

*Supporting Information for:*

## **New synthetic approaches towards analogues of bedaquiline**

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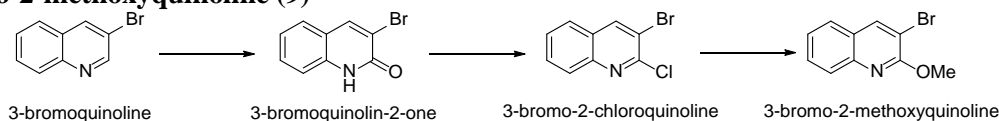
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### **General Experimental:**

All catalysts, reagents and the solvents used in reaction extractions and chromatography were supplied by commercial vendors without further purification or drying. All reactions were performed under an inert atmosphere of anhydrous N<sub>2</sub> (g). Petroleum spirits with a boiling point range of 40-60 °C was used for chromatography. Column (flash) chromatography was performed on 40-60 μm silica gel. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 400.13 and 100.62 MHz, respectively. Chemical shifts (δ, ppm) are reported relative to the solvent peak (CDCl<sub>3</sub>: 7.26 [<sup>1</sup>H] or 77.16 [<sup>13</sup>C]). Proton resonances are annotated as: chemical shift (δ), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant (*J*, Hz), and number of protons. High resolution MS was performed on a TOF LC/MS. All data were acquired and reference mass corrected via a dual-spray electrospray ionisation (ESI) source. Each scan or data point on the total ion chromatogram (TIC) is an average of 13,700 transients, producing a spectrum every second. Mass spectra were created by averaging the scans across each peak and subtracting the background from first 10 sec of the TIC. Acquisition parameters: mode, ESI; drying gas flow, 11 L/min; nebuliser pressure, 45 psi; drying gas temperature, 325°C; voltages: capillary, 4000 V; fragmentor, 160 V; skimmer, 65 V; octapole RF, 750 V; scan range, 100–1500 m/z; positive ion mode internal reference ions, m/z 121.050873 and 922.009798. Preparative HPLC was performed on an Agilent 1260 infinity HPLC system fitted with a Phenomenex Luna C8(2) column running a gradient of 30% MeCN/H<sub>2</sub>O (0.1% TFA) up to 100% MeCN (100%) over 15 minutes.

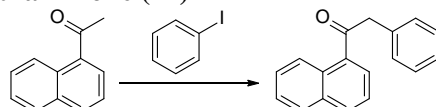
## Specific Experimental:

### 3-bromo-2-methoxyquinoline (9)



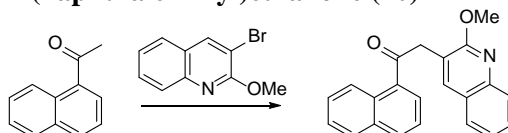
3-bromoquinolin-2-one was prepared as a white solid in two steps from 3-bromoquinoline according to a literature procedure.<sup>[1]</sup> A solution of 3-bromoquinolin-2-one (13.6 g, 60 mmol) in POCl<sub>3</sub> (10 mL) was heated to 110 °C for 4 hours. After this time, the solvent was removed under reduced pressure and the product dissolved in CHCl<sub>3</sub> and washed with H<sub>2</sub>O (3 x 10 mL) and brine. The organic phase was separated, dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford 3-bromo-2-chloroquinoline. Subsequently, 3-bromo-2-chloroquinoline was dissolved in methanol (10 mL) and added to a freshly prepared 3M solution of sodium methoxide (240 mmol Na<sub>(s)</sub> dissolved in 80 mL of methanol) and the resultant solution refluxed for 16 hours. After this time the volatiles were removed under reduced pressure, and the product dissolved in CHCl<sub>3</sub> and washed with H<sub>2</sub>O (3 x 10 mL) and brine. The organic phase was separated, dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford the title product as a white solid (11.36 g, 47.7 mmol, 80% over 2 steps). M.P. = 48.6 – 50.2 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.23 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.61 – 7.65 (m, 2H), 7.37 – 7.41 (m, 1H), 4.14 (s, 3H), ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 157.6, 145.2, 140.8, 129.8, 127.2, 126.5, 126.1, 124.8, 108.0, 54.6 ppm; HRMS (*m/z*) [C<sub>10</sub>H<sub>8</sub>BrNO + H]<sup>+</sup> Calcd. 237.9862, 239.9842, Found 237.9855, 239.9835.

### 1-(naphthalen-1-yl)-2-phenylethan-1-one (11)<sup>[2]</sup>



To an oven dried flask under nitrogen was sequentially added Pd(OAc)<sub>2</sub> (2.2 mg, 1.0 mol%), P(<sup>*t*</sup>Bu)<sub>3</sub>·HBF<sub>4</sub> (5.8 mg, 2.0 mol%), sodium *tert*-butoxide (240 mg, 2.5 mmol) and THF (4.0 mL). After stirring for 5 min, iodobenzene (204 mg, 1.0 mmol) and 1-acetonaphthone (187 mg, 1.1 mmol) were added. The resultant reaction mixture was stirred for 6 hours at 60 °C. After this time, the reaction mixture was cooled to room temperature, diluted with EtOAc (5.0 mL) and filtered through a plug of Celite, which was washed with additional EtOAc. The solvent was evaporated and purification by silica gel column chromatography (1:19 EtOAc/petroleum spirits) afforded the title compound as a colourless solid which was further recrystallized from EtOH (226 mg, 0.92 mmol, 92%). M.P. = 62.5 – 64.1 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.52 (d, *J* = 8.4 Hz, 1H), 7.90 – 7.94 (m, 2H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.42 – 7.54 (m, 3H), 7.19 – 7.30 (m, 5H), 4.33 (s, 2H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 201.5, 135.6, 134.6, 134.0, 132.8, 130.5, 129.5, 128.7, 128.4, 128.0, 127.9, 127.0, 126.5, 125.9, 124.3, 48.9 ppm; MS (*m/z*) = 247.1 (M+H<sup>+</sup>); HRMS (*m/z*) [C<sub>18</sub>H<sub>14</sub>O + H]<sup>+</sup> Calcd. 247.1117, Found 247.1118.

### 2-(2-methoxyquinolin-3-yl)-1-(naphthalen-1-yl)ethanone (10)

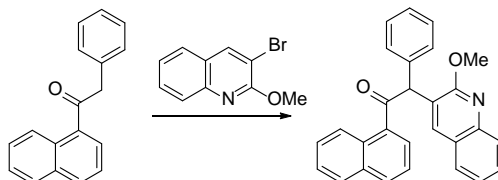


To an oven dried flask under nitrogen was sequentially added Pd(OAc)<sub>2</sub> (2.2 mg, 1.0 mol%), P(<sup>*t*</sup>Bu)<sub>3</sub>·HBF<sub>4</sub> (5.8 mg, 2.0 mol%), sodium *tert*-butoxide (240 mg, 2.5 mmol) and THF (4.0 mL). After stirring for 5 minutes, 3-bromo-2-methoxyquinoline (9) (238 mg, 1.0 mmol) and 1-acetonaphthone (187 mg, 1.1 mmol) were added. The reaction mixture was stirred for 16 hours at 60 °C. After this time, the reaction mixture was cooled to room temperature, diluted with EtOAc (5.0 mL), filtered through a plug of Celite, which was washed with additional EtOAc. The solvent was evaporated and purification by silica gel column chromatography (1:9 EtOAc/petroleum spirits) afforded the title compound as a yellow solid which was further recrystallized from EtOH (301 mg, 0.92 mmol, 92%). M.P. = 122.5 – 123.9 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.62 (dd, *J* = 0.6 and 8.5 Hz, 1H), 8.01 (dd, *J* = 1.2 and 7.2 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.94 (s, 1H), 7.88 (dd, *J* = 1.4 and 8.0 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.71

(dd,  $J = 1.3$  and  $8.0$  Hz, 1H), 7.50 – 7.62 (m, 4H), 7.37 (ddd,  $J = 1.2$ ,  $7.0$  and  $8.0$  Hz, 1H), 4.44 (s, 2H), 4.03 (s, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta = 201.1$ , 160.6, 146.0, 138.9, 135.9, 134.0, 132.7, 130.3, 129.2, 128.4, 127.9, 127.6, 127.2, 126.9, 126.5, 125.8, 125.4, 124.3, 124.1, 120.2, 53.7, 43.8 ppm; MS ( $m/z$ ) = 328.2 ( $\text{M}+\text{H}^+$ ); HRMS ( $m/z$ ) [ $\text{C}_{22}\text{H}_{17}\text{NO}_2 + \text{H}$ ] $^+$  Calcd. 328.1332, Found 328.1328.

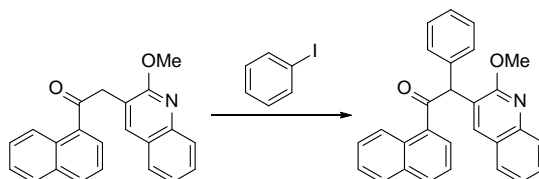
### 2-(2-methoxyquinolin-3-yl)-1-(naphthalen-1-yl)-2-phenylethanone (12)

Method A:



To an oven dried flask under nitrogen was sequentially added  $\text{Pd}(\text{OAc})_2$  (2.2 mg, 1.0 mol%),  $\text{P}(\text{tBu})_3 \cdot \text{HBF}_4$  (5.8 mg, 2.0 mol%), sodium *tert*-butoxide (240 mg, 2.5 mmol) and toluene (4.0 mL). After stirring for 5 minutes, ketone **11** (246 mg, 1.0 mmol) and 3-bromo-2-methoxyquinoline (357 mg, 1.5 mmol) were added and the reaction mixture stirred for 16 hours at  $40^\circ\text{C}$ . After this time, the reaction mixture was cooled to room temperature, diluted with EtOAc (5.0 mL) and filtered through a plug of Celite, which was washed with additional EtOAc. The solvent was evaporated and purification by silica gel column chromatography (1:9 EtOAc/petroleum spirits) afforded the title compound as a white solid which was further recrystallized from EtOH (319 mg, 0.79 mmol, 79%). M.P. =  $184.1 - 185.3^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta = 8.62$  (dd,  $J = 0.9$  and  $8.0$  Hz, 1H), 8.10 (dd,  $J = 1.1$  and  $7.3$  Hz, 1H), 7.97 (d,  $J = 8.2$  Hz, 1H), 7.85 – 7.90 (m, 2H), 7.43 – 7.63 (m, 10H), 7.32 – 7.40 (m, 2H), 6.30 (s, 1H), 4.02 (s, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta = 201.4$ , 159.9, 145.8, 137.9, 136.3, 135.9, 134.0, 132.6, 130.6, 129.8, 129.3, 129.2, 128.4, 127.9, 127.9, 127.7, 127.6, 126.8, 126.4, 125.9, 125.7, 125.4, 124.4, 124.1, 57.3, 53.8 ppm; MS ( $m/z$ ) = 404.3 ( $\text{M}+\text{H}^+$ ); HRMS ( $m/z$ ) [ $\text{C}_{28}\text{H}_{21}\text{NO}_2 + \text{H}$ ] $^+$  Calcd. 404.1645, Found 404.1651.

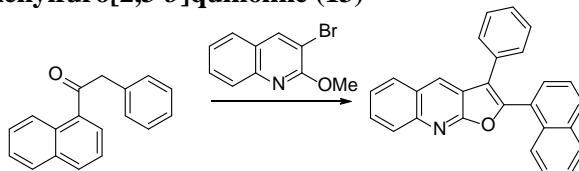
Method B:



To an oven dried flask under nitrogen was sequentially added  $\text{Pd}(\text{OAc})_2$  (2.2 mg, 1.0 mol%),  $\text{P}(\text{tBu})_3 \cdot \text{HBF}_4$  (5.8 mg, 2.0 mol%), sodium *tert*-butoxide (240 mg, 2.5 mmol) and toluene (4.0 mL). After stirring for 5 minutes, ketone **10** (327 mg, 1.0 mmol) and iodobenzene (408 mg, 2.0 mmol) were added. The reaction mixture was stirred for 16 hours at  $40^\circ\text{C}$ . After this time, the reaction mixture was cooled to room temperature, diluted with EtOAc (5.0 mL) and filtered through a plug of Celite, which was washed with additional EtOAc. The solvent was evaporated and purification by silica gel column chromatography (1:9 EtOAc/petroleum spirits) afforded the title compound as a clear solid which was further recrystallized from EtOH (339 mg, 0.84 mmol, 84%). The spectroscopic data was in accordance with that reported above.

### 2-(naphthalen-1-yl)-3-phenylfuro[2,3-*b*]quinoline (13)

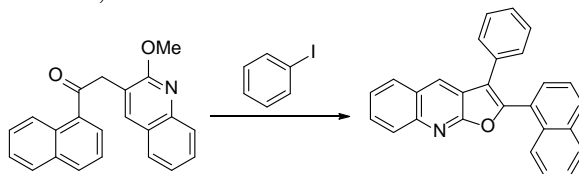
Method A:



To an oven dried flask under nitrogen was sequentially added  $\text{Pd}(\text{OAc})_2$  (2.2 mg, 1.0 mol%),  $\text{P}(\text{tBu})_3 \cdot \text{HBF}_4$  (5.8 mg, 2.0 mol%), sodium *tert*-butoxide (240 mg, 2.5 mmol) and THF (4.0 mL). After stirring for 5 minutes, ketone **11** (246 mg, 1.0 mmol) and 3-bromo-2-methoxyquinoline (357 mg, 1.5 mmol) were added. The reaction mixture was stirred for 16 hours at  $100^\circ\text{C}$ . After this time, the reaction mixture was cooled to room temperature, diluted with EtOAc (5.0 mL) and filtered through a plug of Celite, which was washed with additional EtOAc. The solvent was evaporated and purification by silica gel column chromatography (1:9 EtOAc/petroleum spirits) afforded the title compound as a pale yellow solid which was further recrystallized from EtOH (342 mg, 0.92 mmol, 92%). M.P. =  $179.3 - 180.5^\circ\text{C}$ ;

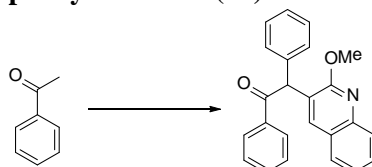
$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 8.53 (s, 1H), 8.22 (d,  $J$  = 8.6 Hz, 1H), 8.15 (d,  $J$  = 8.6 Hz, 1H), 7.93 – 7.98 (m, 2H), 7.90 (d,  $J$  = 8.0 Hz, 1H), 7.75 (ddd,  $J$  = 1.4, 6.8 and 8.5 Hz, 1H), 7.65 (dd,  $J$  = 1.1 and 7.1 Hz, 1H), 7.49 – 7.56 (m, 2H), 7.41 – 7.46 (m, 4H), 7.27 – 7.36 (m, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 161.4, 153.2, 145.2, 133.8, 131.7, 131.4, 130.6, 129.9, 129.1, 129.0, 128.5, 128.4, 128.3, 128.1, 127.7, 127.1, 126.9, 126.7, 126.3, 126.2, 125.1, 125.0, 122.0, 118.3 ppm; MS ( $m/z$ ) = 372.2 ( $\text{M}+\text{H}^+$ ); HRMS ( $m/z$ ) [ $\text{C}_{27}\text{H}_{17}\text{NO} + \text{H}$ ] $^+$  Calcd. 372.1383, Found 372.1387.

*Method B:*



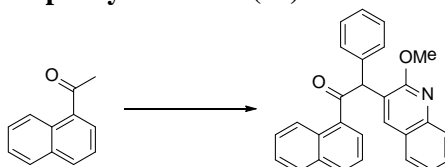
To an oven dried flask under nitrogen was sequentially added  $\text{Pd}(\text{OAc})_2$  (2.2 mg, 1.0 mol%),  $\text{P}(\text{tBu})_3 \cdot \text{HBF}_4$  (5.8 mg, 2.0 mol%), sodium *tert*-butoxide (240 mg, 2.5 mmol) and THF (4.0 mL). After stirring for 5 minutes, ketone **10** (327 mg, 1.0 mmol) and iodobenzene (408 mg, 2.0 mmol) were added. The reaction mixture was stirred for 16 hours at 100 °C. After this time, the reaction mixture was cooled to room temperature, diluted with EtOAc (5.0 mL) and filtered through a plug of Celite, which was washed with additional EtOAc. The solvent was evaporated and purification by silica gel column chromatography (1:9 EtOAc/petroleum spirits) afforded the title compound as a pale yellow solid which was further recrystallized from EtOH (238 mg, 0.64 mmol, 64%). The spectroscopic data was in accordance with that reported above.

### 2-(2-methoxyquinolin-3-yl)-1,2-diphenylethanone (**15**)



To an oven dried flask under nitrogen was added 3-bromo-2-methoxyquinoline (**9**) (238 mg, 1.0 mmol),  $\text{PdCl}_2(\text{D}'\text{BPF})$  (32.5 mg, 5.0 mol%), sodium *tert*-butoxide (240 mg, 2.5 mmol) and THF (4.0 mL). After stirring for 5 minutes, acetophenone (120 mg, 1.0 mmol) was added and the resultant solution was heated to 60 °C for 6 hours. The reaction mixture was cooled to room temperature, iodobenzene added (408 mg, 2.0 mmol) and heating continued at 60 °C for 16 hours. After this time, the reaction mixture was diluted with EtOAc (5.0 mL) and filtered through a plug of Celite, which was washed with additional EtOAc. The solvent was evaporated and purification by silica gel column chromatography (1:9 EtOAc/petroleum spirits) afforded the title compound as a white solid (279 mg, 0.79 mmol, 79%). M.P. = 146.4 – 149.2 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 8.04 (dd,  $J$  = 1.4 and 8.2 Hz, 2H), 7.85 (d,  $J$  = 8.7 Hz, 1H), 7.50 – 7.60 (m, 4H), 7.29 – 7.45 (m, 8H), 6.34 (s, 1H), 4.03 (s, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 198.0, 159.8, 145.7, 137.9, 136.8, 136.3, 133.0, 129.7, 129.2, 129.2, 128.8, 128.6, 127.7, 127.6, 126.8, 125.3, 125.1, 124.0, 53.8, 53.5 ppm; MS ( $m/z$ ) = 354.2 ( $\text{M}+\text{H}^+$ ); HRMS ( $m/z$ ) [ $\text{C}_{24}\text{H}_{19}\text{NO}_2 + \text{H}$ ] $^+$  Calcd. 354.1489, Found 354.1497.

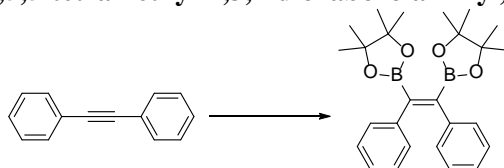
### 2-(2-methoxyquinolin-3-yl)-1,2-diphenylethanone (**12**)



In an oven dried flask under nitrogen was added 3-bromo-2-methoxyquinoline (**9**) (238 mg, 1.0 mmol),  $\text{PdCl}_2(\text{D}'\text{BPF})$  (32.5 mg, 5.0 mol%), sodium *tert*-butoxide (240 mg, 2.5 mmol) and THF (4.0 mL). After stirring for 5 minutes, 1-acetonaphthone (170 mg, 1.0 mmol) was added and the resultant solution was heated to 60 °C for 6 hours. The reaction mixture was cooled to room temperature, iodobenzene added (408 mg, 2.0 mmol) and heating continued at 60 °C for 16 hours. After this time, the reaction mixture was diluted with EtOAc (5.0 mL) and filtered through a plug of Celite, which was washed with additional EtOAc. The solvent was evaporated and purification by silica gel column chromatography

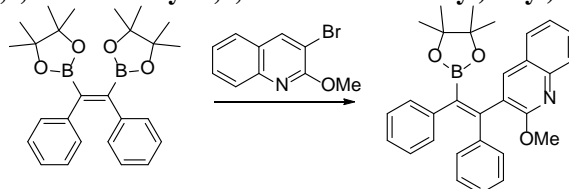
(1:9 EtOAc/petroleum spirits) afforded the title compound as a white solid (274 mg, 0.68 mmol, 68%). The spectroscopic data was in accordance with that reported above (see page S4).

**(Z)-1,2-diphenyl-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethane (17)**<sup>[3]</sup>



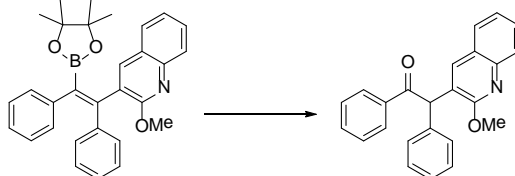
To a degassed solution of diphenylacetylene (1958 mg, 11 mmol) and bis(pinacolato)diboron (2539 mg, 10 mmol) in DMF (10 mL) was added Pt(PPh<sub>3</sub>)<sub>4</sub> (248 mg, 2.0 mol%). The reaction mixture was heated to 80 °C for 24 hours. After this time, the reaction was diluted with Et<sub>2</sub>O (20 mL) and washed with saturated aqueous NH<sub>4</sub>Cl (2 x 10 mL). The organic phase was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Recrystallisation from EtOH afforded the title compound as a white solid (3803 mg, 8.8 mmol, 88%). M.P. = 174.9 – 177.9 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.02 – 7.09 (m, 6H), 6.94 – 6.96 (m, 4H), 1.32 (s, 24H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 141.3, 129.3, 127.4, 125.8, 84.1, 24.9 ppm.

**(E)-3-(1,2-diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-2-methoxyquinoline (18)**



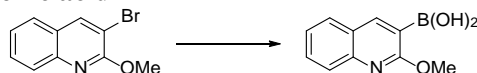
To a microwave reaction vessel under an atmosphere of nitrogen was sequentially added alkenyl bisboronate **17** (432 mg, 1.0 mmol), 3-bromo-2-methoxyquinoline (**9**) (357 mg, 1.5 mmol), K<sub>2</sub>CO<sub>3</sub> (829 mg, 6.0 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (58 mg, 5 mol%), THF (3.5 mL) and H<sub>2</sub>O (0.9 mL, 50 mmol). After stirring for 5 minutes, the reaction mixture was heated at 100 °C for 1 h in a microwave reactor. After this time, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and washed with saturated aqueous NH<sub>4</sub>Cl and brine. The organic layer was separated, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by silica gel column chromatography (1:19 EtOAc/petroleum spirits) afforded the title compound as a white solid (371 mg, 0.8 mmol, 80%). M.P. = 174.8 – 176.1 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.05 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.74 (dd, *J* = 1.2 and 8.0 Hz, 1H), 7.61 (ddd, *J* = 1.5, 7.0 and 8.4, Hz, 1H), 7.39 (ddd, *J* = 1.1, 7.1 and 8.1 Hz, 1H), 6.99 – 7.20 (m, 10H), 3.90 (s, 3H), 0.94 (s, 12H) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 160.8, 147.3, 146.4, 140.8, 140.6, 138.9, 130.1, 129.8, 129.5, 129.3, 128.1, 127.6, 127.4, 127.0, 126.9, 126.2, 125.1, 124.2, 83.7, 53.7, 24.5 ppm; MS (*m/z*) = 464.3 (M+H<sup>+</sup>); HRMS (*m/z*) [C<sub>30</sub>H<sub>30</sub>BNO<sub>3</sub> + H]<sup>+</sup> Calcd. 464.2402, Found 464.2397.

**2-(2-methoxyquinolin-3-yl)-1,2-diphenylethanone (15)**



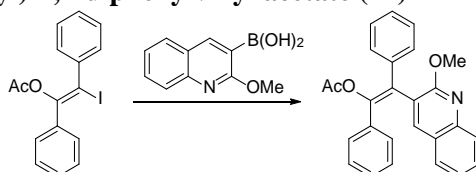
To a stirred solution of vinyl boronate **18** (274 mg, 0.6 mmol) in THF (7.0 mL) and H<sub>2</sub>O (7.0 mL) was added NaBO<sub>3</sub>·4H<sub>2</sub>O (409 mg, 2.7 mmol). The reaction mixture was stirred vigorously for 16 hours at room temperature. After this time, the reaction was quenched by the addition of H<sub>2</sub>O and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by silica gel column chromatography (1:19 EtOAc/petroleum spirits) afforded the title compound as a white solid (170 mg, 0.5 mmol, 81%). The spectroscopic data was in accordance with that reported above (see page S5).

### (2-methoxyquinolin-3-yl)boronic acid<sup>[4]</sup>



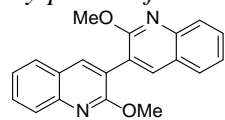
To a solution of 3-bromo-2-methoxyquinoline (2381 mg, 10 mmol) and trimethylborate (2078 mg, 20 mmol) in dry THF at -78 °C was added *n*-butyl lithium dropwise (2.5 M in THF, 4.4 mL, 11 mmol). The reaction mixture was stirred at -78 °C for an additional 2 hours then allowed to slowly warm to 0 °C. The reaction was quenched with a 2M HCl solution, and the pH adjusted to 7 with a solution of NaHCO<sub>3</sub> (2M aqueous). The resulting solution was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Petroleum spirits was then added to precipitate the product as a white solid which was collected by filtration (1706 mg, 8.4 mmol, 84%). M.P. = 152.5 – 154.9 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.65 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.78 (dd, *J* = 1.4 and 8.0 Hz, 1H), 7.67 (ddd, *J* = 1.5, 7.0 and 8.4 Hz, 1H), 7.41 (ddd, *J* = 1.2, 7.0 and 8.0 Hz, 1H), 6.26 (s, 2H), 4.18 (s, 3H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 164.7, 148.7, 147.8, 131.0, 128.3, 127.1, 125.3, 124.5, 53.8 ppm; MS (*m/z*) = 204.1 (M+H<sup>+</sup>).

### (*E*)-2-(2-methoxyquinolin-3-yl)-1,2-diphenylvinyl acetate (**21**)



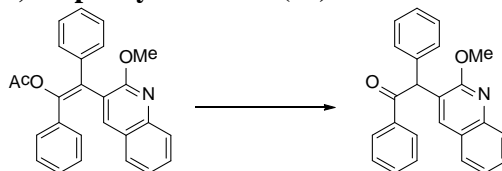
To an oven dried flask under nitrogen was sequentially added Pd(PPh<sub>3</sub>)<sub>4</sub> (58 mg, 5 mol%), (*E*)-2-iodo-1,2-diphenylvinyl acetate<sup>[5]</sup> (364 mg, 1.0 mmol), THF (4 mL) and Cs<sub>2</sub>CO<sub>3</sub> (2.0 equiv., 625 mg in 0.4 mL = 5M aq.). After stirring for 5 minutes, (2-methoxyquinolin-3-yl)boronic acid (**20**) (305 mg, 1.5 mmol) was added and the reaction mixture was stirred for 16 hours at 100 °C. After this time, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and washed with saturated aqueous NH<sub>4</sub>Cl and brine. The organic layer was separated, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by silica gel column chromatography (1:9 EtOAc/petroleum spirits) afforded the title compound as a pale brown solid (336 mg, 0.85 mmol, 85%). M.P. = 150.4 – 151.6 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.73 – 7.75 (m, 2H), 7.50 – 7.54 (m, 2H), 7.19 – 7.28 (m, 8H), 7.08 – 7.10 (m, 3H), 3.77 (s, 3H), 1.99 (s, 3H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 169.7, 160.2, 146.1, 145.7, 140.1, 138.9, 135.9, 129.5, 128.6, 128.3, 128.1, 128.1, 128.1, 127.5, 127.4, 127.0, 126.8, 125.0, 125.0, 124.1, 53.4, 20.9 ppm; MS (*m/z*) = 396.2 (M+H<sup>+</sup>); HRMS (*m/z*) [C<sub>26</sub>H<sub>21</sub>NO<sub>3</sub> + H]<sup>+</sup> Calcd. 396.1594, Found 396.1598.

### By-product from this reaction: 2,2'-dimethoxy-3,3'-biquinoline (**38**)



This compound was isolated from the above reaction as a white solid. M.P. = 146.9 – 149.1 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.02 (s, 2H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.78 (dd, *J* = 1.4 and 8.0 Hz, 2H), 7.67 (ddd, *J* = 1.5, 7.0 and 8.4 Hz, 2H), 7.42 (ddd, *J* = 1.2, 7.0 and 8.0 Hz, 2H), 4.08 (s, 6H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 160.3, 146.4, 138.9, 129.6, 127.5, 127.1, 125.1, 124.2, 122.3, 53.8 ppm; MS (*m/z*) = 317.2 (M+H<sup>+</sup>); HRMS (*m/z*) [C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub> + H]<sup>+</sup> Calcd. 317.1285, Found 317.1294.

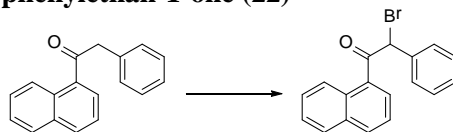
### 2-(2-methoxyquinolin-3-yl)-1,2-diphenylethanone (**15**)



To a solution of enol acetate **21** (791 mg, 2.0 mmol) in methanol (5 mL) was added 2M NaOH (5 mL) and the reaction mixture stirred for 4 hours at room temperature. After this time the volatiles were removed under reduced pressure. The crude product was then dissolved in EtOAc (20 mL) and washed with saturated aqueous NH<sub>4</sub>Cl (10 mL) and brine (10 mL). The organic phase was separated, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by silica gel column chromatography

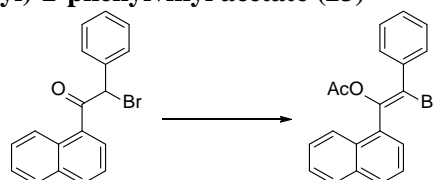
(1:9 EtOAc/petroleum spirits) afforded the title compound as a white solid (685 mg, 1.94 mmol, 97%). The spectroscopic data was in accordance with that reported above (see page S5).

### 2-bromo-(naphthalen-1-yl)-2-phenylethan-1-one (22)



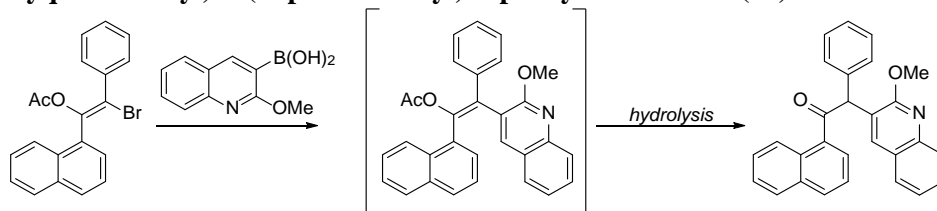
To a solution of ketone **11** (1231 mg, 5.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added a solution of Br<sub>2</sub> (959 mg, 6.0 mmol) in AcOH (30 mL), and the resultant mixture stirred for 16 hours at room temperature. After this time, the volatiles were removed under reduced pressure and purification by silica gel column chromatography (1:1 PhMe/petroleum spirits) afforded the title compound as a clear oil (1384 mg, 4.25 mmol, 85%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.43 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 6.7 Hz, 1H), 7.52 – 7.62 (m, 4H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.30 – 7.39 (m, 3H), 6.39 (s, 1H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 194.6, 135.7, 134.0, 133.9, 133.2, 130.6, 129.23, 129.22, 129.1, 128.5, 128.3, 127.2, 126.8, 125.5, 124.2, 53.9 ppm; MS (*m/z*) = 325.0 (M+H<sup>+</sup>); HRMS (*m/z*) [C<sub>18</sub>H<sub>13</sub>BrO + H]<sup>+</sup> Calcd. 325.0223, Found 325.0216.

### (E)-2-bromo-1-(naphthalen-1-yl)-2-phenylvinyl acetate (23)



To a solution of NaH (240 mg, 60% dispersion in oil, 6.0 mmol) in Et<sub>2</sub>O (5 mL) was added dropwise anhydrous methanol (96 mg, 3.0 mmol) and the resultant mixture stirred for 30 minutes at room temperature. After this time, the reaction mixture was cooled to -10 °C, and a solution of bromoketone **22** (976 mg, 3.0 mmol) in Et<sub>2</sub>O (5 mL) was added dropwise. The reaction mixture was stirred for 30 minutes at -10 °C, after which time acetyl chloride (471 mg, 6.0 mmol) was added and stirring continued for an additional hour. The reaction mixture was filtered and the volatiles removed under reduced pressure. Purification by silica gel column chromatography (1:1 PhMe/petroleum spirits) afforded the title compound as a clear oil (980 mg, 2.67 mmol, 89%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.05 (dd, *J* = 1.0 and 8.7 Hz, 1H), 7.71 – 7.73 (m, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.45 (ddd, *J* = 1.4, 6.8 and 8.4 Hz, 1H), 7.39 (ddd, *J* = 1.4, 6.8 and 8.0 Hz, 1H), 7.34 (dd, *J* = 1.2 and 7.1 Hz, 1H), 7.18 (dd, *J* = 7.1 and 8.2 Hz, 1H), 7.08 – 7.11 (m, 2H), 6.91 – 6.99 (m, 3H), 2.10 (s, 3H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 167.7, 136.9, 133.4, 131.4, 129.9, 129.6, 129.5, 128.42, 128.37, 127.9, 126.7, 126.0, 125.4, 125.1, 117.1, 20.9 ppm; HRMS (*m/z*) [C<sub>20</sub>H<sub>15</sub>BrO<sub>2</sub> + H]<sup>+</sup> Calcd. 389.0148, Found 389.0165.

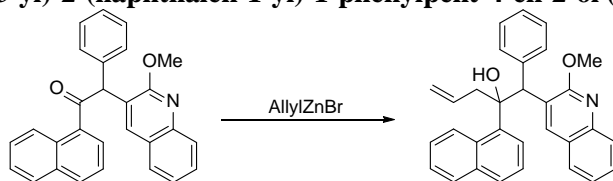
### 2-(2-methoxyquinolin-3-yl)-1-(naphthalen-1-yl)-2-phenylethan-1-one (12)



To an oven dried flask under nitrogen was sequentially added Pd(OAc)<sub>2</sub> (10 mg, 2.5 mol%), XPhos (41 mg, 5.0 mol%), K<sub>3</sub>PO<sub>4</sub> (1081 mg, 5.1 mmol), bromoalkene **23** (624 mg, 1.7 mmol) and PhMe (4 mL). After stirring for 5 minutes, (2-methoxyquinolin-3-yl)boronic acid **20** (694 mg, 3.4 mmol) was added and the reaction mixture was stirred for 48 hours at 110 °C. After this time, the reaction mixture was diluted with EtOAc (10 mL), filtered through a plug of Celite, which was washed with additional EtOAc. The solvent was evaporated and purification by silica gel column chromatography (1% EtOAc in PhMe) afforded the title compound as a white solid (562 mg, 1.39 mmol, 82%). The spectroscopic data was in accordance with that reported above (see page S4).

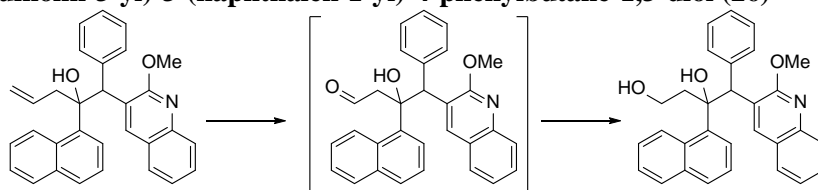


#### 1-(2-methoxyquinolin-3-yl)-2-(naphthalen-1-yl)-1-phenylpent-4-en-2-ol (**24**)



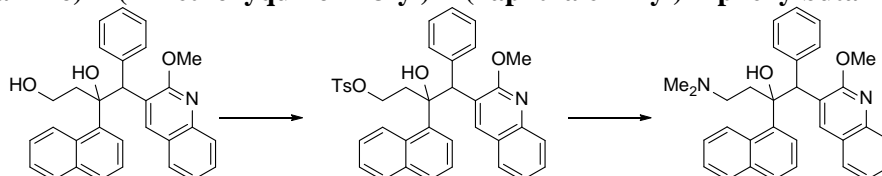
To a freshly prepared solution of allyl zinc bromide<sup>[6]</sup> (15 mmol) in THF (5.0 mL) at 30 °C was added ketone **12** (3026 mg, 7.5 mmol). After stirring for 30 minutes, the reaction was quenched by the addition of aqueous NH<sub>4</sub>Cl (20 mL) and extracted EtOAc (3 x 20 mL). The combined organic phases were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by silica gel column chromatography (1:19 acetone/petroleum spirits) afforded the title compound as a clear oil (3079 mg, 6.91 mmol, 92%). MS (*m/z*) = 446.3 (M+H<sup>+</sup>).

#### 4-(2-methoxyquinolin-3-yl)-3-(naphthalen-1-yl)-4-phenylbutane-1,3-diol (**26**)



A solution containing alkene **24** (3.007 g, 6.75 mmol) and RuCl<sub>3</sub>·H<sub>2</sub>O (67 mg, 5 mol%) in acetonitrile (35 mL, 0.2M) was stirred for 10 minutes. After this time, sodium periodate (3.172 g, 14.85 mmol) was added followed by the portion wise addition of H<sub>2</sub>O (10 x 350 μL over 1 hour). The reaction mixture was stirred for an additional 4 hours, after which time the reaction was quenched by the addition of aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10% w/w). The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic phases dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Subsequently, the aldehyde intermediate **25** [MS (*m/z*) = 448.3 (M+H<sup>+</sup>)] was dissolved in methanol (50 mL) and cooled to 0 °C. Sodium borohydride (511 mg, 13.5 mmol) was added portion wise and the reaction mixture stirred for 16 hours. After this time, the reaction was quenched by the addition of H<sub>2</sub>O and the volatiles removed under reduced pressure. The solution was extracted with EtOAc (3 x 10 mL) and the combined organic fractions washed with aqueous NH<sub>4</sub>Cl and brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by silica gel column chromatography (10→30% acetone/petroleum spirits) afforded the title compound as a white amorphous solid (1732 mg, 3.85 mmol, 57% over 2 steps). MS (*m/z*) = 450.3 (M+H<sup>+</sup>); HRMS (*m/z*) [C<sub>30</sub>H<sub>27</sub>NO<sub>3</sub> + H]<sup>+</sup> Calcd. 450.2064, Found 450.2066.

#### 4-(dimethylamino)-1-(2-methoxyquinolin-3-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (**27**)



To a solution of alcohol **26** (1349 mg, 3.0 mmol) and triethylamine (455 mg, 4.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (857 mg, 4.5 mmol). The resultant solution was allowed to warm to room temperature and stirred for 16 hours. After this time, the reaction was quenched by the addition of aqueous NH<sub>4</sub>Cl (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic fractions were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by silica gel column chromatography (20% acetone/petroleum spirits) afforded the tosylate intermediate as a white amorphous solid (1576 mg, 2.61 mmol, 87%). MS (*m/z*) = 604.3 (M+H<sup>+</sup>). To a solution of tosylate (1207 mg, 2.0 mmol) in THF (2.0 mL) was added dimethylamine (2M in THF, 2.0 mL, 4.0 mmol) and the reaction mixture heated to 60 °C for 16 hours. After this time, the volatiles were removed under reduced pressure and purification by silica gel column chromatography (0.1% NH<sub>4</sub>OH: 1.0% MeOH: 98.9% CH<sub>2</sub>Cl<sub>2</sub>) afforded the title compound as a clear oil (934 mg, 1.96 mmol, 98%). MS (*m/z*) = 477.3 (M+H<sup>+</sup>). HRMS (*m/z*) [C<sub>32</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub> + H]<sup>+</sup> Calcd. 477.2537, Found 477.2540.

The diastereoisomeric pairs were subsequently separated by preparative HPLC using an Agilent 1260 infinity HPLC system fitted with a Phenomenex Luna C8(2) column running a gradient of 30% MeCN/H<sub>2</sub>O (0.1% TFA) to 100% MeCN (100%). Run time = 15 min, *t<sub>R</sub>* = ~11-12 min.

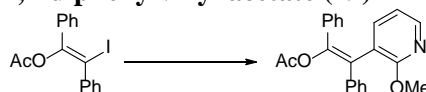
**Isomer A (27a):** Assigned as the *RR* & *SS* diastereoisomer by analogy.<sup>[6]</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.64 (s, 1H), 8.49 (d, *J* = 8.8 Hz, 1H), 8.03 (dd, *J* = 1.0 and 7.4 Hz, 1H), 7.84 (d, *J* = 7.4 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.60 (m, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.36 – 7.41 (m, 3H), 7.21 – 7.30 (m, 3H), 5.77 (s, 1H), 3.34 (s, 3H), 2.70 (brs, 1H), 2.27 – 2.33 (m, 2H), 2.16 (brs, 6H), 1.97 – 2.00 (m, 1H) ppm.

**Isomer B (27b):** Assigned as the *RS* & *SR* diastereoisomer by analogy.<sup>[6]</sup>

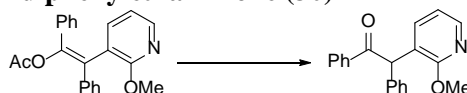
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.97 (s, 1H), 8.66 (d, *J* = 8.0 Hz, 1H), 7.82 – 7.93 (m, 4H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.63 (m, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.39 (ddd, *J* = 1.2, 7.0 and 8.0 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.15 – 7.17 (m, 2H), 6.88 – 6.91 (m, 3H), 5.93 (s, 1H), 4.24 (s, 3H), 2.57 (d, *J* = 12.8 Hz, 1H), 1.92 – 2.20 (m, 9H) ppm.

**(*E*)-2-(2-methoxyppyridin-3-yl)-1,2-diphenylvinyl acetate (29)**



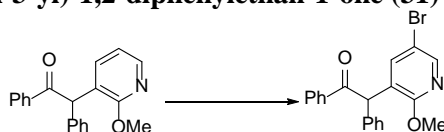
A solution containing iodoalkene **19** (5460 mg, 15 mmol), 2-methoxyppyridine-3-boronic acid (3441 mg, 22.5 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (870 mg, 5 mol%) and Cs<sub>2</sub>CO<sub>3</sub> (30 mmol, 5M aqueous solution, 9750 mg in 6 mL H<sub>2</sub>O) in THF (20 mL) was heated to 70 °C for 16 hours. After this time, the solution was cooled to room temperature, diluted with H<sub>2</sub>O (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over MgSO<sub>4</sub>, filtered and the solvent removed under reduced pressure. Purification by column chromatography (1:19 EtOAc/Pet. Sp.) afforded the title product as pale yellow solid (3730 mg, 10.8 mmol, 72%). M.P. = 113.9 – 116.4 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.95 (dd, *J* = 2.0 and 5.0 Hz, 1H), 7.27 (dd, *J* = 1.9 and 7.3 Hz, 1H), 7.08 – 7.25 (m, 10H), 6.66 (dd, *J* = 5.0 and 7.3 Hz, 1H), 3.58 (s, 3H), 1.94 (s, 3H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 169.8, 161.5, 146.2, 145.3, 140.6, 138.8, 135.9, 128.5, 128.3, 128.2, 128.1, 127.9, 127.4, 126.9, 53.2, 20.9 ppm; MS (*m/z*) = 345.2 (M+H<sup>+</sup>); HRMS (*m/z*) [C<sub>22</sub>H<sub>19</sub>NO<sub>3</sub> + H]<sup>+</sup> Calcd. 346.1438, Found 346.1444.

**2-(2-methoxyppyridin-3-yl)-1,2-diphenylethan-1-one (30)**



To a round bottom flask containing enol acetate **29** (3454 mg, 10 mmol) in methanol (10 mL) was added 2M aqueous NaOH (10 mL, 20 mmol) and the resultant solution stirred at room temperature for 4 hours. After this time, the volatiles were removed under reduced pressure and the reaction mixture diluted with 1M aqueous HCl (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic fractions were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by column chromatography (1:9 EtOAc/Pet. Sp.) afforded the title compound as a clear oil (2700 mg, 8.9 mmol, 89%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 7.99 (dd, *J* = 1.8 Hz, 1H), 7.92 – 7.94 (m, 2H), 7.43 (tt, *J* = 1.3 and 6.6 Hz, 1H), 7.18 – 7.36 (m, 7H), 7.10 (ddd, *J* = 0.7, 1.8 and 7.4 Hz, 1H), 6.73 (dd, *J* = 5.0 and 7.4 Hz, 1H), 6.16 (s, 1H), 3.82 (s, 3H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 198.0, 161.0, 145.3, 138.2, 136.8, 136.6, 132.9, 129.6, 129.1, 128.8, 128.6, 127.5, 123.3, 116.8, 53.6, 52.9 ppm; MS (*m/z*) = 304.2 (M+H<sup>+</sup>); HRMS (*m/z*) [C<sub>20</sub>H<sub>17</sub>NO<sub>2</sub> + H]<sup>+</sup> Calcd. 304.1332, Found 304.1332.

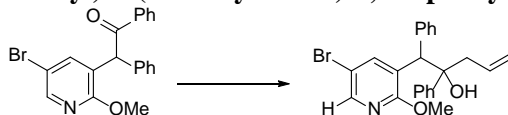
**2-(5-bromo-2-methoxyppyridin-3-yl)-1,2-diphenylethan-1-one (31)**



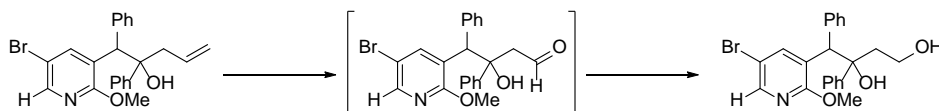
To a solution of pyridine **29** (1517 mg, 5 mmol) in MeCN (20 mL) was added *N*-bromosuccinimide (1068 mg, 6 mmol), and the reaction stirred at 80 °C for 16 hours. After this time, the solvent was

evaporated under reduced pressure, and the residue purified by silica gel flash chromatography (1:19 EtOAc/Pet. Sp.) to afford the title compound as a clear oil (1663 mg, 4.35 mmol, 87%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.00 (d, *J* = 2.2 Hz, 1H), 7.89 – 7.91 (m, 2H), 7.41 (tt, *J* = 1.3 and 7.4 Hz, 1H), 7.26 – 7.34 (m, 4H), 7.19 – 7.23 (m, 3H), 7.14 (dd, *J* = 0.8 and 2.4 Hz, 1H), 6.10 (s, 1H), 3.77 (s, 3H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 197.3, 159.9, 145.9, 140.7, 136.6, 135.8, 133.1, 129.5, 129.4, 128.8, 128.6, 127.9, 125.4, 112.0, 24.0, 52.9 ppm; MS (*m/z*) = 382.0, 384.0 (M+H<sup>+</sup>); HRMS (*m/z*) [C<sub>20</sub>H<sub>16</sub>BrNO<sub>2</sub> + H]<sup>+</sup> Calcd. 382.0437, Found 382.0443, Calcd. 384.0419, Found 384.0427.

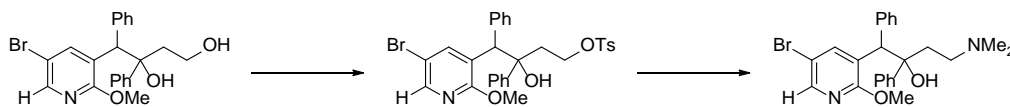
### 1-(5-bromo-2-methoxypyridin-3-yl)-4-(dimethylamino)-1,2-diphenylbutan-2-ol (**32**)



To a freshly prepared solution of allyl zinc bromide<sup>[6]</sup> (10 mmol) in THF (5.0 mL) at 30 °C was added ketone **31** (1911 mg, 5.0 mmol). After stirring for 30 minutes, the reaction was quenched by the addition of aqueous NH<sub>4</sub>Cl (10 mL) and extracted EtOAc (3 x 10 mL). The combined organic phases were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by silica gel column chromatography (1:19 acetone/petroleum spirits) afforded 1-(5-bromo-2-methoxypyridin-3-yl)-1,2-diphenylpent-4-en-2-ol as a clear oil (1888 mg, 4.45 mmol, 89%, d.r. 1:1). MS (*m/z*) = 424.0, 426.0 (M+H<sup>+</sup>).



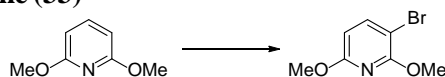
A solution containing 1-(5-bromo-2-methoxypyridin-3-yl)-1,2-diphenylpent-4-en-2-ol (1697 mg, 4.0 mmol) and RuCl<sub>3</sub>·H<sub>2</sub>O (42 mg, 5 mol%) in acetonitrile (20 mL, 0.2M) was stirred for 10 minutes. After this time, sodium periodate (1865 g, 8.8 mmol) was added followed by the portion wise addition of H<sub>2</sub>O (10 x 200 μL over 1 h). The reaction mixture was stirred for an additional 4 hours, after which time the reaction was quenched by the addition of aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10% w/w). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic phases dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Subsequently, the aldehyde intermediate [MS (*m/z*) = 426.1, 428.1 (M+H<sup>+</sup>)] was dissolved in methanol (20 mL) and cooled to 0 °C. Sodium borohydride (303 mg, 8.0 mmol) was added portion wise and the reaction mixture stirred for 16 hours. After this time, the reaction was quenched by the addition of H<sub>2</sub>O and the volatiles removed under reduced pressure. The solution was extracted with EtOAc (3 x 10 mL) and the combined organic fractions washed with aqueous NH<sub>4</sub>Cl and brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by silica gel column chromatography (10→30% acetone/petroleum spirits) afforded 4-(5-bromo-2-methoxypyridin-3-yl)-3,4-diphenylbutane-1,3-diol as a white amorphous solid (1709 mg, 2.52 mmol, 63% over 2 steps). MS (*m/z*) = 428.0, 430.0 (M+H<sup>+</sup>).



To a solution of 4-(5-bromo-2-methoxypyridin-3-yl)-3,4-diphenylbutane-1,3-diol (1500 mg, 3.52 mmol) and triethylamine (534 mg, 5.28 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (1030 mg, 5.28 mmol). The resultant solution was allowed to warm to room temperature and stirred for 16 hours. After this time, the reaction was quenched by the addition of aqueous NH<sub>4</sub>Cl (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic fractions were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by silica gel column chromatography (20% acetone/petroleum spirits) afforded the tosylate intermediate as a white amorphous solid (1910 mg, 3.28 mmol, 92%). MS (*m/z*) = 582.1, 584.1 (M+H<sup>+</sup>). To a solution of tosylate (1748 mg, 3.0 mmol) in THF (3.0 mL) was added dimethylamine (2M in THF, 3.0 mL, 6.0 mmol) and the reaction mixture heated to 60 °C for 16 hours. After this time, the volatiles were removed under reduced pressure and purification by silica gel column chromatography (0.1% NH<sub>4</sub>OH: 1.0% MeOH: 98.9% CH<sub>2</sub>Cl<sub>2</sub>) afforded the title compound **32** as a clear oil (1275 mg, 2.80 mmol, 95%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.64 (d, *J* = 2.5 Hz,

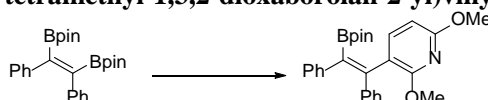
0.5H), 8.40 (d,  $J = 2.4$  Hz, 0.5H), 7.99 (d,  $J = 2.5$  Hz, 0.5H), 7.93 (brs, 0.5H), 7.69 (d,  $J = 2.5$  Hz, 0.5H), 7.61 (d,  $J = 7.2$  Hz, 1H), 7.38 (d,  $J = 7.4$  Hz, 1H), 7.32 (d,  $J = 7.4$  Hz, 1H), 7.23 (t,  $J = 7.2$  Hz, 1H), 7.12 – 7.17 (m, 3H), 7.01 (t,  $J = 7.3$  Hz, 1H), 6.87 – 6.94 (m, 1.5H), 4.65 (s, 0.5H), 4.57 (s, 0.5H), 3.86 (s, 1.5H), 3.56 (s, 1.5H), 2.07 – 2.17 (m, 1H), 1.99 (s, 3H), 1.94 – 1.98 (m, 2H), 1.91 (s, 3H), 1.87 – 1.89 (m, 0.5H), 1.62 – 1.67 (m, 0.5H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta = 160.8, 159.9, 146.8, 146.6, 144.7, 144.1, 141.9, 141.4, 140.8, 140.2, 130.8, 130.1, 127.9, 127.7, 127.6, 127.4, 127.3, 126.5, 126.1, 126.0, 125.9, 125.8, 112.0, 111.6, 81.6, 80.9, 56.0, 55.9, 54.0, 53.6, 52.6, 52.2, 44.7, 35.7, 34.9$  ppm; MS ( $m/z$ ) = 455.1, 457.1 ( $\text{M}+\text{H}^+$ ); HRMS ( $m/z$ ) [ $\text{C}_{24}\text{H}_{27}\text{BrN}_2\text{O}_2 + \text{H}$ ] $^+$  Calcd. 455.1329, Found 455.1336.

### 3-bromo-2,6-dimethoxypyridine (33)



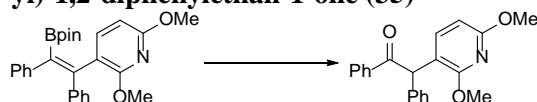
To a solution of 2,6-dimethoxypyridine (6.96 g, 50 mmol) in MeCN (100 mL) was added *N*-bromosuccinimide (8.90 g, 50 mmol), and the reaction stirred at 80 °C for 18 hours. After this time, the solvent was evaporated under reduced pressure, and the residue purified by silica gel flash chromatography (0-6% EtO<sub>2</sub> in Pet. Sp.) to afford the title compound as a pale yellow oil (10.55 g, 48.4 mmol, 97%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.62$  (d,  $J = 8.3$  Hz, 1H), 6.22 (d,  $J = 8.3$  Hz, 1H), 3.99 (s, 3H), 3.89 (s, 3H) ppm;  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta = 162.2, 158.6, 143.8, 102.8, 95.5, 54.4, 53.9$  ppm; MS ( $m/z$ ) = 218.0 ( $\text{M}+\text{H}^+$ ).

### (*E*)-3-(1,2-diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-2,6-dimethoxypyridine (34)



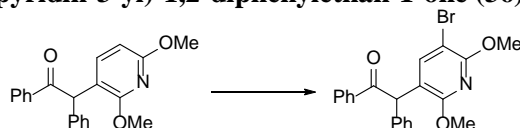
To a microwave reaction vessel under nitrogen was sequentially added 3-bromo-2,6-dimethoxypyridine (1.36 g, 6.25 mmol), bisboronate **17** (2.16 g, 5 mmol),  $\text{K}_2\text{CO}_3$  (4.15 g, 30 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (0.289 g, 5 mol%), THF (15 mL) and water (4.5 mL, 250 mmol). After stirring for 5 minutes, the reaction mixture was heated at 100 °C for 1 hour in a microwave reactor. After this time, the reaction mixture was cooled to room temperature, diluted with EtOAc (30 mL), washed with saturated aqueous  $\text{NH}_4\text{Cl}$  and the aqueous layer extracted with EtOAc (30 mL  $\times$  3). The combined organic layers were washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by silica gel flash chromatography (0-20% EtOAc in Pet. Sp.) afforded the title compound as a white solid (1.44 g, 3.24 mmol, 77%). M.P. = 114.9 – 116.9 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.50$  (d,  $J = 7.9$  Hz, 1H), 7.18 – 6.92 (m, 10H), 6.30 (d,  $J = 7.9$  Hz, 1H), 3.92 (s,  $J = 5.2$  Hz, 3H), 3.79 (s, 3H), 1.07 (s,  $J = 10.8$  Hz, 12H) ppm;  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta = 162.7, 160.4, 146.8, 142.9, 141.6, 141.2, 130.1, 129.8, 128.0, 127.5, 126.6, 125.9, 119.1, 99.8, 83.6, 53.7, 53.6, 24.7$  ppm; MS ( $m/z$ ) = 444.3 ( $\text{M}+\text{H}^+$ ); HRMS ( $m/z$ ) = [ $\text{C}_{27}\text{H}_{30}\text{BNO}_4 + \text{H}$ ] $^+$  Calcd. 444.2345, Found 444.2346.

### 2-(2,6-dimethoxypyridin-3-yl)-1,2-diphenylethan-1-one (35)



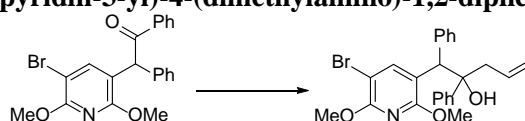
To a solution containing **33** (1.42 g, 3.24 mmol) in THF (25 mL) and water (25 mL) was added sodium perborate tetrahydrate (2.24 g, 14.58 mmol). The reaction mixture was stirred vigorously at room temperature for 16 hours. After this time, the reaction was quenched with water and extracted with EtOAc (100 mL  $\times$  3). The combined organic layers were washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by silica gel flash chromatography (5% EtO<sub>2</sub> in Pet. Sp.) afforded the title compound as a white solid (0.97 g, 2.92 mmol, 90%). M.P. = 91.1 – 93.6 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 8.04$  – 7.95 (m, 2H), 7.53 – 7.48 (m, 1H), 7.44 – 7.37 (m, 2H), 7.37 – 7.23 (m, 5H), 7.18 (d,  $J = 8.1$  Hz, 1H), 6.23 (d,  $J = 8.1$  Hz, 1H), 6.19 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H) ppm;  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta = 198.7, 162.3, 159.5, 141.1, 137.8, 137.0, 133.0, 129.5, 129.0, 128.9, 128.7, 127.4, 113.7, 100.6, 53.71, 53.67, 52.0$  ppm; MS ( $m/z$ ) = 334.2 ( $\text{M}+\text{H}^+$ ); HRMS ( $m/z$ ) = [ $\text{C}_{21}\text{H}_{19}\text{NO}_3 + \text{H}$ ] $^+$  Calcd. 334.1438, found 334.1440.

## 2-(5-bromo-2,6-dimethoxy-pyridin-3-yl)-1,2-diphenylethan-1-one (36)

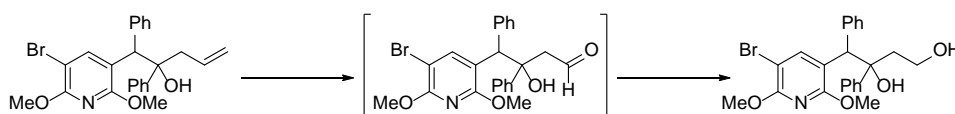


To a solution of **34** (1.32 g, 3.96 mmol) in MeCN (35 mL) was added *N*-bromosuccinimide (0.775 g, 4.36 mmol). The resulting mixture was stirred at 80 °C for 16 hours. After this time, the solvent was evaporated under reduced pressure, and the residue purified by silica gel flash chromatography (5% EtOAc in Pet. Sp.) to afford the title compound as a white solid upon standing (1.53 g, 3.71 mmol, 94%). M.P. = 127.1 – 129.1 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.00 (d, *J* = 7.4 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 – 7.27 (m, 8H), 6.15 (s, 1H), 3.98 (s, 3H), 3.90 (s, 3H) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 198.1, 158.5, 157.6, 143.7, 136.9, 136.8, 133.1, 129.4, 129.3, 128.9, 128.7, 127.7, 115.7, 95.5, 54.5, 54.1, 52.0 ppm; MS (*m/z*) = 412.1 (M+H<sup>+</sup>); HRMS (*m/z*) [C<sub>21</sub>H<sub>18</sub>BrNO<sub>3</sub> + H]<sup>+</sup> Calcd. 412.0546, Found 412.0549.

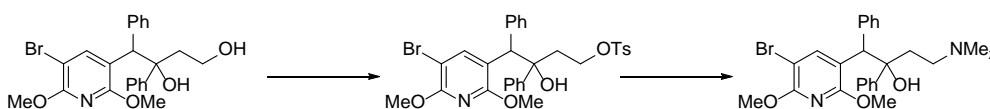
## 1-(5-bromo-2,6-dimethoxy-pyridin-3-yl)-4-(dimethylamino)-1,2-diphenylbutan-2-ol (37)



To a freshly prepared solution of allyl zinc bromide<sup>[6]</sup> (3.0 mmol) in THF (3.0 mL) at 30 °C was added ketone **36** (825 mg, 2.0 mmol). After stirring for 30 minutes, the reaction was quenched by the addition of aqueous NH<sub>4</sub>Cl (10 mL) and extracted EtOAc (3 x 20 mL). The combined organic phases were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by silica gel column chromatography (1:19 acetone/petroleum spirits) afforded 1-(5-bromo-2,6-dimethoxy-pyridin-3-yl)-1,2-diphenylpent-4-en-2-ol as an off white solid (886 mg, 1.95 mmol, 98%). M.P. 133.5 – 136.2 °C; MS (*m/z*) = 454.1 (M+H<sup>+</sup>); HRMS (*m/z*) [C<sub>24</sub>H<sub>24</sub>BrNO<sub>3</sub> + H]<sup>+</sup> Calcd. 454.1012, Found 454.1016.



A solution containing 1-(5-bromo-2,6-dimethoxy-pyridin-3-yl)-1,2-diphenylpent-4-en-2-ol (5.21 g, 11.5 mmol) and RuCl<sub>3</sub>·H<sub>2</sub>O (95 mg, 4 mol%) in acetonitrile (60 mL, ~0.2M) was stirred for 10 minutes. After this time, sodium periodate (5.4g, 25.3 mmol) was added followed by the portion wise addition of H<sub>2</sub>O (10 x 600 μL over 1 h). The reaction mixture was stirred for an additional 14 hours, after which time the reaction was quenched by the addition of aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10% w/w). The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic phases dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Subsequently, the aldehyde intermediate [MS (*m/z*) = 456.1 (M+H<sup>+</sup>)] was dissolved in methanol (60 mL) and cooled to 0 °C. Sodium borohydride (867 mg, 23 mmol) was added portion wise and the reaction mixture stirred for 16 hours. After this time, the reaction was quenched by the addition of H<sub>2</sub>O and the volatiles removed under reduced pressure. The solution was extracted with EtOAc (3 x 10 mL) and the combined organic fractions washed with aqueous NH<sub>4</sub>Cl and brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by silica gel column chromatography (10→30% acetone/petroleum spirits) afforded 4-(5-bromo-2,6-dimethoxy-pyridin-3-yl)-3,4-diphenylbutane-1,3-diol as an off-white amorphous solid (2.88 g, 6.28 mmol, 55% over 2 steps). MS (*m/z*) = 458.1 (M+H<sup>+</sup>); HRMS (*m/z*) [C<sub>23</sub>H<sub>24</sub>BrNO<sub>4</sub> + H]<sup>+</sup> Calcd. 458.0961, Found 458.0958.



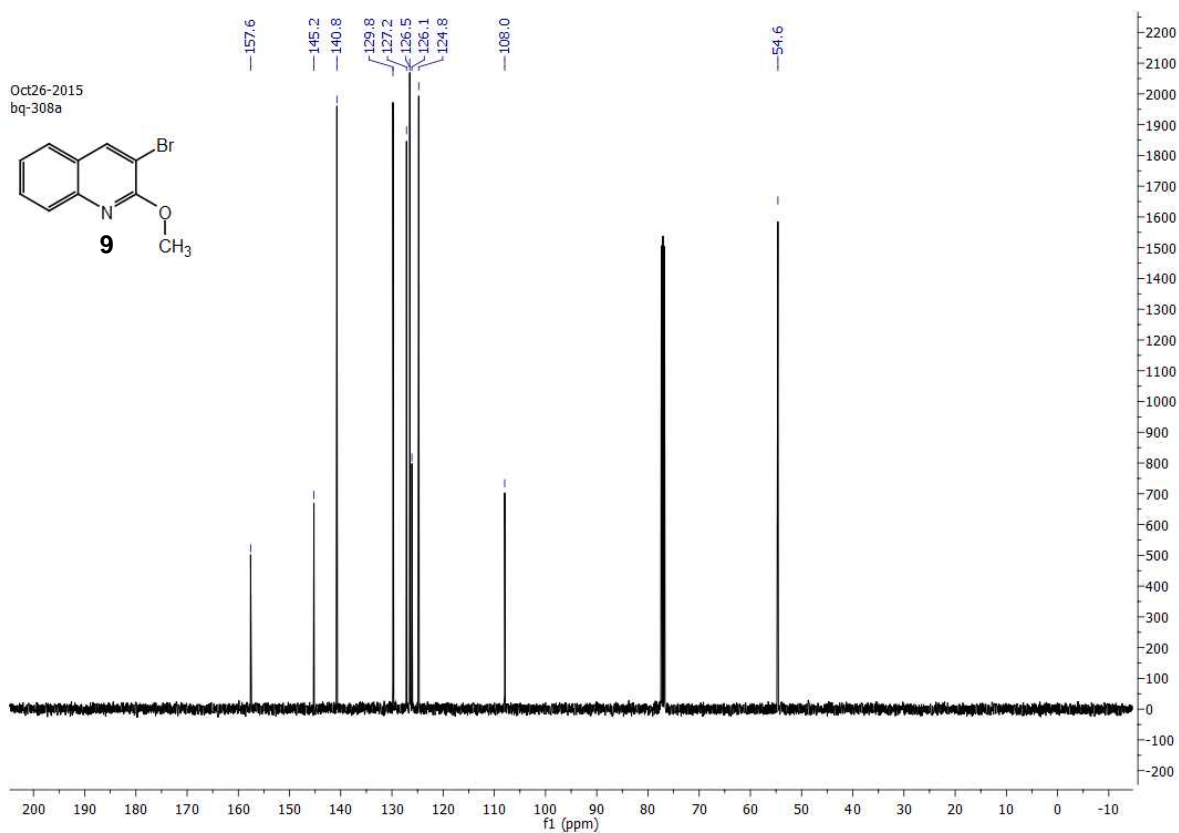
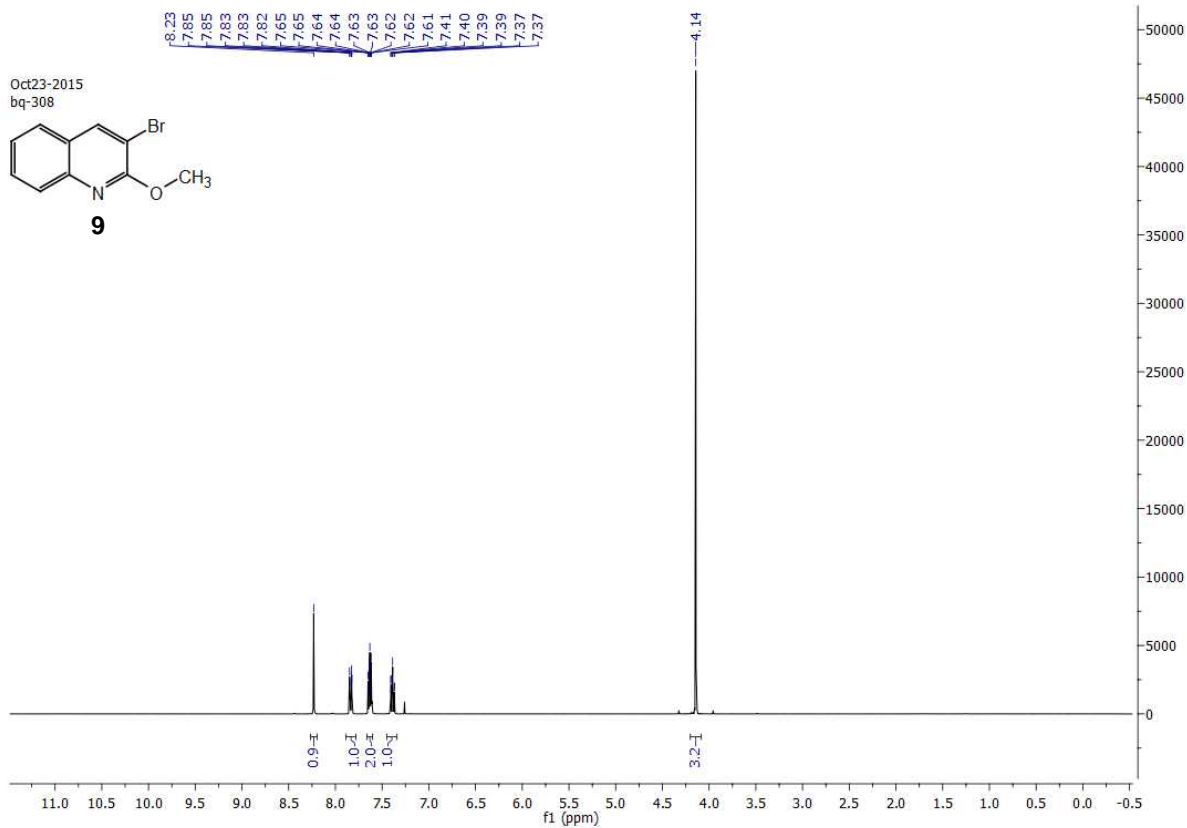
To a solution of 4-(5-bromo-2,6-dimethoxy-pyridin-3-yl)-3,4-diphenylbutane-1,3-diol (2.75 g, 6.0 mmol) and triethylamine (1214 mg, 12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at 0 °C was added *p*-toluenesulfonyl chloride (2340 mg, 12 mmol). The resultant solution was allowed to warm to room temperature and stirred for 16 hours. After this time, the reaction was quenched by the addition of aqueous NH<sub>4</sub>Cl (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic fractions were dried over MgSO<sub>4</sub>

and concentrated under reduced pressure. Purification by silica gel column chromatography (20% acetone/petroleum spirits) afforded the tosylate intermediate as a white amorphous solid (3.08 g, 5.03 mmol, 84%). MS ( $m/z$ ) = 612.1 (M+H<sup>+</sup>). To a solution of tosylate (3.08g, 5.0 mmol) in THF (2.0 mL) was added dimethylamine (2M in THF, 5.0 mL, 10.0 mmol) and the reaction mixture heated to 60 °C for 16 h. After this time, the volatiles were removed under reduced pressure and purification by silica gel column chromatography (0.1% NH<sub>4</sub>OH: 1.0% MeOH: 98.9% CH<sub>2</sub>Cl<sub>2</sub>) afforded the title compound **37** as an off-white amorphous solid (2.07 g, 4.26 mmol, 85%, d.r. ~1:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.74 (s, 0.5H), 8.49 (s, 0.5H), 7.66 – 7.68 (m, 1H), 7.48 (d,  $J$  = 7.6 Hz, 1H), 7.38 – 7.40 (m, 1H), 7.31 (t,  $J$  = 7.2 Hz, 1H), 7.14 – 7.24 (m, 4H), 7.07 – 7.12 (m, 1H), 6.92 – 7.02 (m, 1H), 4.65 (s, 0.5H), 4.57 (s, 0.5H), 3.98 (s, 1.5H), 3.95 (s, 1.5H), 3.79 (s, 1.5H), 3.65 (s, 1.5H), 2.18 – 2.28 (m, 1.5H), 2.05 – 2.10 (m, 3.5H), 1.94 – 2.03 (4H), 1.68 – 1.73 (m, 0.5H), 1.57 – 1.62 (m, 0.5H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 159.4, 158.5, 156.5, 155.9, 147.2, 147.1, 145.1, 144.6, 141.9, 141.1, 130.8, 130.1, 127.9, 127.72, 127.66, 127.4, 126.4, 126.3, 126.1, 126.0, 125.7, 118.3, 118.2, 95.5, 94.9, 81.8, 81.2, 56.2, 56.1, 54.2, 54.0, 53.9, 53.6, 52.2, 51.8, 44.9, 35.9, 35.1 ppm; MS ( $m/z$ ) = 484.8 (M+H<sup>+</sup>). HRMS ( $m/z$ ) [C<sub>25</sub>H<sub>29</sub>BrN<sub>2</sub>O<sub>3</sub> + H]<sup>+</sup> Calcd. 485.1434, Found 485.1448.

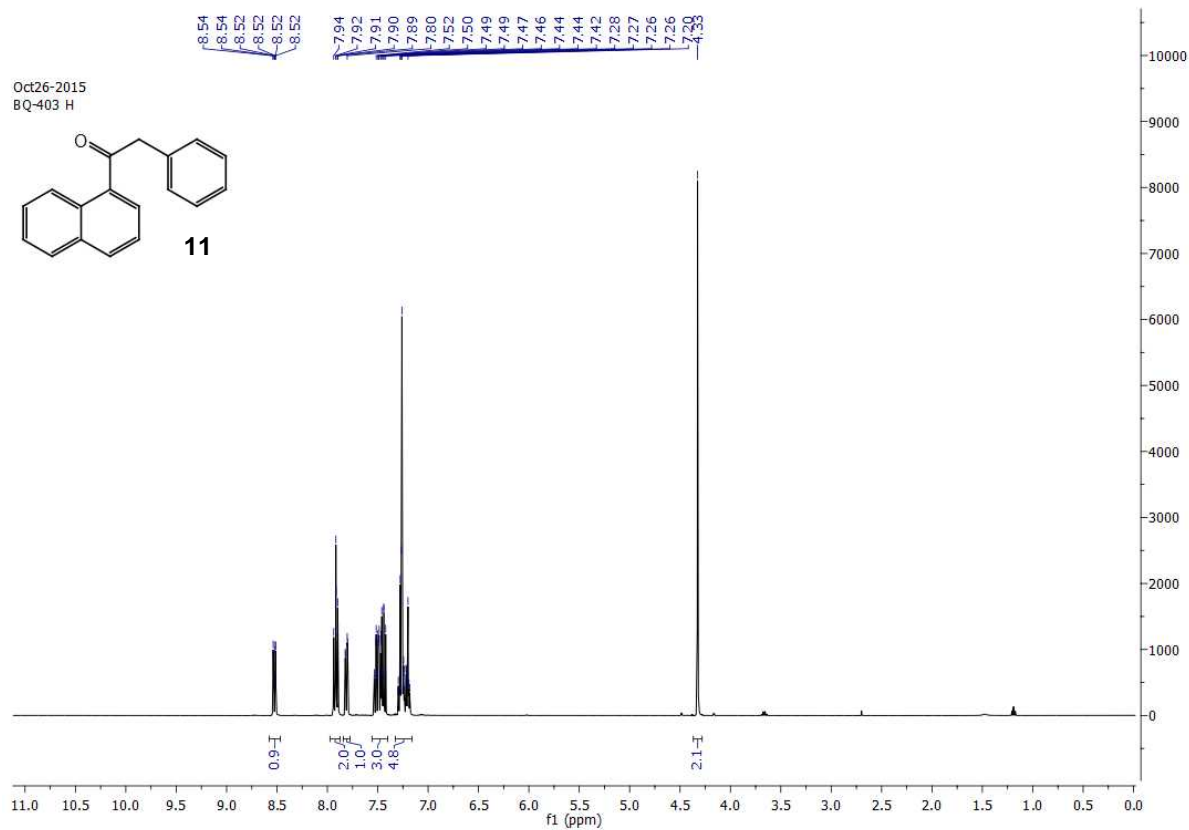
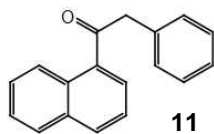
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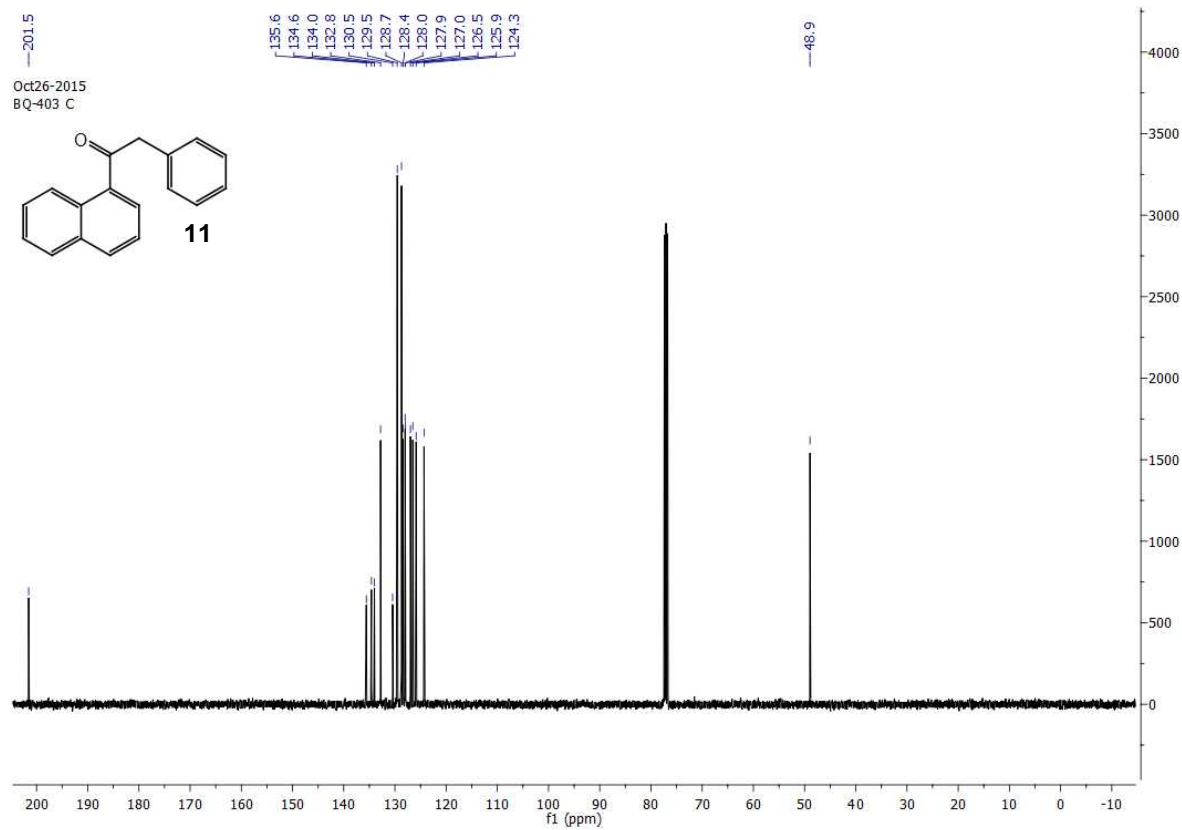
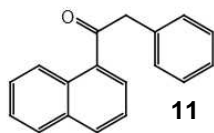
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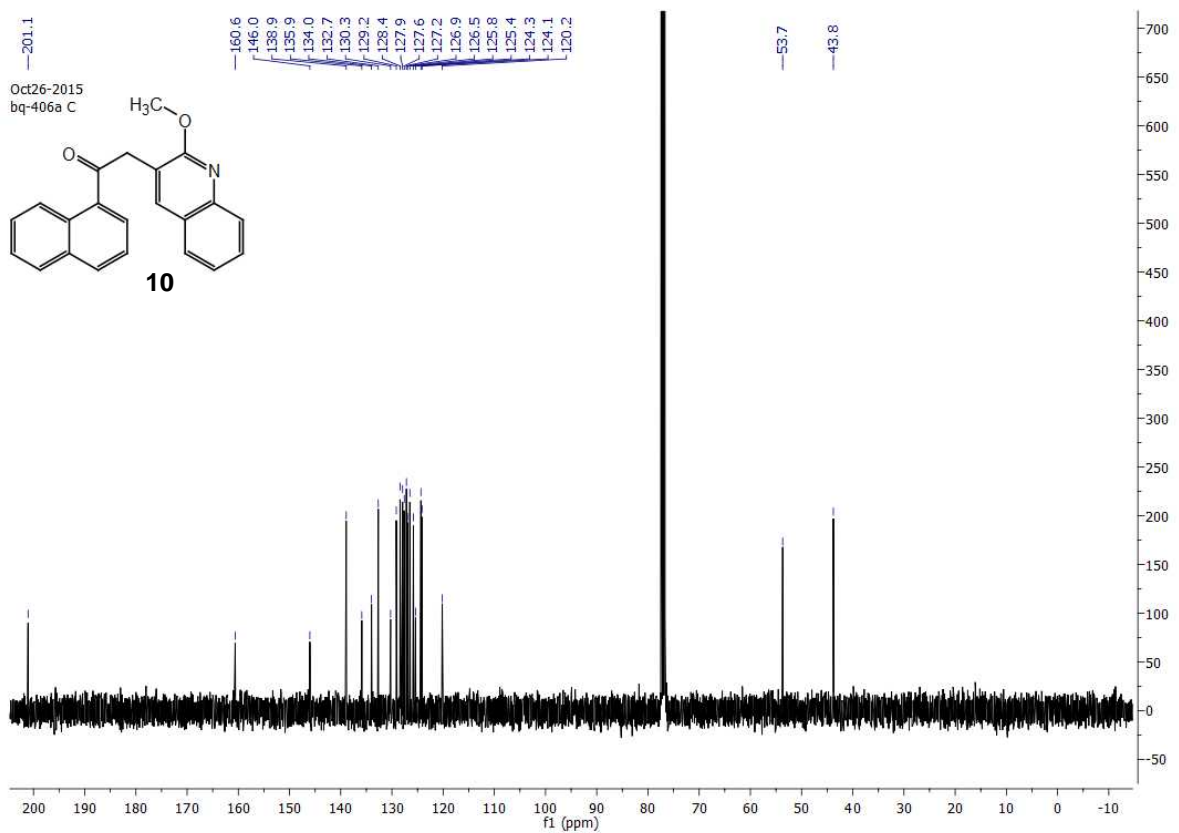
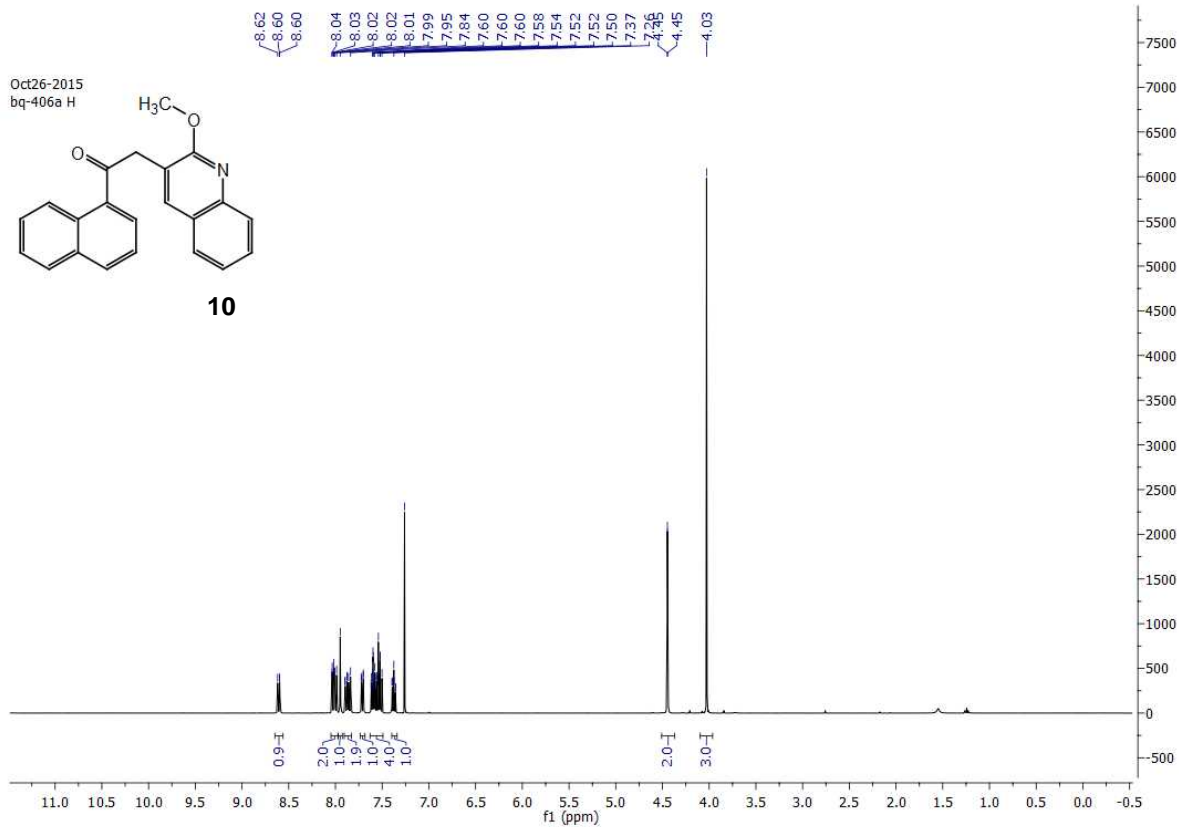
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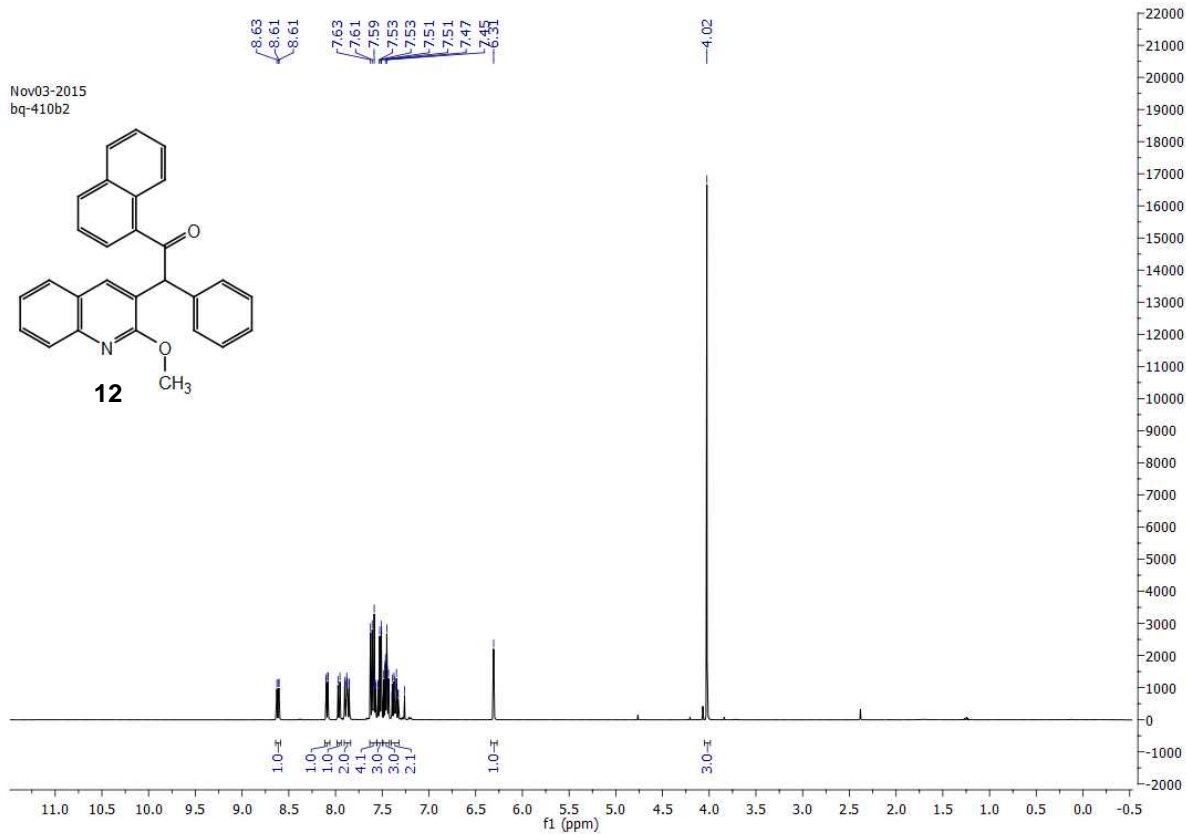
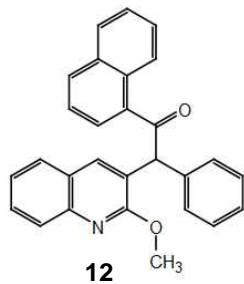
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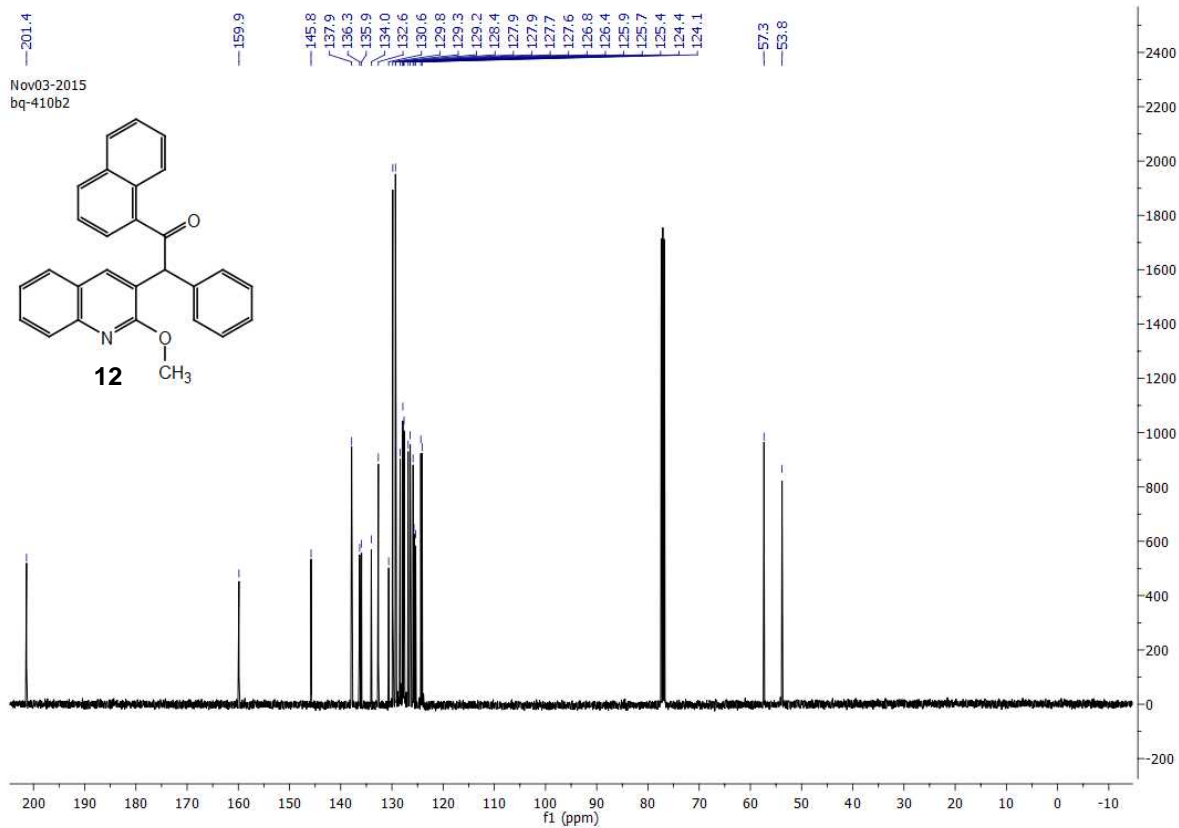
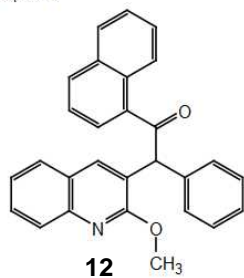




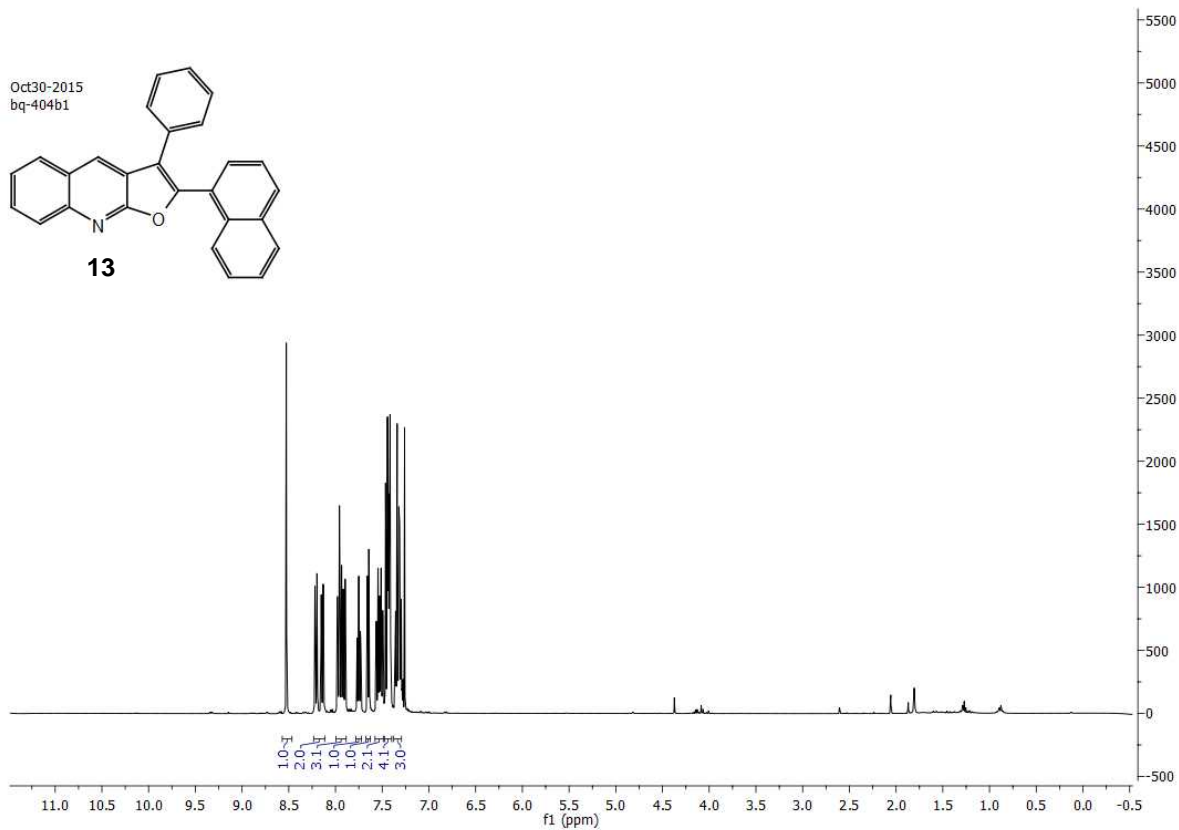
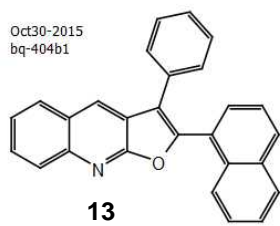
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bq-410b2



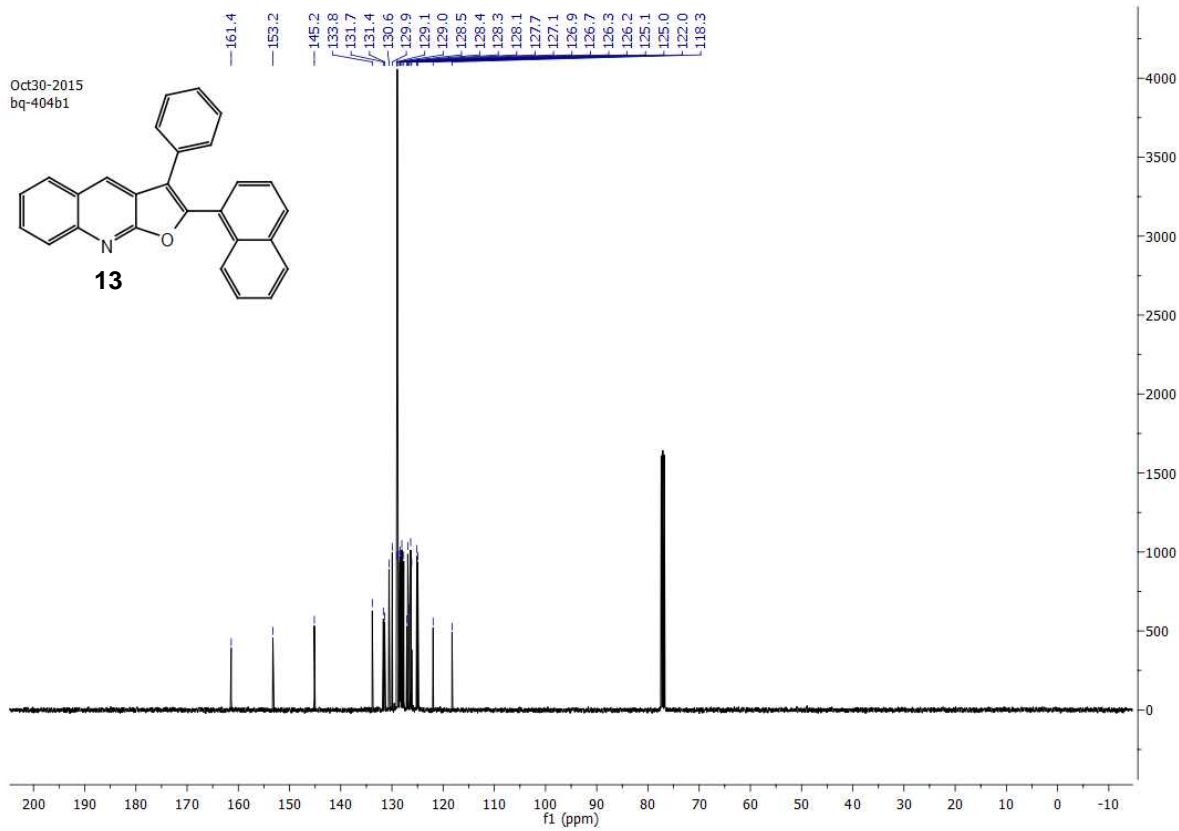
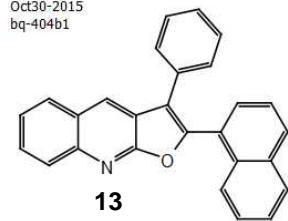
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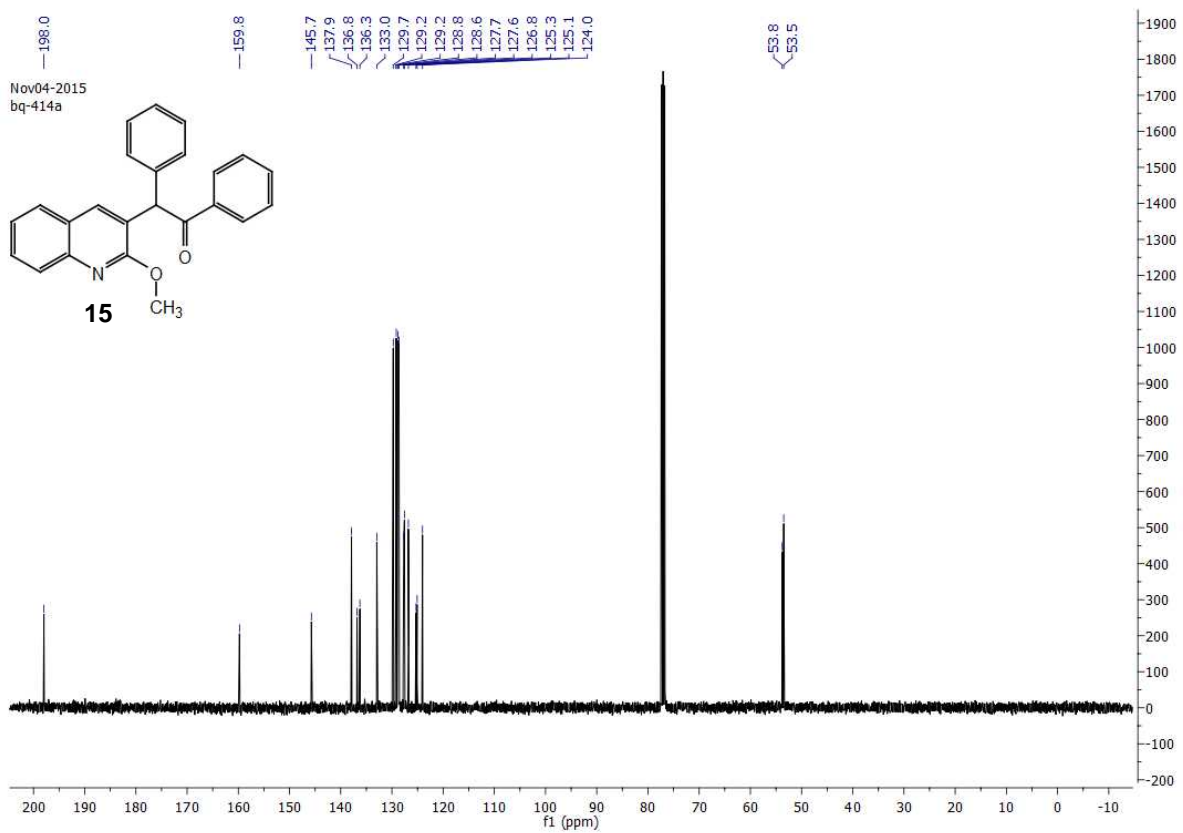
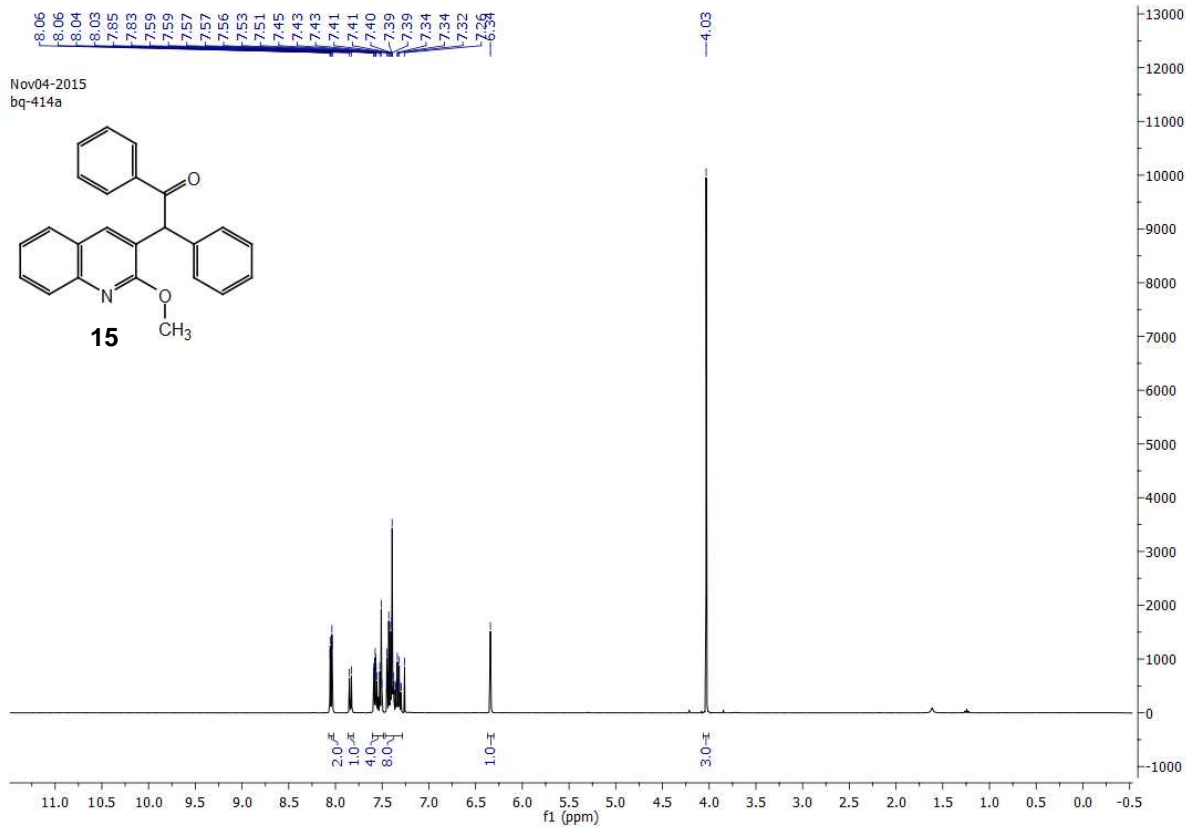


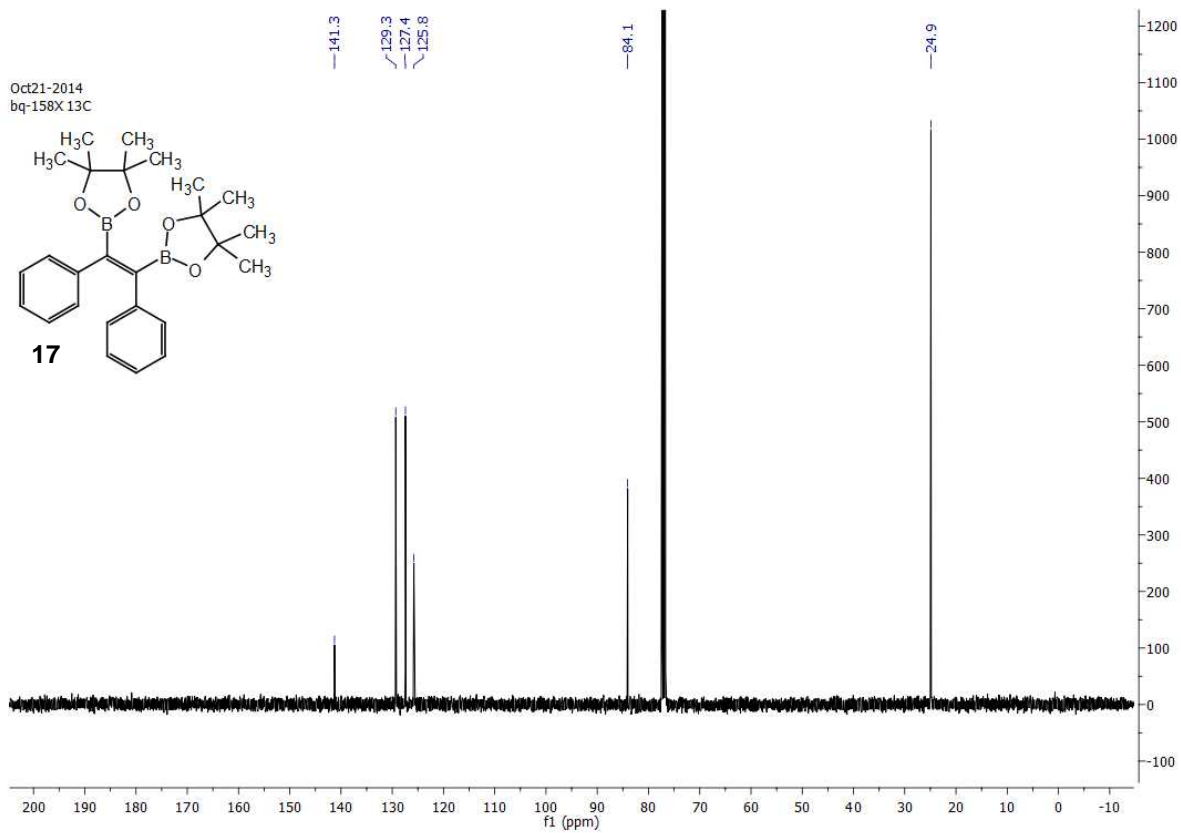
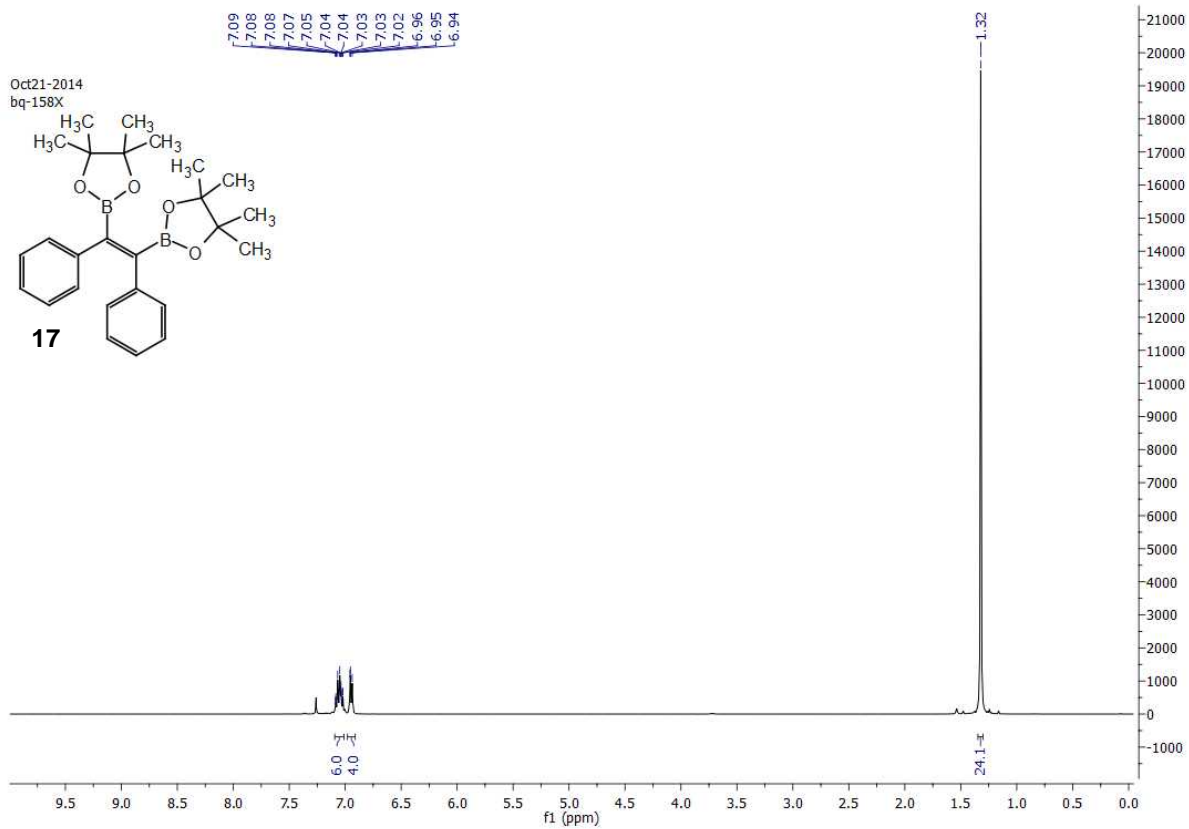
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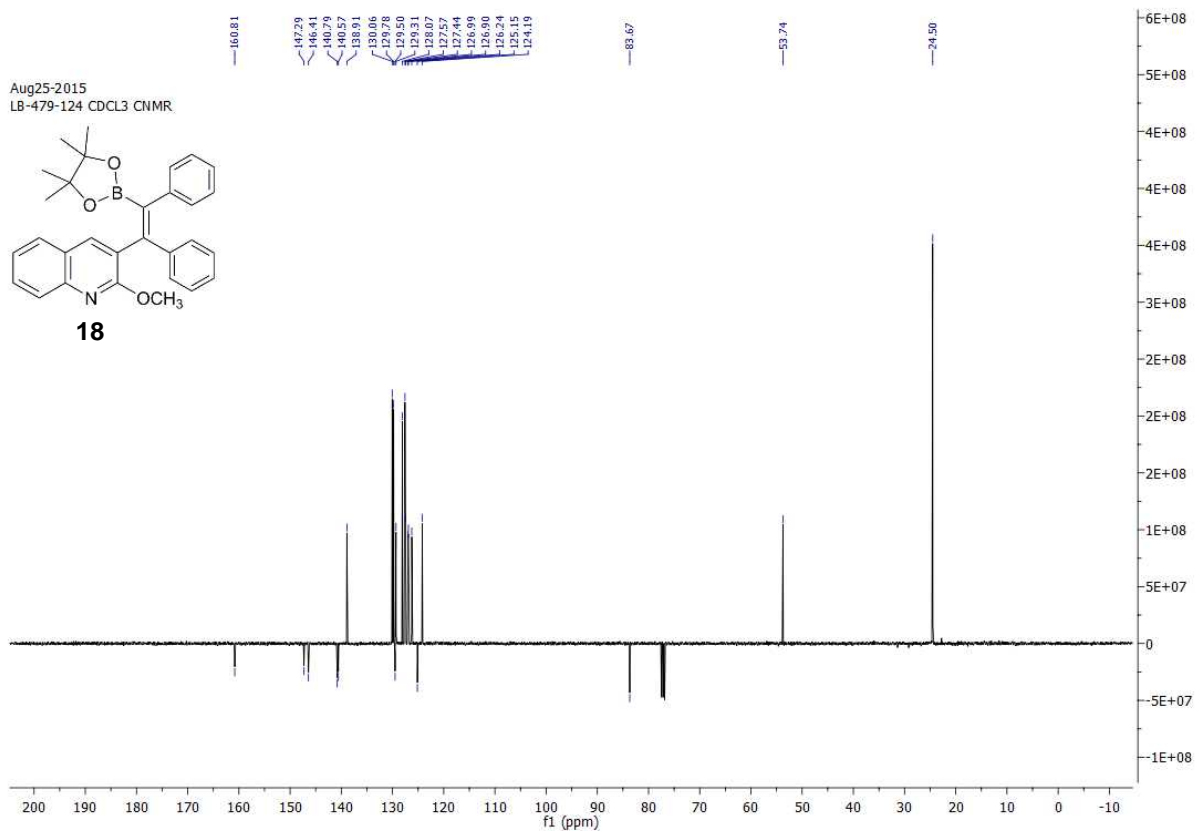
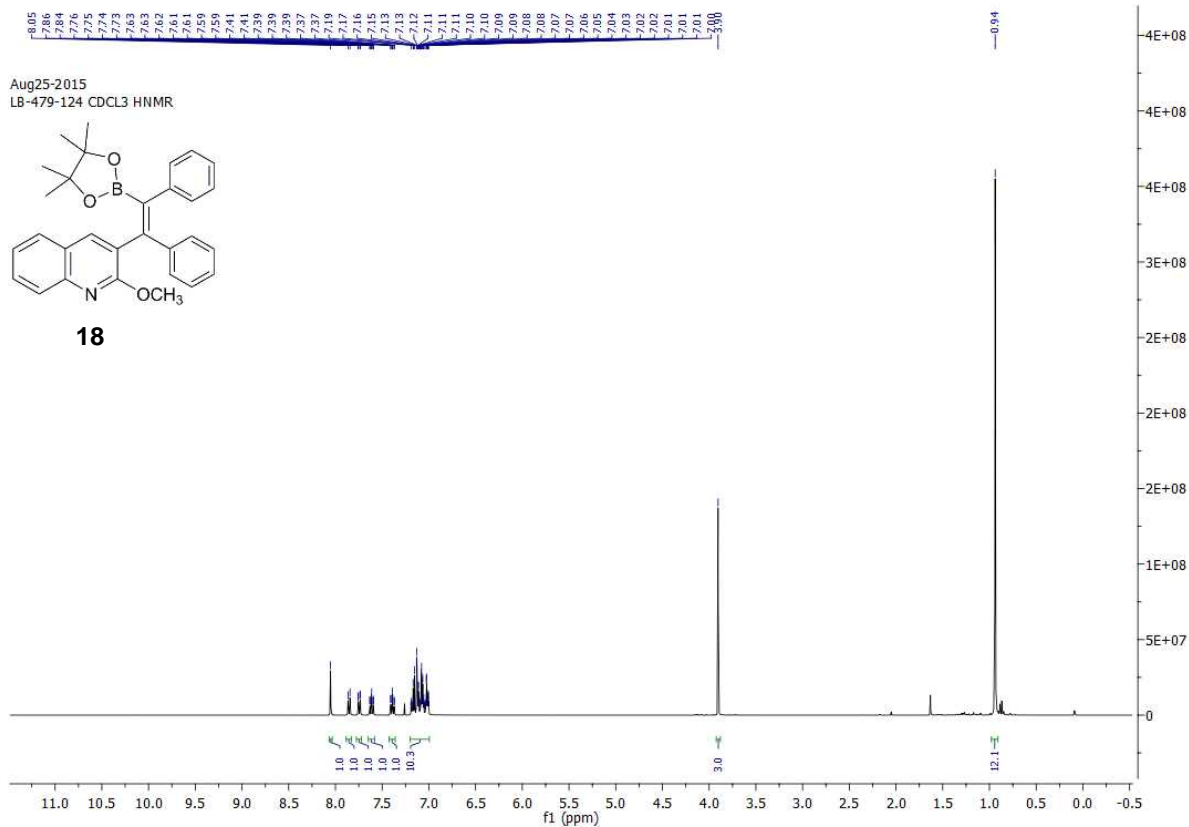


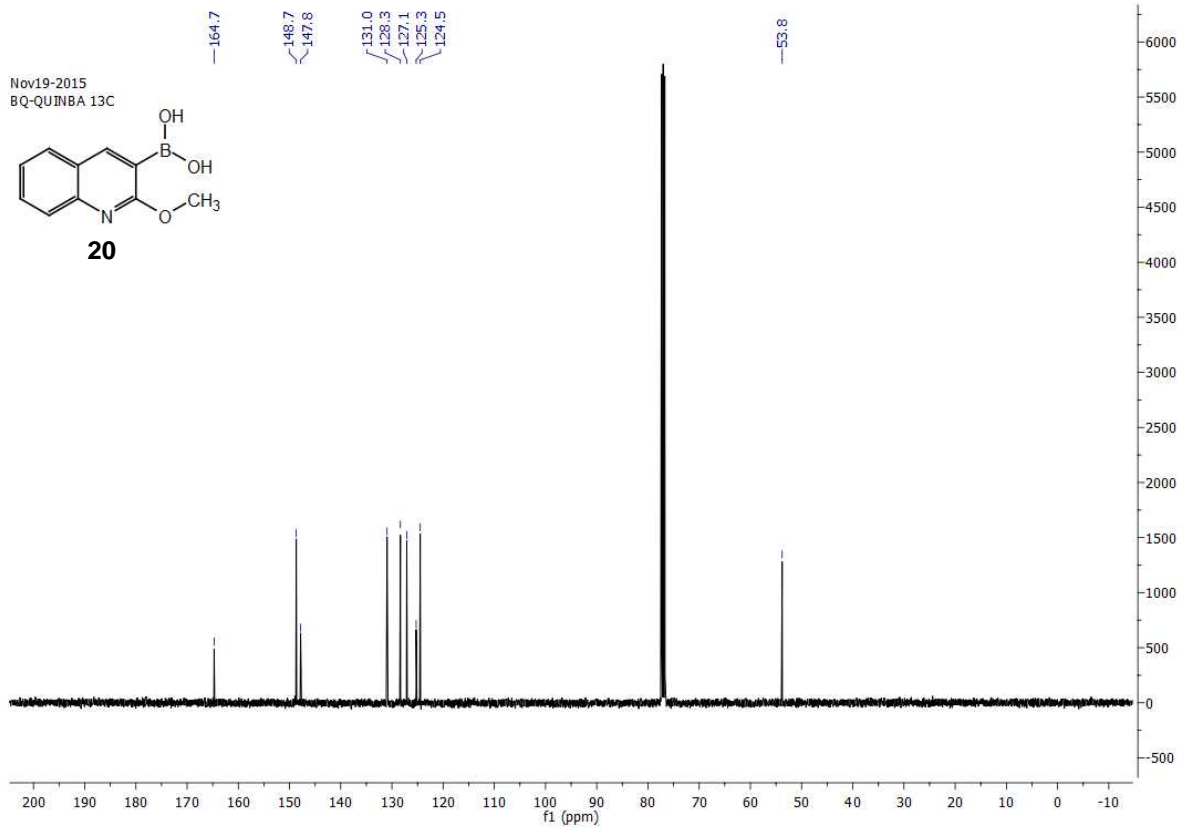
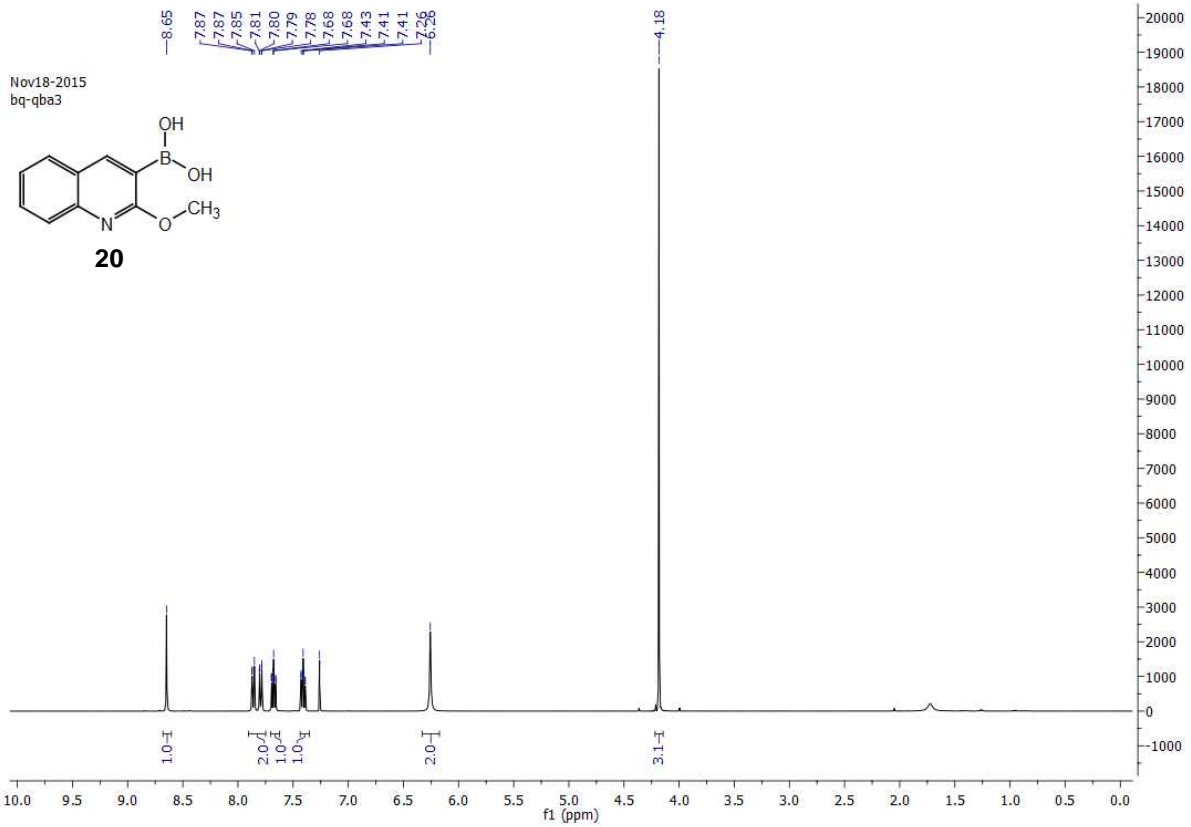
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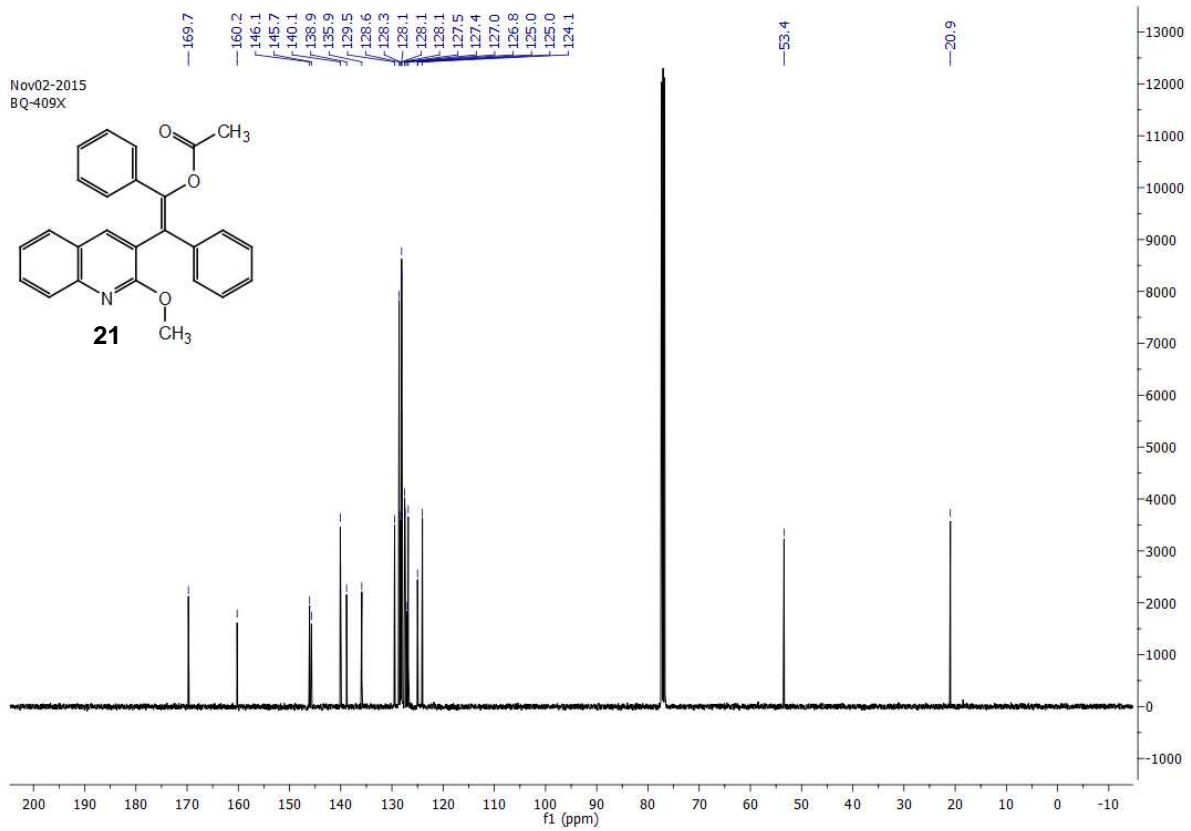
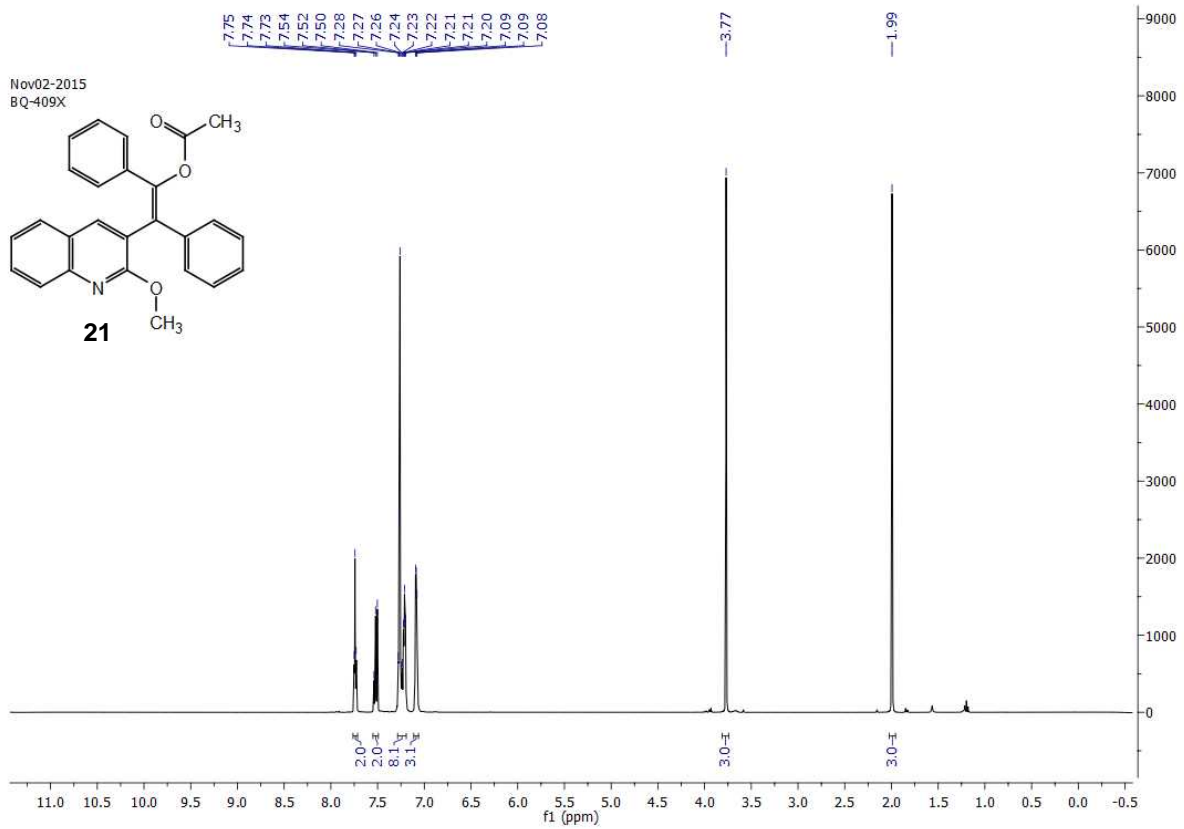




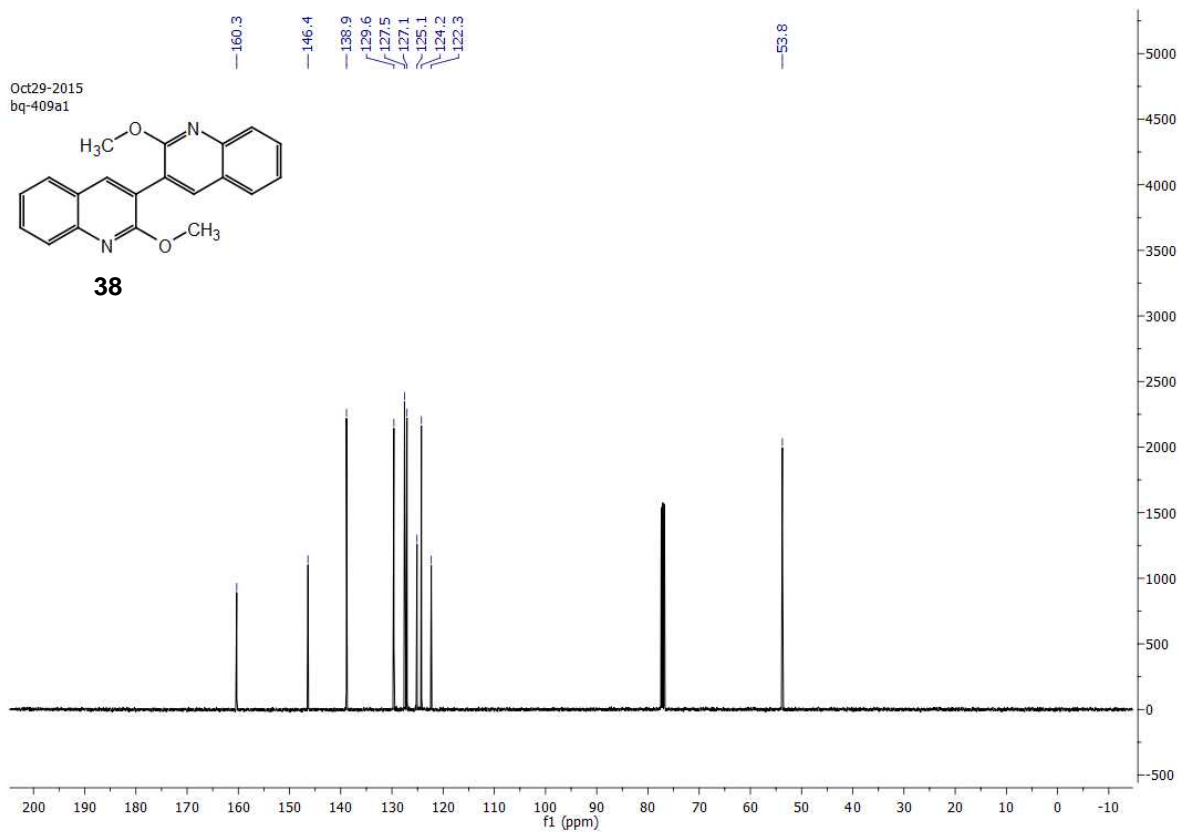
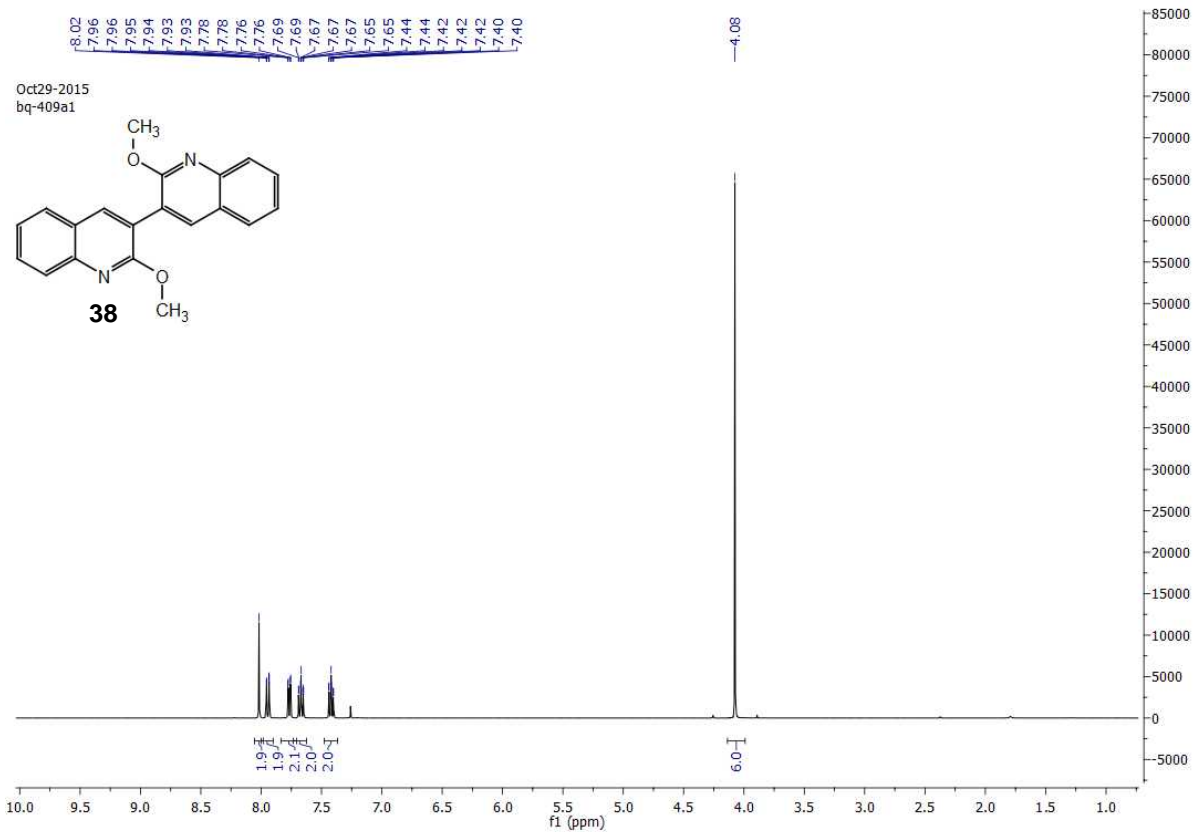


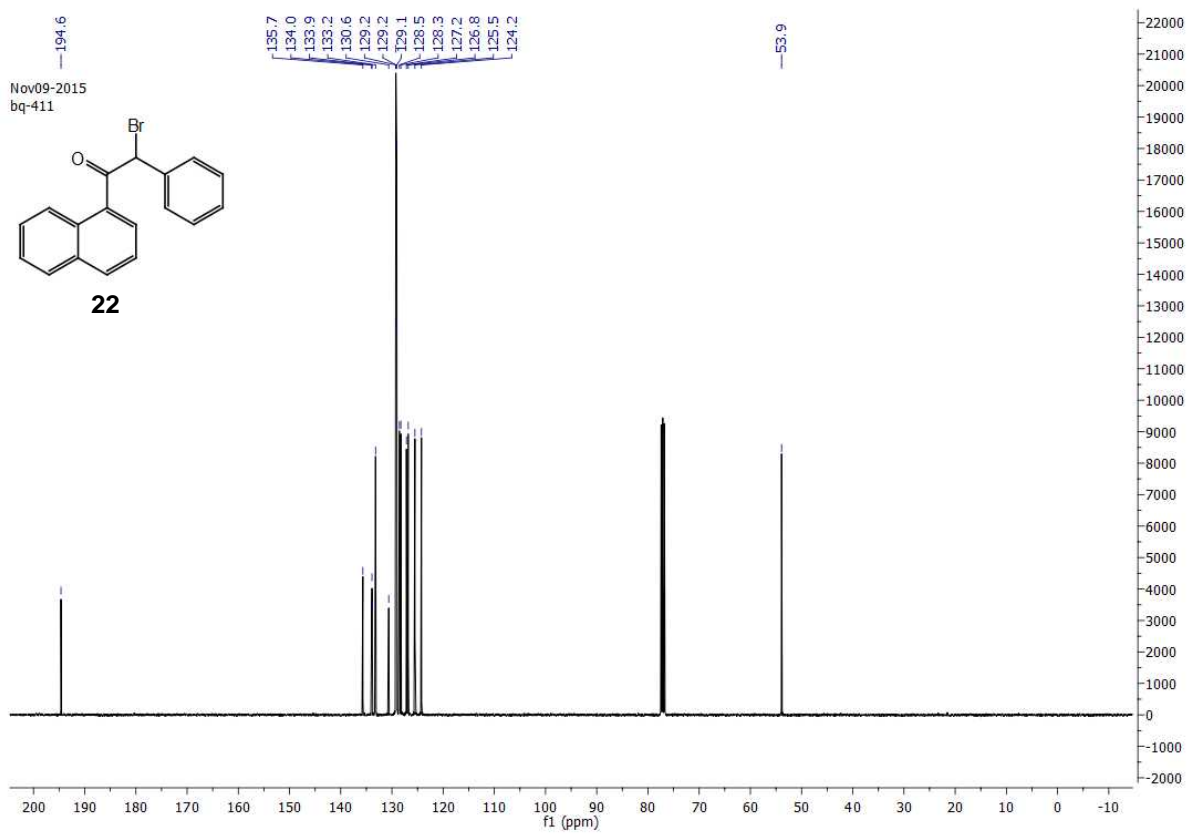
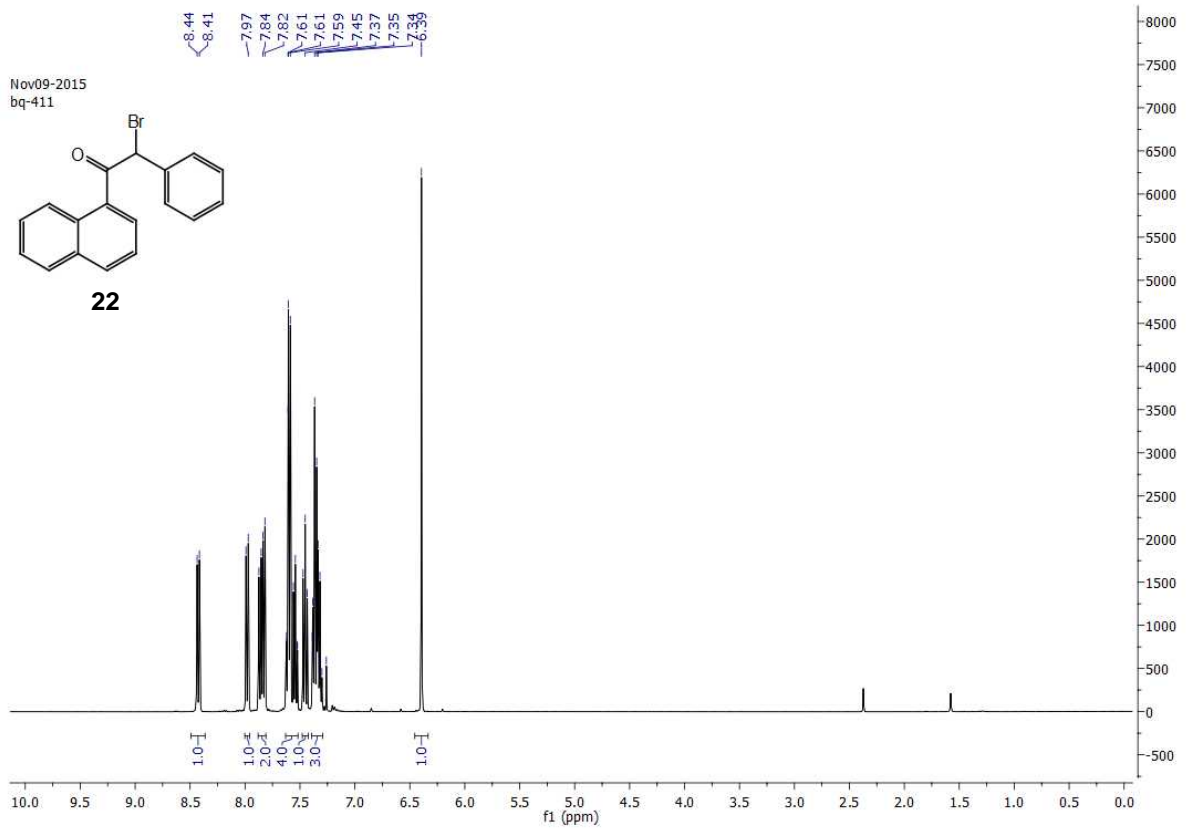


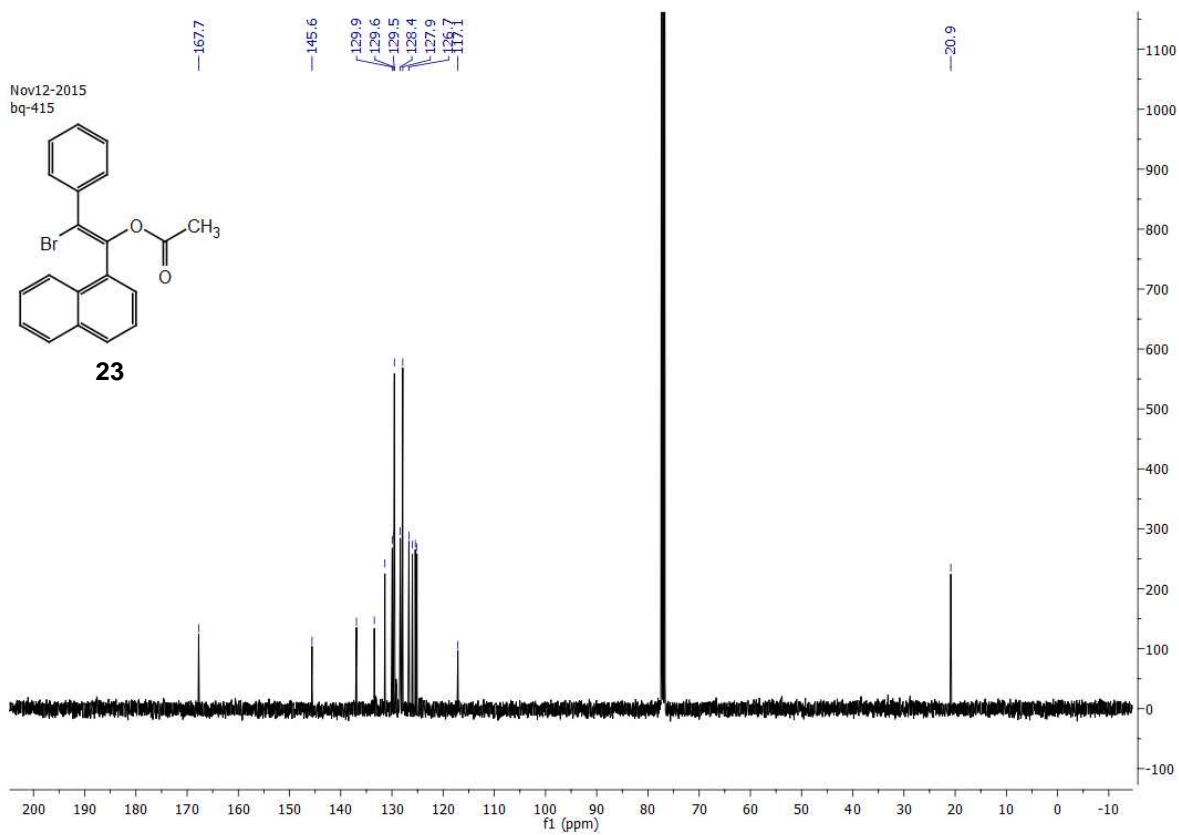
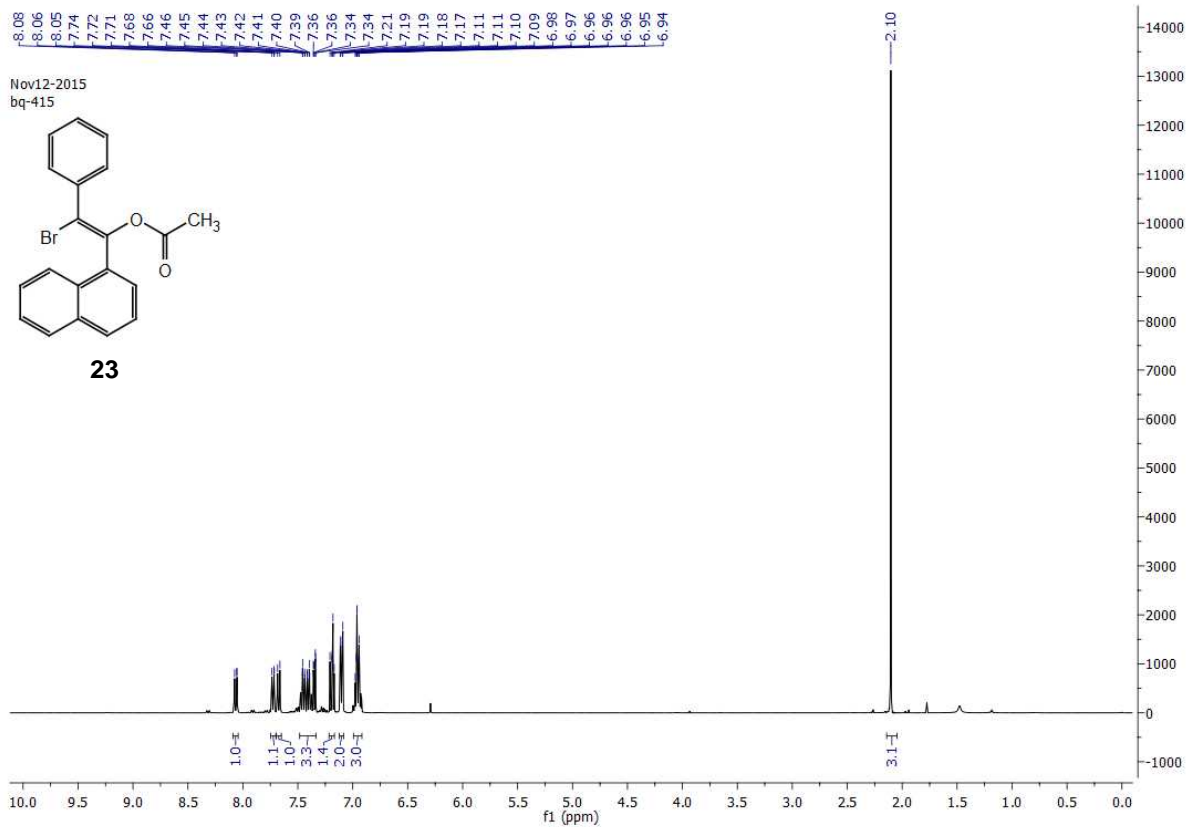


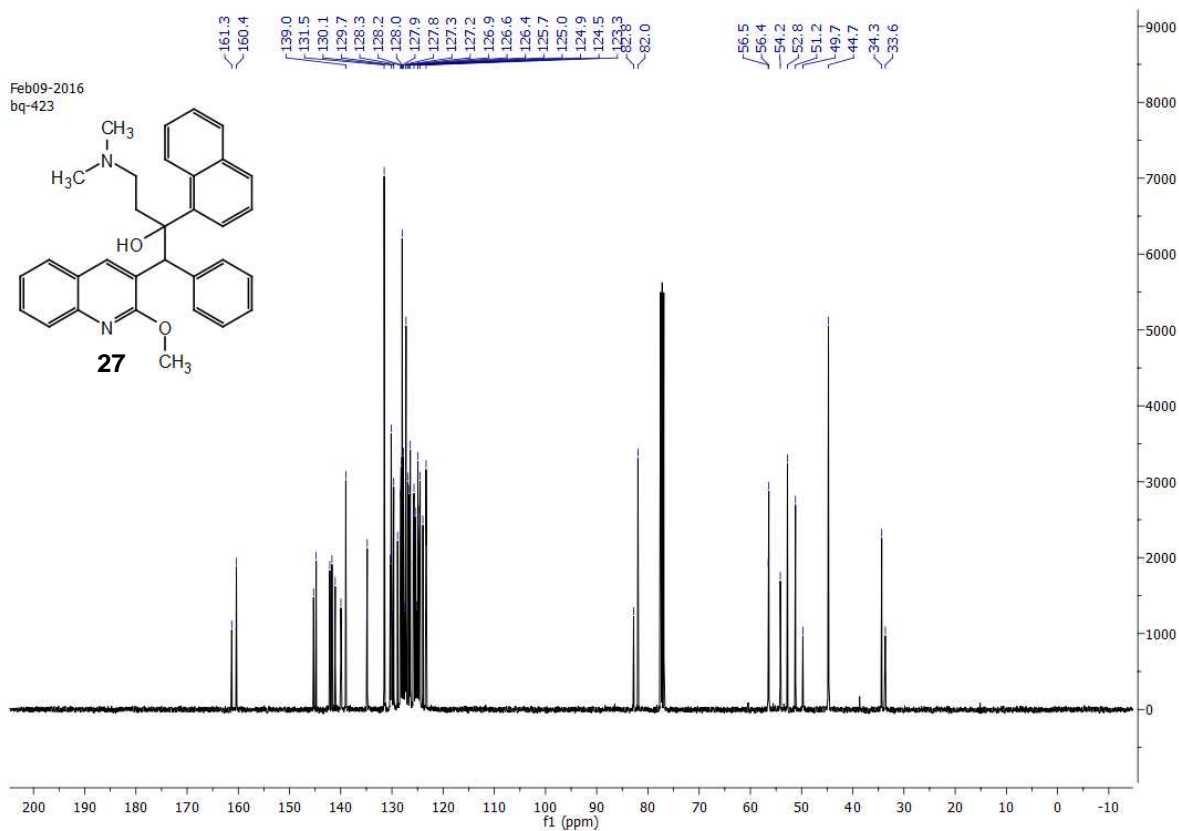
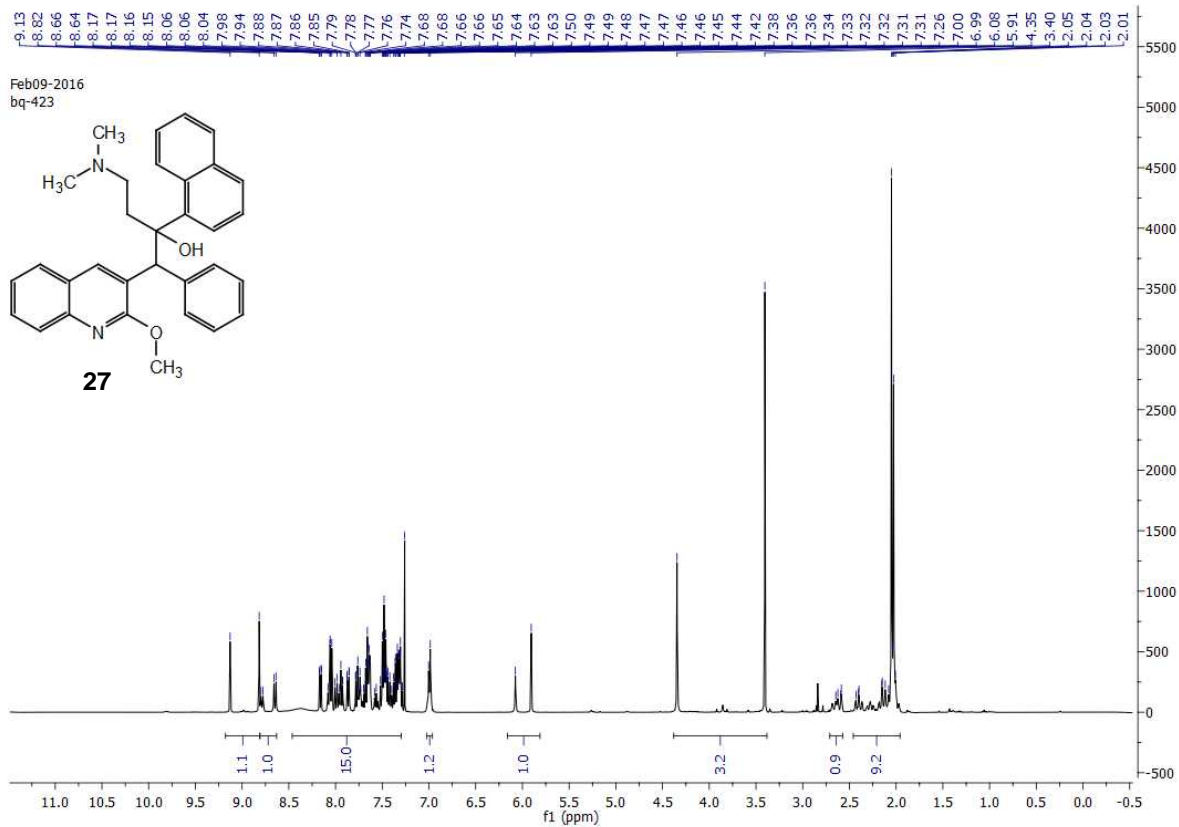




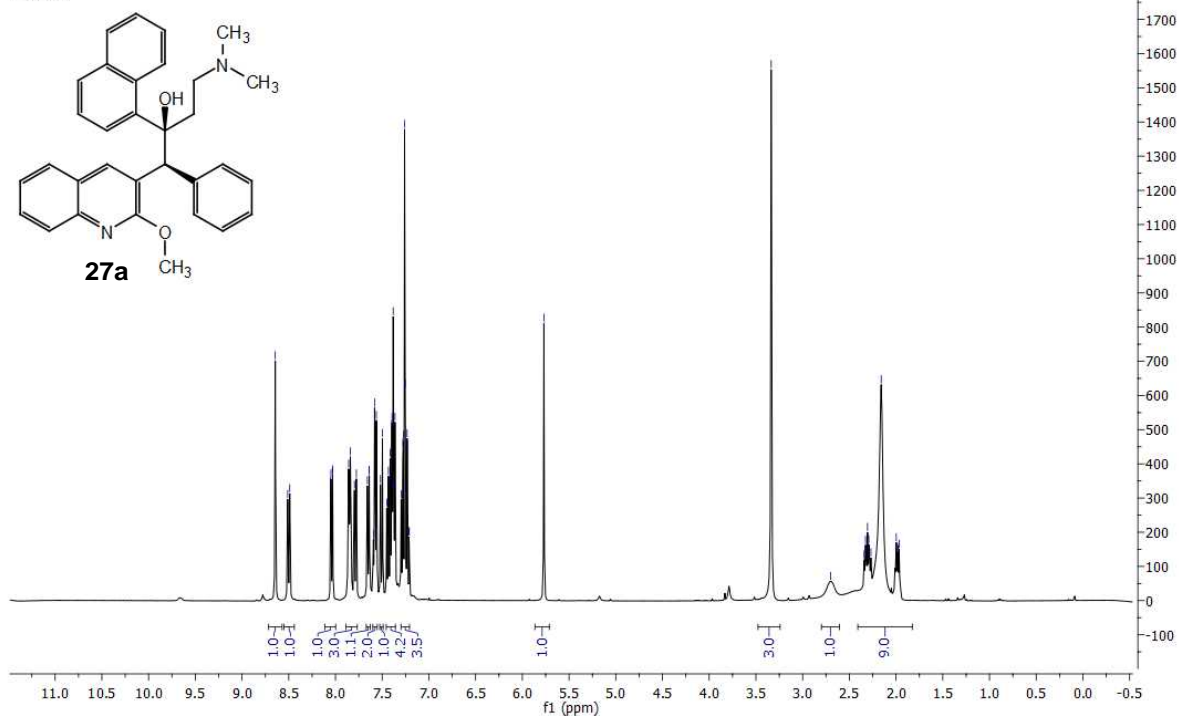




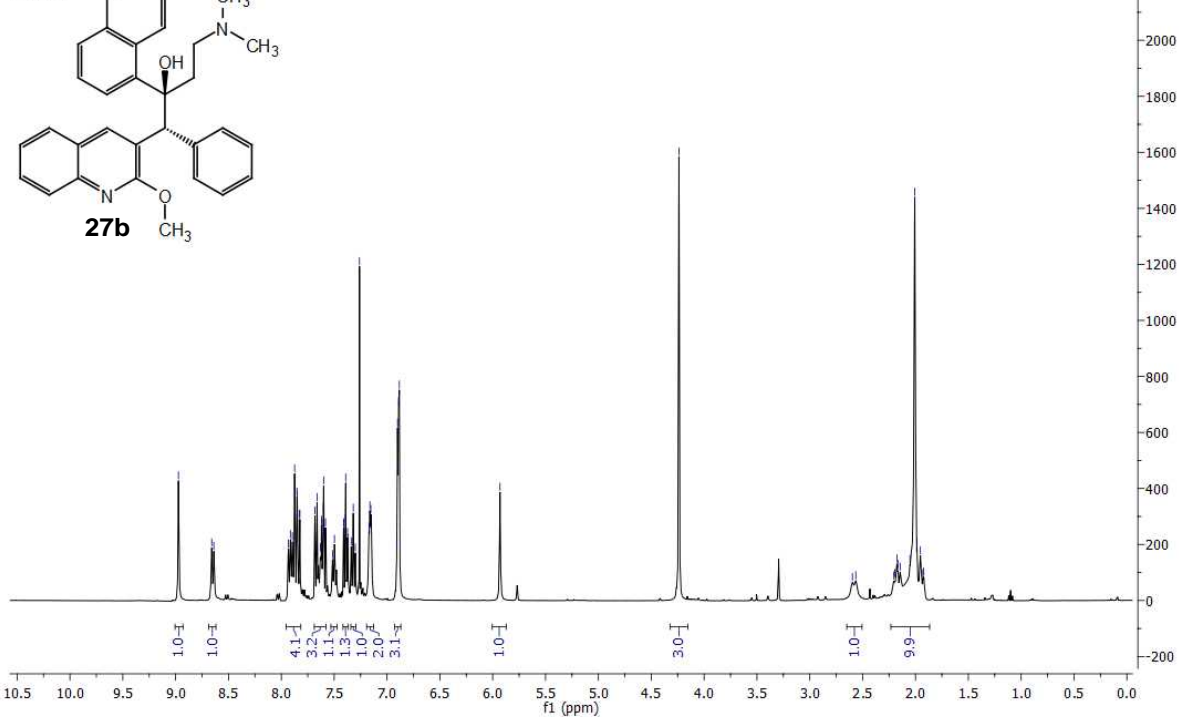


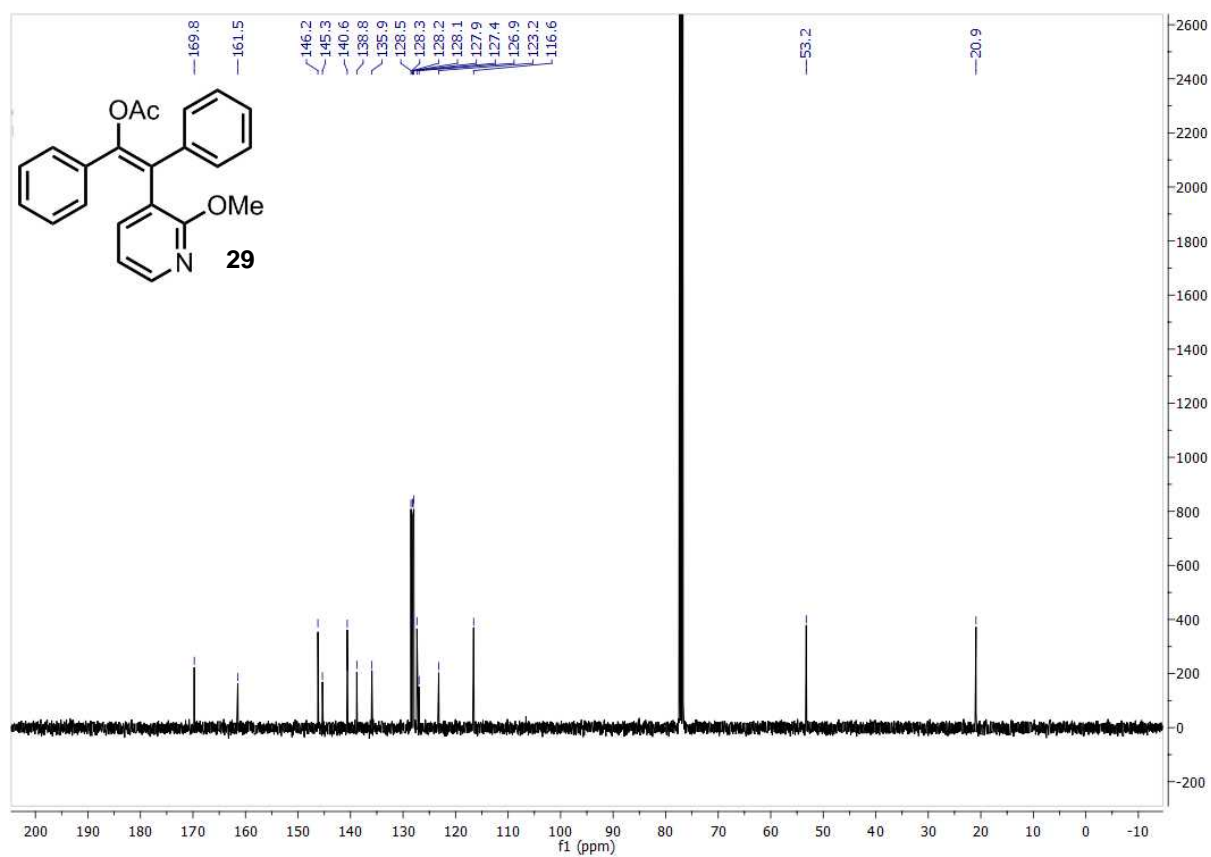
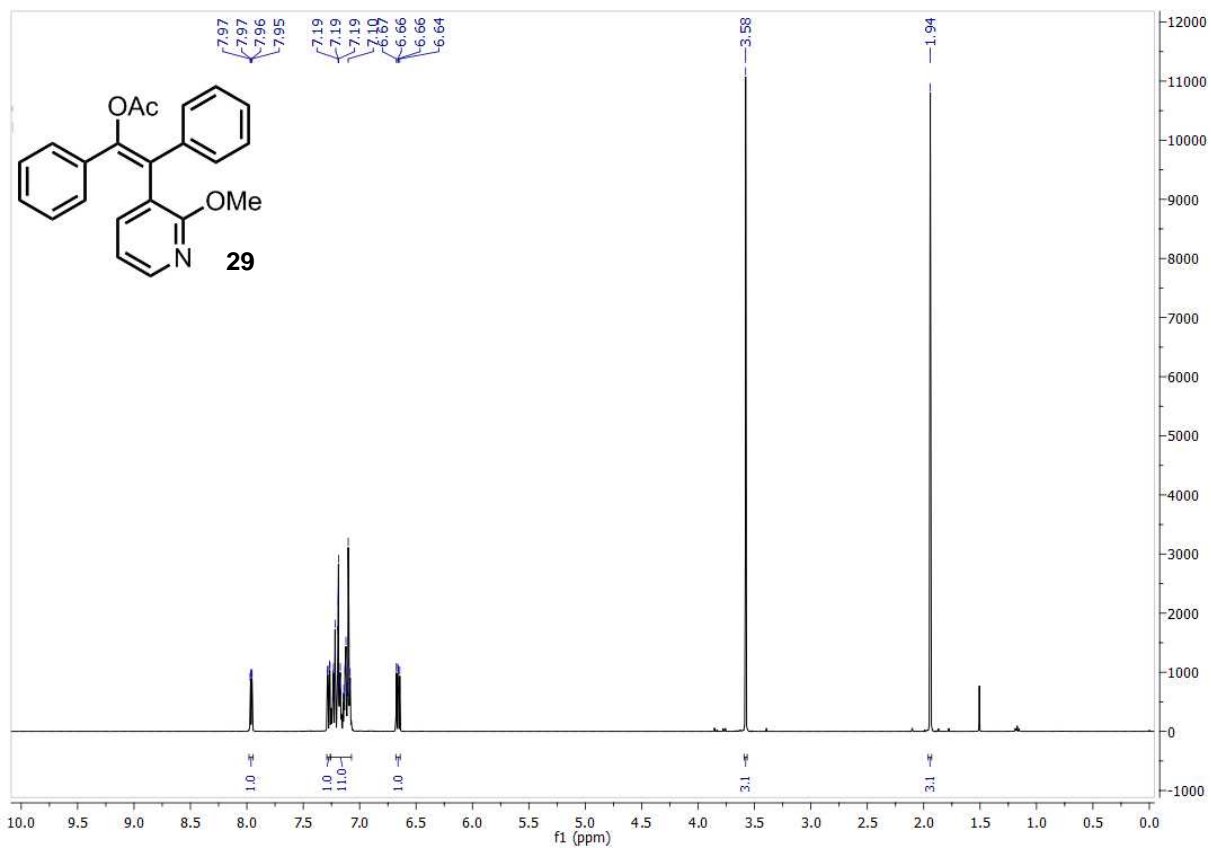


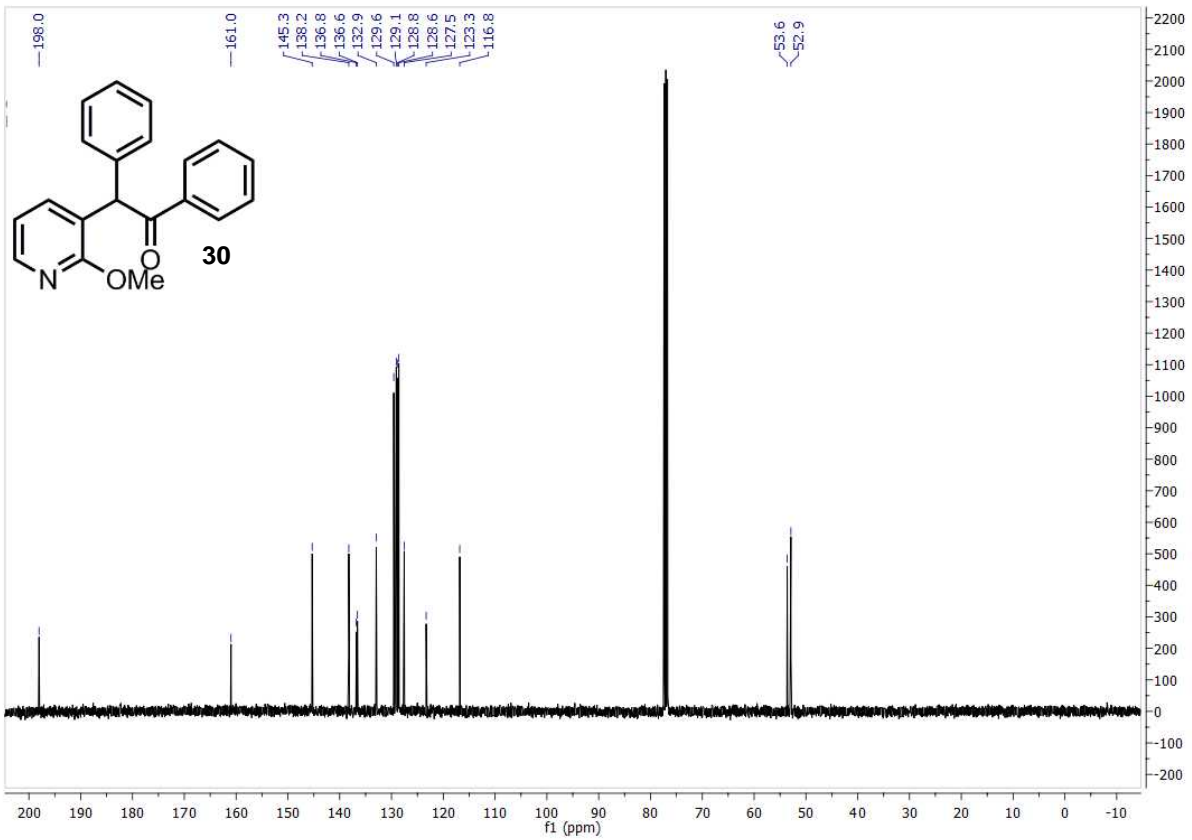
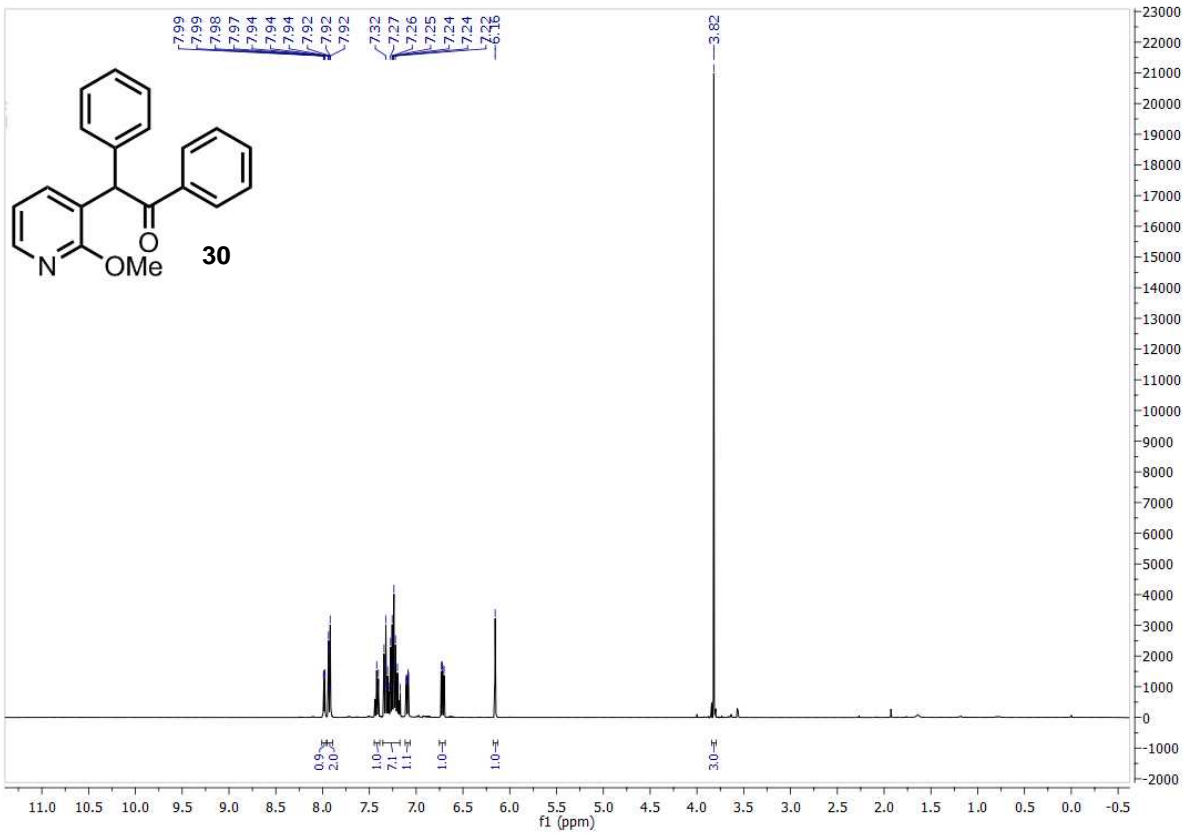
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BQ-423A

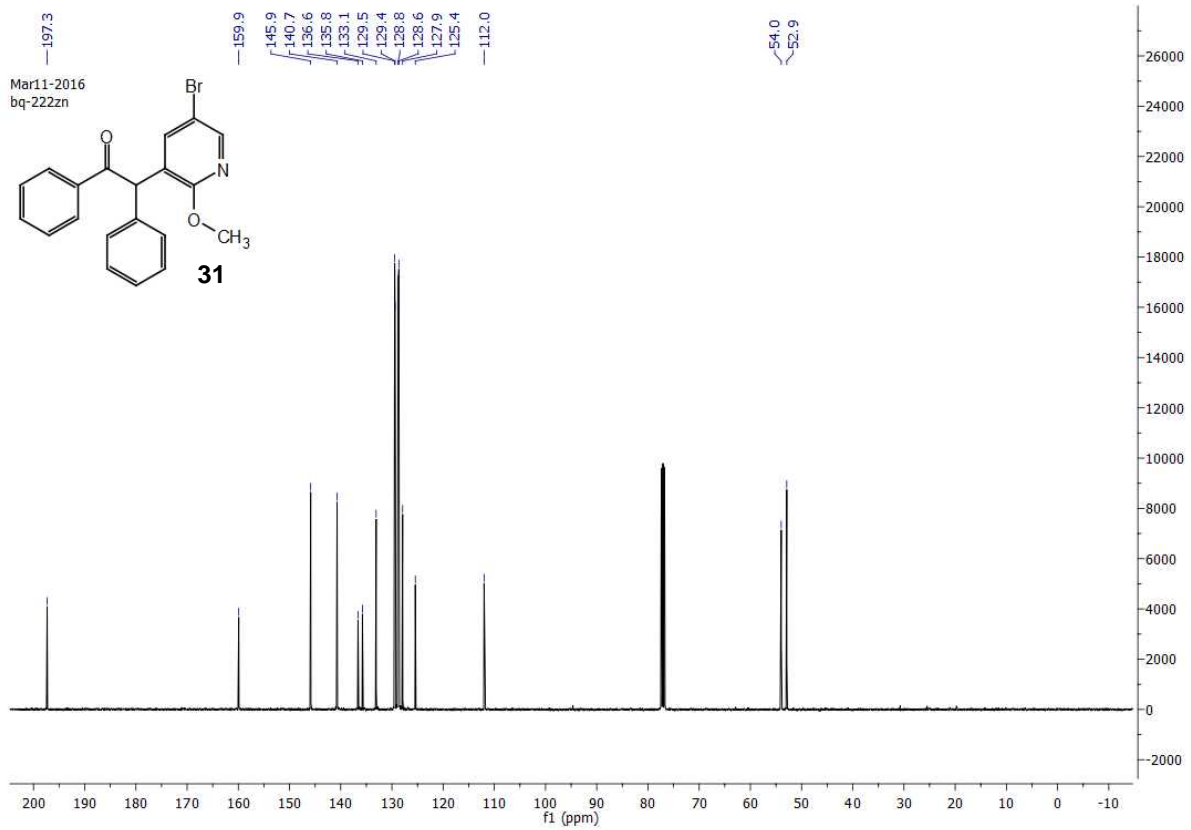
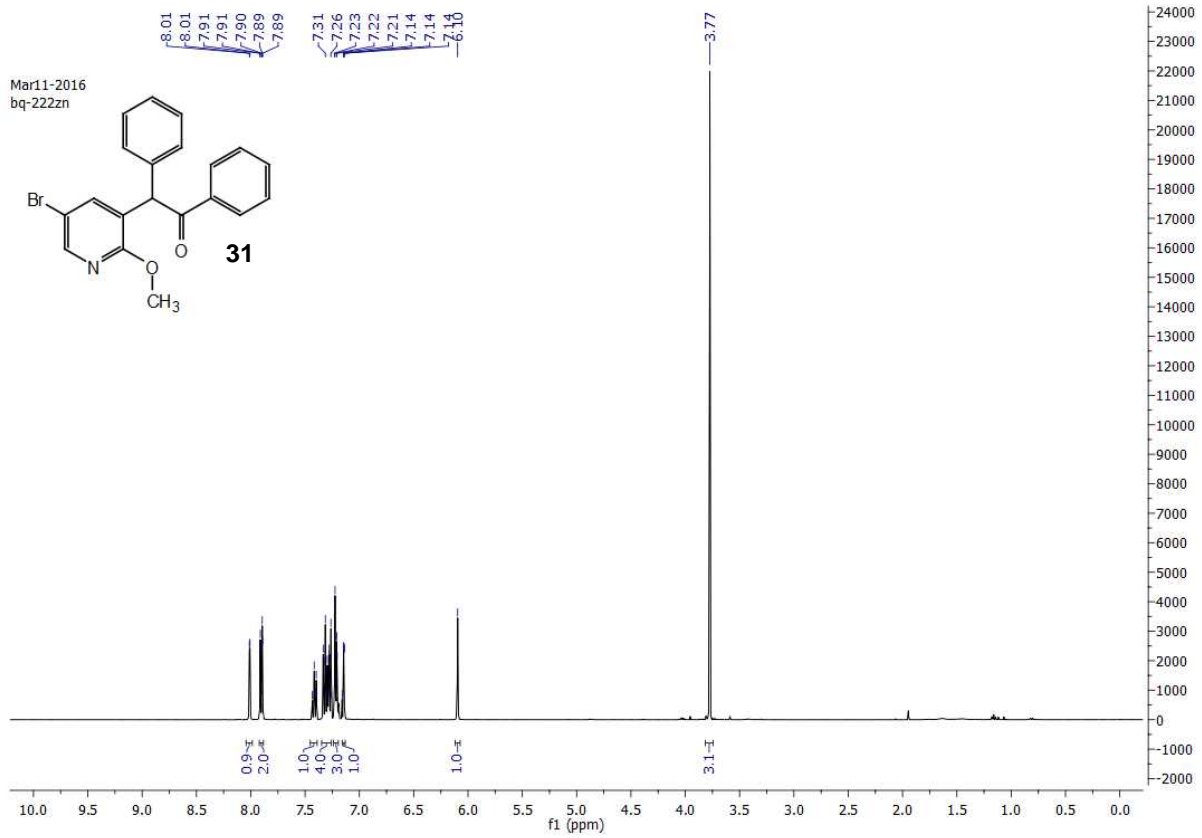


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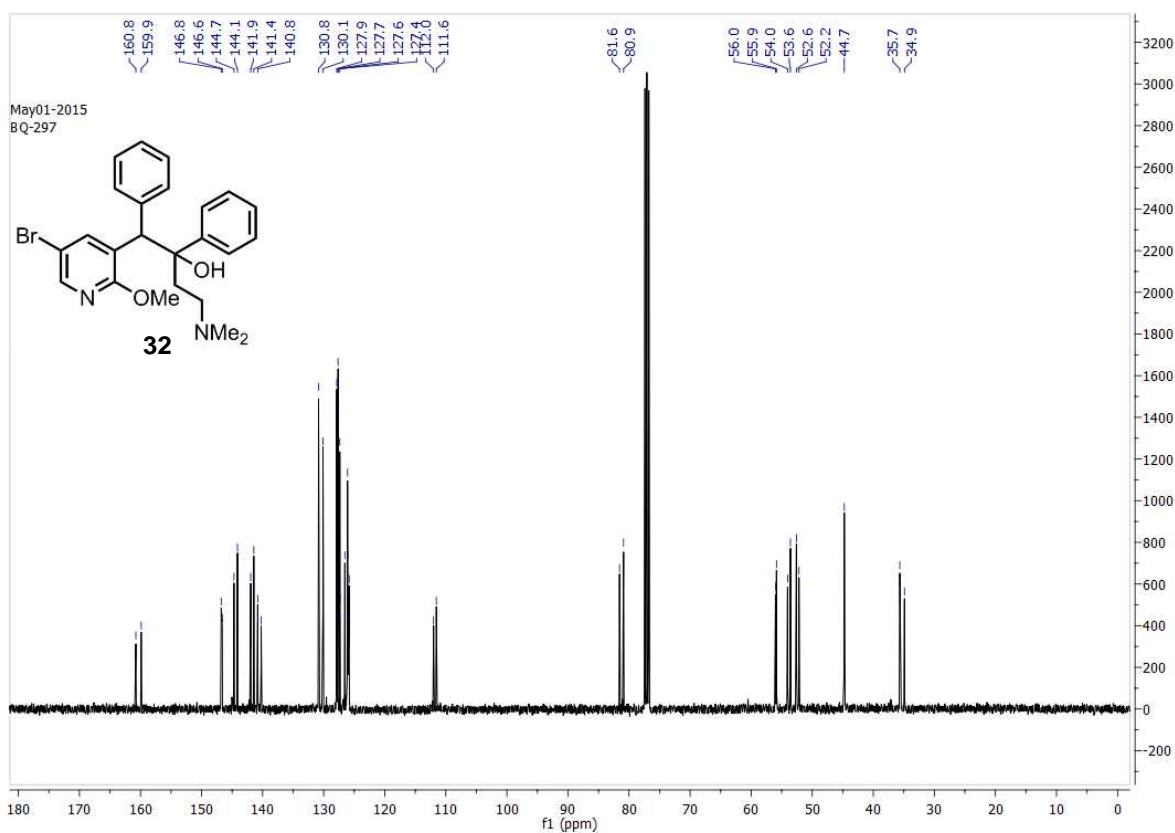
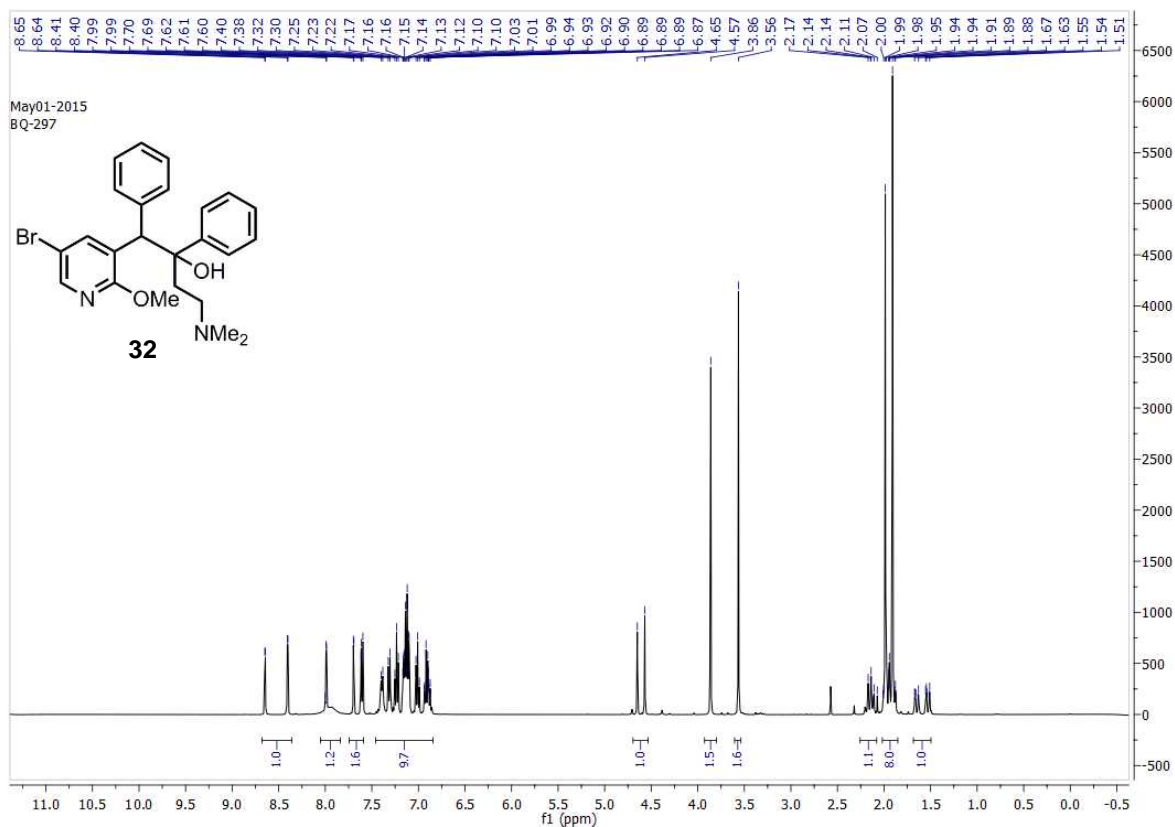




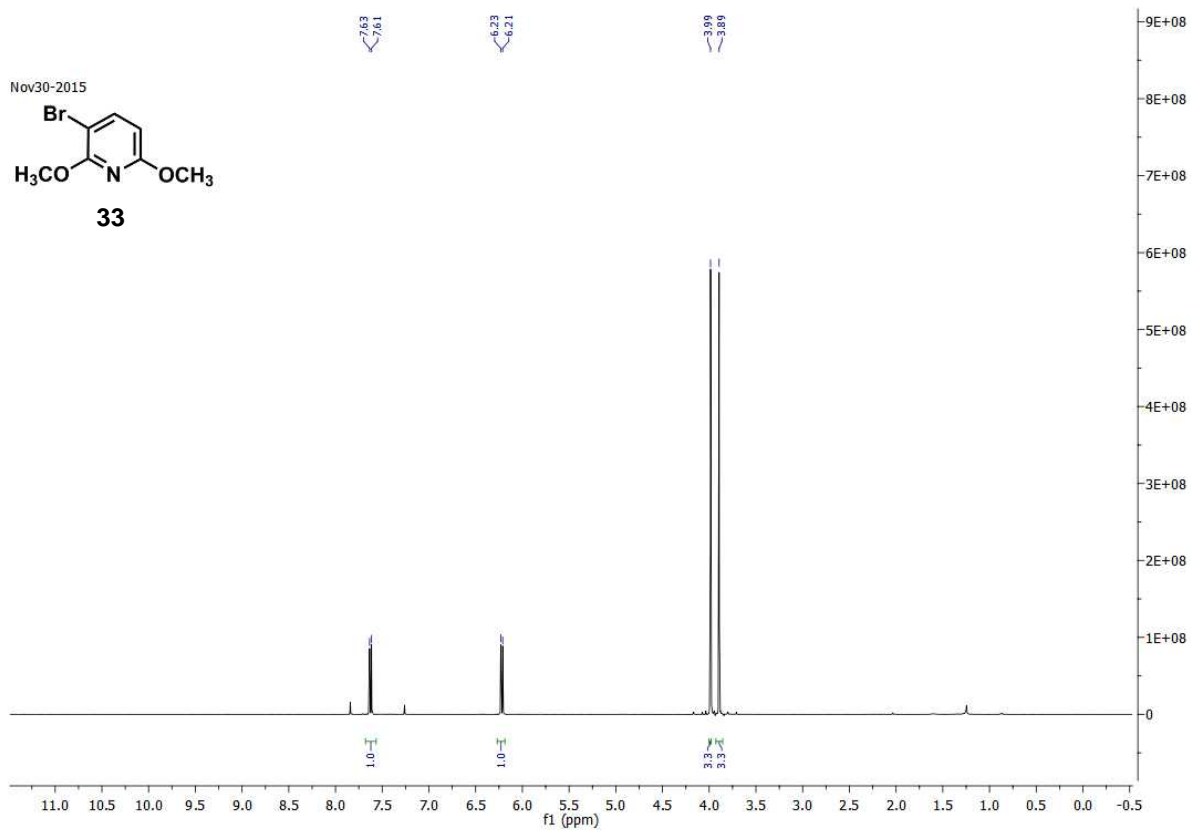
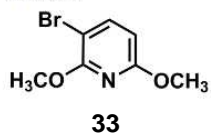




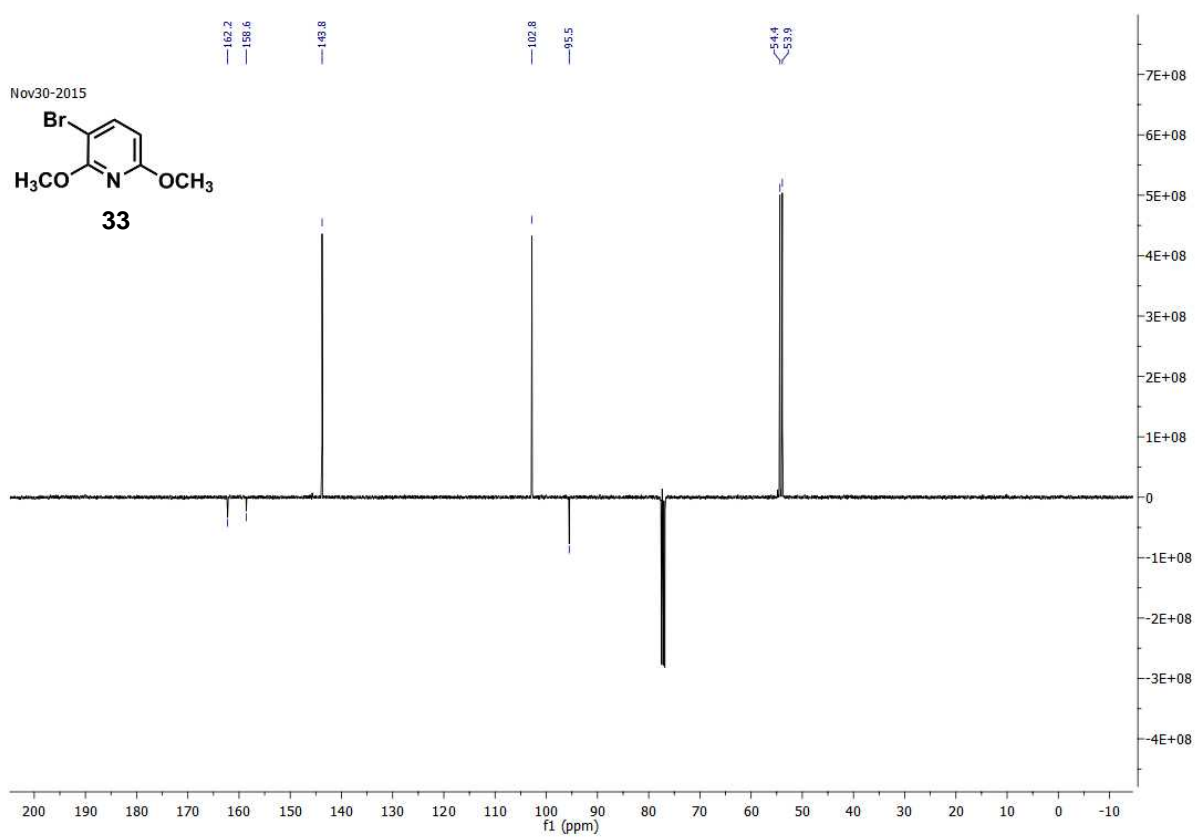
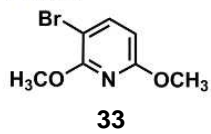




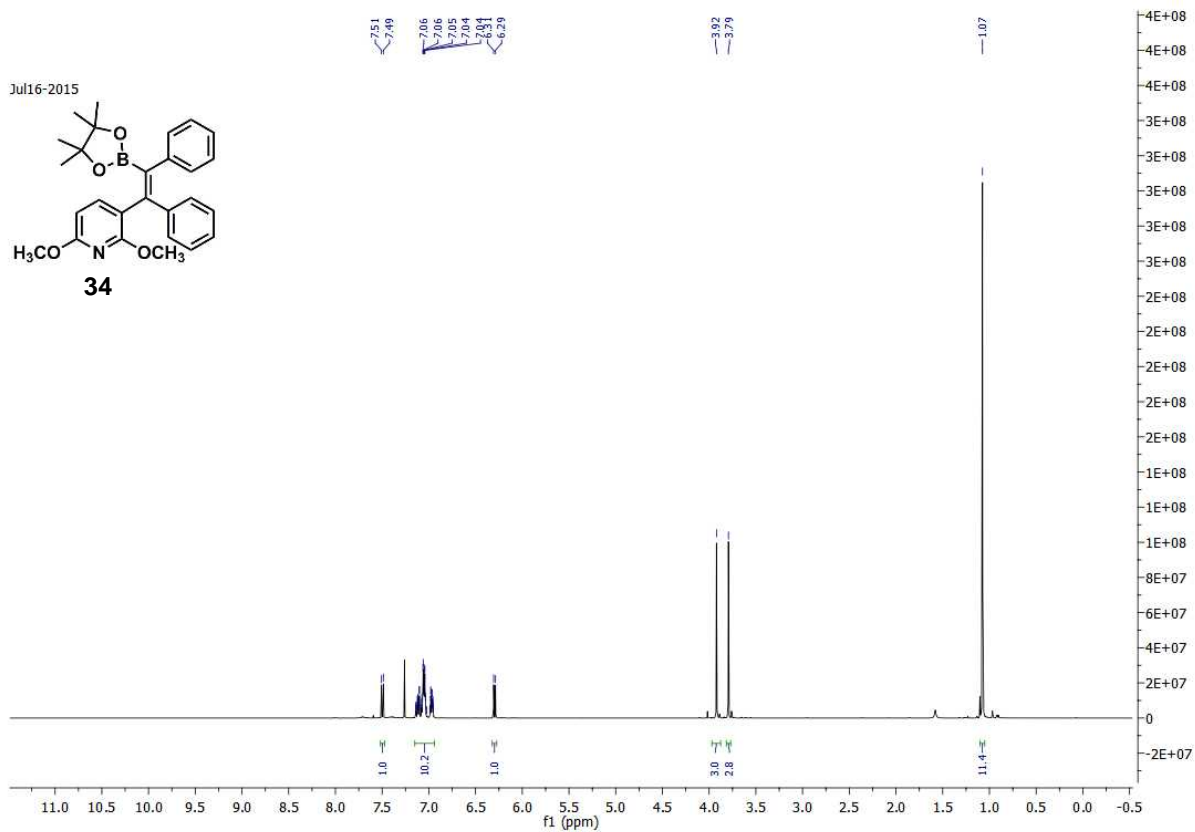
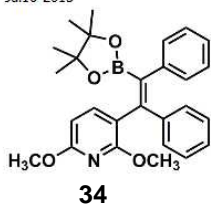
Nov30-2015



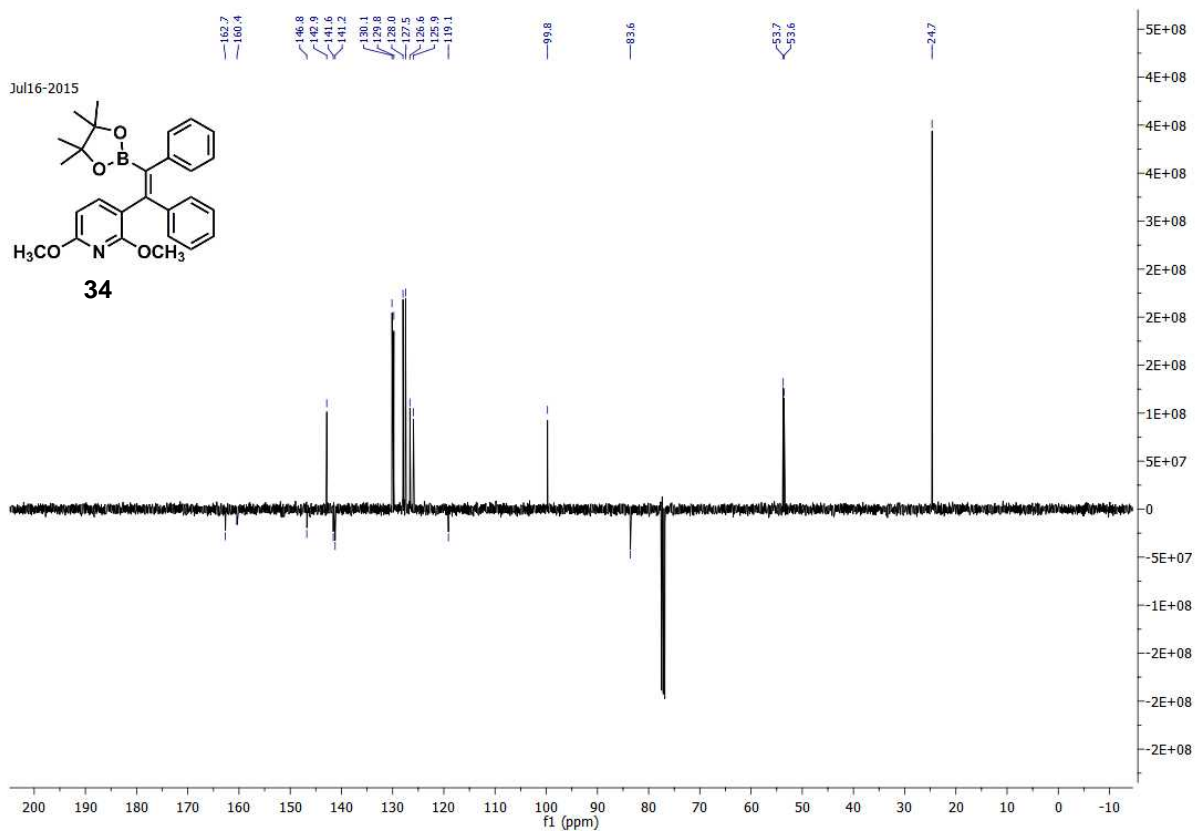
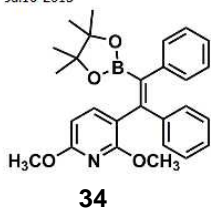
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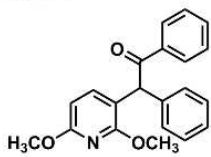
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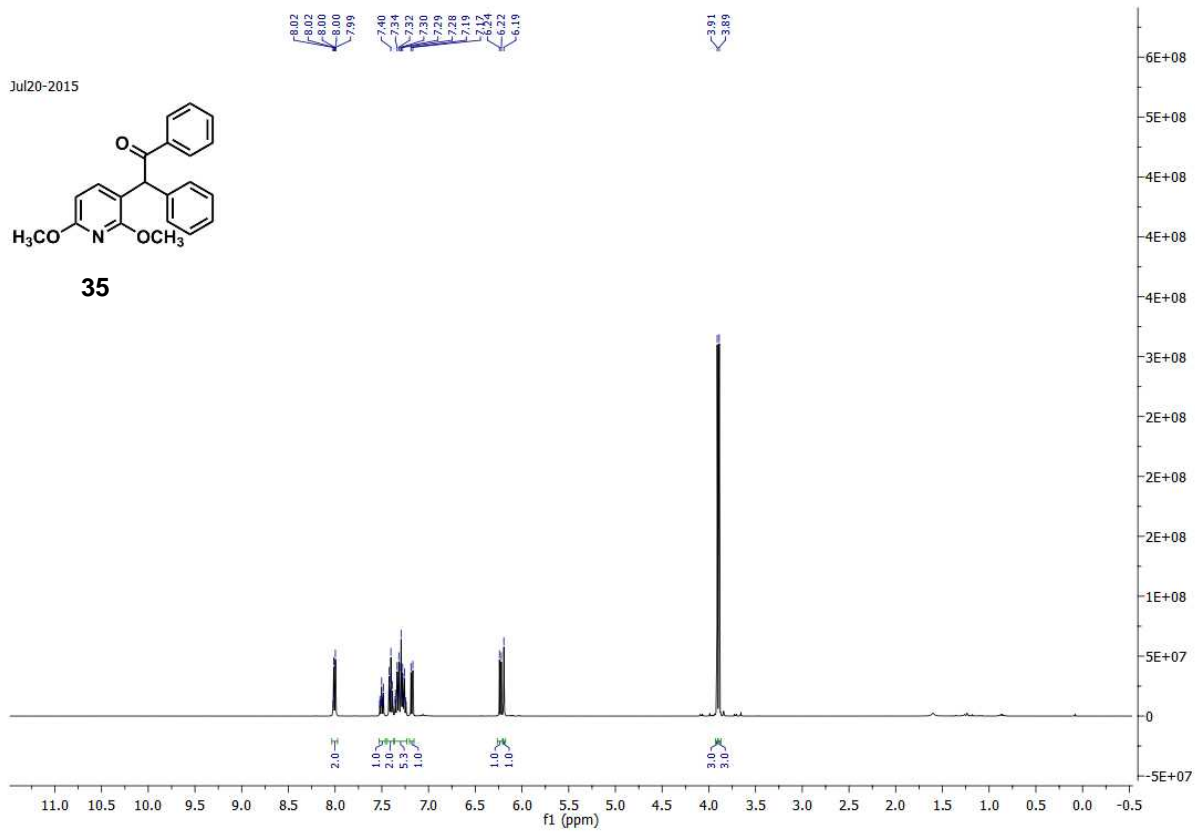
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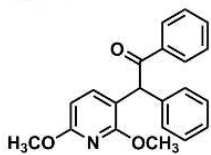
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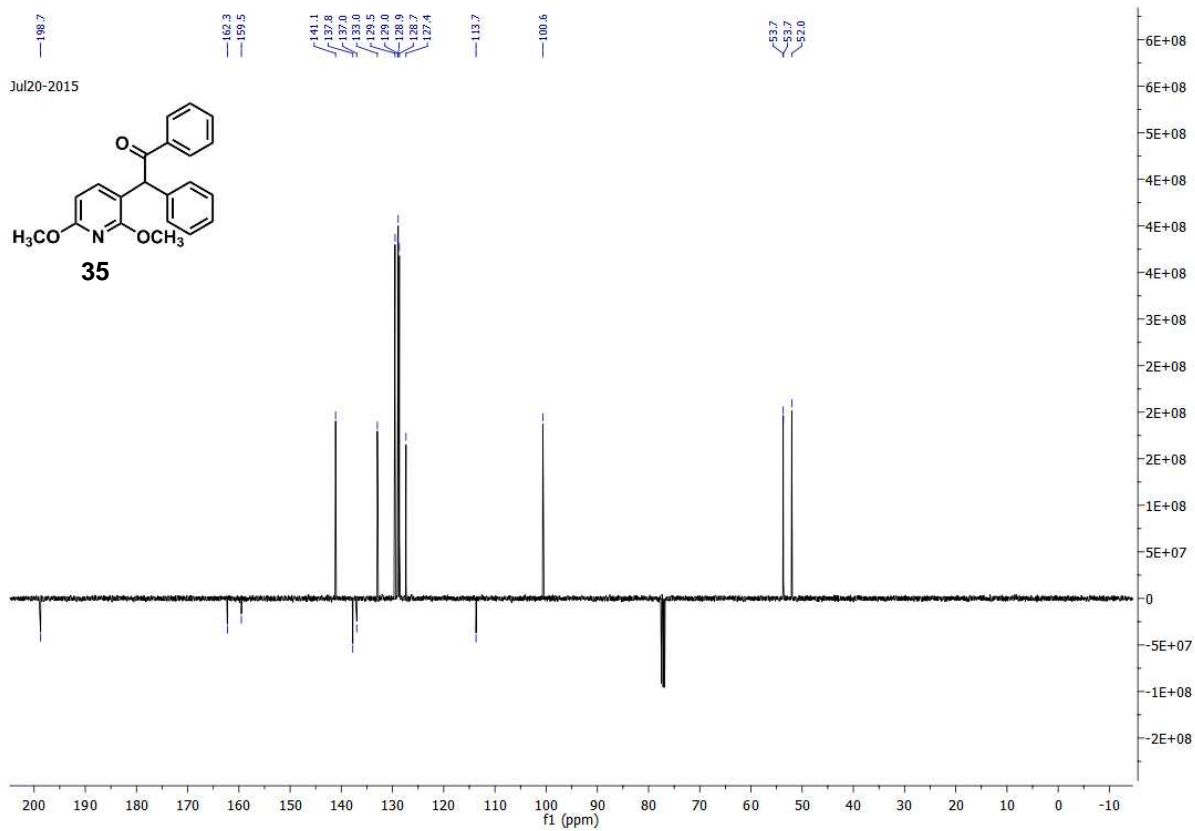
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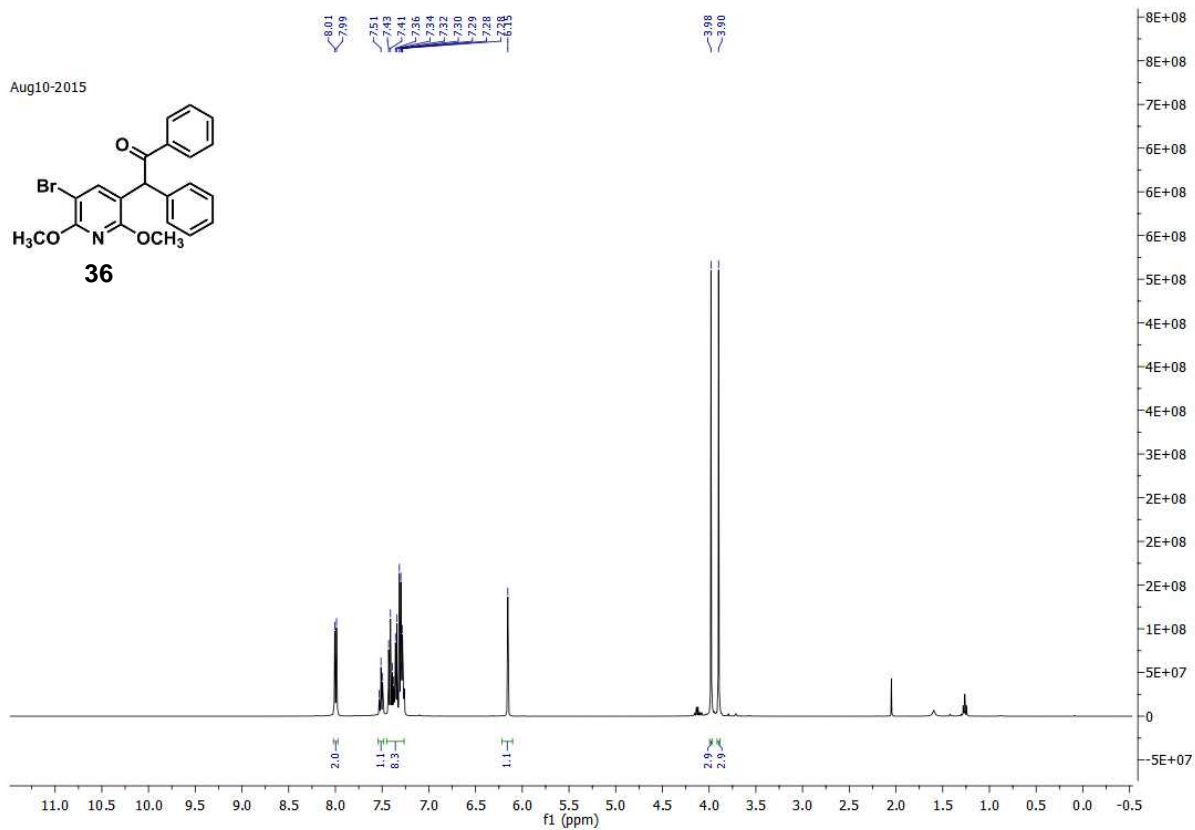
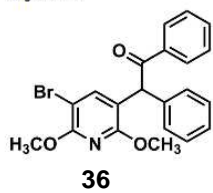
Jul20-2015



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Aug10-2015



Jul21-2015

