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Supplementary Information

Milled Dry Ice as a C1 Source for the Carboxylation of Aryl Halides

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General Information

Unless otherwise stated, all commercial reagents and solvents were purchased from Sigma-Aldrich, Combi-Blocks, TCI Corporation, or Fischer Scientific, and were used without additional purification. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker Advance III (400 MHz) spectrometer and are internally referenced to residual protio solvent signals (note: DMSO-d_6 referenced at δ 2.50 ppm for ^{1}H, and δ 39.52 for ^{13}C; Chloroform-*d* referenced at δ 7.26 ppm for ^{1}H, and δ 77.16 ppm for ^{13}C; Methanol-d_4 referenced at δ 3.31 ppm for ^{1}H, and δ 49.00 for ^{13}C). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, tdd = triplet of doublet of doublets, m = multiplet, br = broad), integration, coupling constant (Hz), and assignment. The raw fid files were processed into the included NMR spectra using MestReNova 11.0, (Mestrelab Research S. L.). Flash chromatography was performed using SiliaFlash P60 silica gel (40-63 μm) purchased from Silicycle. Organic solutions were concentrated under reduced pressure on a Heidolph rotary evaporator. Unless otherwise noted, all reaction yields are reported as the average isolated yields of two separate trials.

General Procedures

General Procedure for the Milling of Dry Ice Pellets

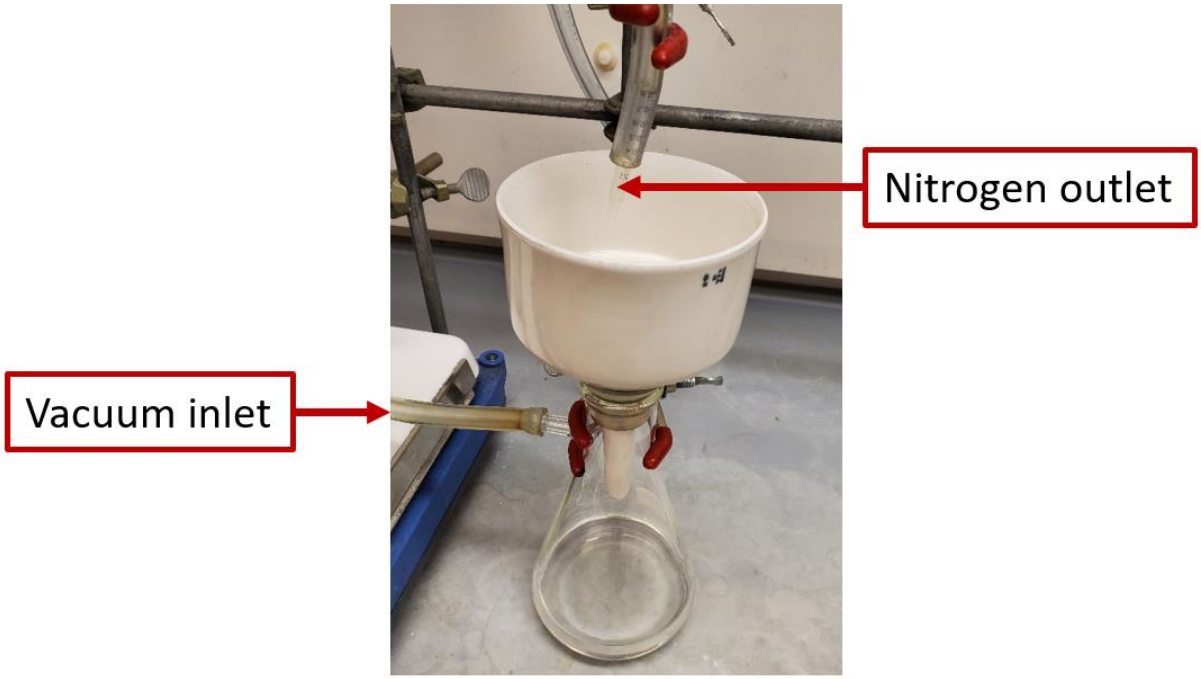
A mortar and pestle were used to mill the dry ice pellets to granular size pieces. The average particle size of the milled dry ice used in the reaction is less than 1 mm:

The freshly milled dry ice was quickly transferred to the Erlenmeyer flask as described in **General Procedure for the Drying of Milled Dry Ice.**

General Procedure for the Drying of Milled Dry Ice

Note: To minimize the deleterious effects of water condensation onto the dry ice, the water was removed through a general procedure:

Under a constant stream of nitrogen, approximately 50 mL of anhydrous THF was added to a flame-dried, 250 mL Erlenmeyer flask and cooled to -78 °C. Approximately 75 grams of freshly milled dry ice (from **General Procedure for the Milling of Dry Ice Pellets**) was then slowly added to the flask via powder funnel. The flask was vigorously swirled, ensuring that the milled dry ice was completely submerged by the solvent. The resulting slurry was then filtered via vacuum filtration under a constant stream of nitrogen:

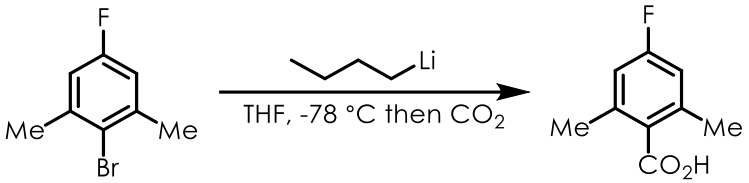


After removal of THF via vacuum filtration, the resulting milled dry ice was quickly transferred to the round-bottom reaction flask (described in **General Procedure A**) via powder funnel.

Safety Note: the sublimation of dry ice produces a large amount of gas. To prevent a dangerous buildup of pressure, the reaction flask was left open to the atmosphere after dry ice addition.

General Procedures

General Procedure A: Carboxylation of Aryl Bromides



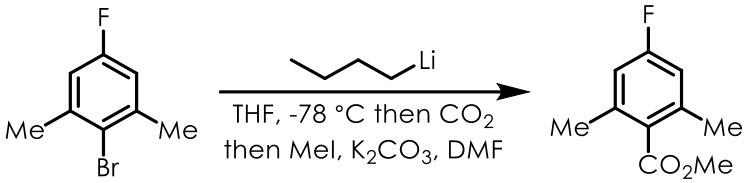
Under positive pressure of nitrogen, 2-bromo-5-fluoro-1,3-dimethylbenzene (3.040 g, 1.0 Eq, 14.97 mmol) was added to a flame-dried, 100 mL round-bottom flask, before being diluted in anhydrous THF (20 mL) and cooled to -78 °C. Under positive pressure of nitrogen, *n*-butyllithium (1.055 g, 10.29 mL, 1.6 molar, 1.1 Eq, 16.47 mmol) was added dropwise. After complete addition, the resulting solution was allowed to stir at -78 °C for 1 hour.

Separately, under a constant stream of nitrogen, approximately 50 mL of anhydrous THF was added to a flame-dried, 250 mL Erlenmeyer flask and cooled to -78 °C. Approximately 75 grams of freshly milled dry ice was then slowly added to the Erlenmeyer flask via powder funnel. The flask was vigorously swirled, ensuring that the milled dry ice was completely submerged by the solvent. The resulting slurry was then filtered via vacuum filtration under a constant stream of nitrogen. After complete removal of the solvent via vacuum filtration, the resulting milled dry ice was quickly transferred to the original round-bottom reaction flask via powder funnel (*Note*: see **General Procedure for the Milling of Dry Ice Pellets**, and **General Procedure for the Drying of Milled Dry Ice** above for additional information). The resulting reaction mixture was removed from the cooling bath and was allowed to stir at rt until complete sublimation of the dry ice was observed (*Safety Note*: the sublimation of dry ice produces a large amount of gas. To prevent a dangerous buildup of pressure, the reaction flask was left open to the atmosphere after dry ice addition).

The reaction solution was concentrated *in vacuo*. The resulting residue was then dissolved in water (25 mL) and DCM (25 mL). The resulting bilayer was transferred to a separatory funnel and the organic layer was removed. The aqueous layer was washed thrice with DCM (25 mL). The aqueous layer was then made acidic (pH 2-3) using aq. 1M HCl. The resulting aqueous solution was then extracted with DCM (4 washings, 25 mL portions). The organic layers were collected, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 4-fluoro-2,6-dimethylbenzoic acid (**1**) (2.409 g, 14.32 mmol, 95.68 % yield, n=4) as a white solid.

Spectral data are in agreement with those previously published.[1]
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.81 (d, *J* = 9.3 Hz, 2H), 2.47 (s, 6H).

General Procedure B: Ester formation via Aryl Bromides



Under positive pressure of nitrogen, 2-bromo-5-fluoro-1,3-dimethylbenzene (203 mg, 1.0 Eq, 1.00 mmol) was added to a flame-dried 100 mL round-bottom flask, before being diluted in anhydrous THF (10 mL) and cooled to -78 °C. Under positive pressure of nitrogen, *n*-butyllithium (377.6 mg, 3.684 mL, 1.6 molar, 1.1 Eq, 5.894 mmol) was added dropwise. After complete addition, the resulting solution was allowed to stir at -78 °C for 1 hour.

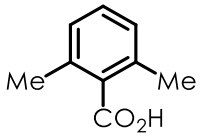
Separately, under a constant stream of nitrogen, approximately 50 mL of anhydrous THF was added to a flame-dried, 250 mL Erlenmeyer flask and cooled to -78 °C. Approximately 75 grams of freshly milled dry ice was then slowly added to the Erlenmeyer flask via powder funnel. The flask was vigorously swirled, ensuring that the milled dry ice was completely submerged by the solvent. The resulting slurry was then filtered via vacuum filtration under a constant stream of nitrogen. After complete removal of the solvent via vacuum filtration, the resulting milled dry ice was quickly transferred to the original round-bottom reaction flask via powder funnel (*Note*: see **General Procedure for the Milling of Dry Ice Pellets**, and **General Procedure for the Drying of Milled Dry Ice** above for additional information). The resulting reaction mixture was removed from the cooling bath and was allowed to stir at rt until complete sublimation of the dry ice was observed (*Safety Note*: the sublimation of dry ice produces a large amount of gas. To prevent a dangerous buildup of pressure, the reaction flask was left open to the atmosphere after dry ice addition).

The reaction solution was concentrated *in vacuo*. The resulting residue was then dissolved in anhydrous DMF (10 mL). To the reaction mixture was added potassium carbonate (1.111 g, 1.5 Eq, 8.037 mmol) and methyl iodide (912.7 mg, 402.1 µL, 1.2 Eq, 6.430 mmol) successively. The reaction mixture was then capped, fitted with a balloon, and allowed to stir at rt for 24 hours.

The resulting solution was diluted in water (25 mL) and ether (100 mL). The resulting bilayer was transferred to a separatory funnel and the aqueous layer was removed. The resulting organic layer was washed with brine (3 portions, 25 mL) and water (2 portions, 25 mL). The organic layers were collected, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in a minimal amount of DCM and transferred to a silica plug. The silica plug was eluted with a 1:1 solution of hexanes:EtOAC. The filtrate was collected and concentrated *in vacuo* to give methyl 4-fluoro-2,6-dimethylbenzoate (**19**) (79 mg, 0.43 mmol, 43 %) as a colorless oil.

Spectral data are in agreement with those previously published by our group.[4]
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.76 (d, *J* = 9.3 Hz, 2H), 3.92 (s, 3H), 2.33 (s, 6H).

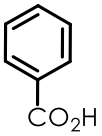
Product Characterization



2,6-dimethylbenzoic acid (**2**)

Synthesized according to **General Procedure A** using 2-bromo-1,3-dimethylbenzene (185 mg, 1.0 Eq, 1.00 mmol), yielding 2,6-dimethylbenzoic acid (140 mg, 932 µmol, 93.2 %, n=2) as a white solid.

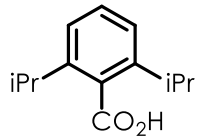
Spectral data are in agreement with those previously published.[2]
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (s, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 2H), 2.27 (s, 6H).



benzoic acid (**3**)

Synthesized according to **General Procedure A** using bromobenzene (157 mg, 1.0 Eq, 1.00 mmol), yielding benzoic acid (89 mg, 0.73 mmol, 73 %, n=2) as a white solid.

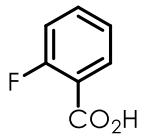
Spectral data are in agreement with those previously published.[5]
^{1}H NMR (600 MHz, DMSO-d_6) δ 12.98 (s, 1H), 7.98 – 7.94 (m, 2H), 7.65 – 7.61 (m, 1H), 7.51 (t, *J* = 7.8 Hz, 2H).



2,6-diisopropylbenzoic acid (**4**)

Synthesized according to **General Procedure A** using 2-bromo-1,3-diisopropylbenzene (241 mg, 1.0 Eq, 1.00 mmol), yielding 2,6-diisopropylbenzoic acid (147 mg, 713 µmol, 71.3 %, n=3) as a white solid.

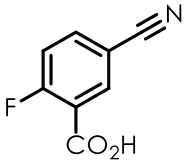
Spectral data are in agreement with those previously published.[6]
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.41 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 2H), 3.08 (hept, *J* = 6.8 Hz, 2H), 1.32 (d, *J* = 6.9 Hz, 12H).



2-fluorobenzoic acid (**5**)

Synthesized according to **General Procedure A** using 1-bromo-2-fluorobenzene (175 mg, 1.0 Eq, 1.00 mmol), yielding 2-fluorobenzoic acid (115 mg, 821 µmol, 82.1 %, n=2) as a white solid.

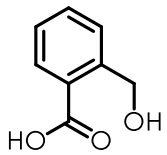
Spectral data are in agreement with those previously published.[7]
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (s, 1H), 7.91 – 7.83 (m, 1H), 7.65 (tdd, *J* = 7.5, 4.9, 1.8 Hz, 1H), 7.36 – 7.24 (m, 2H).



5-cyano-2-fluorobenzoic acid (**6**)

Synthesized according to **General Procedure A** using 3-Bromo-4-Fluoro benzonitrile (200 mg, 1.0 Eq, 1.00 mmol), yielding 5-cyano-2-fluorobenzoic acid (94 mg, 0.57 mmol, 57 %, n=2) as a white solid.

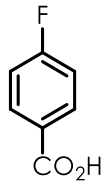
Spectral data are in agreement with those previously published.[8]
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.81 (s, 1H), 8.31 (dd, *J* = 6.8, 2.2 Hz, 1H), 8.16 (ddd, *J* = 8.8, 4.4, 2.3 Hz, 1H), 7.59 (dd, *J* = 10.5, 8.7 Hz, 1H).



2-(hydroxymethyl)benzoic acid (**7**)

Synthesized according to a modified **General Procedure A** using (2-bromophenyl)methanol (187 mg, 1.0 Eq, 1.00 mmol) and *n*-butyllithium (135 mg, 840 µL, 2.5 molar, 2.1 Eq, 2.10 mmol), yielding 2-(hydroxymethyl)benzoic acid (106 mg, 697 µmol, 69.7 %, n=2) as a white solid.

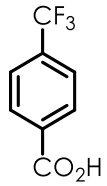
Spectral data are in agreement with those previously published.[9]
^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.54 (td, *J* = 7.6, 1.4 Hz, 1H), 7.35 (td, *J* = 7.6, 1.3 Hz, 1H), 4.91 (s, 2H).



4-fluorobenzoic acid (**8**)

Synthesized according to **General Procedure A** using 1-bromo-4-fluorobenzene (175 mg, 1.0 Eq, 1.00 mmol), yielding 4-fluorobenzoic acid (102 mg, 728 µmol, 72.8 %, n=2) as a white solid.

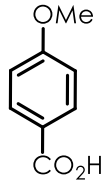
Spectral data are in agreement with those previously published.[3]
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 8.06 – 7.95 (m, 2H), 7.33 (t, *J* = 8.7 Hz, 2H).



4-(trifluoromethyl)benzoic acid (**9**)

Synthesized according to **General Procedure A** using 1-bromo-4-(trifluoromethyl)benzene (225 mg, 1.0 Eq, 1.00 mmol), yielding 4-(trifluoromethyl)benzoic acid (134 mg, 705 µmol, 70.5 %, n=2) as a white solid.

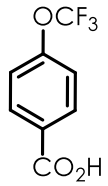
Spectral data are in agreement with those previously published.[10]
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.49 (s, 1H), 8.14 (d, *J* = 8.1 Hz, 2H), 7.89 (d, *J* = 8.1 Hz, 2H).



4-methoxybenzoic acid (**10**)

Synthesized according to **General Procedure A** using 1-bromo-4-methoxybenzene (187 mg, 1.0 Eq, 1.00 mmol), yielding 4-methoxybenzoic acid (99 mg, 0.65 mmol, 65 %, n=2) as a white solid.

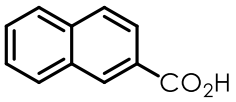
Spectral data are in agreement with those previously published.[3]
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.62 (s, 1H), 7.94 – 7.86 (m, 2H), 7.06 – 6.98 (m, 2H), 3.83 (s, 3H).



4-(trifluoromethoxy)benzoic acid (**11**)

Synthesized according to **General Procedure A** using 1-bromo-4-(trifluoromethoxy)benzene (241 mg, 1.0 Eq, 1.00 mmol), yielding 4-(trifluoromethoxy)benzoic acid (142 mg, 689 µmol, 69% yield, n = 2) as a white solid.

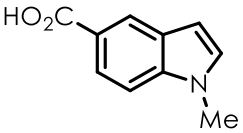
Spectral data are in agreement with those previously published.[11]
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.24 (s, 1H), 8.11 – 8.03 (m, 2H), 7.49 (d, *J* = 8.3 Hz, 2H).



2-naphthoic acid (**12**)

Synthesized according to **General Procedure A** using 2-bromonaphthalene (207 mg, 1.0 Eq, 1.00 mmol), yielding 2-naphthoic acid (137 mg, 796 µmol, 79.6 %, n=2) as a light brown solid.

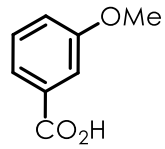
Spectral data are in agreement with those previously published.[2]
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 8.61 (d, *J* = 1.5 Hz, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 8.05 – 7.96 (m, 3H), 7.70 – 7.58 (m, 2H).



1-methyl-1H-indole-5-carboxylic acid (**13**)

Synthesized according to **General Procedure A** using 5-bromo-1-methyl-1H-indole (synthesized according to literature procedure) (210 mg, 1.0 Eq, 1.00 mmol), yielding 1-methyl-1H-indole-5-carboxylic acid (108 mg, 616 µmol, 61.6 %, n=2) as a white solid.

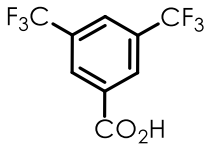
Spectral data are in agreement with those previously published.[12]
^{1}H NMR (600 MHz, DMSO-d_6) δ 12.44 (s, 1H), 8.23 (d, J = 1.6 Hz, 1H), 7.77 (dd, J = 8.6, 1.6 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.44 (d, J = 3.1 Hz, 1H), 6.58 (dd, J = 3.1, 0.8 Hz, 1H), 3.83 (s, 3H).



3-methoxybenzoic acid (**14**)

Synthesized according to **General Procedure A** using 1-bromo-3-methoxybenzene (187 mg, 1.0 Eq, 1.00 mmol), yielding 3-methoxybenzoic acid (105 mg, 690 µmol, 69.0 %, n=2) as a white solid.

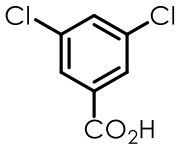
Spectral data are in agreement with those previously published.[2]
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.75 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.65 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.19 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 3.90 (s, 3H).



3,5-bis(trifluoromethyl)benzoic acid (**15**)

Synthesized according to **General Procedure A** using 1-bromo-3,5-bis(trifluoromethyl)benzene (293 mg, 1.0 Eq, 1.00 mmol), yielding 3,5-bis(trifluoromethyl)benzoic acid (233 mg, 903 µmol, 90.3 %, n=2) as a white solid.

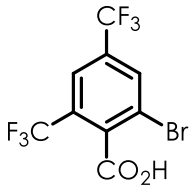
Spectral data are in agreement with those previously published.[5]
^{1}H NMR (600 MHz, DMSO-d_6) δ 14.06 (s, 1H), 8.44 (m, 3H).



3,5-dichlorobenzoic acid (**16**)

Synthesized according to a modified **General Procedure A** using 1-bromo-3,5-dichlorobenzene (226 mg, 1.0 Eq, 1.00 mmol) and *n*-butyllithium (67.3 mg, 420 µL, 2.5 molar, 1.05 Eq, 1.05 mmol), yielding 3,5-dichlorobenzoic acid (153 mg, 801 µmol, 80.1 %, n=2) as a white solid.

Spectral data are in agreement with those previously published.[4]
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 2.0 Hz, 2H), 7.64 (t, *J* = 2.0 Hz, 1H).



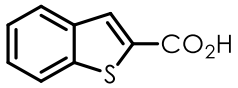
2-bromo-4,6-bis(trifluoromethyl)benzoic acid (**17**)

Note: 2,2,6,6-tetramethylpiperidine was distilled under reduced pressure prior to use.
Synthesized according to a modified **General Procedure A**: Under positive pressure of nitrogen, 2,2,6,6-tetramethylpiperidine (1.446 g, 1.73 mL, 1.0 Eq, 10.24 mmol) was added to a flame-dried 100 mL round-bottom flask before being diluted in anhydrous THF (20 mL) and cooled to -78 °C. Under positive pressure of nitrogen, *n*-butyllithium (655.9 mg, 6.399 mL, 1.6 molar, 1.0 Eq, 10.24 mmol) was added dropwise. After complete addition, the resulting solution was allowed to stir at -78 °C for 10 min. A solution of 3,5-bis-trifluoromethylbromobenzene (3.000 g, 1.78 mL, 1.0 Eq, 10.24 mmol) in THF (10 mL) was then slowly added dropwise. After complete addition, the resulting solution was allowed to stir at -78 °C for 1 hour.

Approximately 75 grams of dry ice was finely milled using a mortar and pestle before being added to the reaction mixture via powder funnel. The resulting slurry was removed from the cooling bath and was allowed to stir at rt until complete sublimation of the dry ice was observed.

The resulting solution was diluted in water (25 mL) and ether (25 mL). The resulting bilayer was transferred to a separatory funnel and the aqueous layer was extracted. The resulting organic layer was extracted thrice with water (25 mL). The aqueous washings were combined and made acidic (pH 2-3) using aq. 1M HCl. The resulting aqueous solution was added to a separatory funnel and extracted with DCM (4 washings, 25 mL portions). The organic layers were collected, dried over $MgSO_4$, filtered, and concentrated *in vacuo* yielding 2-bromo-4,6-bis(trifluoromethyl)benzoic acid (2.801 g, 8.311 mmol, 81.16 %, n=2) as a white solid.

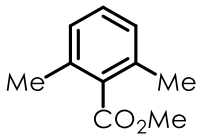
Spectral data are in agreement with those previously published.[13]
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.12 (s, 1H), 7.95 (s, 1H).



benzo[b]thiophene-2-carboxylic acid (**18**)

Synthesized according to a modified **General Procedure A**: the reaction was carried out according **General Procedure A** using benzo[b]thiophene (134 mg, 1.0 Eq, 1.00 mmol). After complete sublimation of the dry ice in the reaction mixture was observed, the reaction solution was concentrated *in vacuo*. The resulting residue was dissolved in water (25 mL) and DCM (25 mL). The resulting bilayer was transferred to a separatory funnel and the organic layer was removed. The aqueous layer was washed thrice with DCM (25 mL). The aqueous layer was then made acidic (pH 2-3) using aq. 1M HCl. The resulting aqueous solution was extracted with EtOAc (4 washings, 25 mL portions). The organic layers were collected, dried over $MgSO_4$, filtered, and concentrated *in vacuo*, yielding benzo[b]thiophene-2-carboxylic acid (177 mg, 993 µmol, 99.3 %, n = 2) as a white solid.

Spectral data are in agreement with those previously published.[14]
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 0.8 Hz, 1H), 8.05 (dq, *J* = 8.1, 0.9 Hz, 1H), 8.01 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.51 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.46 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H).



methyl 2,6-dimethylbenzoate (**20**)

Synthesized according to **General Procedure B** using 2-bromo-1,3-dimethylbenzene (185 mg, 1.0 Eq, 1.00 mmol), yielding methyl 2,6-dimethylbenzoate (72 mg, 0.44 mmol, 44 %, n=2) as a colorless oil.

Spectral data are in agreement with those previously published by our group.[4]
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 2H), 3.94 (s, 3H), 2.34 (s, 6H).

References

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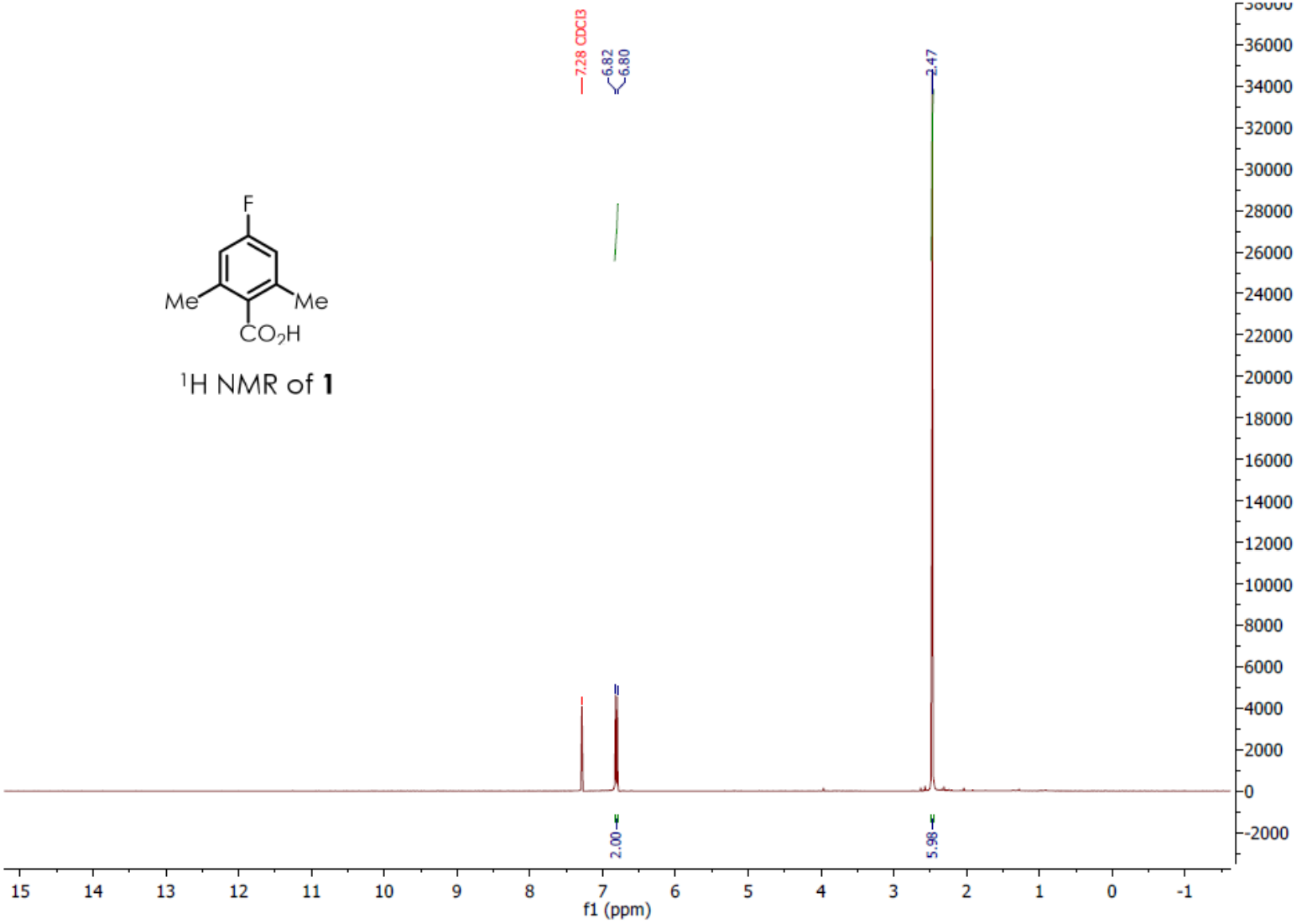
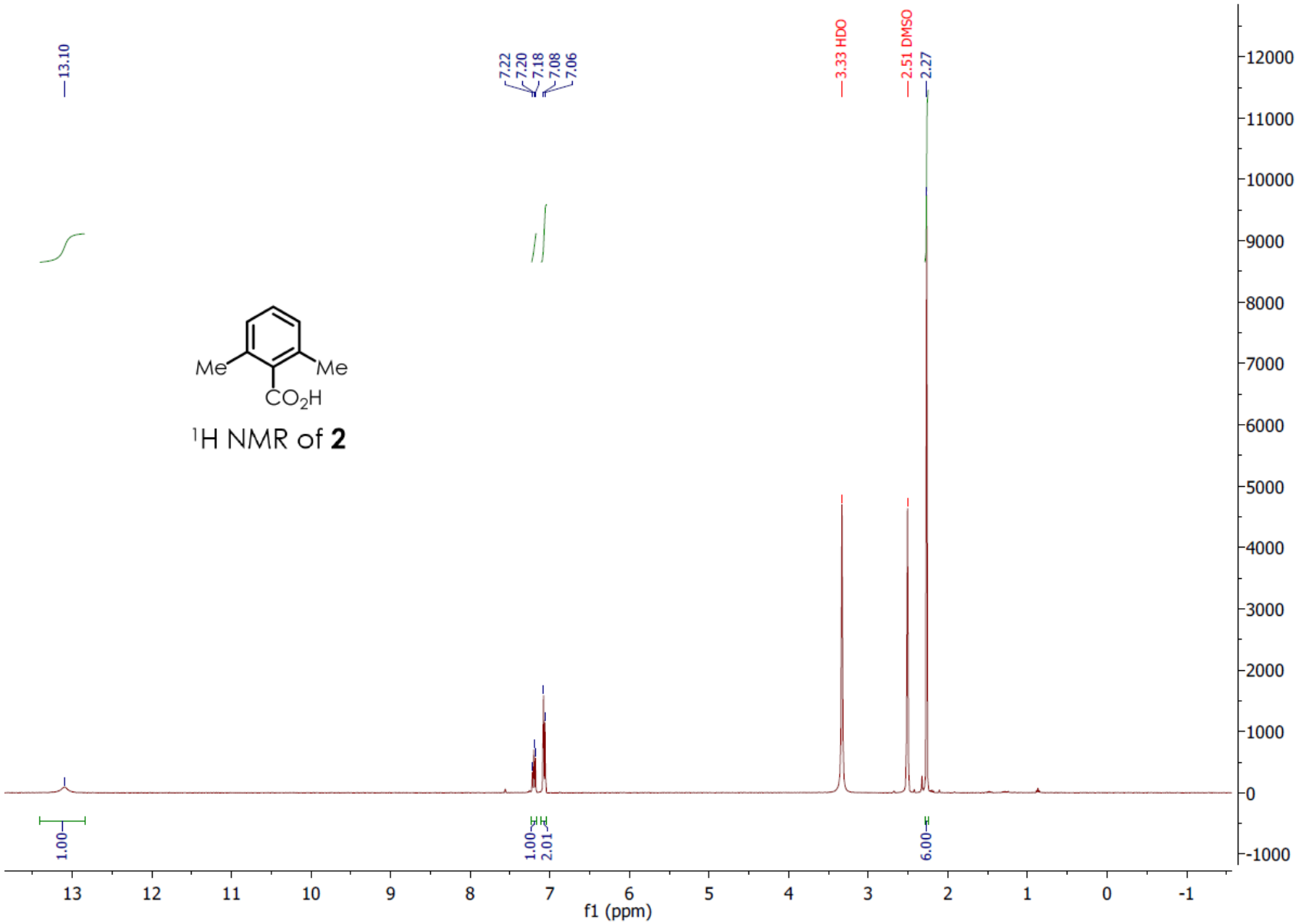
Spectral Data

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7.22
7.20
7.18
7.08
7.06
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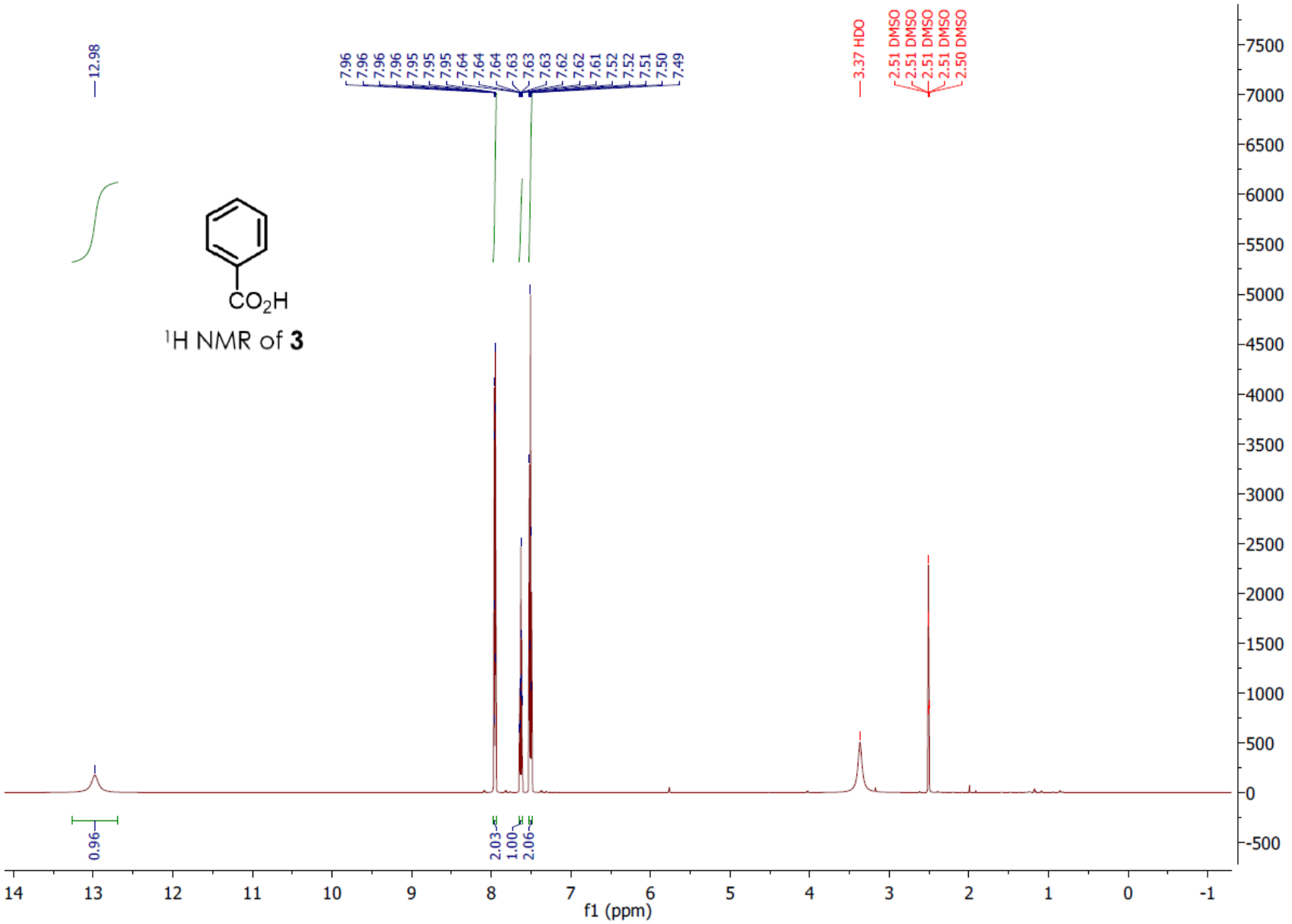
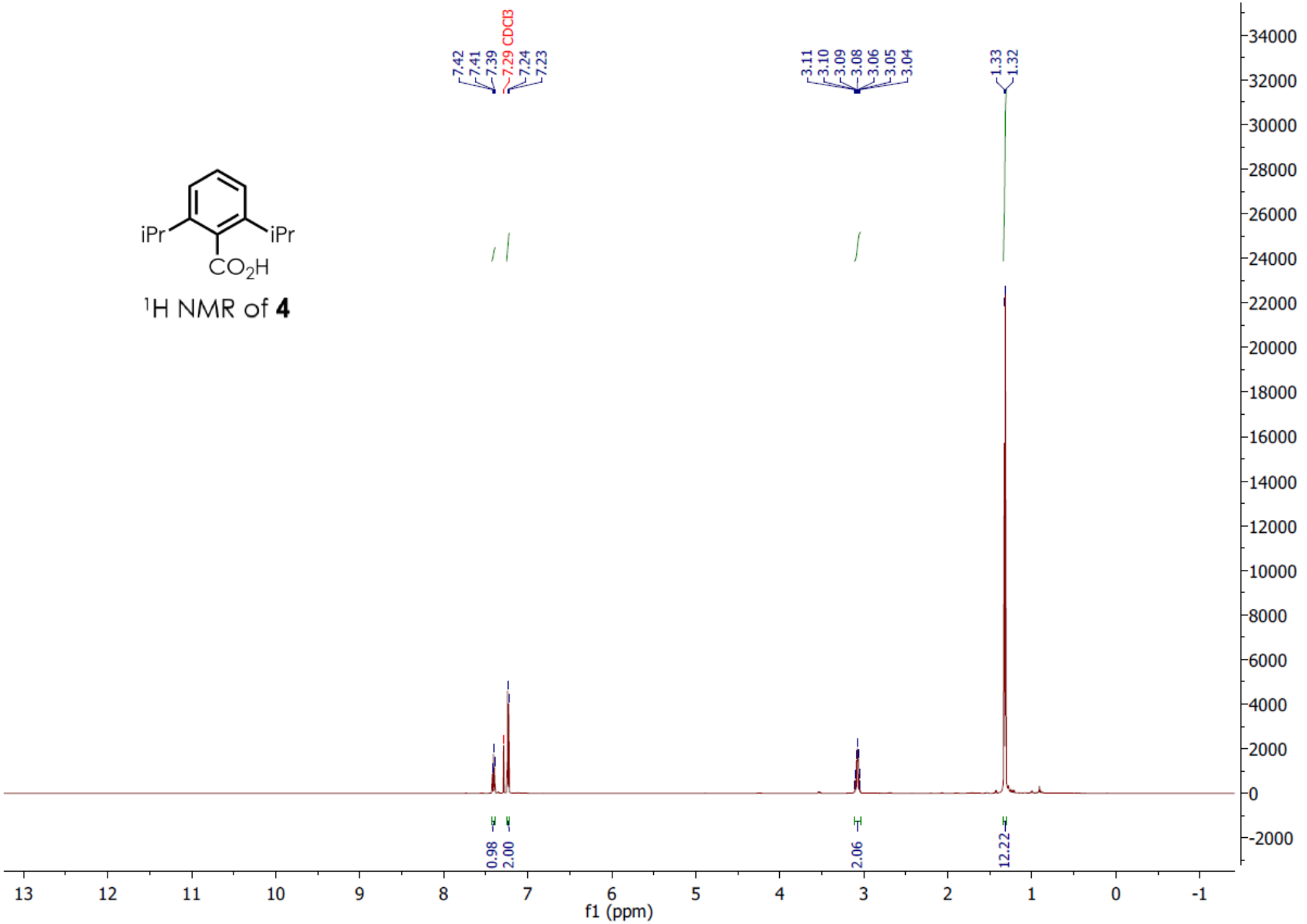
2.51 DMSO
2.27
Me
Me
CO2H
1H NMR of 2
1.00
1.00
2.01
6.00
f1 (ppm)


12.98
7.96
7.96
7.96
7.96
7.95
7.95
7.95
7.64
7.64
7.64
7.63
7.63
7.63
7.62
7.62
7.61
7.52
7.52
7.51
7.50
7.49
3.37 HDO
2.51 DMSO
2.51 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
CO2H
1H NMR of 3
0.96
2.03
1.00
2.06
f1 (ppm)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iPr
CO2H
1H NMR of 4
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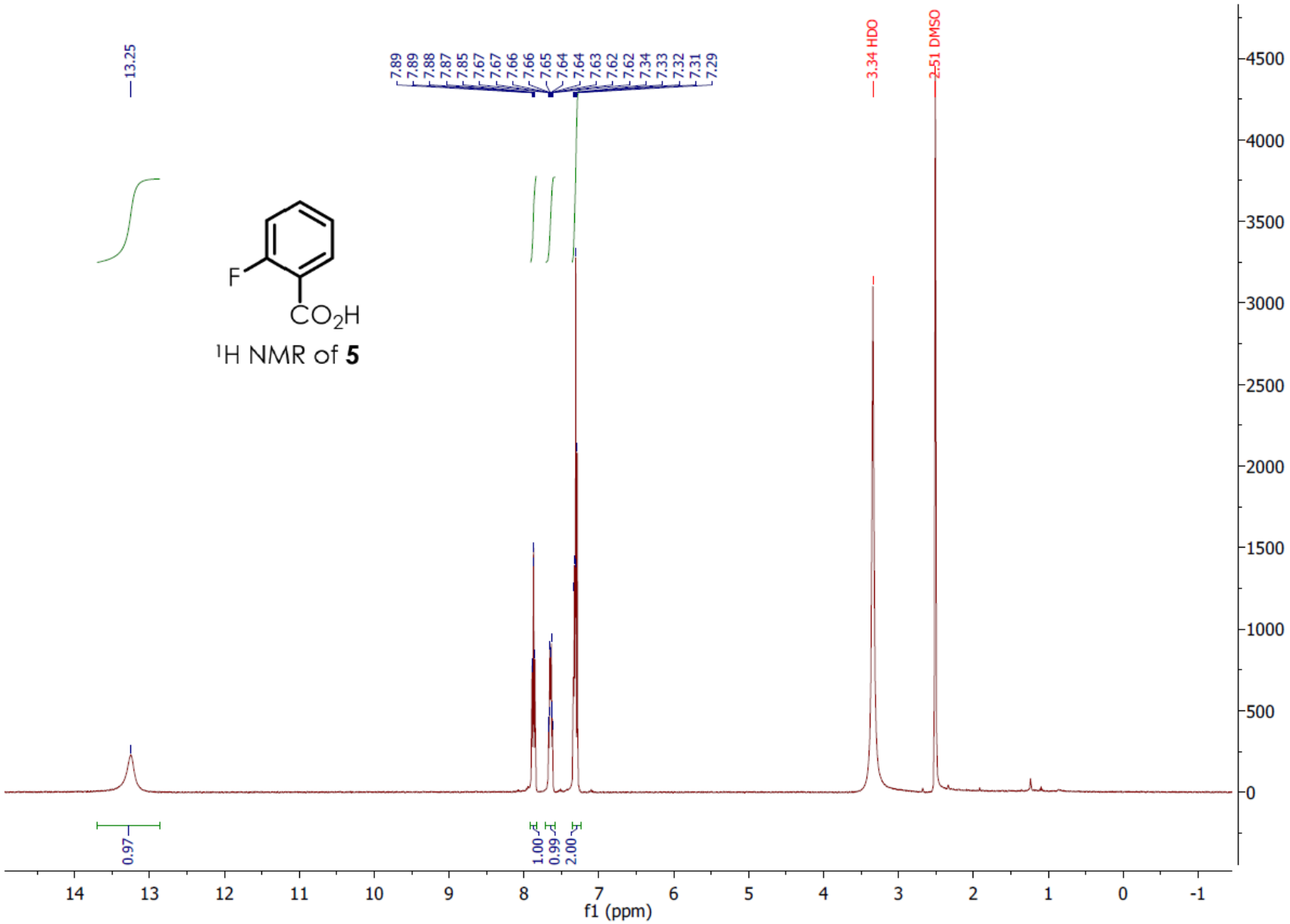
7.41
7.39
7.29 CDCl3
7.24
7.23
3.11
3.10
3.09
3.08
3.06
3.05
3.04
1.33
1.32
0.98
2.00
2.06
12.22
f1 (ppm)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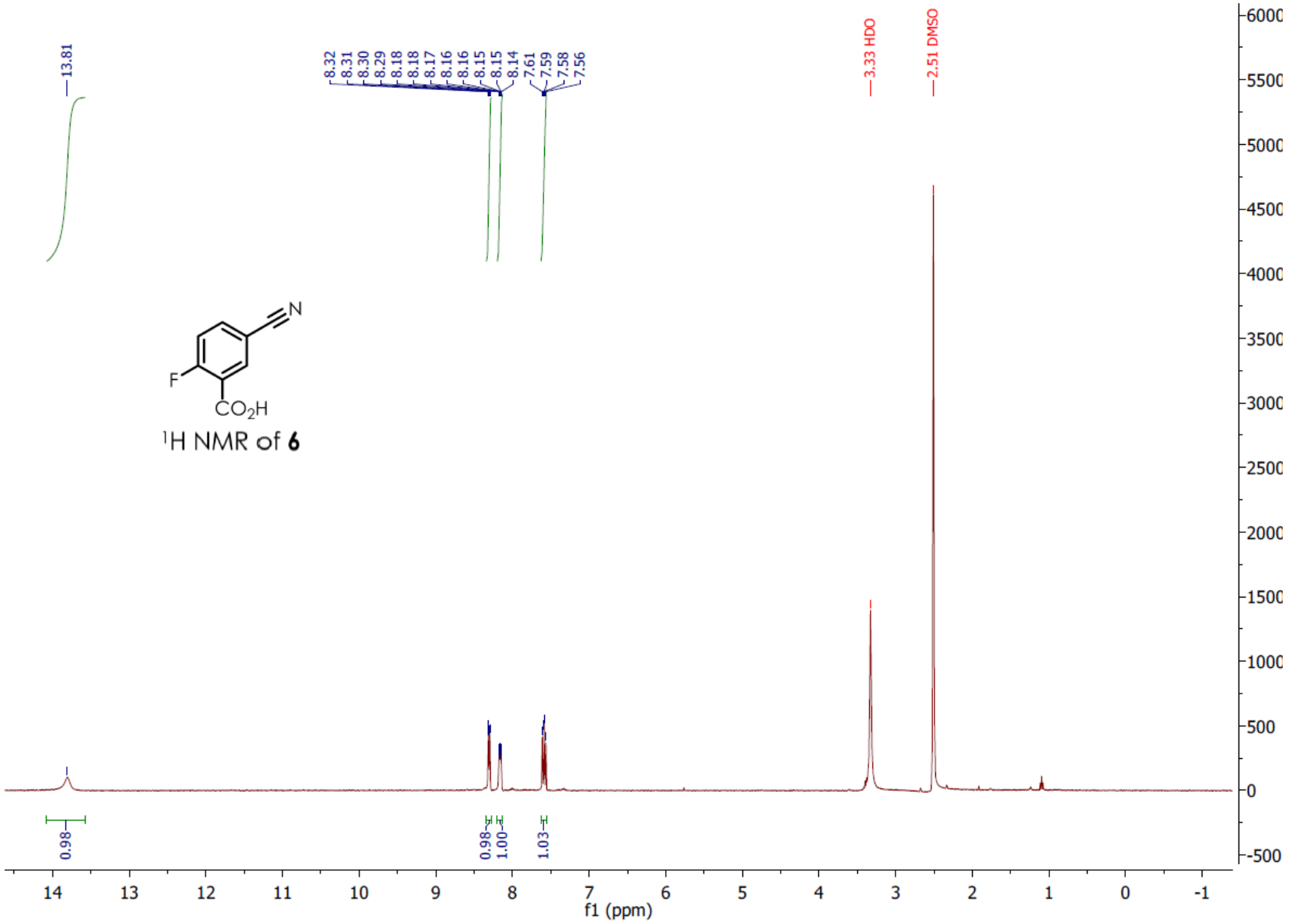
7.89
7.89
7.88
7.87
7.85
7.67
7.67
7.66
7.66
7.65
7.64
7.64
7.63
7.62
7.62
7.34
7.33
7.32
7.31
7.29
3.34 HDO
2.51 DMSO
F
CO2H
1H NMR of 5
0.97
1.00
0.99
2.00
f1 (ppm)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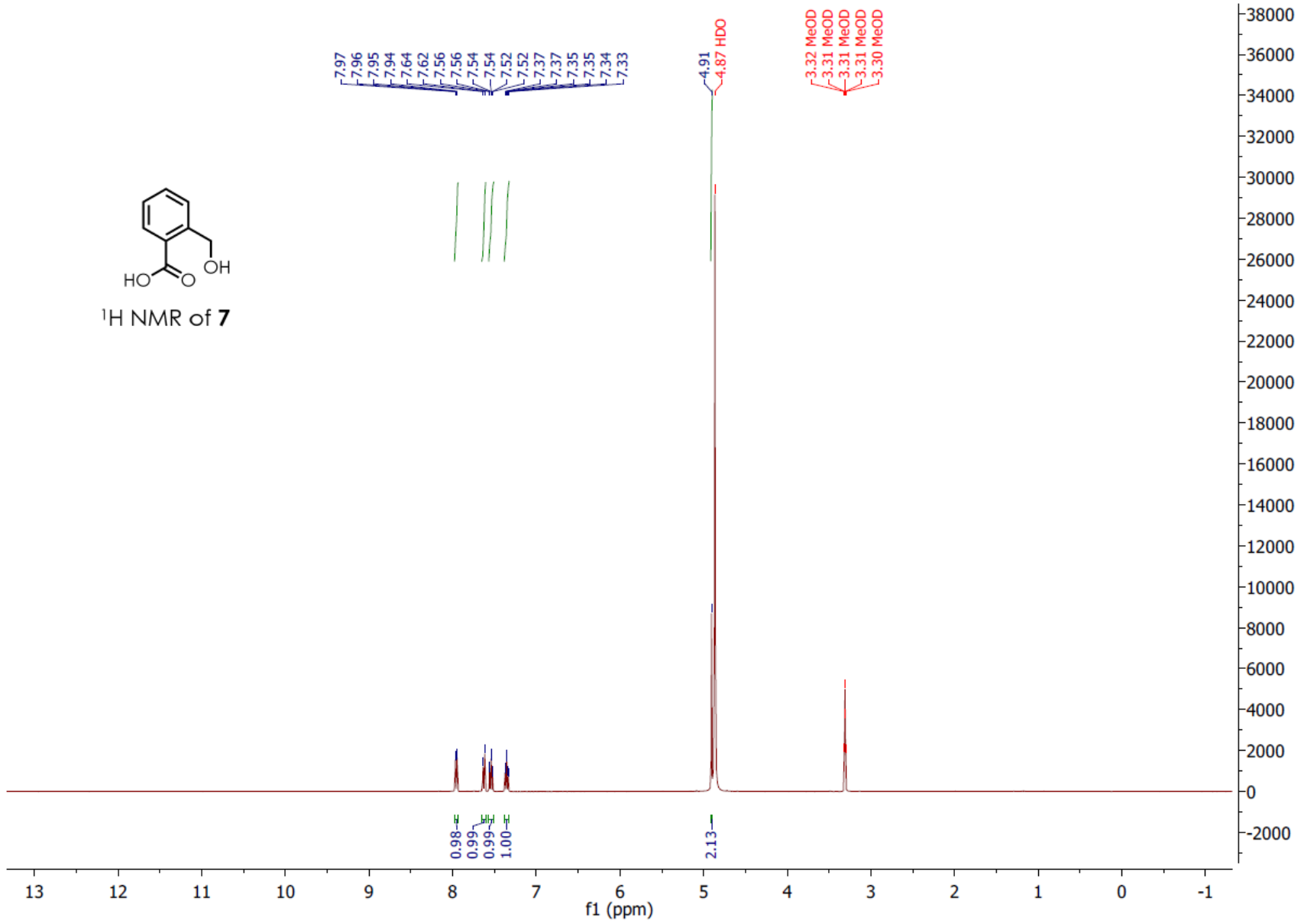
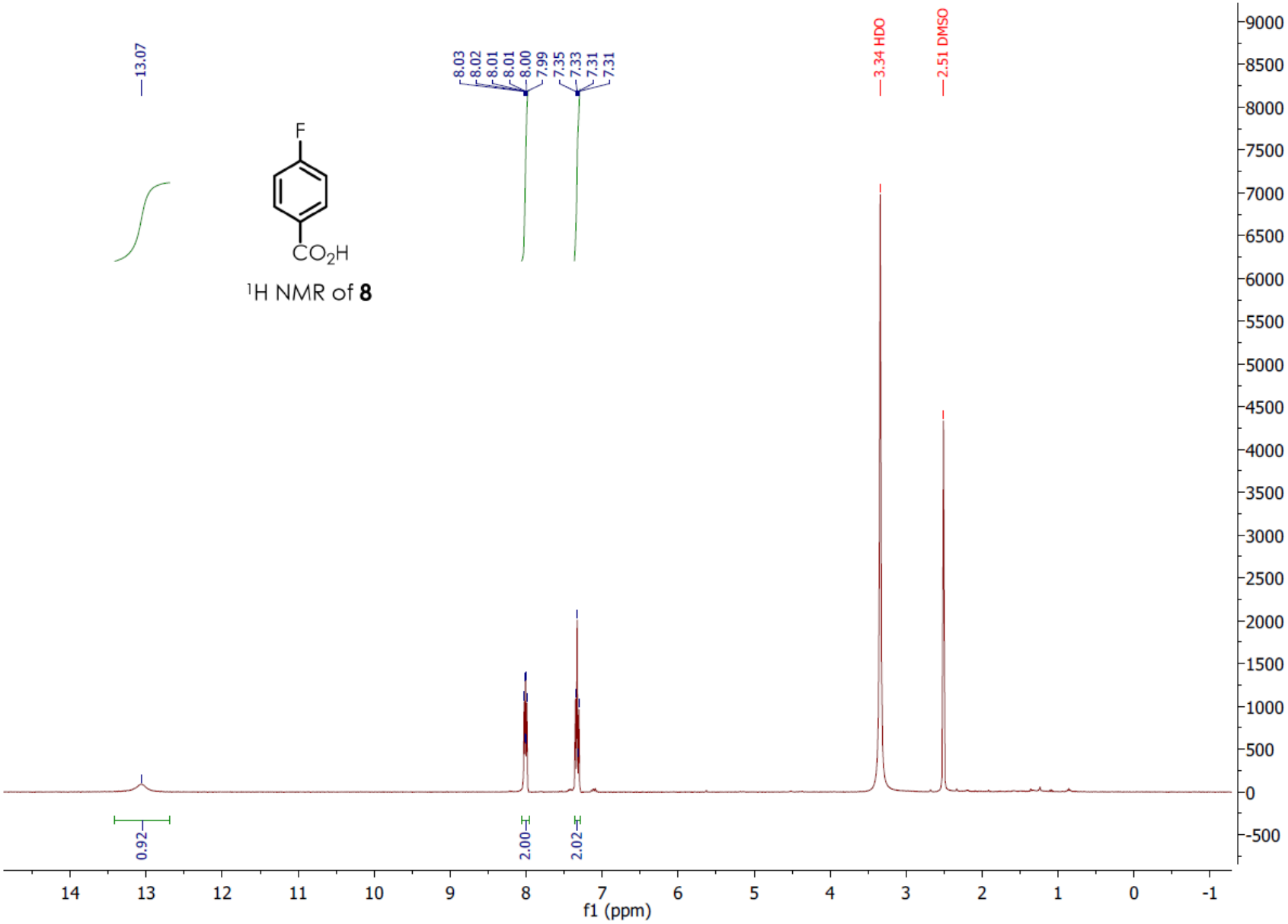
8.32
8.31
8.30
8.29
8.18
8.18
8.17
8.16
8.16
8.15
8.15
8.14
7.61
7.59
7.58
7.56
3.33 HDO
2.51 DMSO
F
N
CO2H
0.98
0.98
1.00
1.03
f1 (ppm)

^{1}H NMR of **6**


7.97
7.96
7.95
7.94
7.64
7.62
7.56
7.56
7.54
7.54
7.52
7.52
7.37
7.37
7.35
7.35
7.34
7.33
4.91
4.87 HDO
3.32 MeOD
3.31 MeOD
3.31 MeOD
3.31 MeOD
3.30 MeOD
HO
O
OH
0.98
0.99
0.99
1.00
2.13
f1 (ppm)

^{1}H NMR of **7**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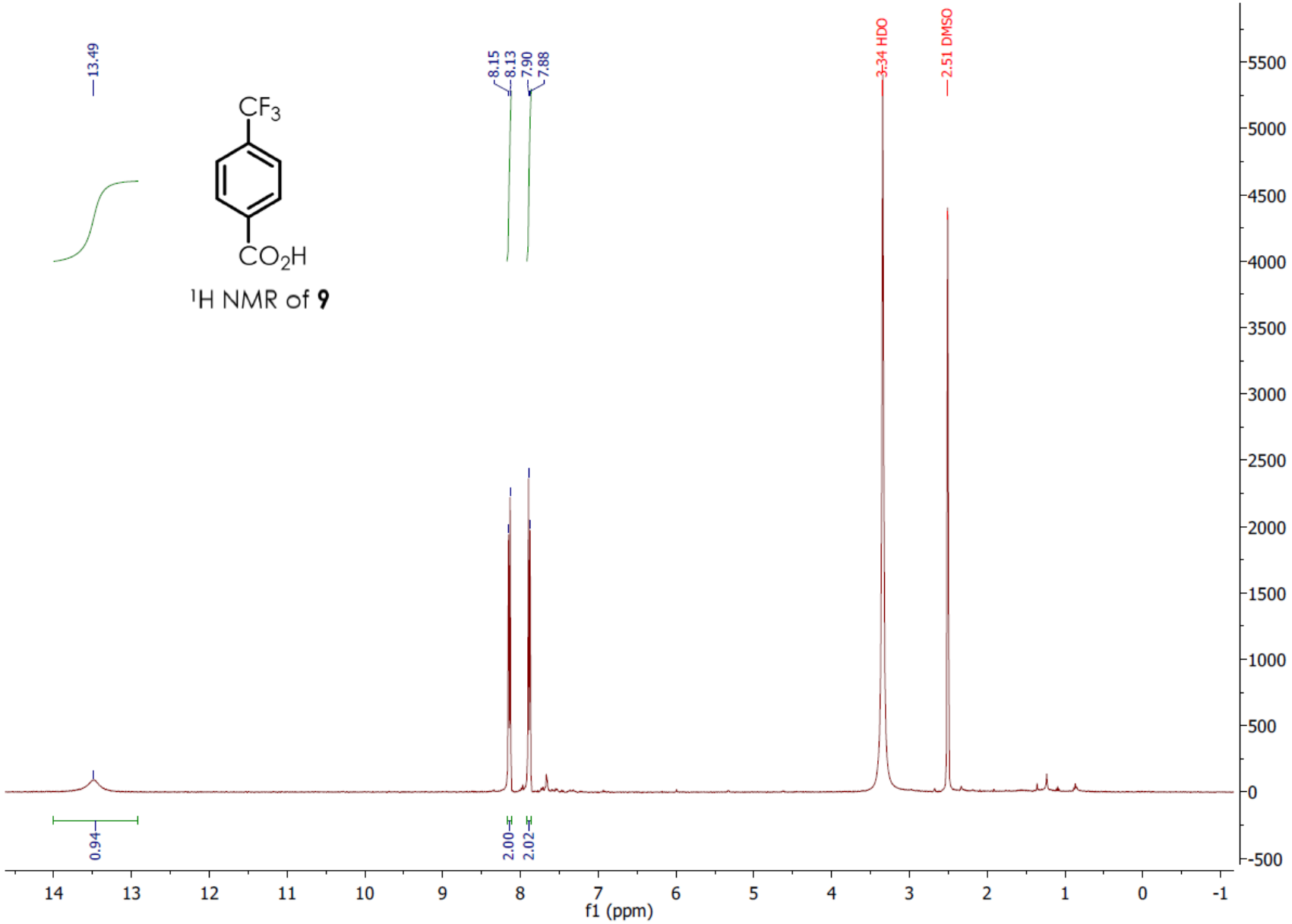
8.03
8.02
8.01
8.01
8.00
7.99
7.35
7.33
7.31
7.31
3.34 HDO
2.51 DMSO
F
CO2H
1H NMR of 8
0.92
2.00
2.02
f1 (ppm)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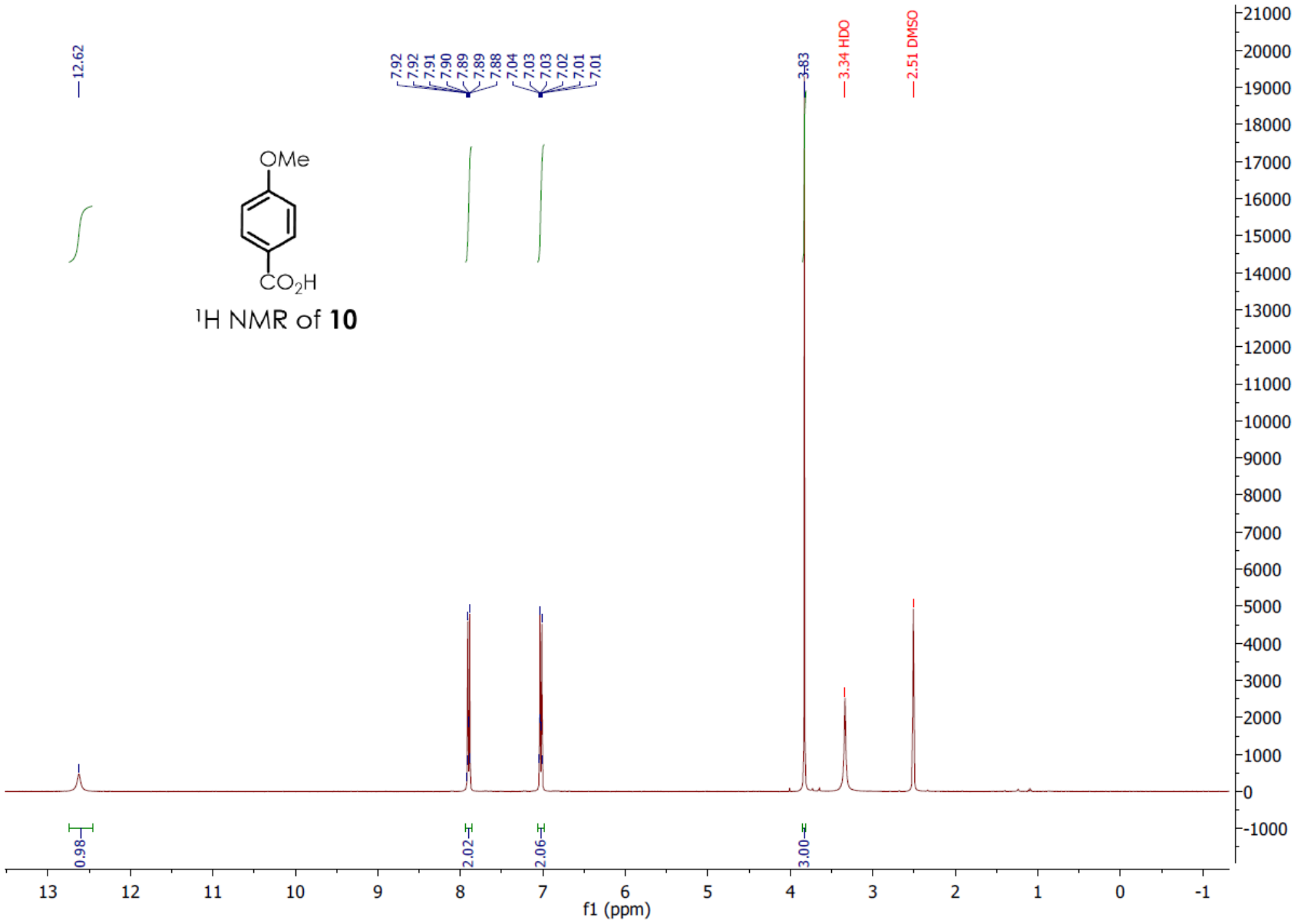
8.15
8.13
7.90
7.88
3.34 HDO
2.51 DMSO
CF3
CO2H
0.94
2.00
2.02
f1 (ppm)

^{1}H NMR of **9**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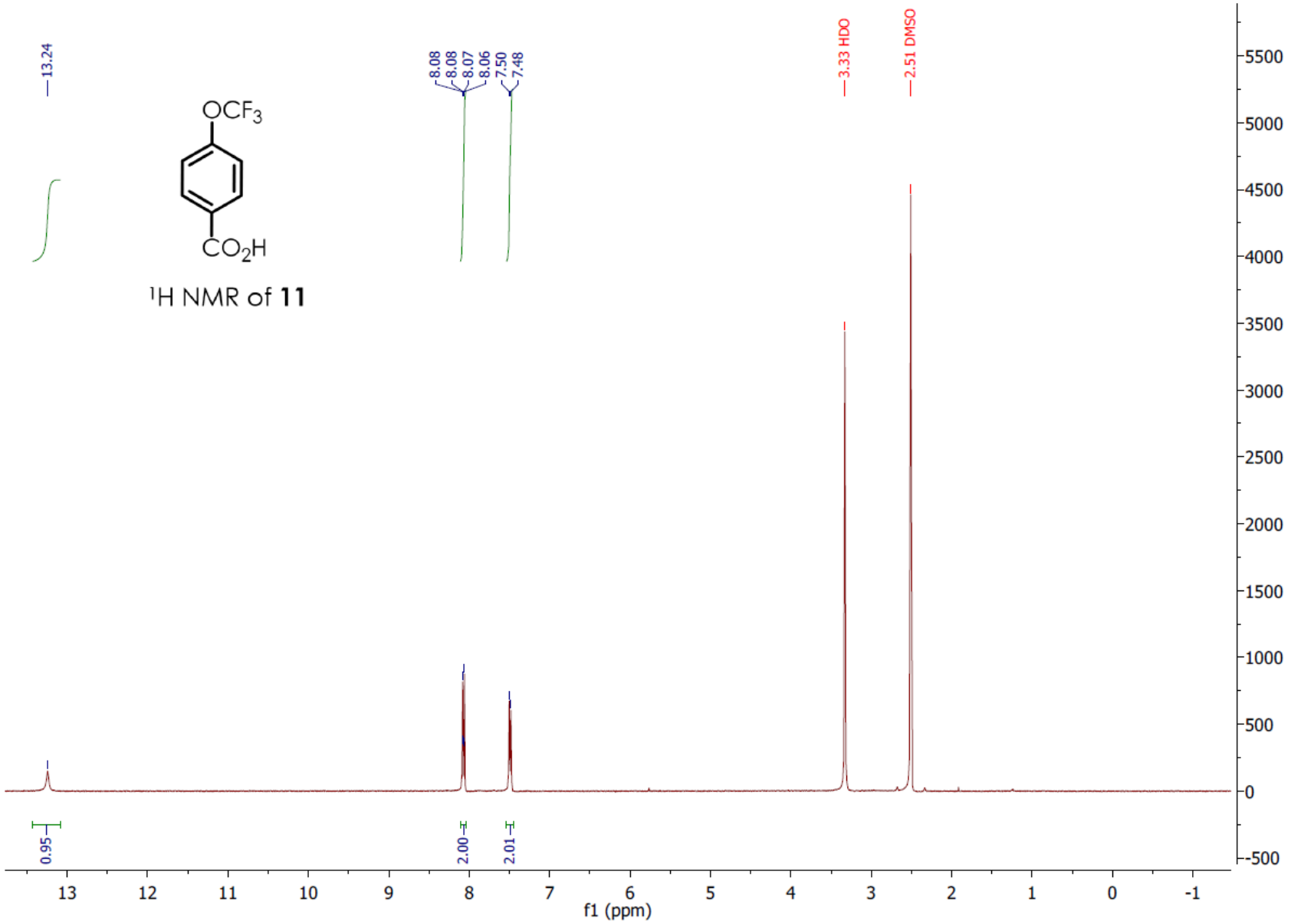
7.92
7.92
7.91
7.90
7.89
7.89
7.88
7.04
7.03
7.03
7.02
7.01
7.01
3.83
3.34 HDO
2.51 DMSO
OMe
CO2H
1H NMR of 10
0.98
2.02
2.06
3.00
f1 (ppm)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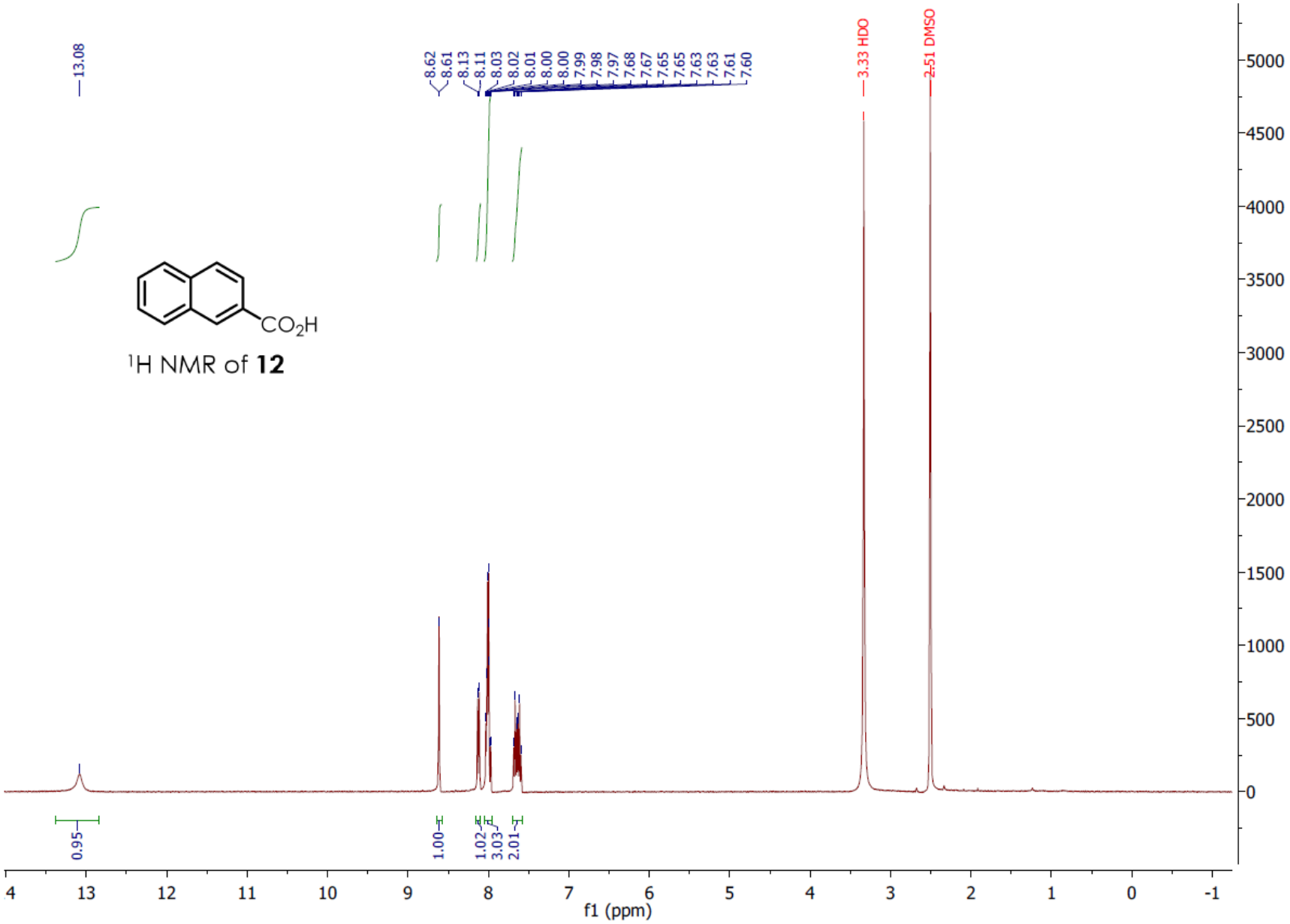
8.08
8.08
8.07
8.06
7.50
7.48
3.33 HDO
2.51 DMSO
OCF3
CO2H
0.95
2.00
2.01
f1 (ppm)

^{1}H NMR of **11**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8.62
8.61
8.13
8.11
8.03
8.02
8.01
8.00
8.00
7.99
7.98
7.97
7.68
7.67
7.65
7.65
7.63
7.63
7.61
7.60
3.33 HDO
2.51 DMSO
CO2H
1H NMR of 12
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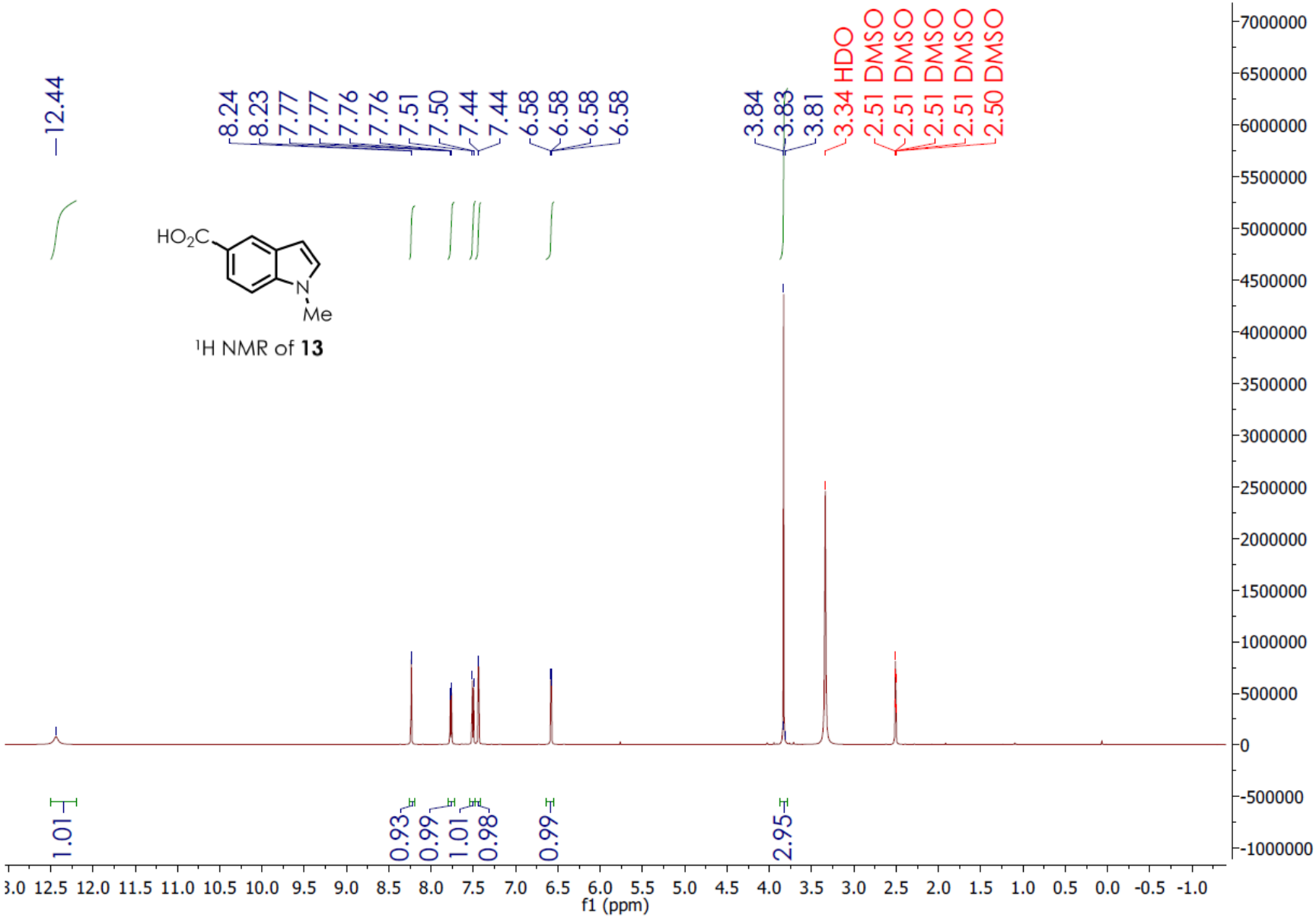
1.00
1.02
3.03
2.01
f1 (ppm)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7.77
7.76
7.76
7.51
7.50
7.44
7.44
6.58
6.58
6.58
6.58
3.84
3.83
3.81
3.34 HDO
2.51 DMSO
2.51 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
HO2C
N
Me
1H NMR of 13
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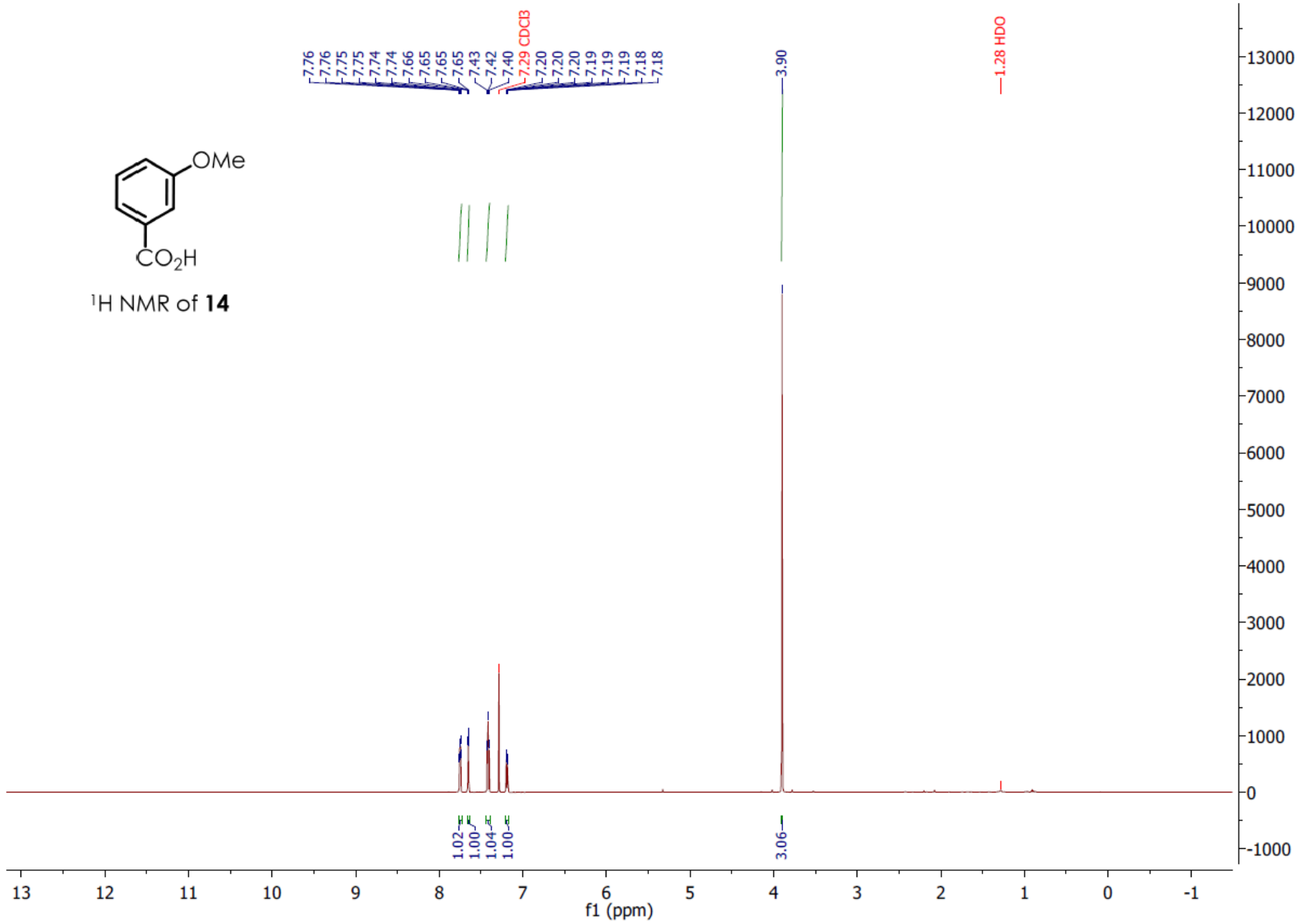
0.93
0.99
1.01
0.98
0.99
2.95
f1 (ppm)


OMe
CO2H
1H NMR of 14
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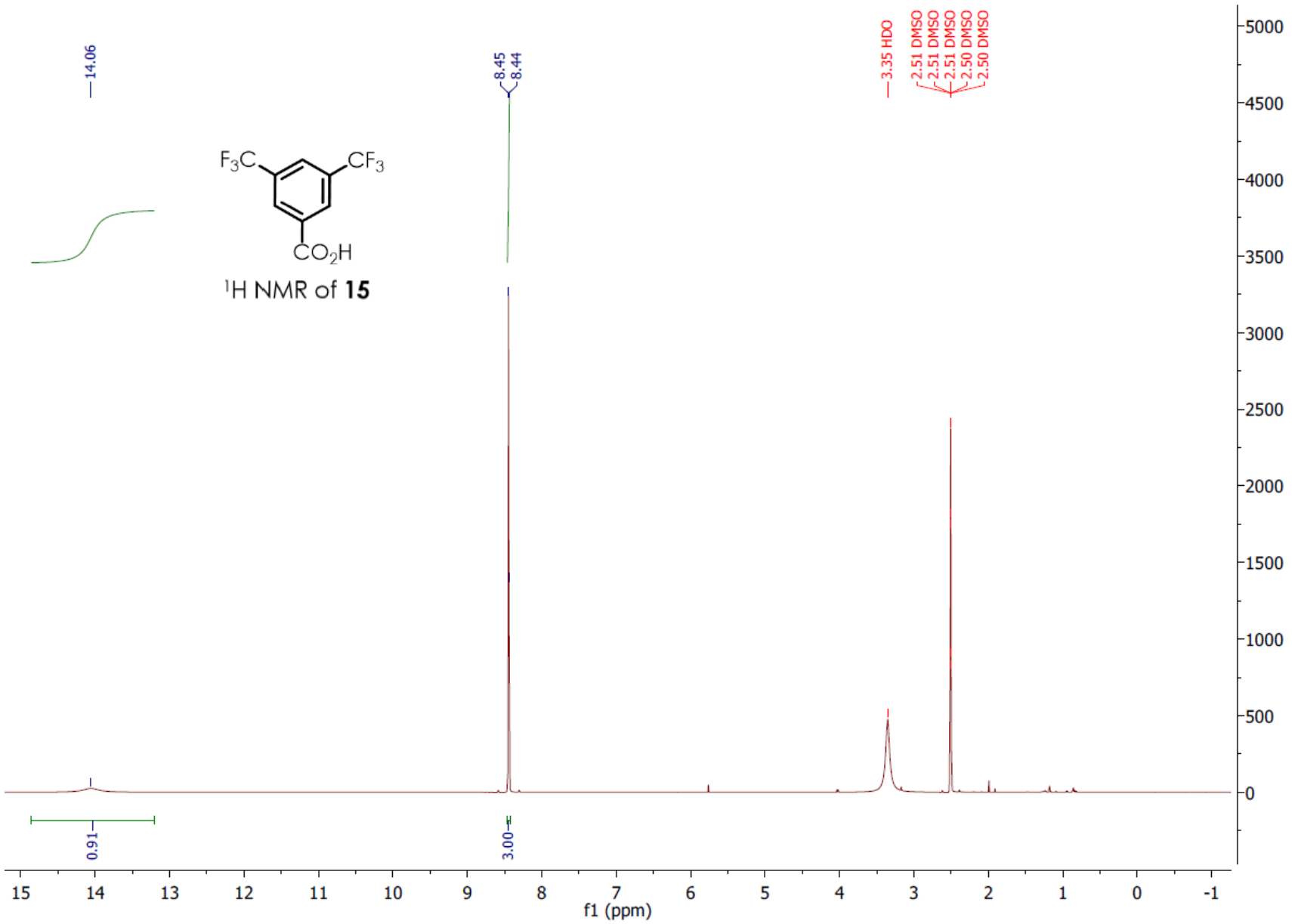
7.76
7.75
7.75
7.74
7.74
7.66
7.65
7.65
7.65
7.43
7.42
7.40
7.29 CDCl3
7.20
7.20
7.20
7.19
7.19
7.19
7.18
7.18
3.90
1.28 HDO
1.02
1.00
1.04
1.00
3.06
f1 (ppm)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8.45
8.44
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2.51 DMSO
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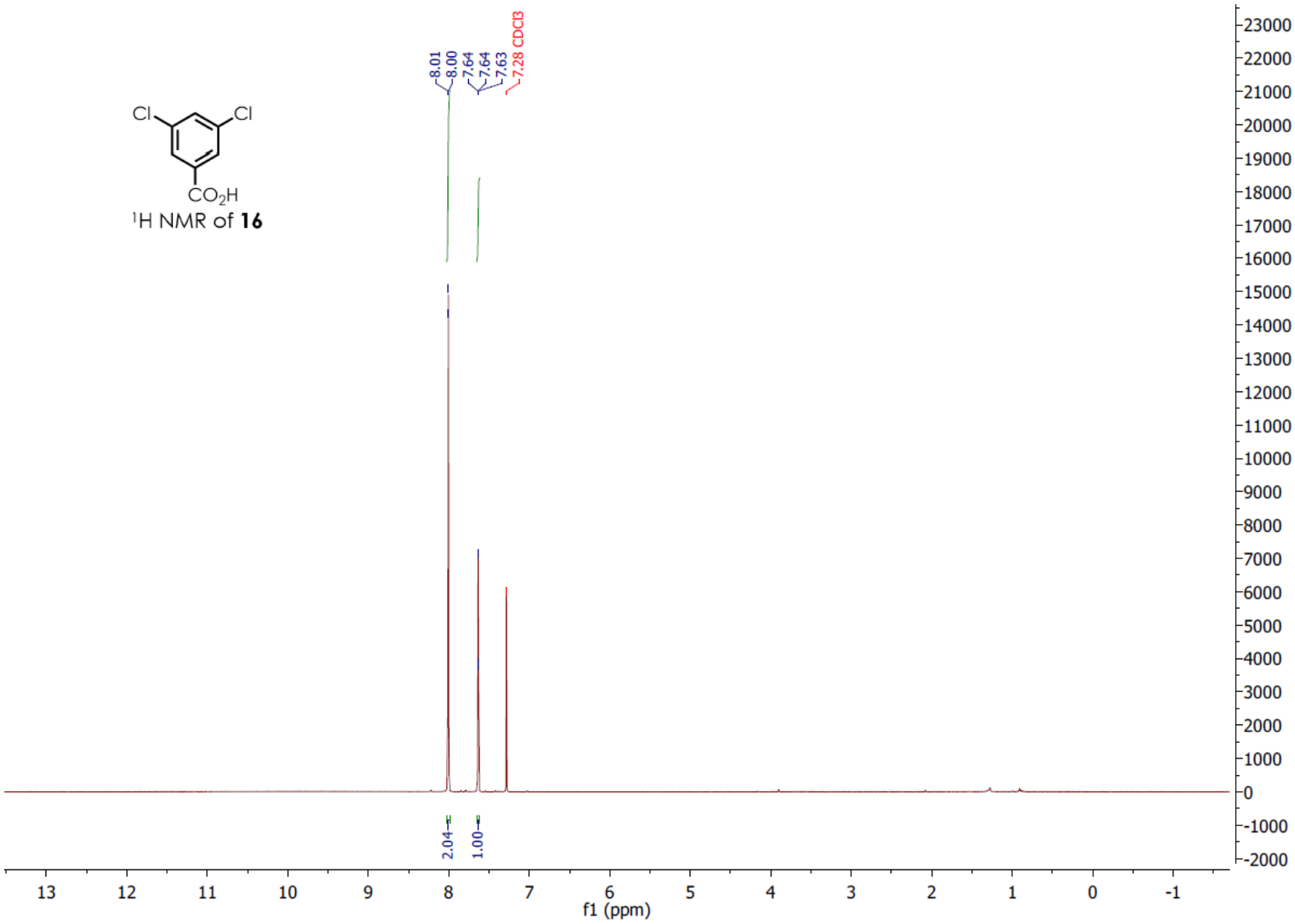
2.50 DMSO
2.50 DMSO
F3C
CF3
CO2H
1H NMR of 15
0.91
3.00
f1 (ppm)


Cl
Cl
CO2H
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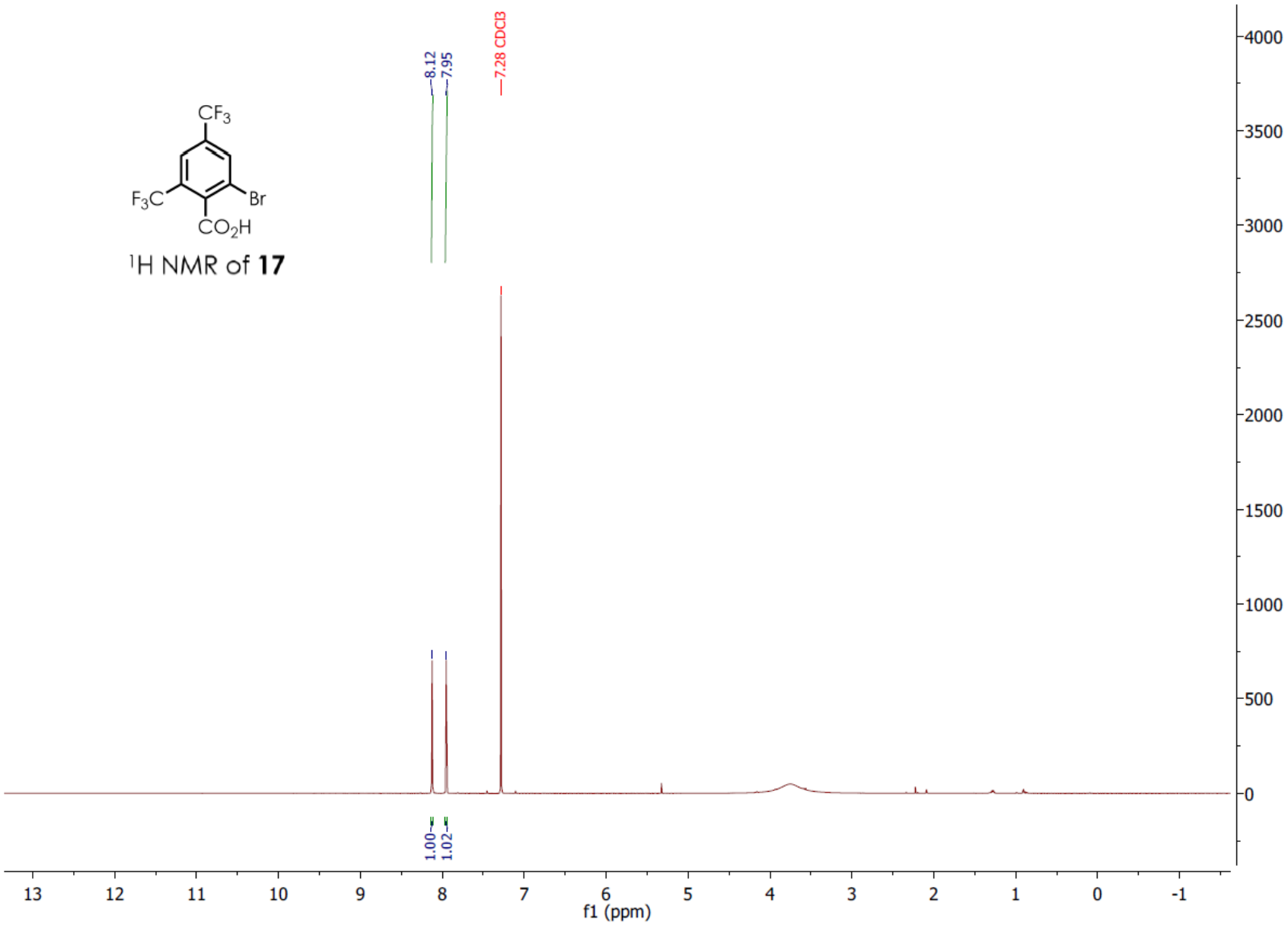
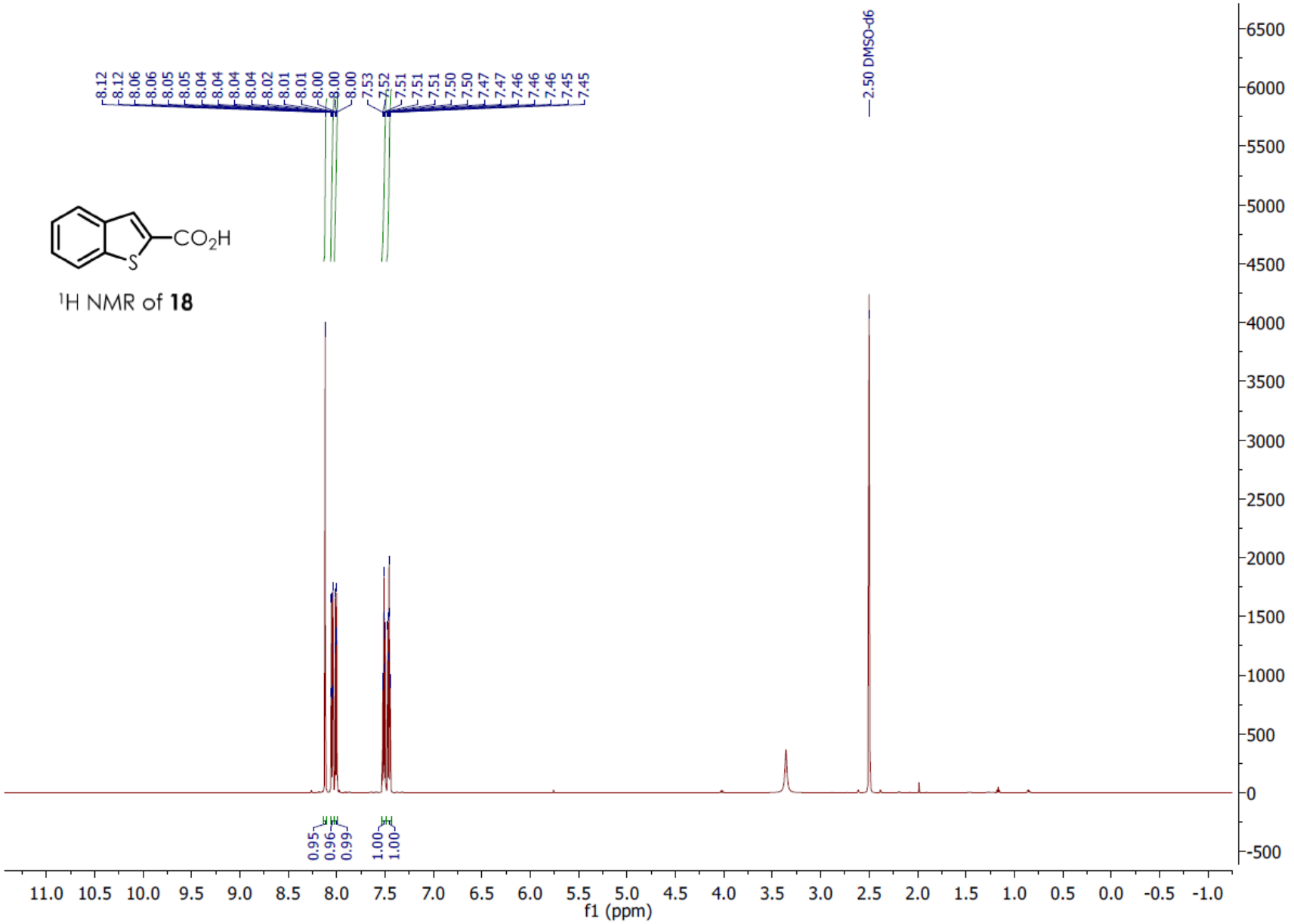
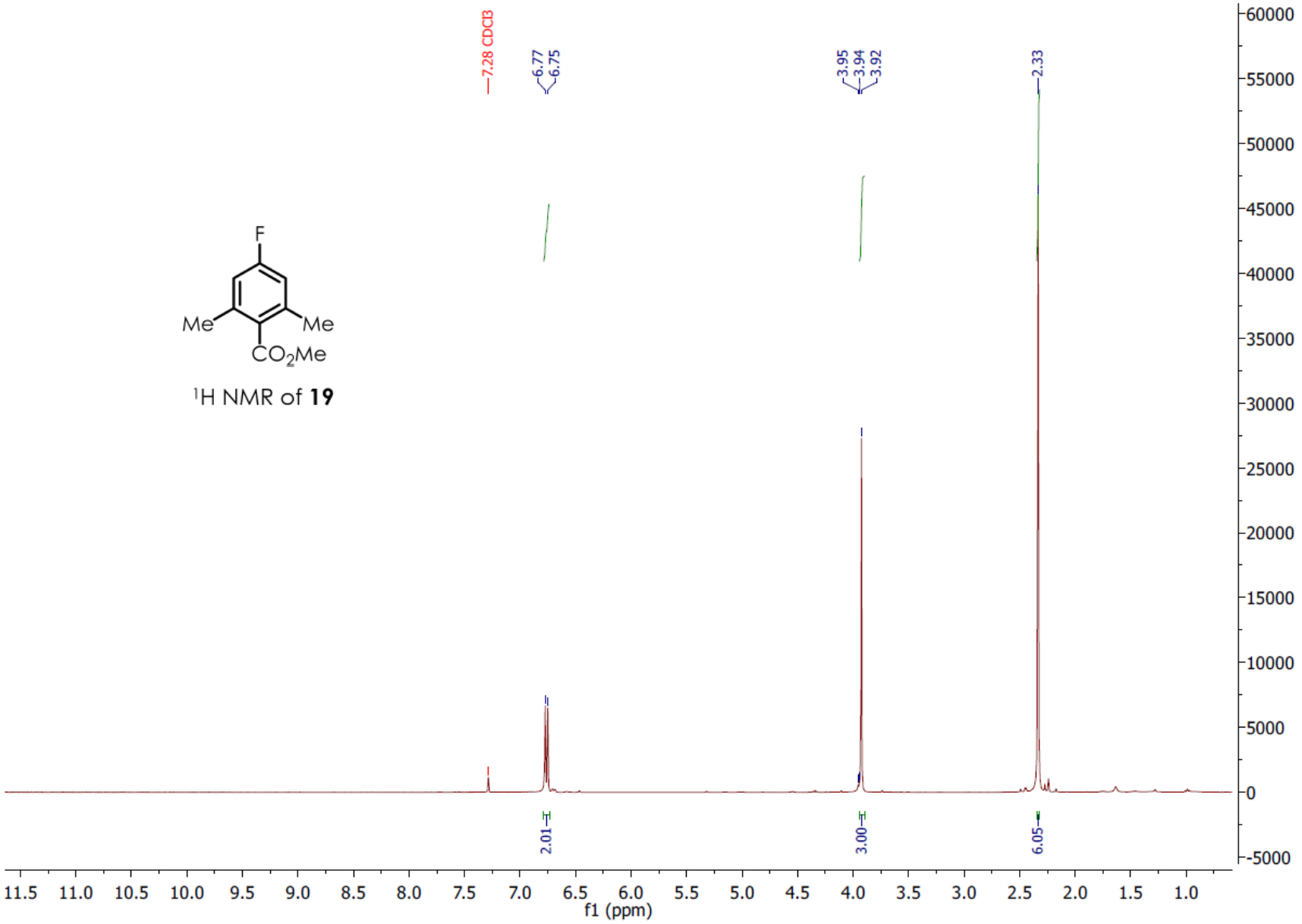
8.00
7.64
7.64
7.63
7.28 CDCl3
2.04
1.00
f1 (ppm)


CF3
F3C
Br
CO2H
1H NMR of 17
8.12
7.95
7.28 CDCl3
1.00
1.02
4000
3500
3000
2500
2000
1500
1000
500
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


8.12
8.12
8.06
8.06
8.05
8.05
8.04
8.04
8.04
8.04
8.02
8.01
8.01
8.00
8.00
8.00
7.53
7.52
7.51
7.51
7.51
7.50
7.50
7.47
7.47
7.46
7.46
7.46
7.45
7.45
2.50 DMSO-d6
CO2H
S
1H NMR of 18
0.95
0.96
0.99
1.00
1.00
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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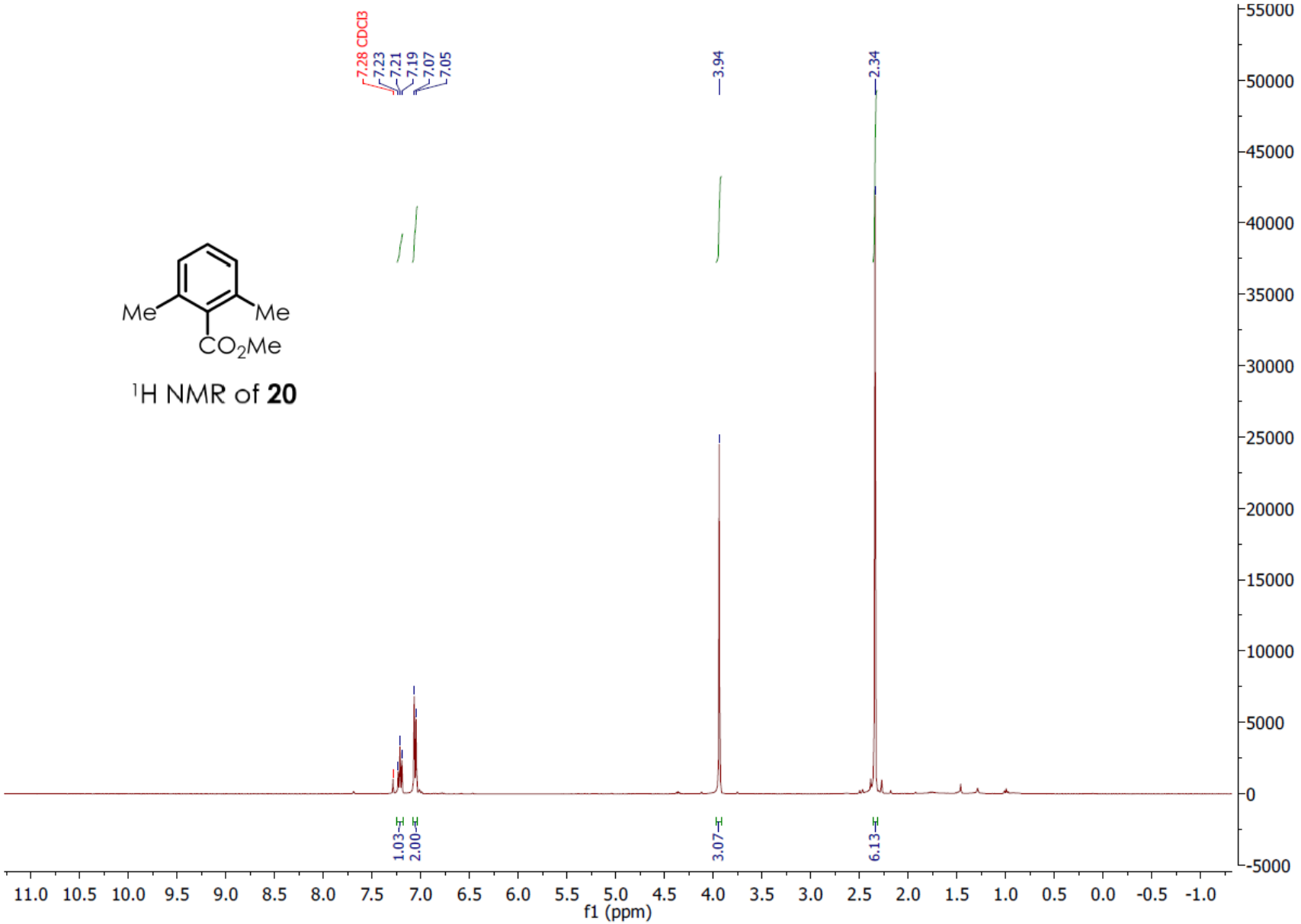
6.77
6.75
3.95
3.94
3.92
2.33
F
Me
Me
CO2Me
1H NMR of 19
2.01
3.00
6.05
f1 (ppm)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7.05
3.94
2.34
Me
Me
CO2Me
1H NMR of 20
1.03
2.00
3.07
6.13
f1 (ppm)