

Supporting Information

Transition-metal-free Synthesis of Indolizines via [3+2]-Annulation from α -Bromoaldehydes and 2-Substituted Azaarenes

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Table of Contents

| | |
|---|------------|
| I. General..... | S2 |
| II. General Procedure for the Synthesis of Substrates and their Characterization Data..... | S3 |
| III. General Procedure for the synthesis of and Products and their Characterization Data | S4 |
| IV. Transformation of 3a..... | S13 |
| V. References | S15 |
| VI. ¹H and ¹³C -NMR Spectra of the Substrates and Products..... | S16 |

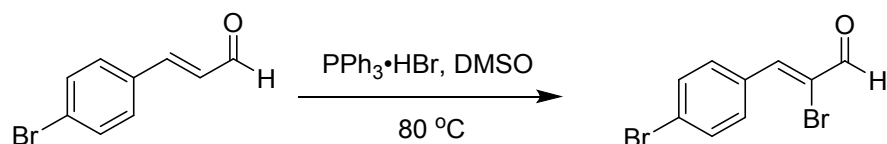
1. General

Unless otherwise noted, all reagents were obtained commercially from Acros, Aldrich, Fisher, Adamas-beta Co. Ltd. or TCI and used without further purification. ^1H NMR spectra was recorded at 400 MHz, ^{13}C NMR spectra was recorded at 100 MHz. ^1H NMR spectra was recorded with tetramethylsilane ($\delta = 0.00$ ppm) as internal reference; ^{13}C NMR spectra was recorded with CDCl_3 ($\delta = 77.00$ ppm) as internal reference. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br).

2. General Procedure for the Synthesis of Substrates and their Characterization Data

2-1. Synthesis of Bromoenal Derivatives 2

Bromoenal derivatives were synthesized according to the method reported in the literature.¹

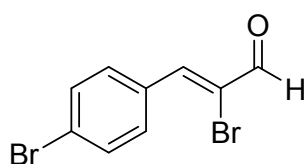


PPh₃·HBr (1.0 g, 3 mmol) was placed in a 25 mL two-neck round bottom flask under N₂ atmosphere with condenser. Dry DMSO (3.0 mL) was added dropwisely at room temperature. 4-BromoCinnaMaldehyde (316 mg, 1.5 mmol) was introduced into the reaction mixture and the resulting mixture was stirred at 80 °C for 24 h. After completion of the reaction (TLC), saturated ammonium chloride solution was added, and the product was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and filtered, and the filtrate was concentrated under reduced pressure to get crude residue. The obtained residue was purified by column chromatography to obtain (Z)-2-Bromo-3-(4-bromophenyl)acrylaldehyde (326 mg, 75%).

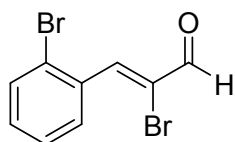
2-2. Synthesis of Pyridine Derivatives

Ethyl-2-(pyridin-2-yl)acetates, 2-acetylpyridine, and di(pyridin-2-yl)methane were synthesized according to the method reported in the literature.²

2-3. Characterization Data for Substrates



(Z)-2-Bromo-3-(4-bromophenyl)acrylaldehyde (2d). 348 mg, 80% yield, yellow solid, ¹H NMR (400 MHz, CDCl₃): δ 9.35 (s, 1H), 7.90 - 7.83 (m, 3H), 7.63 (d, *J* = 8.6 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 186.83, 147.54, 132.16, 131.77, 126.19, 124.92; HRMS (EI) *m/z* calcd for C₉H₆Br₂O: 287.8785; found: 287.8783.



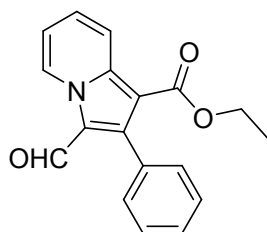
(Z)-2-Bromo-3-(2-bromophenyl)acrylaldehyde (2j). 261 mg, 60% yield, yellow solid, ^1H NMR (400 MHz, CDCl_3): δ 9.34 (s, 1H), 7.91 - 7.82 (m, 3H), 7.62 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3): δ 186.83, 147.59, 132.16, 131.78, 126.18, 124.91; HRMS (EI) m/z calcd for $\text{C}_9\text{H}_6\text{Br}_2\text{O}$: 287.8785; found: 287.8789.

3. General Procedure for the synthesis of and Products and their Characterization Data

3-1. General Procedure for the Synthesis of Products.

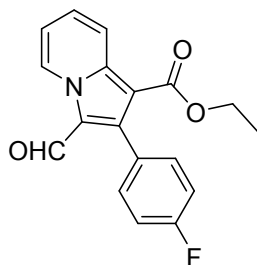
To a solution of **2a** (84.4 mg, 0.4 mmol) in 2 mL DMF, cesium carbonate (98 mg, 0.3 mmol) was added. Then **1a** (30.5 μL , 0.2 mmol) was added to the solution. The mixture was stirred for 12 h at room temperature. After completion of the reaction monitored by TLC, water (2 mL) was added. Then the solvent was extracted with ethyl acetate (10 mL) for three times. After washed in brine and dried over Na_2SO_4 , the combined organic phases was under reduced pressure and the residue was purified by flash chromatography (PE/EA 30:1, neutral Al_2O_3) to give the desired product **3a**.

3-2. Characterization Data for Products

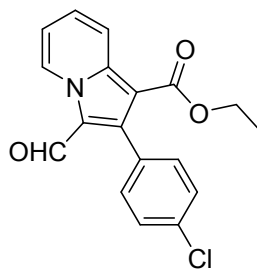


Ethyl 3-formyl-2-phenylindolizine-1-carboxylate (3a). 50 mg, 86% yield, yellow solid; ^1H NMR (400 MHz, CDCl_3): δ 9.87 (d, $J = 7.2$ Hz, 1H), 9.47 (s, 1H), 8.46 (d, $J = 8.8$ Hz, 1H), 7.51 (t, $J = 8.4$ Hz, 1H), 7.44 (s, 5H), 7.11 (t, $J = 7.2$ Hz, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 1.10 (t, $J = 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 180.0, 164.1,

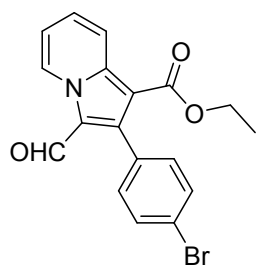
144.8, 139.4, 132.2, 130.7, 128.7, 128.6, 128.3, 127.6, 122.3, 119.8, 115.9, 105.5, 60.0, 14.0; HRMS (EI) m/z calcd for $C_{18}H_{15}NO_3$ $[M]^+$: 293.1052; found: 293.1053.



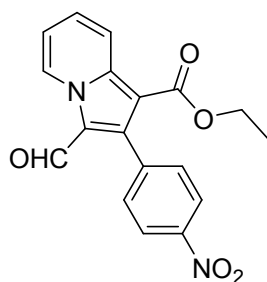
Ethyl 2-(4-Fluorophenyl)-3-formylindolizine-1-carboxylate (3b). 50 mg, 81% yield, yellow solid; 1H NMR (400 MHz, $CDCl_3$): δ 9.87 (d, $J = 6.8$ Hz, 1H), 9.46 (s, 1H), 8.46 (d, $J = 9.2$ Hz, 1H), 7.52 (t, $J = 7.6$ Hz, 1H), 7.44 - 7.40 (m, 2H), 7.17 - 7.11 (m, 3H), 4.20 (q, $J = 7.2$ Hz, 2H), 1.14 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 164.2, 164.0, 161.8, 143.6, 139.4, 132.4 (d, $J_{C-F} = 9.0$ Hz, F), 128.9, 128.6, 128.1 (d, $J_{C-F} = 3.0$ Hz, F), 122.3, 119.9, 116.0, 114.7 ($J_{C-F} = 21.0$ Hz, F) 105.5, 60.0, 14.1; HRMS (EI) m/z calcd for $C_{18}H_{14}FNO_3$ $[M]^+$: 311.0958; found: 311.0959.



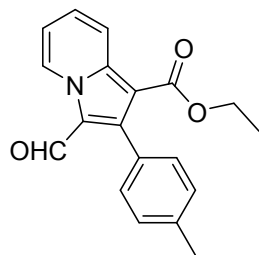
Ethyl 2-(4-Chlorophenyl)-3-formylindolizine-1-carboxylate (3c). 54 mg, 82% yield, yellow solid; 1H NMR (400 MHz, $CDCl_3$): δ 9.87 (d, $J = 7.2$ Hz, 1H), 9.46 (s, 1H), 8.45 (d, $J = 9.2$ Hz, 1H), 7.52 (t, $J = 8.8$ Hz, 1H), 7.43 (d, $J = 8.4$ Hz, 2H), 7.38 (d, $J = 8.4$ Hz, 2H), 7.13 (t, $J = 7.2$ Hz, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 1.15 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6, 163.8, 143.3, 139.4, 134.6, 132.1, 130.7, 128.9, 128.6, 127.9, 122.2, 119.9, 116.0, 105.5, 60.1, 14.1; HRMS (EI) m/z calcd for $C_{18}H_{14}ClNO_3$ $[M]^+$: 327.0662; found: 327.0663.



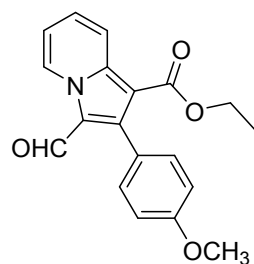
Ethyl 2-(4-Bromophenyl)-3-formylindolizine-1-carboxylate (3d). 56 mg, 75% yield, solid; ^1H NMR (400 MHz, CDCl_3): δ 9.87 (d, $J = 6.8$ Hz, 1H), 9.47 (s, 1H), 8.45 (d, $J = 9.2$ Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 2H), 7.52 (t, $J = 8.0$ Hz, 1H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.13 (t, $J = 6.8$ Hz, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 1.16 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 179.6, 163.8, 143.3, 139.4, 132.3, 131.2, 130.9, 128.9, 128.6, 122.8, 122.1, 119.9, 116.1, 105.4, 60.1, 14.2; HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{14}\text{BrNO}_3$ $[\text{M}]^+$: 371.0157; found: 371.0158.



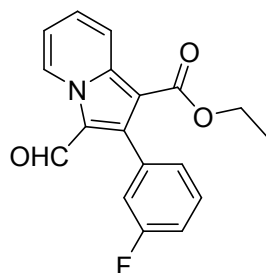
Ethyl 3-formyl-2-(4-Nitrophenyl)indolizine-1-carboxylate (3e). 54 mg, 80% yield, brown solid; ^1H NMR (400 MHz, CDCl_3): δ 9.86 (d, $J = 7.2$ Hz, 1H), 9.43 (s, 1H), 8.47 (d, $J = 9.2$ Hz, 1H), 8.31 (d, $J = 8.0$ Hz, 2H), 7.64 (d, $J = 8.4$ Hz, 2H), 7.56 (t, $J = 7.6$ Hz, 1H), 7.17 (t, $J = 6.8$ Hz, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 1.13 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 178.9, 163.5, 147.9, 141.7, 139.5, 139.3, 131.7, 129.3, 128.6, 122.8, 122.0, 120.0, 116.5, 105.6, 60.3, 14.2; HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_5$ $[\text{M}]^+$: 338.0903; found: 338.0904.



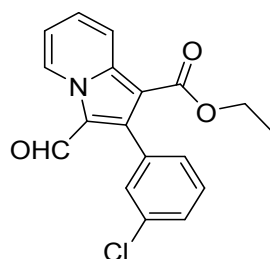
Ethyl 3-formyl-2-(*p*-tolyl)indolizine-1-carboxylate (3f). 49 mg, 81% yield, yellow solid; ^1H NMR (400 MHz, CDCl_3): δ 9.88 (d, $J = 6.8$ Hz, 1H), 9.51 (s, 1H), 8.45 (d, $J = 8.8$ Hz, 1H), 7.50 (t, $J = 8.4$ Hz, 1H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.10 (t, $J = 6.8$ Hz, 1H), 4.23 (q, $J = 7.2$ Hz, 2H), 2.45 (s, 3H), 1.17 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 180.1, 164.0, 145.0, 139.3, 138.1, 130.7, 128.9, 128.5, 128.5, 128.3, 122.3, 119.8, 115.7, 105.3, 59.9, 21.4, 14.1; HRMS (EI) m/z calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_3$ $[\text{M}]^+$: 307.1208; found: 307.1207.



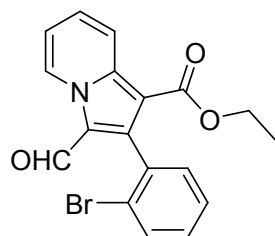
Ethyl 3-formyl-2-(4-Methoxyphenyl)indolizine-1-carboxylate (3g). 49 mg, 75% yield, yellow solid; ^1H NMR (400 MHz, CDCl_3): δ 9.87 (d, $J = 6.8$ Hz, 1H), 9.50 (s, 1H), 8.44 (d, $J = 8.8$ Hz, 1H), 7.50 (t, $J = 7.6$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 2H), 7.09 (t, $J = 6.8$ Hz, 1H), 6.98 (d, $J = 8.4$ Hz, 2H), 4.21 (q, $J = 6.8$ Hz, 2H), 3.88 (s, 3H), 1.18 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 180.1, 164.1, 159.8, 144.7, 139.5, 132.1, 128.6, 128.5, 124.1, 122.3, 119.8, 115.7, 113.1, 105.3, 59.9, 55.4, 14.2; HRMS (EI) m/z calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_4$ $[\text{M}]^+$: 323.1158; found: 323.1160.



Ethyl 2-(3-fluorophenyl)-3-formylindolizine-1-carboxylate (3h). 44 mg, 70% yield, yellow solid; ^1H NMR (400 MHz, CDCl_3): δ 9.86 (d, $J = 6.8$ Hz, 1H), 9.47 (s, 1H), 8.47 (d, $J = 8.8$ Hz, 1H), 7.53 (t, $J = 8.4$ Hz, 1H), 7.41 (dd, $J_1 = 10.0$ Hz, $J_2 = 8.0$ Hz, 1H), 7.22 - 7.12 (m, 4H), 4.18 (q, $J = 7.2$ Hz, 2H), 1.12 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 179.6, 163.8, 163.3, 160.8, 142.9 (d, $J_{\text{C-F}} = 2.0$ Hz, F), 139.4, 134.4 (d, $J_{\text{C-F}} = 8.0$ Hz, F), 129.1 (d, $J_{\text{C-F}} = 9.0$ Hz, F), 128.9, 128.5, 126.5 (d, $J_{\text{C-F}} = 3.0$ Hz, F), 122.1, 119.9, 117.9 (d, $J_{\text{C-F}} = 23.0$ Hz, F), 116.1, 115.3 (d, $J_{\text{C-F}} = 20.0$ Hz, F), 105.5, 60.0, 14.0; HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{14}\text{FNO}_3$ $[\text{M}]^+$: 311.0958; found: 311.0959.

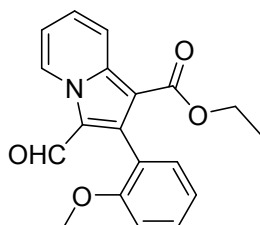


Ethyl 2-(3-chlorophenyl)-3-formylindolizine-1-carboxylate (3i). 47 mg, 72% yield, yellow solid; ^1H NMR (400 MHz, CDCl_3): δ 9.83 (d, $J = 6.8$ Hz, 1H), 9.45 (s, 1H), 8.44 (d, $J = 8.8$ Hz, 1H), 7.49 (t, $J = 8.0$ Hz, 1H), 7.44 - 7.29 (m, 4H), 7.10 (t, $J = 8.0$ Hz, 1H), 4.16 (q, $J = 6.8$ Hz, 2H), 1.10 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 179.4, 163.7, 142.6, 139.3, 134.0, 133.4, 130.8, 128.9, 128.8, 128.8, 128.4, 128.4, 122.0, 119.8, 116.0, 105.4, 60.0, 13.9; HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{14}\text{ClNO}_3$ $[\text{M}]^+$: 327.0662; found: 327.0663.

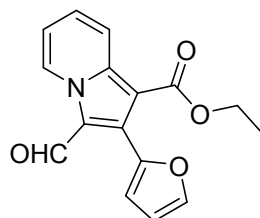


Ethyl 2-(2-Bromophenyl)-3-formylindolizine-1-carboxylate (3j). 30 mg, 40% yield, yellow solid, ^1H NMR (400 MHz, CDCl_3) δ 9.86 (d, $J = 6.9$ Hz, 1H), 9.40 (s, 1H), 8.51 (d, $J = 9.0$ Hz, 1H), 7.71 (d, $J = 7.9$ Hz, 1H), 7.59 - 7.50 (m, 1H), 7.38 (qd, $J =$

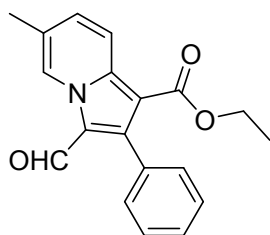
14.7, 7.4 Hz, 3H), 7.16 (t, $J = 6.9$ Hz, 1H), 4.17 (dd, $J = 19.6, 7.1$ Hz, 2H), 1.06 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 179.1, 163.6, 142.6, 139.2, 134.0, 132.2, 131.6, 129.7, 128.6, 128.5, 126.6, 124.3, 119.8, 115.9, 106.0, 59.8, 13.8; HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{14}\text{BrNO}_3$ $[\text{M}]^+$: 371.0157; found: 371.0158.



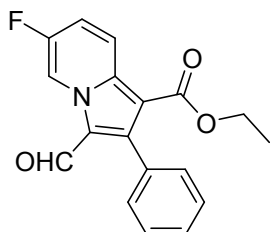
Ethyl 3-formyl-2-(2-Methoxyphenyl)indolizine-1-carboxylate (3k). 33 mg, 50% yield, yellow solid, ^1H NMR (400 MHz, CDCl_3) δ 9.84 (d, $J = 6.9$ Hz, 1H), 9.48 (s, 1H), 8.44 (d, $J = 9.0$ Hz, 1H), 7.44 (dd, $J = 20.8, 7.7$ Hz, 2H), 7.29 (d, $J = 7.3$ Hz, 1H), 7.04 (dt, $J = 14.4, 8.2$ Hz, 3H), 4.23-4.07 (m, 2H), 1.08 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 179.8, 164.0, 157.4, 140.8, 139.4, 131.9, 129.9, 128.4, 128.1, 121.8, 121.3, 119.9, 119.6, 115.4, 110.5, 106.1, 59.6, 55.5, 13.9. HRMS (EI) m/z calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_4$ $[\text{M}]^+$: 323.1158; found: 323.1160.



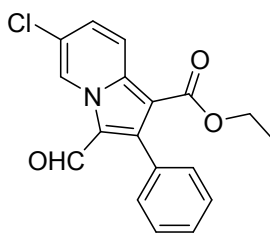
Ethyl 3-formyl-2-(furan-2-yl)indolizine-1-carboxylate (3l). 42 mg, 75% yield, green solid; ^1H NMR (400 MHz, CDCl_3): δ 9.88 (d, $J = 6.0$ Hz, 2H), 8.40 (d, $J = 8.8$ Hz, 1H), 7.63 (s, 1H) 7.46 (t, $J = 8.0$ Hz, 1H), 7.08 (t, $J = 6.8$ Hz, 1H), 6.86 (d, $J = 3.2$ Hz, 1H), 6.58 (d, $J = 1.6$ Hz, 1H), 4.33 (q, $J = 6.8$ Hz, 2H), 1.31 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 180.6, 163.7, 145.0, 143.9, 139.6, 131.8, 128.6, 128.6, 122.0, 120.0, 116.0, 114.2, 111.5, 105.0, 60.3, 14.4; HRMS (EI) m/z calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_4$ $[\text{M}]^+$: 283.0845; found: 283.0848.



Ethyl 3-formyl-6-methyl-2-phenylindolizine-1-carboxylate (3m). 47 mg, 77% yield, yellow solid; ^1H NMR (400 MHz, CDCl_3): δ 9.68 (s, 1H), 9.42 (s, 1H), 8.32 (d, $J = 9.2$ Hz, 1H), 7.42 (s, 5H), 7.34 (d, $J = 8.8$ Hz, 1H), 4.15 (q, $J = 6.8$ Hz, 2H), 2.41 (s, 3H), 1.08 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 179.8, 164.1, 144.4, 138.1, 132.3, 131.5, 130.7, 128.2, 127.5, 126.6, 125.9, 122.0, 119.0, 105.1, 59.8, 18.5, 14.0; HRMS (EI) m/z calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_3$ $[\text{M}]^+$: 307.1208; found: 307.1211.

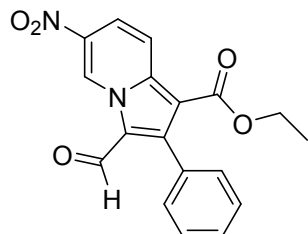


Ethyl 6-fluoro-3-formyl-2-phenylindolizine-1-carboxylate (3n). 50mg, 80% yield, yellow solid, ^1H NMR (400 MHz, CDCl_3) δ 9.90 (dd, $J = 4.7, 2.0$ Hz, 1H), 9.49 (s, 1H), 8.48 (dd, $J = 9.8, 5.6$ Hz, 1H), 7.48-7.39 (m, 6H), 4.18 (q, $J = 7.1$ Hz, 2H), 1.09 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 180.14, 163.72, 155.00 (d, $J_{\text{C-F}} = 238.8$ Hz, F), 144.42, 136.57, 131.73, 130.62, 128.36, 127.58, 122.62, 120.34 (d, $J_{\text{C-F}} = 8.2$ Hz, F), 119.79 (d, $J_{\text{C-F}} = 23.6$ Hz, F), 115.70 (d, $J_{\text{C-F}} = 41.7$ Hz, F), 105.94, 60.03, 13.91; HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{14}\text{FNO}_3$ $[\text{M}]^+$: 311.0958; found: 311.0959.

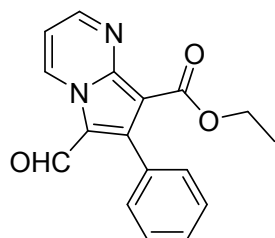


Ethyl 6-chloro-3-formyl-2-phenylindolizine-1-carboxylate (3o). 51 mg, 78% yield, yellow solid; ^1H NMR (400 MHz, CDCl_3): δ 9.96 (s, 1H), 9.48 (s, 1H), 8.41 (d, $J =$

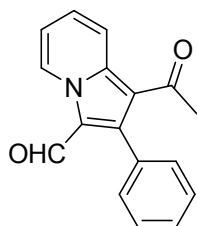
9.6 Hz, 1H), 7.47-7.41 (m, 6H), 4.18 (q, $J = 6.8$ Hz, 2H), 1.09 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 180.2, 163.7, 144.5, 137.4, 131.7, 130.7, 129.6, 128.5, 127.7, 126.4, 124.1, 122.2, 120.2, 106.1, 60.2, 14.0; HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{14}\text{ClNO}_3$ $[\text{M}]^+$: 327.0662; found: 327.0663.



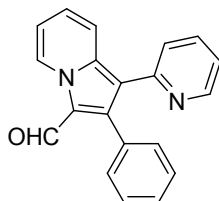
Ethyl 3-formyl-6-nitro-2-phenylindolizine-1-carboxylate (3p). 27mg, 40% yield, yellow solid; ^1H NMR (400 MHz, CDCl_3) δ 10.88 (s, 1H), 9.60 (s, 1H), 8.56 (d, $J = 9.9$ Hz, 1H), 8.20 (d, $J = 9.9$ Hz, 1H), 7.53 – 7.42 (m, 6H), 4.21 (q, $J = 7.1$ Hz, 2H), 1.11 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 180.7, 163.2, 146.9, 139.2, 139.21, 130.8, 130.6, 129.0, 127.9, 127.8, 123.3, 121.6, 119.7, 107.6, 60.6, 13.9. HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_5$ $[\text{M}]^+$: 338.0903; found: 338.0904.



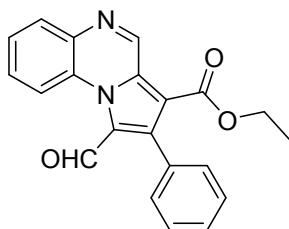
Ethyl 6-formyl-7-phenylpyrrolo[1,2-a]pyrimidine-8-carboxylate (3q). 35 mg, 60% yield, yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 10.02 (d, $J = 6.8$ Hz, 1H), 9.53 (s, 1H), 8.78 (d, $J = 2.4$ Hz, 1H), 7.44 (s, 5H), 7.12 (dd, $J_1 = 6.8$ Hz, $J_2 = 4.4$ Hz, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 1.04 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 180.7, 163.0, 152.4, 145.5, 144.3, 135.0, 131.4, 130.6, 128.6, 127.8, 118.4, 111.4, 105.5, 60.4, 13.9; HRMS (EI) m/z calcd for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3$ $[\text{M}]^+$: 294.1004; found: 294.1006.



1-Acetyl-2-phenylindolizine-3-carbaldehyde (3r). 29 mg, 55% yield, white solid; ^1H NMR (400 MHz, CDCl_3): δ 9.83 (d, $J = 6.8$ Hz, 1H), 9.35 (s, 1H), 8.66 (d, $J = 9.2$ Hz, 1H), 7.54 (t, $J = 7.6$ Hz, 1H), 7.49-7.45 (m, 5H), 7.13 (t, $J = 6.8$ Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 194.8, 179.8, 143.8, 139.1, 132.5, 130.4, 129.9, 129.0, 128.5, 128.2, 122.2, 120.6, 116.7, 115.3, 30.7; HRMS (EI) m/z calcd for $\text{C}_{17}\text{H}_{13}\text{NO}_2$ $[\text{M}]^+$: 263.0946; found: 263.0947.



2-Phenyl-1-(pyridin-2-yl)indolizine-3-carbaldehyde (3s). 30 mg, 50% yield, brown solid; ^1H NMR (400 MHz, CDCl_3): δ 9.89 (d, $J = 7.2$ Hz, 1H), 9.57 (s, 1H), 8.68 (d, $J = 4.4$ Hz, 1H), 8.40 (d, $J = 8.8$ Hz, 1H), 7.42-7.34 (m, 7H), 7.08 (t, $J = 6.4$ Hz, 1H), 7.03 (t, $J = 7.2$ Hz, 1H), 6.82 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 178.9, 153.5, 149.4, 140.0, 137.5, 135.9, 132.5, 131.1, 128.6, 128.4, 128.3, 127.0, 124.5, 121.3, 120.9, 119.4, 115.4, 115.3; HRMS (EI) m/z calcd for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}$ $[\text{M}]^+$: 298.1106; found: 298.1107.

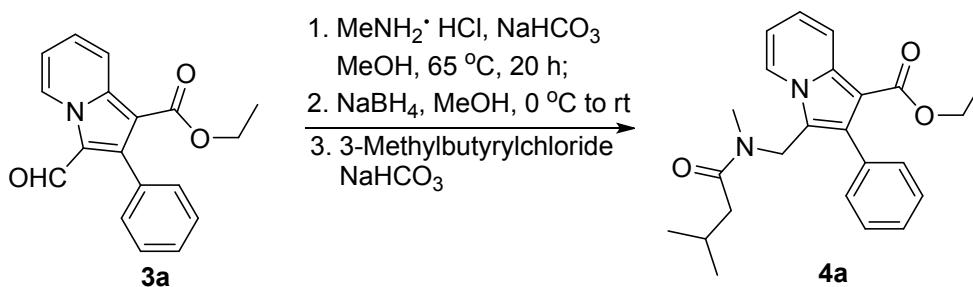


Ethyl 1-formyl-2-phenylpyrrolo[1,2-a]quinoxaline-3-carboxylate (3t). 31 mg, 45%, white solid; ^1H NMR (400 MHz, CDCl_3): δ 9.87 (s, 1H), 9.62 (s, 1H), 9.27 (d, $J = 8.4$ Hz, 1H), 8.14 (d, $J = 7.6$ Hz, 1H), 7.73-7.66 (m, 2H), 7.48 - 7.43 (m, 5H), 4.22 (q, $J =$

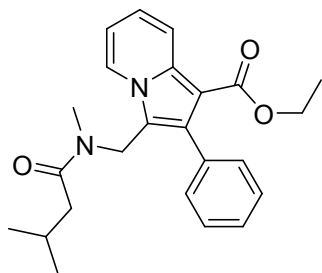
7.2 Hz, 2H), 1.11 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 180.4, 163.0, 147.1, 145.4, 138.4, 132.2, 131.6, 130.7, 130.4, 129.1, 128.7, 128.2, 127.9, 127.9, 120.8, 111.1, 60.8, 13.9; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_3$ $[\text{M}]^+$: 344.1161; found: 344.1163.

4. Transformation of 3a

4.1 Synthesis of 4a



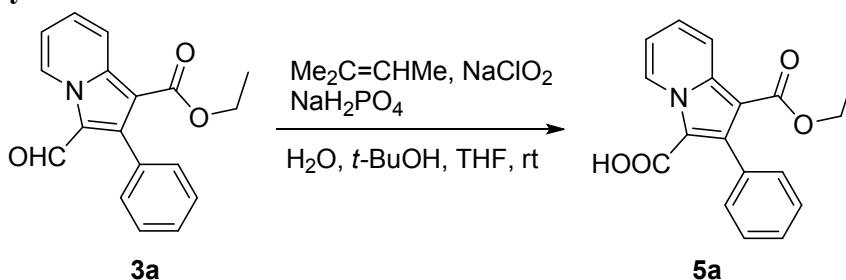
A mixture of **3a** (58 mg, 0.2 mmol), methylamine hydrochloride (40 mg, 0.6 mmol) and NaHCO_3 (50 mg, 0.6 mmol) in MeOH (2 mL) was stirred at 65 °C for 20 h. The reaction mixture was cooled to 0 °C before addition of NaBH_4 (23 mg, 0.6 mmol) in portion. The resulting mixture was then warmed to rt and stirred for another 10 min. The solvent was evaporated under reduced pressure. Saturated aqueous Na_2CO_3 (10 mL) was added and the mixture was extracted with EtOAc (5×3 mL). The combined organic layers were then washed with brine and dried over anhydrous Na_2SO_4 . The concentrated crude product was subjected to the next step without further purification. To a mixture of the above crude product, NaHCO_3 (50 mg, 0.6 mmol) in anhydrous THF (2 mL), 3-methylbutyrylchloride (48 mg, 0.4 mmol) was added dropwise. The resulting mixture was stirred at rt for 30 min. Saturated aqueous NaHCO_3 (15 mL), and EtOAc (10 mL) were added to the reaction mixture. The organic phase was separated, and the aqueous phase was further extracted with EtOAc (5×2 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to provide 68 mg of **4a** in 90% yield over three steps.



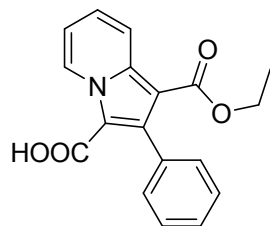
Ethyl 3-((N-Methylisobutyramido)methyl)-2-phenylindolizine-1-carboxylate (4a) .

68 mg, 90%, white solid; ^1H NMR (400 MHz, CDCl_3): δ 8.39 (d, $J = 6.8$ Hz, 1H), 8.29 (d, $J = 9.2$ Hz, 1H), 7.44-7.37 (m, 3H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.14 (t, $J = 7.2$ Hz, 1H), 6.79 (t, $J = 7.2$ Hz, 1H), 4.88 (s, 2H), 4.16 (q, $J = 7.2$ Hz, 2H), 2.53 (s, 3H), 2.15 - 2.08 (m, 3H), 1.10 (t, $J = 7.2$ Hz, 3H), 0.93 (d, $J = 6.0$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.9, 164.9, 136.4, 134.9, 133.2, 130.5, 127.7, 127.2, 125.3, 123.1, 119.8, 118.8, 113.0, 102.1, 59.2, 42.3, 38.7, 33.7, 25.6, 22.7, 14.1; HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 393.2178; found: 393.2177.

4.2 Synthesis of 5a



The compound **3a** (58 mg, 0.2 mmol) was suspended in 2 mL of *t*-BuOH. To this suspension were added a solution of NaH_2PO_4 (72 mg, 0.6 mmol) in 1 mL of H_2O , a 2 M solution of 2-methyl-2-butene in THF (0.6 mL, 1.2 mmol) and NaClO_2 (108.5 mg, 1.2 mmol) in small portions. After stirring at rt for 18 h, once more a solution of NaH_2PO_4 (72 mg, 0.6 mmol) in 1 mL of H_2O , a 2 M solution of 2-methyl-2-butene in THF (0.6 mL, 1.2 mmol) and NaClO_2 (108.5 mg, 1.2 mmol) were added again and stirring was continued for another 48 h. Then 20 mL of a 1:1 mixture of brine and EA were added, the organic phase was separated, and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography to provide 37 mg of the target compound **5a** in 60% yield.



1-(ethoxycarbonyl)-2-phenylindolizine-3-carboxylic acid (5a). 37 mg, 60%, white solid; ^1H NMR (400 MHz, CDCl_3): δ 9.63 (d, $J = 6.8$ Hz, 1H), 8.43 (d, $J = 9.2$ Hz, 1H), 7.40 - 7.32 (m, 6H), 7.01 (t, $J = 6.8$ Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 0.99 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 165.7, 164.2, 141.3, 139.5, 135.4, 129.3, 128.7, 127.3, 126.7, 119.7, 114.9, 112.2, 106.0, 59.6, 13.8. HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_4$ $[\text{M}]^+$: 309.1001; found: 309.1002.

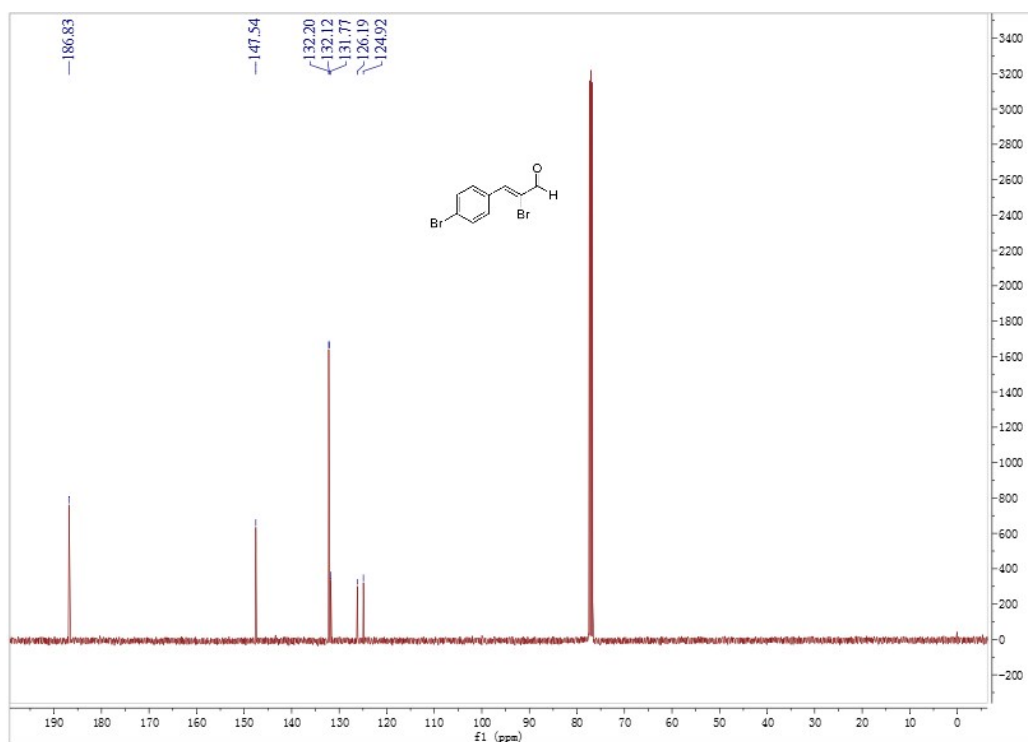
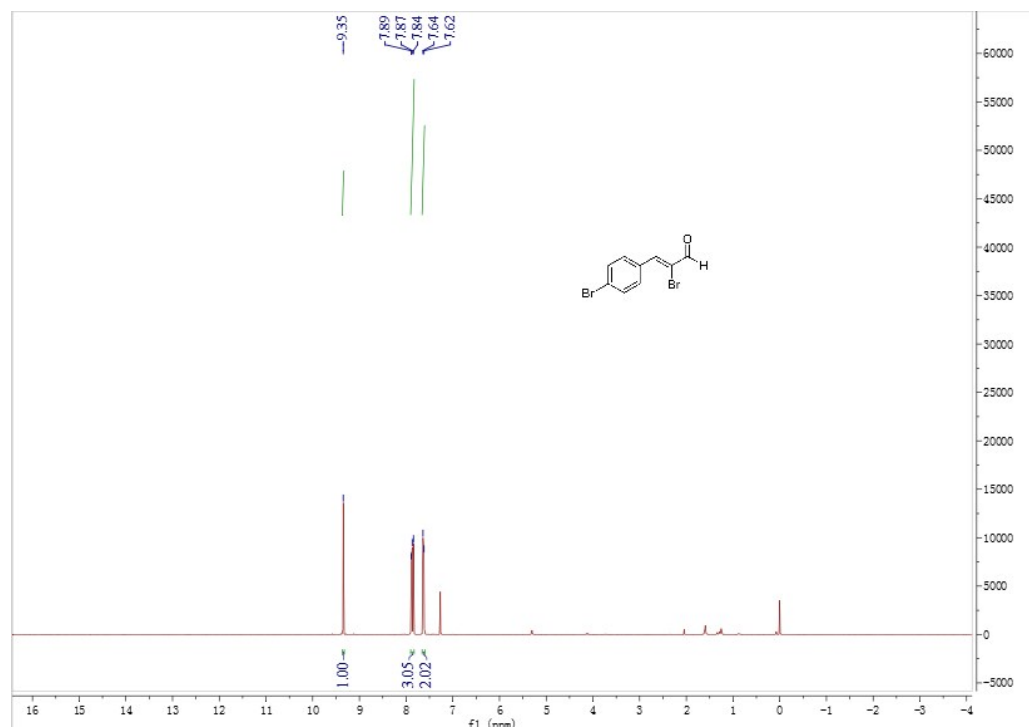
4.3 Gram-scale reaction of 3a.

To a solution of **2a** (2.10 g, 10 mmol) in 40 mL DMF, cesium carbonate (2.43 g, 0.75 mmol) was added. Then **1a** (0.83 g, 5 mmol) was added into the solution. The mixture was stirred for 12 h at room temperature. After completion of the reaction monitored by TLC, water (40 mL) was added. The solvent was extracted with ethyl acetate (100 mL) for three times. After washed with brine and dried over Na_2SO_4 , the combined organic phases was vacuumed under the reduced pressure and the residue was purified by flash chromatography to give 1.17 g **3a** in 80% yield.

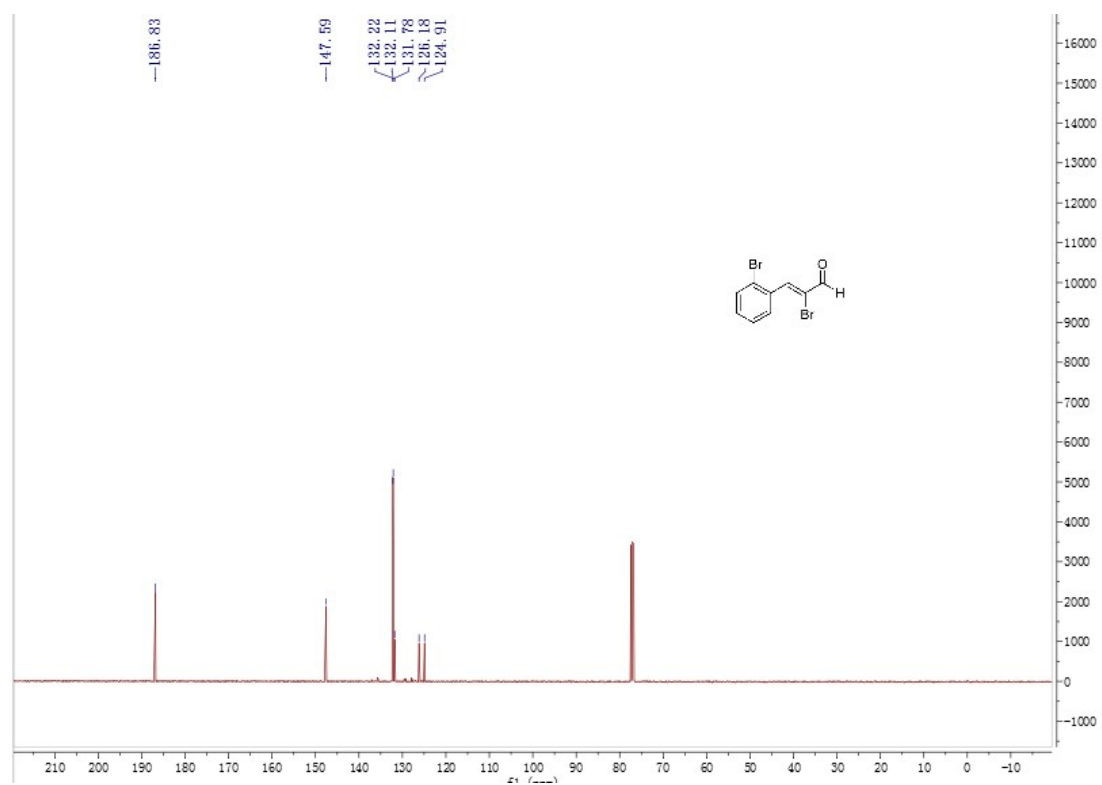
5. References

1. K. Mal, A. Sharma, P. R. Maulik and I. Das, *Chem. Eur. J.* 2014, **19**, 662.
2. H. Li, X. Li, Y. Yu, J. Li, Y. Liu, H. Li and W. Wang, *Org. Lett.*, 2017, **19**, 2010.

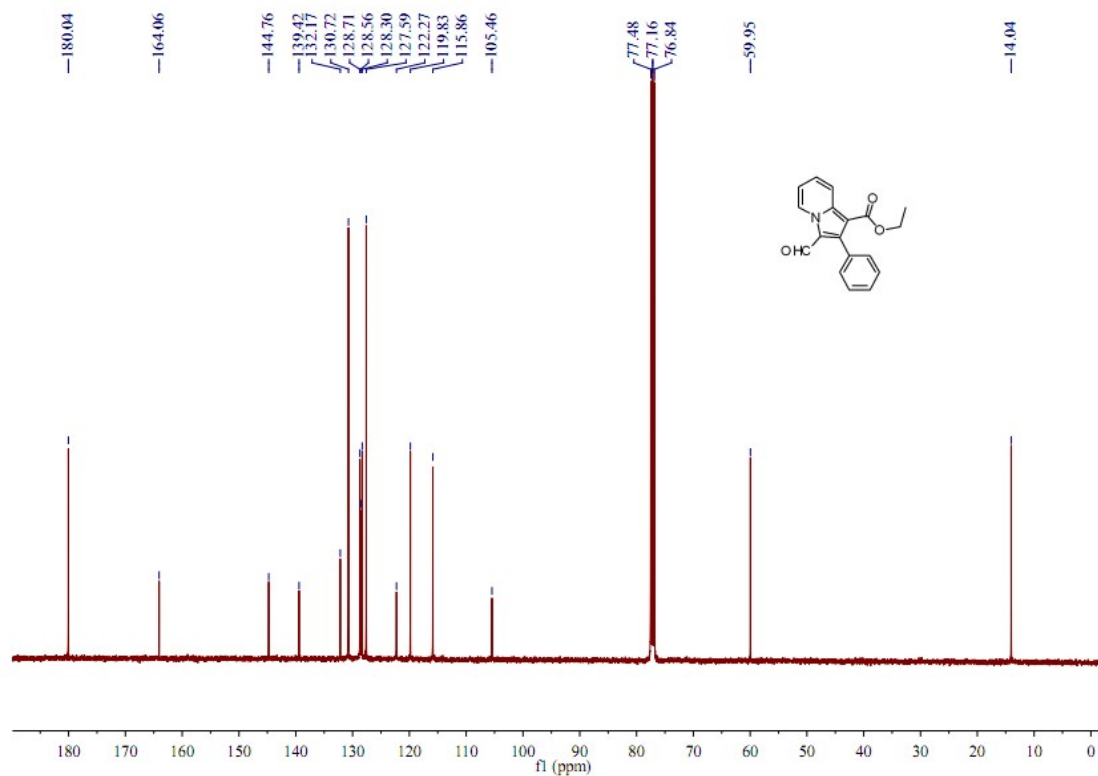
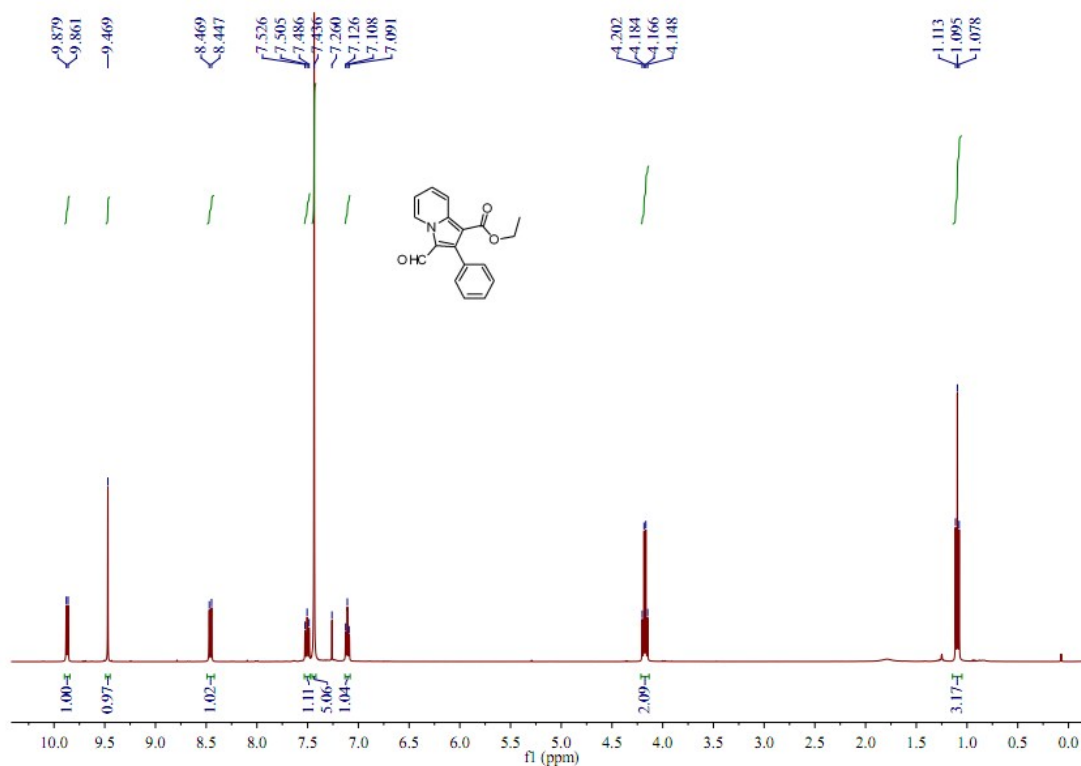
6. ^1H and ^{13}C -NMR Spectra of the Substrates and Products (*Z*)-2-Bromo-3-(4-bromophenyl)acrylaldehyde (2d)



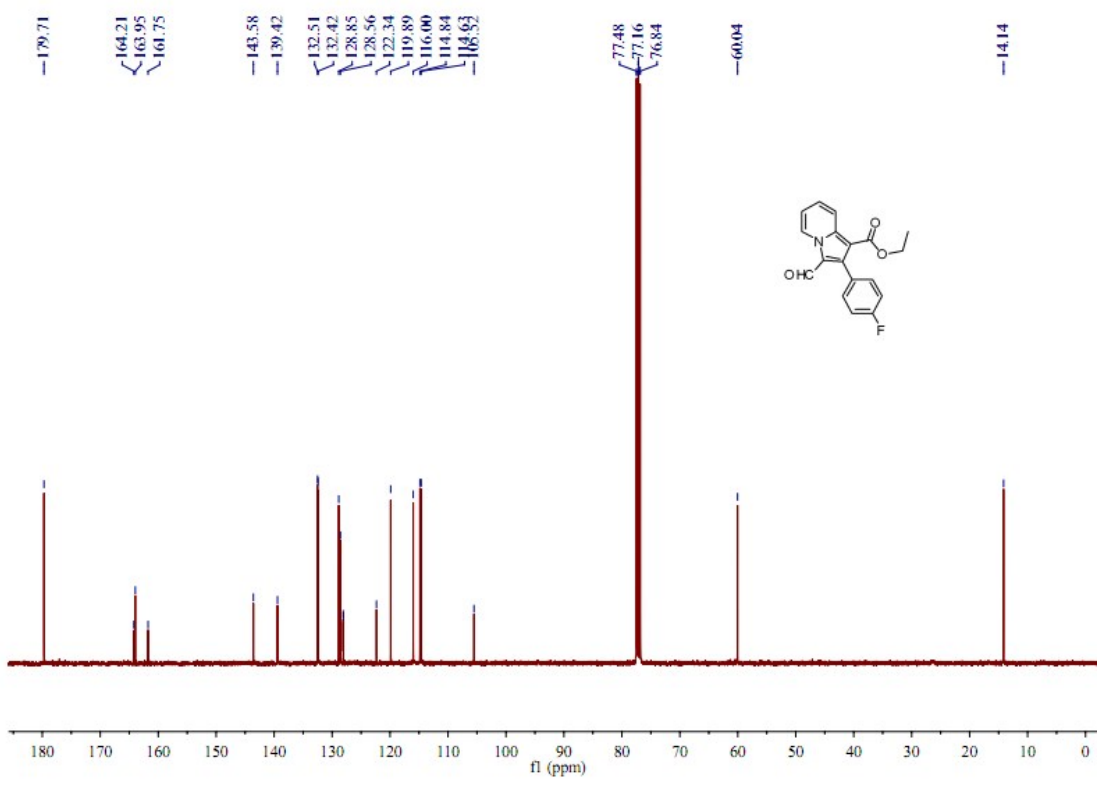
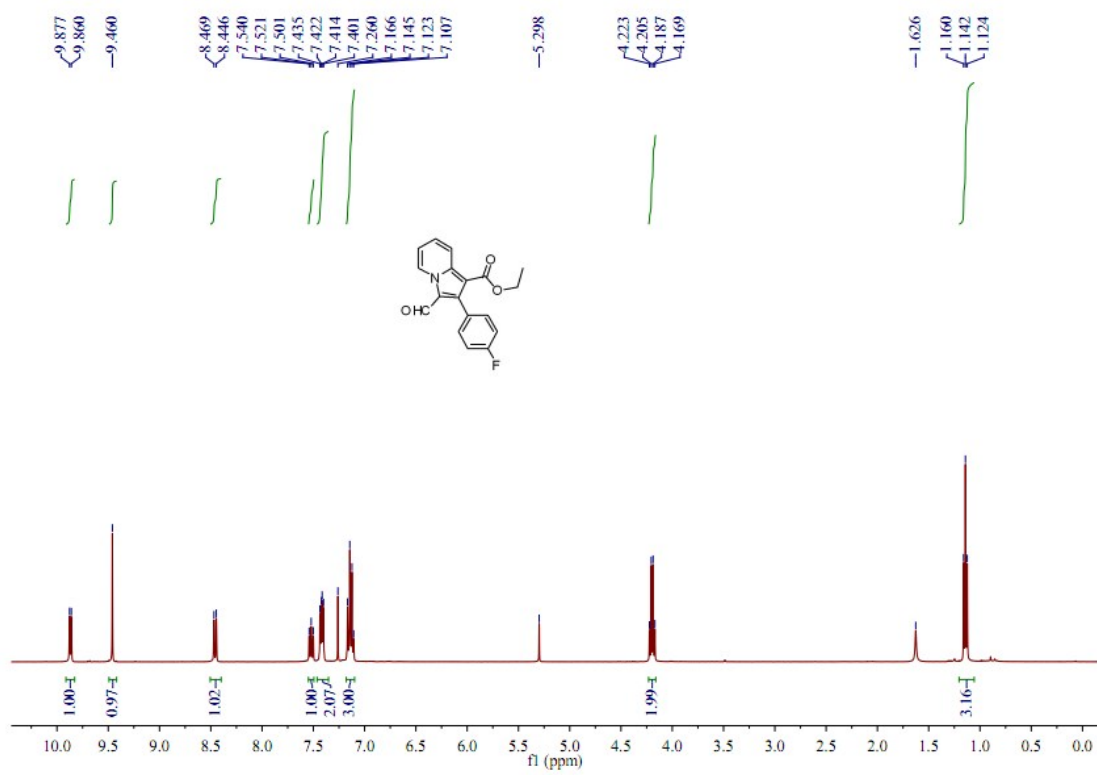
(Z)-2-Bromo-3-(2-bromophenyl)acrylaldehyde (2j)



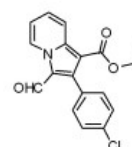
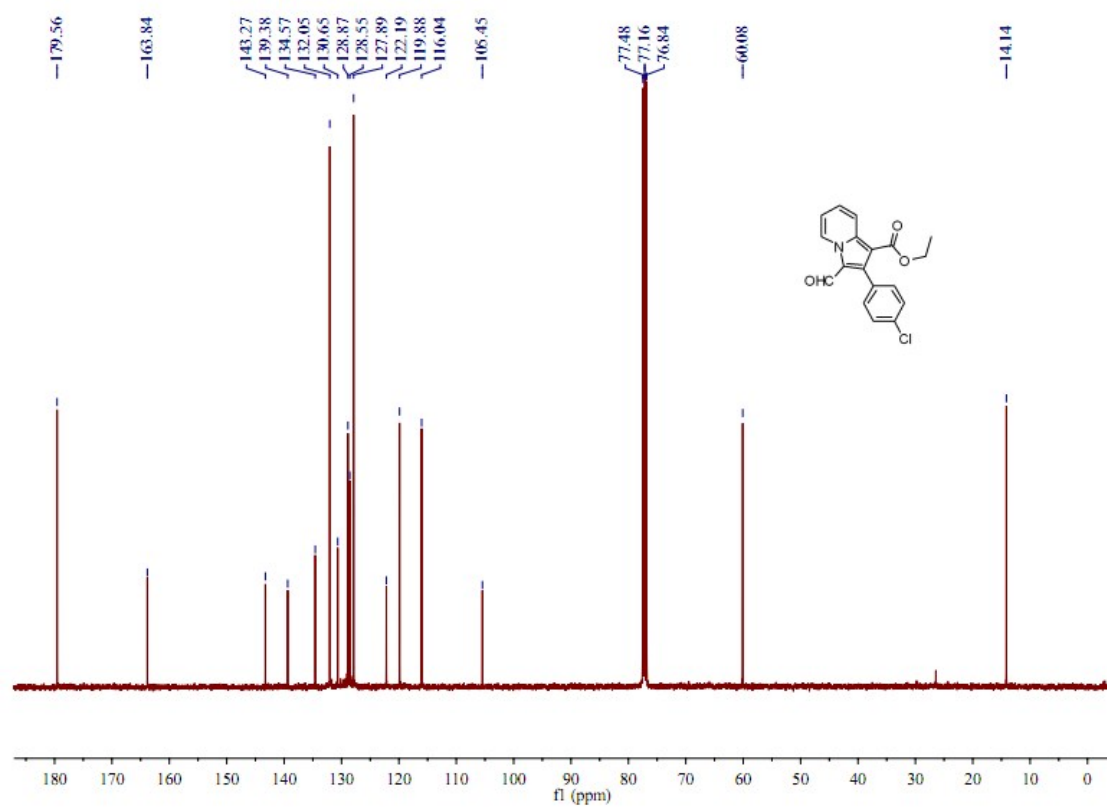
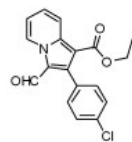
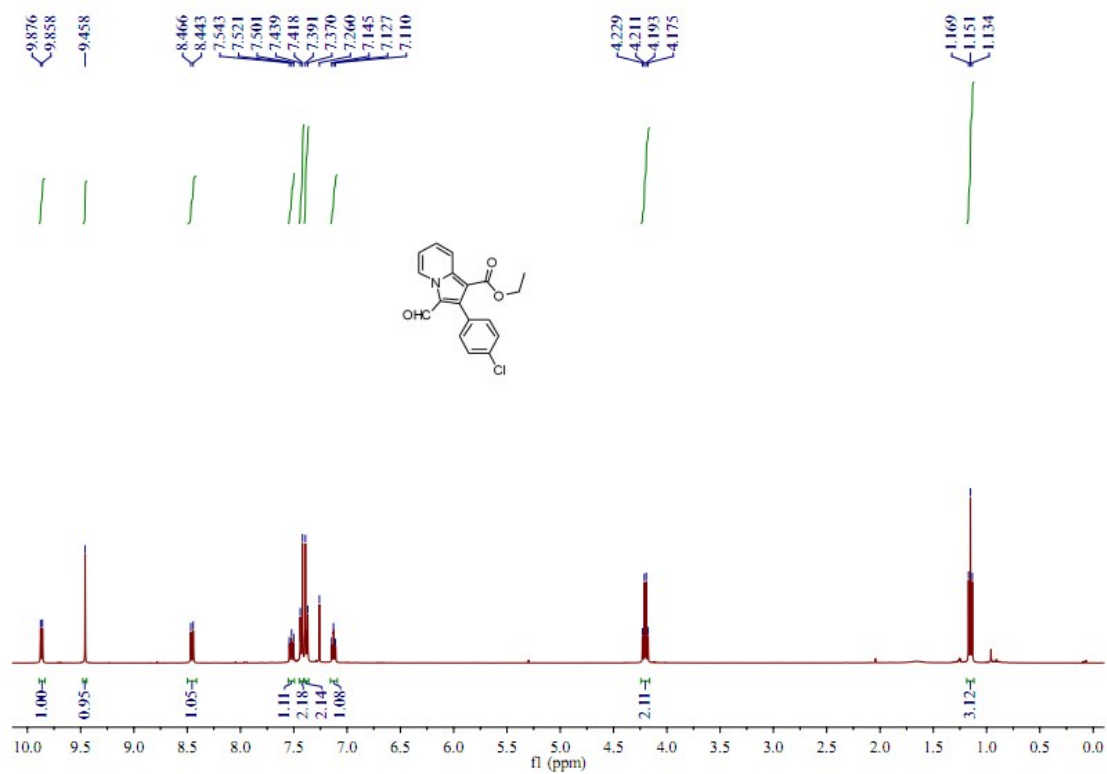
Ethyl 3-formyl-2-phenylindolizine-1-carboxylate (3a)



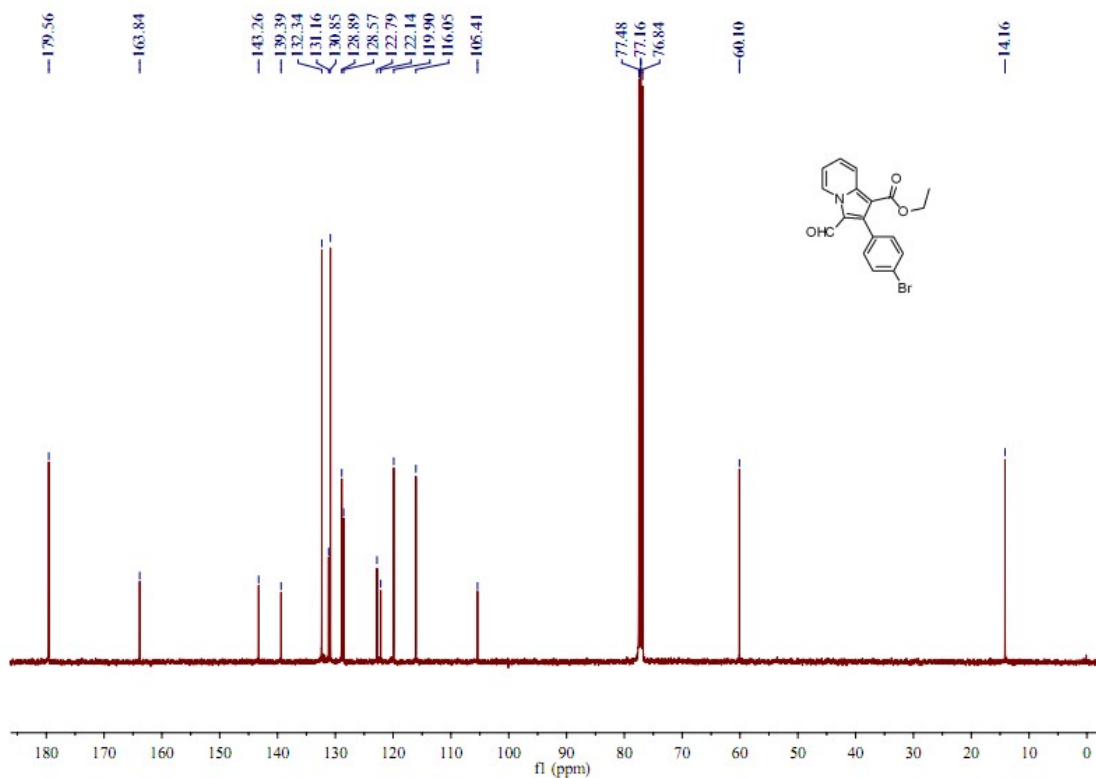
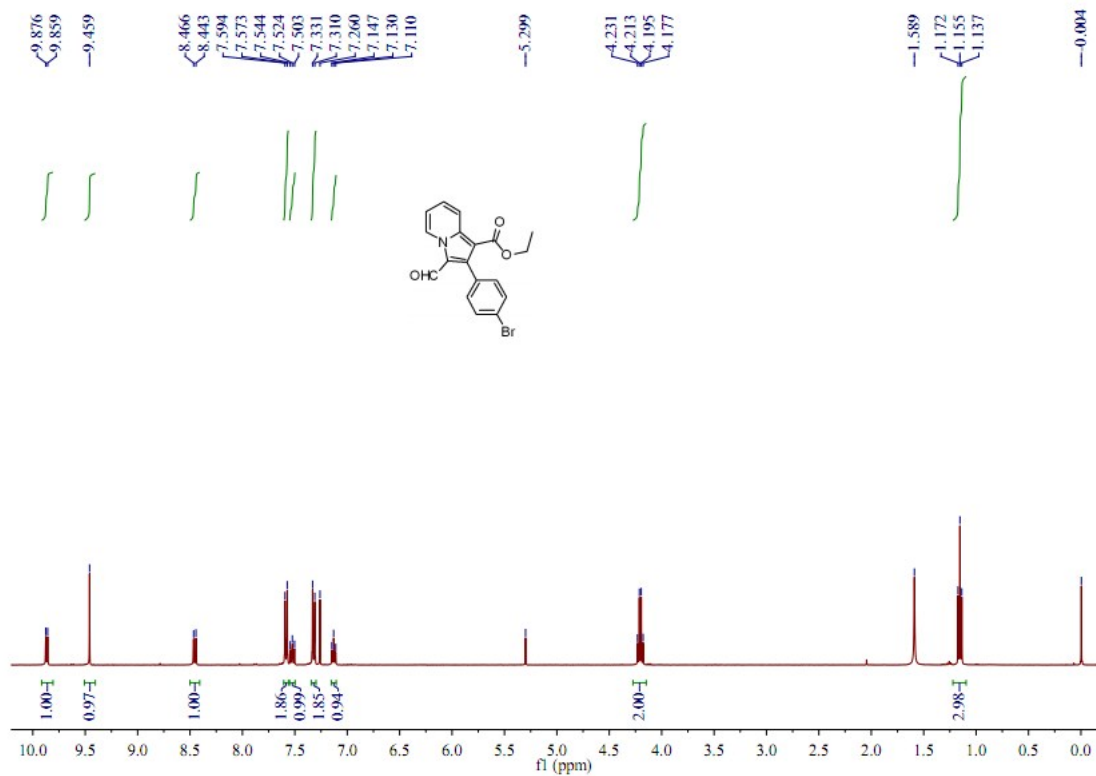
Ethyl 2-(4-Fluorophenyl)-3-formylindolizine-1-carboxylate (3b)



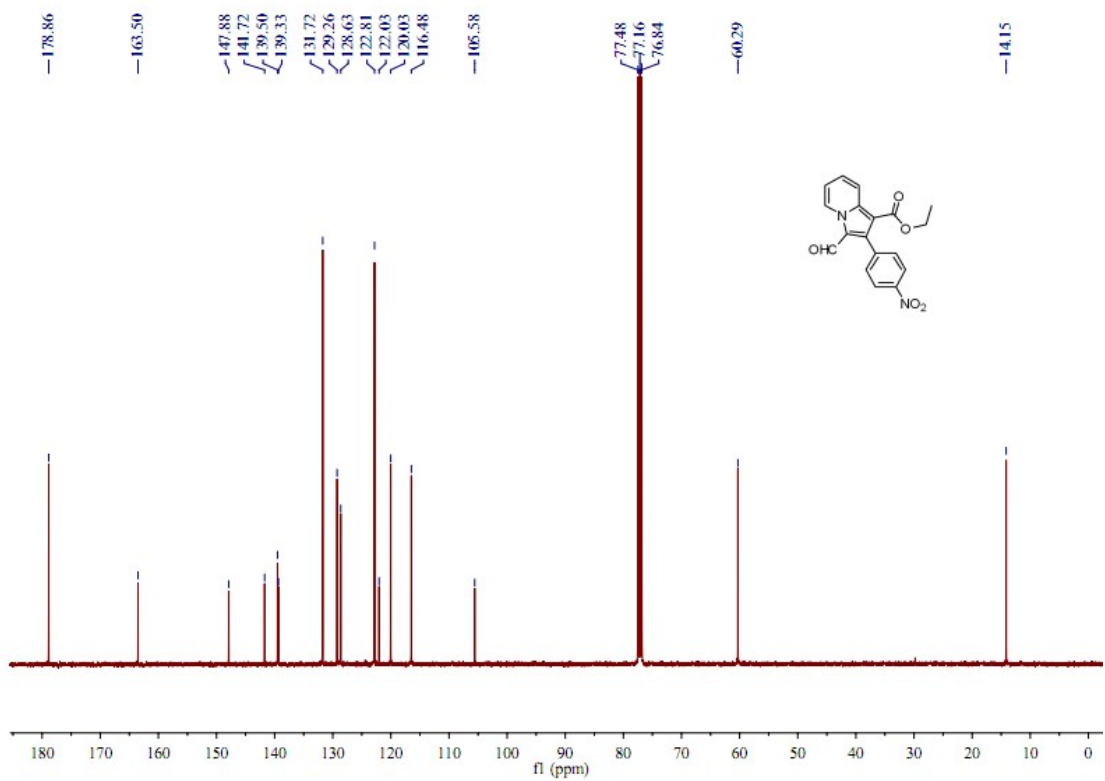
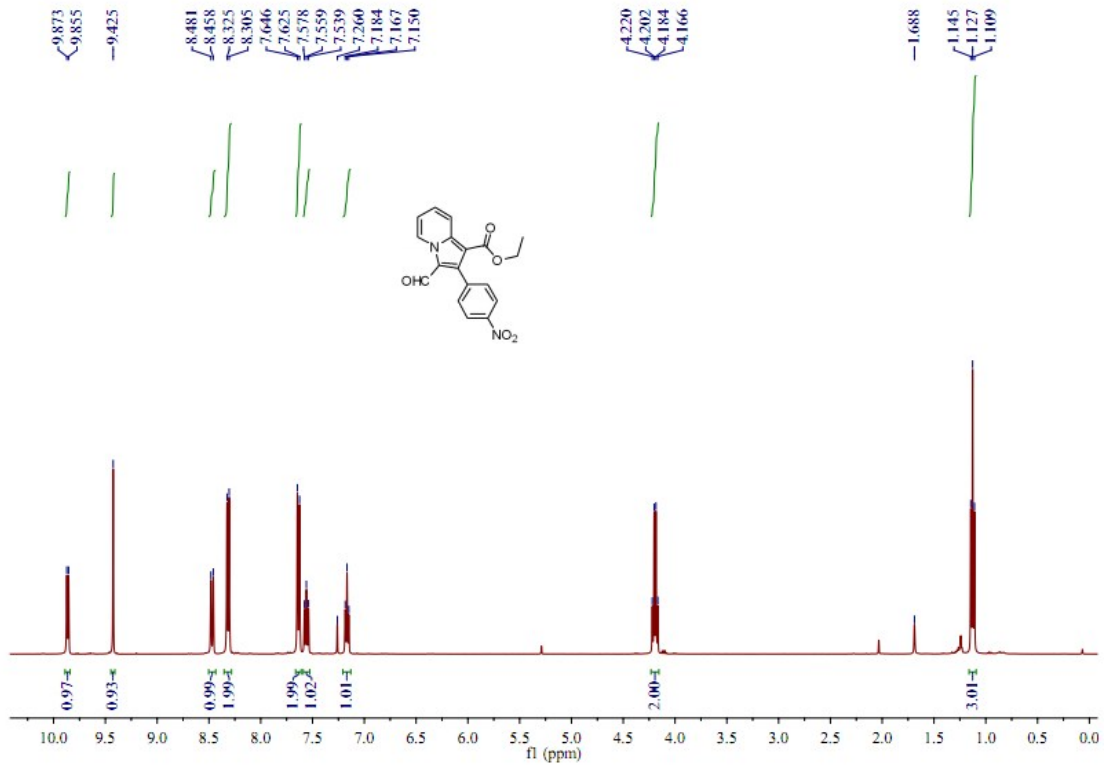
Ethyl 2-(4-Chlorophenyl)-3-formylindolizine-1-carboxylate (3c)



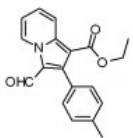
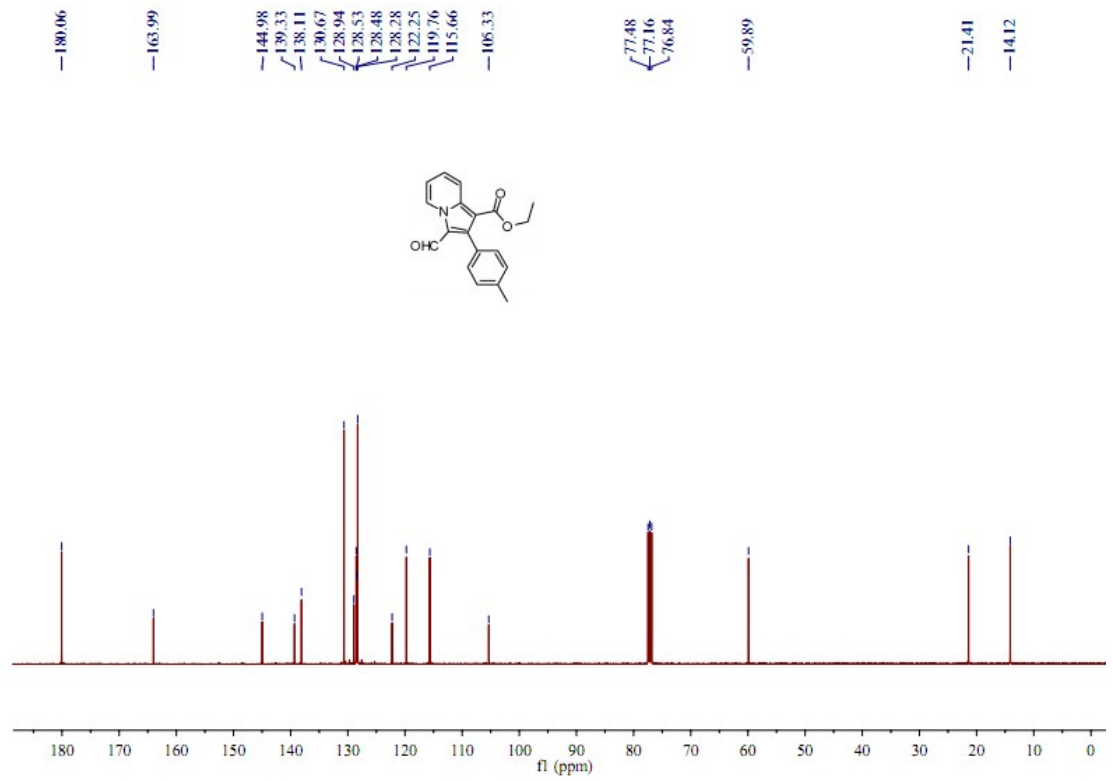
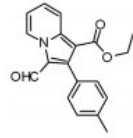
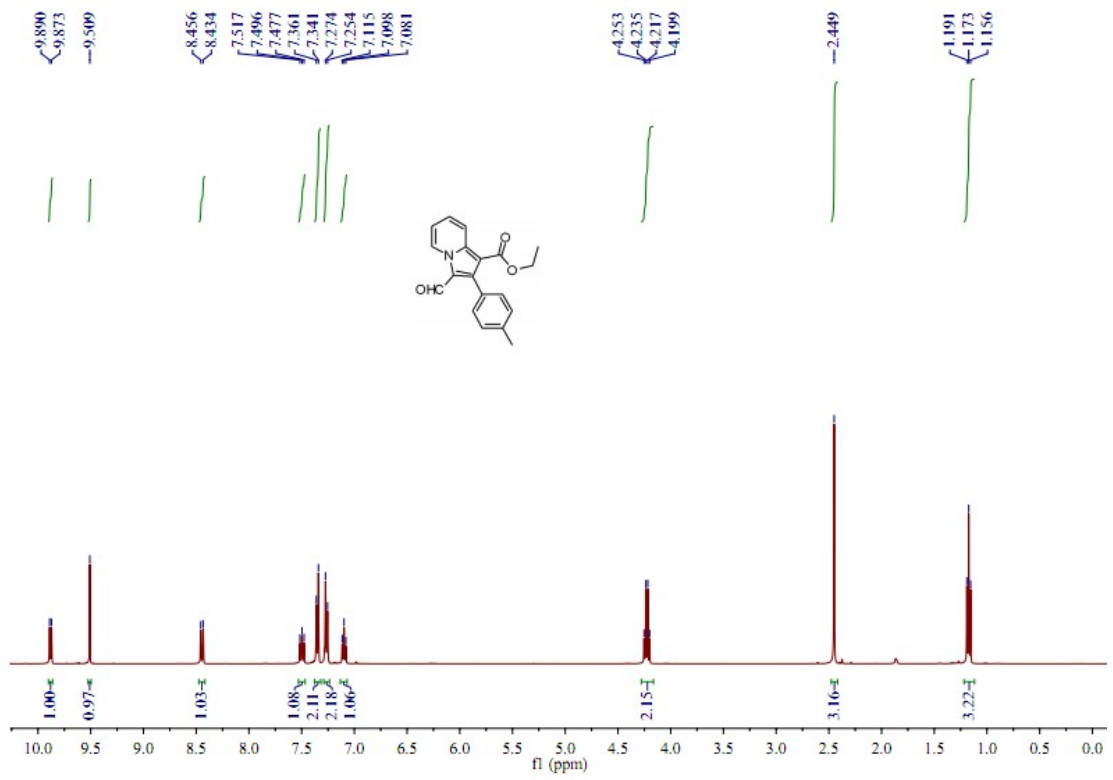
Ethyl 2-(4-Bromophenyl)-3-formylindolizine-1-carboxylate (3d)



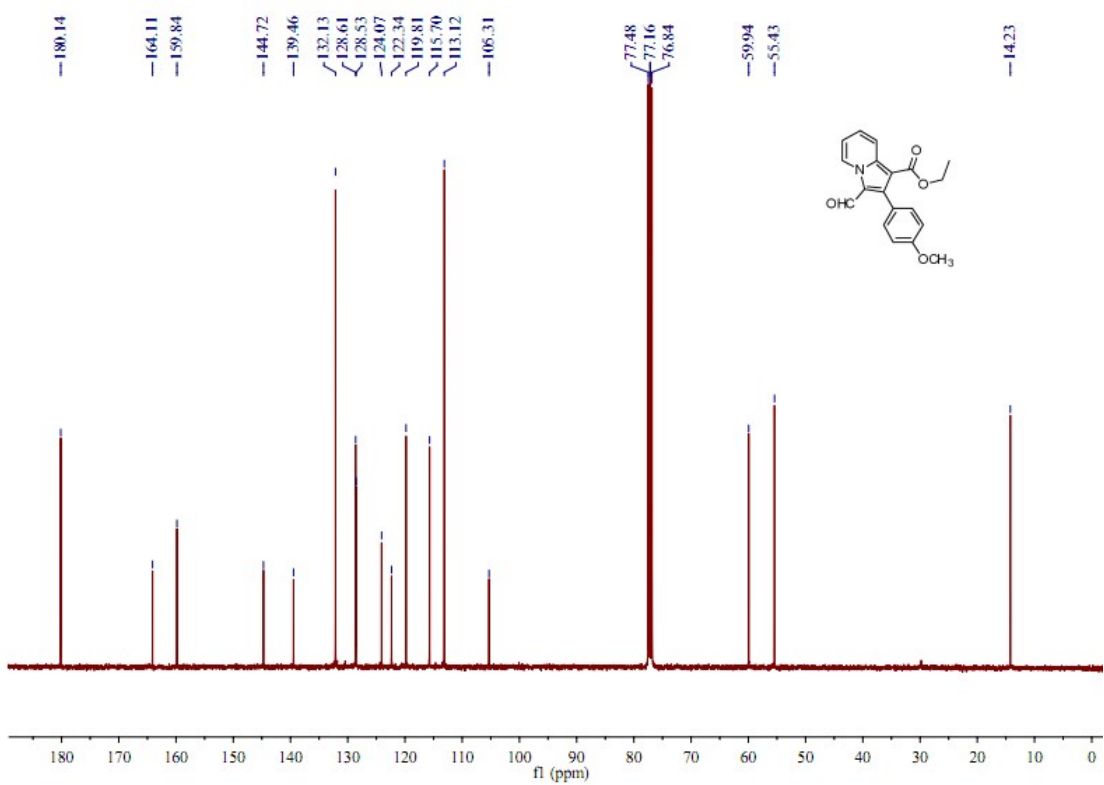
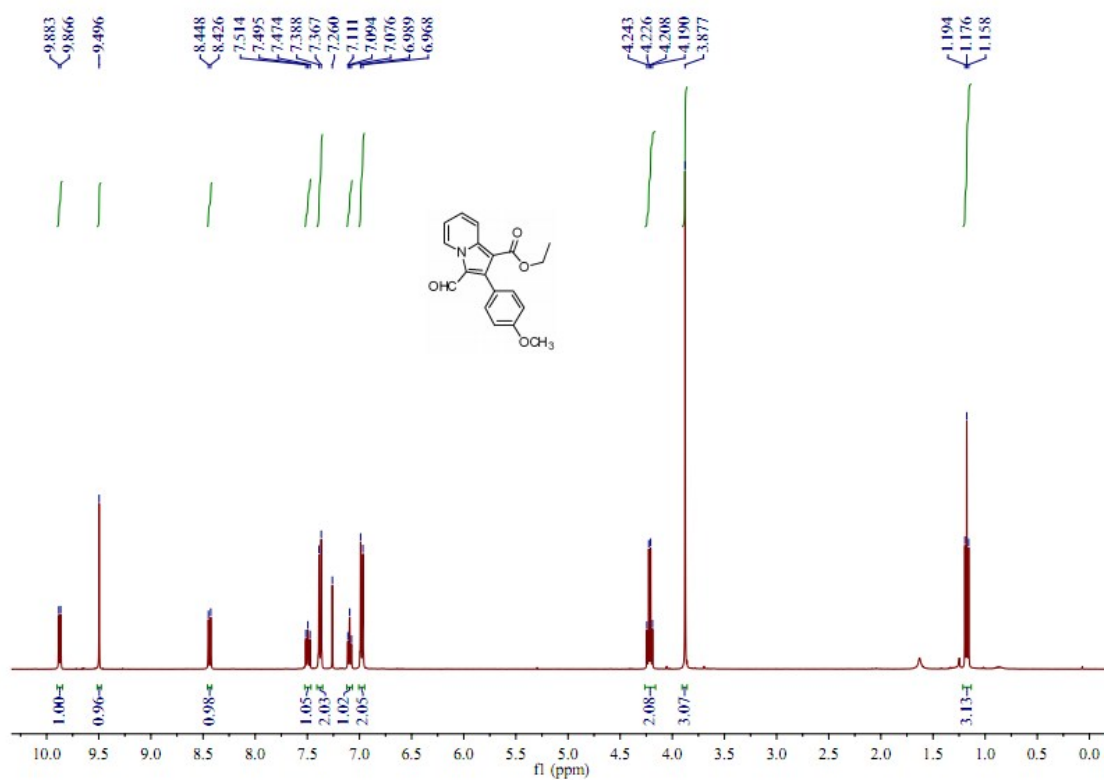
Ethyl 3-formyl-2-(4-Nitrophenyl)indolizine-1-carboxylate (3e)



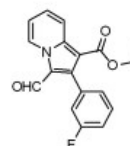
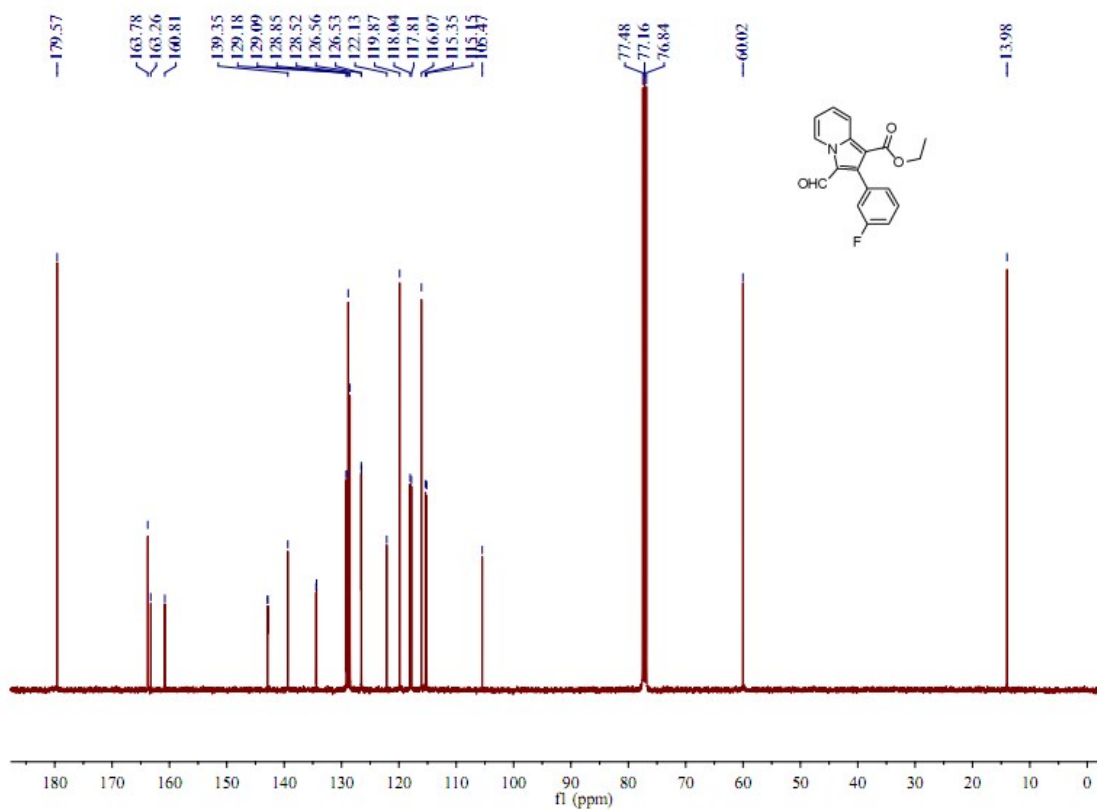
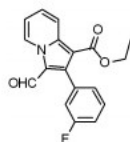
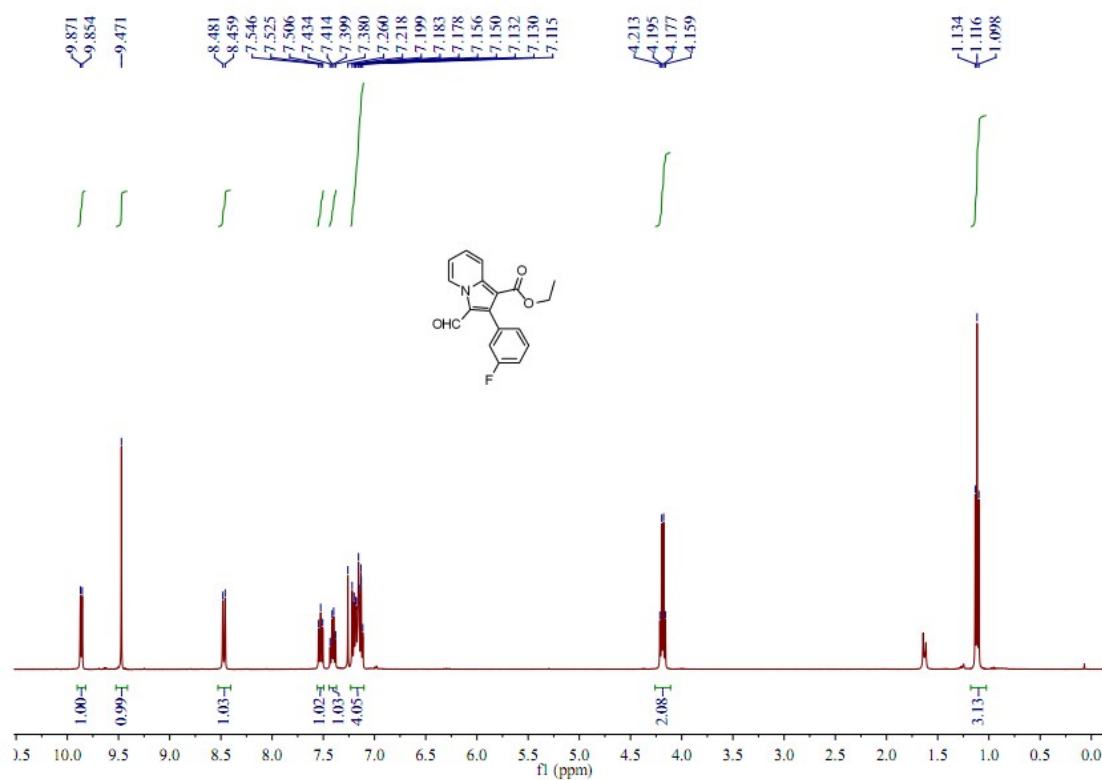
Ethyl 3-formyl-2-(p-tolyl)indolizine-1-carboxylate (3f)



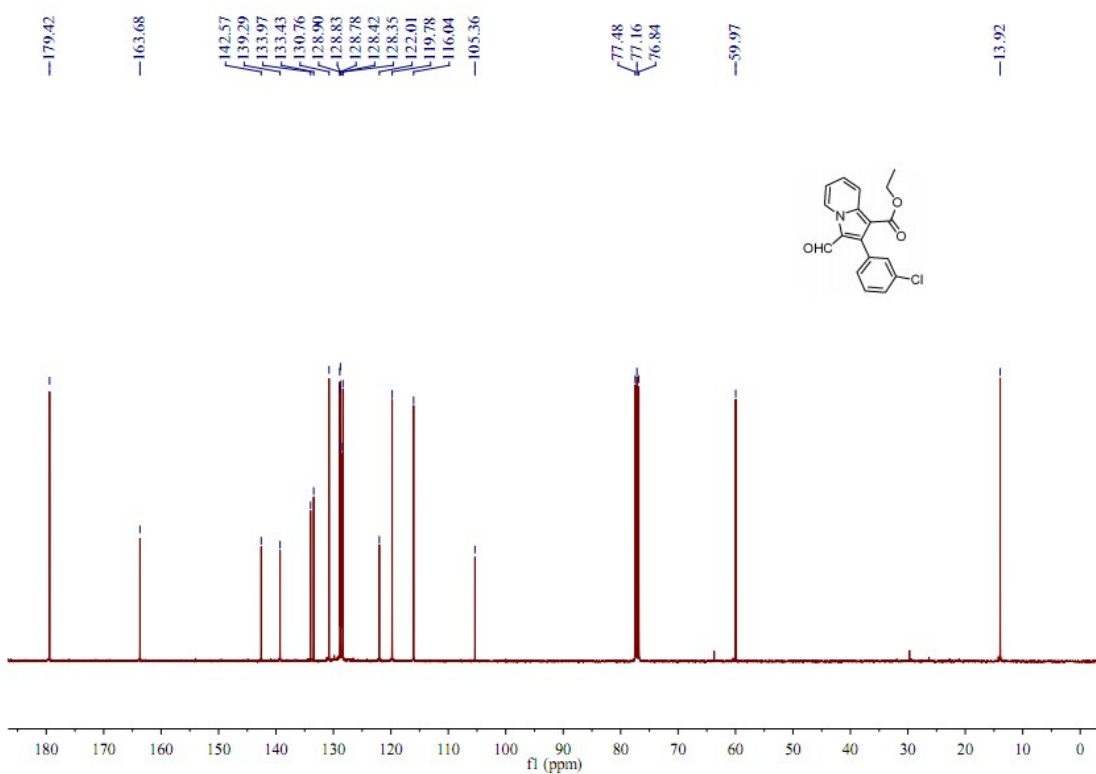
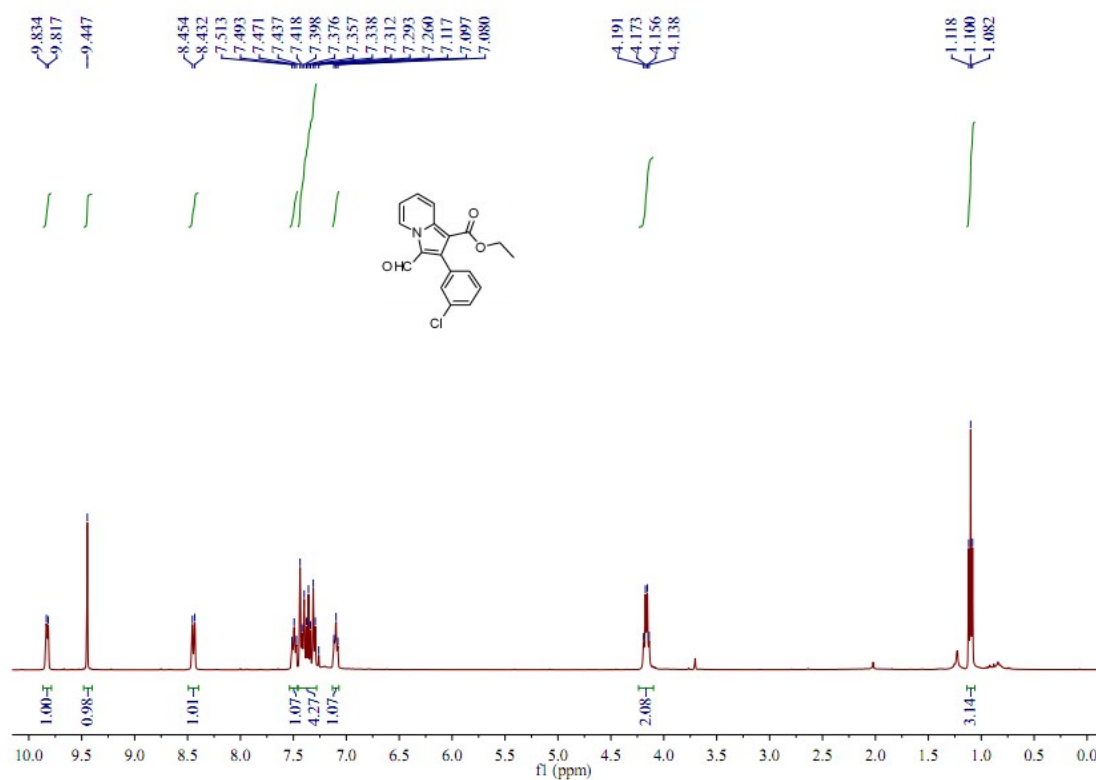
Ethyl 3-formyl-2-(4-Methoxyphenyl)indolizine-1-carboxylate (3g)



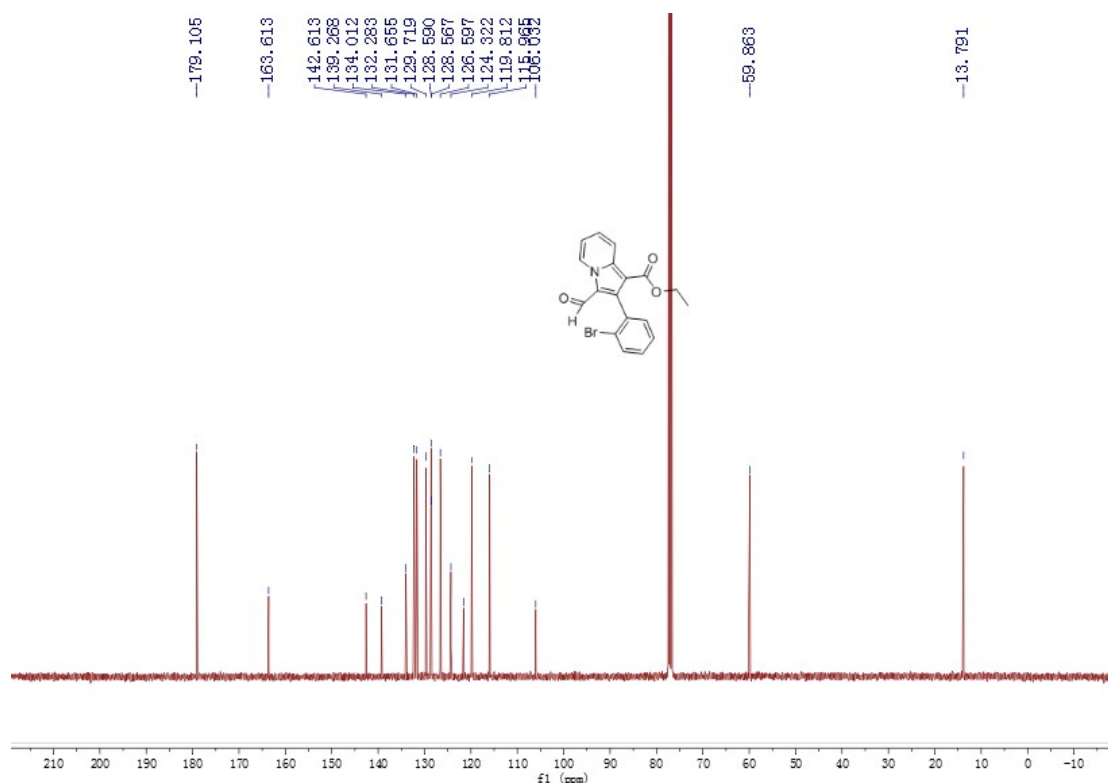
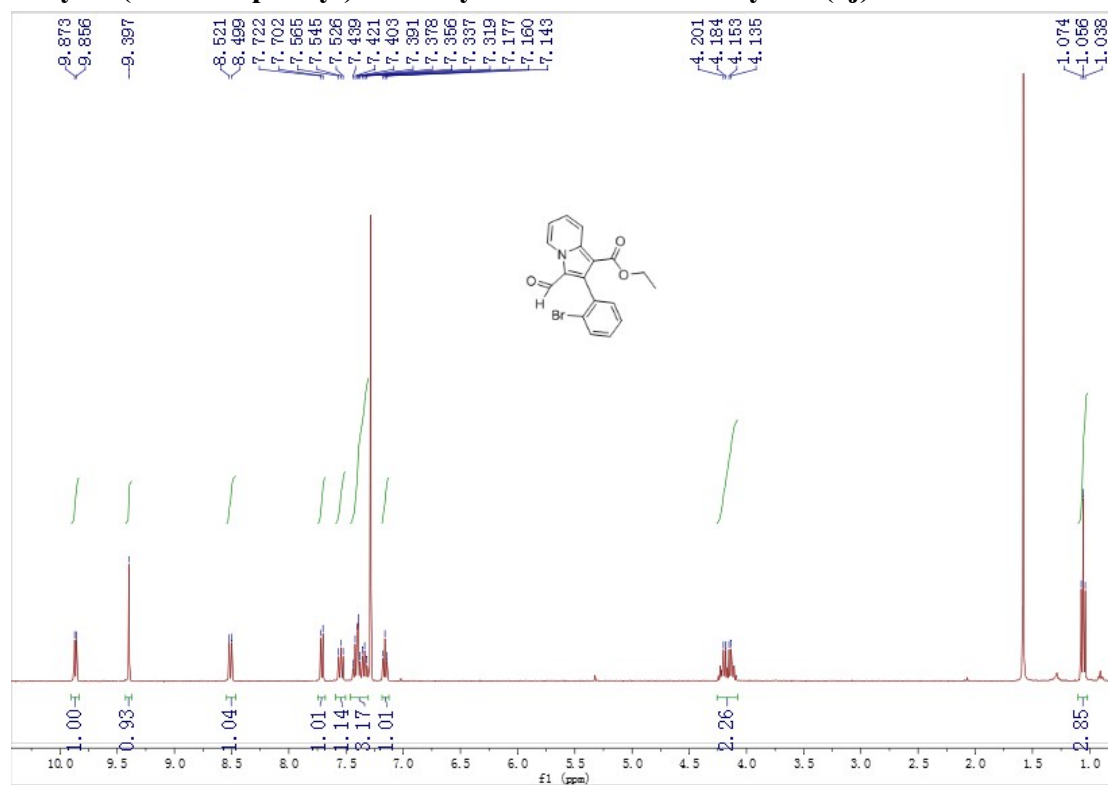
Ethyl 2-(3-Fluorophenyl)-3-formylindolizine-1-carboxylate (3h)



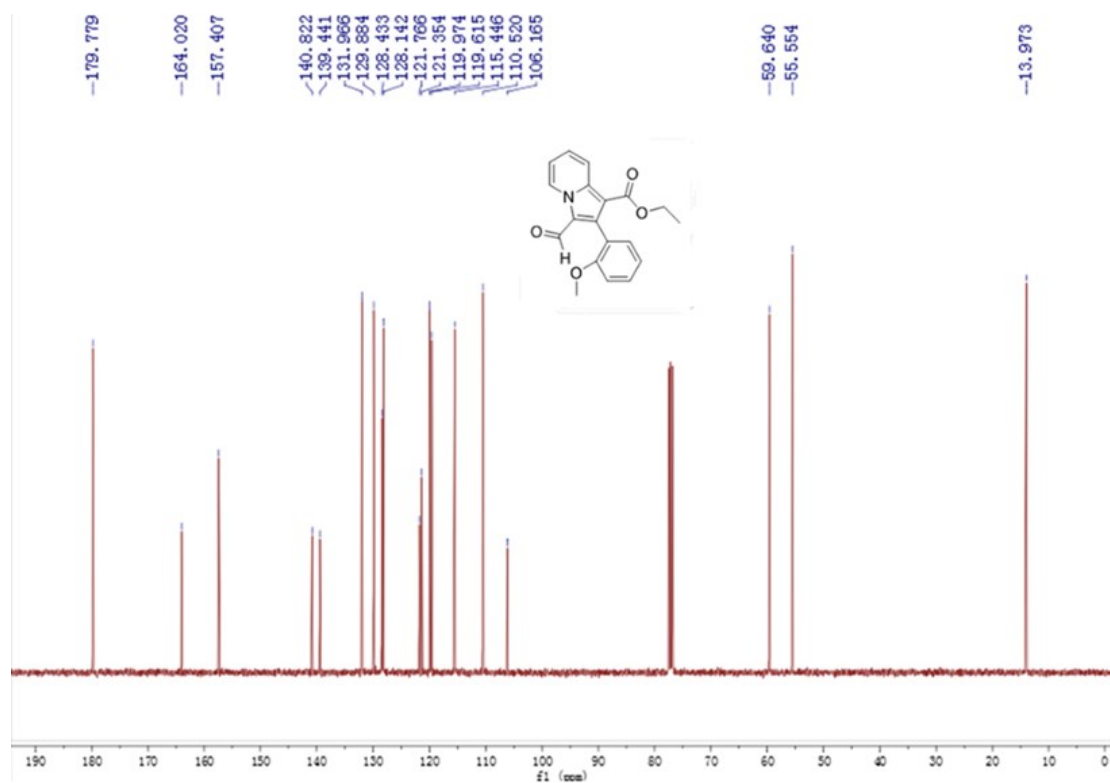
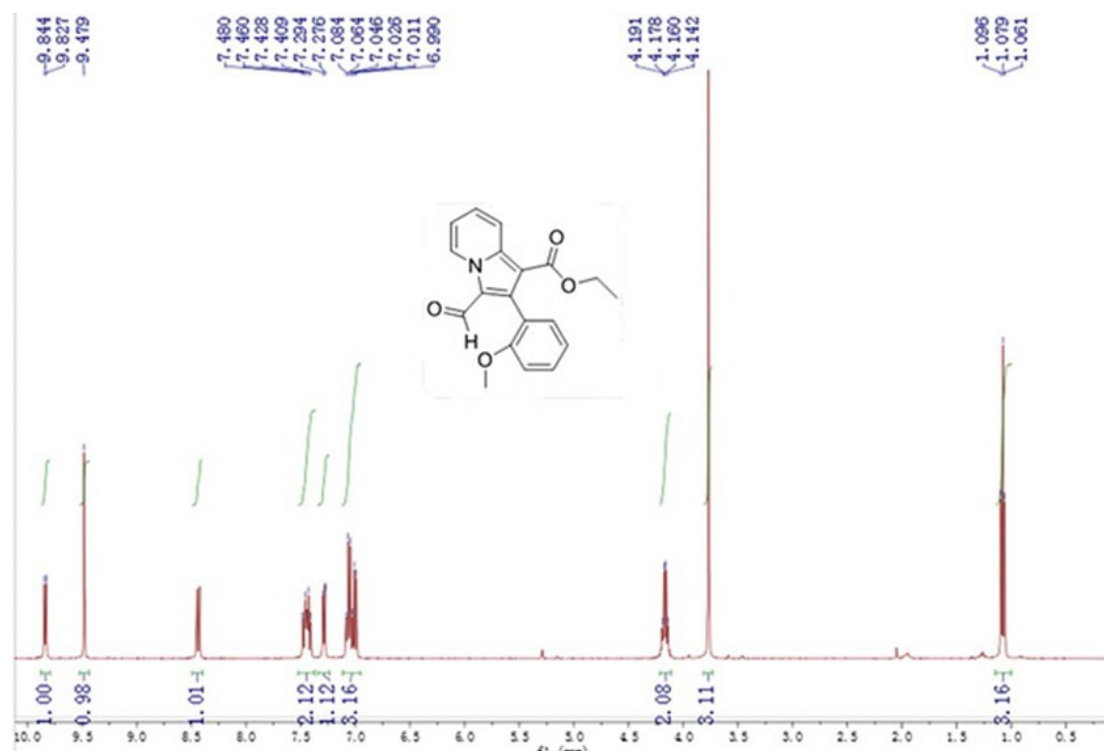
Ethyl 2-(3-Chlorophenyl)-3-formylindolizine-1-carboxylate (3i)



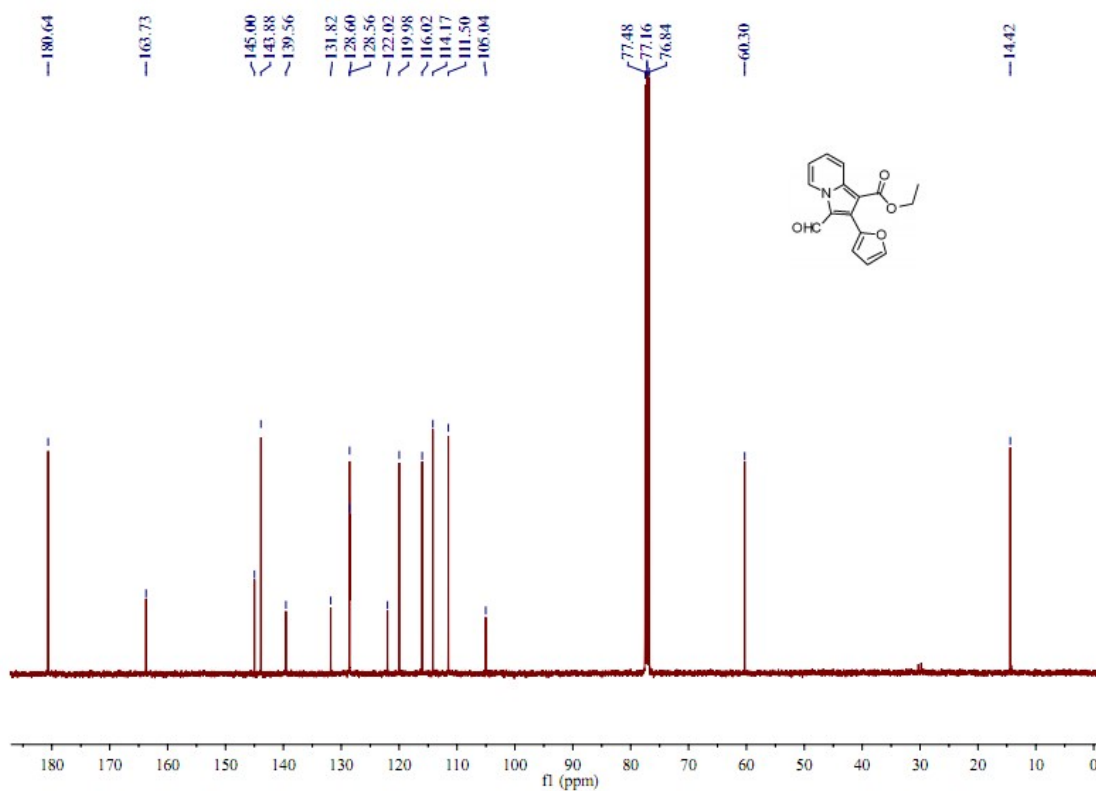
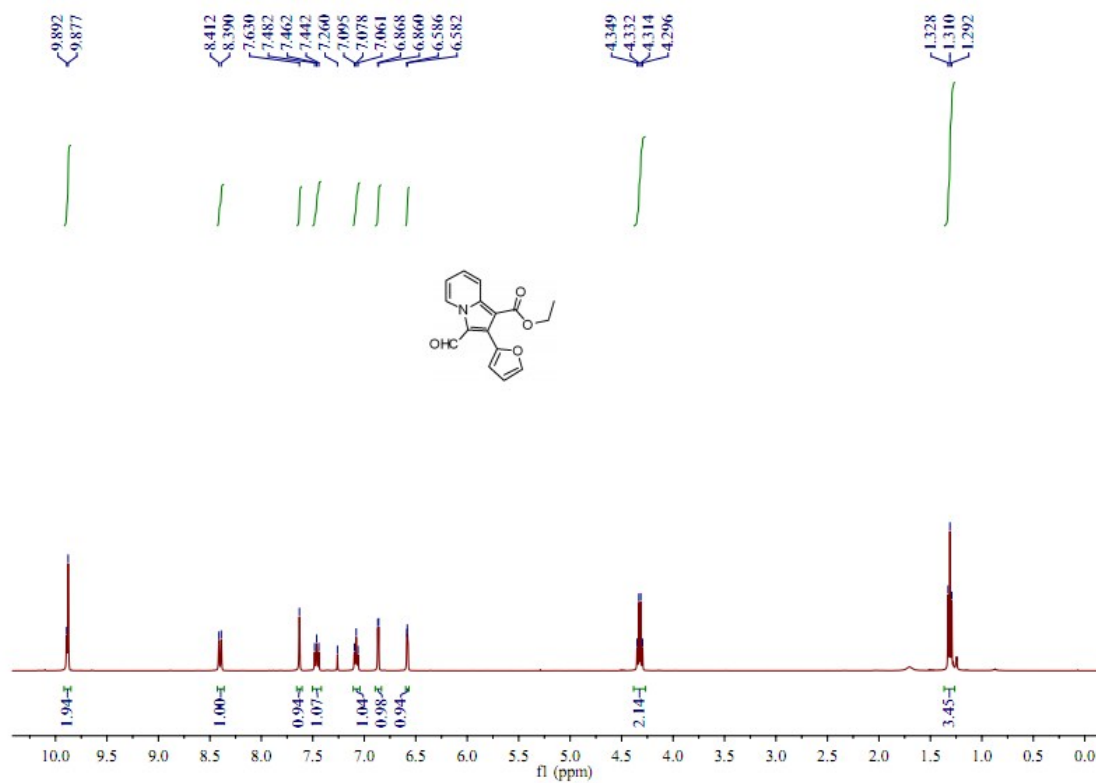
Ethyl 2-(2-Bromophenyl)-3-formylindolizine-1-carboxylate (3j)



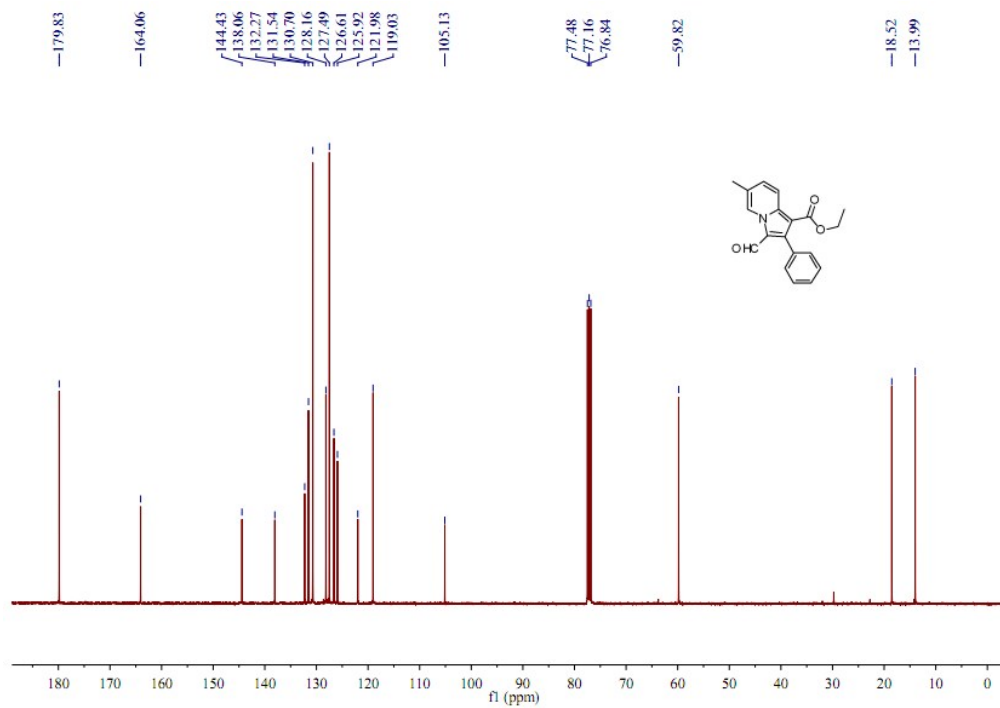
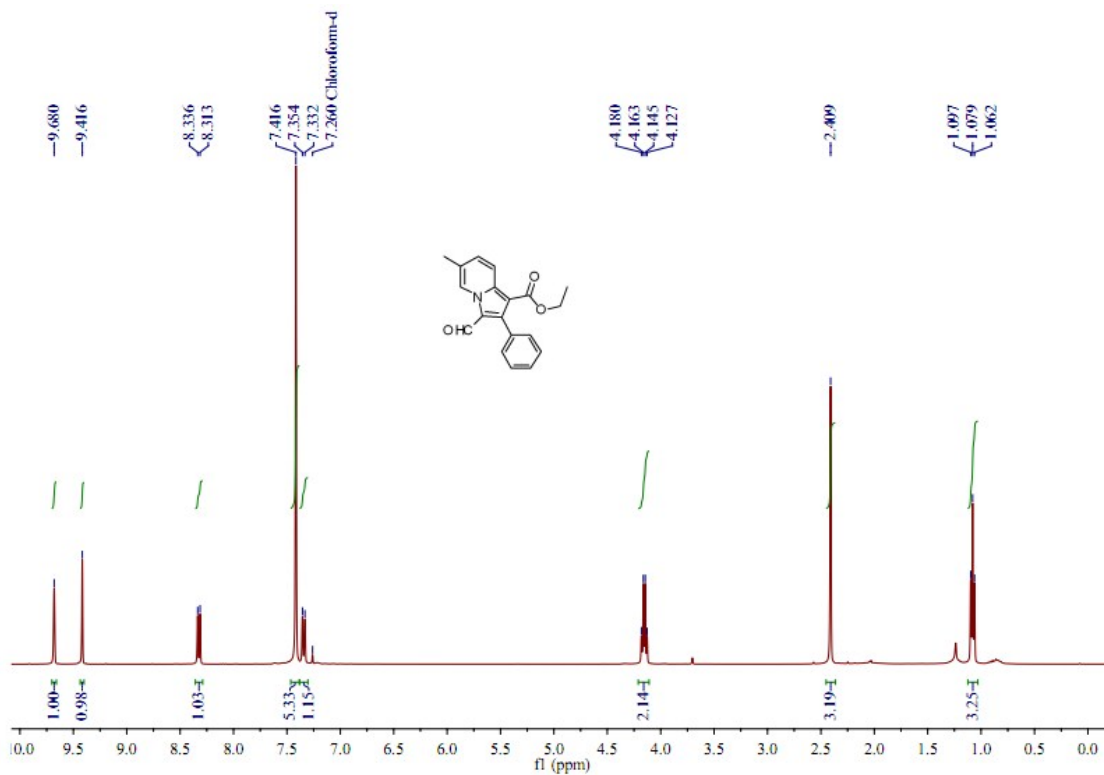
Ethyl 3-formyl-2-(2-Methoxyphenyl)indolizine-1-carboxylate (3k)



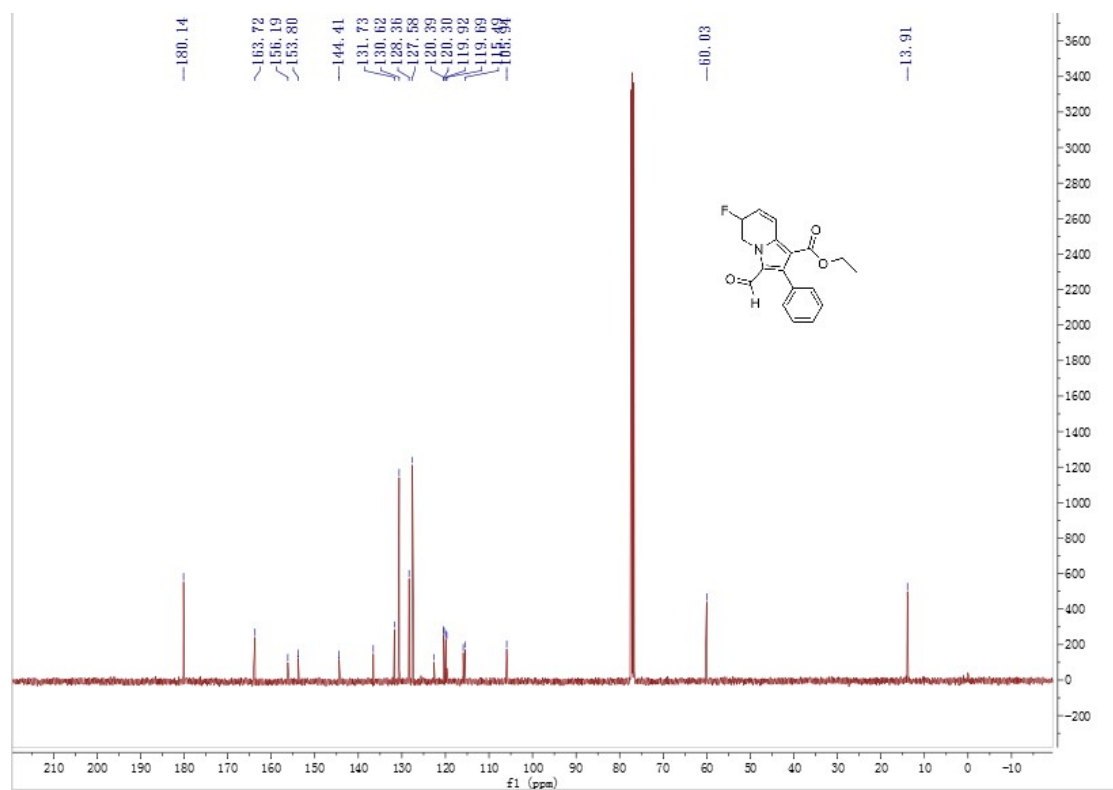
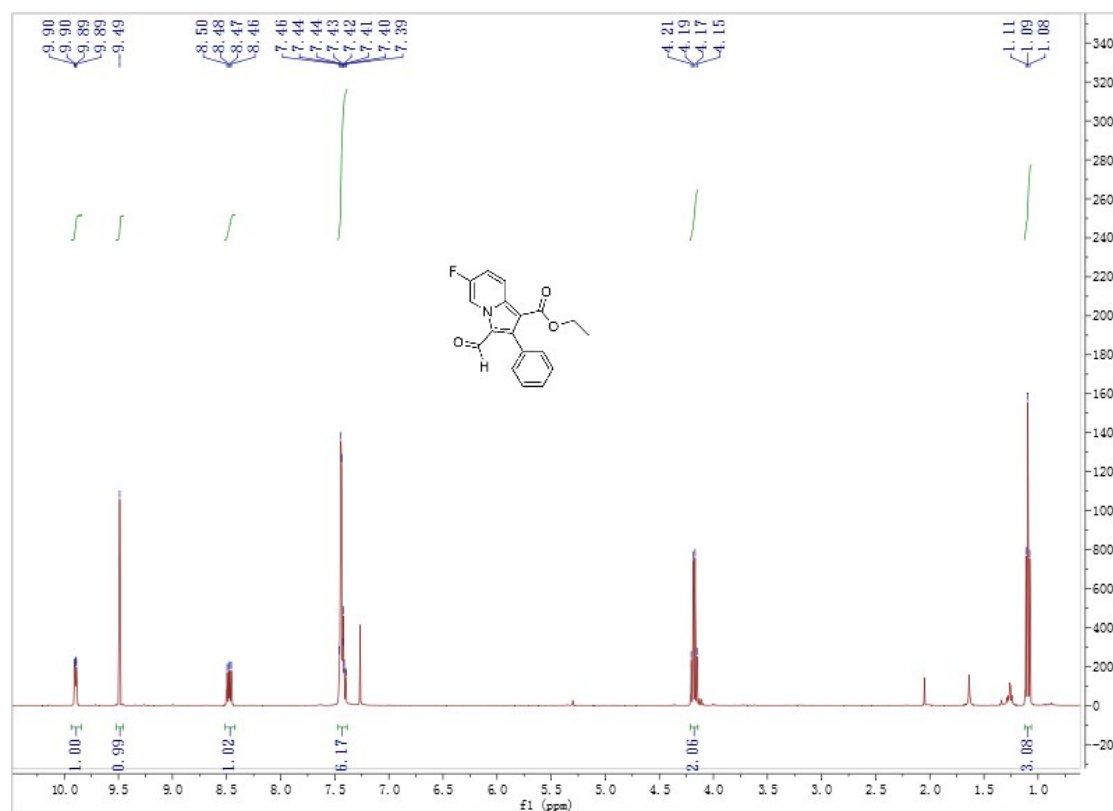
Ethyl 3-formyl-2-(Furan-2-yl)indolizine-1-carboxylate (3l)



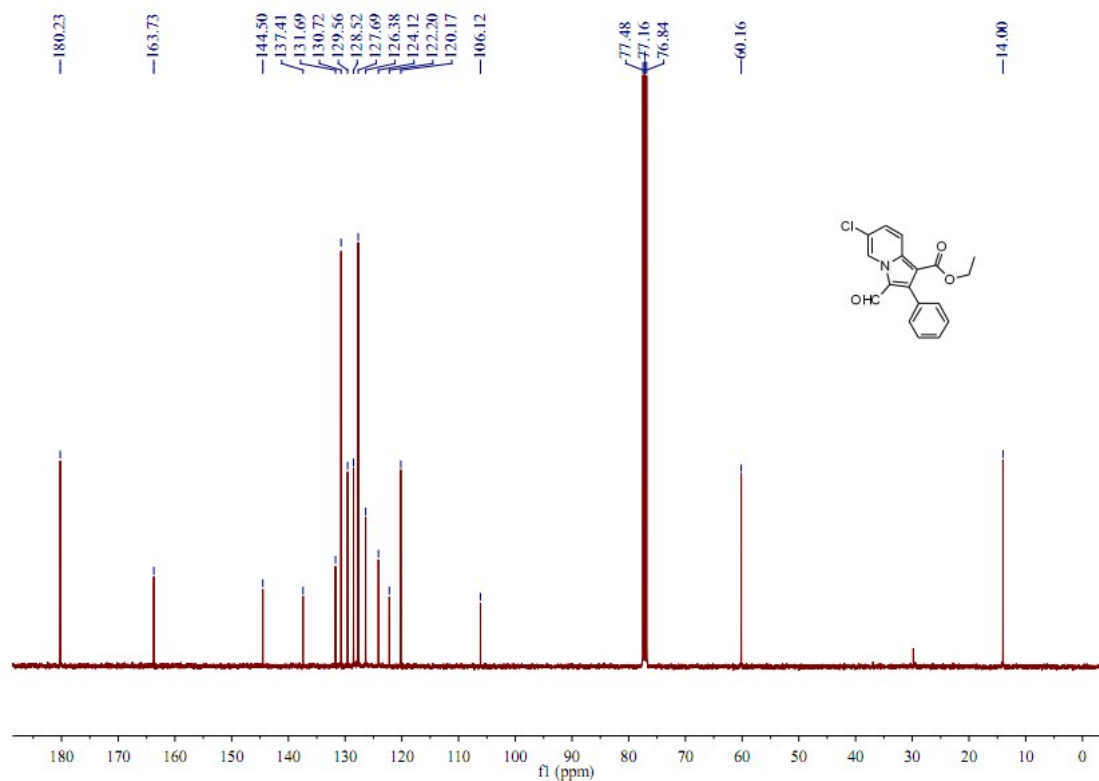
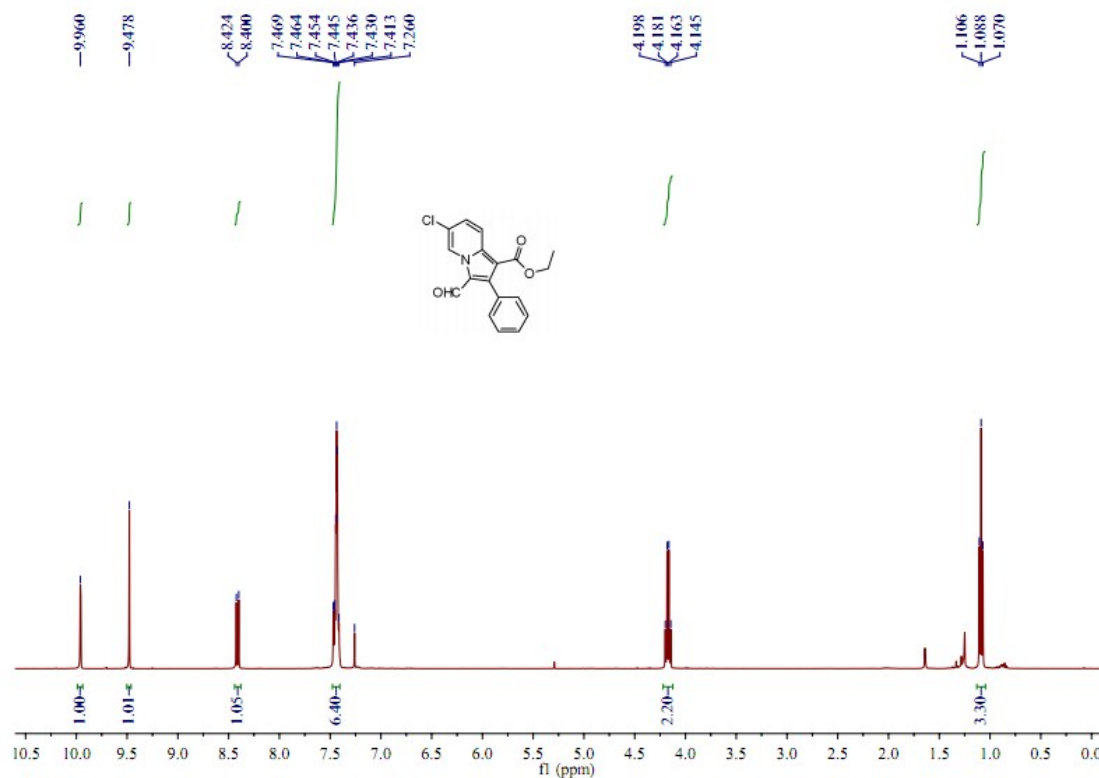
Ethyl 3-formyl-6-Methyl-2-phenylindolizine-1-carboxylate (3m)



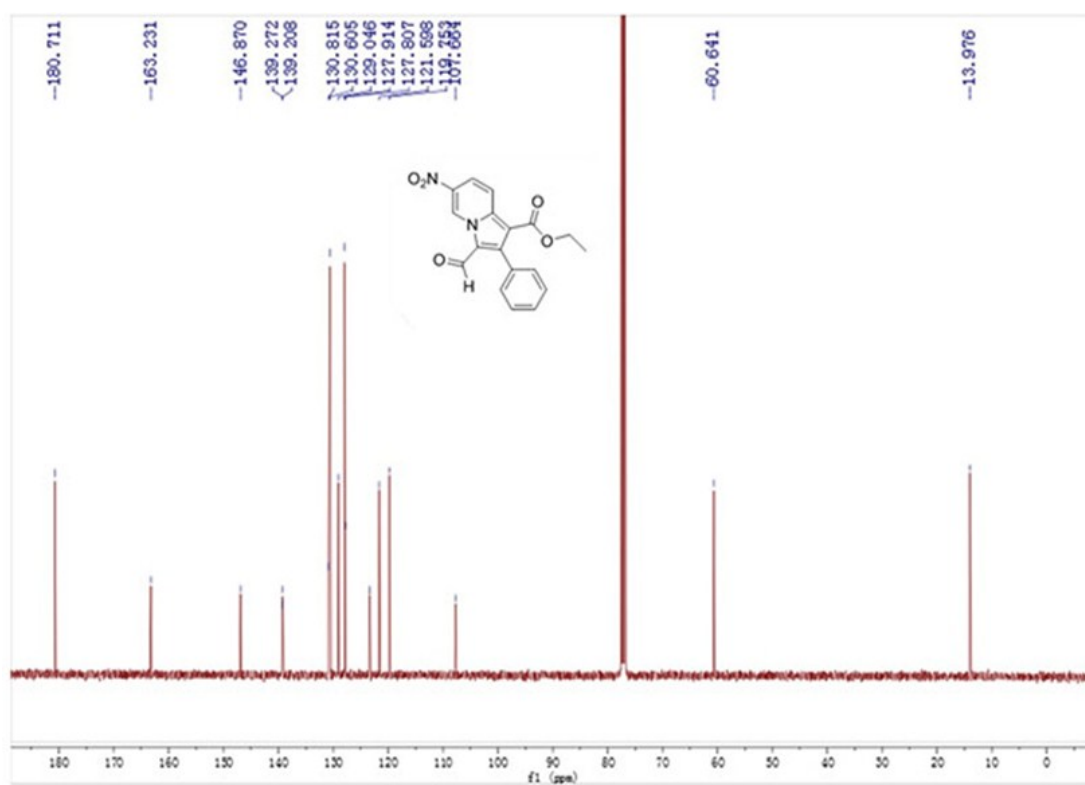
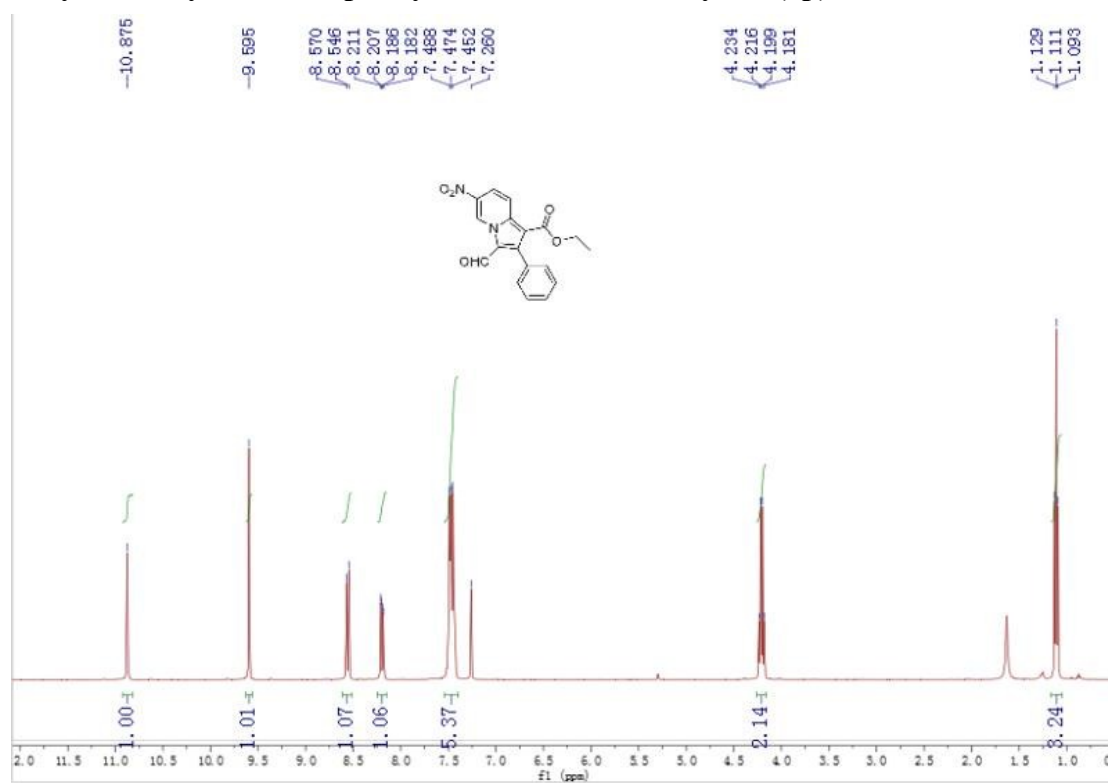
Ethyl 6-fluoro-3-formyl-2-phenylindolizine-1-carboxylate(3n)



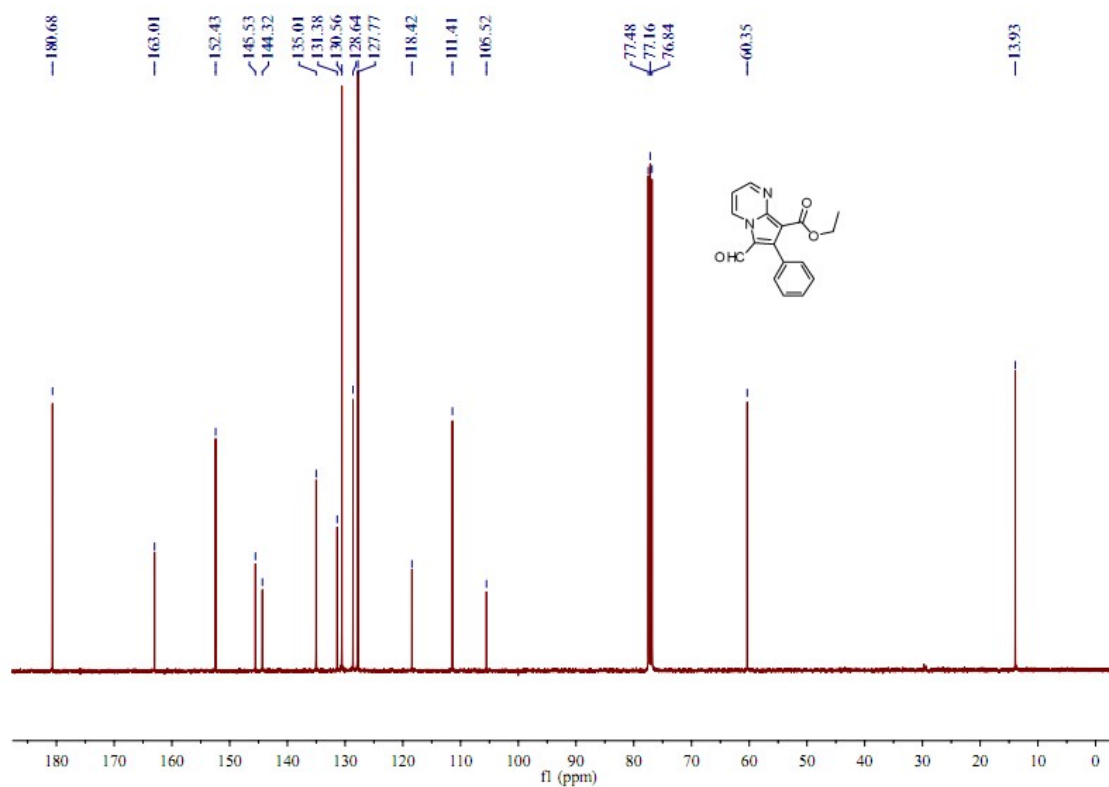
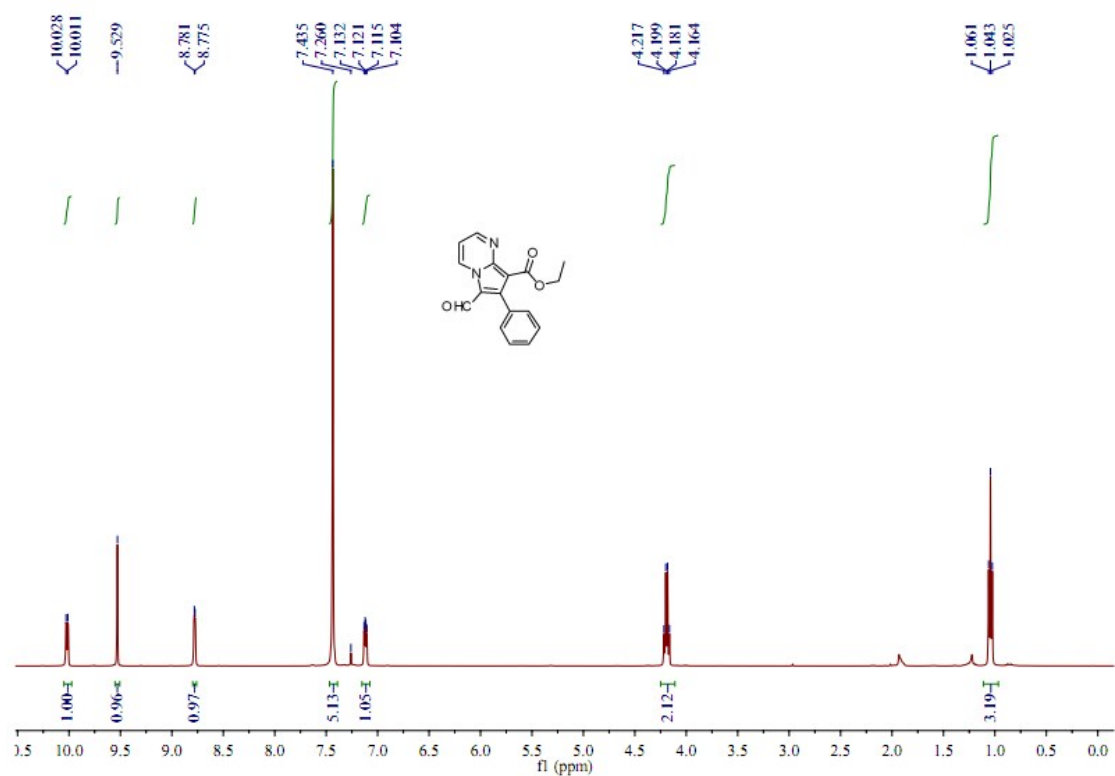
Ethyl 6-Chloro-3-formyl-2-phenylindolizine-1-carboxylate (3o)



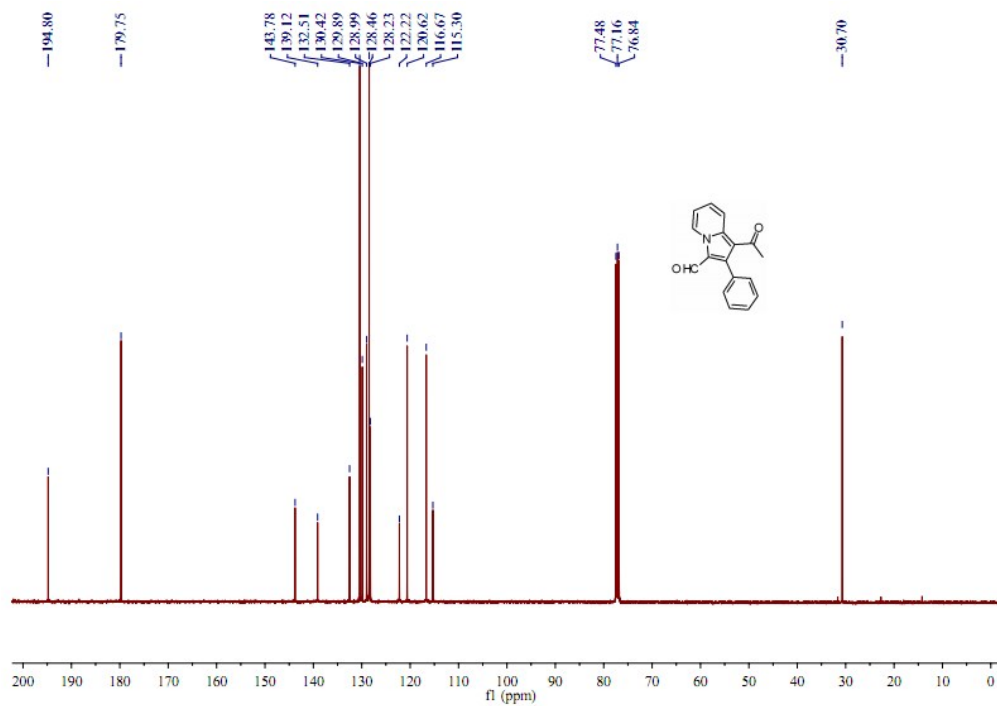
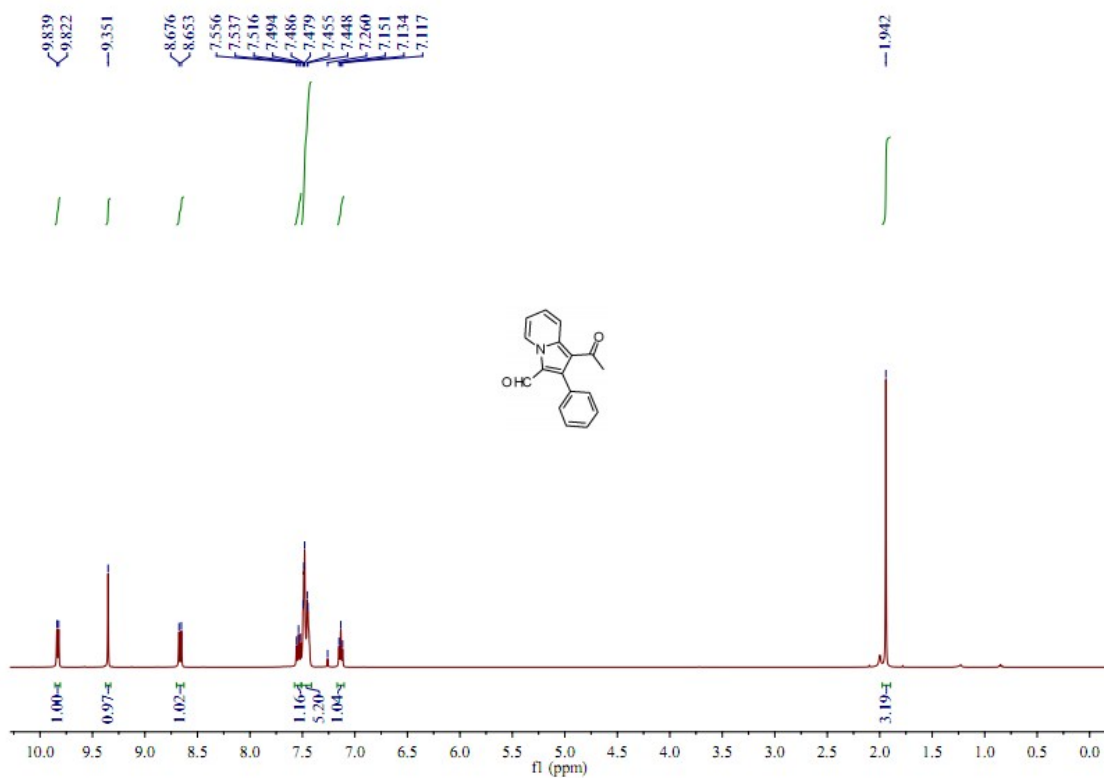
Ethyl 3-formyl-6-nitro-2-phenylindolizine-1-carboxylate (3p)



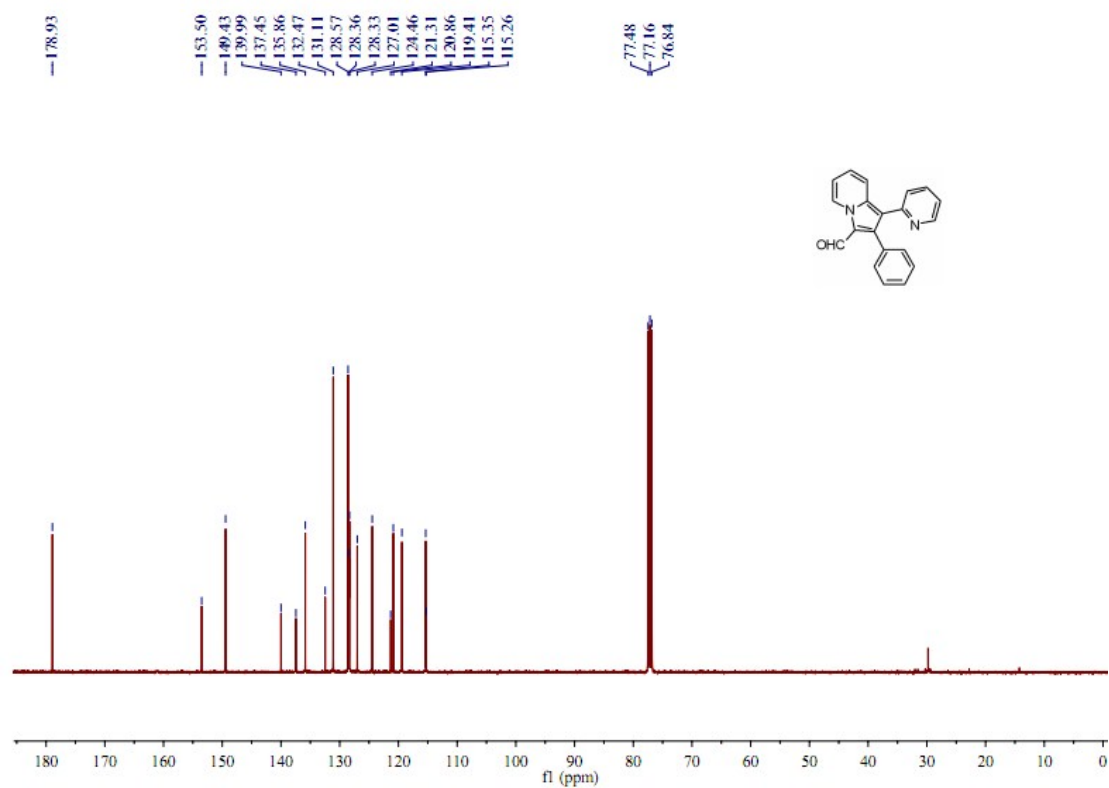
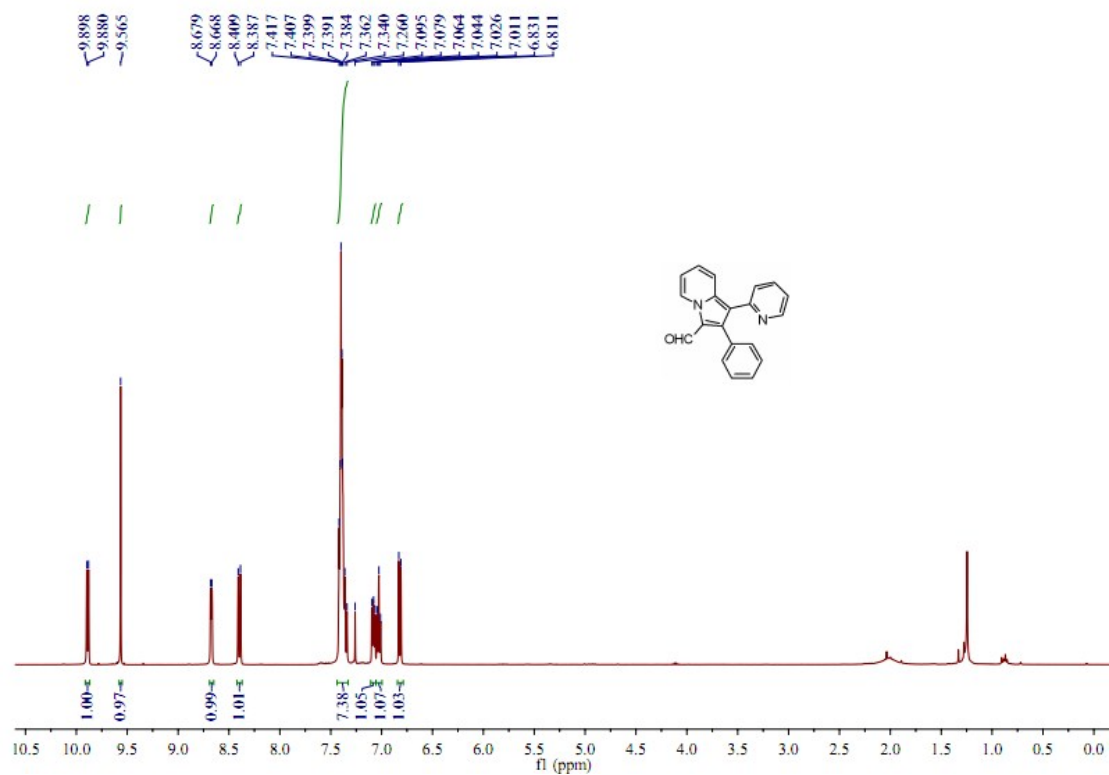
Ethyl 6-formyl-7-phenylpyrrolo[1,2-a]pyrimidine-8-carboxylate (3q)



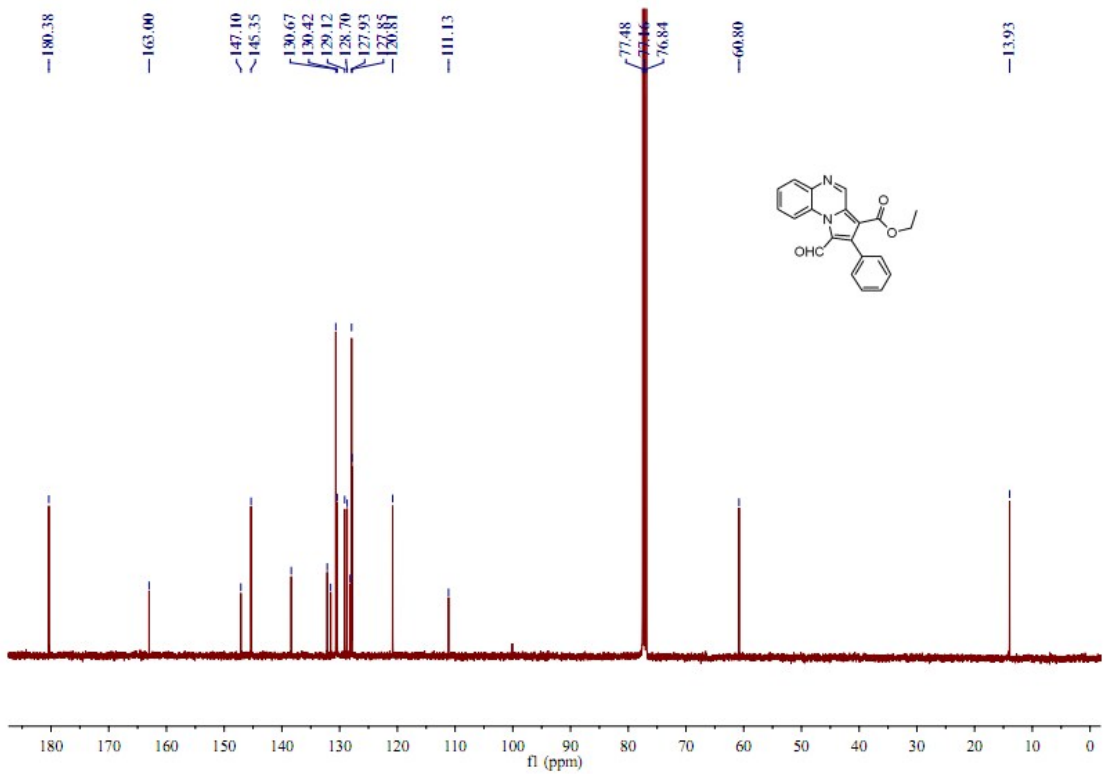
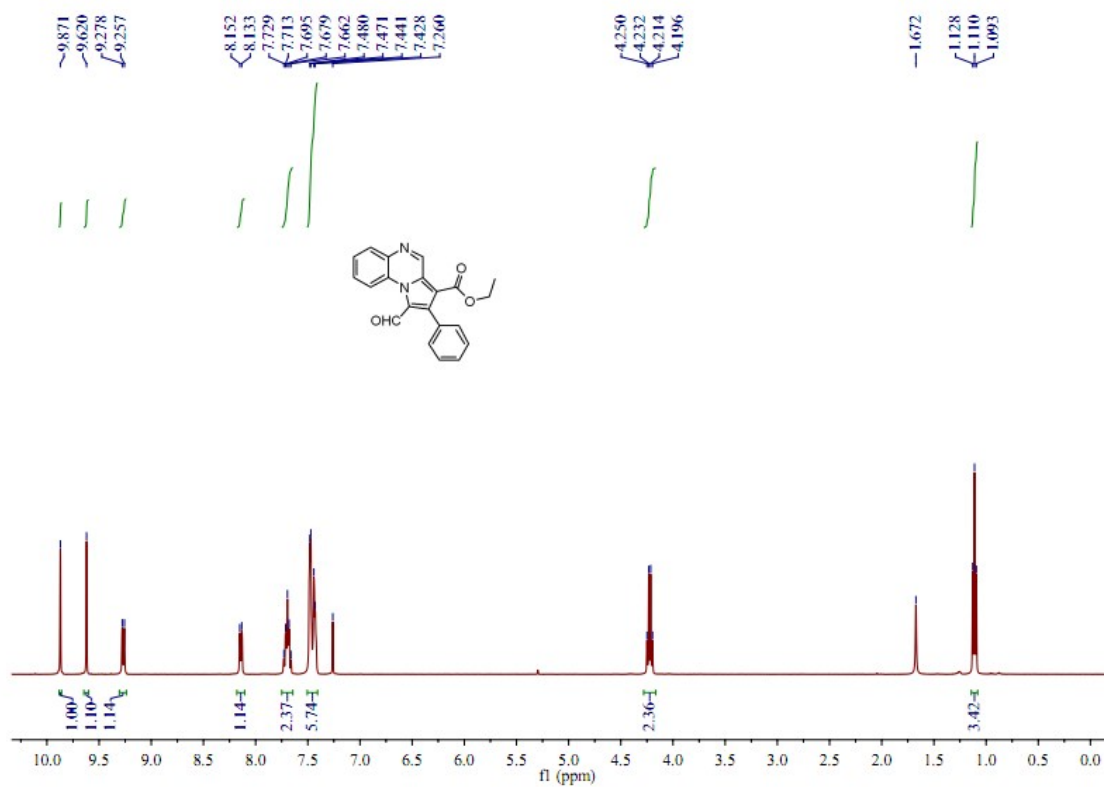
1-Acetyl-2-phenylindolizine-3-carbaldehyde (3r)



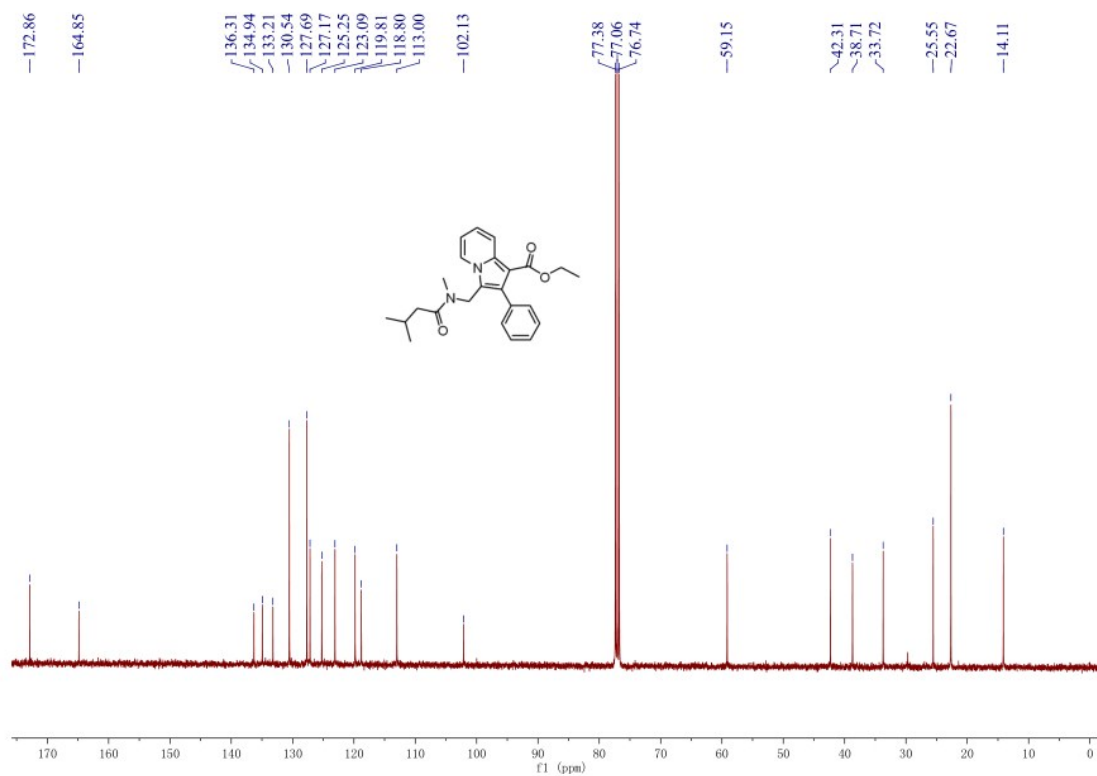
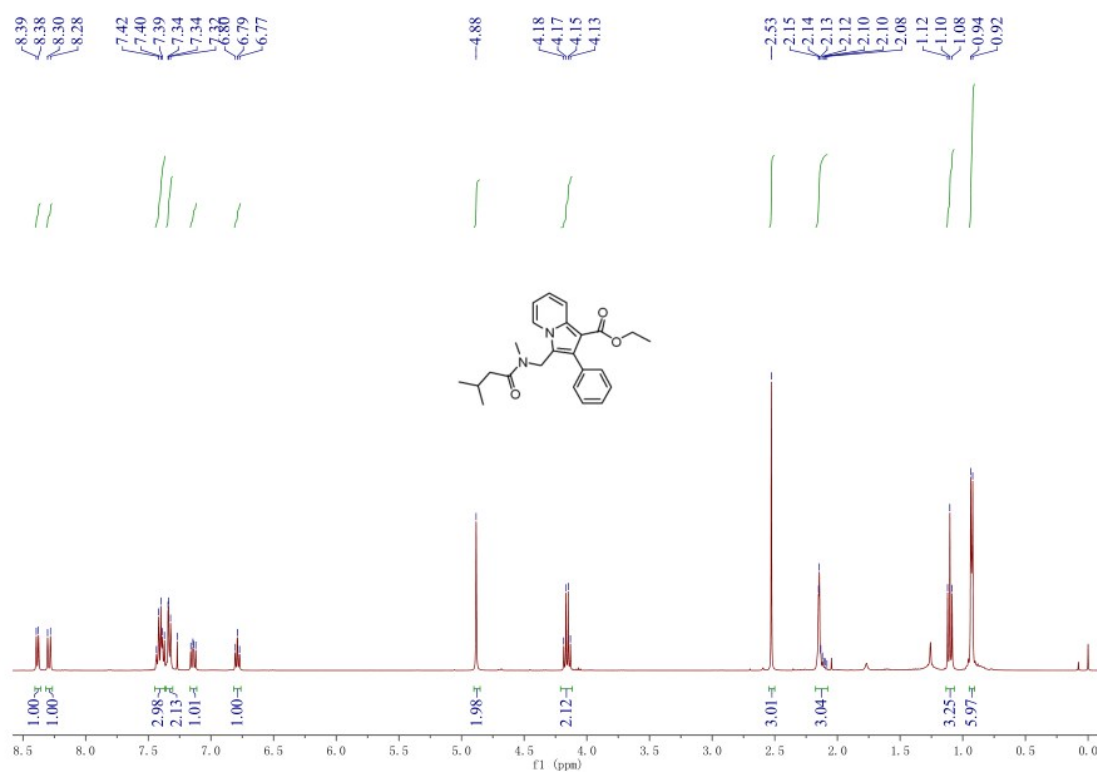
2-Phenyl-1-(Pyridin-2-yl)indolizine-3-carbaldehyde (3s)



Ethyl 1-formyl-2-phenylpyrrolo[1, 2-a]quinoxaline-3-carboxylate (3t)



Ethyl 3-((*N*-Methylisobutyramido)methyl)-2-phenylindolizine-1-carboxylate (4a)



1-(Ethoxycarbonyl)-2-phenylindolizine-3-carboxylic acid (5a)

