Electronic Supplementary Material (ESI) for Chemical Communications

A regioselective synthesis of 1-haloisoquinolines via ruthenium-catalyzed cyclization of *O*-methylbenzohydroximoyl halides with alkynes

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Electronic Supplementary Information (ESI)

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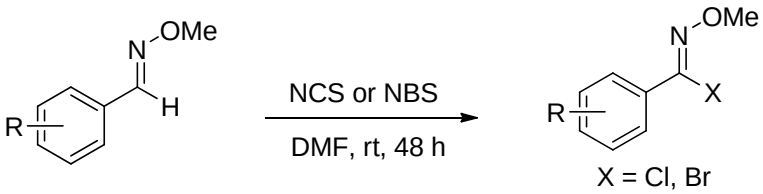
Experimental Section

General procedure for the preparation of starting materials 1.[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 fitted with a septum. 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**.

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

General procedure for the cyclization of *O*-methylbenzohydroximoyl halides with alkynes 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 CsOAc (25 mol %) was evacuated and purged with nitrogen gas three times. To the tube were then added *O*-methylbenzohydroximoyl halides **1** (1.00 mmol), alkynes **2** (1.20 mmol) and CF_3CH_2OH (2.0 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 **3**.

General procedure for the HBr hydrolysis.[2]

A mixture of *O*-alkyl isoquinoline **3f** (0.30 mmol, 70 mg) and 48% HBr in AcOH (2.0 mL) n a sealed tube was heated at 50 ˚C for 2 h. The reaction mixture was cooled to room temperature and poured into a mixture of ice and saturated aq. $NaHCO_3$ solution. The reaction mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure to yield the corresponding pure isoquinolone derivative **4a** (purification is not necessary). A similar procedure was used for the preparation of compounds **4b-d**. For the chlorination and bromination reactions, the corresponding compounds were used directly without further purification.

Ref. 2: Li, J.; Chen, L.; Chin, E.; Lui, A. S.; Zecic, H. *Tetrahedron Lett*. **2010**, *51*, 6422.

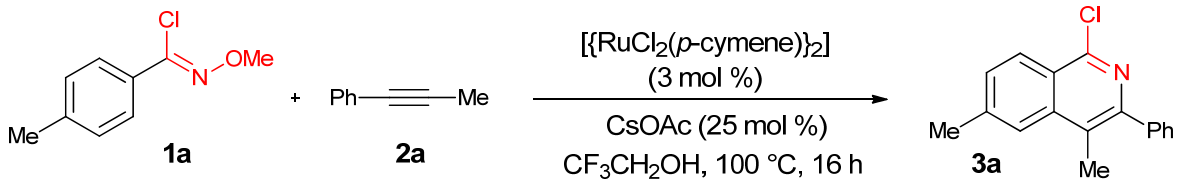
General procedure for the chlorination or bromination reaction.[3]

In a 50 mL round-bottom flask fitted with a condenser, a suspension of isoquinolone (100 mg) in phosphorus oxychloride ($POCl_3$) or phosphorus tribromide (PBr_3) (2.0 mL) was heated at 100 ˚C for 2 h (100 ˚C for chlorination and 130 ˚C for bromination). The reaction was monitored on TLC. After completion the reaction (approx. 2.0 h for chlorination and approx. 6.0 h for bromination), the reaction mixture was cooled to ambient temperature, and poured in ice and added saturated $NaHCO_3$, extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4. The solution was concentrated under reduced pressure to provide crude 1-halo isoquinolines **4e-i**. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **4e-i**.

Ref. 3: Tobe, M.; Isobe, Y.; Tomizawa, H.; Nagasaki, T.; Takahashi, H.; Fukazawa, T.; Hayashi, H. *Bioorg. Med. Chem*. **2003**, *11*, 383.

Spectral data and copies of ^{1}H and ^{13}C NMR spectra of all compounds are listed below (pages 10 – 76).

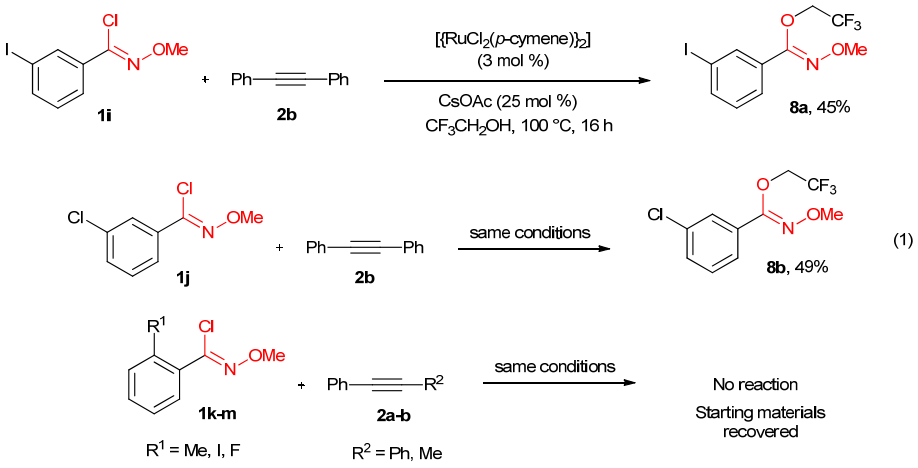
Optimization studies



Initially, the ruthenium-catalyzed cyclization of **1a** and **2a** was conducted in the presence of catalytic amount of NaOAc (25 mol %) in MeOH at 100 °C for 16 h. Usually, alcoholic solvent and acetate base is suitable for this type of cyclization reaction. Thus, the catalytic reaction was tested with various alcoholic solvents such as MeOH, *iso*-PrOH, *tert*-BuOH and *tert*-amyl alcohol in the presence of NaOAc. However, no cyclization product **3a** was observed in the reaction. Finally, the catalytic reaction was carried out in the presence of CF_3CH_2OH. Surprisingly, in the reaction, product **3a** was observed in 84% NMR yield. The yield of product **3a** was determined by the ^1H NMR integration method using mesitylene as an internal standard. In order to increase the yield of **3a**, the catalytic reaction was carried out in the presence of various acetate bases such as KOAc, LiOAc, CsOAc and $Cu(OAc)_2$. As like NaOAc, CsOAc base was also equally effective, yielding product **3a** in 86% NMR yield. The remaining bases were less effective, giving **3a** in 50%, 60% and 10% NMR yields, respectively.

Meta and *ortho* substituted *N*-methoxybenzimidoyl halides reactions

In fact, the cyclization reaction of various meta and *ortho* substituted I, Cl and F substituted *N*-methoxybenzimidoyl halides with diphenylacetylene (**2b**) was tested. However, in these reactions, no expected cyclization product **3** was observed; instead a different type of nucleophilic addition of solvent TFE at the Cl group substituted carbon of imidoyl moiety was observed (eq. 1). For example, in the reaction of meta iodo **1i** or chloro **1j** substituted *N*-methoxybenzimidoyl halides with diphenylacetylene (**2b**), only TFE addition products **8a-b** were observed instead of cyclization products (eq. 1). Whereas, no cyclization as well as TFE addition products were observed in the reaction of ortho Me **1k** or Cl **1l** or F **1m** substituted *N*-methoxybenzimidoyl halides with diphenylacetylene (**2b**).



Final conclusion: Based on these reactions, we have concluded that in the *meta* substituted *N*-methoxybenzimidoyl halide substrates **1i-j**, nucleophilic addition of solvent TFE at the Cl substituted carbon of imidoyl moiety takes place before the cyclization reaction. At this stage, further cyclization reaction was stopped completely. Thus, the cyclization product was not observed. Whereas, in the *para* substituted *N*-methoxybenzimidoyl halide substrates **1a-i**, nucleophilic addition of the solvent TFE at the Cl substituted carbon of imidoyl moiety takes place after the cyclization reaction. Thus, the expected cyclization product was observed **3** without any problem. In the meantime, *ortho* substituted *N*-methoxybenzimidoyl halides were not suitable substrates for the reaction.

In addition, nature of the substituent present on the aromatic ring of **1** also plays an important role especially for the nucleophilic addition of TFE. Electron-donating alkyl substituents do not encourage the TFE addition at the Cl substituted carbon of imidoyl moiety. But, electron-withdrawing substituents such as I, Br, Cl and F favor the TFE addition at the Cl substituted carbon of imidoyl moiety.

Regioselective studies

X-Ray Analysis

6-Chloro-4-methyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (3h).

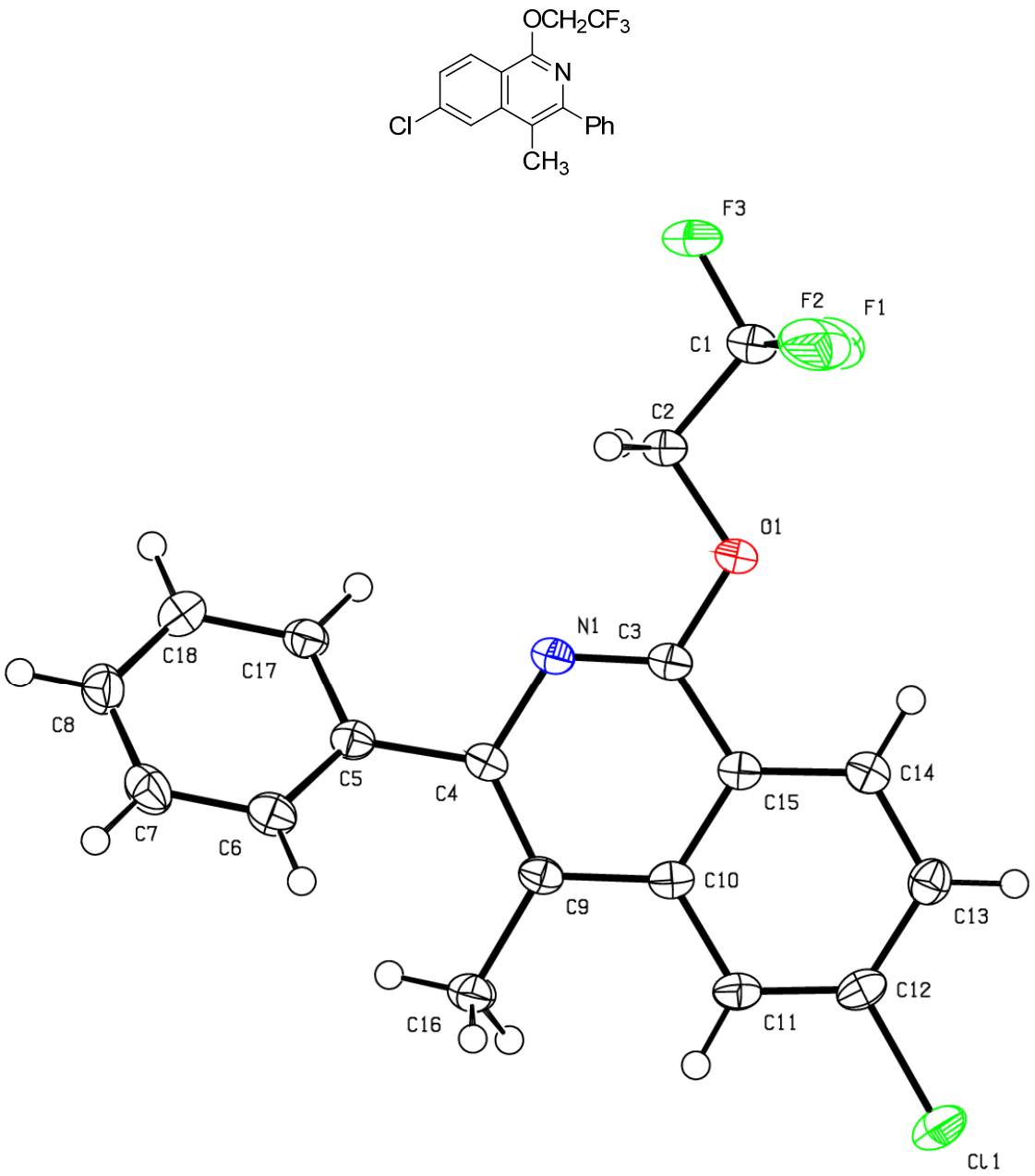


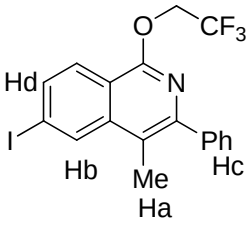
Table 1.Crystal data and structure refinement for (**3h**).

Identification code	7d
Empirical formula	C18 H13 Cl F3 N O
Formula weight	351.74
Temperature	200(2) K
Wavelength	0.71073 Å

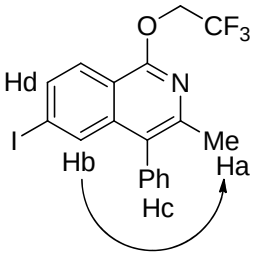
Crystal system	'Monoclinic'	
Space group	'P121/n1'	
Unit cell dimensions	a = 11.5379(13) Å	α= 90°.
	b = 7.0208(8) Å	β= 94.958(3)°.
	c = 19.335(2) Å	γ = 90°.
Volume	1560.4(3) $Å^3$	
Z	4	
Density (calculated)	1.497 Mg/m^3	
Absorption coefficient	0.282 mm^{-1}	
F(000)	720	
Crystal size	0.14 x 0.12 x 0.06 mm^3	
Theta range for data collection	1.98 to 28.36°.	
Index ranges	-15<=h<=15, -9<=k<=8, -25<=l<=25	
Reflections collected	27160	
Independent reflections	3907 [R(int) = 0.0437]	
Completeness to theta = 28.36°	99.9 %	
Max. and min. transmission	0.9833 and 0.9616	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3907 / 0 / 219	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2sigma(I)]	R1 = 0.0361, wR2 = 0.0901	
R indices (all data)	R1 = 0.0544, wR2 = 0.1004	
Extinction coefficient	0.0009(5)	
Largest diff. peak and hole	0.345 and -0.287 $e.Å^{-3}$	

B. NOESY Studies

Copy of NOESY Experiment of Compound **3f**.

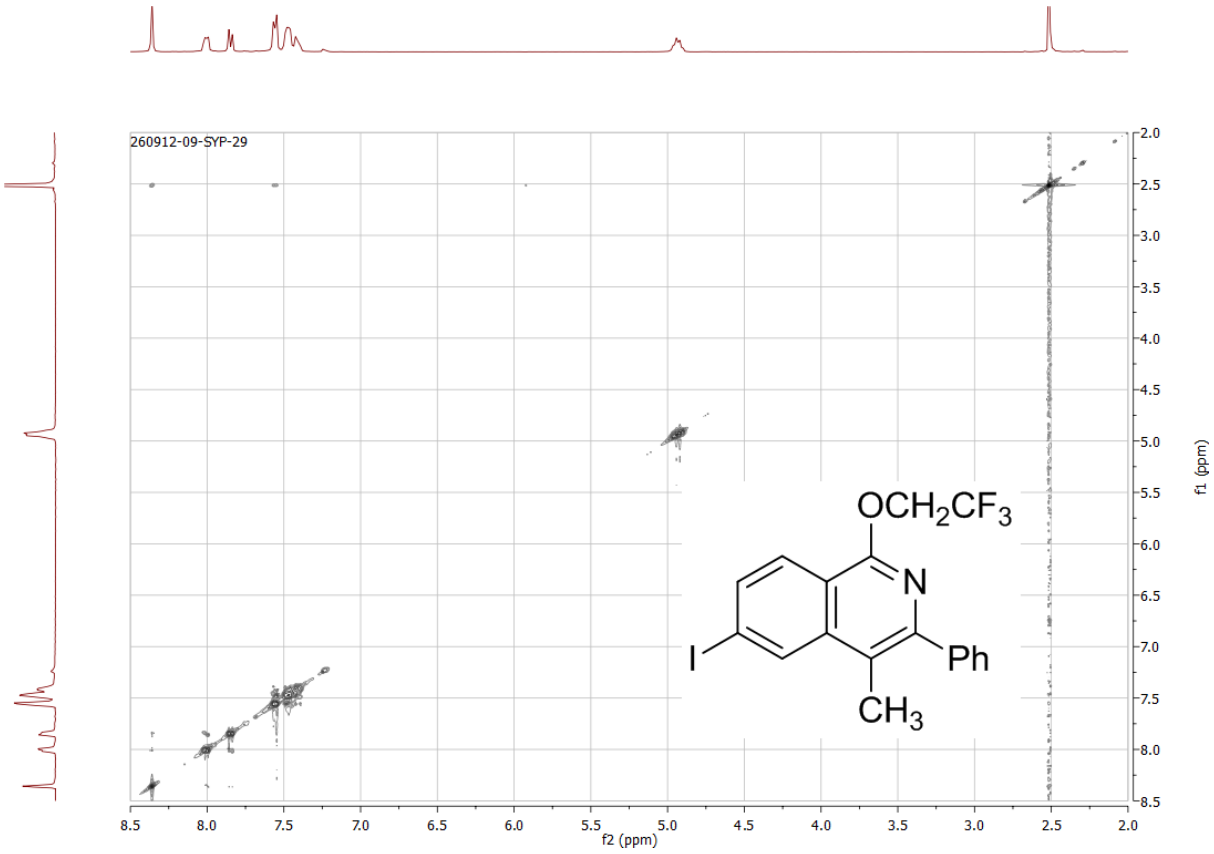


Ha δ = 2.52; Hb = 8.36; Hc = 7.48 - 7.42
Hd δ = 8.01
Observed

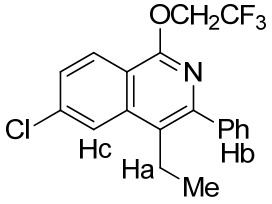


No signal
Not observed

There is a NOE correlation between Ha (δ 2.52, s) and Hb (δ 8.36, s). In meantime, there is also correlation between Ha (δ 2.52, s) and Hc (δ 7.48 – 7.42, m). However, there is no correlation between Hb (δ 8.36, s) and Hc (δ 7.48 – 7.42, m). These results clearly revealed that the regiochemistry of compound **3f** is correct.

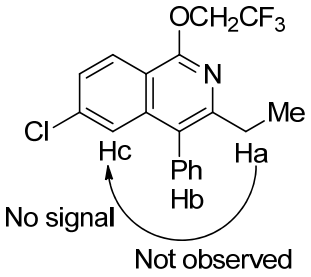


Copy of NOESY Experiment of Compound **3j**.

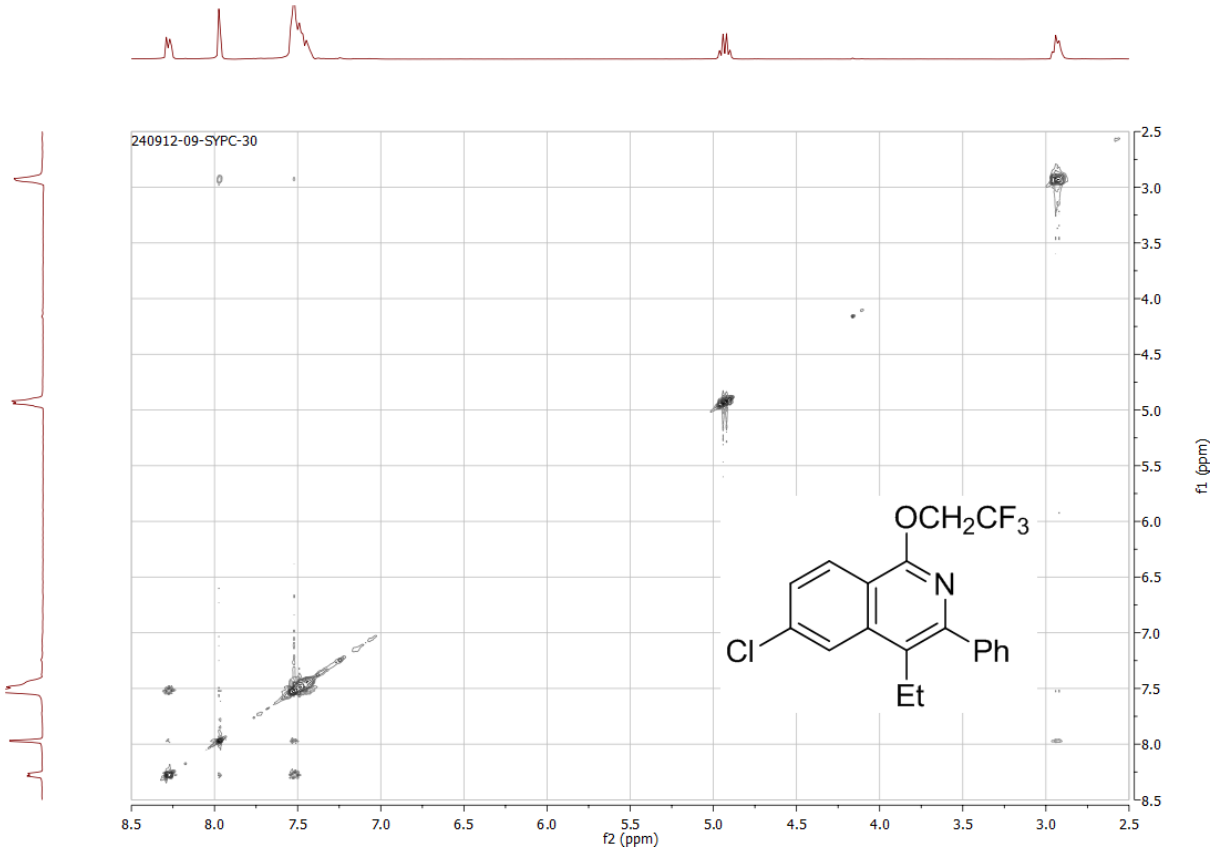


Ha δ = 2.93; Hb = 7.54 - 7.43; Hc = 7.97

Observed

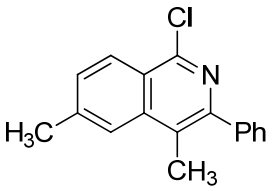


There is a NOE correlation between Ha (δ 2.93, q) and Hc (δ 7.97, s). In meantime, there is also correlation between Ha (δ2.93, q) and Hb (δ 7.54 – 7.43, m). If the other regioisomer is formed, there should not be correlation between Ha (δ 2.93, q) and Hc (δ 7.97, s). However, there is correlation between Ha (δ 2.93, q) and Hc ((δ 7.97, s). Thus, these results clearly revealed that the regiochemistry of compound **3j** is correct.



Spectral Data of all Compounds

1-Chloro-4,6-dimethyl-3-phenylisoquinoline (**3a**).



Brown semisolid; eluent (3% ethyl acetate in hexanes)

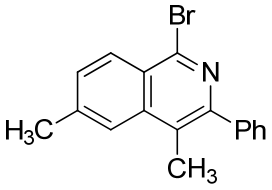
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922, 1722, 1621, 1482, 1308, 1242 and 1091.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25(d, *J* = 8.0 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 2 H), 7.47 – 7.42 (m, 3 H), 7.40 (s, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 2.52 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6, 151.2, 145.8, 138.9, 133.4, 129.7, 129.5, 129.3, 128.2, 123.5, 118.4, 109.1, 22.3, 13.6.

HRMS (ESI): calc. for [($C_{17}H_{14}ClN$)H] (M+H) 268.0893, measured 268.0897.

1-Bromo-4,6-dimethyl-3-phenylisoquinoline (3b).



Brown semisolid; eluent (3% ethyl acetate in hexanes)

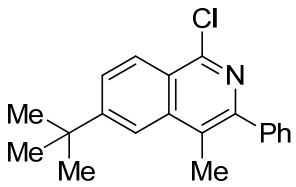
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2911, 1591, 1417, 1121 and 1038.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, *J* = 8.0 Hz, 1 H), 7.56 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.46 – 7.40 (m, 4 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 2.51 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 151.3, 145.9, 138.9, 133.5, 129.8, 129.6, 129.3, 128.3, 123.6, 118.5, 109.1, 22.4, 13.7.

HRMS (ESI): calc. for [($C_{17}H_{14}BrN$)H] (M+H) 312.0388, measured 312.0385.

6-(*tert*-Butyl)-1-chloro-4-methyl-3-phenylisoquinoline (**3c**).



Yellow liquid; eluent (3% ethyl acetate in hexanes).

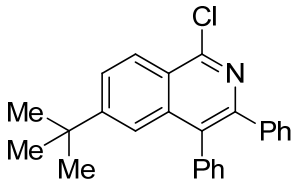
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2961, 1728, 1601, 1482, 1308, 1247, 1100 and 1037.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, *J* = 8.0 Hz, 1 H), 7.60 – 7.58 (m, 3 H), 7.56 (d, *J* = 4.0 Hz, 1 H), 7.47 – 7.41 (m, 3 H), 2.32 (s, 3 H), 1.40 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6, 158.7, 151.2, 138.7, 133.5, 129.6, 129.5, 129.3, 128.3, 125.9, 119.6, 118.4, 109.4, 35.7, 31.2, 13.6.

HRMS (ESI): calc. for [($C_{20}H_{20}ClN$)H] (M+H) 310.1363, measured 310.1366.

6-(*tert*-Butyl)-1-chloro-3,4-diphenylisoquinoline (3d).



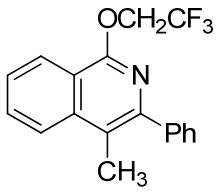
Colorless solid; eluent (3% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (d, *J* = 8.0 Hz, 1 H), 7.57 (dd, *J* = 4.0, 4.0 Hz, 1 H) 7.42 – 7.38 (m, 3 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.26 – 7.23 (m, 2 H), 7.21 – 7.15 (m, 4 H), 1.22 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.3, 158.6, 150.9, 138.7, 134.4, 133.1, 131.3, 129.4, 129.3, 129.0, 128.8, 128.1, 127.9, 126.0, 121.7, 118.0, 117.3, 35.5, 30.9.

HRMS (ESI): calc. for [($C_{25}H_{22}ClN$)H] (M+H) 372.1519, measured 372.1516.

4-Methyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3e**).



Colorless solid; eluent (1% ethyl acetate in hexanes).

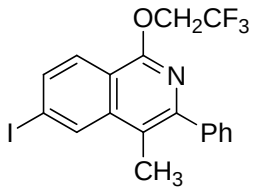
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2923, 2855, 1729, 1624, 1580, 1454, 1350, 1272, 1107 and 1034.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (d, *J* = 8.0 Hz, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 7.77 (t, *J* = 8.0 Hz, 1 H), 7.60 (t, *J* = 8.0 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 2 H), 7.48 (t, *J* = 8.0 Hz, 2), 7.42 – 7.38 (m, 1 H), 4.96 (q, *J* = 8.0 Hz, 2 H), 2.57 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.1, 147.2, 140.8, 138.8, 130.9, 130.0, 128.0, 127.7, 126.5, 125.4 (due to F – Coupling), 124.2, 123.7, 122.6 (due to F – Coupling), 119.2, 118.0, 62.1 (q, *J* = 36.0 Hz), 15.2.

HRMS (ESI): calc. for [($C_{18}H_{14}F_3NO$)H] (M+H) 318.1106, measured 318.1109.

6-Iodo-4-methyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3f**).



Colorless solid; eluent (1% ethyl acetate in hexanes)

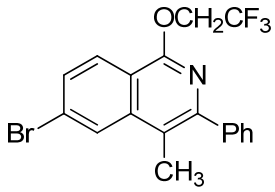
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1605, 1415, 1268, 1168, 1109 and 1054.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (s, 1 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 2 H), 7.48 (t, *J* = 8.0 Hz, 2 H), 7.42 (t, *J* = 8.0 Hz, 1 H) 4.94 (q, *J* = 8.0 Hz, 2 H) 2.52 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.1, 148.4, 140.4, 140.3, 135.3, 133.0, 129.9, 128.1, 127.9, 125.6, 125.3 and 122.5 (due to F – coupling), 118.0, 116.7, 98.9, 62.1 (d, *J* = 37.0 Hz), 15.2.

HRMS (ESI): calc. for [($C_{18}H_{13}F_3INO$)H] (M+H) 444.0072, measured 444.0076.

6-Bromo-4-methyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3g**).



Colorless solid; eluent (1% ethyl acetate in hexanes).

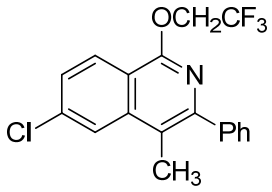
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1584, 1414, 1264, 1169, 1109 and 1034.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (d, *J* = 8.0 Hz, 1 H), 8.13 (s, 1 H), 7.66 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.56 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.48 (t, *J* = 8.0 Hz, 2 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 4.94 (q, *J* = 8.0 Hz, 2 H), 2.52 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.0, 148.6, 140.4, 140.2, 129.9, 128.1, 127.9, 126.4, 126.2, 126.0, 125.3 and 122.5 (due to F – coupling), 118.4, 116.4, 62.0 (q, *J* = 36), 15.2.

HRMS (ESI): calc. for [($C_{18}H_{13}BrF_3NO$)H] (M+H) 396.0211, measured 396.0214.

6-Chloro-4-methyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (3h).



Colorless solid; eluent (1% ethyl acetate in hexanes).

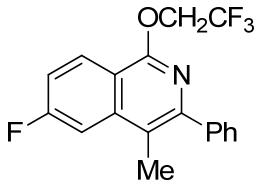
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1585, 1414, 1263, 1166, 1107 and 1035.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, *J* = 8.0 Hz, 1 H), 7.93 (s, 1 H), 7.58 (d, *J* = 8.0, Hz, 2 H), 7.53 – 7.47 (m, 3 H) 7.42 (t, *J* = 8.0, Hz, 1 H), 4.95 (q, *J* = 8.0, Hz, 2 H), 2.53 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9, 148.6, 140.4, 139.9, 137.5, 129.9, 128.1, 127.9, 127.3, 126.0, 125.3 (due to F – coupling), 123.1, 122.5 (due to F – coupling), 118.5, 116.2, 62.2 (q, *J* = 35.0 Hz), 15.2.

HRMS (ESI): calc. for $[(C_{18}H_{13}ClF_3NO)H]$ (M+H) 352.0716, measured 352.0713.

6-Fluoro-4-methyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3i**).



Colorless solid; eluent (1% ethyl acetate in hexanes)

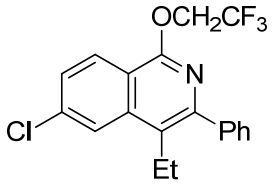
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1568, 1417, 1260, 1150, 1109 and 1035.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.34 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.59 – 7.54 (m, 3 H), 7.48 (t, *J* = 8.0 Hz, 2 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.33 (t, *J* = 8.0 Hz, 1 H), 4.95 (q, *J* = 8.0 Hz, 2 H), 2.51 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.4, 162.9, 155.9, 148.5, 141.0 (d, *J* = 9.0 Hz), 140.5, 129.9, 128.1 (d, *J* = 18.0 Hz), 127.4 (d, *J* = 10.0 Hz), 125.3 and 122.5 (due to F – coupling), 118.9 (d, *J* = 5.0 Hz), 116.4 (d, *J* = 24.0 Hz), 114.9, 108.3 (d, *J* = 22.0 Hz), 62.1 (q, *J* = 36.0 Hz), 15.3.

HRMS (ESI): calc. for $[(C_{18}H_{13}F_4NO)H]$ (M+H) 336.1012, measured 336.1017.

6-Chloro-4-ethyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3j**).



Colorless solid; eluent (1% ethyl acetate in hexanes)

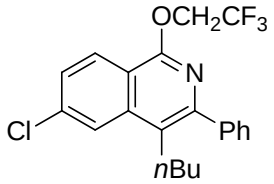
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 1612, 1579, 1416, 1269, 1167, 1109 and 1054.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (d, *J* = 8.0 Hz, 1 H), 7.97 (s, 1 H), 7.54 – 7.43 (m, 6 H), 4.93 (q, *J* = 8.0 Hz, 2 H), 2.93 (q, *J* = 8.0 Hz, 2 H), 1.28 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9, 148.8, 140.8, 138.9, 137.5, 129.2, 128.2, 127.9, 127.3, 126.2, 125.3 (due to F – coupling), 125.0, 123.1, 122.5 (F – coupling), 116.7, 62.2 (q, *J* = 35.0 Hz), 21.4, 15.7.

HRMS (ESI): calc. for [($C_{19}H_{15}ClF_3NO$)H] (M+H) 366.0873, measured 366.0878.

4-Butyl-6-chloro-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3k**).



Colorless solid; eluent (1% ethyl acetate in hexanes)

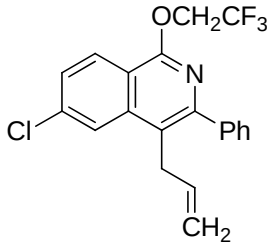
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2951, 2868, 1614, 1510, 1467, 1371, 1254, 1162 and 1037.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.92 (s 1 H), 7.52 – 7.40 (m, 6 H), 4.90 (q, *J* = 8.0 Hz, 2 H), 2.87 (t, *J* = 8.0 Hz, 2 H), 1.63 – 1.55 (m, 2 H), 1.37 – 1.28 (m, 2 H), 0.85 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.8, 149.0, 140.8, 139.1, 137.4, 129.3, 128.1, 127.8, 127.2, 126.2, 125.3 (due to F – coupling), 123.8, 123.1, 122.5 (due to F – coupling), 116.6, 62.2 (q, *J* = 36.0 Hz), 33.3, 27.9, 22.8, 13.8.

HRMS (ESI): calc. for [($C_{21}H_{19}ClF_3NO$)H] (M+H) 394.1186, measured 394.1189.

4-Allyl-6-chloro-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3l**).



Yellow liquid; eluent (1% ethyl acetate in hexanes)

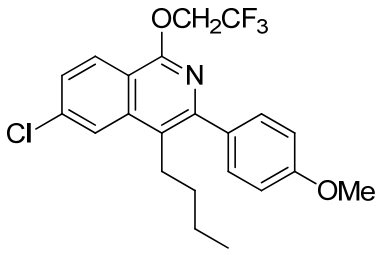
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1614, 1580, 1490, 1414, 1376, 1271, 1166 and 1030.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (d, *J* = 8.0 Hz, 1 H), 7.90 (s, 1 H), 7.61 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.52 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.48 – 7.42 (m, 2 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 6.19 – 6.10 (m, 1 H) 5.20 (dd, *J* = 8.0, 4.0 Hz, 1 H), 4.96 (q, *J* = 8.0 Hz, 2 H), 4.90 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.67 (q, *J* = 8.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.4, 149.8, 140.2, 139.5, 137.6, 136.9, 131.5, 129.2, 128.2, 128.1, 127.4, 126.0, 125.3 (due to F – coupling), 123.8, 122.5 (due to F – coupling), 120.0, 117.1, 116.5, 62.2 (q, *J* = 36.0 Hz), 32.8.

HRMS (ESI): calc. for [($C_{20}H_{15}ClF_3NO$)H] (M+H) 378.0873, measured 378.0874.

4-Butyl-6-chloro-3-(4-methoxyphenyl)-1-(2,2,2-trifluoroethoxy)isoquinoline (**3m**).



Yellow semi solid; eluent (3% ethyl acetate in hexanes)

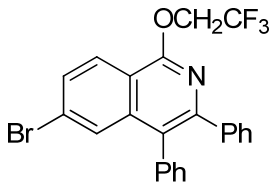
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957, 2863, 1610, 1515, 1462, 1375, 1259, 1169 and 1034.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, *J* = 8.0 Hz, 1 H), 7.91 (s, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 2 H), 7.00 (d, *J* = 8.0 Hz, 2 H), 4.91 (q, *J* = 8.0 Hz, 2 H) 3.88 (s, 3 H), 2.90 (t, *J* = 8.0 Hz, 2 H), 1.64 – 1.57 (m, 2 H), 1.40 – 1.31 (m, 2 H), 0.88 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3, 155.7, 148.7, 139.2, 137.3, 133.4 133.3, 130.6, 127.0, 126.2, 125.3 (due to F – coupling), 123.6, 123.1, 122.5 (due to F – coupling), 116.5, 113.5, 62.1 (q, *J* = 37.0 Hz), 55.4, 33.3, 28.0, 22.9, 13.8.

HRMS (ESI): calc. for [($C_{22}H_{21}ClF_3NO_2$)H] (M+H) 424.1291, measured 424.1296.

6-Bromo-3,4-diphenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3n**).



Yellow solid; eluent (1% ethyl acetate in hexanes)

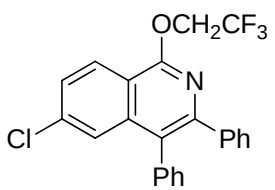
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 1581, 1454, 1361, 1272, 1132 and 1045.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21(d, *J* = 8.0 Hz, 1 H), 7.72 (s, 1 H), 7.66 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.38 – 7.32 (m, 5 H), 7.20 – 7.18 (m, 5 H), 5.04 (q, *J* = 8.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.1, 147.8, 140.1, 139.8, 136.6, 131.4, 130.3, 130.2, 128.7, 128.4, 128.0, 127.7, 127.6, 126.4, 125.9, 125.6, 125.3 and 122.5 (due to F – coupling), 116.3, 62.4 (q, *J* = 36.0 Hz).

HRMS (ESI): calc. for [($C_{23}H_{15}BrF_3NO$)H] (M+H) 458.0367, measured 458.0367.

6-Chloro-3,4-diphenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3o**).



Yellow solid; eluent (1% ethyl acetate in hexanes).

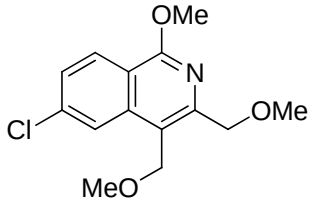
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922, 1584, 1458, 1419, 1364, 1270, 1122 and 1040.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, *J* = 8.0 Hz, 1 H), 7.54 (s, 1 H), 7.51 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.38 – 7.32 (m, 5 H), 7.20 – 7.18 (m, 5 H), 5.04 (q, *J* = 8.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.0, 147.8, 139.9, 139.8, 137.7, 136.7, 131.4, 130.4, 130.2, 128.7, 128.4, 127.7, 127.3, 125.9, 125.8 (due to F – coupling), 125.6, 125.2 (due to F – coupling), 124.8, 116.0, 62.3 (q, *J* = 37 Hz).

HRMS (ESI): calc. for [($C_{23}H_{15}ClF_3NO$)H] (M+H) 414.0873, measured 414.0871.

6-Chloro-1-methoxy-3,4-bis(methoxymethyl)isoquinoline (3p).



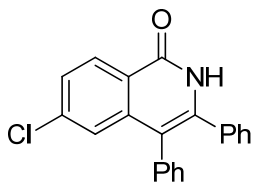
Pale yellow semisolid; eluent (20% ethyl acetate in hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (d, *J* = 8.0 Hz, 1 H), 7.40 (s, 1 H), 7.16 (dd, *J* = 8.0, 4.0 Hz, 1 H), 4.55 (s, 2 H), 4.54 (s, 2 H), 4.11 (s, 3 H), 3.37 (s, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.1, 145.9, 142.6, 135.0, 132.7, 129.2, 126.9, 121.6, 121.0, 67.1, 66.0, 63.8, 58.5, 58.3.

HRMS (ESI): calc. for [($C_{14}H_{16}ClNO_3$)H] (M+H) 282.0897, measured 282.0903.

6-Chloro-3,4-diphenylisoquinolin-1(2*H*)-one (4a).



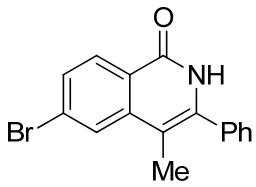
Colorless solid; eluent (25% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.77 (bs, 1H), 8.36 (d, *J* = 8.0 Hz, 1 H), 7.41 (dd, *J* = 4.0, 4.0 Hz, 1 H) 7.32 – 7.29 (m, 4 H), 7.27 – 7.20 (m, 5 H), 7.15 – 7.13 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4, 154.9, 140.1, 139.5, 138.7, 135.0, 134.6, 131.7,129.3, 128.9, 128.7, 128.4, 127.7, 127.2, 125.1, 123.4, 116.5.

HRMS (ESI): calc. for [($C_{21}H_{14}ClNO$)H] (M+H) 332.0842, measured 332.0840.

6-Bromo-4-methyl-3-phenylisoquinolin-1(2*H*)-one (4b).



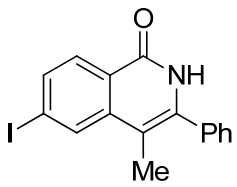
Colorless solid; eluent (25% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.14 (bs, 1H), 8.25 (d, *J* = 8.0 Hz, 1 H), 7.87 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1 H) 7.51 – 7.42 (m, 5 H), 2.21 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 181.4, 140.5, 139.8, 134.9, 130.1, 129.7, 129.5, 129.4, 128.8, 127.5, 126.7, 124.7, 106.9, 13.9.

HRMS (ESI): calc. for [($C_{16}H_{12}BrNO$)H] (M+H) 314.0181, measured 314.0183.

6-Iodo-4-methyl-3-phenylisoquinolin-1(2*H*)-one (4c).



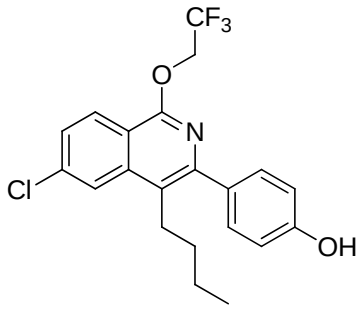
Colorless solid; eluent (25% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.08 (bs, 1H), 8.10 (d, *J* = 4.0 Hz, 1 H), 8.09 (s, 1H), 7.80 (dd, *J* = 4.0, 4.0 Hz, 1 H), 7.50 – 7.46 (m, 3 H) 7.45 – 7.41 (m, 2 H), 2.20 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.7, 140.3, 139.5, 135.2, 135.0, 132.8, 130.1, 129.3, 129.2, 128.7, 125.0, 106.7, 102.0, 13.9.

HRMS (ESI): calc. for [($C_{16}H_{12}INO$)H] (M+H) 362.0042, measured 362.0040.

4-(4-Butyl-6-chloro-1-(2,2,2-trifluoroethoxy)isoquinolin-3-yl)phenol (4d).



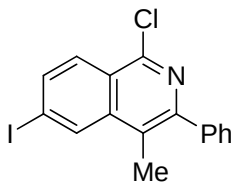
Colorless solid; eluent (15% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, *J* = 8.0 Hz, 1 H), 7.90 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1 H) 7.39 (d, *J* = 8.0 Hz, 2 H), 6.92 (d, *J* = 8.0 Hz, 2 H), 5.13 (bs, 1H), 4.90 (q, *J* = 8.0 Hz, 2 H), 2.88 (d, *J* = 8.0 Hz, 2 H), 1.59 (qt, *J* = 8.0 Hz, 2 H), 1.35 (m, 2 H), 0.88 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.7, 155.3, 148.6, 139.2, 137.4, 133.5, 130.8, 127.1, 126.2, 123.6, 123.1, 122.5, 116.5, 115.0, 62.9 – 62.2 (q), 33.3, 28.0, 22.9, 13.8.

HRMS (ESI): calc. for [($C_{22}H_{19}ClF_3NO_2$)H] (M+H) 410.1135, measured 410.1133.

1-Chloro-6-iodo-4-methyl-3-phenylisoquinoline (4e).



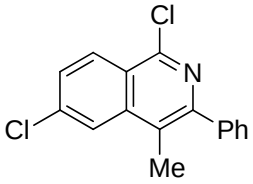
Pale yellow oil; eluent (5% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.44 (s, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 2.57 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.9, 148.9, 139.7, 139.6, 136.6, 133.6, 129.9, 128.3, 128.2, 124.4, 123.2, 99.3, 15.6.

HRMS (ESI): calc. for [($C_{16}H_{11}ClIN$)H] (M+H) 379.9703, measured 379.9711.

1,6-Dichloro-4-methyl-3-phenylisoquinoline (4f).



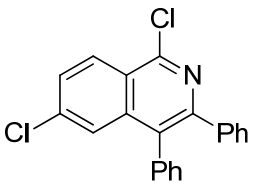
Pale yellow oil; eluent (5% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (d, *J* = 8.0 Hz, 1 H), 8.01 (s, 1 H), 7.60 (dd, *J* = 8.0 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz, 2 H), 7.41 (t, *J* = 8.0 Hz, 1 H), 2.58 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.0, 148.8, 139.5, 139.3, 137.9, 129.9, 128.8, 128.7, 128.3, 128.2, 123.9, 123.6, 123.5, 15.6.

HRMS (ESI): calc. for [($C_{16}H_{11}Cl_2N$)H] (M+H) 288.0347, measured 288.0353.

1,6-Dichloro-3,4-diphenylisoquinoline (4g).



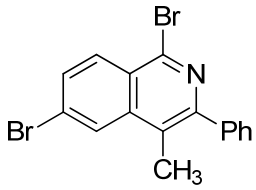
Pale yellow oil; eluent (5% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (d, *J* = 8.0 Hz, 1 H), 7.62 (s, 1 H), 7.59 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.39 – 7.37 (m, 3 H), 7.34 – 7.32 (m, 2 H), 7.21 – 7.18 (m, 5 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.9, 150.4, 139.1, 139.0, 138.0, 135.9, 131.1, 130.3, 130.1, 129.0, 128.8, 128.3, 128.1, 127.9, 125.3, 123.9.

HRMS (ESI): calc. for [($C_{21}H_{13}Cl_2N$)H] (M+H) 350.0503, measured 350.0510.

1,6-Dibromo-4-methyl-3-phenylisoquinoline (4h).



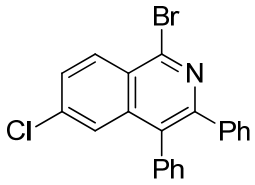
Pale yellow oil; eluent (5% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 – 8.16 (m, 2 H), 7.73 (t, *J* = 8.0 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 2.56 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.6, 142.3, 139.4, 139.1, 131.5, 131.0, 129.9, 128.3, 126.9, 126.6, 126.1, 123.8, 14.6.

HRMS (ESI): calc. for [($C_{16}H_{11}Br_2N$)H] (M+H) 375.9336, measured 375.9335.

1-Bromo-6-chloro-3,4-diphenylisoquinoline (4i).



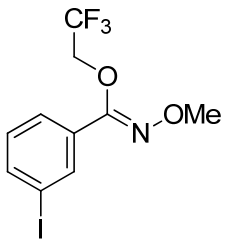
Pale yellow oil; eluent (5% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.47 – 7.45 (m, 2 H), 7.25 – 7.23 (m, 3 H), 7.20 – 7.18 (m, 2 H), 7.10 – 7.03 (m, 5 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.2, 143.8, 138.8, 138.6, 137.9, 135.7, 130.9, 130.5, 130.2, 129.1, 128.7, 128.0, 127.7, 125.9, 125.2.

HRMS (ESI): calc. for [($C_{21}H_{13}BrClN$)H] (M+H) 393.9998, measured 394.0007.

(*Z*)-2,2,2-Trifluoroethyl 3-iodo-*N*-methoxybenzimidate (8a).



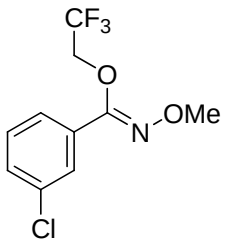
Pale Yellow semi solid; eluent (1% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (s, 1 H), 7.76 (d, *J* = 8.0, Hz, 1 H), 7.74 (d, *J* = 8.0, Hz, 1 H), 7.12 (t, *J* = 8.0, Hz, 1 H), 4.73 (q, *J* = 8.0, Hz, 2 H), 3.96 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.4, 139. 4, 135.4, 132.1, 130.1, 125.7, 124.5 – 121.7 (F coupling), 94.1, 69.0 – 67.9 (q, due to fluorine coupling), 63.0.

HRMS (ESI): calc. for [($C_{10}H_9F_3INO_2$)H] (M+H) 359.9708, measured 359.9703.

(*Z*)-2,2,2-Trifluoroethyl 3-chloro-*N*-methoxybenzimidate (8b).



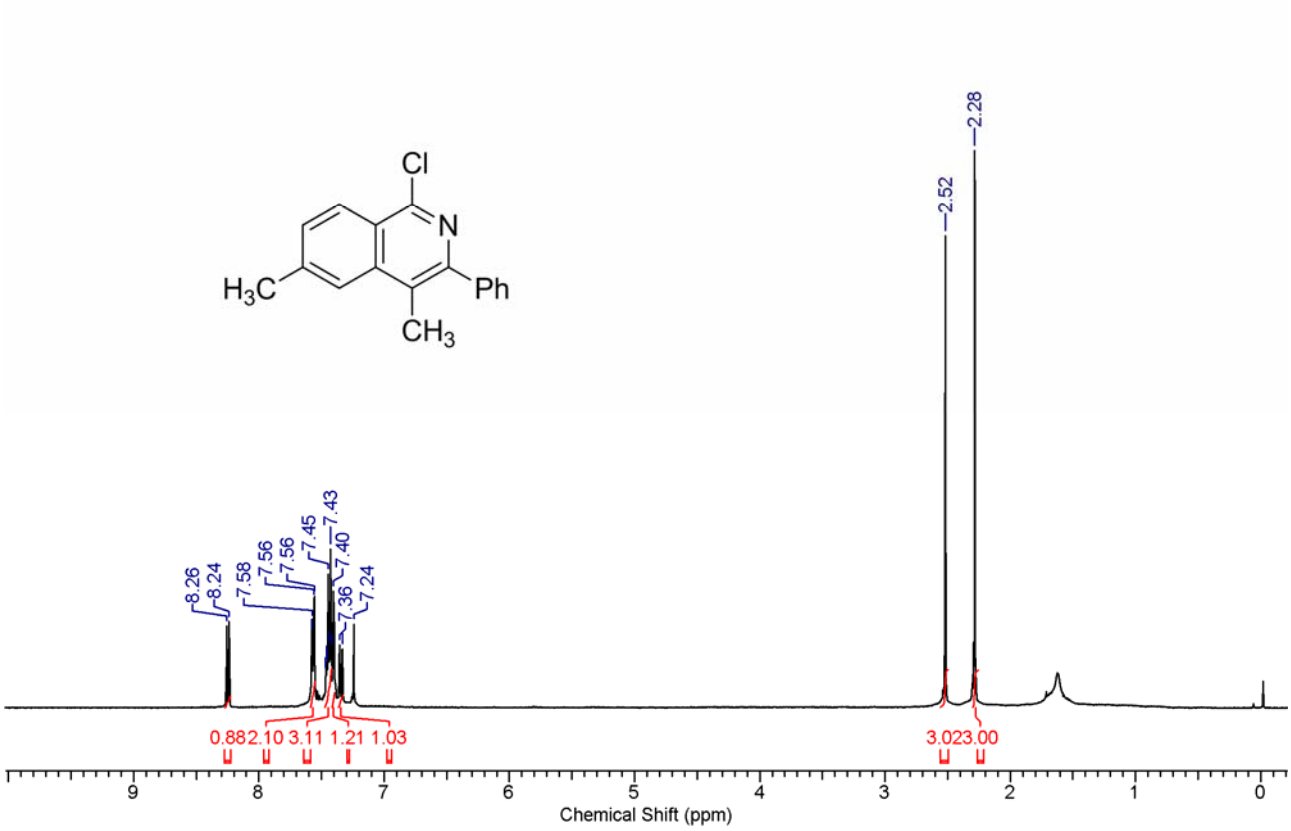
Pale Yellow semi solid; eluent (1% ethyl acetate in hexanes).

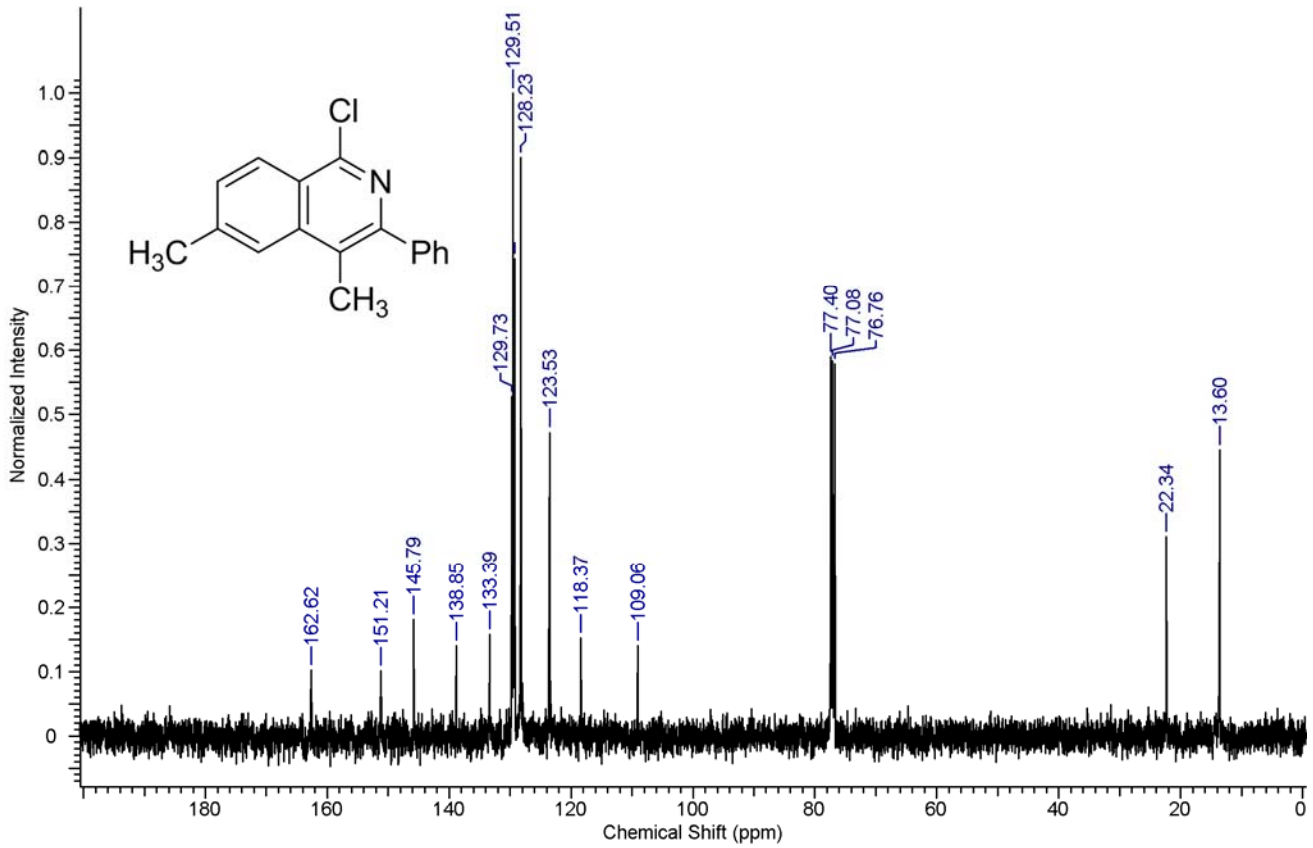
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (s, 1 H), 7.67 (d, *J* = 8.0, Hz, 1 H), 7.39 (d, *J* = 8.0, Hz, 1 H), 7.32 (t, *J* = 8.0, Hz, 1 H), 4.74 (q, *J* = 8.0, Hz, 2 H), 3.96 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.7, 134.6, 131.9, 130.5, 129.7, 126.6, 124.6, 124.5 – 121.7 (F coupling), 69.0 – 67.9 (q, due to fluorine coupling), 63.0.

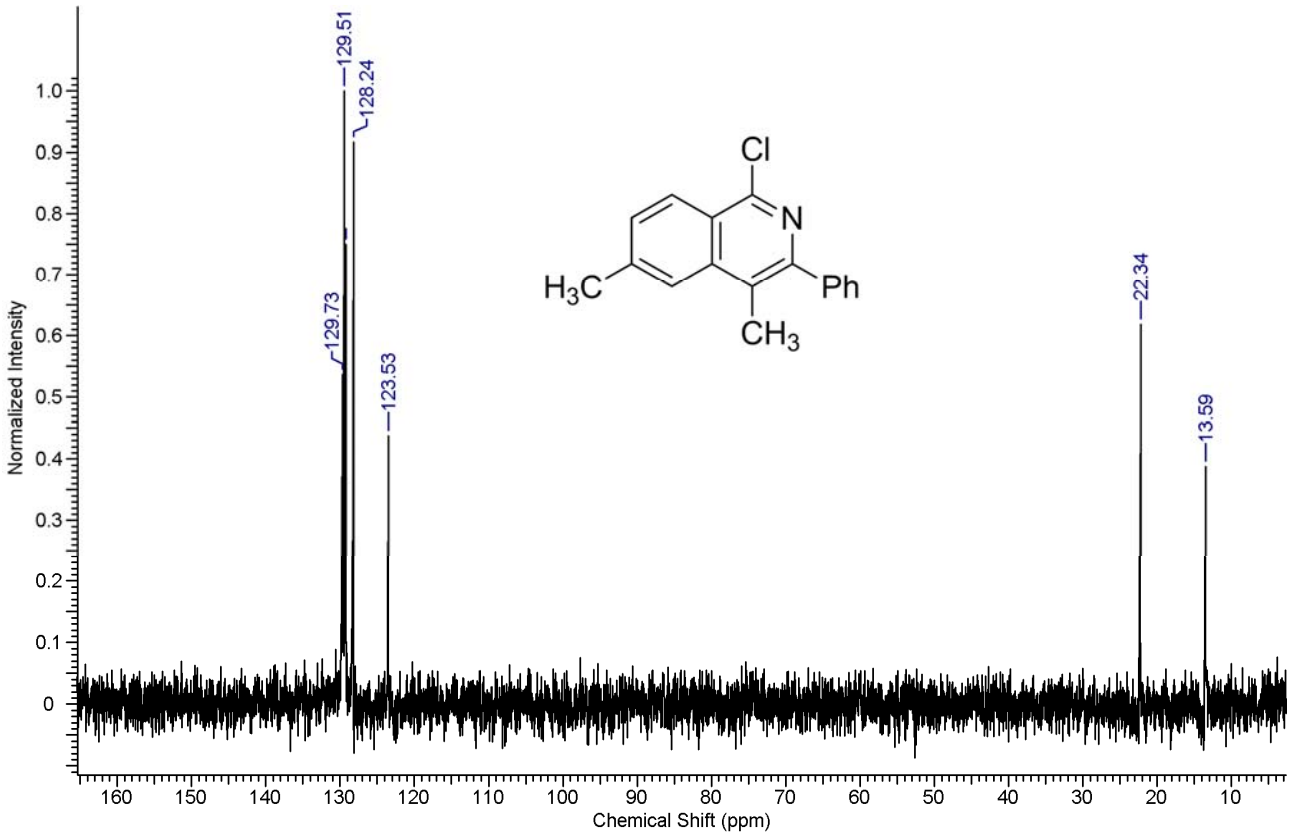
HRMS (ESI): calc. for [($C_{10}H_9ClF_3NO_2$)H] (M+H) 268.0352, measured 268.0350.

^{1}H and ^{13}C NMR Spectra of Compound **3a.**

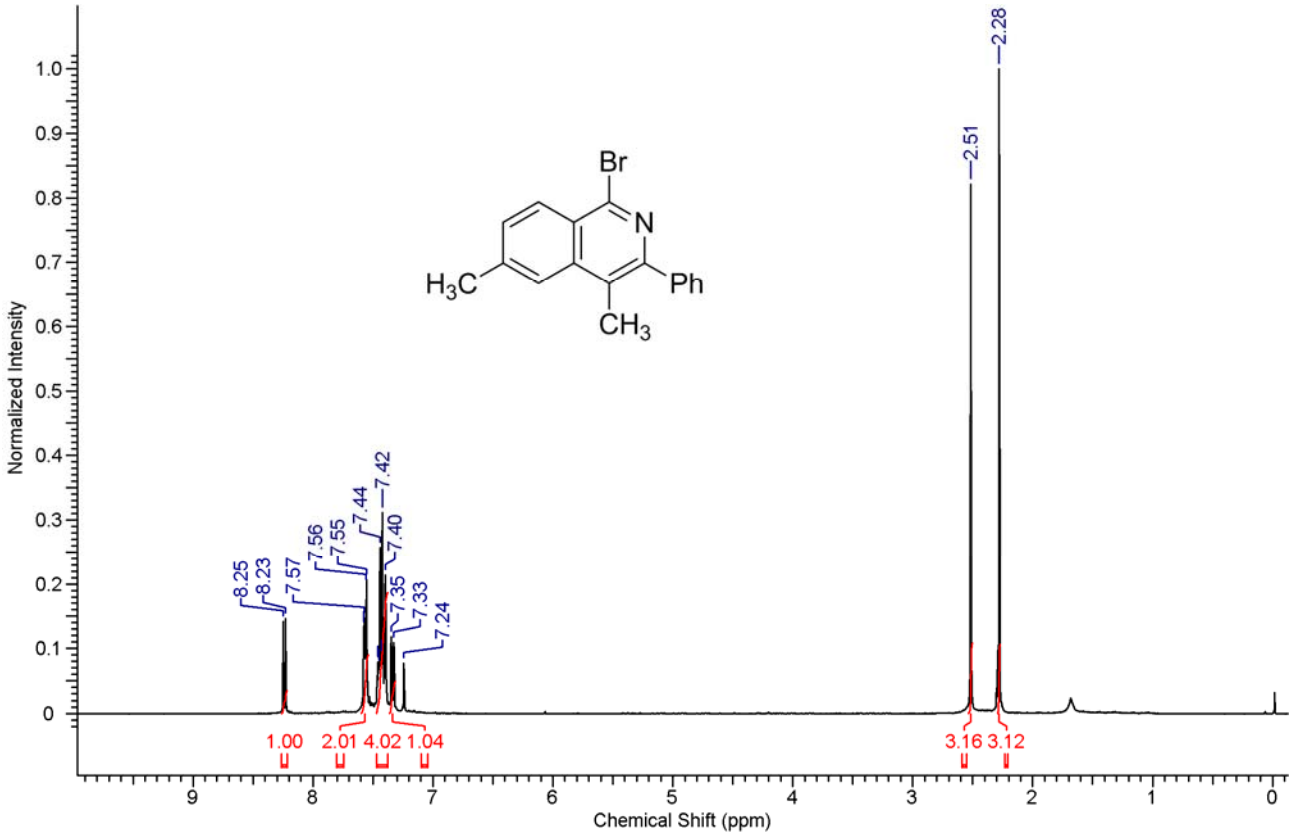


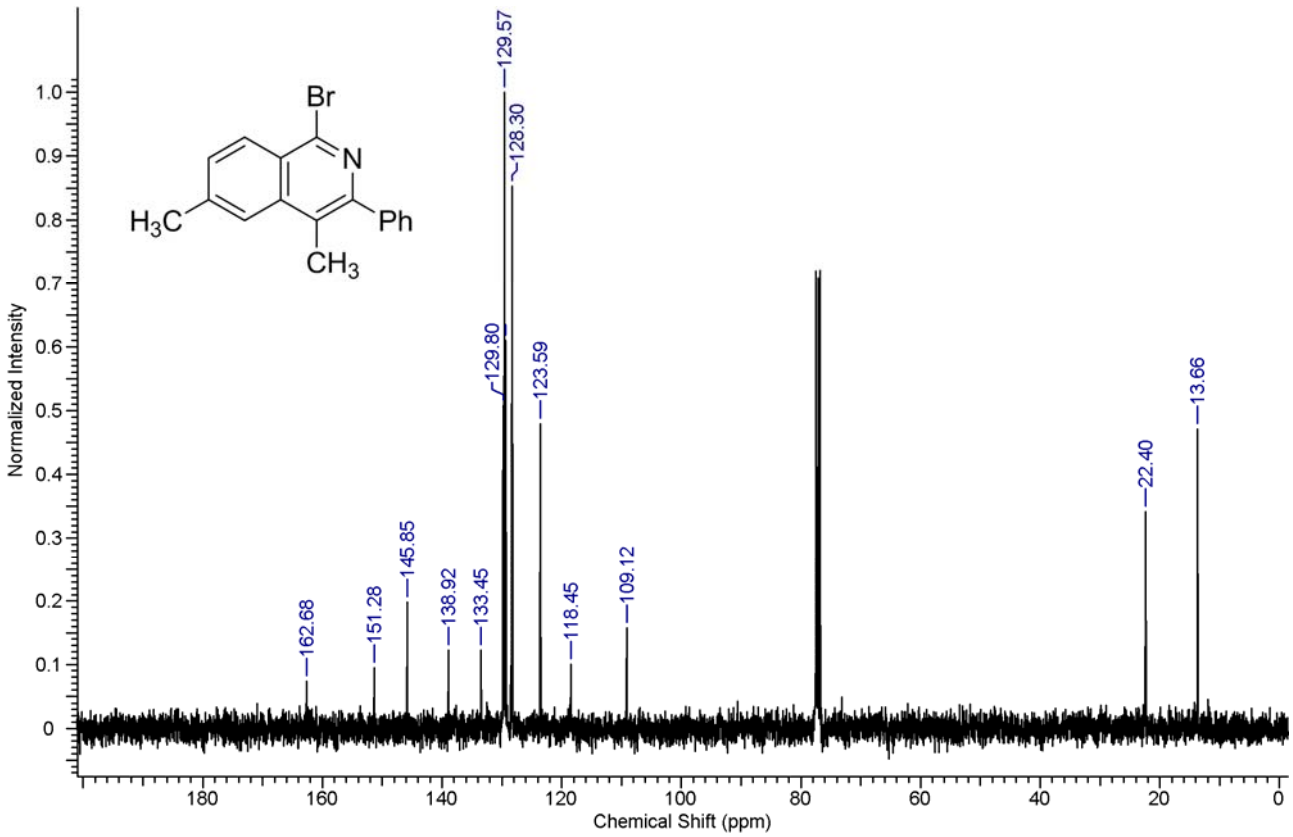


DEPT (135) NMR Spectrum of Compound **3a.**

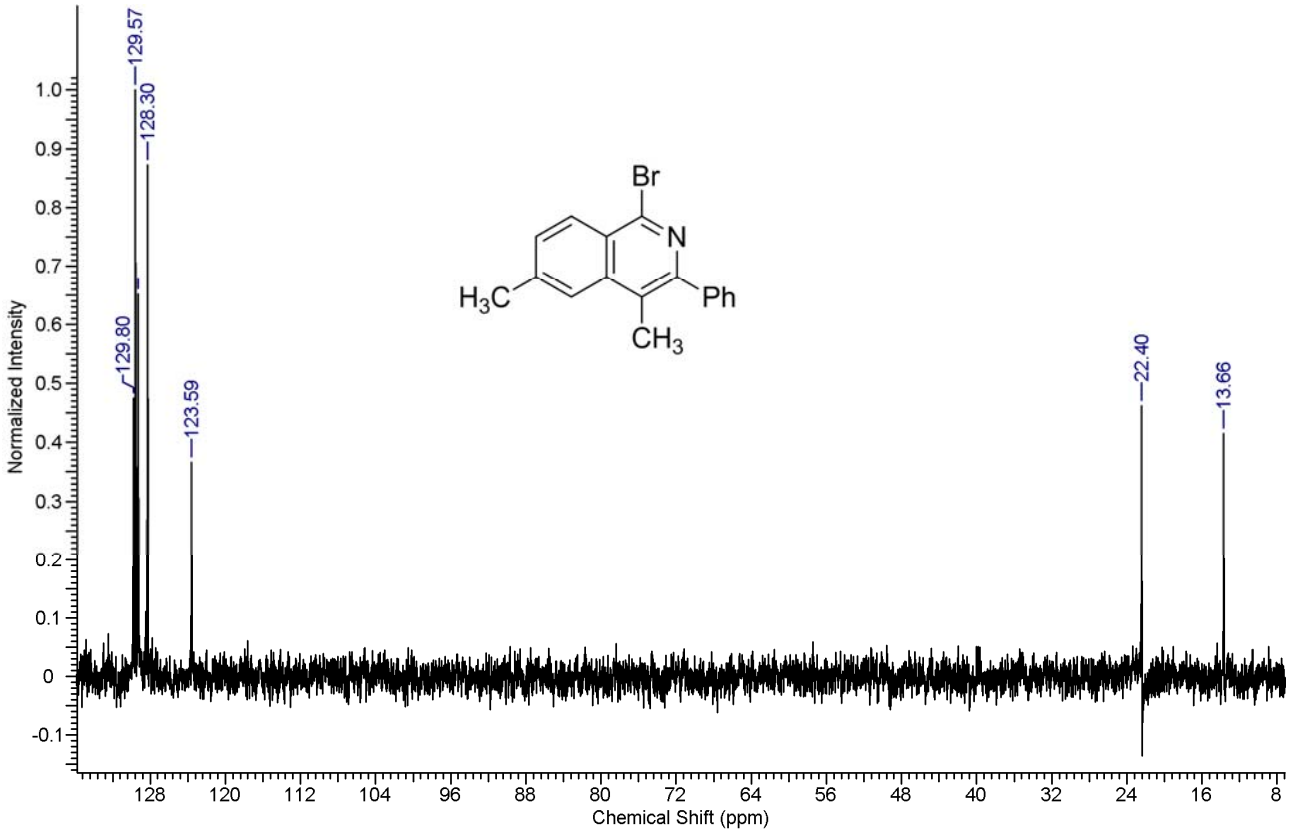


^{1}H and ^{13}C NMR Spectra of Compound **3b.**

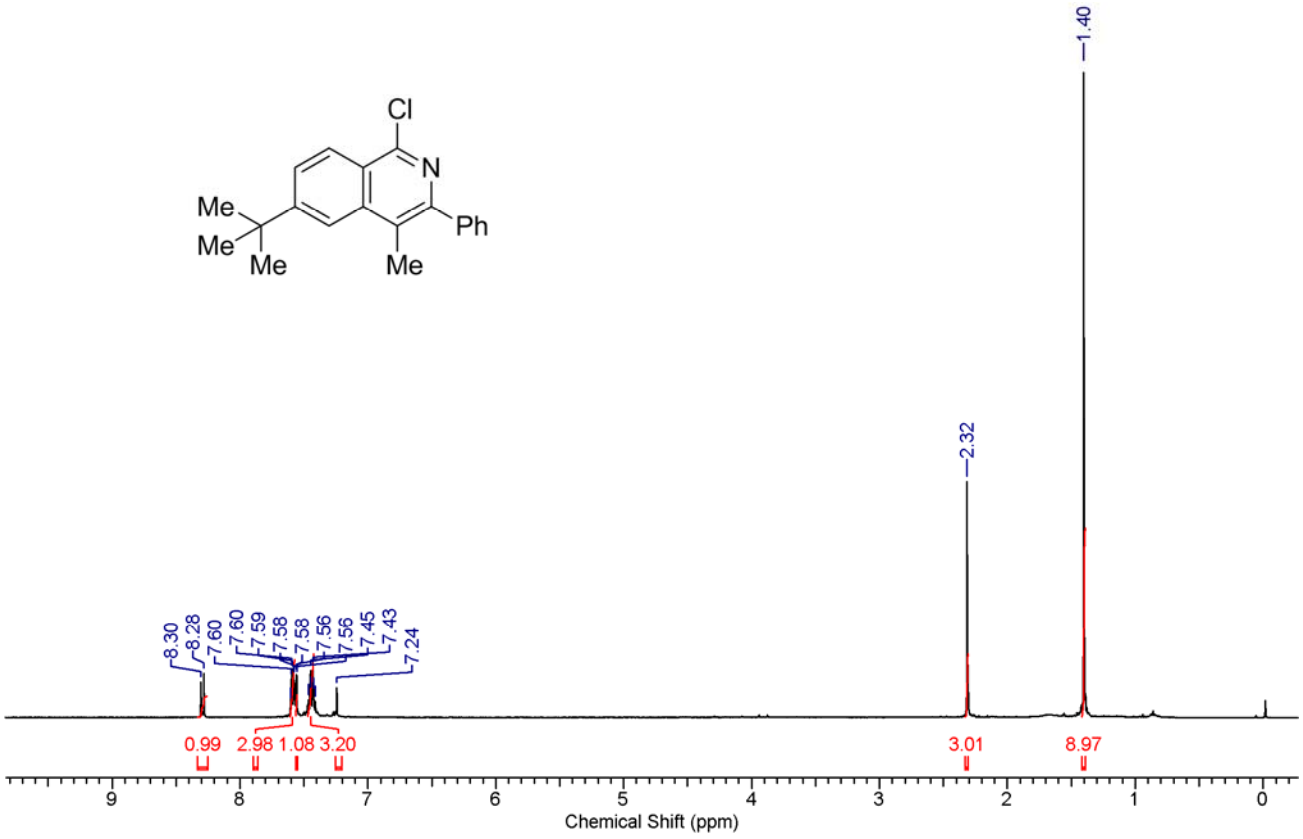


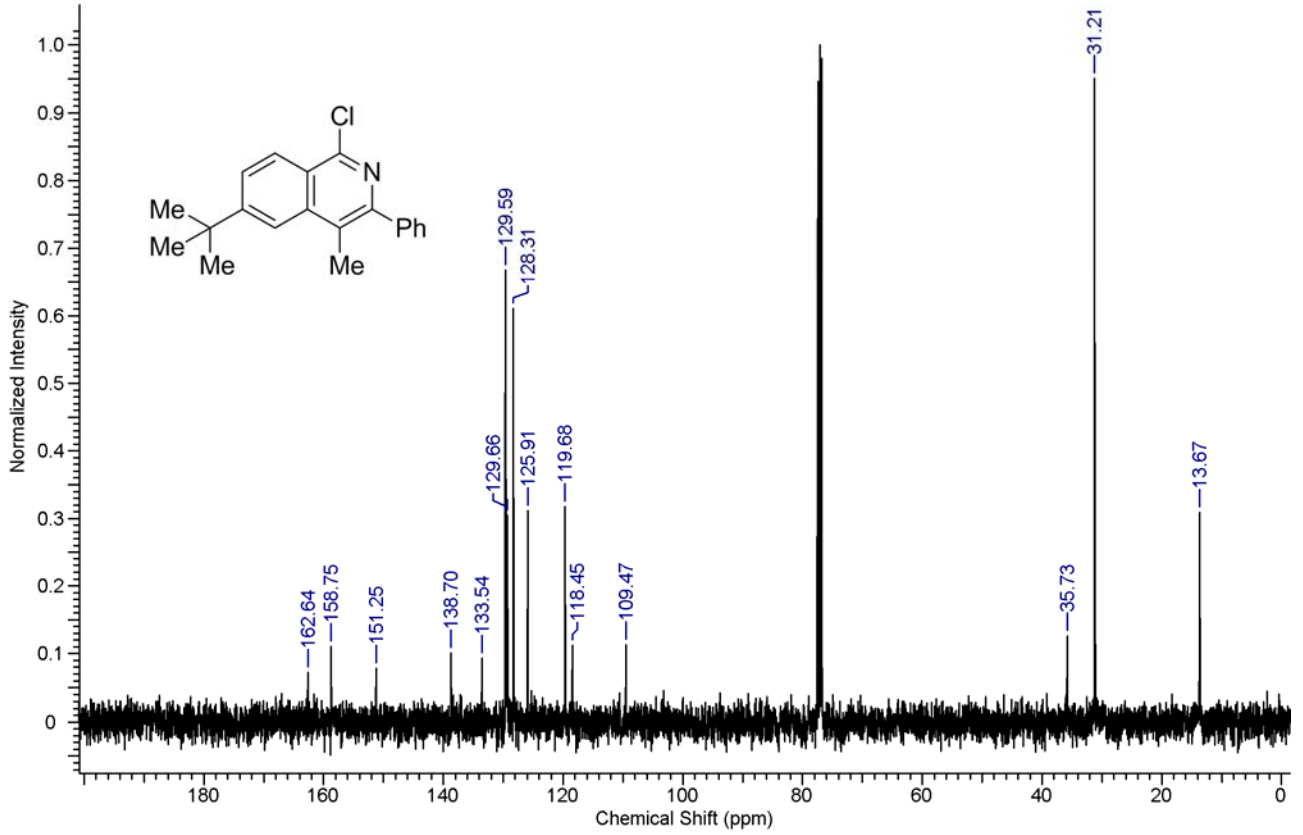


DEPT (135) NMR Spectrum of Compound **3b.**

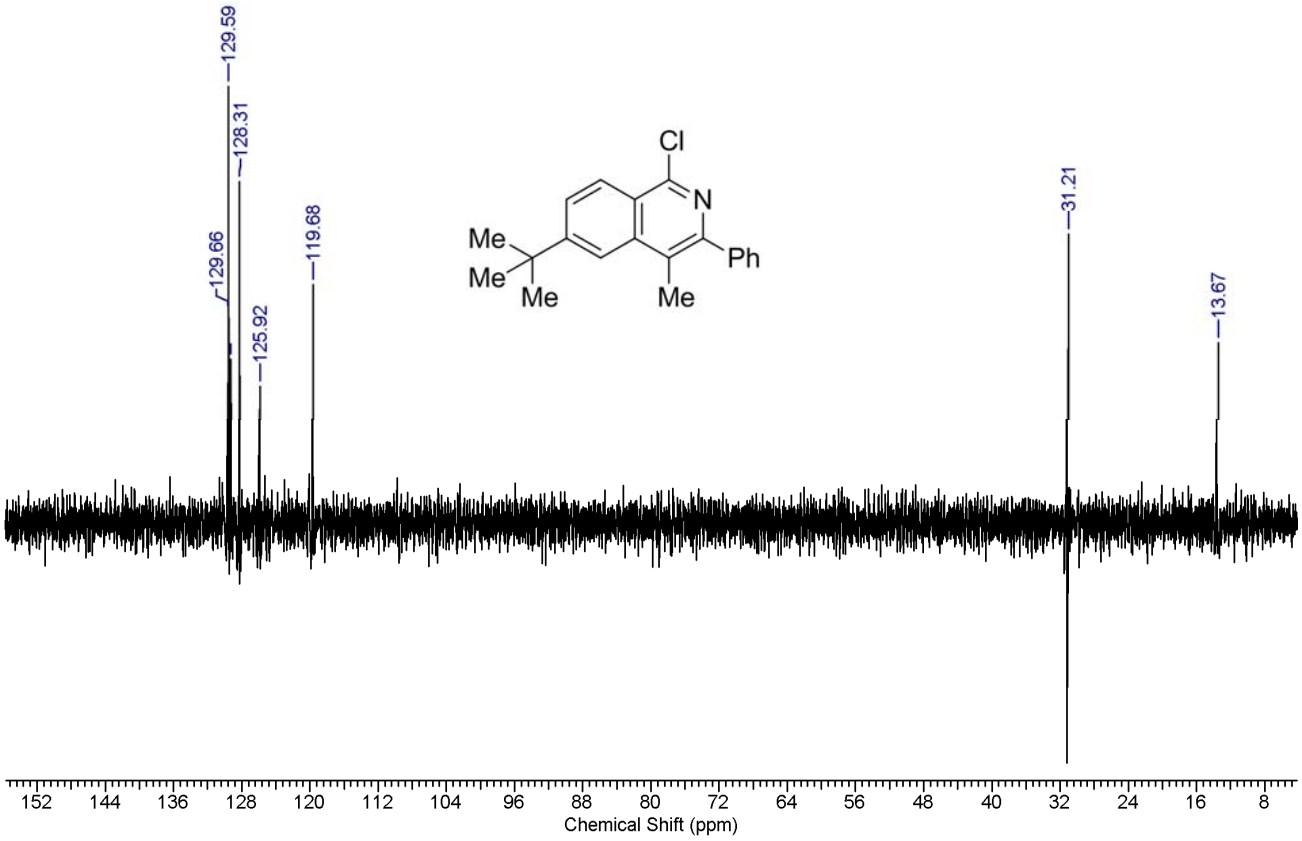


^{1}H and ^{13}C NMR Spectra of Compound **3c.**

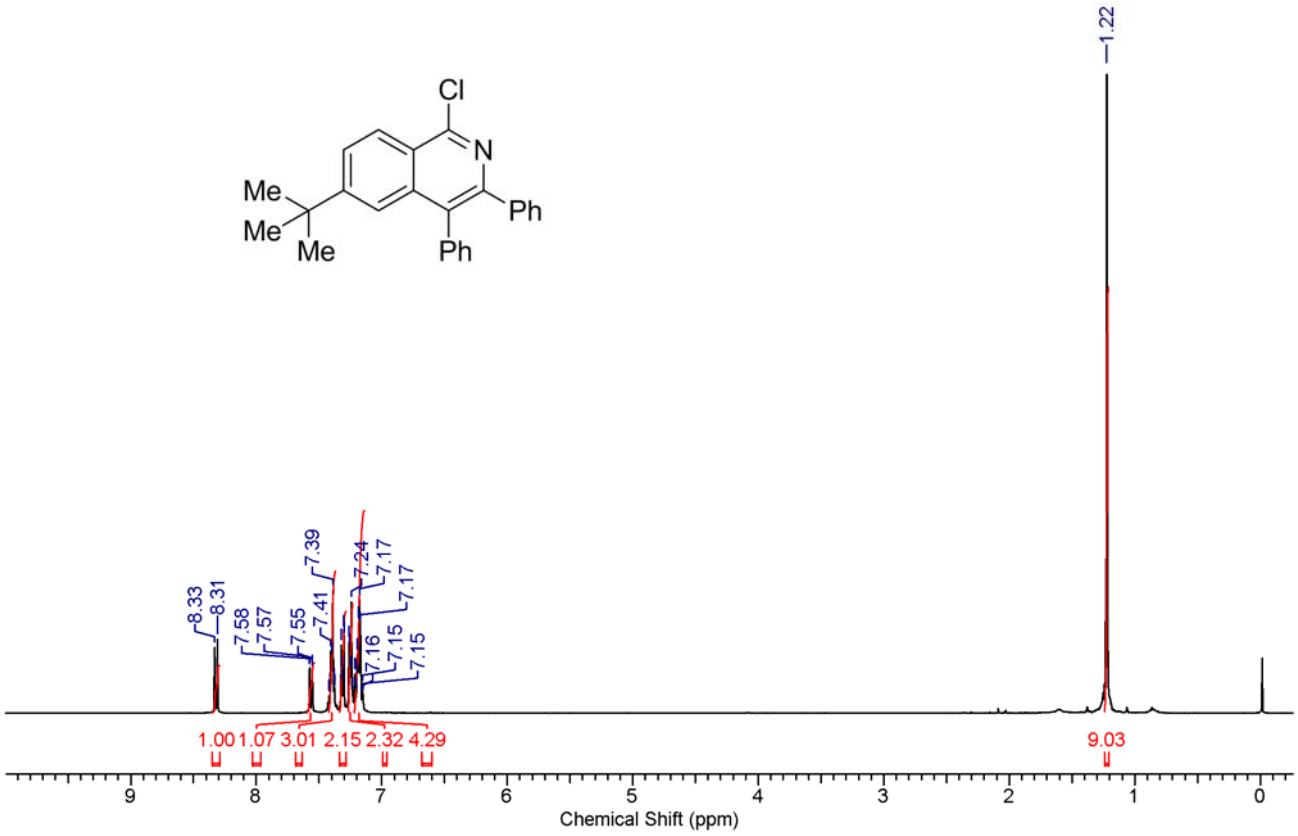


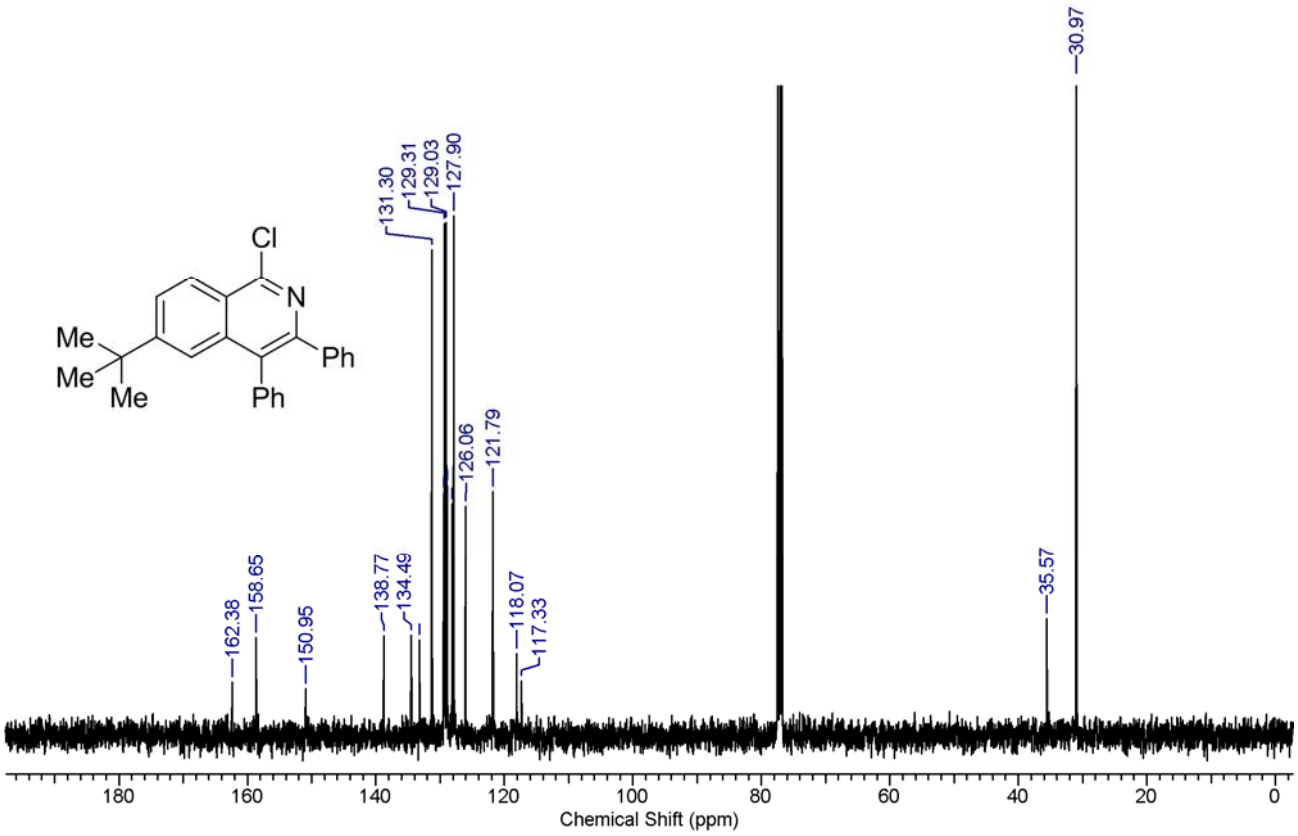


DEPT (135) NMR Spectrum of Compound **3c.**

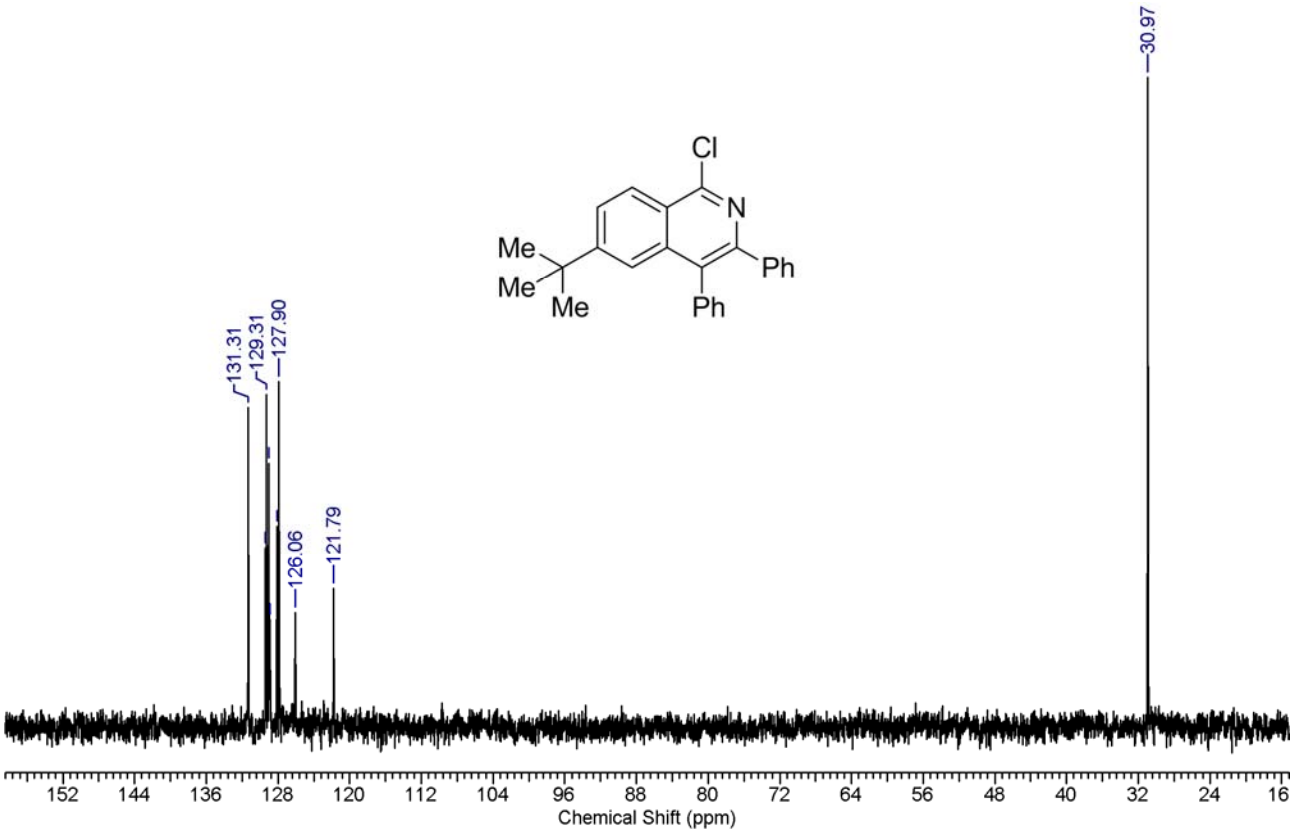


^{1}H and ^{13}C NMR Spectra of Compound **3d.**

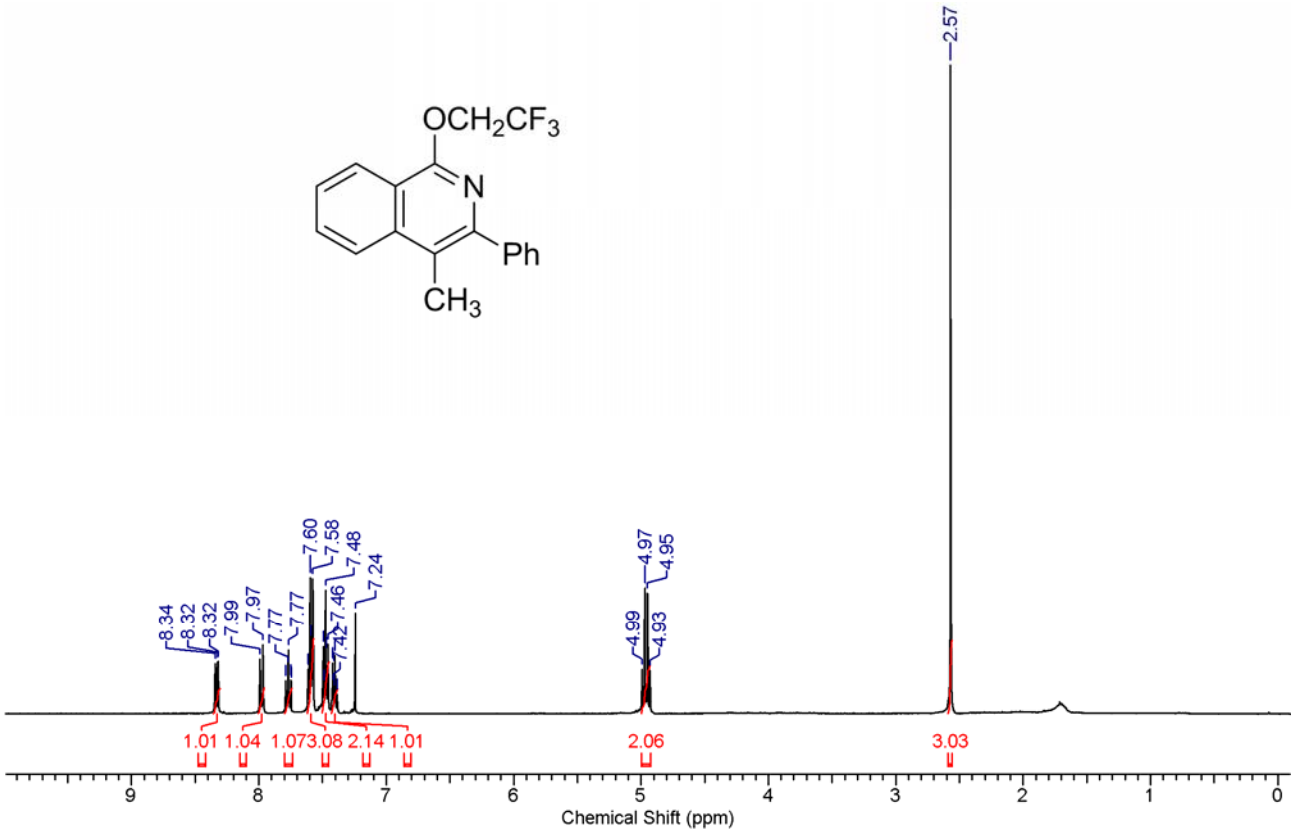


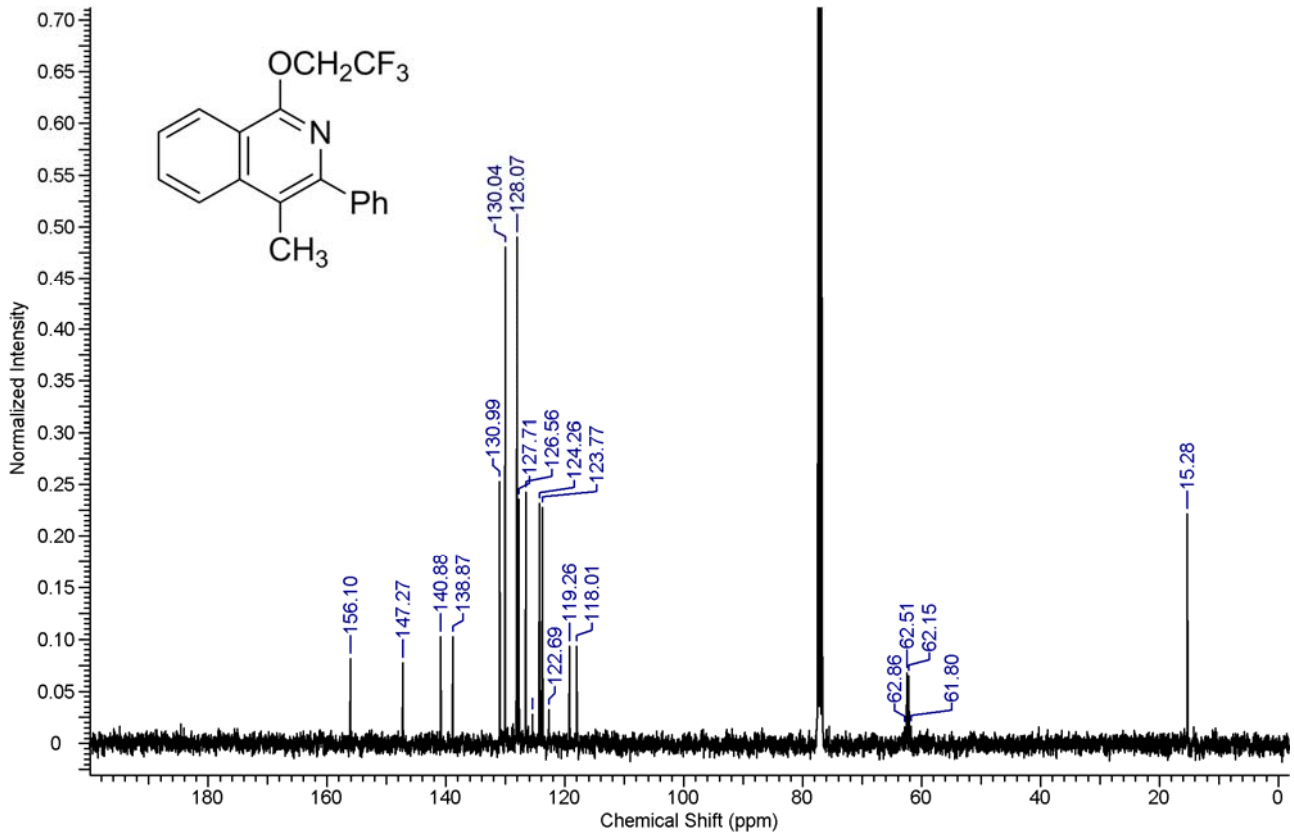


DEPT (135) NMR Spectrum of Compound **3d.**

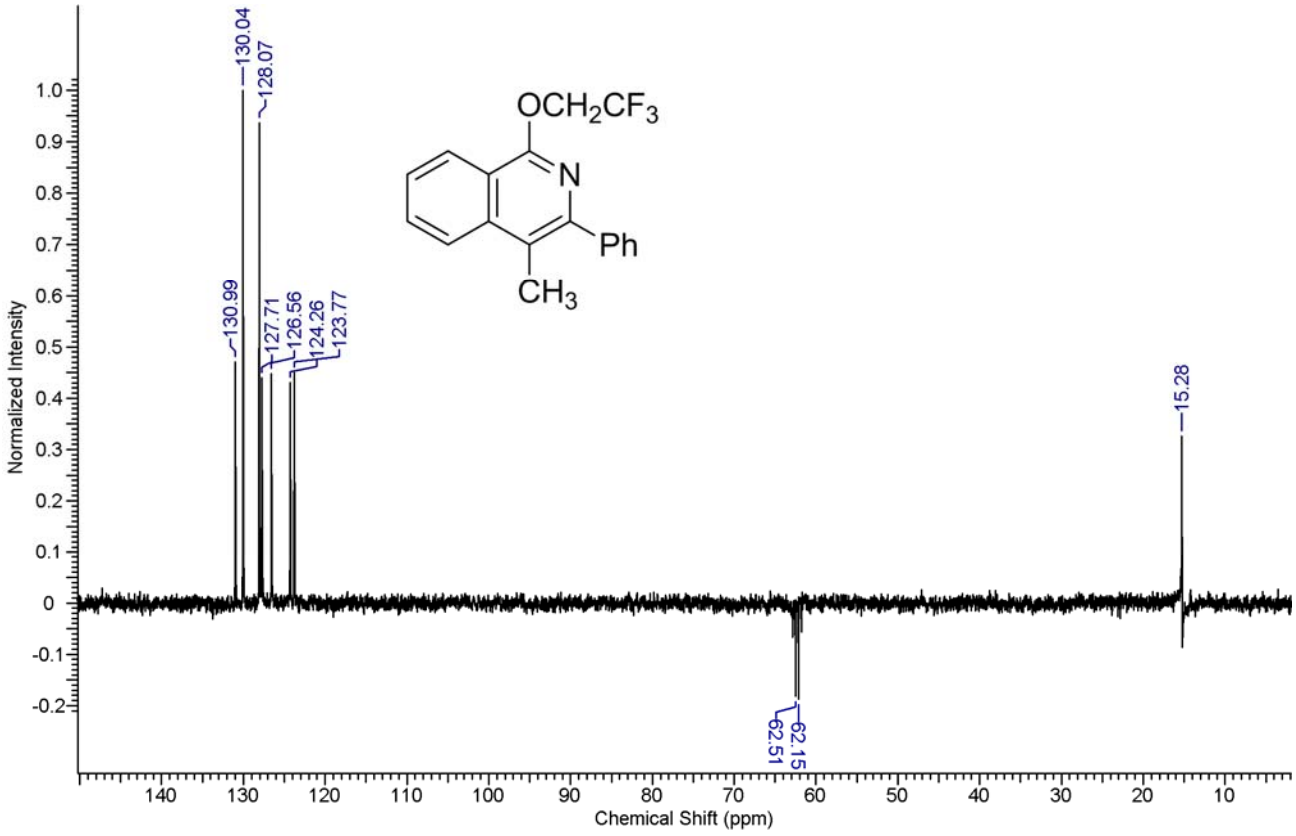


^{1}H and ^{13}C NMR Spectra of Compound **3e.**

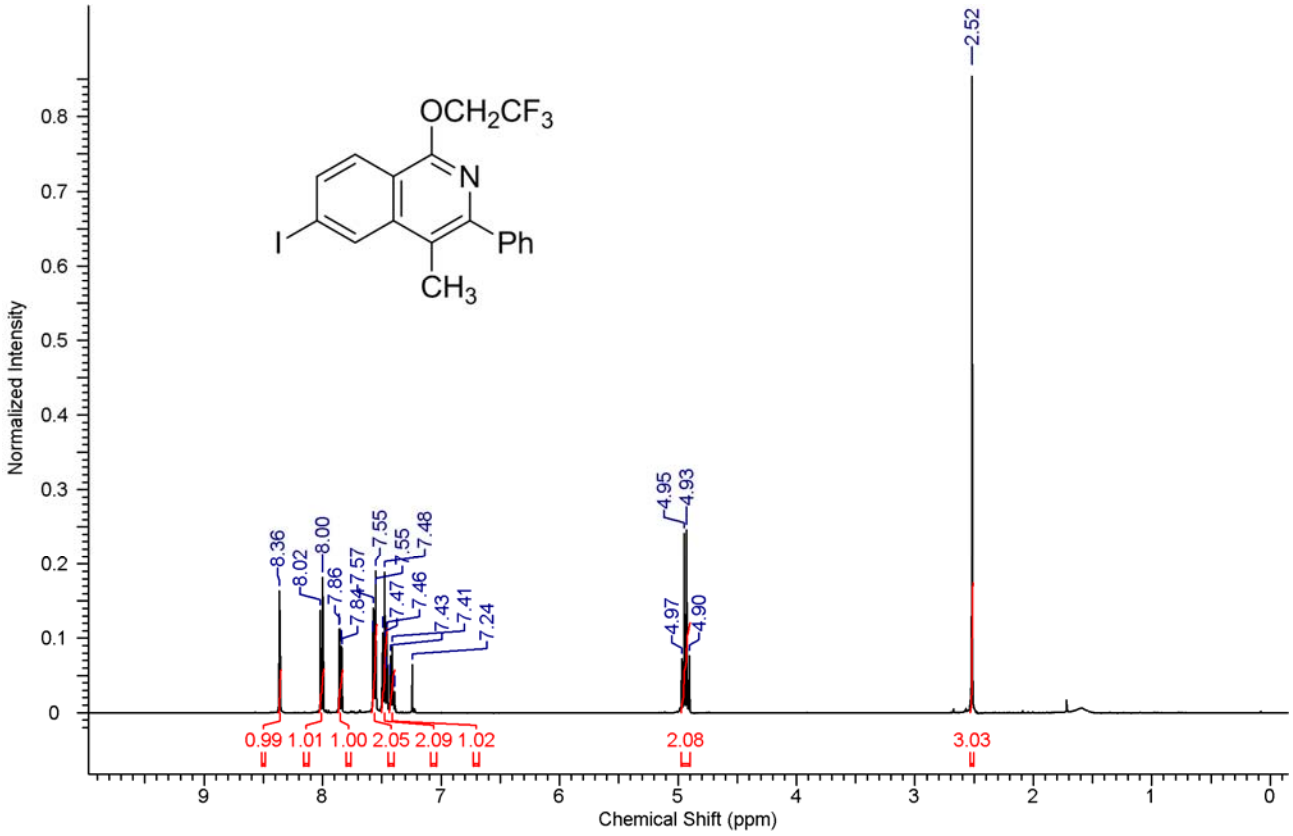


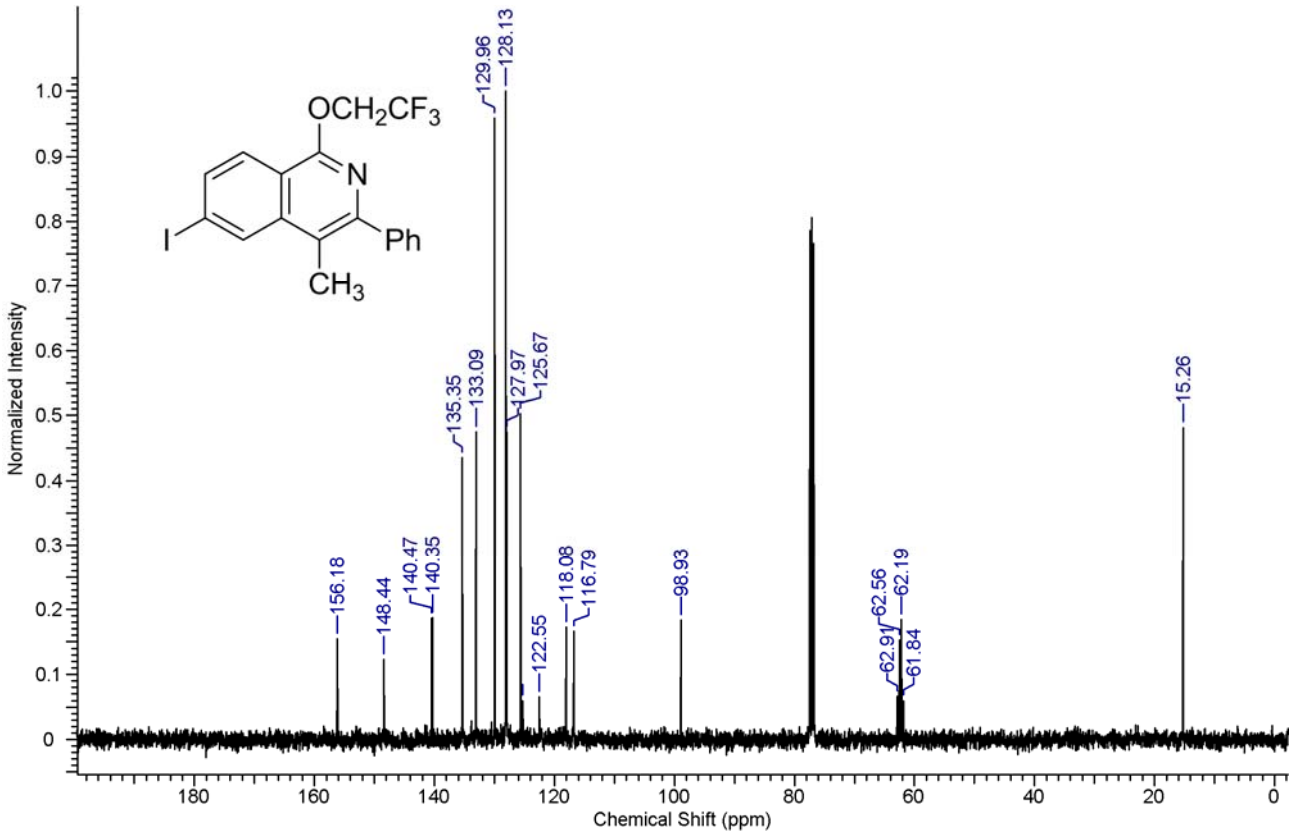


DEPT (135) NMR Spectrum of Compound **3e.**

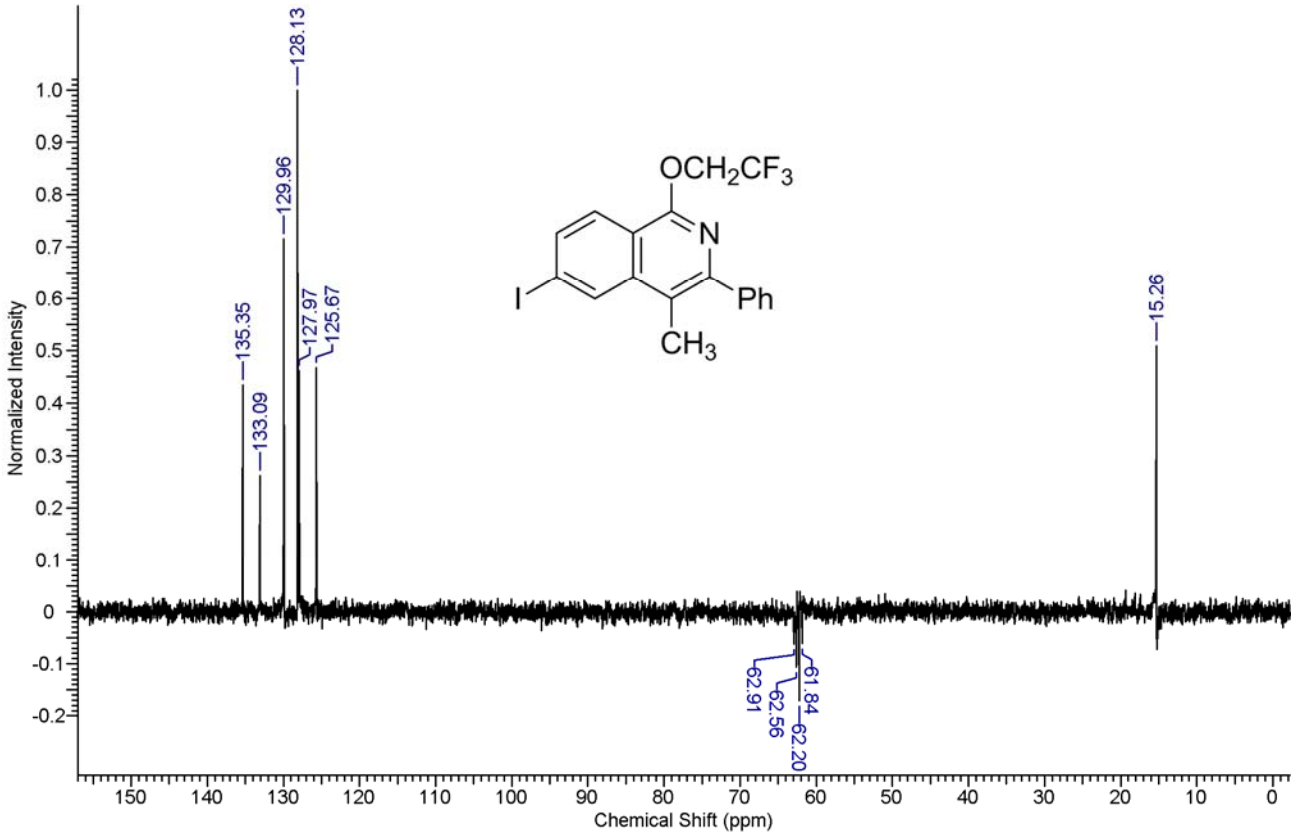


^{1}H and ^{13}C NMR Spectra of Compound **3f.**

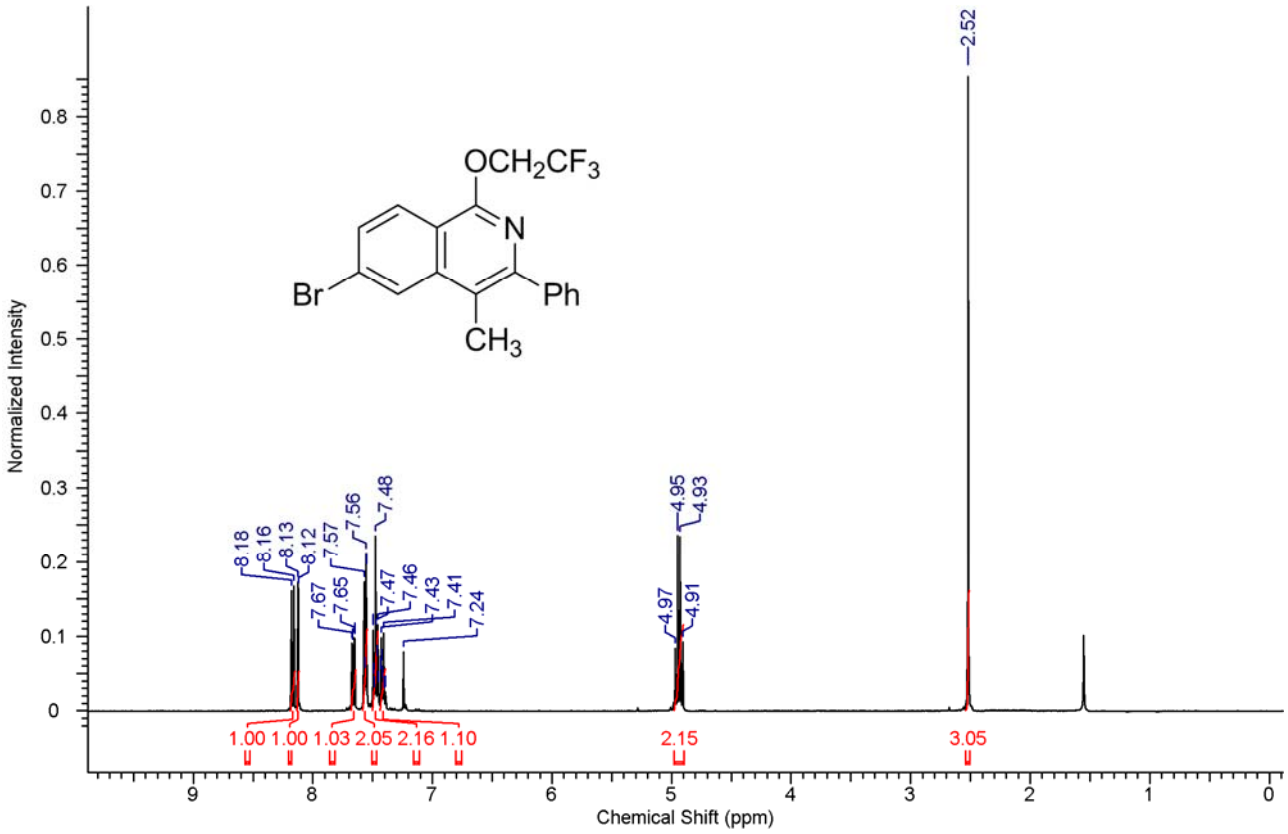


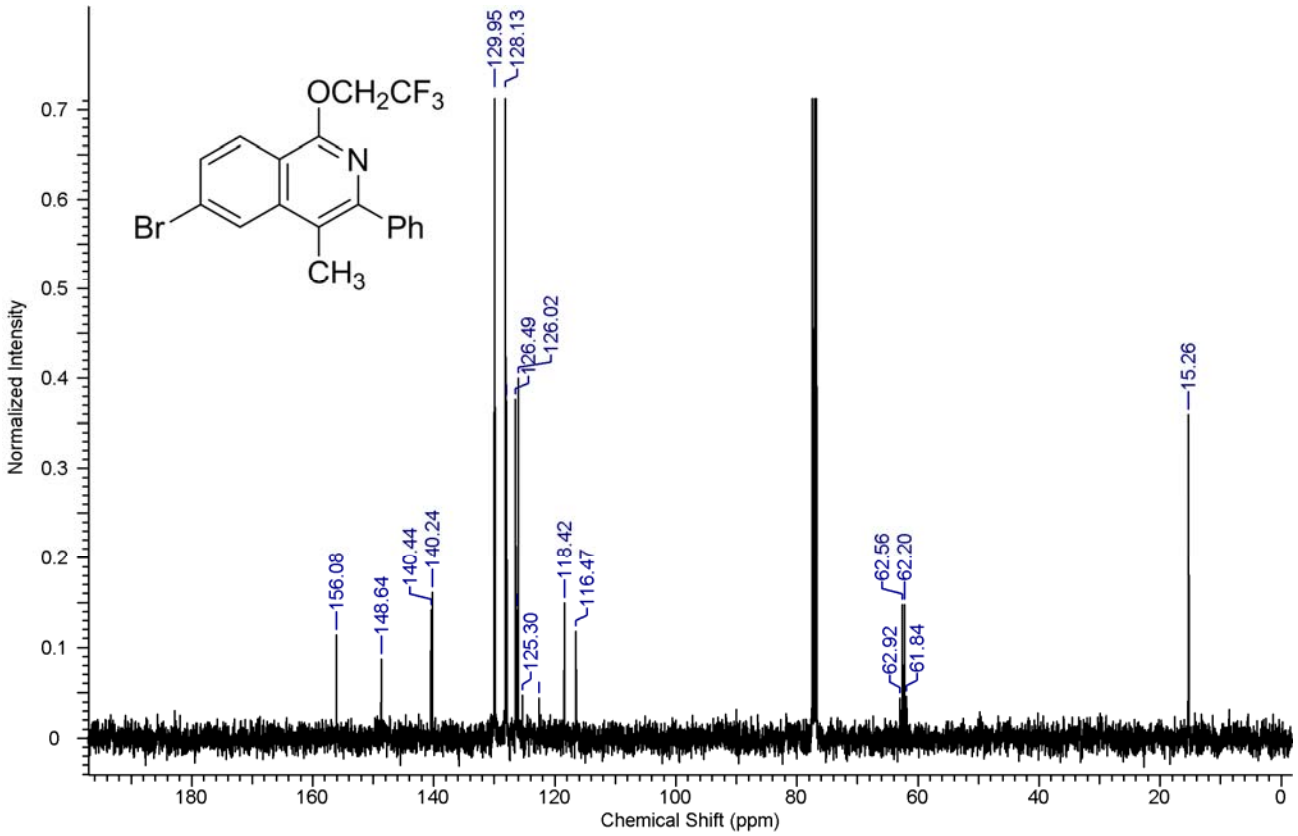


DEPT (135) NMR Spectrum of Compound **3f.**

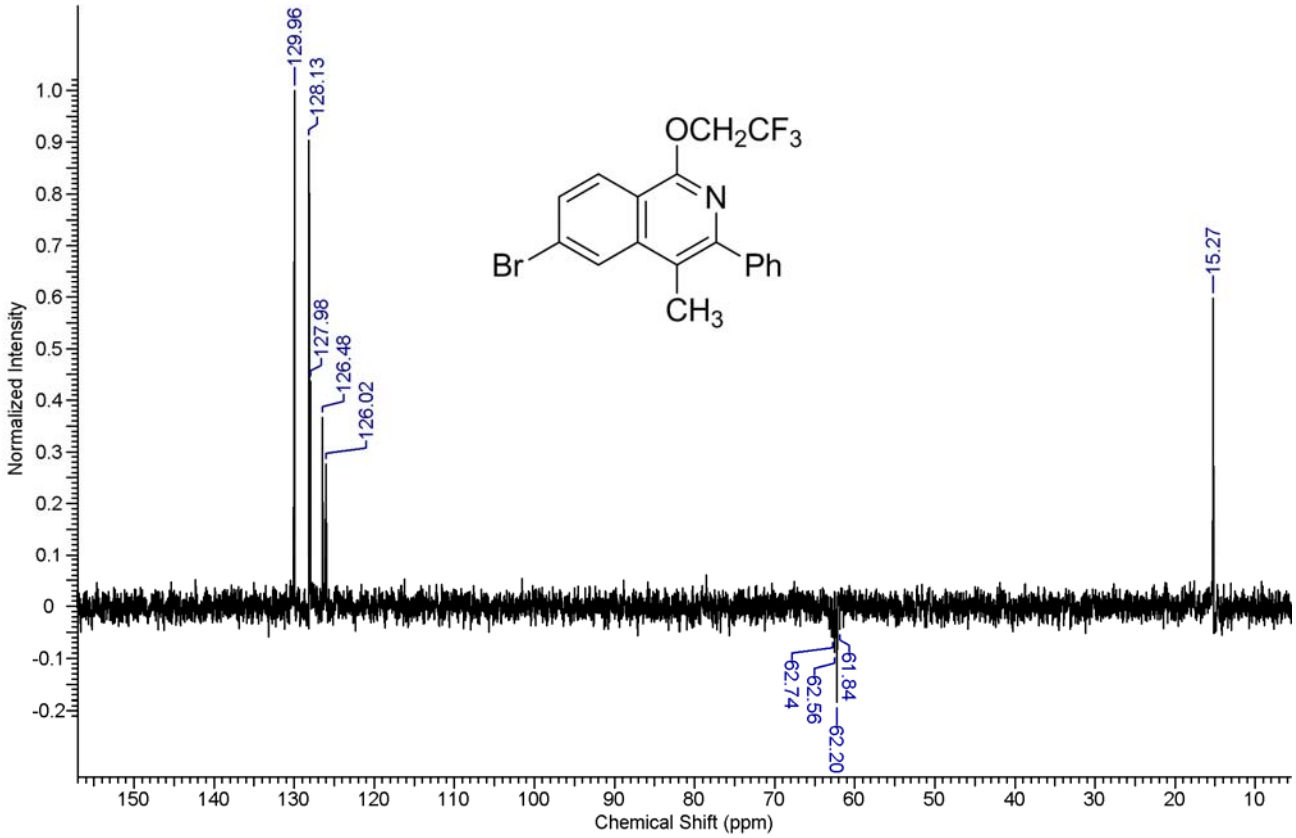


^{1}H and ^{13}C NMR Spectra of Compound **3g.**

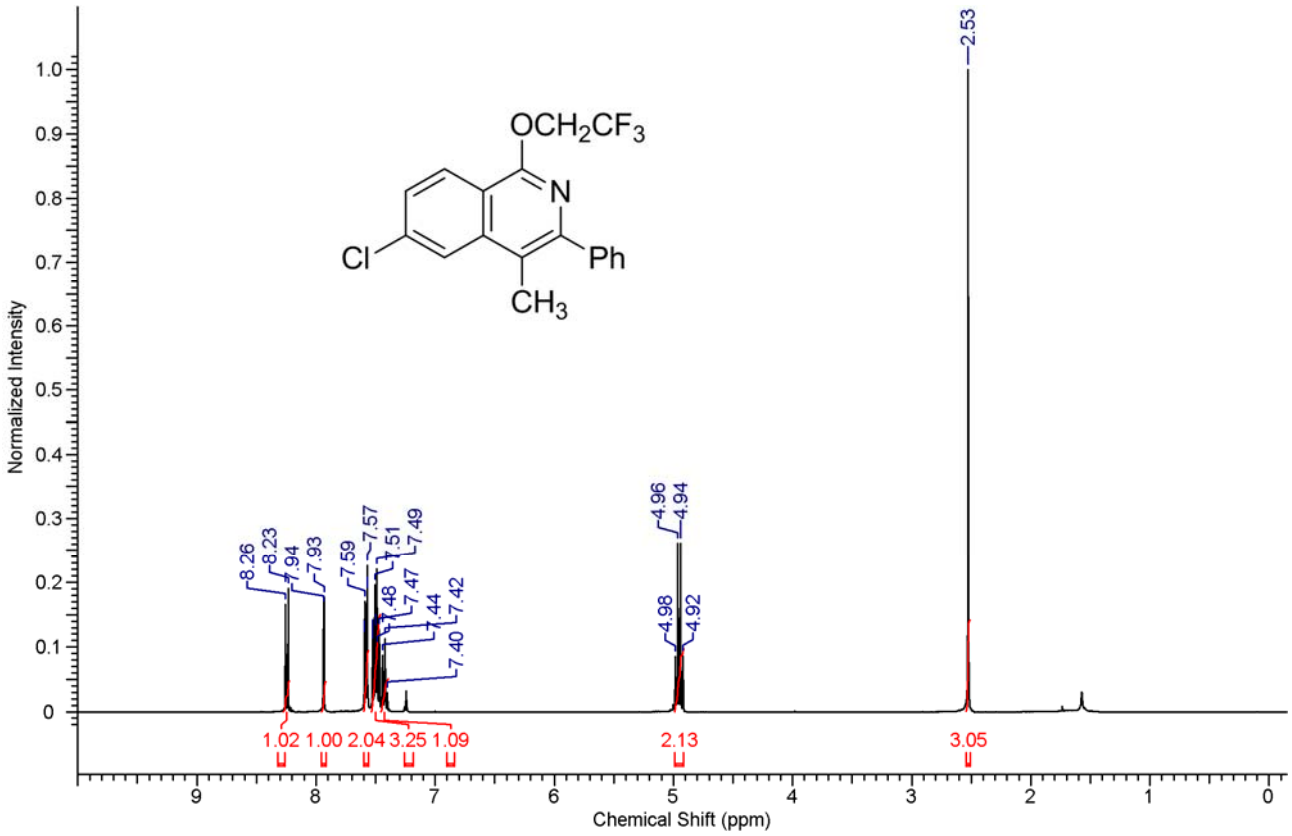


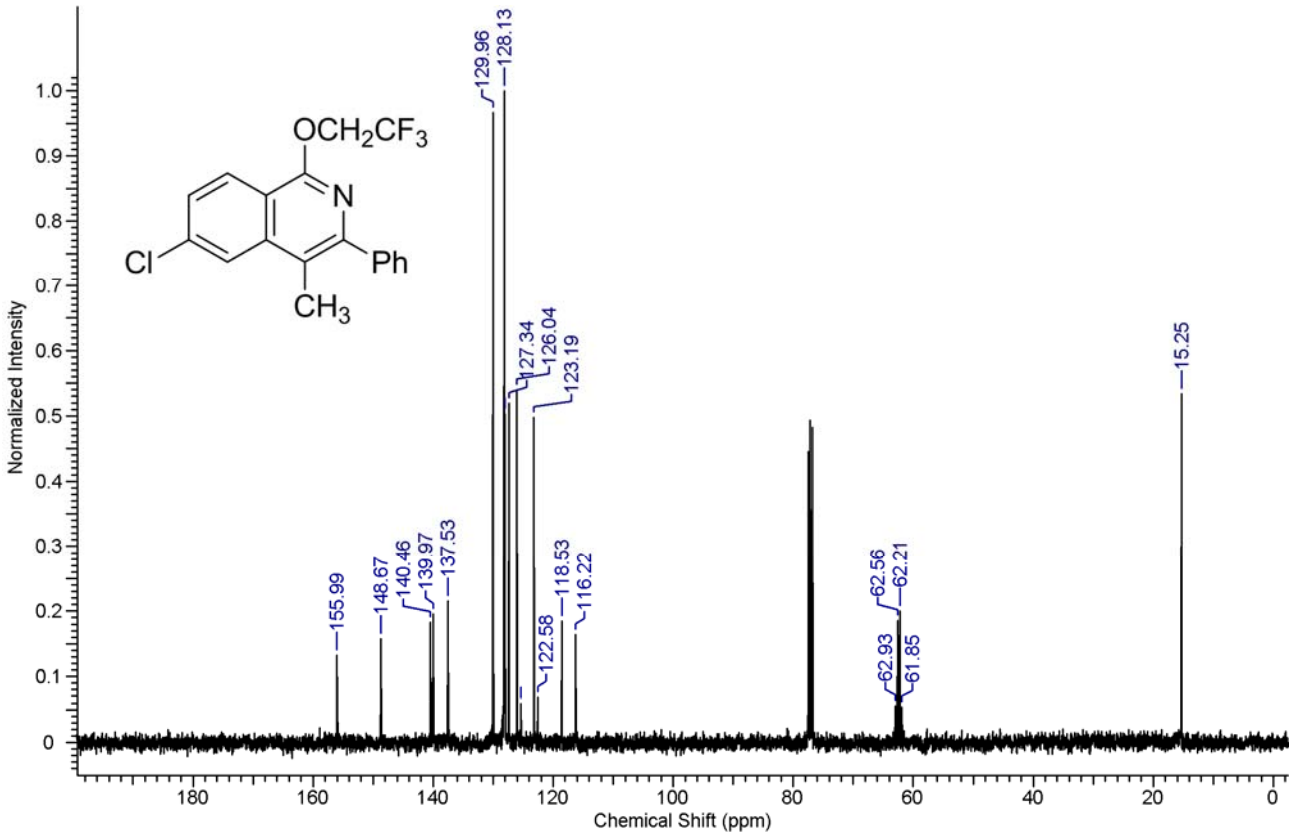


DEPT (135) NMR Spectrum of Compound **3g.**

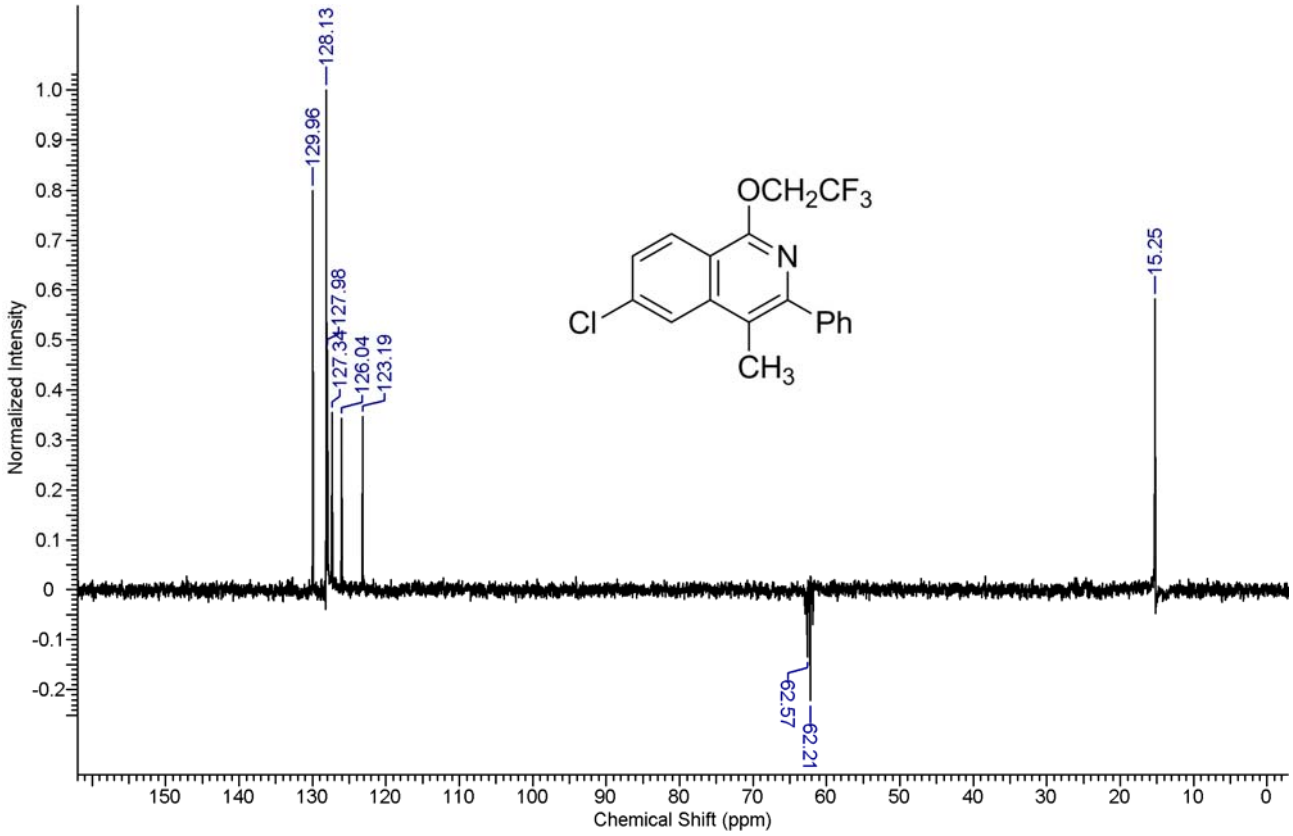


^{1}H and ^{13}C NMR Spectra of Compound **3h.**

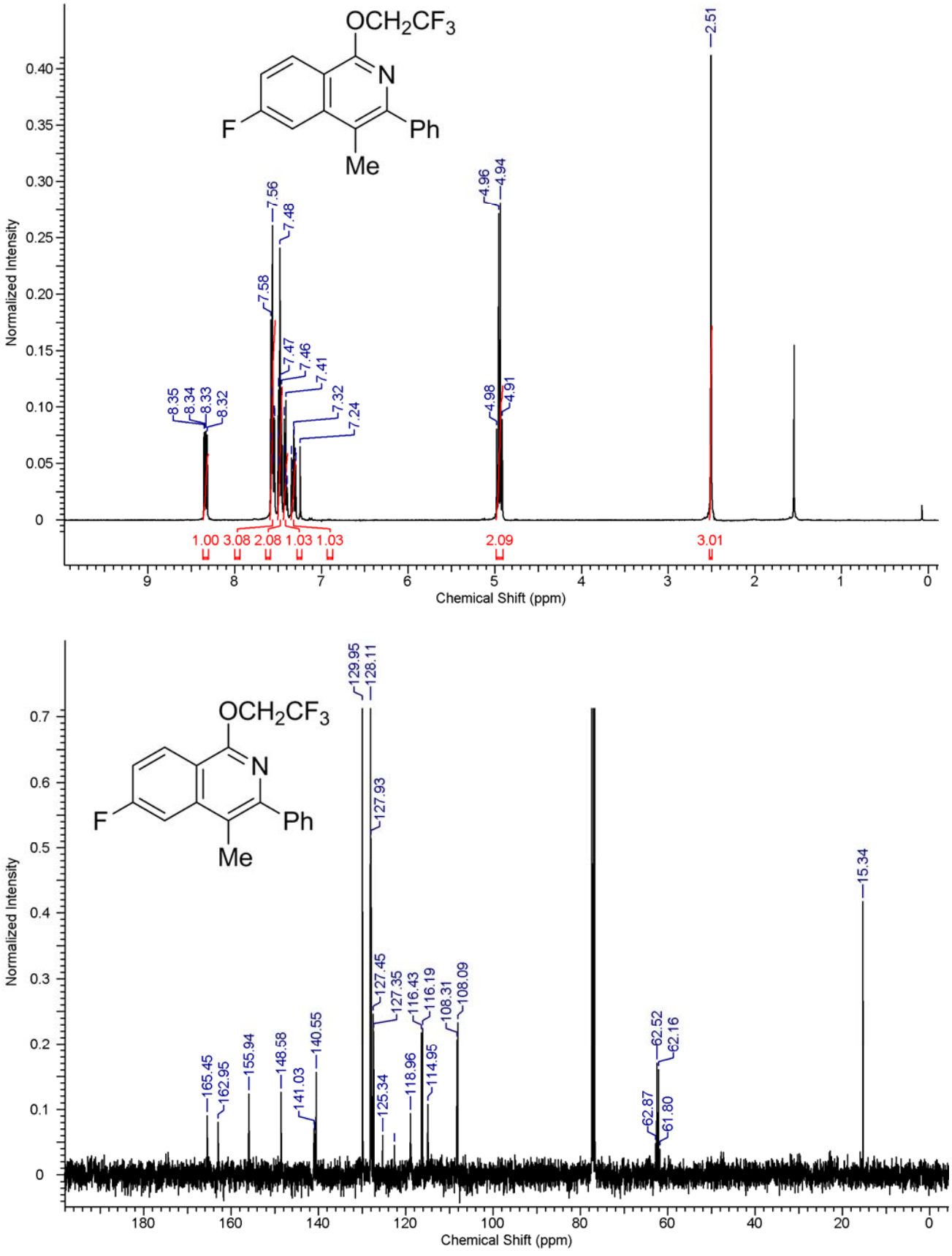




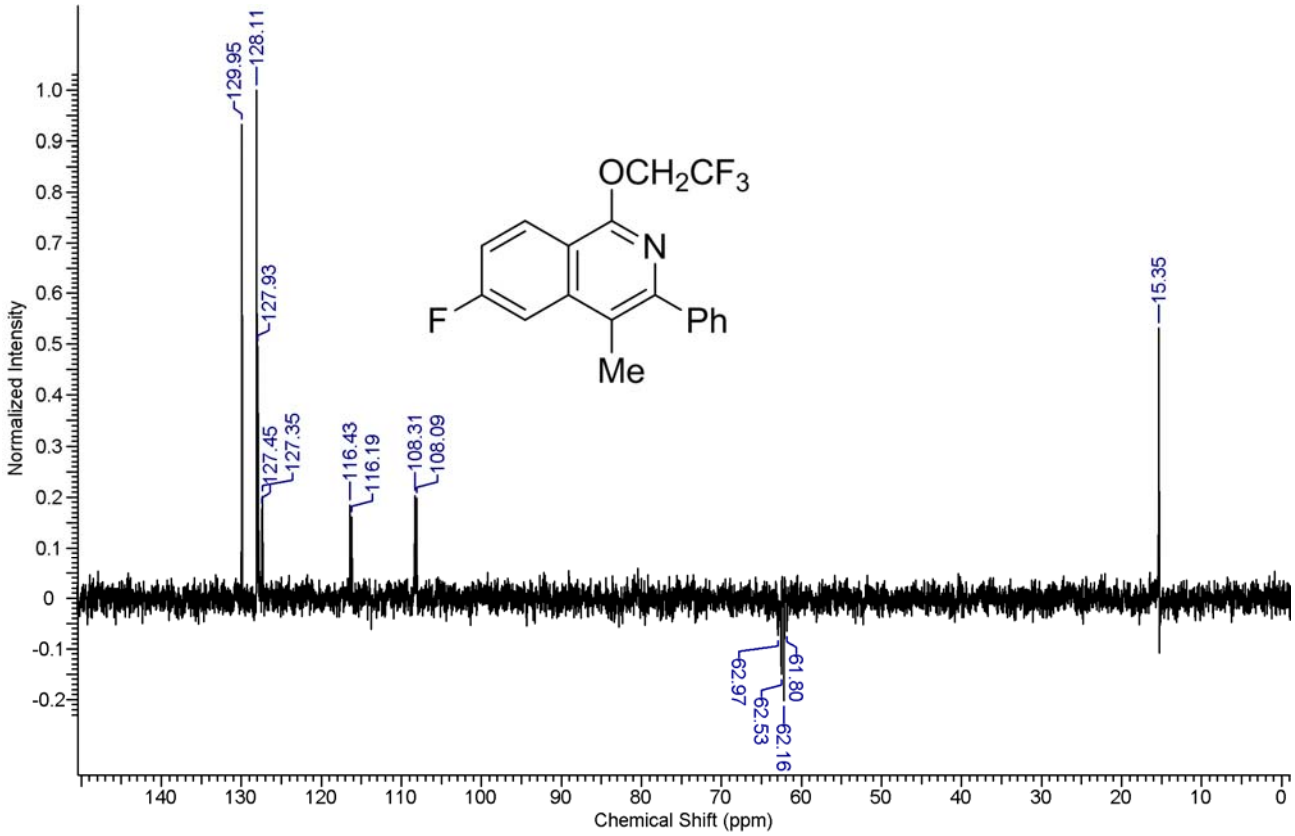
DEPT (135) NMR Spectrum of Compound **3h.**



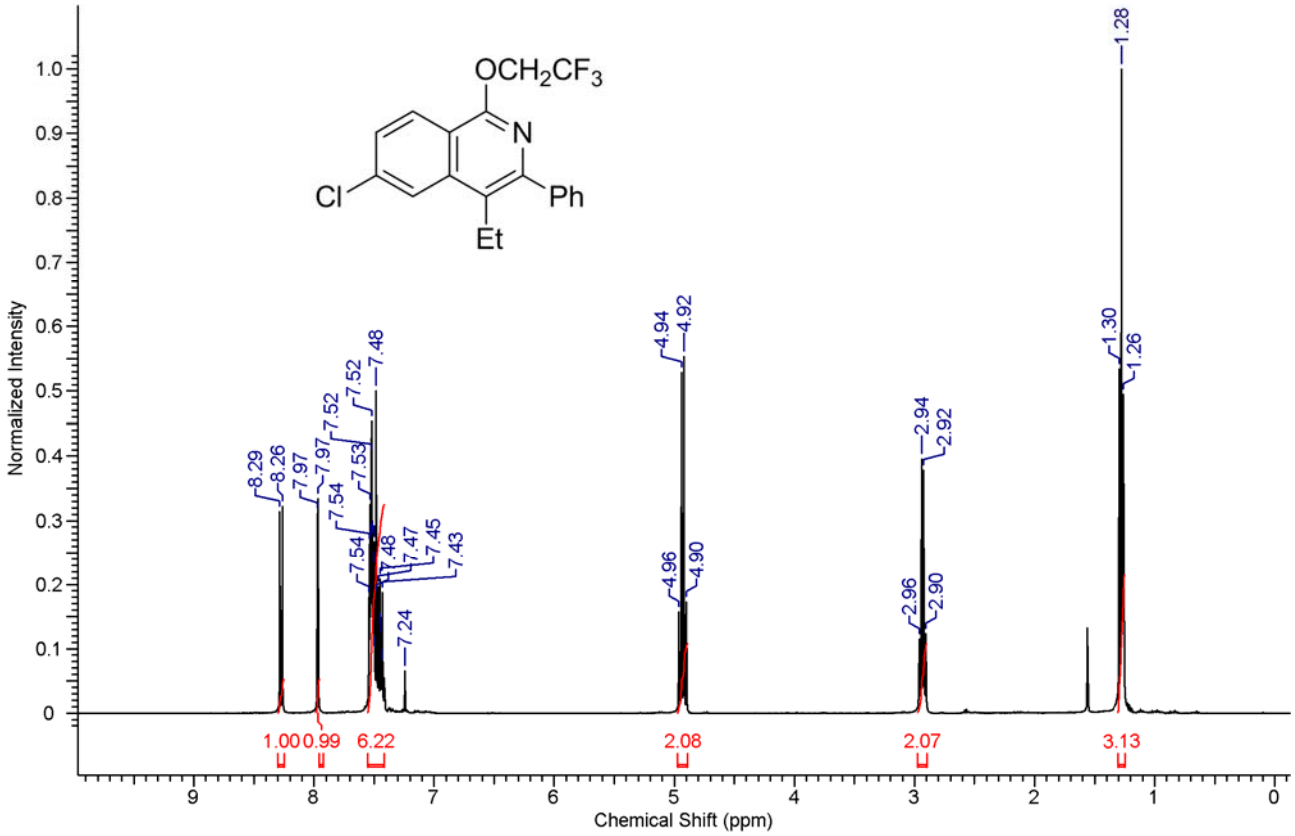
^{1}H and ^{13}C NMR Spectra of Compound **3i.**

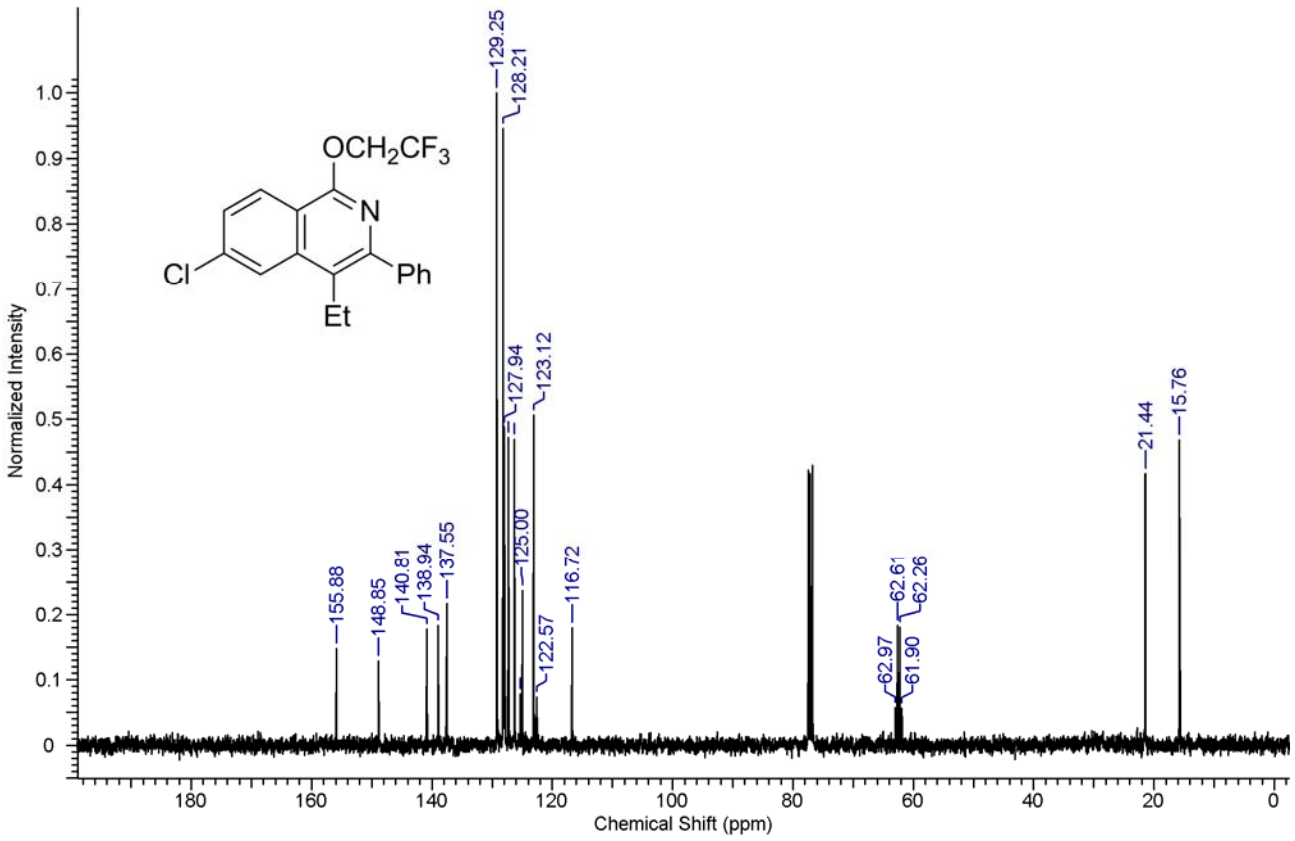


DEPT (135) NMR Spectrum of Compound **3i.**

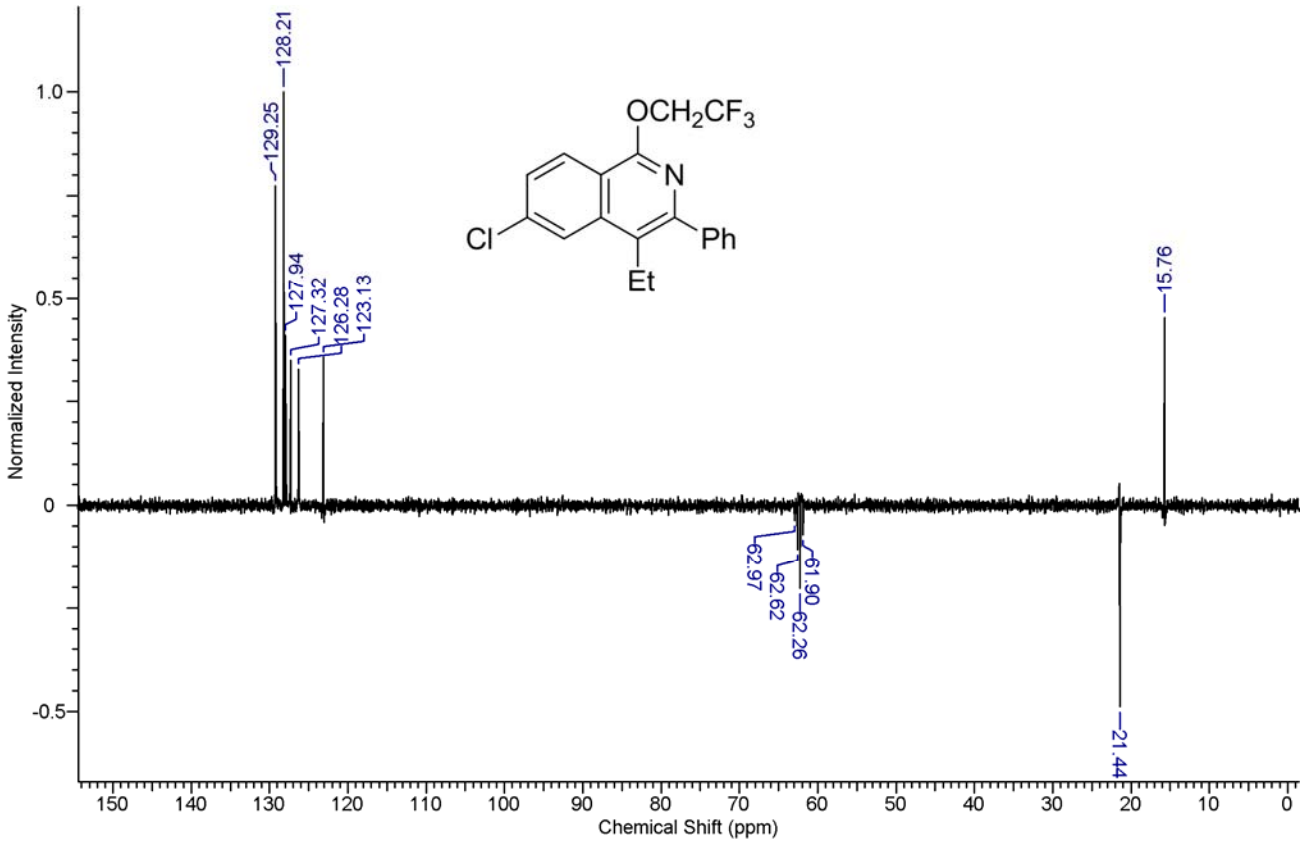


^{1}H and ^{13}C NMR Spectra of Compound **3j.**

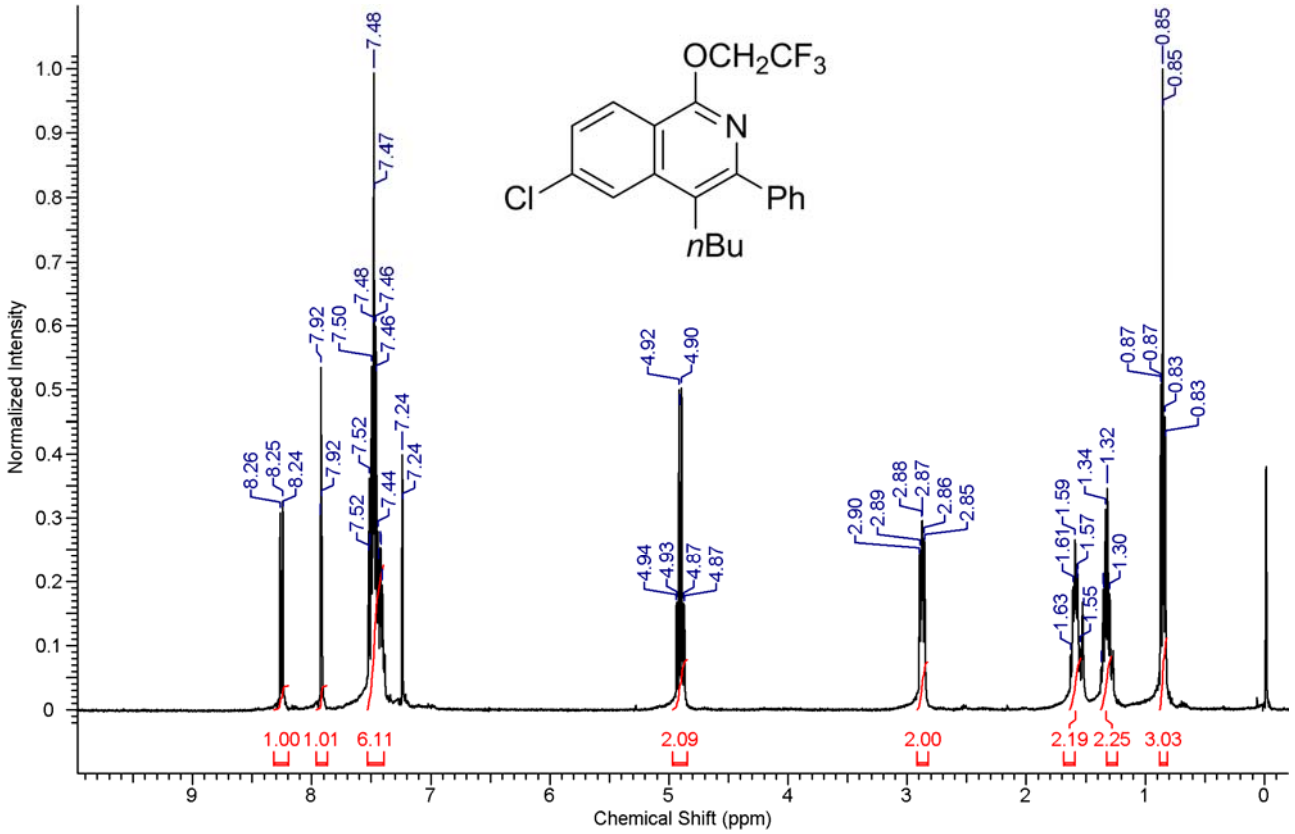


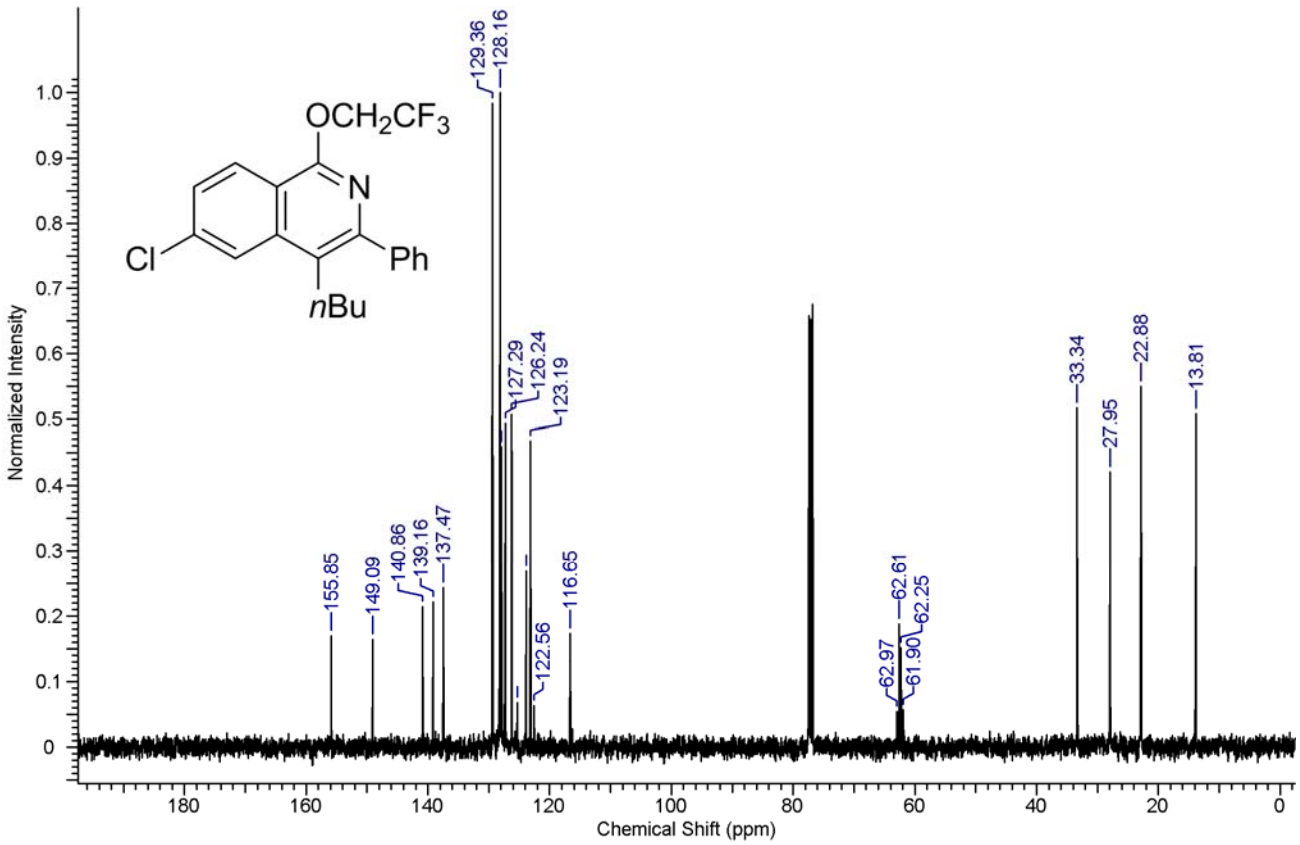


DEPT (135) NMR Spectrum of Compound **3j.**

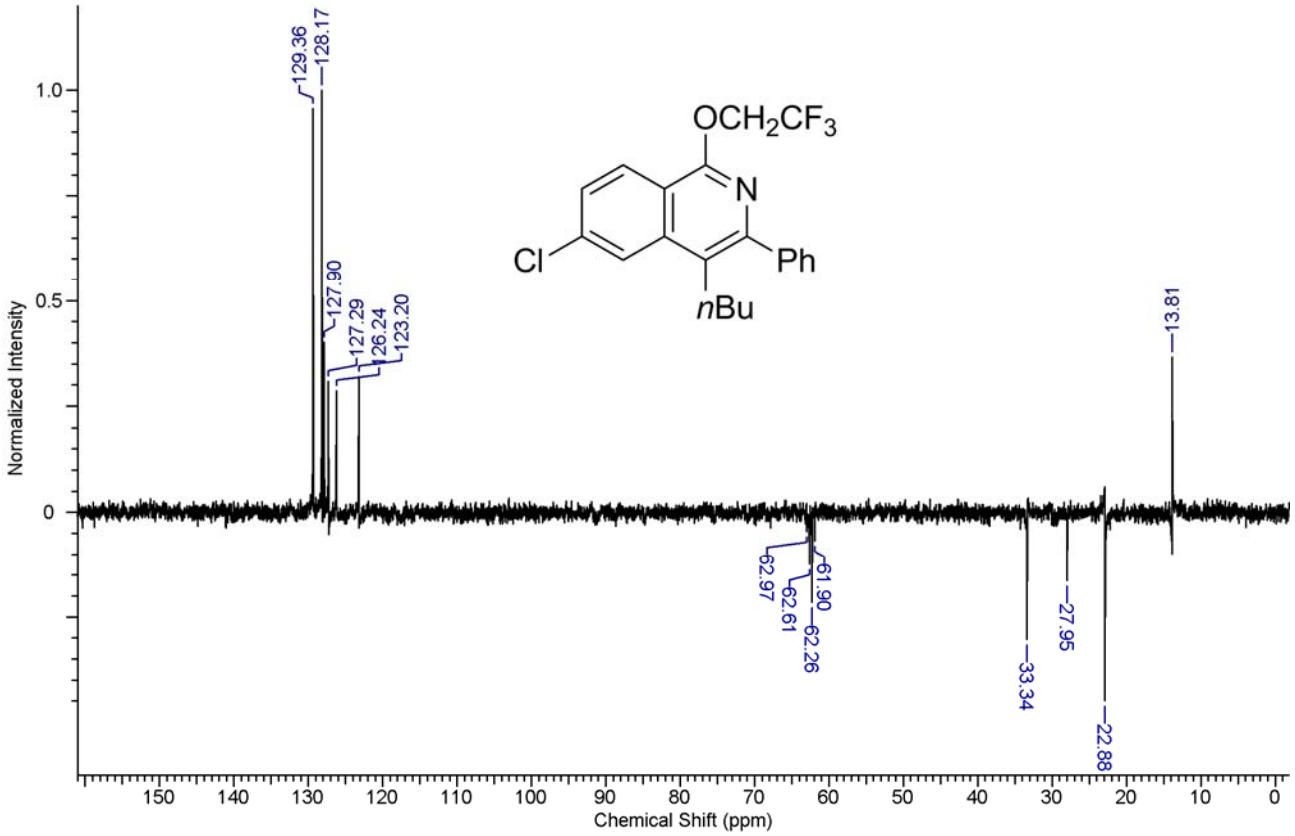


^{1}H and ^{13}C NMR Spectra of Compound **3k.**

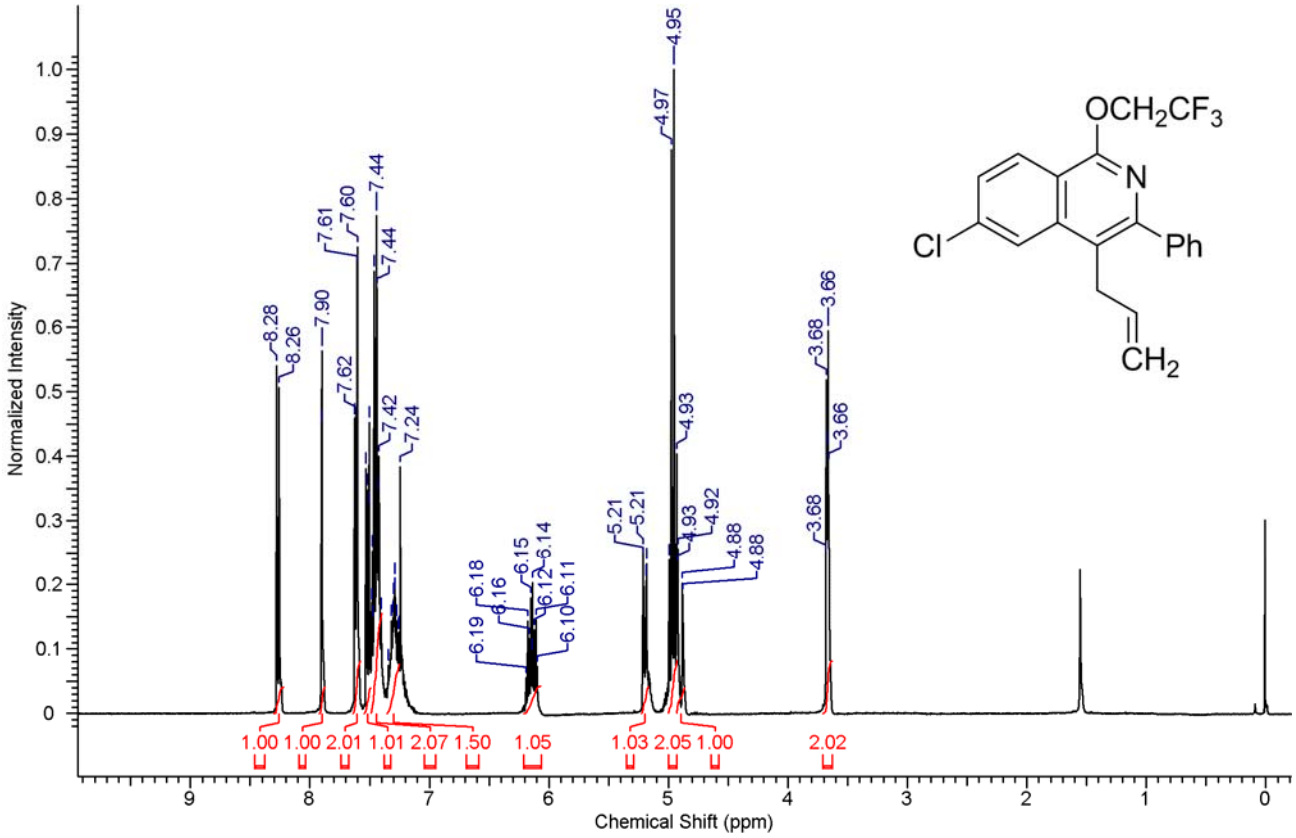


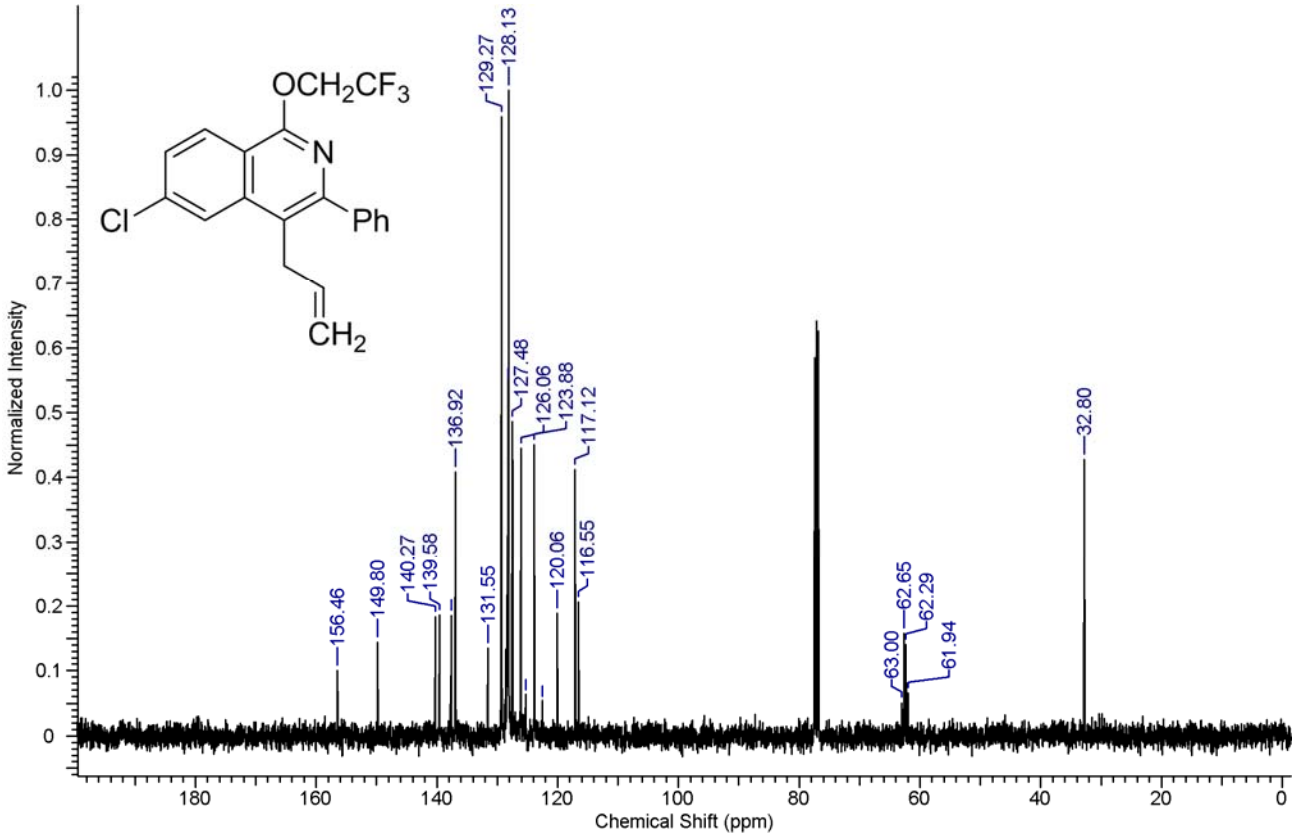


DEPT (135) NMR Spectrum of Compound **3k.**

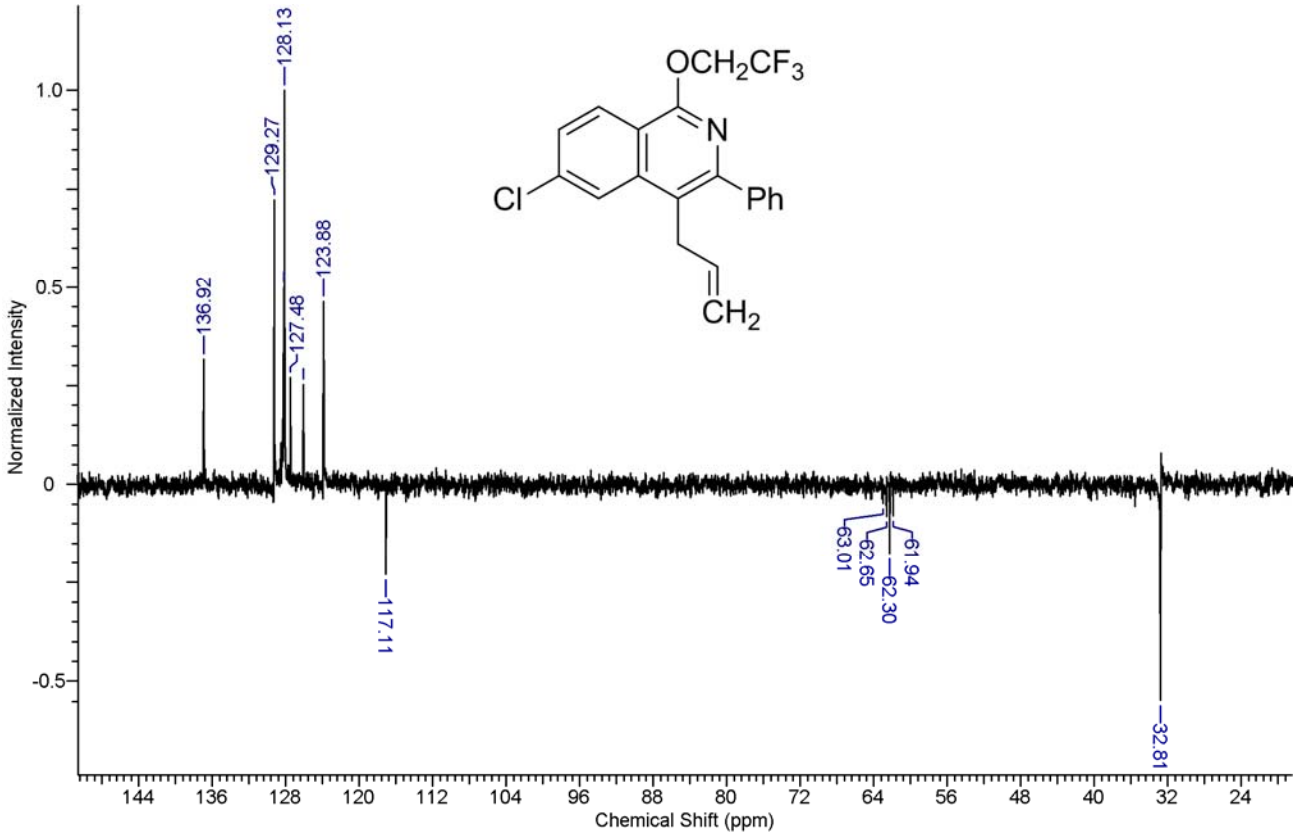


^{1}H and ^{13}C NMR Spectra of Compound **3l.**

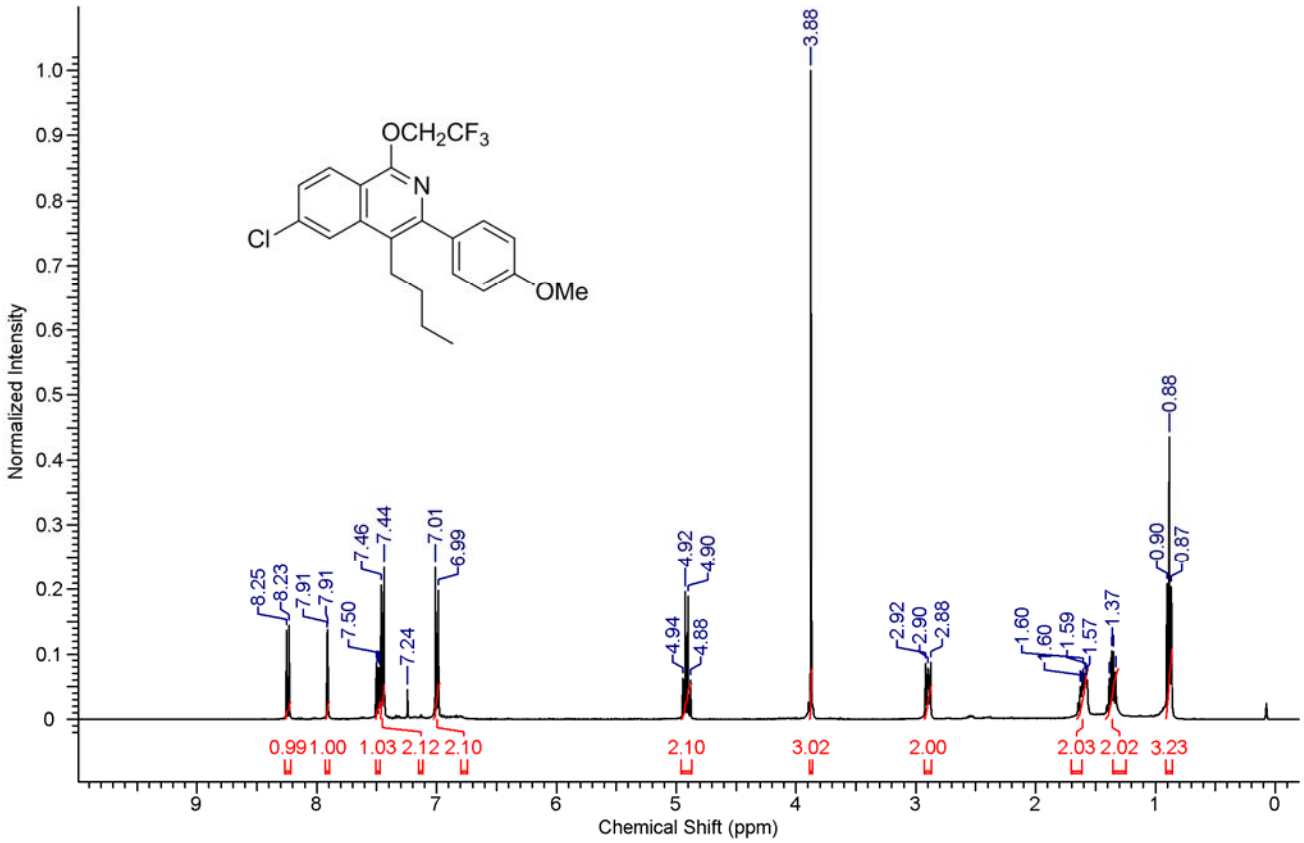


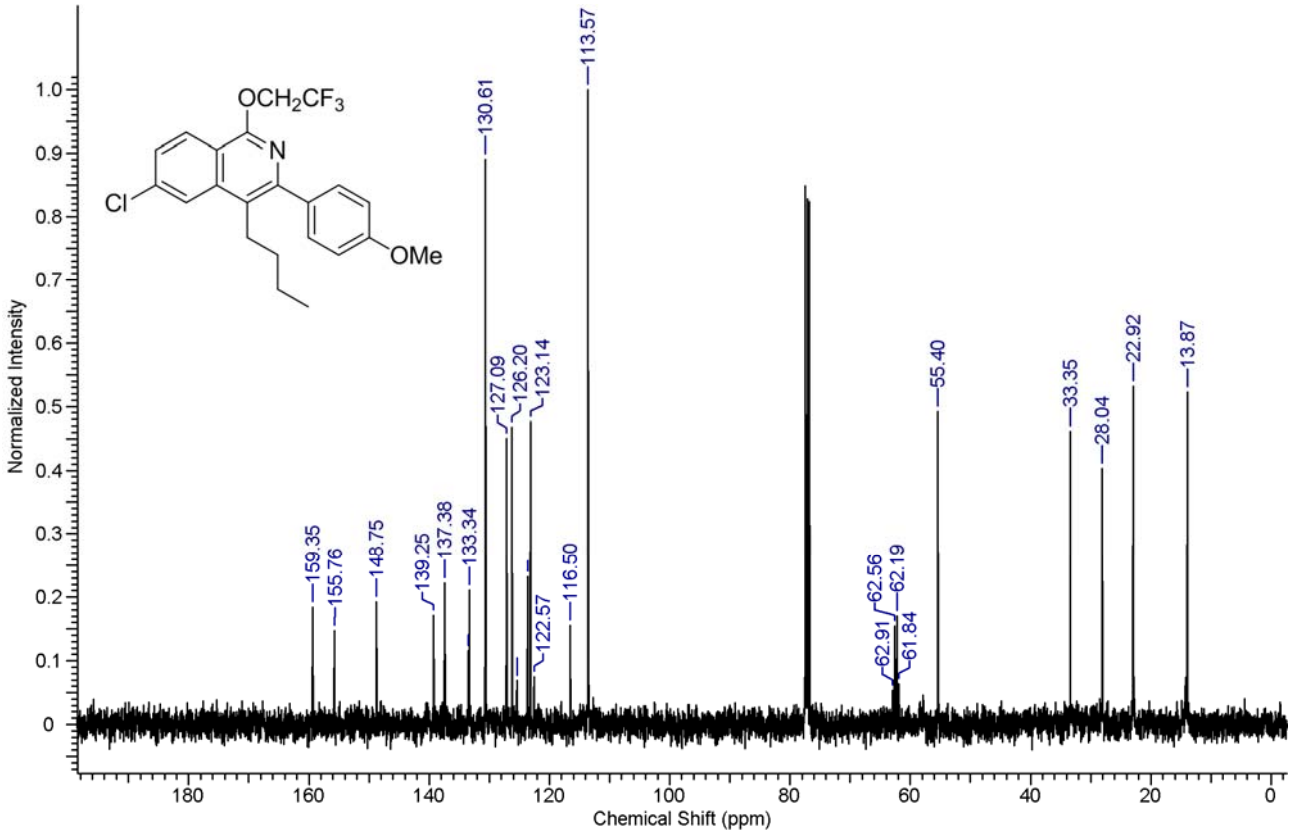


DEPT (135) NMR Spectrum of Compound **3l.**

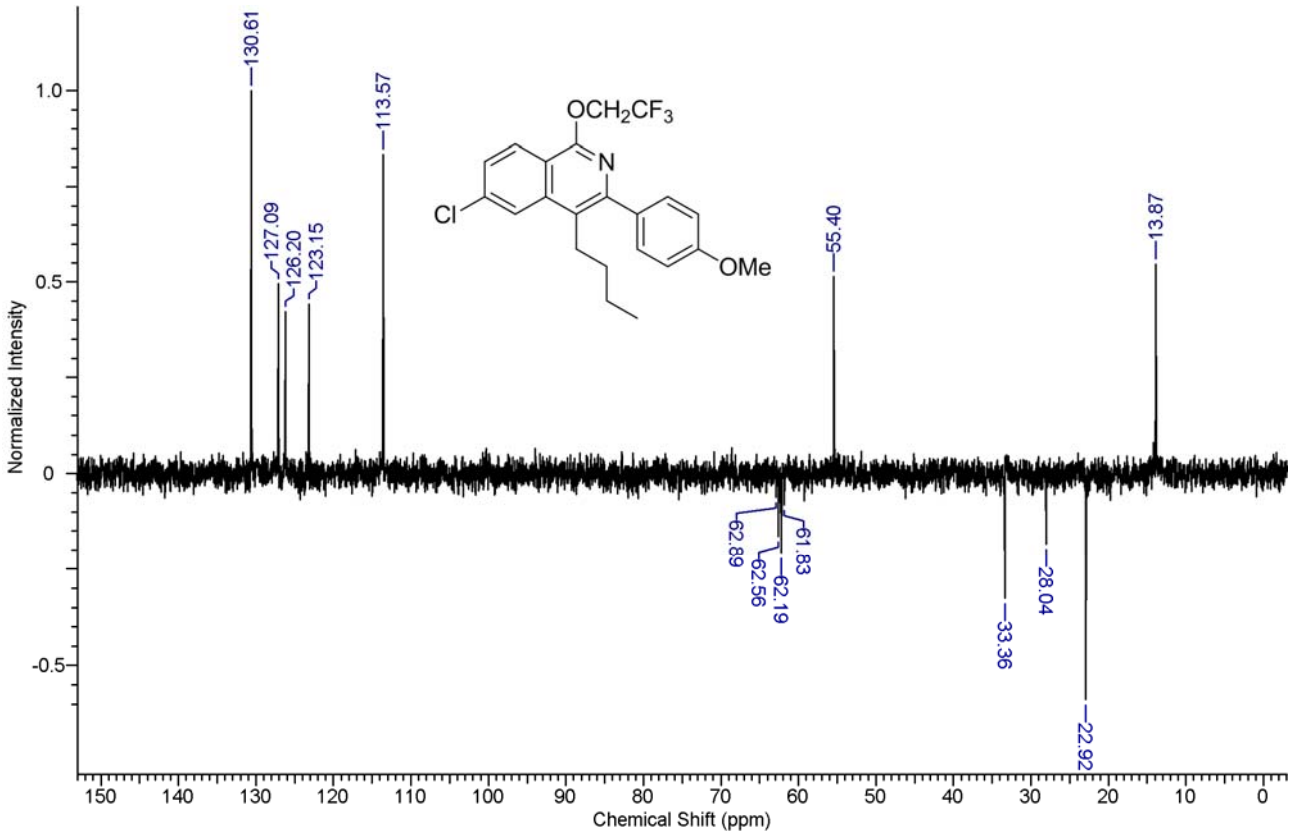


^{1}H and ^{13}C NMR Spectra of Compound **3m.**

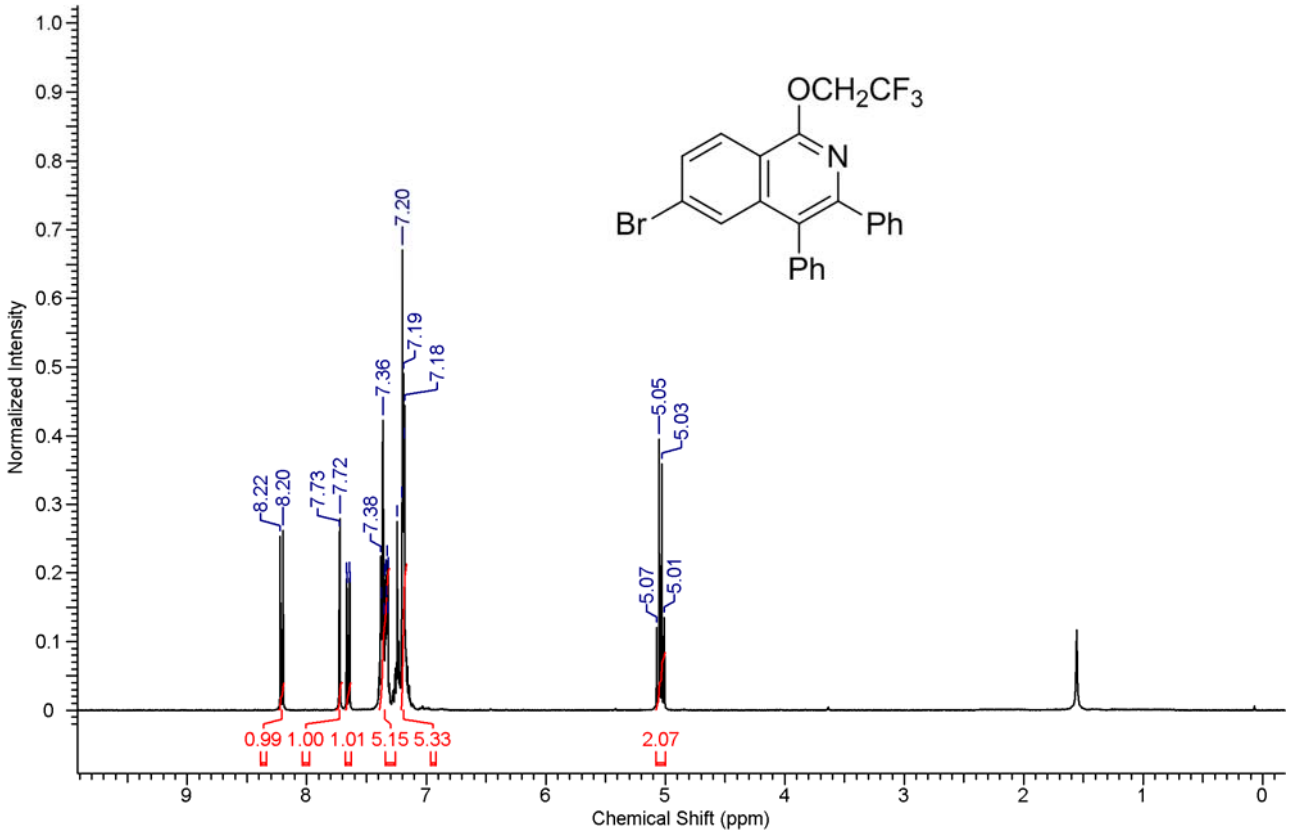


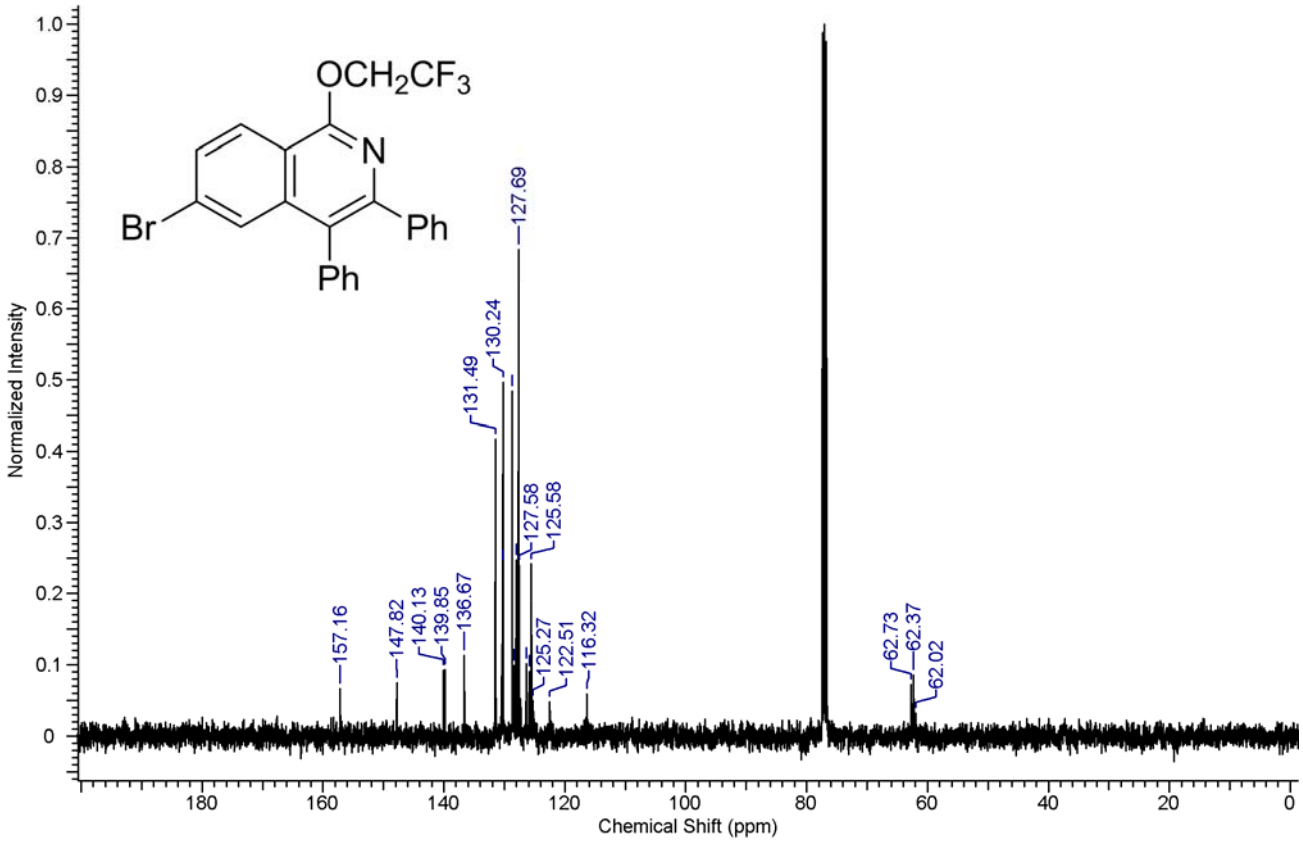


DEPT (135) NMR Spectrum of Compound **3m.**

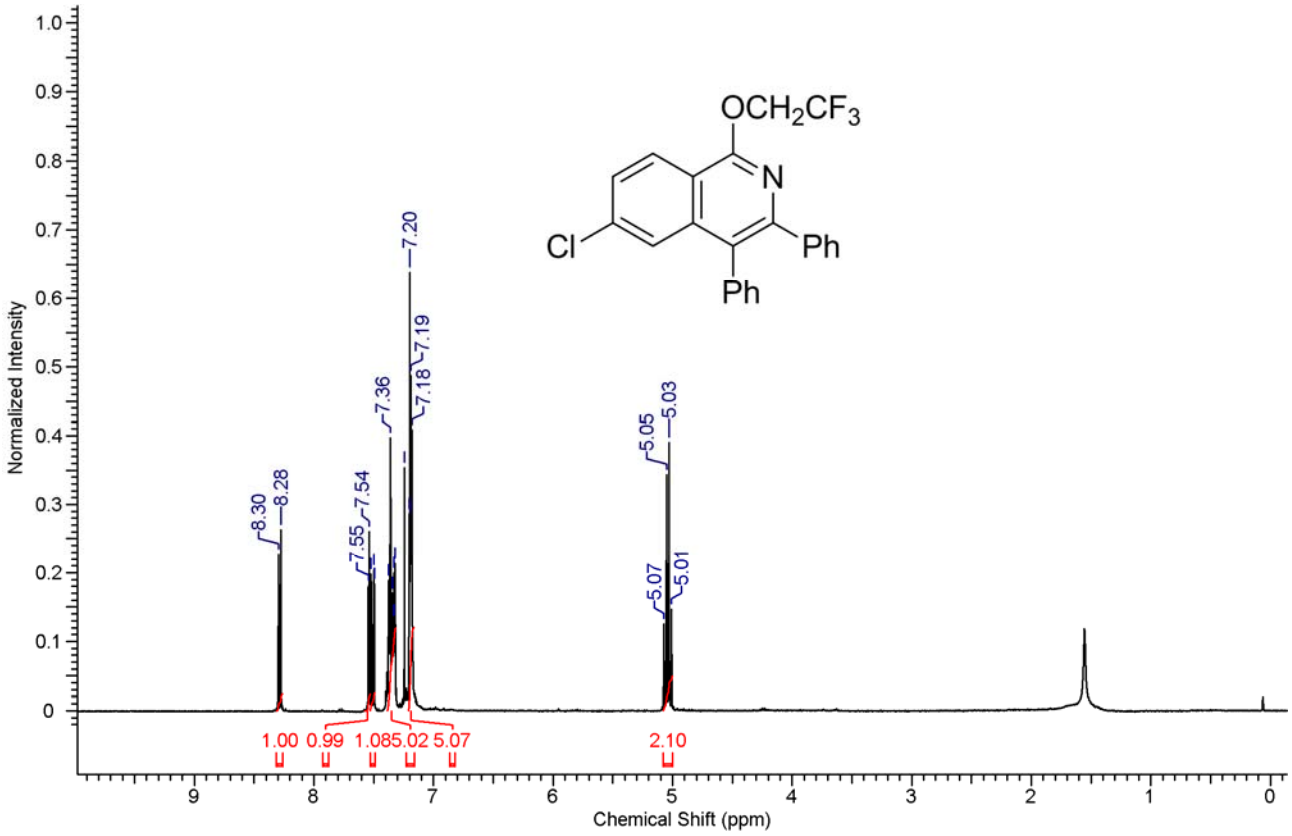


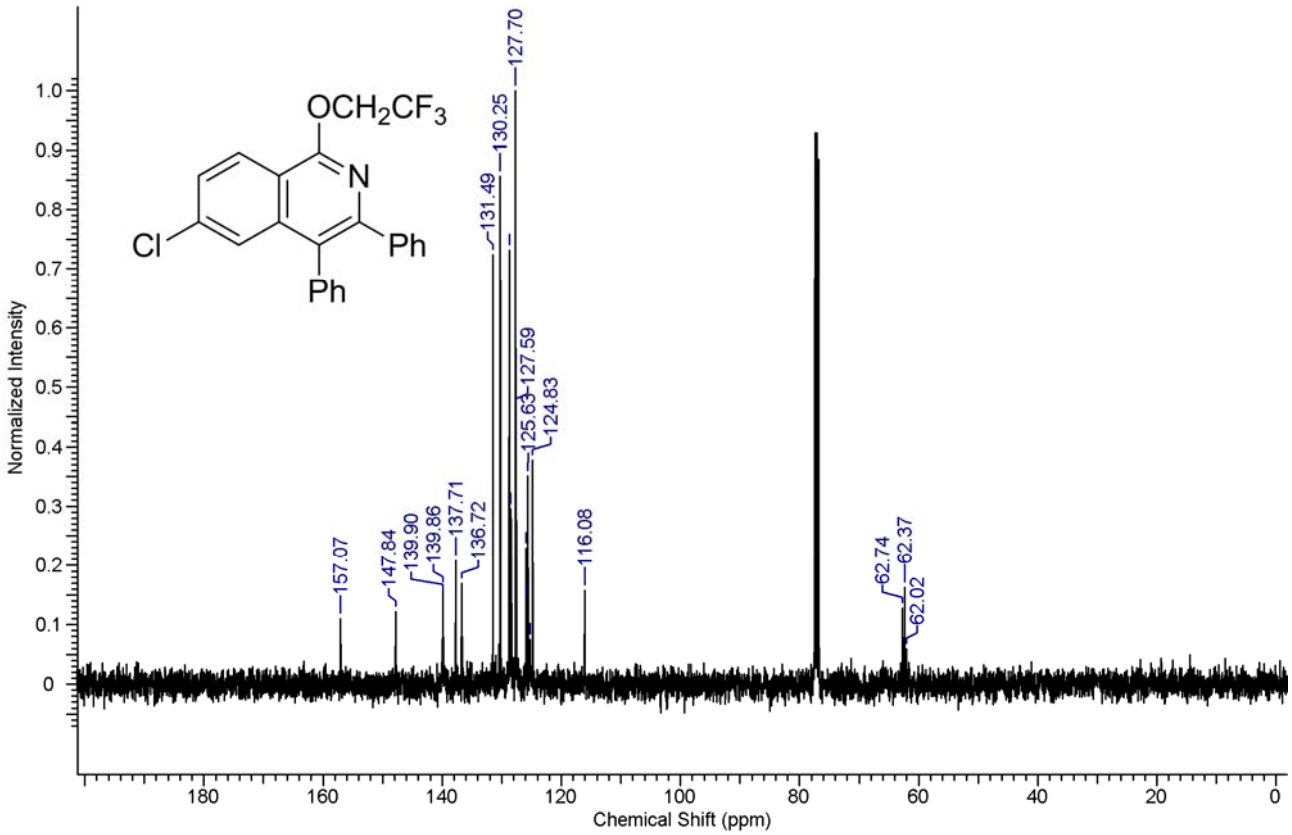
^{1}H and ^{13}C NMR Spectra of Compound **3n.**



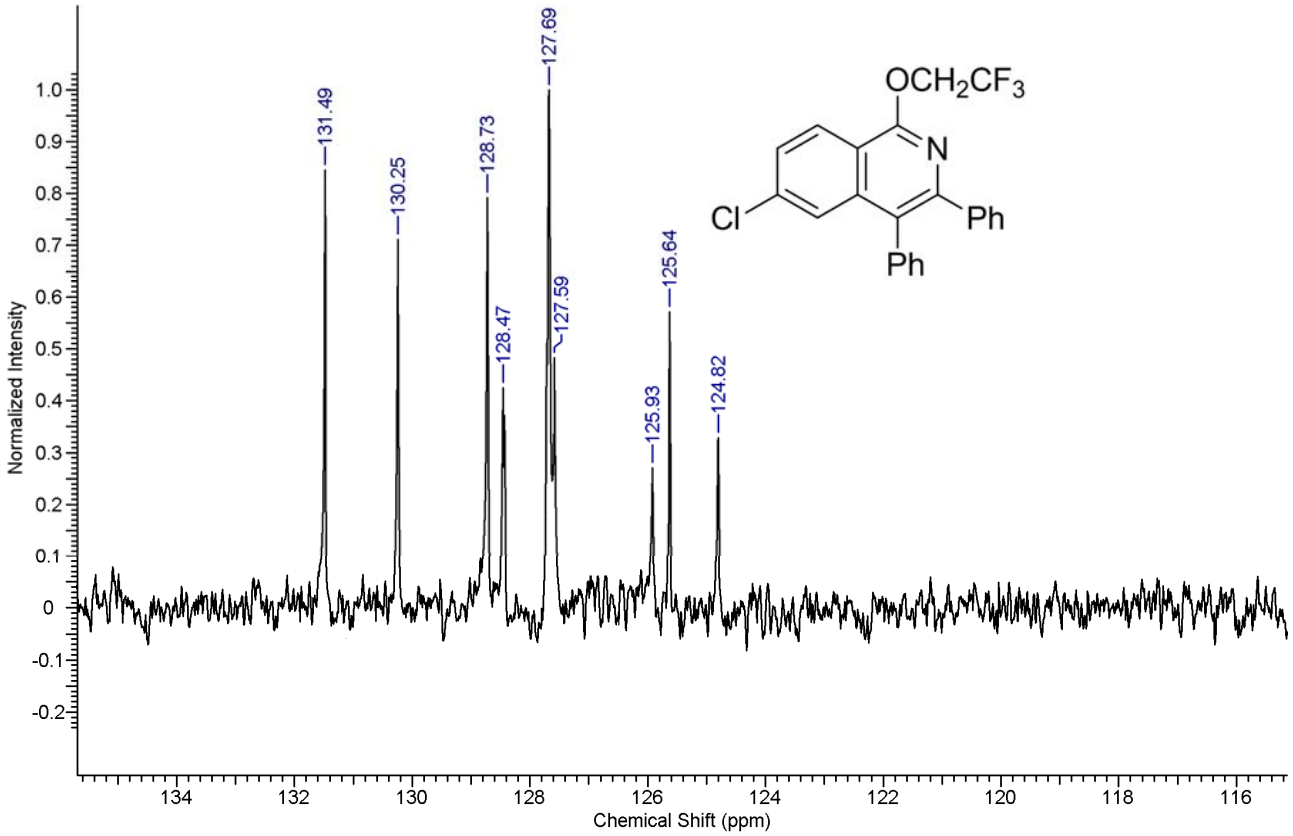


^{1}H and ^{13}C NMR Spectra of Compound **3o.**

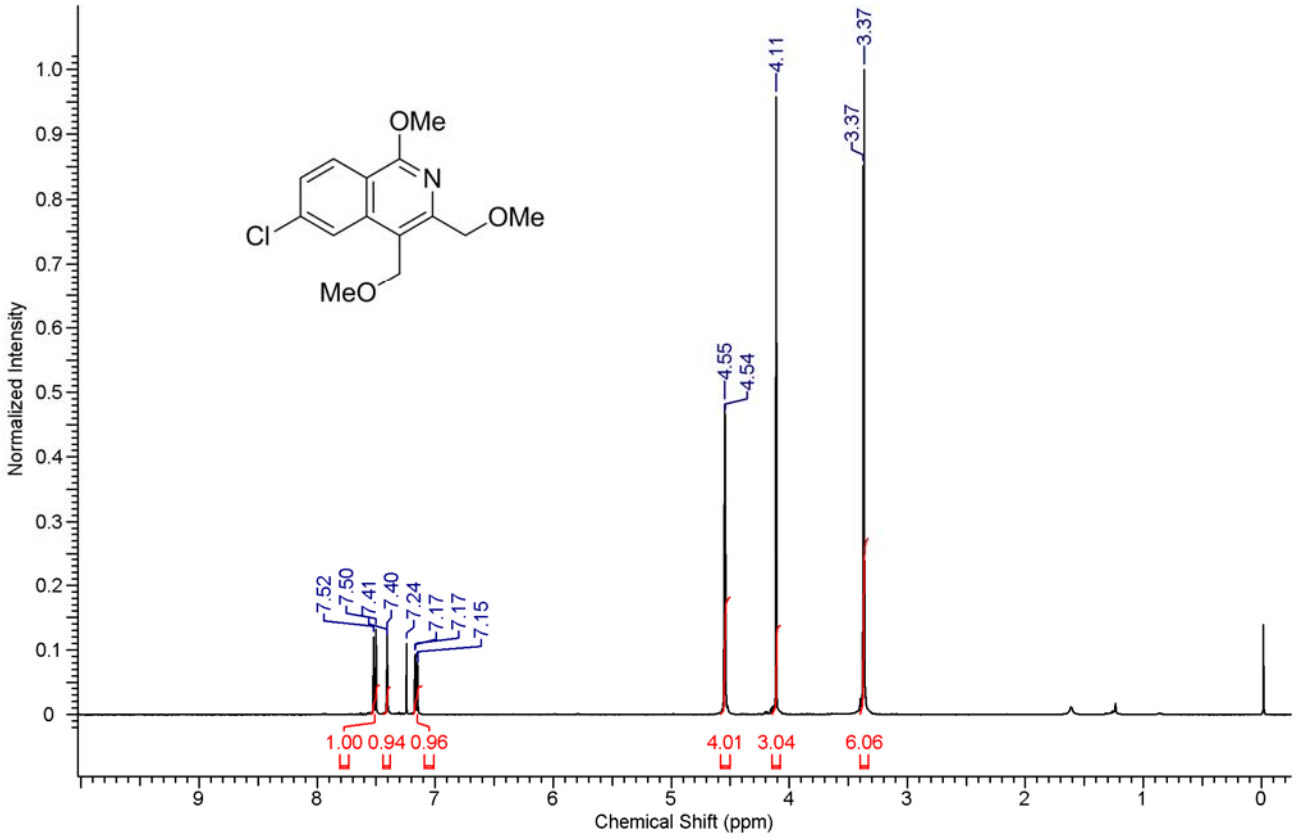


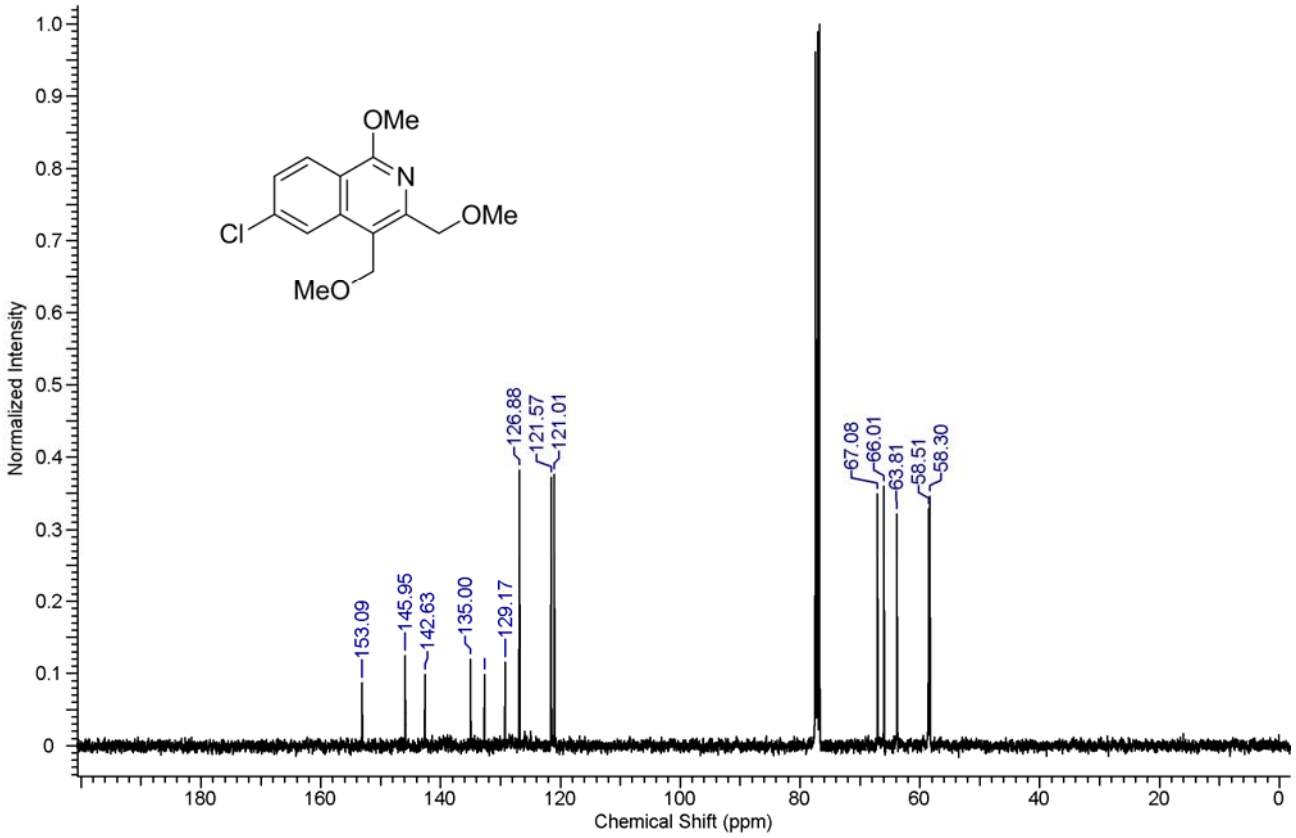


DEPT (135) NMR Spectrum of Compound **3o.**

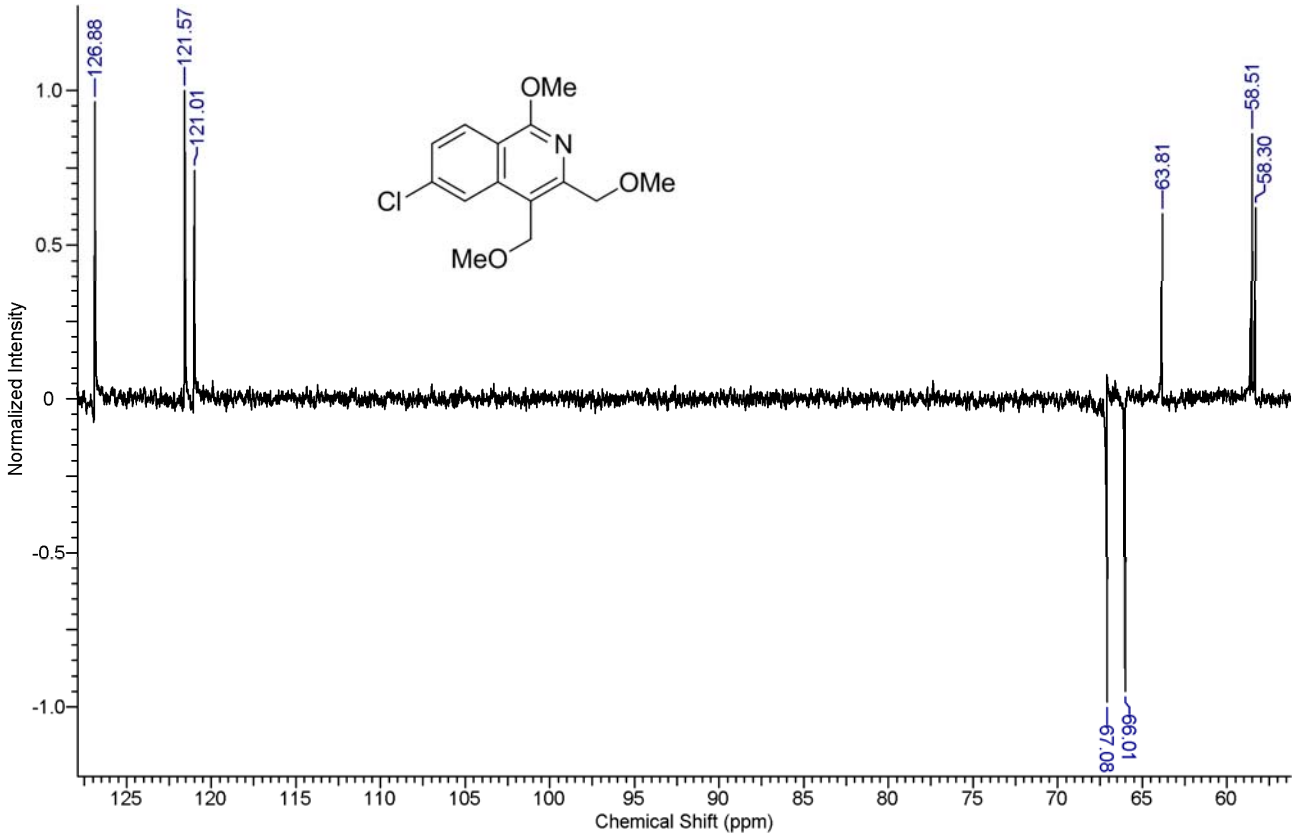


^{1}H and ^{13}C NMR Spectra of Compound **3p.**

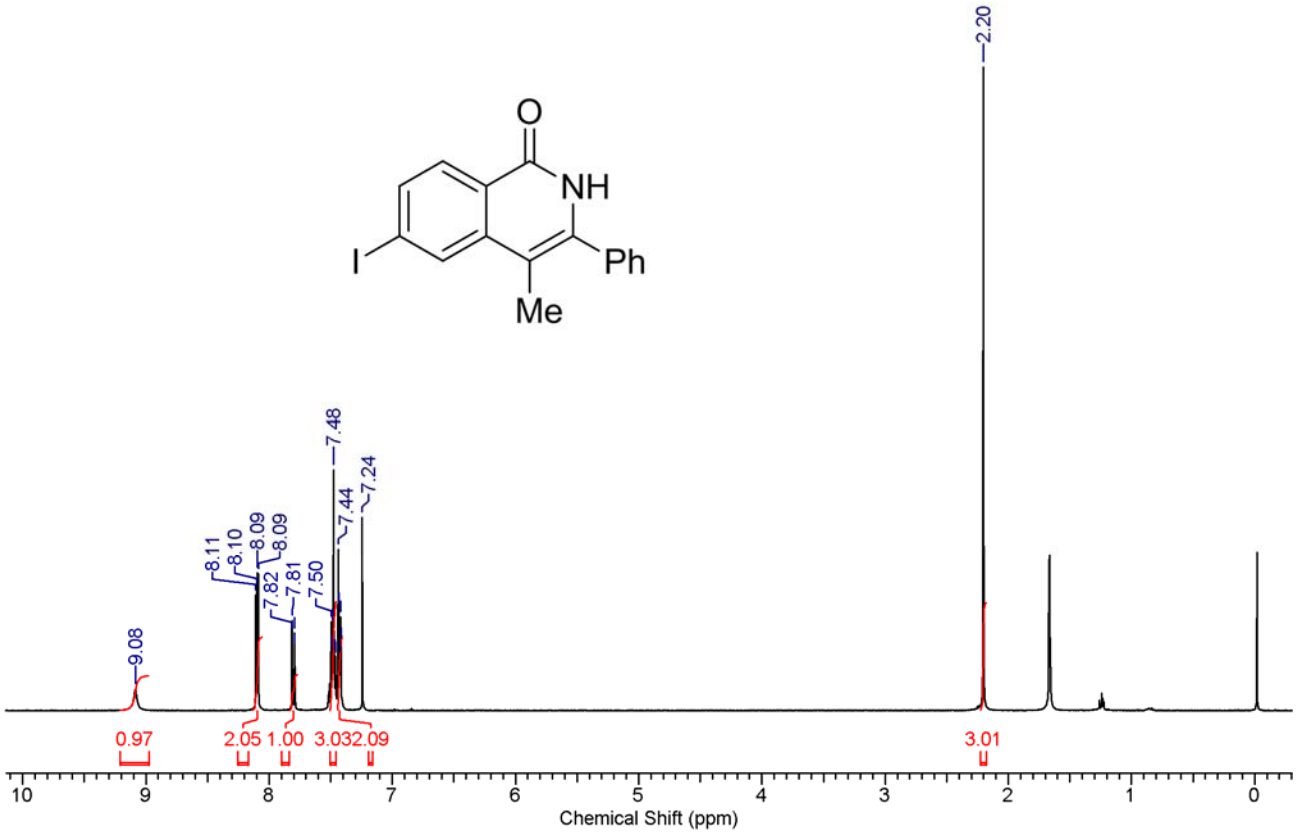


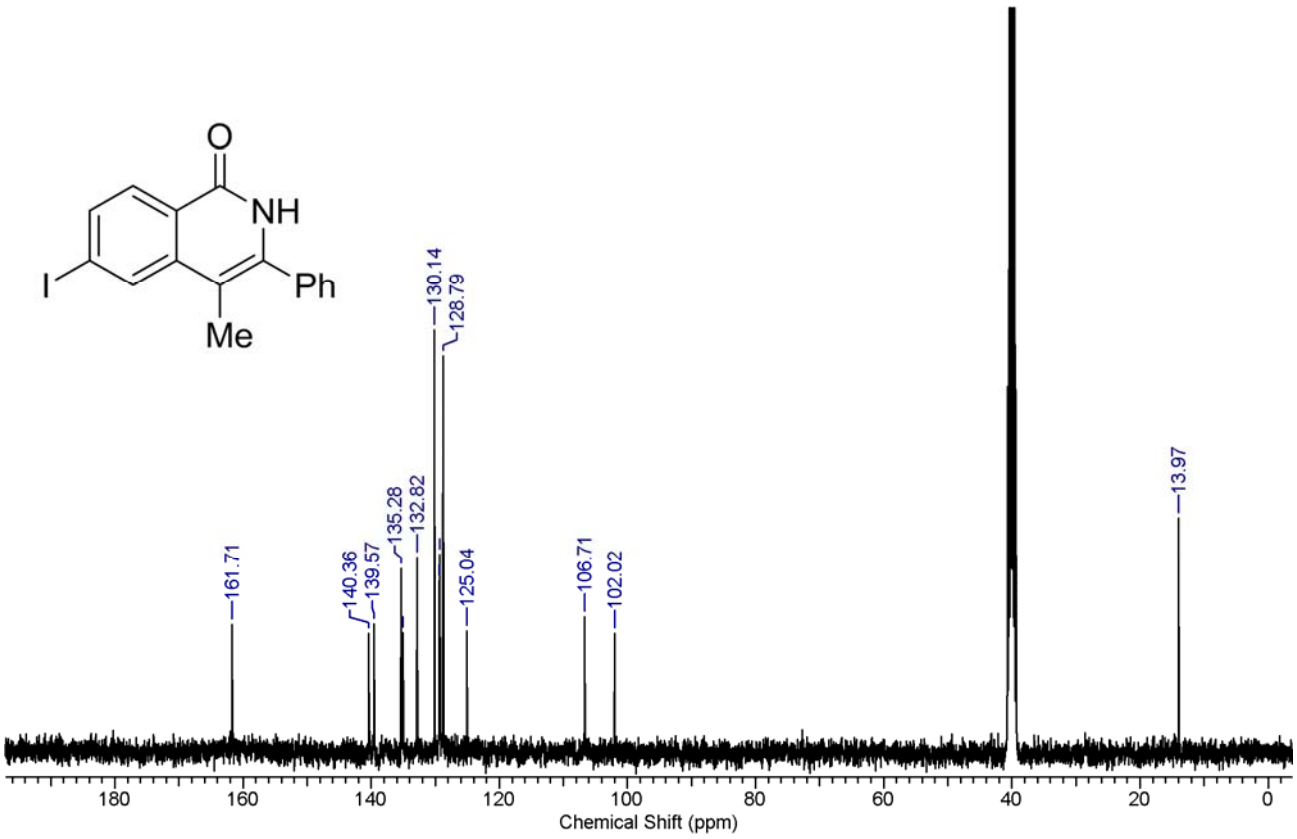


DEPT (135) NMR Spectrum of Compound **3p.**

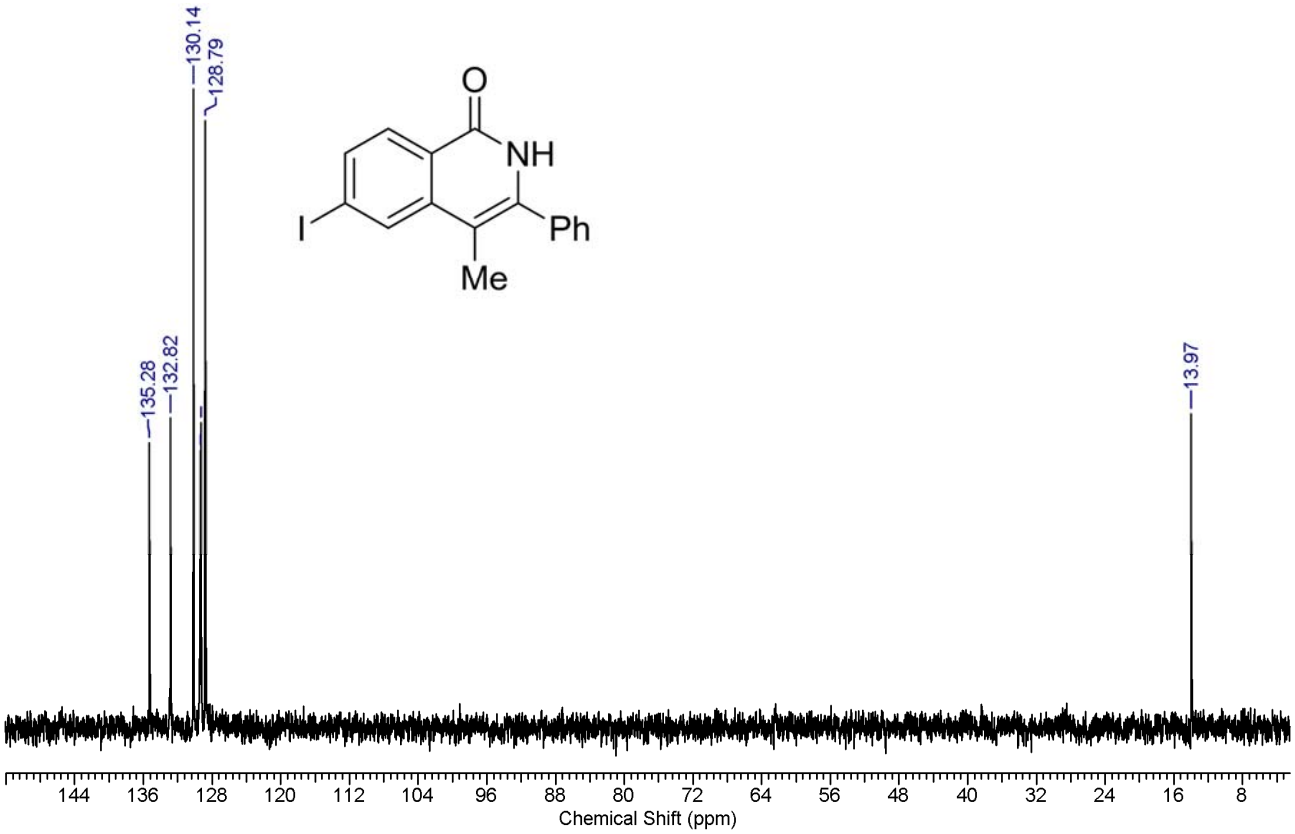


^{1}H and ^{13}C NMR Spectra of Compound **4a.**

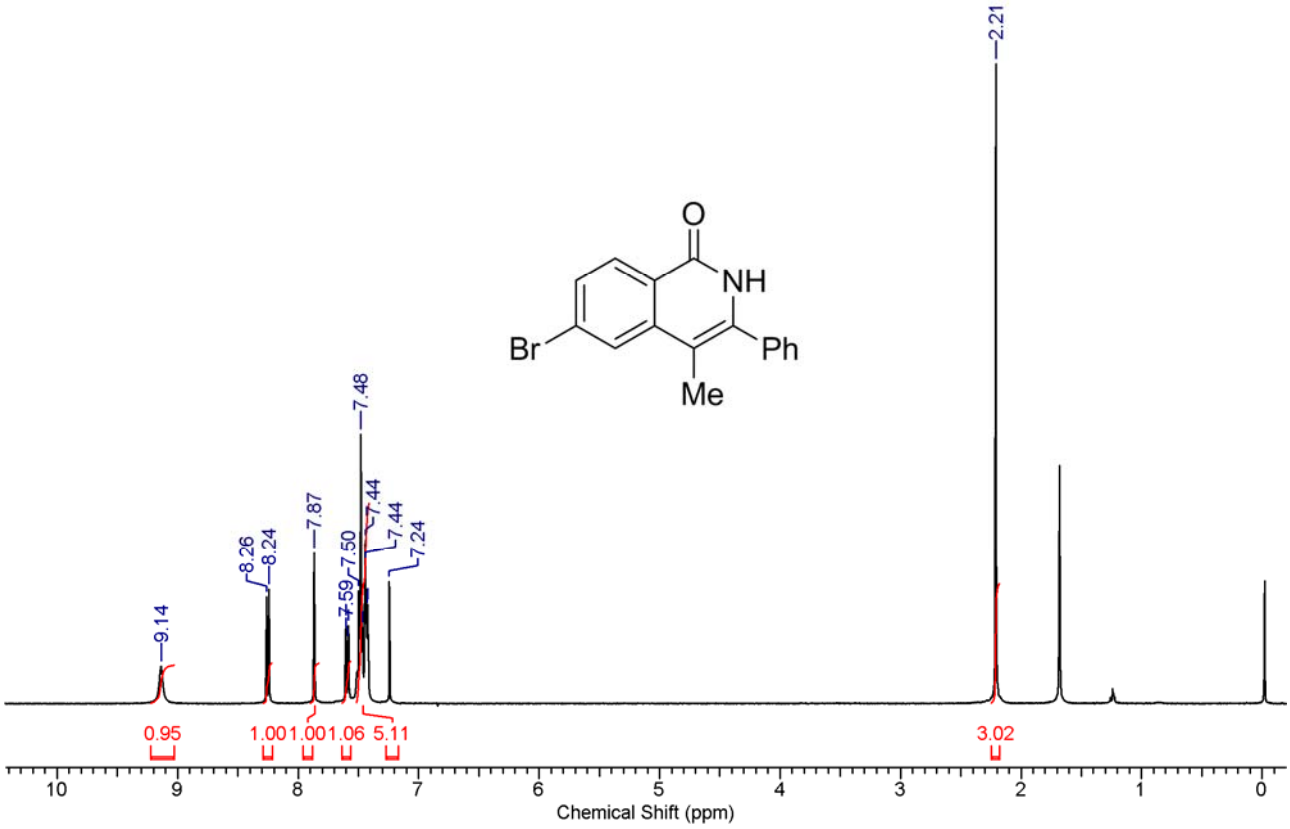


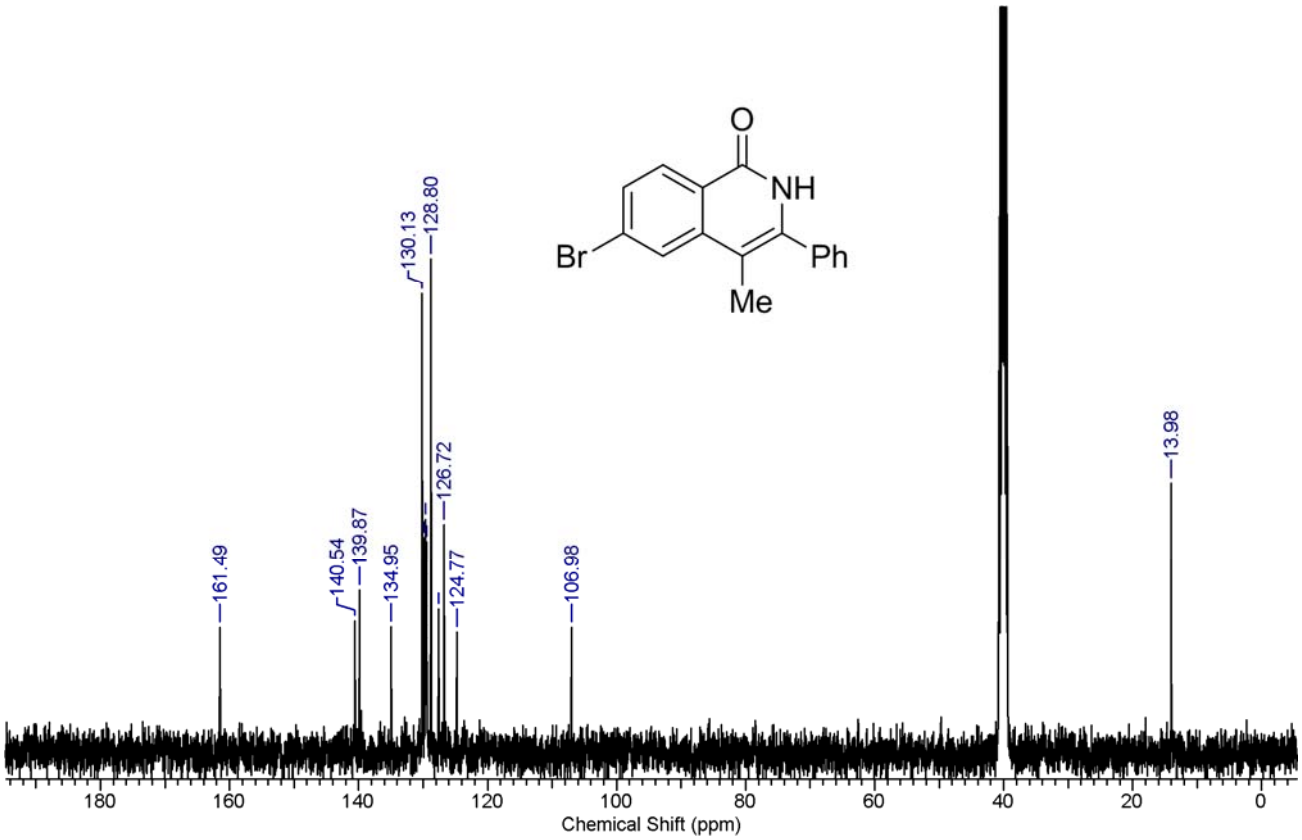


DEPT (135) NMR Spectrum of Compound **4a.**

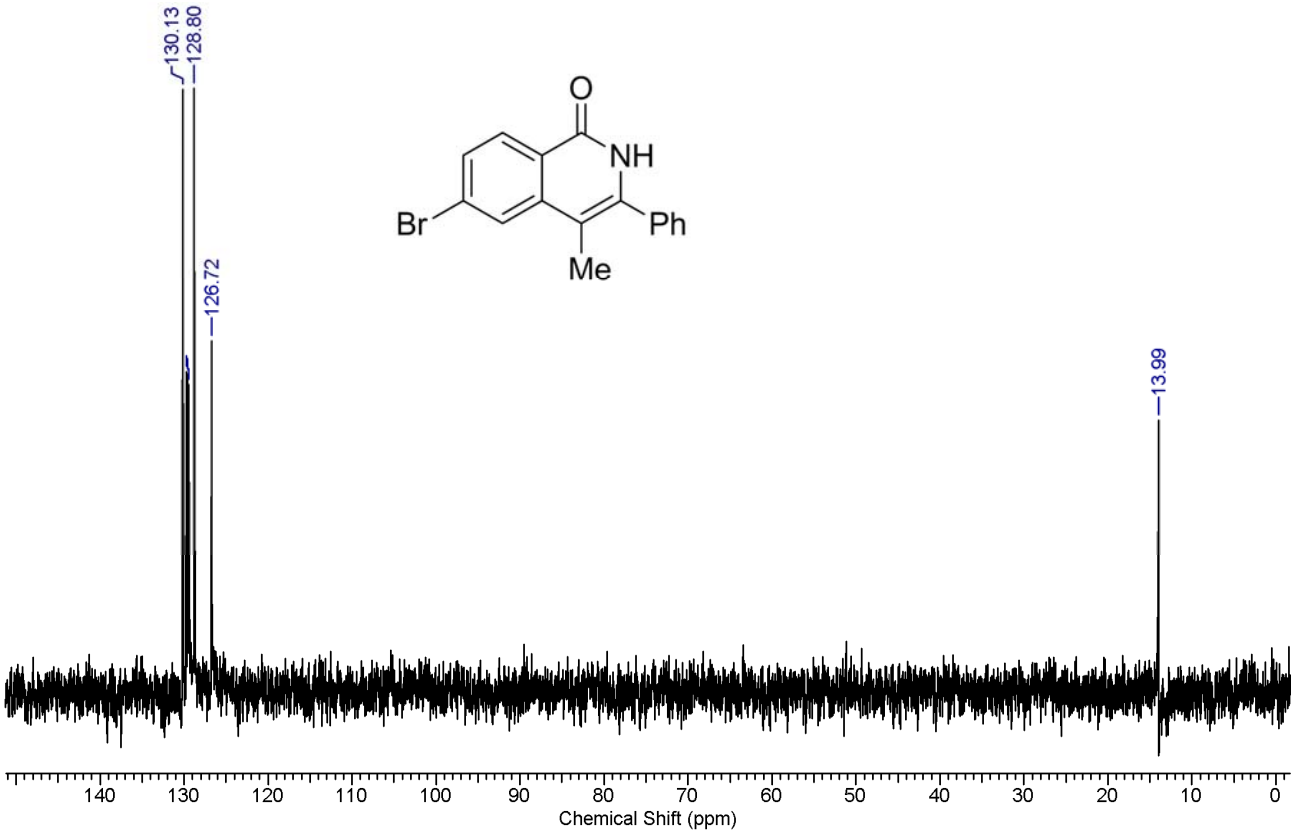


^{1}H and ^{13}C NMR Spectra of Compound **4b.**

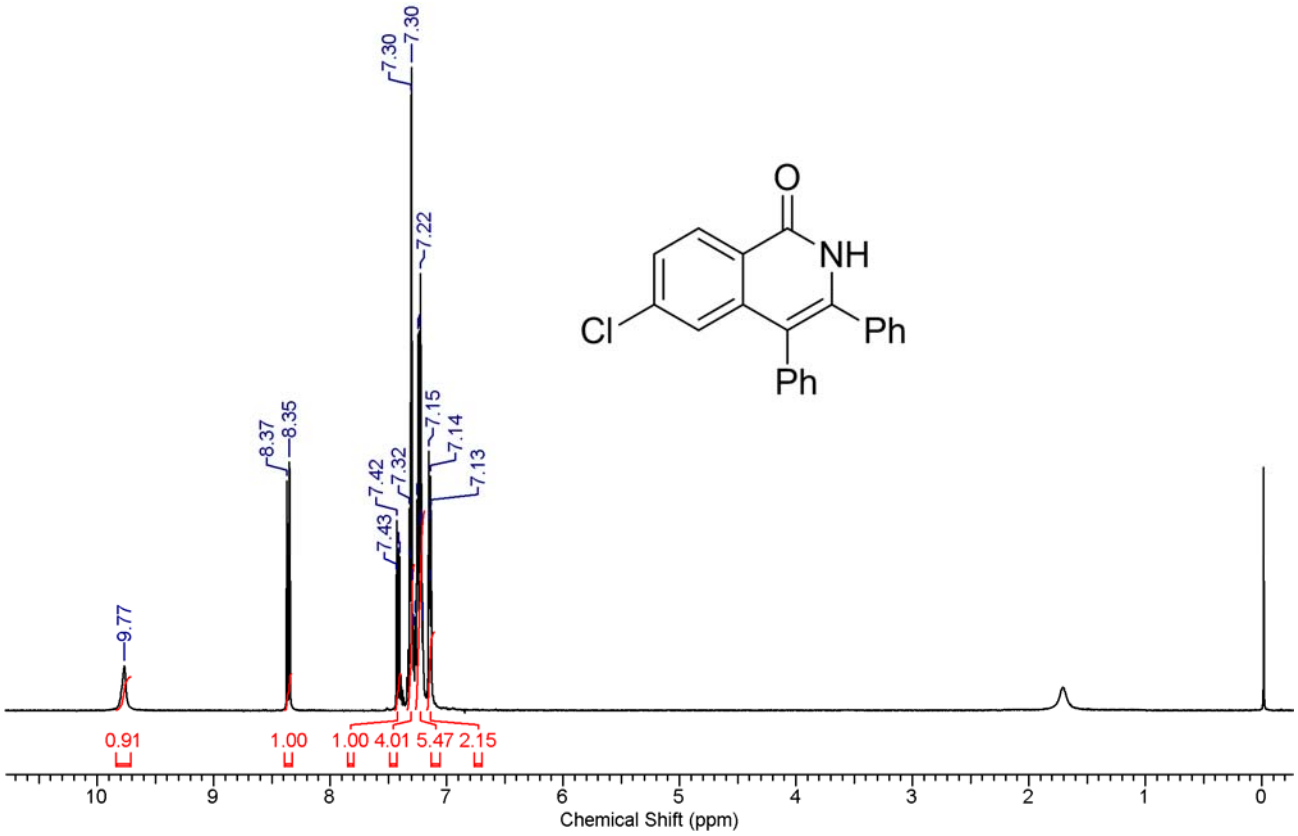


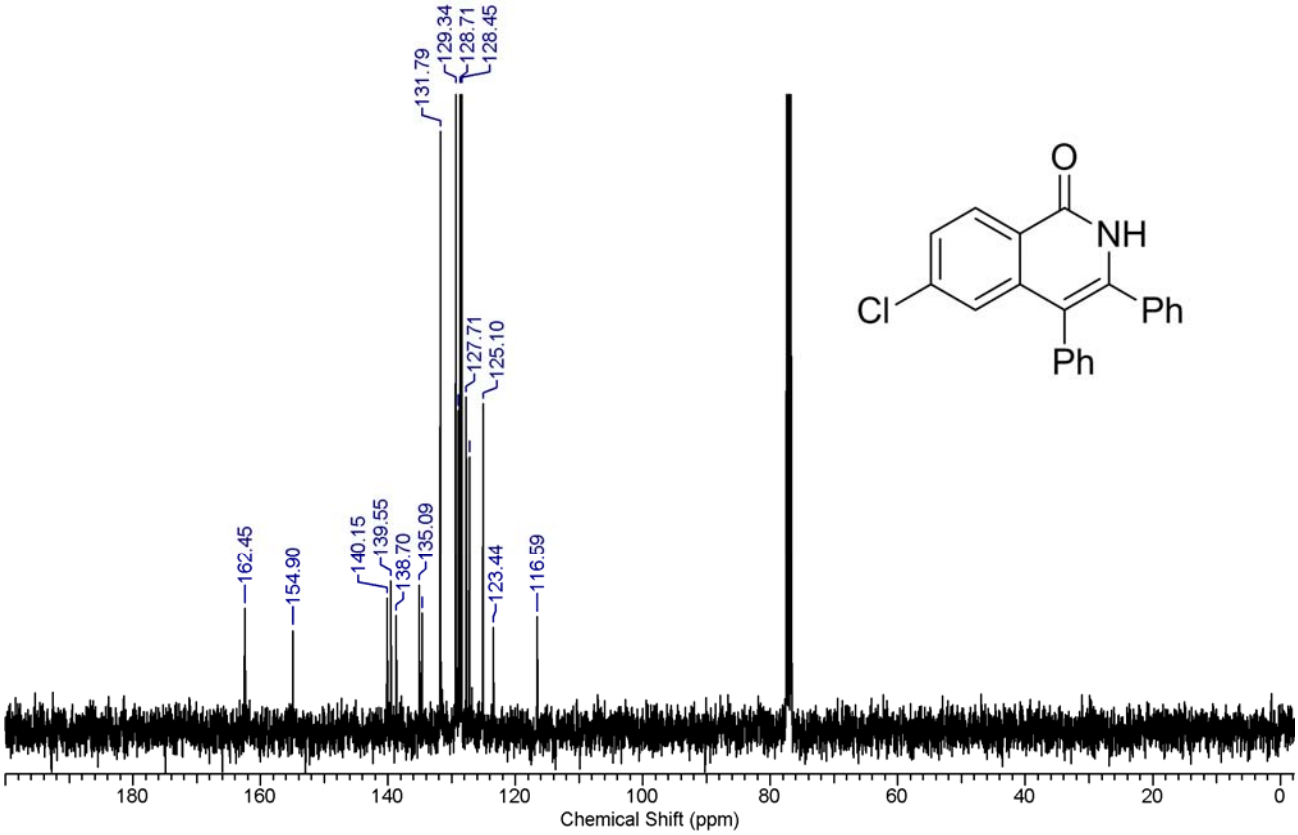


DEPT (135) NMR Spectrum of Compound **4b.**

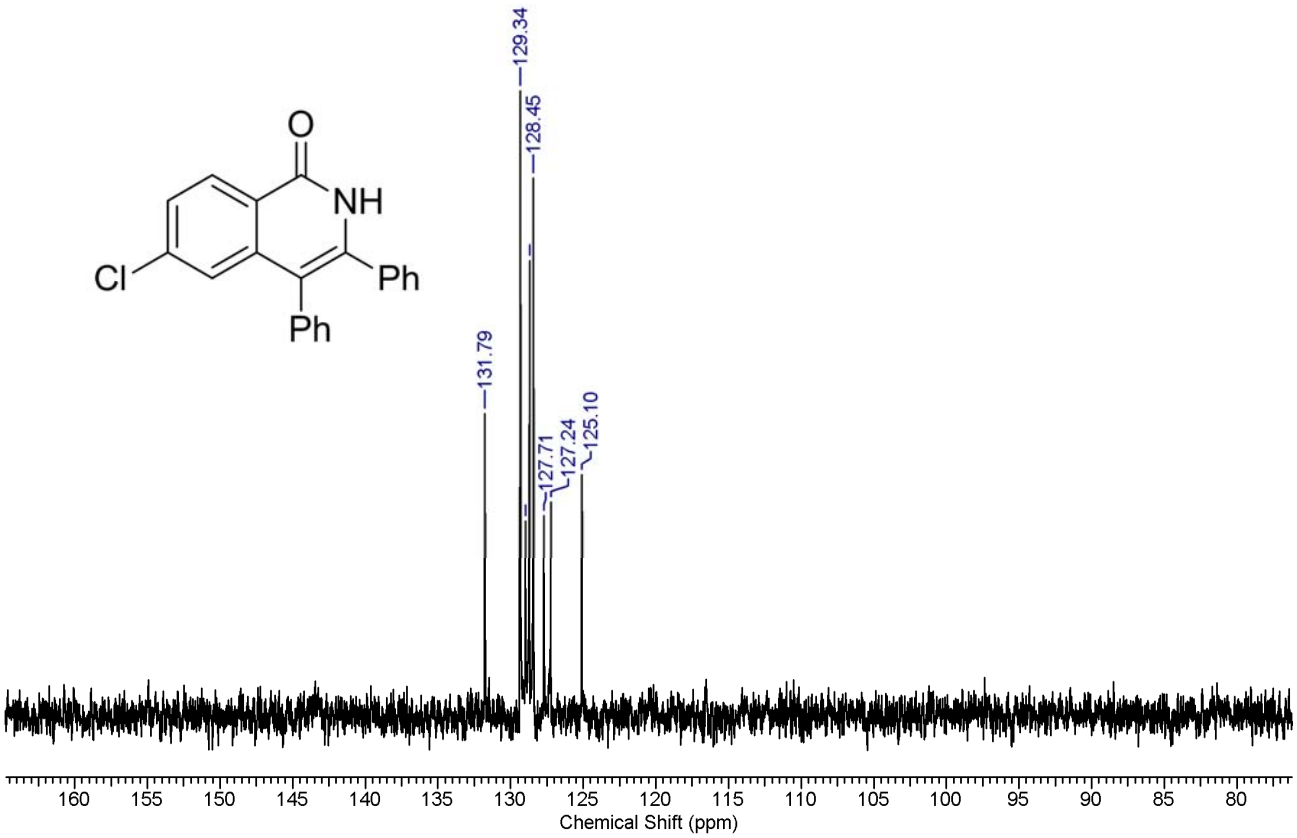


^{1}H and ^{13}C NMR Spectra of Compound **4c.**

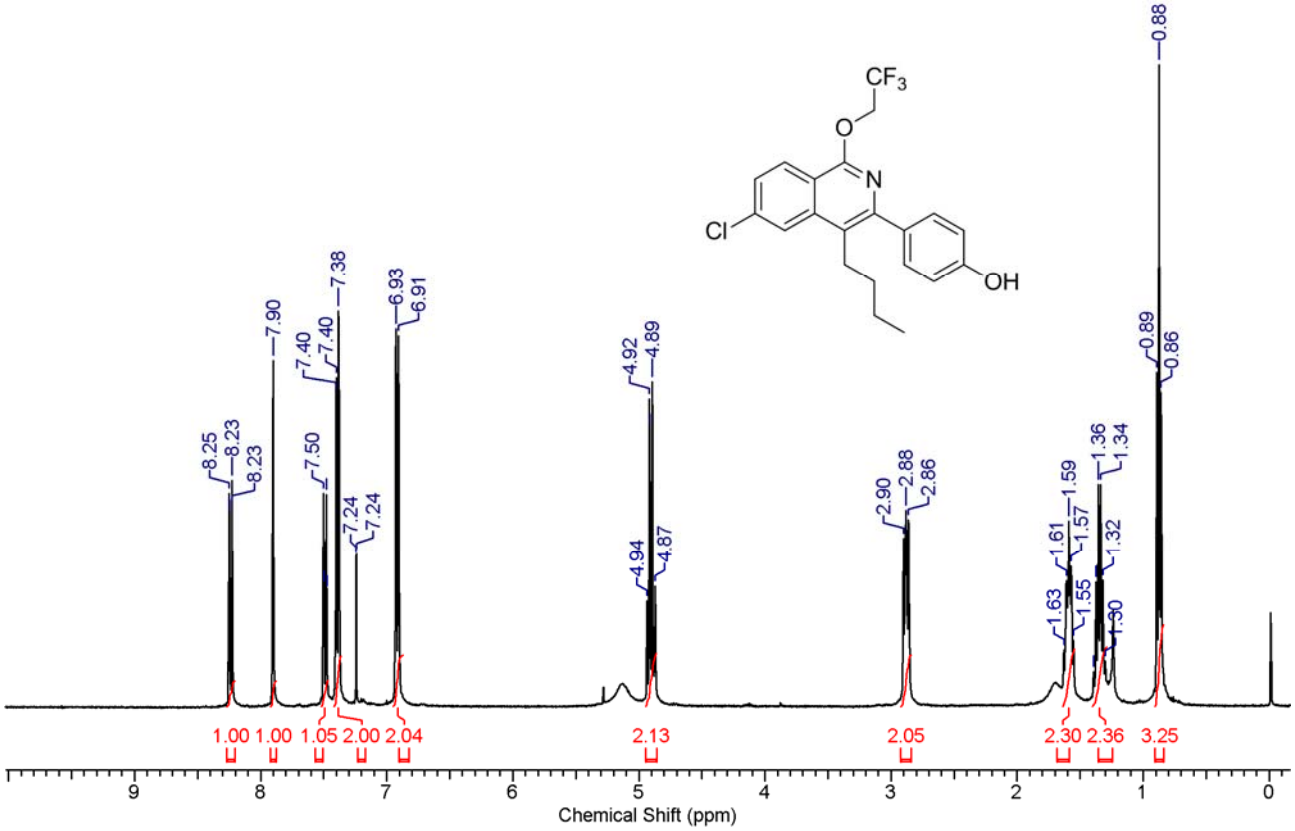


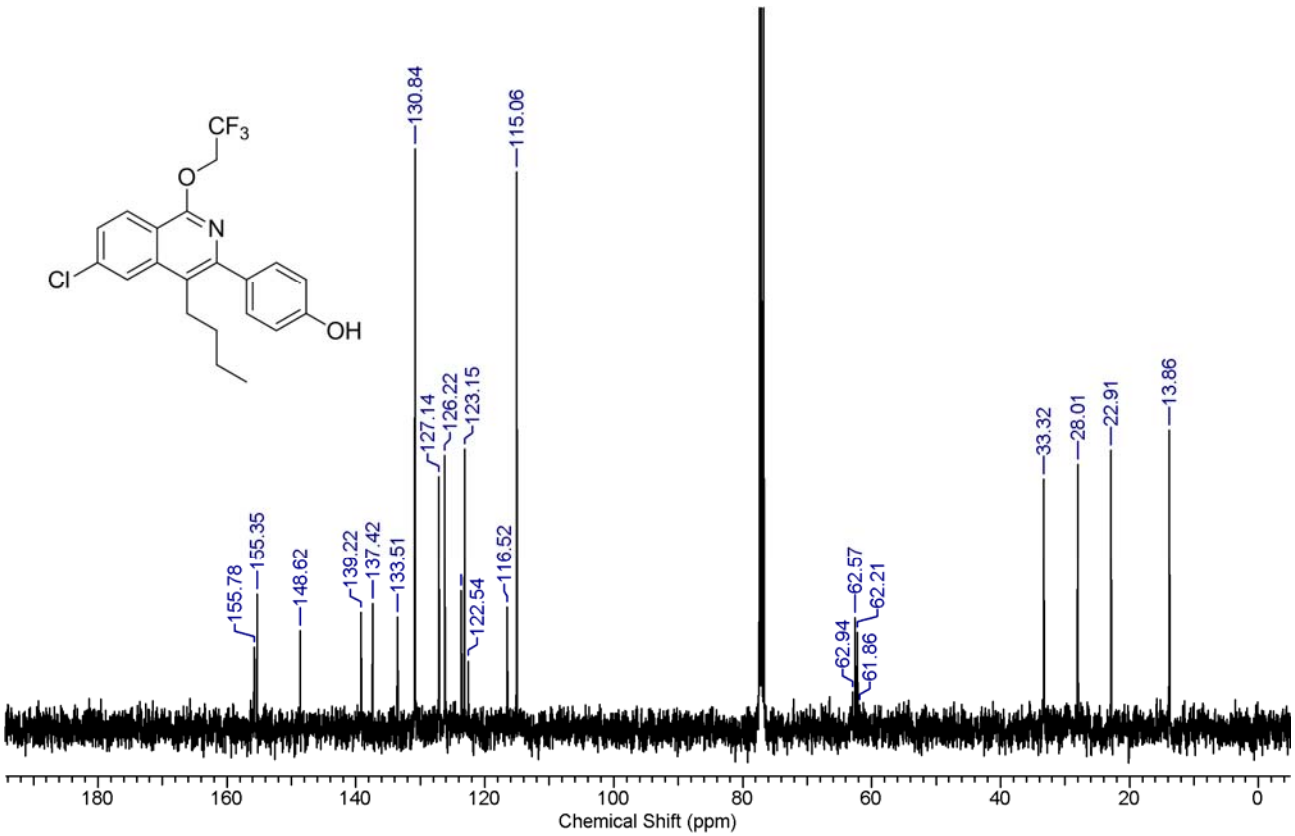


DEPT (135) NMR Spectrum of Compound **4c.**

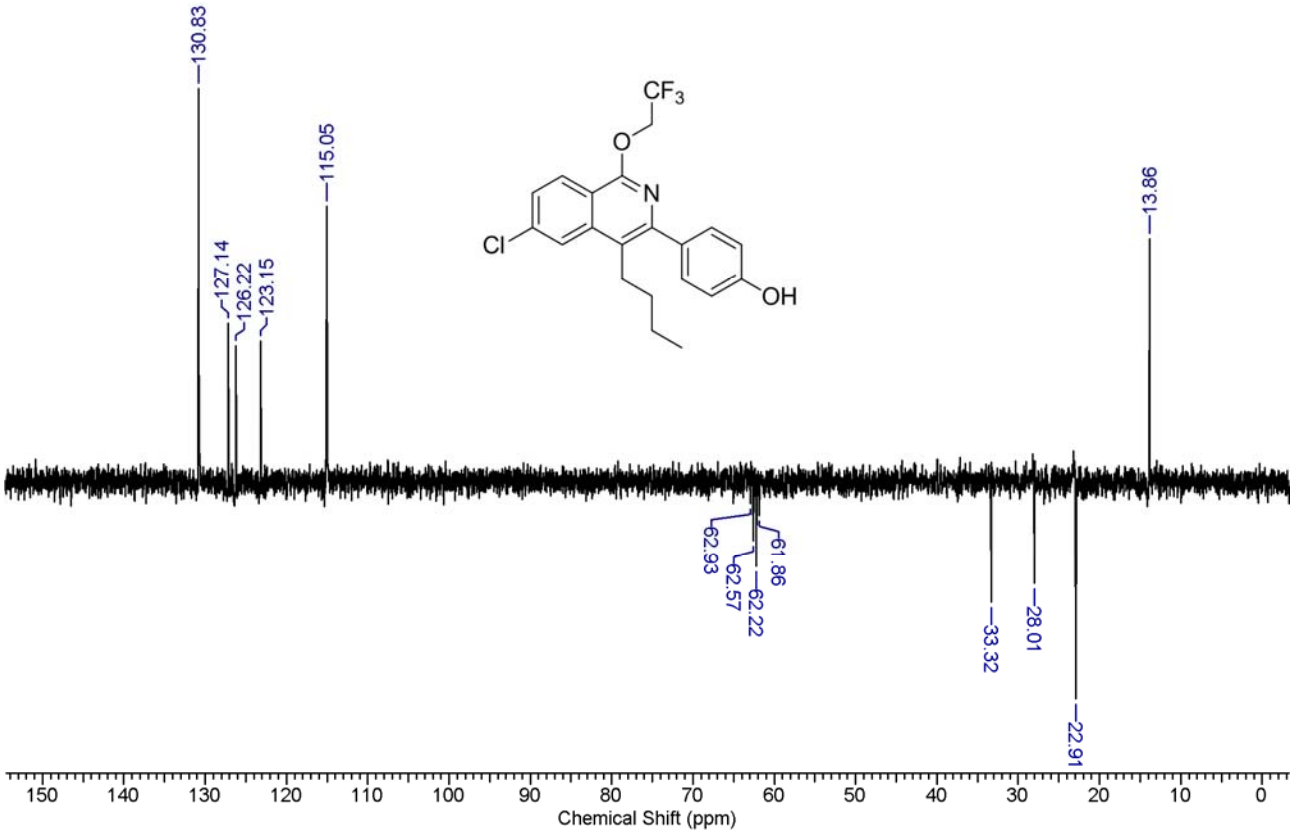


^{1}H and ^{13}C NMR Spectra of Compound **4d.**

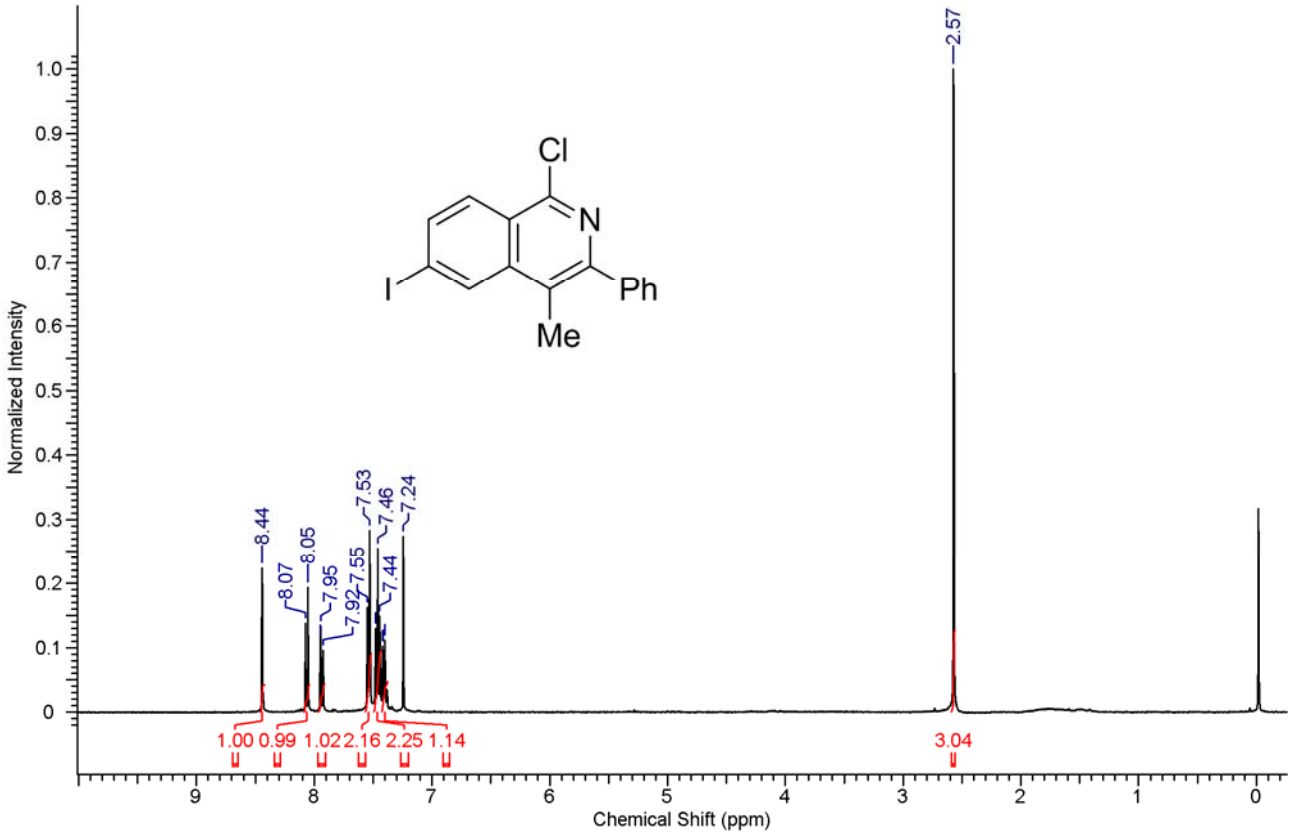


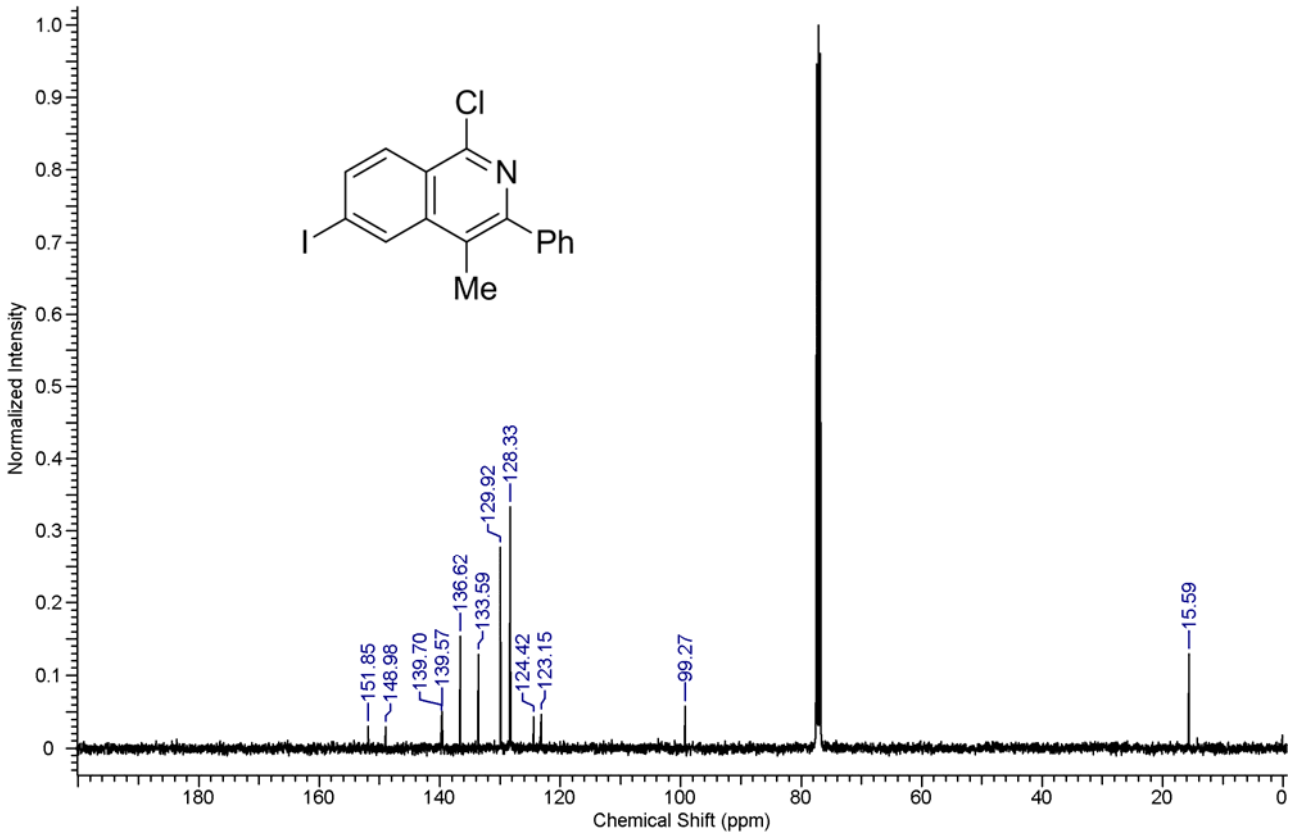


DEPT (135) NMR Spectrum of Compound **4d.**

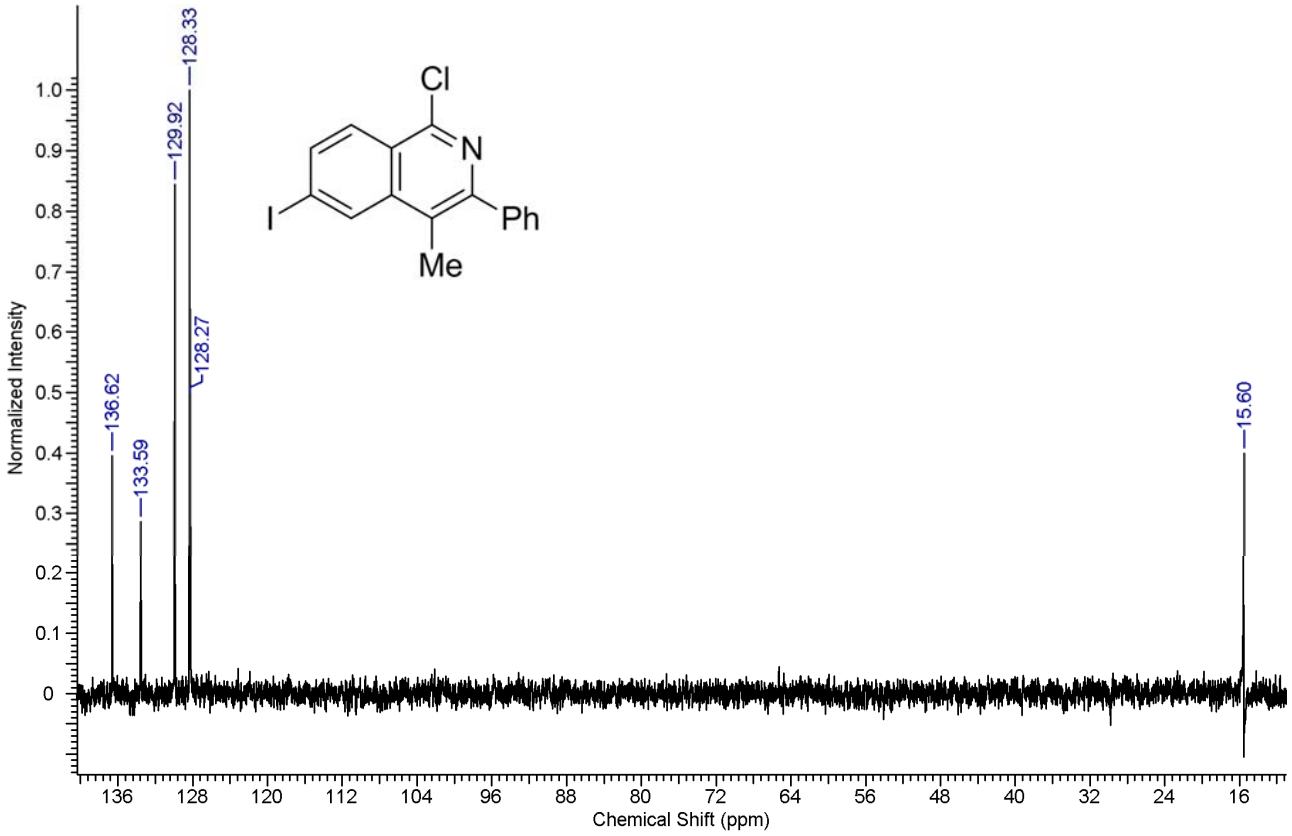


^{1}H and ^{13}C NMR Spectra of Compound **4e.**

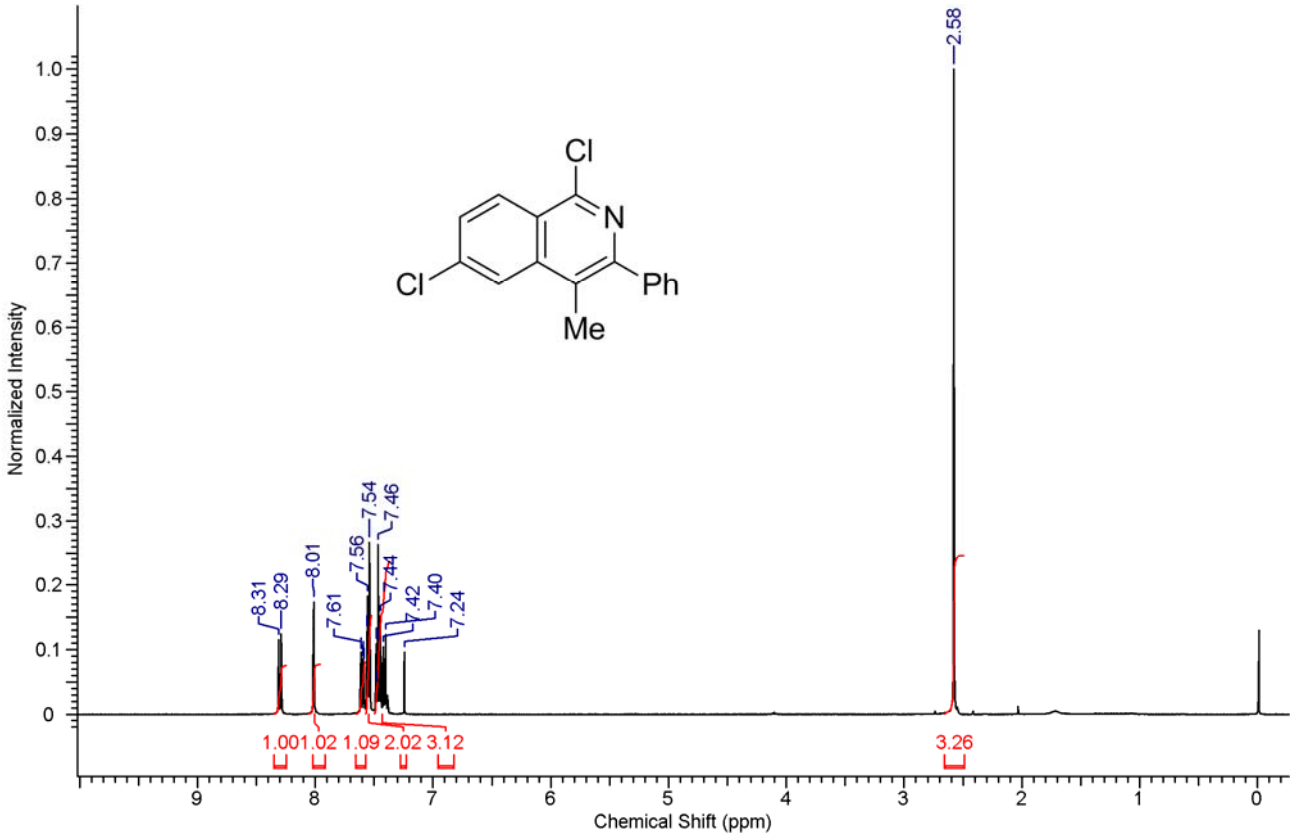


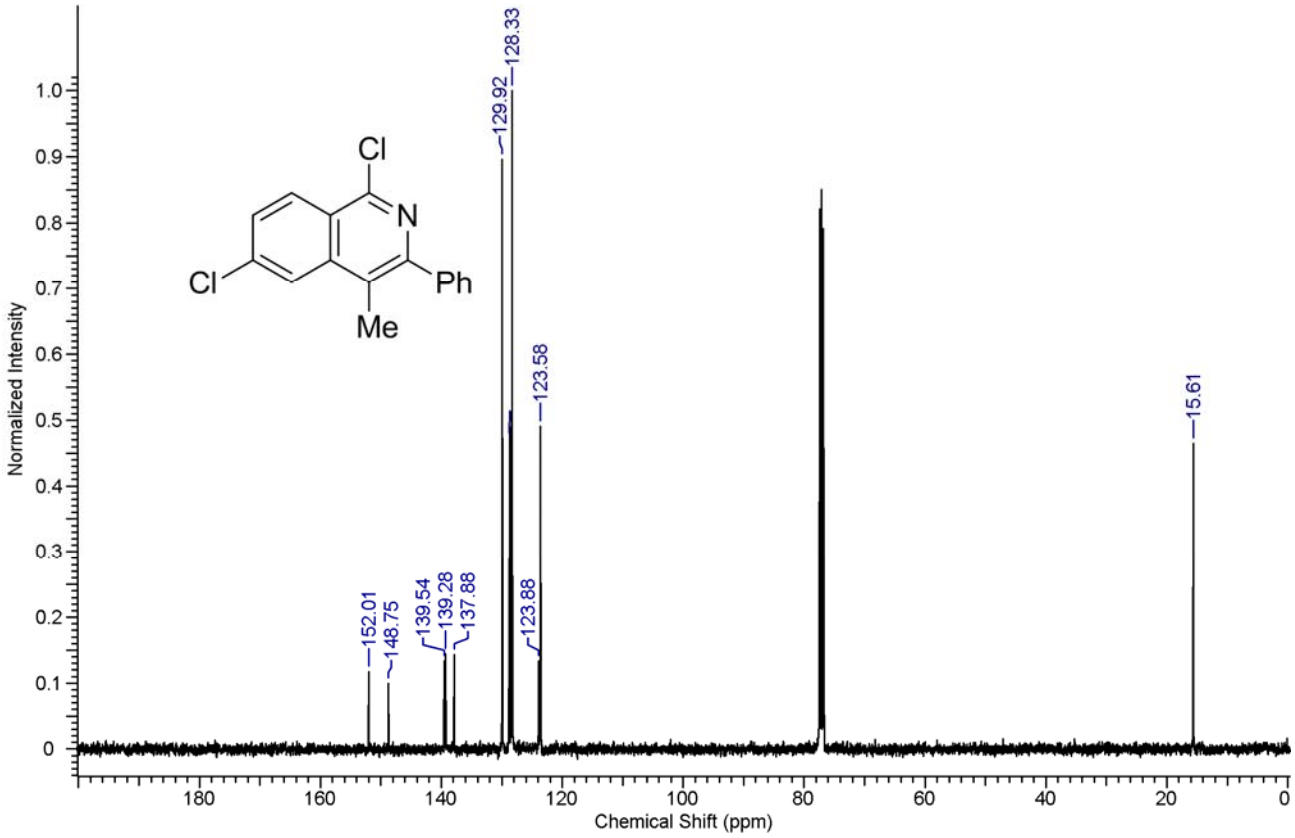


DEPT (135) NMR Spectrum of Compound **4e.**

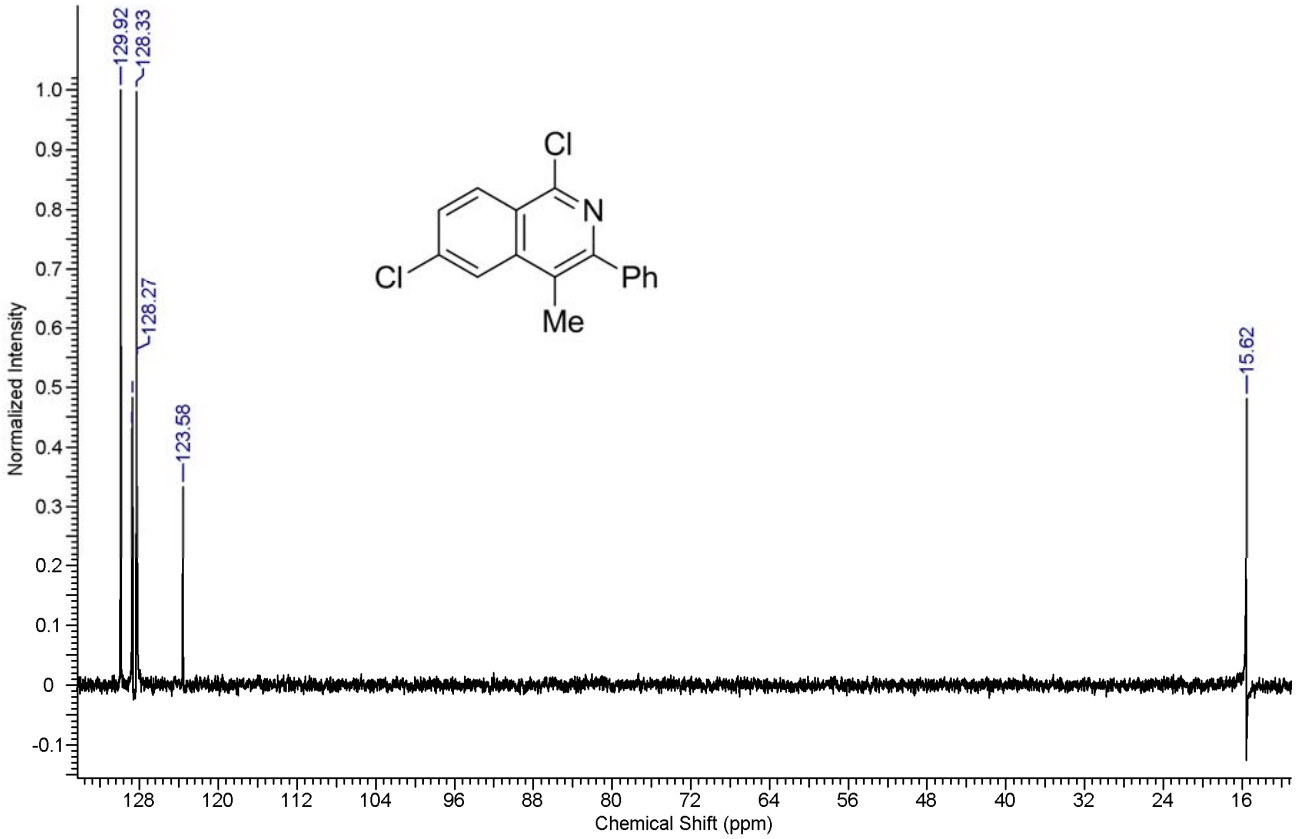


^{1}H and ^{13}C NMR Spectra of Compound **4f.**

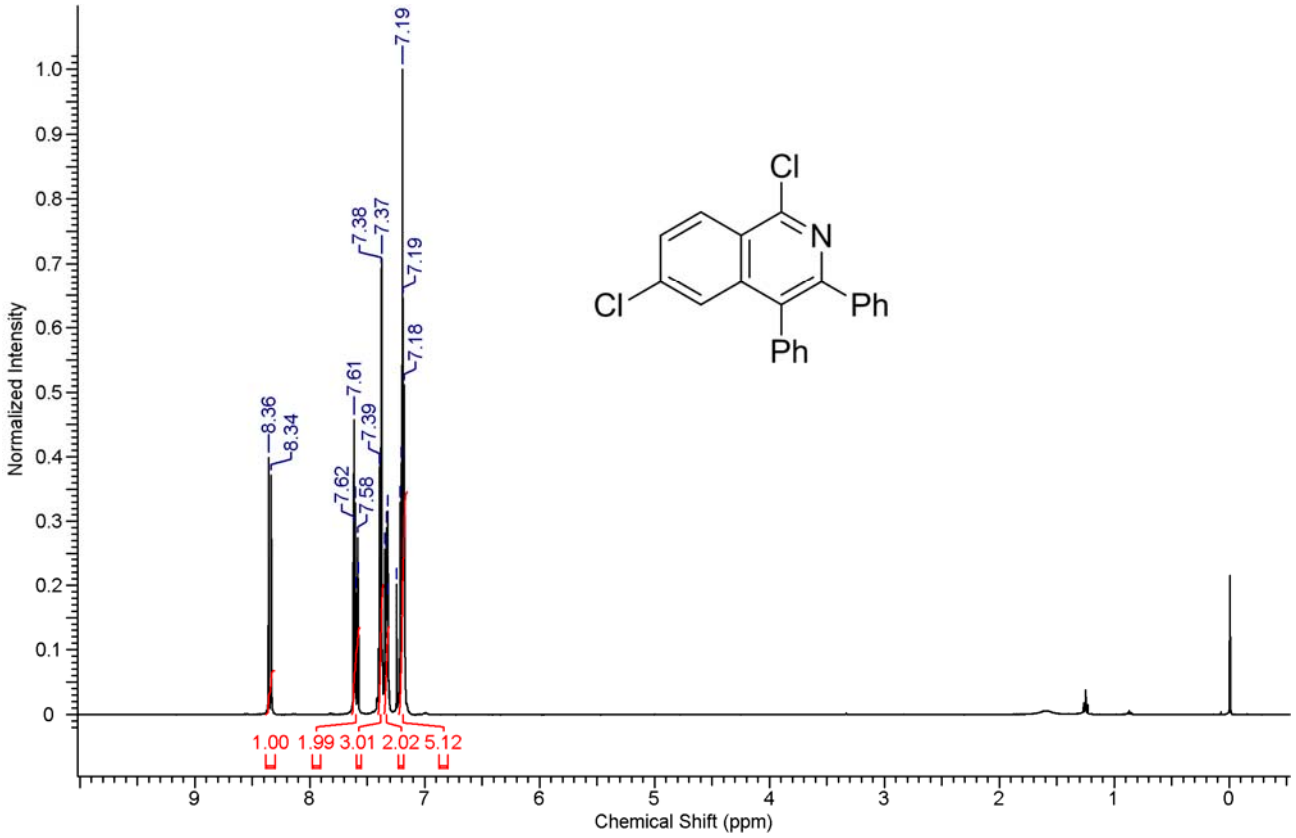


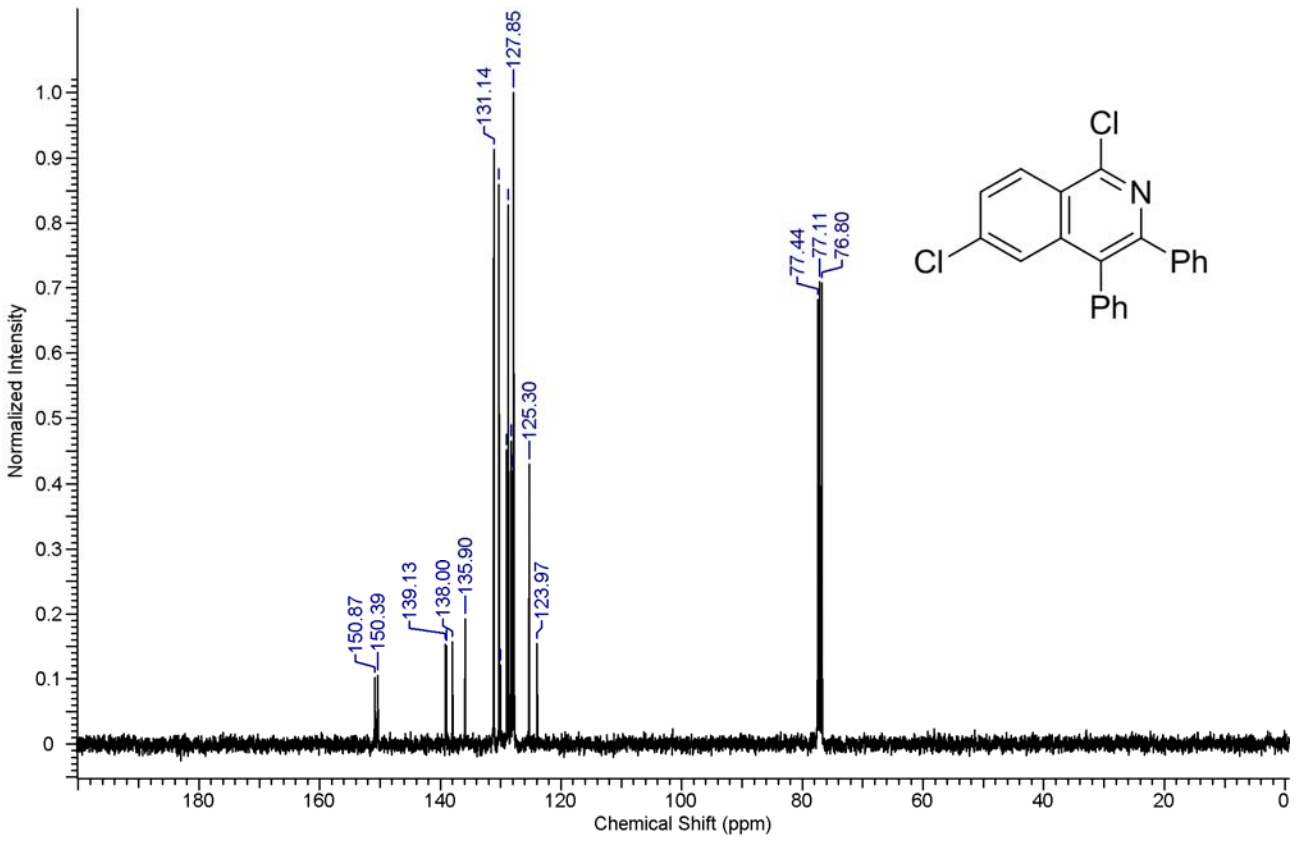


DEPT (135) NMR Spectrum of Compound **4f.**

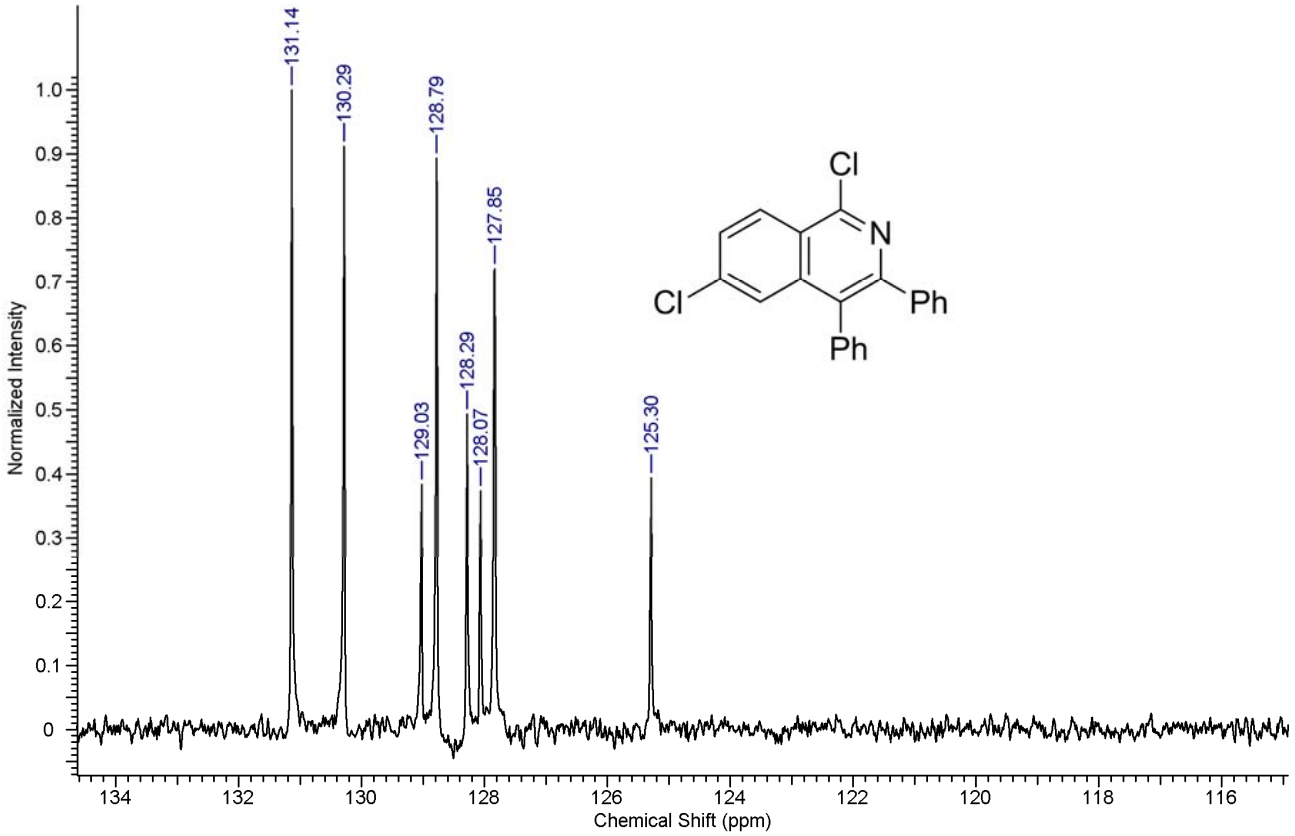


^{1}H and ^{13}C NMR Spectra of Compound **4g.**

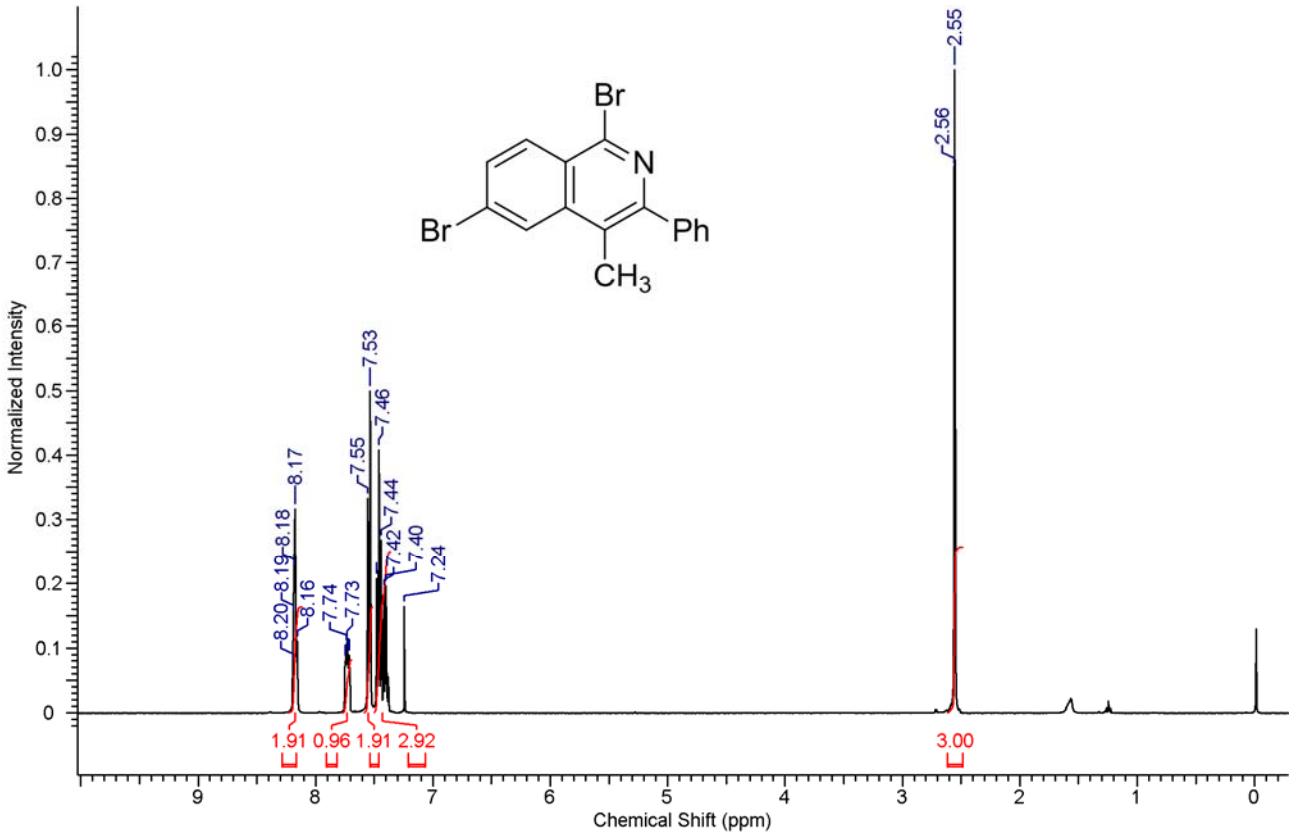


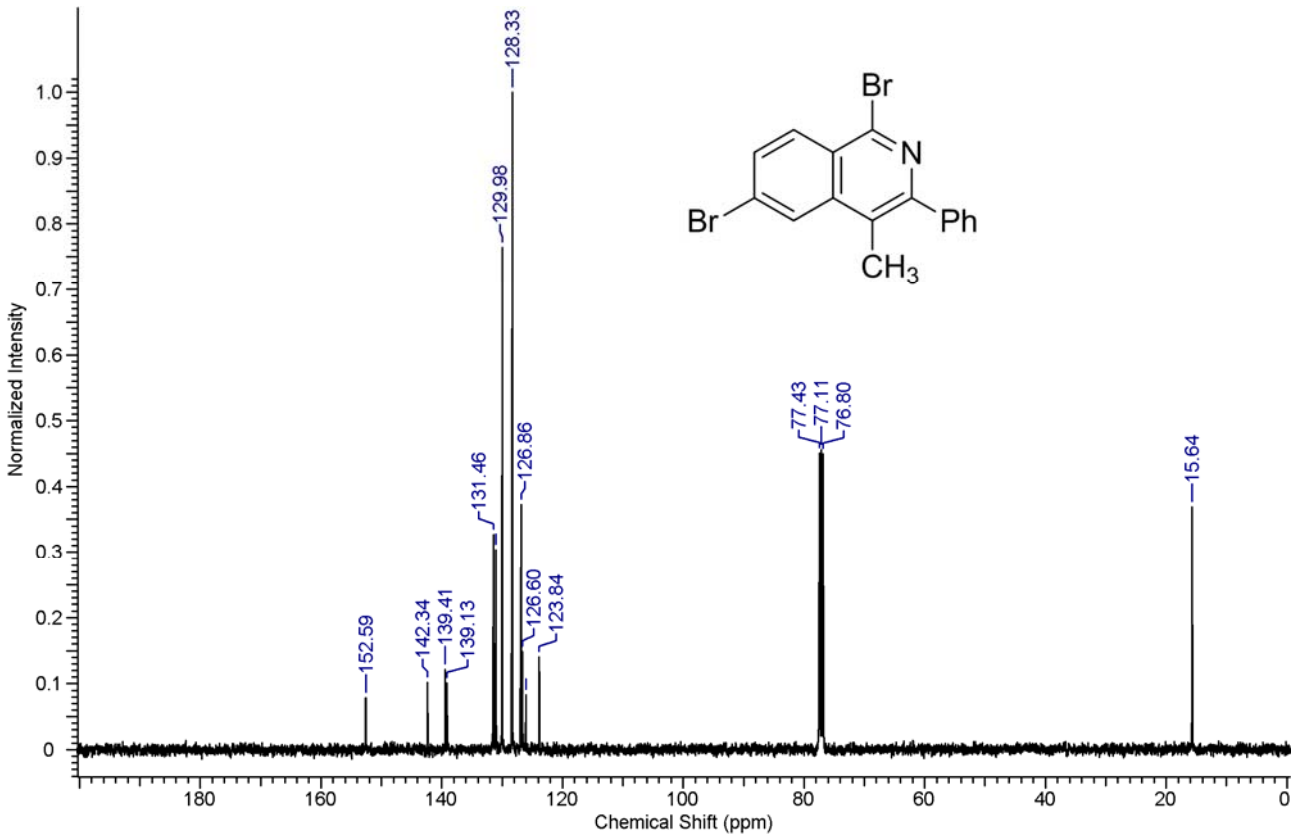


DEPT (135) NMR Spectrum of Compound **4g.**

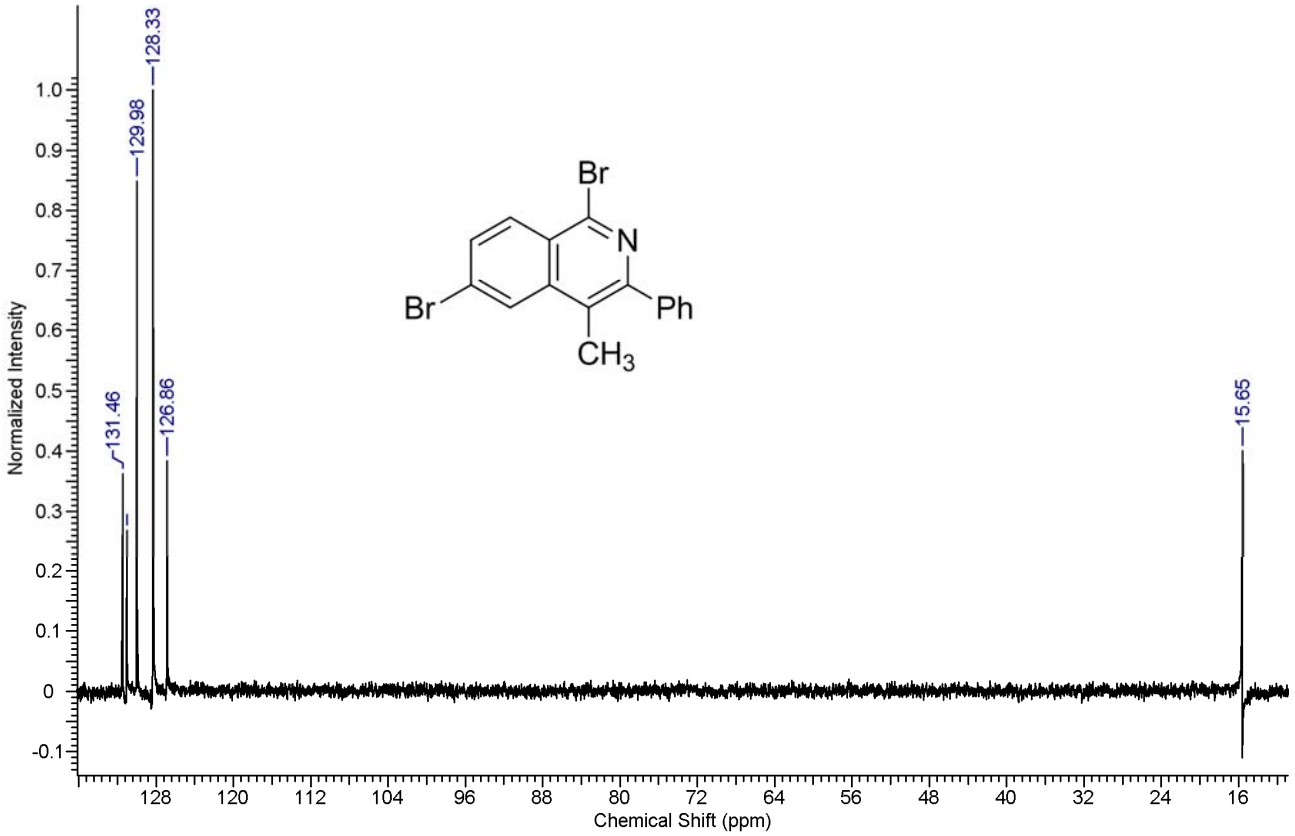


^{1}H and ^{13}C NMR Spectra of Compound **4h.**

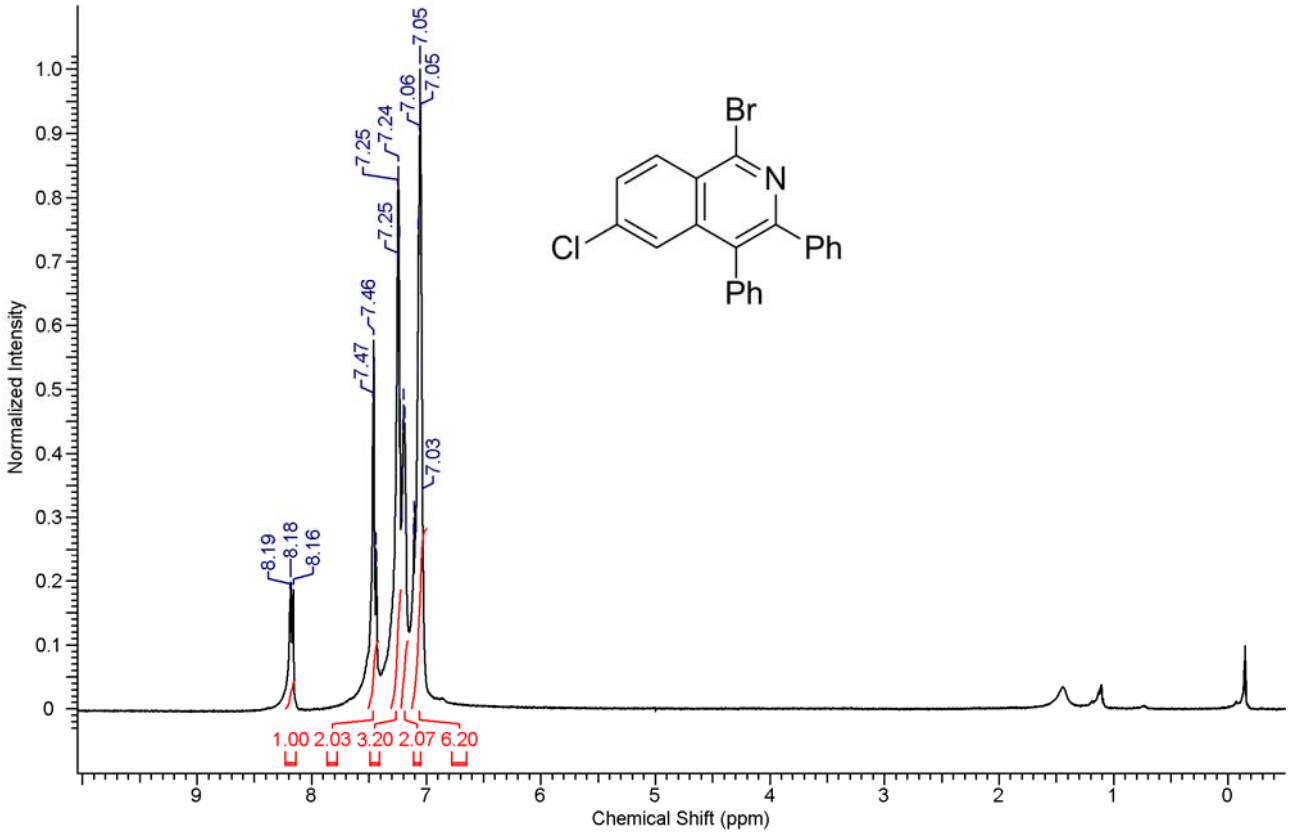


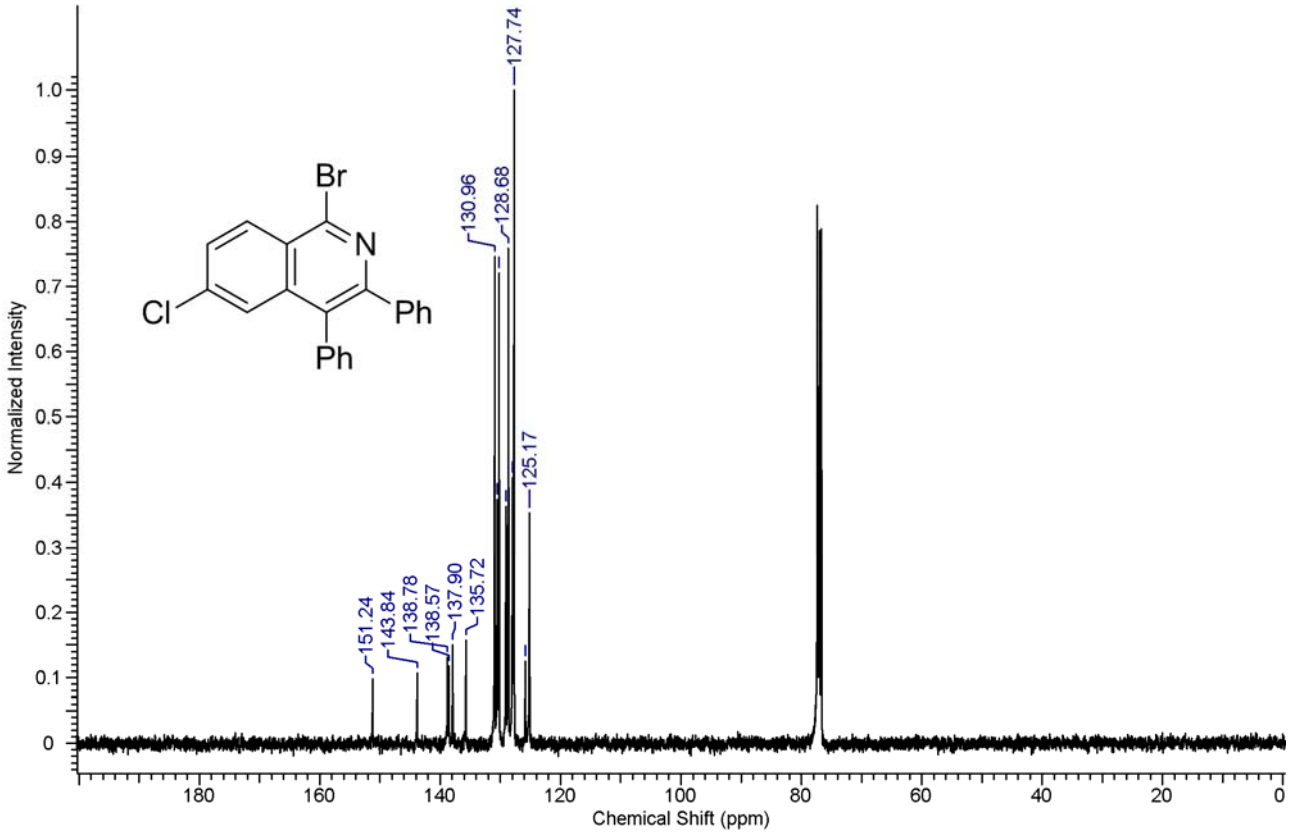


DEPT (135) NMR Spectrum of Compound **4h.**

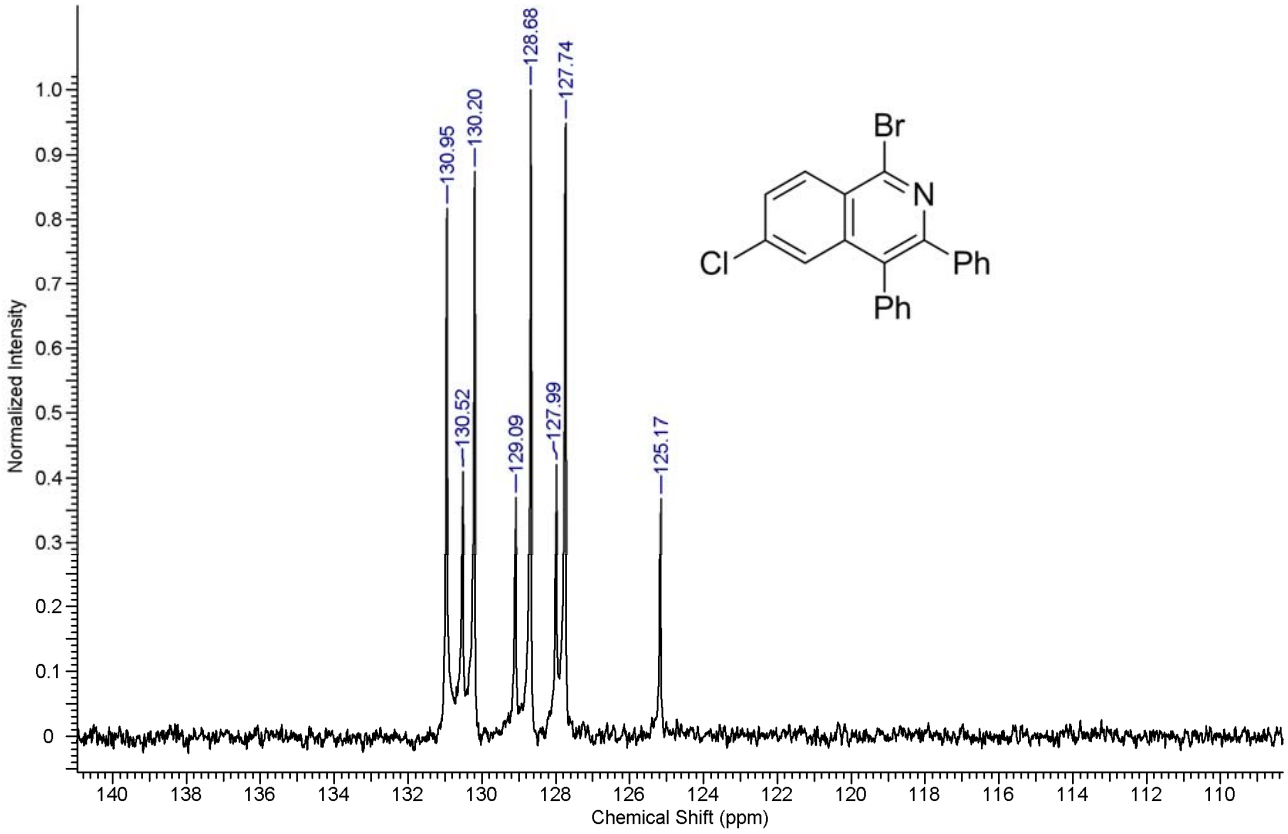


^{1}H and ^{13}C NMR Spectra of Compound **4i.**

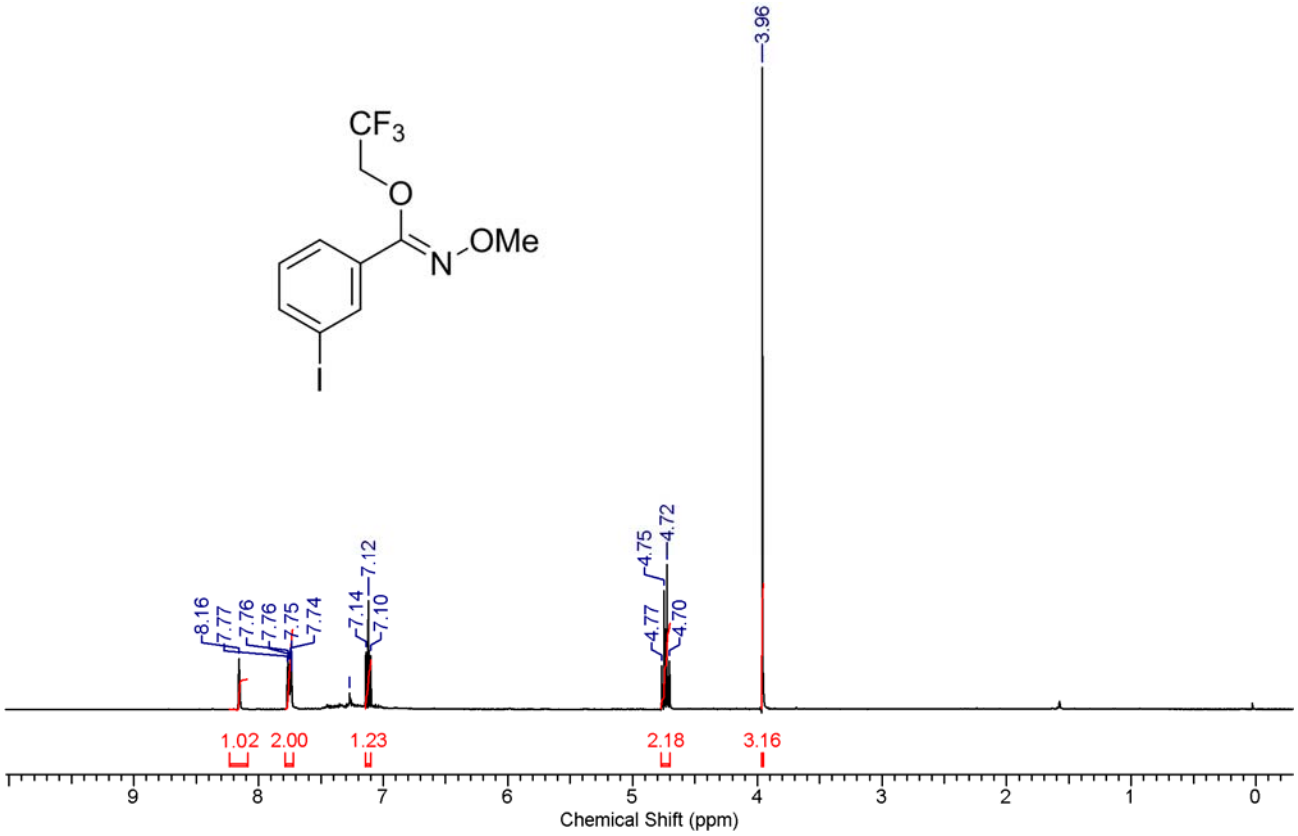


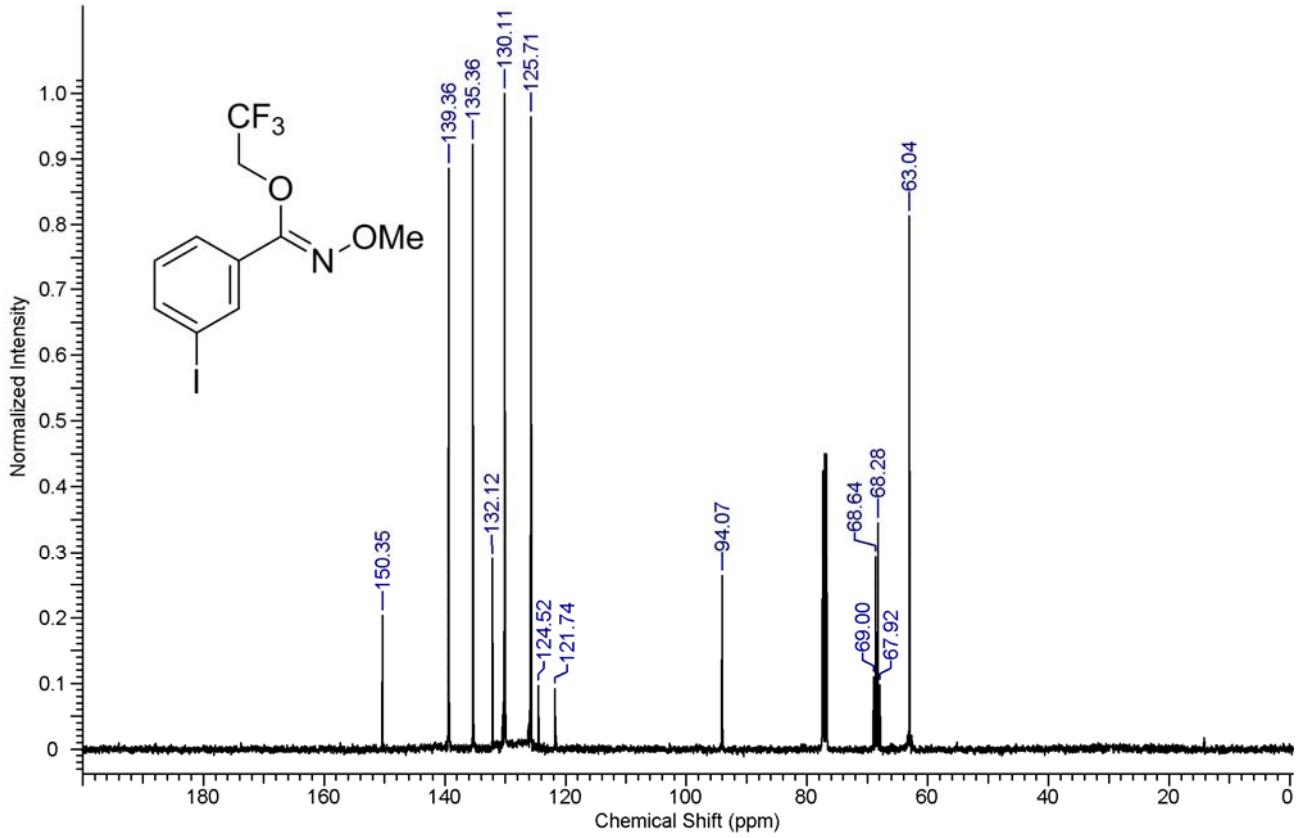


DEPT (135) NMR Spectrum of Compound **4i.**

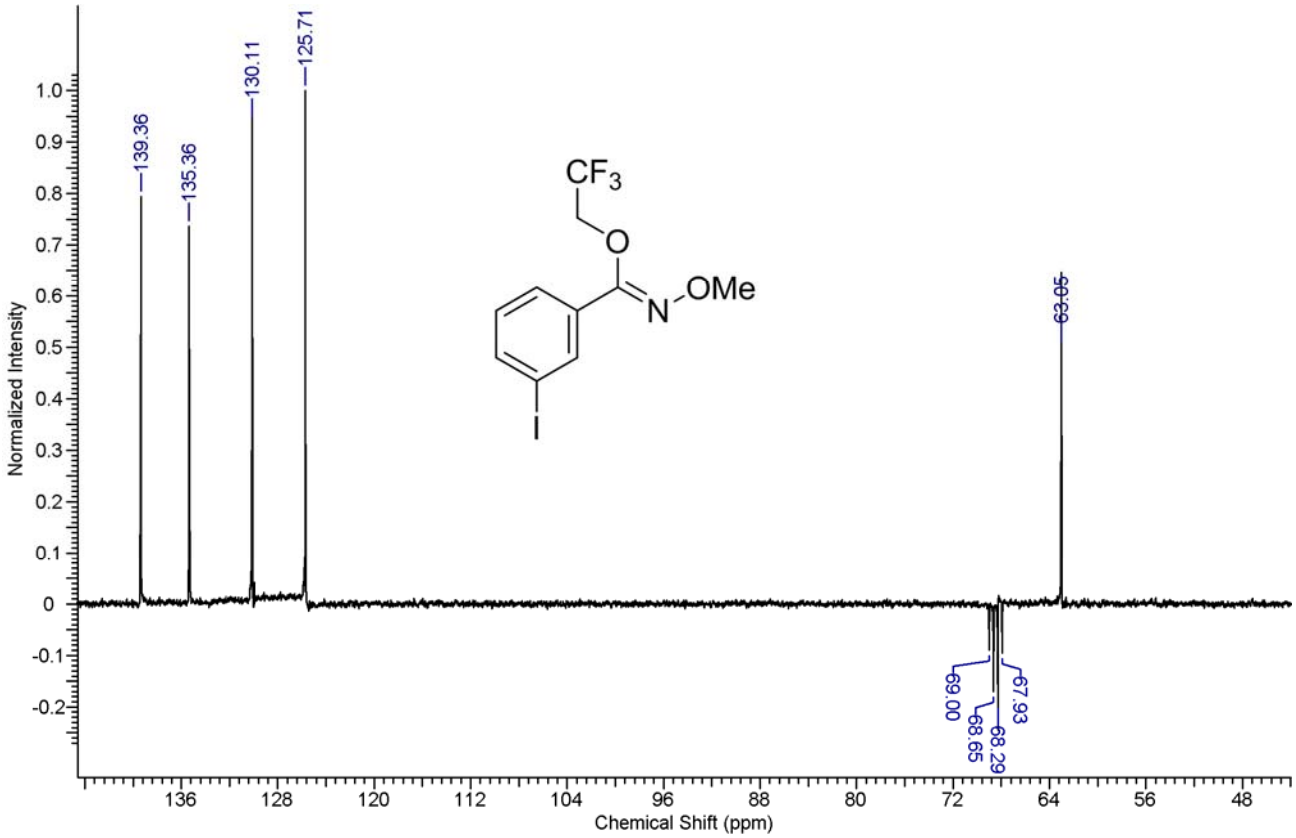


^{1}H and ^{13}C NMR Spectra of Compound **8a.**





DEPT (135) NMR Spectrum of Compound **8a.**



^{1}H and ^{13}C NMR Spectra of Compound **8b.**