Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

DBU-promoted cyclization of vinyl isocyanides with ethers via functionalization of C(sp^3)–H bond for the synthesis of isoquinolines

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1. General informaiton

Vinyl isocyanide **1** were synthesized according to literature.[1] The other reagents were obtained from commercial suppliers and used without further purification. The reactions were conducted under an atmosphere of N_2 and were monitored by TLC. Solvents were dried and distilled prior to use. Flash chromatography was performed using silica gel 60 (300–400 mesh). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AVANCE400M spectrometer. Melting points were uncorrected. Infrared spectra were obtained on a Bruker Vector 22 in KBr pellets. HRMS were conducted on an Agilent 6540Q-TOF LC/MS equipped with an electrospray ionization (ESI) probe operating in positive or negative ion mode.

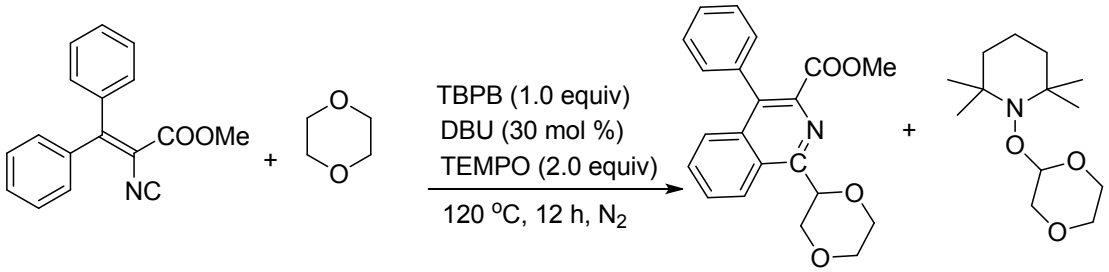
Reference

1. Wang, H.; Yu, Y.; Hong, X.; Xu, B. *Chem. Commun.* **2014**, *50*, 13485.

2. General procedure for radical cyclization between vinyl isocyanide with ethers

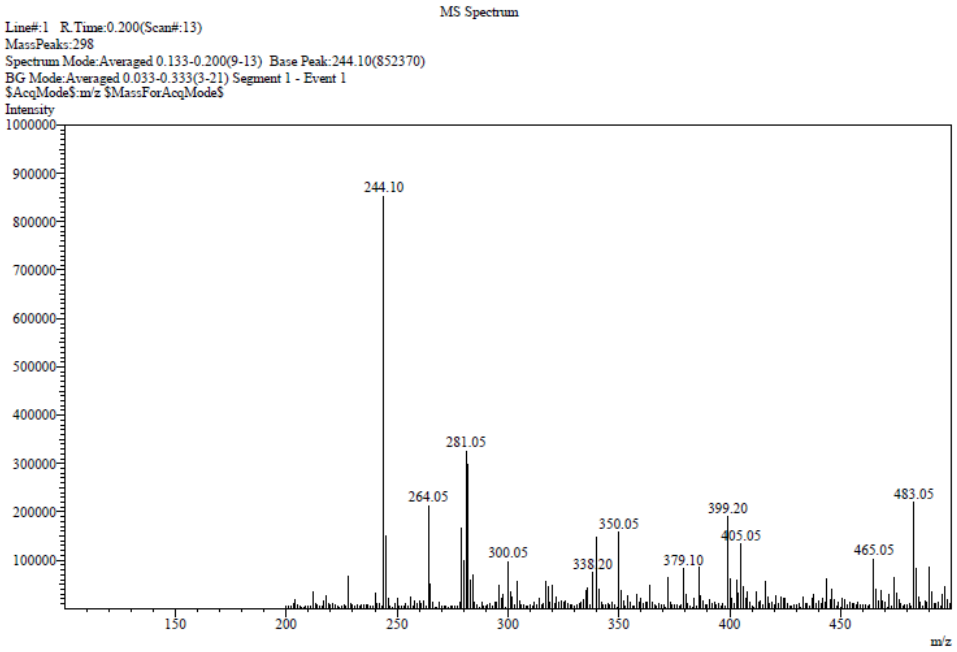
Into an oven-dried reaction vial flushed with N_2 was added methyl 2-isocyano-3,3-diphenylacrylate (**1a**) (0.2 mmol), 1,4-dioxane (**2a**, 2 mL), TBPB (0.2 mmol), DBU (0.06 mmol). Then the reaction mixture was stirred for 12 hours at 120 ^{o}C under nitrogen atmosphere. After cooling, dichloromethane (30 mL) was added into the reaction, and the mixture was washed with saturated K_2CO_3 solution (1 × 20 mL), water (1 × 30 mL) and brine solution (1 × 30 mL). After drying over anhydrous Na_2SO_4, solvent was removed. The crude mixture was charged onto silica gel and purified by flash chromatography to furnish the corresponding product **3aa**.

3. ESI-Mass analysis of 4

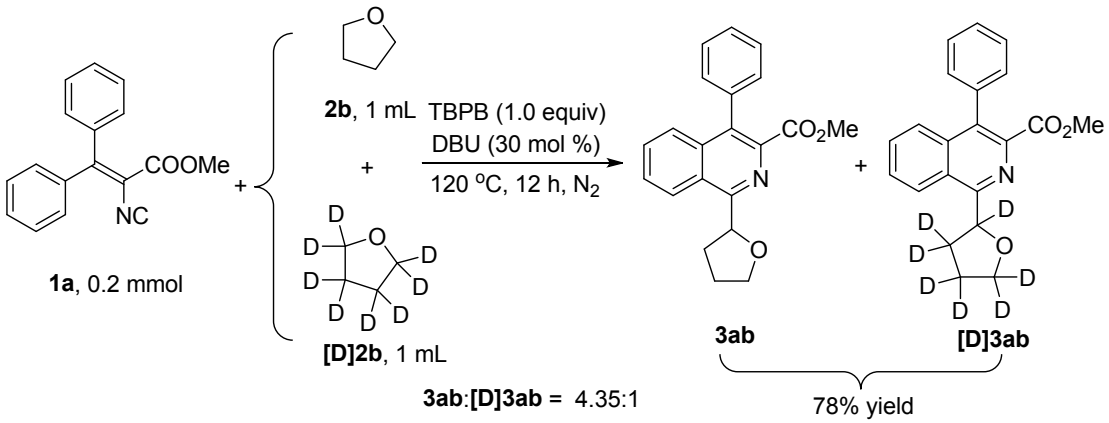


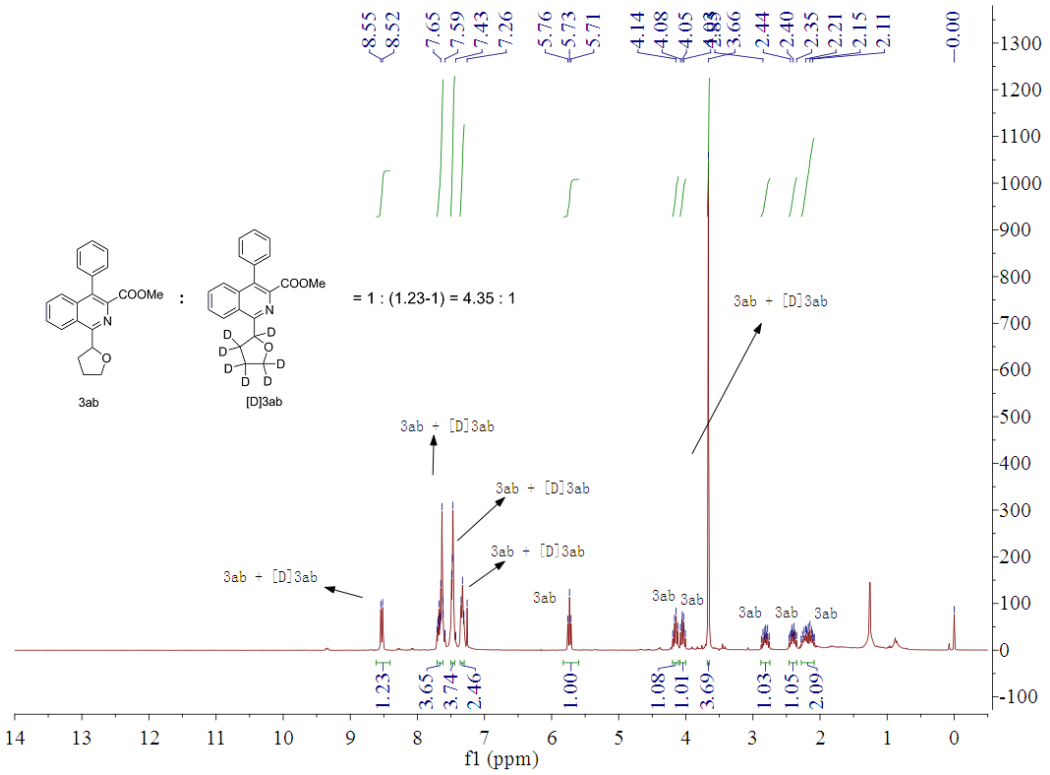
1a, 0.2 mmol **2a**, 2 mL **3aa**, trace **4**

A mixture of methyl 2-isocyano-3,3-diphenylacrylate (**1a**, 0.2 mmol), 1,4-dioxane (**2a**, 2 mL), TBPB (0.2 mmol), DBU (0.06 mmol) and TEMPO (0.4 mmol) was stirred at 120 °C under nitrogen atmosphere. After 12 h, the reaction mixture was subjected to ESI-mass (positive mode) spectroscopic analysis. Copied below is the ESI-mass spectrum we obtained. LCMS (ESI) for **4**: calcd for $C_{13}H_{26}NO_3$ $[M+H]^+$ 244.19, found 244.10.

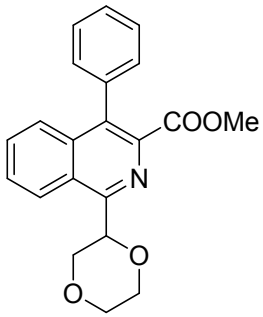


4. KIE studies of the cyclization reaction

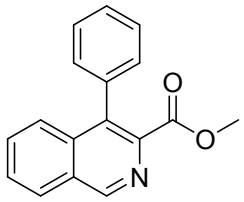




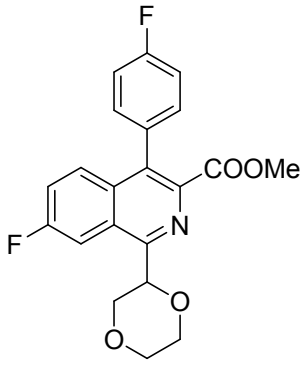
5. Characterization data of compounds 3



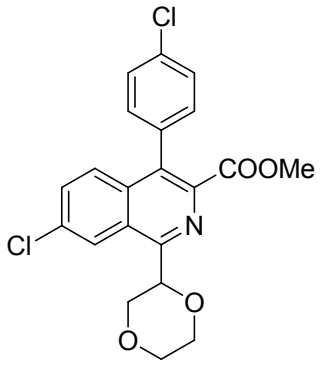
Methyl 1-(1,4-dioxan-2-yl)-4-phenylisoquinoline-3-carboxylate (3aa): Colorless oil (57.2 mg, 82% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 8.4 Hz, 1H), 7.70 (m, 1H), 7.64 (m, 2H), 7.47 (m, 3H), 7.31 (m, 2H), 5.45 (dd, J = 9.5, 3.2 Hz, 1H), 4.32 (qd, J = 12.0, 6.4 Hz, 2H), 4.11 (m, 2H), 3.90 (dd, J = 8.0, 2.2 Hz, 2H), 3.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 155.7, 140.9, 136.3, 135.9, 133.9, 130.6, 129.8, 129.6, 128.5, 128.2, 128.0, 127.2, 127.1, 125.5, 76.6, 69.8, 67.7, 66.5, 52.3. IR (cm^{-1}): v 2955, 2926, 2858, 1732, 1506, 1437, 1396, 1328, 1239, 1170, 1120, 1092, 913, 774, 699. HRMS (ESI): calcd for $C_{21}H_{19}NO_4Na$ $[M+Na]^+$ 372.1212, found: 372.1214.



Methyl 4-phenylisoquinoline-3-carboxylate (3aa'): White solid, mp 86-88 ^{o}C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.09 (dd, J = 6.8, 1.9 Hz, 1H), 7.68 (m, 3H), 7.51 (m, 3H), 7.34 (m, 2H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 151.8, 140.9, 136.0, 135.7, 134.9, 131.1, 129.5, 129.04, 128.8, 128.2, 128.0, 127.6, 126.6, 52.5. IR (cm^{-1}): v 2952, 2921, 2850, 1728, 1564, 1502, 1448, 1433, 1376, 1332, 1288, 1222, 1158, 1101, 982, 773, 710, 585. HRMS (ESI): calcd for $C_{17}H_{14}NO_2$ $[M+H]^+$ 264.1025, found: 264.1019.



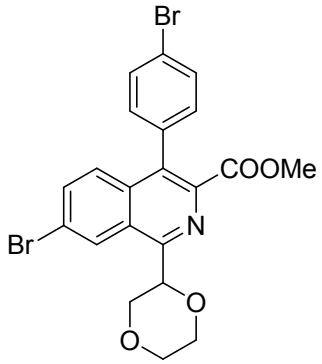
Methyl 1-(1,4-dioxan-2-yl)-7-fluoro-4-(4-fluorophenyl)isoquinoline-3-carboxylate (3ba): White solid (50.8 mg, 66% yield), mp 157-160 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, J = 10.0, 2.5 Hz, 1H), 7.63 (dd, J = 9.3, 5.5 Hz, 1H), 7.43 (ddd, J = 9.4, 8.0, 2.6 Hz, 1H), 7.27 (m, 2H), 7.19 (t, J = 8.3 Hz, 2H), 5.33 (dd, J = 7.6, 5.0 Hz, 1H), 4.30 (m, 2H), 4.10 (m, 2H), 3.90 (m, 2H), 3.70 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.06, -113.27. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 162.7 (d, J = 247.9 Hz), 161.6 (d, J = 251.9 Hz), 155.4 (d, J = 5.6 Hz), 140.4 (d, J = 2.5 Hz), 133.5, 133.0 (d, J = 1.3 Hz), 131.5 (d, J = 8.0 Hz), 131.5, 131.3 (d, J = 8.2 Hz), 129.8 (d, J = 8.9 Hz), 128.5 (d, J = 9.1 Hz), 121.2 (d, J = 25.1 Hz), 115.5 (d, J = 21.6 Hz), 109.8 (d, J = 22.4 Hz), 76.8, 69.5, 67.6, 66.5, 52.4. IR (cm^{-1}): ν 3092, 2984, 2912, 2859, 1736, 1623, 1604, 1516, 1440, 1404, 1375, 1292, 1228, 1188, 1167, 1116, 1089, 1051, 960, 912, 887, 849, 795, 698. HRMS (ESI): calcd for $C_{21}H_{17}F_2NO_4Na$ $[M+Na]^+$ 408.1023, found: 408.1023.



Methyl 7-chloro-4-(4-chlorophenyl)-1-(1,4-dioxan-2-yl)isoquinoline-3-carboxylate (3ca):

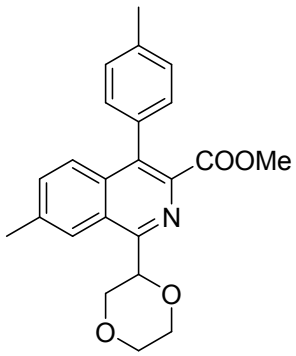
Yellow solid (58.3 mg, 70% yield), mp 178-180 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 1.8 Hz, 1H), 7.59 (dd, J = 9.1, 2.0 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.48

(d, J = 8.0 Hz, 2H), 7.23 (m, 2H), 5.35 (dd, J = 7.9, 4.8 Hz, 1H), 4.29 (m, 2H), 4.11 (m, 2H), 3.90 (m, 2H), 3.71 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 155.3, 140.8, 134.9, 134.6, 134.5, 133.8, 132.8, 131.8, 131.0, 130.9, 128.7, 128.5, 127.9, 124.9, 76.5, 69.5, 67.6, 66.5, 52.5. IR (cm^{-1}): ν 3085, 2974, 2948, 2858, 1735, 1598, 1552, 1498, 1434, 1402, 1291, 1234, 1167, 1117, 1093, 1084, 1030, 948, 909, 884, 839, 783. HRMS (ESI): calcd for $C_{21}H_{17}Cl_2NO_4Na$ $[M+Na]^+$ 440.0432, found: 440.0432.

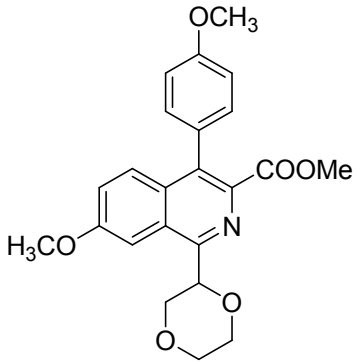


Methyl 7-bromo-4-(4-bromophenyl)-1-(1,4-dioxan-2-yl)isoquinoline-3-carboxylate (3da):

Yellow solid (73.5 mg, 73% yield), mp 67-69 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 1.8 Hz, 1H), 7.72 (dd, J = 9.0, 1.9 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 9.0 Hz, 1H), 7.16 (q, J = 3.6 Hz, 2H), 5.35 (dd, J = 7.9, 4.8 Hz, 1H), 4.29 (m, 2H), 4.11 (m, 2H), 3.90 (m, 2H), 3.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 155.2, 140.7, 134.7, 134.3, 134.3, 132.8, 131.6, 131.3, 131.1, 128.5, 128.2, 128.2, 123.4, 122.7, 76.4, 69.5, 67.6, 66.5, 52.5. IR (cm^{-1}): ν 2949, 2924, 2860, 1733, 1492, 1436, 1391, 1307, 1230, 1165, 1120, 1011, 957, 822, 802, 775, 728. HRMS (ESI): calcd for $C_{21}H_{17}Br_2NO_4Na$ $[M+Na]^+$ 527.9422, found: 527.9418.

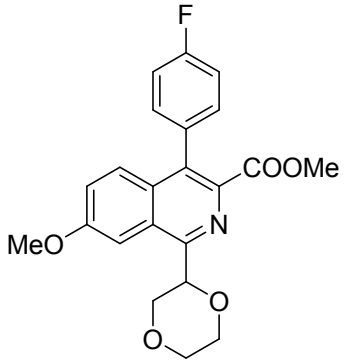


Methyl 1-(1,4-dioxan-2-yl)-7-methyl-4-(p-tolyl)isoquinoline-3-carboxylate (3ea): **C**olorless solid (66.3 mg, 88%), mp 179-181 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.28 (t, J = 5.8 Hz, 2H), 7.18 (d, J = 7.4 Hz, 2H), 5.43 (dd, J = 9.6, 2.7 Hz, 1H), 4.29 (m, 2H), 4.11 (m, 2H), 3.91 (m, 2H), 3.69 (s, 3H), 2.59 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 154.5, 140.1, 138.8, 137.6, 134.7, 134.1, 133.0, 132.7, 129.6, 129.4, 128.9, 127.4, 127.0, 124.1, 76.3, 69.8, 67.6, 66.5, 52.2, 22.20, 21.4. IR (cm^{-1}): v 2945, 2918, 2850, 1733, 1518, 1434, 1405, 1328, 1289, 1237, 1168, 1120, 1088, 1052, 1027, 1000, 950, 913, 886, 829, 726. HRMS (ESI): calcd for $C_{23}H_{23}NO_4Na$ $[M+Na]^+$ 400.1525, found: 400.1520.

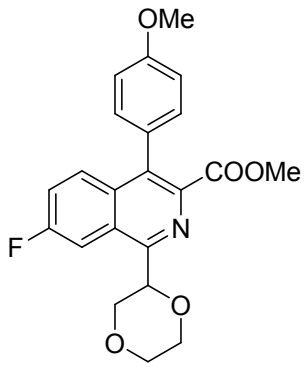


Methyl 1-(1,4-dioxan-2-yl)-7-methoxy-4-(4-methoxyphenyl)isoquinoline-3-carboxylate (3fa): Colorless oil (57.2 mg, 70%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 2.5 Hz, 1H), 7.59 (d, J = 9.3 Hz, 1H), 7.28 (m, 1H), 7.21 (d, J = 6.6 Hz, 2H), 7.01 (d, J = 8.0 Hz, 2H), 5.37 (dd, J = 9.6, 3.0 Hz, 1H), 4.31 (m, 2H), 4.10 (m, 2H), 3.99 (s, 3H), 3.91 (m, 1H), 3.88 (s, 3H), 3.83 (m, 1H), 3.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.8, 159.4, 159.2, 153.5, 139.2, 134.0, 132.0, 130.9, 130.7, 128.9, 128.2, 122.9, 113.7, 103.7, 76.9, 69.6, 67.6, 66.6, 55.5, 55.3, 52.3. IR (cm^{-1}): v 2950,

2849, 1721, 1618, 1519, 1462, 1414, 1396, 1327, 1248, 1225, 1117, 1088, 1044, 1021, 836, 736. HRMS (ESI): calcd for $C_{23}H_{23}NO_6Na$ $[M+Na]^+$ 432.1423, found: 432.1423.

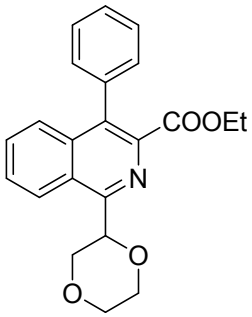


Methyl 1-(1,4-dioxan-2-yl)-4-(4-fluorophenyl)-7-methoxyisoquinoline-3-carboxylate (3ga): Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, J = 10.0, 2.3 Hz, 1H), 7.72 (dd, J = 9.3, 5.6 Hz, 1H), 7.41 (m, 1H), 7.22 (d, J = 6.6 Hz, 2H), 7.02 (d, J = 7.9 Hz, 2H), 5.32 (dd, J = 7.9, 4.7 Hz, 1H), 4.29 (m, 2H), 4.09 (m, 2H), 3.89 (m, 5H), 3.70 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.62. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 161.5 (d, J = 251.3 Hz), 159.6, 154.8 (d, J = 5.6 Hz), 140.8 (d, J = 2.5 Hz), 133.7, 133.5 (d, J = 1.1 Hz), 130.9 (d, J = 17.9 Hz), 130.1 (d, J = 8.9 Hz), 128.5 (d, J = 9.1 Hz), 127.5, 120.9 (d, J = 25.1 Hz), 113.8, 109.6 (d, J = 22.3 Hz), 76.9, 69.5, 67.6, 66.5, 55.3, 52.4. IR (cm^{-1}): v 2952, 2924, 2856, 1735, 1624, 1610, 1558, 1517, 1441, 1398, 1235, 1191, 1164, 1117, 1089, 1033, 911, 771, 700. HRMS (ESI): calcd for $C_{22}H_{20}FNO_5Na$ $[M+Na]^+$ 420.1223, found: 420.1223.

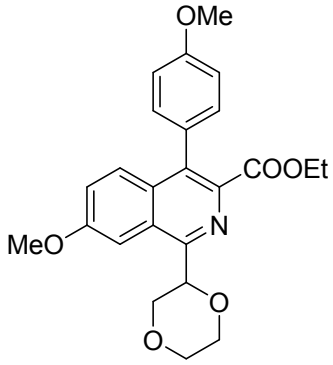


Methyl 1-(1,4-dioxan-2-yl)-7-fluoro-4-(4-methoxyphenyl)isoquinoline-3-carboxylate (3ha): Colorless solid, mp 87-90 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 2.5 Hz, 1H), 7.50 (d, J = 9.3 Hz, 1H), 7.30 (dd, J = 9.3, 2.5 Hz, 1H), 7.25 (m,

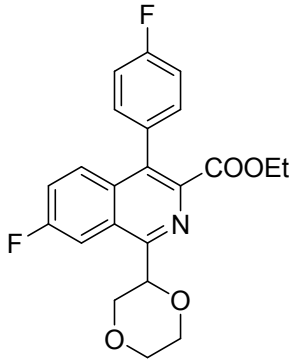
2H), 7.18 (t, J = 8.3 Hz, 2H), 5.38 (dd, J = 9.6, 3.0 Hz, 1H), 4.31 (ddd, J = 15.0, 12.0, 6.4 Hz, 2H), 4.11 (m, 2H), 4.01 (s, 3H), 3.90 (m, 2H), 3.69 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.90. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 162.6 (d, J = 247.2 Hz), 159.4, 154.0, 138.8, 133.5, 132.1 (d, J = 3.5 Hz). 131.8, 131.4 (d, J = 8.0 Hz), 131.2 (d, J = 8.1 Hz), 128.9, 128.6, 115.3 (d, J = 21.6 Hz), 103.8, 76.8, 69.6, 67.6, 66.6, 55.5, 52.3. IR (cm^{-1}): ν 2954, 2918, 2815, 1720, 1618, 1515, 1466, 1415, 1396, 1378, 1328, 1303, 1227, 1160, 1119, 1089, 1025, 1002, 911, 840, 802. HRMS (ESI): calcd for $C_{22}H_{20}FNO_5Na$ $[M+Na]^+$ 420.1223, found: 420.1221.



Ethyl 1-(1,4-dioxan-2-yl)-4-phenylisoquinoline-3-carboxylate (3ia): Colorless oil (53.7 mg, 74% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 8.3 Hz, 1H), 7.67 (m, 3H), 7.48 (m, 3H), 7.33 (m, 2H), 5.44 (dd, J = 9.5, 3.1 Hz, 1H), 4.33 (m, 2H), 4.09 (m, 4H), 3.89 (d, J = 5.8 Hz, 2H), 0.96 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 155.7, 141.4, 136.2, 136.0, 133.4, 130.5, 123.0, 129.8, 128.3, 128.2, 128.2, 128.0, 127.2, 126.9, 125.6, 76.5, 69.7, 67.7, 66.5, 61.2, 13.6. IR (cm^{-1}): ν 2961, 2919, 2855, 1729, 1558, 1456, 1443, 1404, 1328, 1291, 1256, 1237, 1227, 1181, 1119, 1091, 1031, 915, 883, 765, 699. HRMS (ESI): calcd for $C_{22}H_{21}NO_4Na$ $[M+Na]^+$ 386.1368, found: 386.1366.

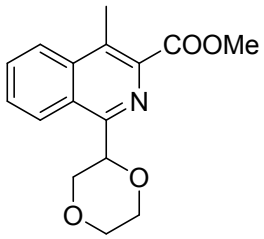


Ethyl 1-(1,4-dioxan-2-yl)-7-methoxy-4-(4-methoxyphenyl)isoquinoline-3-carboxylate (3ja): Light yellow solid (47.3 mg, 56%), mp 130-132 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 9.3 Hz, 1H), 7.25 (m, 3H), 7.00 (d, J = 8.1 Hz, 2H), 5.37 (dd, J = 9.5, 2.7 Hz, 1H), 4.32 (m, 2H), 4.10 (m, 4H), 3.97 (d, J = 13.2 Hz, 3H), 3.88 (m, 5H), 1.03 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 159.4, 159.1, 153.6, 139.9, 133.4, 131.9, 131.1, 130.8, 128.8, 128.7, 128.3, 122.8, 113.7, 103.7, 74.9, 69.6, 67.6, 67.1, 66.6, 66.4, 61.1, 55.5, 55.4, 13.8. IR (cm^{-1}): v 2965, 2924, 2834, 1731, 1609, 1515, 1452, 1419, 1382, 1290, 1246, 1220, 1114, 1092, 1026, 905, 839, 810, 564. HRMS (ESI): calcd for $C_{24}H_{25}NO_6Na$ $[M+Na]^+$ 446.1580, found: 446.1577.

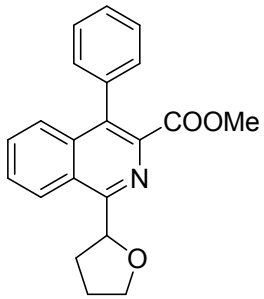


Ethyl 1-(1,4-dioxan-2-yl)-7-fluoro-4-(4-fluorophenyl)isoquinoline-3-carboxylate (3ka): Colorless oil (51.8 mg, 65%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, J = 10.0, 2.5 Hz, 1H), 7.63 (dd, J = 9.3, 5.5 Hz, 1H), 7.43 (ddd, J = 9.3, 7.9, 2.6 Hz, 1H), 7.29 (m, 2H), 7.19 (m, 2H), 5.32 (m, 1H), 4.32 (m, 2H), 4.10 (m, 4H), 3.88 (m, 2H), 1.04 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.33, -113.41. ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 162.8 (d, J = 247.9 Hz), 161.5 (d, J = 251.6 Hz). 155.4 (d, J = 5.7 Hz), 141.1 (d, J = 2.4 Hz), 133.4, 132.4, 131.61 (d, J = 8.1 Hz), 131.6 (d, J = 3.4

Hz),131.4 (d, *J* = 8.1 Hz), 129.6 (d, *J* = 8.9 Hz), 128.4 (d, *J* = 9.2 Hz), 121.1 (d, *J* = 25.2 Hz), 115.4 (d, *J* = 21.7 Hz), 109.9 (d, *J* = 22.4 Hz), 76.7, 69.5, 67.6, 66.5, 61.4, 13.8. IR (cm^{-1}): *v* 3075, 2962, 2917, 2855, 1731, 1624, 1603, 1516, 1463, 1401, 1323, 1289, 1266, 1116, 1026, 911, 880, 839. HRMS (ESI): calcd for $C_{22}H_{19}F_2NO_4Na$ $[M+Na]^+$ 422.1180, found: 422.1180.

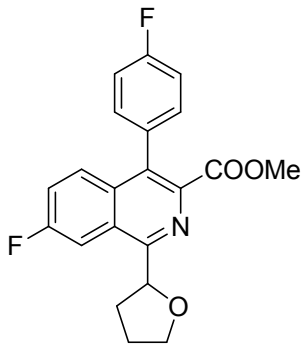


Methyl 1-(1,4-dioxan-2-yl)-4-methylisoquinoline-3-carboxylate (3la): White solid (29.2 mg, 51% yield), mp 148-151 ^oC, ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 5.36 (dd, *J* = 9.6, 2.7 Hz, 1H), 4.23 (m, 2H), 4.07 (m, 5H), 3.87 (m, 2H), 2.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 154.0, 140.7, 136.6, 130.4, 129.4, 128.3, 127.0, 126.0, 124.8, 76.7, 69.8, 67.6, 66.5, 52.6, 14.4. IR (cm^{-1}): *v* 2976, 2926, 2856, 1727, 1431, 1332, 1254, 1242, 1198, 1166, 1118, 1100, 1062, 1053, 1027, 913, 880, 865, 764. HRMS (ESI): calcd for $C_{16}H_{17}NO_4Na$ $[M+Na]^+$ 310.1055, found: 310.1052.

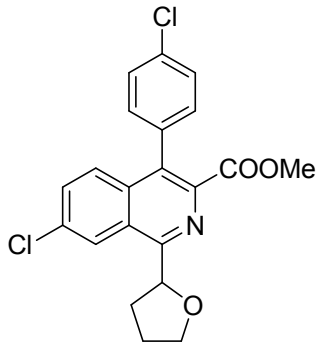


Methyl 4-phenyl-1-(tetrahydrofuran-2-yl)isoquinoline-3-carboxylate (3ab): Colorless oil (57.2 mg, 86%), ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.3 Hz, 1H), 7.67 (m, 3H), 7.48 (m, 3H), 7.33 (m, 2H), 5.73 (t, *J* = 7.0 Hz, 1H), 4.16 (dd, *J* = 14.5, 7.5 Hz, 1H), 4.04 (td, *J* = 7.9, 6.1 Hz, 1H), 3.66 (s, 3H), 2.81 (ddd, *J* = 15.6, 12.6, 7.2 Hz, 1H), 2.41 (m, 1H), 2.18 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 158.8,

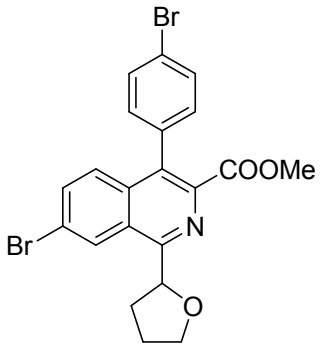
140.4, 136.3, 136.2, 133.5, 130.3, 129.9, 129.6, 128.3, 128.2, 128.2, 127.9, 127.2, 127.0, 125.8, 79.8, 69.1, 52.2, 29.8, 26.2. IR (cm^{-1}): *v* 3058, 3027, 2950, 2873, 1737, 1614, 1558, 1505, 1445, 1396, 1327, 1234, 1166, 1117, 1055, 991, 918, 771, 700. HRMS (ESI): calcd for $C_{21}H_{19}NO_3Na$ $[M+Na]^+$ 356.1263, found: 356.1263.



Methyl 7-fluoro-4-(4-fluorophenyl)-1-(tetrahydrofuran-2-yl)isoquinoline-3-carboxylate (3bb): Yellow solid (37.6 mg, 51% yield), mp 96-98 ^oC, ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 10.1, 2.5 Hz, 1H), 7.61 (dd, *J* = 9.3, 5.6 Hz, 1H), 7.41 (m, 1H), 7.29 (m, 2H), 7.19 (m, 2H), 5.60 (t, *J* = 7.1 Hz, 1H), 4.14 (dd, *J* = 14.6, 7.4 Hz, 1H), 4.04 (dd, *J* = 14.1, 7.9 Hz, 1H), 3.70 (s, 3H), 2.79 (td, *J* = 15.7, 7.5 Hz, 1H), 2.40 (td, *J* = 12.7, 7.5 Hz, 1H), 2.17 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.41, -114.38. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 162.6 (d, *J* = 247.7 Hz), 161.5 (d, *J* = 251.5 Hz), 158.5 (d, *J* = 5.6 Hz), 140.1, 132.5, 131.8 (d, *J* = 3.6 Hz), 131.5 (d, *J* = 8.1 Hz), 131.3 (d, *J* = 8.1 Hz), 129.7 (d, *J* = 8.9 Hz), 128.5 (d, *J* = 9.0 Hz), 120.9 (d, *J* = 25.0 Hz), 115.5 (d, *J* = 21.6 Hz), 110.1 (d, *J* = 22.3 Hz), 80.2, 69.1, 52.4, 29.7, 26.1. IR (cm^{-1}): *v* 2954, 2928, 2873, 1736, 1624, 1603, 1516, 1501, 1439, 1399, 1312, 1237, 1197, 1160, 1114, 1056, 1017, 840, 521. HRMS (ESI): calcd for $C_{21}H_{17}F_2NO_3Na$ $[M+Na]^+$ 392.1074, found: 392.1074.

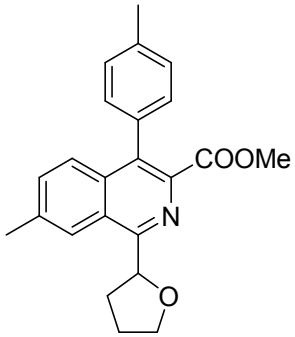


Methyl 7-chloro-4-(4-chlorophenyl)-1-(tetrahydrofuran-2-yl)isoquinoline-3-carboxylate (3cb): Yellow oil (48.1 mg, 60% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 1.4 Hz, 1H), 7.57 (m, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.24 (m, 2H), 5.63 (t, *J* = 6.9 Hz, 1H), 4.13 (dd, *J* = 14.6, 7.3 Hz, 1H), 4.05 (dd, *J* = 14.0, 7.7 Hz, 1H), 3.72 (s, 3H), 2.80 (td, *J* = 15.2, 7.5 Hz, 1H), 2.40 (dt, *J* = 12.3, 7.4 Hz, 1H), 2.17 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 158.4, 140.5, 134.7, 134.6, 134.3, 134.2, 132.3, 131.5, 131.1, 130.9, 128.7, 128.6, 128.4, 128.0, 125.3, 79.8, 69.1, 52.5, 29.7, 26.1. IR (cm^{-1}): *v* 3086, 2952, 2925, 2855, 1732, 1653, 1598, 1567, 1555, 1496, 1455, 1437, 1309, 1230, 1165, 1092, 1056, 1017, 837, 803. HRMS (ESI): calcd for $C_{21}H_{17}Cl_2NO_3Na$ $[M+Na]^+$ 424.0483, found: 424.0482.

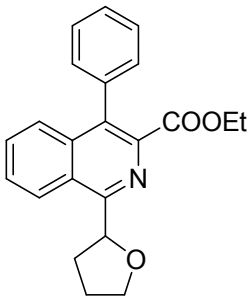


Methyl 7-bromo-4-(4-bromophenyl)-1-(tetrahydrofuran-2-yl)isoquinoline-3-carboxylate (3db): light yellow oil (64.4 mg, 66% yield), ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.73 (d, *J* = 1.8 Hz, 1H), 7.70 (m, 1H), 7.63 (m, 2H), 7.44 (d, *J* = 9.0 Hz, 1H), 7.18 (m, 2H), 5.63 (t, *J* = 7.0 Hz, 1H), 4.08 (m, 2H), 3.72 (s, 3H), 2.80 (m, 1H), 2.40 (m, 1H), 2.17 (m, 2H). ^{13}C NMR (101MHz, $CDCl_3$) *δ* 167.2, 158.4, 140.4, 134.7, 134.6, 134.1, 132.4, 131.6, 131.4, 131.2, 128.6, 128.4, 128.3, 123.1, 122.5, 79.8, 69.1, 52.4, 29. 7, 26.1. IR (cm^{-1}): *v* 3084, 2950, 2872, 2688, 2560, 2248, 1772, 1732, 1591,

1552, 1493, 1481, 1437, 1390, 1309, 1232, 1167, 1122, 1017, 958, 836, 732. HRMS (ESI): calcd for $C_{21}H_{17}Br_2O_3NNa$ $[M+Na]^+$ 511.9473, found: 511.9469.

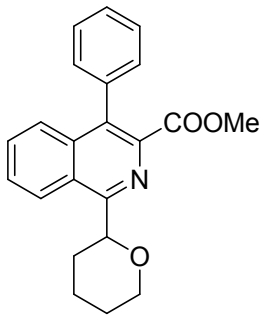


Methyl 7-methyl-1-(tetrahydrofuran-2-yl)-4-(p-tolyl)isoquinoline-3-carboxylate (3eb): Colorless oil (59.2 mg, 82 %), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.43 (dd, J = 8.7, 1.4 Hz, 1H), 7.27 (t, J = 6.8 Hz, 2H), 7.19 (t, J = 8.2 Hz, 2H), 5.71 (t, J = 7.0 Hz, 1H), 4.14 (dd, J = 14.5, 7.4 Hz, 1H), 4.04 (td, J = 7.9, 6.2 Hz, 1H), 3.69 (s, 3H), 2.83 (m, 1H), 2.56 (s, 3H), 2.44 (s, 3H), 2.37 (m, 1H), 2.18 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 158.7, 139.6, 138.5, 137.5, 134.7\, 133.7, 133.4, 132.4, 129.7, 129.4, 128.9, 128.9, 127.5, 127.0, 124.6, 79.5, 69.0, 52.2, 29.6, 26.2, 22.2, 21.4. IR (cm^{-1}): ν 2949, 2924, 2869, 1737, 1622, 1518, 1436, 1397, 1321, 1233, 1167, 1120, 1055, 1024, 1008, 962, 832, 819, 747. HRMS (ESI): calcd for $C_{23}H_{23}NO_3Na$ $[M+Na]^+$ 384.1577, found: 384.1576.

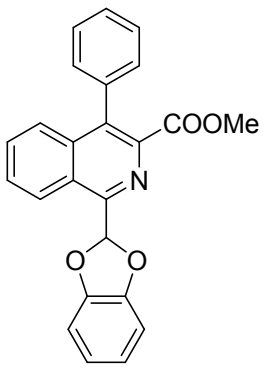


Ethyl 4-phenyl-1-(tetrahydrofuran-2-yl)isoquinoline-3-carboxylate (3ib): Colorless oil (43.0 mg, 62%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 8.2 Hz, 1H), 7.57 (m, 3H), 7.40 (m, 3H), 7.27 (m, 2H), 5.67 (t, J = 7.0 Hz, 1H), 4.01 (m, 4H), 2.77 (m, 1H), 2.32 (m, 1H), 2.12 (m, 2H), 0.89 (t, J = 7.1 Hz, 3H).^{13}C NMR (101 MHz,

$CDCl_3$) δ 166.6, 157.8, 140.1, 135.3, 135.2, 131.9, 129.3, 129.1, 128.8, 127.2, 127.1, 126.8, 126.2, 125.9, 124.8, 78.7, 68.0, 60.1, 28.7, 25.1, 12.6. IR (cm^{-1}): v 3058, 3027, 2977, 2929, 2873, 1732, 1674, 1557, 1505, 1444, 1403, 1375, 1327, 1230, 1176, 1116, 1019, 771, 700. HRMS (ESI): calcd for $C_{22}H_{21}NO_3Na$ $[M+Na]^+$ 370.1419, found: 370.1419.

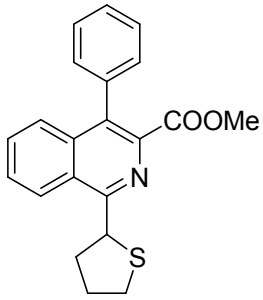


Methyl 4-phenyl-1-(tetrahydro-2H-pyran-2-yl)isoquinoline-3-carboxylate (3ac): Colorless oil (38.1 mg, 55% yield), ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 8.3 Hz, 1H), 7.64 (m, 3H), 7.46 (m, 3H), 7.32 (m, 2H), 5.18 (dd, J = 11.3, 2.2 Hz, 1H), 4.23 (m, 1H), 3.79 (td, J = 11.6, 2.1 Hz, 1H), 3.66 (s, 3H), 2.32 (m, 1H), 2.08 (m, 2H), 1.84 (m, 2H), 1.69 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 159.3, 140.6, 136.5, 136.3, 133.6, 130.3, 129.8, 129.7, 128.2, 128.1, 128.0, 127.9, 127.0, 126.9, 126.3, 81.4, 69.4, 52.3, 30.4, 26.0, 23.7. IR (cm^{-1}): v 3057, 2924, 2851, 1735, 1682, 1613, 1556, 1505, 1443, 1377, 1337, 1232, 1166, 1084, 1042, 1003, 906, 770, 700. HRMS (ESI): calcd for $C_{22}H_{21}NO_3Na$ $[M+Na]^+$ 370.1419, found: 370.1415.

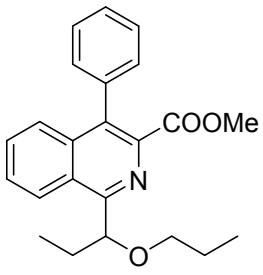


Methyl 1-(benzo[*d*][1,3]dioxol-2-yl)-4-phenylisoquinoline-3-carboxylate (3ad): Yellow solid (19.2 mg, 25% yield), mp 177-179 ^oC, ^1H NMR (400 MHz, $CDCl_3$) δ

8.18 (d, J = 8.2 Hz, 1H), 7.57 (m, 3H), 7.43 (d, J = 6.2 Hz, 3H), 7.31 (s, 1H), 7.27 (d, J = 7.1 Hz, 2H), 6.91 (s, 4H), 3.63 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 150.8, 146.2, 139.3, 136.0, 135.5, 134.6, 129.9, 128.5, 128.2, 127.3, 127.2, 126.4, 125.7, 123.8, 121.3, 111.5, 108.3, 51.5. IR (cm^{-1}): ν 3033, 2950, 2920,2851, 1732, 1561, 1482, 1452, 1434, 1348, 1318, 1231, 1192, 1166, 1089, 1024, 983, 937, 743, 670. HRMS (ESI): calcd for $C_{24}H_{17}NO_4Na$ $[M+Na]^+$ 406.1055, found: 406.1053.

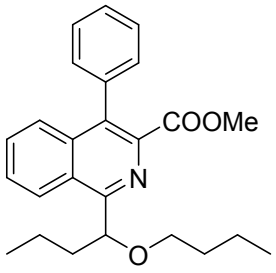


Methyl 4-phenyl-1-(tetrahydrothiophen-2-yl)isoquinoline-3-carboxylate (3ae): Colorless oil (20.9 mg, 30%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.3 Hz, 1H), 7.68 (m, 1H), 7.62 (m, 2H), 7.49 (m, 3H), 7.32 (m, 2H), 5.33 (t, J = 6.4 Hz, 1H), 3.64 (s, 3H), 3.12 (m, 3H), 2.58 (dt, J = 12.2, 6.2 Hz, 1H), 2.33 (td, J = 12.3, 6.3 Hz, 1H), 2.24 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 160.3, 140.8, 136.2, 136.0, 132.5, 130.3, 129.9, 129.7, 128.3, 128.2, 127.9, 127.3, 127.2, 125.1, 52.1, 48.7, 34.2, 33.8, 31.4. IR (cm^{-1}): ν 3063, 2947, 2858, 1732, 1644, 1573, 1557, 1506, 1443, 1393, 1329, 1229, 1190, 1167, 1032, 770, 700. HRMS (ESI): calcd for $C_{21}H_{19}NO_2SNa$ $[M+Na]^+$ 372.1212, found: 372.1210.

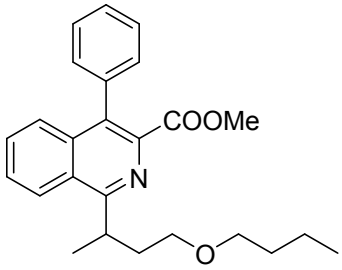


Methyl 4-phenyl-1-(1-propoxypropyl)isoquinoline-3-carboxylate (3af): Colorless oil (37.2 mg, 51% yield). (major isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (m, 1H),

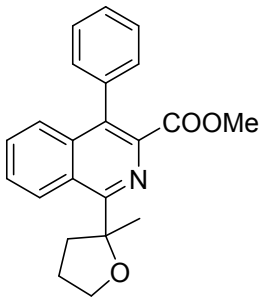
7.64 (m, 3H), 7.48 (m, 3H), 7.36 (m, 2H), 4.91 (dd, J = 8.8, 5.4 Hz, 1H), 3.66 (s, 3H), 3.45 (dt, J = 9.1, 6.6 Hz, 1H), 3.36 (dt, J = 9.2, 6.6 Hz, 1H), 2.22 (m, 1H), 2.01 (m, 1H), 1.61 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 160.3, 139.8, 135.3, 135.2, 132.0, 129.4, 128.8, 128.7, 127.2, 126.9, 126.7, 125.9, 125.7, 125.3, 86.6, 70.4, 51.3, 28.4, 22.2, 10.0, 9.7. IR (cm^{-1}): v 3059, 2964, 2935, 2875, 1738, 1556, 1505, 1445, 1435, 1379, 1346, 1227, 1168, 1115, 1008, 953, 917, 772, 700. HRMS (ESI): calcd for $C_{23}H_{25}NO_3Na$ $[M+Na]^+$ 386.1732, found: 386.1730.



Methyl 1-(1-butoxybutyl)-4-phenylisoquinoline-3-carboxylate (3ag1): Colorless oil (46 mg, 58% yield). (major isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (m, 1H), 7.64 (m, 3H), 7.48 (m, 3H), 7.35 (m, 2H), 4.99 (dd, J = 9.1, 5.1 Hz, 1H), 3.65 (s, 3H), 3.47 (m, 1H), 3.39 (m, 1H), 2.18 (m, 1H), 1.92 (m, 1H), 1.70 (m, 1H), 1.57 (m, 2H), 1.43 (m, 1H), 1.35 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 161.5, 140.8, 136.4, 136.2, 133.0, 130.4, 129.8, 129.8, 128.2, 127.9, 127.8, 127.0, 126.7, 126.3, 86.1, 69.4, 52.3, 38.6, 32.1, 19.9, 19.4, 14.0, 13.9. IR (cm^{-1}): v 2958, 2931, 2871, 1739, 1613, 1505, 1463, 1445, 1379, 1346, 1313, 1239, 1222, 1167, 1115, 1094, 773, 700. HRMS (ESI): calcd for $C_{25}H_{29}NO_3Na$ $[M+Na]^+$ 414.2045, found: 414.2044.

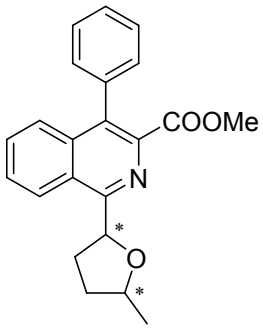


Methyl 1-(4-butoxybutan-2-yl)-4-phenylisoquinoline-3-carboxylate (3ag2): Colorless oil (3.4 mg, 4% yield). (minor isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (m, 1H), 7.64 (m, 3H), 7.47 (m, 3H), 7.36 (m, 2H), 4.10 (dd, J = 13.9, 6.9 Hz, 1H), 3.65 (s, 3H), 3.53 (dt, J = 9.7, 6.0 Hz, 1H), 3.34 (m, 3H), 2.39 (m, 1H), 2.04 (m, 1H), 1.52 (m, 2H), 1.48 (d, J = 6.8 Hz, 3H), 1.34 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 163.9, 140.5, 135.4, 134.7, 130.1, 129.0, 128.9, 127.2, 127.1, 126.9, 126.8, 126.2, 126.0, 123.9, 69.6, 67.8, 51.1, 35.3, 31.8, 30.9, 19.5, 18.4, 12.9. IR (cm^{-1}): ν 2959, 2930, 2870, 1739, 1556, 1506, 1446, 1395, 1328, 1232, 1168, 1115, 1031, 771, 700. HRMS (ESI): calcd for $C_{25}H_{29}NO_3Na$ $[M+Na]^+$ 414.2045, found: 414.2043.



Methyl 1-(2-methyltetrahydrofuran-2-yl)-4-phenylisoquinoline-3-carboxylate (3ah1): White solid (33.1 mg, 48% yield), mp 119-121^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (m, 1H), 7.53 (m, 3H), 7.39 (m, 3H), 7.26 (d, J = 7.1 Hz, 2H), 4.02 (m, 1H), 3.69 (m, 1H), 3.57 (s, 3H), 3.42 (m, 1H), 1.91 (m, 3H), 1.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 162.9, 139.9, 136.8, 136.4, 132.8, 129.9, 129.8, 129.8, 128.2, 128.2, 128.1, 127.8, 127.5, 127.0, 126.7, 88.5, 68.1, 52.1, 37.4, 28.4, 25.2. IR (cm^{-1}): ν 2974, 2948, 2867, 1728, 1505, 1445, 1396, 1370, 1237, 1168, 1116, 1030, 913, 783, 710. HRMS (ESI): calcd for $C_{22}H_{21}NO_3Na$ $[M+Na]^+$ 370.1419, found:

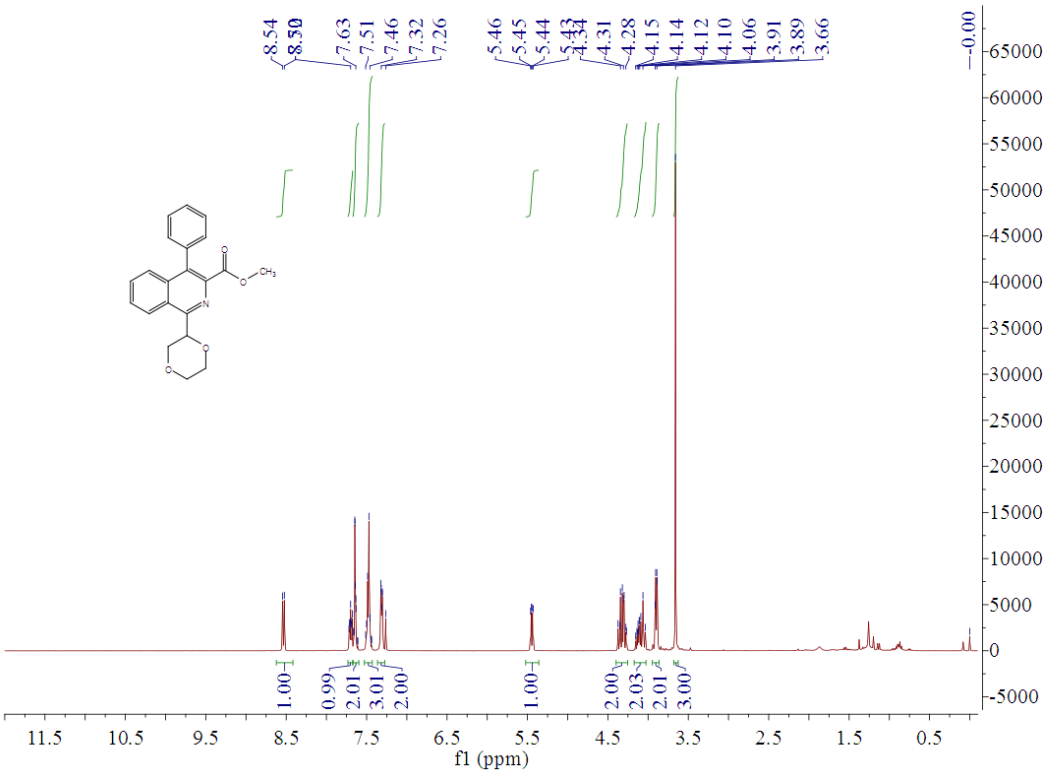
370.1417.

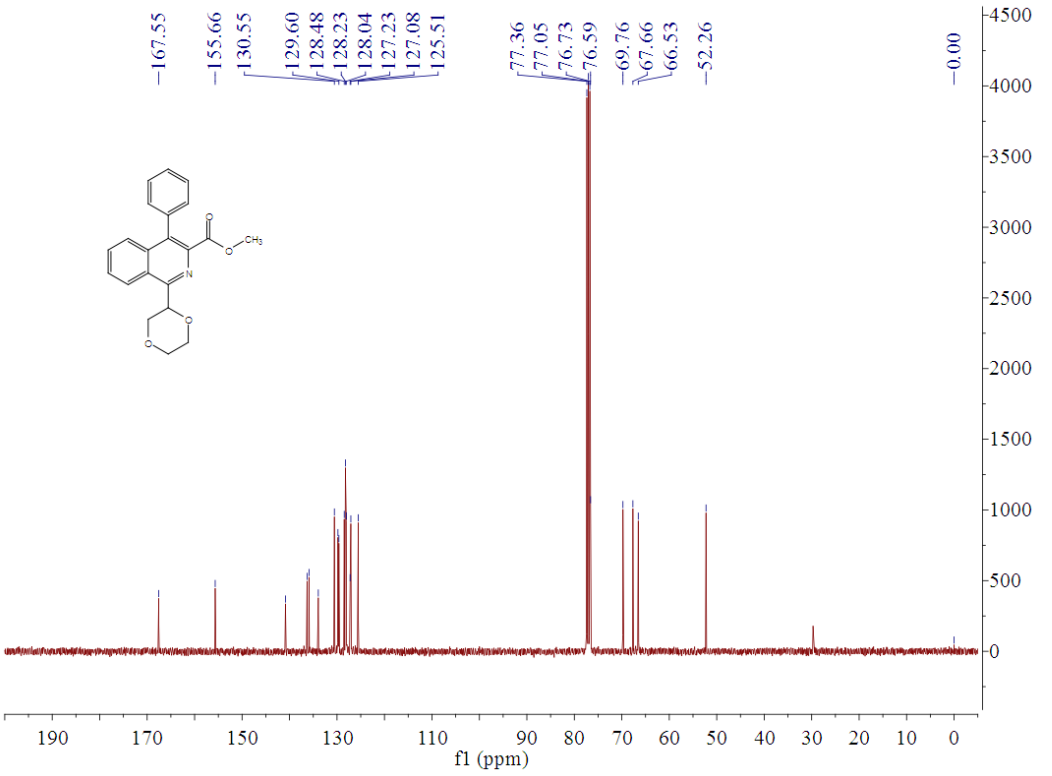


Methyl 1-(5-methyltetrahydrofuran-2-yl)-4-phenylisoquinoline-3-carboxylate (3ah2): Colorless oil (25.1 mg, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 8.3 Hz, 1H), 7.65 (m, 3H), 7.47 (m, 3H), 7.33 (m, 2H), 5.88 (t, J = 7.0 Hz, 1H), 4.43 (m, 1H), 3.66 (s, 3H), 2.84 (m, 1H), 2.34 (m, 2H), 1.80 (m, 1H), 1.37 (d, J=6.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 167.8, 159.3, 158.7, 140.4, 140.3, 136.4, 136.3, 136.3, 136.3, 133.7, 133.4, 130.3, 129.9, 129.8, 129.6, 128.3, 128.2, 128.1, 127.9, 127.3, 127.2, 127.0, 126.0, 125.8, 80.5, 79.1, 76.0, 52.2, 34.0, 33.1, 30.4, 30.0, 21.4, 21.2. IR (cm^{-1}): v 2965, 2928, 2870, 1738, 1557, 1505, 1445, 1379, 1326, 1235, 1167, 1116, 1077, 994, 771, 700. HRMS (ESI): calcd for $C_{22}H_{21}NO_3Na$ $[M+Na]^+$ 370.1419, found: 370.1419.

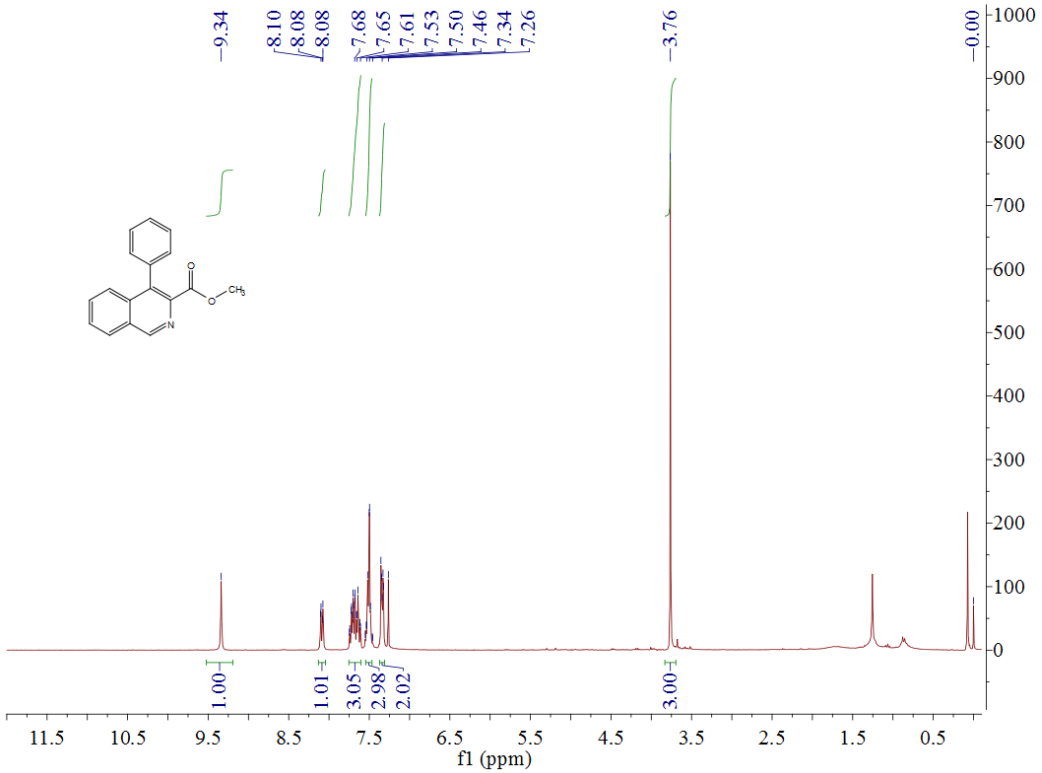
6. ^{1}H and ^{13}C NMR spectra for compound 3

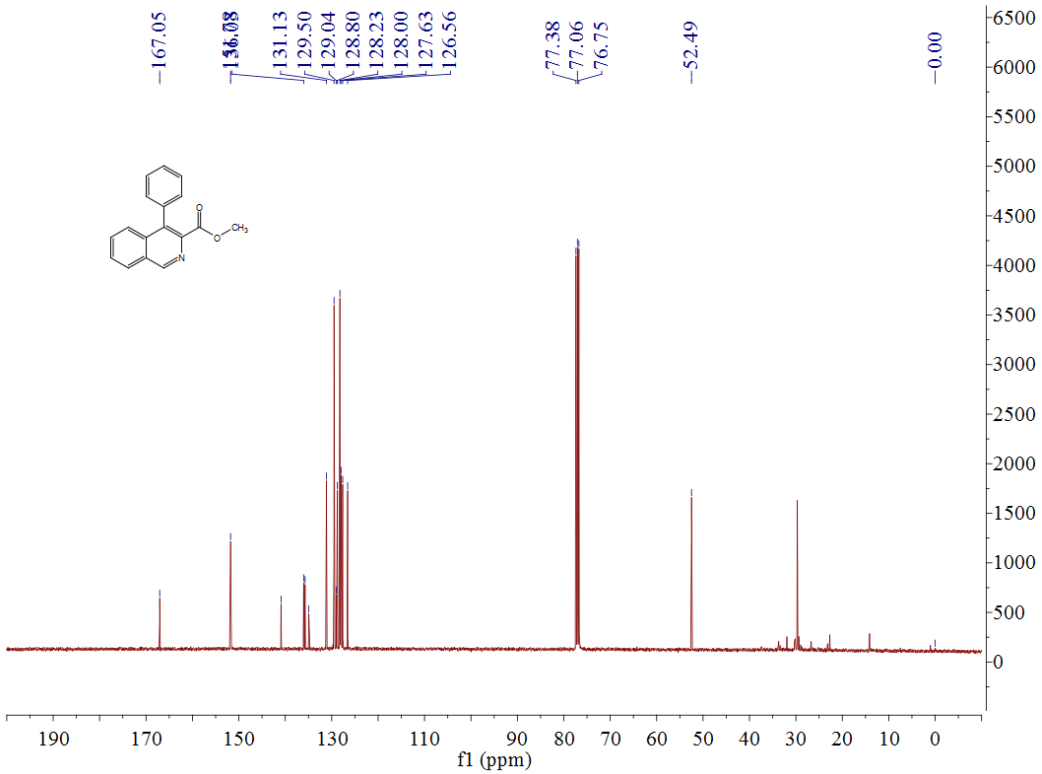
^{1}H NMR and ^{13}C NMR spectrum of **3aa**



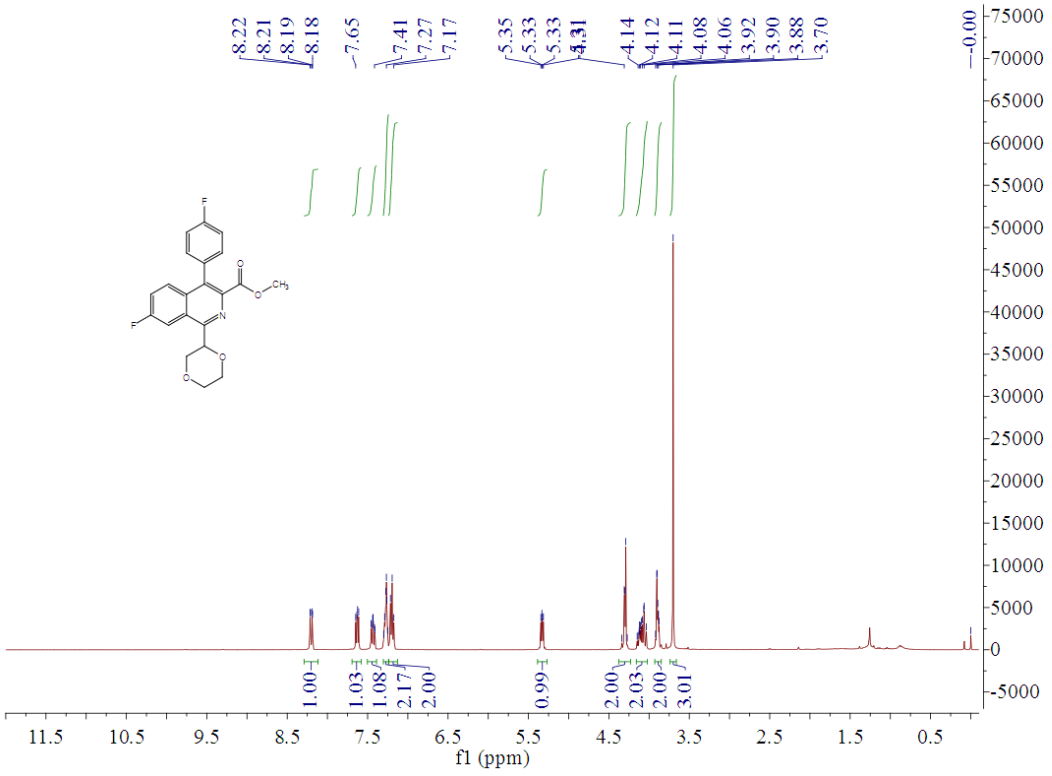


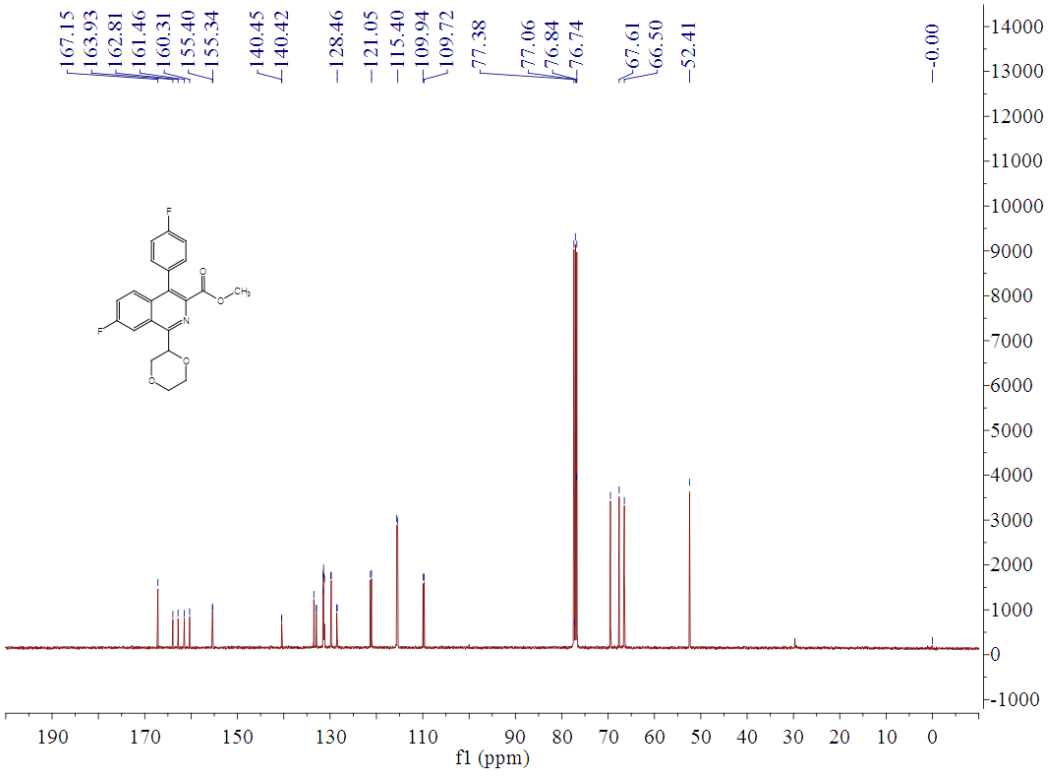
^{1}H NMR and ^{13}C NMR spectrum of **3aa'**



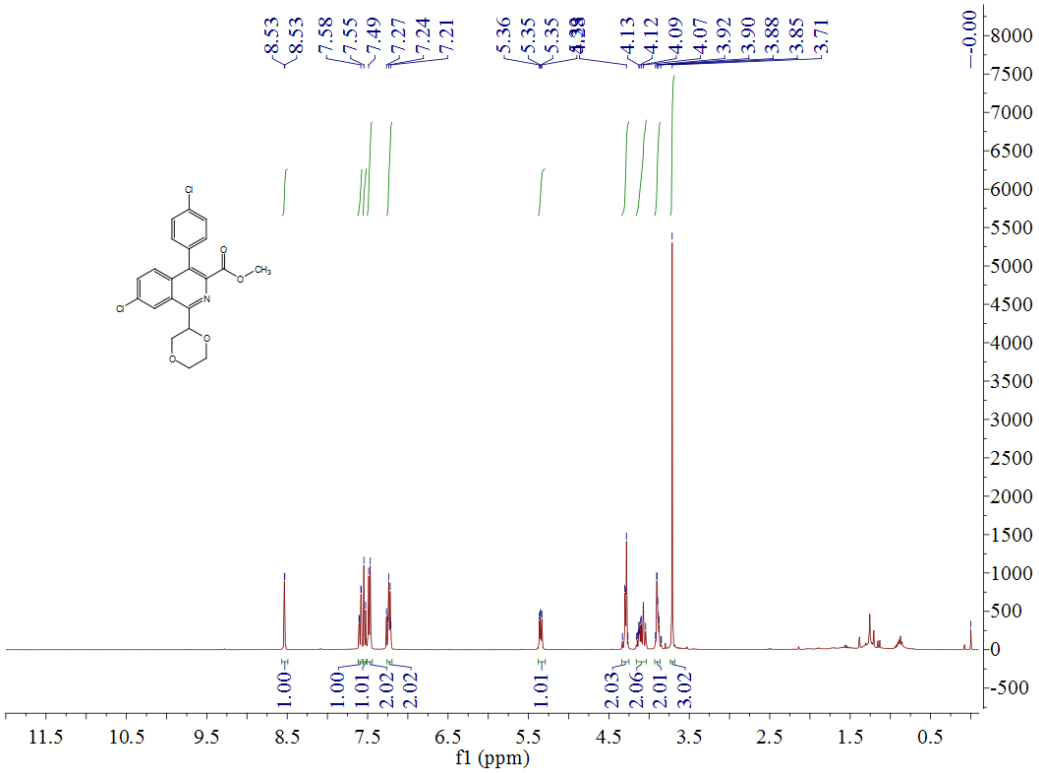


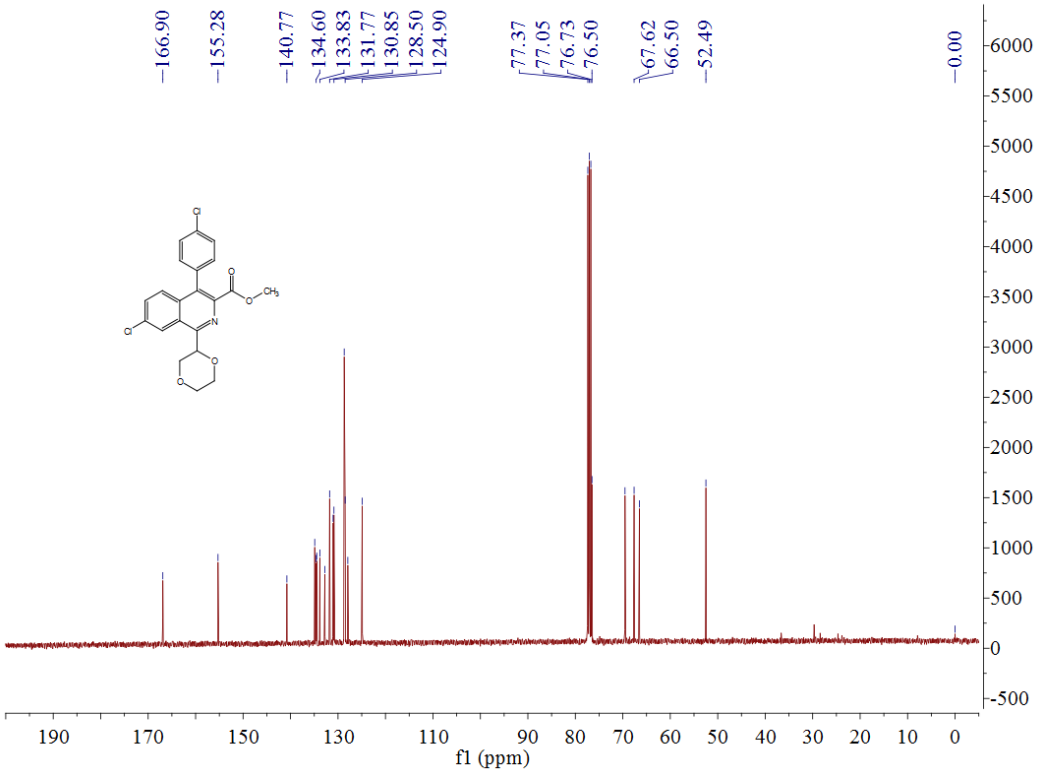
^{1}H NMR and ^{13}C NMR spectrum of **3ba**



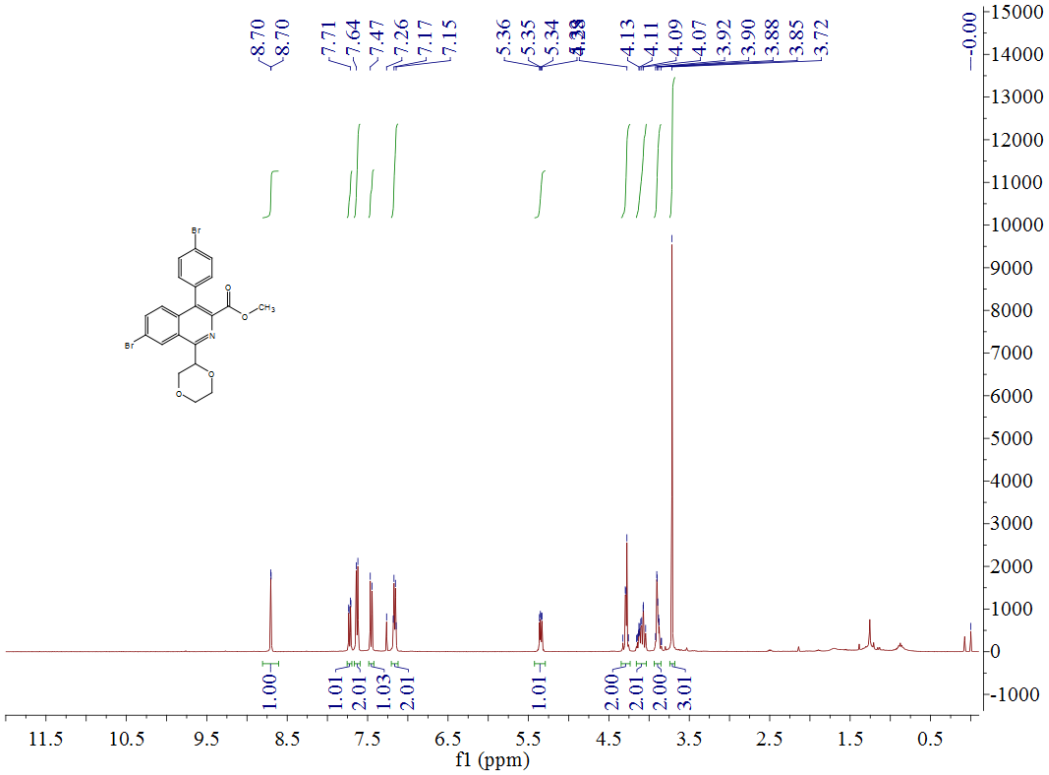


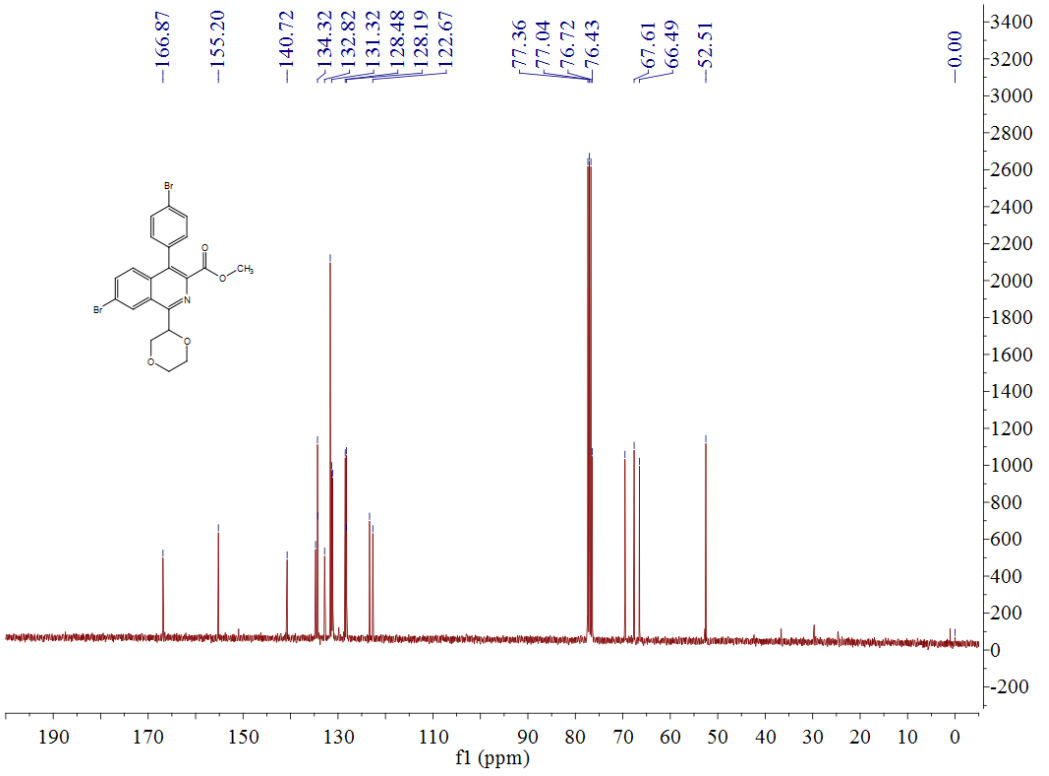
^{1}H NMR and ^{13}C NMR spectrum of **3ca**



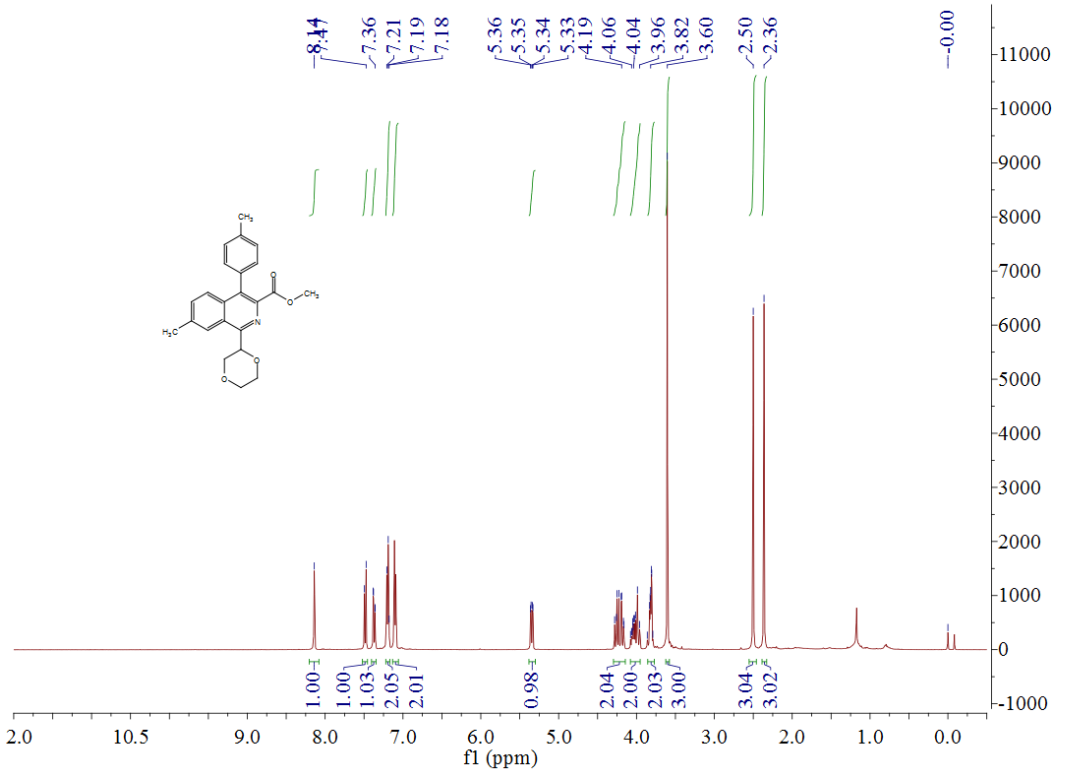


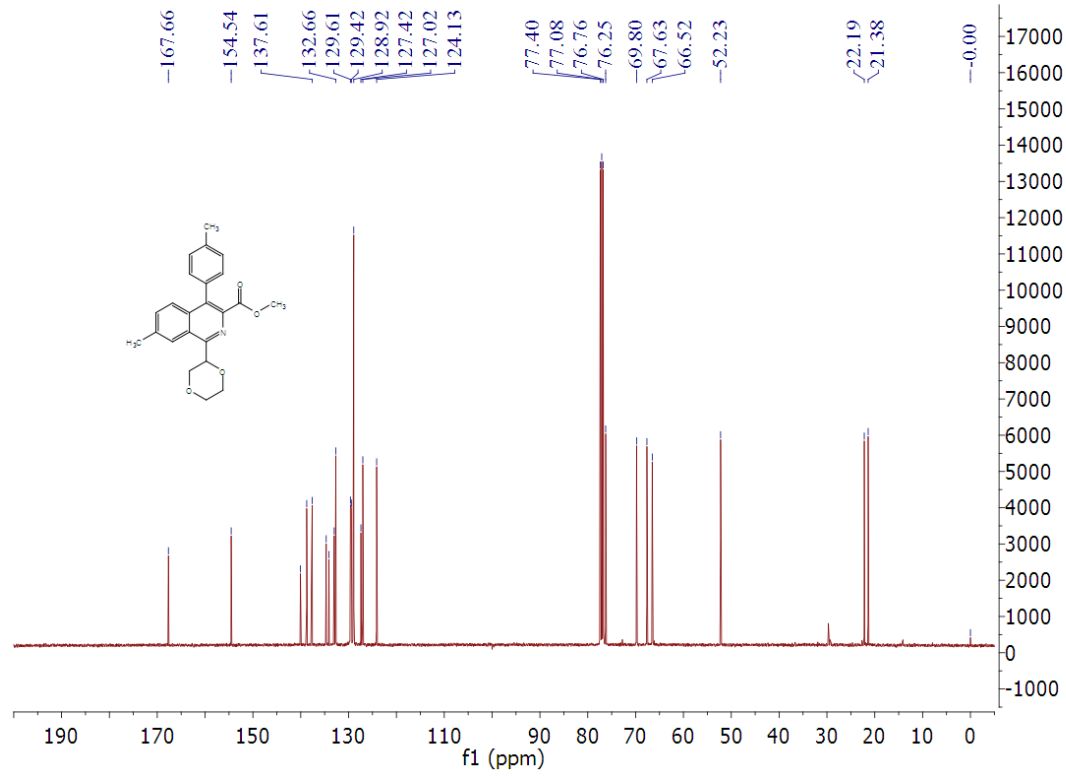
^{1}H NMR and ^{13}C NMR spectrum of **3da**



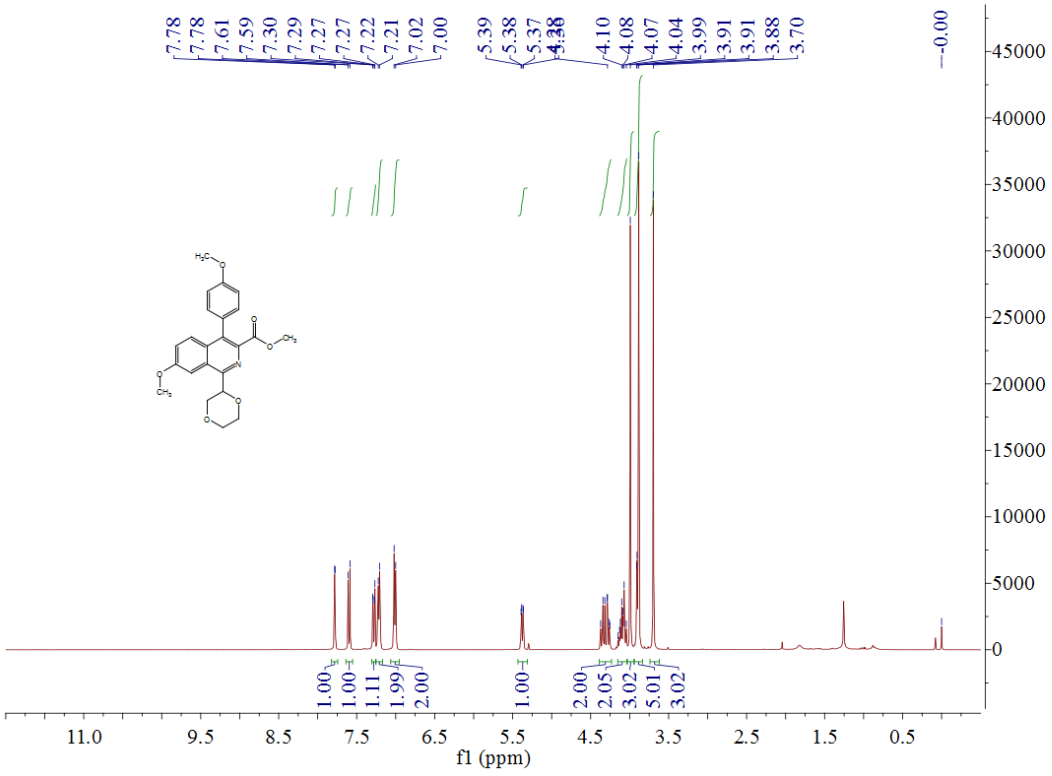


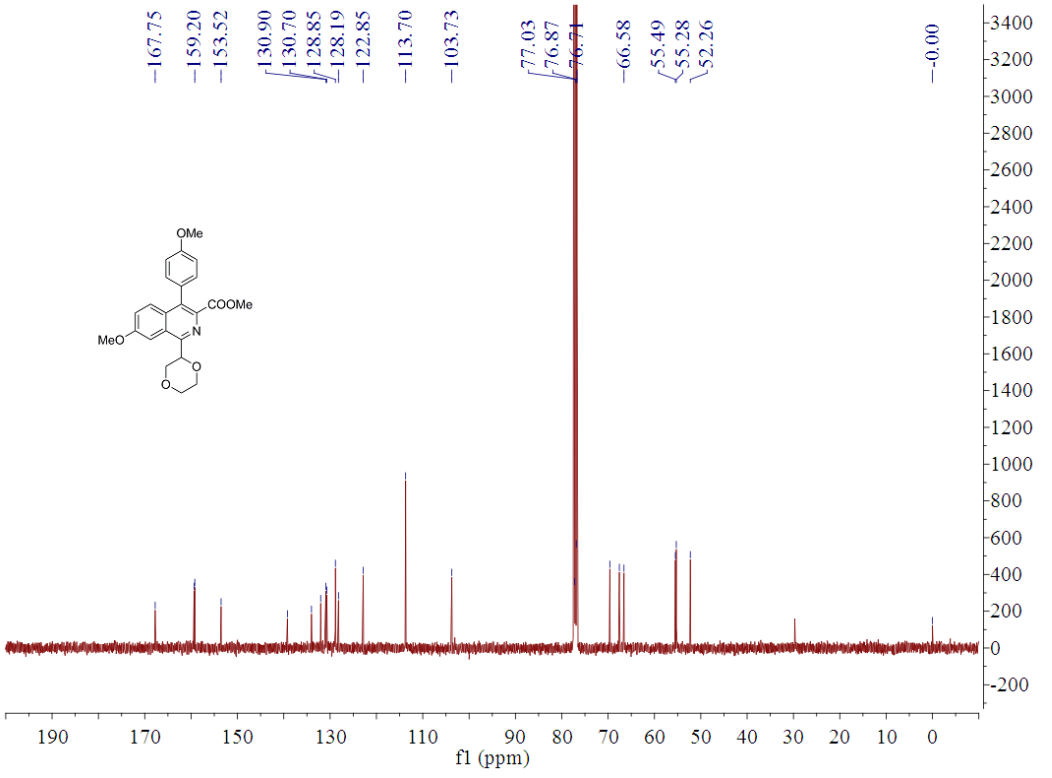
^{1}H NMR and ^{13}C NMR spectrum of **3ea**



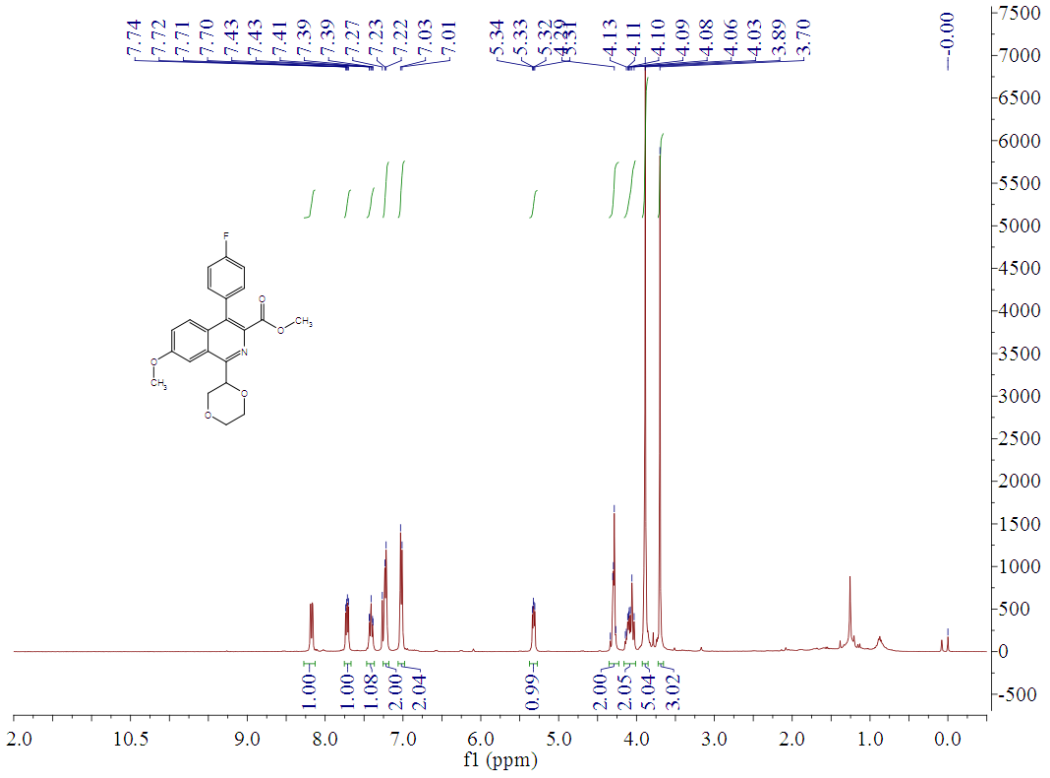


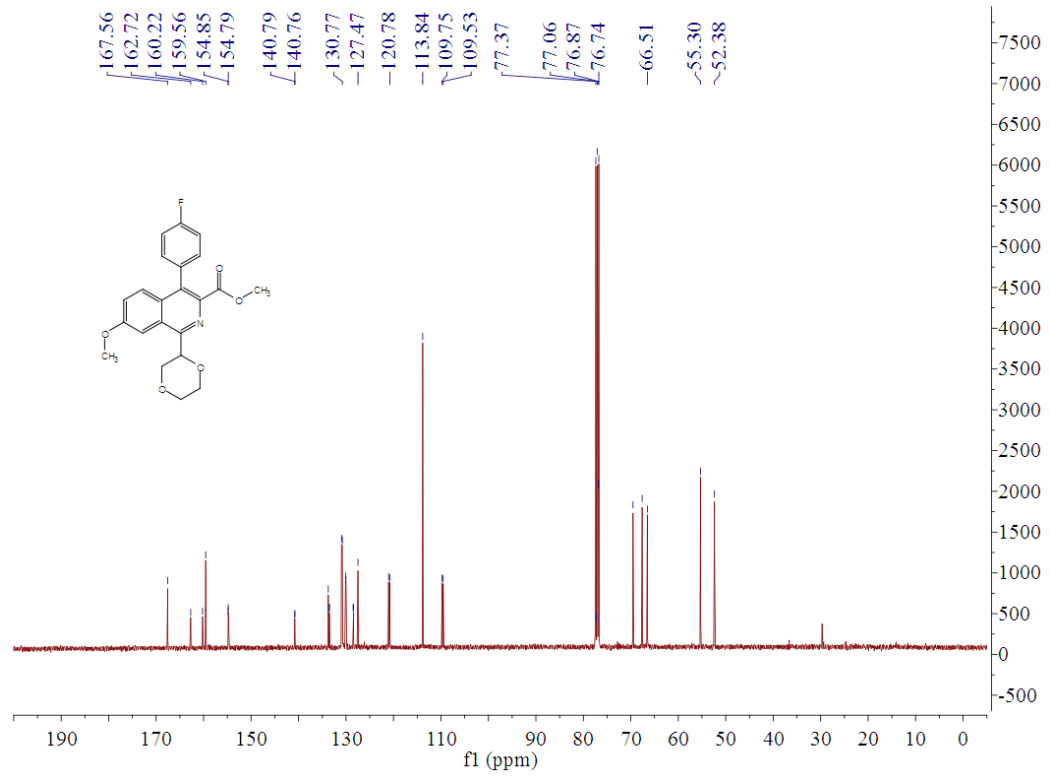
^{1}H NMR and ^{13}C NMR spectrum of **3fa**



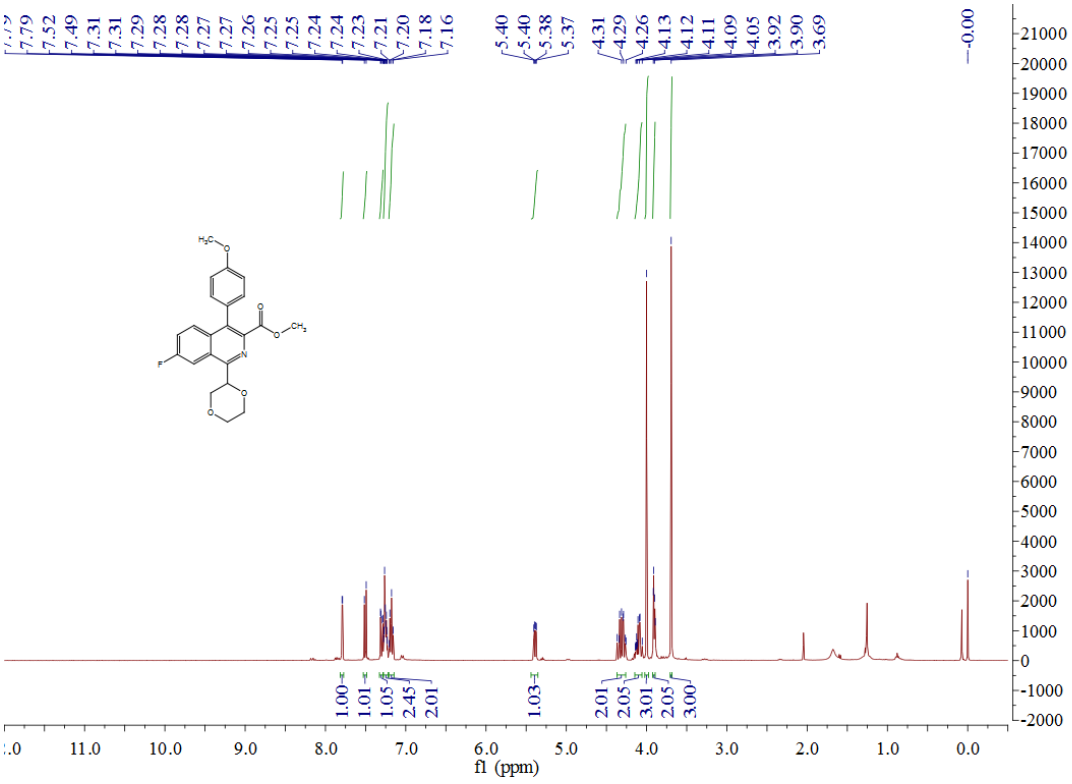


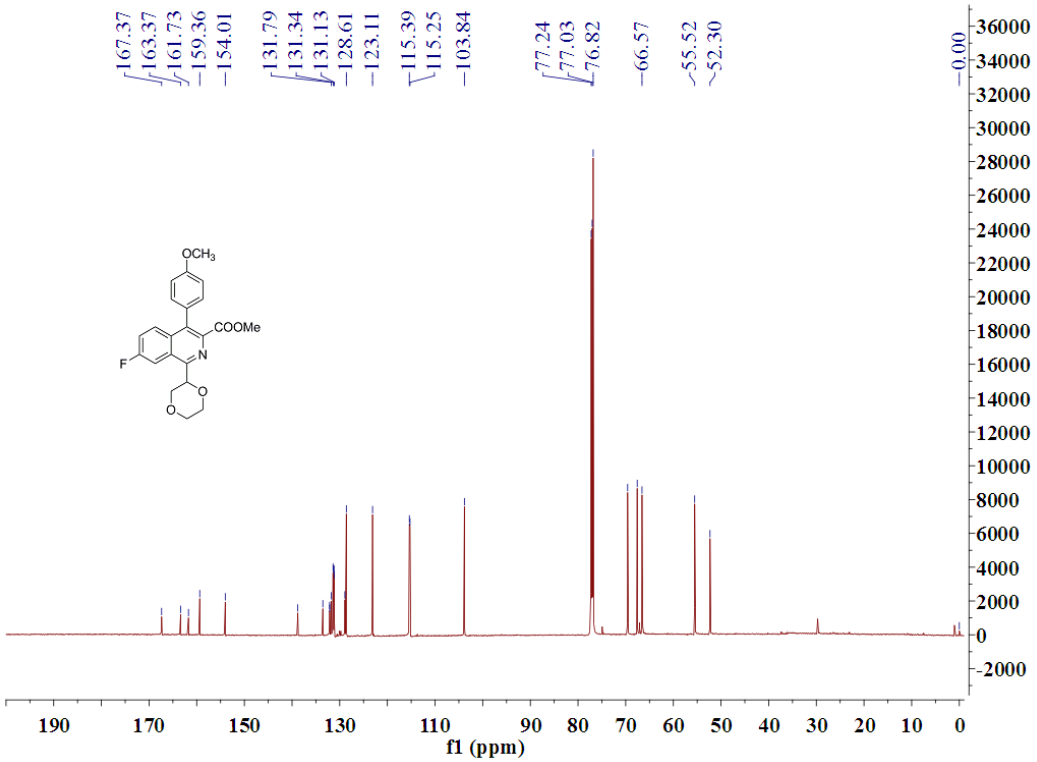
^{1}H NMR and ^{13}C NMR spectrum of **3ga**



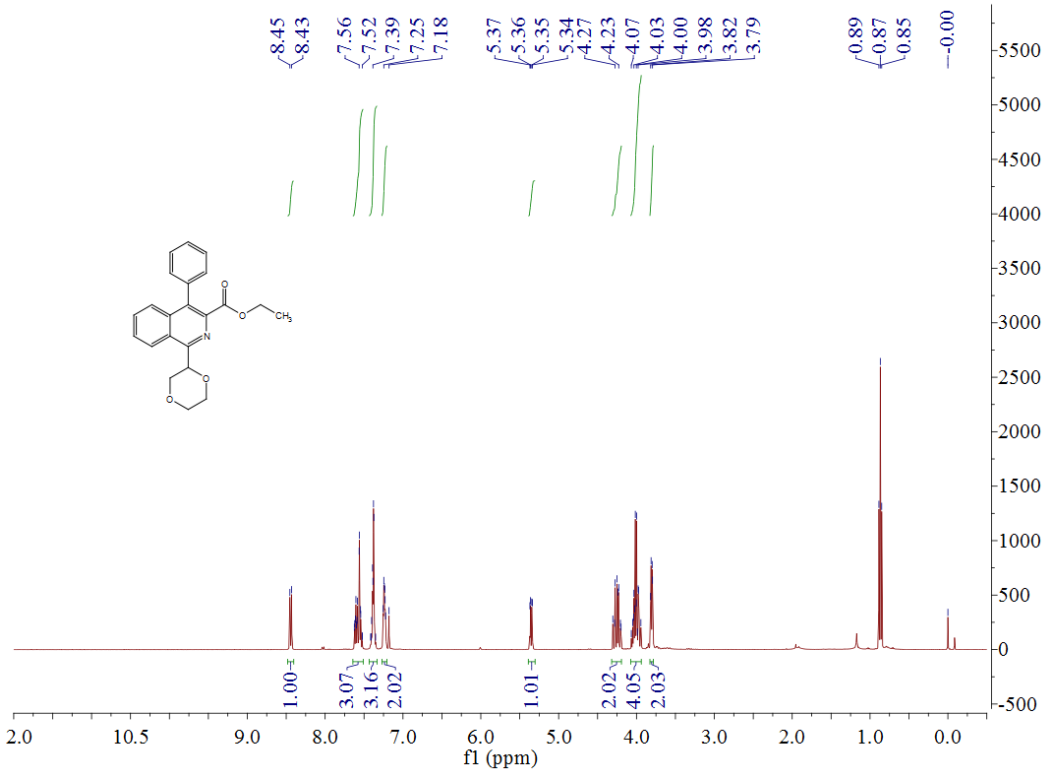


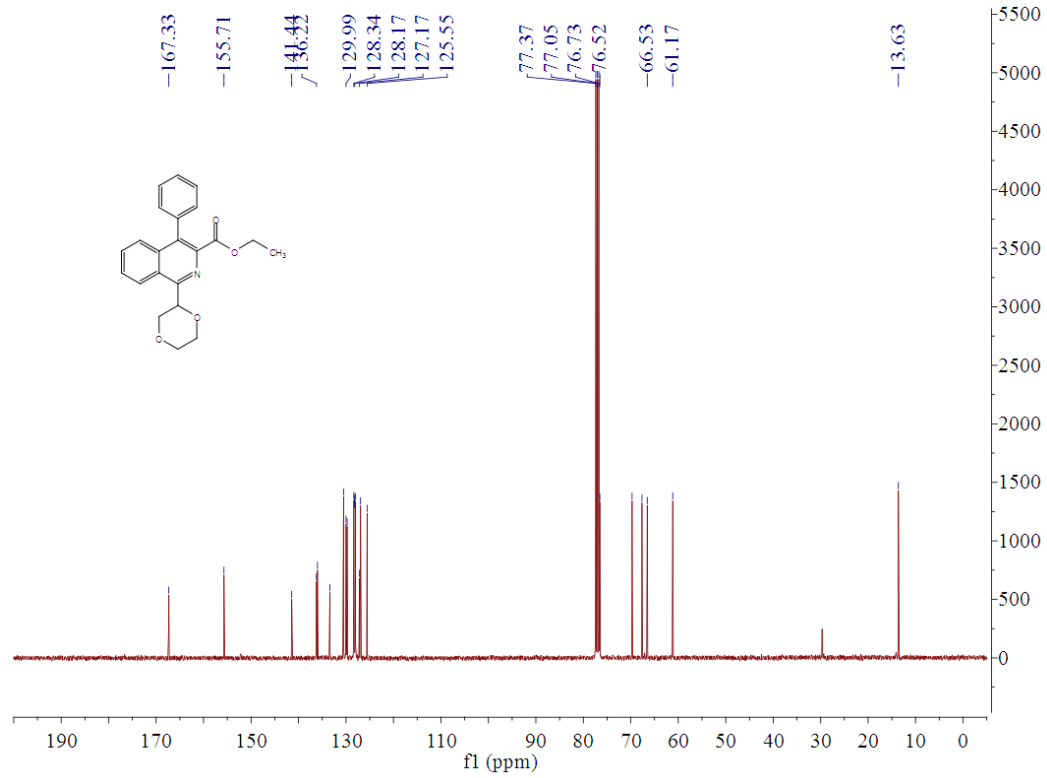
^{1}H NMR and ^{13}C NMR spectrum of **3ha**



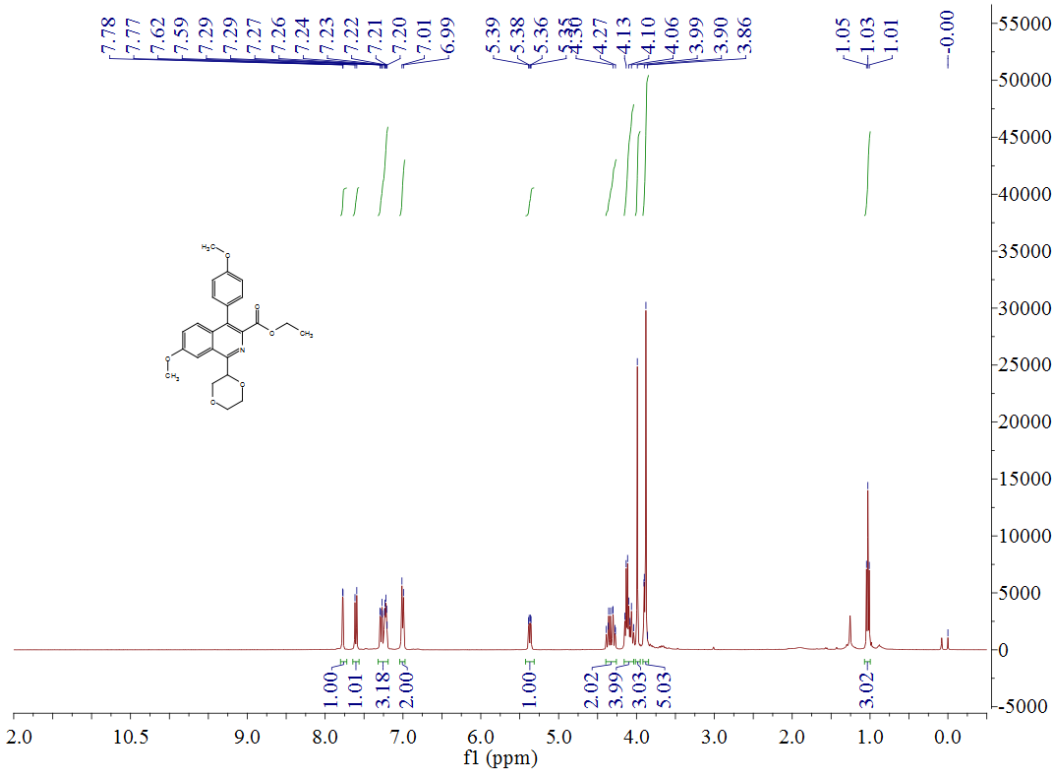


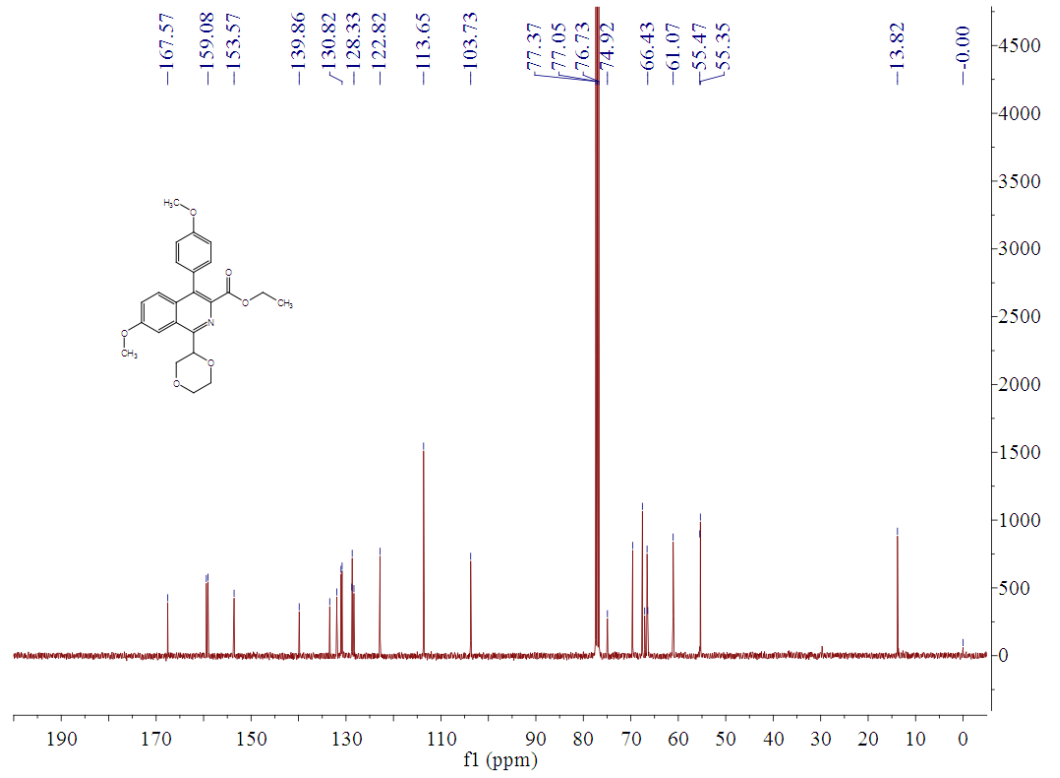
^{1}H NMR and ^{13}C NMR spectrum of **3ia**



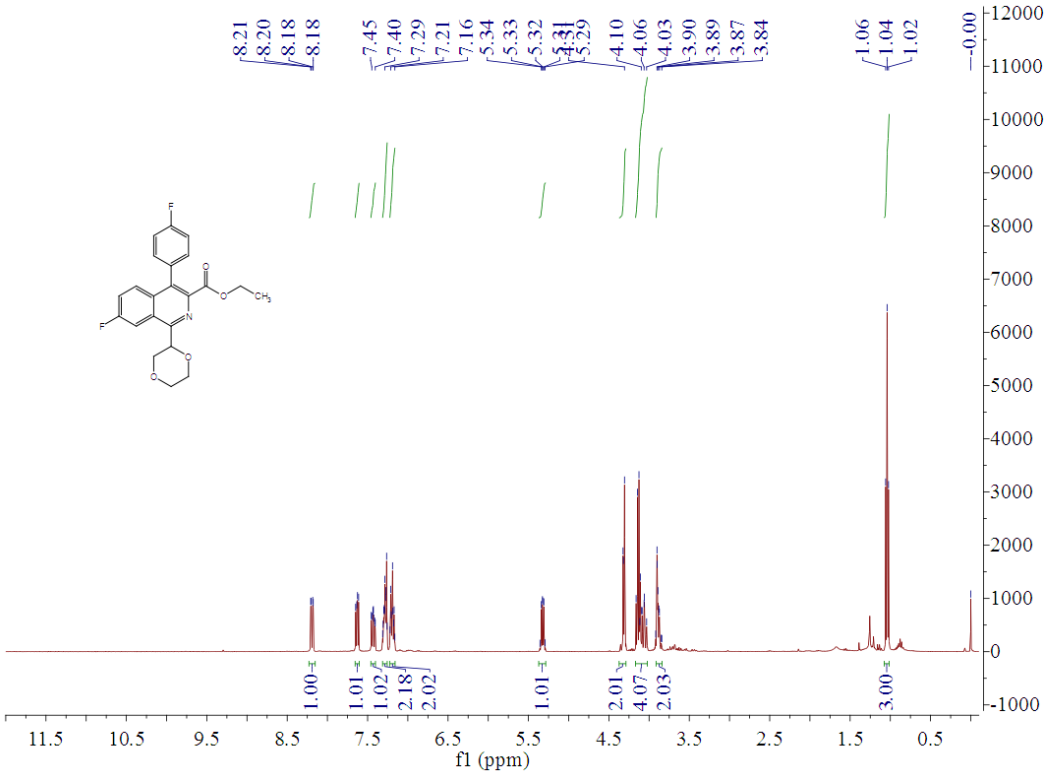


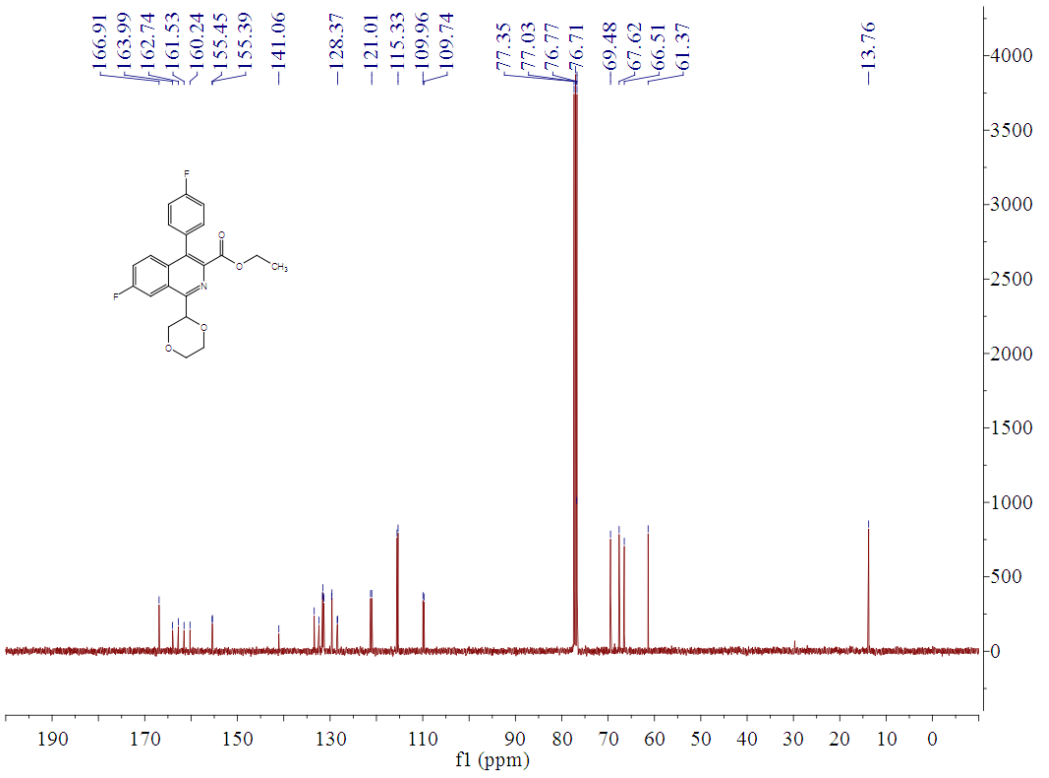
^{1}H NMR and ^{13}C NMR spectrum of **3ja**



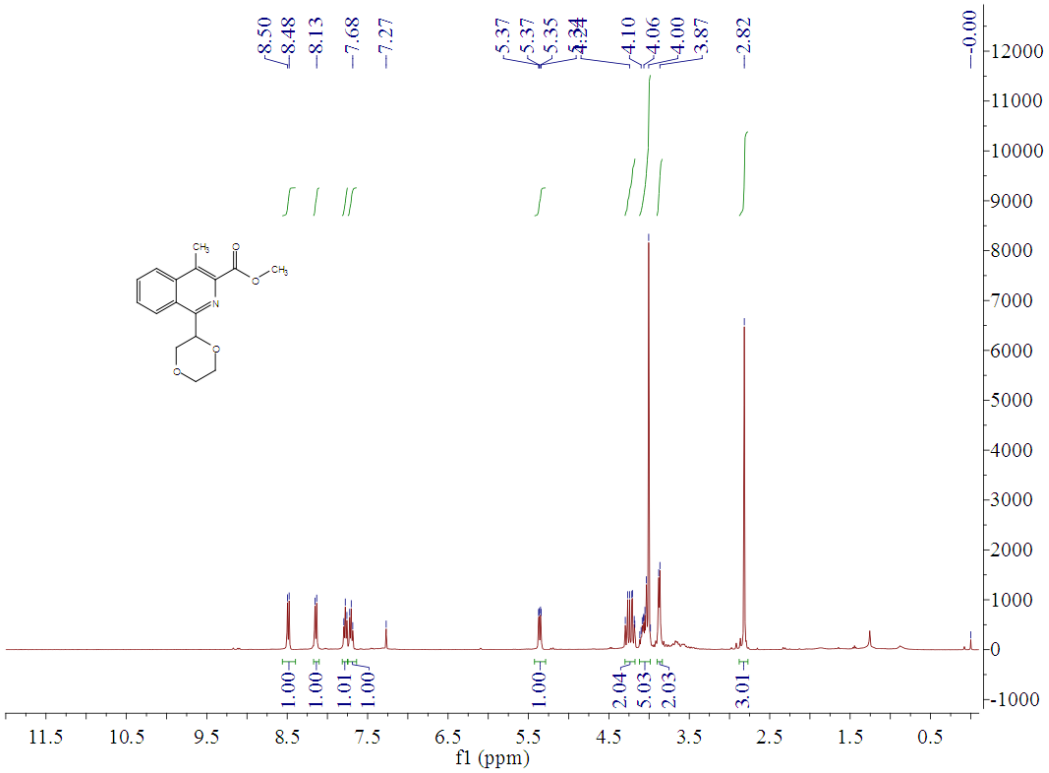


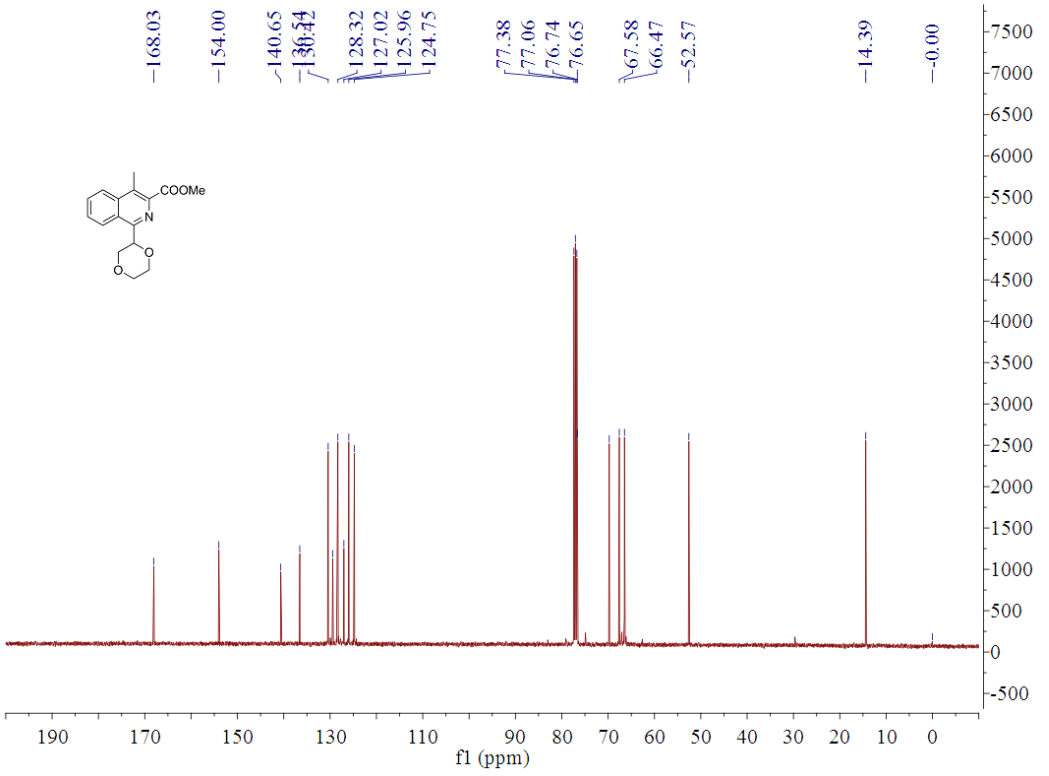
^{1}H NMR and ^{13}C NMR spectrum of **3ka**



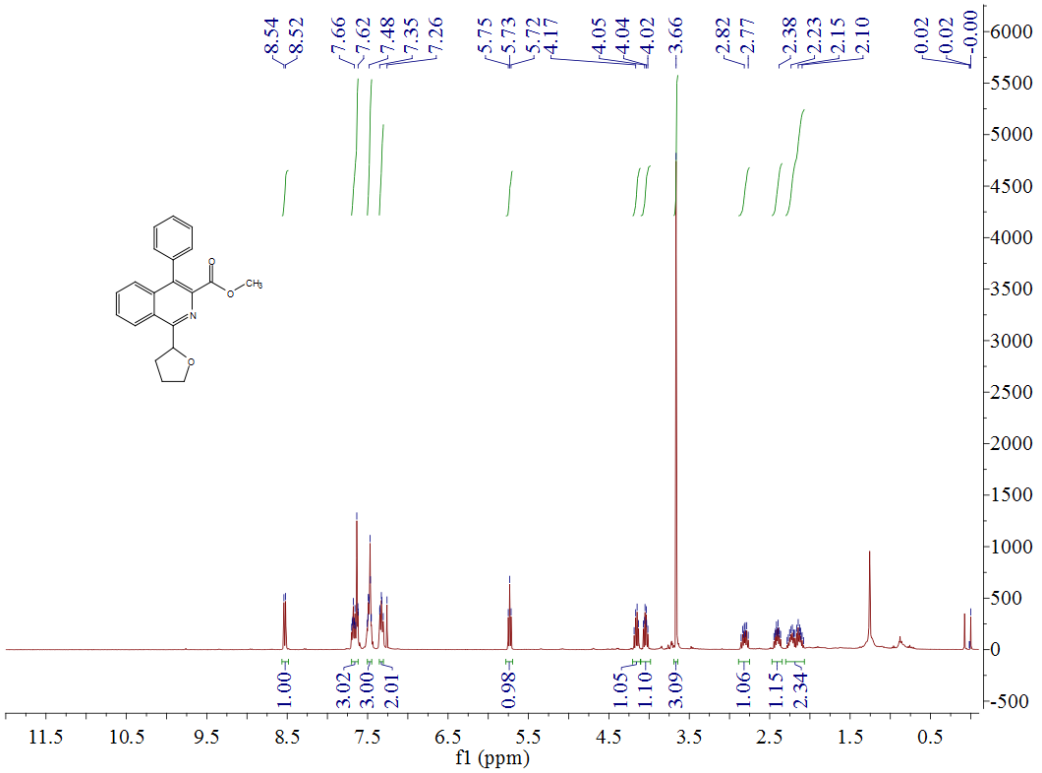


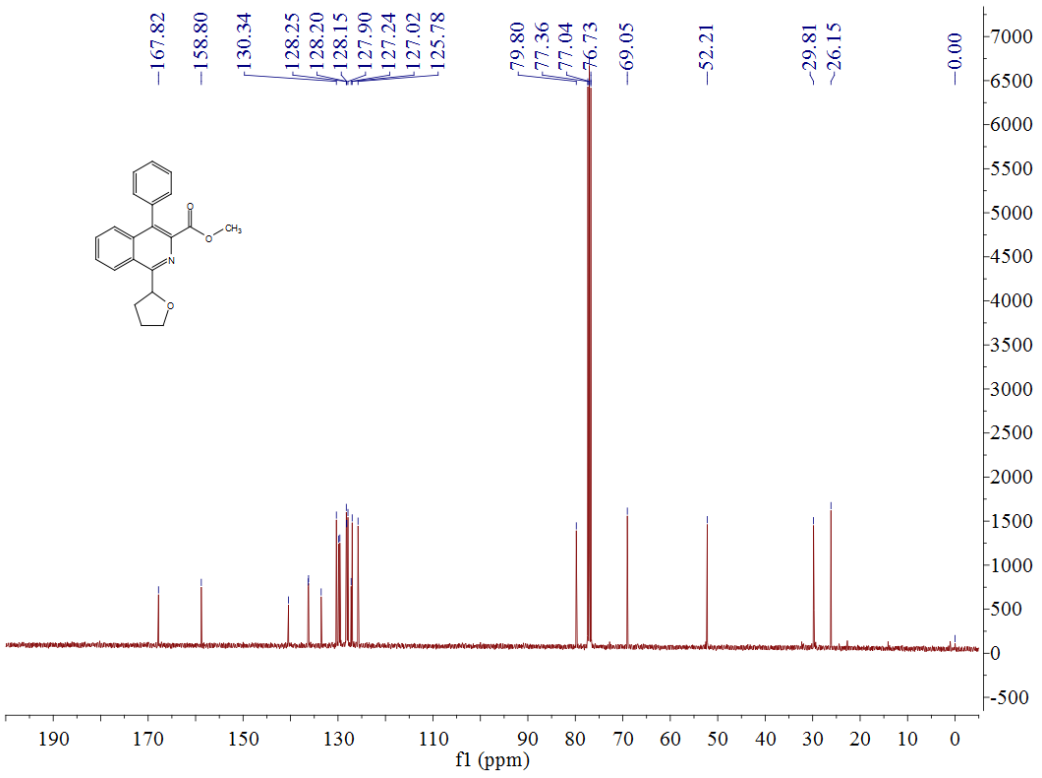
^{1}H NMR and ^{13}C NMR spectrum of **3la**



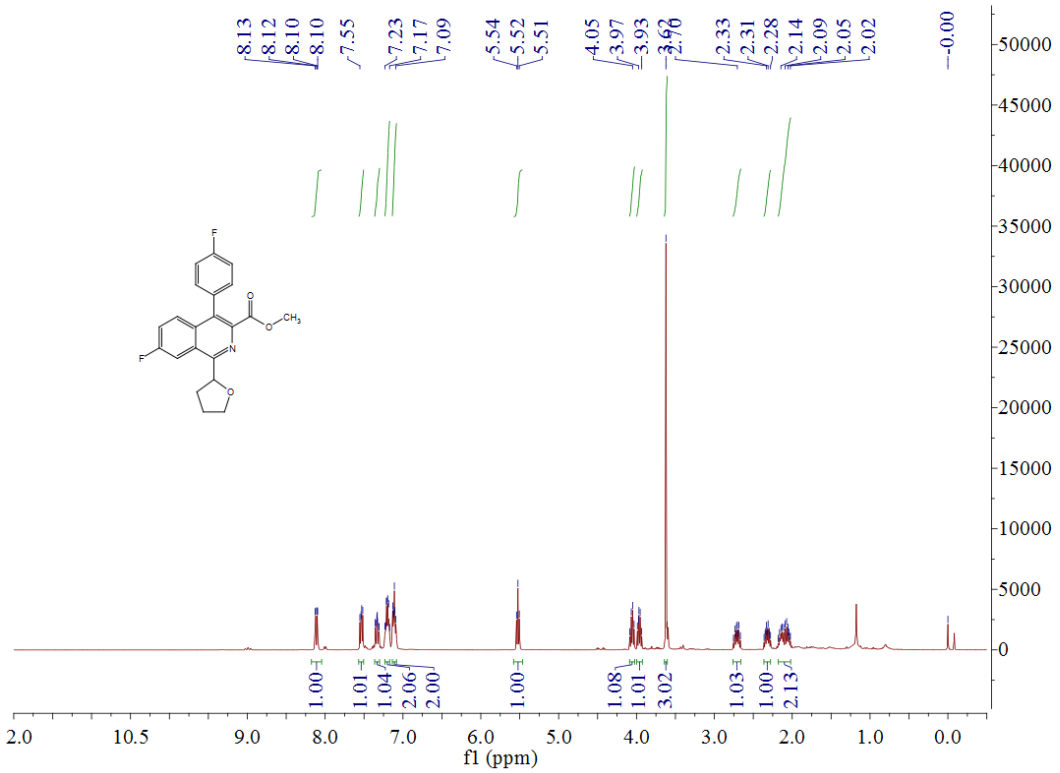


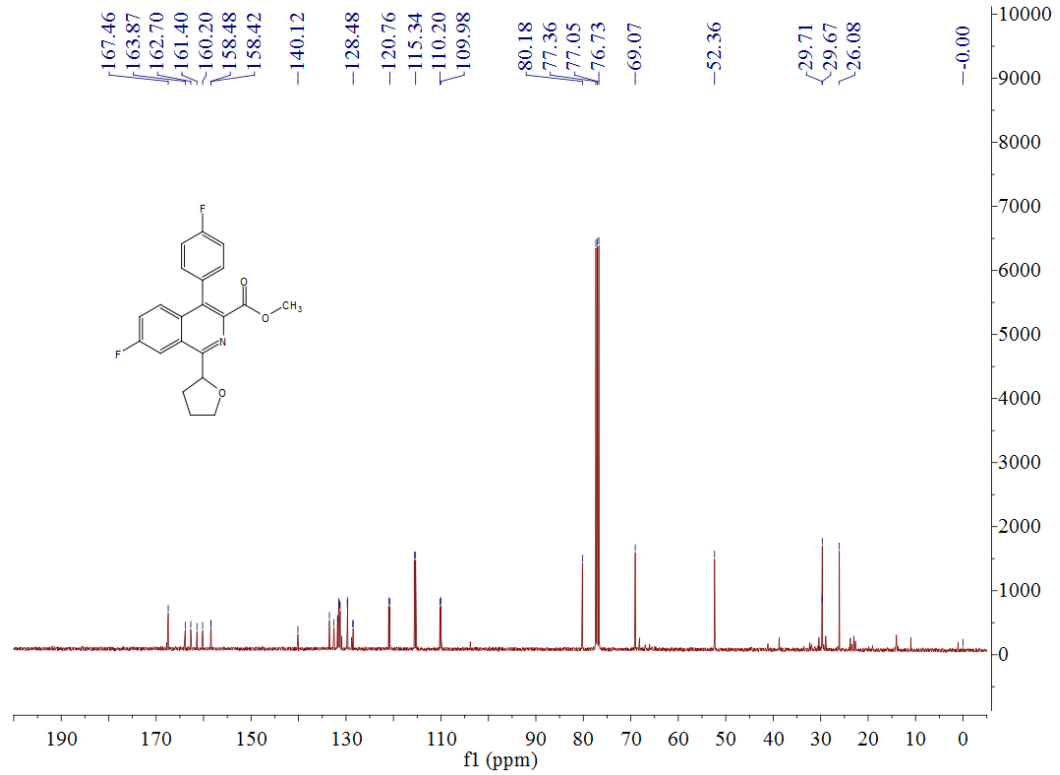
^{1}H NMR and ^{13}C NMR spectrum of **3ab**



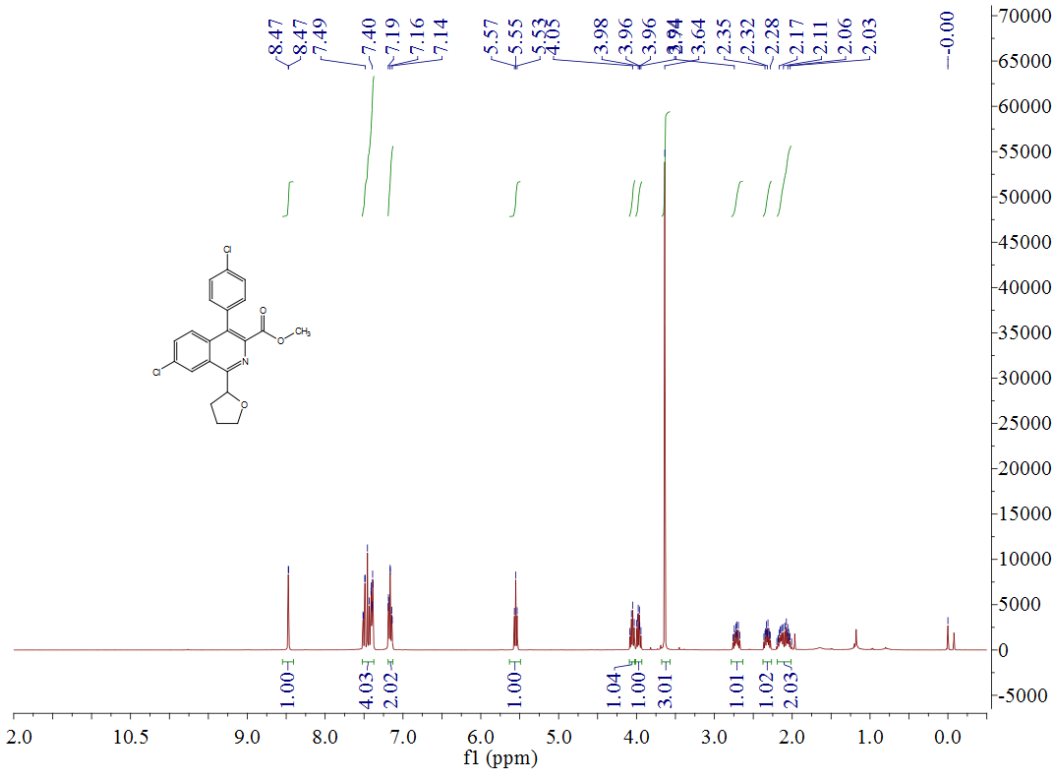


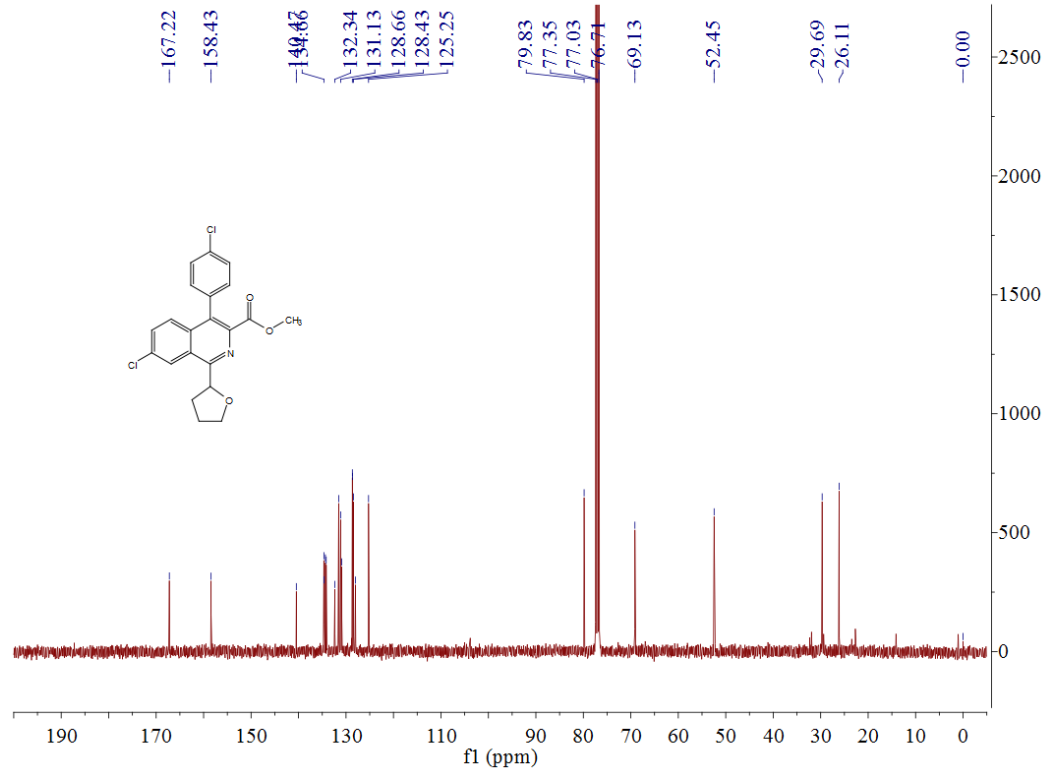
^{1}H NMR and ^{13}C NMR spectrum of **3bb**



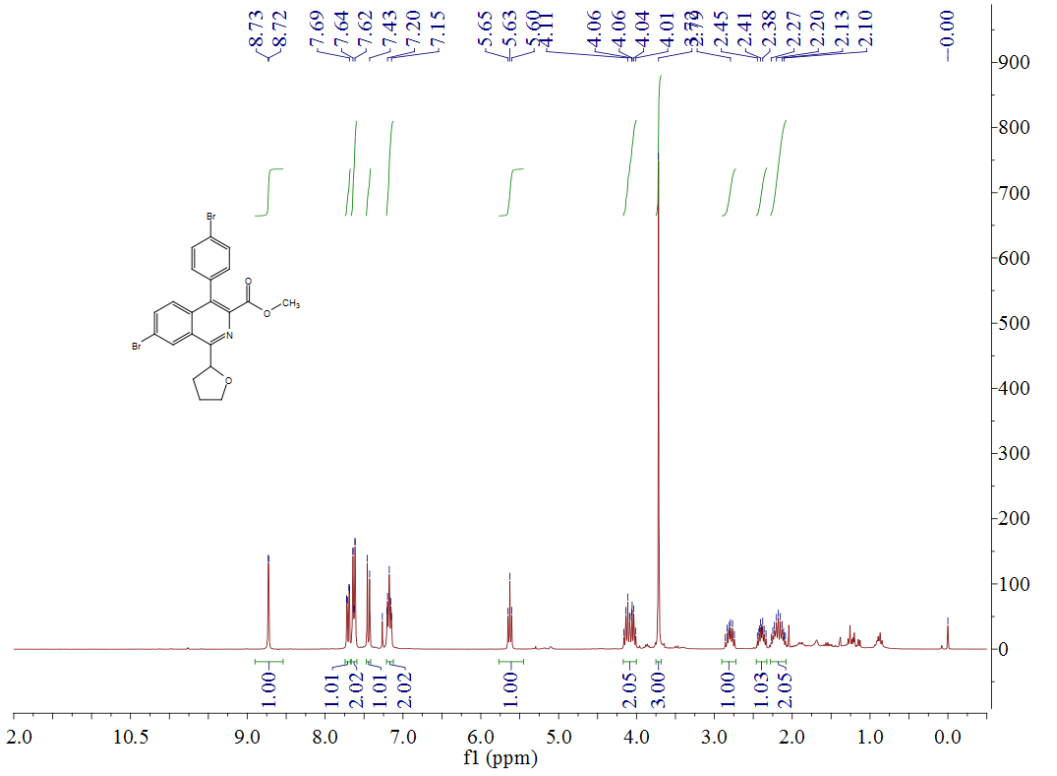


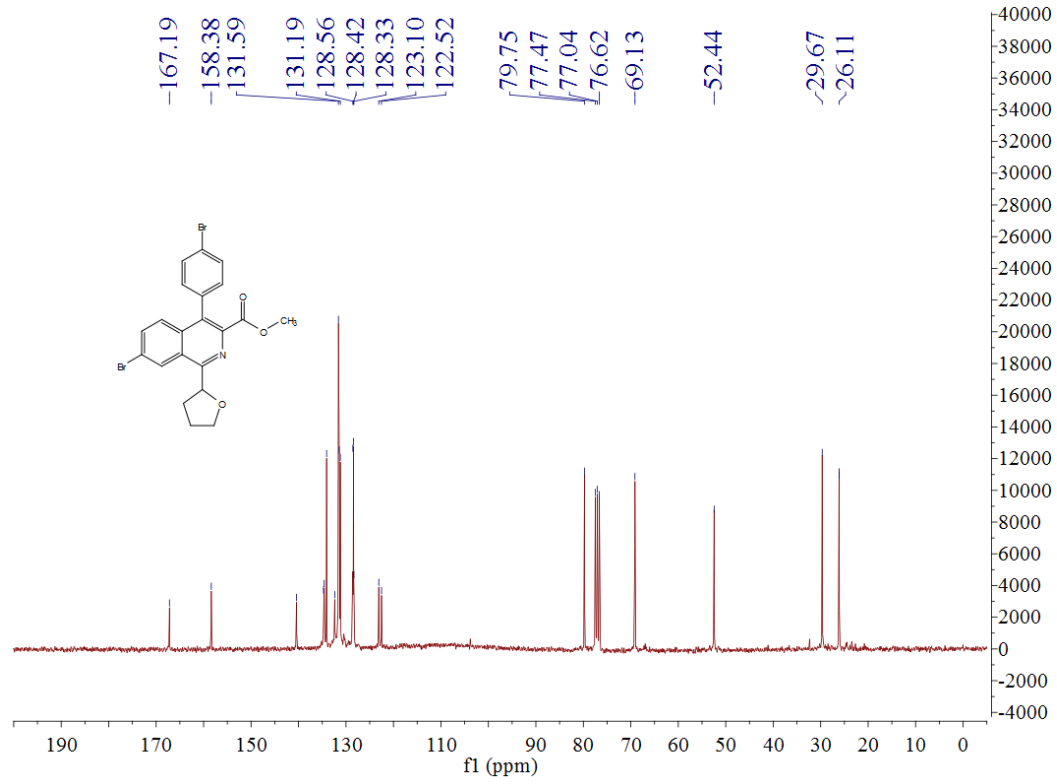
^{1}H NMR and ^{13}C NMR spectrum of **3cb**



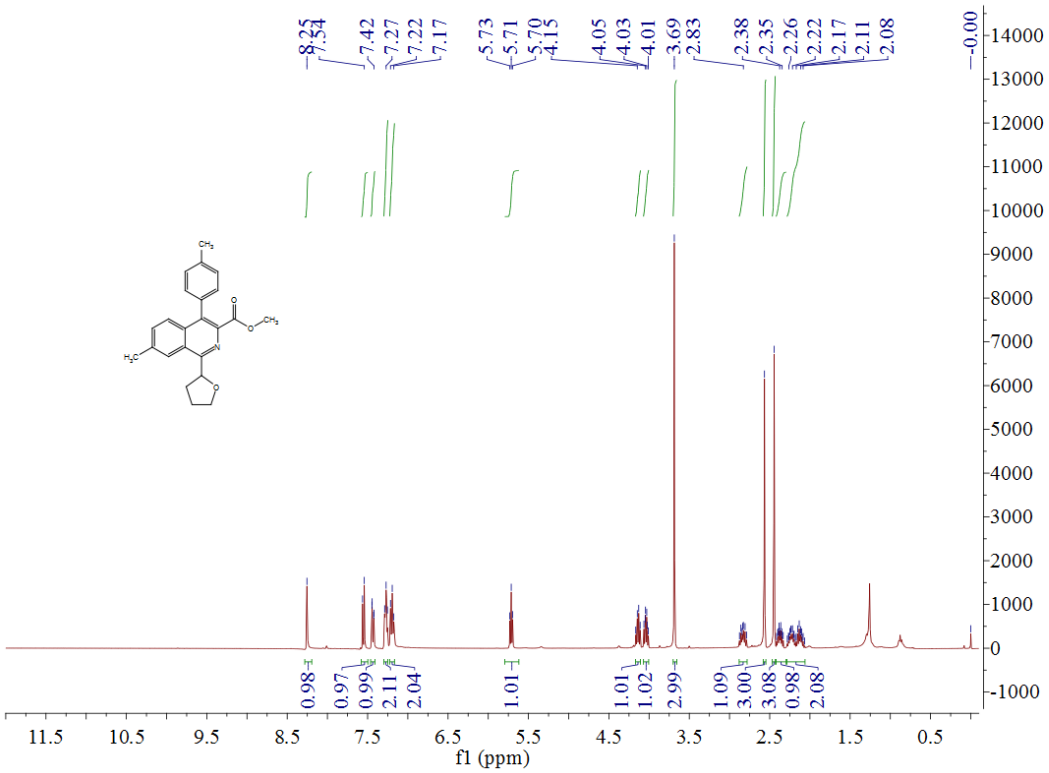


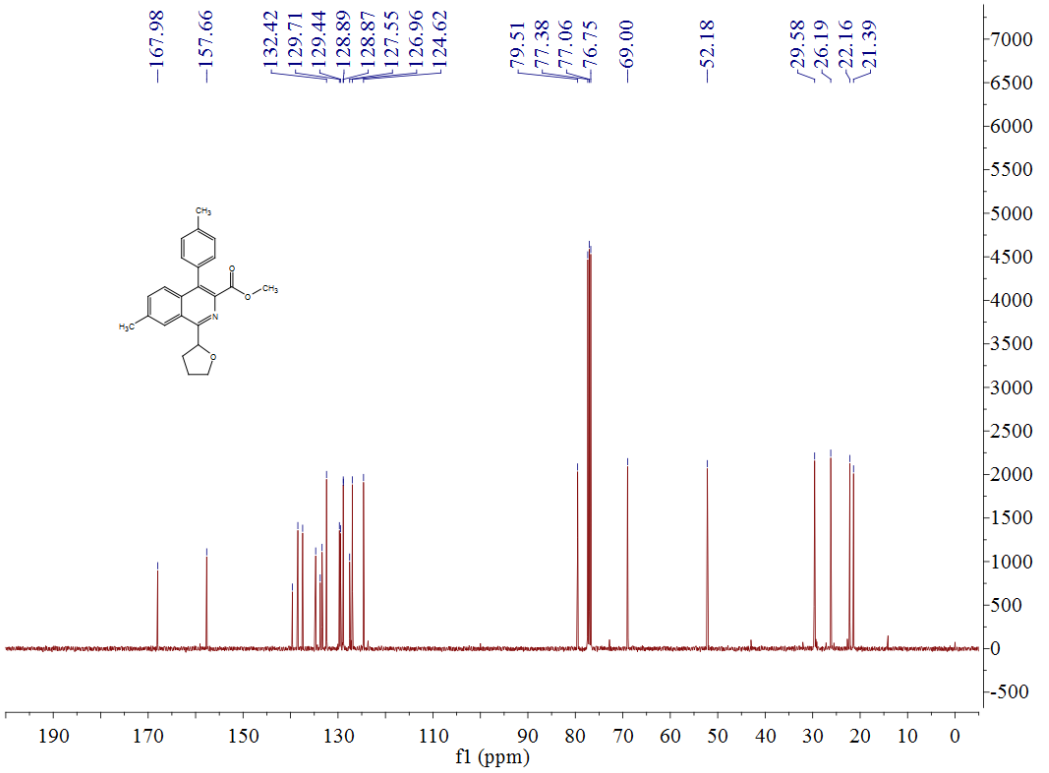
^{1}H NMR and ^{13}C NMR spectrum of **3db**



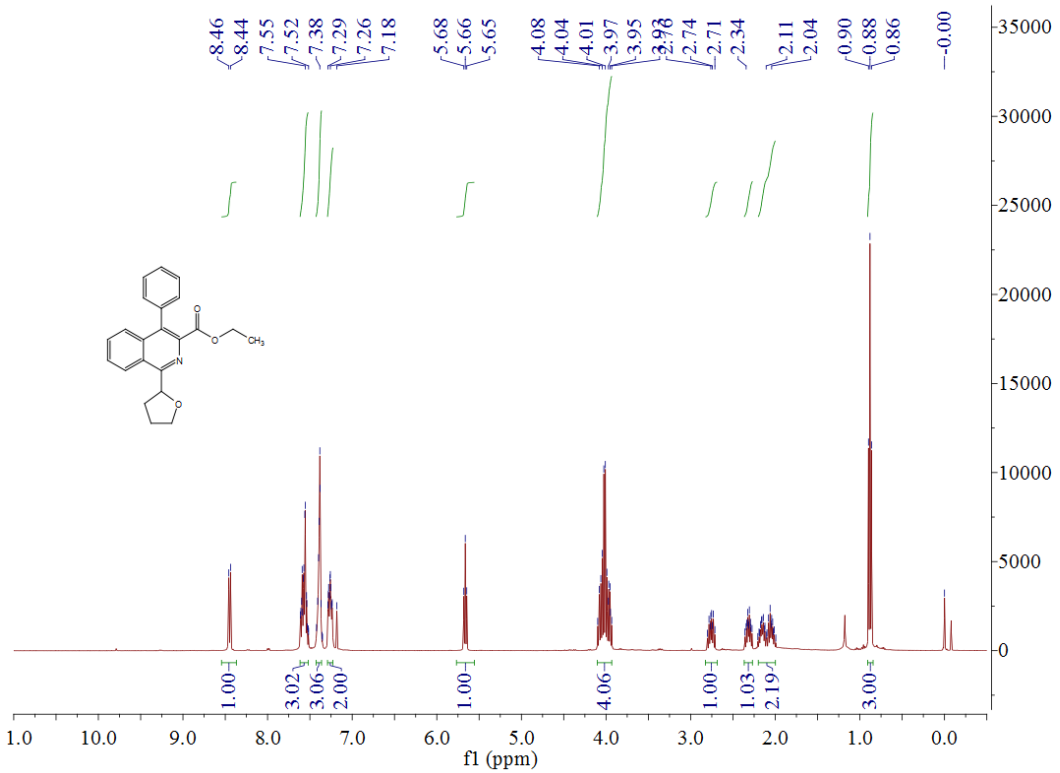


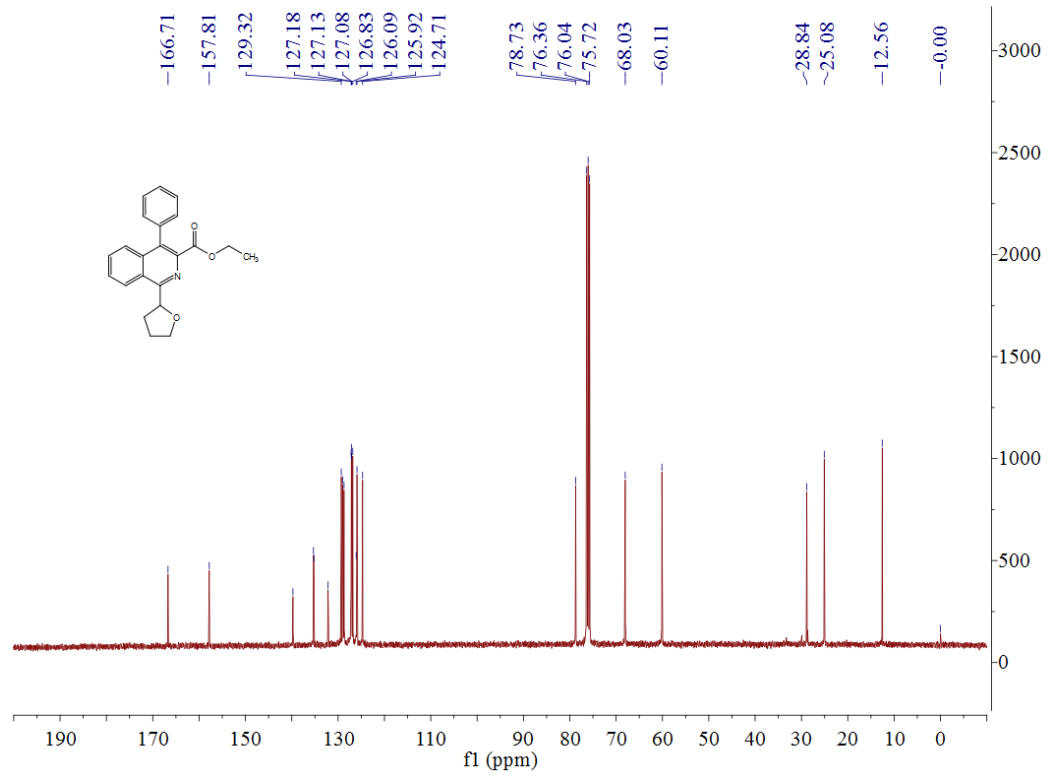
^{1}H NMR and ^{13}C NMR spectrum of **3eb**



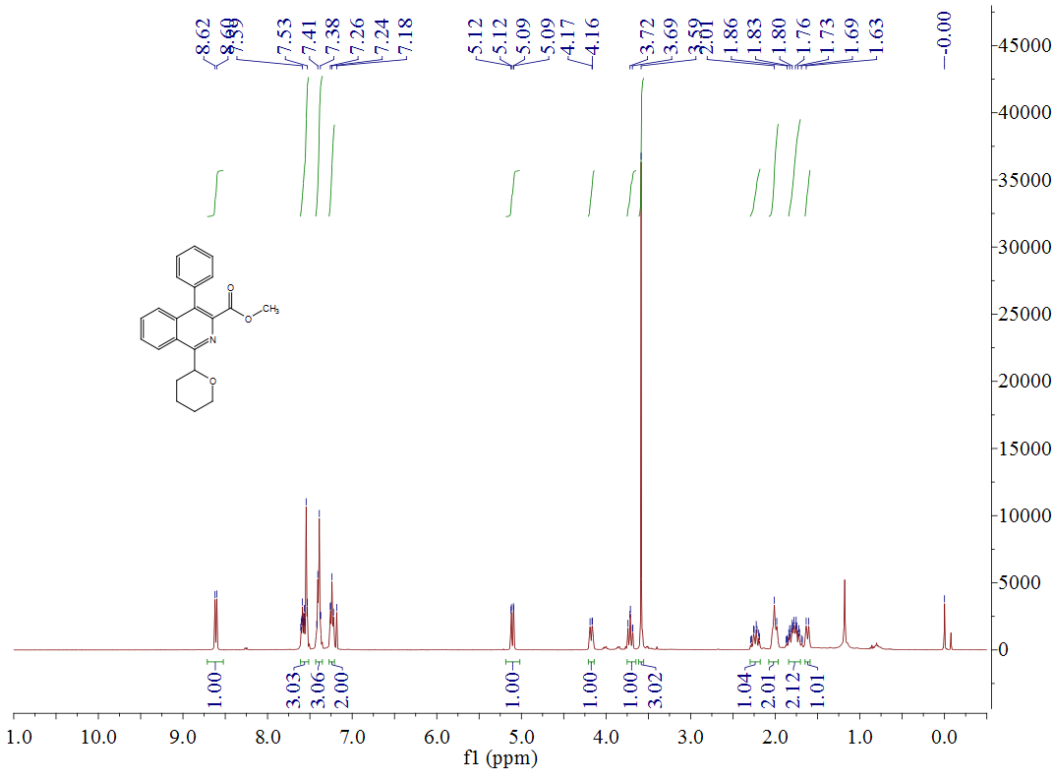


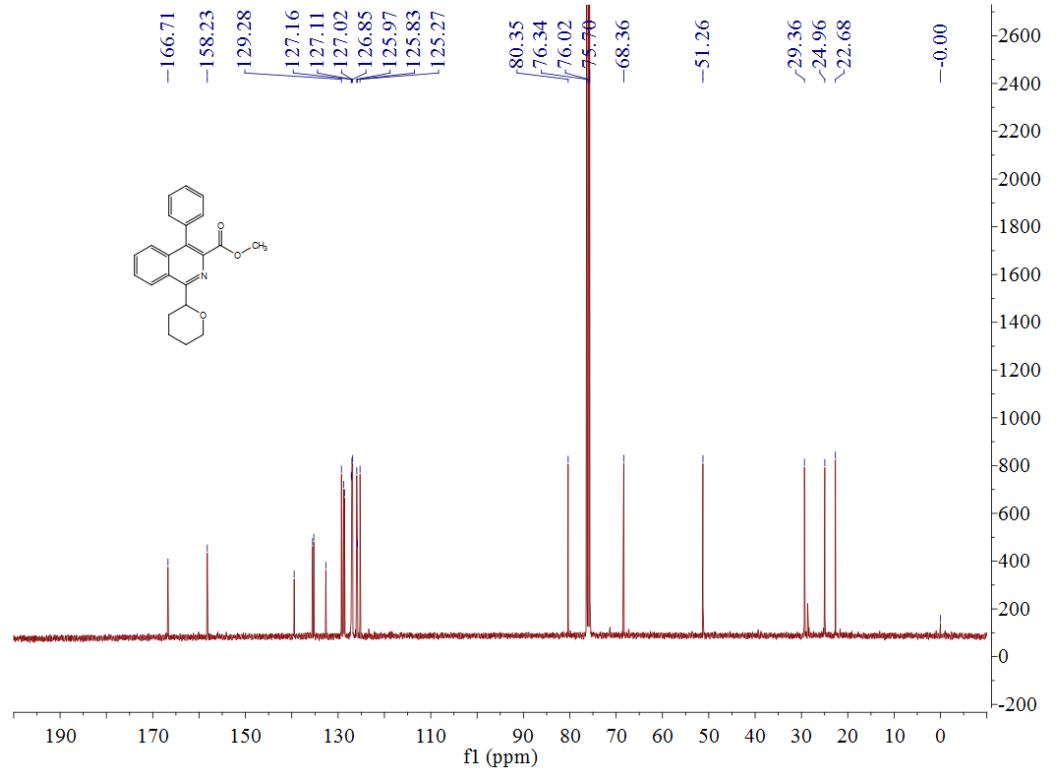
^{1}H NMR and ^{13}C NMR spectrum of **3ib**



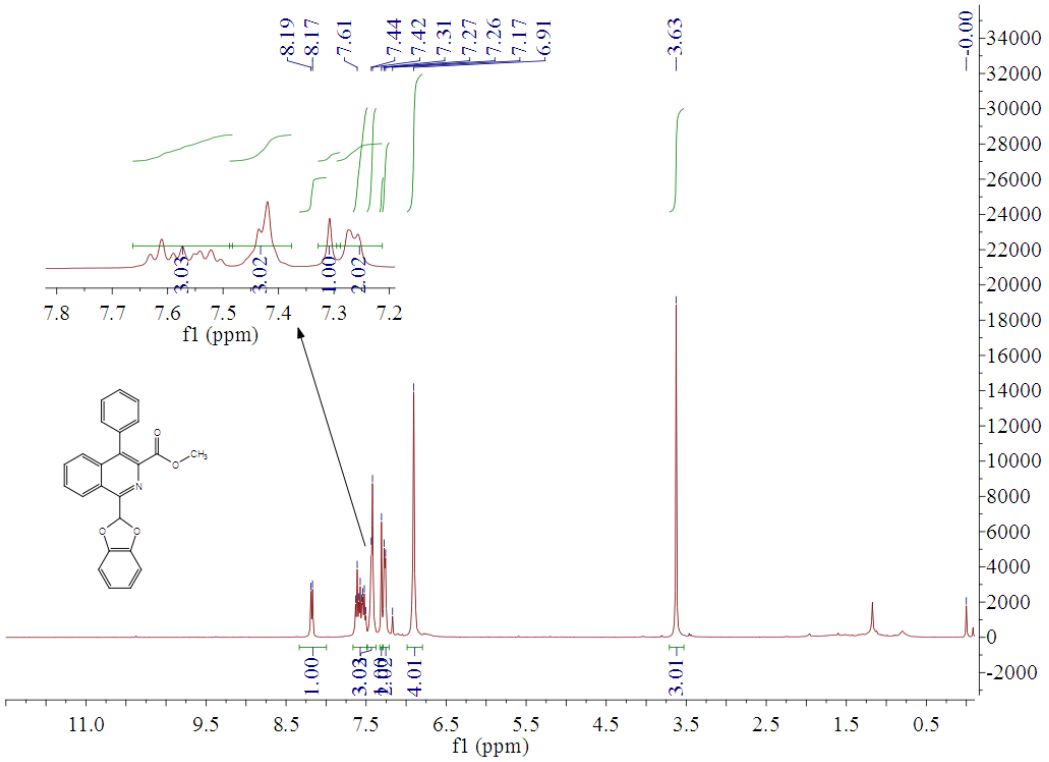


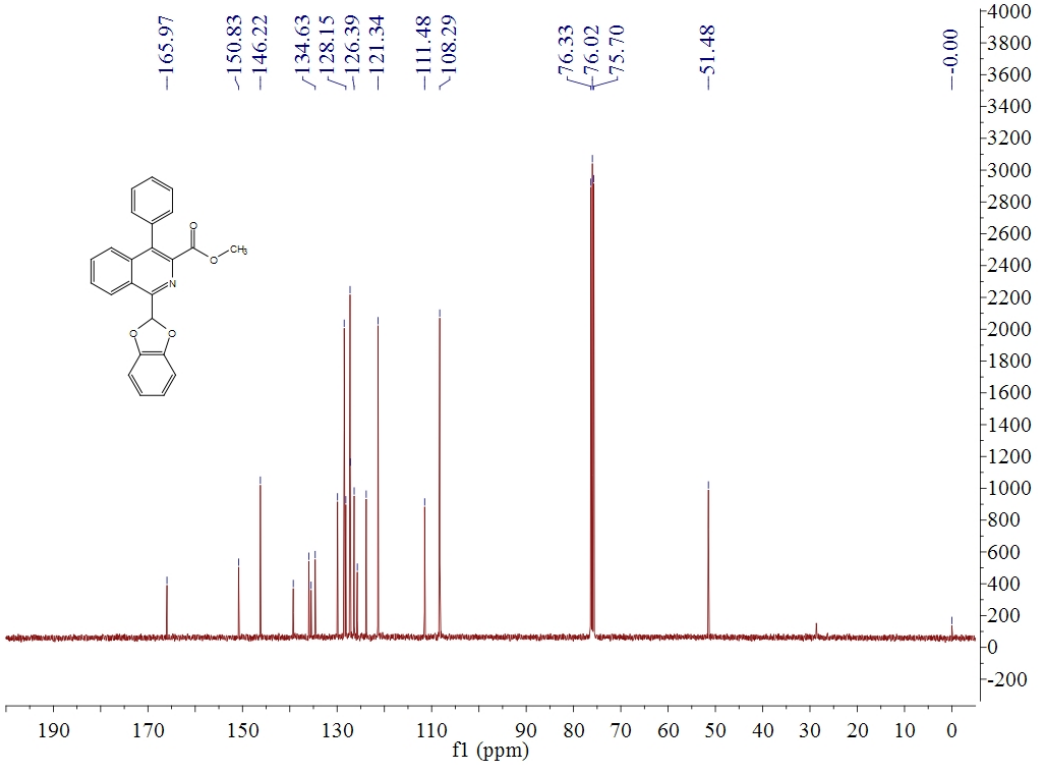
^{1}H NMR and ^{13}C NMR spectrum of **3ac**



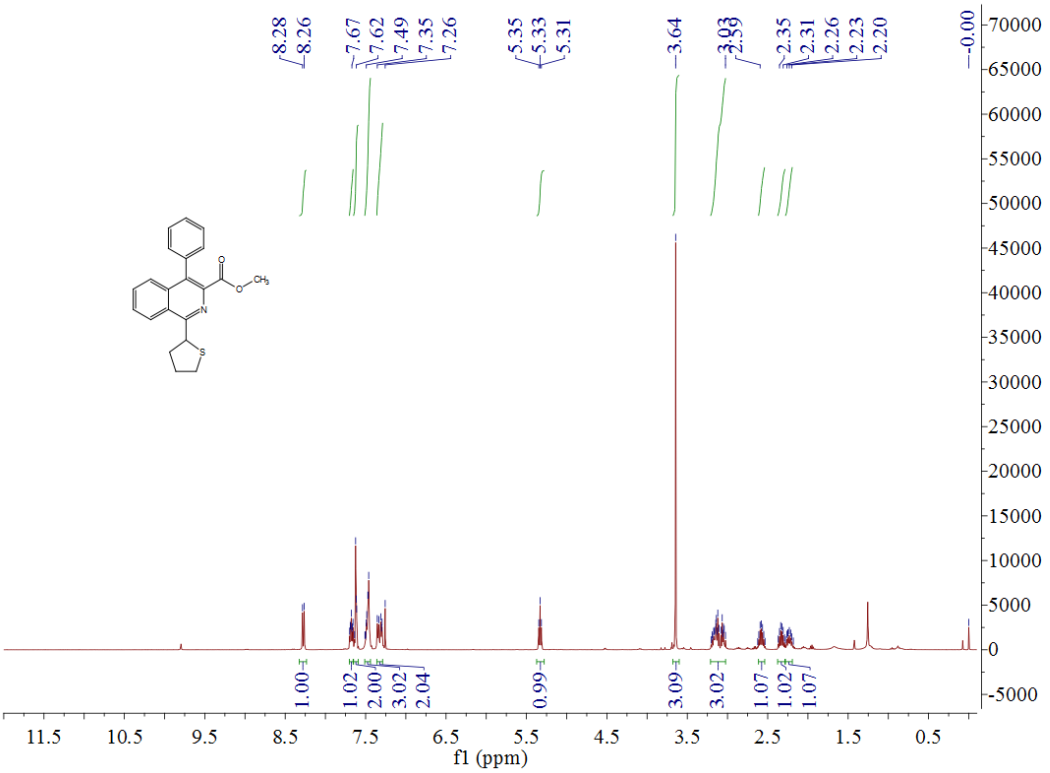


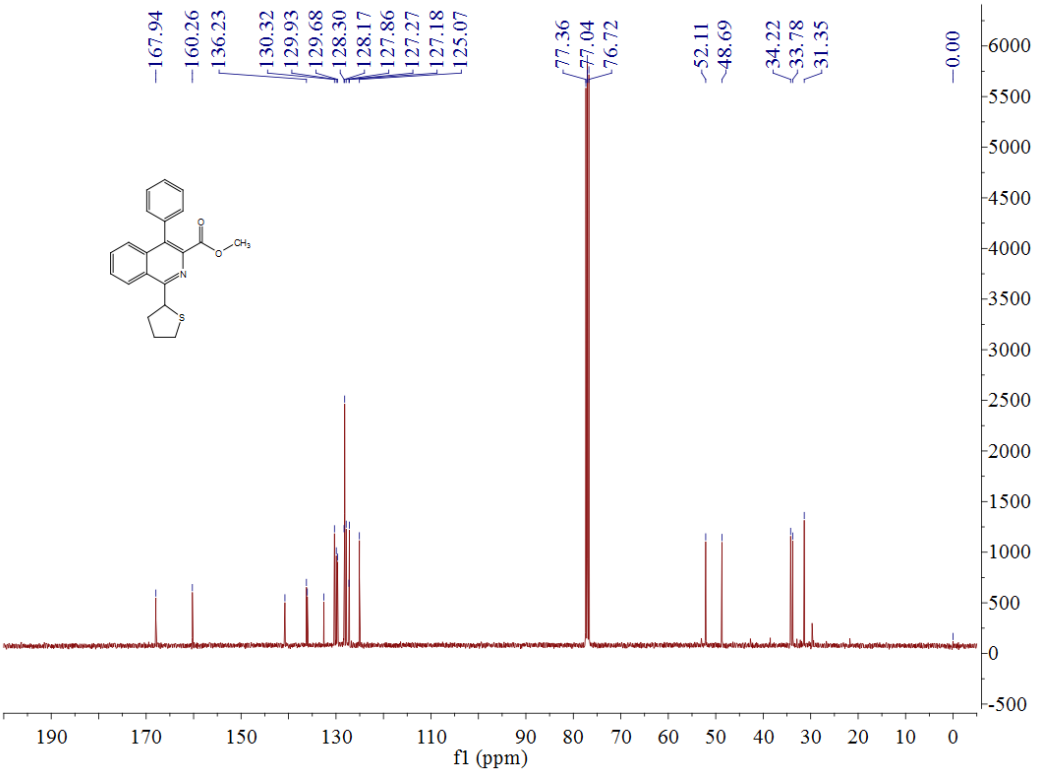
^{1}H NMR and ^{13}C NMR spectrum of **3ad**



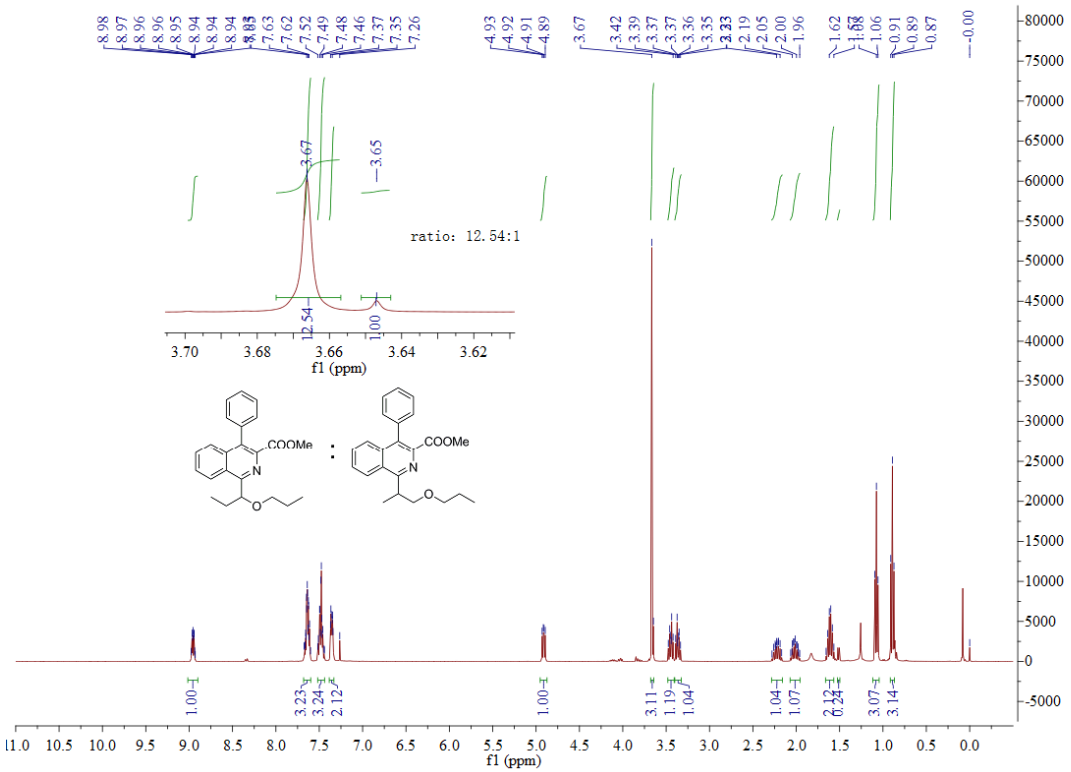


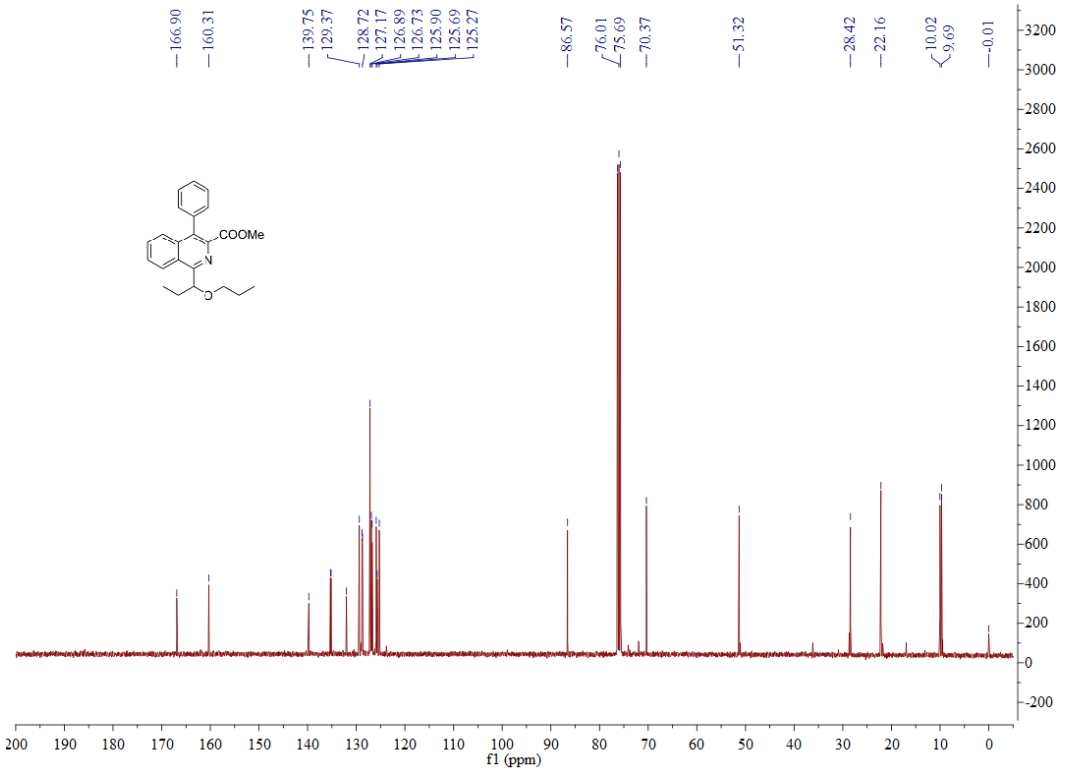
^{1}H NMR and ^{13}C NMR spectrum of **3ae**



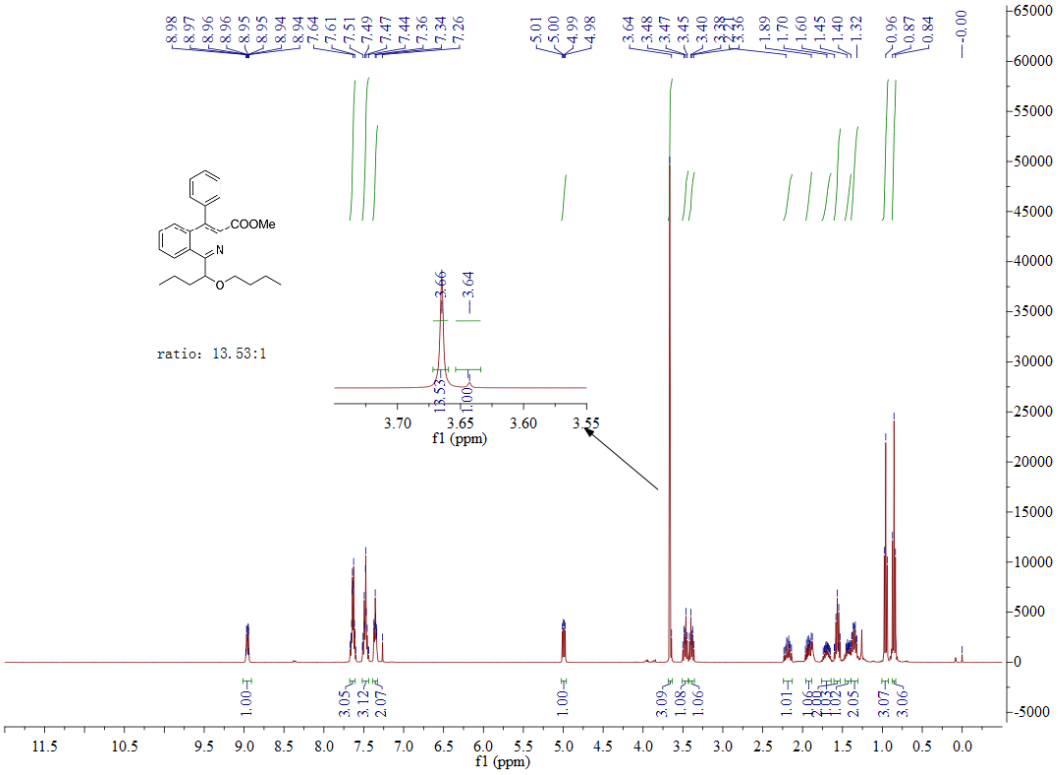


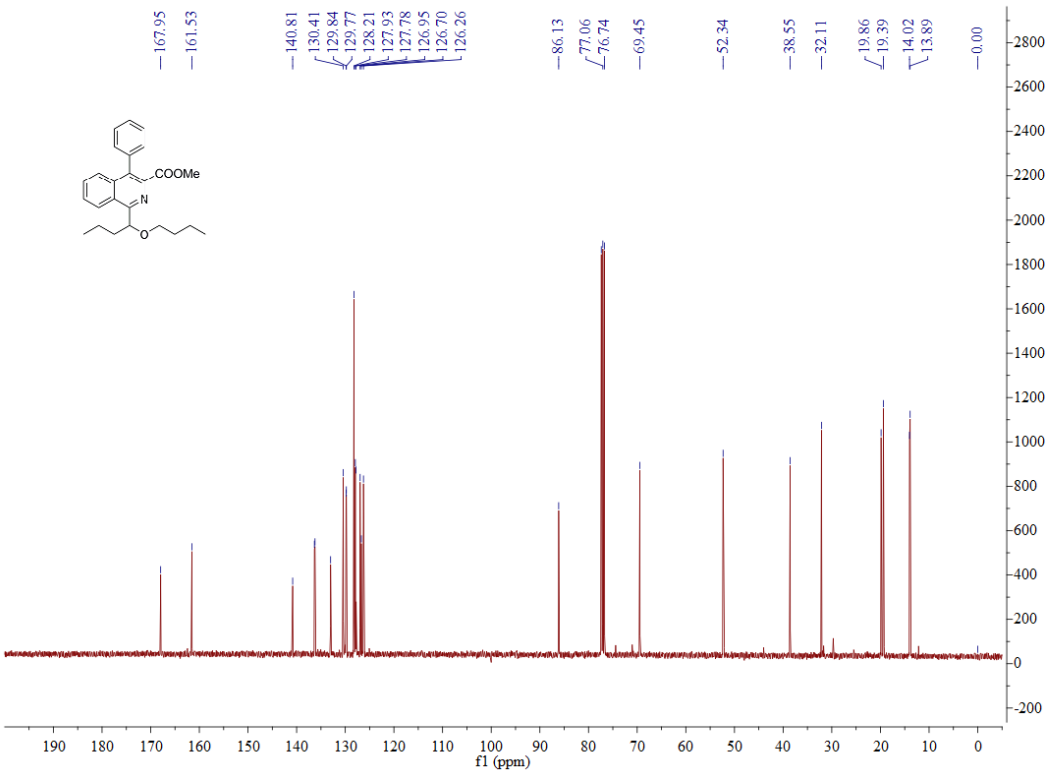
^{1}H NMR and ^{13}C NMR spectrum of **3af**



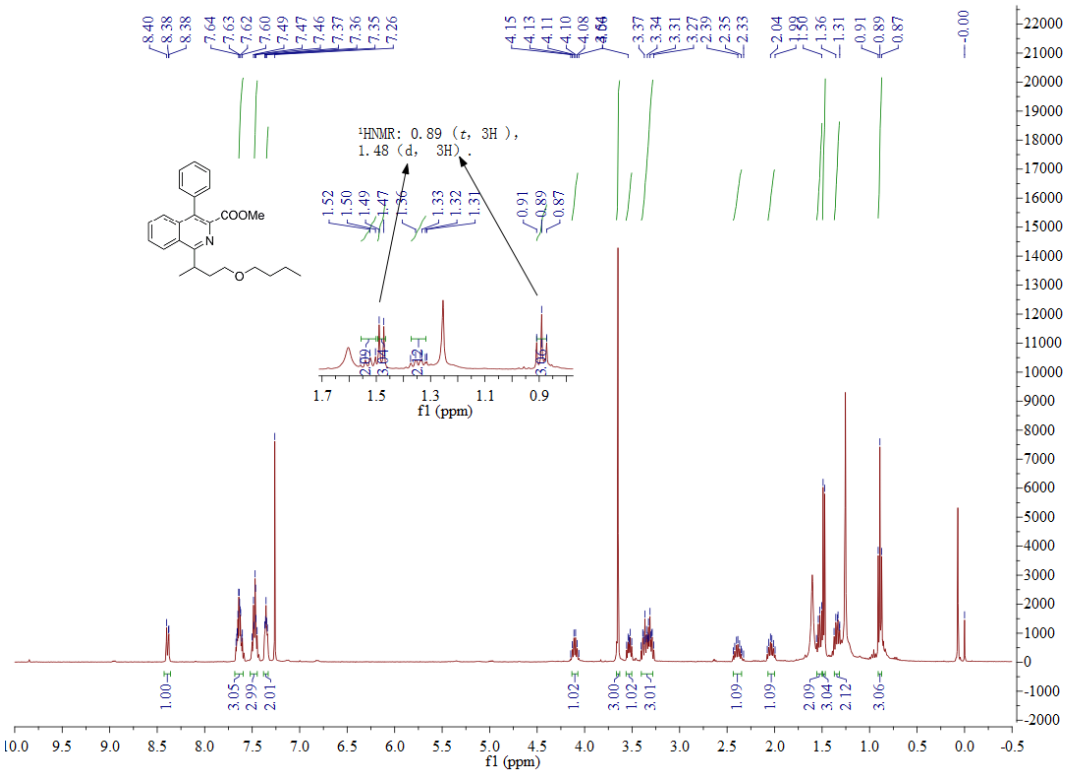


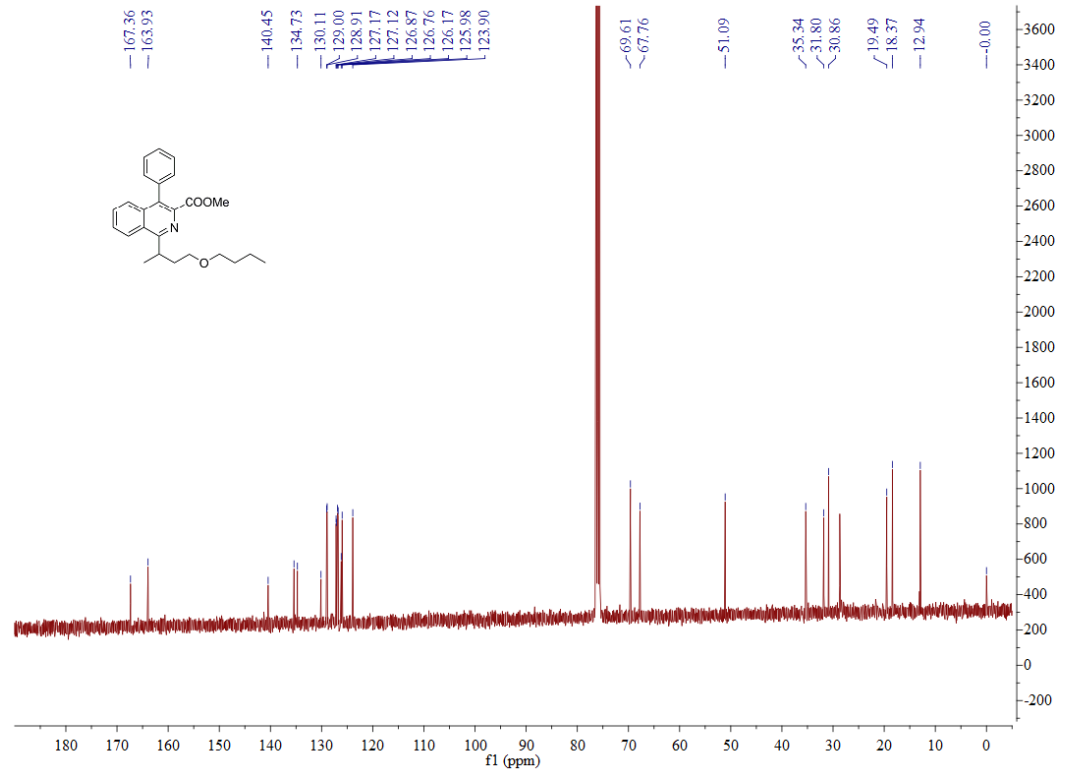
^{1}H NMR and ^{13}C NMR spectrum of **3ag1**



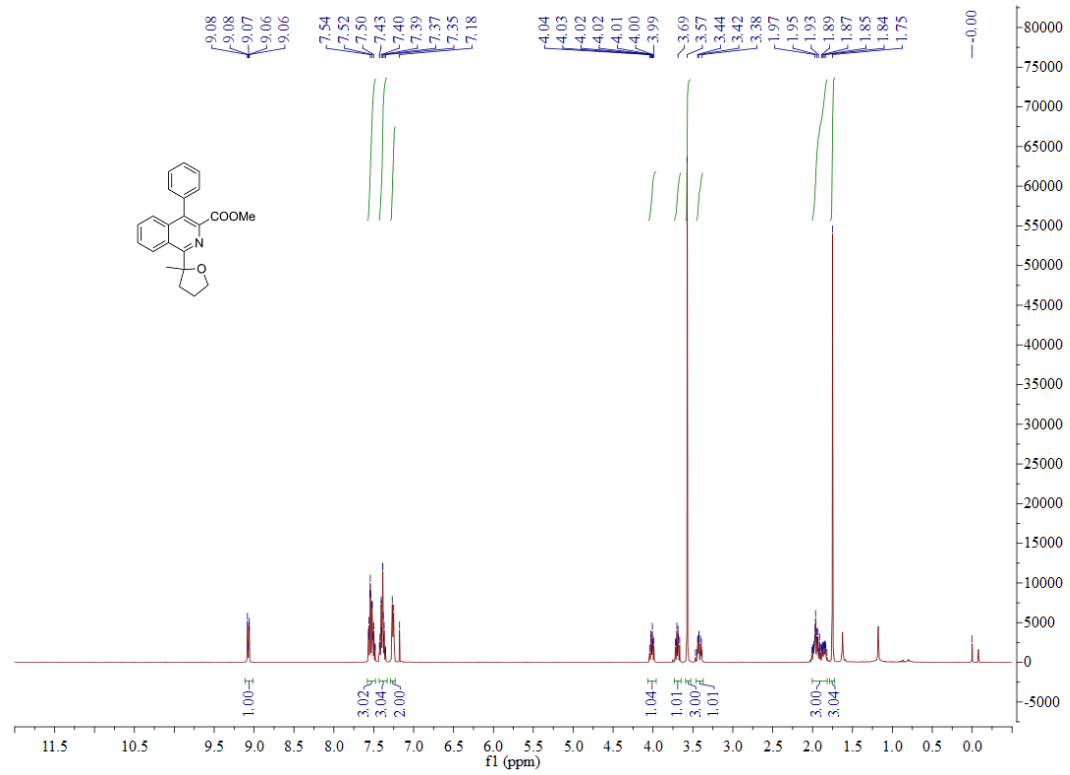


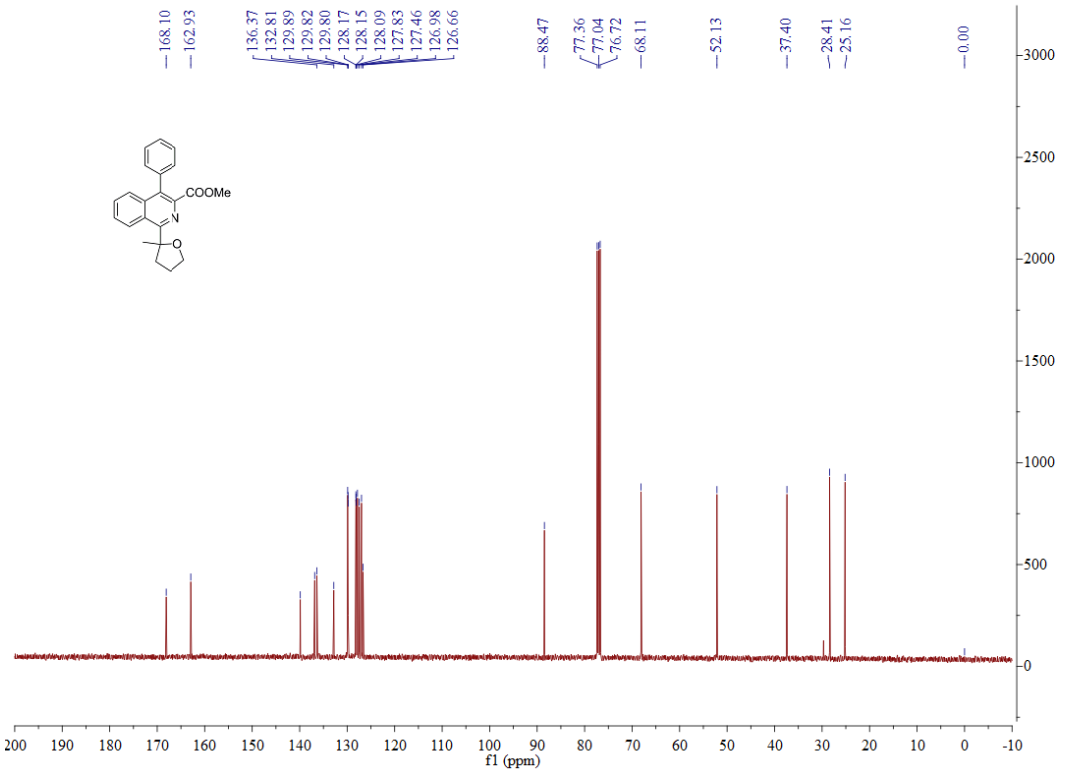
^{1}H NMR and ^{13}C NMR spectrum of **3ag2**





^{1}H NMR and ^{13}C NMR spectrum of **3ah1**





^{1}H NMR and ^{13}C NMR spectrum of **3ah2**