Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Probing the reactivity of *o*-phthalaldehydic acid/methyl ester: Synthesis of *N*-isoindolinones and 3-arylaminophthalides

Sreeman K. Mamidyala* and Matthew A. Cooper*

Institute for Molecular Bioscience, University of Queensland, St Lucia, QLD 4072 Australia
Email: s.mamidyala@uq.edu.au; m.cooper@uq.edu.au

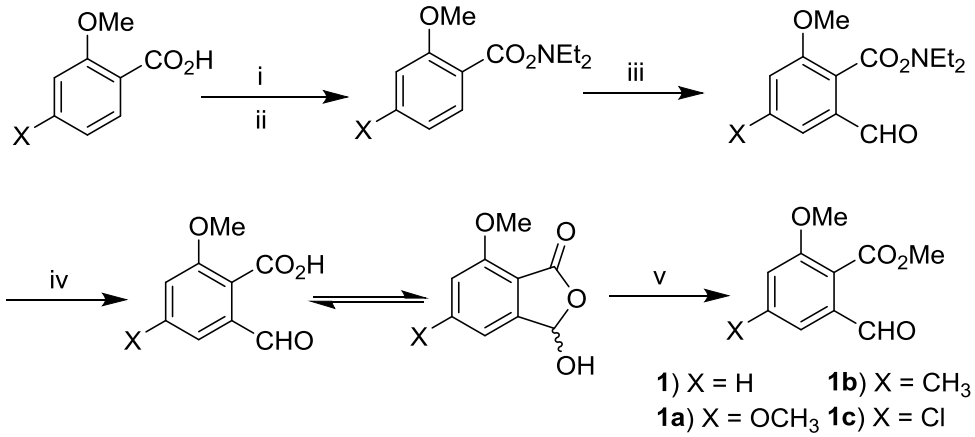
Contents

General

Reagents and anhydrous solvents (THF, dichloromethane, and acetonitrile) were used as received. Triphenylphosphine, polymer-bound (100-200 mesh, 1.6 mmol/g) was purchased from Sigma-Aldrich. Reaction progress was monitored by TLC using Merck silica gel 60 F-254 with UV detection. Silica gel 60 (Merck 40–63 μm) was used for column chromatography. The following stain solutions have been used in addition to UV light with fluorescent TLC plates: phosphomolybdic acid, anisaldehyde/EtOH. Reactions requiring anhydrous conditions were performed under nitrogen. NMR data were collected and calibrated in *d4*-MeOH or $CDCl_3$ at 298K on a Varian Unity 400 MHz Hz spectrometer. HPLC and routine mass spectra were acquired on an Agilent Technologies 1200 Series instrument, fitted with a G1316A UV-Vis detector, 1200 Series ELSD and 6110 quadrupole ESI-MS. High resolution mass spectrometry (HRMS) was performed on the Bruker MicroTOF mass spectrometer.

Experimental procedures

Preparation of *o*-phthalaldehydic acid methyl ester derivatives[1]



Scheme 1. i) $SOCl_2$, reflux, 3 h; ii) Et_2NH, CH_2Cl_2, 0 ^oC - RT, 12 h; iii) s-BuLi/TMEDA, -78 ^oC, DMF; iv) AcOH/HCl, reflux, 12 h; v) DBU-MeI, MeCN, RT.

Preparation of aromatic azides[2]

A solution of aromatic amines (4.0 mmol) in CH_3CN (8 mL) was cooled to 0°C in an ice bath. To this stirred mixture was added *t*-BuONO (6.0 mmol) followed by $TMSN_3$ (6.0 mmol) drop wise. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (hexane) to give the azides **2** in quantitative yields.

Preparation of benzylic and aliphatic azides

To a solution of benzylic/aliphatic halides (4.0 mmol) in THF (10 mL) was added NaN_3 (8.0 mmol) in water (1.0 ml). The resulting solution was stirred at 80 ^oC for 3 h. The reaction mixture diluted with EtOAc (20 mL) and washed with water (20 ml) and brine (20 mL). The organic layer was separated dried ($MgSO_4$) and concentrated under vacuum to give the azides **2** in quantitative yields.

General procedure for the synthesis of *N*-isoindolinones through aza-Wittig/cyclisation reaction

Method A: using triphenylphosphine

To a stirred solution of *o*-phthalaldehydic acid methyl ester **1** (0.2 mmol) and azides **2** (0.3 mmol) in dry THF (5.0 mL) was added triphenylphosphine (0.4 mmol). The mixture was stirred at room temperature for 6 h. $NaBH_3CN$ (0.4 mmol) was added and the reaction mixture was stirred at room temperature under nitrogen. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc, washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (EtOAc/hexanes) gave the products.

Method B: using polymer-bound triphenylphosphine

To a stirred solution of *o*-phthalaldehydic acid methylester **1** (0.2 mmol) and azides **2** (0.4 mmol) in dry THF (5.0 mL) was added polymer-bound triphenylphosphine (0.4 mmol). The mixture was stirred at room temperature for 3 h. The resin was filtered, $NaBH_3CN$ (0.4 mmol) was added and the reaction mixture was stirred at reflux temperature under nitrogen. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc, washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (EtOAc/hexanes) gave the products.

Synthesis of 3-arylaminophthalides through aza-Wittig/cyclisation reaction using polymer-bound triphenylphosphine

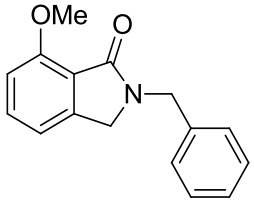
To a stirred solution of *o*-phthalaldehydic acid **5** (0.2 mmol) and azides **2** (0.4 mmol) in dry MeOH (5.0 mL) was added polymer-bound triphenylphosphine (0.4 mmol). The mixture was stirred at reflux temperature for 5 h. The resin was filtered and the solvent was evaporated to dryness. The crude residue was recrystallised using dry MeOH to obtain the 3-arylamino phthalides **6**.

Synthesis of 3-arylaminophthalides using known procedure for the comparison of spectral data[3]

A solution of *o*-phthalaldehydic acid **5** (0.2 mmol) and aromatic amines (0.2 mmol) in dry MeOH (5.0 mL) was refluxed for 30 min. The solvent was evaporated to dryness and crude residue was recrystallised using dry MeOH to obtain the 3-arylamino phthalides.

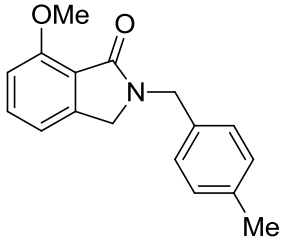
Characterisation of compounds

Compound 4a



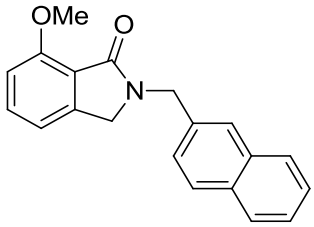
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd (merged), *J* = 8.0 Hz, 1H), 7.05 – 7.37 (m, 5H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 4.75 (s, 2H), 4.20 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 157.5, 144.0, 137.3, 133.0, 128.7, 128.2, 127.5, 114.8, 110.0, 55.8, 48.9, 46.1; HRMS (ESI) calcd. for $C_{16}H_{16}NO_2$ $[M+H]^+$ 254.1176, found 254.1186.

Compound 4b



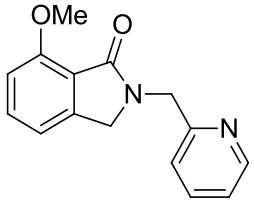
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd (merged), *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 4.71 (s, 2H), 4.19 (s, 2H), 3.98 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 157.5, 144.0, 137.2, 134.3, 133.0, 132.9, 132.8, 129.4, 128.3, 120.0, 114.9, 110.1, 55.8, 48.9, 45.8, 21.1; HRMS (ESI) calcd. for $C_{17}H_{18}NO_2$ $[M+H]^+$ 268.1332, found 268.1344.

Compound 4c



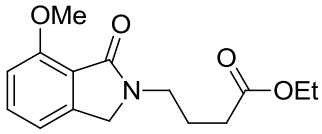
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.83 (m, 4H), 7.35 – 7. 49 (m, 4H), 6.84 – 6.92 (m, 2H), 4.88 (s, 2H), 4.19 (s, 2H), 3.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 157.5, 144.0, 134.8, 133.3, 133.0, 132.8, 128.6, 127.7, 126.9, 126.8, 126.2, 125.9, 119.8, 114.9, 110.1, 55.8, 49.0, 46.3; HRMS (ESI) calcd. for $C_{20}H_{18}NO_2$ $[M+H]^+$ 304.1332, found 304.1336.

Compound 4d



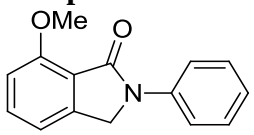
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.0 Hz, 1H), 7.63 (dd, *J* = 8.0 Hz, 1H), 7.46 (dd (merged), *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 4.88 (s, 2H), 4.40 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 157.6, 157.3, 149.1, 144.3, 137.1, 133.1, 122.8, 122.5, 119.7, 114.9, 110.1, 55.8, 49.8, 48.1; HRMS (ESI) calcd. for $C_{20}H_{25}N_2O_4$ $[M+H]^+$ 255.1128, found 255.1141.

Compound 4e



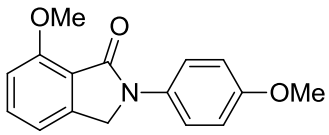
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd (merged), *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 4.36 (s, 2H), 4.04 (q, *J* = 8.0 Hz, 2H), 3.98 (s, 3H), 3.60 (t, *J* = 8.0 Hz, 2H), 2.37 (t, *J* = 8.0 Hz, 2H), 1.70 – 2.06 (m, 2H), 1.20 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 168.1, 157.0, 143.9, 133.3, 119.7, 115.3, 110.3, 60.6, 56.0, 49.7, 41.6, 31.4, 23.6, 14.1; ESI-MS: m/z 278.1 $[(M+H)^+$, 100); HRMS (ESI) calcd. for $C_{15}H_{20}NO_4$ $[M+H]^+$ 278.1387, found 278.1434.

Compound 4f



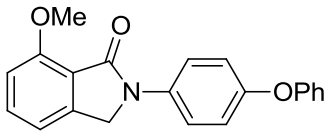
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.52 (dd (merged), *J* = 8.0 Hz, 1H), 7.40 (dd, *J* = 8.0 Hz, 2H), 7.15 (dd, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 4.80 (s, 2H), 4.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 157.9, 142.8, 139.7, 133.7, 129.0, 124.0, 119.2, 114.6, 110.3, 55.9, 50.1; HRMS (ESI) calcd. for $C_{15}H_{14}NO_2$ $[M+H]^+$ 240.1019, found 240.1027.

Compound 4g



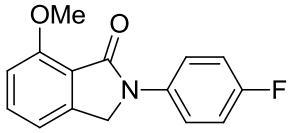
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.50 (dd (merged), *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 4.75 (s, 2H), 3.99 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 157.8, 156.2, 142.8, 133.4, 132.9, 121.1, 121.1, 114.6, 114.2, 110.3, 55.9, 55.5, 50.5; HRMS (ESI) calcd. for $C_{16}H_{16}NO_3$ $[M+H]^+$ 270.1125, found 270.1136.

Compound 4h



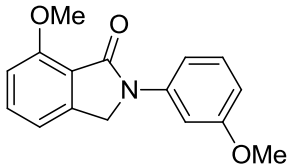
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz 2H), 7.48 (dd (merged), *J* = 8.0 Hz, 1H), 7.26 – 7.37 (m, 2H), 6.98 – 7.07 (m, 5H), 6.85 – 6.96 (m, 2H), 4.71 (s, 2H), 3.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 157.8, 157.4, 153.34, 142.8, 135.2, 133.7, 129.7, 123.1, 120.9, 119.5, 118.5, 114.6, 110.4, 55.9, 50.3; HRMS (ESI) calcd. for $C_{21}H_{18}NO_3$ $[M+H]^+$ 332.1281, found 332.1264.

Compound 4i



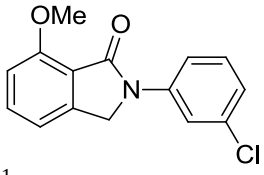
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.0, 4.0 Hz 2H), 7.52 (dd (merged), *J* = 8.0 Hz, 1H), 7.02 - 7.14 (m, 3H), 6.93 (d, *J* = 8.0 Hz, 1H), 4.76 (s, 2H), 4.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 160.4, 157.9, 142.6, 133.8, 120.9, 115.8, 115.5, 114.6, 110.4, 55.9, 50.3; HRMS (ESI) calcd. for $C_{15}H_{13}NO_2$ $[M+H]^+$ 258.0925, found 258.0936.

Compound 4j



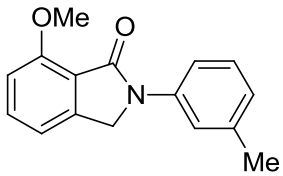
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.53 (dd (merged), *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.71 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.78 (s, 2H), 4.01 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 160.2, 157.9, 142.7, 141.0, 133.8, 129.5, 114.6, 110.5, 110.4, 110.3, 104.6, 104.6, 55.9, 55.3, 50.2; HRMS (ESI) calcd. for $C_{16}H_{16}NO_3$ $[M+H]^+$ 270.1125, found 270.1133.

Compound 4k



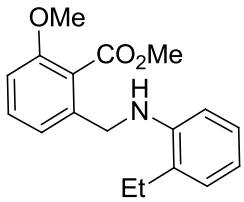
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.54 (dd (merged), *J* = 8.0 Hz, 1H), 7.32 (dd, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0, Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 4.78 (s, 2H), 4.01 (s, 3H); ^{13}C NMR (101 MHz, $cdcl_3$) δ 166.1, 157.8, 142.4, 140.6, 134.6, 133.9, 129.8, 123.7, 119.8, 118.8, 116.6, 114.4, 110.3, 55.7, 49.8; HRMS (ESI) calcd. for $C_{15}H_{13}ClNO_2$ $[M+H]^+$ 274.0629, found 274.0632.

Compound 4l



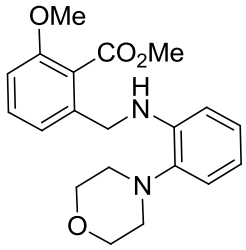
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.51 (dd (merged), *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 4.78 (s, 2H), 4.00 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 157.9, 142.9, 139.6, 138.8, 133.7, 128.8, 124.9, 120.5, 120.1, 116.3, 114.6, 110.3, 55.9, 50.2, 21.7; HRMS (ESI) calcd. for $C_{16}H_{16}NO_2$ $[M+H]^+$ 254.1176, found 254.1188.

Compound 3m



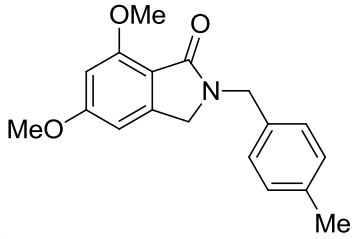
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd (merged), *J* = 8.0 Hz, 1H), 7.09 (dd, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.72 (dd, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 4.34 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.50 (q, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 156.7, 145.2, 138.4, 130.9, 127.8, 127.8, 126.9, 122.8, 120.6, 117.5, 110.3, 110.2, 56.0, 55.9, 52.4, 52.3, 46.3, 23.7, 12.9; HRMS (ESI) calcd. for $C_{18}H_{22}NO_3$ $[M+H]^+$ 300.1594, found 300.1601.

Compound 3n



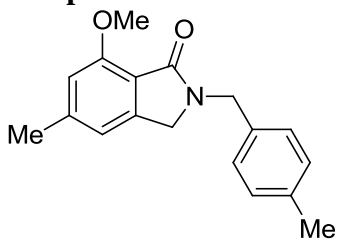
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd (merged), *J* = 8.0 Hz, 1H), 6.96 – 7.06 (m, 3H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.68 – 6.78 (m, 1H), 6.60 (dd, *J* = 8.0, 1.4 Hz, 1H), 5.14 (br s, 1H), 4.33 (d, *J* = 4.4 Hz, 2H), 3.85 (s, 6H), 3.75 – 3.90 (m, 4H), 2.86 – 2.95 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 156.6, 142.7, 138.6, 130.6, 125.2, 124.7, 122.3, 119.9, 119.5, 118.5, 117.1, 115.1, 110.4, 110.0, 67.5, 55.9, 51.7, 51.3, 46.0; HRMS (ESI) calcd. for $C_{20}H_{25}N_2O_4$ $[M+H]^+$ 357.1809, found 357.1814.

Compound 4ab



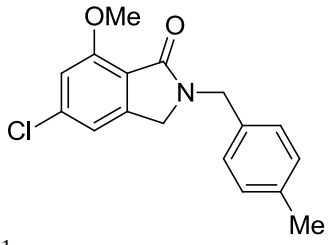
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.42 (s, 1H), 6.41 (s, 2H), 4.67 (s, 2H), 4.13 (s, 2H), 3.93 (s, 3H), 3.82 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 164.2, 158.4, 145.9, 137.1, 134.5, 129.3, 128.2, 113.3, 99.1, 99.0, 98.2, 98.1, 55.9, 55.7, 49.0, 45.7, 21.1; HRMS (ESI) calcd. for $C_{18}H_{20}NO_3$ $[M+H]^+$ 298.1438, found 268.1381.

Compound 4bb



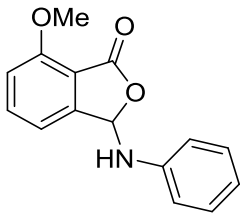
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.72 (s, 1H), 6.68 (s, 1H), 4.68 (s, 2H), 4.13 (s, 2H), 3.95 (s, 3H), 2.39 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 157.2, 144.3, 143.9, 137.1, 134.4, 129.3, 128.2, 117.5, 115.5, 115.5, 111.0, 111.0, 55.8, 48.8, 45.8, 22.2, 21.1; HRMS (ESI) calcd. for $C_{18}H_{20}NO_2$ $[M+H]^+$ 282.1489, found 282.1480.

Compound 4cb



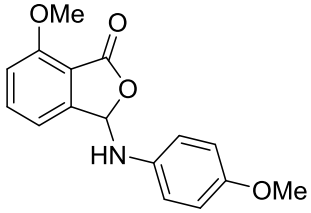
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.91 (s, 1H), 6.87 (s, 1H), 4.68 (s, 2H), 4.16 (s, 2H), 3.96 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 157.7, 145.1, 138.7, 137.3, 133.9, 129.4, 128.2, 118.7, 115.3, 111.1, 56.1, 48.6, 45.8, 21.1; HRMS (ESI) calcd. for $C_{17}H_{17}NO_2$ $[M+H]^+$ 302.0942, found 302.0869.

Compound 6f



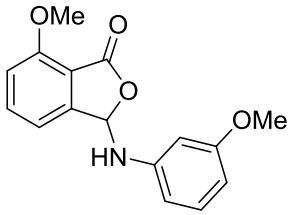
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd (merged), *J* = 8.0 Hz, 1H), 7.28 (dd, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.88 – 6.98 (m, 3H), 6.71 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 158.2, 148.0, 143.6, 136.4, 129.3, 120.7, 114.9, 114.9, 114.7, 112.3, 85.8, 55.9; HRMS (ESI) calcd. for $C_{15}H_{14}NO_3$ $[M+H]^+$ 256.0968, found 256.0986.

Compound 6g



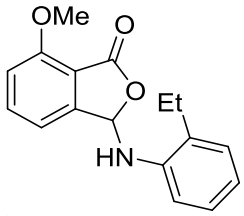
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd (merged), *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.61 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 3.99 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 158.3, 154.5, 148.2, 137.3, 136.4, 117.3, 115.0, 114.8, 112.3, 87.4, 56.1, 55.6; ESI-MS: m/z 286.0 $[(M+H)^+$, 100]; HRMS (ESI) calcd. for $C_{16}H_{16}NO_4$ $[M+H]^+$ 286.1074, found 286.1127.

Compound 6j



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd (merged), *J* = 8.0 Hz, 1H), 7.11 – 7.23 (m, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 12.0 Hz, 1H), 6.43 – 6.57 (m, 3H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.01 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 160.8, 158.4, 148.0, 145.1, 136.5, 130.2, 115.0, 114.8, 112.5, 107.6, 106.2, 101.2, 85.8, 56.1, 55.2; ESI-MS: m/z 286.0 [$(M+H)^+$, 100]; HRMS (ESI) calcd. for $C_{16}H_{16}NO_4$ $[M+H]^+$ 286.1074, found 286.1122.

Compound 6m

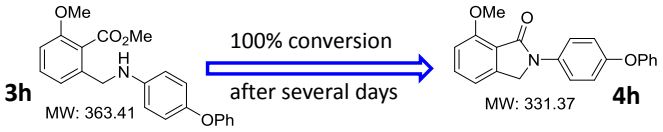


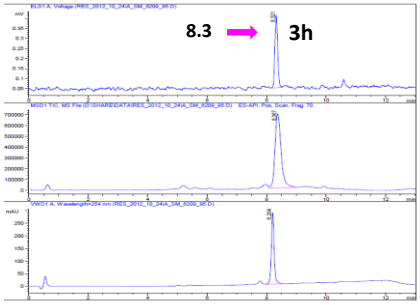
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd (merged), *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.12 – 7.19 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.89 – 7.00 (m, 1H), 6.72 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.03 (s, 3H), 2.43 – 2.60 (m, 2H), 1.24 (t, *J* = 7.5 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 158.4, 148.5, 141.4, 136.6, 129.9, 128.4, 127.2, 121.1, 115.1, 114.8, 114.1, 112.5, 86.4, 56.2, 23.9, 13.1; ESI-MS: m/z 284.1 [$(M+H)^+$, 100]; 286.1074 HRMS (ESI) calcd. for $C_{17}H_{18}NO_4$ $[M+H]^+$ 284.1281, found 284.1352.

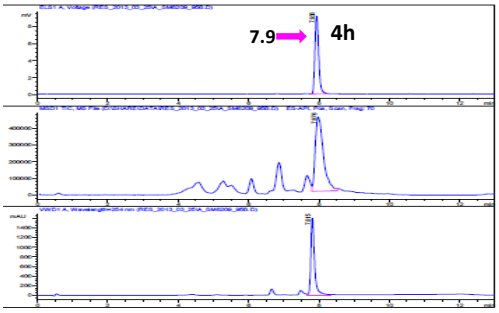
References

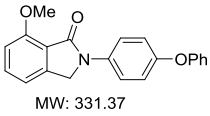
1. S. K. Mamidyala, S. Ramu, J. X. Huang, A. A. Robertson and M. A. Cooper, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1667-1670.
2. a)A. D. M. Karine Barral, and John E. Moses, *Org. Lett.*, 2007, **9**, 1809-1811; b)S. N. P. Jagattaran Das, Riti Awasthi, C. Prasad Narasimhulu, Sanjay Trehan, *Synthesis*, 2005, 1801-1806.
3. Y. Kubota, Tatsuno, T, *Chem. Pharm. Bull.*, 1971, **19**, 1226-1223.

LCMS data

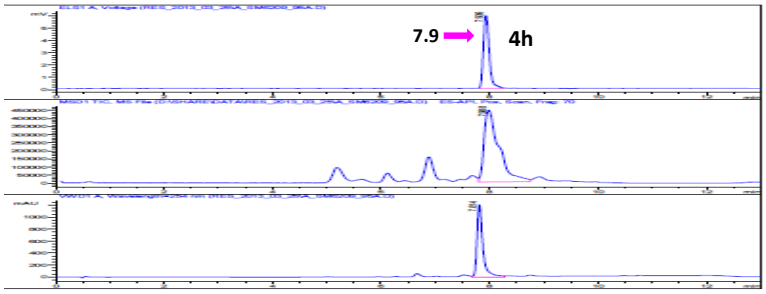


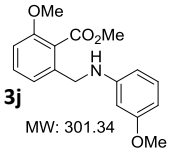


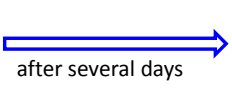


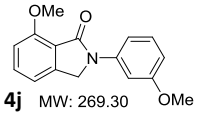


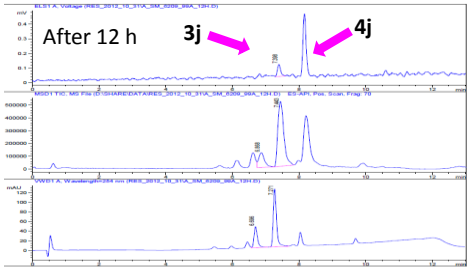
Isolated pure compound **4h**

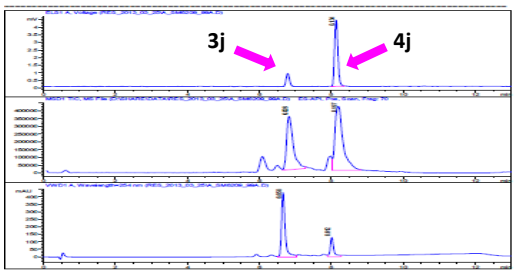


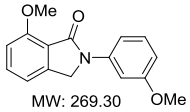




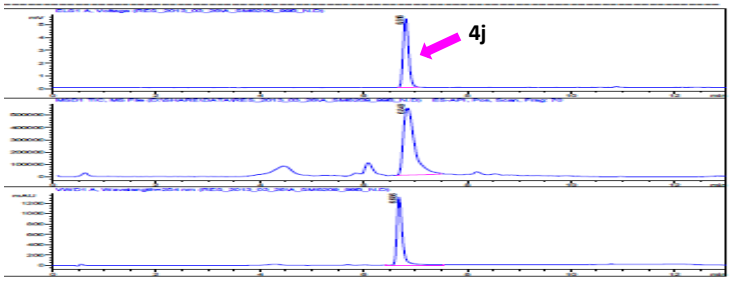


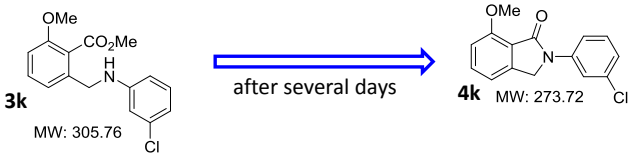


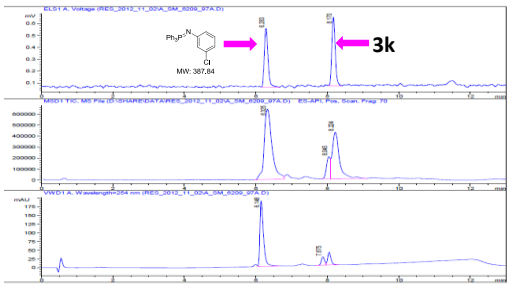


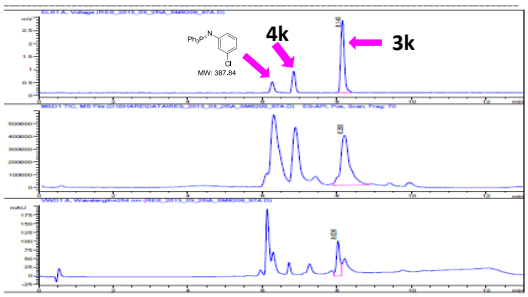


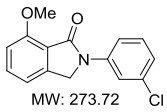
Isolated pure compound **4j**



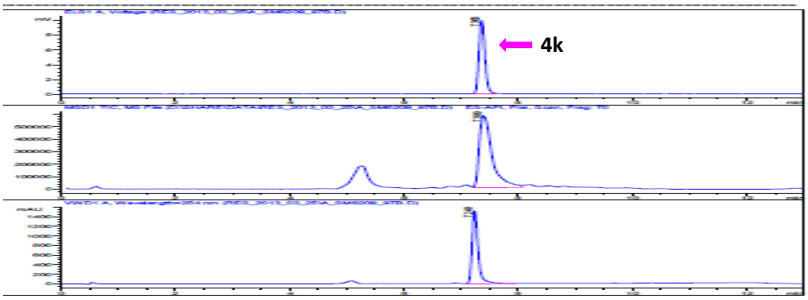


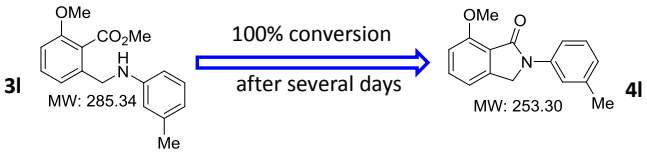


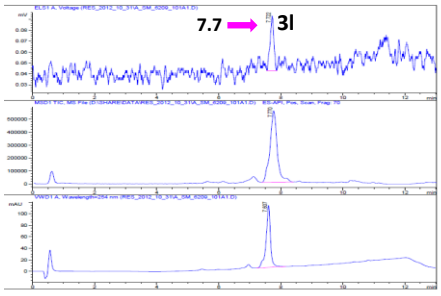


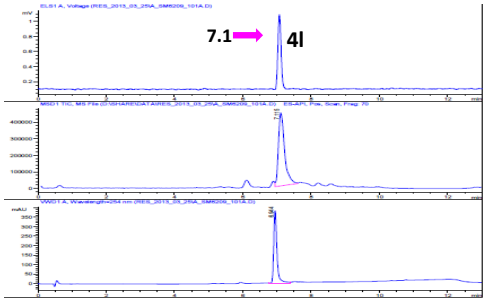


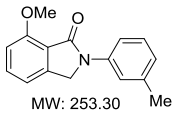
Isolated pure compound **4k**



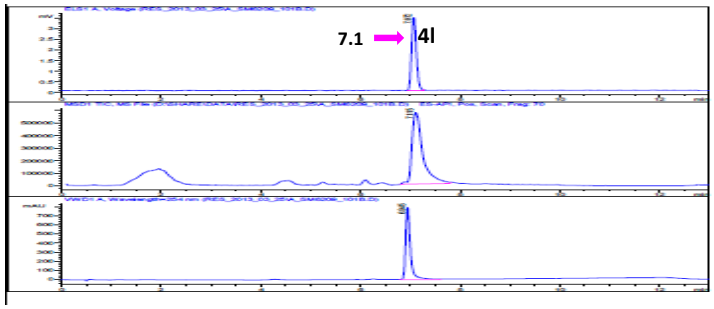


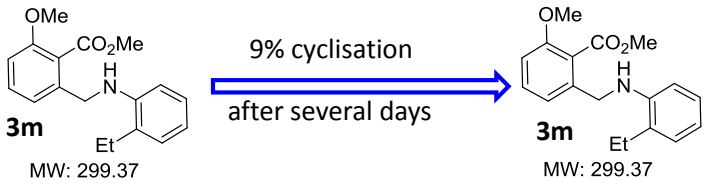






Isolated pure compound **4l**




OMe
CO2Me
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N
Et
3m
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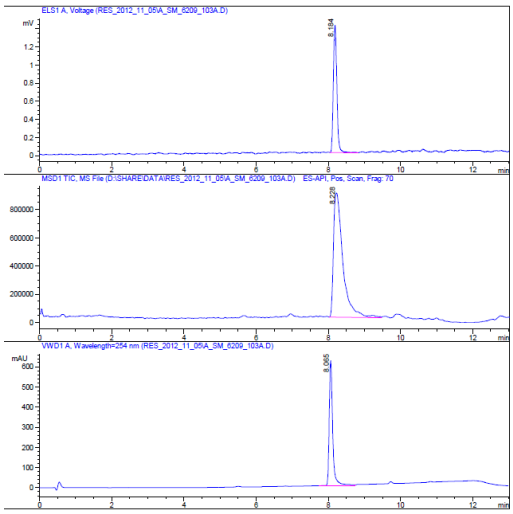
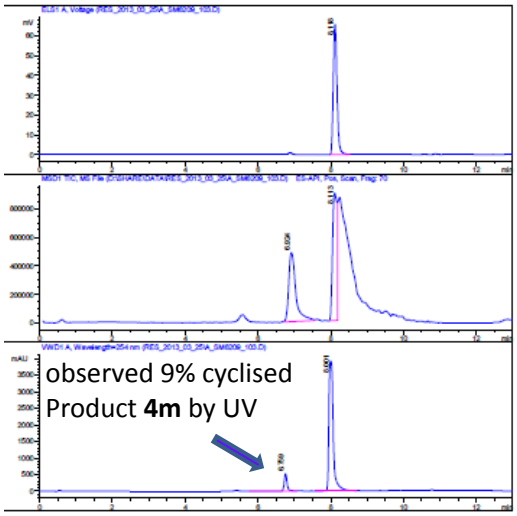
9% cyclisation
after several days
OMe
CO2Me
H
N
Et
3m
MW: 299.37

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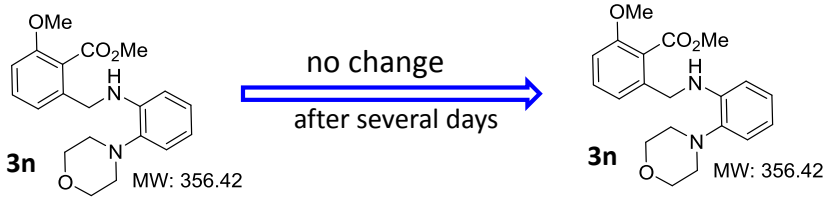
Product 4m by UV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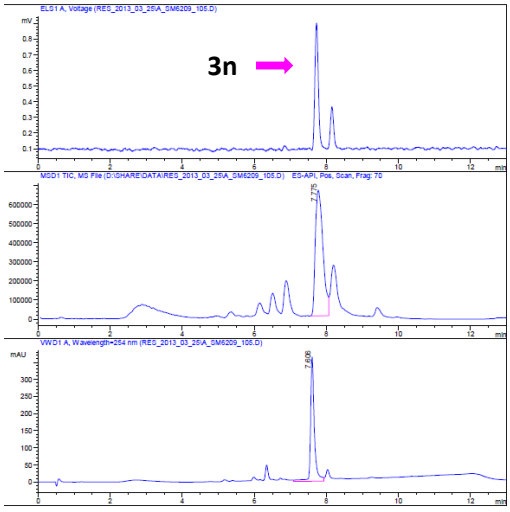
MW: 356.42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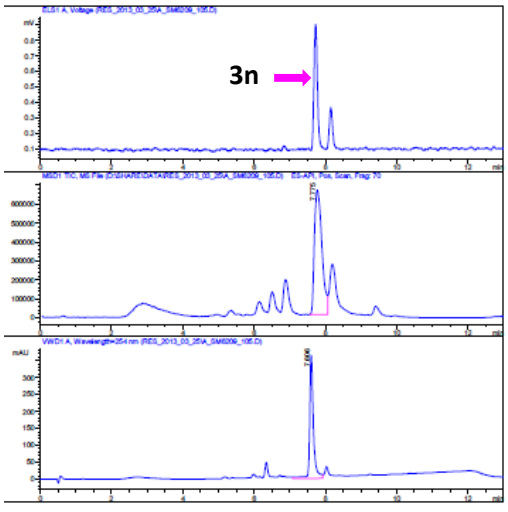
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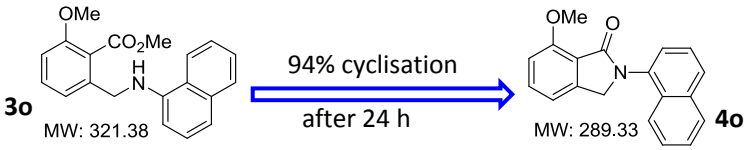
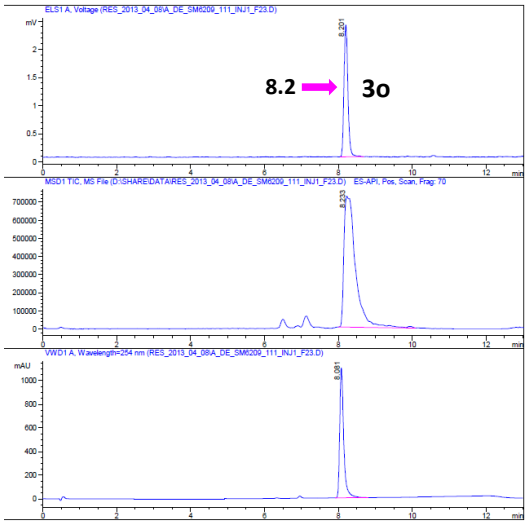
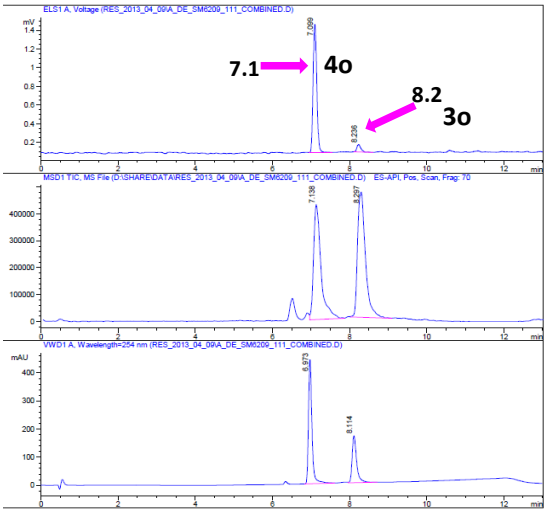
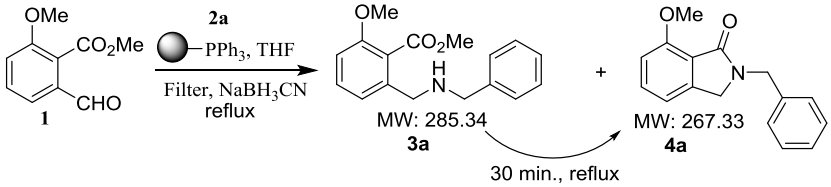
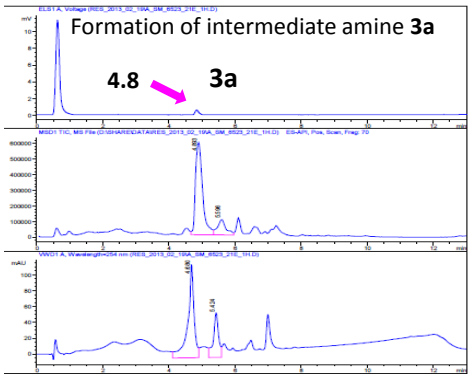
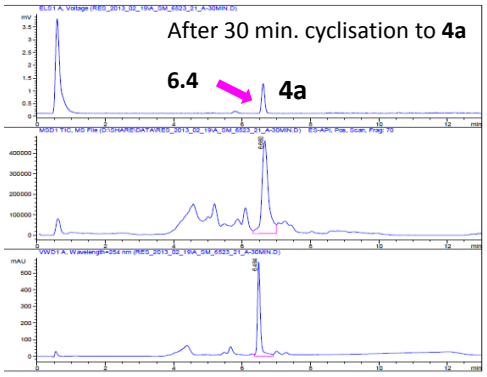


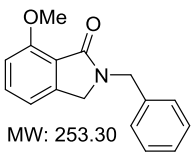




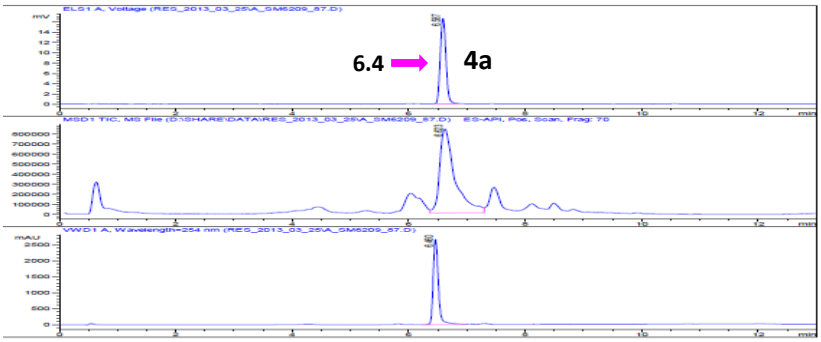


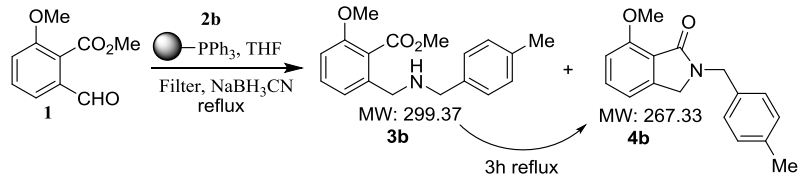






Isolated pure compound **4a**

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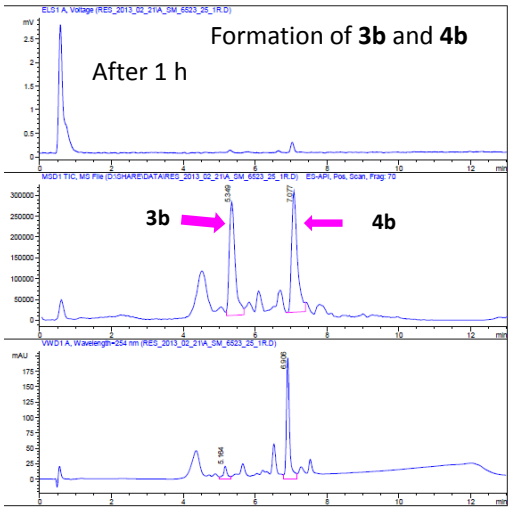
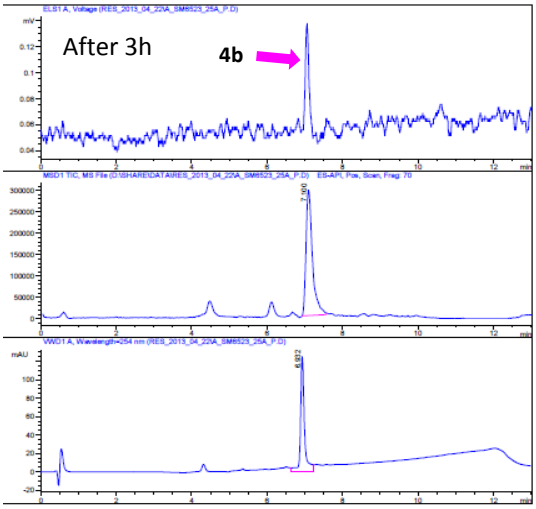
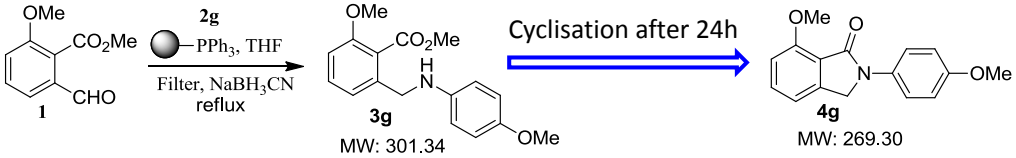
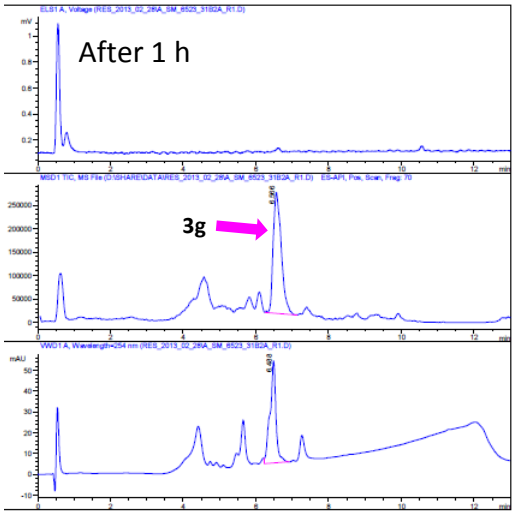
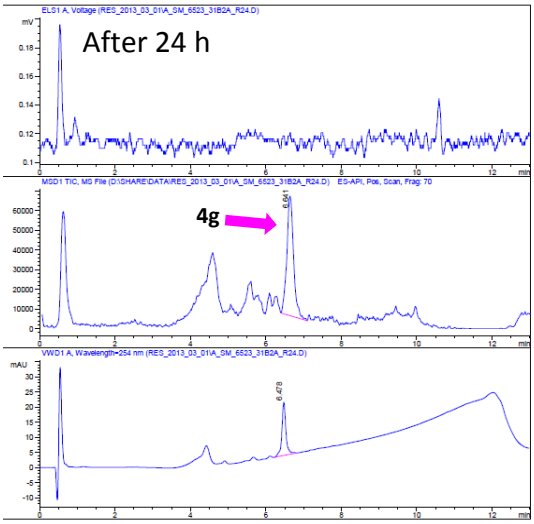
4b
Me

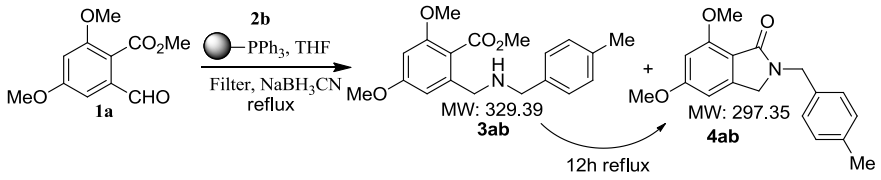

Formation of 3b and 4b
After 1 h
3b
4b

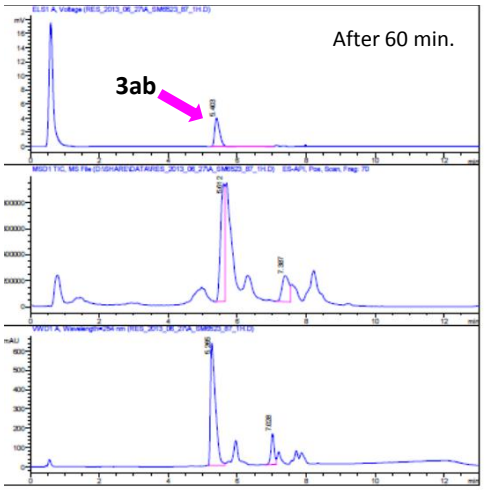

After 3h
4b

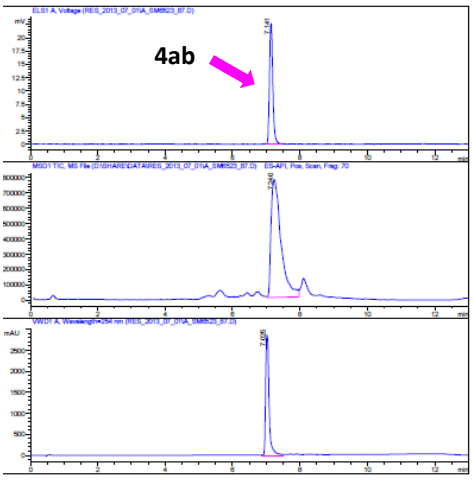

OMe
CO2Me
CHO
1
2g
PPh3, THF
Filter, NaBH3CN
reflux
3g
MW: 301.34
Cyclisation after 24h
4g
MW: 269.30

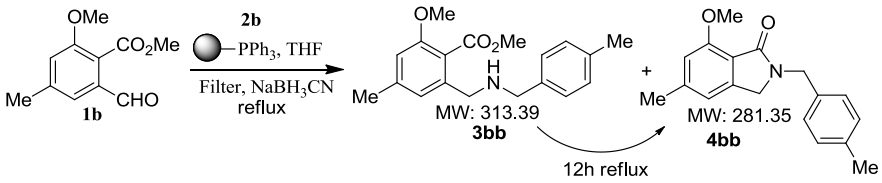

After 1 h
3g

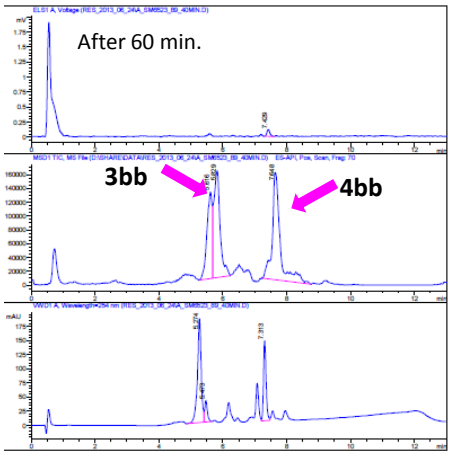

After 24 h
4g

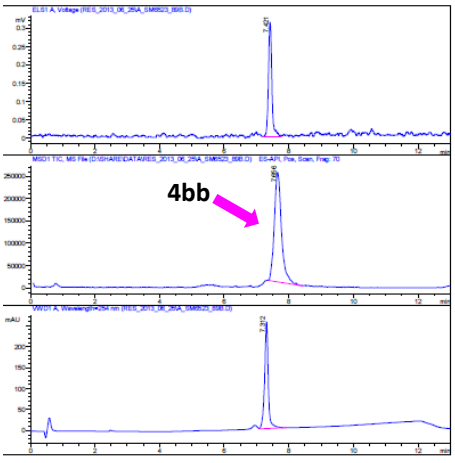

OMe
CO2Me
MeO
CHO
1a
2b
PPh3, THF
Filter, NaBH3CN
reflux
MW: 329.39
3ab
MW: 297.35
4ab
12h reflux
Me

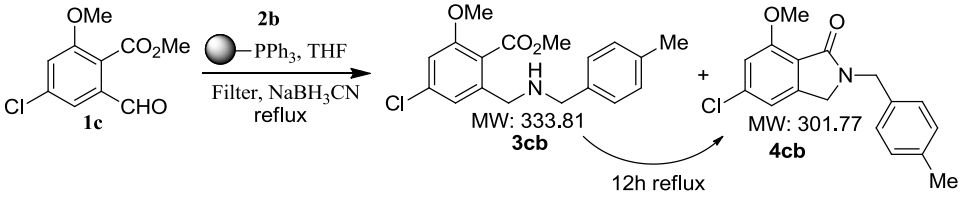

After 60 min.
3ab

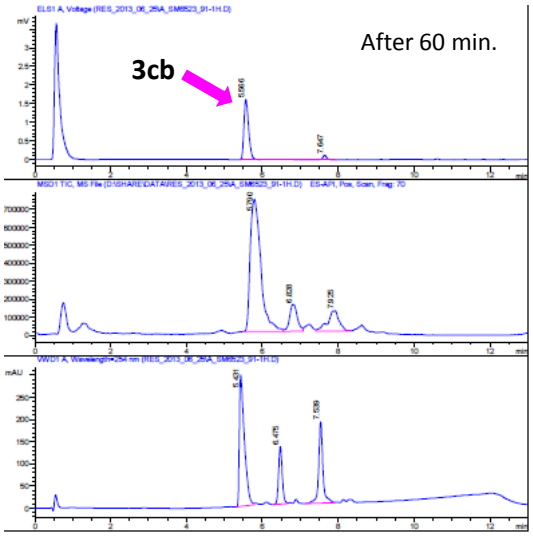

4ab

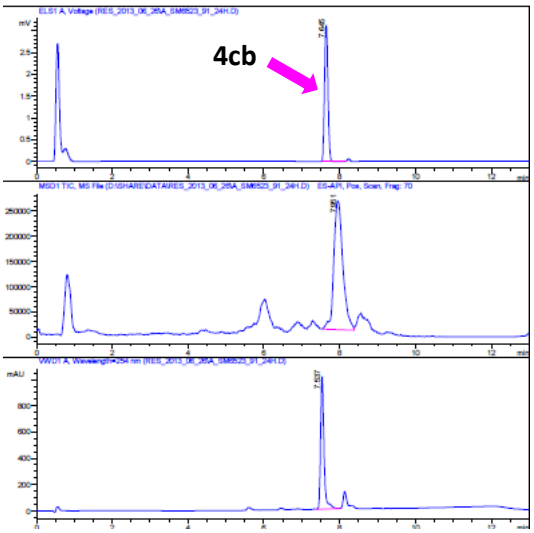

OMe
CO2Me
Me
CHO
1b
2b
PPh3, THF
Filter, NaBH3CN
reflux
MW: 313.39
3bb
MW: 281.35
4bb
12h reflux


After 60 min.
3bb
4bb

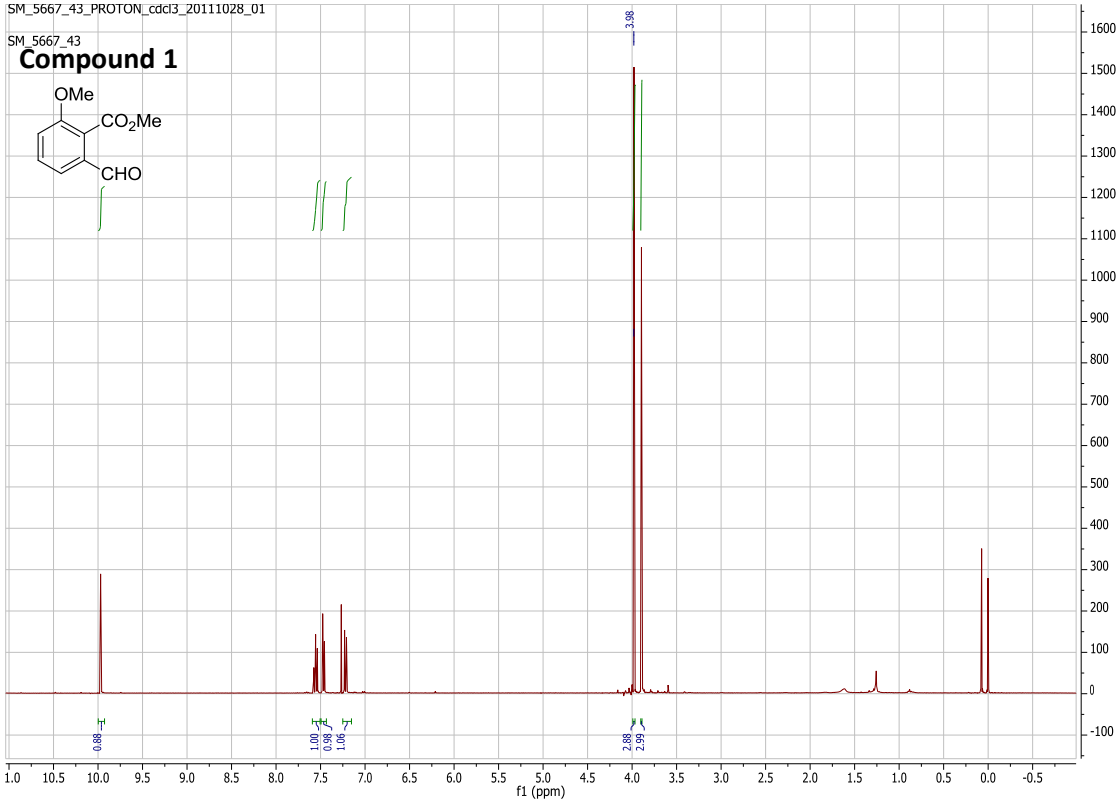

4bb

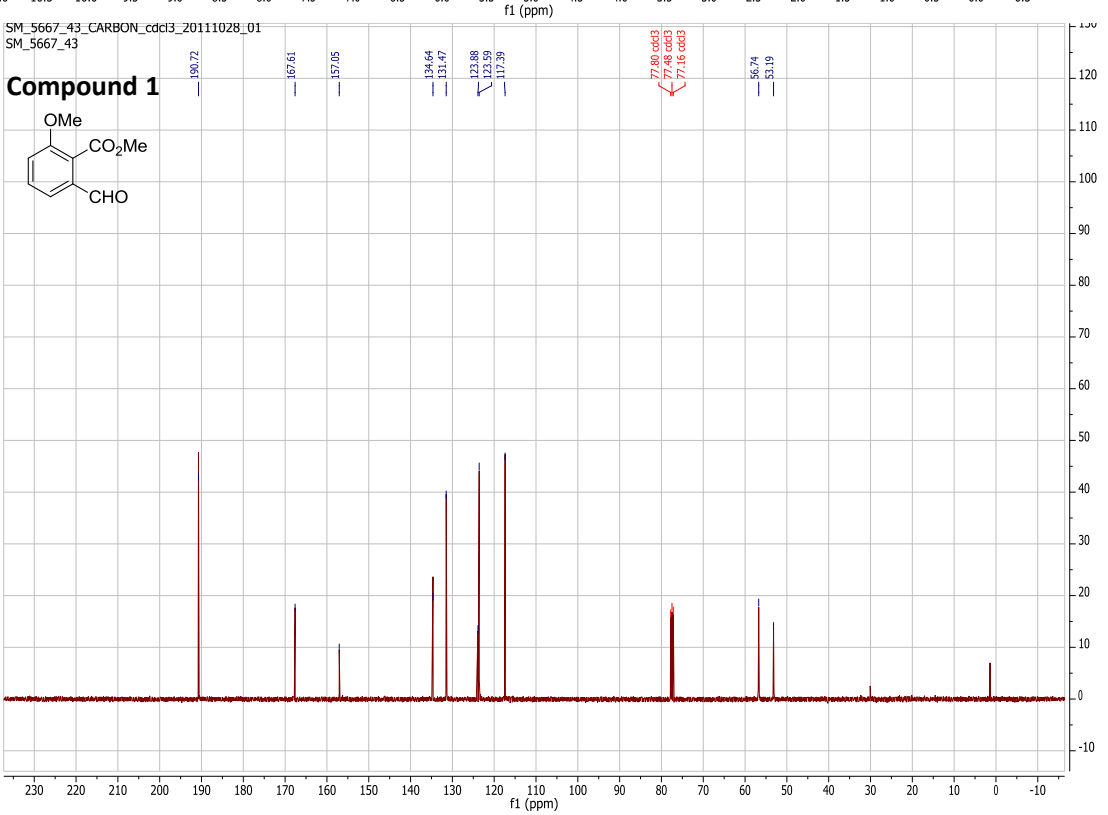

OMe
CO2Me
Cl
CHO
1c
2b
PPh3, THF
Filter, NaBH3CN
reflux
OMe
CO2Me
H
N
Me
Cl
MW: 333.81
3cb
12h reflux
OMe
O
N
Cl
MW: 301.77
4cb
Me

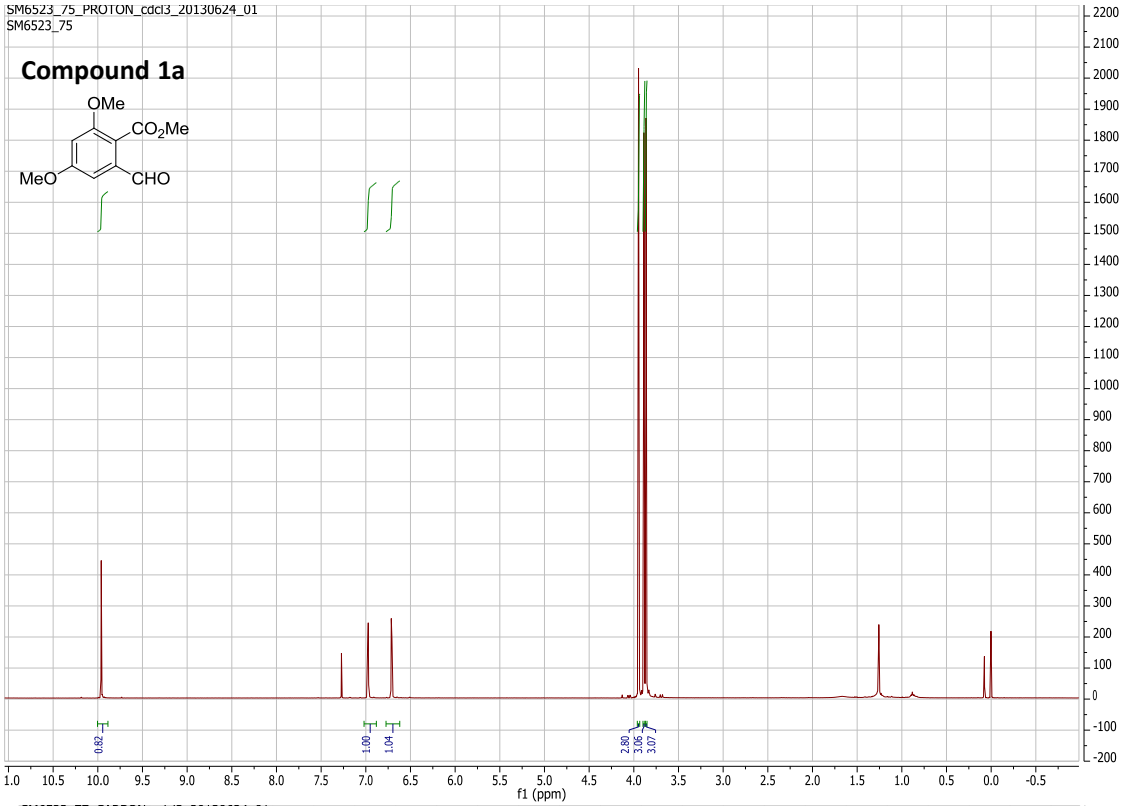

After 60 min.
3cb

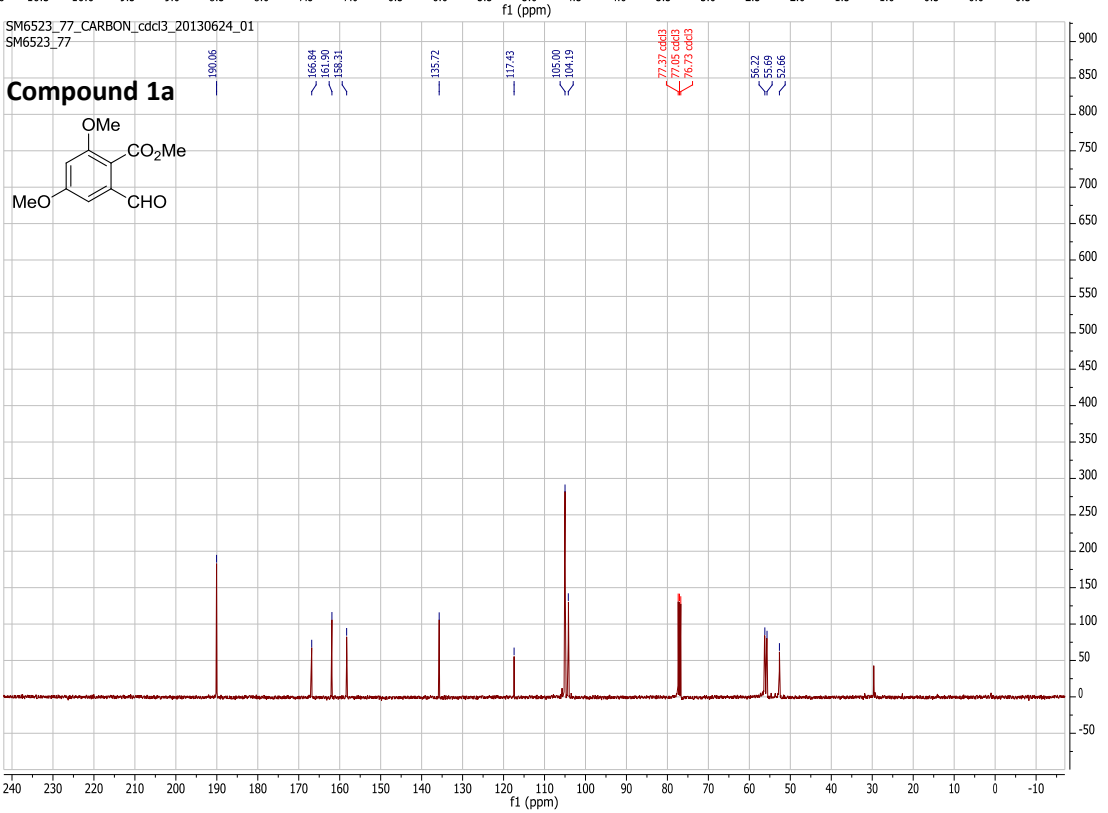

4cb

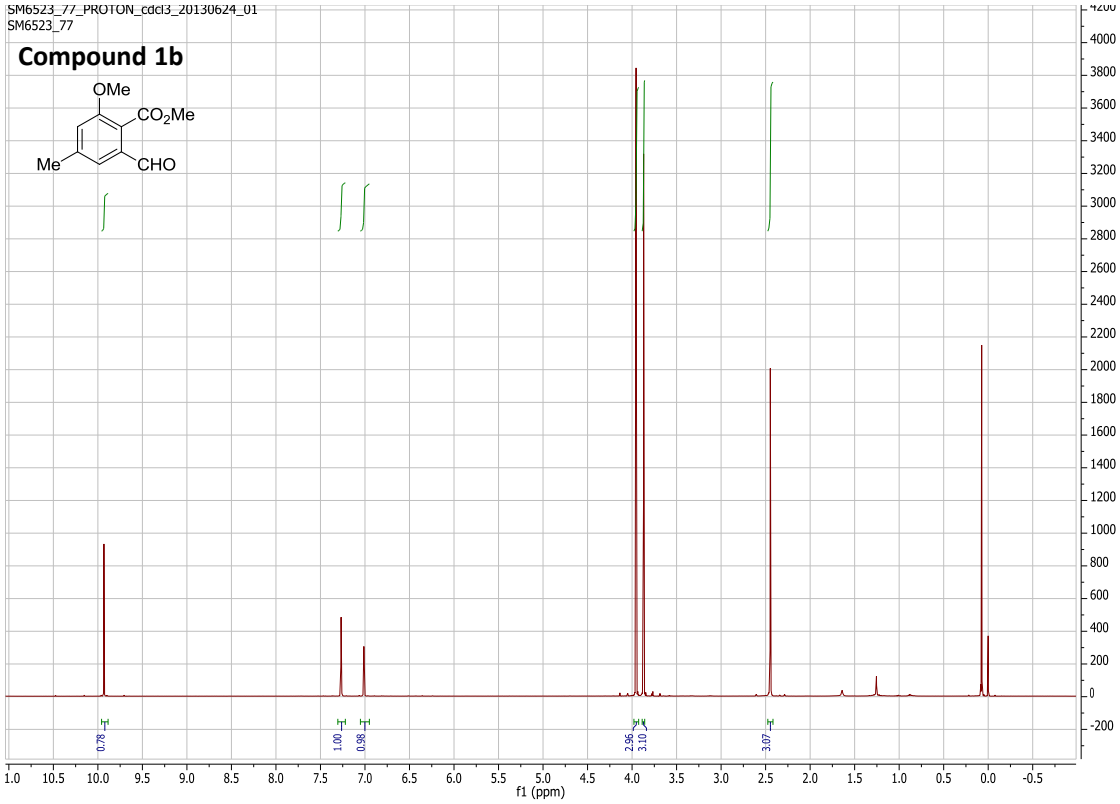
Copies of 1H NMR and 13C NMR spectra

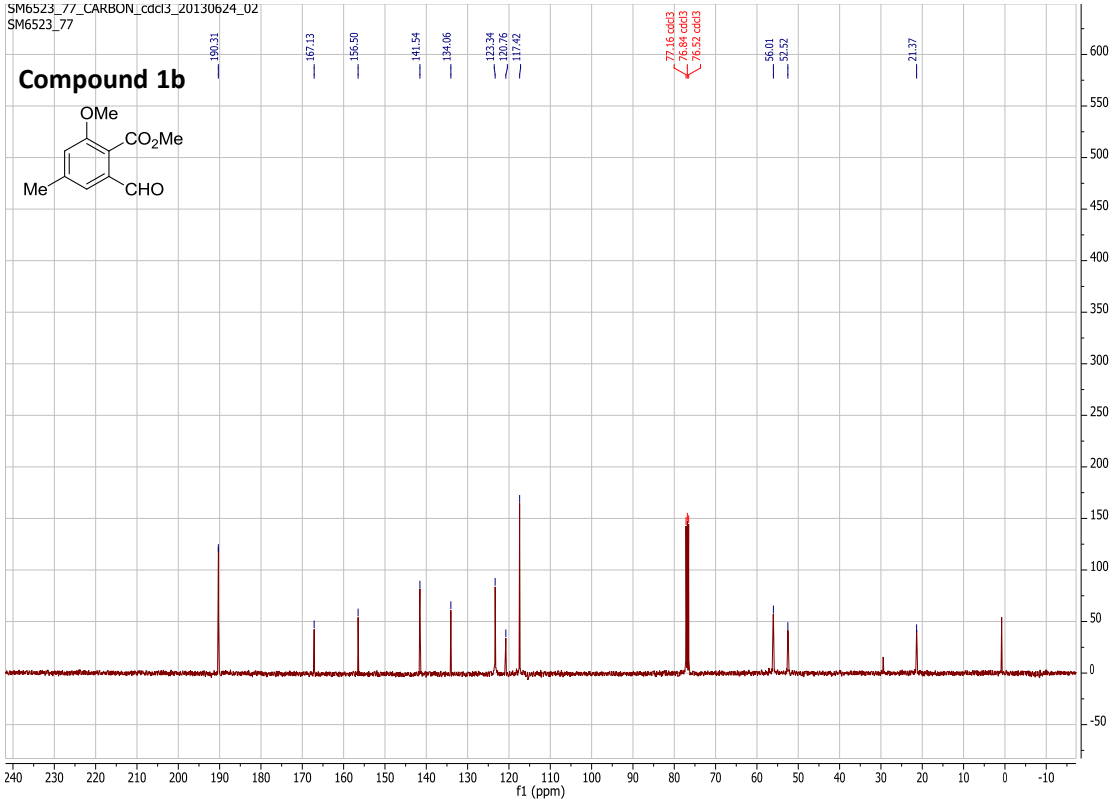


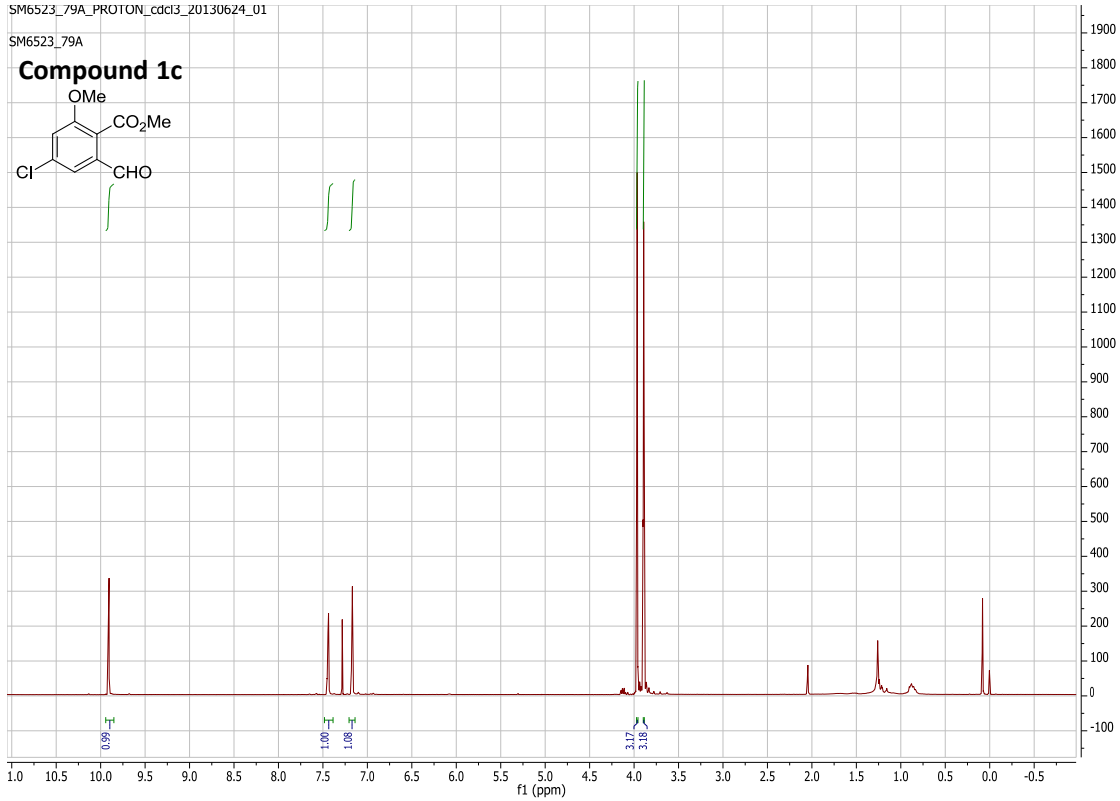


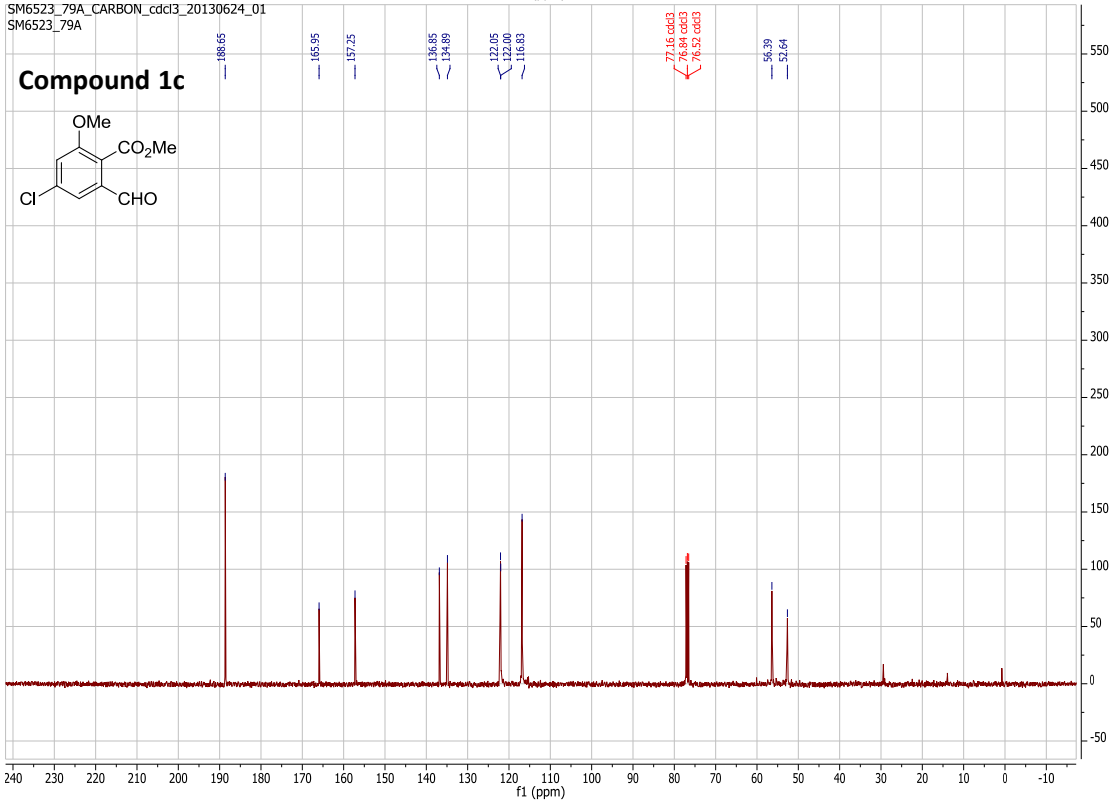

SM6523_75_PROTON_cdcl3_20130624_01
SM6523_75
Compound 1a
OMe
CO2Me
MeO
CHO
0.82
1.00
1.04
2.80
3.06
3.07
f1 (ppm)

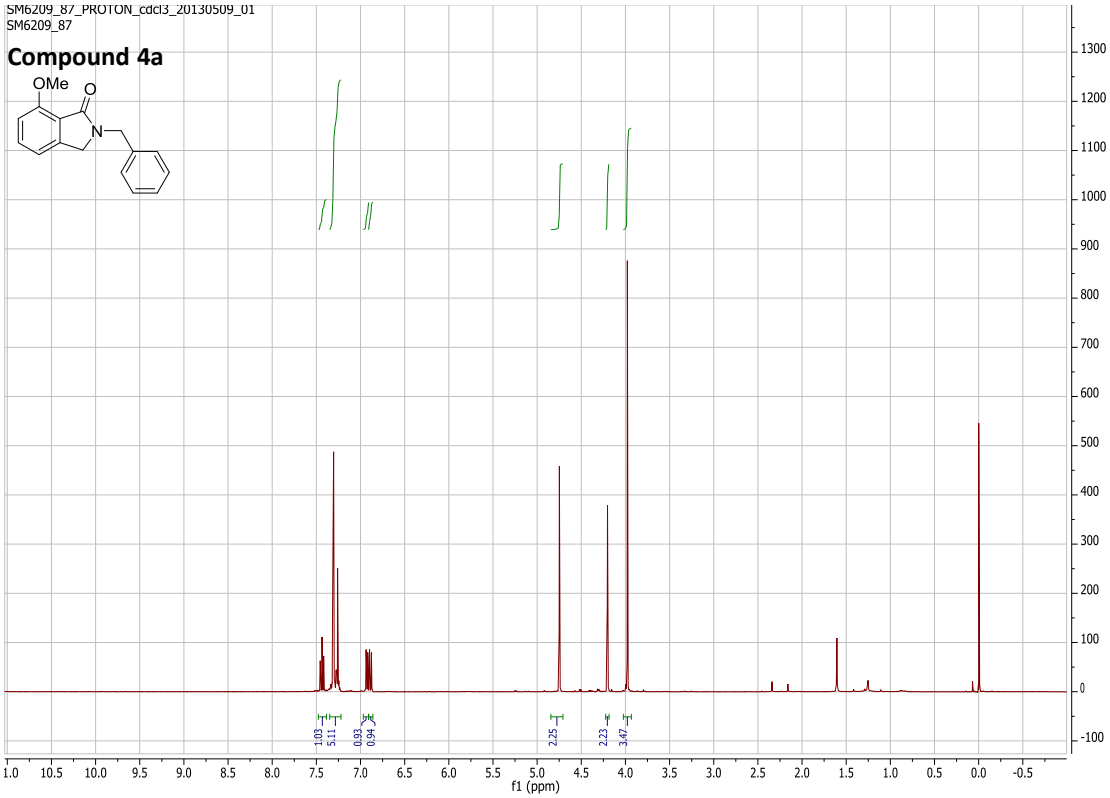

SM6523_77_CARBON_cdcl3_20130624_01
SM6523_77
Compound 1a
OMe
CO2Me
MeO
CHO
190.06
166.84
161.90
158.31
135.72
117.43
105.00
104.19
77.37 cdcl3
77.05 cdcl3
76.73 cdcl3
56.22
55.69
52.66
f1 (ppm)

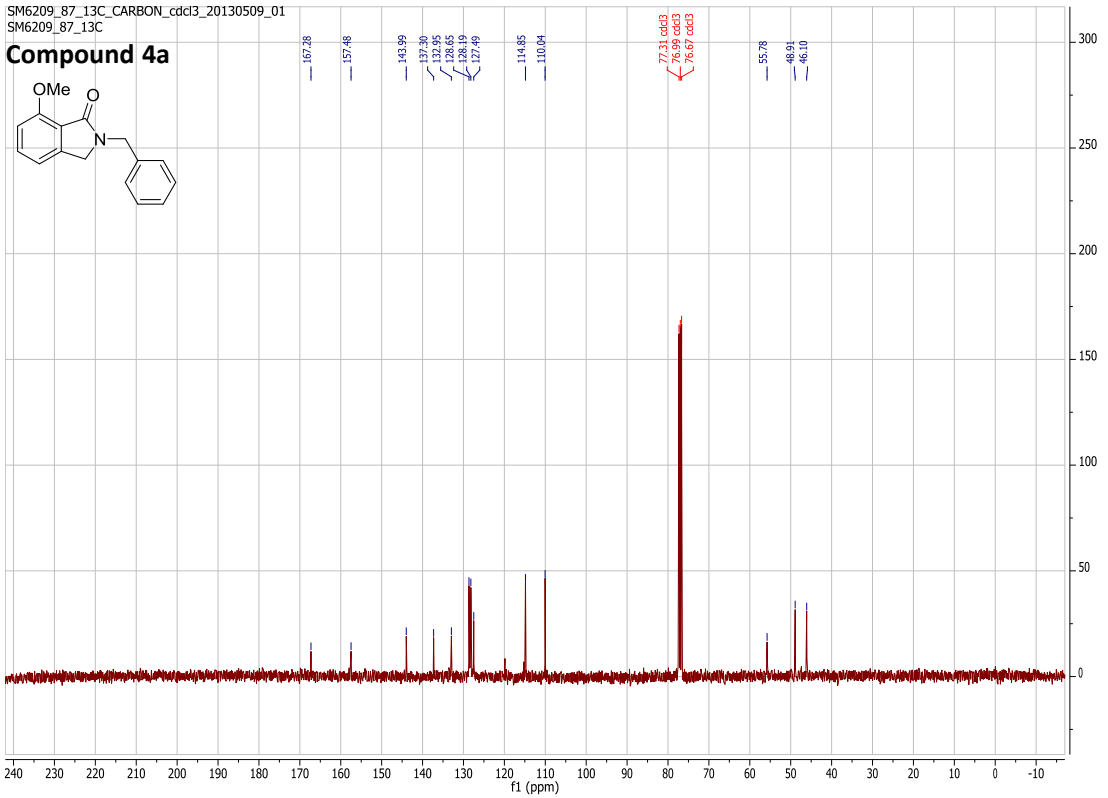

SM6523_77_PROTON_cdcl3_20130624_01
SM6523_77
Compound 1b
OMe
CO2Me
Me
CHO
0.78
1.00
0.98
2.95
3.10
3.07
f1 (ppm)

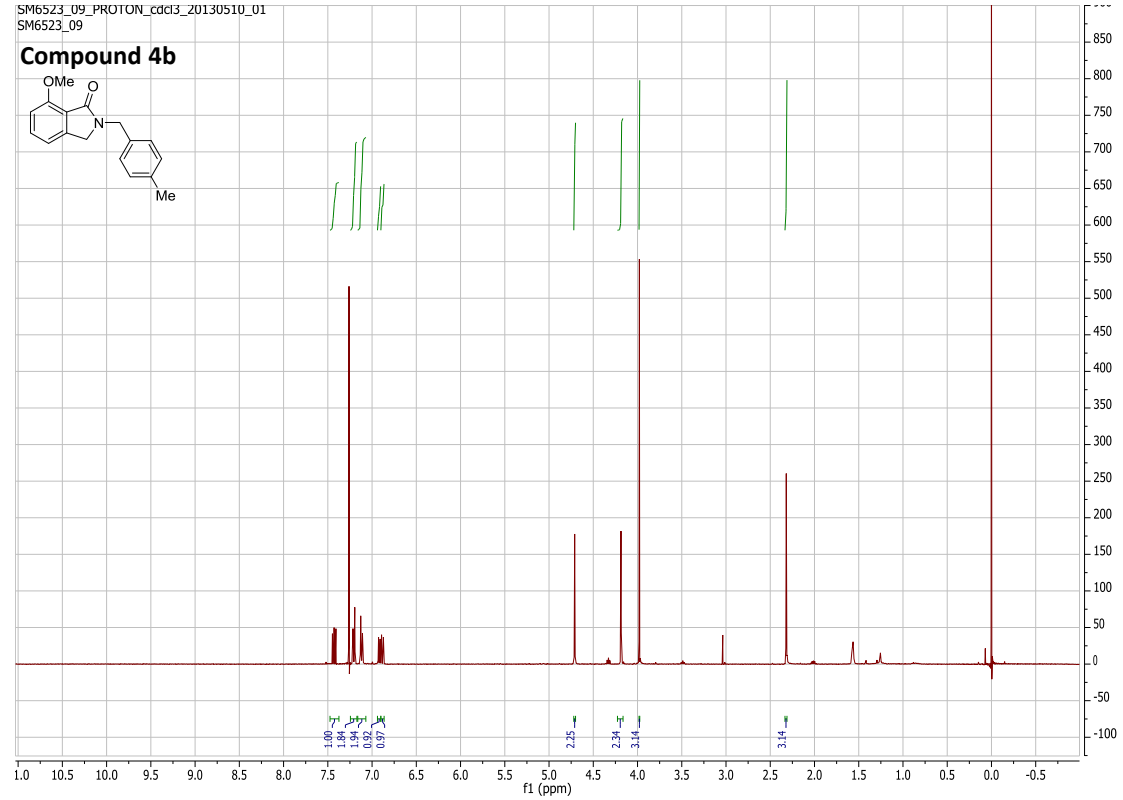

SM6523_77_CARBON_cdcl3_20130624_02
SM6523_77
Compound 1b
OMe
CO2Me
Me
CHO
190.31
167.13
156.50
141.54
134.06
123.34
120.76
117.42
77.16 cdcl3
76.84 cdcl3
76.52 cdcl3
56.01
52.52
21.37
f1 (ppm)

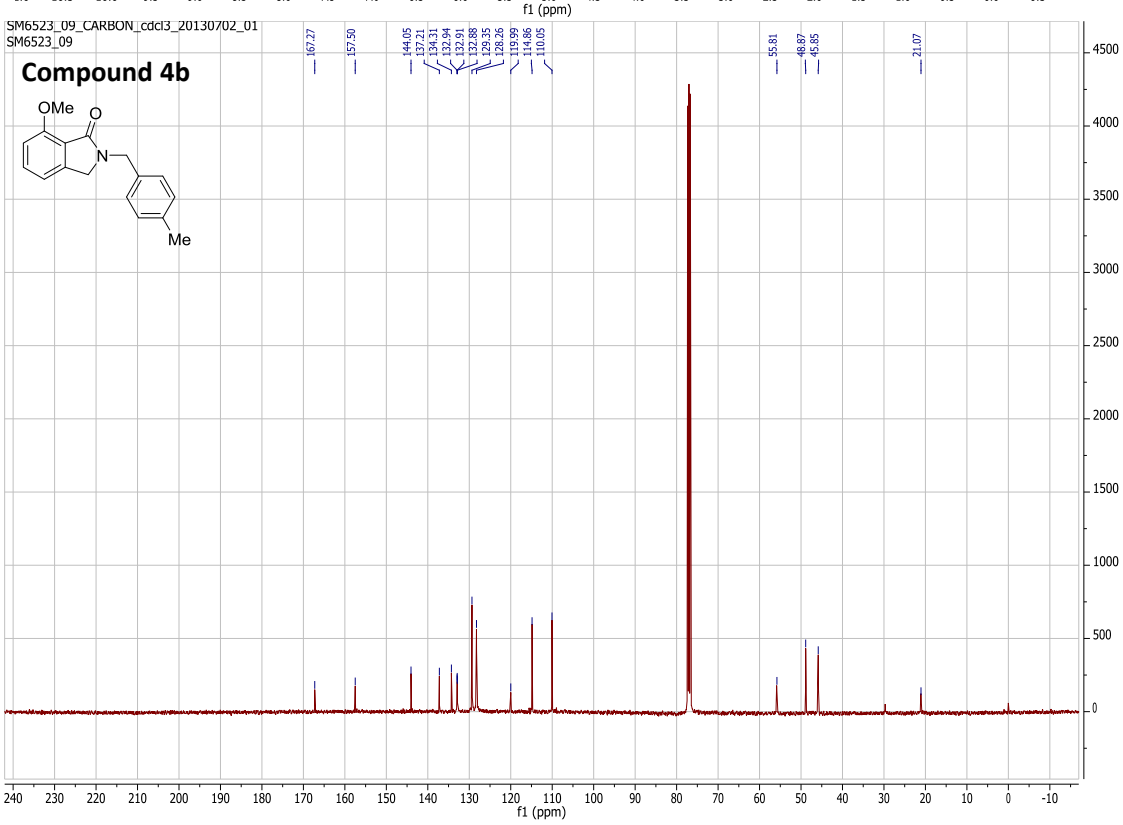

SM6523_79A_PROTON_cdcl3_20130624_01
SM6523_79A
Compound 1c
OMe
CO2Me
Cl
CHO
0.99
1.00
1.08
3.17
3.18
f1 (ppm)

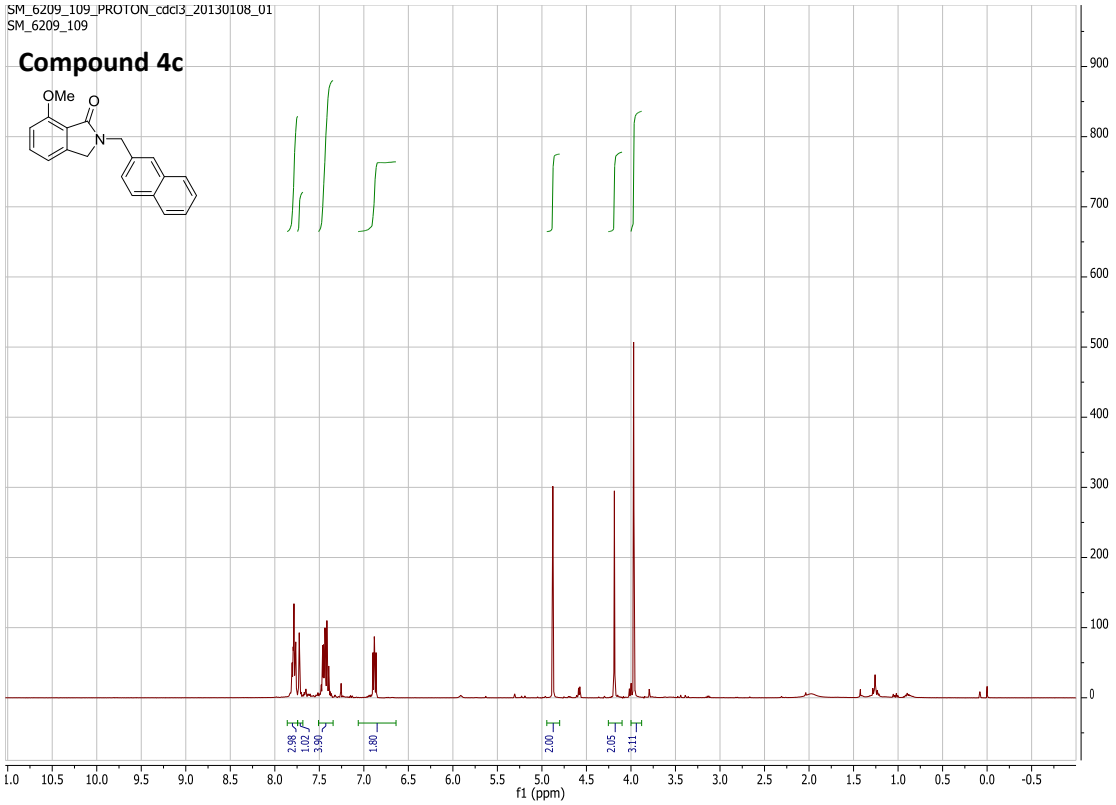

SM6523_79A_CARBON_cdcl3_20130624_01
SM6523_79A
Compound 1c
OMe
CO2Me
Cl
CHO
188.65
165.95
157.25
136.85
134.89
122.05
122.00
116.83
77.16 cdcl3
76.84 cdcl3
76.52 cdcl3
56.39
52.64
f1 (ppm)

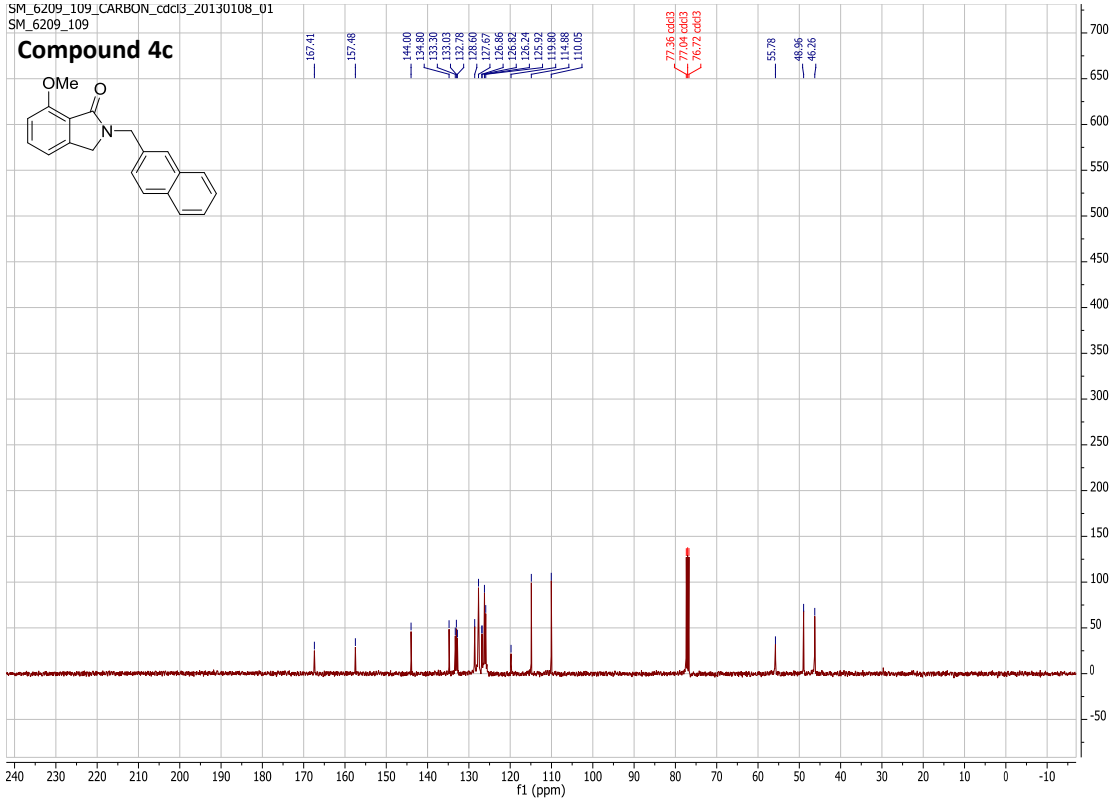

SM6209_87_PROTON_cdcl3_20130509_01
SM6209_87
Compound 4a
OMe
O
N
1.03
5.11
0.93
0.94
2.25
2.23
3.47
f1 (ppm)

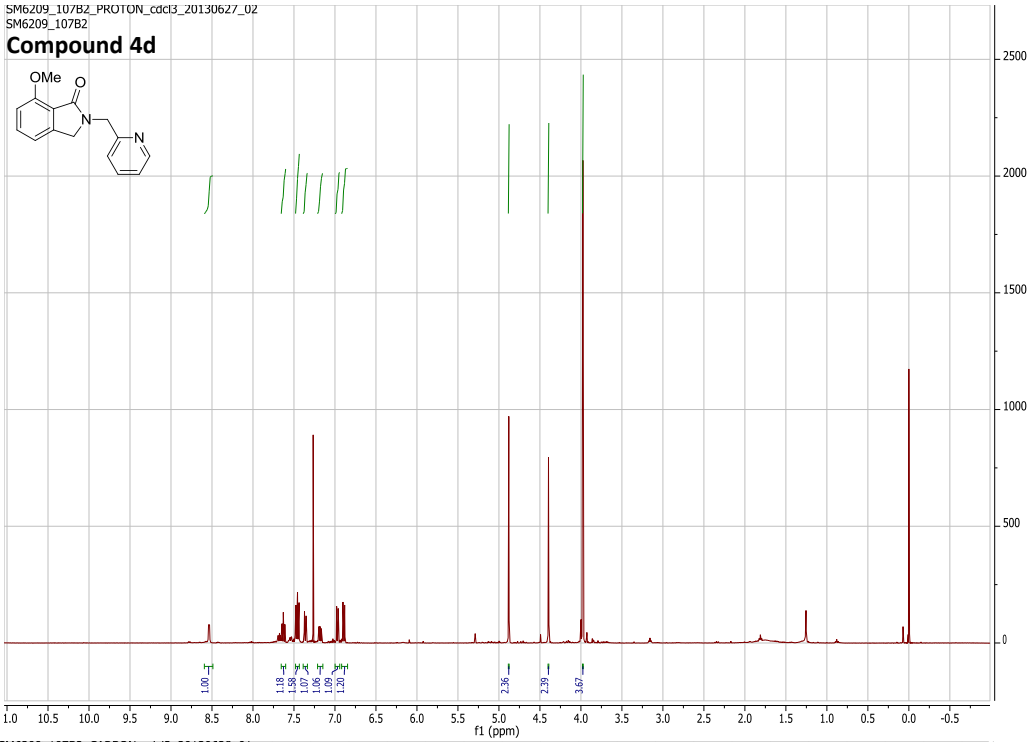

SM6209_87_13C_CARBON_cdcl3_20130509_01
SM6209_87_13C
Compound 4a
OMe
O
N
167.28
157.48
143.99
137.30
132.95
128.65
128.49
127.49
114.85
110.04
77.31 cdcl3
76.99 cdcl3
76.67 cdcl3
55.78
48.91
46.10
f1 (ppm)

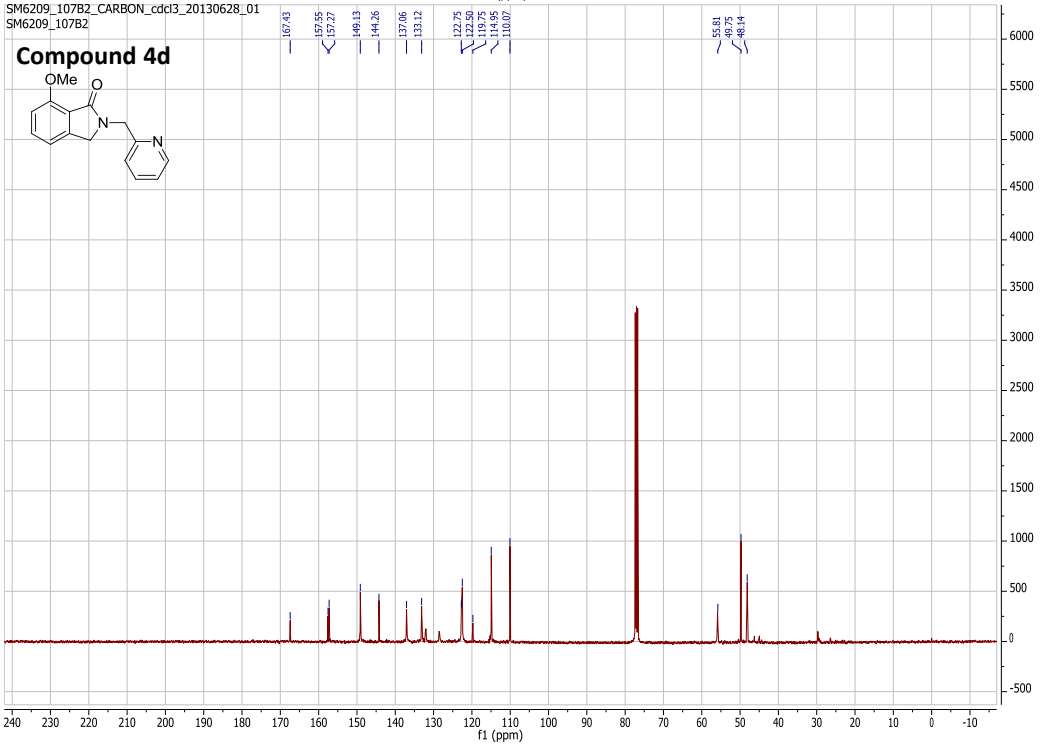

SM6523_09_PROTON_cdcl3_20130510_01
SM6523_09
Compound 4b
OMe
O
N
Me
1.00
1.84
1.94
0.92
0.97
2.25
2.34
3.14
3.14
f1 (ppm)

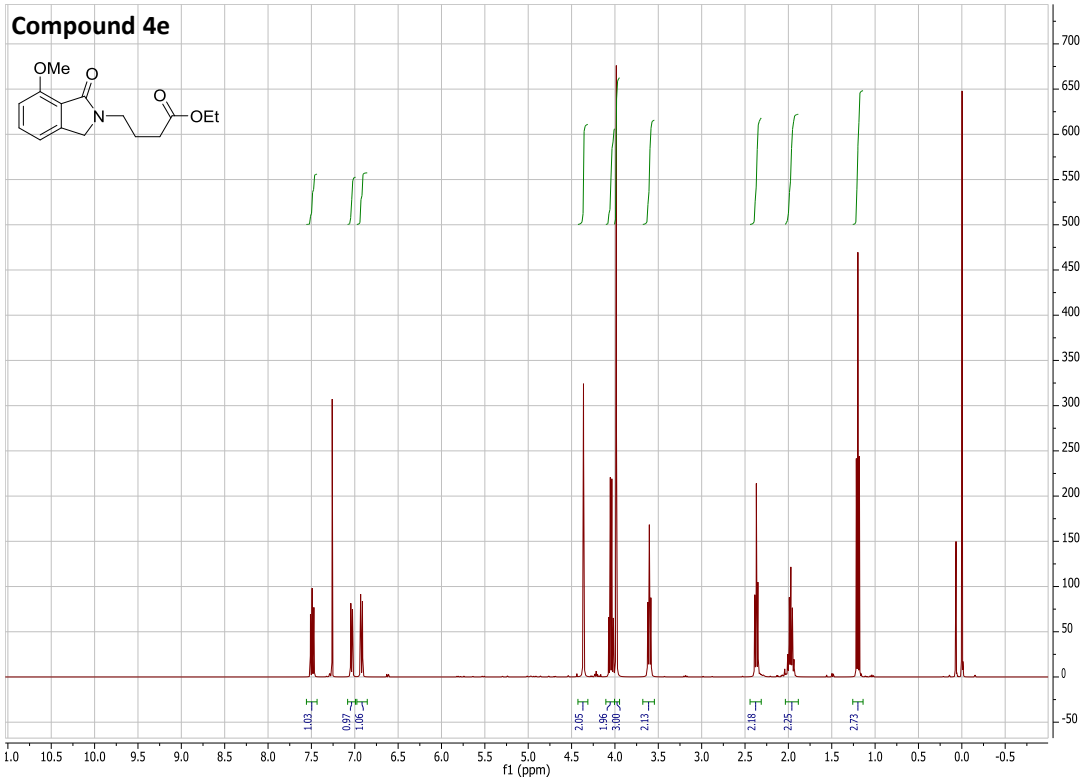

SM6523_09_CARBON_cdcl3_20130702_01
SM6523_09
Compound 4b
OMe
O
N
Me
167.27
157.50
144.05
137.21
134.31
132.94
132.91
132.88
129.35
128.26
119.99
114.86
110.05
55.81
48.87
45.85
21.07
f1 (ppm)

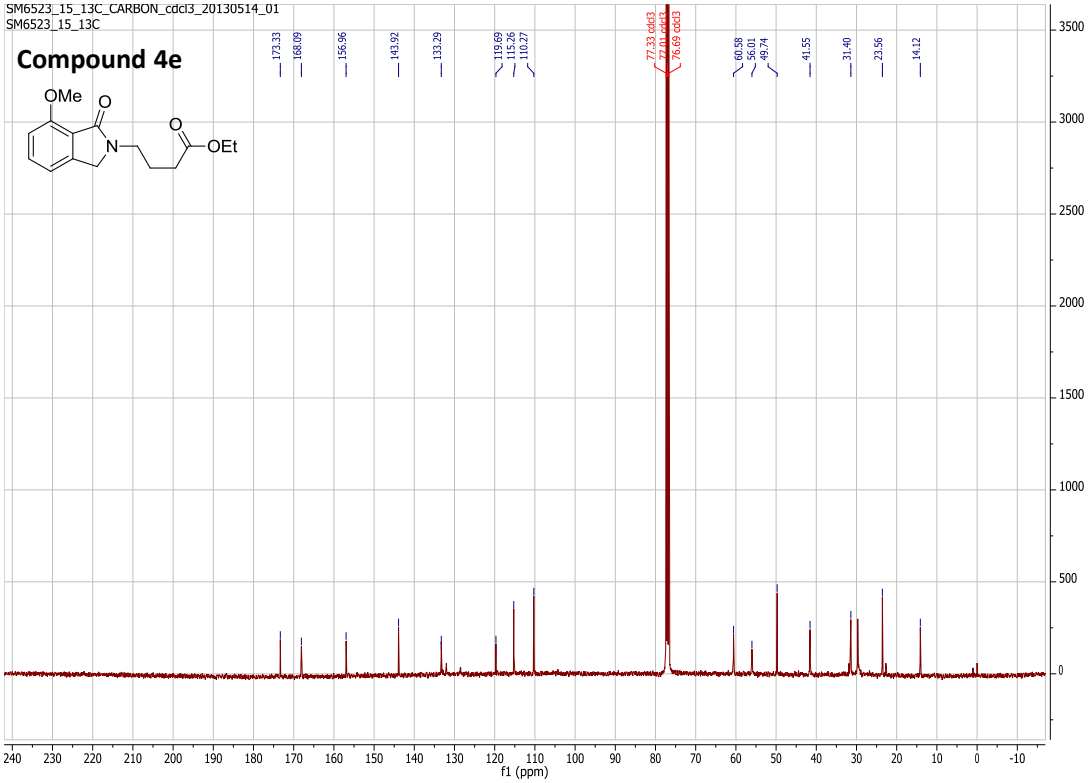

SM_6209_109_PROTON_cdcl3_20130108_01
SM_6209_109
Compound 4c
OMe
O
N
2.98
1.02
3.90
1.80
2.00
2.05
3.11
f1 (ppm)

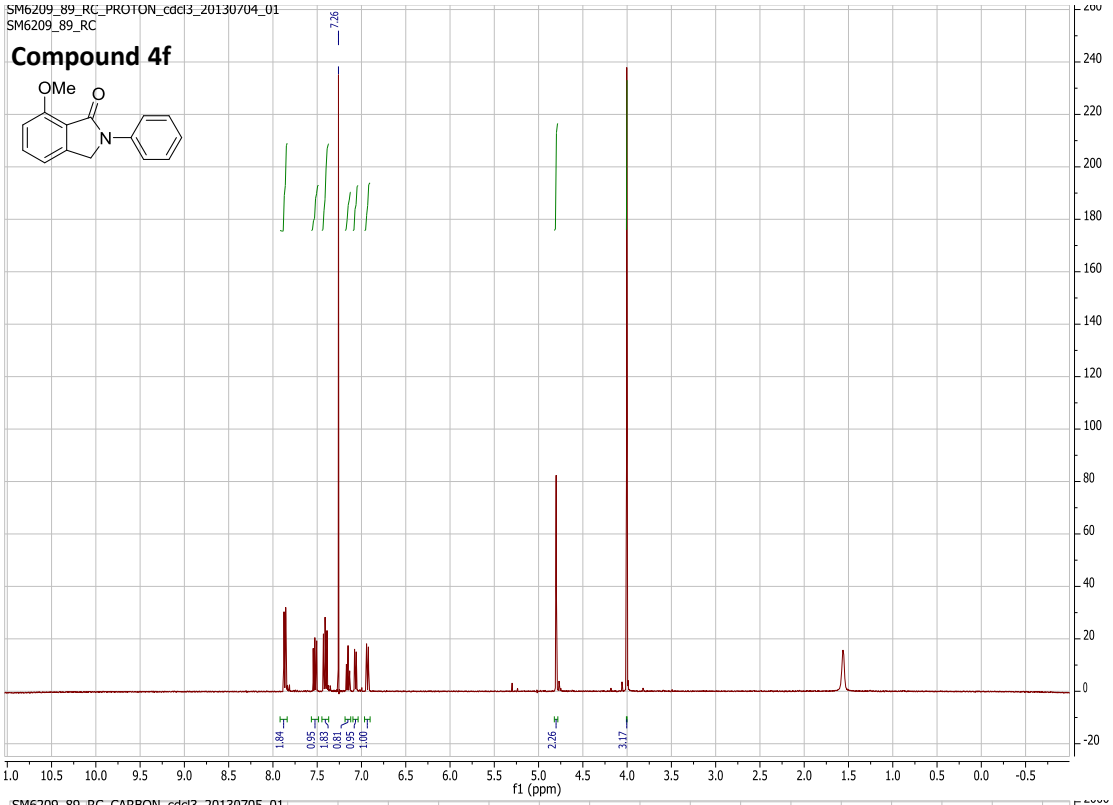

SM_6209_109_CARBON_cdcl3_20130108_01
SM_6209_109
Compound 4c
OMe
O
N
167.41
157.48
144.00
134.80
133.30
133.03
132.78
128.60
127.67
126.86
126.82
126.24
125.92
119.80
114.88
110.05
77.36 cdcl3
77.04 cdcl3
76.72 cdcl3
55.78
48.96
46.26
f1 (ppm)

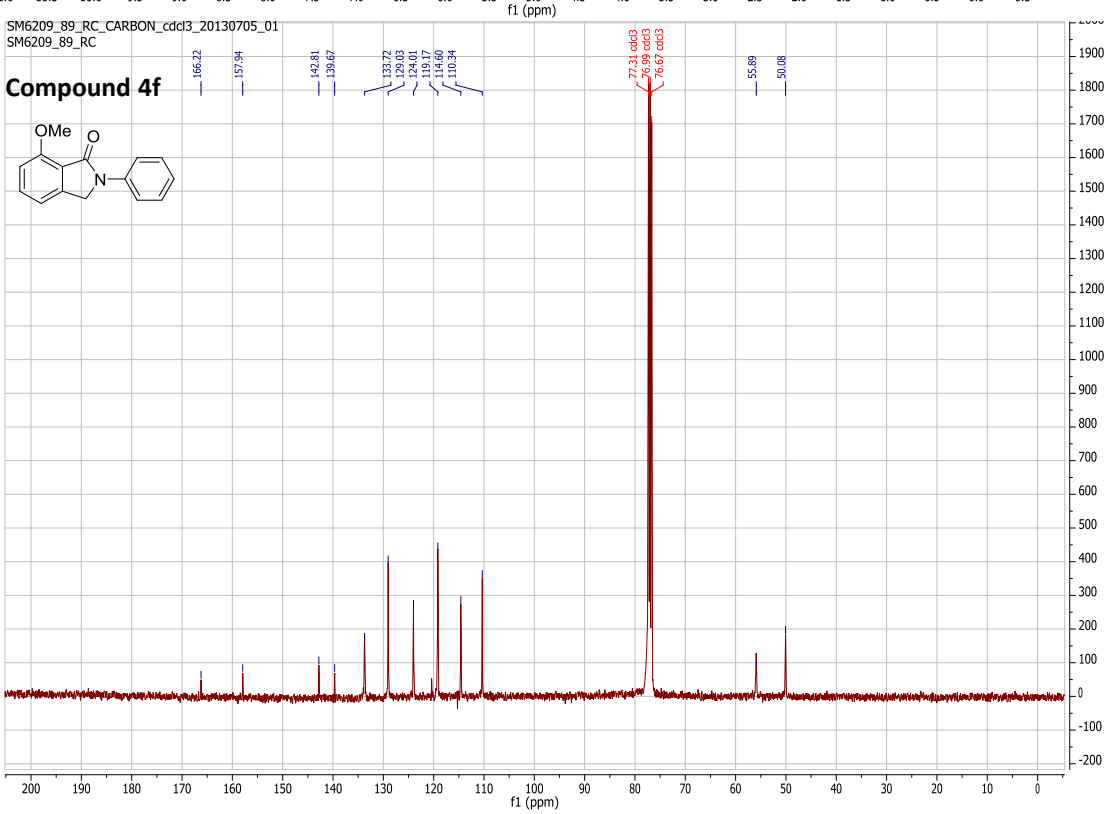

SM6209_107B2_PROTON_cdcl3_20130627_02
SM6209_107B2
Compound 4d
OMe
O
N
N
1.00
1.18
1.58
1.07
1.06
1.09
1.20
2.36
2.39
3.67
f1 (ppm)

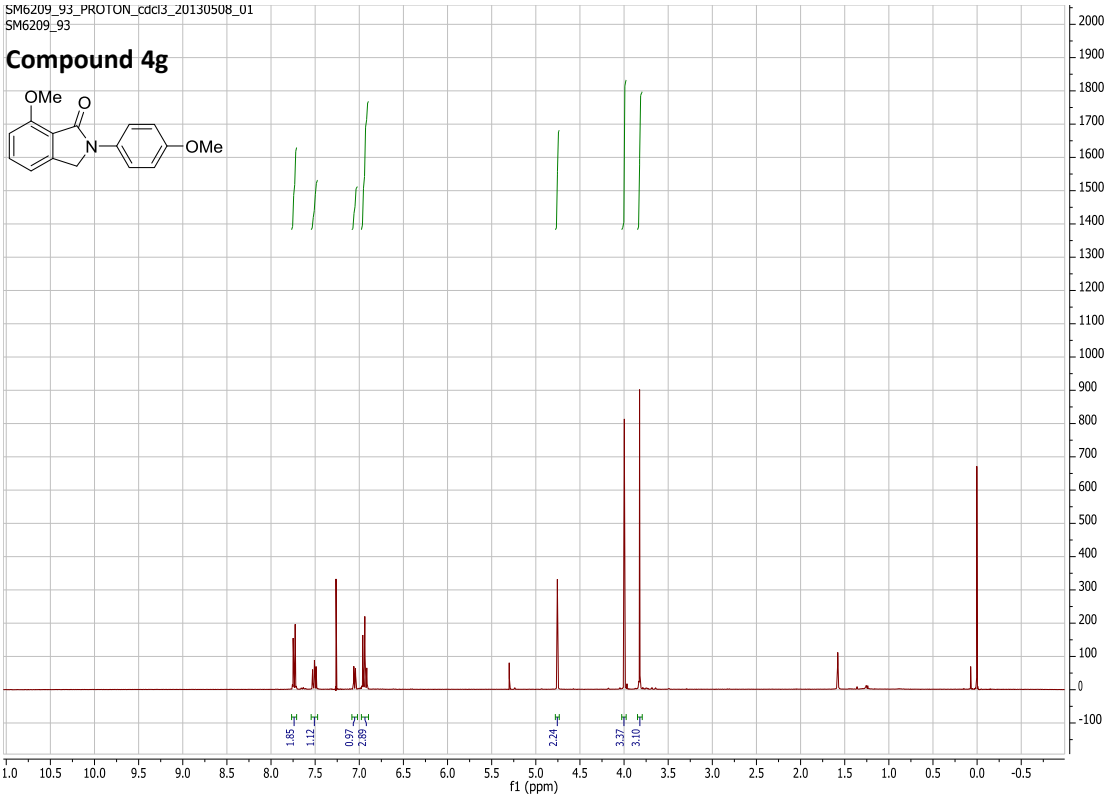

SM6209_107B2_CARBON_cdcl3_20130628_01
SM6209_107B2
Compound 4d
OMe
O
N
N
167.43
157.55
157.27
149.13
144.26
137.06
133.12
122.75
122.50
119.75
114.95
110.07
55.81
49.75
48.14
f1 (ppm)

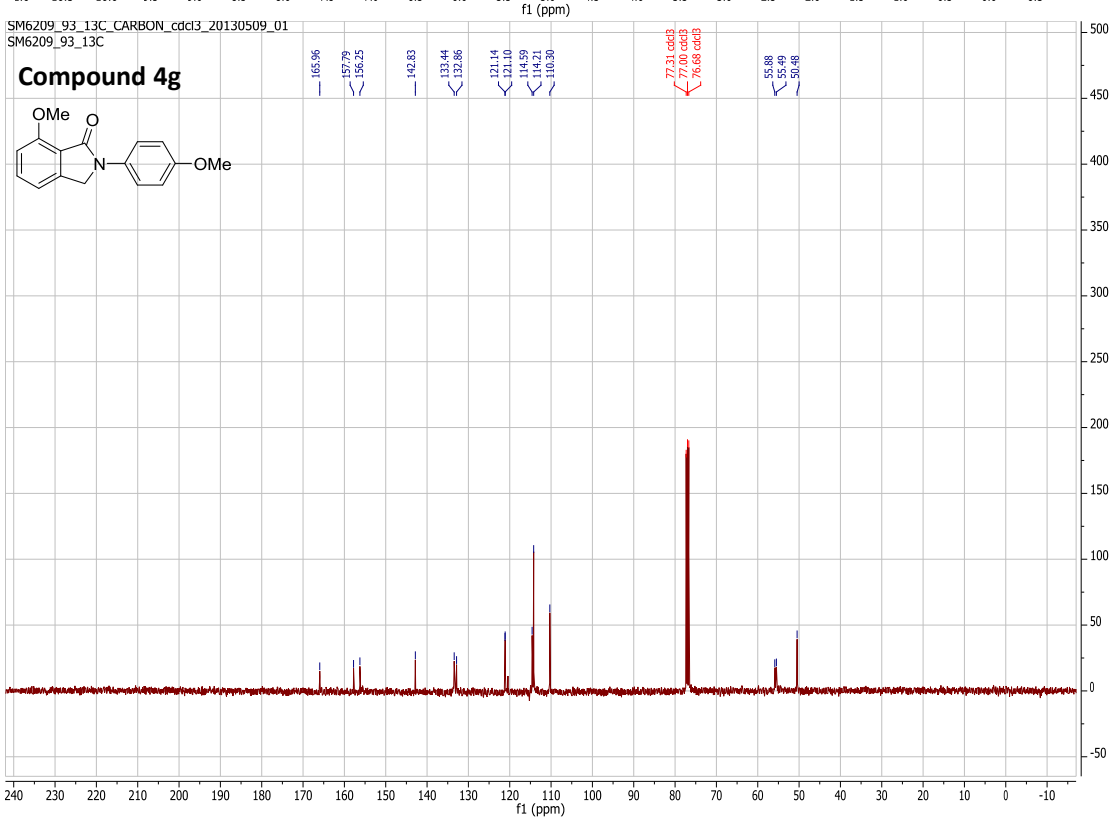

Compound 4e
OMe
O
N
O
OEt
1.03
0.97
1.08
2.05
1.96
3.00
2.13
2.18
2.25
2.73
f1 (ppm)

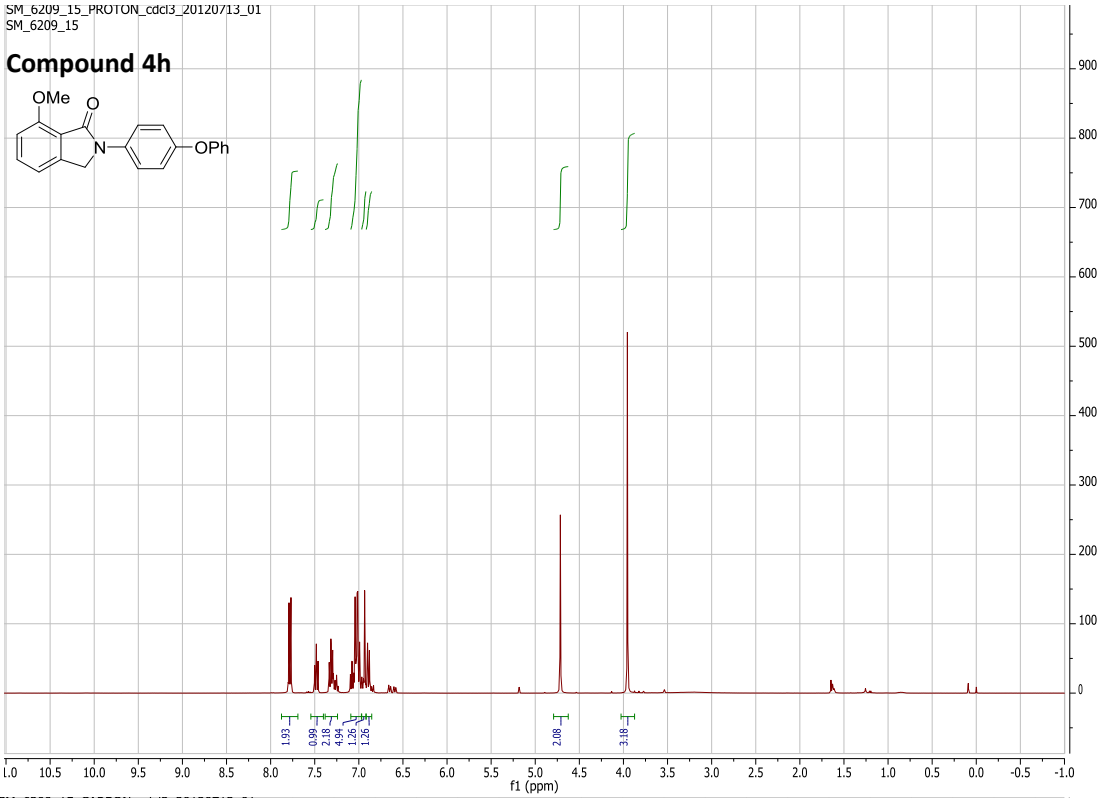

SM6523_15_13C_CARBON_cdcl3_20130514_01
SM6523_15_13C
Compound 4e
OMe
O
N
O
OEt
173.33
168.09
156.96
143.92
133.29
119.69
115.26
110.27
77.33 cdcl3
77.01 cdcl3
76.69 cdcl3
60.58
56.01
49.74
41.55
31.40
23.56
14.12
f1 (ppm)

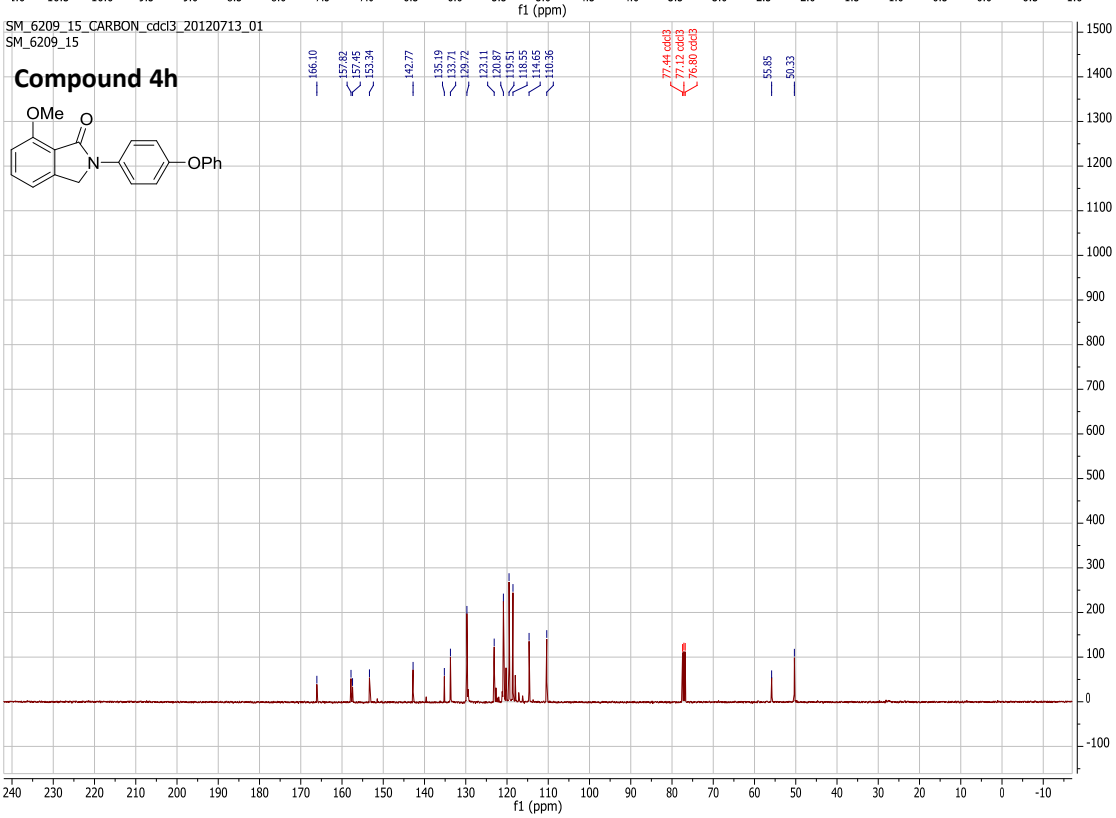

SM6209_89_RC_PROTON_cdcl3_20130704_01
SM6209_89_RC
Compound 4f
OMe
O
N
7.26
1.84
0.95
1.83
0.81
0.95
1.00
2.26
3.17
f1 (ppm)

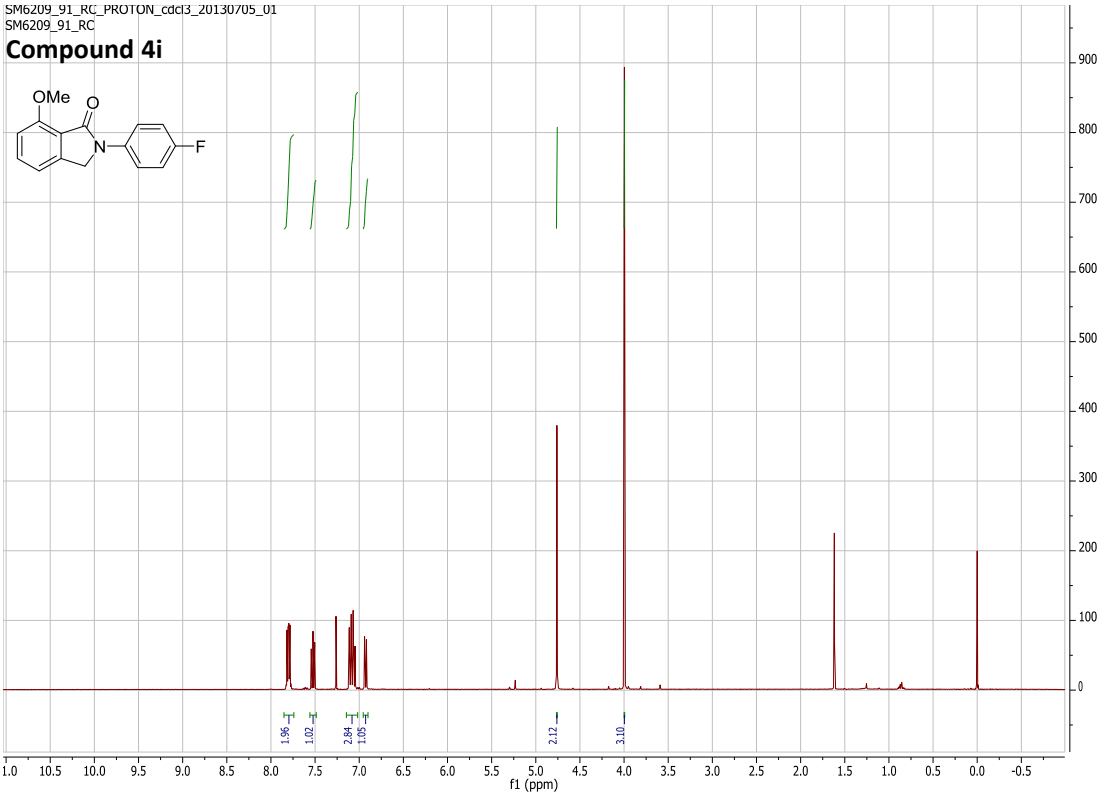

SM6209_89_RC_CARBON_cdcl3_20130705_01
SM6209_89_RC
Compound 4f
OMe
O
N
166.22
157.94
142.81
139.67
133.72
129.03
124.01
119.17
114.60
110.34
77.31 cdcl3
76.99 cdcl3
76.67 cdcl3
55.89
50.08
f1 (ppm)

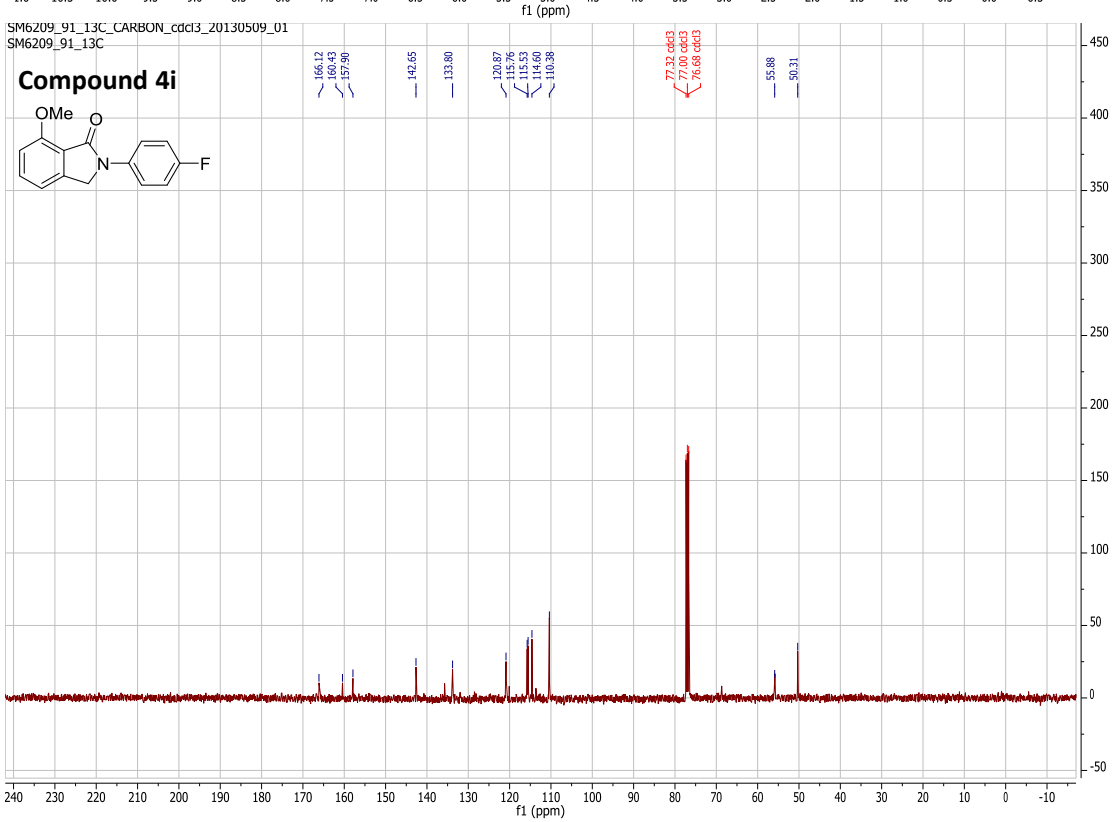

SM6209_93_PROTON_cdcl3_20130508_01
SM6209_93
Compound 4g
OMe
O
N
OMe
1.85
1.12
0.97
2.89
2.24
3.37
3.10
f1 (ppm)

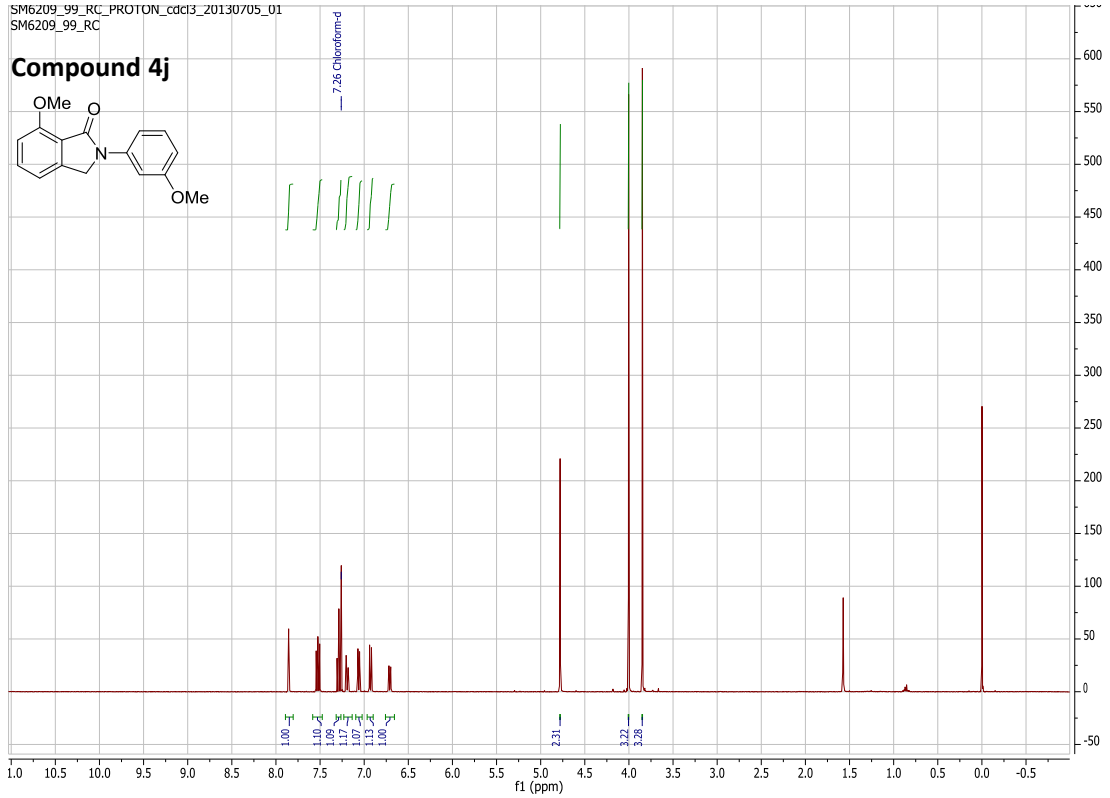

SM6209_93_13C_CARBON_cdcl3_20130509_01
SM6209_93_13C
Compound 4g
OMe
O
N
OMe
165.96
157.79
156.25
142.83
133.44
132.86
121.14
121.10
114.59
114.21
110.30
77.31 cdcl3
77.00 cdcl3
76.68 cdcl3
55.88
55.49
50.48
f1 (ppm)

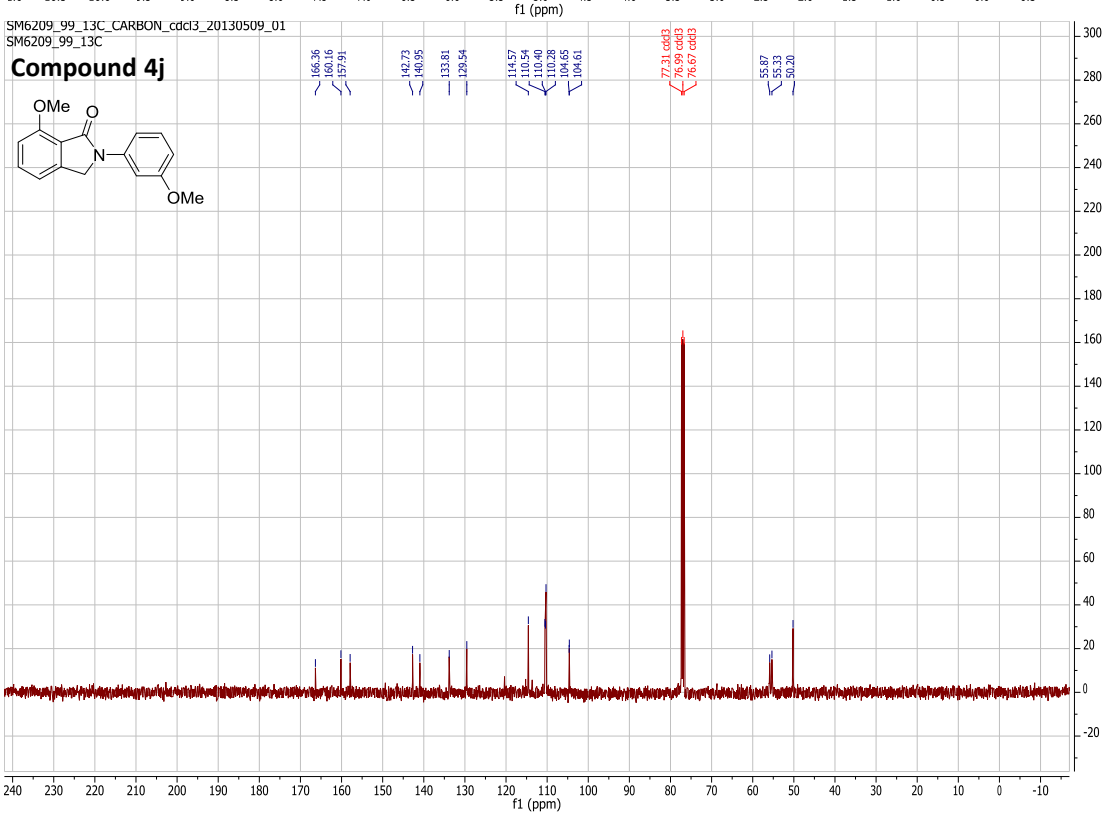

SM_6209_15_PROTON_cdcl3_20120713_01
SM_6209_15
Compound 4h
OMe
O
N
OPh
1.93
0.99
2.18
4.94
1.26
1.26
2.08
3.18
f1 (ppm)

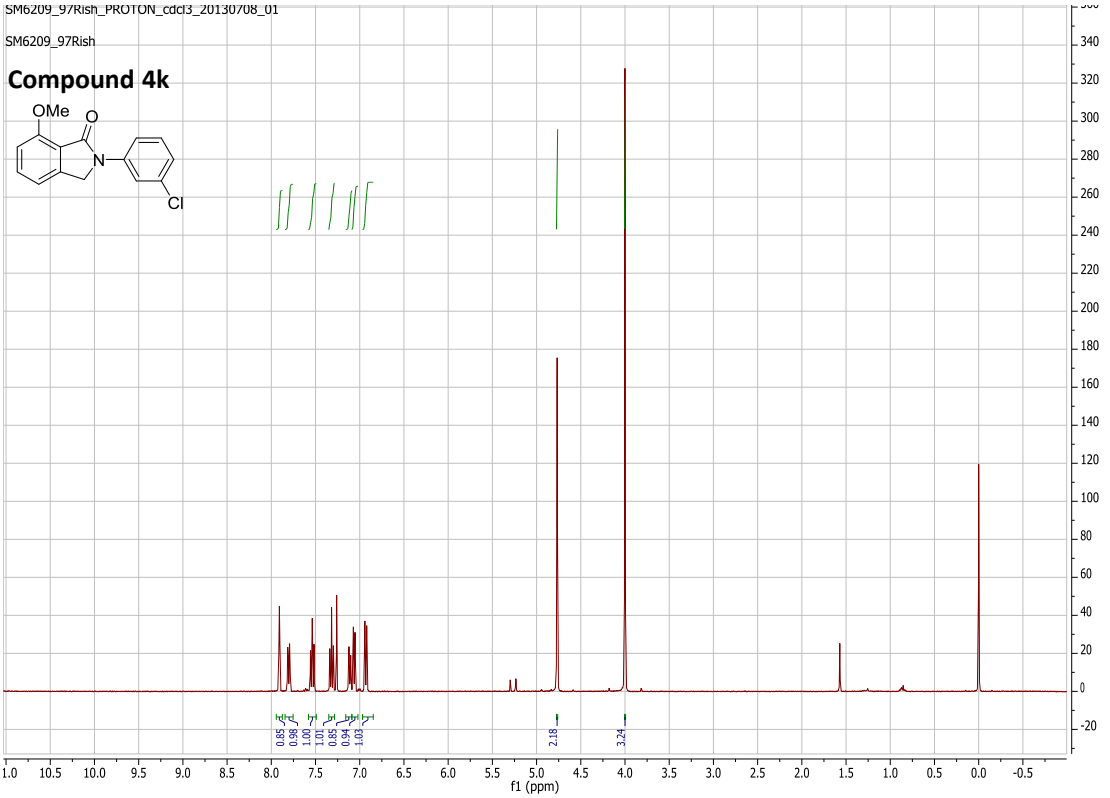

SM_6209_15_CARBON_cdcl3_20120713_01
SM_6209_15
Compound 4h
OMe
O
N
OPh
166.10
157.82
157.45
153.34
142.77
135.19
133.71
129.72
123.11
120.87
119.51
118.55
114.65
110.36
77.44 cdcl3
77.12 cdcl3
76.80 cdcl3
55.85
50.33
f1 (ppm)

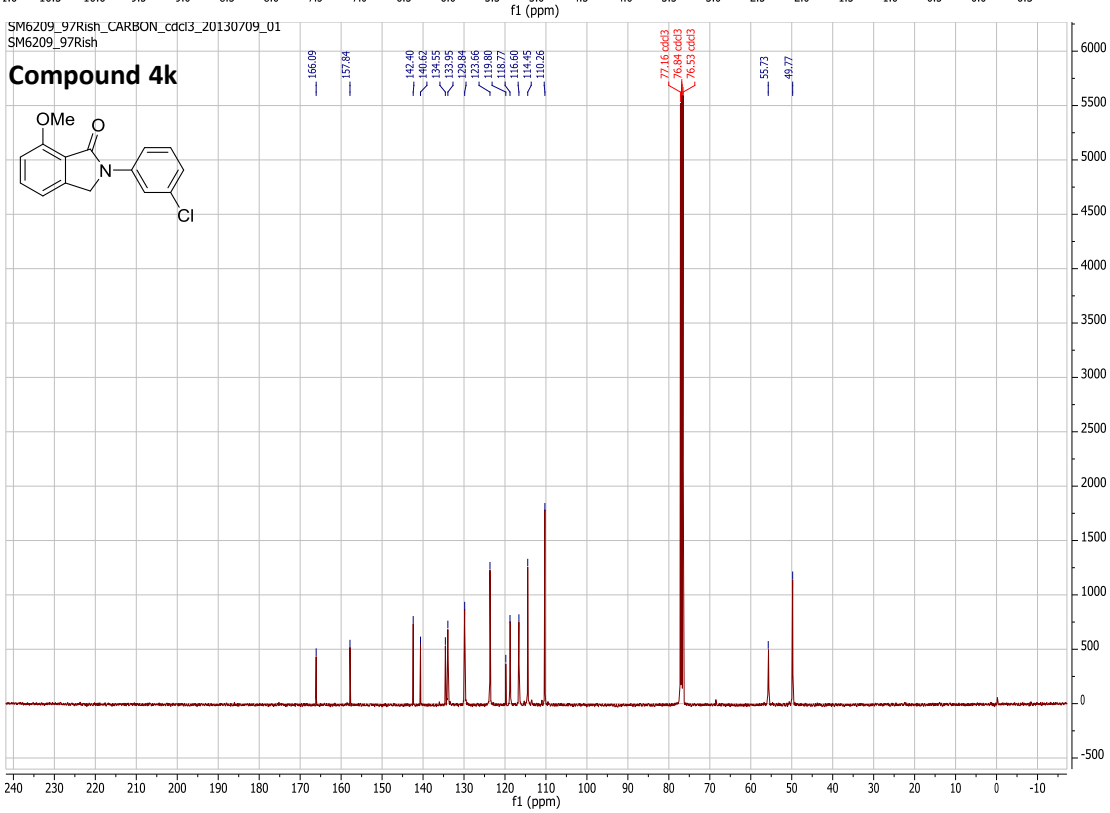

SM6209_91_RC_PROTON_cdcl3_20130705_01
SM6209_91_RC
Compound 4i
OMe
O
N
F
1.96
1.02
2.84
1.05
2.12
3.10
f1 (ppm)

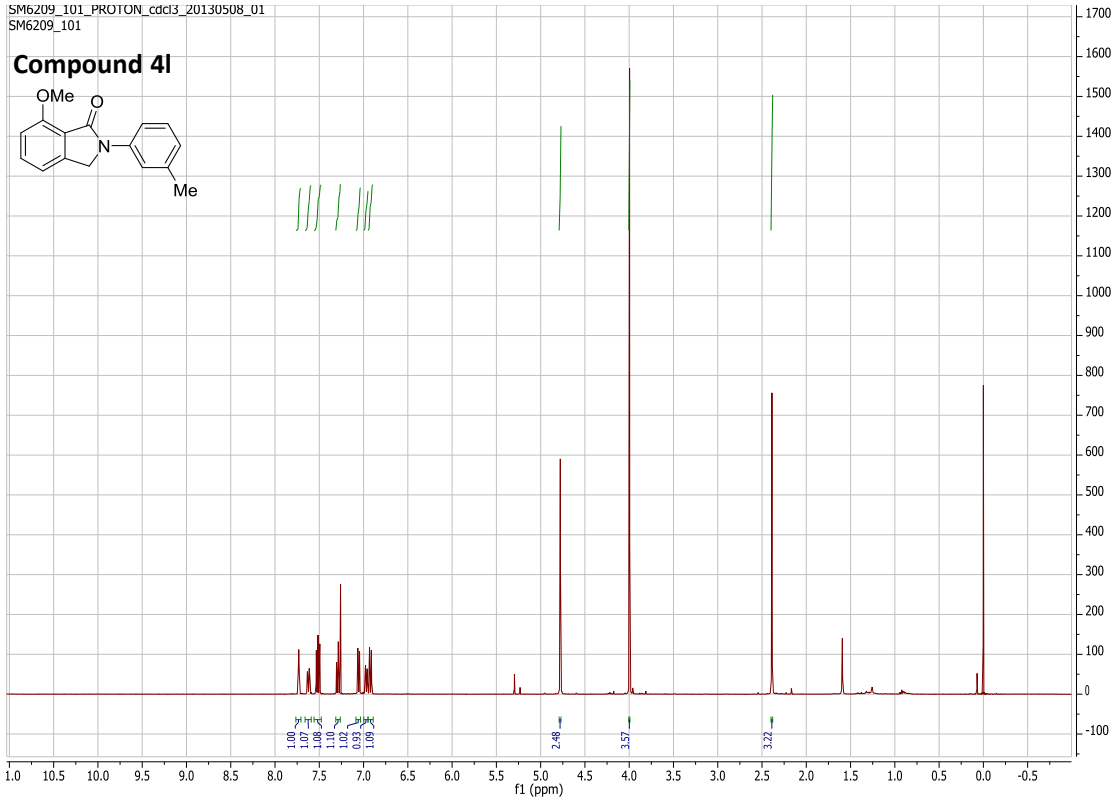

SM6209_91_13C_CARBON_cdcl3_20130509_01
SM6209_91_13C
Compound 4i
OMe
O
N
F
166.12
160.43
157.90
142.65
133.80
120.87
115.76
115.53
114.60
110.38
77.32 cdcl3
77.00 cdcl3
76.68 cdcl3
55.88
50.31
f1 (ppm)

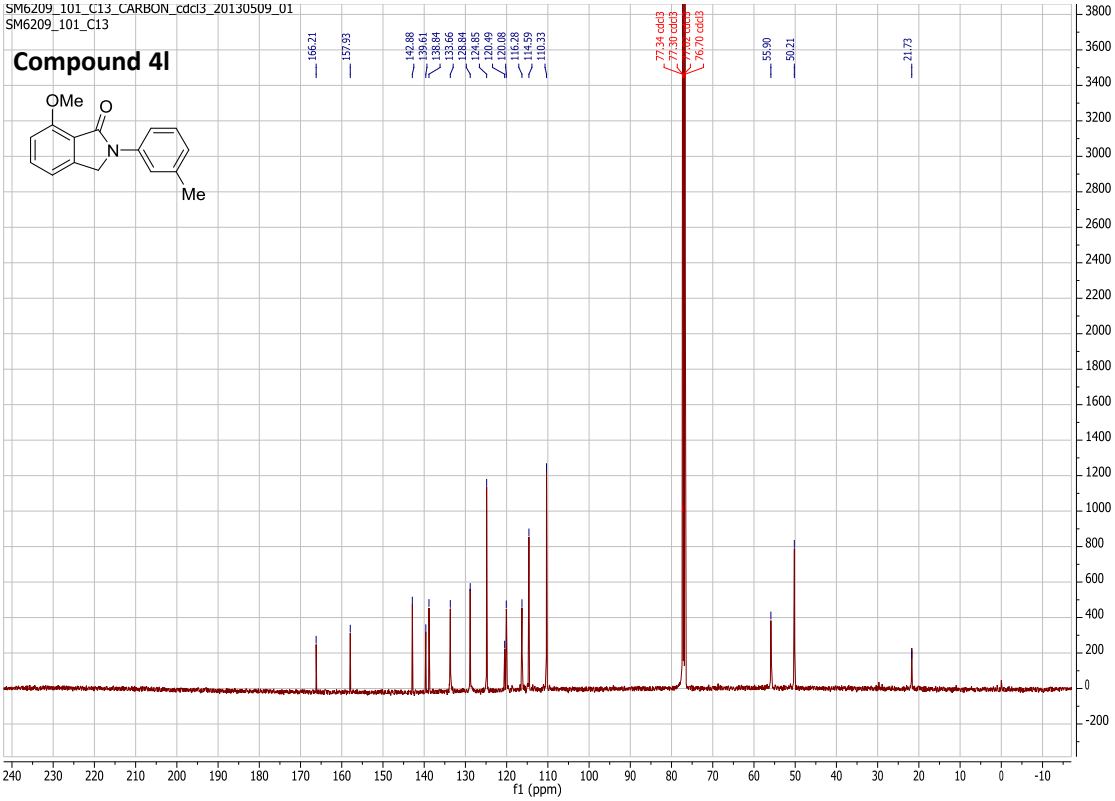

SM6209_99_RC_PROTON_cdcl3_20130705_01
SM6209_99_RC
Compound 4j
OMe
O
N
OMe
7.26 Chloroform-d
1.00
1.10
1.09
1.17
1.07
1.13
1.00
2.31
3.22
3.28
f1 (ppm)

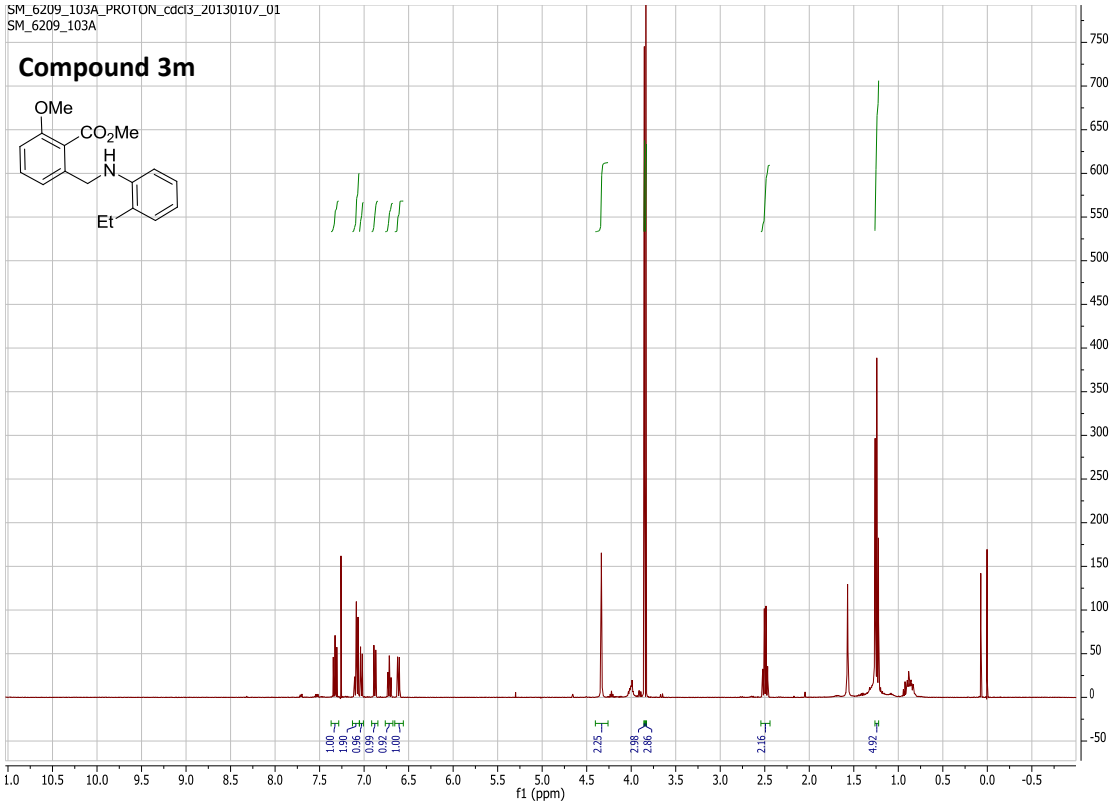

SM6209_99_13C_CARBON_cdcl3_20130509_01
SM6209_99_13C
Compound 4j
OMe
O
N
OMe
166.36
160.16
157.91
142.73
140.95
133.81
129.54
114.57
110.54
110.40
110.28
104.65
104.61
77.31 cdcl3
76.99 cdcl3
76.67 cdcl3
55.87
55.33
50.20
f1 (ppm)

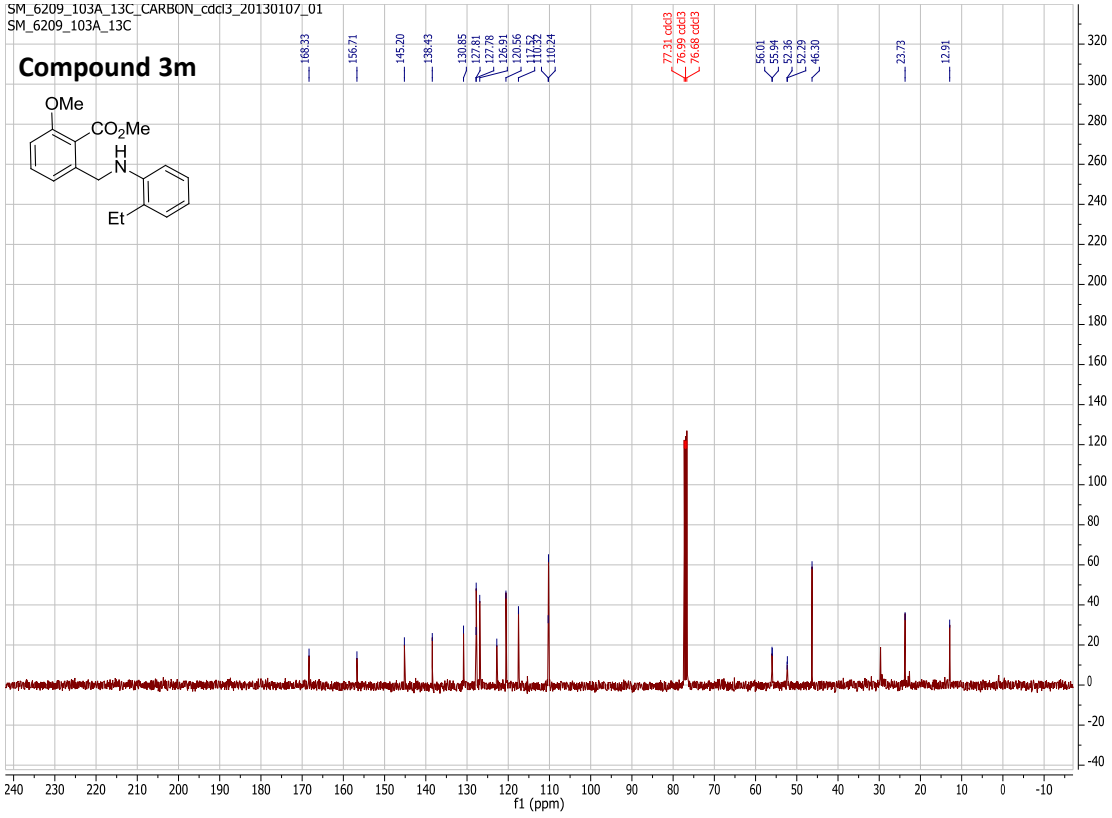

SM6209_97Rish_PROTON_cdcl3_20130708_01
SM6209_97Rish
Compound 4k
OMe
O
N
Cl
0.85
0.98
1.00
1.01
0.85
0.94
1.03
2.18
3.24
f1 (ppm)

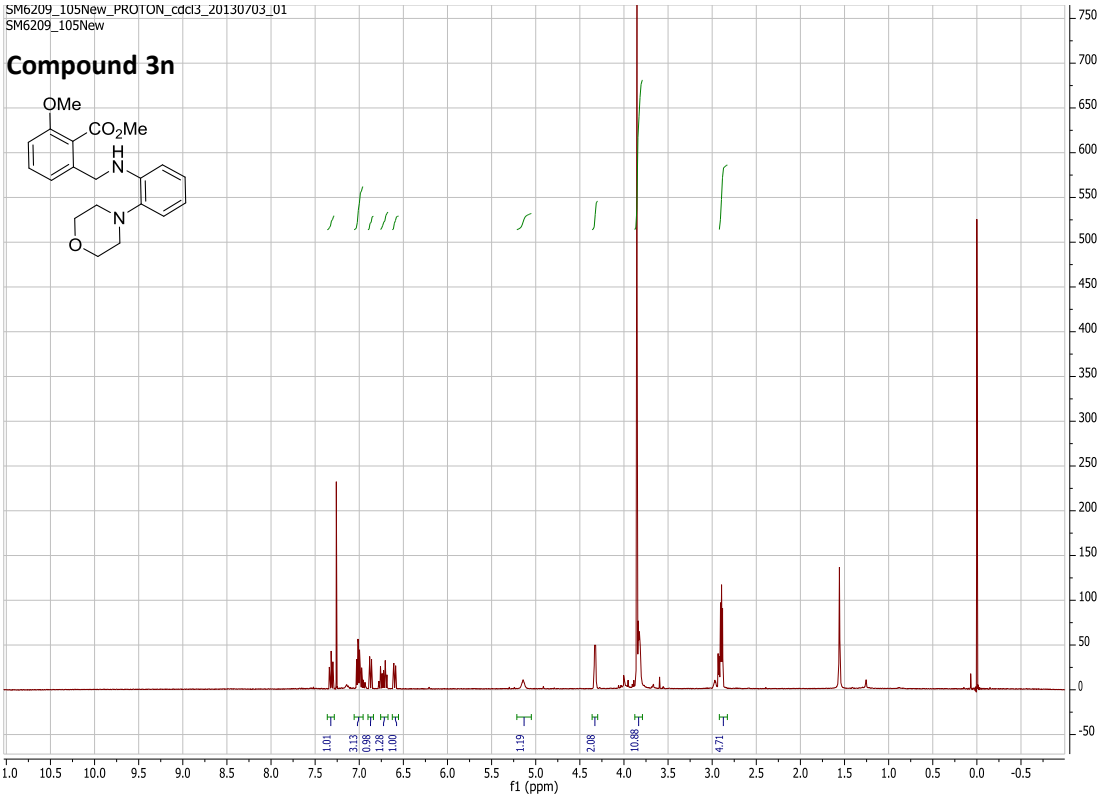

SM6209_97Rish_CARBON_cdcl3_20130709_01
SM6209_97Rish
Compound 4k
OMe
O
N
Cl
166.09
157.84
142.40
140.62
134.55
133.95
129.84
123.66
119.80
118.77
116.60
114.45
110.26
77.16 cdcl3
76.84 cdcl3
76.53 cdcl3
55.73
49.77
f1 (ppm)

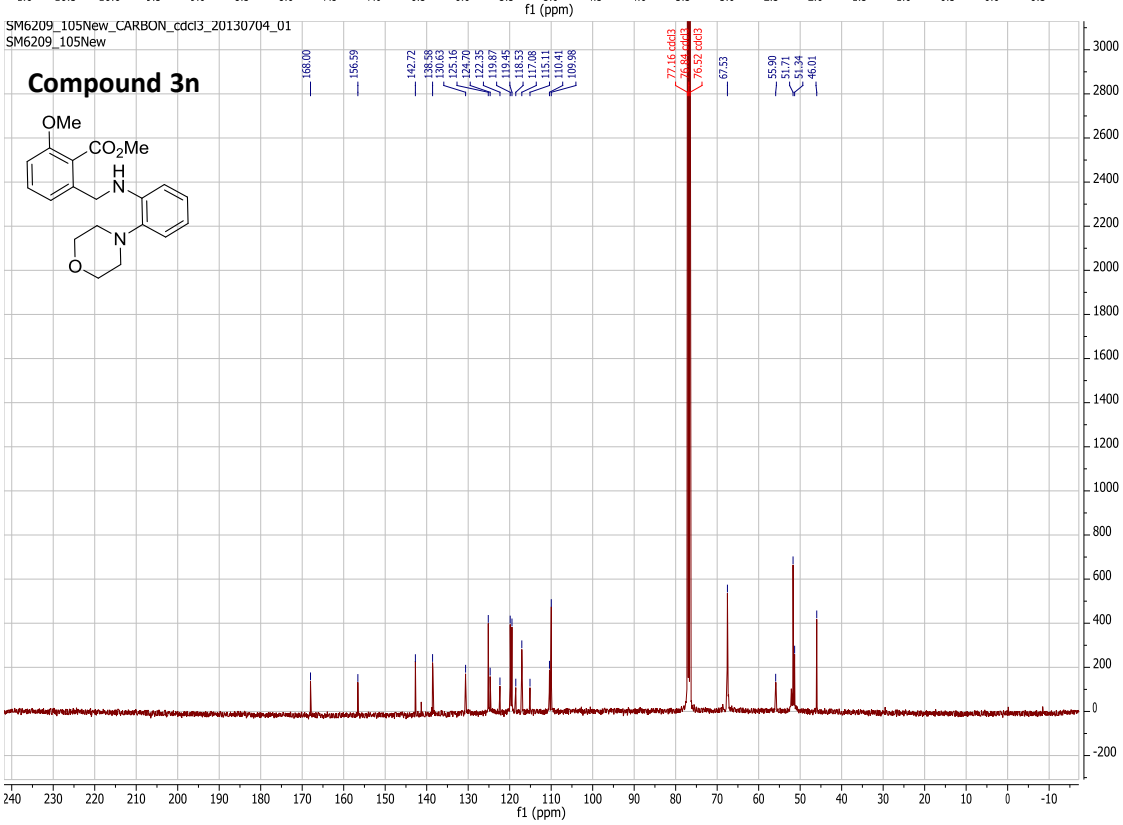

SM6209_101_PROTON_cdcl3_20130508_01
SM6209_101
Compound 4l
OMe
O
N
Me
1.00
1.07
1.08
1.10
1.03
0.93
1.09
2.48
3.57
3.22
f1 (ppm)

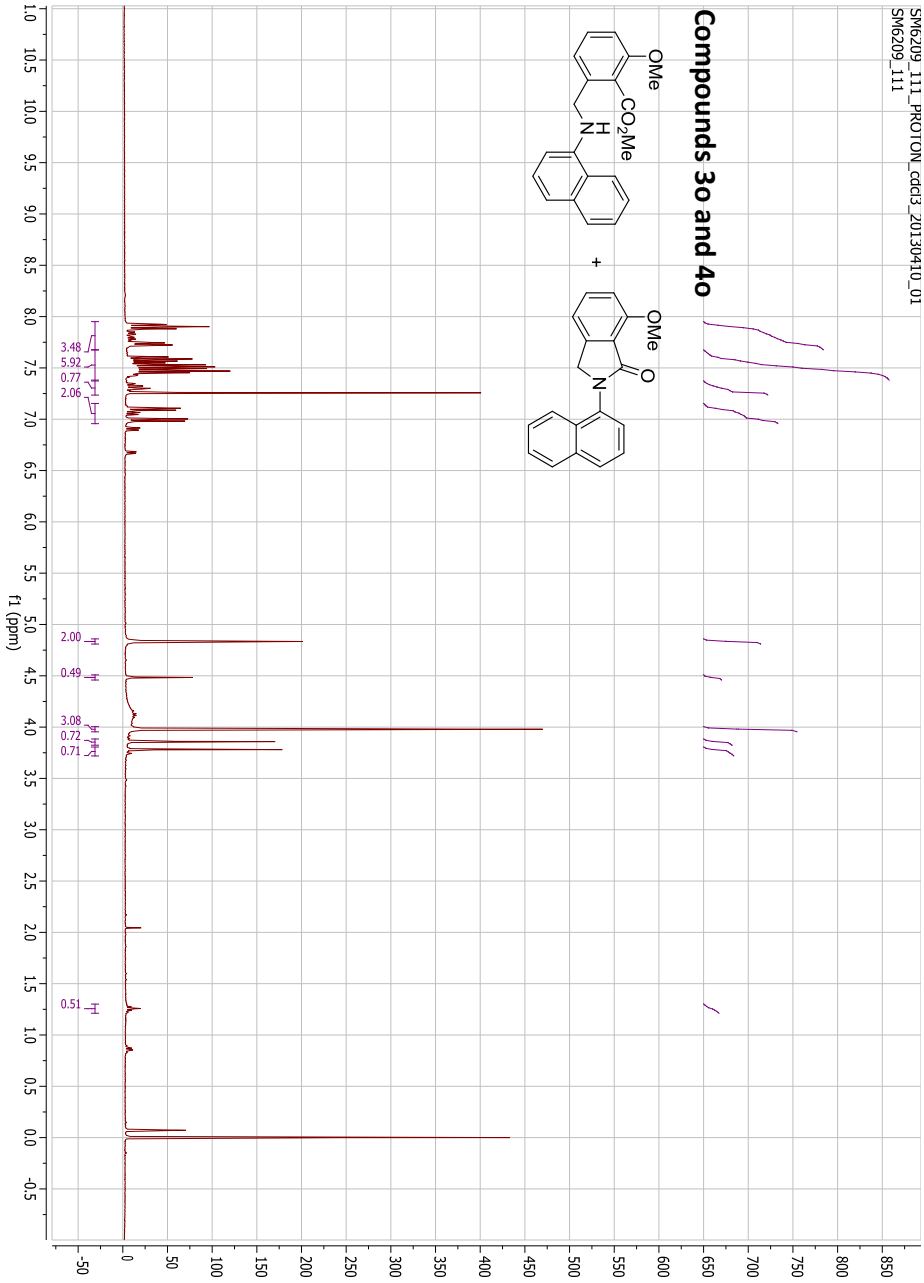

SM6209_101_C13_CARBON_cdcl3_20130509_01
SM6209_101_C13
Compound 4l
OMe
O
N
Me
166.21
157.93
142.88
139.61
138.84
133.66
128.84
124.85
120.49
120.08
116.28
114.59
110.33
77.34 cdcl3
77.30 cdcl3
76.70 cdcl3
55.90
50.21
21.73
f1 (ppm)

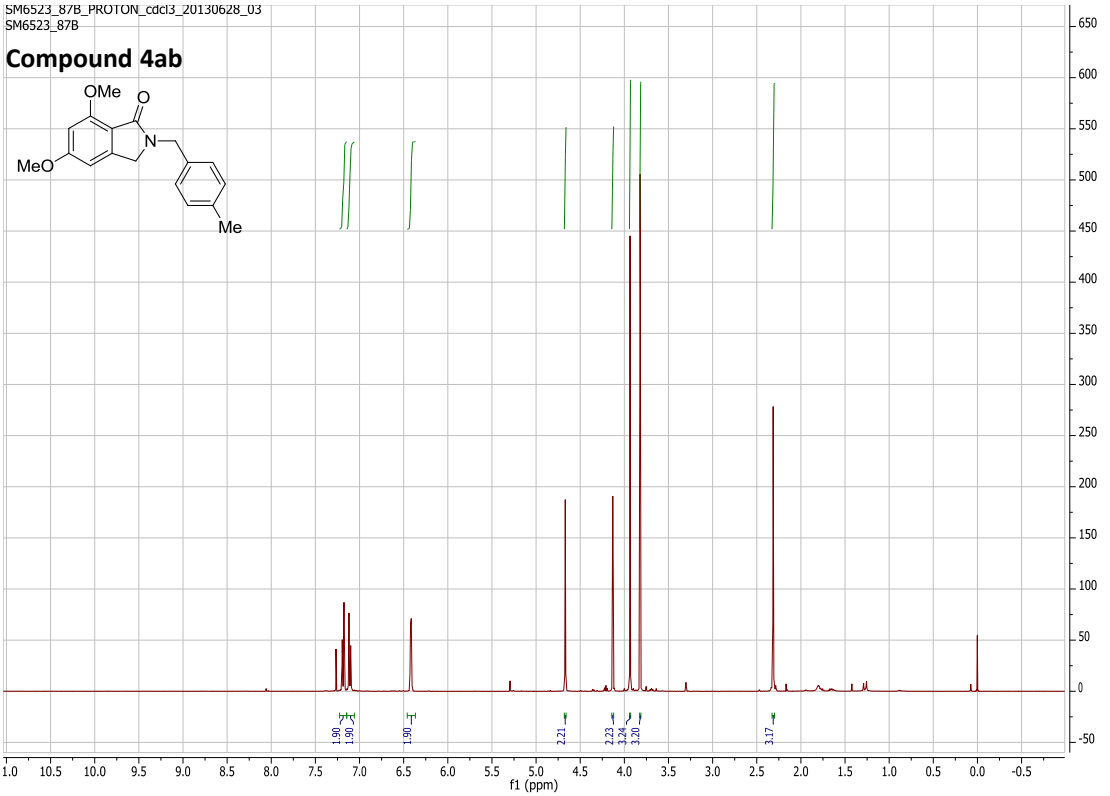

SM_6209_103A_PROTON_cdcl3_20130107_01
SM_6209_103A
Compound 3m
OMe
CO2Me
H
N
Et
1.00
1.90
0.96
0.99
0.92
1.00
2.25
2.98
2.86
2.16
4.92
f1 (ppm)

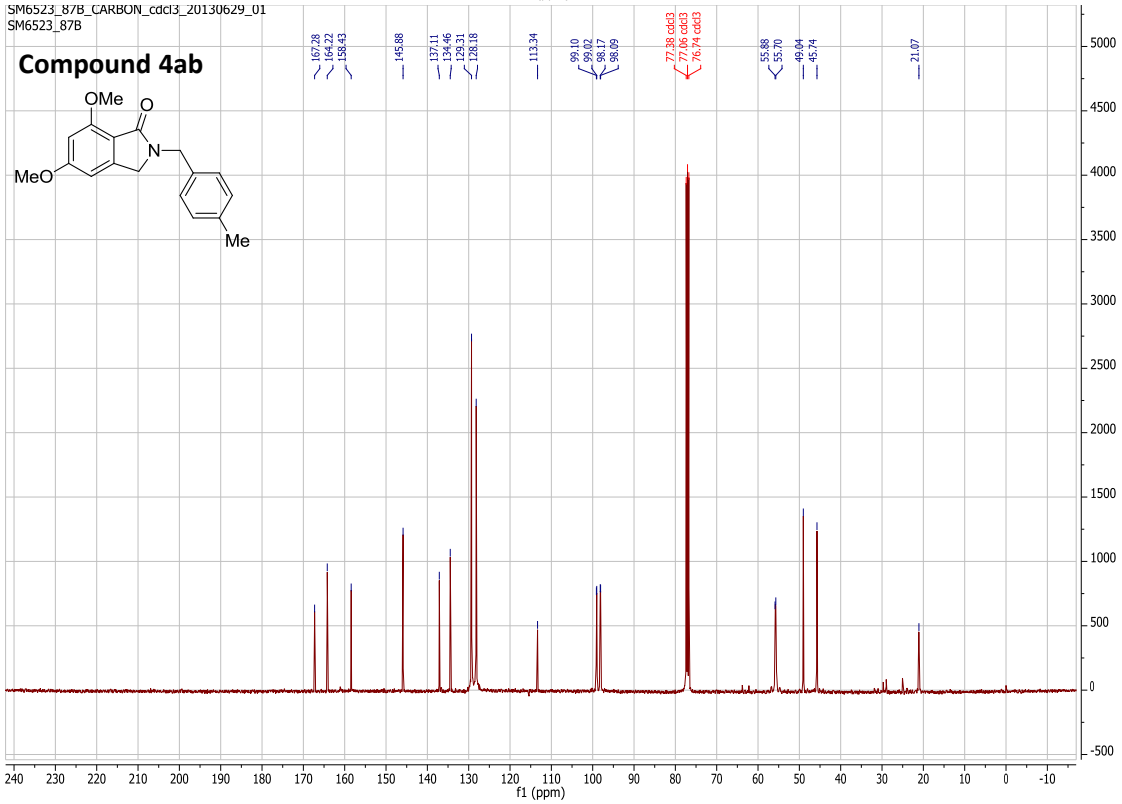

SM_6209_103A_13C_CARBON_cdcl3_20130107_01
SM_6209_103A_13C
Compound 3m
OMe
CO2Me
H
N
Et
168.33
156.71
145.20
138.43
130.85
127.81
127.78
126.91
120.56
110.52
110.24
77.31 cdcl3
76.99 cdcl3
76.68 cdcl3
56.01
55.94
52.36
52.29
46.30
23.73
12.91
f1 (ppm)

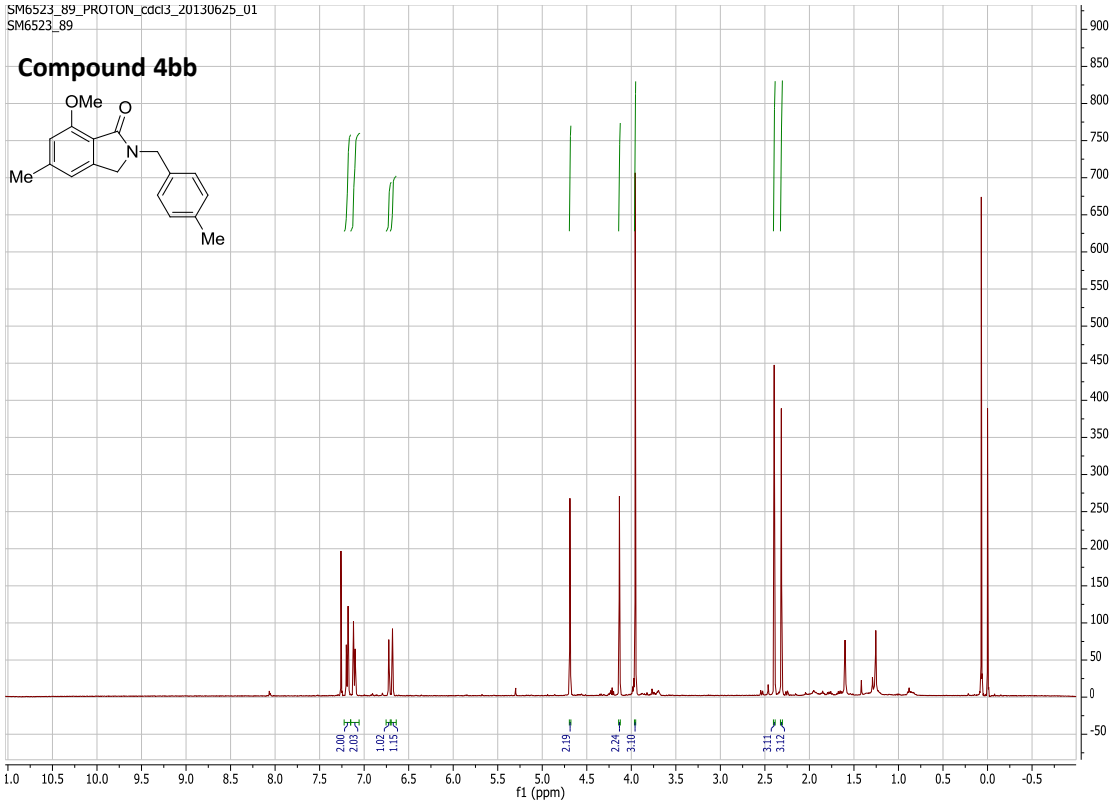

SM6209_105New_PROTON_cdcl3_20130703_01
SM6209_105New
Compound 3n
OMe
CO2Me
H
N
N
O
1.01
3.13
0.98
1.28
1.00
1.19
2.08
10.88
4.71
f1 (ppm)

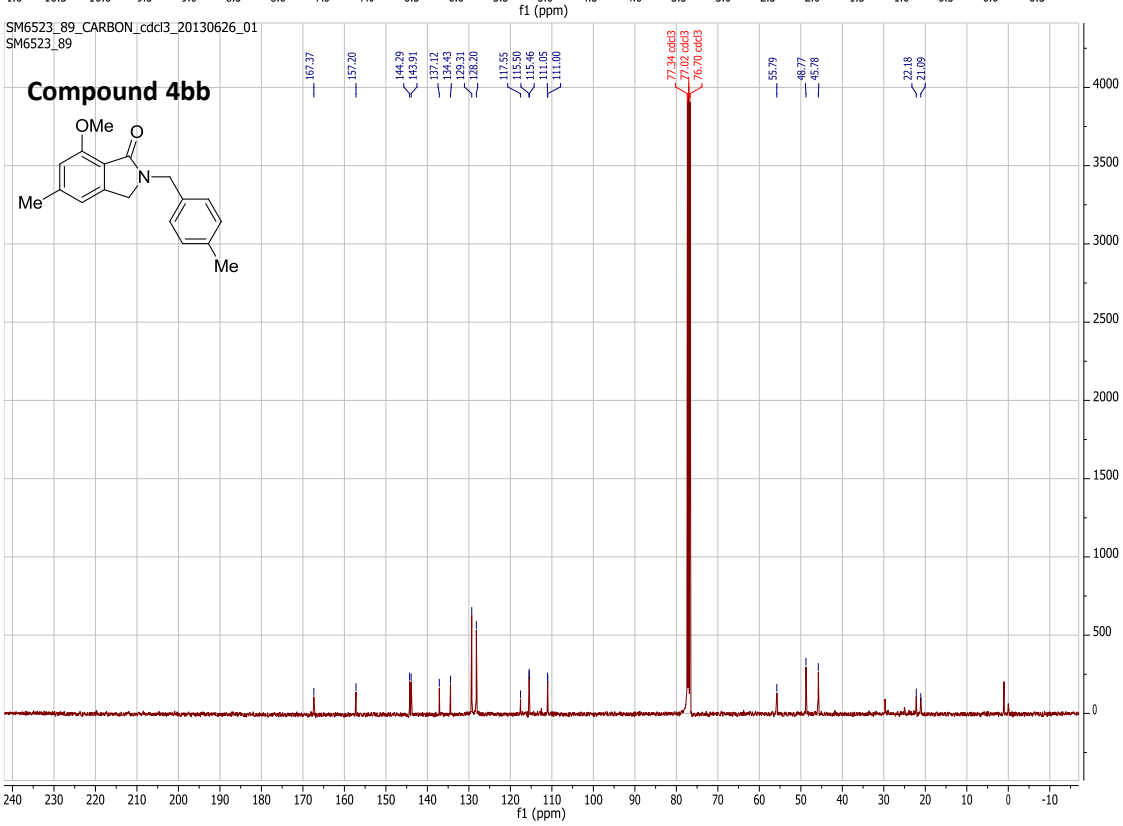

SM6209_105New_CARBON_cdcl3_20130704_01
SM6209_105New
Compound 3n
OMe
CO2Me
H
N
N
O
168.00
156.59
142.72
138.58
130.63
125.16
124.70
122.35
119.07
118.45
118.53
117.08
115.11
110.41
109.98
77.16 cdcl3
76.84 cdcl3
76.52 cdcl3
67.53
55.90
53.71
51.34
46.01
f1 (ppm)

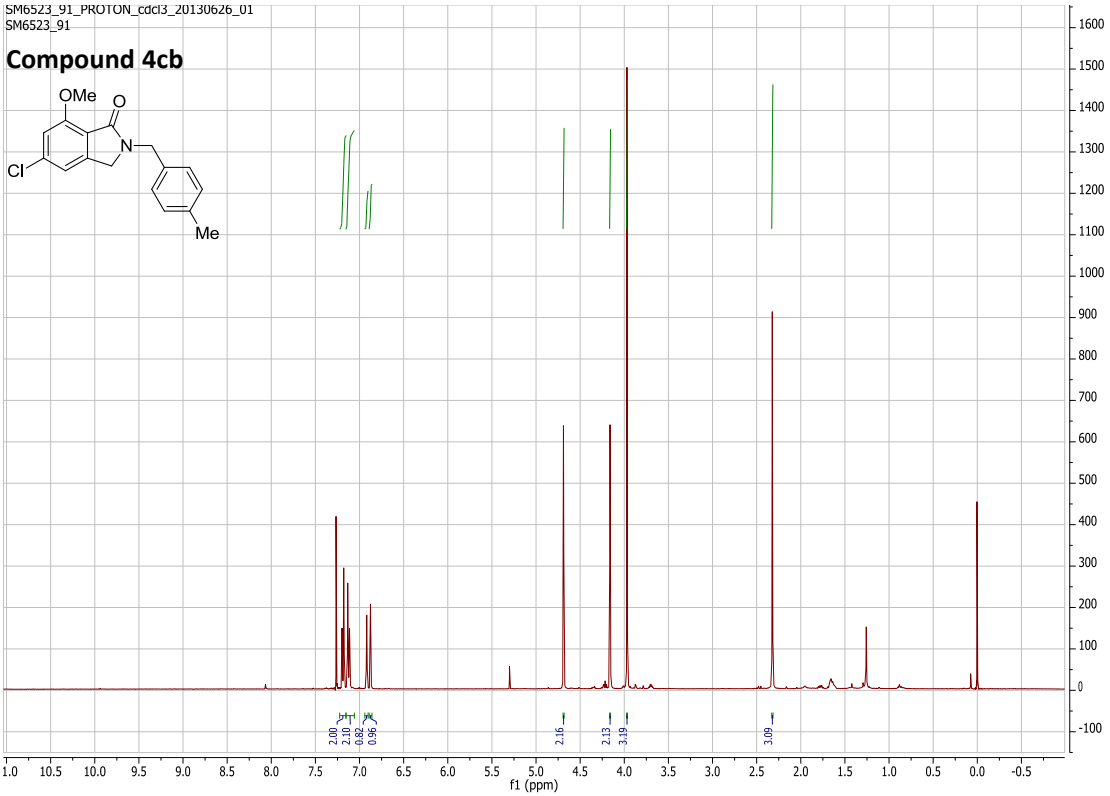

SM6209_111_PROTON_cdcl3_20130410_01
SM6209_111
Compounds 3o and 4o
OMe
CO2Me
N
H
+
OMe
O
N
3.48
5.92
0.77
2.06
2.00
0.49
3.08
0.72
0.71
0.51
f1 (ppm)

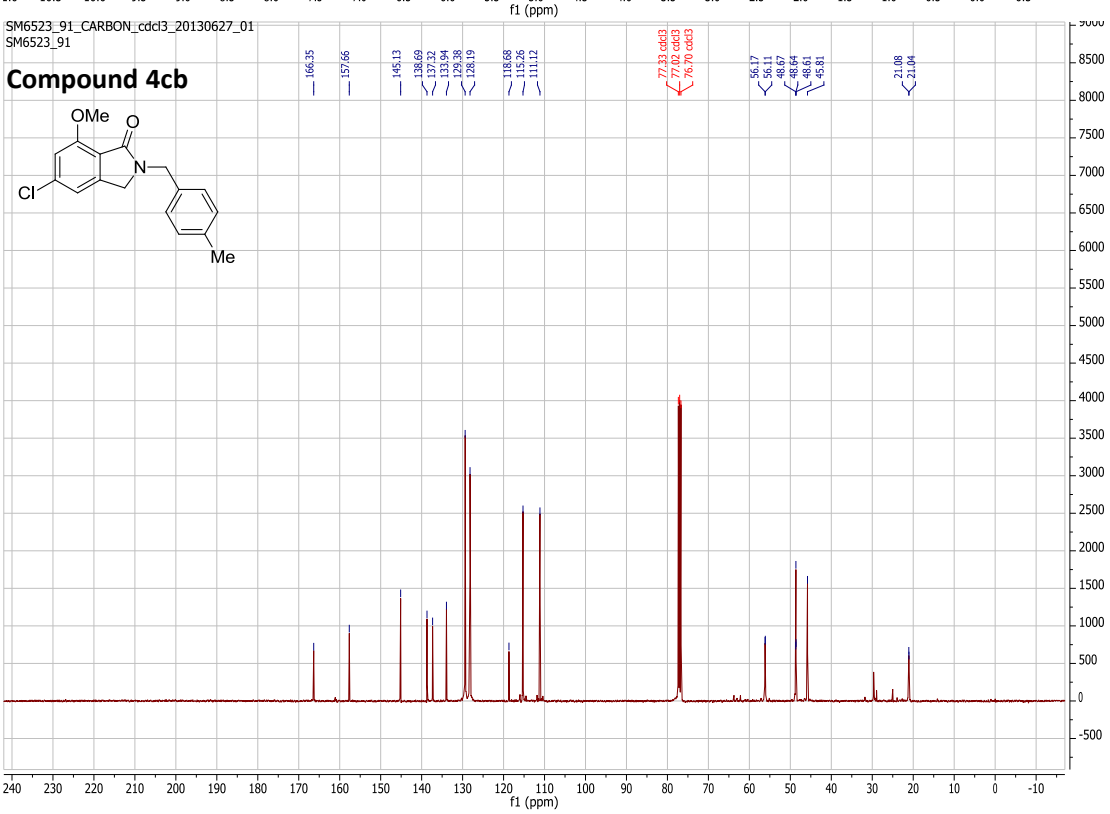

SM6523_87B_PROTON_cdcl3_20130628_03
SM6523_87B
Compound 4ab
OMe
O
N
MeO
Me
1.90
1.90
1.90
2.21
2.23
3.24
3.20
3.17
f1 (ppm)

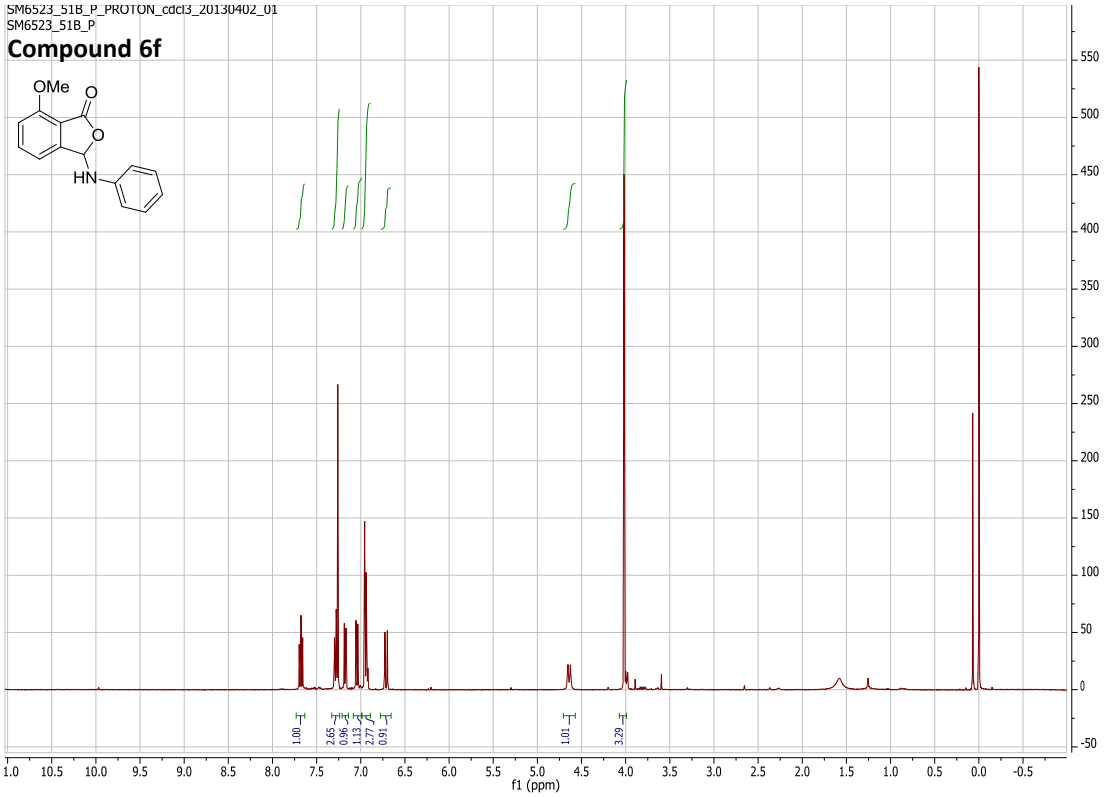

SM6523_87B_CARBON_cdcl3_20130629_01
SM6523_87B
Compound 4ab
OMe
O
N
MeO
Me
167.28
164.22
158.43
145.88
137.11
134.46
129.31
128.18
113.34
99.10
99.02
98.17
98.09
77.38 cdcl3
77.06 cdcl3
76.74 cdcl3
55.88
55.70
49.04
45.74
21.07
f1 (ppm)

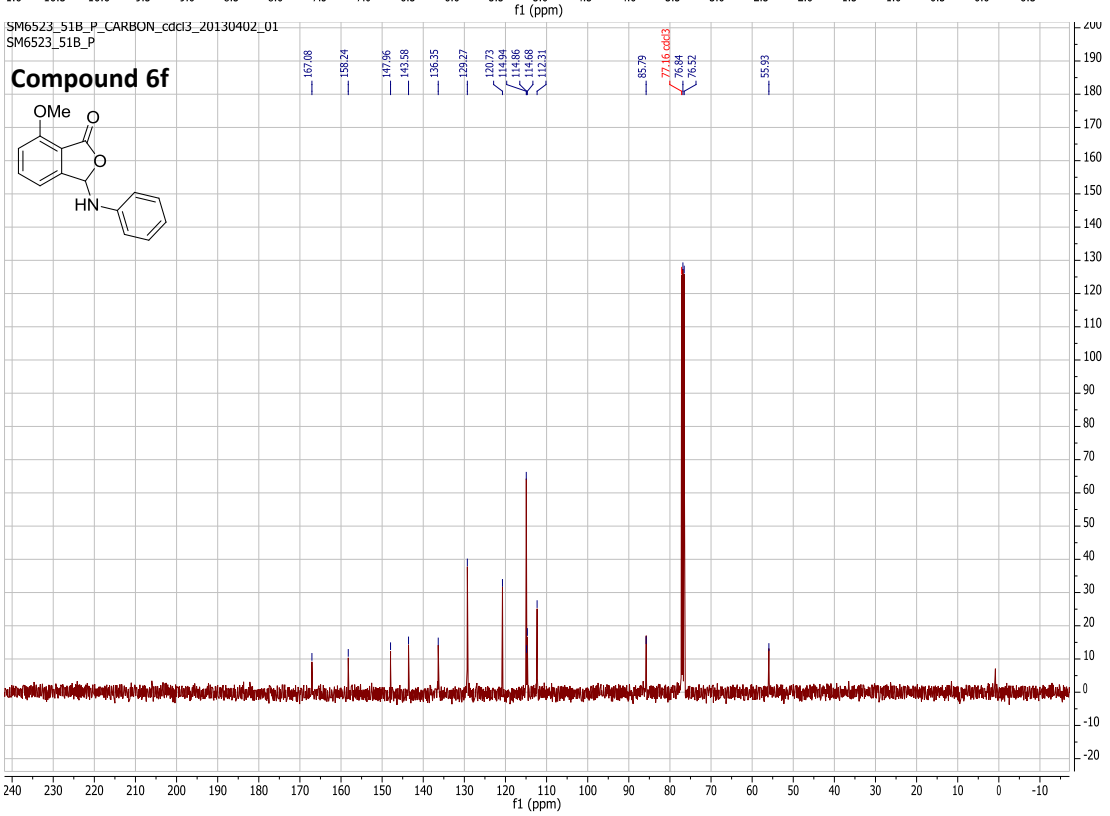

SM6523_89_PROTON_cdcl3_20130625_01
SM6523_89
Compound 4bb
OMe
O
N
Me
Me
2.00
2.03
1.02
1.15
2.19
2.24
3.10
3.11
3.12
f1 (ppm)

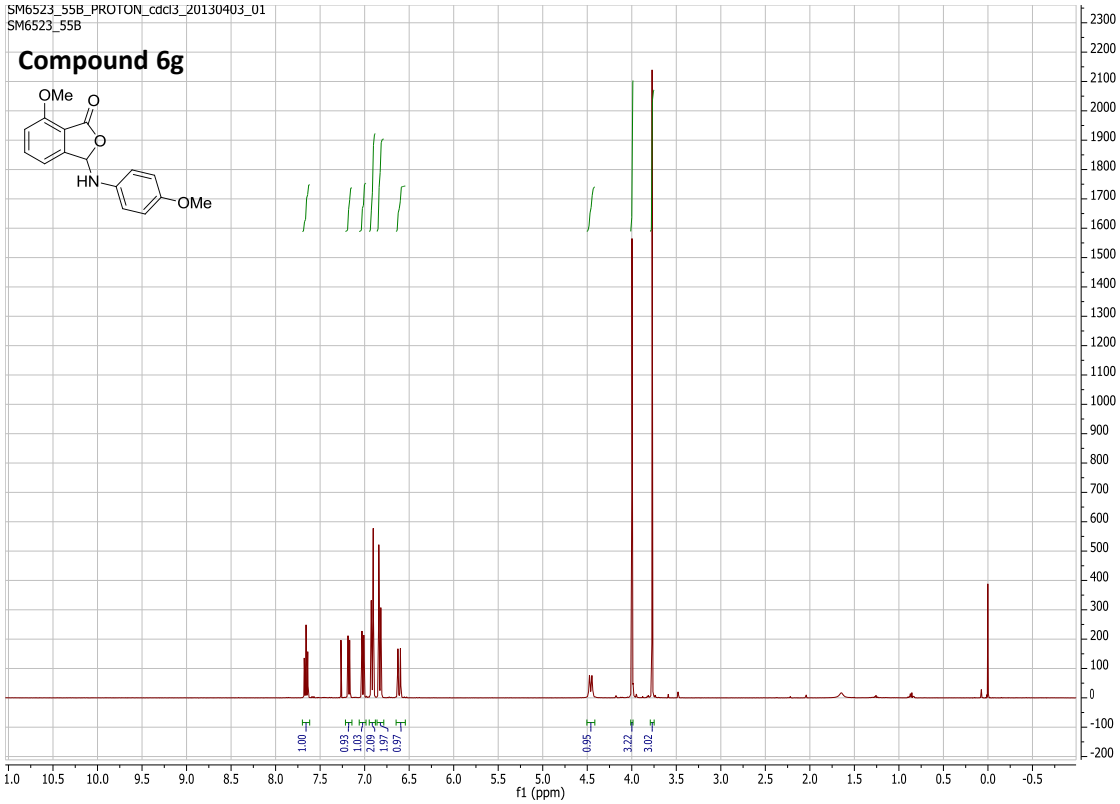

SM6523_89_CARBON_cdcl3_20130626_01
SM6523_89
Compound 4bb
OMe
O
N
Me
Me
167.37
157.20
144.29
143.91
137.12
134.43
129.31
128.20
117.55
115.50
115.46
111.05
111.00
77.34 cdcl3
77.02 cdcl3
76.70 cdcl3
55.79
48.77
45.78
22.18
21.09
f1 (ppm)

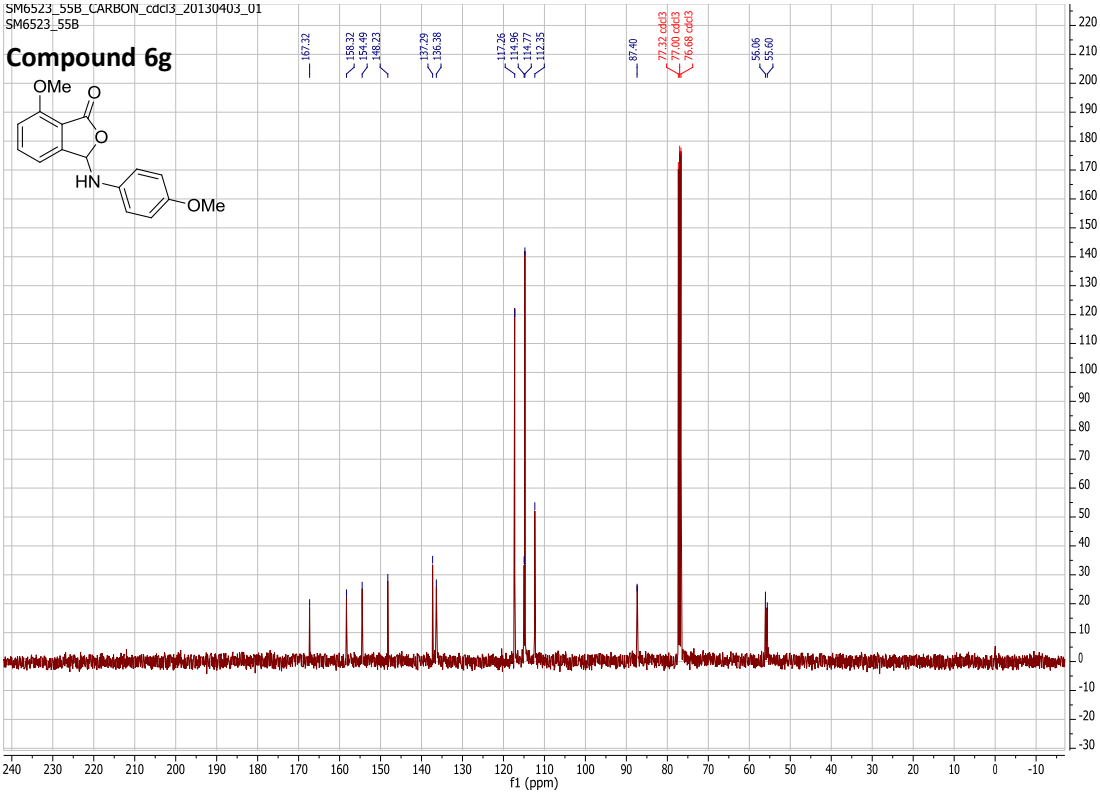

SM6523_91_PROTON_cdcl3_20130626_01
SM6523_91
Compound 4cb
OMe
O
N
Cl
Me
2.00
2.10
0.82
0.96
2.16
2.13
3.19
3.09
f1 (ppm)

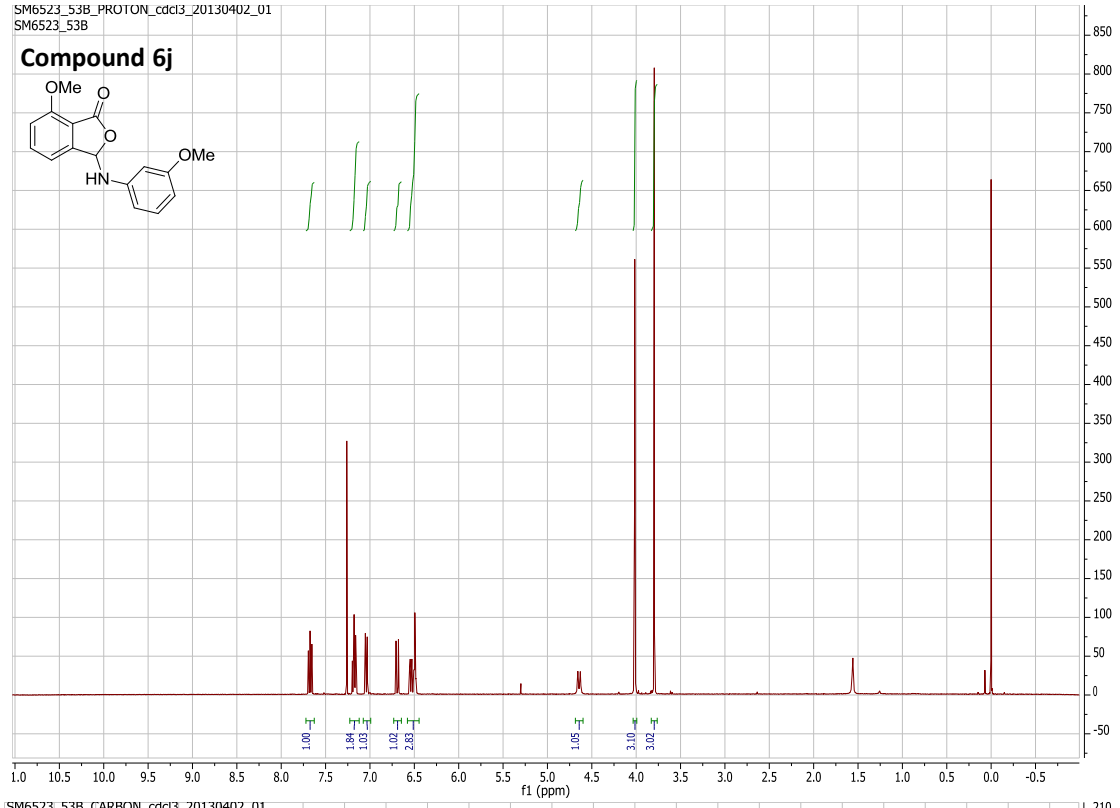

SM6523_91_CARBON_cdcl3_20130627_01
SM6523_91
Compound 4cb
OMe
O
N
Cl
Me
166.35
157.66
145.13
138.69
137.32
133.94
129.38
128.19
118.68
115.26
111.12
77.33 cdcl3
77.02 cdcl3
76.70 cdcl3
56.17
56.11
48.67
48.64
48.61
45.81
21.08
21.04
f1 (ppm)

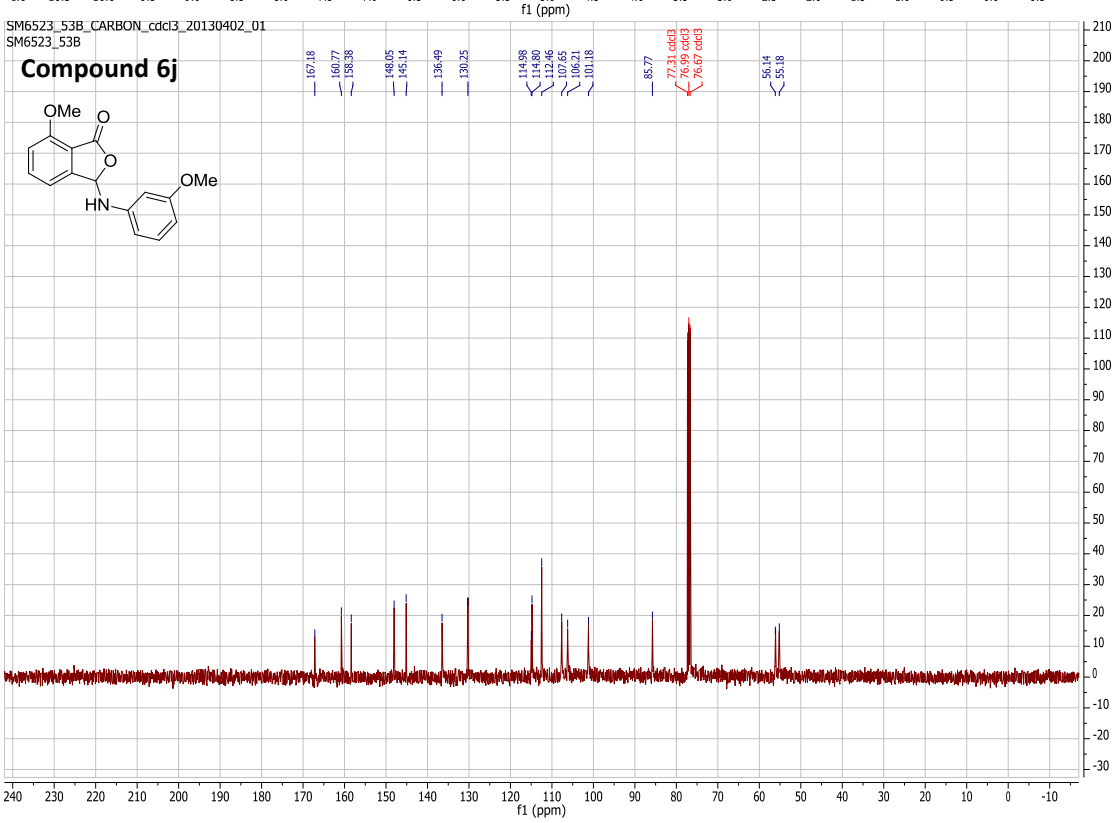

SM6523_51B_P_PROTON_cdcl3_20130402_01
SM6523_51B_P
Compound 6f
OMe
O
O
HN
1.00
2.65
0.96
1.13
2.77
0.91
1.01
3.29
f1 (ppm)

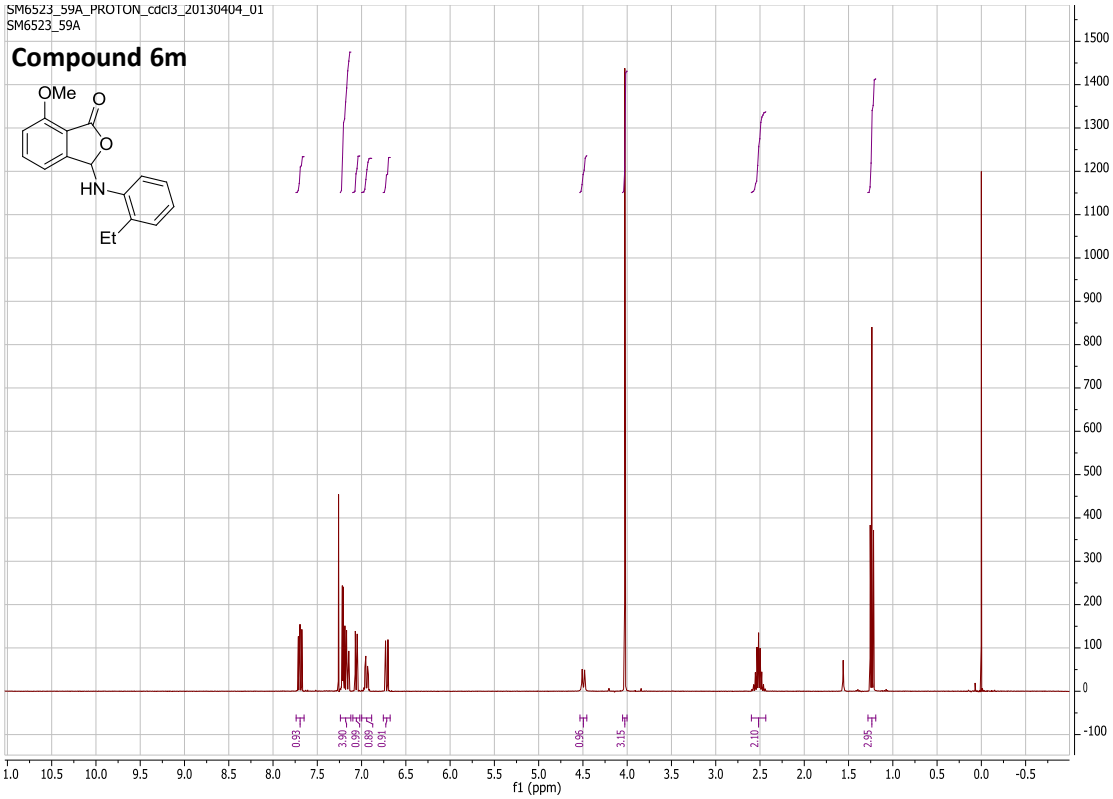

SM6523_51B_P_CARBON_cdcl3_20130402_01
SM6523_51B_P
Compound 6f
OMe
O
O
HN
167.08
158.24
147.96
143.58
136.35
129.27
120.73
114.94
114.86
114.68
112.31
85.79
77.16 cdcl3
76.84
76.52
55.93
f1 (ppm)

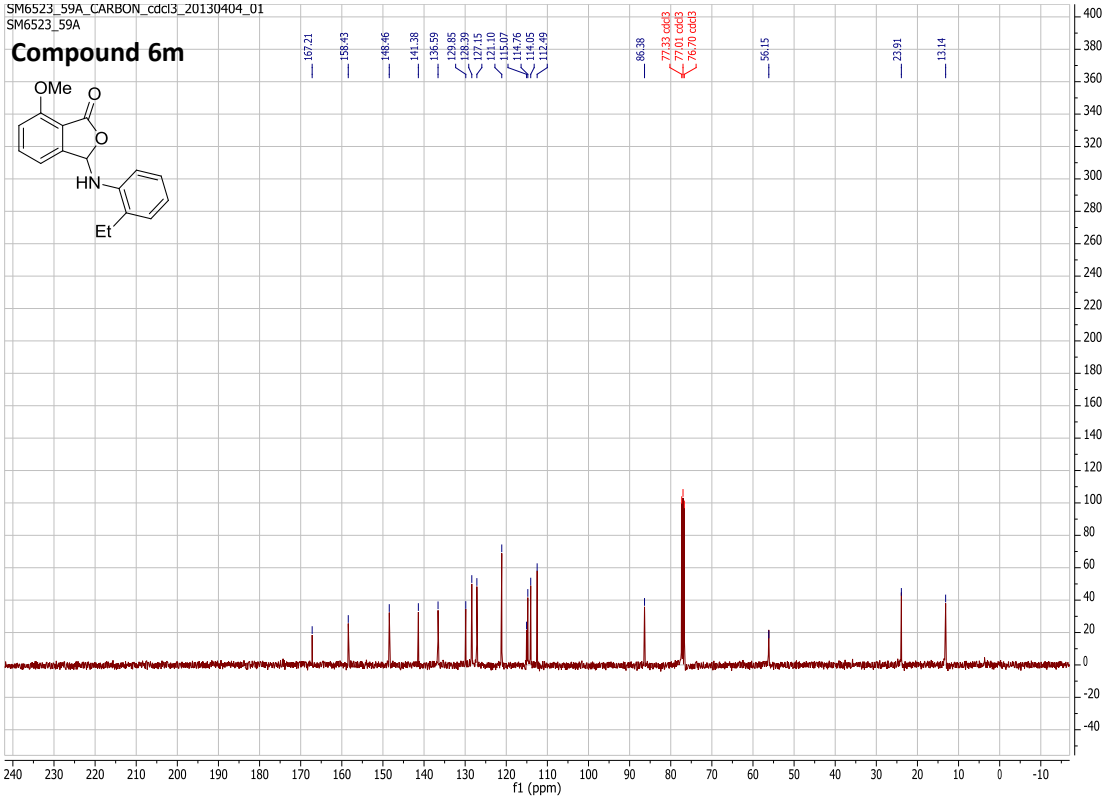

SM6523_55B_PROTON_cdcl3_20130403_01
SM6523_55B
Compound 6g
OMe
O
O
HN
OMe
1.00
0.93
1.03
2.09
1.97
0.97
0.95
3.22
3.02
f1 (ppm)


SM6523_55B_CARBON_cdcl3_20130403_01
SM6523_55B
Compound 6g
OMe
O
O
HN
OMe
167.32
158.32
154.49
140.23
137.29
136.38
117.26
114.96
114.77
112.35
87.40
77.32 cdcl3
77.00 cdcl3
76.68 cdcl3
56.06
55.60
f1 (ppm)


SM6523_53B_PROTON_cdcl3_20130402_01
SM6523_53B
Compound 6j
OMe
O
O
HN
OMe
1.00
1.84
1.03
1.02
2.83
1.05
3.10
3.02
f1 (ppm)


SM6523_53B_CARBON_cdcl3_20130402_01
SM6523_53B
Compound 6j
OMe
O
O
HN
OMe
167.18
160.77
158.38
148.05
145.14
136.49
130.25
114.98
114.80
112.46
107.55
105.21
101.18
85.77
77.31 cdcl3
76.99 cdcl3
76.67 cdcl3
56.14
55.18
f1 (ppm)


SM6523_59A_PROTON_cdcl3_20130404_01
SM6523_59A
Compound 6m
OMe
O
O
HN
Et
0.93
3.90
0.89
0.91
0.96
3.15
2.10
2.95
f1 (ppm)


SM6523_59A_CARBON_cdcl3_20130404_01
SM6523_59A
Compound 6m
OMe
O
O
HN
Et
167.21
158.43
148.46
141.38
136.59
129.85
128.39
127.15
121.10
115.07
114.76
114.05
112.49
86.38
77.33 cdcl3
77.01 cdcl3
76.70 cdcl3
56.15
23.91
13.14
f1 (ppm)