Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information for

PIDA-Mediated N–N Bond Formation to Access Pyrazolidine-3,5-diones: Novel Process for Uricosuric Agents G-25671 and Sulfinpyrazone

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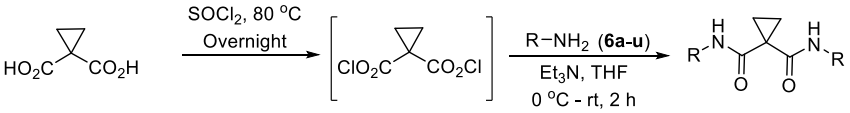
1. General Considerations:

All reagents and solvents were used as received from commercial sources unless and other-wise noted. All experiments were carried out in a round bottom flask or Schlenk tube equipped with a stirring bar. Aluminium plates precoated with silica gel 60 PF254, 0.25 mm or 0.5 mm, were utilized for thin-layer chromatography (TLC) to monitor the progress of a reaction. Visualization of the developed TLC plate was performed by irradiation with UV light. Column chromatographic purifications were carried out on flash silica gel (240−400 mesh) using ethyl acetate, acetone, DCM and petroleum ether as eluents. The ^{1}H and ^{13}C NMR spectra were recorded on 400/500 MHz and 100/125 MHz NMR spectrometers respectively, in $CDCl_3$ or DMSO-d_6. Chemical shifts were reported as δ values from standard peaks. The multiplicities of signals are designated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), m (multiplet). Coupling constants (J) are reported in hertz. Melting points are uncorrected. High-resolution mass spectrometry (HRMS) was performed on a TOF/Q-TOF mass spectrometer. The substrate cyclopropane-1,1-dicarboxylic acid **7** was prepared using known literature procedure.[1] The dianildies **5y** and **5z** were prepared as per the literature procedure.[2]

2. Experimental Procedures:

I] General Experimental Procedure for the Synthesis of Dianilides 5a-s, 5w, 5x:



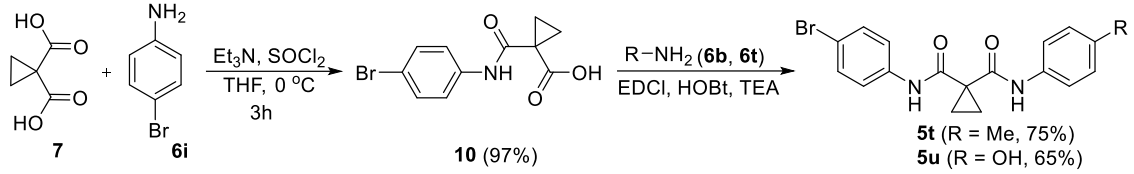
7 **7'** **5a-s, 5w, 5x**

An oven dried two-neck round bottom flask was charged with cyclopropane-1,1-dicarboxylic acid **7** (1.54 mmol, 1 equiv.) and thionyl chloride (5 ml) under argon. After overnight stirring at refluxing condition (90 °C), the excess of thionyl chloride was removed by distillation, yielding the dichloride **7'** as an yellow oil. The product was used in the next step without further purification.

To the solution of cyclopropane-1,1-dicarbonylchloride **7'** (1.54 mmol, 1 equiv.) in THF (10 ml), the solution of amines **6a-u** (3.85 mmol, 2.5 equiv.) and triethyl amine (4.62 mmol, 3 equiv.) in THF (5 ml) was added dropwise at 0 °C temperature with vigorous stirring. Combination of these two solutions caused the precipitation of triethylamine hydrochloride as a finely dispersed powder. After two hours stirring at room temperature, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3 x 30 mL). The organic layer was separated and washed with brine solution once and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuo to dryness followed by the purification of the crude product using column chromatography pet ether: ethyl acetate (4:1 to 1:4) provided the expected dianilides **5a-s, 5w, 5x** in very good yields.

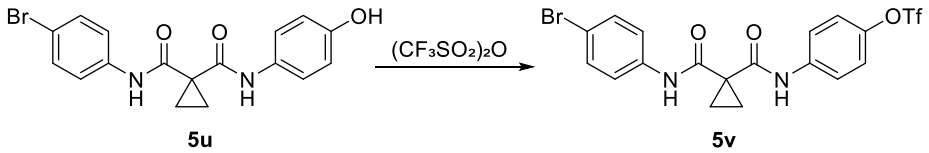
The known dianilides **5a-d**, **5g**, **5i-k**, **5m**, **5o**, **5q-r**, **5w** were prepared by the same procedure and their structure was confirmed by comparing their analytical data with the reported literature.[3]

Synthesis of Dianilides 5t-u:



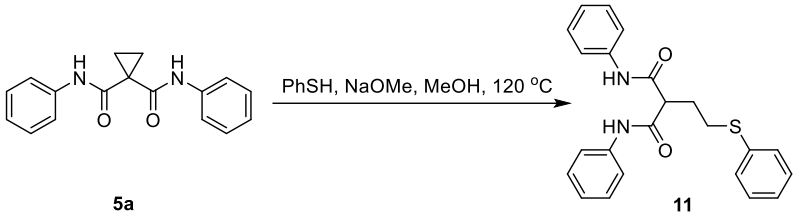
The intermediate **10** was prepared by following the reported procedure and used for the next step directly.[4] Similarly, dianilides **5t** and **5u** were synthesized following the reported procedure by slightly modifying the coupling reagent.[5]

Synthesis of Dianilides 5v:



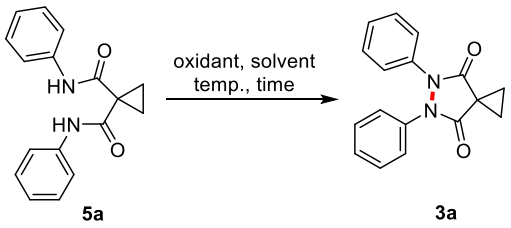
Dianilide **5v** was synthesized by treatment of triflic anhydride with the danilide **5u** using known literature procedure.[5]

Experimental Procedure for the Synthesis of dianilide 11:



An oven dried pressure tube was charged with sodium methoxide (5.8 mg, 0.11 mmol, 1.5 equiv.) under argon atmosphere. Dry methanol (0.7 ml, 0.1 M) followed by the thiophenol (7.9 mg, 0.07 mmol, 1 equiv.) was added and the reaction mixture was kept for 30 min. at room temperature before adding the dianilide **5a** (20 mg, 0.07 mmol, 1 equiv.). After stirring the reaction mixture at 120 °C for the completion of the reaction (monitored by TLC, approx. 12h), the solvent was evaporated and the residue was mixed with water (5 ml) and EtOAc (5 ml). The aqueous part was extracted with EtOAc (3 x 5 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified by flash column chromatography using pet ether: ethyl acetate (4:1) to provide pure sulfide compound **11** in 81% (16.6 mg) yield as a colorless sticky solid.

Table 1: Optimization of Reaction Conditions to obtain **3a**[a]

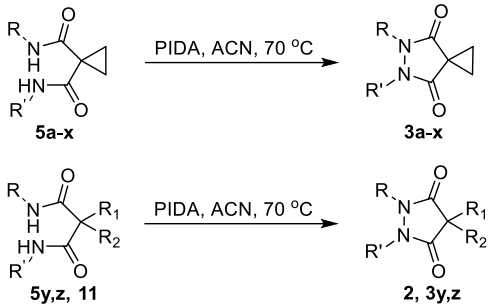


5a **3a**

Sr. no	Conditions	Solvent	Temp. (ºC)	Time (h)	Yield[b] (%)
1.	$KMnO_4$ (2.5 equiv.)	acetone	60	24	NR
2.	$CuBr_2$ (20 mol%), O_2	DMSO	120	24	NR
3.	[Mes-acr]$^+$ BF_4^-,(1 mol%)	HFIP	25	24	NR
4.	PIDA (1 equiv.)	HFIP	40	16	30 (43)[c]
5.	PIDA (1equiv.)	HFIP	70	16	24
6.	PIDA (1.5 equiv.)	HFIP	70	16	30
7.	PIDA (2 equiv.)	HFIP	70	16	40
8.	PhIO (2 equiv.)	HFIP	70	16	38
9.	PIFA (2 equiv.)	HFIP	70	16	15
10.	PIDA (2 equiv.)	DMF/EtOH/ THF/IPA/ MeOH/DCE/^{t}BuOH	70	16	NR
11.	PIDA (2 equiv.)	ACN	70	16	56 (74)[c]
12.	PhIO (2 equiv.)	ACN	70	16	41 (64)[c]
13.	PhI (20 mol%), *m*-CPBA (1.2 equiv.)	ACN	25	12	44
14.	PhI (20 mol%), Oxone (3 equiv.)	HFIP	70	17	NR
15.	PIDA (2 equiv.), HFIP (3 equiv.)	MeOH	70	16	24
16.	PIDA (2 equiv.), HFIP (3 equiv.)	toluene	70	16	34
17.	PIDA (2 equiv.), HFIP (3 equiv.)	ACN	70	16	68 (72)[c]
18.	PIDA (2 equiv.)	HFIP:MeOH (1:1)	70	16	37
19.	PIDA (2 equiv.)	HFIP:toluene (1:1)	70	16	20
20.	PIDA (2equiv.)	HFIP: heptane (1:1)	70	16	38
21.	PIDA (2 equiv.)	HFIP:hexane (1:1)	70	16	30
22.	PIDA (2 equiv.)	HFIP: ACN (1:1)	70	16	61(75)[c]
23.	**PIDA (2 equiv.), under argon**	**Dry ACN**	**70**	**16**	**87 (92)**[c]
24.	PIDA (2 equiv.), under argon, 4A^{o}MS	ACN	70	16	61 (74)[c]
25.	PIDA (2equiv.), under argon, 3A^{o}MS	ACN	70	16	63 (71)[c]
26.	PhIO (2 equiv.), under argon	Dry ACN	70	16	23
27.	IBX (2 equiv.), under argon	Dry ACN	70	16	NR
28.	DMP (2 equiv.), under argon	Dry ACN	70	16	NR
29.	PhI (20 mol%), *m*-CPBA (3 equiv)	Dry ACN	70	16	26
30.	PhI (20 mol%), Oxone (3 equiv)	Dry ACN	70	16	NR

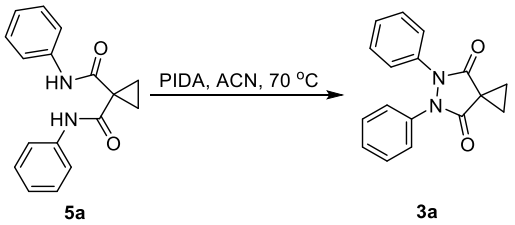
[a]Reaction conditions: **5a** (20 mg, 1.0 equiv.), Oxidant in solvent (0.1 M, 0.7 ml). [b]Isolated yield. [c]Yield in the parentheses is based on the recovered starting material.

II] General Experimental Procedure for the Preparation of Pyrazolidine-3,5-dione Derivatives 3a-z:



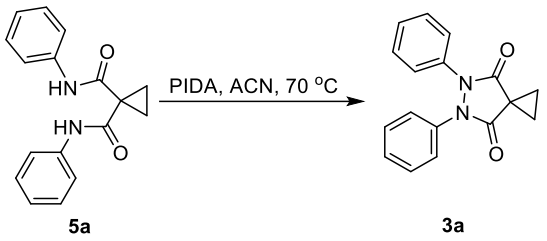
To an oven dried Schlenk tube containing dianilide **5a-z**, **11** (50 mg, 1 equiv.) and diacetoxyiodobenzene (2 equiv.) under argon was added dry acetonitrile (0.1 M). The reaction mixture was placed in a preheated oil bath at 70 °C and stirred for 16 hours. After completion of the reaction (TLC) it was cooled to room temperature and the solvent was evaporated on a rotatory evaporator. The residue was purified by flash silica gel column chromatography using a gradient of pet ether: ethyl acetate (4:1 to 3:2) to afford the corresponding pyrazolidine-3,5-dione derivatives **2**, **3a-z** in good to excellent yield.

III] Typical Experimental Procedure for the Preparation of Representative Product 3a:



To an oven dried Schlenk tube containing dianilide **5a** (50 mg, 0.18 mmol, 1 equiv.) and diacetoxyiodobenzene (115 mg, 0.36 mmol, 2 equiv.) was added dry acetonitrile (1.8 ml, 0.1 M). The reaction mixture was placed on preheated oil bath at 70 °C and stirred for 16 hours. After completion of the reaction (TLC) it was cooled to room temperature and the solvent was evaporated on a rotatory evaporator. The residue was purified by flash silica gel column chromatography using a gradient of pet ether: ethyl acetate (6:1) to afford the corresponding pyrazolidine-3,5-dione derivative **3a** as a white solid in 87% yield (43.2 mg) and in based on the recovery of starting material 92% yield.

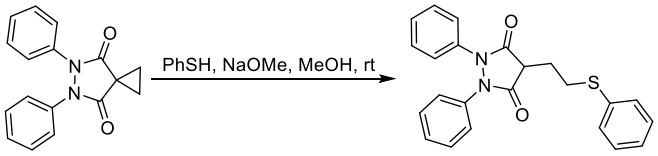
IV] Gram Scale Experimental Procedure for the Preparation of Representative Product 3a:



5a **3a**

To an oven dried Schlenk tube containing dianilide **5a** (1 gm, 3.6 mmol, 1 equiv.) and diacetoxyiodobenzene (2.3 g, 7.14 mmol, 2 equiv.) was added dry acetonitrile (36 ml, 0.1 M). The reaction mixture was placed on preheated oil bath at 70 °C and stirred for 24 hours. After completion of the reaction (TLC) it was cooled to room temperature and the solvent was evaporated on a rotatory evaporator. The residue was purified by flash silica gel column chromatography using a gradient of pet ether: ethyl acetate (6:1) to afford the corresponding pyrazolidine-3,5-dione derivative **3a** as a white solid in 63% yield (0.626 g) and in based on the recovery of starting material 67 % yield.

V] Synthesis of G-25671 (2):

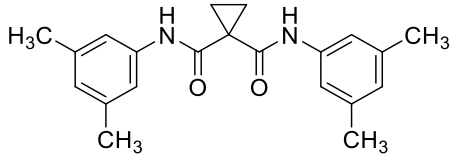


3a **2**

An oven dried two-neck round bottom flask was charged with sodium methoxide (14.6 mg, 0.27 mmol, 1.5 equiv.) under argon atmosphere. Dry methanol (1.8 ml, 0.1 M) followed by the thiophenol (19.8 mg, 0.18 mmol, 1 equiv.) was added and the reaction mixture was kept for 30 min at room temperature before adding the key intermediate **3a** (50 mg, 0.18 mmol, 1 equiv.). After the completion of the reaction (monitored by TLC, approx. 2h), the solvent was evaporated and the residue was mixed with water (5 ml) and EtOAc (5 ml). The aqueous part was extracted with EtOAc (3 x 5 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified using flash column chromatography pet ether: ethyl acetate (4:1 to 1:1) to provide pure sulfide compound **2** in 88% (61.4 mg) as a colorless to solid.

3. Characterization Data of Compounds:

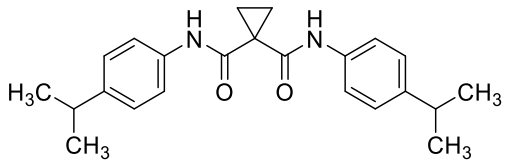
N,N'-bis(3,5-Dimethylphenyl)cyclopropane-1,1-dicarboxamide (**5e**)



5e

Reaction time: 2h; R*f*: 0.3 (1:4, EtOAc: Pet. ether); White solid; Mp = 185-187 ^{o}C; 485.9 mg, 94% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.87 (brs, 2H), 7.16 (s, 4H), 6.79 (s, 2H), 2.31 (s, 12H), 1.61 (s, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.7, 138.7, 137.1, 126.5, 118.4, 29.6, 21.3, 17.0; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{25}N_2O_2$ 337.1911, found 337.1895.

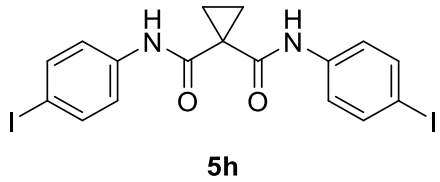
N,N'-bis(4-Isopropylphenyl)cyclopropane-1,1-dicarboxamide (**5f**)



5f

Reaction time: 2h; R*f*: 0.5 (1:4, EtOAc:Pet. ether); White solid; Mp = 130-132 ^{o}C; 520.8 mg, 93% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.96 (brs, 2H), 7.42 (d, *J* = 8.5 Hz, 4H), 7.20 (d, *J* = 8.4 Hz, 4H), 2.89 (septet, *J* = 6.9 Hz, 2H), 1.61 (s, 4H), 1.25 (s, 6H), 1.23 (s, 6H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.8, 145.6, 134.9, 126.9, 120.8, 33.6, 29.6, 24.0, 17.0; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{23}H_{29}O_2N_2$ 365.2224, found 365.2224.

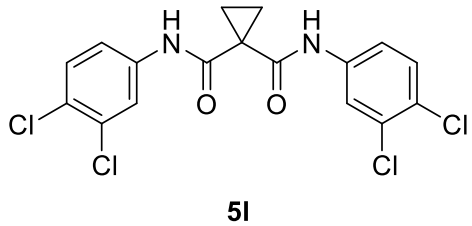
N,N'-bis(4-Iodophenyl)cyclopropane-1,1-dicarboxamide (**5h**)



5h

Reaction time: 2h; R*f*: 0.4 (2:3, EtOAc:Pet. ether); Brown solid; Mp = 195-197 ^{o}C; 703.9 mg, 86% yield; **^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.09 (brs, 2H), 7.63 (d, *J* = 8.8 Hz, 4H), 7.46 (d, *J* = 8.7 Hz, 4H), 1.43 (s, 4H); **^{13}C NMR (100 MHz, DMSO-d_6)** δ 168.1, 138.8, 137.1, 122.5, 87.2, 32.1, 15.4; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{15}O_2N_2I_2$ 532.9217, found 532.9210.

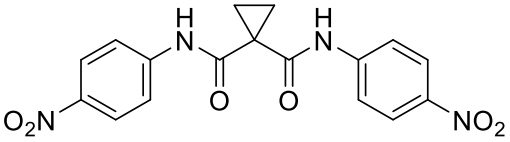
N,N'-bis(3,4-Dichlorophenyl)cyclopropane-1,1-dicarboxamide (**5l**)



5l

Reaction time: 2h; R*f*: 0.4 (2:3, EtOAc:Pet. ether); Yellowish solid; Mp = 213-215 ^{o}C; 531.2 mg, 83% yield; **^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.28 (brs, 2H), 8.11-7.95 (m, 2H), 7.56-7.54 (m, 4H), 1.44 (s, 4H); **^{13}C NMR (100 MHz, DMSO-d_6)** δ 168.0, 139.2, 130.7, 130.4, 124.9, 121.5, 120.2, 32.4, 15.4; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{13}O_2N_2Cl_4$ 416.9726, found 416.9723.

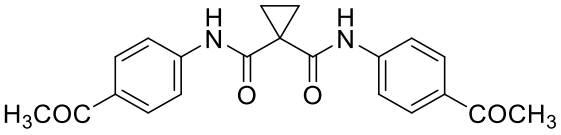
N,N'-bis(4-Nitrophenyl)cyclopropane-1,1-dicarboxamide (**5n**)



5n

Reaction time: 2h; R*f*: 0.2 (3:2, EtOAc:Methanol); White solid; Mp = 265-267 °C; 296 mg, 52% yield; **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 10.61 (brs, 2H), 8.27-8.16 (m, 4H), 7.92-7.86 (m, 4H), 1.51 (s, 4H); **^{13}C NMR (100 MHz, DMSO-d$_6$)** δ 168.5, 145.4, 142.5, 124.8, 119.9, 33.1, 15.8; **HRMS** (ESI-TOF) m/z: $[M-H]^-$calcd for $C_{17}H_{13}O_6N_4$ 369.0830, found 369.0846.

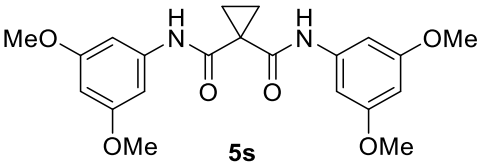
N,N'-bis(4-Acetylphenyl)cyclopropane-1,1-dicarboxamide (**5p**)



5p

Reaction time: 2h; R*f*: 0.4 (4:1, EtOAc:Pet. ether); Yellow solid; Mp = 213-215 °C; 336 mg, 60% yield; **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 10.32 (brs, 2H), 7.92 (d, *J* = 8.7 Hz, 4H), 7.78 (d, *J* = 8.8 Hz, 4H), 2.53 (s, 6H), 1.50 (s, 4H); **^{13}C NMR (100 MHz, DMSO-d$_6$)** δ 196.6, 168.3, 143.4, 131.9, 129.2, 119.4, 32.5, 26.4, 15.6; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{21}O_4N_2$ 365.1496, found 365.1494.

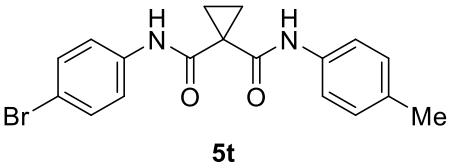
N,N'-bis(3,5-Dimethoxyphenyl)cyclopropane-1,1-dicarboxamide (**5s**)



5s

Reaction time: 2h; R*f*: 0.4 (3:7, EtOAc:Pet. ether); White solid; Mp = 195-197 °C; 480 mg, 78% yield; **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 9.90 (brs, 2H), 6.91 (d, *J* = 2.1 Hz, 4H), 6.22 (t, *J* = 2.3 Hz, 2H), 3.70 (s, 12H), 1.43 (s, 4H); **^{13}C NMR (100 MHz, DMSO-d$_6$)** δ 168.2, 160.3, 140.6, 98.6, 95.8, 55.1, 32.0, 15.3; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{25}O_6N_2$ 401.1707, found 401.1704.

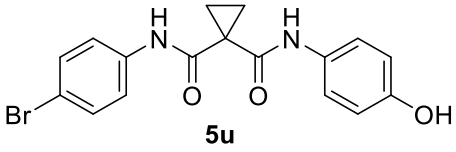
N-(4-Bromophenyl)-N-(p-tolyl)cyclopropane-1,1-dicarboxamide (**5t**)



5t

Reaction time: 15h; R*f*: 0.4 (1:4, EtOAc: Pet. ether); White solid; Mp = 220-222 °C; 73% yield over two steps from **7**; **^{1}H NMR (400 MHz, DMSO-d^6)** δ 10.17 (brs, 1H), 9.88 (brs, 1H), 7.60 (d, *J* = 7.9 Hz, 2H), 7.46 (d. *J* = 7.9 Hz, 4H), 7.10 (d, *J* = 7.9 Hz, 2H), 2.25 (s, 3H), 1.45 (s, 4H); **^{13}C NMR (100 MHz, DMSO-d^6)** δ 168.4, 167.9, 138.2, 136.2, 132.6, 131.3, 128.8, 122.3, 120.6, 115.2, 31.5, 20.4, 15.5; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{18}H_{18}BrN_2O_2$ 373.0546, found 373.0553.

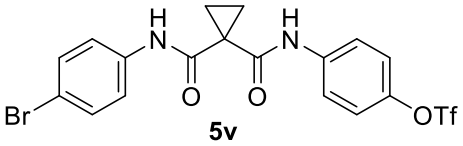
N-(4-Bromophenyl)-N-(4-hydroxyphenyl)cyclopropane-1,1-dicarboxamide (**5u**)



5u

Reaction time: 15h; R*f*: 0.6 (1:19, MeOH: DCM); White solid; Mp = 162-164 °C; 63% yield over two steps; **^{1}H NMR (400 MHz, DMSO-d^{6})** δ 10.27 (brs, 1H), 9.66 (brs, 1H), 9.21 (brs, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 6.68 (d, *J* = 8.0 Hz, 2H), 1.44 (s, 4H); **^{13}C NMR (100 MHz, DMSO-d^{6})** δ 168.4, 167.8, 153.8, 138.2, 131.3, 130.1, 122.6, 122.2, 115.1, 114.8, 31.1, 15.5; **HRMS** (ESI-TOF) m/z: $[M+H]^{+}$calcd for $C_{17}H_{16}BrN_2O_3$ 375.0339, found 375.0333.

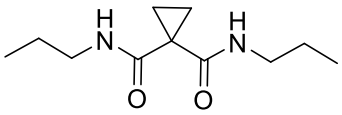
4-(1-((4-Bromophenyl)carbamoyl)cyclopropane-1-carboxamido)phenyl trifluoromethanesulfonate (**5v**)



5v

Reaction time: 12h; R*f*: 0.4 (1:4, EtOAc: Pet. ether); White solid; Mp = 135-137 °C; 60.8 mg, 90% yield; **^{1}H NMR (400 MHz, DMSO-d^{6})** δ 10.28, (brs, 1H), 10.10 (brs, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.56-7.36 (m, 4H), 1.45 (s, 4H); **^{13}C NMR (100 MHz, DMSO-d^{6})** δ 168.2, 167.9, 144.4, 139.4, 138.3, 131.3, 122.3, 121.8, 121.6, 118.3 (q, *J* = 320.4 Hz, CF_3), 115.2, 32.0, 15.4; **HRMS** (ESI-TOF) m/z: $[M+H]^{+}$calcd for $C_{18}H_{15}BrF_3N_2O_5S$ 506.9832, found 506.9832.

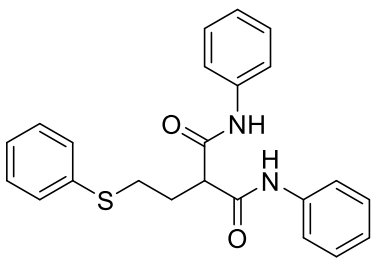
N,N'-Dipropylcyclopropane-1,1-dicarboxamide (**5x**)



5x

Reaction time: 2h; R*f*: 0.5 (2:3, EtOAc:Pet. ether); White solid; Mp = 48-50 °C; 254.4 mg, 78% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.11 (brs, 2H), 3.25-3.17 (m, 4H), 1.58-1.48 (m, 4H), 1.35 (s, 4H), 0.92 (t, *J* = 7.4 Hz, 6H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 170.7, 41.5, 28.2, 22.6, 16.1, 11.4; **HRMS** (ESI-TOF) m/z: $[M+H]^{+}$calcd for $C_{11}H_{21}O_2N_2$ 213.1598, found 213.1600.

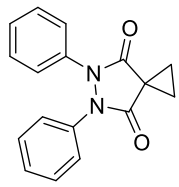
N^{1},N^{3}-Diphenyl-2-(2-(phenylthio)ethyl)malonamide (**11**)



11

Reaction time: 12h; R*f*: 0.3 (1:4, EtOAc: Pet. ether); colorless sticky solid; 16.6 mg, 81% yield; **^{1}H NMR (200 MHz, CDCl$_3$)** δ 9.07 (brs, 2H), 7.56 (d, *J* = 7.6 Hz, 4H), 7.36-7.31 (m, 6H), 7.23-7.13 (m, 5H), 3.74 (t, *J* = 7.5 Hz, 1H), 3.06 (t, *J* = 7.0 Hz, 2H), 2.39 (q, *J* = 7.1 Hz, 2H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 168.7, 137.2, 134.8, 129.9, 129.05, 129.01, 126.6, 124.9, 120.3, 54.7, 32.5, 31.7; **HRMS** (ESI-TOF) m/z: $[M+H]^{+}$calcd for $C_{23}H_{23}N_2O_2S$ 391.1475, found 391.1475.

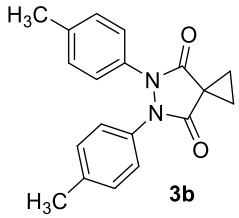
5,6-Diphenyl-5,6-diazaspiro[2.4]heptane-4,7-dione (**3a**)



3a

Reaction time: 16h; R*f*: 0.5 (1:4, EtOAc:Pet. ether); White solid; Mp = 163-165 ^{o}C; 43.2 mg, 87% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.41-7.30 (m, 8H), 7.22-7.15 (m, 2H), 1.92 (s, 4H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.2, 136.4, 128.9, 126.5, 122.2, 26.9, 21.8; **HRMS** (ESI-TOF) m/z: [M+H]$^{+}$calcd for $C_{17}H_{15}O_2N_2$ 279.1128, found 279.1126.

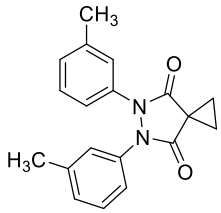
5,6-Di-p-tolyl-5,6-diazaspiro[2.4]heptane-4,7-dione (**3b**)



3b

Reaction time: 16h; R*f*: 0.6 (1:4, EtOAc: Pet. ether); White solid; Mp = 160-162 ^{o}C; 44.2 mg, 89% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.24 (d, *J* = 8.4 Hz, 4H), 7.13 (d, *J* = 8.4 Hz, 4H), 2.29 (s, 6H), 1.89 (s, 4H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.2, 136.5, 133.8, 129.5, 122.6, 26.8, 21.5, 21.0; **HRMS** (ESI-TOF) m/z: [M+H]$^{+}$calcd for $C_{19}H_{19}O_2N_2$ 307.1441, found 307.1435.

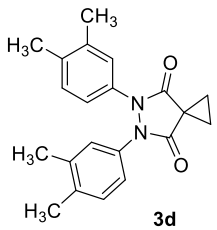
5,6-Di-m-tolyl-5,6-diazaspiro[2.4]heptane-4,7-dione (**3c**)



3c

Reaction time: 16h; R*f*: 0.6 (1:4, EtOAc:Pet. ether); Thick oil; 23.3 mg, 47% yield (brsm-52%); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.24 (s, 2H), 7.20 (t, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 7.5 Hz, 2H), 2.33 (s, 6H), 1.90 (s, 4H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.3, 138.9, 136.4, 128.7, 127.4, 123.3, 119.4, 26.9, 21.7, 21.4; **HRMS** (ESI-TOF) m/z: [M+H]$^{+}$calcd for $C_{19}H_{19}O_2N_2$ 307.1441, found 307.1438.

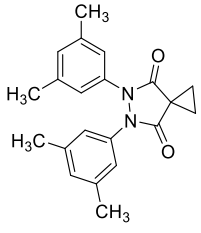
5,6-bis(3,4-Dimethylphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3d**)



3d

Reaction time: 16h; R*f*: 0.4 (1:4, EtOAc:Pet. ether); White solid; Mp = 127-129 ^{o}C; 35.3 mg, 71% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.20 (d, *J* = 1.3 Hz, 2H), 7.09-6.99 (m, 4H), 2.22 (s, 6H), 2.18 (s, 6H), 1.87 (s, 4H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.4, 137.3, 135.4, 134.1, 129.9, 124.3, 120.2, 26.8, 21.4, 19.9, 19.3; **HRMS** (ESI-TOF) m/z: [M+H]$^{+}$calcd for $C_{21}H_{23}O_2N_2$ 335.1754, found 335.1756.

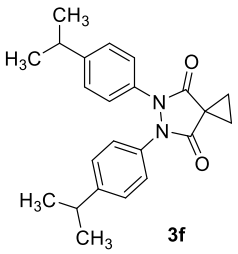
5,6-bis(3,5-Dimethylphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3e**)



3e

Reaction time: 16h; R*f*: 0.5 (1:4, EtOAc:Pet. ether); White Solid; Mp = 172-174 ^{o}C; 36.8 mg, 74% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 6.99 (s, 4H), 6.82 (s, 2H), 2.27 (s, 12H), 1.87 (s, 4H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.5, 138.6, 136.4, 128.6, 120.5, 26.8, 21.5, 21.3; **HRMS** (ESI-TOF) m/z: [M+H]$^{+}$calcd for $C_{21}H_{23}O_2N_2$ 335.1754, found 335.1755.

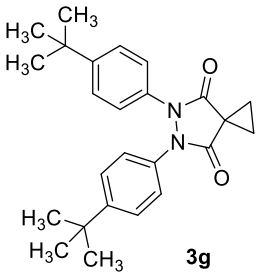
5,6-bis(4-isoPropylphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3f**)



3f

Reaction time: 16h; R*f*: 0.4 (1:4, EtOAc:Pet. ether); White solid; Mp = 80-82 °C; 34.8 mg, 70% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.29 (d, *J* = 8.5 Hz, 4H), 7.18 (d, *J* = 8.4 Hz, 4H), 2.86 (septate, *J* = 6.9 Hz, 2H), 1.89 (s, 4H), 1.21 (s, 6H), 1.19 (s, 6H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.4, 147.2, 134.1, 126.9, 122.3, 33.6, 26.9, 23.8, 21.7; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{23}H_{27}O_2N_2$ 363.2067, found 363.2069.

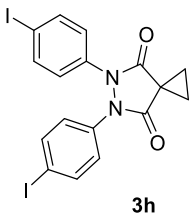
5,6-bis(4-(tert-Butyl)phenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3g**)



3g

Reaction time: 16h; R*f*: 0.6 (1:4, EtOAc:Pet. ether); White solid; Mp = 145-147 °C; 41.3 mg, 83% yield; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.35 (d, *J* = 8.2 Hz, 4H), 7.30 (d, *J* = 8.5 Hz, 4H), 1.89 (s, 4H), 1.27 (s, 18H); **^{13}C NMR (125 MHz, CDCl$_3$)** δ 171.5, 149.4, 133.9, 125.8, 121.8, 34.5, 31.2, 26.8, 21.7; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{25}H_{31}O_2N_2$ 391.2380, found 391.2385.

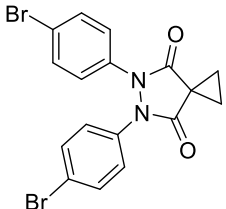
5,6-bis(4-Iodophenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3h**)



3h

Reaction time: 16h; R*f*: 0.4 (1:4, EtOAc:Pet. ether); White solid; Mp = 207-209 °C; 47.8 mg, 96% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.66 (d, *J* = 8.9 Hz, 4H), 7.10 (d, *J* = 8.9 Hz, 4H), 1.94 (s, 4H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.0, 138.1, 136.0, 123.6, 91.1, 26.8, 22.4; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{13}O_2N_2I_2$ 530.9061, found 530.9064.

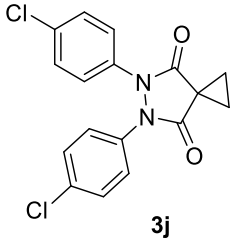
5,6-bis(4-Bromophenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3i**)



3i

Reaction time: 16h; R*f*: 0.4 (1:4, EtOAc:Pet. ether); Brown solid; Mp = 183-185 °C; 43.8 mg, 88% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.52-7.42 (m, 4H), 7.26-7.21 (m, 4H), 1.94 (s, 4H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.0, 135.3, 132.2, 123.5, 120.0, 26.8, 22.4; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{13}O_2N_2{}^{79}Br_2$ 434.9338, found 434.9333.

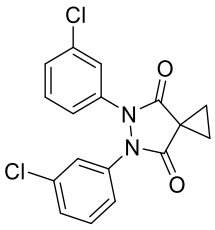
5,6-bis(4-Chlorophenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3j**)



3j

Reaction time: 16h; R*f*: 0.3 (1:4, EtOAc:Pet. ether); Yellow solid; Mp = 162-164 °C; 42.8 mg, 86% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.40-7.19 (m, 8H), 1.94 (s, 4H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.1, 134.7, 132.2, 129.2, 123.2, 26.8, 22.3; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{13}O_2N_2Cl_2$ 347.0349, found 347.0346.

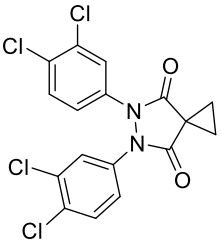
5,6-bis(3-Chlorophenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3k**)



3k

Reaction time: 16h; R*f*: 0.3 (1:4, EtOAc: Pet. ether); Thick oil; 27.8 mg, 56% yield (brsm-83%); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.44 (t, *J* = 1.9 Hz, 2H), 7.32-7.26 (m, 2H), 7.25-7.17 (m, 4H), 1.96 (s, 4H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.2, 137.5, 134.9, 130.1, 126.9, 122.1, 119.8, 26.8, 22.5; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{13}O_2N_2Cl_2$ 347.0349, found 347.0348.

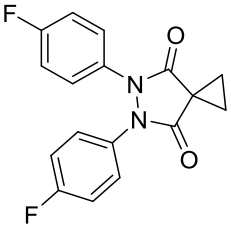
5,6-bis(3,4-Dichlorophenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3l**)



3l

Reaction time: 16h; R*f*: 0.3 (1:4, EtOAc:Pet. ether); White solid; Mp = 175-177 ^{o}C; 29.4 mg, 59% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.54 (d, *J* = 2.5 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.18 (dd, *J* = 8.8 & 2.5 Hz, 2H), 1.98 (s, 4H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.1, 135.5, 133.3, 130.8, 130.7, 123.6, 120.7, 26.7, 22.9; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{11}O_2N_2Cl_4$ 414.9569, found 414.9562.

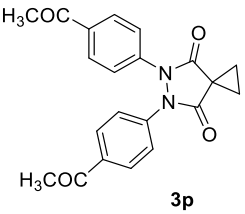
5,6-bis(4-Fluorophenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3m**)



3m

Reaction time: 16h; R*f*: 0.4 (1:4, EtOAc:Pet. ether); White solid; Mp = 110-112 ^{o}C; 27.8 mg, 56% yield; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.38-7.29 (m, 4H), 7.09-7.00 (m, 4H), 1.93 (s, 4H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.3, 160.9 (d, *J* = 247.2 Hz), 132.1 (d, *J* = 3.1 Hz), 124.4 (d, *J* = 8.4 Hz), 116.0 (d, *J* = 22.9 Hz), 26.7, 22.0; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{17}H_{13}O_2N_2F_2$ 315.0940, found 315.0939.

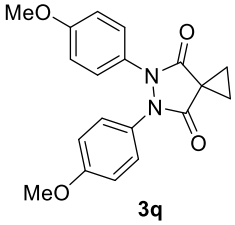
5,6-bis(4-Acetylphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3p**)



3p

Reaction time: 16h; R*f*: 0.4 (2:3, EtOAc: Pet. ether); Thick oil; 19.9 mg (100 mg scale), 20% yield (brsm-29%); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.00-7.90 (m, 4H), 7.55-7.39 (m, 4H), 2.56 (s, 6H), 2.0 (s, 4H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 196.6, 170.9, 140.2, 134.8, 129.4, 121.1, 27.0, 26.5, 22.8; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{19}O_4N_2$ 363.1339, found 363.1341.

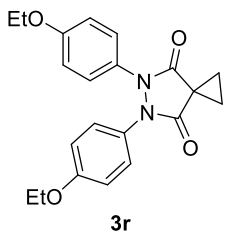
5,6-bis(4-Methoxyphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3q**)



3q

Reaction time: 16h; R*f*: 0.4 (1:1, EtOAc: Pet. ether); White solid; Mp = 185-187 ^{o}C; 32.8 mg (100 mg scale), 33% yield ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.26 (d, *J* = 9.0 Hz, 4H), 6.84 (d, *J* = 9.0 Hz, 4H), 3.76 (s, 6H), 1.89 (s, 4H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.2, 158.3, 128.9, 125.2, 114.2, 55.4, 26.8, 21.3; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{19}H_{19}O_4N_2$ 339.1339, found 339.1344.

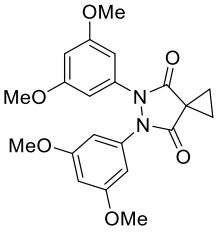
5,6-Bis(4-Ethoxyphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3r**)



3r

Reaction time: 16h; R*f*: 0.3 (1:9, Acetone:Pet. ether); Brown solid; Mp = 158-160 °C; 28.8 mg (100 mg scale), 29% yield (brsm-35%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.26-7.20 (m, 4H), 6.85-6.79 (m, 4H), 3.97 (q, *J* = 7.0 Hz, 4H), 1.88 (s, 4H), 1.38 (t, *J* = 6.9 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 171.2, 157.8, 128.7, 125.3, 114.7, 63.6, 26.8, 21.2, 14.7; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{23}O_4N_2$ 367.1652, found 367.1647.

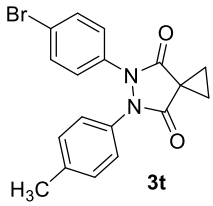
5,6-bis(3,5-Dimethoxyphenyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3s**)



3s

Reaction time: 16h; R*f*: 0.4 (2:3, EtOAc:Pet. ether); White solid; Mp = 173-175 °C; 24.9 mg (100 mg scale), 25% yield (brsm-30%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.57 (d, *J* = 2.3 Hz, 4H), 6.30 (t, *J* = 2.2 Hz, 2H), 3.73 (s, 12H), 1.90 (s, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 171.3, 160.9, 138.3, 100.8, 98.8, 55.5, 27.0, 22.0; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{21}H_{23}O_6N_2$ 399.1551, found 399.1555.

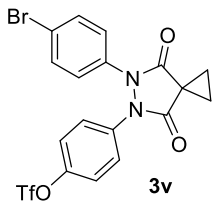
5-(4-Bromophenyl)-6-(p-tolyl)-5,6-diazaspiro[2.4]heptane-4,7-dione (**3t**)



3t

Reaction time: 16h; R*f*: 0.5 (1:4, EtOAc: Pet. ether); White solid; Mp = 140-142 °C; 35.8 mg, 72% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.36-7.06 (m, 6H), 2.31 (s, 3H), 1.92 (s, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 171.3, 171.0, 136.8, 135.3, 133.8, 132.0, 129.7, 123.7, 122.4, 119.7, 26.8, 21.9, 21.0; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{18}H_{16}BrN_2O_2$, 371.0390 found 371.0392.

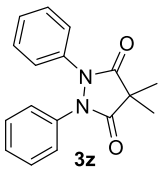
4-(6-(4-Bromophenyl)-4,7-dioxo-5,6-diazaspiro[2.4]heptan-5-yl)phenyl trifluoromethanesulfonate (**3v**)



3v

Reaction time: 16h; R*f*: 0.6 (1:4, EtOAc: Pet. ether); Yellowish sticky solid; 35.3 mg, 71% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.52-7.41 (m, 4H), 7.35-7.09 (m, 4H), 1.96 (s, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 171.2, 171.1, 146.9, 136.1, 135.4, 132.3, 123.3, 123.0, 122.1, 120.2, 118.6 (q, *J* = 321.2 Hz, CF_3), 26.8, 22.7; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{18}H_{13}BrF_3N_2O_5S$ 504.9675, found 504.9693.

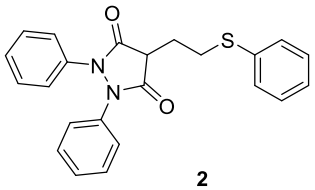
4,4-dimethyl-1,2-diphenylpyrazolidine-3,5-dione (**3z**)[6]



3z

Reaction time: 16h; R*f*: 0.4 (1:4, EtOAc: Pet. ether); colorless sticky solid; 9.5 mg (20 mg scale), 48% yield (brsm-72%); **^{1}H NMR (200 MHz, $CDCl_3$)** δ 7.37-7.30 (m, 8H), 7.23-7.16 (m, 2H), 1.52 (s, 6H); **GC-MS** m/z: $[M]^+$calcd for $C_{17}H_{16}N_2O_2$ 280.3, found 280.3.

1,2-Diphenyl-4-(2-(phenylthio)ethyl)pyrazolidine-3,5-dione (**2**)[7]



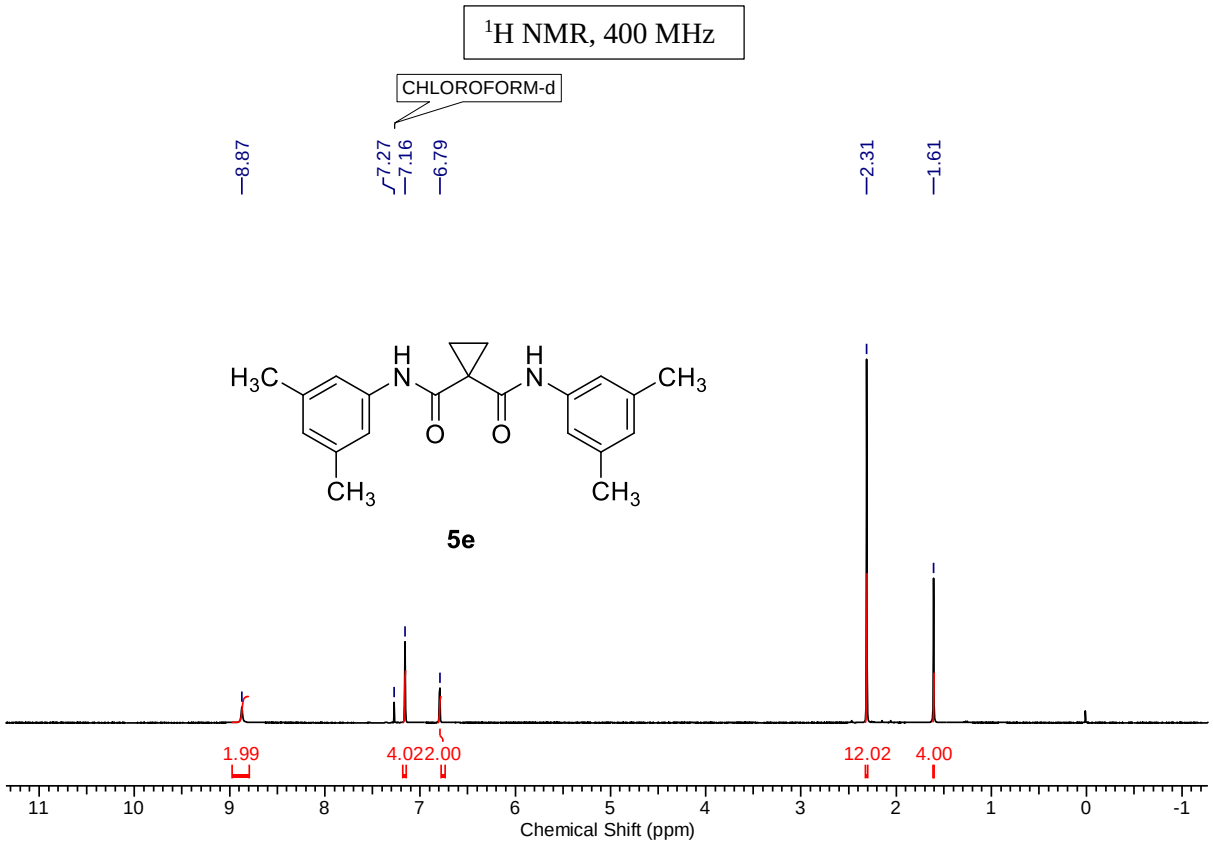
2

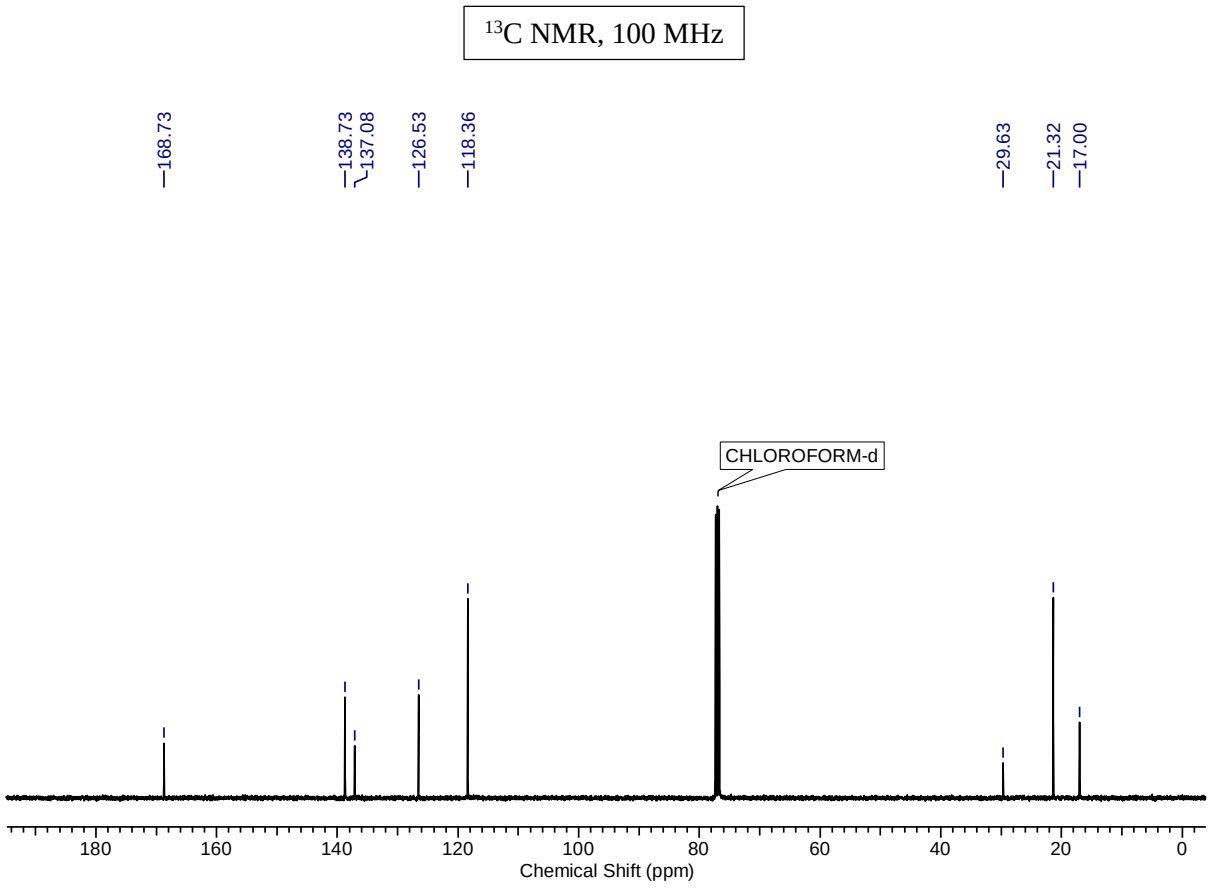
Reaction time: 2h; R*f*: 0.6 (3:7, EtOAc:Pet. ether); White solid; Mp = 100-102 ^{o}C (lit.[3] Mp = 110-113 ^{o}C); 61.4 mg (50 mg scale), 88% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.36-7.23 (m, 12H), 7.23-7.11 (m, 3H), 3.64 (t, *J* = 6.3 Hz, 1H), 3.22 (t, *J* = 7.1 Hz, 2H), 2.37 (q, *J* = 6.7 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.6, 135.7, 134.7, 129.9, 129.0, 128.9, 126.8, 126.5, 122.6, 44.4, 30.3, 27.0; **HRMS** (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{23}H_{21}O_2N_2S$ 389.1318, found 389.1315.

4. References:

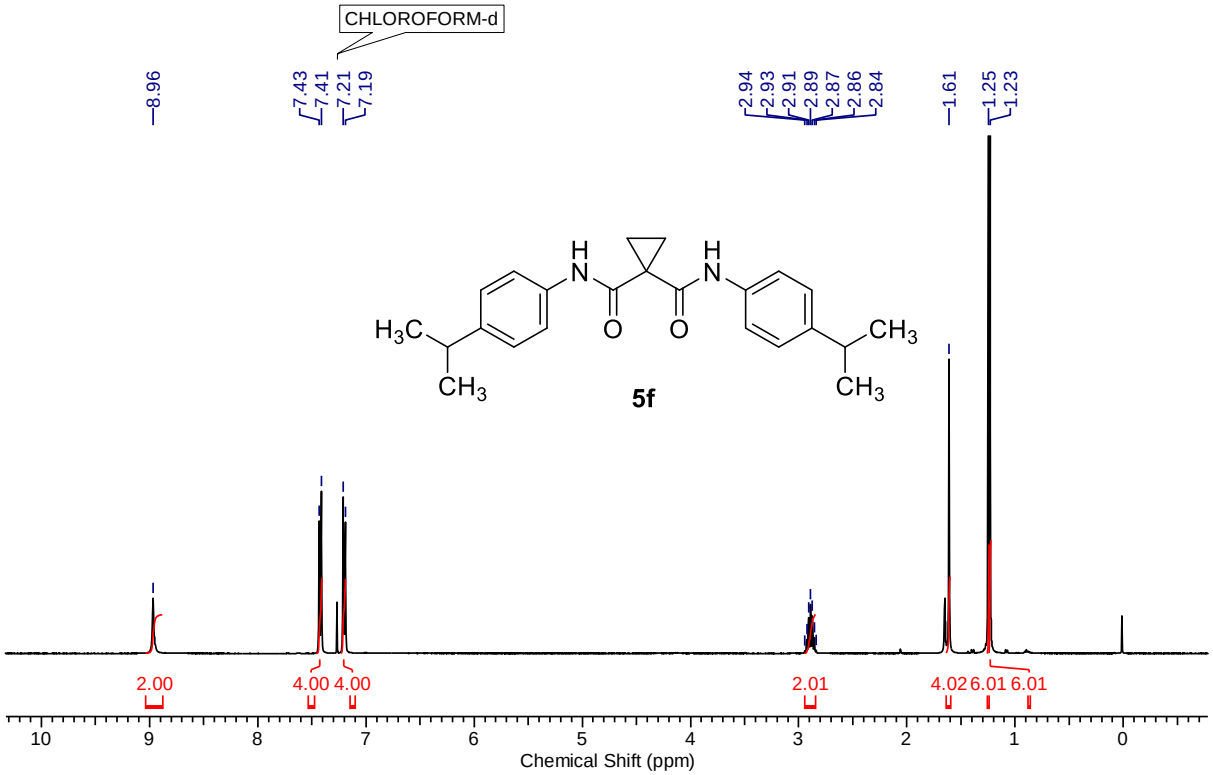
1. X. Zhen, X. Wan, W. Zhang, Q. Li, D. Zhang-Negrerie and Y. Du, *Org. Lett*., 2019, **21**, 890.
2. (a) B. Sun, X. Tang, R. Shi, Z. Yan, B. Li, C. Tang, C. Jin, C. L. Wu, and R. P. Shen, *Asian J. Org. Chem.* 2021, **10**, 3390. (b) G. Spedalotto, R. Gericke, M. Lovisari, E. R. Farquhar, B. Twamley, and A. R. McDonald, *Chem. Eur. J.*, 2019, **25**, 11983.
3. (a) L.-J. Min, Z.-H. Shen, J. Bajsa-Hirschel, C. L. Cantrell, L. Han, X.-W. Hua, X.-H. Liu and S. O. Duke, PESTIC BIOCHEM PHYS, 2022, **188**, 105228; (b) X. Liu, Y. Wen, Z. Shen, J. Weng and C. Tan, *Faming Zhuanli Shenqing*, 2020, CN 112142619 A; (b) V. Karaluka, R. M. Lanigan, P. M. Murray, M. Badlandc and T. D. *Org. Biomol. Chem*., 2015, **13**, 10888.
4. Z. Zhan, J. Ai, Q. Liu, Y. Ji, T. Chen, Y. Xu, M. Geng, and W. Duan, *ACS Med. Chem. Lett*., 2014, **5**, 673.
5. T. Gieshoff, A. Kehl, D. Schollmeyer, K. D. Moeller and S. R. Waldvogel, *J. Am. Chem. Soc.*, 2017, **139**, 12317.
6. H. Li, J. Zhao, S. Yi, K.Hu, and P. Feng, *Organometallics*, 2021, **40**, 880.
7. R. Pfister and F. Hafliger, *Helvetica Chimica Acta*, 1961, **44**, 232.

5. Copies of ^{1}H NMR and ^{13}C NMR Spectra:

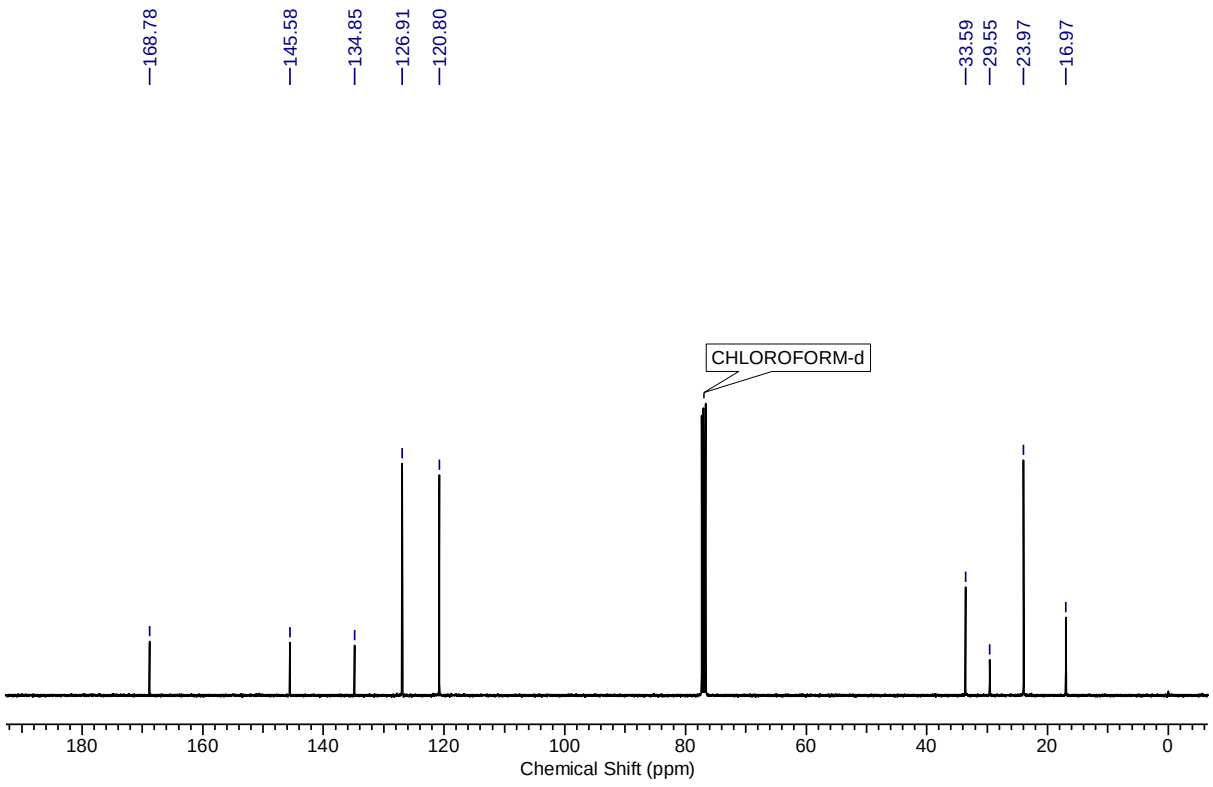




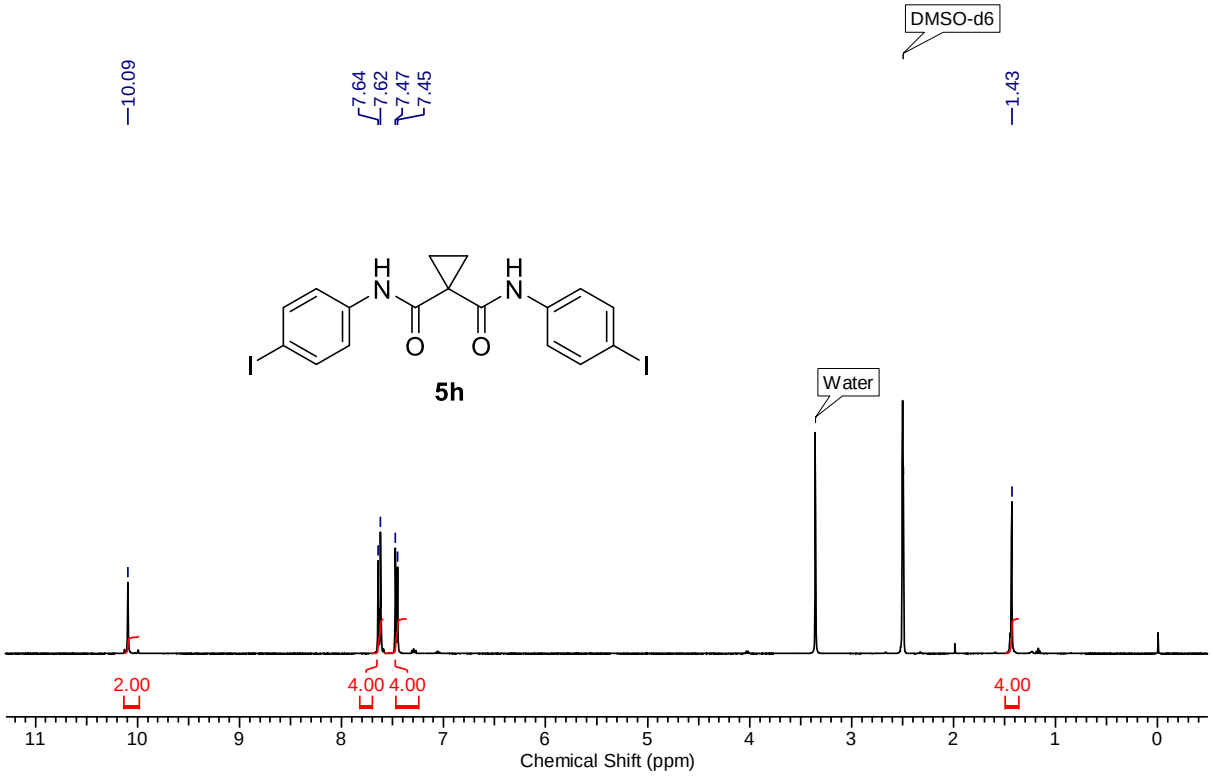
^{1}H NMR, 400 MHz



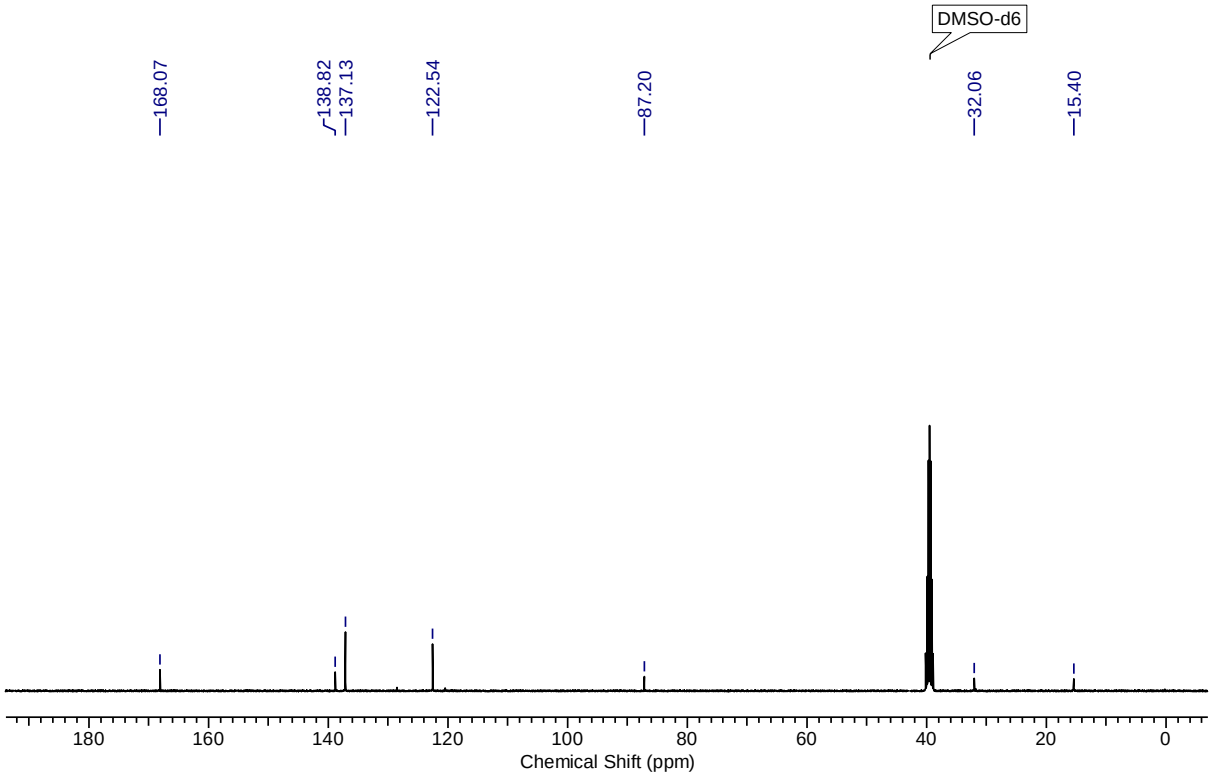
^{13}C NMR, 100 MHz



^{1}H NMR, 400 MHz



^{13}C NMR, 100 MHz



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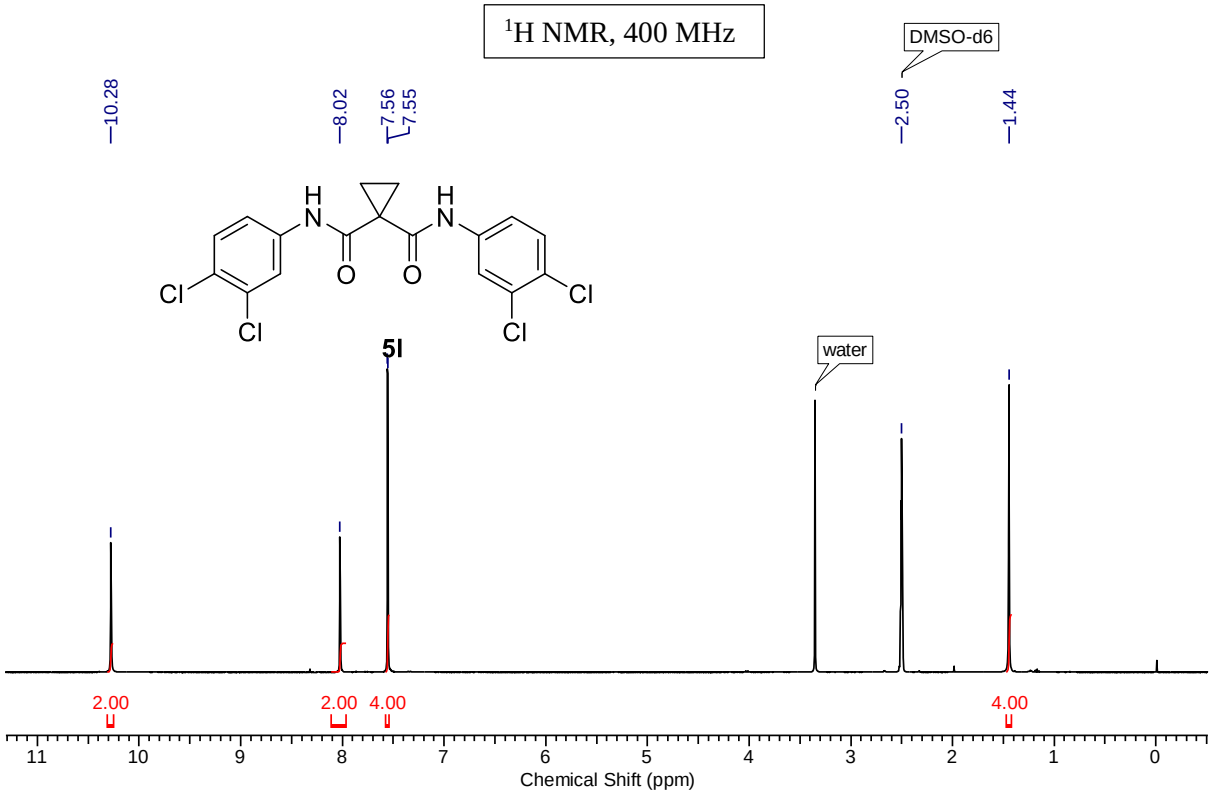

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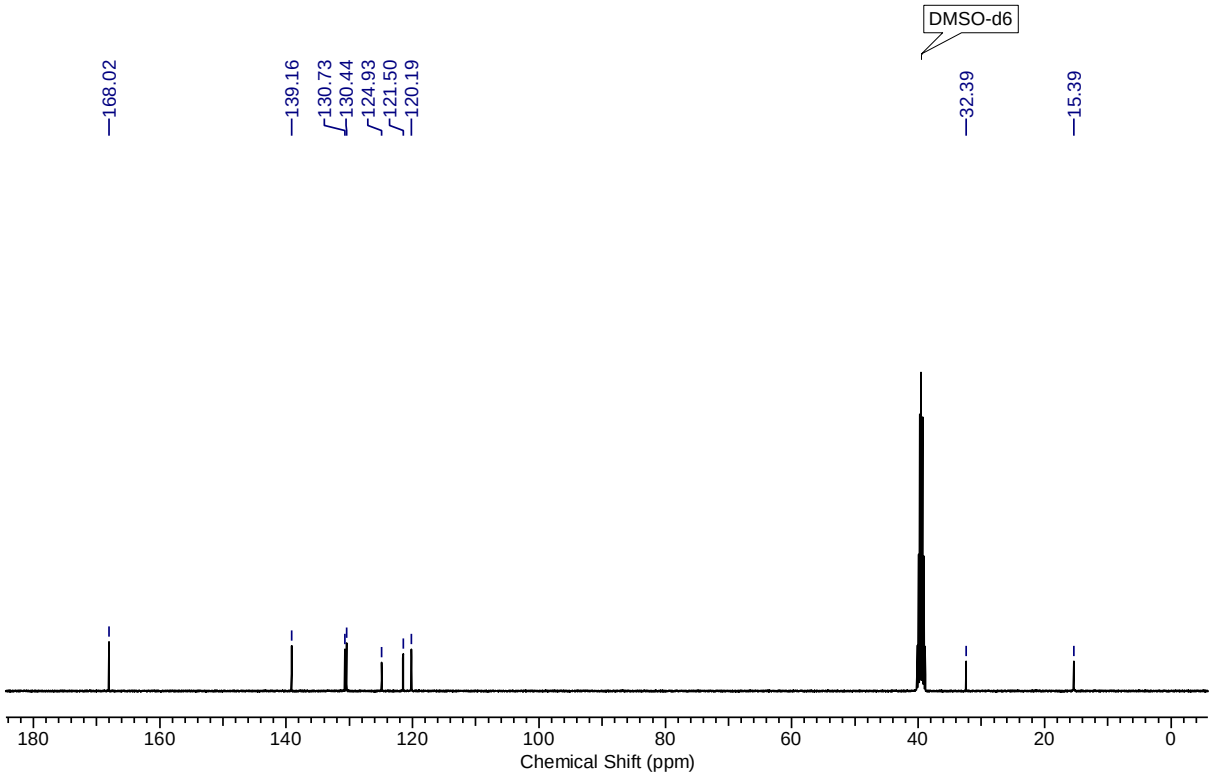

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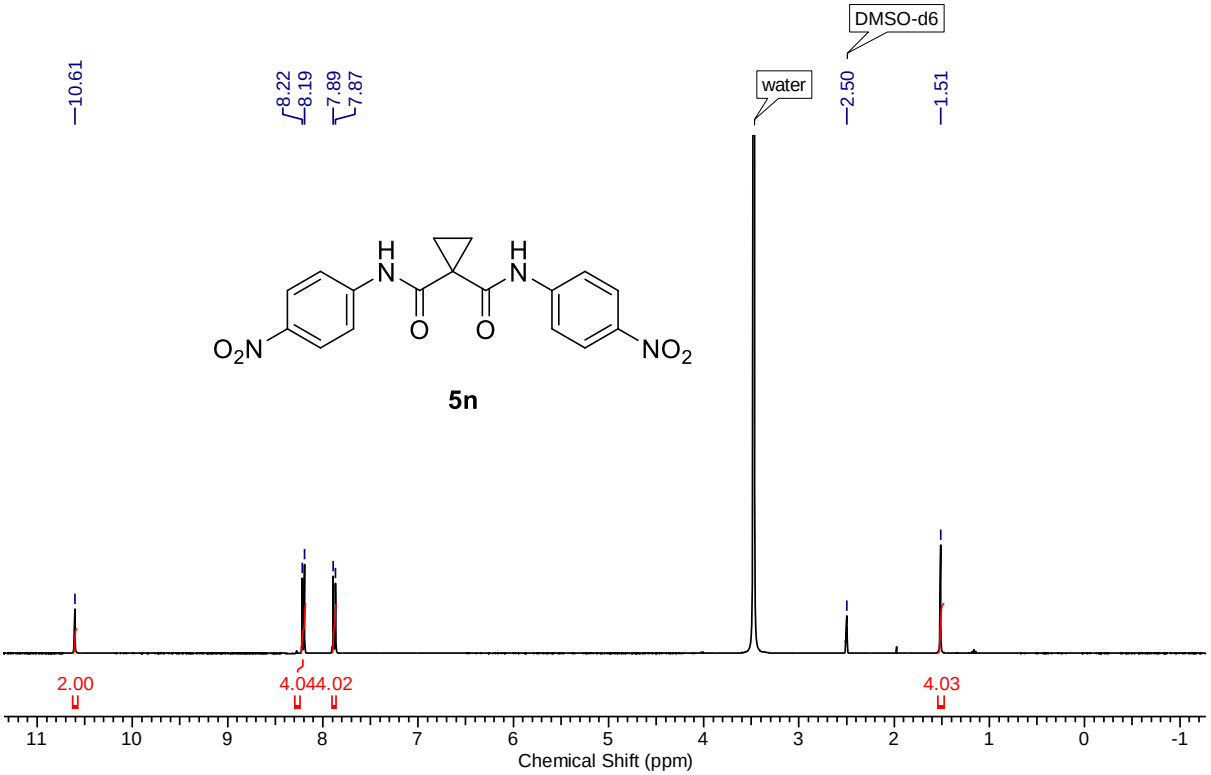
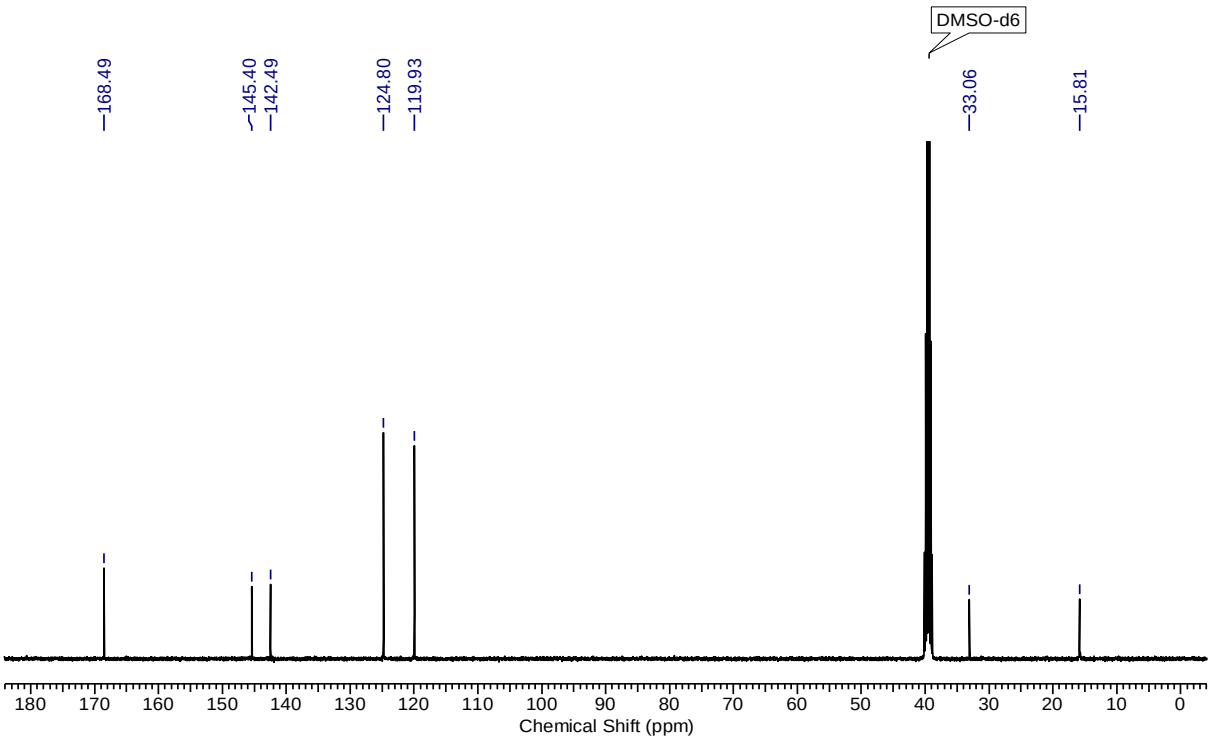


^{13}C NMR, 100 MHz



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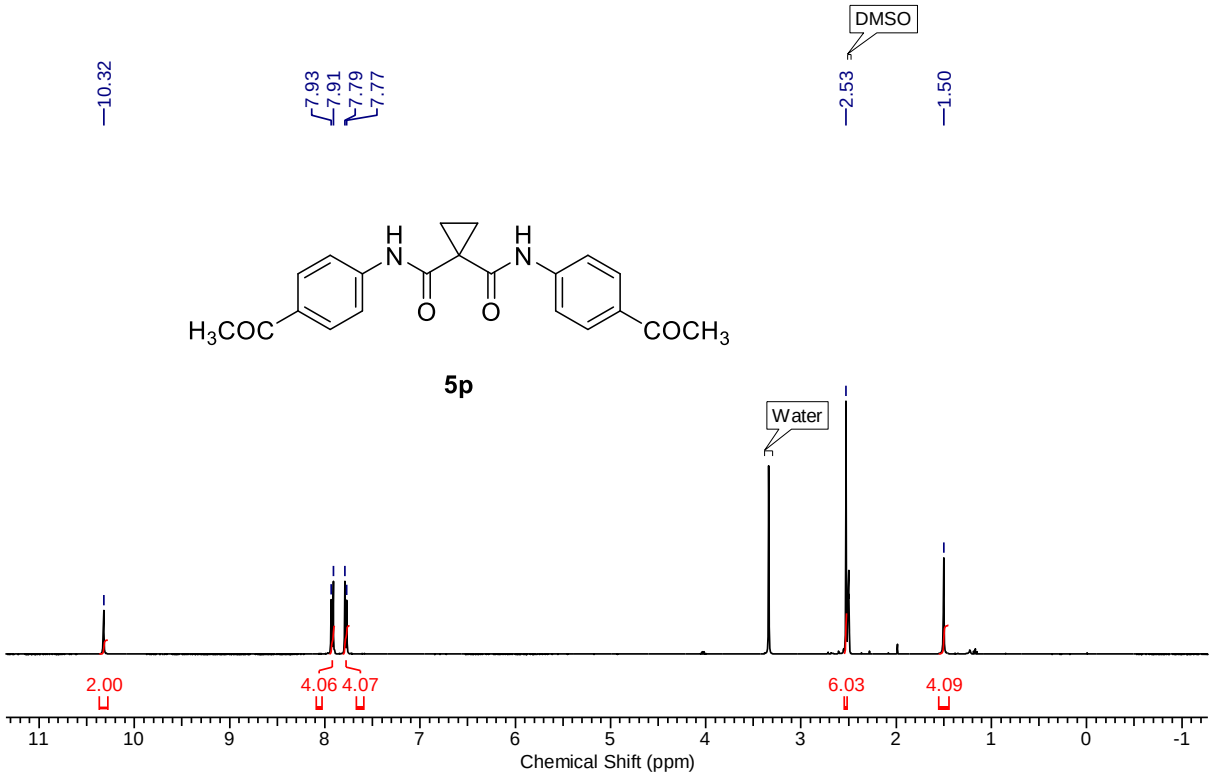
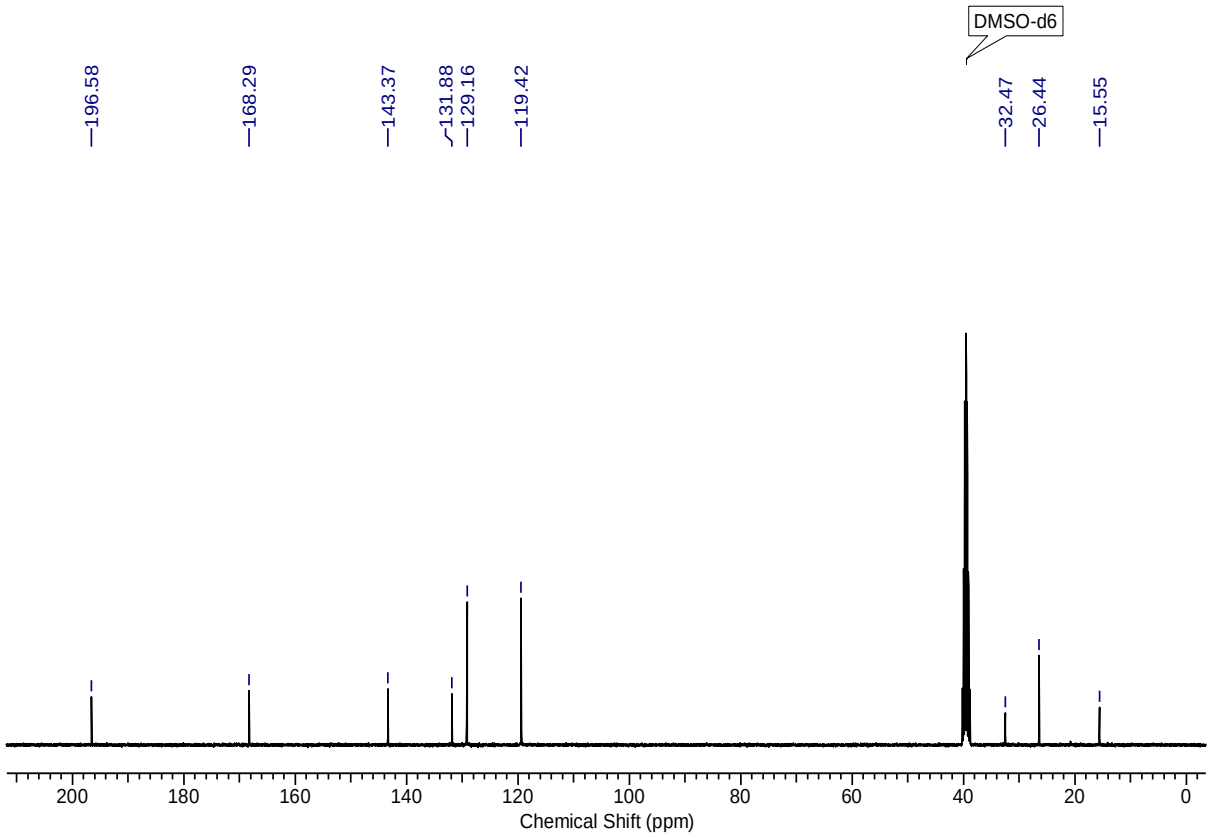
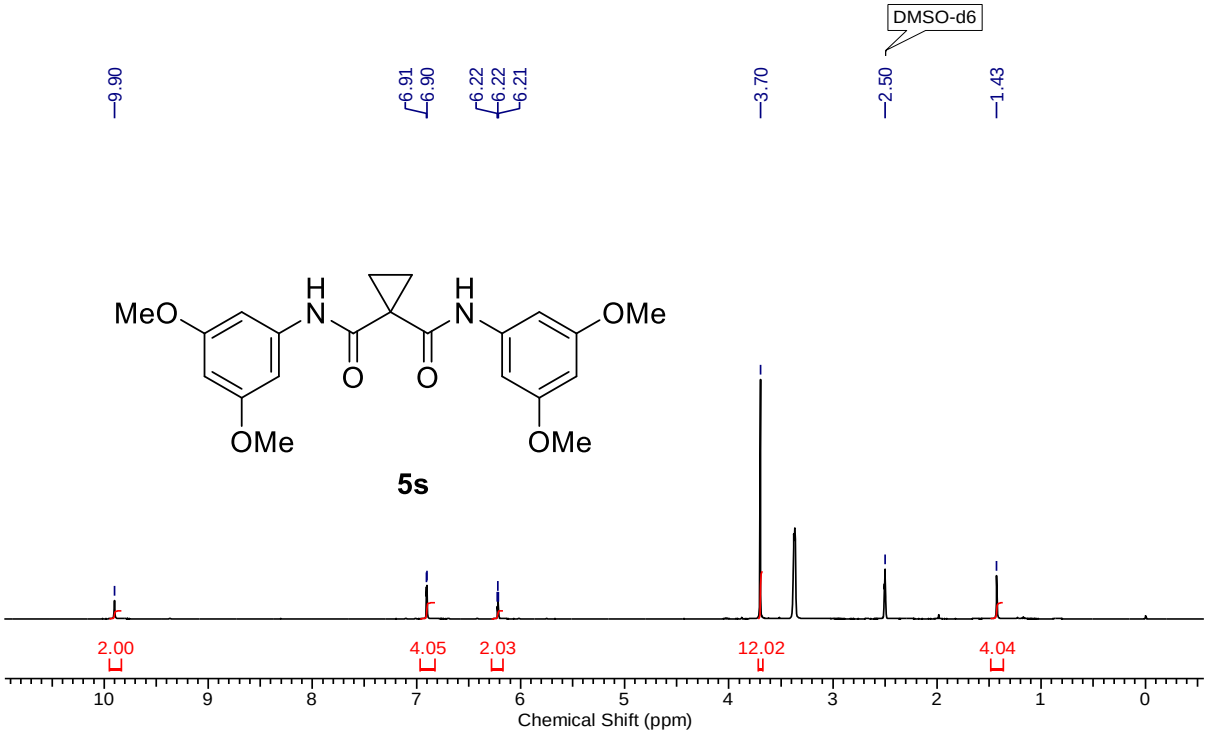


5p

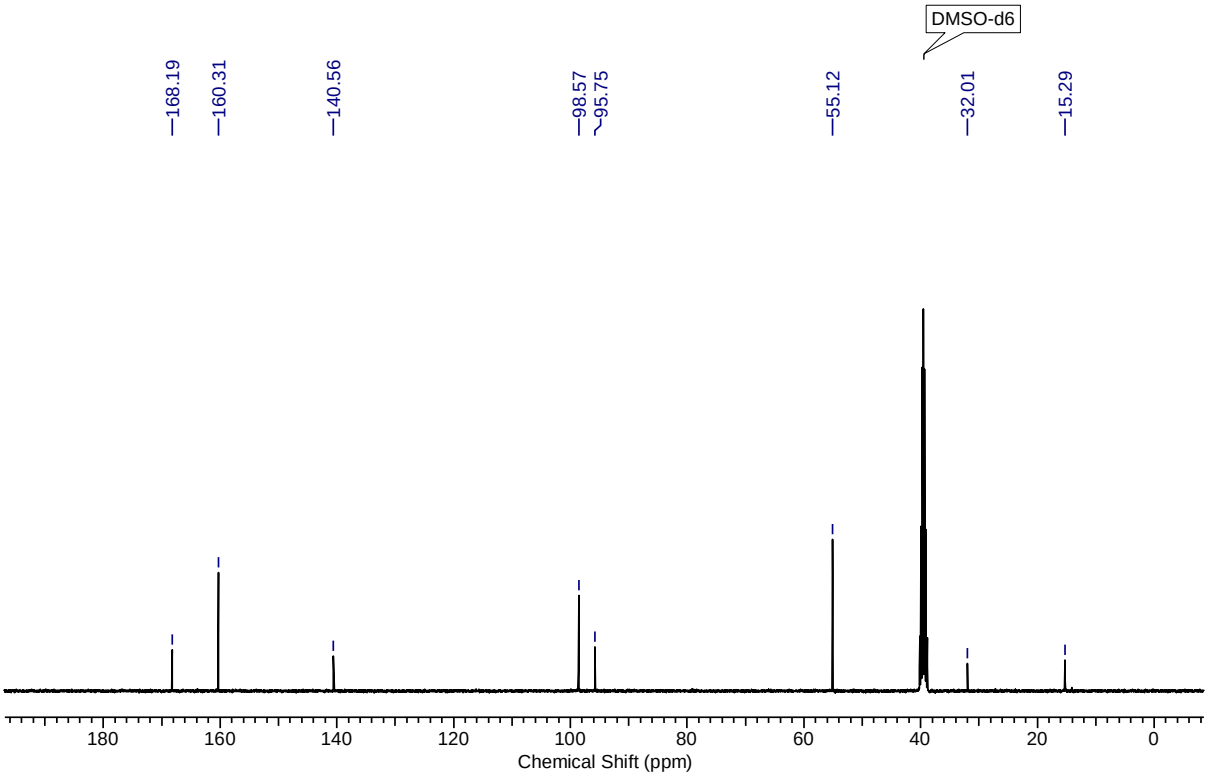
^{13}C NMR, 100 MHz



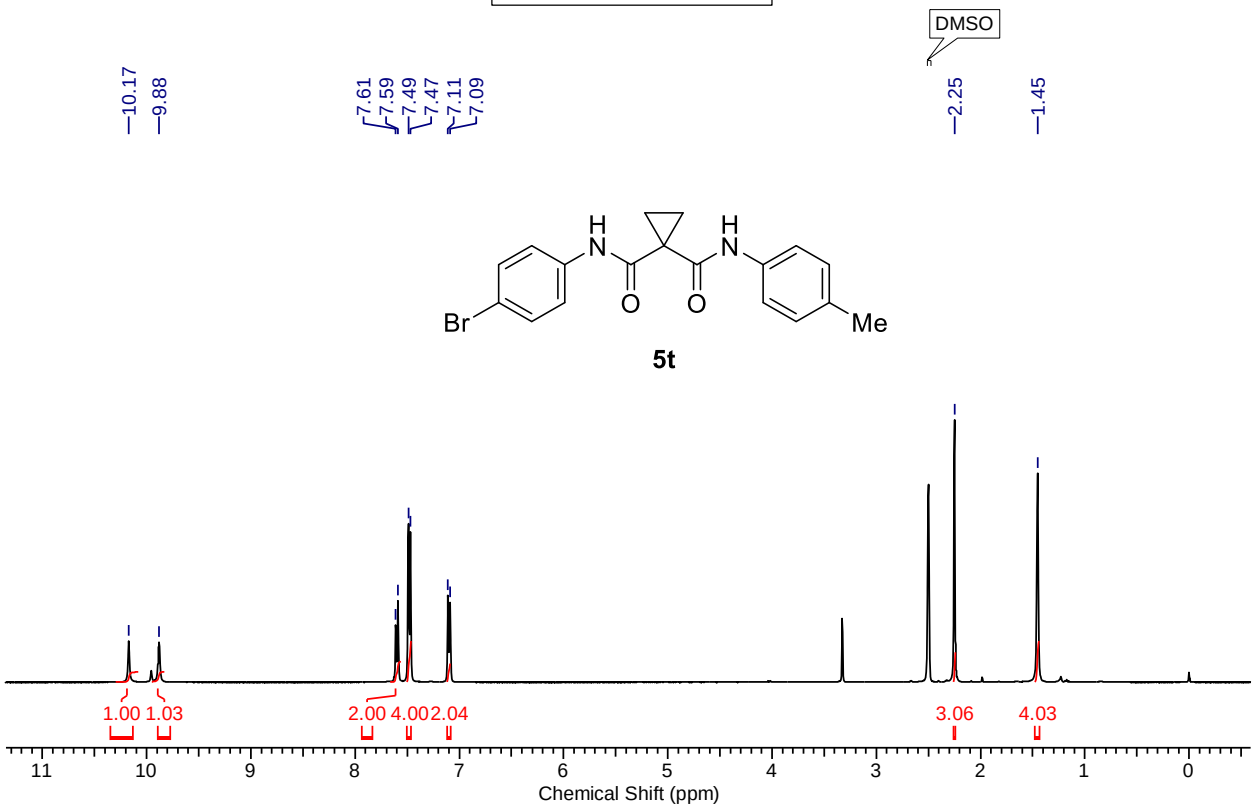
^{1}H NMR, 400 MHz



^{13}C NMR, 100 MHz



^{1}H NMR, 400 MHz



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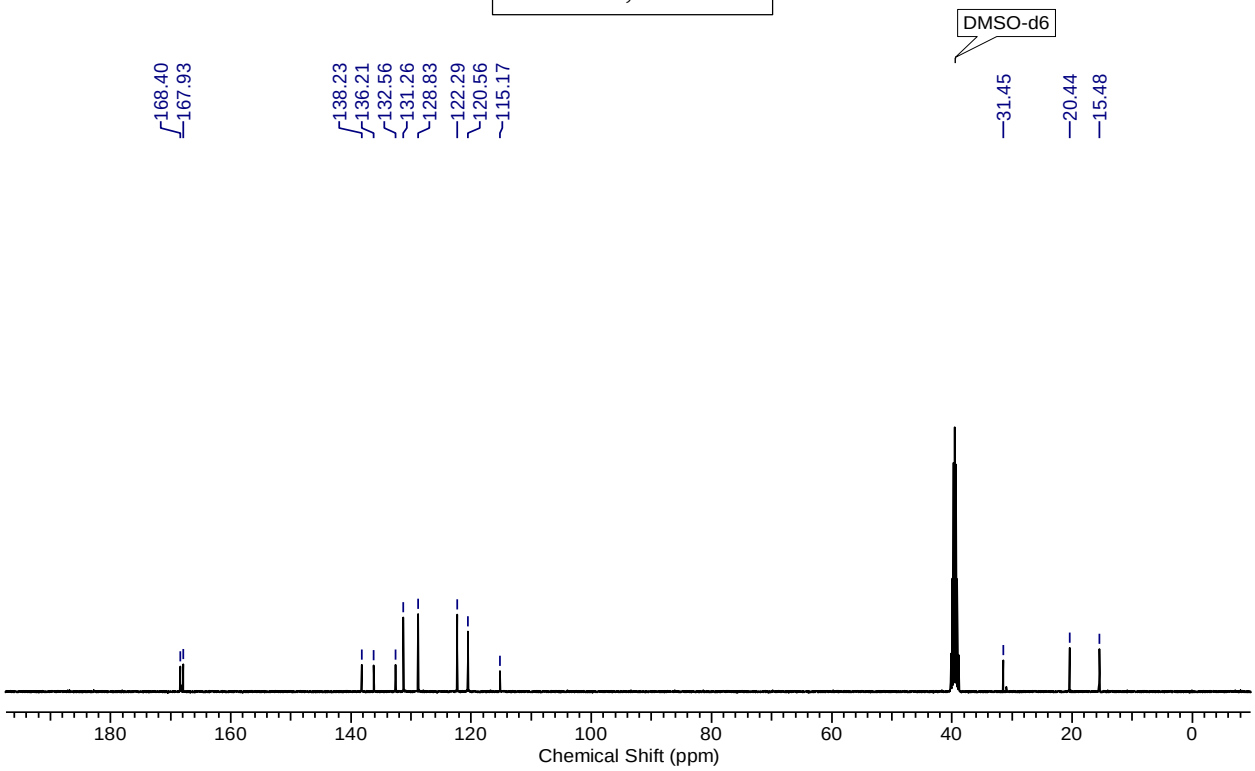

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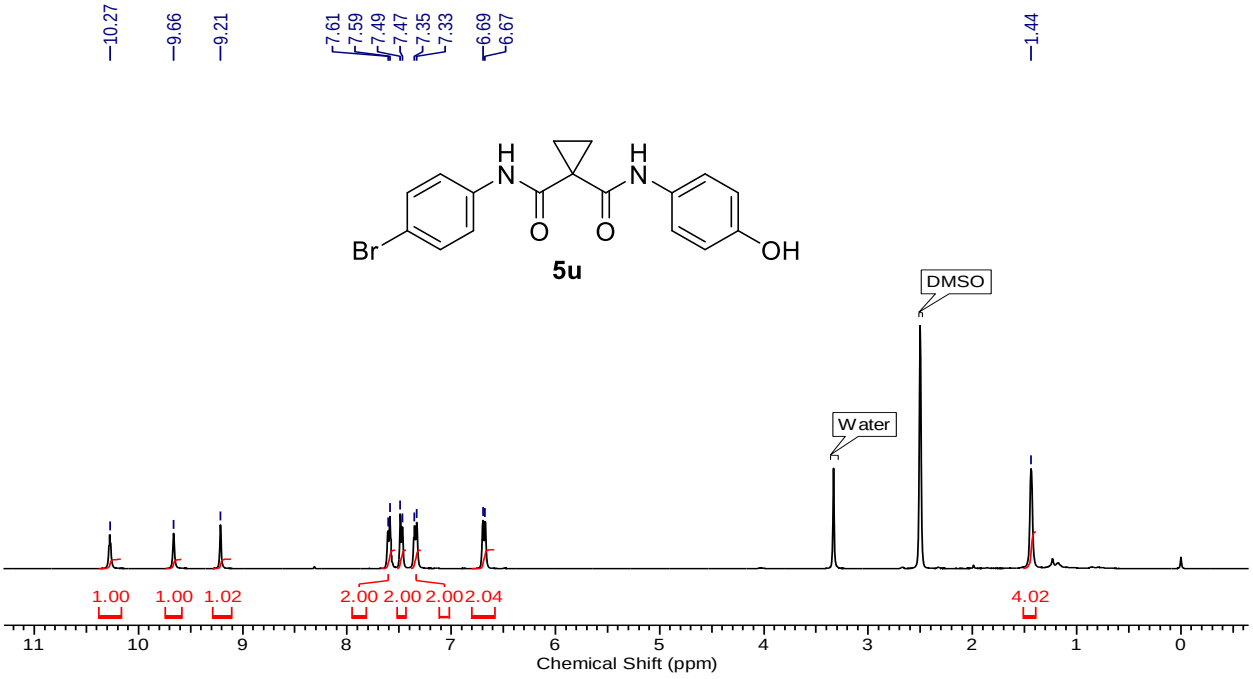

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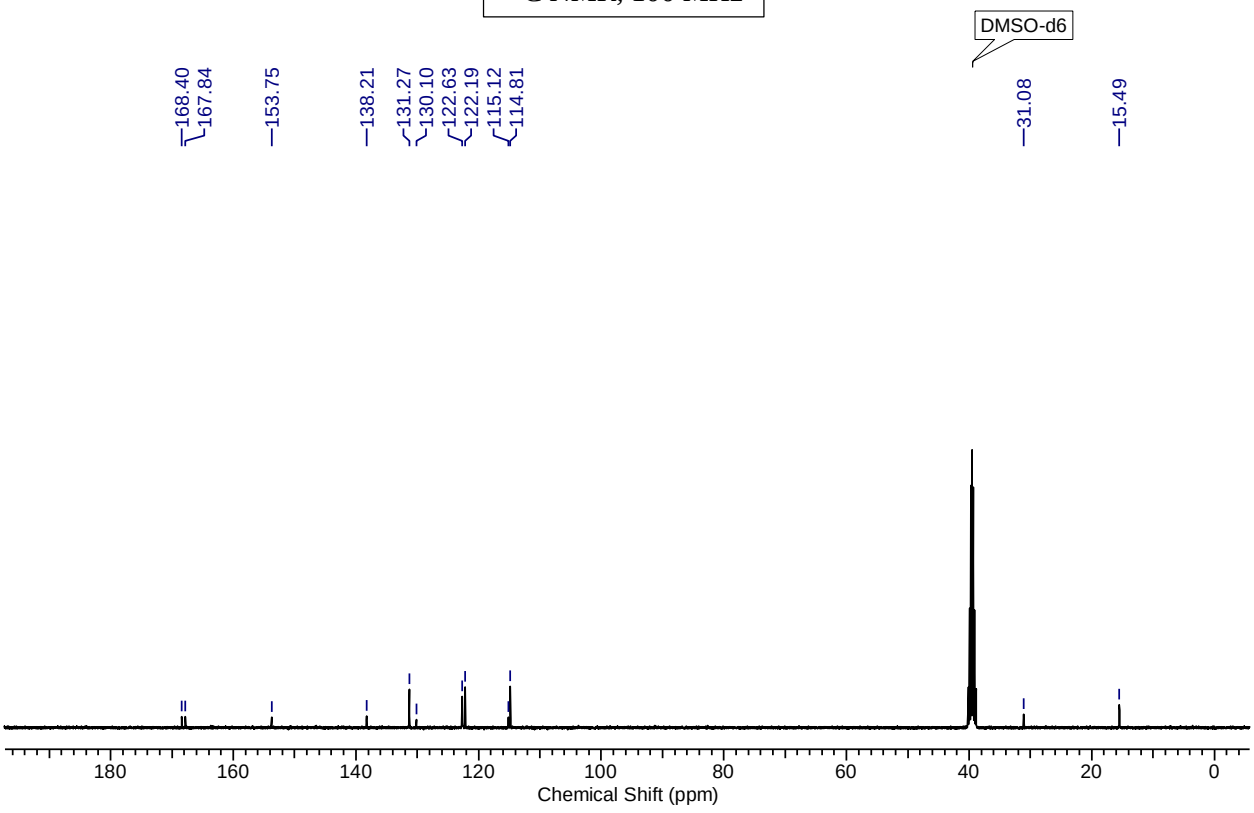
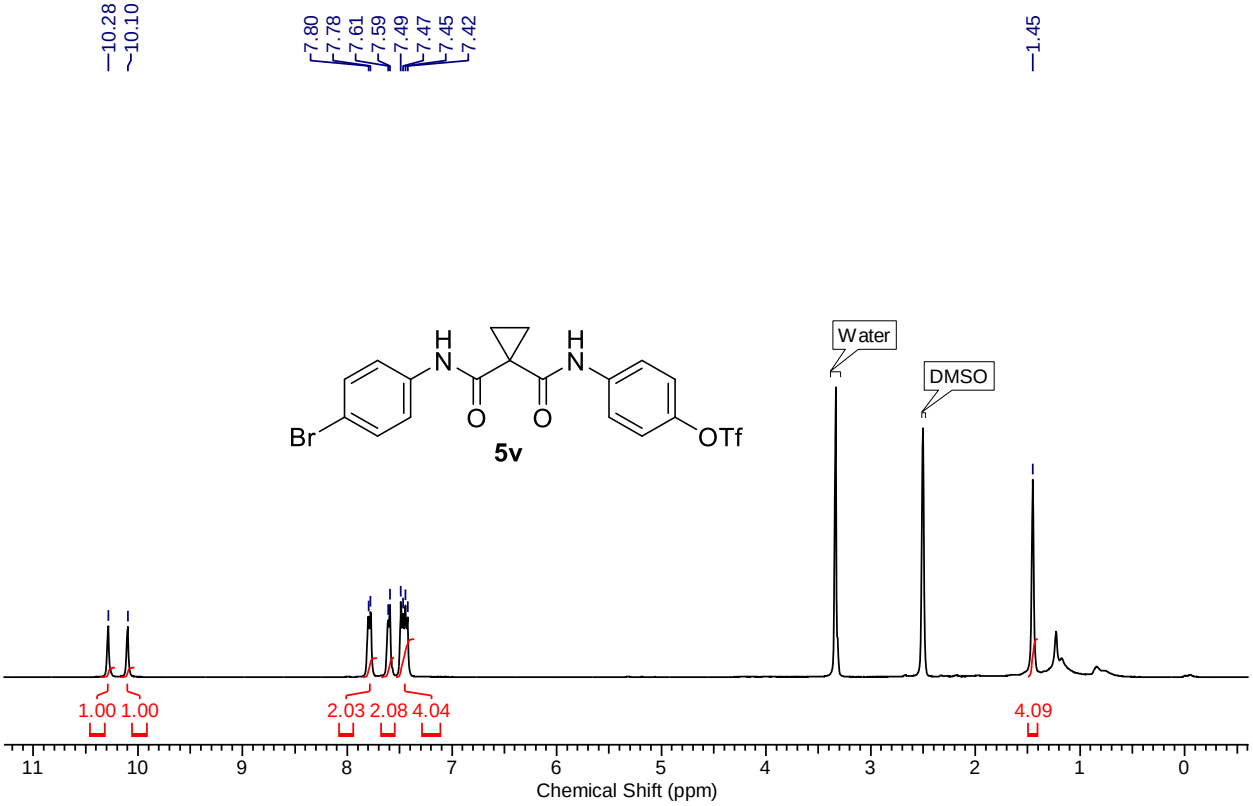


^{1}H NMR, 400 MHz



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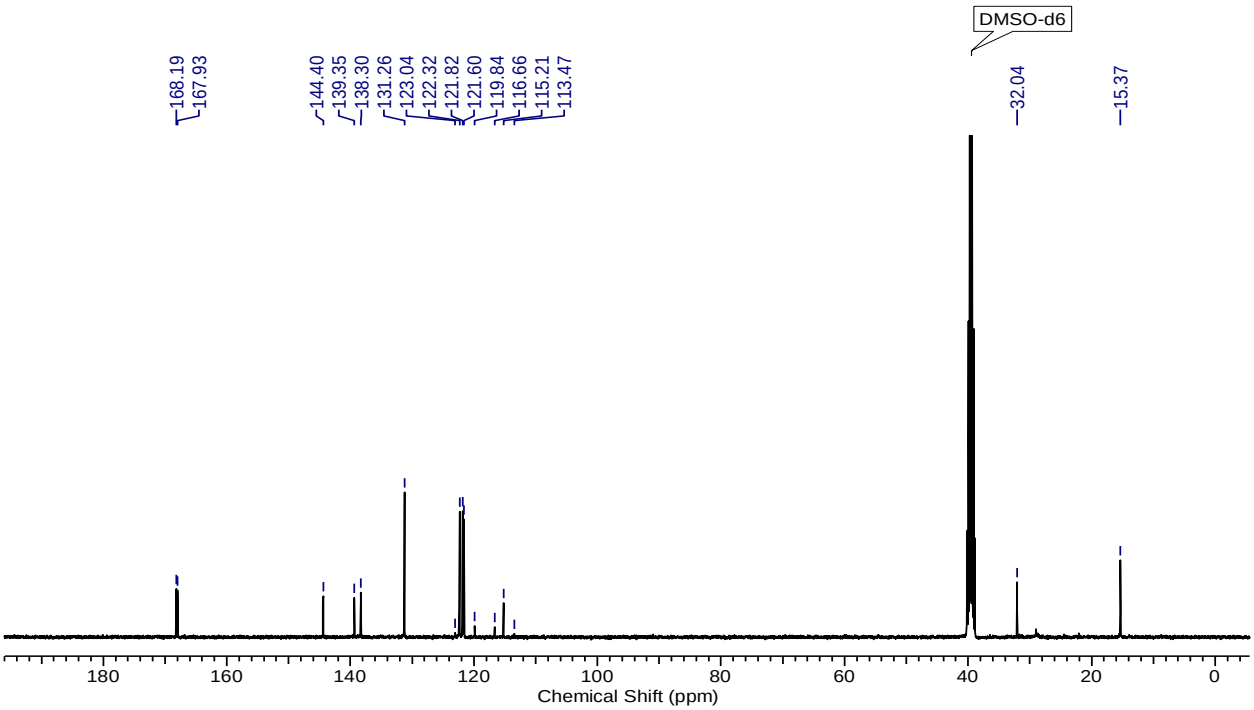

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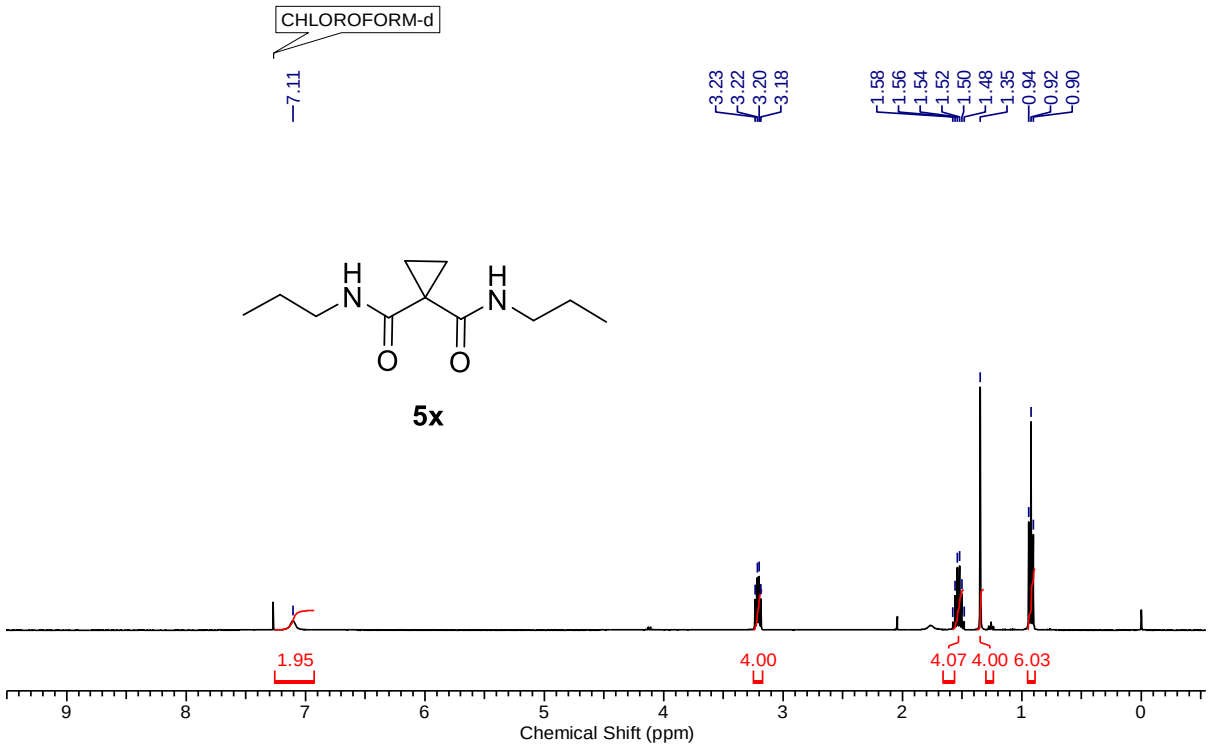
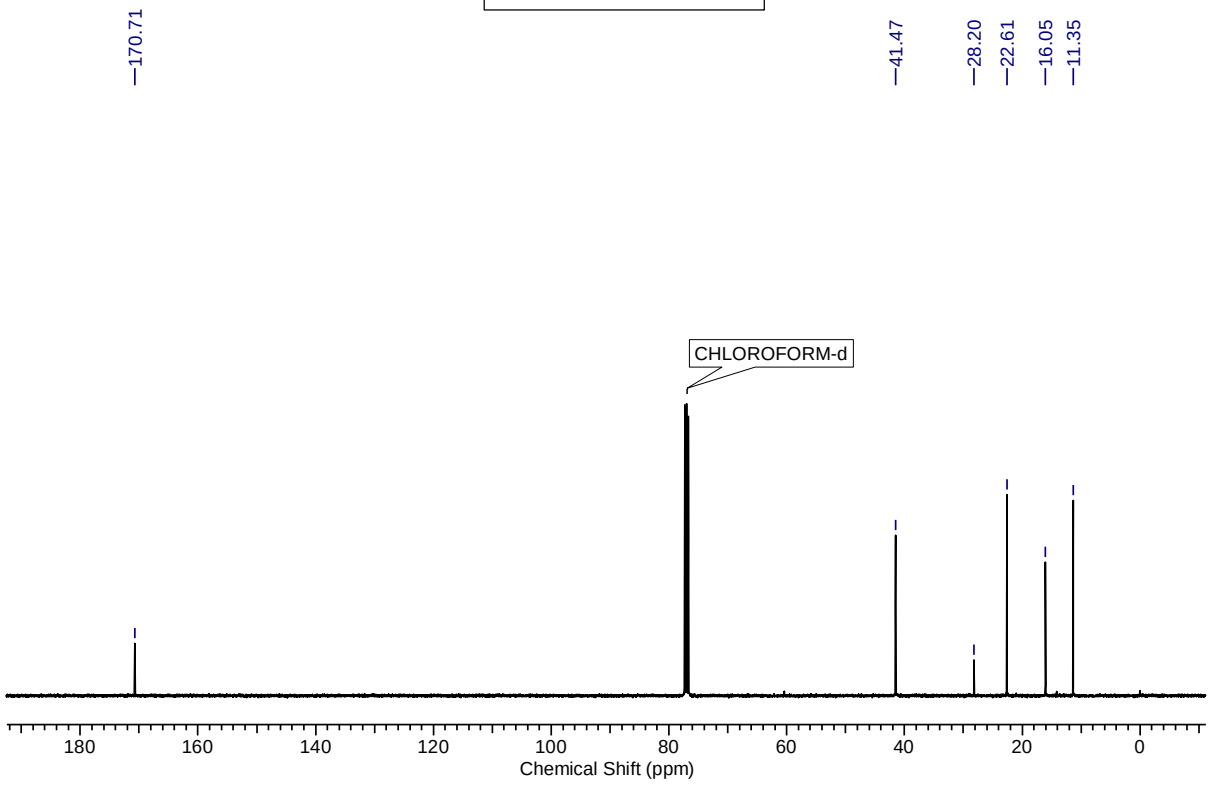


5x

^{13}C NMR, 100 MHz



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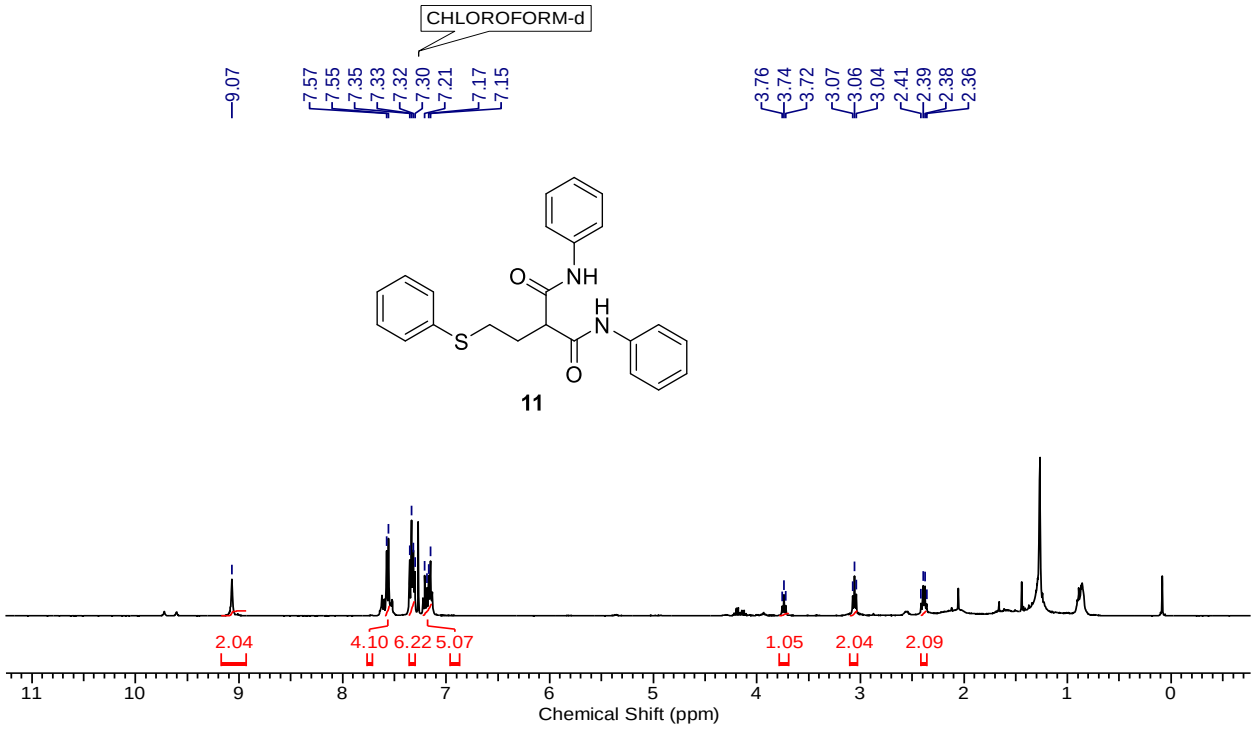

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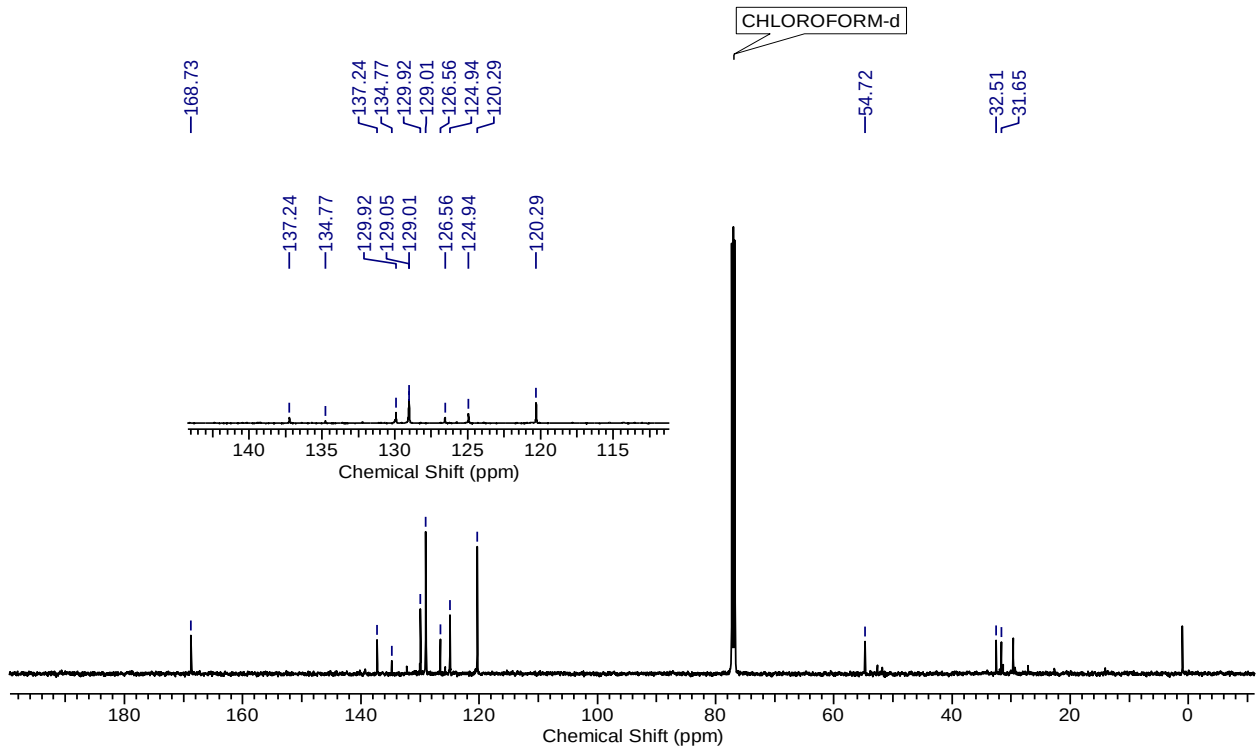

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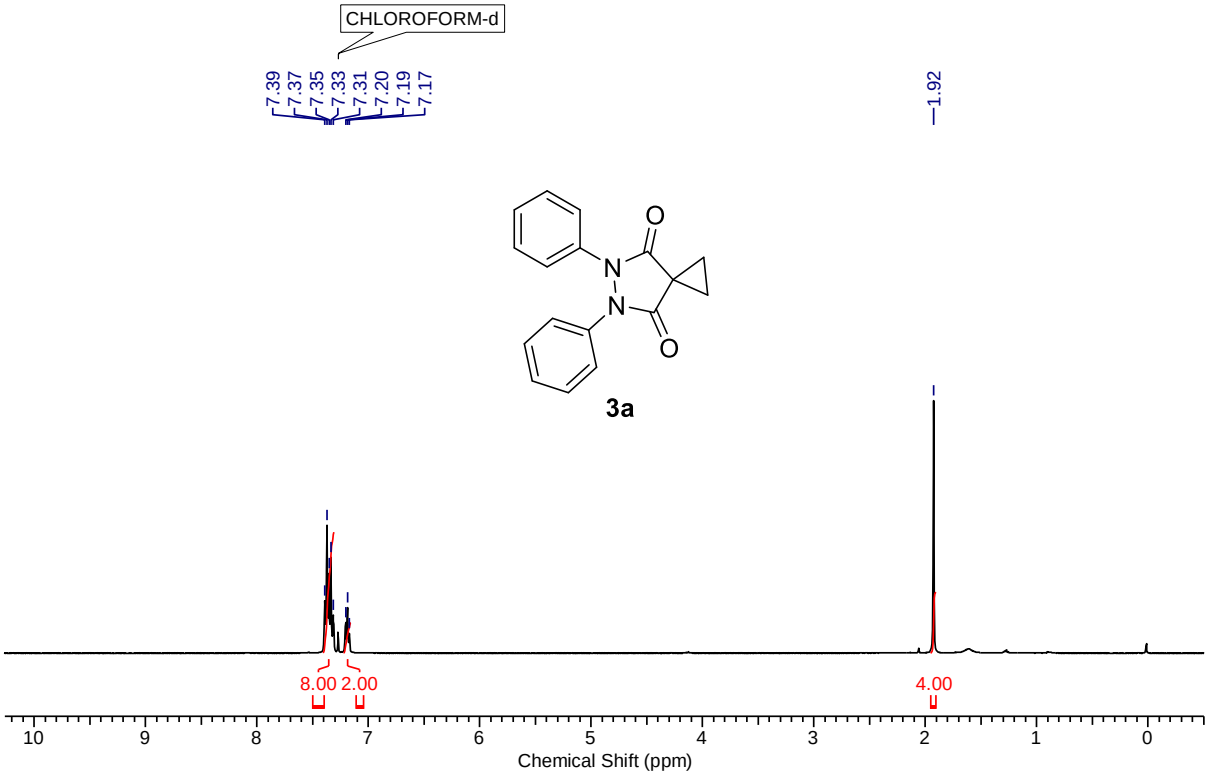
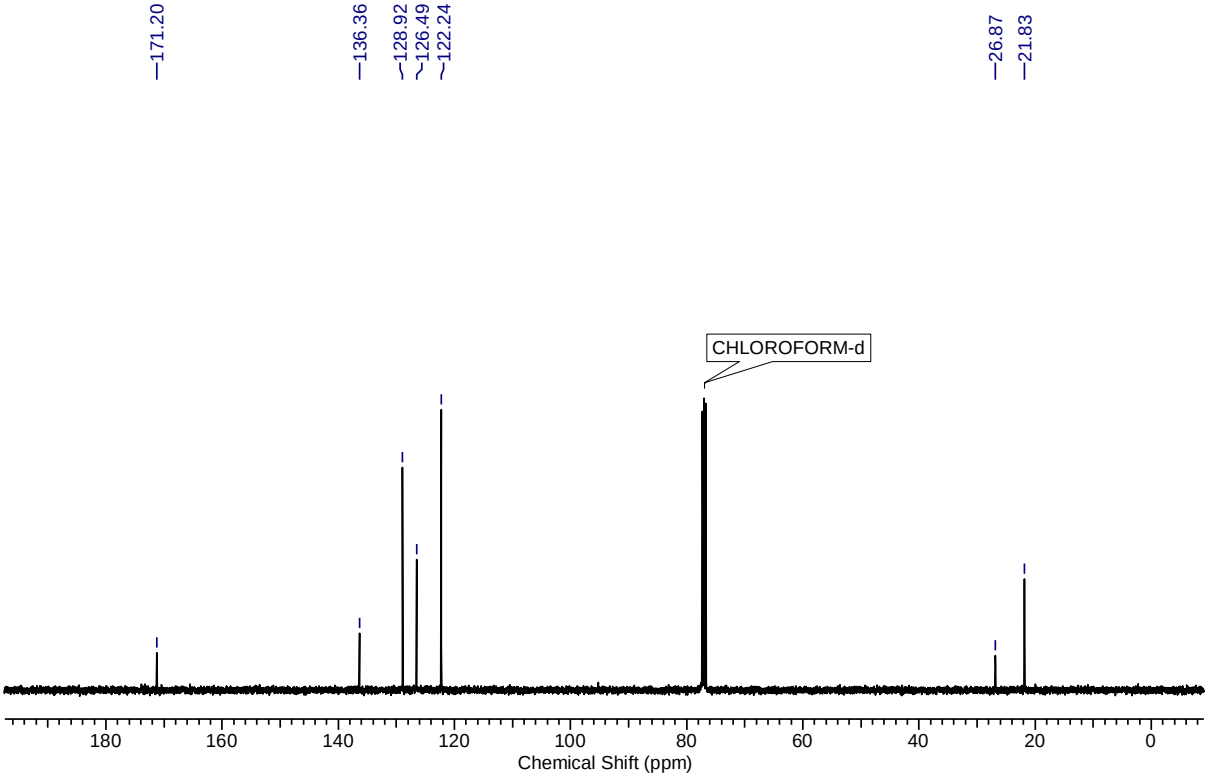
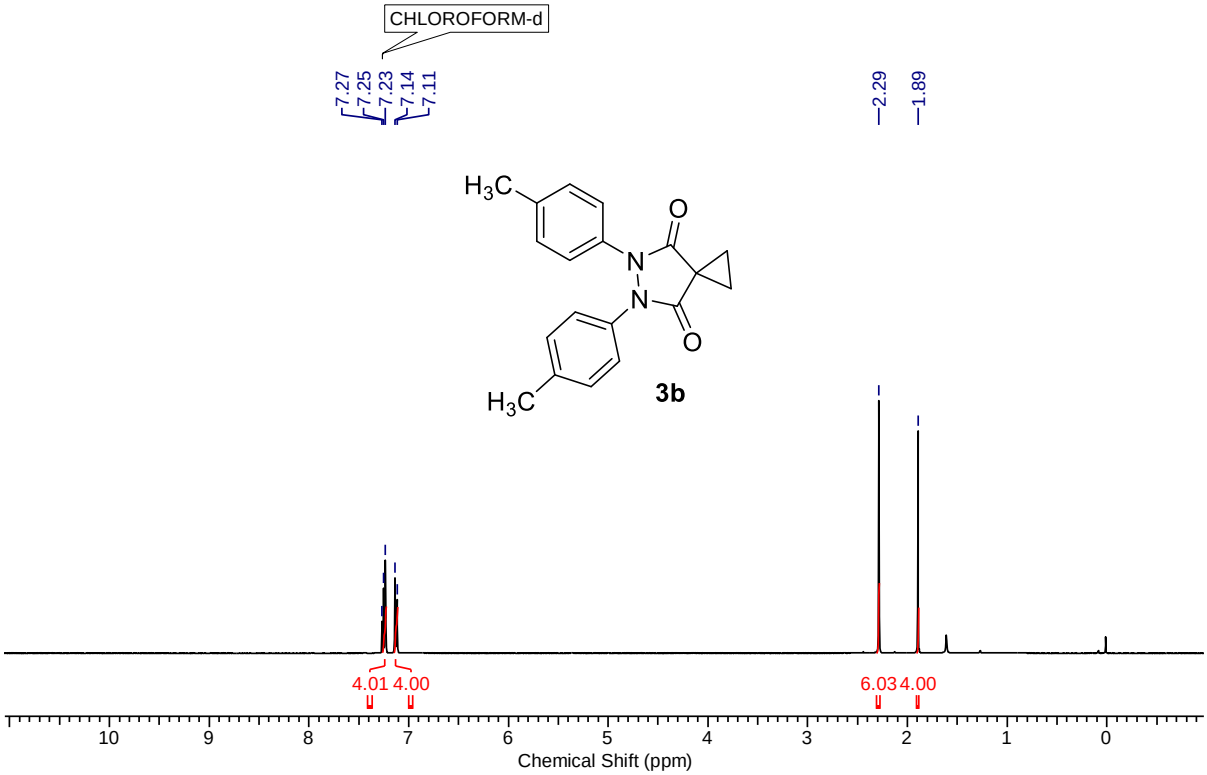


^{13}C NMR, 100 MHz



^{1}H NMR, 400 MHz



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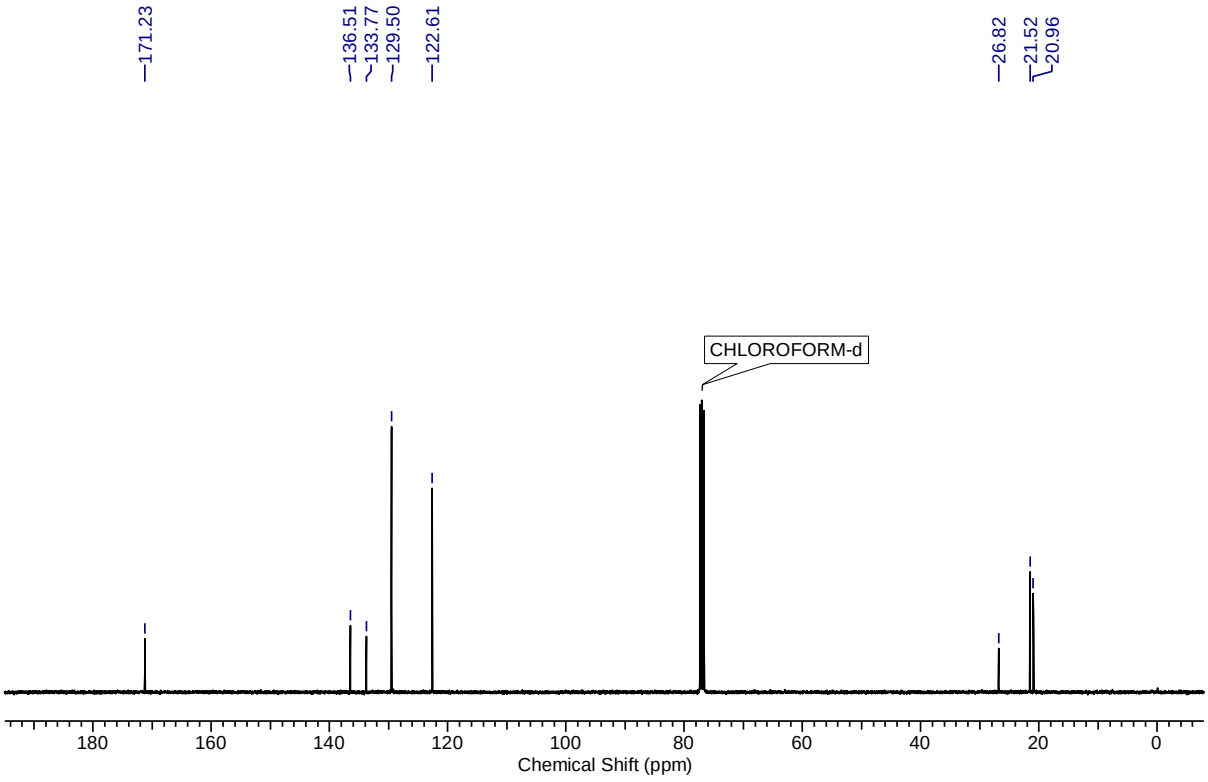
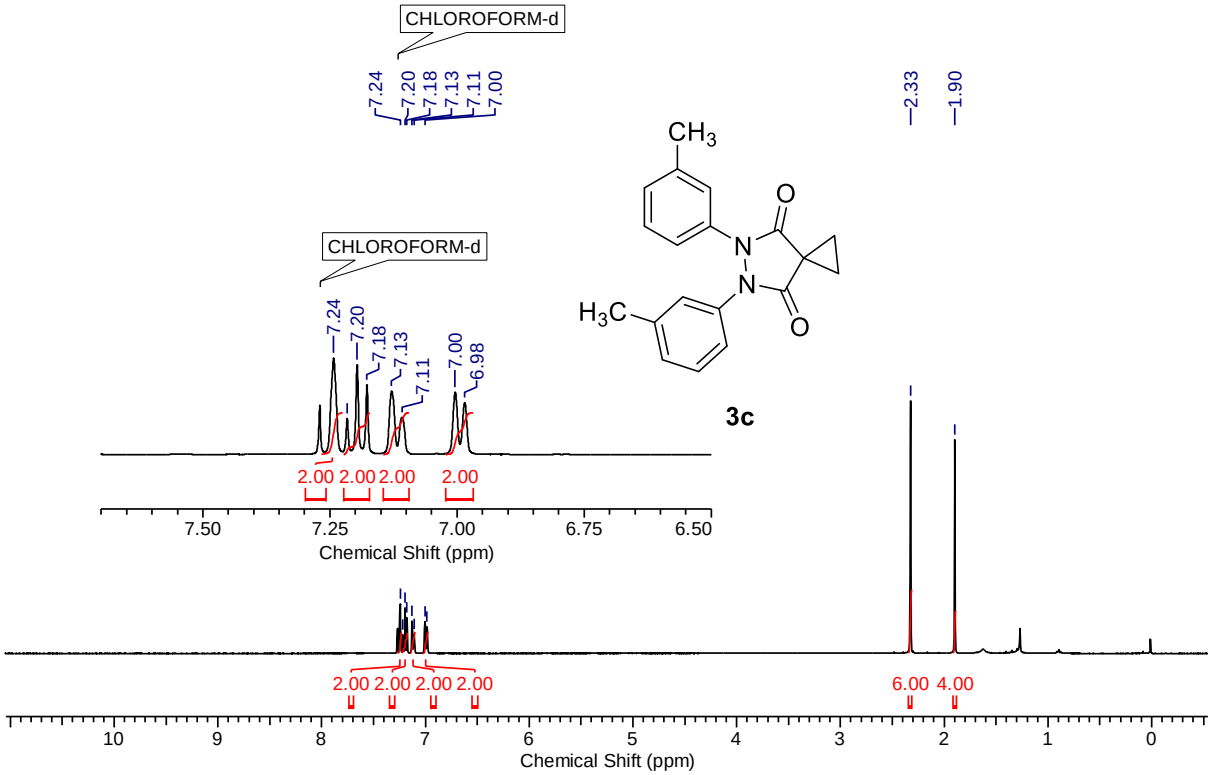
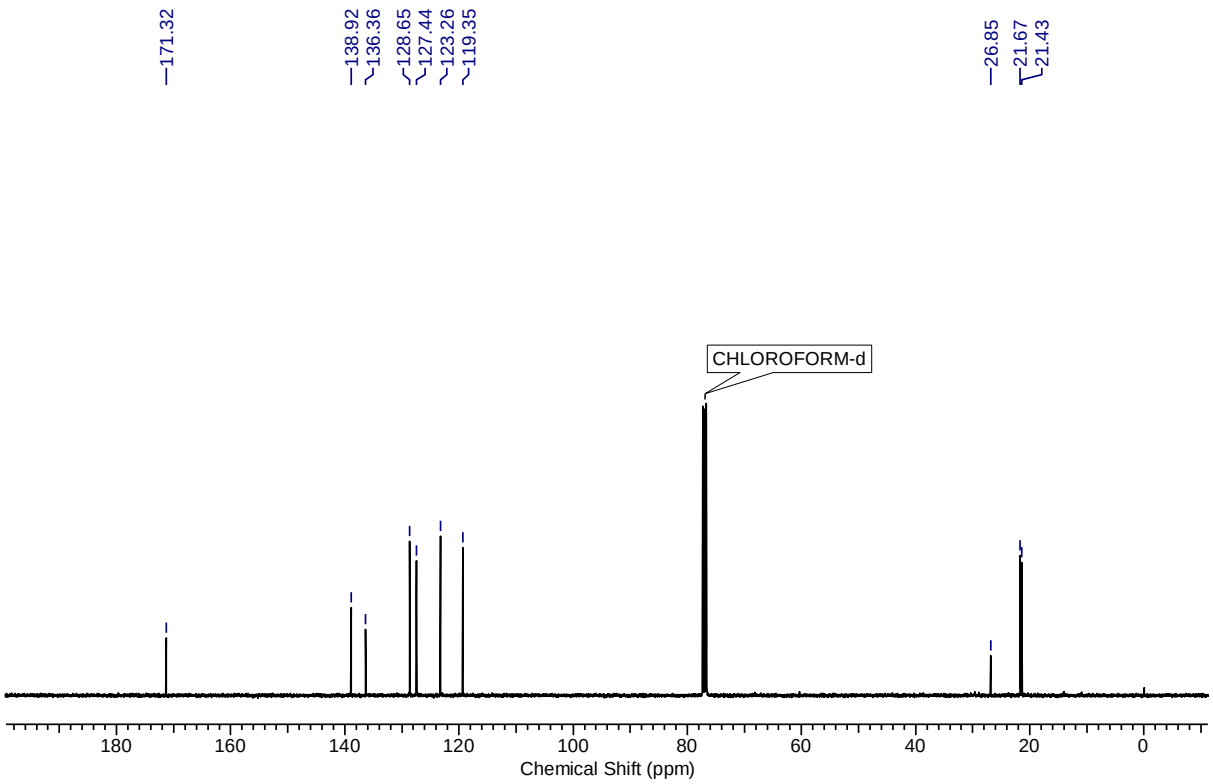


^{1}H NMR, 400 MHz



^{13}C NMR, 100 MHz



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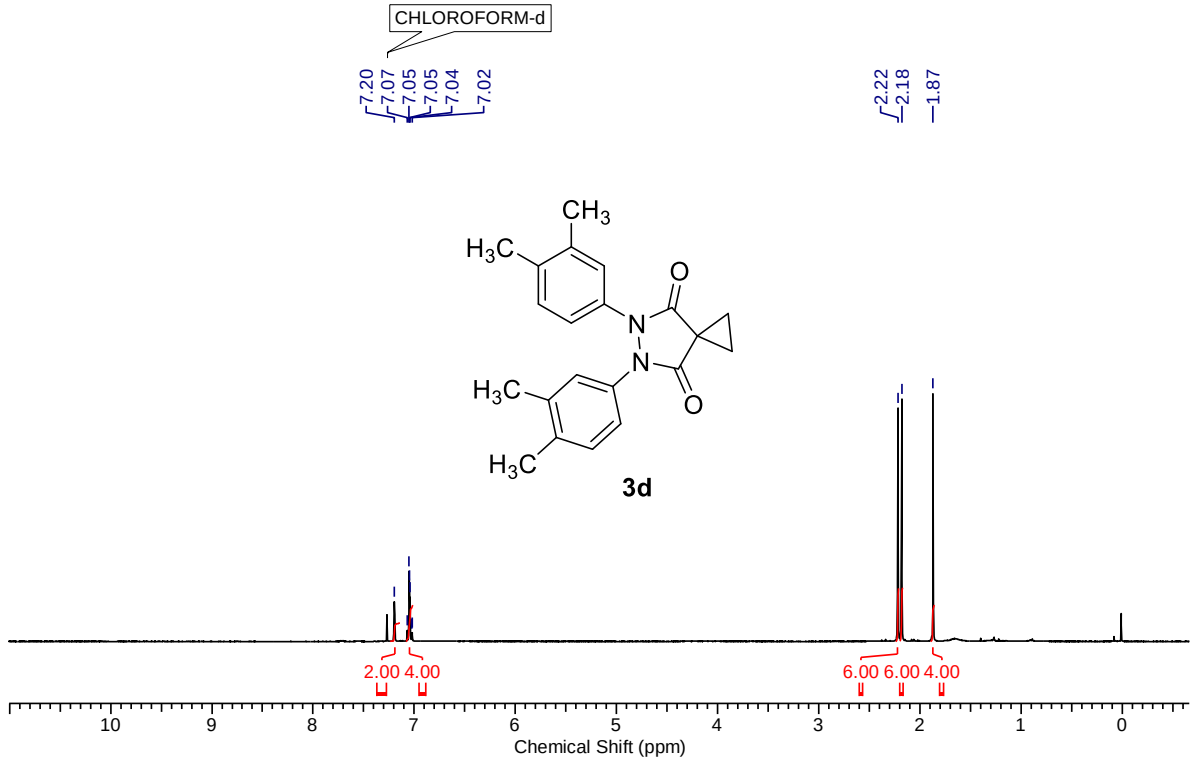

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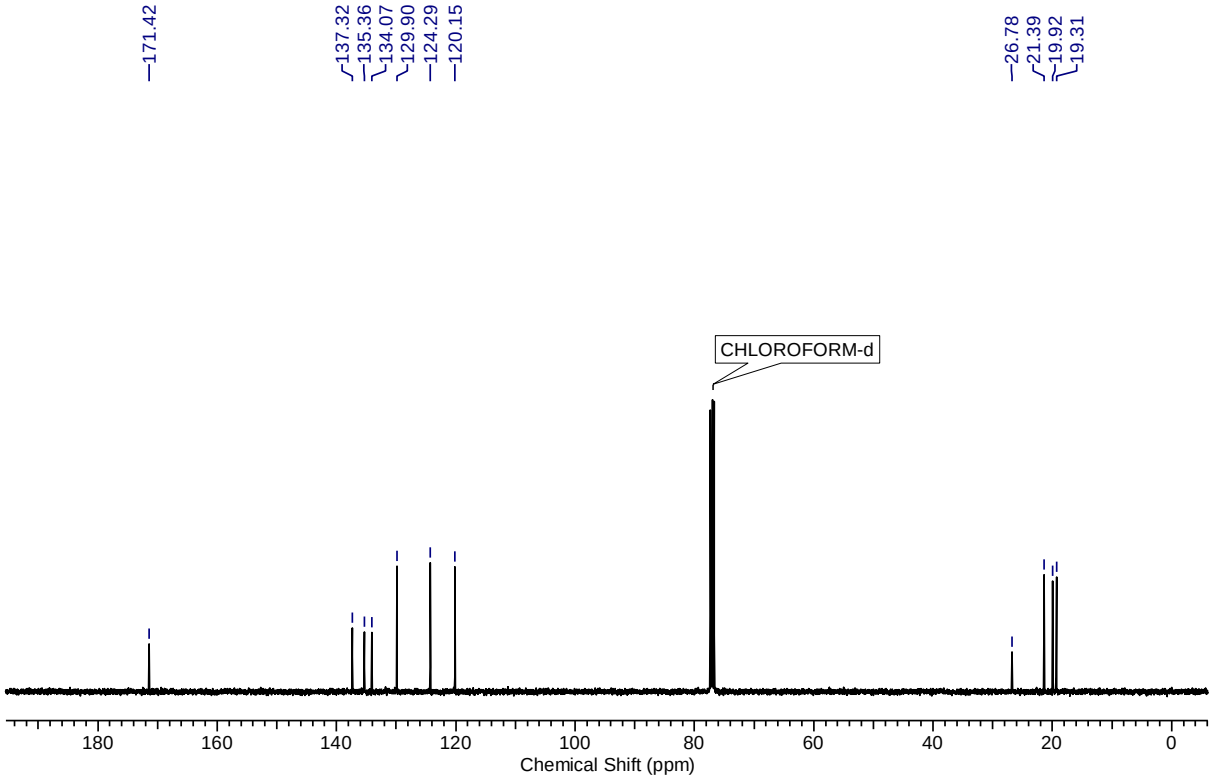

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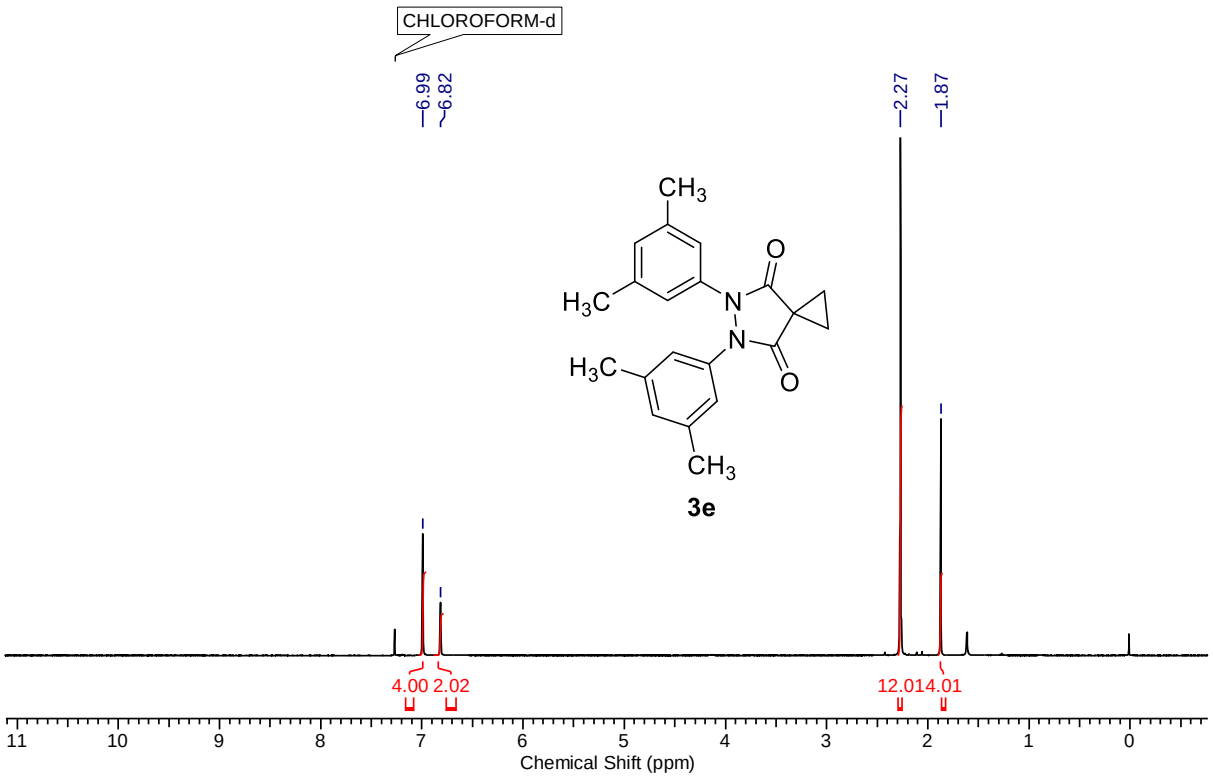

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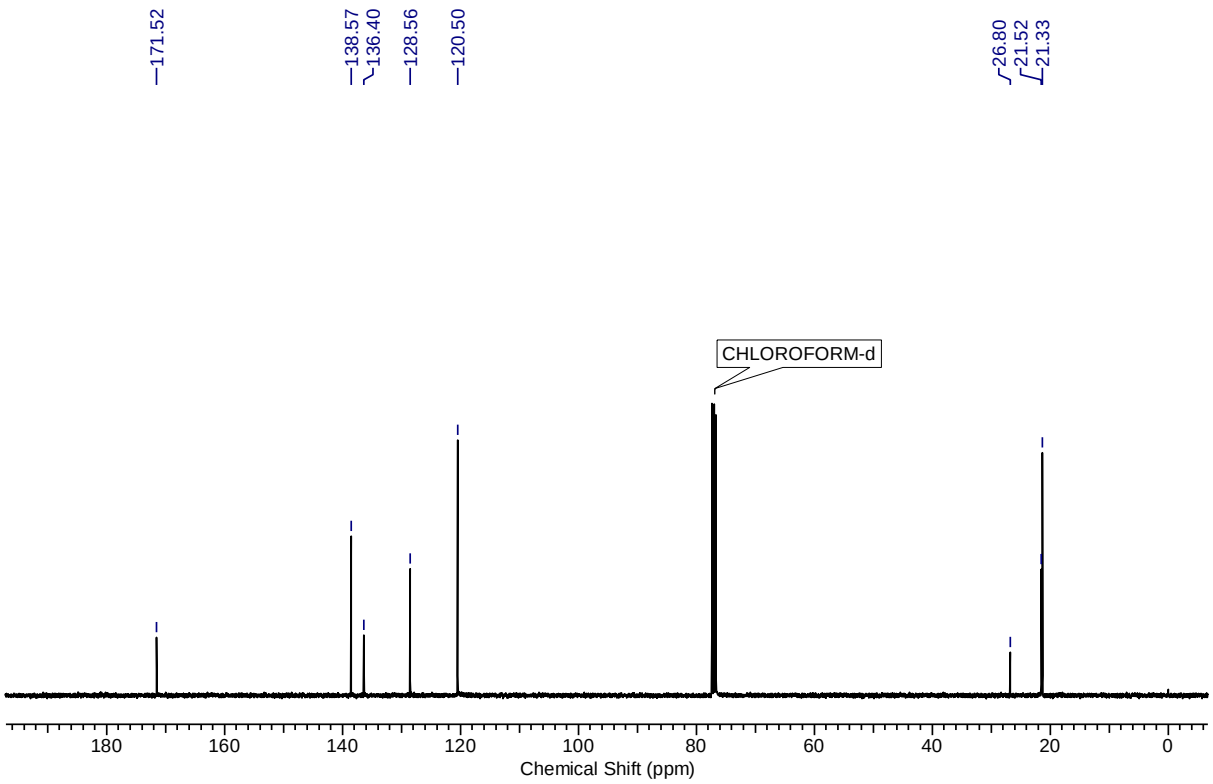
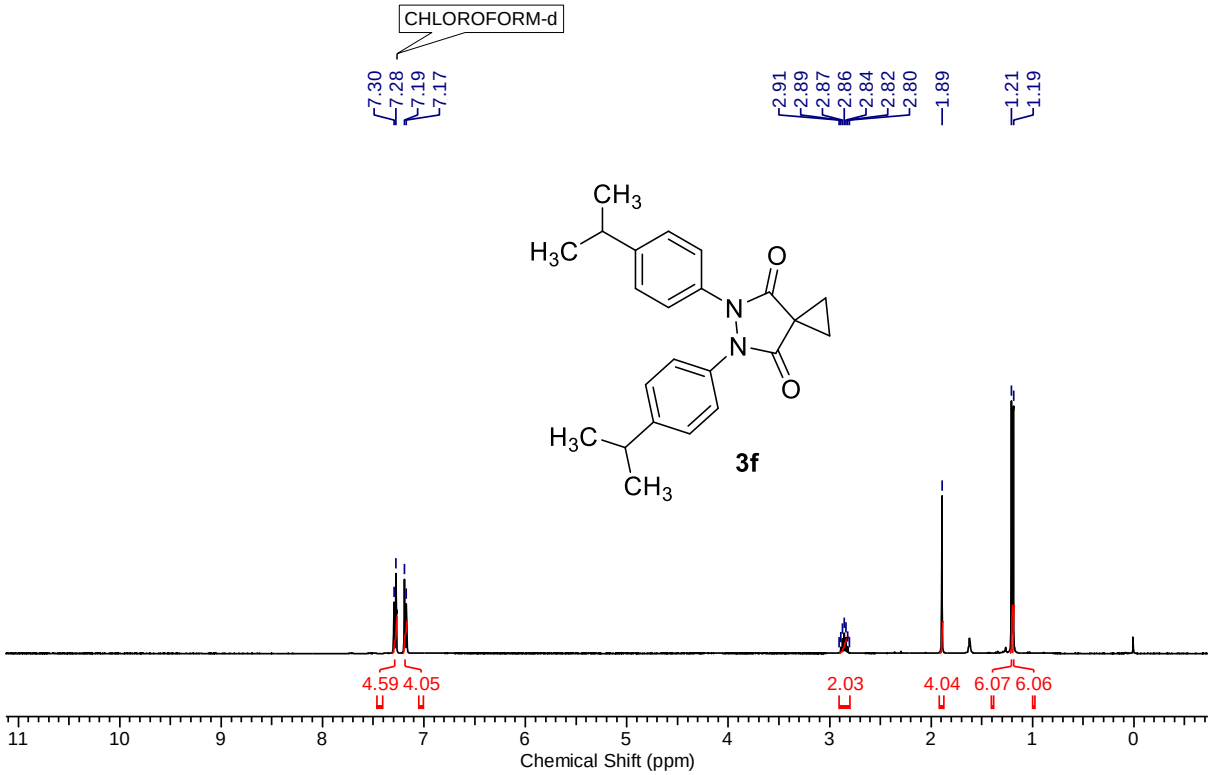
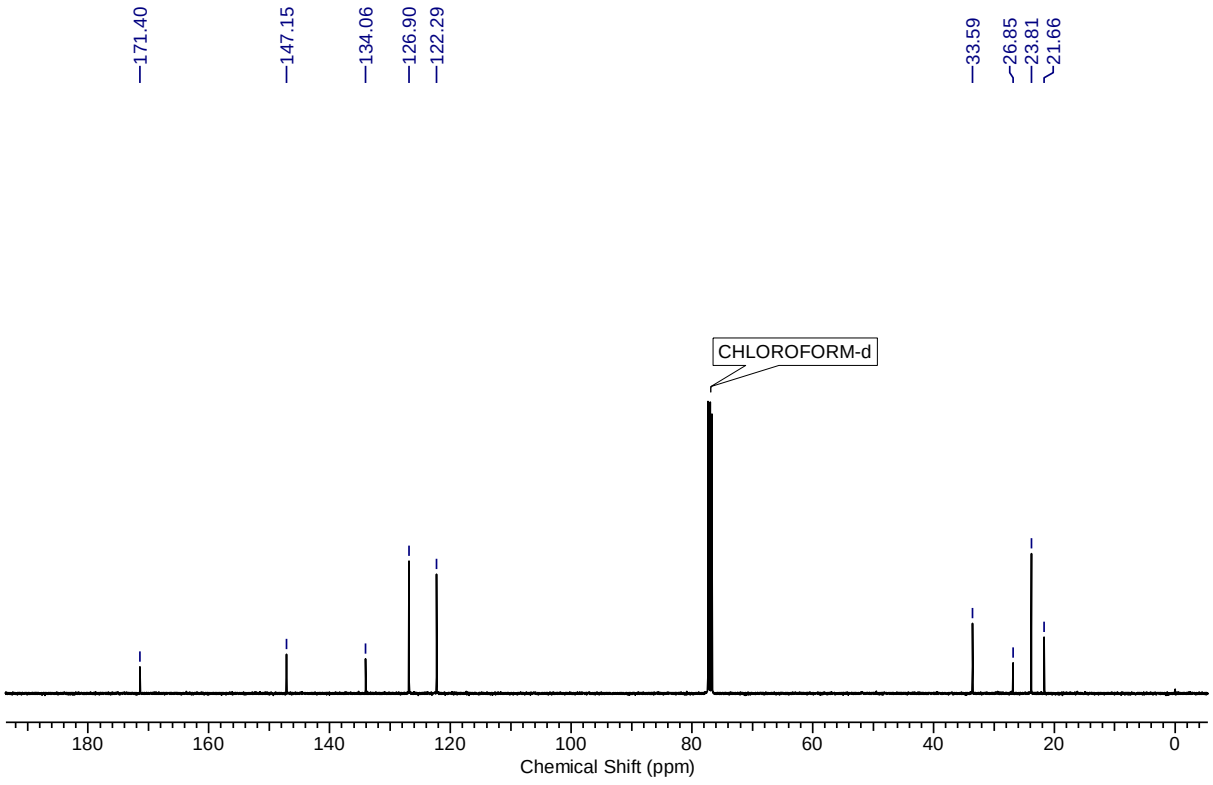


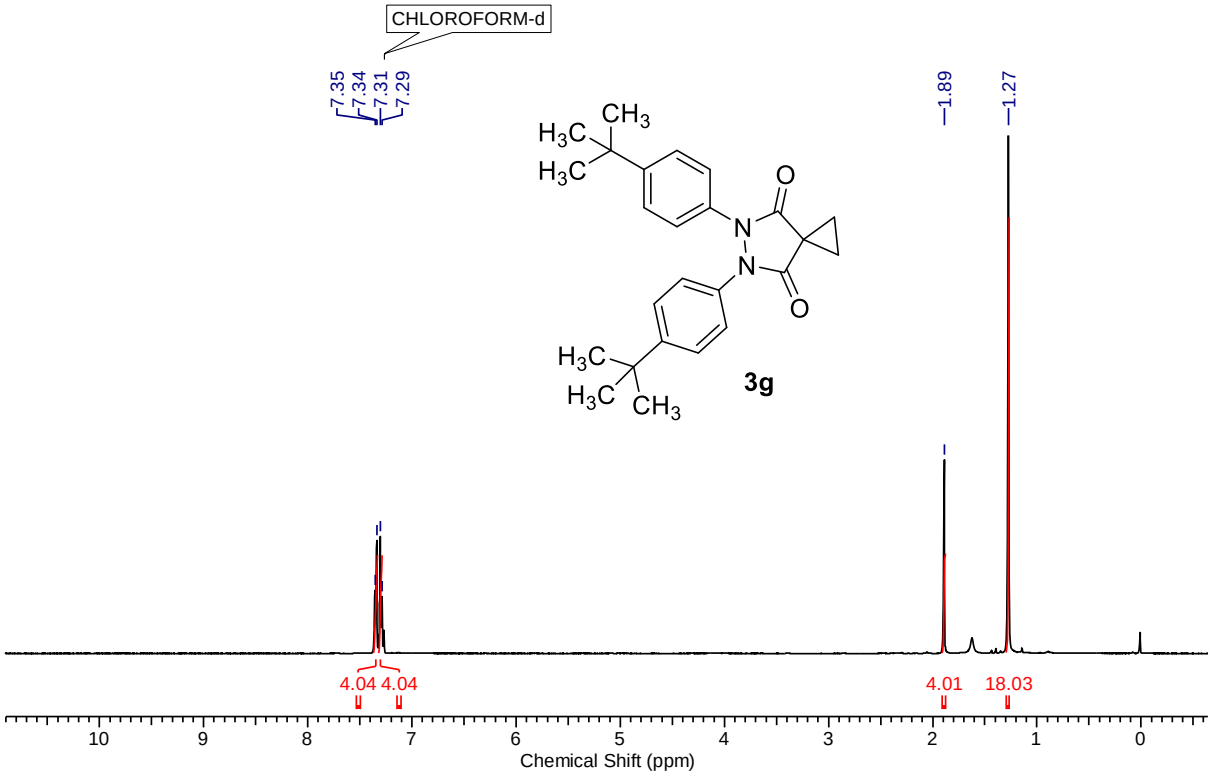
^{1}H NMR, 400 MHz



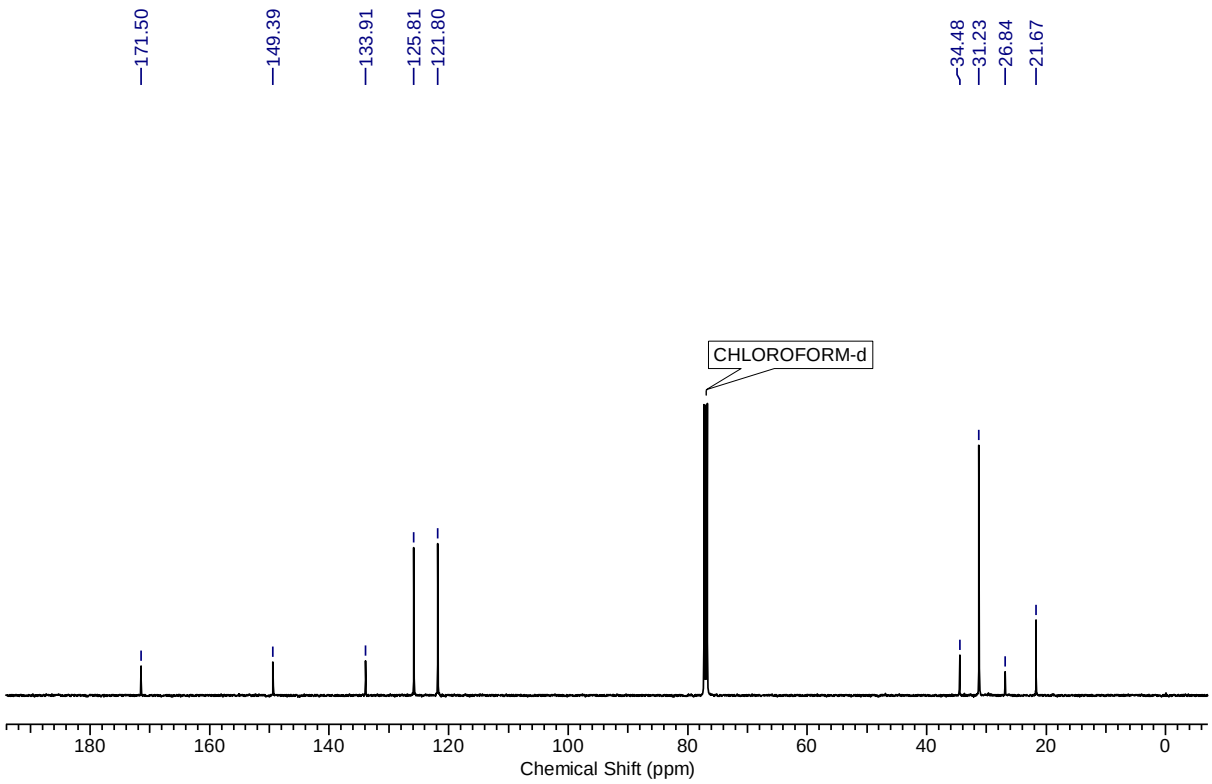
^{13}C NMR, 100 MHz



^{1}H NMR, 500 MHz



^{13}C NMR, 125 MHz



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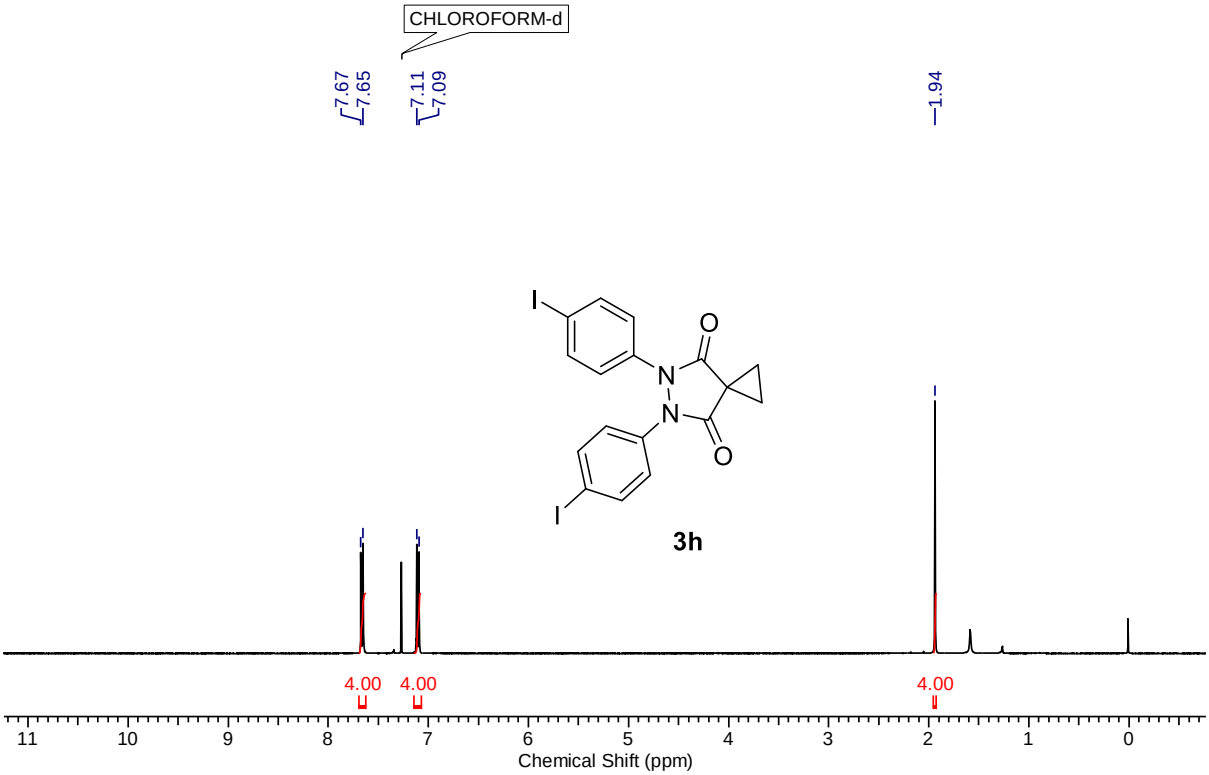

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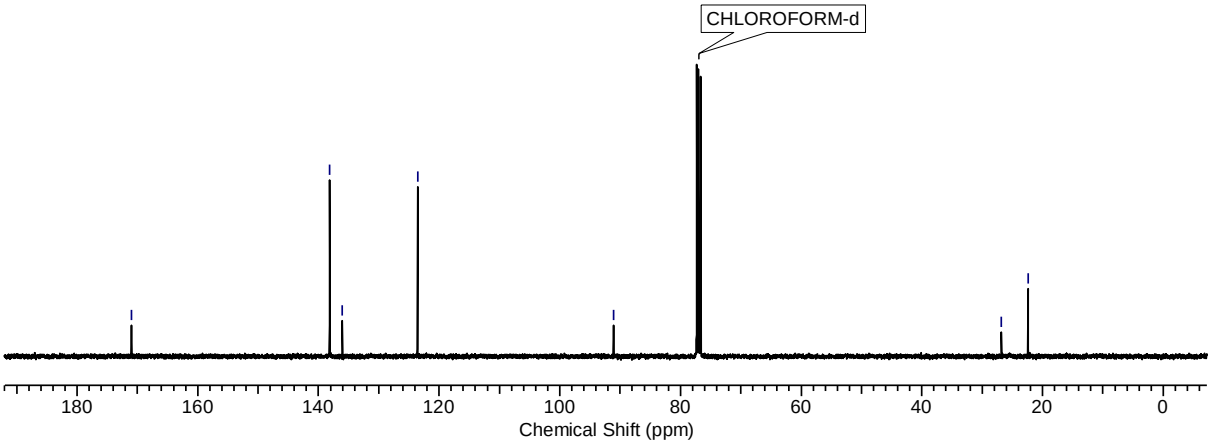

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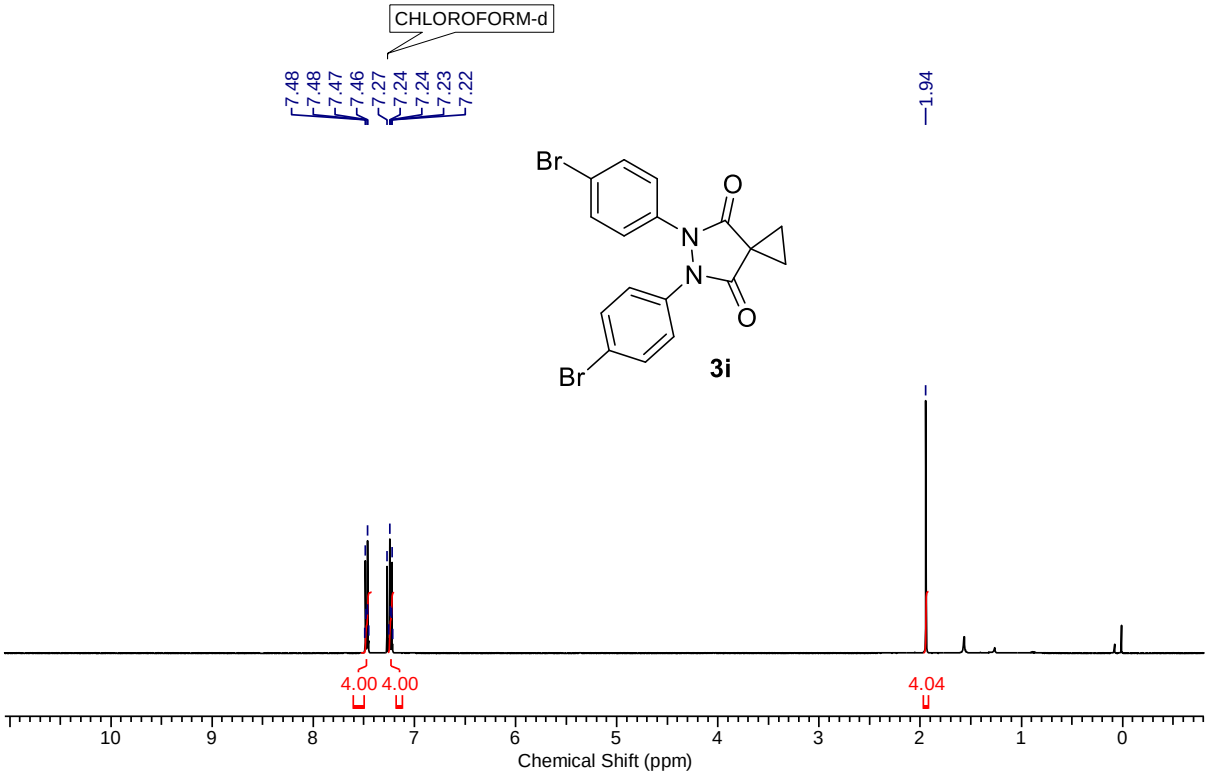
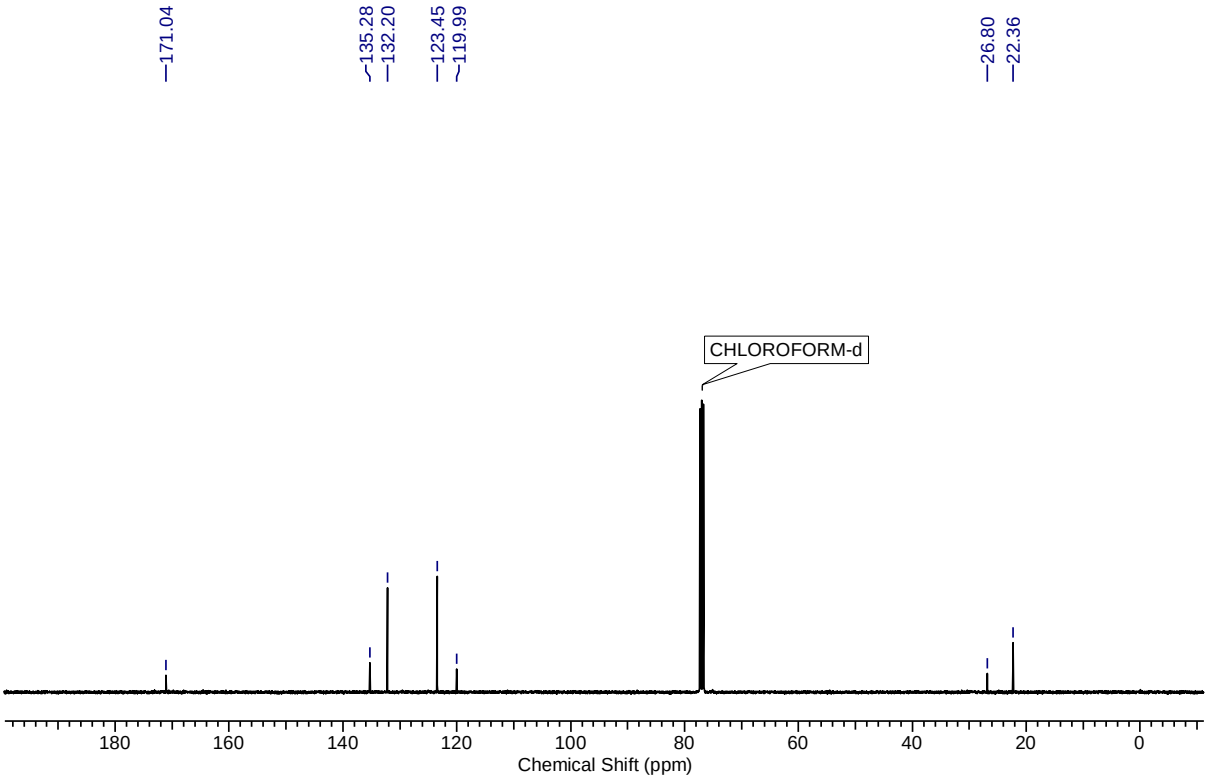
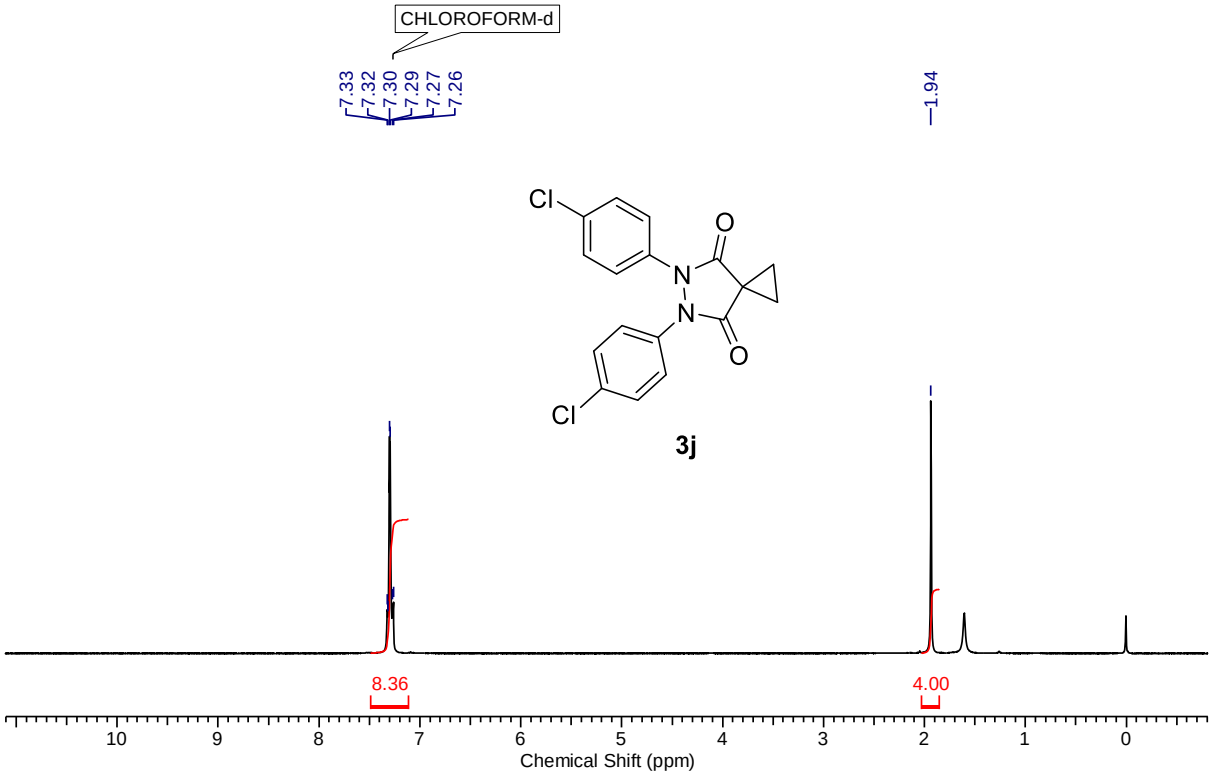


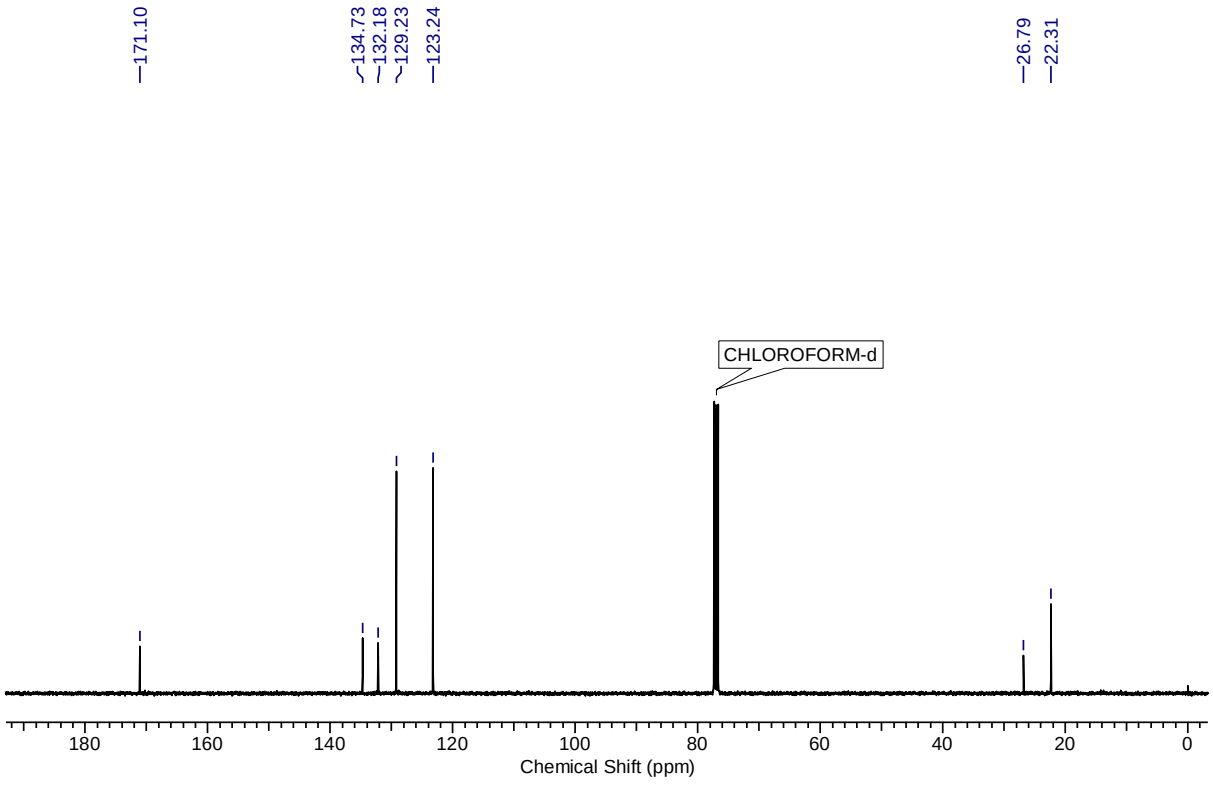
^{13}C NMR, 100 MHz



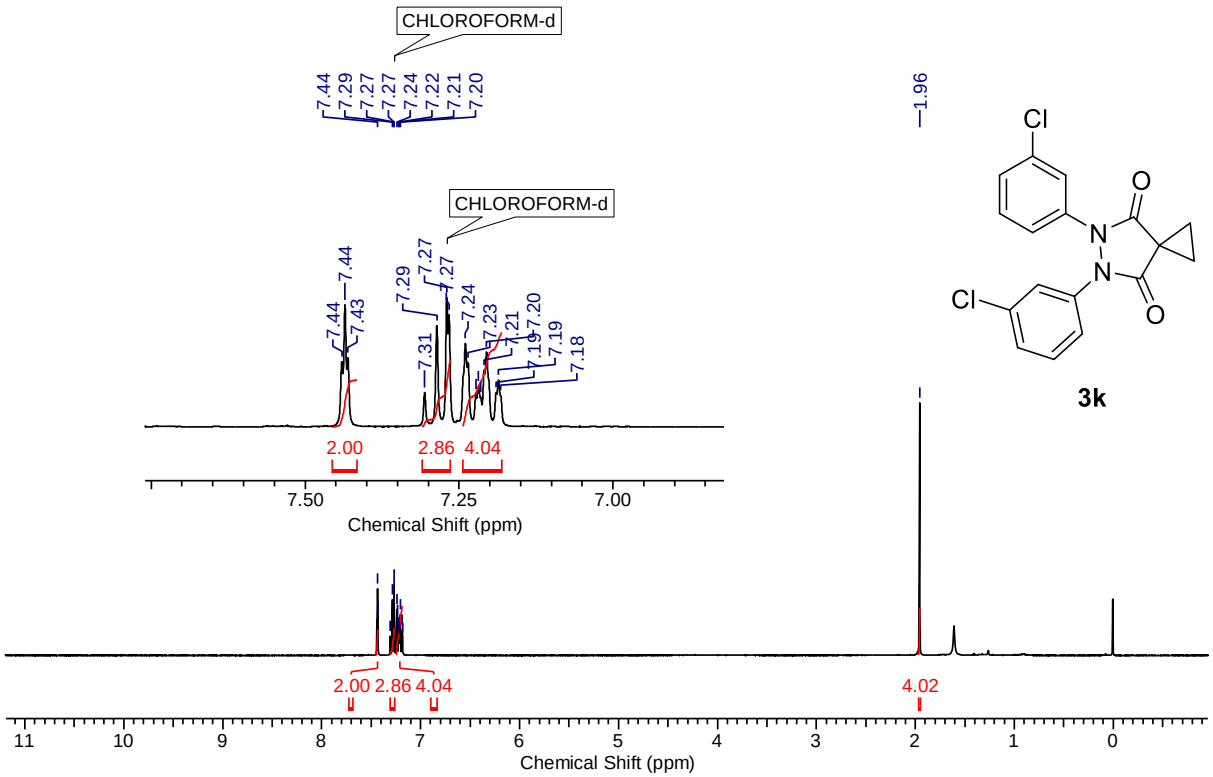
^{1}H NMR, 400 MHz



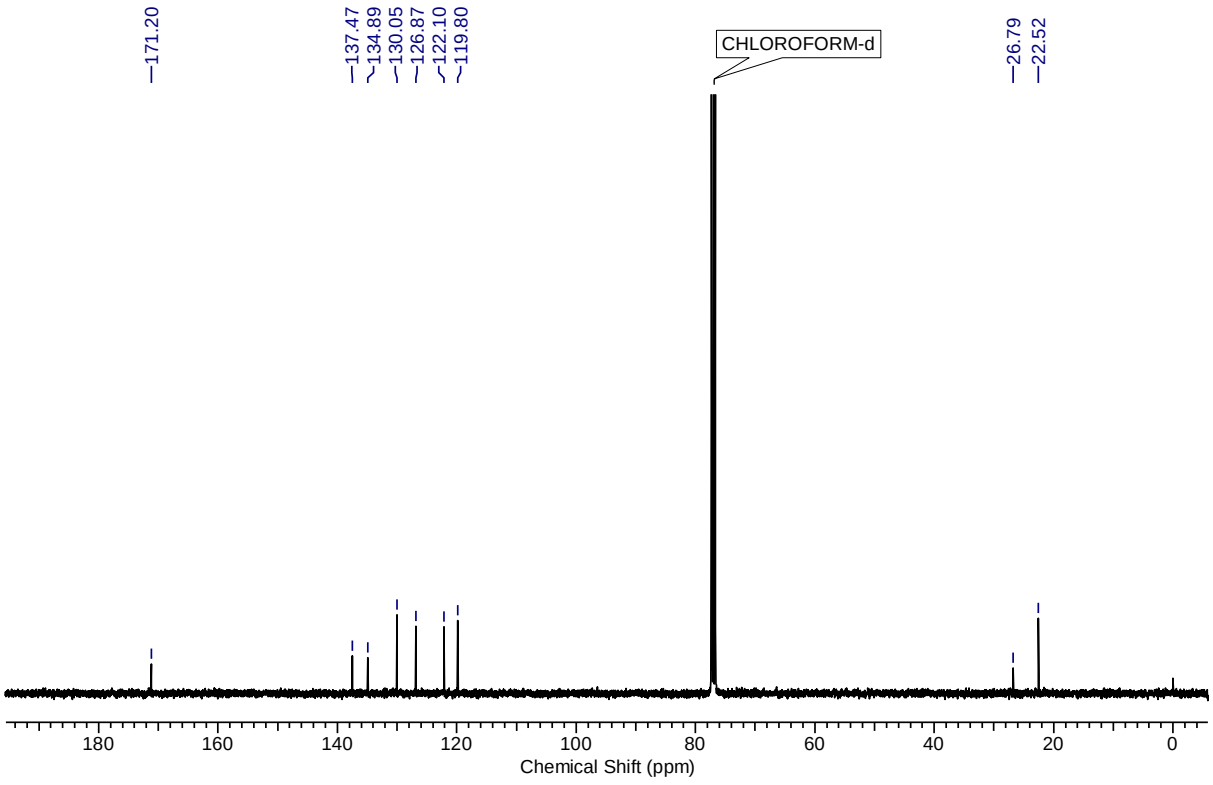
^{13}C NMR, 100 MHz



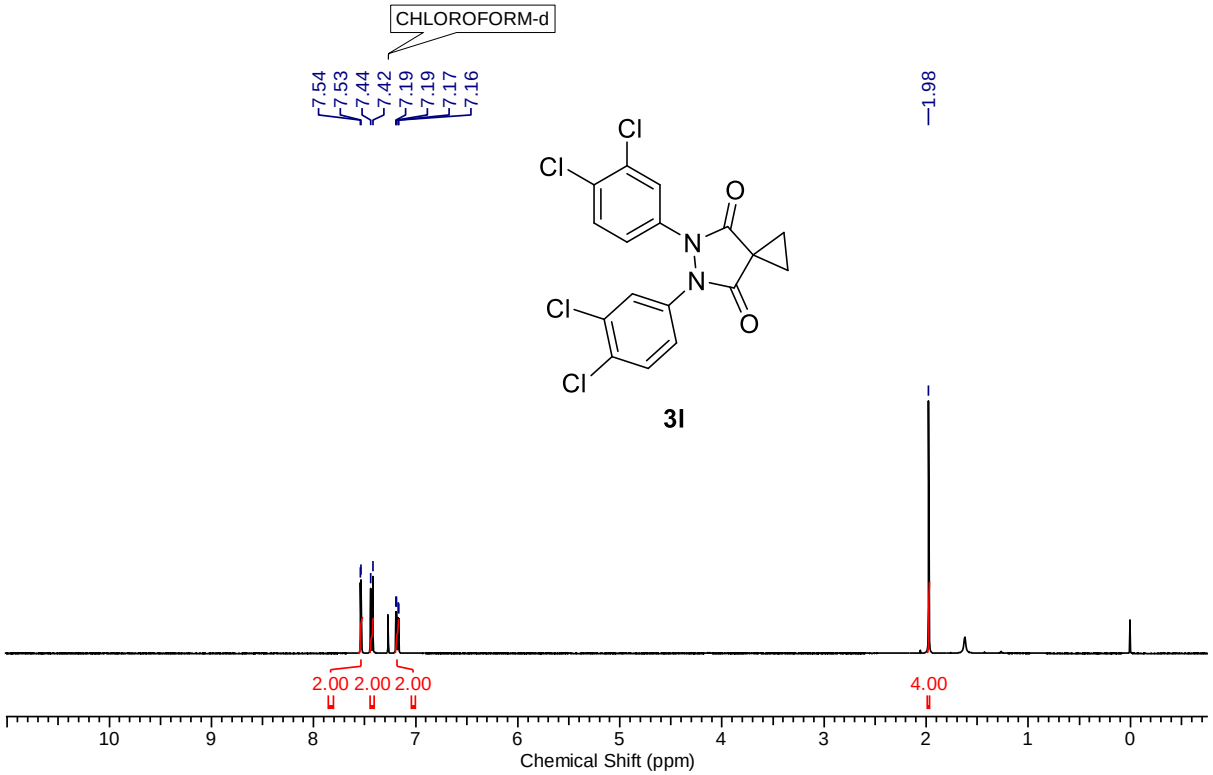
^{1}H NMR, 400 MHz



^{13}C NMR, 100 MHz

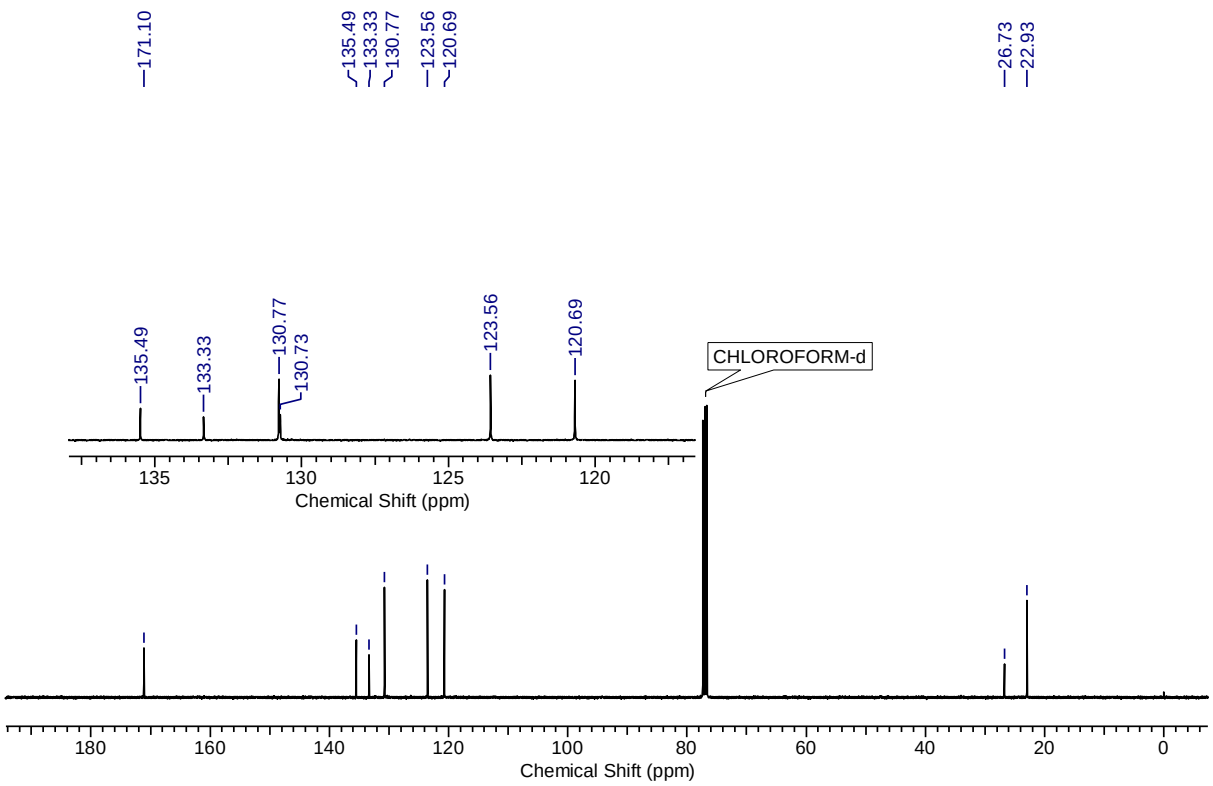


^{1}H NMR, 400 MHz

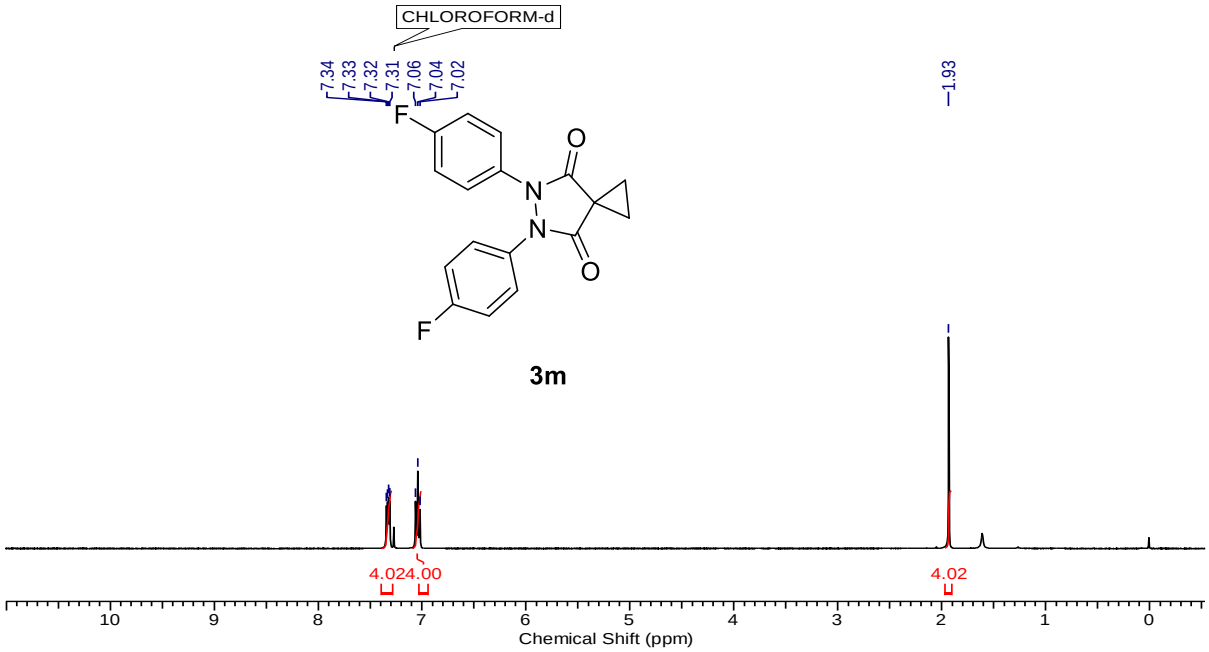


3l

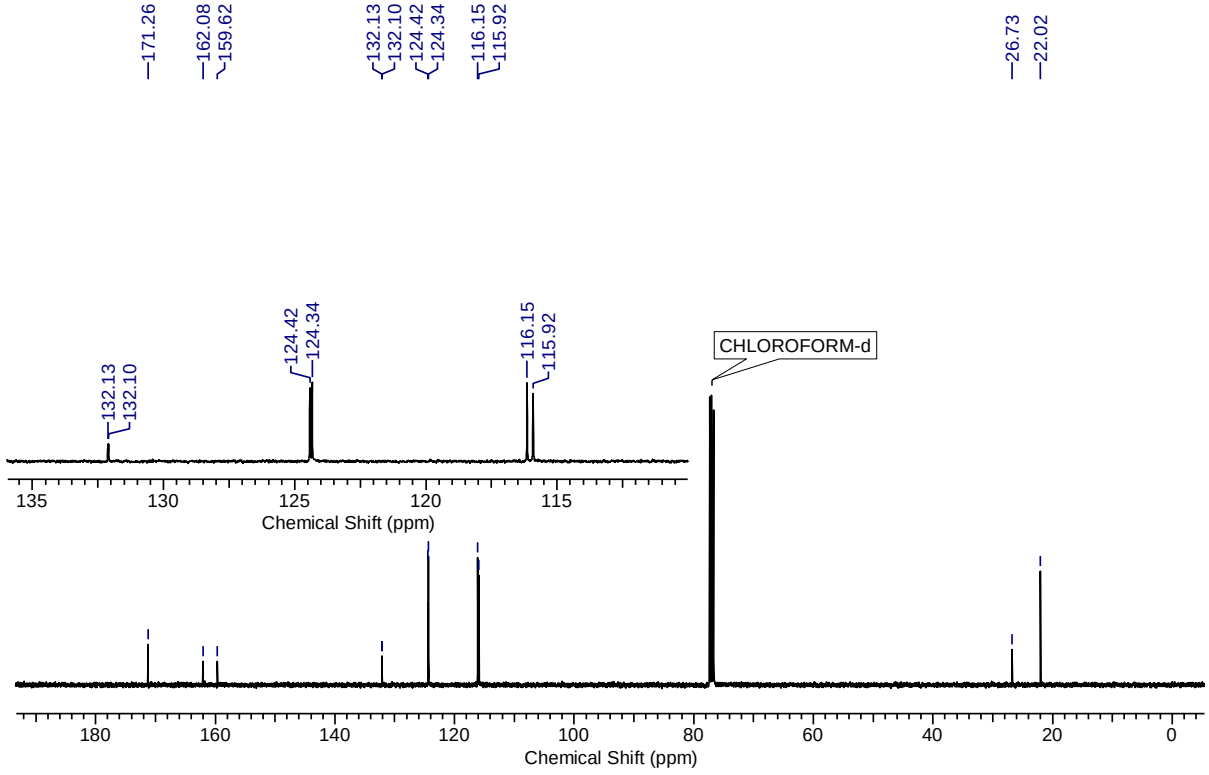
^{13}C NMR, 100 MHz



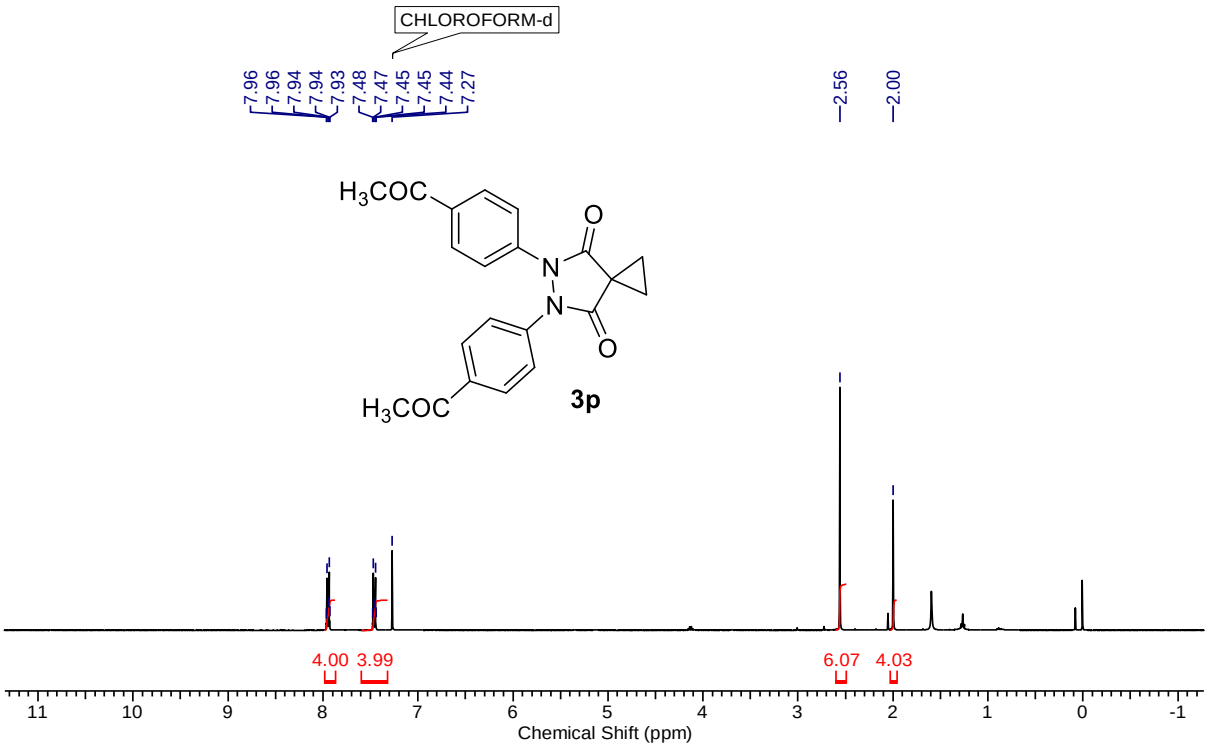
^{1}H NMR, 400 MHz



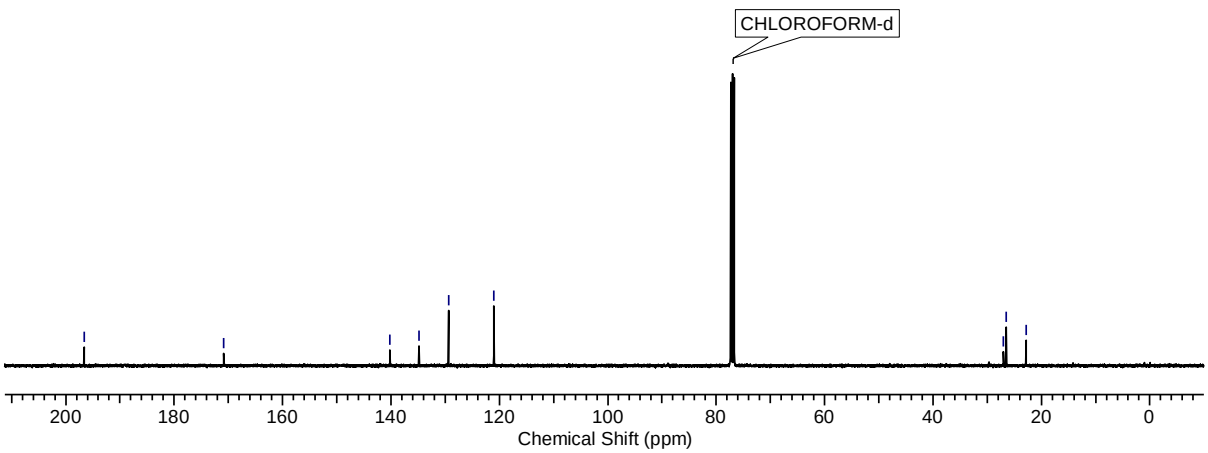
^{13}C NMR, 100 MHz



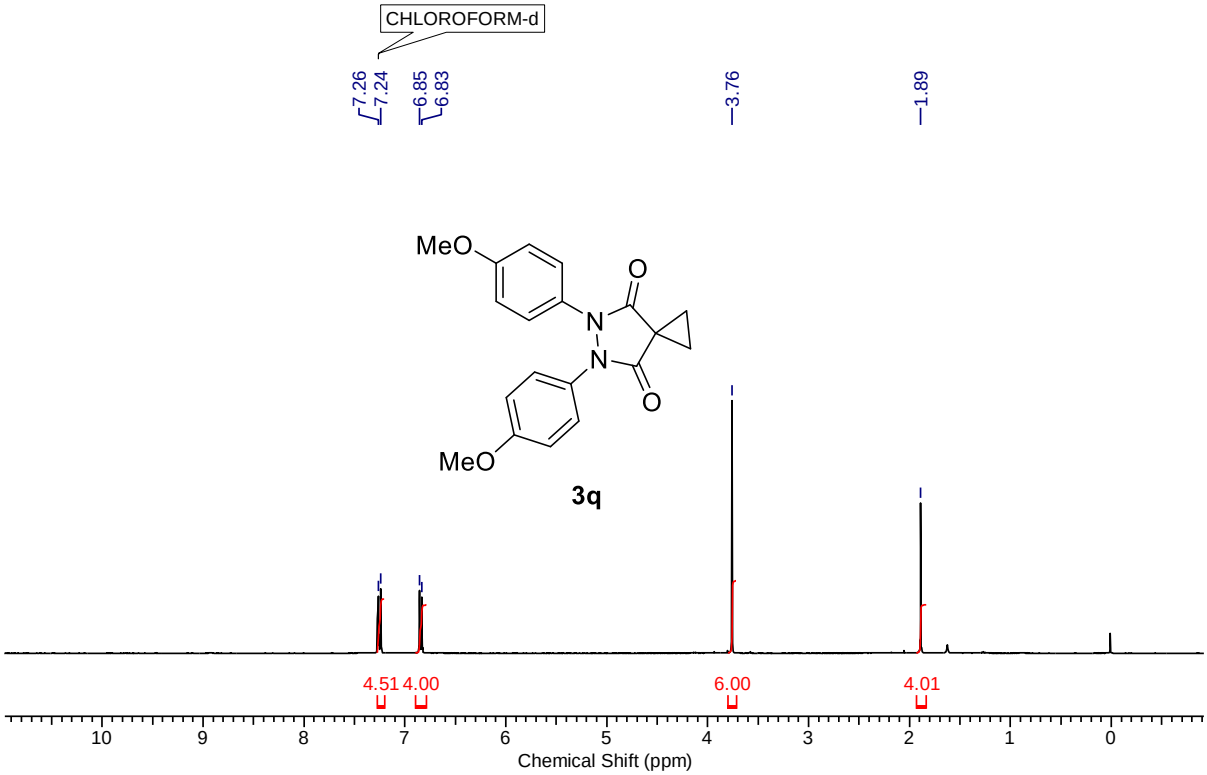
^{1}H NMR, 400 MHz



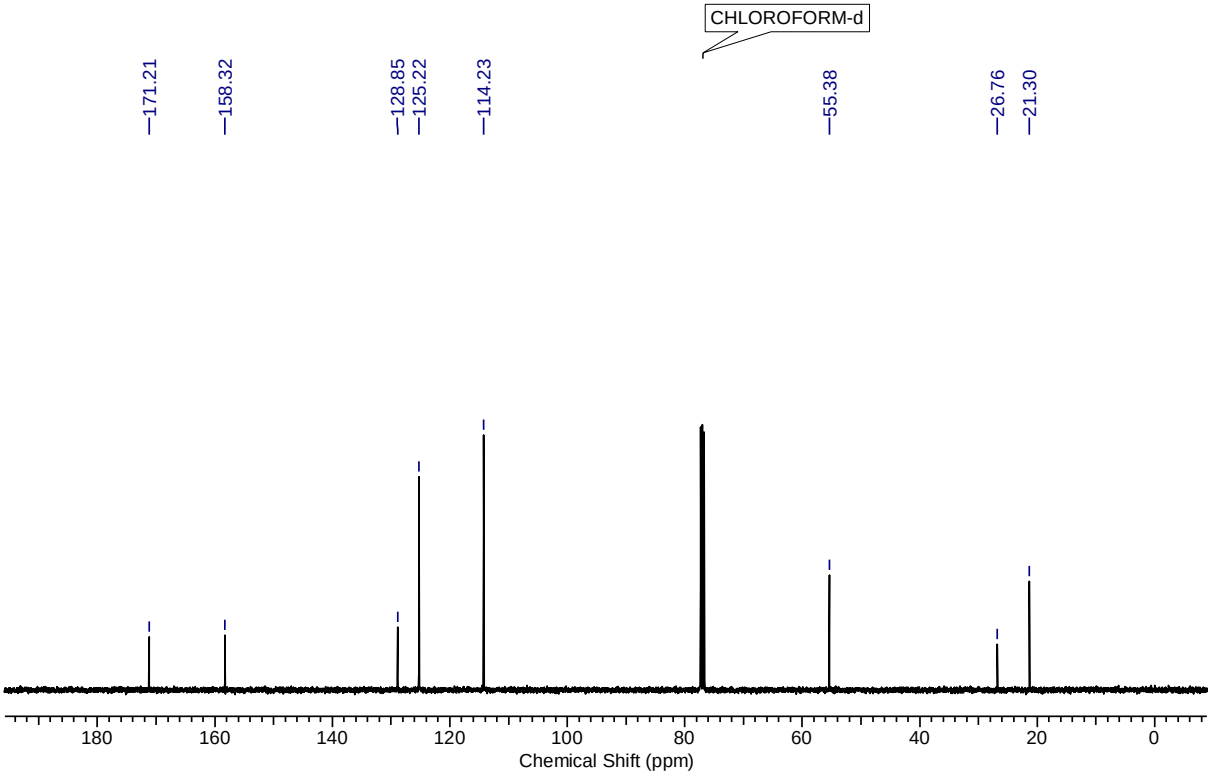
^{13}C NMR, 100 MHz



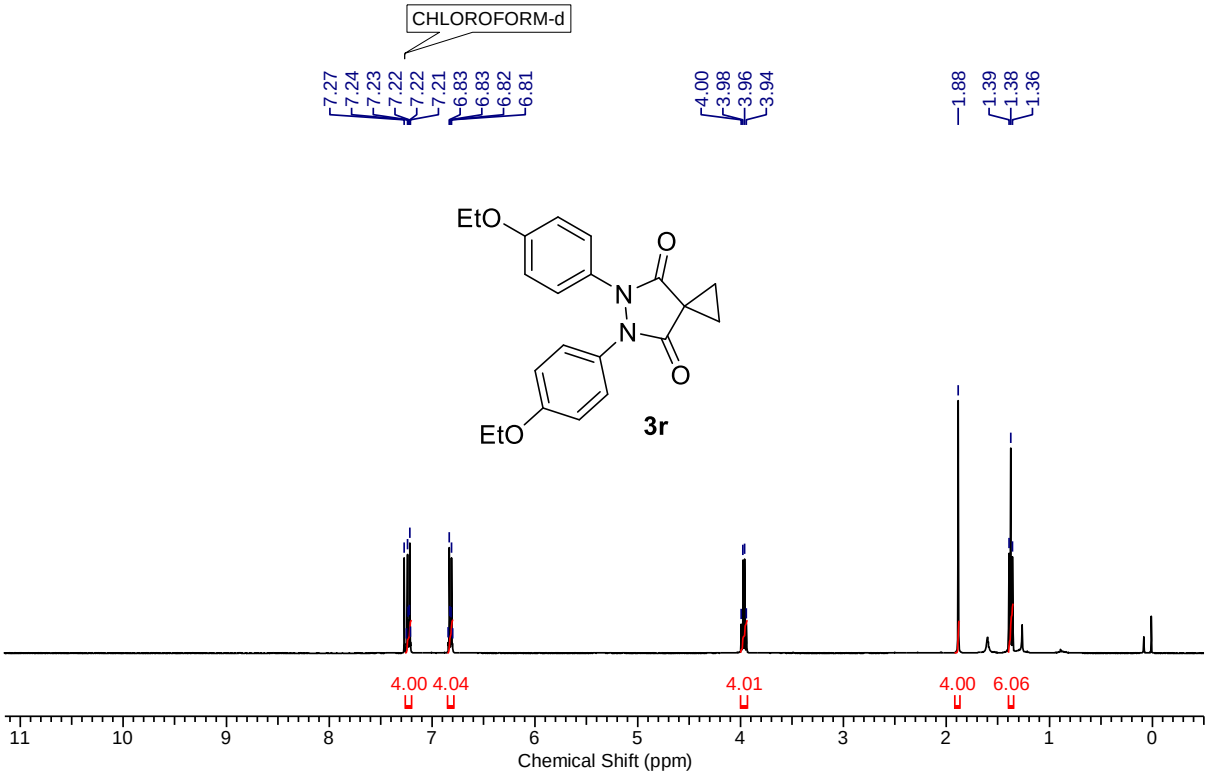
^{1}H NMR, 400 MHz



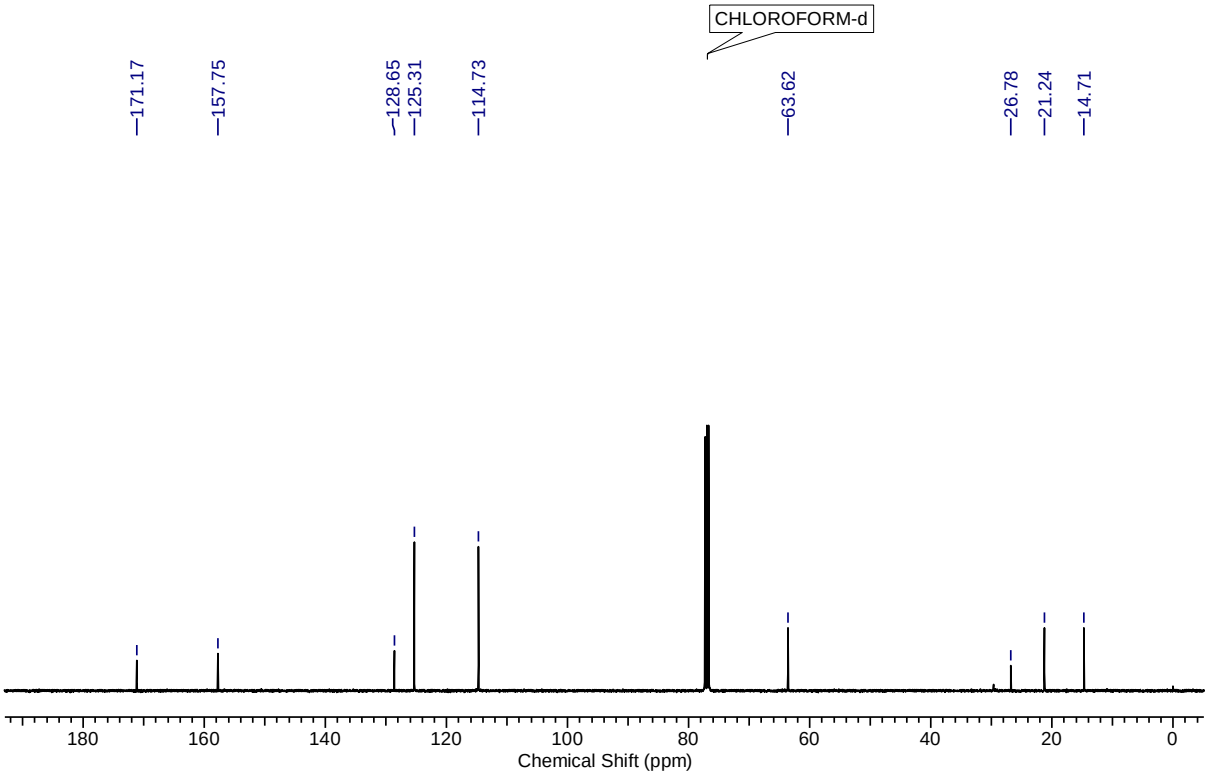
^{13}C NMR, 100 MHz



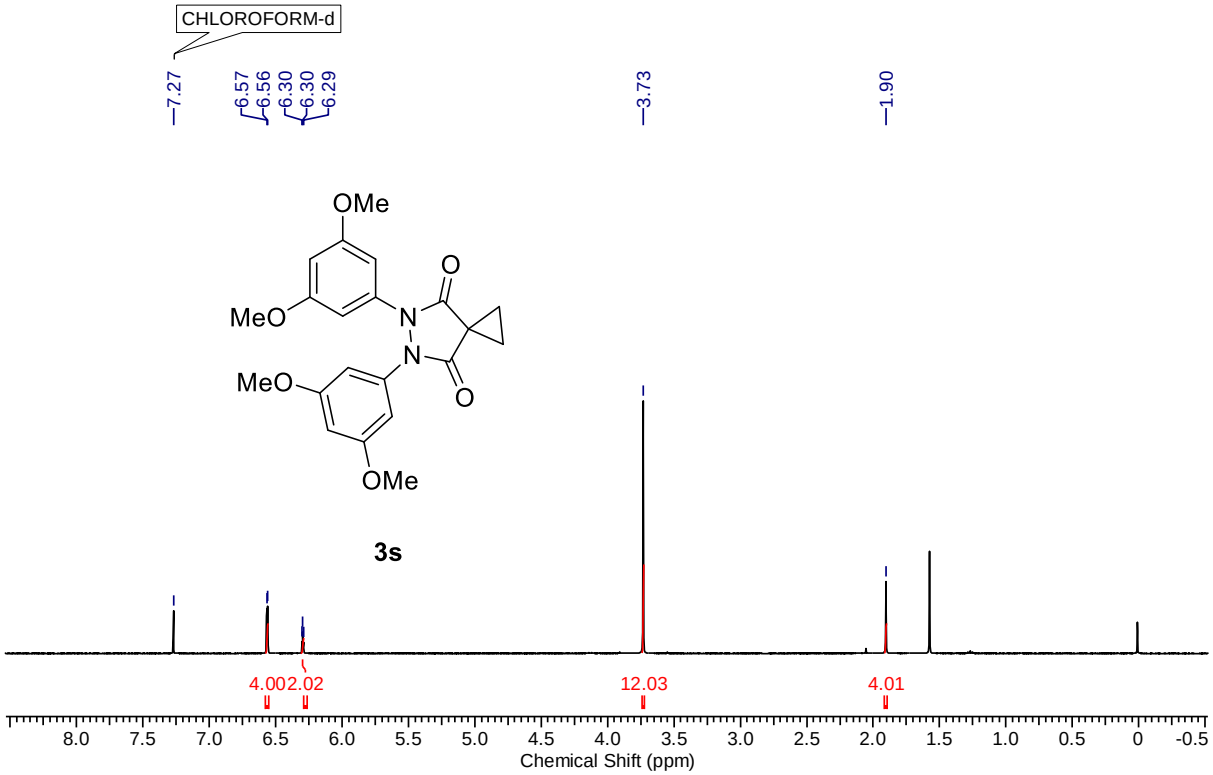
^{1}H NMR, 400 MHz



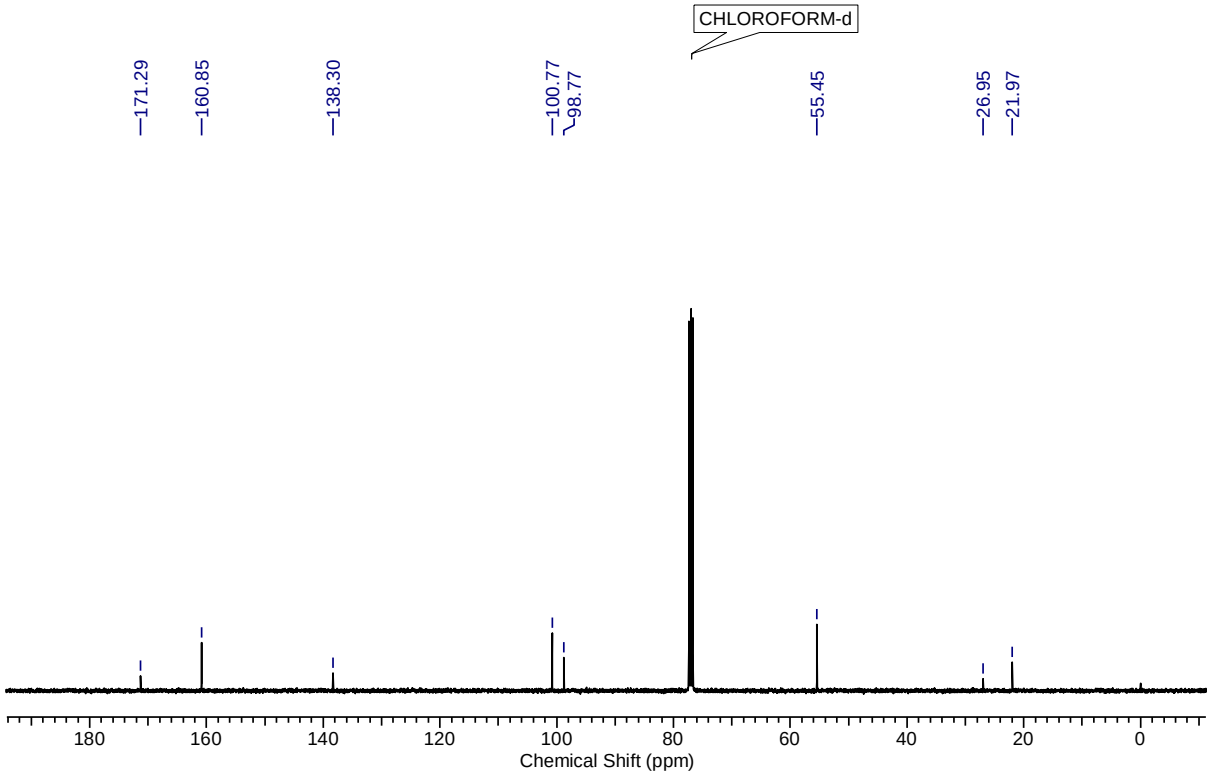
^{13}C NMR, 100 MHz



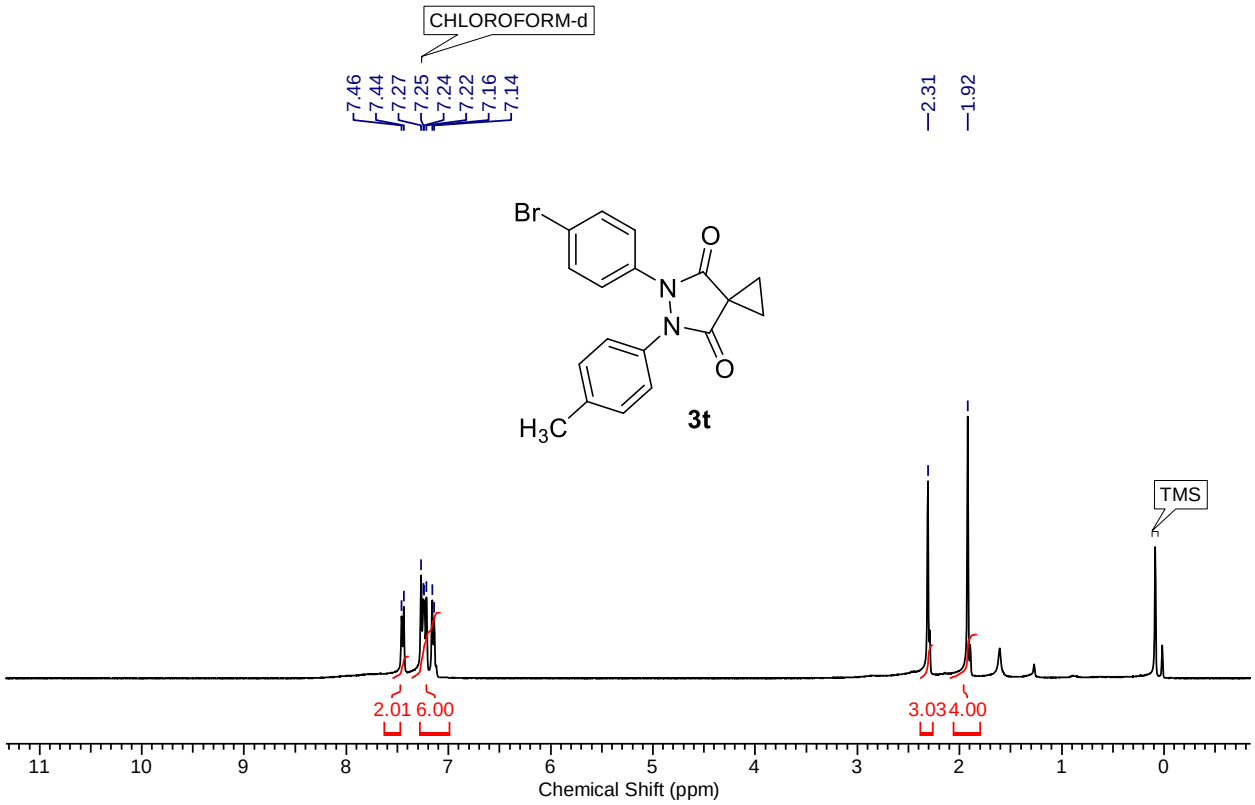
^{1}H NMR, 400 MHz



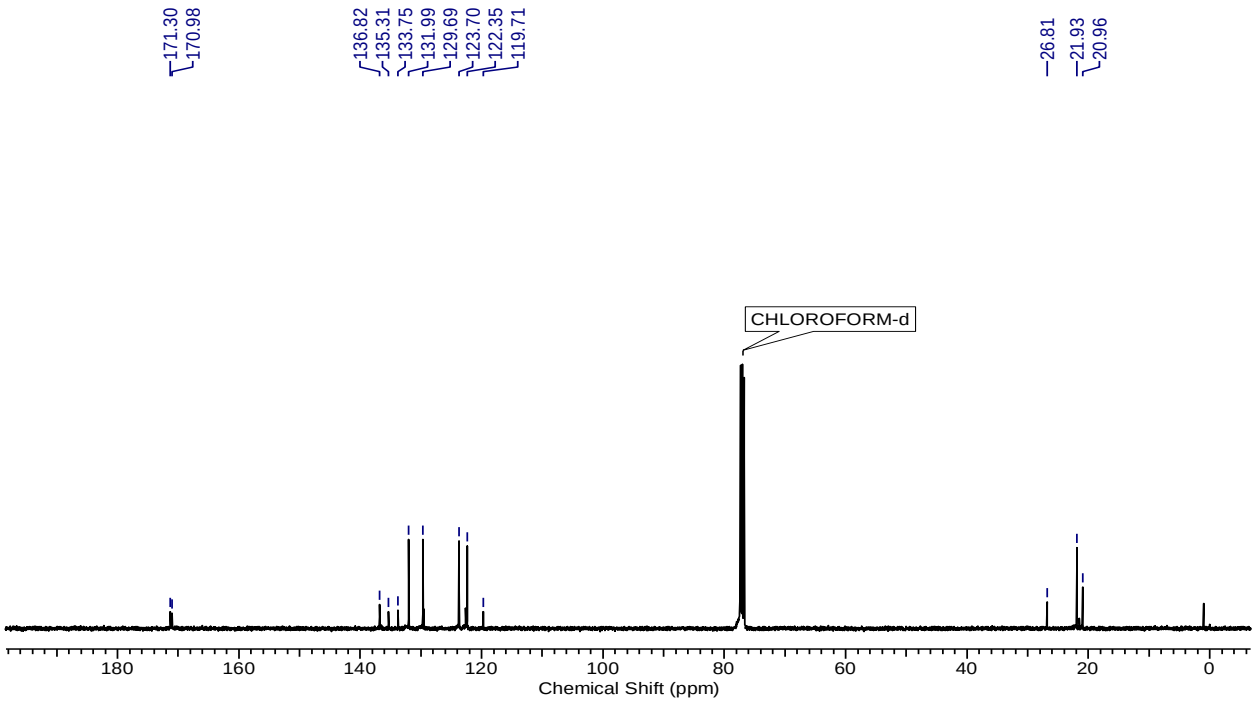
^{13}C NMR, 100 MHz



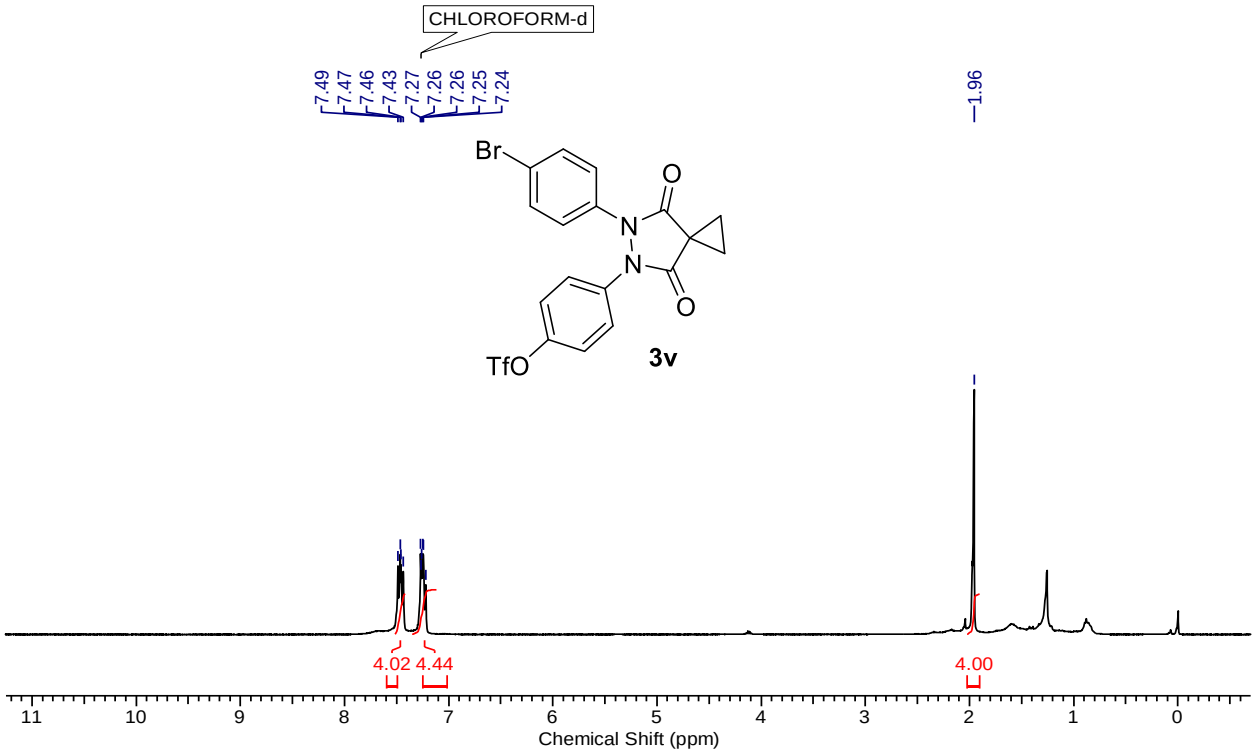
^{1}H NMR, 400 MHz



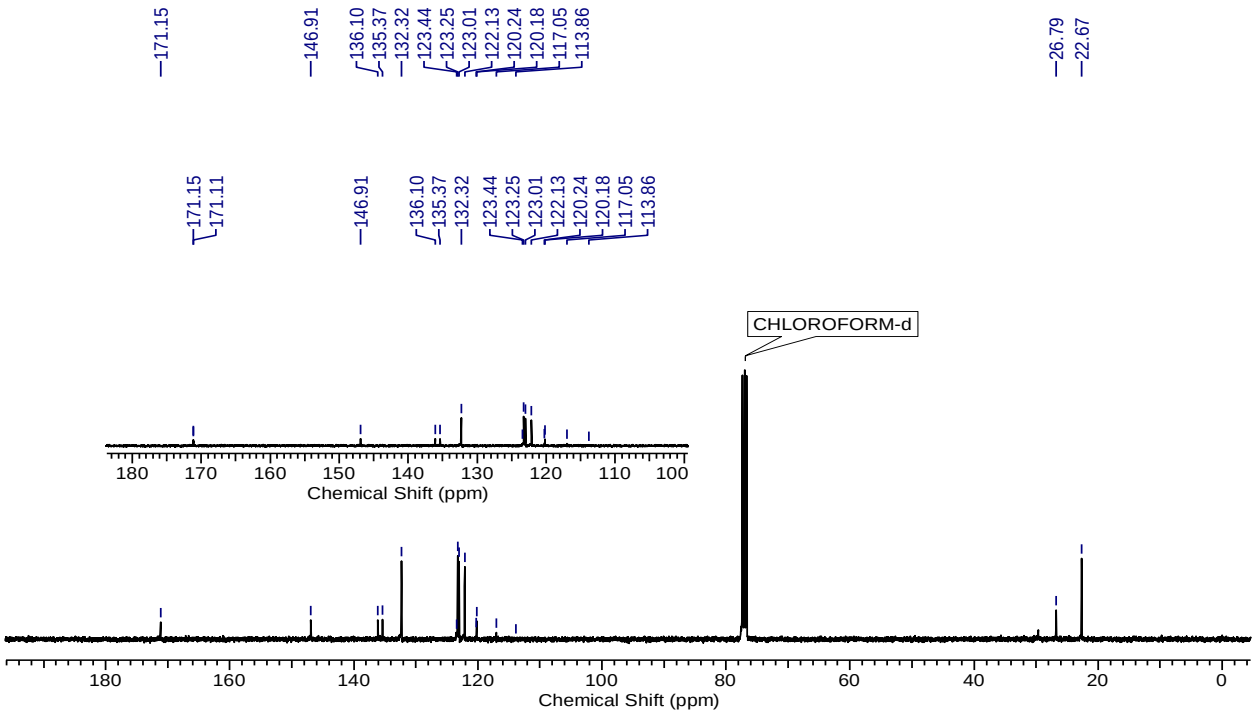
^{13}C NMR, 100 MHz



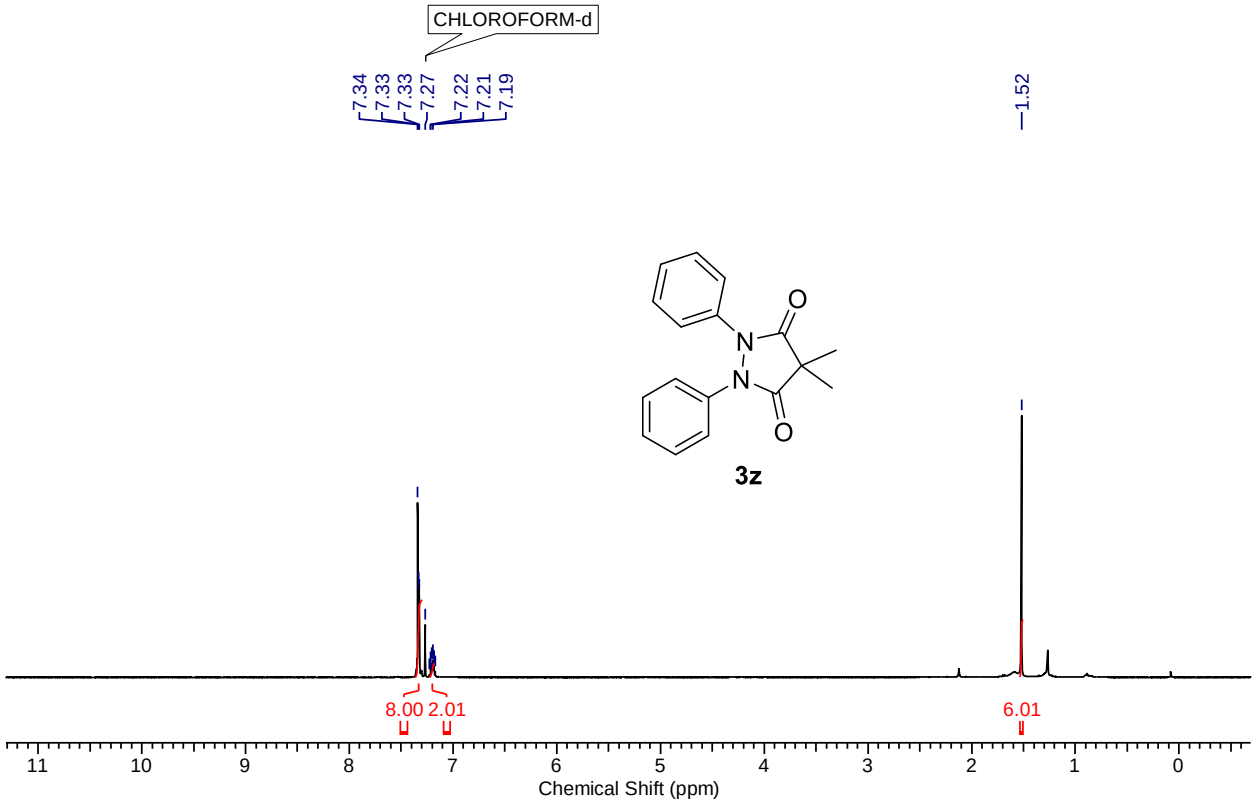
^{1}H NMR, 400 MHz



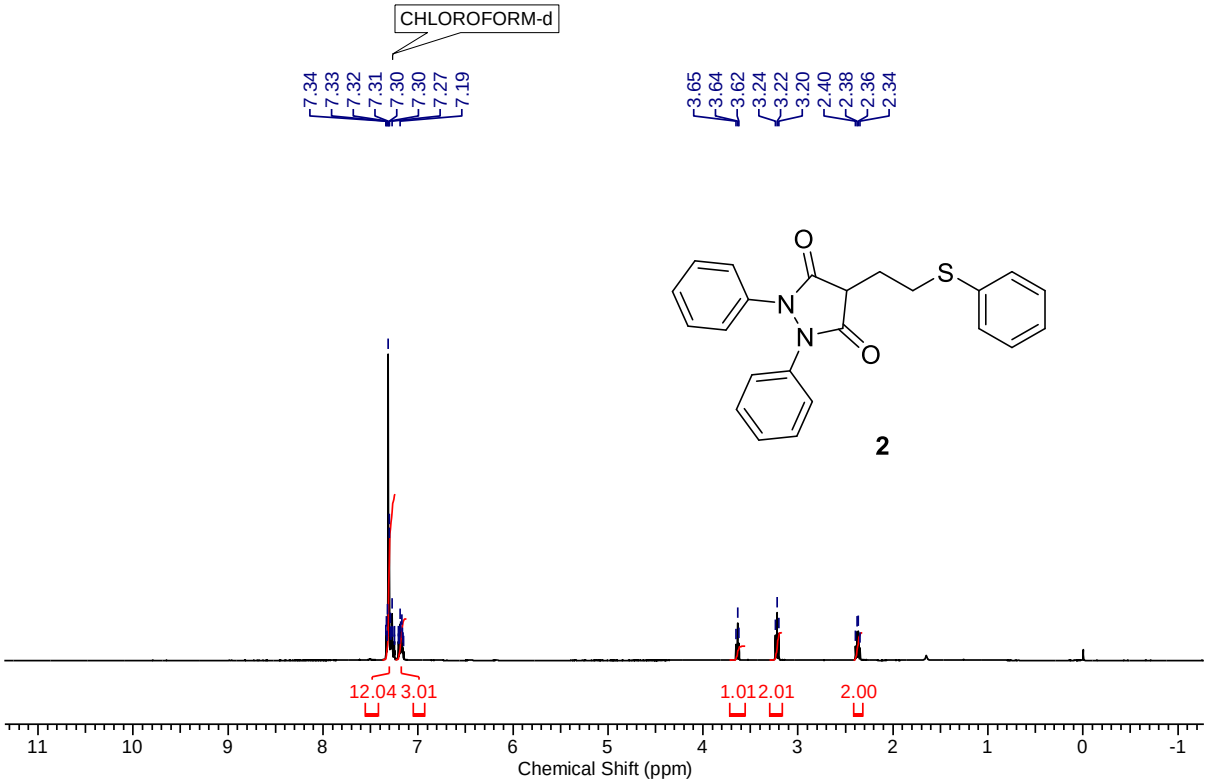
^{13}C NMR, 100 MHz



^{1}H NMR, 200 MHz



^{1}H NMR, 400 MHz



^{13}C NMR, 100 MHz