

## Supplementary Information

### **Rh(I)- and Rh(II)-catalyzed C-H alkylation of benzylamines with alkenes and its application in flow**

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## 1. General information

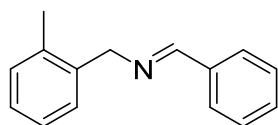
All chemicals were measured and added to a J-Young Schlenk tube or a sealed vial under argon atmosphere. The reaction vial was then closed and kept in an oil bath.  $^1\text{H}$  NMR (400 MHz),  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz), and  $^{19}\text{F}$  NMR (376 Hz) spectra were recorded on a JEOL ECS-400 spectrometer in  $\text{CDCl}_3$  with tetramethylsilane as an internal standard. All  $^1\text{H}$  NMR chemical shifts were recorded in ppm ( $\delta$ ) and referenced to tetramethylsilane. All  $^{13}\text{C}\{^1\text{H}\}$  NMR chemical shifts are given in ppm ( $\delta$ ) relative to carbon resonances in  $\text{CDCl}_3$  at  $\delta$  77.16. Infrared spectra (IR) were recorded on a JASCO FT/IR-4200 spectrometer using the ATR method. High resolution mass spectra (HRMS) were obtained using a JEOL JMS-700 spectrometer and recorded by EI using a double-focusing mass spectrometer. Melting points were determined using a Stanford Research Systems MPA100 apparatus equipped with a digital thermometer. Flash column chromatography was performed using  $\text{SiO}_2$  F60 (0.040–0.0663 mm, 230–400 mesh). Some compounds were isolated by LC-908 HPLC (GPC) or HPLC (Phenomenex Luna 5u Silica (2) 100  $\times$  21.20 mm column with hexane/EtOAc as an eluent). Intelligent UI-22 (plunger pump), back pressure regulator (auto BPR BP-11) from EYELA and stainless-steel loop coil, connectors from GL Sciences were used for flow reactions.

## 2. Materials

$[\text{Rh}(\text{OAc})(\text{cod})]_2$  was prepared from  $\text{RhCl}_3 \cdot \text{H}_2\text{O}$  by following the literature procedure.<sup>1</sup>  $\text{Rh}_2(\text{OAc})_4$  was purchased from Wako Pure Chemical Industries, Ltd.  $[\text{RhCl}(\text{cod})]_2$ ,  $[\text{RhCl}(\text{PPh}_3)_3]_2$  and  $[\text{Cp}^*\text{RhCl}_2]_2$ , were purchased from Tokyo Chemical Industry Co., Ltd. and Sigma-Aldrich accordingly. All the chemicals were used as received without further purification. Substrates **1aa**,<sup>3</sup> **1ab**,<sup>3</sup> **1ac**,<sup>2</sup> **1a**,<sup>2</sup> **1ad**,<sup>5</sup> **1b-1k**,<sup>2</sup> **1l-1m**,<sup>5</sup> **1a-D**<sup>4</sup> and **1a-ND**<sup>2</sup> were prepared following literatures. Toluene, dichloromethane, tetrahydrofuran was purchased from Wako Pure Chemical Industries, Ltd. as dry solvents and used as received. Solvents (DCM, toluene, diethyl ether, EtOAc, hexane, and  $\text{CDCl}_3$ ) were used without further purification.

## 3. Preparation of substrates

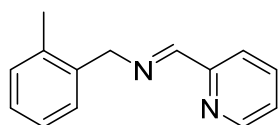
**(E)-N-(2-methylbenzyl)-1-phenylmethanimine (1aa)**



**1aa** was prepared following a literature procedure with minor modifications.<sup>3</sup> Anhydrous dichloromethane (DCM, 4.0 mL, 0.50 M) was added to activated MS 4A (2.0 g) under an argon atmosphere with stirring. An equimolar amount of 2-methylbenzylamine (0.62 mL, 5.0 mmol) and benzaldehyde (0.51 mL, 5.0 mmol) were added sequentially to the solution which was then stirred for 12 hours at room temperature. After filtering the solution through a plug of celite and quenching the reaction with 2 mL of 1 N aq. NaOH solution. The organic phase was extracted with ethyl acetate and washed repeatedly with brine, and then dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure to give the corresponding product as a colorless oil (963 mg, 92% yield).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.32 (s, 1H), 7.76 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.39 (dd, *J* = 4.9, 1.7 Hz, 3H), 7.27 (s, 1H), 7.17 (d, *J* = 2.7 Hz, 3H), 4.80 (s, 2H), 2.37 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 161.87, 137.59, 136.40, 136.31, 130.79, 130.25, 128.68, 128.56, 128.32, 127.22, 126.18, 77.48, 77.16, 76.84, 62.77, 19.40. IR (neat, v/cm<sup>-1</sup>) 2840, 1601, 1544, 1449, 1376, 1311, 1217, 1012, 908, 735, 691. HRMS (EI<sup>+</sup>) *m/z*: [M]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>15</sub>N 209.1204; found 209.1205.

**(E)-N-(2-methylbenzyl)-1-(pyridin-2-yl)methanimine (1ab)**

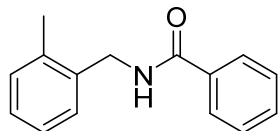


**1ab** was prepared following the procedure for **1aa** except for the use of pyridine-2-carboxaldehyde instead of benzaldehyde to give the corresponding product as a colorless oil (1.02 g, 97% yield).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.61 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.43 (s, 1H), 8.05 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.75 – 7.63 (m, 1H), 7.31 – 7.24 (m, 2H), 7.20 – 7.13 (m, 3H), 4.86 (d, *J* = 1.4 Hz, 2H), 2.37 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 162.65, 154.67, 149.37, 136.86, 136.52, 136.40, 130.28, 128.81, 127.37, 126.17, 124.77, 121.27, 77.48, 77.16, 76.84, 62.56, 19.31. IR (neat, v/cm<sup>-1</sup>) 3015, 2860, 1738, 1647, 1586, 1567, 1466, 1436,

1361, 1329, 1226, 1045, 991, 762, 741. HRMS (EI<sup>+</sup>) *m/z*: [M]<sup>+</sup> Calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub> 210.1157; found 210.1156.

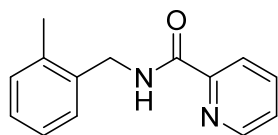
#### ***N*-(2-methylbenzyl)benzamide (1ac)**



**1ac** was prepared following a literature procedure with minor modifications.<sup>2</sup> Anhydrous DCM (10 mL, 0.50 M) and 0.50 mL of anhydrous DMF were added to a 200 mL three-necked round bottomed flask containing benzoic acid (611 mg, 5.0 mmol, 1.0 equiv) with stirring under an argon atmosphere. Oxalyl chloride (0.51 mL, 6.0 mmol, 1.2 equiv) in anhydrous DCM (10 mL) was added dropwise at 0 °C and the resulting solution was then stirred for 5 hours at room temperature. The crude benzoyl chloride was obtained by evaporation under vacuum and dissolved in anhydrous DCM (10 mL, 0.50 M) under an argon atmosphere with stirring. To the solution, 2-methylbenzylamine (0.93 mL, 7.5 mmol, 1.5 equiv) and triethylamine (1.39 mL, 10 mmol, 2.0 equiv) in dry DCM (10 mL) were added dropwise at 0 °C and the resulting solution stirred for 12 hours at room temperature. The solvent was evaporated and the crude mixture was extracted with ethyl acetate and the ethyl acetate was washed with brine repeatedly and then dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography using *n*-hexane/EtOAc = 2/1 as the eluent to obtain the corresponding product as a white solid (867 mg, 77% yield).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.85 – 7.69 (m, 2H), 7.55 – 7.45 (m, 1H), 7.45 – 7.34 (m, 2H), 7.32 – 7.27 (m, 1H), 7.25 – 7.15 (m, 3H), 6.25 (s, 1H), 4.64 (d, *J* = 5.3 Hz, 2H), 2.37 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 167.35, 136.77, 135.89, 134.52, 131.66, 130.79, 128.87, 128.73, 128.07, 127.06, 126.43, 77.48, 77.16, 76.84, 42.51, 19.19. IR (neat, *v*/cm<sup>-1</sup>) 3317, 3058, 2917, 1636, 1604, 1577, 1548, 1491, 1462, 1414, 1310, 1260, 990, 741, 695. HRMS (EI<sup>+</sup>) *m/z*: [M]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>15</sub>NO 225.1154; found 225.1153. M.p = 114–116 °C.

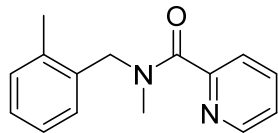
#### ***N*-(2-methylbenzyl)picolinamide (1a)**



**1a** was prepared following the procedure for **1ac** except for the use of pyridine-2-carboxylic acid instead of benzoic acid to give the corresponding product as an off white solid (928 mg, 82% yield).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.52 (ddd,  $J = 4.7, 1.7, 0.9$  Hz, 1H), 8.30 – 8.13 (m, 2H), 7.86 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.42 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.32 (dd,  $J = 4.8, 2.7$  Hz, 1H), 7.25 – 7.14 (m, 3H), 4.67 (d,  $J = 5.8$  Hz, 2H), 2.38 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.19, 149.94, 148.20, 137.54, 136.68, 135.98, 130.66, 128.74, 127.88, 126.37, 126.35, 122.49, 77.48, 77.16, 76.84, 41.83, 19.26. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3390, 2922, 2360, 1672, 1569, 1523, 1464, 1434, 1305, 1221, 999, 912, 745, 689. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$  226.1106; found 226.1103. M.p = 56-58 °C.

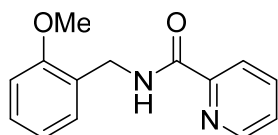
#### ***N*-methyl-*N*-(2-methylbenzyl)picolinamide (**1ad**)**



**1ad** was synthesized according to a literature procedure with minor modifications.<sup>5</sup> To a stirred solution of a 60% dispersion of NaH (80 mg, oil, 2.0 mmol, 2.0 equiv) in anhydrous THF (2 mL) at 0 °C a solution of **1a** (226 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (2 mL) was added portion wise under an argon atmosphere. The reaction mixture was then warmed to room temperature and stirred for 1 hour. After cooling to 0 °C, methyl iodide (75  $\mu\text{L}$ , 1.2 mmol, 1.2 equiv) was added dropwise to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 12 hours, aqueous  $\text{NH}_4\text{Cl}$  was then added to quench the reaction mixture and the resulting solution was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography using *n*-hexane/EtOAc = 1/1 as the eluent to give **1ad** as a thick colorless oil (223 mg, 93% yield). The product was obtained as a mixture of rotational isomers.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.61 (d,  $J = 4.4$  Hz, 0.55H), 8.55 (d,  $J = 4.5$  Hz, 0.45H), 7.80 (td,  $J = 7.7, 1.7$  Hz, 0.56H), 7.74 (td,  $J = 7.7, 1.7$  Hz, 0.44H), 7.67 (t,  $J = 7.7$  Hz, 1H), 7.38 – 7.27 (m, 1H), 7.26 – 7.08 (m, 4H), 4.81 (s, 1.11H), 4.72 (s, 0.89H), 3.05 (s, 1.35H), 2.94 (s, 1.65H), 2.38 (s, 1.67H), 2.16 (s, 1.33H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  169.68, 168.99, 154.77, 154.58, 148.46, 148.39, 137.15, 137.11, 136.92, 135.76, 134.87, 134.41, 130.69, 130.56, 128.33, 127.63, 127.48, 127.11, 126.42, 126.26, 124.54, 124.48, 123.78, 123.72, 77.48, 77.16, 76.84, 52.50, 49.24, 36.57, 33.77, 19.34, 19.17. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 2928, 2243, 1631, 1566, 1493, 1459, 1402, 1308, 1078, 1045, 908, 808, 725. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$  240.1263; found 240.1264.

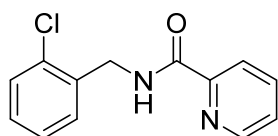
### ***N*-(2-methoxybenzyl)picolinamide (1b)**



**1b** was prepared following the procedure for **1a** except for the use of 2-methoxybenzylamine instead of 2-methylbenzylamine to give the corresponding product as an off white solid (957 mg, 79% yield).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.54 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.45 (s, 1H), 8.21 (dt,  $J = 7.8, 1.1$  Hz, 1H), 7.83 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.40 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.35 (dd,  $J = 7.4, 1.6$  Hz, 1H), 7.30 – 7.23 (m, 1H), 6.96 – 6.87 (m, 2H), 4.67 (d,  $J = 6.2$  Hz, 2H), 3.90 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.21, 157.78, 150.30, 148.18, 137.42, 129.75, 128.93, 126.42, 126.15, 122.48, 120.76, 110.49, 77.48, 77.16, 76.84, 55.55, 39.22. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3394, 2932, 2838, 1670, 1590, 1569, 1522, 1494, 1463, 1436, 1289, 1244, 1118, 1029, 820, 751, 690. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2$  242.1055; found 242.1053. M.p = 95-97  $^\circ\text{C}$ .

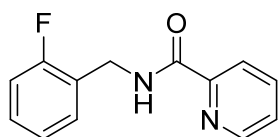
### ***N*-(2-chlorobenzyl)picolinamide (1c)**



**1c** was prepared following the procedure for **1a** except for the use of 2-chlorobenzylamine instead of 2-methylbenzylamine to give the corresponding product as an off white solid (950 mg, 77% yield).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.61 – 8.53 (m, 1H), 8.49 (s, 1H), 8.22 (dd,  $J = 7.9, 0.9$  Hz, 1H), 7.85 (tt,  $J = 7.8, 1.7$  Hz, 1H), 7.53 – 7.33 (m, 3H), 7.30 – 7.18 (m, 2H), 4.77 (d,  $J = 6.3$  Hz, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.46, 149.88, 148.28, 137.51, 135.80, 133.86, 130.14, 129.69, 129.01, 127.22, 126.40, 122.51, 77.48, 77.16, 76.84, 41.50. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3384, 3060, 1670, 1591, 1570, 1518, 1466, 1435, 1290, 1244, 1160, 1042, 1000, 820, 748, 681. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{13}\text{H}_{11}\text{ClN}_2\text{O}$  246.0560; found 246.0564. M.p = 84-86 °C.

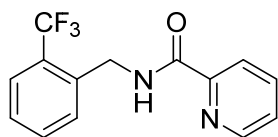
#### ***N*-(2-fluorobenzyl)picolinamide (1d)**



**1d** was prepared following the procedure for **1a** except for the use of 2-fluorobenzylamine instead of 2-methylbenzylamine to give the corresponding product as an off white solid (829 mg, 72% yield).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.54 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.41 (s, 1H), 8.22 (dt,  $J = 7.9, 1.1$  Hz, 1H), 7.85 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.50 – 7.35 (m, 2H), 7.33 – 7.23 (m, 1H), 7.17 – 7.02 (m, 2H), 4.73 (d,  $J = 6.2$  Hz, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.46, 162.43, 159.97, 149.86, 148.25, 137.53, 130.36, 130.32, 129.46, 129.38, 126.41, 125.41, 125.26, 124.46, 122.51, 115.66, 115.45, 81.96, 77.48, 77.16, 76.84, 37.54, 37.50.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -118.68. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3386, 2924, 1669, 1521, 1491, 1460, 1434, 1289, 1228, 1183, 1103, 1000, 821, 751, 689. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{13}\text{H}_{11}\text{FN}_2\text{O}$  230.0855; found 230.0853. M.p = 76-78 °C.

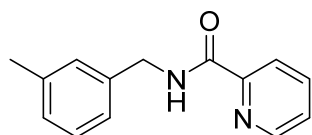
#### ***N*-(2-(trifluoromethyl)benzyl)picolinamide (1e)**



**1e** was prepared following the procedure for **1a** except for the use of 2-trifluoromethylbenzylamine instead of 2-methylbenzylamine to give the corresponding product as an off white solid (939 mg, 67% yield).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.55 (ddd,  $J = 4.7, 1.7, 0.9$  Hz, 1H), 8.45 (s, 1H), 8.23 (dt,  $J = 7.8, 1.1$  Hz, 1H), 7.86 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.66 (dd,  $J = 15.0, 7.8$  Hz, 2H), 7.52 (t,  $J = 7.6$  Hz, 1H), 7.47 – 7.33 (m, 2H), 4.86 (d,  $J = 6.4$  Hz, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.50, 149.75, 148.32, 137.54, 136.81, 132.46, 130.61, 128.54, 128.24, 128.17, 126.47, 126.22, 126.16, 126.11, 126.05, 125.97, 123.25, 122.53, 77.48, 77.16, 76.84, 40.10.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -59.42. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3297, 2923, 1660, 1524, 1465, 1422, 1310, 1266, 1172, 1155, 1126, 1104, 1036, 1004, 768, 747, 686. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{14}\text{H}_{11}\text{F}_3\text{N}_2\text{O}$  280.0823; found 280.0824. M.p = 129-131 °C.

#### ***N*-(3-methylbenzyl)picolinamide (1f)**

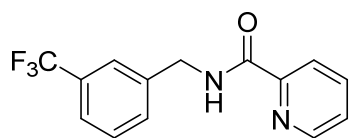


**1f** was prepared following the procedure for **1a** except for the use of 3-methylbenzylamine instead of 2-methylbenzylamine to give the corresponding product as a yellow oil (781 mg, 69% yield).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.53 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.35 (s, 1H), 8.24 (dt,  $J = 7.8, 1.0$  Hz, 1H), 7.86 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.43 (ddd,  $J = 7.6, 4.8, 1.3$  Hz, 1H), 7.28 – 7.07 (m, 4H), 4.64 (d,  $J = 6.1$  Hz, 2H), 2.35 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.31, 150.00, 148.20, 138.57, 138.25, 137.54, 128.80, 128.75, 128.38, 126.34, 125.07, 122.53, 77.48, 77.16, 76.84, 43.64, 21.53. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3383, 2920, 2360, 1669, 1523, 1465, 1434, 1288, 1249, 1044, 1000, 821, 747, 699. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$  226.1106; found 226.1110.



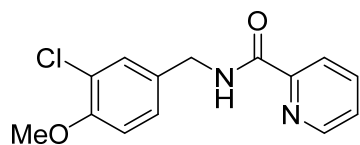
### *N*-(3-(trifluoromethyl)benzyl)picolinamide (**1g**)



**1g** was prepared following the procedure for **1a** except for the use of 3-trifluoromethylbenzylamine instead of 2-methylbenzylamine to give the corresponding product as an off white solid (995 mg, 71% yield).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.55 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.46 (s, 1H), 8.33 – 8.17 (m, 1H), 7.88 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.69 – 7.51 (m, 3H), 7.49 – 7.40 (m, 2H), 4.73 (d,  $J = 6.3$  Hz, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.58, 149.66, 148.29, 139.47, 137.65, 131.31, 129.34, 126.58, 124.64, 124.60, 124.51, 124.47, 122.61, 77.48, 77.16, 77.16, 76.84, 43.13.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.47. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3383, 2925, 1669, 1524, 1330, 1166, 1123, 1074, 1002, 799, 749, 702. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{14}\text{H}_{11}\text{F}_3\text{N}_2\text{O}$  280.0823; found 280.0825. M.p = 70-72 °C.

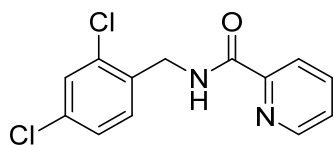
### *N*-(3-chloro-4-methoxybenzyl)picolinamide (**1h**)



**1h** was prepared following the procedure for **1a** except for the use of 3-chloro-4-methoxybenzylamine instead of 2-methylbenzylamine to give the corresponding product as a white solid (1.01 g, 73% yield).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.60 – 8.47 (m, 1H), 8.35 (s, 1H), 8.23 (dt,  $J = 7.8, 0.9$  Hz, 1H), 7.86 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.48 – 7.40 (m, 1H), 7.38 (d,  $J = 2.2$  Hz, 1H), 7.28 – 7.21 (m, 1H), 6.89 (d,  $J = 8.4$  Hz, 1H), 4.58 (d,  $J = 6.2$  Hz, 2H), 3.89 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.34, 154.47, 149.80, 148.22, 137.51, 131.59, 129.86, 127.44, 126.40, 122.65, 122.48, 112.25, 77.48, 77.16, 76.84, 56.32, 42.57. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3379, 2839, 1666, 1520, 1501, 1463, 1435, 1284, 1256, 1147, 1064, 1022, 1000, 817, 748, 690. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{14}\text{H}_{13}\text{ClN}_2\text{O}_2$  276.7200; found 276.0668. M.p = 76-78 °C.

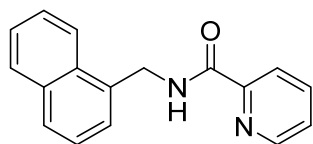
### ***N*-(2,4-dichlorobenzyl)picolinamide (1i)**



**1i** was prepared following the procedure for **1a** except for the use of 2,4-dichlorobenzylamine instead of 2-methylbenzylamine to give the corresponding product as a white sticky solid (1.14 g, 81% yield).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.54 (ddd, *J* = 11.1, 6.3, 4.1 Hz, 2H), 8.26 – 8.15 (m, 1H), 7.85 (tdd, *J* = 7.7, 4.5, 1.7 Hz, 1H), 7.51 – 7.30 (m, 3H), 7.20 (ddd, *J* = 7.8, 4.7, 2.1 Hz, 1H), 4.71 (dt, *J* = 7.8, 3.9 Hz, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 164.51, 149.63, 148.25, 137.46, 134.45, 134.32, 133.96, 130.80, 129.39, 127.37, 126.44, 122.42, 77.48, 77.16, 76.84, 40.86. IR (neat, v/cm<sup>-1</sup>) 3383, 3059, 1670, 1589, 1567, 1517, 1467, 1433, 1290, 1244, 1103, 1045, 1001, 864, 821, 747, 687. HRMS (EI<sup>+</sup>) *m/z*: [M]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>10</sub>ClN<sub>2</sub>O 280.0170; found 280.0170.

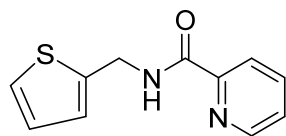
### ***N*-(naphthalen-1-ylmethyl)picolinamide (1j)**



**1j** was prepared following the procedure for **1a** except for the use of 1-naphthylmethylamine instead of 2-methylbenzylamine to give the corresponding product as an off white solid (1.10 g, 84% yield).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.46 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.35 (s, 1H), 8.29 – 8.21 (m, 1H), 8.17 – 8.04 (m, 1H), 7.92 – 7.77 (m, 3H), 7.60 – 7.35 (m, 5H), 5.13 (d, *J* = 5.8 Hz, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 164.14, 149.89, 148.20, 137.50, 134.03, 133.66, 131.67, 128.89, 128.73, 126.78, 126.34, 126.09, 125.58, 123.71, 122.52, 77.48, 77.16, 76.84, 41.72. IR (neat, v/cm<sup>-1</sup>) 3381, 3055, 1668, 1569, 1518, 1464, 1433, 1398, 1287, 1167, 998, 777, 748, 688. HRMS (EI<sup>+</sup>) *m/z*: [M]<sup>+</sup> Calcd for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O 262.1106; found 262.1108. M.p = 100-102 °C.

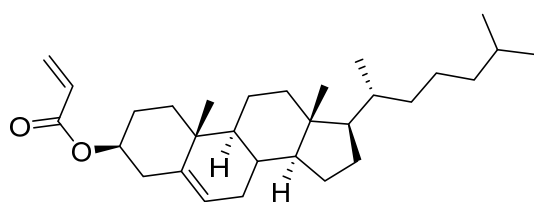
***N*-(thiophen-2-ylmethyl)picolinamide (1k)**



**1k** was prepared following the procedure for **1a** except for the use of 2-thienylmethylamine instead of 2-methylbenzylamine to give the corresponding product as an off white solid (688 mg, 63% yield).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.53 (d,  $J = 4.5$  Hz, 1H), 8.39 (s, 1H), 8.23 (d,  $J = 7.8$  Hz, 1H), 7.85 (t,  $J = 7.7$  Hz, 1H), 7.50 – 7.35 (m, 1H), 7.33 – 7.16 (m, 1H), 7.06 (d,  $J = 2.5$  Hz, 1H), 7.02 – 6.87 (m, 1H), 4.84 (d,  $J = 6.0$  Hz, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.15, 149.78, 148.24, 140.91, 137.50, 127.04, 126.42, 126.26, 125.34, 122.53, 77.48, 77.16, 76.84, 38.32. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3318, 2929, 1662, 1651, 1518, 1464, 1431, 1365, 1292, 1219, 1169, 1144, 1042, 998, 834, 820, 750, 698. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{11}\text{H}_{10}\text{N}_2\text{OS}$  218.0514; found 218.0517. M.p = 102-104 °C.

**(3*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acrylate (1l)**

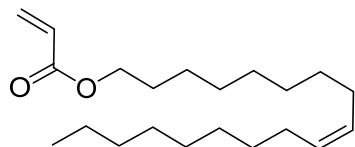


**1l** was synthesized according to a literatura procedure with minor modifications.<sup>5</sup> To a stirred solution of a 60% dispersion of NaH (400 mg, 10.0 mmol, 2.0 equiv) in anhydrous THF (10 mL) at 0 °C, a solution of cholesterol (1.93 g, 5.0 mmol, 1.0 equiv) in anhydrous THF (10 mL) was added portion wise under an argon atmosphere. The reaction mixture was then warmed to room temperature and stirred for 1 hour. After cooling to 0 °C, acrylyl chloride (0.61 mL, 7.5 mmol, 1.5 equiv) was added dropwise to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 12 hours. After adding aqueous  $\text{NH}_4\text{Cl}$  to quench the reaction and the resulting solution extracted with ethyl acetate. The combined organic layers were then washed with a brine solution and dried

over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography using *n*-hexane/EtOAc = 9/1 as the eluent to give **11** as a white solid (727 mg, 33% yield).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.44 – 6.35 (m, 1H), 6.18 – 6.06 (m, 1H), 5.83 – 5.74 (m, 1H), 5.37 (t, *J* = 10.2 Hz, 1H), 4.77 – 4.60 (m, 1H), 2.36 (d, *J* = 7.9 Hz, 2H), 2.04 – 1.82 (m, 5H), 1.68 – 1.41 (m, 8H), 1.39 – 1.24 (m, 4H), 1.22 – 1.05 (m, 8H), 1.02 – 0.96 (m, 3H), 0.93 – 0.85 (m, 10H), 0.68 (s, 3H). <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 165.78, 139.74, 130.39, 129.17, 122.86, 77.48, 77.16, 76.84, 74.26, 56.82, 56.27, 50.16, 42.45, 39.87, 39.66, 38.24, 37.12, 36.74, 36.32, 35.94, 32.05, 32.00, 28.37, 28.15, 27.90, 24.43, 23.97, 22.97, 22.71, 21.17, 19.47, 18.86, 12.00. IR (neat, v/cm<sup>-1</sup>) 2934, 2906, 1720, 1465, 1409, 1297, 1201, 1011, 984, 965, 805, 761, 737, 688. HRMS (EI<sup>+</sup>) *m/z*: [M]<sup>+</sup> Calcd for C<sub>30</sub>H<sub>48</sub>O<sub>2</sub> 440.3654; found 440.3649. M.p = 115-117 °C.

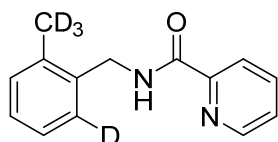
#### (*Z*)-octadec-9-en-1-yl acrylate (**1m**)



**1m** was prepared following the procedure for **11** except for the use of oleyl alcohol instead of cholesterol to give the corresponding product as a colorless oil (1.50 g, 93% yield).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.40 (dd, *J* = 17.3, 1.5 Hz, 1H), 6.12 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.81 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.41 – 5.29 (m, 2H), 4.20 – 4.08 (m, 2H), 2.01 (dd, *J* = 12.4, 6.6 Hz, 4H), 1.71 – 1.62 (m, 2H), 1.34 – 1.26 (m, 22H), 0.88 (t, *J* = 6.9 Hz, 3H). <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 166.50, 130.56, 130.13, 129.93, 128.80, 77.48, 77.16, 76.84, 64.86, 32.05, 29.91, 29.87, 29.67, 29.55, 29.47, 29.37, 29.34, 28.75, 27.36, 27.32, 26.06, 22.83, 14.26. IR (neat, v/cm<sup>-1</sup>) 2924, 2854, 1728, 1464, 1407, 1295, 1270, 1188, 1060, 984, 965, 913, 810, 743. HRMS (EI<sup>+</sup>) *m/z*: [M]<sup>+</sup> Calcd for C<sub>21</sub>H<sub>38</sub>O<sub>2</sub> 322.2872; found 322.2873.

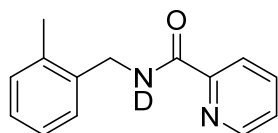
#### *N*-(2-methylbenzyl)picolinamide (**1a-D**)



**1a-D** was synthesized according to a literature procedure with minor modifications.<sup>4</sup> To a solution of **1a** (453 mg, 2.0 mmol, 1.0 equiv) and Pd(OAc)<sub>2</sub> (68 mg, 0.30 mmol, 0.15 equiv) in 10 mL of *o*-xylene was added D<sub>2</sub>O (1.2 mL) under air and the resulting solution stirred at 130 °C for 12 hours. The reaction mixture was then cooled to room temperature, EtOAc was added, and the resulting solution filtered through a pad of celite. The volatiles were removed by evaporation. The resulting crude mixture was purified by flash silica gel column chromatography using *n*-hexane/EtOAc = 2/1 as an eluent to give **1a-D** as an off white solid (364 mg, 79% yield). The isolated product had a deuterium content of 95% on the sp<sup>2</sup> (C-H) position and a 93% deuterium content on the sp<sup>3</sup> (C-H) position, as evidenced by <sup>1</sup>H NMR spectroscopy.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.52 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.31 – 8.09 (m, 2H), 7.85 (td, *J* = 7.7, 1.7 Hz, 1H), 7.42 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.34 – 7.31 (m, 0.05H), 7.26 – 7.15 (m, 3H), 4.67 (d, *J* = 5.8 Hz, 2H), 2.36 – 2.34 (m, 0.21H).

#### ***N*-(2-methylbenzyl)picolinamide (1a-ND)**



**1a-ND** was synthesized according to a literature procedure with minor modifications.<sup>2</sup> To a stirred solution of a 60% dispersion of NaH in oil (160 mg, 4.0 mmol, 2.0 equiv) in anhydrous THF (2 mL) at 0 °C, a solution of **1a** (452 mg, 2.0 mmol, 1.0 equiv) in anhydrous THF (2 mL) was added portion wise under an argon atmosphere. The reaction mixture was then warmed to room temperature and stirred for 1 hour. D<sub>2</sub>O (1.0 mL) was then added dropwise to the reaction mixture which was then stirred for a further 2 hours at room temperature. After adding Et<sub>2</sub>O (10 mL) to the reaction mixture, the organic layer was separated. The organic layer was then washed with D<sub>2</sub>O and dried over Na<sub>2</sub>SO<sub>4</sub>. The volatiles were removed by evaporation to give **1a-ND** as a white solid (432 mg, 95% yield),

which was stored inside a glove box. The isolated product was obtained with a 100% deuterium content on the nitrogen atom, as evidenced by  $^1\text{H}$  NMR spectroscopy.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.52 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.23 (dt,  $J = 7.8, 1.1$  Hz, 1H), 7.85 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.42 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.33 – 7.31 (m, 1H), 7.23 – 7.17 (m, 3H), 4.66 (s, 2H), 2.38 (s, 3H).

#### 4. Evaluation of directing group (Table 1)

##### General procedure:

To a sealed tube equipped with a magnetic stirring bar were added the benzylamine derived substrate (**1aa** or **1ab** or **1ac** or **1a** or **1ad**) (0.20 mmol, 1.0 equiv), catalyst  $[\text{Rh}(\text{OAc})(\text{cod})]_2$  (5.4 mg, 0.01 mmol, 5.0 mol%), pivalic acid (40.8 mg, 0.40 mmol, 2.0 equiv) and toluene (1.0 mL, 0.20 M) under an argon atmosphere. To this mixture, ethyl acrylate (43  $\mu\text{L}$ , 0.40 mmol, 2.0 equiv) was added and the resulting mixture was stirred at 160  $^\circ\text{C}$  for 16 h. The yield of the corresponding product was determined by  $^1\text{H}$  NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as internal standard.

#### 5. Optimization of reaction conditions with **1a** (Table 2)

##### General procedure:

To a sealed tube equipped with a magnetic stir bar were added **1a** (45.3 mg, 0.20 mmol, 1.0 equiv), catalyst (0.01 mmol, 5.0 mol%), pivalic acid (xx equiv) and toluene (1.0 mL, 0.20 M) under an argon atmosphere. To this mixture, ethyl acrylate (yy equiv) was added and the resulting mixture was stirred at specified temperature for 16 h. The yield of the corresponding product was determined by  $^1\text{H}$  NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as internal standard.

#### 6. Substrate scope (Table 3)

##### General procedure: *Condition A*

To a sealed tube equipped with a magnetic stirring bar were added the benzylamine derived substrates (**1a-1i**) or 1-naphthylmethylamine derived substrate (**1j**) or 2-thienylmethylamine derived substrate (**1k**) (0.20 mmol, 1.0 equiv), catalyst

[Rh(OAc)(cod)]<sub>2</sub> (5.4 mg, 0.01 mmol, 5.0 mol%), pivalic acid (40.8 mg, 0.40 mmol, 2.0 equiv) and toluene (1.0 mL, 0.20 M) under an argon atmosphere. To this mixture  $\alpha,\beta$ -unsaturated compound (0.40 mmol, 2.0 equiv) was added and the resulting mixture was stirred at 160 °C for 16 h. After the reaction, the solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography using *n*-hexane/EtOAc (17/3-7/3) as an eluent to afford the desired products.

#### **General procedure: Condition B**

To a sealed tube equipped with a magnetic stirring bar were added benzylamine derived substrates (**1a-1i**) or 1-naphthylmethylamine derived substrate (**1j**) or 2-thienylmethylamine derived substrate (**1k**) (0.20 mmol, 1.0 equiv), catalyst [Rh<sub>2</sub>(OAc)<sub>4</sub>] (5.4 mg, 0.01 mmol, 5.0 mol%), pivalic acid (40.8 mg, 0.40 mmol, 2.0 equiv) and toluene (1.0 mL, 0.20 M) under a argon atmosphere. To this mixture  $\alpha,\beta$ -unsaturated compound (0.40 mmol, 2.0 equiv) was added and the resulting mixture was stirred at 170 °C for 16 h. After the reaction, the solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography using *n*-hexane/EtOAc (17/3-7/3) as an eluent to afford the desired products.

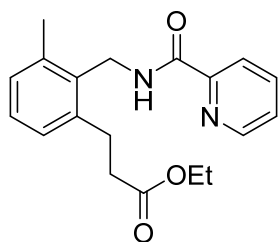
#### **Supporting for formation of Rh(IV) species:**

In the case of condition B, Rh<sub>2</sub>(OAc)<sub>4</sub> was used as the catalyst for the C-H alkylation reaction. According to the proposed mechanism (Scheme 4), Rh<sub>2</sub>(OAc)<sub>4</sub> undergoes oxidative addition via an *NH*-insertion process. Thus, the Rh(IV) species would be expected to be formed from the Rh(II) catalyst. At 10 minutes after all of the reagents are added at room temperature, a dark purple solution is formed, which is consistent with the formation of a Rh(IV) species in the reaction mixture (Figure S1).<sup>6</sup>



**Figure S1.** Dark purple reaction mixture for Rh(II) catalyzed condition

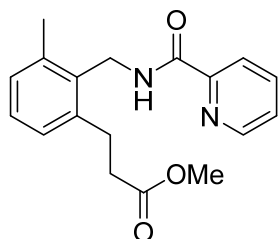
**Ethyl 3-(3-methyl-2-(picolinamidomethyl)phenyl)propanoate (2a)**



**2a** was prepared following the procedure of condition A (54.2 mg, 83%) or condition B (55.5 mg, 85%) to give the corresponding product as a colorless sticky oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.47 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.22 (dt,  $J = 7.8, 1.0$  Hz, 1H), 7.97 (s, 1H), 7.84 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.40 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.18 (dd,  $J = 8.4, 6.6$  Hz, 1H), 7.10 (d,  $J = 7.6$  Hz, 2H), 4.71 (d,  $J = 5.0$  Hz, 2H), 4.10 (q,  $J = 7.1$  Hz, 2H), 3.08 (t,  $J = 8.0$  Hz, 2H), 2.62 (t,  $J = 8.0$  Hz, 2H), 2.41 (s, 3H), 1.20 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.76, 164.16, 149.83, 148.15, 140.13, 138.32, 137.41, 133.61, 129.19, 128.22, 127.44, 126.25, 122.31, 77.48, 77.16, 76.84, 60.57, 37.85, 36.05, 28.32, 19.99, 14.27. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3392, 2924, 1730, 1674, 1516, 1465, 1433, 1373, 1242, 1157, 1040, 999, 774, 751, 701. HRMS (EI $^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3$  326.1630; found 326.1627.

**Methyl 3-(3-methyl-2-(picolinamidomethyl)phenyl)propanoate (2b)**



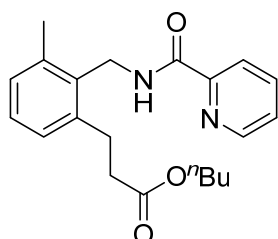
**2b** was prepared following the procedure of condition A (38.1 mg, 61%) or condition B (55.6 mg, 89%) to give the corresponding product as a yellow sticky oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.48 (d,  $J = 4.2$  Hz, 1H), 8.23 (d,  $J = 7.8$  Hz, 1H), 7.97 (s, 1H), 7.85 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.40 (ddd,  $J = 7.6, 4.8, 1.1$  Hz, 1H), 7.23 – 7.14 (m, 1H), 7.10 (dd,  $J = 7.4, 2.8$  Hz, 2H), 4.70 (d,  $J = 5.0$  Hz, 2H), 3.65 (s, 3H), 3.09 (t,  $J = 7.8$  Hz, 2H), 2.63 (t,  $J = 7.8$  Hz, 2H), 2.41 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  173.23,



164.20, 149.83, 148.18, 140.09, 138.38, 137.45, 133.63, 129.26, 128.29, 127.42, 126.29, 122.35, 77.48, 77.16, 76.84, 51.79, 37.85, 35.86, 28.30, 20.03. IR (neat,  $\nu/\text{cm}^{-1}$ ) 2984, 1738, 1679, 1517, 1373, 1241, 1046, 917, 734. HRMS (EI<sup>+</sup>)  $m/z$ : [M]<sup>+</sup> Calcd for C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub> 312.1474; found 312.1475.

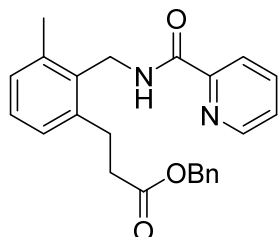
### Butyl 3-(3-methyl-2-(picolinamidomethyl)phenyl)propanoate (2c)



**2c** was prepared following the procedure of condition A (40.4 mg, 57%) or condition B (60.3 mg, 85%) to give the corresponding product as a colorless sticky oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.47 (ddd,  $J = 4.8, 1.6, 0.9$  Hz, 1H), 8.23 (dt,  $J = 7.9, 1.1$  Hz, 1H), 7.97 (s, 1H), 7.84 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.40 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.18 (dd,  $J = 8.4, 6.6$  Hz, 1H), 7.10 (d,  $J = 7.5$  Hz, 2H), 4.71 (d,  $J = 5.0$  Hz, 2H), 4.05 (t,  $J = 6.7$  Hz, 2H), 3.08 (t,  $J = 8.0$  Hz, 2H), 2.63 (t,  $J = 8.0$  Hz, 2H), 2.41 (s, 3H), 1.62 – 1.48 (m, 2H), 1.31 (ddd,  $J = 10.3, 9.4, 4.8$  Hz, 2H), 0.89 (t,  $J = 7.4$  Hz, 3H). <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  172.86, 164.16, 149.82, 148.13, 140.11, 138.31, 137.40, 133.59, 129.18, 128.21, 127.40, 126.24, 122.31, 77.48, 77.16, 76.84, 64.50, 37.84, 36.02, 30.68, 28.33, 19.98, 19.16, 13.78. IR (neat,  $\nu/\text{cm}^{-1}$ ) 2959, 1730, 1673, 1514, 1464, 1433, 1241, 1218, 1178, 999, 911, 819, 749, 701, 665. HRMS (EI<sup>+</sup>)  $m/z$ : [M]<sup>+</sup> Calcd for C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub> 354.1943; found 354.1946.

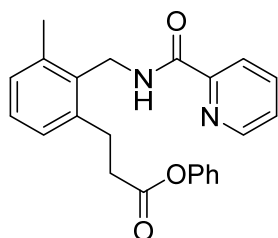
### Benzyl 3-(3-methyl-2-(picolinamidomethyl)phenyl)propanoate (2d)



**2d** was prepared following the procedure of condition B to give the corresponding product as a colorless sticky oil (66.8 mg, 86%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.44 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.21 (dt,  $J = 7.8, 1.1$  Hz, 1H), 7.97 (s, 1H), 7.82 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.42 – 7.34 (m, 1H), 7.30 (dtdd,  $J = 8.4, 7.0, 4.4, 2.6$  Hz, 5H), 7.19 – 7.12 (m, 1H), 7.08 (t,  $J = 7.1$  Hz, 2H), 5.09 (s, 2H), 4.70 (d,  $J = 5.1$  Hz, 2H), 3.11 (t,  $J = 8.0$  Hz, 2H), 2.69 (t,  $J = 8.0$  Hz, 2H), 2.40 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.59, 164.15, 149.79, 148.14, 139.95, 138.33, 137.40, 135.95, 133.63, 129.22, 128.60, 128.30, 128.25, 127.41, 126.23, 122.30, 77.48, 77.16, 76.84, 66.41, 37.82, 35.95, 28.24, 20.01. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3390, 3063, 1732, 1673, 1590, 1570, 1516, 1464, 1433, 1242, 1153, 998, 819, 785, 749, 699. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_3$  388.1787; found 388.1789.

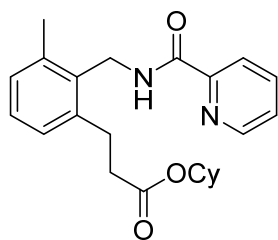
### Phenyl 3-(3-methyl-2-(picolinamidomethyl)phenyl)propanoate (2e)



**2e** was prepared following the procedure of condition B to give the corresponding product as a white solid (39.7 mg, 53%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.48 – 8.36 (m, 1H), 8.22 (d,  $J = 7.8$  Hz, 1H), 8.02 (s, 1H), 7.87 – 7.76 (m, 1H), 7.41 – 7.29 (m, 3H), 7.28 – 7.10 (m, 4H), 7.00 (d,  $J = 7.7$  Hz, 2H), 4.75 (d,  $J = 5.1$  Hz, 2H), 3.21 (t,  $J = 7.7$  Hz, 2H), 2.89 (t,  $J = 7.7$  Hz, 2H), 2.44 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  171.30, 164.22, 150.73, 149.79, 148.17, 139.73, 138.44, 137.44, 133.77, 129.46, 129.43, 128.34, 127.61, 126.28, 125.88, 122.33, 121.66, 77.48, 77.16, 76.84, 37.90, 36.06, 28.31, 20.06. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3389, 2921, 1757, 1674, 1591, 1518, 1465, 1242, 1195, 1162, 1132, 999, 751, 692. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_3$  374.1630; found 374.1629. M.p = 88-90 °C.

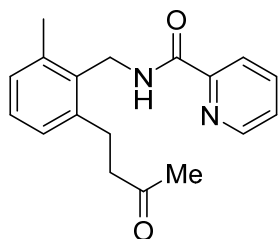
### Cyclohexyl 3-(3-methyl-2-(picolinamidomethyl)phenyl)propanoate (2f)



**2f** was prepared following the procedure of condition B to give the corresponding product as a colorless sticky oil (61.6 mg, 81%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.52 – 8.44 (m, 1H), 8.23 (dt,  $J = 7.8, 0.8$  Hz, 1H), 7.97 (s, 1H), 7.84 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.40 (ddd,  $J = 7.6, 4.8, 1.1$  Hz, 1H), 7.21 – 7.13 (m, 1H), 7.13 – 7.04 (m, 2H), 4.76 – 4.69 (m, 3H), 3.08 (t,  $J = 8.0$  Hz, 2H), 2.61 (t,  $J = 8.0$  Hz, 2H), 2.41 (s, 3H), 1.78 (dd,  $J = 9.4, 3.7$  Hz, 2H), 1.73 – 1.59 (m, 2H), 1.51 (ddd,  $J = 12.4, 5.5, 3.0$  Hz, 1H), 1.39 – 1.21 (m, 5H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.24, 164.17, 149.84, 148.14, 140.16, 138.28, 137.40, 133.59, 129.14, 128.18, 127.42, 126.23, 122.32, 77.48, 77.16, 76.84, 72.84, 37.88, 36.31, 31.63, 28.40, 25.45, 23.82, 19.99. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3391, 2936, 2858, 1727, 1676, 1516, 1465, 1433, 1244, 1180, 1041, 999, 782, 751, 663. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_3$  380.2100; found 380.2101.

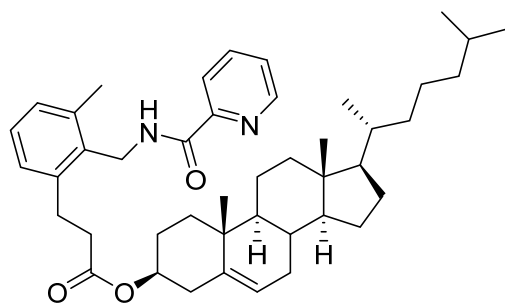
***N*-(2-Methyl-6-(3-oxobutyl)benzyl)picolinamide (2g)**



**2g** was prepared following the procedure of condition B to give the corresponding product as a colorless sticky oil (27.3 mg, 46%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.48 (ddd,  $J = 4.7, 1.7, 0.9$  Hz, 1H), 8.22 (dt,  $J = 7.8, 1.1$  Hz, 1H), 7.98 (s, 1H), 7.85 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.41 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.17 (t,  $J = 7.5$  Hz, 1H), 7.08 (t,  $J = 7.4$  Hz, 2H), 4.69 (d,  $J = 5.1$  Hz, 2H), 3.01 (t,  $J = 8.0$  Hz, 2H), 2.75 (t,  $J = 8.0$  Hz, 2H), 2.42 (s, 3H), 2.11 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  207.75, 164.18, 149.84, 148.20, 140.69, 138.35, 137.50, 133.59, 129.09, 128.29, 127.59, 126.33, 122.38, 77.48, 77.16, 76.84, 45.41, 37.89, 30.10, 27.14, 20.06. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3390, 2918, 1712, 1674, 1590, 1465, 1434, 1358, 1313, 1245, 1162, 1119, 999, 821, 777, 752, 701. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2$  296.1525; found 296.1529.

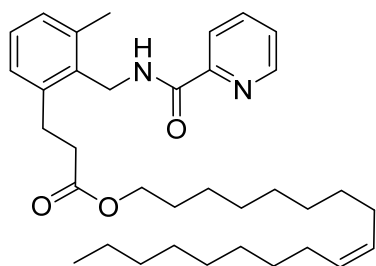
**(3*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 3-(3-methyl-2-(picolinamidomethyl)phenyl)propanoate (2h)**



**2h** was prepared following the procedure of condition B to give the corresponding product as a white solid (105 mg, 79%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.47 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.23 (dt,  $J = 7.8, 1.0$  Hz, 1H), 7.97 (s, 1H), 7.84 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.40 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.17 (dd,  $J = 8.4, 6.6$  Hz, 1H), 7.09 (d,  $J = 7.6$  Hz, 2H), 5.34 (d,  $J = 3.7$  Hz, 1H), 4.71 (d,  $J = 5.0$  Hz, 2H), 4.67 – 4.50 (m, 1H), 3.07 (t,  $J = 7.8$  Hz, 2H), 2.60 (t,  $J = 7.8$  Hz, 2H), 2.41 (s, 3H), 2.24 (d,  $J = 7.6$  Hz, 2H), 2.07 – 1.90 (m, 2H), 1.89 – 1.72 (m, 4H), 1.59 – 1.04 (m, 20H), 0.99 (s, 3H), 0.91 (d,  $J = 6.5$  Hz, 3H), 0.86 (dd,  $J = 6.6, 1.8$  Hz, 6H), 0.67 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.21, 164.18, 149.87, 148.17, 140.15, 139.78, 138.32, 137.41, 133.63, 129.18, 128.21, 127.51, 126.25, 122.70, 122.36, 77.48, 77.36, 77.16, 76.84, 74.21, 56.79, 56.24, 50.12, 42.42, 39.84, 39.63, 38.13, 37.90, 37.09, 36.68, 36.33, 36.30, 35.91, 32.01, 31.96, 28.44, 28.35, 28.13, 27.80, 24.40, 23.94, 22.95, 22.69, 21.14, 20.01, 19.44, 18.84, 11.97. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3393, 2936, 1729, 1677, 1591, 1515, 1465, 1434, 1242, 1173, 911, 817, 750, 665. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{44}\text{H}_{62}\text{N}_2\text{O}_3$  666.4760; found 666.4766. M.p = 76-78 °C.

**(Z)-octadec-9-en-1-yl 3-(3-methyl-2-(picolinamidomethyl)phenyl)propanoate (2i)**

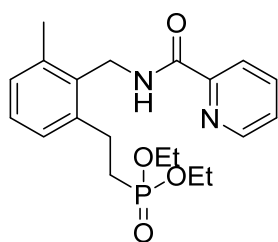


**2i** was prepared following the procedure of condition B to give the corresponding product as a colorless sticky oil (76.8 mg, 70%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.47 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.23 (dt,  $J = 7.9, 1.1$  Hz, 1H), 7.97 (s, 1H), 7.84 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.40 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.17 (dd,  $J = 8.4, 6.6$  Hz, 1H), 7.09 (d,  $J = 7.5$  Hz, 2H), 5.44 – 5.23 (m, 2H), 4.71 (d,  $J =$

5.0 Hz, 2H), 4.03 (t,  $J = 6.8$  Hz, 2H), 3.06 (t,  $J = 7.8$  Hz, 2H), 2.63 (t,  $J = 7.8$  Hz, 2H), 2.41 (s, 3H), 2.03 – 1.96 (m, 4H), 1.61 – 1.52 (m, 2H), 1.31 – 1.26 (m, 22H), 0.88 (t,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.90, 164.19, 149.86, 148.17, 140.15, 138.35, 137.43, 133.64, 130.56, 130.38, 130.10, 129.91, 129.22, 128.24, 127.43, 126.26, 122.35, 77.48, 77.36, 77.16, 76.84, 64.84, 37.88, 36.05, 32.74, 32.03, 29.89, 29.78, 29.65, 29.53, 29.45, 29.36, 28.68, 28.36, 27.34, 25.99, 22.81, 20.03, 14.25. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3394, 2924, 2853, 1734, 1679, 1590, 1515, 1464, 1433, 1243, 1162, 998, 778, 749, 701. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{35}\text{H}_{52}\text{N}_2\text{O}_3$  548.3978; found 548.3977.

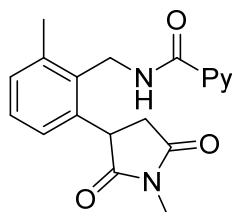
### Diethyl (3-methyl-2-(picolinamidomethyl)phenethyl)phosphonate (2j)



**2j** was prepared following the procedure of condition B to give the corresponding product as a colorless sticky oil (70.3 mg, 90%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.47 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.22 (dt,  $J = 7.9, 1.1$  Hz, 1H), 7.94 (s, 1H), 7.85 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.40 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.23 – 7.15 (m, 1H), 7.15 – 7.07 (m, 2H), 4.69 (d,  $J = 5.0$  Hz, 2H), 4.16 – 3.98 (m, 4H), 3.04 (ddd,  $J = 10.4, 8.5, 5.2$  Hz, 2H), 2.41 (s, 3H), 2.12 – 1.97 (m, 2H), 1.28 (t,  $J = 7.1$  Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.11, 149.77, 148.14, 140.76, 140.60, 138.41, 137.42, 133.39, 129.28, 128.35, 127.38, 126.27, 122.28, 77.48, 77.16, 76.84, 61.76, 61.70, 37.83, 28.61, 27.23, 26.20, 26.16, 19.96, 16.51, 16.46. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3393, 2981, 1673, 1519, 1466, 1245, 1162, 1054, 1028, 966, 773. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_4\text{P}$  390.1708; found 390.1708.

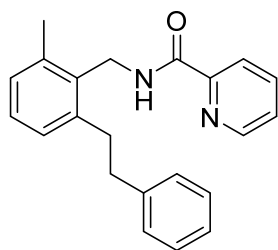
### *N*-(2-methyl-6-(1-methyl-2,5-dioxopyrrolidin-3-yl)benzyl)picolinamide (2k)



**2k** was prepared following the procedure of condition B to give the corresponding product as a yellow solid (51.9 mg, 77%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.56 – 8.48 (m, 1H), 8.31 (s, 1H), 8.19 (d,  $J = 7.8$  Hz, 1H), 7.84 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.41 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.33 – 7.15 (m, 2H), 6.91 (d,  $J = 6.8$  Hz, 1H), 4.99 (dd,  $J = 14.8, 6.8$  Hz, 1H), 4.69 – 4.51 (m, 2H), 3.21 (dd,  $J = 18.4, 9.5$  Hz, 1H), 3.06 (s, 3H), 2.73 (dd,  $J = 18.5, 4.7$  Hz, 1H), 2.48 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.61, 176.46, 164.13, 149.60, 148.34, 138.73, 137.69, 137.48, 134.75, 130.45, 128.90, 126.40, 124.40, 122.39, 77.48, 77.16, 76.84, 42.56, 37.92, 37.59, 25.35, 20.41. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3383, 3012, 1775, 1695, 1668, 1517, 1464, 1433, 1382, 1281, 1119, 952, 819, 748, 686, 665. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_3$  337.1426; found 337.1422. M.p = 53-55  $^\circ\text{C}$ .

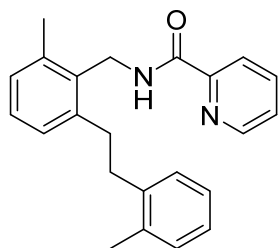
***N*-(2-methyl-6-phenethylbenzyl)picolinamide (2l)**



**2l** was prepared following the procedure of condition B except for the use of 7.5 mol%  $\text{Rh}_2(\text{OAc})_4$  and 5 equiv of styrene to give the corresponding product as a white solid (55.5 mg, 84%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.46 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.22 (dt,  $J = 7.8, 1.1$  Hz, 1H), 7.91 (s, 1H), 7.83 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.38 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.30 – 7.22 (m, 2H), 7.21 – 7.15 (m, 4H), 7.09 (d,  $J = 7.5$  Hz, 2H), 4.70 (d,  $J = 5.0$  Hz, 2H), 3.02 (dd,  $J = 9.6, 5.0$  Hz, 2H), 2.89 (dd,  $J = 9.6, 5.0$  Hz, 2H), 2.42 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.10, 149.84, 148.14, 141.61, 141.42, 138.16, 137.43, 133.56, 128.89, 128.58, 128.51, 128.13, 127.94, 126.26, 126.12, 122.32, 77.48, 77.16, 76.84, 38.61, 37.86, 35.68, 20.04. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3391, 2922, 1673, 1513, 1464, 1433, 1283, 1241, 1154, 998, 819, 781, 748, 700. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}$  330.1732; found 330.1734. M.p = 69-71  $^\circ\text{C}$ .

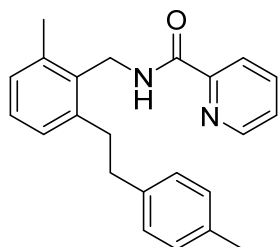
***N*-(2-methyl-6-(2-methylphenethyl)benzyl)picolinamide (2m)**



**2m** was prepared following the procedure of condition B except for the use of 7.5 mol% Rh<sub>2</sub>(OAc)<sub>4</sub> and 5 equiv of 2-methylstyrene to give the corresponding product as a white sticky solid (44.8 mg, 65%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.45 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.22 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.91 (s, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.38 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 7.21 – 7.08 (m, 7H), 4.71 (d, *J* = 5.0 Hz, 2H), 3.01 – 2.97 (m, 2H), 2.90 – 2.86 (m, 2H), 2.43 (s, 3H), 2.29 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 164.13, 149.84, 148.16, 141.66, 139.83, 138.26, 137.46, 135.99, 133.55, 130.33, 129.08, 128.93, 128.22, 127.95, 126.32, 126.28, 126.21, 122.32, 77.48, 77.16, 76.84, 37.94, 36.01, 34.32, 20.06, 19.42. IR (neat, v/cm<sup>-1</sup>) 3392, 2922, 1677, 1570, 1519, 1463, 1434, 1241, 1157, 999, 819, 747, 700. HRMS (EI<sup>+</sup>) *m/z*: [M]<sup>+</sup> Calcd for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O 344.1889; found 344.1888.

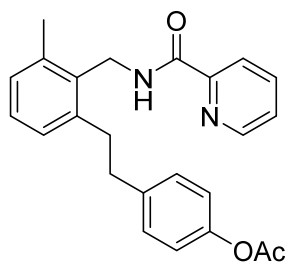
#### ***N*-(2-methyl-6-(4-methylphenethyl)benzyl)picolinamide (2n)**



**2n** was prepared following the procedure of condition B except for the use of 7.5 mol% Rh<sub>2</sub>(OAc)<sub>4</sub> and 5 equiv of 4-methylstyrene to give the corresponding product as a white solid (57.9 mg, 84%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.45 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.22 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.90 (s, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.38 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 7.20 – 7.05 (m, 7H), 4.70 (d, *J* = 5.0 Hz, 2H), 3.00 (dd, *J* = 9.2, 5.2 Hz, 2H), 2.85 (dd, *J* = 9.2, 5.2 Hz, 2H), 2.42 (s, 3H), 2.29 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 164.13, 149.89, 148.17, 141.58, 138.59, 138.18, 137.45, 135.58, 133.56, 129.21, 128.87, 128.46, 128.14, 127.95, 126.26, 122.35, 77.48, 77.16, 76.84, 38.20, 37.92, 35.85, 21.13, 20.06. IR (neat, v/cm<sup>-1</sup>) 3391, 3010, 1739, 1671, 1513, 1464, 1433, 1217, 998, 909, 810, 748, 701. HRMS (EI<sup>+</sup>) *m/z*: [M]<sup>+</sup> Calcd for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O 344.1889; found 344.1892. M.p = 87-89 °C.

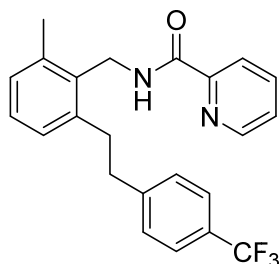
#### 4-(3-methyl-2-(picolinamidomethyl)phenethyl)phenyl acetate (2o)



**2o** was prepared following the procedure of condition B except for the use of 7.5 mol% Rh<sub>2</sub>(OAc)<sub>4</sub> and 5 equiv of 4-acetoxystyrene to give the corresponding product as a white solid (47.4 mg, 61%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.45 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.22 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.94 (s, 1H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.37 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.22 – 7.13 (m, 3H), 7.13 – 7.04 (m, 2H), 7.02 – 6.93 (m, 2H), 4.70 (d, *J* = 5.1 Hz, 2H), 3.01 (dd, *J* = 9.8, 5.2 Hz, 2H), 2.87 (dd, *J* = 9.8, 5.2 Hz, 2H), 2.42 (s, 3H), 2.26 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 169.67, 164.04, 149.74, 148.95, 148.11, 141.16, 139.14, 138.10, 137.41, 133.51, 129.47, 128.90, 128.11, 127.91, 126.24, 122.28, 121.47, 77.48, 77.16, 76.84, 37.91, 37.78, 35.57, 21.18, 20.01. IR (neat, v/cm<sup>-1</sup>) 3391, 2922, 1761, 1674, 1590, 1509, 1465, 1433, 1194, 1166, 1015, 911, 819, 750, 701. HRMS (EI<sup>+</sup>) *m/z*: [M]<sup>+</sup> Calcd for C<sub>24</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub> 388.1787; found 388.1780. M.p = 84-86 °C.

#### *N*-(2-methyl-6-(4-(trifluoromethyl)phenethyl)benzyl)picolinamide (2p)



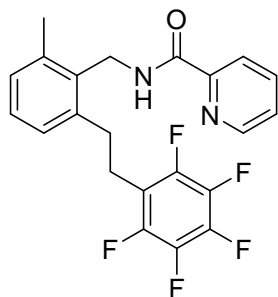
**2p** was prepared following the procedure of condition B except for the use of 7.5 mol% Rh<sub>2</sub>(OAc)<sub>4</sub> and 5 equiv of 4-trifluoromethylstyrene to give the corresponding product as a white solid (69.3 mg, 87%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.47 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.23 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.94 (s, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.40 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 6.8 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 4.71 (d, *J* = 5.1 Hz, 2H), 3.04 (dd, *J* = 9.4, 5.0 Hz, 2H), 2.94 (dd, *J* = 9.4, 5.0 Hz, 2H), 2.44 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 164.13,



149.79, 148.20, 145.68, 140.81, 138.24, 137.52, 133.60, 129.12, 128.94, 128.23, 127.94, 126.35, 125.44, 125.40, 122.38, 77.48, 77.16, 76.84, 38.23, 37.83, 35.18, 20.08.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.17. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3392, 3064, 1674, 1618, 1590, 1514, 1465, 1433, 1323, 1161, 1118, 1066, 1018, 825, 749, 701. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{23}\text{H}_{21}\text{F}_3\text{N}_2\text{O}$  398.1606; found 398.1605. M.p = 92-94 °C.

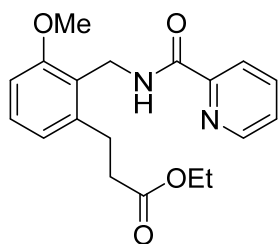
***N*-(2-methyl-6-(2-(perfluorophenyl)ethyl)benzyl)picolinamide (2q)**



**2q** was prepared following the procedure of condition B except for the use of 7.5 mol%  $\text{Rh}_2(\text{OAc})_4$  and 5 equiv of pentafluorostyrene to give the corresponding product as a white solid (79.1 mg, 94%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.47 (ddd,  $J = 4.8, 1.6, 0.9$  Hz, 1H), 8.23 (dt,  $J = 7.8, 1.1$  Hz, 1H), 7.92 (s, 1H), 7.85 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.40 (ddd,  $J = 7.6, 4.8, 1.3$  Hz, 1H), 7.20 – 7.10 (m, 2H), 7.01 (dd,  $J = 7.3, 1.2$  Hz, 1H), 4.73 (d,  $J = 5.0$  Hz, 2H), 3.06 – 2.95 (m, 4H), 2.43 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  164.18, 149.78, 148.19, 139.66, 138.48, 137.49, 133.66, 129.56, 128.26, 127.79, 126.32, 122.35, 77.48, 77.16, 76.84, 37.81, 32.81, 24.65, 20.03.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -143.88, -143.94, -157.21, -157.28, -157.34, -162.44, -162.50, -162.55. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3393, 3104, 1679, 1519, 1502, 1465, 1120, 964, 947, 701. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{22}\text{H}_{17}\text{F}_5\text{N}_2\text{O}$  420.1261; found 420.1265. M.p = 104-106 °C.

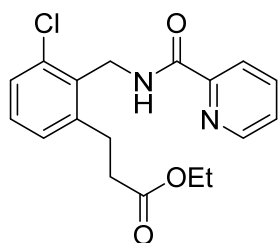
**Ethyl 3-(3-methoxy-2-(picolinamidomethyl)phenyl)propanoate (2r)**



**2r** was prepared following the procedure of condition B to give the corresponding product as a colorless sticky oil (56.2 mg, 82%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.50 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.36 (s, 1H), 8.20 (dt,  $J = 7.8, 1.1$  Hz, 1H), 7.81 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.37 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.20 (t,  $J = 8.0$  Hz, 1H), 6.89 – 6.74 (m, 2H), 4.73 (d,  $J = 5.8$  Hz, 2H), 4.11 (q,  $J = 7.1$  Hz, 2H), 3.89 (s, 3H), 3.17 (t,  $J = 7.7$  Hz, 2H), 2.62 (t,  $J = 7.7$  Hz, 2H), 1.21 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.85, 163.86, 158.66, 150.30, 148.12, 141.00, 137.28, 128.78, 126.01, 124.48, 122.36, 121.98, 108.81, 77.48, 77.16, 76.84, 60.48, 55.75, 36.01, 34.99, 28.19, 14.28. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3402, 2979, 1730, 1673, 1587, 1519, 1465, 1435, 1264, 1180, 1157, 1039, 788, 750, 661. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_4$  342.1580; found 342.1584.

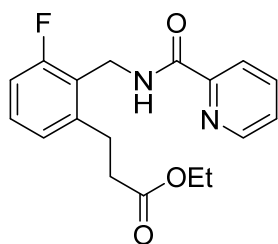
### Ethyl 3-(3-chloro-2-(picolinamidomethyl)phenyl)propanoate (2s)



**2s** was prepared following the procedure of condition B to give the corresponding product as a colorless sticky oil (42.3 mg, 61%). Trace alkenylation product was observed.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.51 (ddd,  $J = 4.8, 1.5, 0.9$  Hz, 1H), 8.36 (s, 1H), 8.20 (dt,  $J = 7.8, 1.0$  Hz, 1H), 7.83 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.40 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.32 – 7.26 (m, 1H), 7.22 – 7.12 (m, 2H), 4.85 (d,  $J = 5.8$  Hz, 2H), 4.10 (q,  $J = 7.1$  Hz, 2H), 3.22 (t,  $J = 7.6$  Hz, 2H), 2.63 (t,  $J = 7.6$  Hz, 2H), 1.21 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.54, 164.04, 149.85, 148.24, 142.26, 137.41, 135.93, 133.71, 129.18, 128.46, 128.14, 126.29, 122.40, 77.48, 77.16, 76.84, 60.64, 37.99, 35.83, 28.57, 14.28. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3391, 2980, 1731, 1678, 1570, 1517, 1464, 1435, 1244, 1175, 1042, 999, 774, 750, 700. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{18}\text{H}_{19}\text{ClN}_2\text{O}_3$  346.1084; found 346.1085.

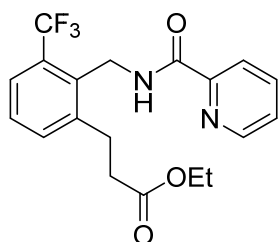
### Ethyl 3-(3-fluoro-2-(picolinamidomethyl)phenyl)propanoate (2t)



**2t** was prepared following the procedure of condition B to give the corresponding product as a white solid (42.3 mg, 64%). 6-9% alkenylation product was also observed.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.51 (dd,  $J = 4.8, 0.8$  Hz, 1H), 8.27 (s, 1H), 8.23 – 8.14 (m, 1H), 7.88 – 7.79 (m, 1H), 7.43 – 7.37 (m, 1H), 7.22 (td,  $J = 7.9, 6.1$  Hz, 1H), 7.07 – 6.91 (m, 2H), 4.76 (dd,  $J = 5.8, 1.5$  Hz, 2H), 4.11 (q,  $J = 7.2$  Hz, 2H), 3.16 (t,  $J = 7.6$  Hz, 2H), 2.64 (t,  $J = 7.6$  Hz, 2H), 1.21 (t,  $J = 7.2$  Hz, 3H). Peaks obtained from minor amount (6-9% alkenylation product) of formation of alkenylation product:  $\delta$  6.38 (d,  $J = 15.8$  Hz, 0.06H), 4.82 (dd,  $J = 5.8, 1.2$  Hz, 0.18H), 4.27 (q,  $J = 7.1$  Hz, 0.16H), 1.32 (t,  $J = 7.1$  Hz, 0.25H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.61, 164.03, 163.46, 161.01, 149.83, 148.20, 142.14, 137.42, 129.40, 129.31, 126.30, 125.19, 123.54, 123.40, 122.41, 113.80, 113.58, 77.48, 77.16, 76.84, 60.63, 35.69, 34.14, 34.09, 27.64, 14.27.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -116.56. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3395, 2982, 1730, 1677, 1522, 1465, 1435, 1247, 1184, 1042, 772, 751, 701. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{18}\text{H}_{19}\text{FN}_2\text{O}_3$  330.1380; found 330.1382. M.p = 71-73 °C.

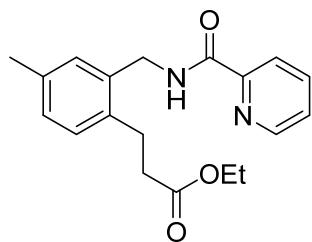
#### Ethyl 3-(2-(picolinamidomethyl)-3-(trifluoromethyl)phenyl)propanoate (**2u**)



**2u** was prepared following the procedure of condition B to give the corresponding product as a colorless sticky oil (63.1 mg, 83%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.49 (ddd,  $J = 4.7, 1.6, 0.9$  Hz, 1H), 8.22 (dt,  $J = 7.9, 1.0$  Hz, 1H), 8.12 (s, 1H), 7.84 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.64 – 7.57 (m, 1H), 7.48 (d,  $J = 7.5$  Hz, 1H), 7.44 – 7.34 (m, 2H), 4.87 (d,  $J = 5.5$  Hz, 2H), 4.08 (q,  $J = 7.1$  Hz, 2H), 3.16 (t,  $J = 7.5$  Hz, 2H), 2.63 (t,  $J = 7.5$  Hz, 2H), 1.18 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.44, 163.70, 149.67, 148.25, 142.98, 137.44, 133.82, 133.67, 130.61, 130.31, 128.36, 126.36, 126.03, 124.72, 124.66, 122.48, 77.48, 77.16, 76.84, 60.65, 36.84, 35.51, 27.45, 14.23.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -58.08. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3398, 2982, 1733, 1680, 1591, 1520, 1465, 1435, 1315, 1165, 1115, 1042, 1000, 816, 753, 696. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{19}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_3$  380.1348; found 380.1346.

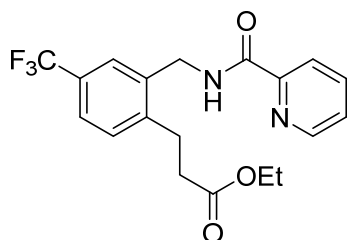
#### Ethyl 3-(4-methyl-2-(picolinamidomethyl)phenyl)propanoate (**2v**)



**2v** was prepared following the procedure of condition B to give the corresponding product as a colorless sticky oil (30.0 mg, 46%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.52 (ddd,  $J = 4.7, 1.7, 0.9$  Hz, 1H), 8.36 – 8.18 (m, 2H), 7.85 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.42 (ddd,  $J = 7.6, 4.8, 1.3$  Hz, 1H), 7.16 (d,  $J = 0.7$  Hz, 1H), 7.12 – 7.04 (m, 2H), 4.67 (d,  $J = 5.8$  Hz, 2H), 4.11 (q,  $J = 7.1$  Hz, 2H), 3.01 (t,  $J = 7.8$  Hz, 2H), 2.61 (t,  $J = 7.8$  Hz, 2H), 2.30 (s, 3H), 1.21 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.93, 164.18, 149.95, 148.21, 137.46, 136.56, 135.93, 135.56, 130.12, 129.38, 128.82, 126.30, 122.46, 77.48, 77.16, 76.84, 60.58, 41.18, 35.66, 27.23, 21.10, 14.31. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3387, 2925, 1730, 1674, 1522, 1465, 1434, 1293, 1247, 1162, 1041, 1000, 821, 751, 691. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3$  326.1630; found 326.1633.

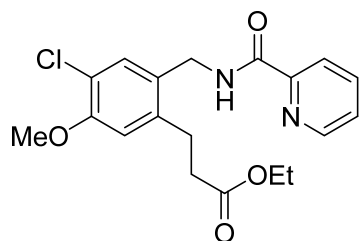
#### Ethyl 3-(2-(4-(trifluoromethyl)phenyl)acetamido)propanoate (**2w**)



**2w** was prepared following the procedure of condition B to give the corresponding product as a colorless sticky oil (52.5 mg, 69%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.54 (ddd,  $J = 4.7, 1.7, 0.9$  Hz, 1H), 8.38 (s, 1H), 8.23 (dt,  $J = 7.8, 1.0$  Hz, 1H), 7.87 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.61 (d,  $J = 0.7$  Hz, 1H), 7.50 (d,  $J = 8.1$  Hz, 1H), 7.45 (ddd,  $J = 7.6, 4.8, 1.3$  Hz, 1H), 7.34 (d,  $J = 8.0$  Hz, 1H), 4.76 (d,  $J = 6.0$  Hz, 2H), 4.12 (q,  $J = 7.1$  Hz, 2H), 3.11 (t,  $J = 7.7$  Hz, 2H), 2.66 (t,  $J = 7.7$  Hz, 2H), 1.22 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.45, 164.40, 149.63, 148.29, 143.06, 137.57, 136.96, 129.81, 129.43, 129.10, 126.53, 125.77, 124.82, 122.55, 77.48, 77.16, 76.84, 60.79, 40.82, 34.91, 27.39, 14.28.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.32. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3381, 2982, 1730, 1673, 1522, 1466, 1331, 1296, 1163, 1120, 1084, 1042, 1001, 750, 694. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{19}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_3$  380.1348; found 380.1350.

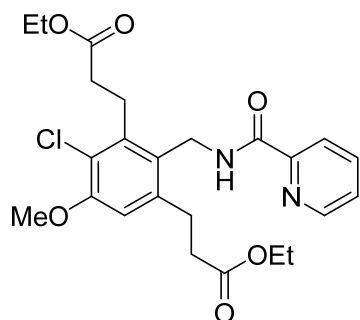
**Ethyl 3-(4-chloro-5-methoxy-2-(picolinamidomethyl)phenyl)propanoate (2x)**



**2x** was prepared following the procedure of condition B to give the corresponding product as a white sticky solid (31.6 mg, 42%). Trace alkenylation product along with 28% di-alkylation product were observed.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.53 (ddd,  $J = 4.8, 1.6, 0.9$  Hz, 1H), 8.36 – 8.17 (m, 2H), 7.86 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.43 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 7.35 (s, 1H), 6.80 (s, 1H), 4.62 (d,  $J = 5.9$  Hz, 2H), 4.12 (q,  $J = 7.1$  Hz, 2H), 3.88 (s, 3H), 3.02 (t,  $J = 7.7$  Hz, 2H), 2.62 (t,  $J = 7.7$  Hz, 2H), 1.22 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.64, 164.20, 154.51, 149.75, 148.25, 138.99, 137.53, 130.98, 129.03, 126.43, 122.48, 120.58, 113.33, 77.48, 77.16, 76.84, 60.75, 56.34, 40.24, 35.51, 27.69, 14.32. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3378, 2978, 1730, 1673, 1602, 1570, 1521, 1501, 1465, 1278, 1219, 1163, 1059, 1000, 913, 772, 748. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{19}\text{H}_{21}\text{ClN}_2\text{O}_4$  376.1190; found 376.1194.

**Diethyl 3,3'-(4-chloro-5-methoxy-2-(picolinamidomethyl)-1,3-phenylene)dipropionate (2x')**

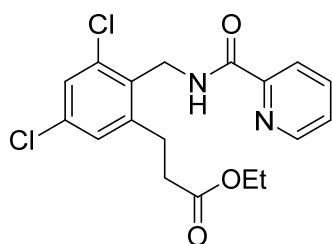


**2x'** was obtained as a di-alkylation product from the reaction to prepare **2x** as a white sticky solid (26.7 mg, 28%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.48 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.21 (dt,  $J = 7.9, 1.1$  Hz, 1H), 7.97 (s, 1H), 7.85 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.41 (ddd,  $J = 7.6, 4.8, 1.2$  Hz, 1H), 6.76 (s, 1H), 4.67 (d,  $J = 5.0$  Hz, 2H), 4.12 – 3.89 (m, 4H), 3.89 (s, 3H), 3.25 – 3.18 (m, 2H), 3.07 (t,  $J = 7.7$  Hz, 2H), 2.67 – 2.54 (m, 4H), 1.24 – 1.19 (m, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.55, 164.01, 154.86, 149.69, 148.20, 140.18, 139.92, 137.46, 127.01, 126.36,

122.37, 121.68, 111.59, 77.48, 77.16, 76.84, 60.74, 60.69, 56.29, 37.84, 35.95, 33.77, 28.74, 26.18, 14.30. IR (neat,  $\nu/\text{cm}^{-1}$ ) 3381, 2980, 1730, 1673, 1589, 1516, 1464, 1436, 1373, 1283, 1178, 1090, 1040, 772, 750, 696. HRMS (EI<sup>+</sup>)  $m/z$ : [M]<sup>+</sup> Calcd for C<sub>24</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>6</sub> 476.1714; found 476.1712.

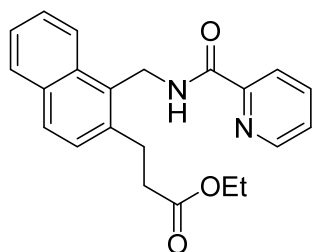
### Ethyl 3-(3,5-dichloro-2-(picolinamidomethyl)phenyl)propanoate (2y)



**2y** was prepared following the procedure of condition B to give the corresponding product as a colorless sticky oil (54.1 mg, 71%). A trace amount of an alkenylation product was observed.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.52 (ddd,  $J = 4.8, 1.6, 0.9$  Hz, 1H), 8.36 (s, 1H), 8.19 (dt,  $J = 7.9, 1.1$  Hz, 1H), 7.83 (td,  $J = 7.7, 1.7$  Hz, 1H), 7.41 (ddd,  $J = 7.6, 4.8, 1.3$  Hz, 1H), 7.31 (d,  $J = 2.1$  Hz, 1H), 7.16 (d,  $J = 2.1$  Hz, 1H), 4.80 (d,  $J = 5.9$  Hz, 2H), 4.12 (q,  $J = 7.1$  Hz, 2H), 3.21 (t,  $J = 7.5$  Hz, 2H), 2.63 (t,  $J = 7.5$  Hz, 2H), 1.22 (t,  $J = 7.1$  Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  172.20, 164.07, 149.70, 148.26, 143.62, 137.44, 136.53, 134.22, 132.50, 128.56, 127.89, 126.37, 122.40, 77.48, 77.16, 76.84, 60.77, 37.54, 35.47, 28.45, 14.28. IR (neat,  $\nu/\text{cm}^{-1}$ ) 3389, 2980, 1730, 1677, 1587, 1562, 1515, 1464, 1434, 1400, 1373, 1297, 1244, 1175, 1041, 999, 858, 819, 750, 700. HRMS (EI<sup>+</sup>)  $m/z$ : [M]<sup>+</sup> Calcd for C<sub>18</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub> 380.0694; found 380.0687.

### Ethyl 3-(1-(picolinamidomethyl)naphthalen-2-yl)propanoate (2z)

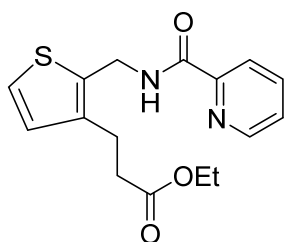


**2z** was prepared following the procedure of condition B to give the corresponding product as a colorless sticky oil (60.2 mg, 83%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.40 (ddd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.26 (dt,  $J = 7.9, 1.1$  Hz, 1H), 8.18 (s, 1H), 8.16 – 8.11 (m, 1H), 7.86 – 7.77 (m, 3H), 7.53 (ddd,  $J = 8.5, 6.8, 1.4$

Hz, 1H), 7.46 (ddd,  $J = 8.0, 6.9, 1.1$  Hz, 1H), 7.41 – 7.32 (m, 2H), 5.16 (d,  $J = 5.2$  Hz, 2H), 4.12 (q,  $J = 7.1$  Hz, 2H), 3.28 (t,  $J = 7.8$  Hz, 2H), 2.71 (t,  $J = 7.8$  Hz, 2H), 1.20 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.69, 164.10, 149.80, 148.12, 137.80, 137.39, 132.86, 132.61, 130.27, 128.95, 128.68, 127.93, 127.11, 126.23, 125.56, 123.93, 122.38, 77.48, 77.16, 76.84, 60.69, 36.79, 36.21, 28.82, 14.28. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3386, 2978, 1729, 1672, 1590, 1570, 1514, 1465, 1433, 1245, 1178, 1040, 999, 819, 749, 688. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_3$  362.1630; found 362.1626.

### Ethyl 3-(2-(picolinamidomethyl)thiophen-3-yl)propanoate (**2za**)



**2za** was prepared following the procedure of condition B except for the use of 7.5 mol% of  $\text{Rh}_2(\text{OAc})_4$  to give the corresponding product as a white sticky solid (45.2 mg, 71%). 18% alkenylation product was also observed.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.53 (tdd,  $J = 4.8, 1.7, 0.9$  Hz, 1H), 8.35 (s, 1H), 8.23 (ddt,  $J = 7.8, 3.2, 1.1$  Hz, 1H), 7.89 – 7.79 (m, 1H), 7.43 (tdd,  $J = 7.6, 4.8, 1.3$  Hz, 1H), 7.19 (dd,  $J = 24.8, 3.0$  Hz, 1H), 6.86 (d,  $J = 5.2$  Hz, 1H), 4.80 (d,  $J = 5.9$  Hz, 2H), 4.13 (q,  $J = 7.1$  Hz, 2H), 2.99 (t,  $J = 7.5$  Hz, 2H), 2.61 (t,  $J = 7.5$  Hz, 2H), 1.22 (t,  $J = 7.1$  Hz, 3H). Peaks obtained from minor amount (18% alkenylation product) of formation of alkenylation product:  $\delta$  6.28 (d,  $J = 15.8$  Hz, 0.18H), 4.94 (d,  $J = 6.0$  Hz, 0.38H), 4.26 (q,  $J = 7.1$  Hz, 0.38H), 1.34 (t,  $J = 7.1$  Hz, 0.54H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.91, 164.09, 149.84, 148.22, 142.77, 138.14, 137.44, 135.39, 134.98, 134.20, 128.61, 126.54, 126.35, 125.22, 124.23, 122.51, 118.95, 77.16, 60.65, 36.08, 35.33, 23.46, 14.45, 14.30. IR (neat,  $\text{v}/\text{cm}^{-1}$ ) 3383, 2928, 1700, 1671, 1519, 1465, 1434, 1383, 1285, 1244, 1121, 1046, 999, 820, 751, 698. HRMS ( $\text{EI}^+$ )  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$  318.1038; found 318.1044.

## 7. Flow optimization and system design (Table 4)

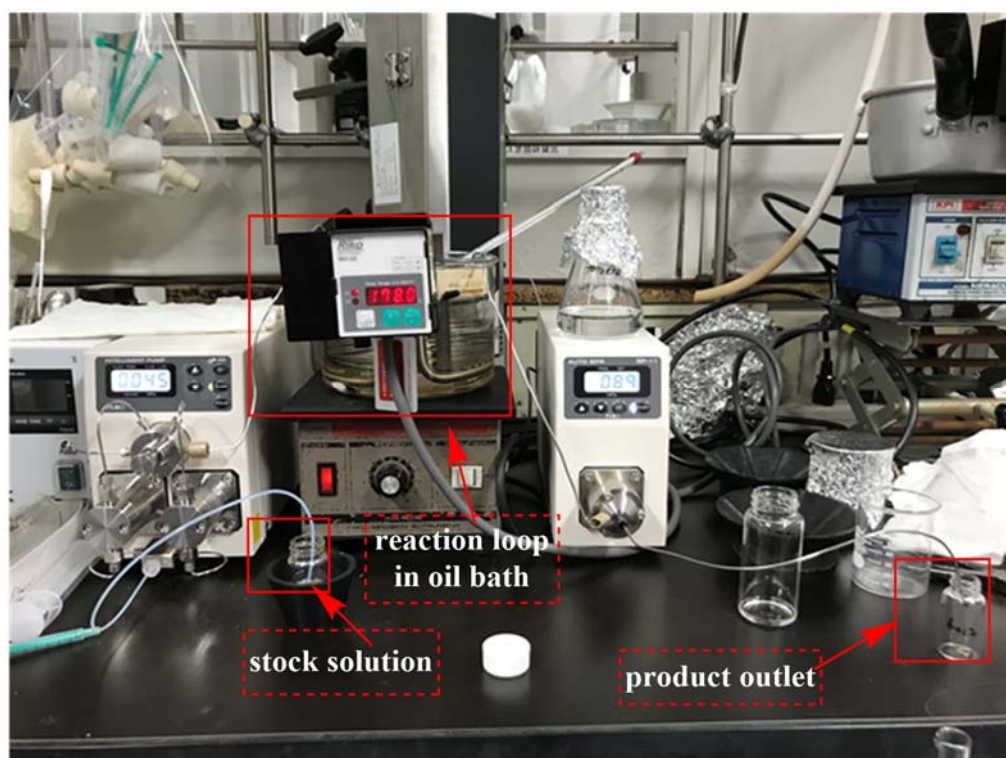
### General procedure:

At first solvent dry toluene was flowed using the plunger pump before introducing starting material solution at room temperature. The temperature was gradually increased to 170 °C. After that the flow system was kept flowing with solvent toluene for 1 hour to be stabilized.

The stock solution was prepared by dissolving **1a** (0.20 mmol, 1.0 equiv), Rh(OAc)(cod)]<sub>2</sub> (0.01 mmol, 5.0 mol%), pivalic acid (0.40 mmol, 2.0 equiv) and ethyl acrylate (0.40 mmol, 2.0 equiv) in 1 mL of toluene. This stock solution was then flowed at a specified flow rate (xx mL/min) through the loop (xx meter) made of stainless steel and further connected to a back-pressure regulator (set pressure: 1 MPa). The product was obtained directly from the outlet of the loop and collected in a vial at room temperature. The yields were measured by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. Three measurements of the product solution were performed between 200 minutes to 230 minutes to determine accurate yields during this period.

### **Optimized condition for flow (Figure S2)**

- Flow rate 0.04 mL/min (set at 0.045 mL/min).
- Reaction temperature 170 °C (set temp. of oil bath 178 °C).
- Loop length 10 meter (residence time 196 minutes).



**Figure S2.** Flow set up for Rh(I) catalyzed alkylation of benzylamine derivatives

## **8. Substrate scope under flow and comparison between flow and batch (Table 5)**

**General procedure for comparison reaction performed under batch:**



To a sealed tube equipped with a magnetic stirring bar were added benzylamine derived substrates (**1a** or **1b**) or 1-naphthylmethylamine derived substrate (**1j**) (0.20 mmol, 1.0 equiv), catalyst [Rh(OAc)(cod)]<sub>2</sub> (5.4 mg, 0.01 mmol, 5.0 mol%), pivalic acid (40.8 mg, 0.40 mmol, 2.0 equiv) and toluene (1.0 mL, 0.20 M) under argon atmosphere. To the mixture,  $\alpha,\beta$ -unsaturated compound (0.40 mmol, 2.0 equiv) was added and the resulting mixture was stirred at 170 °C for 196 minutes (residence time for flow reaction). Yield of the corresponding product was determined by <sup>1</sup>H NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as internal standard.

### 9. Deuterium labelling experiments (Scheme 2 and Scheme 3)

To a sealed tube equipped with a magnetic stir barring were added **1a** or deuterated substrates **1a-D** or **1a-ND** (0.20 mmol, 1.0 equiv), catalyst Rh<sub>2</sub>(OAc)<sub>4</sub> or [Rh(OAc)(cod)]<sub>2</sub> (5.0 mol% or 7.5 mol%), pivalic acid or deuterated pivalic acid PivOD (40.8 mg, 0.40 mmol, 2.0 equiv) and toluene (1.0 mL, 0.20 M) under argon atmosphere. To this mixture,  $\alpha,\beta$ -unsaturated compound (0 equiv or 2.0 equiv or 5.0 equiv) was added and the resulting mixture was stirred at 170 °C for specified time. After the reaction, the solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography using *n*-hexane/EtOAc (17/3-7/3) as eluent to afford the desired products.

### 10. Determination of KIE value (Figure 1)

Kinetic isotopic effect was determined by performing two individual experiments of substrate **1a** or deuterated substrate **1a-D** and styrene as a coupling partner. Crude <sup>1</sup>H NMR spectra were recorded at a specified time interval for a period of initial 7 hours to evaluate the yield of the reaction. After plotting yield (%) vs time (hour), the *k<sub>H</sub>/k<sub>D</sub>* ratio of 1.02 was obtained.

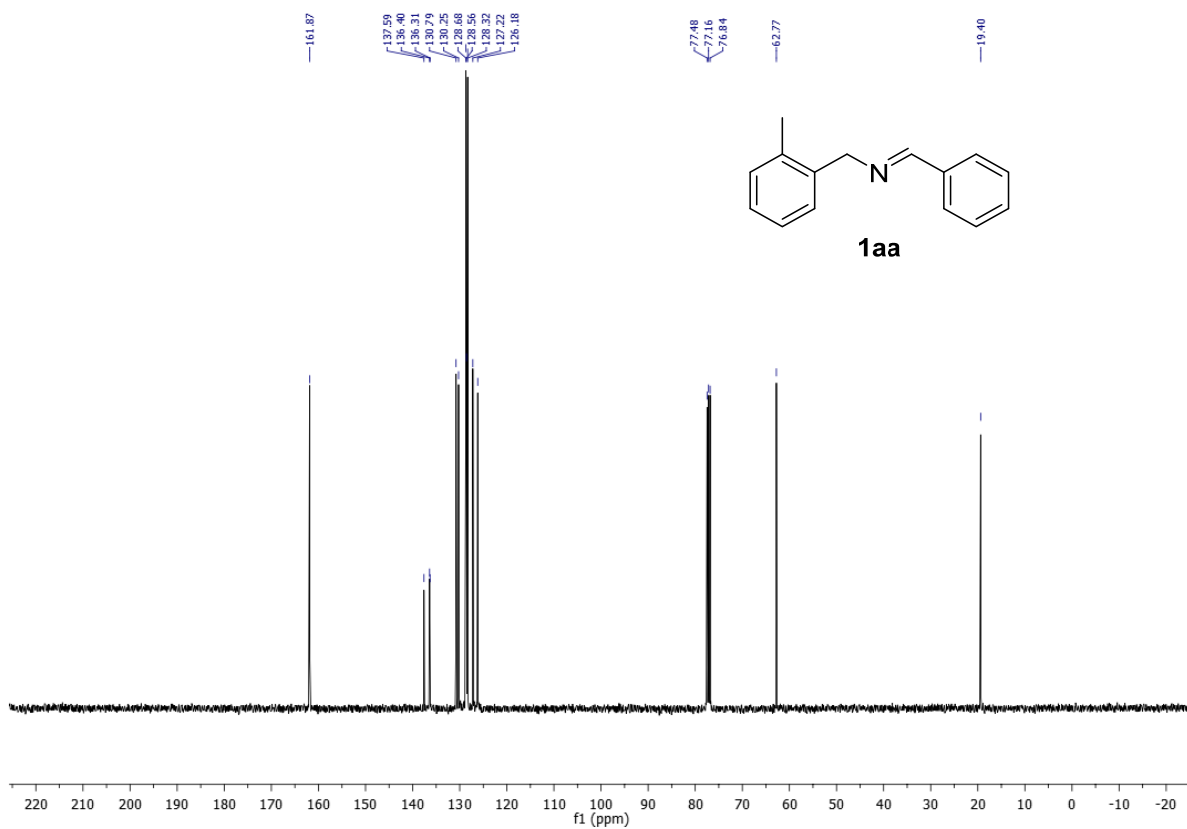
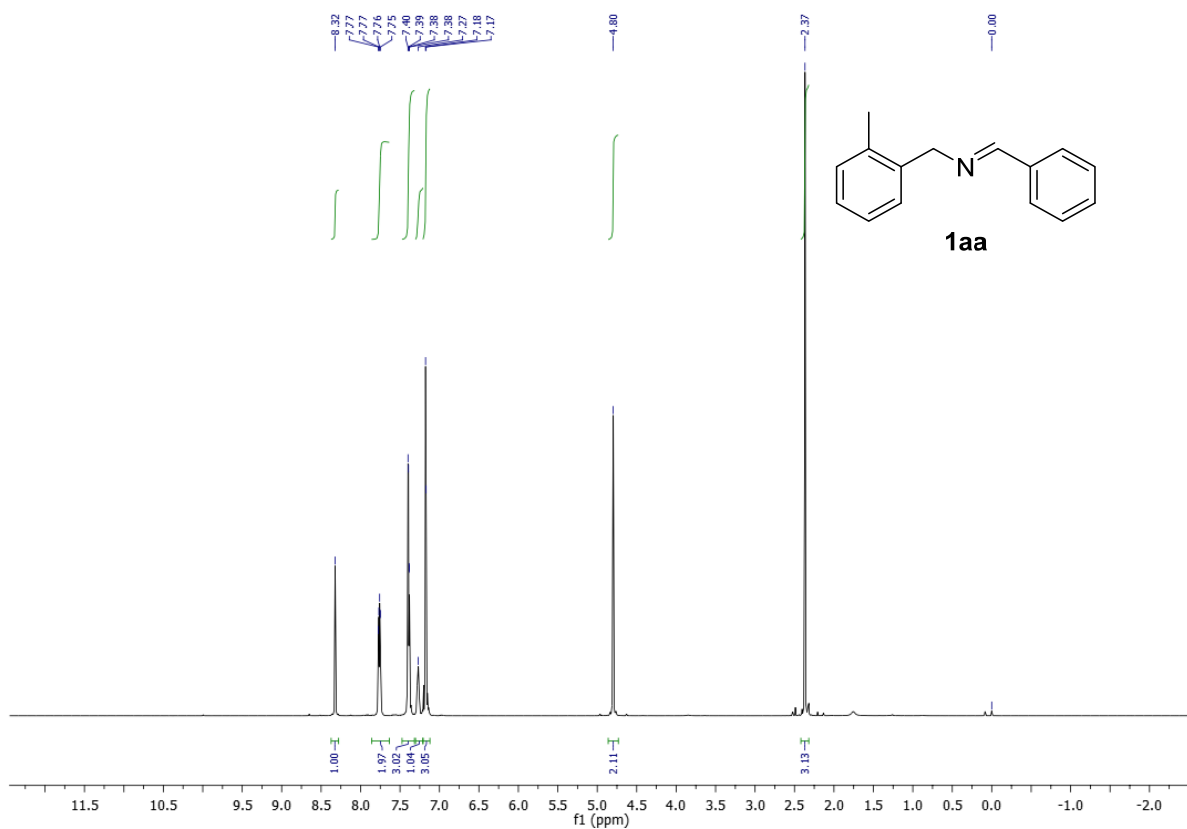
### 11. References

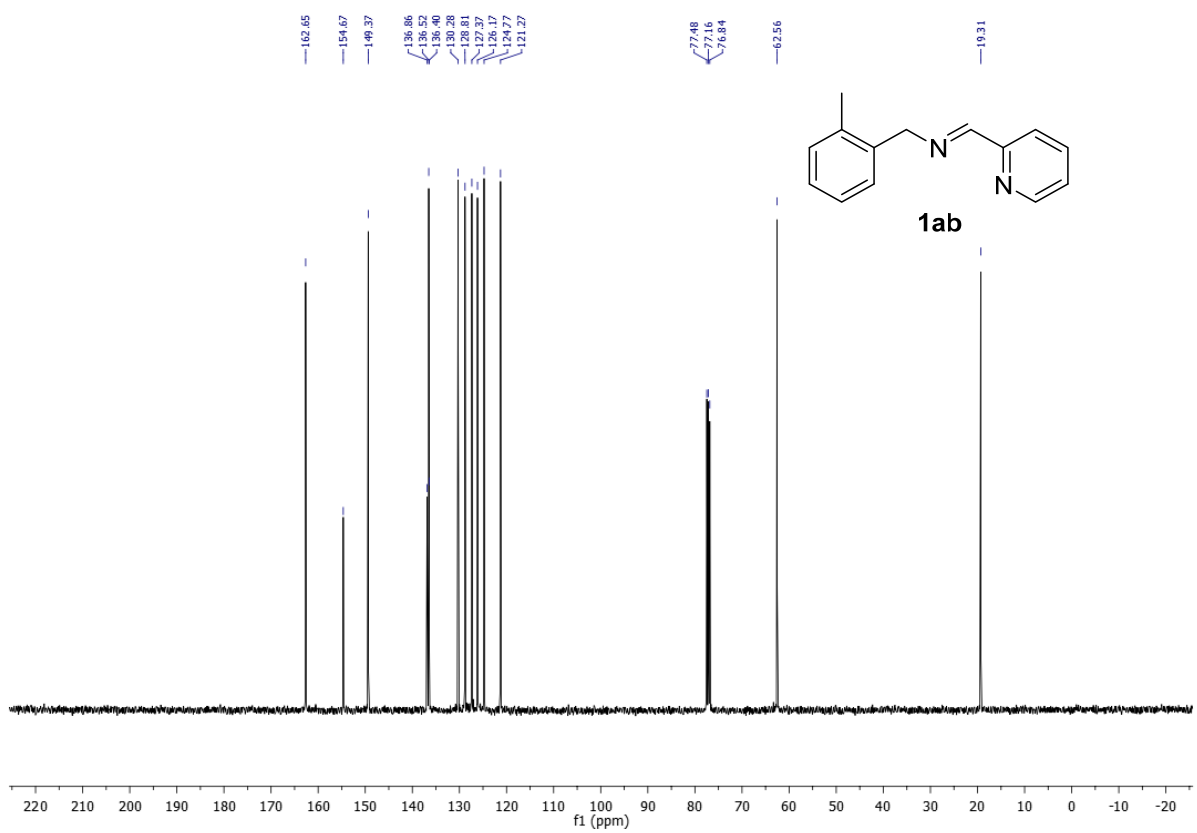
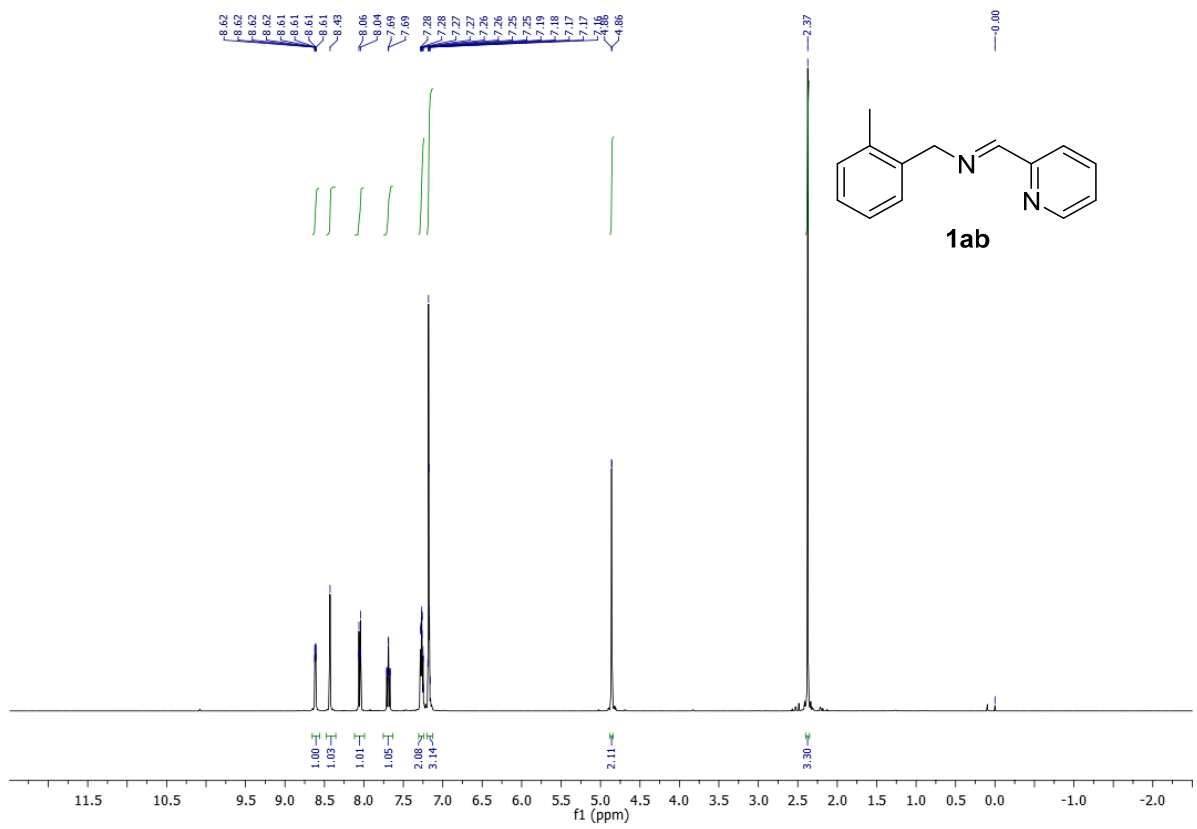
- <sup>1</sup> J. Chatt and L. M. Venanzi, *J. Chem. Soc.*, 1957, 4735–4741.
- <sup>2</sup> G. Rouquet and N. Chatani, *Chem. Sci.*, 2013, **4**, 2201–2208.
- <sup>3</sup> A. Poeschl and D. M. Mountford, *Org. Biomol. Chem.*, 2014, **12**, 7150–7158.
- <sup>4</sup> S. Pradhan, P. B. De and T. Punniyamurthy, *J. Org. Chem.*, 2017, **82**, 4883–4890.
- <sup>5</sup> T. Sahoo, C. Sen, H. Singh, E. Suresh and S. C. Ghosh, *Adv. Synth. Catal.*, 2019, **361**, 3950–3957.

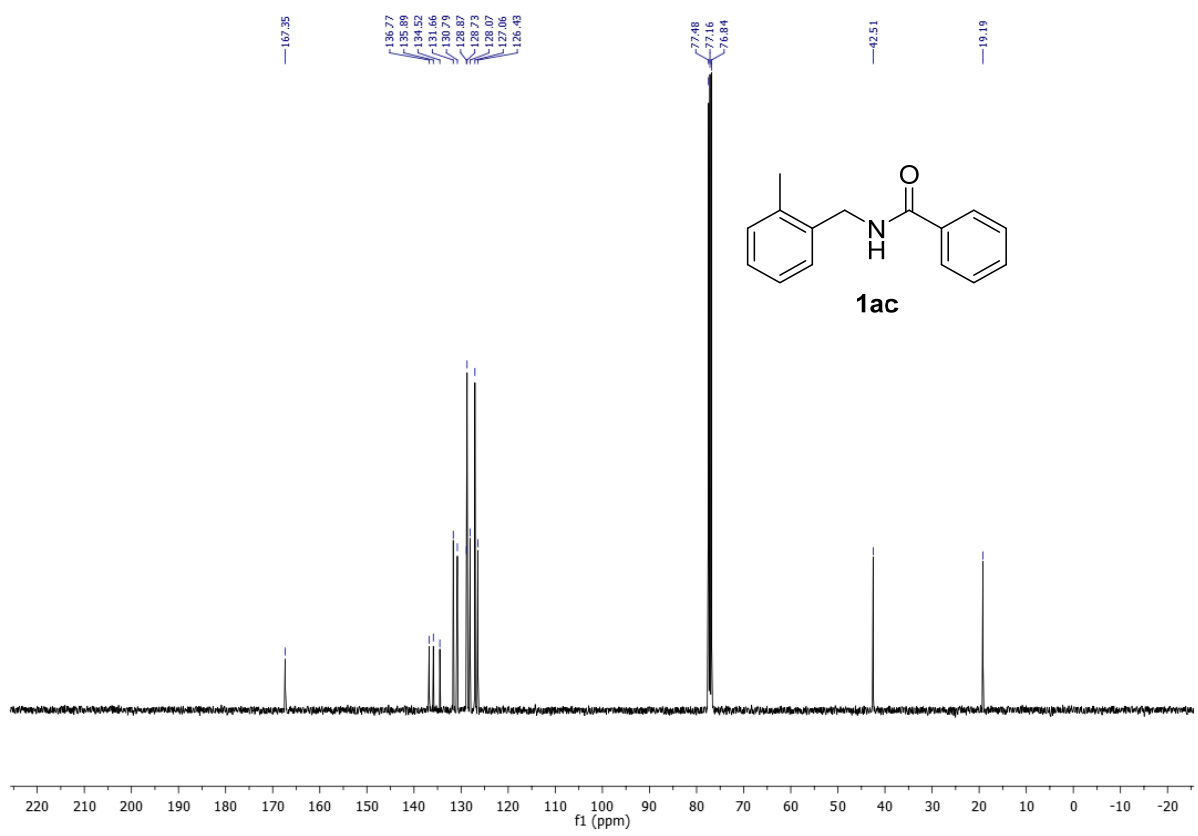
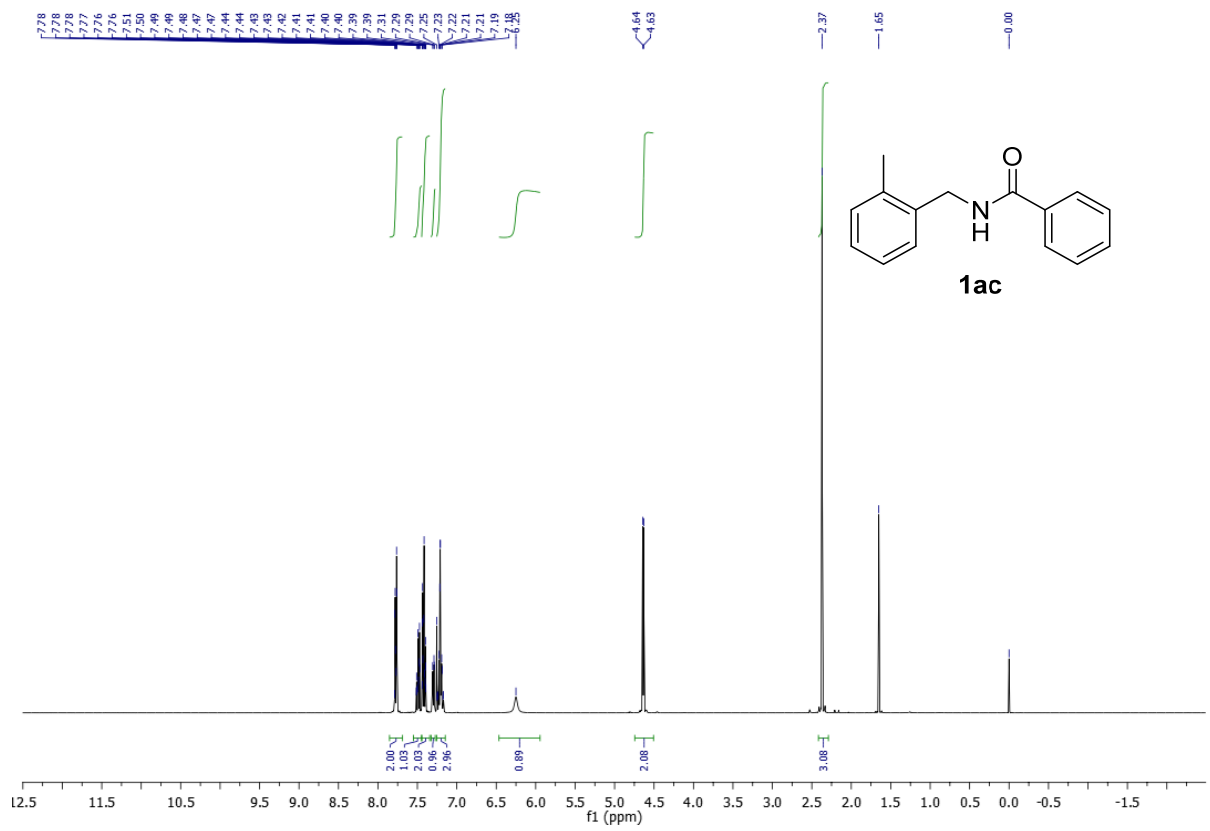
<sup>6</sup>S. B. Sinha, D. Y. Shopov, L. S. Sharninghausen, D. J. Vinyard, B. Q. Mercado, G. W. Brudvig and R. H. Crabtree, *J. Am. Chem. Soc.*, 2015, **137**, 15692–15695.

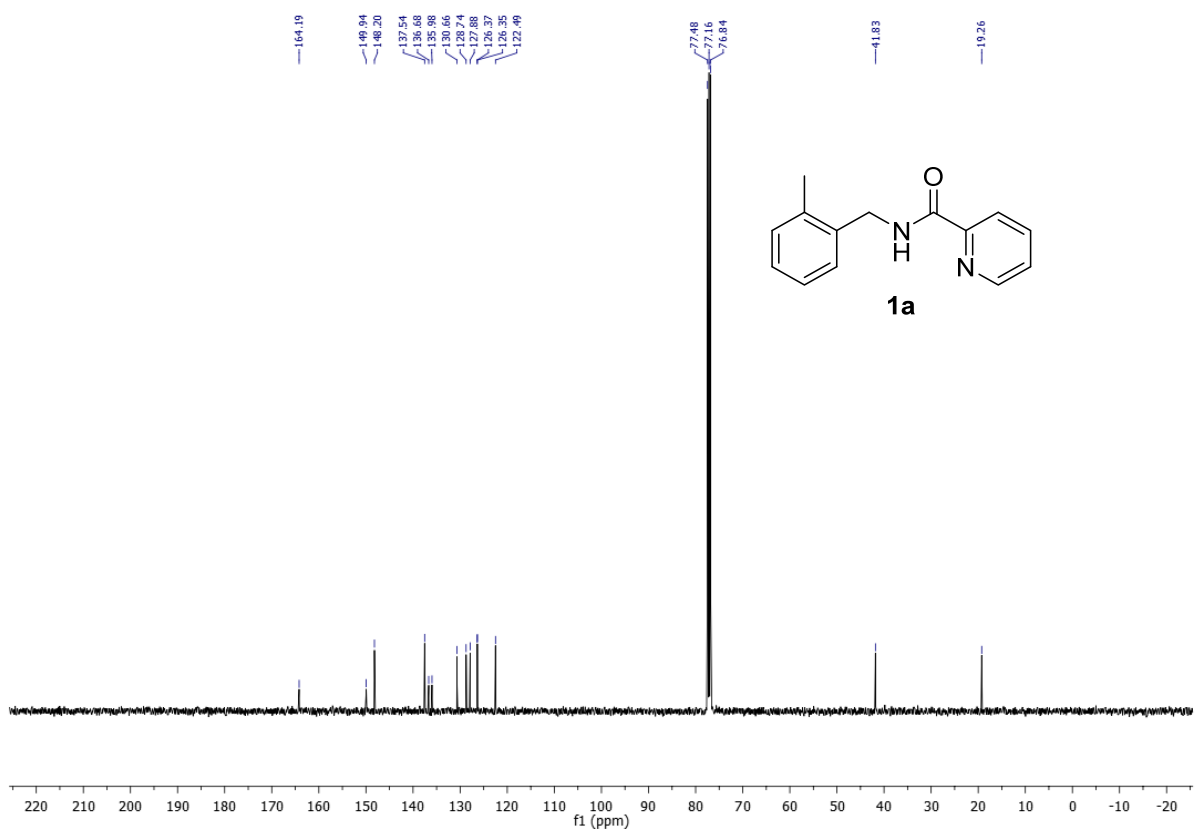
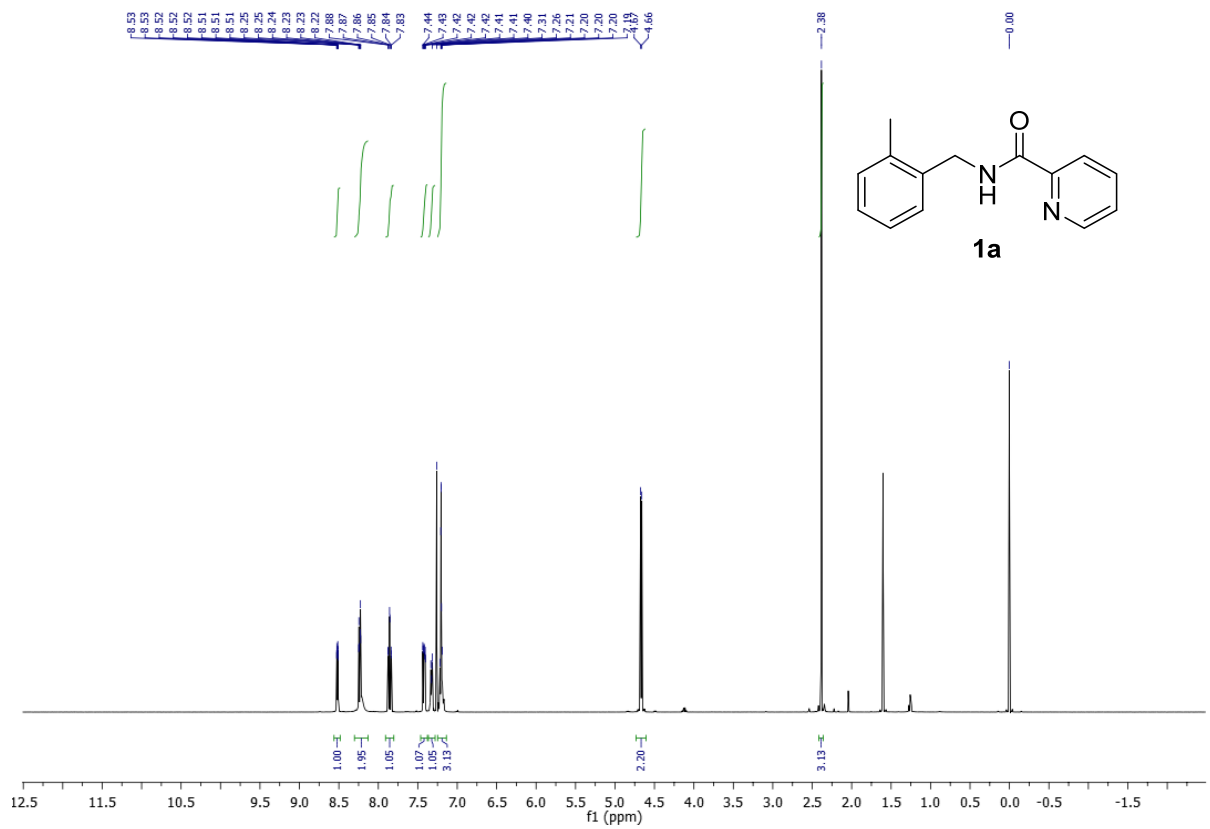
## 12. <sup>1</sup>H and <sup>13</sup>C NMR spectra of compounds

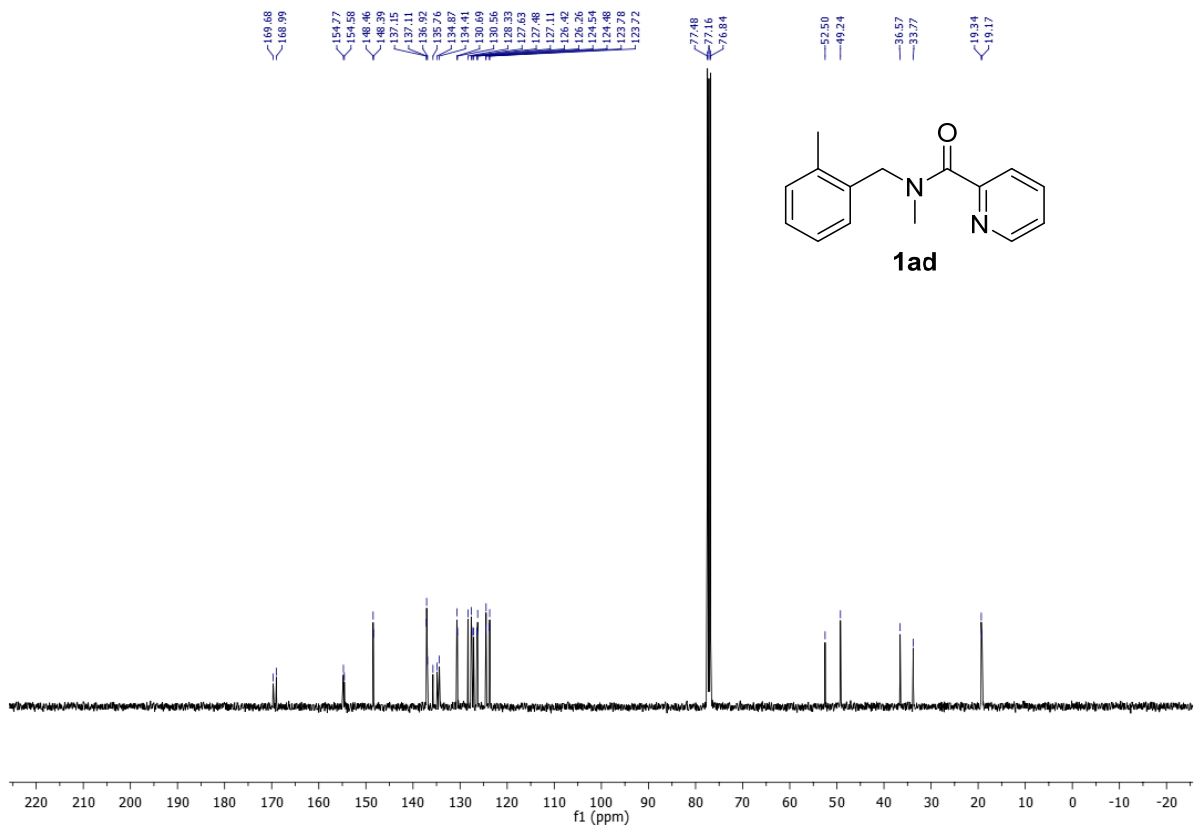
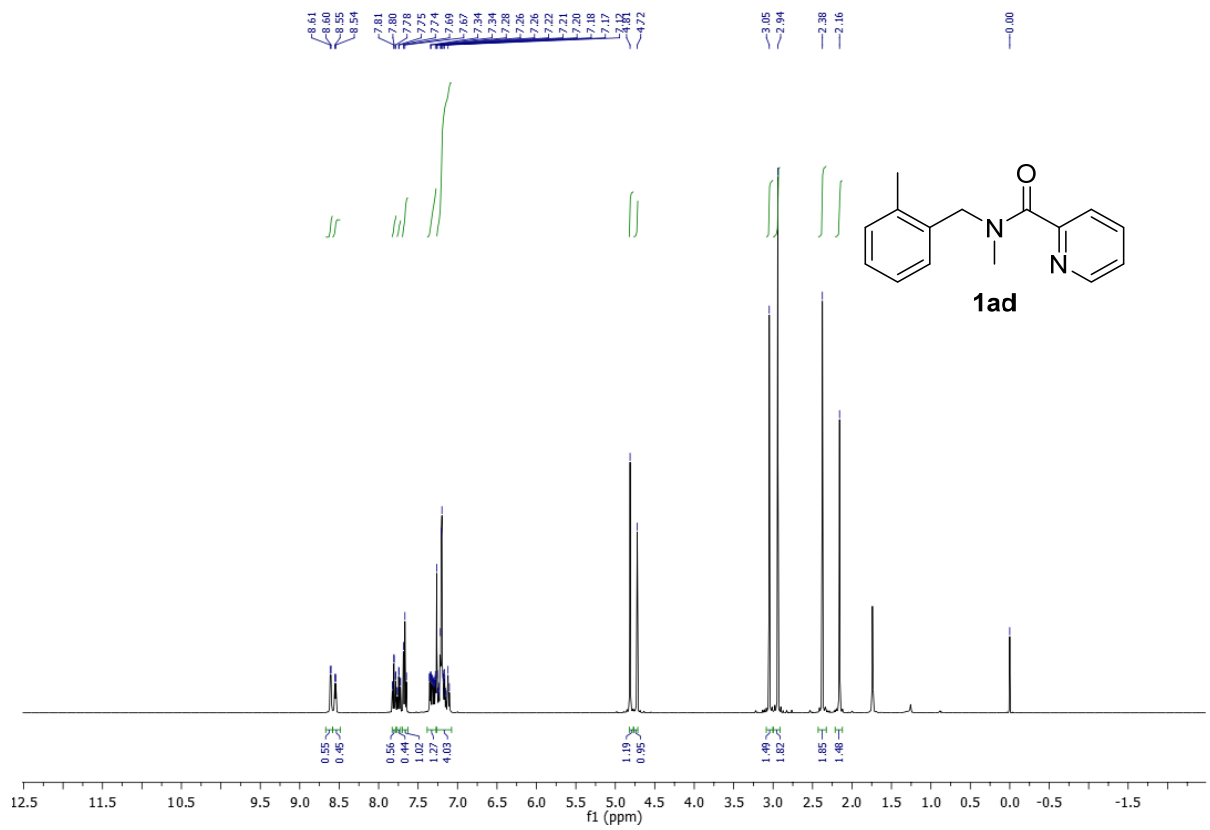
# NMR spectra of starting materials

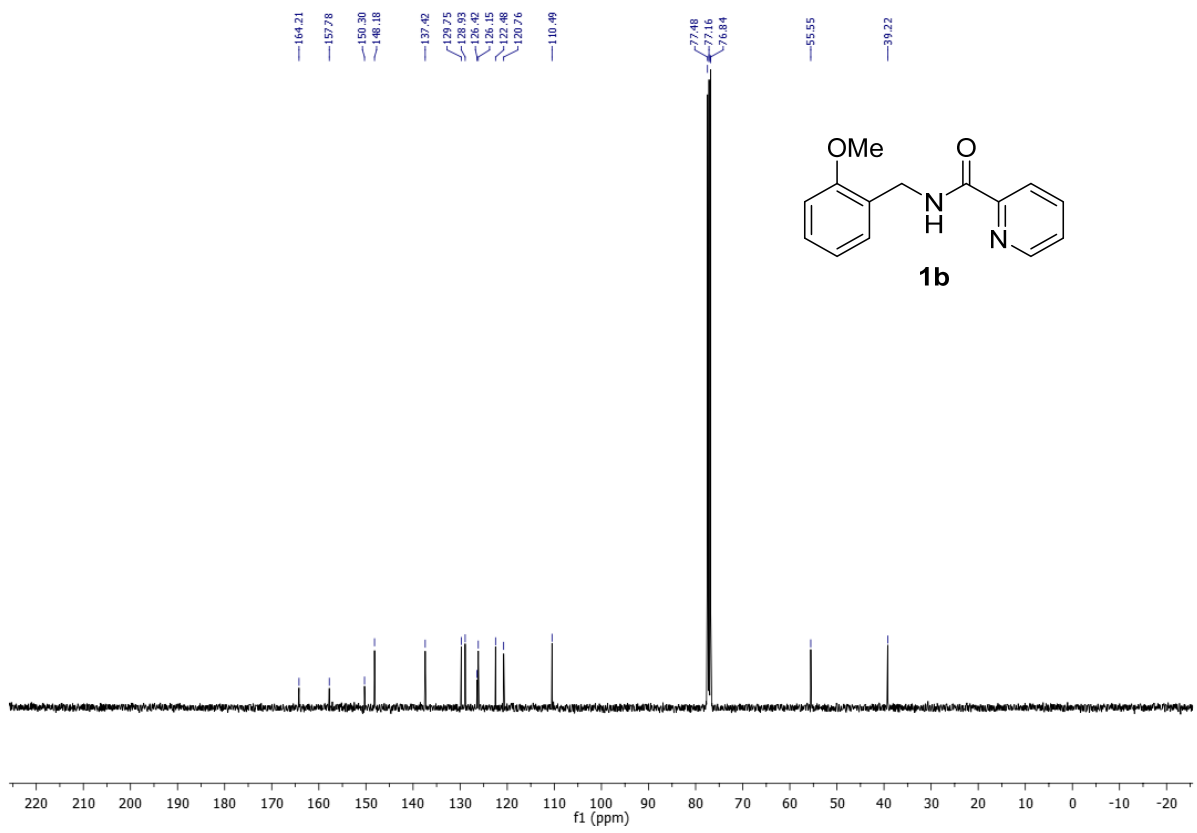
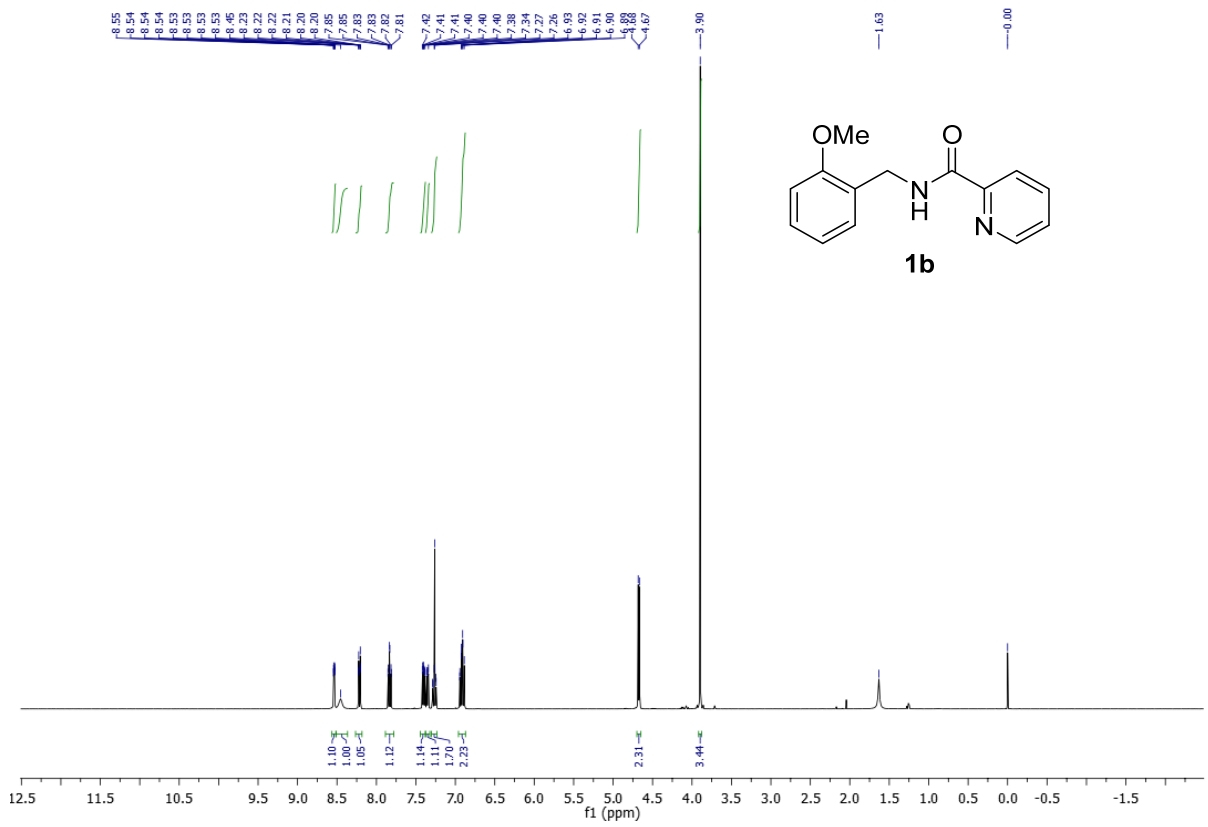




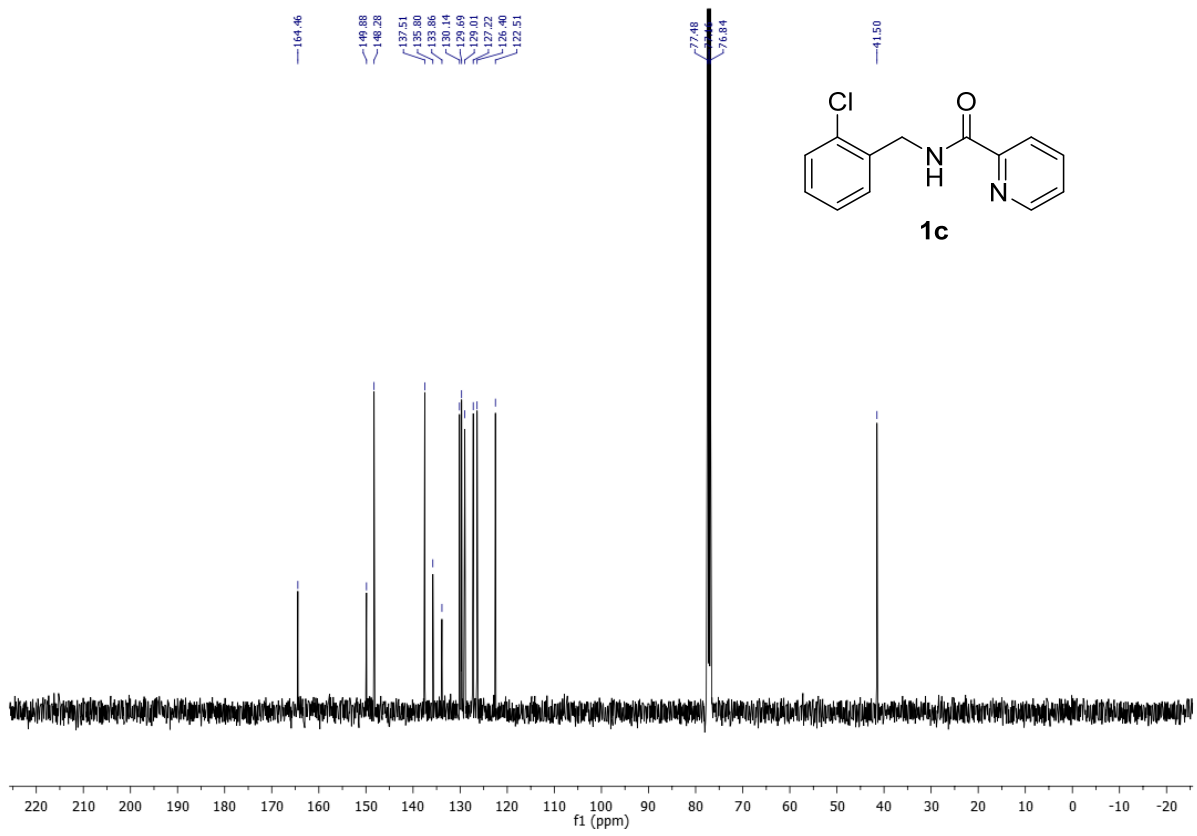
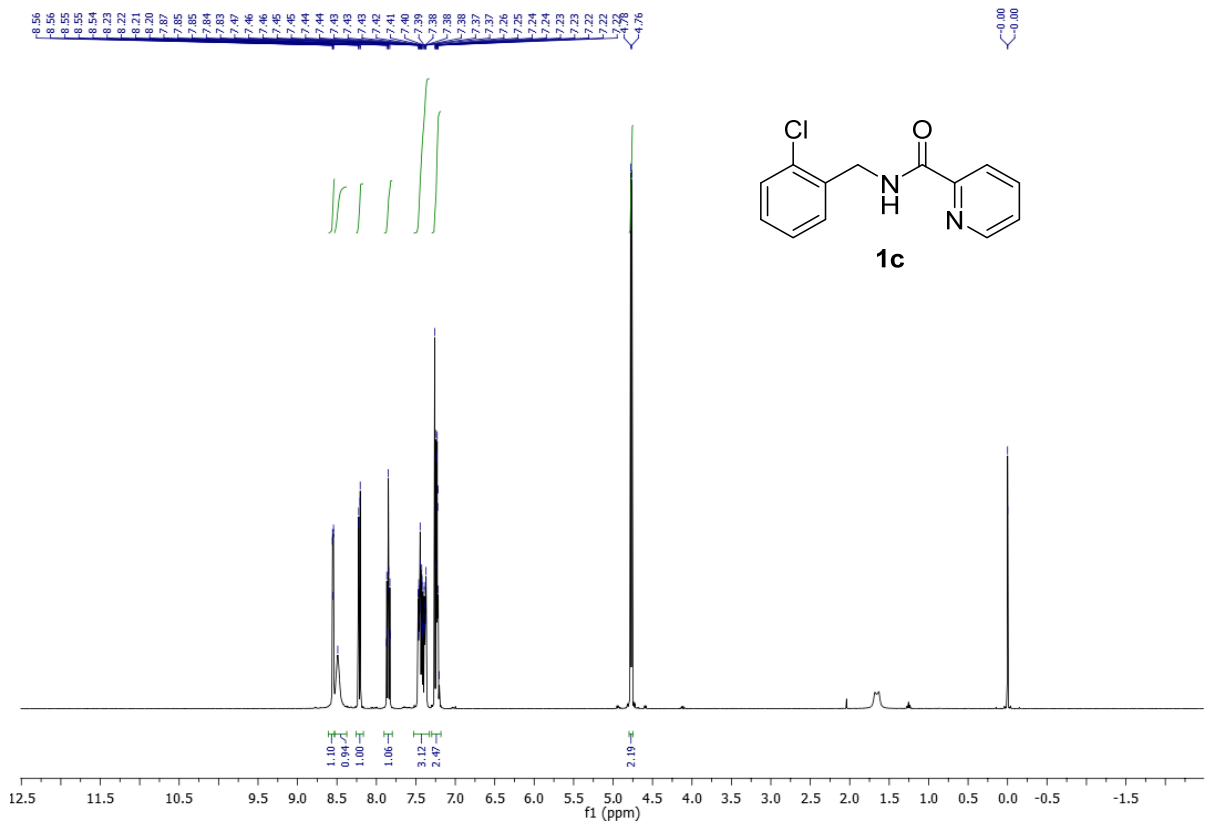


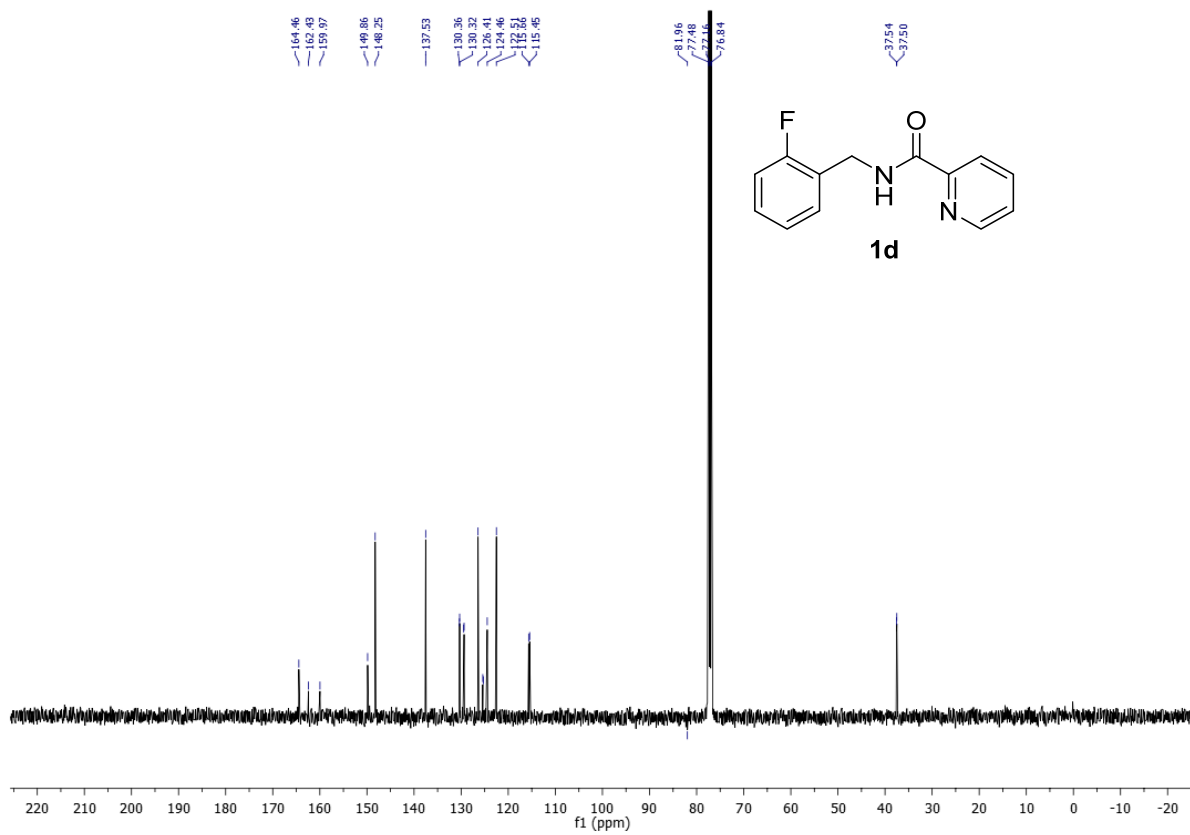
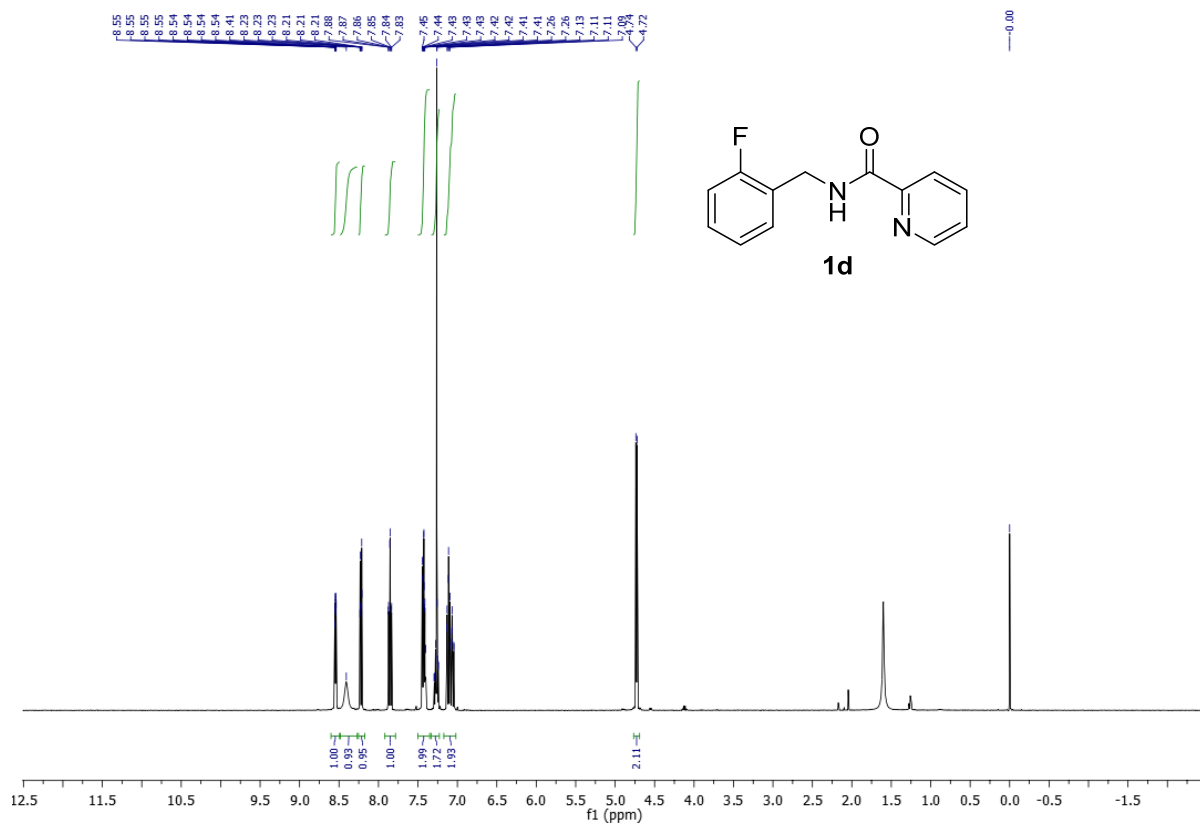


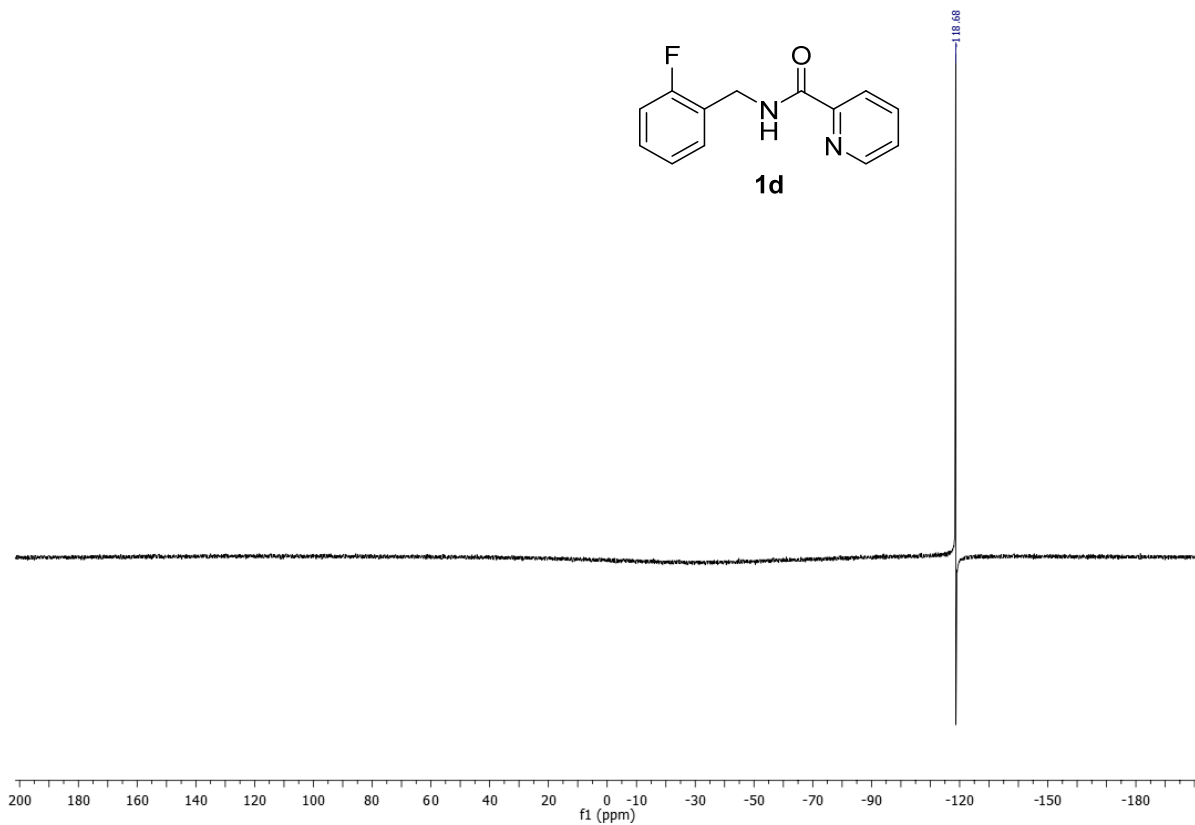
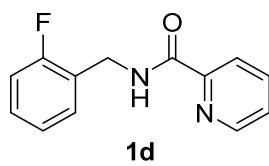


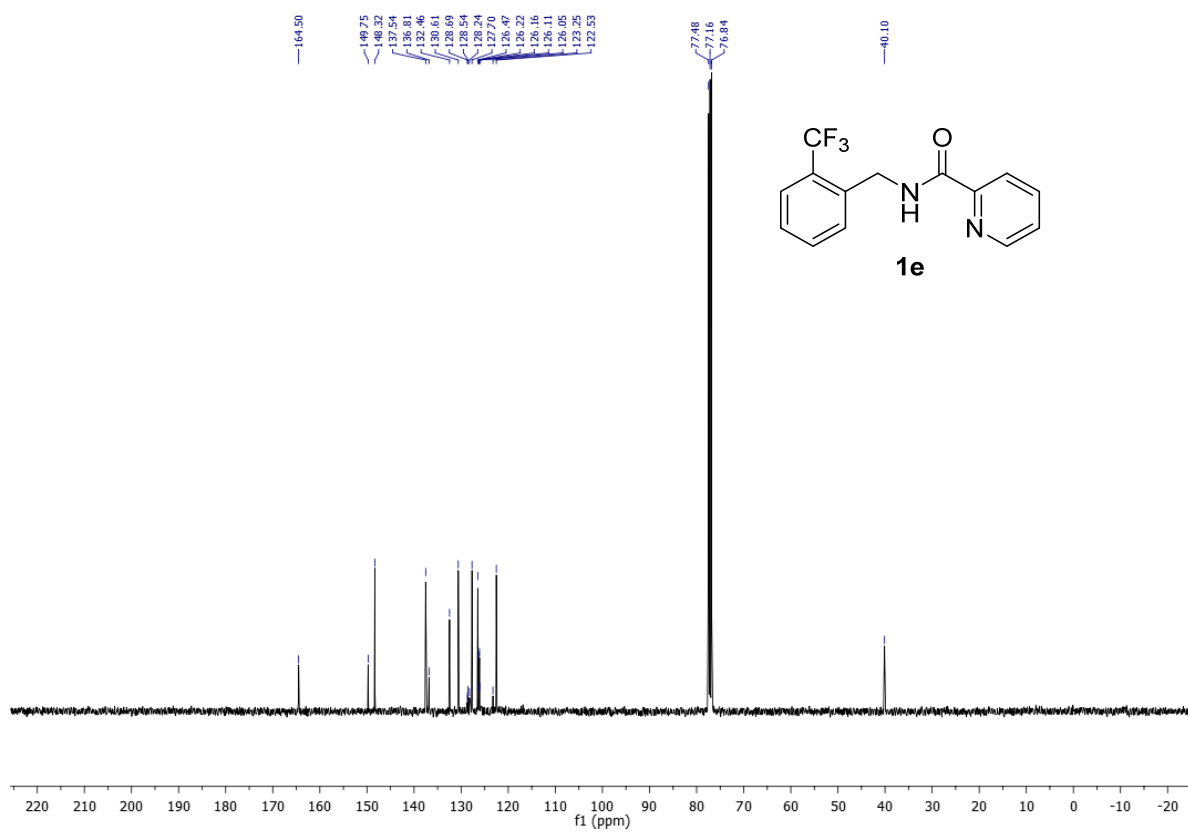
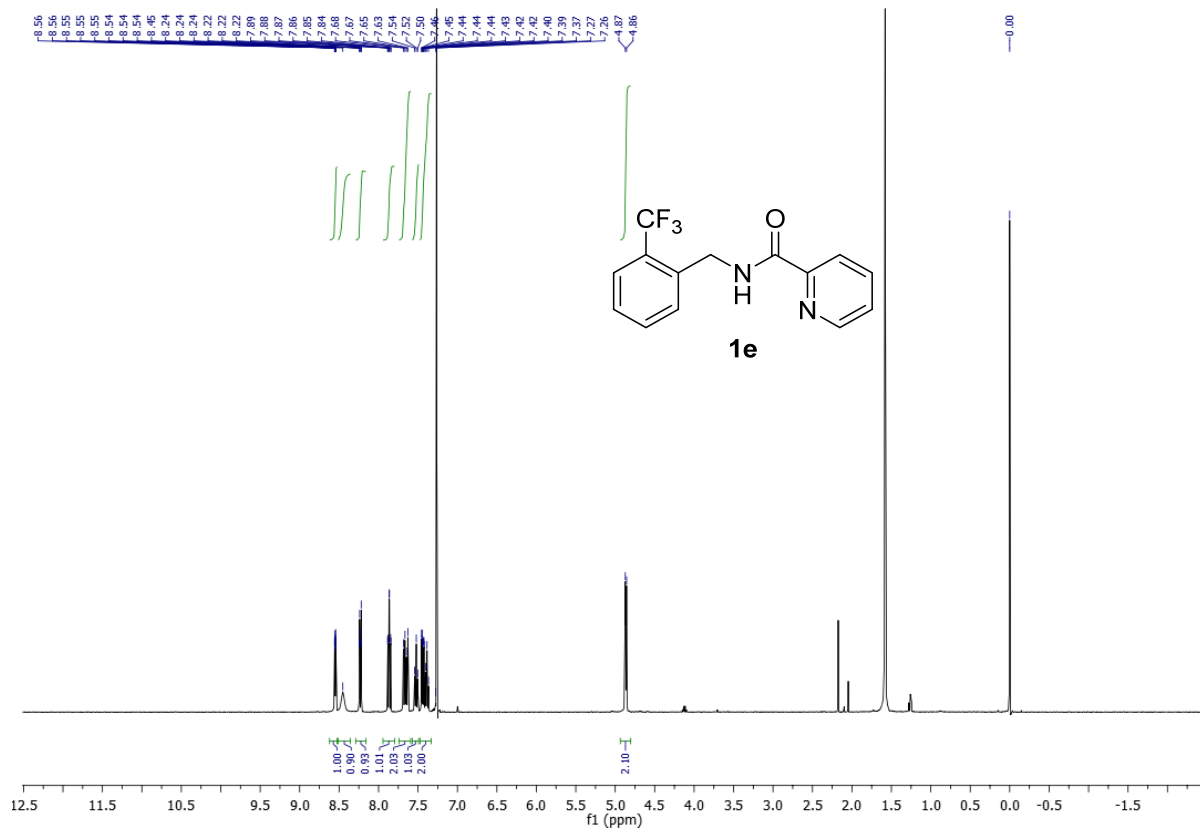


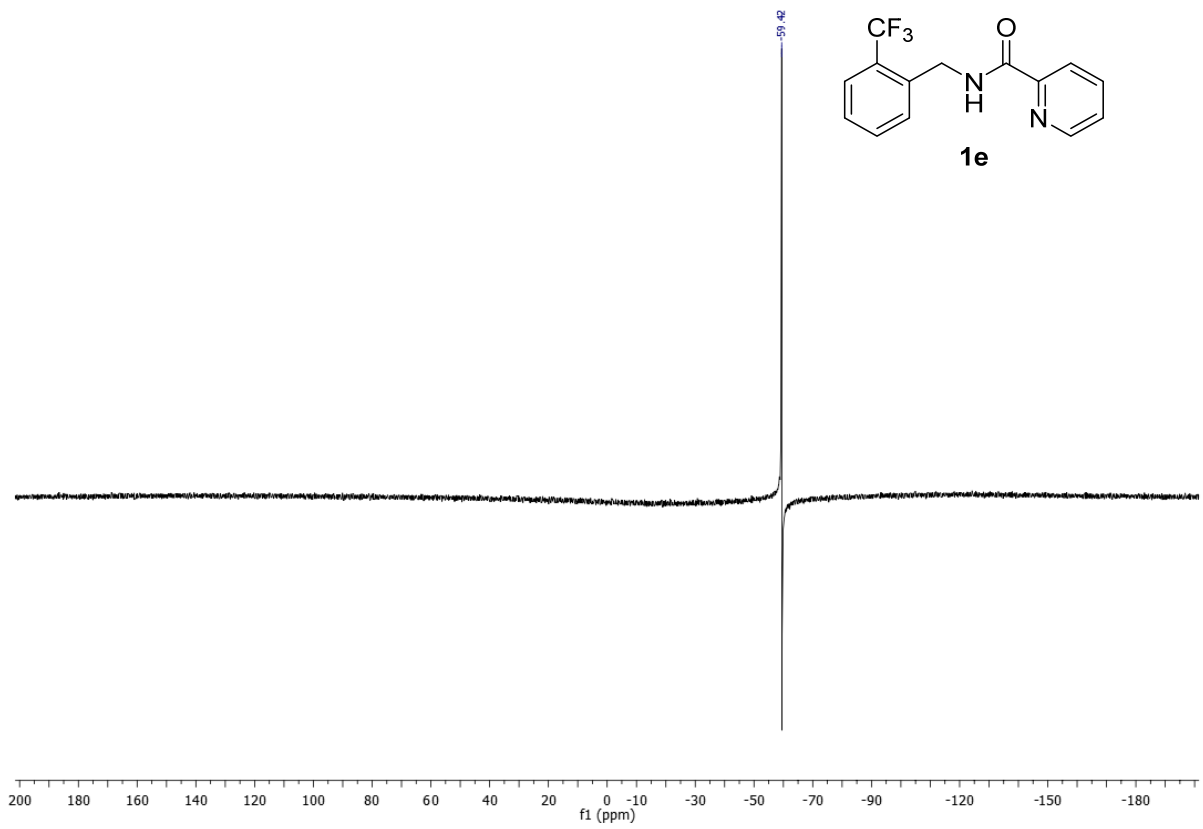


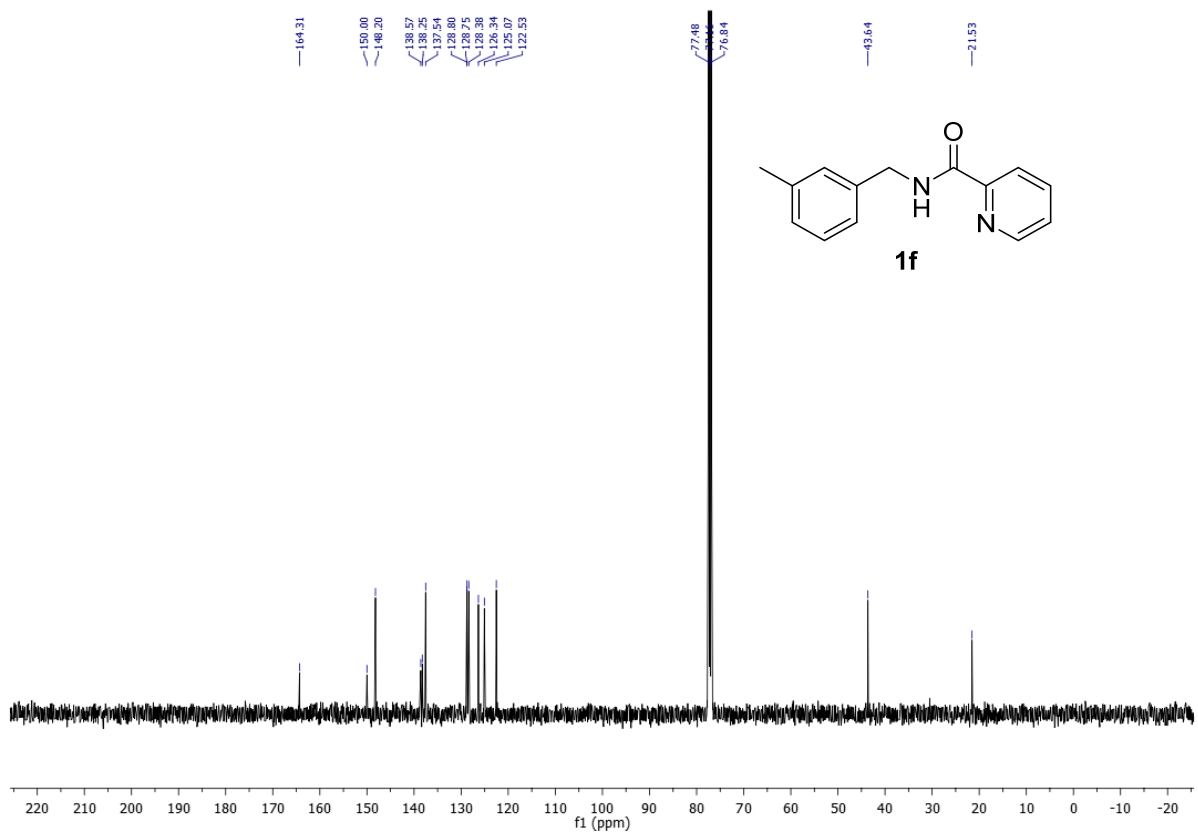
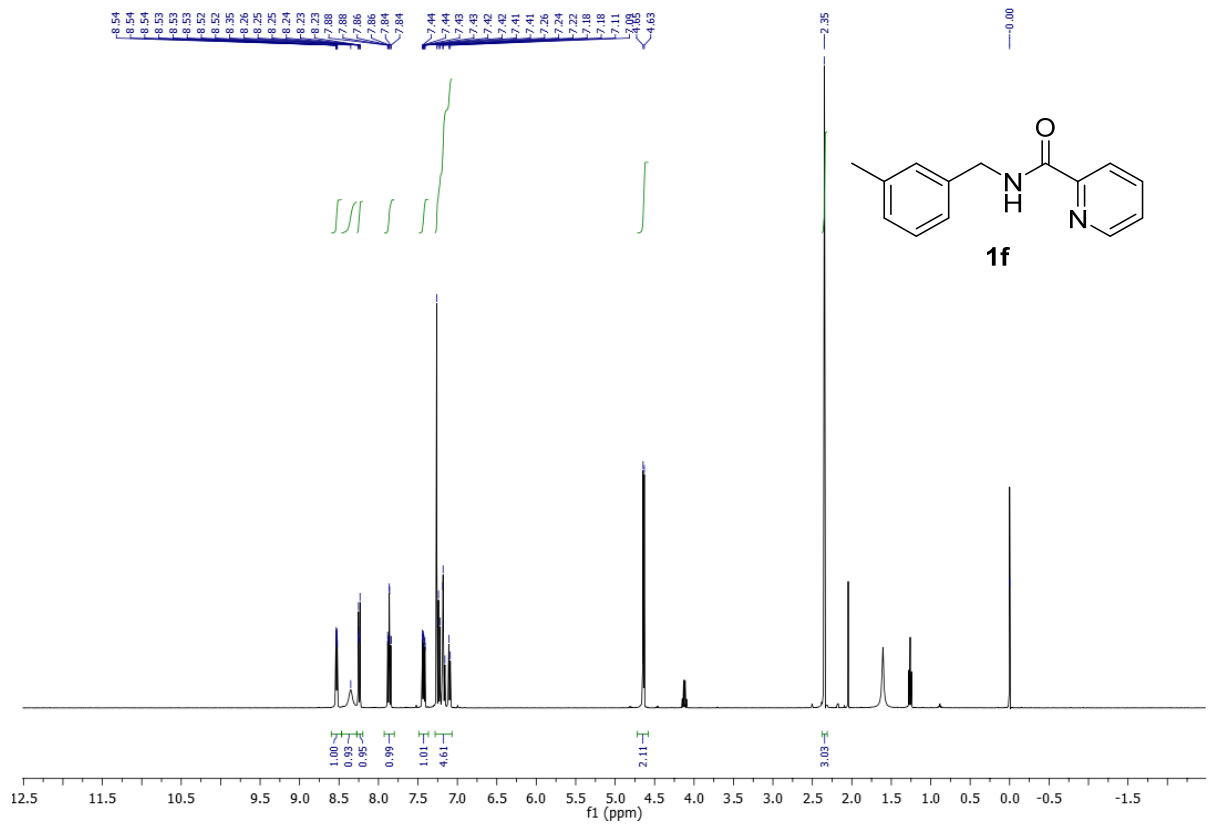


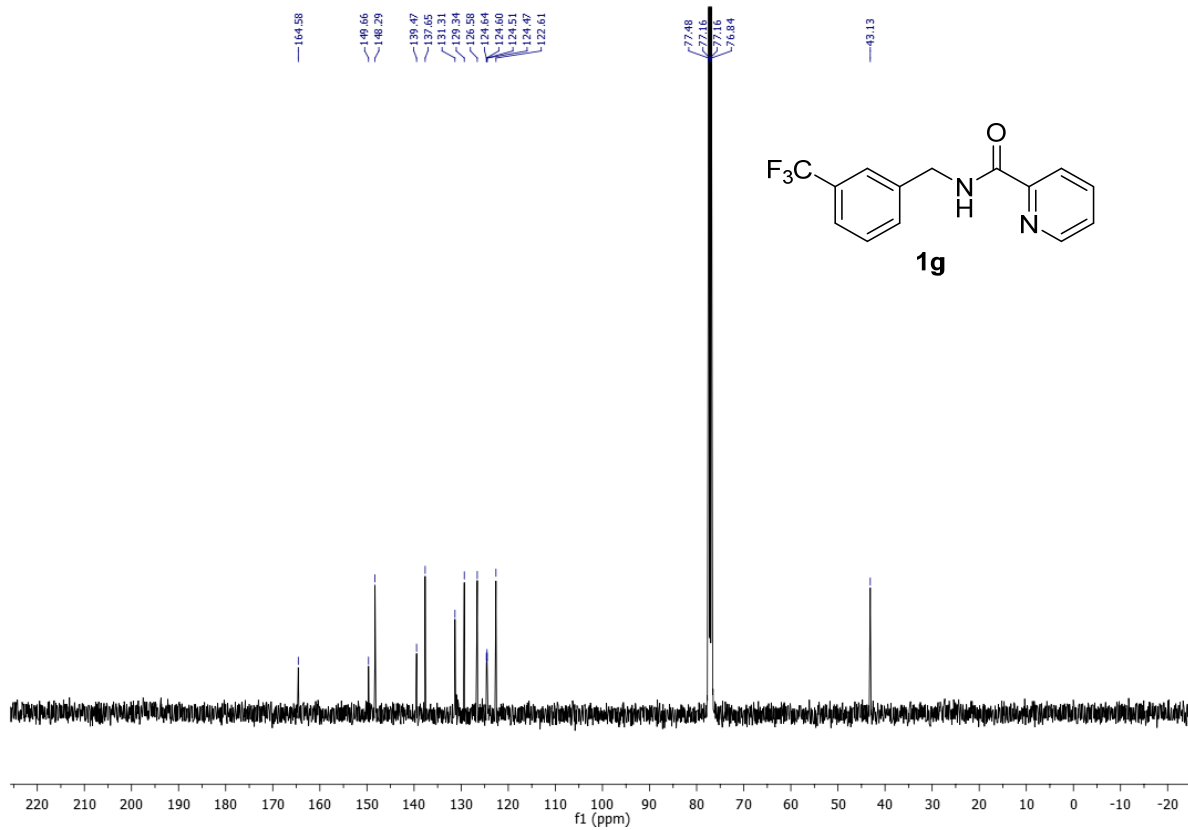
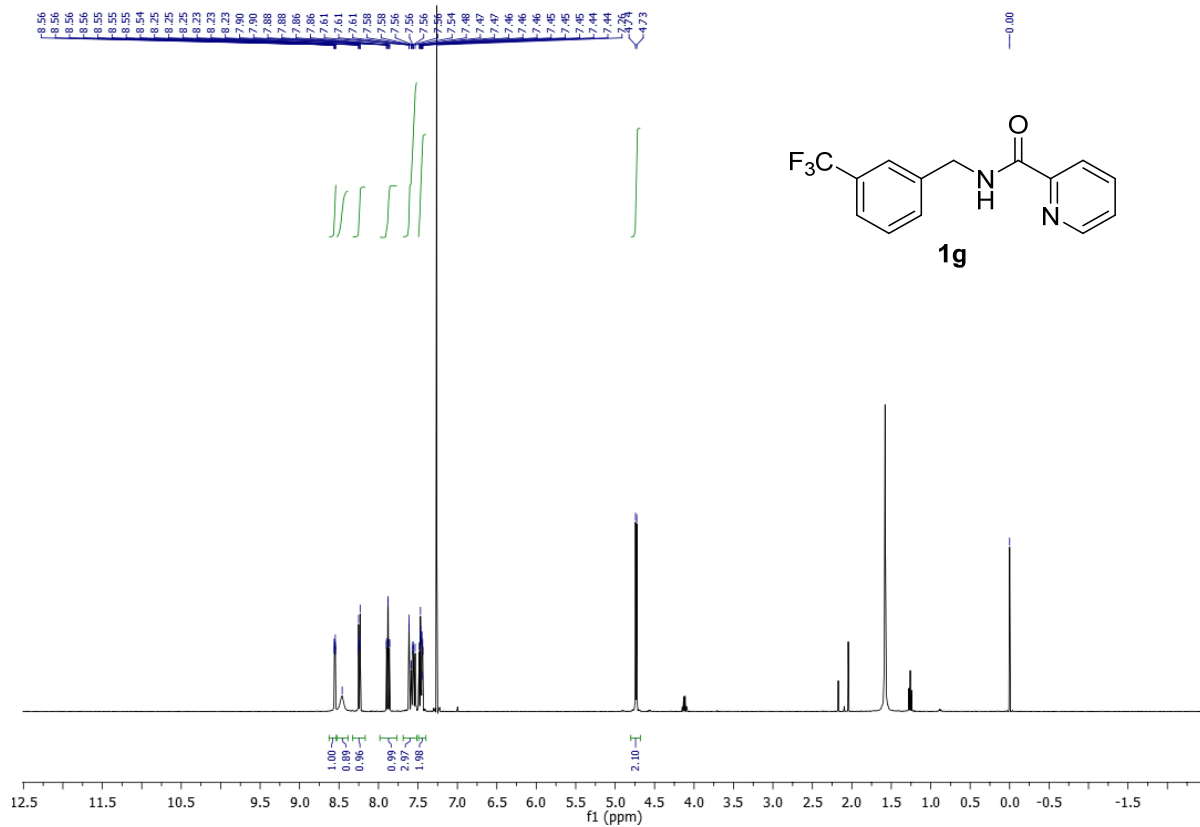


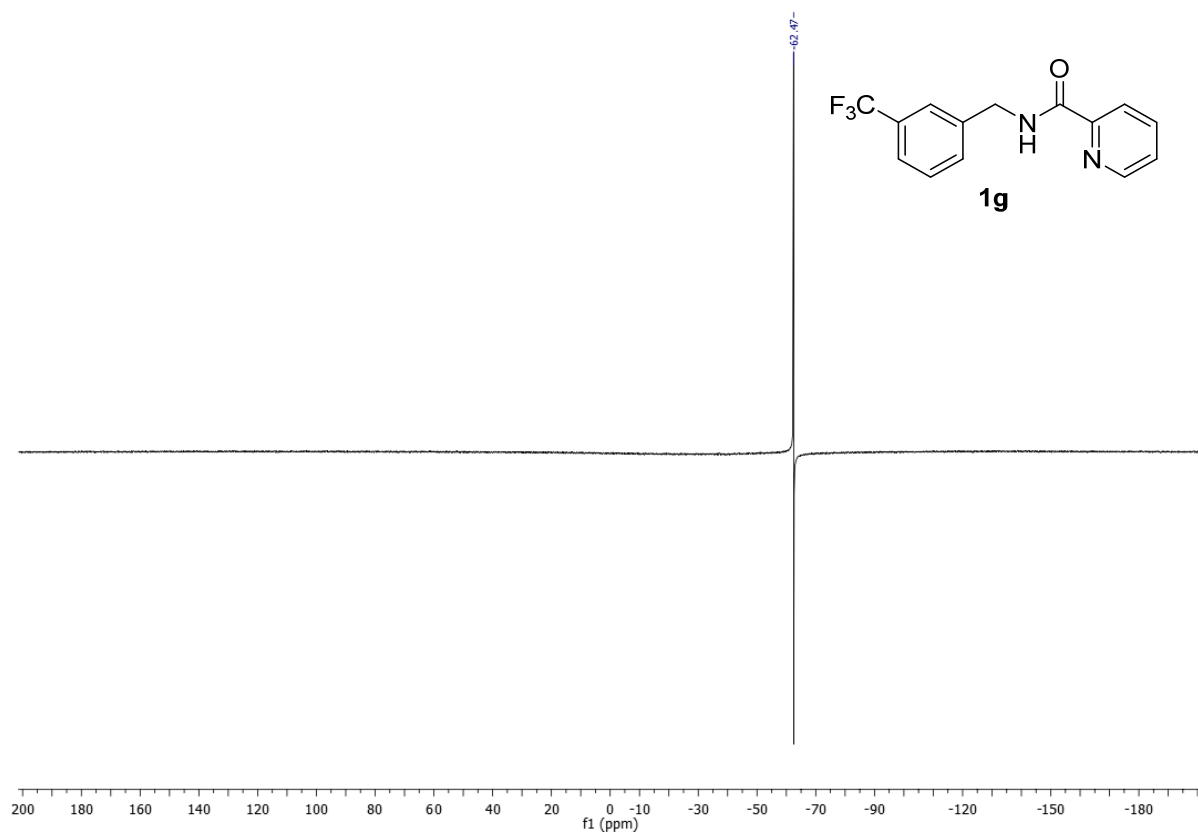




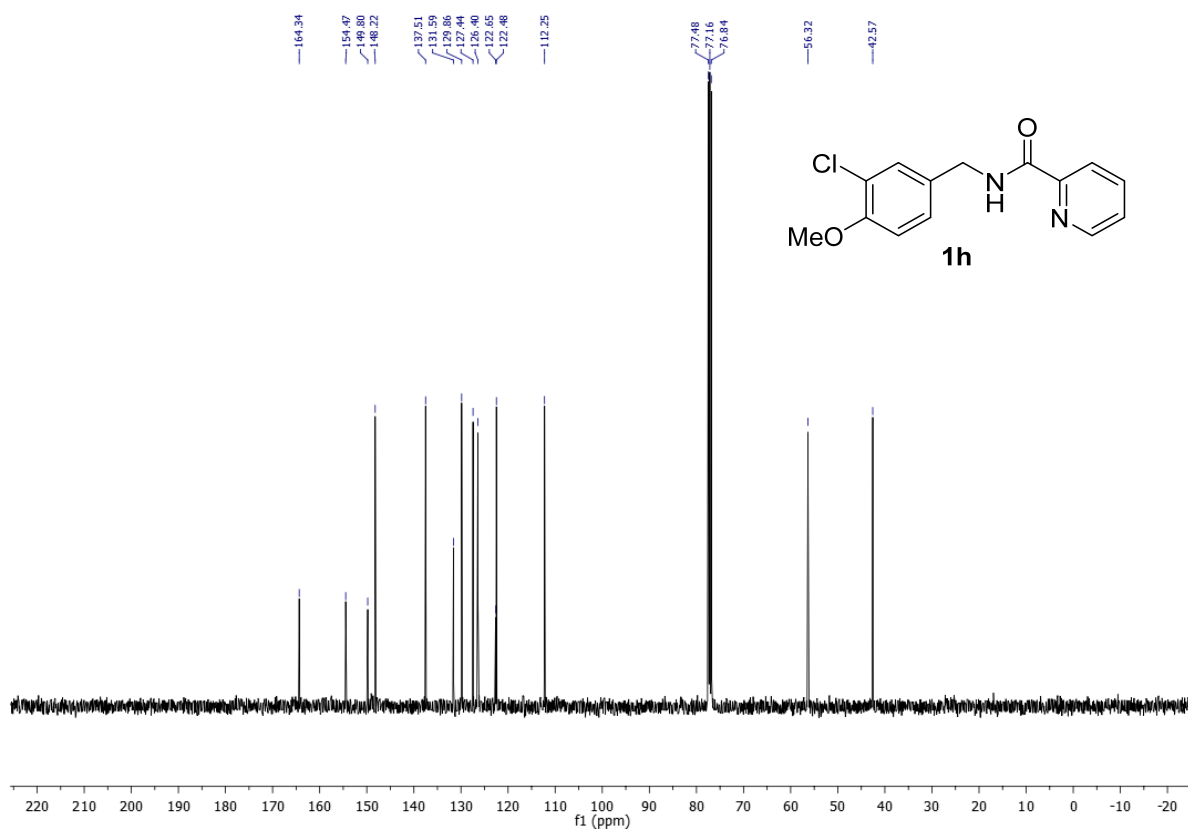
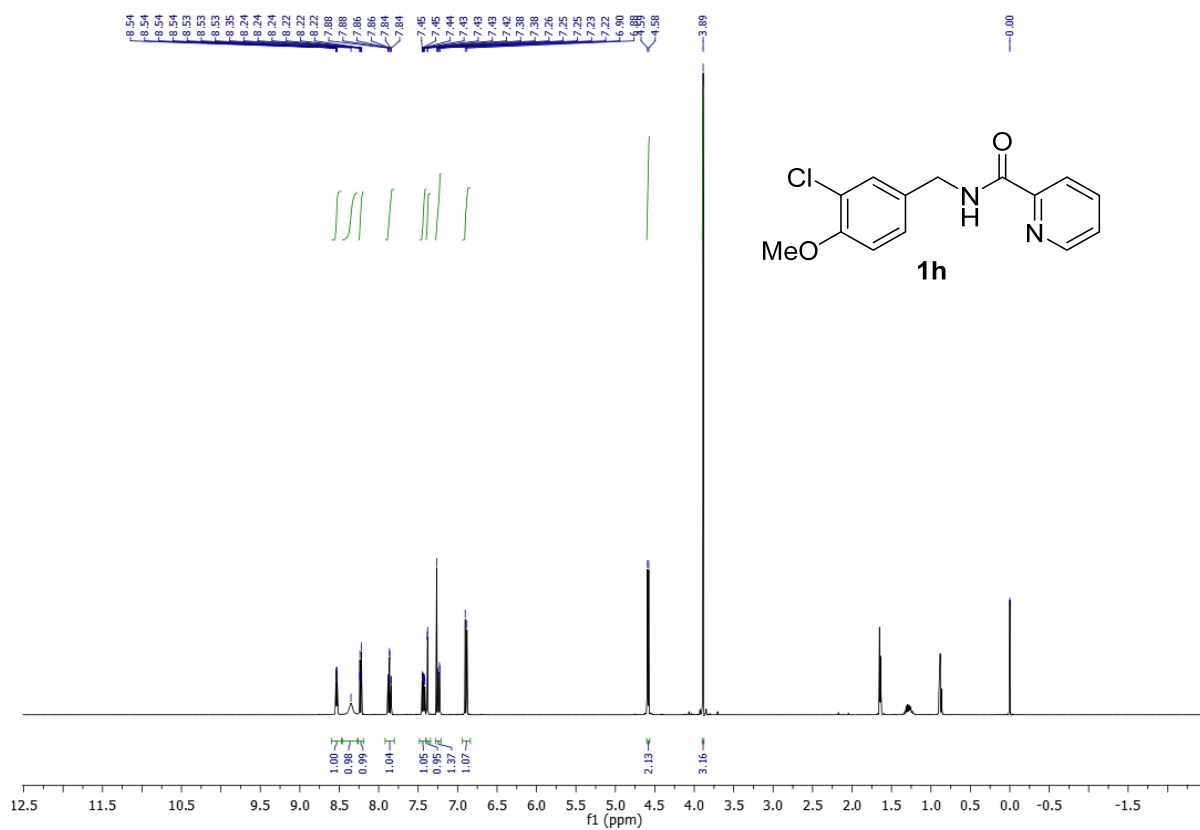


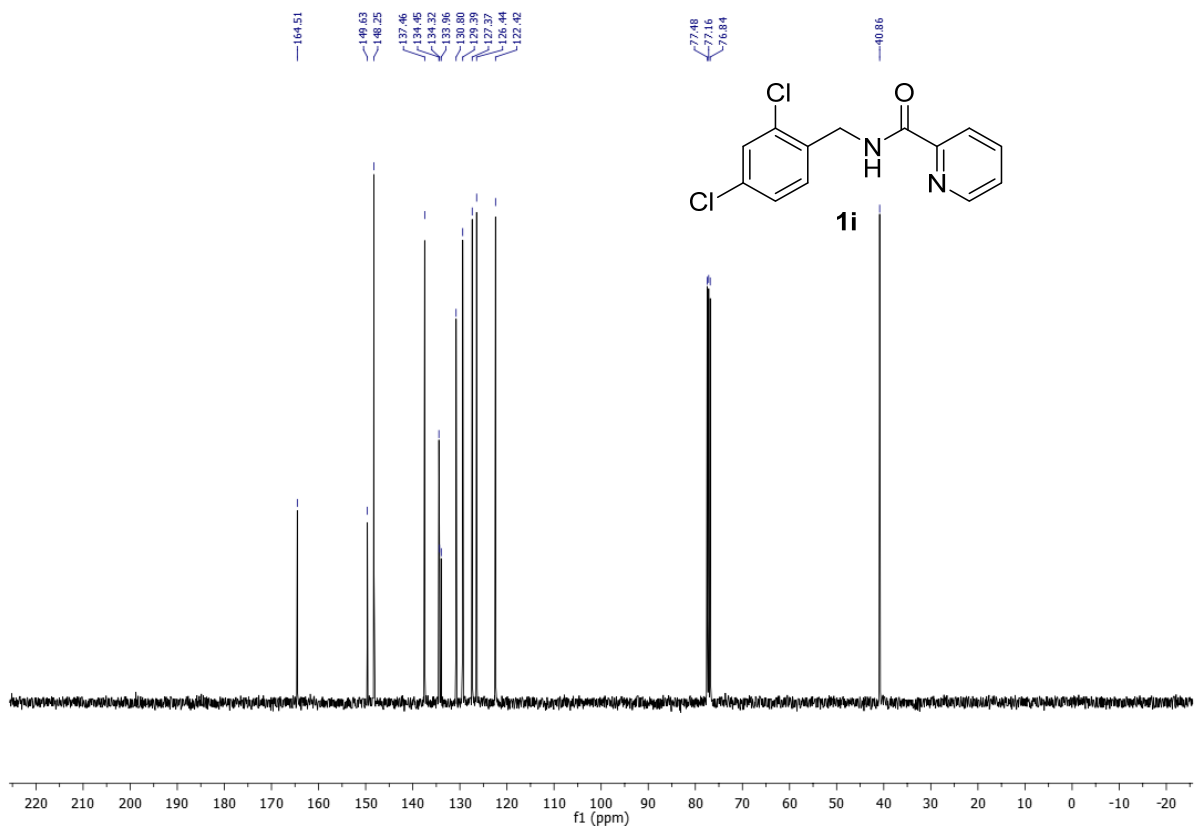
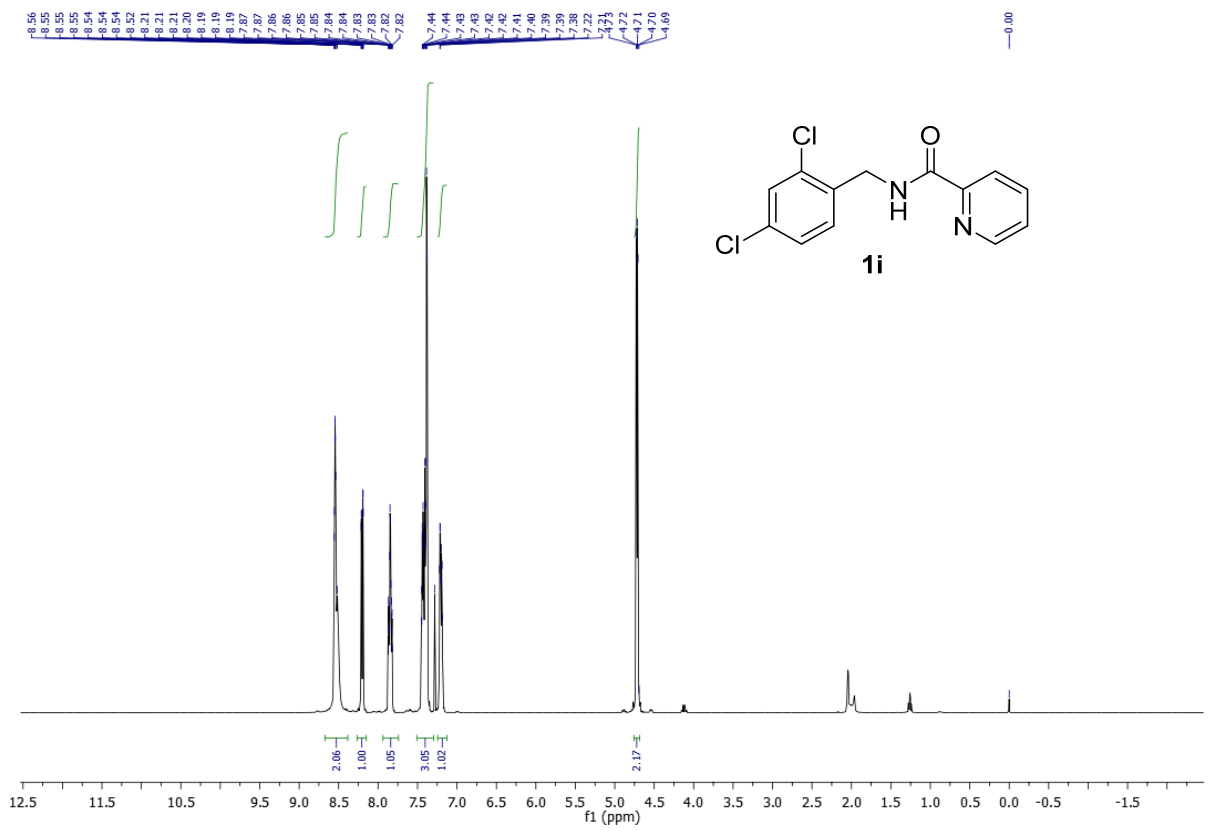


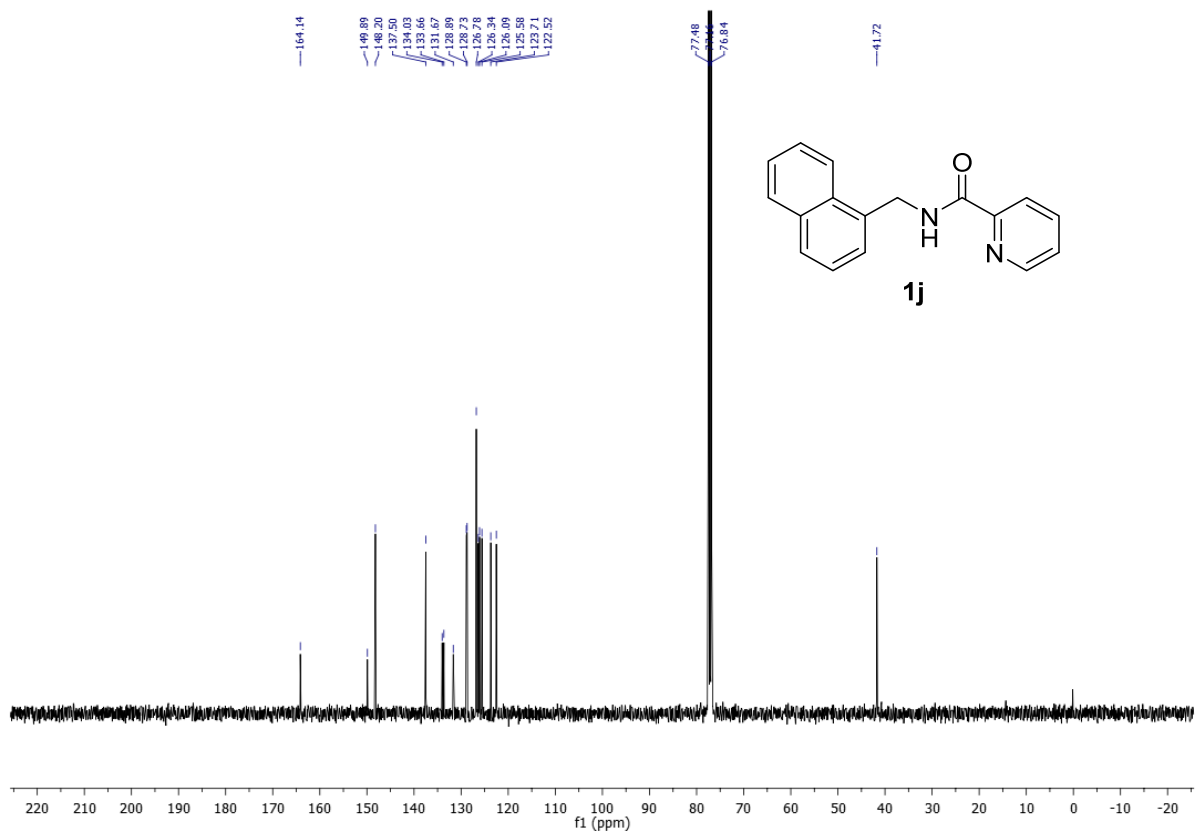
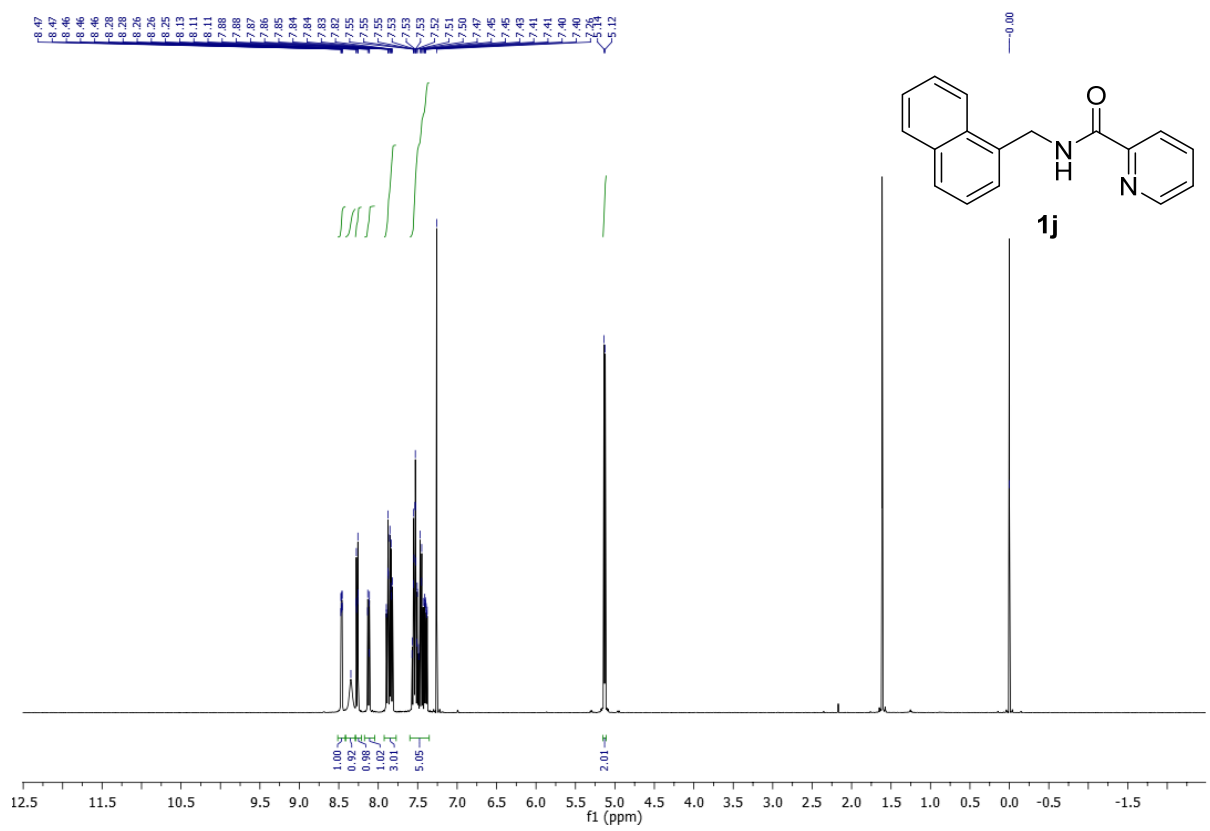


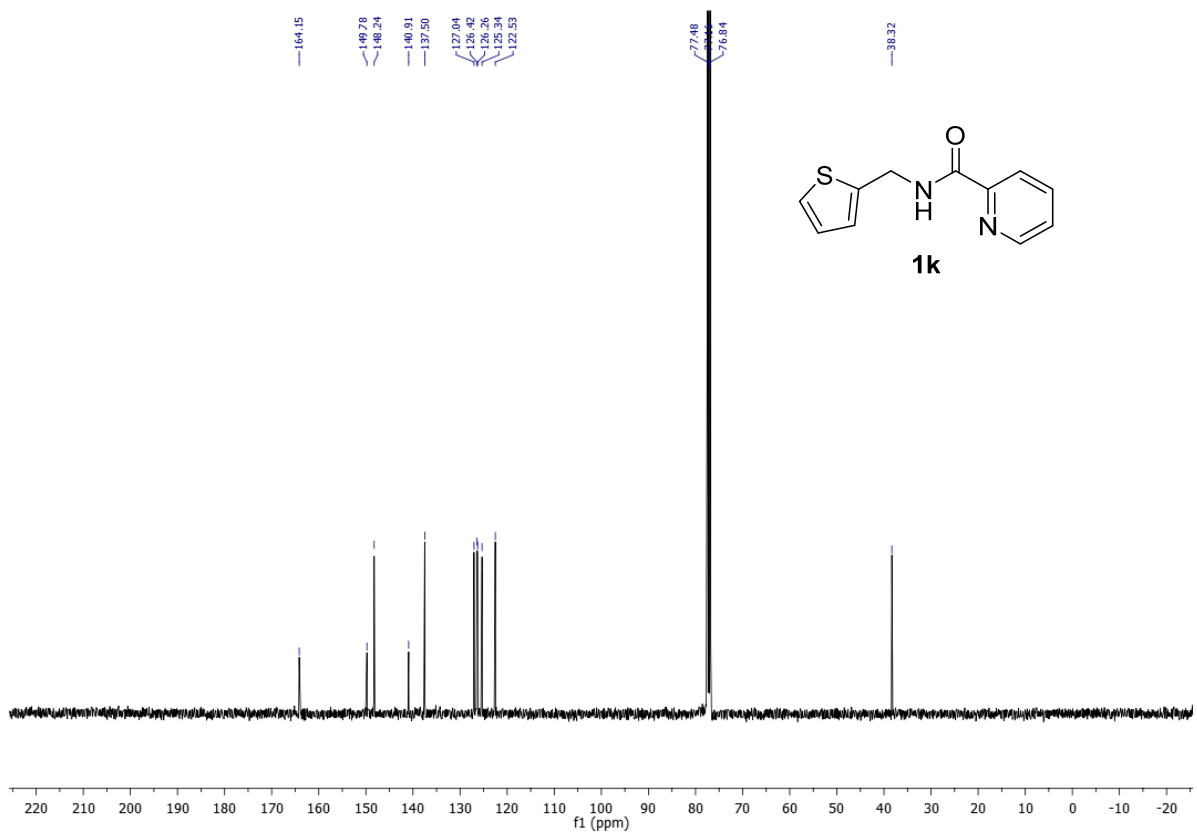
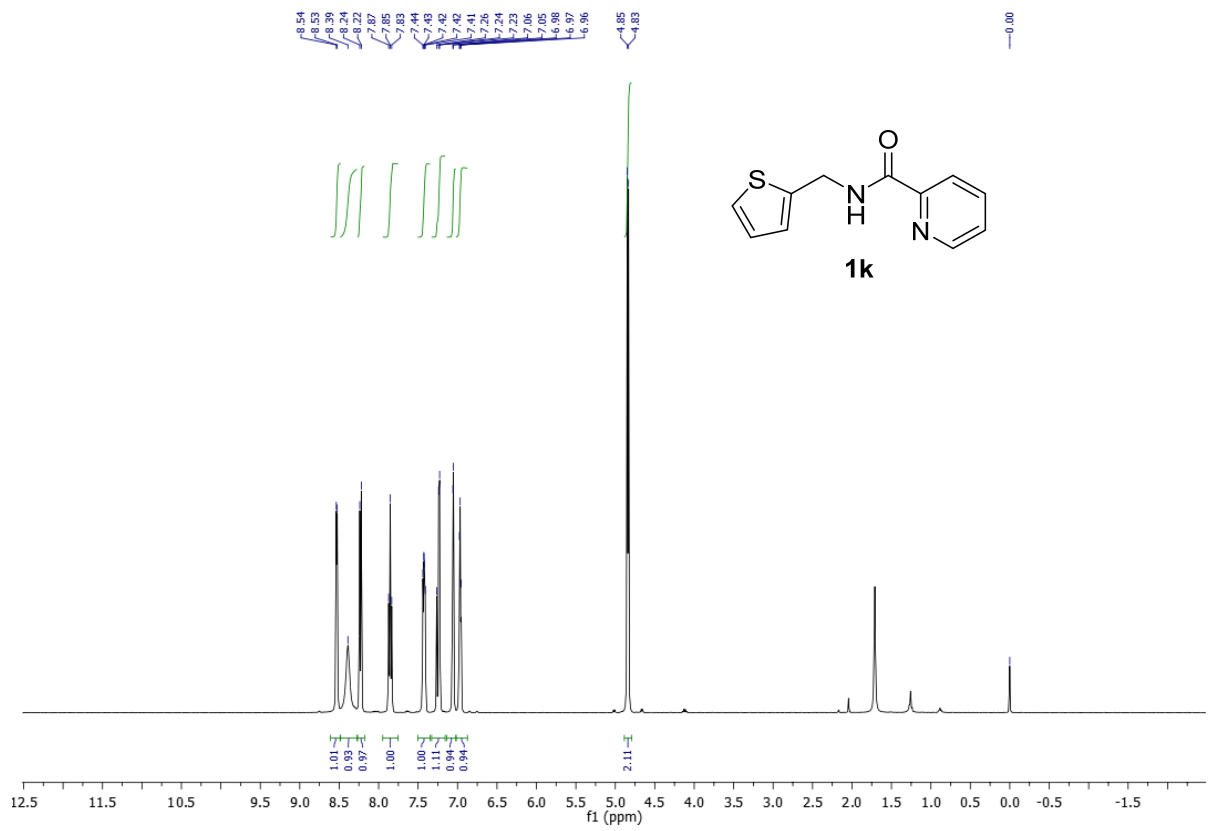


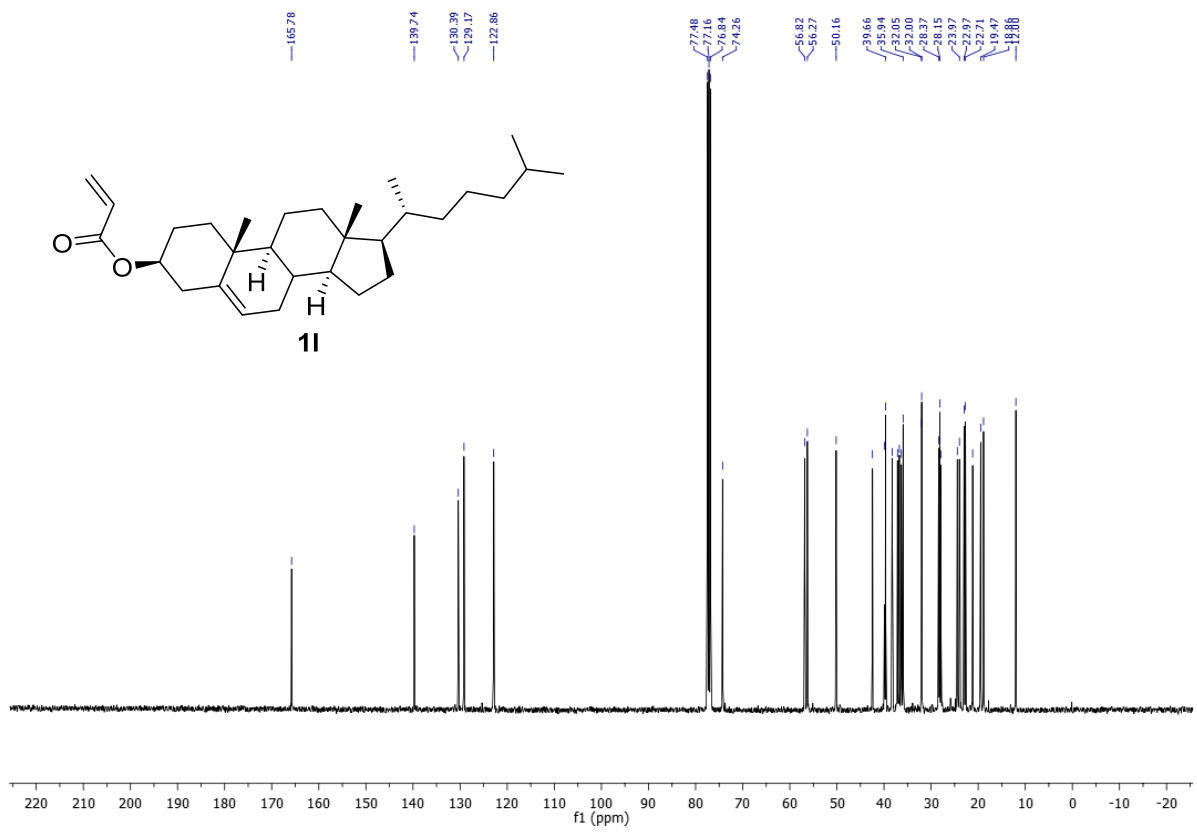
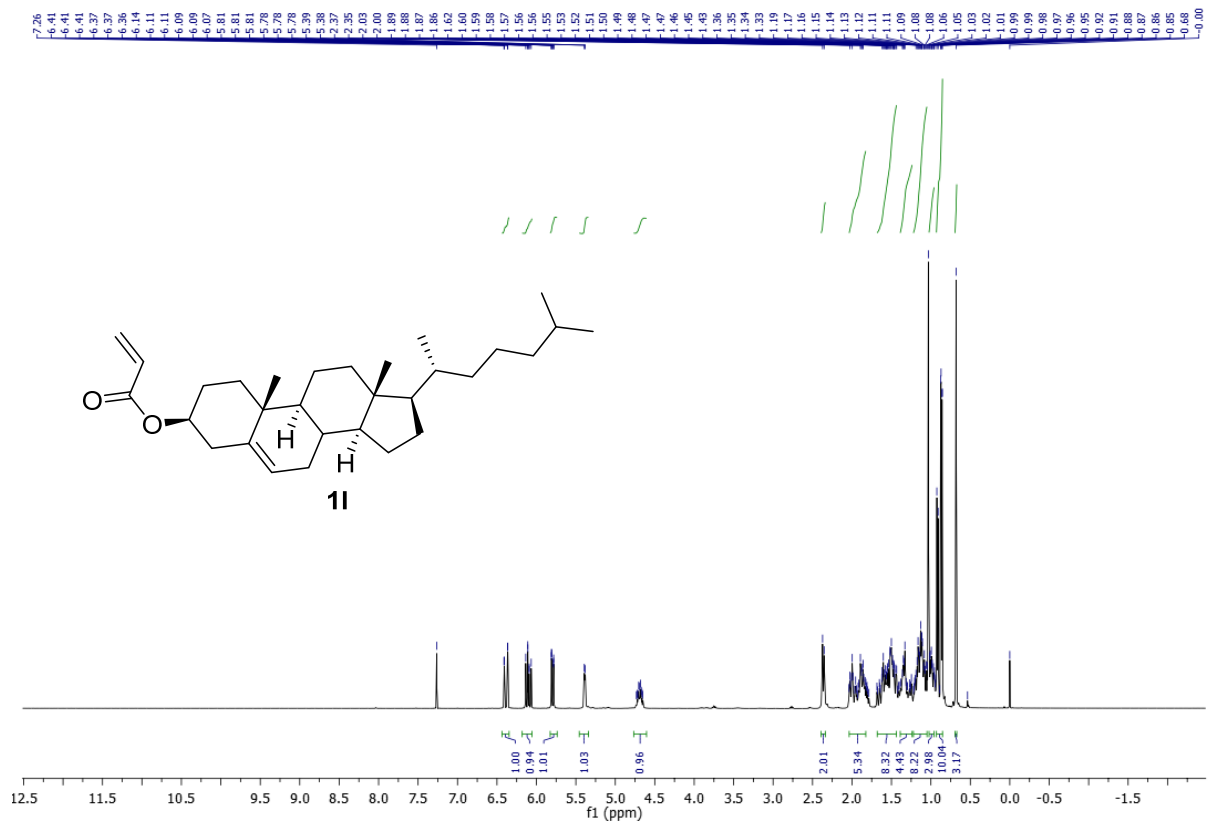


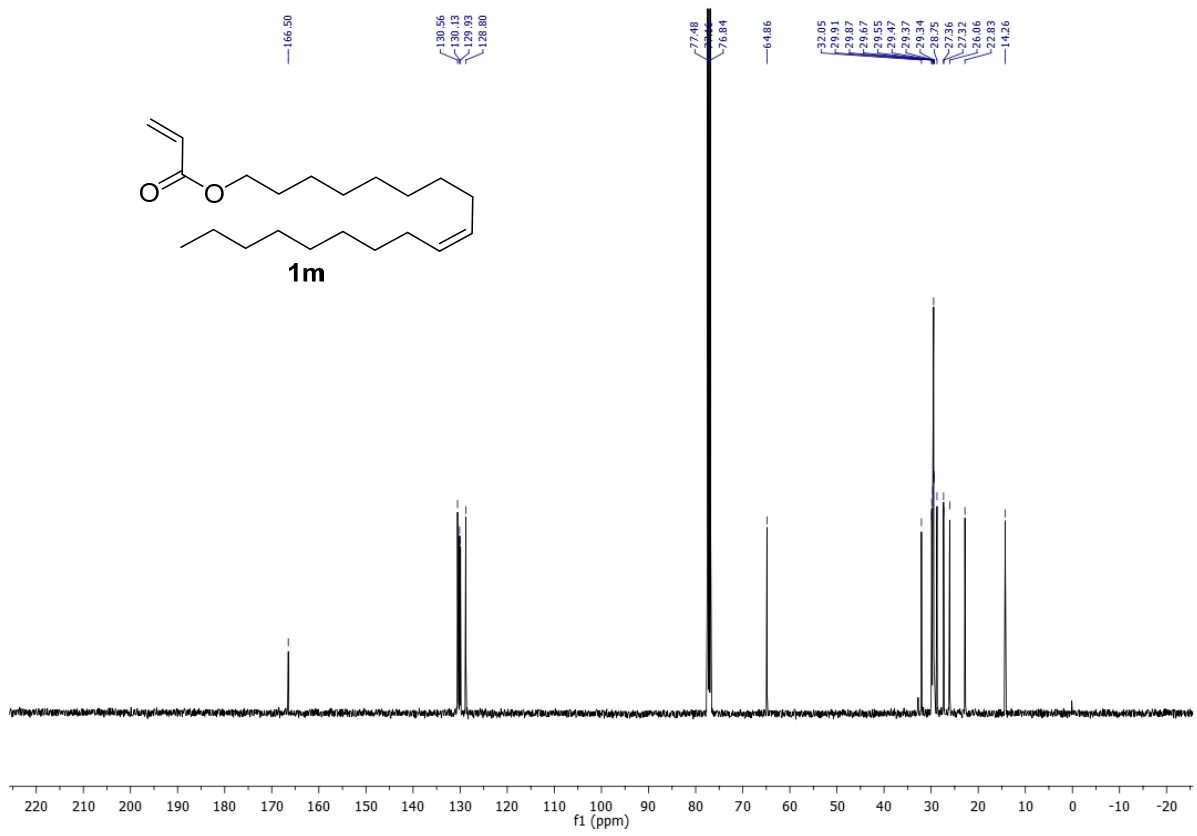
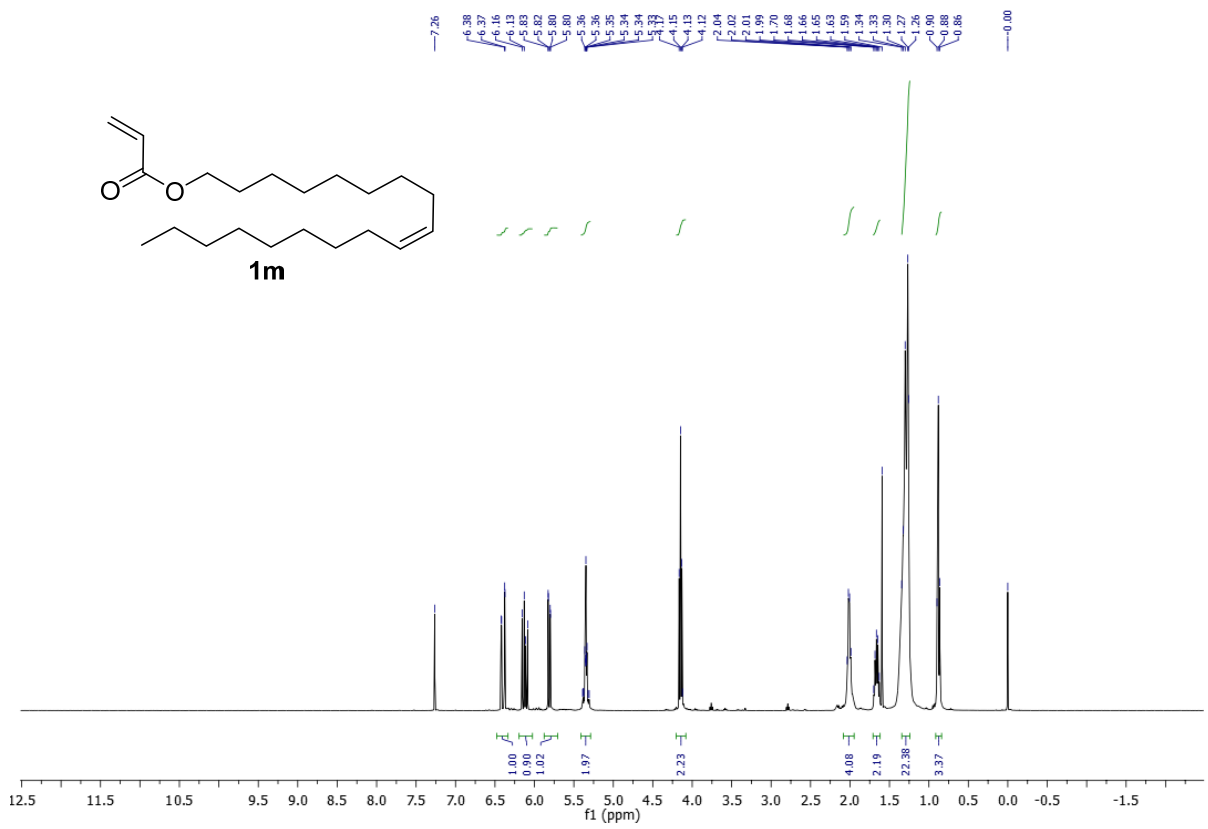


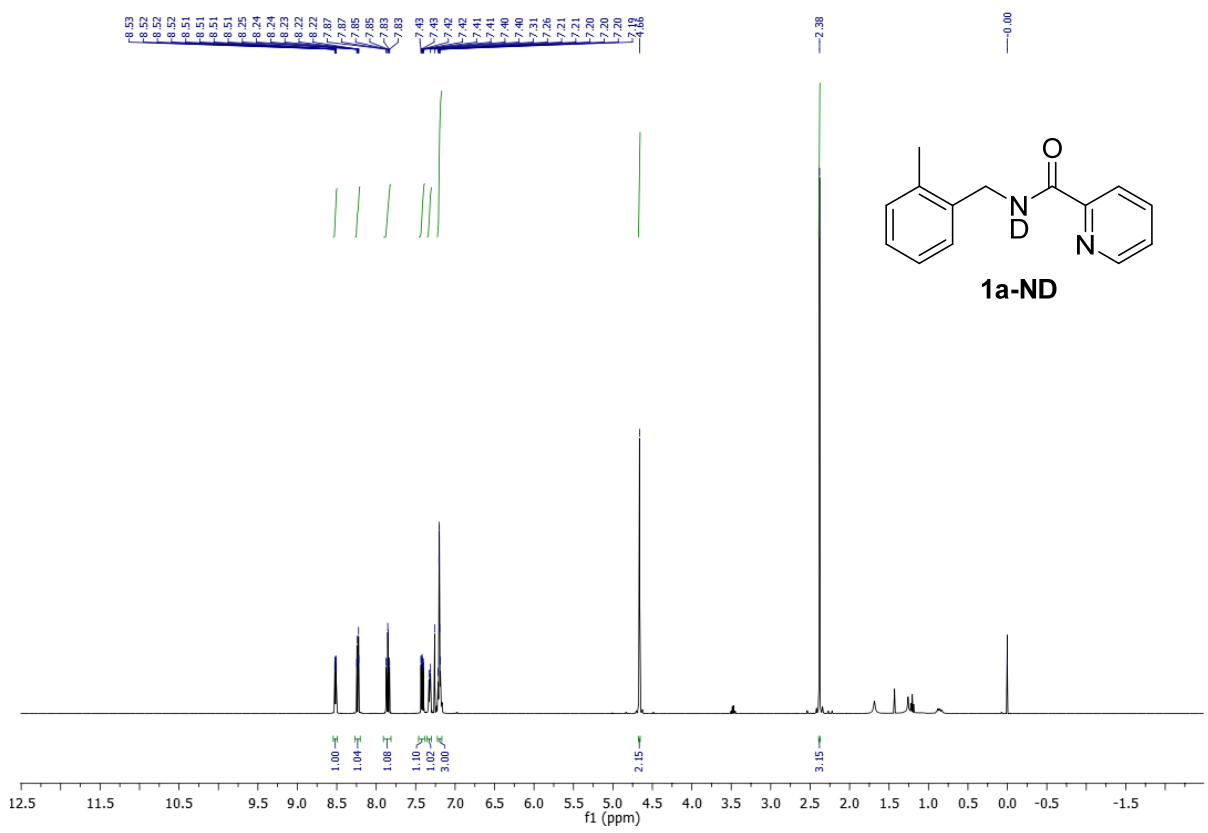
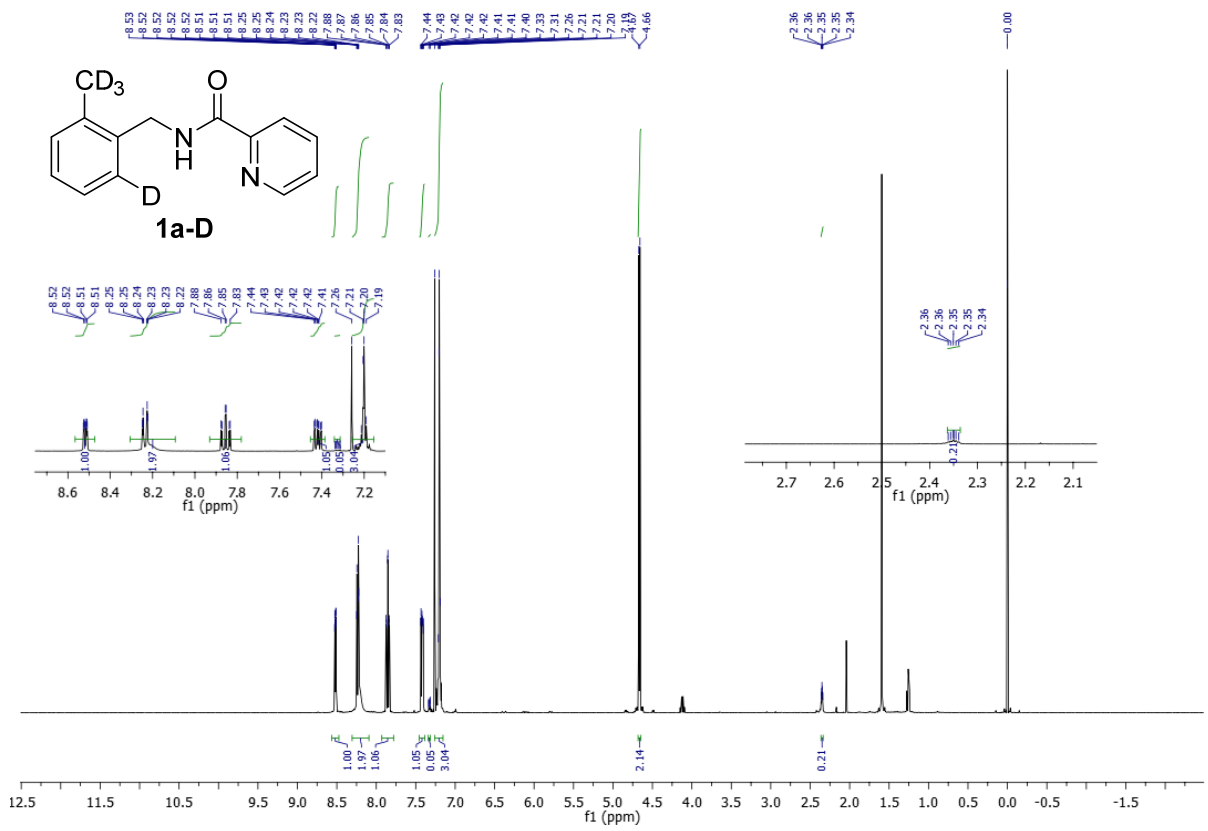












# NMR spectra of products

