

Directed *ortho* Metalation – Boronation and Suzuki-Miyaura Cross Coupling of Pyridine Derivatives. A One-pot Protocol to Substituted Azabiaryls

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General Methods. Melting points were obtained with a Fisher Scientific Melting Point Apparatus and are uncorrected. IR spectra were recorded as KBr pellets or as thin films using a BOMEM FT-IR spectrometer. ^1H 200, 300 and 400 MHz and ^{13}C 50, 75.43 and 100 MHz NMR spectra were obtained on a Bruker AC 200, Avance-300, or Avance-400 spectrometer. THF was freshly distilled from sodium benzophenone ketyl under nitrogen whereas toluene and Na_2CO_3 2 M solution were degassed with argon for 1 h under sonication. HN^iPr_2 was freshly distilled from CaH_2 under nitrogen. *n*-Butyllithium was purchased from Aldrich as solution in hexanes, stored in resealable containers, and titrated periodically against *sec*-butanol using 1,10-phenanthroline as indicator.¹ All experiments were carried out under argon in flame-dried glassware, using syringe-septum cap techniques. Flash column chromatography was carried out using Silicycle Silia-P Flash Silica Gel (particle size: 40-63 μm , 60A). The React IR study was carried out with a Mettler Toledo ReaactIRTM 4000 equipped with a SiComp sensor.

***N2,N2*-Diethyl-2-pyridinecarboxamide (5).** A slurry of picolinic acid (10.2 g; 83.3 mmol) in SOCl_2 (100 mL) was stirred for 10 min at rt and DMF (0.32 mL, 4.2 mmol) was added dropwise *via* syringe (*caution: vigorous SO_2 evolution*). The mixture was stirred for 3 h at rt and concentrated *in vacuo* (3 \times PhMe chase to remove residual SOCl_2). The residue was dissolved in dry CH_2Cl_2 (100 mL), cooled to 0 $^\circ\text{C}$ and Et_2NH (34.5 mL, 330 mmol) was added over 10 min. The resulting slurry was stirred overnight

and passed through Celite. The filtrate was poured into water, the layers were separated, and the aqueous layer was back-extracted with CH_2Cl_2 ($\times 3$). The combined organic layer was washed (1N NaOH, water, brine), dried (Na_2SO_4), subjected to filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by bulb-to-bulb distillation (115°C/0.25 mm Hg) to afford 13.1 g (88%) of **5** as a colorless oil whose IR and ^1H NMR spectra were found to be consistent with those reported.²

N2,N2-Diethyl-3-(2-pyridylcarbonyl)-2-pyridinecarboxamide (7). This compound, prepared by a known procedure,² was shown to exhibit spectral data consistent with those reported.

tert-Butyl-6-[(diethylamino)carbonyl]nicotinate (9). A. Methyl 6-[(diethylamino)carbonyl]nicotinate. To a solution of Et_2NH (3.18 mL, 30.8 mmol) in PhMe (100 mL) at 0 °C was added AlMe_3 (30.8 mmol; 15.4 mL of a 2 M solution in heptane), dropwise over 30 min (*caution: methane evolution*). The solution was warmed to rt, stirred (45 min), and slowly added to a suspension of dimethyl 2,5-pyridinedicarboxylate (5.46 g 28.0 mmol) in PhMe (30 mL) at 0 °C. The mixture was then refluxed under argon for 40 h, cooled to 0 °C, and hydrolyzed by slow addition of 0.67 N HCl (46 mL). The mixture was stirred (45 min), the precipitated solids were removed by filtration, and the layers of the biphasic filtrate were separated. The aqueous layer was adjusted to pH 7 with satd Na_2CO_3 , subjected to filtration, and the filtrate was extracted with CH_2Cl_2 ($\times 3$). The combined CH_2Cl_2 extract was washed (20% citric acid, water), dried (Na_2SO_4), subjected to filtration, and the filtrate was concentrated *in vacuo*. The residue was purified *via*

flash chromatography (1:1 EtOAc/hexanes), affording 3.67 g (56%) of methyl 6-[(diethylamino)carbonyl]nicotinate as a yellow oil: IR (film) ν_{\max} 1730, 1638 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.12 (d, 1H, $J = 2.1$ Hz), 8.33 (dd, 1H, $J = 8.0, 2.2$ Hz), 7.60 (d, 1H, $J = 8.0$ Hz), 3.92 (s, 3H), 3.52 (q, 2H, $J = 7.1$ Hz), 3.28 (q, 2H, $J = 7.1$ Hz), 1.22 (t, 3H, $J = 7.1$ Hz), 1.11 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 167.8, 165.3, 158.6, 149.7, 138.1, 126.2, 122.7, 52.7, 43.3, 40.3, 14.4, 12.9; MS (*i*-butane CI) m/z 238 (M+2, 15), 237 (M+H, 100); HRMS calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_3$ 236.1161, found 236.0905.

B. *tert*-Butyl-6-[(diethylamino)carbonyl]nicotinate (9). To a solution of *t*-BuOLi³ (16.0 mmol) in THF (60 mL) at -10 $^{\circ}\text{C}$ was added a solution of methyl 6-[(diethylamino)carbonyl]nicotinate as prepared above (3.42 g; 14.5 mmol) in THF (5 mL) over 15 min. The resulting solution was warmed to rt, aged for 4.5 h, diluted with Et_2O , poured into water, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 ($\times 3$). The combined organic extract was dried (Na_2SO_4), subjected to filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (25% EtOAc/hexanes \rightarrow 1:1 EtOAc/hexanes), affording 3.56 g (88%) of **9** as an orange oil: IR (film) ν_{\max} 1719, 1638 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.08 (dd, 1H, $J = 2.1, 0.8$ Hz), 8.27 (dd, 1H, $J = 7.9, 2.1$ Hz), 7.58 (dd, 1H, $J = 7.9, 0.8$ Hz), 3.53 (q, 2H, $J = 7.1$ Hz), 3.30 (q, 2H, $J = 7.1$ Hz), 1.59 (s, 9H), 1.23 (t, 3H, $J = 7.1$ Hz), 1.11 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 168.0, 163.9, 158.2, 149.7, 137.9, 127.8, 122.6, 82.5, 43.3, 40.3, 28.2, 14.4, 12.9; MS (*i*-butane CI) m/z 280 (M+2, 16), 279 (M+H, 100); HRMS calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_3$ 278.1630, found 278.1622.

***N2,N2*-Diethyl-5-([1-(*tert*-butyl)-1,1-dimethylsilyl]oxymethyl)-2-pyridinecarboxamide (**10**).** To a solution held at $-40\text{ }^{\circ}\text{C}$ of methyl 6-[(diethylamino)carbonyl]nicotinate as prepared above was added a solution of lithium diisopropylaminoborohydride⁴ (25.4 mmol) in THF (10 mL) over 1 h. The resulting mixture was stirred for 30 min, warmed to $0\text{ }^{\circ}\text{C}$ and hydrolyzed with 2N HCl (15 mL). The whole was concentrated *in vacuo*, diluted with 1N NaOH, and exhaustively extracted with CHCl_3 ($20 \times 50\text{ mL}$). The combined organic extract was dried (Na_2SO_4), subjected to filtration, and the filtrate was concentrated *in vacuo*. The residue was dissolved in DMF (30 mL) and to the resulting solution was added Et_3N (3.51 mL; 25.4 mmol), DMAP (259 mg; 2.12 mmol), and a solution of TBSCl (3.84 g; 25.4 mmol) in DMF (10 mL). After stirring for 1 h at rt, the mixture was poured into water and the whole was extracted with CH_2Cl_2 ($\times 3$). The combined organic extract was washed (water, brine), dried (Na_2SO_4), subjected to filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (40% EtOAc/hexanes), affording 5.73 g (84%) of **10** as a waxy, colorless solid: mp $44\text{--}45\text{ }^{\circ}\text{C}$; IR (film) ν_{max} 1635 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 8.53 (d, 1H, $J = 2.1\text{ Hz}$), 7.74 (dd, 1H, $J = 7.9, 2.1\text{ Hz}$), 7.56 (d, 1H, $J = 8.1\text{ Hz}$), 4.79 (s, 2H), 3.57 (q, 2H, $J = 7.1$), 3.36 (q, 2H, $J = 7.1\text{ Hz}$), 1.27 (t, , 3H $J = 7.1\text{ Hz}$), 1.15 (t, 3H, $J = 7.0\text{ Hz}$), 0.95 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (50 MHz, CDCl_3) δ 167.8, 153.3, 145.6, 136.6, 134.0, 122.1, 62.0, 42.6, 39.6, 25.3, 17.7, 13.7, 12.3, 5.9; MS (EI, 70eV) m/z 322 (M^+ , 35), 323 (9), 265 (37), 251 (42); HRMS calcd for $\text{C}_{17}\text{H}_{30}\text{N}_2\text{O}_2\text{Si}$ 322.2077, found 322.2086.

***tert*-Butyl-6-[(diethylamino)carbonyl]-5-hydroxynicotinate (13).** Prepared according to general procedure 1 from **9** (2.99 g; 10.8 mmol), B(O*i*Pr)₃ (7.45 mL; 32.2 mmol), and LDA (12.4 mmol). Oxidative workup (11 mL × 30 wt% H₂O₂, 2 h) and flash chromatography (20% EtOAc/hexanes) afforded 2.51 g (78%) of **13** as a pale yellow oil: IR (film) ν_{max} 3418, 1721, 1624 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 12.35 (bs, 1H), 8.61 (d, 1H, *J* = 2.1 Hz), 7.80 (d, 1H, *J* = 1.8 Hz), 3.96 (q, 2H, *J* = 6.9 Hz), 3.54 (q, 2H, *J* = 6.6 Hz), 1.59 (s, 9H), 1.25 – 1.34 (m, 6H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 168.3, 163.9, 158.1, 139.2, 137.5, 130.7, 126.6, 82.5, 44.9, 43.1, 28.3, 14.6, 12.7 ppm; MS (*i*-butane CI) *m/z* 295 (M+H, 100), 296 (17), 279 (70); HRMS calcd for C₁₅H₂₂N₂O₄ 294.1580, found 294.1573.

***N*2,*N*2-Diethyl-5-([1-(*tert*-butyl)-1,1-dimethylsilyl]oxymethyl)-3-hydroxy-2-pyridine-carboxamide (14).** Prepared according to general procedure 1 from **10** (5.43 g; 16.8 mmol), B(O*i*-Pr)₃ (11.6 mL; 50.4 mmol), and LDA (21.9 mmol). Oxidative workup (10 mL × 30 wt% H₂O₂, 25 min) and flash chromatography (10% EtOAc/hexanes) afforded 5.06 g (89%) of **14** as a colorless oil: IR (film) ν_{max} 3386, 1622 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 12.46 (bs, 1H), 8.04 (d, 1H, *J* = 2.1 Hz), 7.26 (d, 1H, *J* = 2.5 Hz), 4.74 (s, 2H), 4.00 (bs, 2H), 3.55 (bs, 2H), 1.30 (t, 6H, *J* = 7.0 Hz), 0.95 (s, 9H), 0.12 (s, 6H) ppm; ¹³C NMR (50 MHz, CDCl₃) δ 168.8, 158.5, 141.2, 136.5, 133.5, 122.9, 62.3, 25.9, 18.4, -5.3 ppm; MS (EI, 70eV) *m/z* 338 (M+, 45), 293 (28), 267 (44); HRMS calcd for C₁₇H₃₀N₂O₃Si 338.2026, found 338.2025.

3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine-2-carboxylic acid diethylamide (16a). Prepared according to general procedure 2 from **15a** (0.52 g, 2.9 mmol) in 5 mL of THF, B(O^{*i*}Pr)₃ (0.80 mL, 3.5 mmol) and LDA (5.0 mL, 3.5 mmol, 0.7M) to obtain **16a** as a colourless solid (0.180 g, 20 %): mp 76-80 °C (hexanes/CH₂Cl₂); IR (KBr disk) ν_{max} 3450, 3042, 2979, 2948, 1627, 1577, 1464, 1379, 1157, 1026, 708 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 8.52 (dd, 1H, *J* = 4.81 Hz), 8.01 (dd, 1H, *J* = 7.49), 7.33 (dd, 1H, *J* = 7.63 Hz), 4.35 (q, 2H, *J* = 6.99 Hz), 3.69 (q, 2H, *J* = 7.17 Hz), 1.37-1.28 (m, 18H); ¹³C NMR (50 MHz, CDCl₃) δ 168.9, 153.8, 148.7, 139.7, 125.9, 80.8, 44.7, 43.5, 25.2, 13.9, 12.4; LRMS 304 (M⁺, 19), 245 (100), 221 (57), 189 (29), 131 (28), 104 (27), 72 (54); HRMS calculated for C₁₆H₂₅BN₂O₃: 304.1958, found 304.1953.

***N,N*-Diethyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-isonicotinamide (16c).** Prepared according to general procedure 2 from **15c** (0.52 g, 2.9 mmol) in 5 mL of THF, B(O^{*i*}Pr)₃ (0.80 mL, 3.5 mmol) and LDA (5.0 mL, 3.5 mmol, 0.7M) to obtain **16c** as a colourless solid (0.364 g, 41 %): mp 47-48 °C (hexanes/CH₂Cl₂); IR (KBr disk) ν_{max} 2973, 2929, 2854, 2359, 1631, 1458, 1358, 1270, 1164, 1102, 1032, 751 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 9.0 (s, 1), 8.69 (d, 1H, *J* = 5.03), 7.17 (d, 1H, *J* = 4.85), 3.56 (q, 4H, *J* = 7.04 Hz), 3.10 (q, 2H, *J* = 7.12 Hz), 1.32-1.28 (m, 15H), 1.04 (t, 3H, *J* = 7.27 Hz); ¹³C NMR (50 MHz, CDCl₃) δ 209.8, 159.6, 156.4, 120.3, 84.5, 42.9, 39.1, 25.0, 13.8, 12.5; LRMS 304 (M⁺, 15) 303 (36), 246 (100), 245 (45), 203 (88), 175 (93), 159 (67), 131 (91), 103 (27); HRMS calculated for C₁₆H₂₅BN₂O₃: 304.1958, found 304.1956.

3-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (16d). Prepared according to general procedure 2 from **15d** (0.29 g, 3 mmol) in 5 mL of THF, B(O^{*i*}Pr)₃ (1.1 mL, 4.5 mmol) and LDA (6.4 mL, 4.5 mmol, 0.7M) to obtain **16d** as a colourless solid (0.20 g, 30 %): mp 110-115 °C (sublimes, hexanes/CH₂Cl₂); IR (KBr disk) ν_{max} 3399, 3129, 2972, 2930, 2858, 2239, 1475, 1427, 1186, 1150, 1036, 904, 777, 651 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 8.47 (bs, 1H), 8.44 (apparent bdd, 1H, *J* = 2.01, 4.80 Hz), 7.60 (apparent bt, 1H, *J* = 4.67 Hz), 1.37 (s, 1H); ¹³C NMR (50 MHz, CDCl₃) δ 163.1 (d, *J* = 260.16 Hz), 145.2 (d, *J* = 4.58 Hz), 138.4 (d, *J* = 26.70 Hz), 129.8 (d, *J* = 4.58 Hz), 84.9, 25.0; LRMS 224 (M+1, 100), 223 (M+, 30), 180 (13), 139 (6), 93 (4); HRMS calculated for C₁₁H₁₅BFNO₂: 223.1180, found 223.1176.

3-[1,3,6,2]Dioxazaborocan-2-yl-pyridine-2-carboxylic acid diethylamide (17a). Prepared according to general procedure 2 from **15a** (0.52 g, 2.9 mmol) in 5 mL of THF, B(O^{*i*}Pr)₃ (0.80 mL, 3.5 mmol) and LDA (5.0 mL, 3.5 mmol, 0.7M) to obtain **17a** as a colourless solid (0.34 g, 40 %): mp 139-141 °C (hexanes/CH₂Cl₂); IR (KBr disk) ν_{max} 3407, 2993, 2950, 2883, 2110, 1647, 1598, 1458, 1403, 1220, 1105, 1068, 751, 636 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 8.43 (dd, 1H, *J* = 1.72, 4.92 Hz), 8.13 (dd, 1H, *J* = 1.84, 7.51 Hz), 7.23 (m, 1H), 6.40 (bs, 1H), 4.15-3.86 (m, 4H), 3.55 (q, 2H, *J* = 7.13), 3.40-3.30 (m, 2H), 3.20 (q, 2H, *J* = 7.13 Hz), 2.84-2.77 (m, 2H), 1.27 (t, 3H, *J* = 7.13), 1.14 (t, 3H, *J* = 7.13 Hz); ¹³C NMR (50 MHz, CDCl₃) δ 172.8, 159.0, 147.2, 143.1, 123.1, 63.5, 51.0, 43.6, 39.3, 13.2, 12.9; LRMS 291 (M+, 2) 260 (2), 218 (4), 178 (18), 149 (13), 114 (25), 78 (16), 72(100); HRMS calculated for C₁₄H₂₂BN₃O₃: 291.1754, found 291.1763.

4-[1,3,6,2]Dioxazaborocan-2-yl-N,N-diethyl-nicotinamide (17b). Prepared according to general procedure 2 from **15b** (0.5 g, 2.8 mmol) in 5 mL of THF, B(O^{*i*}Pr)₃ (3.36 mmol, 0.77 mL) and LDA (4.80 mL, 3.36 mmol, 0.7M) stock solution to obtain **17b** as a colourless solid (0.30 g, 37 %): mp 132-133 °C (hexanes/CH₂Cl₂); IR (KBr disk) ν_{max} 3471, 2980, 2943, 2881, 2160, 1638, 1594, 1451, 1277, 1221, 1078, 842, 755, 656 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 8.50 (d, 1H, *J* = 4.92 Hz), 8.32 (s, 1H), 7.74 (d, 1H, *J* = 4.67 Hz), 6.29 (bs, 1H), 4.10-3.92 (m, 4H), 3.58-3.48 (m, 4H), 3.23 (q, 2H, *J* = 7.13 Hz), 2.82 (bs, 2H), 1.26 (t, 3H, *J* = 7.14 Hz), 1.12 (t, 3H, *J* = 7.14 Hz); ¹³C NMR (50 MHz, CDCl₃) δ 173.0, 149.0, 145.0, 137.4, 129.5, 63.6, 51.0, 44.0, 39.1, 13.5, 12.9; LRMS 290 (M-1, 1) 260 (4), 218 (7), 178 (15), 177 (20), 114 (50), 106 (45), 86 (56), 72 (100); HRMS calculated for C₁₄H₂₂BN₃O₃: 291.1754, found 291.1755.

3-[1,3,6,2]Dioxazaborocan-2-yl-N,N-diethyl-isonicotinamide (17c). Prepared according to general procedure 2 from **15c** (0.52 g, 2.9 mmol) in 5 mL of THF, B(O^{*i*}Pr)₃ (0.80 mL, 3.5 mmol) and LDA (5.0 mL, 3.5 mmol, 0.7M) to obtain **17c** as a colourless solid (0.50 g, 59 %): mp 162-164 °C (hexanes/CH₂Cl₂); IR (KBr disk) ν_{max} 3403, 2991, 2942, 2874, 2118, 1644, 1595, 1460, 1288, 1220, 1066, 839, 636 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 8.96 (s, 1H), 8.52 (d, 1H, *J* = 4.55 Hz), 6.98 (d, 1H, *J* = 4.48 Hz), 5.98 (bs, 1H), 4.11-3.88 (m, 4H), 3.57-3.17 (m, 6H), 2.88-2.78 (m, 2H), 1.24 (t, 3H, *J* = 7.04), 1.10 (t, 3H, *J* = 7.04 Hz); ¹³C NMR (50 MHz, CDCl₃) δ 172.8, 156.1, 149.2, 148.7, 119.2, 63.7, 63.4, 50.9, 43.5, 38.8, 13.3, 12.8; LRMS 290 (M-1, 1) 260 (8), 218 (10), 178 (34), 177 (30), 114 (100), 107 (61), 106 (46), 72 (93); HRMS calculated for C₁₄H₂₂BN₃O₃: 291.1754, found 291.1755.

2-(3-Fluoro-pyridin-4-yl)-[1,3,6,2]dioxazaborocane (17d). Prepared according to general procedure 2 from **15d** (0.29 g, 3 mmol) in 5 mL of THF, B(O^{*i*}Pr)₃ (1.1 mL, 4.5 mmol) and LDA (6.4 mL, 4.5 mmol, 0.7M) to obtain **17d** as a colourless solid (0.22 g, 35 %): mp 133-135 °C (hexanes/CH₂Cl₂); IR (KBr disk) ν_{\max} 3418, 3280, 2973, 2936, 2860, 2247, 2115, 1658, 1402, 1270, 1201, 1032, 820, 763, 625 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 8.24 (s, 1H), 8.23 (apparent dd, 1H, *J* = 2.30 Hz), 7.42 (apparent t, 1H, *J* = 4.92 Hz), 7.32 (bs, 1H), 3.92-3.68 (m, 4H), 3.26-3.09 (m, 2H), 2.95-2.84 (m, 2H); ¹³C NMR (50 MHz, CDCl₃) δ 163.3 (d, *J* = 247.96 Hz), 144.3 (d, *J* = 3.82 Hz), 136.1 (d, *J* = 28.22 Hz), 129.0 (d, *J* = 8.39 Hz), 62.7, 50.7; LRMS 211 (M+1, 61), 210 (M+, 26), 138 (3), 114 (100), 70 (16); HRMS calculated for C₉H₁₂BFN₂O₂: 210.0976, found 210.0974.

4-[1,3,6,2]Dioxazaborocan-2-yl-pyridine-3-sulfonic acid diethylamide (17e). Prepared according to general procedure 2 from **15e** (0.54 g, 2.52 mmol) in 5 mL of THF, B(O^{*i*}Pr)₃ (0.70 mL, 3.0 mmol) and LDA (4.3 mL, 3.0 mmol, 0.7M) to obtain **17e** as a colourless solid (0.33 g, 40 %): mp 133-135 °C (hexanes/CH₂Cl₂); IR (KBr disk) ν_{\max} 3385, 2986, 2943, 2882, 2360, 2115, 1673, 1643, 1458, 1317, 1207, 1158, 1066, 937, 851, 783, 679 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 8.75 (s, 1H), 8.61 (d, 1H, *J* = 4.92 Hz), 8.02 (d, 1H, *J* = 4.67 Hz), 6.52 (bs, 1H), 4.19-4.07 (m, 2H), 4.01-3.91 (m, 2H), 3.69-3.37 (m, 6H), 3.00-2.88 (m, 2H), 1.23 (t, 6H, *J* = 7.14 Hz); ¹³C NMR (50 MHz, CDCl₃) δ 151.7, 146.6, 139.9, 131.4, 63.2, 51.9, 42.7, 42.3, 14.8, 14.3; LRMS 328 (M+1, 1) 296 (4), 225 (7), 199 (14), 192 (16) 149 (6), 114 (36), 93 (68), 72(100); HRMS calculated for C₁₃H₂₂BN₃O₄S: 296.1240, found 296.12441.

Diethyl carbamic acid 4-[1,3,6,2]dioxazaborocan-2-yl-pyridin-3-yl ester (17f).

Prepared according to general procedure 2 (with the exception that the reaction was performed at $-78\text{ }^{\circ}\text{C}$ with slow warm up to $0\text{ }^{\circ}\text{C}$ over 30 min) from **15f** (0.51 g, 2.63 mmol) in 5 mL of THF, $\text{B}(\text{O}^i\text{Pr})_3$ (0.72 mL, 3.15 mmol) and LDA (4.5 mL, 3.15 mmol, 0.7M) to obtain **17f** as a colourless solid (0.49 g, 61 %): mp $156\text{--}159\text{ }^{\circ}\text{C}$ (hexanes/ CH_2Cl_2); IR (KBr disk) ν_{max} 3380, 2992, 2867, 1690, 1464, 1408, 1277, 1201, 1064, 751 cm^{-1} ; ^1H NMR δ = 8.37 (d, 1H, J = 4.68 Hz), 8.16 (s, 1H), 7.64 (d, 1H, J = 4.67 Hz), 6.06 (bs, 1H), 4.17-3.94 (m, 4H), 3.51 (q, 2H, J = 7.13 Hz), 3.39 (q, 2H, J = 7.14 Hz), 3.29-3.12 (m, 2H), 2.89-2.77 (m, 2H), 1.30 (t, 3H, J = 7.14 Hz), 1.22 (t, 3H, J = 7.13 Hz); ^{13}C NMR δ = 155.8, 151.9, 145.9, 142.9, 129.9, 63.6, 51.0, 42.0, 41.9, 13.7, 13.4; LRMS 308 ($\text{M}+1$, 1), 276 (9), 213 (10), 194(11), 189(14), 175 (43), 114(83), 100 (100), 96 (65), 72 (100). HRMS calculated for $\text{C}_{14}\text{H}_{22}\text{BN}_3\text{O}_4$: 307.1737, found 307.1725.

N,N-Diethyl-4-phenyl-nicotinamide (18).⁵

A mixture of N,N-Diethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-nicotinamide (**16b**) (0.1266 g 0.42 mmol), iodobenzene (0.5 mmol, 0.056 mL), Na_2CO_3 (2.1 mmol, 2M solution in H_2O , degassed), and $\text{Pd}(\text{PPh}_3)_4$ (5 mol%, 0.024 g) in freshly distilled toluene was refluxed for 18 hours. Upon cooling to room temperature a saturated solution of NH_4Cl (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The crude material was purified by flash column chromatography using hexanes/ethyl acetate (1:1) as the

solvent system to give a yellow oil (0.094 g, 88 %). IR (thin film) ν_{\max} 3461, 3054, 2979, 2936, 2879, 1627, 1546, 1452, 1289, 1107, 838, 744 cm^{-1} ; ^1H NMR δ = 8.66 (d, 1H, J = 4.92 Hz), 8.61 (s, 1H), 7.55-7.39 (m, 5H), 7.35 (d, 1H, J = 5.17 Hz), 3.75-2.73 (m, 4H), 0.97 (t, 3H, J = 7.13 Hz), 0.75 (t, 3H, J = 7.13 Hz) ppm; ^{13}C NMR δ = 168.1, 150.1, 148.1, 146.0, 137.3, 132.3, 129.2, 128.7, 128.5, 123.6, 42.6, 38.9, 13.6, 12.1 ppm; LRMS 254 (M^+ , 10), 253 (56), 182 (100), 154 (59), 126 (60), 77 (45); HRMS calculated for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$: 254.1419, found 254.1412.

3-(4-Methoxy-phenyl)-pyridine-2-carboxylic acid diethylamide (19a). Prepared according to representative procedure 3 from **15a** (0.5 g, 2.8 mmol) and 4-bromoanisole (0.56g, 3.08 mmol). Flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 19.65/0.35) of the crude residue and Kugelrohr distillation (150 $^\circ\text{C}$ /0.13 mmHg) afforded **19a** (62% yield) as clear oil: IR (thin film) ν_{\max} 1637 cm^{-1} ; ^1H NMR (400 MHz, CD_3Cl) δ 8.58 (bs, 1H), 7.72 (d, 1H, J = 8 Hz), 7.44 (d, 1H, J = 8 Hz), 7.36 (dd, 2H, J = 8.0, 4.8 Hz), 6.94 (d, 2H, J = 8 Hz), 3.83 (s, 3H), 3.43 (q, 2H, J = 7.2 Hz), 2.88 (q, 2H, J = 7.2 Hz), 1.04 (t, 3H, J = 7.2 Hz), 0.84 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 168.3, 159.7, 153.4, 147.6, 137.1, 133.9, 130.0, 129.4, 123.5, 114.0, 55.2, 42.4, 38.6, 13.4, 12.2; EI MS m/z 284 (M^+ , 61), 269 (5), 255, (3), 213 (40), 212 (22), 185 (64), 184 (44); 72 (100); HRMS calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_2$, 284.1525, found 284.1534.

3-(4-Cyano-phenyl)-pyridine-2-carboxylic acid diethylamide (19b). Prepared according to representative procedure 3 from **15a** (0.5 g, 2.8 mmol) and 4-bromobenzonitrile (0.56 g, 3.08 mmol). Flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 19.75/0.25) and

recrystallization (hexanes/EtOAc) afforded **19b** (71% yield) as colourless needles: mp 140.5-142 °C (hexanes/EtOAc); IR (KBr disk) ν_{max} 2223, 1632 cm^{-1} ; ^1H NMR (400 MHz, CD_2Cl_2) δ 8.63 (dd, 1H, $J = 4.8, 1.6$ Hz), 7.77 (dd, 1H, $J = 8.0, 1.6$ Hz), 7.72 (d, 2H, $J = 8$ Hz), 7.60 (d, 2H, $J = 8.8$ Hz), 7.43 (dd, 1H, $J = 8.0, 4.8$ Hz), 3.38 (q, 2H, $J = 7.2$ Hz), 2.93 (q, 2H, $J = 7.2$ Hz), 0.99 (t, 3H, $J = 7.22$ Hz), 0.91 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.0, 154.3, 149.5, 142.6, 137.8, 133.2, 132.8, 130.1, 124.3, 119.0, 112.6, 43.1, 39.3, 12.9, 12.5; MS m/z 280 ($M+1$, 6), 279 (34), 264, (6), 207 (22), 179 (94), 100 (7), 72 (100); HRMS calcd for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}$ 279.1372, found 279.1377.

3-(2,4-Dimethoxy-phenyl)-pyridine-2-carboxylic acid diethylamide (19c). Prepared according to representative procedure 3 from **15a** (0.5 g, 2.8 mmol) and 1-bromo-2,4-dimethoxybenzene (0.67 g, 3.08 mmol). Flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 19.6/0.4) of the crude residue and distillation (170 °C / 0.6 mmHg) afforded **19c** (37% yield) as a thick clear oil: IR (film) ν_{max} 1636 cm^{-1} ; ^1H NMR (300 MHz, CD_2Cl_2) δ 8.53 (dd, 1H, $J = 4.8, 1.5$ Hz), 7.73 (d, 1H, $J = 7.8, 1.5$ Hz), 7.35 (dd, 1H, $J = 7.8, 4.8$ Hz), 7.21 (d, 1H, $J = 9.0$ Hz), 6.55 (m, 2H), 3.86 (s, 3H), 3.75 (s, 3H), 3.36 (q, 2H, $J = 7.2$ Hz), 3.04 (q, 2H, $J = 7.2$ Hz), 1.03 (t, 3H, $J = 7.2$ Hz); 0.96 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.4, 161.9, 158.2, 152.7, 148.5, 145.0, 132.7, 132.4, 121.2, 118.2, 105.0, 99.0, 55.94, 55.90, 42.7, 38.7, 14.0, 12.5; MS m/z 314 (M^+ , 46), 283 (12), 243, (47), 214 (100), 199 (57), 184 (44), 156 (24); HRMS calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_3$ 314.1630, found 314.1632.

3-(4-Nitrophenyl)-pyridine-2-carboxylic acid diethylamide (19d). Prepared according to representative procedure 3 from **15a** (0.5 g, 2.8 mmol) and 1-bromo-4-nitrobenzene (0.622 g, 3.08 mmol). Flash chromatography (Hexanes/EtOAc 4/1) of the crude residue and recrystallization (Hexanes/CH₂Cl₂) furnished **19d** (37% yield) as pale yellow plates: mp 127-128 °C (hexanes/EtOAc); IR (KBr disk) ν_{max} 1628, 1512, 1351 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.69 (dd, 1H, *J* = 4.7, 1.5 Hz), 8.28 (d, 2H, *J* = 8.8 Hz), 7.79 (d, 1H, *J* = 7.9, 1.5 Hz), 7.69 (d, 2H, *J* = 8.8 Hz), 7.46 (1H, dd, *J* = 7.9, 4.7 Hz), 3.44 (q, 2H, *J* = 7.0 Hz), 2.99 (q, 2H, *J* = 7.0 Hz), 1.05 (t, 3H, *J* = 7.3 Hz), 0.96 (t, 3H, *J* = 7.04 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 167.5, 153.6, 149.2, 147.7, 143.9, 137.4, 132.4, 129.8, 123.9, 123.7, 42.7, 39.0, 13.6, 12.3; MS *m/z* 299 (M⁺, 16), 269 (14), 228 (8), 227 (11), 200 (20), 199 (35), 72 (100); HRMS calcd for C₁₆H₁₇N₃O₃ 299.1270, found 299.1275.

N,N-diethyl-4-(4-methoxyphenyl)nicotinamide (19e). Prepared according to representative procedure 3 from **15b** (0.5 g, 2.8 mmol) and 4-bromoanisole (0.56 g, 3.08 mmol). Flash chromatography (EtOAc/MeOH 9/1) and Kugelrohr distillation (125 °C/0.4 mmHg) afforded **20e** (71% yield) as a clear oil: IR (film) ν_{max} 1621, 1244 cm⁻¹; ¹H NMR (400.3 MHz, CDCl₃) δ 8.63 (d, 1H, *J* = 4.8 Hz), 8.57 (s, 1H), 7.47 (d, 2H, *J* = 8.4 Hz), 7.33 (d, 1H, *J* = 4.8 Hz), 6.95 (d, 1H, *J* = 8.4 Hz), 3.84 (s, 3H), 3.67-3.78 (m, 1H), 3.07-3.16 (m, 1H), 2.83-2.92 (m, 1H), 2.65-2.73 (m, 1H), 1.04 (t, 3H, *J* = 7.2 Hz), 0.76 (t, 3H, *J* = 7.2 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 168.3, 160.4, 149.9, 148.0, 145.4, 131.7, 129.9, 129.5, 123.2, 114.2, 55.4, 42.5, 38.8, 13.5, 12.2; MS *m/z* 284 (M⁺, 47), 283 (85), 269 (4), 255 (6), 212 (100), 184 (6); HRMS calcd for C₁₇H₁₉N₂O₂, (M-H) 283.1447, found 283.1451.

4-(3,4-dimethoxyphenyl)-N,N-diethylnicotinamide (19f). Prepared according to representative procedure 3 from **15b** (0.5 g, 2.8 mmol) and 1-bromo-3,4-dimethoxybenzene (0.67 g, 3.08 mmol). Flash chromatography (EtOAc/MeOH 9/1) afforded **19f** (42% yield) as yellow oil: IR (film) ν_{max} 1617, 1204 cm^{-1} ; ^1H NMR (400.3 MHz, CDCl_3) δ 8.57 (s, 1H), 8.54 (d, 1H, $J = 5.2$ Hz), 7.30 (d, 1H, $J = 5.2$ Hz), 7.22 (m, 1H), 6.50 (m, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 3.60-3.80 (m, 1H), 2.95-2.65 (m, 3H), 0.90 (t, 3H, $J = 7.2$ Hz), 0.83 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 168.3, 161.5, 157.2, 149.0, 147.7, 143.3, 132.8, 131.7, 125.7, 118.6, 104.4, 98.6, 55.4, 55.3, 42.3, 38.5, 13.7, 12.2; MS m/z 314 (M^+ , 54), 313 (60), 299 (4), 283 (50), 242 (100), 212 (100), 184 (6); HRMS calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_3$ (M-H) 313.1552, found 313.1550.

4-(4-cyanophenyl)-N,N-diethylnicotinamide (19g). Prepared according to representative procedure 3 from **15b** (0.5 g, 2.8 mmol) and 4-bromo-benzonitrile (0.56 g, 3.08 mmol). Recrystallization of the crude mixture afforded **19g** (73% yield) as colourless needles: mp 118-119 $^{\circ}\text{C}$ (Hexanes/EtOAc). IR (KBr disk) ν_{max} 2212, 1618 cm^{-1} ; ^1H NMR (400.3 MHz, CDCl_3) δ 8.72 (d, 1H, $J = 5.2$ Hz), 8.64 (s, 1H), 7.73 (d, 2H, $J = 6.4$ Hz), 7.64 (d, 2H, $J = 6.4$ Hz), 7.34 (d, 1H, $J = 5.2$ Hz), 2.7-3.9 (bm, 4H), 0.980 (t, 3H, $J = 6.8$ Hz), 0.824 (t, 3H, $J = 6.8$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 167.3, 150.4, 148.0, 143.9, 141.7, 132.5, 131.7, 129.3, 123.2, 118.2, 113.0, 42.7, 38.9, 13.7, 12.1; MS m/z 279 (M^+ , 37), 278 (100), 264, (4), 250 (9), 207 (81), 179 (31); HRMS calcd for $\text{C}_{17}\text{H}_{16}\text{N}_3\text{O}$ (M-H) 278.1293, found 278.1294.

N,N-Diethyl-4-(3-methoxy-phenyl)-nicotinamide (19h). Prepared according to representative procedure 3 from **15b** (1.5 g, 8.4 mmol) and 3-bromoanisole (1.73 g, 9.24 mmol). Flash chromatography (EtOAc/MeOH 9.65/0.35) afforded **19h** (57% yield) as a clear oil: IR (film) ν_{\max} 1631, 1579, 1433, 1219 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.66 (d, 1H, $J = 5.1$ Hz), 8.60 (s, 1H), 7.38-7.31 (m, 2H), 7.11-7.06 (m, 2H), 6.99-6.94 (m, 1H), 3.83 (s, 3H), 3.65-3.90 (bs, 1H), 3.20-3.65 (m, 3H), 0.99 (t, 3H, $J = 4.2$ Hz), 0.78 (t, 3H, $J = 4.2$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 168.0, 159.7, 150.0, 147.9, 145.8, 138.5, 131.9, 129.8, 123.4, 120.8, 114.8, 113.8, 55.4, 42.5, 38.7, 13.5, 12.0; MS m/z 284 (M, 26), 283 (74), 213 (17), 212 (100), 185 (12), 169 (27); HRMS calcd for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_2$ (M-H) 283.1447, found 283.1436.

3-(2,4-Dimethoxy-phenyl)-N,N-diethyl-isonicotinamide (19i). Prepared according to representative procedure 3 from **15c** (0.5 g 2.8 mmol) and 1-bromo-2,4-dimethoxybenzene (0.67 g, 3.08 mmol). Flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 19.75/0.25) of the crude mixture (156 °C/0.13 mmHg) followed by Kugelrohr distillation afforded **19i** (33% yield) as colourless oil: IR (thin film) ν_{\max} 3483, 1628; ^1H NMR (400 MHz, CD_2Cl_2) δ 8.56 (s, 1H), 8.52 (d, 1H, $J = 4.8$ Hz), 7.22 (dd, 1H, $J = 4.8, 0.8$ Hz), 7.16 (dd, 1H, $J = 7.6, 0.8$ Hz), 6.51-6.53 (m, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 3.5-3.7 (bm, 1H), 2.6-3.2 (bm, 3H), 0.87 (t, 3H, $J = 7.2$ Hz), 0.85 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CD_2Cl_2) δ : 168.4, 161.9, 158.1, 152.7, 148.5, 145.0, 132.7, 130.7, 121.2, 118.2, 104.9, 98.9, 55.94, 55.89, 42.7, 38.7, 14.0, 12.5; EI MS (m/z): 314 (M^+ , 90), 313 (92); 283 (53), 242, (47), 227 (63), 191 (100); HRMS calcd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_3$ (M+H) 315.1709, found 315.1716.

3-(4-Cyano-phenyl)-N,N-diethyl-isonicotinamide (19k). Prepared according to representative procedure 3 from **15c** (0.5 g, 2.8 mmol) and 4-bromo-benzonitrile (0.56 g, 3.08 mmol). Flash chromatography (CH₂Cl₂/MeOH 19.75/0.25) followed by recrystallization afforded **19k** (75% yield) as colourless needles: mp 112-113 °C (hexanes/EtOAc); IR (KBr disk) ν_{max} 3406, 2224, 1636; ¹H NMR (400 MHz, CDCl₃) δ 8.73 (d, 1H, *J* = 5.1 Hz), 8.7 (s, 1H), 7.74 (d, 2H, *J* = 8.4 Hz), 7.64 (d, 2H, *J* = 8.8 Hz), 7.32 (s, 1H, *J* = 4.8 Hz), 3.70-2.70 (bm, 4H), 0.97 (t, 3H, *J* = 7.2 Hz), 0.84 (t, 3H, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 167.4, 150.2, 143.7, 141.0, 132.7, 131.6, 129.9, 121.2, 118.6, 112.6, 42.7, 38.9, 13.8, 12.3; MS *m/z* 279 (M⁺, 55), 278 (75), 264 (3), 250 (14), 207, (100), 179 (35), 152 (32); HRMS calcd for C₁₇H₁₇N₃O 279.1372, found 279.1367.

3-(3-Chloro-phenyl)-N,N-diethyl-isonicotinamide (19l). Prepared according to representative procedure 3 from **15c** (0.5 g, 2.8 mmol) and 1-bromo-3-chlorobenzene (0.59 g, 3.08 mmol). Flash chromatography (CH₂Cl₂/MeOH 19.7/0.3) followed by recrystallization (hexanes/EtOAc) afforded **19l** (61% yield) as colourless needles: mp 73-75 °C (hexanes); IR (KBr disk) ν_{max} 3489, 1632; ¹H NMR (400 MHz, CD₂Cl₂) δ 8.65-8.63 (m, 2H), 7.47-7.49 (m, 1H), 7.38-7.40 (m, 3H), 7.26 (dd, 1H, *J* = 4.8, 0.8 Hz), 3.60-3.90 (bm, 1H), 2.65-3.15 (bm, 3H), 0.96 (t, 3H, *J* = 7.2 Hz), 0.80 (t, 3H, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 167.9, 150.6, 150.0, 144.2, 138.7, 134.9, 132.3, 130.6, 129.3, 128.9, 127.8, 121.4, 43.0, 39.1, 13.9, 12.3; MS *m/z* 290 (16), 289 (28), 288 (M⁺, 50), 287

(65), 259 (10), 218 (31), 216 (100), 190 (10), 188 (29); HRMS calcd for $C_{16}H_{16}N_2OCl$ (M-H) 287.0951, found 287.0947.

3-(2-Diethylcarbamoyl-phenyl)-N,N-diethyl-isonicotinamide (19m). Prepared according to representative procedure 3 from **15c** (0.5 g, 2.8 mmol) and 2-Bromo-N,N-diethylbenzamide (0.79 g, 3.08 mmol). Flash chromatography (hexanes / Et₂O) of the crude residue and recrystallization (hexanes/ Et₂O) afforded **19m** (67% yield) as colourless needles: mp 110-111 °C; IR (KBr disk) ν_{\max} 1628; ¹H NMR (400 MHz, CD₂Cl₂) δ 8.56 (d, 1H, J = 5.8 Hz), 8.47 (s, 1H), 7.34-7.45 (m, 4H), 7.22 (d, 1H, J = 4.8 Hz), 2.80-3.90 (bm, 8H), 1.90 (t, 3H, J = 7.2 Hz), 1.04 (t, 3H, J = 7.0), 0.95 (t, 3H, J = 7.0 Hz), 0.88 (t, 3H, J = 7.0 Hz); ¹³C NMR (400 MHz, CD₂Cl₂) δ 169.9, 168.0, 150.7, 149.3, 144.9, 137.7, 134.1, 132.1, 131.3, 129.0, 128.5, 127.0, 121.4, 43.4, 43.0, 39.0, 38.9, 14.2, 14.0, 12.5, 12.4; MS m/z 353 (54), 352 (50), 282 (25), 281 (25), 253 (11), 183 (42), 182 (100), 100 (13), 72 (35); HRMS calcd for $C_{21}H_{27}N_3O_2$ 353.2103, found 353.2099.

N,N-Diethyl-3-thiophen-2-yl-isonicotinamide (19n). Prepared according to representative procedure 3 from **15c** (0.5 g, 2.8 mmol) and 2-bromothiophene (0.50 g, 3.08 mmol). Flash chromatography (EtOAc/Et₃N 99/1) of the crude residue afforded **19n** (85% yield) as a colourless oil: IR (thin film) ν_{\max} 1630 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.75 (s, 1H), 8.60 (d, 1H, J = 5.2 Hz), 7.51 (dd, 1H, J = 3.2, 1.6 Hz), 7.39 (dd, 1H, J = 5.2, 3.2 Hz), 7.29 (dd, 1H, J = 5.2, 1.2 Hz), 7.24 (d, 1H, J = 5.2 Hz), 3.70 (bm, 1H), 3.20 (bs, 1H), 2.83 (m, 2H), 1.070 (t, 3H, J = 6.8 Hz), 0.76 (t, 3H, J = 7.2 Hz); ¹³C

NMR (100 MHz, CDCl₃) δ 168.1, 149.7, 148.5, 143.1, 136.4, 128.2, 127.8, 126.4, 124.4, 121.0, 42.4, 38.7, 13.4, 12.2; MS m/z 260 (M⁺, 75), 245 (3), 231 (17), 189 (42), 188 (100), 161 (87), 160 (58); HRMS calcd for C₁₄H₁₆N₂OS 260.0983, found 260.0985.

Representative Procedure 5 for the One-Pot DoM – Boronation – Suzuki-Miyaura Cross Coupling of 15g. 3-Chloro-4-(4-methoxy-phenyl)-pyridine (19o).

A stock solution of LDA (0.7 M) was prepared as in representative procedure 3. (Experimental Section) A 50 mL flame-dried round bottom flask was charged with **15g** (0.5 g, 4.4 mmol), THF (5 mL) and B(O^{*i*}Pr)₃ (0.91 mL, 4.84 mmol). To this solution cooled to -78 °C, LDA (6.91 mL, 4.8 mmol), prepared as in representative procedure 2, was added and the mixture was stirred at -78 °C for 2 hours. Pinacol (0.62 g, 5.28 mmol) was added and the mixture was allowed to reach rt and was stirred for 1 hour. The solvent was completely evaporated *in vacuo* and Pd(PPh₃)₄ (0.255 g, 0.22 mmol, 5 % mol) and 4-bromoanisole (0.905 g, 4.84 mmol) were added with care to minimize exposure of the mixture to air. After flushing briefly with argon, a water condenser was fitted to the flask and a degassed 2 M aqueous solution of Na₂CO₃ (11 mL, 22 mmol) and 10 mL of degassed toluene were added through a septum sealing the top of the condenser. The mixture was refluxed for 12 h, cooled, and extracted with EtOAc (6 x 10 mL). The combined organic extract was washed with brine (40 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Kugelrohr distillation of the residue (150 °C/0.20 mmHg) furnished 0.460 g (3.3 mmol, 48%) of **19o** as colourless flakes: mp 82-85 °C (of bulb-to-bulb distilled material which crystallized); IR (KBr disk) ν_{max} 1613, 1517, 1474, 1251, 1046, 814 cm⁻¹; ¹H NMR (400.3 MHz, CDCl₃) δ 8.67 (s, 1H), 8.51 (d, 1H, *J* = 5.2 Hz),

7.47 (d, 2H, $J = 8.4$ Hz), 7.30 (d, 1H, $J = 5.2$ Hz), 7.03 (d, 2H, $J = 8.8$ Hz), 3.89 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.1, 150.1, 147.7, 147.1, 130.3, 130.1, 128.7, 125.2, 113.8, 55.3; MS m/z 221 ($M+2$, 28) 219 (M^+ , 100), 204 (15); HRMS calcd for $\text{C}_{12}\text{H}_{10}\text{NOCl}$ 219.0451, found 219.0454.

4-(3-Chloro-pyridin-4-yl)-benzonitrile (19p). Prepared according to representative procedure 5 from **15g** (0.5 g, 4.4 mmol) and 4-bromobenzonitrile (0.88 g, 4.84 mmol). Flash chromatography (EtOAc/MeOH 8/2) and recrystallization (hexanes/ EtOAc) yielded **19p** (55% yield) as colourless crystals: mp 136-138 °C (hexanes/ EtOAc); IR (KBr disk) ν_{max} 2227, 1587, 1474, 1400 cm^{-1} ; ^1H NMR (400.3 MHz, CDCl_3) δ 8.75 (s, 1H), 8.61 (d, 1H, $J = 3.6$ Hz), 7.81 (d, 2H, $J = 8.0$ Hz), 7.61 (d, 2H, $J = 8.0$), 7.30 (d, 1H, $J = 4.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 150.2, 148.0, 145.6, 140.8, 132.2, 129.75, 129.67, 124.7, 118.2, 112.8; MS m/z 216 ($M+2$, 31) 214 (M^+ , 100), 179 (18); HRMS calcd for $\text{C}_{12}\text{H}_7\text{N}_2\text{Cl}$ 214.0298, found 214.0300.

3-Chloro-4-(4-nitrophenyl)-pyridine (19q). Prepared according to representative procedure 5 from **15g** (0.5 g, 4.4 mmol) and 1-bromo-4-nitrobenzene (0.98 g, 4.84 mmol). Flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9.5/0.5) and recrystallization (hexanes/ EtOAc) yielded **19q** (43% yield) as yellow flakes, mp 156-157 °C (hexanes/ EtOAc); IR (KBr disk) ν_{max} 3016, 1596, 1582, 1511, 1467, 1350 cm^{-1} ; ^1H NMR (400.3 MHz, CDCl_3) δ 8.77 (s, 1H), 8.62 (d, 1H, $J = 5.2$ Hz), 8.38 (d, 1H, 8.8 Hz), 7.68 (d, 2H, $J = 8.4$), 7.32 (d, 1H, $J = 4.8$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 150.3, 148.05,

148.01, 145.4, 142.6, 130.0, 129.8, 124.8, 123.7; MS m/z 236 (31), 235 (10), 234 (100); HRMS calcd for $C_{11}H_7N_2O_2Cl$ 234.0196, found 234.0194.

2-Fluoro-3-(3-methoxy-phenyl)-pyridine (19r). Prepared according to representative procedure 3 from **15h** (0.5 g, 5.15 mmol) and 3-bromoanisole (1.06 g, 5.66 mmol). Kugelrohr distillation of the crude residue (135 °C/0.5 mmHg) furnished **19r** (66% yield) as a colourless oil: IR (thin film) ν_{max} 3059, 3002, 2940, 2836, 1603, 1584, 1460, 1437, 1413, 1233, 1019, 782 cm^{-1} ; 1H NMR (400.3 MHz, $CDCl_3$) δ 8.19 (dt, 1H, $J = 4.8$ Hz and 1.5 Hz), 7.86 (ddd, 1H, $J_{1,3(H-F)} = 9.7$ Hz and $J = 7.5, 2.0$ Hz), 7.37 (t, 1H, $J = 7.8$ Hz), 7.26 (ddd, 1H, $J_{1,2} = 7.5$, $J_{1,2} = 4.8$ and $J_{1,4(H-F)} = 1.8$ Hz), 7.14 (d, 1H, $J = 7.6$ Hz), 7.13 (d, 1H, $J = 2.7$ Hz), 6.95 (dd, 1H, $J = 8.3, 2.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4 (d, $J = 240.7$ Hz), 159.7, 146.3 (d, $J = 14.6$ Hz), 140.7 (d, $J = 5.1$ Hz), 135.2 (d, $J = 5.1$ Hz), 129.7, 123.8 (d, $J = 28.5$ Hz), 121.8 (d, $J = 4.4$ Hz), 121.2 (d, $J = 2.9$ Hz), 114.6 (d, $J = 3.6$ Hz), 113.9, 55.3; MS m/z 203 (100), 173 (37), 172 (15), 160 (32); HRMS calcd for $C_{12}H_{10}NOF$ 203.0746, found 203.0752

3-(3-Chloro-phenyl)-2-fluoro-pyridine (19s). Prepared according to representative procedure 3 from **15h** (0.5 g, 5.15 mmol) and 1-bromo-3-chlorobenzene (1.08 g, 5.66 mmol). Kugelrohr distillation of the crude residue (125 °C/0.5 mmHg) furnished **19s** (73% yield) as colourless flakes: mp 57-60 °C (of bulb-to-bulb distilled material which crystallized); IR (KBr disk) ν_{max} 3055, 1610, 1572, 1441, 1398, 778, 692 cm^{-1} ; 1H NMR (400.3 MHz, $CDCl_3$) δ 8.25 (d, 1H, $J = 4.8$ Hz), 7.88 (t, 1H, $J = 8.0$ Hz), 7.58 (s, 1H), 7.40-7.51 (m, 3H), 7.32 (t, 1H, $J = 5.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (d, $J =$

240.7 Hz), 146.9 (d, $J = 14.6$ Hz), 140.6 (d, $J = 4.4$ Hz), 135.6 (d, $J = 5.1$ Hz), 134.6, 130.0, 128.8 (d, $J = 2.9$ Hz), 128.5; MS m/z 209 (33); 207 (100), 172 (23); HRMS calcd for $C_{11}H_7NFCI$ 207.0251, found 207.0255.

Diethyl-carbamic acid 4-(4-methoxy-phenyl)-pyridin-3-yl ester (19t). A 50 mL flame-dried round bottom flask was charged with **15f** (0.5 g, 2.6 mmol), THF (5 mL) and $B(O^iPr)_3$ (3.1 mmol, 0.72 mL). A stock solution of LDA (4.10 mL, 2.9 mmol, 0.7M), prepared as in general procedure 3, was added to this mixture cooled to -78 °C and the reaction was allowed to reach 0 °C over 30 min. *N*-Methyldiethanolamine (0.37 g, 3.1 mmol) was added and the mixture was stirred for 2 h at 0 °C. After complete *in vacuo* evaporation of the solvent, in a glove-bag filled with nitrogen, $Pd(OAc)_2$ (29 mg, 0.13 mmol), S-Phos (0.107 g, 0.26 mmol), K_2CO_3 (1.10 g, 7.8 mmol), CuI (49 mg, 0.26 mmol) were added to the residue. A water condenser was fitted to the flask and 4-bromoanisole (0.32 g, 1.7 mmol) and degassed ethanol (15 mL) were added through a septum sealing at the top of the condenser. The mixture was refluxed for 3h, cooled and subjected to filtration. The solvent was evaporated to dryness and the residue, suspended in water, was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic extract was washed with brine (40 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification of this residue by flash column chromatography (hexanes/EtOAc/MeOH 16/4/0.5) yielded **19t** (0.47 g, 64%) as clear oil: IR (thin film) ν_{max} 1718 cm^{-1} ; 1H NMR (400.3 MHz, $CDCl_3$) δ 8.46 (m, 2H), 7.40 (d, 2H, $J = 8.0$ Hz), 7.30 (d, 1H, $J = 4.4$ Hz), 6.95 (d, 2H, $J = 8.0$ Hz), 3.84 (s, 3H), 3.32-3.34 (m, 4H), 1.05-1.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 153.4, 146.4, 145.3, 142.1, 129.9, 127.6, 124.4, 113.9, 55.3, 42.2, 41.8,

14.0, 13.1; MS m/z 301 (M+H, 5), 300 (29), 100 (100), 72 (37); HRMS calcd for $C_{17}H_{20}N_2O_3$ 300.1474, found 300.1413.

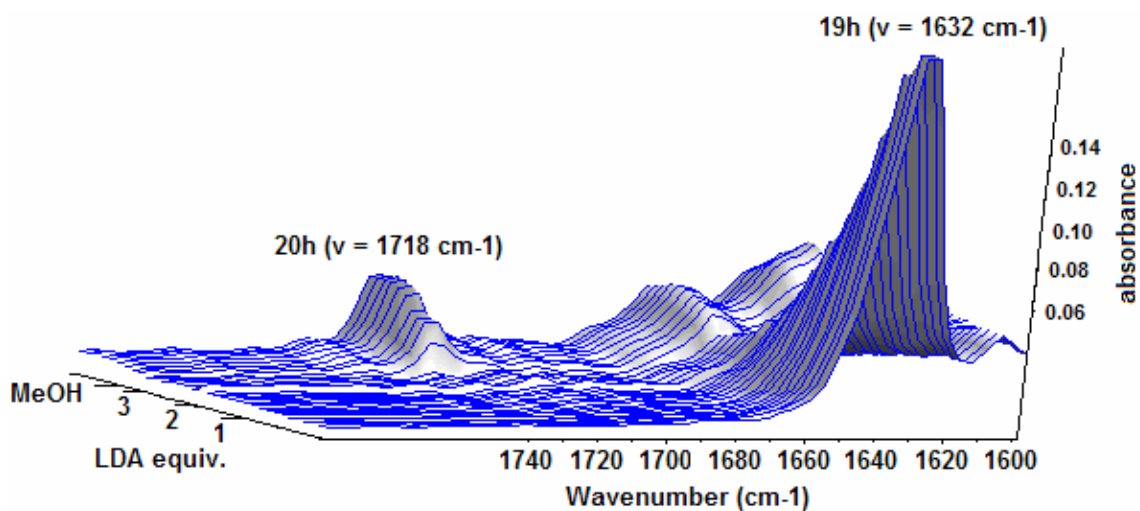
9-Oxo-9H-indeno[2,1-b]pyridine-7-carbonitrile (20b). Prepared according to representative procedure 4 from **19b** (0.25 g, 0.90 mmol) in 40 mL of dry THF. To this solution cooled to $-78\text{ }^{\circ}\text{C}$ LDA (2.6 mL, 1.8 mmol) was added dropwise and the reaction was allowed to reach -10 ° over 90 min, then quenched with NH_4Cl . Purification of the crude (Hexanes/EtOAc 1/9) yielded 102 mg of **20b** (55%) as a yellow solid: mp 205-207 (hexanes/dichloromethane); IR (KBr) ν_{max} 2230, 1729, 1612, 800, 753, 584 cm^{-1} ; ^1H NMR (300. MHz, CD_3CN) δ 8.82-8.65 (m, 2H), 7.68 (d, 1H, $J = 8.2\text{ Hz}$), 7.54 (dd, 1H, $J = 4.8, 1.0\text{ Hz}$), 7.22 (d, 1H, $J = 2.3\text{ Hz}$), 7.15 (dd, 1H, $J = 8.2, 2.3\text{ Hz}$), 3.89 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 190.1, 152.9, 152.0, 145.1, 139.1, 138.5, 132.5, 129.0, 127.9, 127.6, 121.8, 117.6, 113.7; MS m/z 207 (M+H, 5), 206 (100), 178 (23), 152 (14), 151 (4); HRMS calcd for $C_{13}H_6N_2O$ 206.0480, found 206.0489.

7-Methoxy-2-azafluorenone (20e). Prepared according to representative procedure 4 from **19e** (0.167 g, 0.59 mmol) in 27 mL of dry THF. To this solution cooled to $-40\text{ }^{\circ}\text{C}$ LDA (2.5 mL, 1.8 mmol) was added dropwise and the reaction was allowed to reach $10\text{ }^{\circ}\text{C}$ over 2 h, then quenched with NH_4Cl . Purification of the crude ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9.85/0.15) yielded 70 mg of **20e** (56%) as a yellow solid. This compound exhibits spectral data consistent with those reported in literature.⁶

8-Methoxy-2-azafluorenone (20h). Prepared according to representative procedure 4 from **19h** (0.250 g, 0.88 mmol) in 40 mL of dry THF. To this solution cooled to -40 °C LDA (3.8 mL, 2.64 mmol) was added dropwise and the reaction was allowed to reach 10 °C over 2 h, then quenched with NH₄Cl. Purification of the crude (CH₂Cl₂/MeOH 9.85/0.15) yielded 115 mg of **20h** (63%) as a yellow solid. This compound exhibits spectral data consistent with those reported in literature.⁶

React IR Study for the Directed Remote Metalation of 19h.

A stock solution of LDA (10 mL, 1M) was prepared by addition of *n*-BuLi (10 mmol, 4.3 mL, 2.30M) to a solution of DIPA (10 mmol, 1.4 mL) in dry THF (9.0 mL) at 0 °C. A 100 mL two-neck flask containing a small stirring bar was fitted to the IR probe while the other neck was sealed with a rubber septum through which a temperature probe was inserted. Anhydrous THF (2.5 mL) was added and a background spectrum was acquired at -7 °C. **19h** (200 mg, 0.70 mmol) dissolved in THF (0.5 mL) was injected and, after briefly stirring, spectra (averages of 120 scans) were acquired every 2 min. LDA (2.1 mL, 2.1 mmol) was slowly added (ca. 0.1 mL/5 min) at -7 °C and the consumption of **19h** was monitored. When further additions of LDA caused no change in the amide carbonyl absorption band, ν 1632 cm⁻¹(C=O), a few drops of ice-cold MeOH were slowly added to the mixture causing the appearance of the fluorenone carbonyl band, ν 1718 cm⁻¹. In a control experiment, the addition of THF (2.1 mL) rather than a THF solution of LDA did not greatly reduce the absorption band of **19h**, neither did the addition of MeOH cause the appearance of relevant signals at ν 1718 cm⁻¹.



¹ Watson, S. C.; Eastham, J.F. *J. Organometallic Chem.* **1967**, 9, 165-168.

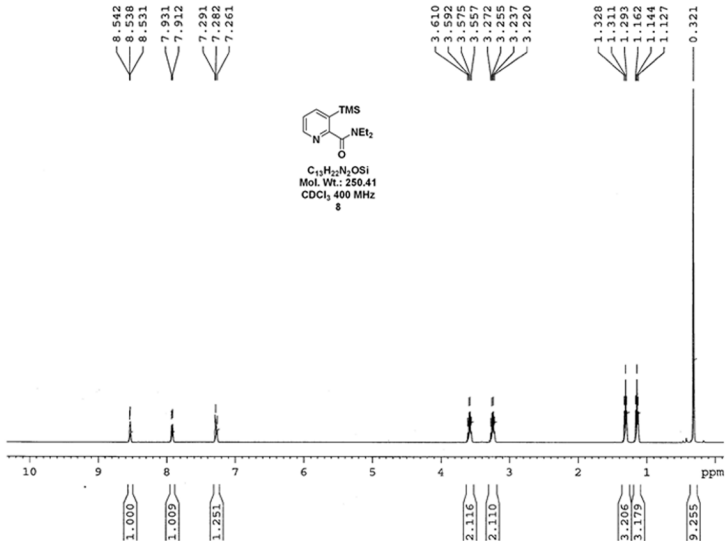
² Villacampa, M.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **1995**, 51, 1259-1264.

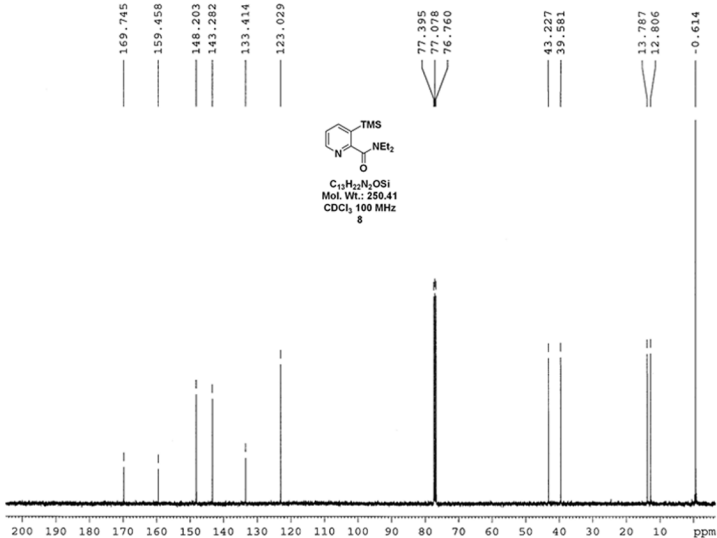
³ Meth-Cohn, O. *J. Chem. Soc., Chem. Commun.* **1986**, 9, 695-697.

⁴ Fisher, G.; Fuller, J.C.; Harrison, J.; Alvarez, S.G.; Burkhardt, E.R.; Goralski, C.T.; Singaram, B. *J. Org. Chem.* **1994**, 59, 6378-6385.

⁵ Although this compound is known (Butler, D. E.; Dodd, J. H.; Moos, W. H.; Tecle, H. Warner-Lambert Co., US Patent No. 4745123, **1988**) no characterization data has been reported.

⁶ Shiao, M.-J.; Peng, C.-J.; Wang, J.-S.; Ma, Y.-T. *J. Chin. Chem. Soc.* **1992**, 39, 173-176





9.178
9.174

8.395
8.386
8.382
8.381

7.667
7.665
7.640
7.638



$C_{12}H_{10}N_2O_3$
Mol. Wt.: 236.27
 $CDCl_3$ 300 MHz
Precursor to 9

3.969
3.608
3.584
3.560
3.527
3.521
3.348
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3.300

1.300
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1.292
1.178
1.155
1.131

1.000

1.068

1.056

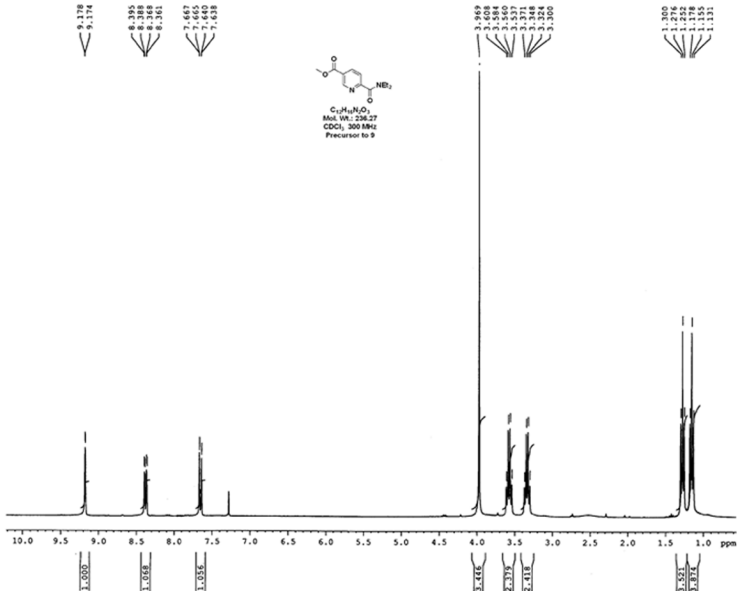
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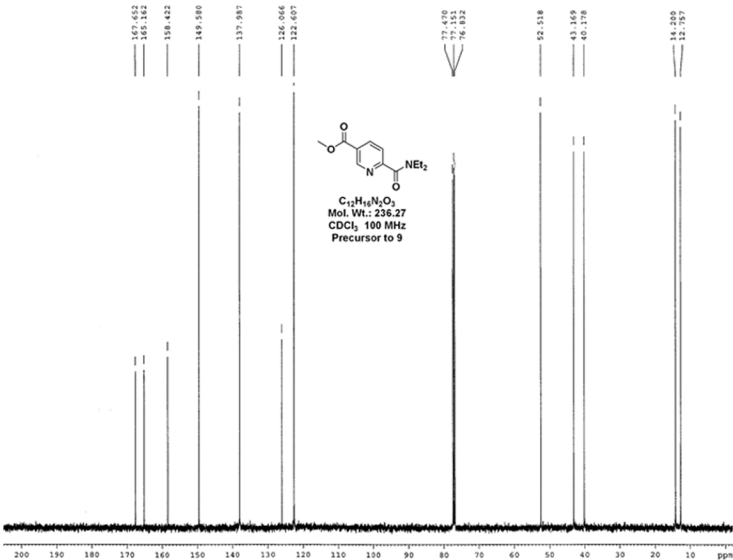
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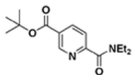
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3.521

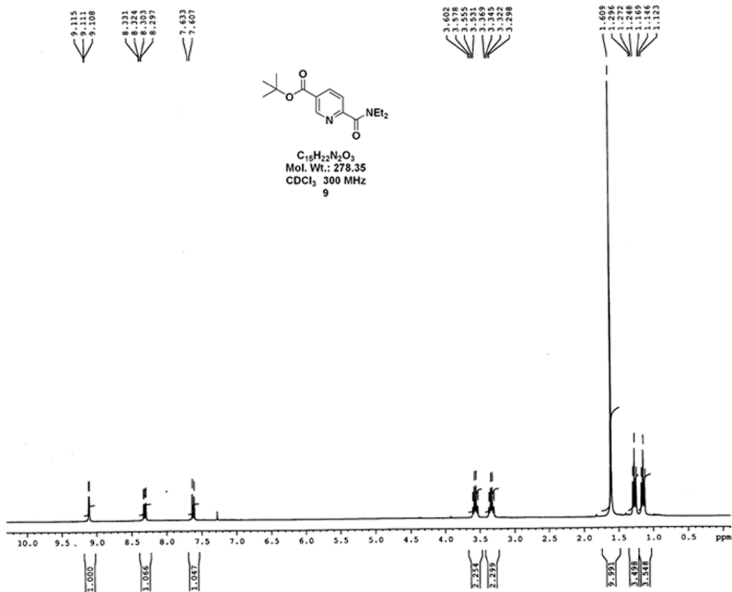
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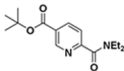




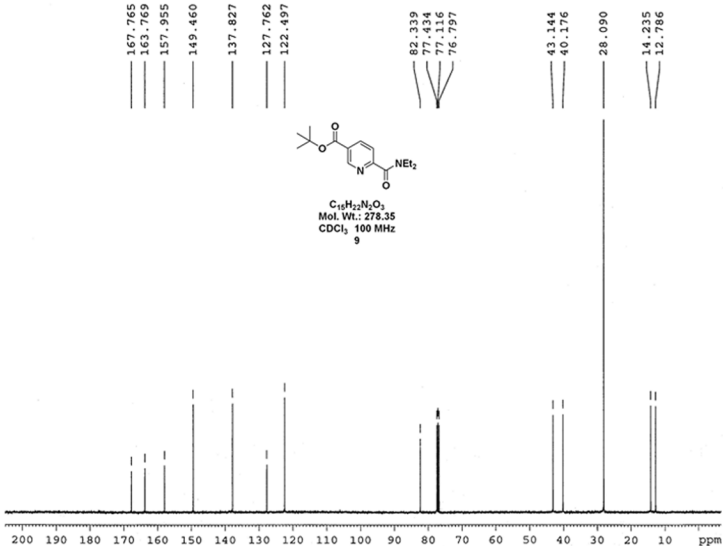


$C_{15}H_{22}N_2O_3$
 Mol. Wt.: 278.35
 $CDCl_3$ 300 MHz
 9





$C_{15}H_{22}N_2O_3$
 Mol. Wt.: 278.35
 $CDCl_3$ 100 MHz
 9





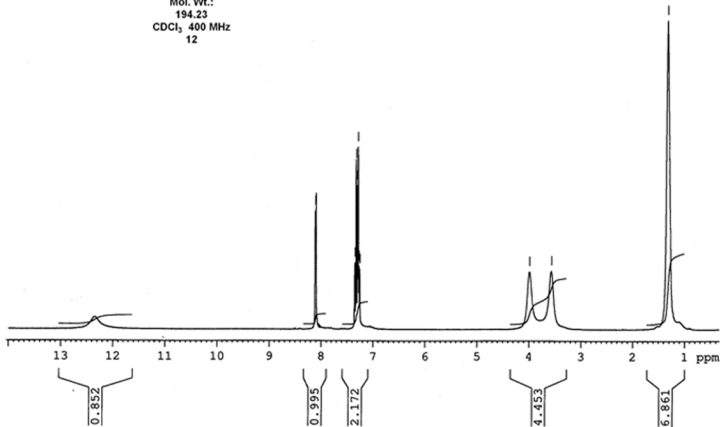
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 Mol. Wt.:
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 12

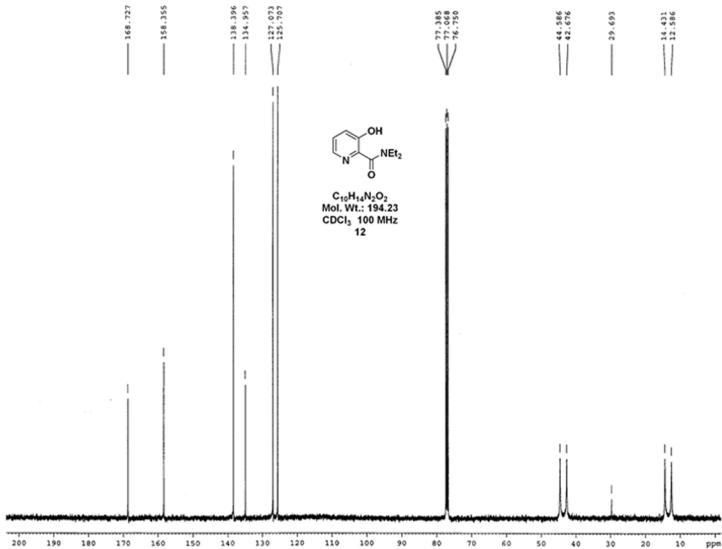
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 7.249

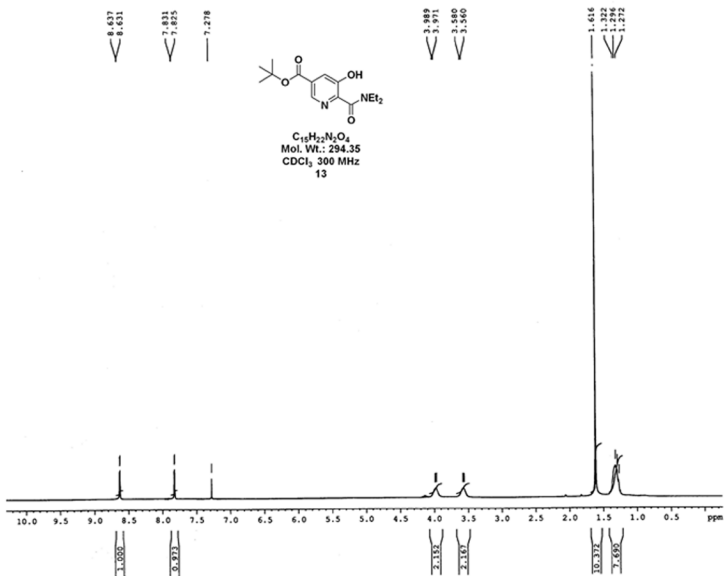
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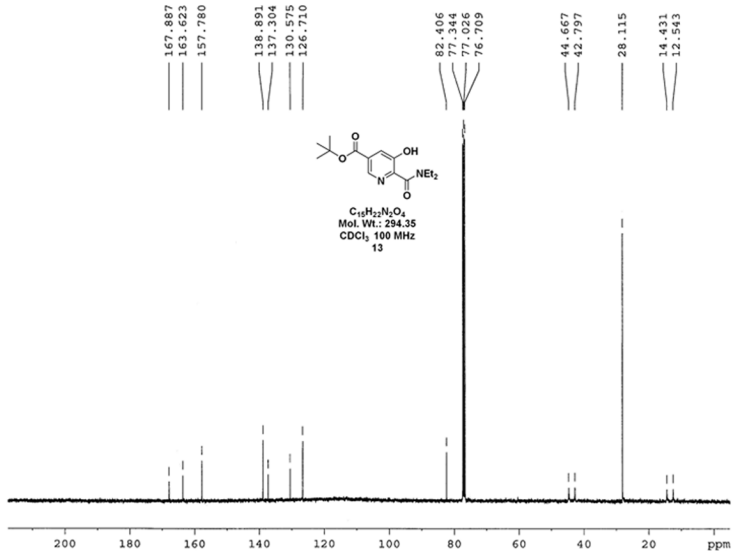
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1.311

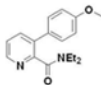








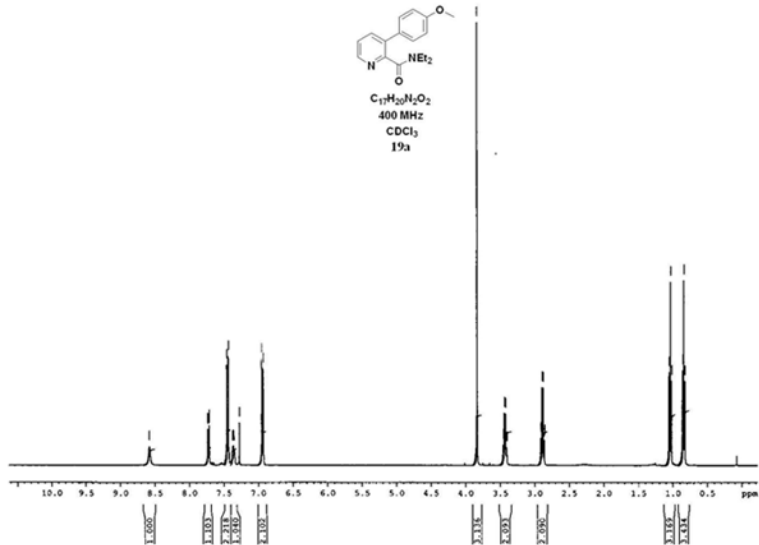
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8.430
8.373
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8.254
8.211
8.954
8.947
8.941
8.930
8.925



$C_{17}H_{20}N_2O_2$
400 MHz
 $CDCl_3$
19a

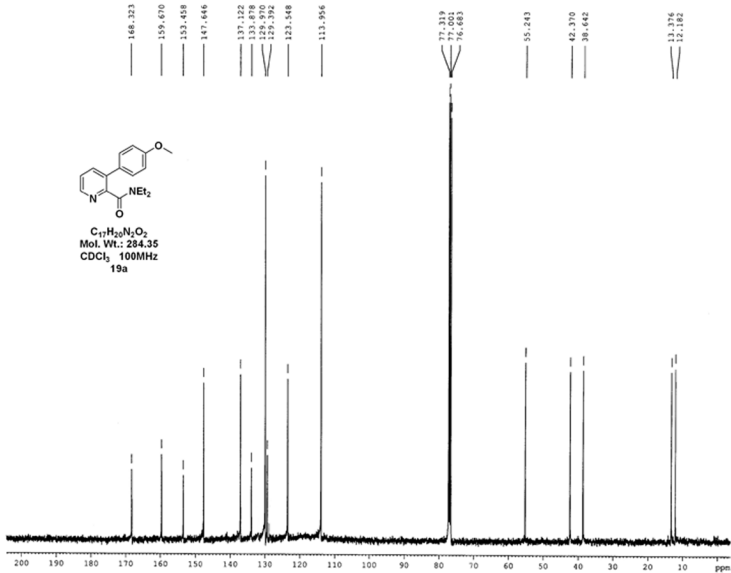
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2.857

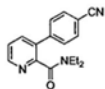
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0.842
0.824





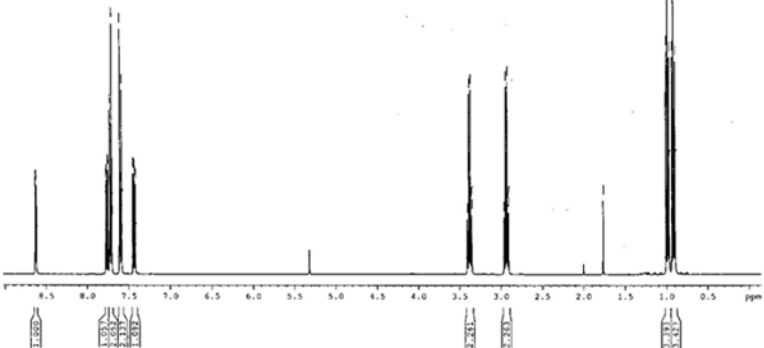
$C_{17}H_{20}N_2O_2$
 Mol. Wt.: 284.35
 $CDCl_3$ 100MHz
19a





400 Mhz CD₂Cl₂

19b

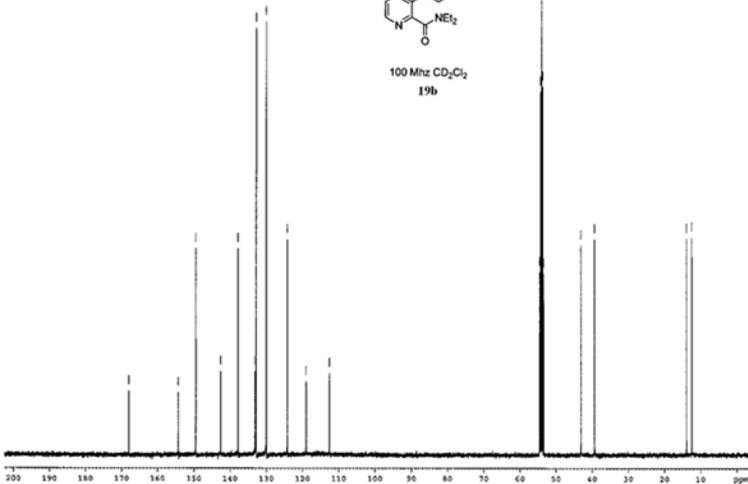


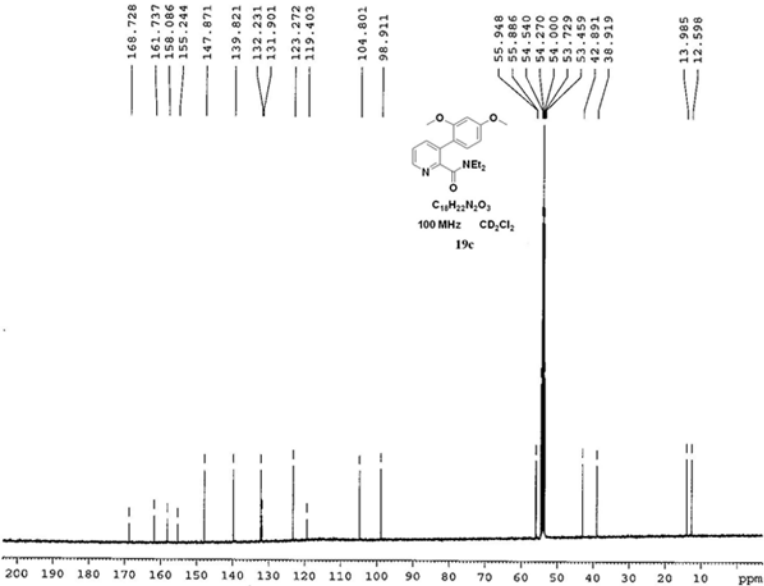
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 142.645
 137.846
 133.226
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 130.089
 124.278
 119.043
 112.584



100 Mhz CD₂Cl₂
19b

54.543
 54.271
 54.000
 53.730
 53.459
 43.132
 39.238
 13.936
 12.485



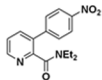


8.703
8.699
8.691
8.687
8.300
8.294
8.289
8.277
8.272
8.266
8.050
7.994
7.780
7.776
7.708
7.702
7.697
7.685
7.680
7.674
7.474
7.462
7.454
7.442
7.271

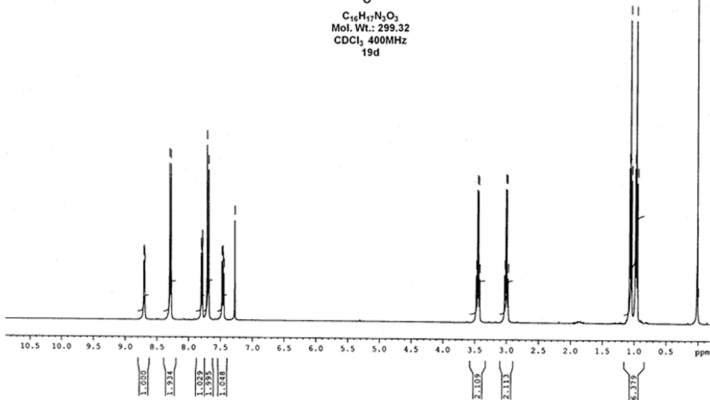
3.469
3.451
3.451
3.434
3.416
3.021
3.003
2.985
2.968

1.066
1.048
1.030
1.025
0.958
0.940

0.011
0.003



$C_{16}H_{17}N_3O_3$
Mol. Wt.: 299.32
 $CDCl_3$ 400MHz
19d



167.499

153.640

149.327

147.473

143.926

137.417

132.449

129.806

121.863

121.733

77.409

77.090

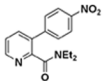
76.771

42.721

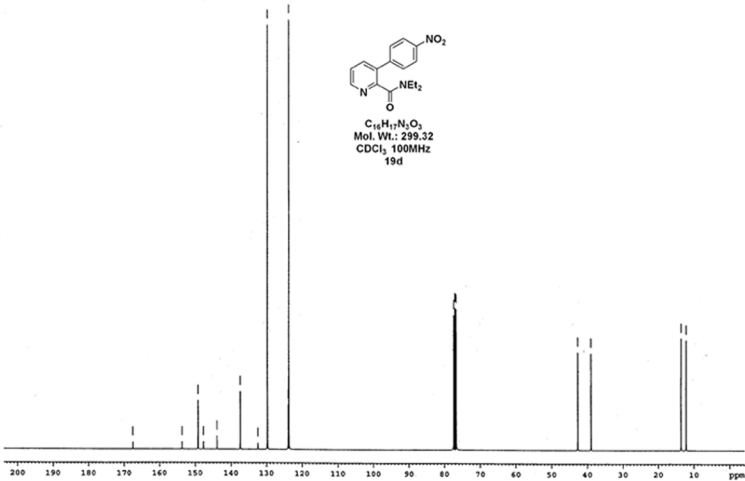
39.013

13.652

12.251

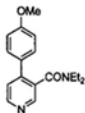


$C_{16}H_{17}N_3O_3$
Mol. Wt.: 299.32
 $CDCl_3$ 100MHz
19d



8.634
8.622
8.573

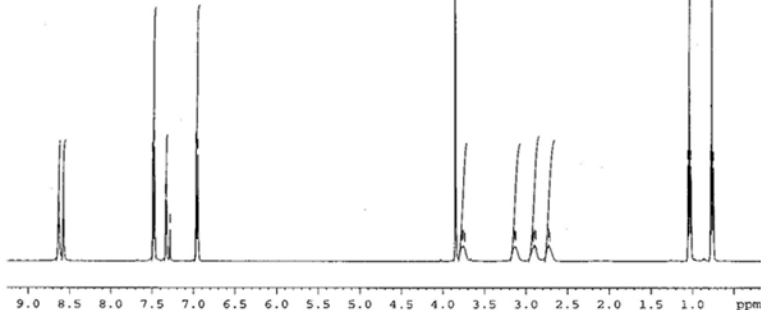
7.489
7.468
7.335
7.322
7.284
6.966
6.945



400 MHz CDCl₃
19e

3.848
3.779
3.767
3.752
3.737
3.155
3.140
3.125
2.917
2.901
2.885
2.741
2.724
2.709

1.054
1.036
1.018
0.782
0.764
0.747



1.000
1.010

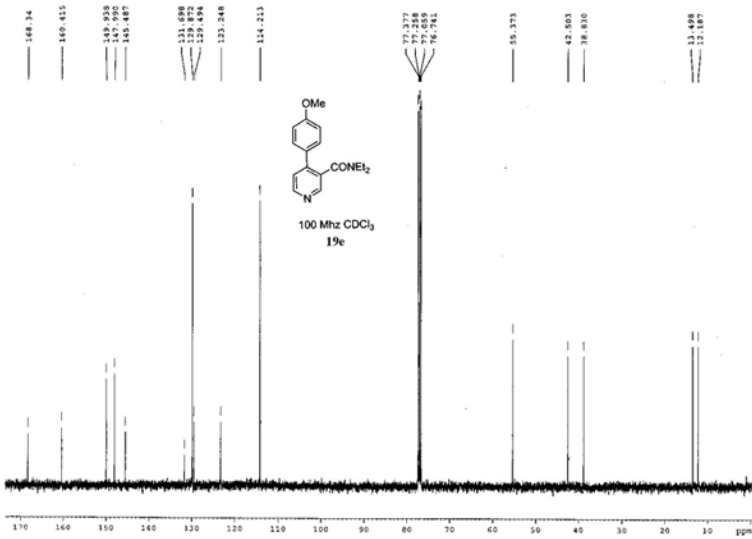
2.094
1.052

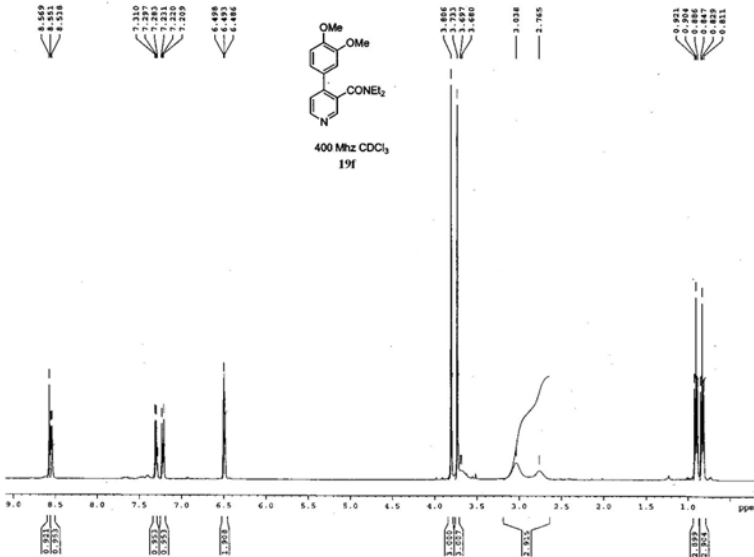
2.111

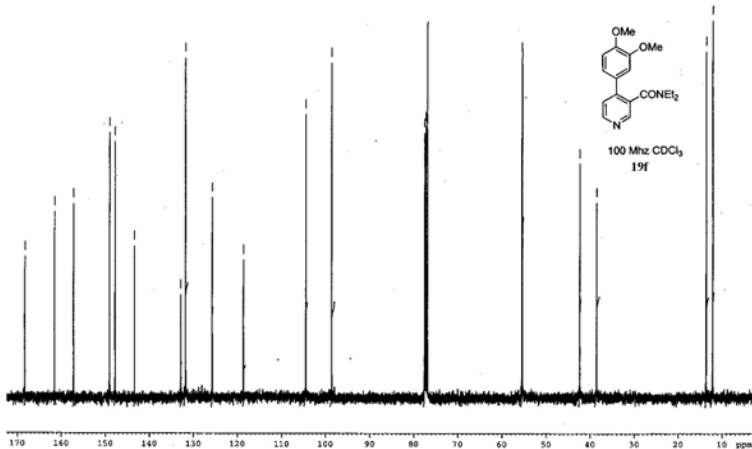
3.180
0.984

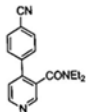
0.977
1.043
1.008

3.175
3.200









400 Mhz CDCl₃

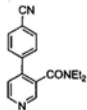
19g

2.860



11 10 9 8 7 6 5 4 3 2 1 0 ppm

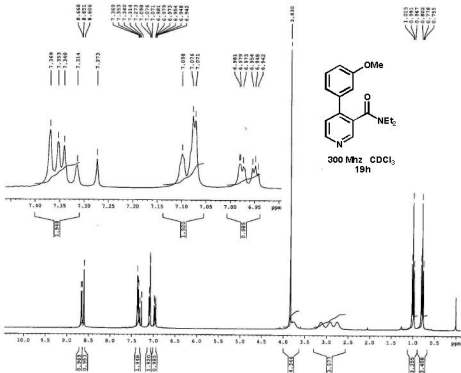




100 Mhz CDCl₃
19g

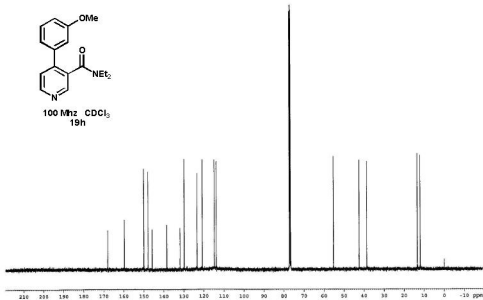


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm





100 Mhz CDCl₃
19h



8.544
8.541
8.537
8.528

7.229
7.227
7.216
7.215
7.213
7.197
7.175
7.158
7.155

6.534
6.533
6.529

5.323
5.320
5.317

3.673
3.758

1.589

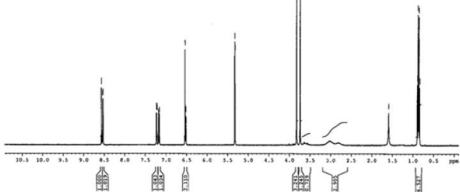
0.982
0.979
0.970
0.934
0.932
0.934



$C_{19}H_{22}N_2O_3$

400 MHz CD_2Cl_2

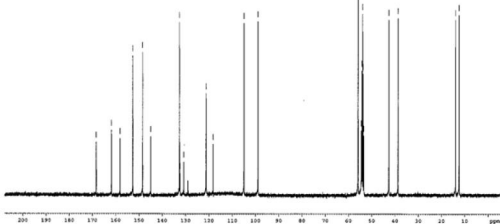
19i

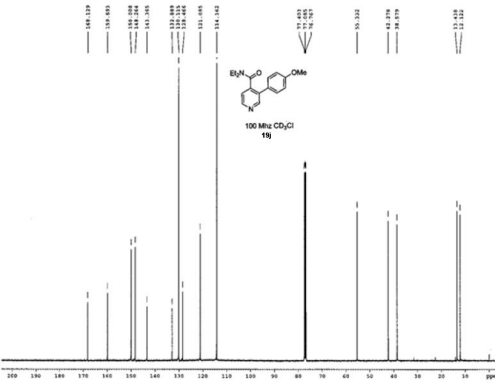


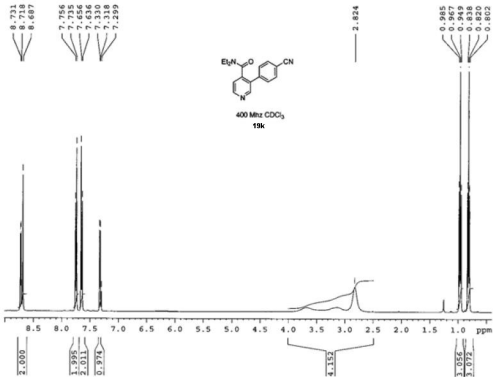


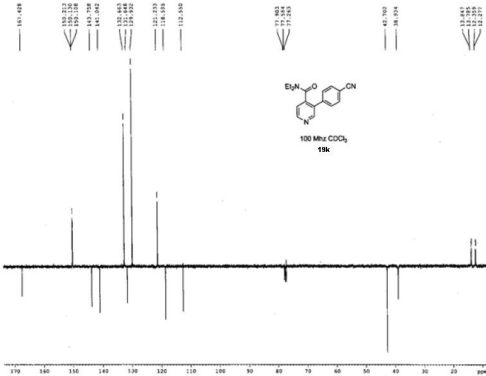
100 MHz CD_2Cl_2

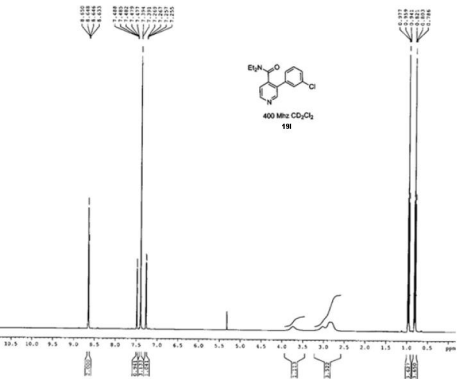
19i

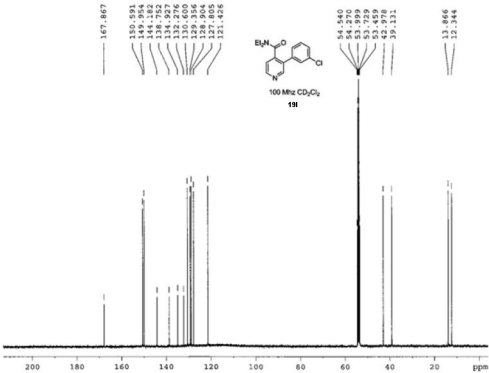


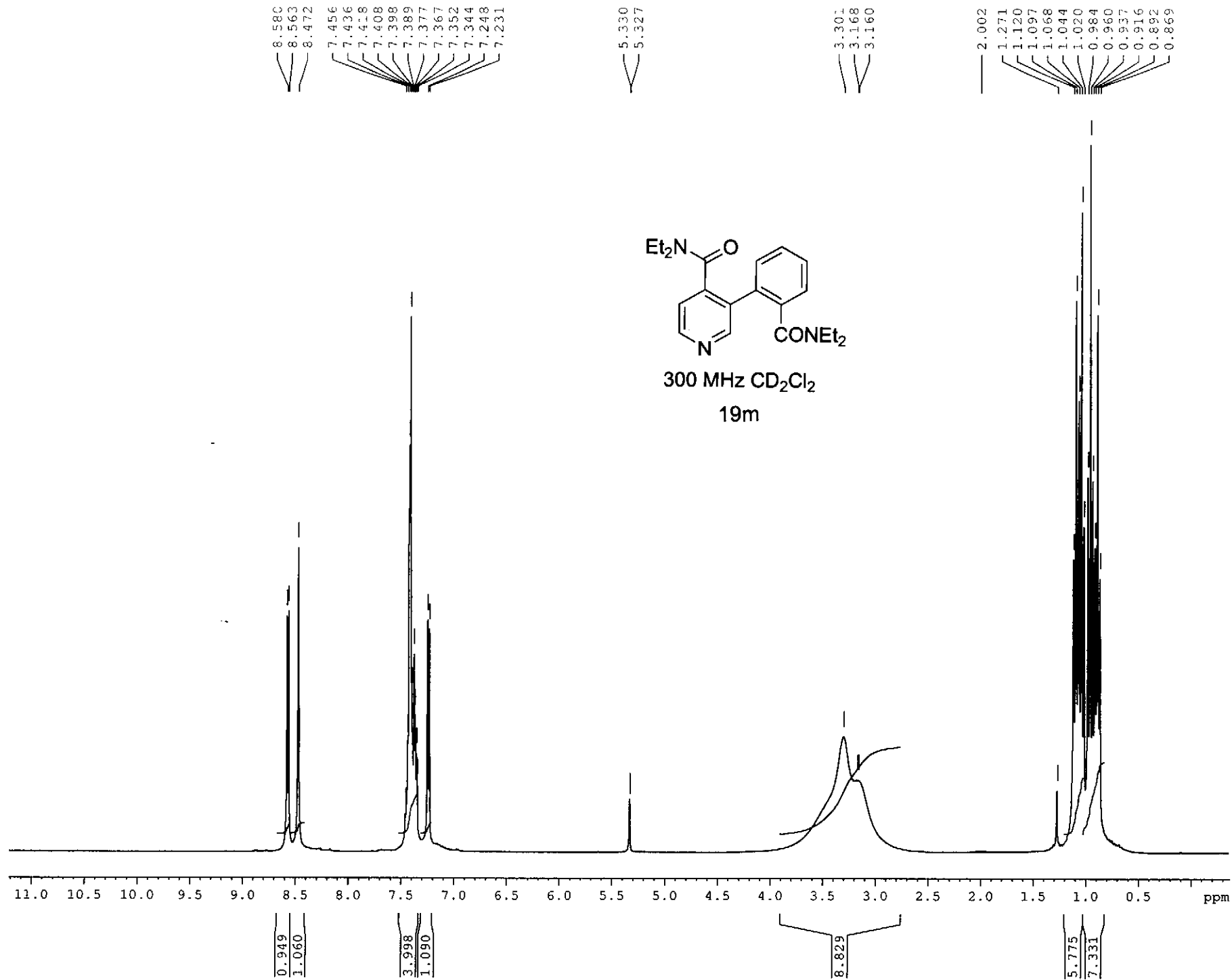


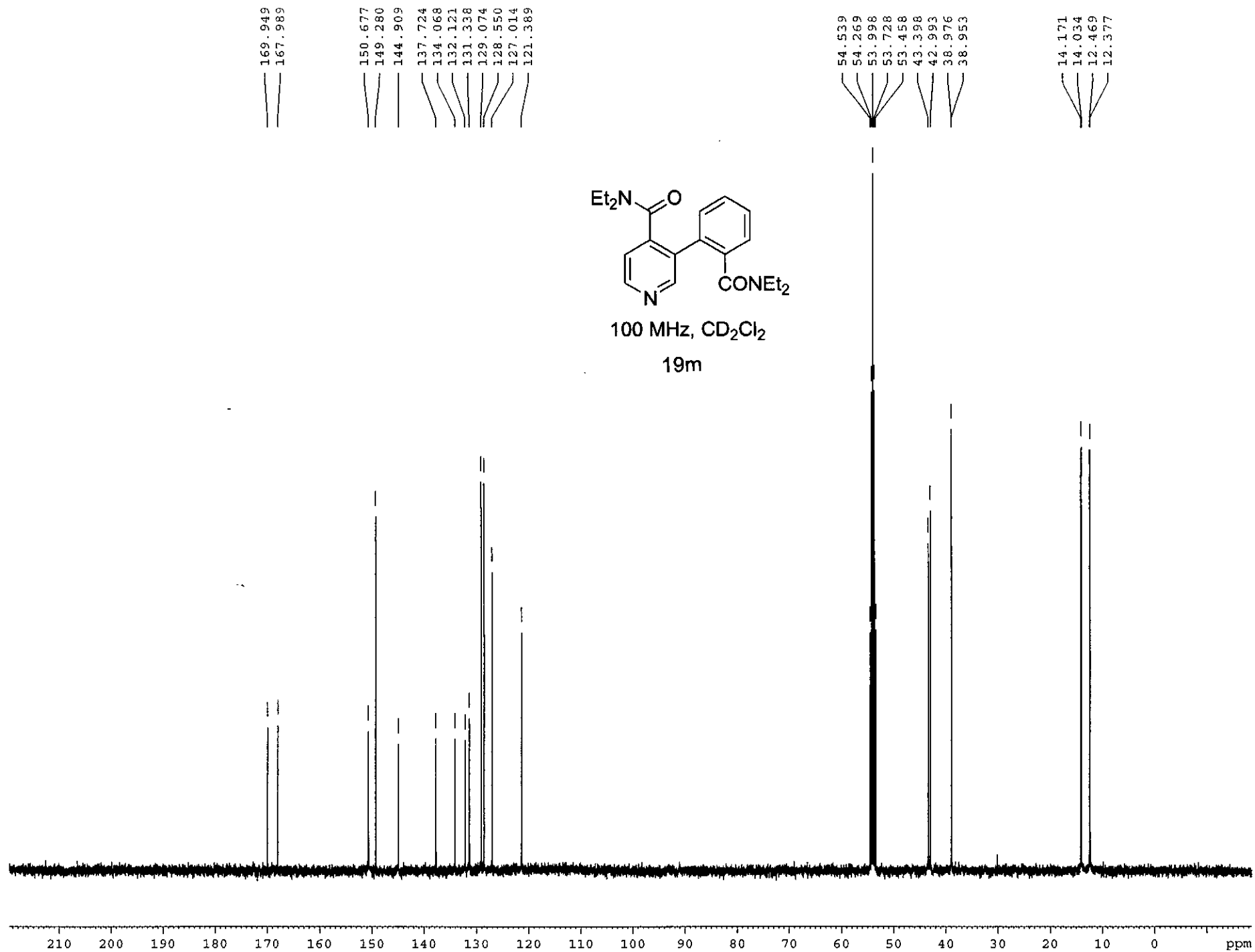


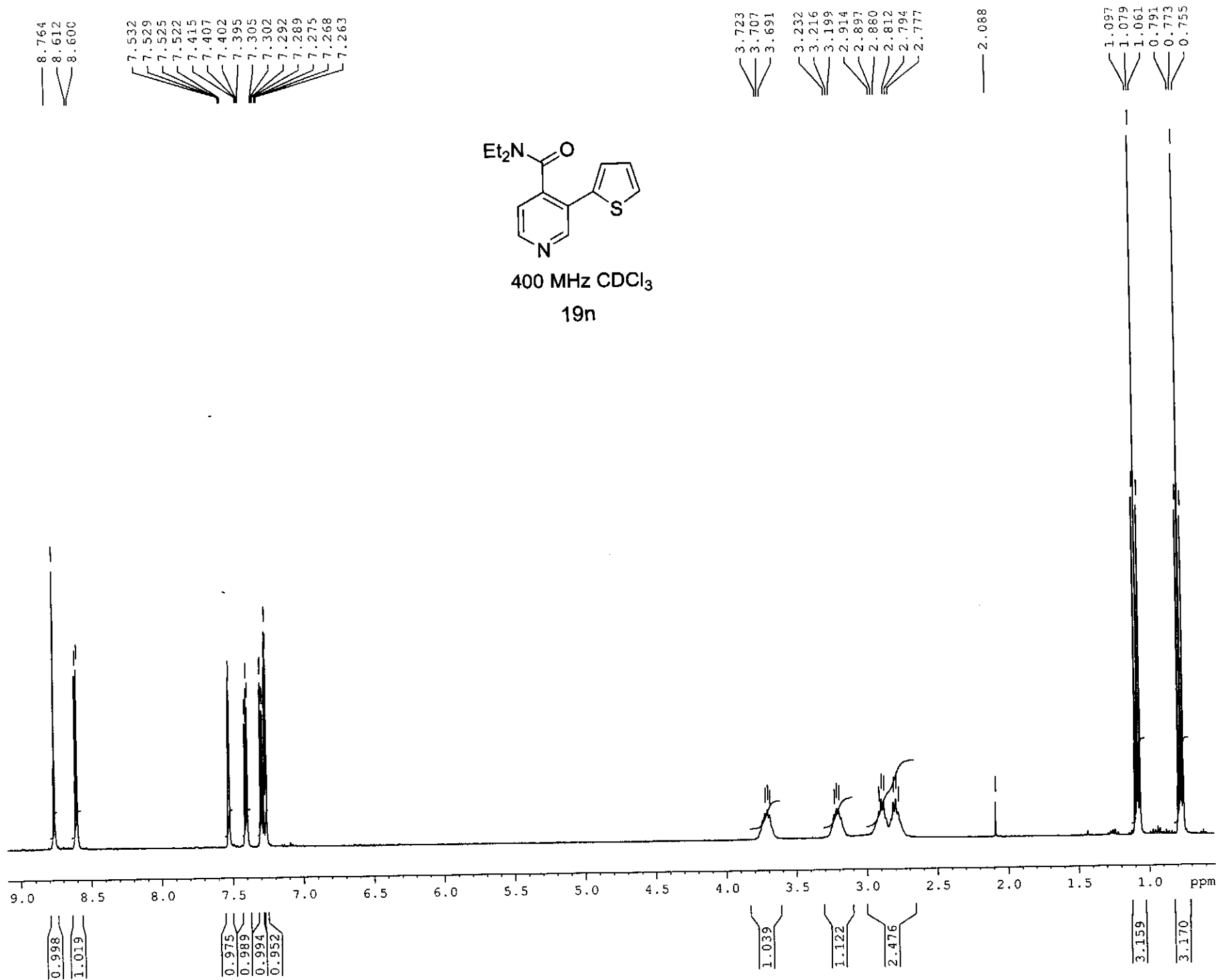


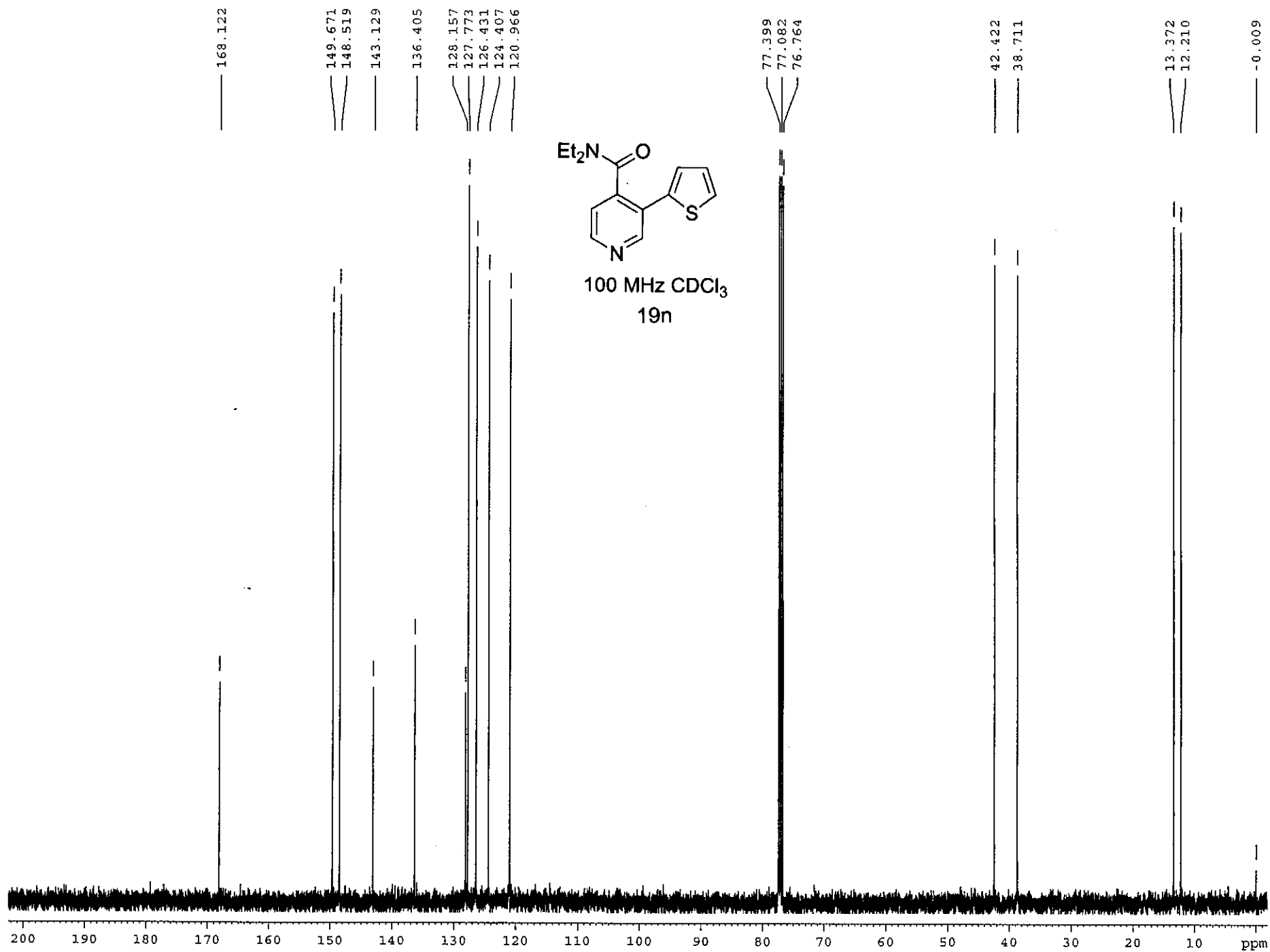


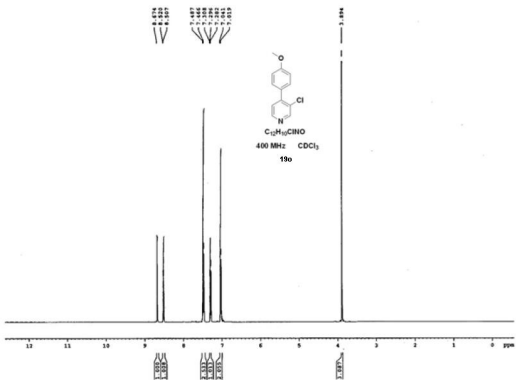


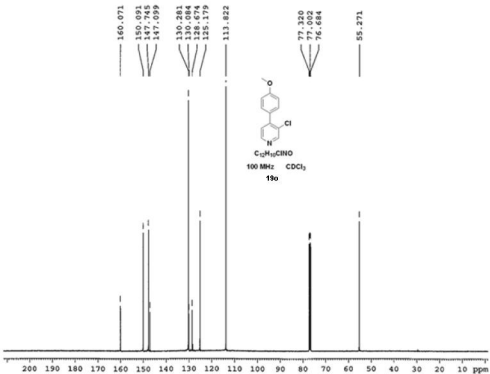


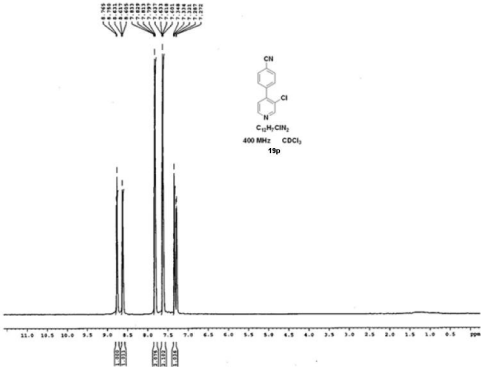


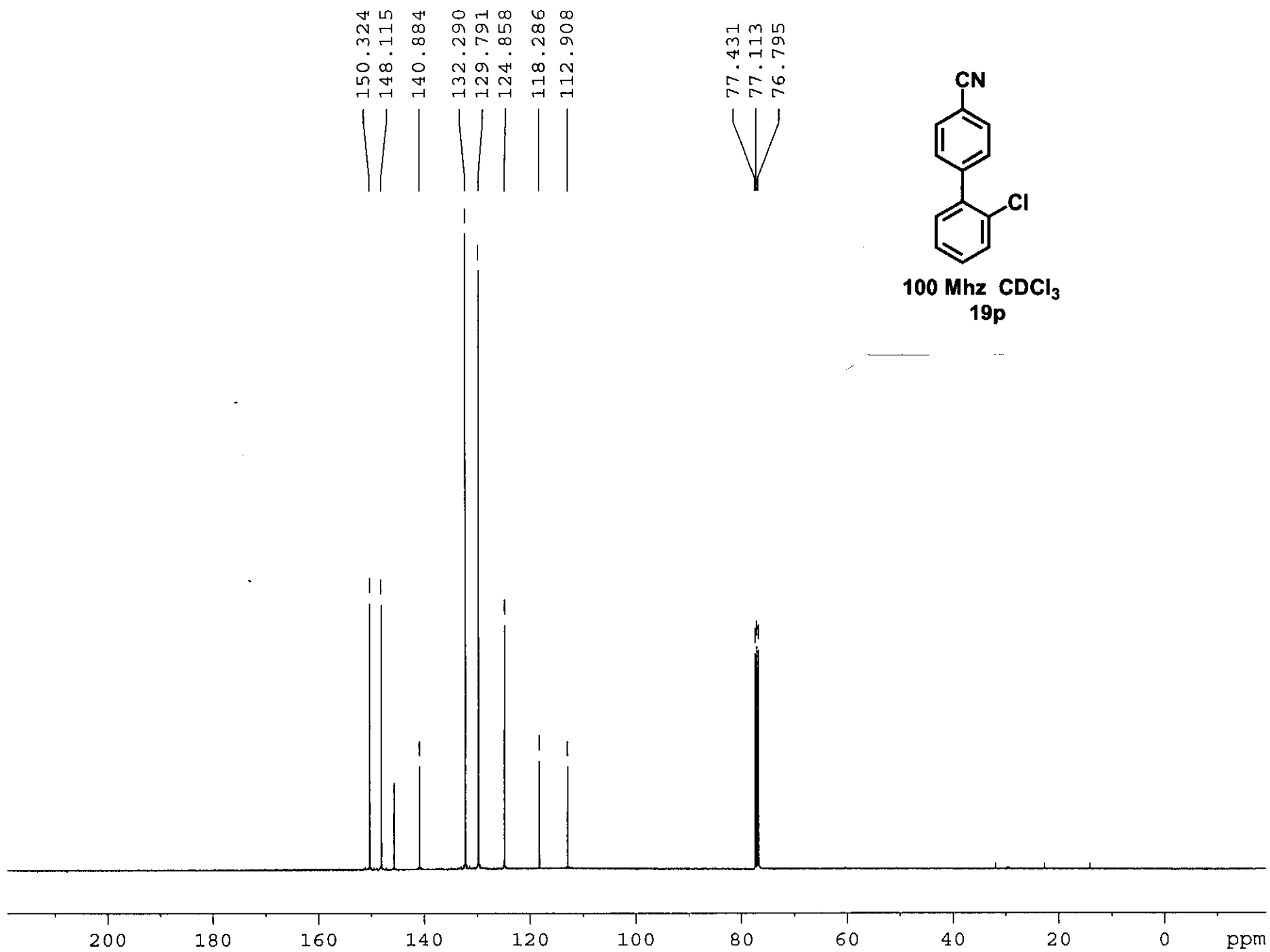


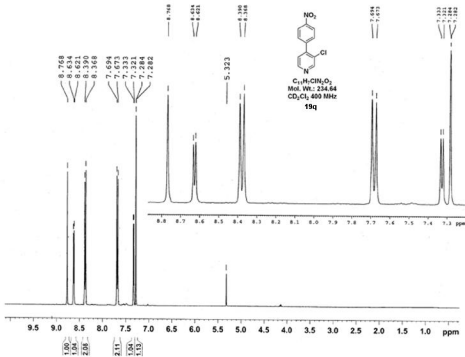


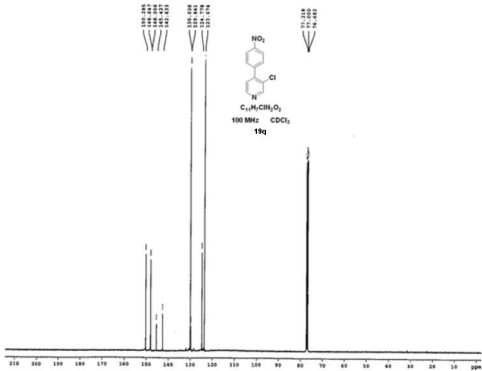


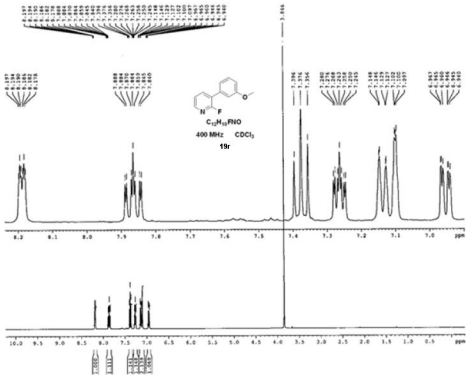


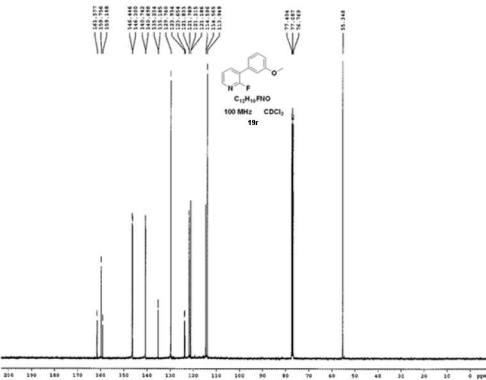


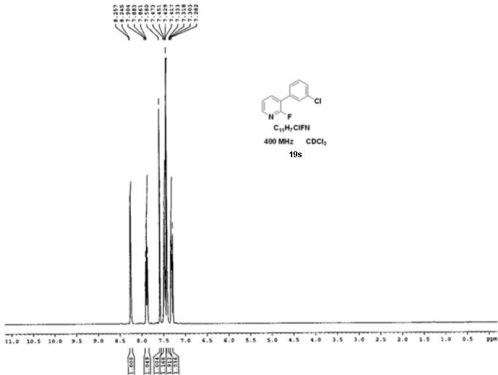


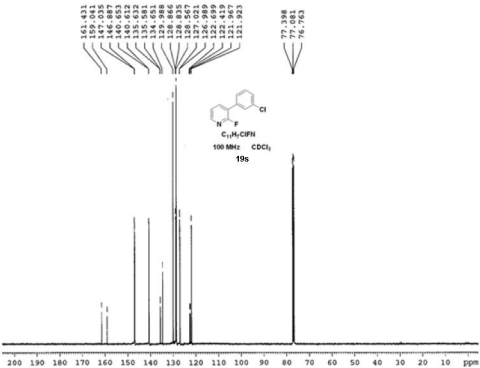












8.477
8.464
8.453

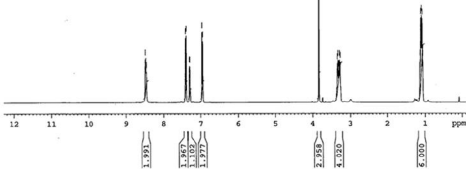
7.415
7.395
7.308
7.297
6.969
6.949

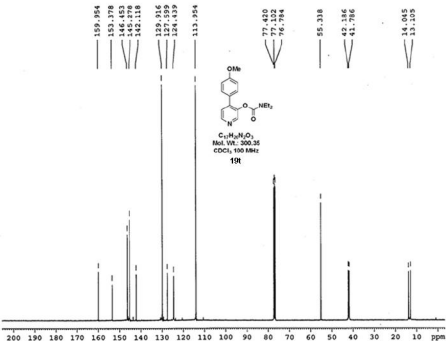
3.841
3.346
3.329
3.310
3.292
3.274

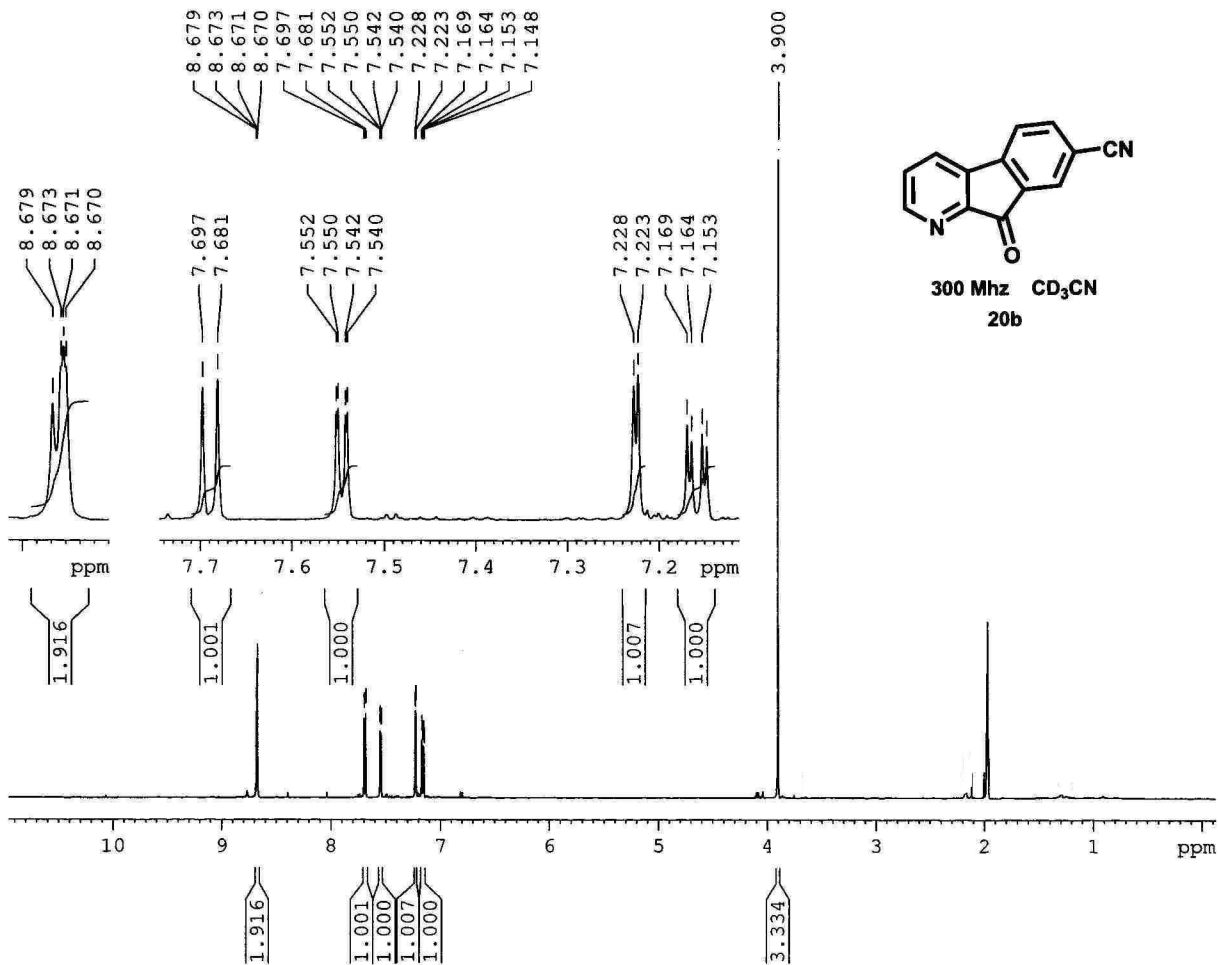
1.132
1.115
1.097
1.079
1.061

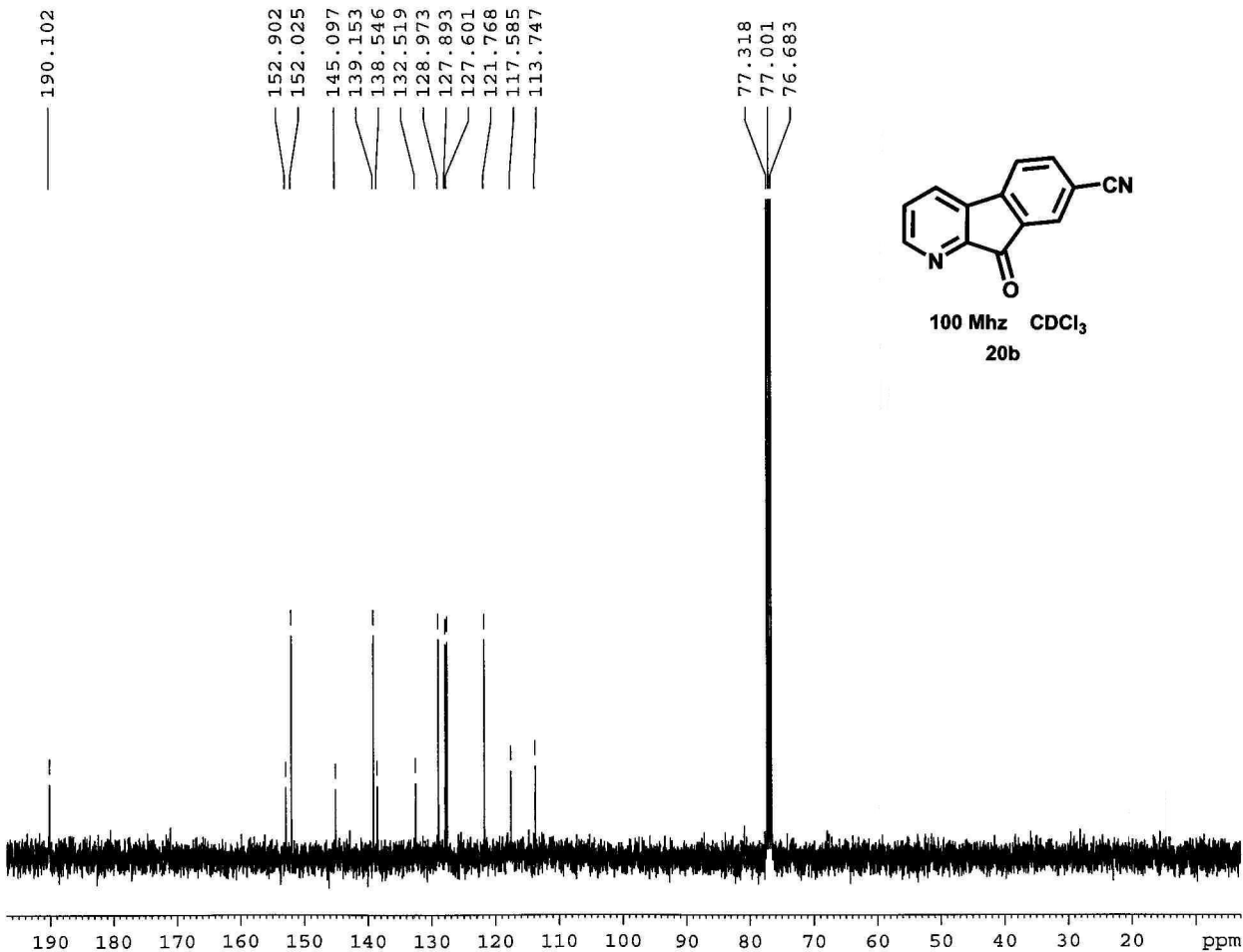


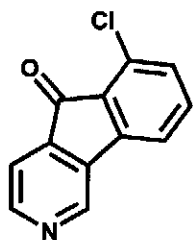
$C_{17}H_{20}N_2O_3$
Mol. Wt.: 300.35
 $CDCl_3$ 400 MHz
19t











CDCl₃, 400 MHz
201

