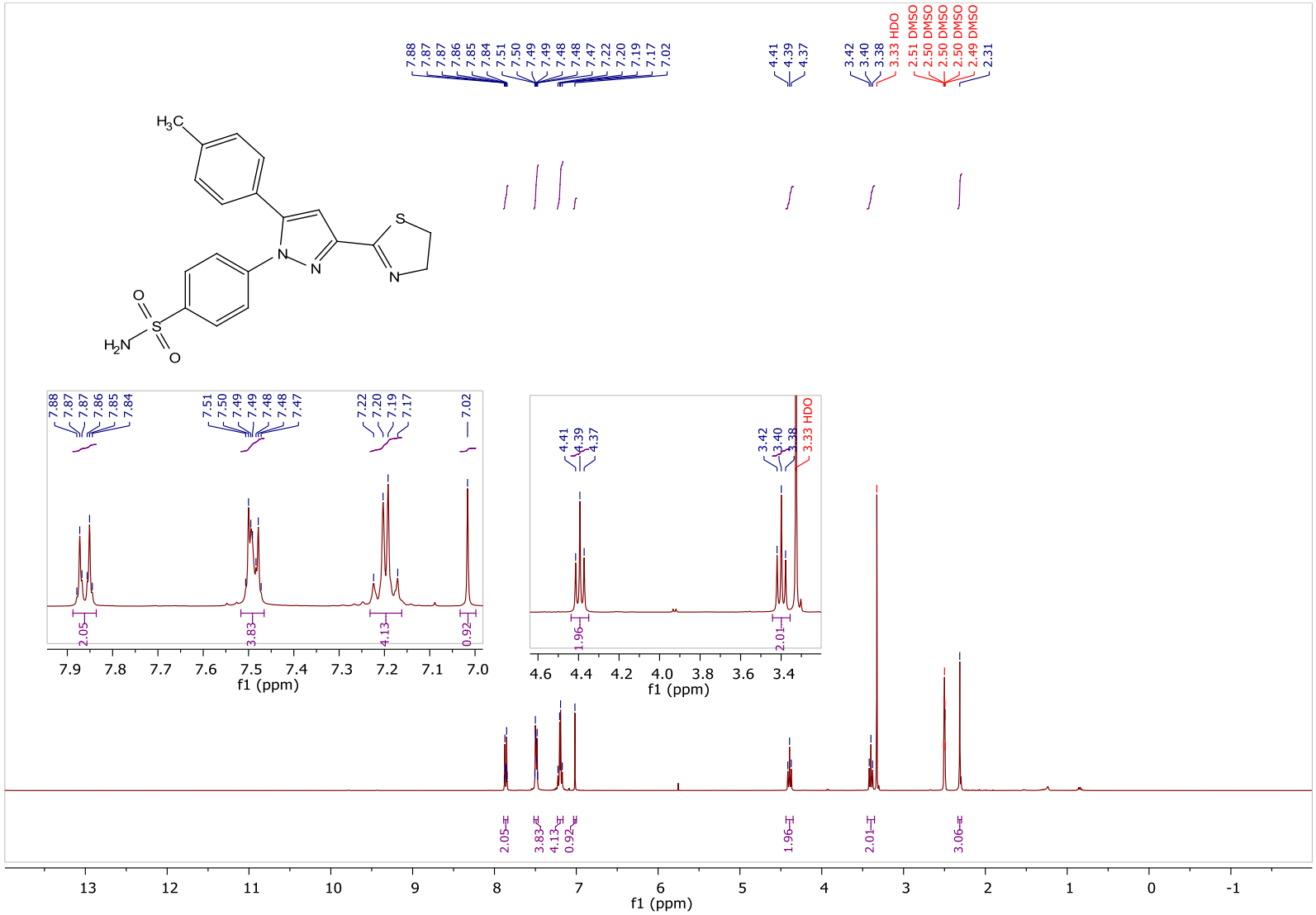
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **2d.**



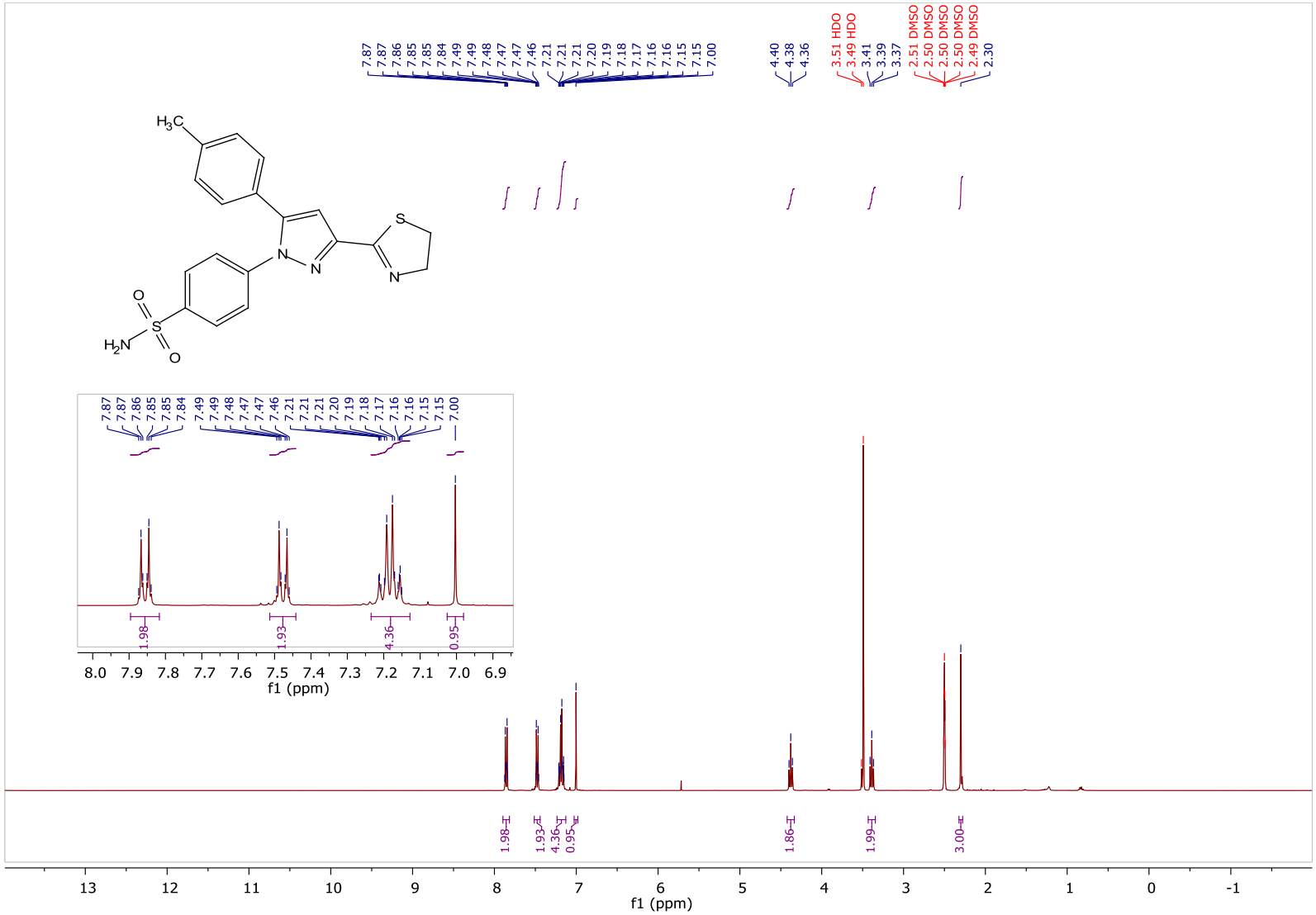
^{1}H-NMR (400 MHz, DMSO-d_6) of **3d.**



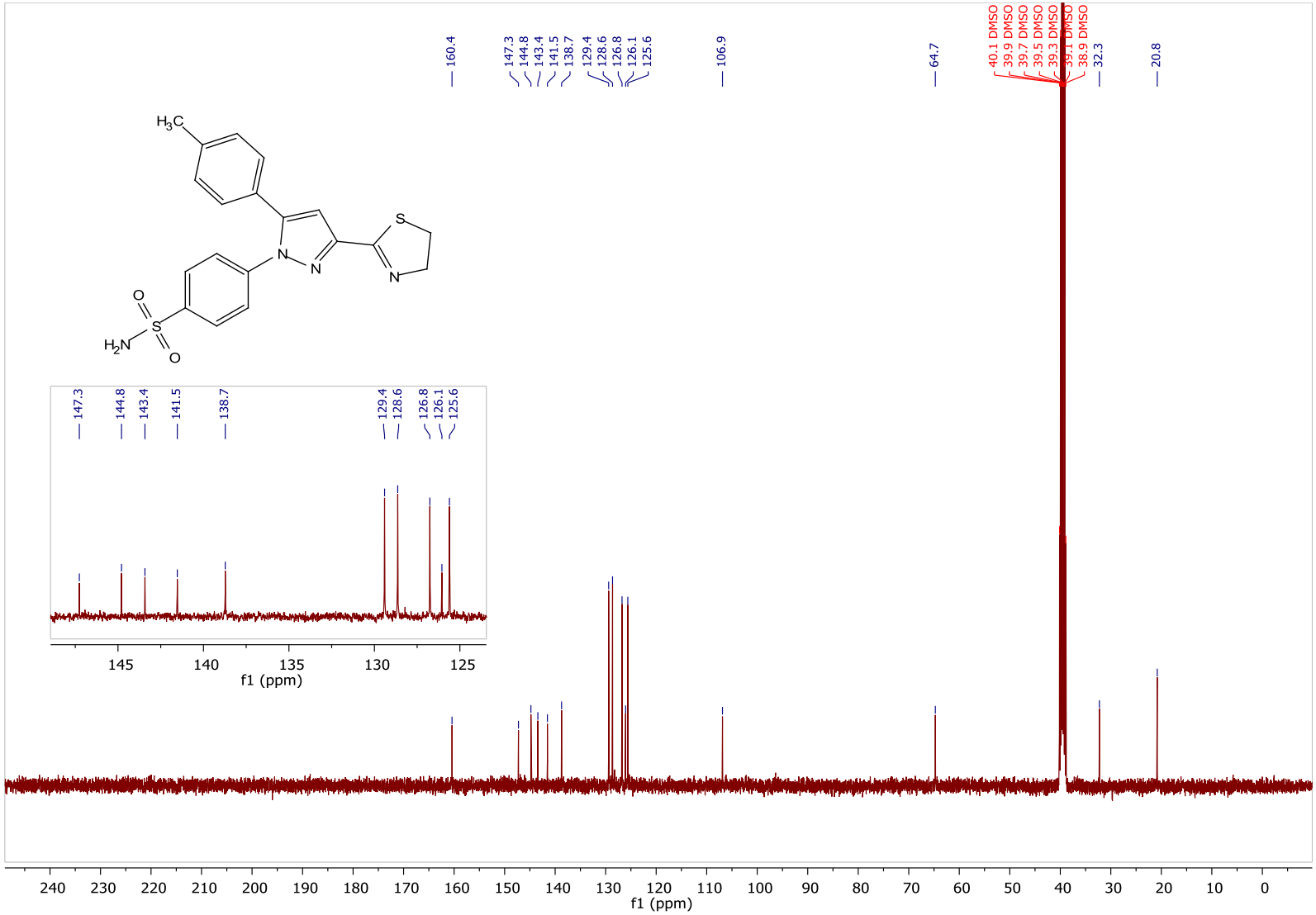
$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) of **3d.**



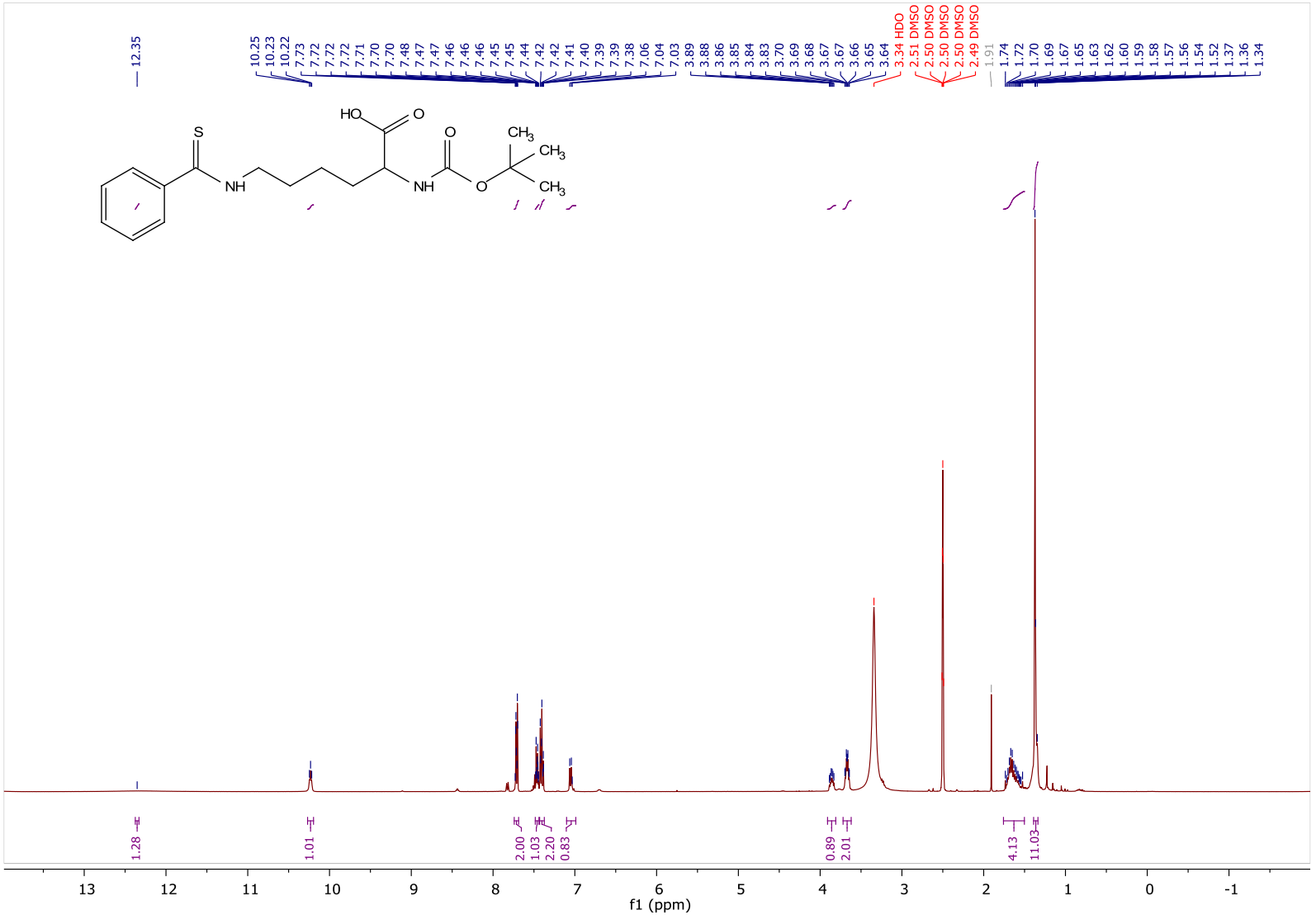
^{1}H-NMR (400 MHz, DMSO-d_6) of **4d.**



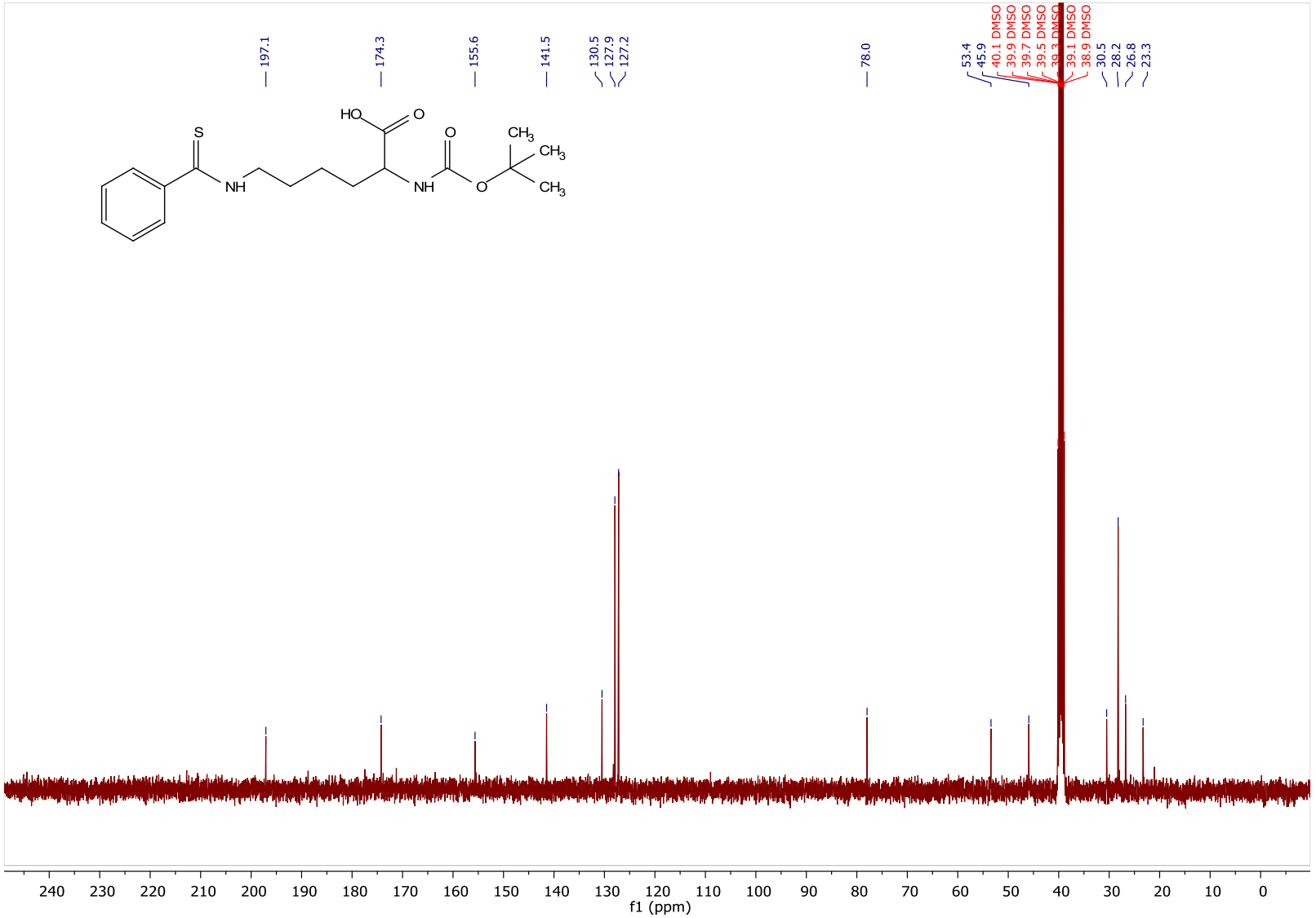
^{1}H-NMR (400 MHz, DMSO-*d*$_6$) with added D_2O of **4d.**



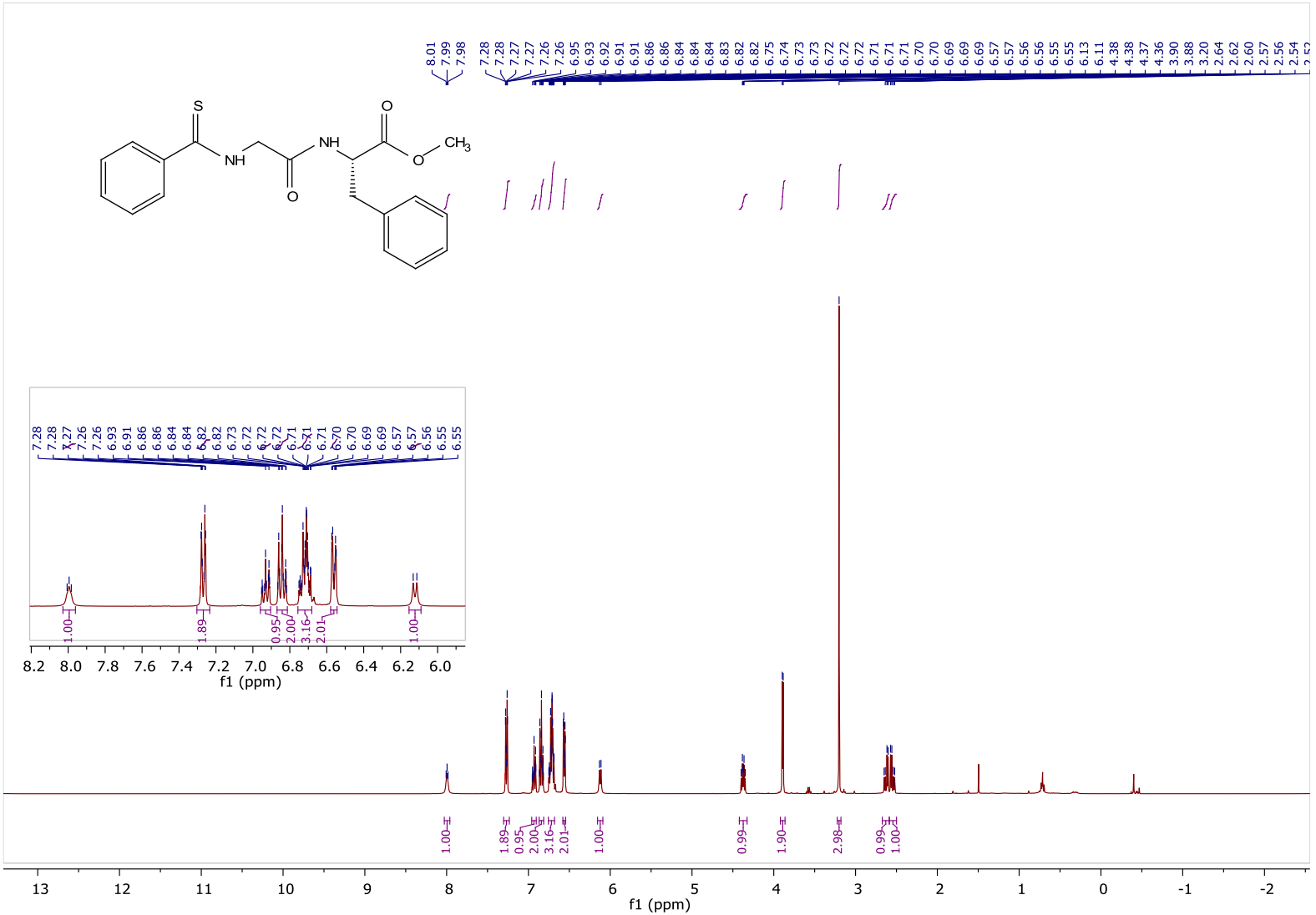
$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) of **4d.**



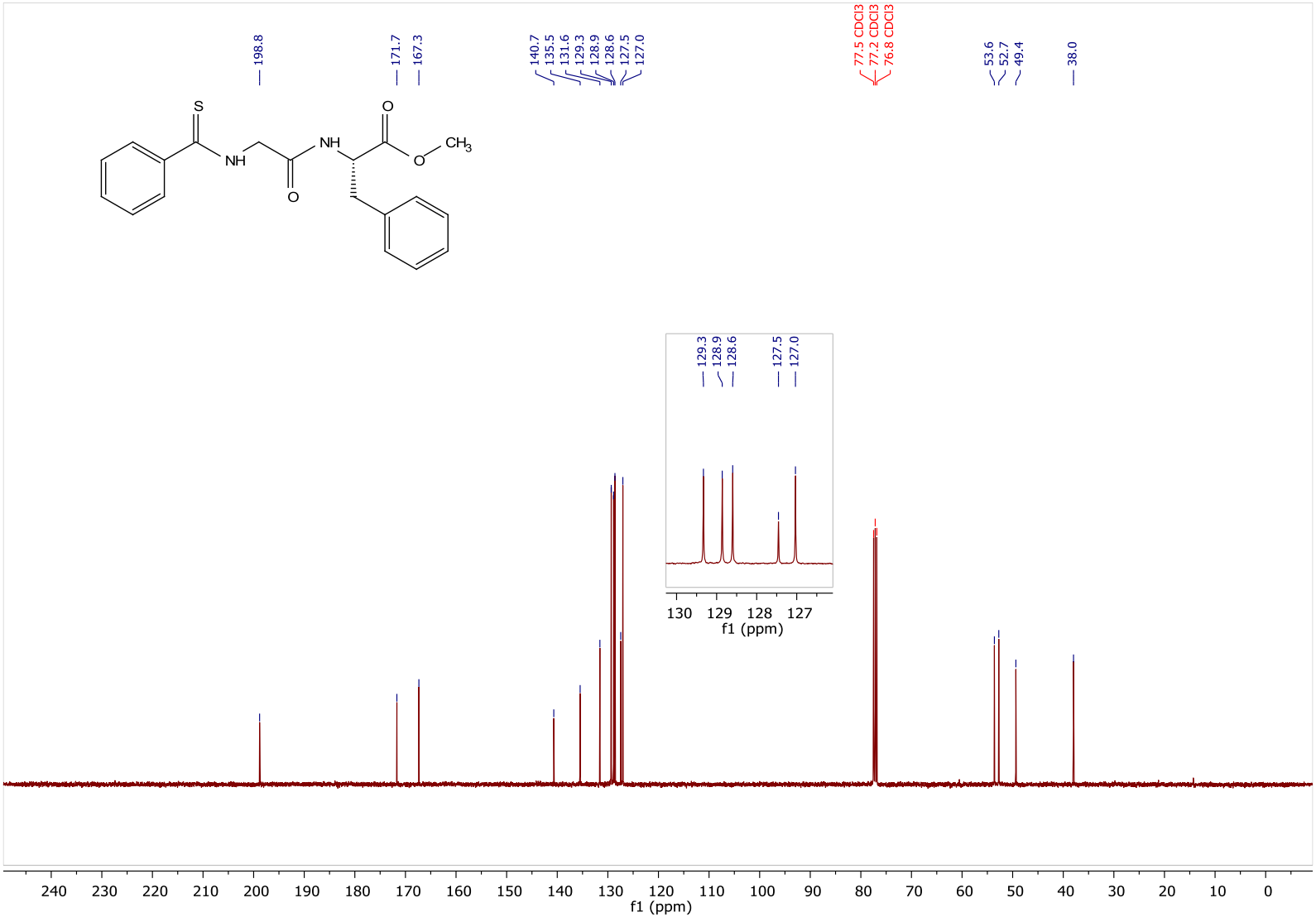
^{1}H-NMR (400 MHz, DMSO d_6) of **5d**.



$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO d_6) of **5d.**

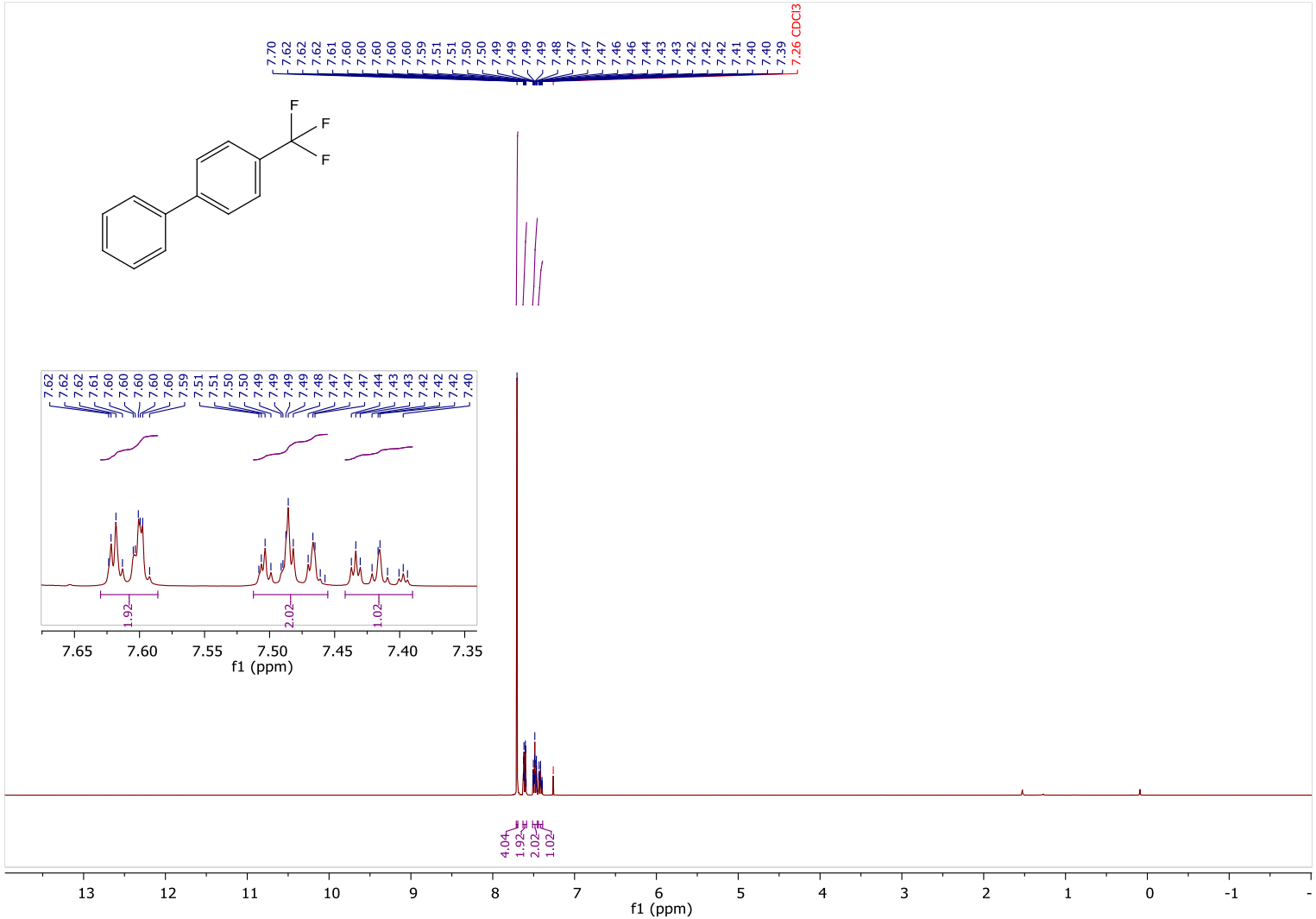


^{1}H-NMR (400 MHz, $CDCl_3$) of **6d**.

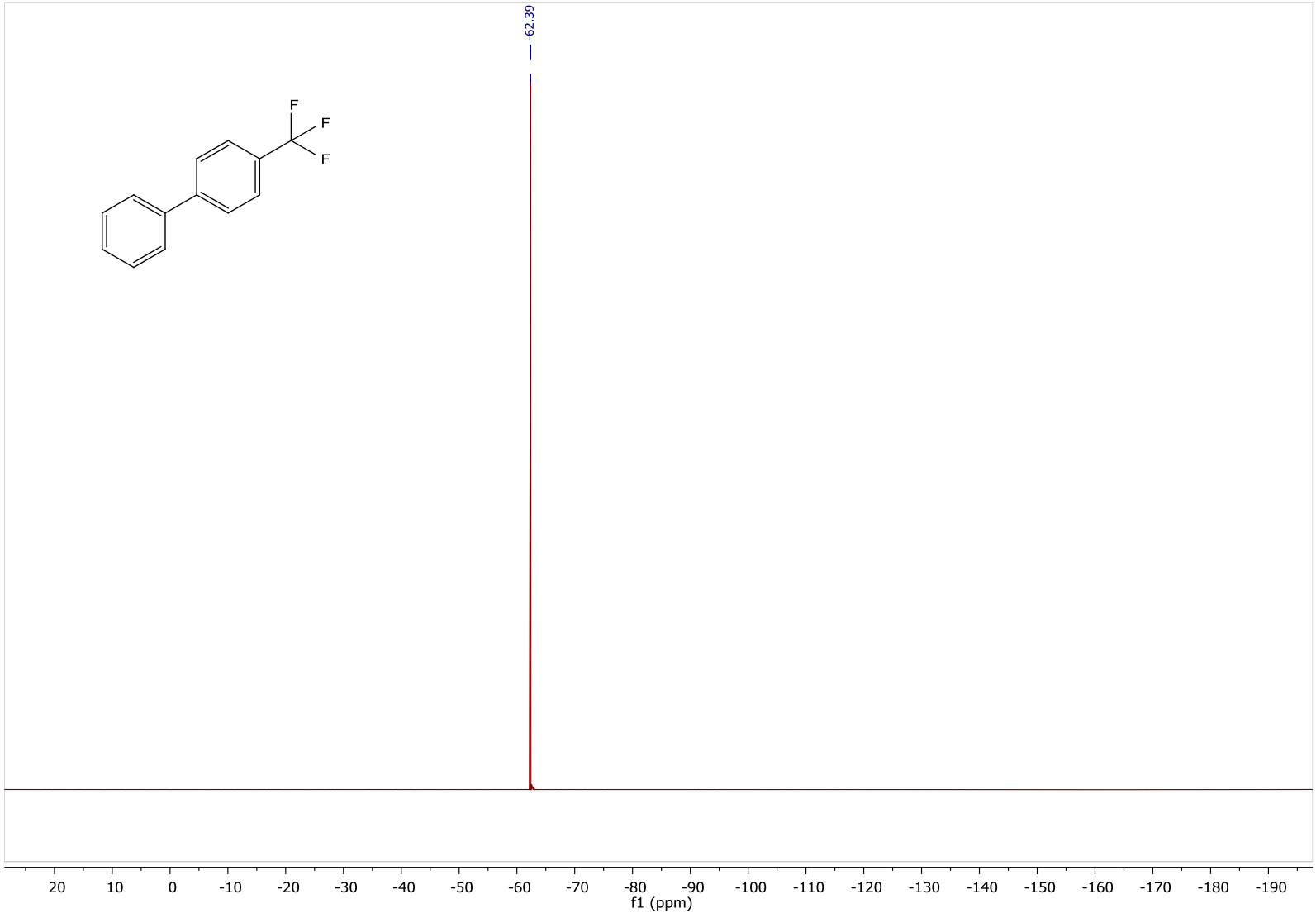


$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **6d.**

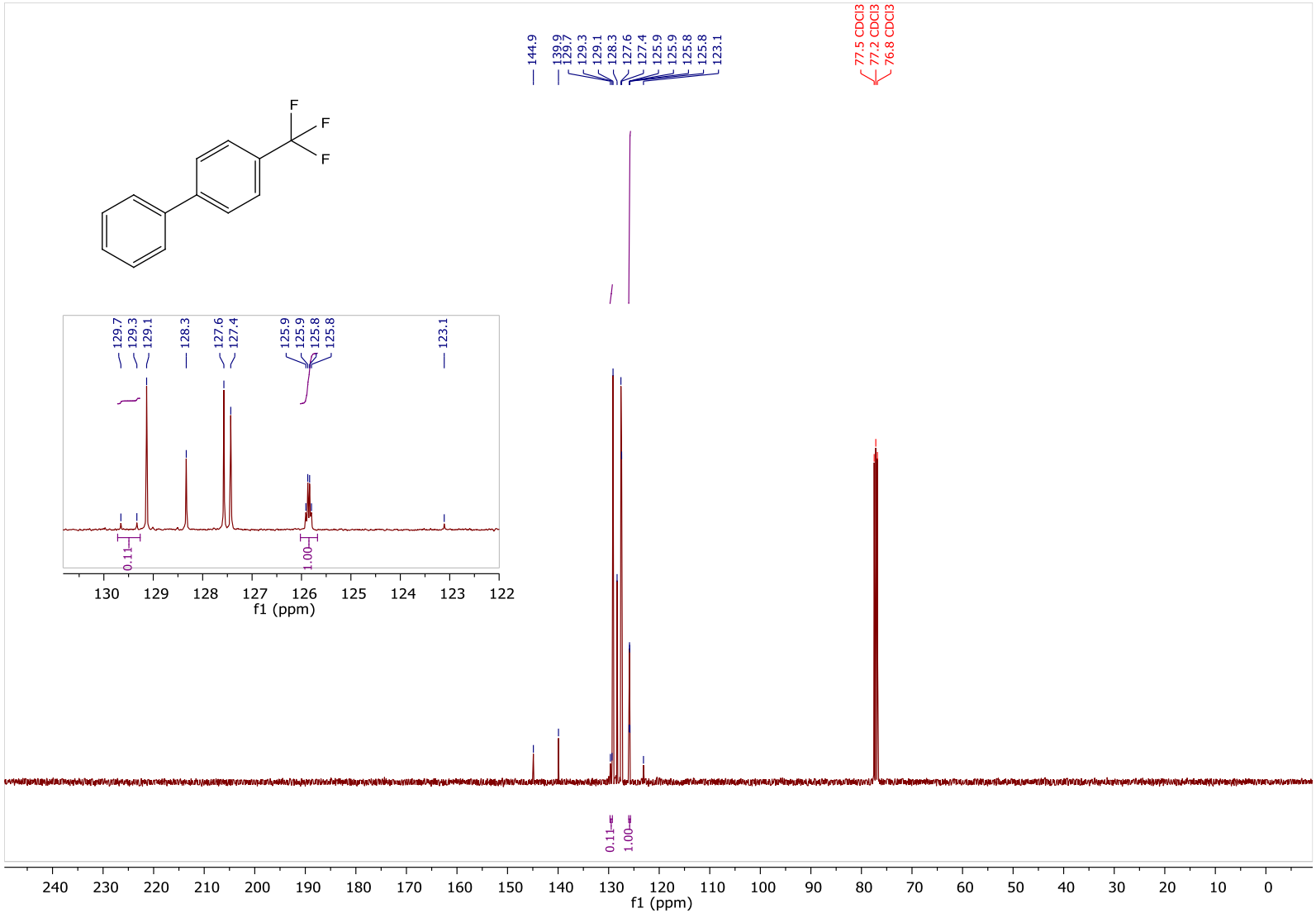
NMR Spectra **14a** and **Fmoc-Gly-Phe-OMe**



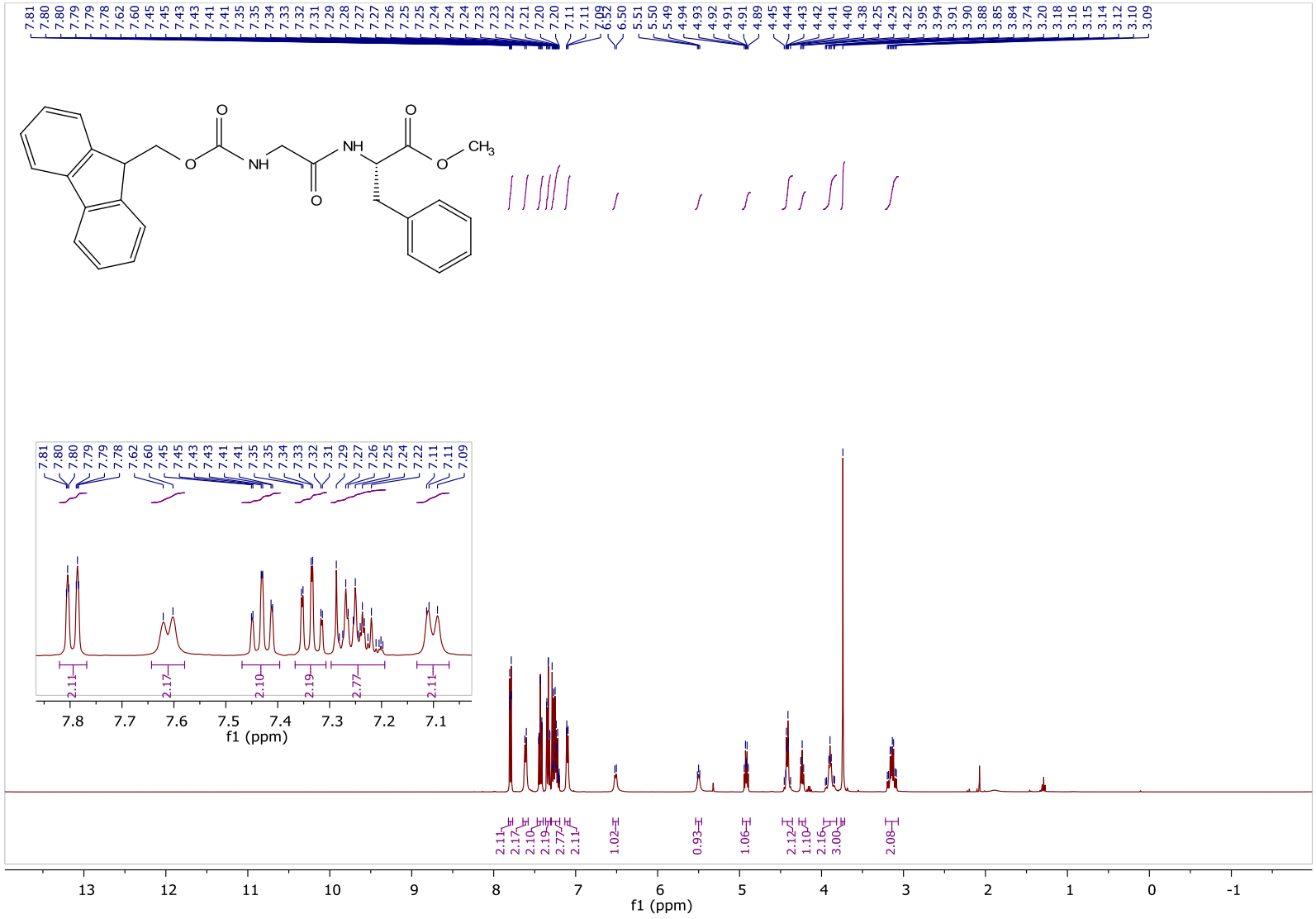
^{1}H-NMR (400 MHz, $CDCl_3$) of **14a**



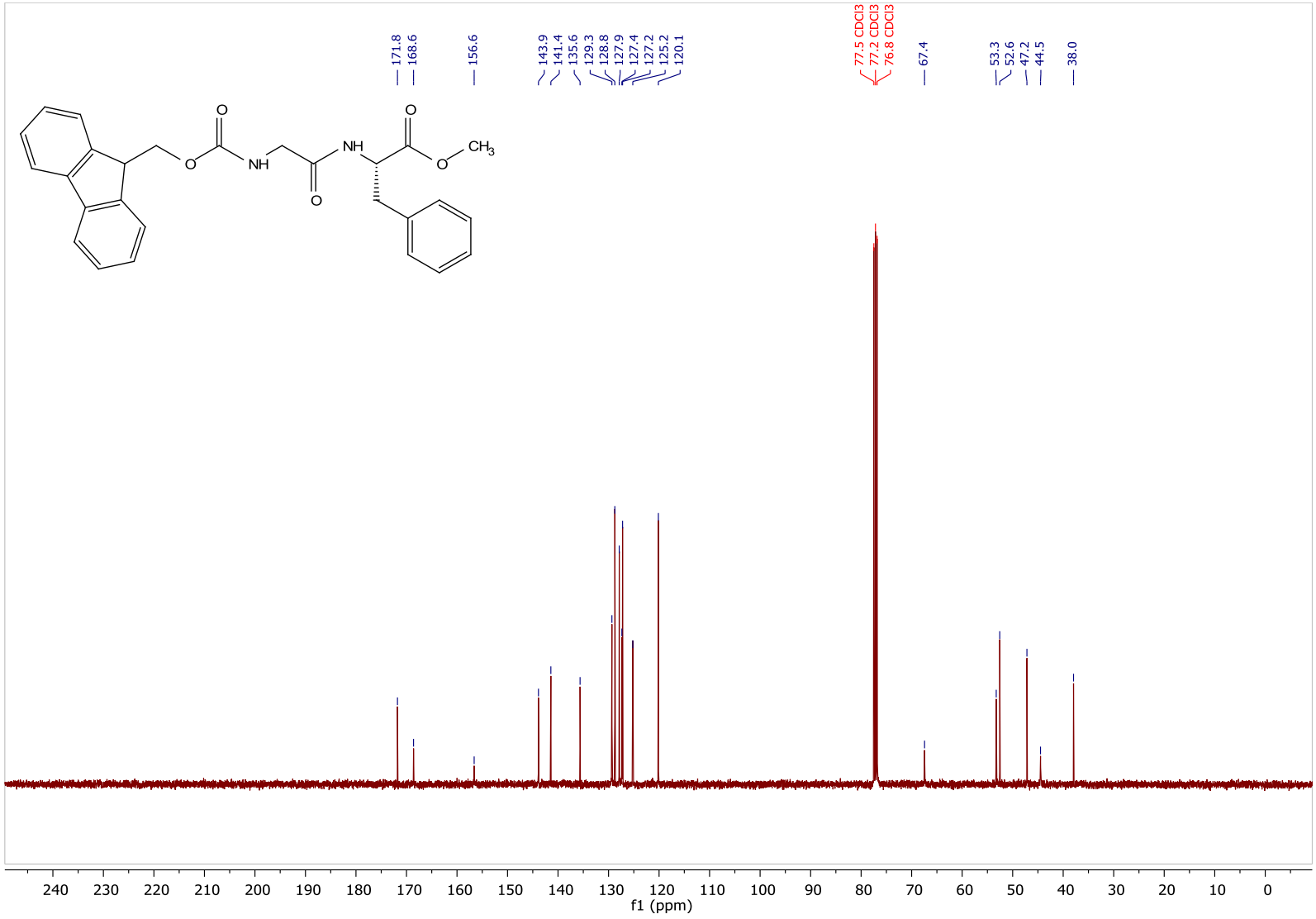
^{19}F NMR (376 MHz, $CDCl_3$) of **14a**



$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **14a**



^{1}H-NMR (400 MHz, $CDCl_3$) of **Fmoc-Gly-Phe-OMe**



$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **Fmoc-Gly-Phe-OMe**