Defluorinative Thio-functionalization: Direct Synthesis of Methyl-Dithioesters from Trifluoromethylarenes

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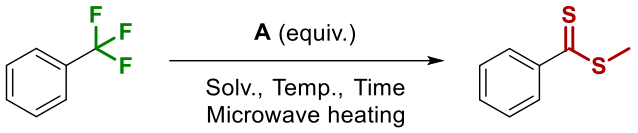
Contents

Optimization

Table S1. Optimization of the transformation of trifluoromethyl to methyl-dithioester.

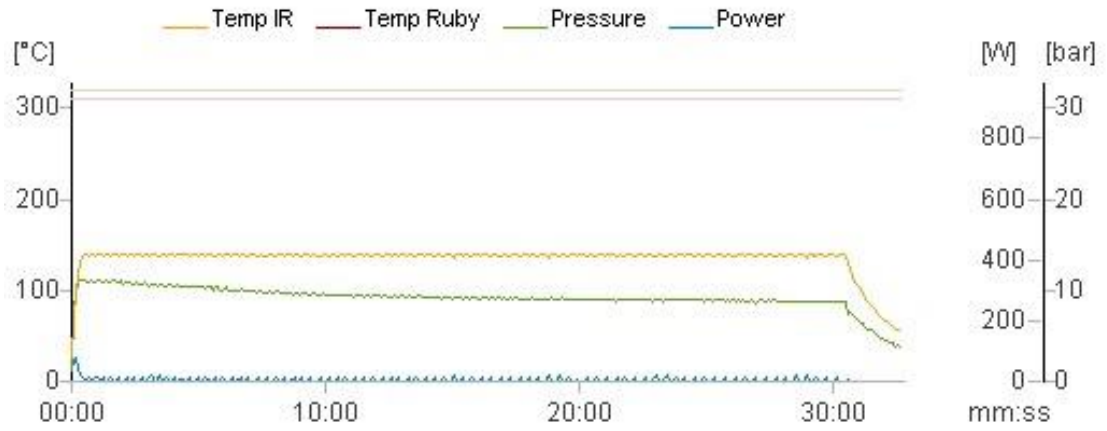


1a **1b**

Entry	**A** (equiv.)	Temp.	Solv.	Time	Yield[a]
1	BF_3SMe_2 (2)	120 ºC	DCM	60 min	46%
2	BF_3SMe_2 (3)	120 ºC	DCM	60 min	74%
3	BF_3SMe_2 (4)	120 ºC	DCM	60 min	73%
4	BF_3SMe_2 (3)	100 ºC	DCM	60 min	69%
5	BF_3SMe_2 (3)	80º C[b]	DCM	24 h	69%
6	BF_3OEt_2 (3)[c]	120 ºC	DCM	60 min	-[d]
7	BF_3SMe_2 (3)	120 ºC	neat	60 min	64%
8	BF_3SMe_2 (3)	120 ºC	*i*-hexane	60 min	65%
9	BF_3SMe_2 (3)	120 ºC	toluene	60 min	69%
10	BF_3SMe_2 (3)	120 ºC	DCE	60 min	83%
11	BF_3SMe_2 (3)	140 ºC	DCE	60 min	86%
12	BF_3SMe_2 (3)	160 ºC	DCE	60 min	81%
13	**BF_3SMe_2 (3)**	**140 ºC**	**DCE**	**30 min**	**86%**
14	BF_3SMe_2 (3)	140 ºC	DCE	10 min	67%
15	BF_3/SMe_2 (1.5/1.5)[e]	140 ºC	DCE	30 min	30%

Reactions performed with microwave heating at 0.5 mmol scale in 1 mL of solvent. [a]Isolated yield. [b]Conventional heating. [c]3 equiv. MeSSMe used as sulfur source. [d]Not detected. [e]1.5 equiv. BF_3SMe_2 and 1.5 equiv. SMe_2 used.

General Readout for Microwave Experiment Method A

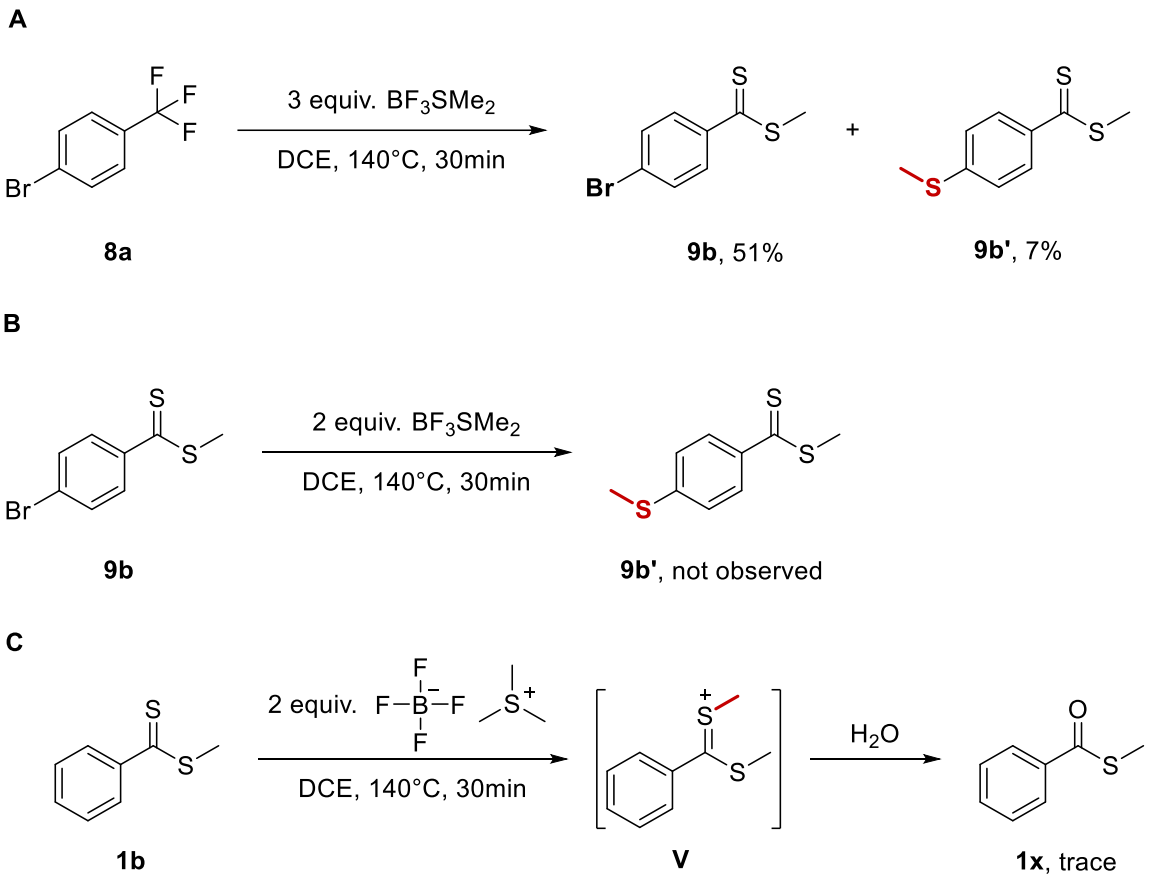


Steps

Step	Program	Temperature	Time	Power	Cooling	Stirrer Speed
		°C	hh:mm:ss	W		rpm
1	Heat as fast as possible	140	-	850	Off	1000
2	Hold	-	00:30:00	850	Off	1000
3	Cool down	55	-	-	On	600

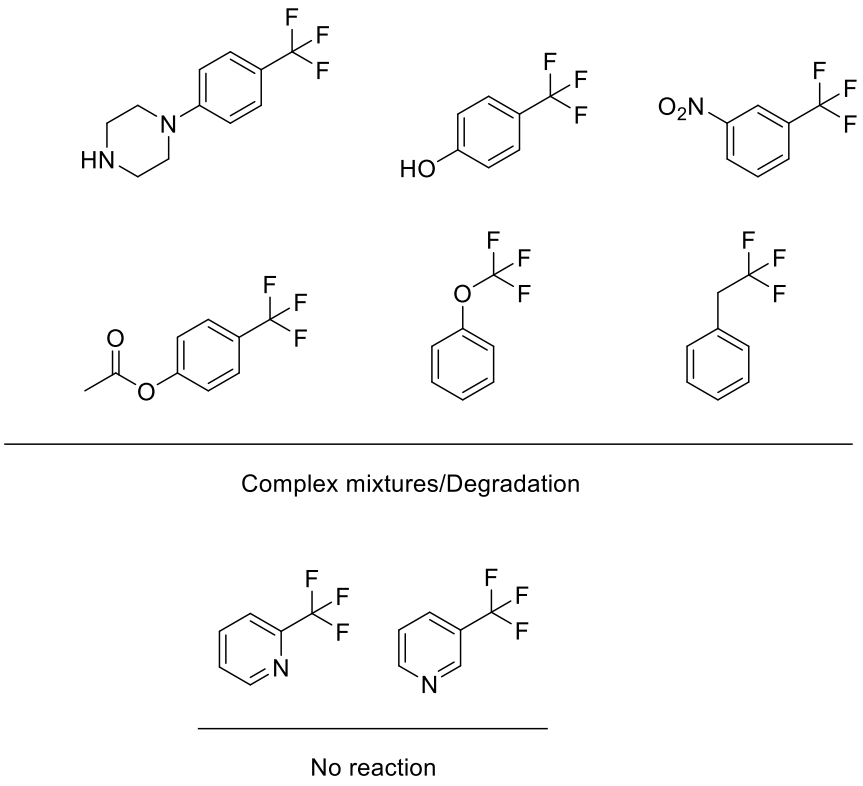
Figure S1. General readout during a microwave experiment (Anton Paar Monowave 400) using standard conditions. Above experiment is performed on trifluorotoluene.

Additional Experiments



Scheme S1. Additional experiments. **A**: Formation of the side product **9b'** using standard reaction conditions with 1-bromo-4-(trifluoromethyl)benzene (**9a**). **B**: Control experiment with **9b** to determine if the bromo-substitution occurs after dithioester formation or during reaction. No substituted product observed in control experiment concluding that the substitution is likely to occur during the trifluoro-transformation step. **C**: Control experiment investigating if the suggested intermediate **V** is formed due to the presence of the potential methylator trimethylsulfonium tetrafluoroborate. Analysis of the crude reaction mixture showed virtually only **1b** remaining, with traces of the suggested hydrolyzed product **1x**, indicating that trimethylsulfonium tetrafluoroborate has none to limited impact on the formation of suggested intermediate **V**.

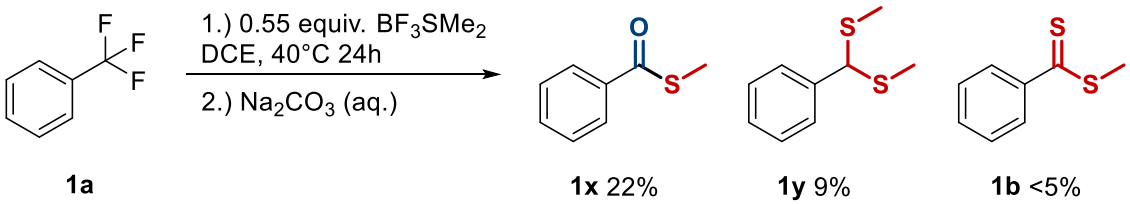
Unsuccessful substrates



Scheme S2. Substrates unsuccessful towards the optimized conditions.

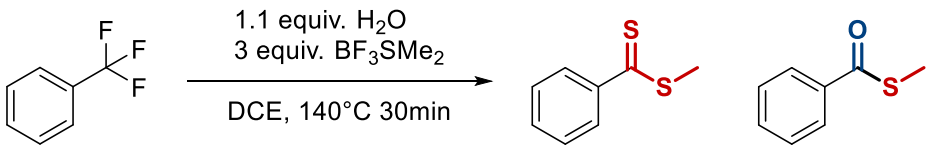
Mechanistic Experiments

Experiment 1



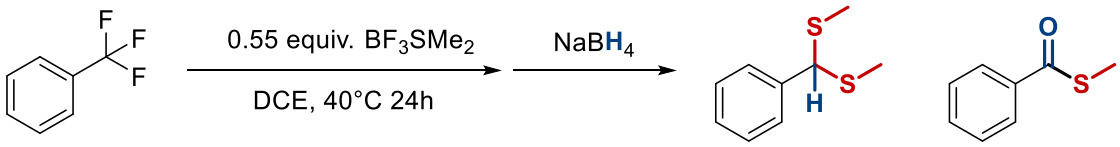
1a **1x** 22% **1y** 9% **1b** <5%

Experiment 2



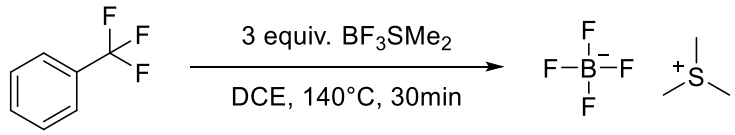
1a **1b** 64% **1x** <5%

Experiment 3



1a **1y** 33% **1x** <1%

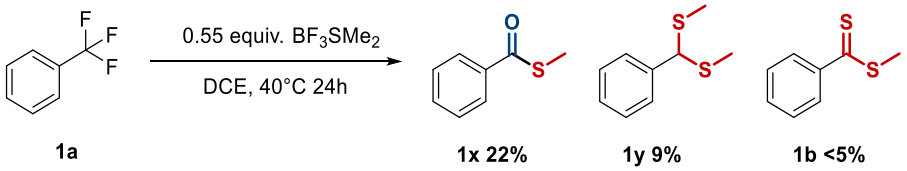
Experiment 4



1a *Confirmed by NMR*

Scheme S3. Mechanistic experiments to explore the reaction mechanism. Yields determined by NMR using dimethyl terephthalate (DMTP) as internal standard.

Experiment 1



1a **1x 22%** **1y 9%** **1b <5%**

0.5 mmol (71.3 mg) trifluorotoluene was added to an oven-dried vial and dissolved in 1 mL dry DCE. 0.55 equiv. BF_3SMe_2 (0.06 mL, 0.55 mmol) was added under nitrogen and the mixture was heated to 40 ºC for 24h. The mixture was poured into 10 mL sat. Na_2CO_3 and extracted with 3x10 mL DCM. The organics were pooled, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in $CDCl_3$, 0.1 mmol (19.4 mg) dimethyl terephthalate (DMTP) was added as internal standard, and analyzed by NMR.

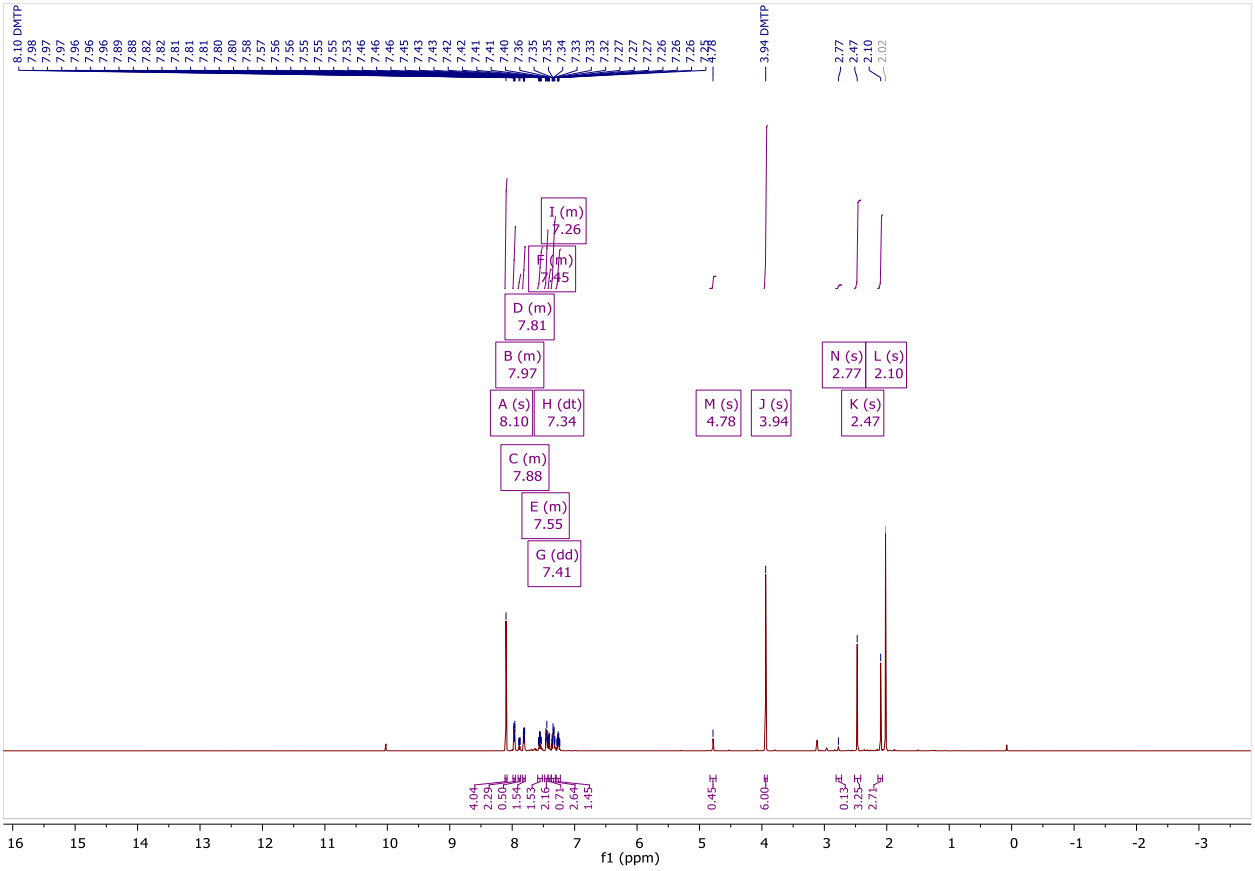
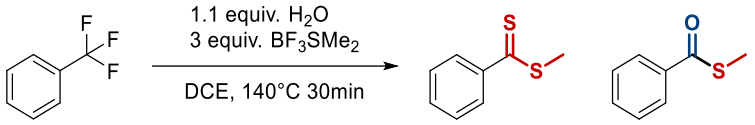


Figure S2. Crude NMR of mechanistic experiment 2 with 0.1 mmol DMTP as internal standard.

Experiment 2



0.5 mmol (71.3 mg) trifluorotoluene was added to an oven-dried vial and dissolved in 1 mL dry DCE. 1.1 equiv. (10 µL) H_2O was added. 3 equiv. BF_3SMe_2 (0.32 mL, 3 mmol) was added under nitrogen and the mixture was heated to 140 ºC for 30 min. The mixture was poured into 10 mL sat. Na_2CO_3 and extracted with 3x10 mL DCM. The organics were pooled, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in $CDCl_3$, 0.1 mmol (19.4 mg) dimethyl terephthalate (DMTP) was added as internal standard, and analyzed by NMR.

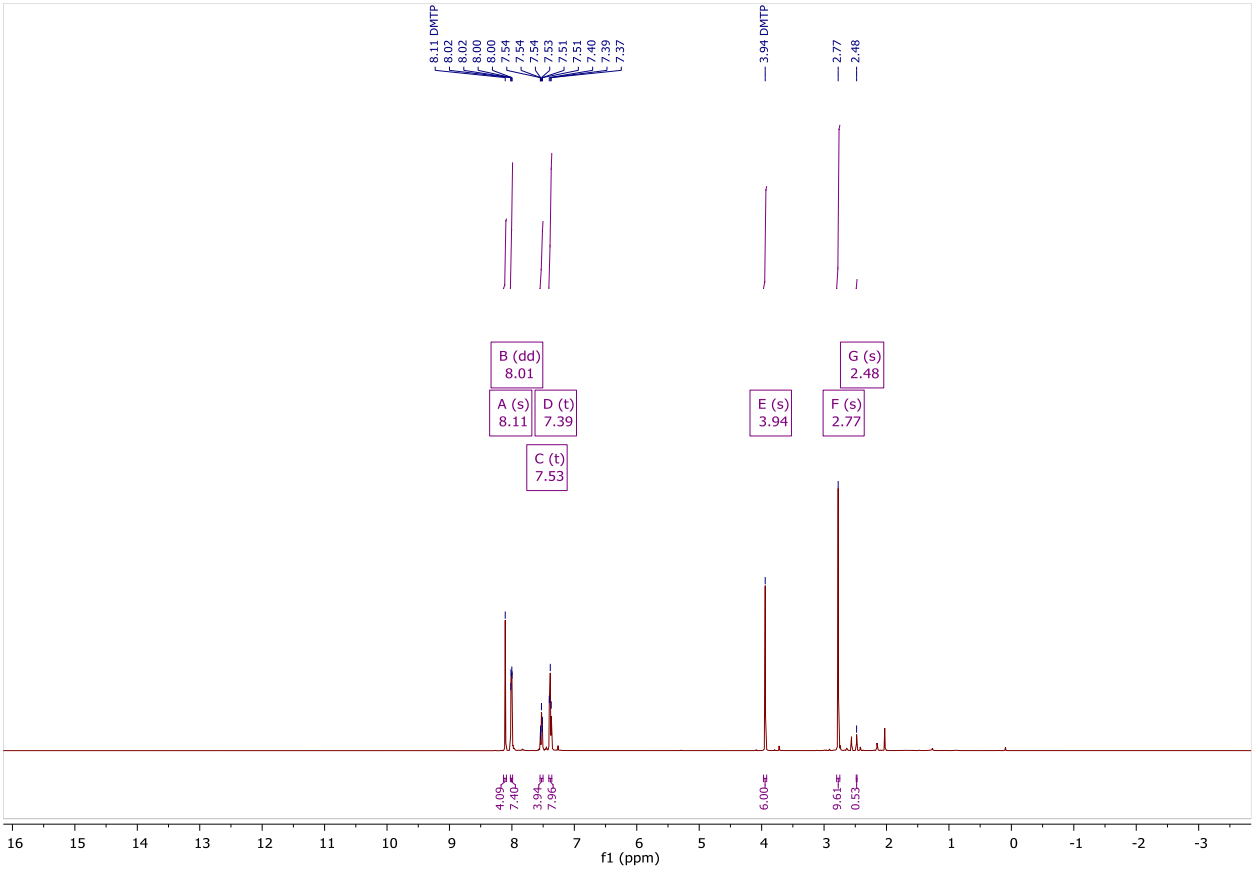
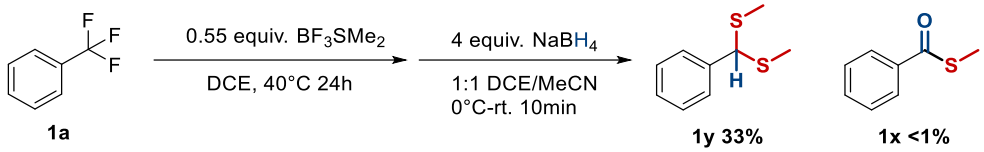


Figure S3. Crude NMR of mechanistic experiment 3 with 0.1 mmol DMTP as internal standard.

Figure

Experiment 3



0.5 mmol (71.3 mg) trifluorotoluene was added to an oven-dried vial and dissolved in 1 mL dry DCE. 0.55 equiv. BF_3SMe_2 (0.06 mL, 0.55 mmol) was added under nitrogen and the mixture was heated to 40 ºC for 24h. The mixture was cooled to 0 ºC, followed by addition of 4 equiv. (75.7 mg) $NaBH_4$ and 1 mL MeCN. The mixture was allowed to reach room temperature and stirred for 10 min. The mixture was poured into 10 mL sat. Na_2CO_3 and extracted with 3x10 mL DCM. The organics were pooled, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in $CDCl_3$, 0.1 mmol (19.4 mg) dimethyl terephthalate (DMTP) was added as internal standard, and analyzed by NMR.

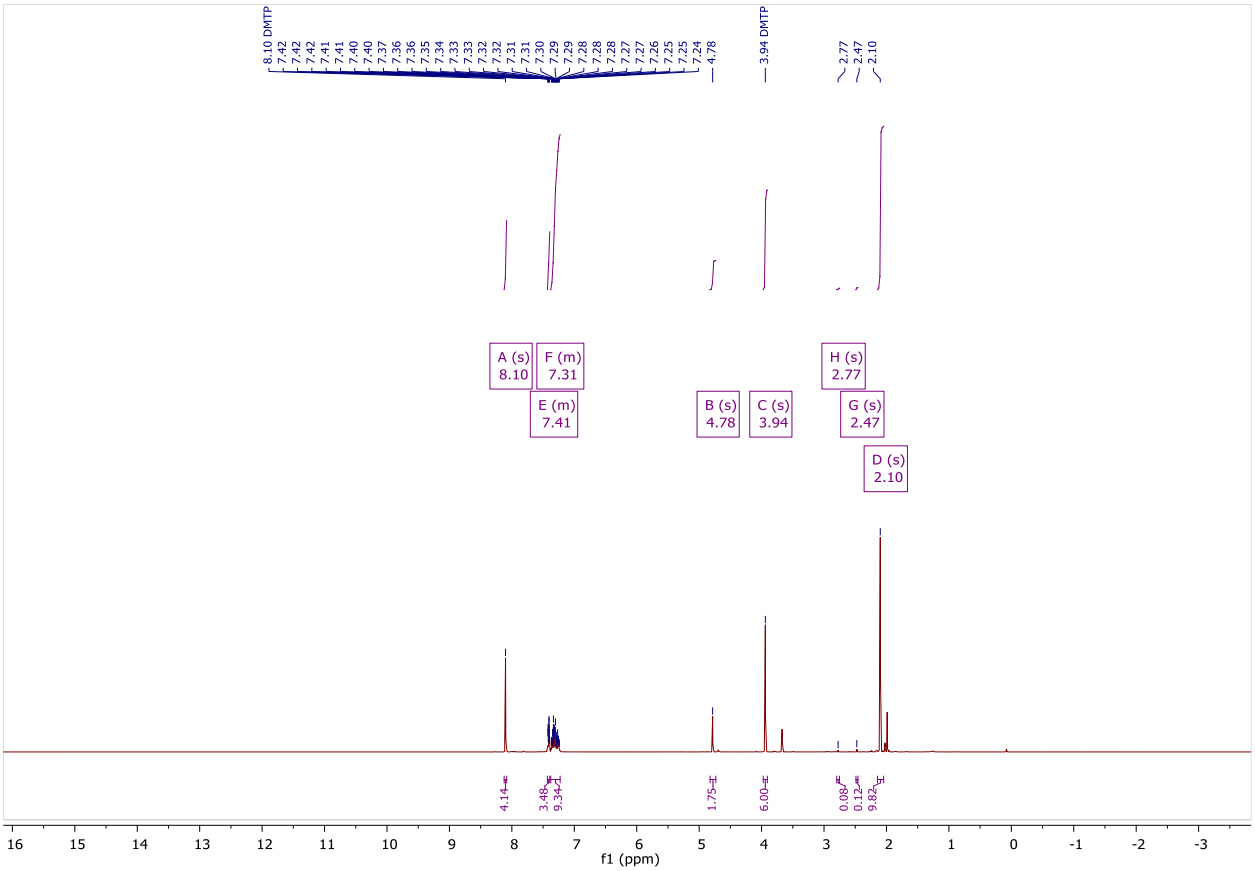
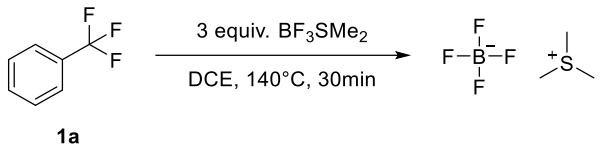


Figure S4. Crude NMR of mechanistic experiment 4 with 0.1 mmol DMTP as internal standard.

Experiment 4



1a

0.5 mmol (73.1 mg) trifluorotoluene was added to an oven-dried vial and dissolved in 1 mL dry DCE. 3 equiv. BF_3SMe_2 (0.32 mL, 3 mmol) was added under nitrogen and the mixture was heated to 140 ºC (MW) for 30 min. The mixture was cooled to ambient and the headspace was purged into MeOH with nitrogen stream for 5 min. The resulting mixture was treated with 5 mL *i*-hexane, which resulted in a residue forming in the bottom of the vial. The *i*-hexane was removed and the residue was washed with additional 2x5 mL *i*-hexane, and then 3x2 mL DCM. The residue was dried under vacuum, resulting in of an off-white solid. The solid was analyzed using NMR. ^{1}H NMR (601 MHz, D_2O) δ 2.94 (s, 6H). ^{19}F NMR (565 MHz, D_2O) δ -151.2 ^{13}C{^{1}H} NMR (101 MHz, D_2O) δ 26.5. Data consistent with commercial sample of trimethyl sulfonium tetrafluoroborate.

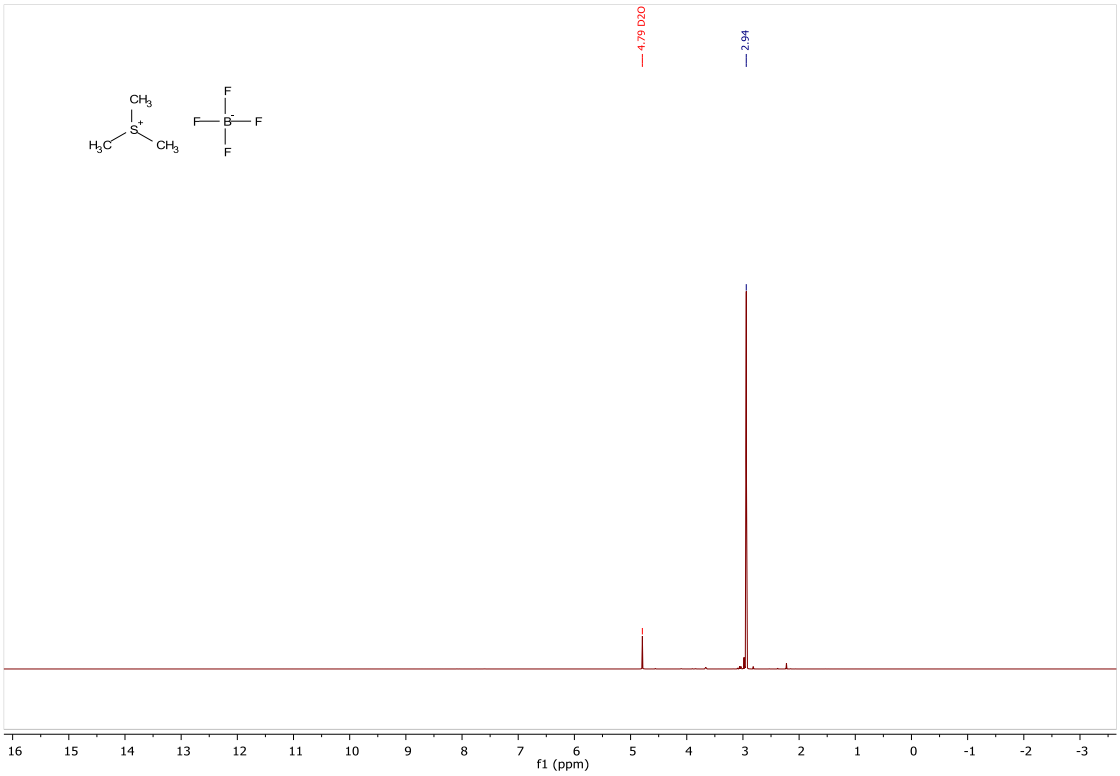


Figure S5. ^{1}H NMR (601 MHz, D_2O) of trimethyl sulfonium tetrafluoroborate.

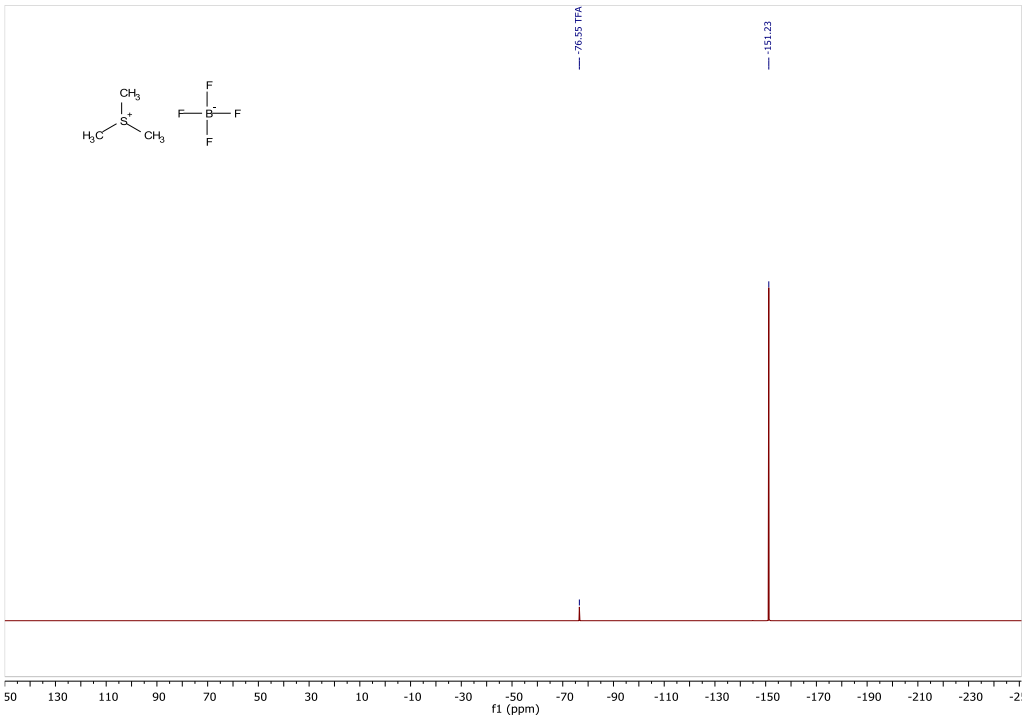


Figure S6. ^{19}F NMR (565 MHz, D_2O) of trimethyl sulfonium tetrafluoroborate with added TFA as chemical shift reference.

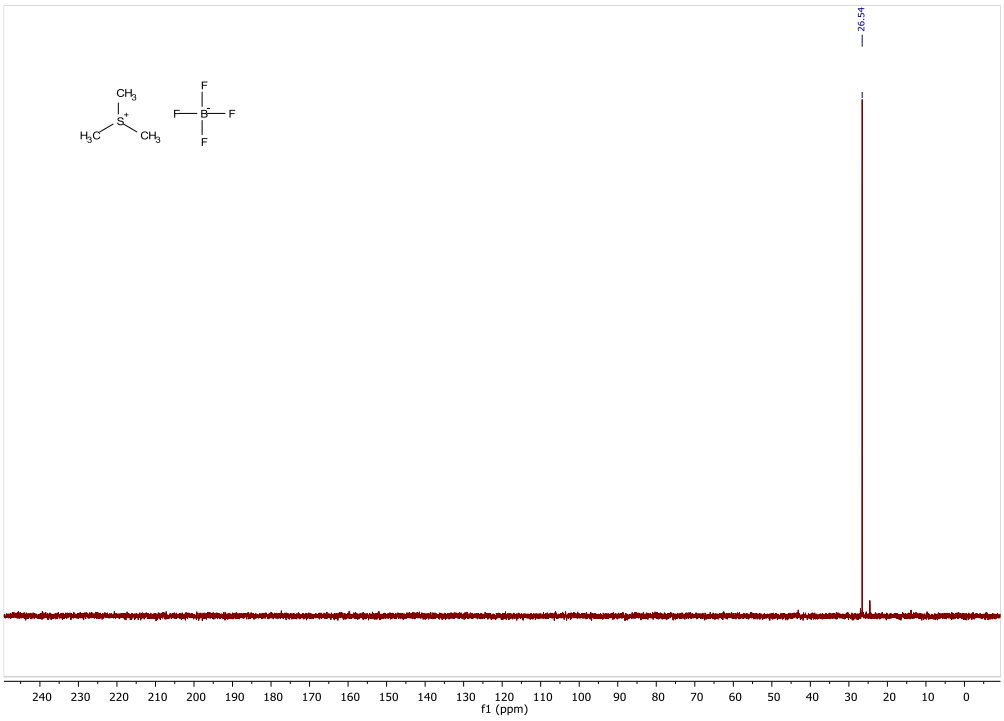


Figure S7. $^{13}C\{^1H\}$ NMR (101 MHz, D_2O) of trimethyl sulfonium tetrafluoroborate.

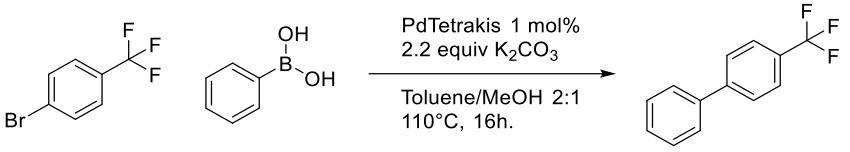
Experimental Procedures

General Methods

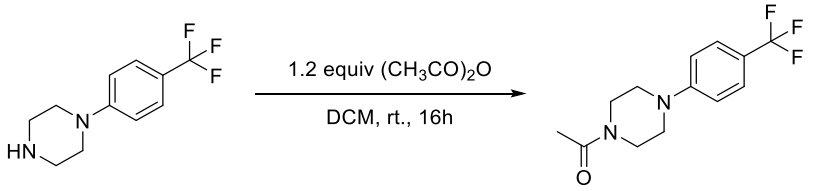
Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F-254 plates and visualized with UV light. Flash column chromatography was performed using silica gel 60 (40–63 μm). Microwave reactions were carried out in a Biotage Initiator single-mode reactor, or in an Anton Paar Monowave 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. All chemicals purchased from commercial sources with exception of **4a** and **14a**

Procedure A for synthesis of compounds 1b - 24b and 9b'. An oven dried vial was charged with trifluoromethyl substrate (0.5 mmol) and 1 mL dry DCE. BF_3SMe_2 (3 mmol, 0.32 mL, 3 equiv.) was added under nitrogen and the vial was sealed and heated in microwave irradiation at 140 ºC for 10-120 min. The reaction mixture was cooled to ambient temperature, 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 methyl-dithioester.

Synthesis of Starting Materials **4a** and **14a**

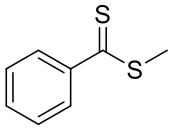


*4-(trifluoromethyl)-1,1'-biphenyl (**4a**)*. 4-bromobenzotrifuoride (2.0 mmol, 450 mg) and phenylboronic acid (2.2 mmol, 268 mg) was dissolved in 4 mL toluene and 2 mL MeOH. K_2CO_3 (4.4 mmol, 608 mg) and PdTetrakis (1 mol%, 23.1 mg) was added and the mixture was degassed and purged 3 times with N_2. The mixture was heated to 110 ºC for 16h under N_2 atmosphere. The mixture was cooled to ambient temperature, 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. Isolated as a white solid (269.9 mg, 61%). ^{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.[17a]



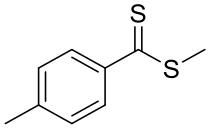
*1-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)ethan-1-one (**14a**)*. 460 mg (2.0 mmol) 1-[4-(trifluoromethyl)phenyl]piperazine was dissolved in 10 mL dry DCM. 0.23 mL (2.43 mmol) acetic anhydride was added dropwise to the stirred solution. The mixture was stirred at ambient temperature for 16h. The mixture was washed with 2x10 mL sat. Na_2CO_3, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purified over silica using 1-10% MeOH in DCM gradient. Isolated as a white solid. (539.5 mg, 99%.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.45 (m, 2H), 6.96 – 6.88 (m, 2H), 3.81 – 3.74 (m, 2H), 3.66 – 3.59 (m, 2H), 3.33 – 3.22 (m, 4H), 2.14 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.5. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.2, 153.0, 126.64 (q, *J* = 3.7 Hz), 124.70 (q, *J* = 271.2 Hz), 121.45 (q, *J* = 32.9 Hz), 115.1, 77.5, 77.2, 76.8, 48.4, 48.2, 46.0, 41.1, 21.4. Data in accordance with reported literature.[17b]

Detailed Procedures for **1b** – **24b** and **9b'**

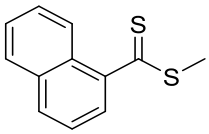


*Methyl benzodithioate (**1b**).* Synthesized according to procedure A from trifluorotoluene (0.5 mmol, 73.1 mg). Heated in MW for 30 min. Purified over silica using 0-1% EtOAc in *i*-hexane gradient (rf = 0.30), affording 72.1 mg (86%) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.99 (m, 2H), 7.58 – 7.50 (m, 1H), 7.45 – 7.35 (m, 2H), 2.79 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 229.3, 145.1, 132.3, 128.4, 126.9, 20.8. Data in accordance with reported literature.[13b]

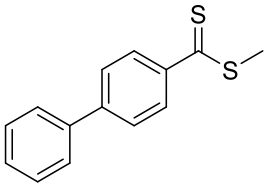
*5 mmol scale synthesis of Methyl benzodithioate (**1b**).* Synthesized according to procedure A from trifluorotoluene (5 mmol (731 mg), BF_3SMe_2 (30 mmol, 3.2 mL) in 10 mL dry DCE. Heated in MW for 30 min (**caution** high pressure). Purified over silica using 0-1% EtOAc in *i*-hexane gradient (rf = 0.30), affording 711.8 mg (85%) as a red oil.



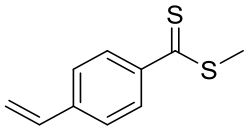
*Methyl 4-methylbenzodithioate (**2b**).* Synthesized according to procedure A from 4-methylbenzotrifluoride (0.5 mmol, 80.1 mg). Heated in MW for 30 min. Purified over silica using 0-5% toluene in *i*-hexane gradient (rf = 0.37), affording 72.6 mg (80%) as a red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 2.77 (s, 3H), 2.38 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 228.8, 143.3, 142.7, 129.1, 126.9, 21.6, 20.6. Data in accordance with reported literature.[17c]



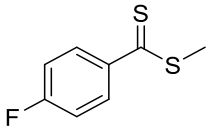
*Methyl naphthalene-1-carbodithioate (**3b**).* Synthesized according to procedure A from 1-(trifluoromethyl)naphthalene (0.5 mmol, 98.1 mg). Heated in MW for 30 min. Purified over silica using 0-5% toluene in *i*-hexane gradient (rf = 0.37), affording 67.9 mg (62%) as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 – 8.13 (m, 1H), 7.91 – 7.84 (m, 2H), 7.53 – 7.48 (m, 3H), 7.46 (dd, *J* = 8.0, 7.1 Hz, 1H), 2.86 (s, 3H).$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 232.2, 145.4, 133.8, 130.1, 129.5, 128.3, 127.0, 126.5, 125.1, 124.8, 124.1, 21.2. Data in accordance with reported literature.[17d]



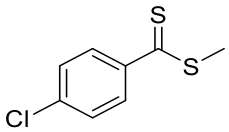
*Methyl [1,1'-biphenyl]-4-carbodithioate (**4b**).* Synthesized according to procedure A from 4-(trifluoromethyl)biphenyl (**4a**) (0.5 mmol, 111.1 mg). Heated in MW for 30 min. Purified over silica using 0-5% toluene in *i*-hexane gradient (rf = 0.28), affording 87.2 mg (71%) as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.10 (m, 2H), 7.67 – 7.60 (m, 4H), 7.51 – 7.45 (m, 2H), 7.44 – 7.38 (m, 1H), 2.81 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 228.3, 145.2, 143.8, 140.0, 129.1, 128.3, 127.5, 127.3, 127.1, 20.7. Data in accordance with reported literature.[17d]



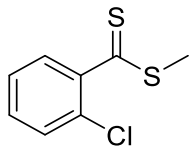
*Methyl 4-vinylbenzodithioate (**5b**).* Synthesized according to procedure A from 1-(trifluoromethyl)-4-vinylbenzene (0.5 mmol, 86.1 mg). Heated in MW for 10 min. Purified over silica using 0-5% toluene in *i*-hexane gradient (rf = 0.38), affording 10.4 mg (11%) as a pink oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H), 7.45 – 7.39 (m, 2H), 6.74 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.87 (dd, *J* = 17.6, 0.7 Hz, 1H), 5.39 (dd, *J* = 10.8, 0.7 Hz, 1H), 2.78 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 228.2, 144.2, 141.6, 136.1, 127.3, 126.2, 116.4, 20.7. HRMS (APCI) calculated for $C_{10}H_{11}S_2$ $[M+H]^+$: 195.0297; Found: 195.0298.



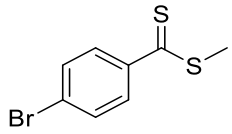
*Methyl 4-fluorobenzodithioate (**6b**).* Synthesized according to procedure A from 4-fluorobenzotrifluoride (0.5 mmol, 82.1 mg). Heated in MW for 30 min. Purified over silica using 0-1% EtOAc in *i*-hexane gradient (rf = 0.22), affording 77.4 mg (83%) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.01 (m, 2H), 7.12 – 7.02 (m, 2H), 2.77 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.16 (tt, *J* = 8.4, 5.4 Hz). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 227.0, 165.7 (d, *J* = 254.2 Hz), 141.3 (d, *J* = 3.2 Hz), 129.2 (d, *J* = 9.0 Hz), 115.4 (d, *J* = 22.0 Hz), 20.8. Data in accordance with reported literature.[17e]



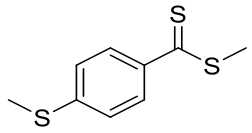
*Methyl 4-chlorobenzodithioate (**7b**).* Synthesized according to procedure A from 4-chlorobenzotrifluoride (0.5 mmol, 90.3 mg). Heated in MW for 60 min. Purified over silica using 0-1% EtOAc in *i*-hexane gradient (rf = 0.67), affording 81.7 mg (81%) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.91 (m, 2H), 7.42 – 7.32 (m, 2H), 2.77 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 227.1, 143.2, 138.8, 128.6, 128.1, 20.8. Data in accordance with reported literature.[17f]



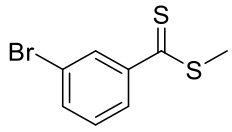
*Methyl 2-chlorobenzodithioate (**8b**).* Synthesized according to procedure A from 2-chlorobenzotrifluoride (0.5 mmol, 90.3 mg). Heated in MW for 60 min. Purified over silica using 0-1% EtOAc in *i*-hexane gradient (rf = 0.29), affording 74.2 mg (73%) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 1H), 7.34 – 7.27 (m, 3H), 2.79 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 228.8, 145.9, 130.4, 130.3, 129.4, 128.3, 126.7, 20.9. HRMS (MALDI) calculated for $C_8H_{17}ClS_2$ $[M+H]^+$: 202.9756; Found: 202.9754.



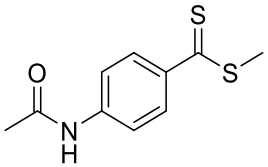
*Methyl 4-bromobenzodithioate (**9b**).* Synthesized according to procedure A from 4-bromobenzotrifluoride (0.5 mmol, 112.5 mg). Heated in MW for 30 min. Purified over silica using 0-1% EtOAc in *i*-hexane gradient (rf = 0.50), affording 62.6 mg (51%) as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.84 (m, 2H), 7.56 – 7.48 (m, 2H), 2.77 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 227.3, 143.6, 131.6, 128.3, 127.5, 20.8. Data in accordance with reported literature.[17d]



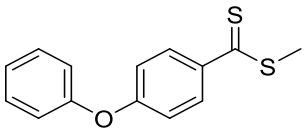
*Methyl 4-(methylthio)benzodithioate (**9b'**).* Synthesized according to procedure A from 4-bromobenzotrifluoride (0.5 mmol, 112.5 mg). Heated in MW for 30 min. Purified over silica using 0-10% toluene in *i*-hexane gradient (rf = 0.35), affording 7.0 mg (7%) as a pink solid. Mp: 50 - 52 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.97 (m, 2H), 7.24 – 7.17 (m, 2H), 2.77 (s, 3H), 2.52 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 227.3, 145.4, 141.4, 127.3, 125.0, 20.6, 15.1. HRMS (APCI) calculated for $C_9H_{11}S_3$ $[M+H]^+$: 215.0017; Found: 215.0018.



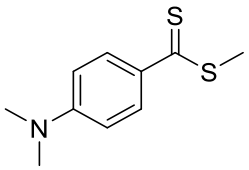
*Methyl 3-bromobenzodithioate (**10b**).* Synthesized according to procedure A from 3-bromobenzotrifluoride (0.5 mmol, 112.5 mg). Heated in MW for 120 min. Purified over silica using 0-1% EtOAc in *i*-hexane gradient (rf = 0.62), affording 94.8 mg (77%) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 1.9 Hz, 1H), 7.90 (ddd, *J* = 7.9, 1.8, 1.0 Hz, 1H), 7.64 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.30 – 7.21 (m, 1H), 2.77 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 226.9, 146.4, 134.9, 129.9, 129.8, 125.3, 122.6, 20.9. HRMS (APCI) calculated for $C_8H_8BrS_2$ $[M+H]^+$: 246.9245; Found: 246.9244.



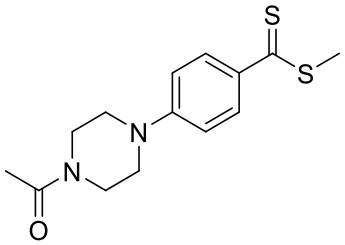
*Methyl 4-acetamidobenzodithioate (**11b**).* Synthesized according to procedure A from 4-(trifluoromethyl)acetanilide (0.5 mmol, 101.6. mg). Heated in MW for 10 min. Purified over silica using 0-5% MeCN in DCM gradient (rf = 0.27), affording 86.3 mg (77%) as a red solid. Mp: 156 - 158 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.06 – 8.00 (m, 2H), 7.72 – 7.66 (m, 2H), 2.76 (s, 3H), 2.09 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 226.8, 169.0, 144.0, 138.7, 127.7, 118.1, 24.2, 20.1. HRMS (ESI) calculated for $C_{10}H_{12}NOS_2$ [M+H]$^+$: 226.0360; Found: 226.0352.



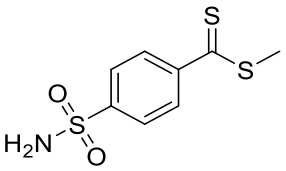
*Methyl 4-phenoxybenzodithioate (**12b**).* Synthesized according to procedure A from 1-phenoxy-4-(trifluoromethyl)benzene (0.5 mmol, 119.1 mg). Heated in MW for 10 min. Purified over silica using 0-5% toluene in *i*-hexane gradient (rf = 0.25), affording 90.4 mg (69%) as a red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.04 (m, 2H), 7.43 – 7.37 (m, 2H), 7.23 – 7.17 (m, 1H), 7.11 – 7.06 (m, 2H), 6.98 – 6.93 (m, 2H), 2.78 (s, 3H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 227.1, 161.9, 155.7, 139.8, 130.1, 128.9, 124.6, 120.2, 117.3, 20.6. HRMS (APCI) calculated for $C_{14}H_{13}OS_2$ [M+H]$^+$: 261.0402; Found: 261.0400.



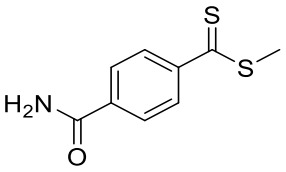
*Methyl 4-(dimethylamino)benzodithioate (**13b**).* Synthesized according to procedure A from *N*,*N*-dimethyl-4-(trifluoromethyl)aniline (0.5 mmol, 94.6 mg). Heated in MW for 10 min. Purified over silica using 0-30% DCM in *i*-Hexane gradient (rf = 0.32), affording 68.1 mg (64%) as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.12 (m, 2H), 6.63 – 6.57 (m, 2H), 3.06 (s, 6H), 2.76 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 224.5, 153.9, 133.6, 129.3, 110.6, 40.2, 19.9. Data in accordance with reported literature.[17g]



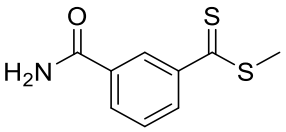
*Methyl 4-(4-acetylpiperazin-1-yl)benzodithioate (**14b**).* Synthesized according to procedure A from 1-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)ethan-1-one (**14a**) (0.5 mmol, 136.1 mg). Heated in MW for 10 min. Purified over silica using 0-10% MeCN in DCM gradient (rf = 0.16), affording 58.7 mg (40%) as an orange solid. Mp: 165 - 167 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 – 8.07 (m, 2H), 6.83 – 6.77 (m, 2H), 3.81 – 3.75 (m, 2H), 3.66 – 3.61 (m, 2H), 3.42 – 3.37 (m, 2H), 3.37 – 3.32 (m, 2H), 2.76 (s, 3H), 2.15 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 225.6, 169.2, 153.8, 136.2, 129.0, 113.6, 47.6, 47.4, 45.8, 41.0, 21.5, 20.2. HRMS (ESI) calculated for $C_{14}H_{19}N_2OS_2$ [M+H]$^+$: 295.0939; Found: 295.0932.



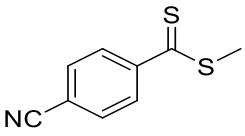
*Methyl 4-sulfamoylbenzodithioate (**15b**).* Synthesized according to procedure A from 4-(trifluoromethyl)benzenesulfonamide (0.5 mmol, 112.6 mg). Heated in MW for 60 min. Purified over silica using 0-10% MeCN in toluene gradient (rf = 0.19), affording 77.3 mg (63%) as a pink solid. Mp: 139 - 141 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 – 8.06 (m, 2H), 7.93 – 7.89 (m, 2H), 7.55 (s, 2H), 2.82 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 228.0, 147.0, 146.5, 127.0, 126.1, 20.8. HRMS (ESI) calculated for $C_8H_8NO_2S_3$ [M-H]$^{\cdot}$: 245.9723; Found: 245.9718.



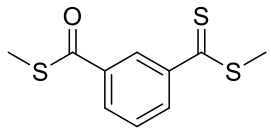
*Methyl 4-carbamoylbenzodithioate (**16b**).* Synthesized according to procedure A from 4-(trifluoromethyl)benzamide (0.5 mmol, 94.6 mg). Heated in MW for 120 min. Purified over silica using 0-30% MeCN in toluene gradient (rf = 0.31), affording 37.2 mg (35%) as a pink solid. Mp: 182 - 185 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 7.56 (s, 1H), 2.81 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 228.5, 167.0, 146.1, 137.7, 127.8, 126.3, 20.6. HRMS (ESI) calculated for $C_9H_{10}NOS_2$ [M+H]$^{+}$: 212.0204; Found: 212.0210.



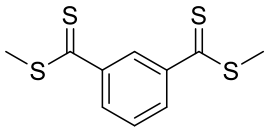
*Methyl 3-carbamoylbenzodithioate (**17b**).* Synthesized according to procedure A from 3-(trifluoromethyl)benzamide (0.5 mmol, 94.6 mg). Heated in MW for 60 min. Purified over silica using 0-10% MeCN in DCM gradient (rf = 0.19), affording 76.4 mg (72%) as a pink solid. Mp: 153 - 155 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (dd, J = 1.8 Hz, 1H), 8.17 (s, 1H), 8.14 – 8.09 (m, 1H), 8.09 – 8.04 (m, 1H), 7.60 – 7.53 (m, 2H), 2.81 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 228.8, 166.9, 144.4, 134.7, 131.2, 128.9, 128.8, 125.5, 20.6. HRMS (ESI) calculated for $C_9H_{10}NOS_2$ [M+H]$^{+}$: 212.0204; Found: 212.0201.



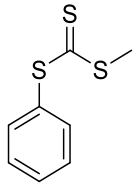
*Methyl 4-cyanobenzodithioate (**18b**).* Synthesized according to procedure A from 4-(trifluoromethyl)benzonitrile (0.5 mmol, 85.6 mg). Heated in MW for 120 min. Purified over silica using 0-30% DCM in *i*-hexane gradient (rf = 0.22), affording 42.3 mg (44%) as a red solid. Mp: 100 - 102 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.01 (m, 2H), 7.71 – 7.66 (m, 2H), 2.80 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 226.6, 147.8, 132.3, 127.4, 118.3, 115.3, 21.0. HRMS (APCI) calculated for $C_9H_8NS_2$ [M+H]$^{+}$: 194.0093; Found: 194.0091.



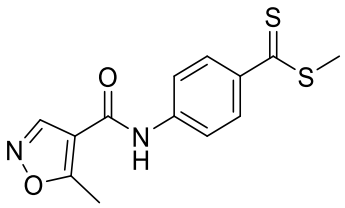
*S-methyl 3-((methylthio)carbonothioyl)benzothioate (**19b**).* Synthesized according to procedure A, using 4 equiv. BF_3SMe_2 (4 mmol, 0.42 mL), from 3-(trifluoromethyl)benzoic acid (0.5 mmol (95.1 mg). Heated in MW for 60 min. Purified over silica using 0-30% DCM in *i*-hexane gradient (rf = 0.35), affording 59.8 mg (49%) as a red solid. Mp: 43 - 45 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 1.9 Hz, 1H), 8.16 (ddd, *J* = 7.9, 1.9, 1.1 Hz, 1H), 8.09 (ddd, *J* = 7.9, 1.3 Hz, 1H), 7.47 (dd, *J* = 7.8 Hz, 1H), 2.79 (s, 3H), 2.50 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 227.6, 191.8, 145.3, 137.3, 131.4, 130.4, 128.9, 125.4, 21.0, 12.0. HRMS (APCI) calculated for $C_{10}H_{11}OS_3$ $[M+H]^+$: 242.9967; Found: 242.9963.



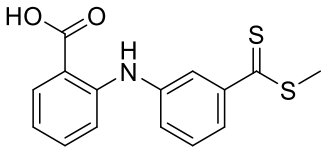
*Dimethyl benzene-1,3-dicarbodithioate (**20b**).* Synthesized according to procedure A, using 6 equiv. BF_3SMe_2 (6 mmol, 0.63 mL), from 1,3-bis(trifluoromethyl)benzene (0.5 mmol, 107.1 mg) or from 1-(trichloromethyl)-3-(trifluoromethyl)benzene (0.5 mmol, 131.7 mg). Heated in MW for 60 min. Purified over silica using 0-10% toluene in *i*-hexane gradient (rf = 0.37), affording 94.7 mg (73%) as a red solid from 1,3-bis(Trifluoromethyl)benzene and 106.2 mg (82%) as a red solid from 1-(trichloromethyl)-3-(trifluoromethyl)benzene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (ddd, *J* = 1.9, 0.5 Hz, 1H), 8.14 (dd, *J* = 7.8, 1.9 Hz, 2H), 7.41 (ddd, *J* = 7.8, 0.5 Hz, 1H), 2.80 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 227.8, 144.9, 130.2, 128.5, 125.0, 20.9. Data in accordance with reported literature.[13b]



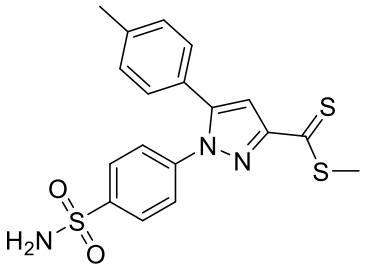
*Methyl phenyl carbonotrithioate (**21b**).* Synthesized according to procedure A from 4-(trifluoromethyl)benzonitrile (0.5 mmol, 89.1 mg). Heated in MW for 10 min. Purified over silica using 0-5% toluene in *i*-hexane gradient (rf = 0.32), affording 41.8 mg (42%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.58 (m, 2H), 7.56 – 7.46 (m, 3H), 2.64 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 226.2, 135.9, 131.0, 130.3, 129.7, 20.8. HRMS (APCI) calculated for $C_8H_9S_3$ $[M+H]^+$: 200.9861; Found: 200.9861.



*Methyl-dithioate-leflunomide (**22b**).* Synthesized according to procedure A from leflunomide (0.5 mmol, 135.1 mg). Heated in MW for 10 min. Purified over silica using 0-2% MeCN in DCM gradient (rf = 0.30), affording 51.9 mg (36%) as a pink solid. Mp: 160 - 162 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 9.10 (s, 1H), 8.11 – 8.05 (m, 2H), 7.87 – 7.80 (m, 2H), 2.78 (s, 3H), 2.69 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 226.9, 173.4, 159.5, 149.0, 143.3, 139.3, 127.5, 119.3, 119.2, 111.8, 20.2, 12.2. HRMS (ESI) calculated for $C_{13}H_{11}N_2O_2S_2$ [M-H]$^-$: 291.0267; Found: 291.0263.



*Methyl-dithioate-flufenamic acid (**23b**).* Synthesized according to modified procedure A from flufenamic acid (0.5 mmol, 140.6 mg). Heated conventionally at 80ºC for 18 h. Purified over silica using 0-25% EtOAc in *i*-hexane gradient with 1% formic acid modifier (rf = 0.44), affording 101.0 mg (67%) as an orange solid. Mp: 148 - 150 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.20 (s, 1H), 9.71 (s, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 6.86 (t, *J* = 7.5 Hz, 1H), 2.78 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 229.0, 169.8, 145.9, 145.5, 141.2, 134.2, 132.0, 129.9, 124.7, 120.3, 118.5, 118.0, 114.5, 113.8, 20.5. HRMS (ES+) calculated for $C_{15}H_{14}NO_2S_2$ [M+H]$^+$: 304.0466; Found: 304.0466.



*Methyl-dithioate-celecoxib (**24b**).* Synthesized according to procedure A from celecoxib (0.5 mmol, 190.7 mg). Heated in MW for 120 min. Purified over silica using 0-10% MeCN in toluene gradient (rf = 0.16), affording 53.5 mg (27%) as a red solid. Mp: 177 - 180 ºC. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.91 – 7.86 (m, 2H), 7.58 – 7.53 (m, 2H), 7.51 (s, 2H), 7.21 (s, 4H), 7.20 (s, 1H), 2.75 (s, 3H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d$_6$) δ 217.9, 156.0, 145.1, 143.8, 141.4, 138.9, 129.4, 128.7, 126.8, 125.8, 125.6, 108.7, 20.8, 18.5. HRMS (ES+) calculated for $C_{18}H_{18}N_3O_2S_3$ [M+H]$^+$: 404.0561; Found: 404.0564.

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13 *(b)* I. Abrunhosa, M. Gulea and S. Masson, Synthesis (Stuttg)., 2004, 928–934.

17 *(a)* S. T. Keaveney and F. Schoenebeck, *Angew. Chemie Int. Ed.*, 2018, **57**, 4073–4077. *(b)* R. Devine, M. Kelada, S. Leonard, D. S. D. Martin, J. M. D. Walsh, C. J. Breen, R. B. Driver, G. K. Kinsella, J. B. C. Findlay and J. C. Stephens, *Eur. J. Med. Chem.*, 2020, **202**, 112416. *(c)* S. Kato, N. Kitaoka, O. Niyomura, Y. Kitoh, T. Kanda and M. Ebihara, *Inorg. Chem.*, 1999, **38**, 496–506. *(d)* S. Furuta, M. Kuroboshi and T. Hiyama, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 805–819. *(e)* T. Roberie, N. S. Bhacca, D. Lankin and J. Selbin, *Can. J. Chem.*, 1980, **58**, 2314–2317. *(f)* R. Takayama, A. Yamada, K. Fuchibe and J. Ichikawa, *Org. Lett.*, 2017, **19**, 5050–5053. *(g)* A. Acharya, S. Vijay Kumar, B. Saraiah and H. Ila, *J. Org. Chem.*, 2015, **80**, 2884–2892.

NMR Spectra of **1b** - **24b**

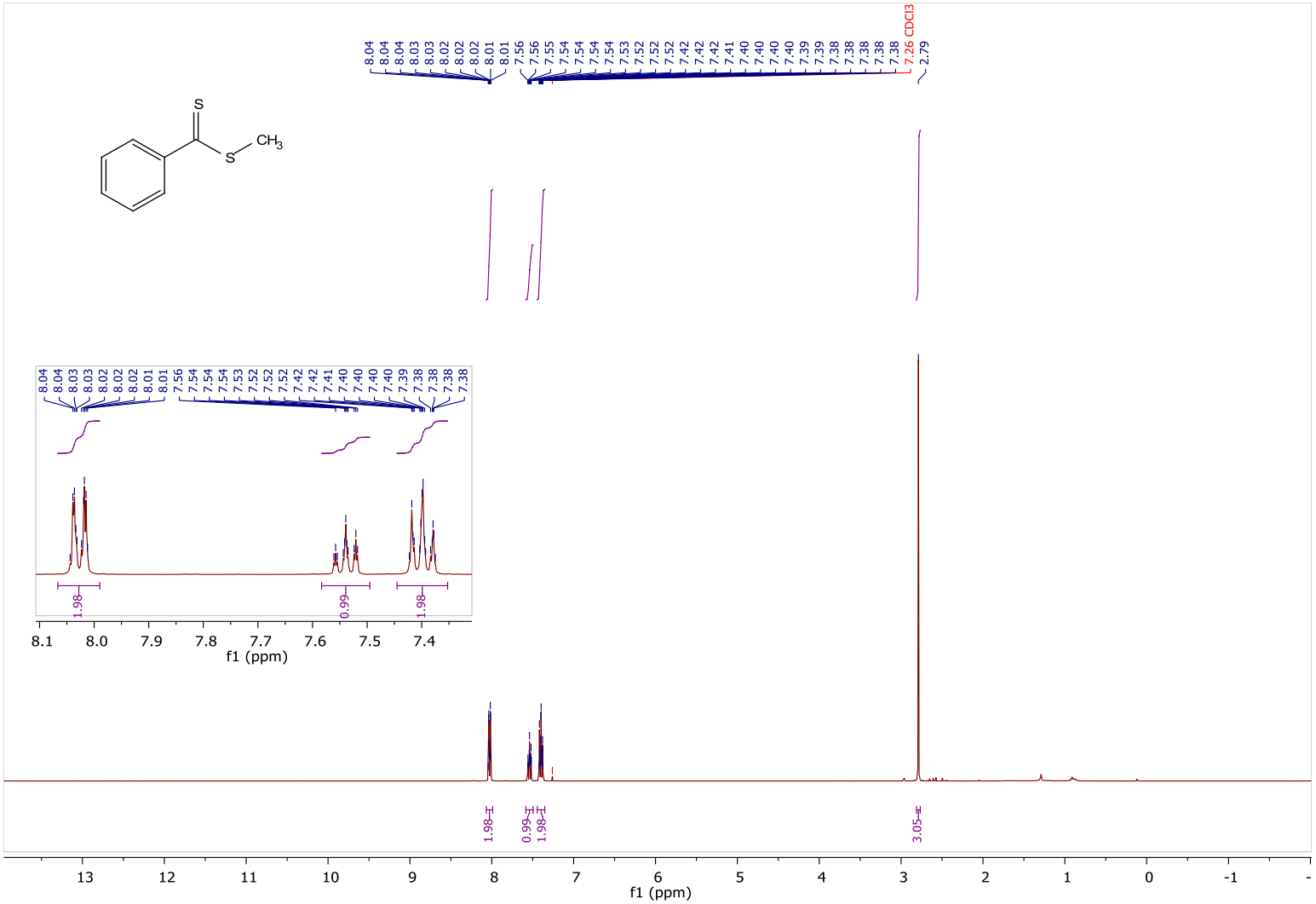

Figure S8. ^{1}H-NMR (400 MHz, $CDCl_3$) of **1b.**

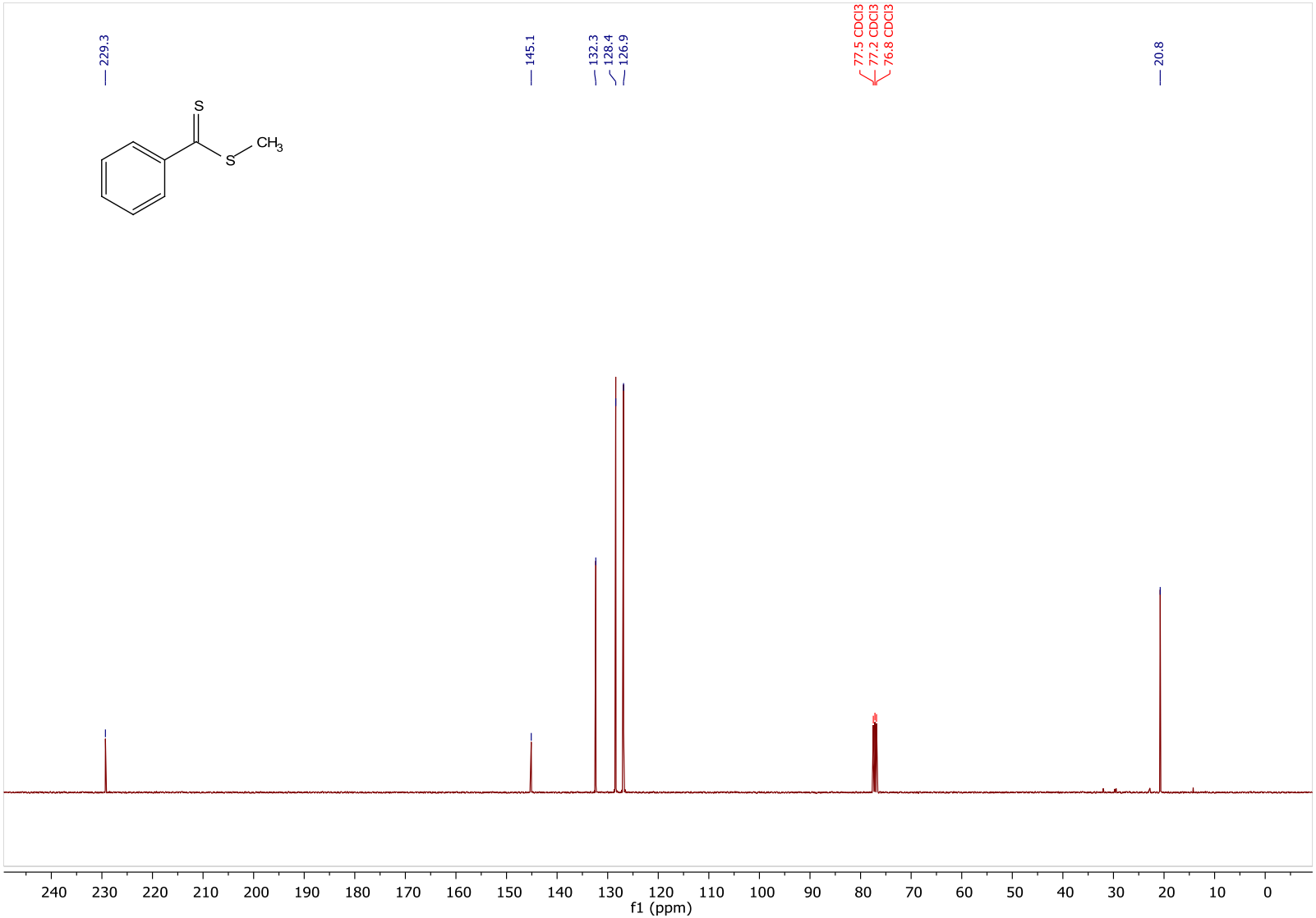

Figure S9. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **1b.**

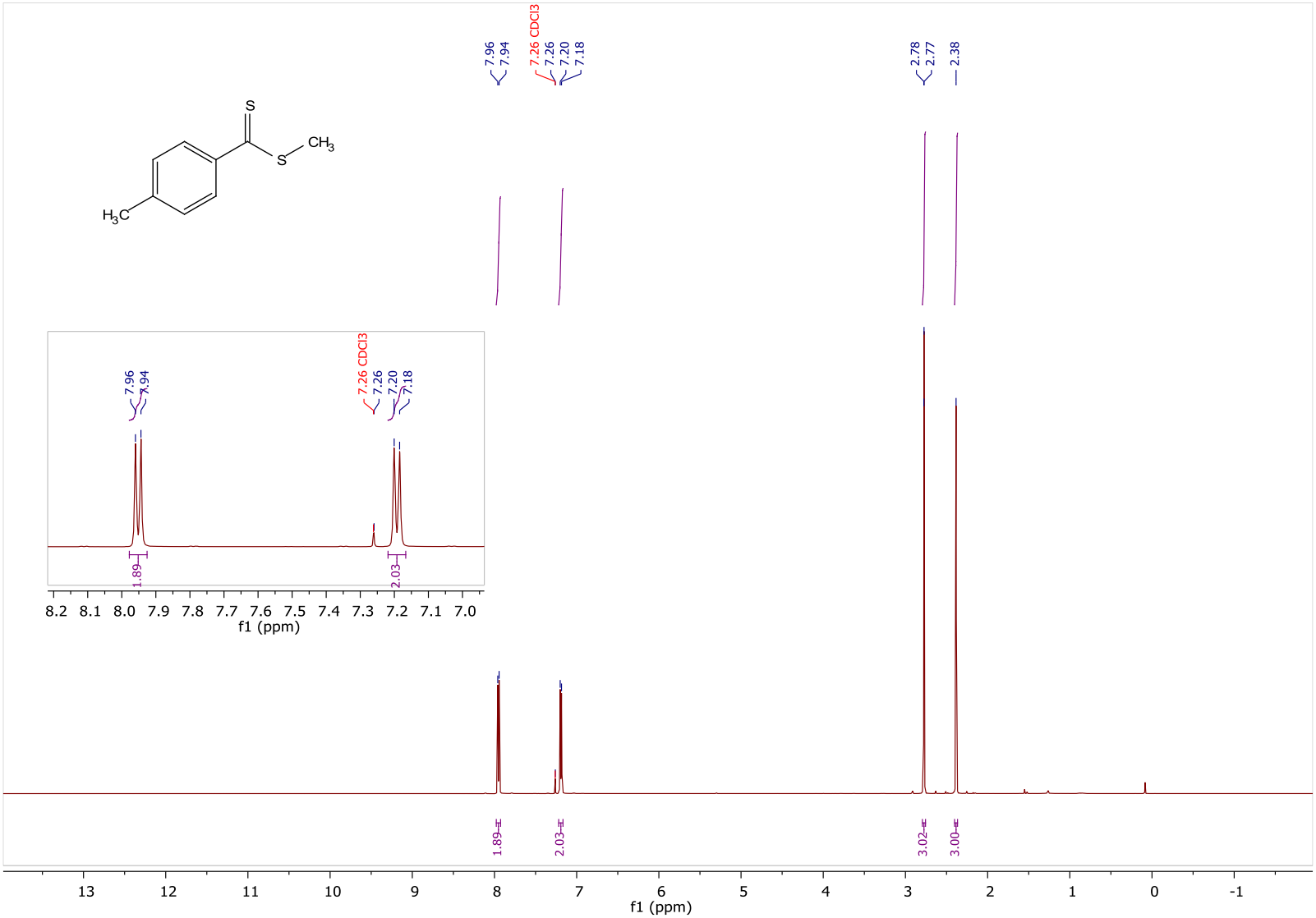

Figure S10. ^{1}H-NMR (500 MHz, $CDCl_3$) of **2b.**

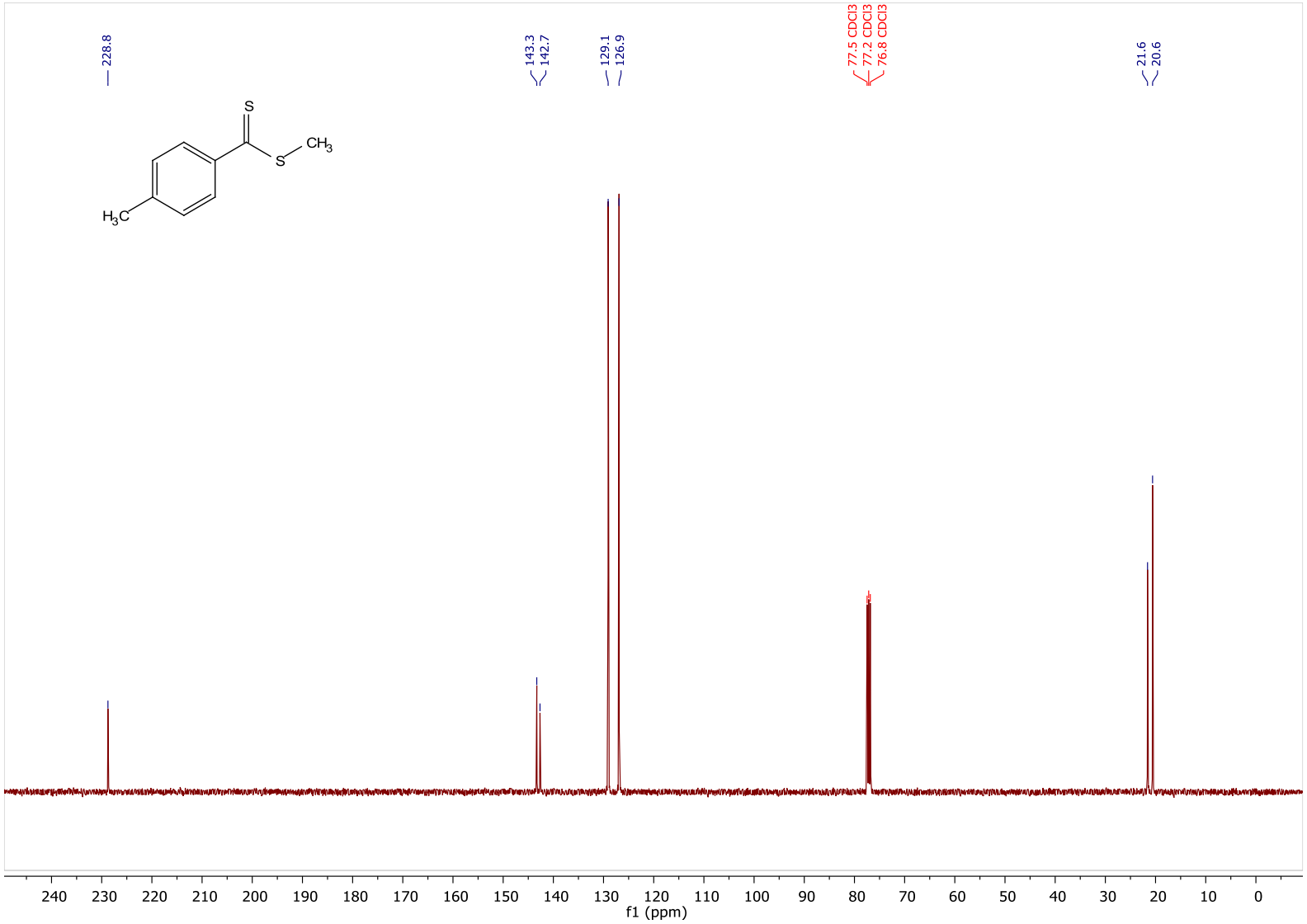

Figure S11. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **2b.**

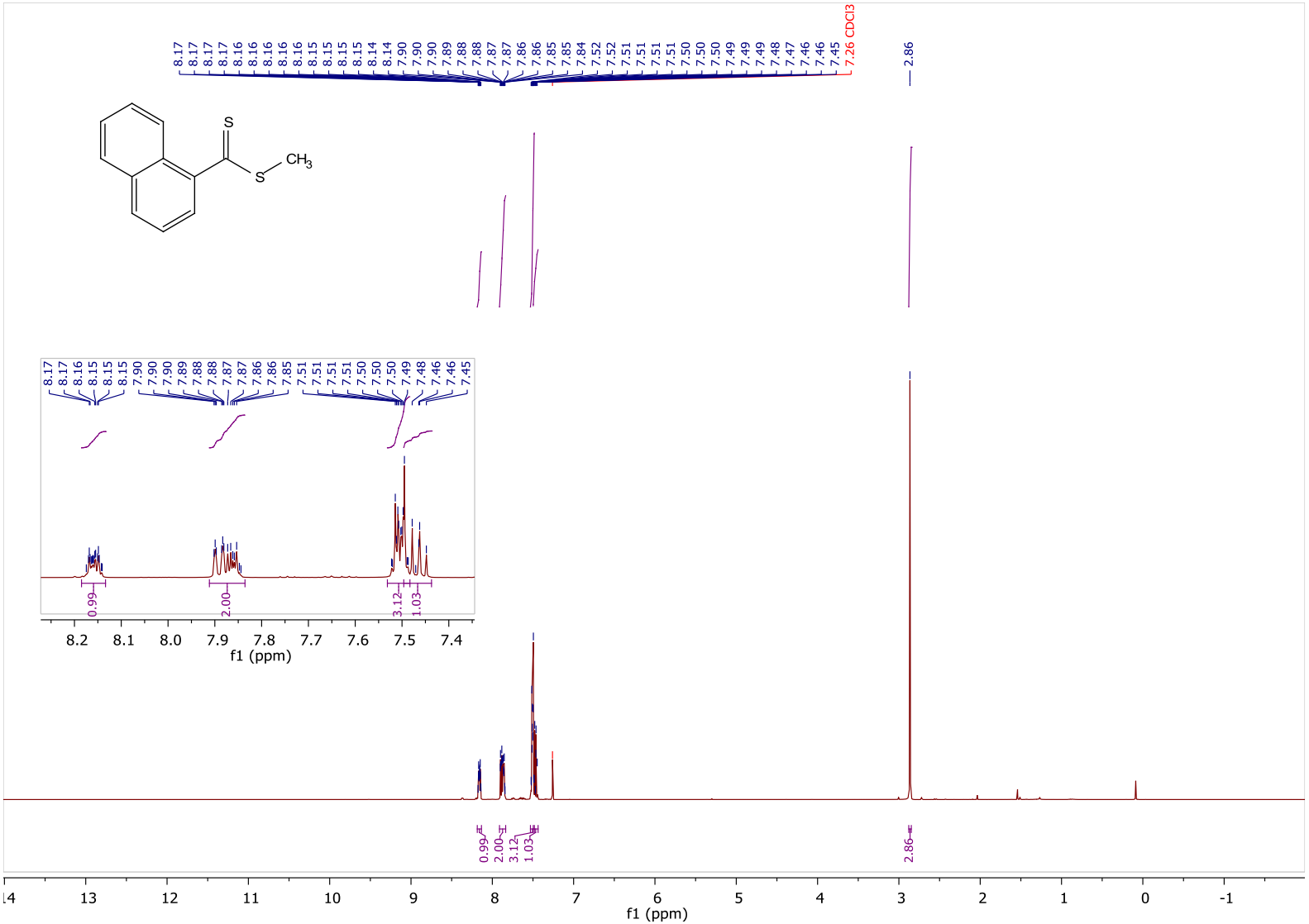

Figure S12. ^{1}H-NMR (500 MHz, $CDCl_3$) of **3b.**

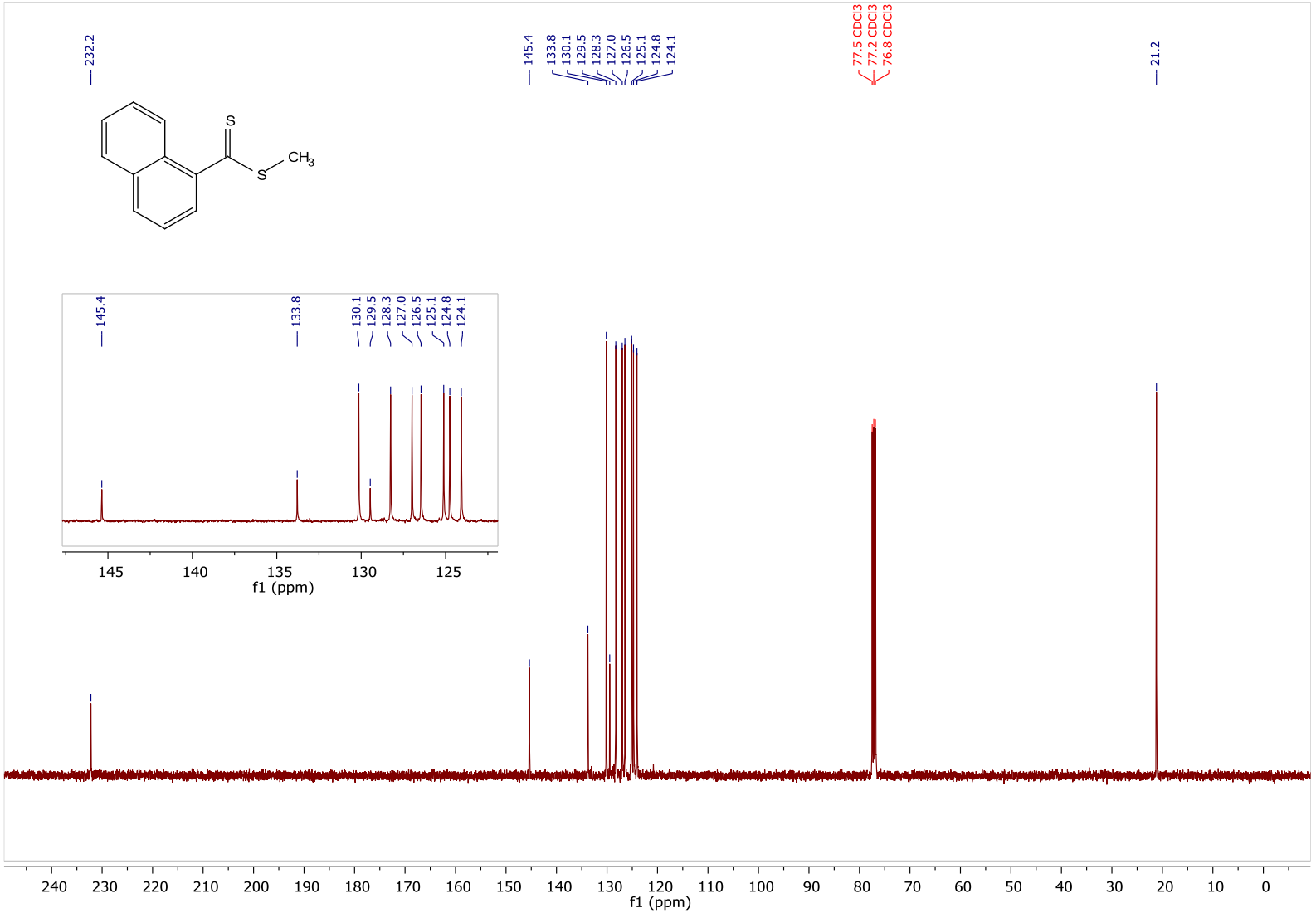

Figure S13. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **3b.**

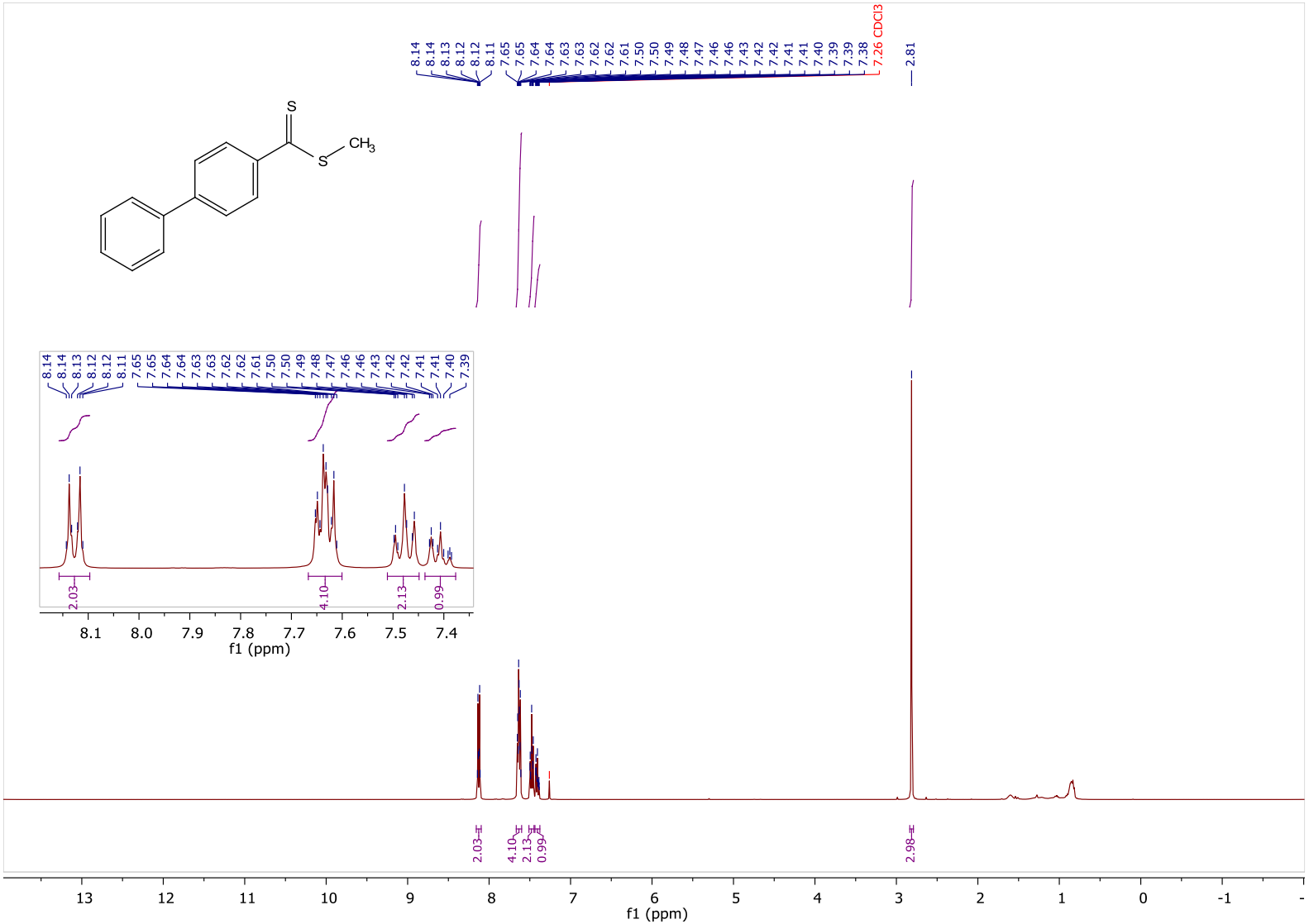

Figure S14. ^{1}H-NMR (400 MHz, $CDCl_3$) of **4b.**

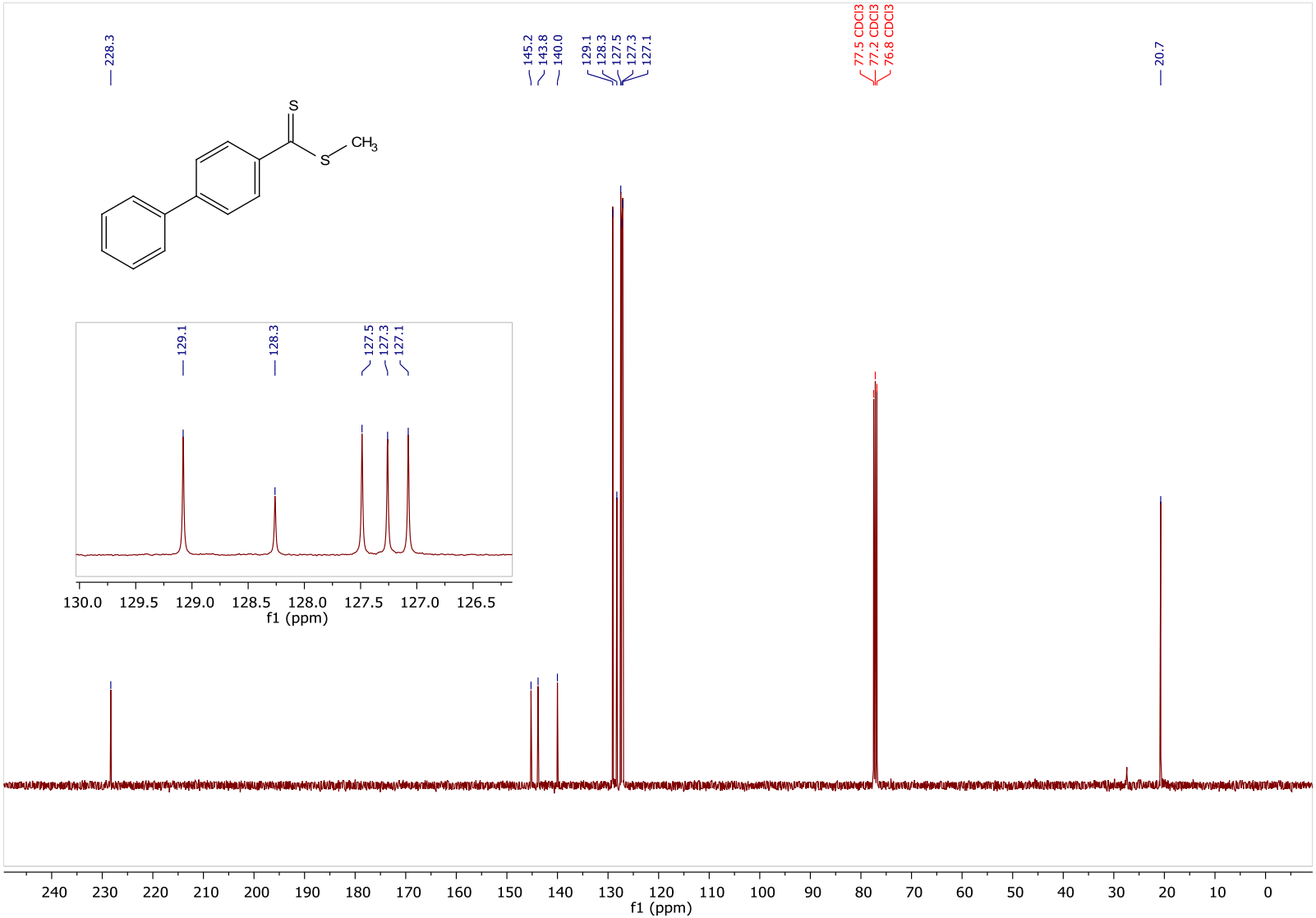

Figure S15. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **4b.**

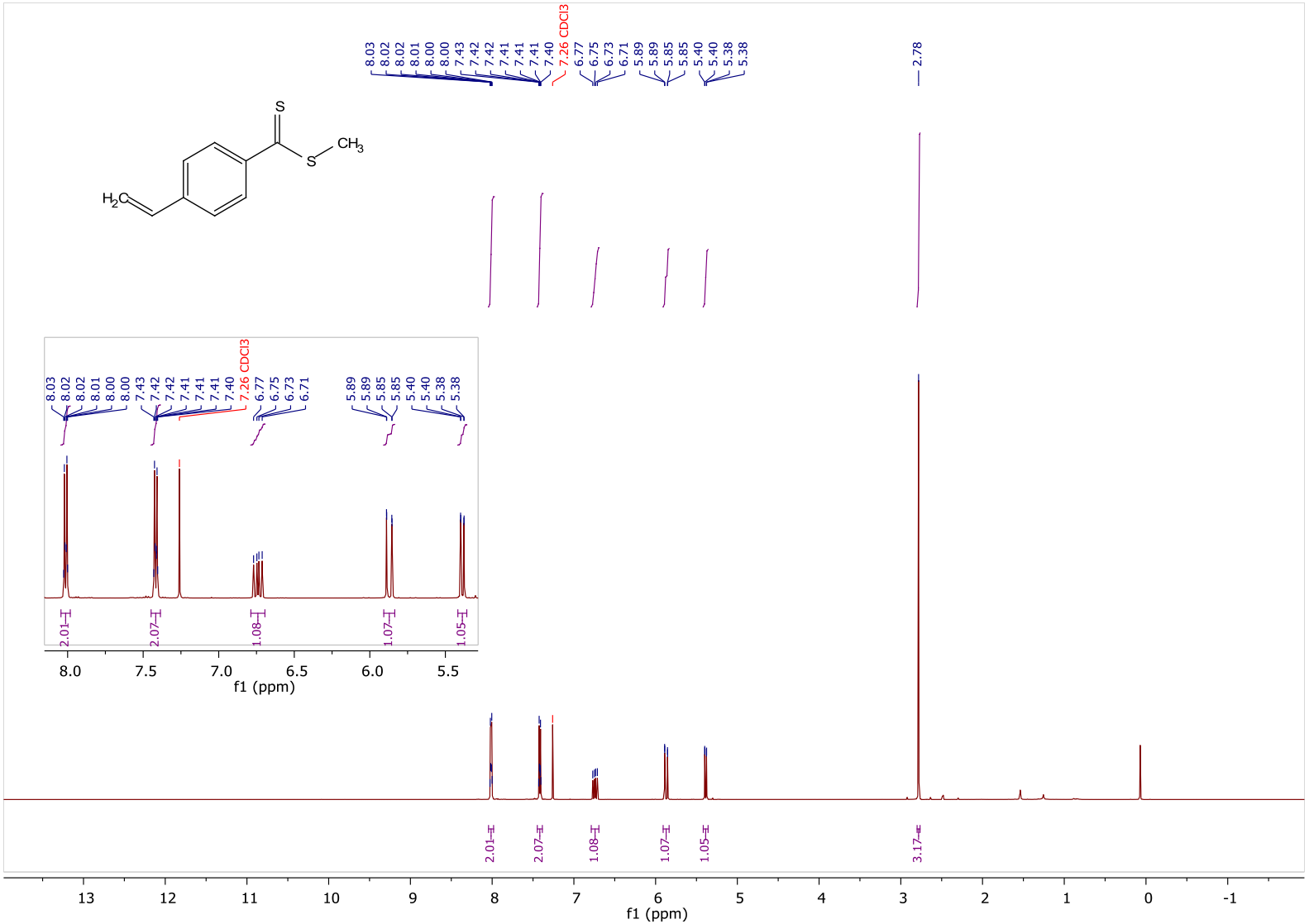

Figure S16. ^{1}H-NMR (500 MHz, $CDCl_3$) of **5b.**

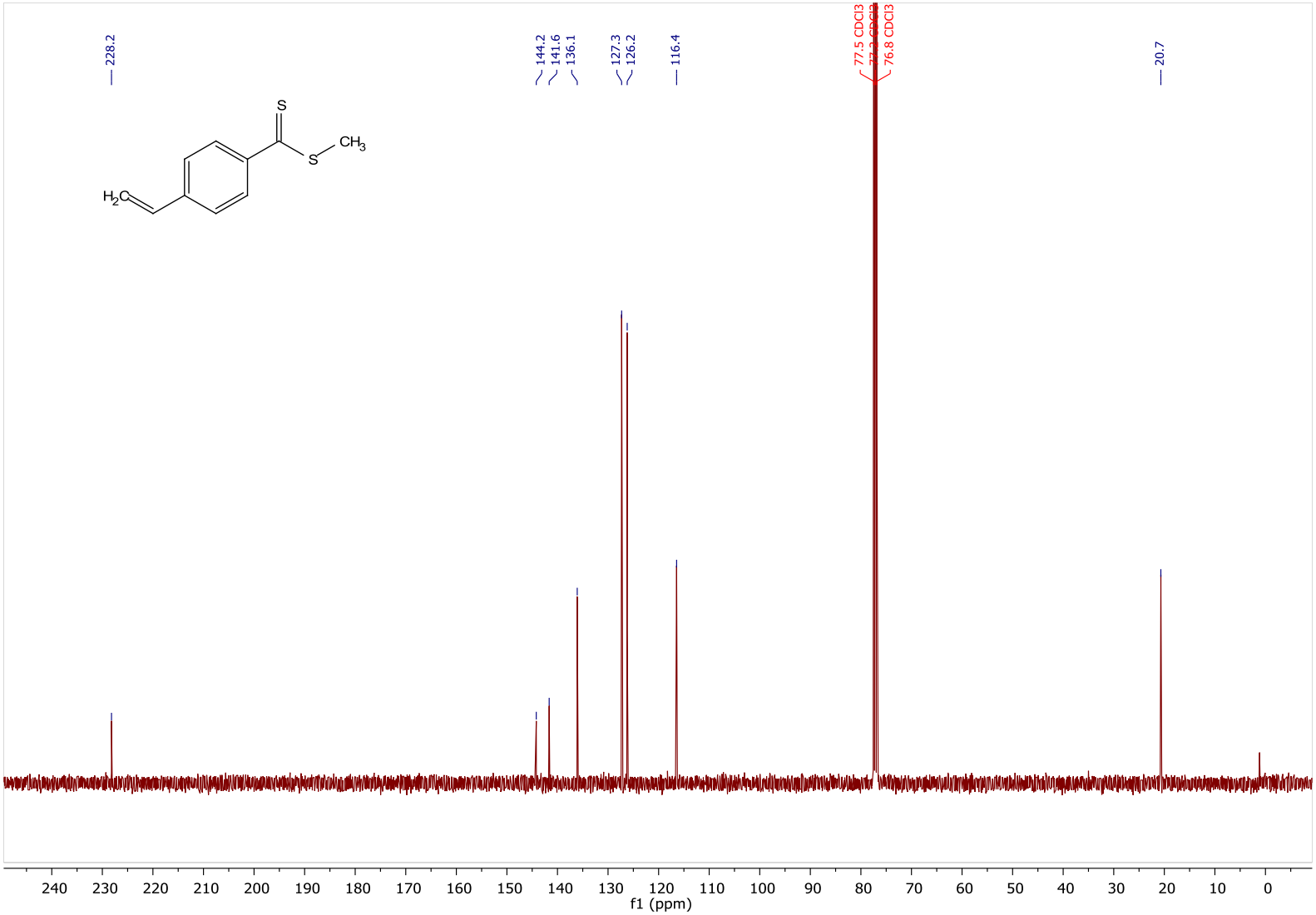

Figure S17. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **5b.**

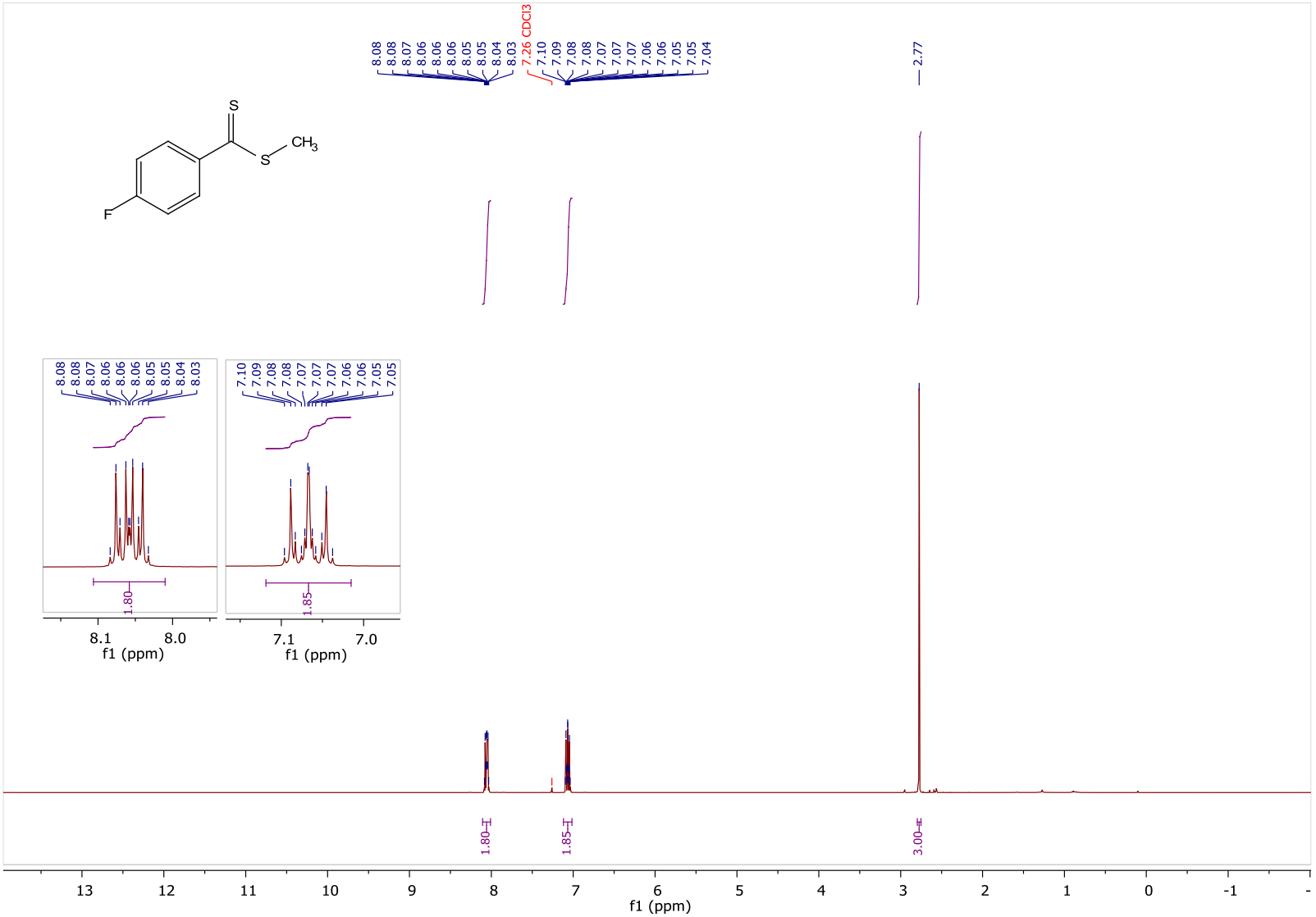

Figure S18. ^{1}H-NMR (400 MHz, $CDCl_3$) of **6b.**

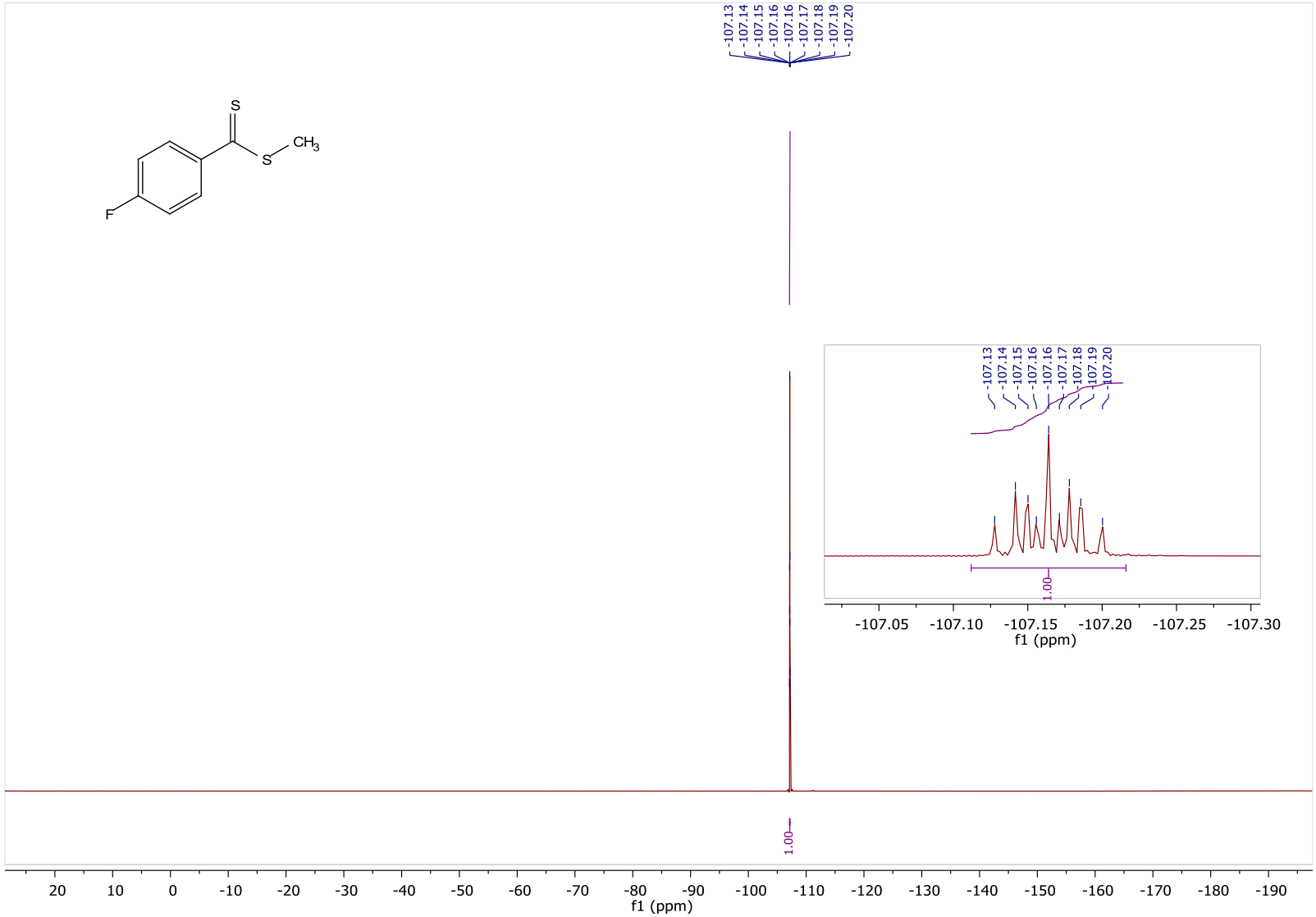

Figure S19. ^{19}F NMR (376 MHz, $CDCl_3$) of **6b.**

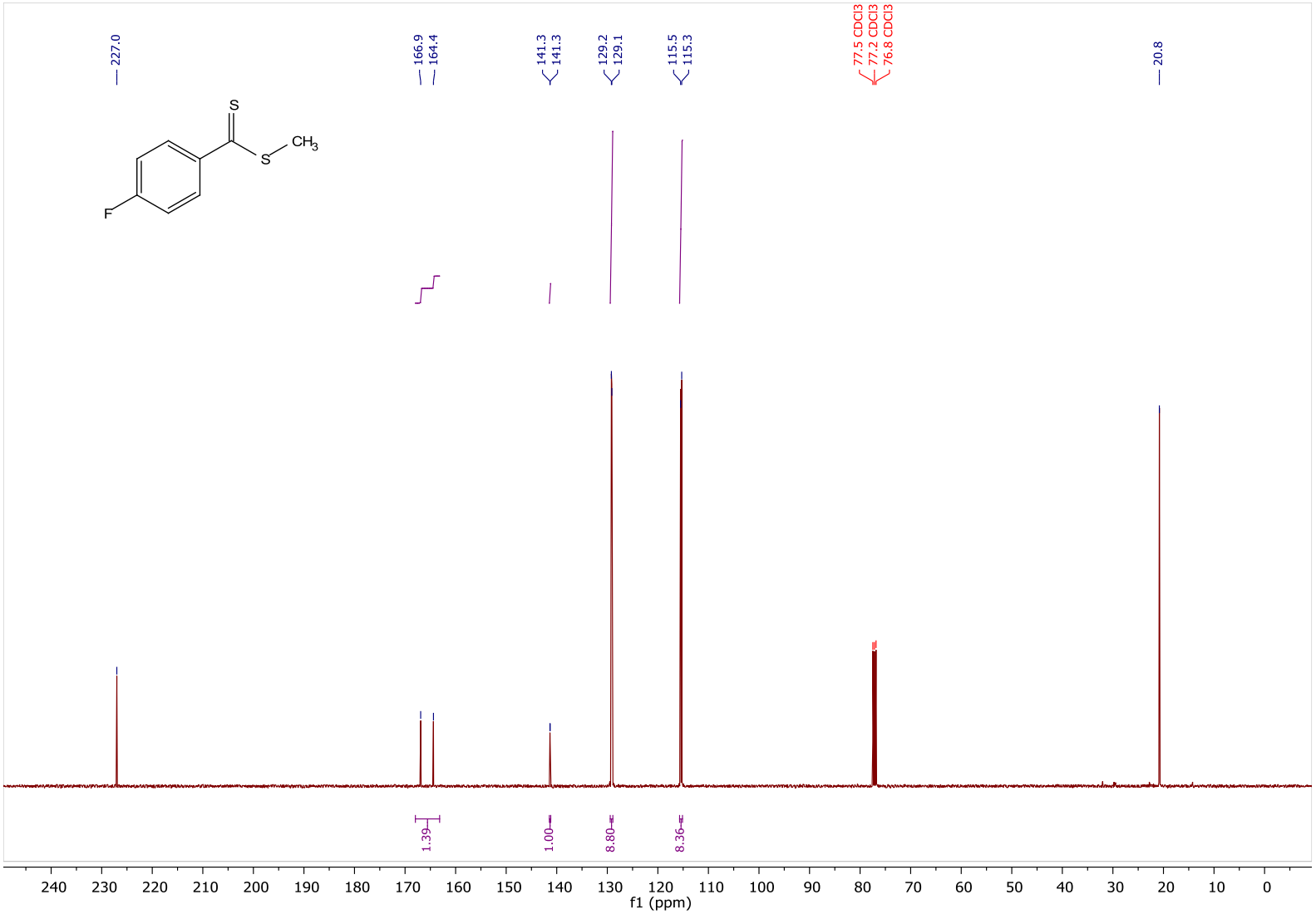

Figure S20. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **6b.**

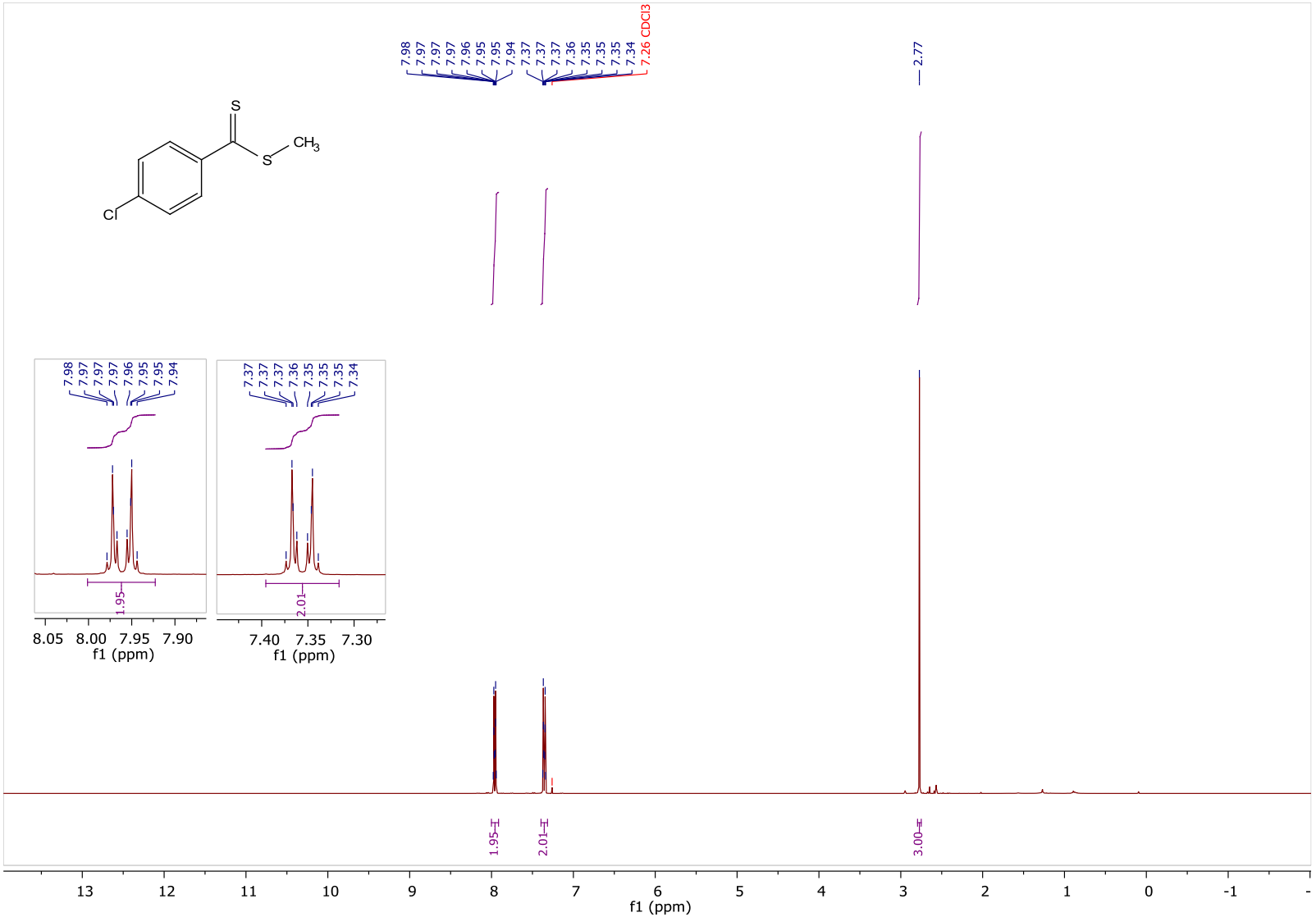

Figure S21. ^{1}H-NMR (400 MHz, $CDCl_3$) of **7b.**

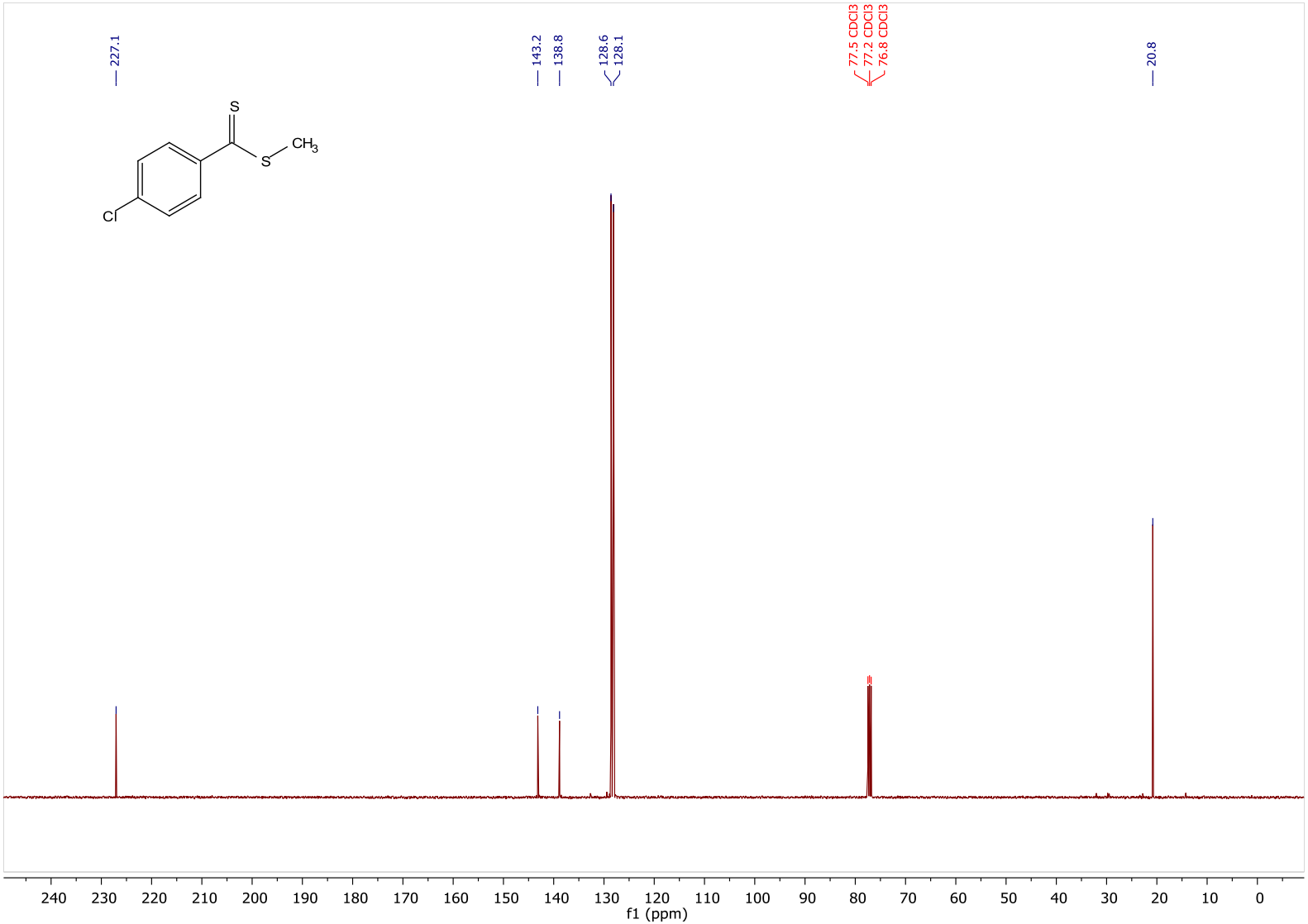

Figure S22. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **7b.**

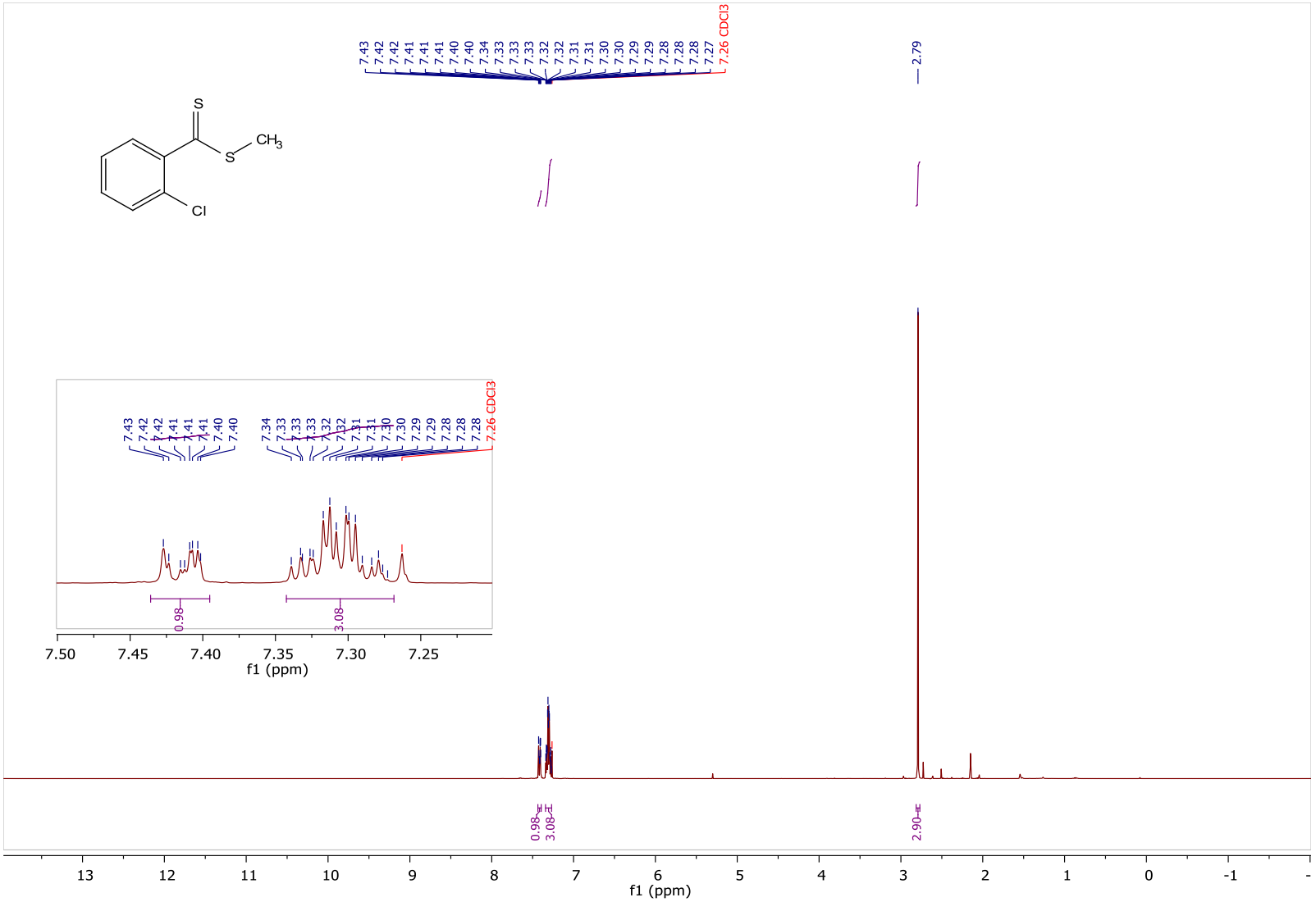

Figure S23. ^{1}H-NMR (400 MHz, $CDCl_3$) of **8b.**

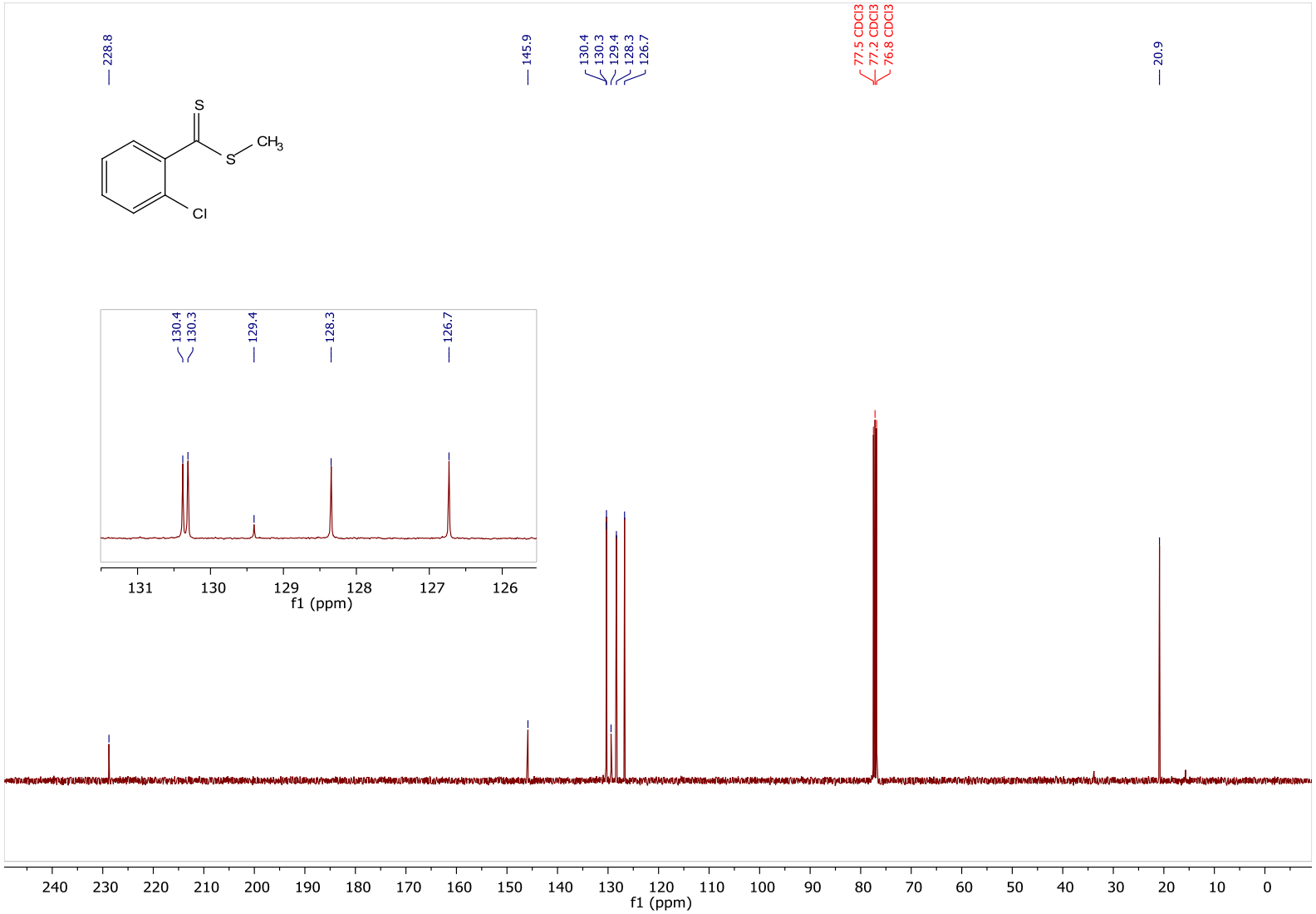

Figure S24. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **8b.**

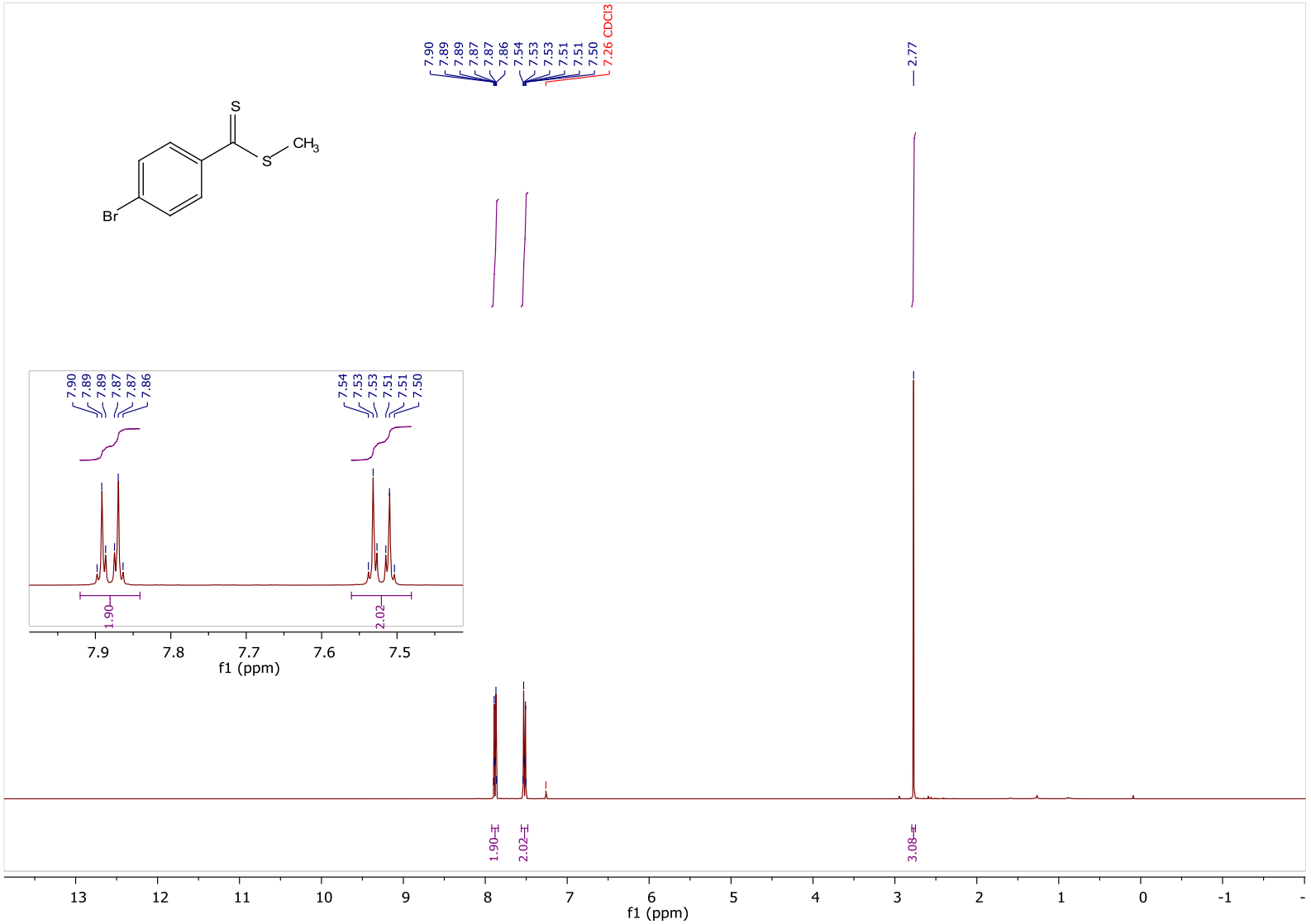

Figure S25. ^{1}H-NMR (400 MHz, $CDCl_3$) of **9b.**

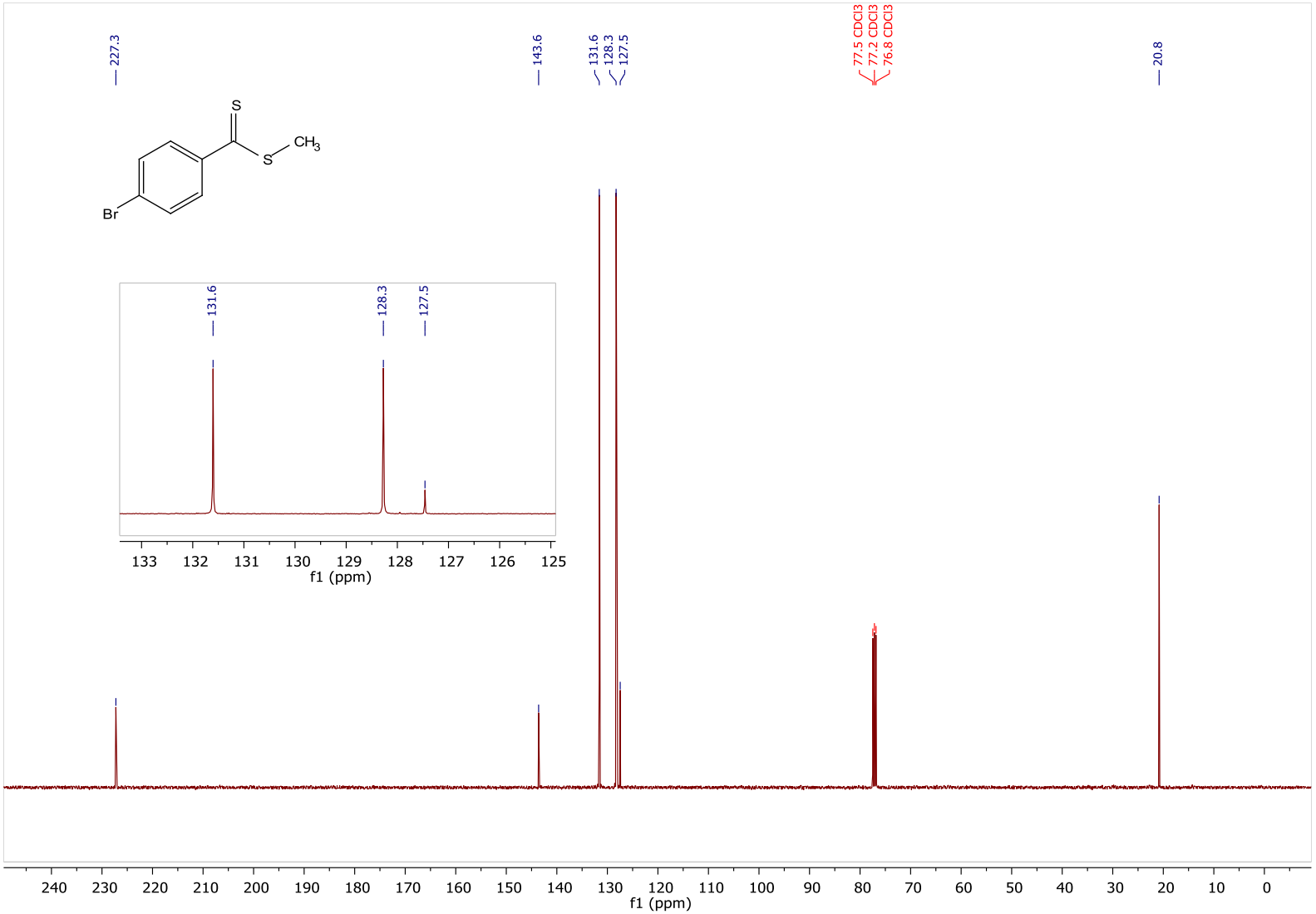

Figure S26. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **9b.**

Figure S27. ^{1}H-NMR (500 MHz, $CDCl_3$) of **9b'.**

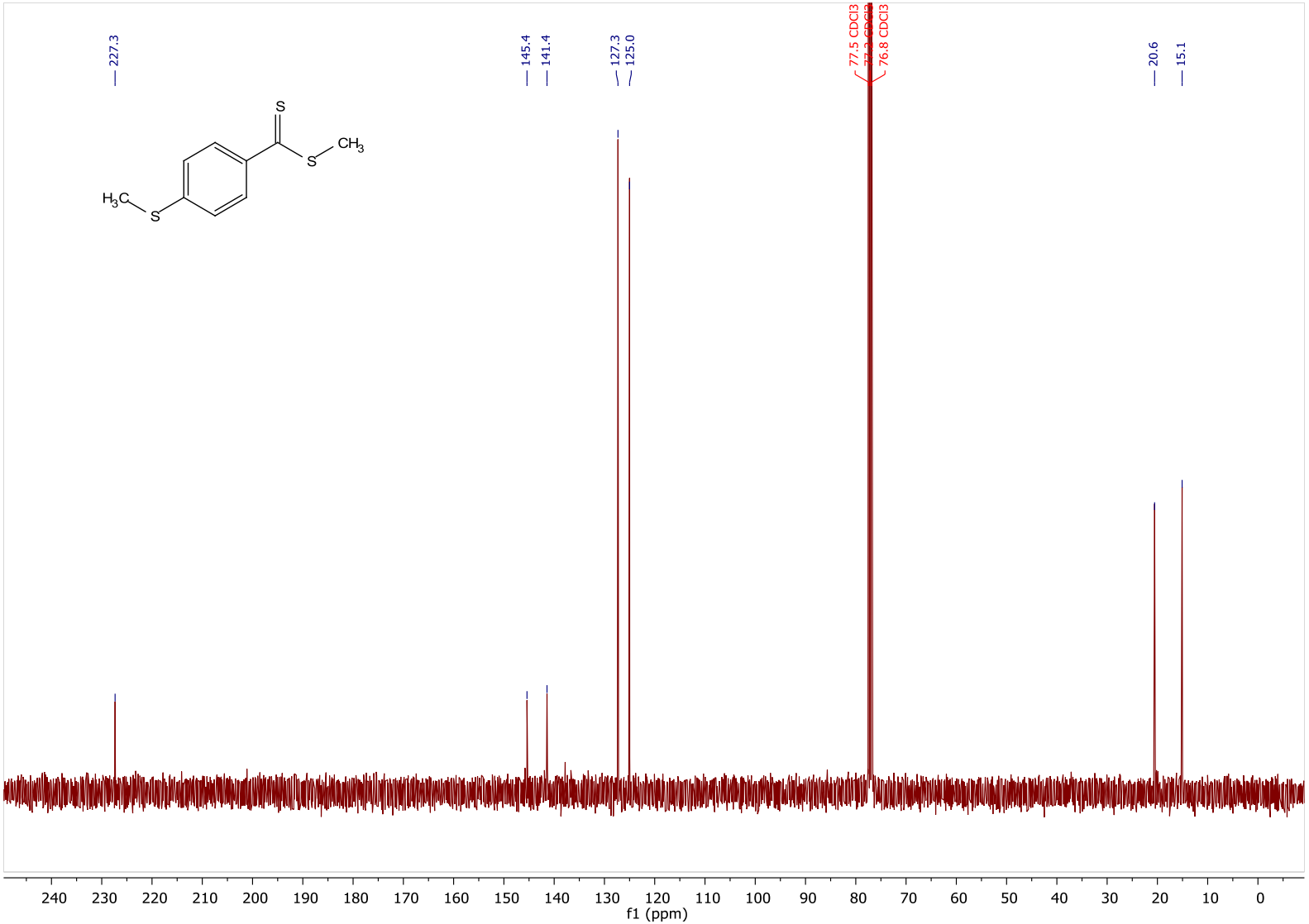

Figure S28. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **9b'.**

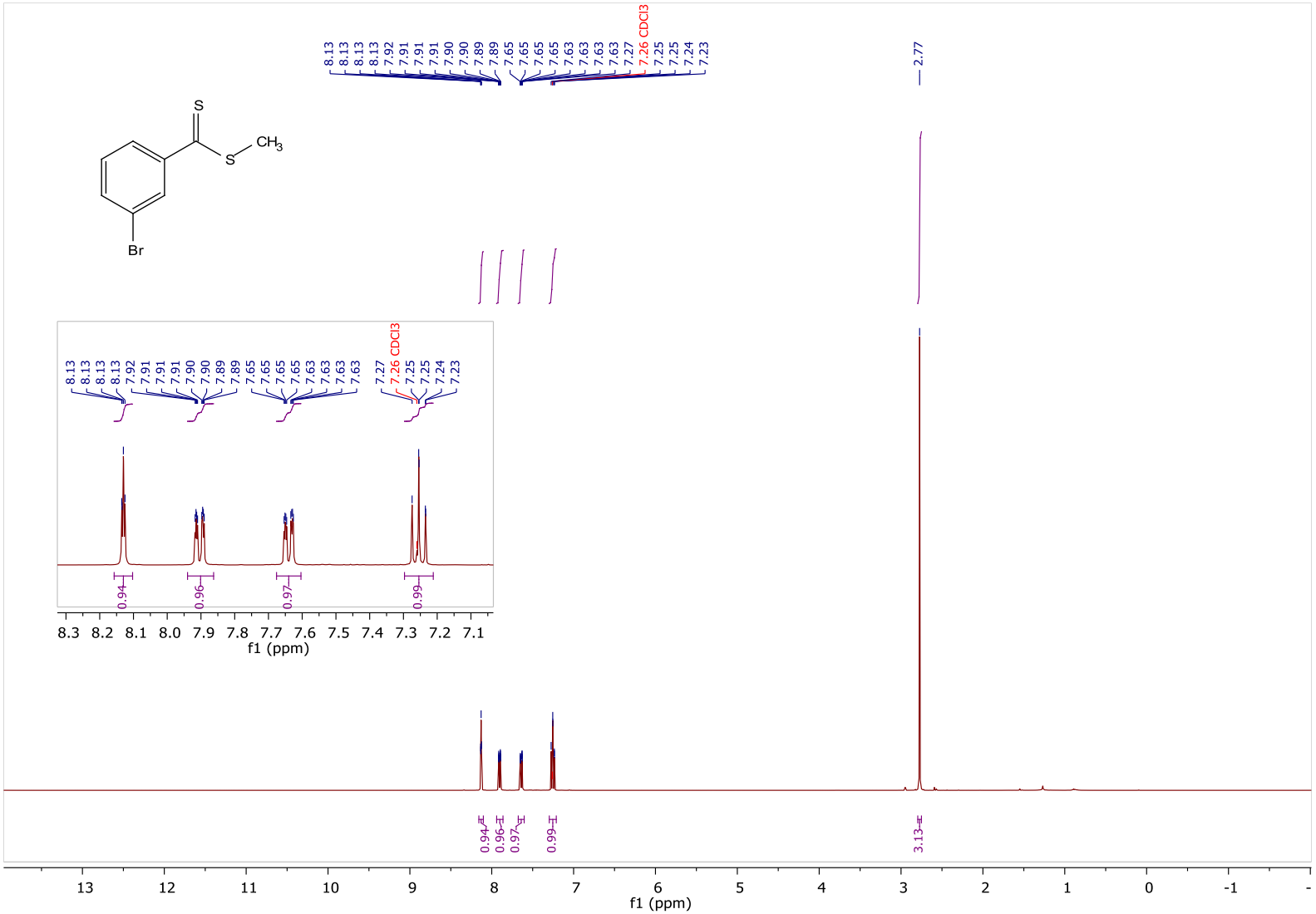

Figure S29. ^{1}H-NMR (400 MHz, $CDCl_3$) of **10b.**

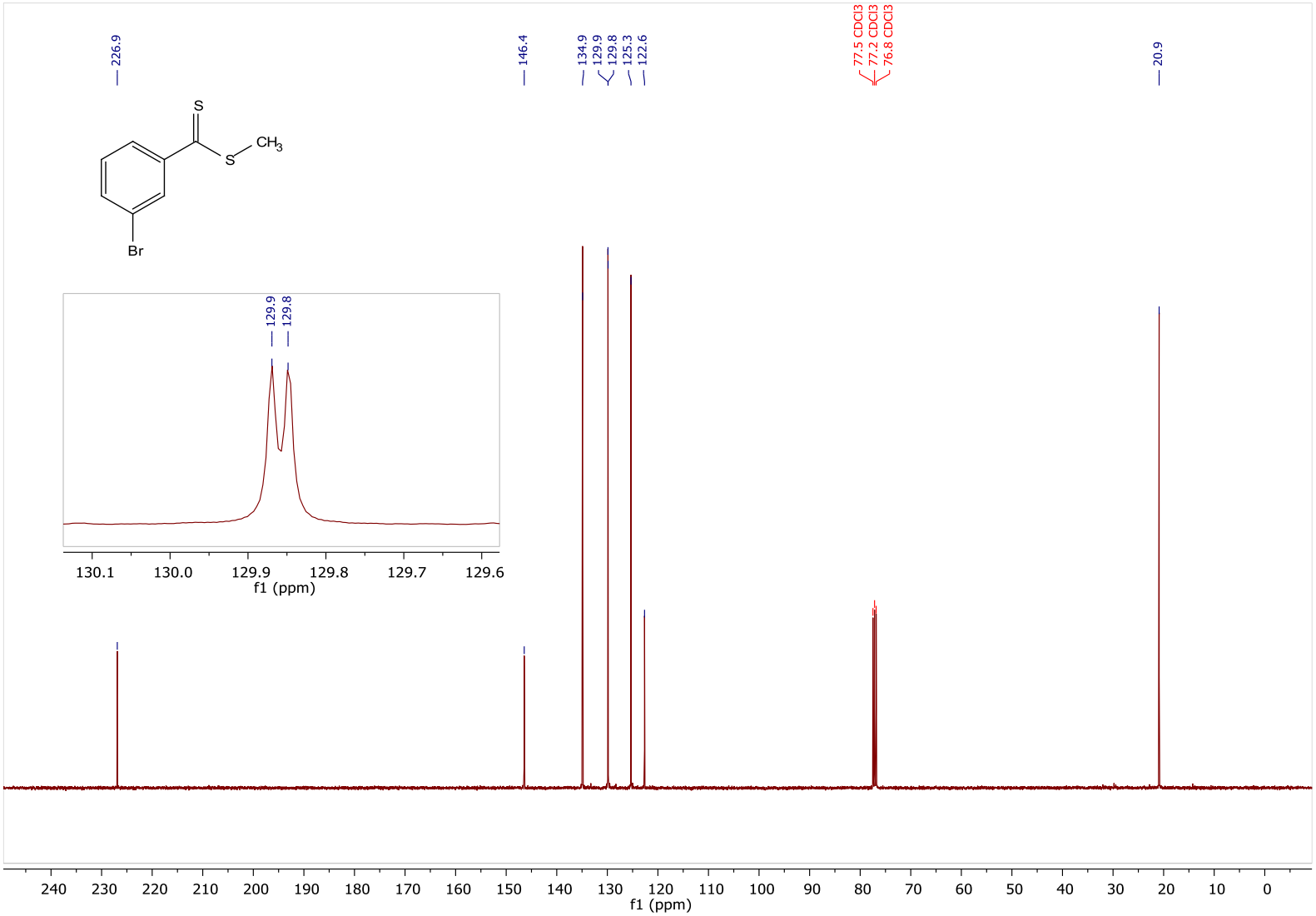

Figure S30. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **10b.**

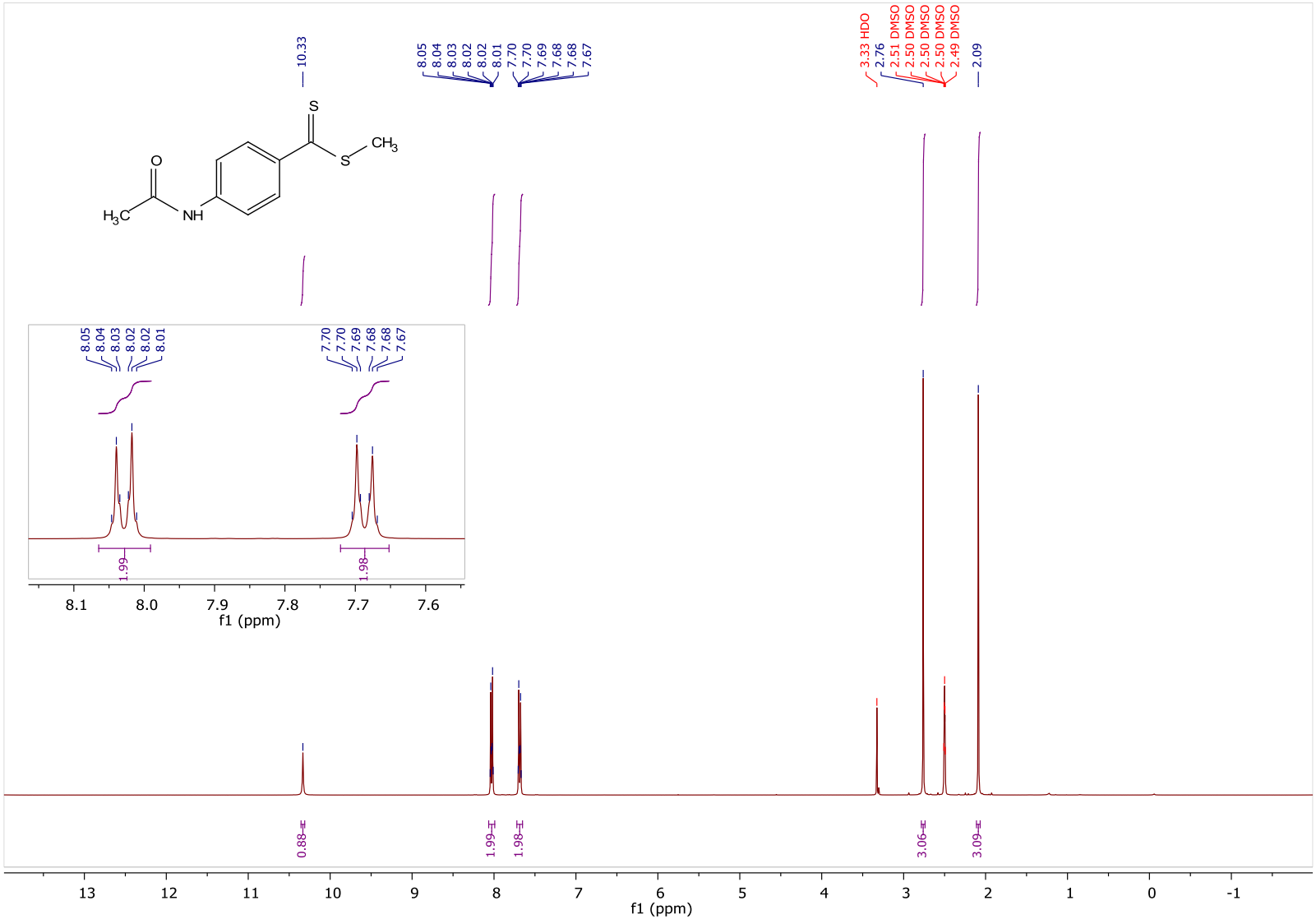

Figure S31. ^{1}H-NMR (400 MHz, DMSO-d_6) of **11b.**

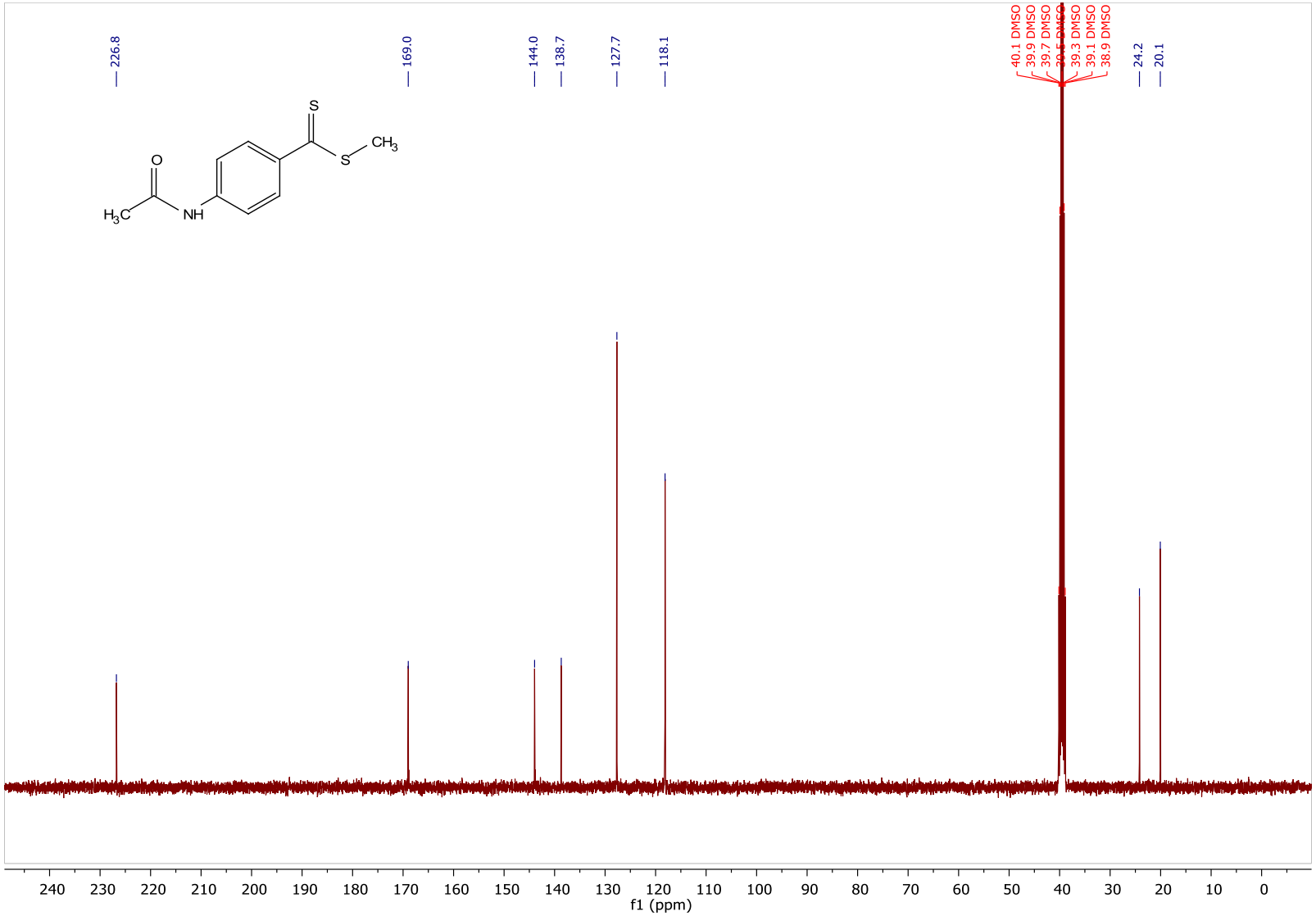

Figure S32. $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) of **11b.**

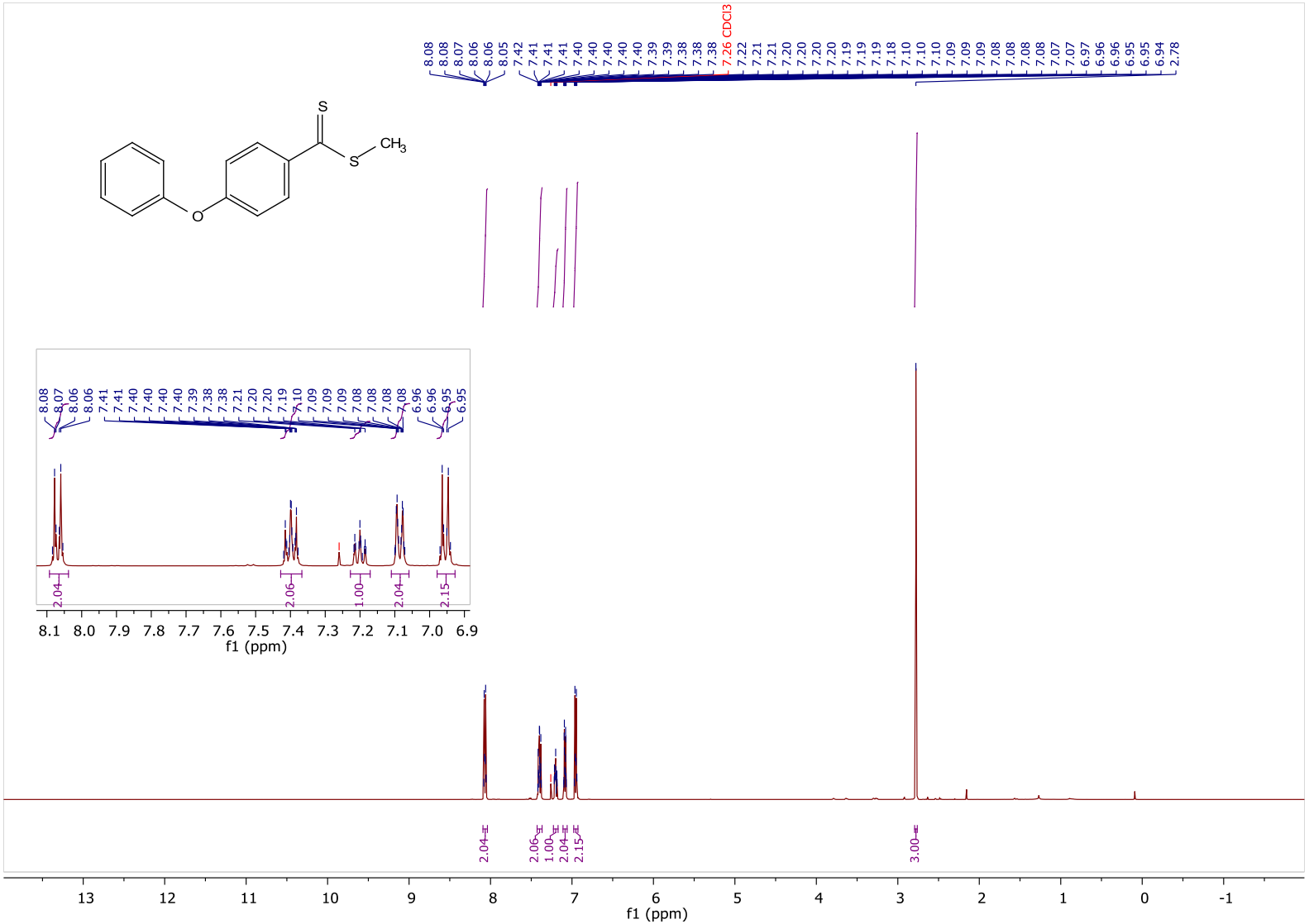

Figure S33. ^{1}H-NMR (500 MHz, $CDCl_3$) of **12b.**

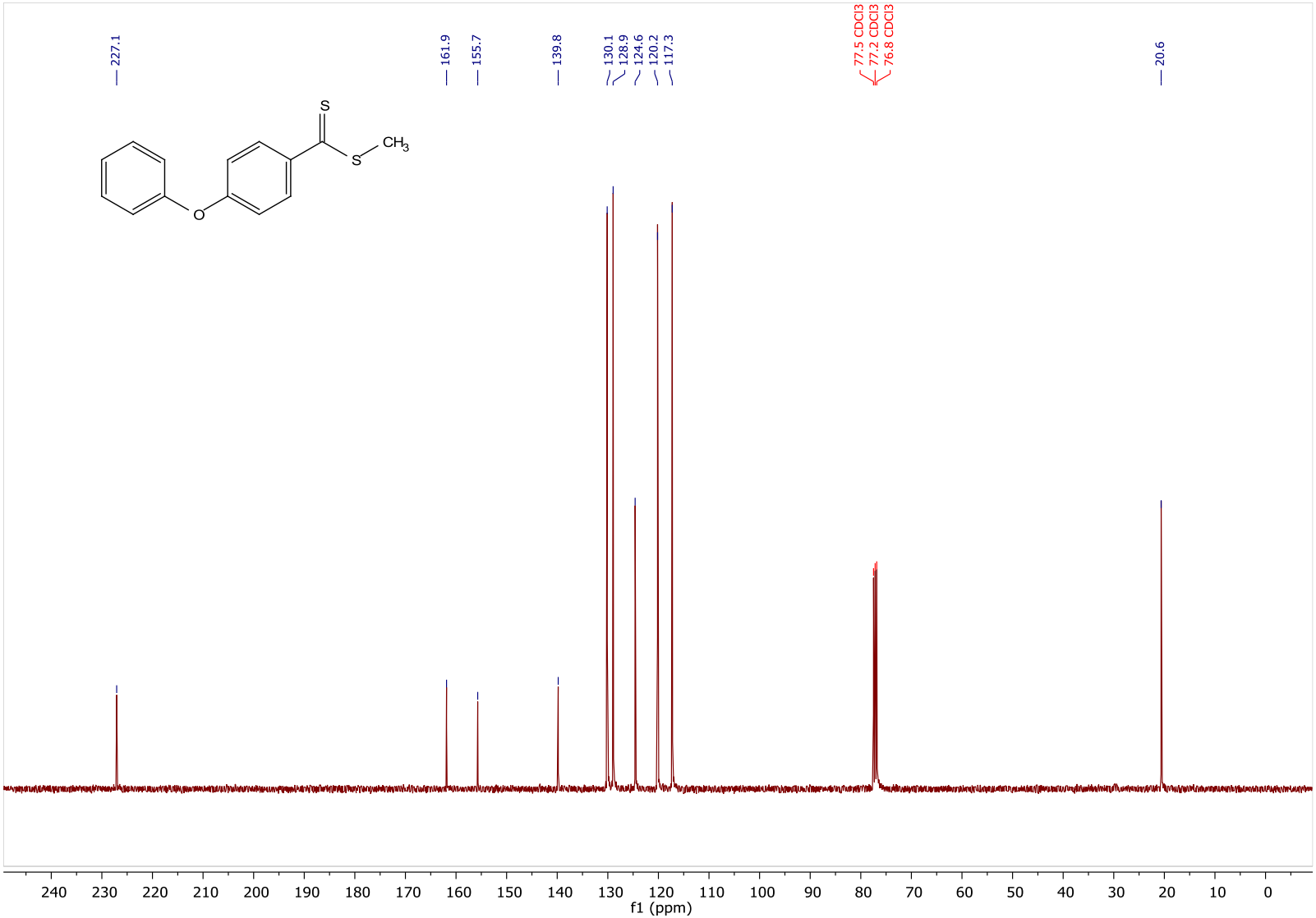

Figure S34. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **12b.**

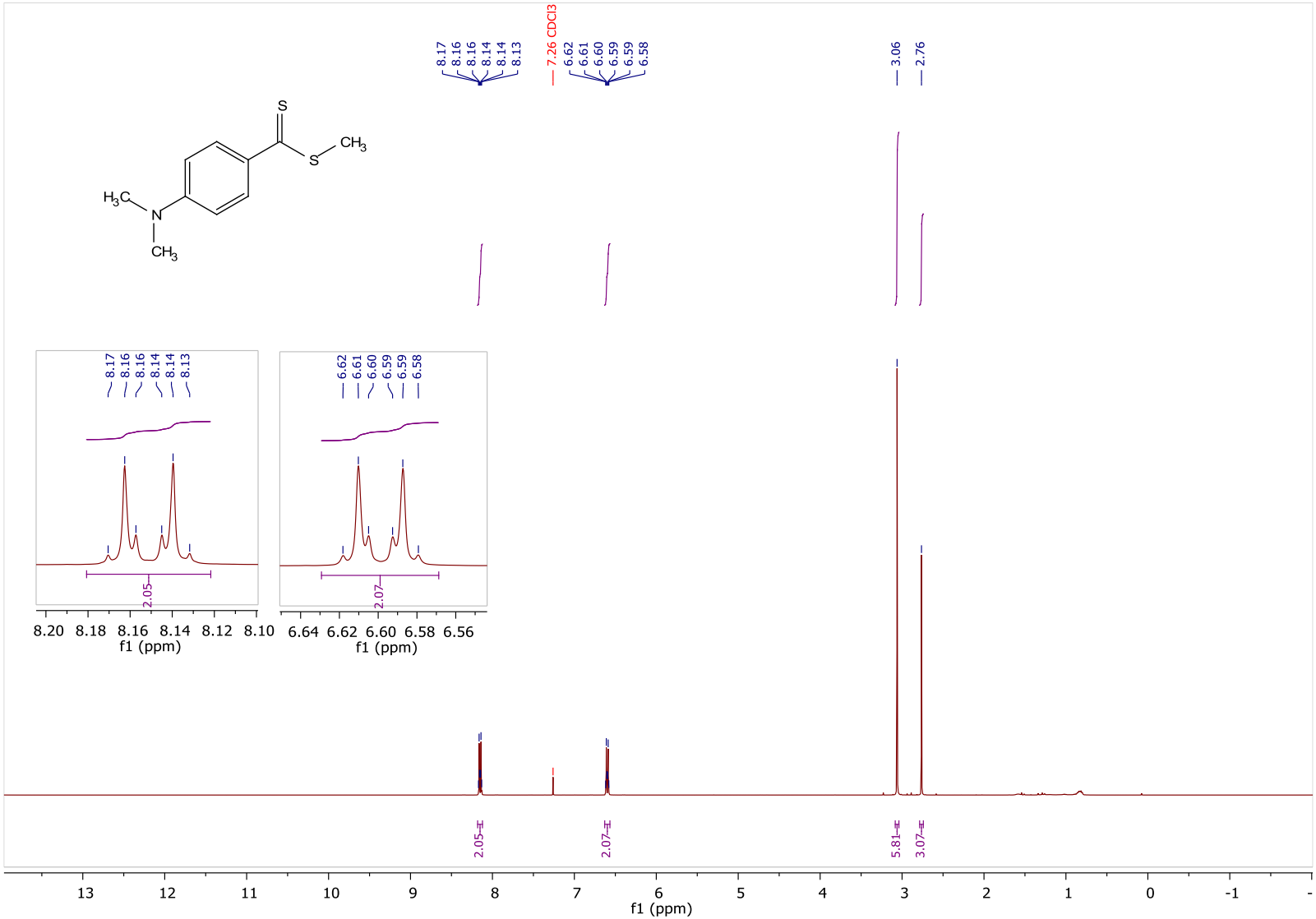

Figure S35. ^{1}H-NMR (400 MHz, $CDCl_3$) of **13b.**

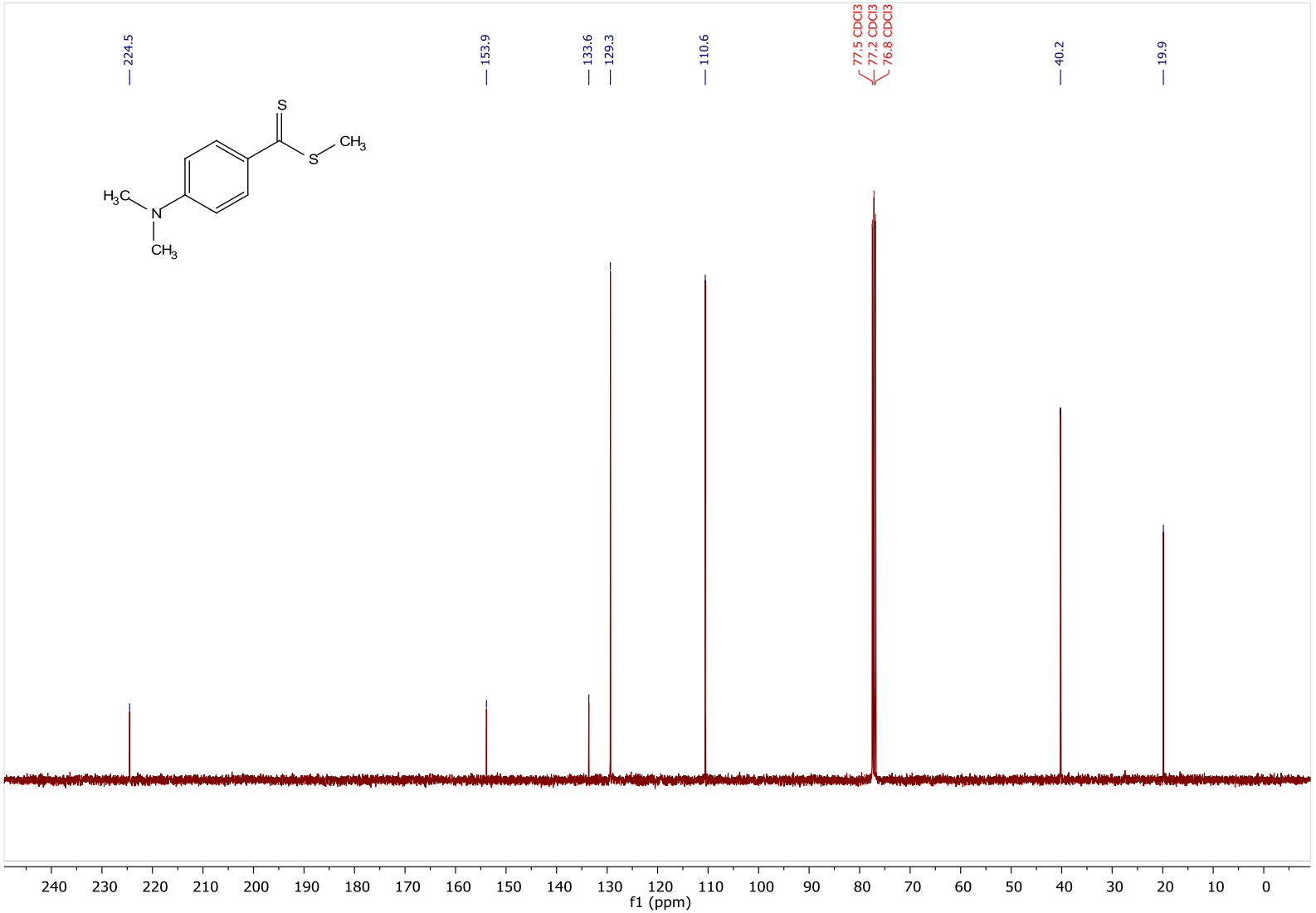

Figure S36. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **13b.**

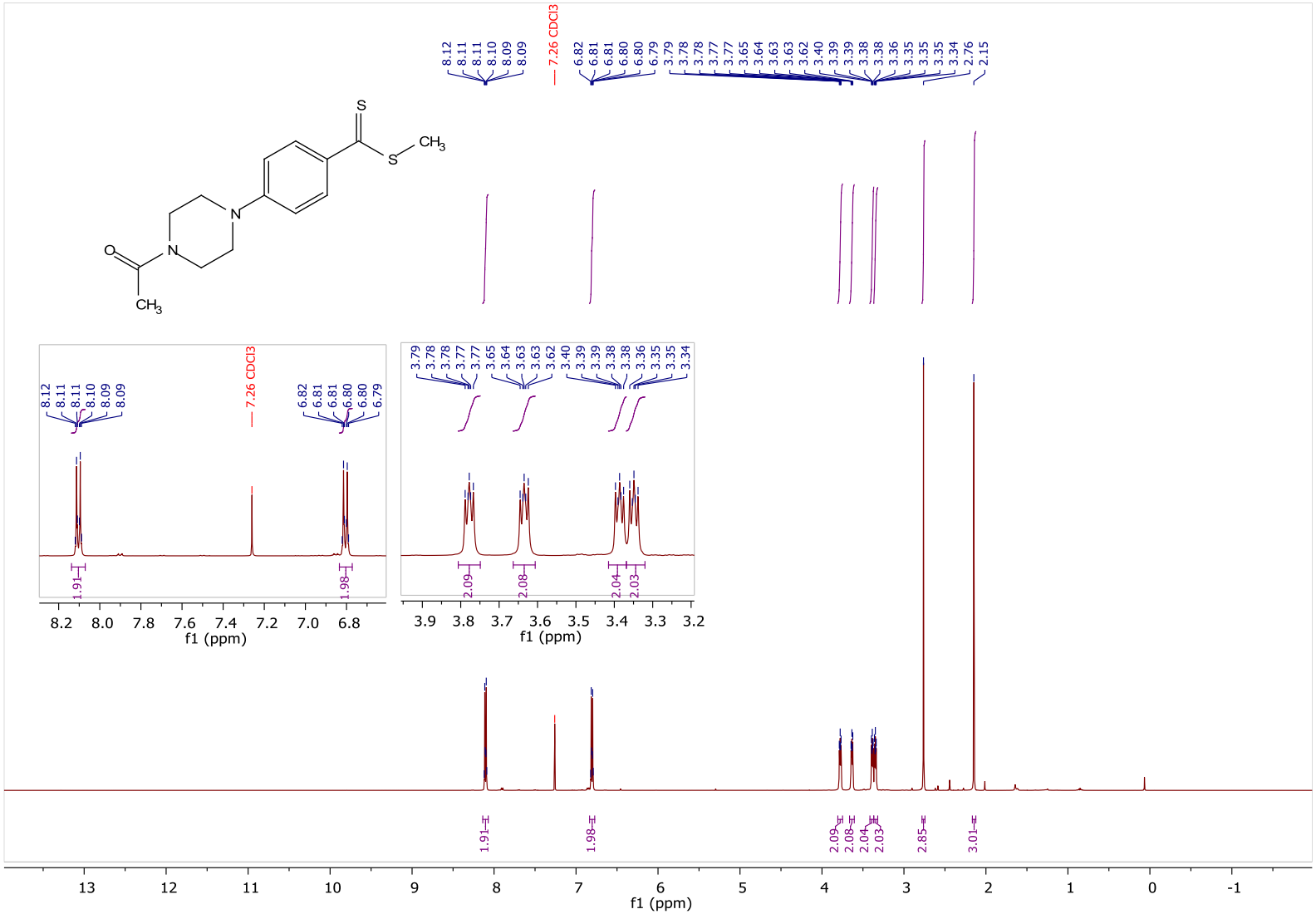

Figure S37. ^{1}H-NMR (500 MHz, $CDCl_3$) of **14b.**

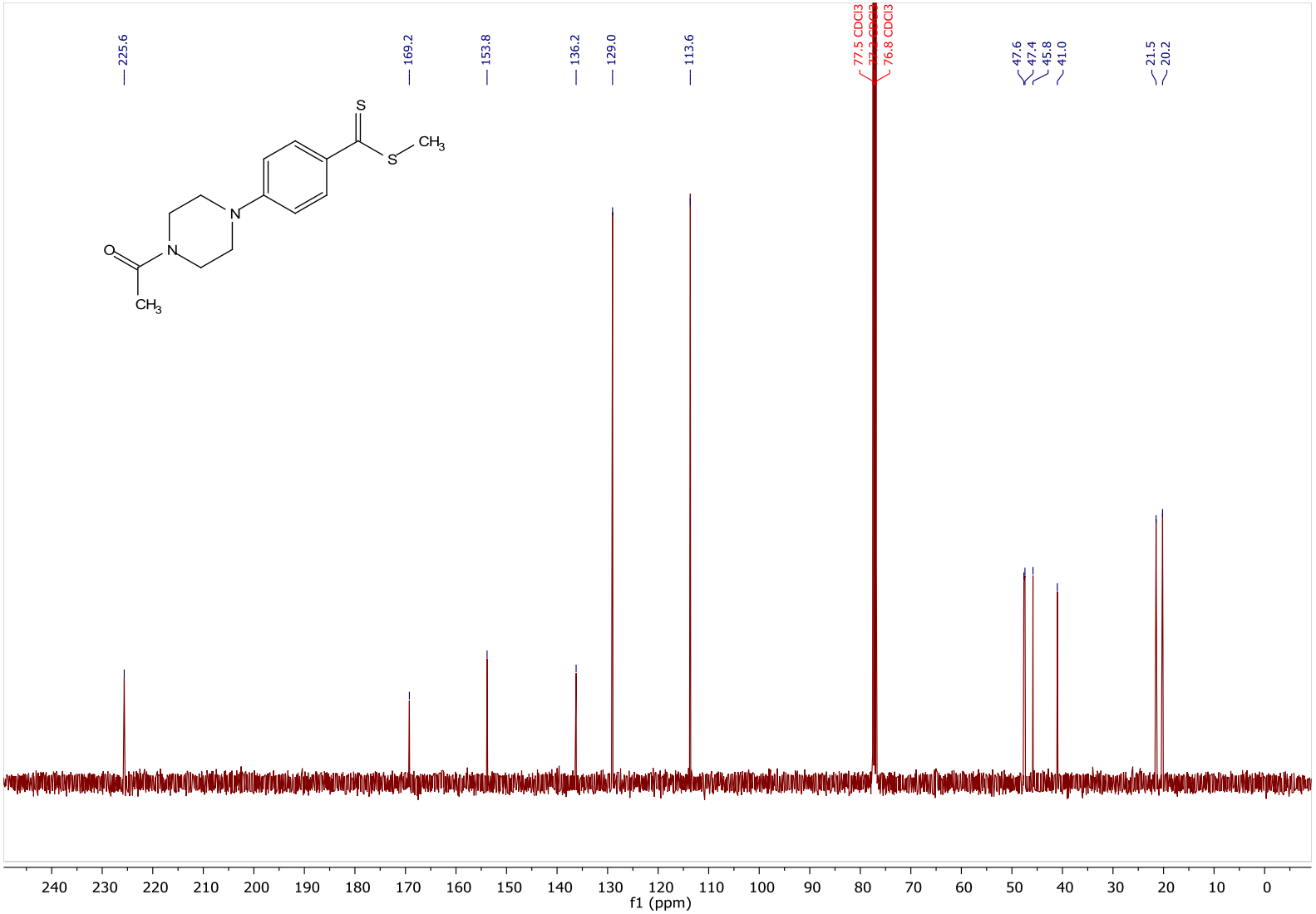

Figure S38. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **14b.**

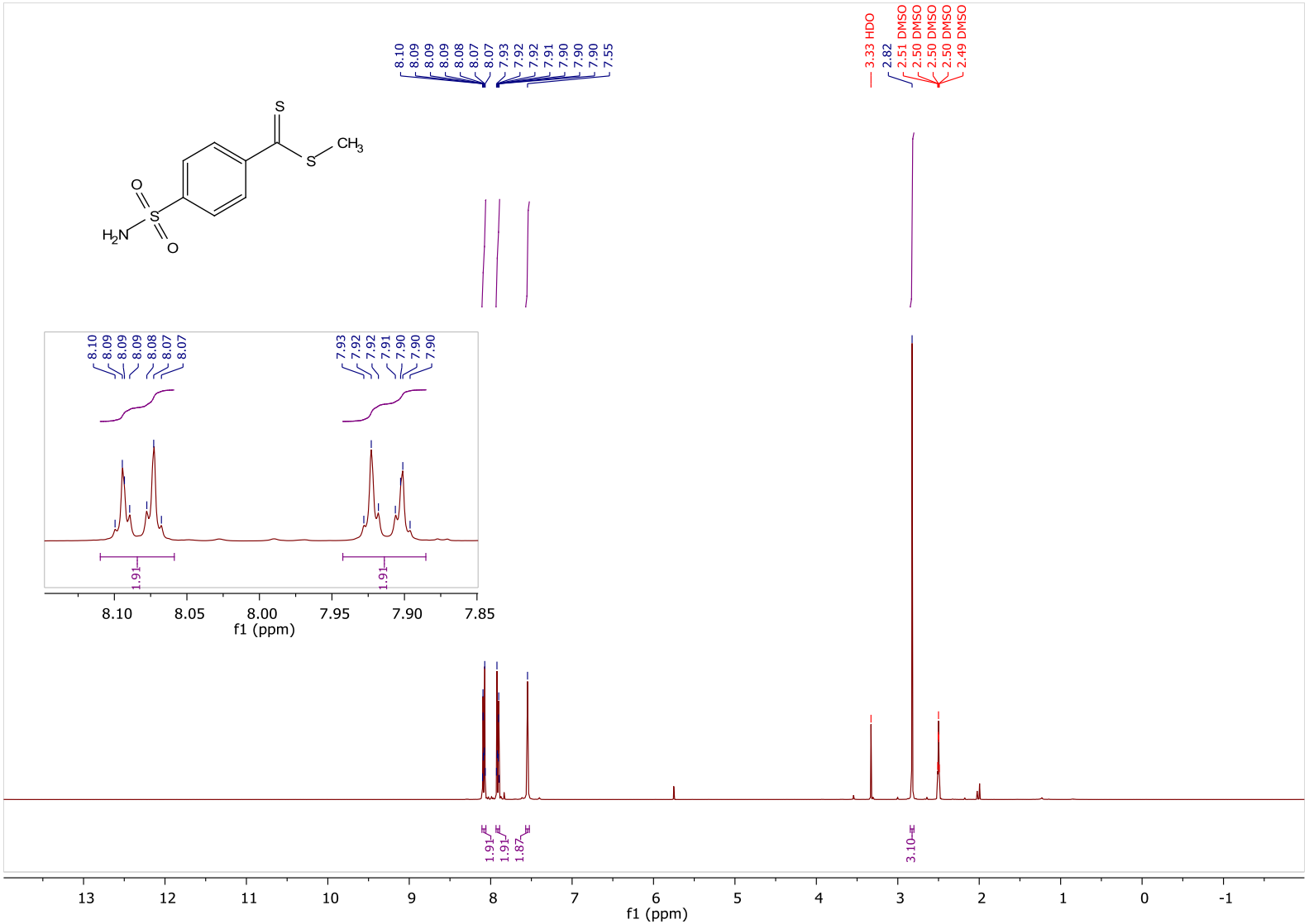

Figure S39. ^{1}H-NMR (400 MHz, DMSO-d_6) of **15b.**

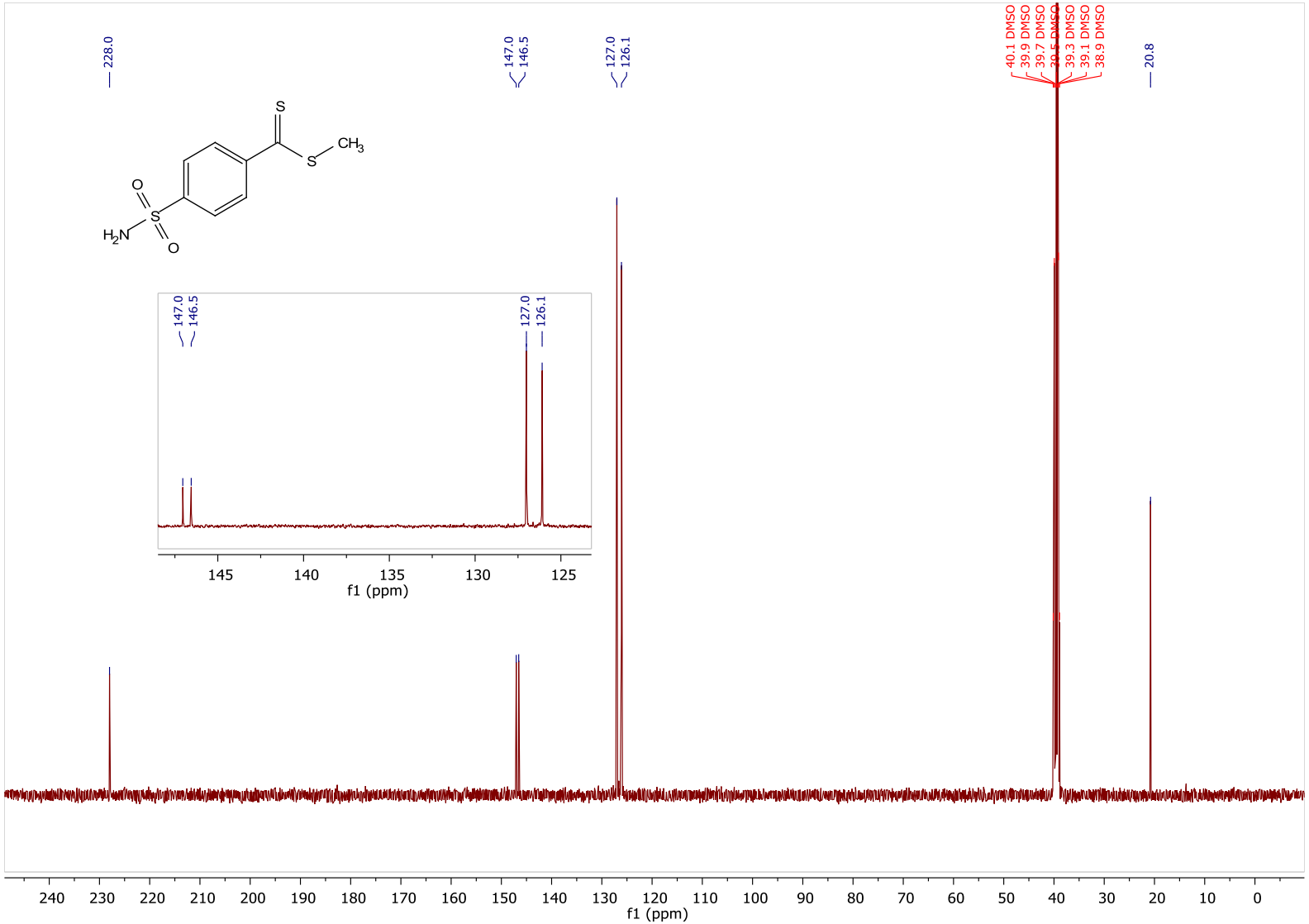

Figure S40. $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) of **15b.**

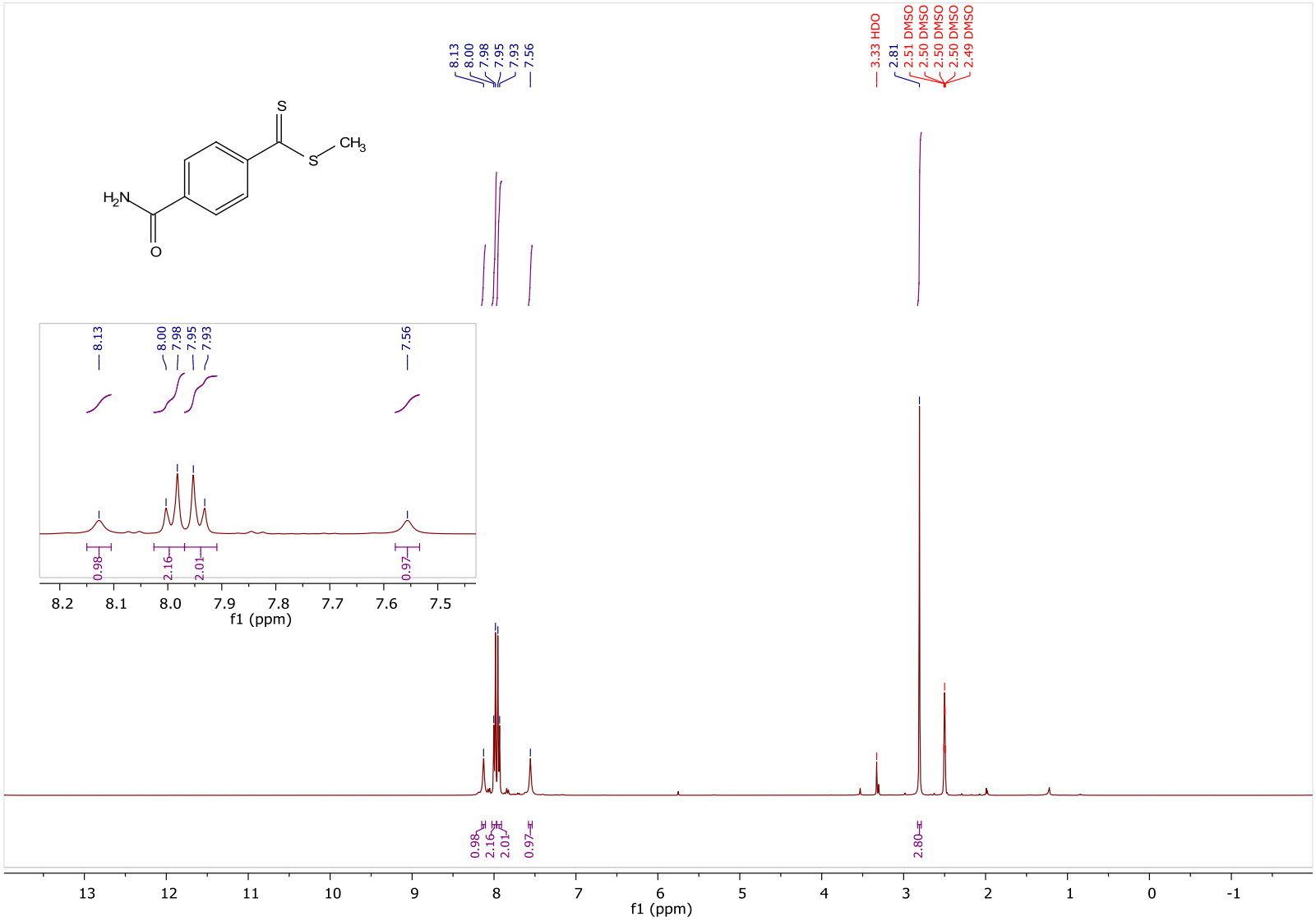

Figure S41. ^{1}H-NMR (400 MHz, DMSO-d_6) of **16b.**

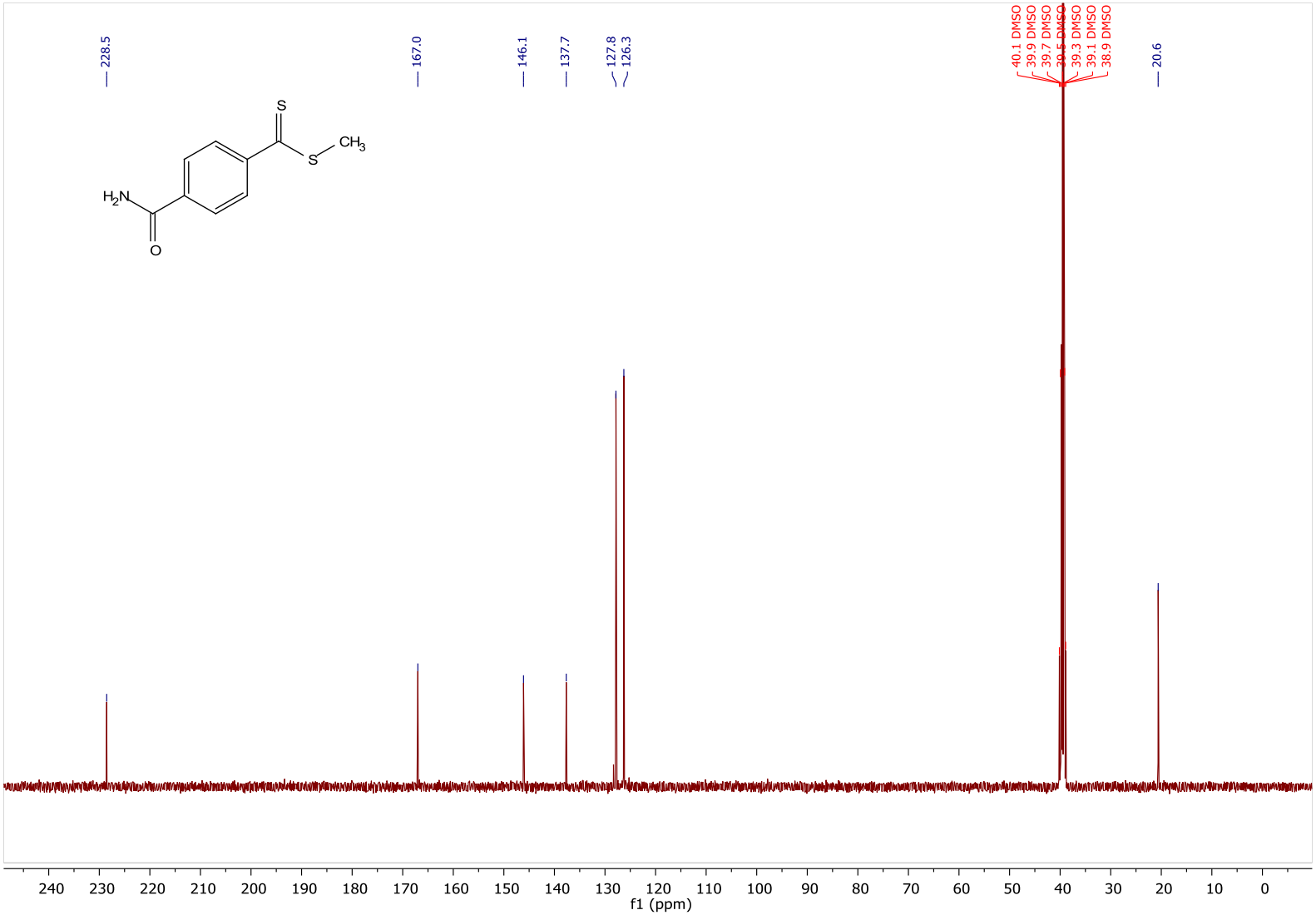

Figure S42. $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) of **16b.**

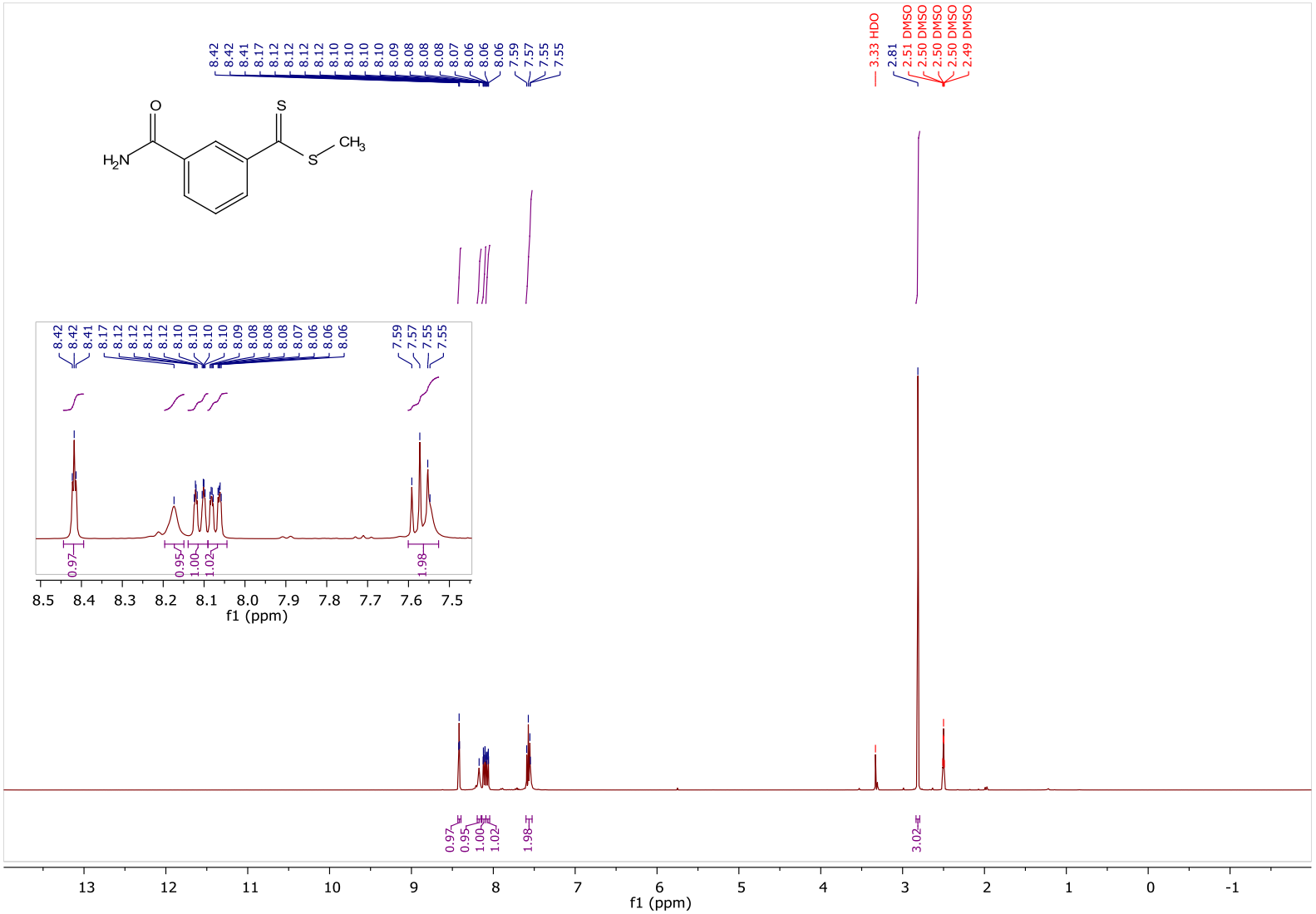

Figure S43. ^{1}H-NMR (400 MHz, DMSO-d_6) of **17b.**

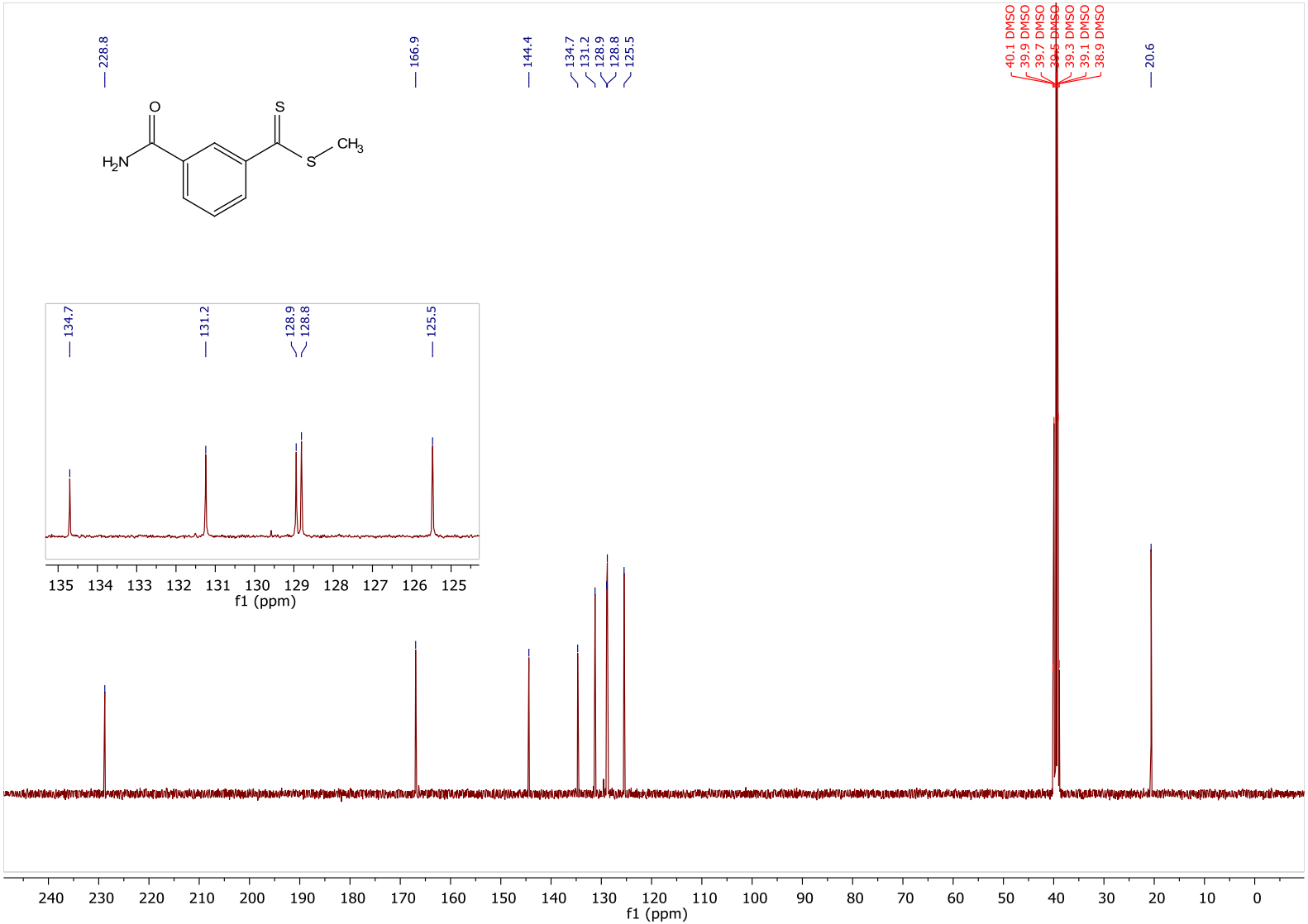

Figure S44. $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) of **17b.**

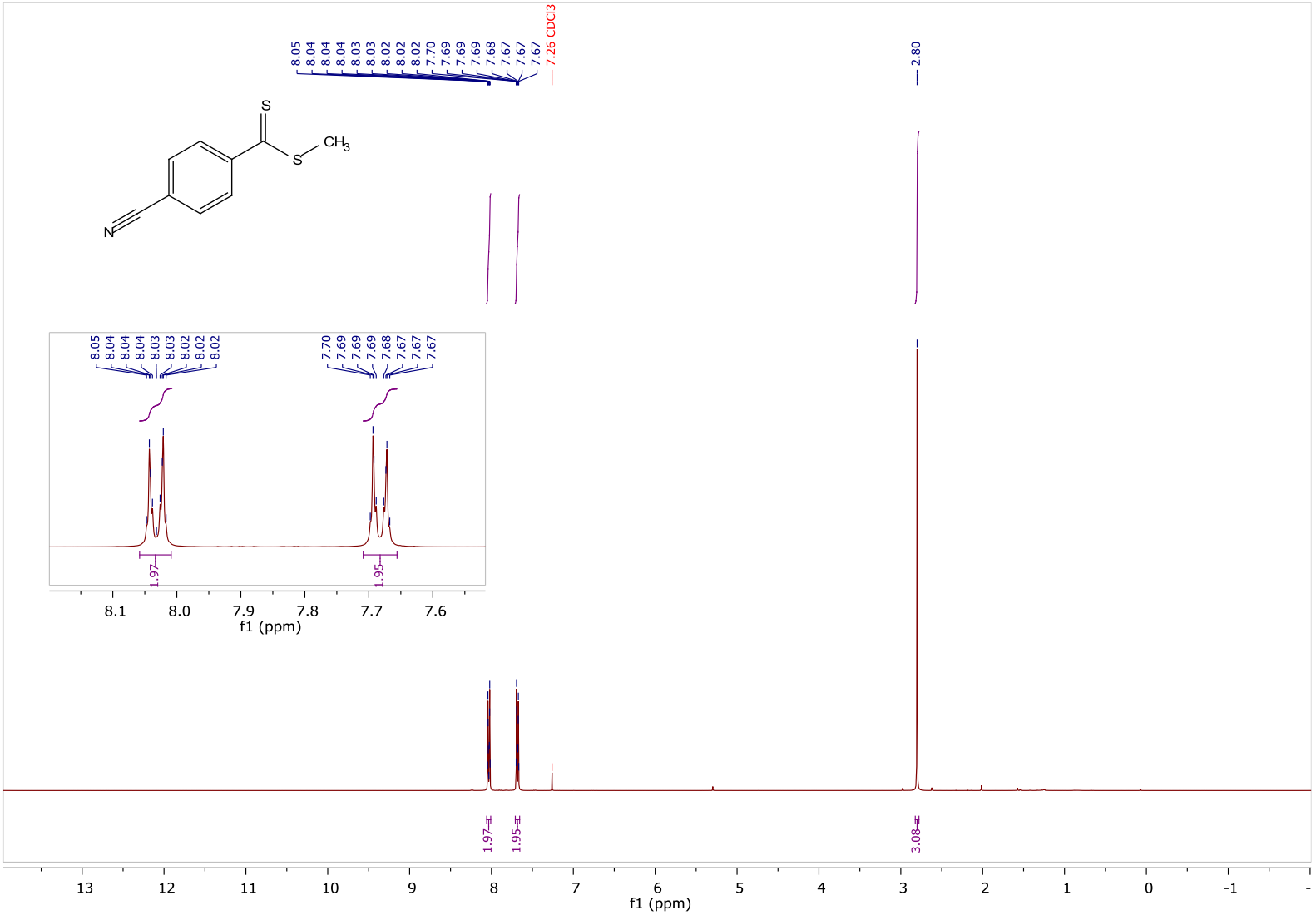

Figure S45. ^{1}H-NMR (400 MHz, $CDCl_3$) of **18b.**

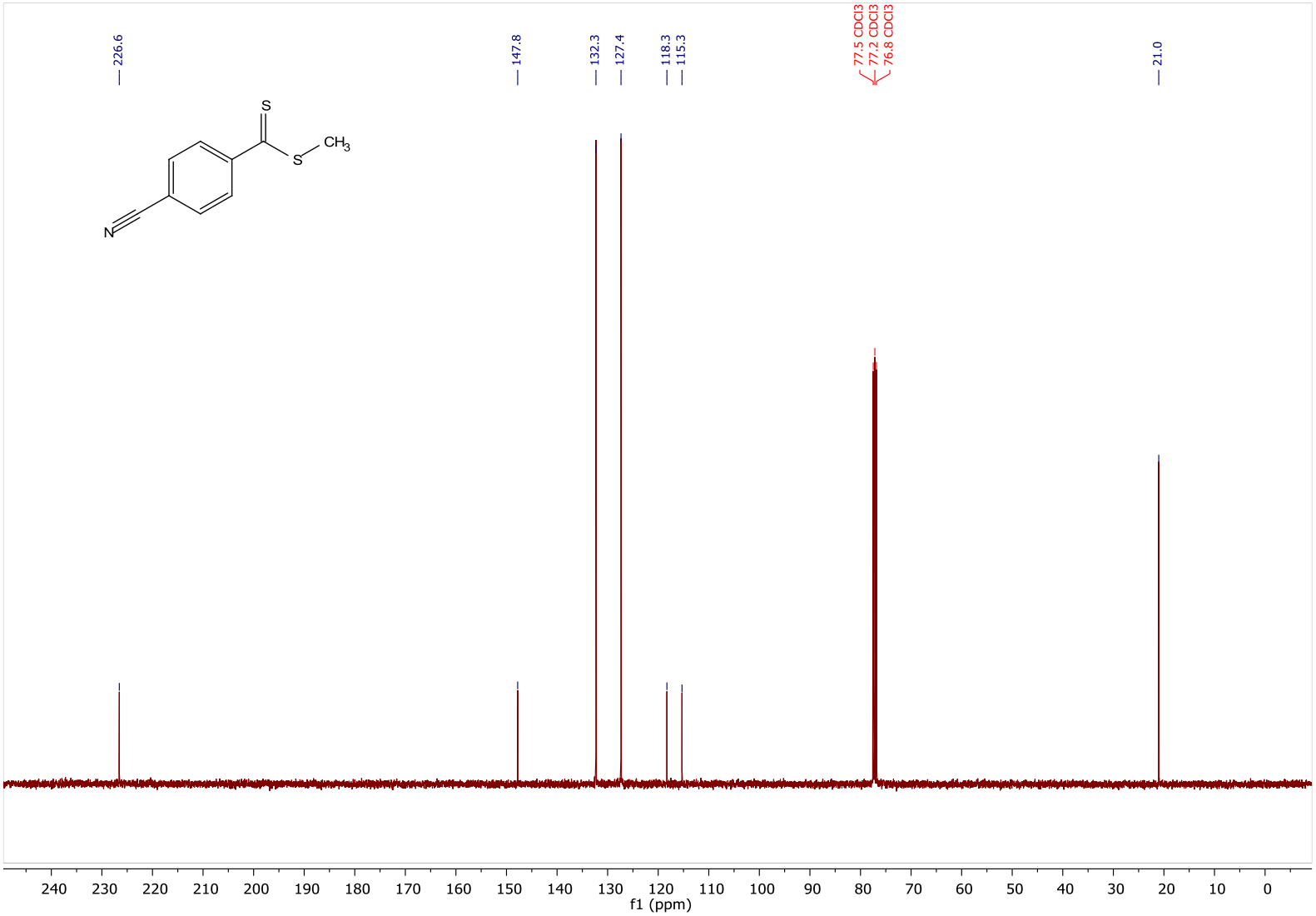

Figure S46. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **18b.**

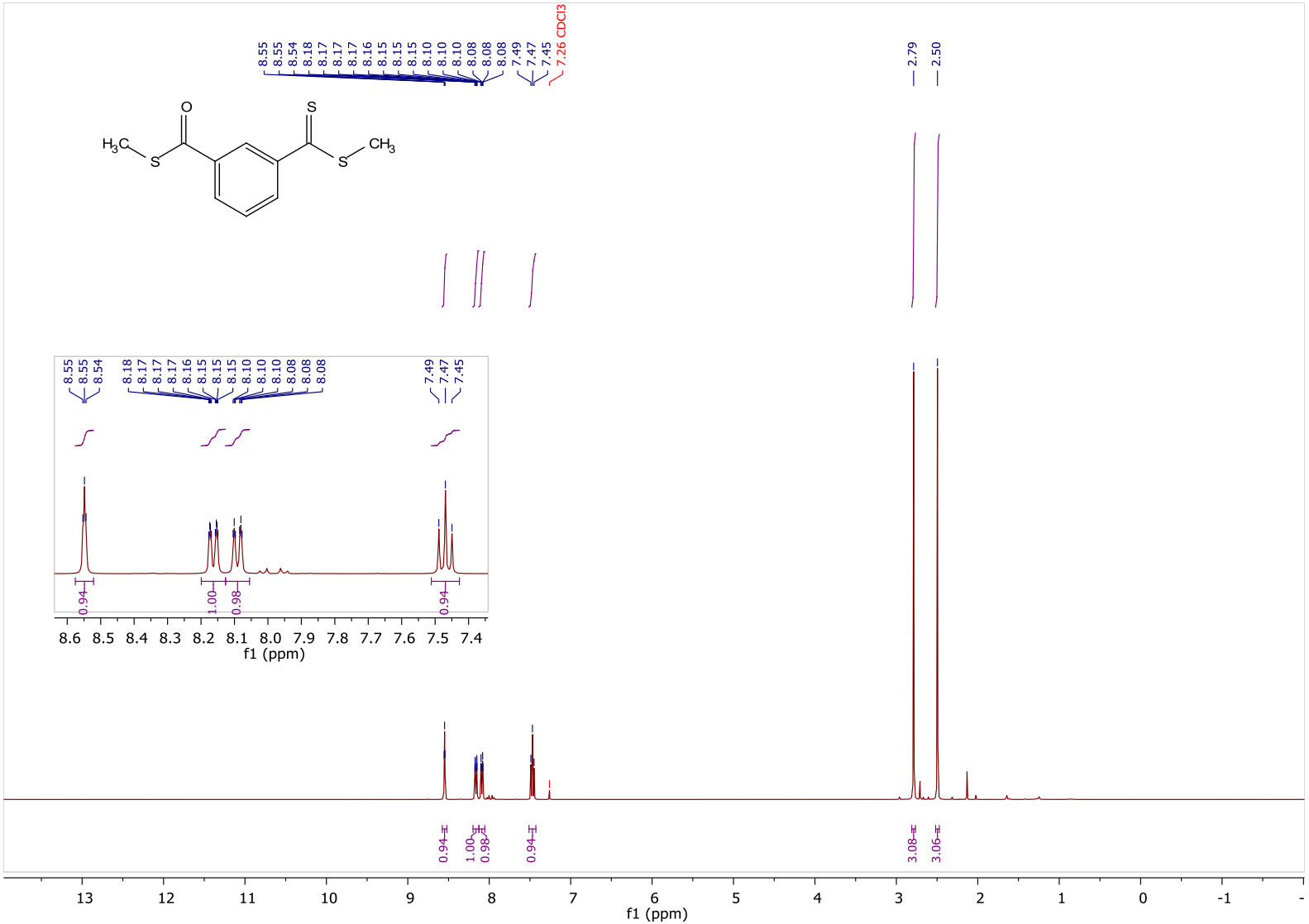

Figure S47. ^{1}H-NMR (400 MHz, $CDCl_3$) of **19b.**

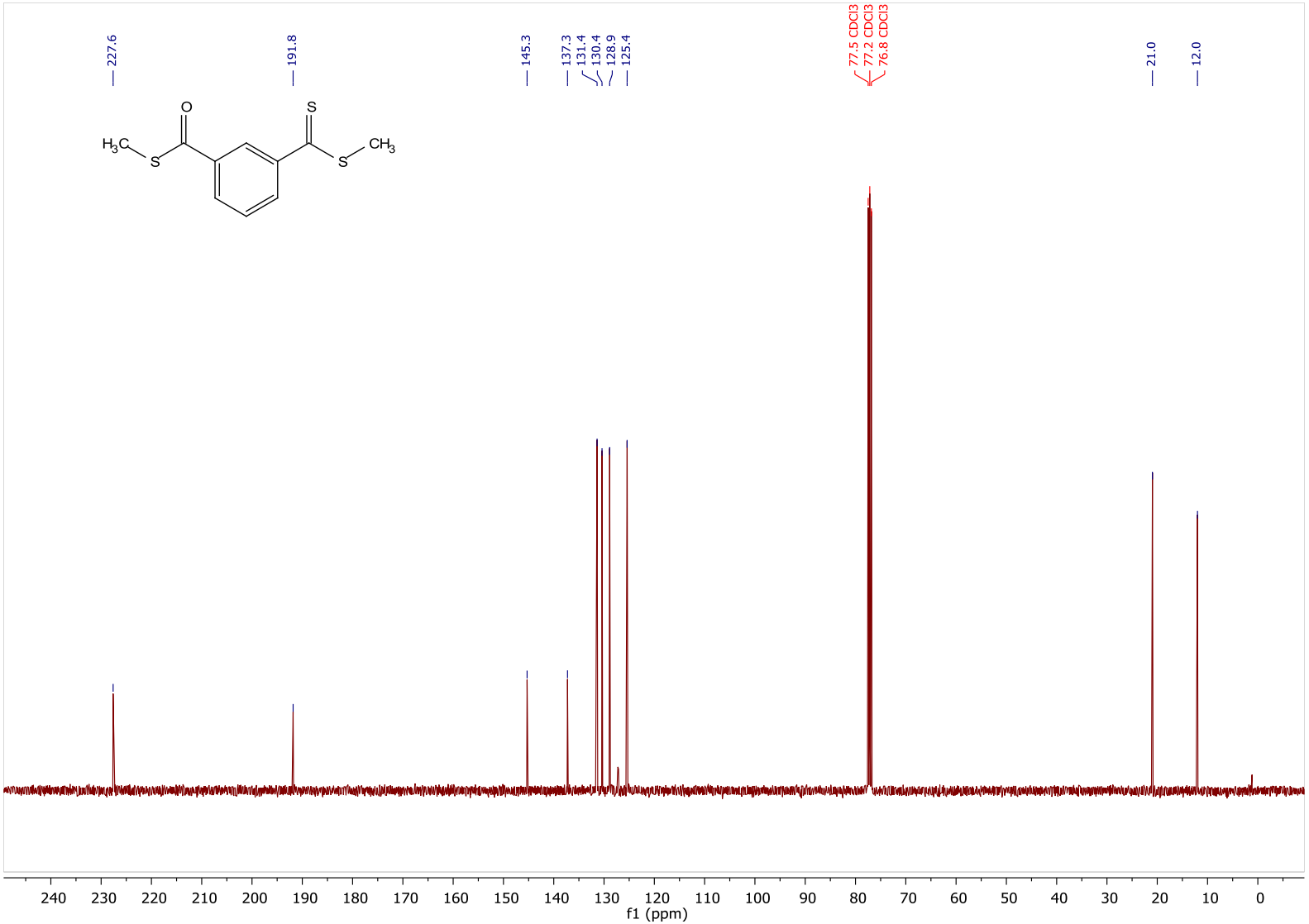

Figure S48. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **19b.**

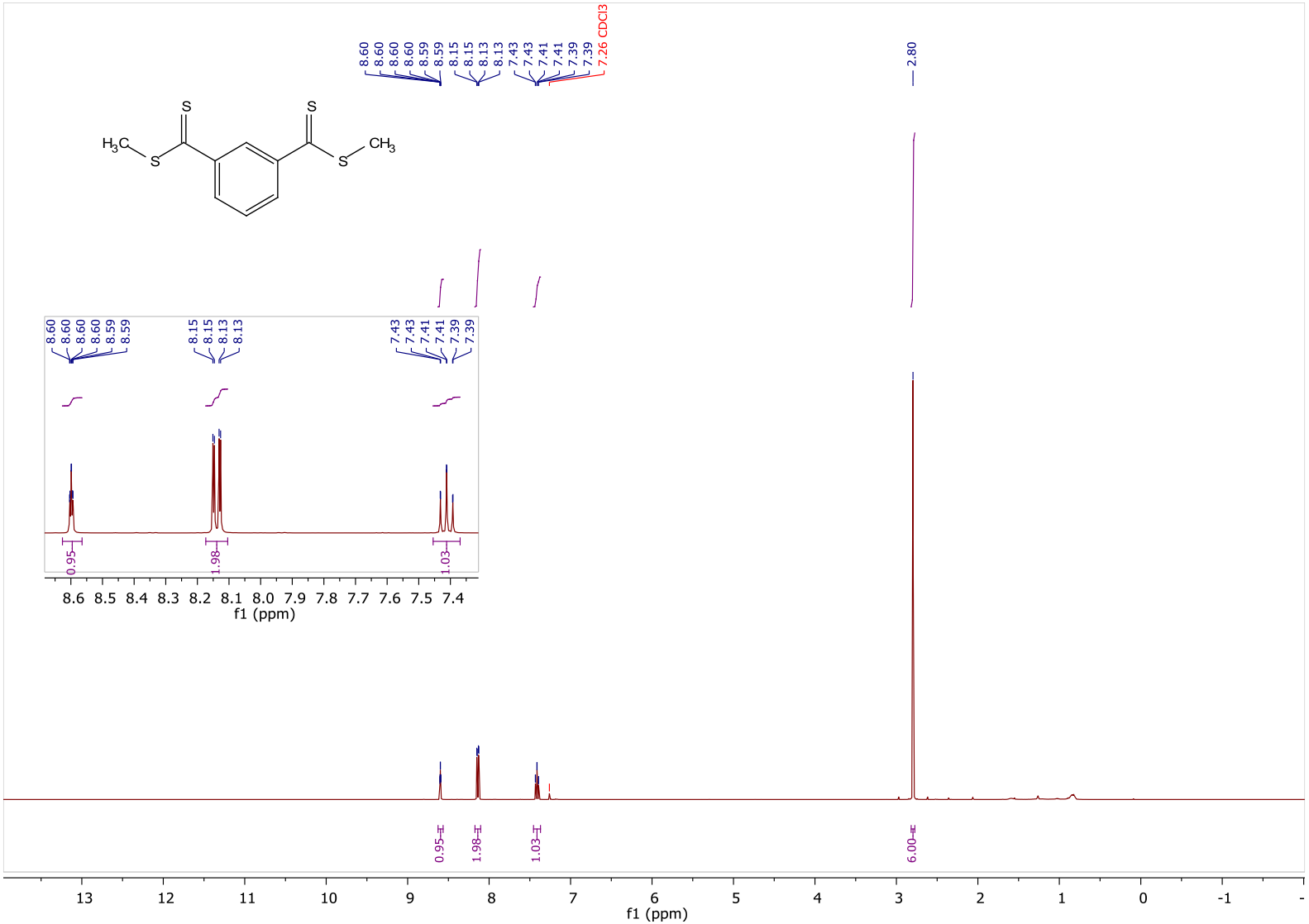

Figure S49. ^{1}H-NMR (400 MHz, $CDCl_3$) of **20b.**

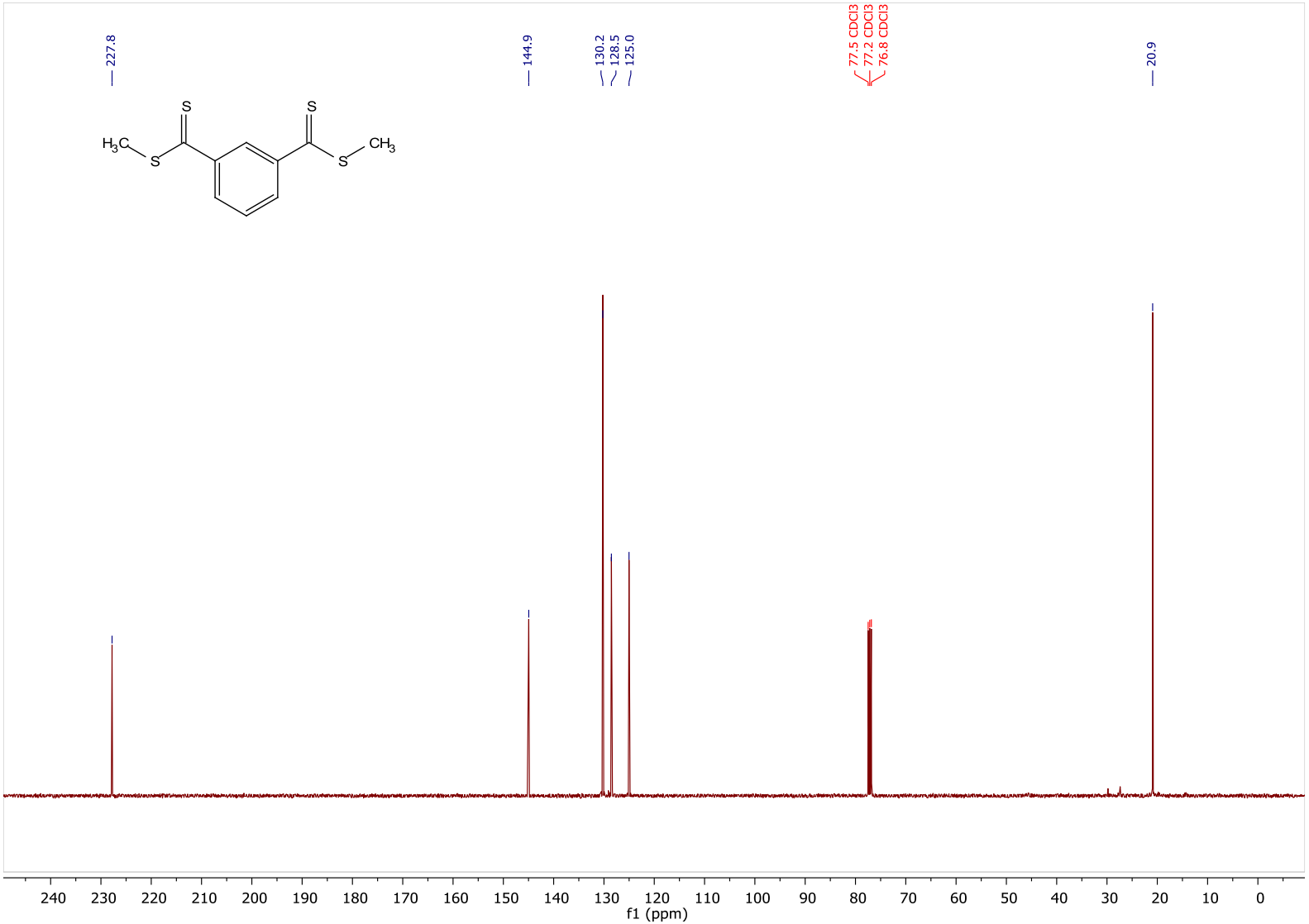

Figure S50. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **20b.**

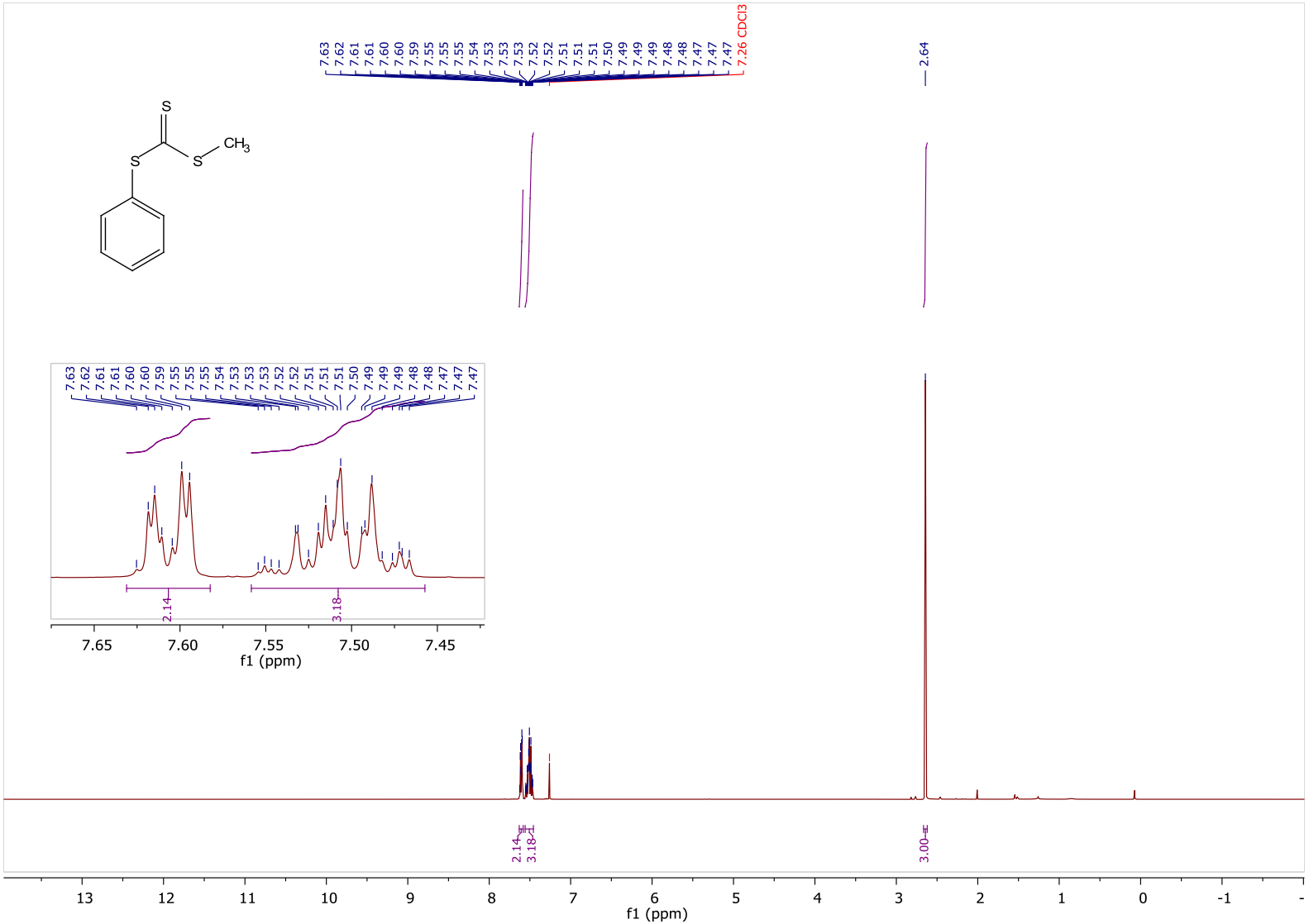

Figure S51. ^{1}H-NMR (400 MHz, $CDCl_3$) of **21b.**

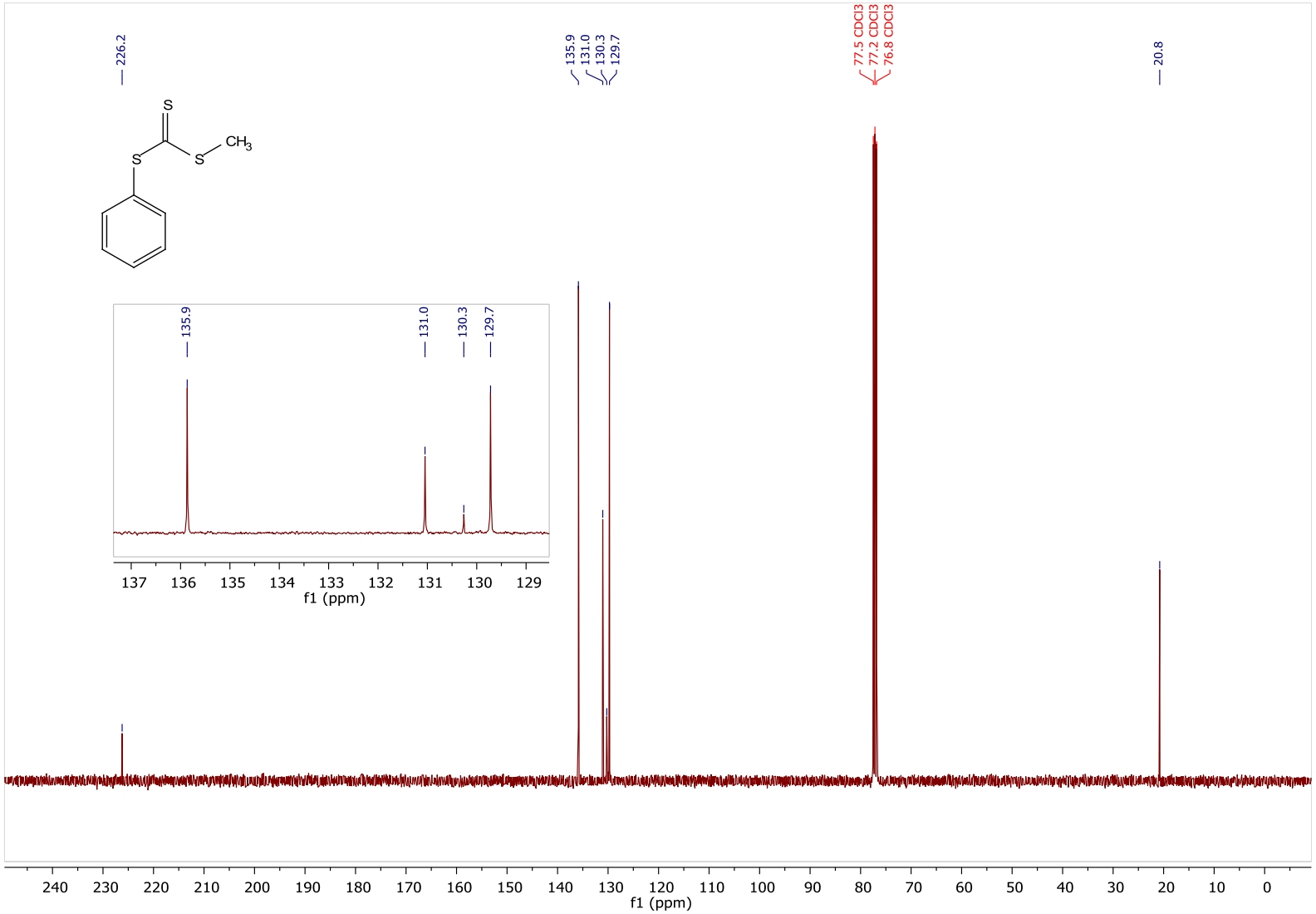

Figure S52. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **21b.**

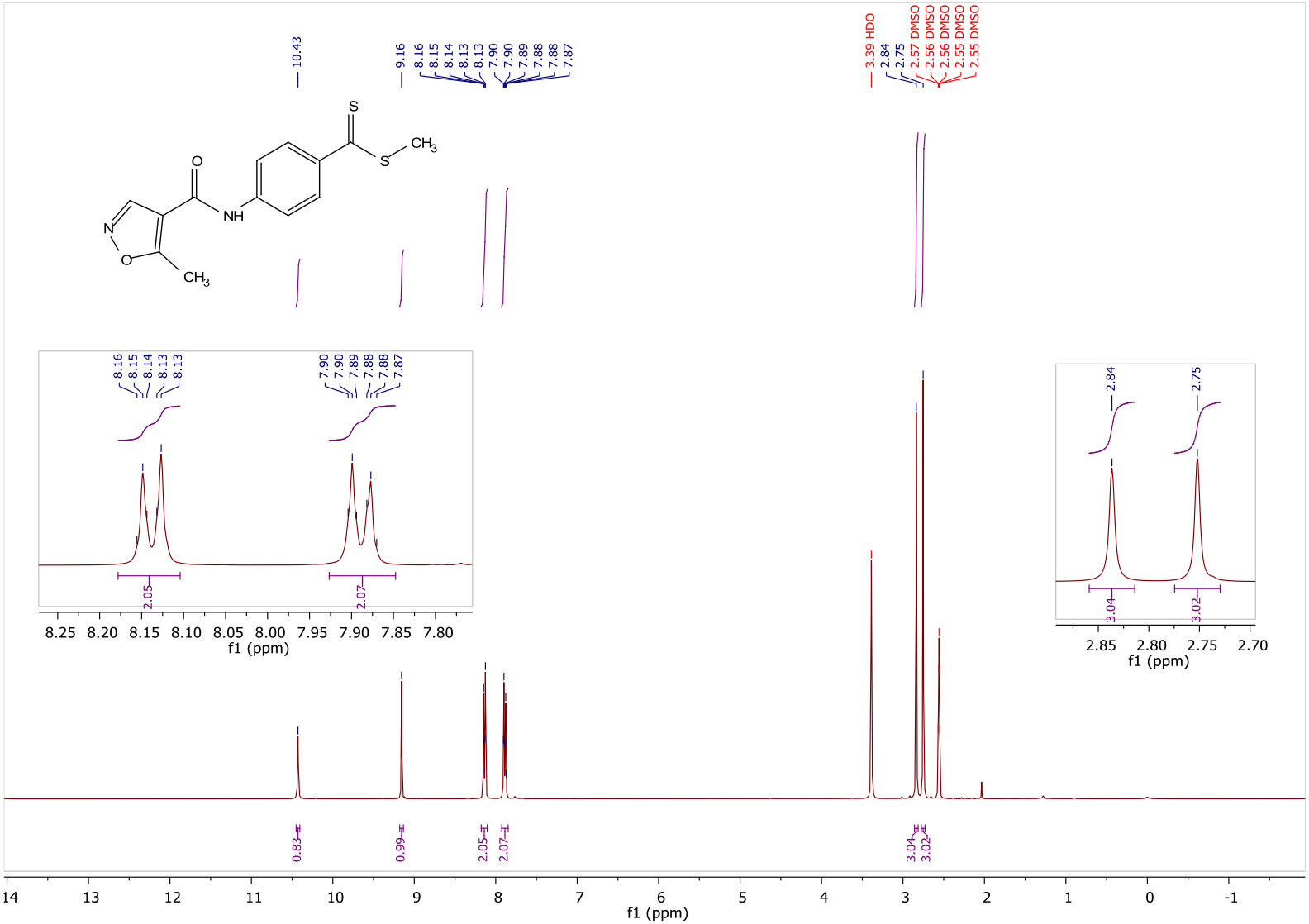

Figure S53. ^{1}H-NMR (400 MHz, DMSO-d_6) of **22b.**

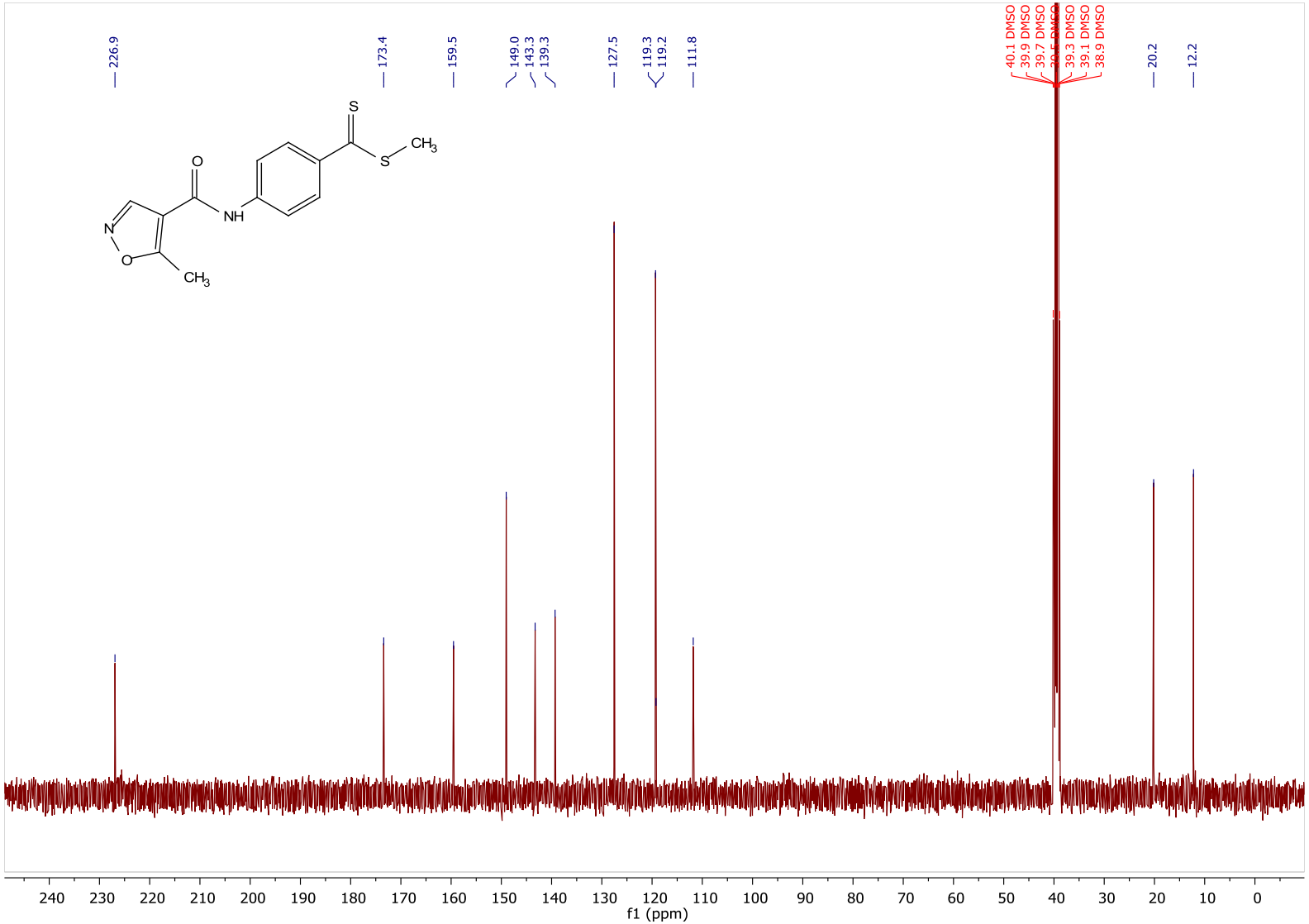

Figure S54. $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) of **22b.**

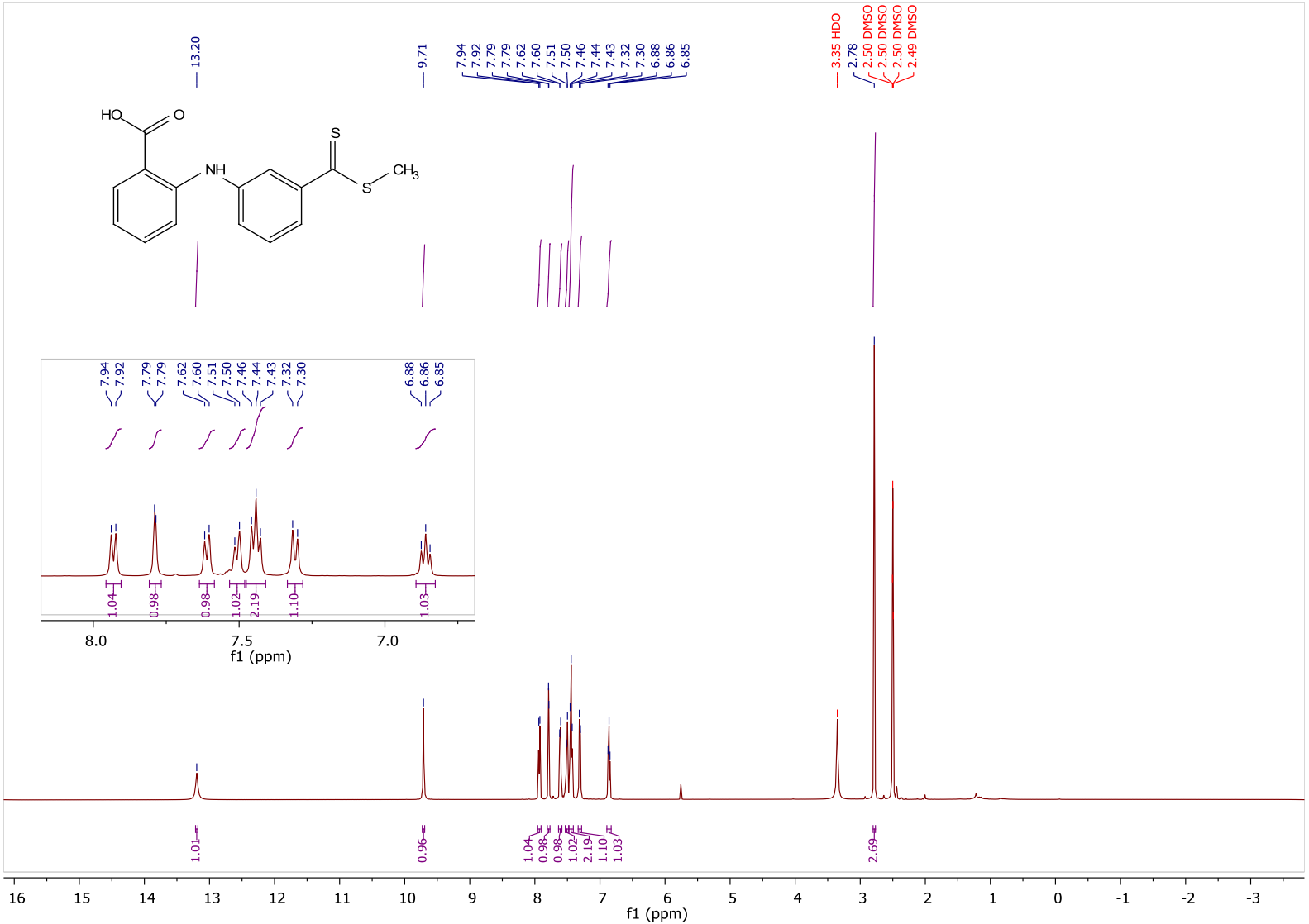

Figure S55. ^{1}H-NMR (500 MHz, $CDCl_3$) of **23b.**

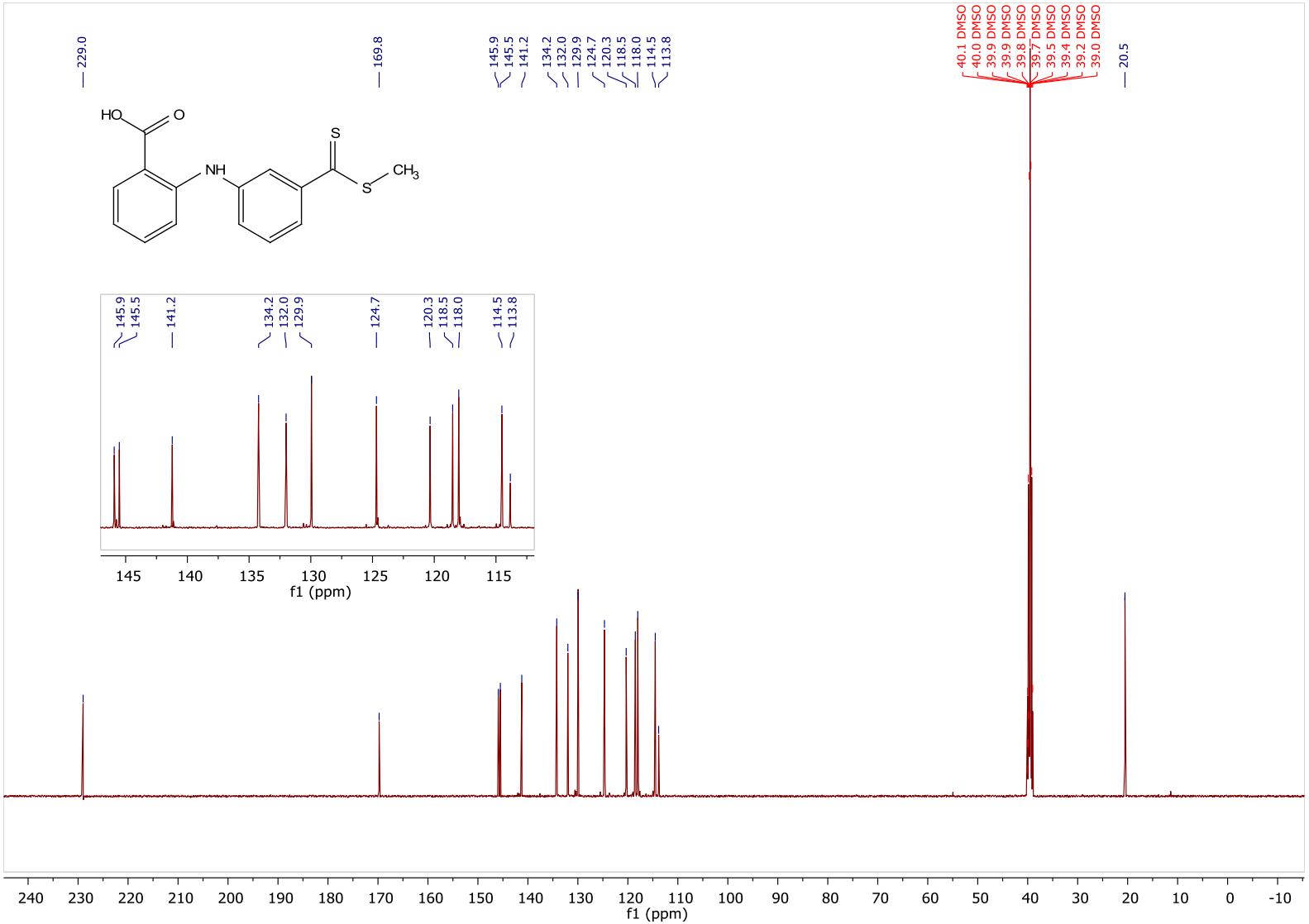

Figure S56. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) of **23b.**

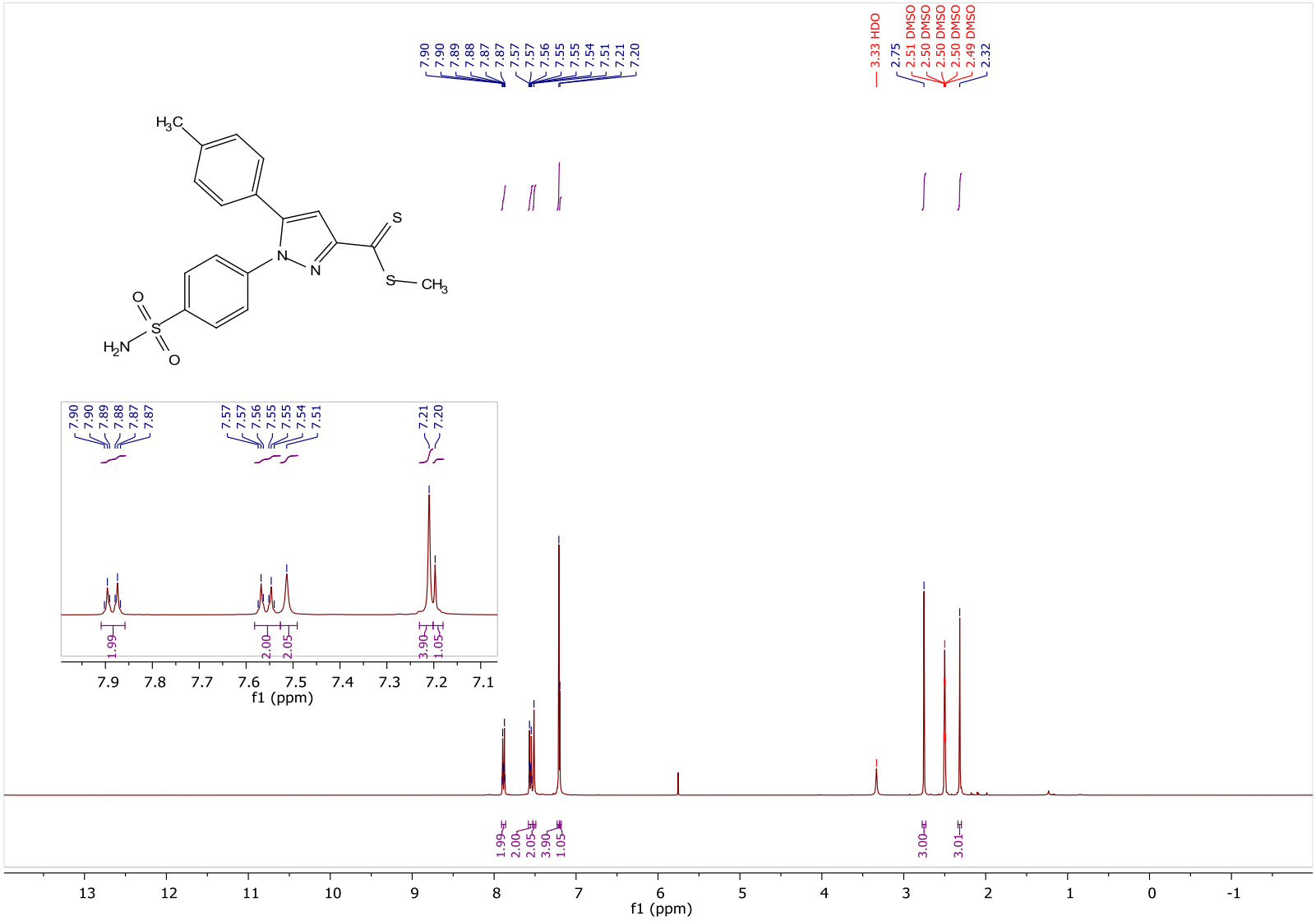

Figure S57. ^{1}H-NMR (400 MHz, DMSO-d_6) of **24b.**

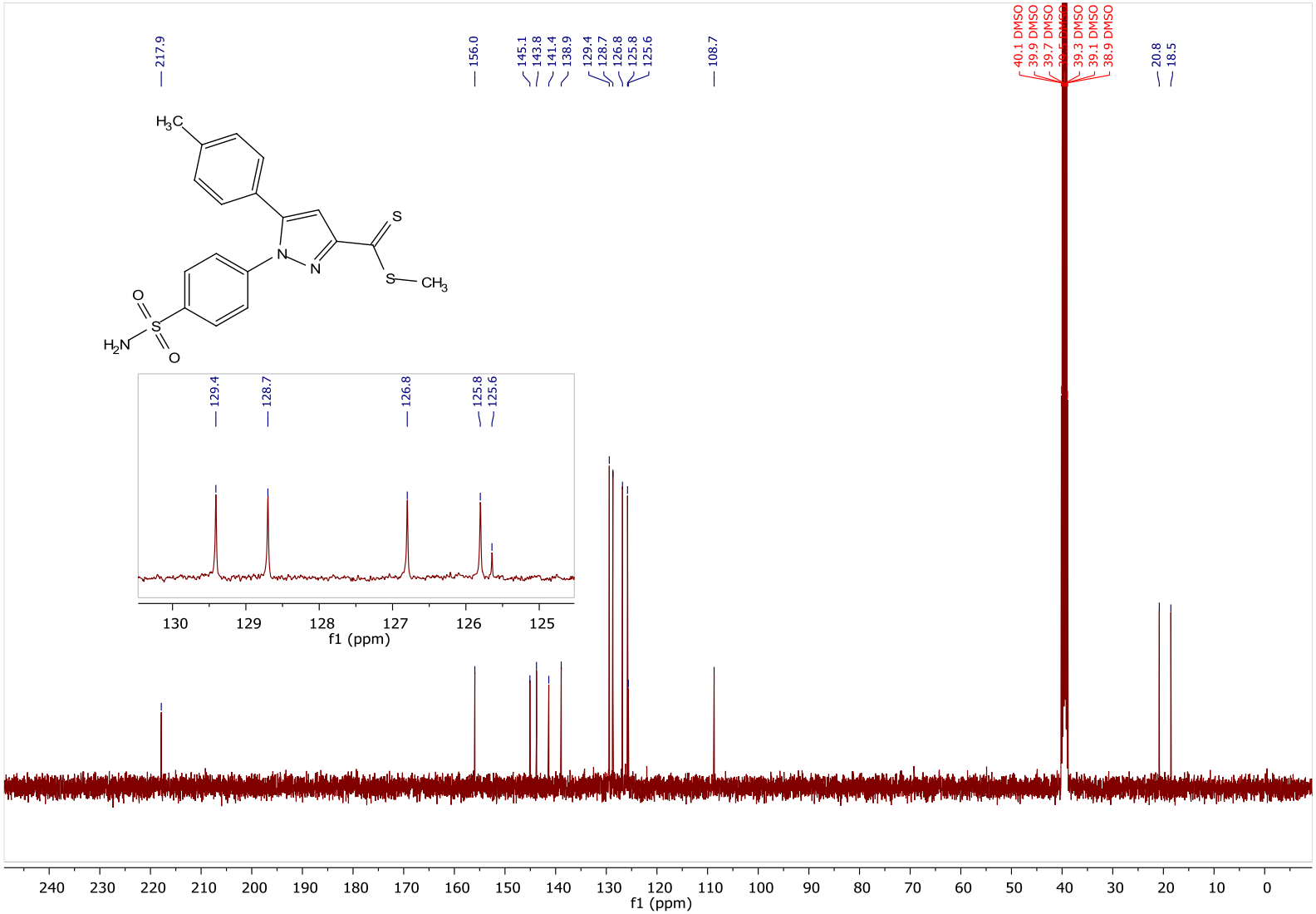

Figure S58. $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) of **24b.**

NMR Spectra of **4a** and **14a**

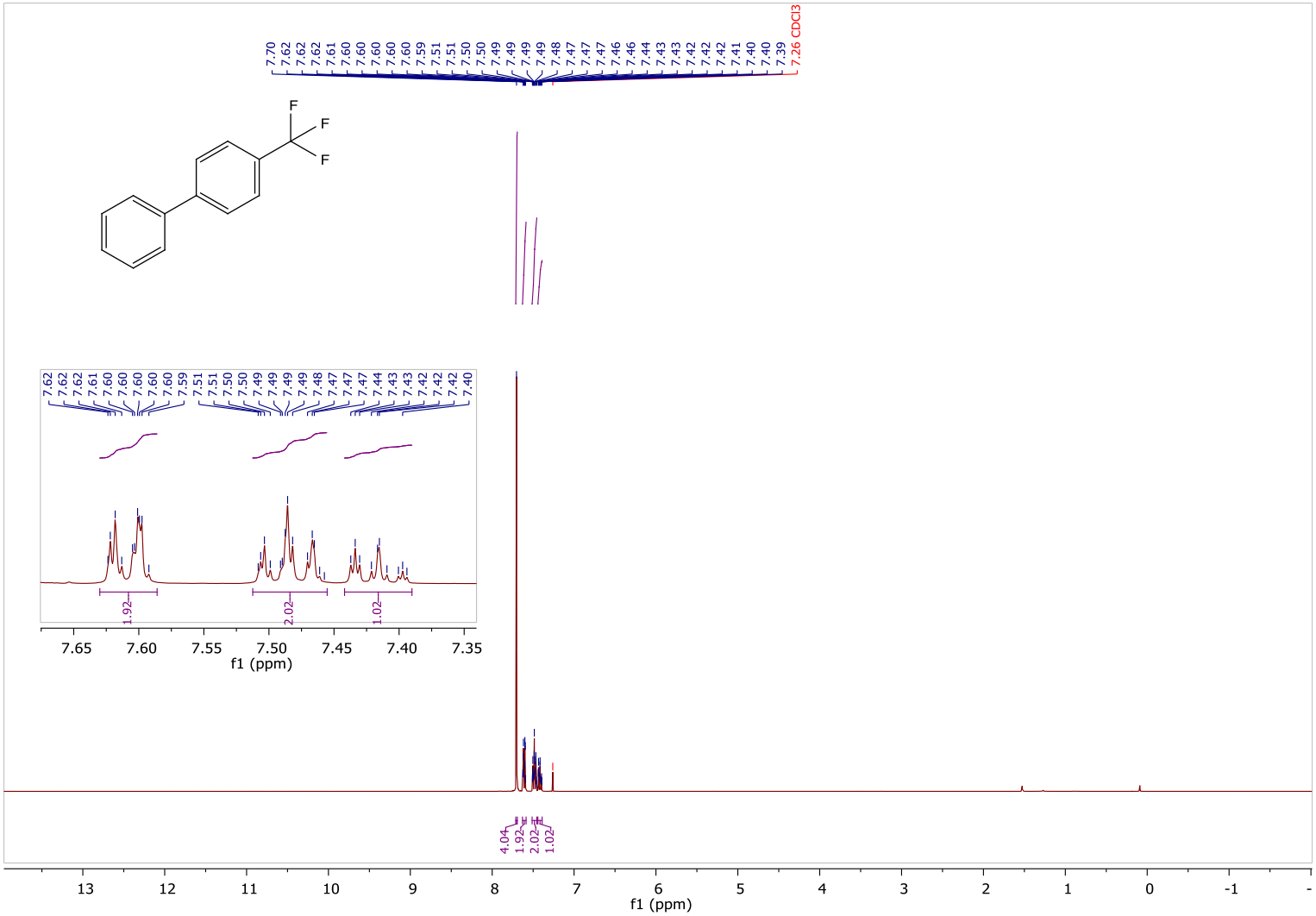

Figure S59. ^{1}H-NMR (400 MHz, $CDCl_3$) of **4a**

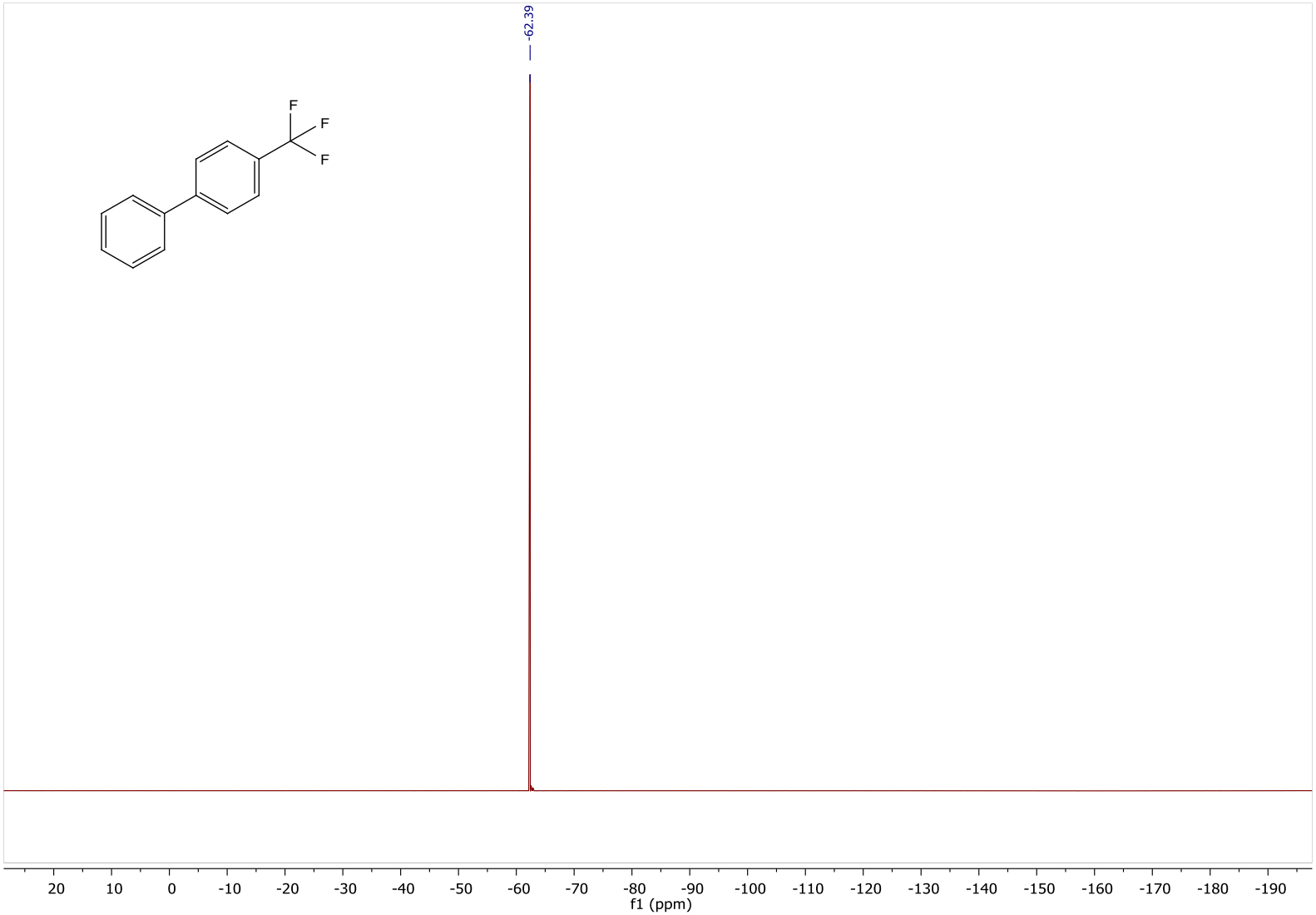

Figure S60. ^{19}F NMR (376 MHz, $CDCl_3$) of **4a**

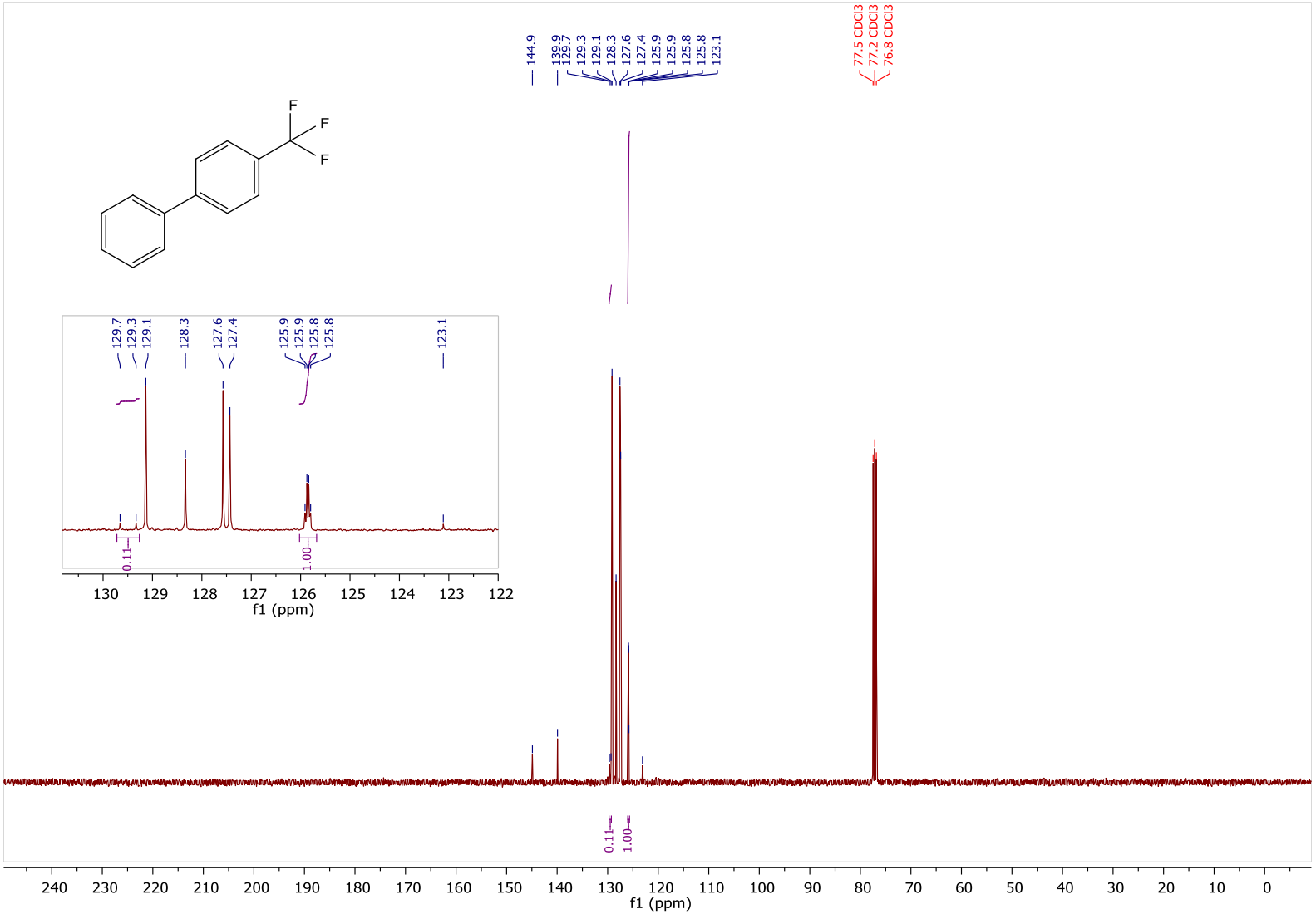

Figure S61. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **4a**

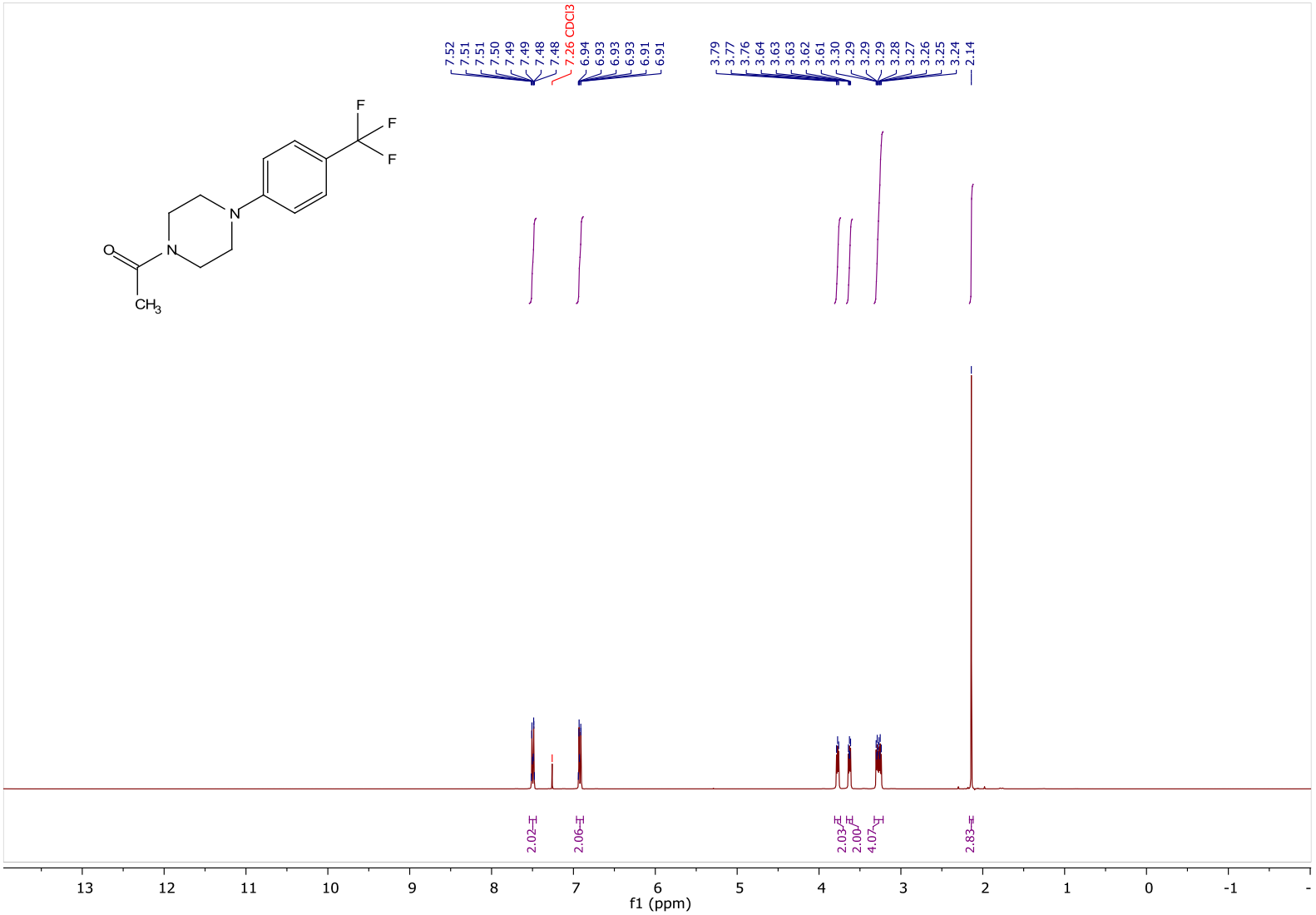

Figure S62. ^{1}H-NMR (400 MHz, $CDCl_3$) of **14a**

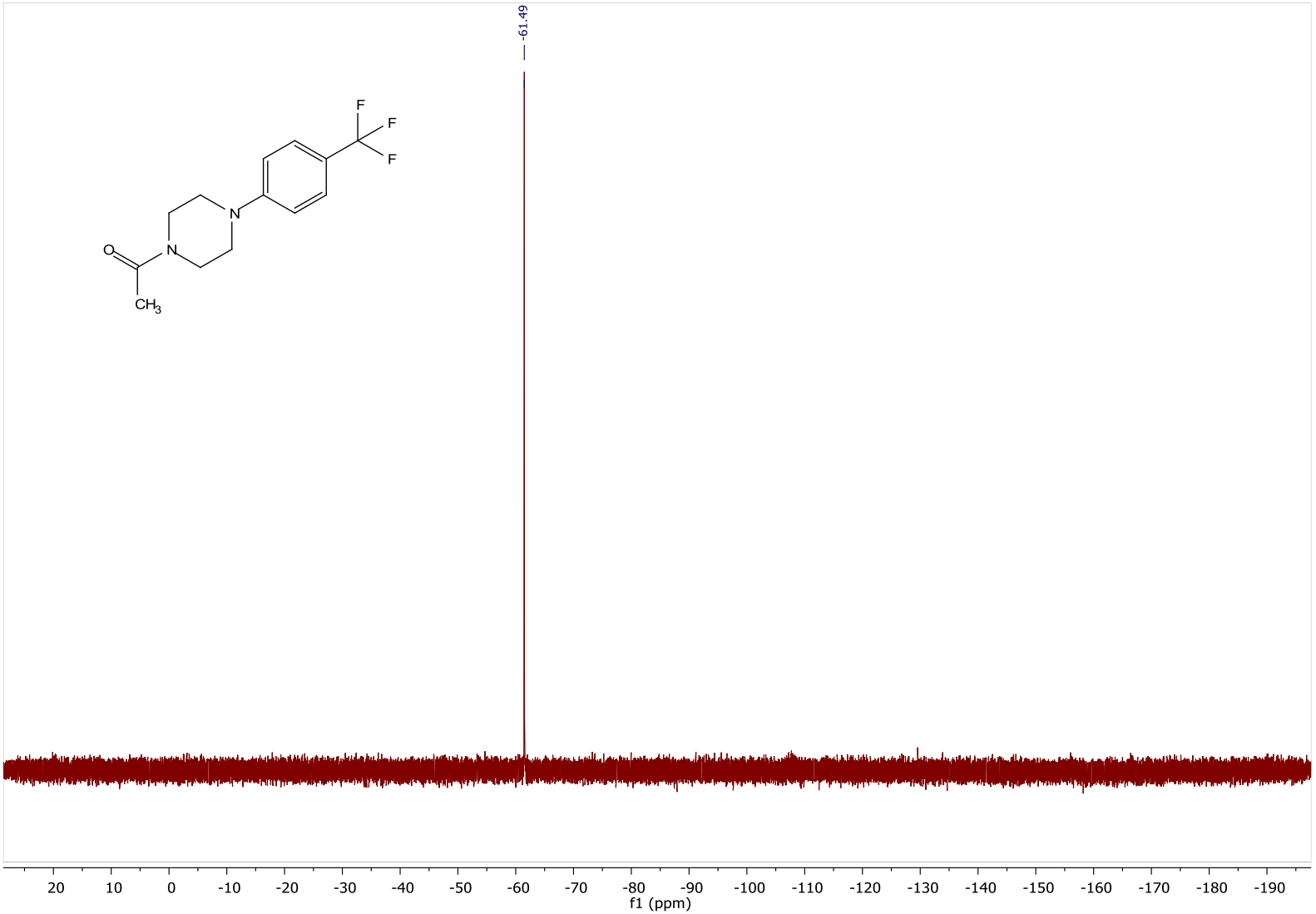

Figure S63. ^{19}F NMR (376 MHz, $CDCl_3$) of **14a**

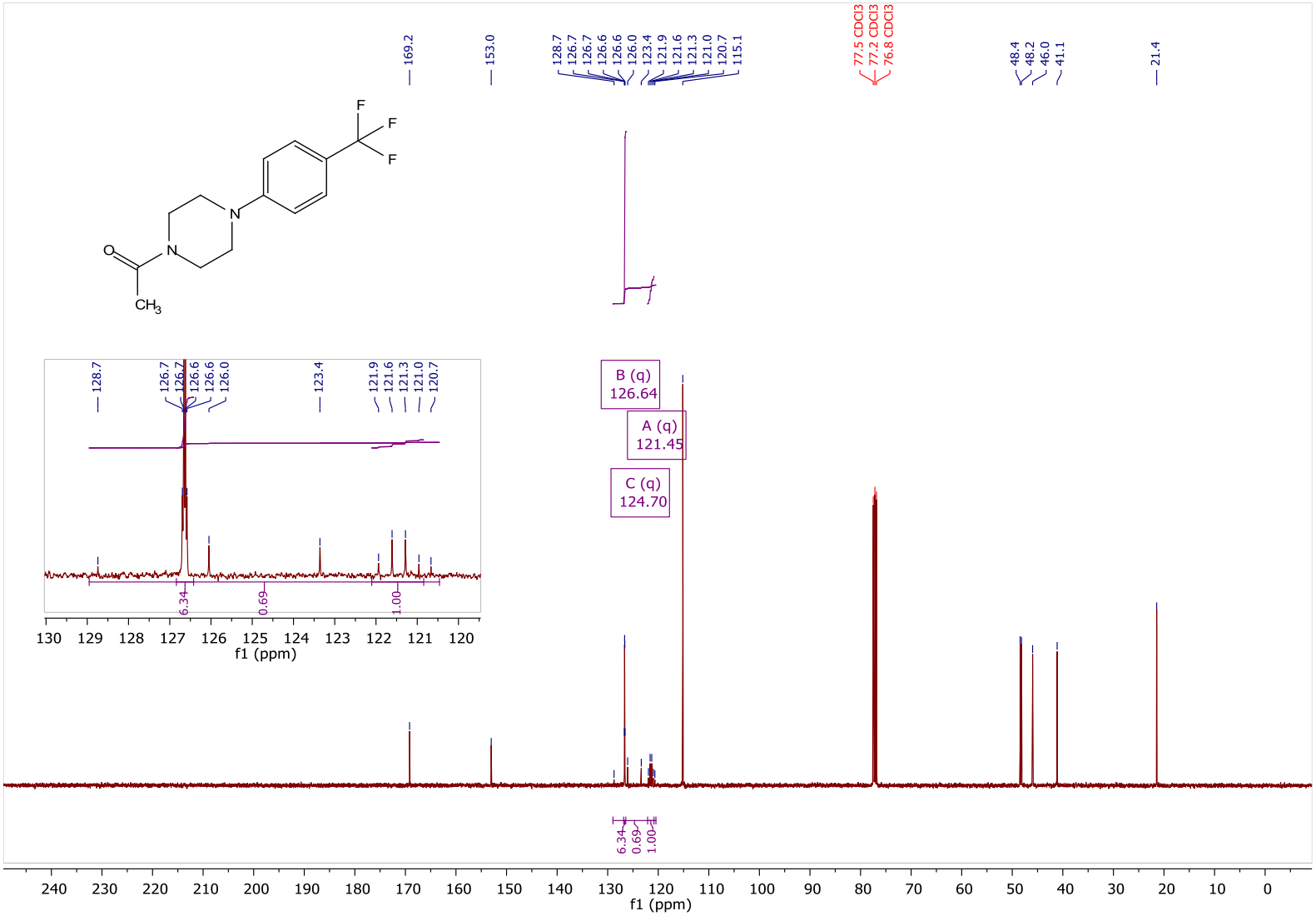

Figure S64. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) of **14a**