Cu–Catalyzed Transannulation Reaction of Pyridotriazoles with Terminal Alkynes under Aerobic Conditions: Efficient Synthesis of Indolizines

V. Helan, A. V. Gulevich, and V. Gevorgyan*
Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607

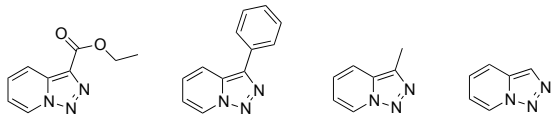
Table of contents

General information

GC/MS analysis was performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). Column chromatography was carried out employing Silicycle Silica-P flash silica gel (40-63 μm). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography. NMR spectra were recorded on Bruker Avance DRX-500 (500 MHz) or DPX-400 (400 MHz) instrument. All manipulations with transition metal catalysts were conducted in oven-dried glassware under inert atmosphere using a glovebox unless otherwise noted. Anhydrous solvents purchased from Sigma-Aldrich were additionally purified on PureSolv PS-400-4 by Innovative Technology, Inc. purification system and/or stored over calcium hydride. The starting materials were purchased from Sigma-Aldrich and Alfa Aesar.

1. Synthesis of Pyridotriazoles (1)

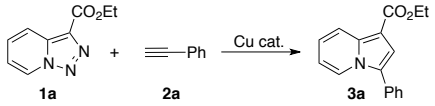
[1,2,3]triazolo[1,5-*a*]pyridines **1a**,**b**[1] and **1c**,**d**[2] were synthesized according to the literature procedures.



1a **1b** **1c** **1d**

[1] Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757.
[2] Hirayama, T.; Ueda, S.; Okada, T.; Tsurue, N.; Okuda, K.; Nagasawa, H. et al *Chem Eur. J.* **2014**, *20*, 4156.

2. Optimization of the Cu-catalyzed Transannulation Reaction Conditions[a]



An oven dried 1 mL Wheaton V-vial capped with a mininert syringe valve, containing a stirring bar, was charged with a pyridotriazole **1a** (0.1 mmol, 1 equiv), catalyst (0.015 mmol, 15 mol %), dry toluene (0.1 mL, 1M), and phenylacetylene (3 or 1.2 equiv) under Ar or air atmosphere. The reaction mixture was stirred at the indicated temperature for about 4 hours and analyzed by GC-MS using pentadecane as internal standard.

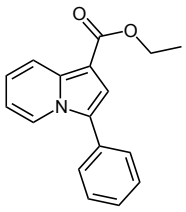
Entry	***Catalyst***		***Solvent***	***T (°C)***	***Yield[b]***
1	No catalyst	-	Toluene	100 °C	N.R.
2	$Rh_2(hfb)_4$	15 mol %	Toluene	100 °C	N.R.[c]
3	CuBr	15 mol %	Toluene	100 °C	N.R.
4	$CuBr_2$	15 mol %	Toluene	100 °C	N.R.
5	CuCl	15 mol %	Toluene	100 °C	N.R.
6	$CuCl_2$	15 mol %	Toluene	100 °C	N.R.
7	CuI	15 mol %	Toluene	100 °C	N.R.
8	$Cu(OAc)_2$	15 mol %	Toluene	100 °C	N.R.
9	$CuOTf•0.5C_6H_6$	15 mol %	Toluene	100 °C	38%
10	$Cu(OTf)_2$	15 mol %	Toluene	100 °C	25%
11	$Cu(MeCN)_4PF_6$	15 mol %	Toluene	100 °C	50%
12[d]	$Cu(MeCN)_4PF_6$	15 mol %	Toluene	120 °C	96%
13[d]	$Cu(MeCN)_4PF_6$	15 mol %	DCE	120 °C	89%
14[d]	$Cu(MeCN)_4PF_6$	15 mol %	DMA	120 °C	28%
15[d]	$Cu(MeCN)_4PF_6$	15 mol %	Toluene	130 °C	99%
16[d]	$Cu(MeCN)_4PF_6$	10 mol %	Toluene	130 °C	91%
17[d]	$Cu(MeCN)_4PF_6$	5 mol %	Toluene	130 °C	49%
18[e]	$Cu(MeCN)_4PF_6$	15 mol %	Toluene	130 °C	99%

[a] Triazole (1 equiv), Alkyne (3 equiv), Catalyst (15 mol %), solvent (1M). [b] GCMS yields are given. [c] Polymerization of the alkyne was observed. [d] 1.2 equiv of alkyne was used. [e] In air with 1.2 equiv of alkyne. hfb = heptafluorobutyrate.

3. General procedure for the synthesis of indolizines (3)

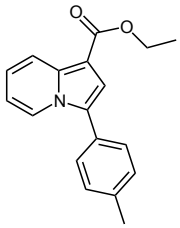
An oven dried 3 mL Wheaton V-vial capped with a mininert syringe valve, containing a stirring bar, was charged with a pyridotriazole (0.5 mmol, 1 equiv), $Cu(MeCN)_4PF_6$ (28 mg, 0.075 mmol, 15 mol %), dry toluene (0.5 mL, 1M), and a terminal alkyne (0.6 mmol, 1.2 equiv) in air. The reaction mixture was stirred at 130 °C for 1 to 12h. The residue was then directly purified by column chromatography on triethylamine-treated silica gel (EtOAc/Hexane) to afford the corresponding indolizine **3**.

Ethyl 3-phenylindolizine-1-carboxylate (3a)



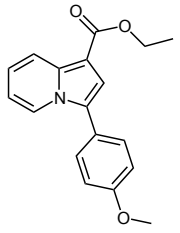
Reaction time: 4h; 70% yield (0.35 mmol, 93 mg), eluent: EtOAc/Hex = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.29-8.27 (m, 2H), 7.54 (d, *J* = 7.1 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.32 (s, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.69 (t, *J* = 6.8 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm165.02, 136.34, 131.26, 129.08, 128.59, 127.99, 126.41, 123.33, 122.22, 120.17, 116.11, 112.58, 104.27, 59.55, 14.70. HRMS (ES+) calcd. for $C_{17}H_{15}NO_2$ [M]+: 266.1181, found: 266.1182.

Ethyl 3-(p-tolyl)indolizine-1-carboxylate (3b)



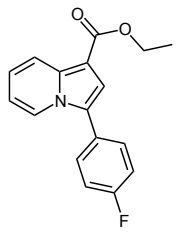
Reaction time: 4h; 74% yield (0.37 mmol, 103 mg), eluent: EtOAc/Hex = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.27-8.25 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.28 (s, 1H), 7.05 (dd, *J* = 9.4, 6.6 Hz, 1H), 6.68 (t, *J* = 7.2 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 165.06, 137.93, 136.21, 129.76, 128.56, 128.30, 126.49, 123.39, 122.05, 120.14, 115.80, 112.46, 104.12, 59.51, 21.32, 14.70. HRMS (ES+) calcd. for $C_{18}H_{17}NO_2$ [M]+: 280.1338, found: 280.1334.

Ethyl 3-(4-methoxyphenyl)indolizine-1-carboxylate (3c)



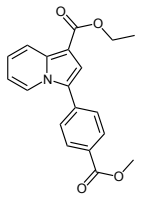
Reaction time: 4h; 65% yield (0.325 mmol, 96 mg) eluent: EtOAc/Hex = 1/6. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.25 (d, *J* = 9.0 Hz, 1H), 8.20 (d, *J* = 7.1 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.24 (s, 1H), 7.04 (m, 3H), 6.68 (t, *J* = 6.8 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 165.08, 159.45, 136.02, 130.14, 126.23, 123.56, 123.31, 121.95, 120.09, 115.59, 114.51, 112.42, 103.96, 59.49, 55.39, 14.69. HRMS (ES+) calcd. for $C_{18}H_{17}NO_3$ [M]+: 296.1287, found: 296.1282.

Ethyl 3-(4-fluorophenyl)indolizine-1-carboxylate (3d)



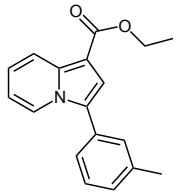
Reaction time: 4h; 70% yield (0.35 mmol, 99 mg), eluent: EtOAc/Hex = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δppm 8.26 (d, *J* = 9.0 Hz, 1H), 8.18 (d, *J* = 7.1 Hz, 1H), 7.50 (dd, *J* = 8.1, 5.4 Hz, 2H), 7.27 (s, 1H), 7.19 (t, *J* = 8.4 Hz, 2H), 7.07 (dd, *J* = 8.3, 7.3 Hz, 1H), 6.71 (t, *J* = 6.8 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm164.94, 163.40, 161.43, 136.23, 130.58, 130.51, 127.33, 127.30, 125.24, 123.08, 122.23, 120.21, 116.26, 116.13, 116.08, 112.70, 104.24, 59.58, 14.67. HRMS (ES+) calcd. for $C_{17}H_{14}FNO_2$ [M]+: 284.1087, found: 284.1085.

Ethyl 3-(4-(methoxycarbonyl)phenyl)indolizine-1-carboxylate (3e)



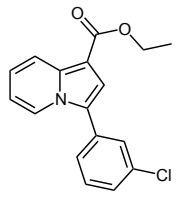
Reaction time: 4h; 48% yield (0.24 mmol, 78 mg), eluent: EtOAc/Hex = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.35 (d, *J* = 7.1 Hz, 1H), 8.28 (d, *J* = 9.0 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.39 (s, 1H), 7.10 (dd, *J* = 8.4, 7.2 Hz, 1H), 6.75 (t, *J* = 6.8 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 166.60, 164.77, 136.95, 135.77, 130.39, 129.12, 127.80, 125.26, 123.27, 122.73, 120.36, 117.14, 113.08, 104.93, 59.67, 52.23, 14.64. HRMS (ES+) calcd. for $C_{19}H_{17}NO_4$ [M]+: 324.1236, found:324.1239.

Ethyl 3-(m-tolyl)indolizine-1-carboxylate (3f)



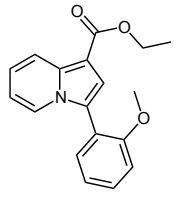
Reaction time: 4h; 57% yield (0.285 mmol, 76 mg), eluent: EtOAc/Hex = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.30 (d, *J* = 7.1 Hz, 1H), 8.27 (d, *J* = 9.1 Hz, 1H), 7.37 (m, 3H), 7.30 (s, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.06 (dd, *J* = 9.0, 6.7 Hz, 1H), 6.70 (t, *J* = 6.8 Hz, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 2.43 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 165.05, 138.84, 136.30, 131.18, 129.33, 128.93, 128.78, 126.57, 125.59, 123.46, 122.12, 120.14, 115.99, 112.49, 104.18, 59.52, 21.49, 14.68. HRMS (ES+) calcd. for $C_{18}H_{17}NO_2$ [M]+: 280.1338, found: 280.1337.

Ethyl 3-(3-chlorophenyl)indolizine-1-carboxylate (3g)



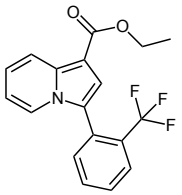
Reaction time: 4h; 60% yield (0.3 mmol, 90 mg), eluent: EtOAc/Hex = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.28 (d, *J* = 8.7 Hz, 2H), 7.55 (t, *J* = 1.2 Hz, 1H), 7.44-7.41 (m, 2H), 7.37 (dt, *J* = 6.4, 2.4 Hz, 1H), 7.33 (s, 1H), 7.10 (dd, *J* = 9.6, 7.0 Hz, 1H), 6.74 (t, *J* = 6.7 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 164.83, 136.58, 134.99, 133.05, 130.34, 128.41, 127.99, 126.52, 124.81, 123.15, 122.52, 120.29, 116.65, 112.93, 104.58, 59.63, 14.66. HRMS (ES+) calcd. for $C_{17}H_{14}ClNO_2$ [M]+: 300.0791, found: 300.0789.

Ethyl 3-(2-methoxyphenyl)indolizine-1-carboxylate (3h)



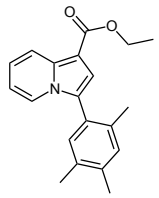
Reaction time: 4h; 94% yield (0.47 mmol, 139 mg), eluent: EtOAc/Hex = 1/6. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.28 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 7.1 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.31 (s, 1H), 7.08 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.67 (t, *J* = 6.8 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 165.14, 157.43, 136.18, 132.40, 130.17, 125.21, 123.74, 122.03, 121.04, 119.93, 119.67, 116.61, 111.70, 111.09, 103.77, 59.40, 55.44, 14.74. HRMS (ES+) calcd. for $C_{18}H_{17}NO_3$ [M]+: 296.1287, found: 296.1282.

Ethyl 3-(2-(trifluoromethyl)phenyl)indolizine-1-carboxylate (3i)



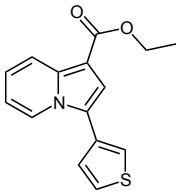
Reaction time: 4h; 78% yield (0.39 mmol, 130 mg), eluent: EtOAc/Hex = 1/9. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.26 (d, *J* = 9.1 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 7.0 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.29 (s, 1H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.64 (t, *J* = 6.8 Hz, 1H), 4.39 (t, *J* = 6.5 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 165.01, 135.73, 133.58, 132.08, 131.40 (q, ^2J = 30 Hz), 129.61; 129.37, 126.83 (m); 123.71, 123.58 (q, ^1J = 274.9 Hz), 122.23, 121.33, 119.83, 117.61, 112.46, 104.05, 59.57, 14.64. HRMS (ES+) calcd. for $C_{18}H_{14}F_3NO_2$ [M]+: 334.1055, found: 334.1054.

Ethyl 3-(2,4,5-trimethylphenyl)indolizine-1-carboxylate (3j)



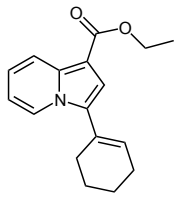
Reaction time: 4h; 75% yield (0.375 mmol, 115 mg), eluent: EtOAc/Hex = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.26 (d, *J* = 9.1 Hz, 1H), 7.63 (d, *J* = 7.0 Hz, 1H), 7.20 (s, 1H), 7.13 (s, 1H), 7.10 (s, 1H), 7.06 (dd, *J* = 9.0, 6.6 Hz, 1H), 6.65 (t, *J* = 6.8 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.32 (s, 3H), 2.27 (s, 3H), 2.05 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 165.21, 137.55, 135.56, 135.52, 134.33, 132.49, 131.81, 127.64, 125.76, 123.81, 121.80, 119.90, 116.02, 112.20, 103.52, 59.46, 19.55, 19.18, 19.04, 14.71. HRMS (ES+) calcd. for $C_{20}H_{21}NO_2$ [M]+: 308.1651, found: 308.1642.

Ethyl 3-(thiophen-3-yl)indolizine-1-carboxylate (3k)



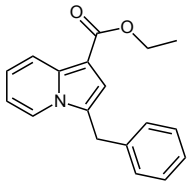
Reaction time: 12h; 33% yield (0.165 mmol, 45 mg), eluent: EtOAc/Hex = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.28 (d, *J* = 7.1 Hz, 1H), 8.26 (d, *J* = 9.5 Hz, 1H), 7.48 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.46 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.33 (s, 1H), 7.32 (dd, *J* = 5.5, 1.9 Hz, 1H), 7.07 (dd, *J* = 8.4, 7.1 Hz, 1H), 6.74 (t, *J* = 6.8 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 164.96, 136.17, 131.55, 127.56, 126.51, 123.67, 122.67, 122.09, 121.74, 120.11, 116.08, 112.71, 104.04, 59.57, 14.67. HRMS (ES+) calcd. for $C_{15}H_{13}NO_2S$ [M^+]: 272.0745, found: 272.0743.

Ethyl 3-(cyclohex-1-en-1-yl)indolizine-1-carboxylate (3l)



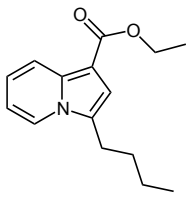
Reaction time: 5h; 67% yield (0.335 mmol, 90 mg), eluent: EtOAc/Hex = 1/9. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.23 (d, *J* = 7.1 Hz, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.10 (s, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.66 (t, *J* = 6.8 Hz, 1H), 6.05 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.35-2.25 (m, 4H), 1.83-1.70 (m, 4H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 165.12, 135.98, 128.39, 128.27, 128.09, 124.45, 121.56, 119.99, 114.15, 112.02, 103.33, 59.39, 29.07, 25.51, 22.88, 22.05, 14.67. HRMS (ES+) calcd. for $C_{17}H_{19}NO_2$ [M]+: 270.1494, found: 270.1495.

Ethyl 3-benzylindolizine-1-carboxylate (3m)



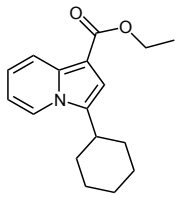
Reaction time: 4h; 68% yield (0.34 mmol, 95 mg), eluent: EtOAc/Hex = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.23 (d, *J* = 9.1 Hz, 1H), 7.72 (d, *J* = 7.0 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.10 (s, 1H), 7.03 (dd, *J* = 8.5, 7.2 Hz, 1H), 6.65 (t, *J* = 6.8 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.20 (s, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 165.09, 136.89, 136.08, 128.77, 128.37, 126.80, 123.51, 123.06, 121.52, 119.96, 115.95, 112.27, 103.02, 59.45, 32.39, 14.71. HRMS (ES+) calcd. for $C_{18}H_{17}NO_2$ [M]+: 280.1338, found: 280.1335.

Ethyl 3-butylindolizine-1-carboxylate (3n)



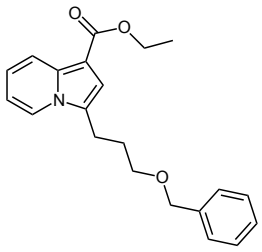
Reaction time: 5h; 82% yield (0.41 mmol, 100 mg), eluent: EtOAc/Hex = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.18 (d, *J* = 9.0 Hz, 1H), 7.82 (d, *J* = 7.0 Hz, 1H), 7.03 (s, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.72 (t, *J* = 6.8 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 1.74 (quintet, *J* = 7.6 Hz, 2H), 1.45 (q, *J* = 7.5 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 165.17, 135.61, 125.68, 122.67, 121.06, 119.98, 113.61, 112.06, 102.79, 59.34, 28.98, 25.39, 22.55, 14.70, 13.89. HRMS (ES+) calcd. for $C_{15}H_{19}NO_2$ [M]+:246.1494, found:246.1493.

Ethyl 3-cyclohexylindolizine-1-carboxylate (3o)



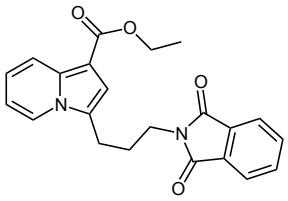
Reaction time: 5h; 83% yield (0.42 mmol, 112 mg), eluent: EtOAc/Hex = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.20 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 7.1 Hz, 1H), 7.03 (s, 1H), 7.00 (dd, *J* = 8.6, 7.1 Hz, 1H), 6.72 (t, *J* = 6.3 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.80-2.76 (m, 1H), 2.09 (d, *J* = 8.6 Hz, 2H), 1.89-1.87 (m, 2H), 1.82-1.44 (m, 6H), 1.41 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 165.21, 135.60, 131.11, 122.79, 121.08, 120.15, 111.98, 111.67, 102.86, 59.35, 34.97, 31.61, 26.45, 26.27, 14.71. HRMS (ES+) calcd. for $C_{17}H_{21}NO_2$ [M]+: 272.1651, found: 272.1648.

Ethyl 3-(3-(benzyloxy)propyl)indolizine-1-carboxylate (3p)



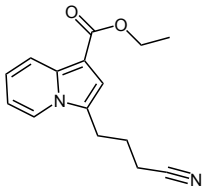
Reaction time: 10h; 53% yield (0.265 mmol, 89 mg), eluent: EtOAc/Hex = 1/6. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.20 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 7.0 Hz, 1H), 7.36 (d, *J* = 4.5 Hz, 4H), 7.30 (dd, *J* = 8.8, 4.6 Hz, 1H), 7.04-7.01 (m, 2H), 6.73 (t, *J* = 6.8 Hz, 1H), 4.53 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.58 (t, *J* = 6.0 Hz, 2H), 2.92 (t, *J* = 7.5 Hz, 2H), 2.08 (dt, *J* = 14.1, 6.8 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 165.15, 138.37, 135.70, 128.42, 127.67, 127.64, 125.03, 122.80, 121.21, 119.96, 113.81, 112.15, 102.87, 73.05, 69.24, 59.39, 27.39, 22.32, 14.70. HRMS (ES+) calcd. for $C_{21}H_{23}NO_3$ [M]+: 338.1756, found: 338.1756.

Ethyl 3-(3-(1,3-dioxoisoindolin-2-yl)propyl)indolizine-1-carboxylate (3q)



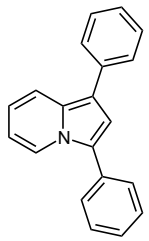
Reaction time: 12h; 82% yield (0.41 mmol, 154 mg), eluent: EtOAc/Hex = 1/9. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.16 (d, *J* = 9.0 Hz, 1H), 7.83-7.80 (m, 3H), 7.70 (dd, *J* = 5.1, 5.5 Hz, 2H), 7.07 (s, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.74 (t, *J* = 6.6 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.85 (t, *J* = 6.9 Hz, 2H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.20 (quintet, *J* = 7.4 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δppm 168.36, 164.98, 135.77, 133.99, 131.99, 123.91, 123.24, 122.58, 121.30, 119.96, 113.73, 112.30, 102.95, 59.35, 37.68, 25.85, 23.30, 14.67. HRMS (ES+) calcd. for $C_{22}H_{20}N_2O_4$ [M]+: 377.1501, found: 377.1496.

Ethyl 3-(3-cyanopropyl)indolizine-1-carboxylate (3r)



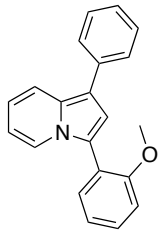
Reaction time: 12h; 66% yield (0.33 mmol, 84 mg), eluent: EtOAc/Hex = 1/4. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.21 (d, *J* = 9.1 Hz, 1H), 7.84 (d, *J* = 6.3 Hz, 1H), 7.06 (s, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.78 (t, *J* = 6.8 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.99 (t, *J* = 7.4 Hz, 2H), 2.47 (t, *J* = 6.9 Hz, 2H), 2.13 (quintet, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 164.90, 135.95, 122.42, 121.61, 120.17, 119.12, 114.24, 112.63, 103.21, 59.52, 24.41, 22.85, 16.76, 14.67. HRMS (ES+) calcd. for $C_{15}H_{16}N_2O_2$ [M^+]: 257.1290, found: 257.1290.

1,3-diphenylindolizine (3s)



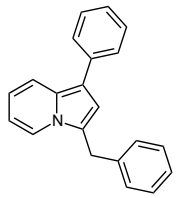
Reaction time: 4h; 77% yield (0.358 mmol, 104 mg), eluent: EtOAc/Hex = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.31 (d, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 9.1 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 6.9 Hz, 1H), 7.08 (s, 1H), 6.78 (dd, *J* = 9.1, 6.4 Hz, 1H), 6.54 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 136.29, 132.21, 130.21, 129.04, 128.80, 128.26, 127.62, 127.36, 126.34, 125.77, 125.49, 122.68, 118.56, 118.12, 113.87, 111.15. HRMS (ES+) calcd. for $C_{20}H_{15}N$ [M]+: 270.1283, found: 270.1279.

3-(2-methoxyphenyl)-1-phenylindolizine (3t)



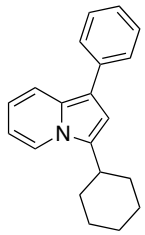
Reaction time: 4h; 80% yield (0.4 mmol, 120 mg), eluent: EtOAc/Pentane = 1/9. ^{1}H NMR (500 MHz, $CDCl_3$): δppm 7.82 (d, *J* = 9.1 Hz, 1H), 7.68 (t, *J* = 6.0 Hz, 3H), 7.46 (m, 4H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.11-7.08 (m, 2H), 7.07 (s, 1H), 6.79 (dd, *J* = 9.1, 6.4 Hz, 1H), 6.51 (t, *J* = 6.8 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δppm 157.24, 136.58, 132.24, 129.96, 129.45, 128.68, 127.61, 125.18, 124.62, 122.82, 120.96, 118.05, 117.80, 114.67, 114.36, 111.11, 110.11, 55.48. HRMS (ES+) calcd. for $C_{21}H_{17}NO$ [M]+: 300.1388, found: 300.1385.

3-benzyl-1-phenylindolizine (3u)



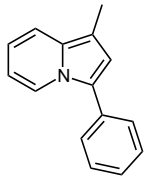
Reaction time: 4h; 67% yield (0.34 mmol, 95 mg), eluent: EtOAc/Hexane = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δppm 7.78 (d, *J* = 9.1 Hz, 1H), 7.66 (d, *J* = 7.1 Hz, 1H), 7.62 (d, *J* = 7.1 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.27-7.23 (m, 4H), 6.82 (s, 1H), 6.73 (dd, *J* = 9.1, 6.5 Hz, 1H), 6.49 (t, *J* = 6.8 Hz, 1H), 4.27 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δppm 137.65, 136.55, 129.34, 128.71, 128.68, 128.51, 127.42, 126.59, 125.14, 122.77, 122.33, 118.34, 117.07, 113.61, 110.62, 32.56. HRMS (ES+) calcd. for $C_{21}H_{17}N$ [M]+: 284.1439, found: 284.1445.

3-cyclohexyl-1-phenylindolizine (3v)



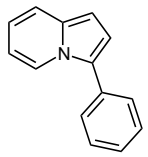
Reaction time: 8h; 50% yield (0.25 mmol, 69 mg), eluent: EtOAc/Pentane = 1/19. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.81 (d, *J* = 7.1 Hz, 1H), 7.74 (d, *J* = 9.1 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.78 (s, 1H), 6.69 (dd, *J* = 8.7, 6.8 Hz, 1H), 6.53 (t, *J* = 6.3 Hz, 1H), 2.84 (quintet, *J* = 9.5 Hz, 1H), 2.16-190 (m, 4H), 1.57-1.45 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 136.77, 130.40, 128.65, 127.41, 124.98, 122.11, 116.58, 113.58, 110.30, 109.36, 35.21, 31.77, 26.61, 26.40. HRMS (ES+) calcd. for $C_{20}H_{21}N$ [M]+: 276.1752, found: 276.1748.

1-methyl-3-phenylindolizine (3w)



Reaction time: 12h; 41% yield (0.205 mmol, 42 mg), eluent: EtOAc/pentane = 1/50. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm8.24 (d, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.74 (s, 1H), 6.63 (dd, *J* = 8.8, 6.5 Hz, 1H), 6.43 (t, *J* = 6.7 Hz, 1H), 2.42 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 132.67, 131.13, 128.92, 127.83, 126.80, 124.16, 122.07, 117.83, 115.42, 115.23, 110.28, 108.92, 10.51. HRMS (ES+) calcd. for $C_{15}H_{13}N$ [M]+: 208.1126, found: 208.1119.

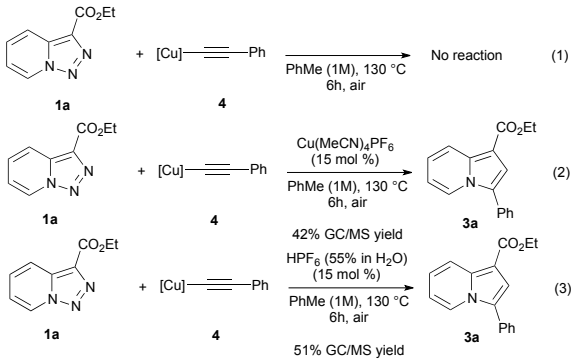
3-phenylindolizine (3x)



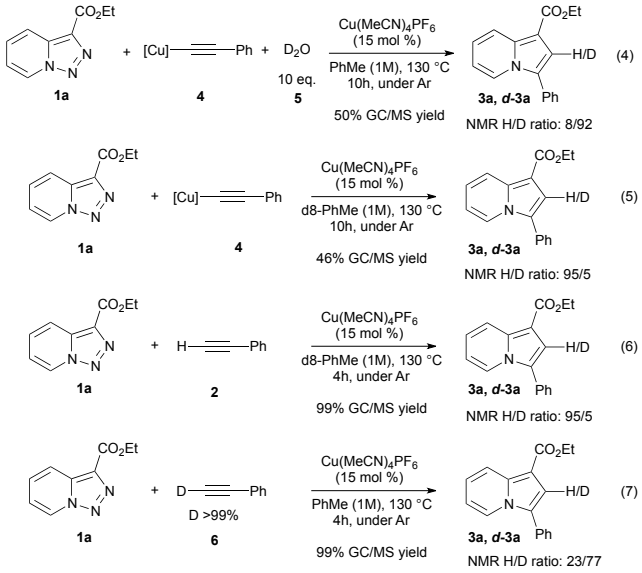
Reaction time: 1h; 54% yield (0.27 mmol, 52 mg), eluent: Hexanes. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.29 (d, *J* = 7.2 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 9.0 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 3.9 Hz, 1H), 6.68 (t, *J* = 7.8 Hz, 1H), 6.55 (d, *J* = 3.7 Hz, 1H), 6.48 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm 133.88, 132.60, 128.93, 128.05, 127.03, 125.42, 122.29, 119.64, 116.88, 114.11, 110.63, 99.78. HRMS (ES+) calcd. for $C_{14}H_{11}N$ [M]+: 194.0970, found: 194.0970.

4. Mechanistic Studies of the Cu-Catalyzed Transannulation Reaction

In order to verify a potential involvement of the Cu-acetylide **4** in this transformation, we performed several test-experiments. First, it was found that the reaction of pyridotriazole **1a** with only **4** did not produce the expected indolizine (eq. 1). However, the reaction of **1a** with **4** can be catalyzed by both $Cu(MeCN)_4PF_6$ (eq. 2) and $HPF_{6(aq.)}$ (eq. 3) to furnish indolizine **3a** in reasonable yields.



Deuterium-labeling experiments were performed to gain an additional insight into the reaction mechanism. It was found that addition of D_2O to the reaction of **1a** with **4** produced mainly the deuterium-incorporated product ***d*-3a** (eq. 4). Moreover, toluene solvent can also act as a marginal proton source (eq. 5-6). Finally, the reaction of **1a** with deuterium-labeled phenylacetylene[3] showed that the D^+ released upon formation of copper acetylide **4** (path a, Scheme 2) or copper carbene **C** (path b, Scheme 2) was mainly incorporated in the indolizine product ***d*-3a** (eq.7).



Procedure: An oven dried 1 mL Wheaton V-vial capped with a mininert syringe valve,

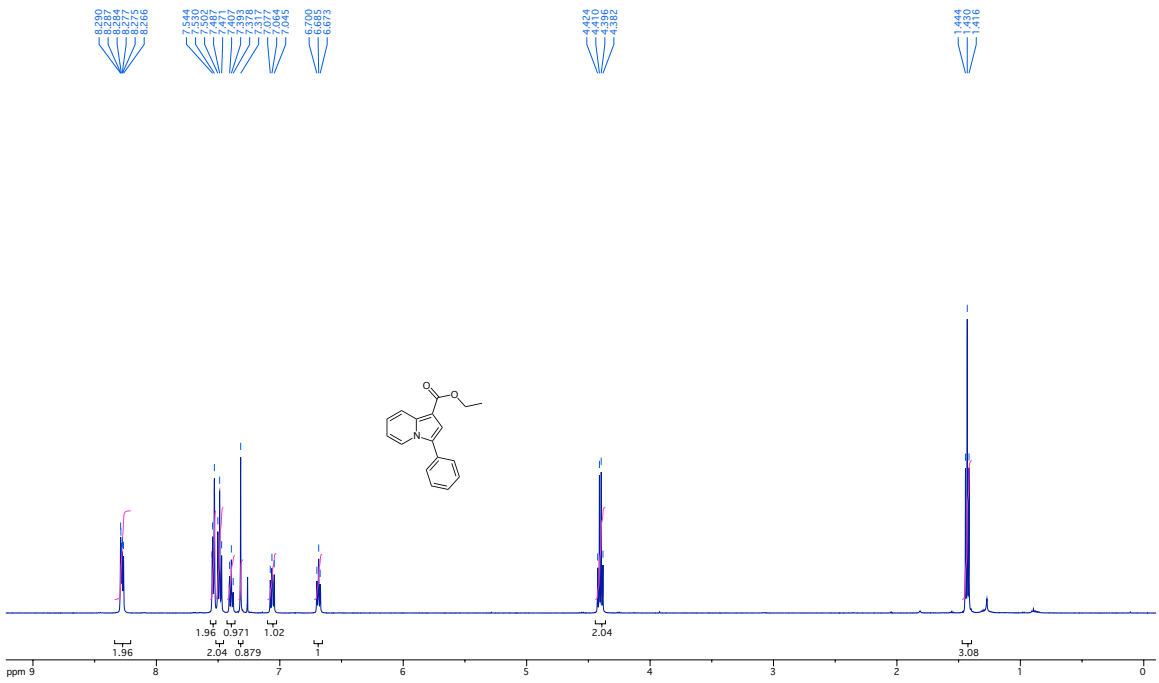
[3] After 2h, scrambling of deuterium-labeled phenylacetylene was observed with GC/MS: H/D ratio 20:80.

containing a stirring bar, was charged with a pyridotriazole **1a** (38.2 mg, 0.2 mmol, 1 equiv), catalyst (15 mol %), toluene (0.2 mL, 0.1M), additive, and phenylacetylene derivative[4] (0.24 mmol, 1.2 equiv) under the indicated atmosphere. The reaction mixture was stirred at 130 °C upon completion then was quenched with DCM and analyzed with GC-MS using pentadecane as internal standard (GC yields are given). The residue was then purified by column chromatography on triethylamine-treated silica gel (3% EtOAc/Hexane) to afford the corresponding indolizine **3** and calculate the H/D ratio.

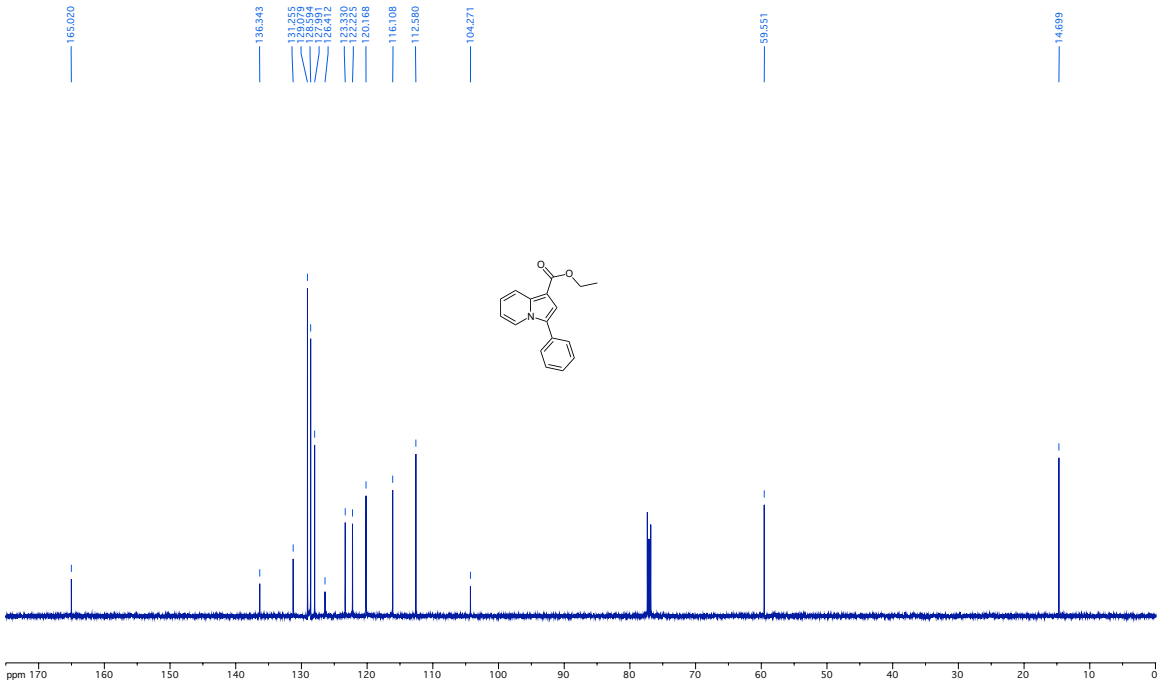
[4] Prepared according to the literature procedure: M. Fukushima, D. Takushima, H. Satomura, G. Onodera and M. Kimura, *Chem.-Eur. J.,* 2012, **18**, 8019.

5. Copies of ^{1}H and ^{13}C NMR Spectra for Indolizines (3)

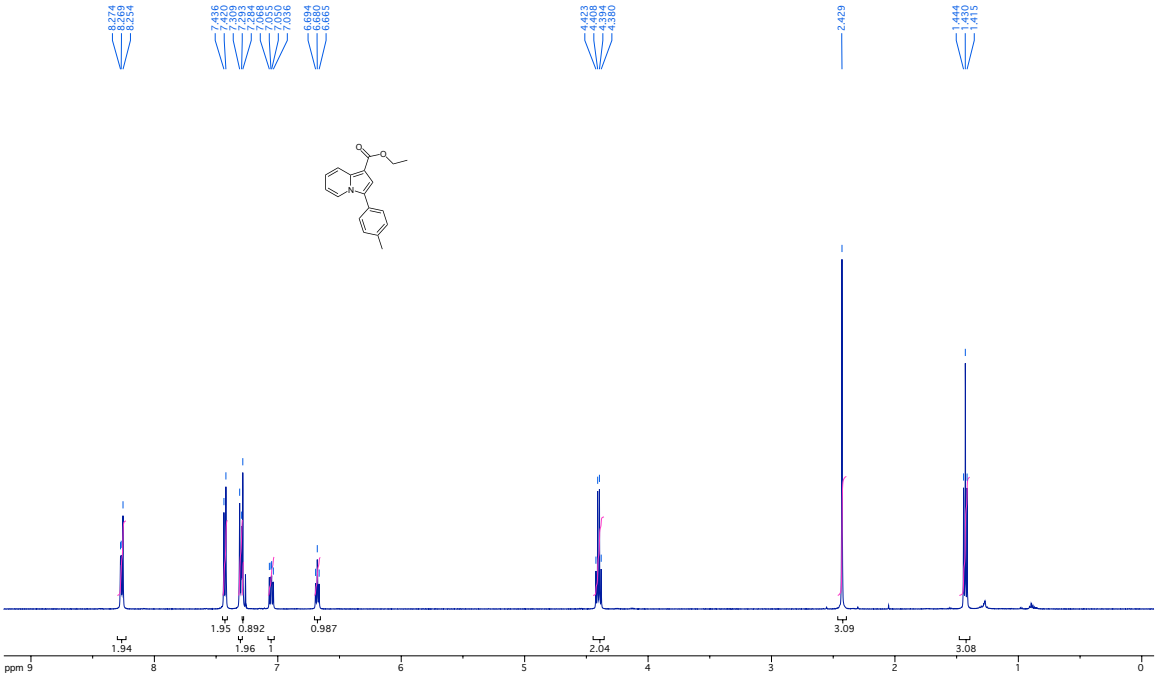
^{1}H NMR spectrum of (**3a**)



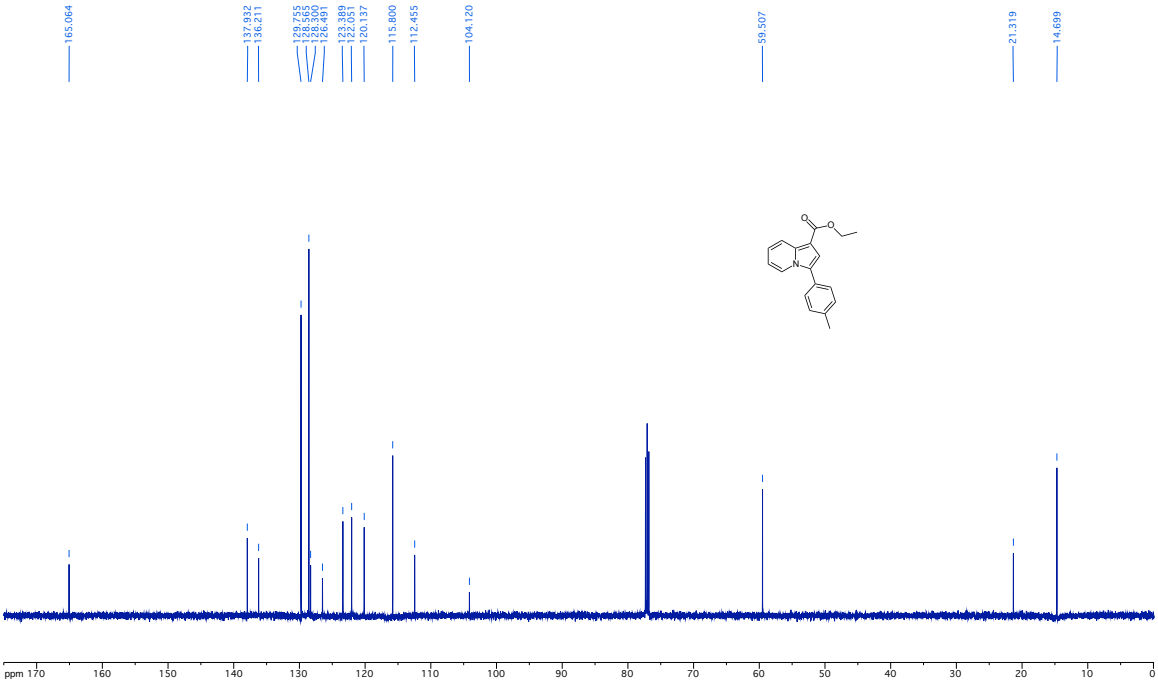
^{13}C NMR spectrum of (**3a**)



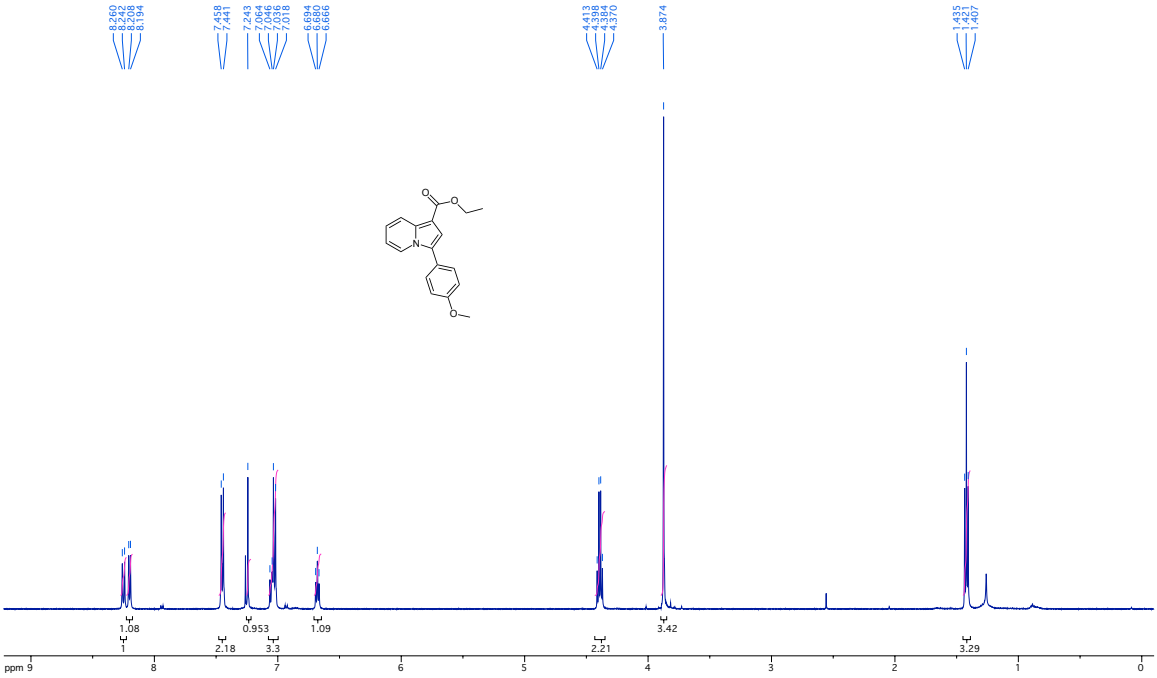
^{1}H NMR spectrum of (**3b**)



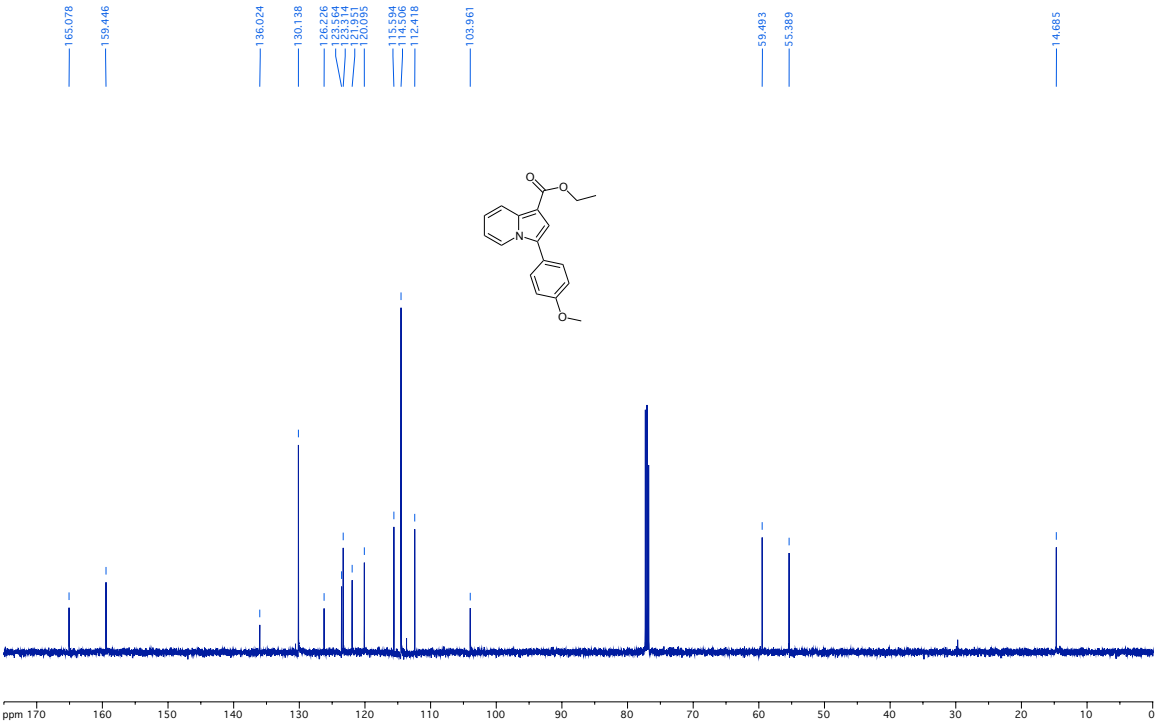
^{13}C NMR spectrum of (**3b**)



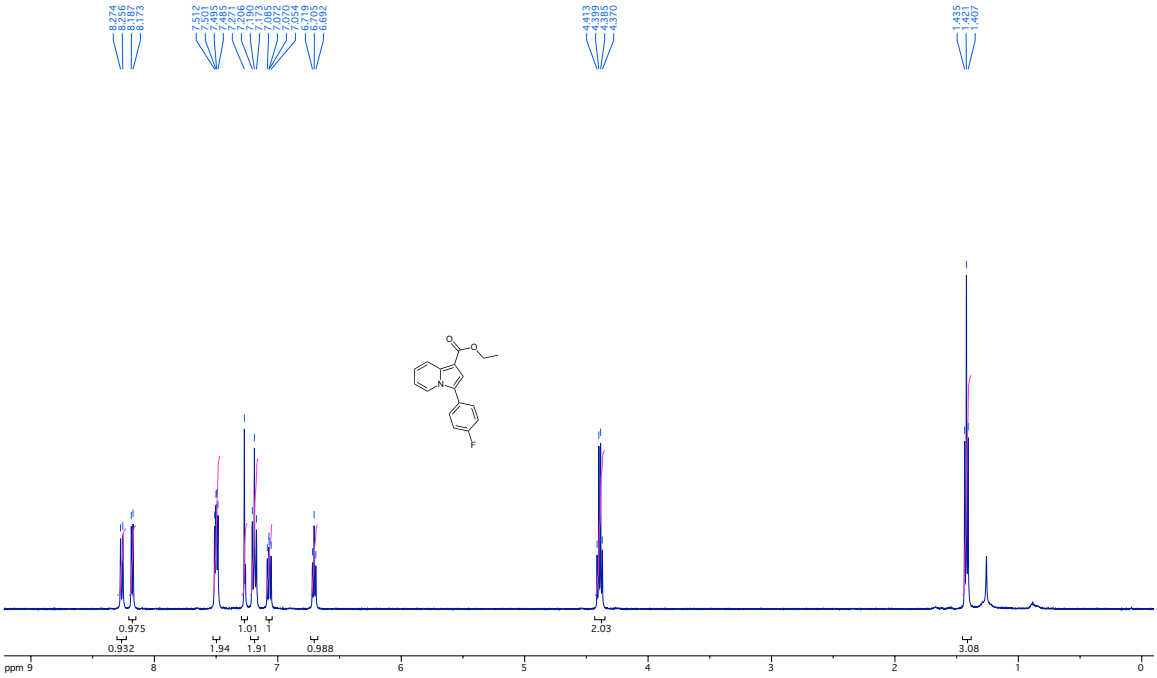
^{1}H NMR spectrum of (**3c**)



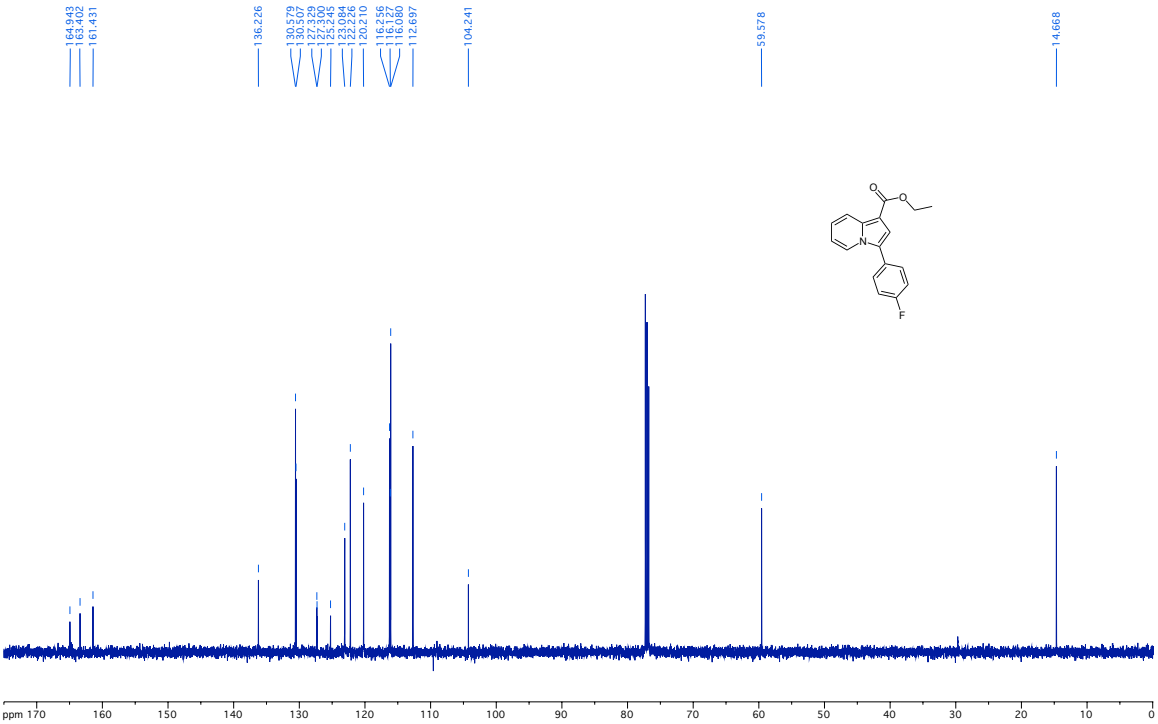
^{13}C NMR spectrum of (**3c**)



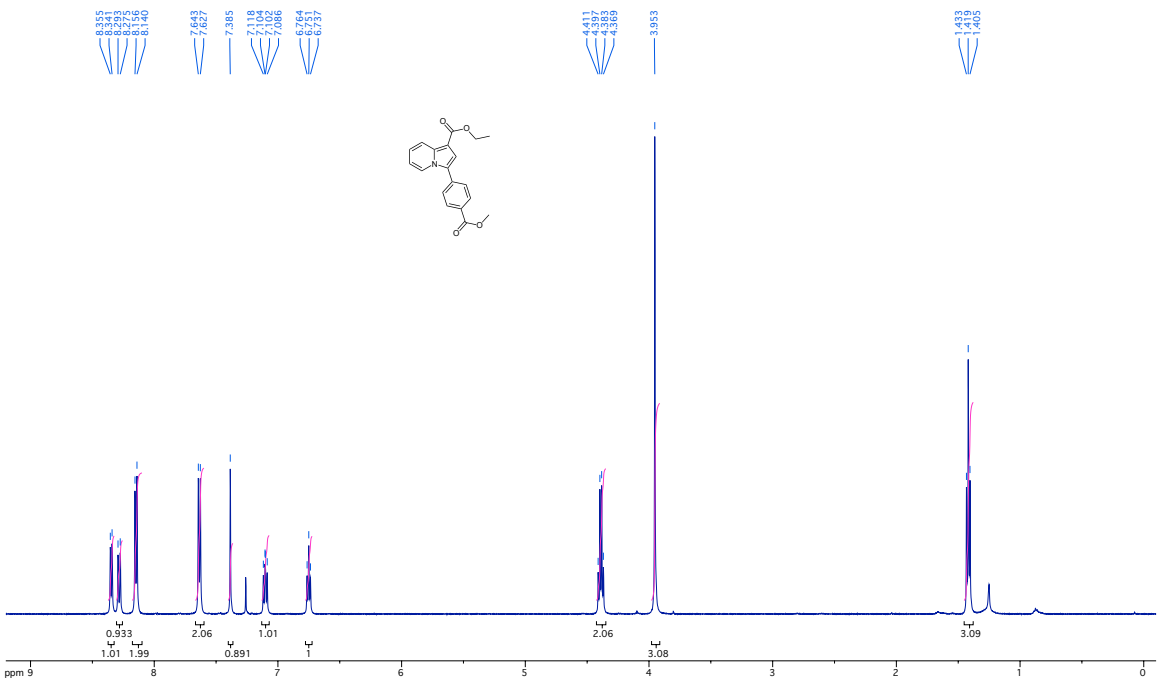
^{1}H NMR spectrum of (**3d**)



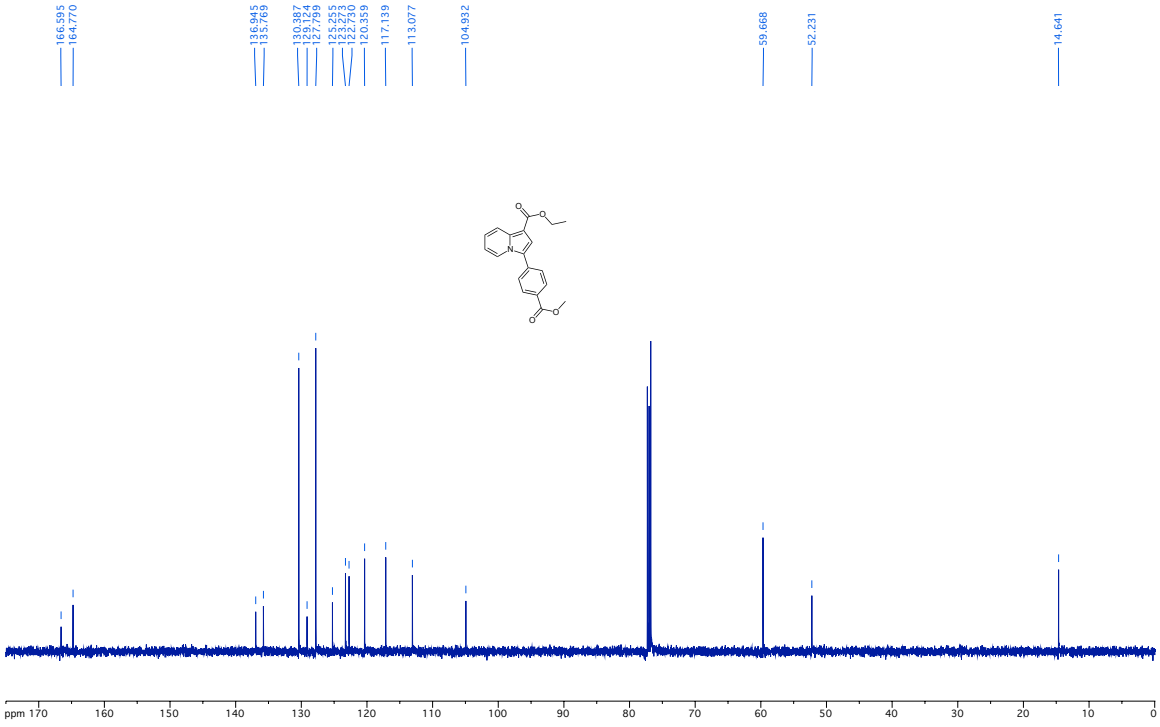
^{13}C NMR spectrum of (**3d**)



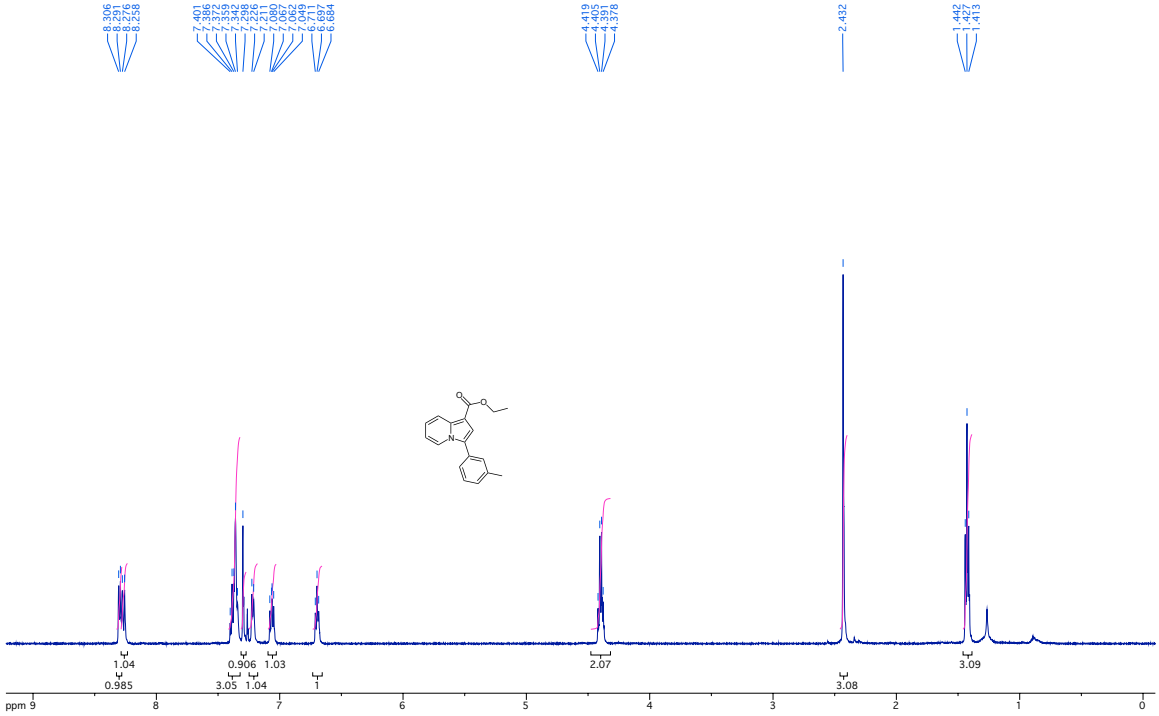
^{1}H NMR spectrum of (**3e**)



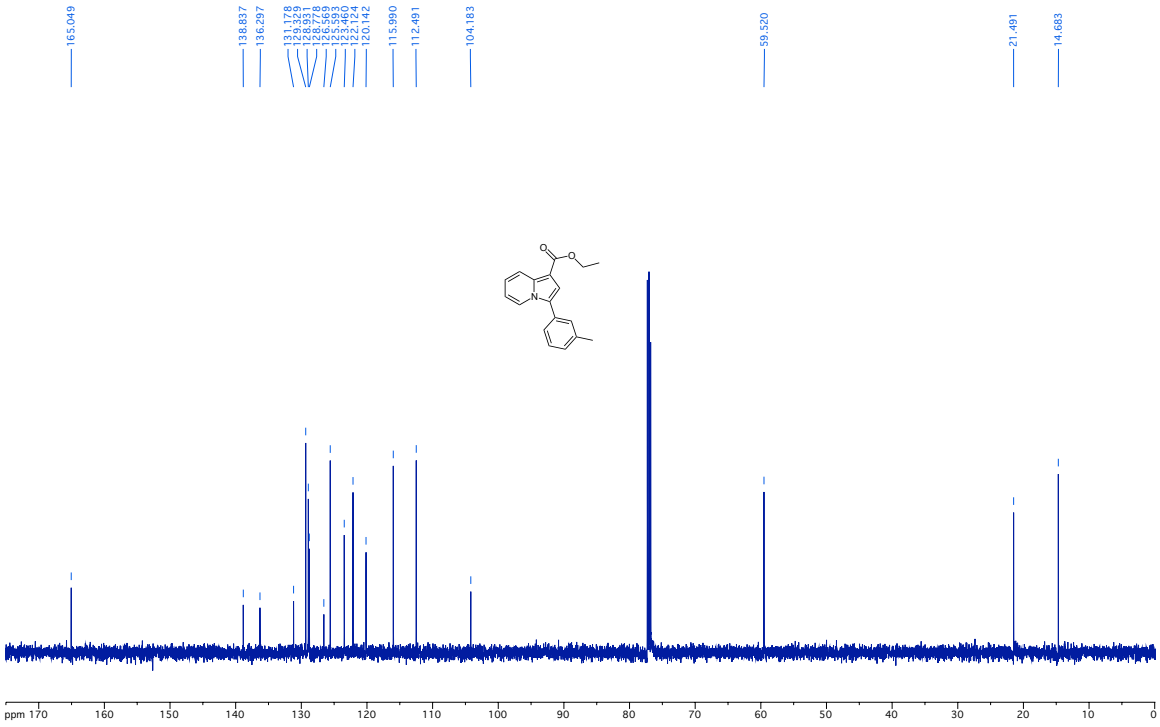
^{13}C NMR spectrum of (**3e**)



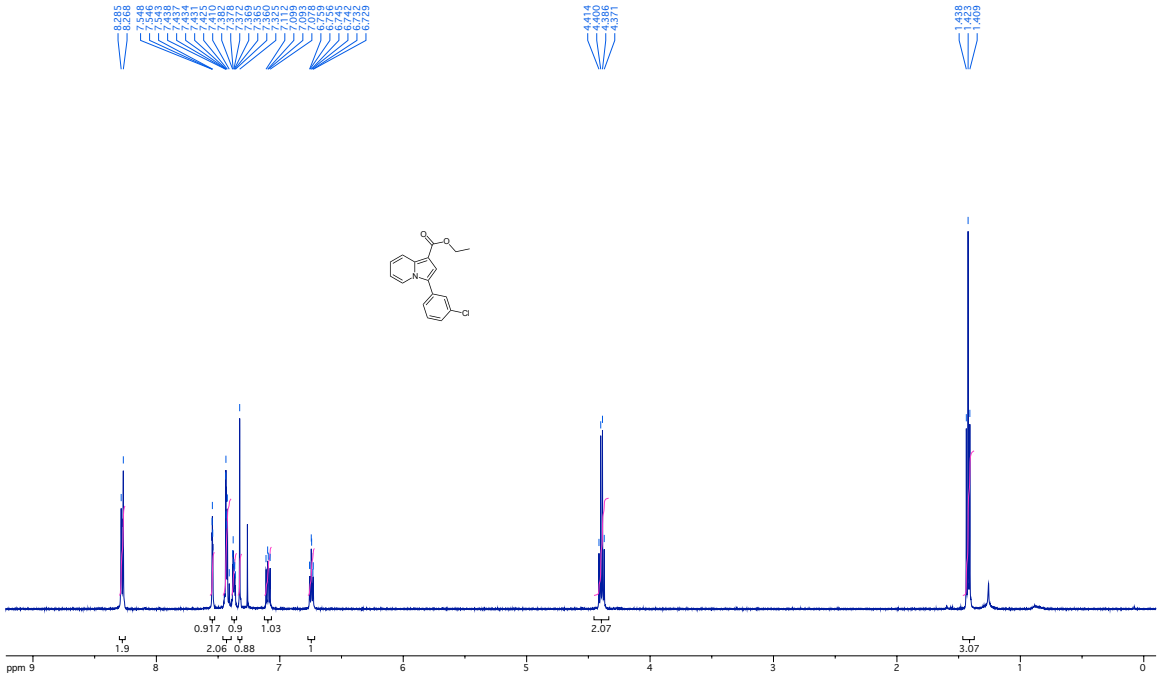
^{1}H NMR spectrum of (**3f**)



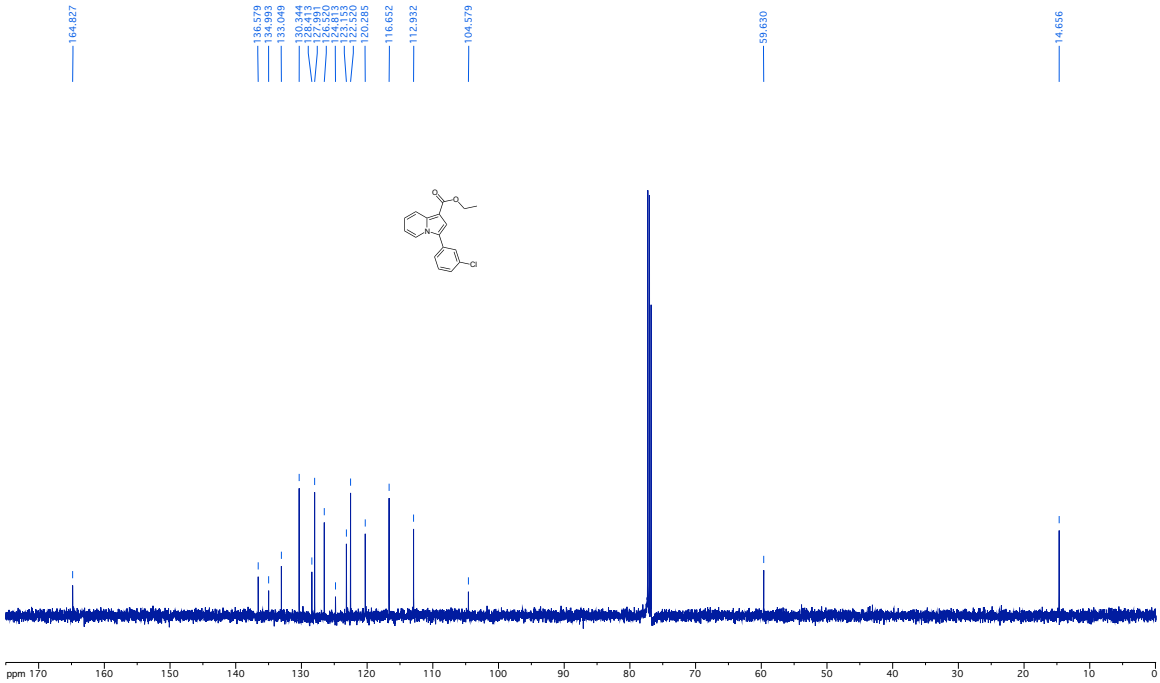
^{13}C NMR spectrum of (**3f**)



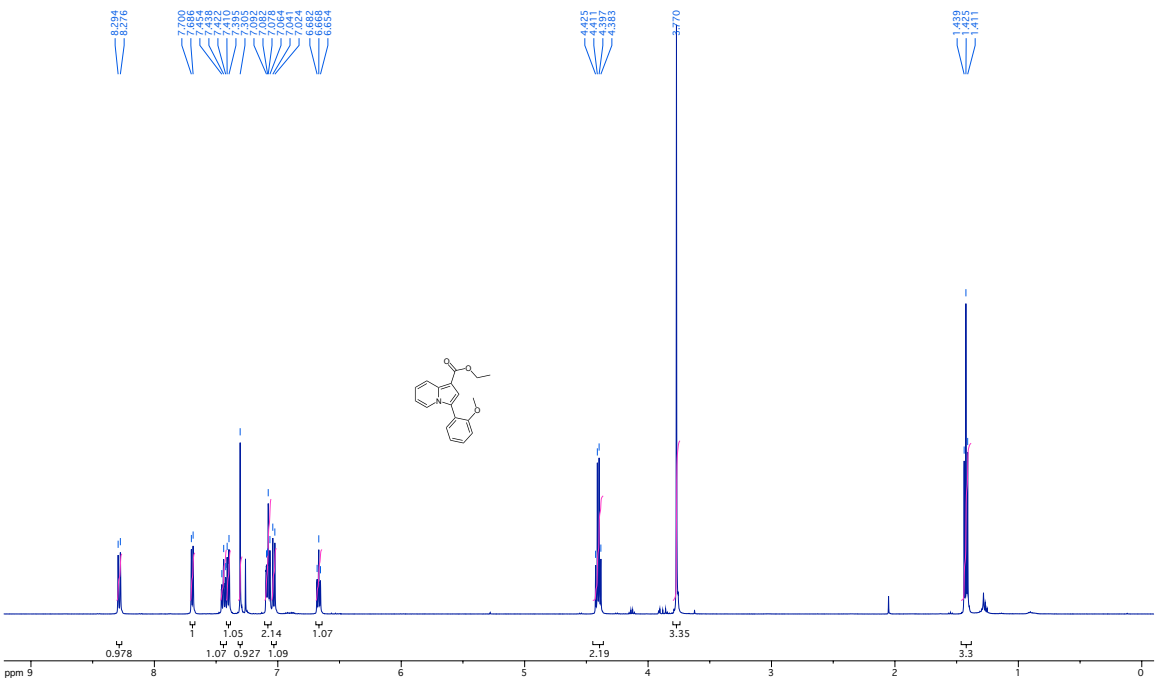
^{1}H NMR spectrum of (**3g**)



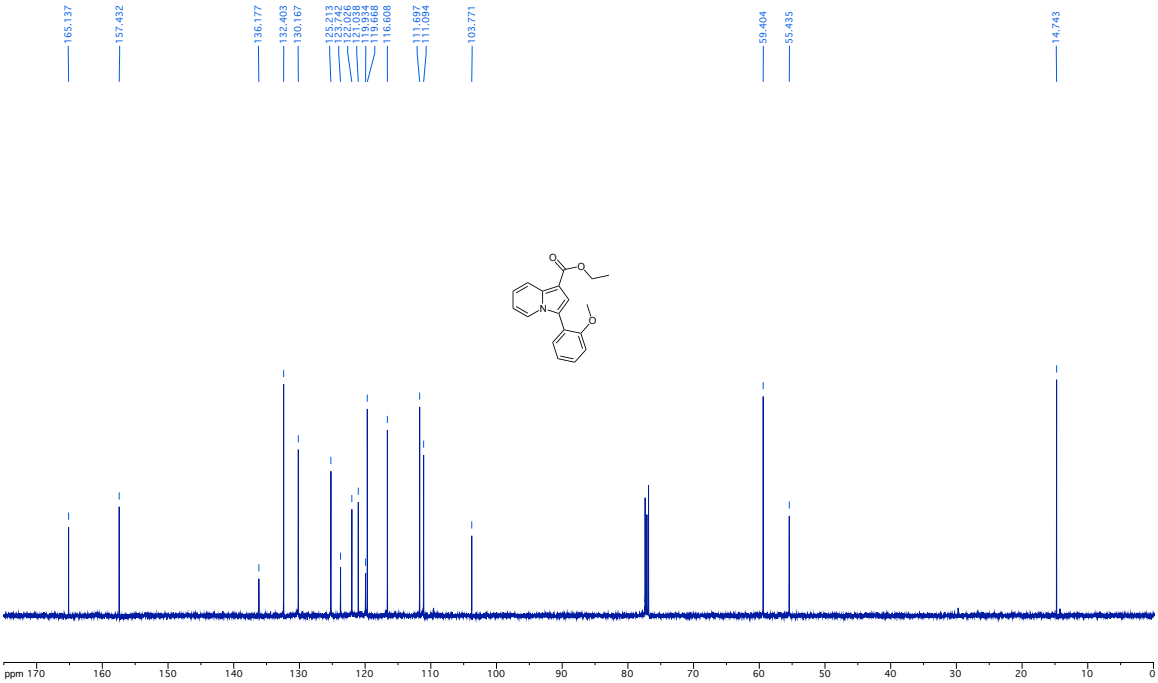
^{13}C NMR spectrum of (**3g**)



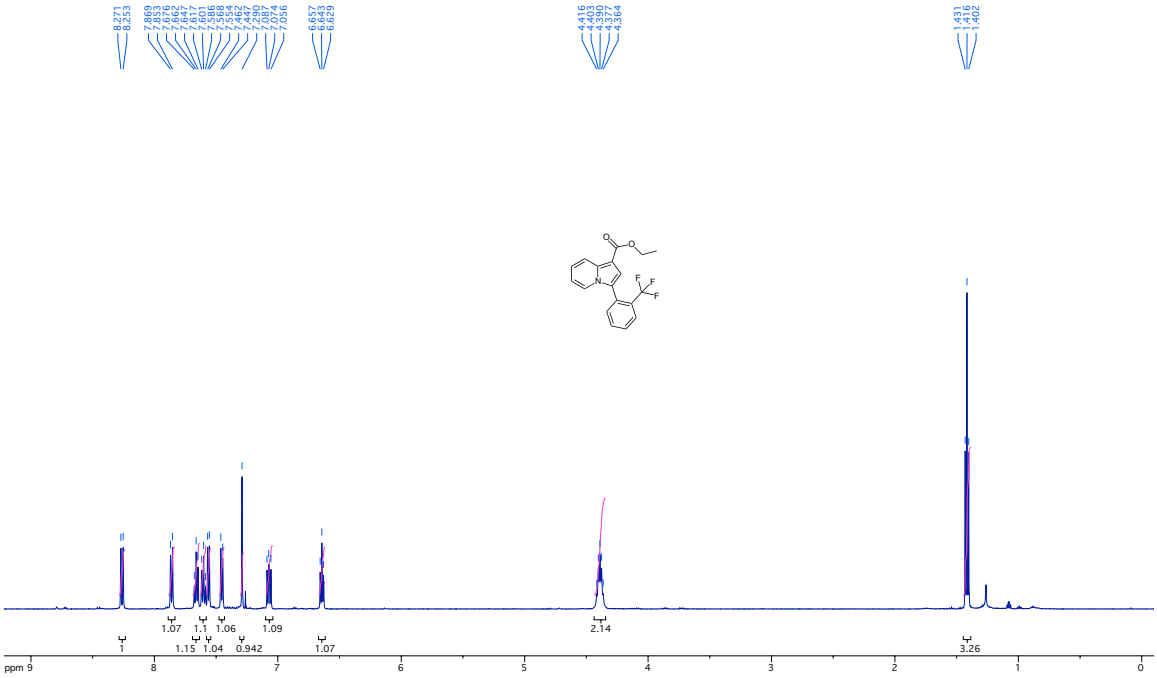
^{1}H NMR spectrum of (**3h**)



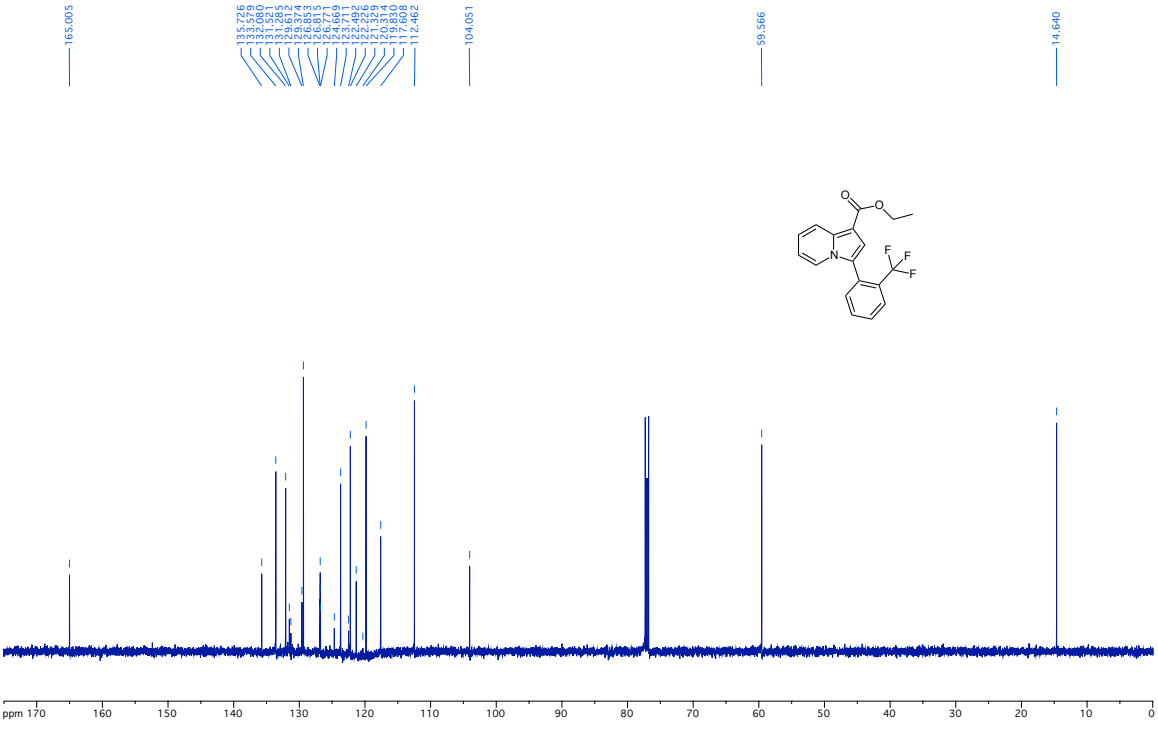
^{13}C NMR spectrum of (**3h**)



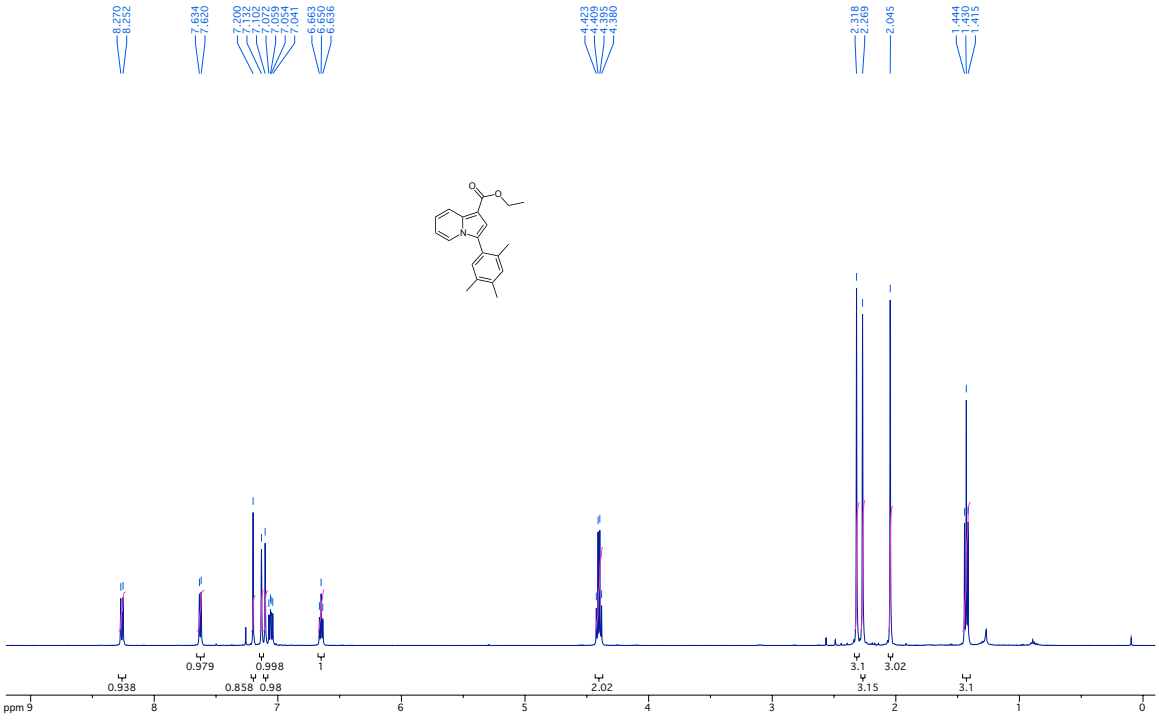
^{1}H NMR spectrum of (**3i**)



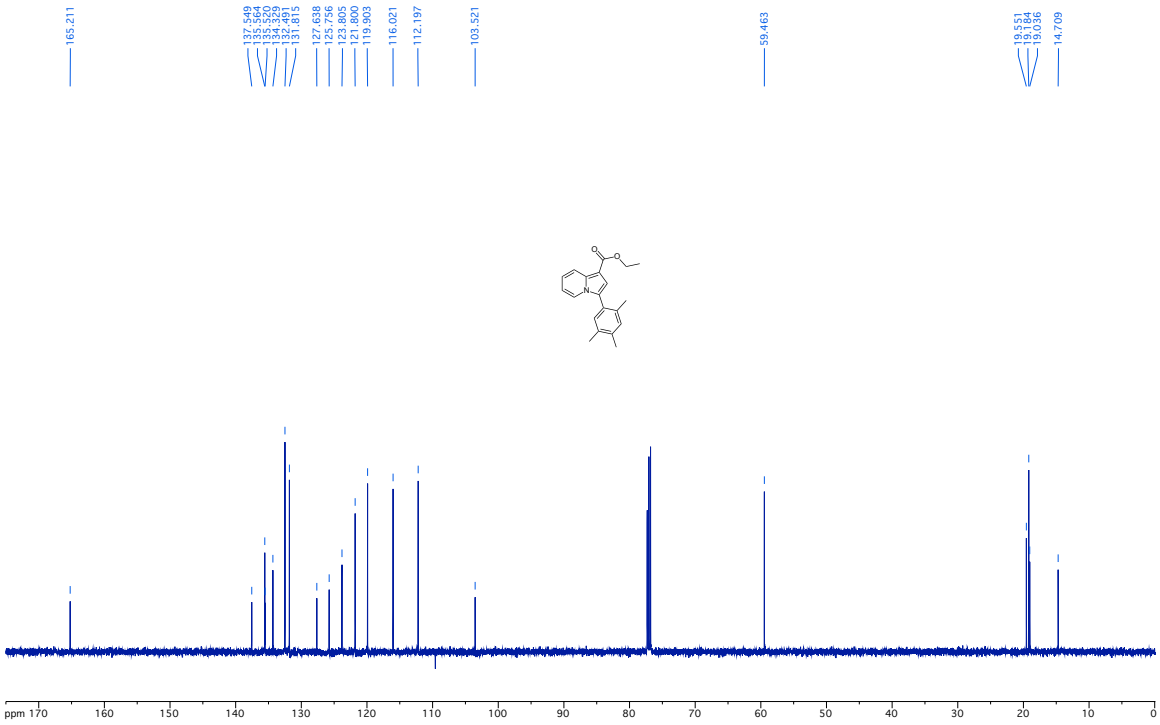
^{13}C NMR spectrum of (**3i**)



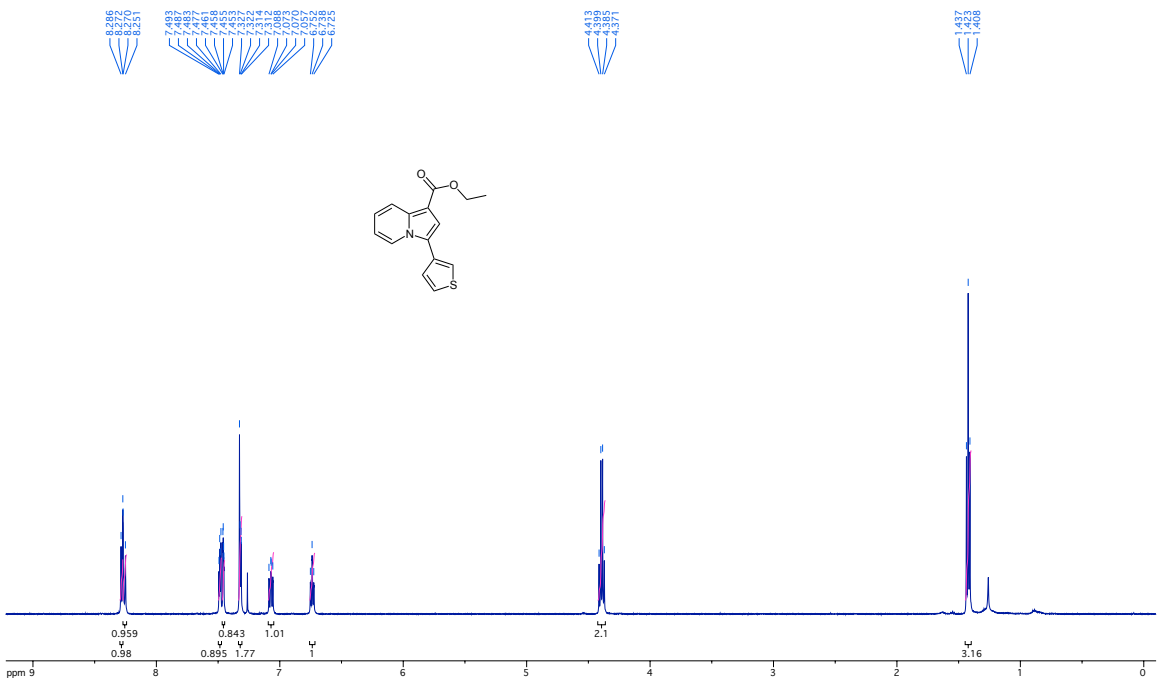
^{1}H NMR spectrum of (**3j**)



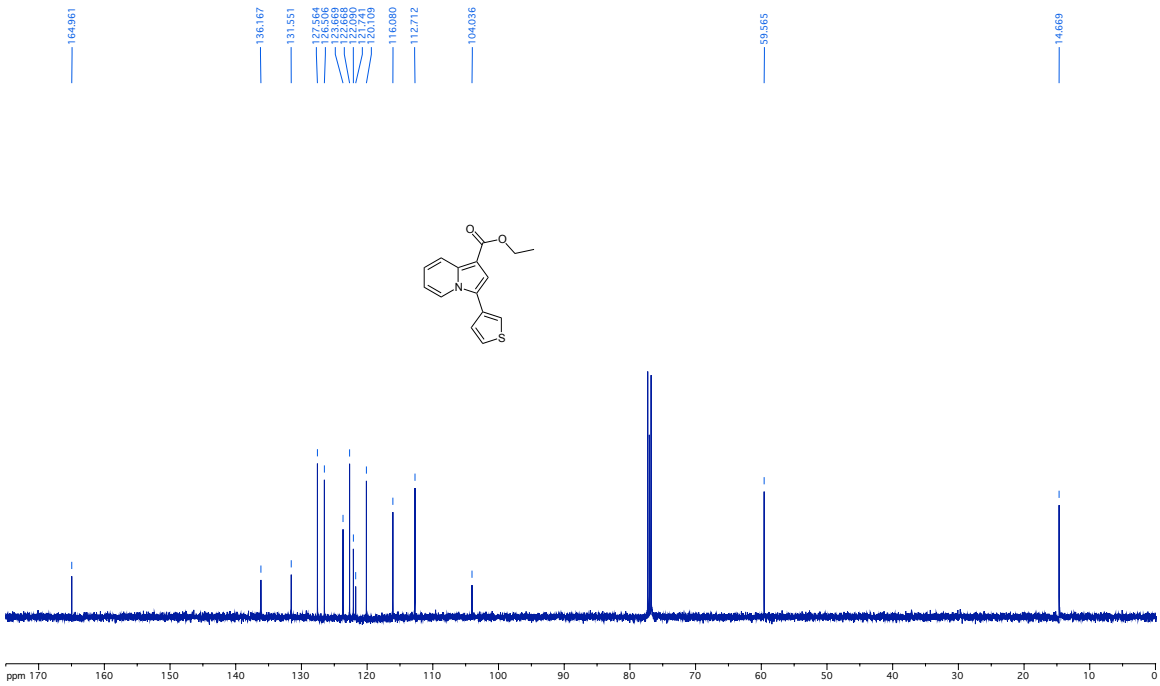
^{13}C NMR spectrum of (**3j**)



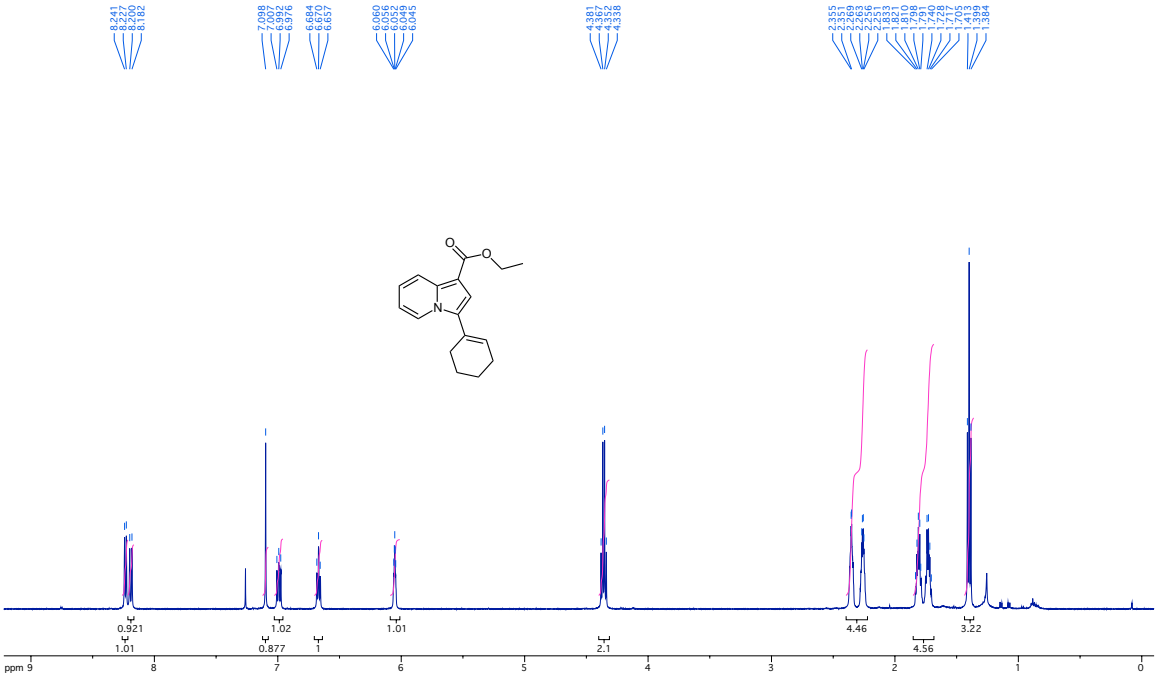
^{1}H NMR spectrum of (**3k**)



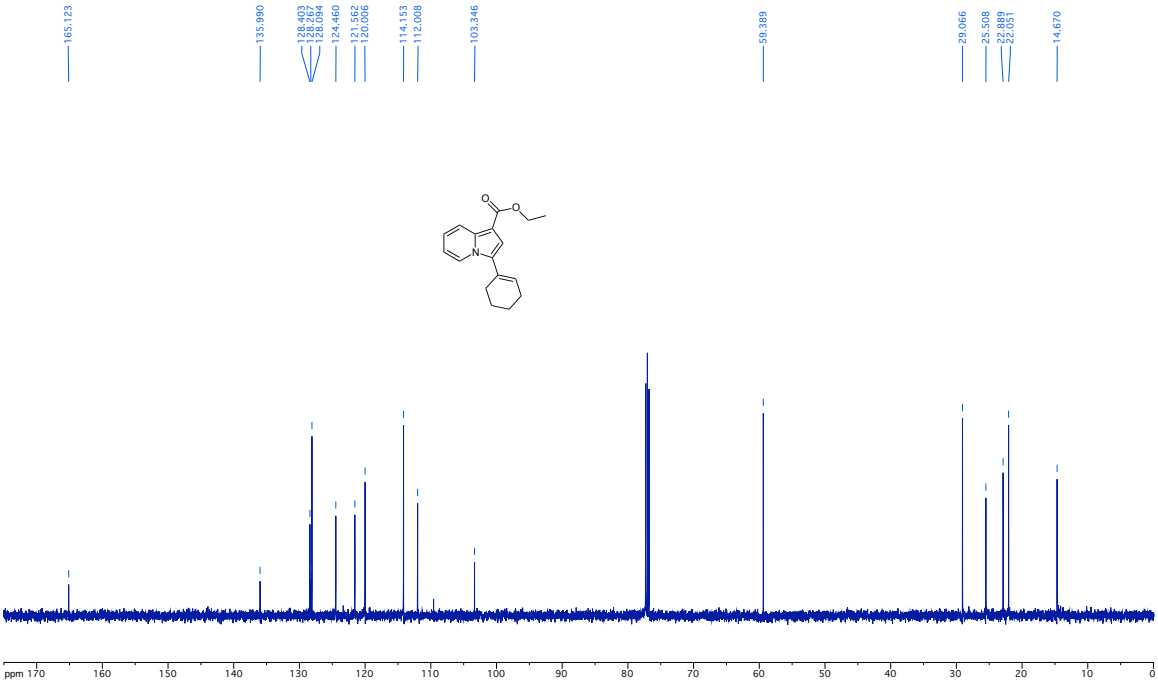
^{13}C NMR spectrum of (**3k**)



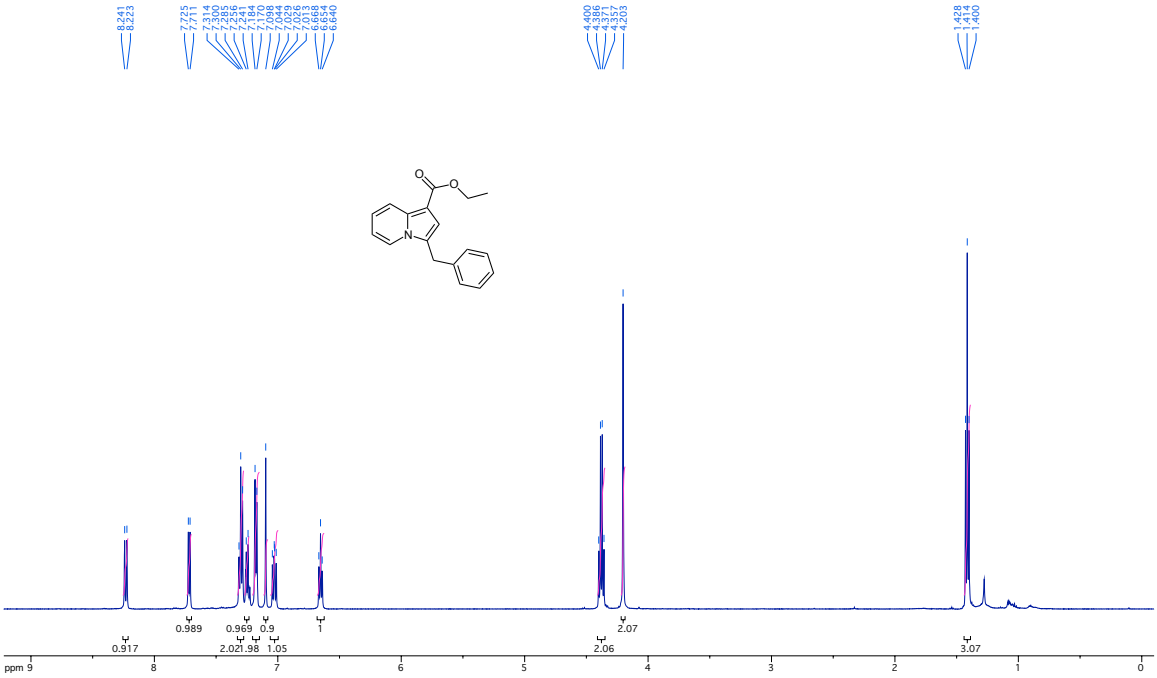
^{1}H NMR spectrum of (**3l**)



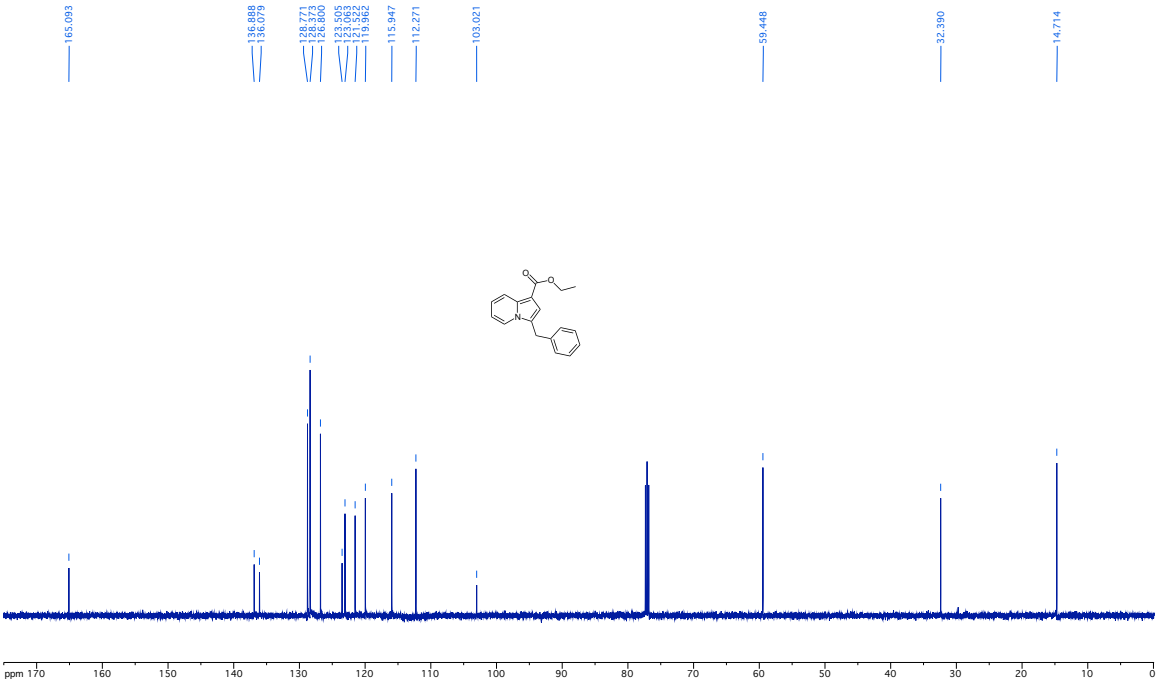
^{13}C NMR spectrum of (**3l**)



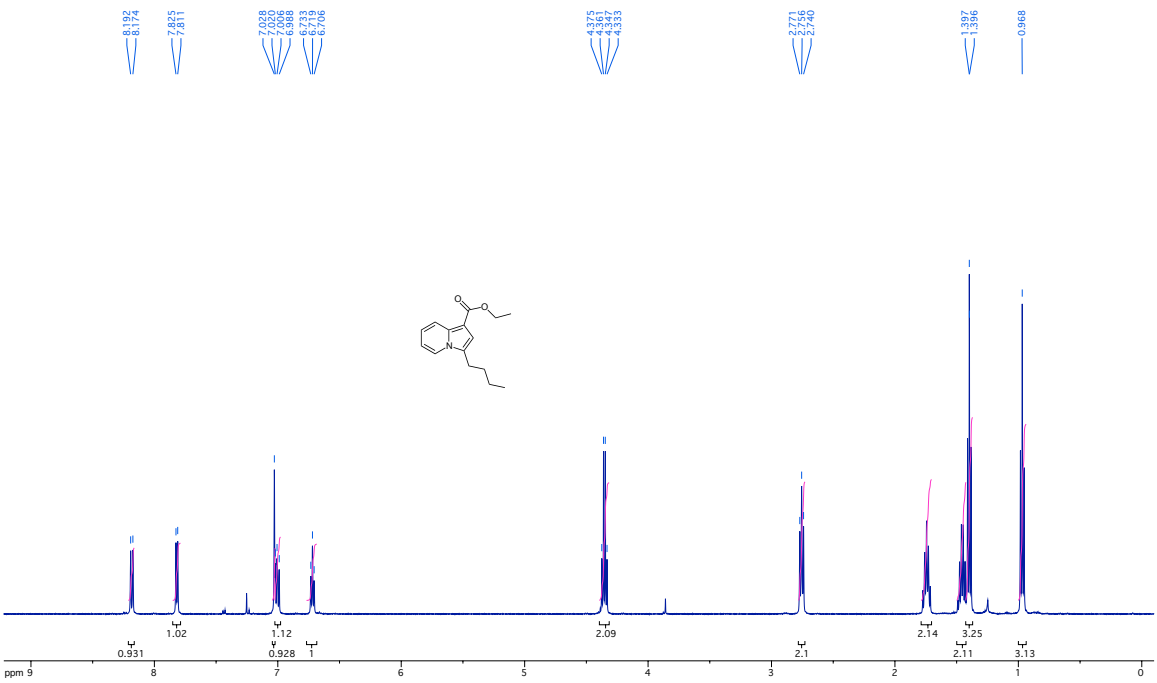
^{1}H NMR spectrum of (**3m**)



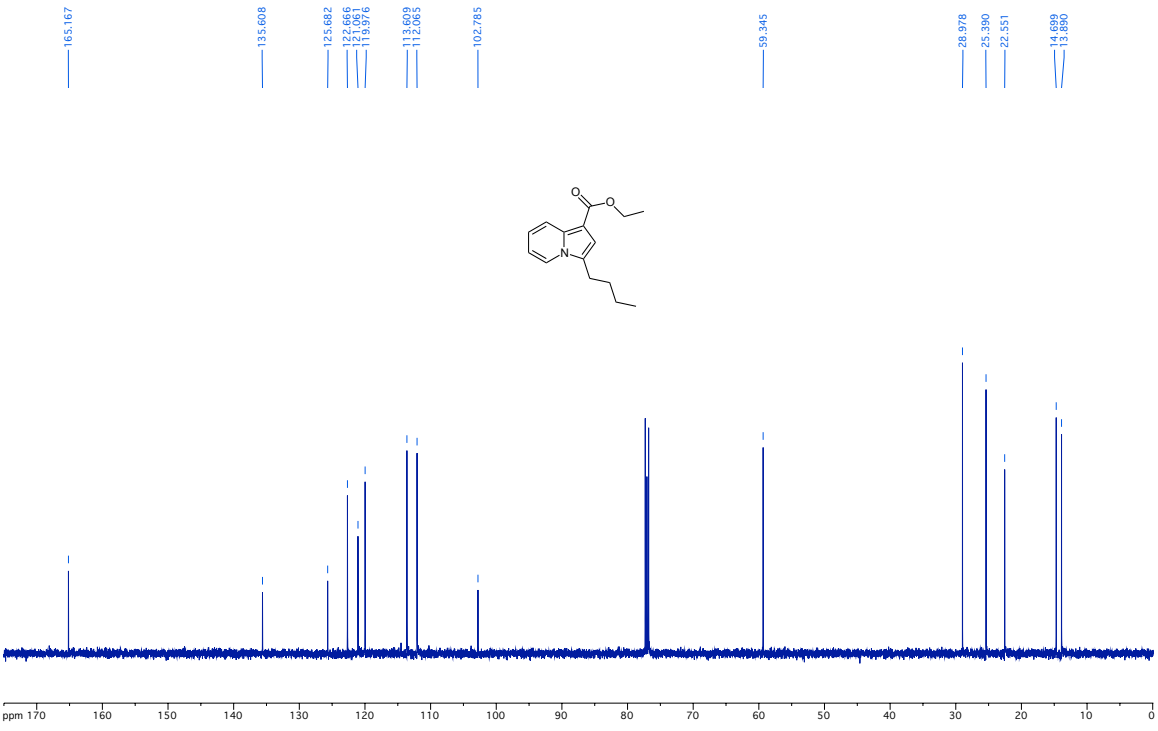
^{13}C NMR spectrum of (**3m**)



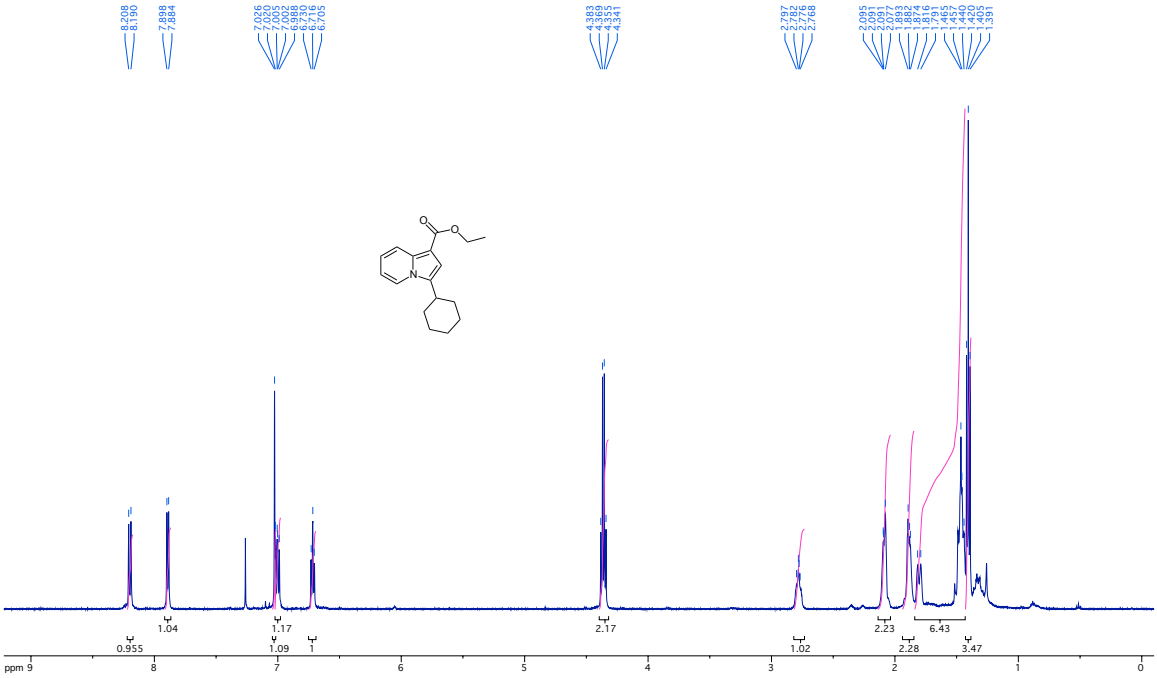
^{1}H NMR spectrum of (**3n**)



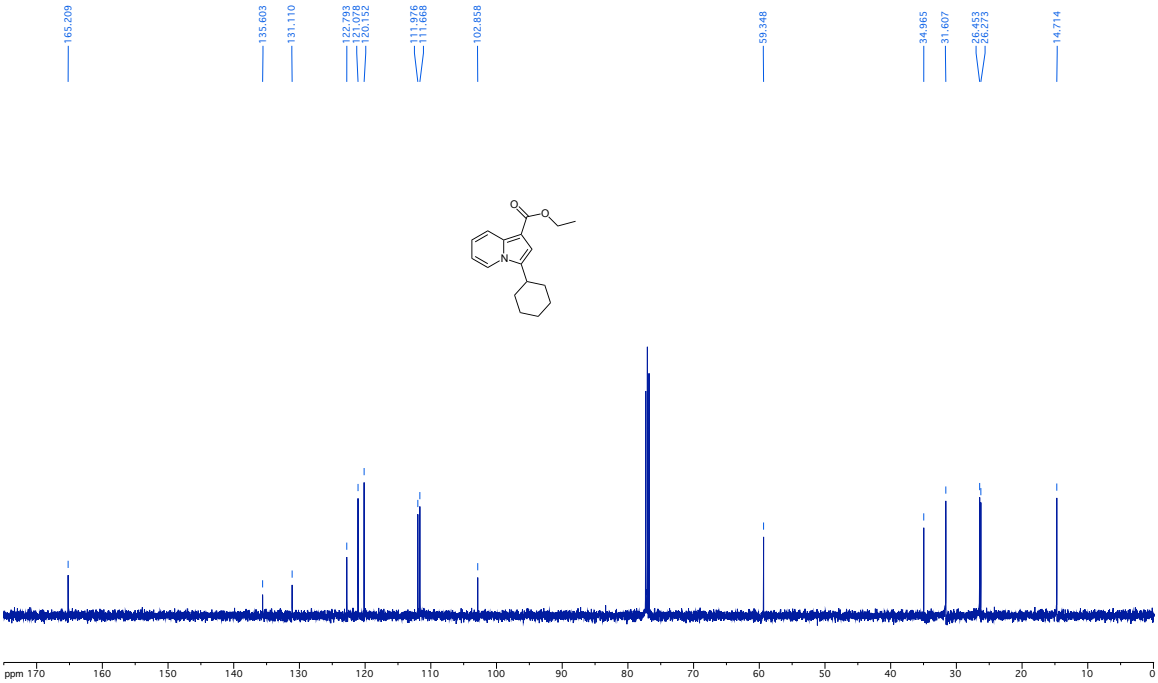
^{13}C NMR spectrum of (**3n**)



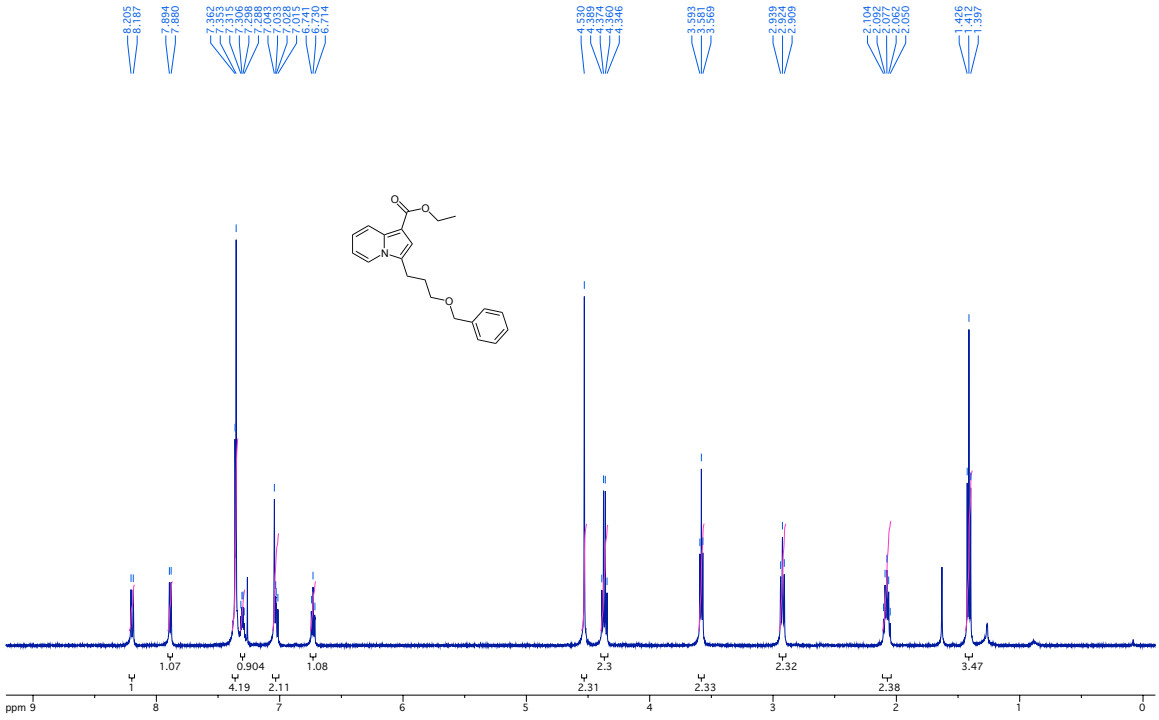
^{1}H NMR spectrum of (**3o**)



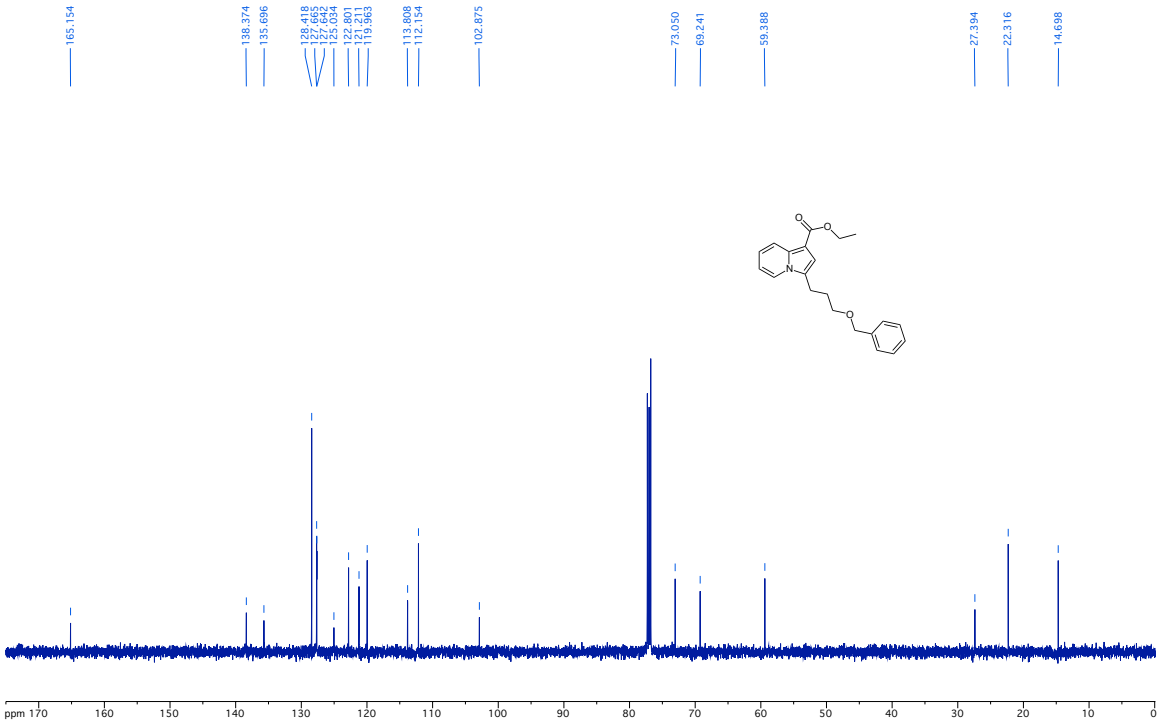
^{13}C NMR spectrum of (**3o**)



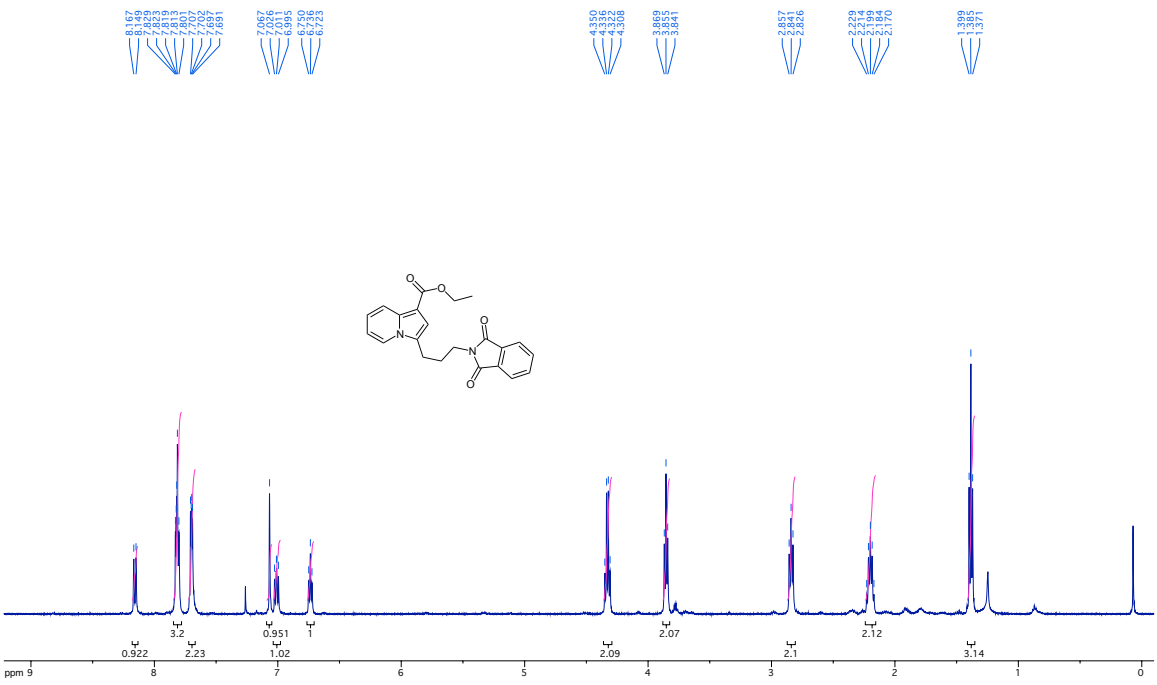
^{1}H NMR spectrum of (**3p**)



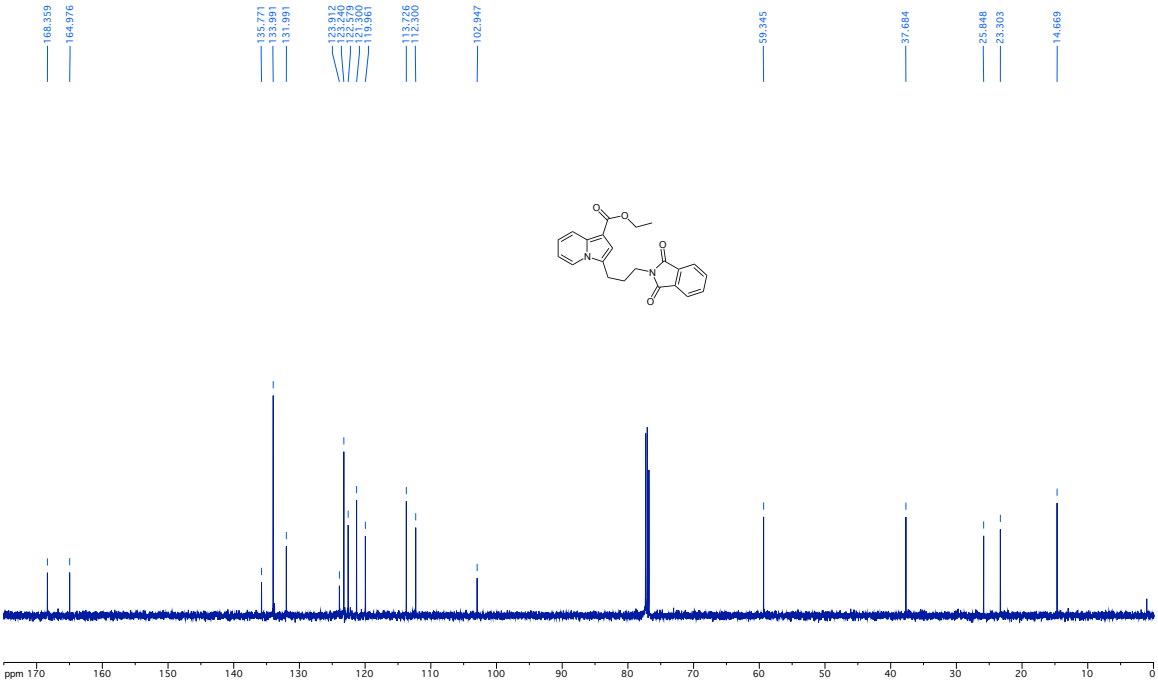
^{13}C NMR spectrum of (**3p**)



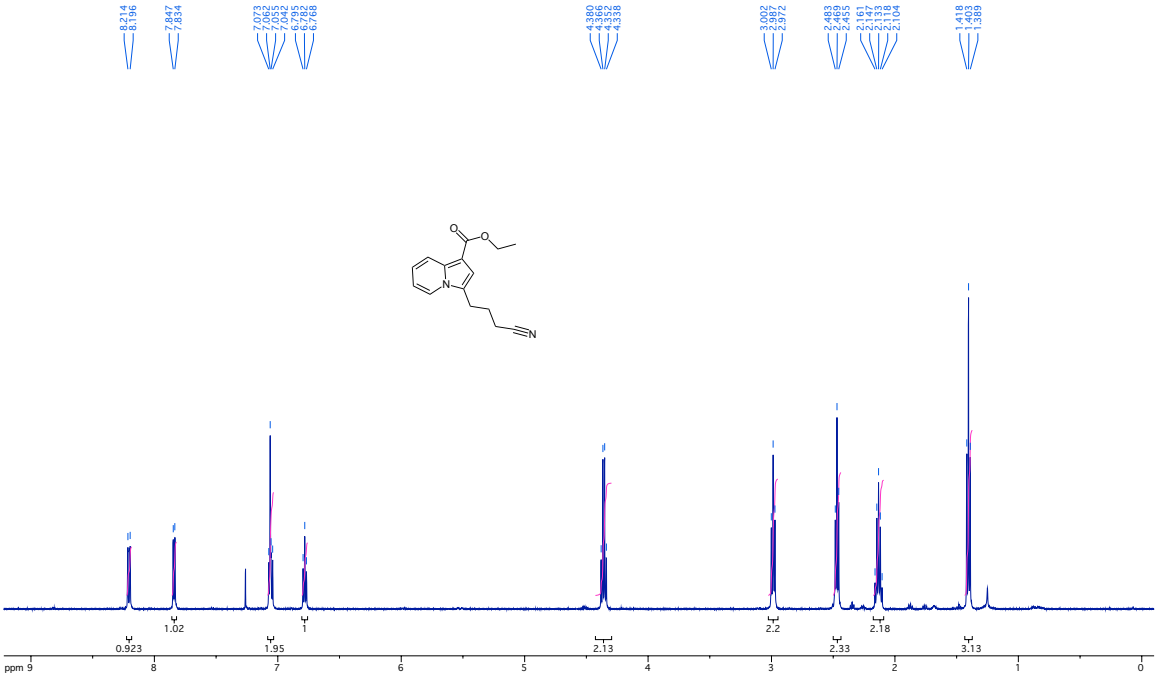
^{1}H NMR spectrum of (**3o**)



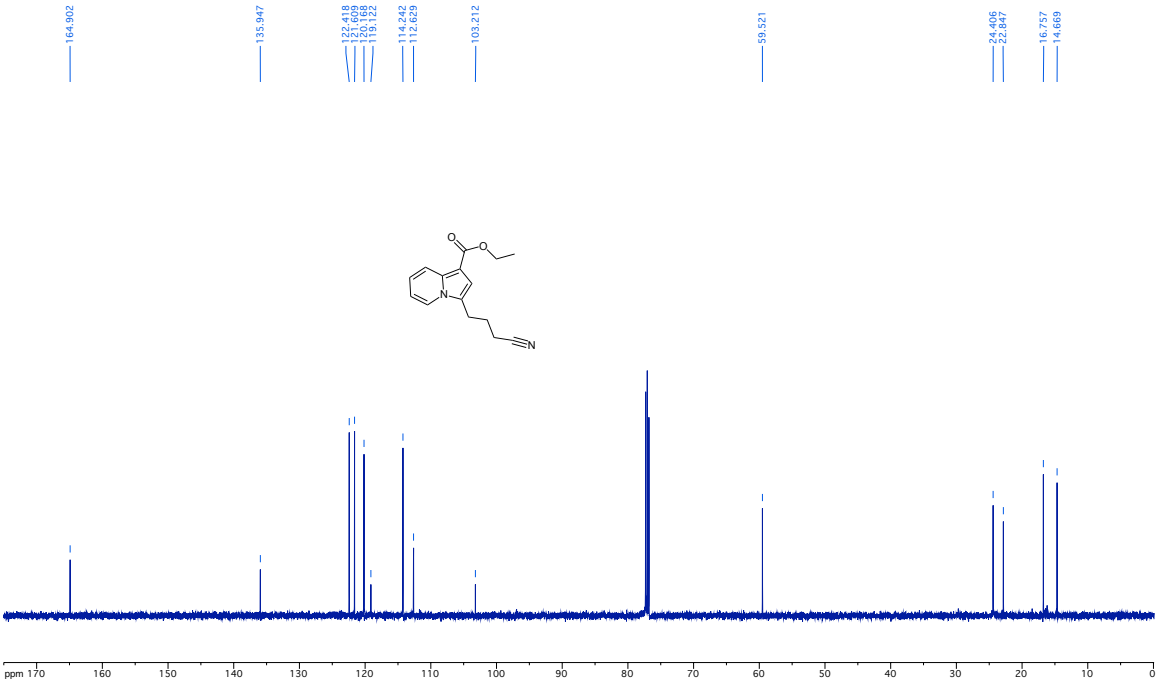
^{13}C NMR spectrum of (**3o**)



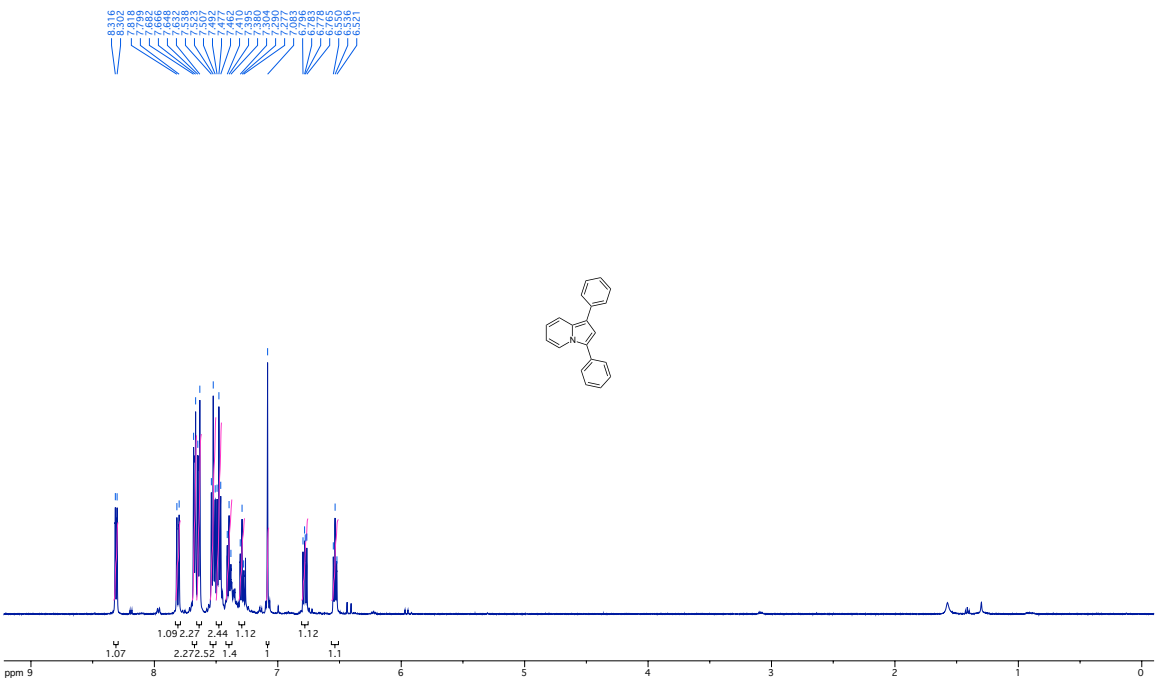
^{1}H NMR spectrum of (**3r**)



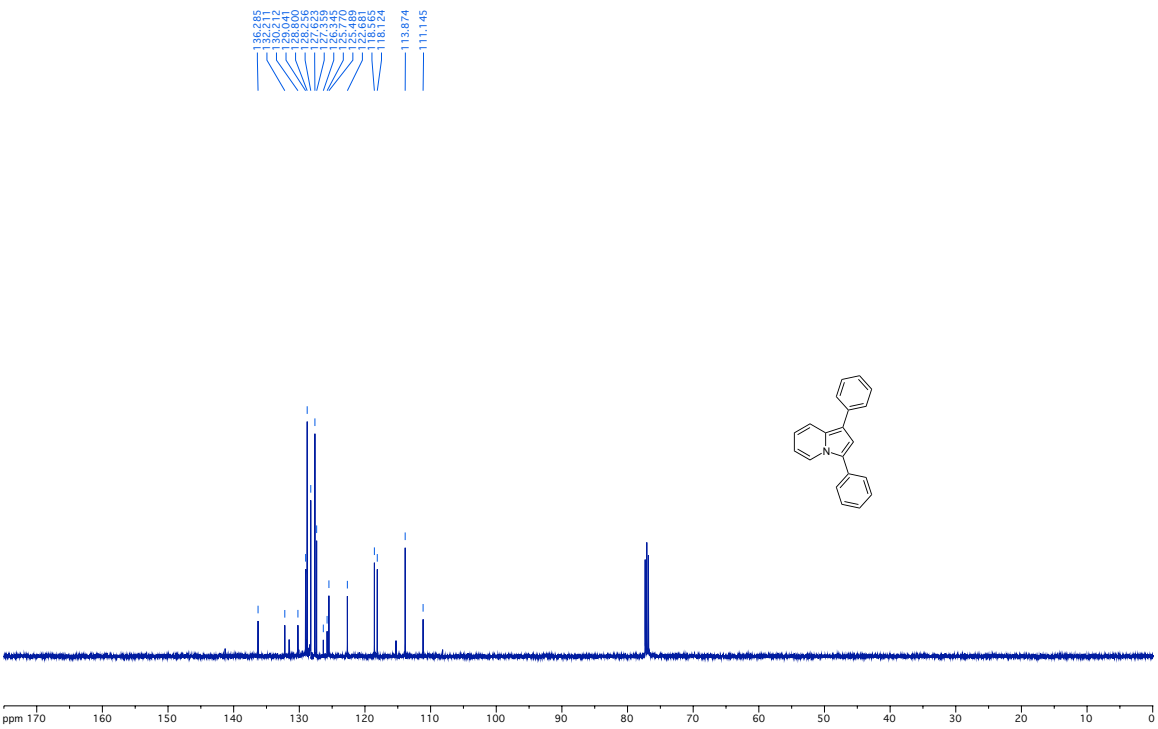
^{13}C NMR spectrum of (**3r**)



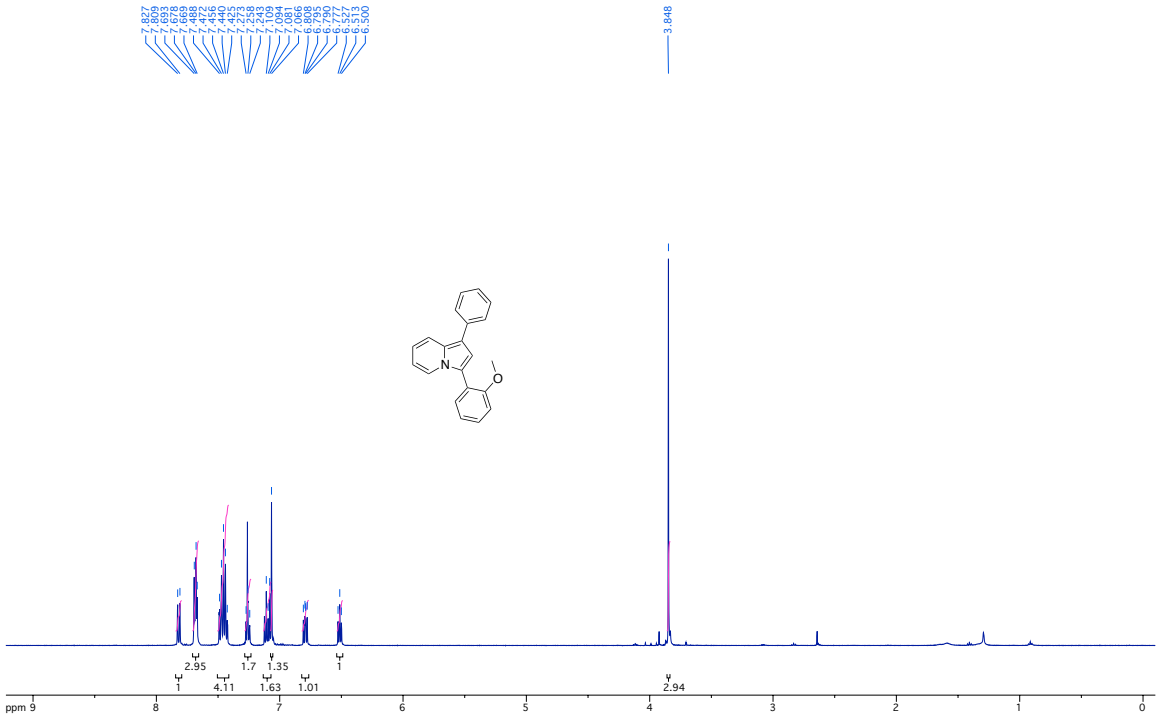
^{1}H NMR spectrum of (**3s**)



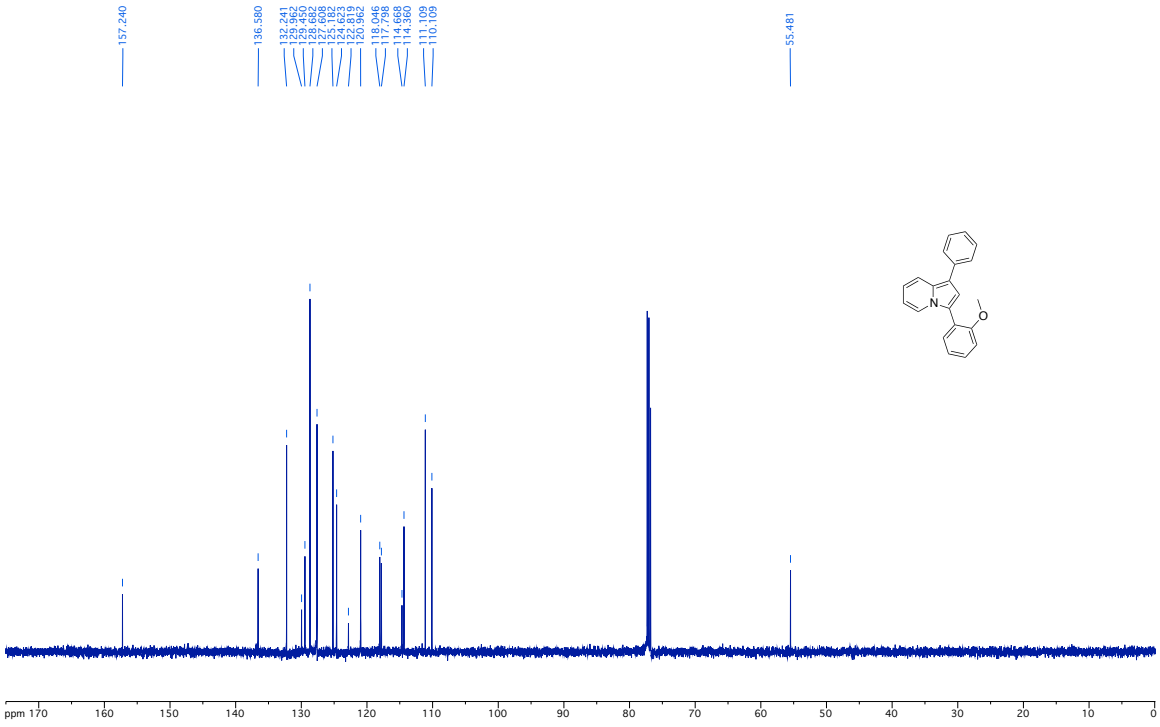
^{13}C NMR spectrum of (**3s**)



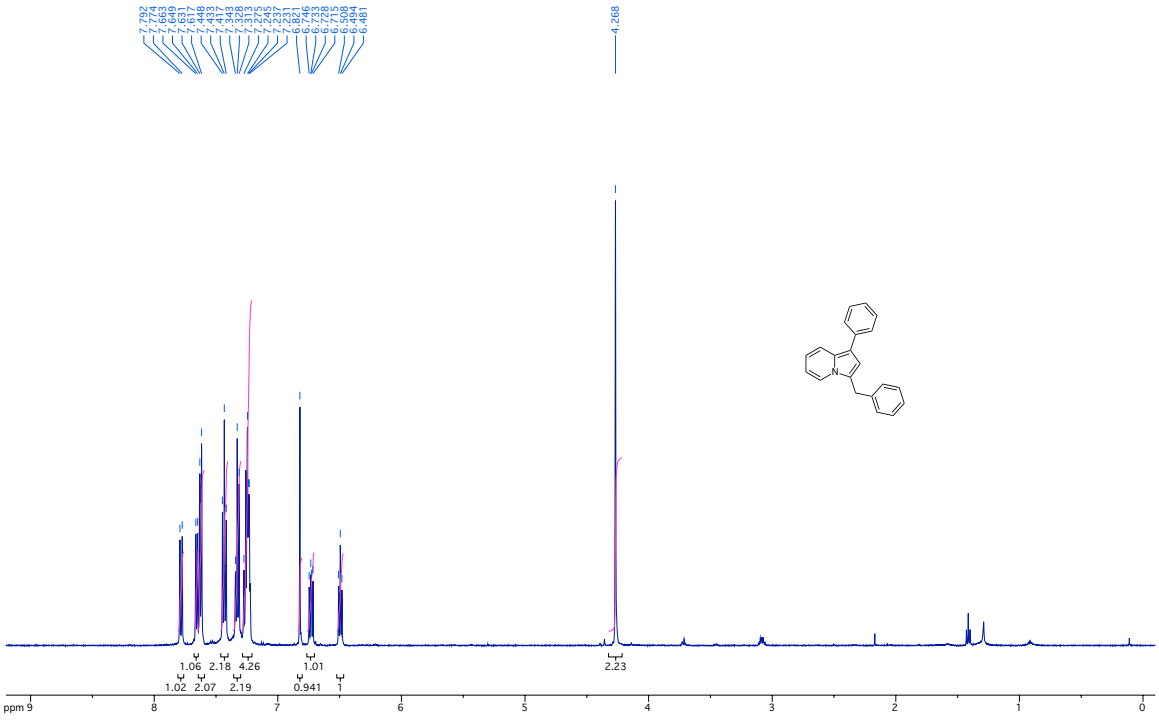
^{1}H NMR spectrum of (**3t**)



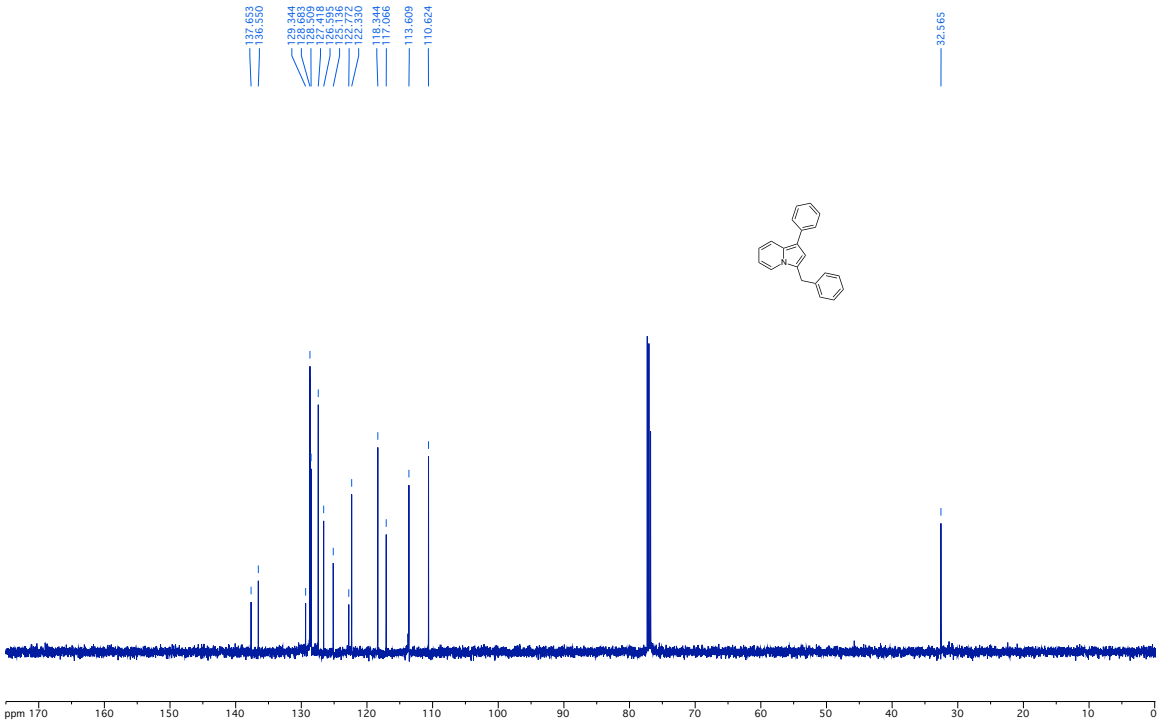
^{13}C NMR spectrum of (**3t**)



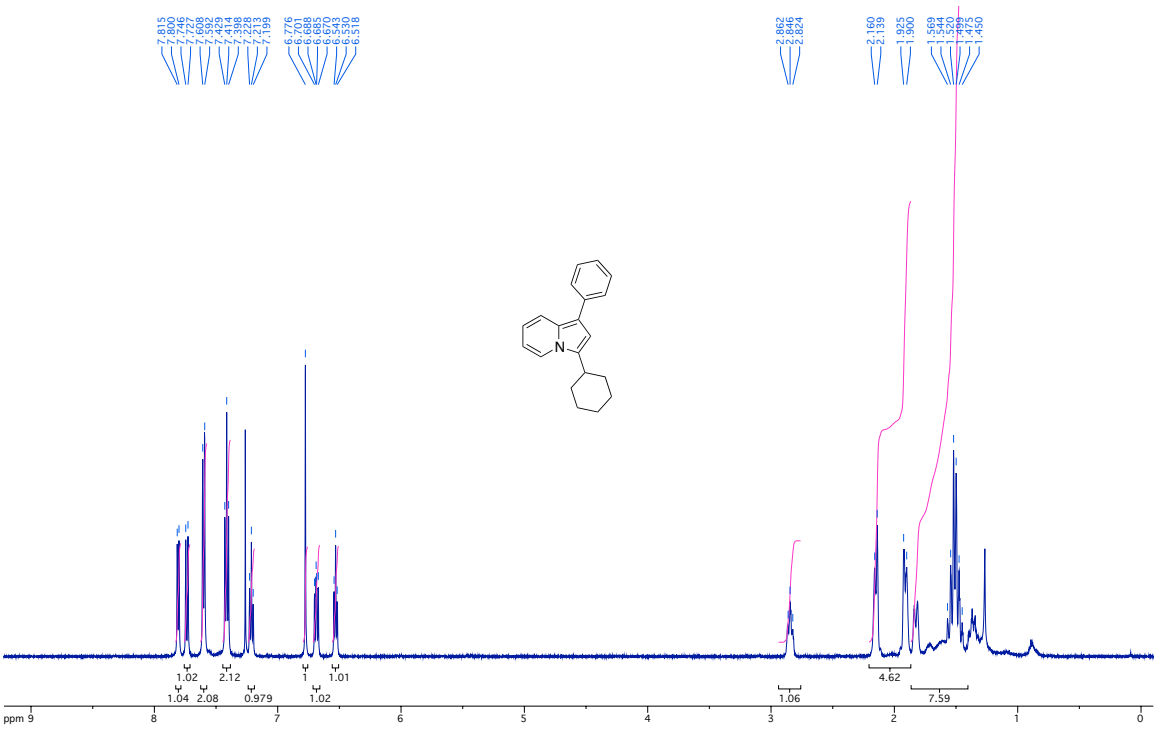
^{1}H NMR spectrum of (**3u**)



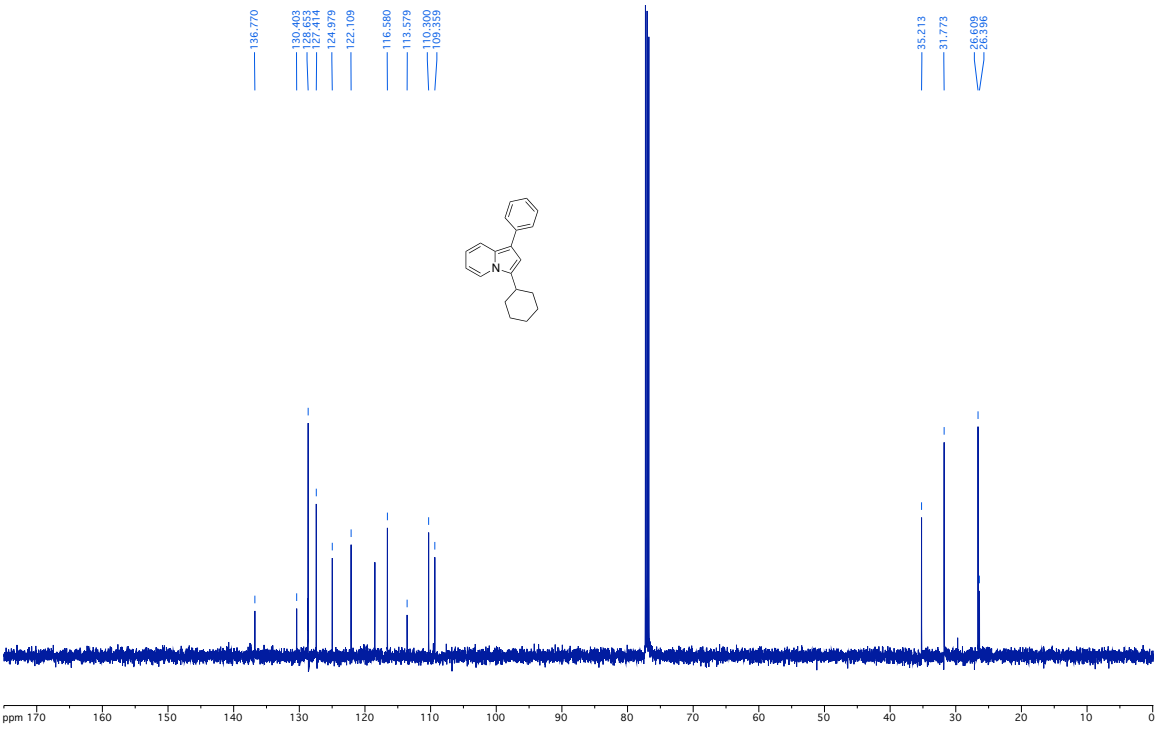
^{13}C NMR spectrum of (**3u**)



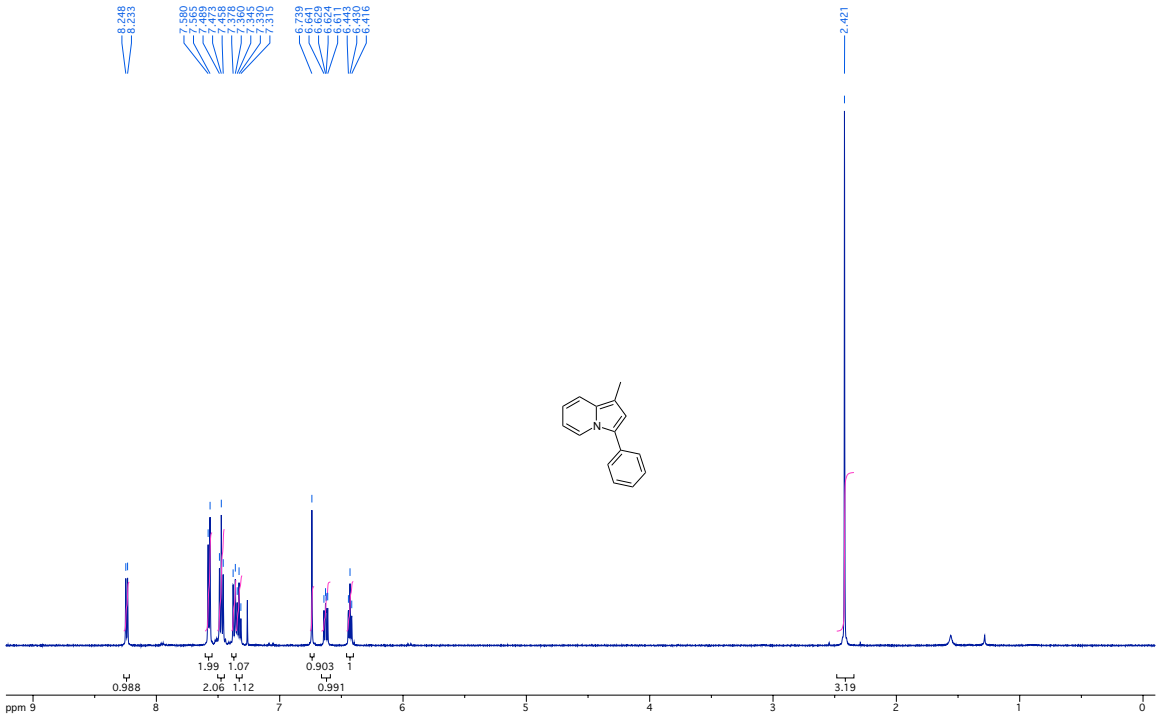
^{1}H NMR spectrum of (**3v**)



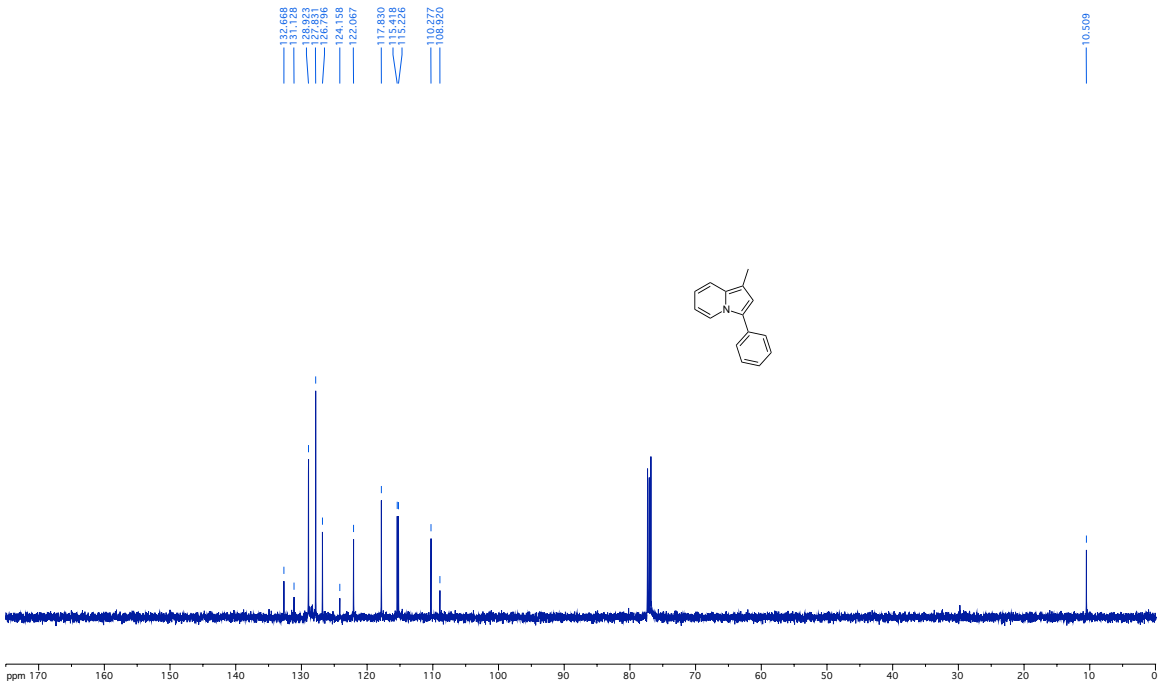
^{13}C NMR spectrum of (**3v**)



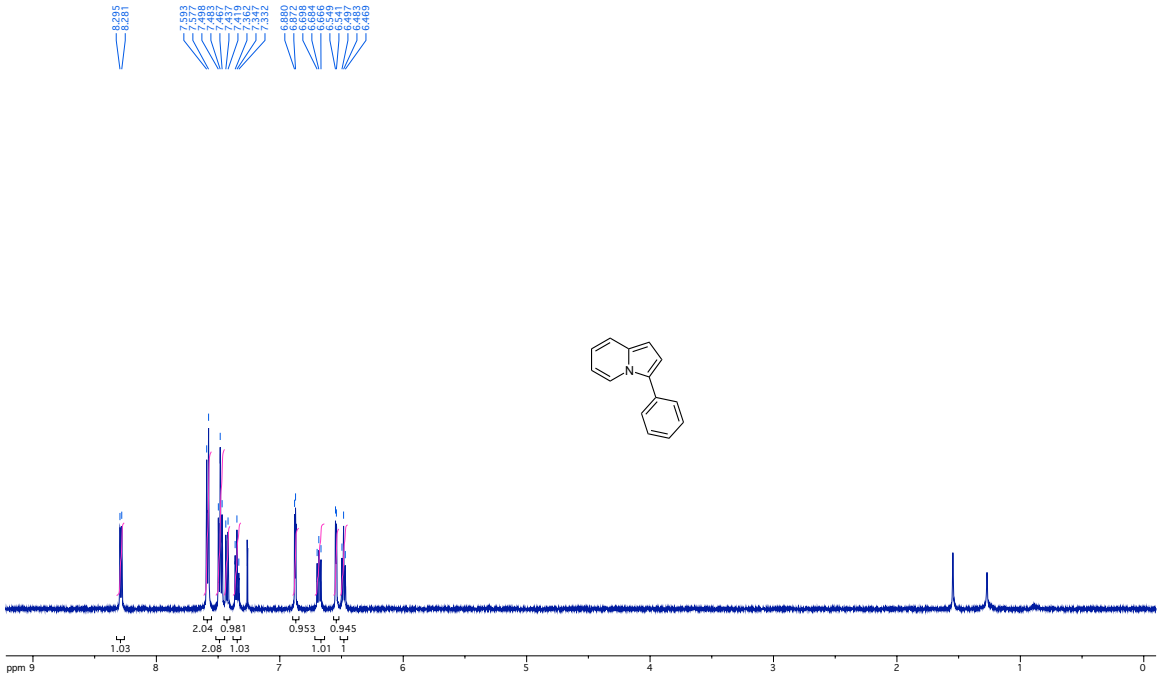
^{1}H NMR spectrum of (**3w**)



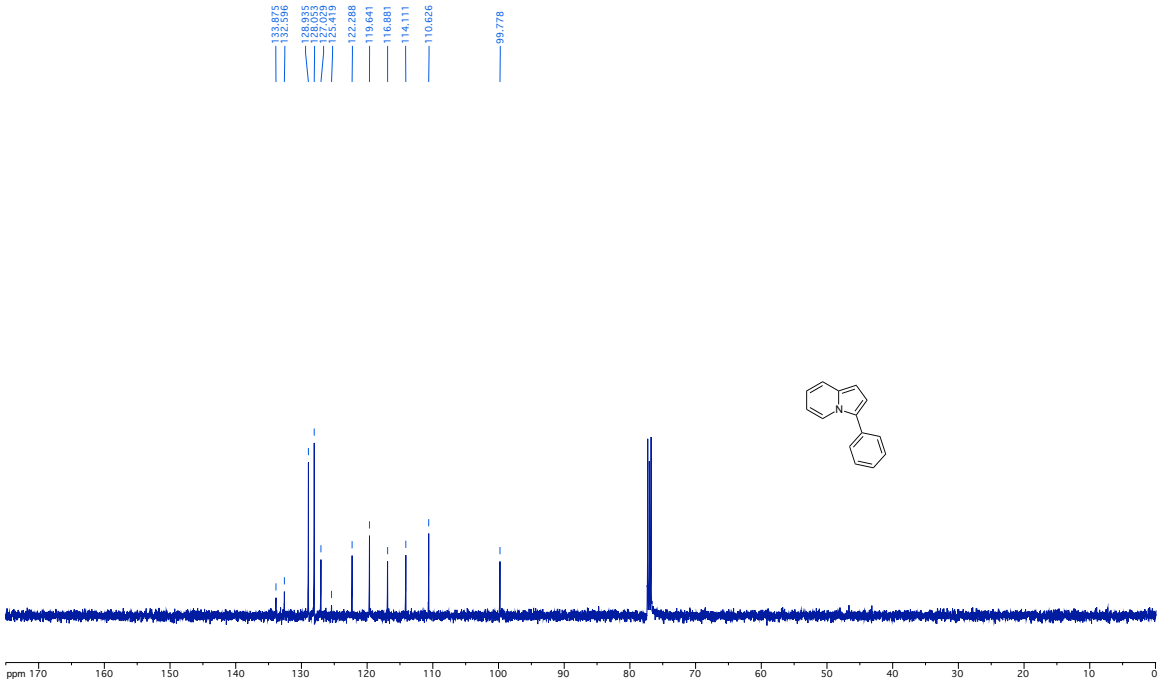
^{13}C NMR spectrum of (**3w**)



^{1}H NMR spectrum of (**3x**)

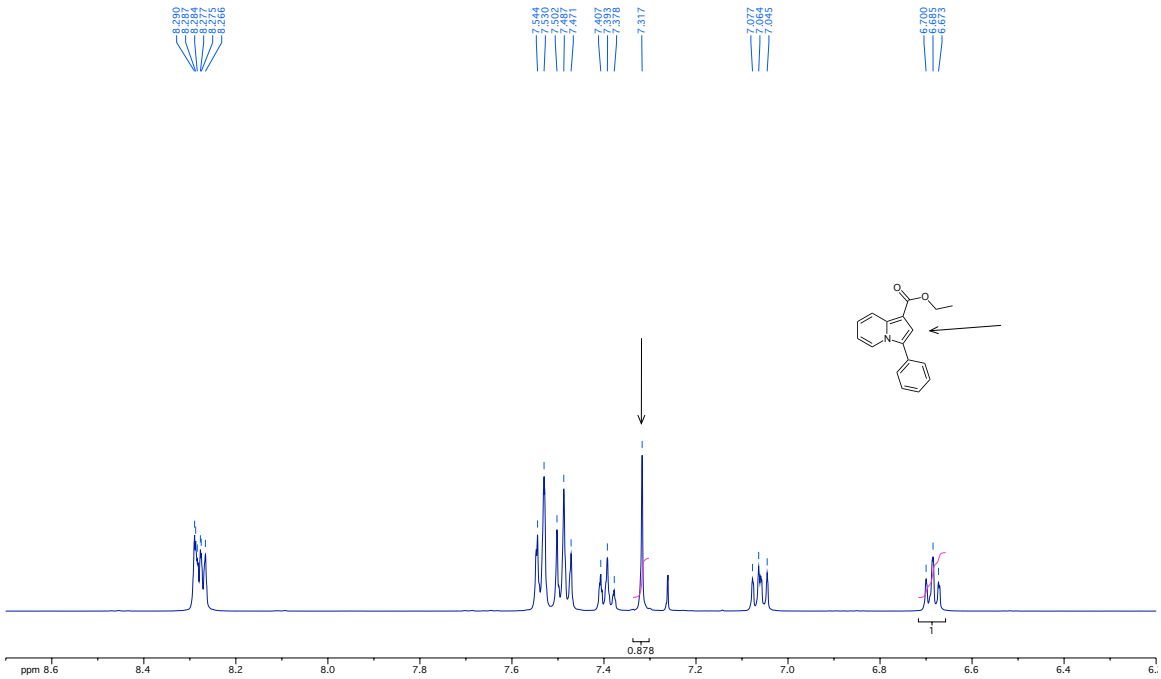


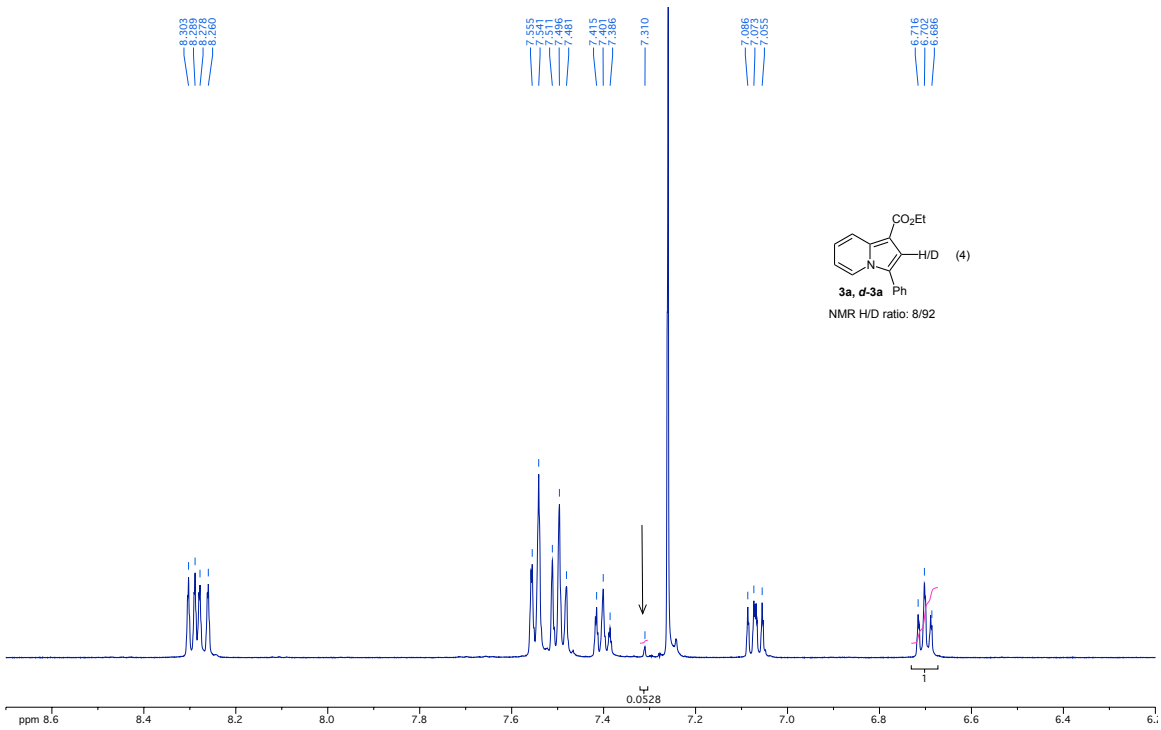
^{13}C NMR spectrum of (**3x**)

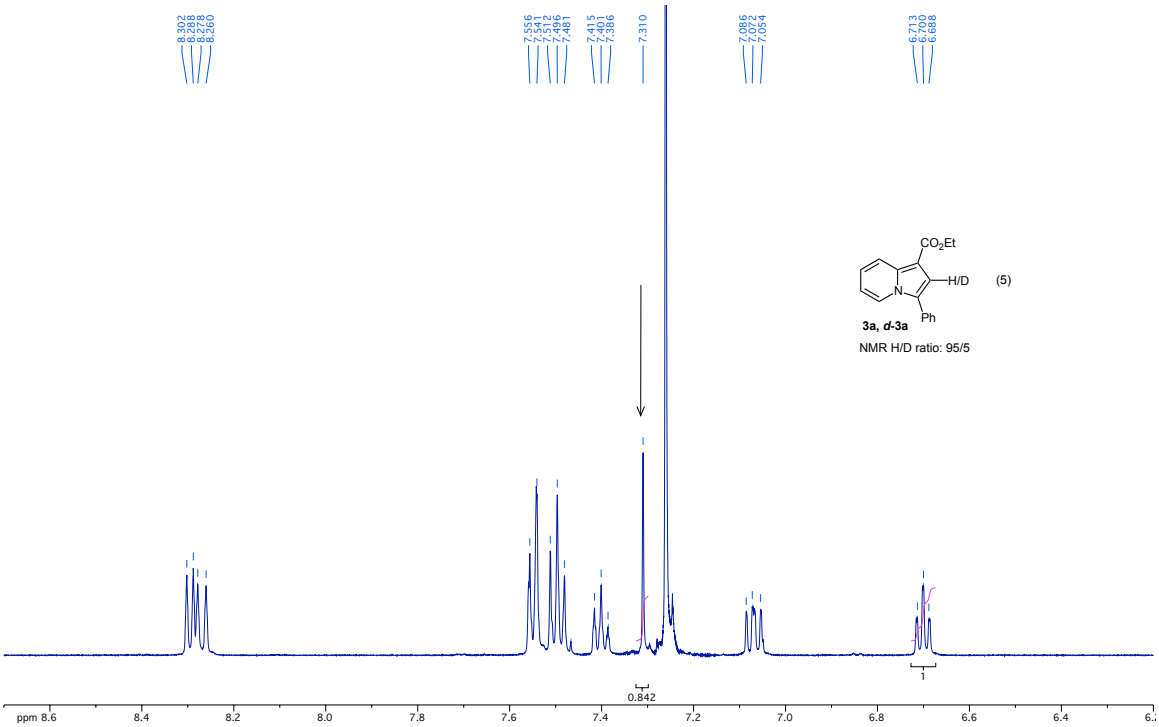


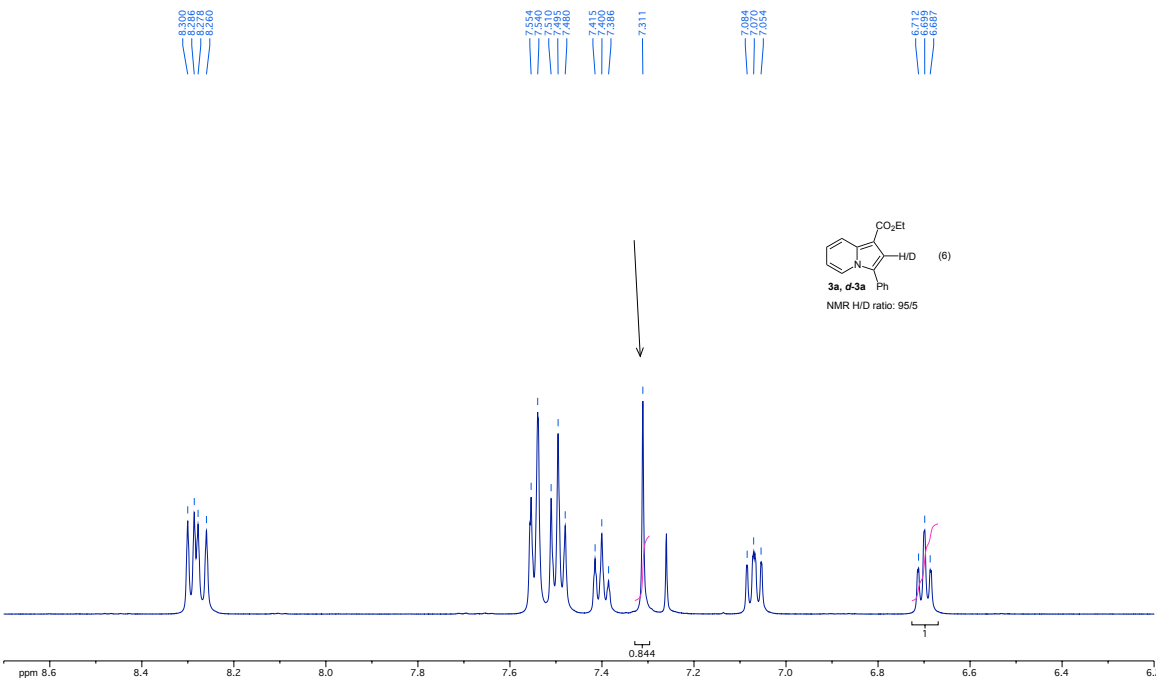
6. Copies of ^{1}H NMR Spectra for Deuterium-Labeling Studies

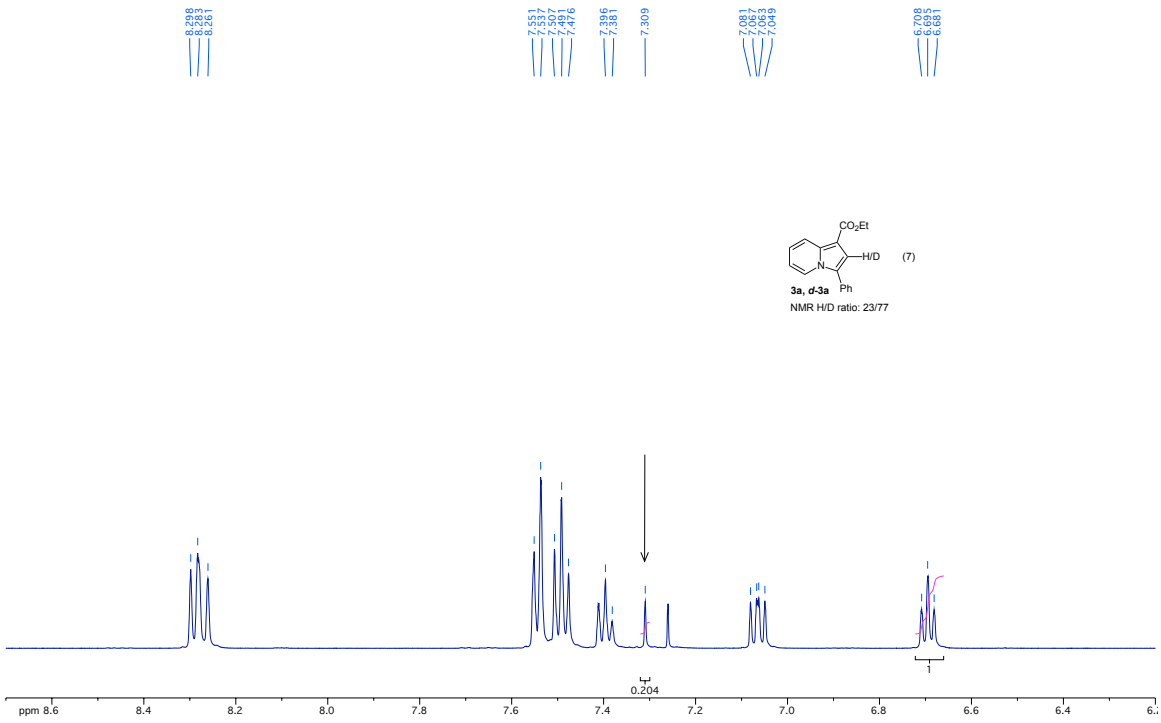
The spectra presented were zoomed in to the area containing the proton of interest.






8.302
8.288
8.278
8.260
7.556
7.541
7.512
7.496
7.481
7.415
7.401
7.386
7.310
7.086
7.072
7.054
6.713
6.700
6.688
CO2Et
H/D
(5)
Ph
3a, d-3a
NMR H/D ratio: 95/5
0.842
1
ppm 8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4


8.300
8.286
8.278
8.260
7.554
7.540
7.510
7.495
7.480
7.415
7.400
7.386
7.311
7.094
7.070
7.054
6.712
6.699
6.687
CO2Et
H/D
(6)
Ph
3a, d-3a
NMR H/D ratio: 95/5
0.844
1
ppm 8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4


8.298
8.283
8.261
7.551
7.537
7.507
7.491
7.476
7.396
7.381
7.309
7.081
7.067
7.063
7.049
6.708
6.695
6.681
CO2Et
H/D
(7)
N
Ph
3a, d-3a
NMR H/D ratio: 23/77
0.204
1
ppm 8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4