Direct, Catalytic and Regioselective Synthesis of 2-Alkyl, Aryl, and Alkenyl-Substituted *N*-Heterocycles from *N*-Oxides

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General Procedures

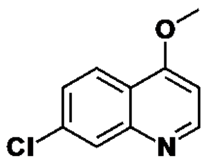
Materials and methods: Anhydrous ether was collected under argon from an LC Technologies solvent purification system, having been passed through two columns packed with molecular sieves. Ethanol, acetonitrile, and methanol were dried over 4Å molecular sieves. All other chemicals were used as commercially available (Sigma-Aldrich, Acros, Alfa Aesar, Combi-Blocks, Strem). All reactions were conducted with continuous magnetic stirring under an atmosphere of argon in oven-dried glassware. Reactions were monitored by TLC until deemed complete using silica gel-coated glass plates (Merck Kieselgel 60 F254). Plates were visualized under ultraviolet light (254 nm).

Purification: Column chromatography was performed using CombiFlash Rf-200 (Teledyne-Isco) automated flash chromatography system with self-packed RediSep columns.

Characterization: ^{1}H, ^{13}C NMR, ^{19}F spectra were recorded at 300 and 500 MHz (^{1}H), 75.5 and 125 MHz (^{13}C), and 252 MHz (^{19}F) on Varian Mercury VX 300 and Agilent Inova 500 instruments in $CDCl_3$ solutions if not otherwise specified. Chemical shifts (δ) are reported in parts per million (ppm) from the residual solvent peak and coupling constants (*J*) in Hz. Proton multiplicity is assigned using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (quart), quintet (quint), septet (sept), multiplet (m), broad (br s).

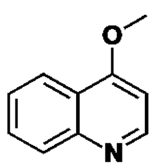
Infrared measurements were carried out neat on a Bruker Vector 22 FT-IR spectrometer fitted with a Specac diamond attenuated total reflectance (ATR) module.

7-Chloro-4-methoxyquinoline[1] (S1)



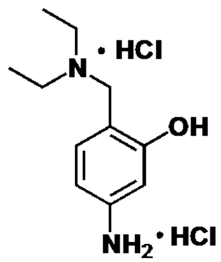
To a solution of 4,7-dichloroquinoline (5 g, 25.51 mmol) in methanol (50 mL) was added sodium methoxide (6.88 g, 127.55 mmol, 5 equiv). The reaction was heated at 95 °C for 12 h, then concentrated under reduced pressure and diluted with EtOAc (30 mL) and washed with H_2O (2 x 20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield **S1** (4.78 g, 97 %) as colorless solid. – ^{1}H NMR (300 MHz): 3.19 (3 H, s), 6.58 (1 H, d, *J* = 5.5 Hz), 7.32 (1 H, dd, *J* = 2, 9 Hz), 7.92 (1 H, d, *J* = 2 Hz), 7.98 (1 H, d, *J* = 9 Hz), 8.62 (1 H, d, *J* = 5 Hz) ppm. – ^{13}C NMR (75 MHz): 55.71, 100.26, 119.66, 123.36, 126.34, 127.64, 135.54, 149.45, 152.42, 162.16 ppm. – IR: 982, 1070, 1209, 1360, 1425, 1503, 1616, 2984, 3050 cm^{-1}.

4-Methoxyquinoline[1] (S2)



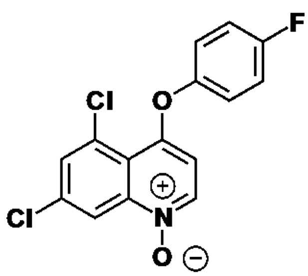
To a solution of **S1** (3 g, 15.54 mmol) in ethanol (103 mL) was added palladium (333 mg, 10 % palladium on charcoal) and lithium carbonate (2.51 g, 34.50 mmol, 2.22 equiv). Hydrogen was bubbled through the reaction, followed by stirring under a positive hydrogen pressure at 23 °C for 12 h. The reaction was filtered through celite, and the celite pad was washed with dichloromethane (3 x 25 mL). The solution was concentrated under reduced pressure to yield **S2** (2.4 g, 97 %) as white solid. – m.p.: 38–41 °C[2]. – ^{1}H NMR (300 MHz): 4.03 (3 H, s), 6.71 (1 H, d, *J* = 5 Hz), 7.49 (1 H, t, *J* = 7 Hz), 7.68 (1 H, t, *J* = 7 Hz), 8.03 (1 H, d, *J* = 8 Hz), 8.19 (1 H, d, *J* = 8 Hz), 8.75 (1 H, d, *J* = 5 Hz) ppm. – ^{13}C NMR (75 MHz): 55.65, 100.02, 121.75, 125.58, 128.30, 128.87, 129.72, 149.12, 151.38, 162.24 ppm. – IR: 1156, 1311, 1457, 1540, 2999, 3135 cm^{-1}.

5-Amino-2-((diethylamino)methyl)phenol dihydrochloride (S3)



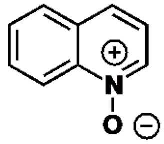
S3 was prepared according to the literature procedure.[3]

5,7-Dichloro-4-(4-fluorophenoxy)quinoline 1-oxide[4] (S4)



Quinoxyfen (200 mg, 0.649 mmol) was reacted with *meta*-chloroperoxybenzoic acid (322 mg, 0.937 mmol, 1.5 equiv, 52 % purity) in dichloromethane (2 mL). After 12h the reaction was diluted with a 1:1 mixture of sodium carbonate and sodium thiosulfate (5 mL). After separating the organic layer, the aqueous layer was extracted with chloroform (3 x 5 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford **S4** (172 mg, 82 %) as yellow solid. – ^{1}H NMR (500 MHz): 6.57 (1 H, d, *J* = 6.5 Hz), 7.06–7.12 (4 H, m), 7.63 (1 H, d, *J* = 1.5 Hz), 8.34 (1 H, 6.5 Hz), 8.72 (1 H, s) ppm. – ^{13}C NMR (125 MHz): 107.70, 117.19 (d, *J* = 23.5 Hz), 119.26 (d, *J* = 51 Hz), 121.75 (d, *J* = 8.5 Hz), 128.24, 131.77 (d, *J* = 74 Hz) 137.03, 143.61, 150.05 (d, *J* = 2 Hz), 153.01, 158.99, 160.94 ppm. – ^{19}F NMR (252 MHz): –116.42 ppm. – IR: 1012, 1091, 1174, 1254, 1303, 1415, 1563, 1641, 2988, 3071, 3102 cm^{-1}.

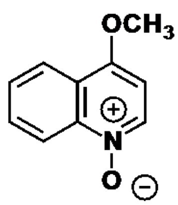
Quinoline 1-oxide[4a] (1)



1 was prepared according to literature procedure.[4a] – m.p.: 60–62 °C.[5] – ^{1}H NMR (300 MHz): 7.29 (1 H, dd, *J* = 6, 8 Hz), 7.64 (1 H, dt, *J* = 1, 7 Hz), 7.72–7.79 (2 H, m), 7.86 (1 H, dd, *J* = 1.5, 8 Hz), 8.52 (1 H, dd, *J* = 1, 6

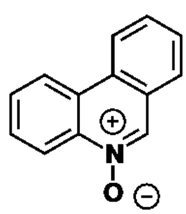
Hz) ppm. – ^{13}C NMR: 119.81, 120.96, 125.87, 128.12, 128.76, 130.41, 130.50, 135.60 ppm. – IR: 1157, 1311, 1452, 1554, 2931, 2995, 3025 cm^{-1}.

4-Methoxyquinoline 1-oxide[4a, 6] (4b)



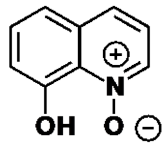
S2 (2.76 g, 17.36 mmol) was reacted with *meta*-chloroperoxybenzoic acid (8.61 g, 26.04 mmol, 1.5 equiv, 52 % purity) in dichloromethane (35 mL). After 12 h the reaction was diluted with a 1:1 mixture of sodium carbonate and sodium thiosulfate (60 mL). After separating the organic layer, the aqueous layer was extracted with chloroform (3 x 30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afforded **4b** (2.14 g, 71 %) as red oil. – ^{1}H NMR (500 MHz): 4.00 (3 H, s), 6.74 (1 H, d, *J* = 6.5 Hz), 7.48 (1 H, dt, *J* = 1, 7 Hz), 7.68 (1 H, dt, *J* = 1, 7 Hz), 8.08 (1 H, d, *J* = 8.5 Hz), 8.14 (1 H, dd, *J* = 1, 8.5 Hz), 8.73 (1 H, d, *J* = 4.5 Hz) ppm. – ^{13}C NMR (125 MHz): 56.09, 121.96, 122.63, 126.15, 127.31, 128.27, 130.56, 131.13, 150.11, 163.42 ppm. – IR: 1156, 1394, 1507, 2999, 3125 cm^{-1}.

Phenanthridine 5-oxide[4a, 7] (4c)



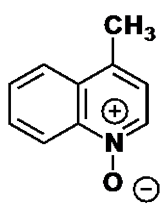
4c was prepared according to literature procedure.[4a] – ^{1}H NMR (500 MHz): 7.25–8.09 (5 H, m), 8.53–8.63 (2 H, m), 8.97 (1 H, d, *J* = 2 Hz), 9.19 (1 H, d, *J* = 2 Hz) ppm. – ^{13}C NMR (125 MHz): 120.67, 122.13, 122.77, 127.06, 128.18, 128.99, 129.53, 129.71, 129.91, 130.15, 130.46, 133.83, 169.27 ppm. – IR: 1071, 1191, 1473, 1559, 1647, 3071 cm^{-1}.

8-Hydroxyquinoline 1-oxide[4a, 8] (4d)



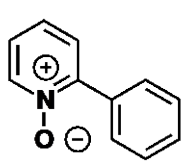
4d was prepared according to literature procedure.[4a] – ^{1}H NMR (300 MHz): 7.05 (1 H, d, *J* = 5.5 Hz), 7.21–7.27 (2 H, m), 7.48 (1 H, t, *J* = 8.5 Hz), 7.80 (1 H, d, *J* = 8.5 Hz), 8.30 (1 H, dd, *J* = 0.5, 5.5 Hz) ppm. – ^{13}C NMR (75 MHz): 115.06, 116.88, 120.41, 128.11, 130.07, 130.60, 134.76, 153.79, 168.71 ppm. – IR: 1047, 1153, 1201, 1312, 1436, 1598, 1698, 2950, 3066 cm^{-1}.

4-Methylquinoline 1-oxide[4a,9] (4e)



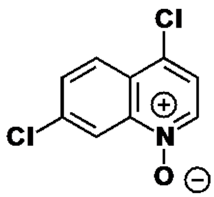
4e was prepared according to literature procedure.[4a] – ^{1}H NMR (500 MHz): 2.65 (3 H, s), 7.11 (1 H, d, *J* = 6 Hz), 7.66 (1 H, t, *J* = 7 Hz), 7.76 (1 H, t, *J* = 7 Hz), 7.96 (1 H, d, *J* = 7), 8.44 (1 H, d, *J* = 7 Hz), 8.80 (1 H, t, *J* = 9 Hz) ppm. – ^{13}C NMR (125 MHz): 18.38, 120.32, 121.41, 124.73, 128.51, 129.83, 130.18, 135.02, 135.11, 140.86 ppm. – IR: 1058, 1277, 1394, 1473, 1559, 1653, 2949, 3024, 3081 cm^{-1}.

2-Phenylpyridine 1-oxide[4a,10] (4f)



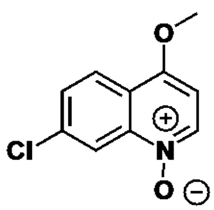
4f was prepared according to literature procedure.[4a] – m.p.: 150–152 °C[11] – ^{1}H NMR (300 MHz): 7.21–7.31 (2 H, m), 7.40–7.49 (4 H, m), 7.80 (2 H, dd, *J* = 2.5, 5.5 Hz), 8.32 (1 H, d, *J* = 5.5 Hz) ppm. – ^{13}C NMR (75 MHz): 124.51, 125.76, 127.38, 128.27, 129.25, 129.58, 132.59, 140.39, 149.25 ppm. – IR: 995, 1073, 1158, 1259, 1416, 1476, 2925, 3032 cm^{-1}.

4,7-Dichloroquinoline 1-oxide[4a,12] (4g)



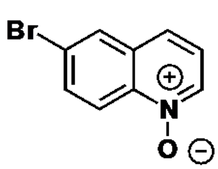
4g was prepared according to literature procedure.[4a] – m.p.: 164–165 °C[13]. – ^{1}H NMR (500 MHz): 7.36 (1 H, d, *J* = 6.5 Hz), 7.68 (1 H, d, *J* = 9 Hz), 8.13 (1 H, d, *J* = 9 Hz), 8.43 (1 H, d, *J* = 6.5 Hz), 8.77 (1 H, s) ppm. – ^{13}C NMR (125 MHz): 119.93, 121.22, 121.42, 125.60, 126.52, 126.75, 128.68, 129.85, 130.80, 135.96, 138.22, 142.33, 150.88 ppm. – IR: 829, 1091, 1291, 1367, 1412, 1555, 1609, 3025, 3094 cm^{-1}.

7-Chloro-4-methoxyquinoline 1-oxide[4a] (4h)



S1 (1.6 g, 5.54 mmol) was reacted with *meta*-chloroperoxybenzoic acid (2.75 g, 8.31 mmol, 1.5 equiv, 52 % purity) in dichloromethane (10 mL). After 12 h the reaction was diluted with a 1:1 mixture of sodium carbonate and sodium thiosulfate (30 mL). After separating the organic layer, the aqueous layer was extracted with chloroform (3 x 15 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afforded **4h** (1.12 g, 97 %) as colorless solid. – m.p.: 145–147 °C[4a]. – ^{1}H NMR (500 MHz): 4.06 (3 H, s), 6.64 (1 H, d, *J* = 7 Hz), 7.59 (1 H, d, *J* = 2 Hz), 8.15 (1 H, d, *J* = 9 Hz), 8.46 (1 H, d, *J* = 7 Hz), 8.77 (1 H, d, *J* = 2 Hz) ppm. – ^{13}C NMR (125 MHz): 56.34, 99.84, 119.57, 120.99, 123.39, 124.28, 129.06, 136.99, 137.88, 154.26 ppm. – IR: 1082, 1168, 1265, 1345, 1522, 2835, 3026 cm^{-1}. – MS (ESI): found 212.9, MS (HRMS): calc. 210.0316, found 213.9937 [M + H^{+}].

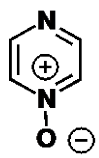
6-Bromoquinoline 1-oxide[4a,6] (4j)



4j was prepared according to literature procedure.[4a] – ^{1}H NMR (300 MHz): 7.31 (1 H, dd, *J* = 1, 2.5 Hz), 7.63 (1 H, d, *J* = 8.5 Hz), 7.79 (1

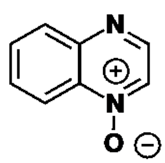
H, dd, *J* = 2, 9.5 Hz), 8.02 (1 H, d, *J* = 2 Hz), 8.52 (1 H, d, *J* = 6 Hz), 6.60 (1 H, d, *J* = 9.5 Hz) ppm. – ^{13}C NMR (75 MHz): 121.72, 122.19, 123.29, 124.98, 130.08, 131.57, 133.83, 135.90, 140.25 ppm. – IR: 1143, 1266, 1421, 1569, 2999, 3026 cm^{-1}.

Pyrazine 1-oxide[4a,14] (4k)



4k was prepared according to literature procedure.[14b]

Quinoxaline 1-oxide[15] (4l)

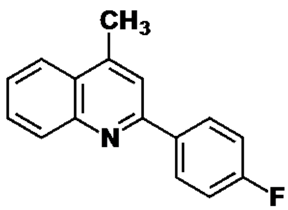


Quinoxaline (200 mg, 1.53 mmol) was reacted *meta*-chloroperoxybenzoic acid (759 mg, 2.29 mmol, 1.5 equiv, 52 % purity) in dichloromethane (3 mL). The isolated product afforded **4l** (210 mg, 94 %) as a red solid – m.p.: 152–155 °C[16] – ^{1}H NMR (300 MHz): 7.33 (2 H, d, *J* = 6.5 Hz), 8.18 (2 H, d, *J* = 5.5 Hz), 8.45 (2 H, s) ppm. – ^{13}C NMR (75 MHz): 124.70, 125.86, 126.90, 129.37, 135.10, 137.58, 140.36, 149.90 ppm. – IR: 1000, 1169, 1305, 1457, 1565, 2990, 3269 cm^{-1}.

General Procedure 1 (GP1) for the synthesis of 5ah–16a:

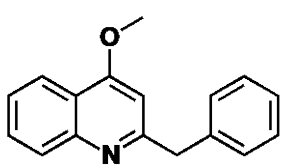
To a solution of *N*-oxide (1 mmol, 1 equiv) in diethyl ether (5 mL) was added copper(I) chloride (5 mol %), magnesium chloride (1.5–4 equiv) and a Grignard reagent (2–4 equiv). The reaction was allowed to stir for 12 h at 23 °C before being neutralized with a saturated aqueous solution of ammonium chloride (20 mL) and the aqueous layer extracted with chloroform (3 x 20 mL). The combined organic fractions were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting oil was purified by column chromatography [hexanes/EtOAc] to give the desired product.

2-(4-Fluorophenyl)-4-methylquinoline[20] (5ea)



According to GP1, **4e** (82 mg, 0.517 mmol) was reacted with copper(I) chloride (5 mg, 0.051 mmol, 10 mol %), magnesium chloride (77 mg, 0.775 mmol, 1.5 eqiuv), and (4-fluorophenyl)magnesium bromide (2.06 mL, 1.03 mmol, 2 eqiuv, 0.5M in tetrahydrofuran) in diethyl ether (2.5 mL). The crude product was purified by column chromatography to yield **5ea** (98 mg, 80 %) as yellow oil. – ^{1}H NMR (300 MHz): 2.76 (3 H, s), 7.17–7.26 (2 H, m), 7.55 (1 H, dt, *J* = 1, 6 Hz), 7.66 (1 H, s), 7.72 (1 H, dt, *J* = 1.5, 7 Hz), 7.99 (1 H, dd, *J* = 1, 8 Hz), 8.12–8.17 (3 H, m) ppm. – ^{13}C NMR (75 MHz): 19.04, 115.68 (d, *J* = 21 Hz), 119.39, 123.61, 126.07, 127.13, 129.36 (d, *J* = 12.5 Hz), 130.14, 135.90 (d, *J* = 2.5 Hz), 144.99, 148.01, 155.93, 162.04, 165.34 ppm. – IR: 1432, 1496, 1569, 1597, 2945, 3026 cm^{-1}.

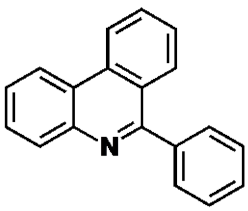
2-Benzyl-4-methoxyquinoline (5bf)



According to GP1, **4b** (70 mg, 0.4 mmol) was reacted with copper(I) chloride (4 mg, 0.04 mmol, 10 mol %), magnesium chloride (80 mg, 0.80 mmol, 2 equiv), and benzylmagnesium bromide (800 μL, 0.80 mmol, 2 equiv, 1M in tetrahydrofuran) in diethyl ether (2 mL). The crude product was purified by column chromatography to yield **5bf** (60 mg, 61 %) as yellow oil. – ^{1}H NMR (500 MHz): 3.93 (3 H, s), 4.72 (2 H, s), 6.56 (1 H, s), 7.24–7.49 (6 H, m), 7.70 (1 H, dt, *J* = 1, 8 Hz), 8.04 (1 H, d, *J* = 8.5 Hz), 8.14 (1 H, d, *J* = 8.5 Hz) ppm. – ^{13}C NMR (125 MHz): 45.99, 55.34, 100.12, 120.13, 121.65, 125.15, 126.48, 127.58, 128.33, 129.14, 129.87, 139.26, 148.59, 162.37, 162.63 ppm. –

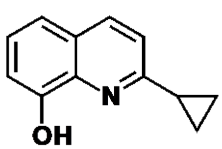
IR: 1113, 1233, 1362, 1446, 1569, 1619, 2867, 2957, 3049 cm^{-1}. – MS (ESI): 249.8, calcd: 250.1226, found: 249.8008 [M^-].

6-Phenylphenanthridine[17a] (5cd)



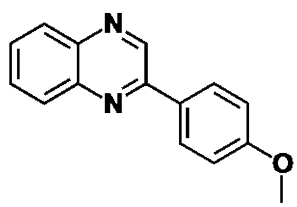
According to GP1, **4c** (234 mg, 1.30 mmol) was reacted with copper(I) chloride (13 mg, 0.13 mmol, 10 mol %), magnesium chloride (193 mg, 1.95 mmol, 1.5 equiv), and phenylmagnesium chloride (1.3 mL, 2.6 mmol, 2 equiv, 2M in tetrahydrofuran) in diethyl ether (6.5 mL). The crude product was purified by column chromatography to yield **5cd** (208 mg, 68 %) as yellow oil. – ^{1}H NMR (300 MHz): 6.66–6.90 (2 H, m), 7.13–7.42 (3 H, m), 7.48–7.91 (4 H, m), 8.12 (1 H, d, *J* = 8 Hz), 8.29 (1 H, dd, *J* = 1.5, 8 Hz), 8.64 (1 H, dd, *J* = 1.5, 8 Hz), 8.72 (1 H, d, *J* = 8 Hz) ppm. – ^{13}C NMR (75 MHz): 115.42, 120.16, 121.98, 122.21, 127.05, 127.83, 128.11, 128.44, 128.98, 129.48, 130.03, 130.74, 133.49, 139.40, 146.22, 156.04, 161.40 ppm. – IR: 1082, 1147, 1313, 1329, 1402, 1446, 1520, 3049 cm^{-1}.

2-Cyclopropylquinolin-8-ol (5dc)



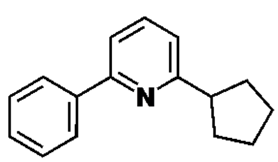
According to GP1, **4d** (28 mg, 0.177 mmol) was reacted with copper(I) chloride (2 mg, 0.017 mmol, 10 mol %), magnesium chloride (26 mg, 0.265 mmol, 1.5 equiv), and cyclopropylmagnesium chloride (1.4 mL, 0.708 mmol, 4 equiv, 0.5M in tetrahydrofuran) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **5dc** (27 mg, 84 %) as yellow oil. – ^{1}H NMR (500 MHz): 1.09–1.13 (2 H, m), 1.18–1.21 (2 H, m), 2.17–2.23 (1 H, m), 7.11 (1 H, dd, *J* = 1, 7.5 Hz), 7.26 (1 H, dd, *J* = 1 H, 8.5 Hz), 7.30–7.35 (2 H, m), 7.99 (1 H, d, *J* = 8.5 Hz) 8.04–8.22 (1 H, br s) ppm. – ^{13}C NMR (75 MHz): 11.19, 17.53, 109.67, 117.61, 121.31, 126.10, 126.72, 135.80, 137.62, 151.32, 161.49 ppm. – IR: 1238, 1318, 1474, 1572, 1697, 2913, 2999, 3034 cm^{-1}. – MS (ESI): 186.7, HRMS: calcd: 186.0913; found 186.0285 [M + H$^+$].

2-(4-Methoxyphenyl)quinoxaline[25] (5lo)



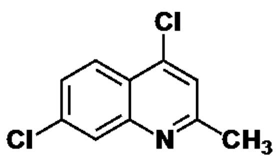
According to GP1, **4l** (26 mg, 0.177 mmol) was reacted with copper(I) chloride (1 mg, 0.008 mmol, 5 mol %), magnesium chloride (26 mg, 0.265 mmol, 1.5 equiv), and (4-methoxyphenyl)magnesium iodide (177 μL, 0.344 mmol, 2 equiv, 2M in tetrahydrofuran) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **5lo** (33 mg, 79 %) as brown oil. – ^{1}H NMR (500 MHz): 3.87 (3 H, s), 7.03 (2 H, d, *J* = 15 Hz), 7.51 (1 H, d, *J* = 14.5 Hz), 7.61 (1 H, td, *J* = 2.5, 2.5, 12 Hz), 7.71–7.85 (2 H, m), 8.02 (2 H, d, *J* = 15 Hz), 8.85 (1 H, d, *J* = 14.5 Hz) ppm. – ^{13}C NMR (125 MHz): 55.39, 113.67, 120.18, 123.08, 125.22, 127.89, 128.13, 129.23, 130.48, 131.20, 142.30, 144.65, 160.47 ppm. – IR: 1030, 1113, 1167, 1240, 1362, 1426, 1508, 2835, 3000, 3340 cm^{-1}.

2-Cyclopentyl-6-phenylpyridine (5fe)



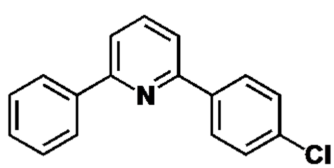
According to GP1, **4f** (25 mg, 0.177 mmol) was reacted with copper(I) chloride (2 mg, 0.018 mmol, 10 mol %), magnesium chloride (26 mg, 0.26 mmol, 1.5 equiv), and cyclopentylmagnesium chloride (177 μL, 0.354 mmol, 2 equiv, 2M in diethyl ether) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **5fe** (26 mg, 67 %) as yellow oil. – ^{1}H NMR (500 MHz): 1.69–2.15 (8 H, m), 3.26 (1 H, quint, *J* = 5 Hz), 7.10 (1 H, dd, *J* = 1, 8 Hz), 7.39 (1 H, td, *J* = 1, 2.5, 2.5 Hz), 7.44–7.48 (2 H, m), 7.52 (1 H, dd, *J* = 1, 8 Hz), 7.64 (1 H, t, *J* = 2.5 Hz), 8.04 (2 H, dd, *J* = 1.5, 8.5 Hz) ppm. – ^{13}C NMR (125 MHz): 25.87, 33.57, 48.04, 117.42, 119.95, 126.89, 128.32, 128.58, 136.68, 139.89, 156.28, 165.61 ppm. – IR: 991, 1164, 1259, 1445, 1590, 2866, 2952, 3060 cm^{-1}. – MS (ESI): 223.9, HRMS: calcd: 224.1434; found 224.1553 [$M + H^+$].

4,7-Dichloro-2-methylquinoline[22] (5gb)



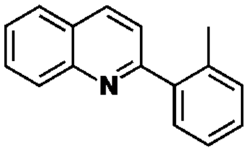
According to GP1, **4g** (43 mg, 0.20 mmol) was reacted with copper(I) chloride (2 mg, 0.02 mmol, 10 mol %), magnesium chloride (30 mg, 0.30 mmol, 1.5 equiv), and methylmagnesium bromide (800 μL, 0.40 mmol, 2 equiv, 0.5M in tetrahydrofuran) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **5gb** (27 mg, 64 %) as yellow oil. – ^{1}H NMR (500 MHz): 2.72 (3 H, s), 7.53 (1 H, d, J = 5.5 Hz), 8.03 (2 H, s), 8.11 (1 H, d, J = 5.5 Hz) ppm. – ^{13}C NMR (75 MHz): 25.17, 122.10, 123.22, 125.32, 127.61, 127.97, 136.39, 142.45, 149.00, 160.26 ppm. – IR: 1176, 1318, 1445, 1551, 1609, 2924, 3083 cm^{-1}.

2-(4-Chlorophenyl)-6-phenylpyridine 5fg



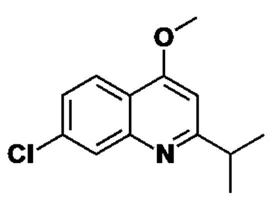
According to GP1, **4f** (30 mg, 0.177 mmol) was reacted with copper(I) chloride (2 mg, 0.017 mmol, 10 mol %), magnesium chloride (26 mg, 0.265 mmol, 1.5 equiv), and (4-chlorophenyl)magnesium chloride (344 μL, 0.354 mmol, 2 equiv, 1M in diethyl ether) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **5fg** (28 mg, 61 %) as colorless oil. – ^{1}H NMR (300 MHz): 7.42–7.54 (5 H, m), 7.65–7.76 (3 H, m), 7.82 (1 H, t, J = 7.5 Hz), 8.13 (3 H, dt, J = 1.5, 8.5 Hz) ppm. – ^{13}C NMR (75 MHz): 118.38, 118.90, 126.94, 128.22, 128.32, 128.71, 128.84, 129.09, 135.05, 137.61, 137.86, 139.25, 155.55, 156.93 ppm. – IR: 1057, 1110, 1179, 1321, 1417, 1541, 1607, 2924, 3020, 3086 cm^{-1}. – MS (ESI): 264.7, HRMS: calcd: 265.0658; found 265.2267 [$M + H^+$].

2-(*o*-Tolyl)quinolone[17] (5ah)



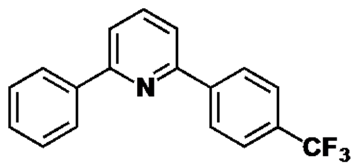
According to GP1, **1** (300 mg, 2.06 mmol) was reacted with copper(I) chloride (20 mg, 0.206 mmol, 10 mol %), lithium fluoride (77 mg, 3.09, 1.5 equiv), and *o*-tolymagnesium chloride (3 mL, 4.12 mmol, 2 equiv, 1.4M in tetrahydrofuran/diethyl ether) in diethyl ether (10 mL). The crude product was purified by column chromatography to yield **5ah** (275 mg, 61 %) as yellow solid. – ^{1}H NMR (300 MHz): 2.46 (3 H, s), 7.36–7.39 (3 H, m), 7.54–7.63 (3 H, m), 7.77–7.81 (1 H m), 7.90–7.92 (1 H, m), 8.20–8.22 (1 H, m) ppm. – ^{13}C NMR (300 MHz): 20.42, 120.34, 122.54, 126.08, 126.53, 127.51, 128.42, 128.65, 129.82, 130.76, 130.91, 136.36, 140.53, 137.72, 160.29 ppm. – IR: 1025, 1145, 1378, 1431, 1552, 1592, 2947, 3026 cm^{-1}.

7-Chloro-2-isopropyl-4-methoxyquinoline (5hi)



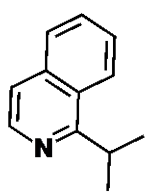
According to GP1, **4h** (42 mg, 0.20 mmol) was reacted with copper(I) chloride (2 mg, 0.02 mmol, 10 mol %), magnesium chloride (30 mg, 0.30 mmol, 1.5 equiv), and cyclopropylmagnesium bromide (800 μL, 0.40 mmol, 2 equiv, 0.5M in tetrahydrofuran) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **5hi** (28 mg, 60 %) as yellow oil. – ^{1}H NMR (500 MHz): 1.39 (6 H, d, *J* = 7 Hz), 3.15–3.22 (1 H, m), 4.05 (3 H, s), 6.65 (1 H, s), 7.38 (1 H, d, *J* = 8.5 Hz), 7.99 (1 H, s), 8.06 (1 H, d, *J* = 8.5 Hz) ppm. – ^{13}C NMR (125 MHz): 22.48, 37.77, 55.57, 97.85, 118.65, 123.10, 125.64, 127.45, 135.54, 149.14, 162.53, 170.38 ppm. – IR: 993, 1118, 1196, 1294, 1328, 1417, 1502, 1614, 2868, 2961 cm^{-1}. – MS (ESI): 236.0868, calcd: 236.0837, found: 238.8 [M + H^{+}].

2-Phenyl-6-(4-(trifluoromethyl)phenyl)pyridine (5fn)



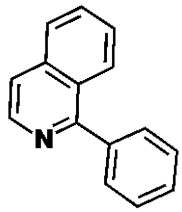
According to GP1, **4f** (70 mg, 0.41 mmol) was reacted with copper(I) chloride (4 mg, 0.041 mmol, 10 mol %), magnesium chloride (81 mg, 0.81 mmol, 2 equiv), and (4-(trifluoromethyl)phenyl)magnesium bromide (810 μL, 0.81 mmol, 2 equiv, 1M in diethyl ether) in diethyl ether (2 mL). The crude product was purified by column chromatography to yield **5fn** (81 mg, 66 %) as colorless oil. – ^{1}H NMR (500 MHz): 7.47–7.49 (1 H, m), 7.53 (2 H, td, *J* = 1.5, 6 Hz), 7.74–7.89 (4 H, m), 7.89 (1 H, t, *J* = 8 Hz), 8.15–8.17 (2 H, m), 8.28 (2 H, d, *J* = 8 Hz) ppm. – ^{13}C NMR (75 MHz): 118.97, 119.50, 125.62 (quart., *J* = 12.5 Hz), 126.96, 127.23, 128.33, 128.77, 129.22, 137.75, 139.08, 142.73, 155.25, 157.12 ppm. – ^{19}F NMR (252 MHz): -62.51 ppm. – IR: 1016, 1171, 1269, 1313, 1419, 1575, 2899, 2957, 3053 cm^{-1}. – MS (ESI): 299.9, calcd: 300.0995, found: 300.0869 [M + H^{+}].

1-Isopropylisoquinoline[23] (**5ii**)



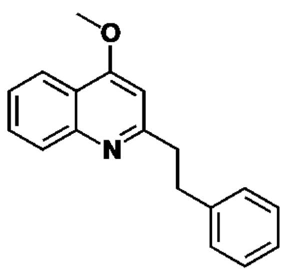
According to GP1, **4i** (25 mg, 0.177 mmol) was reacted with copper(I) chloride (1 mg, 0.008 mmol, 5 mol %), magnesium chloride (53 mg, 0.531 mmol, 3 equiv), and isopropylmagnesium chloride (350 μL, 0.708 mmol, 4 equiv, 2M in diethyl ether) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **5ii** (22 mg, 73 %) as yellow oil. – ^{1}H NMR (500 MHz): 1.56 (6 H, d, *J* = 6.5 Hz), 7.07 (1 H, sept, *J* = 6.5 Hz), 7.43 (1 H, d, *J* = 8 Hz), 7.51 (1 H, dt, *J* = 1.5, 7 Hz), 7.61 (1 H, dt, *J* = 1.5, 7 Hz), 8.35 (1 H, d, *J* = 8.5 Hz), 8.51 (1 H, s) ppm. – ^{13}C NMR (125 MHz): 22.26, 31.13, 114.08, 120.99, 124.97, 126.15, 126.92, 129.76,, 142.02, 153.38, 159.25 ppm. – IR: 1025, 1113, 1435, 1565, 2829, 3025 cm^{-1}.

1-Phenylisoquinoline[17a] (5id)



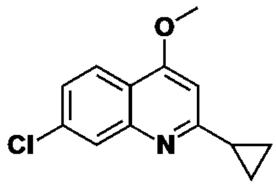
According to GP1, **4i** (120 mg, 0.827 mmol) was reacted with copper(I) chloride (8 mg, 0.083 mmol, 10 mol %), lithium fluoride (31 mg, 1.25 mmol, 1.5 equiv), and phenylmagnesium bromide (515 μL, 1.65 mmol, 2 equiv, 3.2M in diethyl ether) in diethyl ether (4 mL). The crude product was purified by column chromatography to yield **5id** (97 mg, 57 %) as yellow oil. – ^{1}H NMR (300 MHz): 7.49–7.57 (4 H, m), 7.65–7.73 (4 H, m), 7.89 (1 H, dd, *J* = 0.5, 8.5 Hz), 8.11 (1 H, dd, *J* = 0.5, 8.5 Hz), 8.61 (1 H, d, *J* = 5.5 Hz) ppm. – ^{13}C NMR (75 MHz): 119.94, 126.98, 127.17, 127.58, 128.30, 128.33, 128.58, 129.89, 130.03, 136.83, 139.48, 140.71, 142.14 ppm. – IR: 1030, 1211, 1386, 144, 1583, 1632, 2925, 3052 cm^{-1}.

4-Methoxy-2-phenethylquinoline[18] (5bj)



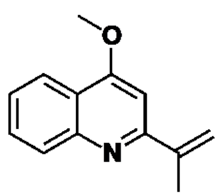
According to GP1, **4b** (70 mg, 0.397 mmol) was reacted with copper(I) chloride (4 mg, 0.039 mmol, 10 mol %), magnesium chloride (80 mg, 0.80 mmol, 2 equiv), and phenethylmagnesium chloride (800 μL, 0.80 mmol, 2 equiv, 1M in tetrahydrofuran) in diethyl ether (2 mL). The crude product was purified by column chromatography to yield **5bj** (53 mg, 51 %) as yellow oil. – ^{1}H NMR (500 MHz): 3.15–3.27 (4 H, m), 3.96 (3 H, s), 6.50 (1 H, s), 7.19–7.34 (5 H, m), 7.46 (1 H, td, *J* = 1, 7 Hz), 7.69 (1 H, td, *J* = 1.5, 7 Hz), 8.02 (1 H, d, *J* = 8.5 Hz), 8.15 (1 H, dd, *J* = 1, 8.5 Hz) ppm. – ^{13}C NMR (125 MHz): 36.01, 41.57, 55.50, 100.25, 120.08, 121.61, 124.90, 125.98, 128.27, 128.56, 128.60, 129.72, 141.57, 148.82, 162.24, 162.94 ppm. – IR: 968, 1112, 1236, 1432, 1508, 1620, 2849, 2930, 3026 cm^{-1}.

7-Chloro-2-cyclopropyl-4-methoxyquinoline (5hc)



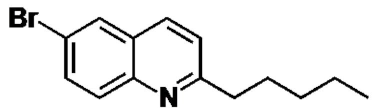
According to GP1, **4h** (42 mg, 0.20 mmol) was reacted with copper(I) chloride (2 mg, 0.02 mmol, 10 mol %), magnesium chloride (30 mg, 0.30 mmol, 1.5 equiv), and cyclopropylmagnesium bromide (800 μL, 0.40 mmol, 2 equiv, 0.5M in tetrahydrofuran) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **5hc** (32 mg, 68 %) as yellow oil. – ^{1}H NMR (500 MHz): 0.85–1.45 (4 H, m), 1.89–2.18 (1 H, m), 4.05 (3 H, s), 6.64 (1 H, s), 7.38 (1 H, d, *J* = 8.5 Hz), 7.99 (1 H, s), 8.07 (1 H, d, *J* = 8.5 Hz) ppm. – ^{13}C NMR (125 MHz): 25.95, 33.48, 49.31, 55.57, 98.80, 118.64, 123.08, 125.58, 127.45, 135.50, 149.12, 162.32, 168.84 ppm. – IR: 906, 1072, 1161, 1237, 1342, 1429, 1550, 1607, 3037, 3094 cm^{-1}. – MS (ESI): 234.6, calcd: 234.0680, found: 234.0370 [M + H^{+}].

4-Methoxy-2-(prop-1-en-2-yl)quinoline (5bk)



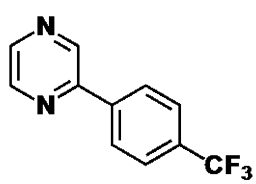
According to GP1, **4b** (28 mg, 0.159 mmol) was reacted with copper(I) chloride (2 mg, 0.016 mmol, 10 mol %), magnesium chloride (24 mg, 0.238 mmol, 1.5 equiv), and isopropenylmagnesium bromide (650 μL, 0.318 mmol, 2 equiv, 0.5M in tetrahydrofuran) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **5bk** (22 mg, 71 %) as yellow oil. – ^{1}H NMR (300 MHz): 2.34 (3 H, s), 4.07 (3 H, s), 5.45 (1 H, s), 5.85 (1 H, s), 6.98 (1 H, s), 7.45 (1 H, td, *J* = 1.5, 11.5 Hz), 7.66 (1 H, td, *J* = 2, 11.5 Hz), 8.02 (1 H, d, *J* = 14 Hz), 8.15 (1 H, d, *J* = 14 Hz) ppm. – ^{13}C NMR (75 MHz): 20.74, 55.49, 96.98, 116.59, 120.47, 121.47, 125.31, 129.08, 130.04, 145.00, 148.56, 159.89, 162.27 ppm. – IR: 1107, 1236, 1377, 1449, 1557, 1617, 2909, 2970, 3042 cm^{-1}. – MS (ESI): 200.0, HRMS: calcd: 200.1070, found: 200.1096 [M + H^{+}].

6-Bromo-2-pentylquinoline[24] (5jl)



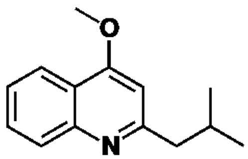
According to GP1, **4j** (40 mg, 0.177 mmol) was reacted with copper(I) chloride (2 mg, 0.018 mmol, 10 mol %), magnesium chloride (26 mg, 0.26 mmol, 1.5 equiv), and pentylmagnesium bromide (177 μL, 0.354 mmol, 2 equiv, 2M in diethyl ether) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **5jl** (38 mg, 78 %) as brown oil. – ^{1}H NMR (500 MHz): 0.90 (3 H, t, *J* = 2.5 Hz), 1.35–1.38 (4 H, m), 1.80 (2 H, quint, *J* = 7.5 Hz), 2.94 (2 H, t, *J* = 8 Hz), 7.30 (1 H, d, *J* = 8.5 Hz), 7.73 (1 H, dd, *J* = 2.5, 9 Hz), 7.89–7.97 (3 H, m) ppm. – ^{13}C NMR (125 MHz): 14.01, 22.54, 29.58, 31.71, 39.30, 118.28, 122.21, 127.82, 129.47, 130.59, 132.67, 135.10, 146.47, 163.62 ppm. – IR: 1059, 1119, 1300, 1386, 1487, 1556, 2855, 2924, 3050 cm^{-1}.

2-(4-(Trifluoromethyl)phenyl)pyrazine (5kn)



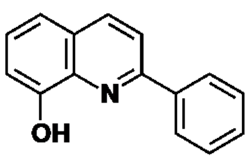
According to GP1, **4k** (40 mg, 0.41 mmol) was reacted with copper(I) chloride (4 mg, 0.04 mmol, 10 mol %), magnesium chloride (81 mg, 0.82 mmol, 2 equiv), and (4-(trifluoromethyl)phenyl)-magnesium bromide (820 μL, 0.82 mmol, 2 equiv, 1M in diethyl ether) in diethyl ether (2 mL). The crude product was purified by column chromatography to yield **5kn** (62 mg, 61 %) as brown oil. – ^{1}H NMR (300 MHz): 7.78 (2 H, dd, *J* = 1, 9 Hz), 8.14 (2 H, dd, *J* = 1, 9 Hz), 8.59 (1 H, d, *J* = 2.5 Hz), 8.68 (1 H, dd, *J* = 1.5, 2.5 Hz), 9.07 (1 H, d, *J* = 1.5 Hz) ppm. – ^{13}C NMR (75 MHz): 125.97, 126.02, 126.06, 127.23, 127.36, 142.30, 143.83, 144.41, 151.30 ppm. – ^{19}F NMR (252 MHz): –62.76 ppm. – IR: 1016, 1131, 1170, 1325, 1419, 3003, 3028, 3113 cm^{-1}. – MS (ESI): 226.0, calcd: 225.0634, found: 226.0895 [M + H^{+}].

2-Isobutyl-4-methoxyquinoline (5bm)



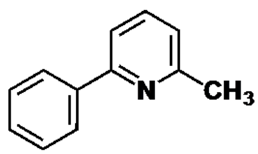
According to GP1, **4b** (16 mg, 0.091 mmol) was reacted with copper(I) chloride (1 mg, 0.009 mmol, 10 mol %), magnesium chloride (13 mg, 0.136 mmol, 1.5 equiv), and isobutylmagnesium chloride (90 μL, 0.182 mmol, 2 equiv, 2M in diethyl ether) in diethyl ether (500 μL). The crude product was purified by column chromatography to yield **5bm** (15 mg, 79 %) as yellow oil. – ^{1}H NMR (500 MHz): 1.00 (6 H, d, *J* = 6 Hz), 2.18–2.29 (1 H, m), 2.81 (2 H, d, *J* = 7.5 Hz), 4.05 (3 H, s), 6.62 (1 H, s), 7.45 (1 H, td, *J* = 1, 7 Hz), 7.67 (1 H, td, *J* = 1.5, 7 Hz), 7.99 (1 H, d, *J* = 8 Hz), 8.15 (1 H, dd, *J* = 1, 8 Hz) ppm. – ^{13}C NMR (125 MHz): 22.59, 29.45, 38.92, 55.55, 100.51, 109.98, 119.99, 121.55, 124.79, 128.28, 128.33, 129.65, 163.37 ppm. – IR: 1078, 1225, 1309, 1365, 1455, 1653, 2986, 2970, 3125 cm^{-1}. – MS (ESI): 216.0, HRMS: calcd: 216.1383, found: 216.1416 [M + H^{+}].

2-Phenylquinolin-8-ol[19] (5dd)



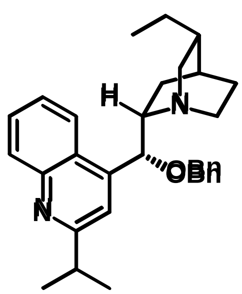
According to GP1, **4d** (300 mg, 1.86 mmol) was reacted with copper(I) chloride (18 mg, 0.186 mmol, 10 mol %), magnesium chloride (736 mg, 7.44 mmol, 4 equiv), and phenylmagnesium chloride (3.7 mL, 7.44 mmol, 4 eqiuv, 2M in tetrahydrofuran) in diethyl ether (9 mL). The crude product was purified by column chromatography to yield **5dd** (288 mg, 71 %) as brown oil. – ^{1}H NMR (300 MHz): 7.19–7.58 (6 H, m), 7.93 (1 H, d, *J* = 8.5 Hz), 8.16 (2 H, d, *J* = 7 Hz), 8.23 (1 H, d, *J* = 8.5 Hz) 8.30–8.44 (1 H, br s) ppm. – ^{13}C NMR (75 MHz): 110.15, 117.62, 119.60, 126.55, 127.38, 127.63, 128.68, 128.88, 129.59, 129.72, 130.03, 136.99, 152.26 ppm. – IR: 1203, 1290, 1403, 1447, 1510, 1660, 3052 cm^{-1}.

2-Methyl-6-phenylpyridine[21] (5fb)



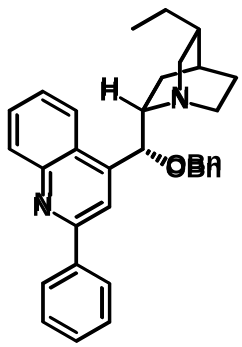
According to GP1, **4f** (25 mg, 0.177 mmol) was reacted with copper(I) chloride (2 mg, 0.018 mmol, 10 mol %), magnesium chloride (53 mg, 0.53 mmol, 3 equiv), and phenylmagnesium bromide (221 μL, 0.708 mmol, 4 equiv, 3.2M in diethyl ether) in ether (1 mL). The crude product was purified by column chromatography to yield **5fb** (22 mg, 76 %) as yellow oil. – ^{1}H NMR (500 MHz): 2.64 (3 H, s), 7.10 (1 H, d, *J* = 7.5 Hz), 7.40 (1 H, d, *J* = 7.5 Hz), 7.45–7.50 (3 H, m), 7.51 (1 H, dd, *J* = 1, 8 Hz), 7.64 (1 H, t, *J* = 7.5 Hz), 7.98 (1 H, dd, *J* = 1, 8 Hz) ppm. – ^{13}C NMR (125 MHz): 24.77, 117.61, 121.57, 126.98, 128.31, 128.66, 136.85, 139.78, 156.97, 158.35 ppm. – IR: 921, 1098, 1232, 1444, 1570, 2851, 2921, 3059 cm^{-1}.

(1*S*,2*S*,4*R*,5*S*)-2-((*R*)-(Benzyloxy)(2-isopropylquinolin-4-yl)methyl)-5-ethylquinuclidine (6a)



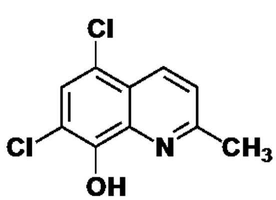
According to GP1, **7** (91 mg, 0.228 mmol) was reacted with copper(I) chloride (2 mg, 0.02 mmol, 10 mol %), magnesium chloride (46 mg, 0.46 mmol, 3 equiv), and isopropylmagnesium chloride (912 μL, 0.912 mmol, 4 equiv, 1M in tetrahydrofuran) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **6a** (63 mg, 65 %) as brown oil. – ^{1}H NMR (300 MHz): 0.82 (3 H, t, *J* = 7.5 Hz), 1.20–1.27 (4 H, m), 1.39 (3 H, d, *J* = 2 Hz), 1.41 (3 H, d, *J* = 2 Hz), 1.98–2.07 (3 H, m), 2.14–2.21 (2 H, m), 2.73–2.80 (1 H, m), 3.02–3.15 (1 H, m), 3.21–3.49 (3 H, m), 3.97–4.11 (1 H, m), 4.48 (1 H, d, *J* = 10.5 Hz), 4.70 (1 H, d, *J* = 10.5 Hz), 6.34–6.46 (1 H, m), 7.60–7.78 (8 H, m), 8.12 (1 H, dd, *J* = 1, 8.5 Hz), 8.56 (1 H, dd, *J* = 0.5, 7.5 Hz) ppm. – ^{13}C NMR (125 MHz): 11.54, 22.44, 22.67, 24.92, 25.39, 27.01, 29.71, 35.74, 37.38, 43.87, 57.06 60.09, 71.82, 123.47, 124.44, 127.17, 128.07, 128.14, 128.23, 128.72, 129.68, 129.85, 136.97, 143.12, 148.19, 167.09 ppm. – IR: 1056, 1123, 1453, 1554, 2867, 3026 cm^{-1}. – MS (ESI): 429.3, calcd: 429.2900, found: 429.2571 [M + H^{+}].

(1*S*,2*S*,4*R*,5*S*)-2-((*R*)-(Benzyloxy)(2-phenylquinolin-4-yl)methyl)-5-ethylquinuclidine[26] (6b)



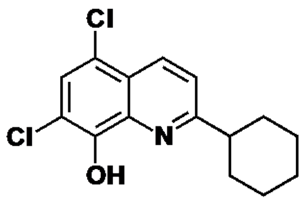
According to GP1, **7**[4a,14a,26] (91 mg, 0.228 mmol) was reacted with copper(I) chloride (2 mg, 0.02, 10 mol %), magnesium chloride (46 mg, 0.46 mmol, 3 equiv), and phenylmagnesium bromide (304 µL, 0.912 mmol, 4 equiv, 3.2M in diethyl ether) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **6b** (60 mg, 37 %) as brown oil. – ^{1}H NMR (300 MHz): 0.80 (3 H, t, *J* = 7 Hz), 1.19–1.90 (3 H, m), 2.55–3.79 (3 H, m), 4.59 (2 H, quart, *J* = 11 Hz), 7.24–7.56 (8 H, m), 7.65 (1 H, dt, *J* = 1, 8 Hz), 7.78 (1 H, t, *J* = 7 Hz), 8.04 (1 H, s), 8.13 (2 H, dd, *J* = 1.5, 8.5 Hz), 8.24 (1 H, d, *J* = 8.5 Hz), 8.42 (1 H, dd, *J* = 1, 8 Hz) ppm. – ^{13}C NMR (75 MHz): 11.77, 20.20, 20.28, 25.13, 26.67, 27.26, 36.44, 43.62, 57.74, 60.27, 71.65, 116.05, 123.31, 125.02, 127.54, 127.86, 128.02, 128.33, 128.64, 128.90, 129.46, 129.77, 130.63, 137.40, 139.54, 145.18, 148.76, 156.88 ppm.

5,7-Dichloro-2-methylquinolin-8-ol[27] (8a)



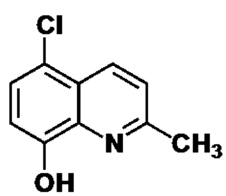
According to GP1, **9** (71 mg, 0.31 mmol) was reacted with copper(I) chloride (3 mg, 0.031 mmol, 10 mol %), magnesium chloride (92 mg, 0.92 mmol, 3 equiv), and methylmagnesium chloride (381 µL, 1.22 mmol, 4 equiv, 3.2M in diethyl ether) in diethyl ether (1.5 mL). The crude product was purified by column chromatography to yield **8a** (44 mg, 63 %) as brown oil. – ^{1}H NMR (500 MHz): 2.72 (3 H, s), 7.34 (1 H, d, *J* = 8.5 Hz), 7.42 (1 H, s), 8.24 (1 H, d, *J* = 8.5 Hz) ppm. – ^{13}C NMR (125 MHz): 24.8, 144.9, 120.6, 122.9, 123.4, 127.0, 133.3, 137.9, 146.9, 158.8 ppm. – IR: 1323, 1449, 1498, 1598, 3419 cm^{-1}.

5,7-Dichloro-2-cyclohexylquinolin-8-ol (8b)



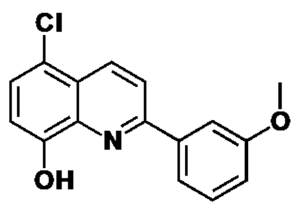
According to GP1, **9** (60 mg, 0.31 mmol) was reacted with copper(I) chloride (3 mg, 0.031 mmol, 10 mol %), magnesium chloride (92 mg, 0.92 mmol, 3 equiv), and cyclohexylmagnesium chloride (938 μL, 1.22 mmol, 4 equiv, 1.3M in tetrahydrofuran/toluene) in diethyl ether (1.5 mL). The crude product was purified by column chromatography to yield **8b** (75 mg, 84 %) as brown oil. – ^{1}H NMR (500 MHz): 0.85–2.02 (10 H, m), 2.88–2.96 (1 H, m), 3.15–3.93 (1 H, br s), 7.46 (1 H, d, *J* = 8.5 Hz), 7.52 (1 H, s), 8.39 (1 H, d, *J* = 8.5 Hz) ppm. – ^{13}C NMR (75 MHz): 25.98, 26.38, 32.57, 46.53, 114.79, 120.57, 121.80, 123.49, 127.10, 133.70, 137.95, 147.24, 166.44 ppm. – IR: 1084, 1146, 1252, 1381, 1497, 2853, 2964, 3025 cm^{-1}. – MS (ESI): 316.0 [M^{-}], calcd: 320.0240, found: 322.9257 [M + H^{+}].

5-Chloro-2-methylquinolin-8-ol[28] (8c)



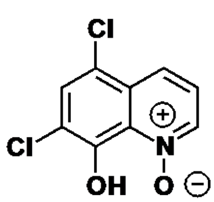
According to GP1, **9b** (60 mg, 0.31 mmol) was reacted with copper(I) chloride (3 mg, 0.031 mmol, 10 mol %), magnesium chloride (92 mg, 0.92 mmol, 3 equiv), and methylmagnesium bromide (387 μL, 1.22 mmol, 4 equiv, 3.2M in diethyl ether) in diethyl ether (1.5 mL). The crude product was purified by column chromatography to yield **8c** (57 mg, 96 %) as brown oil. – ^{1}H NMR (500 MHz): 2.76 (3 H, s), 7.07 (1 H, d, *J* = 8.5 Hz), 7.41–7.45 (2 H, m), 8.39 (1 H, d, *J* = 9 Hz) ppm. – ^{13}C NMR (125 MHz): 24.84, 109.78, 120.27, 123.52, 124.47, 126.36, 133.41, 138.05, 150.75, 157.66 ppm. – IR: 1042, 1204, 1368, 1471, 1624, 3065, 3124, 3206 cm^{-1}.

5-Chloro-2-(3-methoxyphenyl)quinolin-8-ol (8d)



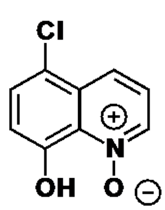
According to GP1, **9b** (60 mg, 0.31 mmol) was reacted with copper(I) chloride (3 mg, 0.031 mmol, 10 mol %), magnesium chloride (92 mg, 0.92 mmol, 3 equiv), and 3-methoxyphenylmagnesium bromide (1.22 µL, 1.22 mmol, 4 equiv, 1M in tetrahydrofuran) in diethyl ether (1.5 mL). The crude product was purified by column chromatography to yield **8d** (42 mg, 54 %) as yellow oil. – ^{1}H NMR (300 MHz): 3.93 (3 H, s), 7.05 (1 H, ddd, *J* = 1, 3, 9 Hz), 7.12 (1 H, d, *J* = 9 Hz), 7.44–7.50 (2 H, m), 7.69–7.72 (2 H, m), 8.00 (1 H, d, *J* = 10 Hz), 8.24–8.39 (1 H, br s), 8.56 (1 H, d, *J* = 10 Hz) ppm. – ^{13}C NMR (75 MHz): 55.48, 110.21, 113.13, 115.31, 119.92, 120.39, 120.44, 125.25, 127.14, 130.01, 134.33, 139.59, 151.31, 155.31, 160.01 ppm. – IR: 1041, 1180, 1221, 1325, 1429, 1507, 2834, 2931, 3071, 3384 cm^{-1}.

5,7-Dichloro-8-hydroxyquinoline 1-oxide[4a,14a,29] (9a)



9a was prepared according to literatrure.[29] – ^{1}H NMR (300 MHz): 7.40 (1 H, dd, *J* = 6, 9 Hz), 7.70 (1 H, s), 8.17 (1 H, d, *J* = 9 Hz), 8.33 (1 H, d, *J* = 6 Hz) ppm. – ^{13}C NMR (75 MHz): 118.89, 118.98, 121.37, 126.96, 128.42, 128.90, 131.39, 135.54, 149.68 ppm. – IR: 906, 1068, 1156, 1208, 1320, 1423, 1513, 2995, 3067, 3078 cm^{-1}.

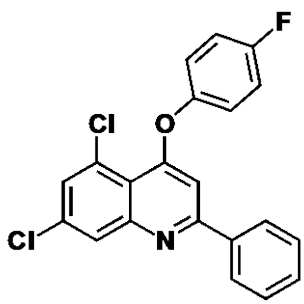
5-Chloro-8-hydroxyquinoline 1-oxide[30] (9b)



9b was prepared according to literature procedure.[30] – ^{1}H NMR (300 MHz): 6.99 (1 H, d, *J* = 8.5 Hz), 7.35–7.40 (1 H, m), 7.56 (1 H, d, *J* = 8.5 Hz), 8.18 (1 H, dd, *J* = 1, 9 Hz), 8.30 (1 H, dd, *J* = 1, 6 Hz) ppm. – ^{13}C

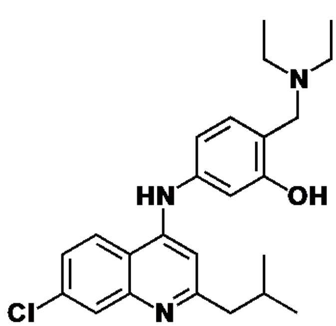
NMR (75 MHz): 114.72, 119.07, 121.28, 126.70, 129.63, 130.70, 134.98, 148.36, 115.28 ppm. – IR: 1049, 1103, 1217, 1300, 1466, 1603, 1739, 2948, 3017, 3369 cm^{-1}.

5,7-Dichloro-4-(4-fluorophenoxy)-2-phenylquinoline (10)



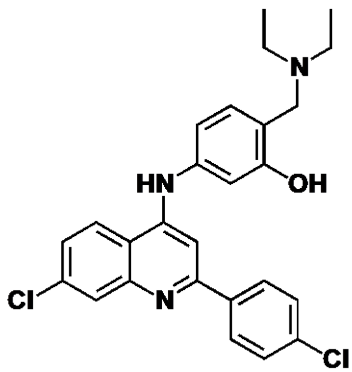
According to GP1, **S4** (25 mg, 0.077 mmol) was reacted with copper(I) chloride (1 mg, 0.008 mmol, 10 mol %), magnesium chloride (14 mg, 0.144 mmol, 2 equiv), and phenylmagnesium bromide (78 μL, 0.233 mmol, 3 equiv, 3.2M in diethyl ether) in diethyl ether (400 μL). The crude product was purified by column chromatography to yield **10** (20 mg, 68 %) as yellow oil. – ^{1}H NMR (500 MHz): 7.09 (1 H, s), 7.19–7.20 (4 H, m), 7.39–7.48 (3 H, m), 7.57 (1 H, d, *J* = 2 Hz), 7.94–7.96 (2 H, m), 8.10 (1 H, d, *J* = 2 Hz) ppm. – ^{13}C NMR (125 MHz): 104.66, 117.15 (d, *J* = 23 Hz), 122.15 (d, *J* = 8.5 Hz), 127.37, 128.07,0 128.88, 129.17, 130.03, 130.14, 135.19, 138.26, 150.11, 151.74, 159.00, 159.57, 160.94, 162.94 ppm. – IR: 1109, 1259, 1340, 1482, 1527, 2978, 3021, 3046 cm^{-1}. – MS (ESI): 383.9, calcd: 384.0353, found: 384.0114 [M + H^{+}].

5-((7-Chloro-2-isobutylquinolin-4-yl)amino)-2-((diethylamino)methyl)phenol (11a)



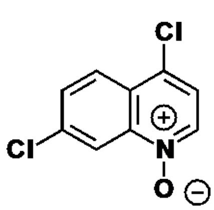
To a solution of **13a** (10 mg, 0.037 mmol) in ethanol (1 mL) was added **S3** (10 mg, 0.037 mmol, 1 equiv) and heated to 100 °C. After 48 h, the reaction was concentrated under reduced pressure and purified by column chromatography [dichloromethane/methanol] to yield **11a** (14 mg, 93 %) as yellow oil. – ^{1}H NMR (500 MHz): 0.97–1.05 (7 H, m), 1.22–1.38 (7 H, m), 2.15–2.58 (5 H, m), 3.71 (1 H, sept, *J* = 6.5 Hz), 5.29 (1 H, d, *J* = 7 Hz), 6.52 (1 H, s), 7.36 (1 H, dd, *J* = 2, 9 Hz), 7.45 (1 H, d, *J* = 7 Hz), 7.70 (1 H, d, *J* = 9 Hz), 8.01 (1 H, d, *J* = 2 Hz) ppm. – ^{13}C NMR (125 MHz): 11.20, 22.52, 29.26, 29.70, 46.28, 56.58, 100.35, 116.06, 120.95, 124.80, 125.77, 128.97, 129.20, 130.62, 134.88, 135.75, 131.77, 148.91, 149.17, 162.09 ppm. – IR: 1098, 1174, 1327, 1387, 1435, 1521, 2956, 2999, 3031 cm^{-1}. – MS (ESI): 411.0, calcd: 412.2150, found: 412.2757 [M + H^+].

5-((7-Chloro-2-(4-chlorophenyl)quinolin-4-yl)amino)-2-((diethylamino)methyl)phenol (11b)



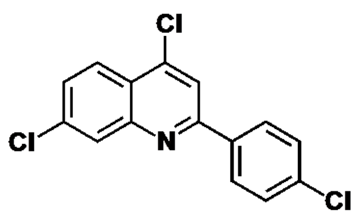
To a solution of **13b** (50 mg, 0.163 mmol) in ethanol (2 mL) was added **S3** (43 mg, 0.163 mmol, 1 equiv) and heated to 100 °C. After 48 h, the reaction was concentrated under reduced pressure and purified by column chromatography [dichloromethane/methanol] to yield **11b** (63 mg, 84 %) as yellow oil. – ^{1}H NMR (500 MHz): 1.16 (6 H, d, *J* = 7.5 Hz), 2.68 (4 H, quart, *J* = 7.5 Hz), 3.82 (2 H, s), 6.70–6.78 (3 H, m), 7.00 (1 H, d, *J* = 8 Hz), 7.17–7.59 (4 H, m), 7.80 (1 H, d, *J* = 9 Hz), 7.90 (2 H, d, *J* = 8 Hz), 8.08 (1 H, s) ppm. – ^{13}C NMR (125 MHz): 11.17, 46.32, 56.56, 100.42, 109.99, 112.57, 117.30, 118.71, 121.12, 125.84, 128.64, 128.76, 128.83, 128.95, 129.33, 135.37, 135.61, 138.33, 139.91, 148.12, 149.12, 157.99, 159.76 ppm – MS (ESI): 467.0, calcd: 467.4096, found: 467.3091 [M + H^+].

4,7-Dichloroquinoline 1-oxide[4a, 12, 14a] (12)



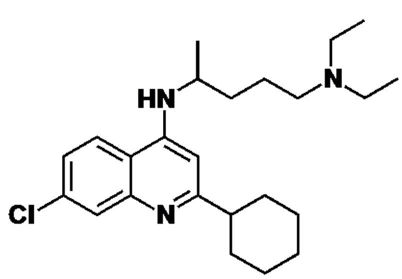
12 was prepared according to literature procedure.[14a] – m.p.: 164–165 °C[13] – ^{1}H NMR (500 MHz): 7.36 (1 H, d, *J* = 6.5 Hz), 7.68 (1 H, d, *J* = 9 Hz), 8.13 (1 H, d, *J* = 9 Hz), 8.43 (1 H, d, *J* = 6.5 Hz), 8.77 (1 H, s) ppm. – ^{13}C NMR (125 MHz): 119.93, 121.22, 125.60, 126.52, 128.68, 130.80, 135.96, 142.33, 150.88 ppm. – IR: 829, 1091, 1291, 1367, 1412, 1555, 1609, 3025, 3094 cm^{-1}.

4,7-Dichloro-2-(4-chlorophenyl)quinoline[31] (13b)



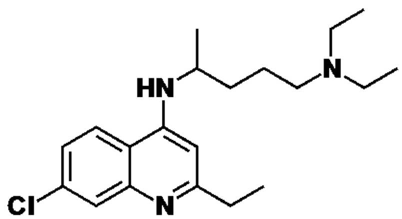
According to GP1, **5g** (38 mg, 0.177 mmol) was reacted with copper(I) chloride (2 mg, 0.017 mmol, 10 mol %), magnesium chloride (26 mg, 0.265 mmol, 1.5 equiv), and (4-chlorophenyl)magnesium chloride (344 μL, 0.354 mmol, 2 equiv, 1M in diethyl ether) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **1b** (54 mg, 91 %) as colorless oil. – ^{1}H NMR (500 MHz): 7.50 (2 H, dd, *J* = 1.5, 8 Hz), 7.36 (1 H, d, *J* = 1.5 Hz), 7.56 (1 H, dt, *J* = 2, 9 Hz), 7.91 (1 H, d, *J* = 1.5 Hz), 8.09 (1 H, dd, *J* = 2, 8.5 Hz), 8.15 (2 H, dd, *J* = 1.5, 8.5 Hz) ppm. – ^{13}C NMR (125 MHz): 109.98, 118.74, 123.82, 125.34, 128.35, 128.73, 128.86, 129.18, 136.44, 136.83, 143.33, 139.32, 156.94 ppm. – IR: 1027, 1093, 1222, 1362, 1447, 1570, 2867, 2952, 3002 cm^{-1}.

N^{4}-(7-Chloro-2-cyclohexylquinolin-4-yl)-*N*^{1},*N*^{1}-diethylpentane-1,4-diamine (15a)



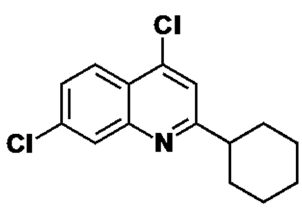
To solution of **16a** (50 mg, 0.179 mmol) in 2-amino-5-diethylaminopentane (1 mL) was added samarium triflate (11 mg, 0.018, 10 mol %) and heated to 140 °C. After 12 h the reaction was concentrated under reduced pressure and purified by column chromatography [dichloromethane /methanol] to yield **15a** (44 mg, 61 %) as yellow oil. – ^{1}H NMR (300 MHz): 1.00 (6 H, t, *J* = 7 Hz), 1.24–2.01 (16 H, m), 2.44–2.57 (7 H, m), 2.68–2.77 (1 H, m), 3.72 (1 H, t, *J* = 5 Hz), 5.12 (1 H, d, *J* = 5.5 Hz), 6.31 (1 H, s), 7.24–7.27 (1 H, m), 7.61 (1 H, d, *J* = 8.5 Hz), 7.91 (1 H, d, *J* = 2 Hz) ppm. – ^{13}C NMR (75 MHz): 11.28, 20.21, 23.72, 26.12, 26.59, 29.71, 32.90, 32.93, 34.55, 46.71, 48.01, 52.49, 97.02, 116.38, 120.8, 124.12, 128.32, 128.88, 134.55, 149.09, 168.72 ppm. – IR: 1147, 1227, 1289, 1379, 1449, 1532, 1609, 2850, 2926, 2957 cm^{-1}. – MS (ESI): 401.0, calcd: 402.2671, found: 402.2671 [M + H^{+}].

N^4-(7-Chloro-2-ethylquinolin-4-yl)-N^1,N^1-diethylpentane-1,4-diamine (15b)



To a solution of **16b** (10 mg, 0.039 mmol) in 2-amino-5-diethylaminopentane (1 mL) was added samarium triflate (2 mg, 3.9 μmol, 10 mol %) and heated to 140 °C. After 48 h, the reaction was concentrated under reduced pressure and purified by column chromatography [dichloromethane/methanol] to yield **15b** (12 mg, 82 %) as red oil. –^{1}H NMR (500 MHz): 0.95 (6 H, d, J = 6.5 Hz), 1.15 (6 H, t, J = 7 Hz), 1.26 (2 H, s), 2.15 (1 H, sept., J = 7 Hz), 2.37 (1 H, s), 2.63–2.71 (6 H, m), 3.81 (2 H, s), 5.31 (1 H, s), 6.69 (1 H, dd, J = 2.5, 8 Hz), 6.73 (1 H, d, J = 2 Hz), 6.96 (1 H, s), 6.99 (1 H, d, J = 8 Hz), 7.79 (2 H, d, J = 8.5 Hz), 8.01 (1 H, d, J = 2 Hz) ppm. – ^{13}C NMR (125 MHz): 11.35, 20.23, 20.25, 23.82, 34.63, 46.73, 46.79, 48.26, 52.53, 103.46, 109.57, 112.22, 116.98, 120.96, 125.28, 129.19, 140.12, 159.63 ppm. – IR: 1090, 1118, 1205, 1353, 1477, 1599, 2836, 2959, 3033, 3390 cm^{-1}. – MS (ESI): 346.0, calcd: 347.2128, found: 347.2817 [M + H$^+$].

4,7-Dichloro-2-cyclohexylquinoline (16a)



According to GP1, **4g** (38 mg, 0.177 mmol) was reacted with copper(I) chloride (2 mg, 0.017 mmol, 10 mol %), magnesium chloride (26 mg, 0.265 mmol, 1.5 equiv), and cyclohexylmagnesium chloride (264 μL, 0.344 mmol, 2 equiv, 1.3M in tetrahydrofuran /toluene) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield **16a** (26 mg, 53 %) as yellow oil. – ^{1}H NMR (500 MHz): 1.25–2.12 (10 H, m), 3.70–3.80 (1 H, m), 7.38 (1 H, s), 7.63 (1 H, dd, J = 1.5, 15 Hz), 8.10 (1 H, d, J = 15 Hz), 8.83 (1 H, d, J = 3 Hz) ppm. – ^{13}C NMR (125 MHz): 26.22, 30.34, 33.53, 37.97, 119.82, 120.12, 124.89, 126.46, 129.63, 137.92, 142.55, 151.45, 154.133 ppm. – IR: 1113, 1328, 1499, 1573, 2842, 3029 cm^{-1}. – MS (ESI): 278.8, HRMS: calcd: 280.0654, found: 279.1800 [M + H$^+$].

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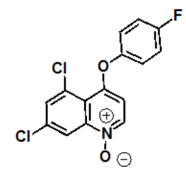

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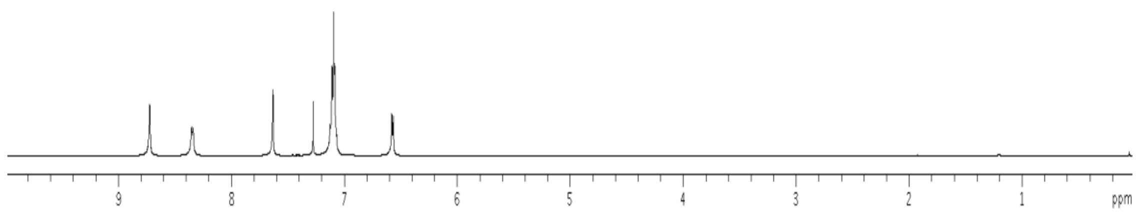

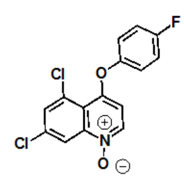

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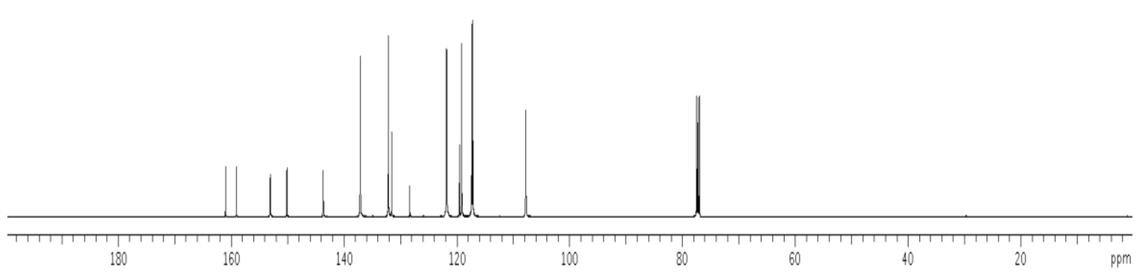

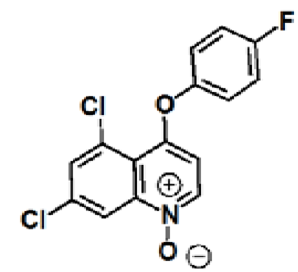

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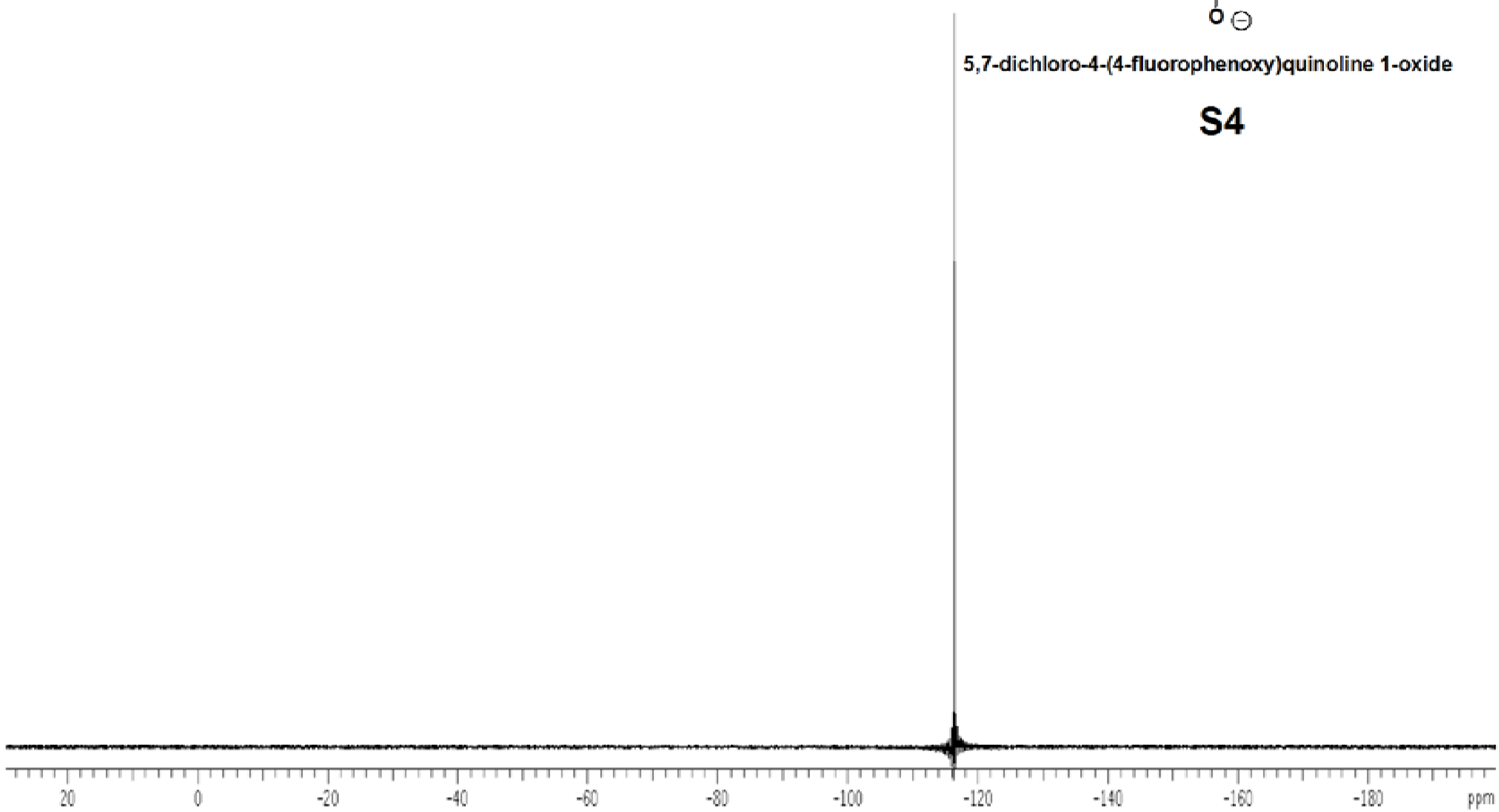

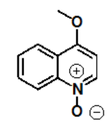

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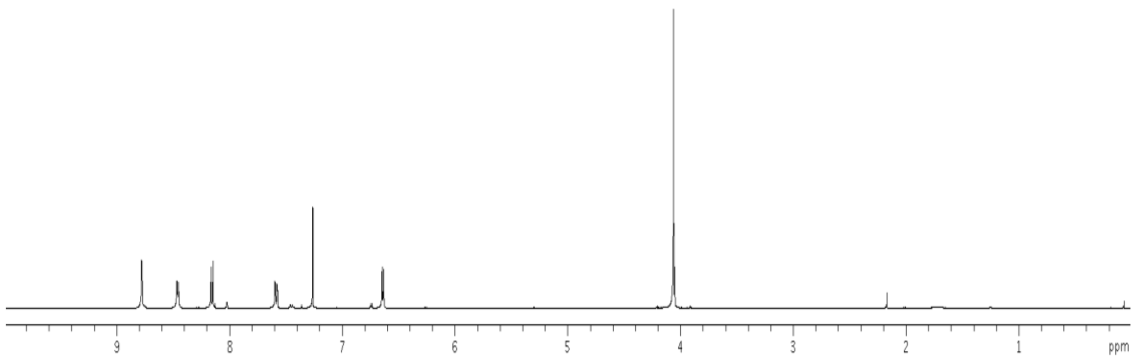

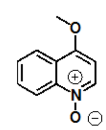

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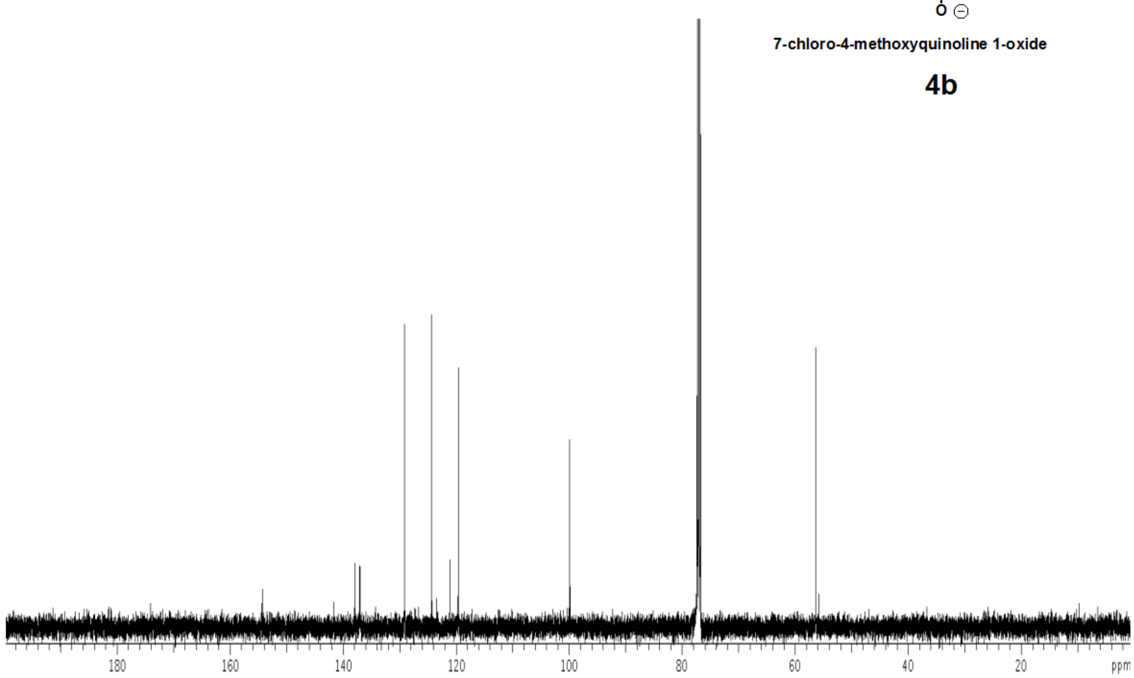

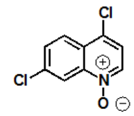

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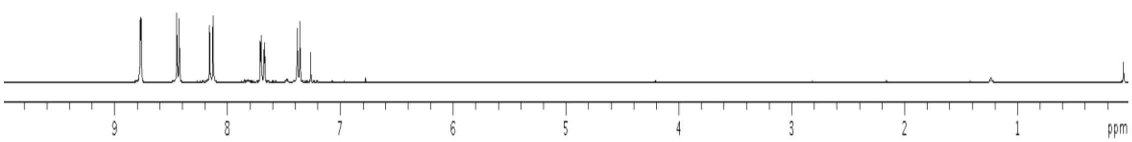

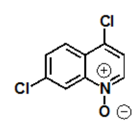

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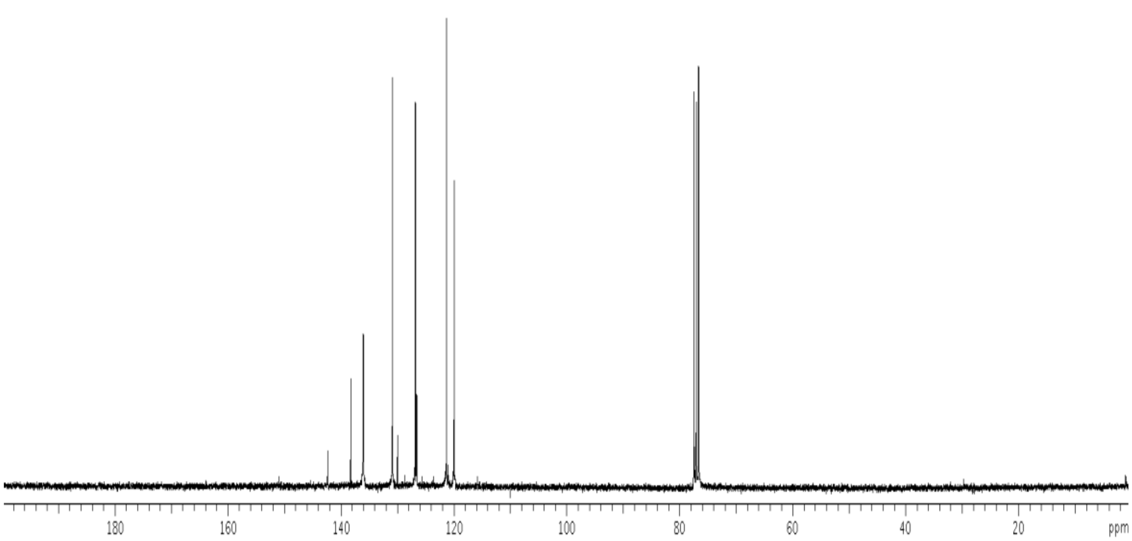

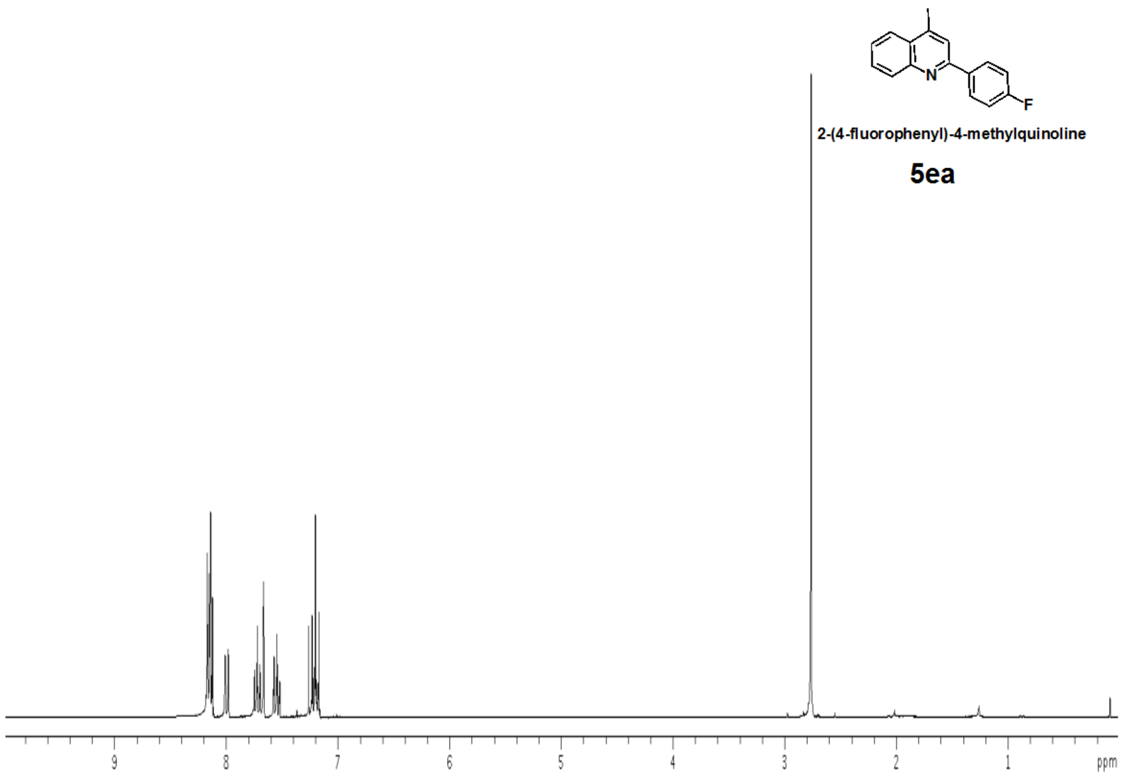

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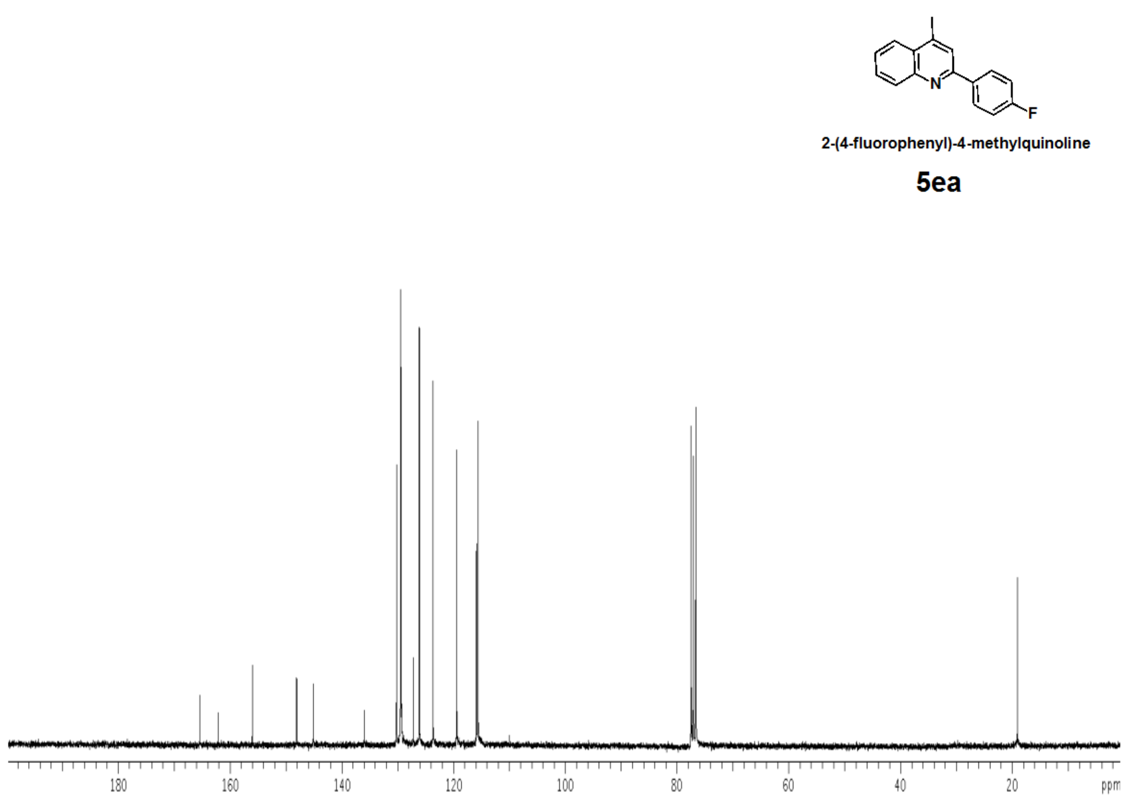

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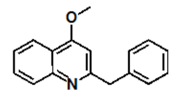

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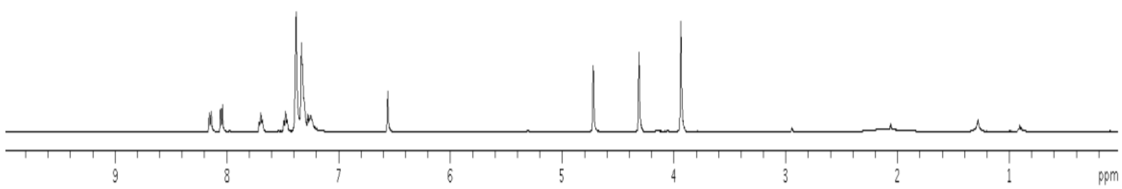

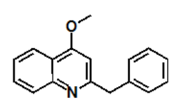

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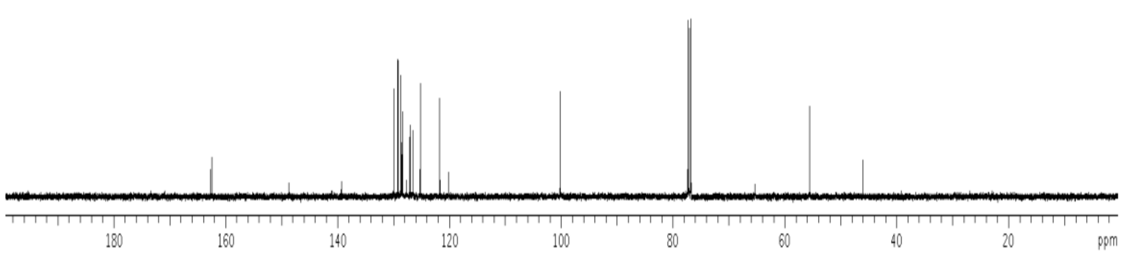

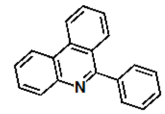

6-phenylphenanthridine

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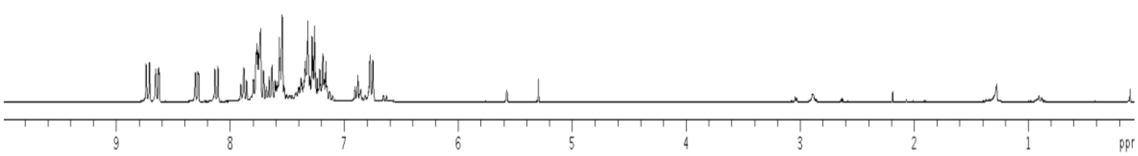

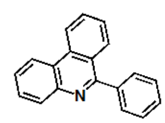

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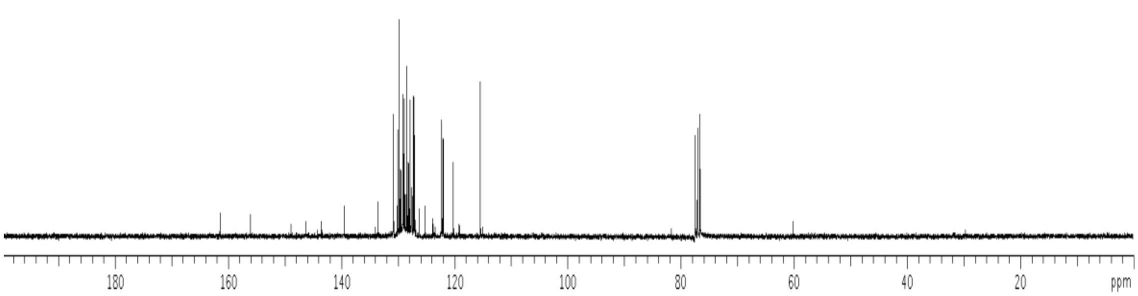

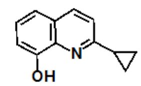

2-cyclopropylquinolin-8-ol

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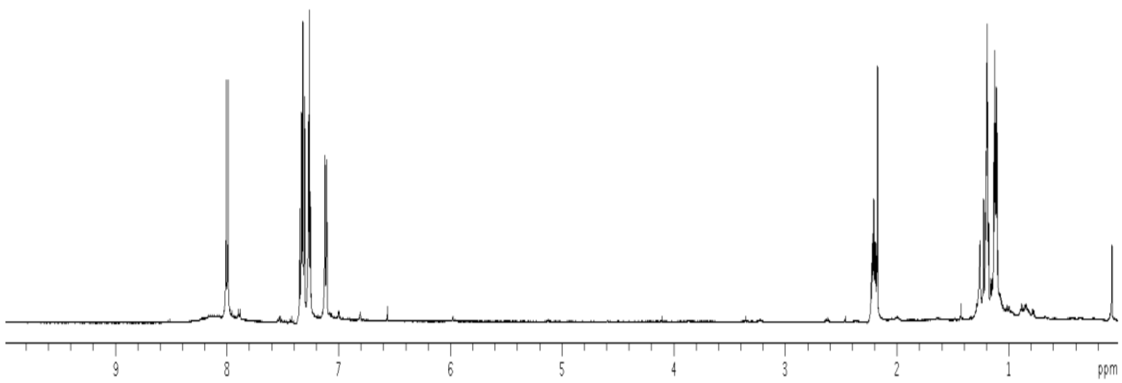

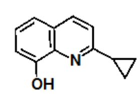

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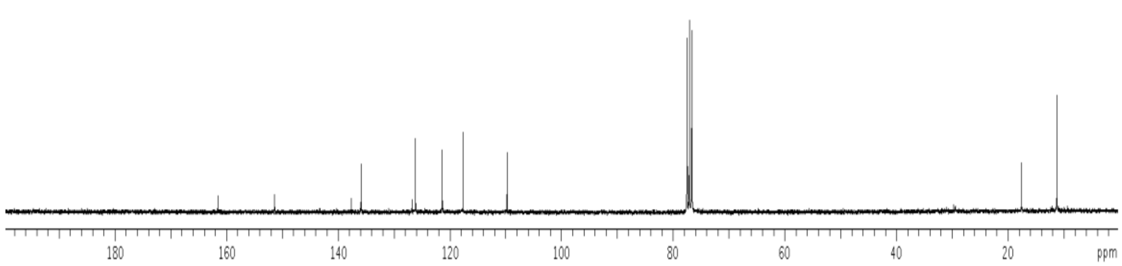

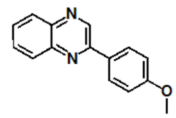

2-(4-methoxyphenyl)quinoxaline

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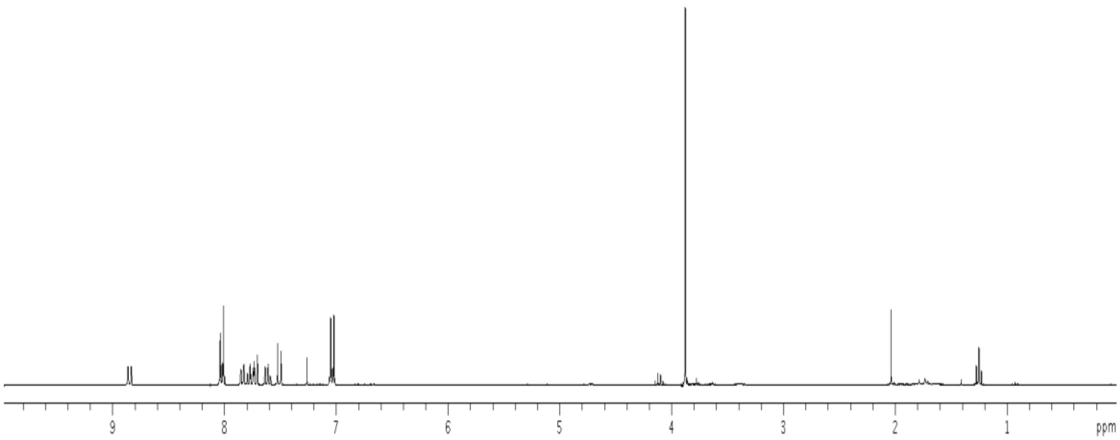

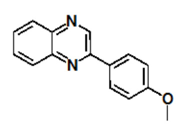

2-(4-methoxyphenyl)quinoxaline

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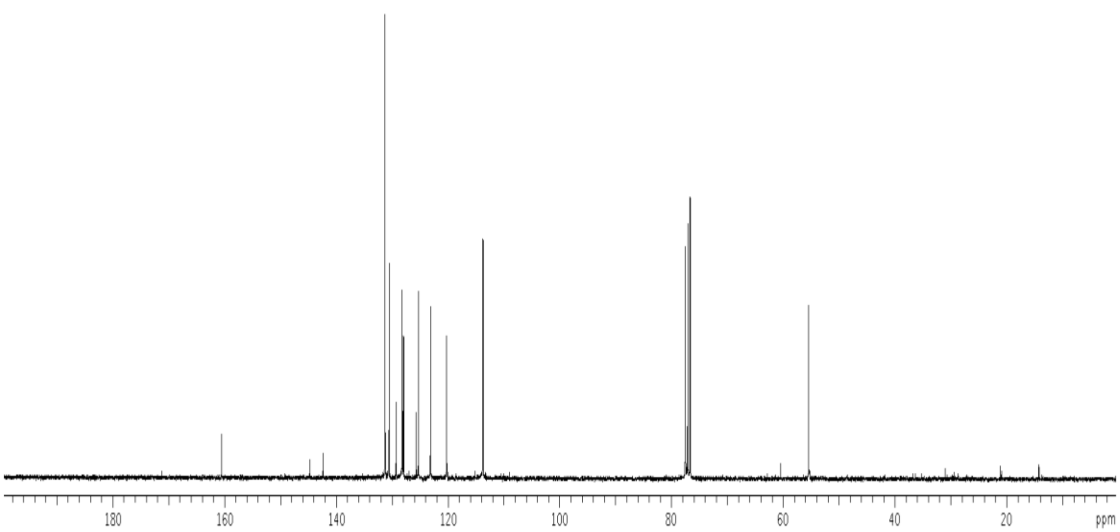

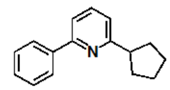

2-cyclopentyl-6-phenylpyridine

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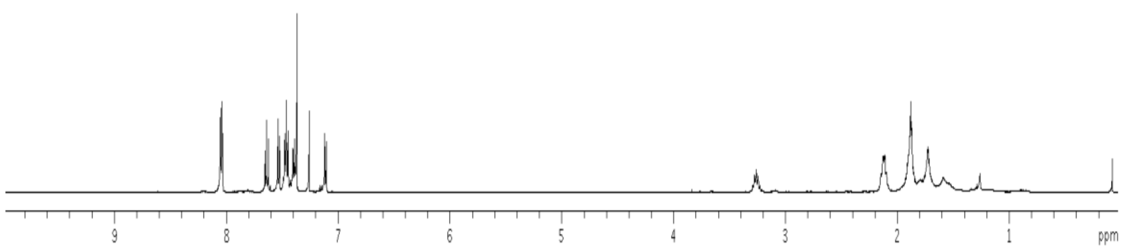

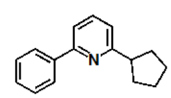

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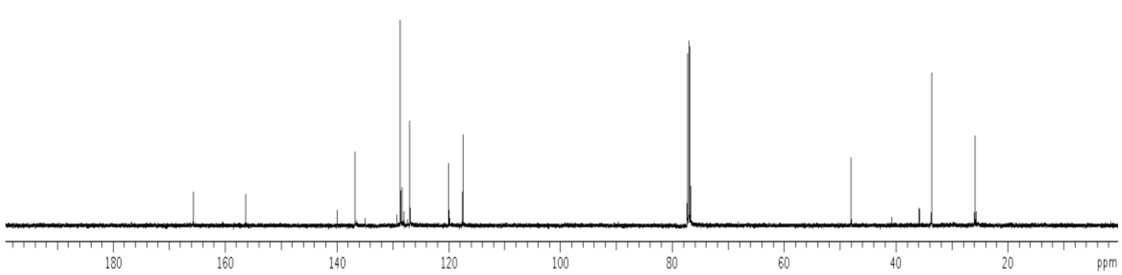

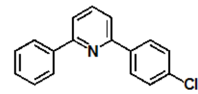

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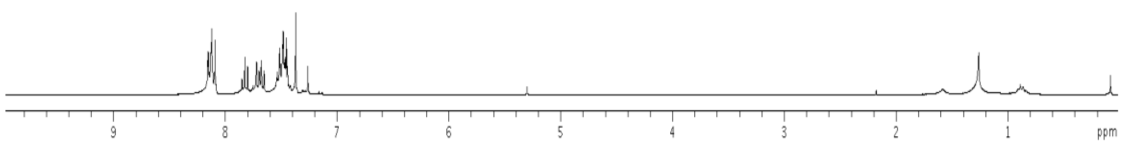

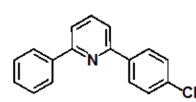

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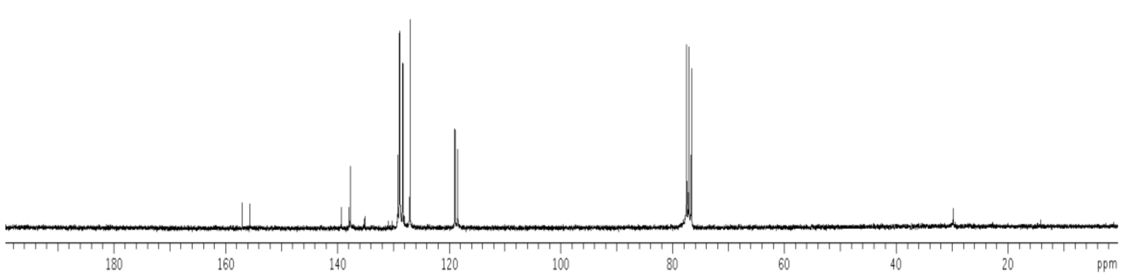

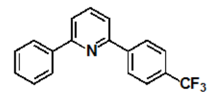

2-phenyl-6-(4-(trifluoromethyl)phenyl)pyridine

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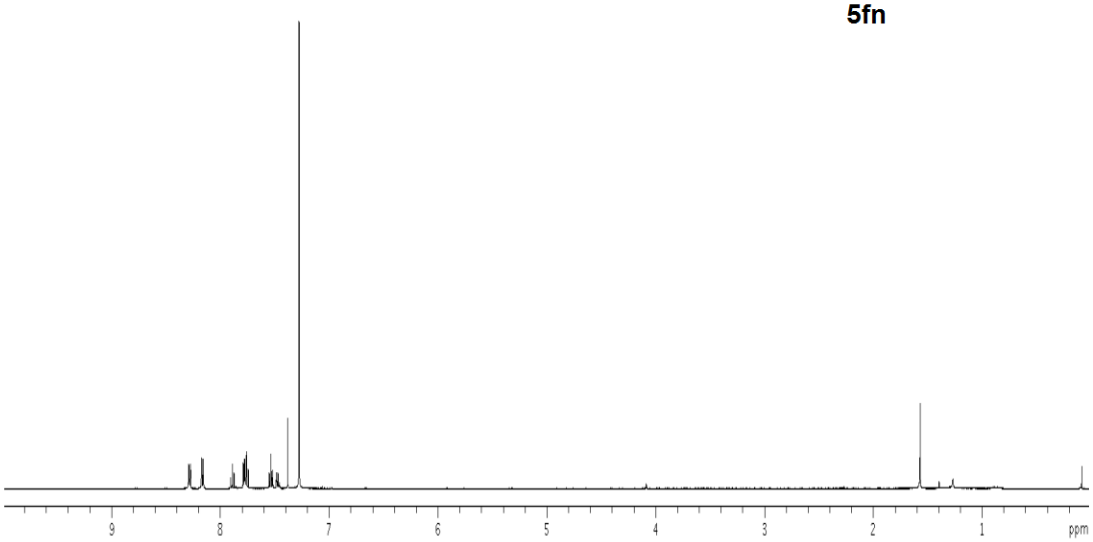

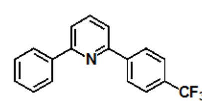

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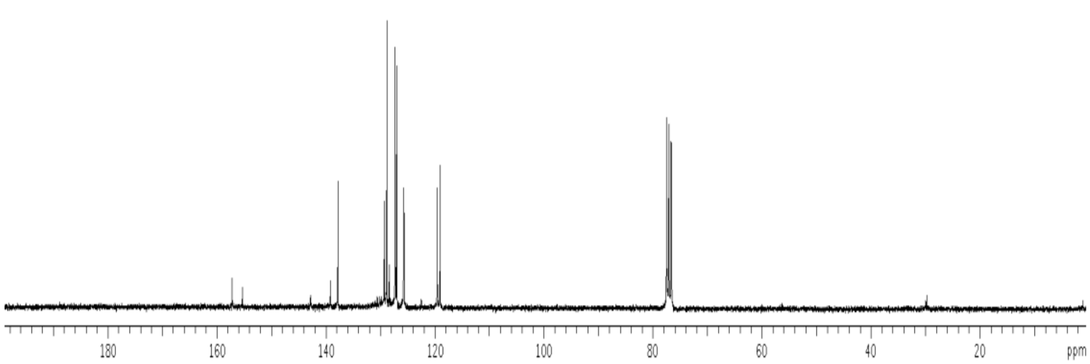

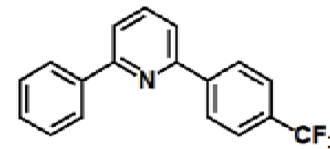

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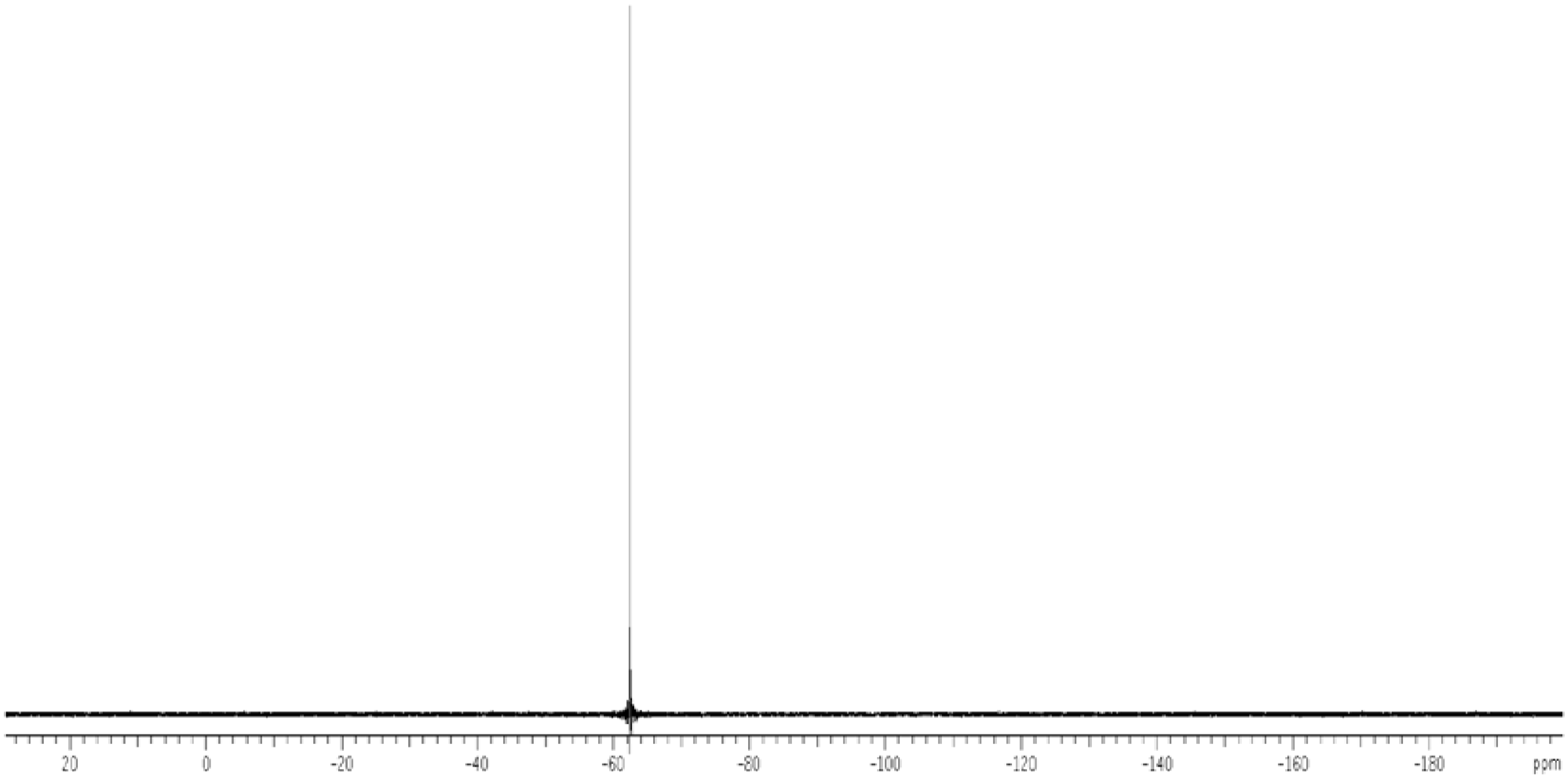

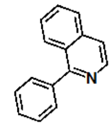

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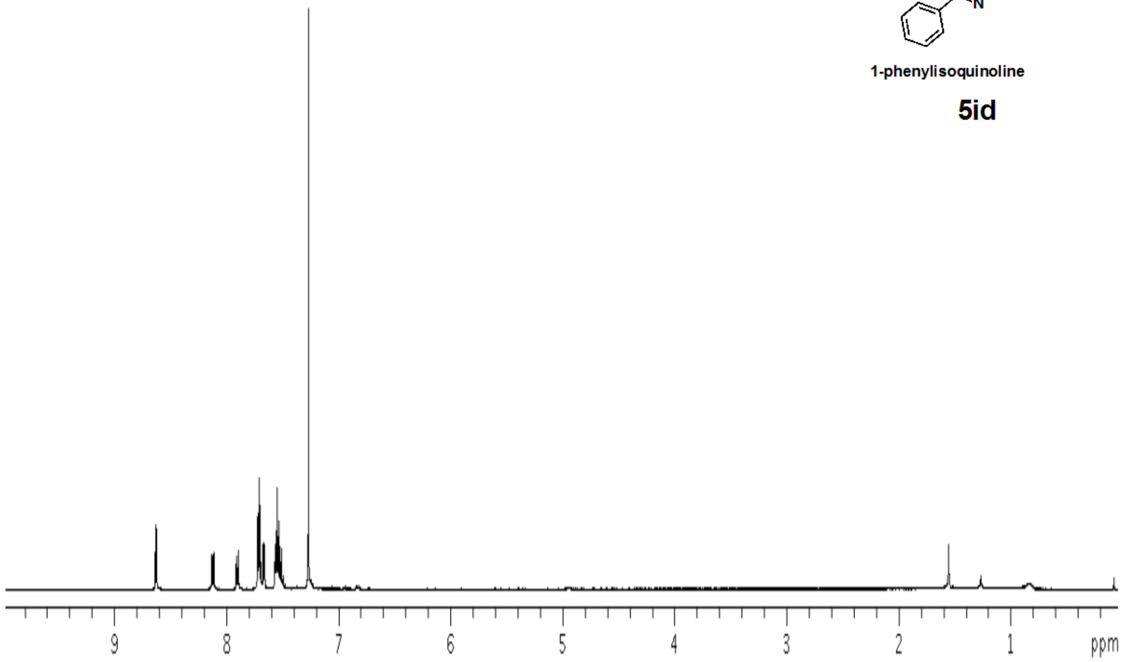

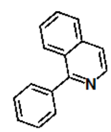

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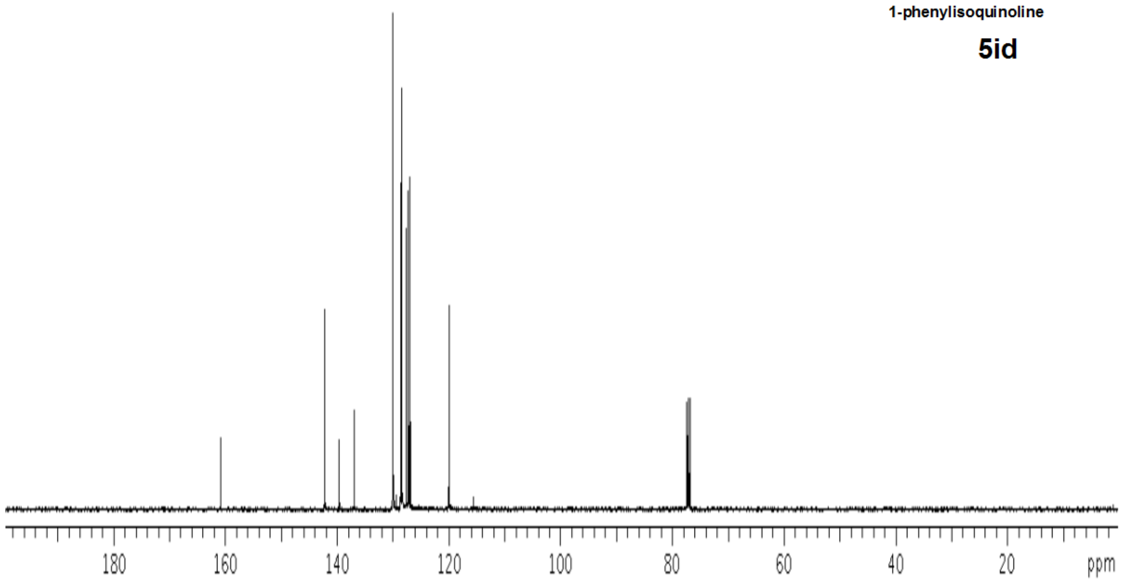

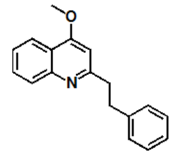

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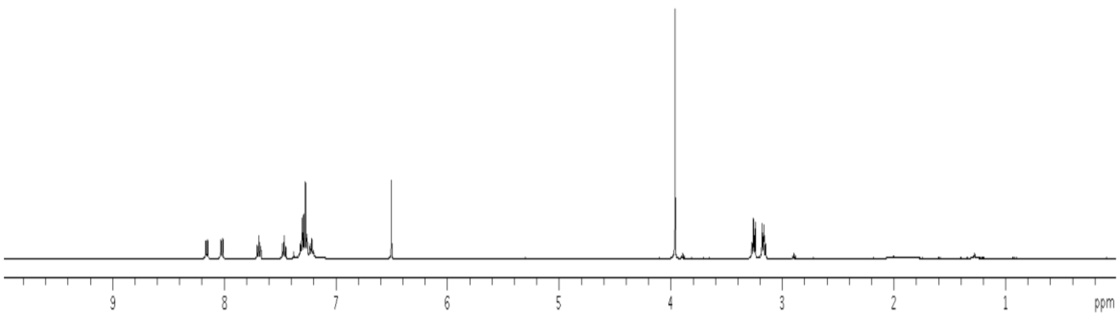

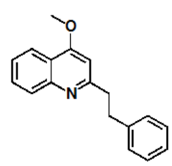

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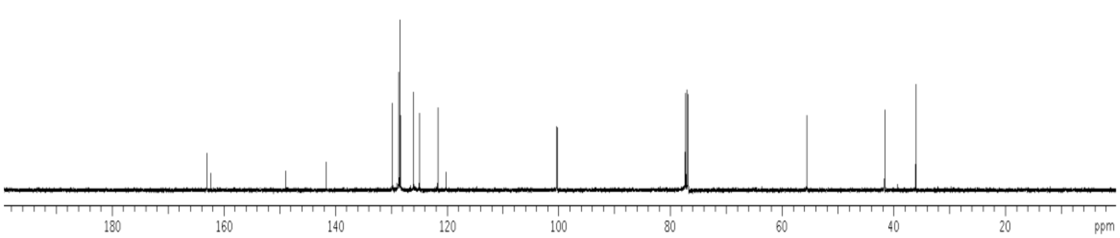

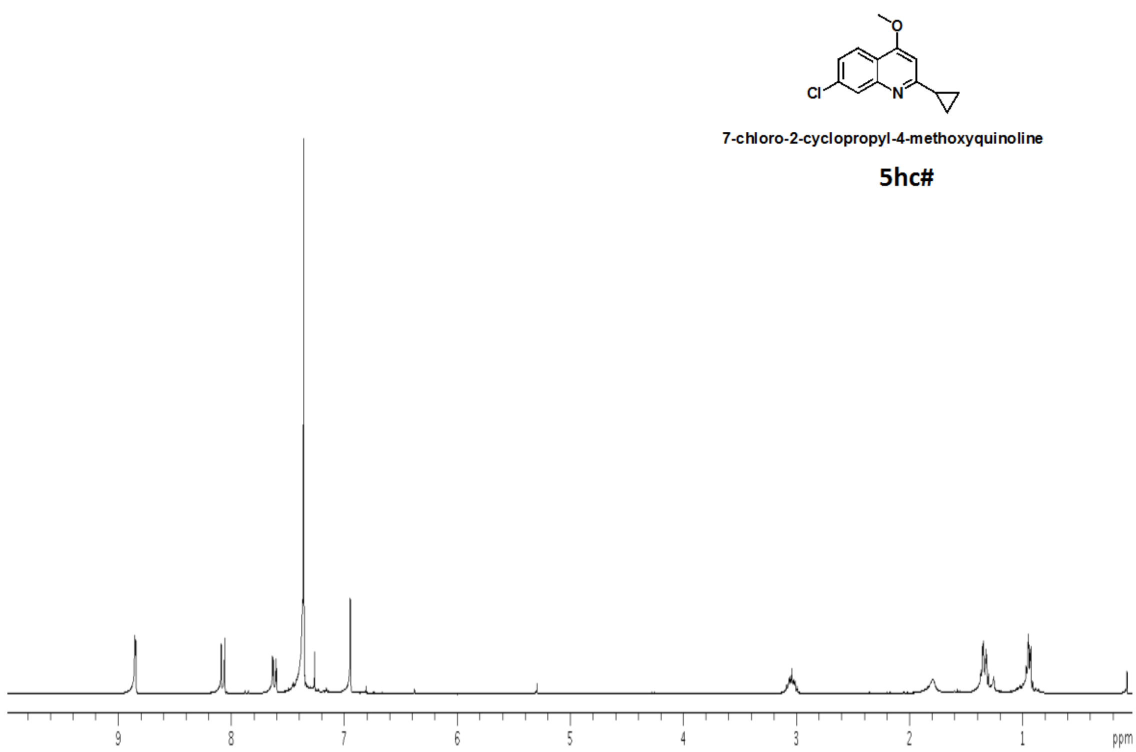
7-chloro-2-cyclopropyl-4-methoxyquinoline
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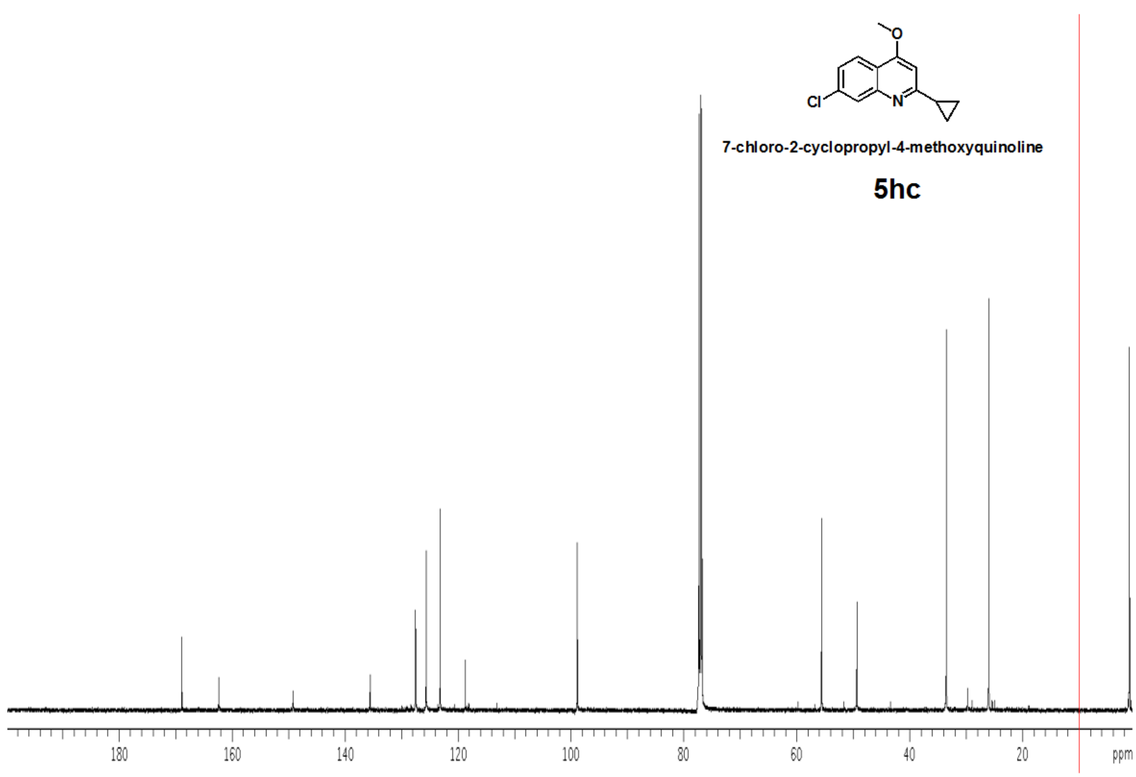
8
7
6
5
4
3
2
1
ppm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140
120
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80
60
40
20
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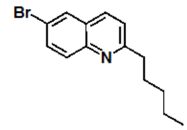

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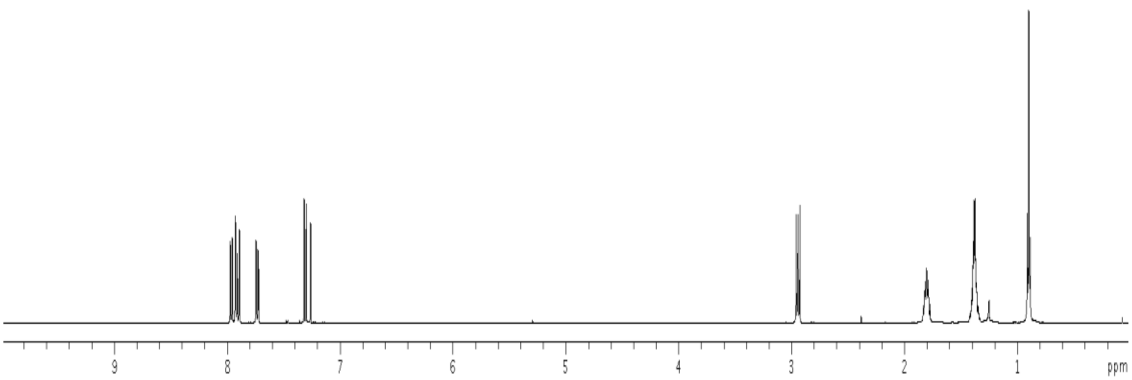

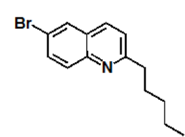

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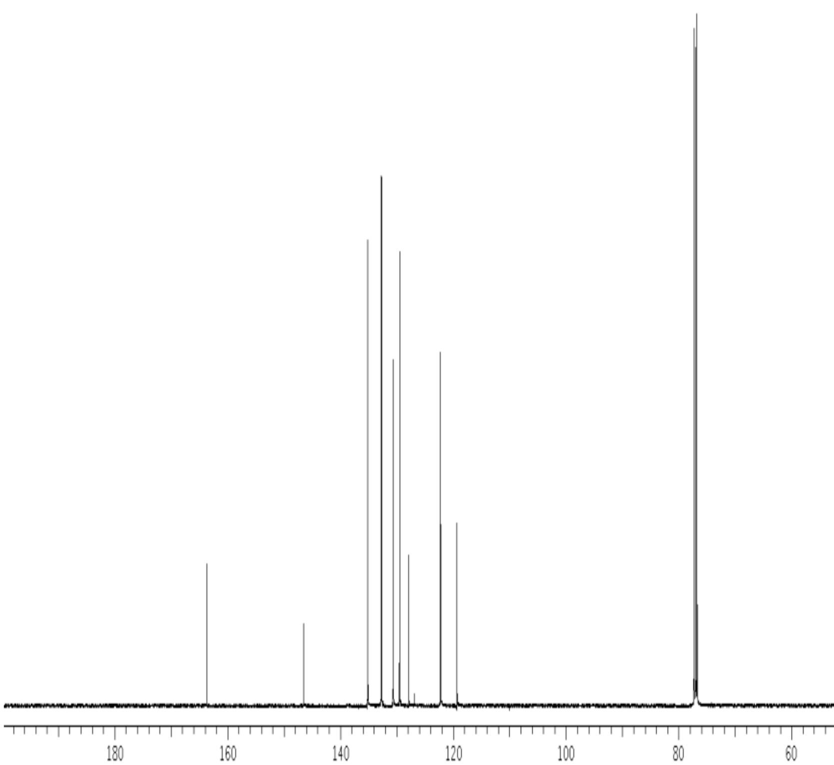
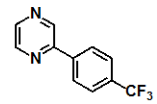
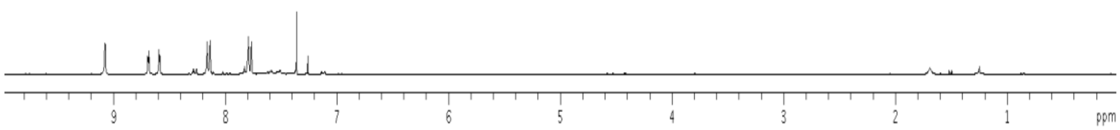
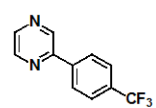




2-(4-(trifluoromethyl)phenyl)pyrazine

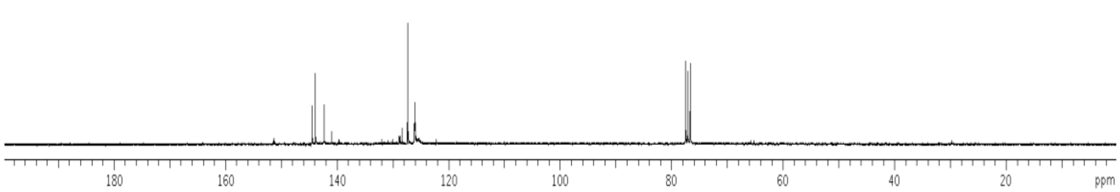
5kn

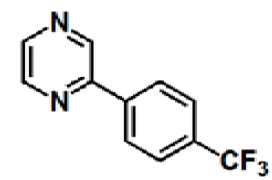




2-(4-(trifluoromethyl)phenyl)pyrazine

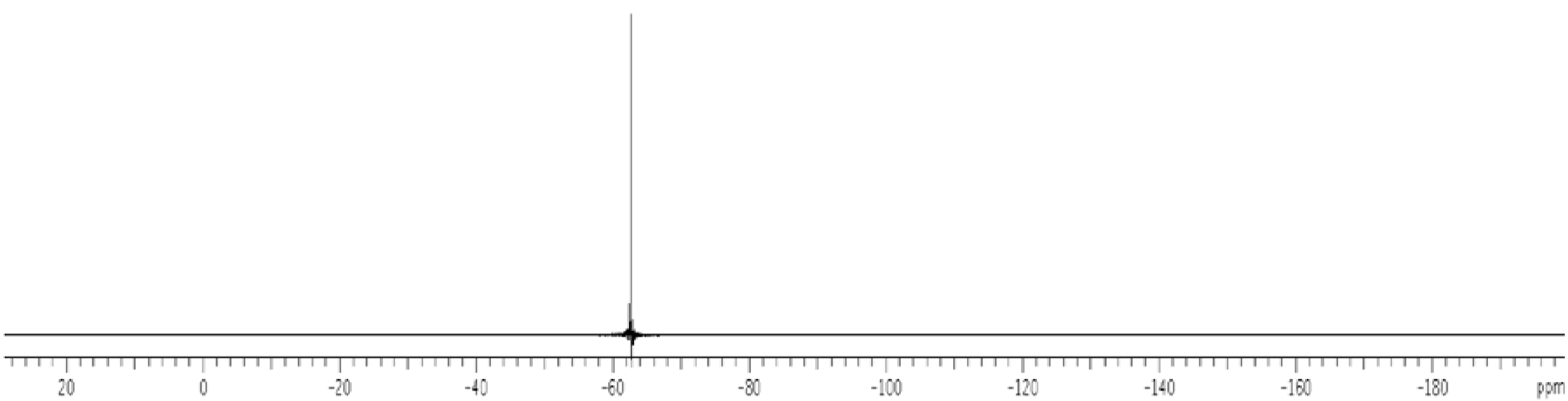
5kn

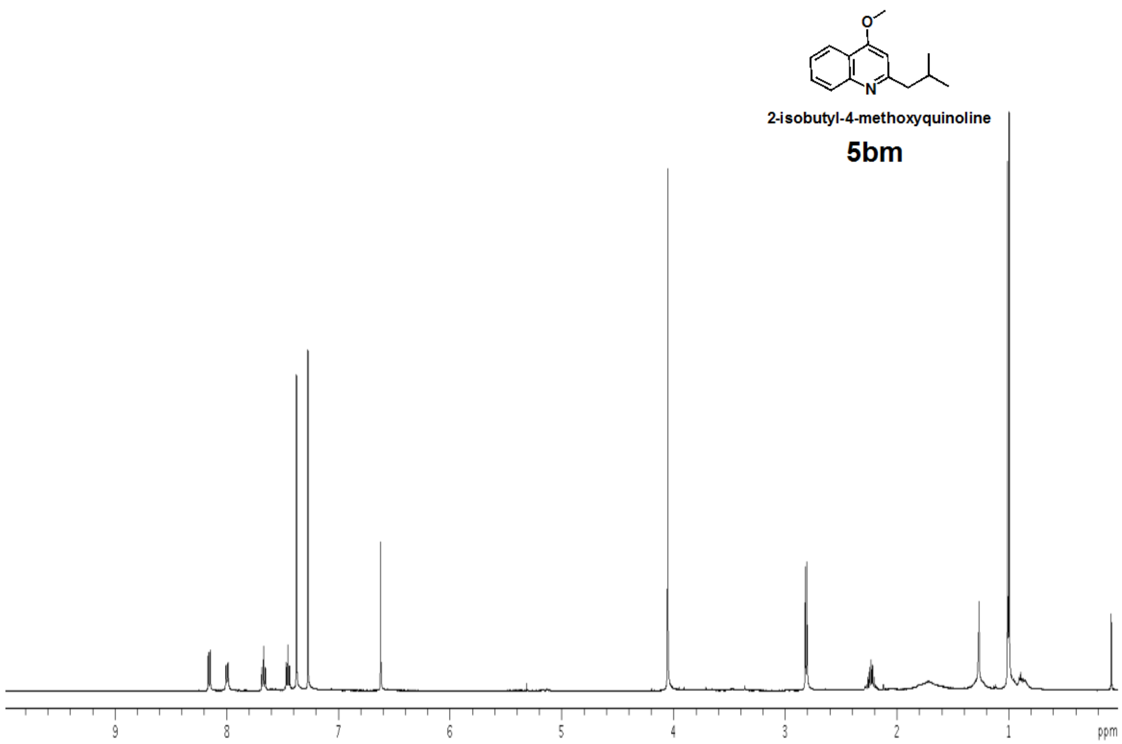


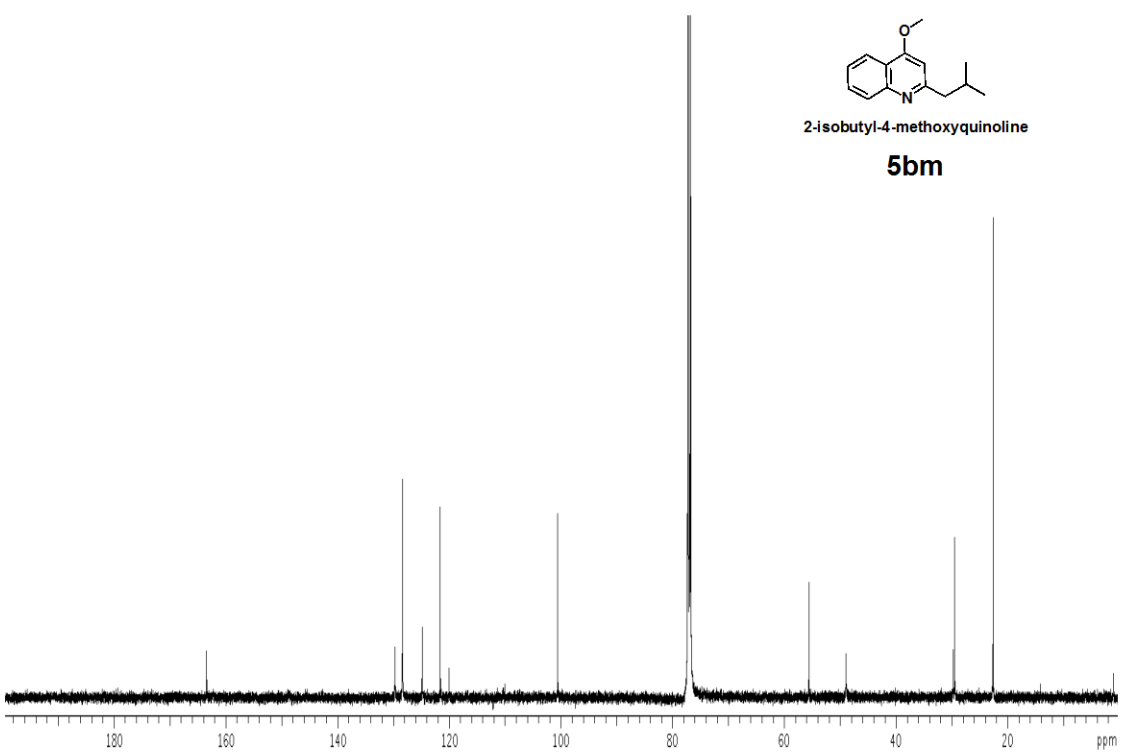


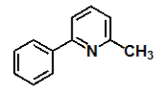
2-(4-(trifluoromethyl)phenyl)pyrazine

5kn



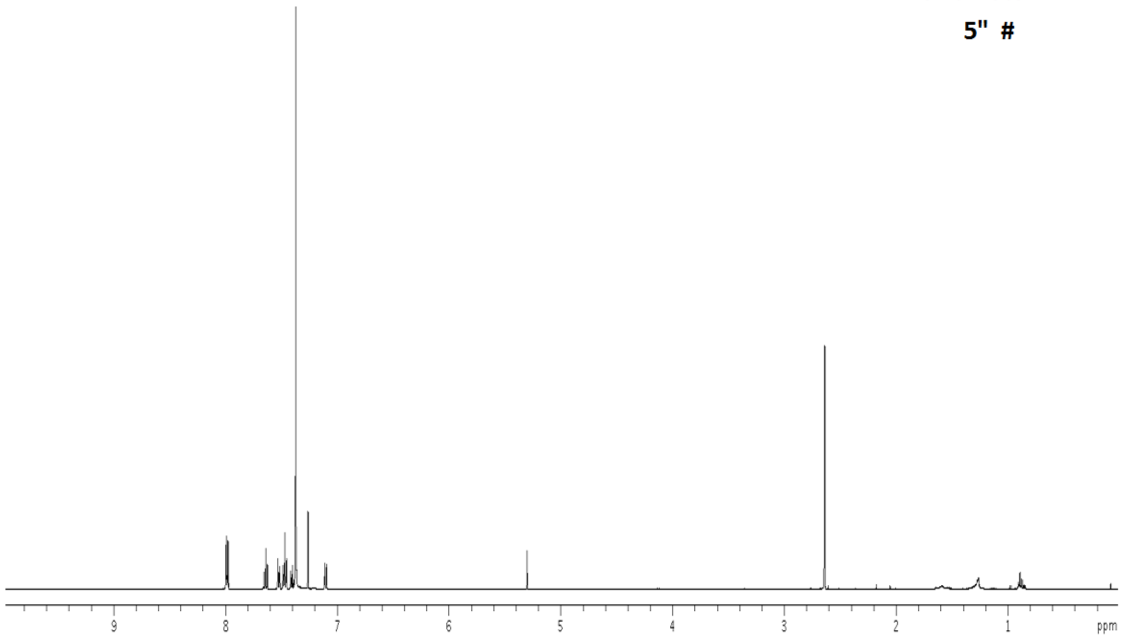

2-isobutyl-4-methoxyquinoline
5bm
9 8 7 6 5 4 3 2 1 ppm

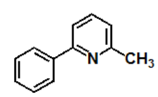

2-isobutyl-4-methoxyquinoline
5bm
180 160 140 120 100 80 60 40 20 ppm



2-methyl-6-phenylpyridine

5'' #





2-methyl-6-phenylpyridine

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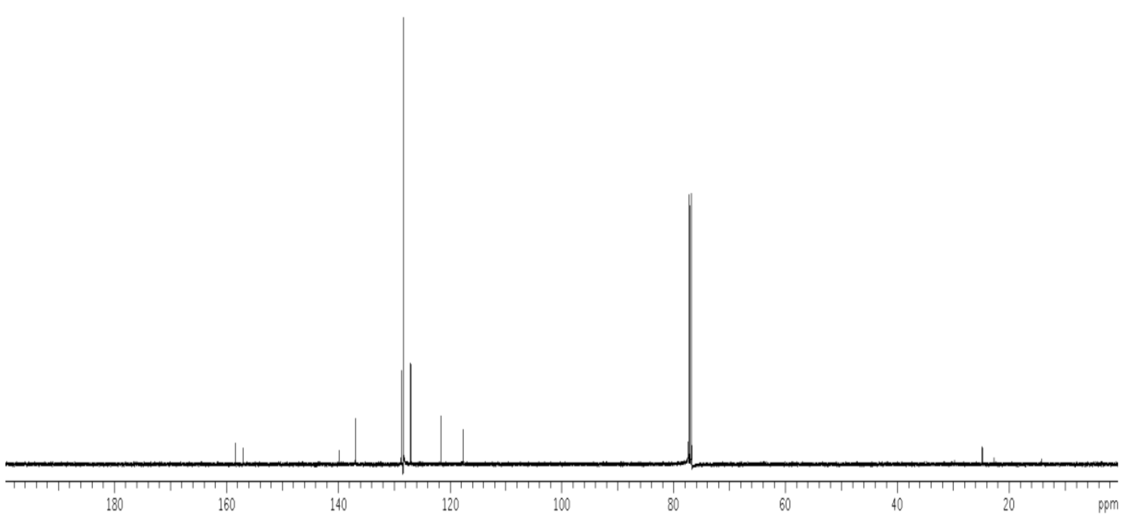
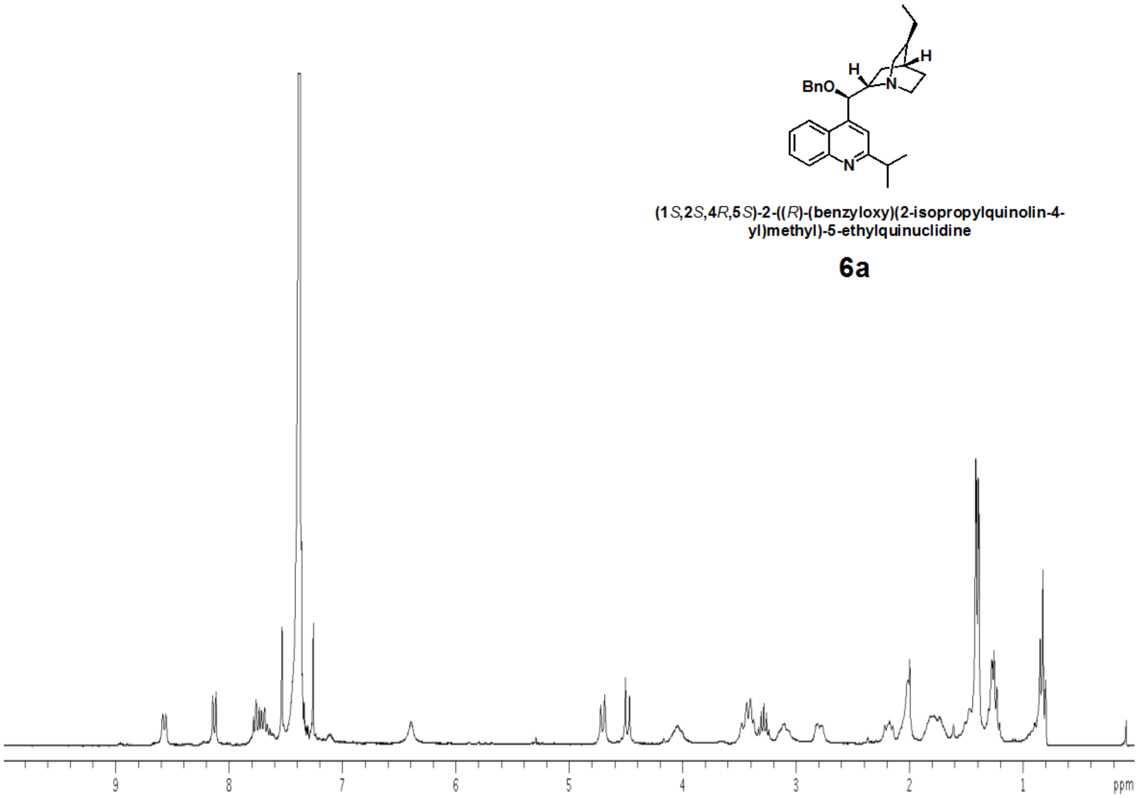
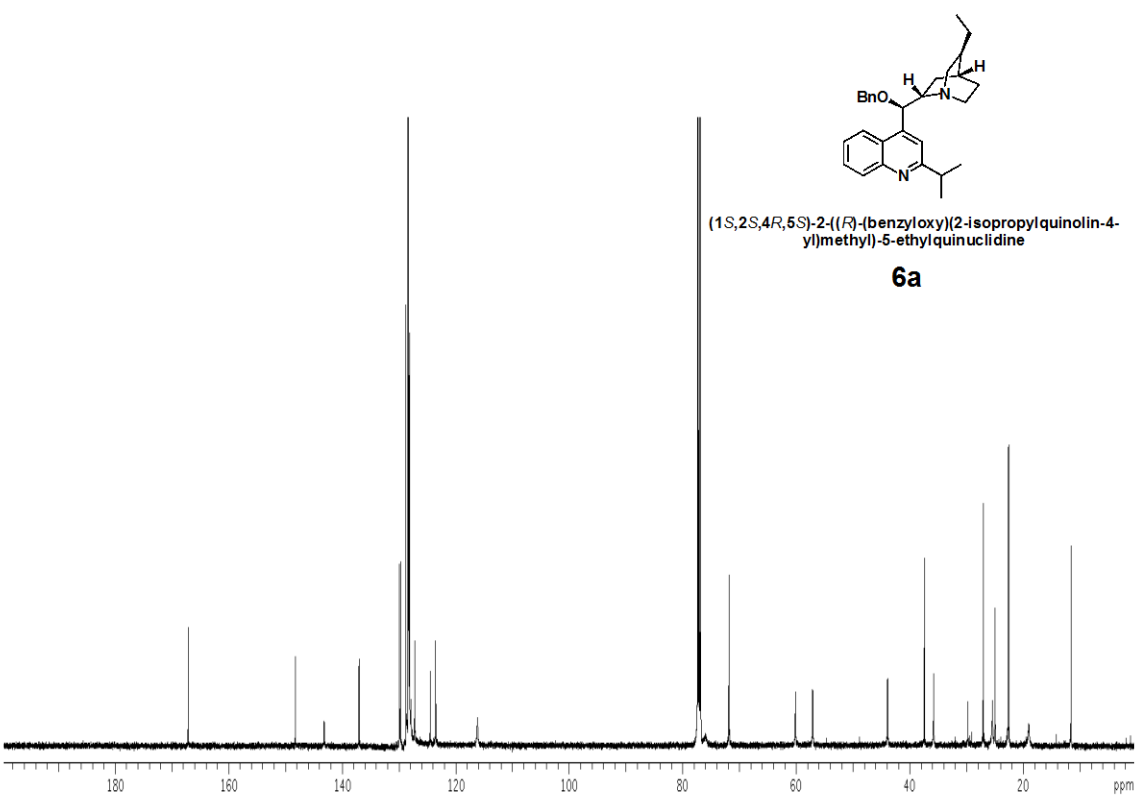




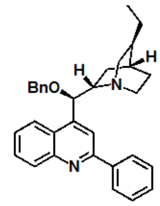
(1*S*,2*S*,4*R*,5*S*)-2-((*R*)-(benzyloxy)(2-isopropylquinolin-4-yl)methyl)-5-ethylquinuclidine

6a



(1*S*,2*S*,4*R*,5*S*)-2-((*R*)-(benzyloxy)(2-isopropylquinolin-4-yl)methyl)-5-ethylquinuclidine

6a



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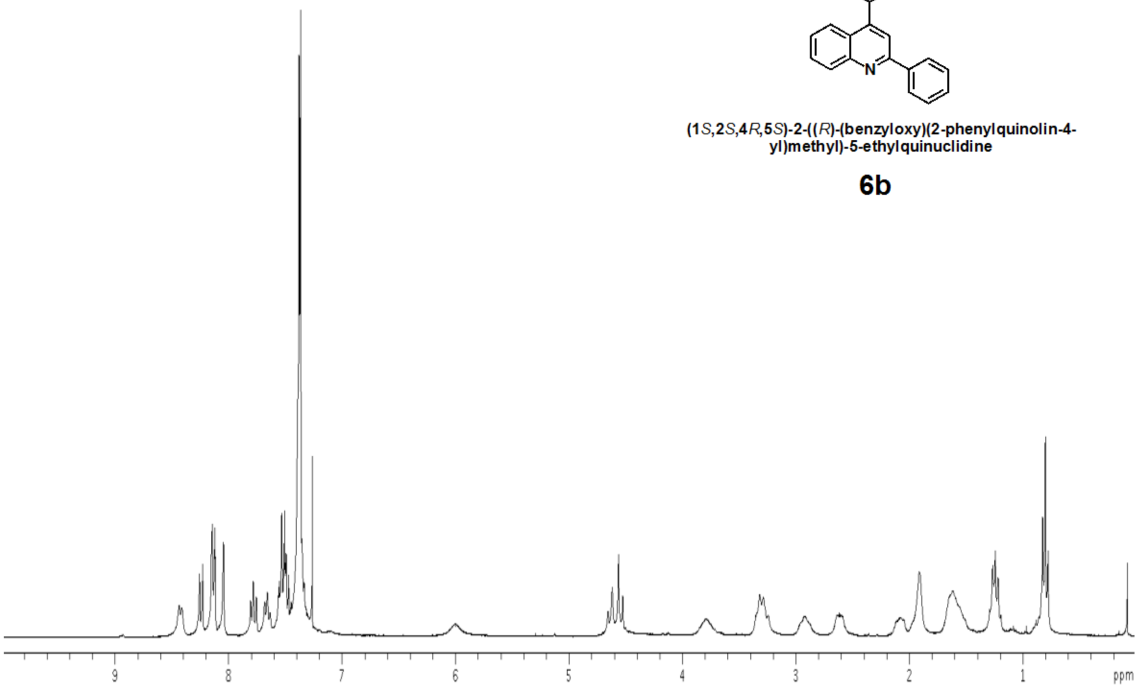
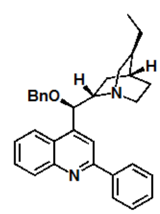
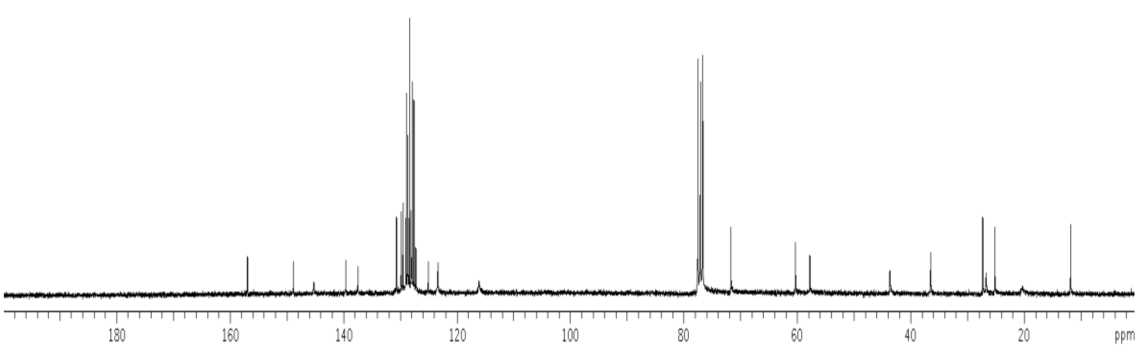
6b

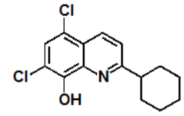




(1*S*,2*S*,4*R*,5*S*)-2-((*R*)-(benzyloxy)(2-phenylquinolin-4-yl)methyl)-5-ethylquinuclidine

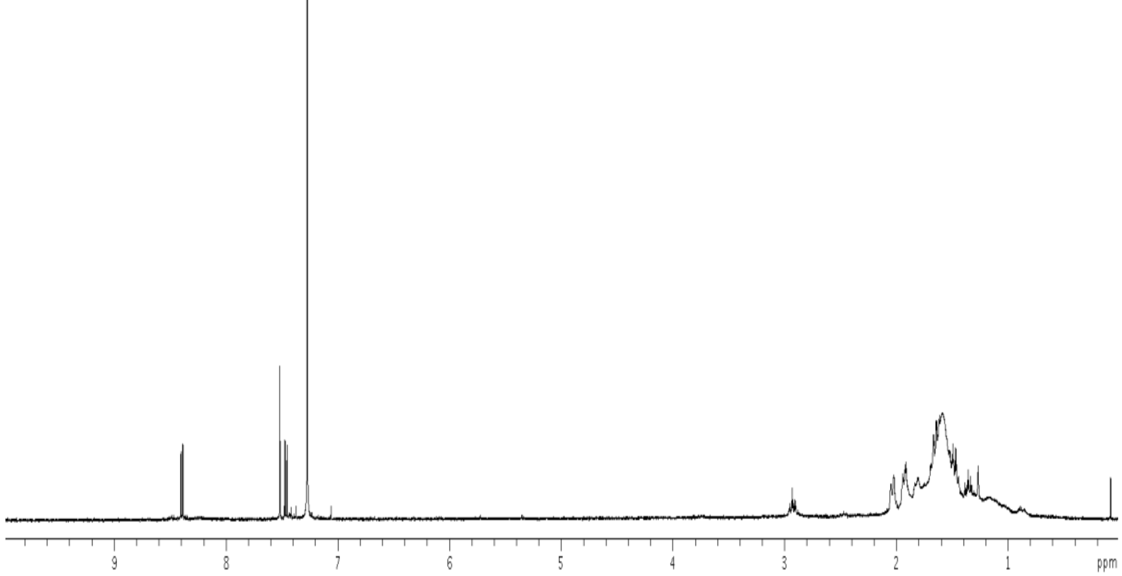
6b

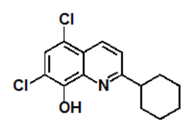




5,7-dichloro-2-cyclohexylquinolin-8-ol

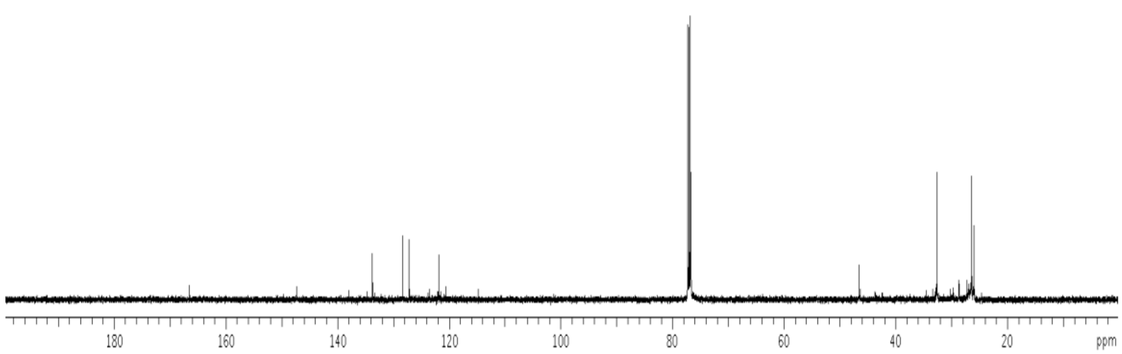
8b

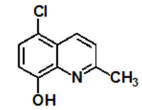




5,7-dichloro-2-cyclohexylquinolin-8-ol

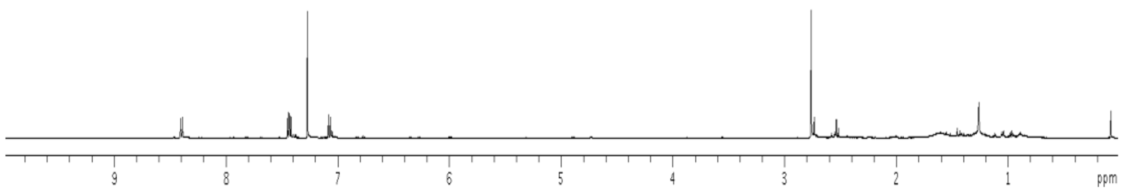
8b

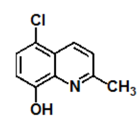




5-chloro-2-methylquinolin-8-ol

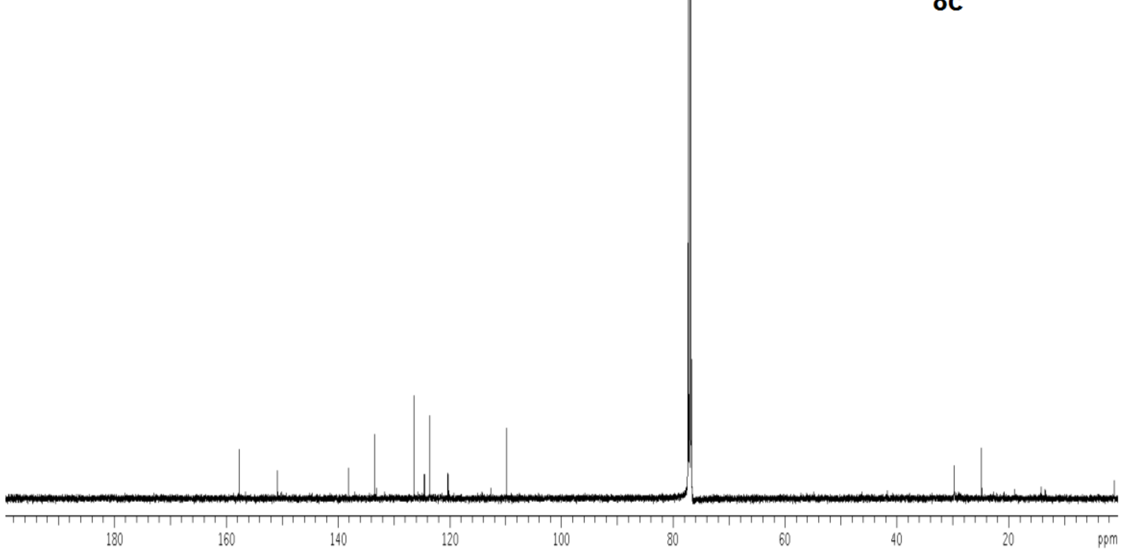
8c

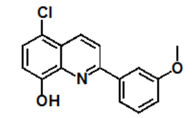




5-chloro-2-methylquinolin-8-ol

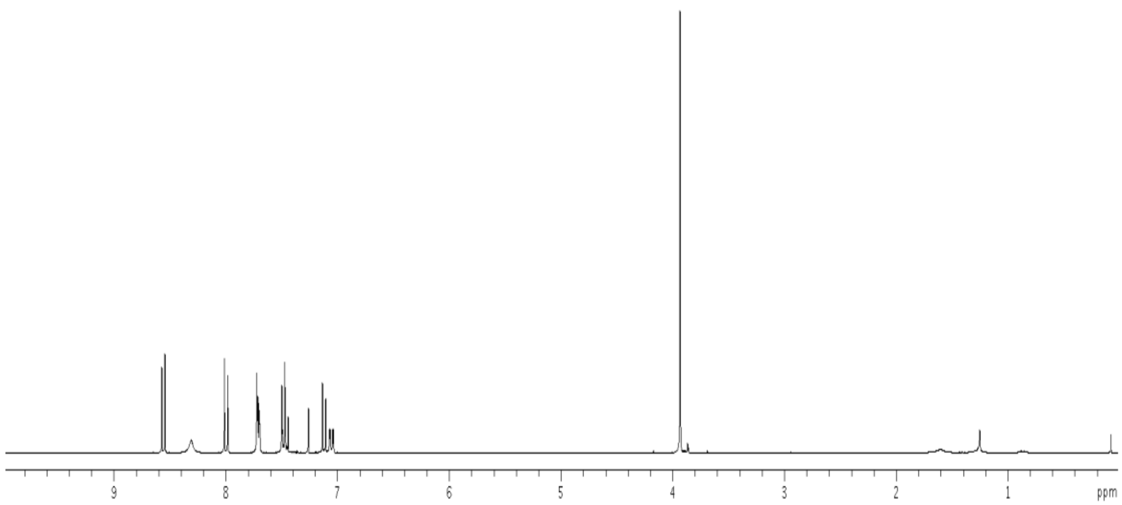
8c

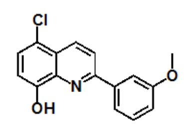




5-chloro-2-(3-methoxyphenyl)quinolin-8-ol

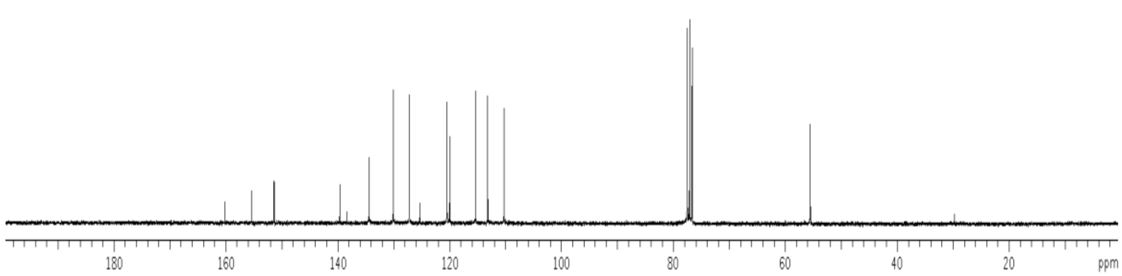
8d

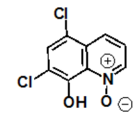




5-chloro-2-(3-methoxyphenyl)quinolin-8-ol

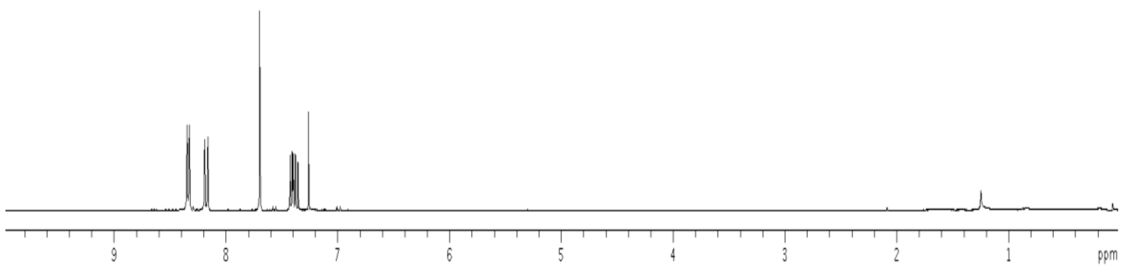
8d

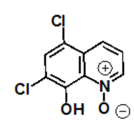




5,7-dichloro-8-hydroxyquinoline 1-oxide

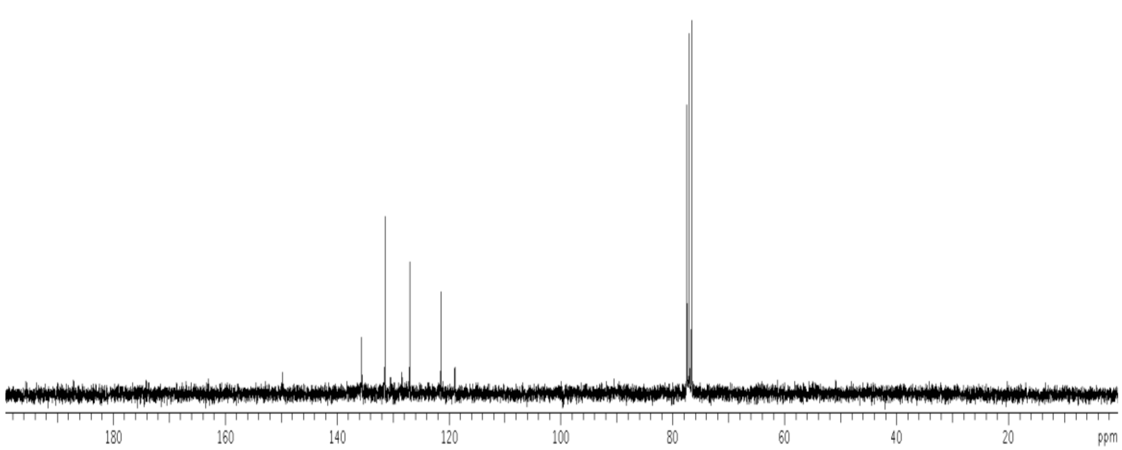
9a

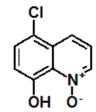




5,7-dichloro-8-hydroxyquinoline 1-oxide

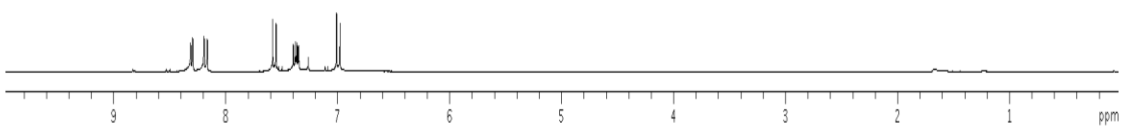
9a

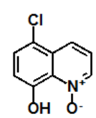




5-chloro-8-hydroxyquinoline 1-oxide

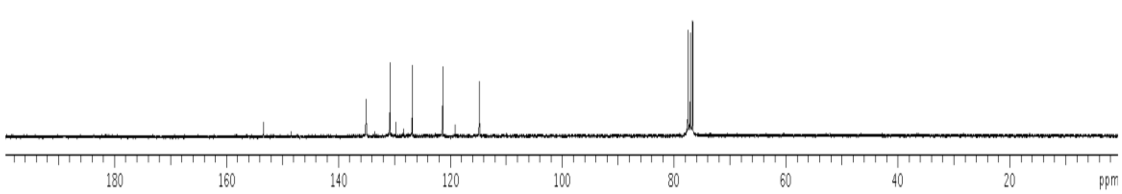
9b

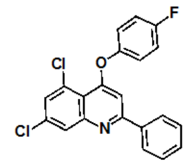




5-chloro-8-hydroxyquinoline 1-oxide

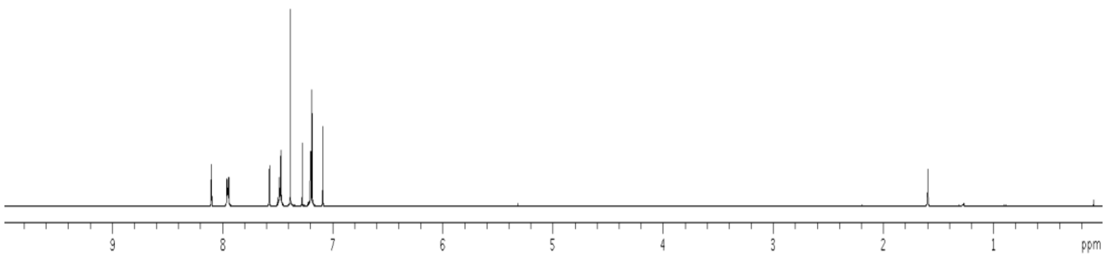
9b

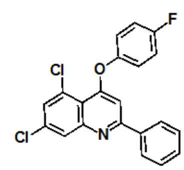




5,7-dichloro-4-(4-fluorophenoxy)-2-phenylquinoline

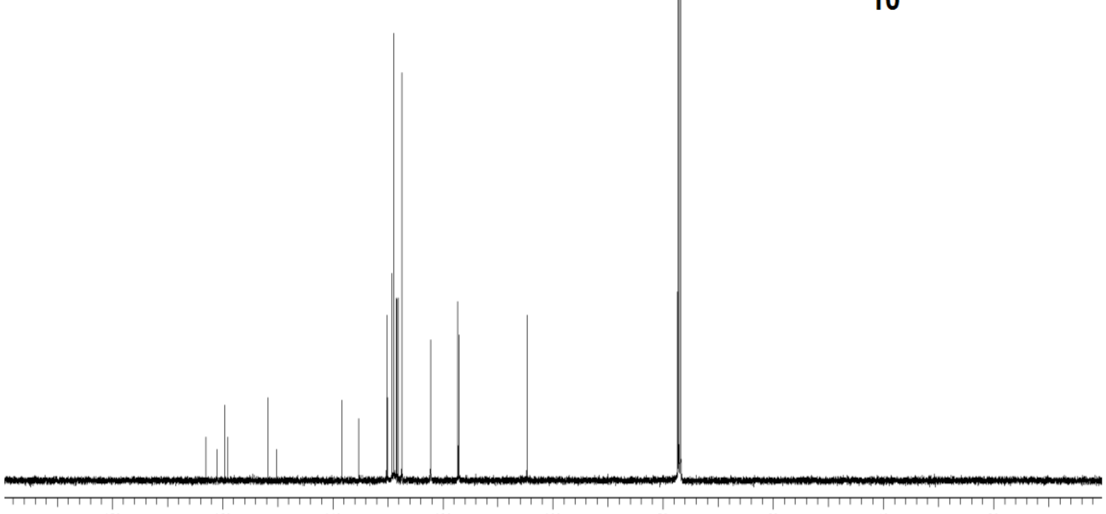
10

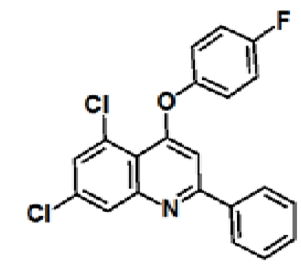




5,7-dichloro-4-(4-fluorophenoxy)-2-phenylquinoline

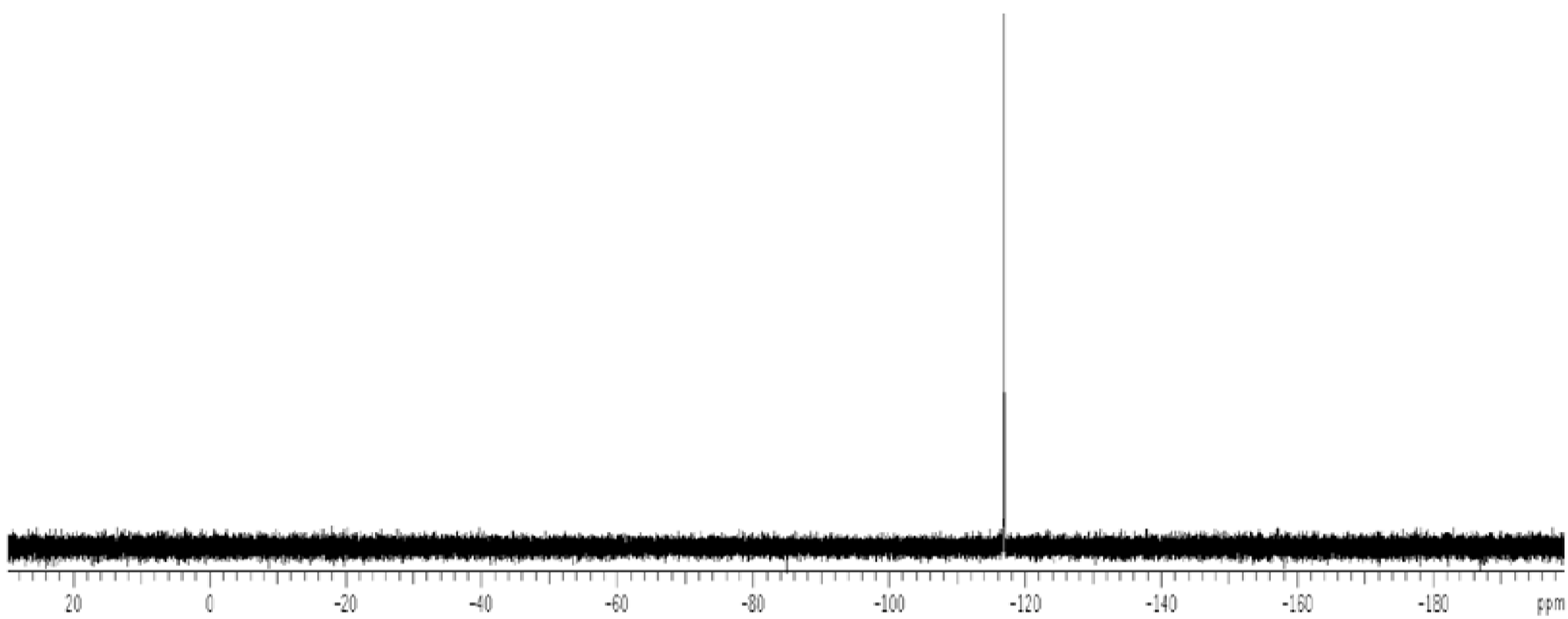
10

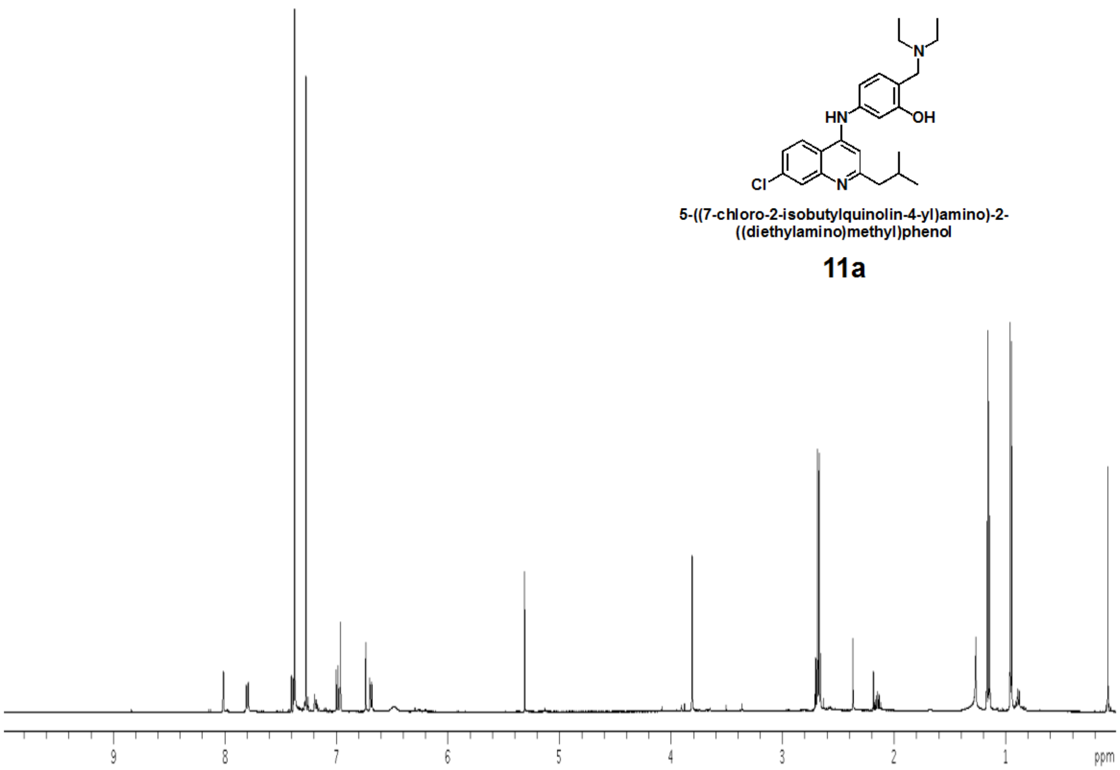


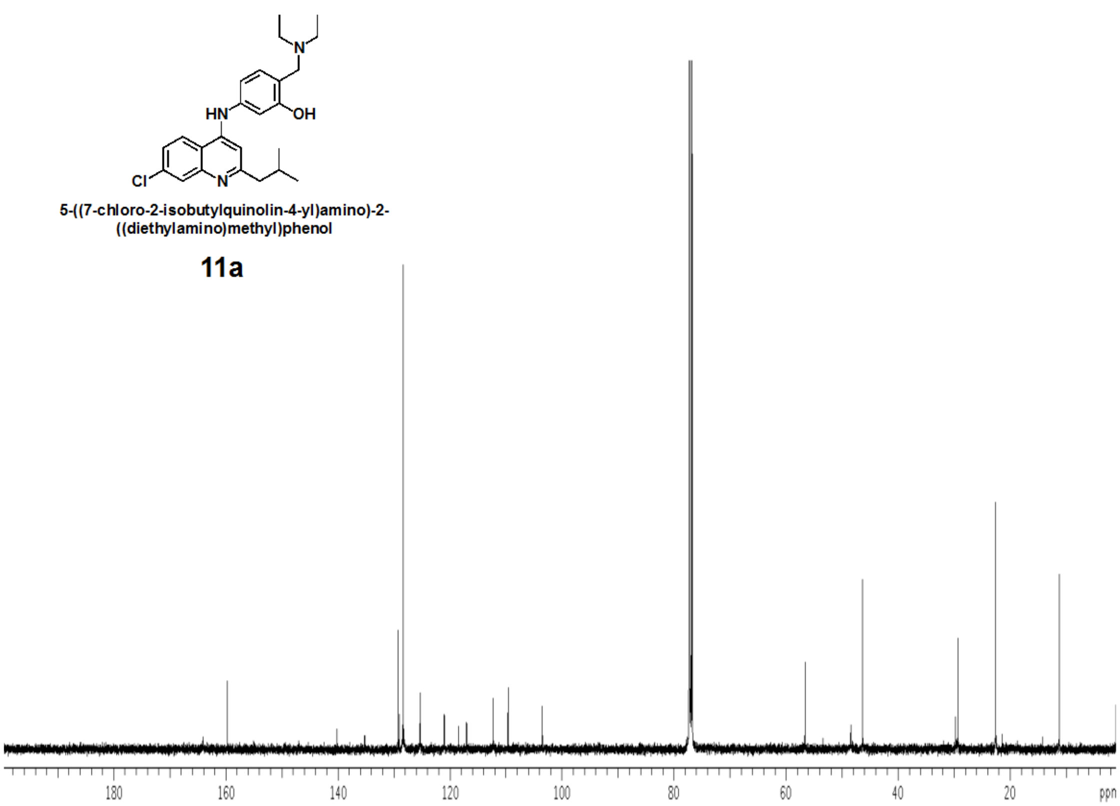


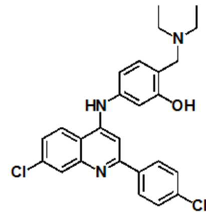
5,7-dichloro-4-(4-fluorophenoxy)-2-phenylquinoline

10



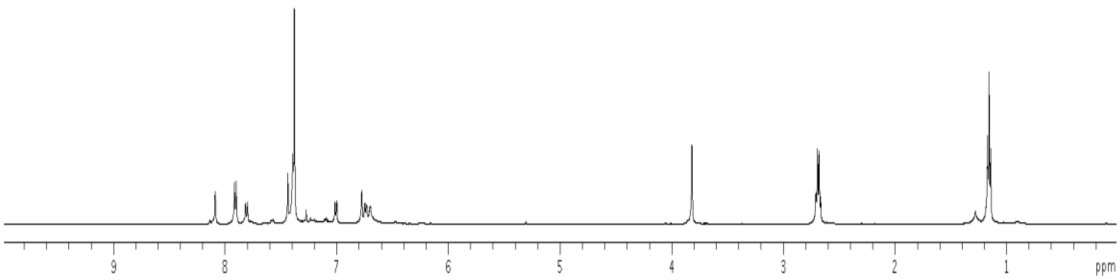

HN
OH
N
Cl
5-((7-chloro-2-isobutylquinolin-4-yl)amino)-2-((diethylamino)methyl)phenol
11a
9
8
7
6
5
4
3
2
1
ppm

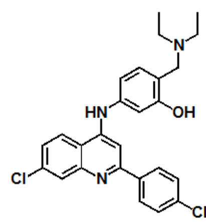

HN
OH
N
Cl
5-((7-chloro-2-isobutylquinolin-4-yl)amino)-2-((diethylamino)methyl)phenol
11a
180
160
140
120
100
80
60
40
20
ppm



5-((7-chloro-2-(4-chlorophenyl)quinolin-4-yl)amino)-2-((diethylamino)methyl)phenol

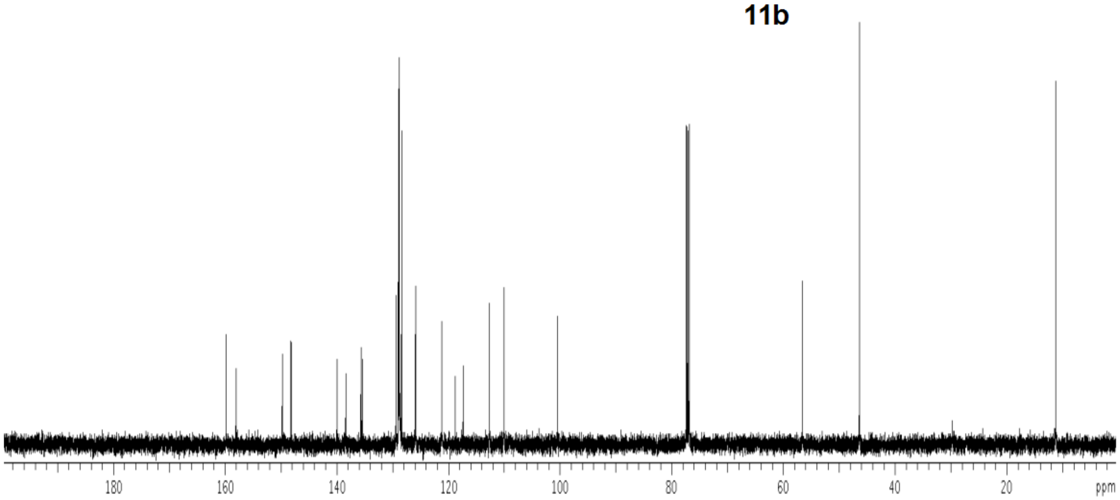
11b

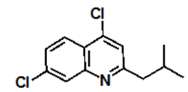




5-((7-chloro-2-(4-chlorophenyl)quinolin-4-yl)amino)-2-((diethylamino)methyl)phenol

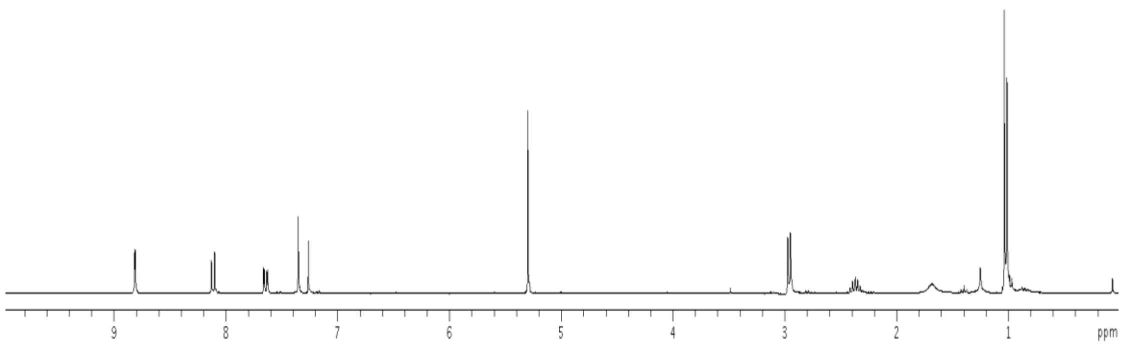
11b

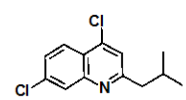




4,7-dichloro-2-isobutylquinoline

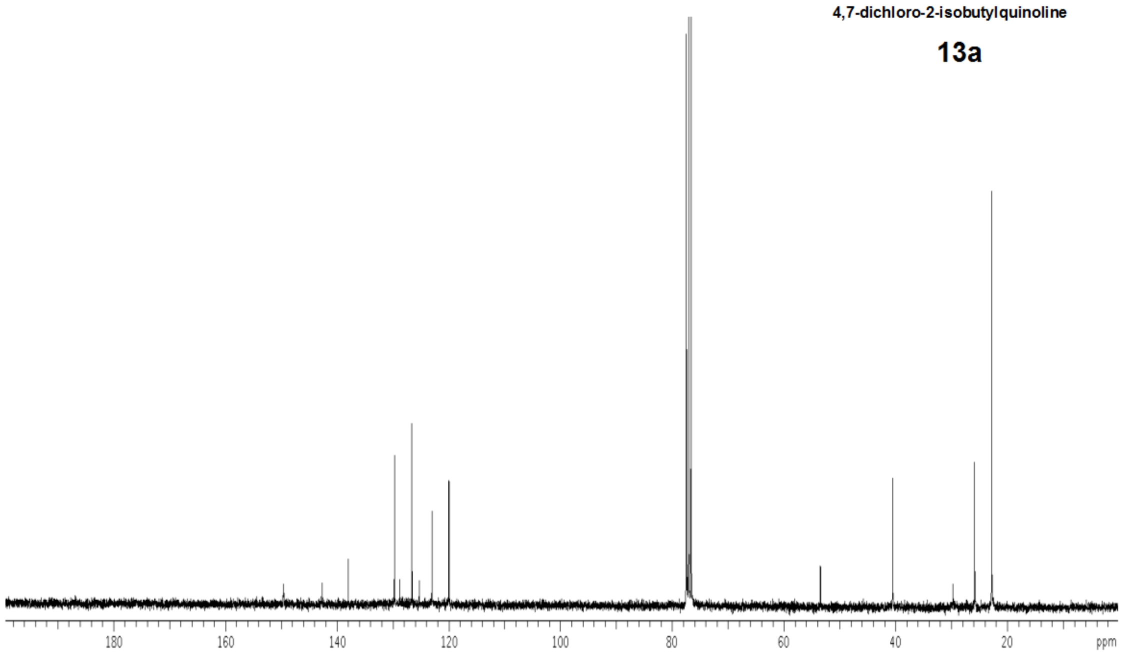
13a

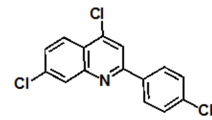




4,7-dichloro-2-isobutylquinoline

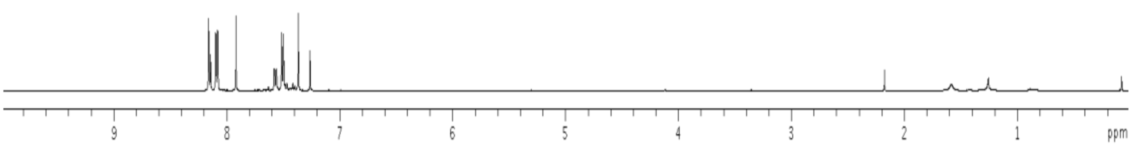
13a

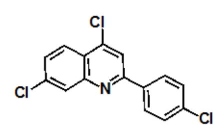




4,7-dichloro-2-(4-chlorophenyl)quinoline

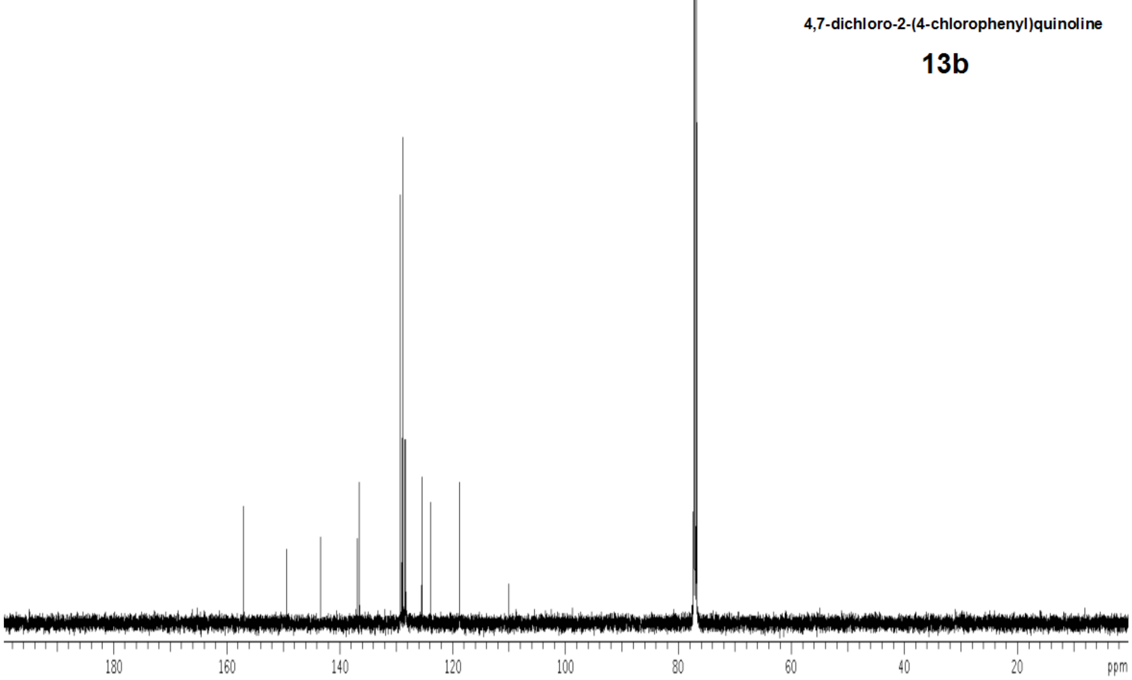
13b#

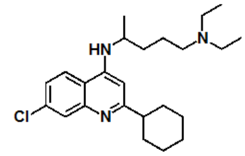




4,7-dichloro-2-(4-chlorophenyl)quinoline

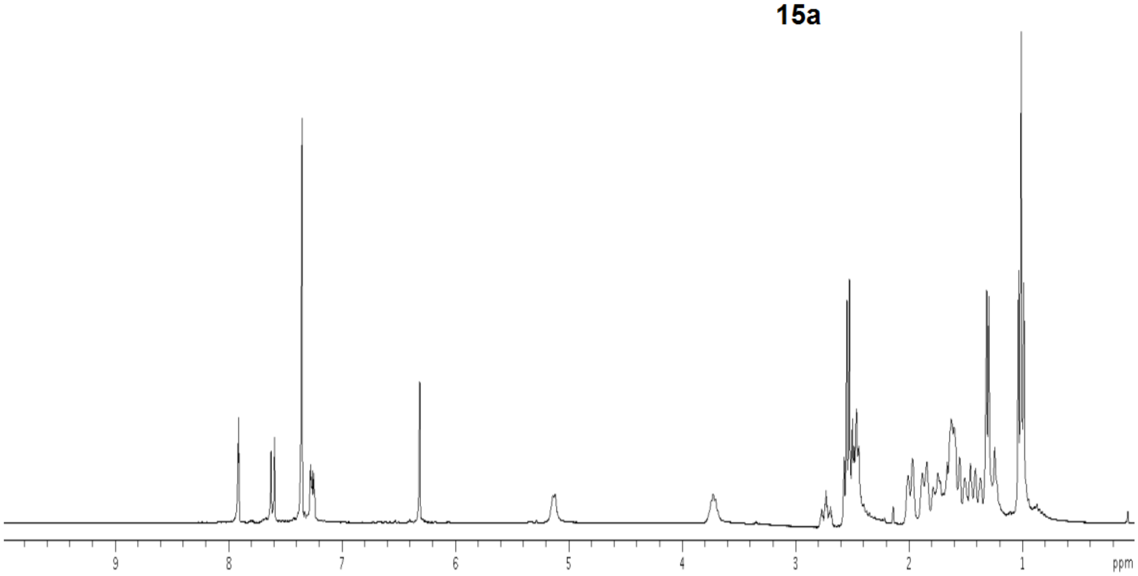
13b

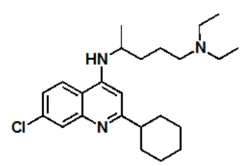




N[4]-(7-chloro-2-cyclohexylquinolin-4-yl)-*N*[1],*N*[1]-diethylpentane-1,4-diamine

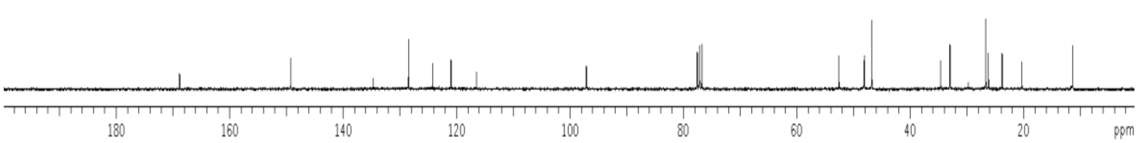
15a

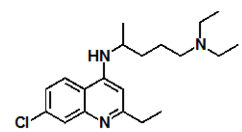




N[4]-(7-chloro-2-cyclohexylquinolin-4-yl)-*N*[1],*N*[1]-diethylpentane-1,4-diamine

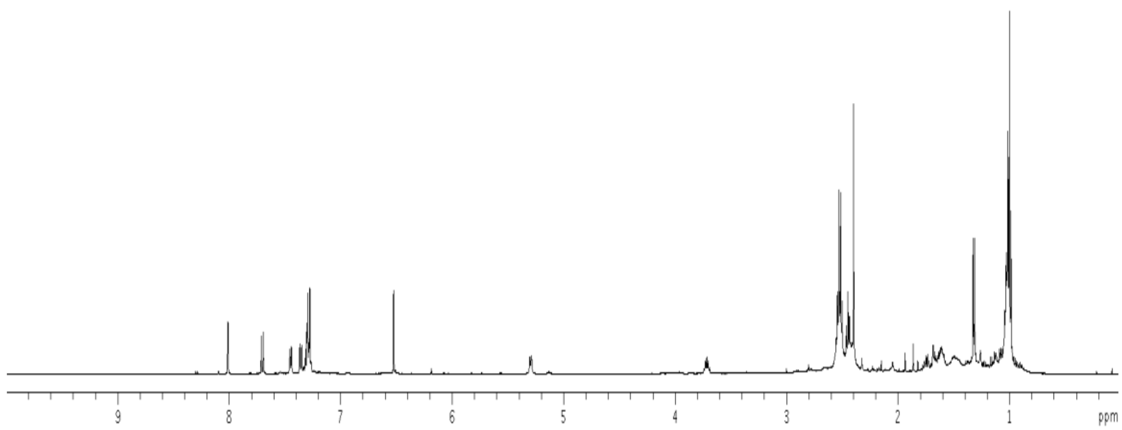
15a

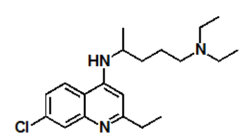




N[4]-(7-chloro-2-ethylquinolin-4-yl)-*N*[1],*N*[1]-diethylpentane-1,4-diamine

15b





N[4]-(7-chloro-2-ethylquinolin-4-yl)-*N*[1],*N*[1]-diethylpentane-1,4-diamine

15b