Ruthenium-catalyzed intramolecular selective halogenation of *O*-methylbenzohydroximoyl halides: a new route to halogenated aromatic nitriles

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Electronic Supplementary Information (ESI)

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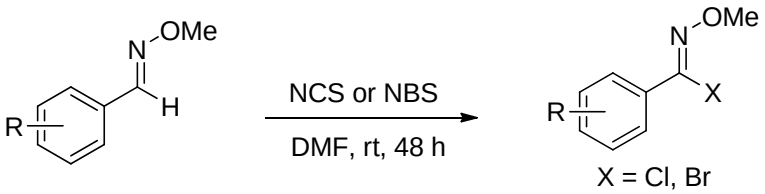
Experimental Section

General Procedure for the Preparation of Starting Materials 1 and 3.

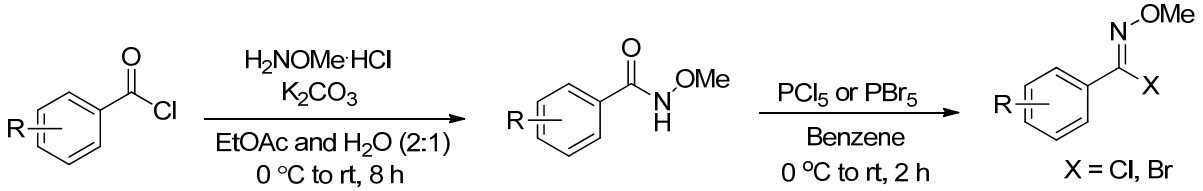
Method A[1]



The appropriate *O*-alkyl benzaldehyde oxime (20 mmol, 1.0 equiv) and DMF (50 mL) was charged in a 250 mL round-bottom flask. Then, *N*-chlorosuccinimide (NCS, 20 mmol, 1.0 equiv) or *N*-bromosuccinimide (NBS, 20 mmol, 1.0 equiv) was slowly added to the reaction mixture. After the addition was complete, the reaction mixture was stirred at room temperature for 48 h. Then, the reaction mixture was poured into ice water (70 mL) and the resulting mixture was extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **1** or **3**.

Ref: 1. H. J. P. Lijser, C. R. Burke, J. Rosenberg and J. Hunter, *J. Org. Chem*. **2009**, *74*, 1679.

Method B[2]



O-Methylhydroxylamine hydrochloride (2.0 g, 24.0 mmol, 1.2 equiv) and K_2CO_3 (5.98 g, 48.0 mmol, 2 equiv) were dissolved in 120 mL of mixture of ethyl acetate and water (2:1) in a round-bottomed flask. The solution was cooled to 0 °C in an ice bath. The corresponding benzoyl chloride (20.0 mmol, 1.0 equiv) was added via syringe and the reaction mixture was stirred at room temperature for 8 h. Then, the aqueous layer in the reaction mixture was separated out and organic layer was washed with water and then brine. After drying over $MgSO_4$, solvents were evaporated under reduced pressure. The crude reaction mixture was transferred into a round-bottom flask with a stir bar, and dry benzene (60 mL) was added. The solution was cooled to 5 °C and PCl_5 (6.25 g, 30.0 mmol, 1.5 equiv) or PBr_5 (6.50 g, 30.0 mmol, 1.5 equiv) was added. The reaction mixture was stirred at 5 °C for 2 h and then allowed to warm at room temperature for 30 min. The resulting mixture was extracted three

times with hexane. The combined organic layers were dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **1** or **3**.

Ref: 2. Y. Lian, R. G. Bergman and J. A. Ellman, *Chem. Sci*. **2012**, *3*, 3088.

General Procedure for Intramolecular Halogenation of *O*-Methylbenzohydroximoyl Halides Catalyzed by Ruthenium Complex.

A 15-mL pressure tube equipped with a magnetic stirrer and septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (0.03 mmol, 3 mol %) and diphenylacetylene (30 mol %) or methyl acrylate (50 mol %) was evacuated and purged with nitrogen gas three times. To the tube were then added *O*-methylbenzohydroximoyl halides **1** or **3** (1.00 mmol) and *iso*-propanol (3.0 mL) via syringes and again the tube was evacuated and purged with nitrogen gas three times. Then, in the pressure tube, septum was taken out and covered with a screw cap immediately under nitrogen atmosphere and the reaction mixture was allowed to stir at 100 °C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **2** and **4**.

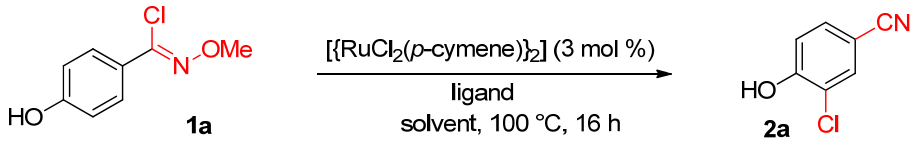
General Procedure for the Preparation of Substituted Tetrazoles.

A 50-mL two-neck round bottom flask equipped with a magnetic stirrer, septum and condenser containing I_2 (20 mol %), NaN_3 (1.5 mmol) and aromatic nitriles **2** (1.0 mmol). To the round bottom flask was then added solvent DMF (3.0 mL) via syringe. Then, the reaction mixture was allowed to stir at 120 °C for 24 h. After cooling to ambient temperature, the reaction mixture was extracted three times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **5**.

Spectral data and copies of ^1H and ^{13}C NMR spectra of all compounds are listed below (pages S16 – S75).

Optimization Studies

Table 1. Optimization Studies[a]

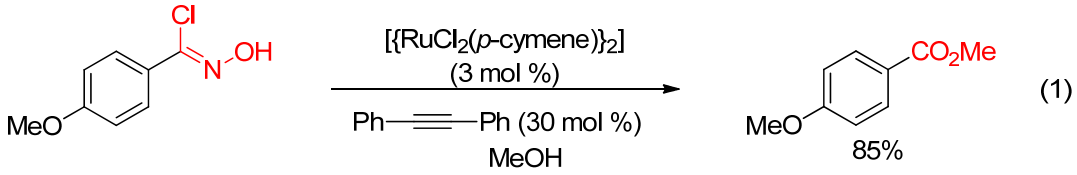


Entry	Ru cat.	Ligand	Solvent	Yield (%)[b]
1	Ru cat	No ligand	MeOH	NR
2	Ru cat	PPh_3 (20 mol %)	MeOH	NR
3	Ru cat	dppe (10 mol %)	MeOH	NR
4	Ru cat	diphenylacetylene (30 mol %)	MeOH	72
5	Ru cat	styrene (30 mol %)	MeOH	NR
6	Ru cat	methyl acrylate (50 mol %)	MeOH	71
7	Ru cat	norbornadiene (50 mol %)	MeOH	NR
8	Ru cat	cyclooctadiene (50 mol %)	MeOH	NR
9	Ru cat	norbornene (50 mol %)	MeOH	NR
10	No Ru cat	diphenylacetylene (30 mol %)	MeOH	NR
11	Ru cat	diphenylacetylene (30 mol %)	*iso*-PrOH	93
12	Ru cat	diphenylacetylene (30 mol %)	*tert*-BuOH	55
13	Ru cat	diphenylacetylene (30 mol %)	DMF	60
14	Ru cat	diphenylacetylene (30 mol %)	THF	NR
15	Ru cat	diphenylacetylene (30 mol %)	CH_3CN	NR
16	Ru cat	diphenylacetylene (30 mol %)	toluene	NR
17	Ru cat	diphenylacetylene (30 mol %)	DCE	NR
18	Ru cat	diphenylacetylene (30 mol %)	CH_3COOH	NR
19	Ru cat	diphenylacetylene (30 mol %)	1,4-dioxane	NR

[a]All reactions were carried out using **1a** (1.0 mmol), ligand and [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %) in solvent (3.0 mL) at 100 °C for 16 h. [b]Yields were determined by the ^{1}H NMR integration method, using mesitylene as an internal standard.

In the beginning of the project, the intramolecular chlorination of **1a** was examined in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %) in MeOH at 100 °C for 16 h. However, in the reaction, no chlorination product **2a** was observed (Table 1, entry 1). Then, the catalytic reaction was tested in the presence of phosphine ligands PPh_3 and dppe and carbon-carbon π-component ligands such as diphenylacetylene, styrene, methyl acrylate, norbornene, norbornadiene and cyclooctadiene (entries 2-9). The corresponding chlorination product **2a** was observed in the presence of ligand, diphenylacetylene, in 72% yield (entry 4). The yield of product **2a** was determined by the ^{1}H NMR integration methods using mesitylene as an internal standard. Methyl acrylate (50 mol %) also worked equally, giving **2a** in 71% yield (entry 6). Other ligands were totally inactive for the reaction. Usually, less coordinating carbon-carbon π-component moieties are suitable ligands for C-H bond activation reaction.

Importantly, diphenylacetylene or methyl acrylate was not involved in the reaction. In the crude reaction mixture, diphenylacetylene or methyl acrylate was found. This was isolated and confirmed by NMR spectroscopy. The reaction was tested without ruthenium catalyst and just only in the presence of ligand. In the reaction, no **2a** was observed (entry 10). This result clearly revealed that both ruthenium and ligand such as diphenylacetylene or methyl acrylate are crucial for the reaction. In order to increase the yield of **2a**, the catalytic reaction was tested with various solvents such as *iso*-PrOH, *tert*-BuOH, DMF, THF, CH_3CN, toluene, 1,2-dichloroethane, acetic acid and 1,4-dioxane (entries 11-19). Among them, *iso*-PrOH was the best solvent, providing **2a** in excellent 93% yield (entry 11). *tert*-BuOH and DMF were also partially active solvent, giving **2a** in 55% and 60% yields, respectively (entries 12 and 13). The remaining solvents were totally ineffective for the reaction. In the meantime, the halogenation reaction was also tested with *N*-hydroxybenzimidoyl chloride instead of *N*-methoxybenzimidoyl chloride **1b** under the optimized reaction conditions (eq. 1). However, in the reaction, no halogenation compound was observed and only methyl 4-methoxybenzoate was observed in 85% yield (eq. 1). In the reaction, imidoyl chloride moiety was converted into ester under the reaction conditions.



(1)

Regioselective Studies

A. X-Ray Analysis

3-Chloro-4-ethoxybenzonitrile (2c).

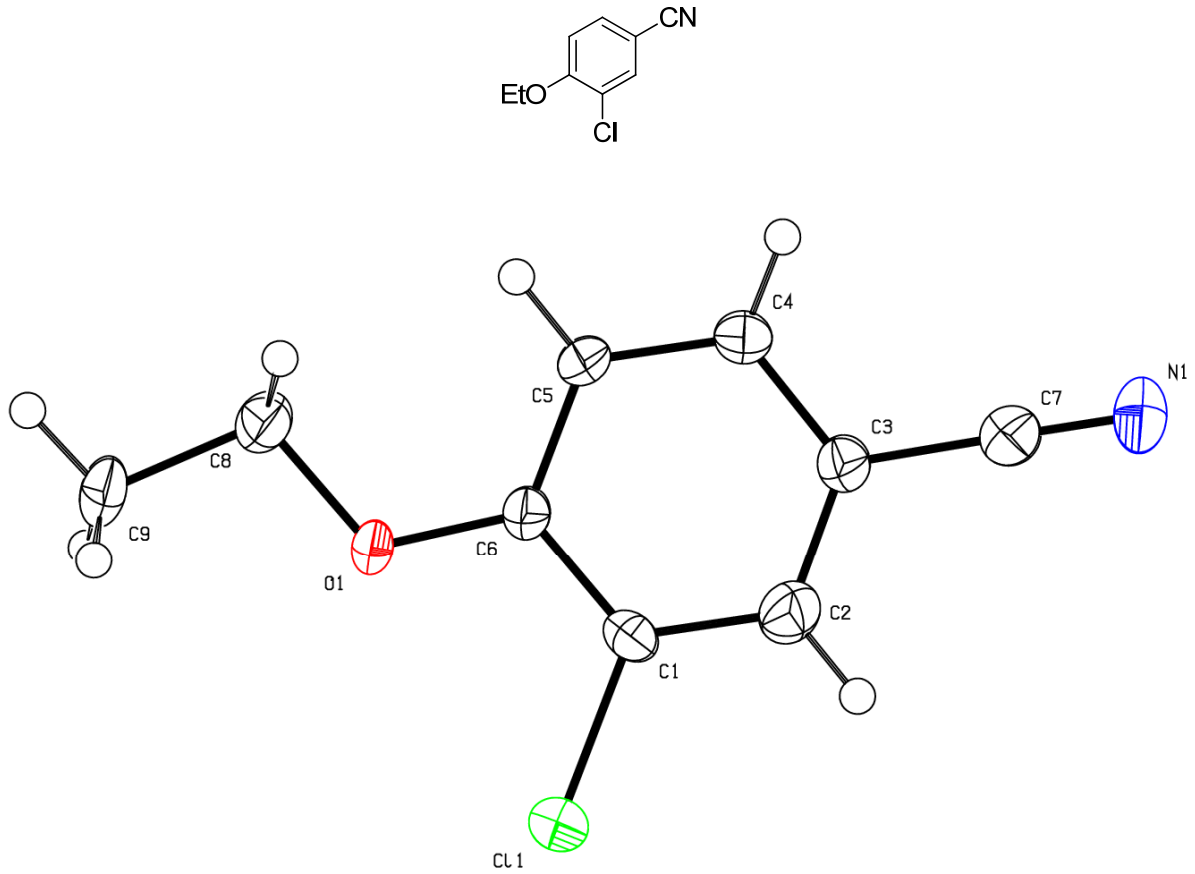


Table 1.Crystal data and structure refinement for (**2c**).

Identification code	2c	
Empirical formula	C9 H8 Cl N O	
Formula weight	181.61	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	'Monoclinic'	
Space group	'C1c1'	
Unit cell dimensions	a = 8.511(5) Å	α= 90°.
	b = 17.062(10) Å	β= 123.831(10)°.
	c = 7.200(4) Å	γ = 90°.
Volume	868.6(9) $Å^3$	
Z	4	

Density (calculated)	1.389 Mg/m^3
Absorption coefficient	0.386 mm^{-1}
F(000)	376
Crystal size	0.16 x 0.12 x 0.08 mm^3
Theta range for data collection	2.39 to 28.29°.
Index ranges	-11<=h<=11, -18<=k<=22, -9<=l<=9
Reflections collected	2102
Independent reflections	1251 [R(int) = 0.0411]
Completeness to theta = 25.00°	84.0 %
Max. and min. transmission	0.9698 and 0.9408
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1251 / 2 / 110
Goodness-of-fit on F^2	1.001
Final R indices [I>2sigma(I)]	R1 = 0.0571, wR2 = 0.1374
R indices (all data)	R1 = 0.0838, wR2 = 0.1513
Absolute structure parameter	0.02(17)
Largest diff. peak and hole	0.571 and -0.268 $e.Å^{-3}$

6-Chlorobenzo[*d*][1,3]dioxole-5-carbonitrile (**2l**).

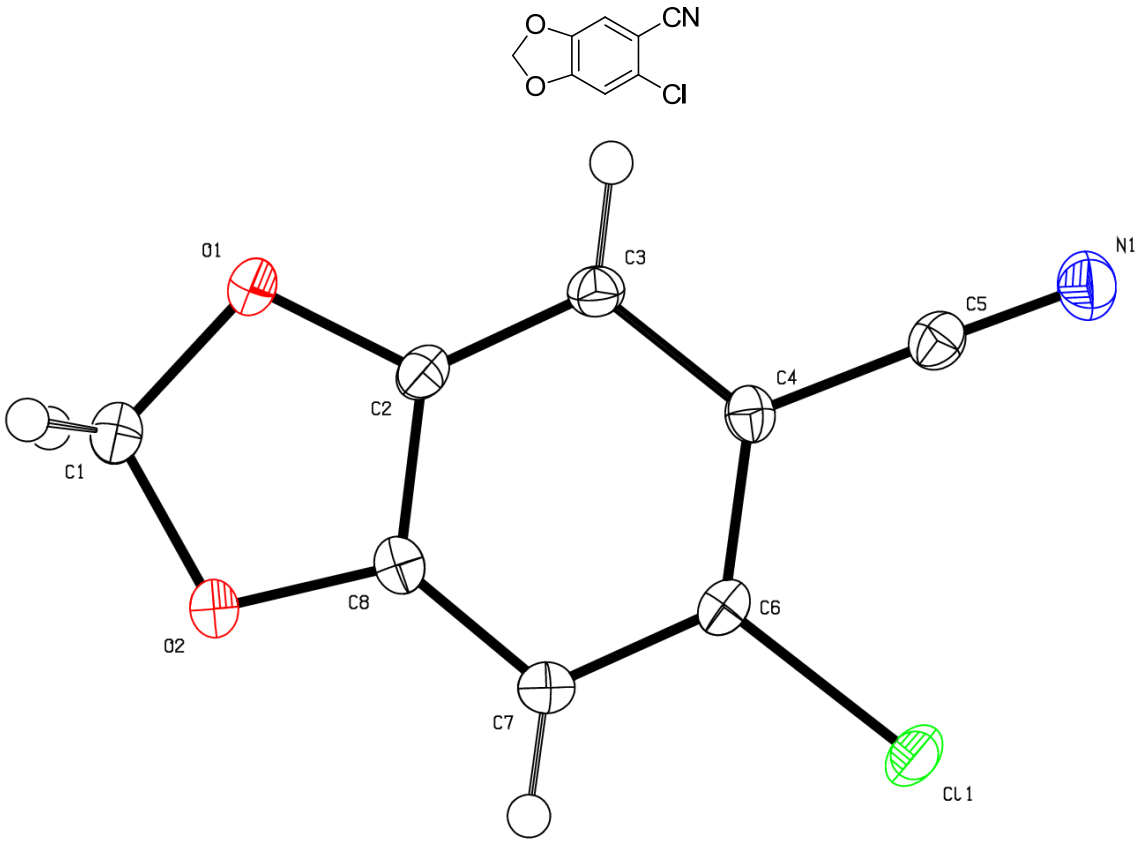
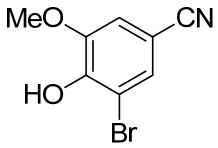


Table 1. Crystal data and structure refinement for **2l**.

Identification code	**2l**	
Empirical formula	C8 H4 Cl N O2	
Formula weight	181.57	
Temperature	150(2) K	
Wavelength	71.073 pm	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 1233.7(3) pm	α= 90°.
	b = 380.23(10) pm	β= 99.168(4)°.
	c = 1560.3(4) pm	γ = 90°.
Volume	0.7226(3) nm^3	
Z	4	
Density (calculated)	1.669 Mg/m^3	
Absorption coefficient	0.474 mm^{-1}	
F(000)	368	
Crystal size	0.490 x 0.320 x 0.160 mm^3	
Theta range for data collection	1.96 to 28.41°.	
Index ranges	-15<=h<=16, -4<=k<=5, -20<=l<=20	

Reflections collected	7021
Independent reflections	1788 [R(int) = 0.0263]
Completeness to theta = 28.41°	98.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.927 and 0.834
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1788 / 0 / 110
Goodness-of-fit on F^2	1.075
Final R indices [I>2sigma(I)]	R1 = 0.0262, wR2 = 0.0719
R indices (all data)	R1 = 0.0275, wR2 = 0.0729
Extinction coefficient	0.006(3)
Largest diff. peak and hole	0.352 and -0.227 e.$Å^{-3}$

3-Bromo-4-hydroxy-5-methoxybenzonitrile (**4f**).



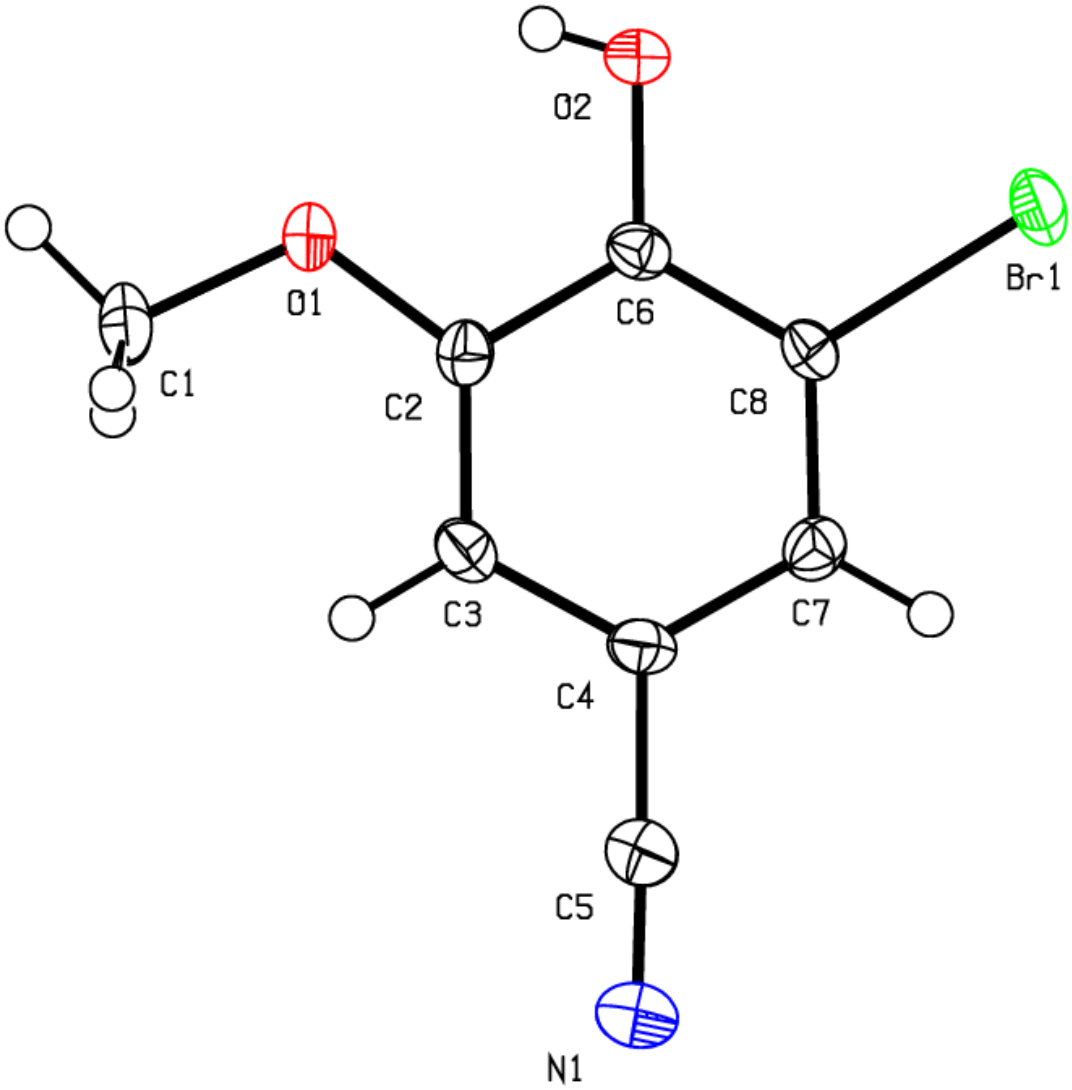


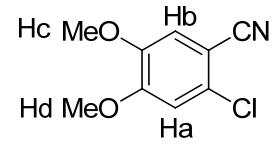
Table 1.Crystal data and structure refinement for (**4f**).

Identification code	4f
Empirical formula	C16 H12 Br2 N2 O4
Formula weight	456.10
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	‘Triclinic’

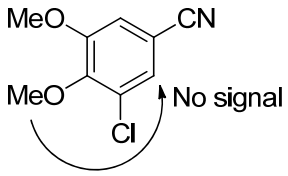
Space group	'P-1'	
Unit cell dimensions	a = 7.2030(10) Å	α= 85.645(3)°.
	b = 9.5004(12) Å	β= 89.563(3)°.
	c = 12.9717(16) Å	γ = 70.248(3)°.
Volume	832.88(19) $Å^3$	
Z	2	
Density (calculated)	1.819 Mg/m^3	
Absorption coefficient	4.889 mm^{-1}	
F(000)	448	
Crystal size	0.16 x 0.13 x 0.11 mm^3	
Theta range for data collection	1.57 to 28.53°.	
Index ranges	-9<=h<=6, -12<=k<=12, -17<=l<=17	
Reflections collected	13496	
Independent reflections	4127 [R(int) = 0.0244]	
Completeness to theta = 28.53°	97.4 %	
Max. and min. transmission	0.6153 and 0.5084	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4127 / 0 / 225	
Goodness-of-fit on F^2	1.043	
Final R indices [I>2sigma(I)]	R1 = 0.0255, wR2 = 0.0592	
R indices (all data)	R1 = 0.0325, wR2 = 0.0613	
Largest diff. peak and hole	1.059 and -0.417 $e.Å^{-3}$	

B. NOESY Studies

Copy of NOESY Experiment of Compound **2j**.

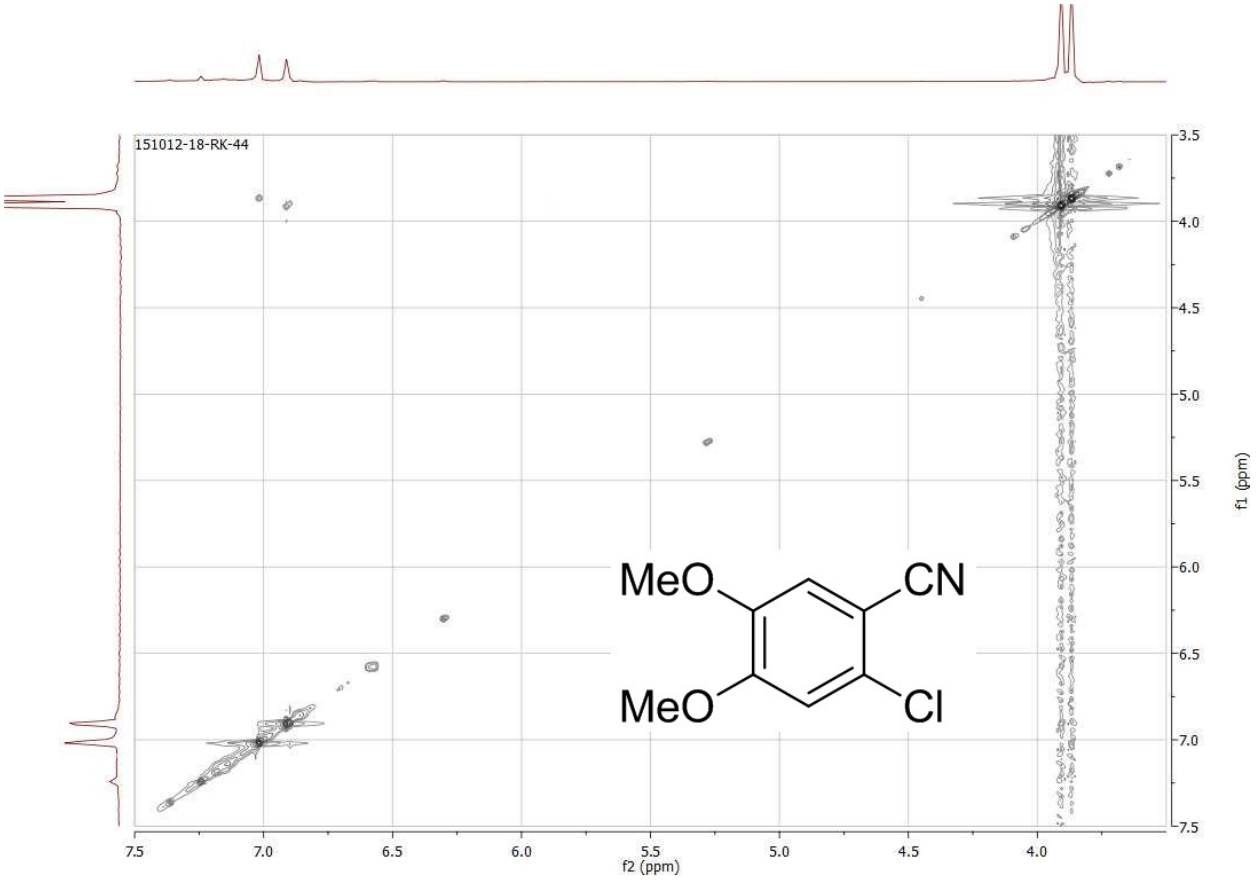


Ha δ = 6.89; Hb = 7.01; Hc = 3.90
Hd δ = 3.85
Observed

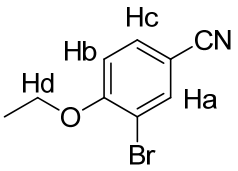


Not observed

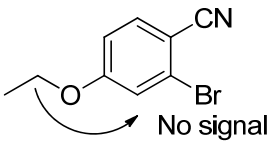
There is a NOE correlation between Ha (δ 6.89, s) and Hd (δ 3.85, s). In meantime, there is also a correlation between Hb (δ 7.01, s) and Hc (δ 3.90, s). These results clearly revealed that the regiochemistry of compound **2j** is correct.



Copy of NOESY Experiment of Compound **4c**.

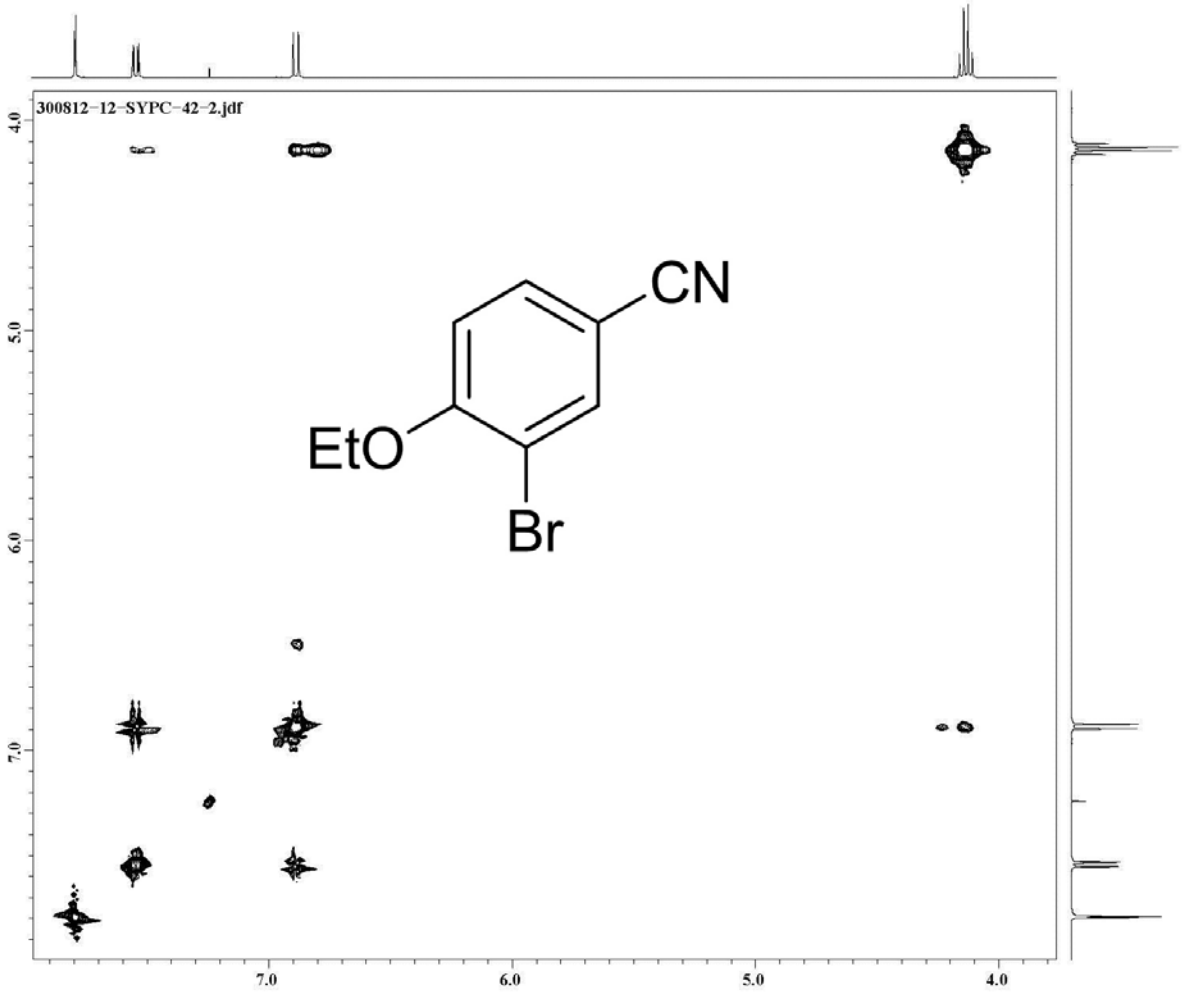


Ha δ = 7.79; Hb = 6.89; Hc = 7.54
Hd δ = 4.14
Observed

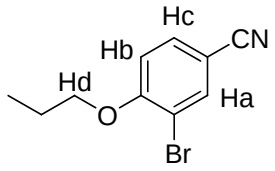


Not observed

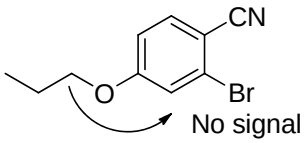
There is a NOE correlation between Hb (δ 6.89, d) and Hd (δ 4.14, q). In meantime, there is also a very weak NOE correlation between Hc (δ 7.54, dd) and Hd (δ 4.14, d). However, there is no correlation between Ha (δ 7.79, s) and Hd (δ 4.14, q). These results clearly revealed that the regiochemistry of compound **4c** is correct.



Copy of NOESY Experiment of Compound **4d**.

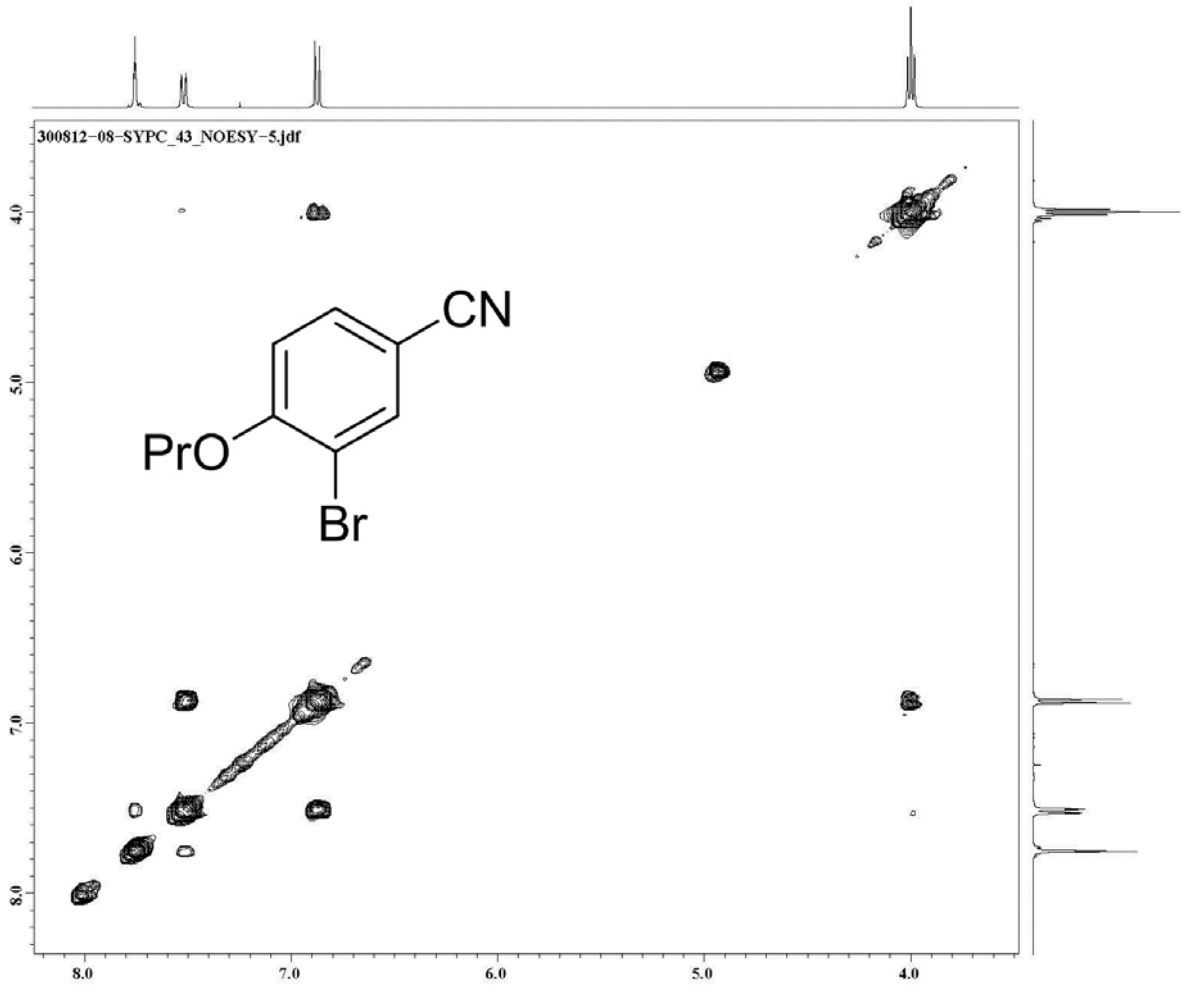


Ha δ = 7.77; Hb = 6.88; Hc = 7.52
Hd δ = 4.01
Observed

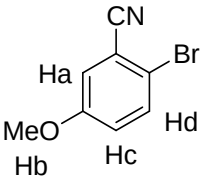


Not observed

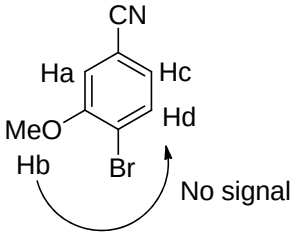
There is a NOE correlation between Hb (δ 6.88, d) and Hd (δ 4.01, q). In meantime, there is also a very weak NOE correlation between Hc (δ 7.52, dd) and Hd (δ 4.01, d). However, there is no correlation between Ha (δ 7.77, s) and Hd (δ 4.01, q). These results clearly revealed that the regiochemistry of compound **4d** is correct.



Copy of NOESY Experiment of Compound **4g**.

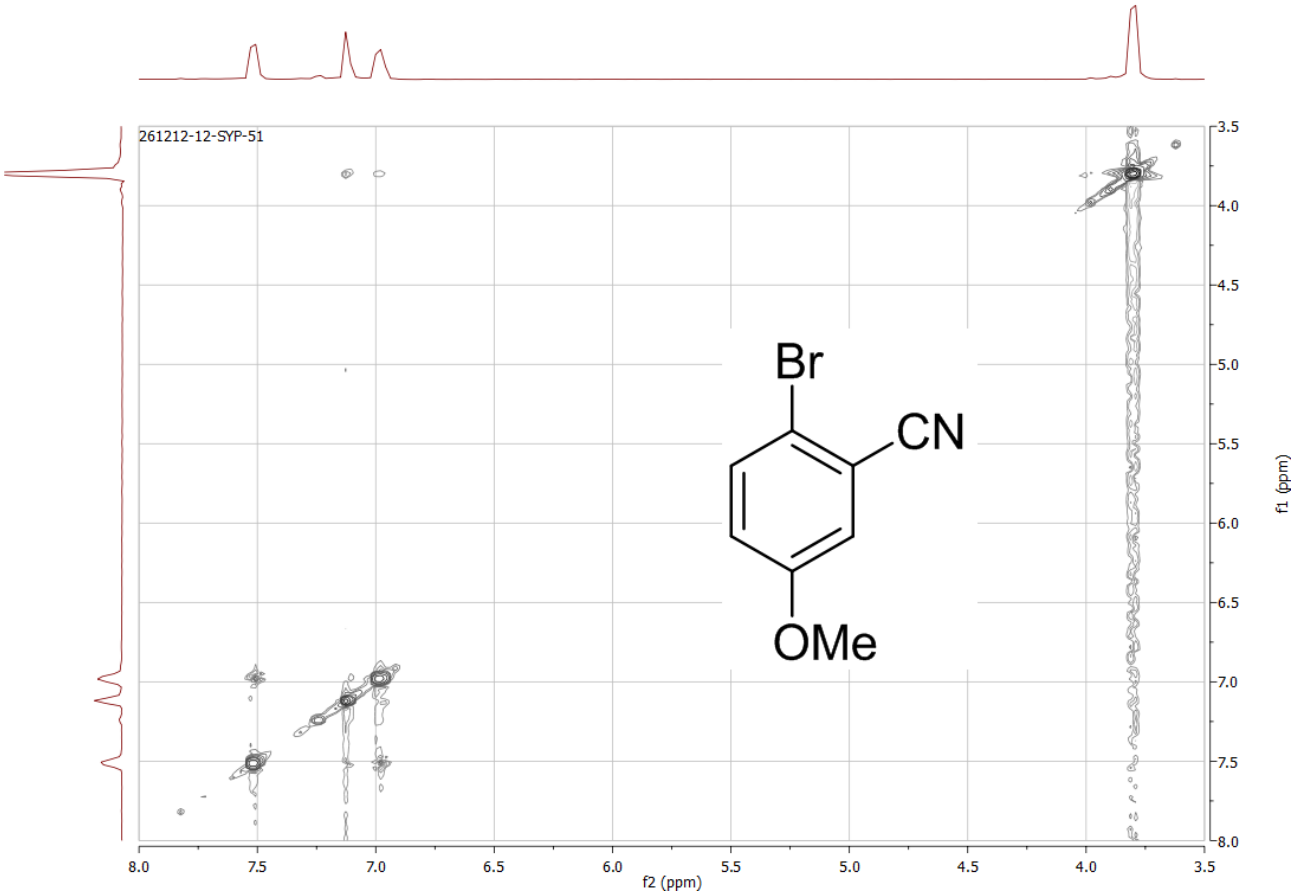


Ha δ = 7.12; Hb = 3.80; Hc = 6.98
Hd δ = 7.52
Observed



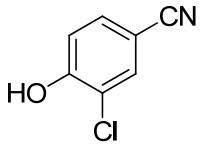
Not observed

There is a NOE correlation between Ha (δ 7.12, s) and Hb (δ 3.80, s). In meantime, there is also a correlation between Hc (δ 6.98, dd) and Hb (δ 3.80, s). These results clearly revealed that the regiochemistry of compound **4g** is correct. If there is a no correlation between Hc (δ 6.98, dd) and Hb (δ 3.80, s), then the other regiochemistry is possible. But, there is a signal.



Spectral Data of all Compounds

3-Chloro-4-hydroxybenzonitrile (2a).



Colorless solid; eluent (10% ethyl acetate in hexanes).

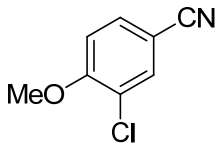
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3419, 2234, 1593, 1411, 1305, 1123 and 1044.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (s, 1 H), 7.46 (dd, J = 8.0, 4.0, Hz, 1 H), 7.06 (d, J = 8.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.8, 133.3, 132.7, 121.0, 117.9, 117.3, 104.7.

HRMS (ESI): calc. for [(C_7H_4ClNO)H] (M+H) 154.0060, measured 154.0063.

3-Chloro-4-methoxybenzonitrile (2b).



Colorless solid; eluent (5% ethyl acetate in hexanes).

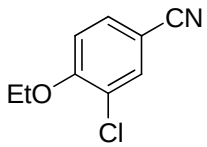
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2923, 2228, 1595, 1500, 1270, 1192 and 1064.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (s, 1 H), 7.53 (dd, J = 8.0, 4.0 Hz, 1 H), 6.96 (d, J = 8.0 Hz, 1 H), 3.94 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.6, 133.6, 132.5, 123.6, 117.9, 112.2, 104.7, 56.5.

HRMS (ESI): calc. for [(C_8H_6ClNO)H] (M+H) 168.0217 measured 168.0217.

3-Chloro-4-ethoxybenzonitrile (2c).



Colorless solid; eluent (5% ethyl acetate in hexanes).

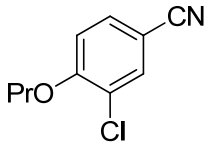
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2229, 1591, 1477, 1298, 1262, 1167, 1125 and 1033.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (s, 1 H), 7.50 (dd, J = 8.0, 4.0 Hz, 1 H), 6.93 (d, J = 8.0 Hz, 1 H), 4.14 (q, J = 8.0 Hz, 2 H), 1.48 (t, J = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.1, 133.6, 132.4, 123.7, 118.1, 112.9, 104.4, 65.2, 14.5.

HRMS (ESI): calc. for [(C_9H_8ClNO)H] (M+H) 182.0373, measured 182.0371.

3-Chloro-4-propoxybenzonitrile (**2d**).



Brown liquid; eluent (5% ethyl acetate in hexanes).

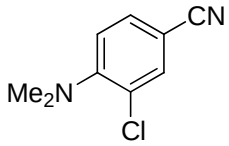
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2968, 2228, 1690, 1594, 1463, 1394, 1270 and 1061.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (s, 1 H), 7.50 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 4.02 (t, *J* = 4.0 Hz, 2 H), 1.89 – 1.84 (m, 2 H), 1.06 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 133.6, 132.4, 123.8, 118.1, 113.0, 104.3, 70.9, 22.3, 10.4.

HRMS (ESI): calc. for [($C_{10}H_{10}ClNO$)H] (M+H) 196.0529, measured 196.0526.

3-Chloro-4-(dimethylamino)benzonitrile (**2e**).



Brown liquid; eluent (5% ethyl acetate in hexanes).

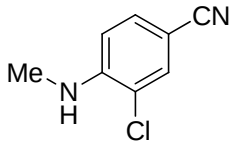
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2968, 2228, 1690, 1594, 1463, 1270, 1195 and 1061.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (s, 1 H), 7.42 (dd, *J* = 8.0, 4.0 Hz 1 H), 6.96 (d, *J* = 8.0 Hz 1 H), 2.89 (s, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.1, 134.4, 131.5, 126.4, 119.4, 118.4, 104.4, 42.9.

HRMS (ESI): calc. for [($C_9H_9ClN_2$)H] (M+H) 181.0533 measured 181.0532.

3-Chloro-4-(methylamino)benzonitrile (**2f**).



Colorless solid; eluent (20% ethyl acetate in hexanes).

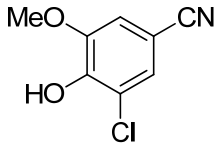
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3325, 2361, 1517, 1235 and 1037.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (s, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 6.58 (d, *J* = 8.0 Hz, 1 H), 4.91 (bs, 1 H), 2.93 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.9, 132.5, 132.3, 119.3, 118.5, 109.9, 98.7, 30.0.

HRMS (ESI): calc. for [($C_8H_7ClN_2$)H] (M+H) 167.0376, measured 167.0371.

3-Chloro-4-hydroxy-5-methoxybenzonitrile (**2g**).



Colorless solid; eluent (10% ethyl acetate in hexanes).

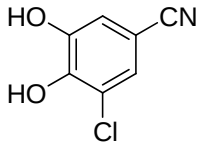
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3427, 2215, 1588, 1500, 1415, 1363, 1293, 1124 and 1044.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 (s, 1 H), 7.00 (s, 1 H), 3.93 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.5, 146.5, 126.9, 120.4, 118.1, 112.4, 103.6, 56.8.

HRMS (ESI): calc. for [($C_8H_6ClNO_2$)H] (M+H) 184.0165, measured 184.0164.

3-Chloro-4,5-dihydroxybenzonitrile (**2h**).



Colorless solid; eluent (20% ethyl acetate in hexanes).

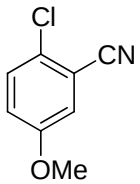
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3433, 2234, 1593, 1411, 1305, 1123 and 1044.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.43 (s, 1 H), 7.03 (s, 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 148.8, 146.9, 127.9, 118.7, 117.6, 110.2, 102.4.

HRMS (ESI): calc. for [($C_7H_4ClNO_2$)H] (M+H) 170.0009, measured 170.0005.

2-Chloro-5-methoxybenzonitrile (**2i**).



Colorless solid; eluent (5% ethyl acetate in hexanes).

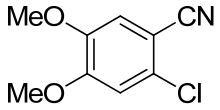
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2365, 1599, 1265, and 1121.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 (d, J = 8.0 Hz, 1 H), 7.12 (s, 1 H), 7.05 (dd, J = 8.0, 4.0 Hz, 1 H), 3.81 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.1, 130.9, 120.7, 118.2, 116.0, 115.8, 113.7, 55.9.

HRMS (ESI): calc. for [(C_8H_6ClNO)H] (M+H) 168.0216, measured 168.0212.

2-Chloro-4,5-dimethoxybenzonitrile (**2j**).



Colorless solid; eluent (7% ethyl acetate in hexanes).

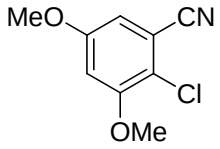
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2229, 1595, 1459, 1382, 1274, 1220, 1121 and 1042.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.01 (s, 1 H), 6.89 (s, 1 H), 3.90 (s, 3 H), 3.85 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.3, 148.0, 130.2, 116.5, 114.6, 112.6, 104.2, 56.5, 56.4.

HRMS (ESI): calc. for [($C_9H_8ClNO_2$)H] (M+H) 198.0322, measured 198.0319.

2-Chloro-3,5-dimethoxybenzonitrile (**2k**).



Colorless solid; eluent (7% ethyl acetate in hexanes).

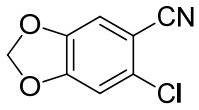
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2230, 1589, 1387, 1225 and 1123.

^1H NMR ($CDCl_3$, 400 MHz): δ 6.71 (s, 1 H), 6.67 (s, 1 H), 3.88 (s, 3 H), 3.81 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 156.4, 117.8, 116.1, 114.2, 108.3, 104.6, 56.5, 56.0.

HRMS (ESI): calc. for [($C_9H_8ClNO_2$)H] (M+H) 198.0322, measured 198.0320.

6-Chlorobenzo[*d*][1,3]dioxole-5-carbonitrile (**2l**).



Yellow solid; eluent (7% ethyl acetate in hexanes).

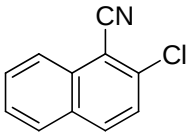
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2235, 1590, 1472, 1414, 1261, 1121 and 1036.

^1H NMR ($CDCl_3$, 400 MHz): δ 6.99 (s, 1 H), 6.90 (s, 1 H), 6.08 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.3, 146.9, 131.8, 116.2, 111.9, 110.6, 105.3, 103.2.

HRMS (ESI): calc. for [($C_8H_4ClNO_2$)H] (M+H) 182.0009, measured 182.0009.

2-Chloro-1-naphthonitrile (**2m**).



Colorless solid; eluent (5% ethyl acetate in hexanes).

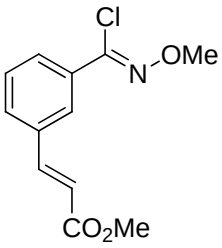
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2355, 1597, 1479, 1135 and 1051.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (d, *J* = 8.0 Hz, 1 H), 8.23 (d, *J* = 8.0 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.77 – 7.69 (m, 2 H), 7.60 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.0, 133.3, 132.2, 130.6, 129.5, 128.7, 125.7, 125.6, 125.3, 117.3, 109.4.

HRMS (ESI): calc. for [($C_{11}H_6ClN$)H] (M+H) 188.0267, measured 188.0265.

(*E*)-Methyl 3-(3-((Z)-chloro(methoxyimino)methyl)phenyl)acrylate (2n).



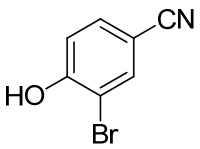
Pale yellow semisolid; eluent (15% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.01 (s, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.72 (d, *J* = 16.0 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 6.51 (d, *J* = 16.0 Hz, 1 H), 4.13 (s, 3 H), 3.82 (s, 3 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 167.2, 143.9, 136.5, 134.8, 133.5, 129.8, 129.1, 128.7, 126.6, 119.0, 63.4, 51.8.

HRMS (ESI): calc. for [($C_{12}H_{12}ClNO_3$)H] (M+H) 254.0584, measured 254.0579.

3-Bromo-4-hydroxybenzonitrile (**4a**).



Brown solid; eluent (10% ethyl acetate in hexanes).

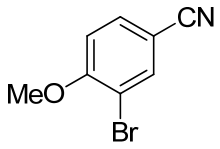
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3431, 2237, 1600, 1507, 1410, 1303, 1222 and 1046.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (s, 1 H), 7.48 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.04 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.7, 136.3, 133.3, 117.7, 116.9, 110.6, 105.0.

HRMS (ESI): calc. for [(C_7H_4BrNO)H] (M+H) 197.9555, measured 197.9559.

3-Bromo-4-methoxybenzonitrile (**4b**).



Colorless solid; eluent (5% ethyl acetate in hexanes).

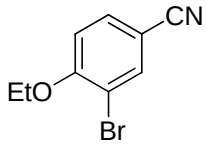
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2235, 1589, 1488, 1294, 1190, 1121 and 1046.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (s, 1 H), 7.58 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 3.94 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 136.7, 133.2, 117.8, 112.3, 111.9, 105.2, 56.6.

HRMS (ESI): calc. for [(C_8H_6BrNO)H] (M+H) 211.9711, measured 211.9713.

3-Bromo-4-ethoxybenzonitrile (**4c**).



Colorless solid; eluent (5% ethyl acetate in hexanes).

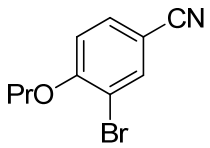
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2224, 1594, 1471, 1295, 1266, 1161, 1120 and 1036.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (s, 1 H), 7.54 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 4.14 (d, *J* = 8.0 Hz, 2 H), 1.48 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.0, 136.7, 133.1, 117.9, 112.7, 112.6, 104.9, 65.3, 14.5.

HRMS (ESI): calc. for [(C_9H_8BrNO)H] (M+H) 225.9868, measured 225.9863.

3-Bromo-4-propoxybenzonitrile (**4d**).



Brown liquid; eluent (5% ethyl acetate in hexanes).

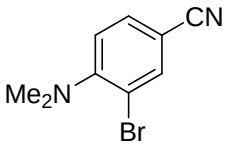
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2971, 2227, 1593, 1491, 1267, 1191 and 1051.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (s, 1 H), 7.52 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 4.01 (t, *J* = 8.0 Hz, 2 H), 1.88 – 1.83 (m, 2 H), 1.05 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 136.6, 133.1, 117.9, 112.7, 112.6, 104.8, 71.0, 22.3, 10.5.

HRMS (ESI): calc. for [($C_{10}H_{10}BrNO$)H] (M+H) 240.0024, measured 240.0020.

3-Bromo-4-(dimethylamino)benzonitrile (**4e**).



Brown liquid; eluent (5% ethyl acetate in hexanes).

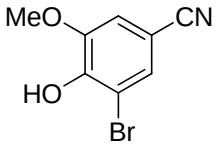
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2223, 1593, 1445, 1339, 1133 and 1045.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (s, 1 H), 7.48 (dd, J = 8.0, 4.0 Hz, 1 H), 6.98 (d, J = 8.0 Hz, 1 H), 2.88 (s, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.7, 137.7, 132.1, 119.8, 118.2, 116.5, 105.3, 43.4.

HRMS (ESI): calc. for [($C_9H_9BrN_2$)H] (M+H) 225.0027, measured 225.0028.

3-Bromo-4-hydroxy-5-methoxybenzonitrile (**4f**).



Colorless solid; eluent (10% ethyl acetate in hexanes).

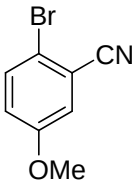
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3454, 2223, 1587, 1492, 1285, 1175, 1126 and 1040.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (s, 1 H), 7.03 (s, 1 H), 3.92 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.6, 147.2, 129.7, 117.9, 112.9, 108.6, 104.2, 56.8.

HRMS (ESI): calc. for [($C_8H_6BrNO_2$)H] (M+H) 227.9660, measured 227.9664.

2-Bromo-5-methoxybenzonitrile(4g).



Colorless solid; eluent (5% ethyl acetate in hexanes).

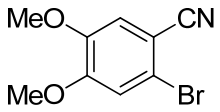
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2237, 1587, 1425, 1141 and 1045.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (d, *J* = 8.0 Hz, 1 H), 7.12 (s, 1 H), 6.98 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.80 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.7, 134.0, 120.9, 118.9, 117.1, 116.2, 115.6, 55.9.

HRMS (ESI): calc. for [(C_8H_6BrNO)H] (M+H) 211.9711, measured 211.9710.

2-Bromo-4,5-dimethoxybenzonitrile (**4h**).



Colorless solid; eluent (7% ethyl acetate in hexanes).

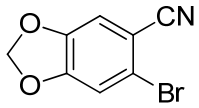
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2925, 2227, 1980, 1590, 1419, 1349, 12367, 1122 and 1036.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.04 (s, 1 H), 7.02 (s, 1 H), 3.90 (s, 3 H), 3.86 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.2, 148.5, 117.7, 117.6, 115.5, 115.3, 106.9, 56.5, 56.4.

HRMS (ESI): calc. for [($C_9H_8BrNO_2$)H] (M+H) 241.9817, measured 241.9812.

6-Bromobenzo[*d*][1,3]dioxole-5-carbonitrile (**4i**).



Yellow solid; eluent (7% ethyl acetate in hexanes).

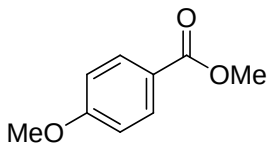
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2360, 1591, 1470, 1259, 1119 and 1031.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.05 (s, 1 H), 6.99 (s, 1 H), 6.08 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.3, 147.5, 119.0, 117.4, 113.4, 112.6, 107.9, 103.1.

HRMS (ESI): calc. for [($C_8H_4BrNO_2$)H] (M+H) 225.9504, measured 225.9500.

Methyl 4-methoxybenzoate.



Colorless solid; eluent (5% ethyl acetate in hexanes)

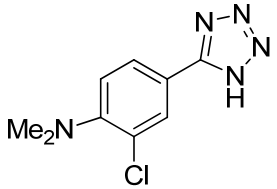
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1711, 1609, 1448, 1321, 1288, 1263, 1170, 1022.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, *J* = 8.0 Hz, 2 H), 6.89 (d, *J* = 8.0 Hz, 2 H), 3.86 (s, 3 H), 3.83 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.5, 163.3, 131.6, 122.6, 113.6, 55.4, 51.9.

HRMS (ESI): calc. for [($C_9H_{10}O_3$)H] (M+H) 167.0708, measured 167.0706.

2-Chloro-*N*,*N*-dimethyl-4-(1*H*-tetrazol-5-yl)aniline (5a).[3]



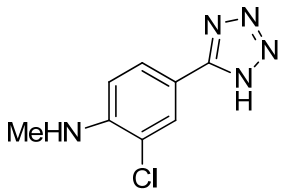
Yellow solid; eluent (20% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56 (s, 1 H), 7.49 (dd, *J* = 10.0, 5.0 Hz, 1 H), 6.67 (d, *J* = 10.0 Hz, 1 H), 4.98 (bs, 1 H), 3.02 (s, 3 H), 3.01 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.1, 132.5, 132.3, 119.3, 118.5, 109.9, 98.7, 30.0.

HRMS (ESI): calc. for [($C_9H_{10}ClN_5$)H] (M+H) 224.0703, measured 224.0710.

2-Chloro-*N*-methyl-4-(1*H*-tetrazol-5-yl)aniline (5b).[3]



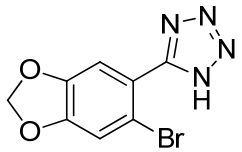
Pale yellow solid; eluent (45% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.52 (s, 1 H), 7.32 (t, *J* = 8.0 Hz, 1 H), 6.72 (d, *J* = 8.0 Hz, 1 H), 4.62 (bs, 2 H), 2.94 (d, *J* = 16.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.1, 133.2, 131.9, 118.9, 118.4, 115.1, 100.7, 36.7.

HRMS (ESI): calc. for [($C_8H_8ClN_5$)H] (M+H) 210.0546, measured 210.0556.

5-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-1*H*-tetrazole (5c).



Colorless solid; eluent (25% ethyl acetate in hexanes).

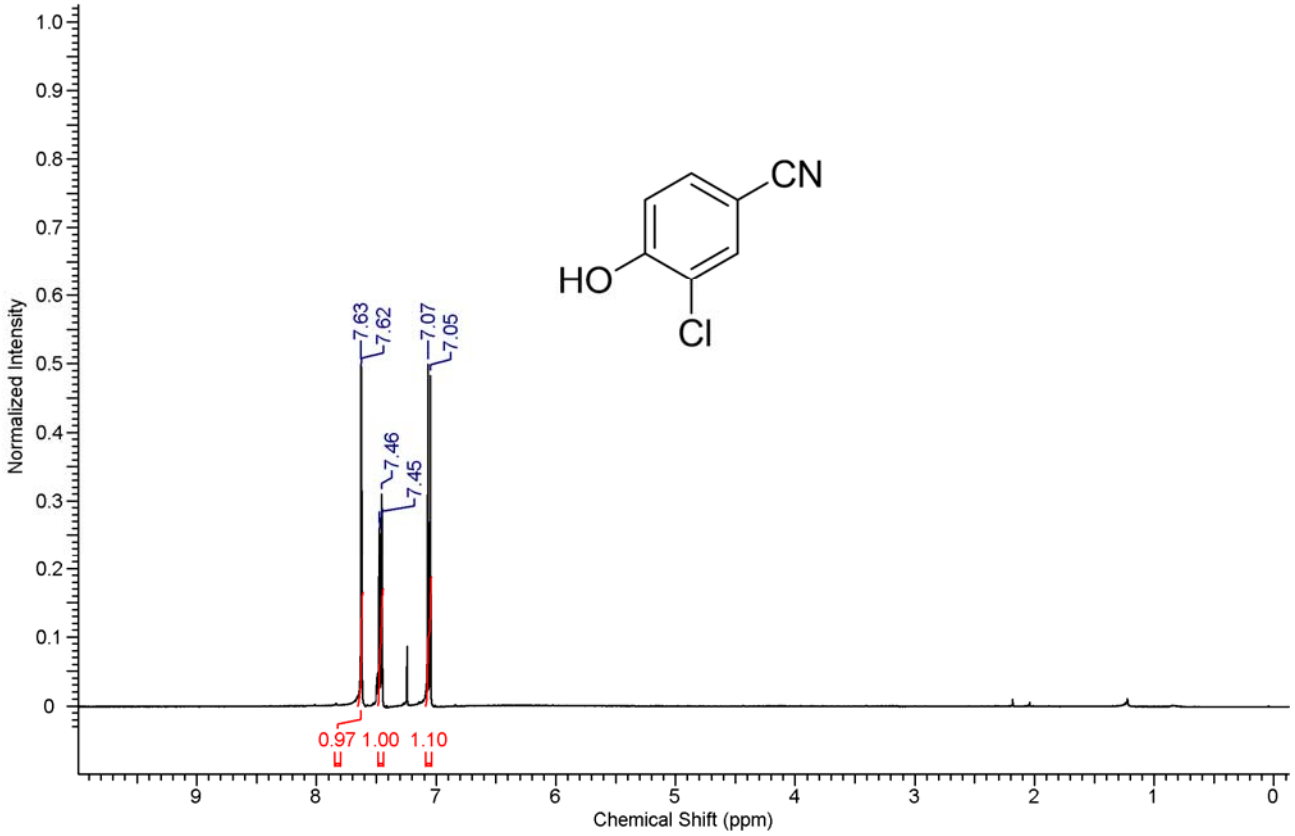
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (s, 1 H), 7.23 (s, 1 H), 6.36 (bs, 1H), 5.23 (s, 2 H).

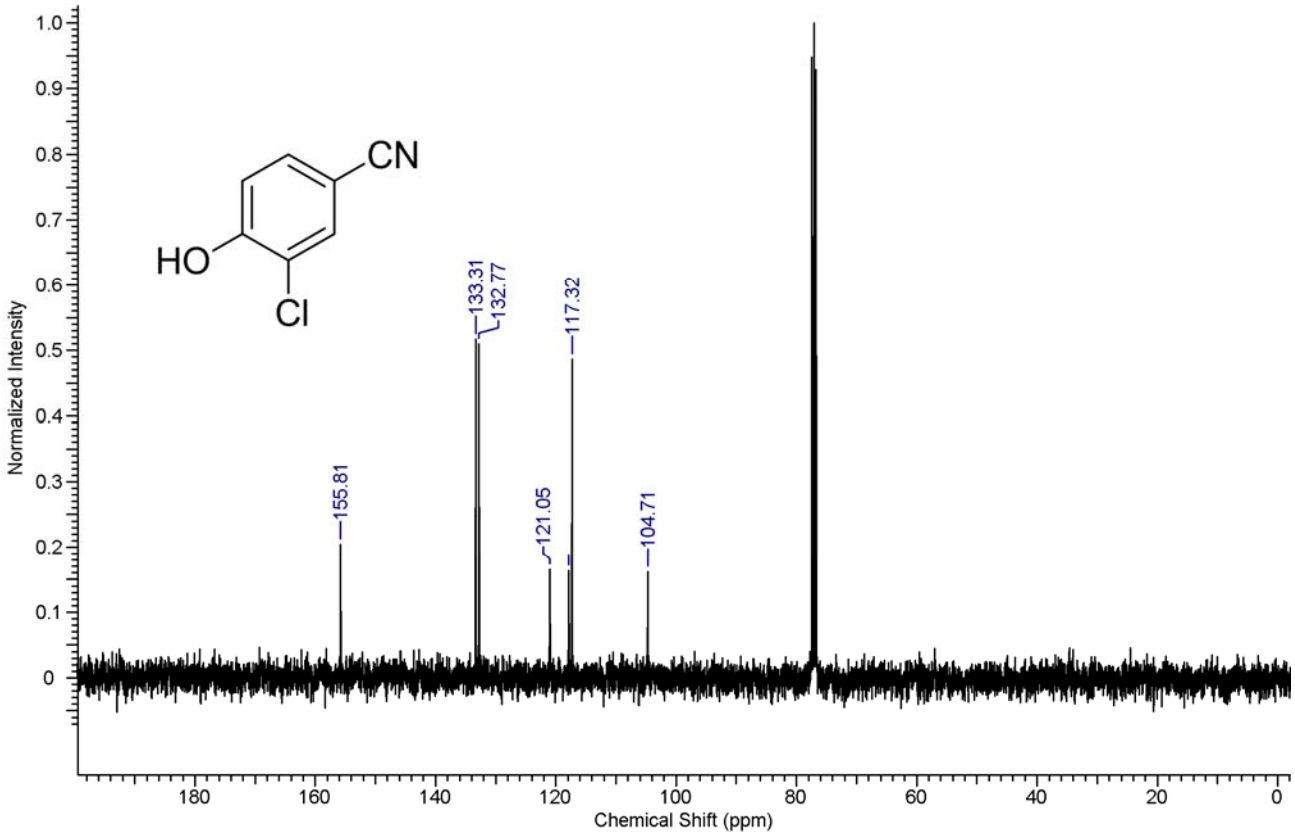
^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.9, 143.0, 120.4, 120.1, 119.1, 117.2, 106.7, 81.0.

HRMS (ESI): calc. for [($C_8H_5BrN_4O_2$)H] (M+H) 268.9674, measured 268.9670.

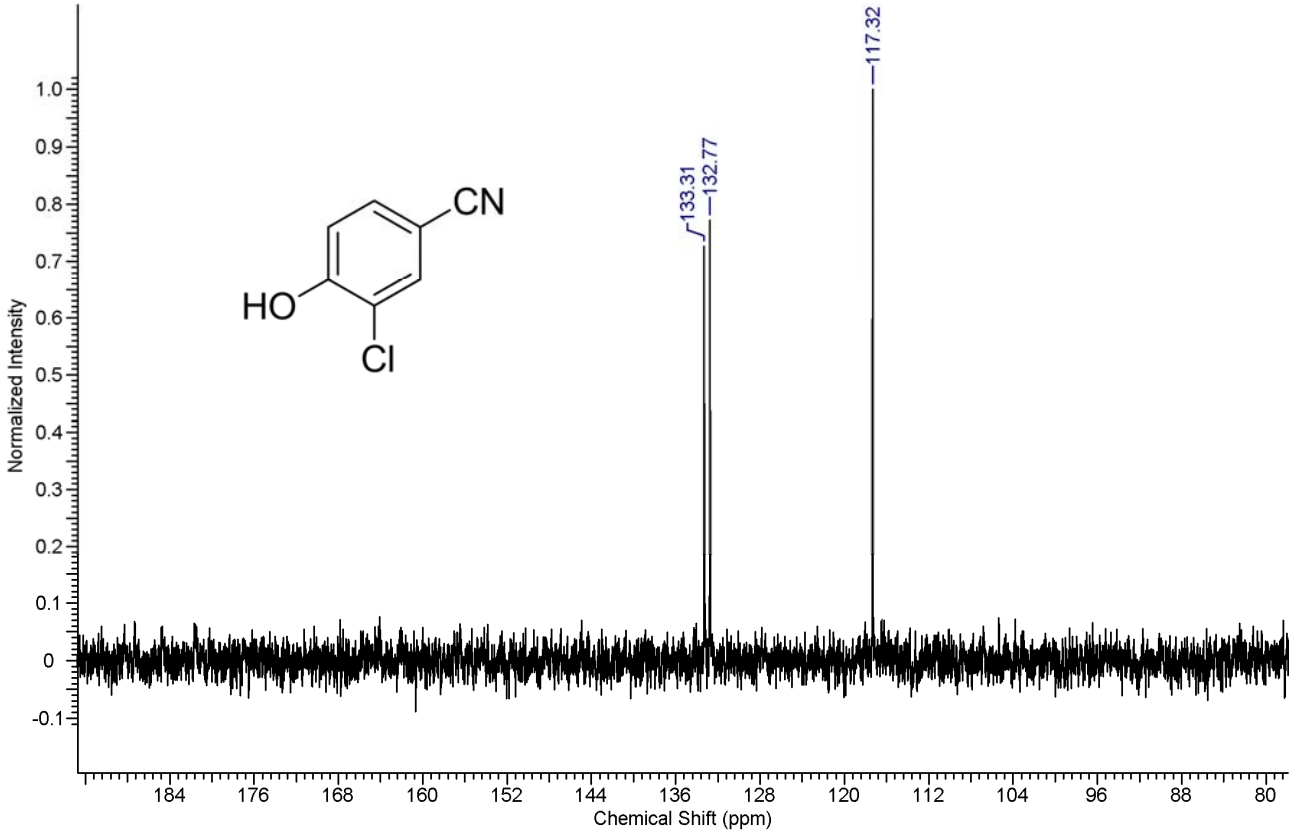
Ref: 3. T. Klabunde, K. U. Wendt, D. Kadereit, V. Brachvogel, H. Burger, A. W. Herling, N. G. Oikonomakos, M. N. Kosmopoulou, D. Schmoll, E. Sarubbi, E. von Roedern, K. Schonafinger and E. Defossa, *J. Med. Chem.* **2005,** *48,* 6178.

^{1}H and ^{13}C NMR Spectra of Compound **2a.**

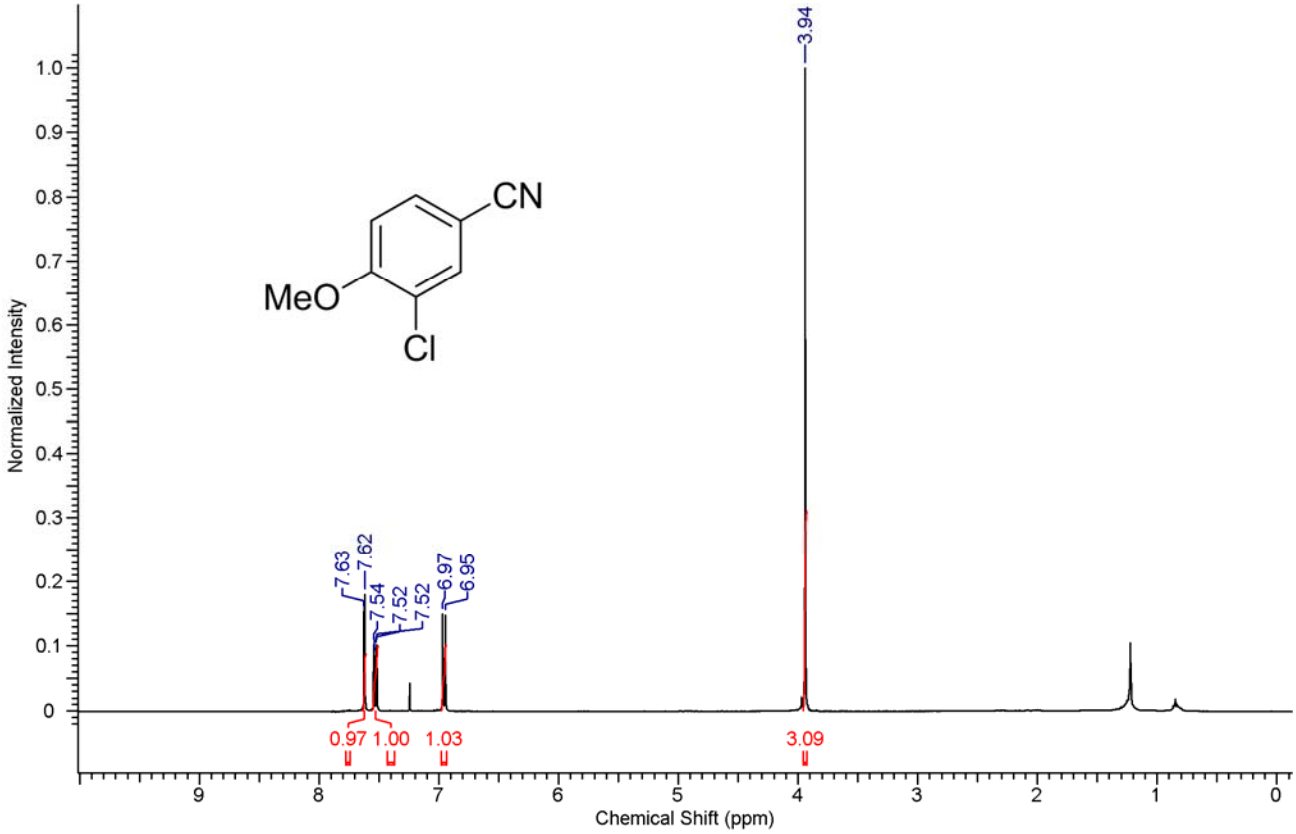


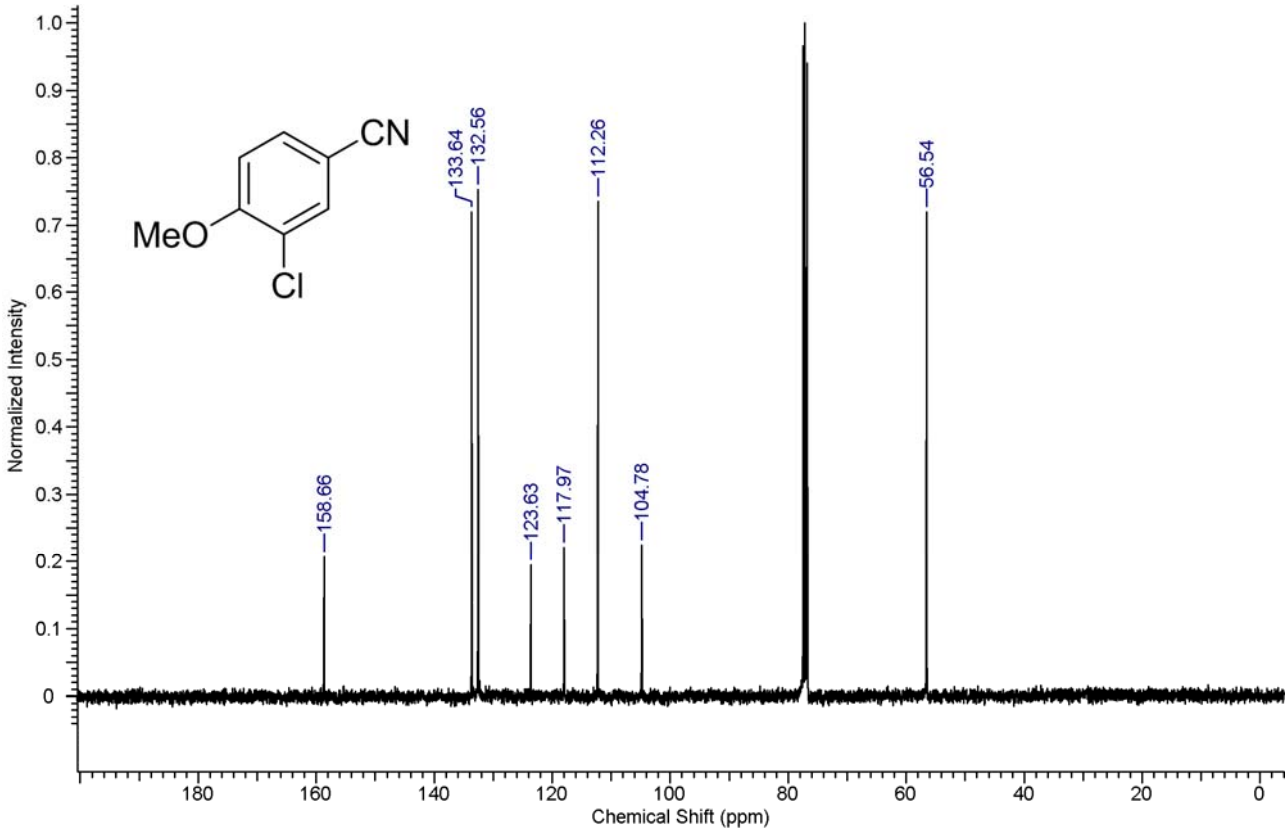


DEPT (135) NMR Spectrum of Compound **2a.**

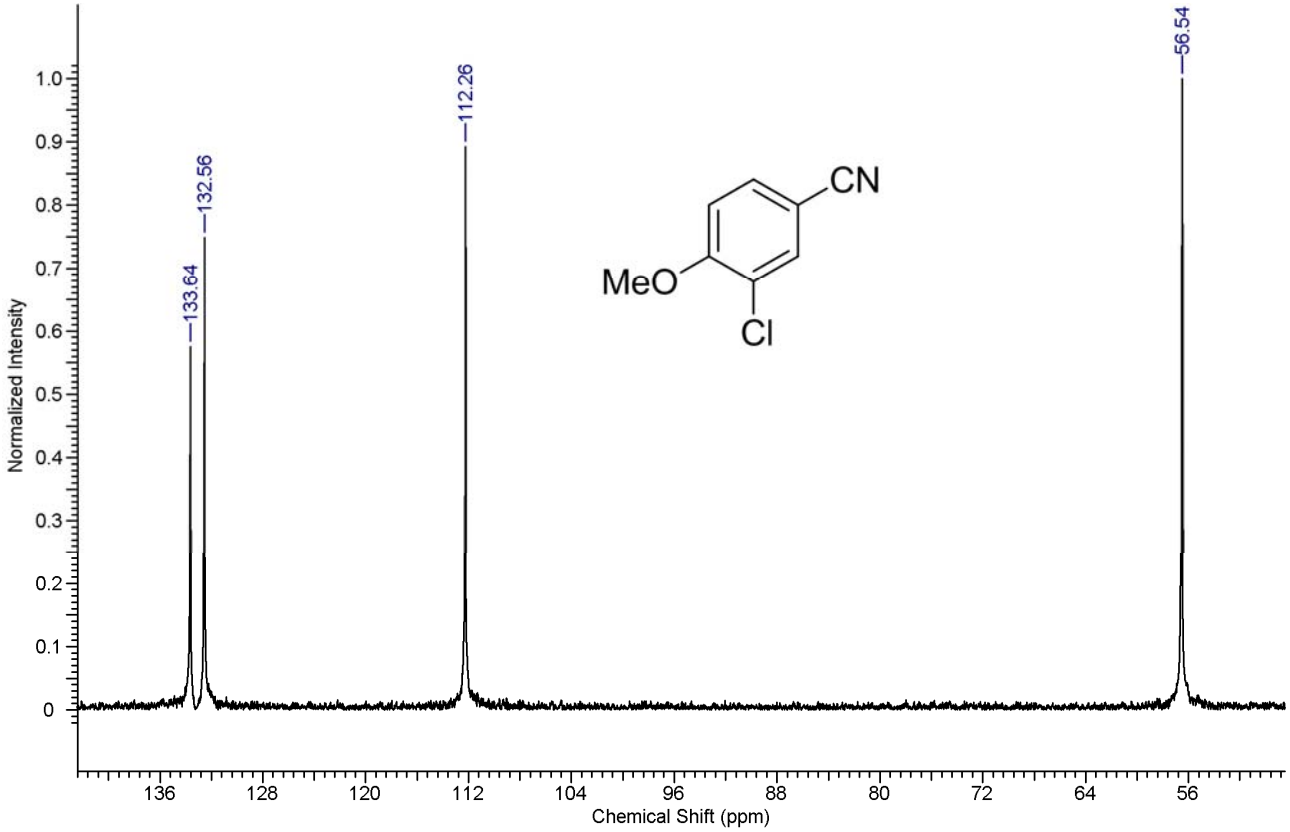


^{1}H and ^{13}C NMR Spectra of Compound **2b.**

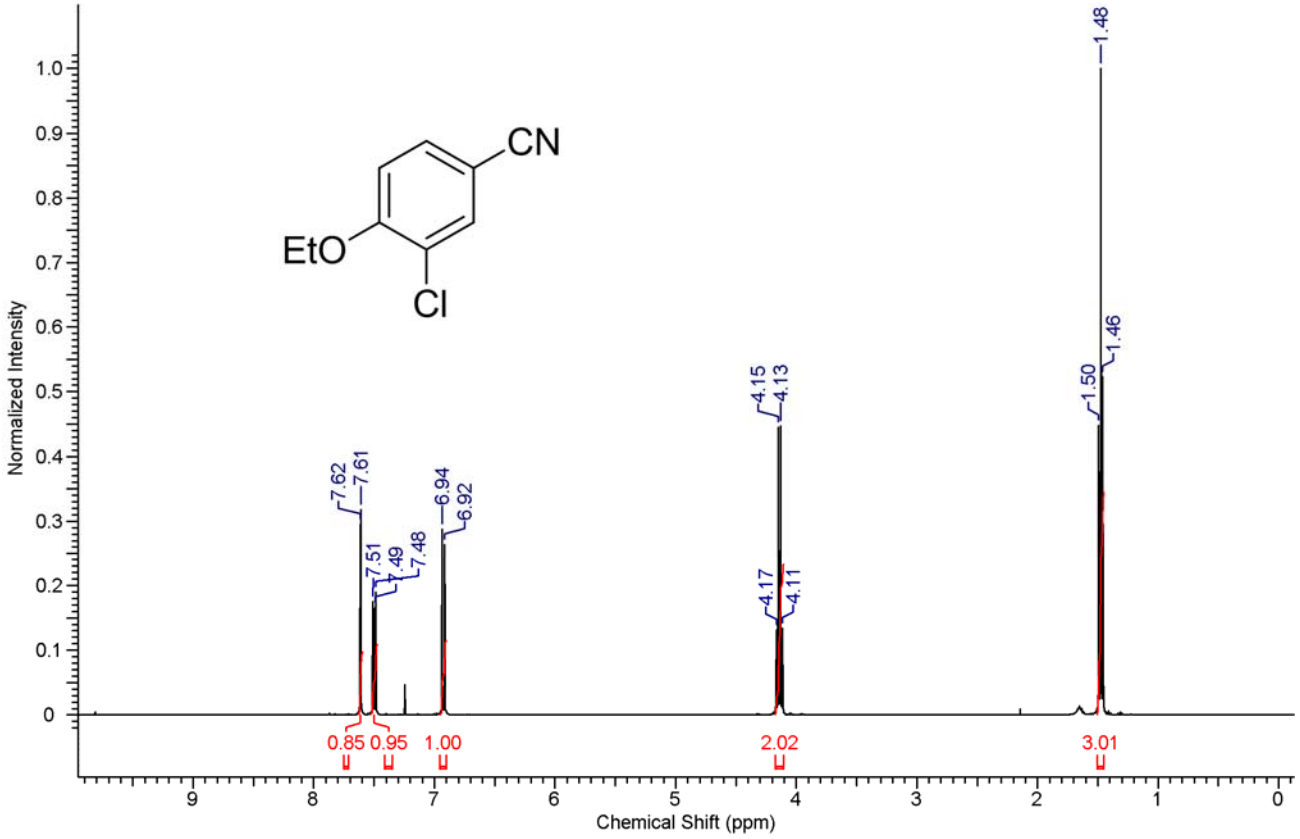


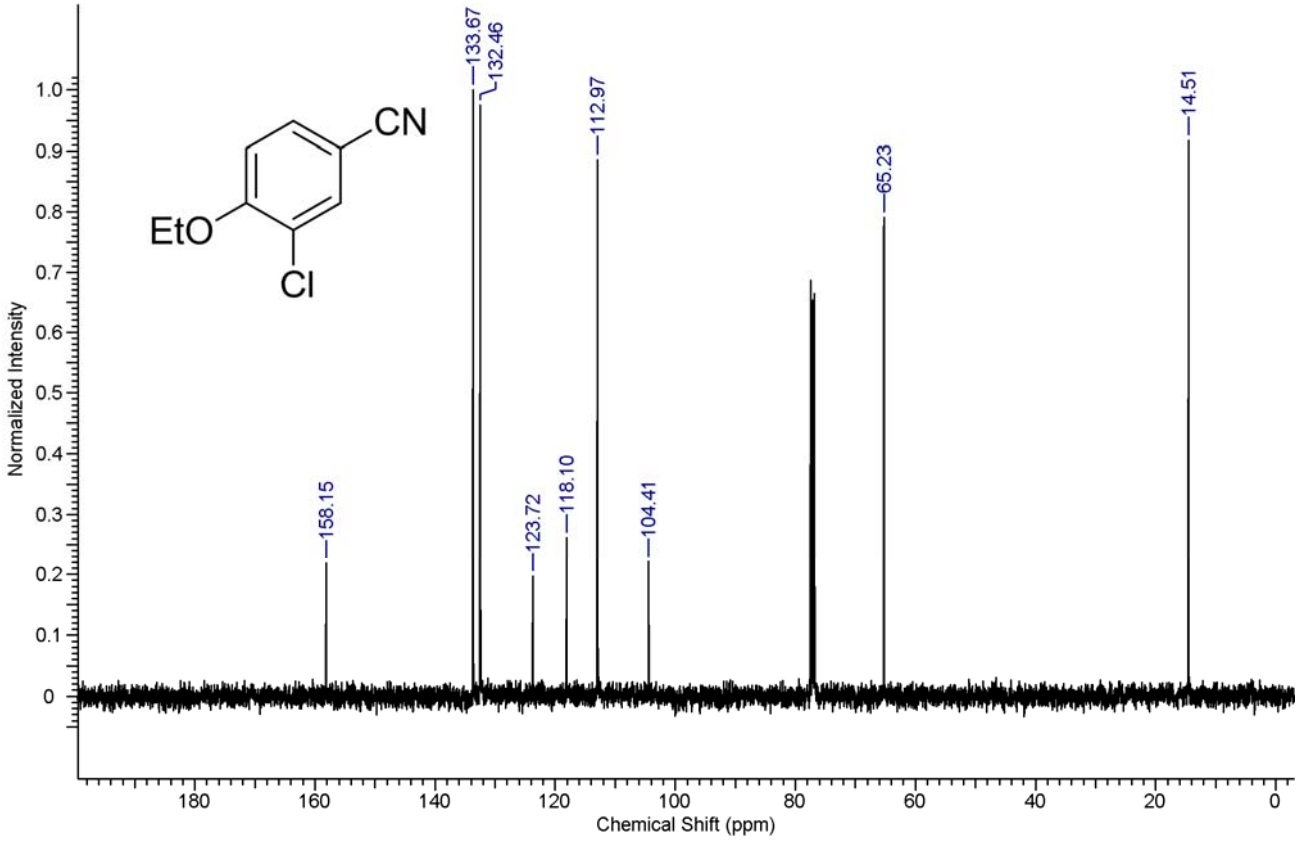


DEPT (135) NMR Spectrum of Compound **2b.**

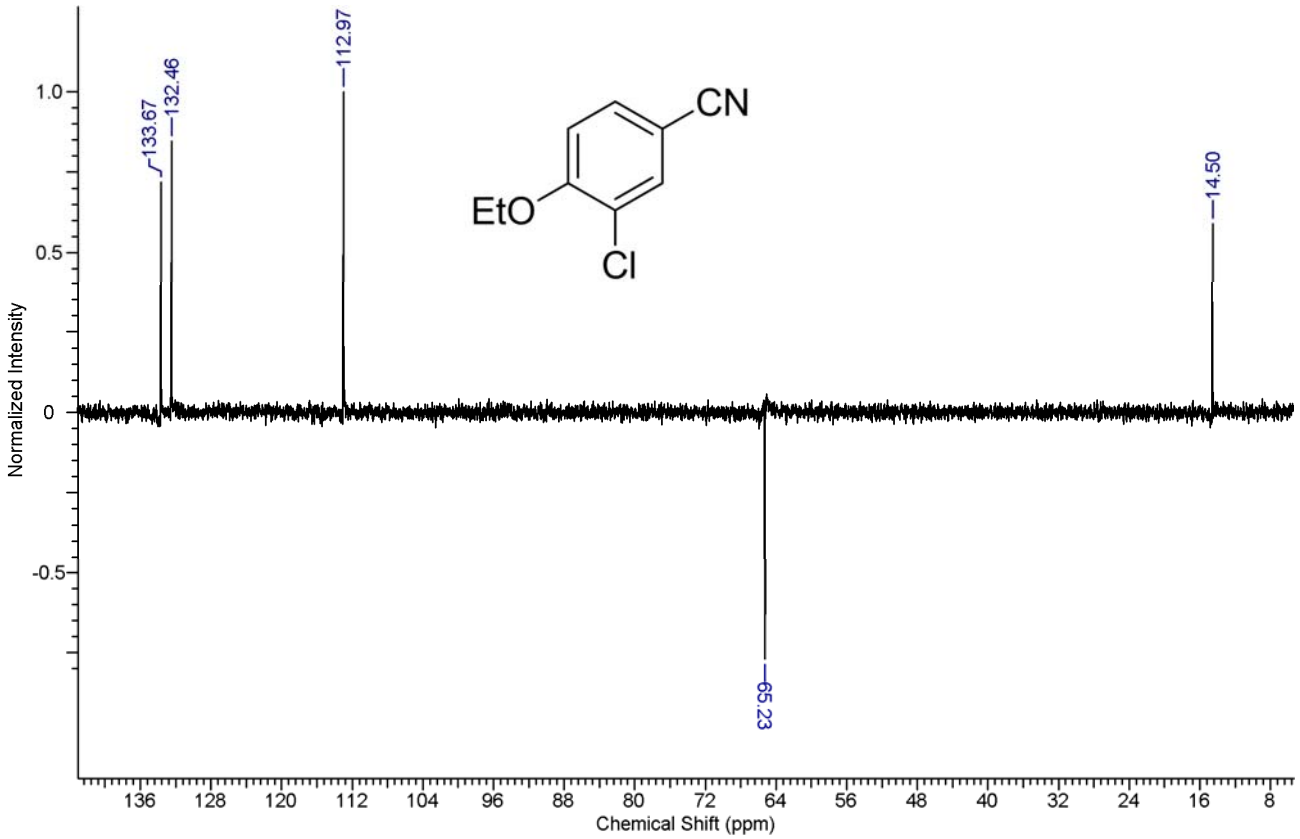


^{1}H and ^{13}C NMR Spectra of Compound **2c.**

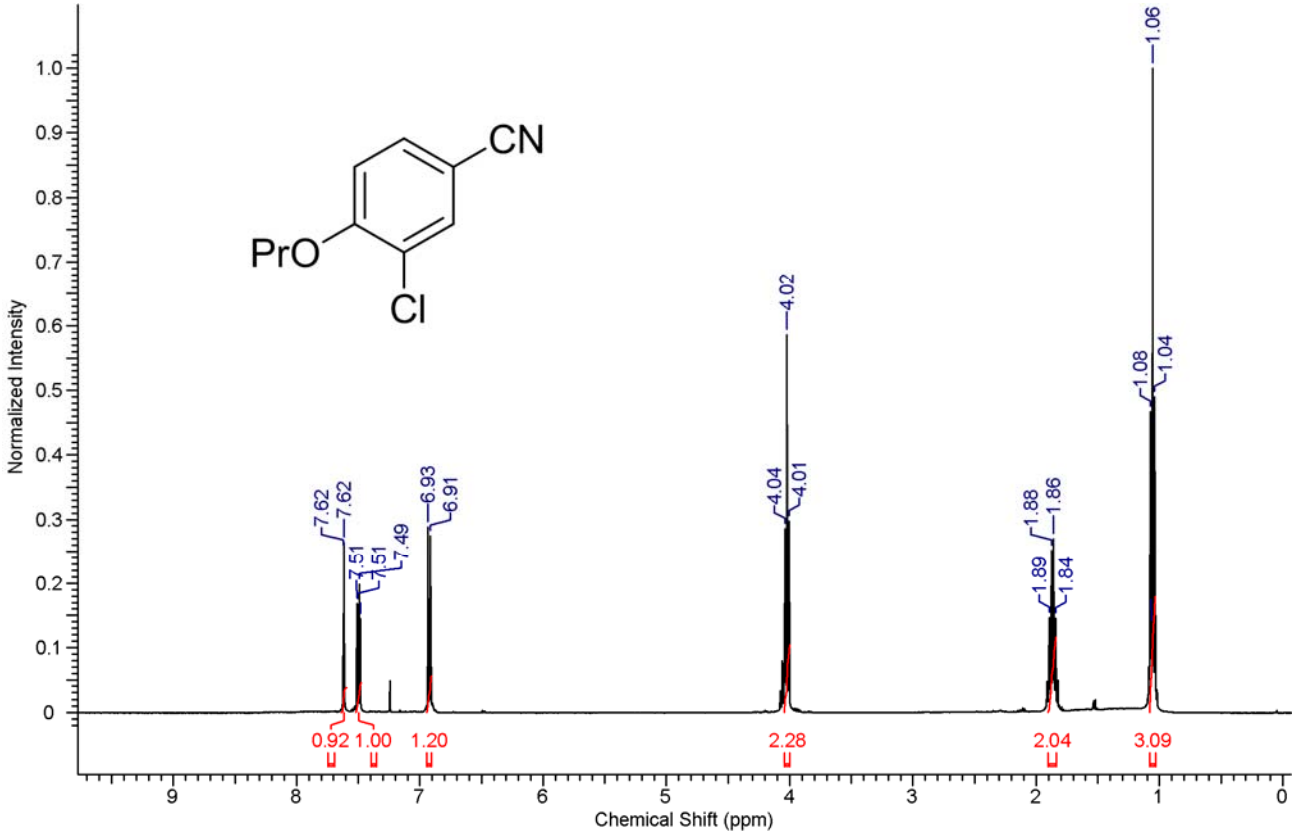


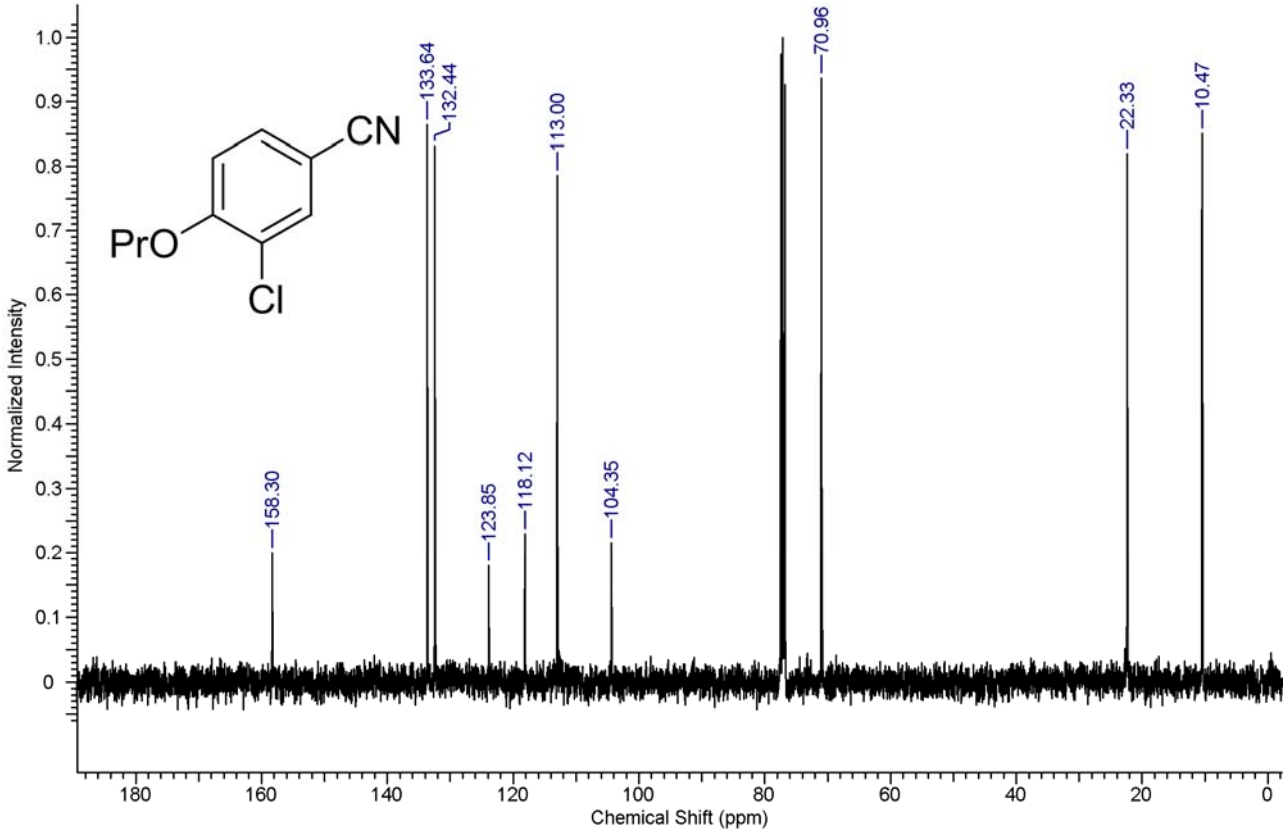


DEPT (135) NMR Spectrum of Compound **2c.**

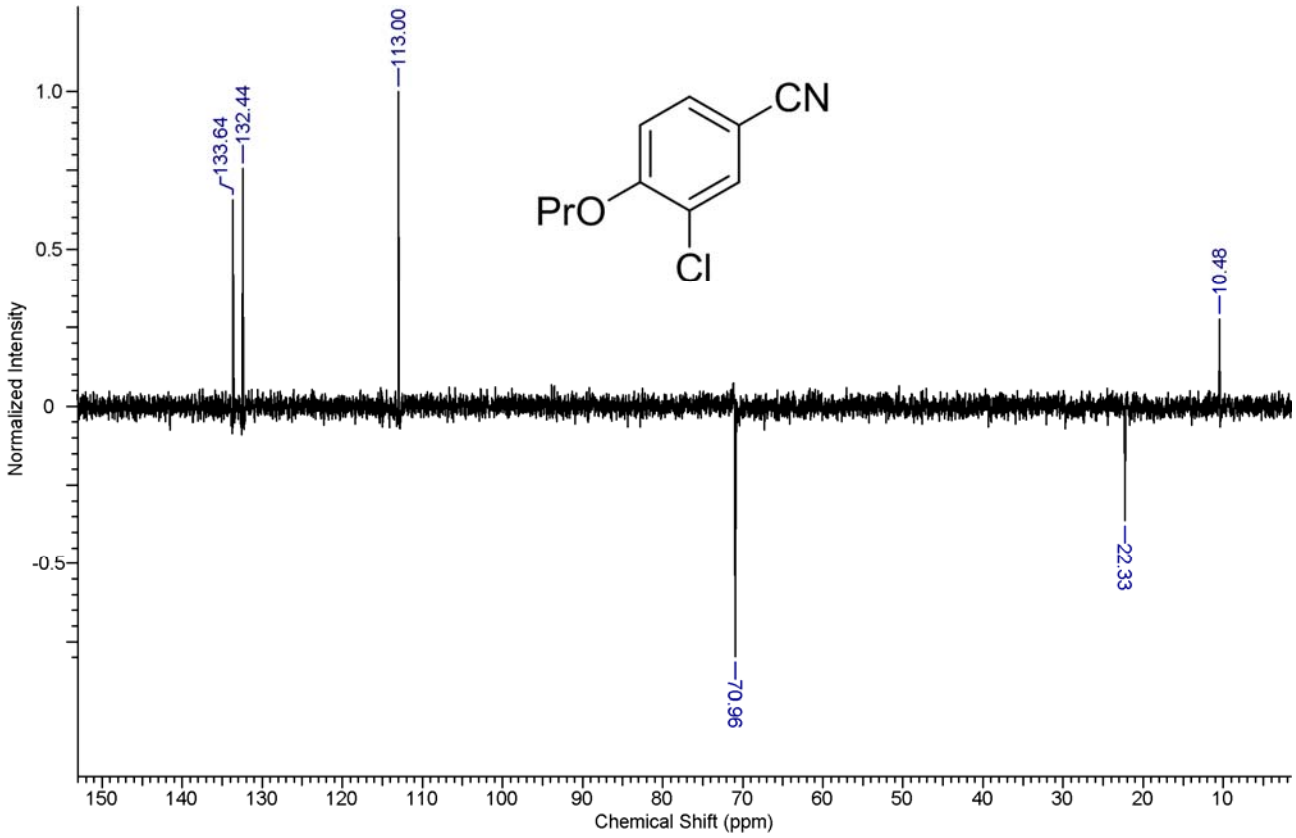


^{1}H and ^{13}C NMR Spectra of Compound **2d.**

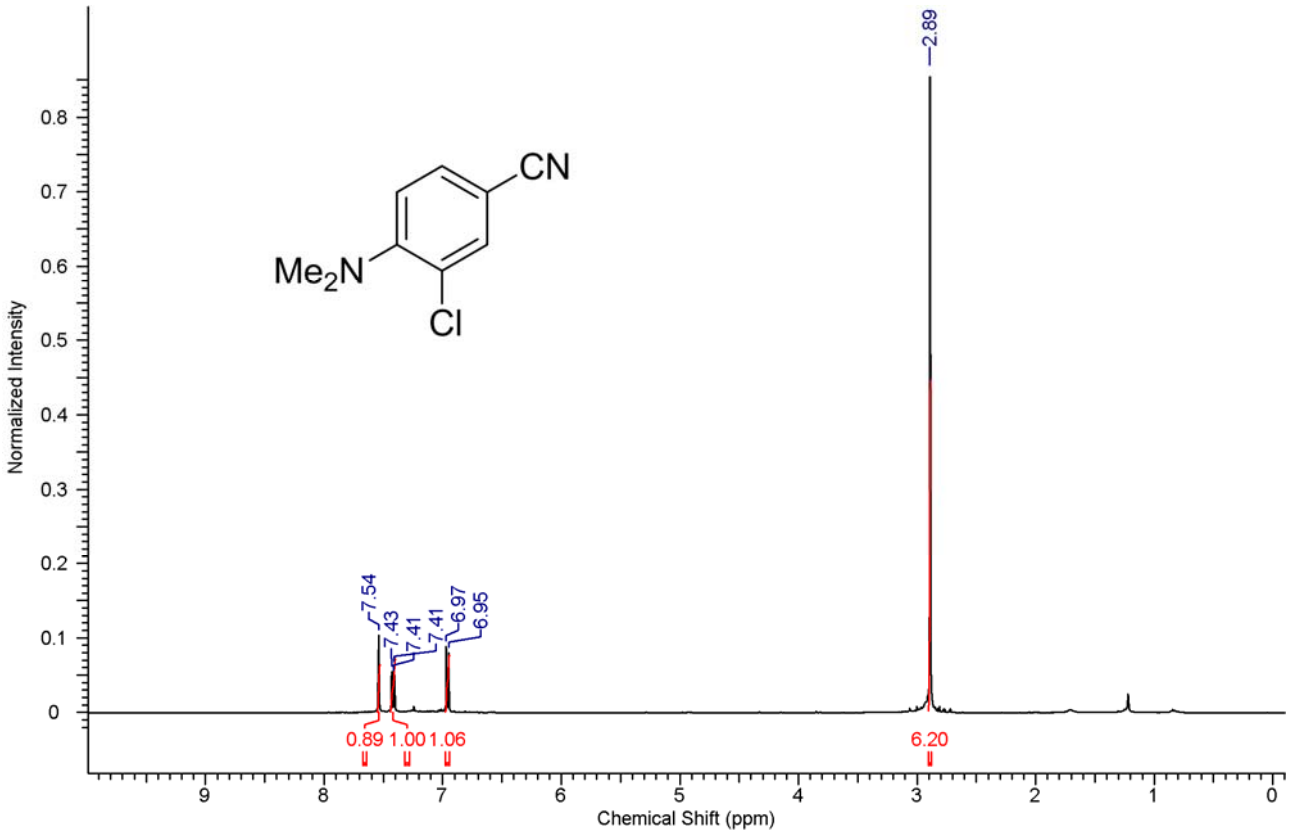


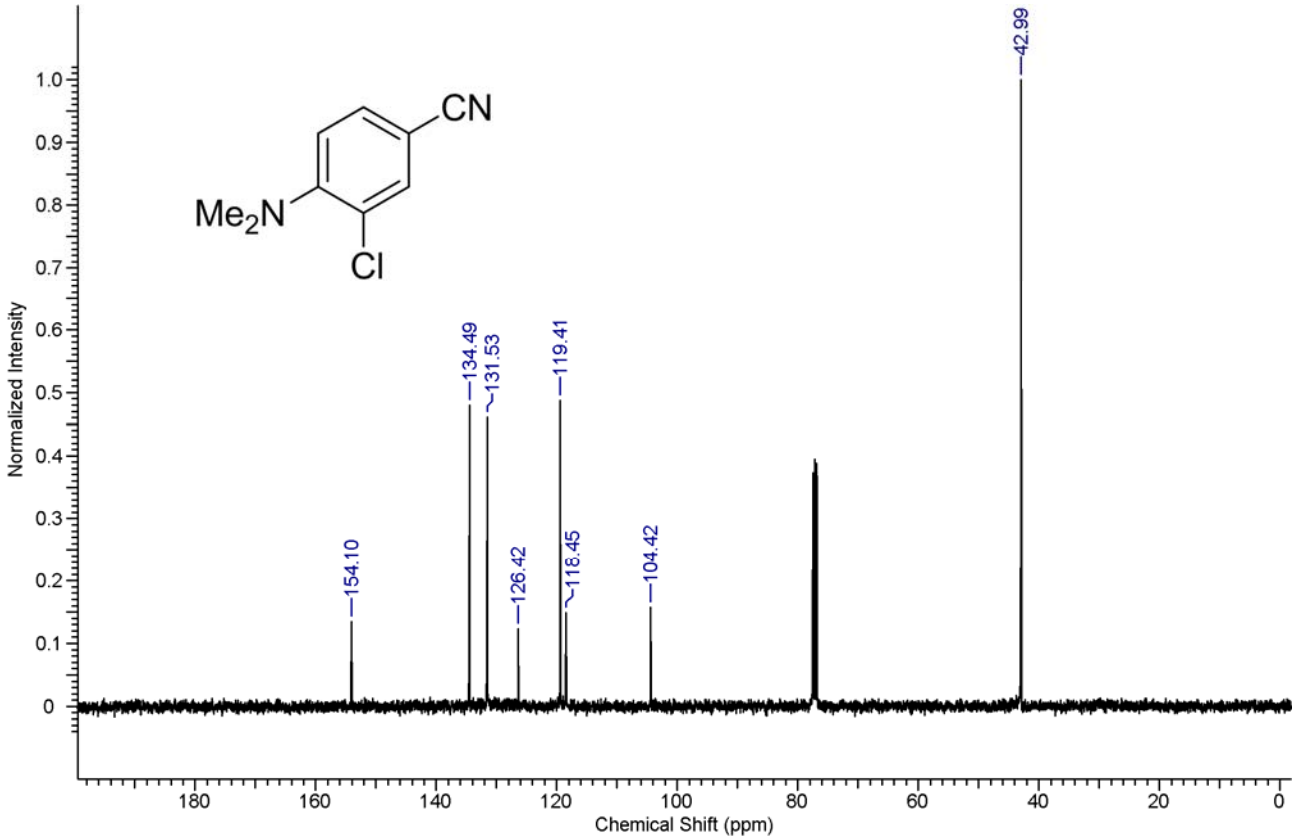


DEPT (135) NMR Spectrum of Compound **2d.**

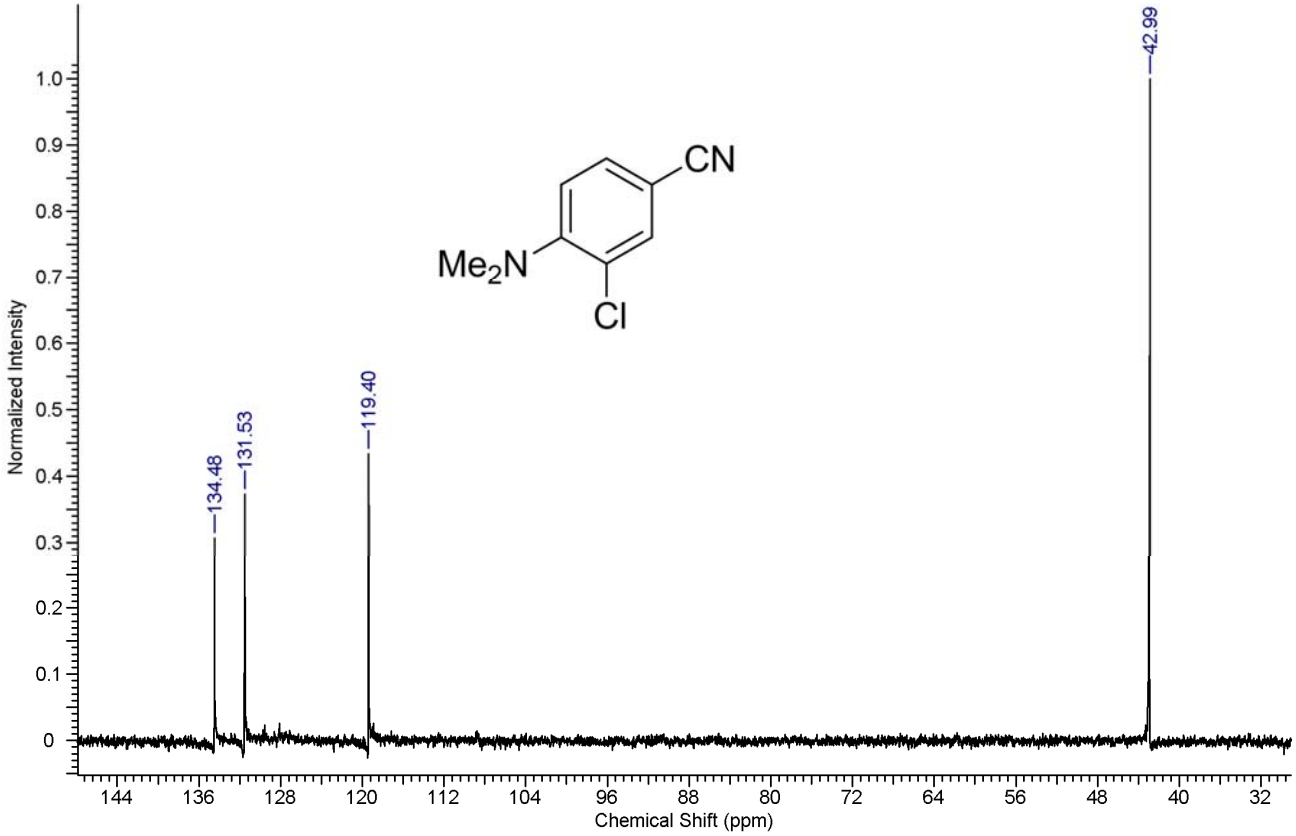


^{1}H and ^{13}C NMR Spectra of Compound **2e.**

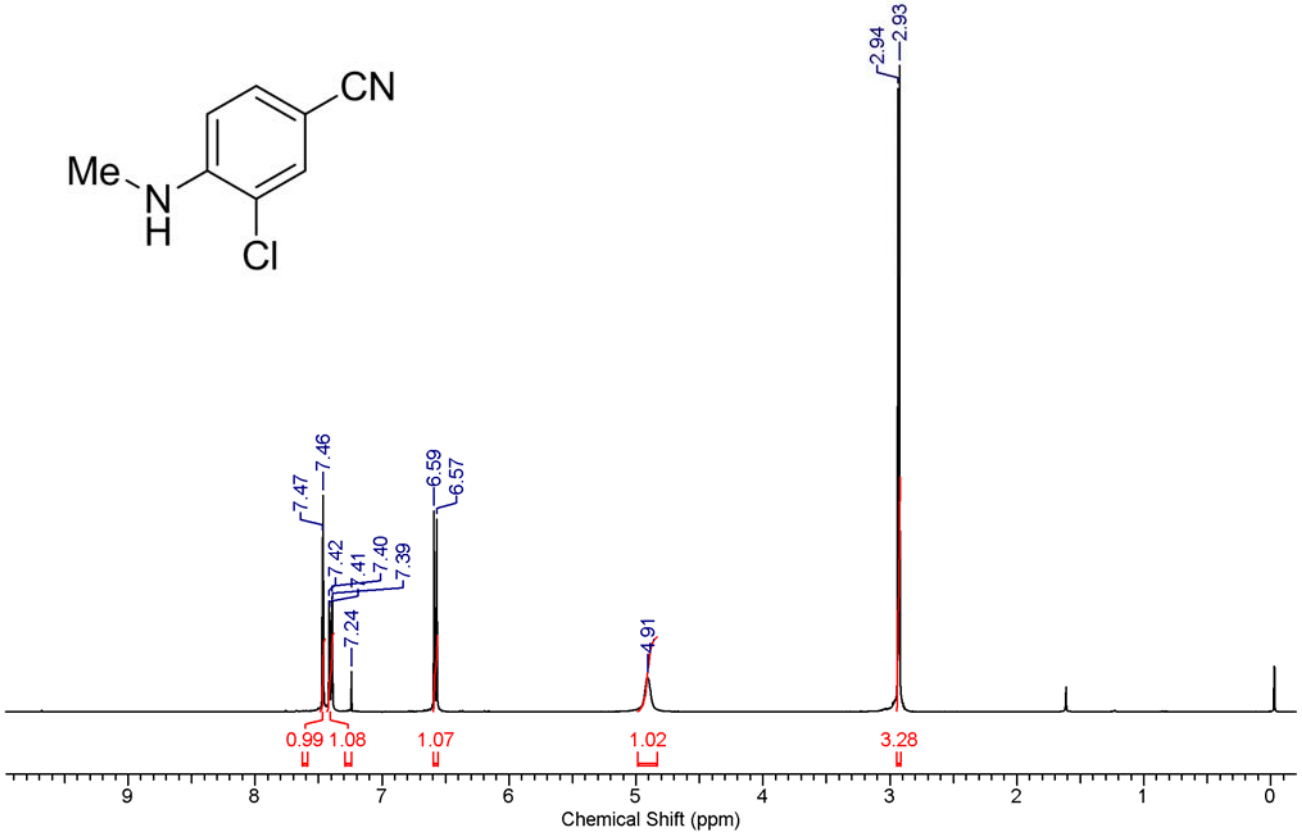


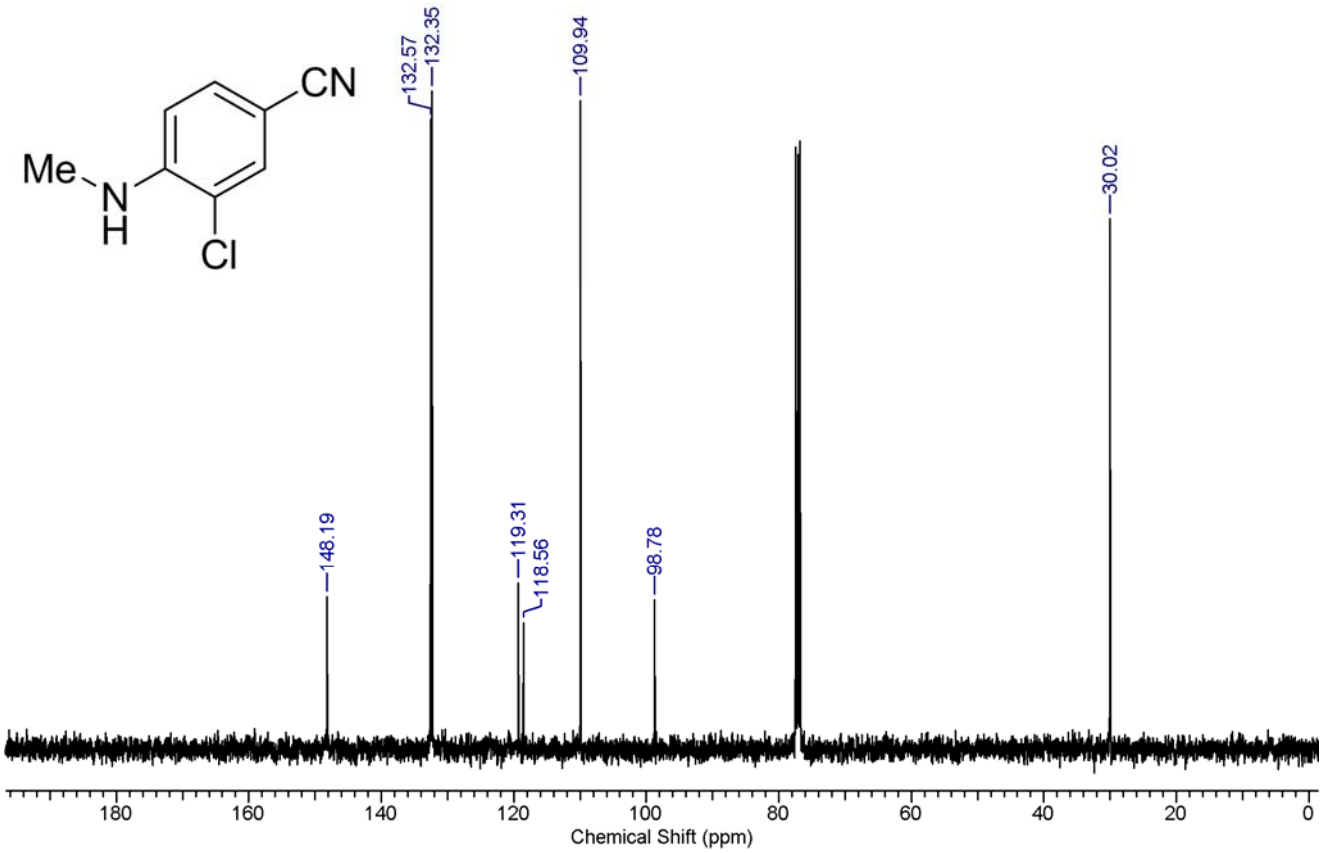


DEPT (135) NMR Spectrum of Compound **2e.**

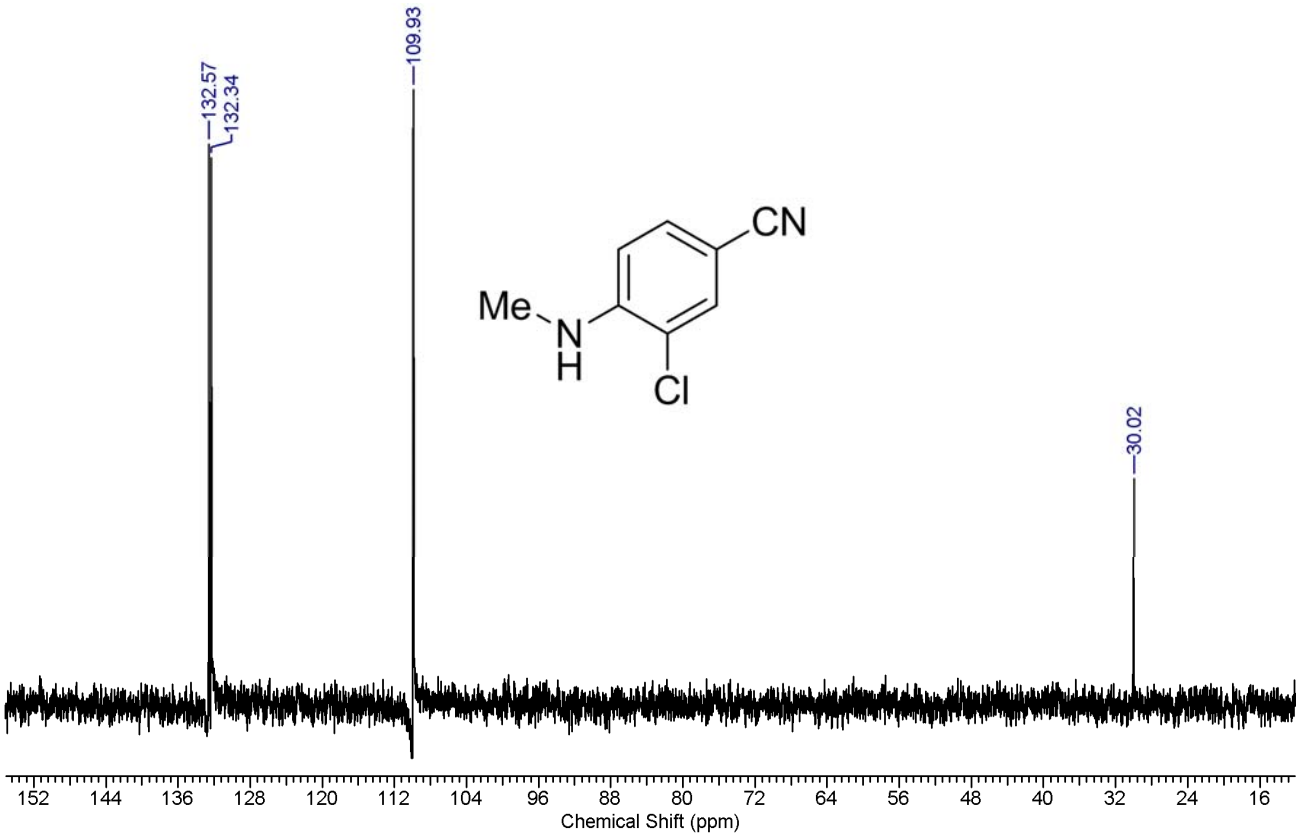


^{1}H and ^{13}C NMR Spectra of Compound **2f.**

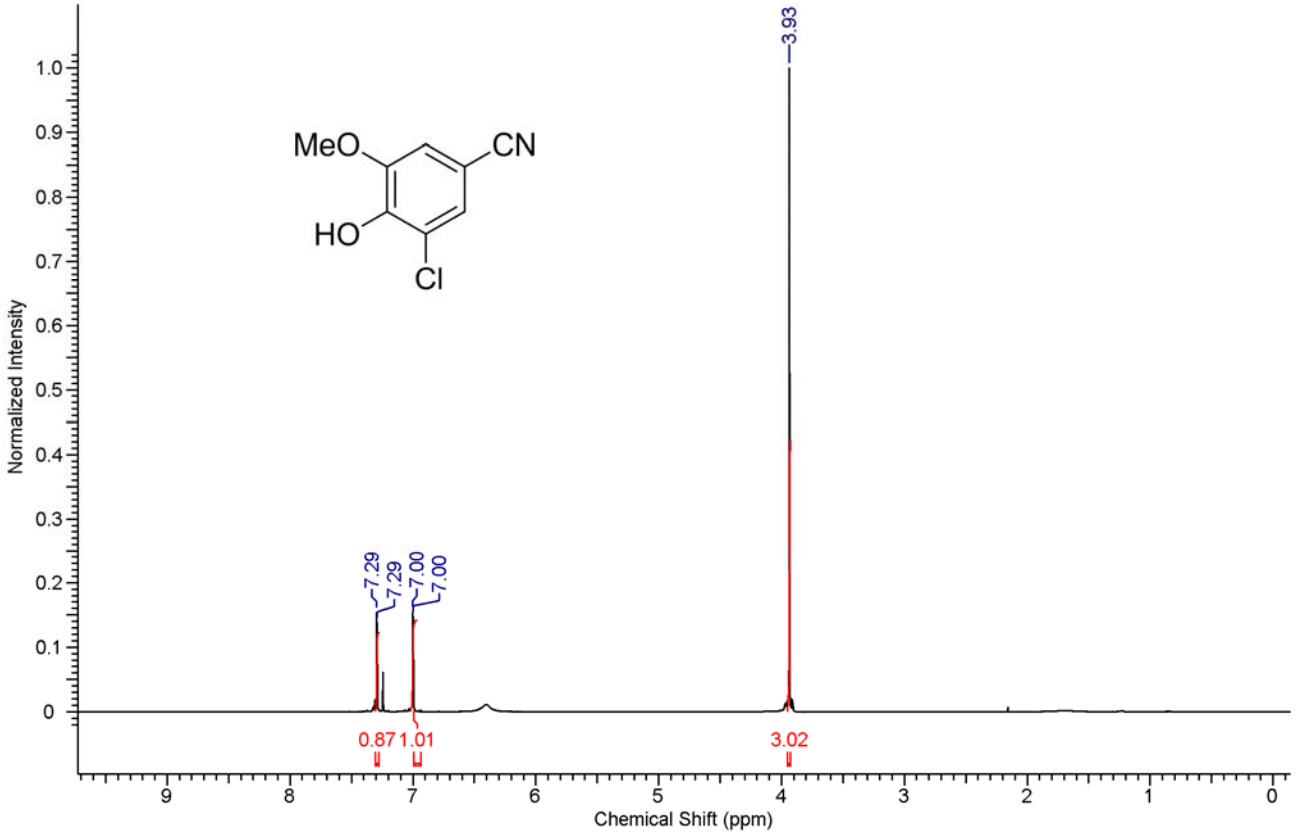


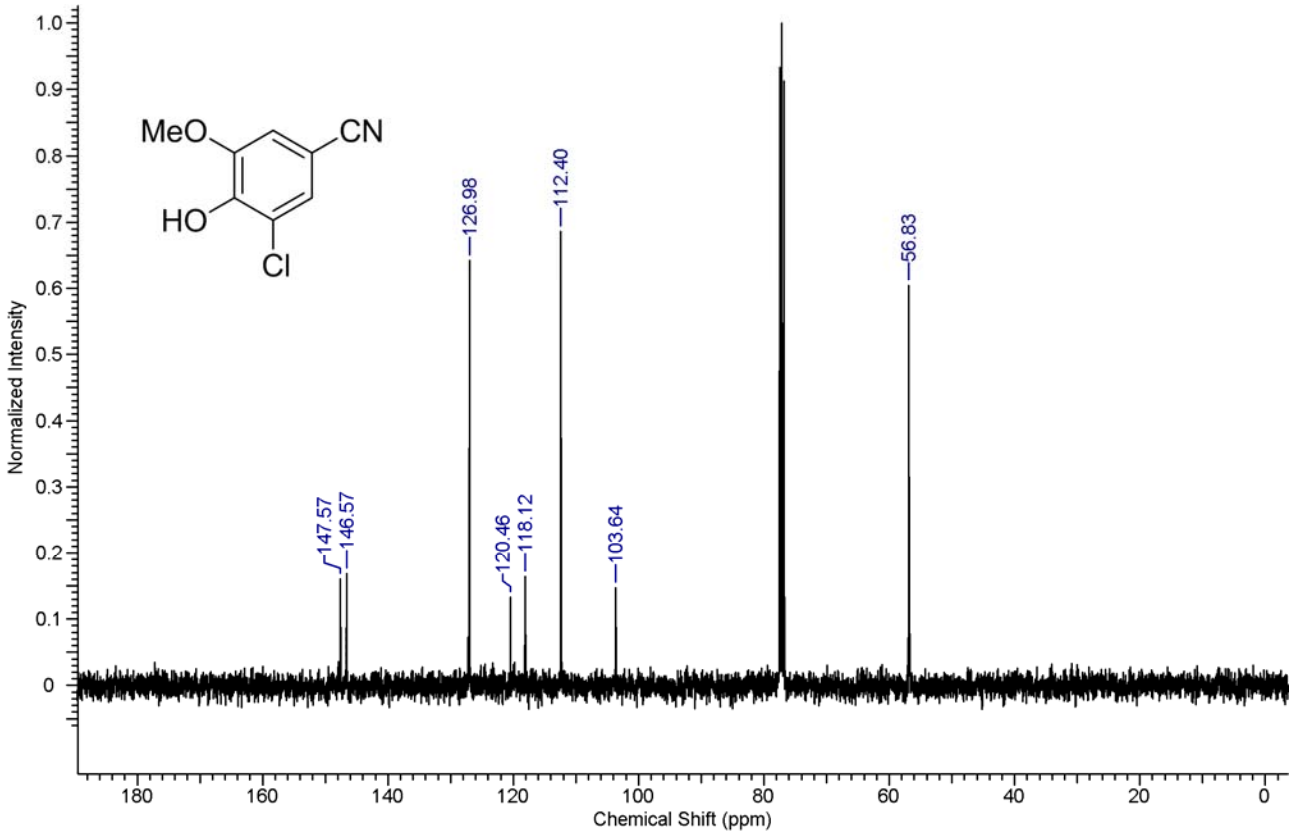


DEPT (135) NMR Spectrum of Compound **2f.**

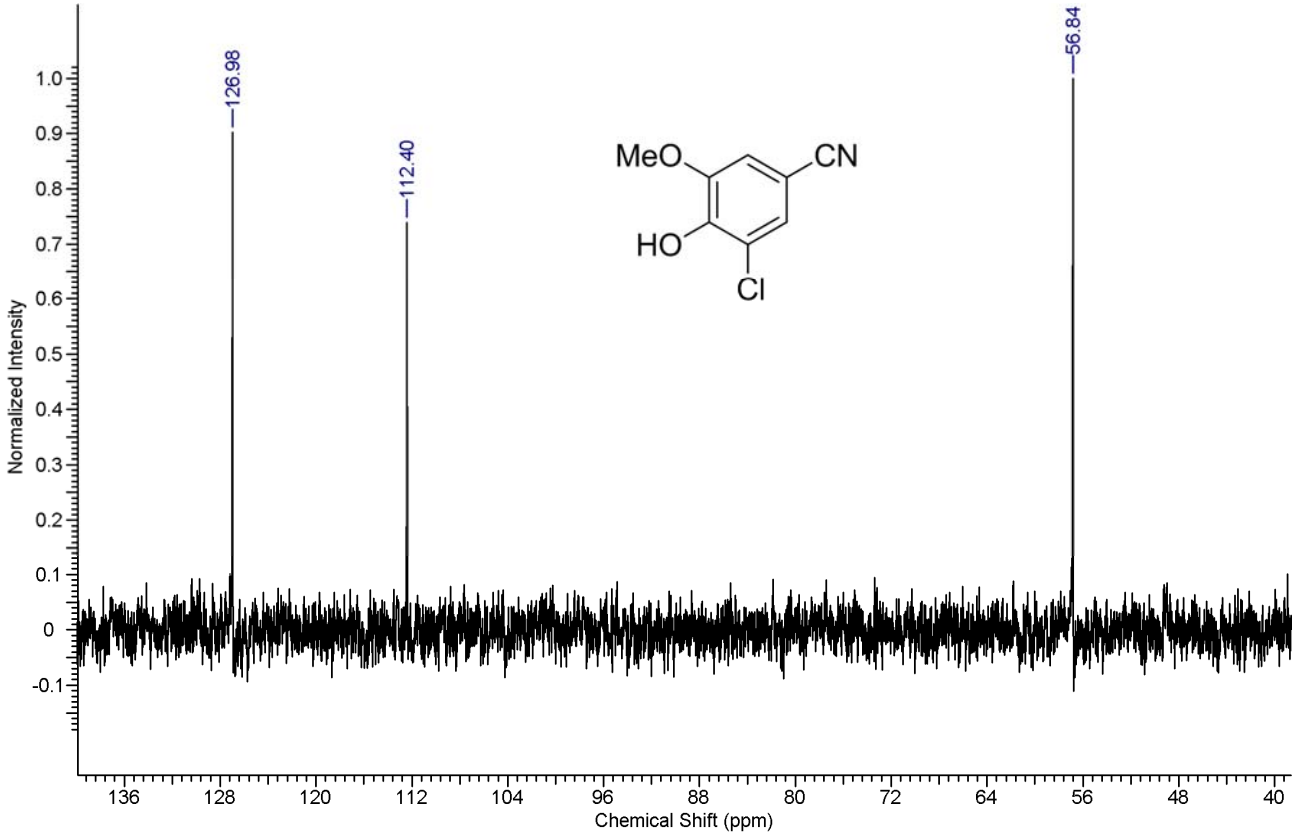


^{1}H and ^{13}C NMR Spectra of Compound **2g.**

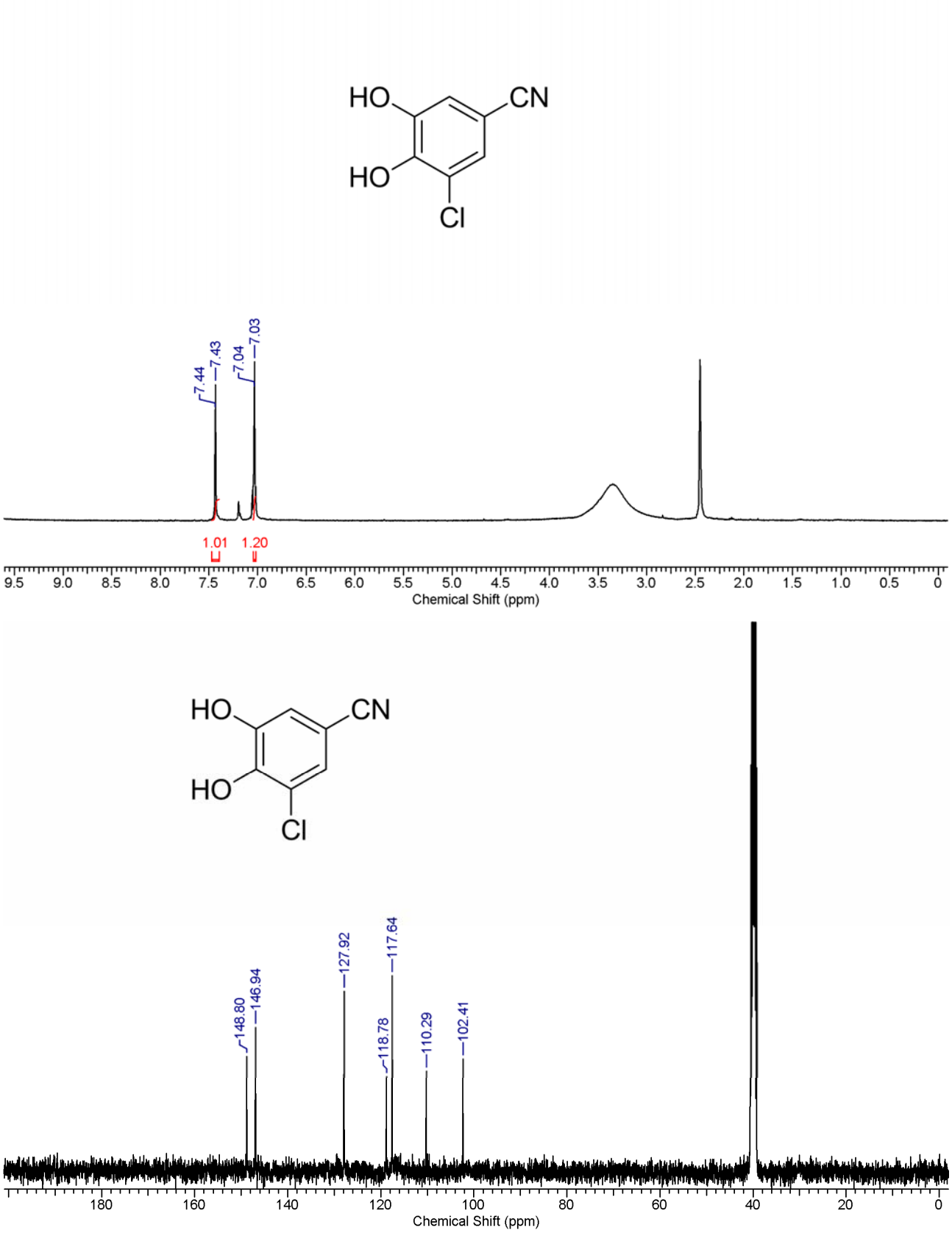




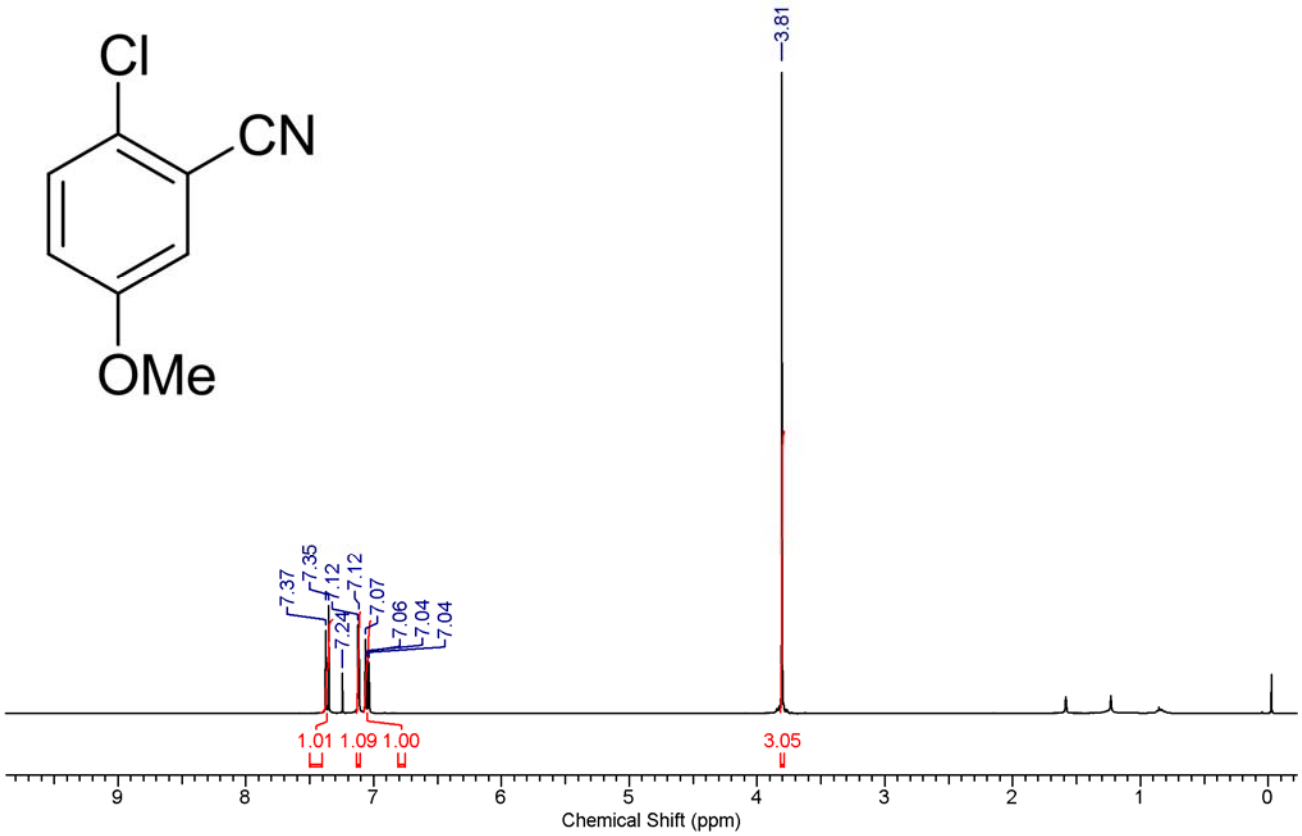
DEPT (135) NMR Spectrum of Compound **2g.**

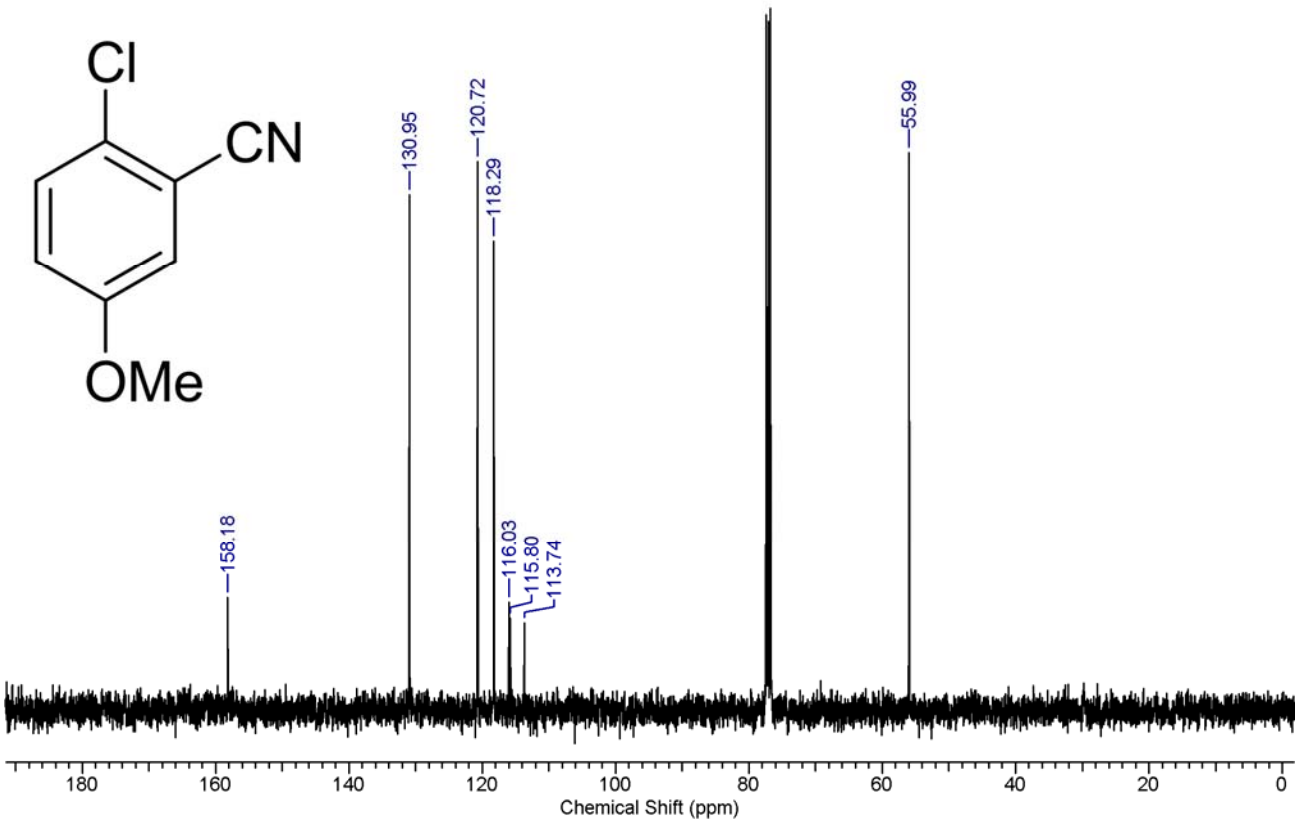


^{1}H and ^{13}C NMR Spectra of Compound **2h** (*d*-DMSO solvent was used).

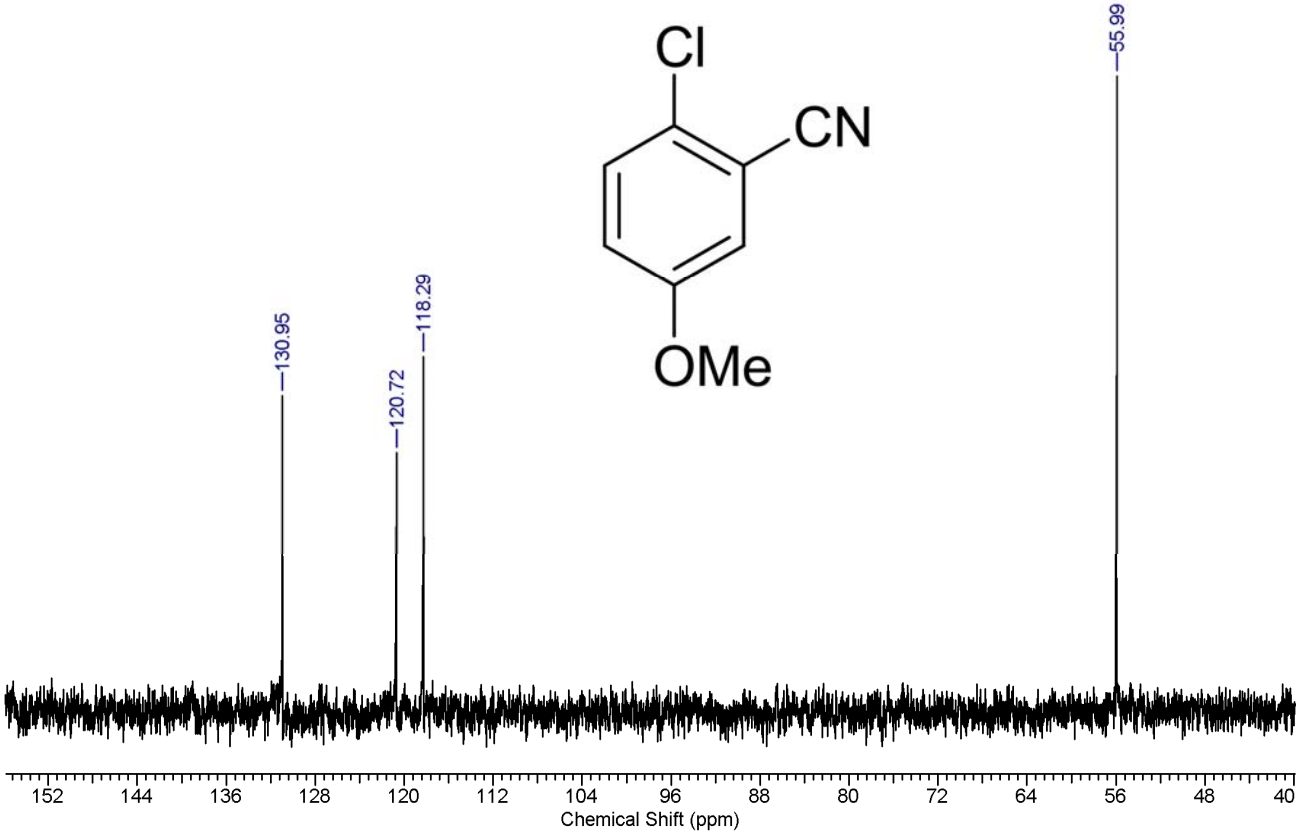


^{1}H and ^{13}C NMR Spectra of Compound **2i.**

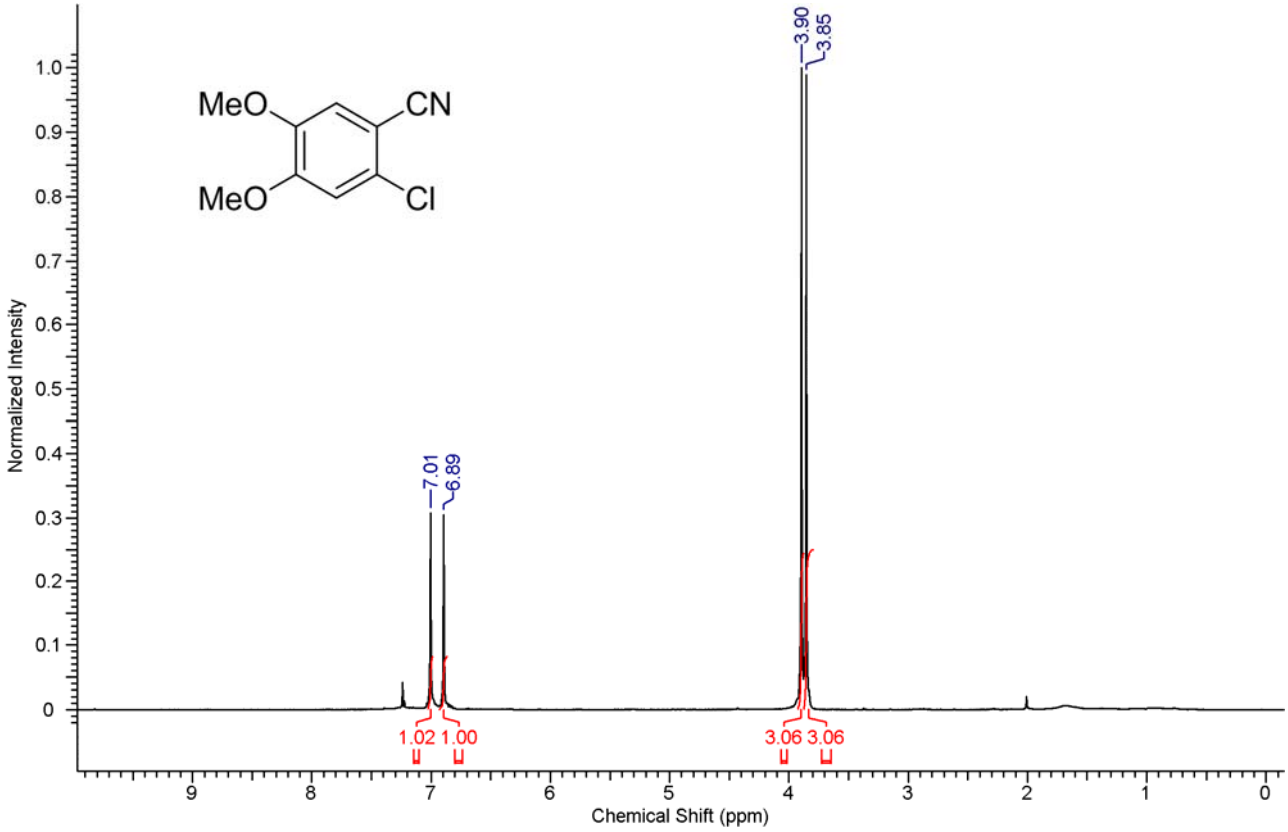


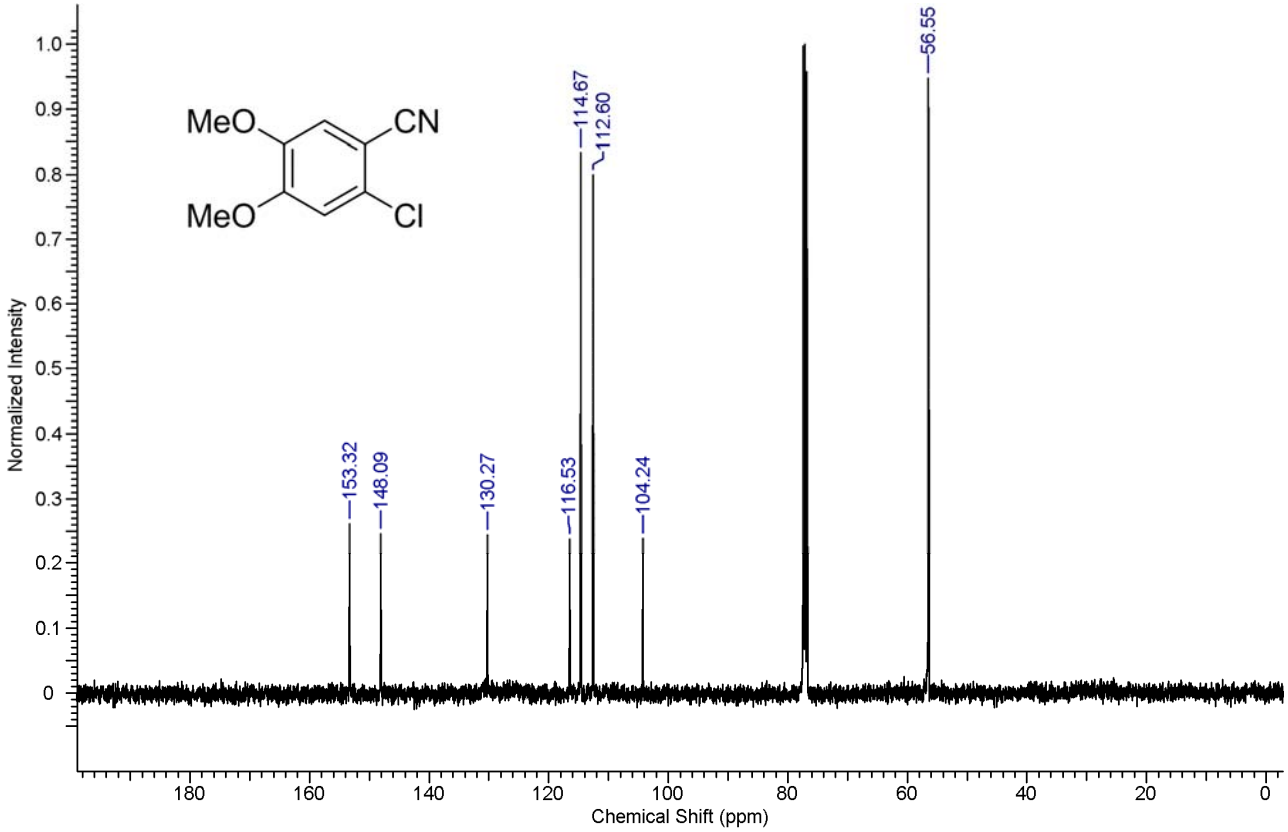


DEPT (135) NMR Spectrum of Compound **2i.**

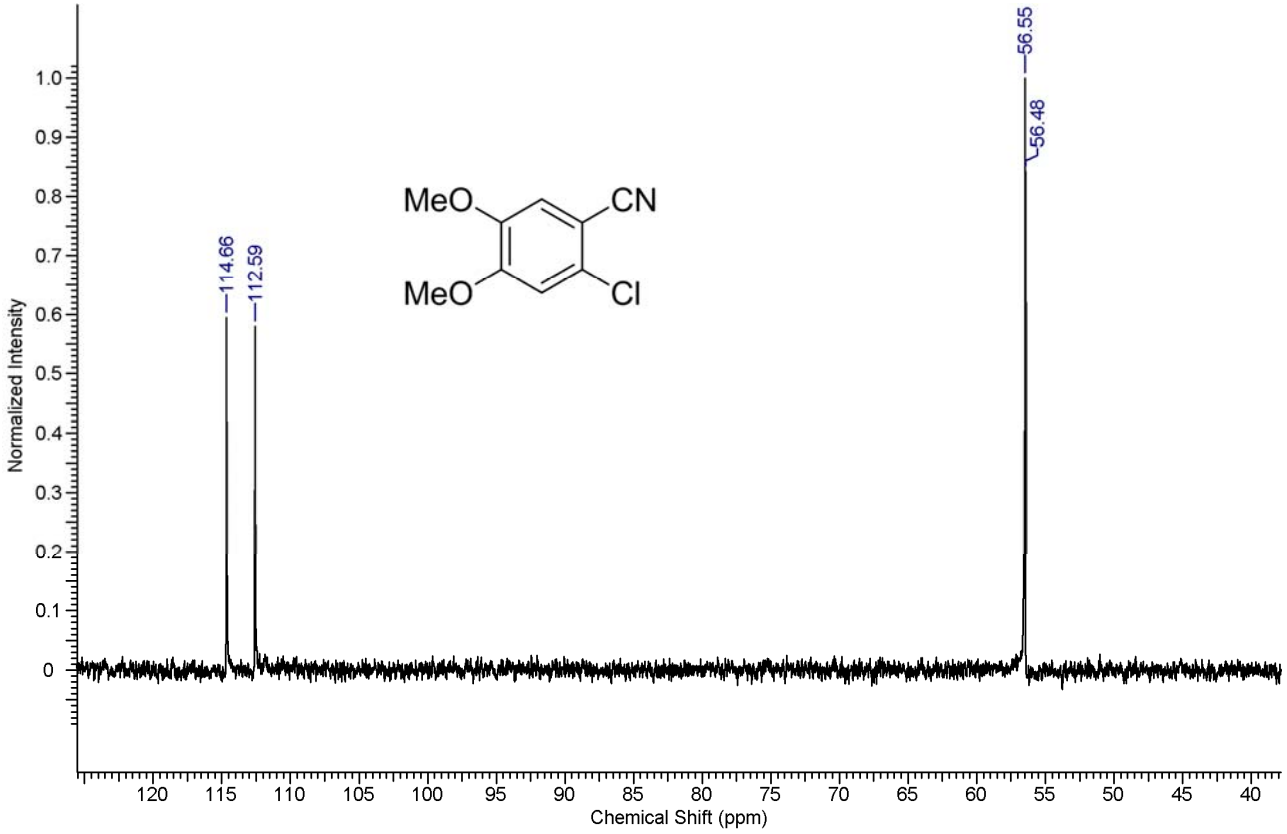


^{1}H and ^{13}C NMR Spectra of Compound **2j.**

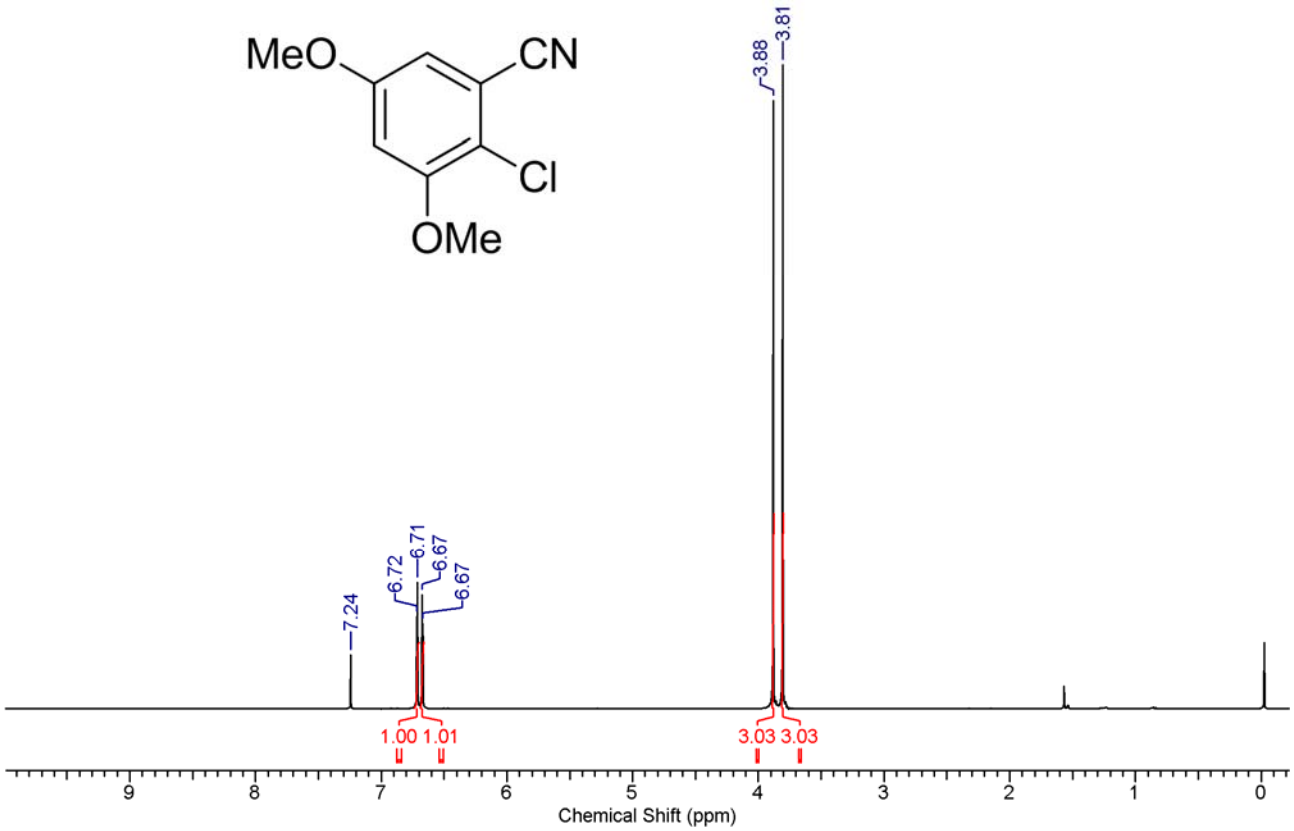


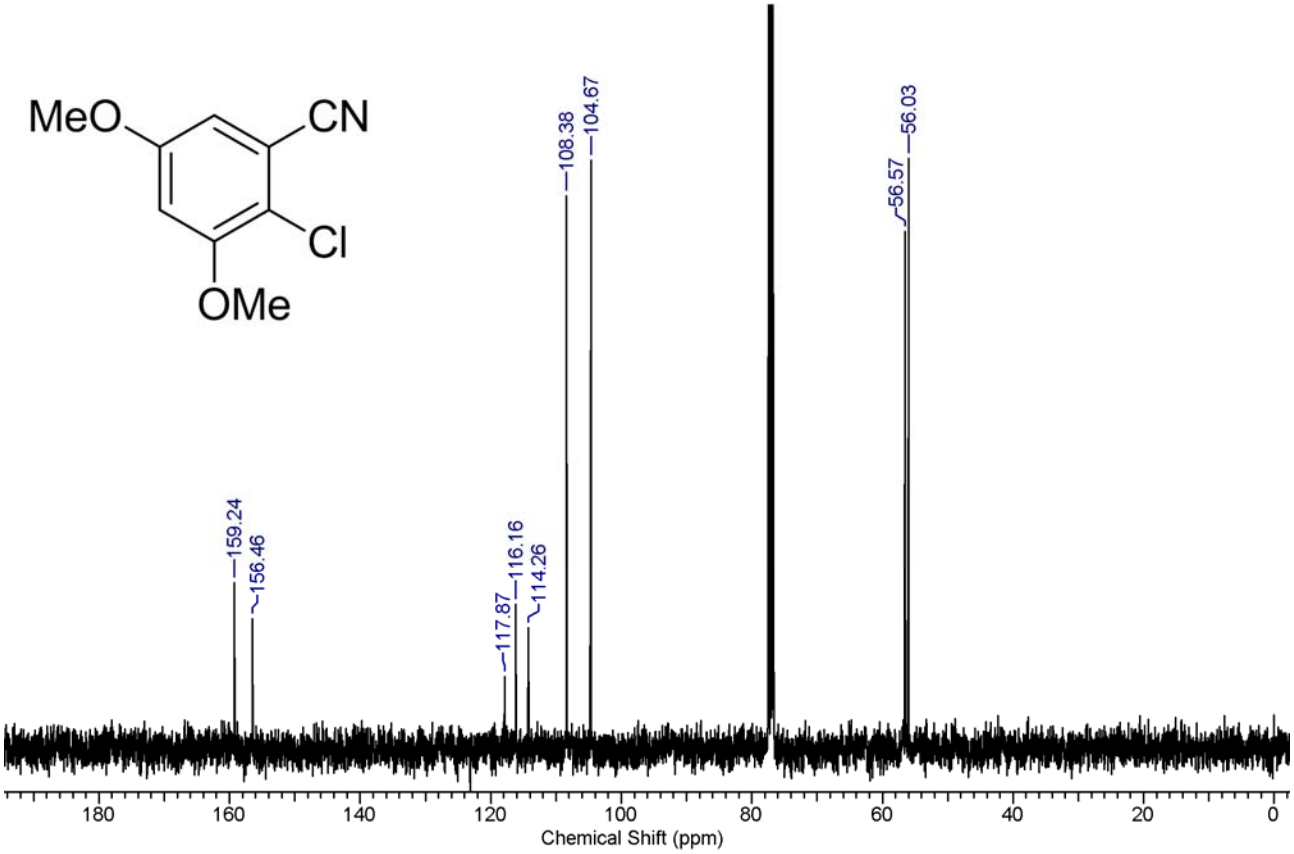


DEPT (135) NMR Spectrum of Compound **2j.**

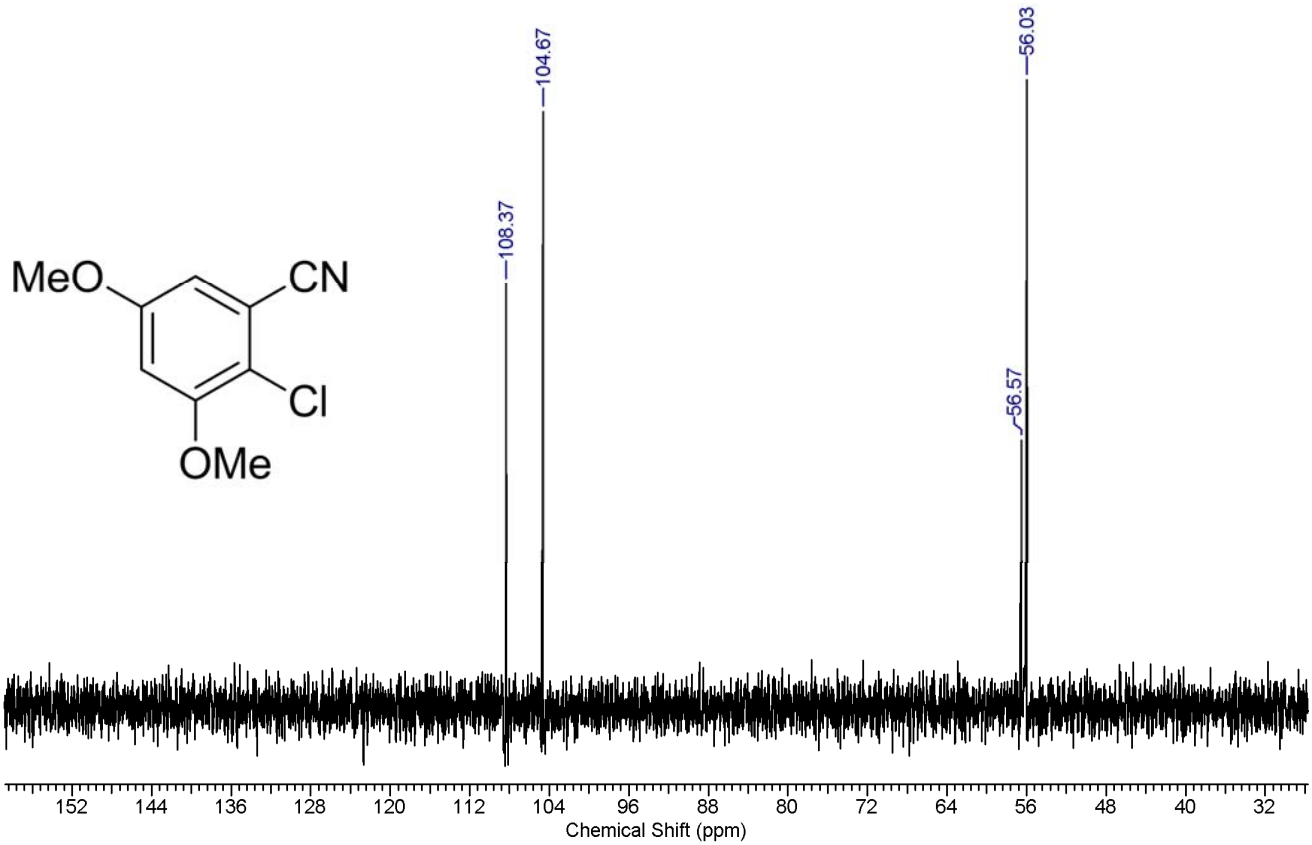


^{1}H and ^{13}C NMR Spectra of Compound **2k.**

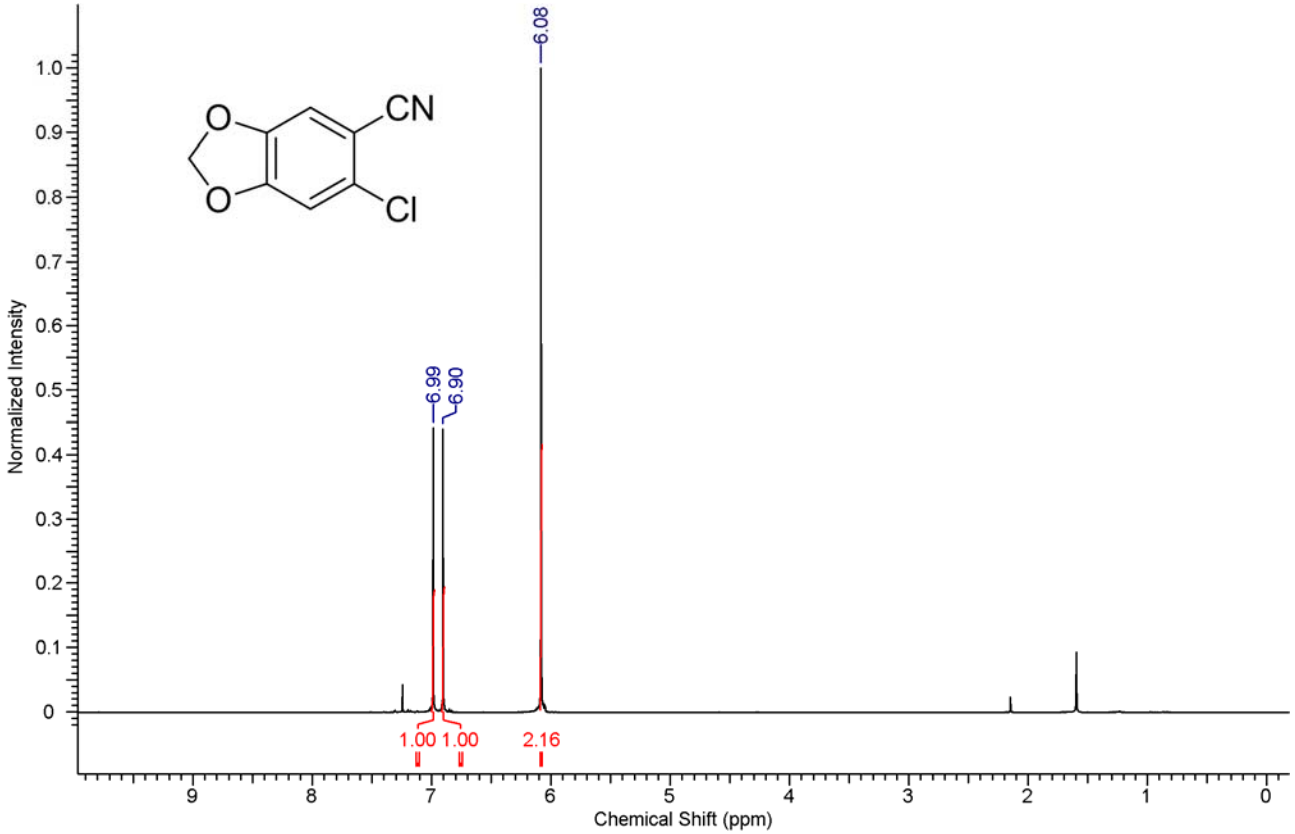


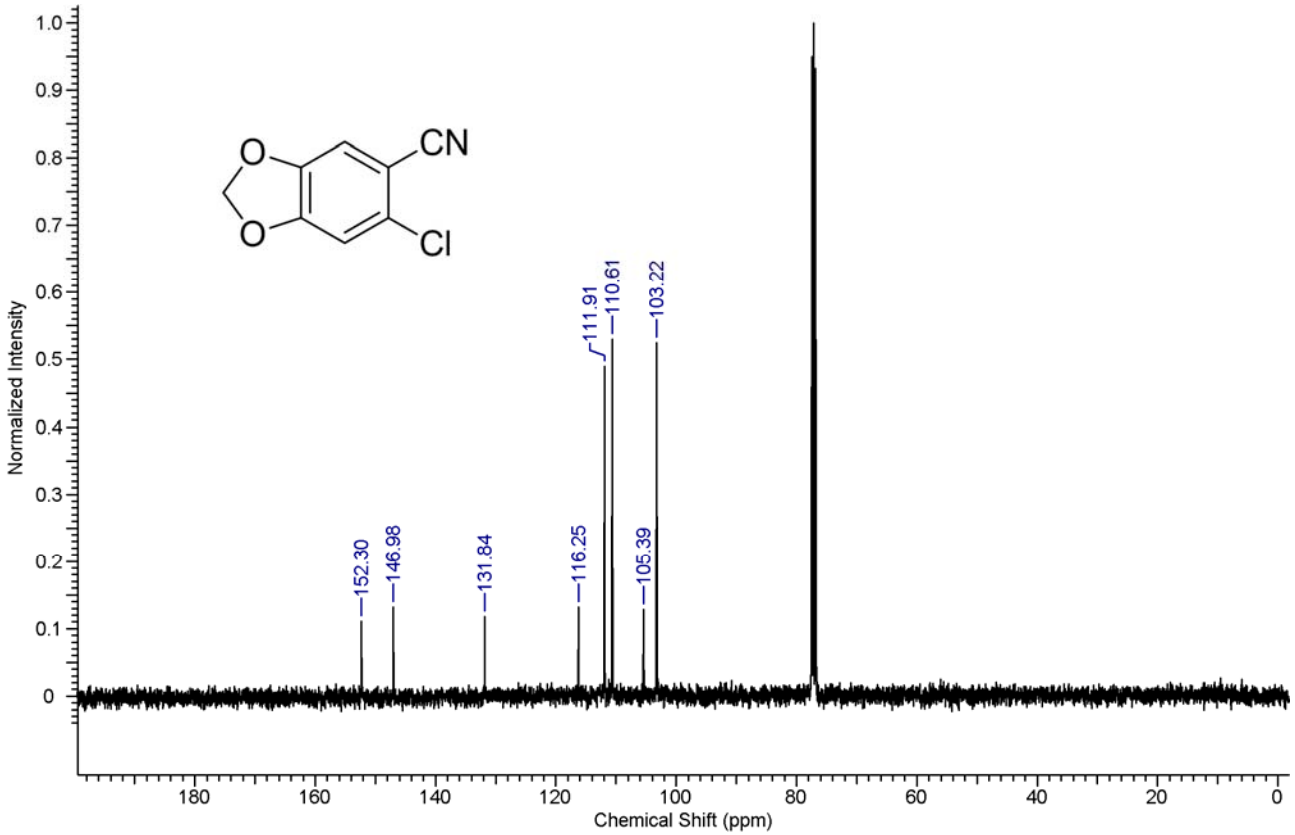


DEPT (135) NMR Spectrum of Compound **2k.**

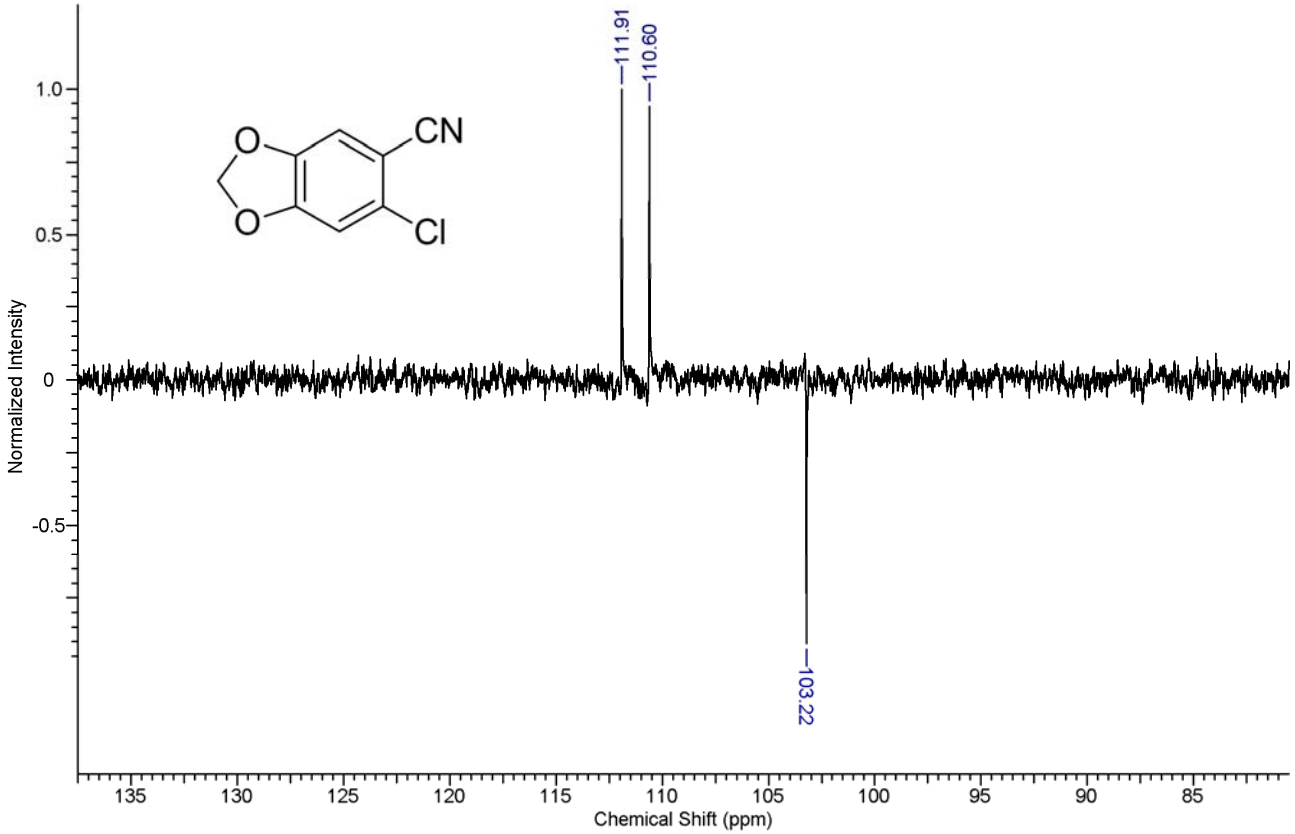


^{1}H and ^{13}C NMR Spectra of Compound **2l.**

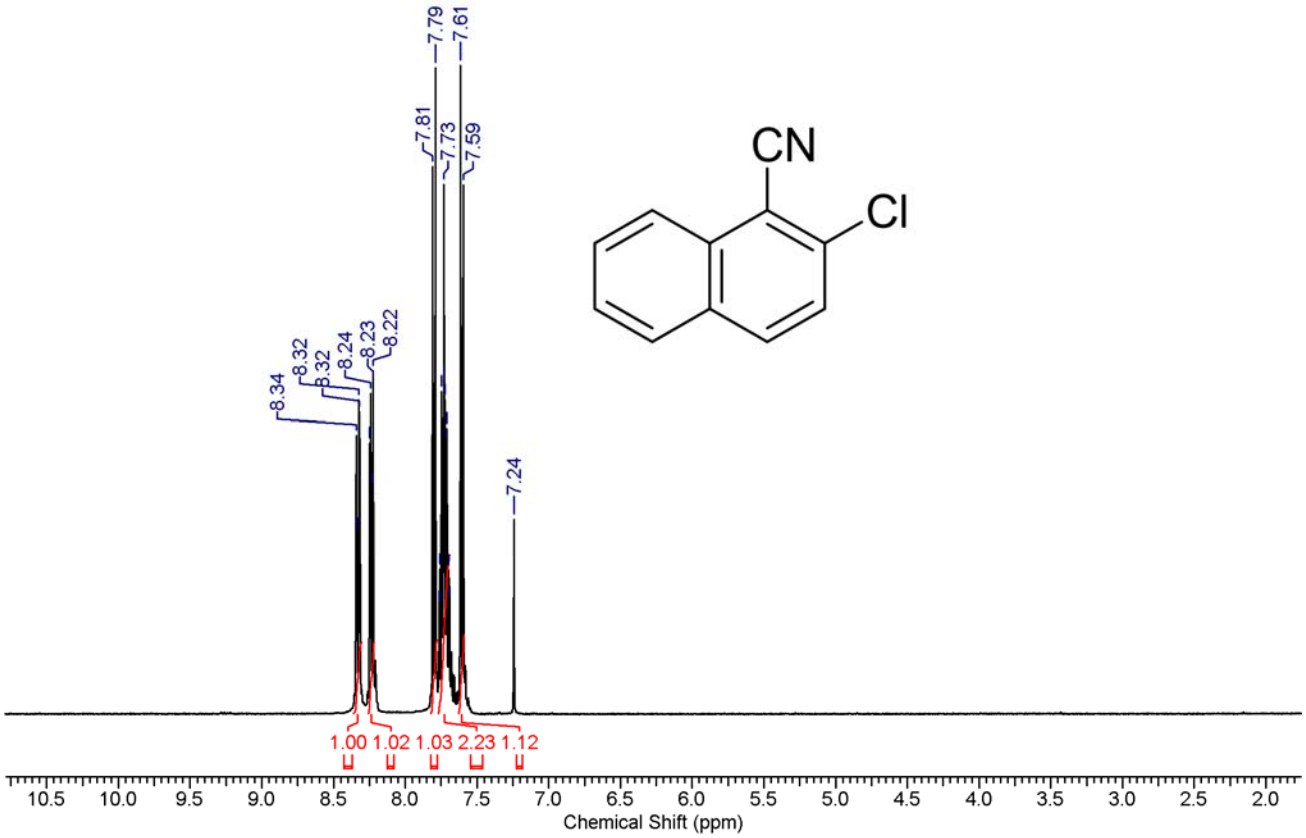


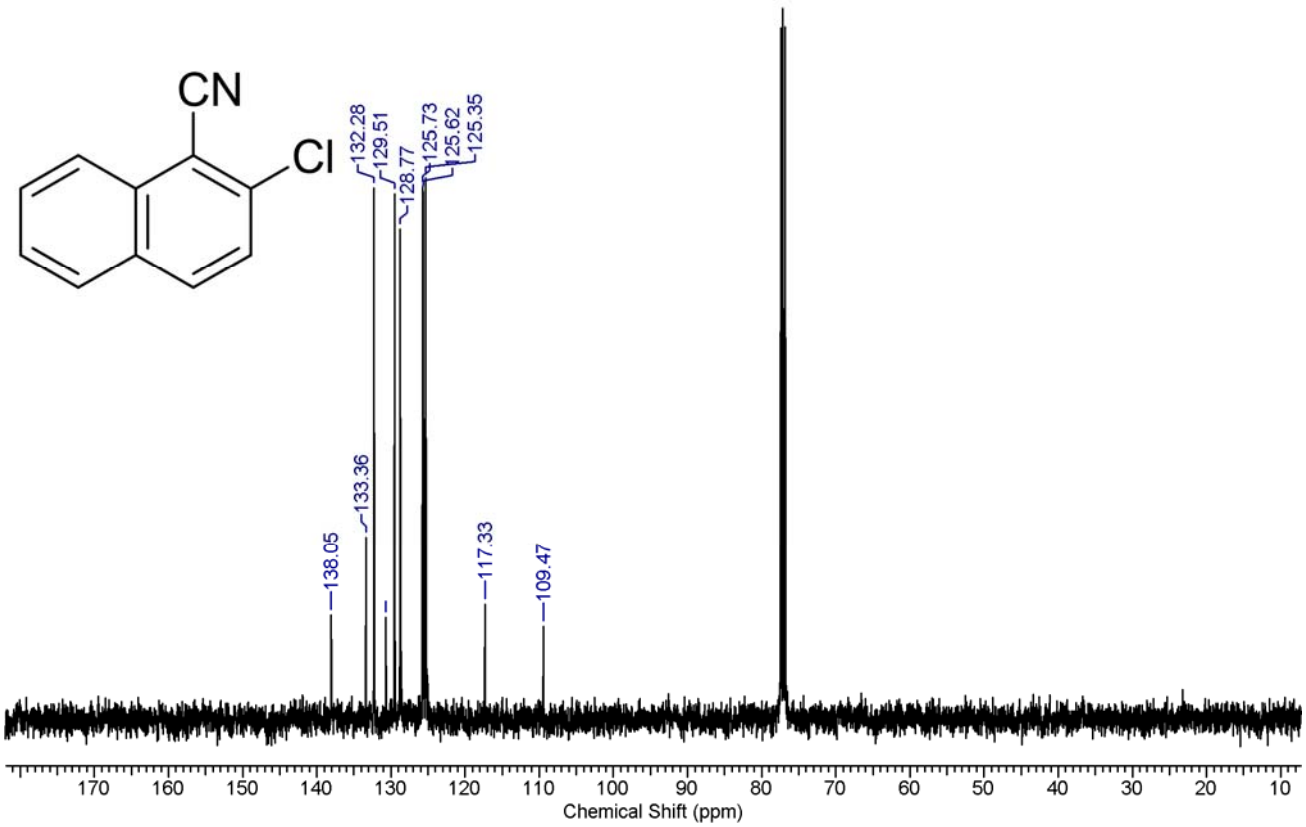


DEPT (135) NMR Spectrum of Compound **2l.**

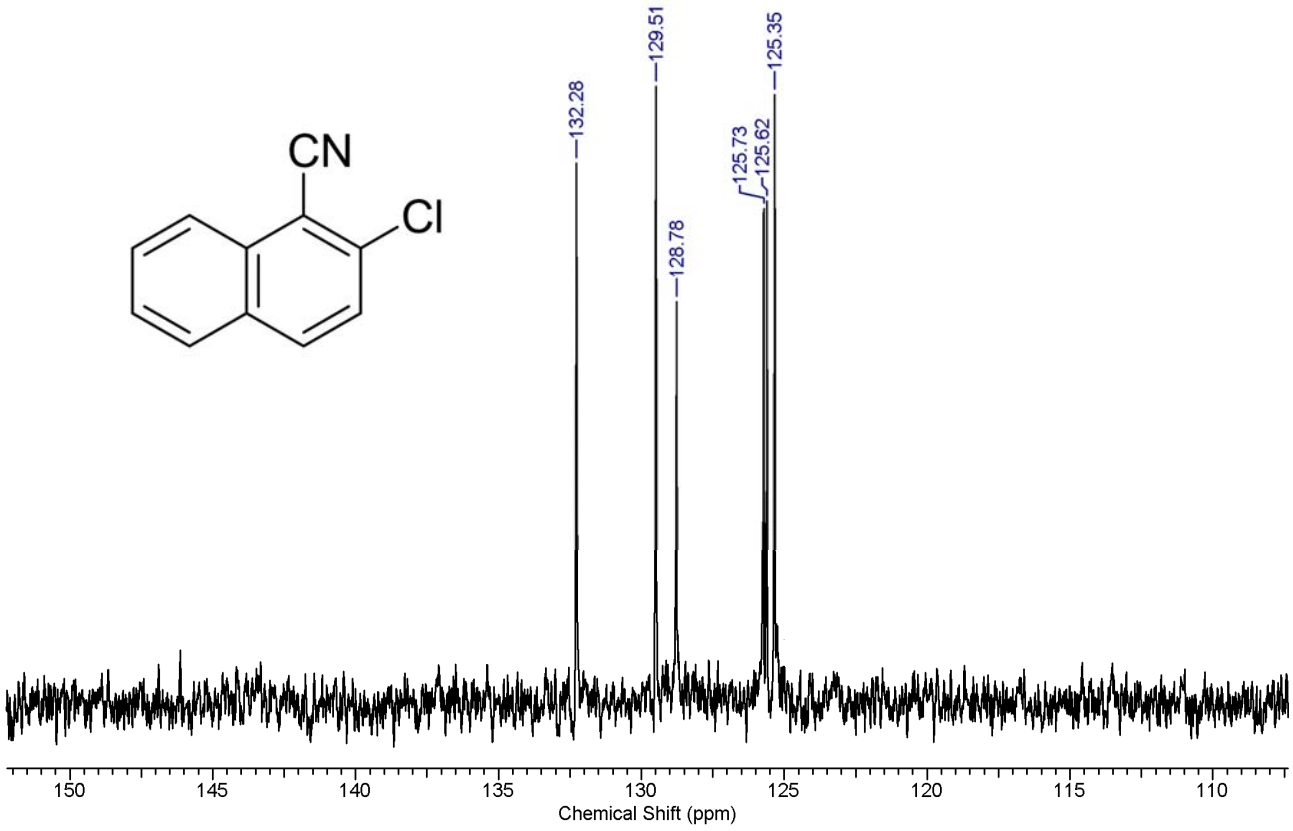


^{1}H and ^{13}C NMR Spectra of Compound **2m.**

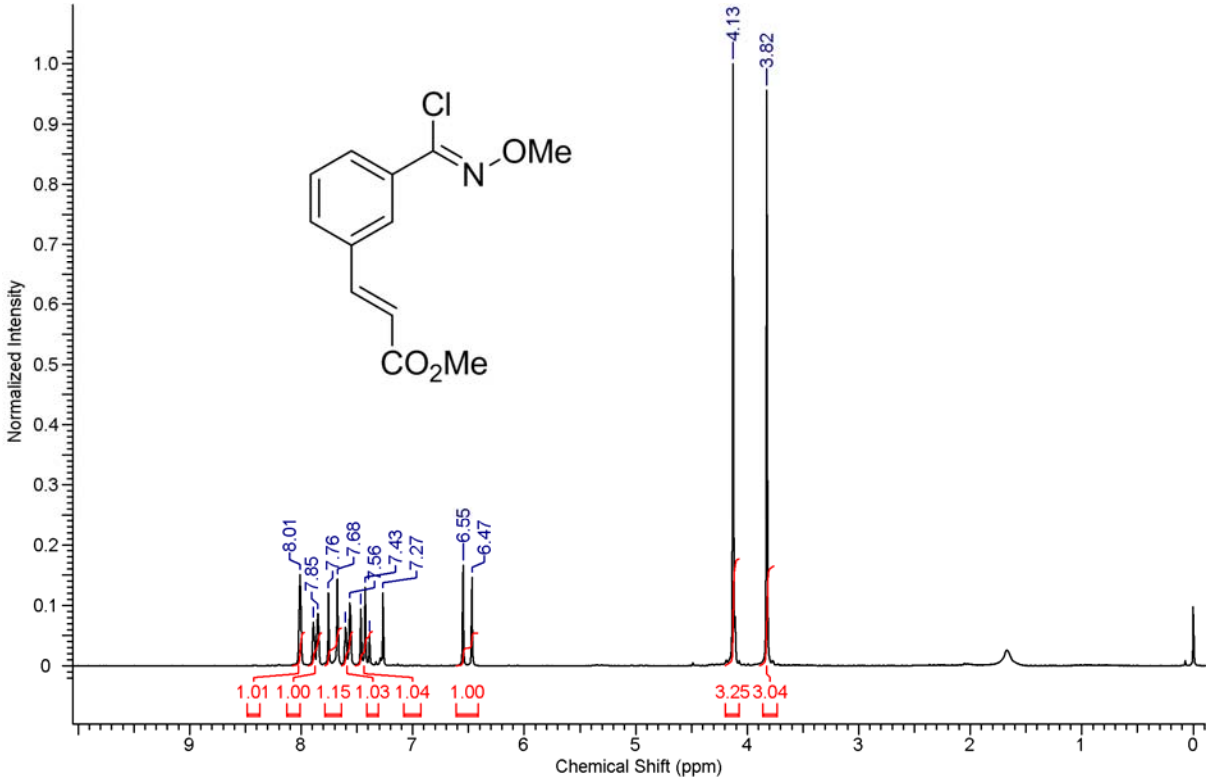


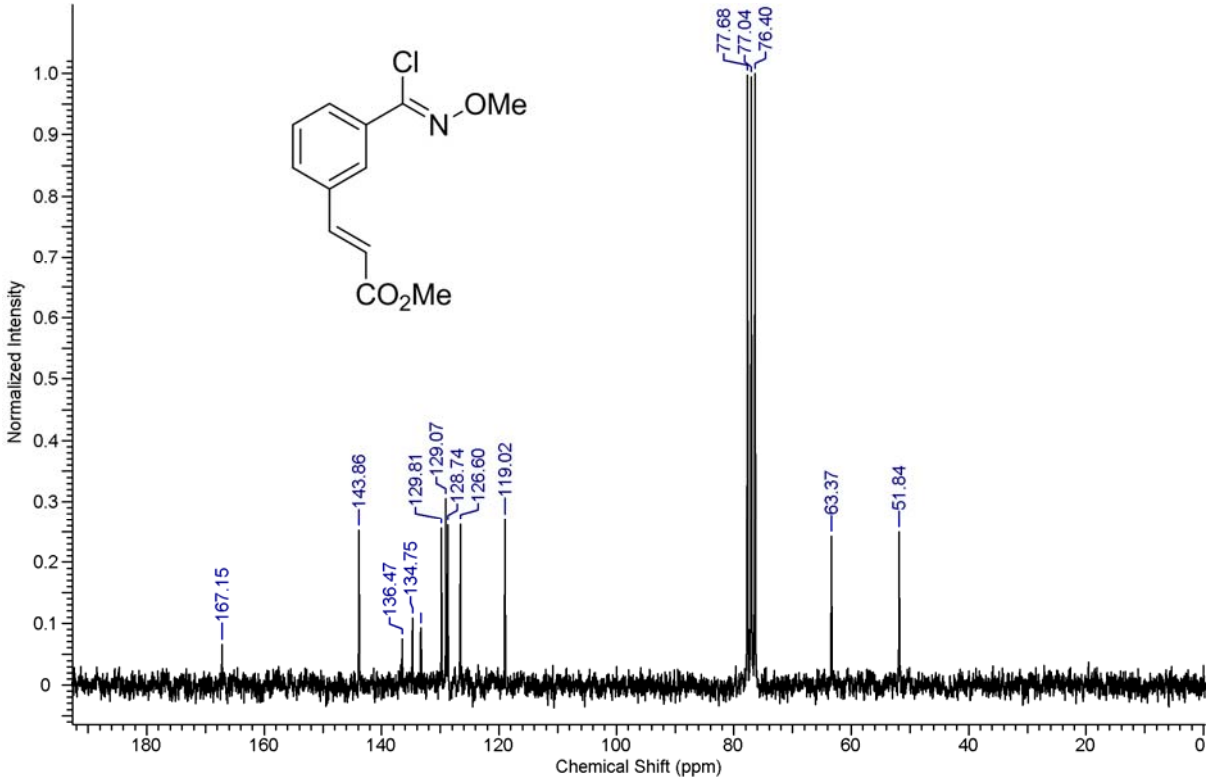


DEPT (135) NMR Spectrum of Compound **2m.**

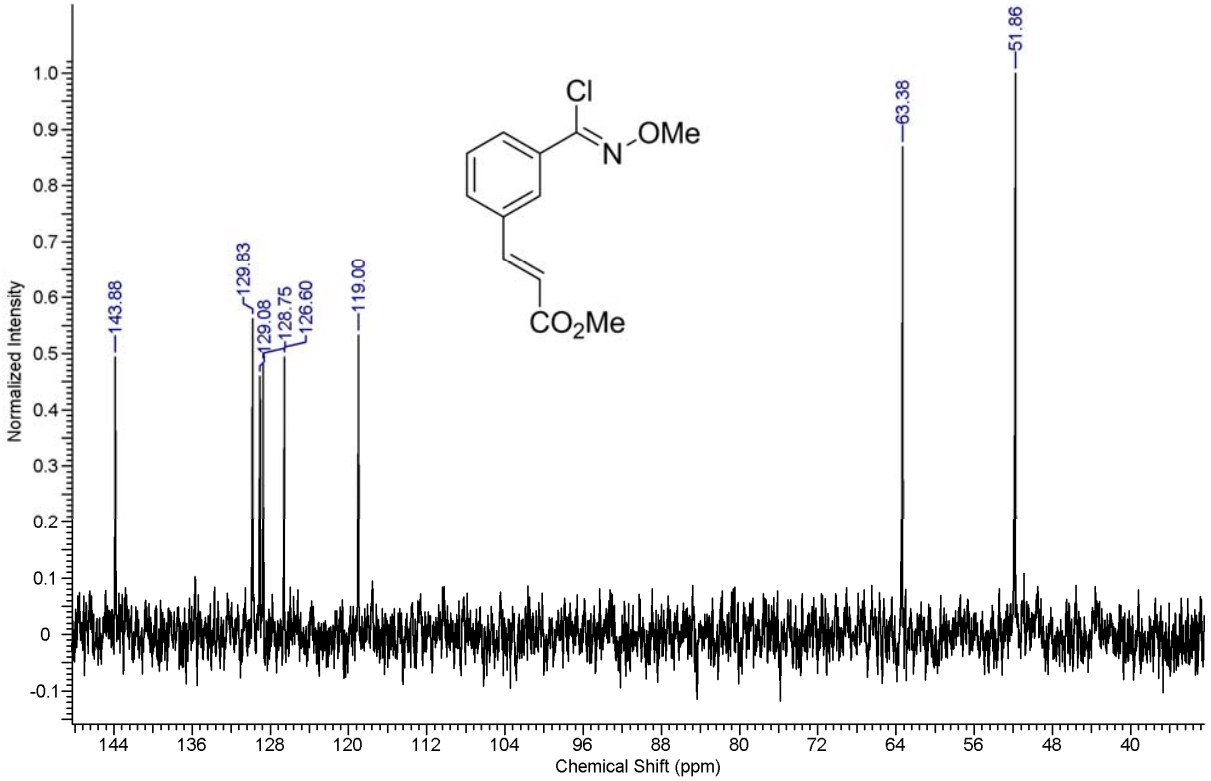


^{1}H and ^{13}C NMR Spectra of Compound **2n.**

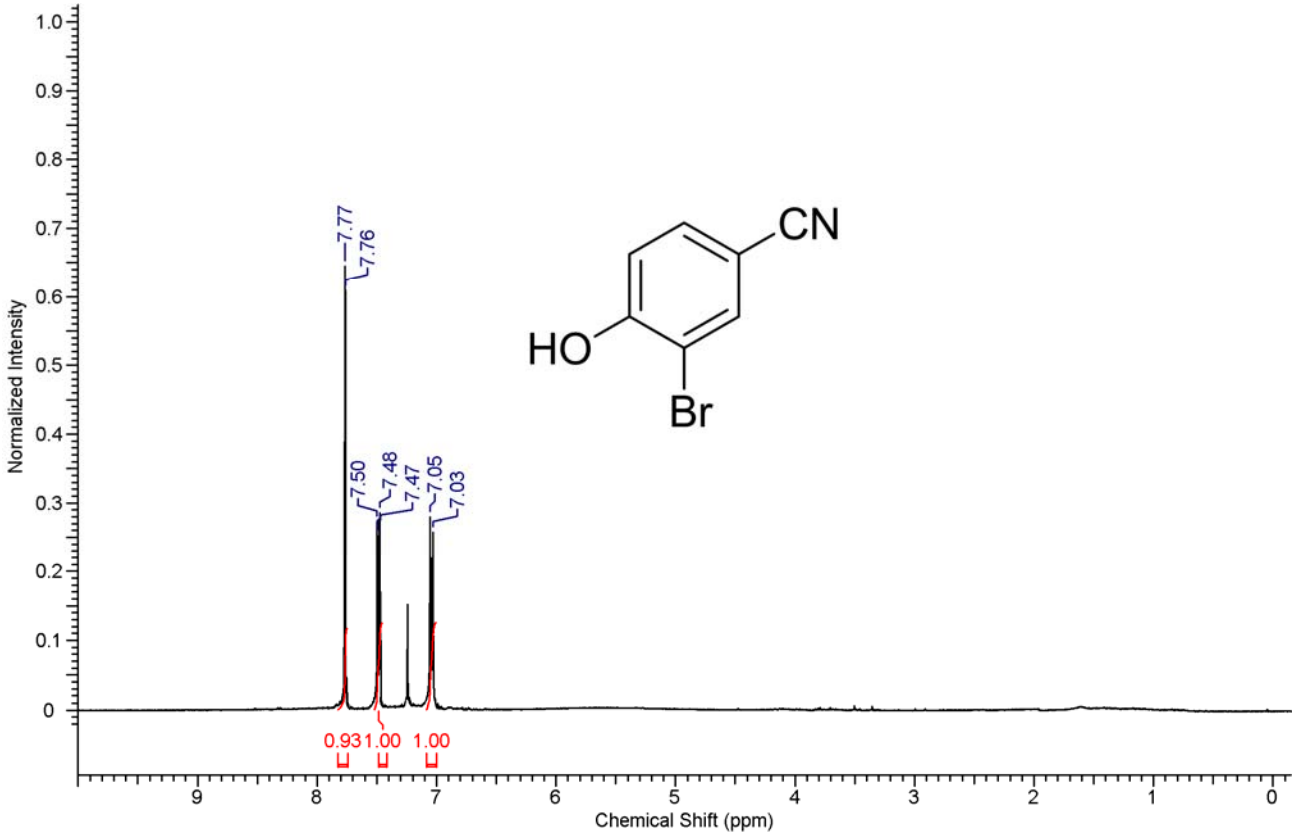


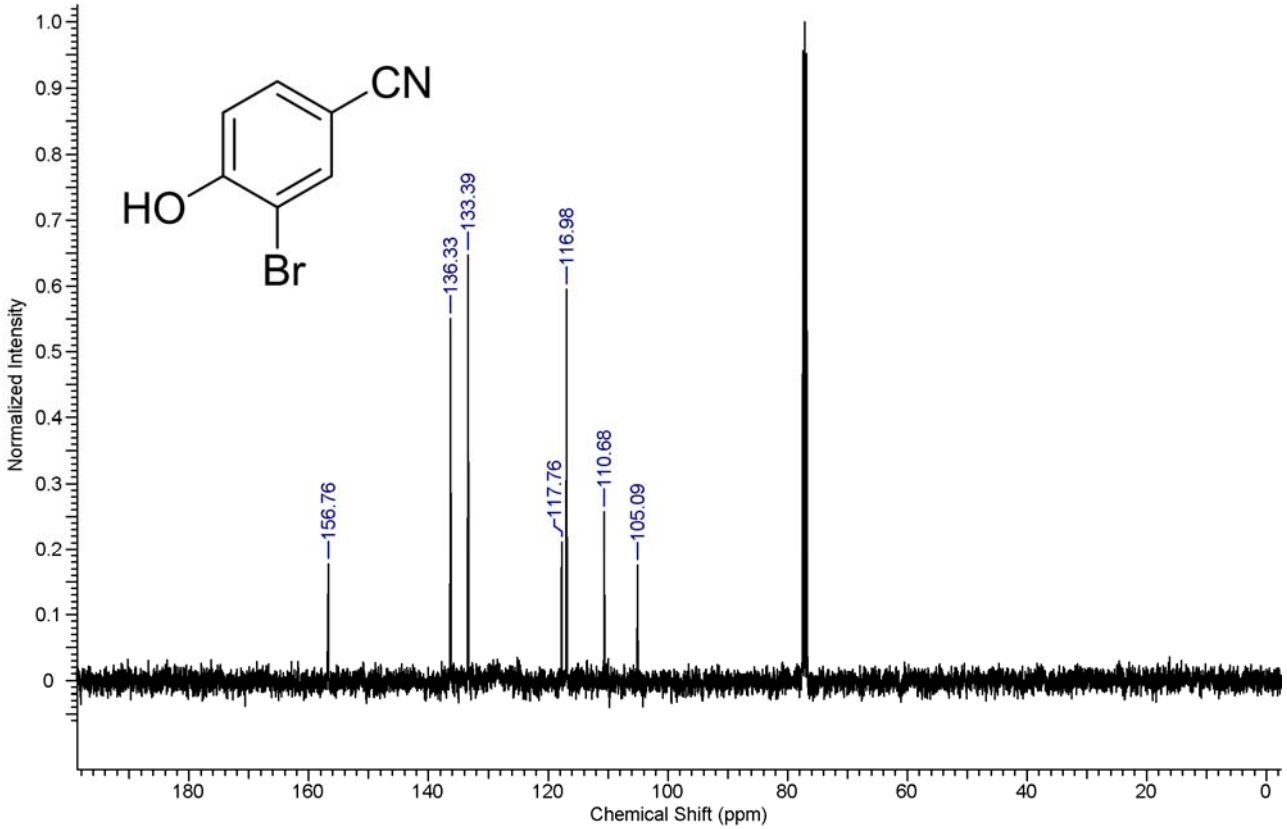


DEPT (135) NMR Spectrum of Compound **2n.**

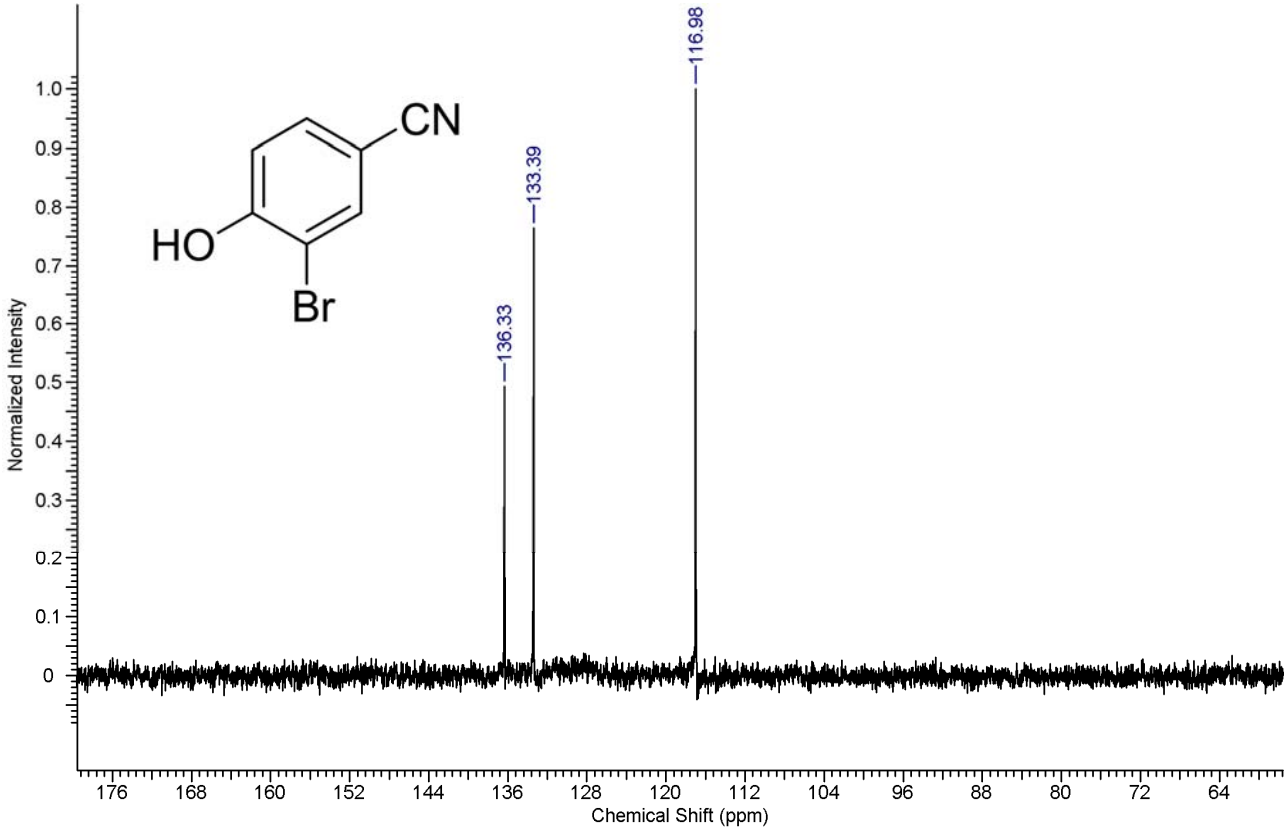


^{1}H and ^{13}C NMR Spectra of Compound **4a.**

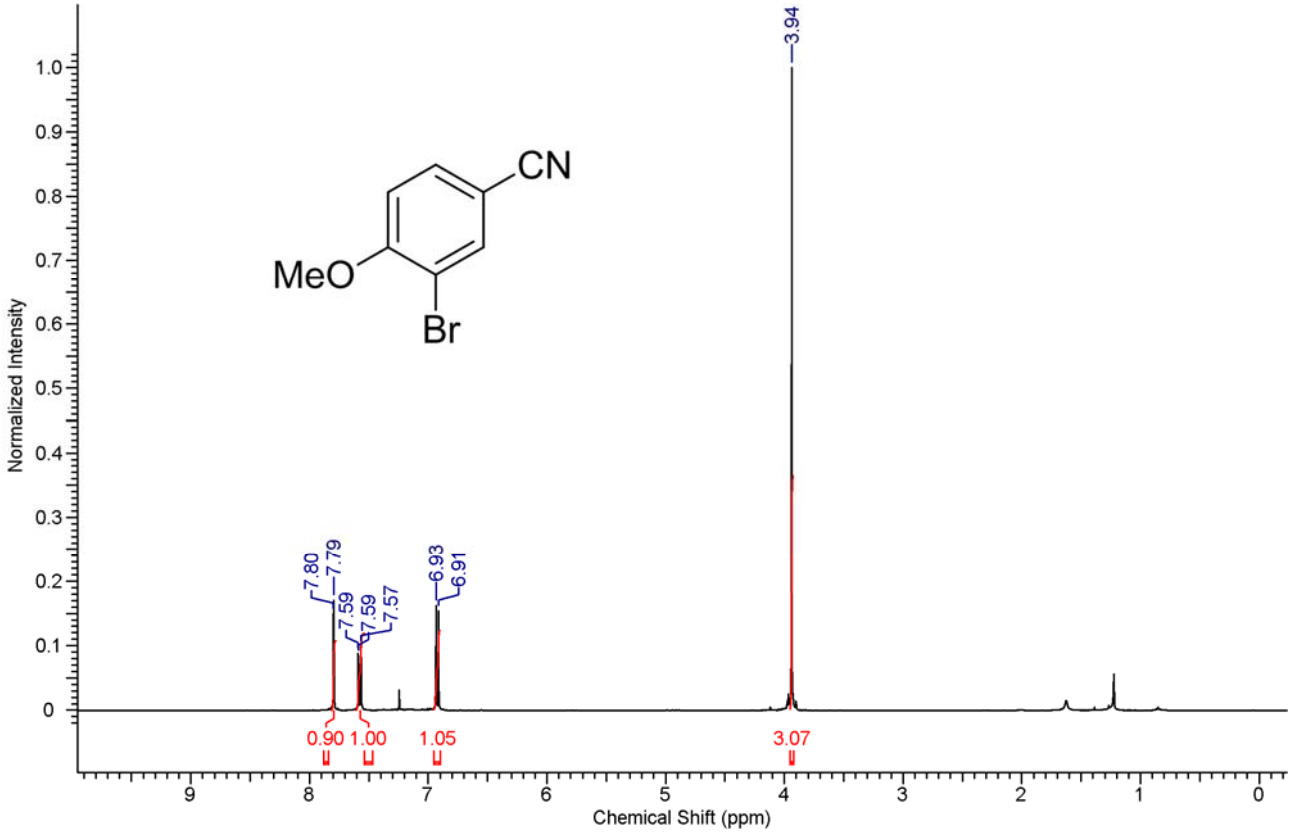


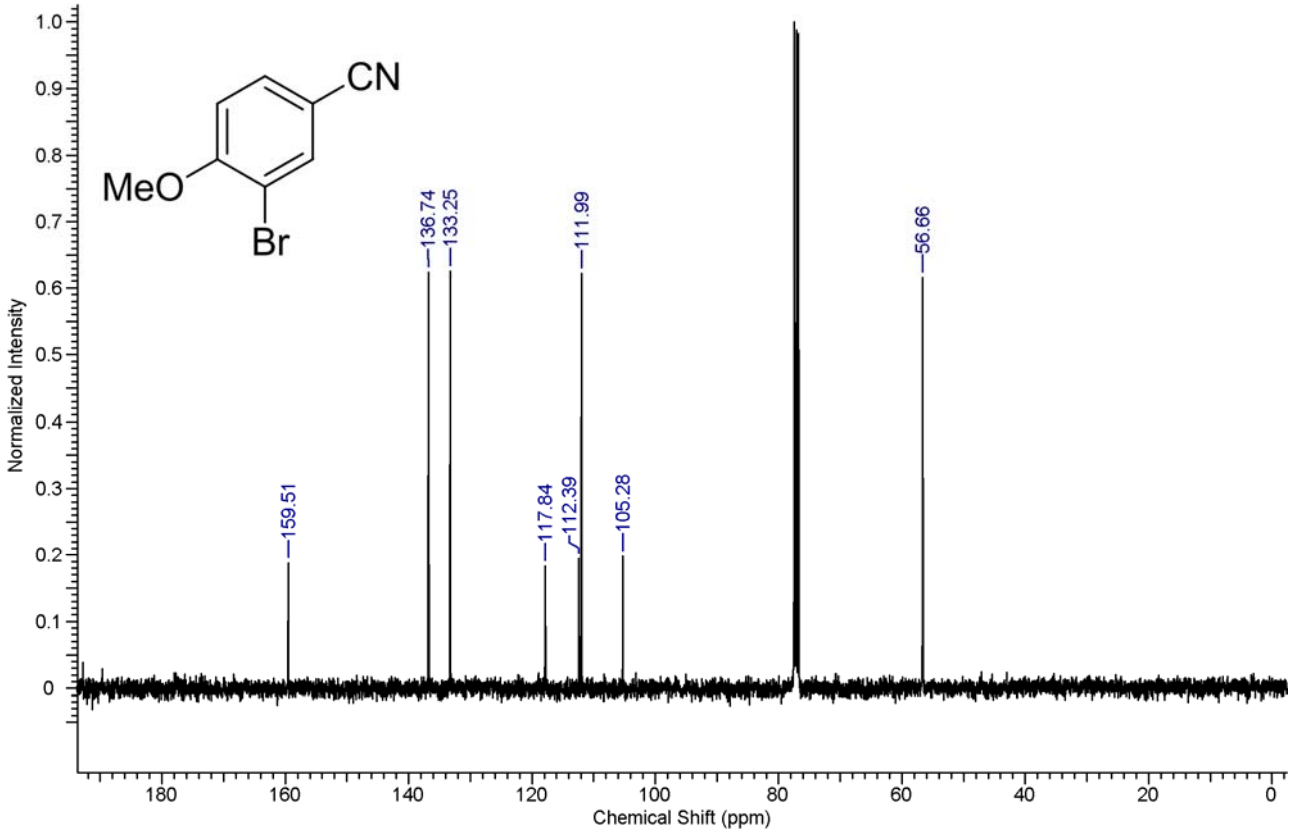


DEPT (135) NMR Spectrum of Compound **4a.**

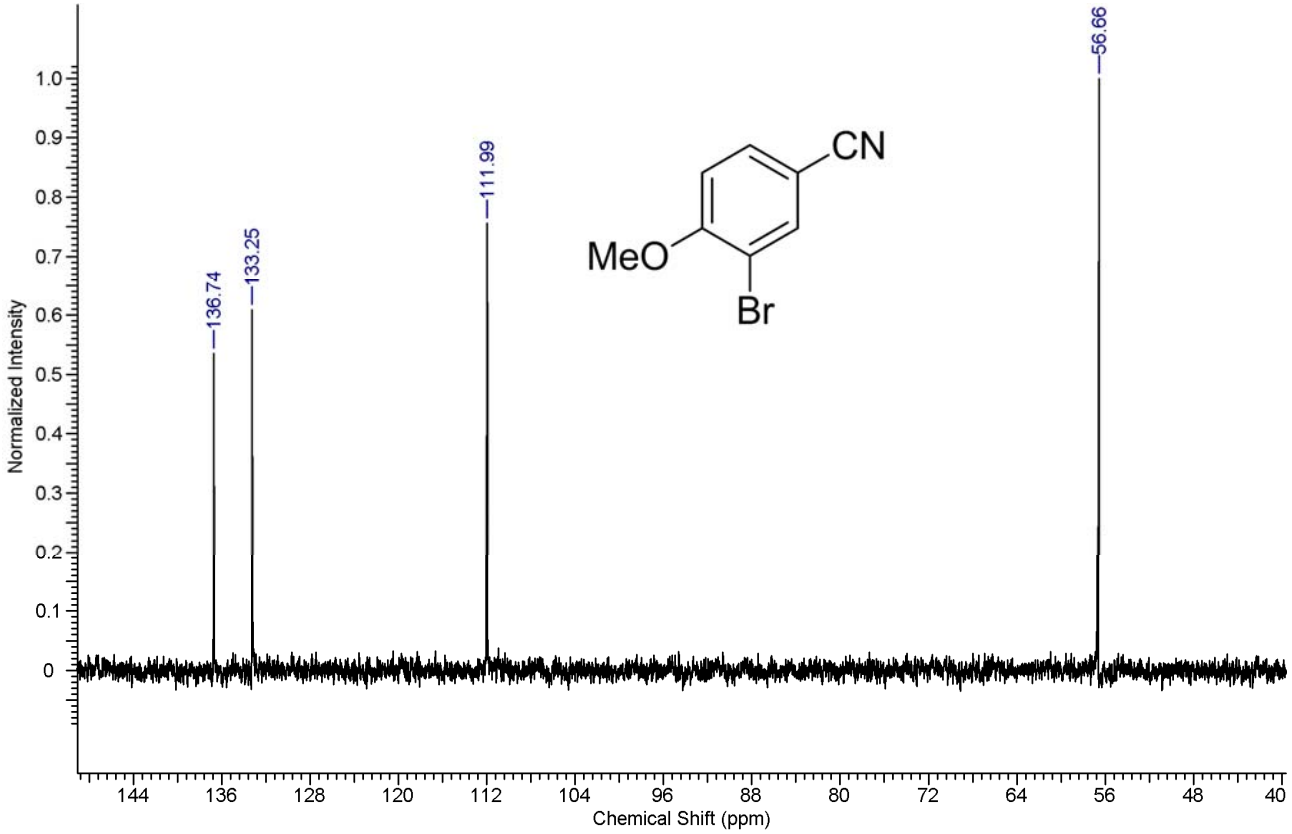


^{1}H and ^{13}C NMR Spectra of Compound **4b.**

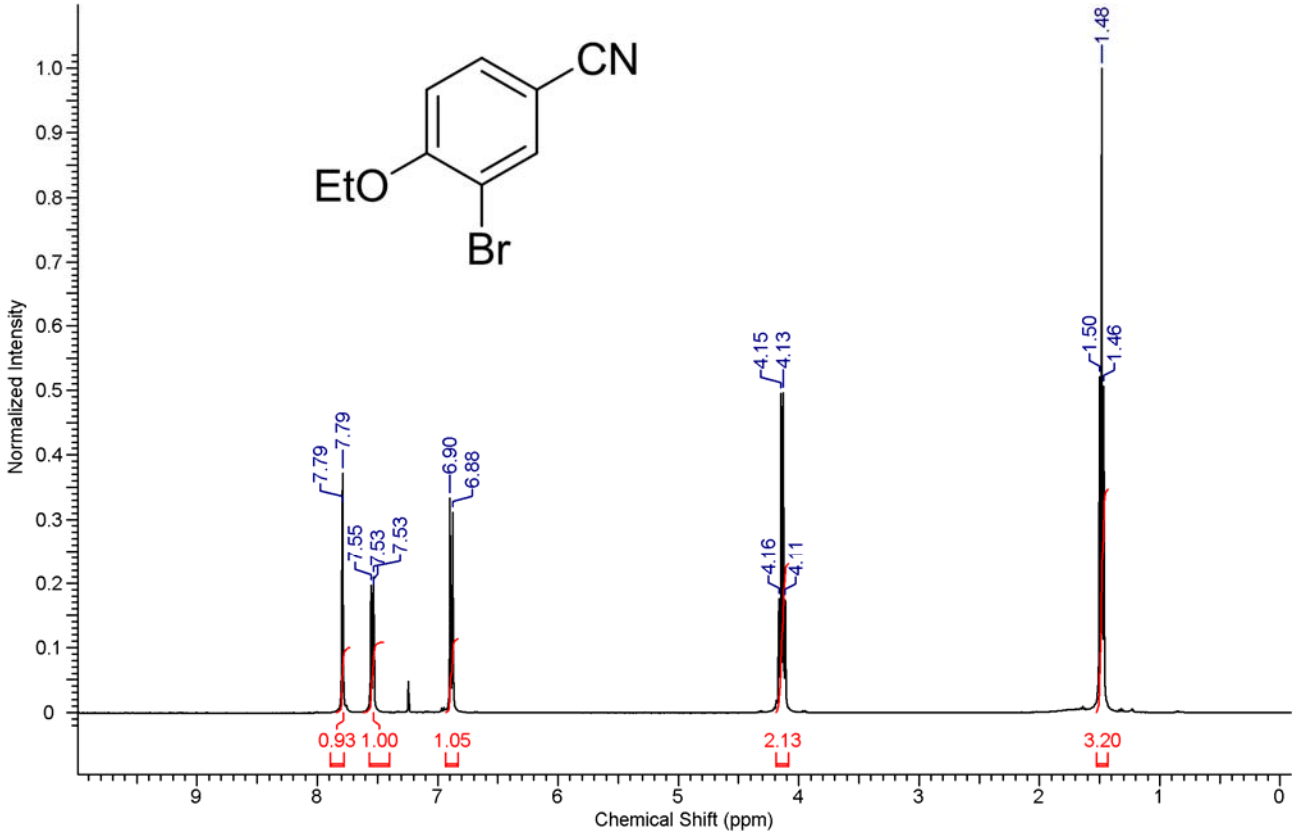


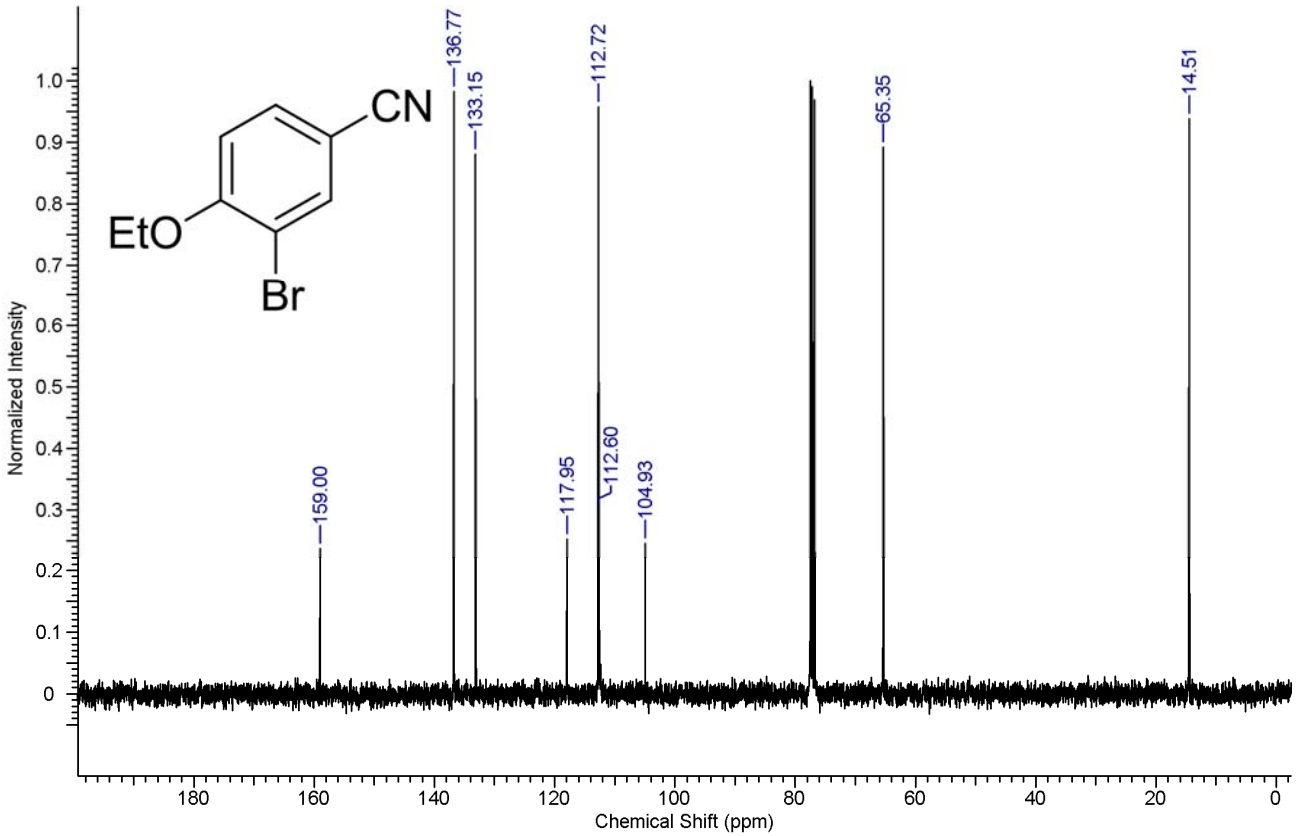


DEPT (135) NMR Spectrum of Compound **4b.**

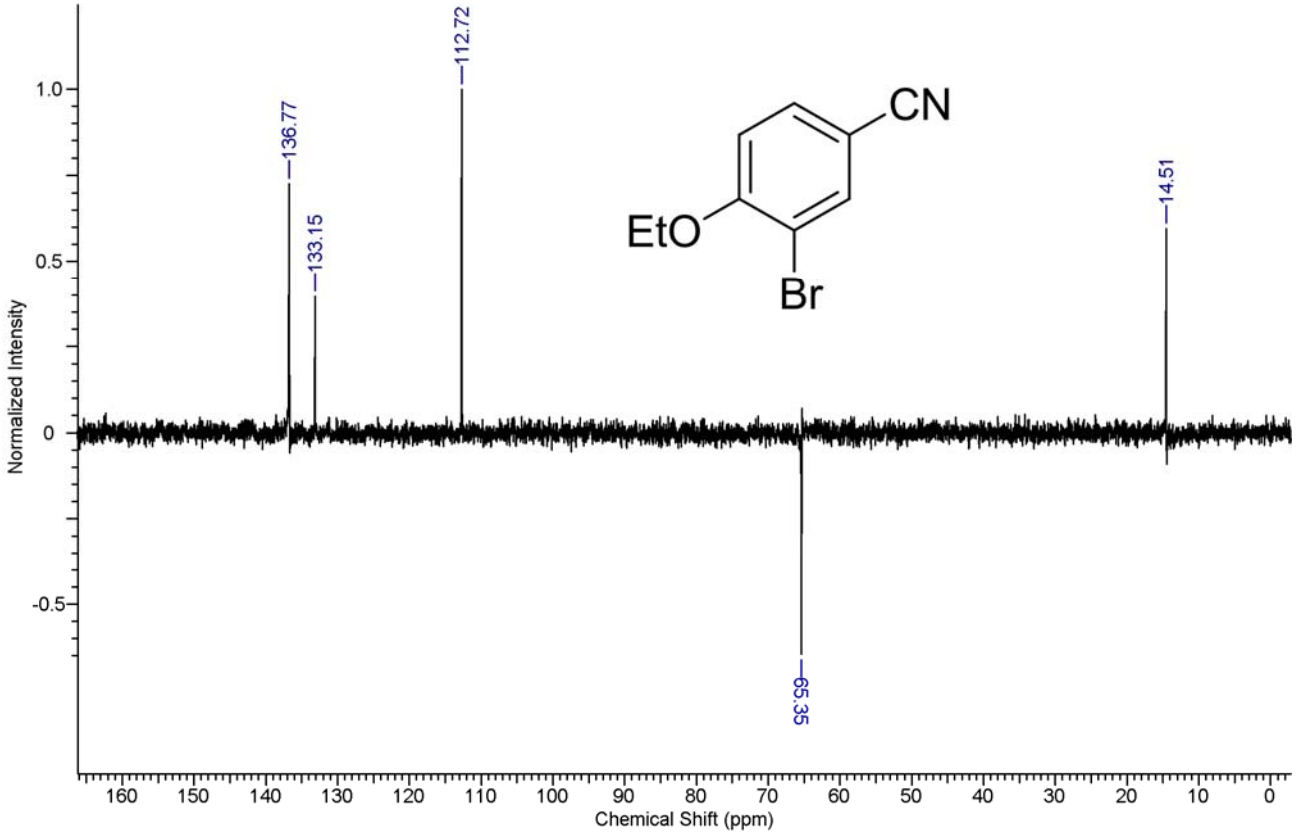


^{1}H and ^{13}C NMR Spectra of Compound **4c.**

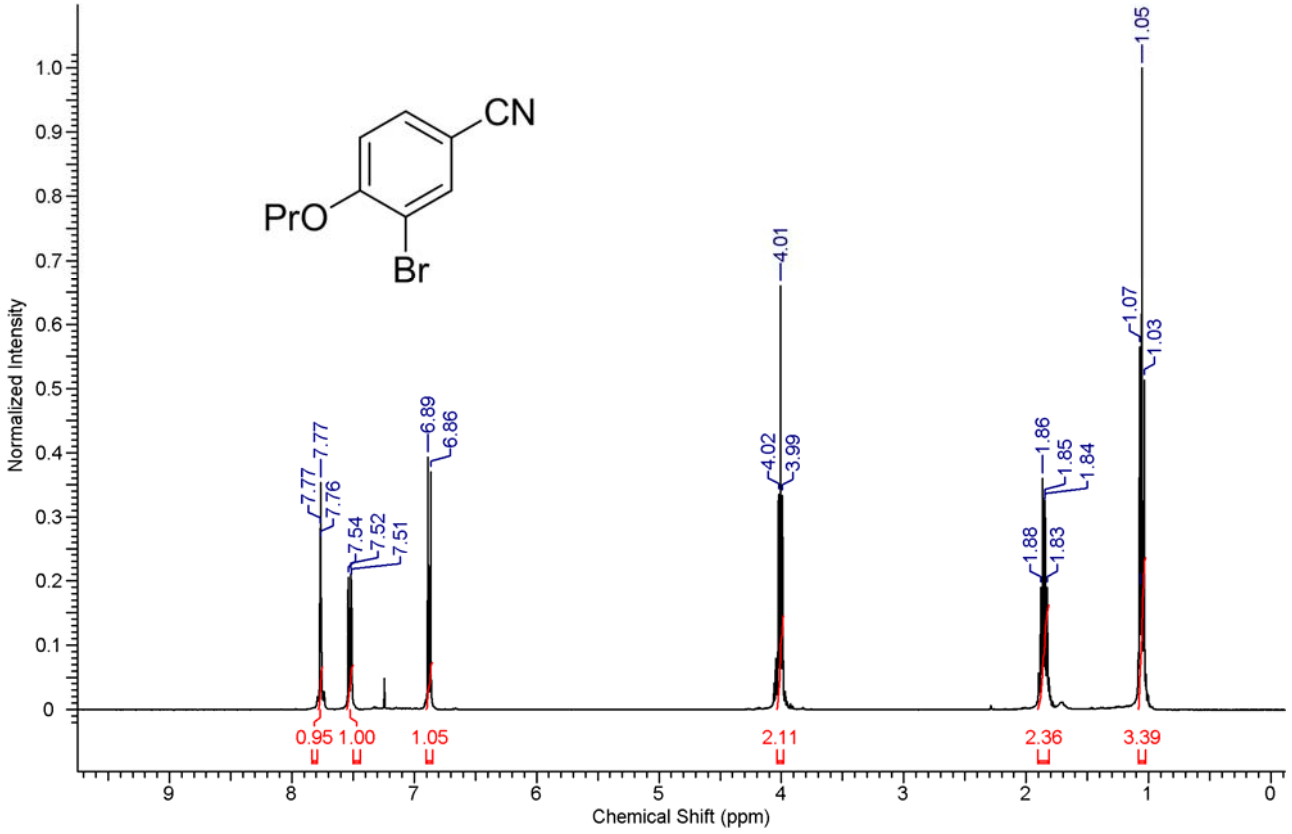


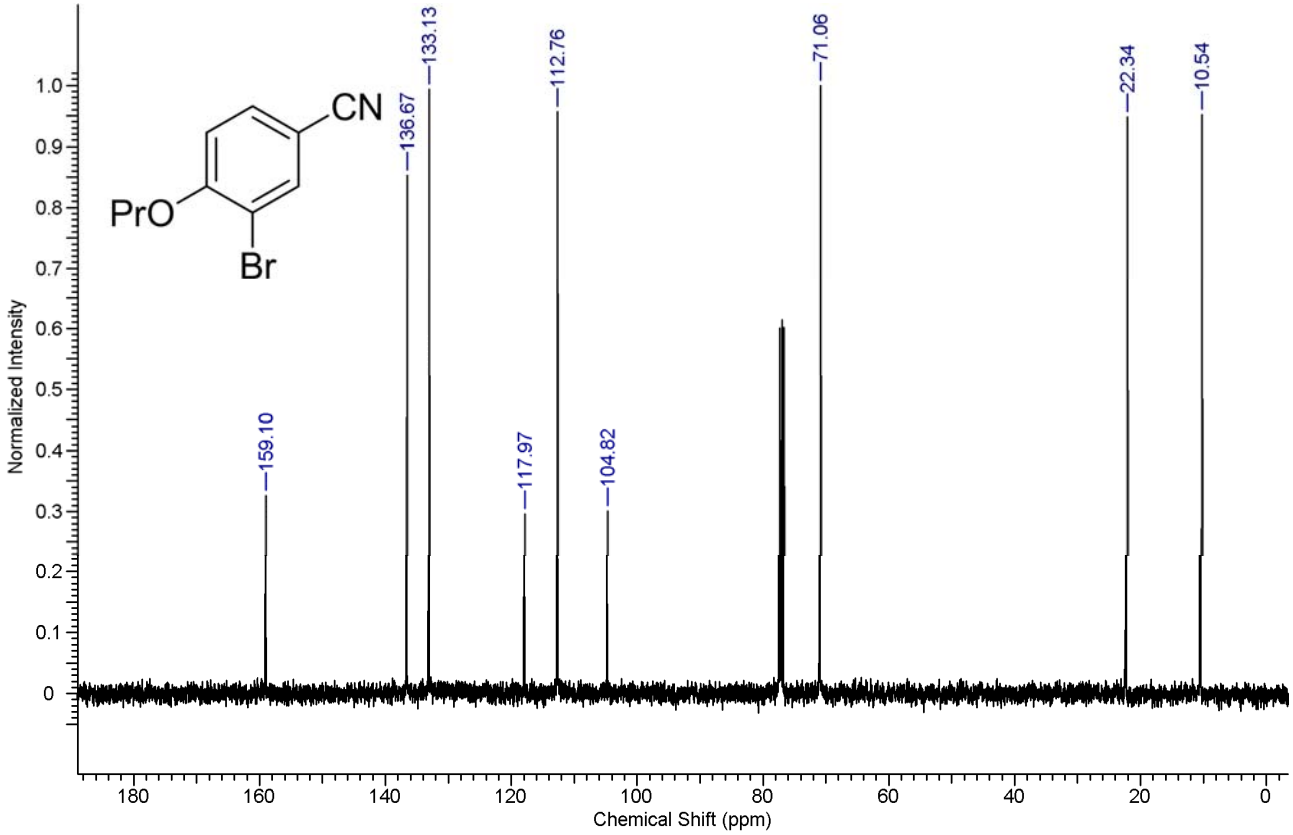


DEPT (135) NMR Spectrum of Compound **4c.**

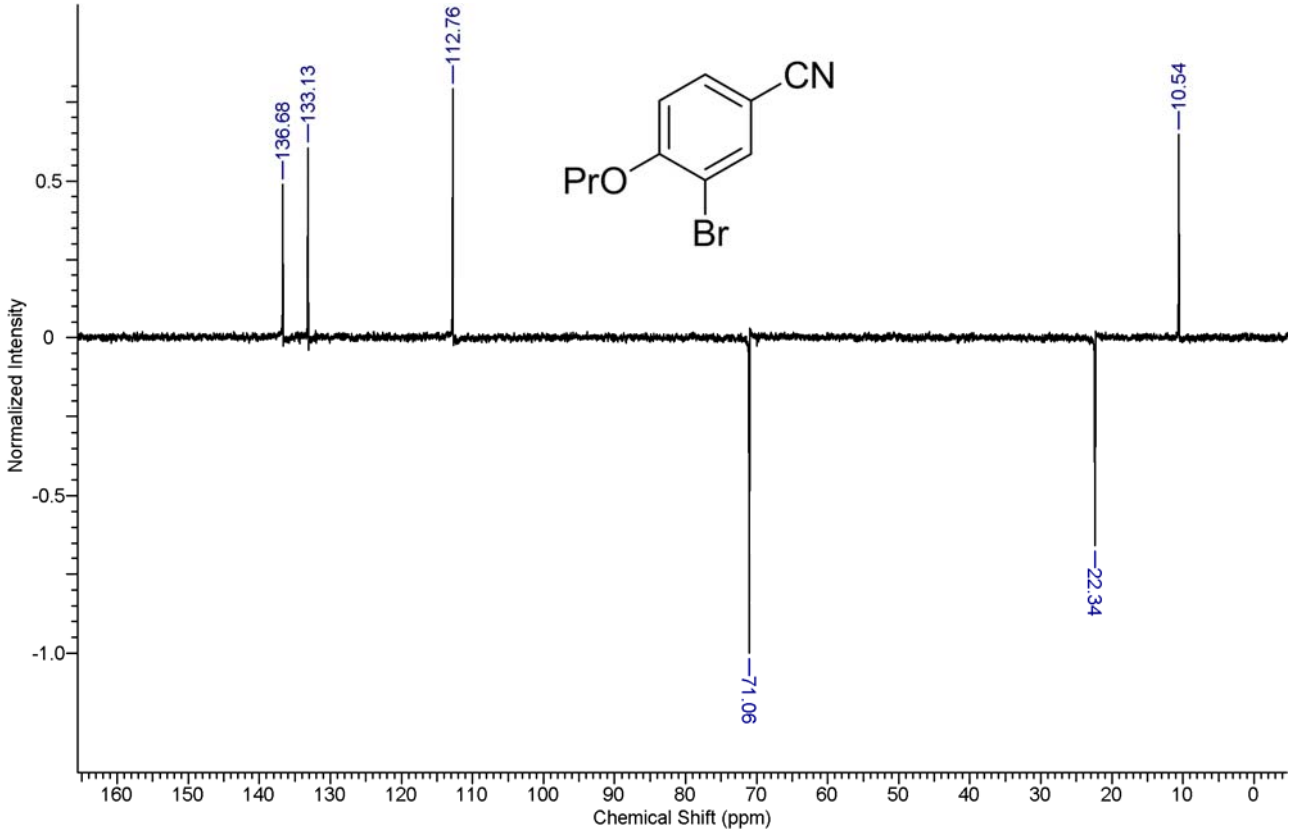


^{1}H and ^{13}C NMR Spectra of Compound **4d.**

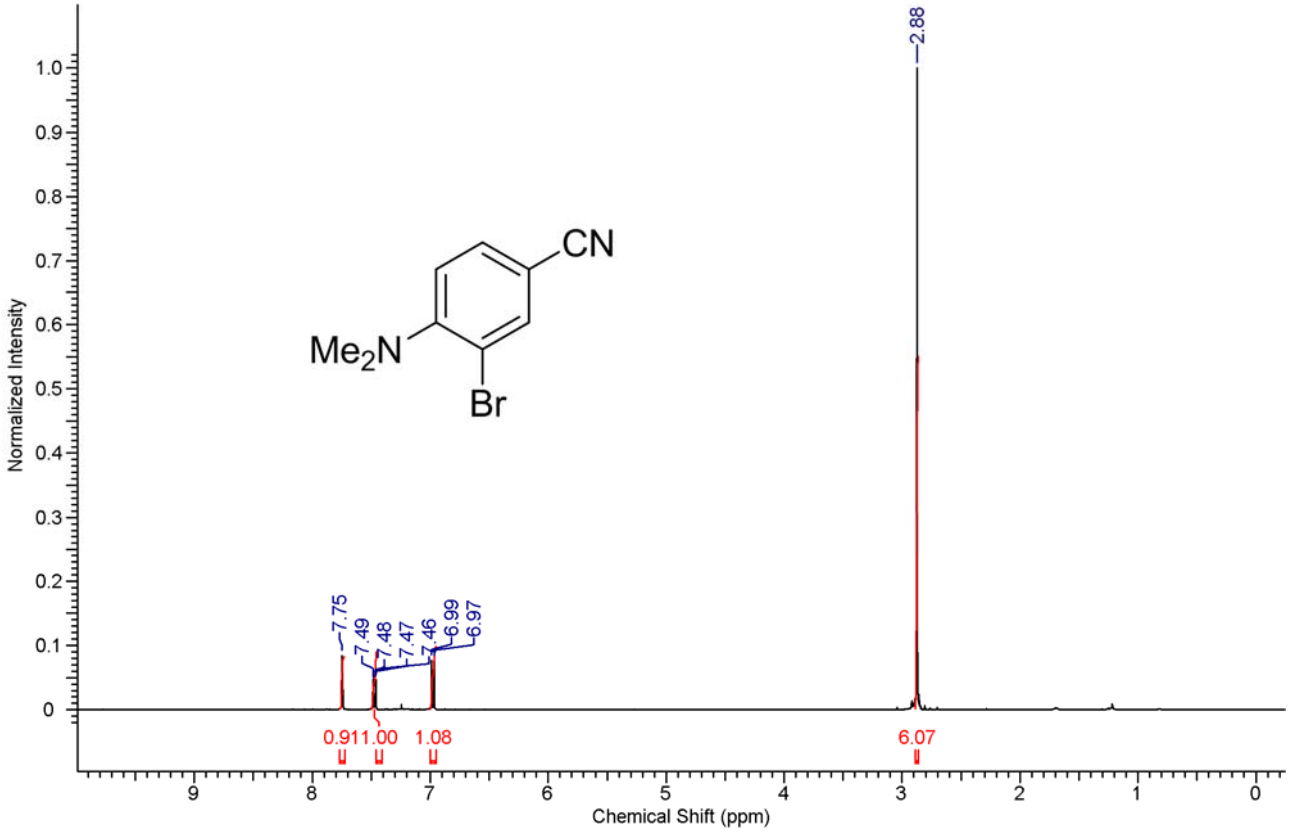


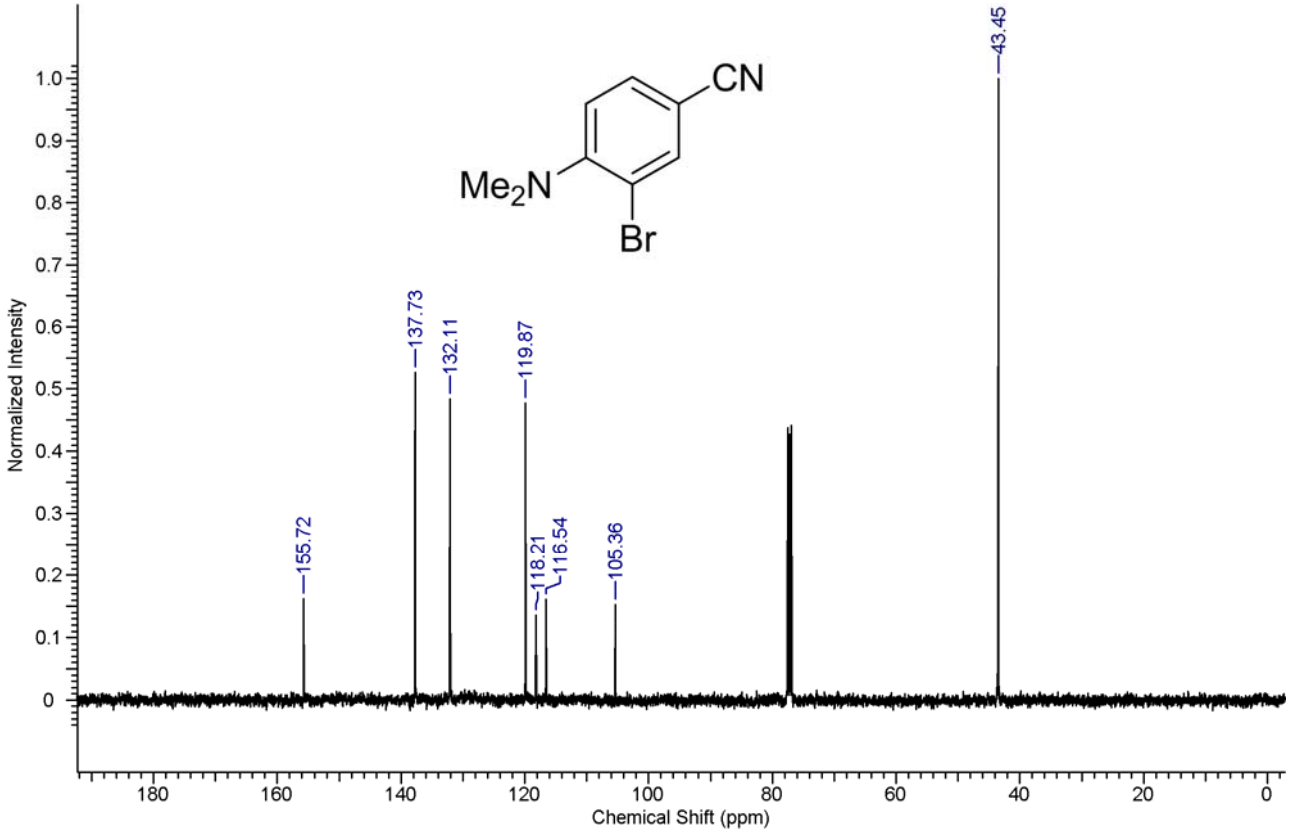


DEPT (135) NMR Spectrum of Compound **4d.**

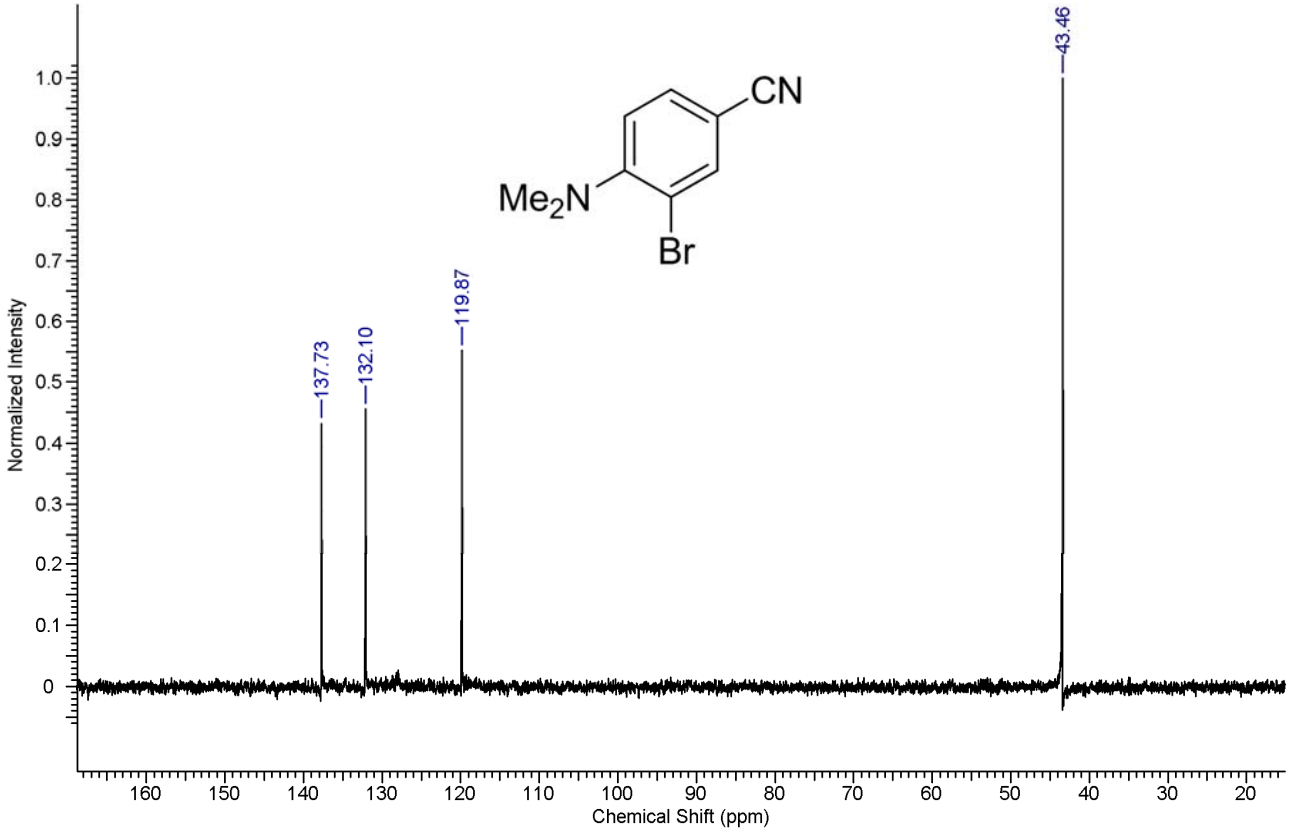


^{1}H and ^{13}C NMR Spectra of Compound **4e.**

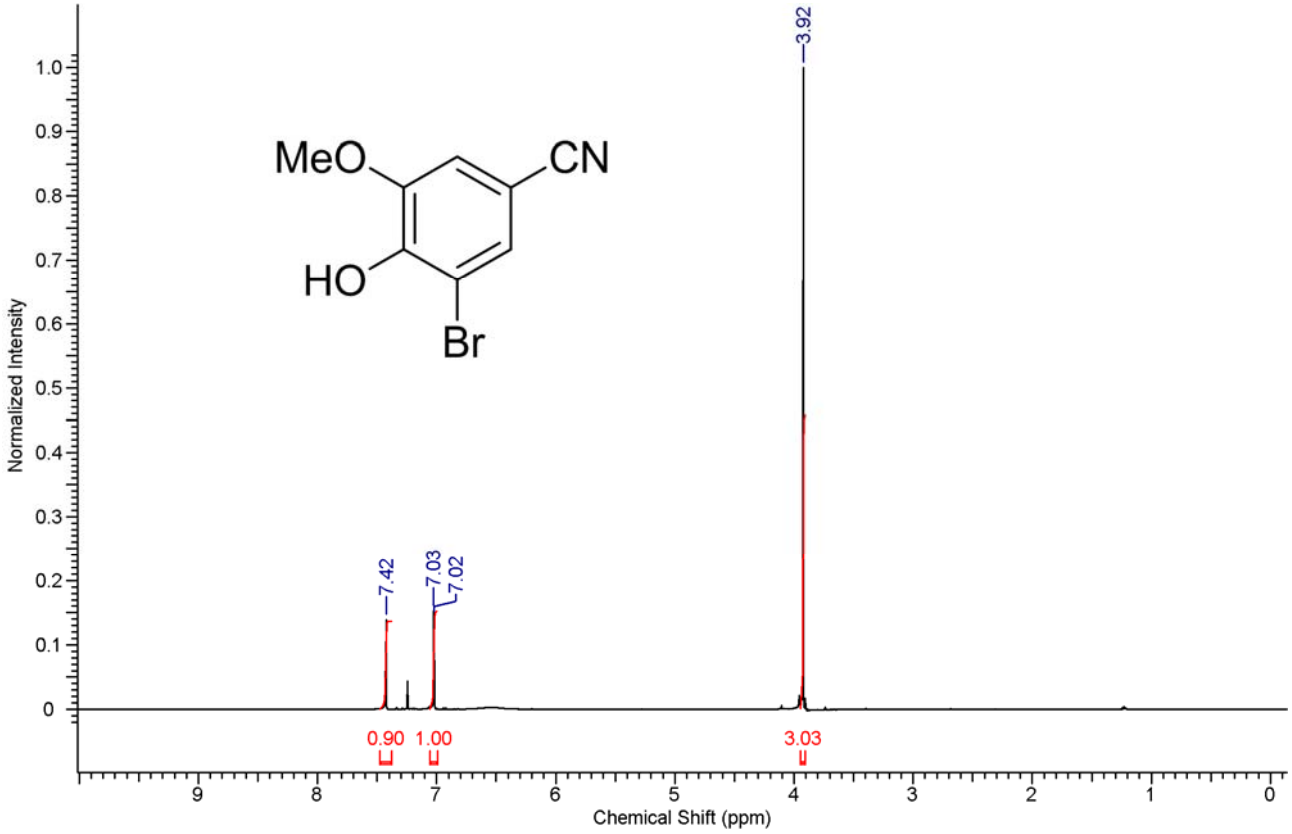


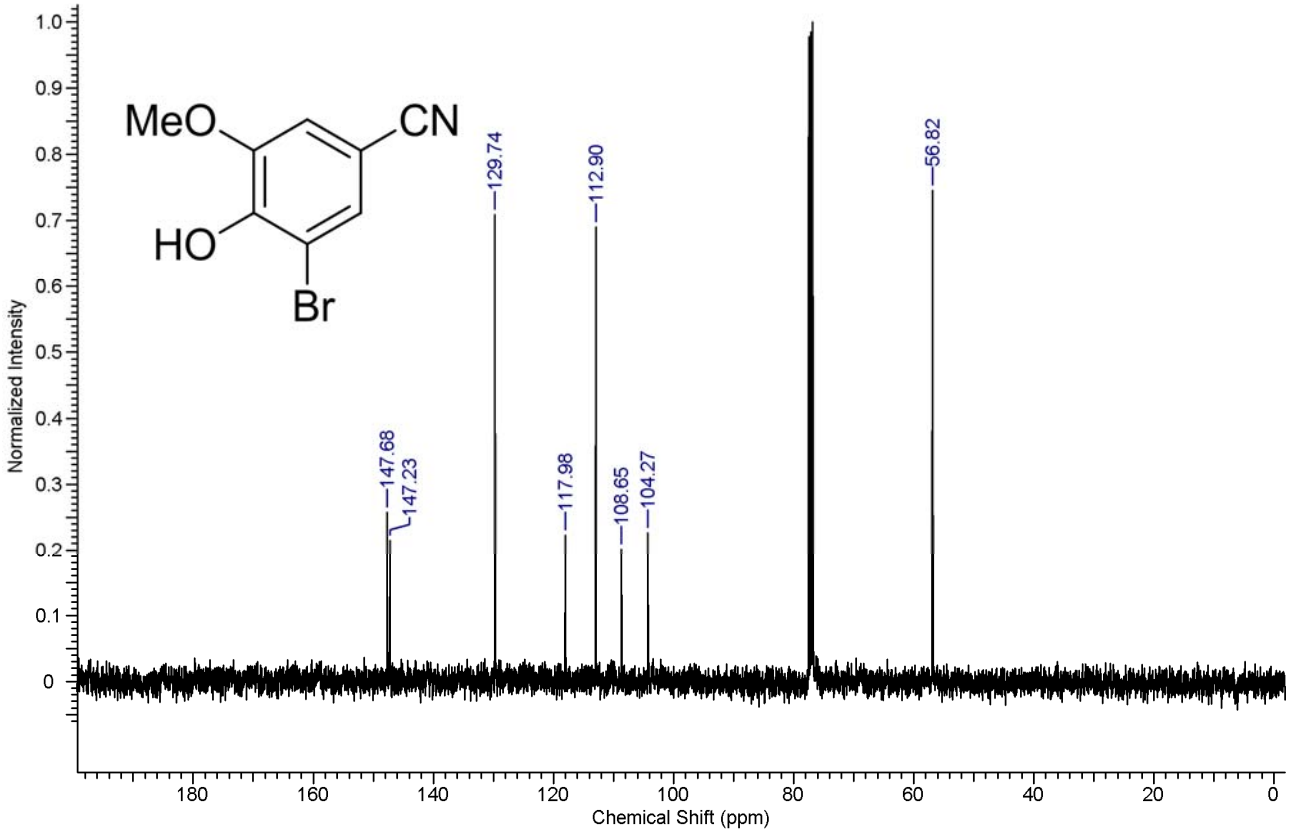


DEPT (135) NMR Spectrum of Compound **4e.**

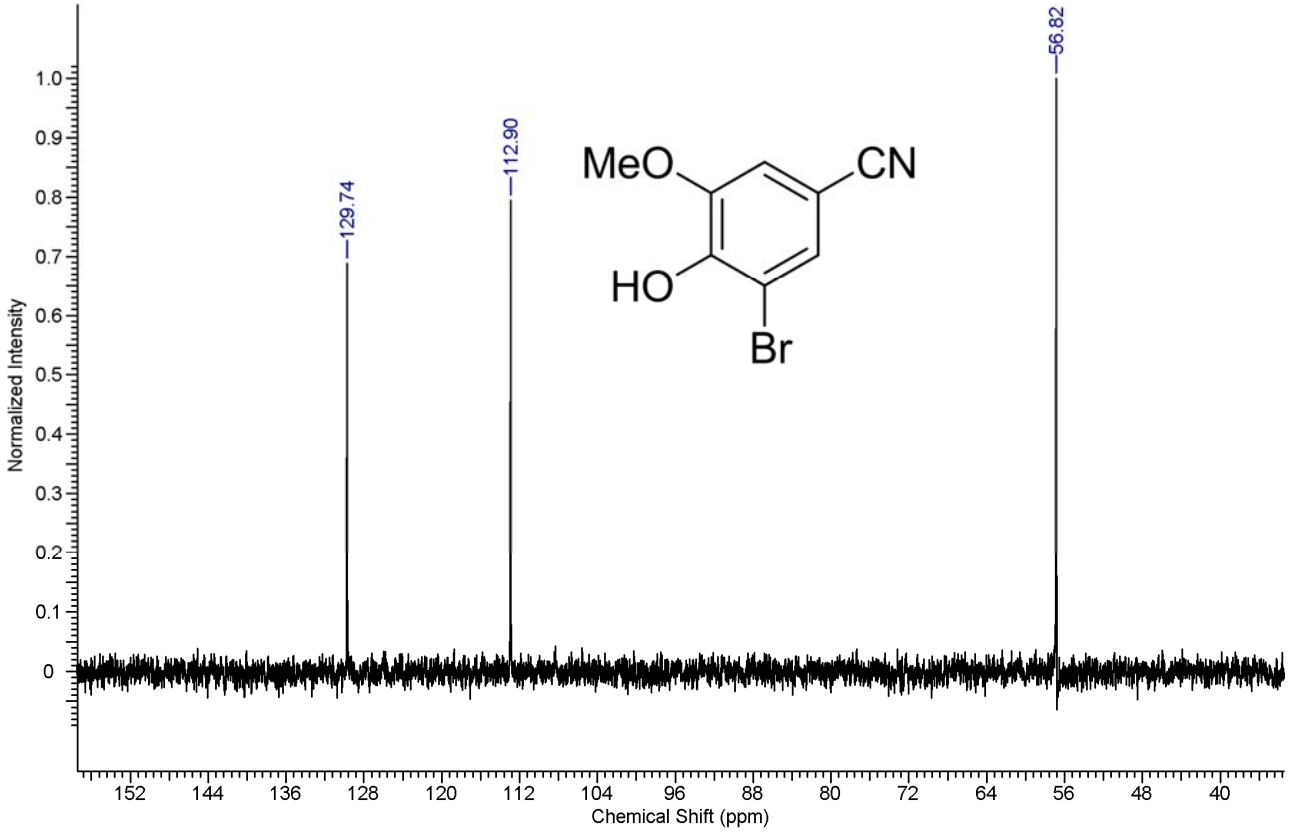


^{1}H and ^{13}C NMR Spectra of Compound **4f.**

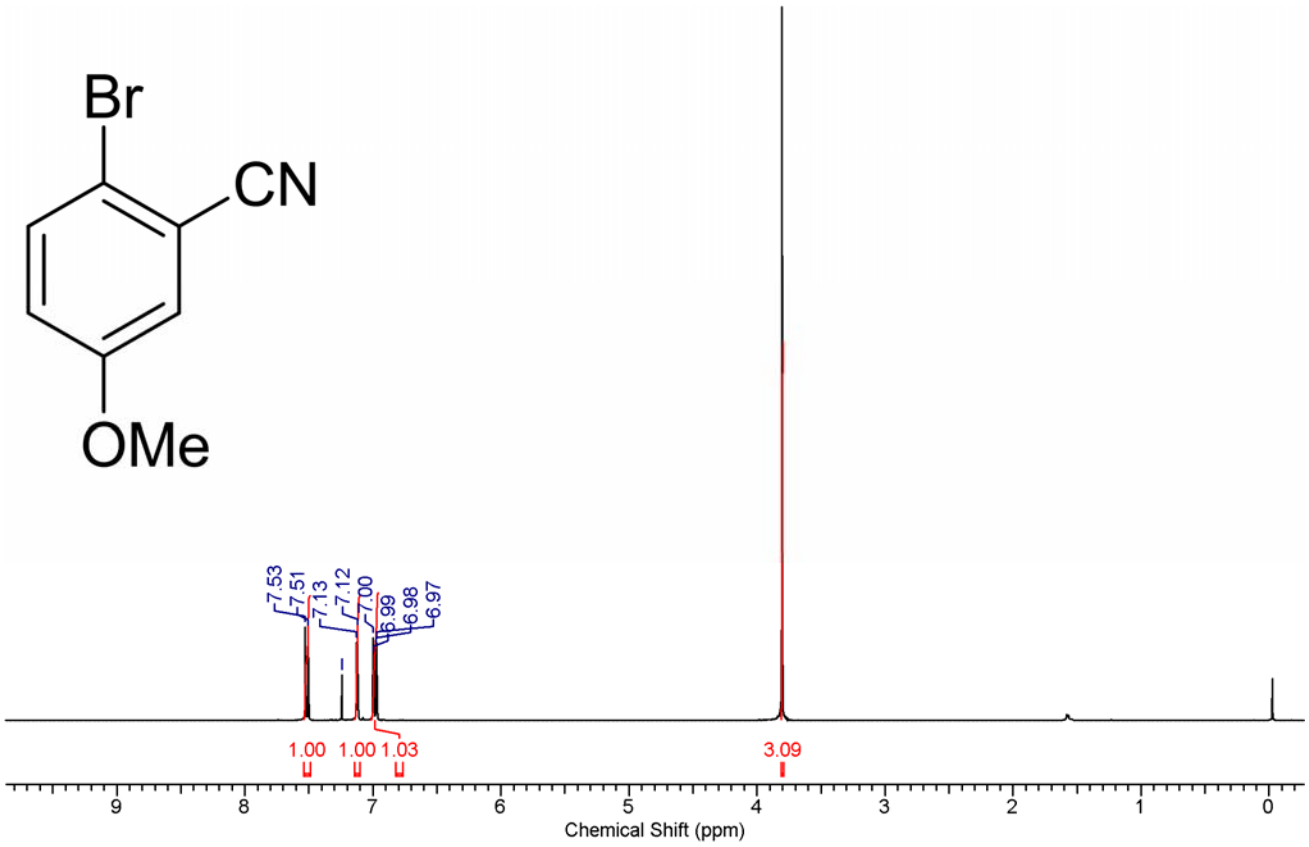


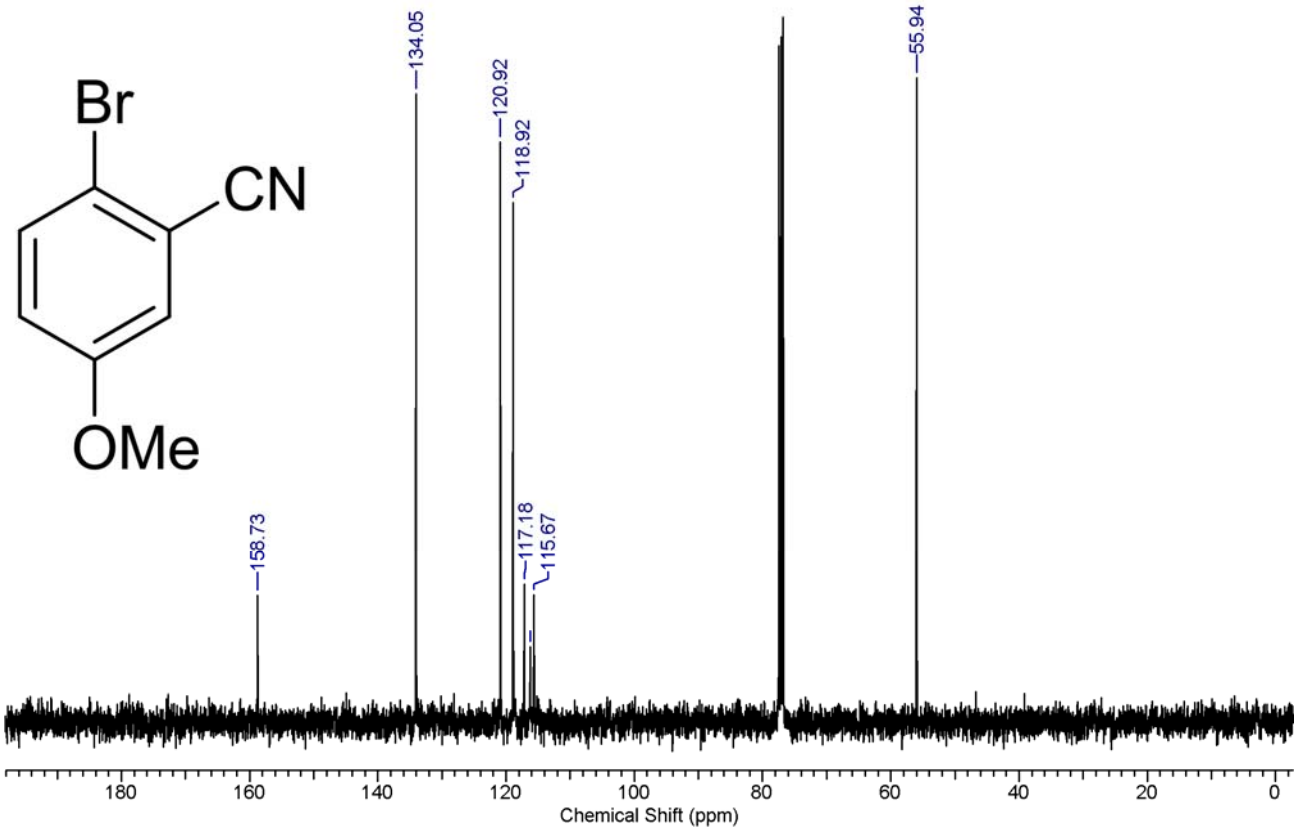


DEPT (135) NMR Spectrum of Compound **4f.**

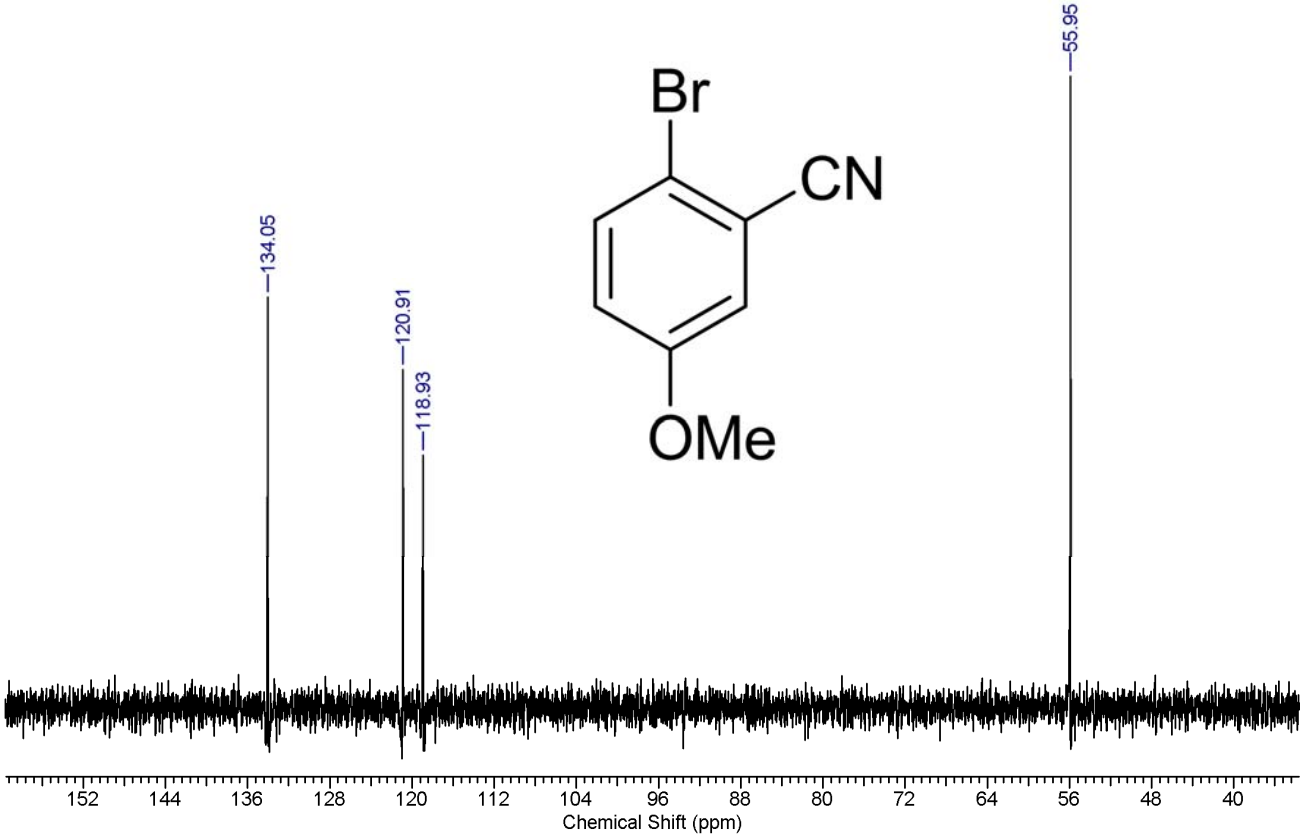


^{1}H and ^{13}C NMR Spectra of Compound **4g.**

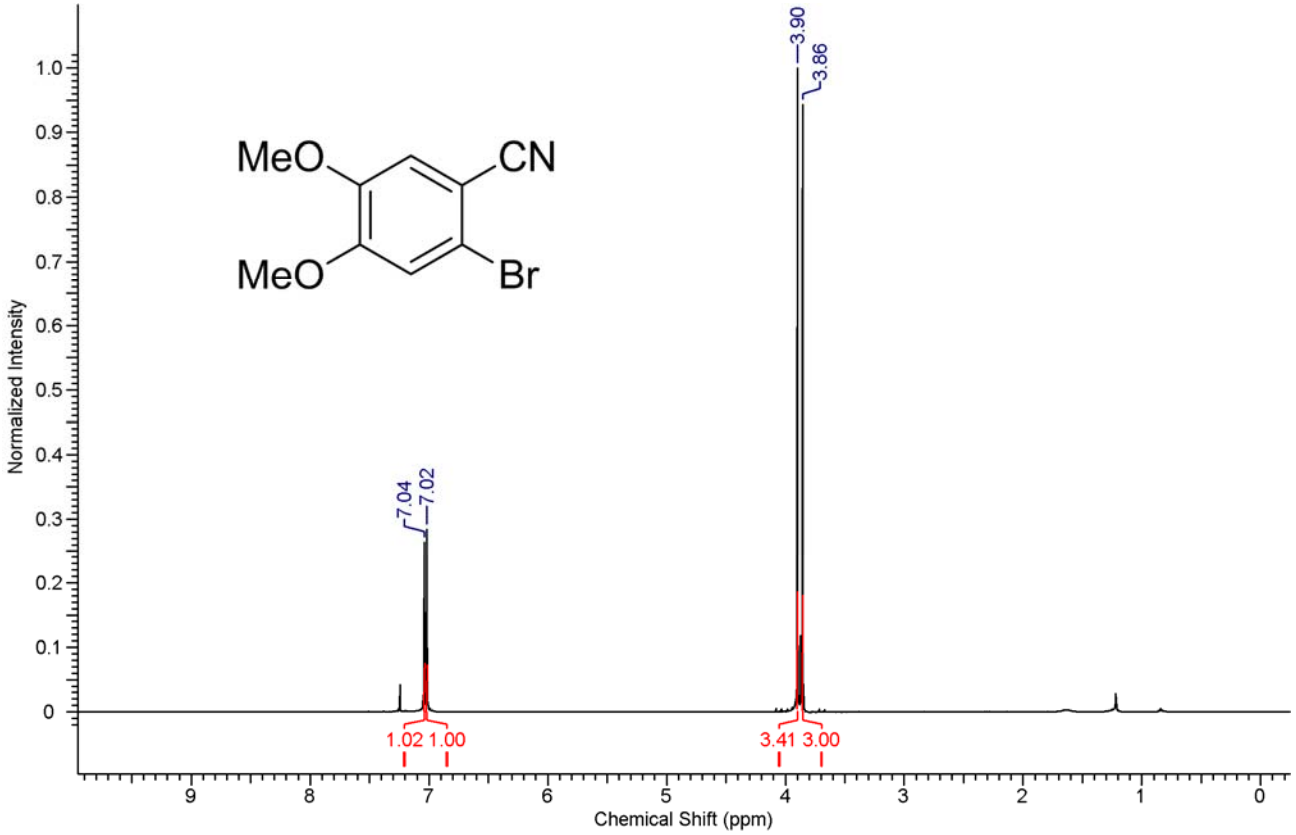


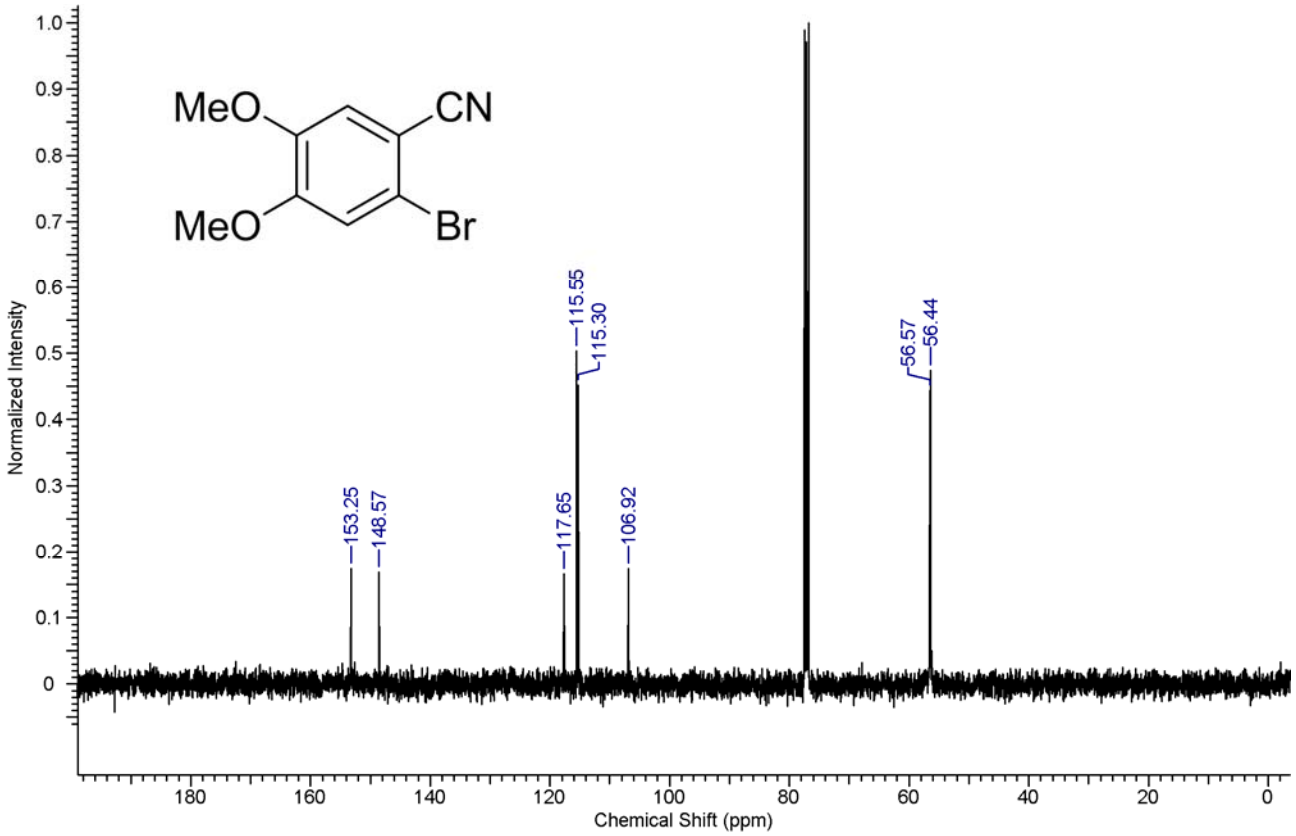


DEPT (135) NMR Spectrum of Compound **4g.**

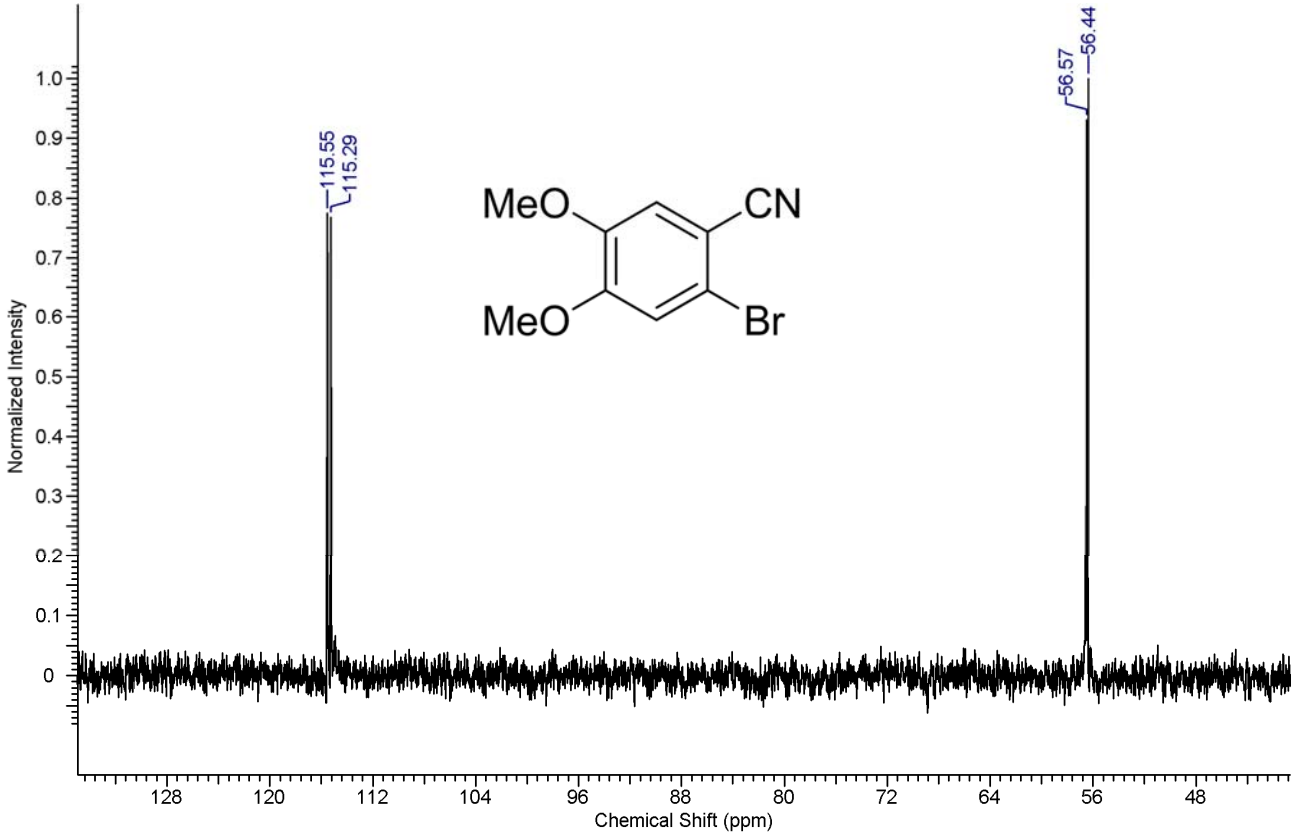


^{1}H and ^{13}C NMR Spectra of Compound **4h.**

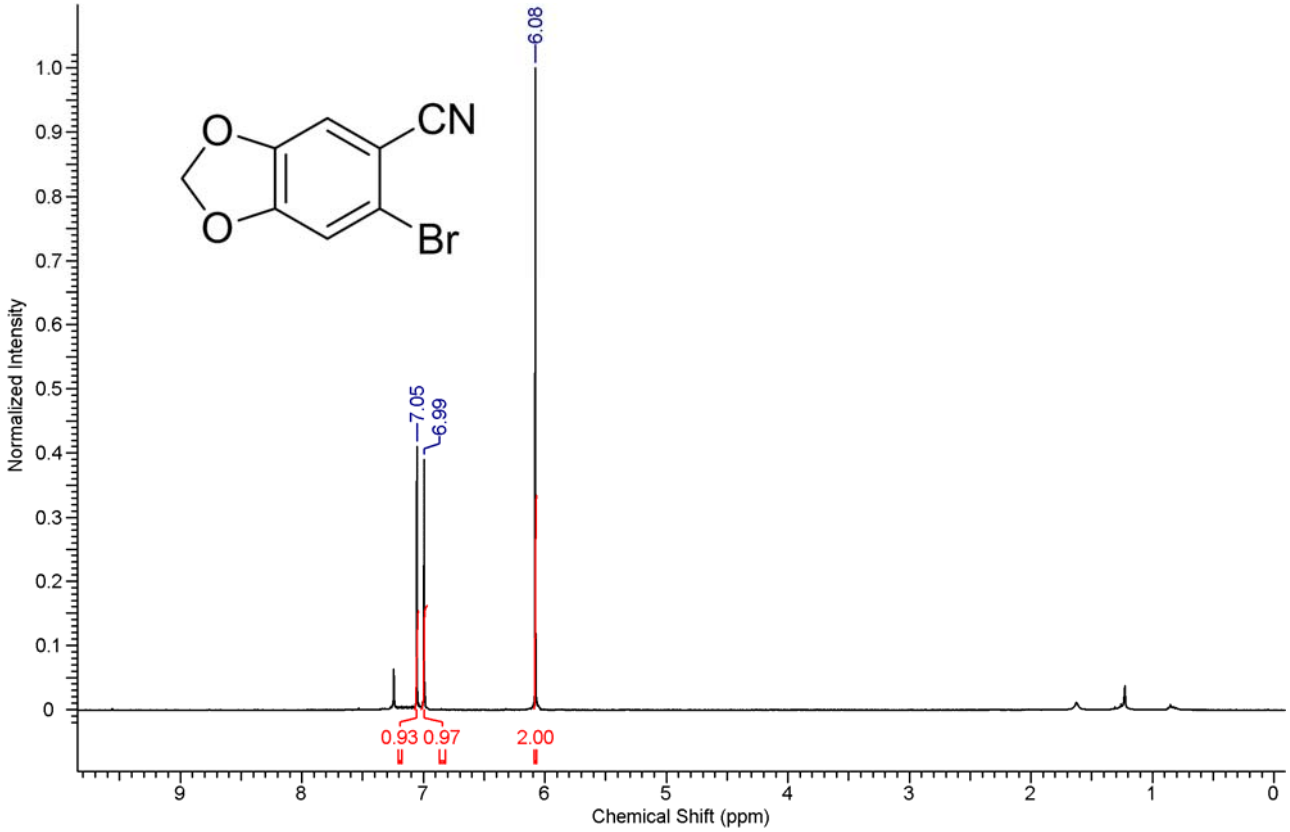


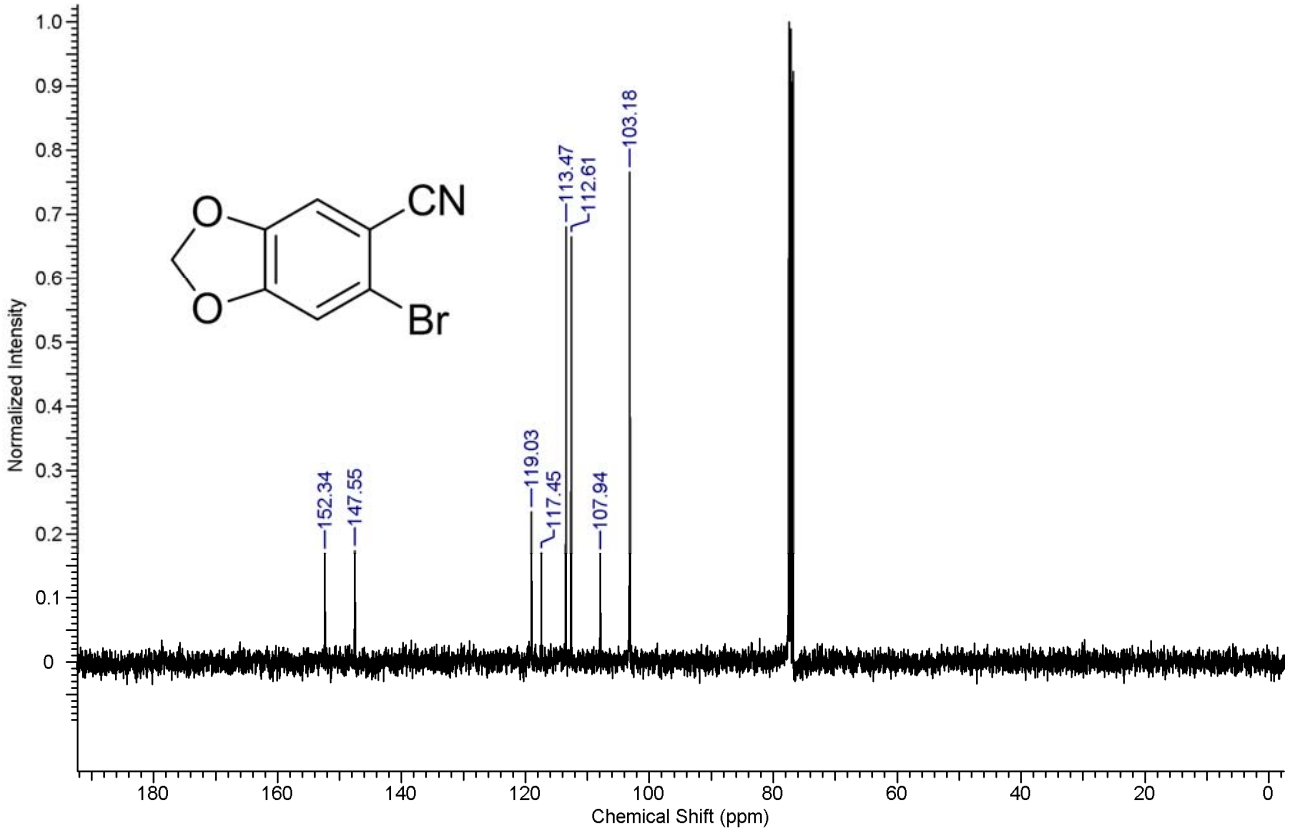


DEPT (135) NMR Spectrum of Compound **4h.**

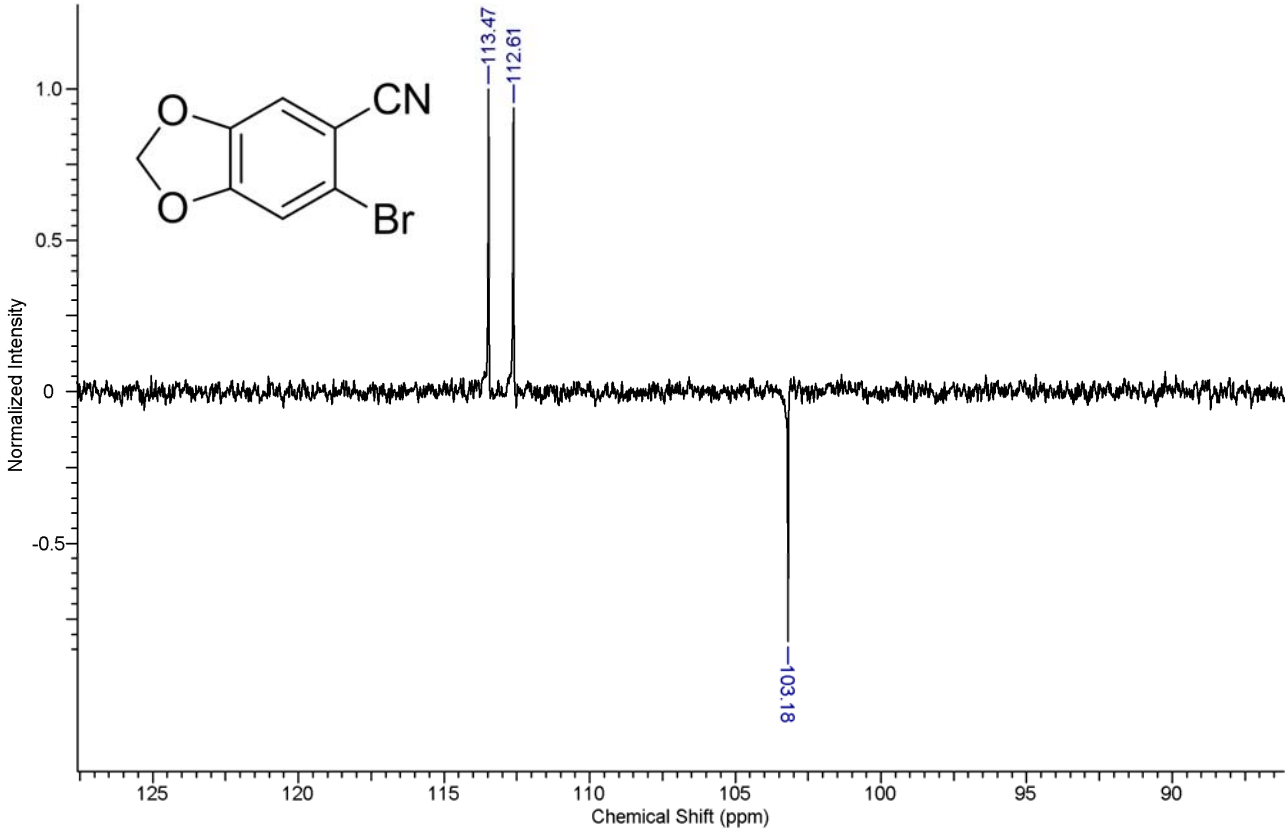


^{1}H and ^{13}C NMR Spectra of Compound **4i.**

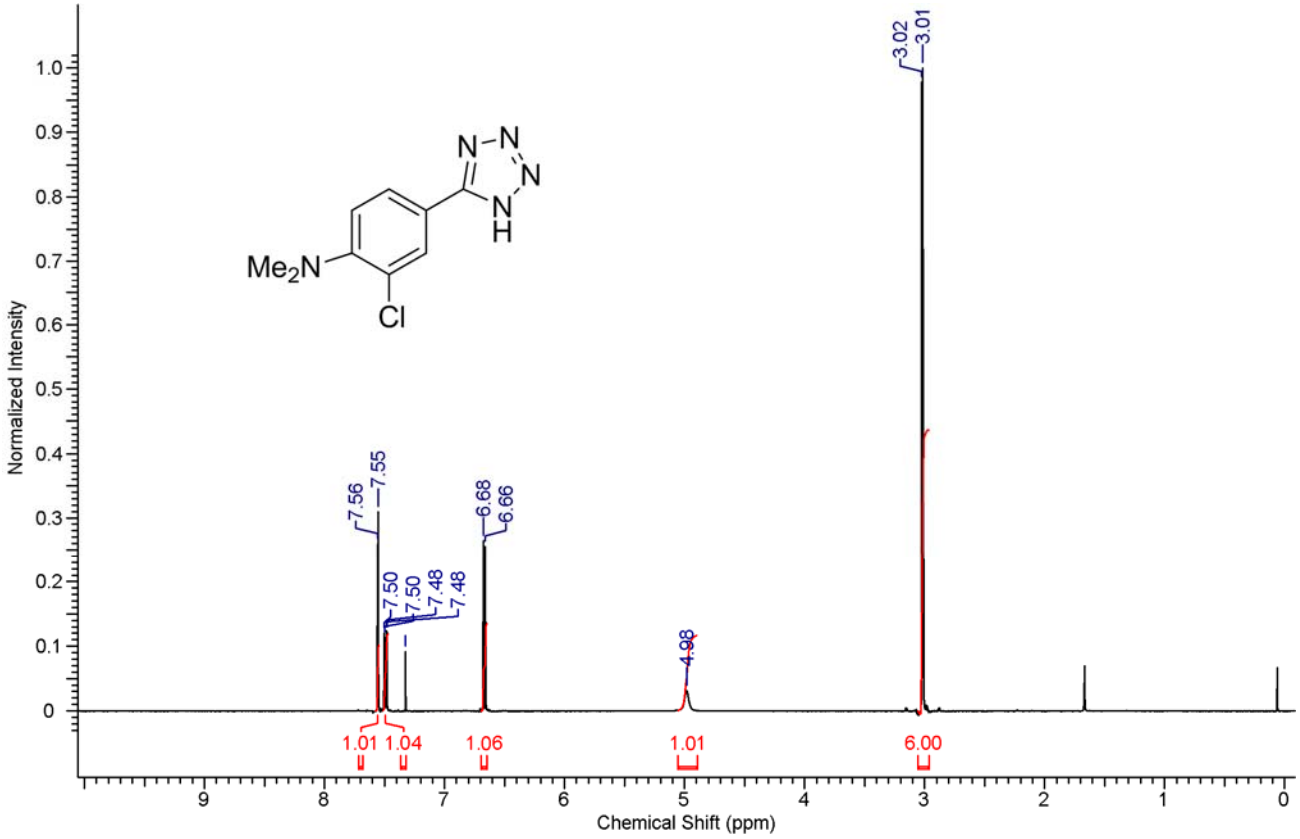


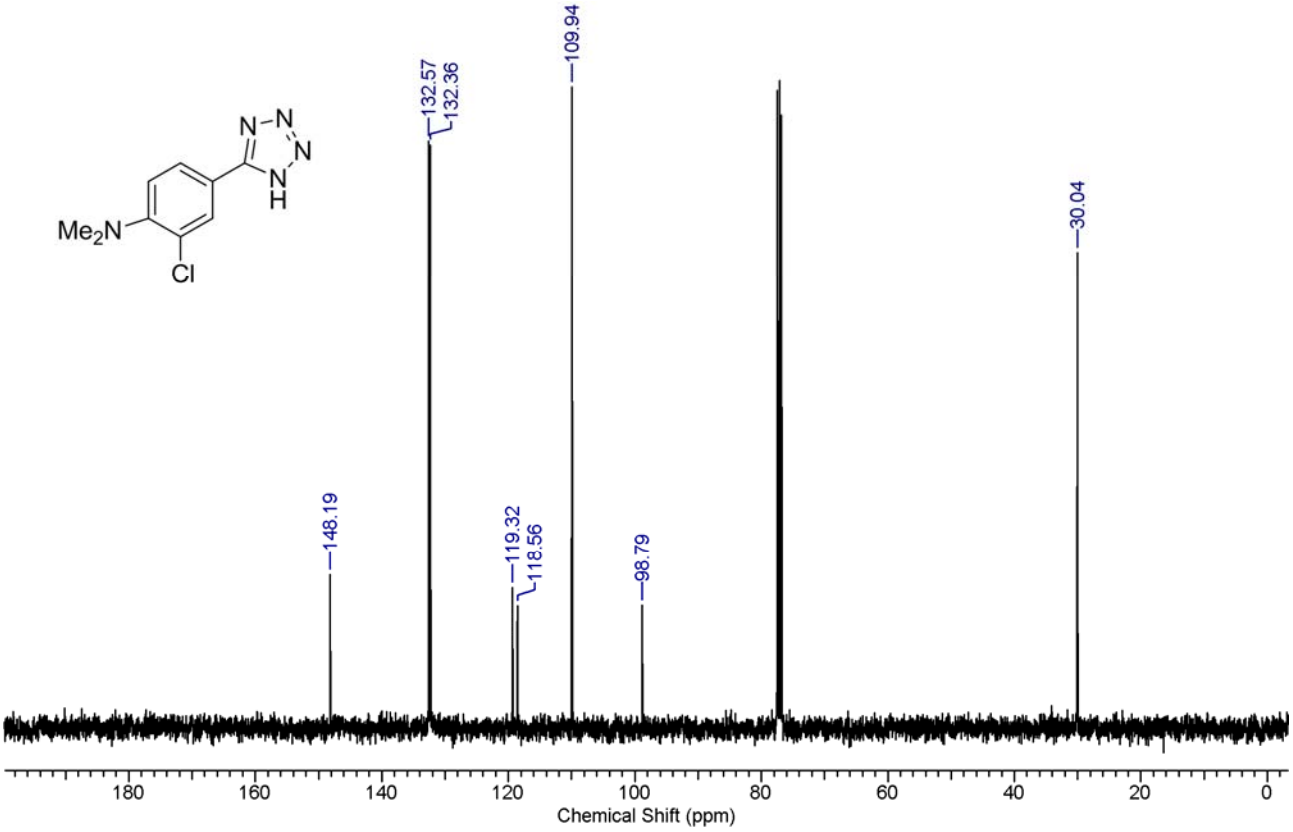


DEPT (135) NMR Spectrum of Compound **4i.**

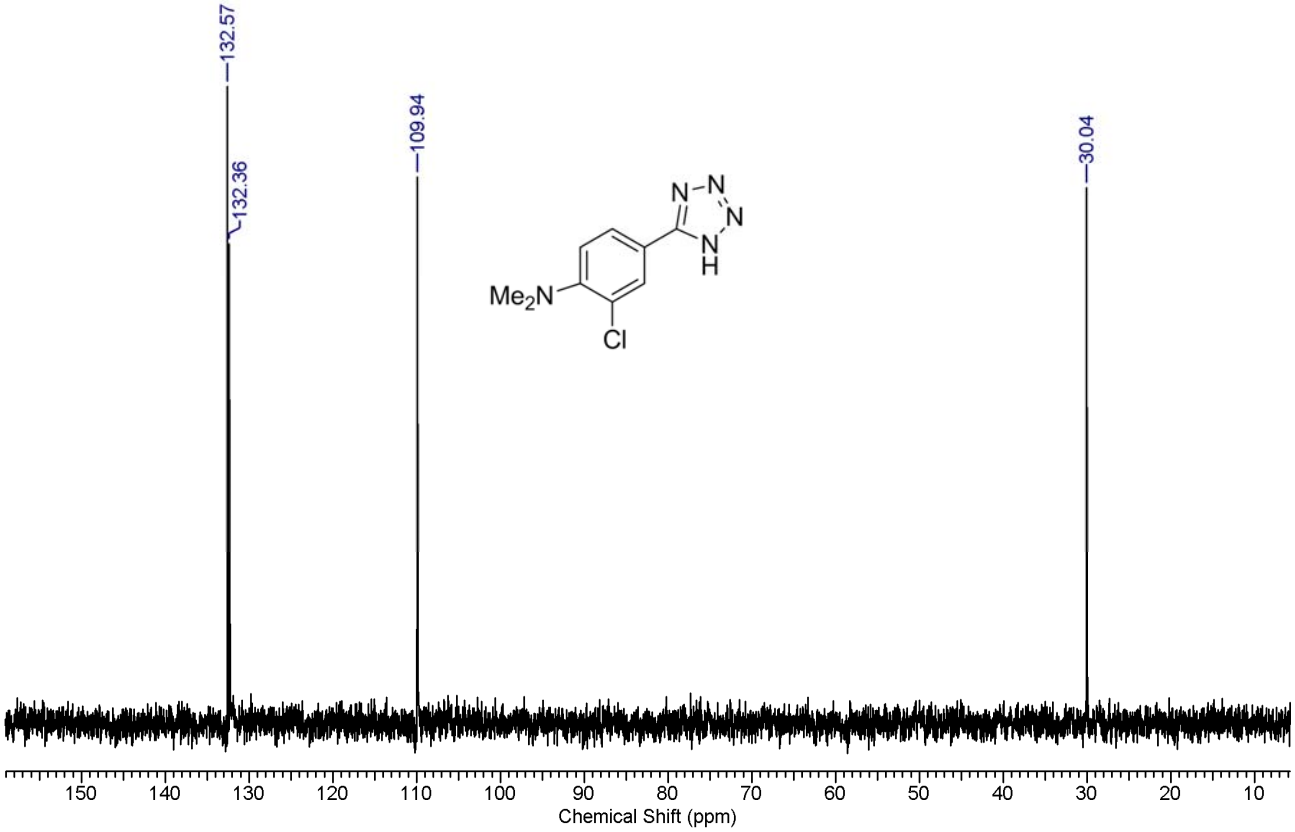


^{1}H NMR Spectrum of Compound **5a.**

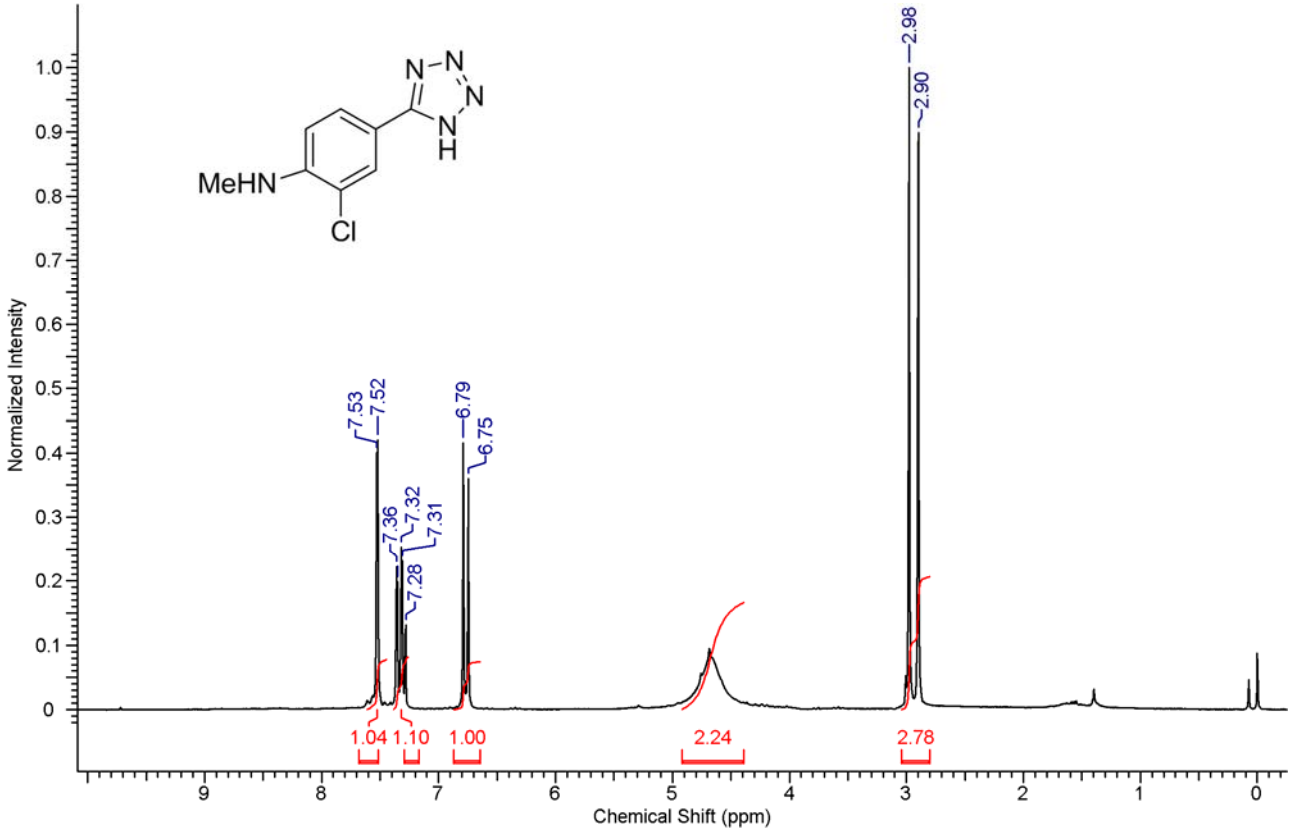


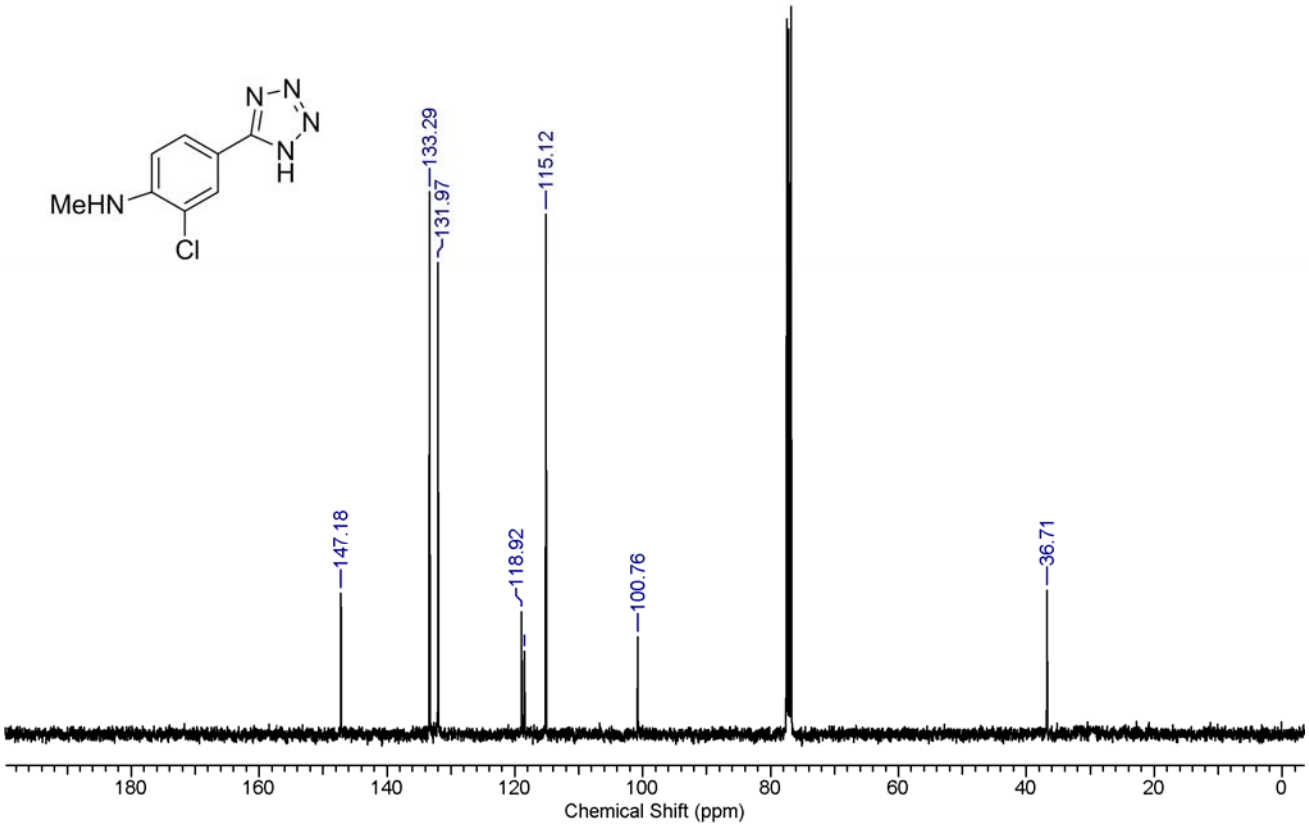


DEPT (135) NMR Spectrum of Compound **5a.**

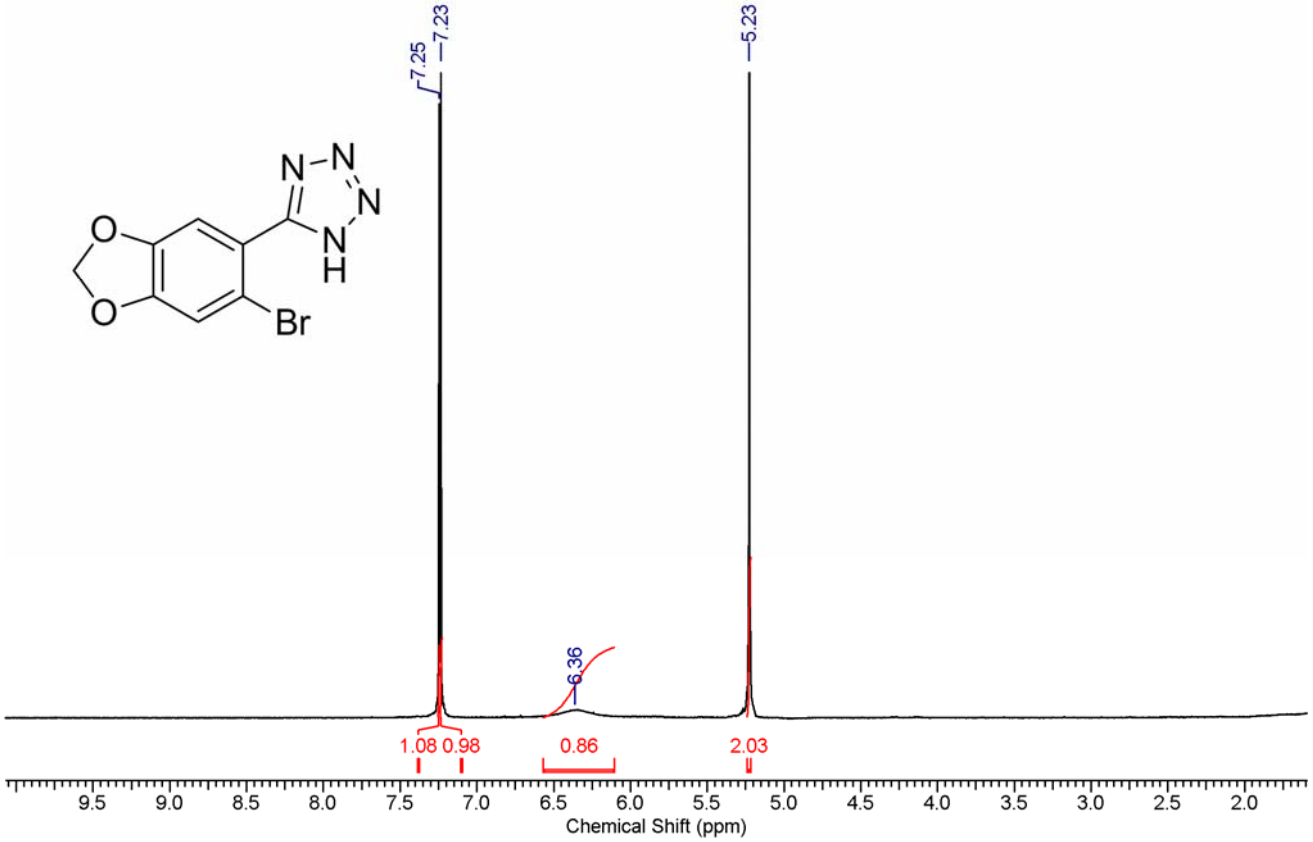


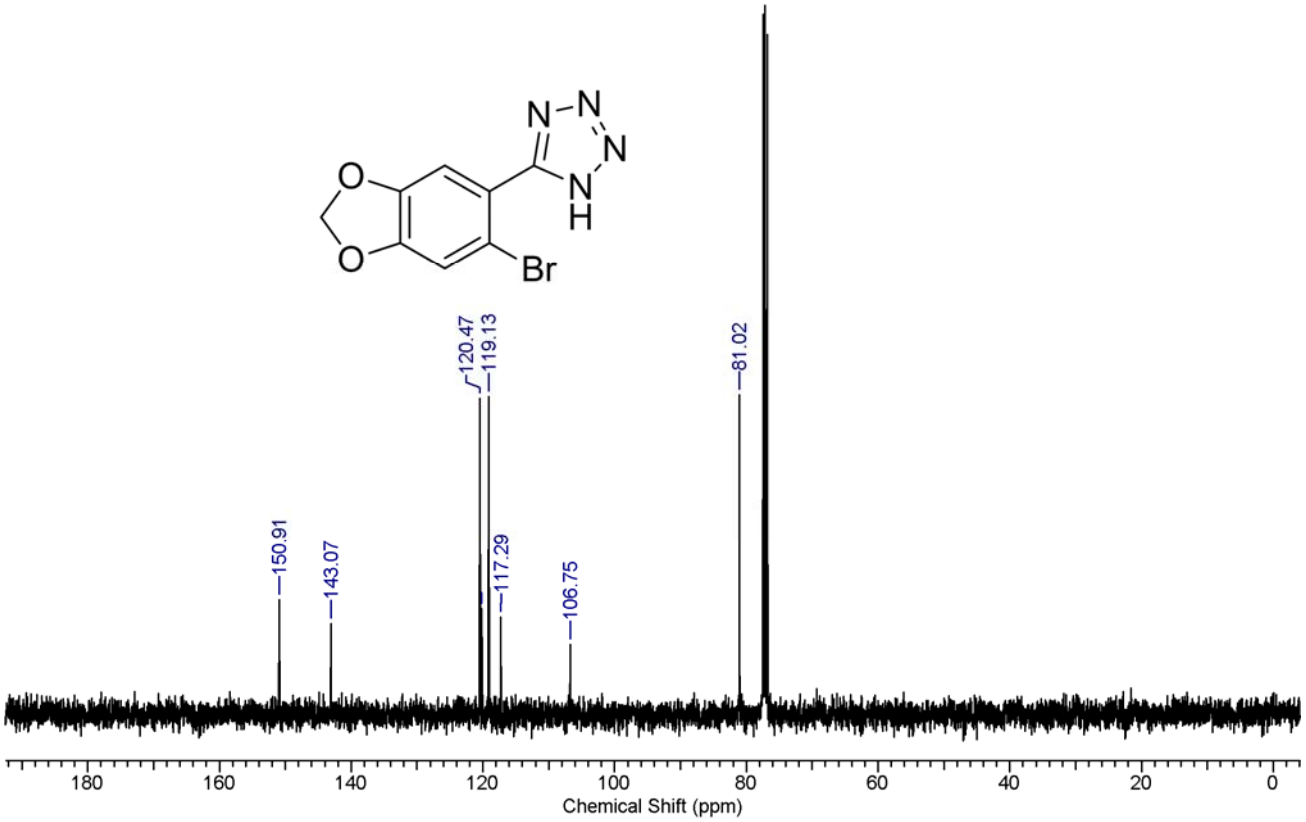
^{1}H NMR Spectrum of Compound **5b.**





^{1}H and ^{13}C NMR Spectra of Compound **5c.**





DEPT (135) NMR Spectrum of Compound **5c.**