# Supporting Information

## REGIOSPECIFIC SYNTHESIS OF 1-(3,4-DIHYDRO-2*H*-BENZO[*b*][1,4]OXAZIN-3-YL)INDOLIZINE DERIVATIVES THROUGH A THREE-STEP SEQUENCE FROM 2-ARYLINDOLIZINE

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**Experimental section**

$^{1}$H NMR spectra were recorded on a Bruker instrument (300 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. Data are reported as follows: chemical shift, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet), coupling constants (Hz) and integration. $^{13}$C NMR spectra were recorded on a Bruker instrument (75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. HRMS values were obtained using (ESI) mass spectrometer (TOF). IR spectra of liquid compounds were recorded neat and KBr plates were used for solid compounds. Melting points were measured using a hot stage apparatus and are reported uncorrected.

**General procedure for the synthesis of indolizine-1,3-dicarbaldehyde 2.**

$POCl_3$ (5.2 mL, 57 mmol) was added dropwise to DMF (35 mL) in an ice bath. After finishing addition, 2-phenylindolizine (4.4 g, 22.8 mmol) was added and the ice bath was removed. The mixture was warmed to room temperature and stirred for 2 h. Then the temperature was raised to 60 $^{o}$C and the mixture was stirred for an additional 3 h. The reaction mixture was cooled to room temperature and slowly poured into saturated aqueous $CH_3COONa$ (200 mL). Dark green solid dissociated from the water phase immediately. The mixture was further stirred for 3 h. Finally, the precipitated product was filtered to afford the desired product without further purification.

**General procedure for the synthesis of Schiff bases 4.**

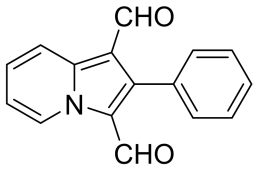
o-aminophenol (0.74 g, 6.8 mmol) and 2-(p-tolyl)indolizine-1,3-dicarbaldehyde

(1.788 g, 6.8 mmol) were added into EtOH (20 mL) and $CH_2Cl_2$ (5 mL), the reaction mixture was stirred at room temperature. The reaction was monitored by TLC. Upon the completion of this reaction, the solid compound was filtered and washed with ethanol to give the desired product.

**General procedure for the synthesis of indolizine derivatives 3.**

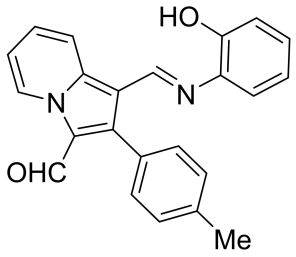
DMAP (25 mg, 0.2 mmol) and $K_2CO_3$ (276 mg, 2 mmol) were added to a solution of 1-(((2-hydroxyphenyl)imino)methyl)-2-arylindolizine-3-carbaldehyde (1.0 mmol), α-bromo ketones (1.5 mmol), and 5 mL PEG 400. The reaction mixture was stirred at 120 $^oC$ for 2 h. Upon completion of this reaction, the mixture was cooled to room temperature, diluted with $CH_2Cl_2$ and washed with water. Organic layers were combined, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica-gel (200-300 mesh) to afford the product **3**.

**$^{1}$H and $^{13}$C NMR spectra data of all products**




2-phenylindolizine-1,3-dicarbaldehyde (**2a**)

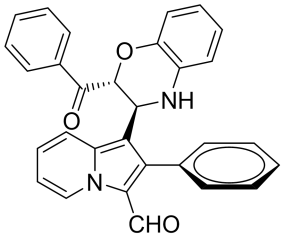
Dark green solid; yield: 75%. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 9.84 (d, *J* = 6.9 Hz, 1H), 9.81 (s, 1H), 9.62 (s, 1H), 8.56 (d, *J* = 8.8 Hz, 1H), 7.60-7.51 (m, 6H), 7.17 (t, *J* = 6.9 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 185.7, 179.5, 146.3, 138.2, 131.3, 130.5, 129.4, 129.3, 128.8, 128.6, 121.4, 119.8, 117.2, 113.6 ppm; IR (KBr): υ 3134, 1634, 1494, 1477, 1442, 1427, 1408, 1383, 1358, 1254, 1139, 1076, 1060, 1027, 1019, 818, 776, 764, 747, 730, 705, 568 $cm^{-1}$; HRMS (ESI): m/z calcd for $C_{16}H_{12}NO_2$ $[M+H]^+$: 250.0868, found: 250.0865.




1-(((2-hydroxyphenyl)imino)methyl)-2-(p-tolyl)indolizine-3-carbaldehyde (**4b**)

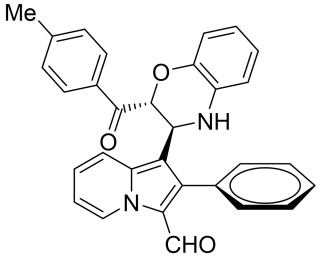
Yellow solid; yield: 86%. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 9.94 (d, *J* = 6.4 Hz, 1H), 9.64 (s, 1H), 8.72 (d, *J* = 8.6 Hz, 1H), 8.64 (s, 1H), 7.57-7.52 (m, 1H), 7.41-7.35 (m, 2H), 7.15-7.10 (m, 3H), 7.04–6.98 (m, 3H), 6.86–6.81 (m, 1H), 2.48 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 179.1, 152.5, 151.3, 139.1, 137.7, 137.3, 131.3, 131.2, 129.4, 129.2, 129.1, 129.0, 127.6, 127.4, 120.2, 120.1, 116.4, 115.9, 114.5, 111.9, 21.4 ppm; IR (KBr): υ 3430, 3034, 2844, 2828, 2808, 1631, 1610, 1587, 1506, 1485,

1428, 1409, 1361, 1304,1288, 1250, 1218, 1179, 1148, 1065, 1036, 818, 753 $cm^{-1}$; HRMS (ESI): m/z calcd for $C_{23}H_{19}N_2O_2$ $[M+H]^+$: 355.1447, found: 355.1445.



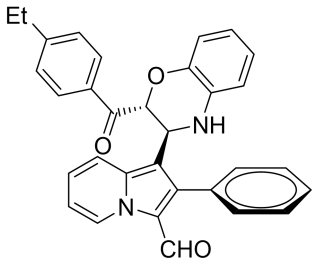

1-(2-benzoyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-phenylindolizine-3-carbald ehyde (**3a**)

Yellow solid; yield: 80%; mp 192-194 °C. $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.20 (s, 1H), 4.96 (d, *J* = 7.8 Hz, 1H), 5.55 (d, *J* = 7.8 Hz, 1H), 6.74 (t, *J* = 8.1 Hz, 2H), 6.86-6.97 (m, 3H), 7.15-7.43 (m, 9H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.94 (d, *J* = 8.7 Hz, 1H), 9.28 (s, 1H), 9.71 (d, *J* = 6.3 Hz, 1H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 49.8, 78.5, 109.6, 114.7, 115.3, 117.2, 118.4, 119.3, 120.8, 122.2, 126.0, 128.1, 128.2, 128.6, 128.7, 130.6, 133.1, 133.3, 135.0, 136.6, 141.3, 142.9, 143.6, 178.3, 194.5 ppm; IR (KBr): υ 3360, 3057, 2358, 2339, 1670, 1635, 1597, 1498, 1371, 1246, 746, 727, 680 $cm^{-1}$; HRMS (ESI): m/z calcd for $C_{30}H_{23}N_2O_3$ $[M+H]^+$: 459.1630, found: 459.1638.




1-(2-(4-methylbenzoyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-phenylindolizin e-3-carbaldehyde (**3b**)

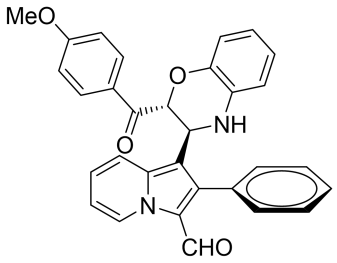
Yellow solid; yield: 81%; mp 178-180 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H), 4.18 (s, 1H), 4.96 (d, *J* = 7.5 Hz, 1H), 5.52 (d, *J* = 7.5 Hz, 1H), 6.74 (t, *J* = 7.8 Hz, 2H), 6.86-7.30 (m, 11H ), 7.56 (d, *J* = 7.5 Hz, 2H), 7.94 (d, *J* = 8.7 Hz, 1H), 9.28 (s, 1H), 9.72 (d, *J* = 6.3 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 21.2, 49.8, 78.4, 109.6, 114.6, 115.3, 117.2, 118.3, 119.2, 120.8, 122.2, 125.9, 127.8, 128.7, 130.5, 133.2, 135.0, 136.7, 138.1, 141.5, 142.3, 178.3, 194.6 ppm. IR (KBr): υ 3352, 3221, 1695, 1612, 1467, 1346, 1244, 1147, 916, 860, 827, 742, 705, 482 cm$^{-1}$; HRMS (ESI): m/z calcd for $C_{31}H_{25}N_2O_3$ $[M+H]^+$: 473.1787, found: 473.1795.




1-(2-(4-ethylbenzoyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-phenylindolizine-3-carbaldehyde (**3c**)

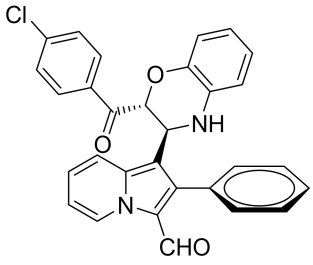
Yellow solid; yield: 82%; mp 182-184 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.5 Hz, 3H), 2.60 (q, *J* = 7.5 Hz, 2H), 4.30 (s, 1H), 4.95 (d, *J* = 7.8 Hz, 1H), 5.53 (d, *J* = 7.8 Hz, 1H), 6.75 (t, *J* = 7.5 Hz, 2H), 6.86-7.31 (m, 11H), 7.56 (d, *J* = 7.8Hz, 2H), 7.94 (d, *J* = 8.4Hz, 1H), 9.26 (s, 1H), 9.68 (d, *J* = 6.6 Hz, 1H) ppm； $^{13}$C NMR (75 MHz, $CDCl_3$): δ 15.2, 28.9, 78.5, 109.7, 114.6, 115.2, 117.1, 118.4, 119.1, 120.7, 122.1, 125.9, 127.6, 128.2, 130.8, 132.7, 133.2, 136.7, 141.3, 136.7, 141.3, 142.9, 150.5, 178.2, 194.1 ppm； IR (KBr): υ 3234, 2956, 2924, 2852, 2360, 2331, 1685, 1608, 1498, 1467, 1346, 1280, 1246, 1224, 1028, 925, 752 cm$^{-1}$； HRMS (ESI): m/z

calcd for $C_{32}H_{27}N_2O_3$ $[M+H]^+$: 487.1943, found: 487.1945.




1-(2-(4-methoxybenzoyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-phenylindolizine-3-carbaldehyde (**3d**)

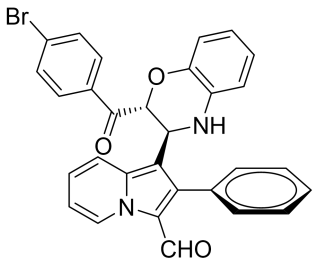
Yellow solid; yield: 84%; mp 90-92 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H), 4.34 (s, 1H), 4.96 (d, *J* = 7.8 Hz, 1H), 5.46 (d, *J* = 7.8 Hz, 1H), 6.63-6.73 (m, 4H), 6.84-7.29 (m, 9H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 1H), 9.25 (s, 1H), 9.69 (d, *J* = 6.3 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 49.7, 55.5, 78.1, 109.9, 113.4, 114.7, 115.3, 117.1, 118.4, 119.1, 120.8, 122.1, 126.0, 128.3, 130.7, 131.2, 133.3, 136.7, 141.4, 142.9, 163.8, 178.2, 192.6 ppm; IR (KBr): υ 3346, 2926, 2839, 1724, 1676, 1627, 1598, 1498, 1463, 1400, 1348, 1259, 1172, 1028, 744, 705 $cm^{-1}$; HRMS (ESI): m/z calcd for $C_{31}H_{25}N_2O_4$ $[M+H]^+$: 489.1736, found: 489.1742.




1-(2-(4-chlorobenzoyl)-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-3-yl)-2-phenylindolizine-3-carbaldehyde (**3e**)

Yellow solid; yield: 72%; mp 148-150 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 9.75 (d, *J* =

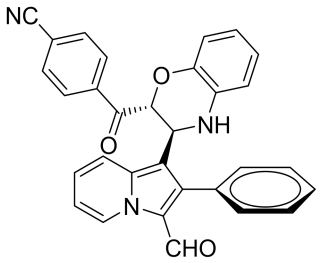
7.0 Hz, 1H), 9.29 (s, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.33 – 7.14 (m, 8H), 6.97 (td, *J* = 6.9, 1.0 Hz, 1H), 6.92 – 6.87 (m, 2H), 6.77 – 6.83 (m, 2H), 5.39 (d, *J* = 8.1 Hz, 1H), 4.99 (d, *J* = 8.1 Hz, 1H), 4.25 (s, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): δ 49.7, 79.9, 109.4, 114.8, 115.4, 117.2, 118.3, 119.4, 120.9, 122.4, 126.0, 128.2, 128.2, 128.6, 128.6, 130.4, 130.8, 133.1, 133.2, 136.6, 140.0, 141.3, 142.6, 178.3, 193.1 ppm; IR (KBr): υ 3334, 3061, 2919, 2855, 1682, 1621, 1589, 1540, 1499, 1468, 1432, 1402, 1366, 1347, 1307, 1278, 1244, 1210, 1188, 1149, 1121, 1091, 1041, 1013, 799, 742, 707 cm$^{-1}$; HRMS (ESI): m/z calcd for $C_{30}H_{22}ClN_2O_3$ $[M+H]^+$:493.9669, found: 493.9665.




1-(2-(4-bromobenzoyl)-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-3-yl)-2-phenylindolizine -3-carbaldehyde (**3f**)

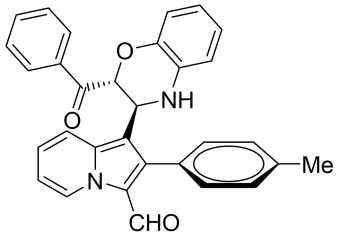
Yellow solid; yield: 75%; mp 165-166 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 9.75 (d, *J* = 7.0 Hz, 1H), 9.29 (s, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.33 – 7.10 (m, 8H), 6.97 (td, *J* = 6.9, 0.9 Hz, 1H), 6.89 (t, *J* = 8.1 Hz, 2H), 6.75 (m, 2H), 5.38 (d, *J* = 8.1 Hz, 1H), 4.99 (d, *J* = 8.1 Hz, 1H), 4.24 (s, 1H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): δ 49.7, 79.9, 109.3, 114.8, 115.4, 117.2, 118.3, 119.4, 120.9, 122.4, 126.0, 128.2, 128.3, 128.6, 128.8, 130.5, 130.8, 131.6, 133.2, 133.4, 136.6, 141.3, 142.6, 178.3, 193.3 ppm; IR (KBr): υ 3331, 3059, 2916, 2851, 1681, 1619, 1610,

1585, 1540, 1500, 1468, 1434, 1401, 1365, 1347, 1307, 1276, 1244, 1210, 1182, 1148, 1103, 1076, 1041, 1009, 897, 829, 799, 766, 740, 707 $cm^{-1}$; HRMS (ESI): m/z calcd for $C_{30}H_{22}BrN_2O_3$ $[M+H]^+$:538.4209, found: 538.4206.



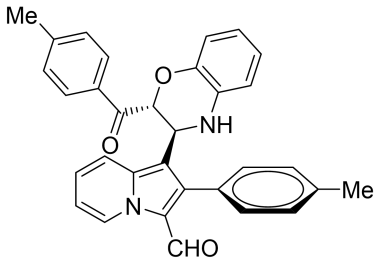

4-(3-(3-formyl-2-phenylindolizin-1-yl)-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazine-2-carbo nyl)benzonitrile (**3g**)

Yellow solid; yield: 78%; mp 213-215 °C. $^1H$ NMR (400 MHz, $CDCl_3$): δ 9.78 (d, *J* = 7.0 Hz, 1H), 9.32 (s, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.33 – 7.26 (m, 6H), 7.00 (td, *J* = 6.9, 1.1 Hz, 1H), 6.94 – 6.89 (m, 2H), 6.78 – 6.75 (m, 2H), 5.38 (d, *J* = 8.1 Hz, 1H), 5.03 (d, *J* = 8.1 Hz, 1H), 4.25 (s, 1H) ppm; $^{13}C$ NMR (101 MHz, $CDCl_3$): δ 49.6, 80.4, 109.0, 114.9, 115.5, 116.4, 117.2, 117.7, 118.2, 119.6, 120.9, 122.6, 126.1, 128.3, 128.3, 128.7, 129.4, 130.8, 131.9, 133.1, 136.5, 137.6, 141.2, 142.3, 178.3, 193.2 ppm; IR (KBr): υ 3328, 3114, 3059, 2921, 2230, 1693, 1620, 1540, 1499, 1469, 1432, 1403, 1366, 1348, 1309, 1272, 1244, 1210, 1149, 1120, 1074, 1041, 744, 730, 710 $cm^{-1}$; HRMS (ESI): m/z calcd for $C_{31}H_{22}N_3O_3$ $[M+H]^+$:484.5349, found: 484.5352.




1-(2-benzoyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-(p-tolyl)indolizine-3-carbal dehyde (**3i**)

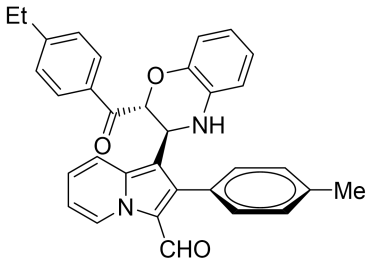
Yellow solid; yield: 82%; mp 193-194 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 4.26 (s, 1H), 4.97 (d, *J* = 7.5 Hz, 1H), 5.53 (d, *J* = 7.5 Hz, 1H), 6.74 (t, *J* = 7.8 Hz, 2H), 6.85-7.19 (m, 9H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 6.9 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 1H), 9.28 (s, 1H), 9.68 (d, *J* = 6.6 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 21.2, 49.8, 78.4, 109.6, 114.6, 115.3, 117.1, 118.3, 119.1, 120.7, 122.1, 125.9, 127.7, 128.5, 130.5, 133.2, 134.9, 136.7, 138.1, 141.5, 142.9, 178.3, 194.6 ppm; IR (KBr): υ 3340, 2360, 2341, 1735, 1678, 1627, 1500, 1465, 1438, 1344, 1246, 1224, 1151, 1022, 918, 837, 744, 700 cm$^{-1}$; HRMS (ESI): m/z calcd for $C_{31}H_{25}N_2O_3$ $[M+H]^+$: 473.1787, found: 473.1784.




1-(2-(4-methylbenzoyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-(p-tolyl)indolizi ne-3-carbaldehyde (**3j**)

Yellow solid; yield:80%; mp 175-178 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.36 (s, 3H), 4.24 (s, 1H), 4.97 (d, *J* = 7.8 Hz, 1H), 5.51 (d, *J* = 7.8 Hz, 1H), 6.74 (t, *J*

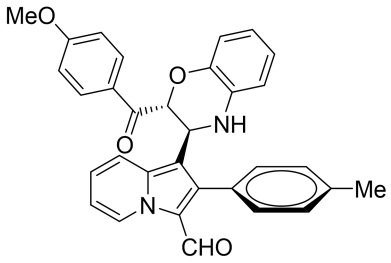
= 7.5 Hz, 2H), 6.85-7.06 (m, 8H), 7.25-7.37 (m, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.93 (d, *J* = 8.7 Hz, 1H), 9.28 (s, 1H), 9.70 (d, *J* = 7.2 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 21.3, 21.7, 49.8, 78.5, 109.7, 114.6, 115.3, 117.2, 118.4, 119.2, 120.8, 122.1, 125.9, 127.7, 128.3, 128.9, 130.5, 132.5, 133.2, 136.7, 138.0, 141.5, 142.9, 144.3, 178.3, 194.0 ppm; IR (KBr): υ 3346, 1741, 1670, 1606, 1500, 1463, 1433, 1400, 1348, 1286, 1242, 1207, 1182, 1120, 1041, 1020, 786, 765, 742 cm$^{-1}$; HRMS (ESI): m/z calcd for $C_{32}H_{27}N_2O_3$ $[M+H]^+$: 487.1943, found: 487.1938.




1-(2-(4-ethylbenzoyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-(p-tolyl)indolizine -3-carbaldehyde (**3k**)

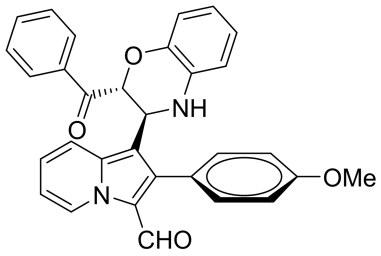
Yellow solid, yield: 81%; mp 77-79 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.4 Hz, 3H), 2.36 (s, 3H), 2.61 (q, *J* = 7.4 Hz, 2H), 4.21 (s, 1H), 4.95 (d, *J* =8.1 Hz, 1H), 5.55 (d, *J* = 8.1 Hz, 1H), 6.75 (t, *J* = 8.1 Hz, 2H), 6.86-7.08 (m, 9H), 7.27-7.32 (m, 1H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.94 (d, *J* = 8.7 Hz, 1H), 9.28 (s, 1H), 9.70 (d, *J* = 6.3 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 15.2, 21.3, 28.9, 49.8, 78.4, 109.6, 114.5, 115.3, 117.2, 118.4, 119.2, 120.7, 122.1, 125.9, 127.5, 127.7, 128.2, 128.5, 128.9, 130.5, 132.7, 133.2, 136.7, 138.0, 141.5, 143.0, 150.5, 178.4, 194.2 ppm; IR (KBr): υ 3336, 3026, 2962, 2926, 2856, 1685, 1678, 1625, 1606, 1498, 1462, 1433, 1348, 1278, 1244, 1149, 1022, 917, 837, 744 cm$^{-1}$; HRMS (ESI): m/z calcd for $C_{33}H_{29}N_2O_3$

[M+H]$^+$: 501.2100 , found: 501.2094.



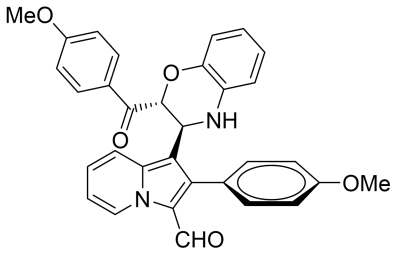

1-(2-(4-methoxybenzoyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-(p-tolyl)indoli zine-3-carbaldehyde (**3l**)

Yellow solid; yield: 83%; mp 163-164 $^o$C. $^1$H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.80 (s, 3H), 4.31 (s, 1H), 4.97 (d, *J* = 7.8 Hz, 1H), 5.45 (d, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 2H), 6.72 (d, *J* = 7.2 Hz, 2H), 6.84-7.05 (m, 7H), 7.27 (t, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 1H), 9.27 (s, 1H), 9.69 (d, *J* = 6.6 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 21.2, 49.8, 55.4, 78.8, 109.8, 113.3, 114.6, 115.3, 117.1, 118.4, 119.1, 120.8, 122.1, 125.9, 127.8, 128.1, 128.9, 130.5, 131.3, 133.3, 136.7, 137.9, 141.5, 142.9, 163.7, 178.3, 192.7 ppm; IR (KBr): υ 3348, 1735, 1662, 1597, 1541, 1500, 1465, 1438, 1400, 1307, 1292, 1263, 1242, 1207, 1168, 1118, 1031, 837, 763, 746 cm$^{-1}$; HRMS (ESI): m/z calcd for $C_{32}H_{27}N_2O_4$ [M+H]$^+$: 503.1893, found: 503.1901.



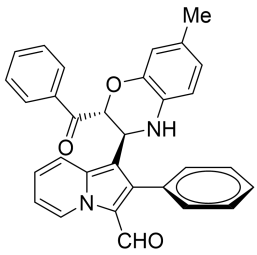

1-(2-benzoyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-(4-methoxyphenyl)indolizi ne-3-carbaldehyde (**3m**)

Yellow solid; yield: 65%; mp 94-95 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 3H), 4.22 (s, 1H), 4.96 (d, *J* = 8.1 Hz, 1H), 5.53 (d, *J* = 8.1 Hz, 1H), 6.71-7.39 (m, 13H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.91 (d, *J* = 8.7 Hz, 1H), 9.25 (s, 1H), 9.67 (d, *J* = 6.9 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 49.8, 55.3, 78.4, 109.6, 113.8, 114.6, 115.3, 117.2, 118.3, 119.3, 120.8, 122.2, 122.8, 126.1, 128.1, 128.6, 128.7, 131.8, 133.2, 133.3, 134.9, 136.8, 141.3, 142.9, 159.6, 178.3, 194.7 ppm; IR (KBr): υ 3331, 1687, 1608, 1498, 1433, 1400, 1346, 1278, 1246, 1222, 1174, 1028, 914, 840, 744, 696 cm$^{-1}$; HRMS (ESI): m/z calcd for $C_{31}H_{25}N_2O_4$ $[M+H]^+$: 489.1736, found: 489.1743.



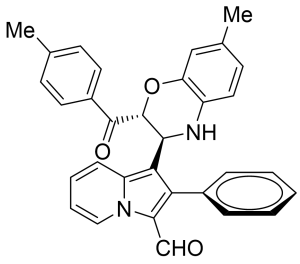

1-(2-(4-methoxybenzoyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-(4-methoxyphenyl)indolizine-3-carbaldehyde (**3n**)

Yellow solid; yield: 67%; mp 140-142 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 6H), 4.20 (s, 1H), 4.99 (d, *J* = 7.8 Hz, 1H), 5.45 (d, *J* = 7.8 Hz, 1H), 6.64-7.02 (m, 11H), 7.26-7.31 (m, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 8.7 Hz, 1H), 9.29 (s, 1H), 9.73 (d, *J* = 6.3 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 49.8, 55.2, 55.4, 79.0, 109.8, 113.4, 113.7, 114.5, 115.3, 117.2, 118.3, 119.2, 120.9, 122.1, 122.9, 125.9, 128.0, 128.5, 131.3, 133.3, 136.7, 141.3, 142.9, 159.5, 163.7, 178.4, 192.7 ppm; IR (KBr): υ 3352, 2837, 1658, 1608, 1571, 1502, 1463, 1436, 1400, 1348, 1307, 1292, 1261, 1244, 1172, 1118, 1029, 839, 767, 748 cm$^{-1}$; HRMS (ESI): m/z calcd for $C_{32}H_{27}N_2O_5$$[M+H]^+$: 519.1842, found: 519.1838.




1-(2-benzoyl-7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-phenylindolizine -3-carbaldehyde (**3p**)

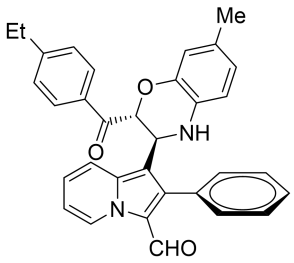
Yellow solid; yield: 85%; mp 76-78 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H), 4.11 (s, 1H), 4.92 (d, *J* = 7.5 Hz, 1H), 5.52 (d, *J* = 7.5 Hz, 1H), 6.61-6.76 (m, 3H), 6.93 (t, *J* = 6.3 Hz, 1H), 7.14-7.39 (m, 9H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 1H), 9.25 (s, 1H), 9.69 (d, *J* = 6.6 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 20.6, 49.9, 78.9, 109.8, 114.6, 115.3, 117.6, 118.5, 120.8, 122.6, 125.9, 128.5, 129.1, 130.6, 130.8, 133.3, 134.9, 136.7, 141.3, 142.8, 178.2, 194.6 ppm; IR (KBr): υ 3331, 2916, 2360, 2331, 1730, 1687, 1625, 1512, 1463, 1436, 1400, 1365, 1348, 1294, 1247, 1149, 1128, 1043, 1028, 804, 761, 744, 700 cm$^{-1}$; HRMS (ESI): m/z calcd for $C_{31}H_{25}N_2O_3$ $[M+H]^+$: 473.1787, found: 473.1792.




1-(7-methyl-2-(4-methylbenzoyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-phenyl indolizine-3-carbaldehyde (**3q**)

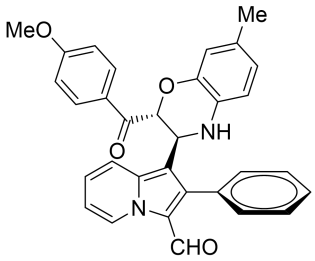
Yellow solid; yield: 84%; mp 104-106 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.31 (s, 3H), 4.08 (s, 1H), 4.93 (d, *J* =7.8 Hz, 1H), 5.49 (d, *J* = 7.8 Hz, 1H), 6.60-7.28

(m, 12H), 7.54 (d, $J$ = 7.5 Hz, 2H), 7.93 (d, $J$ = 8.4 Hz, 1H), 9.25 (s, 1H), 9.70 (d, $J$ = 6.0 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 20.6, 21.7, 49.9, 78.9, 109.9, 114.7, 115.3, 117.6, 118.5, 120.8, 122.6, 125.9, 128.1, 128.2, 128.5, 128.8, 128.9, 129.1, 130.7, 130.9, 132.5, 136.7, 141.3, 142.8, 144.3, 178.3, 194.1 ppm; IR (KBr): υ 3336, 2916, 1685, 1672, 1625, 1510, 1465, 1435, 1400, 1365, 1348, 1294, 1247, 1182, 1149, 1128, 1028, 908, 806, 746, 731, 704 cm$^{-1}$; HRMS (ESI): m/z calcd for $C_{32}H_{27}N_2O_3$ $[M+H]^+$: 487.1943, found: 487.1936.



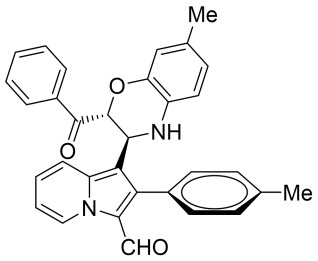

1-(2-(4-ethylbenzoyl)-7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-phenylindolizine-3-carbaldehyde (**3r**)

Yellow solid; yield: 86%; mp 140-142 $^o$C. $^1$H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, $J$ = 7.5 Hz, 3H), 2.26 (s, 3H), 2.61 (q, $J$ = 7.5 Hz, 2H), 4.16 (s, 1H), 4.93 (d, $J$ =7.8 Hz, 1H), 5.52 (d, $J$ = 7.8 Hz, 1H), 6.63-7.29 (m, 12H), 7.57 (d, $J$ = 7.8 Hz, 2H), 7.95 (d, $J$ = 8.7 Hz, 1H), 9.27 (s, 1H), 9.69 (d, $J$ = 6.6 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 15.3, 20.7, 28.9, 49.9, 79.0, 109.9, 114.7, 115.3, 117.6, 118.6, 120.7, 122.6, 125.9, 127.6, 128.2, 128.9, 129.0, 130.7, 132.7, 136.8, 141.3, 142.8, 150.5, 178.2, 194.2 ppm; IR (KBr): υ 3329, 3026, 2964, 2927, 2862, 1685, 1680, 1625, 1510, 1463, 1433, 1400, 1365, 1348, 1294, 1247, 1182, 1149, 1128, 1028, 908, 802, 731, 704 cm$^{-1}$; HRMS (ESI): m/z calcd for $C_{33}H_{29}N_2O_3$ $[M+H]^+$: 501.2100, found: 501.2104.




1-(2-(4-methoxybenzoyl)-7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-phen ylindolizine-3-carbaldehyde (**3s**)

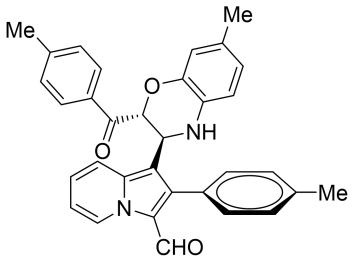
Yellow solid; yield: 80%; mp 90-93 ºC. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H), 3.82 (s, 3H), 4.11 (s, 1H), 4.94 (d, *J* = 7.8 Hz, 1H), 5.47 (d, *J* = 7.8 Hz, 1H), 6.64-7.30 (m, 12H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.96 (d, *J* = 8.7 Hz, 1H), 9.26 (s, 1H), 9.73 (d, *J* = 6.6 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 20.6, 49.9, 55.5, 79.3, 110.0, 113.4, 113.6, 114.5, 117.6, 118.5, 120.8, 128.1, 129.1, 130.7, 136.7, 141.4, 142.8, 163.7, 178.3, 192.7 ppm; IR (KBr): υ 3336, 2918, 2837, 1672, 1624, 1597, 1510, 1462, 1438, 1400, 1365, 1348, 1294, 1249, 1172, 1149, 1128, 1028, 908, 840, 808, 756, 731, 704 $cm^{-1}$; HRMS (ESI): m/z calcd for $C_{32}H_{27}N_2O_4$ $[M+H]^+$ 503.1893, found: 503.1905.




1-(2-benzoyl-7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-(p-tolyl)indolizin e-3-carbaldehyde (**3t**)

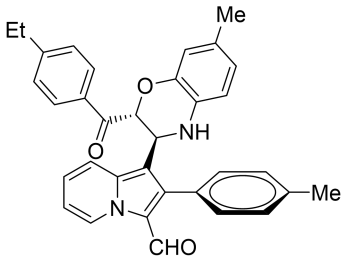
Yellow solid; yield: 79%; mp 95-97 ºC. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.34 (s, 3H), 4.09 (s, 1H), 4.94 (d, *J* = 7.8 Hz, 1H), 5.53 (d, *J* = 7.8 Hz, 1H), 6.63-7.41 (m, 12H), 7.63 (s, 2H), 7.94 (d, *J* = 8.1 Hz, 1H), 9.28 (s, 1H), 9.70 (s, 1H) ppm; $^{13}$C

NMR (75 MHz, $CDCl_3$): δ 20.6, 21.2, 49.9, 78.9, 109.7, 114.5, 115.3, 117.6, 118.4, 120.8, 122.6, 125.8, 127.4, 127.8, 128.1, 128.5, 129.1, 130.6, 133.1, 135.0, 136.7, 138.1, 141.5, 142.8, 178.4, 194.7 ppm; IR (KBr): υ 3334, 2918, 2856, 1685, 1624, 1510, 1463, 1436, 1400, 1348, 1294, 1247, 1149, 1128, 1022, 908, 837, 802, 763, 744, 698 $cm^{-1}$; HRMS (ESI): m/z calcd for $C_{32}H_{27}N_2O_3$ $[M+H]^+$: 487.1943, found: 487.1949.



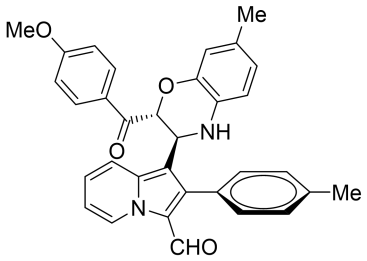

1-(7-methyl-2-(4-methylbenzoyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-(p-toly l)indolizine-3-carbaldehyde (**3u**)

Yellow solid; yield: 80%; mp 145-146 °C. $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.34 (s, 3H), 2.36 (s, 3H), 4.10(s, 1H), 4.95 (d, *J* = 7.8 Hz, 1H), 5.49 (d, *J* = 7.8 Hz, 1H), 6.63-6.69 (m, 3H), 6.96-7.05 (m, 7H), 7.28 (s, 1H), 7.54 (d, *J* = 6.9 Hz, 2H), 7.94 (d, *J* = 8.4 Hz, 1H), 9.29 (s, 1H), 9.71 (d, *J* = 6.6 Hz, 1H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 20.6, 21.3, 21.7, 49.9, 79.0, 109.8, 114.5, 115.3, 117.6, 118.5, 120.8, 122.5, 125.8, 127.8, 128.8, 129.0, 130.6, 132.6, 136.8, 137.9, 141.5, 142.9, 144.2, 178.3, 194.1 ppm; IR (KBr): υ 3342, 2918, 1735, 1670, 1608, 1508, 1465, 1436, 1400, 1365, 1348, 1296, 1244, 1184, 1151, 1041, 840, 806, 765, 744 $cm^{-1}$; HRMS (ESI): m/z calcd for $C_{33}H_{29}N_2O_3$ $[M+H]^+$: 501.2100, found: 501.2107.




1-(2-(4-ethylbenzoyl)-7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-(p-tolyl) indolizine-3-carbaldehyde (**3v**)

Yellow solid; yield: 82%; mp 112-114 °C. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, *J* = 7.5 Hz, 3H), 2.27 (s, 3H), 2.36 (s, 3H), 2.61(q, *J* = 7.5 Hz, 2H), 4.18 (s, 1H), 4.93 (d, *J* = 7.8 Hz, 1H), 5.52 (d, *J* = 7.8 Hz, 1H), 6.66 (q, *J* = 7.8 Hz, 2H), 6.78 (s, 1H), 6.90-7.06 (m, 7H), 7.27 (t, *J* = 6.9 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.93 (d, *J* = 8.7 Hz, 1H), 9.28 (s, 1H), 9.68 (d, *J* = 6.3 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 15.3, 20.7, 21.3, 28.9, 49.9, 78.9, 109.8, 114.5, 115.3, 117.6, 118.5, 120.7, 122.5, 125.9, 127.5, 128.4, 128.9, 130.6, 132.8, 136.8, 137.9, 141.4, 142.9, 150.4, 178.3, 194.3 ppm; IR (KBr): υ 3334, 3026, 2964, 2920, 2864, 1672, 1618, 1514, 1465, 1436, 1400, 1294, 1246, 1182, 1149, 1128, 1045, 1022, 910, 840, 806, 761, 744, 729 $cm^{-1}$; HRMS (ESI): m/z calcd for $C_{34}H_{31}N_2O_3$ $[M+H]^+$: 515.2256, found: 515.2262.

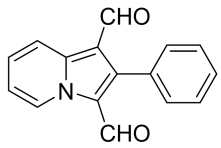


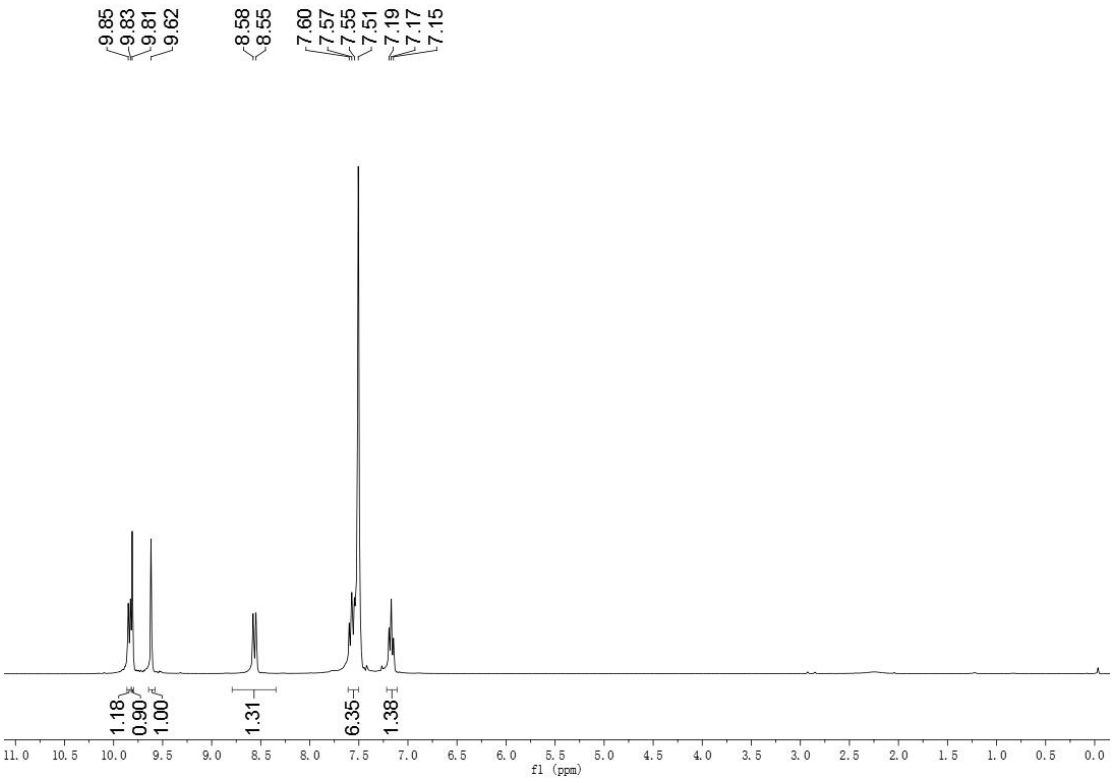

1-(2-(4-methoxybenzoyl)-7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-(p-to lyl)indolizine-3-carbaldehyde (**3w**)

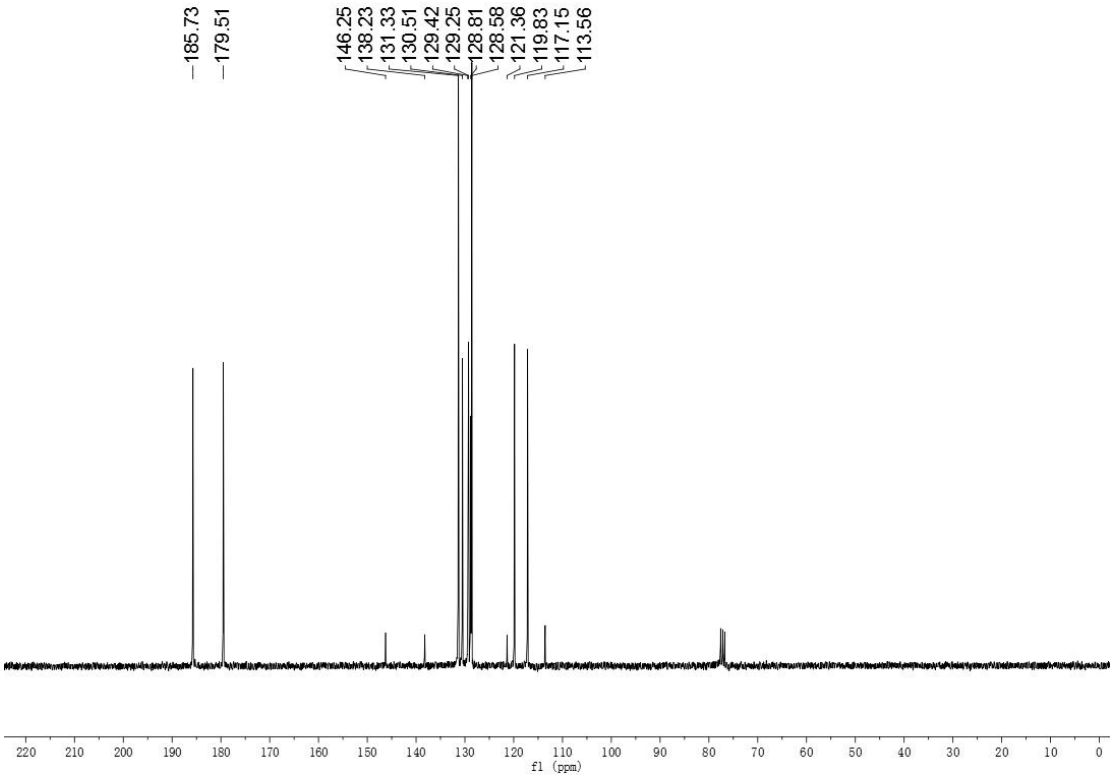
Yellow solid; yield: 85%; mp 105-107 °C. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H),

2.35 (s, 3H), 3.82 (s, 3H), 4.09 (s, 1H), 4.95 (d, *J* =7.8 Hz, 1H), 5.45 (d, *J* = 7.8 Hz, 1H), 6.58-7.05(m, 10H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 8.7 Hz, 1H), 9.28 (s, 1H), 9.73 (d, *J* = 6.6Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 20.6, 21.2, 49.9, 55.4, 79.3, 109.9, 113.3, 114.6, 115.3, 117.6, 118.5, 120.8, 122.5, 125.9, 127.8, 128.0, 128.5, 129.0, 130.7, 131.3, 136.8, 137.9, 141.5, 142.8, 163.7, 178.3, 192.7 ppm; IR (KBr): υ 3336, 2918, 2854, 1672, 1625, 1598, 1510, 1462, 1433, 1400, 1348, 1294, 1259, 1172, 1149, 1128, 1024, 908, 840, 808, 756, 742 $cm^{-1}$; HRMS (ESI): m/z calcd for $C_{33}H_{29}N_2O_4$ $[M+H]^+$: 517.2049, found: 517.2043.

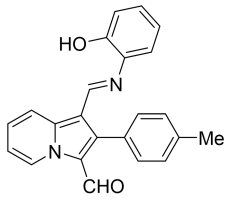
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 2a**

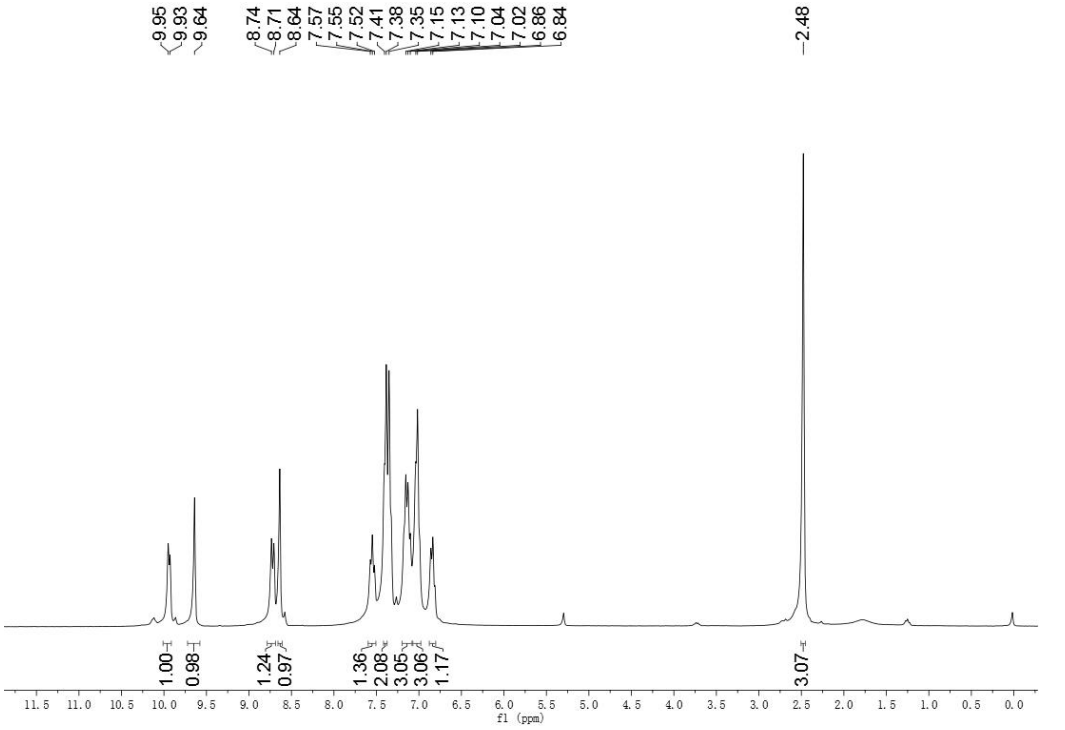


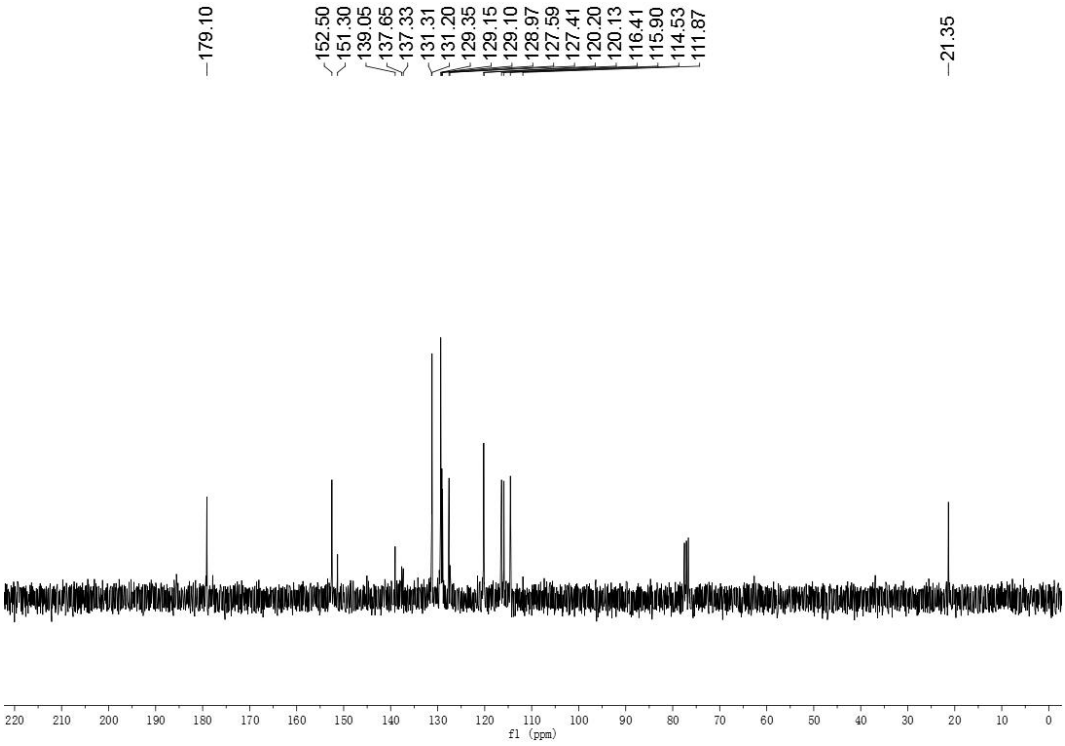



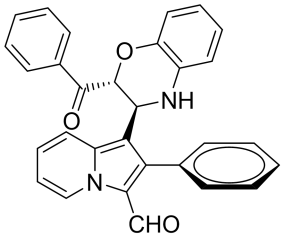
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 4b**

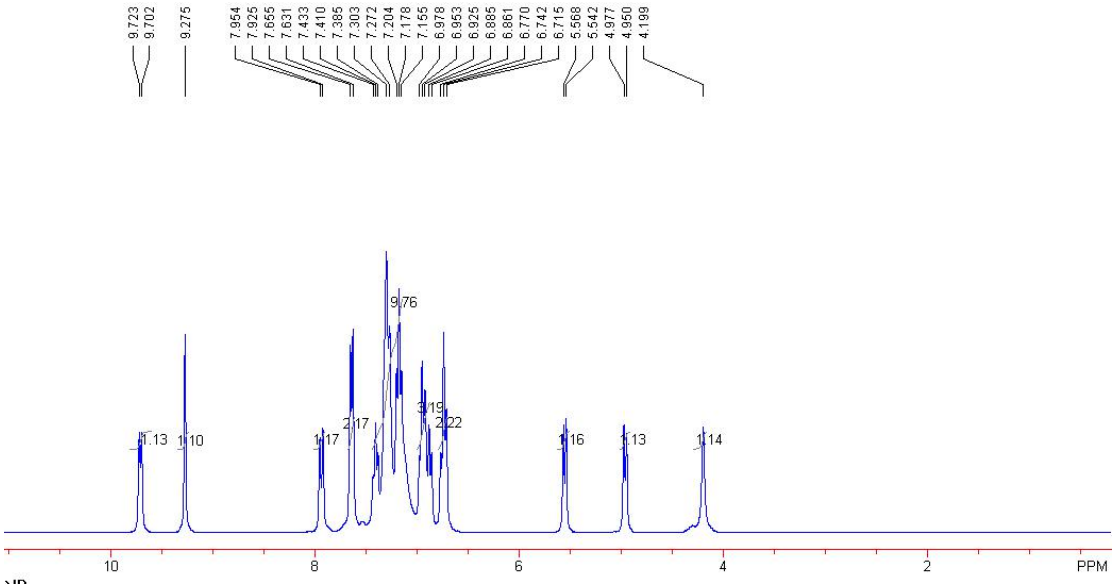


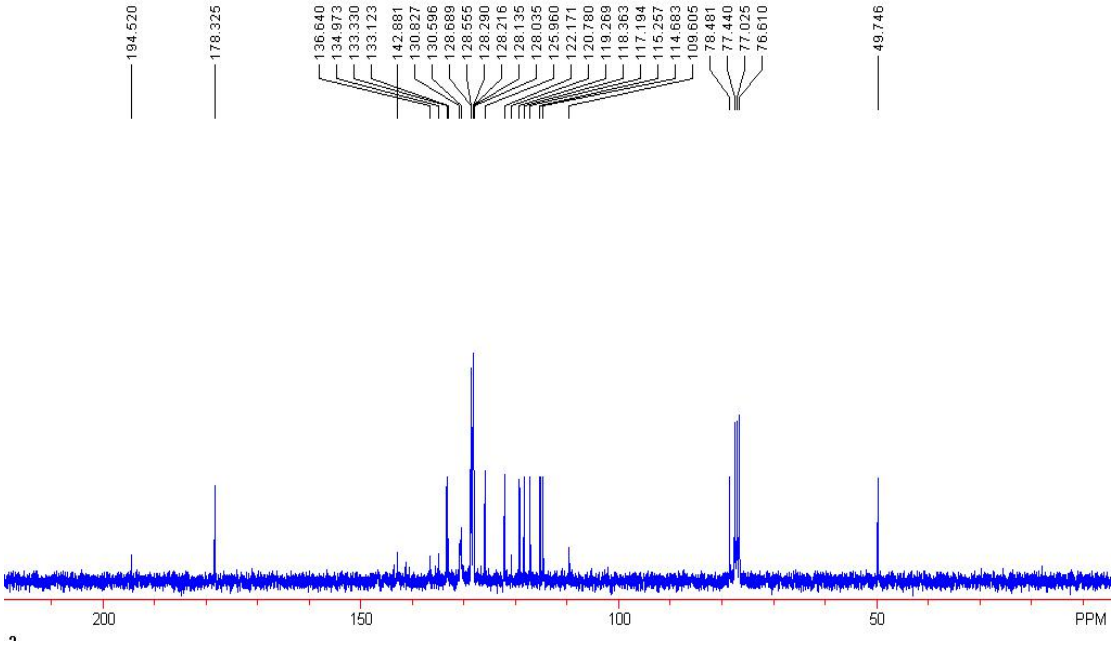



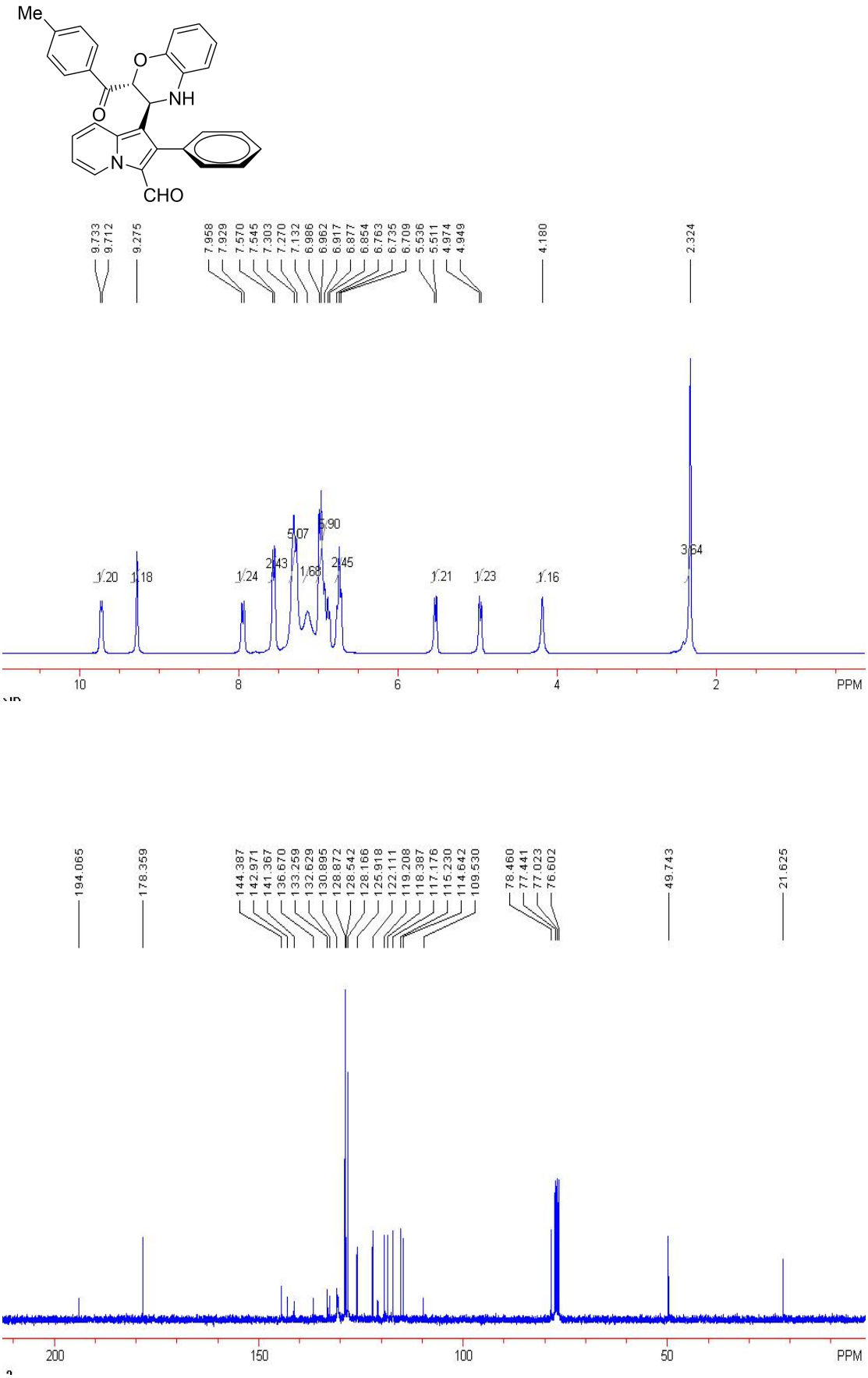
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3a**



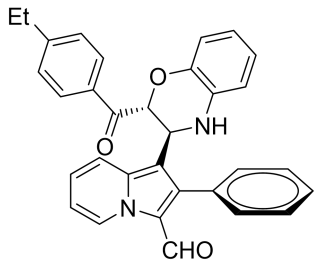



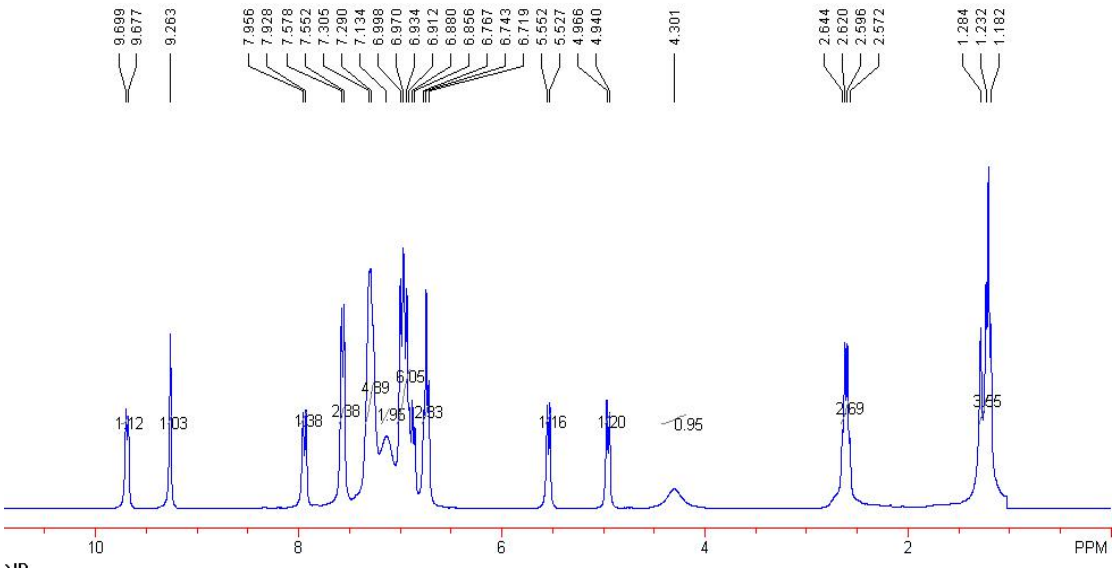



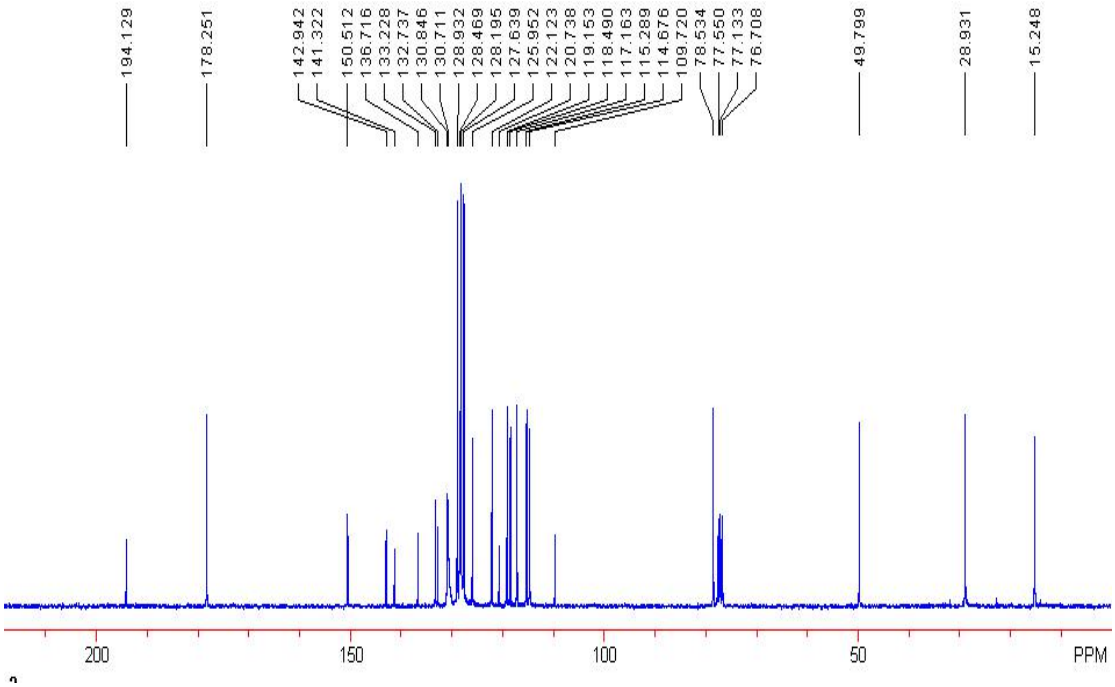
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3b**



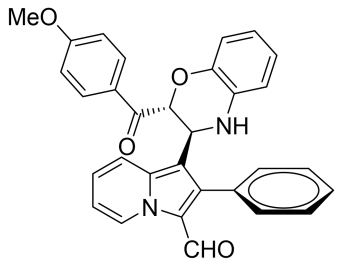
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3c**

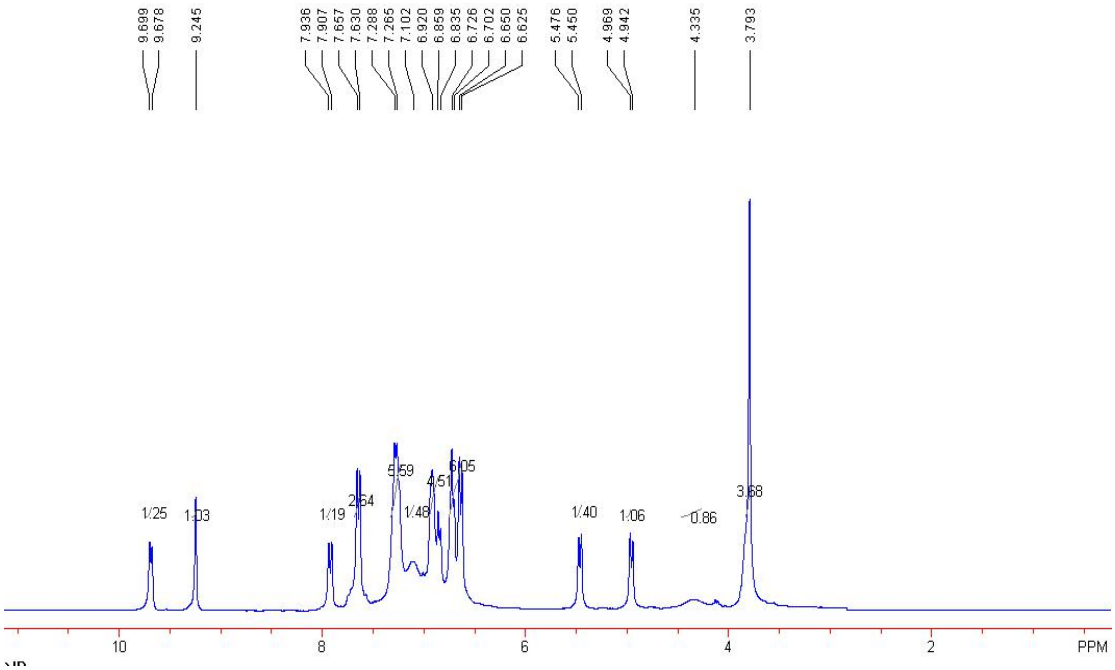


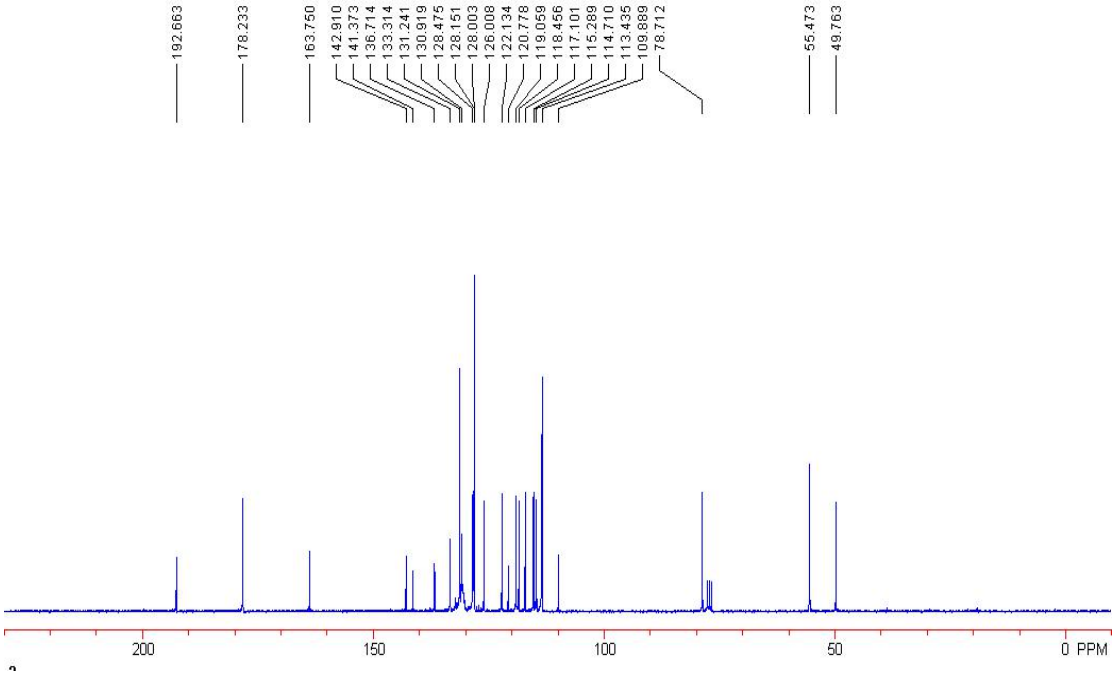



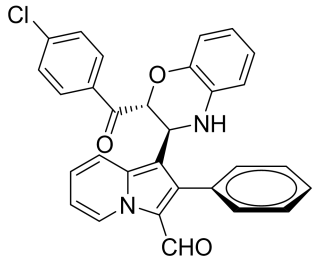
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3d**

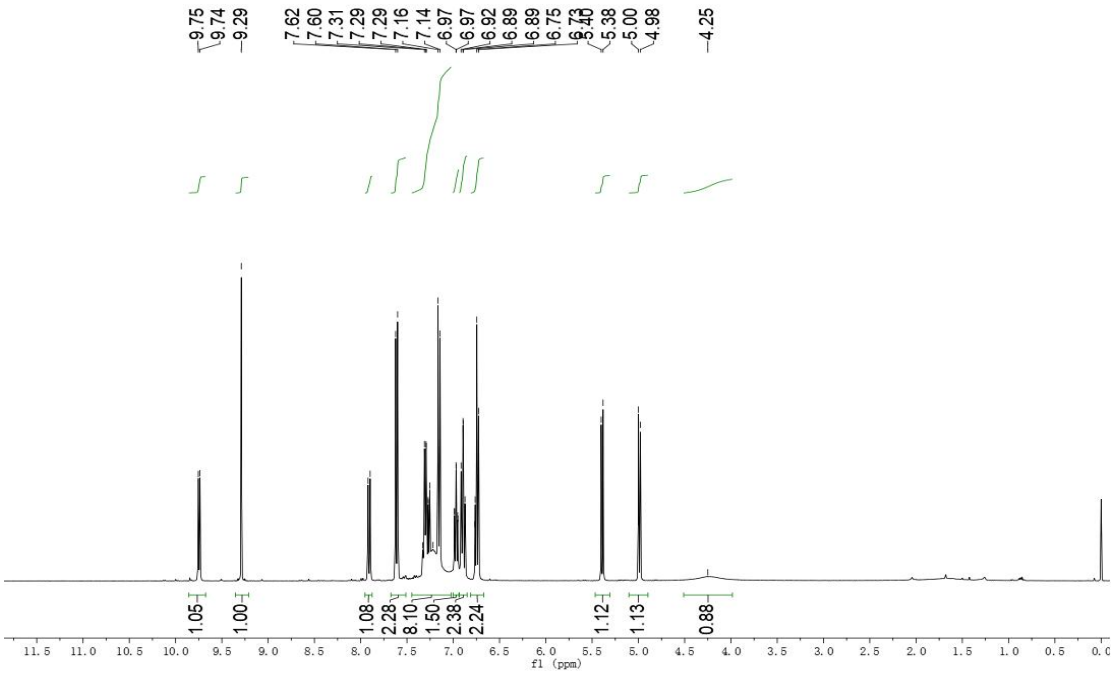


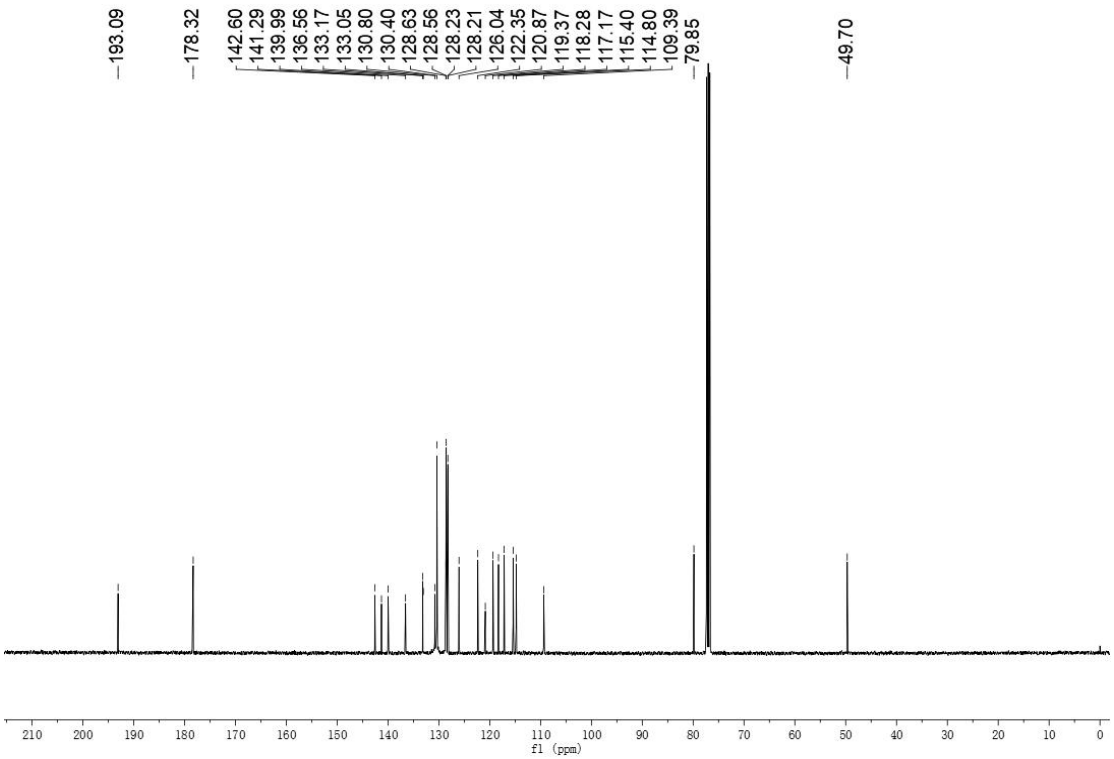



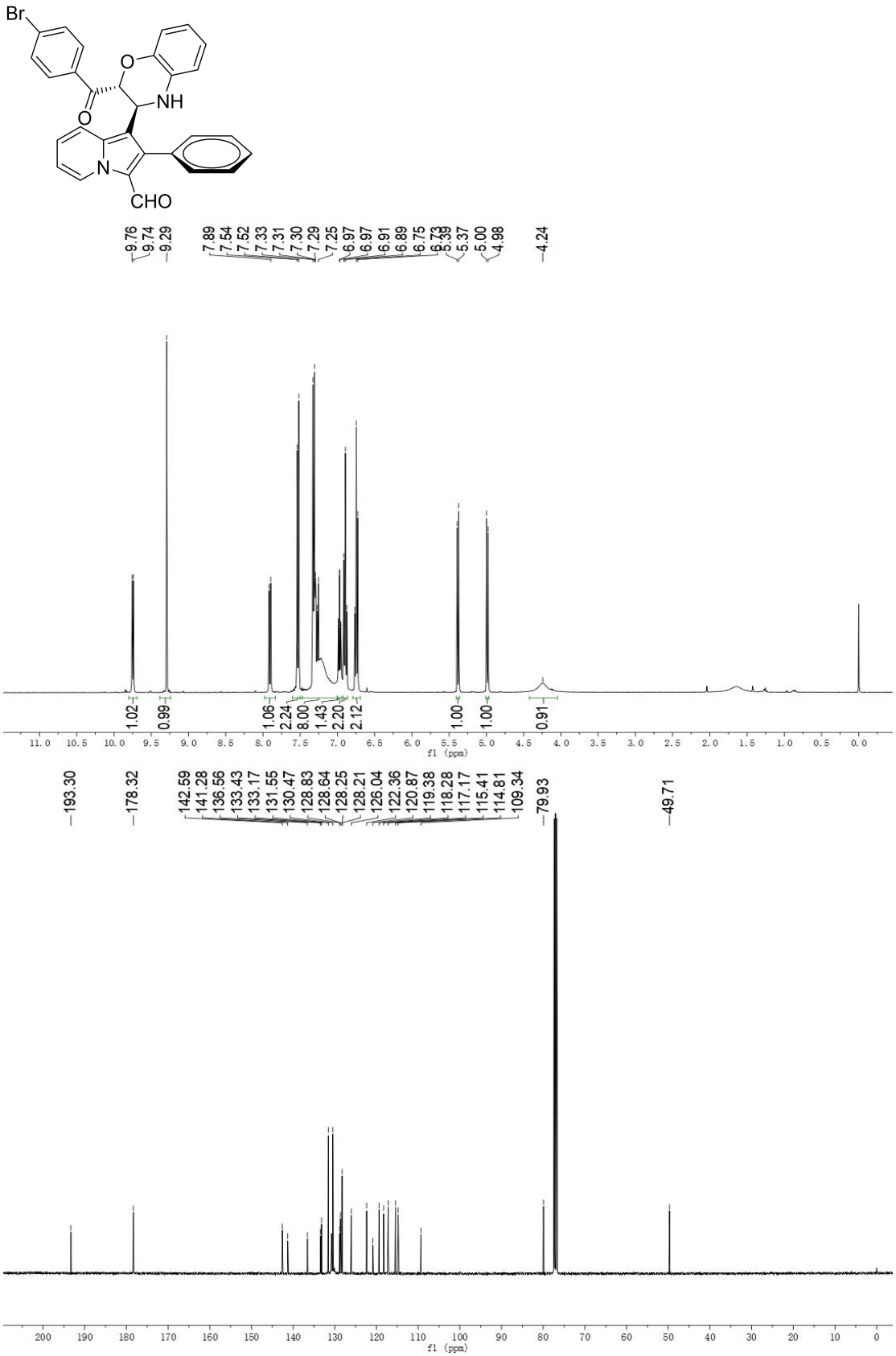
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3e**



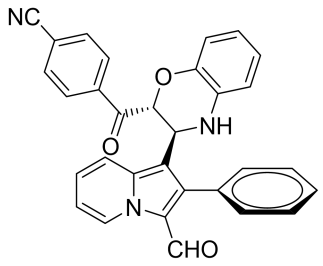



**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3f**

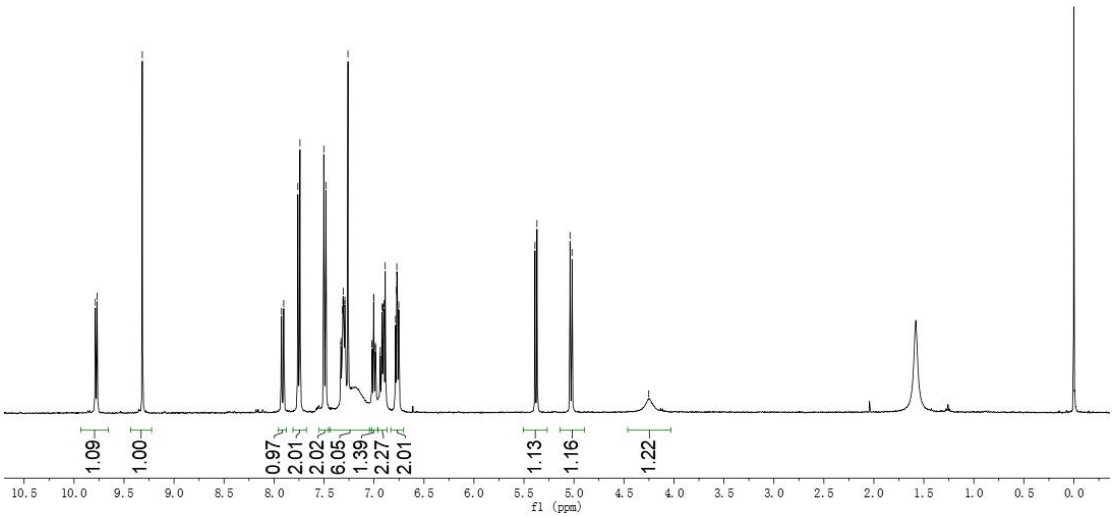


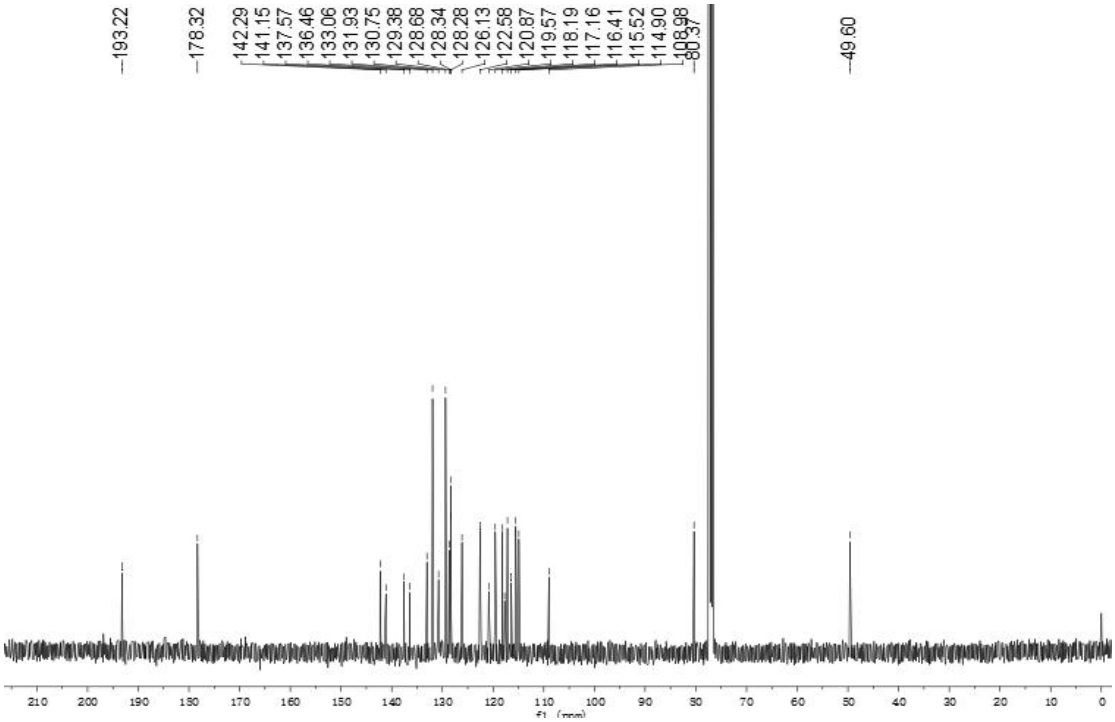
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3g**



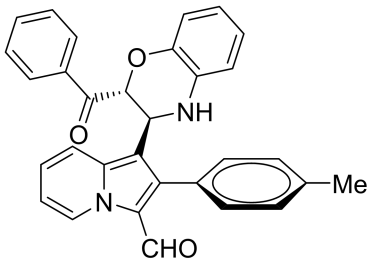


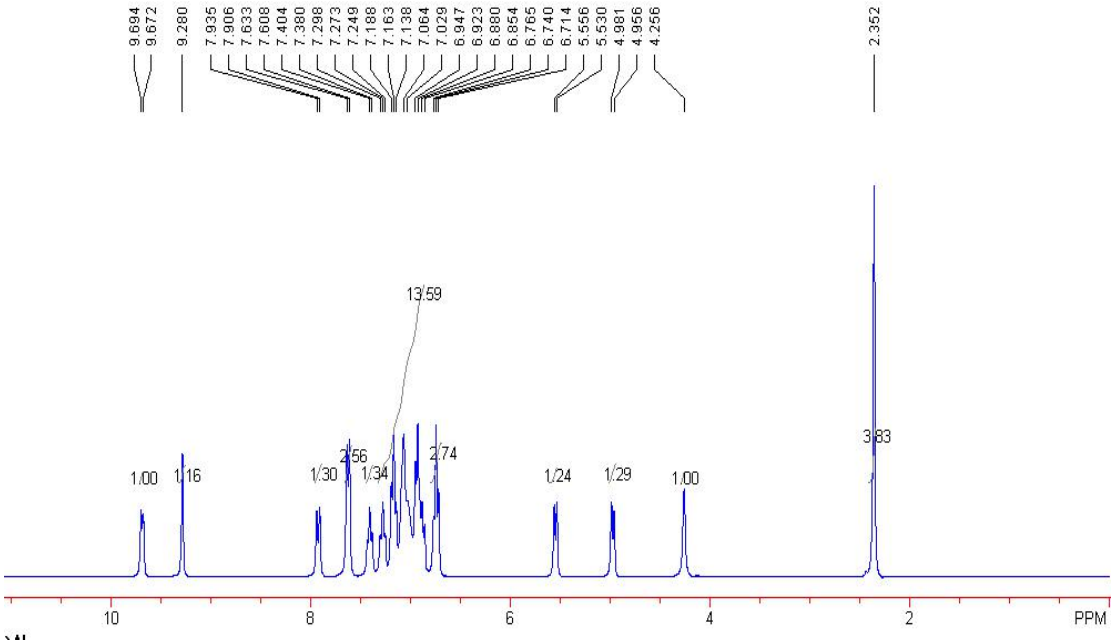


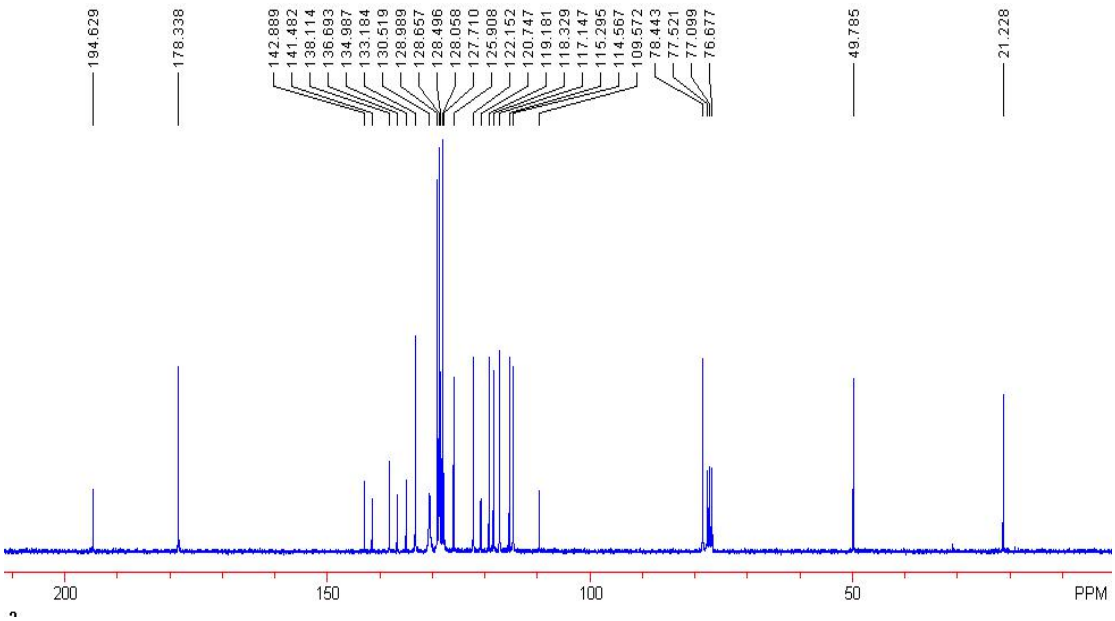


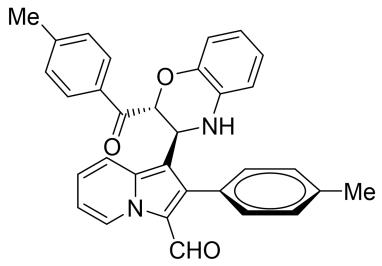
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3i**

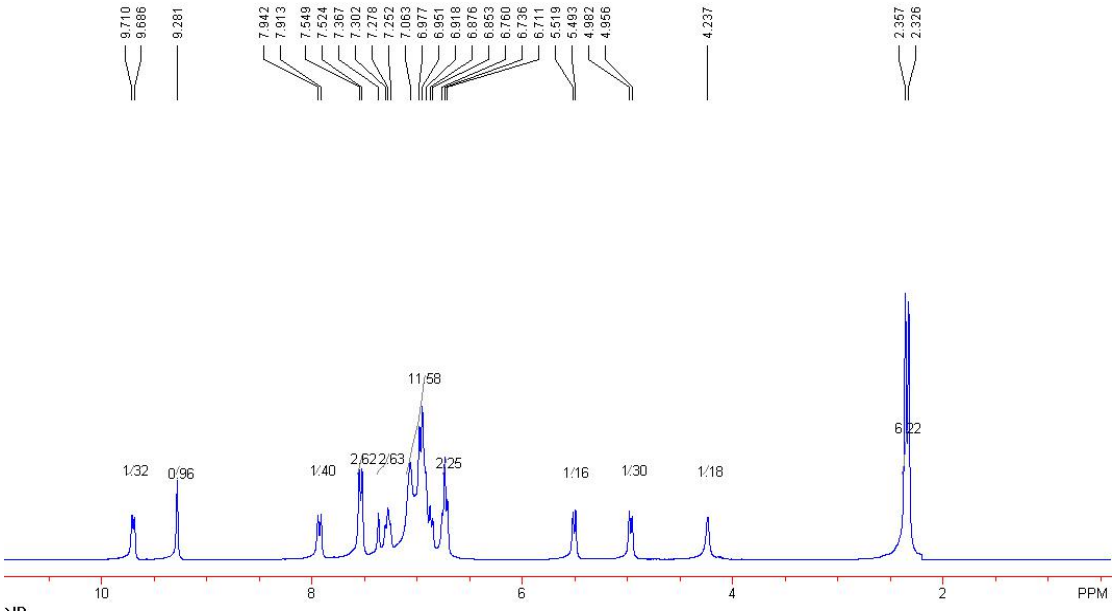


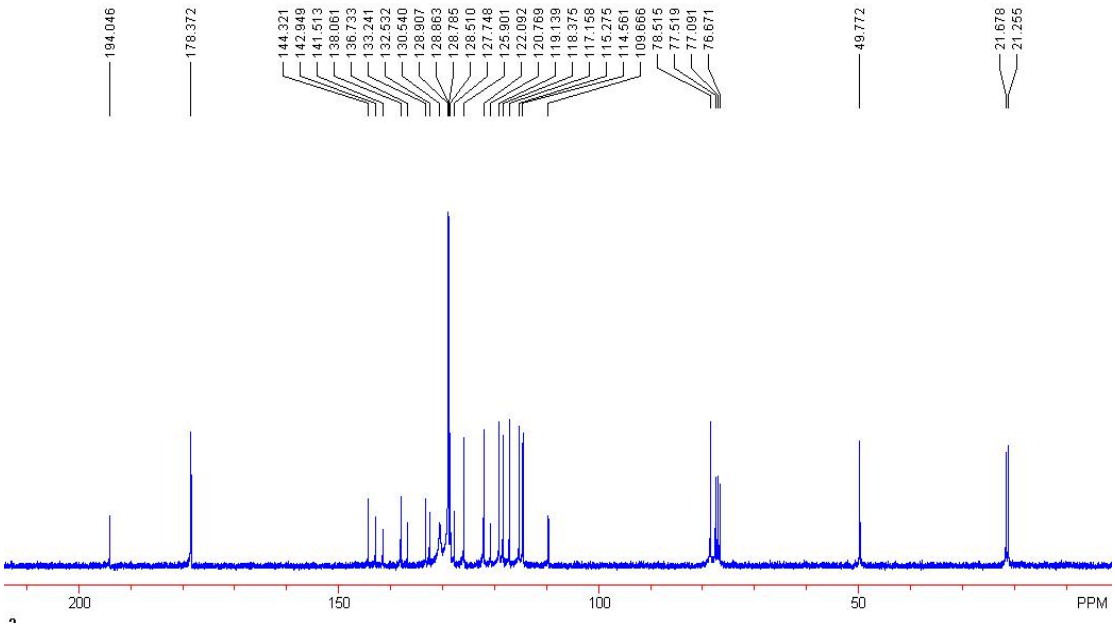



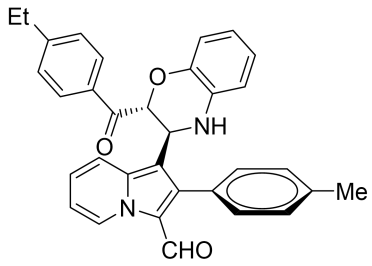
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3j**

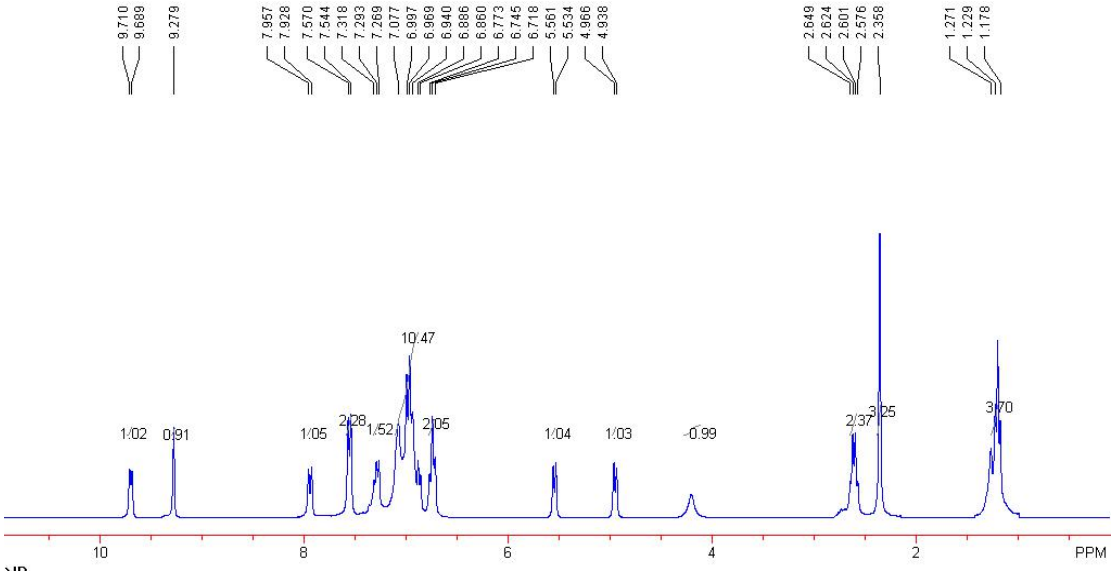


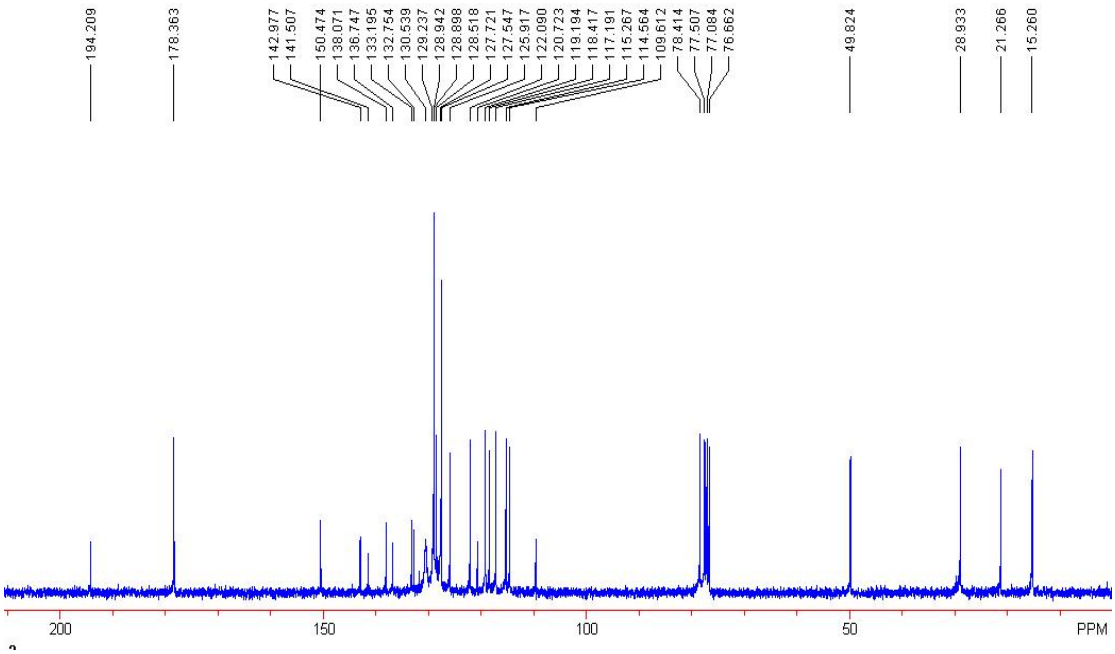



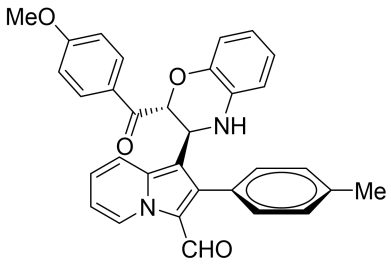
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3k**

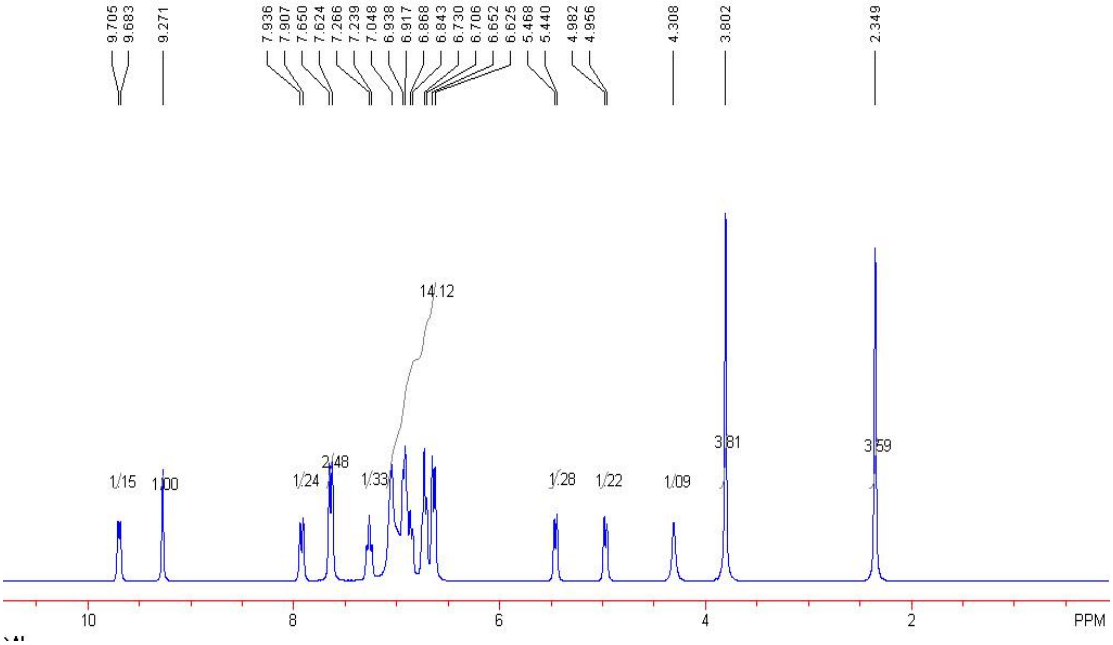


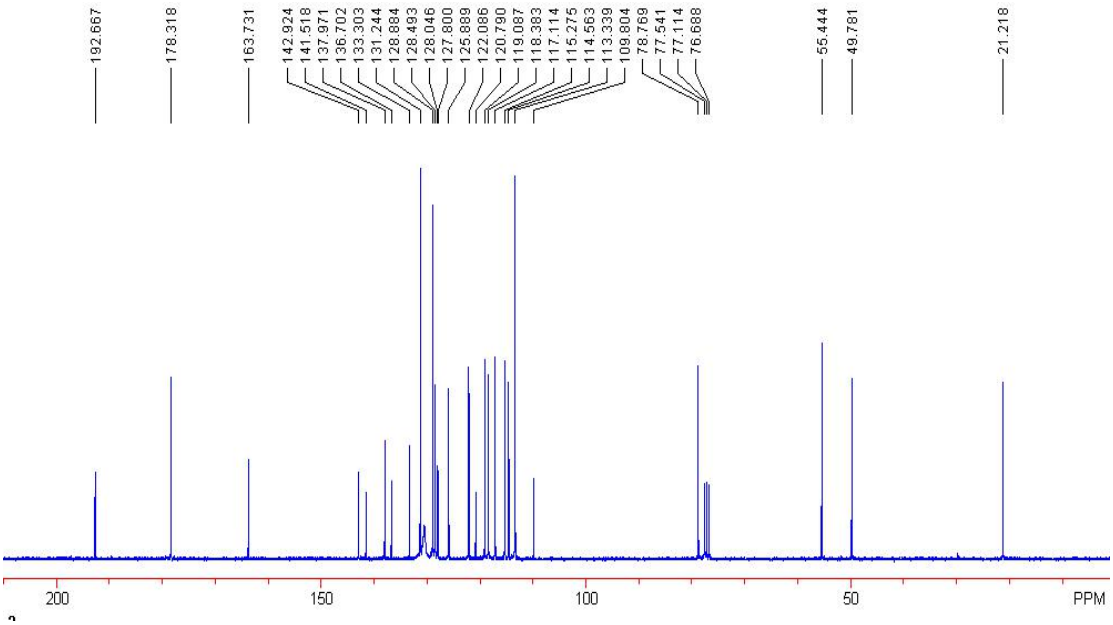



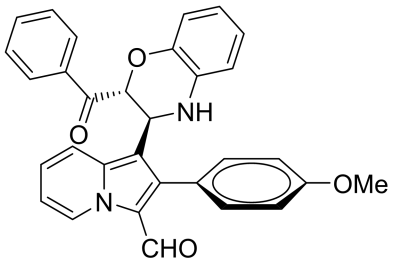
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3l**

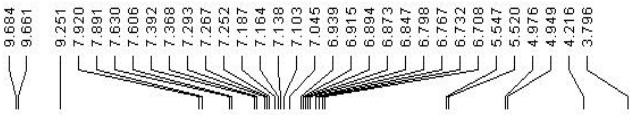


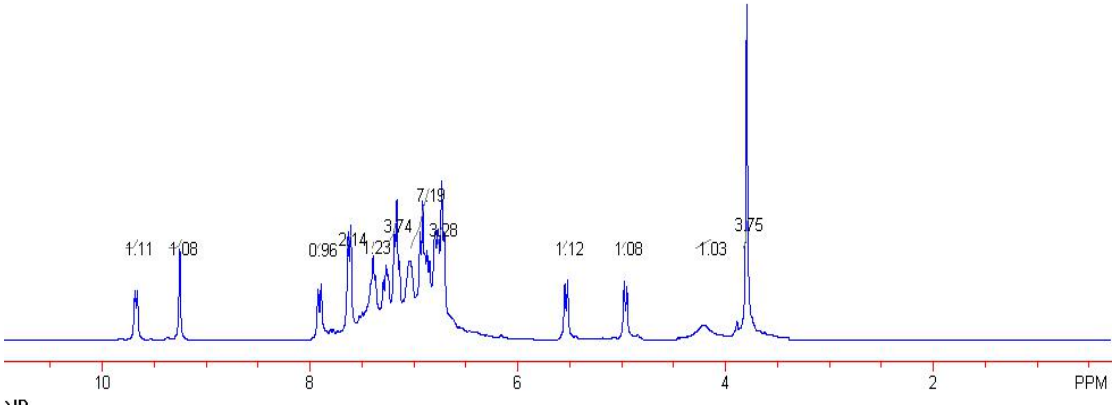



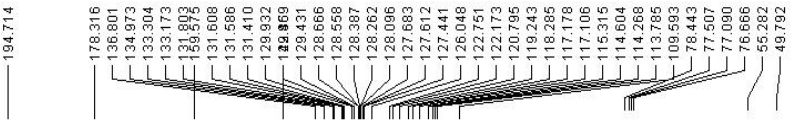



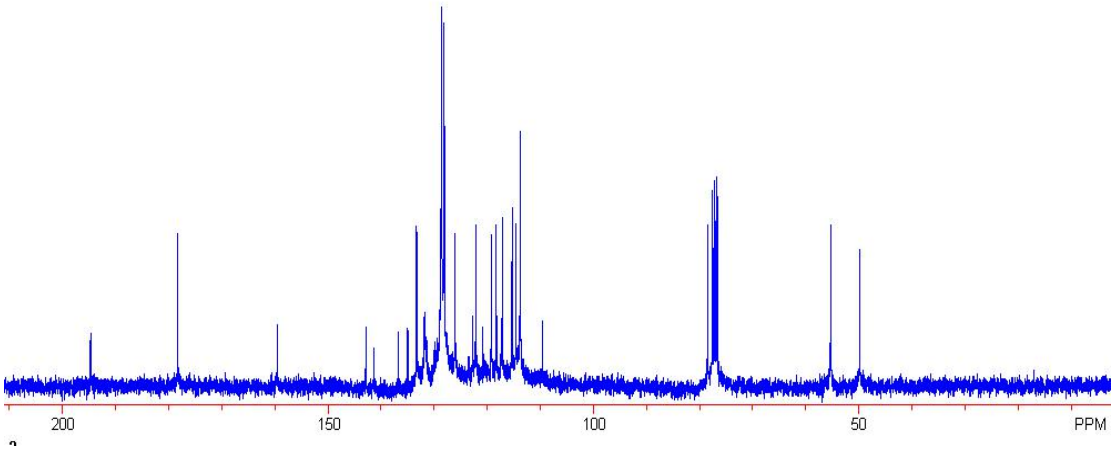
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3m**



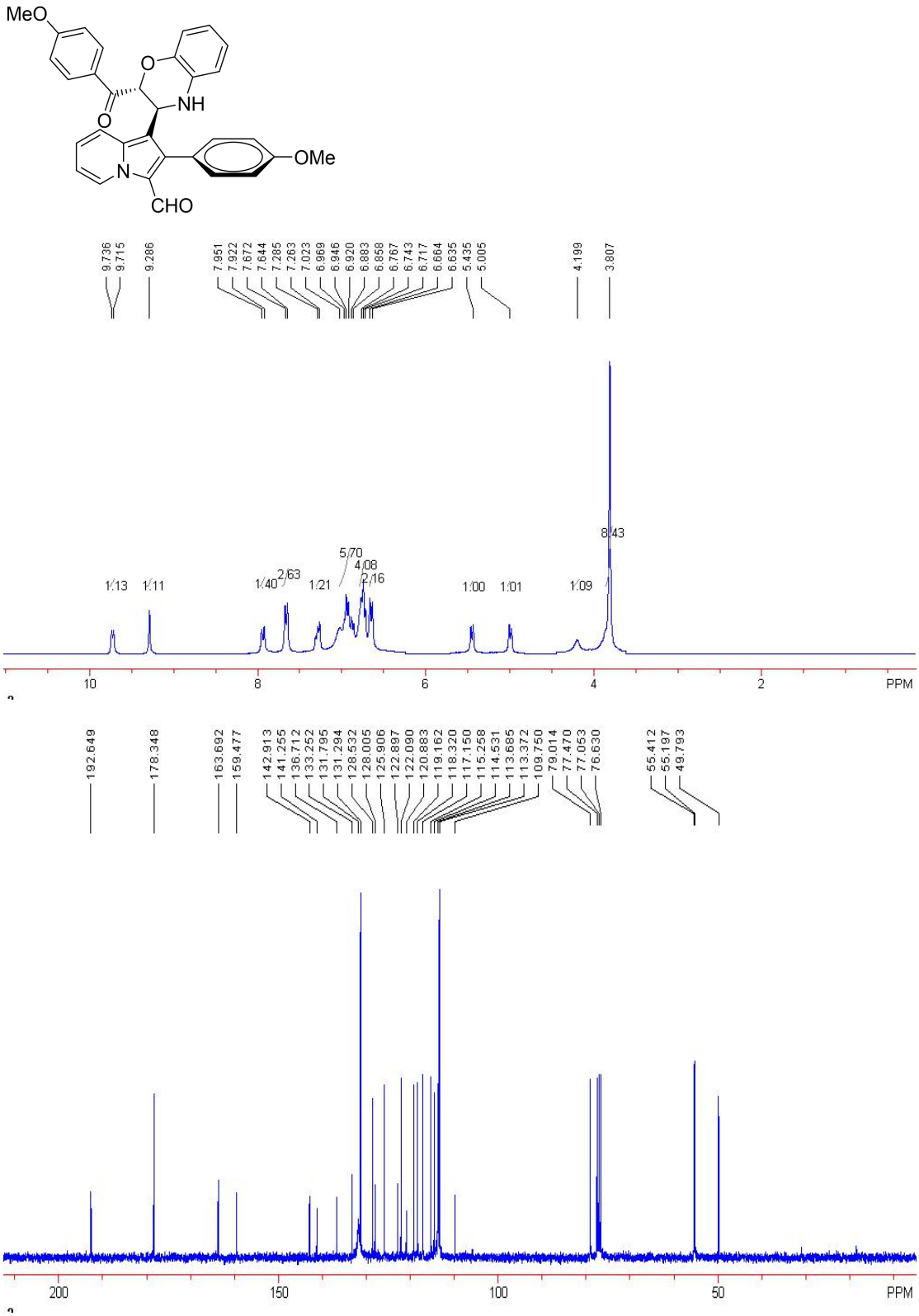



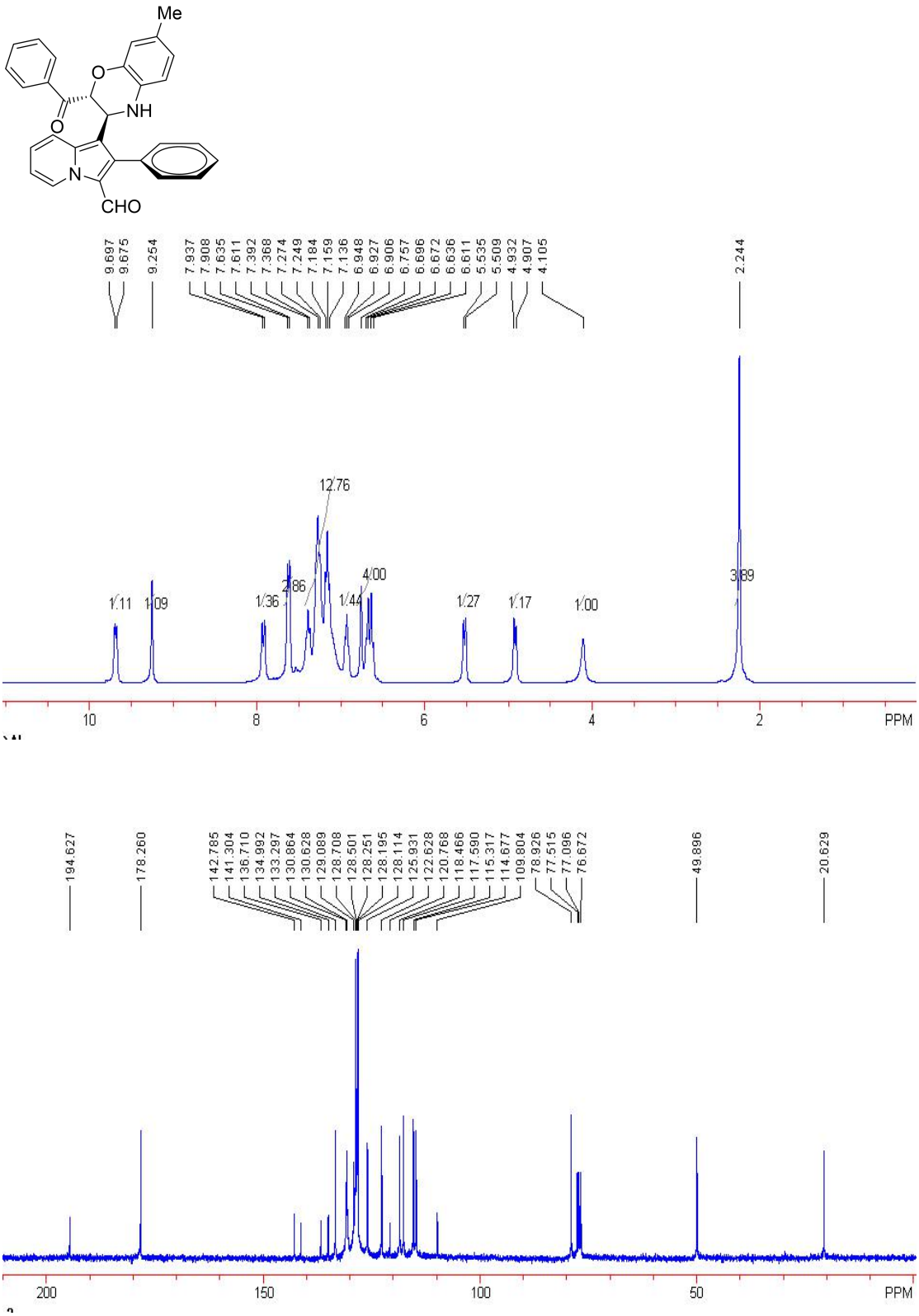



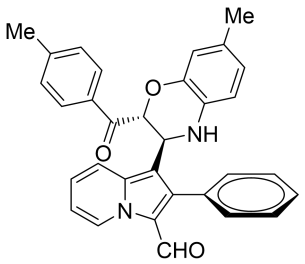
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3n**

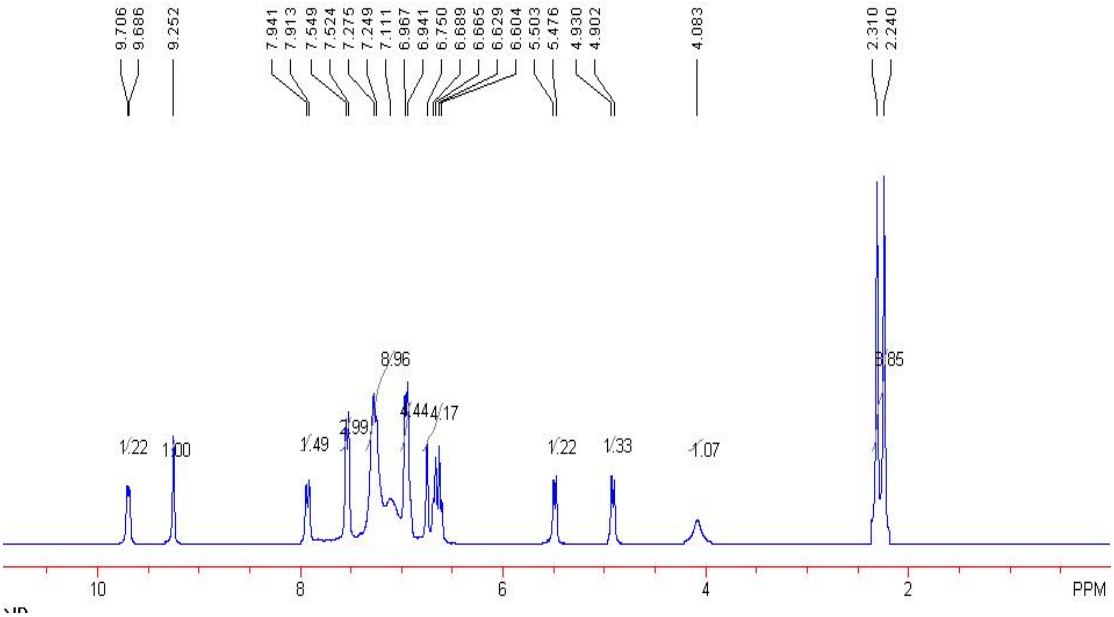


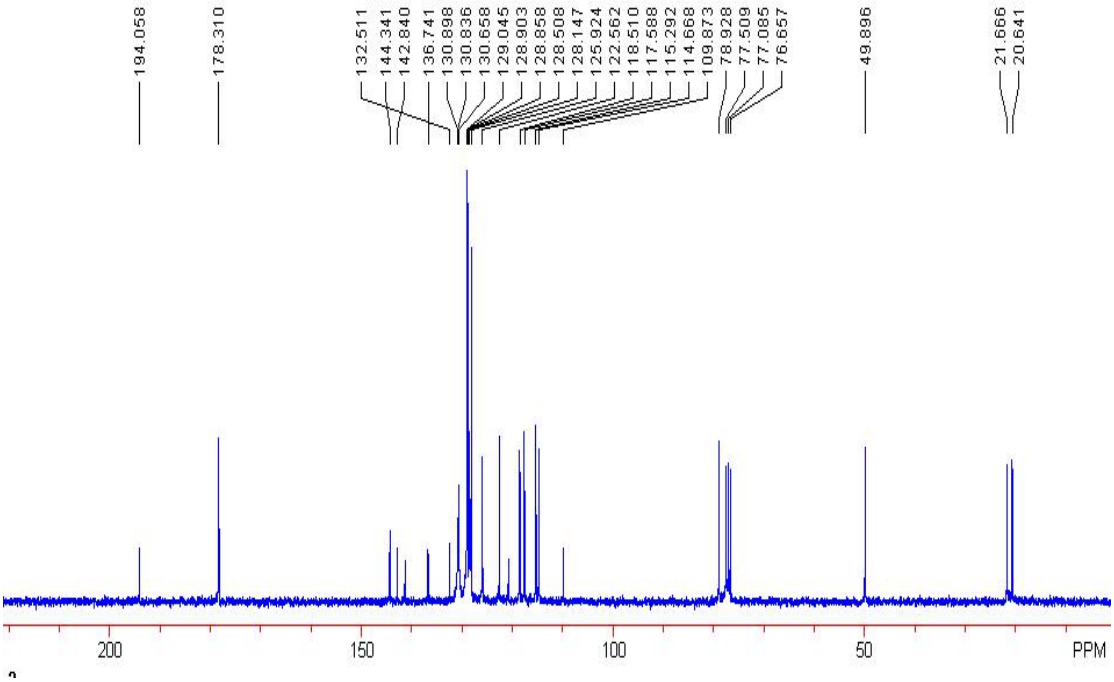
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3p**



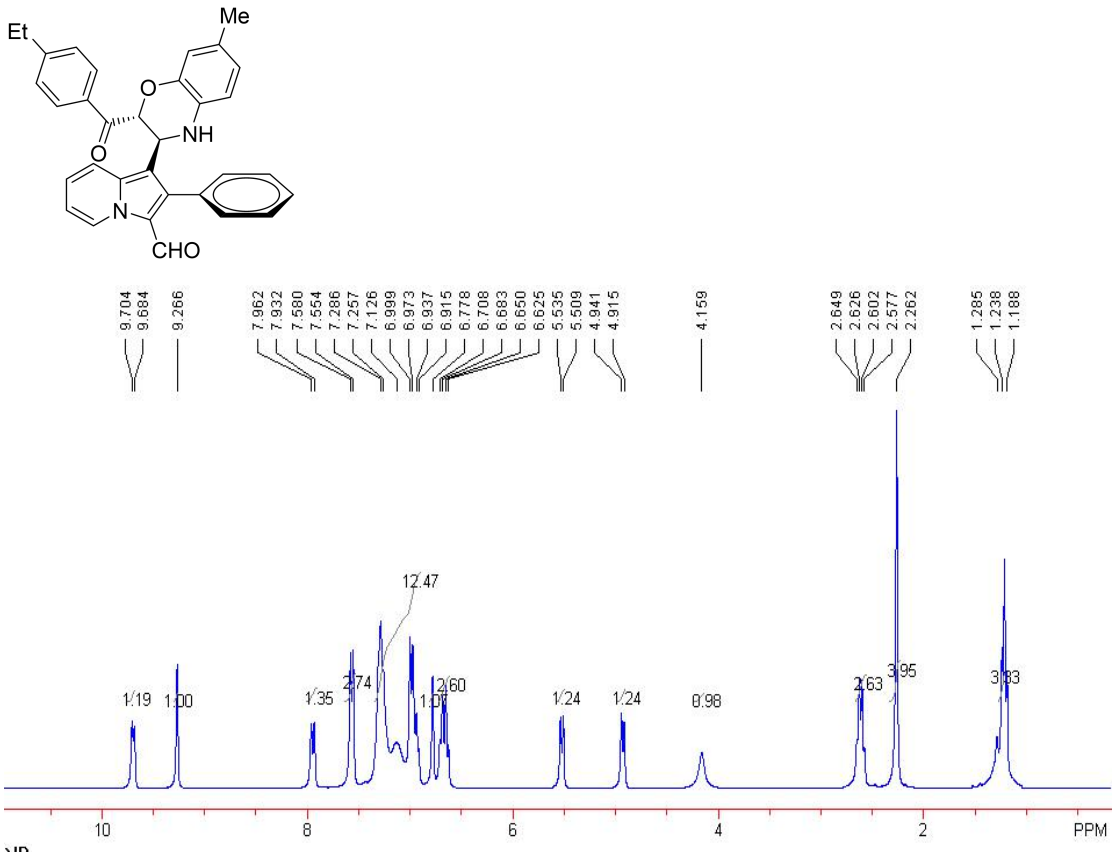
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3q**

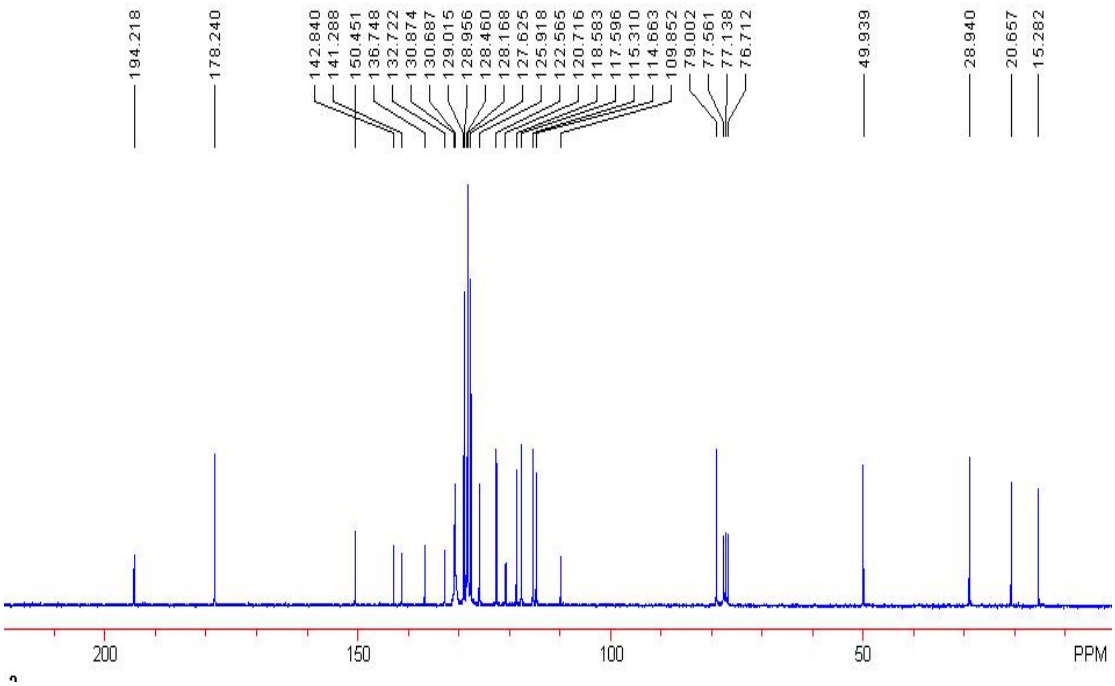


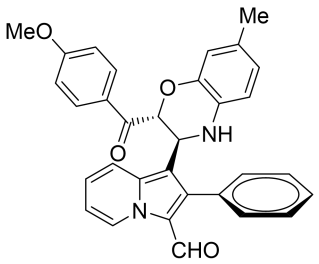



**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3r**

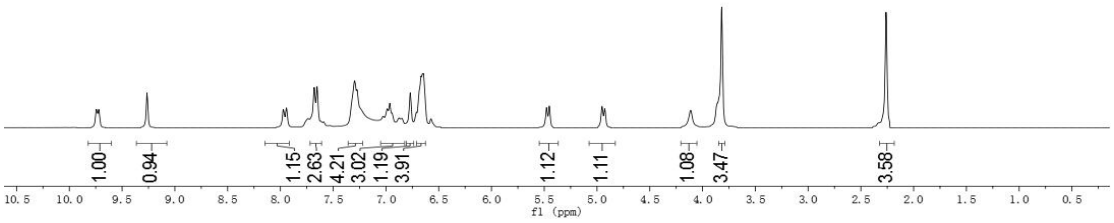


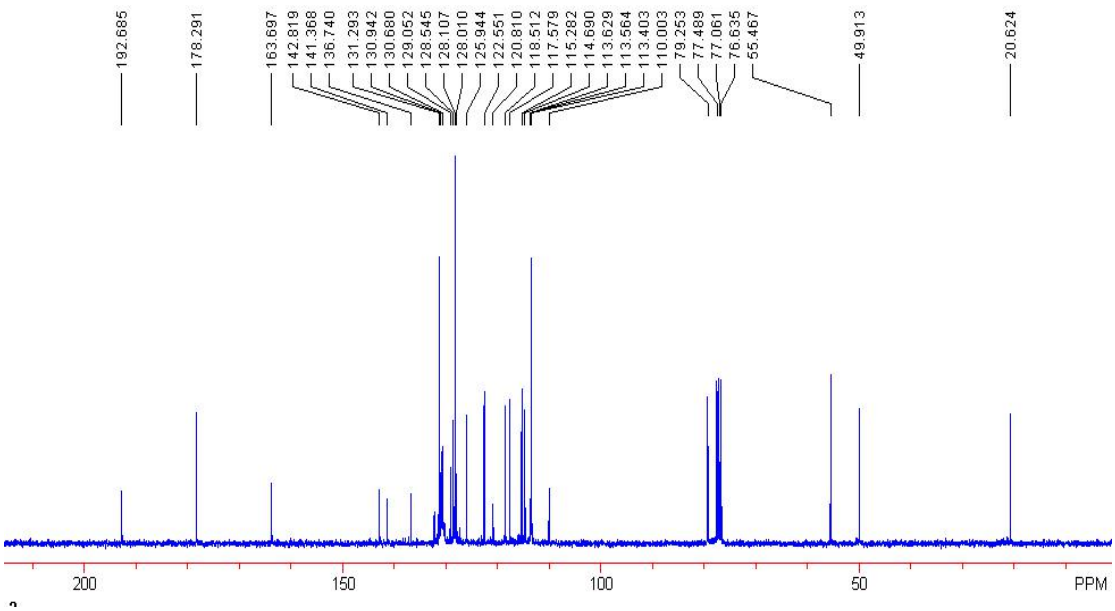



**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3s**

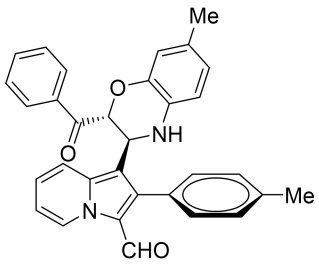


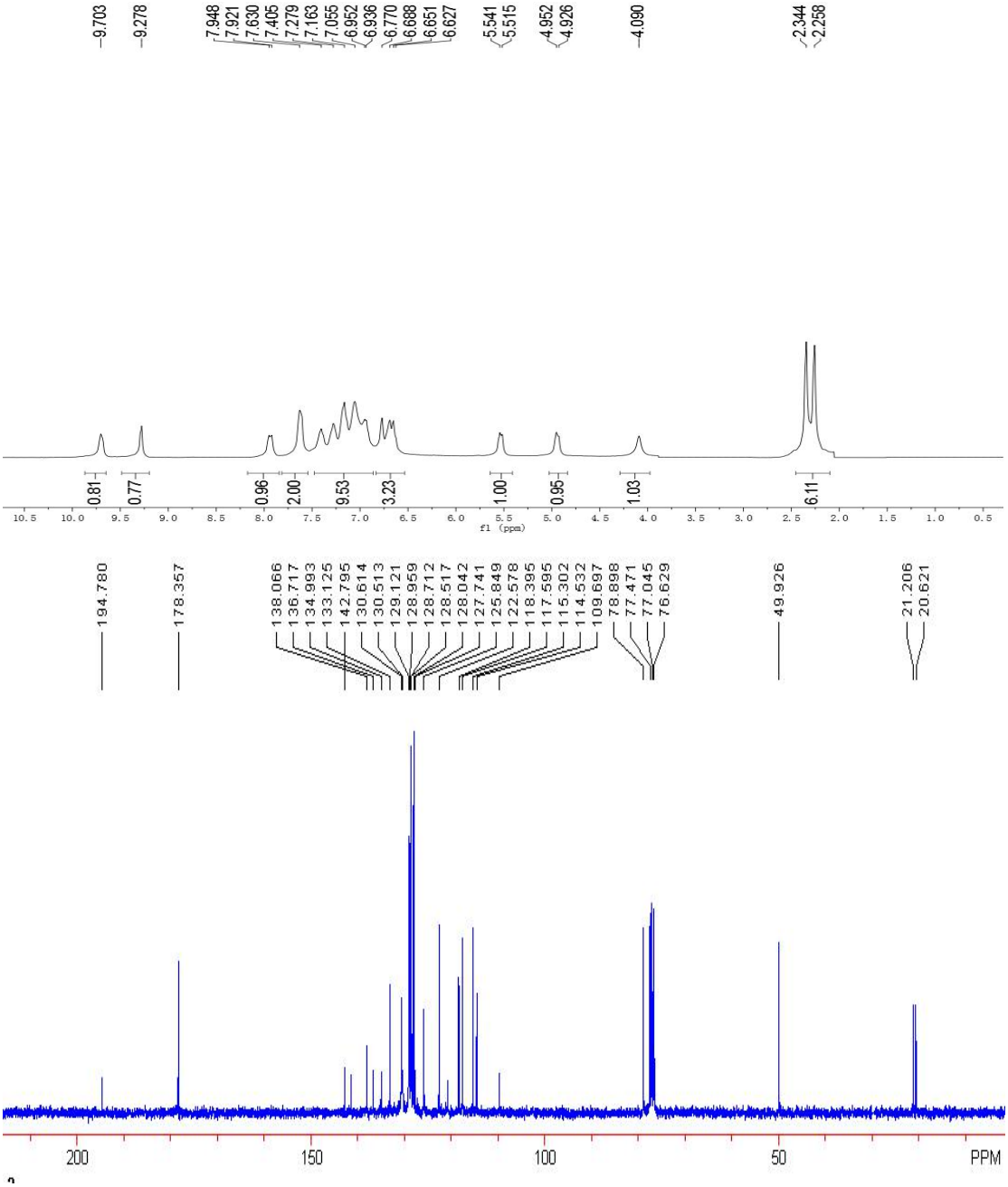




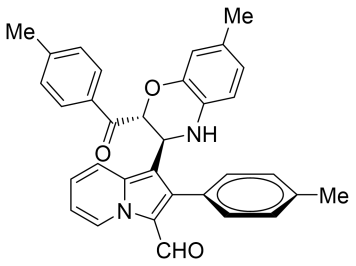



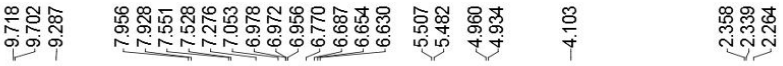
**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3t**

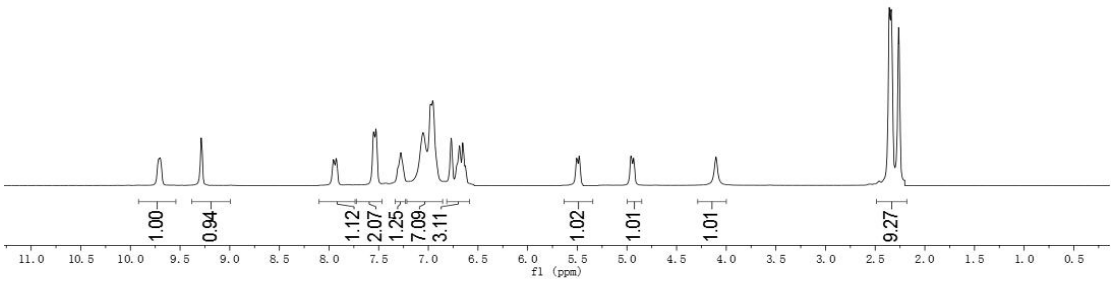


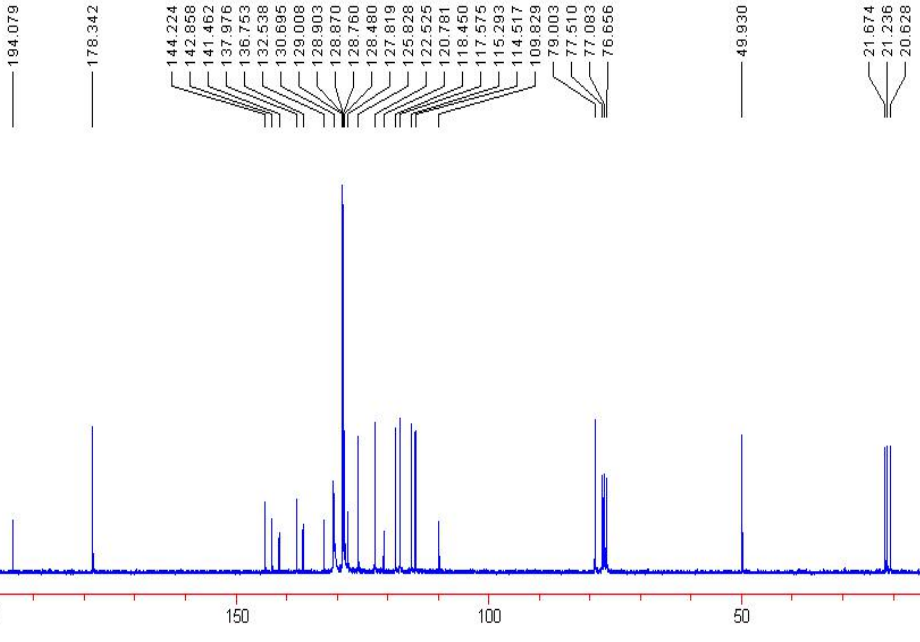



**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3u**

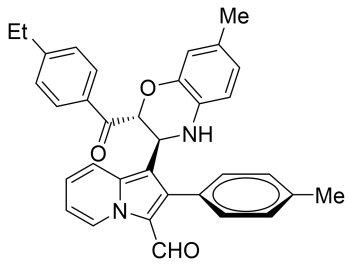


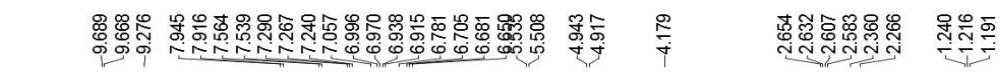



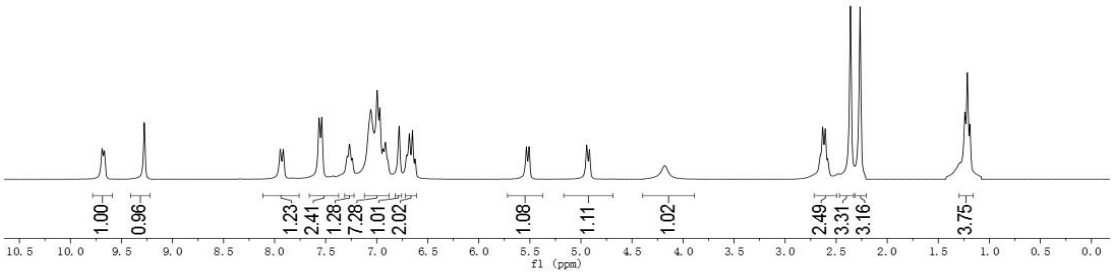



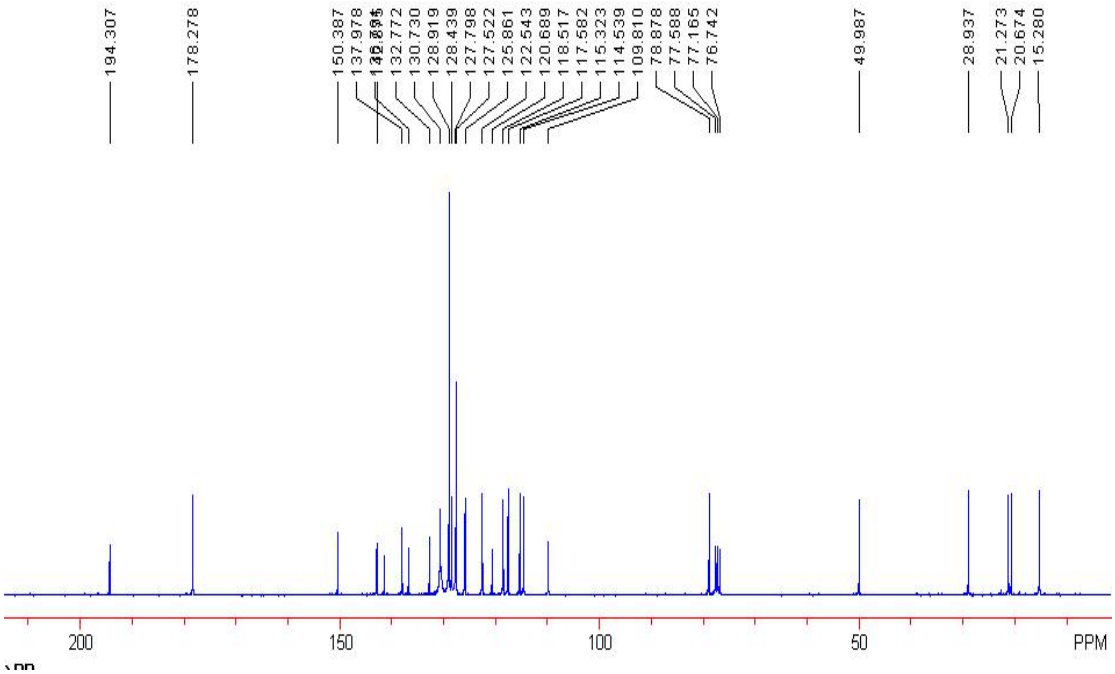



**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3v**

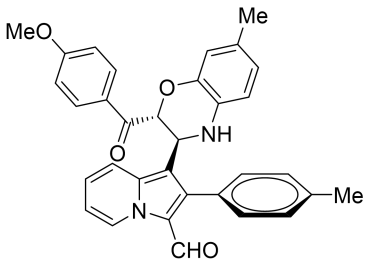


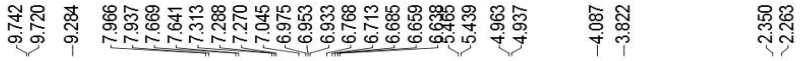



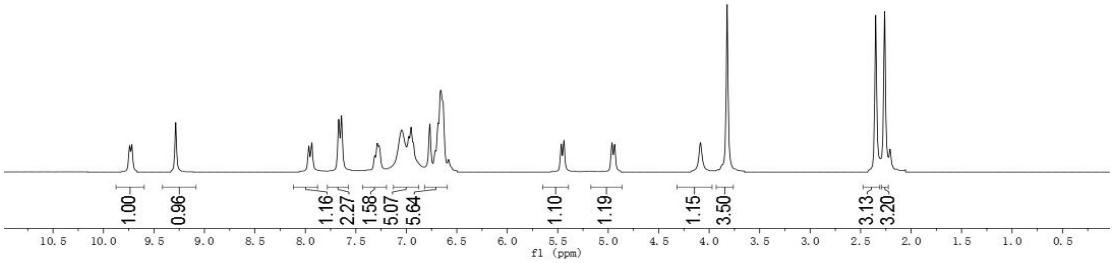



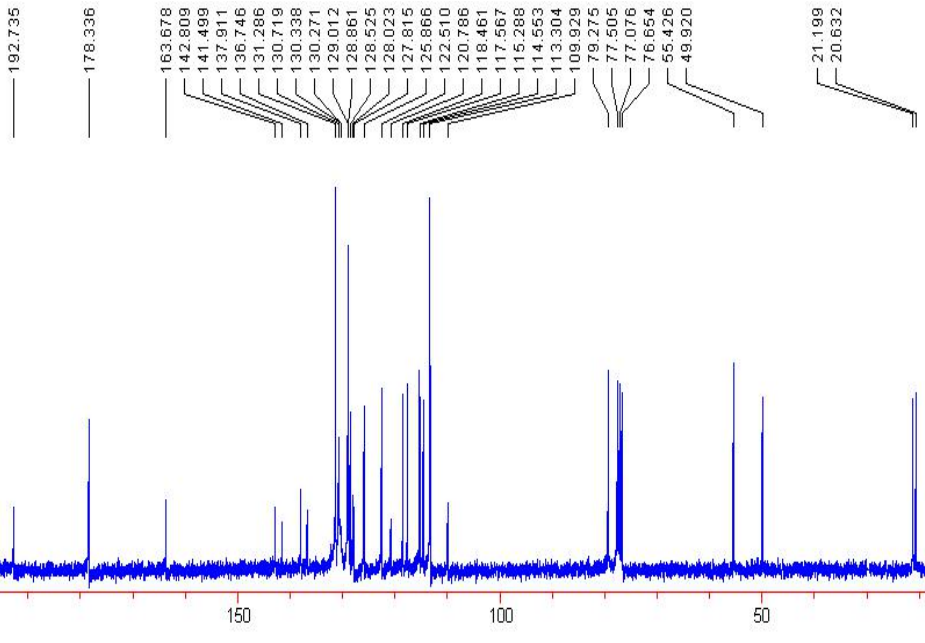



**$^{1}$H and $^{13}$C NMR Spectrum of Compound 3w**

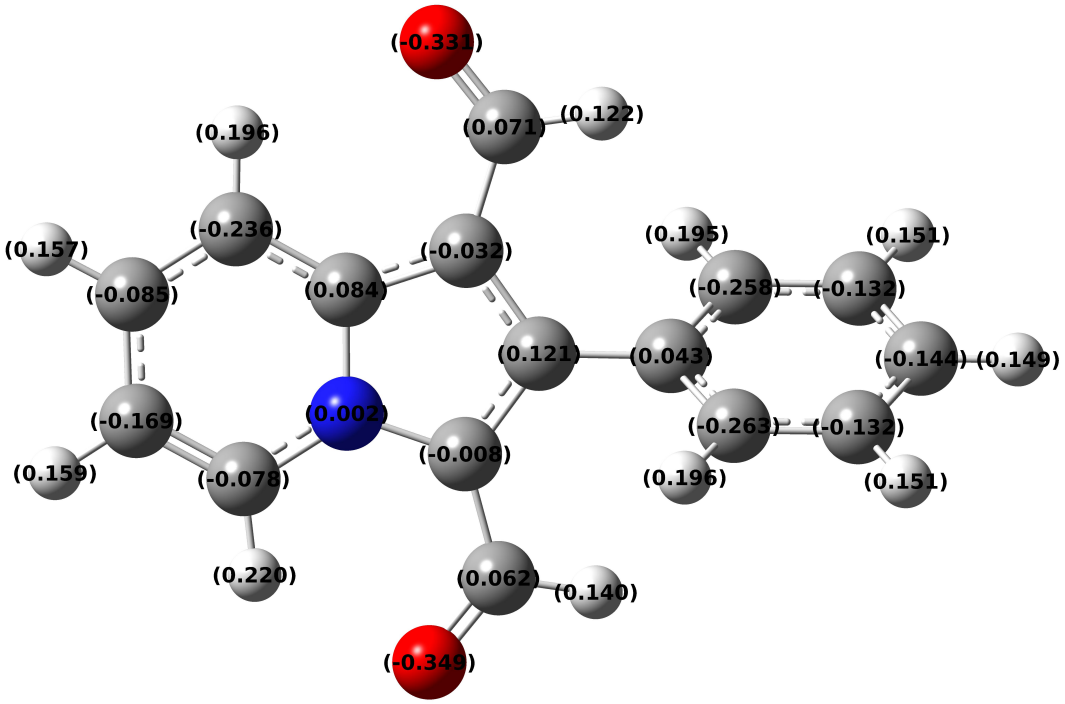


**Charge distribution of 2-phenylindolizine-1,3-dicarbaldehyde**



## Crystal data and structure refinement for 3c

The diffraction data for **3c** were collected on a Bruker SMART APEX diffractometer using Mo K α (λ = 0.71073 Å). The crystallographic data are listed in Table S1. The CIF deposition number: **CCDC-1410567**.

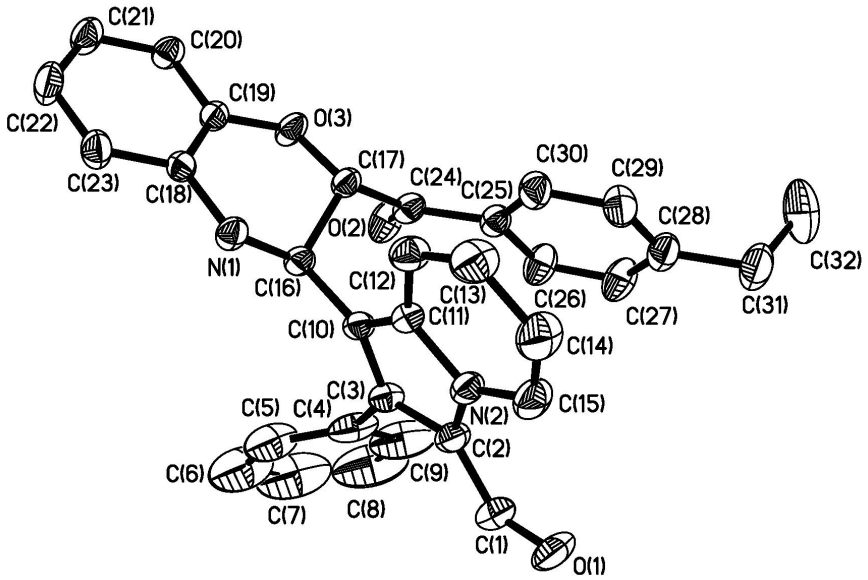
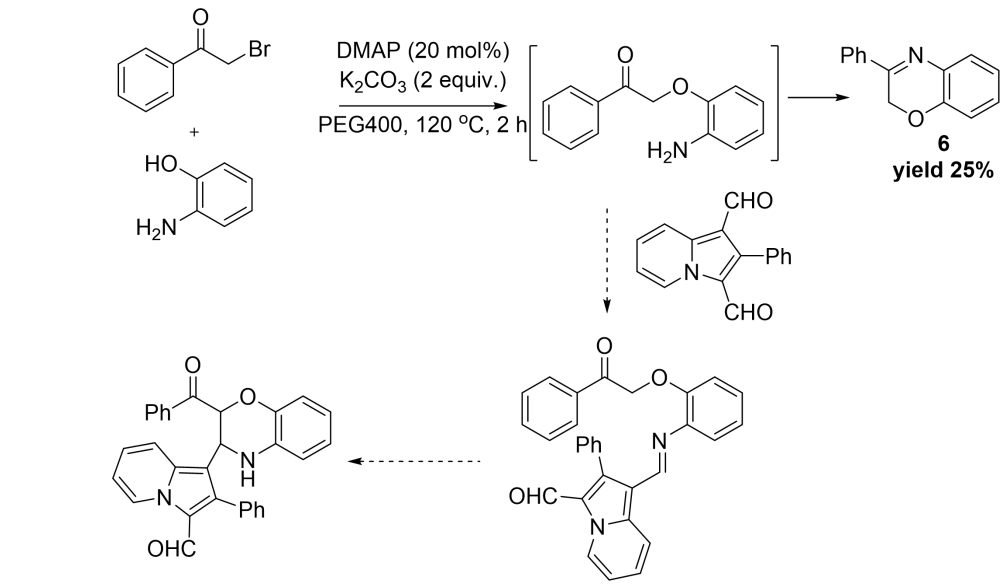



**Table S1.** Crystal data and structure refinement for **3c**.

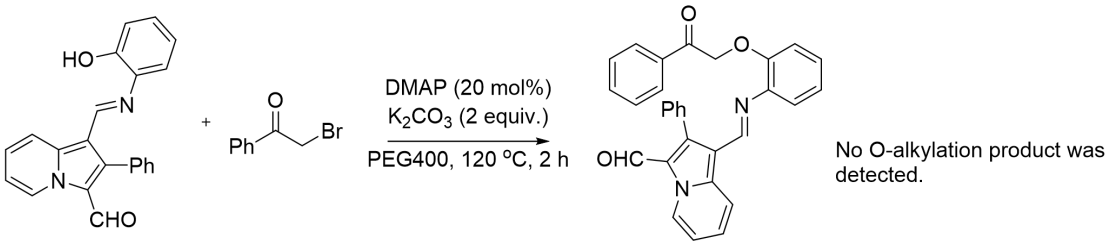
| | |
|---|---|
| Identification code | 091204a |
| Empirical formula | C32 H26 N2 O3 |
| Formula weight | 485.54 |
| Temperature | 293(2) K |
| Wavelength | 0.71073 A |
| Crystal system, space group | Monoclinic, P2(1)/c |
| Unit cell dimensions | a = 9.7305(7) A alpha = 90 deg. |
| | b = 11.2480(9) A beta = 94.0330(10) deg |
| | c = 24.1248(18) A gamma = 90 deg. |

| | |
|---|---|
| Volume | 2633.9(3) A^3 |
| Z, Calculated density | 4, 1.224 Mg/m^3 |
| Absorption coefficient | 0.079 mm^-1 |
| F (000) | 1020 |
| Crystal size | 0.15 x 0.12 x 0.11 mm |
| Theta range for data collection | 2.00 to 27.55 deg |
| Limiting indices | -12<=h<=12, -14<=k<=13, -31<=l<=30 |
| Reflections collected / unique | 22413 / 6051 [R(int) = 0.0384] |
| Completeness to theta = 25.74 | 99.5 % |
| Absorption correction | None |
| Max. and min. transmission | 0.9914 and 0.9882 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 6051 / 36 / 335 |
| Goodness-of-fit on F^2 | 1.022 |
| Final R indices [I>2 sigma (I)] | R1 = 0.0586, wR2 = 0.1514 |
| R indices (all data) | R1 = 0.1007, wR2 = 0.1783 |
| Largest diff. peak and hole | 0.430 and -0.397 e.A^-3 |

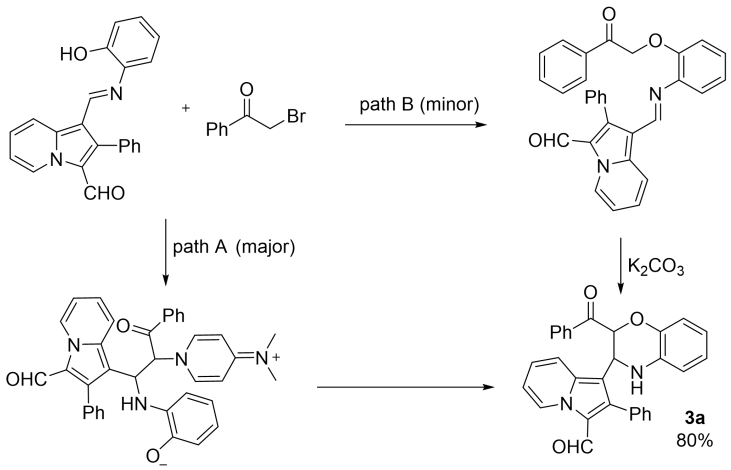
**Evidence of mechanism speculation**




2-bromo-1-phenylethan-1-one and 2-aminophenol were chosen to prepare O-alkylation product, which would react with 2-phenylindolizine-1,3-dicarbaldehyde and then afford compound **3a** via intramolecular Mannich reaction. Indeed, compound **6** was obtained as the sole product in 25% yield in this reaction.




In the reaction between **4a** and **5a**, O-alkylation is possible, while no O-alkylation was detected in the reaction. It is not difficult to draw conclusion that the O-alkylation product proceeded intramolecular ring closure reaction to obtain **3a** (Synthesis, 2012, 44, 2919). In addition, the yield of compound **3a** is much higher than that of compound **6**. Combining with document reports, we believe that path **A** is the main route to form compound **3a**.




Possible mechanism for the synthesis of compound **3a**

$^{1}H$ and $^{13}C$ NMR Spectrum of **6**