

**Nickel catalyzed Cross-Coupling Reactions of Benzylic Zinc
Reagents with Aromatic Bromides, Chlorides and Tosylates
Supporting Information**

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General All reactions were carried out under an argon atmosphere in dried glassware. Commercially available starting materials were used without further purification. All benzylic zinc chlorides were prepared as described in the literature.¹ THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. NMP was distilled from CaH₂ and kept under Ar. Yields refer to isolated yields of compounds estimated to be > 95 % pure as determined by ¹H-NMR and high resolution mass spectroscopy (HRMS).

General procedure 1 (GP1): Preparation of the aromatic tosylates:

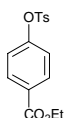
In a round bottom flask equipped with a magnetic stirring bar, the aromatic alcohol was dissolved in THF, then NEt₃ (1.1 equiv) and DMAP (2 mol %) were added at 25 °C. After that, tosyl chloride (1.1 equiv) was added at 0 °C and the reaction mixture was allowed to warm up to 25 °C and stirred for the given time. Then CH₂Cl₂ was added and the reaction mixture was washed 3 times with saturated aqueous NH₄Cl-solution. The combined aqueous layers were extracted 3 times with CH₂Cl₂ and the combined organic layers were washed with brine and dried over Na₂SO₄. Removal of the solvent *in vacuo* and recrystallization afforded the analytically pure product.

General procedure 2 (GP2): Nickel-catalyzed cross-coupling reactions:

In a dry argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, the aromatic bromide, chloride or tosylate (2.00 mmol) was dissolved in NMP (0.4 mL) and PPh₃ (0.1 mL, 0.4 M in THF, 0.40 mmol, 2 mol %) was added. Then, Ni(acac)₂ (0.1 mL, 0.1 M in THF, 0.1 mmol, 0.5 mol %) was added. After the addition of the corresponding benzylic zinc reagent (2.40 mmol, 1.2 equiv), the reaction mixture was warmed to 60 °C and stirred for the given time until GC-analysis showed full conversion of the electrophile. The reaction mixture was quenched with saturated aqueous NH₄Cl-solution and extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and the solvent removed *in vacuo*. The product was purified by flash column chromatography.

Preparation of the aryl tosylates:

Preparation of 4-(toluene-4-sulfonyloxy)-benzoic acid ethyl ester (3h):



4-Hydroxy-benzoic acid ethyl ester (3.34 g, 20.1 mmol) was dissolved in pyridine (20 mL), tosyl chloride (5.00 g, 26.2 mmol) was added portionwise and the reaction mixture was stirred at 25 °C for 20 h. Then, the reaction mixture was poured on ice, EtOAc and 2 M HCl were added. The aqueous layer was extracted 3 times with EtOAc, and the combined organic layers were washed with 2 M HCl, saturated aqueous NaHCO₃-solution, brine and dried over MgSO₄. The solvent was removed *in vacuo* and flash column chromatographical purification (silica; pentane:Et₂O, 6:1) afforded **3h** as a colorless oil (6.65 g, 20.8 mmol, 99%)

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 7.96 (d, *J* = 8.9 Hz, 2 H), 7.69 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.04 (d, *J* = 8.9 Hz, 2 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 2.43 (s, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 165.4, 152.9, 145.7, 132.1, 131.2, 129.8, 129.2, 128.5, 122.2, 61.2, 21.7, 14.2.

MS (70 eV, EI): *m/z* (%): 320 (M⁺, 30), 275 (13), 156 (8), 155 (100), 121 (7), 62 (6), 91 (69), 65 (9).

HRMS: (C₁₆H₁₆O₅S) calculated 320.0718 found 320.0726.

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2980 (w), 2358 (w), 2116 (vw), 1714 (s), 1598 (m), 1498 (m), 1446 (m), 1372 (s), 1272 (vs), 1198 (s), 1174 (vs), 1152 (vs), 1092 (vs), 1016 (s), 864 (vs), 846 (s), 814 (s), 800 (s), 778 (s), 734 (vs), 696 (s), 668 (s).

Preparation of toluene-4-sulfonic acid 2-methoxy-phenyl ester (3i):



According to GP1 2-methoxy-phenol (3.05 g, 25.0 mmol) was reacted with NEt₃ (2.78 g, 27.5 mmol), DMAP (61 mg, 2 mol %) and tosyl chloride (5.24 g, 27.5 mmol) in THF (40 mL) for 20 h. Recrystallization from heptane/EtOAc afforded **3i** as a colorless crystalline solid (5.91 g, 21.2 mmol, 85%).

mp: 77.1-79.5 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 7.74 (d, *J* = 8.3 Hz, 2 H), 7.28 (d, *J* = 9.2 Hz, 2 H), 7.22-7.17 (m, 1 H), 7.16-7.11 (m, 1 H), 6.88 (dd, *J* = 7.9 and 1.8 Hz, 1 H), 6.85-6.80 (m, 1 H), 3.54 (s, 3 H), 2.43 (s, 3 H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 151.8, 144.9, 138.4, 133.3, 129.3, 128.6, 128.0, 124.0, 120.6, 112.7, 55.5, 21.6.

MS (70 eV, EI): *m/z* (%): 278 (M⁺, 39), 207 (25), 124 (28), 123 (100), 109 (17), 95 (46), 91 (52), 77 (28), 65 (19), 52 (12).

HRMS: (C₁₄H₁₄O₄S) calculated 278.0613 found 278.0615.

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3065 (vw), 2946 (vw), 2845 (vw), 1596 (w), 1498 (m), 1455 (m), 1362 (s), 1287 (m), 1257 (s), 1188 (s),

1166 (s), 1158 (s), 1106 (s), 1086 (s), 1041 (m), 1023 (s),
925 (m), 863 (s), 814 (s), 779 (s), 754 (vs), 713 (s), 700
(s), 659 (s), 611 (m).

**Preparation of toluene-4-sulfonic acid quinolin-8-yl ester
(3j):**



According to GP1 quinolin-8-ol (3.63 g, 25.0 mmol) was reacted with NEt_3 (2.78 g, 27.5 mmol), DMAP (61 mg, 2 mol %) and tosyl chloride (5.24 g, 27.5 mmol) in THF (40 mL) for 20 h. Recrystallization from heptane/EtOAc afforded **3j** as a colorless crystalline solid (6.00 g, 20.0 mmol, 80%).

mp: 116.9-119.7 °C.

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) = 8.85 (dd, J = 4.4 and 1.7 Hz, 1 H), 8.16 (dd, J = 8.3 and 1.7 Hz, 1 H), 7.90 (d, J = 8.5 Hz, 2 H), 7.76 (dd, J = 8.3 and 1.5 Hz, 1 H), 7.62 (dd, J = 7.5 and 1.2 Hz, 1 H), 7.64-7.60 (m, 1 H), 7.41 (dd, J = 8.3 and 4.1 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 2 H), 2.42 (s, 3 H).

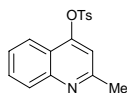
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ (ppm) = 150.6, 145.4, 145.0, 141.3, 135.9, 133.1, 129.6, 129.4, 128.8, 126.9, 126.0, 122.5, 121.8, 21.6.

MS (70 eV, EI): m/z (%): 299 (M^+ , 1), 236 (79), 234 (29), 218 (33), 155 (34), 145 (100), 117 (87), 91 (87).

HRMS: ($\text{C}_{16}\text{H}_{13}\text{NO}_3\text{S}$) calculated 299.0616 found 299.0594.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3064 (vw), 1941 (vw), 1596 (m), 1493 (m), 1470 (m), 1422 (w), 1369 (s), 1355 (m), 1309 (m), 1229 (m), 1188 (m), 1177 (s), 1161 (s), 1079 (s), 1073 (m), 1048 (s), 1029 (m), 1021 (m), 907 (m), 886 (s), 828 (s), 811 (s), 799 (s), 771 (s), 762 (vs), 710 (s), 706 (s), 662 (s), 643 (s), 632 (m), 607 (m).

Preparation of toluene-4-sulfonic acid 2-methyl-quinolin-4-yl ester (3l):



According to GP1 2-methyl-quinolin-4-ol (2.39 g, 15.0 mmol) was reacted with NEt_3 (1.67 g, 16.5 mmol), DMAP (37 mg, 2 mol %) and tosyl chloride (3.15 g, 16.5 mmol) in THF (40 mL) for 20 h. Recrystallization from heptane afforded **31** as colorless crystalline solid (3.85 g, 12.3 mmol, 82%).

mp: 113.5-115.4 °C.

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) = 7.97 (d, J = 8.5 Hz, 1 H), 7.80 (d, J = 8.3 Hz, 2 H), 7.76 (dd, J = 8.8 and 1.7 Hz, 1 H), 7.65 (dt, J = 8.4, 6.9 and 1.5 Hz, 1 H), 7.38 (dt, J = 8.3, 7.0 and 1.0 Hz, 1 H), 7.29 (d, J = 8.5 Hz, 2 H), 7.20 (s, 1 H), 2.71 (s, 3 H), 2.41 (s, 3 H).

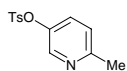
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ (ppm) = 159.8, 153.2, 149.5, 146.0, 132.3, 130.3, 130.0, 128.3, 126.3, 121.3, 120.5, 112.9, 76.4, 25.5, 21.7.

MS (70 eV, EI): m/z (%): 313 (M^+ , 100), 159 (13), 155 (87), 130 (20), 91 (33), 65 (14).

HRMS: ($\text{C}_{17}\text{H}_{15}\text{NO}_3\text{S}$) calculated 313.0773 found 313.0773.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3069 (vw), 3049 (vw), 2917 (vw), 1600 (m), 1557 (m), 1498 (m), 1406 (w), 1376 (s), 1332 (m), 1304 (m), 1230 (m), 1188 (s), 1173 (s), 1151 (m), 1091 (m), 1048 (s), 1018 (m), 993 (m), 965 (s), 870 (s), 814 (s), 804 (s), 786 (m), 765 (vs), 746 (vs), 664 (vs).

Preparation of toluene-4-sulfonic acid 6-methyl-pyridin-3-yl ester (3m):



According to GP1 6-methyl-pyridin-3-ol (2.70 g, 24.7 mmol) was reacted with NEt_3 (2.78 g, 27.5 mmol), DMAP (61 mg, 2 mol %) and tosyl chloride (5.24 g, 27.5 mmol) in THF (40 mL) for 20 h. Recrystallization from heptane/EtOAc afforded **3m** as colorless crystalline solid (4.20 g, 16.0 mmol, 65%).

mp: 104.7-107.0 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 7.97 (d, *J* = 2.7 Hz, 1 H), 7.67 (d, *J* = 8.3 Hz, 2 H), 7.38-7.34 (m, 1 H), 7.31 (d, *J* = 8.8 Hz, 2 H), 7.12 (d, *J* = 8.5 Hz, 1 H), 2.52 (s, 3 H), 2.43 (s, 3 H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 157.2, 145.9, 144.5, 142.7, 131.7, 130.6, 130.0, 128.5, 123.9, 23.8, 21.7.

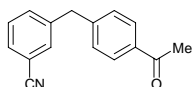
MS (70 eV, EI): *m/z* (%): 263 (M⁺, 38), 155 (54), 91 (100), 65 (7), 53 (6).

HRMS: (C₁₃H₁₃NO₃S) calculated 263.0616 found 263.0622.

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3351 (vw), 3259 (vw), 1596 (m), 1478 (m), 1374 (m), 1365 (s), 1349 (m), 1299 (m), 1284 (m), 1199 (m), 1169 (vs), 1120 (m), 1089 (s), 1021 (s), 923 (m), 860 (s), 845 (s), 840 (s), 815 (s), 801 (s), 793 (vs), 731 (s), 715 (vs), 701 (s), 655 (vs), 638 (s).

Preparation of the cross-coupling products:

Preparation of 3-(4-acetyl-benzyl)-benzonitrile (4a):



According to GP2 the benzylic zinc reagent **1a** (1.75 mL, 1.37 M in THF, 2.40 mmol) was reacted with 1-(4-bromo-phenyl)-ethanone (**3a**) (398 mg, 2.00 mmol). The reaction time was 0.5 h. Flash column chromatographical purification (silica; pentane:Et₂O, 2:1) afforded **4a** as a colorless solid (352 mg, 1.50 mmol, 75%).

mp: 71.6 – 73.9 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 7.90 (d, *J* = 8.2 Hz, 2 H), 7.53-7.50 (m, 1 H), 7.45 (s, 1 H), 7.42-7.40 (m, 2 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 4.06 (s, 2 H), 2.58 (s, 3 H).

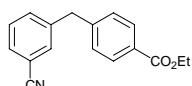
¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 197.6, 144.8, 141.5, 135.7, 133.4, 132.3, 130.2, 129.4, 129.1, 128.9, 126.8, 112.7, 41.3, 26.6.

MS (70 eV, EI): *m/z* (%): 235 (M⁺, 33), 220 (100), 201 (83), 199 (90), 116 (24), 89 (43).

HRMS: (C₁₆H₁₃NO) calculated 235.0997 found 235.1009.

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3516 (m), 2228 (m), 1672 (vs), 1600 (m), 1584 (m), 1568 (w), 1484 (w), 1456 (w), 1412 (m), 1356 (m), 1268 (m), 1200 (w), 1184 (w), 1140 (w), 1112 (w), 1076 (w), 1012 (w), 960 (w), 904 (w), 888 (w), 848 (w), 824 (m), 808 (w), 792 (m), 748 (m), 716 (w), 692 (m), 624 (m), 592 (w), 576 (w), 560 (w).

Preparation of 4-(3-cyano-benzyl)-benzoic acid ethyl ester (4b):



According to GP2 the benzylic zinc reagent **1a** (1.75 mL, 1.37 M in THF, 2.40 mmol) was reacted with 4-chloro-benzoic acid ethyl ester (**3b**) (370 mg, 2.00 mmol). The reaction time was 0.5 h. Flash column chromatographical purification (silica; pentane:Et₂O, 6:1) afforded **4b** as a colorless solid (473 mg, 1.78 mmol, 89%).

mp: 60.5–62.4 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 7.98 (d, J = 8.4 Hz, 2 H), 7.53–7.38 (m, 4 H), 7.22 (d, J = 8.4 Hz, 2 H), 4.36 (q, J = 7.1 Hz, 2 H), 4.05 (s, 2 H), 1.37 (t, J = 7.1 Hz, 3 H).

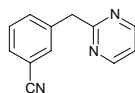
¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 166.5, 144.7, 141.9, 133.6, 132.6, 130.4, 130.3, 129.6, 129.3, 129.1, 118.9, 112.9, 61.2, 41.5, 14.6.

MS (70 eV, EI): m/z (%): 265 (M⁺, 37), 237 (20), 220 (100), 192 (30), 190 (28), 165 (24).

HRMS: (C₁₇H₁₅NO₂) calculated 265.1103 found 265.1077.

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3076 (w), 3052 (w), 3000 (w), 2976 (w), 2956 (w), 2900 (w), 2228 (m), 1708 (vs), 1608 (m), 1576 (w), 1476 (w), 1448 (w), 1436 (w), 1416 (w), 1392 (w), 1364 (m), 1324 (w), 1308 (w), 1276 (vs), 1192 (w), 1176 (m), 1128 (m), 1108 (s), 1020 (m), 980 (w), 940 (w), 908 (w), 876 (w), 856 (w), 788 (m), 764 (m), 728 (m), 700 (w), 688 (m), 652 (w), 560 (w).

Preparation of 3-pyrimidin-2-ylmethyl-benzonitrile (4c):



According to GP2 the benzylic zinc reagent **1a** (1.75 mL, 1.37 M in THF, 2.40 mmol) was reacted with 2-chloro-pyrimidine (**3c**) (230 mg, 2.00 mmol). The reaction time was 0.5 h. Flash column chromatographical purification (silica; Et₂O) afforded **4c** as a yellow oil (269 mg, 1.38 mmol, 69%).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 8.67 (d, *J* = 5.1 Hz, 2 H), 7.64 (s, 1 H), 7.60–7.57 (m, 1 H), 7.52 – 7.48 (m, 1 H), 7.41–7.36 (m, 1 H), 7.16 (t, *J* = 4.9 Hz, 1 H), 4.30 (s, 2 H).

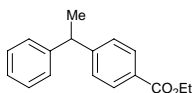
¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 168.7, 157.4, 139.5, 133.7, 132.7, 130.3, 129.2, 119.0, 118.8, 112.5, 45.3.

MS (70 eV, EI): *m/z* (%): 196 (6), 195 (M⁺, 53), 194 (100), 193 (5), 167 (2), 142 (3), 116 (4), 115 (5), 114 (3).

HRMS: (C₁₂H₉N₃) calculated 195.0796 found 195.0803.

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3040 (w), 2972 (vw), 2924 (vw), 2228 (m), 1604 (vw), 1560 (vs), 1484 (w), 1416 (vs), 1320 (vw), 1296 (vw), 1280 (vw), 1232 (w), 1180 (w), 1152 (vw), 1096 (w), 996 (w), 944 (vw), 912 (w), 856 (vw), 792 (m), 716 (w), 688 (m), 636 (w), 584 (w), 564 (w).

Preparation of 4-(1-phenyl-ethyl)-benzoic acid ethyl ester (4d):



According to GP2 the benzylic zinc reagent **1b** (1.78 mL, 1.35 M in THF, 2.40 mmol) was reacted with 4-bromo benzoic acid ethyl ester (**3d**) (458 mg, 2.00 mmol). The reaction time was 12 h. Flash column chromatographical purification (silica; pentane:Et₂O, 98:2) afforded **4d** as a colorless oil (485 mg, 1.91 mmol, 95%).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 7.97 (d, *J* = 8.3 Hz, 2 H), 7.33–7.25 (m, 4 H), 7.23–7.16 (m, 3 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.20 (q, *J* = 7.1 Hz, 1.66 (d, *J* = 7.3 Hz, 3 H), 1.37 (t, *J* = 7.1 Hz, 3 H).

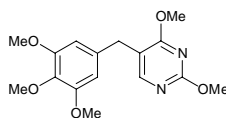
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ (ppm) = 166.5, 151.5, 145.4, 129.7, 128.5, 128.4, 127.6, 127.5, 126.3, 60.7, 44.8, 21.6, 14.3.

MS (70 eV, EI): m/z (%): 254 (M^+ , 100), 239 (45), 209 (40), 181 (41), 165 (57).

HRMS: ($\text{C}_{17}\text{H}_{18}\text{O}_2$) calculated 254.1307 found 254.1305.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3028 (vw), 2973 (w), 2934 (vw), 1712 (s), 1610 (m), 1494 (w), 1451 (w), 1415 (w), 1367 (m), 1310 (w), 1271 (vs), 1178 (m), 1102 (s), 1019 (s), 857 (m), 758 (m), 738 (m), 698 (vs), 646 (w), 595 (w).

Preparation of 2,4-dimethoxy-5-(3,4,5-trimethoxy-benzyl)-pyrimidine (4e):



According to GP2 the benzylic zinc reagent **1c** (2.00 mL, 1.21 M in THF, 2.40 mmol) was reacted with 5-bromo-2,4-dimethoxy-pyrimidine (**3e**) (438 mg, 2.00 mmol). The reaction time was 2 h. Flash column chromatographical purification (silica; pentane:Et₂O, 1:2) afforded **4e** as a colorless solid (551 mg, 1.72 mmol, 86%).

mp: 74.1-76.3 °C.

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) = 7.94 (s, 1 H), 6.39 (s, 2 H), 3.98 (s, 3 H), 3.96 (s, 3 H), 3.80 (s, 9 H), 3.72 (s, 2 H).

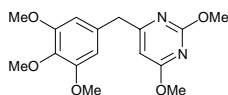
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ (ppm) = 169.2, 164.2, 157.1, 153.2, 136.6, 134.6, 114.5, 105.7, 60.8, 56.1, 54.7, 53.9, 32.7.

MS (70 eV, EI): m/z (%): 320 (M^+ , 100), 305 (45), 289 (9), 230 (14), 181 (62).

HRMS: ($\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_5$) calculated 320.1372 found 320.1348.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2947 (w), 2909 (w), 2842 (w), 2828 (w), 1593 (s), 1573 (s), 1510 (m), 1456 (s), 1403 (s), 1373 (s), 1331 (s), 1286 (s), 1249 (s), 1232 (s), 1193 (s), 1121 (vs), 1076 (vs), 1005 (vs), 976 (s), 935 (m), 859 (s), 833 (s), 784 (vs), 749 (s), 699 (m), 636 (m), 602 (s).

Preparation of 2,4-dimethoxy-6-(3,4,5-trimethoxy-benzyl)-pyrimidine (4f):



According to GP2 the benzylic zinc reagent **1c** (2.00 mL, 1.21 M in THF, 2.40 mmol) was reacted with 4-chloro-2,6-dimethoxy-pyrimidine (**3f**) (349 mg, 2.00 mmol). The reaction time was 2 h. Flash column chromatographical purification (silica; pentan:Et₂O, 1:2) afforded **4f** as a colorless solid (628 mg, 1.96 mmol, 98%).

mp: 60.8-62.9 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 6.49 (s, 2 H), 6.12 (s, 1 H), 3.98 (s, 3 H), 3.91 (s, 3 H), 3.84 (s, 2 H), 3.82 (s, 6 H), 3.81 (s, 3 H).

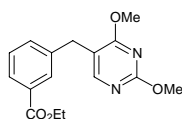
¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 172.0, 171.4, 165.2, 153.2, 136.8, 133.2, 106.3, 99.9, 60.8, 56.1, 54.6, 53.7, 44.0.

MS (70 eV, EI): *m/z* (%): 320 (M⁺, 74), 305 (60), 181 (13), 69 (13), 57 (11), 44 (100).

HRMS: (C₁₆H₂₀N₂O₅) calculated 320.1372 found 320.1360.

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3083 (w), 2945 (w), 2932 (w), 2831 (w), 1588 (s), 1564 (vs), 1505 (s), 1451 (s), 1433 (m), 1419 (s), 1375 (m), 1350 (vs), 1331 (s), 1299 (s), 1244 (s), 1233 (s), 1204 (s), 1193 (m), 1186 (m), 1149 (s), 1121 (vs), 1092 (vs), 1036 (s), 1003 (s), 980 (s), 922 (m), 862 (m), 835 (s), 826 (s), 816 (m), 792 (m), 742 (m), 729 (s), 717 (m), 686 (m), 612 (m), 602 (s).

Preparation of 3-(2,4-dimethoxy-pyrimidin-5-ylmethyl)-benzoic acid ethyl ester (4g):



According to GP2 the benzylic zinc reagent **1d** (1.74 mL, 1.38 M in THF, 2.40 mmol) was reacted with 5-bromo-2,4-dimethoxy-

pyrimidine (**3e**) (438 mg, 2.00 mmol). The reaction time was 1.5 h. Flash column chromatographical purification (silica; pentane:Et₂O, 1:1) afforded **4g** as a colorless oil (505 mg, 1.67 mmol, 84%).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 7.96 (s, 1 H), 7.89–7.86 (m, 2 H), 7.34–7.32 (m, 2 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 3.95 (s, 3 H), 3.95 (s, 3 H), 3.82 (s, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

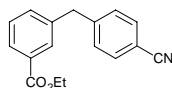
¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 169.2, 166.5, 164.3, 157.1, 139.4, 133.0, 130.7, 129.7, 128.4, 127.6, 114.1, 60.9, 54.7, 53.9, 32.3, 14.3.

MS (70 eV, EI): *m/z* (%): 302 (M⁺, 100), 301 (53), 287 (27), 273 (33), 257 (33), 241 (21), 200 (25).

HRMS: (C₁₆H₁₈N₂O₄) calculated 302.1267 found 302.1269.

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2985 (w), 2957 (w), 2902 (w), 1715 (s), 1600 (s), 1567 (s), 1466 (s), 1398 (s), 1379 (vs), 1350 (m), 1273 (vs), 1239 (m), 1190 (s), 1153 (w), 1104 (m), 1070 (s), 1052 (m), 1015 (s), 788 (w), 763 (w), 744 (m), 694 (w).

Preparation of 3-(4-cyano-benzyl)-benzoic acid ethyl ester (**4h**):



According to GP2 the benzylic zinc reagent **1b** (1.74 mL, 1.38 M in THF, 2.40 mmol) was reacted with 4-chloro-benzonitrile (**3g**) (276 mg, 2.00 mmol). The reaction time was 0.5 h. Flash column chromatographical purification (silica; pentane:Et₂O, 2:1) afforded **4h** as a colorless solid (482 mg, 1.82 mmol, 91%).

mp: 51.0–53.0 °C.

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 7.93–7.89 (m, 1 H), 7.87–7.85 (m, 1 H), 7.56 (d, *J* = 8.3 Hz, 2 H), 7.40–7.30 (m, 2 H), 7.27 (d, *J* = 8.5 Hz, 2 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.07 (s, 2 H), 1.37 (t, *J* = 7.2 Hz, 3 H).

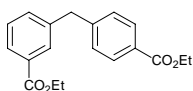
¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 166.3, 146.0, 139.6, 133.3, 132.4, 131.0, 130.0, 129.6, 128.8, 127.9, 118.8, 110.3, 61.0, 41.7, 14.3.

MS (70 eV, EI): m/z (%): 265 (M^+ , 56), 237 (49), 221 (20), 220 (100), 207 (29), 193 (16), 192 (30), 191 (21), 190 (26), 165 (17).

HRMS: ($C_{17}H_{15}NO_2$) calculated 265.1103 found 265.1089.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3054 (vw), 2991 (w), 2983 (w), 2937 (w), 2912 (w), 2874 (vw), 2228 (m), 1707 (vs), 1669 (w), 1604 (m), 1586 (w), 1477 (w), 1446 (m), 1362 (m), 1279 (s), 1188 (s), 1105 (m), 1024 (m), 939 (m), 854 (m), 796 (w), 762 (m), 734 (m), 696 (m), 602 (m).

Preparation of ethyl-3-[4-(ethoxycarbonyl)-benzyl]-benzoate (4i):



According to GP2 the benzylic zinc reagent **1d** (1.74 mL, 1.38 M in THF, 2.40 mmol) was reacted with 4-(toluene-4-sulfonyloxy)-benzoic acid ethyl ester (**3h**) (641 mg, 2.00 mmol). The reaction time was 2 h. Flash column chromatographical purification (silica; pentane:Et₂O, 9:1) afforded **4i** as a yellow oil (385 mg, 1.29 mmol, 65%).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 7.99 (d, J = 8.4 Hz, 2 H), 7.94–7.91 (m, 2 H), 7.41–7.34 (m, 2 H), 7.27 (d, J = 8.6 Hz, 2 H), 4.38 (q, J = 7.2 Hz, 2 H), 4.38 (q, J = 7.1 Hz, 2 H), 4.09 (s, 2 H), 1.40 (t, J = 7.1 Hz, 3 H), 1.40 (t, J = 7.2 Hz, 3 H).

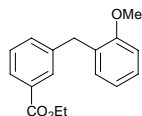
¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 166.5, 166.5, 145.7, 140.4, 140.4, 133.3, 130.8, 130.0, 129.9, 128.8, 128.7, 128.6, 127.6, 61.0, 60.8, 41.6, 14.3.

MS (70 eV, EI): m/z (%): 312 (M^+ , 40), 268 (17), 267 (100), 240 (14), 239 (37), 167 (15), 166 (16), 165 (36), 111 (11).

HRMS: ($C_{19}H_{20}O_4$) calculated 312.1362 found 312.1354.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2982 (w), 2937 (vw), 2906 (vw), 1711 (vs), 1609 (w), 1588 (w), 1444 (w), 1415 (w), 1366 (w), 1270 (vs), 1187 (m), 1177 (m), 1100 (s), 1082 (m), 1020 (m), 940 (w), 855 (w), 746 (m), 710 (m), 689 (w), 637 (vw), 590 (w).

Preparation of 3-(2-methoxy-benzyl)-benzoic acid ethyl ester (4j):



According to GP2 the benzylic zinc reagent **1d** (1.74 mL, 1.38 M in THF, 2.40 mmol) was reacted with toluene-4-sulfonic acid 2-methoxy-phenyl ester (**3i**) (557 mg, 2.00 mmol). The reaction time was 24 h. Flash column chromatographical purification (silica; pentane:Et₂O, 19:1) afforded **4j** as a colorless liquid (370 mg, 1.37 mmol, 69%).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 7.95-7.92 (m, 1 H), 7.86 (d, *J* = 7.5 Hz, 1 H), 7.40-7.35 (m, 1 H), 7.31 (t, *J* = 7.4 Hz, 1 H), 7.20 (td, *J* = 7.8 and 1.9 Hz, 1 H), 7.07 (dd, *J* = 7.9 and 1.8 Hz, 1 H), 6.91-6.84 (m, 2 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 4.01 (s, 2 H), 3.81 (s, 3 H), 1.38 (t, *J* = 7.1 Hz, 3 H).

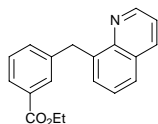
¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 166.8, 157.3, 141.4, 133.4, 130.4, 130.2, 130.1, 129.1, 128.2, 127.6, 127.1, 120.5, 110.5, 60.8, 55.3, 35.8, 14.3.

MS (70 eV, EI): *m/z* (%): 270 (M⁺, 87), 225 (66), 224 (96), 196 (100), 165 (49), 135 (89), 91 (53).

HRMS: (C₁₇H₁₈O₃) calculated 270.1256 found 270.1259.

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2978 (w), 2936 (w), 2835 (vw), 1713 (s), 1586 (m), 1492 (m), 1463 (m), 1438 (m), 1366 (m), 1275 (s), 1241 (vs), 1193 (m), 1182 (s), 1102 (s), 1079 (m), 1049 (m), 1026 (s), 1002 (m), 929 (w), 741 (vs), 714 (m), 691 (m), 670 (m), 619 (m).

Preparation of 3-quinolin-8-ylmethyl-benzoic acid ethyl ester (4k):



According to GP2 the benzylic zinc reagent **1d** (1.74 mL, 1.38 M, 2.40 mmol) was reacted with toluene-4-sulfonic acid quinolin-8-yl ester (**3j**) (599 mg, 2.00 mmol). The reaction time was 3 h. Flash column chromatographical purification (silica; pentane:Et₂O, 6:1) afforded **4k** as a colorless oil (491 mg, 1.69 mmol, 85%).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 8.96 (dd, *J* = 4.3 and 1.8 Hz, 1 H), 8.15 (dd, *J* = 8.3 and 1.7 Hz, 1 H), 8.05-8.02 (m, 1 H), 7.89-7.84 (m, 1 H), 7.72-7.66 (m, 1 H), 7.52-7.47 (m, 1 H), 7.46-7.38 (m, 3 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 4.73 (s, 2 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

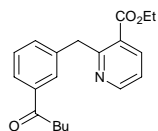
¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 166.8, 149.4, 146.4, 141.6, 139.5, 136.4, 133.9, 130.5, 130.4, 129.6, 128.4, 128.3, 127.2, 126.5, 126.4, 121.1, 60.8, 36.6, 14.3.

MS (70 eV, EI): *m/z* (%): 291 (M⁺, 100), 262 (63), 246 (12), 218 (28), 217 (55), 108 (34).

HRMS: (C₁₉H₁₇NO₂) calculated 291.1259 found 129.1261.

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3033 (vw), 2979 (w), 2928 (w), 2902 (w), 1710 (vs), 1594 (w), 1497 (m), 1442 (m), 1366 (m), 1272 (vs), 1188 (s), 1103 (s), 1081 (s), 1024 (m), 928 (w), 870 (w), 818 (m), 809 (m), 789 (s), 751 (s), 713 (s), 689 (m), 672 (m), 612 (m).

Preparation of 2-(3-pentanoyl-benzyl)-nicotinic acid ethyl ester (4l):



According to GP2 the benzylic zinc reagent **1e** (2.30 mL, 1.06 M in THF, 2.40 mmol) was reacted with 2-chloro-nicotinic acid ethyl ester (**3k**) (371 mg, 2.00 mmol). The reaction time was 1 h. Flash column chromatographical purification (silica; pentane:Et₂O, 6:1 then 1:1) afforded **4l** as a pale yellow liquid (583 mg, 1.79 mmol, 90%).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 8.67 (dd, *J* = 4.9 and 1.9 Hz, 1 H), 8.12 (dd, *J* = 7.9 and 1.8 Hz, 1 H), 7.86 (m, 1 H), 7.75

(m, 1 H), 7.44 (m, 1 H), 7.32 (t, $J = 7.7$ Hz, 1 H), 7.24 (dd, $J = 8.0$ and 4.9 Hz, 1 H), 4.63 (s, 2 H), 4.32 (q, $J = 7.1$ Hz, 2 H), 2.90 (t, $J = 7.3$ Hz, 2 H), 1.67 (quint, $J = 7.4$ Hz, 2 H), 1.37 (sext, $J = 7.5$ Hz, 2 H), 1.32 (t, $J = 7.2$ Hz, 3 H), 0.92 (t, $J = 7.3$ Hz, 3 H).

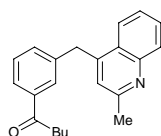
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ (ppm) = 200.6, 166.3, 160.6, 151.9, 140.1, 138.8, 137.1, 133.6, 128.7, 128.4, 126.1, 125.9, 121.4, 61.5, 42.1, 38.3, 26.5, 22.4, 14.1, 13.9.

MS (70 eV, EI): m/z (%): 325 (M^+ , 79), 283 (12), 282 (12), 269 (16), 268 (100), 212 (10), 211 (13), 167 (27), 166 (24).

HRMS: ($\text{C}_{20}\text{H}_{23}\text{NO}_3$) calculated 325.1678 found 325.1666.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2958 (m), 2933 (m), 2872 (w), 1719 (vs), 1681 (s), 1582 (m), 1568 (m), 1436 (m), 1366 (m), 1274 (s), 1256 (vs), 1173 (m), 1158 (m), 1130 (s), 1111 (m), 1079 (s), 1057 (m), 1018 (m), 862 (w), 776 (m), 752 (m), 741 (m), 694 (m), 629 (w), 576 (w).

Preparation of 1-[3-(2-methyl-quinolin-4-ylmethyl)-phenyl]-pentan-1-one (4m):



According to GP2 the benzylic zinc reagent **1e** (2.30 mL, 1.06 M in THF, 2.40 mmol) was reacted with toluene-4-sulfonic acid 2-methyl-quinolin-4-yl ester (**31**) (627 mg, 2.00 mmol). The reaction time was 16 h. Flash column chromatographical purification (silica; pentane:Et₂O, 1:1 then Et₂O) afforded **4m** as a colorless, high viscous oil (585 mg, 1.85 mmol, 92%).

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) = 8.04 (d, $J = 8.5$ Hz, 1 H), 7.92 (d, $J = 9.2$ Hz, 1 H), 7.81 (m, 2 H), 7.64 (t, $J = 7.7$ Hz, 1 H), 7.44 (t, $J = 7.7$ Hz, 1 H), 7.35 (m, 2 H), 7.00 (s, 1 H), 4.43 (s, 2 H), 2.89 (t, $J = 7.4$ Hz, 2 H), 2.68 (s, 3 H), 1.67 (quint, $J = 7.5$ Hz, 2 H), 1.39 (sext, $J = 7.5$ Hz, 2 H), 0.91 (t, $J = 7.3$ Hz, 3 H).

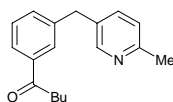
¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 200.4, 158.8, 148.0, 145.8, 139.3, 137.5, 133.2, 129.3, 129.2, 128.9, 128.3, 126.5, 125.8, 125.6, 123.4, 122.7, 38.4, 38.0, 26.4, 25.3, 22.4, 13.9.

MS (70 eV, EI): *m/z* (%): 317 (M⁺, 25), 275 (100), 261 (44), 260 (38), 247 (15), 231 (63), 216 (15), 189 (18), 115 (12).

HRMS: (C₂₂H₂₃NO) calculated 317.1780 found 317.1756.

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3063 (w), 2954 (s), 2930 (m), 2871 (m), 1674 (vs), 1601 (s), 1585 (m), 1562 (w), 1511 (m), 1466 (w), 1437 (m), 1415 (m), 1376 (m), 1336 (m), 1274 (m), 1227 (m), 1158 (m), 1024 (w), 964 (w), 910 (w), 869 (w), 763 (s), 756 (s), 733 (m), 700 (m), 637 (w), 570 (w).

Preparation of 1-[3-(6-methyl-pyridin-3-ylmethyl)-phenyl]-pentan-1-one (4n):



According to GP2 the benzylic zinc reagent **1e** (2.30 mL, 1.06 M, 2.40 mmol) was reacted with toluene-4-sulfonic acid-6-methyl-pyridin-3-yl ester (**3m**) (527 mg, 2.00 mmol). The reaction time was 16 h. Flash column chromatographical purification (silica; pentane:Et₂O, 1:1 then Et₂O) afforded **4n** as a pale yellow liquid (448 mg, 1.68 mmol, 84%).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 8.36 (s, 1 H), 7.78 (m, 2 H), 7.35 (m, 3 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 3.97 (s, 2 H), 2.90 (t, *J* = 7.4 Hz, 2 H), 2.5 (s, 3 H), 1.67 (quint, *J* = 7.4 Hz, 2 H), 1.37 (sext, *J* = 7.4 Hz, 2 H), 0.92 (t, *J* = 7.3 Hz, 3 H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 200.4, 156.4, 149.2, 140.7, 137.4, 136.7, 133.2, 132.7, 128.8, 128.2, 126.2, 123.1, 38.5, 38.3, 26.4, 23.9, 22.4, 13.9.

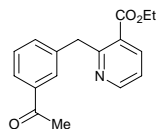
MS (70 eV, EI): *m/z* (%): 268 ([M+H]⁺, 100), 225 (26), 224 (10), 211 (12), 210 (72), 183 (10), 182 (13), 181 (15).

HRMS: (C₁₈H₂₂NO, [M+H]⁺) calculated 268.1701 found 268.1697.

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2957 (s), 2930 (m), 2871 (m), 1681 (vs), 1601 (m), 1585 (w), 1568 (w), 1488 (m), 1465 (m), 1438 (m), 1409 (w), 1392 (m), 1378 (w), 1346 (w), 1320 (w), 1297 (m),

1266 (m), 1256 (m), 1228 (m), 1176 (m), 1159 (m), 1109 (w),
1096 (w), 1029 (m), 913 (w), 812 (w), 792 (w), 754 (m), 728
(m), 693 (m), 646 (w).

Preparation of 2-(3-acetyl-benzyl)-nicotinic acid ethyl ester (4o):



In a dry argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, 2-chloro-nicotinic acid ethyl ester (**3k**) (371 mg, 2.00 mmol) was dissolved in NMP (0.4 mL), PPh₃ (0.1 mL, 0.4 M in THF, 0.40 mmol, 2 mol %) and Ni(acac)₂ (0.1 mL, 0.1 M in THF, 0.1 mmol, 0.5 mol %) were added. Then, the benzylic zinc reagent **1f** (2.24 mL, 1.07 M in THF, 2.40 mmol) was added over 30 min via a syringe pump. The reaction time was 2 h. Flash column chromatographical purification (silica; pentane:Et₂O, 1:1 then 1:3) afforded **4o** as a yellow oil (385 mg, 1.36 mmol, 68%).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 8.67 (dd, *J* = 4.7 and 1.8 Hz, 1 H), 8.19 (dd, *J* = 7.9 and 1.8 Hz, 1 H), 7.88–7.85 (m, 1 H), 7.75 (d, *J* = 7.5 Hz, 1 H), 7.46 (d, *J* = 7.5 Hz, 1 H), 7.32 (t, *J* = 7.7 Hz, 1 H), 7.24 (dd, *J* = 7.9 and 4.7 Hz, 1 H), 4.63 (s, 2 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 2.54 (s, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm) = 198.2, 166.3, 160.5, 151.9, 140.1, 138.8, 137.1, 133.8, 129.0, 128.4, 126.2, 126.0, 121.5, 61.5, 42.1, 26.6, 14.1.

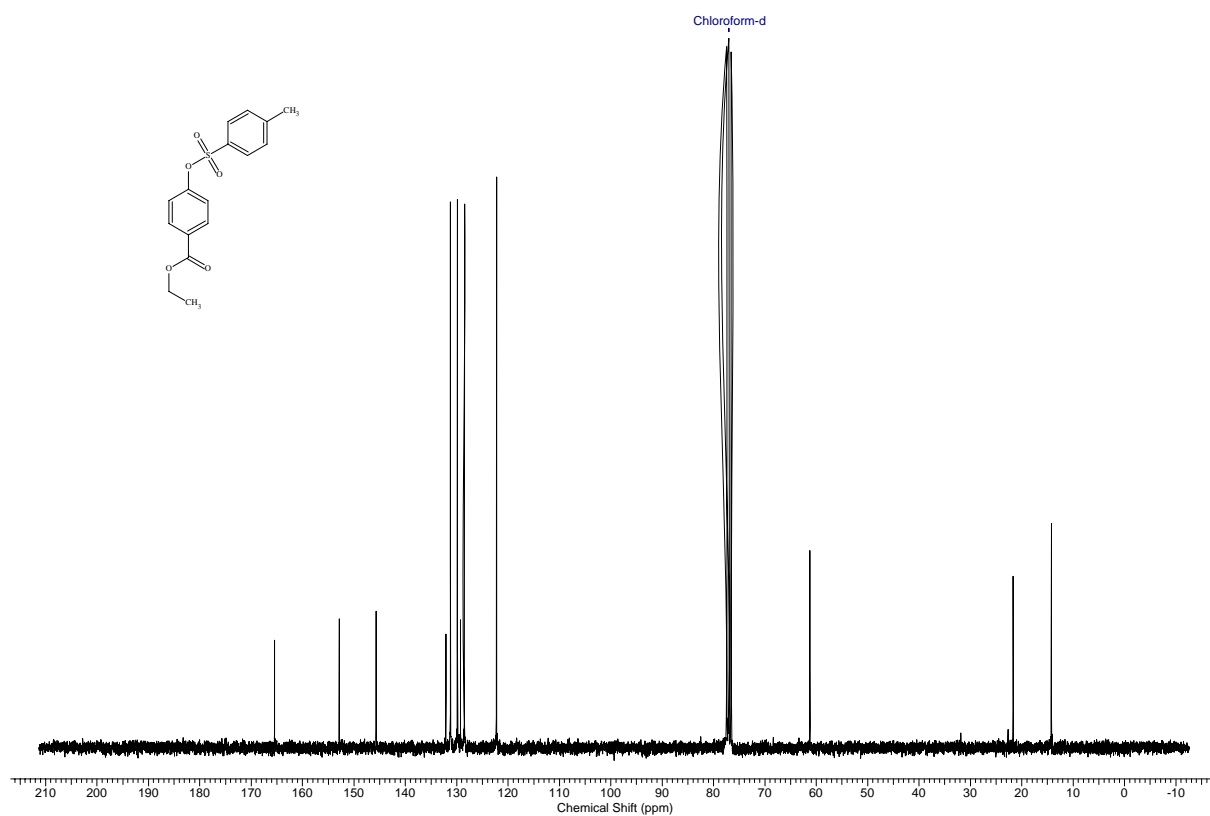
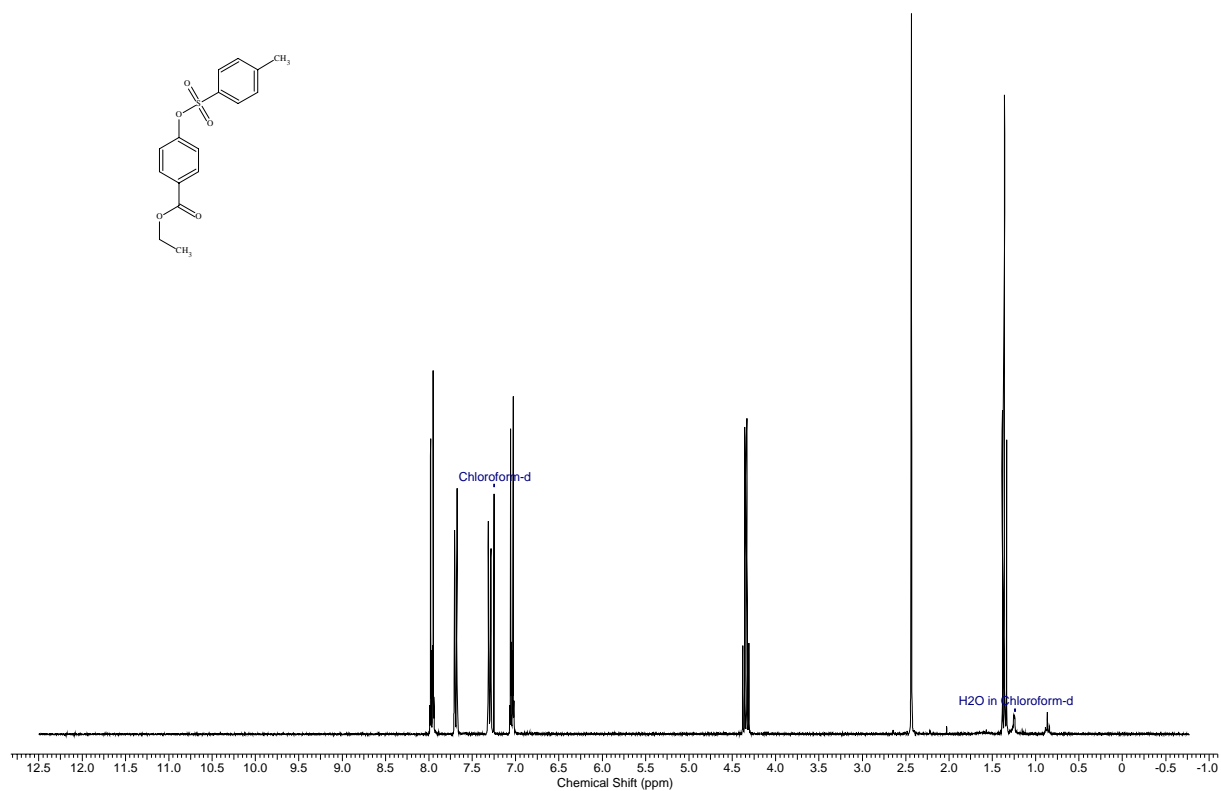
MS (70 eV, EI): *m/z* (%): 283 (100), 267 (37), 210 (39), 195 (13), 167 (29), 135 (12), 43 (58).

HRMS: (C₁₇H₁₇NO₃) calculated 283.1208 found 283.1187.

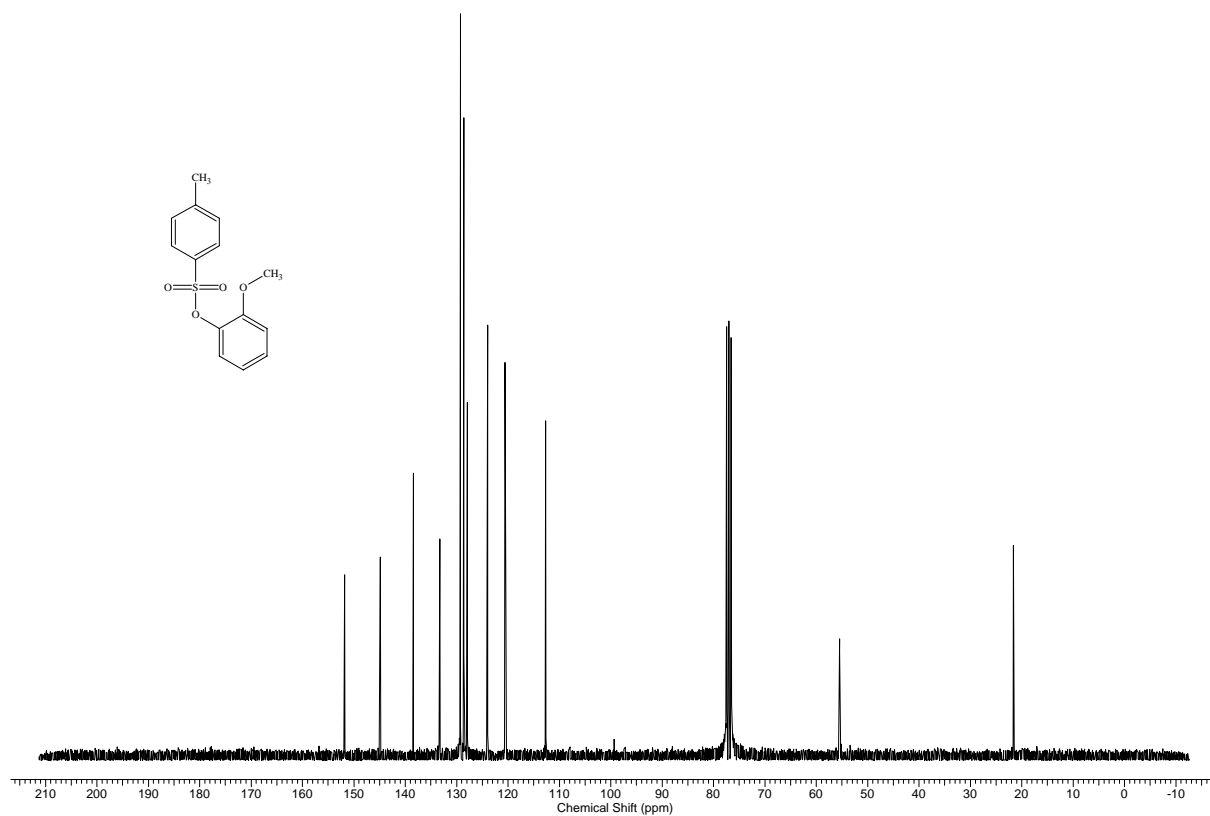
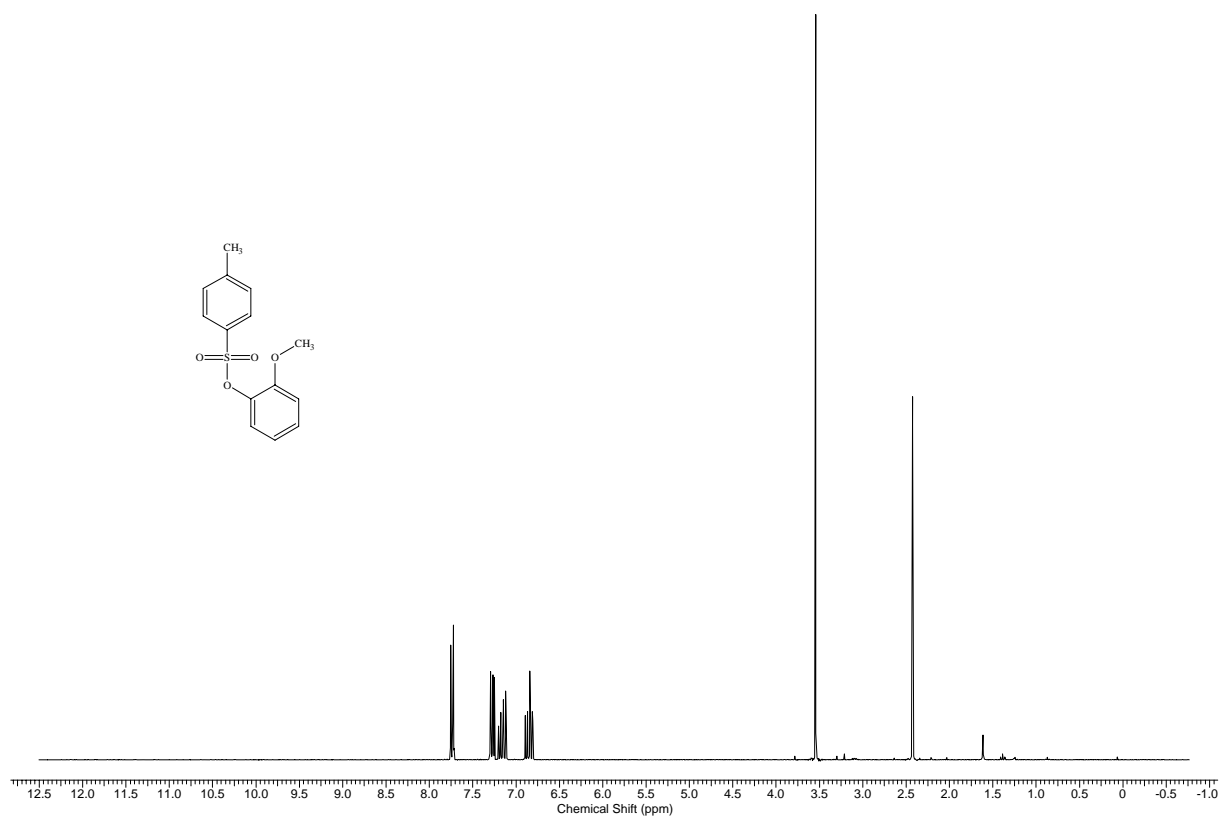
IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3049 (vw), 2982 (w), 2936 (w), 1718 (s), 1681 (vs), 1601 (w), 1582 (m), 1568 (m), 1484 (w), 1436 (m), 1357 (m), 1296 (m), 1258 (vs), 1173 (m), 1130 (m), 1079 (s), 1057 (m), 1018 (w), 976 (w), 956 (w), 863 (w), 777 (m), 741 (m), 693 (m), 589 (w), 577 (w).

Copies of NMR-spectra:

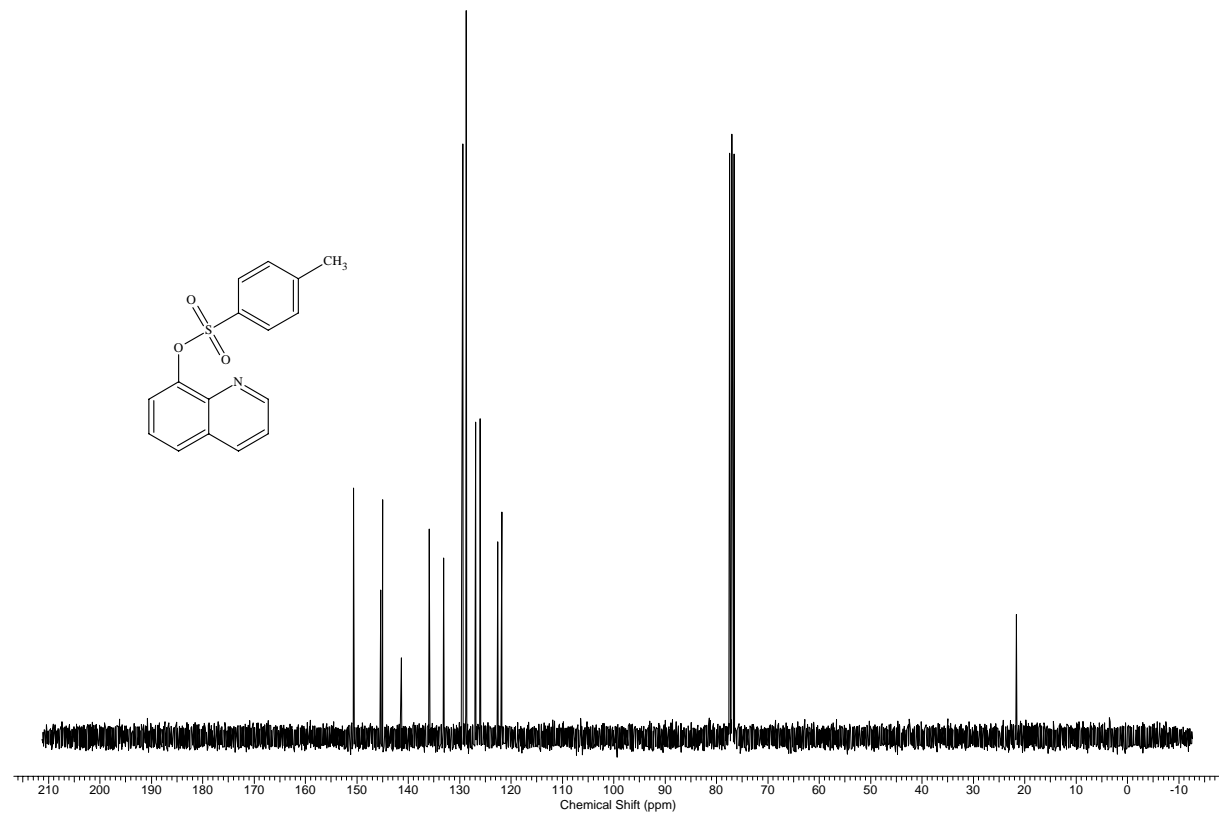
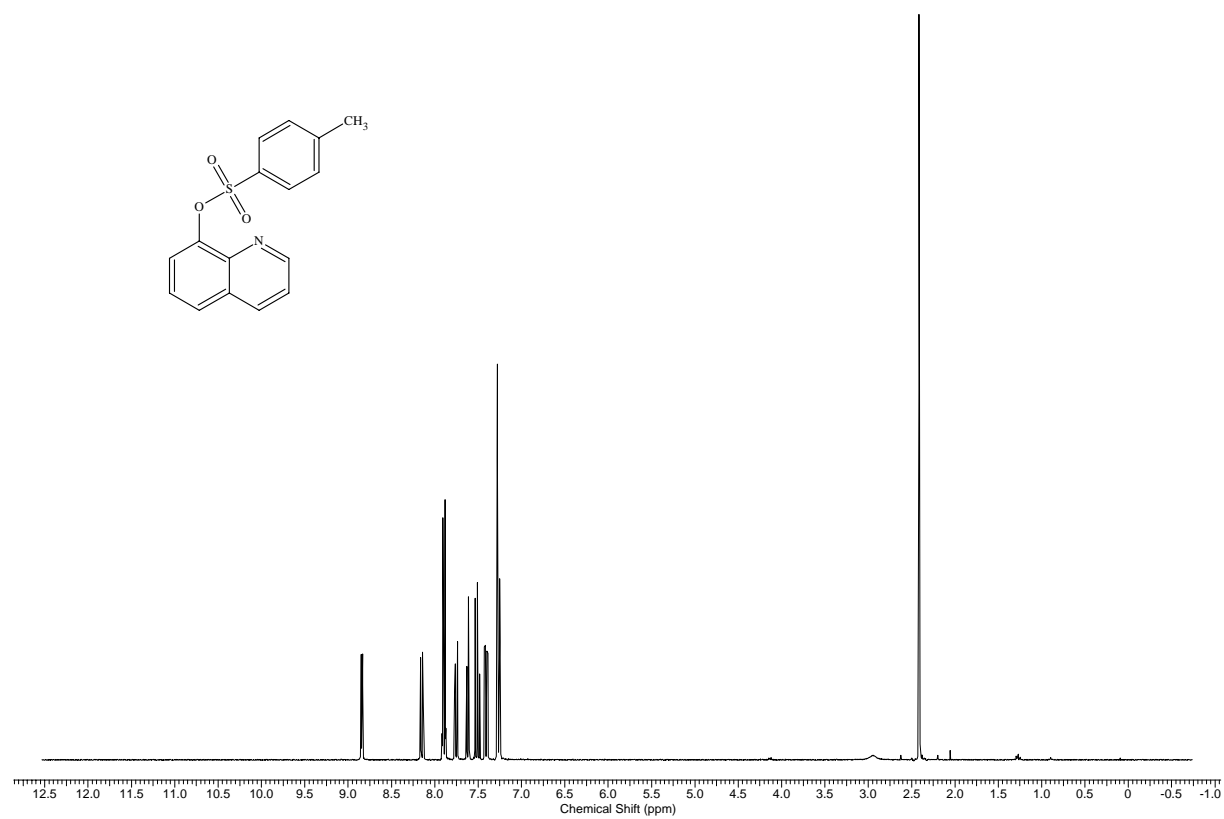
4-(Toluene-4-sulfonyloxy)-benzoic acid ethyl ester (3h):



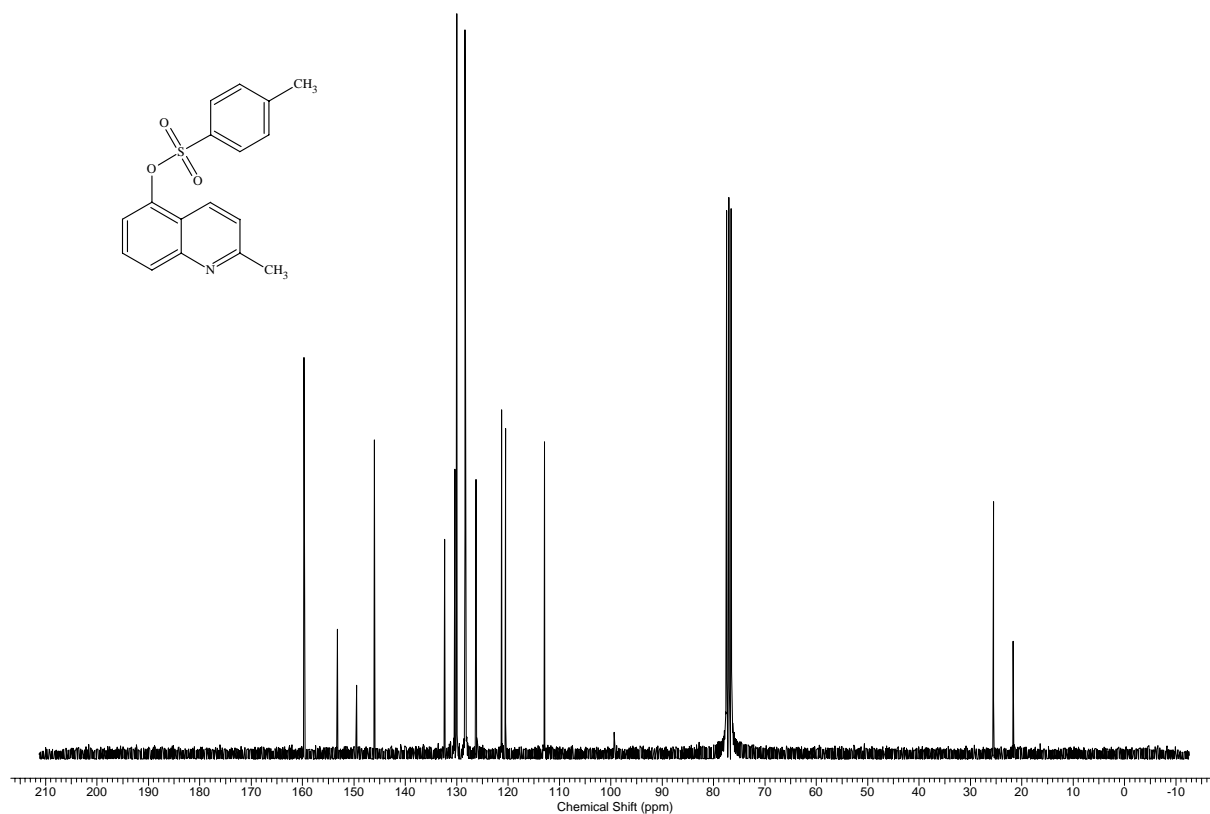
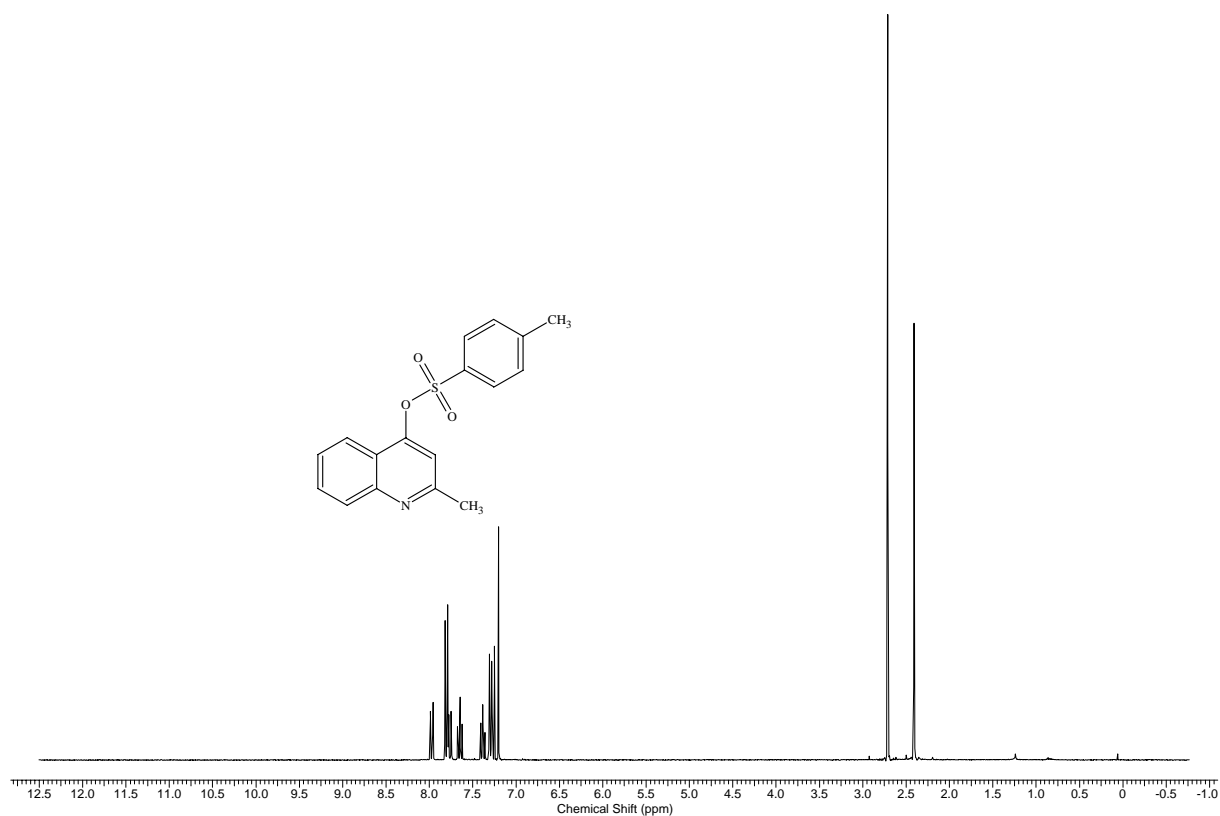
Toluene-4-sulfonic acid 2-methoxy-phenyl ester (3i):



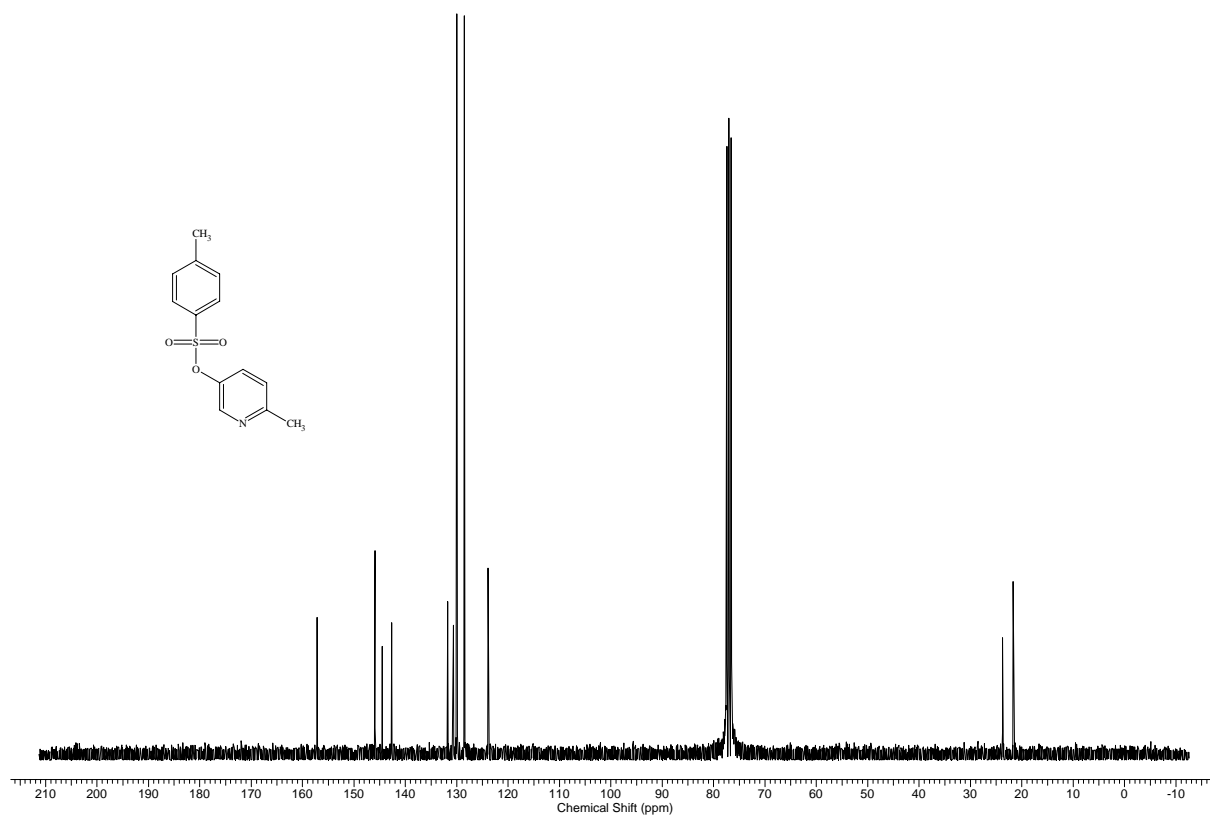
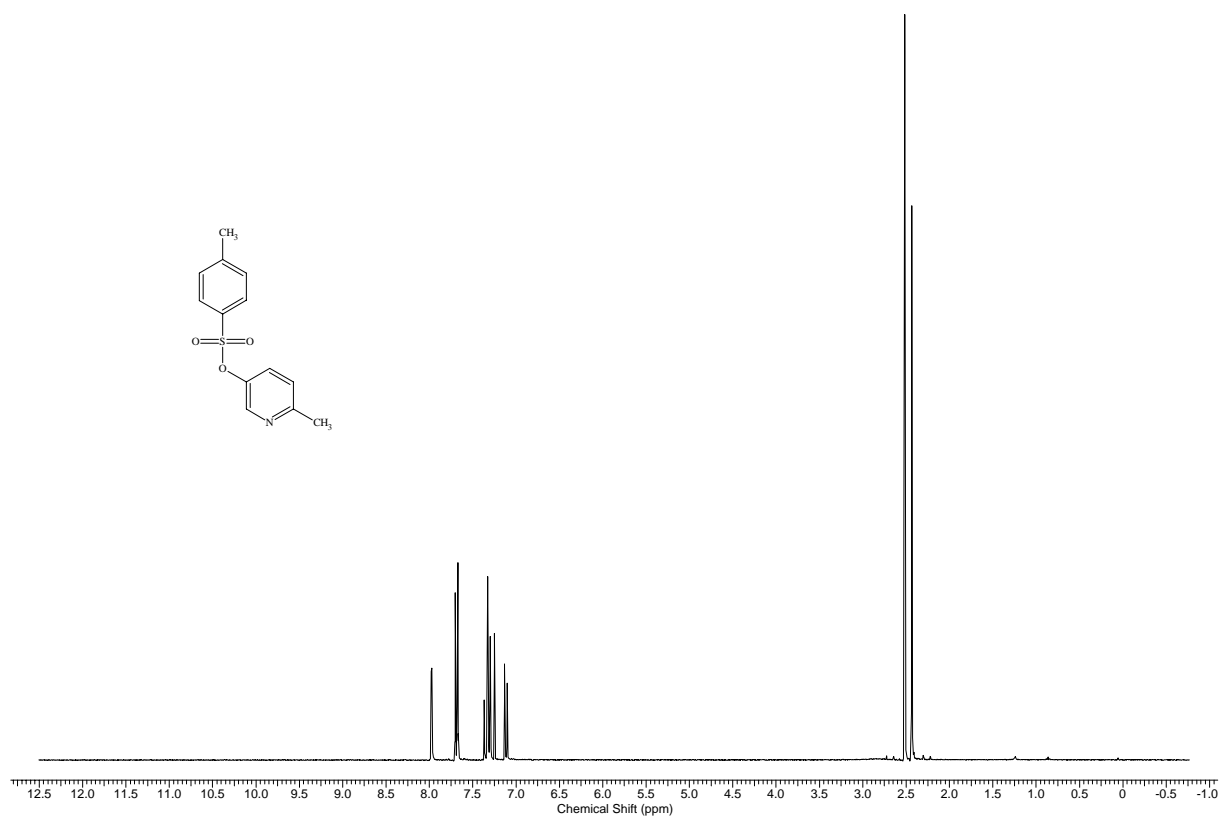
Toluene-4-sulfonic acid quinolin-8-yl ester (3j):



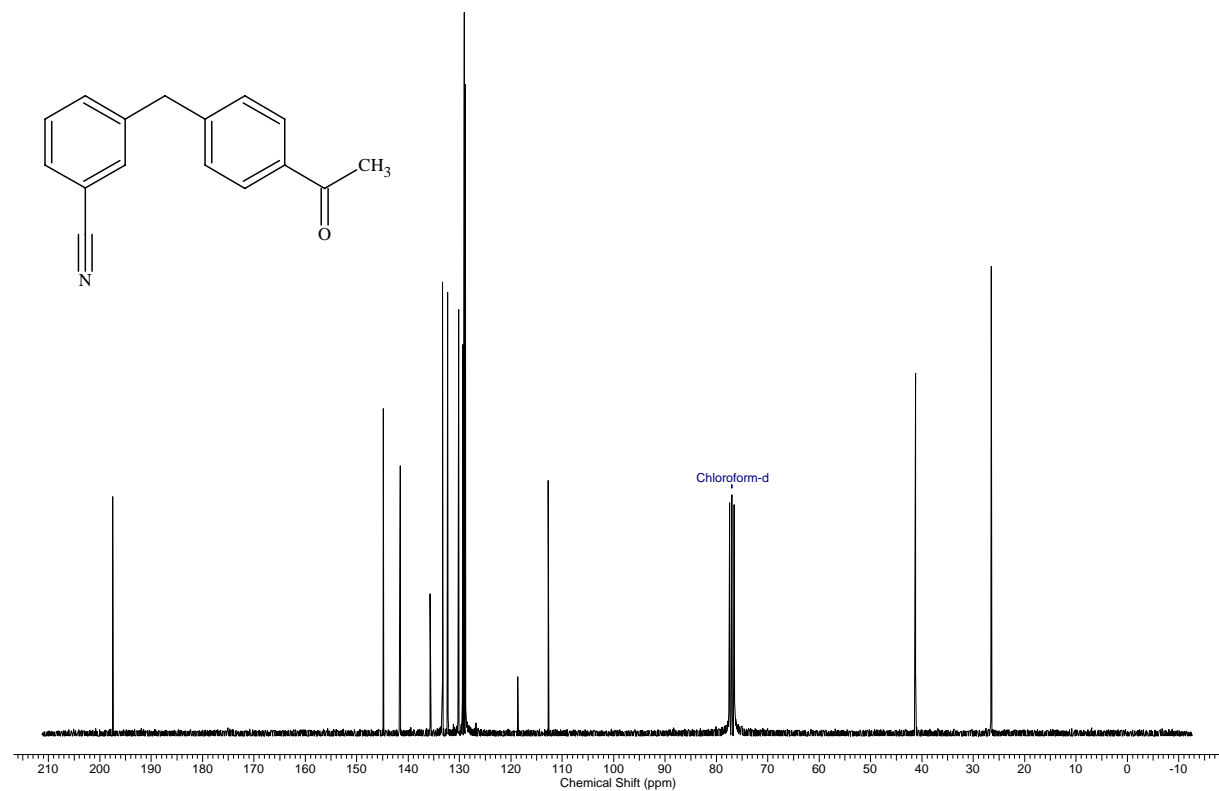
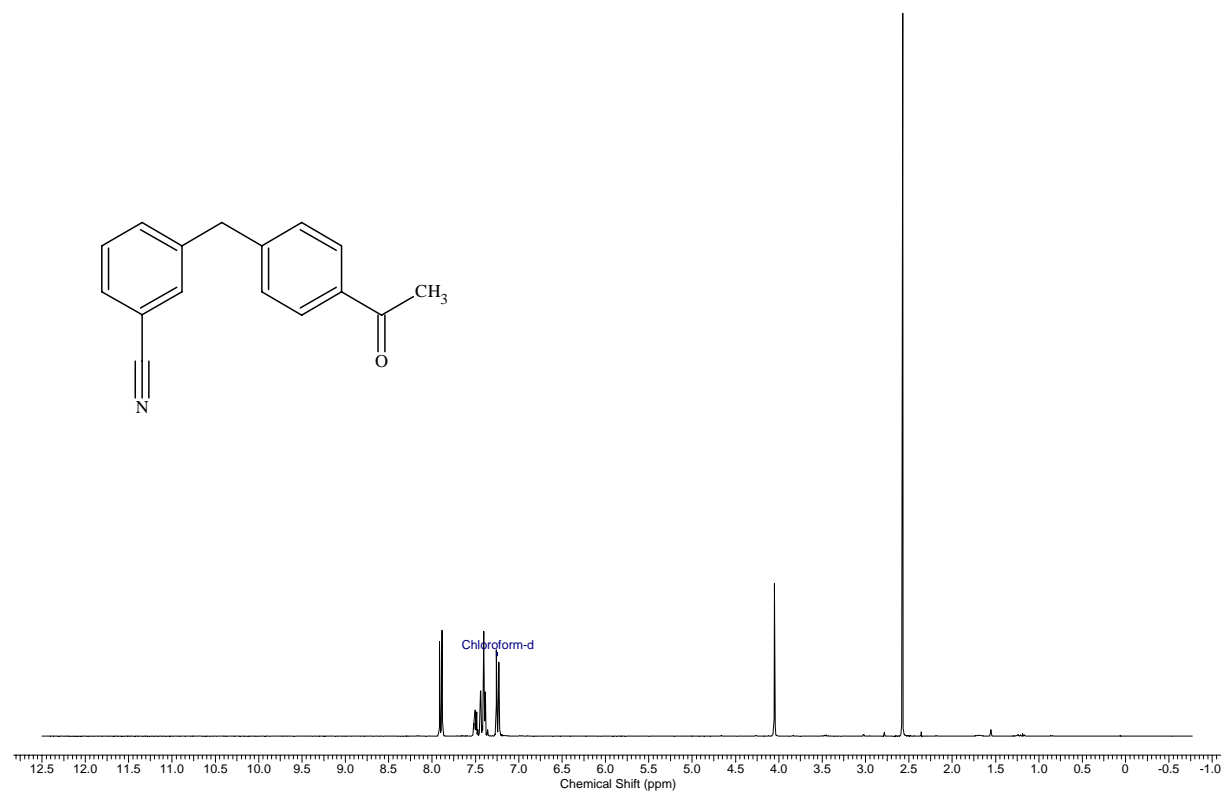
Toluene-4-sulfonic acid 2-methyl-quinolin-4-yl ester (31):



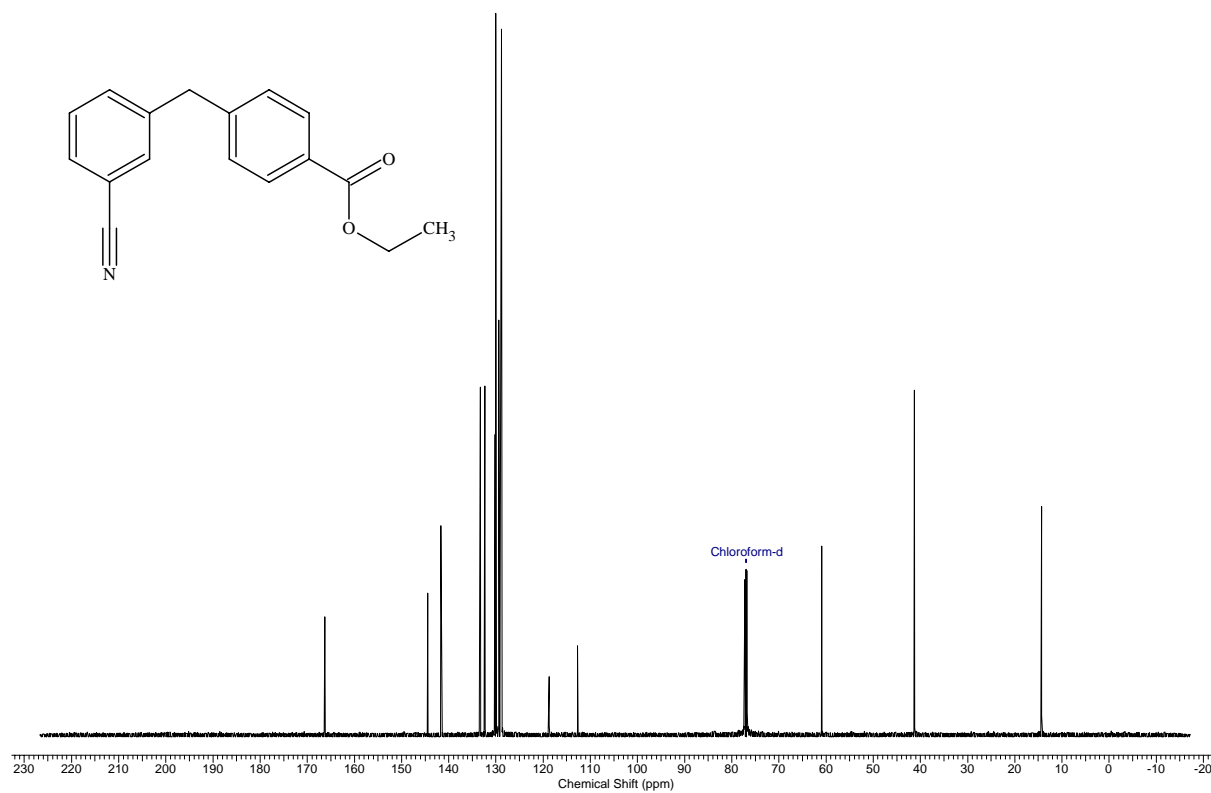
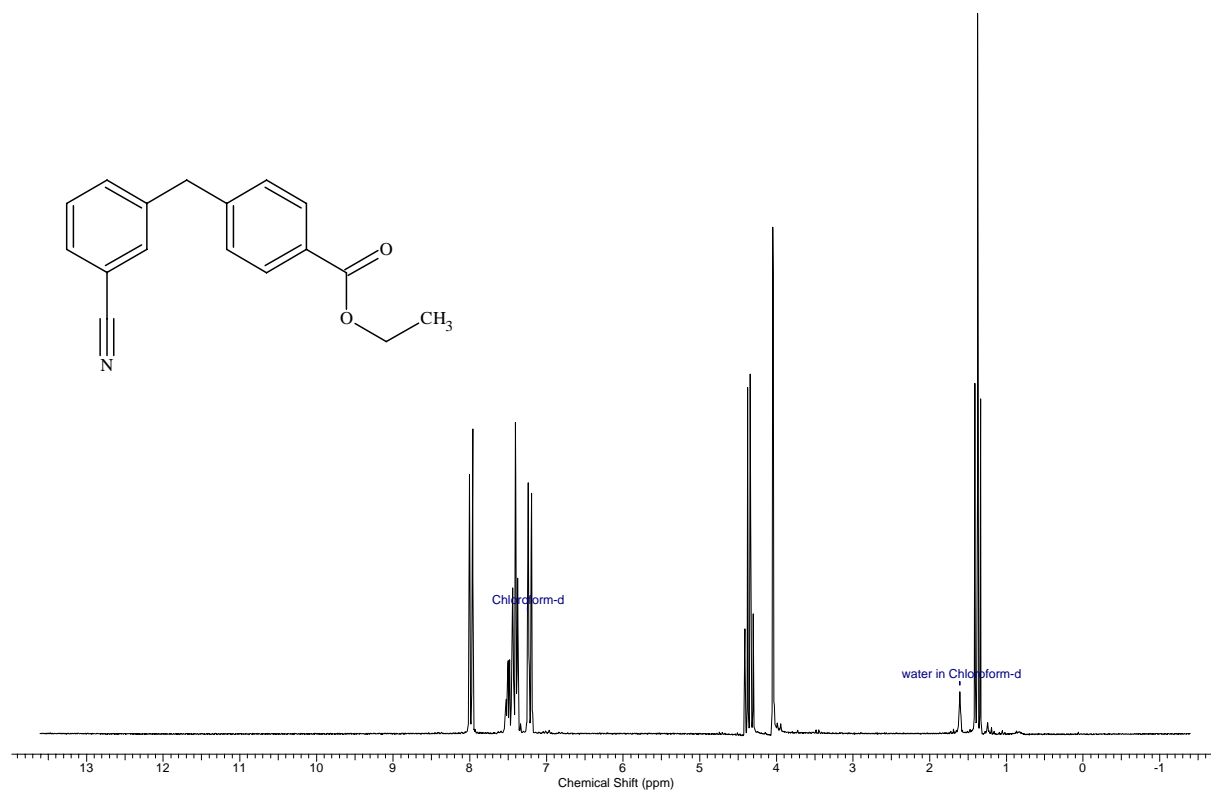
Toluene-4-sulfonic acid 6-methyl-pyridin-3-yl ester (3m):



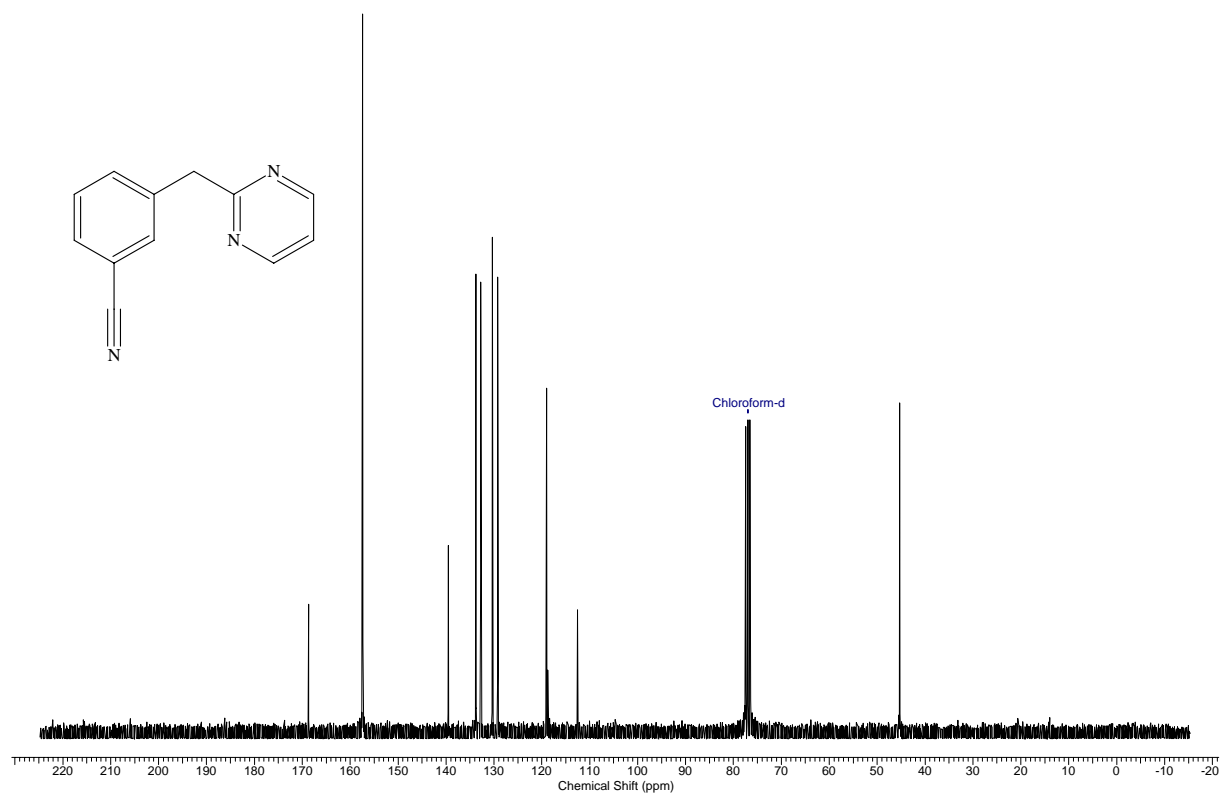
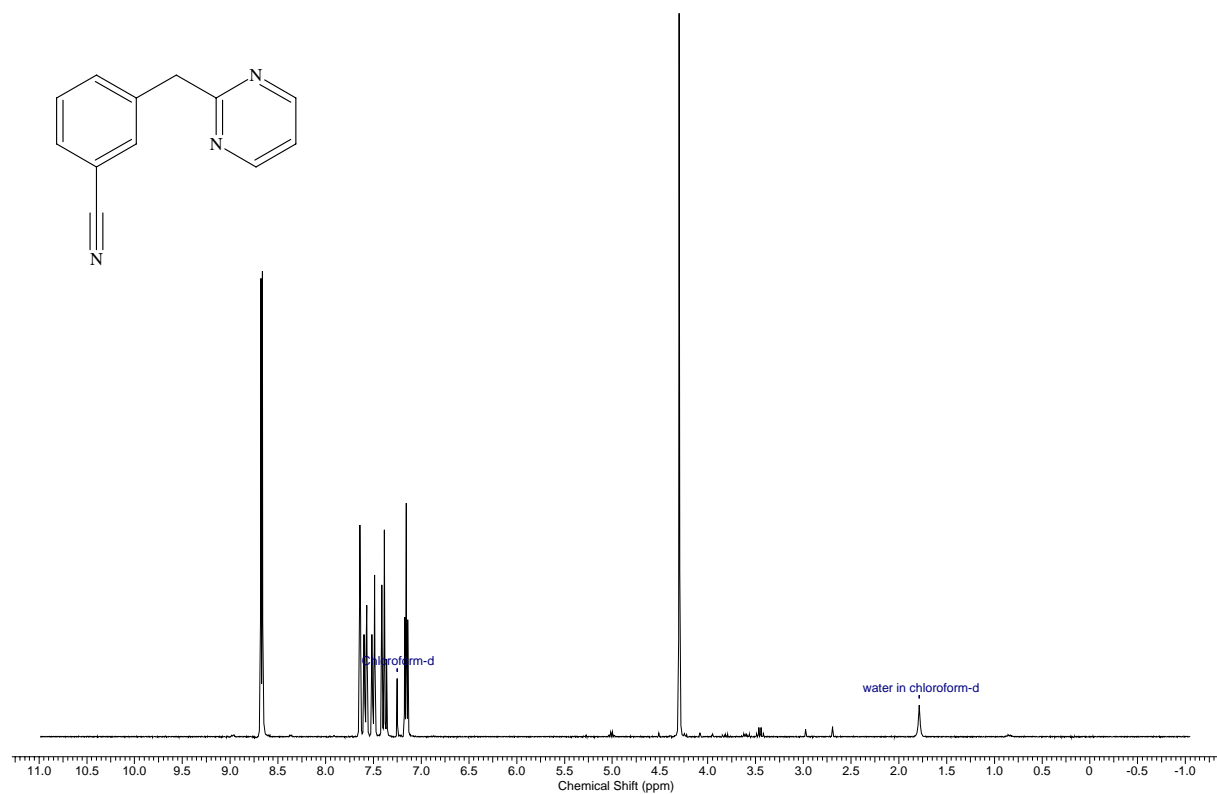
3-(4-Acetyl-benzyl)-benzonitrile (4a) :



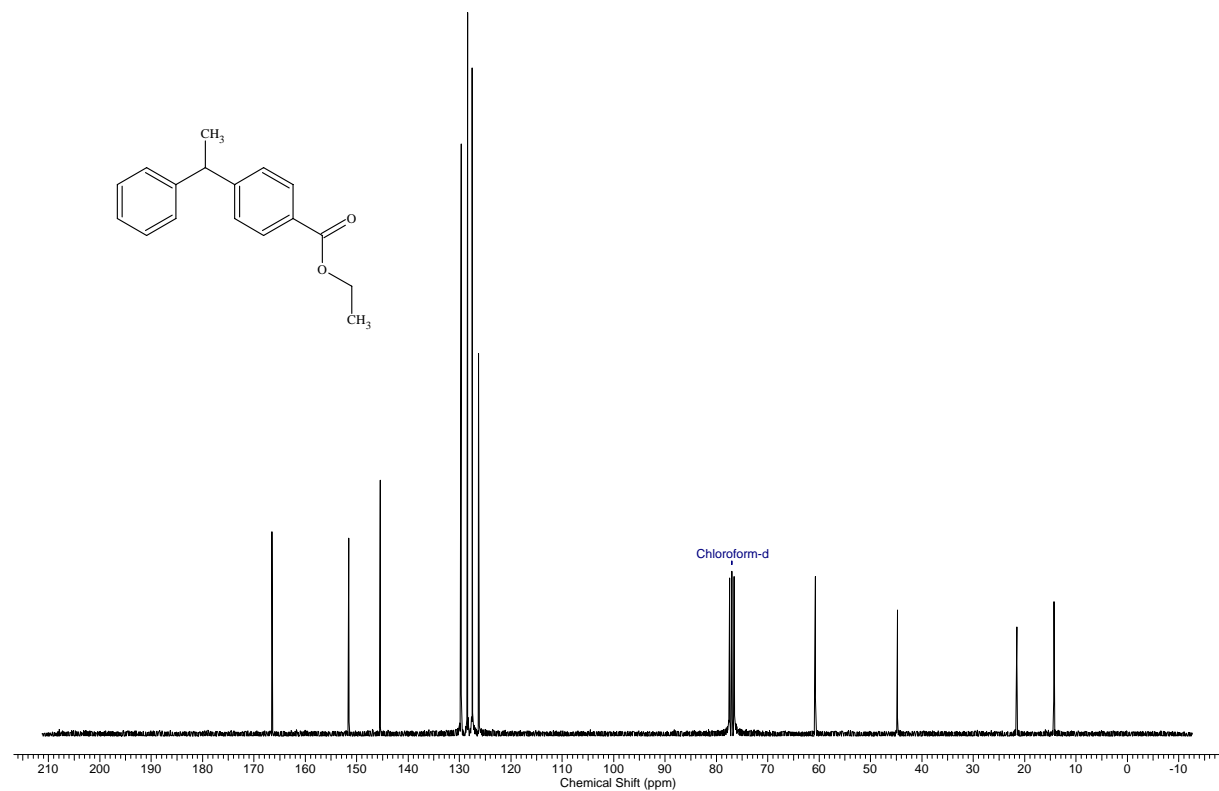
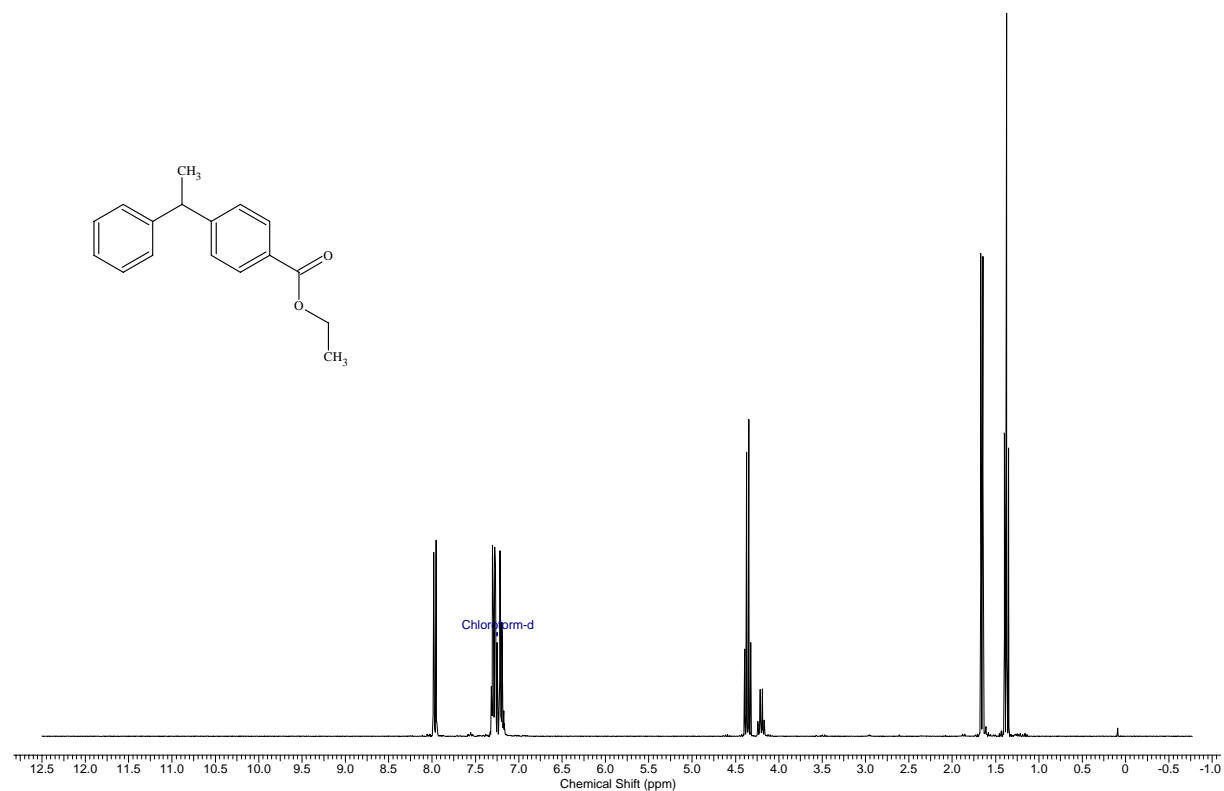
4-(3-Cyano-benzyl)-benzoic acid ethyl ester (4b):



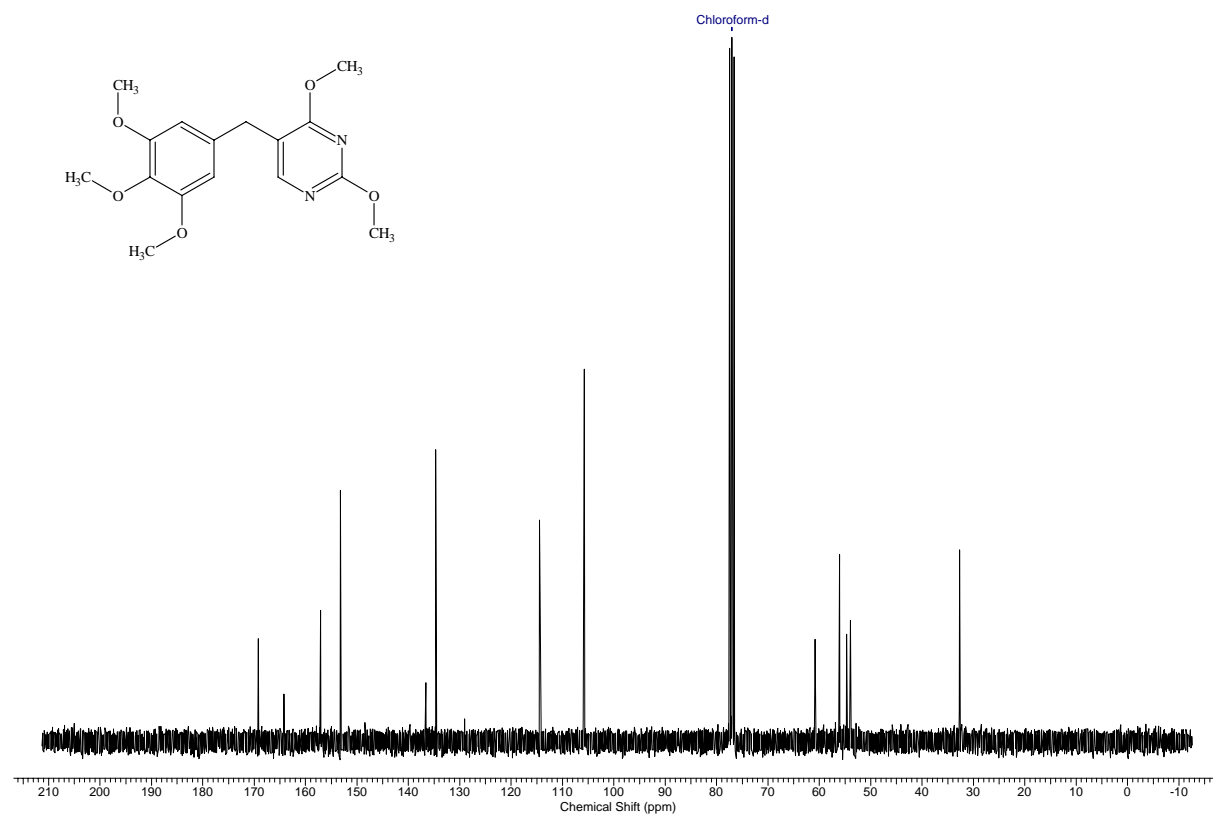
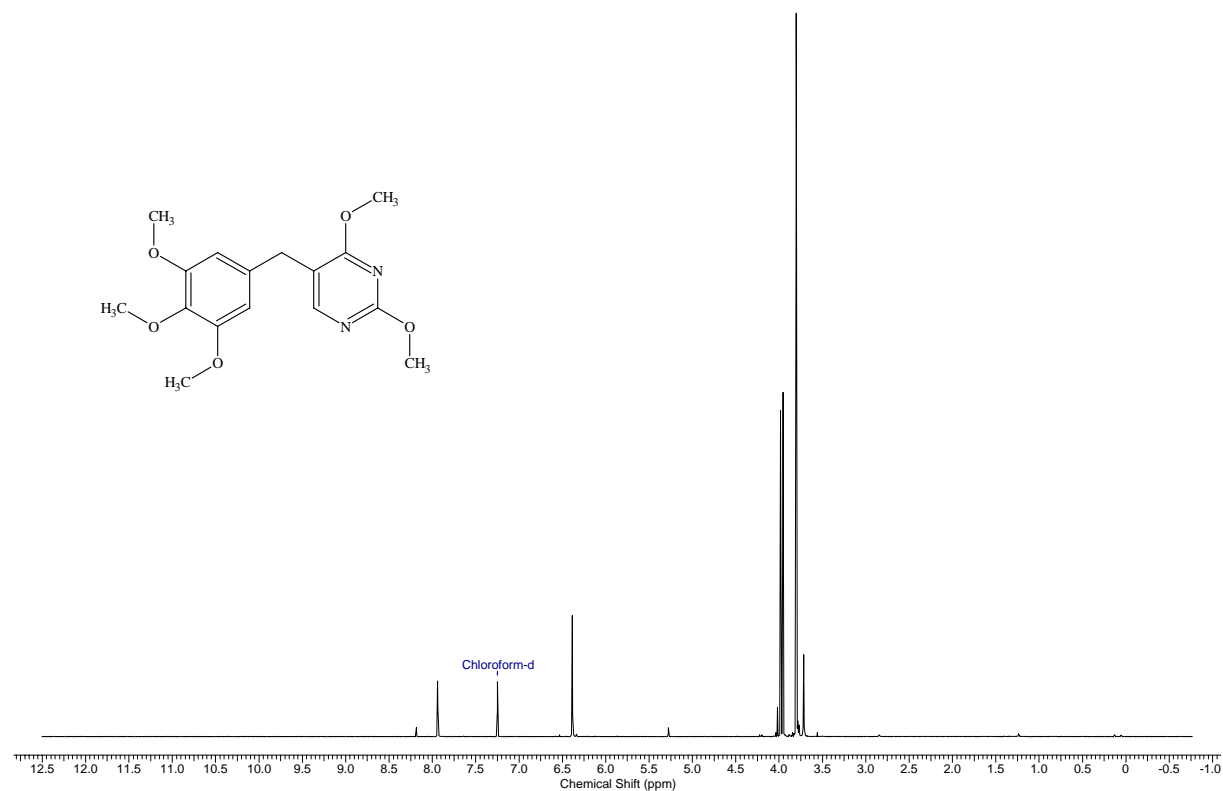
3-Pyrimidin-2-ylmethyl-benzonitrile (4c):



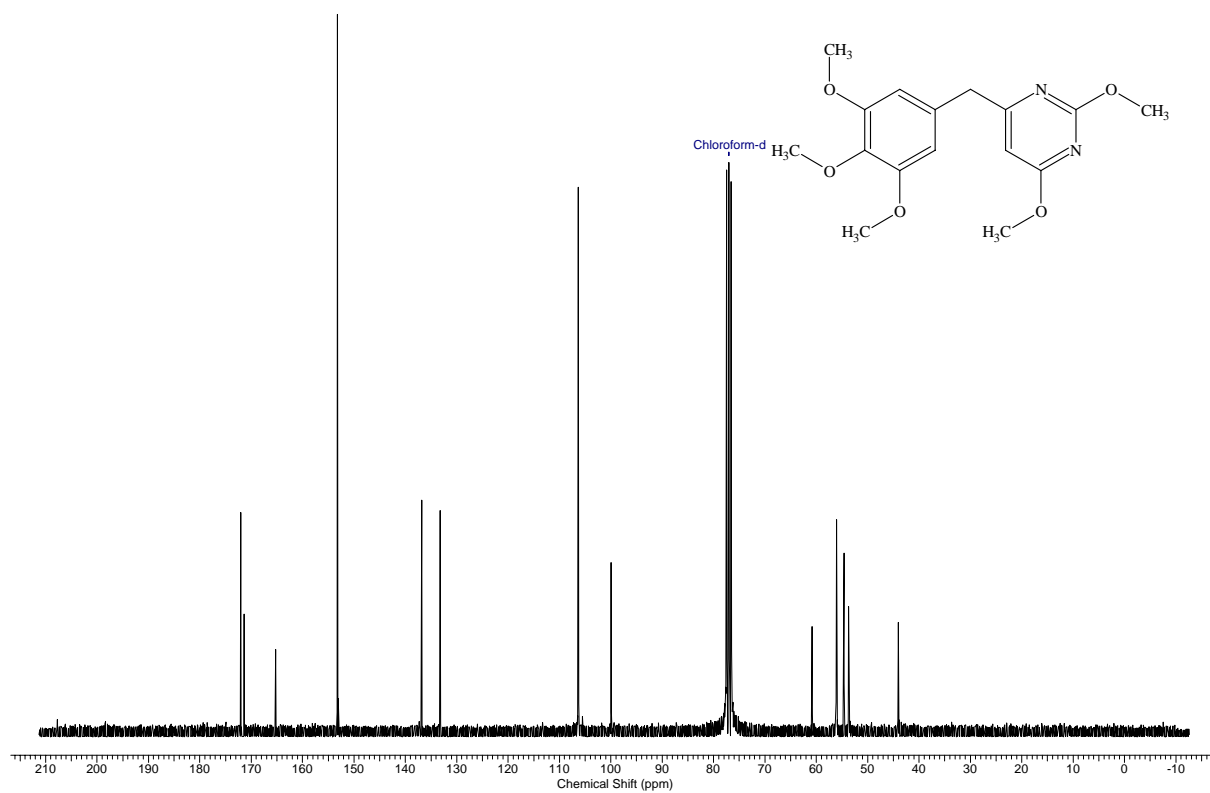
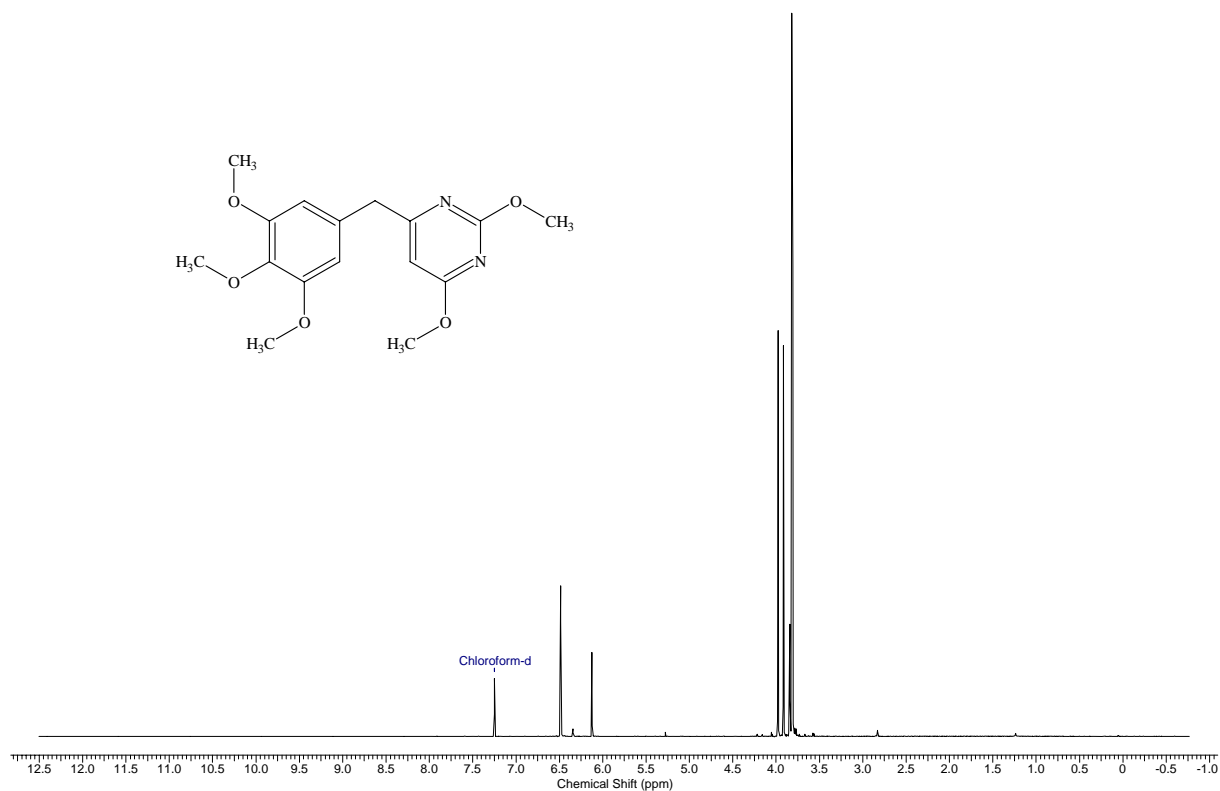
4-(1-Phenyl-ethyl)-benzoic acid ethyl ester (4d):



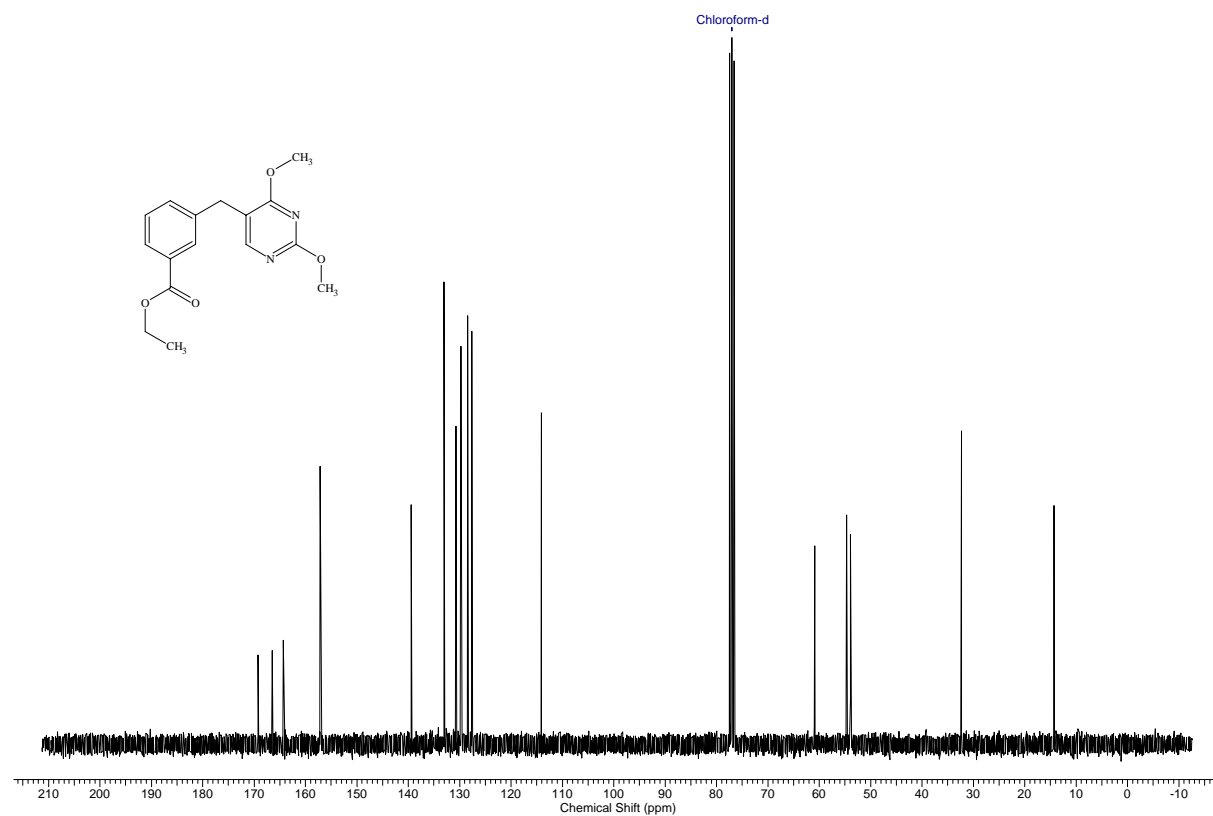
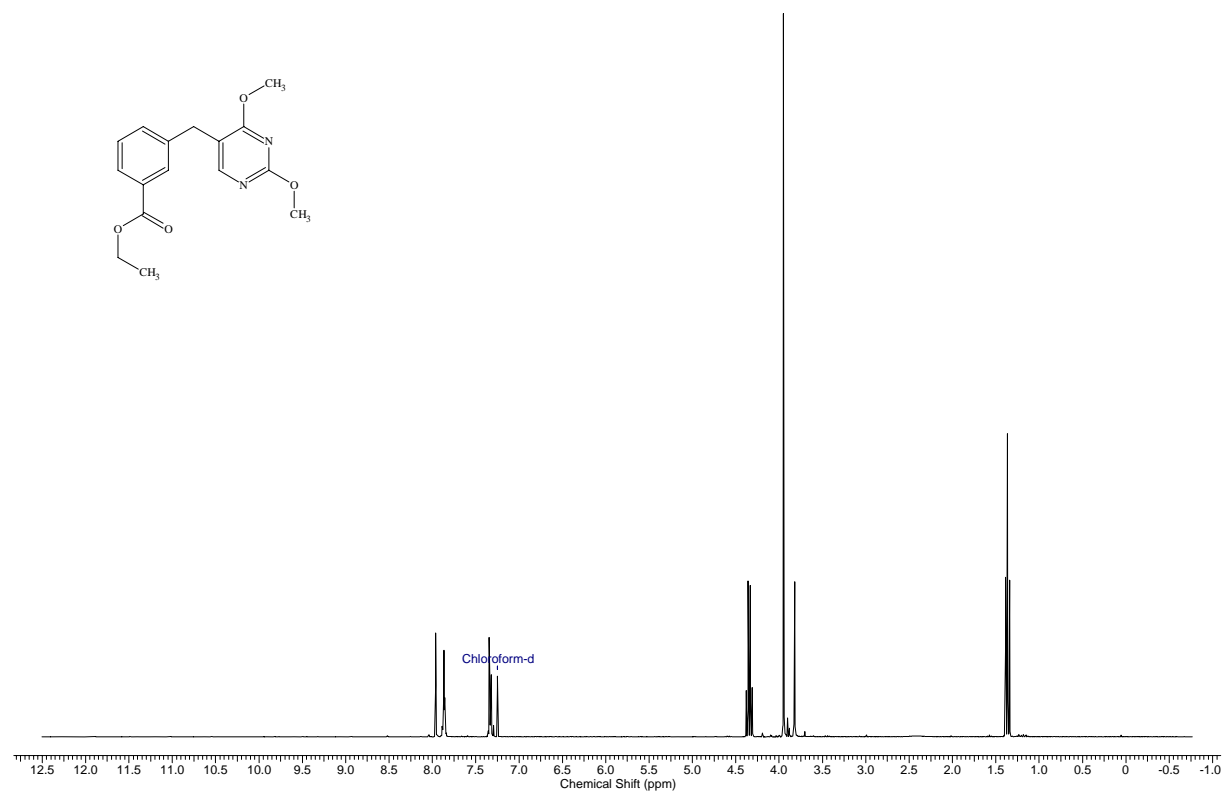
2,4-Dimethoxy-5-(3,4,5-trimethoxy-benzyl)-pyrimidine (4e) :



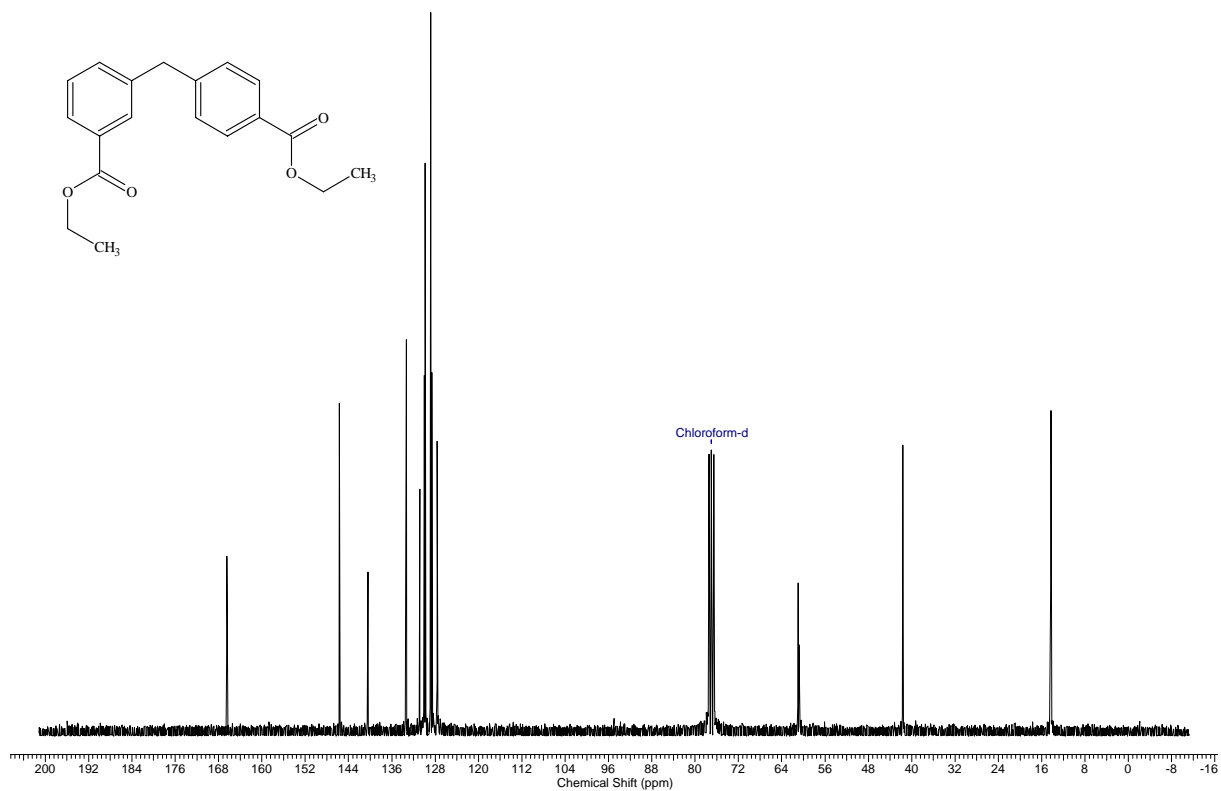
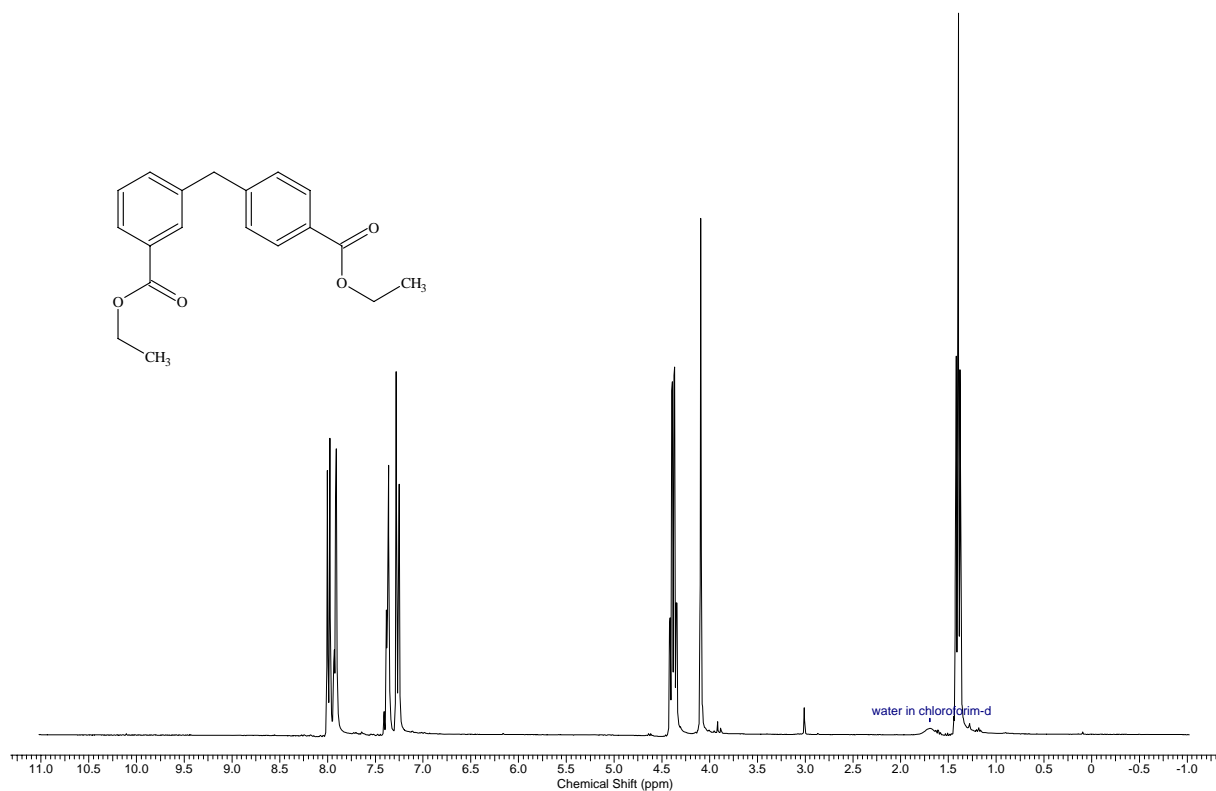
2,4-Dimethoxy-6-(3,4,5-trimethoxy-benzyl)-pyrimidine (4f):



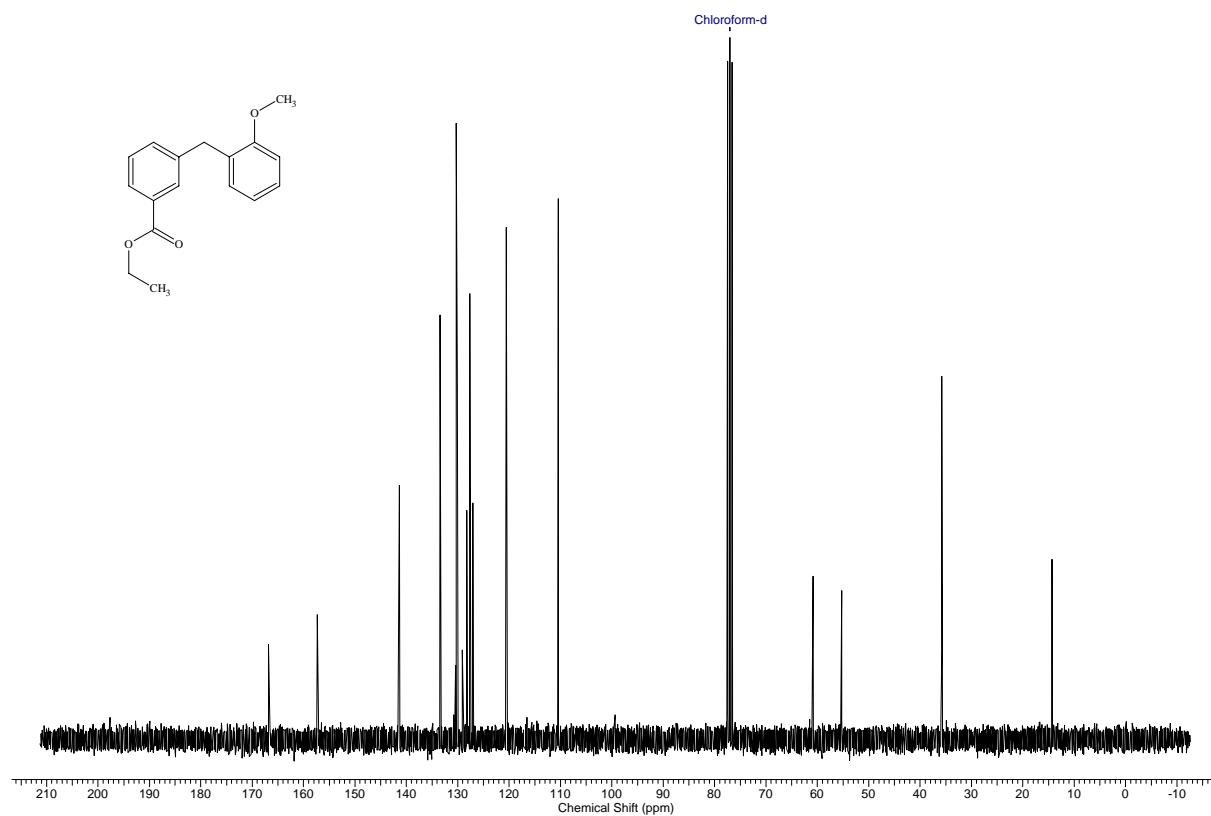
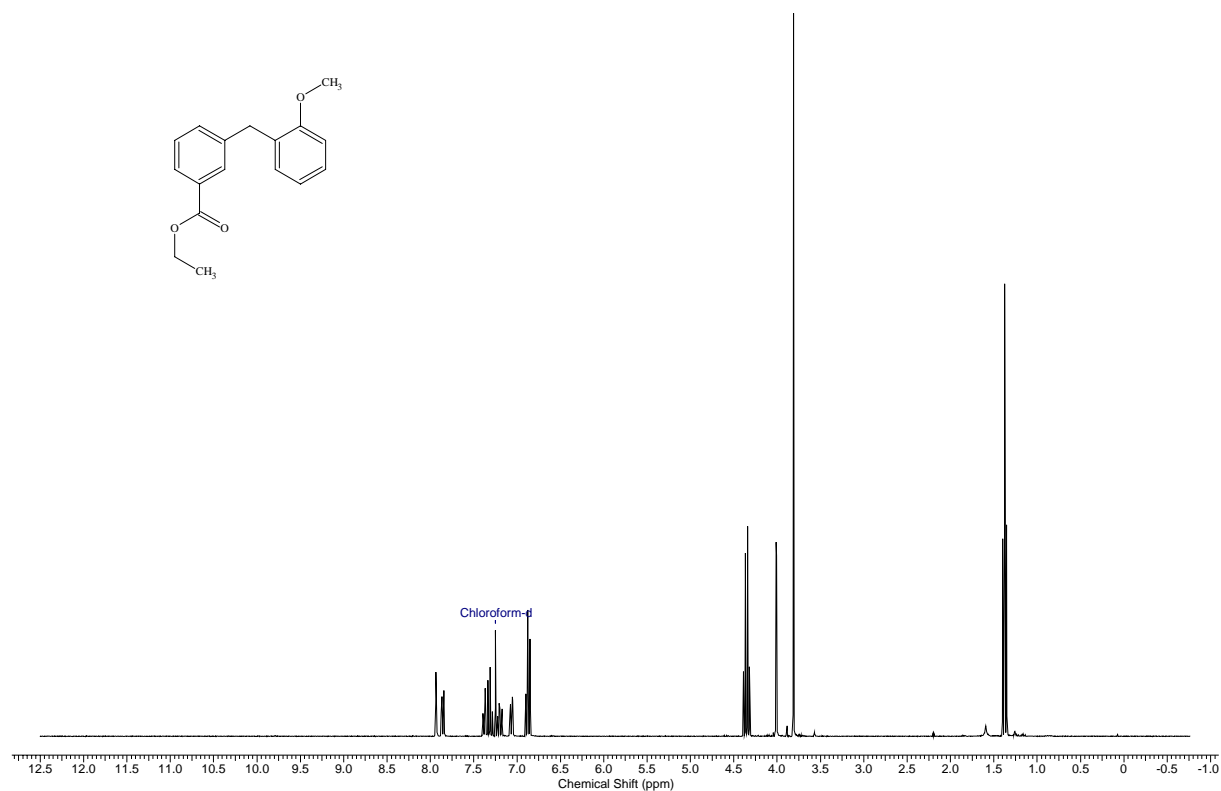
3-(2,4-Dimethoxy-pyrimidin-5-ylmethyl)-benzoic acid ethyl ester (4g):



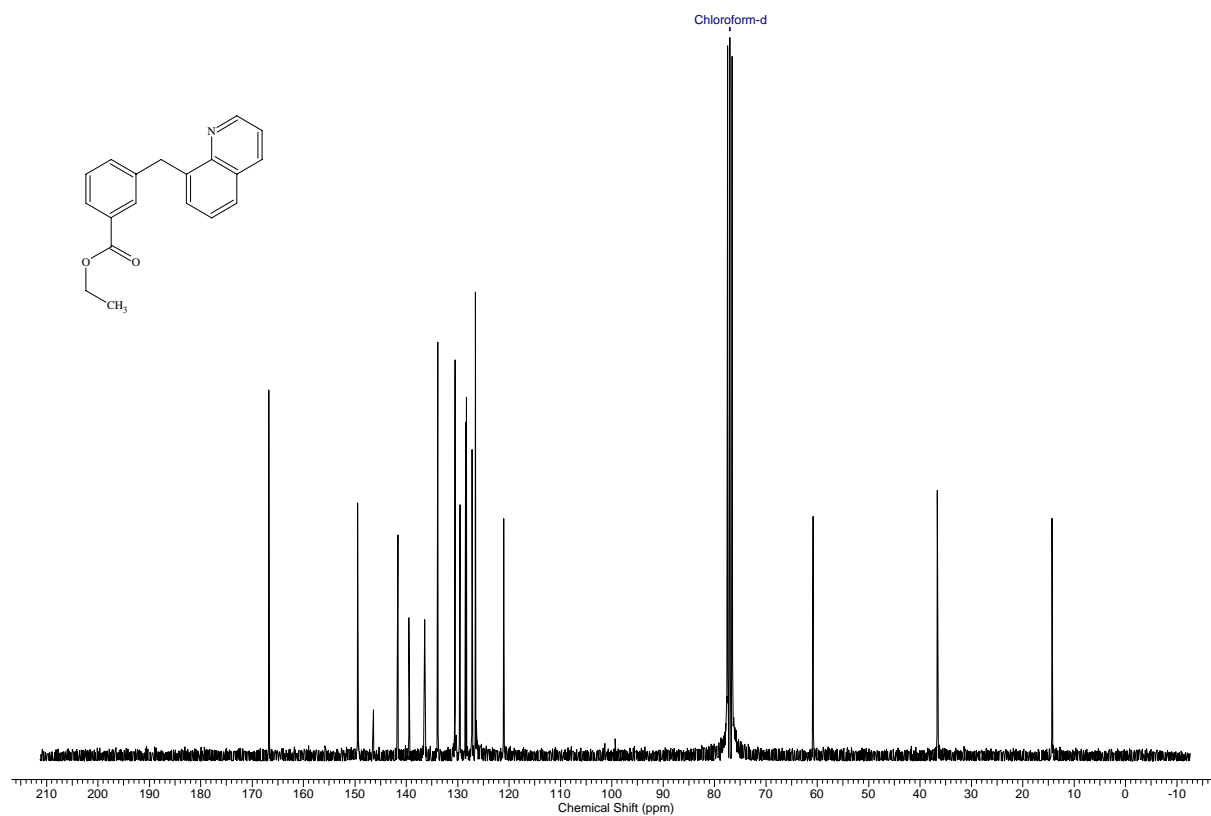
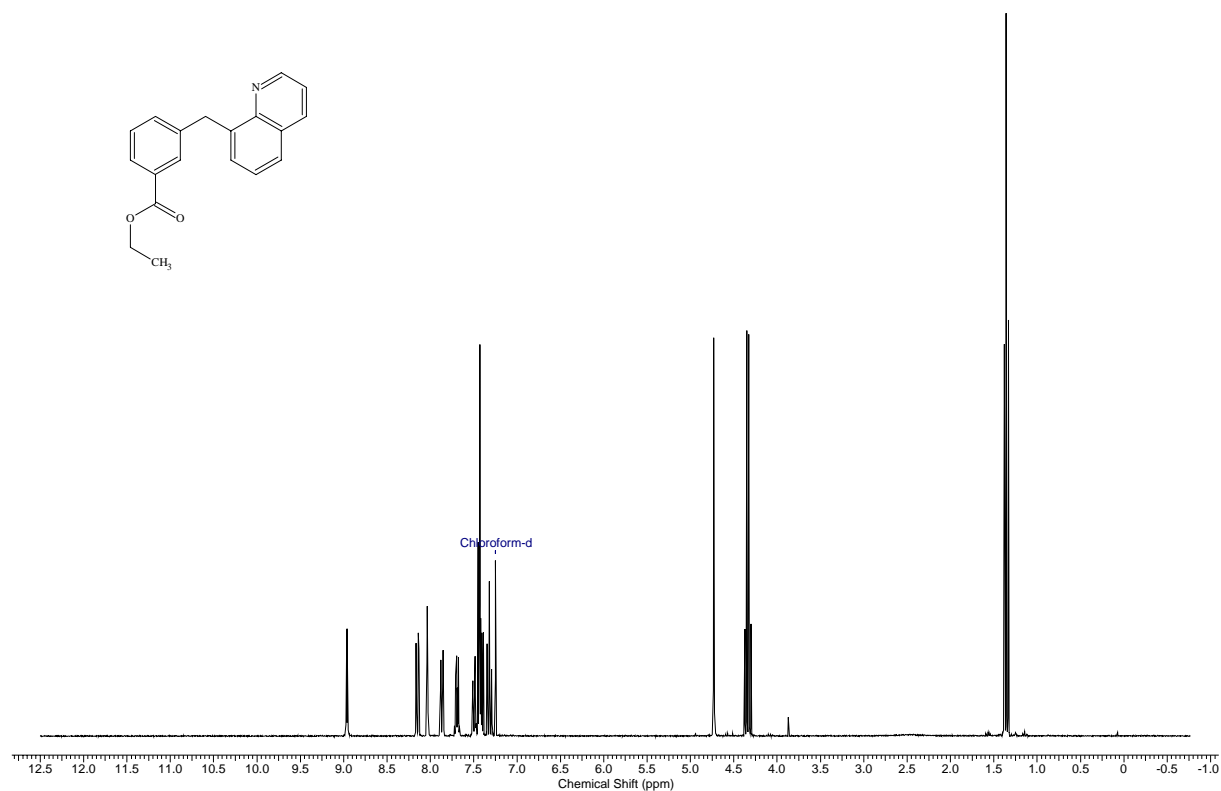
Ethyl-3-[4-(ethoxycarbonyl)-benzyl]-benzoate (4i):



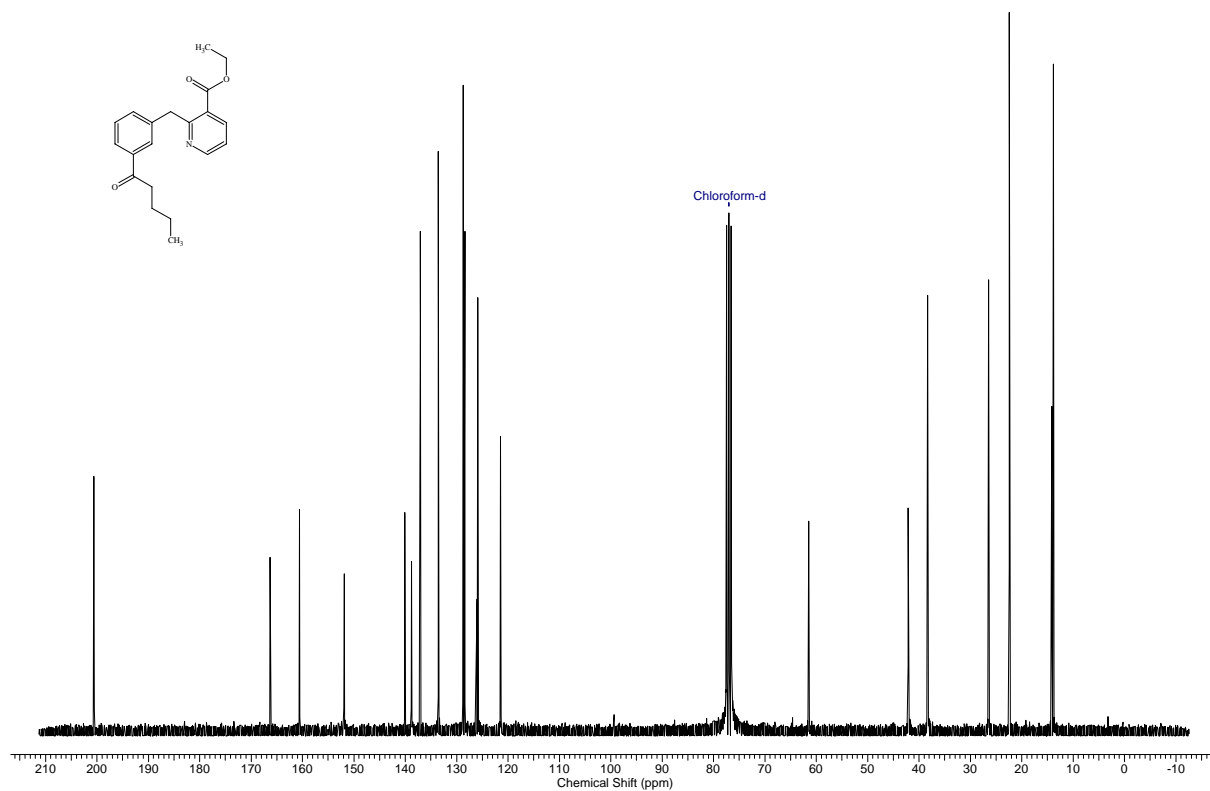
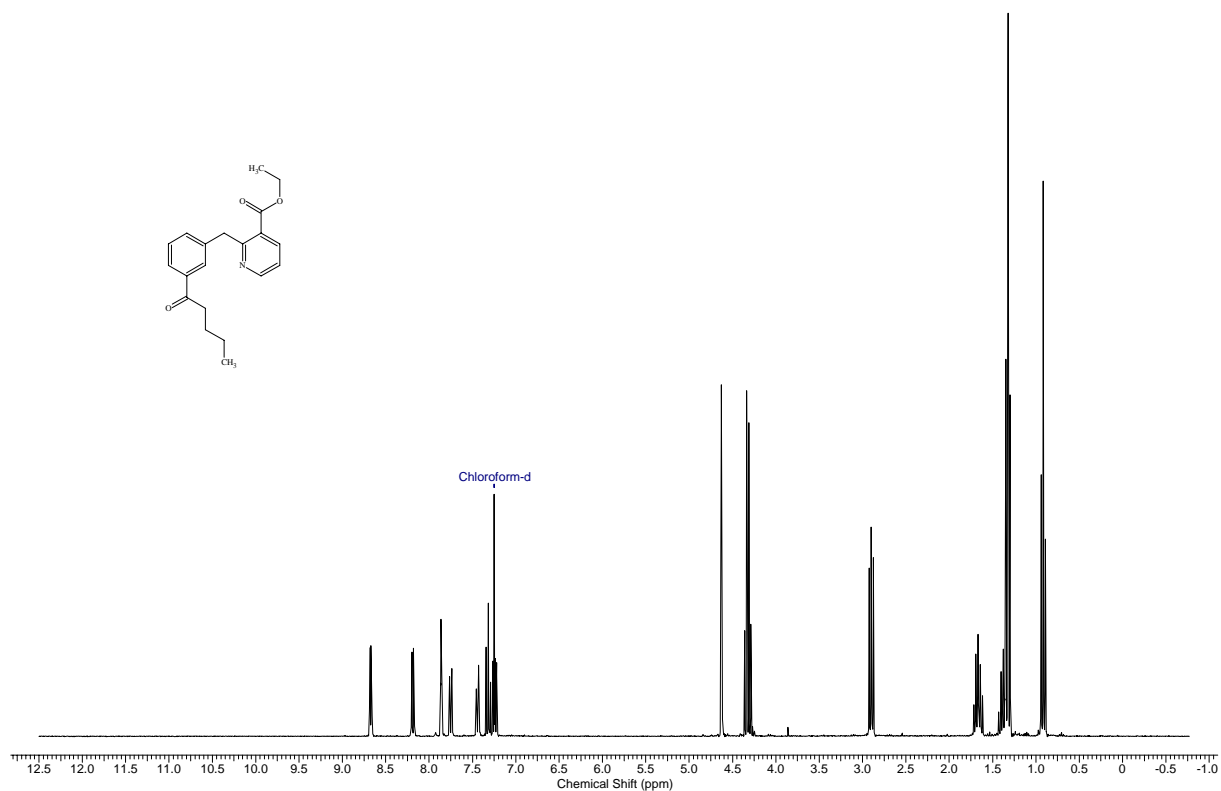
3-(2-Methoxy-benzyl)-benzoic acid ethyl ester (4j):



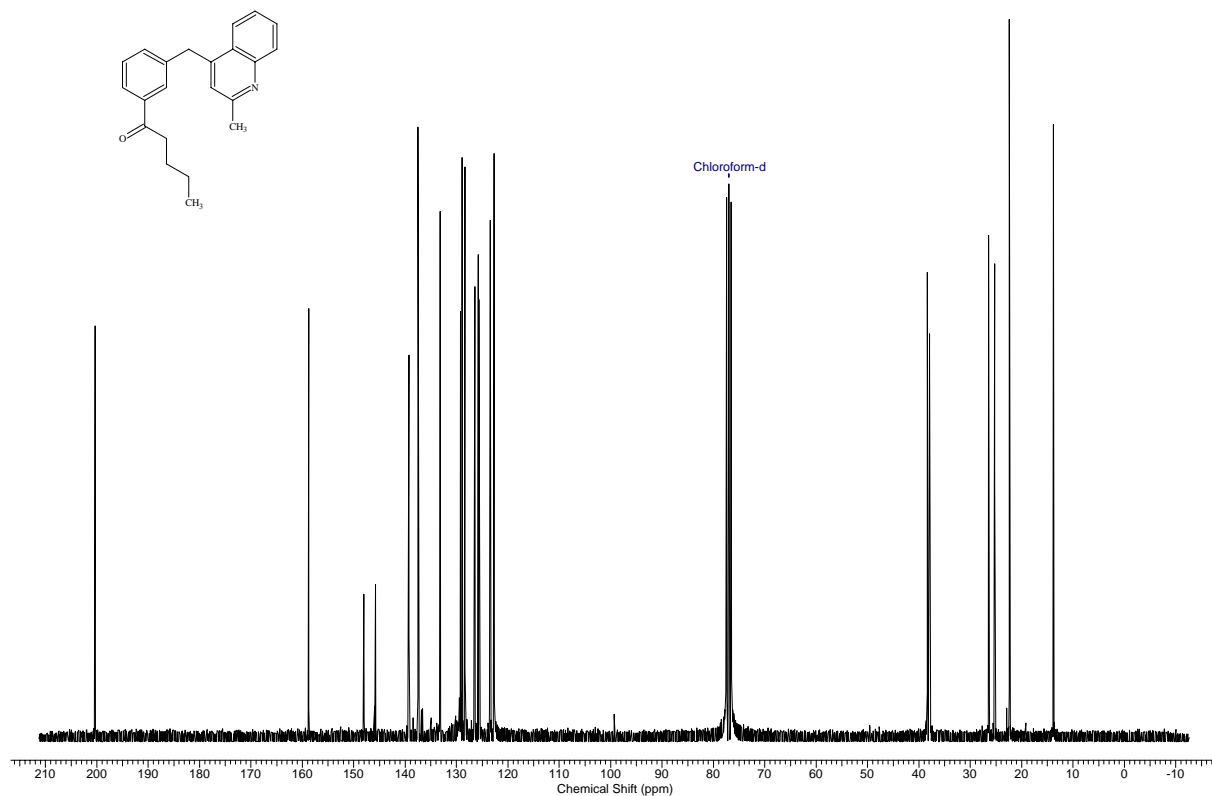
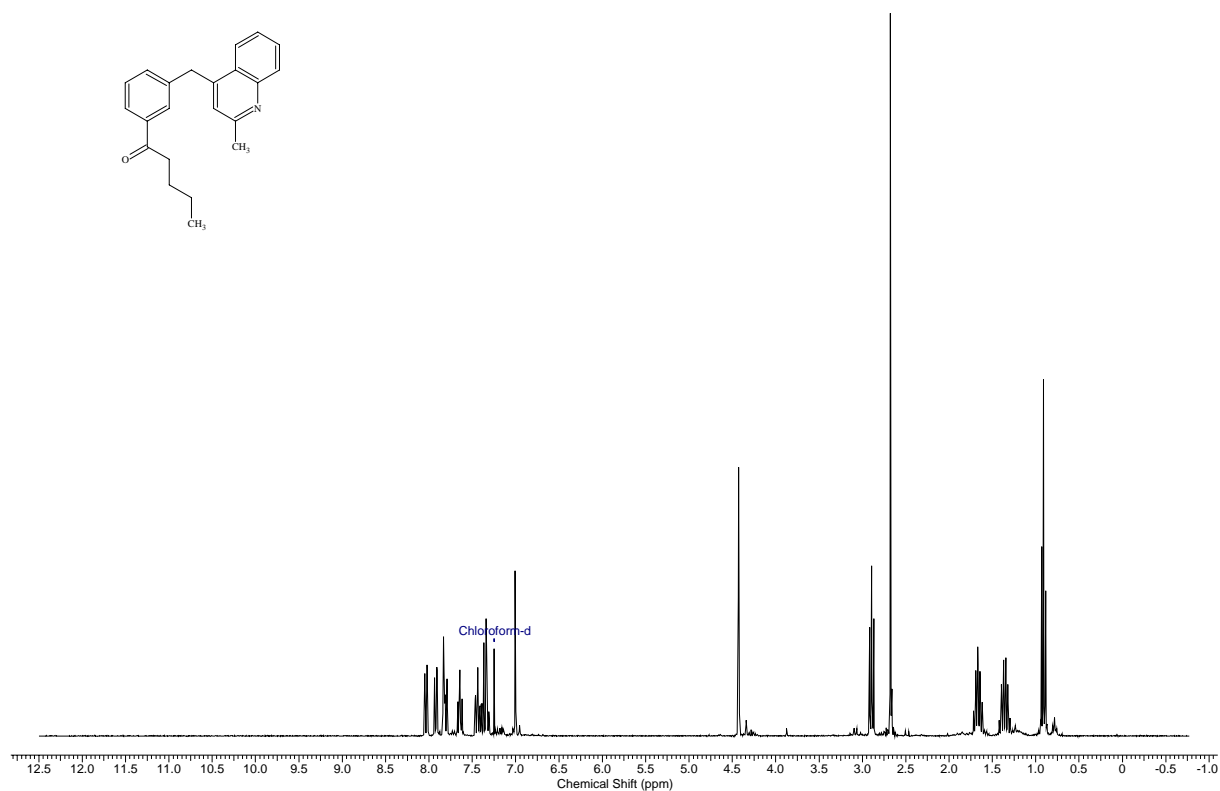
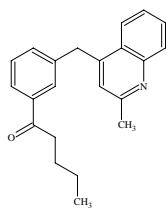
3-Quinolin-8-ylmethyl-benzoic acid ethyl ester (4k):



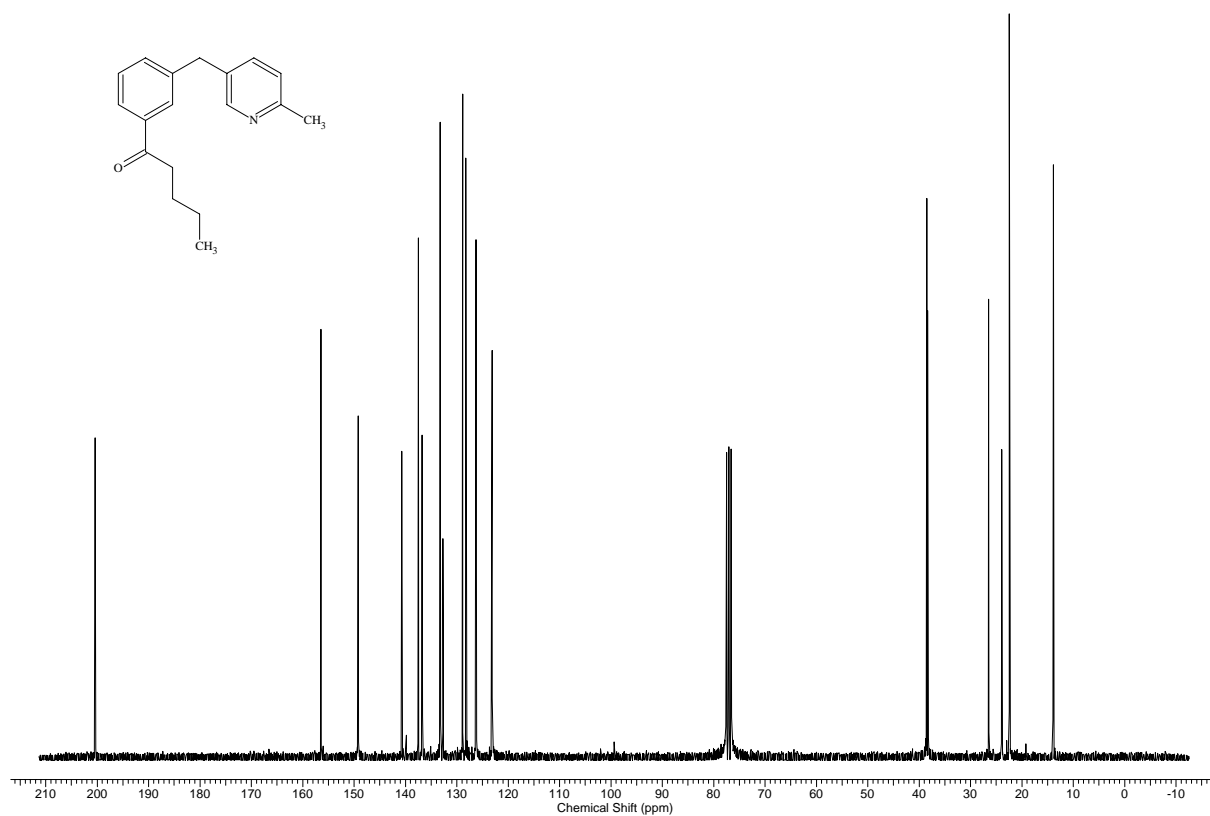
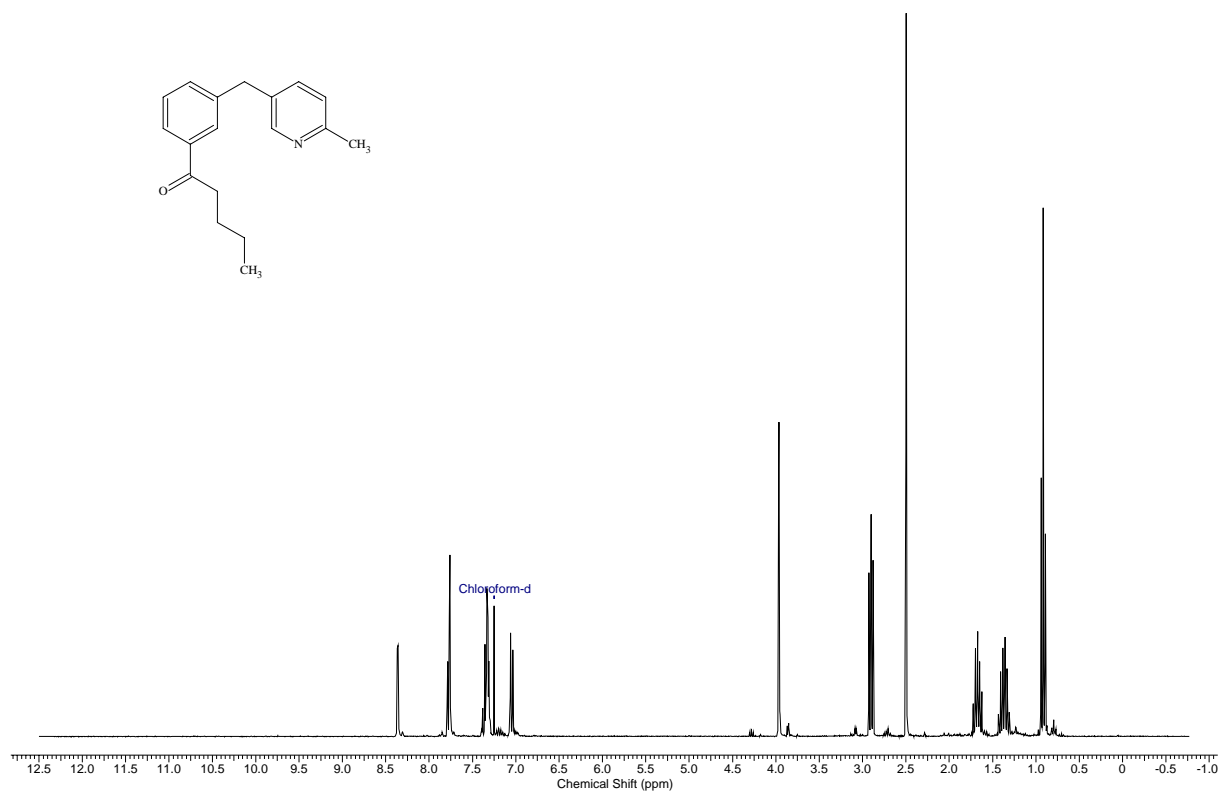
2-(3-Pentanoyl-benzyl)-nicotinic acid ethyl ester (41):



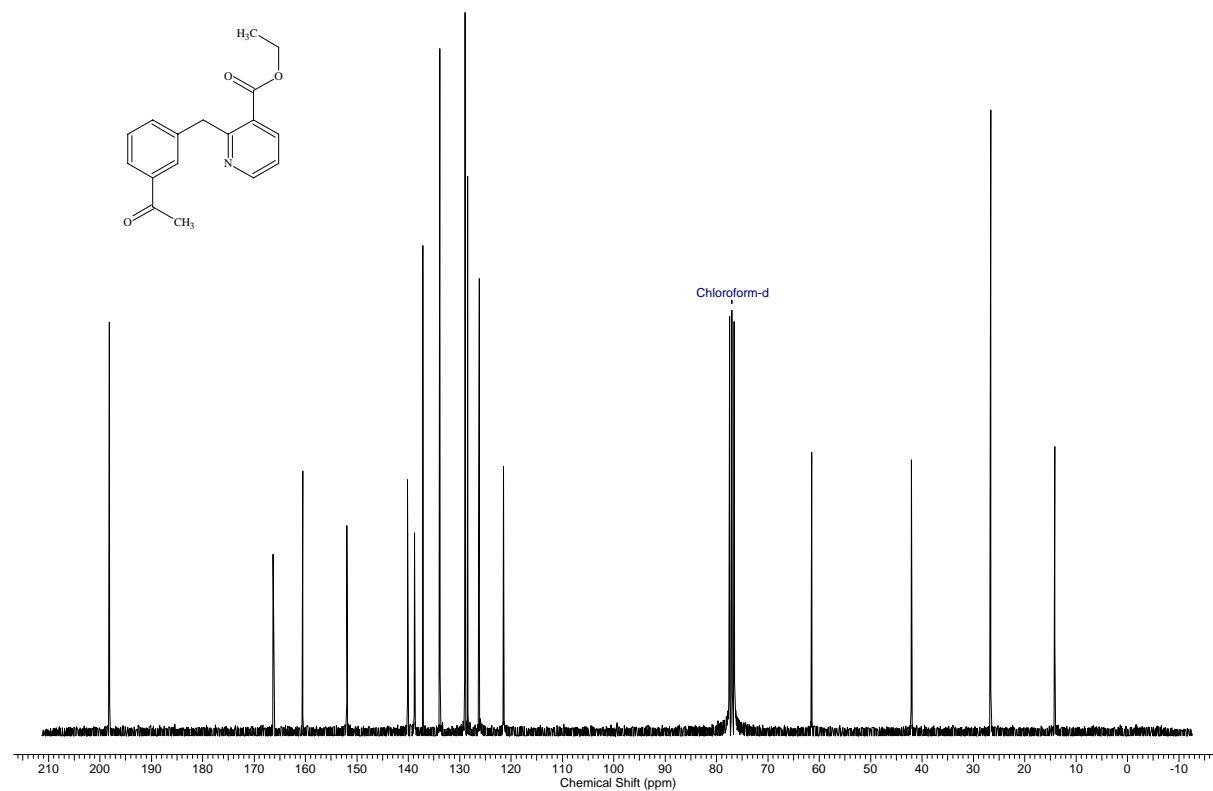
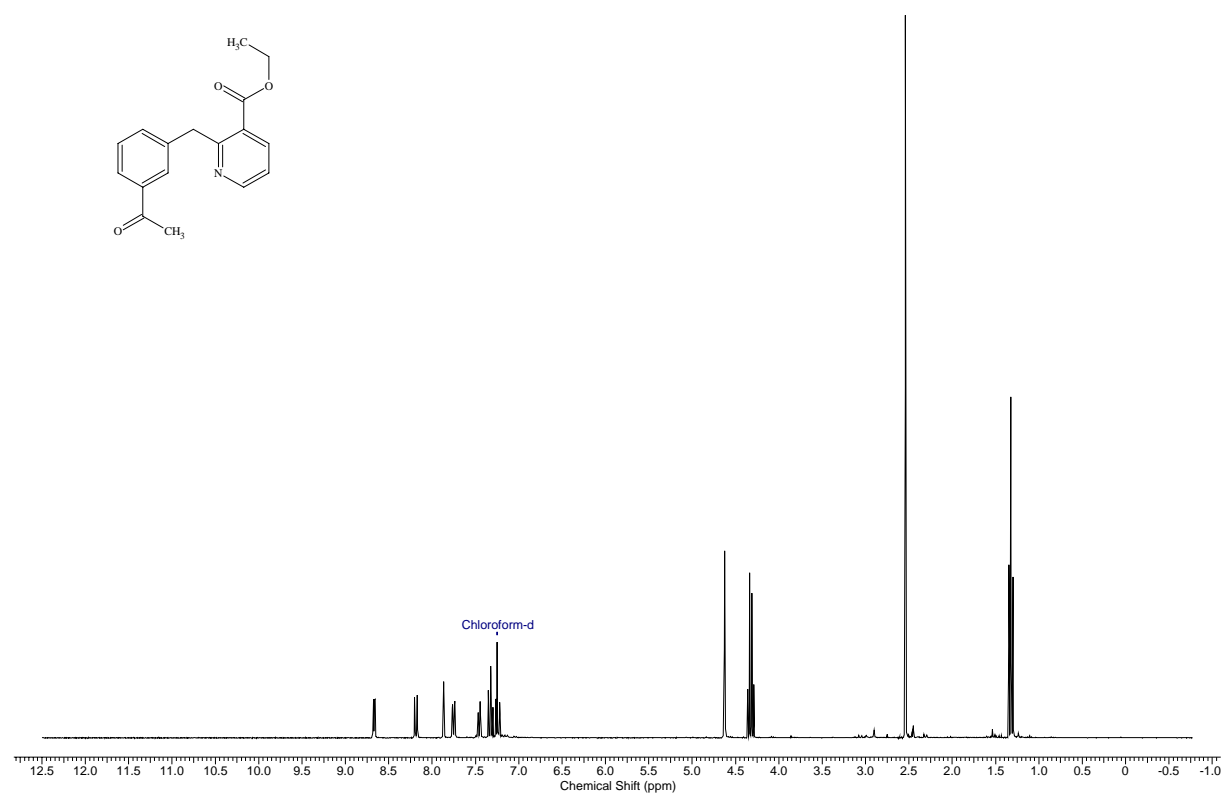
1- [3- (2-Methyl-quinolin-4-ylmethyl) -phenyl] -pentan-1-one (4m) :



1- [3- (6-Methyl-pyridin-3-ylmethyl) -phenyl] -pentan-1-one (4n) :



2-(3-acetyl-benzyl)-nicotinic acid ethyl ester (4o):



¹ A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.*, **2008**, DOI: 10.1021/ol7030697.