

Cation-Directed Enantioselective Synthesis of Quaternary-Substituted Indolenines

Meiling Li,^a Philip A. Woods^a and Martin D. Smith^{*a}

^a Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, UK.

E-mail: martin.smith@chem.ox.ac.uk

SUPPORTING INFORMATION

Contents

1.1 General Information	S2
1.2 General Experimental Procedures	S3
1.3 Experimental Procedures	S5
1.3.1 Catalyst Synthesis	S5
1.3.2 Substrate Synthesis	S6
1.3.2.1 Nitroarylation of Acetonitriles	S6
1.3.2.2 Reduction of Nitrobenzenes	S17
1.3.2.3 Formylation of Aminobenzenes Followed by Dehydration	S29
1.3.3 Phase-Transfer Catalyzed Cyclization of Isocyanides	S42
1.3.4 Derivatizations	S64
1.3.5 Additional Synthesis	S71
1.4 References and Notes	S72
 Appendix I: Further Reaction and Catalyst Optimization	 S73
Appendix II: ¹ H and ¹³ C NMR Spectra	S74
Appendix III: HPLC Data	S152

1.1 General Information

Reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was oven-dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.¹ Water was purified by an Elix® UV-10 system. Reagents were used directly as supplied by major chemical suppliers, or following purification procedures described by Perrin and Armarego.² Thin layer chromatography was performed on aluminium plates coated with 60 F₂₅₄ silica. Flash column chromatography was performed on Kieselgel 60 silica on a glass column. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10⁻¹ deg cm² g⁻¹ and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer using an ATR module. Selected characteristic peaks are recorded in cm⁻¹. UV spectra were recorded on a Perkin-Elmer Lambda 2 UV/Vis spectrometer in MeOH. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass. Analytical chiral HPLC was performed on a Dionex Ultimate 3000 HPLC system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler, TCC-3000SD column compartment and DAD-3000 diode-array detector, equipped with the appropriate Daicel Chiralpak column (dimensions: 4.6 mm × 250 mm) and corresponding guard column (4.0 mm × 10 mm).

1.2 General Experimental Procedures

General Procedure 1: Nitroarylation of Acetonitriles

To a vigorously stirred mixture of the requisite acetonitrile, the requisite nitrobenzene and tetrabutylammonium bisulfate in toluene, was added 50% aqueous NaOH in one portion. Once the reaction was complete, the reaction mixture was acidified with 10% HCl and then extracted with CH₂Cl₂ (×3). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give a crude reaction product.

General Procedure 2: Reduction of Nitrobenzenes

Zinc powder and NH₄Cl were added to a stirred solution of the requisite nitrobenzene in a 5:1 mixture of acetone/H₂O. Once the reaction was complete, the reaction mixture was filtered through a pad of Celite®, and concentrated *in vacuo*. The residue was extracted with EtOAc and water (×3), washed with sat. aq. NaCl, dried over Na₂SO₄, filtered and concentrated to give a crude reaction product.

General Procedure 3: Formylation of Aminobenzenes

To a stirred solution of the requisite aminobenzene in formic acid at 0 °C was added acetic anhydride dropwise (typically over 1-2 hours *via* syringe pump). Once complete, the reaction mixture was concentrated *in vacuo*, washed with sat. aq. NaHCO₃ and extracted with CH₂Cl₂. The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to give a crude reaction product.

General Procedure 4: Dehydration of Formamides

To a solution of the requisite formamide and Et₃N in anhydrous CH₂Cl₂ at -30 °C under argon was added phosphoryl chloride dropwise. The resulting mixture was stirred at -30 °C until the reaction was complete, after which sat. aq. NaHCO₃ was added and the mixture was then

extracted with CH_2Cl_2 ($\times 3$). The combined organic extracts were dried (MgSO_4) and concentrated *in vacuo* to give a crude reaction product.

General Procedure 5: Phase-Transfer Catalyzed Racemic Cyclization of Isocyanides

To a solution of the requisite isocyanide and tetrabutylammonium bromide (10 mol%) in anhydrous PhMe under argon was added aqueous KOH (30% w/w) at 0 °C. The resulting mixture was stirred at 0 °C until the reaction was complete, after which MgSO_4 was added and the mixture was then filtered through a short pad of silica contained within a pipette. Following washing with Et_2O and concentration *in vacuo*, the residue was dissolved in anhydrous THF and sodium triacetoxyborohydride was added in one portion. The resulting mixture was stirred at room temperature until the reaction was complete and was then quenched with H_2O , extracted with Et_2O ($\times 3$), dried (MgSO_4) and concentrated under reduced pressure to give a crude reaction product.

General Procedure 6: Phase-Transfer Catalyzed Asymmetric Cyclization of Isocyanides

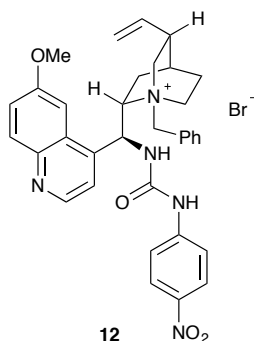
The requisite phase-transfer catalyst (5 mol%) was added to a solution of the requisite isocyanide in the requisite anhydrous solvent under argon. The resulting mixture was stirred at room temperature for thirty minutes, after which the requisite base was added at the requisite temperature. Once the reaction was complete, MgSO_4 was added and the mixture was then filtered through a short pad of silica contained within a pipette. Following washing with Et_2O and concentration *in vacuo*, the residue was dissolved in anhydrous THF and sodium triacetoxyborohydride was added in one portion. The resulting mixture was stirred at room temperature until the reaction was complete and was then quenched with H_2O , extracted with Et_2O ($\times 3$), dried (MgSO_4) and concentrated under reduced pressure to give a crude reaction product.

1.3 Experimental Procedures

1.3.1 Catalyst Synthesis

Catalysts that were not commercially available were prepared following well-established literature procedures. This reaction has not been optimized.

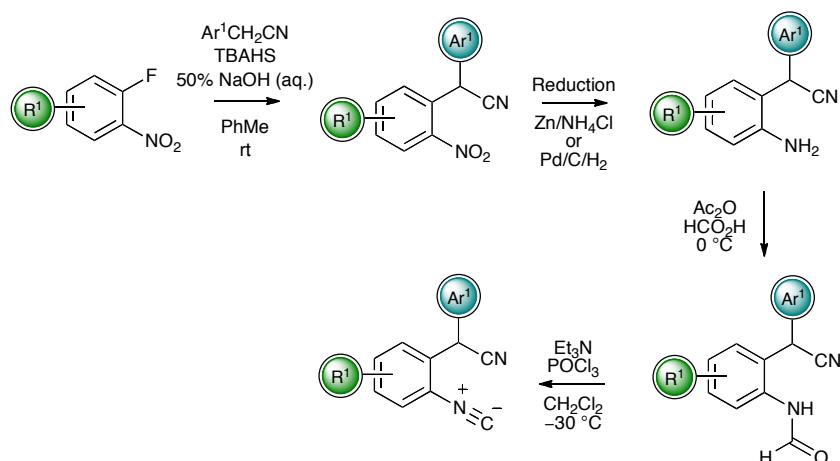
Preparation of (1*S*,2*S*,4*S*,5*R*)-1-benzyl-2-((*S*)-(6-methoxyquinolin-4-yl)(3-(4-nitrophenyl)ureido)methyl)-5-vinylquinuclidin-1-ium bromide **12**



To a solution of 1-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)-3-(4-nitrophenyl)urea³ (389 mg, 0.797 mmol) in PhMe (5 mL) was added benzyl bromide (0.10 mL, 0.837 mmol) at rt. The reaction mixture was heated to 65 °C and stirred overnight. The resulting mixture was concentrated under reduced pressure and purified by flash chromatography (silica; 10:1 CH₂Cl₂/MeOH) to yield **12** as an orange solid; mp 176-179 °C; [α]_D²⁰ -17.0 (*c* 0.7 in MeOH); ν_{max} (film) 3009, 2359, 1696, 1620, 1559, 1507; δ_{H} (500 MHz, CD₃OD) 1.16-1.28 (1H, m), 1.93 (1H, d, *J* 1.9), 2.03-2.25 (3H, m), 2.74 (1H, q, *J* 7.9), 3.49-3.65 (2H, m), 3.71-3.83 (1H, m), 4.02 (2H, s), 4.40-4.55 (1H, m), 4.86 (3H, s), 4.98-5.32 (5H, m), 5.85-5.99 (1H, m), 6.44 (1H, d, *J* 8.2), 7.45 (1H, dd, *J* 9.2, 2.6), 7.47-7.51 (3H, m), 7.54-7.67 (4H, m), 7.74 (1H, s), 7.81 (1H, d, *J* 4.7), 7.98 (1H, d, *J* 9.2), 8.04 (2H, d, *J* 6.4), 8.77 (1H, s); δ_{C} (126 MHz, CD₃OD) 25.7, 28.2, 28.8, 38.7, 51.0, 51.5, 56.7, 62.0, 67.4, 68.8, 102.5, 118.4, 118.9, 120.8, 124.3, 125.9, 128.9, 130.5, 131.8, 132.1, 134.7, 137.6, 143.7, 145.3, 145.6, 146.7, 148.6, 160.7; *m/z* (ESI⁺) 578 (M⁺, 100%); HRMS (ESI⁺) C₃₄H₃₆N₅O₄⁺, (M⁺) requires 578.2762; found 578.2783.

1.3.2 Substrate Synthesis

Substrates were prepared following the general four-step sequence given below.⁴

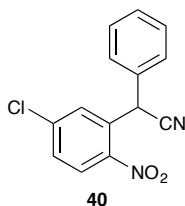


Scheme 1: Substrate synthesis.

1.3.2.1 Nitroarylation of Acetonitriles

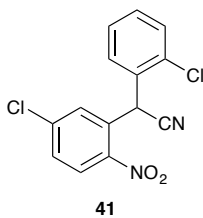
These reactions have not been optimized.

Preparation of (±)-2-(5-chloro-2-nitrophenyl)-2-phenylacetonitrile **40**



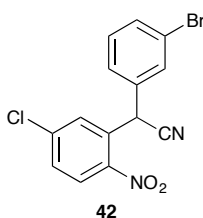
Following **General Procedure 1**, phenylacetonitrile (1.17 g, 10.0 mmol), 4-chloro-2-fluoronitrobenzene (1.75 g, 10.0 mmol) and tetrabutylammonium bisulfate (3.39 g, 10.0 mmol) in toluene (32.0 mL) and 50% aqueous NaOH (4.00 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 8:1 40-60 petrol/Et₂O) gave **40** as a white solid (2.39 g, 87%); mp 60-62 °C; ν_{max} (film) 3029, 1739, 1601, 1570, 1523; δ_{H} (400 MHz, CDCl₃) 6.19 (1H, s), 7.31-7.36 (2H, m), 7.37-7.43 (3H, m), 7.52 (1H, dd, *J* 8.8, 2.1), 7.70 (1H, d, *J* 2.1), 8.05 (1H, d, *J* 8.8); δ_{C} (101 MHz, CDCl₃) 38.2, 118.1, 127.3, 127.9, 129.0, 129.5, 129.9, 131.0, 132.6, 133.4, 140.9, 145.8; *m/z* (ESI⁺) 295 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₄H₉ClN₂NaO₂⁺, ([M+Na]⁺) requires 295.0245; found 295.0241.

Preparation of (±)-2-(5-chloro-2-nitrophenyl)-2-(2-chlorophenyl)acetonitrile **41**



Following **General Procedure 1**, 2-chlorobenzyl cyanide (5.46 g, 35.9 mmol), 4-chloro-2-fluoronitrobenzene (6.32 g, 35.9 mmol) and tetrabutylammonium bisulfate (12.2 g, 35.9 mmol) in toluene (72 mL) and 50% aqueous NaOH (72 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 90:10 40-60 petrol/EtOAc) gave **41** as an orange solid (9.89 g, 90%); mp 128-130 °C; ν_{max} (film) 3457, 3016, 2970, 2947, 2132, 1773, 1705; δ_{H} (400 MHz, CDCl_3) 6.43 (1H, s), 7.38-7.44 (3H, m), 7.46-7.52 (2H, m), 7.57 (1H, dd, J 8.8, 2.2), 8.14 (1H, d, J 8.8); δ_{C} (101 MHz, CDCl_3) 36.6, 117.0, 127.4, 127.9, 129.4, 130.2, 130.7, 130.8, 130.9, 131.2, 131.4, 133.7, 140.9, 146.2; m/z (ESI⁺) 329 ([M+Na]⁺); HRMS (ESI⁺) $\text{C}_{14}\text{H}_8\text{Cl}_2\text{N}_2\text{NaO}_2^+$, ([M+Na]⁺) requires 328.9855; found 328.9854.

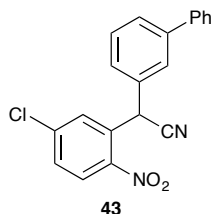
Preparation of (±)-2-(3-bromophenyl)-2-(5-chloro-2-nitrophenyl)acetonitrile **42**



Following **General Procedure 1**, 3-bromophenylacetonitrile (5.00 g, 25.5 mmol), 4-chloro-2-fluoronitrobenzene (4.49 g, 25.5 mmol) and tetrabutylammonium bisulfate (8.67 g, 25.5 mmol) in toluene (51 mL) and 50% aqueous NaOH (51 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 85:15 40-60 petrol/EtOAc) gave **42** as a pale yellow solid (8.50 g, 95%); mp 64-66 °C; ν_{max} (film) 1770, 1524; δ_{H} (400 MHz, CDCl_3) 6.18 (1H, s), 7.28-7.32 (2H, m), 7.47-7.49 (1H, m), 7.51-7.54 (1H, m), 7.58 (1H, dd, J 8.8, 2.2), 7.70 (1H, d, J 2.2),

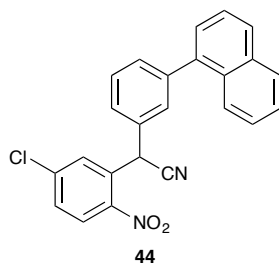
8.11 (1H, d, *J* 8.8); δ_c (101 MHz, CDCl₃) 37.9, 117.6, 123.5, 126.6, 127.6, 130.3, 130.9, 131.0, 131.0, 131.8, 132.3, 135.5, 141.2, 145.7; *m/z* (ESI⁺) 373 ([M+Na]⁺); HRMS (ESI⁺) C₁₄H₈BrClN₂NaO₂⁺, ([M+Na]⁺) requires 372.9350; found 372.9344.

Preparation of (±)-2-([1,1'-biphenyl]-3-yl)-2-(5-chloro-2-nitrophenyl)acetonitrile **43**



Following **General Procedure 1**, [1,1'-biphenyl]-3-acetonitrile (1.93 g, 10.0 mmol), 4-chloro-2-fluoronitrobenzene (1.75 g, 10.0 mmol) and tetrabutylammonium bisulfate (3.39 g, 10.0 mmol) in toluene (32.0 mL) and 50% aqueous NaOH (4.00 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 6:1 40-60 petrol/Et₂O) gave **43** as a yellow oil (3.24 g, 93%); $\nu_{\max}$ (film) 3102, 3035, 2362, 2341, 1601, 1571, 1526; δ_H (400 MHz, CDCl₃) 6.27 (1H, s), 7.32 (1H, d, *J* 7.8), 7.37-7.43 (1H, m), 7.44-7.54 (4H, m), 7.55-7.63 (4H, m), 7.76 (1H, d, *J* 2.2), 8.06 (1H, d, *J* 8.8); δ_c (101 MHz, CDCl₃) 38.3, 118.2, 126.7, 126.7, 127.2, 127.4, 127.9, 128.0, 129.0, 130.0, 130.0, 131.0, 132.5, 134.0, 139.9, 140.9, 142.7, 145.9; *m/z* (ESI⁺) 371 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₂₀H₁₃ClN₂NaO₂⁺, ([M+Na]⁺) requires 371.0558; found 371.0570.

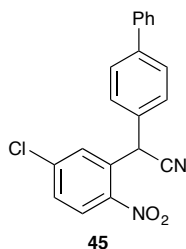
Preparation of (±)-2-(5-chloro-2-nitrophenyl)-2-(3-(naphthalen-1-yl)phenyl)acetonitrile **44**



Following **General Procedure 1**, 2-(3-(naphthalen-1-yl)phenyl)acetonitrile (1.28 g, 5.26 mmol), 4-chloro-2-fluoronitrobenzene (0.924 g, 5.26 mmol) and tetrabutylammonium bisulfate (1.78 g, 5.26 mmol) in toluene (15.0 mL) and 50% aqueous NaOH (2.10 mL) yielded a crude reaction product.

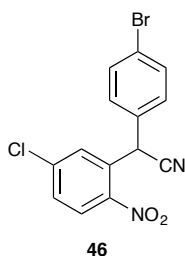
Purification *via* flash column chromatography on silica gel (silica; 6:1 40-60 petrol/Et₂O) gave **44** as a yellow powder (1.68 g, 82%); mp 134-136 °C; ν_{max} (film) 3058, 2361, 2248, 1602, 1571, 1524; δ_{H} (400 MHz, CDCl₃) 6.29 (1H, s), 7.37-7.57 (9H, m), 7.76 (1H, d, *J* 8.4), 7.81 (1H, d, *J* 2.2), 7.91 (2H, dd, *J* 11.9, 8.1), 8.06 (1H, d, *J* 8.8); δ_{C} (101 MHz, CDCl₃) 38.4, 118.1, 125.3, 125.5, 126.0, 126.4, 126.8, 127.1, 127.4, 128.2, 128.4, 129.5, 129.5, 130.0, 130.8, 131.0, 131.3, 132.4, 133.5, 133.8, 138.8, 140.9, 142.2, 145.9; *m/z* (ESI⁺) 397 ([M-H]⁻, 100%); HRMS (ESI⁺) C₂₄H₁₅ClN₂NaO₂⁺, ([M+Na]⁺) requires 421.0714; found 421.0711.

Preparation of (±)-2-([1,1'-biphenyl]-4-yl)-2-(5-chloro-2-nitrophenyl)acetonitrile **45**



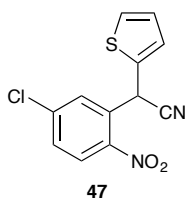
Following **General Procedure 1**, 4-biphenylacetonitrile (0.910 g, 5.45 mmol), 4-chloro-2-fluoronitrobenzene (0.956 g, 5.45 mmol) and tetrabutylammonium bisulfate (1.84 g, 5.45 mmol) in toluene (23.0 mL) and 50% aqueous NaOH (2.15 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 15:1 40-60 petrol/EtOAc) gave **45** as a yellow oil (1.47 g, 88%); ν_{max} (film) 3101, 3032, 2858, 2359, 2337, 2248, 1602, 1571, 1525; δ_{H} (400 MHz, CDCl₃) 6.25 (1H, s), 7.37-7.43 (3H, m), 7.46 (2H, t, *J* 7.6), 7.52-7.59 (3H, m), 7.62 (2H, d, *J* 8.3), 7.76 (1H, d, *J* 2.2), 8.08 (1H, d, *J* 8.8); δ_{C} (101 MHz, CDCl₃) 40.0, 118.1, 127.1, 127.4, 127.9, 128.2, 128.3, 128.9, 130.0, 131.0, 132.3, 132.6, 139.8, 141.0, 142.0, 145.8; *m/z* (ESI⁺) 371 ([M+Na]⁺, 58%); HRMS (ESI⁺) C₂₀H₁₃ClN₂NaO₂⁺, ([M+Na]⁺) requires 371.0558; found 371.0554.

Preparation of (±)-2-(4-bromophenyl)-2-(5-chloro-2-nitrophenyl)acetonitrile **46**



Following **General Procedure 1**, 4-bromophenylacetonitrile (5.00 g, 25.5 mmol), 4-chloro-2-fluoronitrobenzene (4.49 g, 25.5 mmol) and tetrabutylammonium bisulfate (8.67 g, 25.5 mmol) in toluene (51 mL) and 50% aqueous NaOH (51 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 80:20 40-60 petrol/EtOAc) gave **46** a pale yellow solid (8.31 g, 93%); mp 84-86 °C; $\nu_{\max}$ (film) 2980, 2962, 1768, 1754, 1737, 1711, 1603, 1571, 1524; δ_{H} (400 MHz, CDCl_3) 6.16 (1H, s), 7.21-7.25 (2H, m), 7.50-7.57 (3H, m), 7.70 (1H, d, J 2.2), 8.08 (1H, d, J 8.8); δ_{C} (101 MHz, CDCl_3) 37.9, 117.8, 123.4, 127.6, 129.6, 130.2, 130.9, 132.0, 132.5, 132.7, 141.1, 145.7; m/z (ESI⁻) 348 ($[\text{M}-\text{H}]^-$); HRMS (ESI⁺) $\text{C}_{14}\text{H}_8\text{BrClN}_2\text{NaO}_2^+$, ($[\text{M}+\text{Na}]^+$) requires 372.9350; found 372.9340.

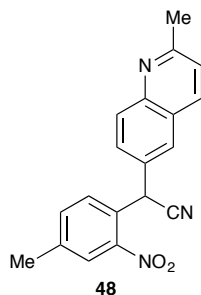
Preparation of (±)-2-(5-chloro-2-nitrophenyl)-2-(thiophen-2-yl)acetonitrile **47**



Following **General Procedure 1**, 2-thiopheneacetonitrile (4.32 mL, 40.7 mmol), 4-chloro-2-fluoronitrobenzene (7.15 g, 40.7 mmol) and tetrabutylammonium bisulfate (13.8 g, 40.7 mmol) in toluene (81 mL) and 50% aqueous NaOH (16 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 20:80 EtOAc/40-60 petrol) gave **47** as a blood red oil (5.29 g, 47%); $\nu_{\max}$ (film) 3457, 2971, 1760, 1712; δ_{H} (400 MHz, CDCl_3) 6.45 (1H, s), 7.01 (1H, dd, J 5.2, 3.6), 7.16 (1H, d, J 3.6), 7.33 (1H, dd, J 5.2, 1.2), 7.54 (1H, dd, J 8.8, 2.2), 7.78 (1H, d, J

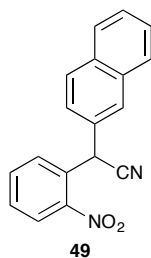
2.2), 8.09 (1H, d, *J* 8.8); δ_c (101 MHz, CDCl₃) 33.9, 117.5, 127.3, 127.4, 127.9, 130.3, 130.5, 132.5, 135.3, 141.2, 145.2; *m/z* (ESI⁺) 300 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₂H₇ClN₂NaO₂S⁺, ([M+Na]⁺) requires 300.9809; found 300.9812.

Preparation of (±)-2-(4-methyl-2-nitrophenyl)-2-(2-methylquinolin-6-yl)acetonitrile **48**



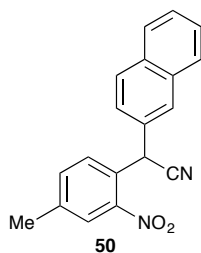
Following **General Procedure 1**, 2-(2-methylquinolin-6-yl)acetonitrile (1.75 g, 9.6 mmol), 4-fluoro-3-nitrotoluene (1.49 g, 9.6 mmol) and tetrabutylammonium bisulfate (3.25 g, 9.6 mmol) in toluene (30.0 mL) and 50% aqueous NaOH (3.8 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/EtOAc) gave **48** as a yellow powder (2.52 g, 86%); mp 98-100 °C; $\nu_{\max}$ (film) 3035, 2925, 2359, 2245, 1603, 1530; δ_H (400 MHz, CDCl₃) 2.46 (3H, s), 2.74 (3H, s), 6.28 (1H, s), 7.32 (1H, d, *J* 8.4), 7.48-7.54 (2H, m), 7.60 (1H, d, *J* 8.0), 7.81 (1H, d, *J* 2.0), 7.90 (1H, d, *J* 0.8), 7.99 (1H, d, *J* 8.8), 8.03 (1H, d, *J* 8.5); δ_c (101 MHz, CDCl₃) 20.9, 25.4, 38.0, 118.6, 122.9, 126.2, 126.3, 126.8, 127.3, 128.6, 130.1, 130.9, 131.5, 135.0, 136.2, 140.8, 147.4, 147.5, 160.2; *m/z* (ESI⁺) 340 ([M+Na]⁺, 58%); HRMS (ESI⁺) C₁₉H₁₅N₃NaO₂⁺, ([M+Na]⁺) requires 340.1056; found 340.1044.

Preparation of (±)-2-(naphthalen-2-yl)-2-(2-nitrophenyl)acetonitrile 49



Following **General Procedure 1**, 2-naphthylacetonitrile (1.19 g, 7.12 mmol), 1-fluoro-2-nitrobenzene (1.00 g, 7.12 mmol) and tetrabutylammonium bisulfate (2.41 g, 7.12 mmol) in toluene (30.0 mL) and 50% aqueous NaOH (2.80 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 10:1 to 5:1 40-60 petrol/Et₂O) gave **49** as a yellow powder (1.30 g, 64%); mp 84-86 °C; ν_{max} (film) 3059, 2360, 2245, 1603; δ_{H} (400 MHz, CDCl₃) 6.35 (1H, s), 7.35 (1H, dd, *J* 8.6, 1.8), 7.50-7.60 (3H, m), 7.66-7.77 (2H, m), 7.81-7.89 (4H, m), 8.10 (1H, d, *J* 8.2); δ_{C} (101 MHz, CDCl₃) 38.4, 118.6, 125.1, 125.8, 127.0, 127.0, 127.2, 127.7, 128.1, 129.5, 129.8, 130.6, 131.2, 131.4, 132.9, 133.2, 134.2, 147.8; *m/z* (ESI⁺) 311 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₈H₁₂N₂NaO₂⁺, ([M+Na]⁺) requires 311.0791; found 311.0787.

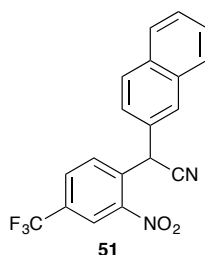
Preparation of (±)-2-(4-methyl-2-nitrophenyl)-2-(naphthalen-2-yl)acetonitrile 50



Following **General Procedure 1**, 2-naphthylacetonitrile (1.67 g, 10.0 mmol), 4-fluoro-3-nitrotoluene (1.55 g, 10.0 mmol) and tetrabutylammonium bisulfate (3.39 g, 10.0 mmol) in toluene (32.0 mL) and 50% aqueous NaOH (4.00 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 4:1 40-60 petrol/Et₂O) gave **50** as a yellow oil (2.70 g, 89%); ν_{max} (film) 3058, 2925, 2360, 2244, 1601, 1530; δ_{H} (400 MHz, CDCl₃) 2.47 (3H, s), 6.29

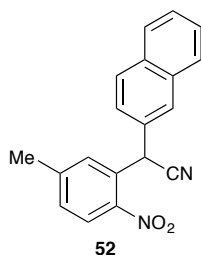
(1H, s), 7.34 (1H, dd, *J* 8.6, 1.9), 7.49 (1H, dd, *J* 8.1, 1.2), 7.51-7.55 (2H, m), 7.60 (1H, d, *J* 8.0), 7.81-7.87 (4H, m), 7.91 (1H, d, *J* 0.9); δ_c (101 MHz, CDCl₃) 20.9, 38.2, 118.8, 125.1, 126.1, 126.9, 127.1, 127.6, 127.7, 128.1, 129.4, 131.0, 131.6, 132.9, 133.2, 134.9, 140.6, 147.5; *m/z* (ESI⁺) 325 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₉H₁₄N₂NaO₂⁺, ([M+Na]⁺) requires 325.0947; found 325.0942.

Preparation of (±)-2-(naphthalen-2-yl)-2-(2-nitro-4-(trifluoromethyl)phenyl)acetonitrile **51**



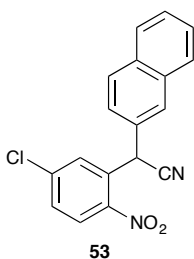
Following **General Procedure 1**, 2-naphthylacetonitrile (1.67 g, 10.0 mmol), 4-fluoro-3-nitrobenzotrifluoride (2.15 g, 10.0 mmol) and tetrabutylammonium bisulfate (3.39 g, 10.0 mmol) in toluene (32.0 mL) and 50% aqueous NaOH (4.00 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 10:1 to 8:1 40-60 petrol/Et₂O) gave **51** as a yellow solid (2.60 g, 73%); mp 88-90 °C; $\nu_{\max}$ (film) 3061, 2357, 2247, 1738, 1629, 1542, 1507; δ_H (400 MHz, CDCl₃) 6.38 (1H, s), 7.33 (1H, d, *J* 8.8), 7.56 (2H, dd, *J* 6.1, 3.2), 7.82-7.89 (4H, m), 7.90-7.97 (2H, m), 8.36 (1H, s); δ_c (101 MHz, CDCl₃) 38.5, 117.9, 122.4 (q, *J* 268.6), 123.2 (q, *J* 3.8), 124.8, 127.2, 127.3, 127.4, 127.8, 128.1, 129.8, 130.4, 130.7 (q, *J* 3.4), 132.2, 132.5 (q, *J* 34.8), 133.1, 133.2, 134.4, 147.7; δ_F (377 MHz, CDCl₃) -63.0; *m/z* (ESI⁺) 379 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₉H₁₁F₃N₂NaO₂⁺, ([M+Na]⁺) requires 379.0665; found 379.0654.

Preparation of (±)-2-(5-methyl-2-nitrophenyl)-2-(naphthalen-2-yl)acetonitrile **52**



Following **General Procedure 1**, 2-naphthylacetonitrile (1.67 g, 10.0 mmol), 3-fluoro-4-nitrotoluene (1.55 g, 10.0 mmol) and tetrabutylammonium bisulfate (3.39 g, 10.0 mmol) in toluene (32.0 mL) and 50% aqueous NaOH (4.00 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 5:1 to 3:1 40-60 petrol/Et₂O) gave **52** as a yellow oil (2.93 g, 97%); $\nu_{\max}$ (film) 3058, 2955, 2855, 2245, 1602, 1519; δ_{H} (400 MHz, CDCl₃) 2.44 (3H, s), 6.40 (1H, s), 7.31 (1H, d, *J* 8.4), 7.37 (1H, dd, *J* 8.6, 1.8), 7.49-7.57 (3H, m), 7.81-7.87 (3H, m), 7.88 (1H, s), 8.02 (1H, d, *J* 8.4); δ_{C} (101 MHz, CDCl₃) 21.6, 38.4, 118.9, 125.1, 126.1, 126.9, 127.0, 127.1, 127.8, 128.1, 129.4, 130.3, 130.5, 131.6, 132.9, 133.2, 145.4, 146.0; *m/z* (ESI⁺) 325 ([M+Na]⁺, 96%); HRMS (ESI⁺) C₁₉H₁₄N₂NaO₂⁺, ([M+Na]⁺) requires 325.0947; found 325.0940.

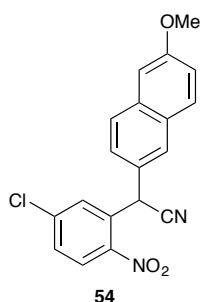
Preparation of (±)-2-(5-chloro-2-nitrophenyl)-2-(naphthalen-2-yl)acetonitrile **53**



Following **General Procedure 1**, 2-naphthylacetonitrile (1.20 g, 7.18 mmol), 4-chloro-2-fluoronitrobenzene (1.26 g, 7.18 mmol) and tetrabutylammonium bisulfate (2.40 g, 7.18 mmol) in toluene (28.0 mL) and 50% aqueous NaOH (2.80 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/Et₂O) gave **53** as a yellow solid (1.69 g, 74%); mp 91-93 °C; $\nu_{\max}$ (film) 3026, 2361, 2247, 1601, 1571, 1524; δ_{H} (400

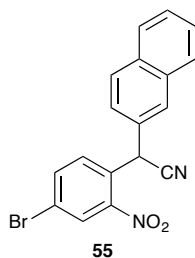
MHz, CDCl₃) 6.36 (1H, s), 7.35 (1H, dd, *J* 8.5, 1.9), 7.49-7.59 (3H, m), 7.71 (1H, d, *J* 2.2), 7.82-7.90 (4H, m), 8.06 (1H, d, *J* 8.8); δ_c (101 MHz, CDCl₃) 38.4, 118.1, 124.9, 127.1, 127.2, 127.3, 127.4, 127.8, 128.2, 129.7, 130.0, 130.6, 131.1, 132.6, 133.0, 133.2, 140.9, 145.9; *m/z* (ESI⁺) 345 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₈H₁₁ClN₂NaO₂⁺, ([M+Na]⁺) requires 345.0401; found 345.0394.

Preparation of (±)-2-(5-chloro-2-nitrophenyl)-2-(6-methoxynaphthalen-2-yl)acetonitrile **54**



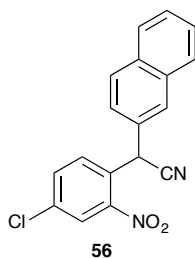
Following **General Procedure 1**, 2-(6-methoxy-2-naphthyl)acetonitrile (0.698 g, 3.54 mmol), 4-chloro-2-fluoronitrobenzene (0.621 g, 3.54 mmol) and tetrabutylammonium bisulfate (1.20 g, 3.54 mmol) in toluene (14.0 mL) and 50% aqueous NaOH (1.40 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 15:1 40-60 petrol/Et₂O) gave **54** as a yellow oil (1.06 g, 91%); ν_{max} (film) 3101, 2938, 2843, 2343, 1632, 1604, 1571, 1526; δ_H (400 MHz, CDCl₃) 3.93 (3H, s), 6.32 (1H, s), 7.13 (1H, d, *J* 2.4), 7.21 (1H, dd, *J* 9.0, 2.5), 7.30 (1H, dd, *J* 8.6, 2.0), 7.51 (1H, dd, *J* 8.8, 2.2), 7.70 (1H, d, *J* 2.2), 7.74 (1H, d, *J* 3.0), 7.77 (2H, dd, *J* 6.0, 1.9), 8.06 (1H, d, *J* 8.8); δ_c (101 MHz, CDCl₃) 38.2, 55.4, 105.7, 118.2, 120.0, 125.4, 127.1, 127.3, 128.2, 128.4, 128.6, 129.6, 129.9, 131.0, 132.8, 134.4, 140.9, 145.9, 158.6; *m/z* (ESI⁺) 375 ([M+Na]⁺, 55%); HRMS (ESI⁺) C₁₉H₁₃ClN₂NaO₃⁺, ([M+Na]⁺) requires 375.0507; found 375.0504.

Preparation of (±)-2-(4-bromo-2-nitrophenyl)-2-(naphthalen-2-yl)acetonitrile **55**



Following **General Procedure 1**, 2-naphthylacetonitrile (1.67 g, 10.0 mmol), 4-bromo-1-fluoro-2-nitrobenzene (2.18 g, 10.0 mmol) and tetrabutylammonium bisulfate (3.39 g, 10.0 mmol) in toluene (32.0 mL) and 50% aqueous NaOH (4.00 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 7:1 40-60 petrol/Et₂O) gave **55** as a yellow oil (3.22 g, 88%); ν_{max} (film) 3059, 2246, 1600, 1530; δ_{H} (400 MHz, CDCl₃) 6.27 (1H, s), 7.32 (1H, dd, *J* 8.7, 1.7), 7.55 (2H, dd, *J* 6.4, 3.2), 7.60 (1H, d, *J* 8.4), 7.81 (1H, dd, *J* 8.4, 2.0), 7.83-7.87 (4H, m), 8.24 (1H, d, *J* 2.0); δ_{C} (101 MHz, CDCl₃) 38.2, 118.1, 123.3, 124.9, 127.1, 127.2, 127.2, 127.8, 128.1, 128.8, 129.6, 129.6, 130.7, 132.5, 133.0, 133.2, 137.2, 148.0; *m/z* (ESI⁺) 388 ([M+Na]⁺, 98%); HRMS (ESI⁺) C₁₈H₁₁BrN₂NaO₂⁺, ([M+Na]⁺) requires 388.9896; found 388.9883.

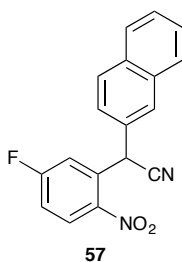
Preparation of (±)-2-(4-chloro-2-nitrophenyl)-2-(naphthalen-2-yl)acetonitrile **56**



Following **General Procedure 1**, 2-naphthylacetonitrile (1.67 g, 10.0 mmol), 5-chloro-2-fluoronitrobenzene (1.75 g, 10.0 mmol) and tetrabutylammonium bisulfate (3.39 g, 10.0 mmol) in toluene (32.0 mL) and 50% aqueous NaOH (4.00 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 8:1 40-60 petrol/Et₂O) gave **56** as a yellow oil (2.80 g, 87%); ν_{max} (film) 3059, 2946, 2871, 2249, 1601, 1531; δ_{H} (400 MHz, CDCl₃)

6.28 (1H, s), 7.32 (1H, dd, *J* 8.7, 1.8), 7.55 (2H, dd, *J* 6.4, 3.1), 7.65-7.67 (2H, m), 7.85 (4H, dt, *J* 5.9, 3.1), 8.09 (1H, d, *J* 1.7); δ_{C} (101 MHz, CDCl_3) 38.1, 118.2, 124.9, 126.0, 127.1, 127.2, 127.2, 127.8, 128.1, 129.1, 129.6, 130.8, 132.3, 133.0, 133.2, 134.3, 135.8, 148.0; *m/z* (ESI^+) 345 ($[\text{M}+\text{Na}]^+$, 100%); HRMS (ESI^+) $\text{C}_{18}\text{H}_{11}\text{ClN}_2\text{NaO}_2^+$, ($[\text{M}+\text{Na}]^+$) requires 345.0401; found 345.0389.

Preparation of ($\pm$)-2-(5-fluoro-2-nitrophenyl)-2-(naphthalen-2-yl)acetonitrile **57**

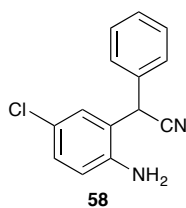


Following **General Procedure 1**, 2-naphthylacetonitrile (1.00 g, 6.00 mmol), 2,4-difluoro-1-nitrobenzene (0.954 g, 6.00 mmol) and tetrabutylammonium bisulfate (2.03 g, 6.00 mmol) in toluene (20.1 mL) and 50% aqueous NaOH (2.40 mL) yielded a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 6:1 40-60 petrol/ Et_2O) gave **57** as a yellow solid (1.93 g, 80%); mp 88-91 °C; ν_{max} (film) 3056, 2361, 2246, 1618, 1590, 1527; δ_{H} (400 MHz, CDCl_3) 6.40 (1H, s), 7.24 (1H, ddd, *J* 12.3, 6.7, 3.2), 7.35 (1H, dd, *J* 8.6, 1.5), 7.41 (1H, dd, *J* 8.8, 2.6), 7.56 (2H, dd, *J* 6.2, 3.2), 7.82-7.90 (4H, m), 8.20 (1H, dd, *J* 9.1, 5.0); δ_{C} (101 MHz, CDCl_3) 38.6, 116.8, 117.0, 118.1, 118.3, 118.6, 124.9, 127.1, 127.2, 127.3, 127.8, 128.1, 128.9, 129.0, 129.7, 130.6, 133.0, 133.2, 134.2, 134.3, 143.7, 165.0; δ_{F} (377 MHz, CDCl_3) -100.1; *m/z* (ESI^+) 329 ($[\text{M}+\text{Na}]^+$, 100%); HRMS (ESI^+) $\text{C}_{18}\text{H}_{11}\text{FN}_2\text{NaO}_2^+$, ($[\text{M}+\text{Na}]^+$) requires 329.0697; found 329.0685.

1.3.2.2 Reduction of Nitrobenzenes

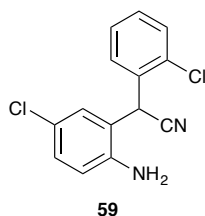
These reactions have not been optimized.

Preparation of (±)-2-(2-amino-5-chlorophenyl)-2-phenylacetonitrile **58**



Following **General Procedure 2**, zinc powder (5.55 g, 85.4 mmol), NH₄Cl (6.78 g, 128 mmol) and **40** (2.33 g, 8.54 mmol) in a 5:1 mixture of acetone/H₂O (170 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/Et₂O) gave **58** as a yellow solid (1.98 g, 96%); mp 88-90 °C; ν_{max} (film) 3452, 3374, 2360, 2244, 1630; δ_{H} (400 MHz, CDCl₃) 3.55 (2H, br s), 5.13 (1H, s), 6.67 (1H, d, *J* 8.5), 7.17 (1H, dd, *J* 8.5, 2.4), 7.29 (1H, d, *J* 2.3), 7.33-7.45 (5H, m); δ_{C} (101 MHz, CDCl₃) 38.9, 118.4, 118.7, 121.5, 124.2, 127.7, 128.9, 129.1, 129.6, 129.6, 133.2, 142.5; *m/z* (ESI⁺) 265 ([M+Na]⁺, 74%); HRMS (ESI⁺) C₁₄H₁₁ClN₂Na⁺, ([M+Na]⁺) requires 265.0503; found 265.0498.

Preparation of (±)-2-(2-amino-5-chlorophenyl)-2-(2-chlorophenyl)acetonitrile **59**

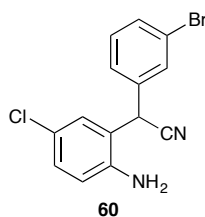


Following **General Procedure 2**, zinc powder (19.2 g, 294 mmol), NH₄Cl (23.6 g, 441 mmol) and **41** (9.02 g, 29.4 mmol) in a 5:1 mixture of acetone/H₂O (490:98 acetone/H₂O) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 80:20 40-60 petrol/EtOAc) gave **59** as an orange oil (8.09 g, 99%); ν_{max} (film) 2245, 1764, 1758, 1714, 1631; δ_{H} (400 MHz, CDCl₃) 3.65 (2H, br s), 5.50 (1H, s), 6.70 (1H, d, *J* 8.5), 7.17 (1H, dd, *J* 8.5, 2.4), 7.26 (1H, d, *J* 2.3), 7.30-7.40 (3H, m), 7.46-7.51 (1H, m); δ_{C} (101 MHz, CDCl₃) 35.6, 117.8, 118.5, 120.4, 124.2,

128.1, 128.5, 129.6, 129.7, 130.4, 130.5, 131.1, 133.7, 142.4; m/z (ESI⁺) 277 ([M+H]⁺); HRMS (ESI⁺)

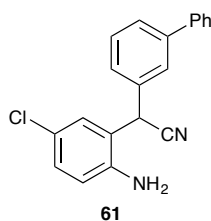
C₁₄H₁₀Cl₂N₂Na⁺, ([M+H]⁺) requires 299.0113; found 299.0104.

Preparation of (±)-2-(2-amino-5-chlorophenyl)-2-(3-bromophenyl)acetonitrile **60**



Following **General Procedure 2**, zinc powder (15.3 g, 235 mmol), NH₄Cl (18.8 g, 352 mmol) and **42** (8.26 g, 23.5 mmol) in a 5:1 mixture of acetone/H₂O (390:79 acetone/H₂O) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 80:20 40-60 petrol/EtOAc) gave **60** as a yellow oil (6.98 g, 92%); $\nu_{\max}$ (film) 3458, 3375, 3027, 2245, 1774, 1752, 1734, 1723, 1717, 1708, 1630, 1592, 1572; δ_{H} (400 MHz, CDCl₃) 3.49 (2H, br s), 5.02 (1H, s), 6.60 (1H, d, J 8.5), 7.09 (1H, dd, J 8.5, 2.4), 7.15-7.23 (3H, m), 7.38-7.45 (2H, m); δ_{C} (101 MHz, CDCl₃) 38.4, 117.9, 119.0, 120.7, 123.6, 124.4, 126.3, 129.2, 130.0, 130.7, 131.0, 132.2, 135.5, 142.4; m/z (ESI⁺) 321 ([M+H]⁺); HRMS (ESI⁺) C₁₄H₁₀BrClN₂Na⁺, ([M+Na]⁺) requires 342.9608; found 342.9603.

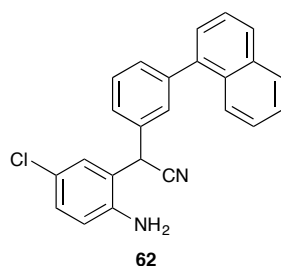
Preparation of (±)-2-([1,1'-biphenyl]-3-yl)-2-(2-amino-5-chlorophenyl)acetonitrile **61**



Following **General Procedure 2**, zinc powder (5.85 g, 90.5 mmol), NH₄Cl (7.08 g, 135 mmol) and **43** (3.15 g, 9.05 mmol) in a 5:1 mixture of acetone/H₂O (168 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 6:1 40-60 petrol/EtOAc) gave **61** as a yellow oil (2.80 g, 97%); $\nu_{\max}$ (film) 3454, 3375, 3060, 3033, 2244, 1629, 1600, 1575; δ_{H} (400 MHz, CDCl₃) 3.60 (2H, br s), 5.20 (1H, s), 6.68 (1H, d, J 8.5), 7.18 (1H, dd, J 8.5, 2.3), 7.31-7.36 (2H, m),

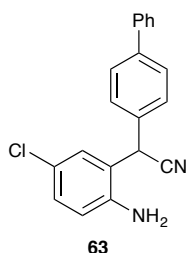
7.37-7.42 (1H, m), 7.48 (3H, q, *J* 8.0), 7.57 (3H, d, *J* 7.2), 7.61 (1H, d, *J* 7.9); δ_c (101 MHz, CDCl₃) 39.0, 118.4, 118.8, 121.4, 124.3, 126.4, 126.5, 127.2, 127.7, 127.9, 129.0, 129.1, 129.7, 130.0, 133.8, 140.0, 142.5, 142.7; *m/z* (ESI⁺) 341 ([M+Na]⁺, 33%); HRMS (ESI⁺) C₂₀H₁₅ClN₂Na⁺, ([M+Na]⁺) requires 341.0816; found 341.0816.

Preparation of (±)-2-(2-amino-5-chlorophenyl)-2-(3-(naphthalen-1-yl)phenyl)acetonitrile **62**



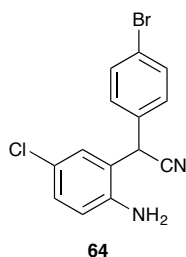
Following **General Procedure 2**, zinc powder (2.67 g, 41.1 mmol), NH₄Cl (3.23 g, 61.6 mmol) and **44** (1.64 g, 4.11 mmol) in a 5:1 mixture of acetone/H₂O (72.0 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 4:1 40-60 petrol/Et₂O) gave **62** as a yellow solid (1.50 g, 98%); mp 47-49 °C; $\nu_{\max}$ (film) 3458, 3376, 3057, 2362, 2244, 1628; δ_H (400 MHz, CDCl₃) 3.64 (2H, br s), 5.22 (1H, s), 6.68 (1H, d, *J* 8.5), 7.17 (1H, dd, *J* 8.5, 2.4), 7.35 (1H, d, *J* 2.3), 7.39-7.58 (8H, m), 7.81 (1H, d, *J* 8.4), 7.92 (2H, dd, *J* 12.9, 8.2); δ_c (101 MHz, CDCl₃) 38.9, 118.4, 118.7, 121.4, 124.3, 125.4, 125.5, 126.0, 126.4, 126.5, 127.1, 128.2, 128.5, 129.1, 129.3, 129.5, 129.7, 130.6, 131.3, 133.4, 133.8, 138.9, 142.2, 142.5; *m/z* (ESI⁺) 391 ([M+Na]⁺, 44%); HRMS (ESI⁺) C₂₄H₁₈ClN₂⁺, ([M+H]⁺) requires 369.1153; found 369.1147.

Preparation of (±)-2-([1,1'-biphenyl]-4-yl)-2-(2-amino-5-chlorophenyl)acetonitrile **63**



Following **General Procedure 2**, zinc powder (2.84 g, 43.7 mmol), NH₄Cl (3.44 g, 65.5 mmol) and **45** (1.41 g, 4.37 mmol) in a 5:1 mixture of acetone/H₂O (82.0 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 10:1 40-60 petrol/EtOAc) gave **63** as a white powder (0.920 g, 78%); mp 138-140 °C; ν_{max} (film) 3458, 3375, 3031, 2244, 1739, 1629; δ_{H} (400 MHz, CDCl₃) 3.60 (2H, br s), 5.18 (1H, s), 6.69 (1H, d, *J* 8.5), 7.19 (1H, dd, *J* 8.5, 2.3), 7.35 (1H, d, *J* 2.3), 7.43 (5H, tt, *J* 15.3, 7.5), 7.59 (2H, d, *J* 7.3), 7.63 (2H, d, *J* 8.3); δ_{C} (101 MHz, CDCl₃) 38.6, 118.4, 118.8, 121.4, 124.3, 127.1, 127.9, 128.1, 128.2, 129.0, 129.1, 129.7, 132.1, 139.9, 141.9, 142.5; *m/z* (ESI⁺) 341 ([M+Na]⁺, 37%); HRMS (ESI⁺) C₂₀H₁₅ClN₂Na⁺, ([M+Na]⁺) requires 341.0816; found 341.0809.

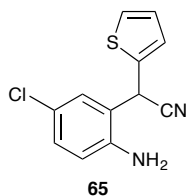
Preparation of (±)-2-(2-amino-5-chlorophenyl)-2-(4-bromophenyl)acetonitrile **64**



Following **General Procedure 2**, zinc powder (13.3 g, 203 mmol), NH₄Cl (16.3 g, 304 mmol) and **46** (7.13 g, 20.3 mmol) in a 5:1 mixture of acetone/H₂O (338:67 acetone/H₂O) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 70:30 40-60 petrol/EtOAc) gave **64** as an orange oil (6.12 g, 94%); ν_{max} (film) 2980, 2243, 1775, 1767, 1762, 1725, 1713, 1704, 1629; δ_{H} (400 MHz, CDCl₃) 3.61 (2H, br s), 5.11 (1H, s), 6.68 (1H, d, *J* 8.5), 7.17 (1H, dd, *J*

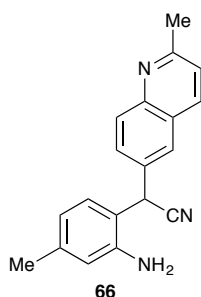
8.5, 2.4), 7.21-7.27 (3H, m), 7.54 (2H, d, *J* 8.4); δ_c (101 MHz, CDCl₃) 38.3, 118.1, 118.9, 120.9, 123.1, 124.3, 129.1, 129.4, 129.9, 132.3, 132.7, 142.5; *m/z* (ESI⁺) 321 ([M+H]⁺); HRMS (ESI⁺) C₁₄H₁₀BrClN₂Na⁺, ([M+Na]⁺) requires 342.9608; found 342.9600.

Preparation of (±)-2-(5-chloro-2-nitrophenyl)-2-(thiophen-2-yl)acetonitrile 65



Following **General Procedure 2**, zinc powder (11.7 g, 179 mmol), NH₄Cl (14.4 g, 268 mmol) and **47** (4.99 g, 17.9 mmol) in a 5:1 mixture of acetone/H₂O (298:60 acetone/H₂O) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 20:80 EtOAc/40-60 petrol) gave **65** as a yellow oil (3.48, 78%); $\nu_{\max}$ (film) 3457, 3020, 1783; δ_H (400 MHz, CDCl₃) 3.68 (2H, br s), 5.35 (1H, s), 6.67 (1H, d, *J* 8.5), 7.00 (1H, dd, *J* 5.2, 3.6), 7.10 (1H, dt, *J* 3.6, 1.1), 7.17 (1H, dd, *J* 8.5, 2.4), 7.32 (1H, dd, *J* 5.2, 1.2), 7.35 (1H, d, *J* 2.4); δ_c (101 MHz, CDCl₃) 34.3, 117.8, 118.9, 121.2, 124.1, 127.2, 127.4, 127.5, 128.5, 130.0, 136.0, 142.7; *m/z* (ESI⁻) 247 ([M-H]⁻, 100%); HRMS (ESI⁺) C₁₂H₉ClN₂NaS⁺, ([M+Na]⁺) requires 271.0067; found 271.0060.

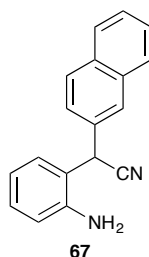
Preparation of (±)-2-(2-amino-4-methylphenyl)-2-(2-methylquinolin-6-yl)acetonitrile 66



(±)-2-(4-methyl-2-nitrophenyl)-2-(2-methylquinolin-6-yl)acetonitrile **48** (1.53 g, 4.82 mmol) and Pd(OH)₂/C (240 mg) were stirred in anhydrous MeOH (240 mL) under an atmosphere of H₂. The reaction was monitored by TLC. Once complete, the mixture was filtered through Celite®, eluted

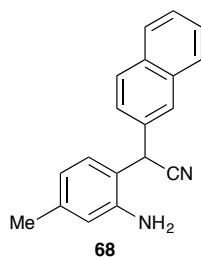
with CH₂Cl₂ (200 mL) and the solvent removed *in vacuo*. The resulting residue was purified by column chromatography (silica; 2:1 40-60 petrol/EtOAc) to afford **66** as a yellow powder (0.845 g, 61%); mp 126-128 °C; ν_{max} (film) 3368, 2921, 2241, 1628, 1603, 1580, 1507; δ_{H} (400 MHz, CDCl₃) 2.30 (3H, s), 2.75 (3H, s), 2.52 (2H, br s), 5.32 (1H, s), 6.57 (1H, s), 6.71 (1H, d, *J* 7.8), 7.19 (1H, d, *J* 7.8), 7.33 (1H, d, *J* 8.5), 7.57 (1H, dd, *J* 8.8, 2.1), 7.83 (1H, d, *J* 1.7), 8.02 (2H, t, *J* 8.1); δ_{C} (101 MHz, CDCl₃) 21.2, 25.4, 38.7, 117.0, 118.3, 118.9, 120.6, 122.9, 126.2, 126.4, 128.6, 129.6, 130.1, 131.5, 136.2, 140.0, 143.8, 147.5, 160.1; *m/z* (ESI⁻) 286 ([M-H]⁻, 100%); HRMS (ESI⁺) C₁₉H₁₇N₃Na⁺, ([M+Na]⁺) requires 310.1315; found 310.1314.

Preparation of (±)-2-(2-aminophenyl)-2-(naphthalen-2-yl)acetonitrile **67**



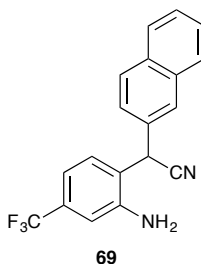
Following **General Procedure 2**, zinc powder (2.81 g, 43.3 mmol), NH₄Cl (3.44 g, 64.9 mmol) and **49** (1.24 g, 4.33 mmol) in a 5:1 mixture of acetone/H₂O (84.0 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/Et₂O) gave **67** as a yellow oil (1.10 g, 97%); ν_{max} (film) 3449, 3373, 3056, 2241, 1626; δ_{H} (400 MHz, CDCl₃) 3.58 (2H, br s), 5.35 (1H, s), 6.74 (1H, dd, *J* 8.0, 0.9), 6.91 (1H, td, *J* 7.5, 1.1), 7.24 (1H, td, *J* 7.7, 1.4), 7.36-7.42 (2H, m), 7.54 (2H, dtdd, *J* 0.0, 2.4, 5.5, 3.3), 7.82-7.88 (3H, m), 7.90 (1H, s); δ_{C} (101 MHz, CDCl₃) 39.3, 117.6, 119.0, 119.6, 120.0, 125.1, 126.7, 126.9, 126.9, 127.8, 128.0, 129.5, 129.7, 129.8, 131.3, 133.0, 133.3, 144.1; *m/z* (ESI⁻) 257 ([M-H]⁻, 96%); HRMS (ESI⁺) C₁₈H₁₄N₂Na⁺, ([M+Na]⁺) requires 281.1049; found 281.1043.

Preparation of (±)-2-(2-amino-4-methylphenyl)-2-(naphthalen-2-yl)acetonitrile **68**



Following **General Procedure 2**, zinc powder (5.52 g, 85.4 mmol), NH₄Cl (6.69 g, 128 mmol) and **50** (2.58 g, 8.54 mmol) in a 5:1 mixture of acetone/H₂O (156 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 4:1 40-60 petrol/EtOAc) gave **68** as a yellow oil (1.88 g, 81%); ν_{max} (film) 3455, 3373, 3056, 3018, 2920, 2361, 2240, 1739, 1629, 1580, 1508; δ_{H} (400 MHz, CDCl₃) 2.32 (3H, s), 3.52 (2H, br s), 5.32 (1H, s), 6.57 (1H, s), 6.73 (1H, s, *J* 7.8), 7.25 (1H, d, *J* 7.8), 7.40 (1H, dd, *J* 8.6, 1.8), 7.51-7.57 (2H, m), 7.82-7.88 (3H, m), 7.90 (1H, s); δ_{C} (101 MHz, CDCl₃) 21.2, 39.0, 117.2, 118.2, 119.1, 120.5, 125.1, 126.6, 126.8, 126.9, 127.8, 128.0, 129.5, 129.6, 131.6, 133.0, 133.3, 139.9, 143.9; *m/z* (ESI⁺) 295 ([M+Na]⁺, 72%); HRMS (ESI⁺) C₁₉H₁₆N₂Na⁺, ([M+Na]⁺) requires 295.1206; found 295.1200.

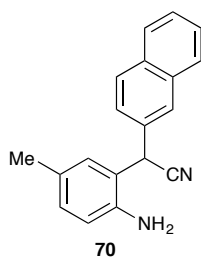
Preparation of (±)-2-(2-amino-4-(trifluoromethyl)phenyl)-2-(naphthalen-2-yl)acetonitrile **69**



Following **General Procedure 2**, zinc powder (4.47 g, 68.8 mmol), NH₄Cl (5.42 g, 103 mmol) and **51** (2.45 g, 6.88 mmol) in a 5:1 mixture of acetone/H₂O (126 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 6:1 40-60 petrol/Et₂O) gave **69** as a yellow solid (1.85 g, 82%); mp 122-124 °C; ν_{max} (film) 3468, 3380, 3059, 2245, 1739, 1631, 1510; δ_{H} (400 MHz, CDCl₃) 3.78 (2H, br s), 5.35 (1H, s), 6.98 (1H, s), 7.14 (1H, d, *J* 8.0), 7.36 (1H, dd, *J* 8.6,

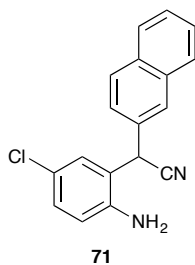
1.8), 7.49 (1H, d, *J* 8.0), 7.56 (2H, dtdd, *J* 0.0, 2.4, 5.5, 3.3), 7.82-7.91 (4H, m); δ_c (101 MHz, CDCl₃) 39.2, 114.0 (q, *J* 3.8), 115.9 (q, *J* 3.8), 118.3, 122.9, 123.8 (q, *J* 268.3), 124.8, 126.8, 127.1, 127.8, 128.0, 129.8, 130.2, 130.2, 132.1 (q, *J* 32.4), 133.1, 133.3, 144.4; δ_f (377 MHz, CDCl₃) -62.9; *m/z* (ESI⁺) 349 ([M+Na]⁺, 25%); HRMS (ESI⁺) C₁₉H₁₃F₃N₂Na⁺, ([M+Na]⁺) requires 349.0923; found 349.0923.

Preparation of (±)-2-(2-amino-5-methylphenyl)-2-(naphthalen-2-yl)acetonitrile **70**



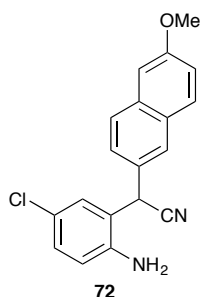
Following **General Procedure 2**, zinc powder (5.81 g, 89.4 mmol), NH₄Cl (7.03 g, 134 mmol) and **52** (2.70 g, 8.94 mmol) in a 5:1 mixture of acetone/H₂O (168 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 6:1 40-60 petrol/EtOAc) gave **70** as a yellow oil (1.87 g, 80%); $\nu_{\max}$ (film) 3437, 3368, 3055, 3021, 2923, 2860, 2240, 1717, 1631, 1601, 1508; δ_H (400 MHz, CDCl₃) 2.32 (3H, s), 3.44 (2H, br s), 5.35 (1H, s), 6.66 (1H, d, *J* 8.0), 7.04 (1H, dd, *J* 8.0, 1.8), 7.22 (1H, d, *J* 0.8), 7.41 (1H, dd, *J* 8.5, 1.8), 7.54 (2H, dtdd, *J* 0.0, 2.4, 5.6, 3.3), 7.83-7.88 (3H, m), 7.90 (1H, s); δ_c (101 MHz, CDCl₃) 20.6, 39.2, 117.9, 119.2, 120.2, 125.2, 126.7, 126.8, 126.9, 127.8, 128.0, 129.2, 129.5, 130.0, 130.3, 131.6, 133.0, 133.3, 141.5; *m/z* (ESI⁺) 295 ([M+Na]⁺, 31%); HRMS (ESI⁺) C₁₉H₁₆N₂Na⁺, ([M+Na]⁺) requires 295.1206; found 295.1209.

Preparation of (±)-2-(2-amino-5-chlorophenyl)-2-(naphthalen-2-yl)acetonitrile **71**



Following **General Procedure 2**, zinc powder (3.16 g, 48.7 mmol), NH₄Cl (3.83 g, 73.0 mmol) and **53** (1.57 g, 4.87 mmol) in a 5:1 mixture of acetone/H₂O (90.0 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/Et₂O) gave **71** as a yellow powder (1.03 g, 74%); mp 118-121 °C; ν_{max} (film) 3455, 3374, 3057, 2242, 1629; δ_{H} (400 MHz, CDCl₃) 3.59 (2H, br s), 5.28 (1H, s), 6.66 (1H, d, *J* 8.5), 7.18 (1H, dd, *J* 8.5, 2.4), 7.33-7.39 (2H, m), 7.56 (2H, dtdd, *J* 0.0, 2.4, 5.5, 3.3), 7.81-7.90 (4H, m); δ_{C} (101 MHz, CDCl₃) 39.1, 118.4, 118.8, 121.3, 124.2, 124.9, 126.8, 127.1, 127.1, 127.8, 128.0, 129.2, 129.7, 129.8, 130.5, 133.1, 133.3, 142.7; *m/z* (ESI⁺) 315 ([M+Na]⁺, 50%); HRMS (ESI⁺) C₁₈H₁₃ClN₂Na⁺, ([M+Na]⁺) requires 315.0659; found 315.0657.

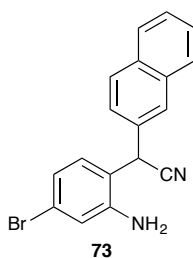
Preparation of (±)-2-(2-amino-5-chlorophenyl)-2-(6-methoxynaphthalen-2-yl)acetonitrile **72**



Following **General Procedure 2**, zinc powder (1.88 g, 28.9 mmol), NH₄Cl (2.27 g, 43.4 mmol) and **54** (1.02 g, 2.89 mmol) in a 5:1 mixture of acetone/H₂O (54.0 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 5:1 40-60 petrol/EtOAc) gave **72** as a yellow powder (0.816 g, 87%); mp 55-58 °C; ν_{max} (film) 3377, 1631, 1606; δ_{H} (400 MHz, CDCl₃) 3.58 (2H, br s), 3.93 (3H, s), 5.25 (1H, s), 6.66 (1H, d, *J* 8.5), 7.15 (1H, d, *J* 2.3), 7.19 (2H, ddd, *J* 13.4,

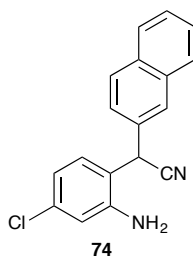
8.7, 2.4), 7.31-7.36 (2H, m), 7.75 (3H, dd, J 14.0, 8.9); δ_c (101 MHz, $CDCl_3$) 39.0, 55.4, 105.7, 118.5, 118.7, 119.9, 121.5, 124.2, 125.4, 126.6, 128.0, 128.5, 128.7, 129.2, 129.5, 129.6, 134.4, 142.6, 158.5; m/z (ESI⁺) 345 ([M+Na]⁺, 46%); HRMS (ESI⁺) $C_{19}H_{15}ClN_2NaO^+$, ([M+Na]⁺) requires 345.0765; found 345.0763.

Preparation of (±)-2-(2-amino-4-bromophenyl)-2-(naphthalen-2-yl)acetonitrile **73**



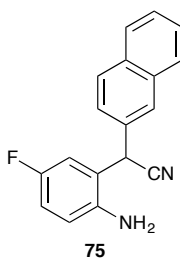
Following **General Procedure 2**, zinc powder (5.52 g, 85.0 mmol), NH_4Cl (6.69 g, 127 mmol) and **55** (3.11 g, 8.50 mmol) in a 5:1 mixture of acetone/ H_2O (156 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 6:1 40-60 petrol/EtOAc) gave **73** as a yellow oil (2.54 g, 89%); ν_{max} (film) 3466, 3376, 3249, 3057, 2243, 1626, 1593, 1571, 1508; δ_H (400 MHz, $CDCl_3$) 3.64 (2H, br s), 5.27 (1H, s), 6.88 (1H, d, J 1.9), 7.01 (1H, dd, J 8.2, 1.9), 7.20 (1H, d, J 8.2), 7.35 (1H, dd, J 8.6, 1.7), 7.55 (2H, dtdd, J 0.0, 2.4, 5.5, 3.3), 7.81-7.89 (4H, m); δ_c (101 MHz, $CDCl_3$) 39.0, 118.5, 118.7, 120.0, 122.3, 123.5, 124.9, 126.7, 127.0, 127.1, 127.8, 128.0, 129.7, 130.6, 131.0, 133.1, 133.2, 145.3; m/z (ESI⁺) 337 ([M+H]⁺, 21%); HRMS (ESI⁺) $C_{18}H_{13}BrN_2Na^+$, ([M+Na]⁺) requires 359.0154; found 359.0143.

Preparation of (±)-2-(2-amino-4-chlorophenyl)-2-(naphthalen-2-yl)acetonitrile **74**



Following **General Procedure 2**, zinc powder (5.22 g, 80.4 mmol), NH₄Cl (6.33 g, 121 mmol) and **56** (2.59 g, 8.04 mmol) in a 5:1 mixture of acetone/H₂O (150 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 5:1 40-60 petrol/EtOAc) gave **74** as a yellow oil (2.13 g, 91%); ν_{max} (film) 3465, 3378, 3058, 2243, 1629, 1600, 1575, 1508; δ_{H} (400 MHz, CDCl₃) 3.66 (2H, br s), 5.28 (1H, s), 6.73 (1H, d, *J* 2.1), 6.86 (1H, dd, *J* 8.2, 2.1), 7.27 (1H, d, *J* 8.2), 7.35 (1H, dd, *J* 8.6, 1.8), 7.55 (2H, dtdd, *J* 0.0, 2.4, 5.5, 3.3), 7.81-7.89 (4H, m); δ_{C} (101 MHz, CDCl₃) 38.9, 117.1, 118.2, 118.5, 119.4, 124.8, 126.7, 127.0, 127.1, 127.8, 128.0, 129.7, 130.7, 130.8, 133.1, 133.2, 135.4, 145.1; *m/z* (ESI⁺) 315 ([M+Na]⁺, 37%); HRMS (ESI⁺) C₁₈H₁₃ClN₂Na⁺, ([M+Na]⁺) requires 315.0659; found 315.0655.

Preparation of (±)-2-(2-amino-5-fluorophenyl)-2-(naphthalen-2-yl)acetonitrile **75**



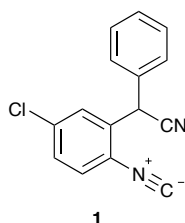
(±)-2-(5-fluoro-2-nitrophenyl)-2-(naphthalen-2-yl)acetonitrile **57** (1.54 g, 5.00 mmol) and 10% Pd/C (154 mg, 10 wt %) were stirred in anhydrous MeOH (150 mL) under an atmosphere of H₂. The reaction was monitored by TLC. Once complete, the mixture was filtered through Celite®, eluted with CH₂Cl₂ (200 mL) and the solvent removed *in vacuo*. The resulting residue was purified by column chromatography (silica; 4:1 40-60 petrol/Et₂O) to afford **75** as a yellow oil (1.13 g, 75%);

$\nu_{\max}$ (film) 3437, 3367, 3058, 2360, 2243, 1632, 1601, 1502; δ_{H} (400 MHz, CDCl_3) 3.45 (2H, br s), 5.33 (1H, s), 6.70 (1H, dd, J 8.7, 4.8), 6.95 (1H, td, J 8.3, 2.8), 7.10 (1H, dd, J 9.0, 2.8), 7.35-7.40 (1H, m), 7.55 (2H, dq, J 6.3, 3.2), 7.81-7.91 (4H, m); δ_{C} (101 MHz, CDCl_3) 39.0, 116.0, 116.2, 116.3, 116.5, 118.5, 118.8, 118.9, 121.8, 121.9, 125.0, 126.9, 127.0, 127.0, 127.8, 128.0, 129.7, 130.7, 133.1, 133.3, 140.0, 156.7; δ_{F} (377 MHz, CDCl_3) -124.1; m/z (ESI^+) 299 ($[\text{M}+\text{Na}]^+$, 100%); HRMS (ESI^+) $\text{C}_{18}\text{H}_{13}\text{FN}_2\text{Na}^+$, ($[\text{M}+\text{Na}]^+$) requires 299.0955; found 299.0945.

1.3.2.3 Formylation of Aminobenzenes Followed by Dehydration

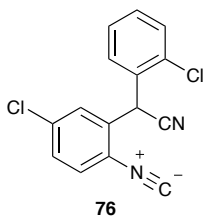
These reactions have not been optimized.

Preparation of ($\pm$)-2-(5-chloro-2-isocyanophenyl)-2-phenylacetonitrile 1



Following **General Procedure 3**, aminobenzene **58** (1.74 g, 7.19 mmol) in formic acid (19.0 mL) and acetic anhydride (10.0 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/EtOAc) gave ($\pm$)-*N*-(4-chloro-2-(cyano(phenyl)methyl)phenyl)formamide (1.67 g, 86%). Following **General Procedure 4**, this formamide (1.66 g, 6.13 mmol) and Et_3N (2.43 mL, 16.5 mmol) in CH_2Cl_2 (45.0 mL) and phosphoryl chloride (0.628 mL, 6.74 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 10:1 40-60 petrol/ Et_2O) gave **1** as a light green powder (0.650 g, 42%); mp 87-89 °C; $\nu_{\max}$ (film) 3066, 3034, 2357, 2248, 2118, 1594, 1572; δ_{H} (400 MHz, CDCl_3) 5.50 (1H, s), 7.35-7.46 (7H, m), 7.61 (1H, s); δ_{C} (101 MHz, CDCl_3) 38.7, 117.7, 127.8, 128.9, 129.1, 129.2, 129.6, 130.0, 132.9, 134.1, 136.5, 171.1; m/z (ESI^+) 275 ($[\text{M}+\text{Na}]^+$, 100%); HRMS (ESI^+) $\text{C}_{15}\text{H}_9\text{ClN}_2\text{Na}^+$, ($[\text{M}+\text{Na}]^+$) requires 275.0346; found 275.0341.

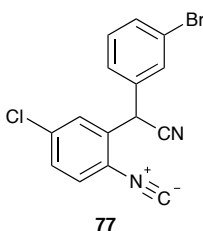
Preparation of (±)-2-(5-chloro-2-isocyanophenyl)-2-(2-chlorophenyl)acetonitrile **76**



Following **General Procedure 3**, aminobenzene **59** (7.81 g, 28.2 mmol) in formic acid (74 mL) and acetic anhydride (41 mL) gave (±)-*N*-(4-chloro-2-((2-chlorophenyl)(cyano)methyl)phenyl)formamide that was used without further purification.

Following **General Procedure 4**, this formamide (1.00 g, 3.28 mmol) and Et₃N (2.28 mL, 16.4 mmol) in CH₂Cl₂ (10 mL) and phosphoryl chloride (0.37 mL, 3.93 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 95:5 40-60 petrol/EtOAc) gave **76** as a dark green solid; mp 114-116 °C; ν_{max} (film) 3457, 3016, 2971, 2947, 2117, 1734; δ_{H} (400 MHz, CDCl₃) 5.77 (1H, s), 7.24 (1H, s), 7.30-7.36 (4H, m), 7.38-7.45 (2H, m); δ_{C} (101 MHz, CDCl₃) 36.3, 116.5, 127.9, 128.9, 129.4, 129.6, 130.2, 130.5, 130.6, 130.8, 132.6, 133.7, 136.4, 171.4; m/z (ESI⁻) 285 ([M-H]⁻); HRMS (ESI⁺) C₁₅H₈Cl₂N₂Na⁺, ([M+Na]⁺) requires 308.9957; found 308.9951.

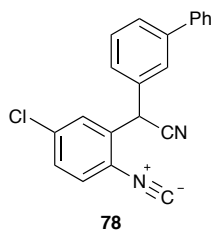
Preparation of (±)-2-(3-bromophenyl)-2-(5-chloro-2-isocyanophenyl)acetonitrile **77**



Following **General Procedure 3**, aminobenzene **60** (6.77 g, 21.0 mmol) in formic acid (55.4 mL) and acetic anhydride (30.7 mL) gave (±)-*N*-(2-((4-bromophenyl)(cyano)methyl)-4-chlorophenyl)formamide that was used without further purification. Following **General Procedure 4**, this formamide (1.00 g, 2.86 mmol) and Et₃N (1.07 mL, 7.71 mmol) in CH₂Cl₂ (20 mL)

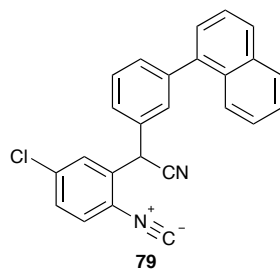
and phosphoryl chloride (0.29 mL, 3.14 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 95:5 40-60 petrol/EtOAc) gave **77** as a dark green solid; mp 108-112 °C; $\nu_{\max}$ (film) 2980, 2117, 1769, 1751, 1735, 1715, 1711, 1702, 1592; δ_{H} (400 MHz, CDCl₃) 5.38 (1H, s), 7.18-7.37 (4H, m), 7.41-7.47 (2H, m), 7.51 (1H, d, *J* 1.6); δ_{C} (101 MHz, CDCl₃) 38.3, 117.2, 123.6, 126.6, 129.0, 129.2, 130.4, 130.7, 131.1, 132.5, 133.3, 134.9, 136.7, 171.6; *m/z* (ESI⁺) 353 ([M+Na]⁺); HRMS (ESI⁺) C₁₆H₁₂BrClN₂NaO⁺, ([M+Na+MeOH]⁺) requires 384.9714; found 384.9702.

Preparation of (±)-2-([1,1'-biphenyl]-3-yl)-2-(5-chloro-2-isocyanophenyl)acetonitrile **78**



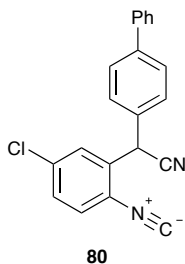
Following **General Procedure 3**, aminobenzene **61** (2.67 g, 8.39 mmol) in formic acid (22.0 mL) and acetic anhydride (12.0 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 2:1 40-60 petrol/EtOAc) gave (±)-N-(2-([1,1'-biphenyl]-3-yl(cyano)methyl)-4-chlorophenyl)formamide (2.40 g, 84%) Following **General Procedure 4**, this formamide (1.90 g, 5.49 mmol) and Et₃N (2.06 mL, 14.8 mmol) in CH₂Cl₂ (60.0 mL) and phosphoryl chloride (0.563 mL, 6.04 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 10:1 40-60 petrol/Et₂O) gave **78** as a light green powder (0.600 g, 40%); mp 108-110 °C; $\nu_{\max}$ (film) 3063, 3034, 2360, 2248, 2117, 1595, 1574; δ_{H} (400 MHz, CDCl₃) 5.56 (1H, s), 7.36-7.43 (4H, m), 7.45-7.53 (3H, m), 7.56-7.63 (4H, m), 7.66 (1H, s); δ_{C} (101 MHz, CDCl₃) 38.9, 117.7, 126.5, 126.6, 127.2, 127.9, 128.0, 129.0, 129.0, 129.2, 130.0, 131.1, 133.5, 134.0, 136.6, 139.9, 142.7, 171.2; *m/z* (ESI⁺) 351 ([M+Na]⁺, 80%); HRMS (ESI⁺) C₂₁H₁₃ClN₂Na⁺, ([M+Na]⁺) requires 351.0659; found 351.0646.

Preparation of (±)-2-(5-chloro-2-isocyanophenyl)-2-(3-(naphthalen-1-yl)phenyl)acetonitrile **79**



Following **General Procedure 3**, aminobenzene **62** (1.41 g, 4.11 mmol) in formic acid (11.0 mL) and acetic anhydride (5.8 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 2:1 40-60 petrol/EtOAc) gave (±)-*N*-(4-chloro-2-(cyano(3-(naphthalen-1-yl)phenyl)methyl)phenyl)formamide (1.20 g, 80%). Following **General Procedure 4**, this formamide (1.13 g, 3.08 mmol) and Et₃N (1.16 mL, 8.32 mmol) in CH₂Cl₂ (35.0 mL) and phosphoryl chloride (0.315 mL, 3.39 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 10:1 40-60 petrol/Et₂O) gave **79** as a light green solid (0.450 g, 43%); mp 157-160 °C; ν_{max} (film) 3060, 2117, 1593; δ_{H} (400 MHz, CDCl₃) 5.59 (1H, s), 7.39-7.58 (10H, m), 7.70 (1H, s), 7.82 (1H, d, *J* 8.4), 7.92 (2H, dd, *J* 11.5, 8.1); δ_{C} (101 MHz, CDCl₃) 38.8, 117.8, 125.4, 125.5, 126.0, 126.5, 126.7, 127.1, 128.3, 128.4, 129.0, 129.3, 129.4, 129.5, 130.1, 130.9, 131.3, 133.1, 133.8, 134.0, 136.6, 138.8, 142.2, 171.3; *m/z* (ESI⁺) 401 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₂₅H₁₅ClN₂Na⁺, ([M+Na]⁺) requires 401.0816; found 401.0806.

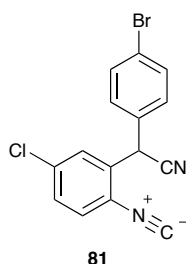
Preparation of (±)-2-([1,1'-biphenyl]-4-yl)-2-(5-chloro-2-isocyanophenyl)acetonitrile **80**



Following **General Procedure 3**, aminobenzene **63** (0.874 g, 2.99 mmol) in formic acid (8.00 mL) and acetic anhydride (4.2 mL) gave a crude reaction product. Purification *via* flash column

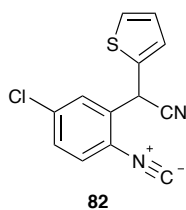
chromatography on silica gel (silica; 3:1 40-60 petrol/EtOAc) gave ($\pm$)-*N*-(2-([1,1'-biphenyl]-4-yl(cyano)methyl)-4-chlorophenyl)formamide (0.850 g, 89%). Following **General Procedure 4**, this formamide (0.816 g, 2.55 mmol) and Et₃N (0.959 mL, 6.88 mmol) in CH₂Cl₂ (25.0 mL) and phosphoryl chloride (0.261 mL, 2.80 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 20:1 40-60 petrol/EtOAc) gave **80** as a green solid (0.450 g, 60%); mp 108-110 °C; ν_{max} (film) 2110, 1739, 1593; δ_{H} (400 MHz, CDCl₃) 5.54 (1H, s), 7.36-7.42 (3H, m), 7.44-7.50 (4H, m), 7.56-7.60 (2H, m), 7.62-7.67 (3H, m); δ_{C} (101 MHz, CDCl₃) 38.5, 117.8, 127.1, 127.9, 128.2, 128.2, 128.9, 129.2, 130.0, 131.8, 134.1, 136.6, 139.8, 142.1, 171.2; m/z (ESI⁻) 327 ([M-H]⁻, 100%); HRMS (ESI⁺) C₂₁H₁₃ClN₂Na⁺, ([M+Na]⁺) requires 351.0659; found 351.0655.

Preparation of ($\pm$)-2-(4-bromophenyl)-2-(5-chloro-2-isocyanophenyl)acetonitrile **81**



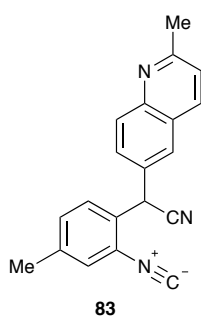
Following **General Procedure 3**, aminobenzene **64** (7.39 g, 23.0 mmol) in formic acid (60.4 mL) and acetic anhydride (33.5 mL) gave ($\pm$)-*N*-(2-((4-bromophenyl)(cyano)methyl)-4-chlorophenyl)formamide that was used without further purification. Following **General Procedure 4**, this formamide (1.00 g, 2.86 mmol) and Et₃N (1.07 mL, 7.71 mmol) in CH₂Cl₂ (20 mL) and phosphoryl chloride (0.29 mL, 3.14 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 95:5 40-60 petrol/EtOAc) gave **81** as a dark green solid; mp 124-126 °C; ν_{max} (film) 3016, 2971, 2118, 1770, 1756, 1738, 1722, 1708, 1703; δ_{H} (400 MHz, CDCl₃) 5.46 (1H, s), 7.26-7.32 (2H, m), 7.39-7.46 (2H, m), 7.54-7.63 (3H, m); δ_{C} (101 MHz, CDCl₃) 38.3, 117.3, 123.5, 129.0, 129.1, 129.5, 130.3, 132.0, 132.8, 133.5, 136.7, 171.4; m/z (ESI⁻) 328 ([M-H]⁻); HRMS (ESI⁻) C₁₅H₇BrClN₂⁻, ([M-H]⁻) requires 328.9487; found 328.9488.

Preparation of (±)-2-(5-chloro-2-isocyanophenyl)-2-(thiophen-2-yl)acetonitrile **82**



Following **General Procedure 3**, aminobenzene **65** (2.00 g, 8.03 mmol) in formic acid (21.1 mL) and acetic anhydride (11.7 mL) gave (±)-*N*-(4-chloro-2-(cyano(thiophen-2-yl)methyl)phenyl)formamide that was used without further purification. Following **General Procedure 4**, this formamide (2.05 g, 7.40 mmol) and Et₃N (2.78 mL, 20.0 mmol) in CH₂Cl₂ (20 mL) and phosphoryl chloride (0.76 mL, 8.14 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 95:5 to 90:10 40-60 petrol/EtOAc) gave **82** as a dark green solid (248 mg); mp 76-80 °C; ν_{max} (film) 3106, 2248, 2117, 1594; δ_{H} (400 MHz, CDCl₃) 5.72 (1H, s), 7.02 (1H, dd, *J* 5.2, 3.6), 7.19 (1H, d, *J* 3.6), 7.35 (1H, dd, *J* 5.1, 0.9); δ_{C} (101 MHz, CDCl₃) 34.3, 117.0, 127.3, 127.4, 127.8, 128.9, 130.3, 133.6, 134.8, 136.6, 171.5; *m/z* (ESI⁺) 280 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₃H₇ClN₂NaS⁺, ([M+Na]⁺) requires 280.9911; found 280.9914.

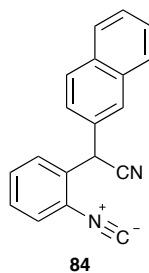
Preparation of (±)-2-(2-isocyano-4-methylphenyl)-2-(2-methylquinolin-6-yl)acetonitrile **83**



Following **General Procedure 3**, aminobenzene **66** (0.850 g, 2.96 mmol) in formic acid (10.0 mL) and acetic anhydride (4.00 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 1:2 40-60 petrol/EtOAc) gave (±)-*N*-(2-(cyano(2-methylquinolin-6-yl)methyl)-5-methylphenyl)formamide (0.840 g, 87%). Following **General**

Procedure 4, this formamide (0.725 g, 2.30 mmol) and Et₃N (0.865 mL, 6.21 mmol) in CH₂Cl₂ (26.0 mL) and phosphoryl chloride (0.233 mL, 2.50 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/EtOAc) gave **83** as a white solid (0.400 g, 58%); mp 102-104 °C; ν_{max} (film) 3057, 2923, 2245, 2116, 1603, 1567; δ_{H} (400 MHz, CDCl₃) 2.37 (3H, s), 2.75 (3H, s), 5.66 (1H, s), 7.25-7.31 (2H, m), 7.33 (1H, dd, *J* 8.4, 2.3), 7.51 (1H, d, *J* 8.0), 7.56 (1H, dd, *J* 8.8, 1.8), 7.88 (1H, s), 8.01 (1H, d, *J* 8.8), 8.06 (1H, d, *J* 8.5); δ_{C} (101 MHz, CDCl₃) 20.8, 25.4, 38.4, 118.3, 123.0, 126.3, 126.7, 128.2, 128.3, 128.9, 129.0, 130.2, 131.0, 131.3, 136.2, 140.5, 147.5, 160.2; *m/z* (ESI⁺) 320 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₂₀H₁₆N₃⁺, ([M+H]⁺) requires 298.1339; found 298.1336.

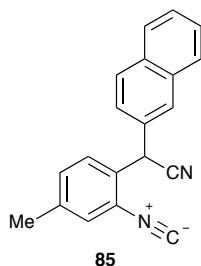
Preparation of (±)-2-(2-isocyanophenyl)-2-(naphthalen-2-yl)acetonitrile **84**



Following **General Procedure 3**, aminobenzene **67** (1.02 g, 3.95 mmol) in formic acid (10.4 mL) and acetic anhydride (5.70 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 2:1 40-60 petrol/EtOAc) gave (±)-*N*-(2-(cyano(naphthalen-2-yl)methyl)phenyl)formamide (1.33 g, 95%). Following **General Procedure 4**, this formamide (1.20 g, 4.19 mmol) and Et₃N (1.57 mL, 11.3 mmol) in CH₂Cl₂ (30.0 mL) and phosphoryl chloride (0.428 mL, 4.61 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 10:1 40-60 petrol/Et₂O) gave **84** as a light green solid (0.707 g, 63%). mp 84-86 °C; ν_{max} (film) 3058, 2252, 2117, 1599, 1506; δ_{H} (400 MHz, CDCl₃) 5.71 (1H, s), 7.38-7.58 (6H, m), 7.66 (1H, d, *J* 7.8), 7.81-7.90 (3H, m), 7.94 (1H, s); δ_{C} (101 MHz, CDCl₃) 38.9, 118.3, 124.8, 127.0, 127.1,

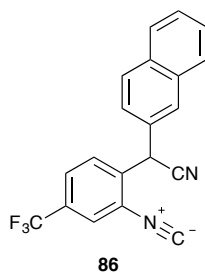
127.8, 127.8, 128.1, 129.2, 129.5, 129.7, 130.4, 130.9, 132.3, 133.0, 133.2, 169.7; m/z (ESI⁺) 291 ([M+Na]⁺, 68%); HRMS (ESI⁺) C₁₉H₁₂N₂Na⁺, ([M+Na]⁺) requires 291.0893; found 291.0892.

Preparation of (±)-2-(2-isocyano-4-methylphenyl)-2-(naphthalen-2-yl)acetonitrile **85**



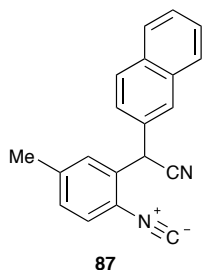
Following **General Procedure 3**, aminobenzene **68** (1.43 g, 5.25 mmol) in formic acid (14.0 mL) and acetic anhydride (7.5 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/EtOAc) gave (±)-*N*-(2-(cyano(naphthalen-2-yl)methyl)-5-methylphenyl)formamide (1.30 g, 82%). Following **General Procedure 4**, this formamide (1.10 g, 3.66 mmol) and Et₃N (1.38 mL, 9.88 mmol) in CH₂Cl₂ (40.0 mL) and phosphoryl chloride (0.376 mL, 4.03 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 10:1 40-60 petrol/Et₂O) gave **85** as a green oil (0.800 g, 77%); ν_{max} (film) 3057, 2924, 2245, 2116, 1602, 1504; δ_{H} (400 MHz, CDCl₃) 2.38 (3H, s), 5.67 (1H, s), 7.28 (2H, d, J 9.0), 7.40 (1H, dd, J 8.6, 1.9), 7.49-7.59 (3H, m), 7.82-7.89 (3H, m), 7.93 (1H, s); δ_{C} (101 MHz, CDCl₃) 20.9, 38.6, 118.5, 124.8, 126.9, 127.0, 127.7, 128.1, 128.1, 128.9, 129.3, 129.5, 131.2, 131.2, 132.9, 133.2, 140.3, 169.1; m/z (ESI⁺) 305 ([M+Na]⁺, 97%); HRMS (ESI⁺) C₂₀H₁₄N₂Na⁺, ([M+Na]⁺) requires 305.1049; found 305.1046.

Preparation of (±)-2-(2-isocyano-4-(trifluoromethyl)phenyl)-2-(naphthalen-2-yl)acetonitrile **86**



Following **General Procedure 3**, aminobenzene **69** (1.75 g, 5.36 mmol) in formic acid (15.0 mL) and acetic anhydride (7.5 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/EtOAc) gave (±)-*N*-(2-(cyano(naphthalen-2-yl)methyl)-5-(trifluoromethyl)phenyl)formamide (1.30 g, 70%). Following **General Procedure 4**, this formamide (1.00 g, 2.82 mmol) and Et₃N (1.05 mL, 7.56 mmol) in CH₂Cl₂ (32.0 mL) and phosphoryl chloride (0.276 mL, 2.96 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 10:1 40-60 petrol/Et₂O) gave **86** as a brown foam (0.300 g, 35%); mp 32-35 °C; ν_{max} (film) 3060, 2120, 1601, 1509; δ_{H} (400 MHz, CDCl₃); δ_{C} (101 MHz, CDCl₃) 39.0, 117.6, 124.6, 125.0 (q, *J* 3.8), 127.1 (q, *J* 3.6), 127.2, 127.3, 127.4, 127.8, 128.1, 129.9, 130.0, 133.1, 133.2, 136.1, 172.3; δ_{F} (377 MHz, CDCl₃) -63.1; *m/z* (ESI⁺) 359 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₂₀H₁₁F₃N₂Na⁺, ([M+Na]⁺) requires 359.0767; found 359.0778.

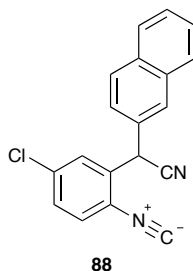
Preparation of (±)-2-(2-isocyano-5-methylphenyl)-2-(naphthalen-2-yl)acetonitrile **87**



Following **General Procedure 3**, aminobenzene **70** (1.75 g, 6.43 mmol) in formic acid (17.0 mL) and acetic anhydride (9.1 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/EtOAc) gave (±)-*N*-(2-(cyano(naphthalen-2-

yl)methyl)-4-methylphenyl)formamide (1.50 g, 80%). Following **General Procedure 4**, this formamide (1.24 g, 4.13 mmol) and Et₃N (1.55 mL, 11.2 mmol) in CH₂Cl₂ (45.0 mL) and phosphoryl chloride (0.423 mL, 4.54 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 10:1 40-60 petrol/Et₂O) gave **87** as a light green powder (0.600 g, 53%); mp 96-98 °C; ν_{max} (film) 3057, 2924, 2244, 2117, 1602, 1509; δ_{H} (400 MHz, CDCl₃) 2.40 (3H, s), 5.69 (1H, s), 7.20 (1H, dd, *J* 8.1, 1.0), 7.34 (1H, d, *J* 8.1), 7.42 (1H, dd, *J* 8.6, 1.9), 7.45 (1H, s), 7.51-7.58 (2H, m), 7.81-7.91 (3H, m), 7.95 (1H, d, *J* 0.7); δ_{C} (101 MHz, CDCl₃) 21.5, 38.8, 118.5, 124.8, 127.0, 127.0, 127.5, 127.8, 128.1, 129.5, 129.6, 130.3, 131.1, 132.0, 133.0, 133.2, 141.2, 168.9; *m/z* (ESI⁺) 305 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₂₀H₁₄N₂Na⁺, ([M+Na]⁺) requires 305.1049; found 305.1048.

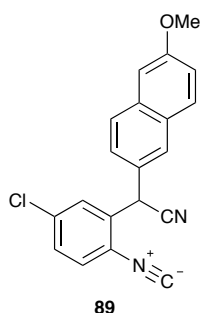
Preparation of (±)-2-(5-chloro-2-isocyanophenyl)-2-(naphthalen-2-yl)acetonitrile **88**



Following **General Procedure 3**, aminobenzene **71** (0.960 g, 3.28 mmol) in formic acid (10.0 mL) and acetic anhydride (4.7 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/EtOAc) gave (±)-*N*-(4-chloro-2-(cyano(naphthalen-2-yl)methyl)phenyl)formamide (0.845 g, 82%). Following **General Procedure 4**, this formamide (0.800 g, 2.50 mmol) and Et₃N (0.940 mL, 6.75 mmol) in CH₂Cl₂ (20.0 mL) and phosphoryl chloride (0.256 mL, 2.75 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 8:1 40-60 petrol/Et₂O) gave **88** as a green powder (0.453 g, 60%); mp 36-38 °C; ν_{max} (film) 3058, 2116, 1572, 1509; δ_{H} (400 MHz, CDCl₃) 5.67 (1H, s),

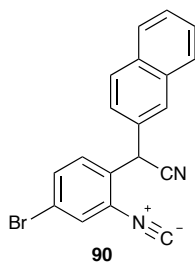
7.37-7.43 (3H, m), 7.53-7.59 (2H, m), 7.63 (1H, d, J 1.0), 7.83-7.92 (3H, m), 7.94 (1H, s); δ_c (101 MHz, $CDCl_3$) 38.8, 117.7, 124.6, 127.2, 127.2, 127.3, 127.8, 128.2, 128.9, 129.3, 129.8, 130.1, 130.1, 133.1, 133.2, 134.0, 136.6, 171.2; m/z (ESI⁺) 325 ([M+Na]⁺, 100%); HRMS (ESI⁺) $C_{19}H_{11}ClN_2Na^+$, ([M+Na]⁺) requires 325.0503; found 325.0498.

Preparation of (±)-2-(5-chloro-2-isocyanophenyl)-2-(6-methoxynaphthalen-2-yl)acetonitrile **89**



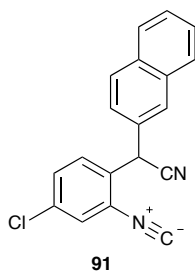
Following **General Procedure 3**, aminobenzene **72** (0.787 g, 2.44 mmol) in formic acid (6.50 mL) and acetic anhydride (3.50 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 2:1 40-60 petrol/EtOAc) gave (±)-*N*-(4-chloro-2-(cyano(6-methoxynaphthalen-2-yl)methyl)phenyl)formamide (0.650 g, 77%). Following **General Procedure 4**, this formamide (0.668 g, 1.90 mmol) and Et₃N (0.715 mL, 5.13 mmol) in CH₂Cl₂ (20.0 mL) and phosphoryl chloride (0.184 mL, 2.09 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 20:1 40-60 petrol/EtOAc) gave **89** as a light green solid (0.330 g, 52%); mp 146-148 °C; ν_{max} (film) 2118, 1632, 1607; δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s), 5.62 (1H, s), 7.14 (1H, d, J 2.3), 7.21 (1H, dd, J 8.9, 2.5), 7.36 (1H, dd, J 8.6, 2.0), 7.39 (2H, d, J 1.3), 7.60-7.63 (1H, m), 7.76 (1H, d, J 1.8), 7.78 (1H, s), 7.84 (1H, s); δ_c (101 MHz, $CDCl_3$) 31.0, 38.7, 55.4, 105.7, 117.9, 120.0, 125.2, 127.0, 127.7, 128.5, 128.6, 128.9, 129.3, 129.6, 130.0, 134.2, 134.4, 136.5, 158.6, 171.1; m/z (ESI⁺) 355 ([M+Na]⁺, 100%); HRMS (ESI⁺) $C_{20}H_{13}ClN_2NaO^+$, ([M+Na]⁺) requires 355.0609; found 355.0607.

Preparation of (±)-2-(4-bromo-2-isocyanophenyl)-2-(naphthalen-2-yl)acetonitrile **90**



Following **General Procedure 3**, aminobenzene **73** (2.27 g, 6.75 mmol) in formic acid (18.0 mL) and acetic anhydride (9.5 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/EtOAc) gave (±)-*N*-(5-bromo-2-(cyano(naphthalen-2-yl)methyl)phenyl)formamide (2.00 g, 82%). Following **General Procedure 4**, this formamide (1.62 g, 4.45 mmol) and Et₃N (1.68 mL, 12.0 mmol) in CH₂Cl₂ (50.0 mL) and phosphoryl chloride (0.456 mL, 4.89 mol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 10:1 40-60 petrol/Et₂O) gave **90** as a green powder (1.00 g, 65%); mp 28-30 °C; ν_{max} (film) 3061, 2246, 2118, 1591, 1509; δ_{H} (400 MHz, CDCl₃) 5.64 (1H, s), 7.37 (1H, dd, *J*, 8.6, 2.0), 7.51 (1H, d, *J* 9.0), 7.54-7.58 (2H, m), 7.60-7.65 (2H, m), 7.83-7.90 (3H, m), 7.92 (1H, d, *J* 1.2); δ_{C} (101 MHz, CDCl₃) 38.7, 117.8, 123.0, 124.6, 127.1, 127.2, 127.8, 128.1, 129.7, 130.3, 130.4, 130.6, 131.4, 133.0, 133.2, 133.7, 171.5; *m/z* (ESI⁺) 347 ([M+H]⁺, 18%); HRMS (ESI⁺) C₁₉H₁₁BrN₂Na⁺, ([M+Na]⁺) requires 368.9998; found 368.9990.

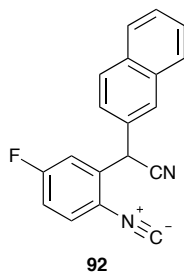
Preparation of (±)-2-(4-chloro-2-isocyanophenyl)-2-(naphthalen-2-yl)acetonitrile **91**



Following **General Procedure 3**, aminobenzene **74** (2.06 g, 7.05 mmol) in formic acid (19.0 mL) and acetic anhydride (10.0 mL) gave a crude reaction product.. Purification *via* flash column

chromatography on silica gel (silica; 2:1 40-60 petrol/EtOAc) gave ($\pm$)-*N*-(5-chloro-2-(cyano(naphthalen-2-yl)methyl)phenyl)formamide (1.50 g, 70%). Following **General Procedure 4**, this formamide (1.20 g, 3.75 mmol) and Et₃N (1.41 mL, 10.1 mmol) in CH₂Cl₂ (40.0 mL) and phosphoryl chloride (0.385 mL, 4.12 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 10:1 40-60 petrol/Et₂O) gave **91** as a dark green foam (0.500 g, 45%); mp 28-30 °C; ν_{max} (film) 3060, 2246, 2119, 1598, 1571, 1509; δ_{H} (400 MHz, CDCl₃) 5.66 (1H, s), 7.38 (1H, dd, *J* 8.6, 1.9), 7.45-7.50 (2H, m), 7.52-7.61 (3H, m), 7.82-7.90 (3H, m), 7.92 (1H, d, *J* 1.0); δ_{C} (101 MHz, CDCl₃) 38.6, 117.9, 124.6, 127.2, 127.7, 127.8, 128.1, 129.7, 130.3, 130.4, 130.8, 130.9, 133.0, 133.2, 135.5, 171.4; *m/z* (ESI⁺) 325 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₉H₁₁ClN₂Na⁺, ([M+Na]⁺) requires 325.0503; found 325.0499.

Preparation of ($\pm$)-2-(5-fluoro-2-isocyanophenyl)-2-(naphthalen-2-yl)acetonitrile **92**

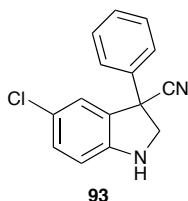


Following **General Procedure 3**, aminobenzene **75** (1.10 g, 3.98 mmol) in formic acid (21.0 mL) and acetic anhydride (5.3 mL) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 2:1 40-60 petrol/EtOAc) gave ($\pm$)-*N*-(2-(cyano(naphthalen-2-yl)methyl)-4-fluorophenyl)formamide (1.10 g, 95%). Following **General Procedure 4**, this formamide (1.08 g, 3.55 mmol) and Et₃N (1.33 mL, 9.58 mmol) in CH₂Cl₂ (43.0 mL) and phosphoryl chloride (0.364 mL, 3.90 mmol) gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 8:1 40-60 petrol/Et₂O) gave **92** as a blue gum (510 mg, 50%); ν_{max} (film) 3056, 2120, 1611, 1592; δ_{H} (400 MHz, CDCl₃) 5.68 (1H, s), 7.09-7.15 (1H, m), 7.35

(1H, dd, *J* 8.5, 2.7), 7.41 (1H, dd, *J* 8.6, 1.8), 7.47 (1H, dd, *J* 8.8, 4.9), 7.53-7.59 (2H, m), 7.83-7.92 (3H, m), 7.95 (1H, s); δ_{C} (101 MHz, CDCl_3) 39.0, 116.5, 116.7, 117.0, 117.2, 117.8, 124.6, 127.2, 127.2, 127.3, 127.8, 128.2, 129.7, 129.8, 129.8, 130.1, 133.1, 133.2, 134.9, 135.0, 162.5, 170.1; δ_{F} (377 MHz, CDCl_3) -105.4; *m/z* (ESI^+) 309 ($[\text{M}+\text{Na}]^+$, 100%); HRMS (ESI^+) $\text{C}_{19}\text{H}_{11}\text{FN}_2\text{Na}^+$, ($[\text{M}+\text{Na}]^+$) requires 309.0798; found 309.0788.

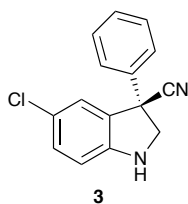
1.3.3 Phase-Transfer Catalyzed Cyclization of Isocyanides

Preparation of (±)-5-chloro-3-phenylindoline-3-carbonitrile **93**



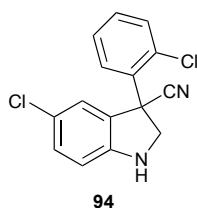
Following **General Procedure 5**, isocyanide **1** (10.0 mg, 0.0400 mmol) and tetrabutylammonium bromide (1.30 mg, 0.00400 mmol) in PhMe (0.400 mL) and aqueous KOH (7.50 μL) gave a crude reaction product. Purification *via* preparative TLC gave **93** as a yellow oil; ν_{max} (film) 3376, 3062, 2876, 2360, 2341, 2238, 1627, 1603; δ_{H} (400 MHz, CDCl_3) 3.86 (1H, dd, *J* 9.7, 1.0), 4.02 (1H, br s), 4.27 (1H, dd, *J* 9.7, 1.7), 6.73 (1H, d, *J* 8.4), 7.09 (1H, d, *J* 1.9), 7.17 (1H, dd, *J* 8.4, 2.1), 7.33-7.47 (5H, m); δ_{C} (101 MHz, CDCl_3) 50.2, 62.3, 111.8, 120.8, 124.8, 125.3, 126.2, 128.6, 129.2, 129.8, 130.2, 138.3, 149.1; *m/z* (ESI^+) 277 ($[\text{M}+\text{Na}]^+$, 74%); HRMS (ESI^+) $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{Na}^+$, ($[\text{M}+\text{Na}]^+$) requires 277.0503; found 277.0502. Daicel CHIRALCEL OD-H, 4.6 mm $\times$ 250 mm, 92:8 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 17.71 min, 21.42 min.

Preparation of (*R*)-5-chloro-3-phenylindoline-3-carbonitrile **3** (Table 1, Entry 13 and Table 2)



Following **General Procedure 6**, catalyst **12** (4.00 mg, 0.00600 mmol) and isocyanide **1** (15.0 mg, 0.0600 mmol) in PhMe (0.600 mL) and 30% aq. CsOH (60.0 μ L) at $-40\text{ }^{\circ}\text{C}$ gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 80:20 40-60 petrol/EtOAc) gave **3** as a yellow oil (81 mg, 80%), which was shown by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm $\times$ 250 mm, 92:8 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 17.51 min (major), 21.54 min (minor)} to have 89:11 er with identical ^1H NMR spectroscopic properties to **93**; $[\alpha]_D^{20}$ -44.0 (*c* 1.1 in CHCl_3).

Preparation of ($\pm$)-5-chloro-3-(2-chlorophenyl)indoline-3-carbonitrile **94**

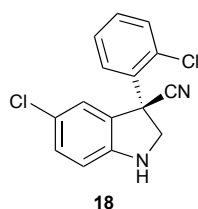


Following **General Procedure 5**, isocyanide **76** (100 mg, 0.348 mmol) and tetrabutylammonium bromide (11 mg, 0.0348 mmol) in PhMe (3.74 mL) and aqueous KOH (0.32 mL) gave a crude reaction product. Purification *via* preparative TLC gave **94** as a yellow oil; ν_{max} (film) 3368, 2980, 2962, 2362, 1763, 1758, 1748, 1715, 1605; δ_{H} (400 MHz, CDCl_3) 3.89 (1H, br s), 4.02 (1H, d, *J* 10.0), 4.23 (1H, dd, *J* 10.0, 1.9), 6.62 (1H, d, *J* 8.4), 6.91 (1H, dd, *J* 7.9, 1.5), 7.10-7.17 (2H, m), 7.20-7.29 (2H, m), 7.41 (1H, dd, *J* 7.9, 1.3); δ_{C} (101 MHz, CDCl_3) 48.9, 59.8, 112.0, 120.0, 124.6, 126.1, 127.2, 127.7, 128.9, 130.3, 130.6, 131.7, 133.3, 134.5, 149.7; *m/z* (ESI $^{+}$) 289 ([*M*+*H*] $^{+}$); HRMS (ESI $^{+}$) $\text{C}_{15}\text{H}_{10}\text{Cl}_2\text{N}_2\text{Na}^{+}$,

([M+Na]⁺) requires 311.0113; found 311.0123; Daicel CHIRALPAK AD-H, 4.6 mm × 250 mm, 10:90

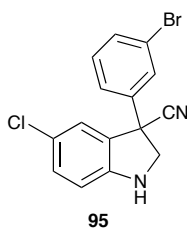
2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 13.25 min, 16.32 min.

Preparation of (S)-5-chloro-3-(2-chlorophenyl)indoline-3-carbonitrile **18** (Table 2)



Following **General Procedure 6**, catalyst **12** (11 mg, 0.0174 mmol) and isocyanide **76** (100 mg, 0.348 mmol) in PhMe (3.48 mL) and 30% aq. CsOH (0.35 mL) at -40 °C gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 80:20 40-60 petrol/EtOAc) gave **18** as a yellow oil (61 mg, 61%), which was shown by chiral HPLC {Daicel CHIRALPAK AD-H, 4.6 mm × 250 mm, 10:90 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 13.27 min (minor), 16.41 min (major)} to have 85:15 er with identical ¹H NMR spectroscopic properties to **94**; [α]_D²⁰ +68.8 (*c* 0.5 in CHCl₃).

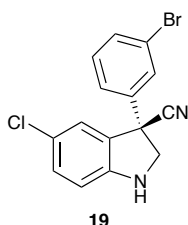
Preparation of (±)-3-(3-bromophenyl)-5-chloroindoline-3-carbonitrile **95**



Following **General Procedure 5**, isocyanide **77** (100 mg, 0.301 mmol) and tetrabutylammonium bromide (10 mg, 0.0301 mmol) in PhMe (3.23 mL) and aqueous KOH (0.28 mL) gave a crude reaction product. Purification *via* preparative TLC gave **95** as a yellow oil; ν_{max} (film) 2240, 1762, 1742, 1713, 1593; δ_{H} (400 MHz, CDCl₃) 3.77 (1H, d, *J* 9.8), 3.91 (1H, br s), 4.20 (1H, dd, *J* 9.7, 1.4), 6.66 (1H, d, *J* 8.4), 7.02 (1H, d, *J* 2.0), 7.11 (1H, dd, *J* 8.4, 2.1), 7.19 (1H, t, *J* 7.9), 7.31 (1H, ddd, *J* 7.9, 1.9, 1.0), 7.42 (1H, ddd, *J* 7.9, 1.8, 1.0), 7.50 (1H, t, *J* 1.9); δ_{C} (101 MHz, CDCl₃) 49.8, 62.1, 112.0,

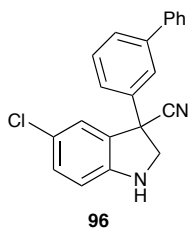
120.2, 123.3, 124.9, 125.1, 125.2, 129.2, 130.5, 130.7, 131.9, 140.6, 148.9; m/z (FI) 332 ([M], 77%); HRMS (FI) $C_{15}H_{10}BrClN_2$, ([M]) requires 331.9716; found 331.9722; Daicel CHIRALCEL OD-H, 4.6 mm $\times$ 250 mm, 10:90 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 13.85 min, 19.30 min.

Preparation of (R)-3-(3-bromophenyl)-5-chloroindoline-3-carbonitrile **19** (Table 2)



Following **General Procedure 6**, catalyst **12** (10 mg, 0.0151 mmol) and isocyanide **77** (100 mg, 0.301 mmol) in PhMe (3.01 mL) and 30% aq. CsOH (0.30 mL) at $-40\text{ }^{\circ}\text{C}$ gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 80:20 40-60 petrol/EtOAc) gave **19** as a yellow oil (79 mg, 79%), which was shown by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm $\times$ 250 mm, 10:90 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 13.80 min (major), 19.26 min (minor)} to have 95:5 er with identical ^1H NMR spectroscopic properties to **95**; $[\alpha]_D^{20}$ -45.4 (c 0.5 in CHCl_3).

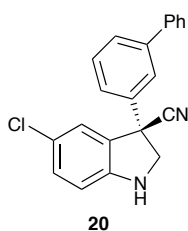
Preparation of ($\pm$)-3-([1,1'-biphenyl]-3-yl)-5-chloroindoline-3-carbonitrile **96**



Following **General Procedure 5**, isocyanide **78** (32.8 mg, 0.100 mmol) and tetrabutylammonium bromide (3.22 mg, 0.0100 mmol) in PhMe (1.00 mL) and aqueous KOH (40.0 μL) gave a crude reaction product. Purification *via* preparative TLC gave **96** as a yellow foam; mp $38\text{--}40\text{ }^{\circ}\text{C}$; ν_{max} (film) 3378, 3061, 3033, 2928, 2874, 2360, 2342, 2240, 1601; δ_{H} (400 MHz, CDCl_3) 3.93 (1H, d J 9.8),

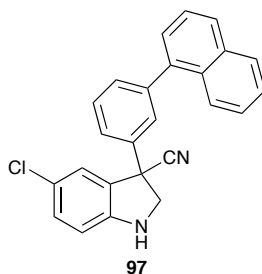
4.04 (1H, br s), 4.31 (1H, d, *J* 9.7), 6.74 (1H, d, *J* 8.3), 7.15-7.21 (2H, m), 7.39-7.44 (2H, m), 7.45-7.51 (3H, m), 7.57-7.64 (3H, m), 7.72 (1H, s); δ_c (101 MHz, $CDCl_3$) 50.4, 62.4, 111.9, 120.9, 124.8, 125.0, 125.1, 125.2, 127.3, 127.5, 127.9, 129.0, 129.6, 129.8, 130.3, 138.9, 140.3, 142.3, 149.2; *m/z* (ESI⁺) 331 ([M+H]⁺, 36%); HRMS (ESI⁺) $C_{21}H_{15}ClN_2Na^+$, ([M+Na]⁺) requires 353.0816; found 353.0804; Daicel CHIRALPAK IA, 4.6 mm × 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 9.87 min, 12.43 min.

Preparation of (R)-3-([1,1'-biphenyl]-3-yl)-5-chloroindoline-3-carbonitrile **20** (Table 2)



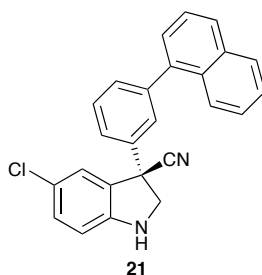
Following **General Procedure 6**, catalyst **12** (9.87 mg, 0.015 mmol) and isocyanide **78** (98.0 mg, 0.300 mmol) in PhMe (3.00 mL) and 30% aq. CsOH (0.300 mL) at −40 °C gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 2:1 40-60 petrol/Et₂O) gave **20** as a yellow foam (82.7 mg, 83% over two steps), which was shown by chiral HPLC {Daicel CHIRALPAK IA, 4.6 mm × 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 9.86 min (major), 12.45 min (minor)} to have 93:7 er with identical ¹H NMR spectroscopic properties to **96**; $[\alpha]_D^{20}$ −52.6 (*c* 3.2 in $CHCl_3$).

Preparation of (±)-5-chloro-3-(3-(naphthalen-1-yl)phenyl)indoline-3-carbonitrile **97**



Following **General Procedure 5**, isocyanide **79** (34.8 mg, 0.100 mmol) and tetrabutylammonium bromide (3.20 mg, 0.0100 mmol) in PhMe (1.00 mL) and aqueous KOH (40.0 μ L) gave a crude reaction product. Purification *via* preparative TLC gave **97** as a yellow solid; mp 127-129 °C; ν_{max} (film) 3379, 3059, 1603; δ_{H} (400 MHz, CDCl_3) 3.96 (2H, d, J 9.5), 4.33 (1H, d, J 8.5), 6.70 (1H, d, J 8.4), 7.16 (1H, dd, J 8.4, 2.1), 7.21 (1H, d, J 2.1), 7.42 (1H, dd, J 7.0, 1.1), 7.44-7.56 (6H, m), 7.57-7.59 (1H, m), 7.82 (1H, d, J 8.4), 7.91 (2H, dd, J 13.1, 7.9); δ_{C} (101 MHz, CDCl_3) 50.3, 62.4, 111.9, 120.7, 124.9, 125.1, 125.2, 125.4, 125.5, 126.0, 126.4, 127.1, 127.9, 128.1, 128.4, 129.1, 129.9, 130.2, 130.4, 131.3, 133.8, 138.5, 139.1, 141.8, 149.1; m/z (ESI^+) 403 ($[\text{M}+\text{Na}]^+$); HRMS (ESI^+) $\text{C}_{25}\text{H}_{17}\text{ClN}_2\text{Na}^+$, ($[\text{M}+\text{Na}]^+$) requires 403.0972; found 403.0965; Daicel CHIRALCEL OD-H, 4.6 mm $\times$ 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 16.37 min, 19.15 min.

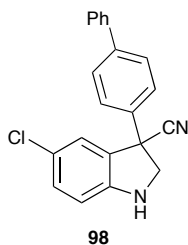
Preparation of (R)-5-chloro-3-(3-(naphthalen-1-yl)phenyl)indoline-3-carbonitrile **21** (Table 2)



Following **General Procedure 6**, catalyst **12** (9.87 mg, 0.0150 mmol) and isocyanide **79** (104 mg, 0.300 mmol) in PhMe (3.00 mL) and 30% aq. CsOH (0.300 mL) at -40 °C gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/ Et_2O) gave **21** as a yellow solid (87.2 mg, 85% over two steps), which was shown by chiral HPLC

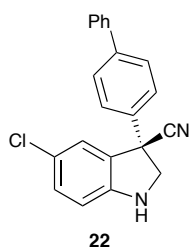
{Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 16.43 min (major), 19.28 min (minor)} to have 94:6 er with identical ¹H NMR spectroscopic properties to **97**; [α]_D²⁰ -47.7 (c 2.5 in CHCl₃).

Preparation of (±)-3-([1,1'-biphenyl]-4-yl)-5-chloroindoline-3-carbonitrile **98**



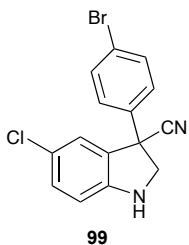
Following **General Procedure 5**, isocyanide **80** (18.0 mg, 0.0600 mmol) and tetrabutylammonium bromide (1.6 mg, 0.00600 mmol) in PhMe (0.600 mL) and aqueous KOH (20.0 μL) gave a crude reaction product. Purification *via* preparative TLC gave **98** as a yellow solid; mp 50-52 °C; ν_{max} (film) 3379, 3031, 2875, 2238, 1603; δ_{H} (400 MHz, CDCl₃) 3.90 (1H, d, *J* 9.7, 0.9), 4.03 (1H, br s), 4.30 (1H, d, *J* 9.7, 1.8), 6.75 (1H, d, *J* 8.4), 7.16 (1H, d, *J* 1.8), 7.20 (1H, dd, *J* 8.4, 2.0), 7.39 (1H, t, *J* 7.3), 7.47 (2H, t, *J* 7.5), 7.53 (2H, d, *J* 8.4), 7.57-7.65 (4H, m); δ_{C} (101 MHz, CDCl₃) 50.0, 62.3, 111.9, 120.8, 124.9, 125.3, 126.7, 127.1, 127.8, 127.8, 128.9, 129.8, 130.3, 137.2, 140.0, 141.6, 149.1; *m/z* (ESI⁺) 331 ([M+H]⁺, 14%); HRMS (ESI⁺) C₂₁H₁₅ClN₂Na⁺, ([M+Na]⁺) requires 353.0816; found 353.0805; Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 15:85 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 25.02 min, 33.15 min.

Preparation of (R)-3-([1,1'-biphenyl]-4-yl)-5-chloroindoline-3-carbonitrile **22** (Table 2)



Following **General Procedure 6**, catalyst **12** (6.60 mg, 0.0100 mmol) and isocyanide **80** (65.0 mg, 0.200 mmol) in PhMe (2.00 mL) and 30% aq. CsOH (0.200 mL) at $-40\text{ }^{\circ}\text{C}$ gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 2:1 40-60 petrol/Et₂O) gave **22** as a yellow solid (49.5 mg, 75% over two steps), which was shown by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm $\times$ 250 mm, 15:85 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 24.61 min (major), 32.98 min (minor)} to have 93:7 er with identical ¹H NMR spectroscopic properties to **98**; $[\alpha]_D^{20} -8.1$ (*c* 2.1 in CHCl₃).

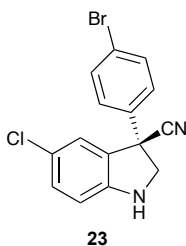
Preparation of (±)-3-(4-bromophenyl)-5-chloroindoline-3-carbonitrile **99**



Following **General Procedure 5**, isocyanide **12** (100 mg, 0.301 mmol) and tetrabutylammonium bromide (10 mg, 0.0301 mmol) in PhMe (3.23 mL) and aqueous KOH (0.28 mL) gave a crude reaction product. Purification *via* preparative TLC gave **99** as a yellow oil; ν_{max} (film) 2980, 2362, 1764, 1758, 1714, 1633; δ_{H} (400 MHz, CDCl₃) 3.73 (1H, d, *J* 9.7), 3.93 (1H, br s), 4.18 (1H, d, *J* 9.7), 6.64 (1H, d, *J* 8.5), 6.99 (1H, d, *J* 2.1), 7.09 (1H, dd, *J* 8.4, 2.1), 7.21-7.26 (2H, m), 7.40-7.46 (2H, m); δ_{C} (101 MHz, CDCl₃) 49.8, 62.1, 112.0, 120.4, 122.9, 125.0, 125.1, 127.9, 129.4, 130.4, 132.3, 137.5, 149.0; *m/z* (ESI⁺) 333 ([M+H]⁺); HRMS (ESI⁺) C₁₅H₁₀BrClN₂Na⁺, ([M+Na]⁺) requires 354.9608; found

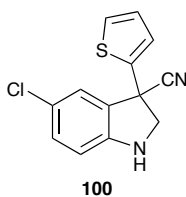
354.9592; Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 10:90 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 13.72 min, 21.99 min.

Preparation of (R)-3-(4-bromophenyl)-5-chloroindoline-3-carbonitrile **23** (Table 2)



Following **General Procedure 6**, catalyst **12** (10 mg, 0.0151 mmol) and isocyanide **81** (100 mg, 0.301 mmol) in PhMe (3.01 mL) and 30% aq. CsOH (0.30 mL) at -40 °C gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 80:20 40-60 petrol/EtOAc) gave **23** as a yellow oil (83 mg, 83%), which was shown by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 10:90 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 13.70 min (major), 22.10 min (minor)} to have 92:8 er with identical ¹H NMR spectroscopic properties to **99**; [α]_D²⁰ -22.2 (c 0.5 in CHCl₃).

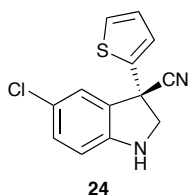
Preparation of (±)-5-chloro-3-(thiophen-2-yl)indoline-3-carbonitrile **100**



Following **General Procedure 5**, isocyanide **82** (19.0 mg, 0.0730 mmol) and tetrabutylammonium bromide (2.20 mg, 0.00700 mmol) in PhMe (0.700 mL) and aqueous KOH (30.0 μL) gave a crude reaction product. Purification *via* preparative TLC gave **100** as a yellow oil; ν_{max} (film) 3375, 3108, 2869, 2361, 2239, 1603; δ_{H} (400 MHz, CDCl₃) 3.93 (1H, d, *J* 9.7), 4.06 (1H, br s), 4.25 (1H, d, *J* 9.6), 6.71 (1H, d, *J* 8.4), 7.01 (1H, dd, *J* 5.1, 3.6), 7.17 (1H, dd, *J* 8.4, 2.1), 7.21-7.24 (2H, m), 7.31 (1H, dd, *J* 5.1, 1.2); δ_{C} (101 MHz, CDCl₃) 46.7, 62.6, 112.0, 120.0, 124.8, 125.0, 126.4, 126.6, 127.1, 129.7, 130.5,

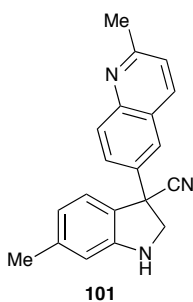
141.2, 148.4; m/z (ESI⁺) 283 ([M+Na]⁺, 49%); HRMS (ESI⁺) C₁₃H₉ClN₂NaS⁺, ([M+Na]⁺) requires 283.0067; found 283.0072; Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 14.70 min, 16.60 min.

Preparation of (S)-5-chloro-3-(thiophen-2-yl)indoline-3-carbonitrile **24** (Table 2)



Following **General Procedure 6**, catalyst **12** (9.80 mg, 0.0150 mmol) and isocyanide **82** (77.2 mg, 0.300 mmol) in PhMe (3.00 mL) and 30% aq. CsOH (0.300 mL) at −40 °C gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 4:1 40-60 petrol/Et₂O) gave **24** as a yellow oil (57.1 mg, 73% over two steps), which was shown by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 14.72 min (major), 16.66 min (minor)} to have 96:4 er with identical ¹H NMR spectroscopic properties to **100**; [α]_D²⁰ −10.8 (*c* 1.0 in CHCl₃).

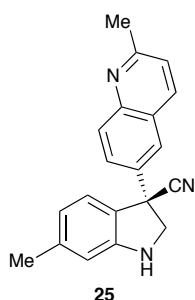
Preparation of (±)-6-methyl-3-(2-methylquinolin-6-yl)indoline-3-carbonitrile **101**



Following **General Procedure 5**, isocyanide **83** (29.7 mg, 0.100 mmol) and tetrabutylammonium bromide (3.20 mg, 0.0100 mmol) in PhMe (1.00 mL) and aqueous KOH (40.0 μL) gave a crude reaction product. Purification *via* preparative TLC gave **101** as a white solid; mp 38-41 °C; ν_{max} (film) 3366, 3260, 2921, 2362, 2238, 1618, 1603; δ_{H} (400 MHz, CDCl₃) 2.34 (3H, s), 2.75 (3H, d, *J* 0.9),

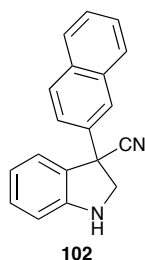
3.91 (1H, d, *J* 9.7), 3.98 (1H, br s), 4.32 (1H, d, *J* 9.6), 6.67 (2H, d, *J* 7.9), 7.03 (1H, d, *J* 7.5), 7.32 (1H, dd, *J* 8.5, 0.8), 7.67 (1H, dd, *J* 8.9, 2.1), 7.92 (1H, s), 8.00 (1H, d, *J* 8.9), 8.05 (1H, d, *J* 8.4); δ_c (101 MHz, CDCl₃) 21.7, 25.4, 50.0, 62.0, 111.8, 121.4, 121.4, 122.8, 124.8, 125.0, 125.3, 126.0, 127.4, 129.8, 136.3, 136.4, 140.7, 147.4, 150.7, 159.9; *m/z* (ESI⁺) 300 ([M+H]⁺, 89%); HRMS (ESI⁺) C₂₀H₁₇N₃Na⁺, ([M+Na]⁺) requires 322.1315; found 322.1314; Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 20:80 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 10.02 min, 17.99 min.

Preparation of (*R*)-6-methyl-3-(2-methylquinolin-6-yl)indoline-3-carbonitrile **25** (Table 2)



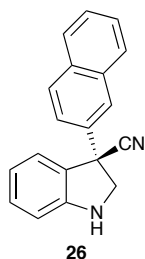
Following **General Procedure 6**, catalyst **12** (8.20 mg, 0.0125 mmol) and isocyanide **83** (75.0 mg, 0.250 mmol) in PhMe (2.50 mL) and 30% aq. CsOH (0.250 mL) at −40 °C gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 2:1 40-60 petrol/EtOAc) gave **25** as a white solid (60.0 mg, 80% over two steps), which was shown by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 20:80 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 10.11 min (major), 18.11 min (minor)} to have 95:5 er with identical ¹H NMR spectroscopic properties to **101**; $[\alpha]_D^{20}$ −98.9 (*c* 0.8 in CHCl₃).

Preparation of (±)-3-(naphthalen-2-yl)indoline-3-carbonitrile **102**



Following **General Procedure 5**, isocyanide **84** (26.8 mg, 0.100 mmol) and tetrabutylammonium bromide (3.22 mg, 0.0100 mmol) in PhMe (1.00 mL) and aqueous KOH (40.0 μ L) gave a crude reaction product. Purification *via* preparative TLC gave **102** as a yellow solid; mp 27-29 $^{\circ}$ C; ν_{max} (film) 3375, 3056, 2971, 2874, 2360, 2341, 2238, 1739, 1629, 1603, 1506; δ_{H} (400 MHz, CDCl_3) 3.92 (1H, d, J 9.7), 4.05 (1H, br s), 4.31 (1H, d, J 9.7), 6.82-6.90 (2H, m), 7.17 (1H, d, J 7.1), 7.25 (1H, td, J 7.7, 1.0), 7.45-7.58 (3H, m), 7.81-7.91 (3H, m), 8.01 (1H, d, J 1.4); δ_{C} (101 MHz, CDCl_3) 50.5, 61.8, 111.1, 120.4, 121.5, 125.2, 125.4, 126.8, 126.8, 127.6, 128.2, 128.3, 129.2, 130.2, 132.9, 133.0, 136.2, 150.6; m/z (ESI $^{+}$) 293 ($[\text{M}+\text{Na}]^{+}$, 50%); HRMS (ESI $^{+}$) $\text{C}_{19}\text{H}_{14}\text{N}_2\text{Na}^{+}$, ($[\text{M}+\text{Na}]^{+}$) requires 293.1049; found 293.1042; Daicel CHIRALPAK IA, 4.6 mm $\times$ 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 11.53 min, 18.74 min.

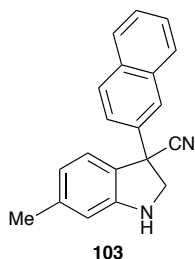
Preparation of (R)-3-(naphthalen-2-yl)indoline-3-carbonitrile **26** (Table 3)



Following **General Procedure 6**, catalyst **12** (6.60 mg, 0.0100 mmol) and isocyanide **84** (53.0 mg, 0.200 mmol) in PhMe (2.00 mL) and 30% aq. CsOH (0.200 mL) at -40° C gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 4:1 40-60 petrol/Et $_2$ O) gave **26** as a yellow solid (48.1 mg, 89% over two steps), which was shown by chiral HPLC

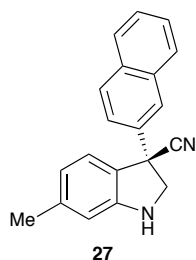
{Daicel CHIRALPAK IA, 4.6 mm × 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 11.47 min (major), 18.85 min (minor)} to have 93:7 er with identical ¹H NMR spectroscopic properties to **102**; [α]_D²⁰ -139.8 (c 2.3 in CHCl₃).

Preparation of (±)-6-methyl-3-(naphthalen-2-yl)indoline-3-carbonitrile **103**



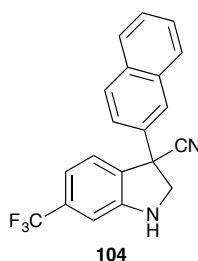
Following **General Procedure 5**, isocyanide **85** (34.0 mg, 0.120 mmol) and tetrabutylammonium bromide (3.80 mg, 0.0120 mmol) in PhMe (1.20 mL) and aqueous KOH (40.0 μL) gave a crude reaction product. Purification *via* preparative TLC gave **103** as a yellow oil; ν_{max} (film) 3372, 3056, 3024, 2970, 2922, 2867, 2360, 2236, 1739, 1616, 1595; δ_{H} (400 MHz, CDCl₃) 2.36 (3H, s), 3.91 (1H, d, *J* 9.7), 3.95 (1H, br s), 4.31 (1H, d, *J* 9.5), 6.69 (2H, d, *J* 9.4), 7.06 (1H, d, *J* 7.6), 7.50 (1H, dd, *J* 8.7, 2.0), 7.52-7.55 (2H, m), 7.82-7.89 (3H, m), 8.01 (1H, d, *J* 1.5); δ_{C} (101 MHz, CDCl₃) 21.7, 50.3, 62.1, 111.8, 121.3, 121.6, 123.9, 124.9, 125.4, 125.5, 126.7, 126.8, 127.6, 128.3, 129.2, 132.9, 133.0, 136.3, 140.5, 150.8; *m/z* (ESI⁺) 285 ([M+H]⁺, 53%); HRMS (ESI⁺) C₂₀H₁₆N₂Na⁺, ([M+Na]⁺) requires 307.1206; found 307.1197; Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 12.74 min, 18.92 min.

Preparation of (R)-6-methyl-3-(naphthalen-2-yl)indoline-3-carbonitrile **27** (Table 3)



Following **General Procedure 6**, catalyst **12** (11.0 mg, 0.0170 mmol) and isocyanide **85** (95.0 mg, 0.330 mmol) in PhMe (3.30 mL) and 30% aq. CsOH (0.330 mL) at $-40\text{ }^{\circ}\text{C}$ gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 7:3 40-60 petrol/Et₂O) gave **27** as a yellow oil (65.0 mg, 70% over two steps), which was shown by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm $\times$ 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 12.78 min (major), 19.14 min (minor)} to have 94:6 er with identical ¹H NMR spectroscopic properties to **103**; $[\alpha]_D^{20}$ -117.3 (*c* 1.9 in CHCl₃).

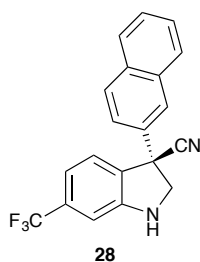
Preparation of (±)-3-(naphthalen-2-yl)-6-(trifluoromethyl)indoline-3-carbonitrile **104**



Following **General Procedure 5**, isocyanide **86** (33.6 mg, 0.100 mmol) and tetrabutylammonium bromide (3.20 mg, 0.0100 mmol) in PhMe (1.00 mL) and aqueous KOH (40.0 μ L) gave a crude reaction product. Purification *via* preparative TLC gave **104** as a yellow solid; mp 38-40 $^{\circ}\text{C}$; ν_{max} (film) 3058, 1617, 1601, 1506; δ_{H} (400 MHz, CDCl₃) 4.02 (1H, dd, *J* 9.8, 1.8), 4.23 (1H, br s), 4.39 (1H, dd, *J* 9.8, 2.2), 7.05 (1H, s), 7.10 (1H, d, *J* 7.9), 7.24 (1H, d, *J* 7.9), 7.46 (1H, dd, *J* 8.7, 1.8), 7.53-7.59 (2H, m), 7.84-7.91 (3H, m), 8.01 (1H, s); δ_{C} (101 MHz, CDCl₃) 50.1, 61.9, 107.4 (*q*, *J* 3.9), 117.1 (*q*, *J* 3.9), 120.8, 123.5, 124.0 (*q*, *J* 272.6), 125.4, 125.6, 127.0, 127.0, 127.7, 128.3, 129.5, 131.7, 132.6 (*q*, *J*

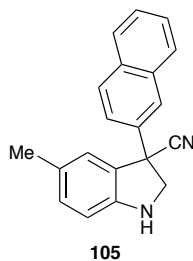
32.1), 132.9, 133.0, 135.3, 150.8; δ_F (377 MHz, $CDCl_3$) -62.6; m/z (ESI⁺) 339 ($[M+H]^+$, 6%); HRMS (ESI⁺) $C_{20}H_{13}F_3N_2Na^+$, ($[M+Na]^+$) requires 361.0923; found 361.0909; Daicel CHIRALCEL OD-H, 4.6 mm $\times$ 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 11.06 min, 17.48 min.

Preparation of (R)-3-(naphthalen-2-yl)-6-(trifluoromethyl)indoline-3-carbonitrile **28** (Table 3)



Following **General Procedure 6**, catalyst **12** (8.20 mg, 0.0125 mmol) and isocyanide **86** (84.0 mg, 0.250 mmol) in PhMe (2.50 mL) and 30% aq. CsOH (0.250 mL) at -40 °C gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 2:1 40-60 petrol/Et₂O) gave **28** as a yellow solid (67.7 mg, 80% over two steps), which was shown by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm $\times$ 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 11.19 min (major), 17.66 min (minor)} to have 92:8 er with identical ¹H NMR spectroscopic properties to **104**; $[\alpha]_D^{20}$ -123.6 (*c* 2.8 in $CHCl_3$).

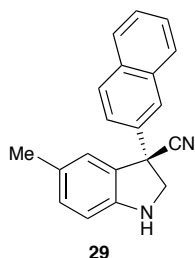
Preparation of (±)-5-methyl-3-(naphthalen-2-yl)indoline-3-carbonitrile **105**



Following **General Procedure 5**, isocyanide **87** (28.2 mg, 0.100 mmol) and tetrabutylammonium bromide (3.20 mg, 0.0100 mmol) in PhMe (1.00 mL) and aqueous KOH (40.0 μ L) gave a crude reaction product. Purification *via* preparative TLC gave **105** as a white solid; mp 157-158 °C; ν_{max}

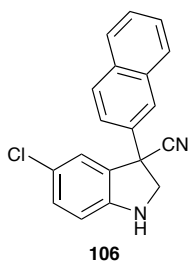
(film) 3371, 3056, 3022, 2920, 2865, 2360, 2236, 1617; δ_{H} (400 MHz, CDCl_3) 2.26 (3H, s), 3.92 (1H, d, J 9.8), 4.31 (1H, d, J 9.8), 6.77 (1H, d, J 8.0), 6.98 (1H, s), 7.06 (1H, d, J 8.0), 7.49 (1H, dd, J 8.7, 1.9), 7.51-7.56 (2H, m), 7.82-7.90 (3H, m), 8.01 (1H, d, J 1.3); δ_{C} (101 MHz, CDCl_3) 20.8, 50.7, 62.0, 111.2, 121.5, 123.8, 125.3, 125.6, 126.7, 126.8, 127.6, 128.3, 128.7, 129.2, 130.2, 130.8, 132.9, 133.0, 136.2, 148.2; m/z (ESI^+) 285 ($[\text{M}+\text{H}]^+$, 34%); HRMS (ESI^+) $\text{C}_{20}\text{H}_{16}\text{N}_2\text{Na}^+$, ($[\text{M}+\text{Na}]^+$) requires 307.1206; found 307.1197; Daicel CHIRALCEL OD-H, 4.6 mm $\times$ 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 12.49 min, 24.37 min.

Preparation of (*R*)-5-methyl-3-(naphthalen-2-yl)indoline-3-carbonitrile **29** (Table 3)



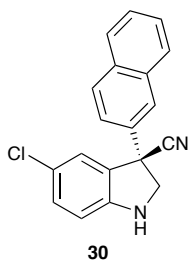
Following **General Procedure 6**, catalyst **12** (8.20 mg, 0.0125 mmol) and isocyanide **87** (70.0 mg, 0.250 mmol) in PhMe (2.50 mL) and 30% aq. CsOH (0.250 mL) at $-40\text{ }^{\circ}\text{C}$ gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 2:1 40-60 petrol/ Et_2O) gave **29** as a white solid (52.5 mg, 74% over two steps), which was shown by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm $\times$ 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 12.63 min (major), 25.04 min (minor)} to have 95:5 er with identical ^1H NMR spectroscopic properties to **105**; $[\alpha]_{\text{D}}^{20}$ -110.8 (c 0.7 in CHCl_3).

Preparation of (±)-5-chloro-3-(naphthalen-2-yl)indoline-3-carbonitrile **106**



Following **General Procedure 5**, isocyanide **88** (30.4 mg, 0.100 mmol) and tetrabutylammonium bromide (3.22 mg, 0.0100 mmol) in PhMe (1.00 mL) and aqueous KOH (40.0 μ L) gave a crude reaction product. Purification *via* preparative TLC gave **106** as a yellow solid; mp 40-42 °C; ν_{max} (film) 3379, 3058, 3022, 2874, 2360, 2342, 2238, 1632, 1603, 1507; δ_{H} (400 MHz, CDCl_3) 3.97 (1H, d, J 9.8), 4.05 (1H, br s), 4.34 (1H, d, J 9.8), 6.76 (1H, d, J 8.4), 7.11 (1H, d, J 1.8), 7.19 (1H, dd, J 8.4, 1.8), 7.46 (1H, dd, J 8.7, 1.8), 7.55 (2H, dt, J 5.0, 2.3), 7.83-7.90 (3H, m), 8.00 (1H, s); δ_{C} (101 MHz, CDCl_3) 50.5, 62.1, 111.9, 120.8, 123.5, 124.9, 125.3, 125.4, 126.9, 127.0, 127.6, 128.3, 129.4, 129.8, 130.3, 132.9, 132.9, 135.3, 149.1; m/z (ESI⁻) 303 ($[\text{M}-\text{H}]^-$, 100%); HRMS (ESI⁺) $\text{C}_{19}\text{H}_{13}\text{ClN}_2\text{Na}^+$, ($[\text{M}+\text{Na}]^+$) requires 327.0659; found 327.0654; Daicel CHIRALPAK IA, 4.6 mm $\times$ 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 10.92 min, 16.54 min.

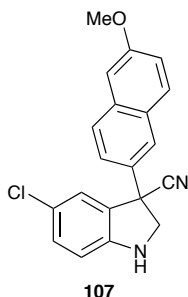
Preparation of (R)-5-chloro-3-(naphthalen-2-yl)indoline-3-carbonitrile **30** (Table 3)



Following **General Procedure 6**, catalyst **12** (6.60 mg, 0.0100 mmol) and isocyanide **88** (60.0 mg, 0.200 mmol) in PhMe (2.00 mL) and 30% aq. CsOH (0.200 mL) at -40 °C gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/Et₂O) gave **30** as a yellow solid (40.7 mg, 67% over two steps), which was shown by chiral HPLC

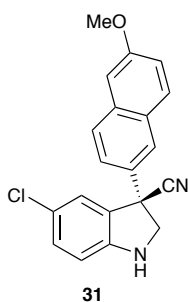
{Daicel CHIRALPAK IA, 4.6 mm × 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 10.90 min (major), 16.64 min (major)} to have 94:6 er with identical ¹H NMR spectroscopic properties to **106**; [α]_D²⁰ -0.3 (c 1.8 in CHCl₃).

Preparation of (±)-5-chloro-3-(6-methoxynaphthalen-2-yl)indoline-3-carbonitrile **107**



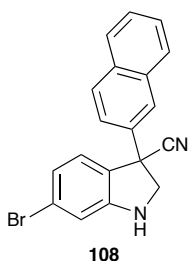
Following **General Procedure 5**, isocyanide **89** (20.0 mg, 0.0600 mmol) and tetrabutylammonium bromide (1.60 mg, 0.00600 mmol) in PhMe (0.600 mL) and aqueous KOH (20.0 μ L) gave a crude reaction product. Purification *via* preparative TLC gave **107** as a yellow solid; mp 34-36 °C; ν_{max} (film) 3376, 2937, 2238, 1739, 1633, 1606, 1505; δ_{H} (400 MHz, CDCl₃) 3.93 (3H, s), 3.95 (1H, s), 4.03 (1H, br s), 4.31 (1H, d, *J* 9.7), 6.74 (1H, d, *J* 8.4), 7.13 (2H, dd, *J* 9.6, 2.1), 7.20 (2H, ddd, *J* 10.4, 8.6, 2.0), 7.42 (1H, dd, *J* 8.6, 1.9), 7.76 (2H, d, *J* 8.8), 7.90 (1H, d, *J* 1.4); δ_{C} (101 MHz, CDCl₃) 50.3, 55.4, 62.2, 105.6, 111.9, 119.8, 121.0, 124.1, 124.8, 125.2, 125.3, 128.2, 128.3, 129.7, 130.0, 130.2, 133.0, 134.3, 149.1, 158.4; *m/z* (ESI⁺) 335 ([M+H]⁺, 42%); HRMS (ESI⁺) C₂₀H₁₅ClN₂NaO⁺, ([M+Na]⁺) requires 357.0765, found 357.0756; Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 15:85 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 15.28 min, 19.93 min.

Preparation of (*R*)-5-chloro-3-(6-methoxynaphthalen-2-yl)indoline-3-carbonitrile **31** (Table 3)



Following **General Procedure 6**, catalyst **12** (6.60 mg, 0.0100 mmol) and isocyanide **89** (66.4 mg, 0.200 mmol) in PhMe (2.00 mL) and 30% aq. CsOH (0.200 mL) at $-40\text{ }^{\circ}\text{C}$ gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 2:1 40-60 petrol/Et₂O) gave **31** as a yellow solid (58.0 mg, 88% over two steps), which was shown by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm $\times$ 250 mm, 15:85 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 15.29 min (major), 20.04 min (minor)} to have 94:6 er with identical ¹H NMR spectroscopic properties to **107**; $[\alpha]_D^{20}$ -30.4 (*c* 2.0 in CHCl₃).

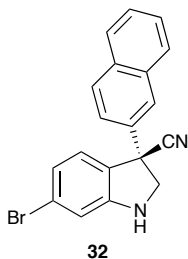
Preparation of ($\pm$)-6-bromo-3-(naphthalen-2-yl)indoline-3-carbonitrile **108**



Following **General Procedure 5**, isocyanide **90** (34.5 mg, 0.100 mmol) and tetrabutylammonium bromide (3.20 mg, 0.0100 mmol) in PhMe (1.00 mL) and aqueous KOH (40.0 μ L) gave a crude reaction product. Purification *via* preparative TLC gave **108** as a yellow oil; ν_{max} (film) 3382, 3058, 3025, 2970, 2928, 2871, 2361, 2239, 1739, 1601, 1507; δ_{H} (400 MHz, CDCl₃) 3.94 (1H, dd, *J* 9.8, 1.5), 4.09 (1H, br s), 4.33 (1H, dd, *J* 9.8, 2.0), 6.93-7.01 (3H, m), 7.45 (1H, dd, *J* 8.7, 2.0), 7.52-7.57 (2H, m), 7.82-7.89 (3H, m), 7.98 (1H, d, *J* 1.7); δ_{C} (101 MHz, CDCl₃) 49.9, 62.0, 113.9, 120.9, 123.1, 123.6, 124.2, 125.4, 126.4, 126.9, 127.0, 127.2, 127.6, 128.3, 129.4, 132.9, 135.5, 151.8; *m/z* (ESI⁺) 349 ([M+H]⁺,

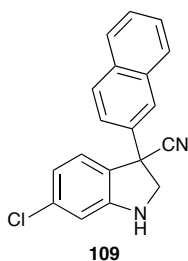
34%); HRMS (ESI⁺) C₁₉H₁₃BrN₂Na⁺, ([M+Na]⁺) requires 371.0154; found 371.0140; Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 15.08 min, 22.44 min.

Preparation of (R)-6-bromo-3-(naphthalen-2-yl)indoline-3-carbonitrile **32** (Table 3)



Following **General Procedure 6**, catalyst **12** (8.20 mg, 0.0250 mmol) and isocyanide **90** (86.0 mg, 0.250 mmol) in PhMe (2.50 mL) and 30% aq. CsOH (0.250 mL) at -40 °C gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/Et₂O) gave **32** as a yellow oil (62.0 mg, 71% over two steps), which was shown by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 15.16 min (major), 22.58 min (minor)} to have 94:6 er with identical ¹H NMR spectroscopic properties to **108**; [α]_D²⁰ -125.1 (*c* 2.1 in CHCl₃).

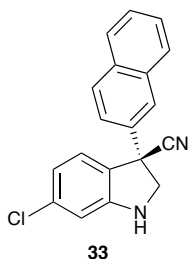
Preparation of (±)-6-chloro-3-(naphthalen-2-yl)indoline-3-carbonitrile **109**



Following **General Procedure 5**, isocyanide **91** (30.2 mg, 0.100 mmol) and tetrabutylammonium bromide (3.20 mg, 0.0100 mmol) in PhMe (1.00 mL) and aqueous KOH (40.0 μL) gave a crude reaction product. Purification *via* preparative TLC gave **109** as a white foam; mp 40-42 °C; ν_{max} (film) 3383, 3058, 2973, 2873, 2361, 2239, 1700, 1603, 1507; δ_{H} (400 MHz, CDCl₃) 3.97 (1H, d, *J* 9.8),

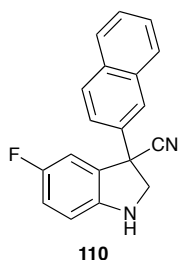
4.36 (1H, d, *J* 9.8), 6.78-6.85 (2H, m), 7.05 (1H, d, *J* 8.5), 7.45 (1H, dd, *J* 8.7, 1.9), 7.51-7.57 (2H, m), 7.82-7.90 (3H, m), 7.98 (1H, d, *J* 1.4); δ_c (101 MHz, CDCl₃) 49.9, 62.1, 111.0, 120.3, 121.0, 123.6, 125.4, 126.1, 126.7, 126.9, 126.9, 127.6, 128.2, 129.4, 132.9, 135.6, 136.1, 151.6; *m/z* (ESI⁺) 305 ([M+H]⁺, 37%); HRMS (ESI⁺) C₁₉H₁₃ClN₂Na⁺, ([M+Na]⁺) requires 327.0659; found 327.0651; Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 14.32 min, 21.15 min.

Preparation of (*R*)-6-chloro-3-(naphthalen-2-yl)indoline-3-carbonitrile **33** (Table 3)



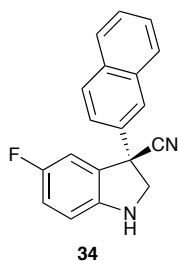
Following **General Procedure 6**, catalyst **12** (6.58 mg, 0.0100 mmol) and isocyanide **91** (60.0 mg, 0.200 mmol) in PhMe (2.00 mL) and 30% aq. CsOH (0.200 mL) at −40 °C gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 2:1 40-60 petrol/Et₂O) gave **33** as a white foam (45.2 mg, 75% over two steps), which was shown by chiral HPLC {Daicel CHIRALCEL OD-H, 4.6 mm × 250 mm, 12:88 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 14.35 min (major), 21.35 min (minor)} to have 93:7 er with identical ¹H NMR spectroscopic properties to **109**; $[\alpha]_D^{20}$ −161.2 (*c* 1.5 in CHCl₃).

Preparation of (±)-5-fluoro-3-(naphthalen-2-yl)indoline-3-carbonitrile **110**



Following **General Procedure 5**, isocyanide **92** (28.6 mg, 0.100 mmol) and tetrabutylammonium bromide (3.22 mg, 0.0100 mmol) in PhMe (1.00 mL) and aqueous KOH (40.0 μ L) gave a crude reaction product. Purification *via* preparative TLC gave **110** as a yellow solid; mp 105-108 °C; ν_{max} (film) 3373, 3059, 2874, 2238, 1601; δ_{H} (400 MHz, CDCl_3) 3.66 (1H, br s), 3.96 (1H, d, J 9.9), 4.34 (1H, d, J 9.9), 6.79 (1H, dd, J 8.6, 4.2), 6.89 (1H, dd, J 7.8, 2.5), 6.97 (1H, td, J 8.7, 2.6), 7.47 (1H, dd, J 8.7, 1.9), 7.51-7.58 (2H, m), 7.82-7.90 (3H, m), 7.99 (1H, d, J 1.3); δ_{C} (101 MHz, CDCl_3) 50.9, 62.4, 111.9, 112.0, 112.3, 112.6, 116.9, 117.2, 120.9, 123.6, 125.5, 126.9, 126.9, 127.6, 128.3, 129.4, 129.7, 129.7, 132.9, 135.3, 146.7, 154.7, 156.4, 158.8; δ_{F} (377 MHz, CDCl_3) -123.0; m/z (ESI⁺) 311 ([M+Na]⁺, 100%); HRMS (ESI⁺) $\text{C}_{19}\text{H}_{13}\text{FN}_2\text{Na}^+$, ([M+Na]⁺) requires 311.0955; found 311.0950; Daicel CHIRALPAK IA, 4.6 mm $\times$ 250 mm, 18:82 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 8.20 min, 12.00 min.

Preparation of (R)-5-fluoro-3-(naphthalen-2-yl)indoline-3-carbonitrile **34** (Table 3)

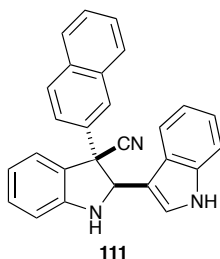


Following **General Procedure 6**, catalyst **12** (8.90 mg, 0.0135 mmol) and isocyanide **92** (78.3 mg, 0.270 mmol) in PhMe (2.70 mL) and 30% aq. CsOH (0.270 mL) at -40 °C gave a crude reaction product. Purification *via* flash column chromatography on silica gel (silica; 3:1 40-60 petrol/Et₂O)

gave **34** as a yellow solid (70.0 mg, 90% over two steps), which was shown by chiral HPLC {Daicel CHIRALPAK IA, 4.6 mm × 250 mm, 18:82 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 8.21 min (major), 12.04 min (minor)} to have 96:4 er with identical ¹H NMR spectroscopic properties to **110**; [α]_D²⁰ -132.4 (*c* 1.1 in CHCl₃).

1.3.4 Derivatizations

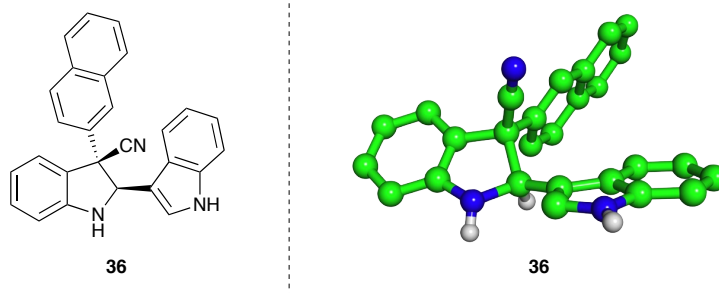
Preparation of (2*R**,3*R**)-2-(1*H*-indol-3-yl)-3-(naphthalen-2-yl)indoline-3-carbonitrile **111**



To a solution of isocyanide **84** (100 mg, 0.373 mmol), and tetrabutylammonium iodide (14 mg, 0.0373 mmol) in anhydrous PhMe (4 mL) under argon was added aqueous KOH (0.34 mL, 30% w/w) at 0 °C. The resulting mixture was stirred at 0 °C until the reaction was complete, after which MgSO₄ was added and the mixture was then filtered through a short pad of cotton wool contained within a pipette. Following washing with PhMe and concentration *in vacuo*, the residue was dissolved in AcOH (1.5 mL) and indole (48 mg, 0.410 mmol) was added. The resulting mixture was stirred at rt overnight, after which NaHCO₃ was added. The mixture was extracted with CH₂Cl₂ (×3), dried (MgSO₄) and concentrated under reduced pressure to give a crude reaction product. Purification *via* preparative TLC gave **111** as a white solid; mp 203-205 °C; ν_{max} (film) 3356, 3055, 2237, 1738, 1696, 1603; δ_{H} (400 MHz, (CD₃)₂CO) 5.68 (1H, s), 5.83 (1H, s), 6.51-6.58 (2H, m), 6.84 (1H, t, *J* 7.5), 6.94-7.03 (3H, m), 7.29 (1H, t, *J* 7.6), 7.38 (1H, d, *J* 8.2), 7.53-7.67 (4H, m), 7.89 (1H, d, *J* 7.7), 7.97-8.04 (3H, m), 10.38 (1H, s); δ_{C} (101 MHz, (CD₃)₂CO) 59.4, 71.8, 110.8, 111.8, 112.5, 119.0, 119.4, 119.8, 119.8, 121.8, 124.9, 125.4, 125.5, 126.9, 127.1, 127.4, 128.1, 128.6, 128.9, 129.1, 130.4, 133.4, 133.5, 136.2, 137.2, 152.1; *m/z* (ESI⁺) 386 ([M+H]⁺, 100%); HRMS (ESI⁺)

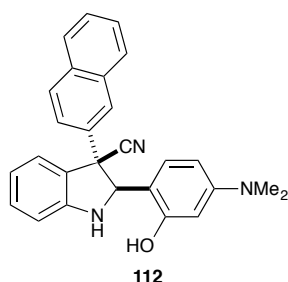
$C_{27}H_{19}N_3Na^+$, ($[M+Na]^+$) requires 408.1471; found 408.1468; Daicel CHIRALPAK IA, 4.6 mm × 250 mm, 30:70 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 10.41 min, 13.68 min.

Preparation of (2R,3R)-2-(1H-indol-3-yl)-3-(naphthalen-2-yl)indoline-3-carbonitrile **36 (Scheme 1)**



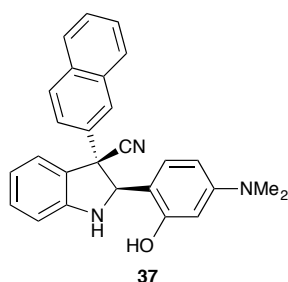
Catalyst **12** (12 mg, 0.0187 mmol) was added to a solution of isocyanide **84** (100 mg, 0.373 mmol) in anhydrous PhMe (3.73 mL) under argon. The resulting mixture was stirred at rt for 30 min, after which 30% aq. CsOH (0.37 mL) was added at $-40\text{ }^{\circ}\text{C}$. Once the reaction was complete, $MgSO_4$ was added and the mixture was then filtered through a short pad of cotton wool contained within a pipette. Following washing with PhMe and concentration *in vacuo*, the residue was dissolved in AcOH (1.5 mL) and indole (48 mg, 0.410 mmol) was added. The resulting mixture was stirred at rt overnight, after which $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (×3), dried ($MgSO_4$) and concentrated under reduced pressure to give crude **36** (>98:2 dr). Purification *via* flash column chromatography on silica gel (silica; 100:0 to 95:5 CH_2Cl_2 /2-propanol) gave **36** as a white solid (137 mg, 95% over two steps, >98:2 dr), which was shown by chiral HPLC {Daicel CHIRALPAK IA, 4.6 mm × 250 mm, 30:70 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 10.36 min (major), 13.85 min (minor)} to have 93:7 er with identical 1H NMR spectroscopic properties to **111**; $[\alpha]_D^{20} +20.0$ (c 0.5 in $CHCl_3$).

Preparation of (2*S**,3*R**)-2-(4-(dimethylamino)-2-hydroxyphenyl)-3-(naphthalen-2-yl)indoline-3-carbonitrile **112**



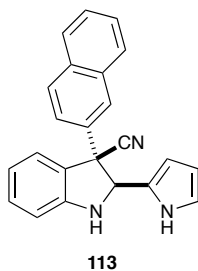
To a solution of isocyanide **84** (100 mg, 0.373 mmol), and tetrabutylammonium iodide (14 mg, 0.0373 mmol) in anhydrous PhMe (4 mL) under argon was added aqueous KOH (0.34 mL, 30% w/w) at 0 °C. The resulting mixture was stirred at 0 °C until the reaction was complete, after which MgSO₄ was added and the mixture was then filtered through a short pad of cotton wool contained within a pipette. Following washing with PhMe and concentration *in vacuo*, the residue was dissolved in AcOH (1.5 mL) and 3-(dimethylamino)phenol (56 mg, 0.410 mmol) was added. The resulting mixture was stirred at rt overnight, after which NaHCO₃ was added. The mixture was extracted with CH₂Cl₂ (×3), dried (MgSO₄) and concentrated under reduced pressure to give a crude reaction product. Purification *via* preparative TLC gave **112** as a pale yellow solid; mp 165-167 °C; ν_{max} (film) 3457, 3016, 2971, 2574, 2245, 2128, 1760, 1722; δ_{H} (400 MHz, CDCl₃) 2.90 (6H, s), 4.56 (1H, d, *J* 3.7), 4.97 (1H, s), 5.97 (1H, dd, *J* 8.6, 2.3), 6.04 (1H, d, *J* 8.6), 6.35 (1H, d, *J* 2.3), 6.95-7.09 (3H, m), 7.29-7.41 (2H, m), 7.51-7.60 (2H, m), 7.81-7.91 (3H, m), 7.95 (1H, s), 9.44 (1H, s); δ_{C} (101 MHz, CDCl₃) 40.2, 58.0, 77.7, 100.8, 103.8, 105.5, 113.0, 118.5, 122.6, 124.7, 126.1, 126.8, 126.9, 127.7, 127.8, 128.4, 128.8, 129.3, 129.9, 130.3, 132.9, 132.9, 134.1, 148.7, 152.2, 158.4; *m/z* (ESI⁻) 404 ([M-H]⁻, 100%); HRMS (ESI⁺) C₂₇H₂₄N₃O⁺, ([M+H]⁺) requires 406.1914; found 406.1901; Daicel CHIRALPAK IA, 4.6 mm × 250 mm, 50:50 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 10.18 min, 20.56 min.

Preparation of (2*S*,3*R*)-2-(4-(dimethylamino)-2-hydroxyphenyl)-3-(naphthalen-2-yl)indoline-3-carbonitrile **37** (Scheme 1)



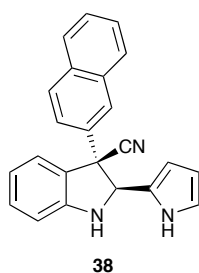
Catalyst **12** (12 mg, 0.0187 mmol) was added to a solution of isocyanide **84** (100 mg, 0.373 mmol) in anhydrous PhMe (3.73 mL) under argon. The resulting mixture was stirred at rt for 30 min, after which 30% aq. CsOH (0.37 mL) was added at $-40\text{ }^{\circ}\text{C}$. Once the reaction was complete, MgSO_4 was added and the mixture was then filtered through a short pad of cotton wool contained within a pipette. Following washing with PhMe and concentration *in vacuo*, the residue was dissolved in AcOH (1.5 mL) and 3-(dimethylamino)phenol (56 mg, 0.410 mmol) was added. The resulting mixture was stirred at rt overnight, after which NaHCO_3 was added. The mixture was extracted with CH_2Cl_2 ($\times 3$), dried (MgSO_4) and concentrated under reduced pressure to give crude **37** (>98:2 dr). Purification *via* flash column chromatography on silica gel (silica; 80:20 40-60 petrol/EtOAc) gave **37** as a pale yellow solid (146 mg, 97% over two steps, >98:2 dr), which was shown by chiral HPLC {Daicel CHIRALPAK IA, 4.6 mm $\times$ 250 mm, 50:50 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 10.34 min (major), 21.05 min (minor)} to have 93:7 er with identical ^1H NMR spectroscopic properties to **112**; $[\alpha]_D^{20}$ -40.0 (c 0.5 in CHCl_3).

Preparation of (2*S**,3*R**)-3-(naphthalen-2-yl)-2-(1*H*-pyrrol-2-yl)indoline-3-carbonitrile **113**



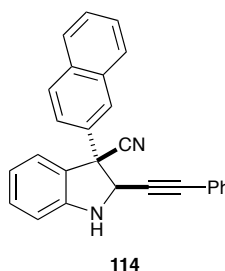
To a solution of isocyanide **84** (100 mg, 0.373 mmol), and tetrabutylammonium iodide (14 mg, 0.0373 mmol) in anhydrous PhMe (4 mL) under argon was added aqueous KOH (0.34 mL, 30% w/w) at 0 °C. The resulting mixture was stirred at 0 °C until the reaction was complete, after which MgSO₄ was added and the mixture was then filtered through a short pad of cotton wool contained within a pipette. Following washing with PhMe and concentration *in vacuo*, the residue was dissolved in AcOH (1.5 mL) and pyrrole (0.23 mL, 3.36 mmol) was added. The resulting mixture was stirred at rt overnight, after which NaHCO₃ was added. The mixture was extracted with CH₂Cl₂ (×3), dried (MgSO₄) and concentrated under reduced pressure to give a crude reaction product. Purification *via* preparative TLC gave **113** as a pale yellow solid; mp 103-105 °C; ν_{max} (film) 2971, 2128, 1766, 1721; δ_{H} (400 MHz, CDCl₃) 4.37 (1H, d, *J* 2.3), 5.14 (1H, d, *J* 2.7), 5.87 (1H, s), 6.18 (1H, q, *J* 2.9), 6.86 (1H, d, *J* 1.4), 6.93 (2H, dd, *J* 13.8, 7.6), 7.08 (1H, d, *J* 7.4), 7.31 (1H, td, *J* 7.7, 0.7), 7.47 (1H, dd, *J* 8.6, 1.8), 7.53-7.60 (2H, m), 7.84-7.93 (3H, m), 7.98 (1H, s), 8.89 (1H, s); δ_{C} (101 MHz, CDCl₃) 57.7, 72.1, 108.5, 108.7, 111.0, 118.8, 119.5, 121.1, 124.6, 125.7, 125.9, 126.8, 126.9, 127.1, 127.2, 127.7, 128.4, 128.9, 130.4, 133.0, 133.0, 134.1, 150.1; *m/z* (ESI⁺) 336 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₃H₁₇N₃Na⁺, ([M+Na]⁺) requires 358.1315; found 358.1302; Daicel CHIRALPAK IA, 4.6 mm × 250 mm, 30:70 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 7.43 min, 21.05 min.

Preparation of (2*S*,3*R*)-3-(naphthalen-2-yl)-2-(1*H*-pyrrol-2-yl)indoline-3-carbonitrile **38** (Scheme 1)



Catalyst **12** (12 mg, 0.0187 mmol) was added to a solution of isocyanide **84** (100 mg, 0.373 mmol) in anhydrous PhMe (3.73 mL) under argon. The resulting mixture was stirred at rt for 30 min, after which 30% aq. CsOH (0.37 mL) was added at $-40\text{ }^{\circ}\text{C}$. Once the reaction was complete, MgSO_4 was added and the mixture was then filtered through a short pad of cotton wool contained within a pipette. Following washing with PhMe and concentration *in vacuo*, the residue was dissolved in AcOH (1.5 mL) and pyrrole (0.23 mL, 3.36 mmol) was added. The resulting mixture was stirred at rt overnight, after which NaHCO_3 was added. The mixture was extracted with CH_2Cl_2 ($\times 3$), dried (MgSO_4) and concentrated under reduced pressure to give crude **38** (>98:2 dr). Purification *via* flash column chromatography on silica gel (silica; 90:10 to 80:20 40-60 petrol/EtOAc) gave **38** as a pale yellow solid (87 mg, 70% over two steps, >98:2 dr), which was shown by chiral HPLC {Daicel CHIRALPAK IA, 4.6 mm $\times$ 250 mm, 30:70 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 7.43 min (major), 21.13 min (minor)} to have 93:7 er with identical ^1H NMR spectroscopic properties to **113**; $[\alpha]_D^{20} -44.0$ (*c* 0.5 in CHCl_3).

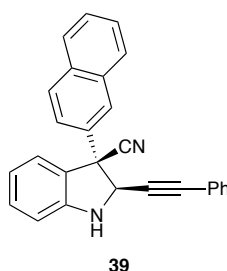
Preparation of (2*R**,3*R**)-3-(naphthalen-2-yl)-2-(phenylethynyl)indoline-3-carbonitrile **114**



To a solution of isocyanide **84** (100 mg, 0.373 mmol), and tetrabutylammonium iodide (14 mg, 0.0373 mmol) in anhydrous PhMe (4 mL) under argon was added aqueous KOH (0.34 mL, 30% w/w) at 0 °C. The resulting mixture was stirred at 0 °C until the reaction was complete, after which MgSO₄ was added and the mixture was then filtered through a short pad of cotton wool contained within a pipette. Following washing with PhMe and concentration *in vacuo*, the residue was dissolved in PhMe (5 mL) and cooled to –60 °C. Phenylethynylmagnesium bromide solution (1.0 M in THF, 1.49 mL, 1.49 mmol) was added and the resulting mixture was stirred at –60 °C overnight. The mixture was then quenched with NH₄Cl, extracted with CH₂Cl₂ (×3), dried (MgSO₄) and concentrated under reduced pressure to give a crude reaction product. Purification *via* preparative TLC gave **114** as a yellow oil; ν_{max} (film) 3016, 1781, 1702; δ_{H} (400 MHz, CDCl₃) 4.44 (1H, s), 4.92 (1H, s), 6.90 (1H, d, *J* 7.9), 6.95 (1H, td, *J* 7.6, 0.7), 7.20 (1H, d, *J* 7.6), 7.28–7.37 (4H, m), 7.52–7.61 (5H, m), 7.85–7.92 (3H, m), 8.13 (1H, s); δ_{C} (101 MHz, CDCl₃) 58.0, 64.4, 84.4, 88.3, 111.6, 119.0, 121.2, 121.9, 124.1, 125.7, 126.6, 126.9, 127.0, 127.7, 128.4, 128.4, 129.0, 129.2, 130.6, 132.1, 133.0, 133.2, 134.4, 149.4; *m/z* (ESI⁺) 371 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₇H₁₈N₂Na⁺, ([M+H]⁺) requires 393.1362; found 393.1360; Daicel CHIRALPAK IA, 4.6 mm × 250 mm, 20:80 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 13.80 min, 15.69 min.

Preparation of (2R,3R)-3-(naphthalen-2-yl)-2-(phenylethynyl)indoline-3-carbonitrile **39**

(Scheme 1)

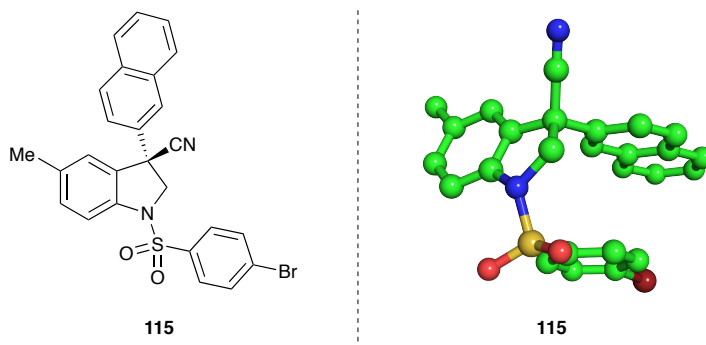


Catalyst **12** (12 mg, 0.0187 mmol) was added to a solution of isocyanide **84** (100 mg, 0.373 mmol) in anhydrous PhMe (3.73 mL) under argon. The resulting mixture was stirred at rt for 30 min, after which 30% aq. CsOH (0.37 mL) was added at $-40\text{ }^{\circ}\text{C}$. Once the reaction was complete, MgSO_4 was added and the mixture was then filtered through a short pad of cotton wool contained within a pipette. Following washing with PhMe and concentration *in vacuo*, the residue was dissolved in PhMe (5 mL) and cooled to $-60\text{ }^{\circ}\text{C}$. Phenylethynylmagnesium bromide solution (1.0 M in THF, 1.49 mL, 1.49 mmol) was added and the resulting mixture was stirred at $-60\text{ }^{\circ}\text{C}$ overnight. The mixture was then quenched with NH_4Cl , extracted with CH_2Cl_2 ($\times 3$), dried (MgSO_4) and concentrated under reduced pressure to give crude **39** ($>98:2$ dr). Purification *via* flash column chromatography on silica gel (silica; 90:10 40-60 petrol/EtOAc) gave **39** as a yellow oil (105 mg, 76% over two steps, $>98:2$ dr), which was shown by chiral HPLC {Daicel CHIRALPAK IA, 4.6 mm $\times$ 250 mm, 20:80 2-propanol/hexane, 1.0 mL/min, retention times of enantiomers: 13.78 min (major), 15.70 min (minor)} to have 92:8 er with identical ^1H NMR spectroscopic properties to **114**; $[\alpha]_D^{20} -216.0$ (c 0.5 in CHCl_3).

1.3.5 Additional Synthesis

This reaction has not been optimized.

Preparation of (R)-1-((4-bromophenyl)sulfonyl)-5-methyl-3-(naphthalen-2-yl)indoline-3-carbonitrile **115**



To a solution of **29** (97.0 mg, 0.340 mmol, >98:2 er) in anhydrous CH₂Cl₂ (6.00 mL) was added Et₃N (95.0 μL, 0.680 mmol), 4-bromobenzenesulfonyl chloride (0.130 g, 0.512 mmol) and DMAP (4.10 mg, 0.0340 mmol). After stirring for 24 h, the reaction mixture was quenched with H₂O and extracted with CH₂Cl₂ (×3). The combined organic layers were dried (MgSO₄), concentrated *in vacuo* and purified by flash chromatography (silica; 8:1 40-60 petrol/Et₂O) to yield **115** (150 mg, 87%) as white crystals; mp 168-170 °C; $[\alpha]_D^{20}$ -100.5 (*c* 1.0 in CHCl₃); $\nu_{\max}$ (film) 2970, 2360, 2251, 1739, 1574; δ_H (400 MHz, CDCl₃) 2.31 (3H, s), 4.33 (1H, d, *J* 11.8), 4.66 (1H, d, *J* 11.8), 6.96-7.03 (2H, m), 7.23-7.29 (1H, m), 7.43 (2H, d, *J* 8.6), 7.51-7.59 (5H, m), 7.73 (3H, dd, *J* 11.6, 8.7), 7.81-7.86 (1H, m); δ_C (101 MHz, CDCl₃) 21.0, 48.7, 63.5, 115.7, 120.1, 122.9, 125.7, 126.4, 127.2, 127.3, 127.6, 128.2, 128.6, 129.1, 129.6, 130.7, 131.7, 132.5, 132.7, 132.8, 135.3, 135.4, 135.8, 139.0; *m/z* (ESI⁺) 525 ([M+Na]⁺, 84%); HRMS (ESI⁺) C₂₆H₁₉BrN₂NaO₂S⁺, ([M+Na]⁺) requires 525.0243; found 525.0241.

1.4 References and Notes

- ¹ A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics*, **1996**, *15*, 1518-1520.
- ² W. L. F. Armarego and D. D. Perrin, in *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, 1996.
- ³ Prepared from (S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methanamine and 4-nitrophenyl isocyanate following a standard procedure (see: A. F. Kyle, P. Jakubec, D. M. Cockfield, E. Cleator, J. Skidmore and D. J. Dixon, *Chem. Comm.*, **2011**, *47*, 10037-10039).
- ⁴ Nitroarylation of acetonitriles: M. Małosza and A. A. Tomaszewskij, *J. Org. Chem.*, **1995**, *60*, 5425-5429.

Appendix I: Further Reaction and Catalyst Optimization

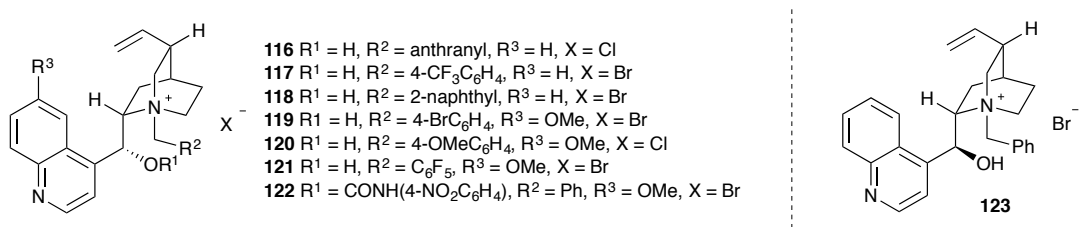
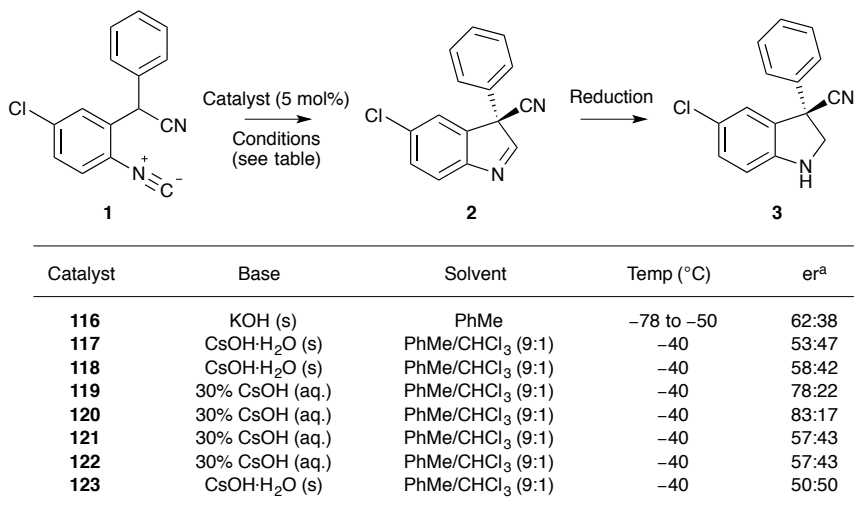


Table 1: Further reaction and catalyst optimization. ^a er established by chiral HPLC analysis.

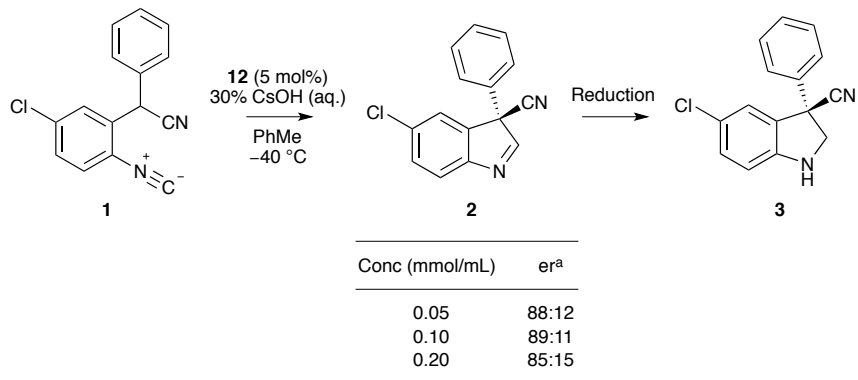
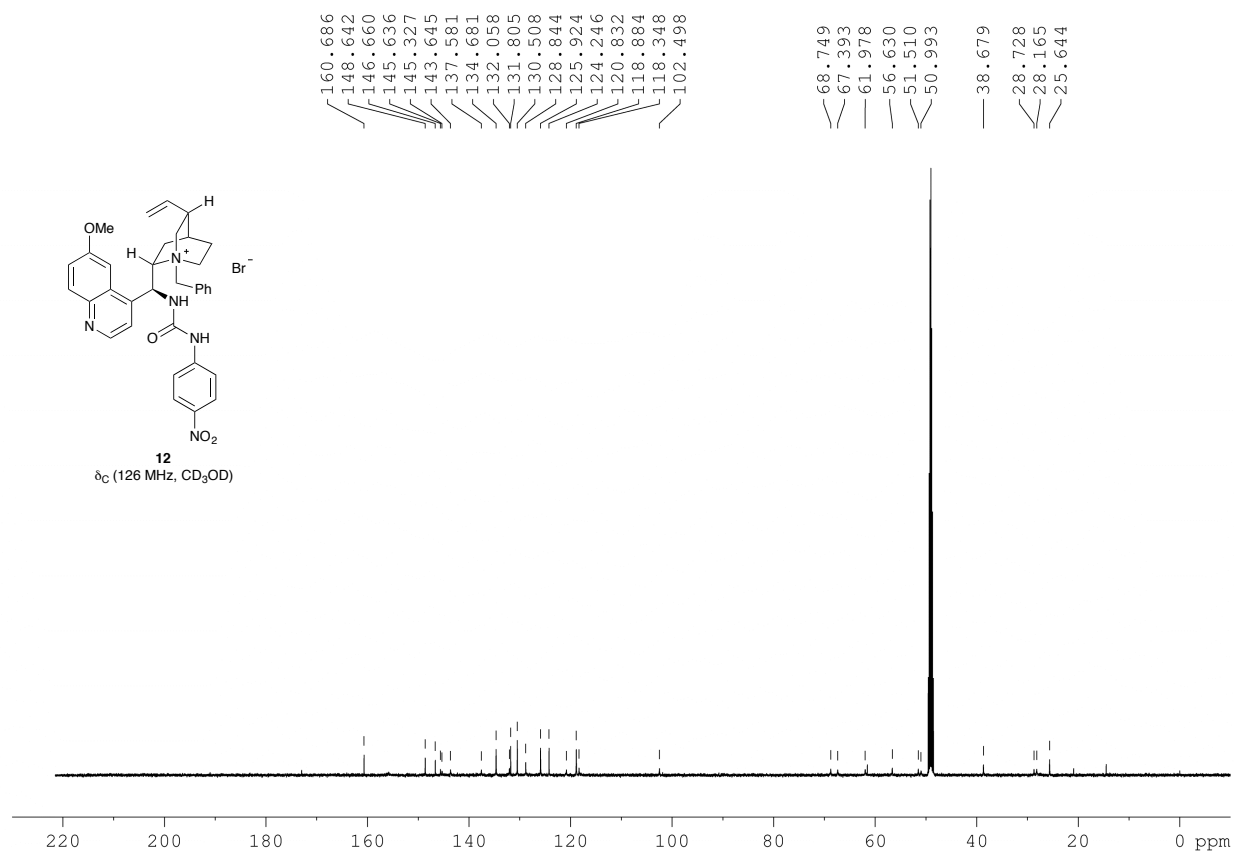
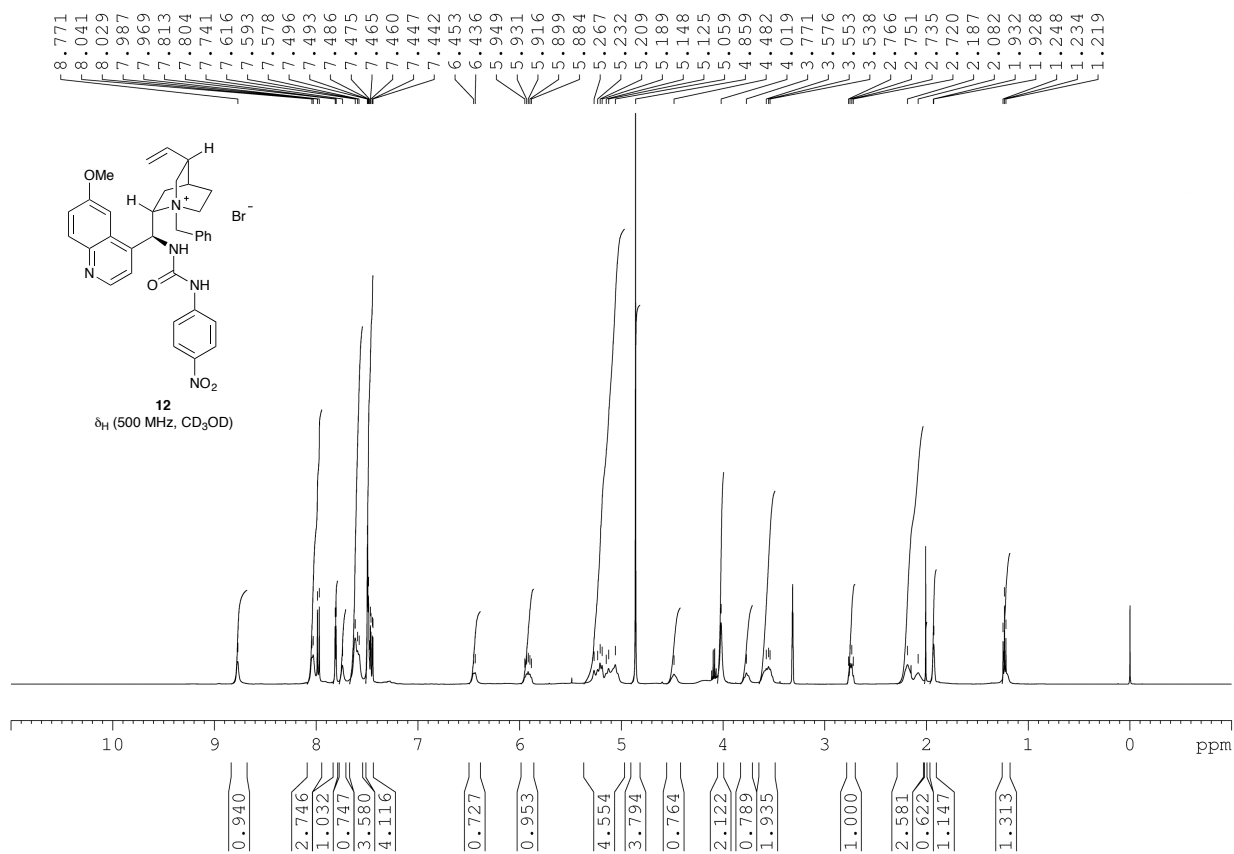
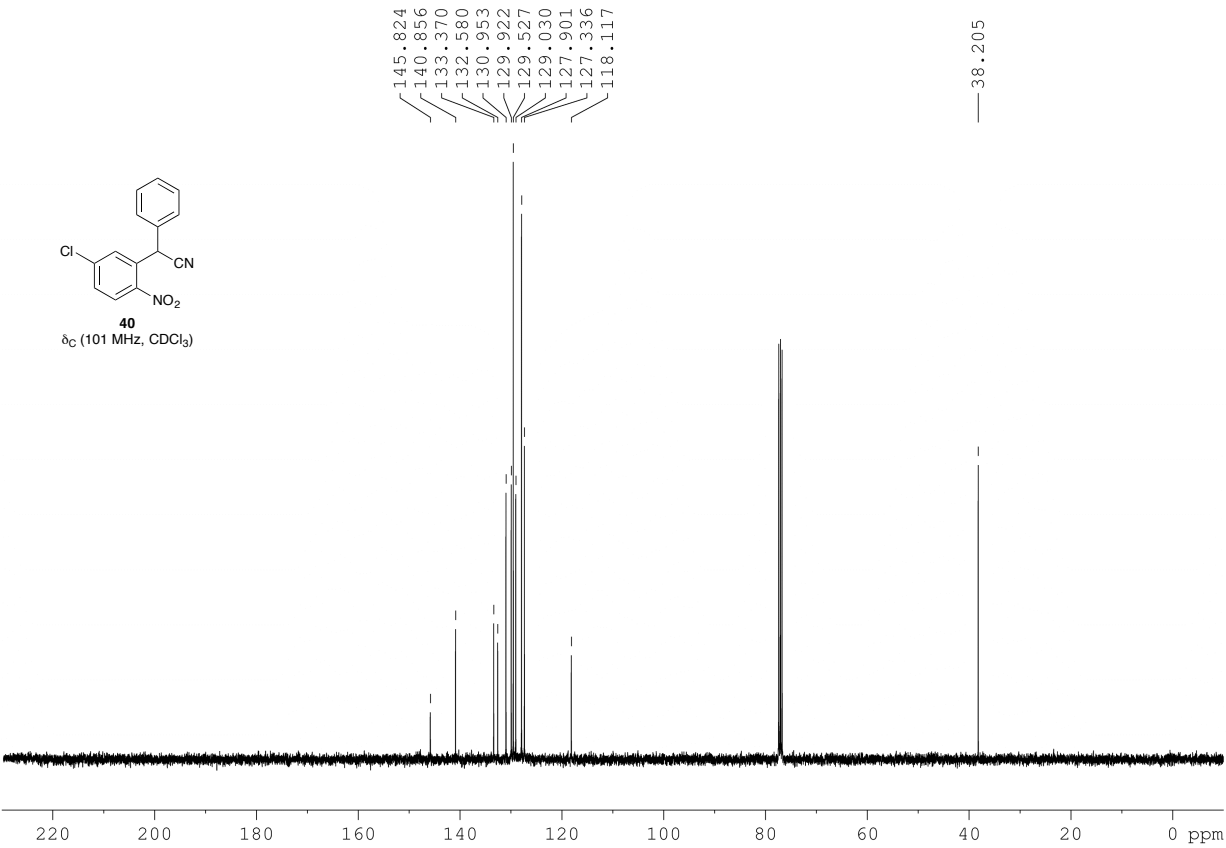
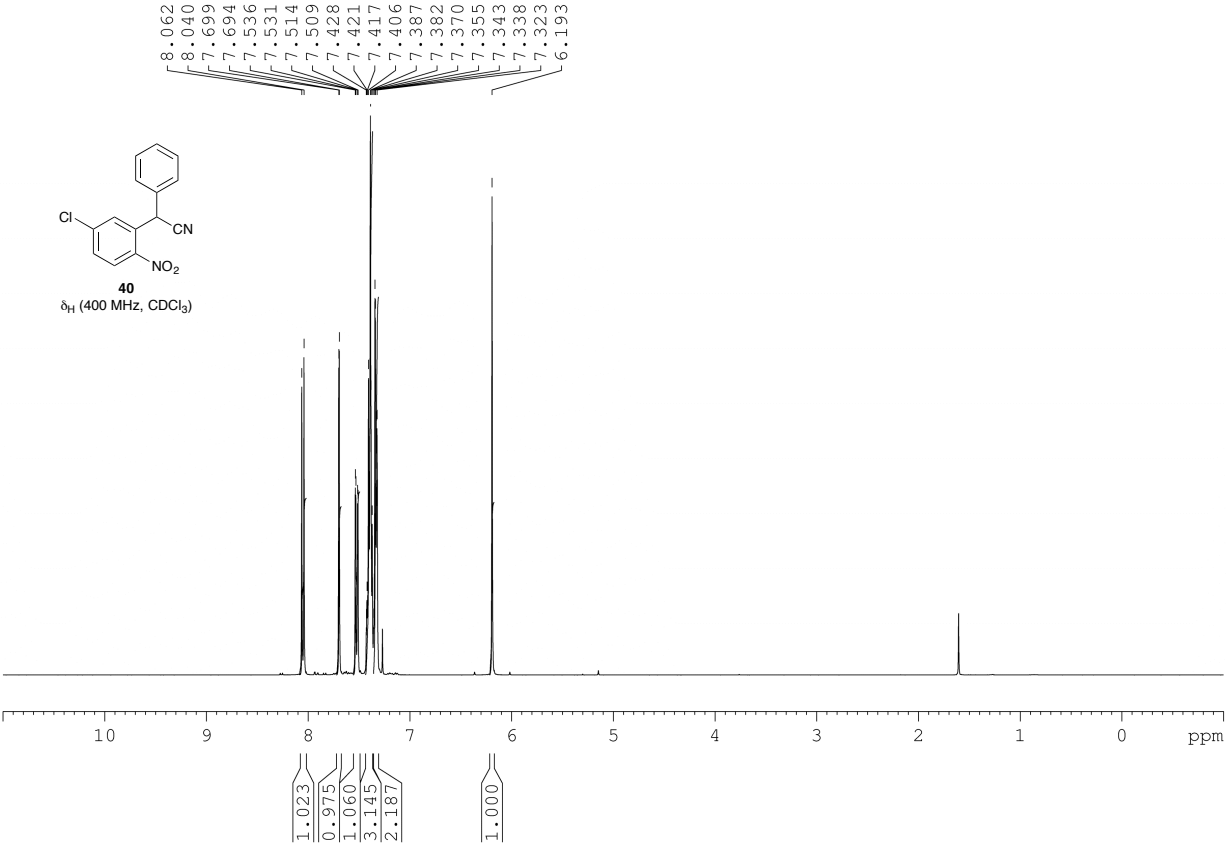
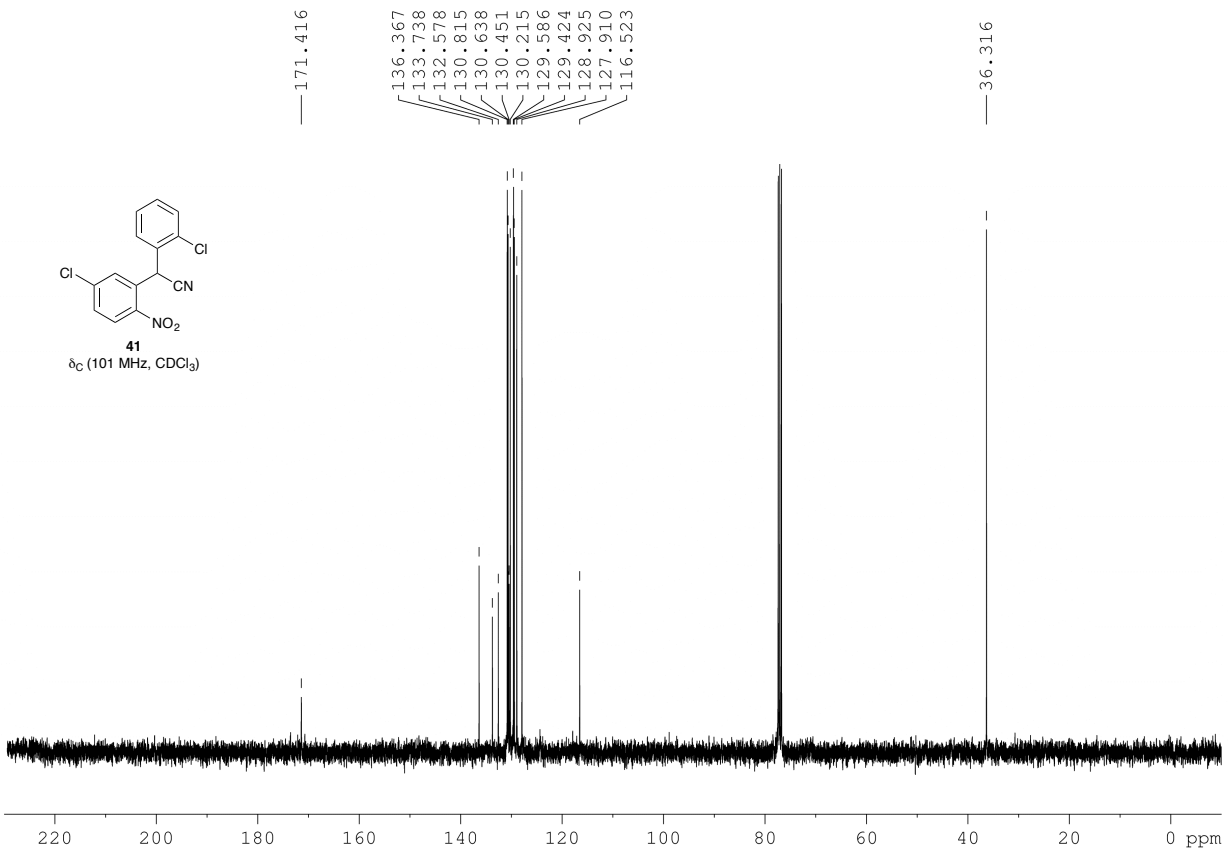
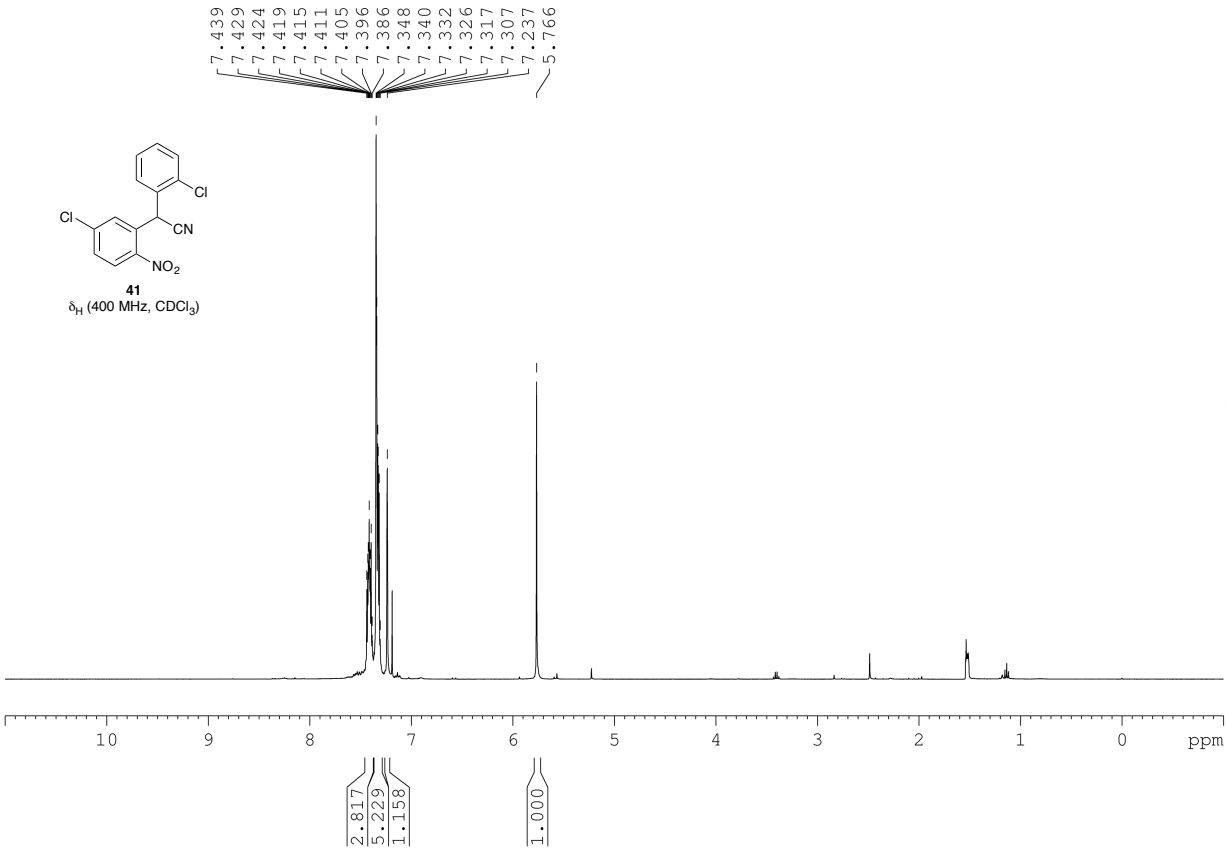


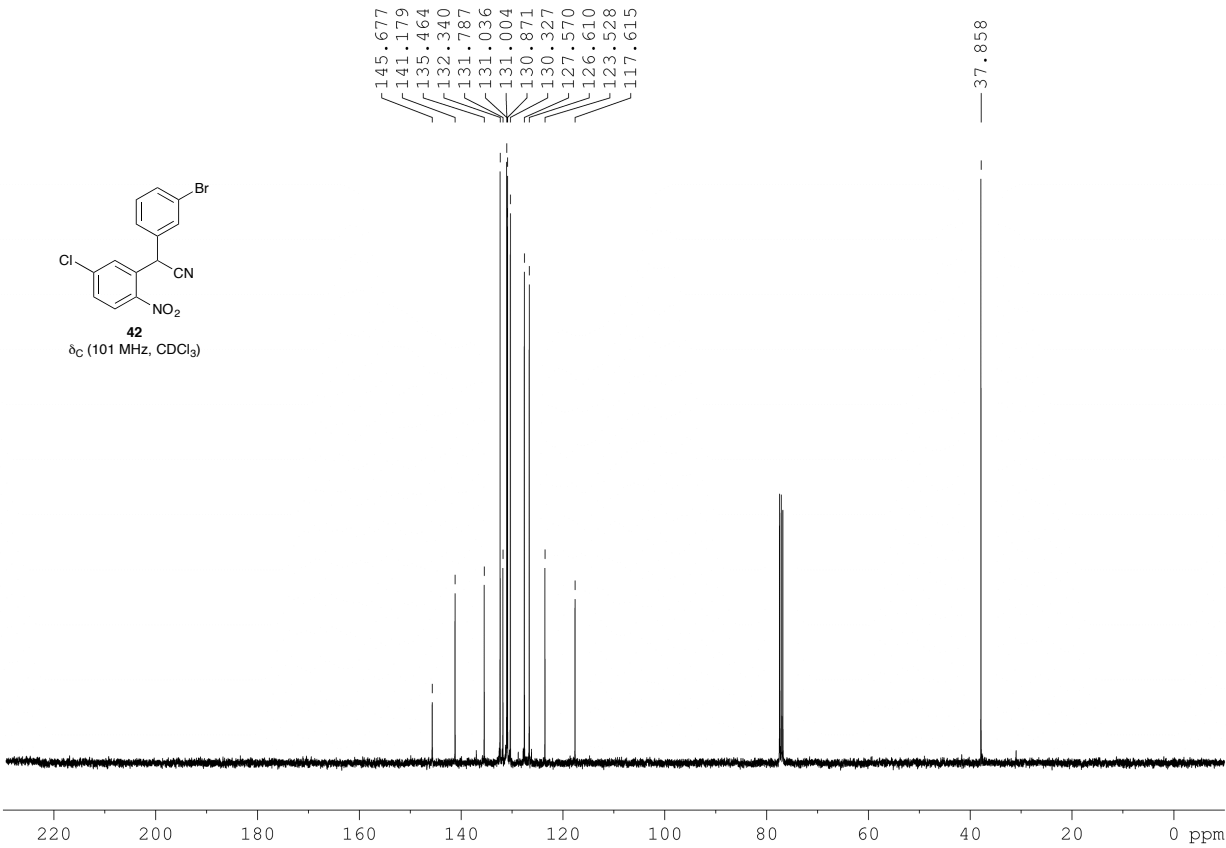
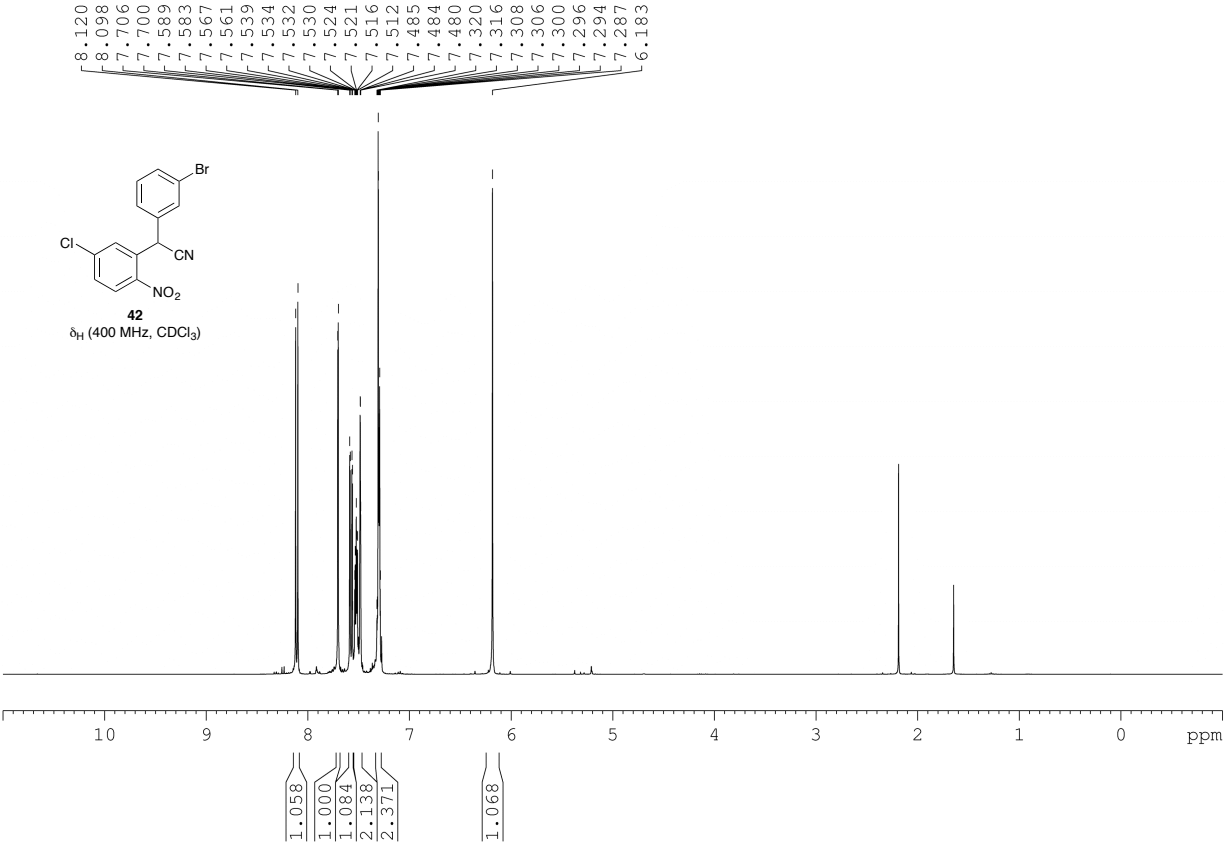
Table 2: A concentration study with catalyst **12**. ^a er established by chiral HPLC analysis.

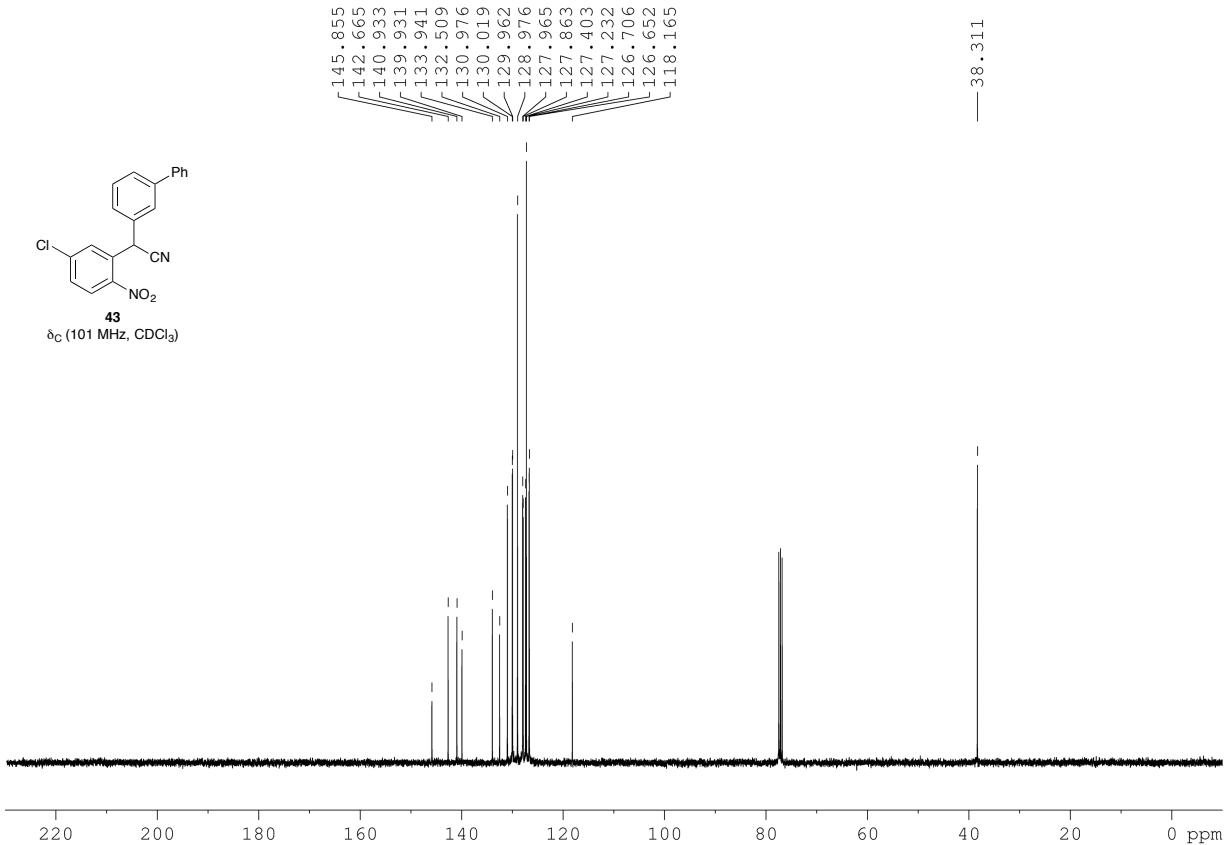
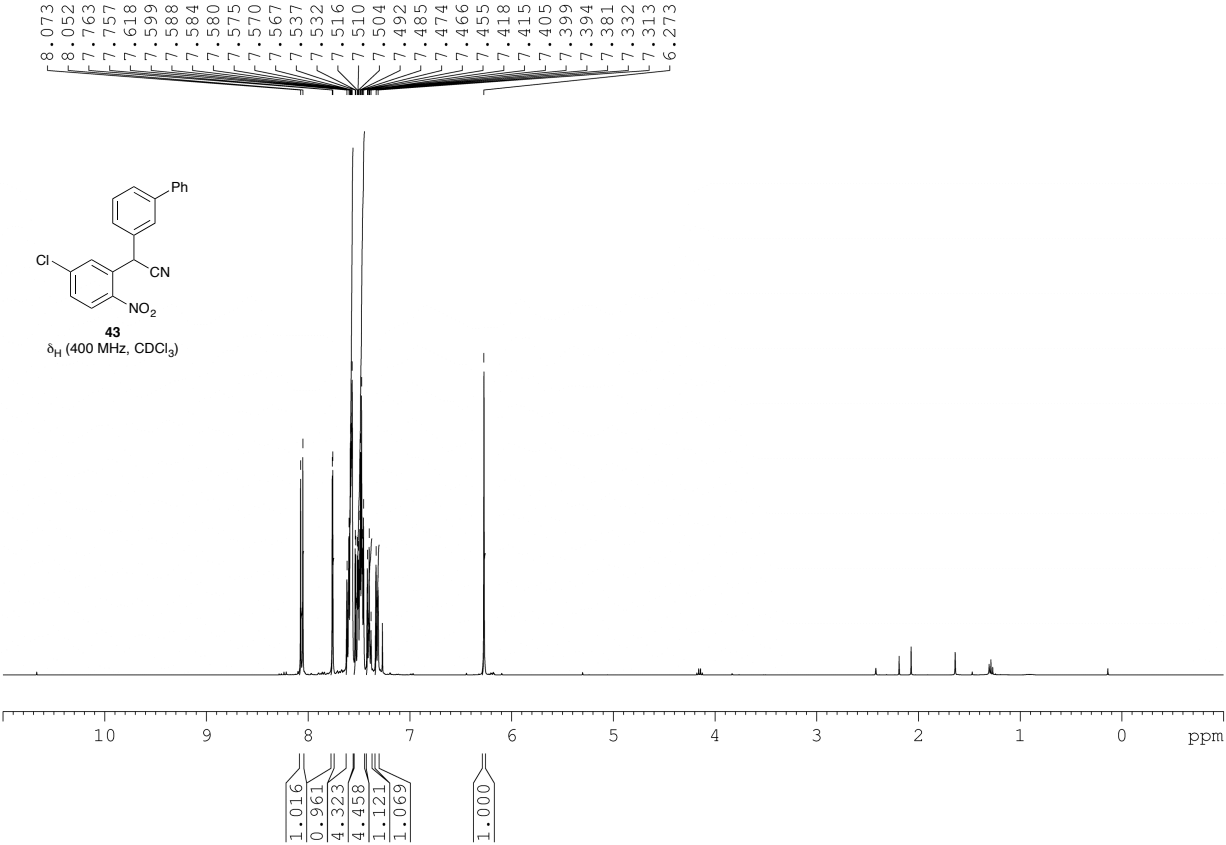
Appendix II: ^1H and ^{13}C NMR Spectra

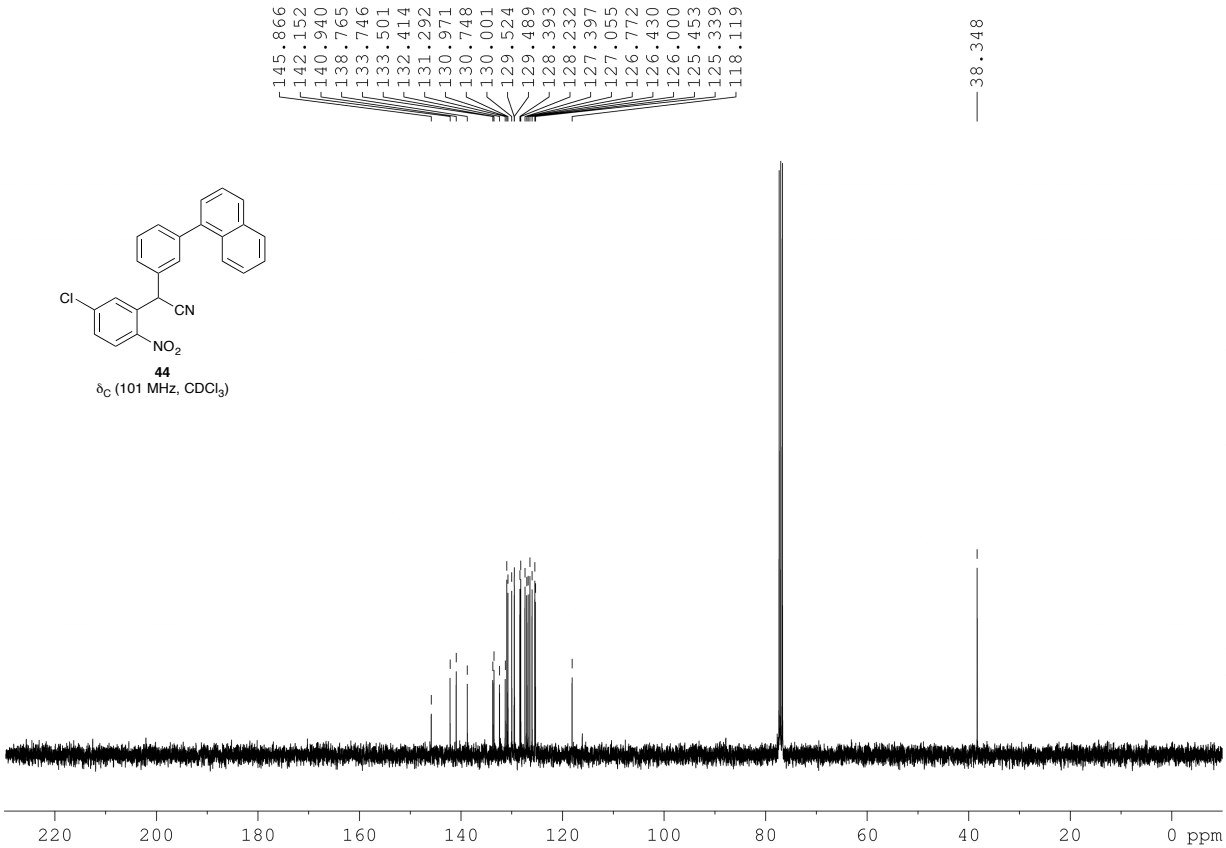
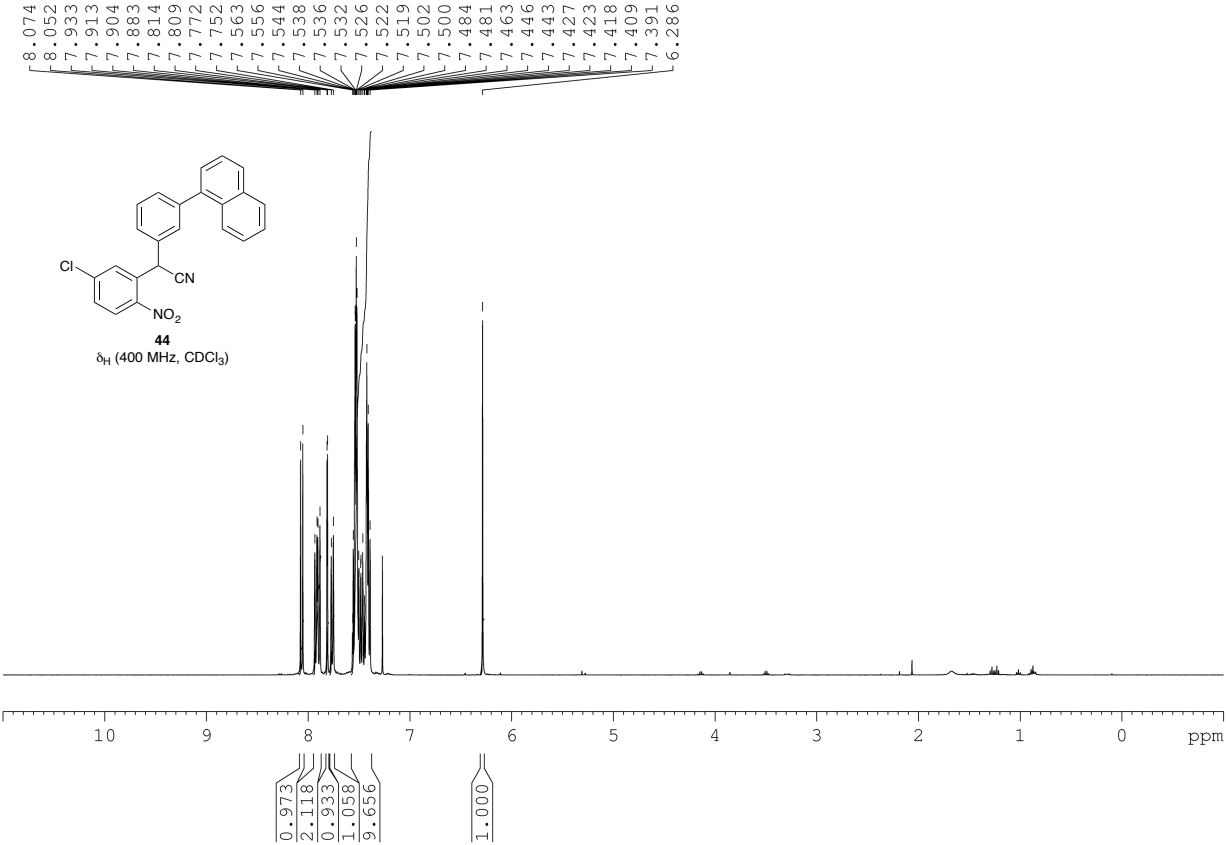


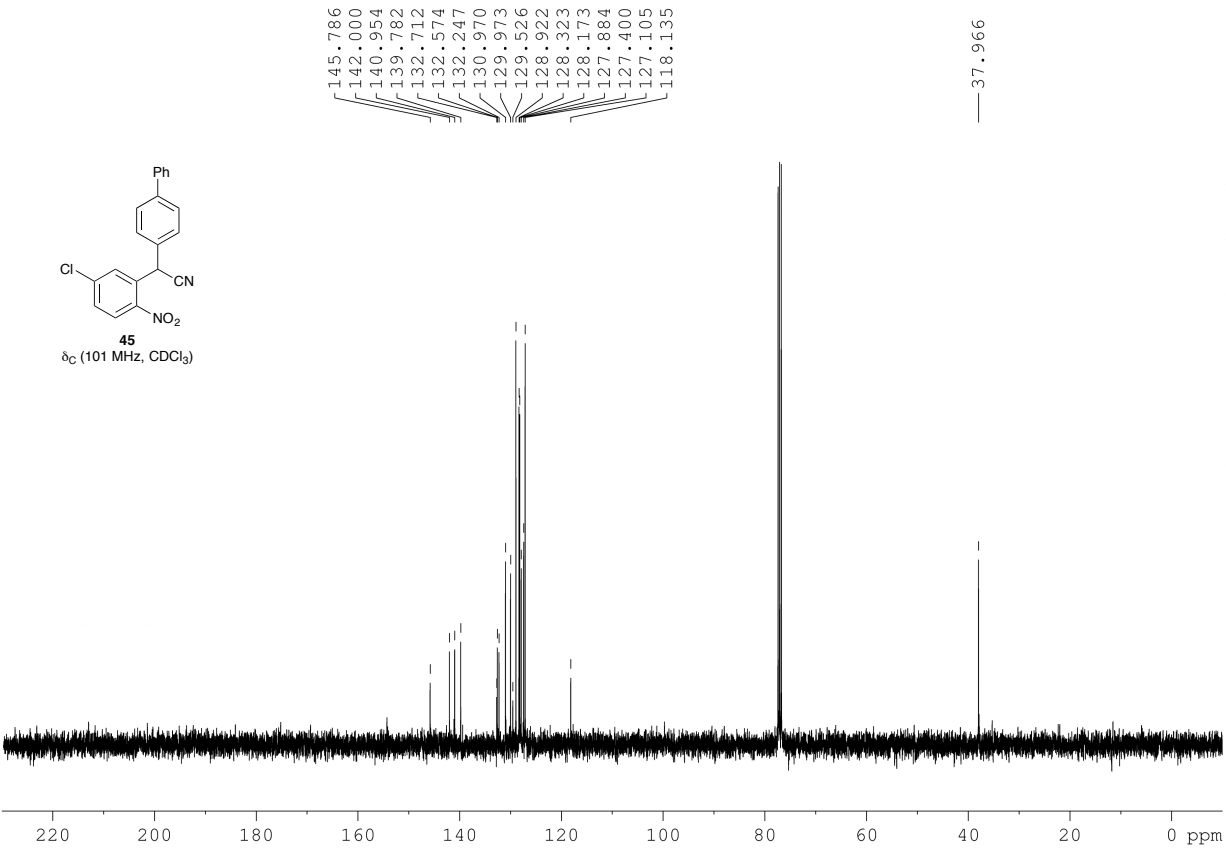
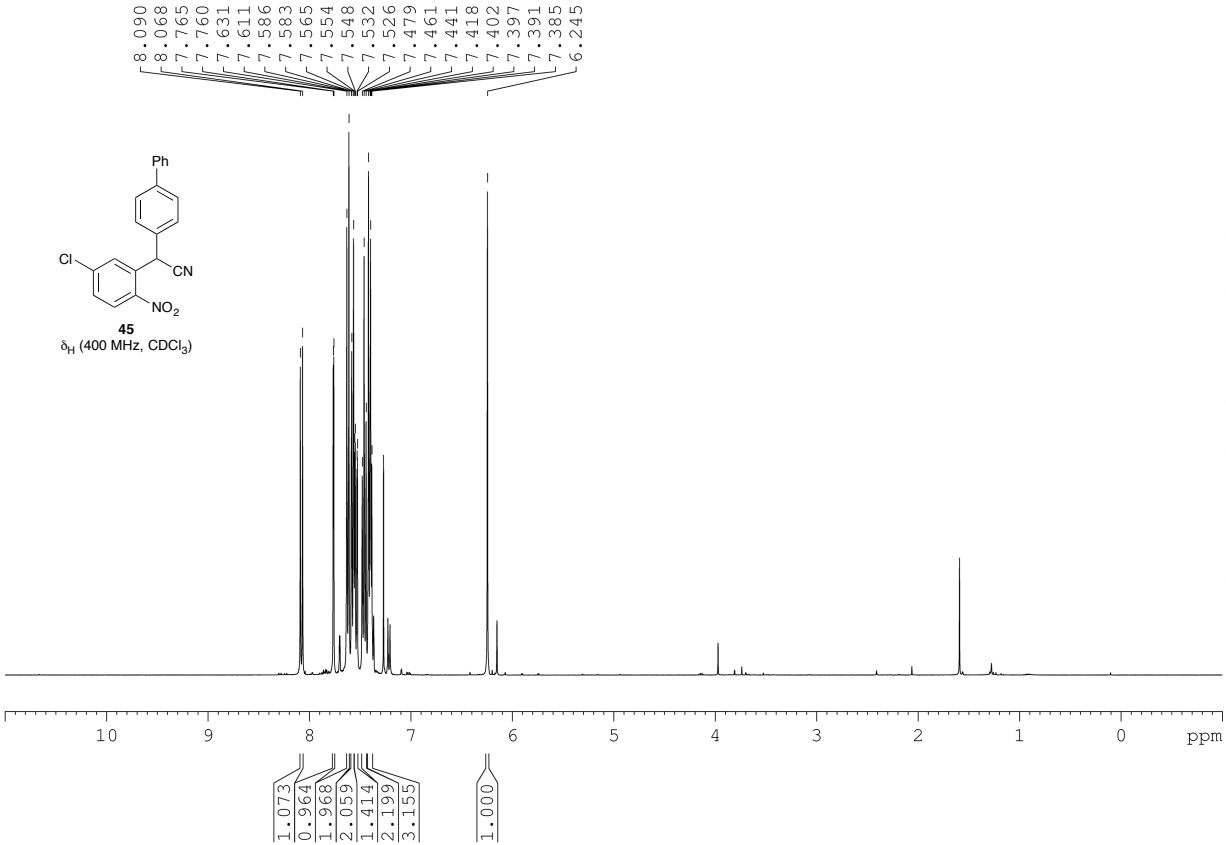


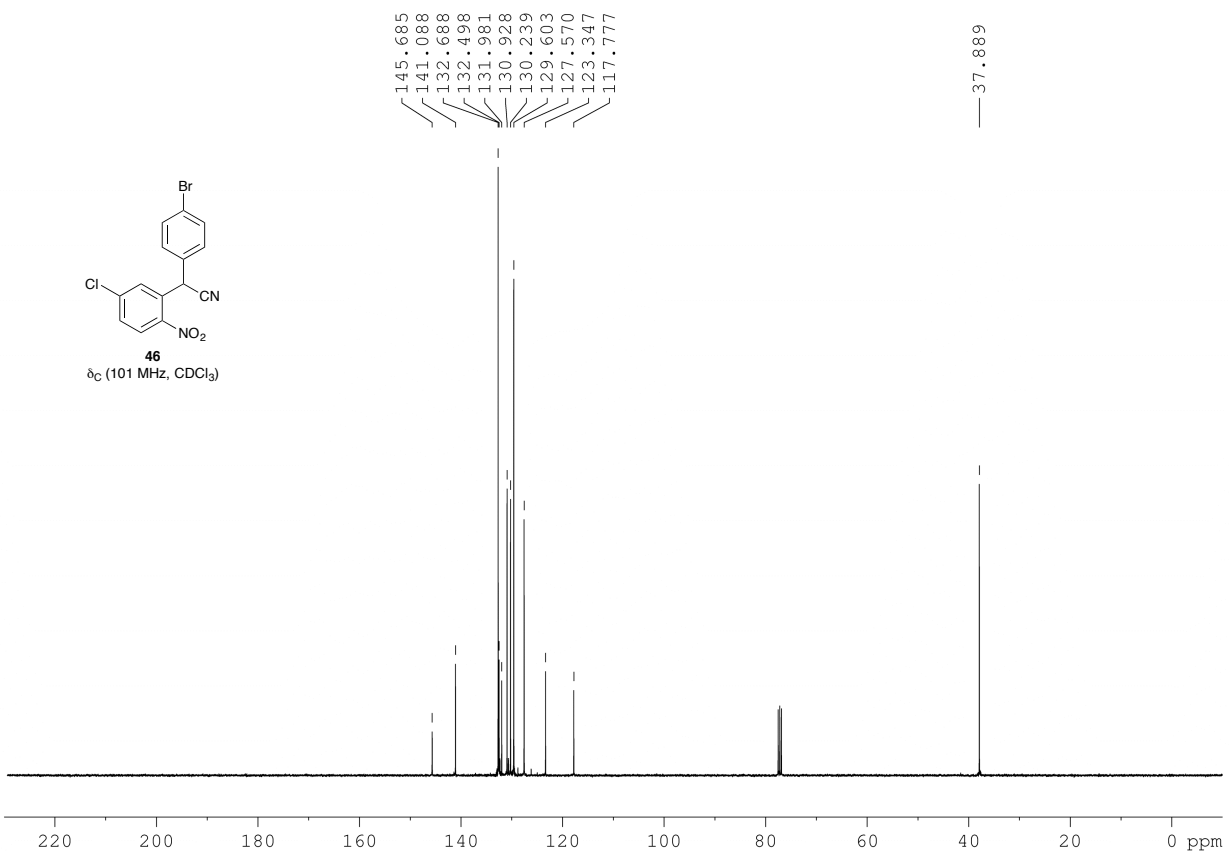
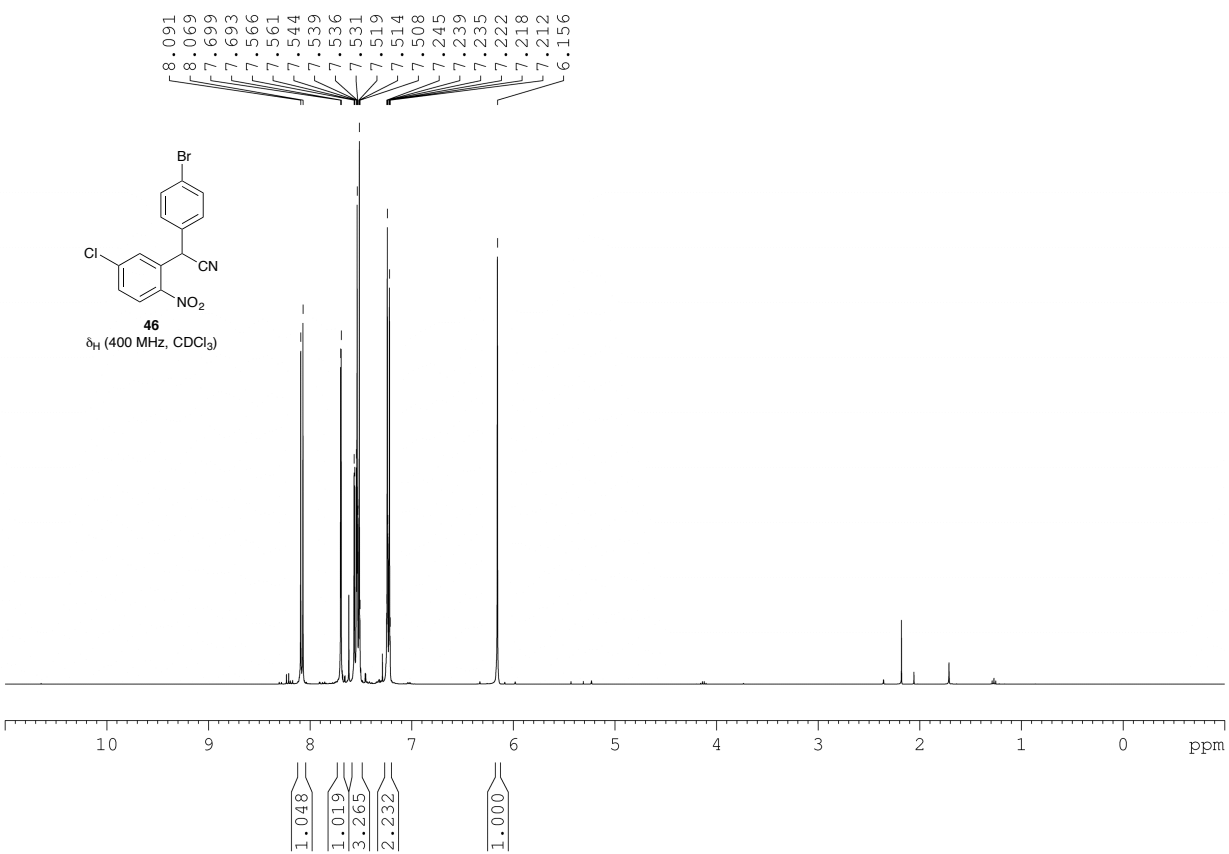


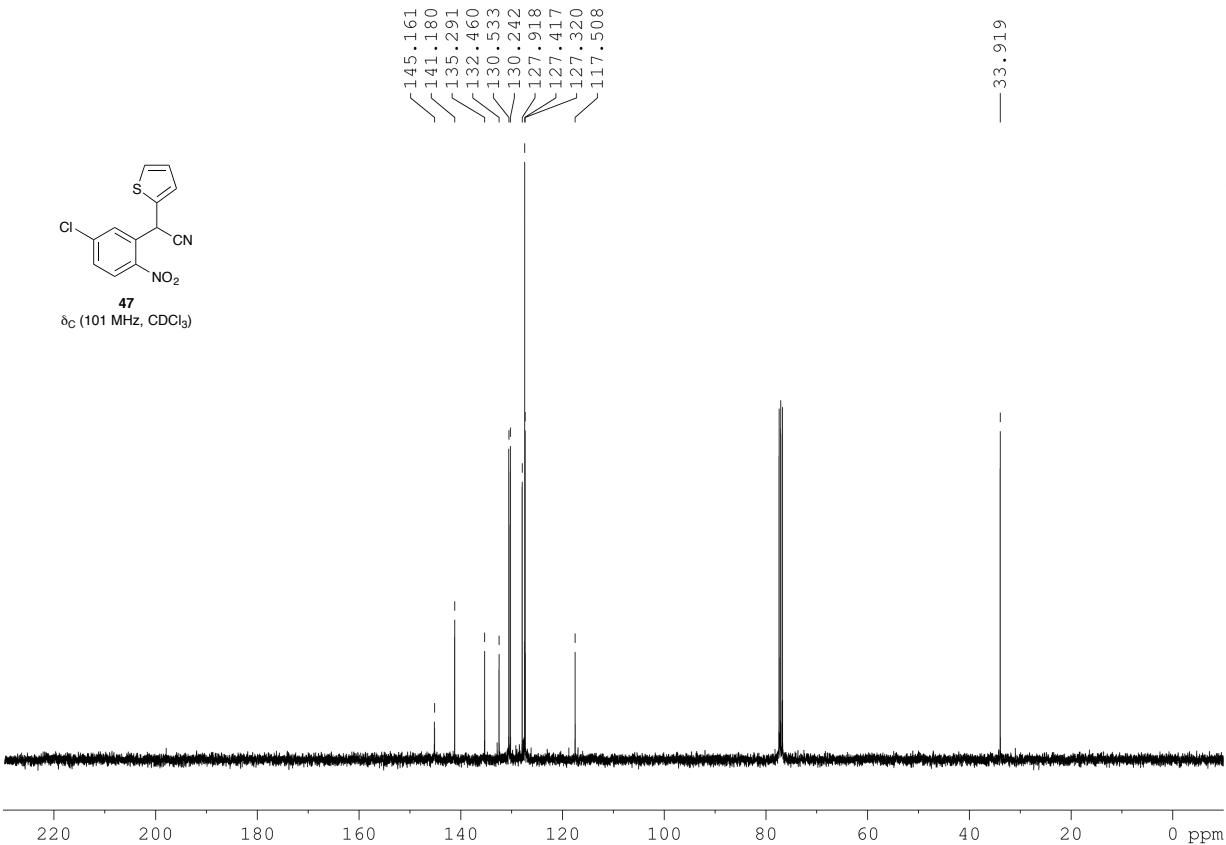
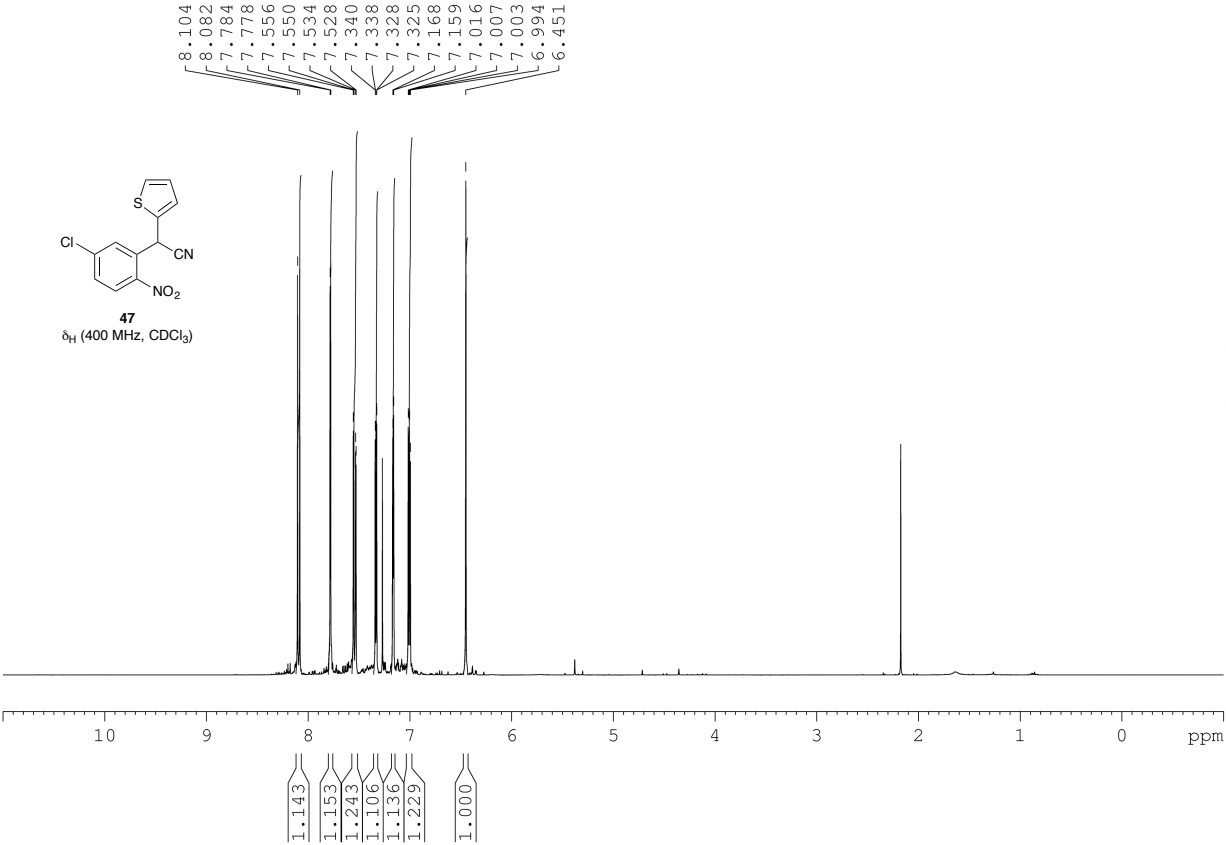


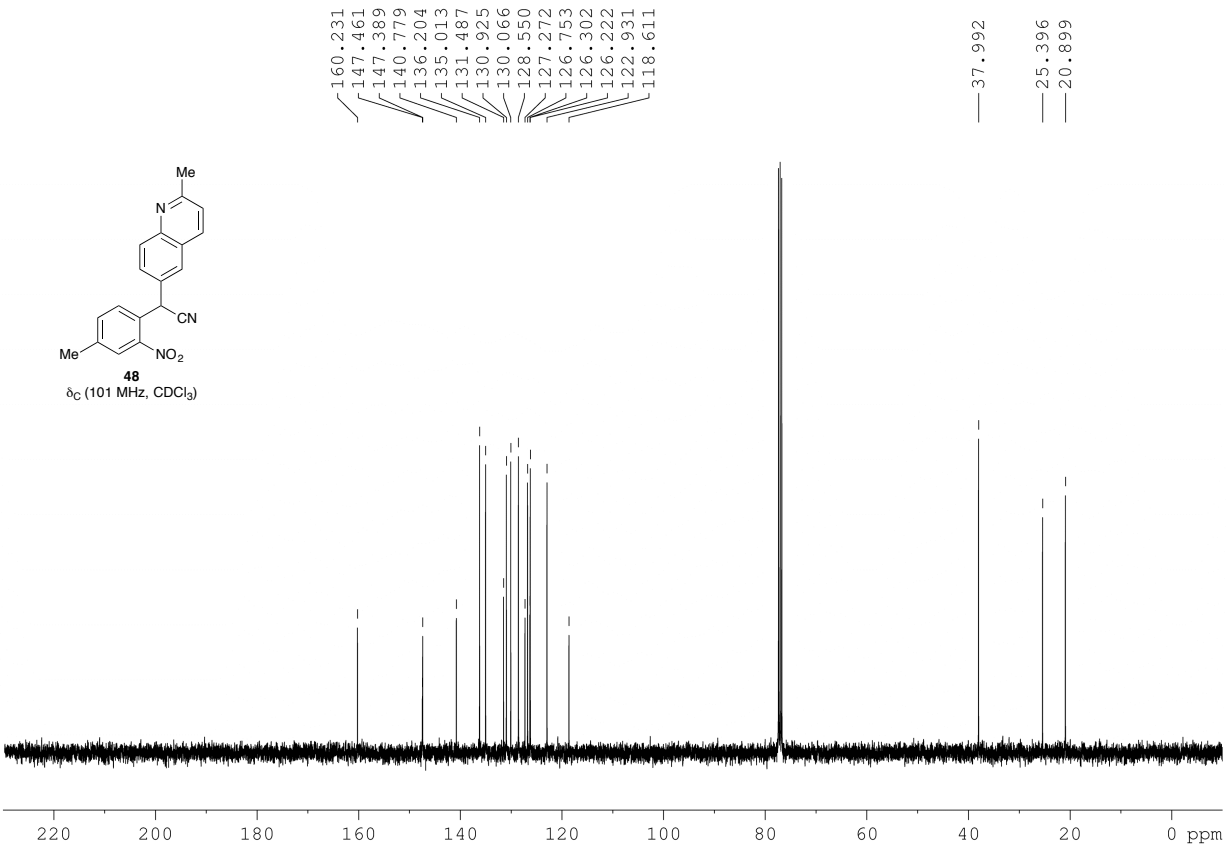
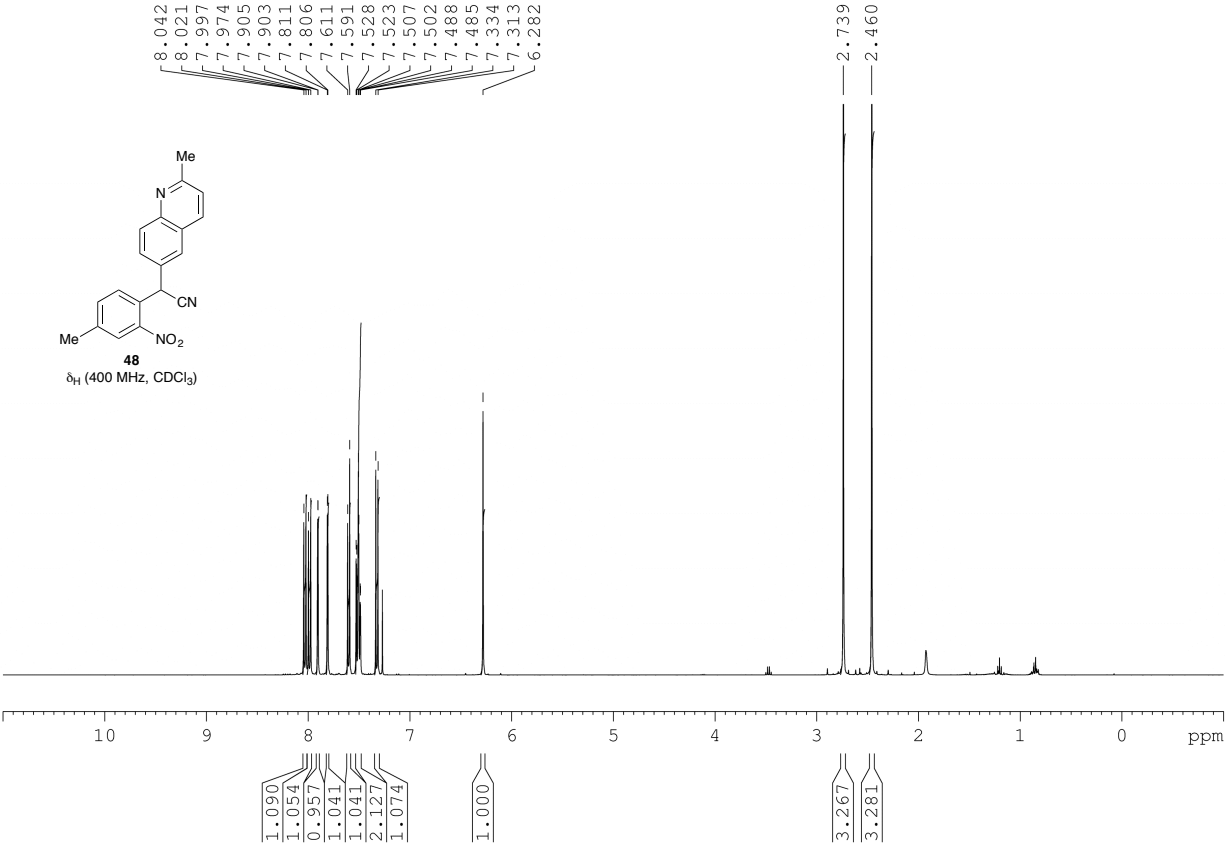


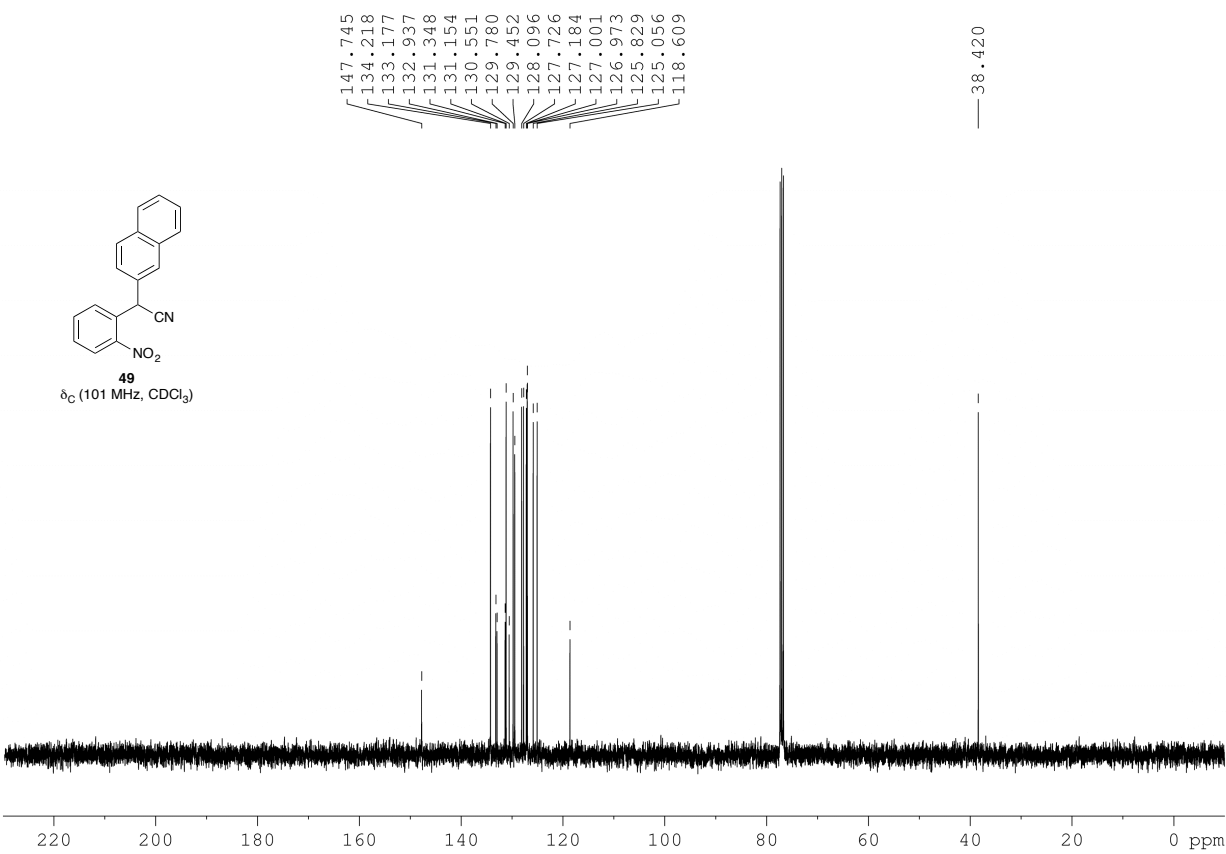
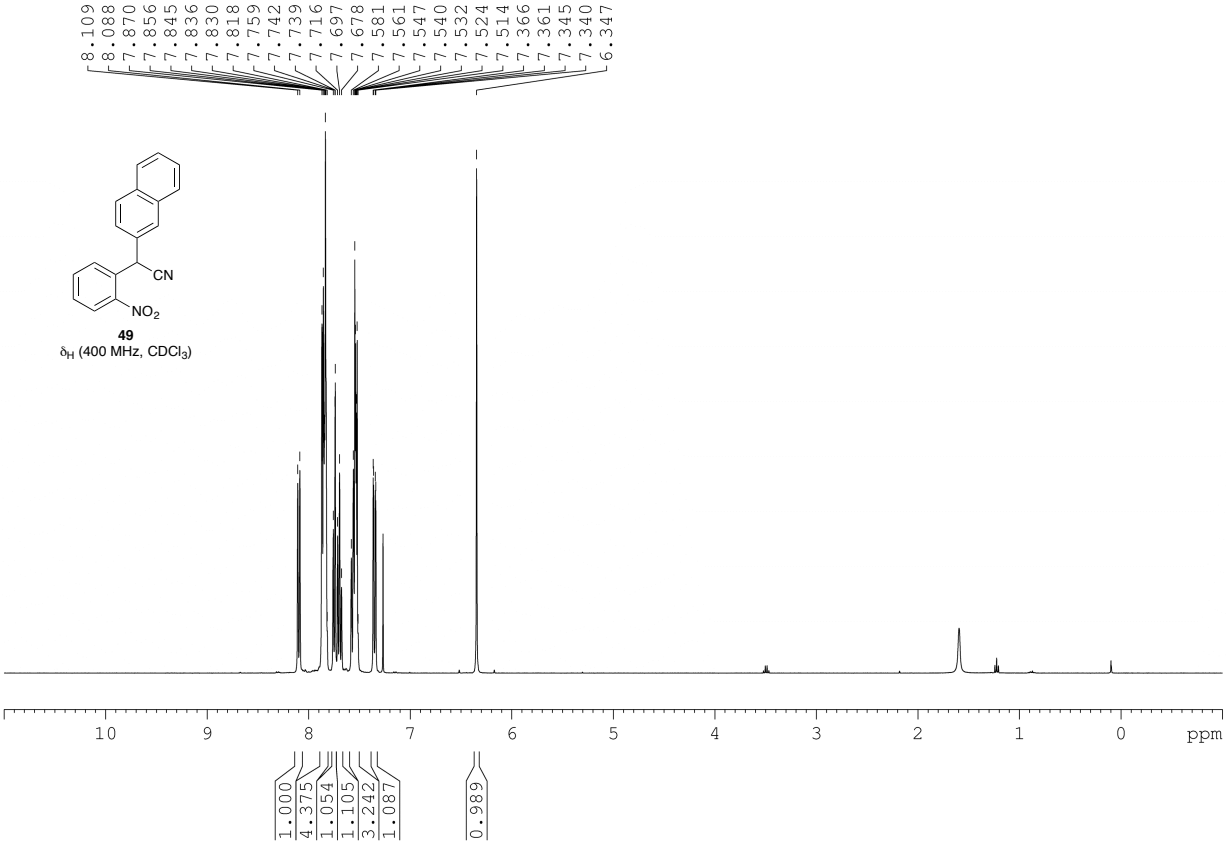


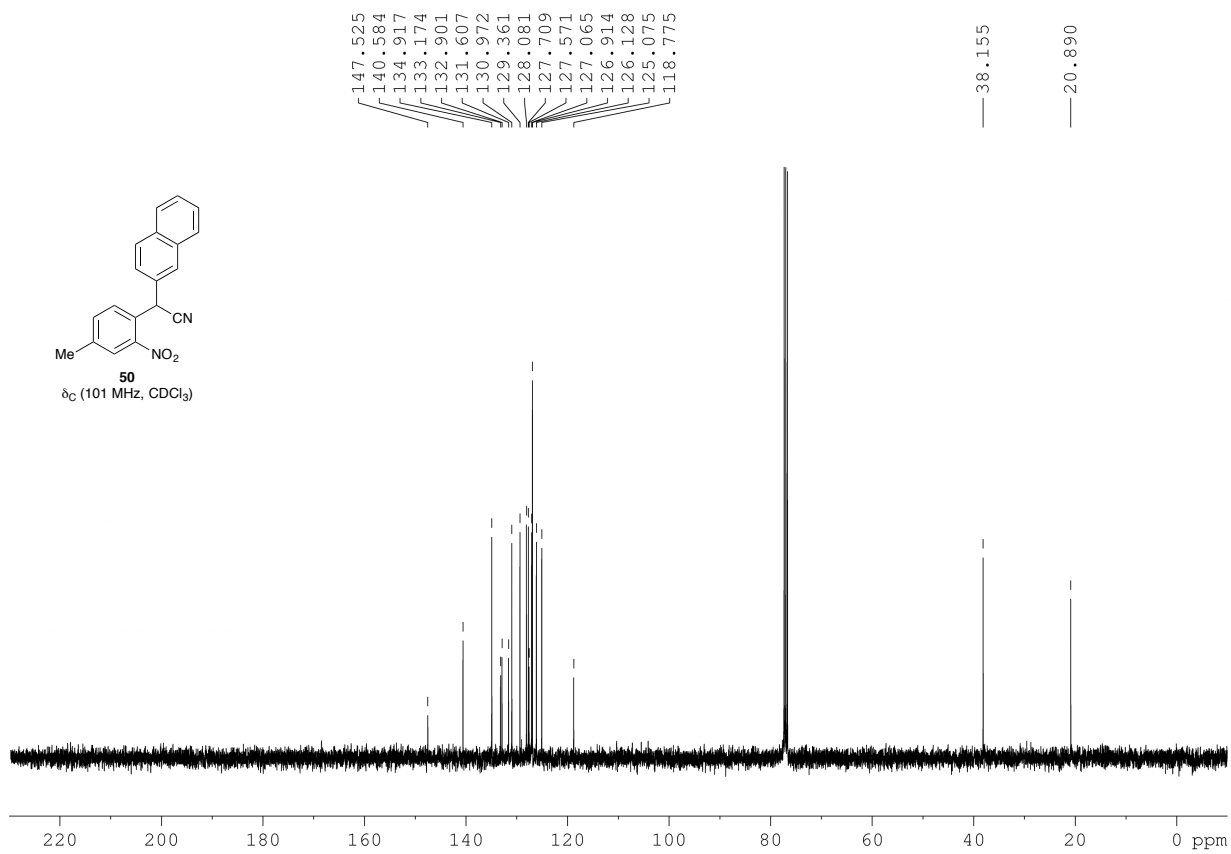
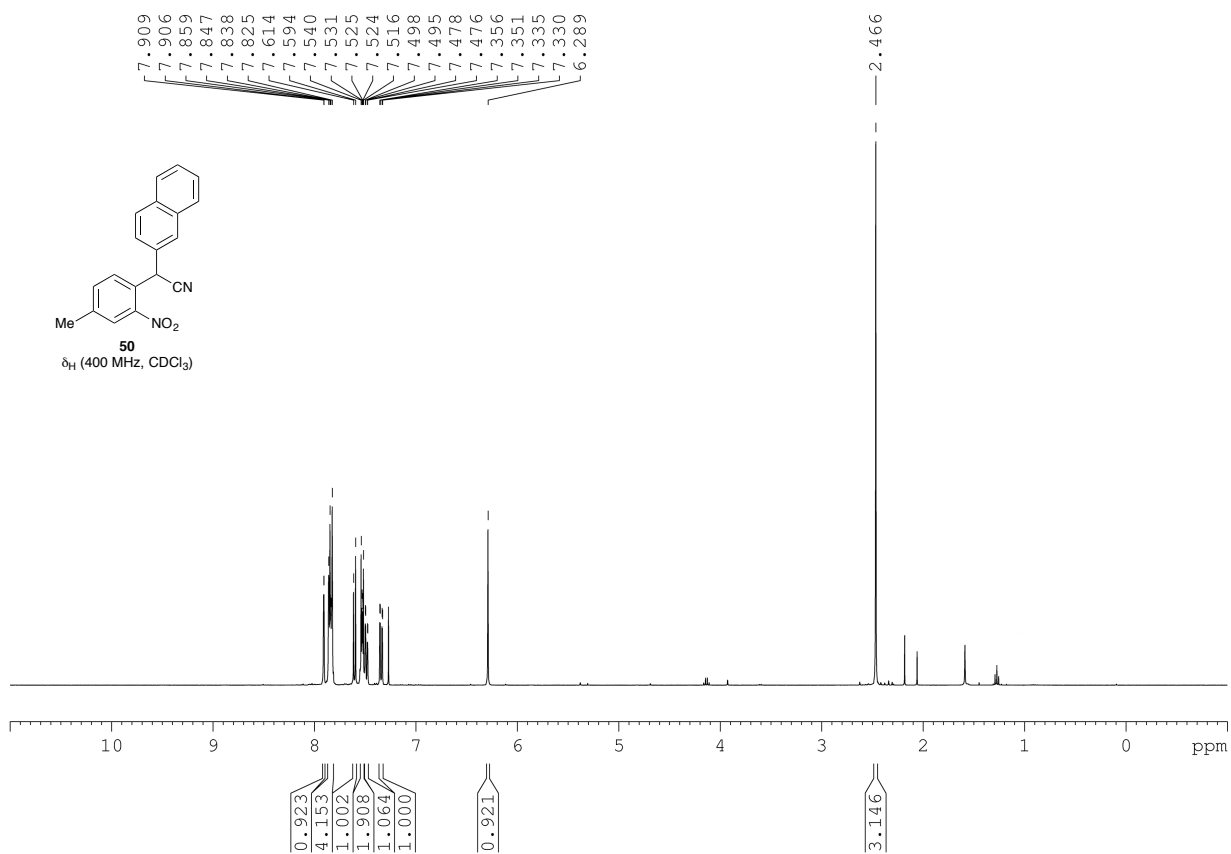


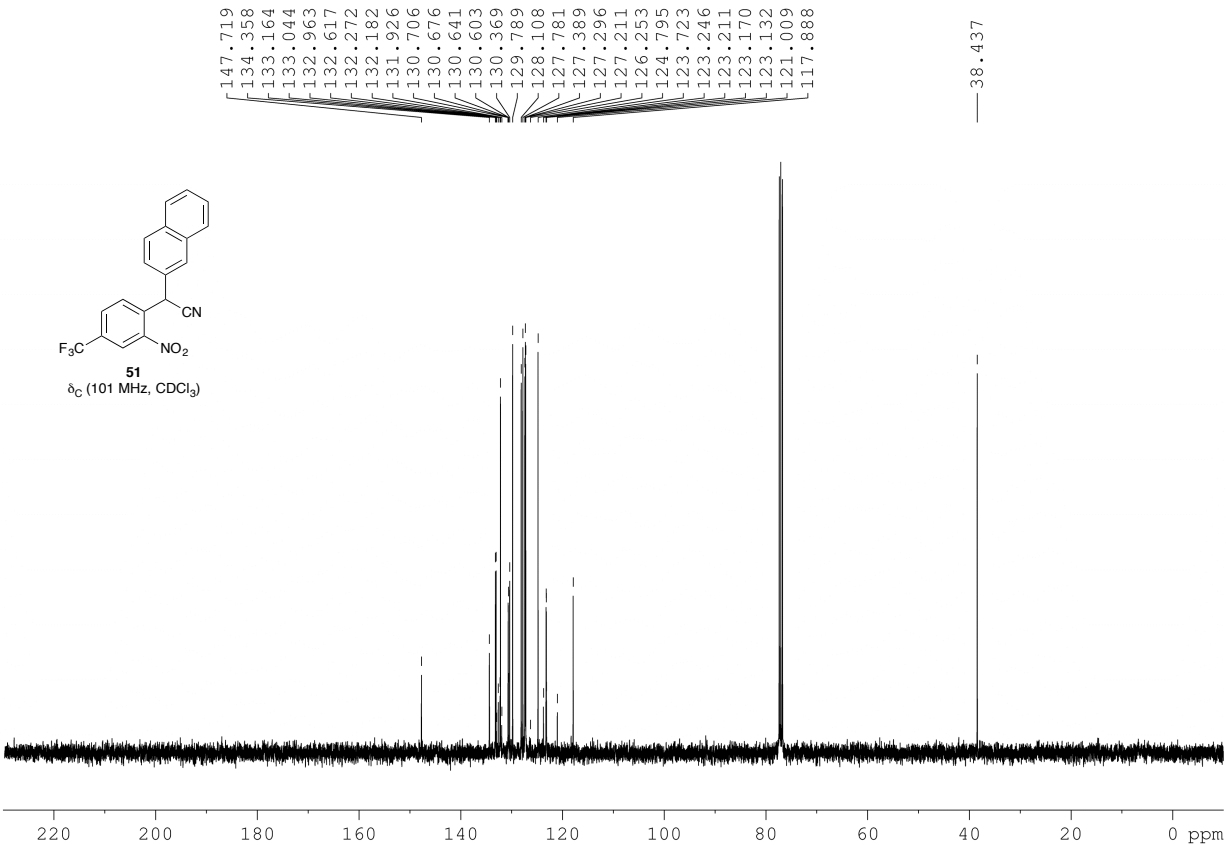
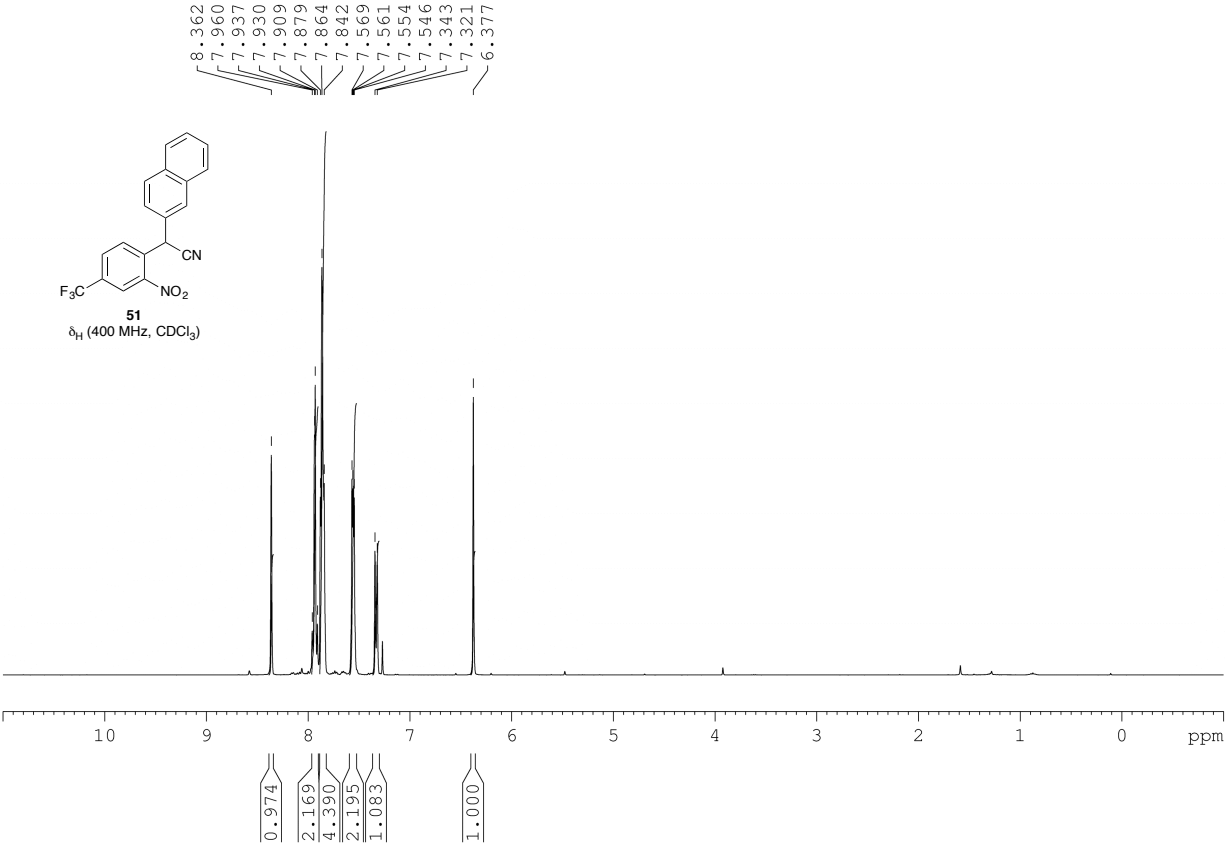


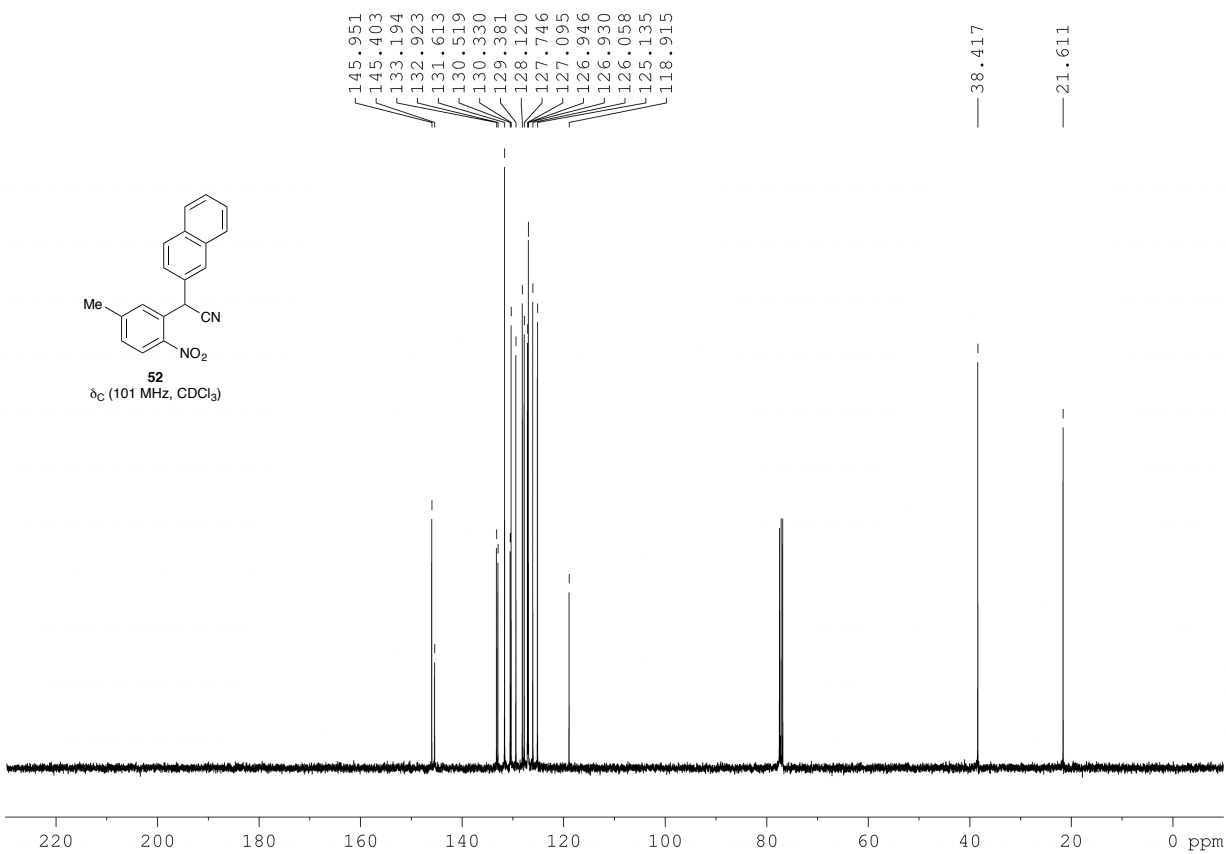
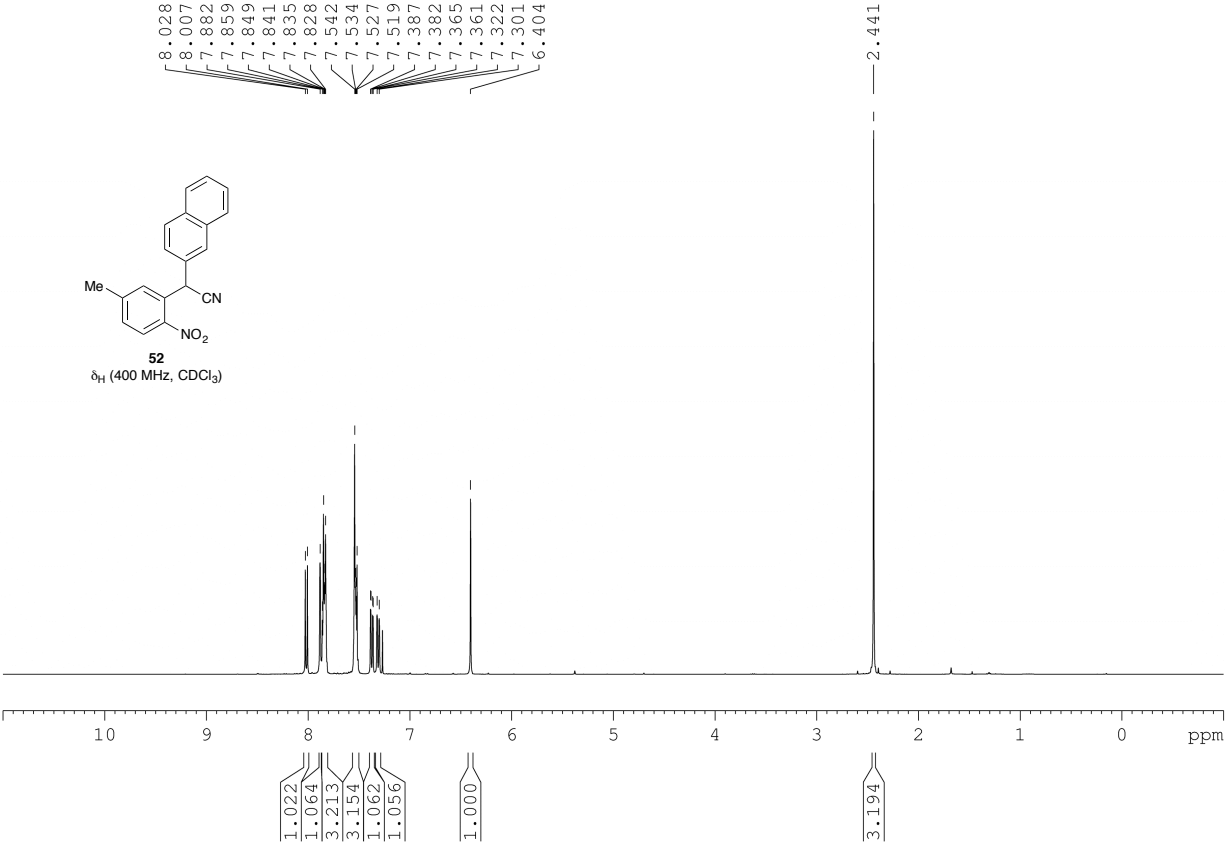


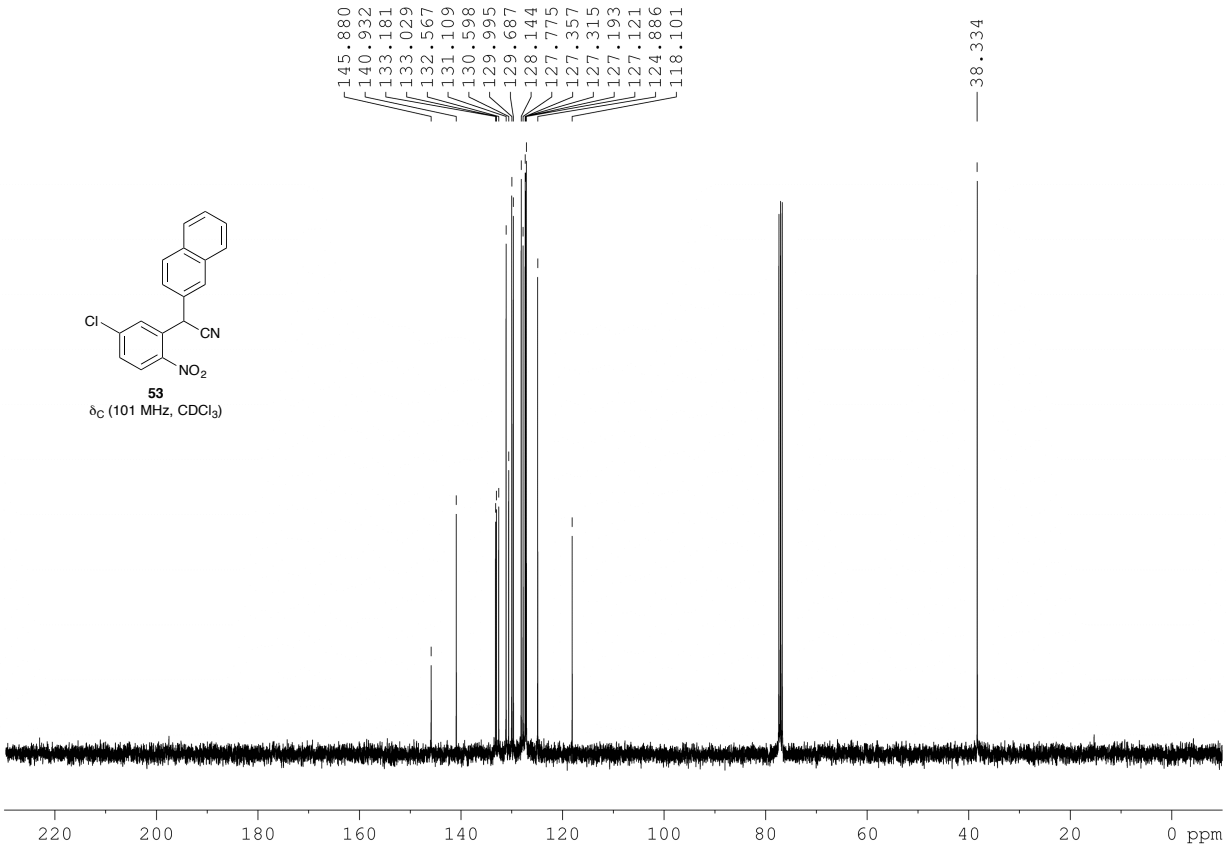
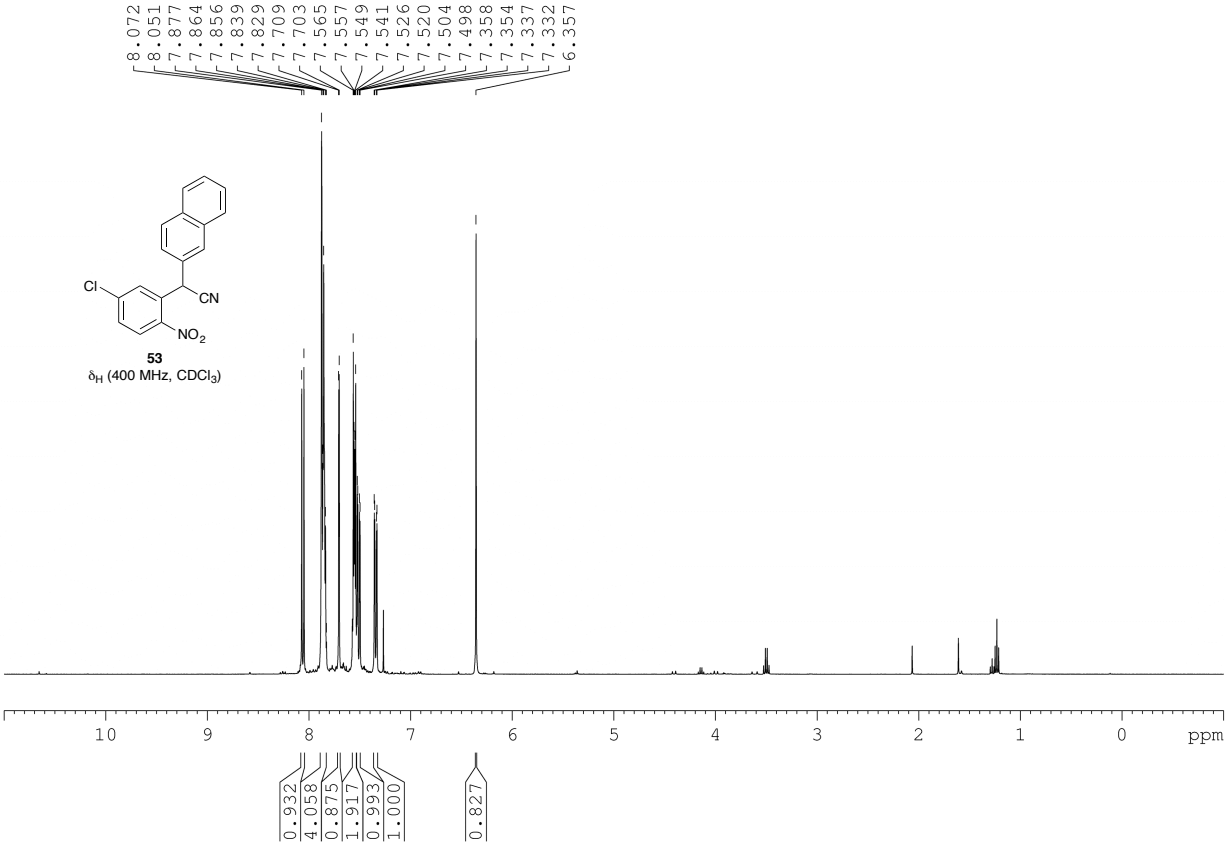


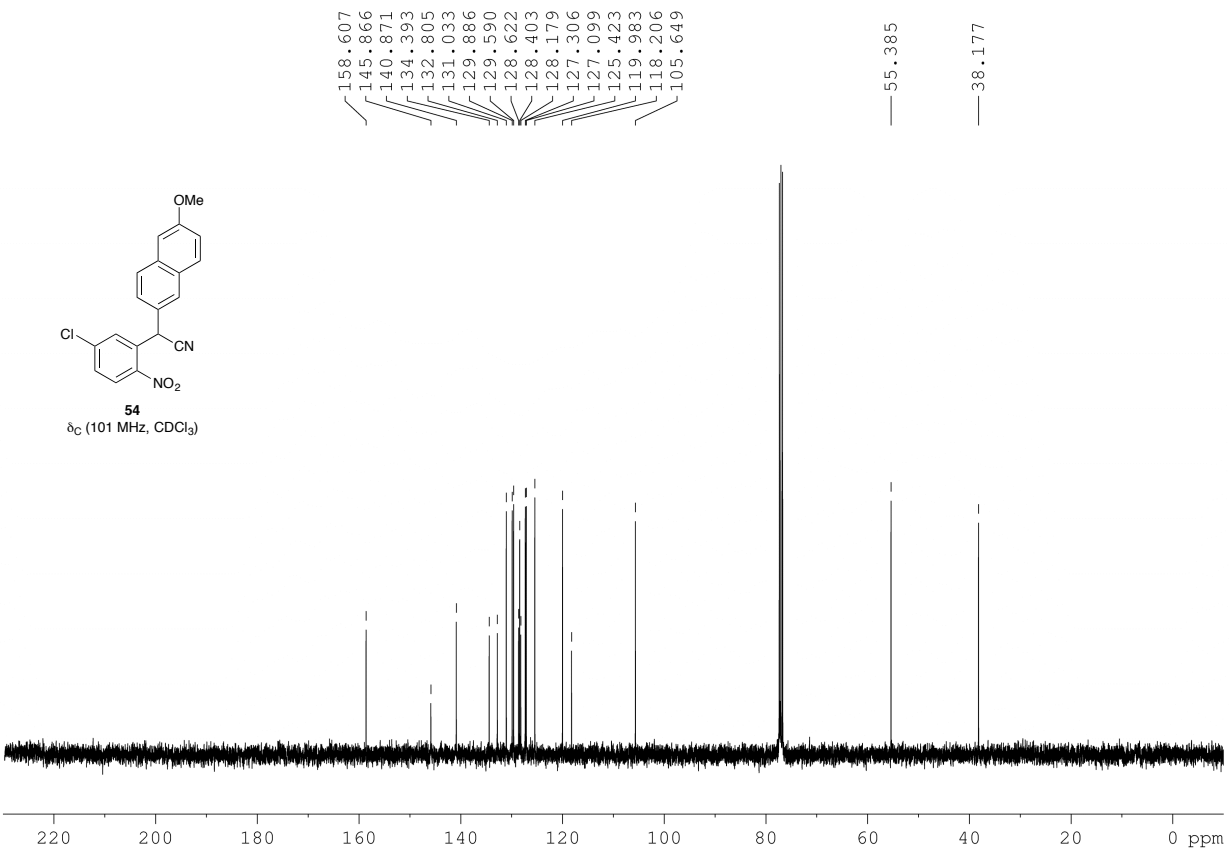
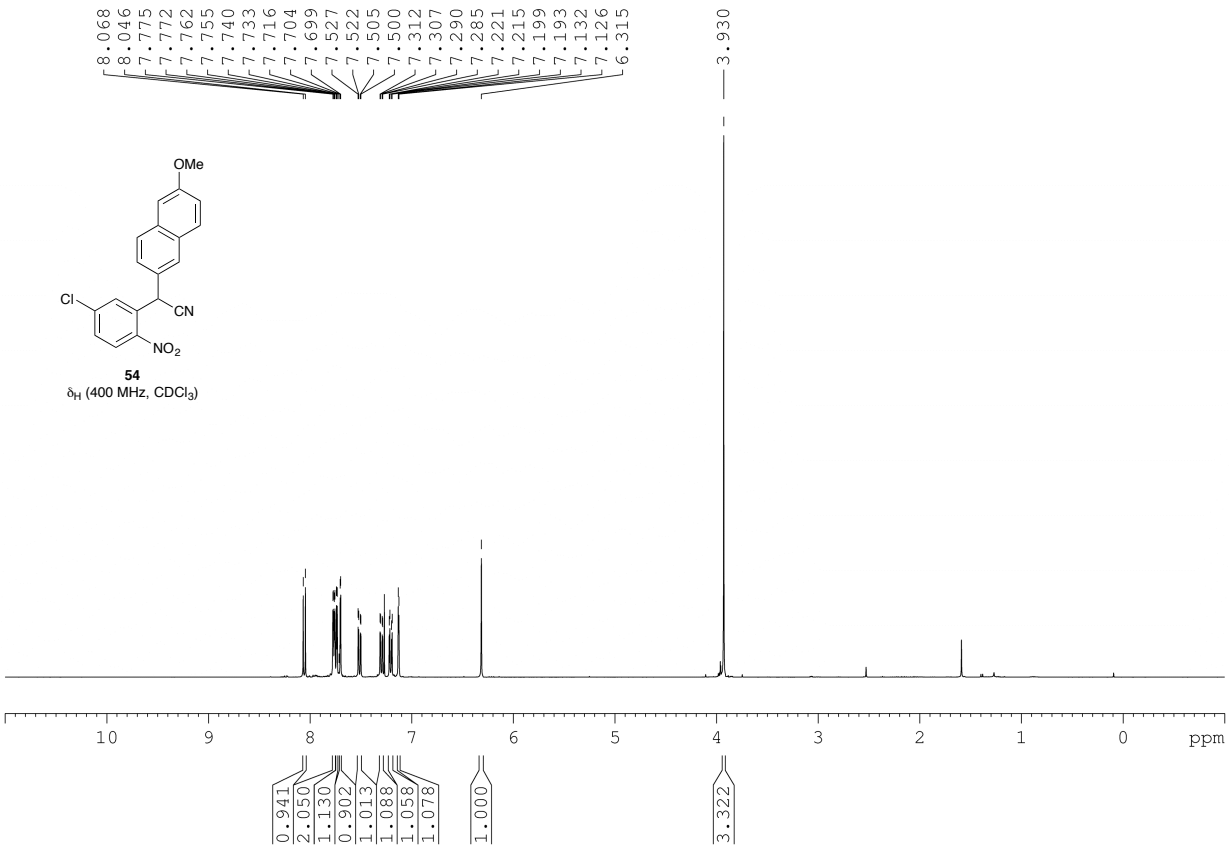


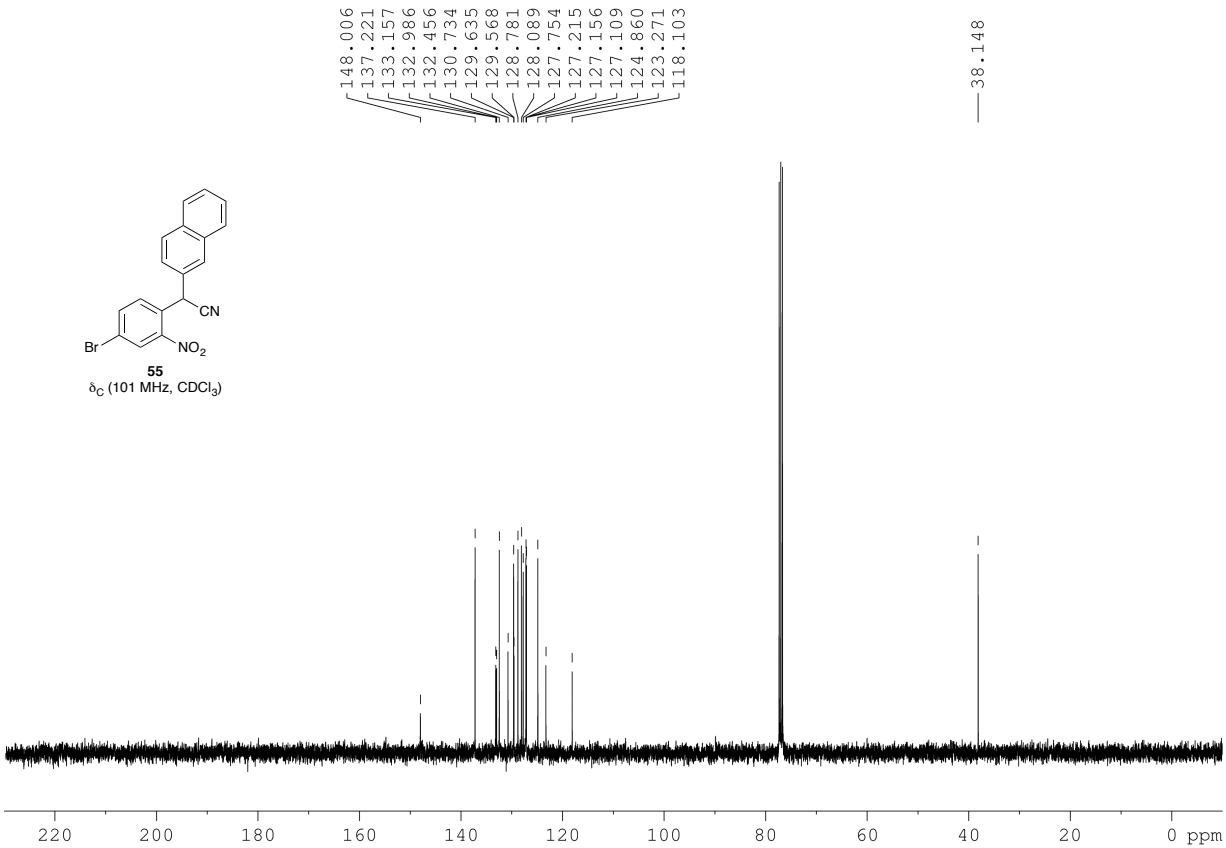
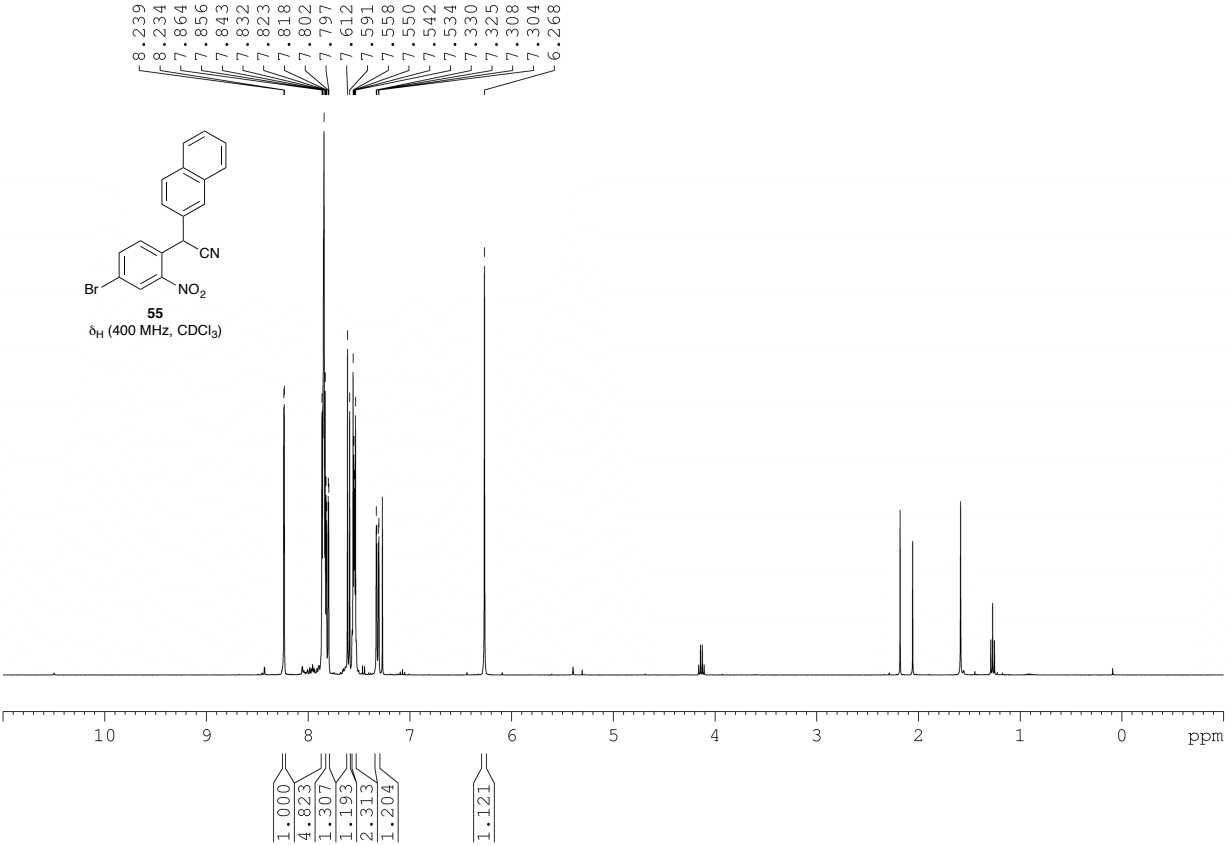


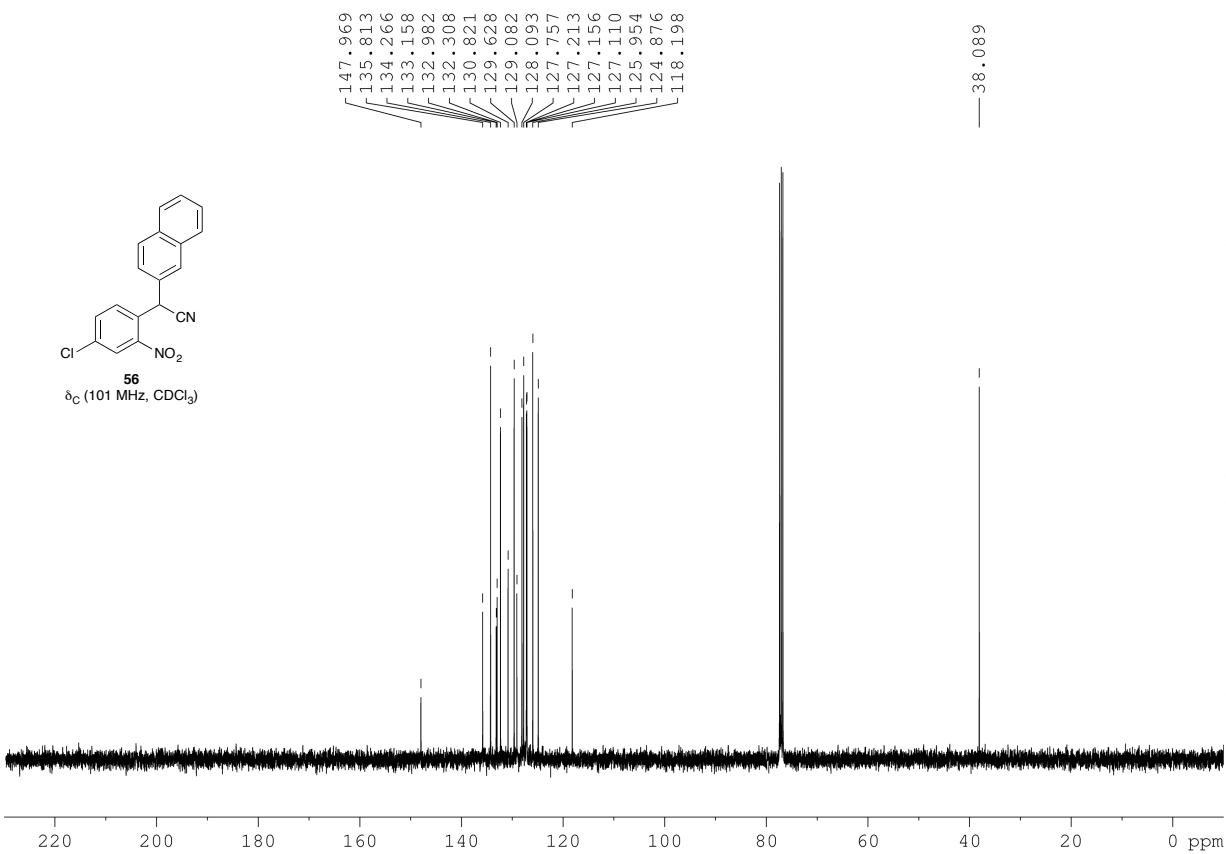
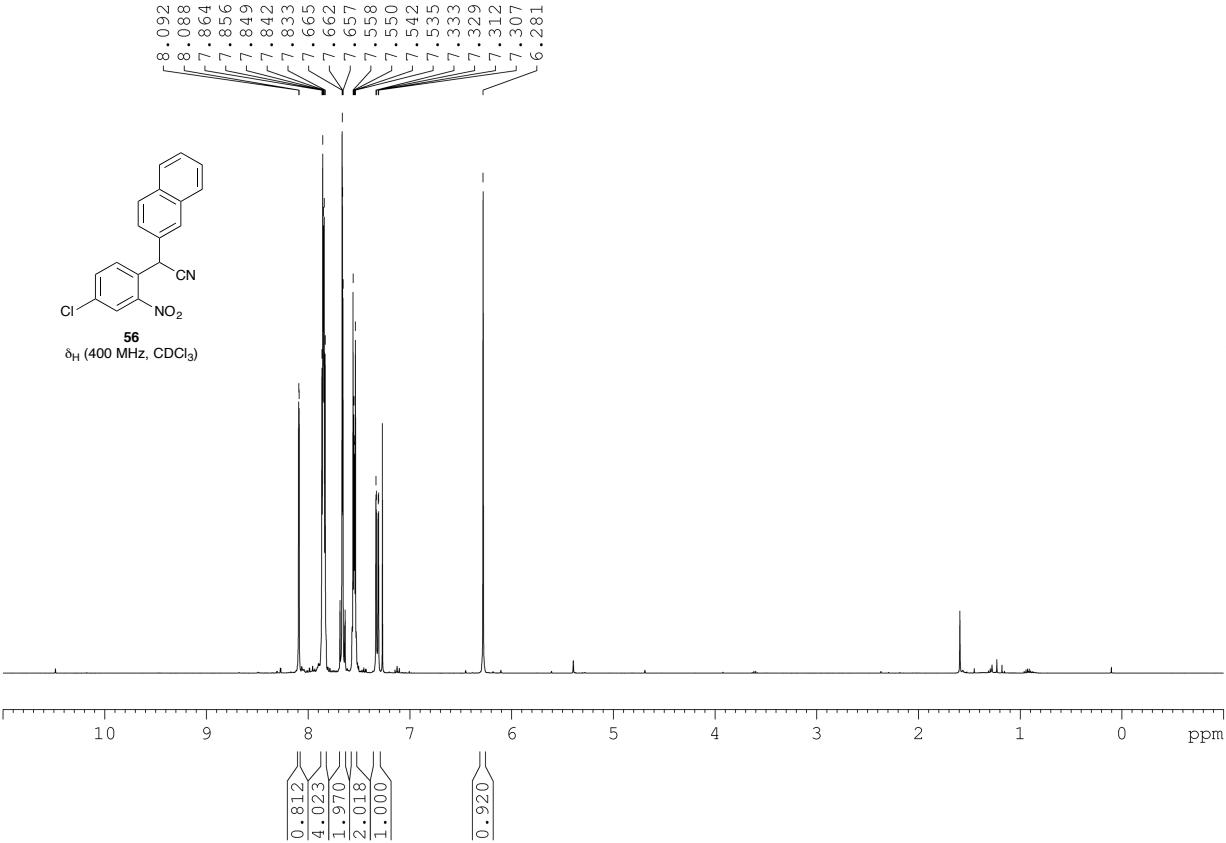


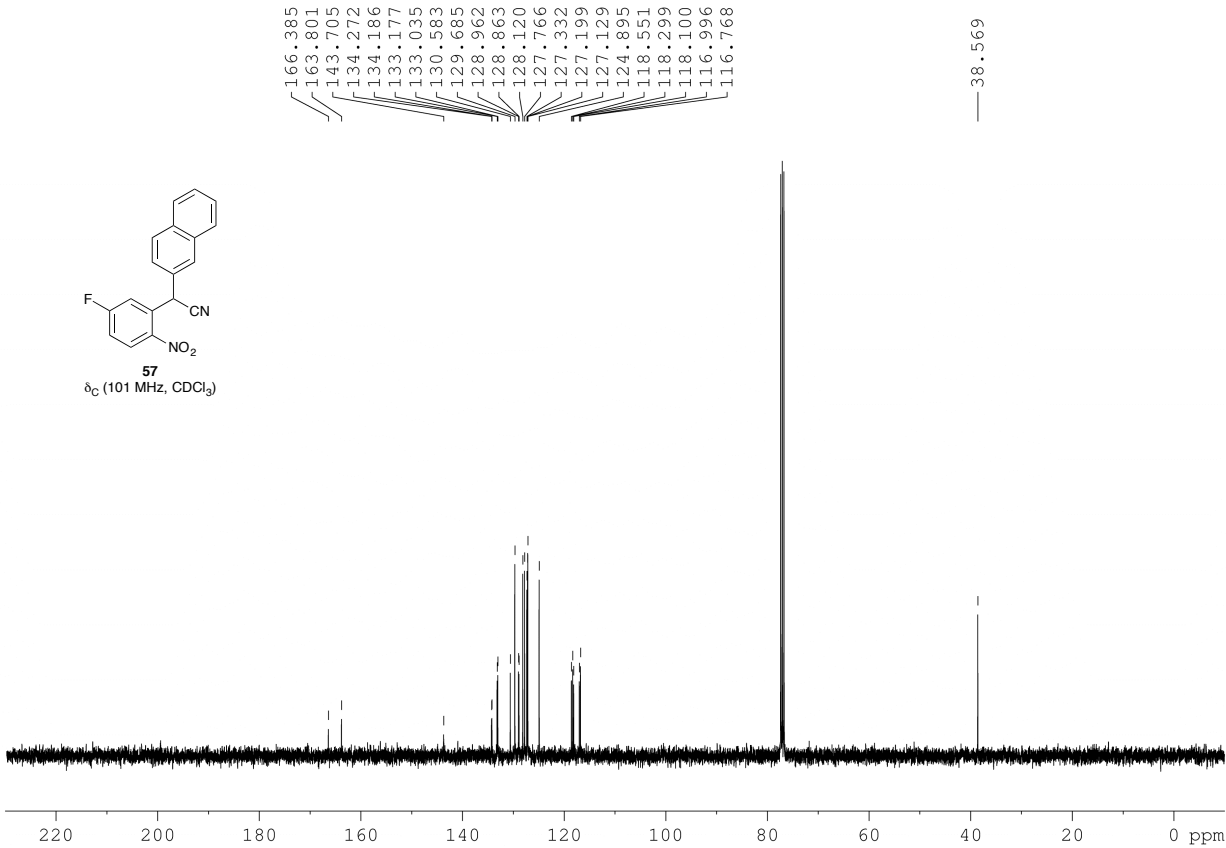
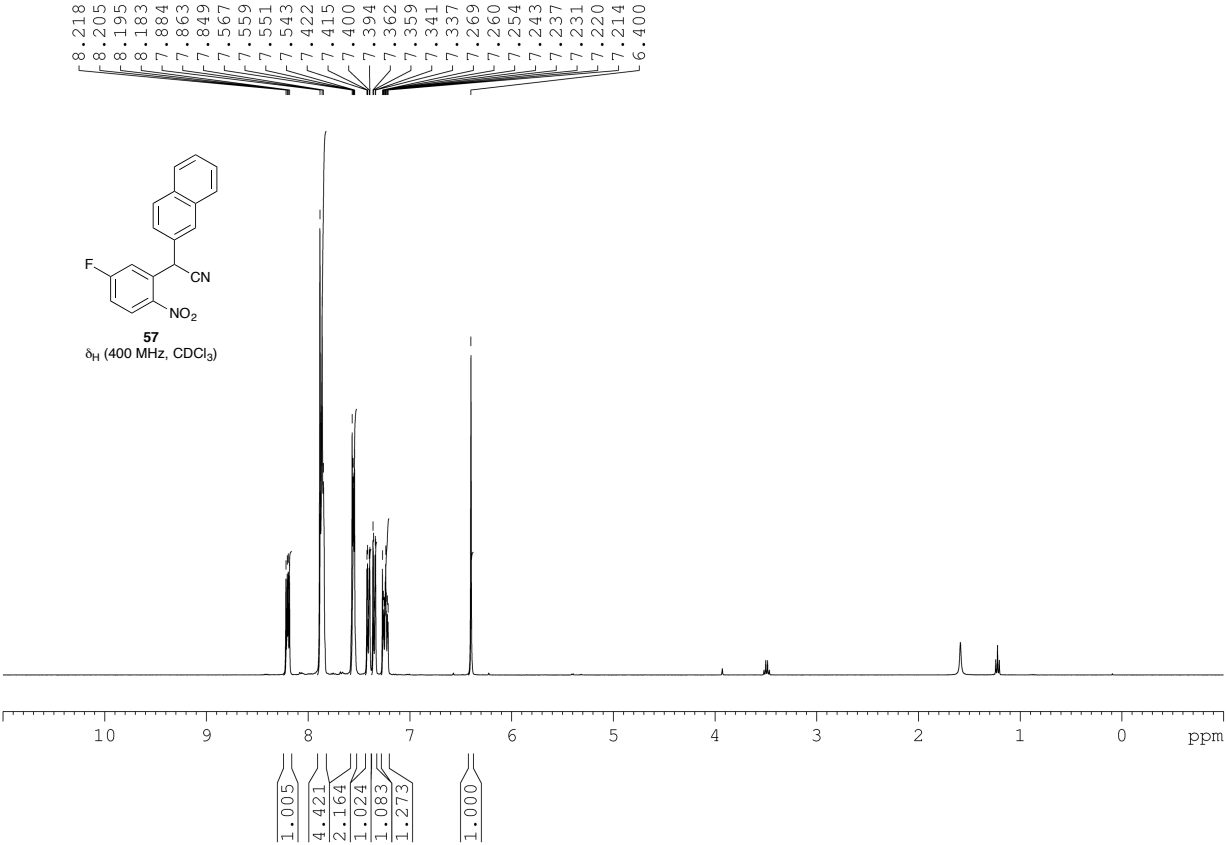


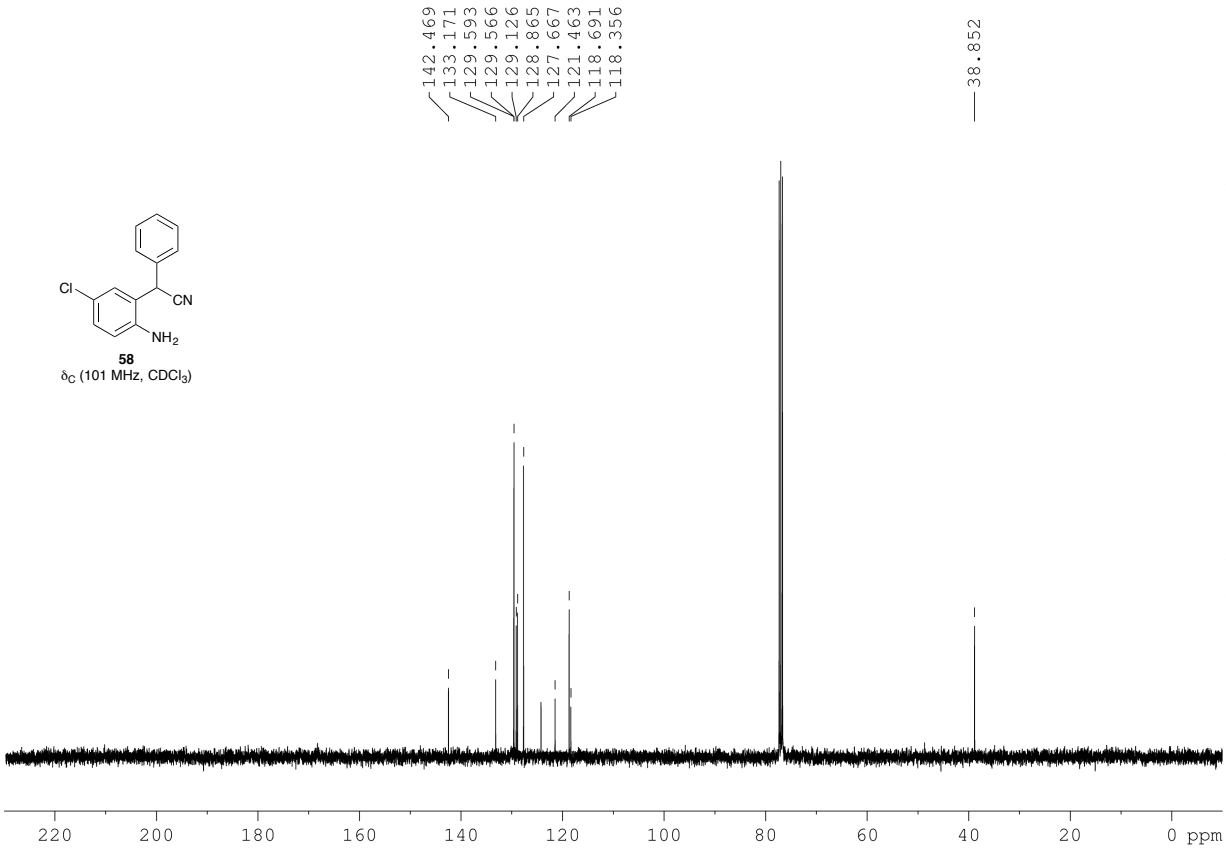
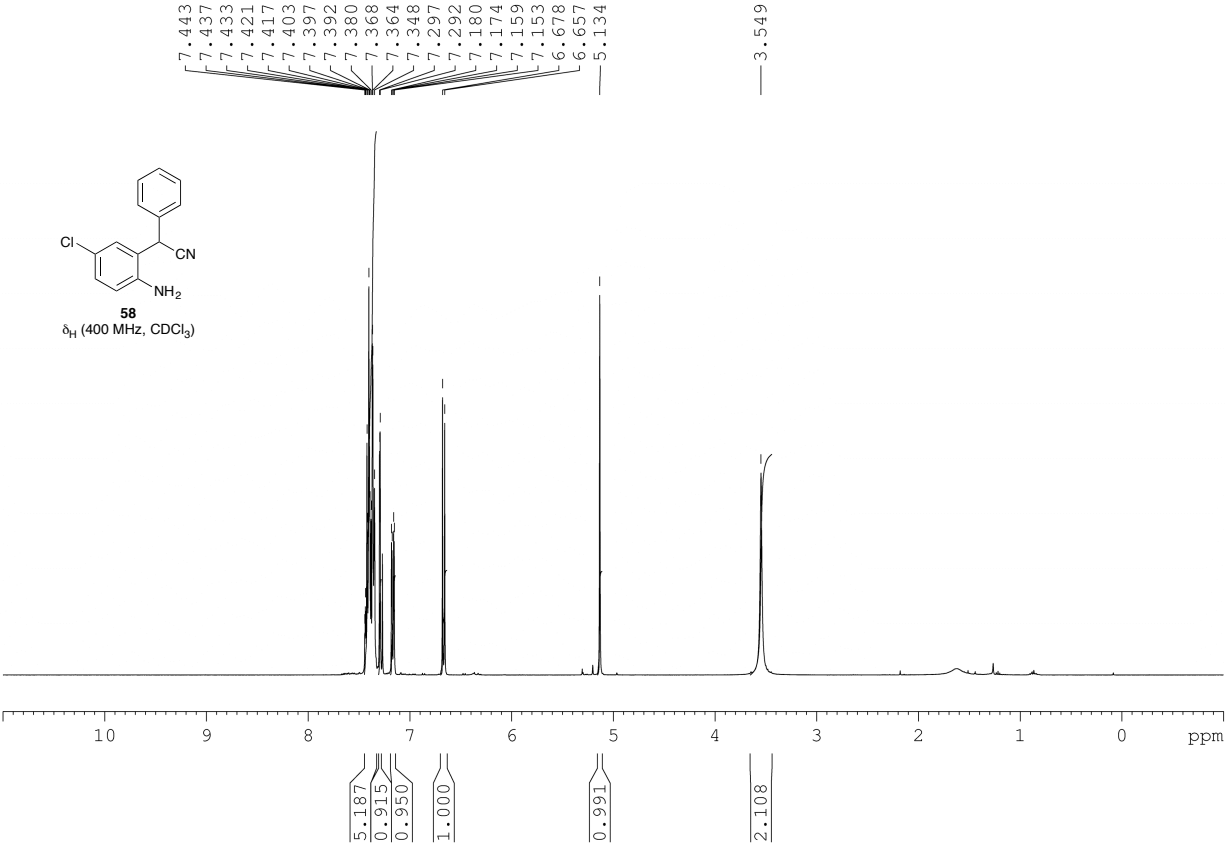


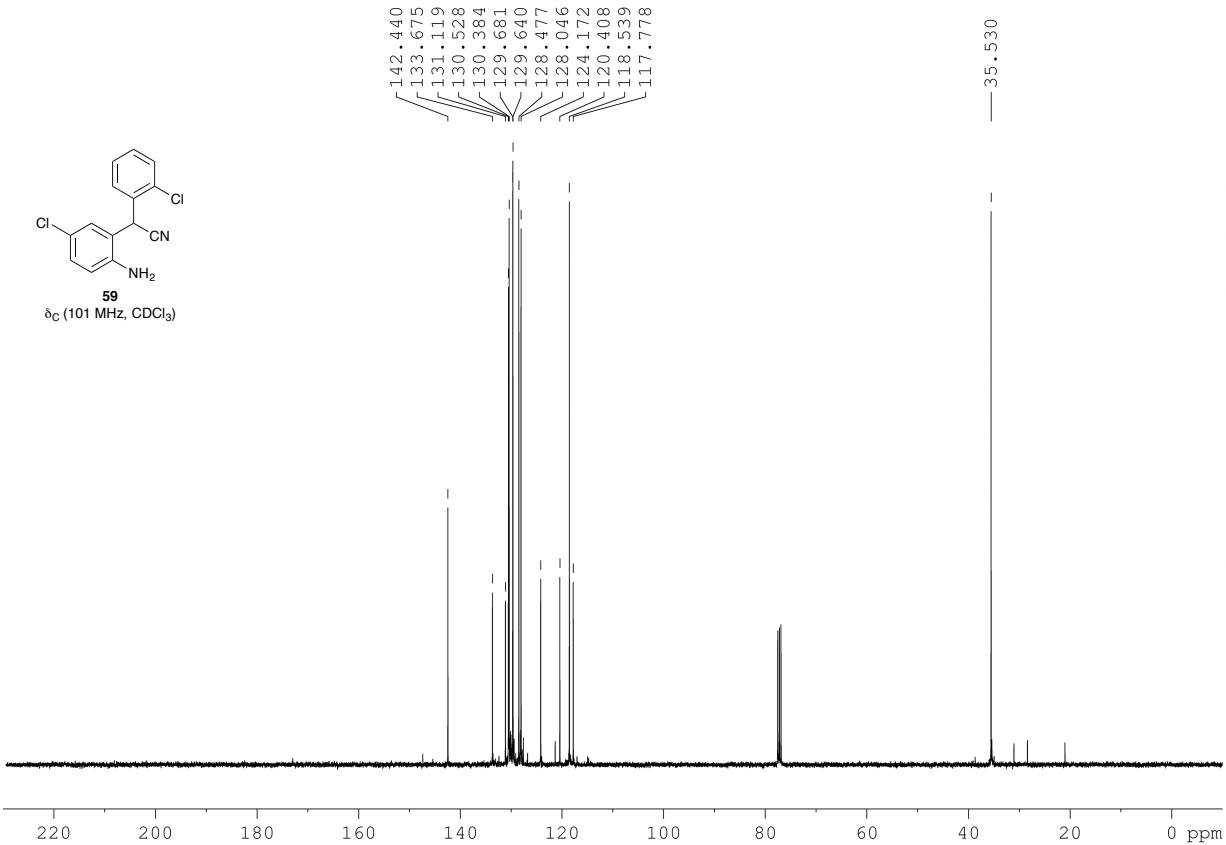
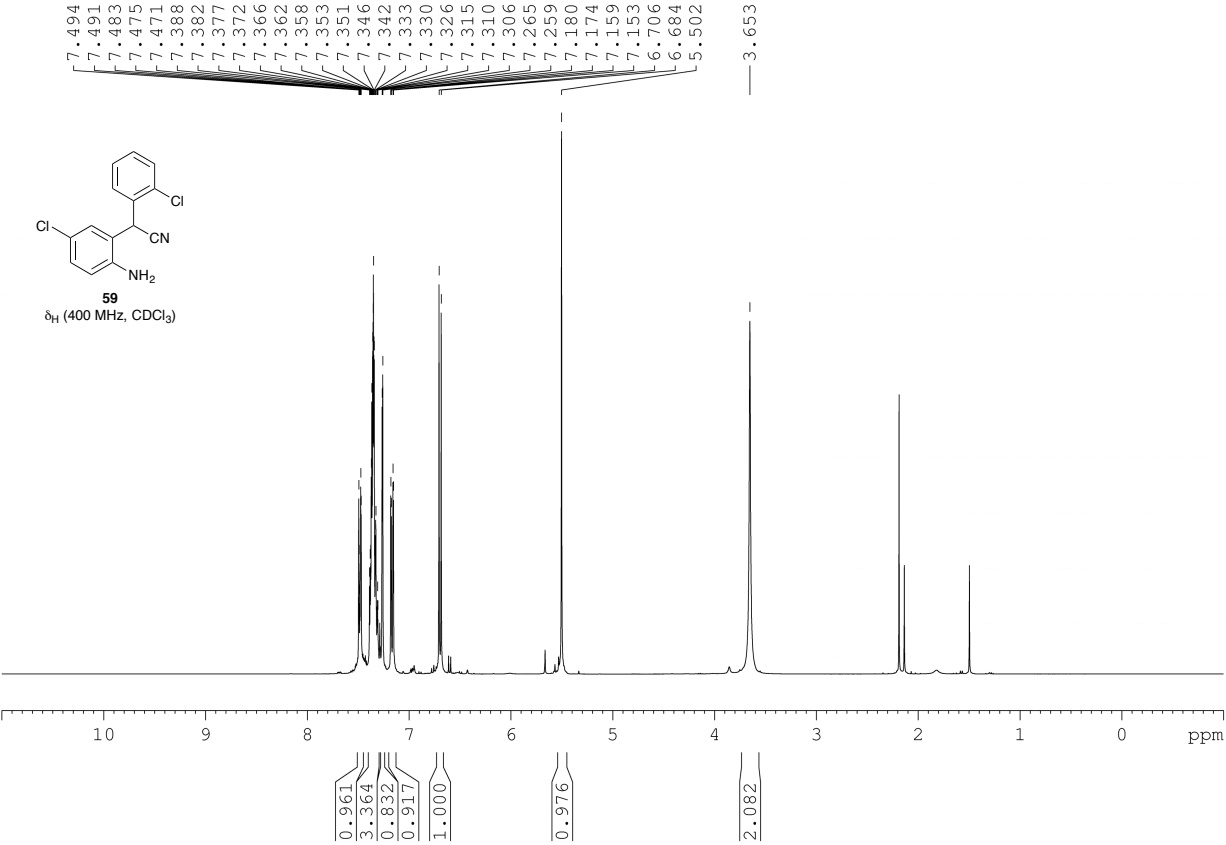


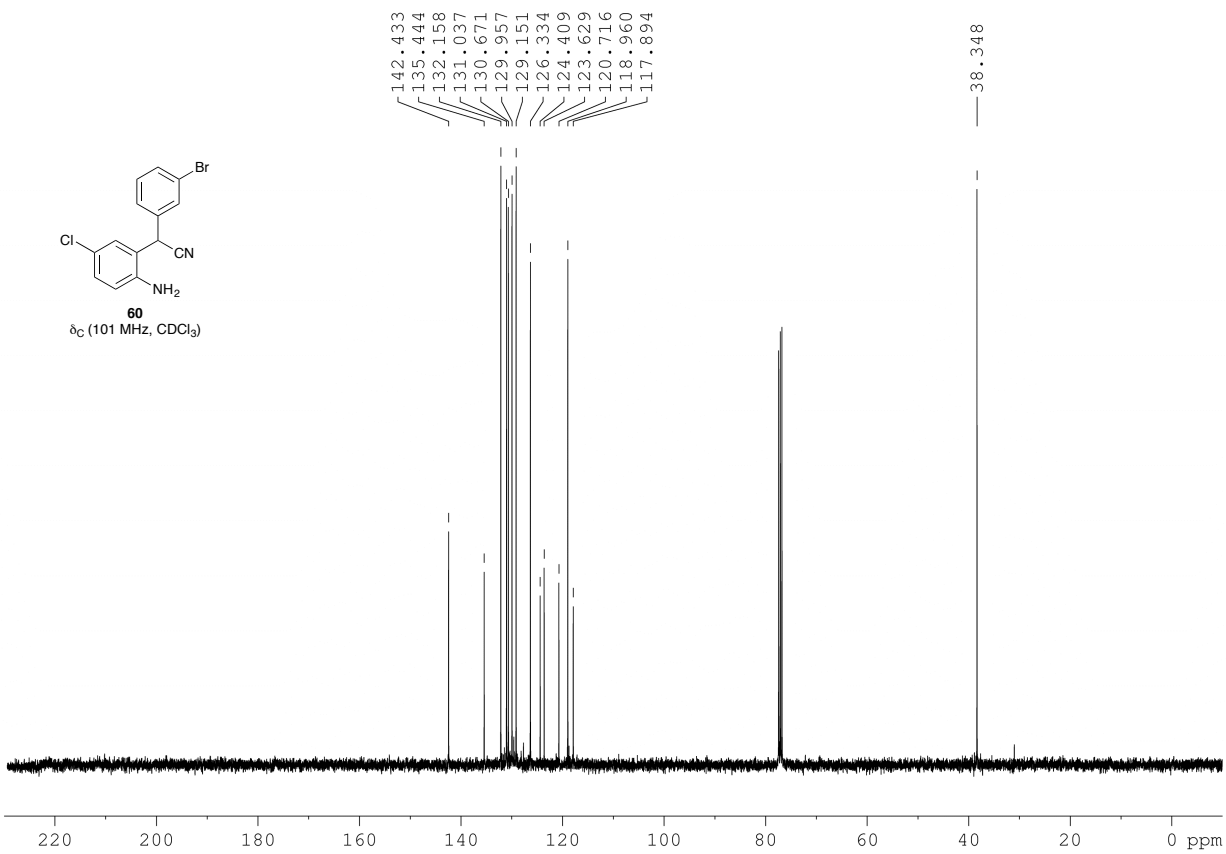
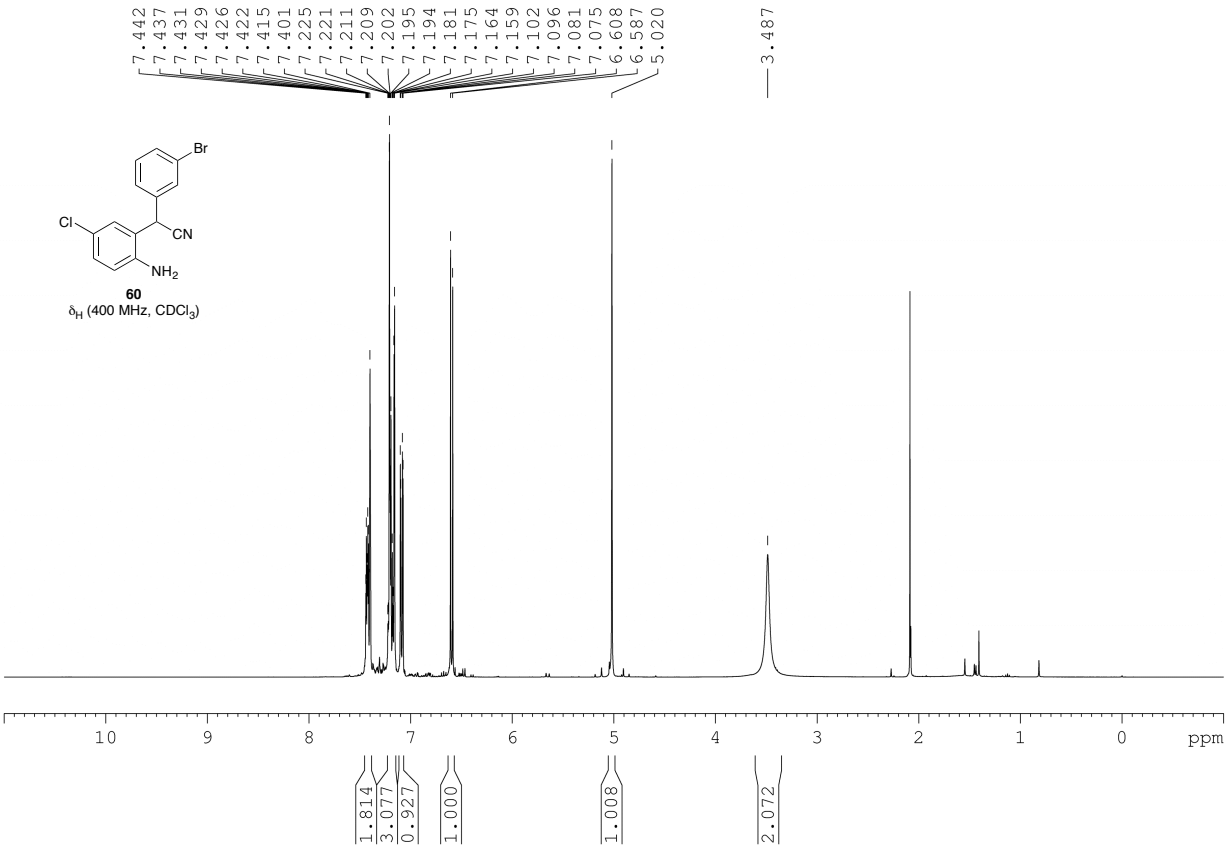


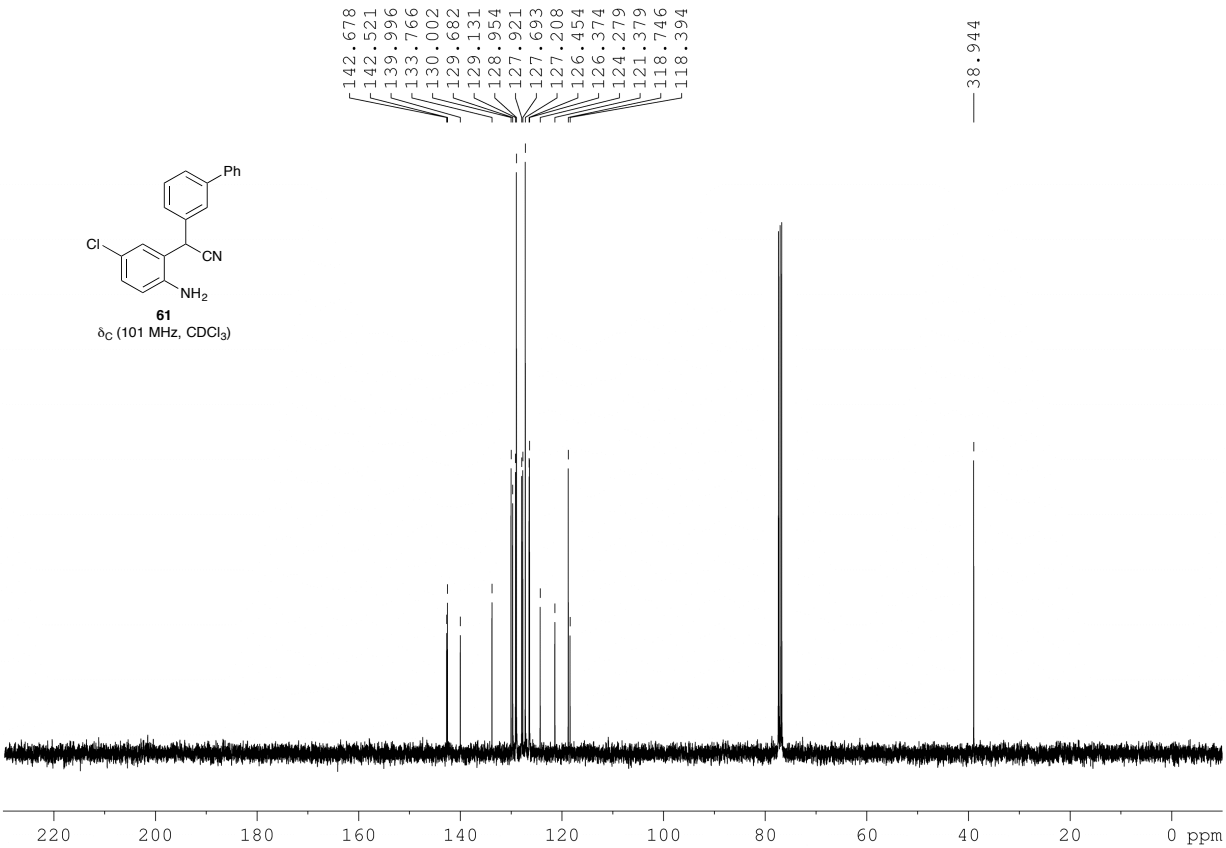
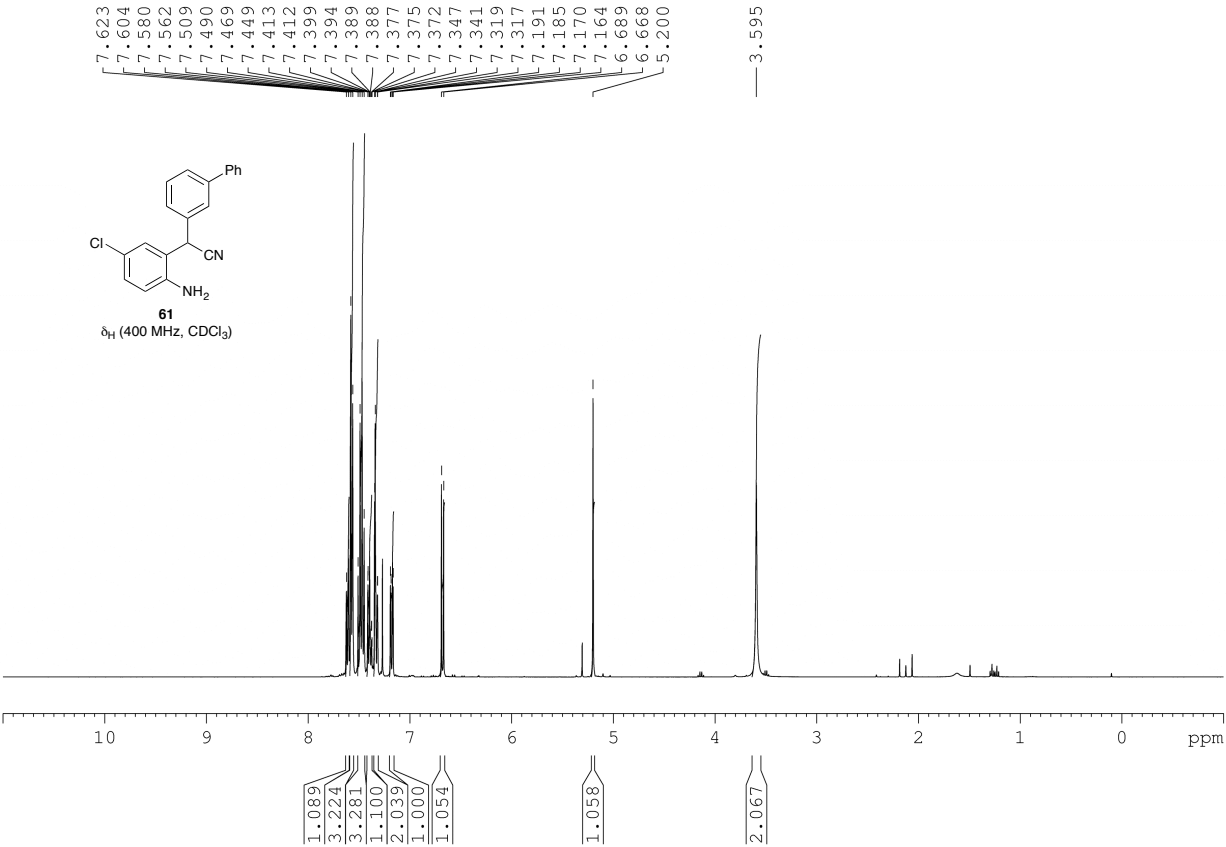


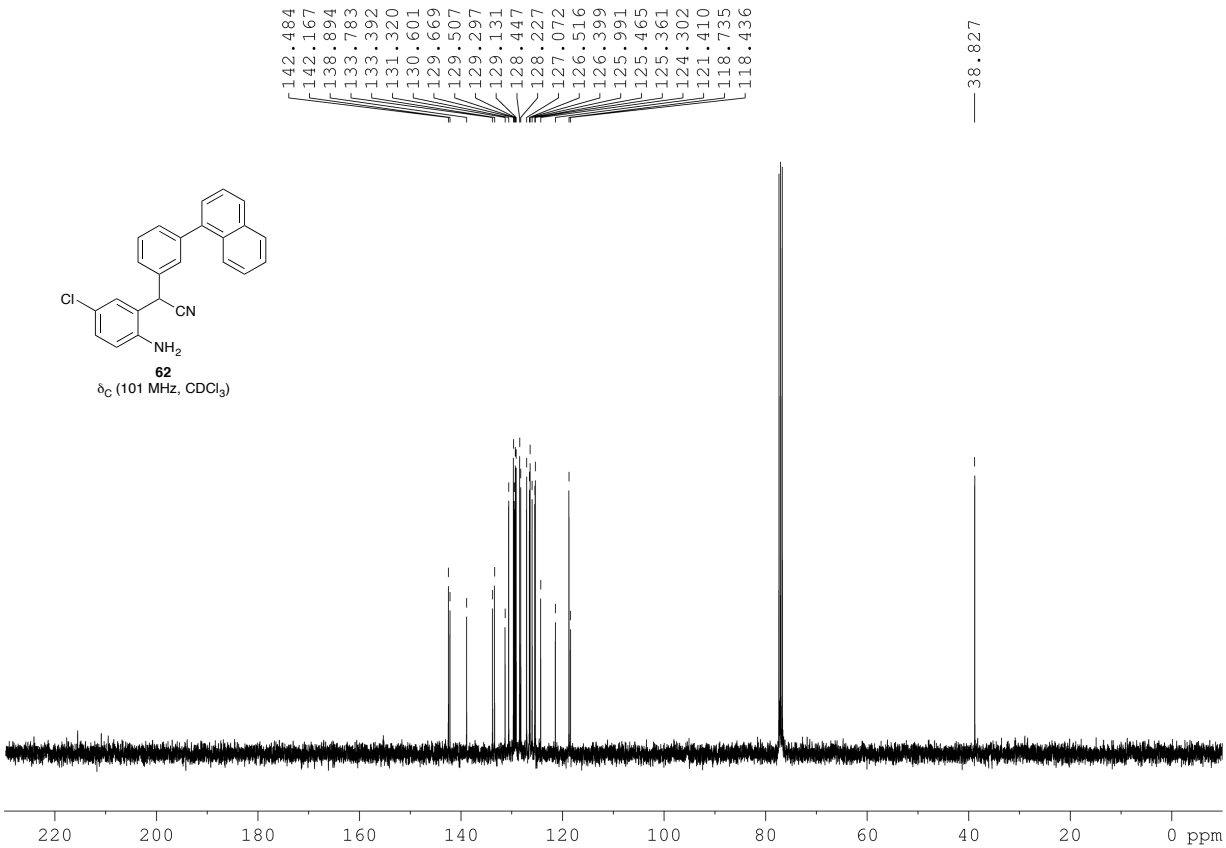
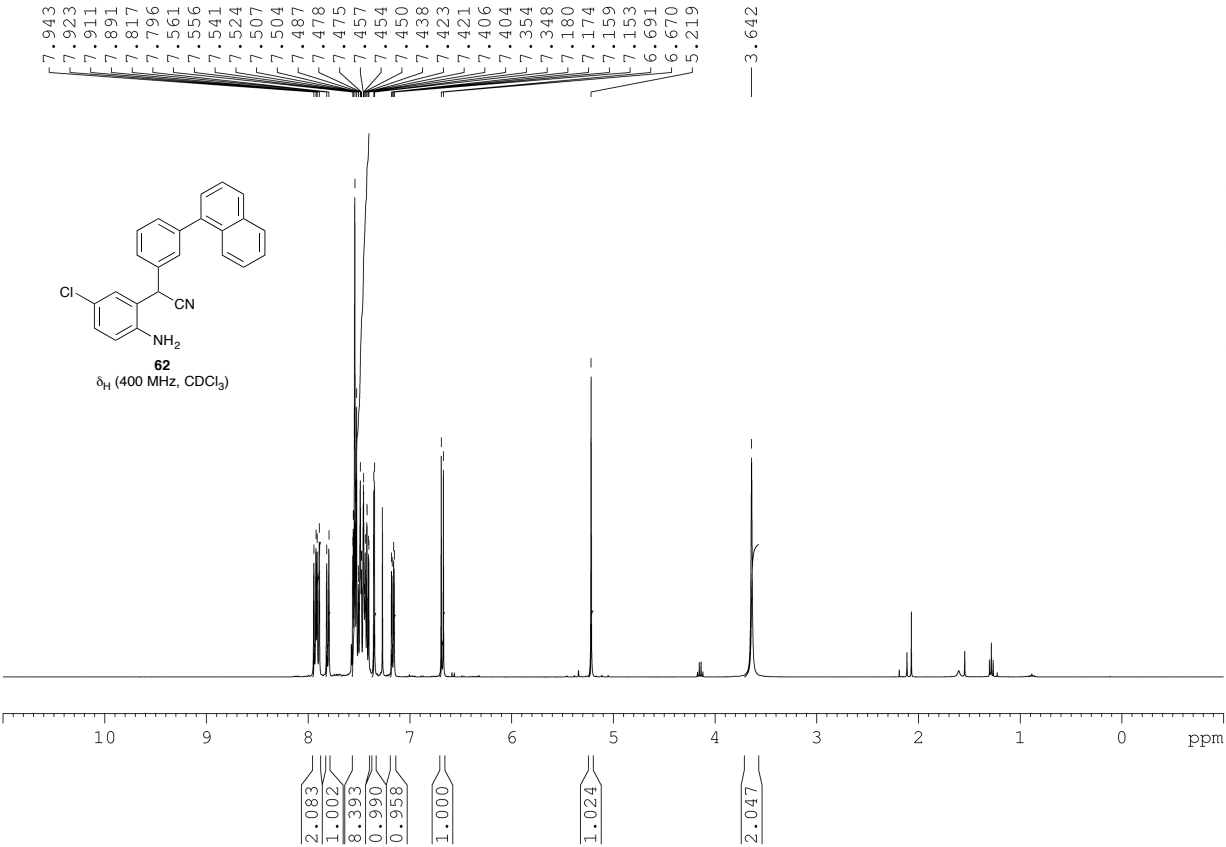


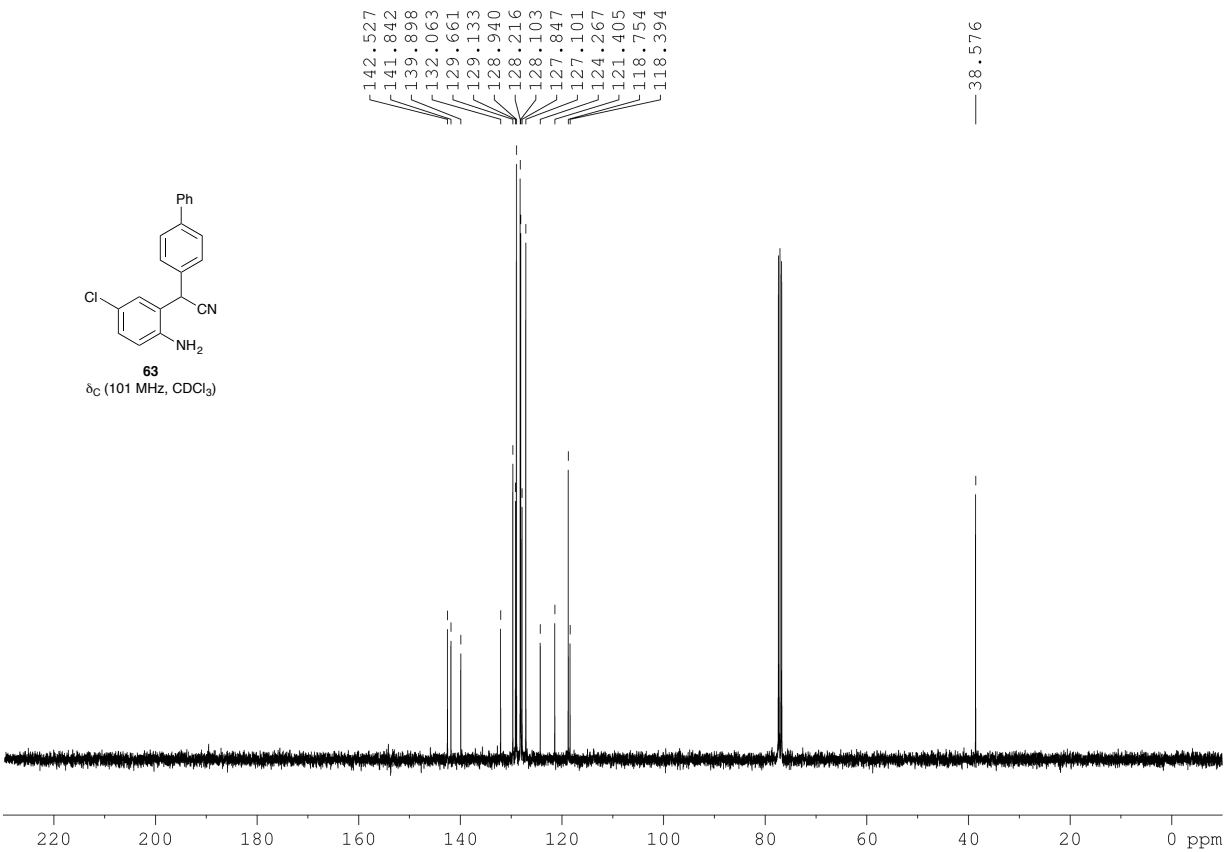
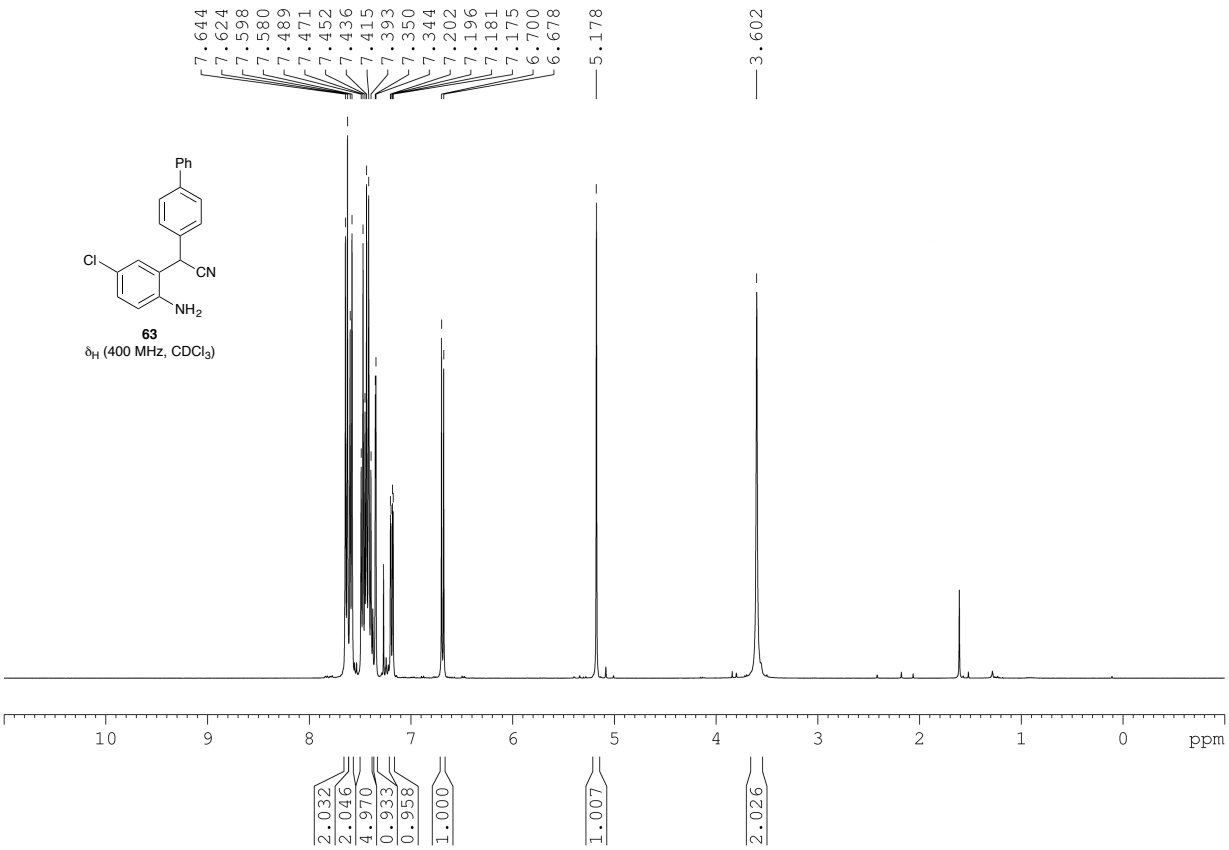


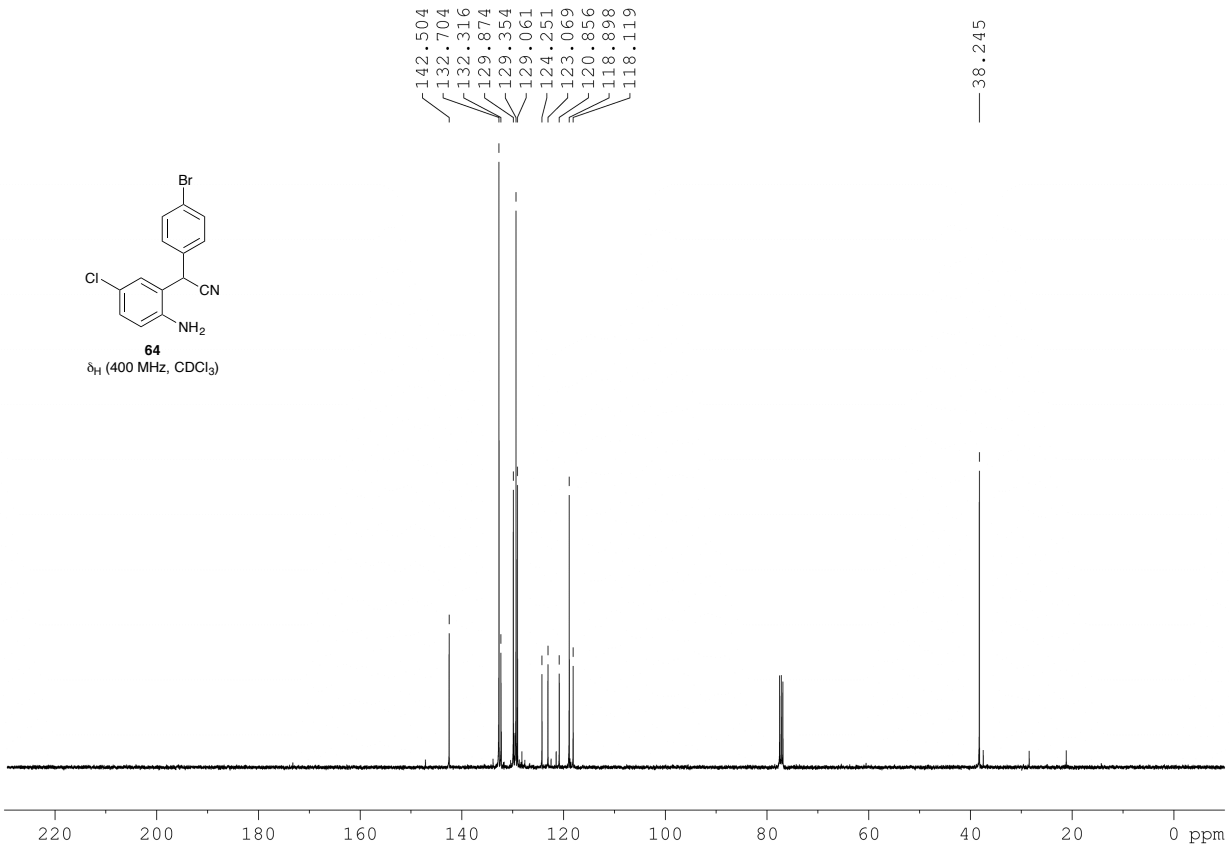
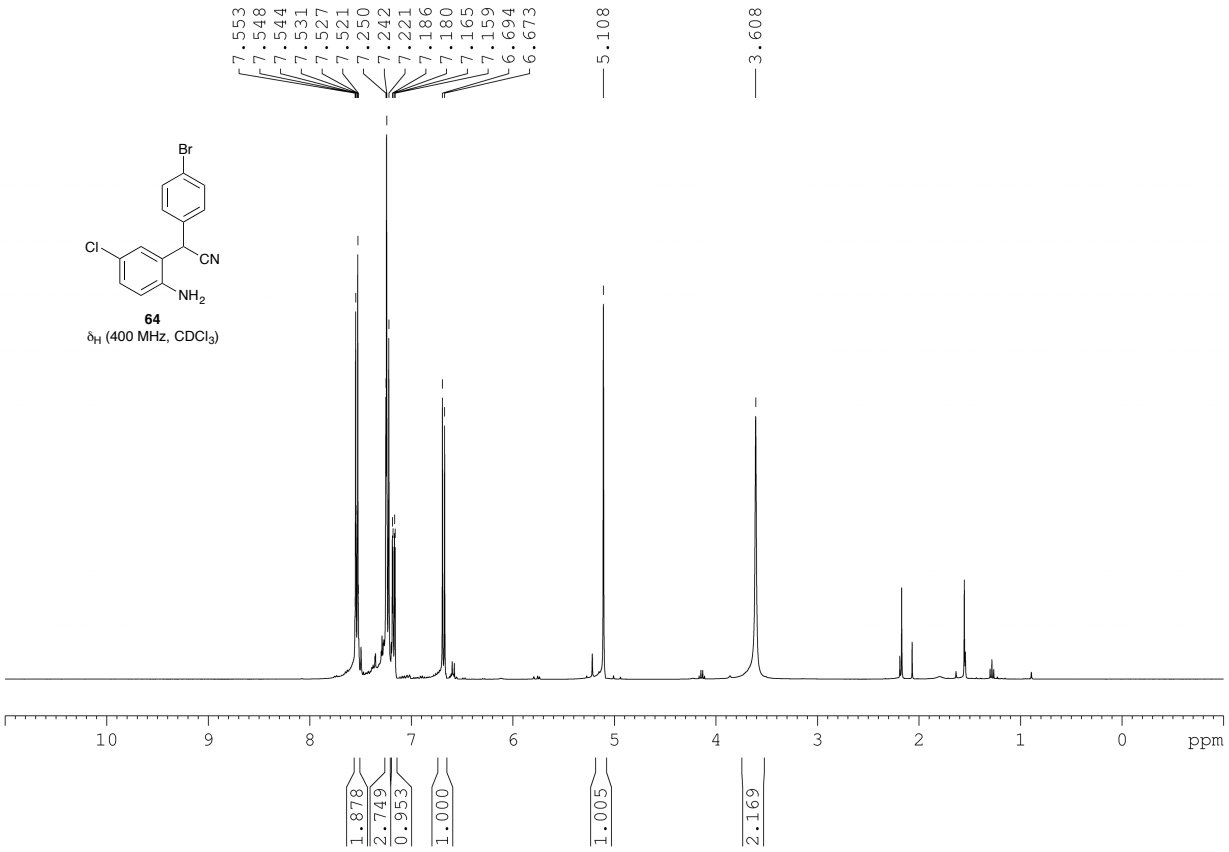


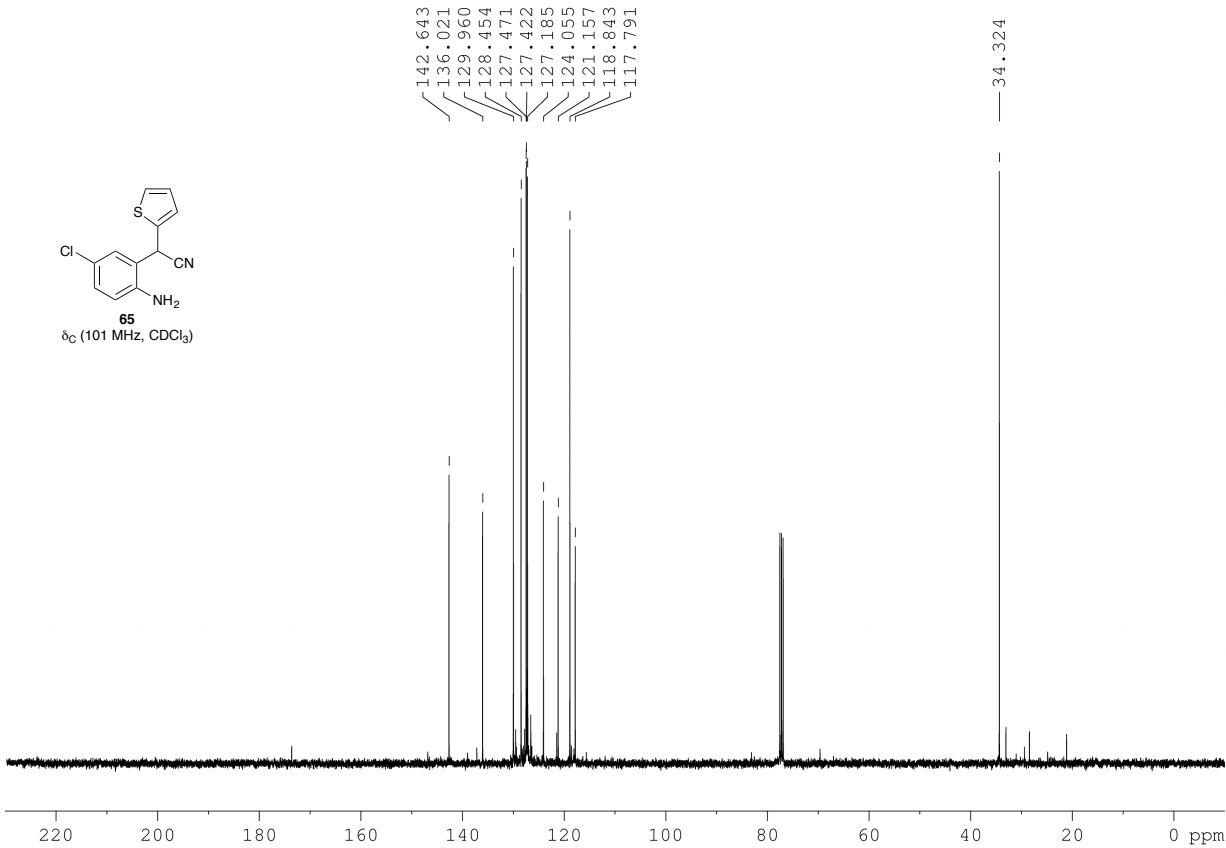
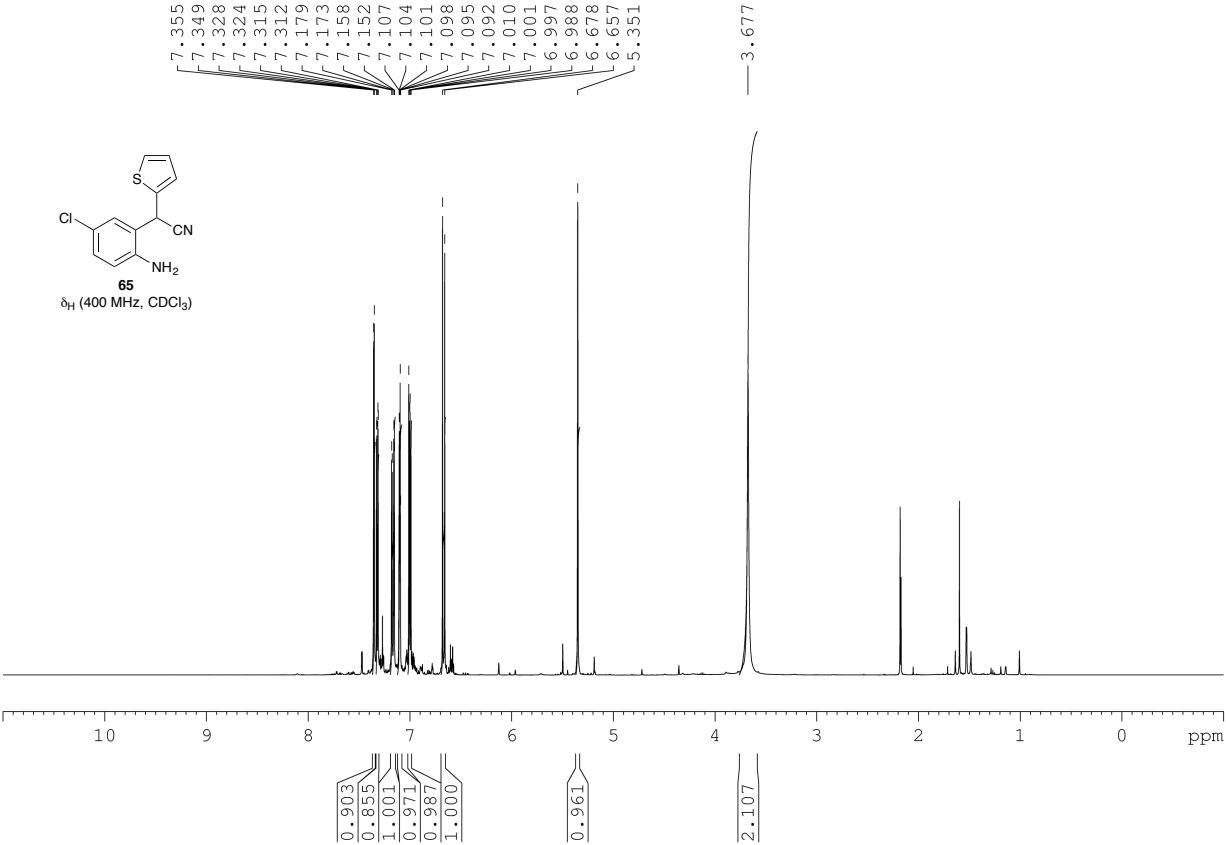


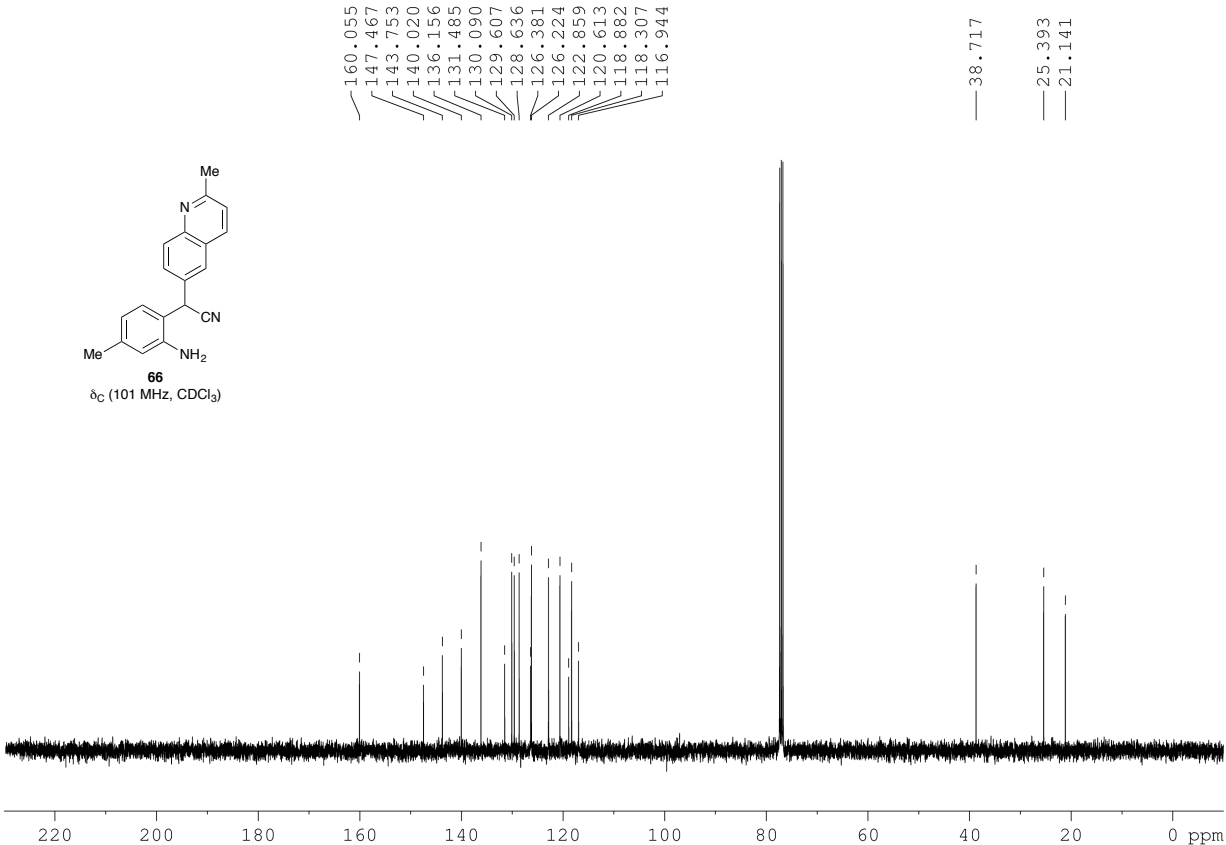
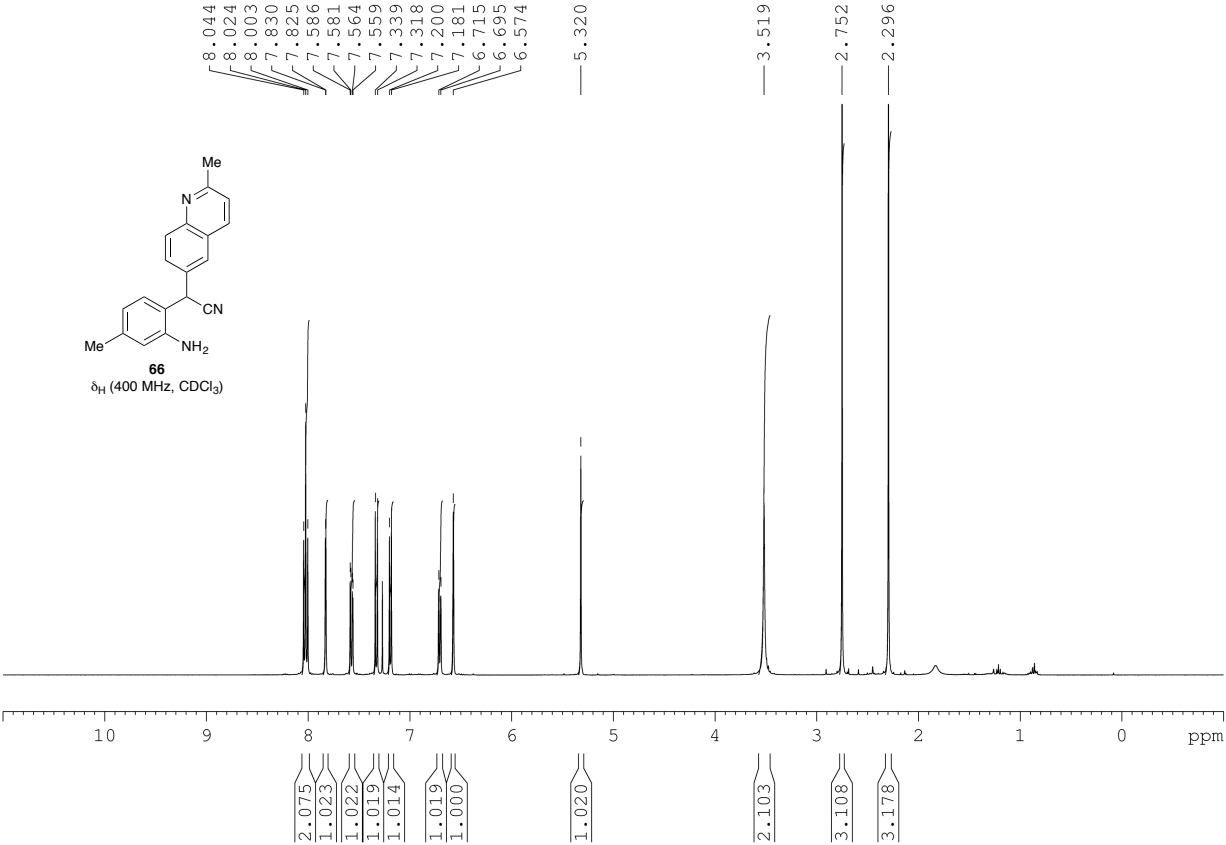


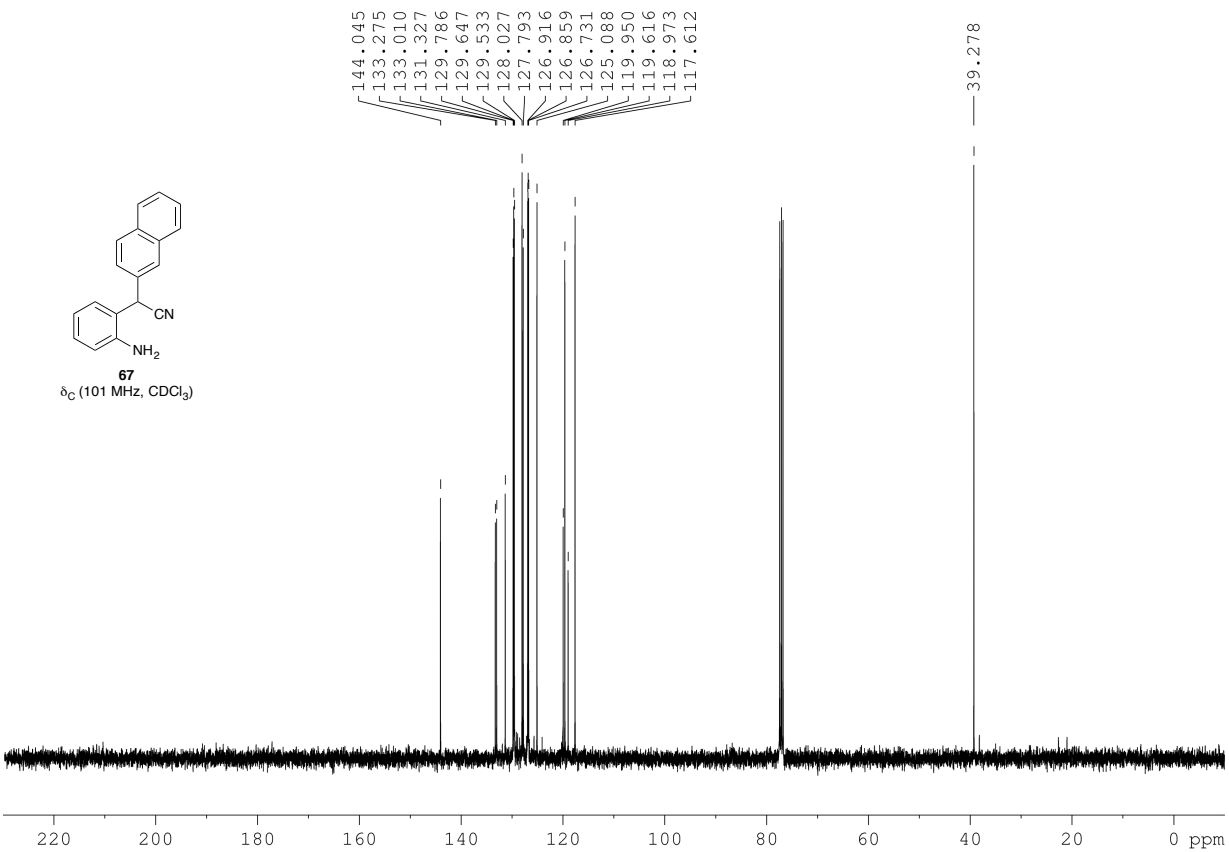
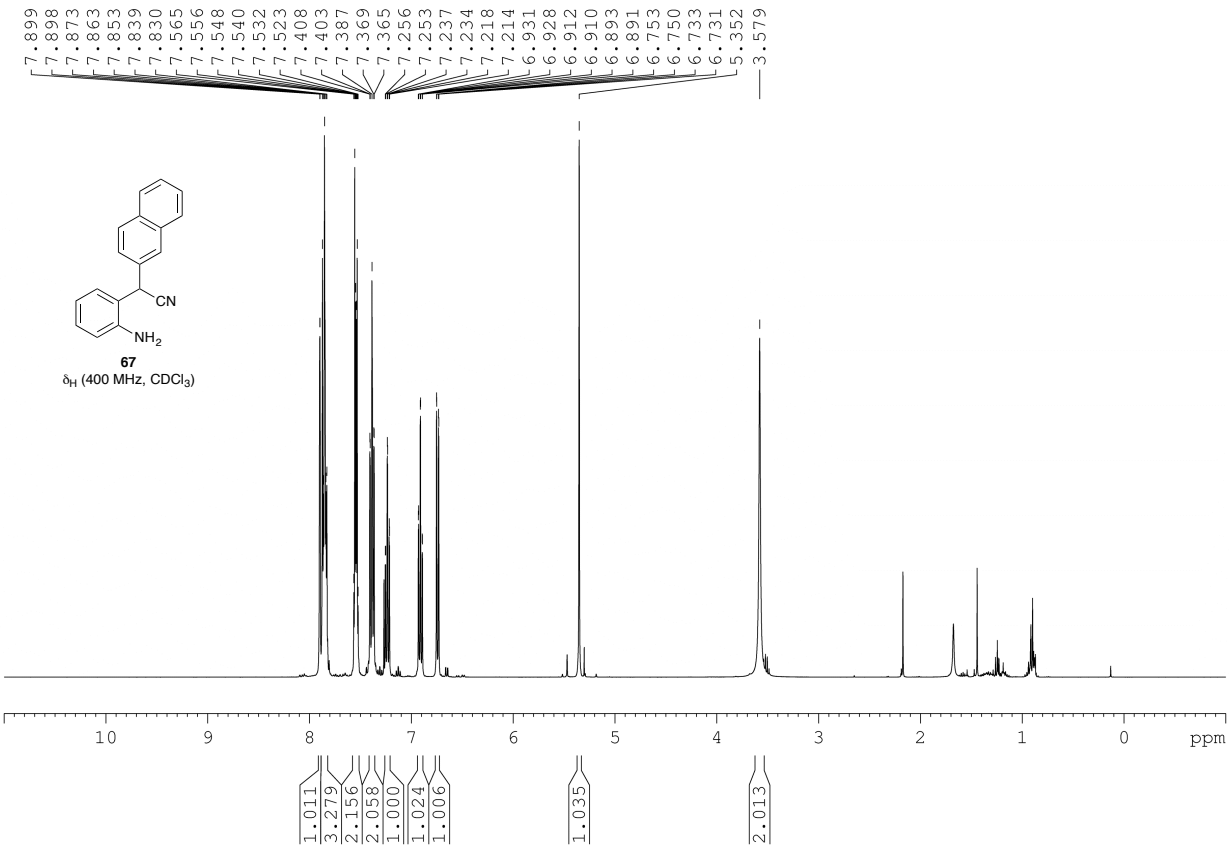


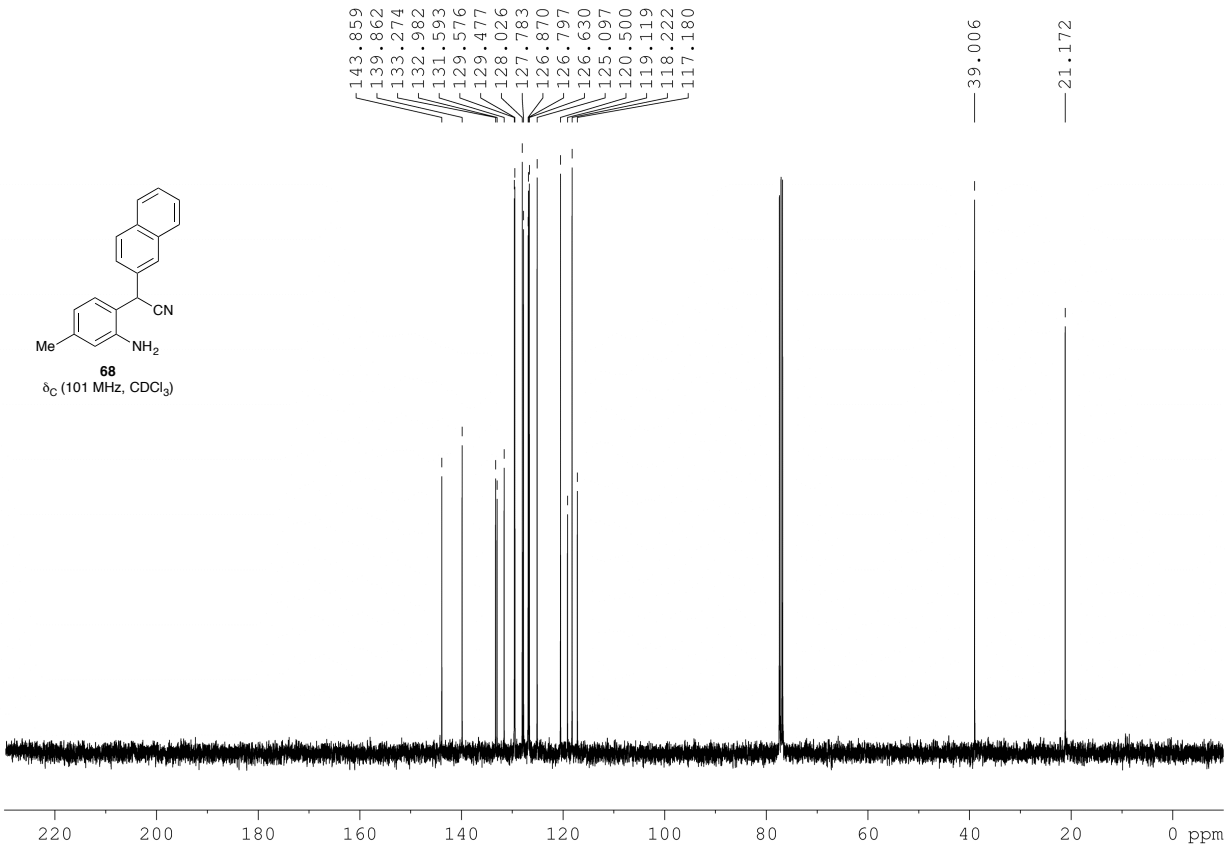
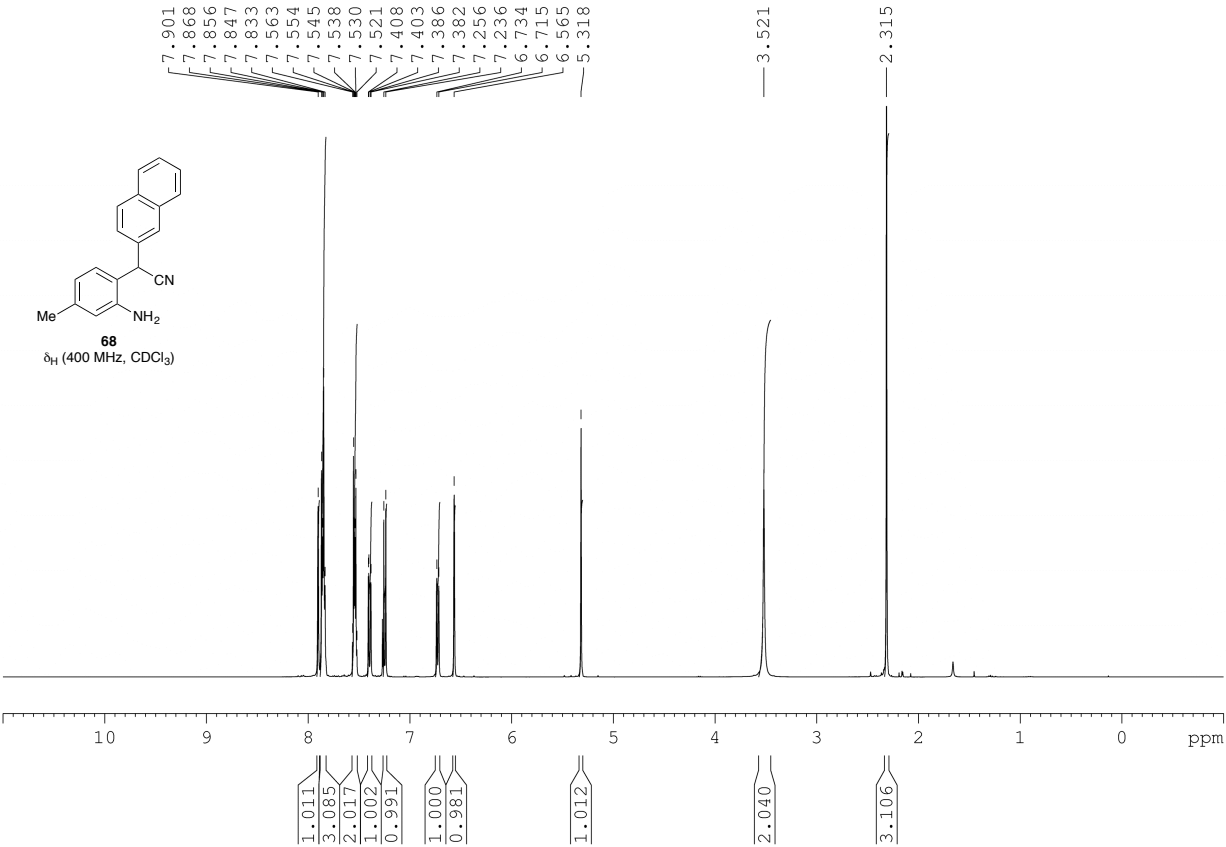


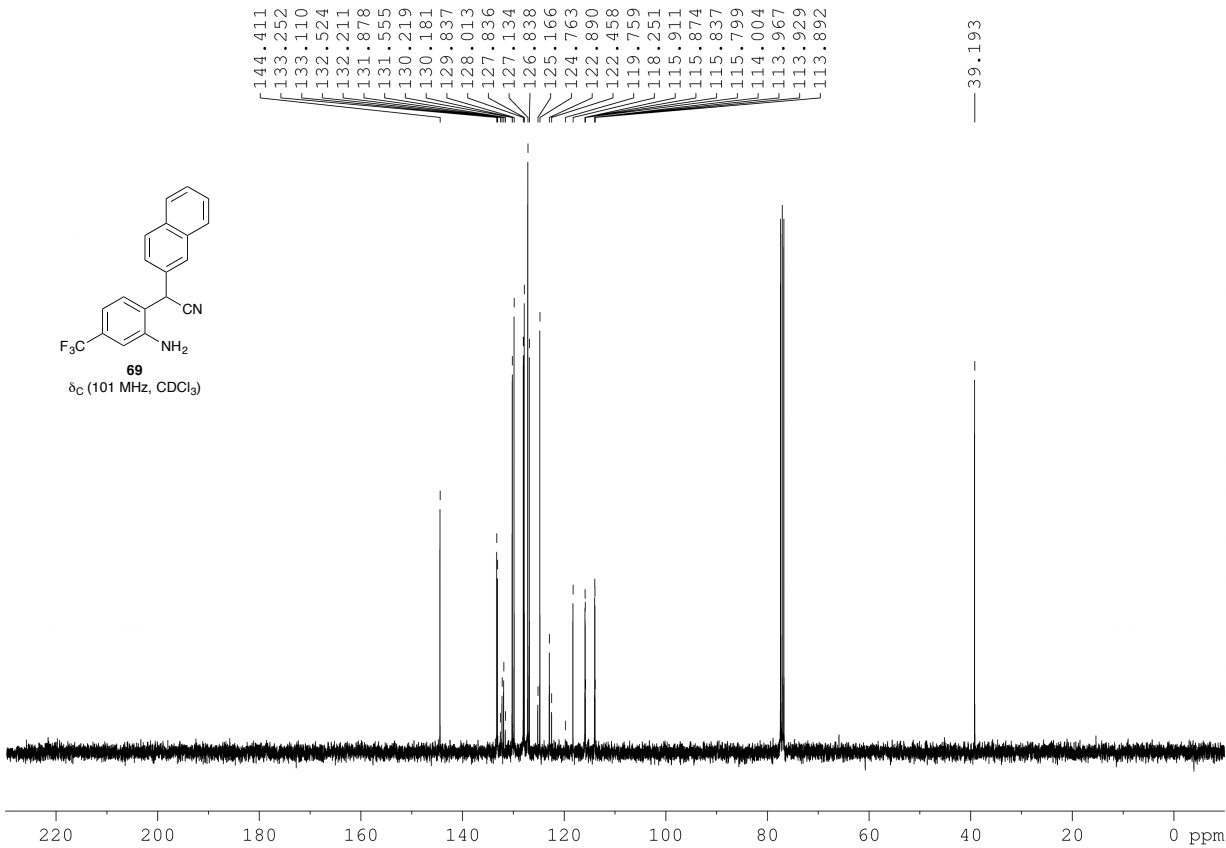
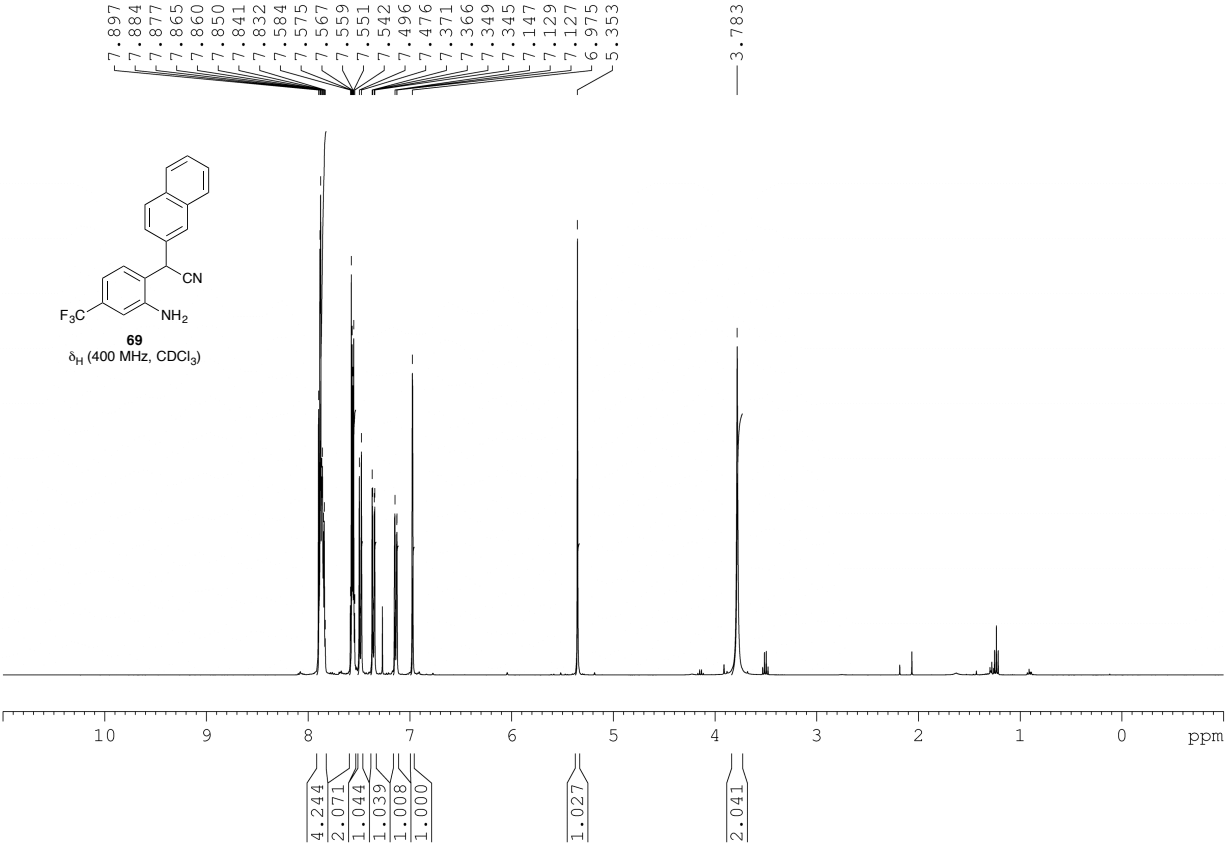


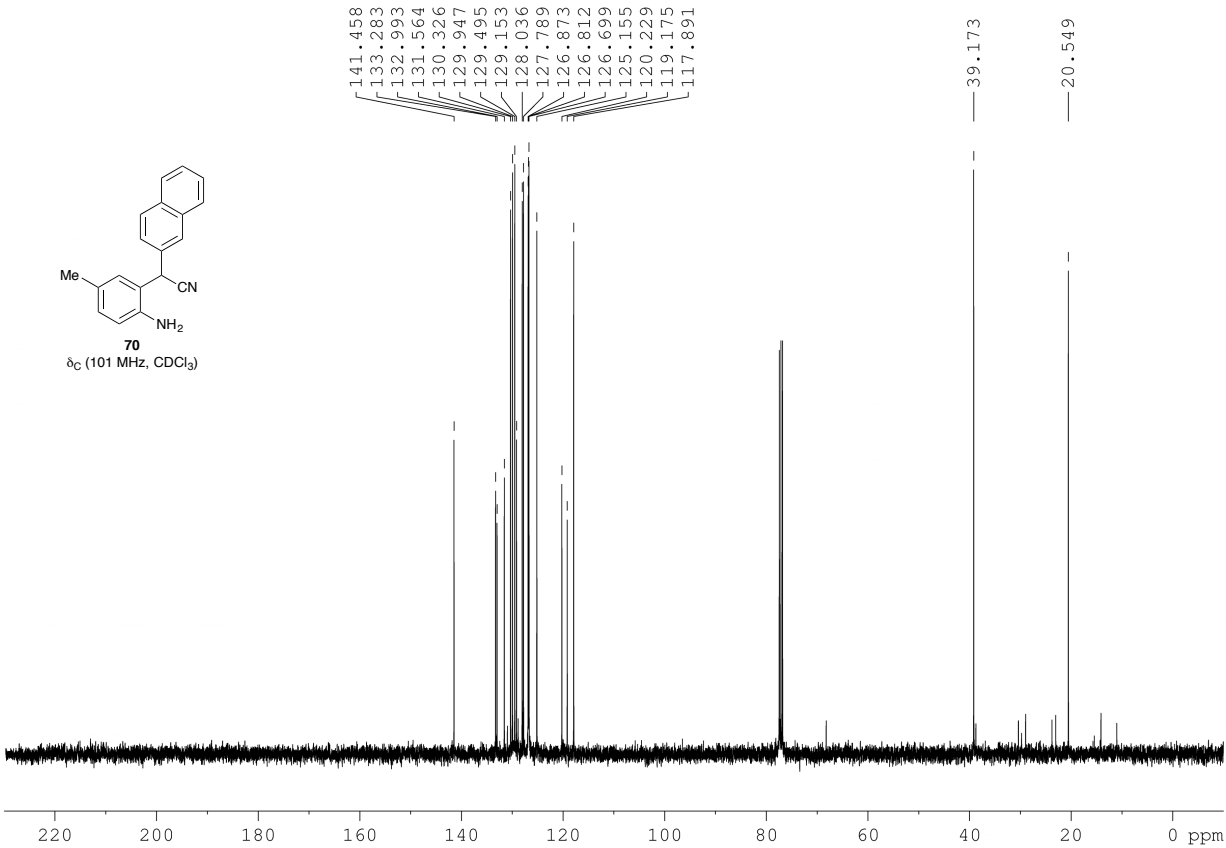
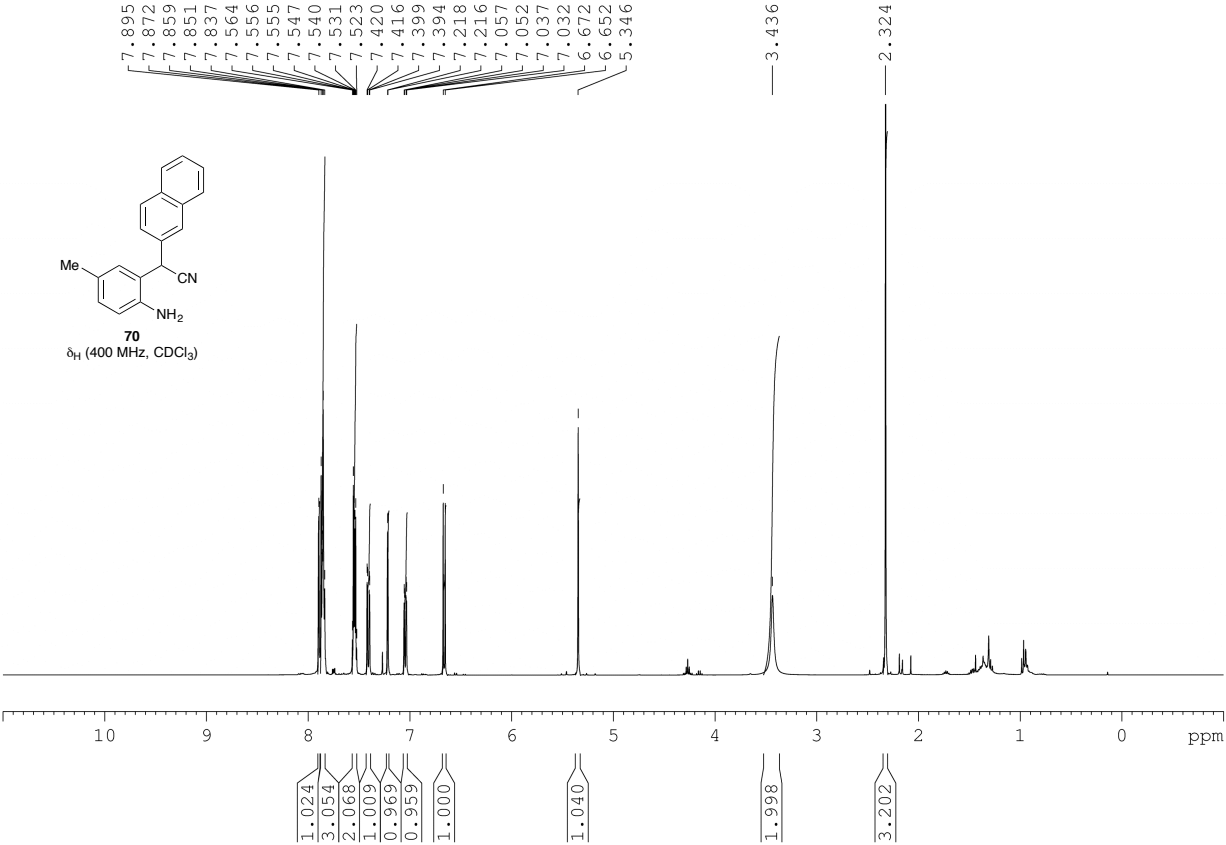


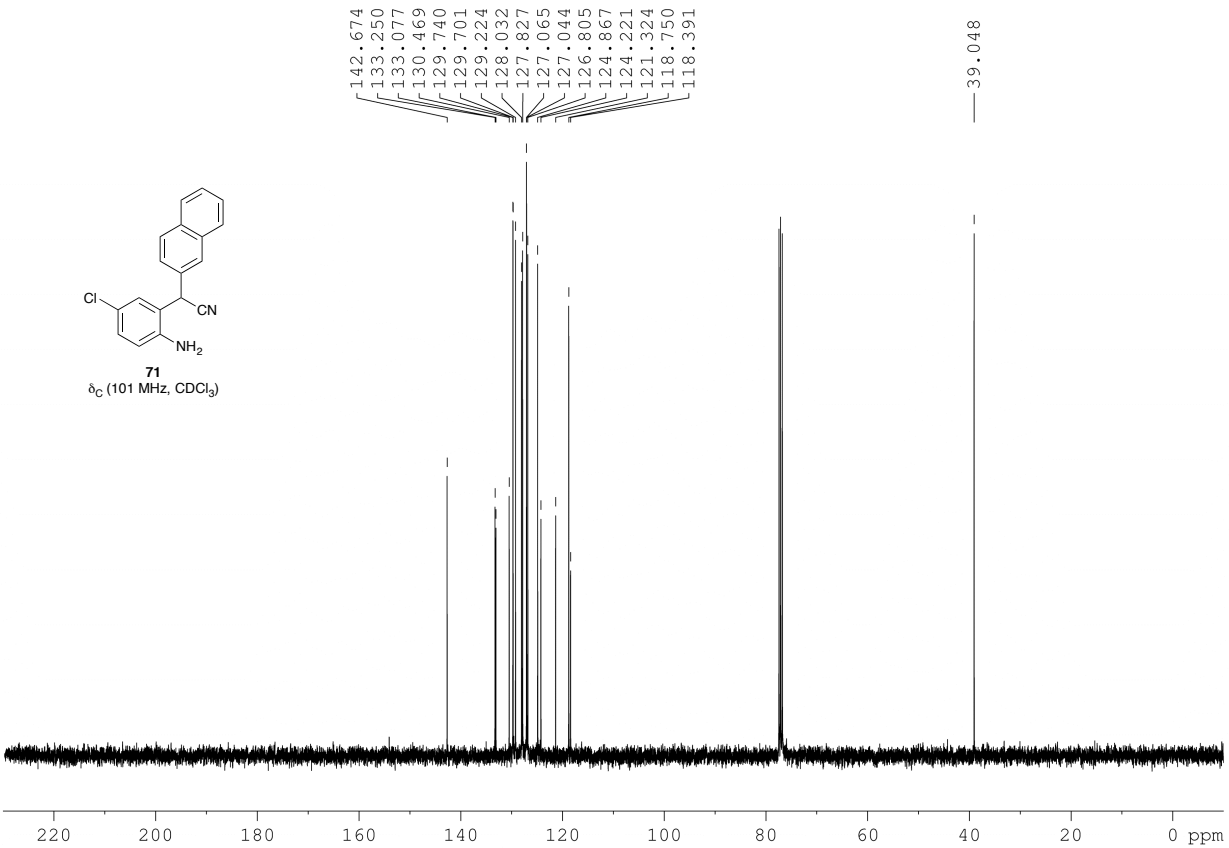
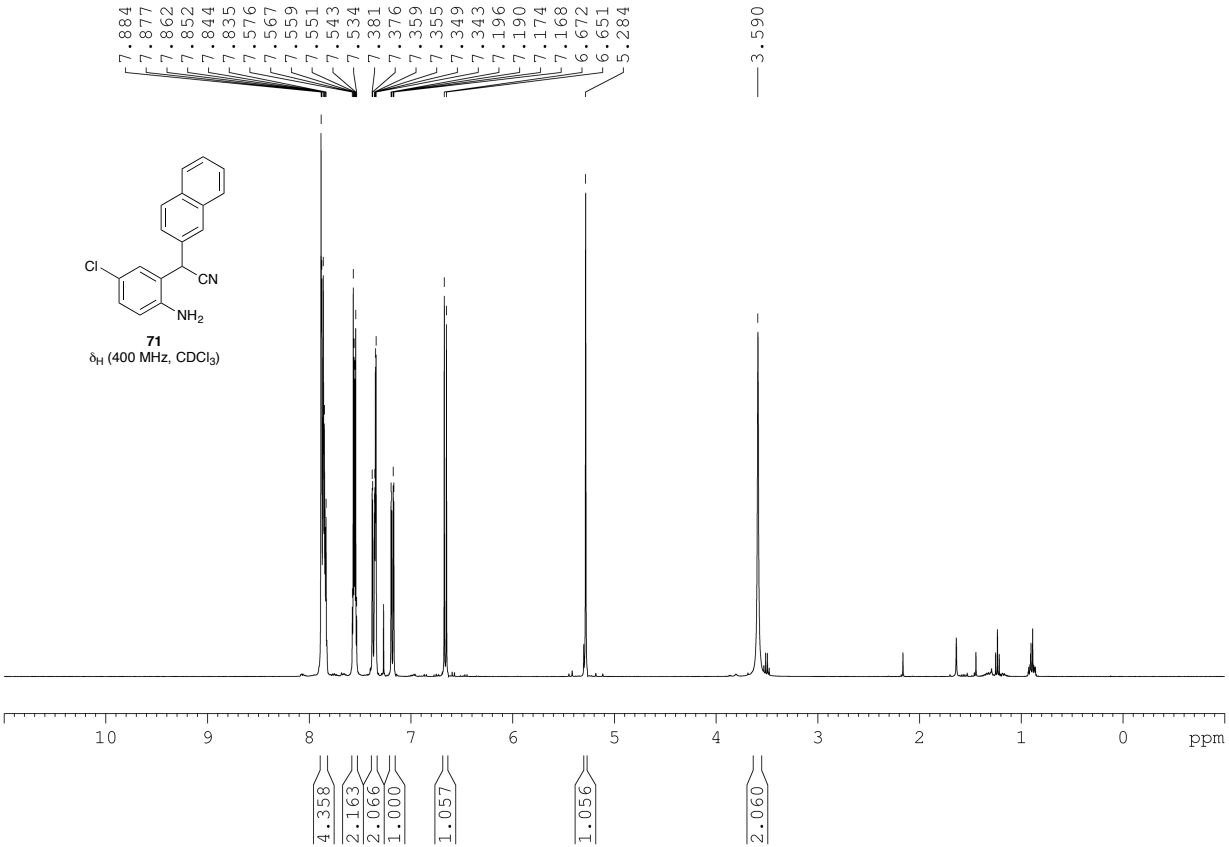


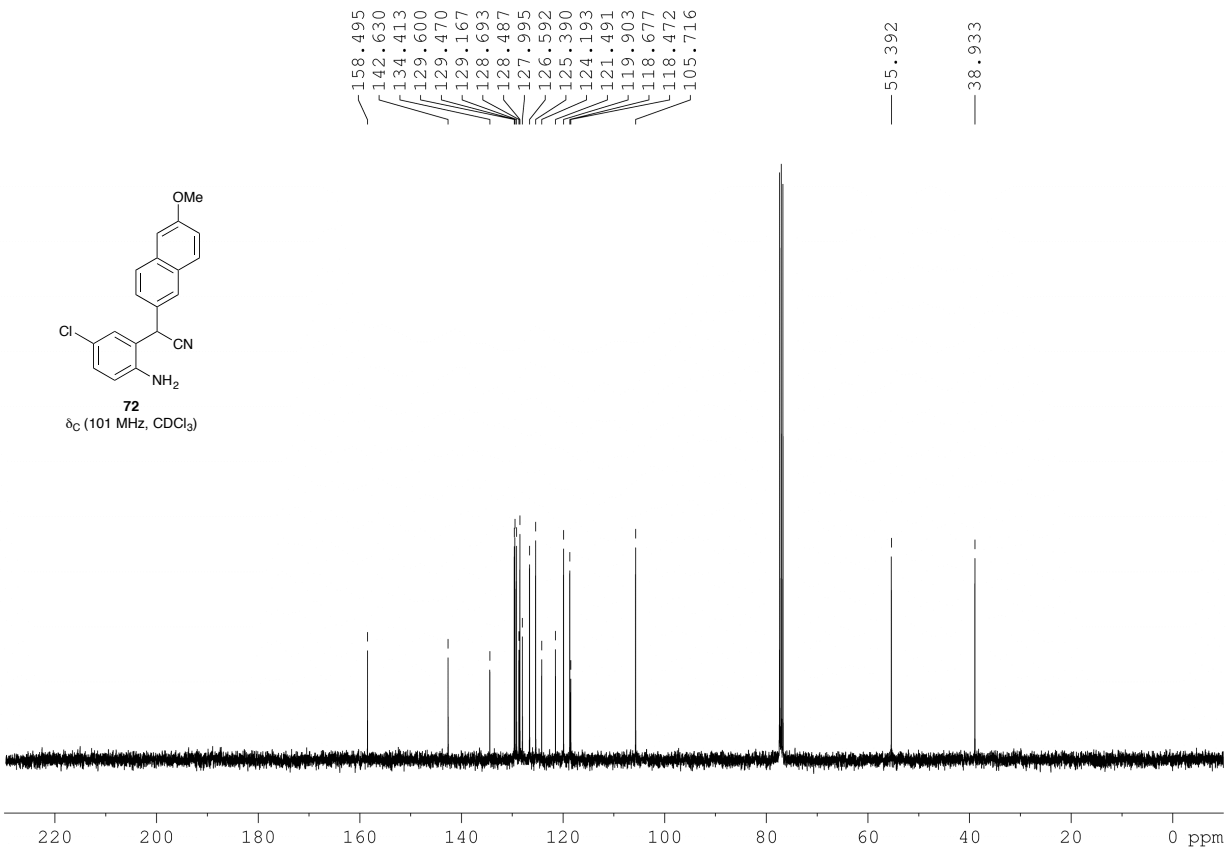
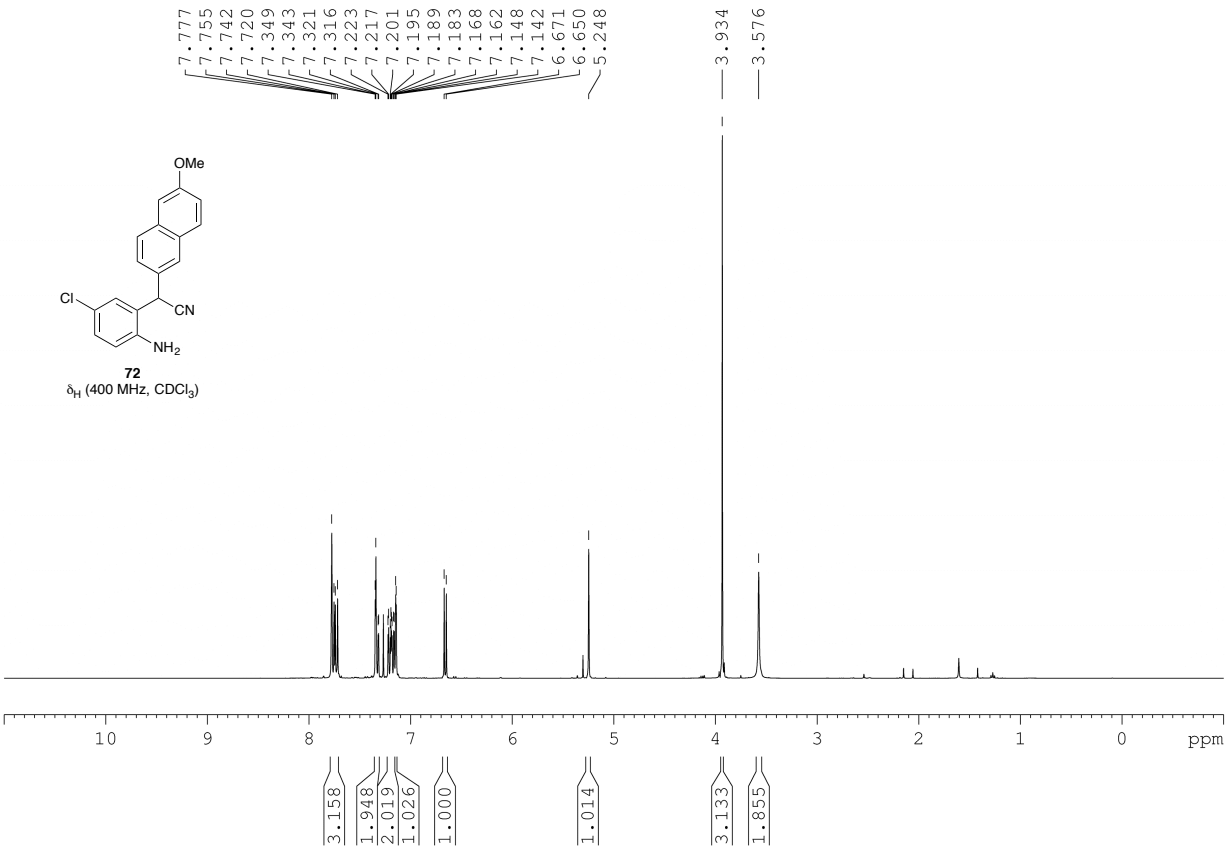


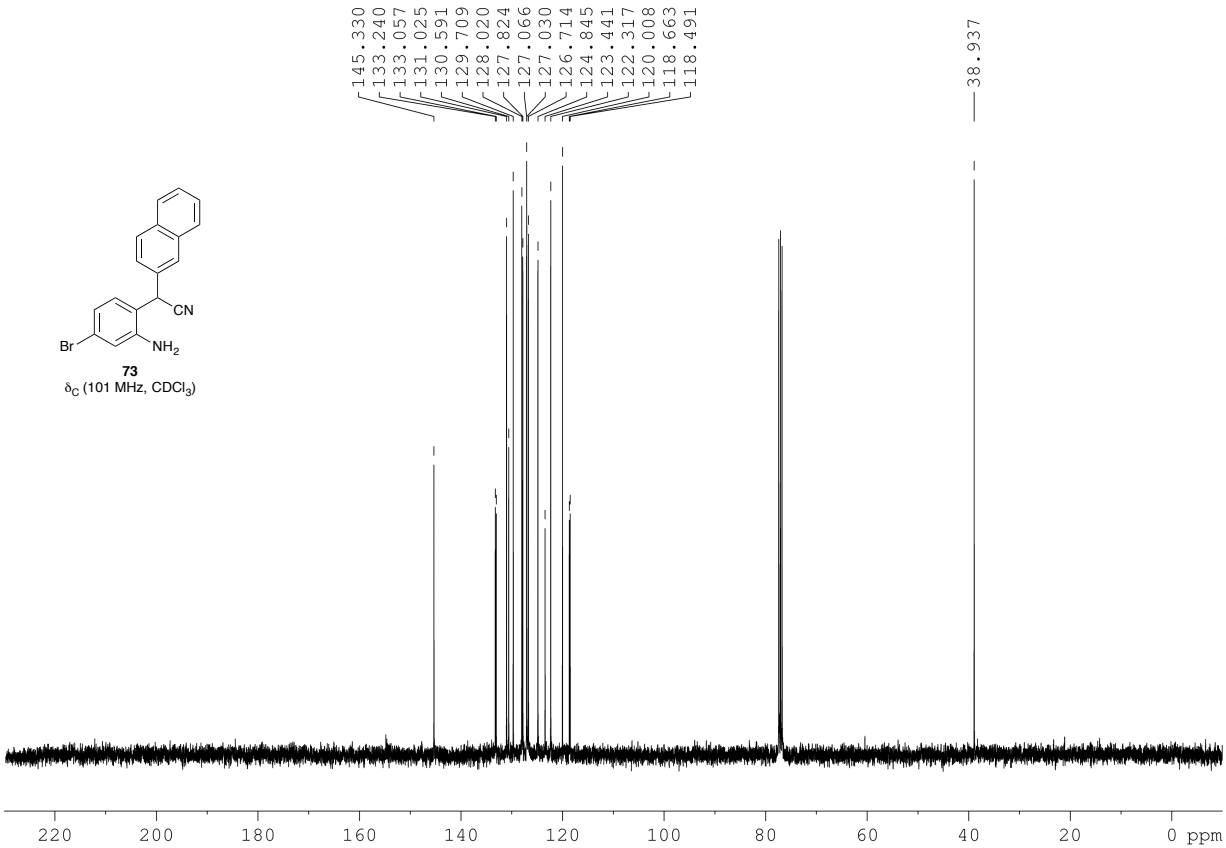
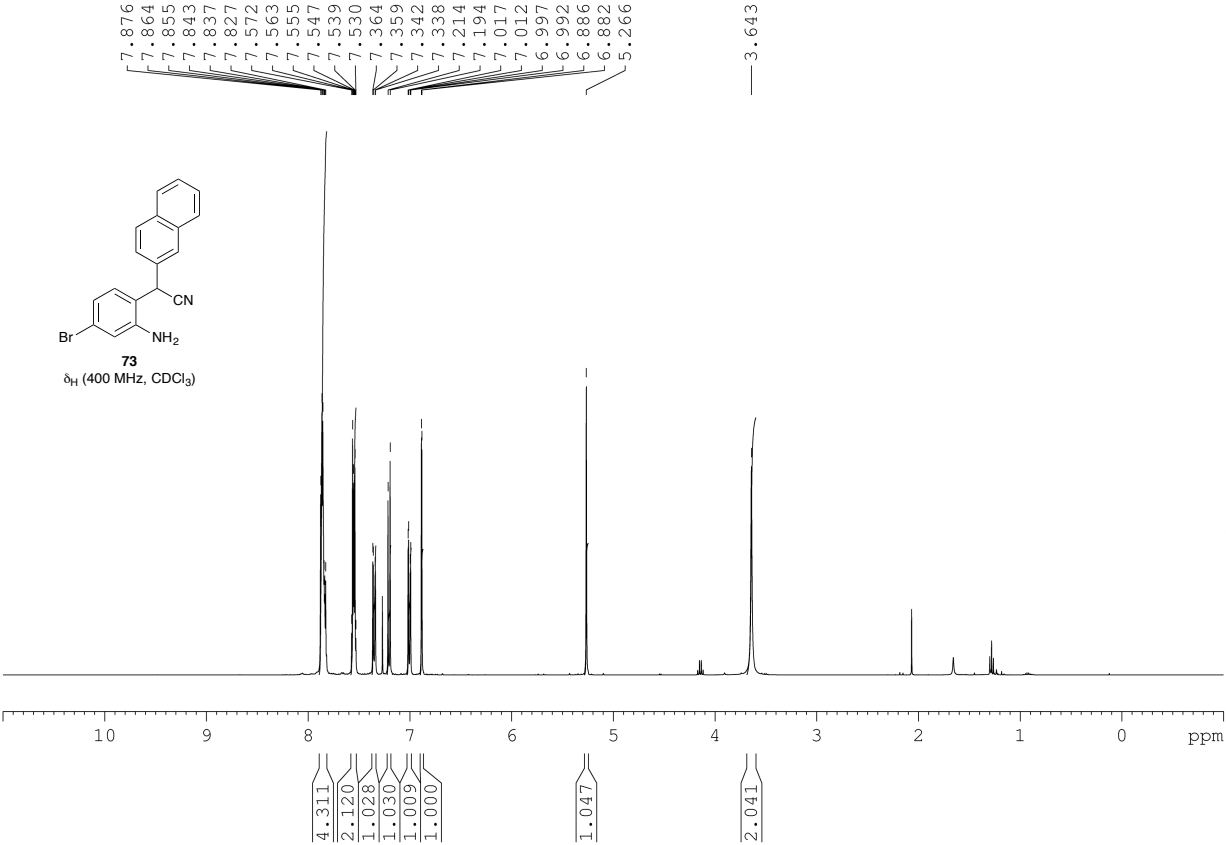


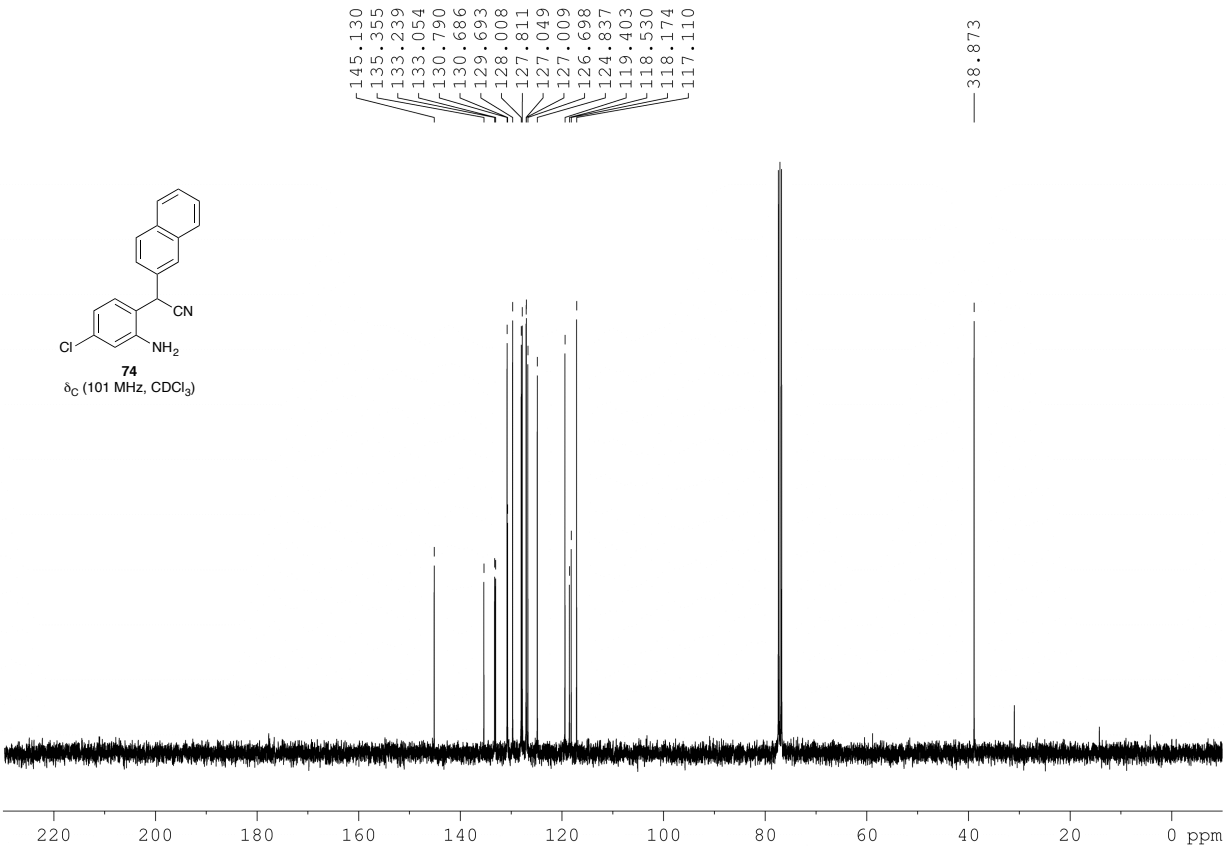
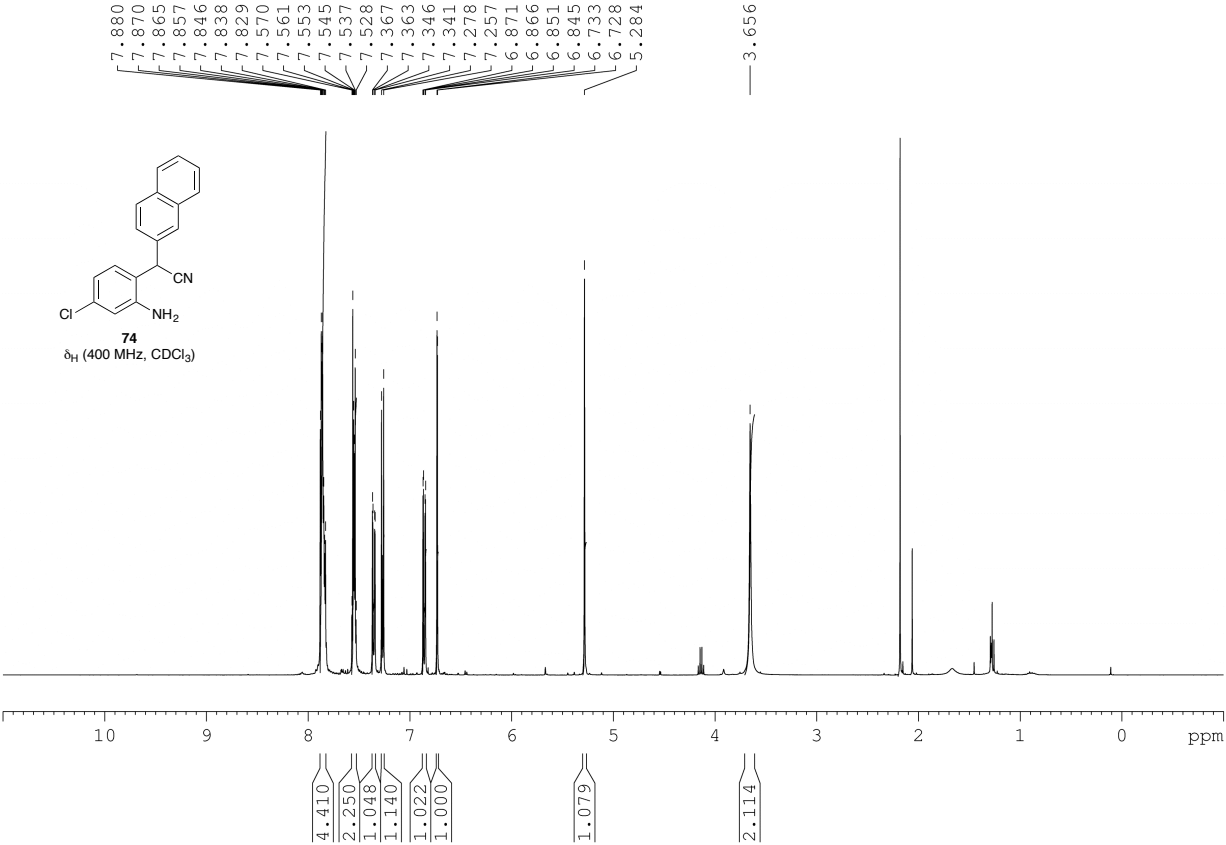


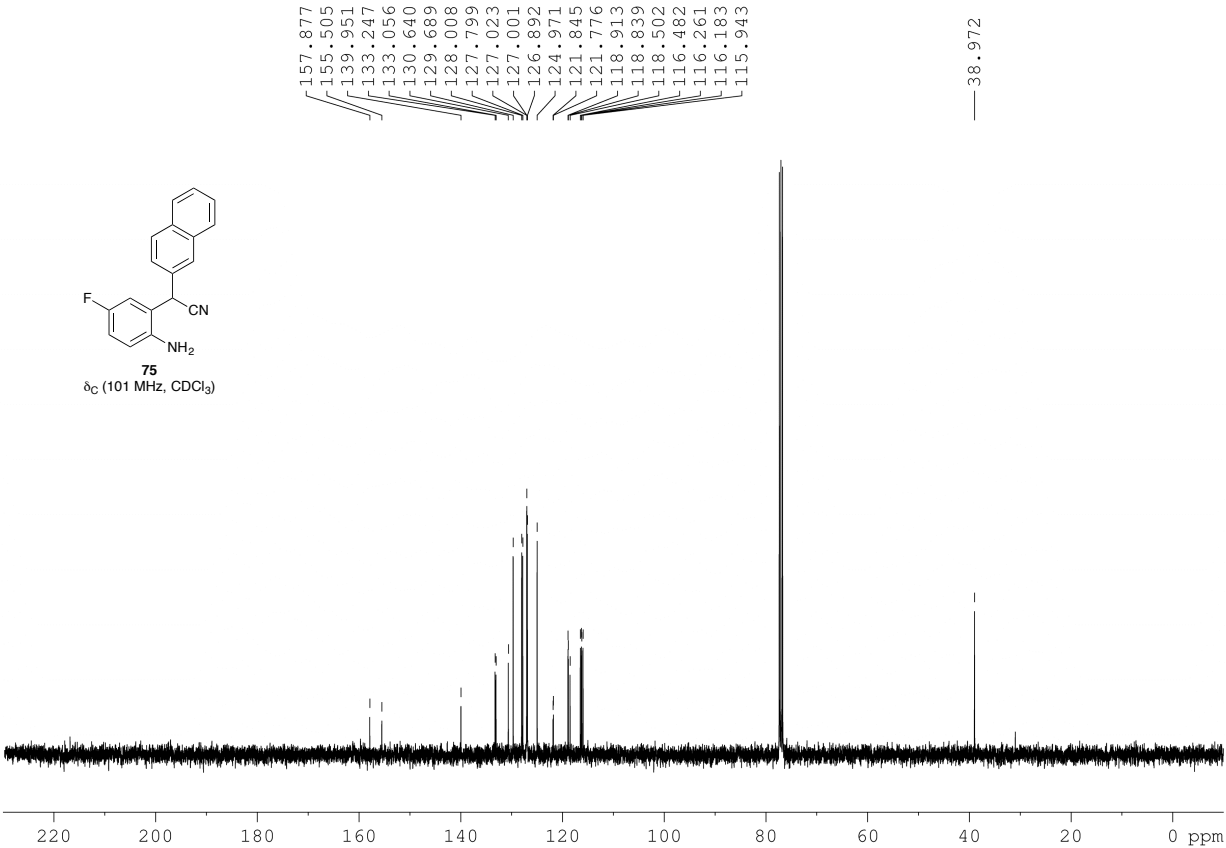
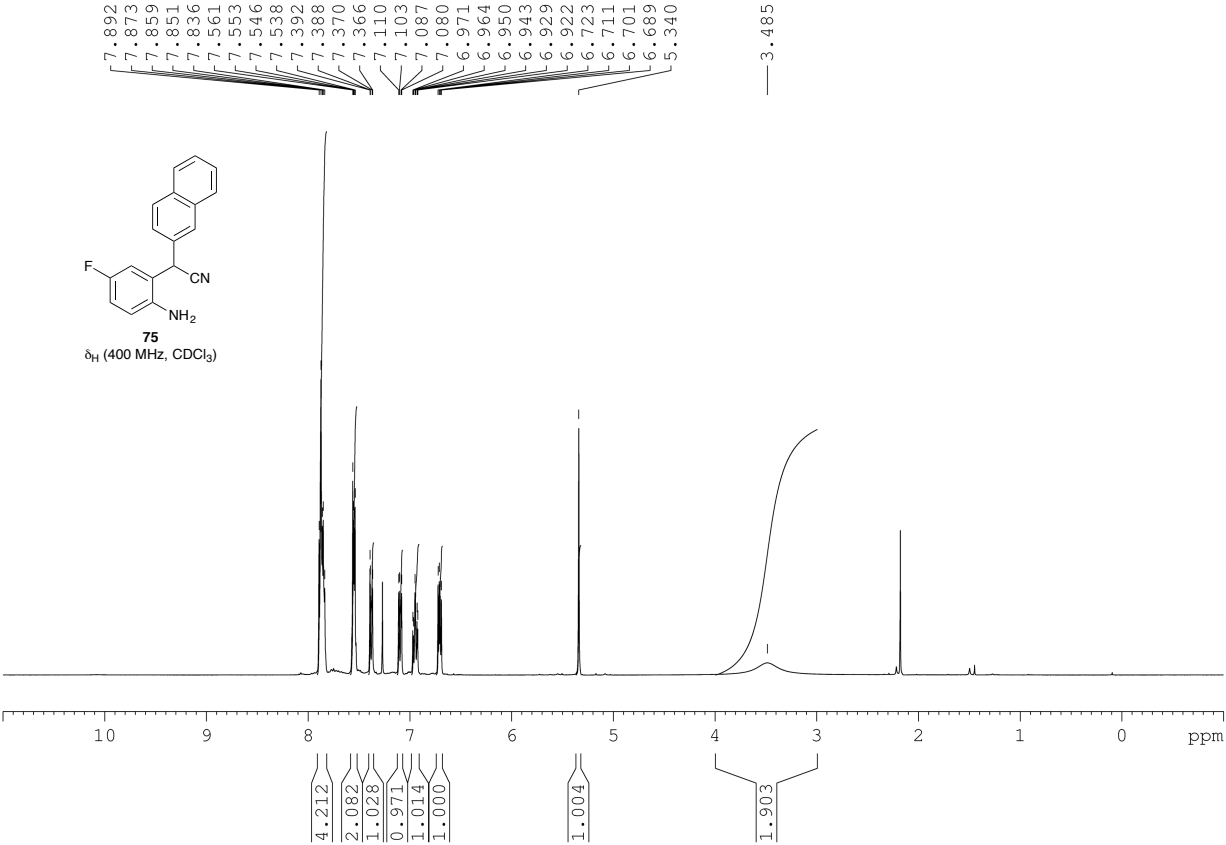


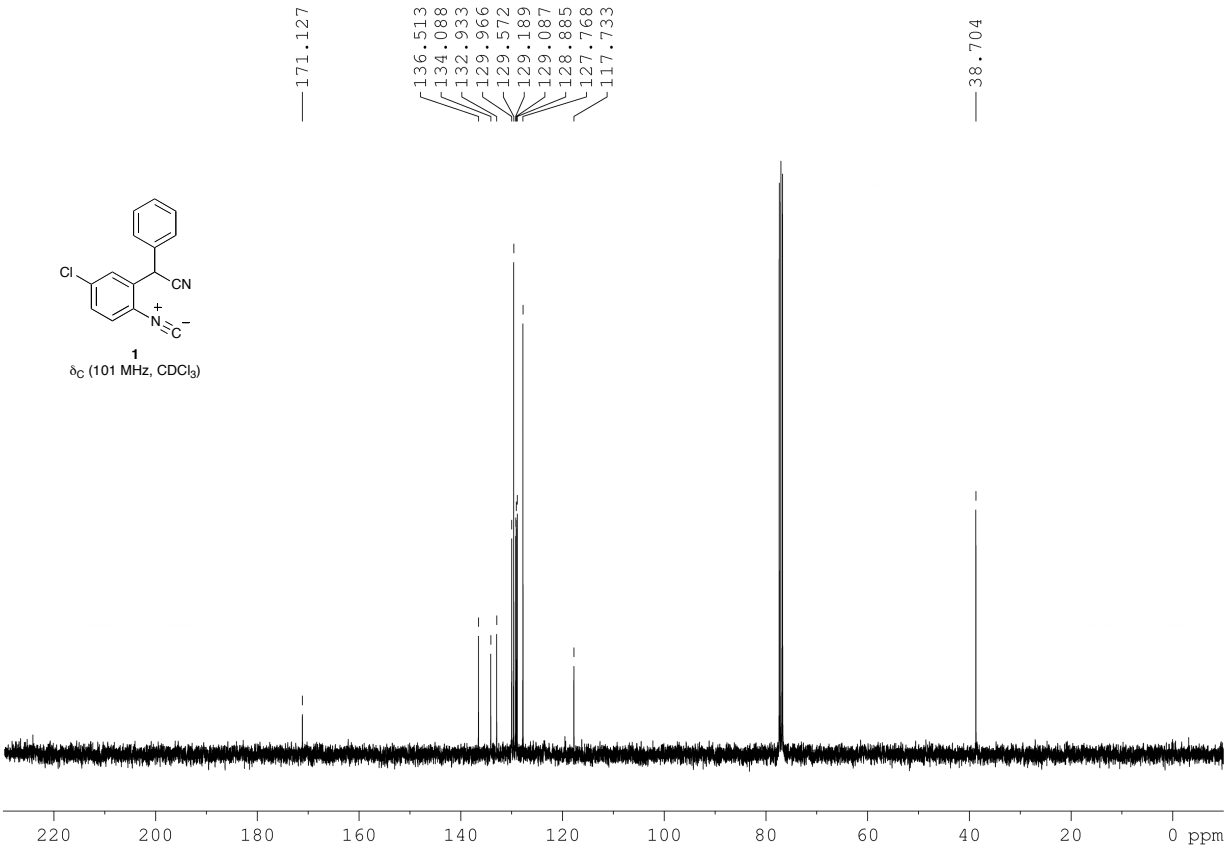
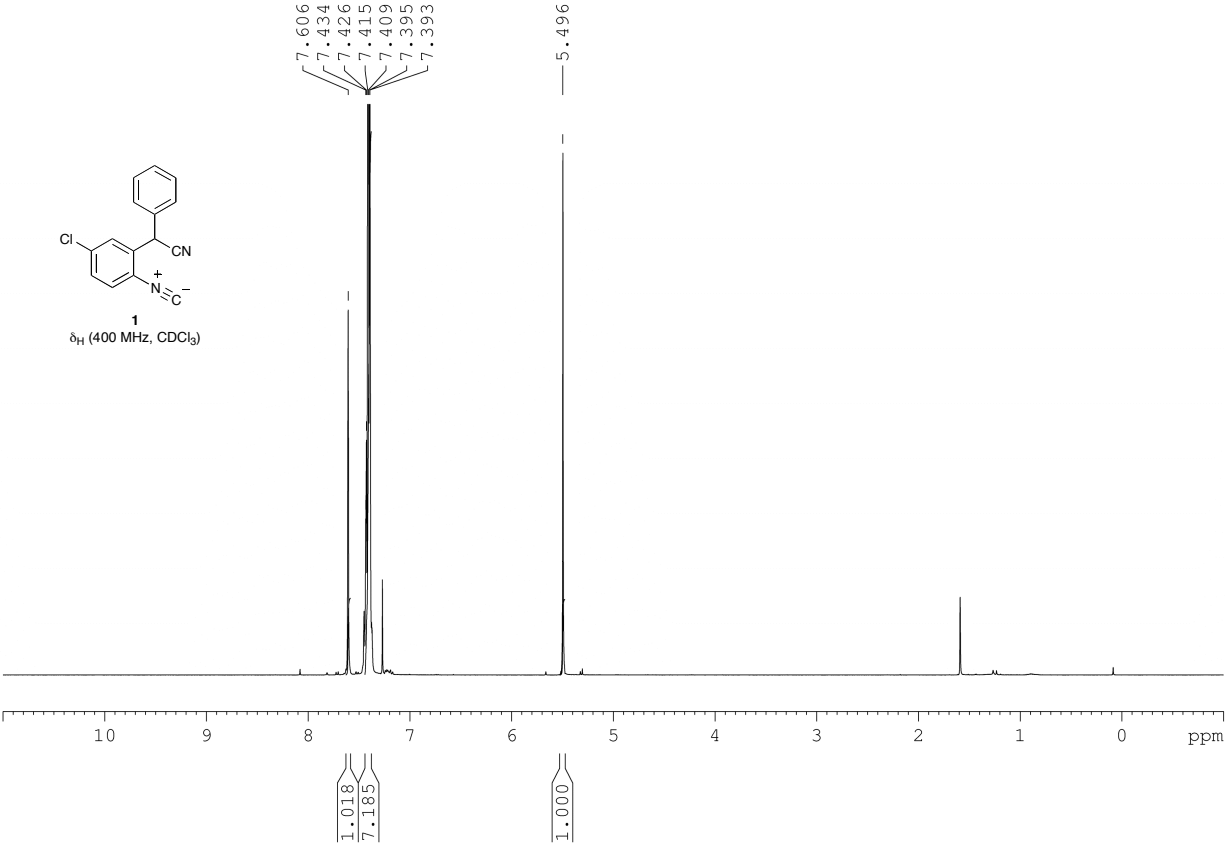


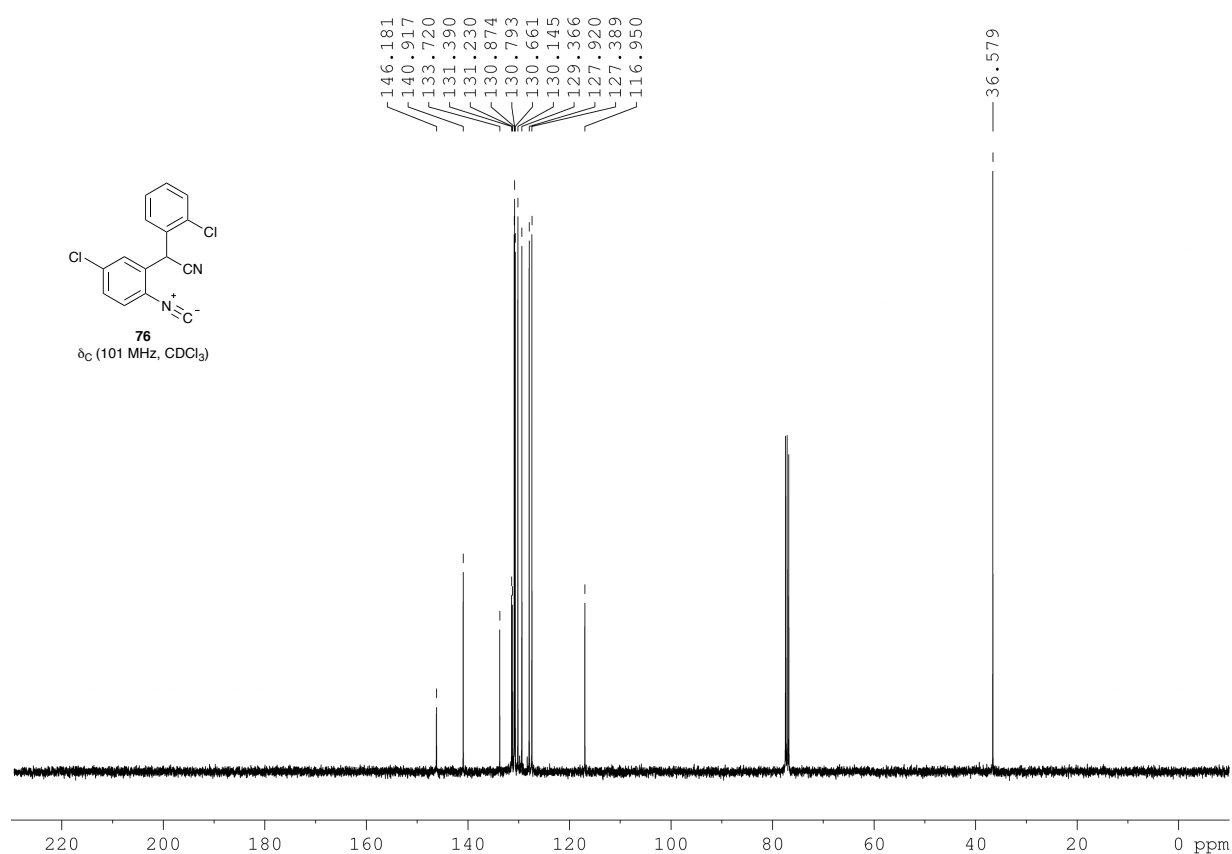
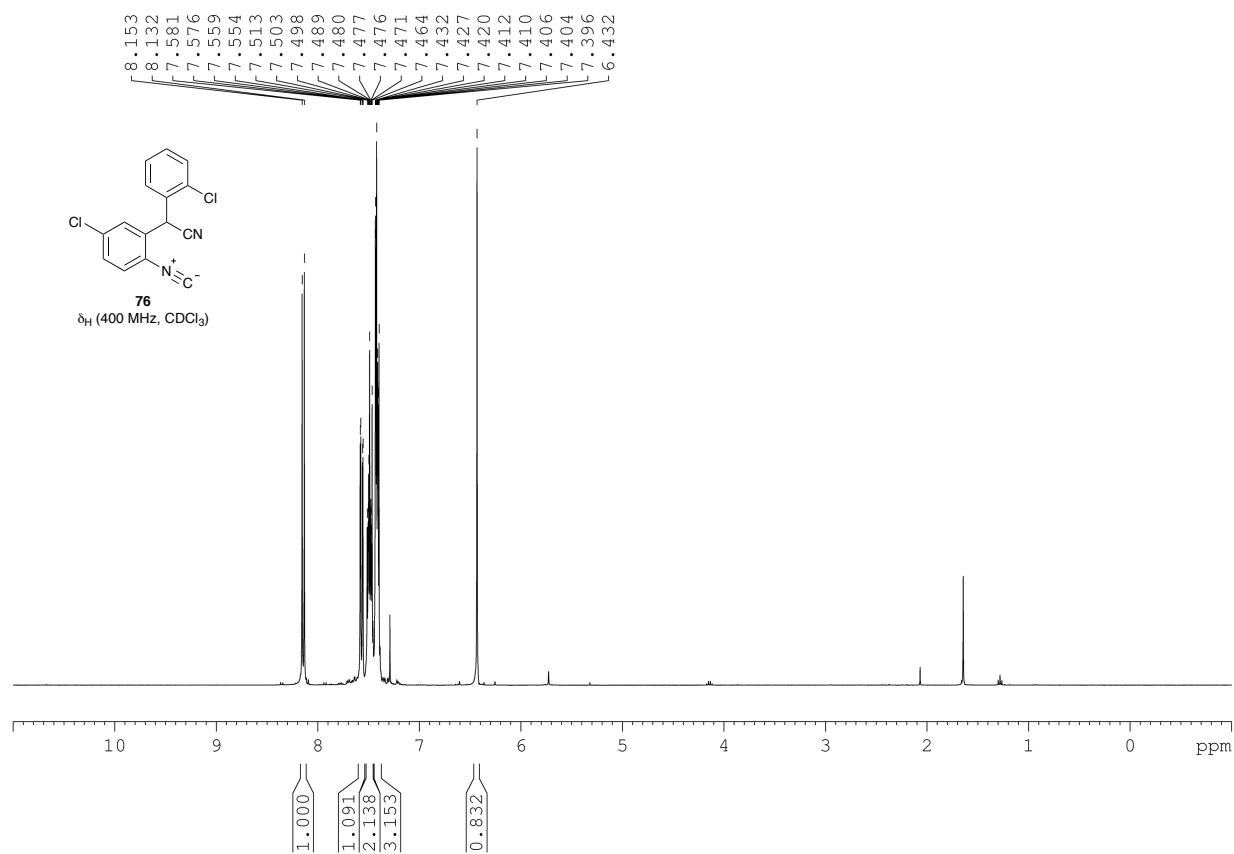


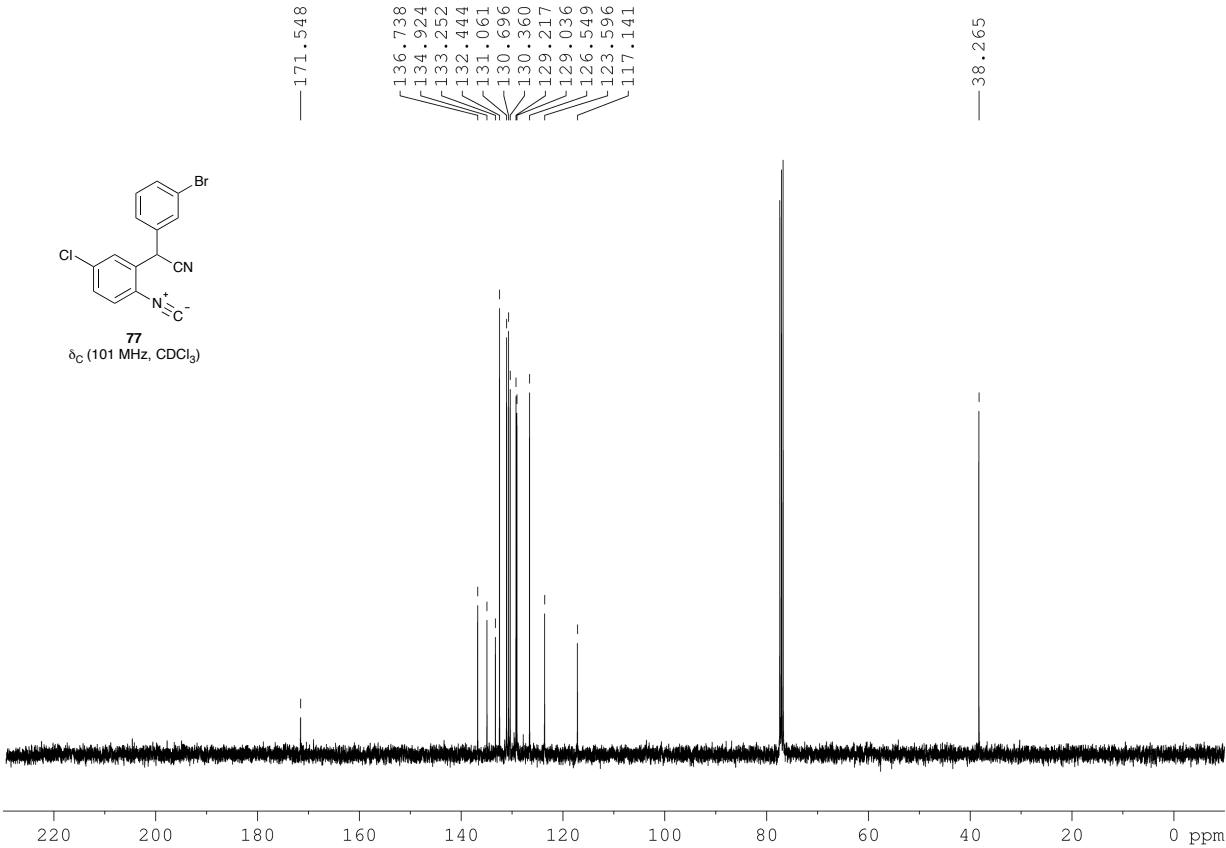
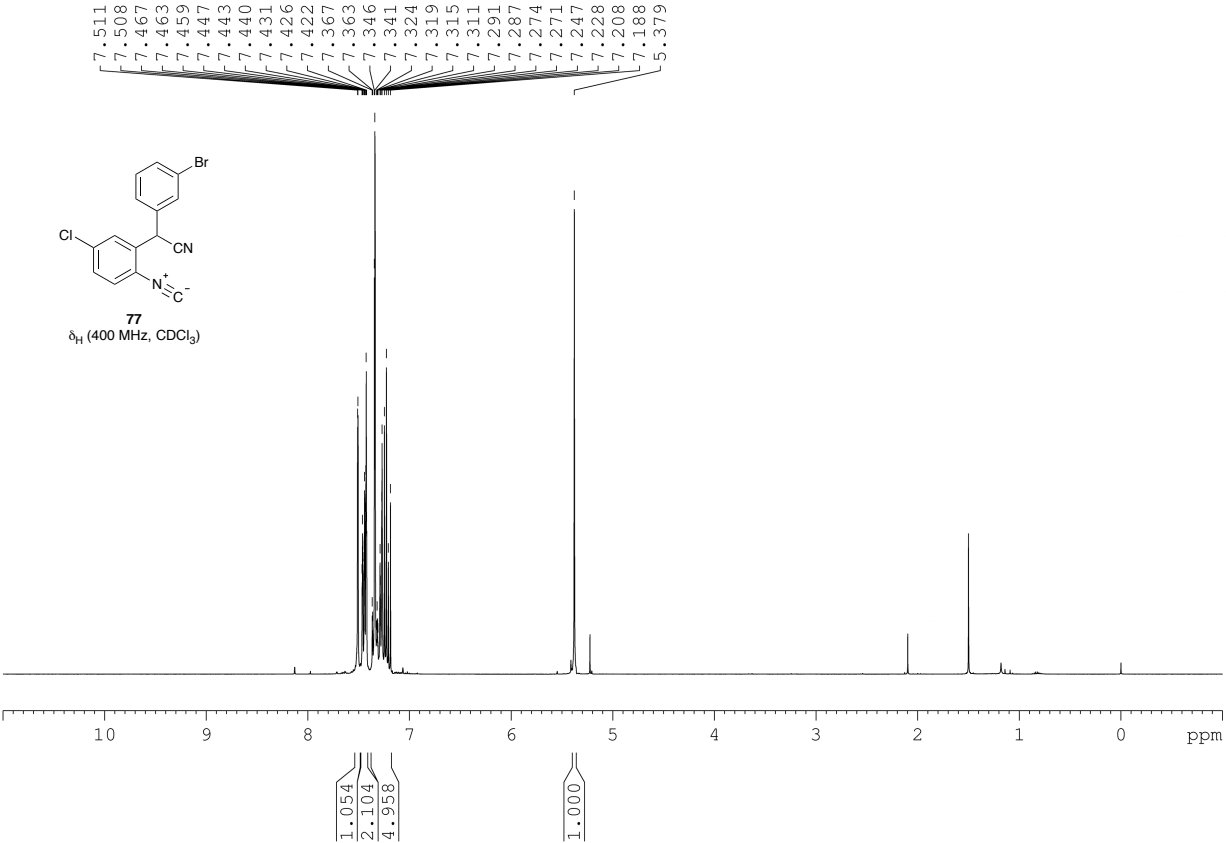


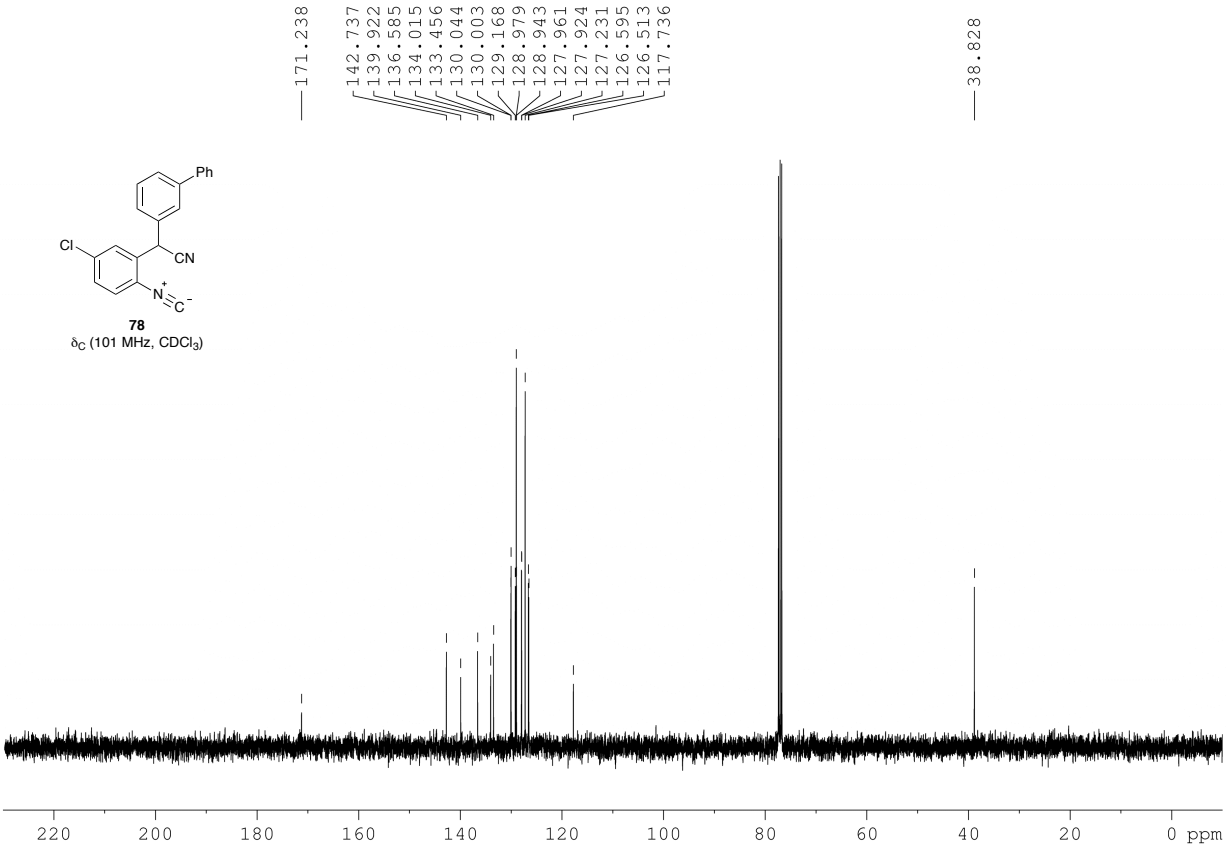
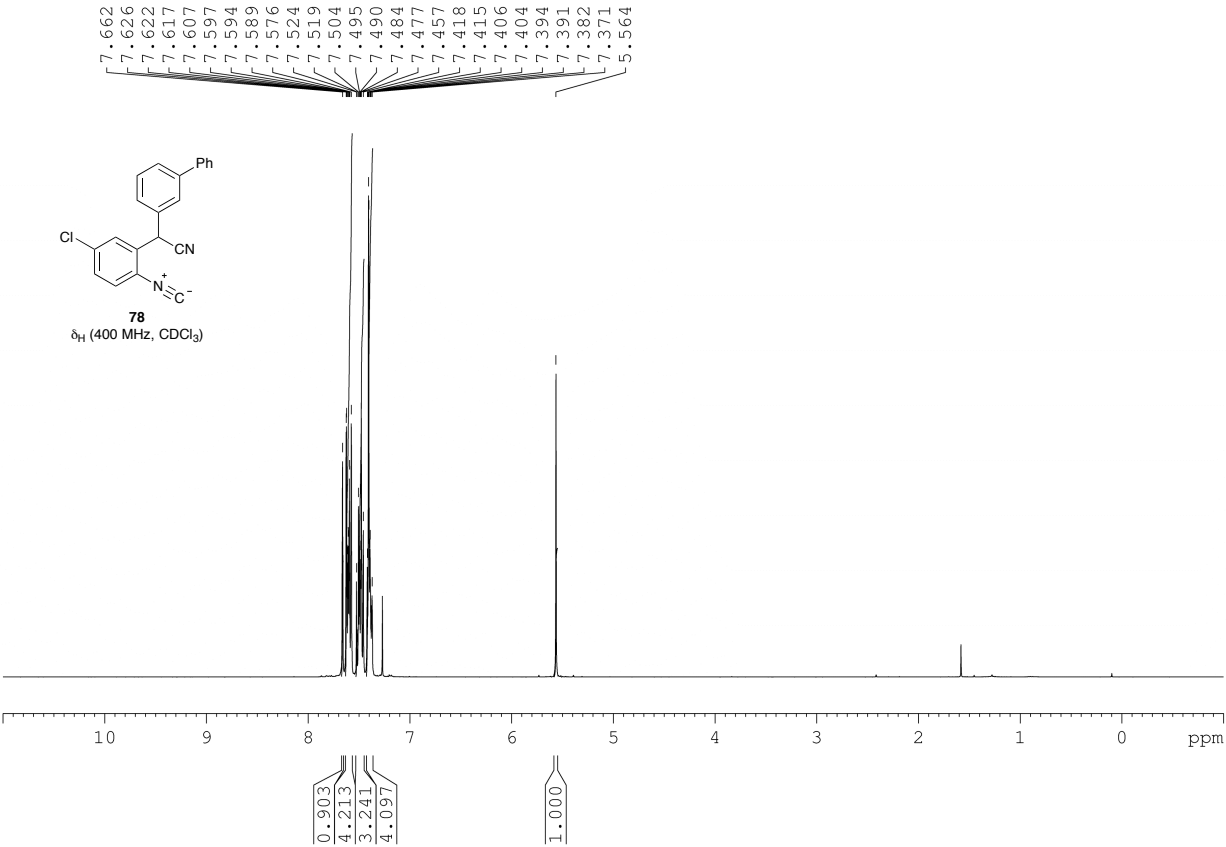


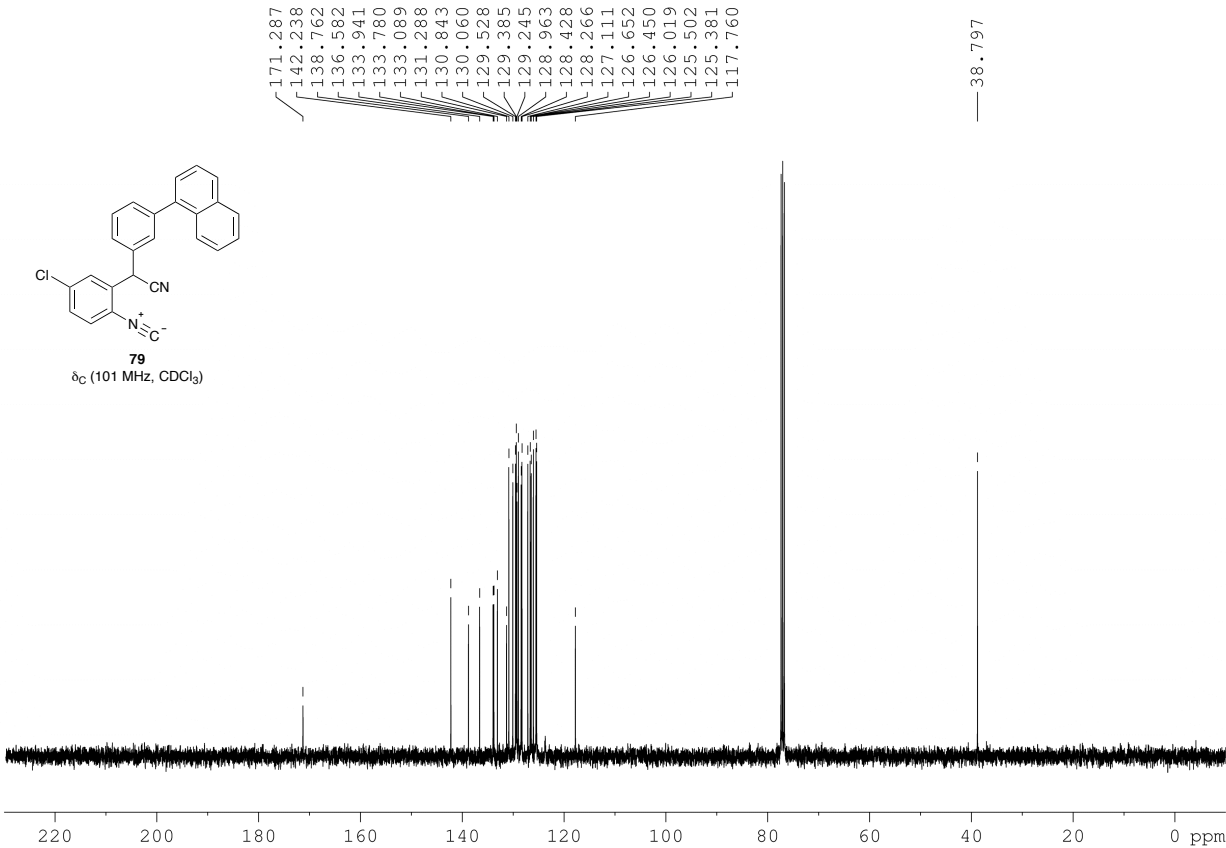
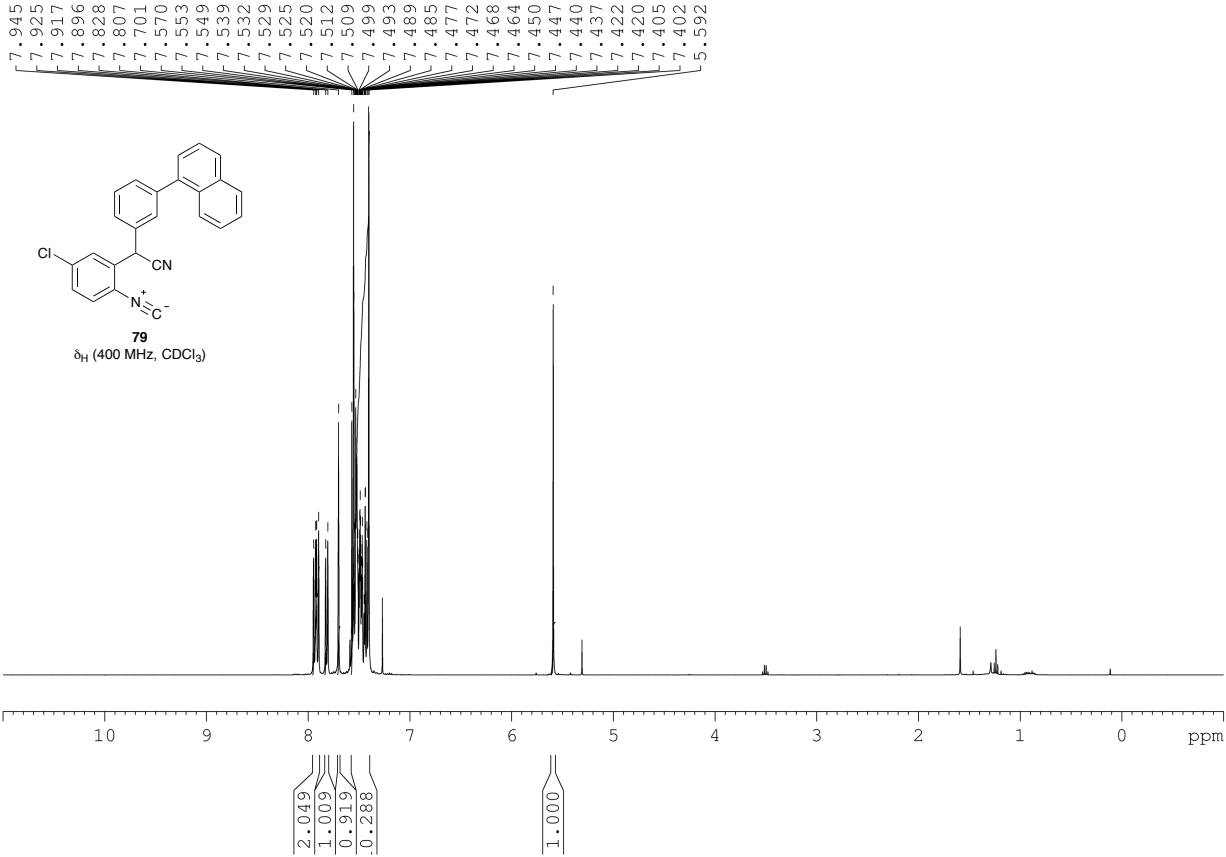


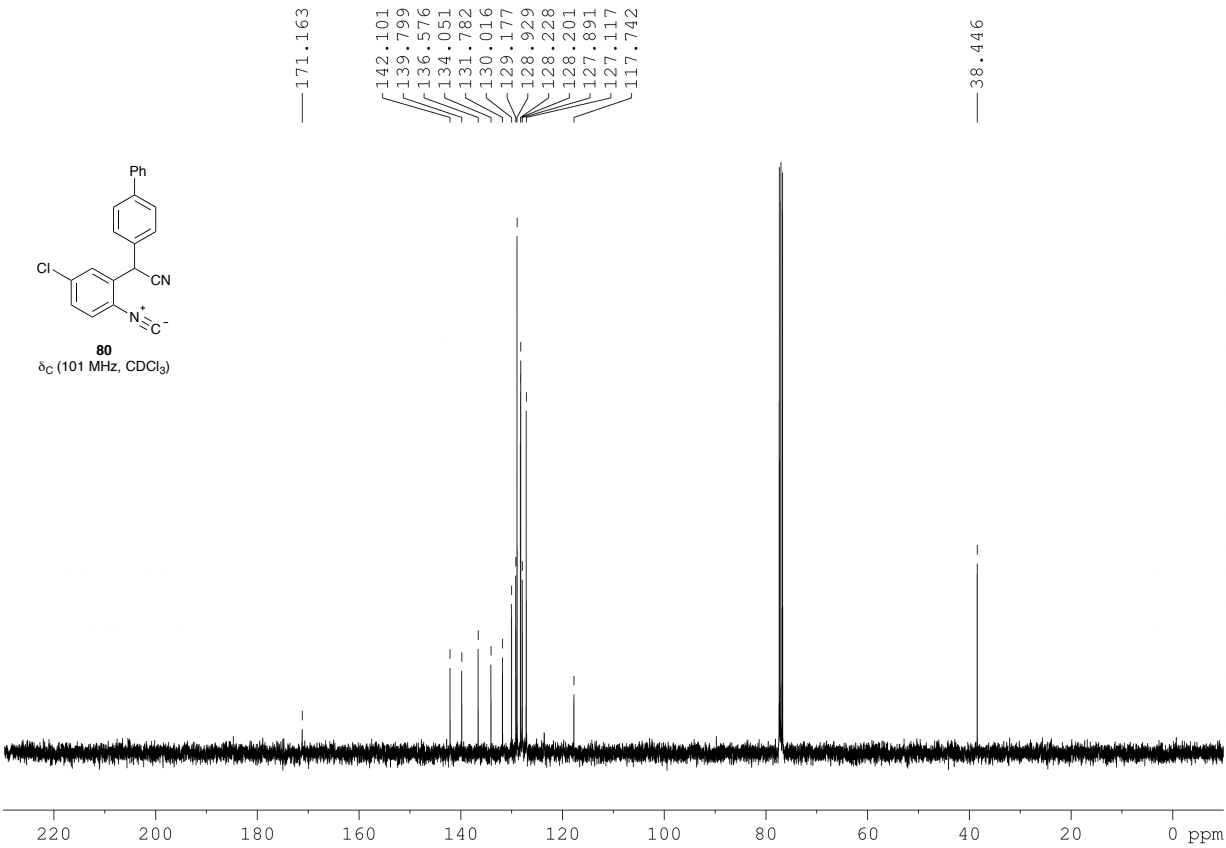
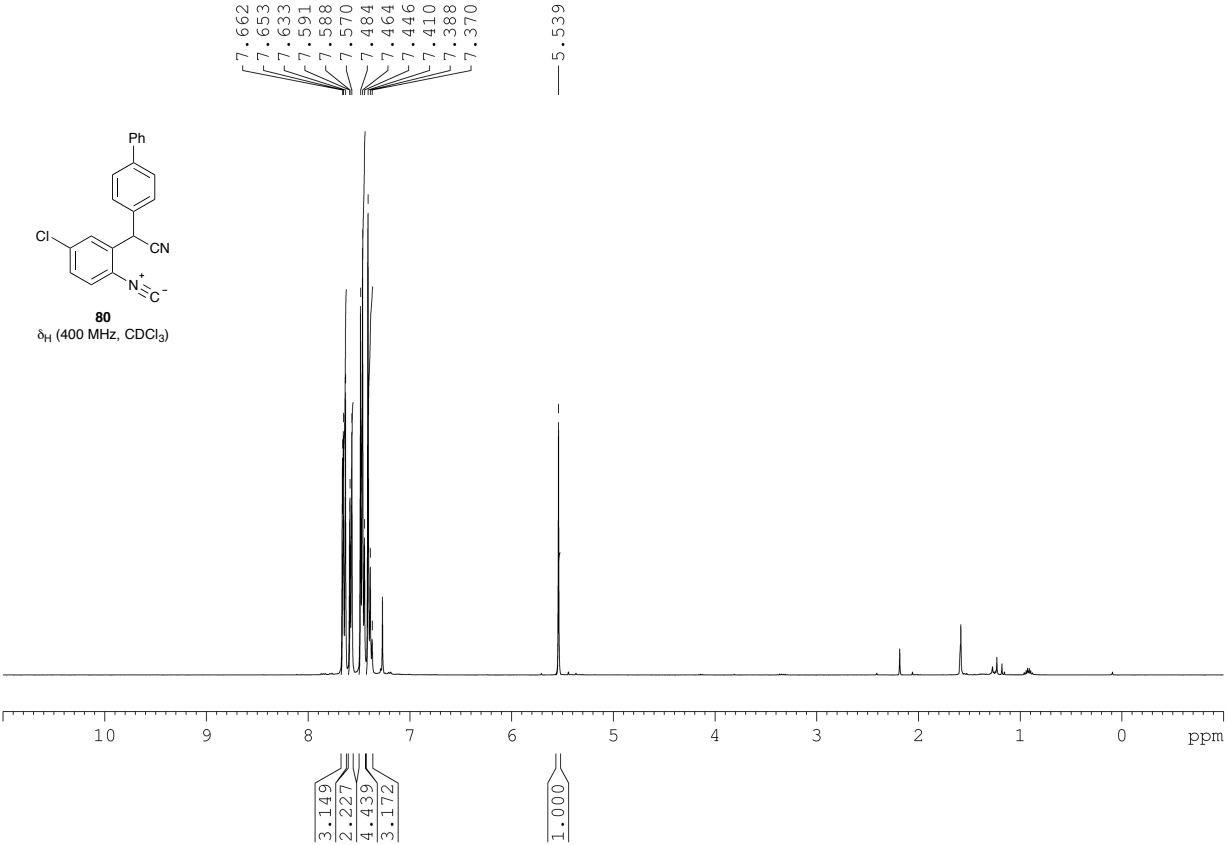


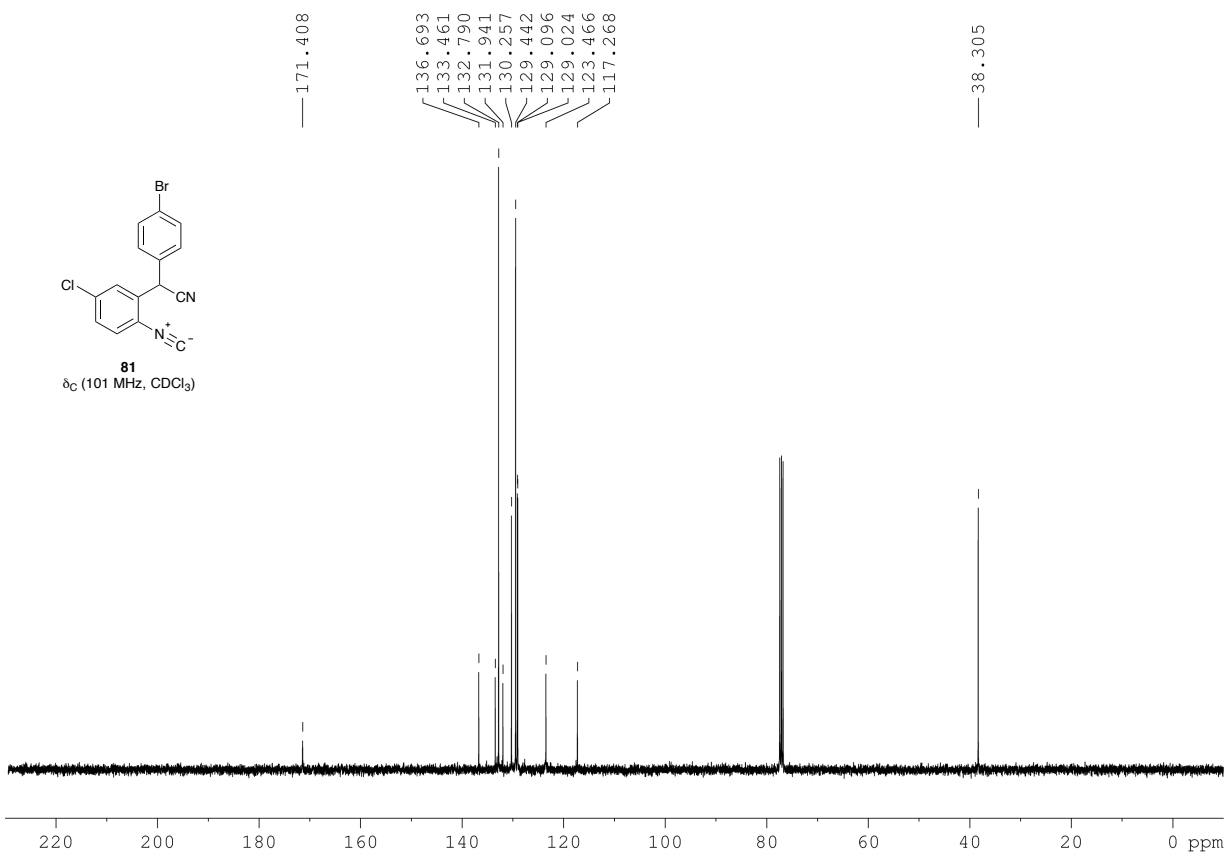
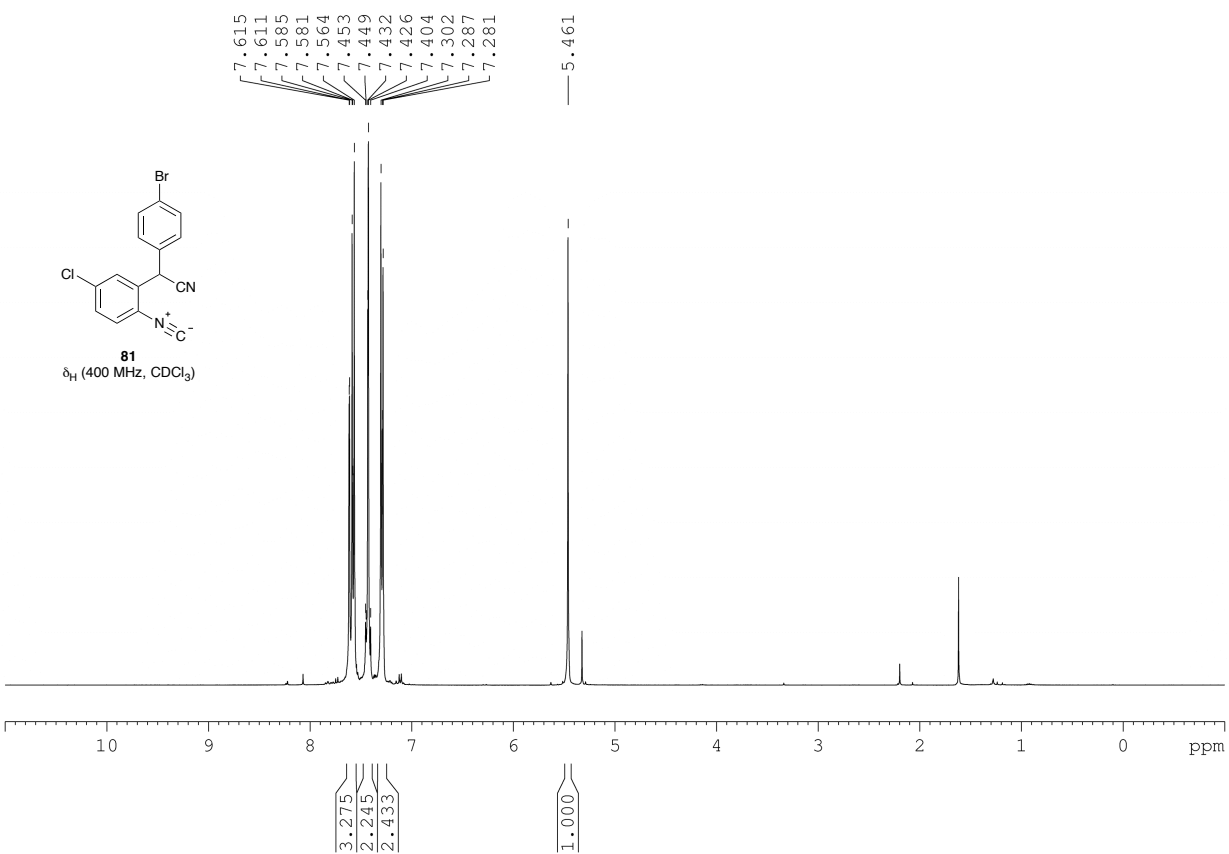


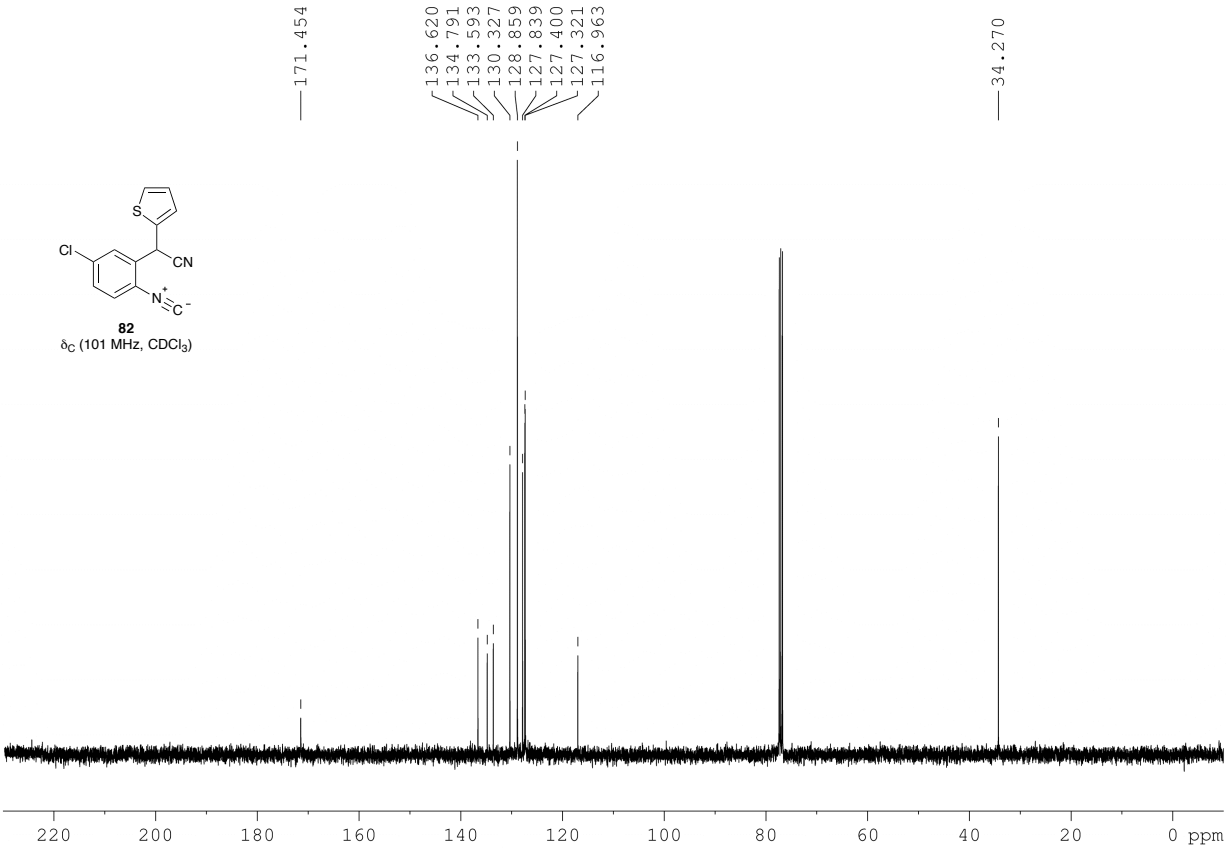
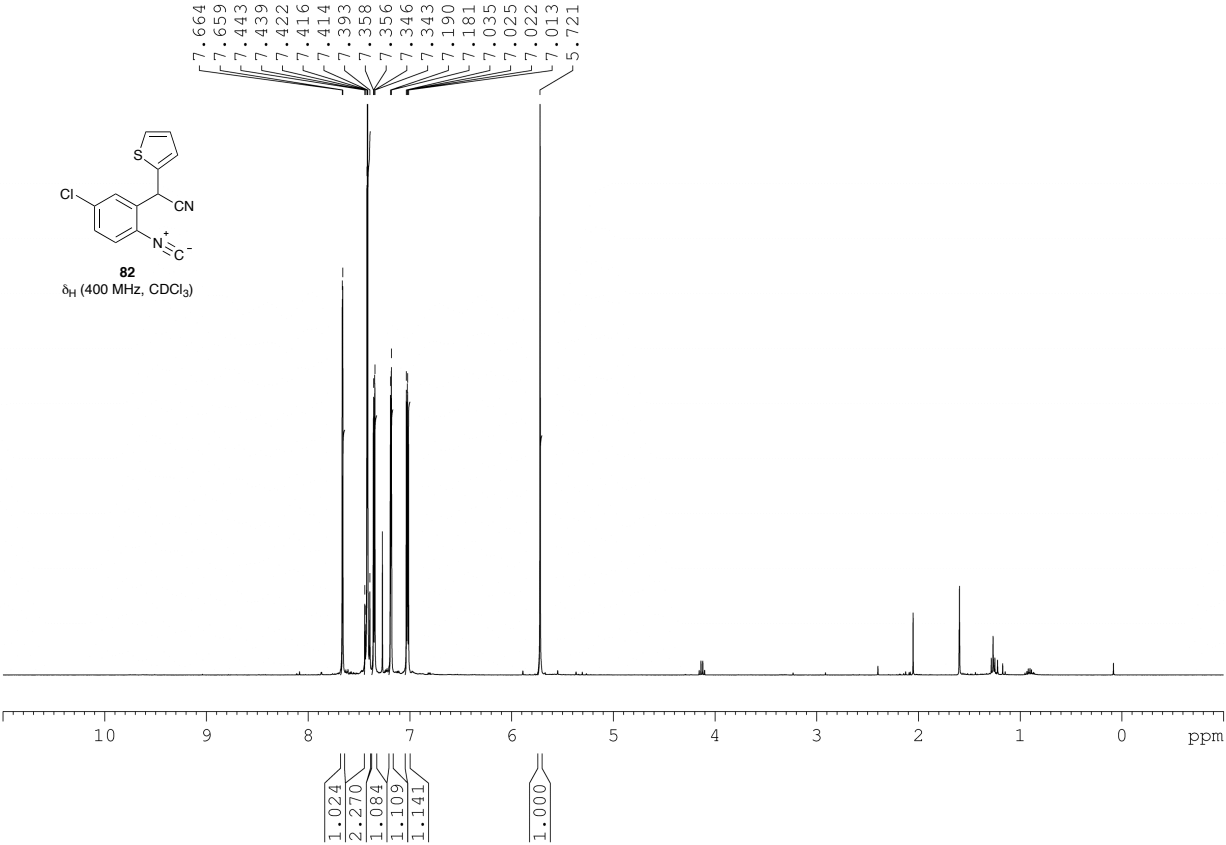


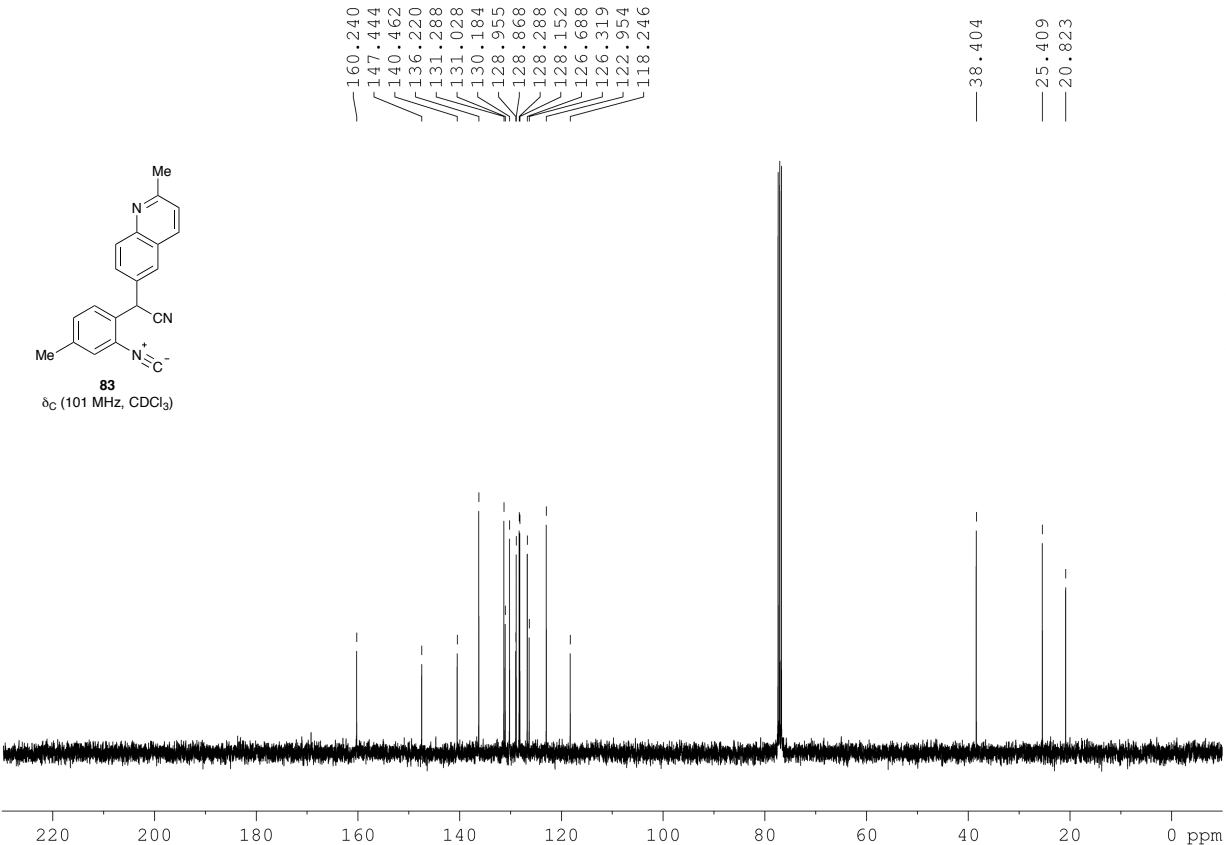
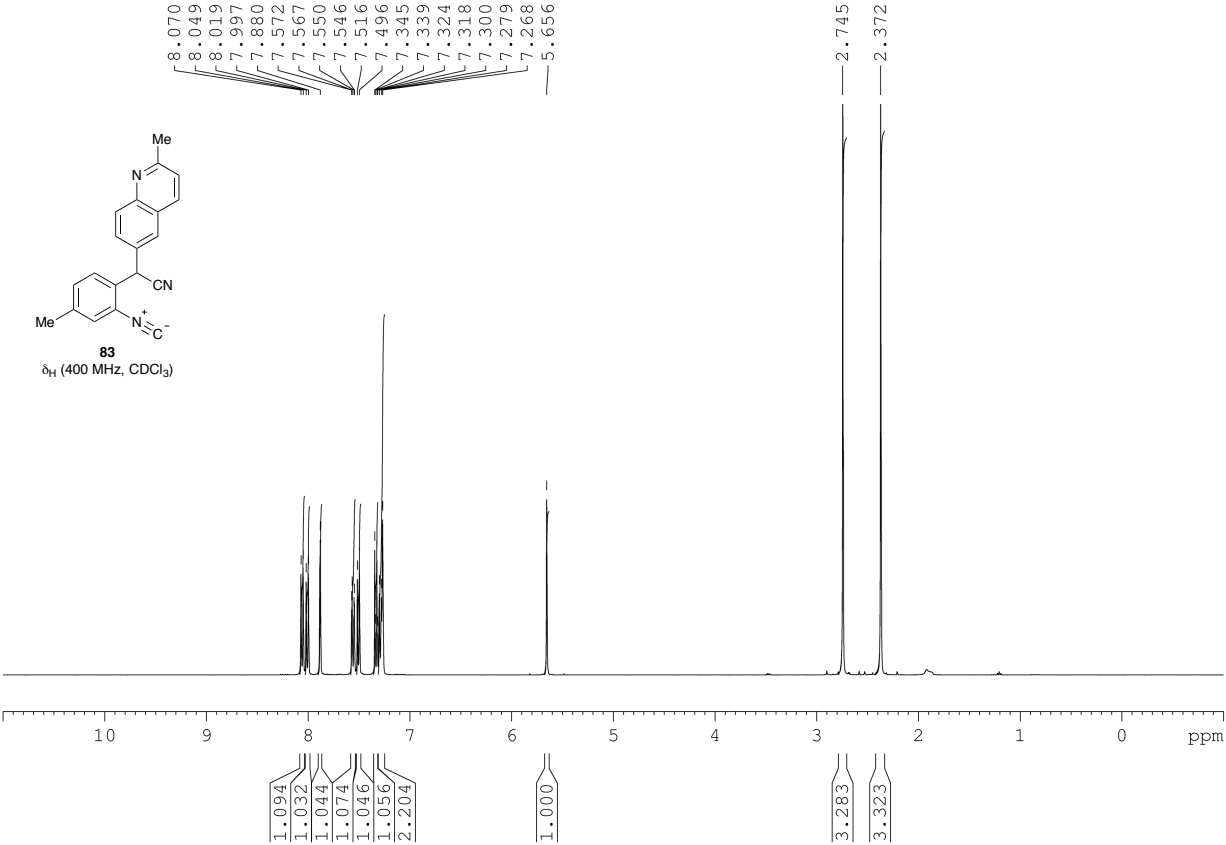


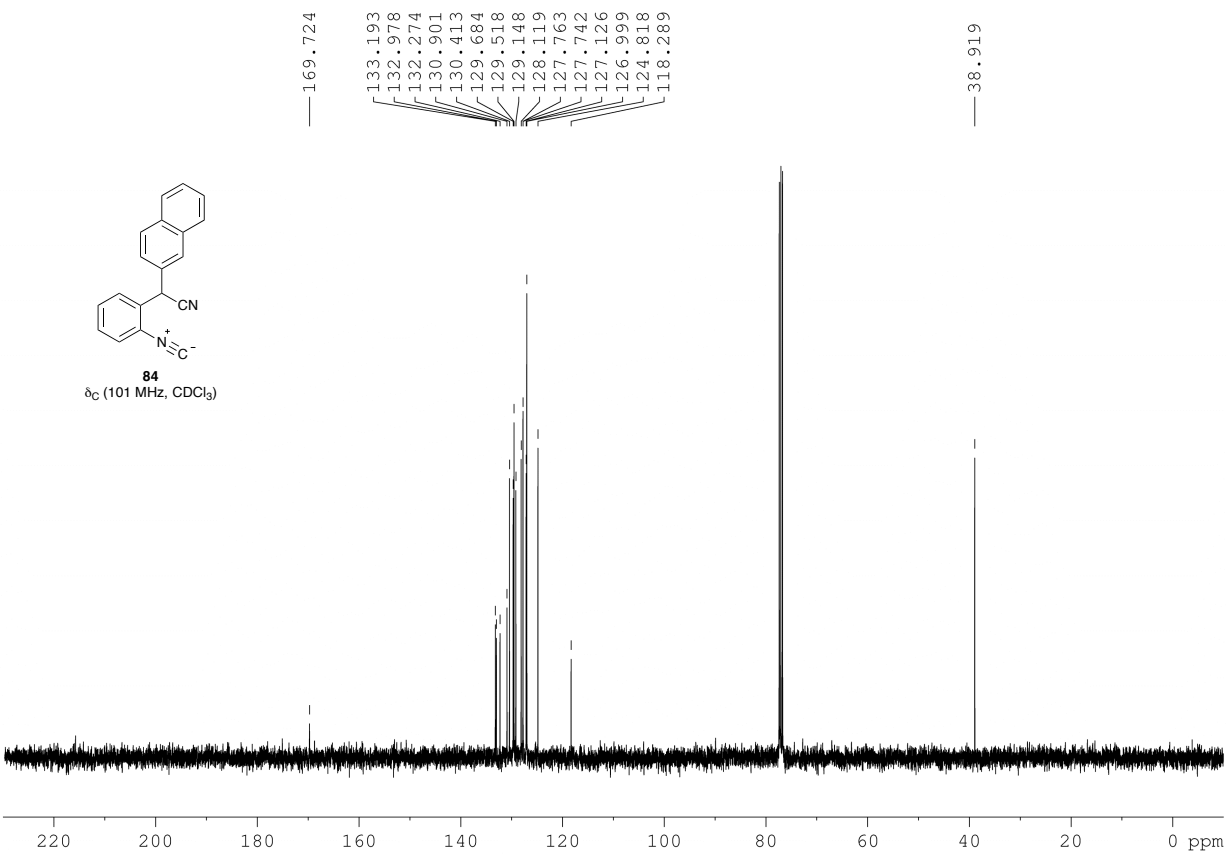
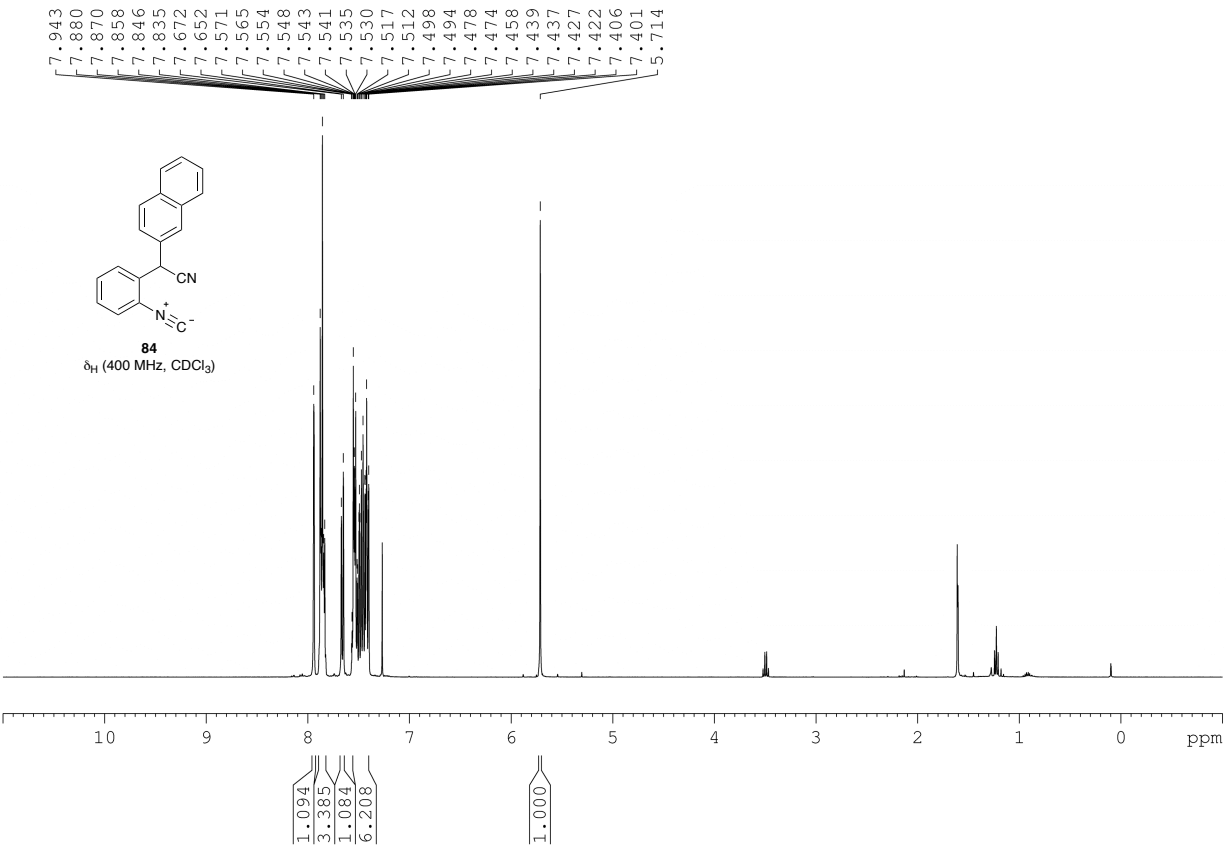


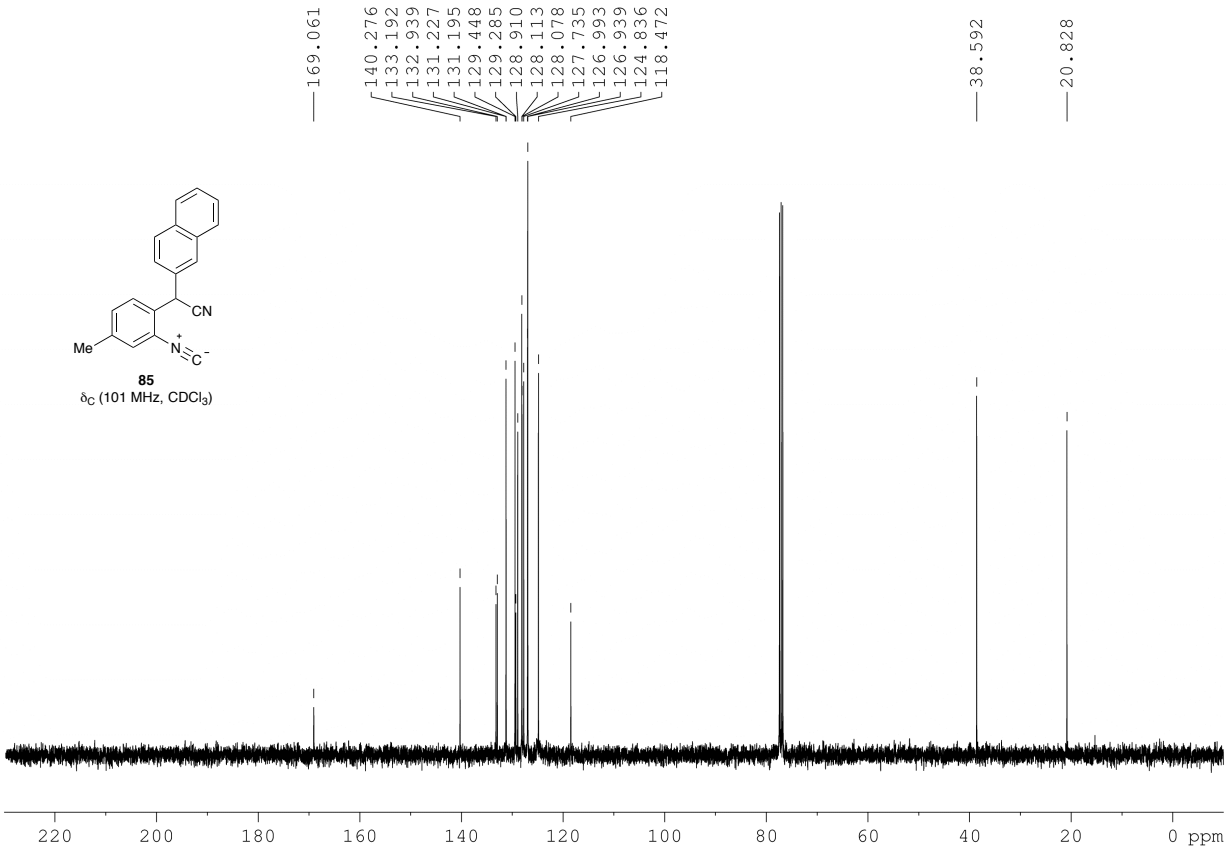
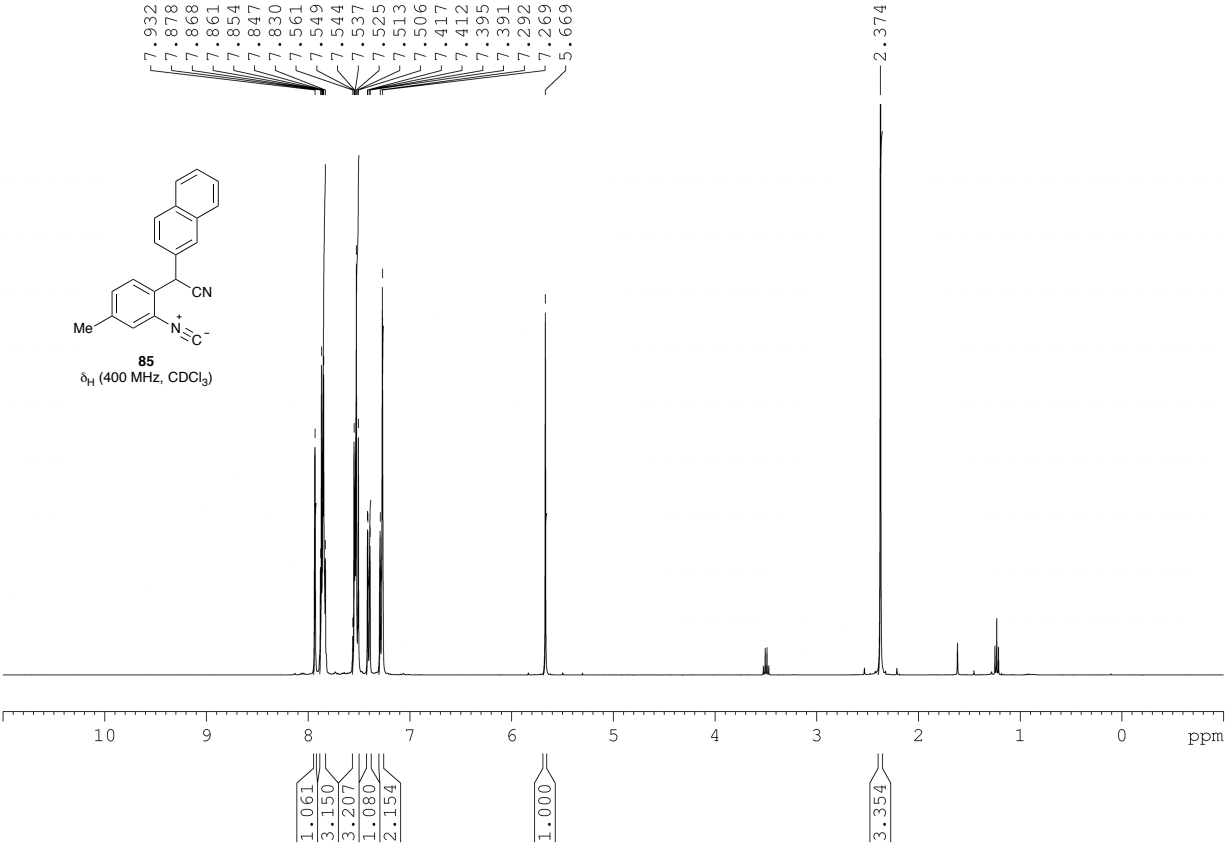


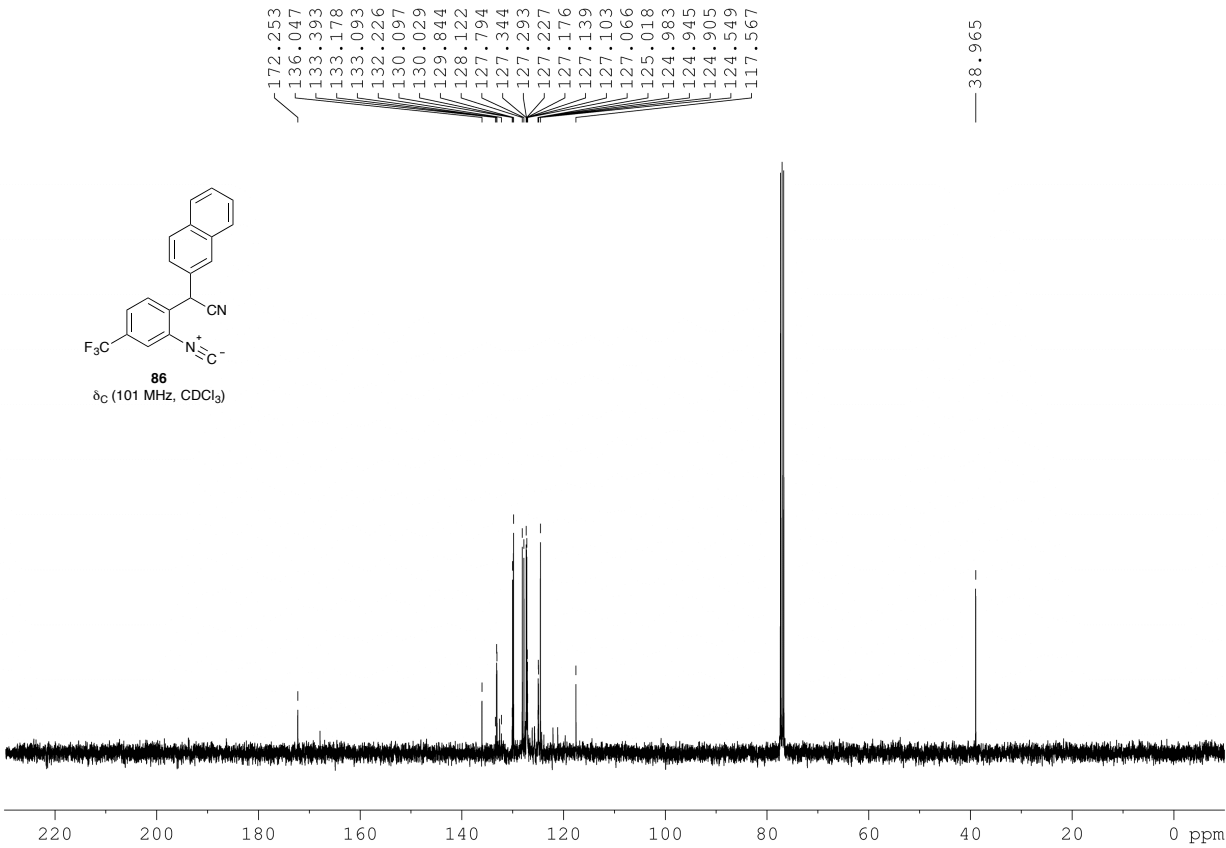
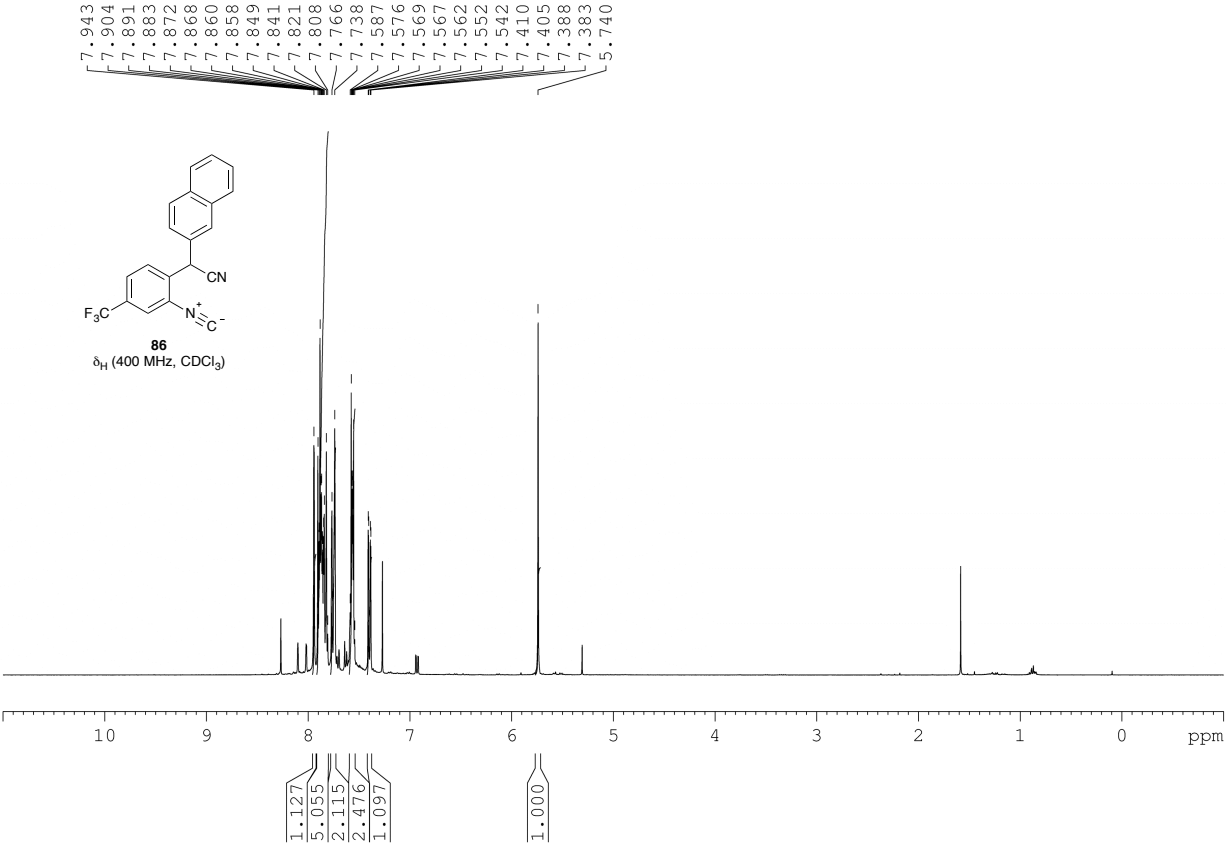


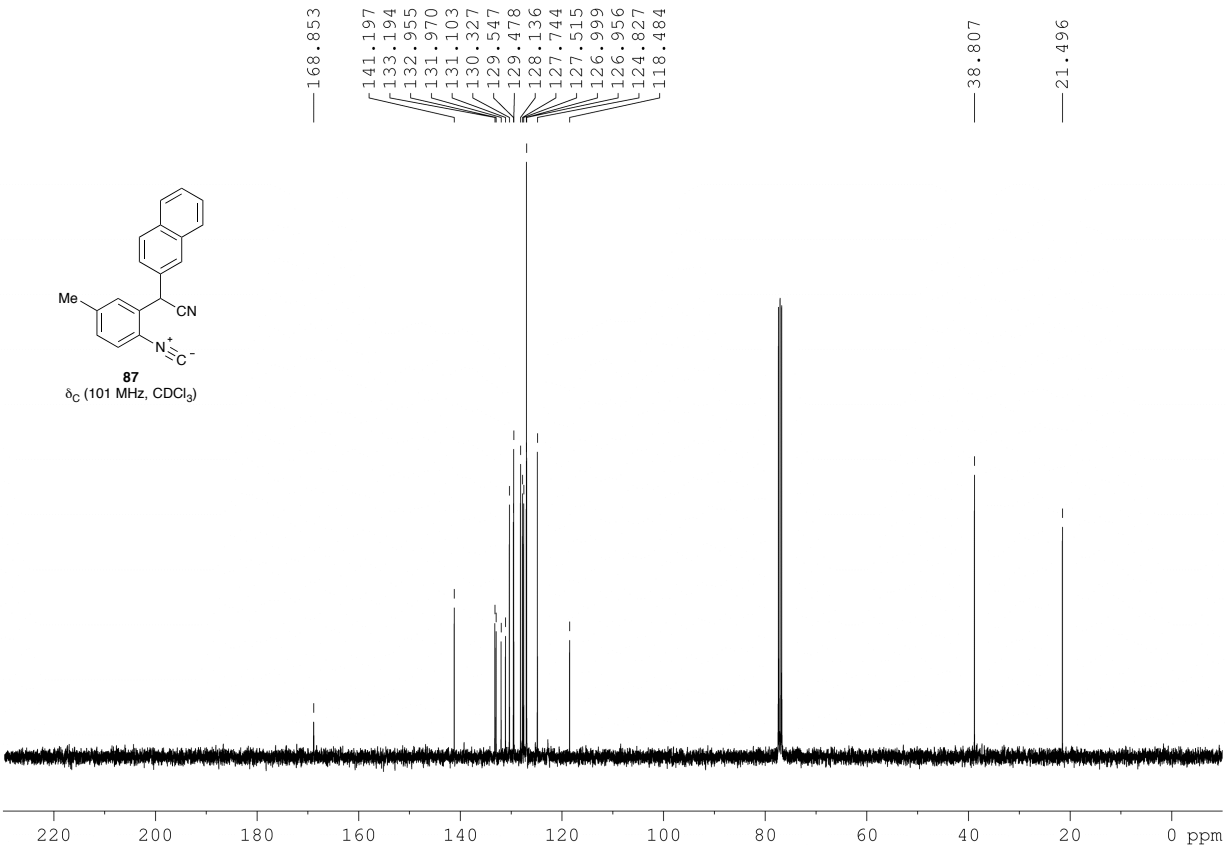
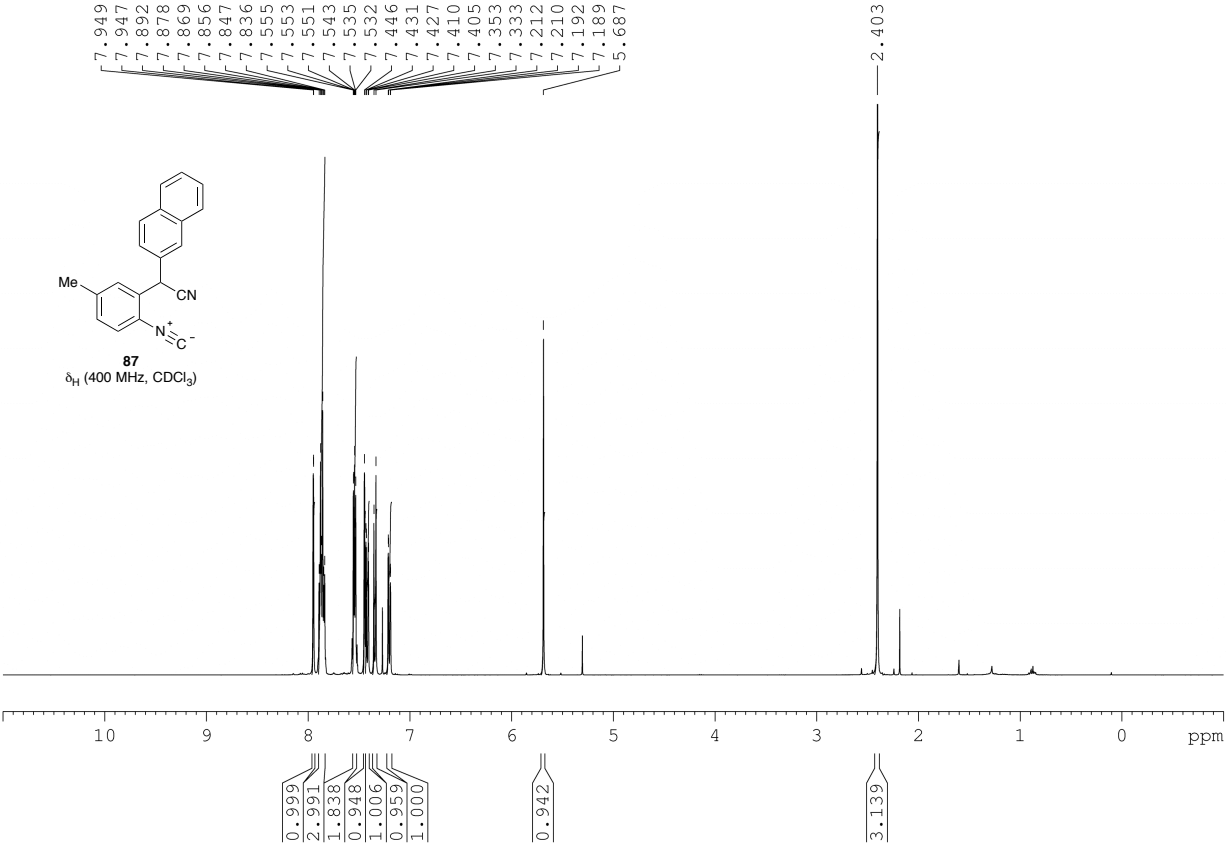


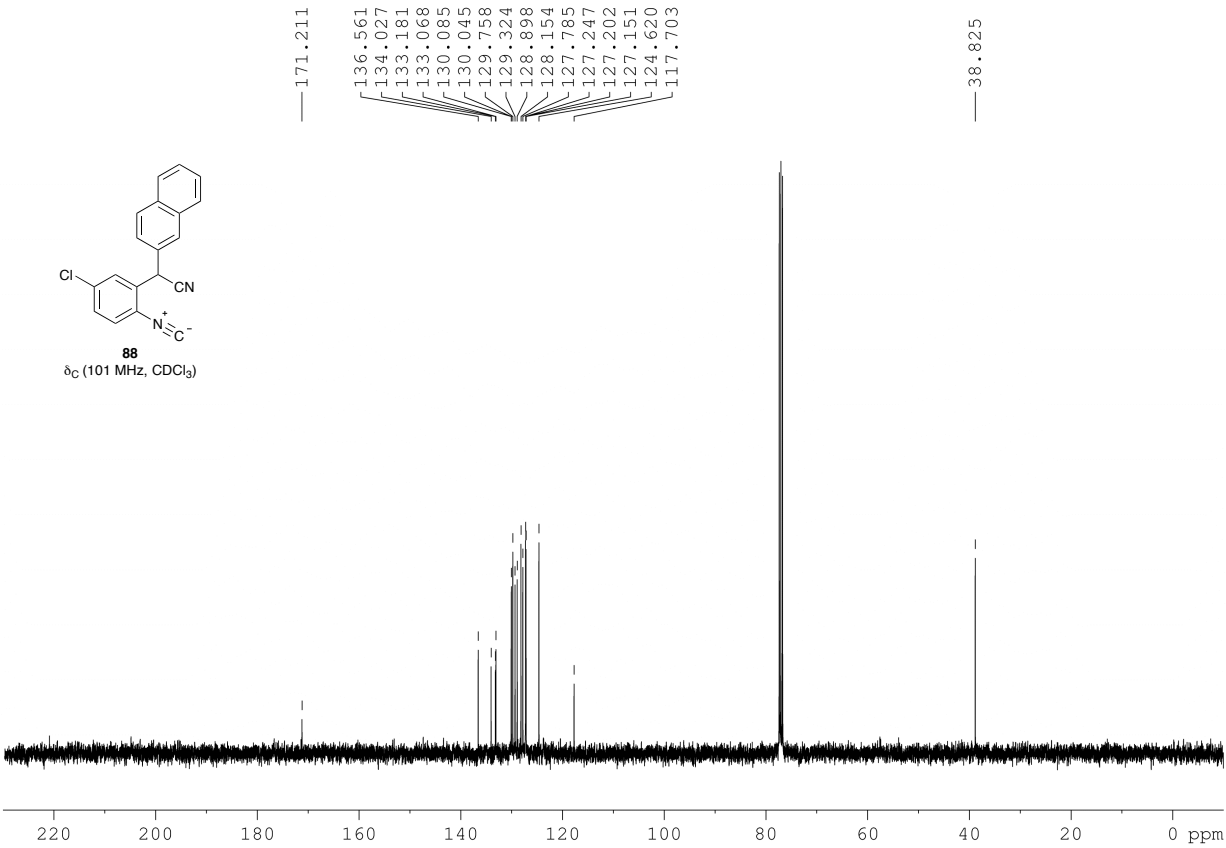
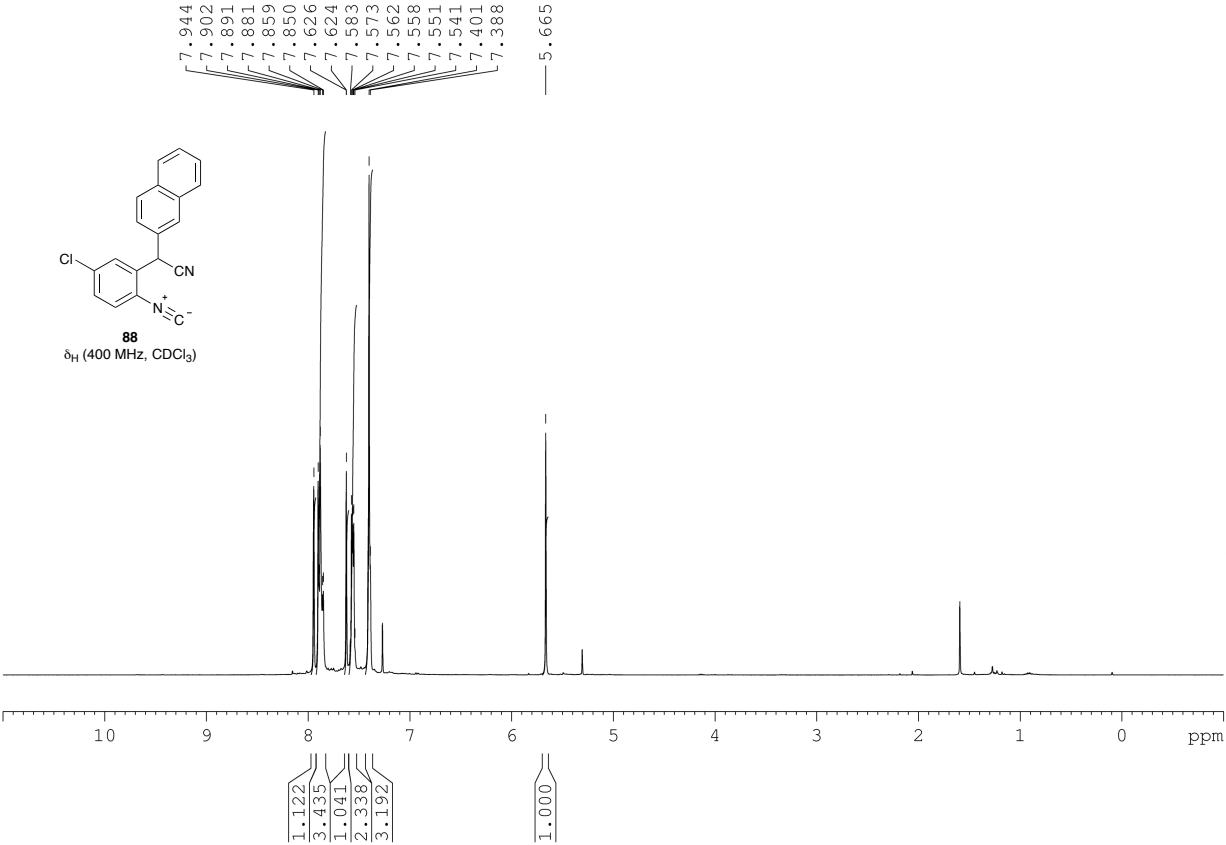


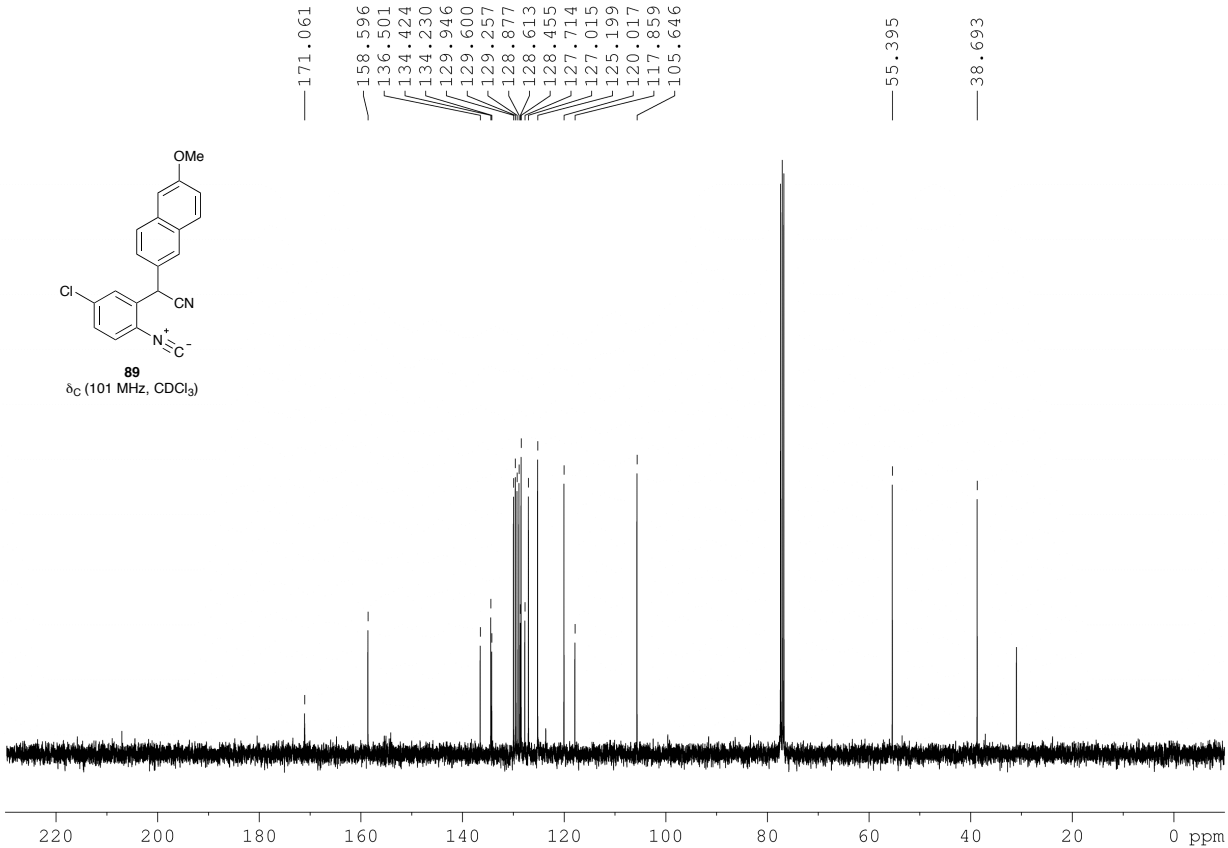
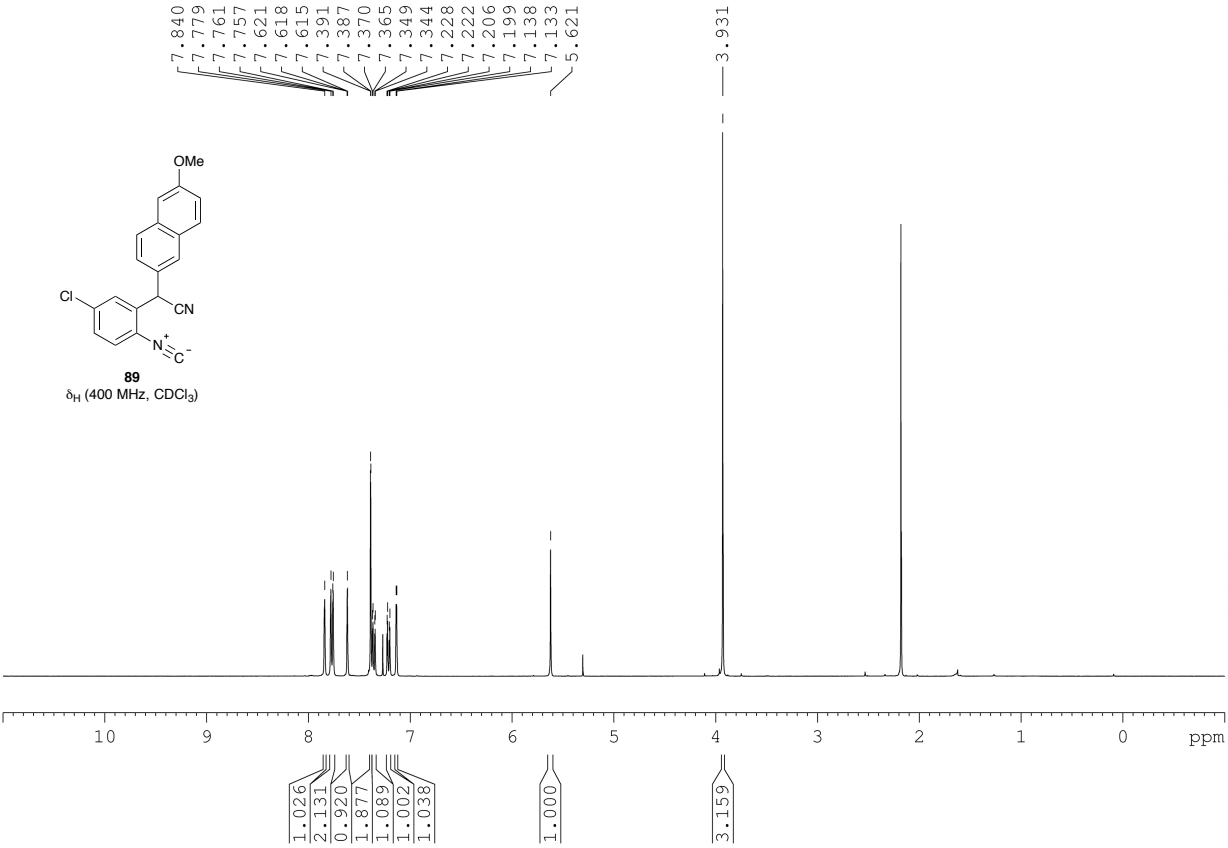


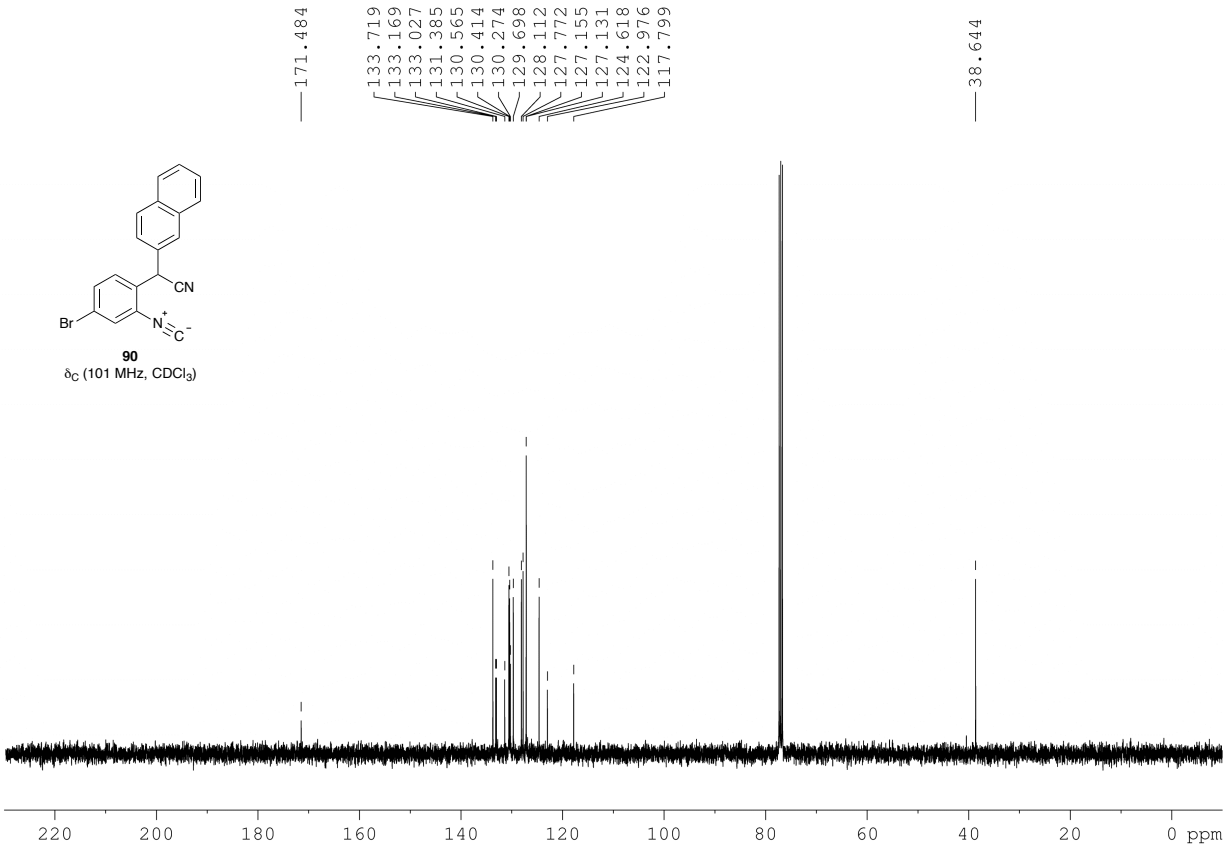
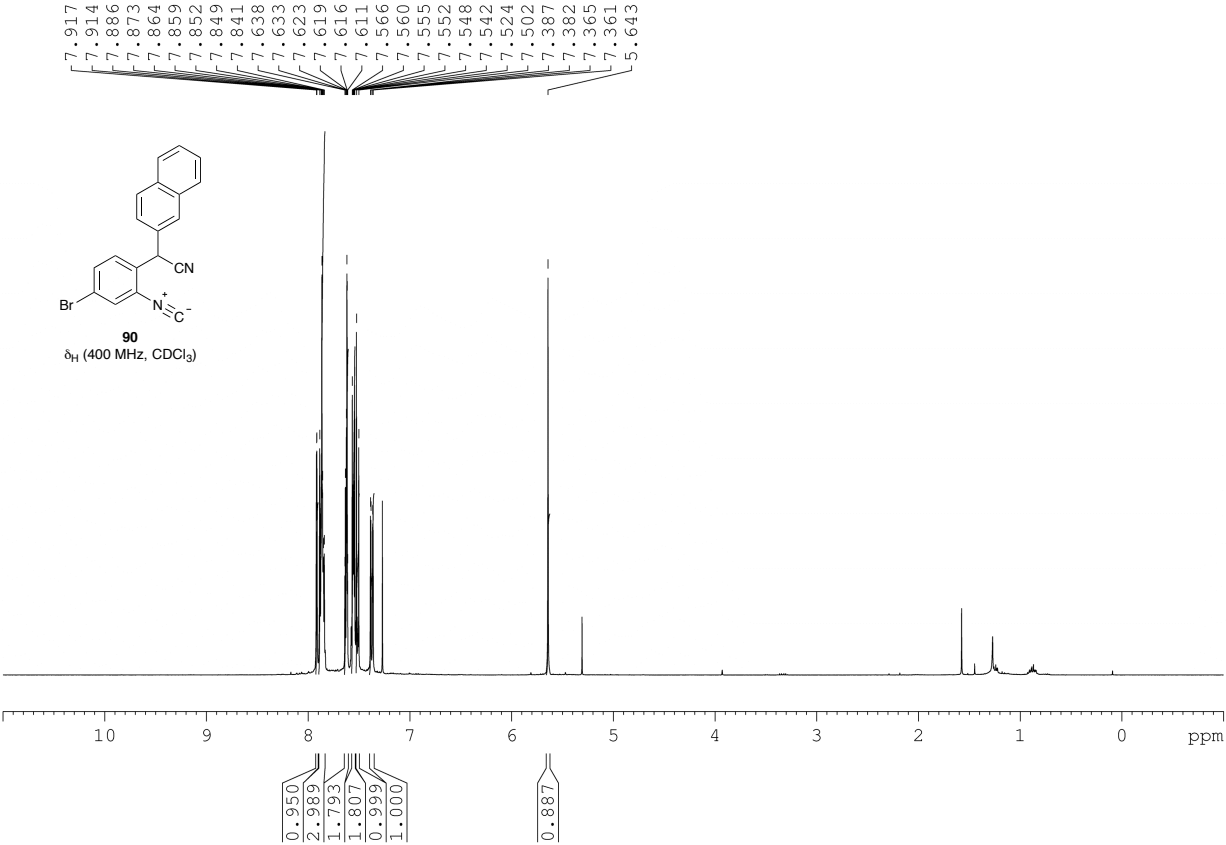


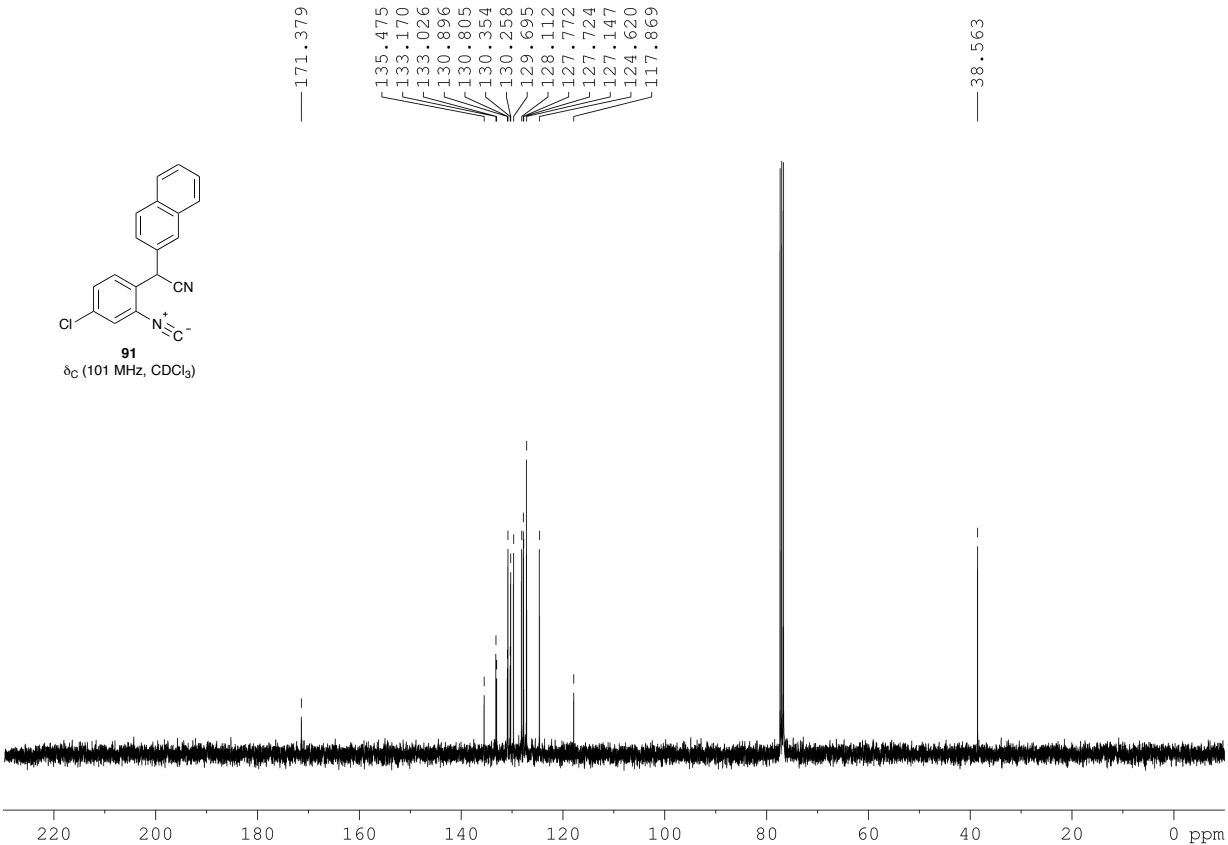
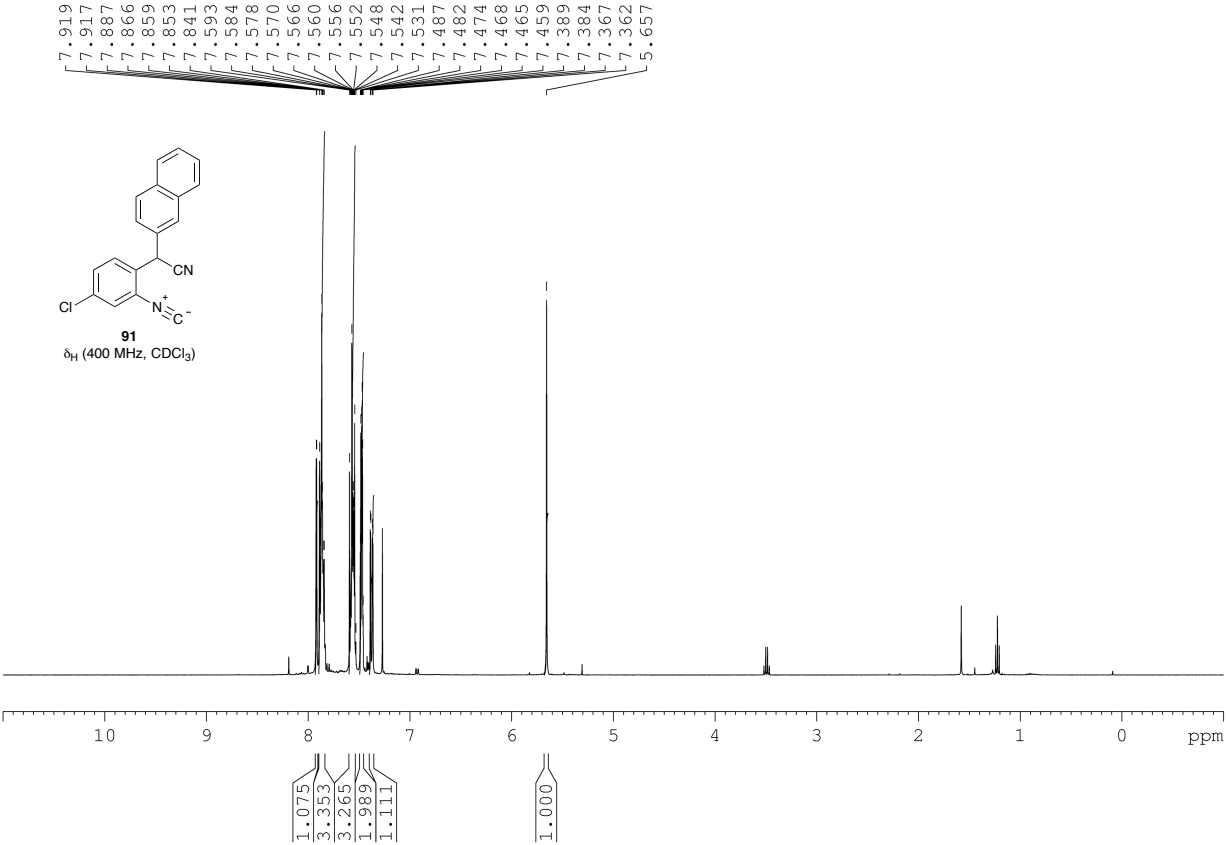


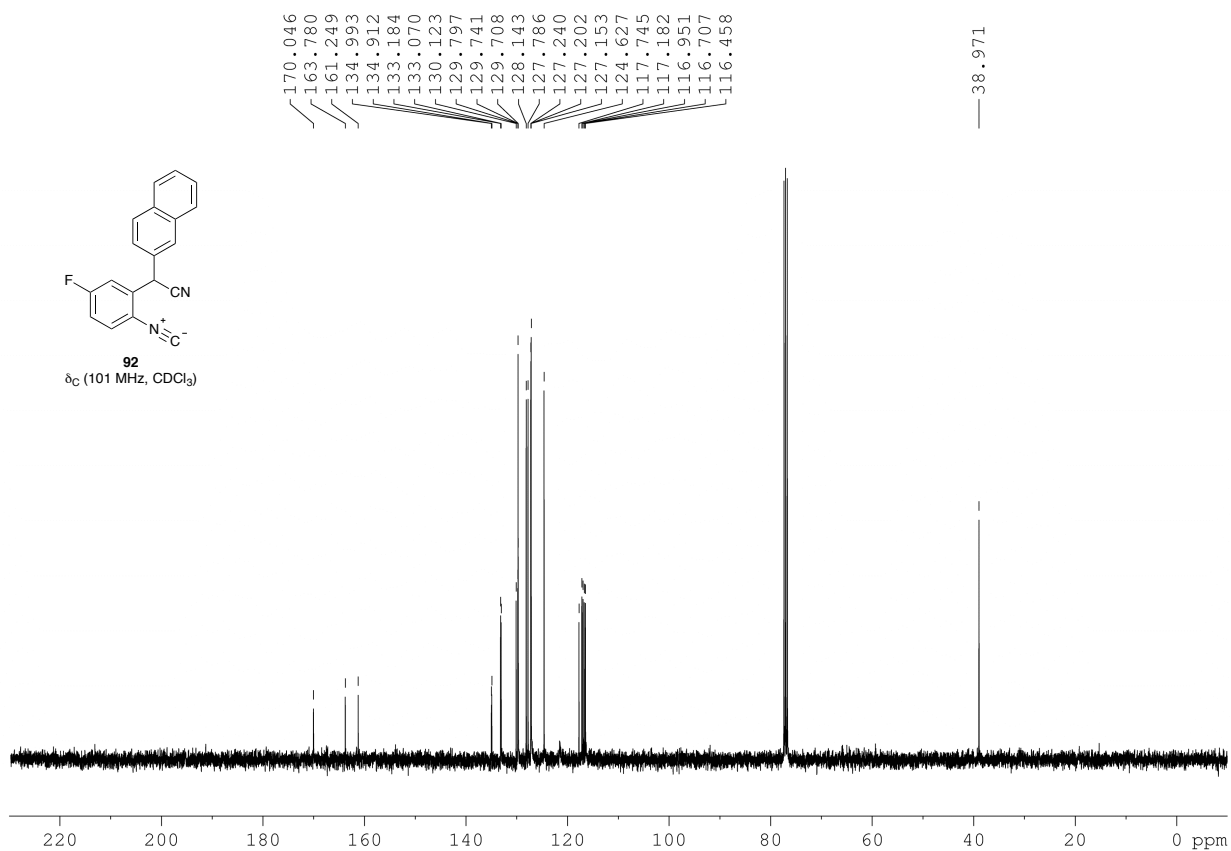


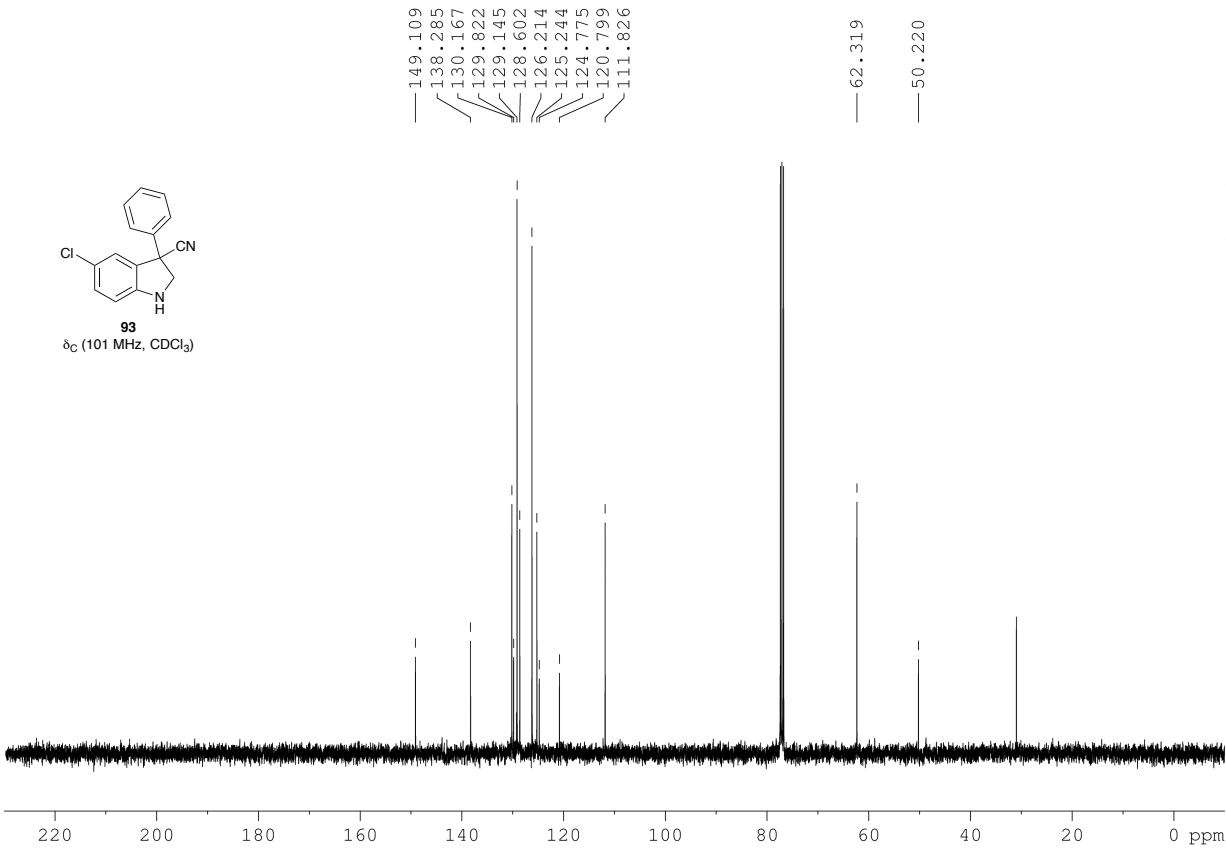
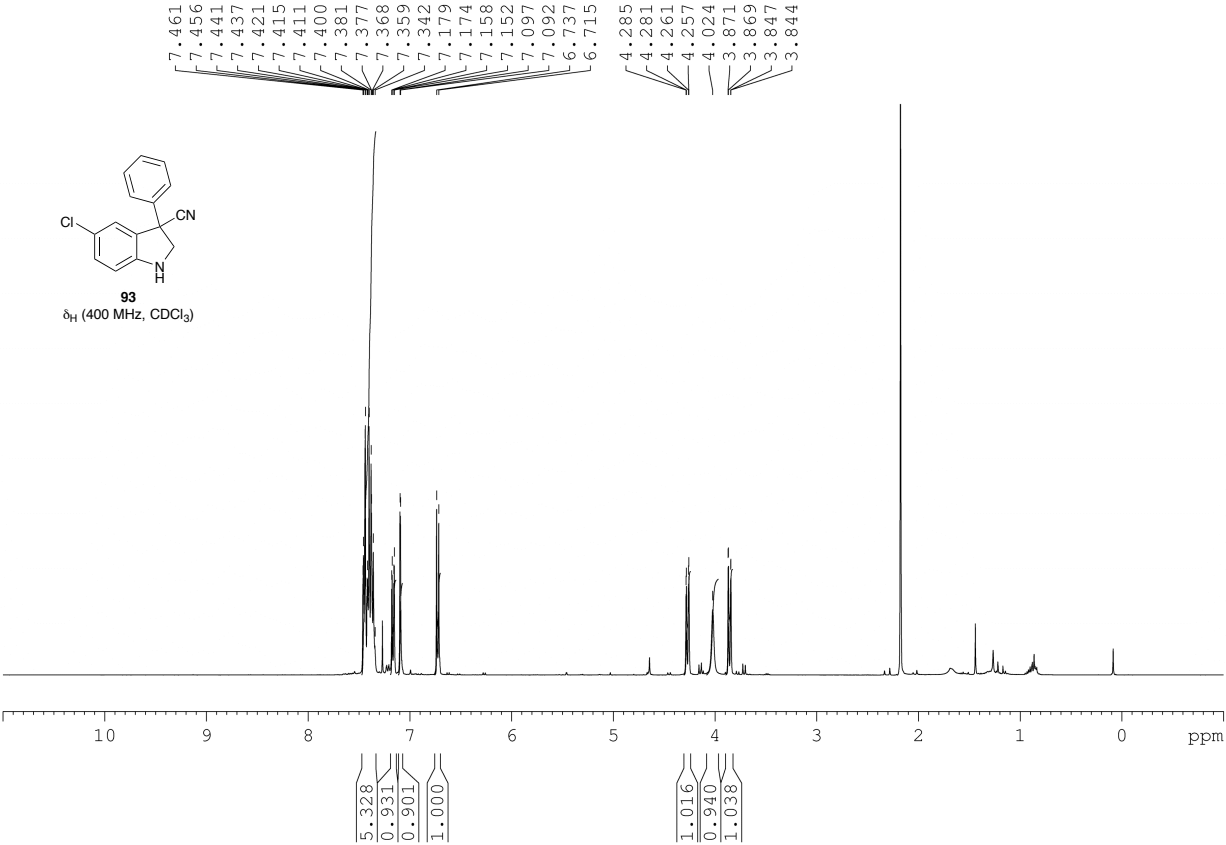


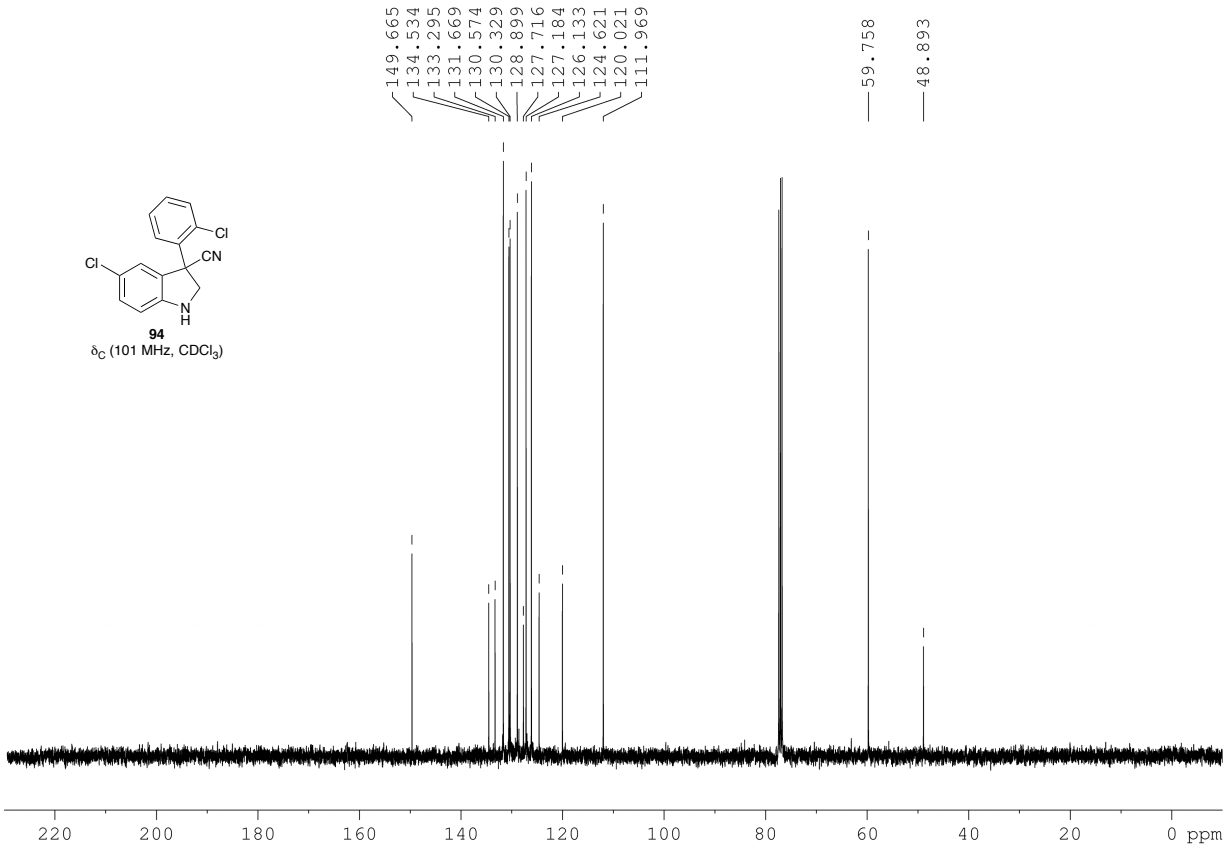
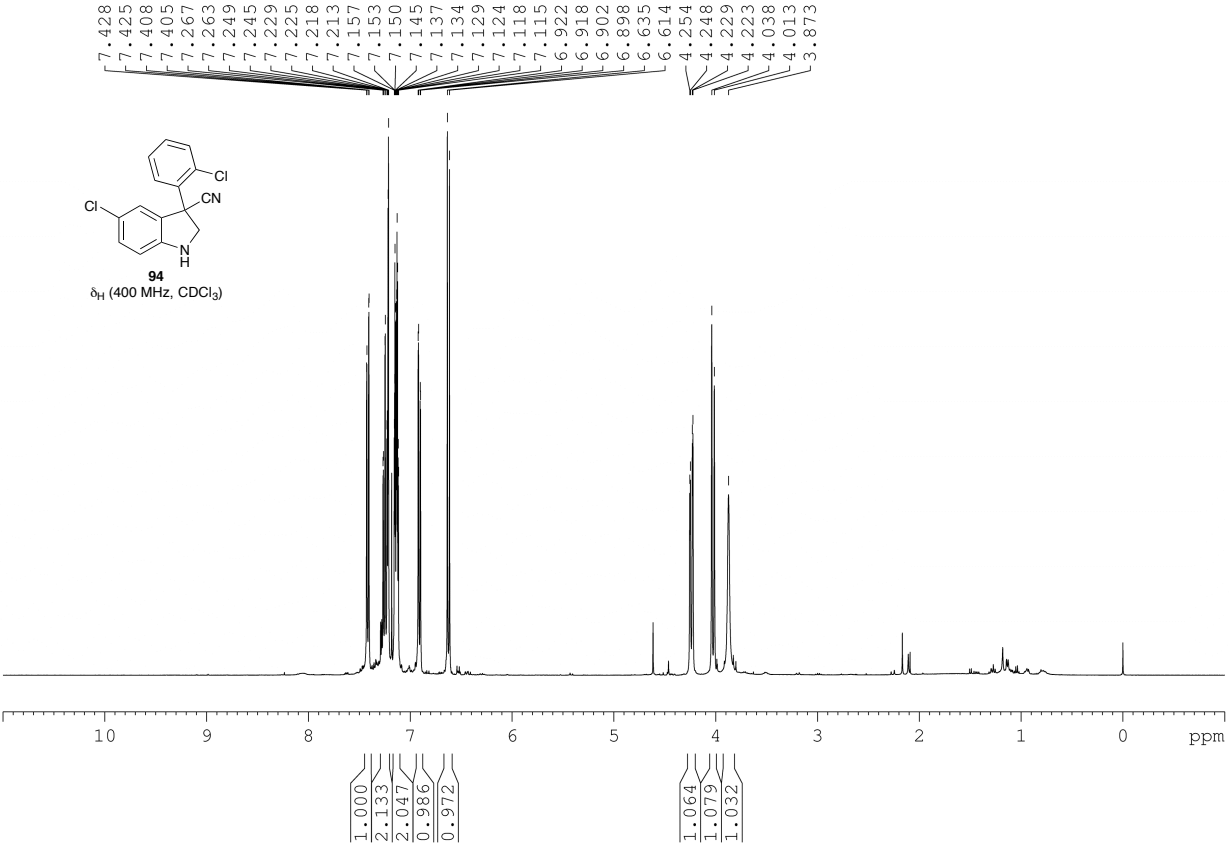


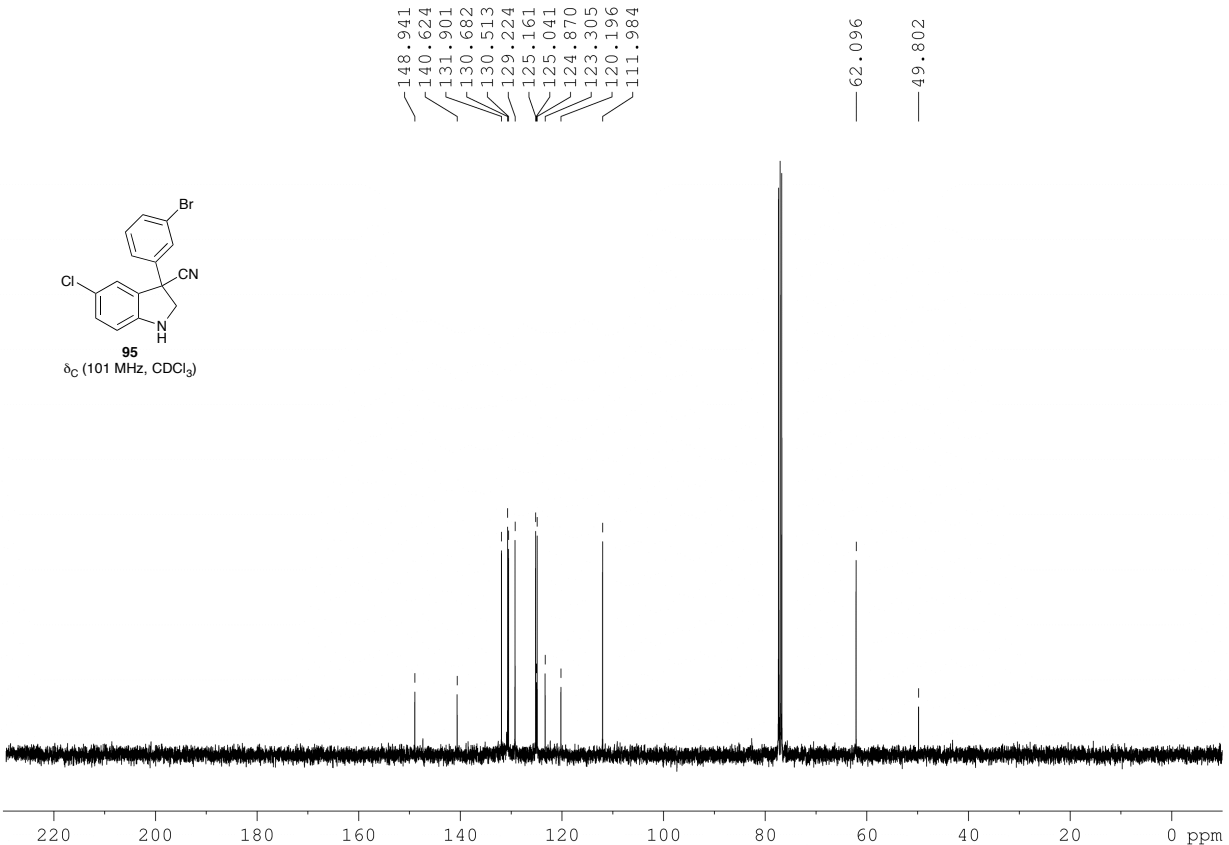
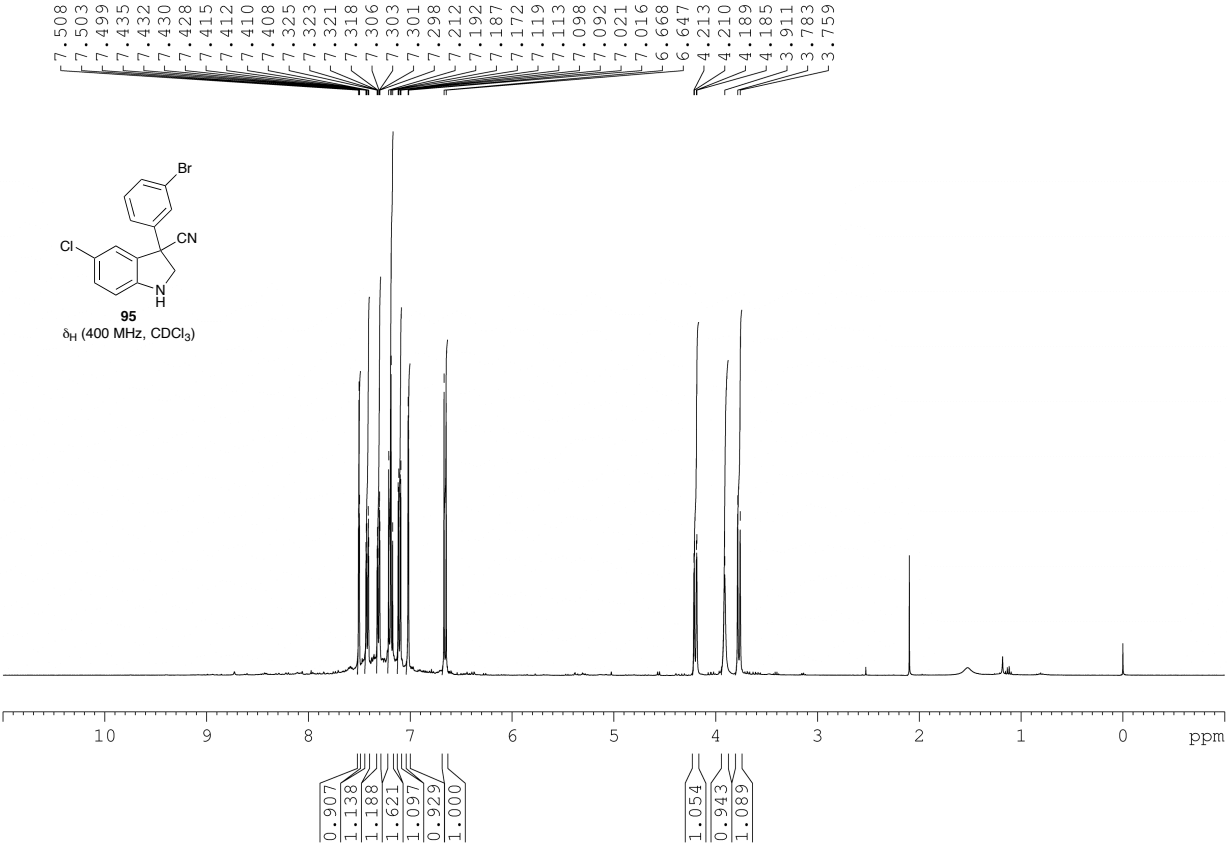


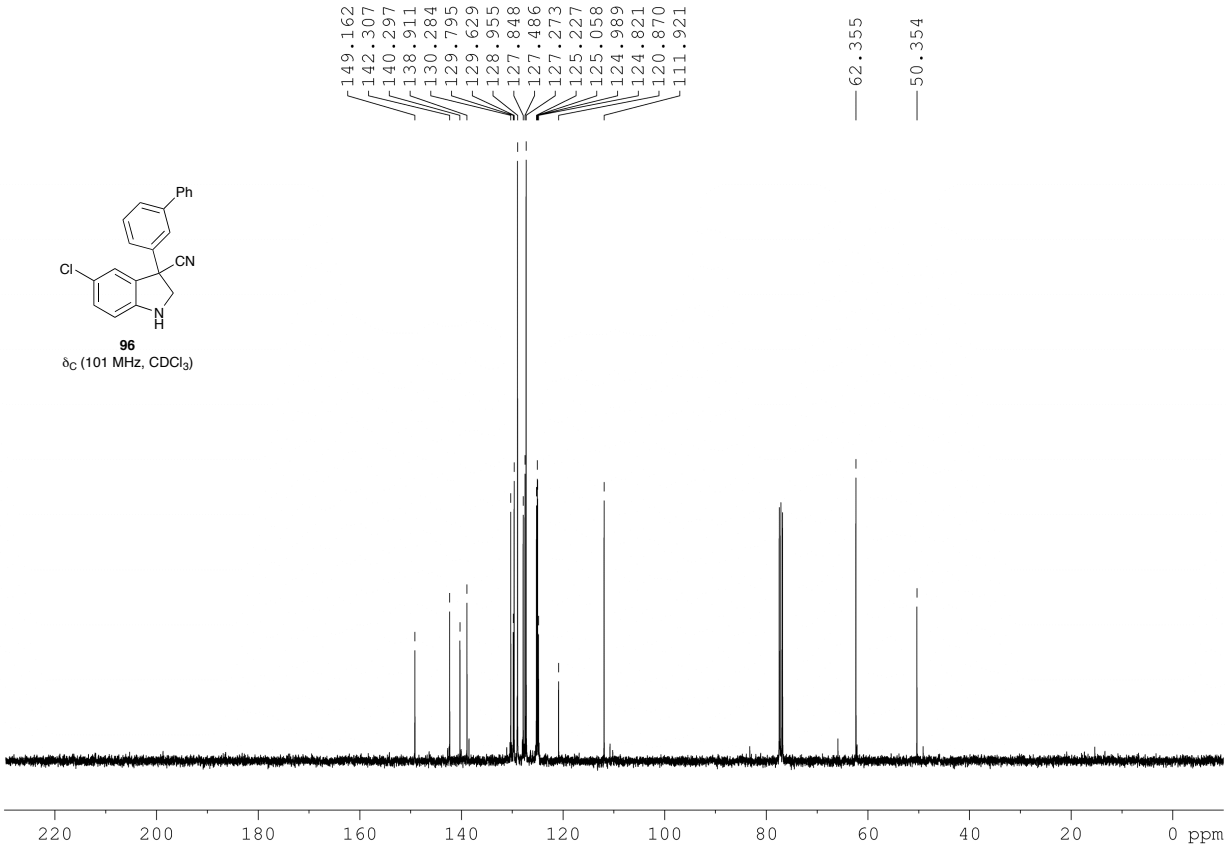
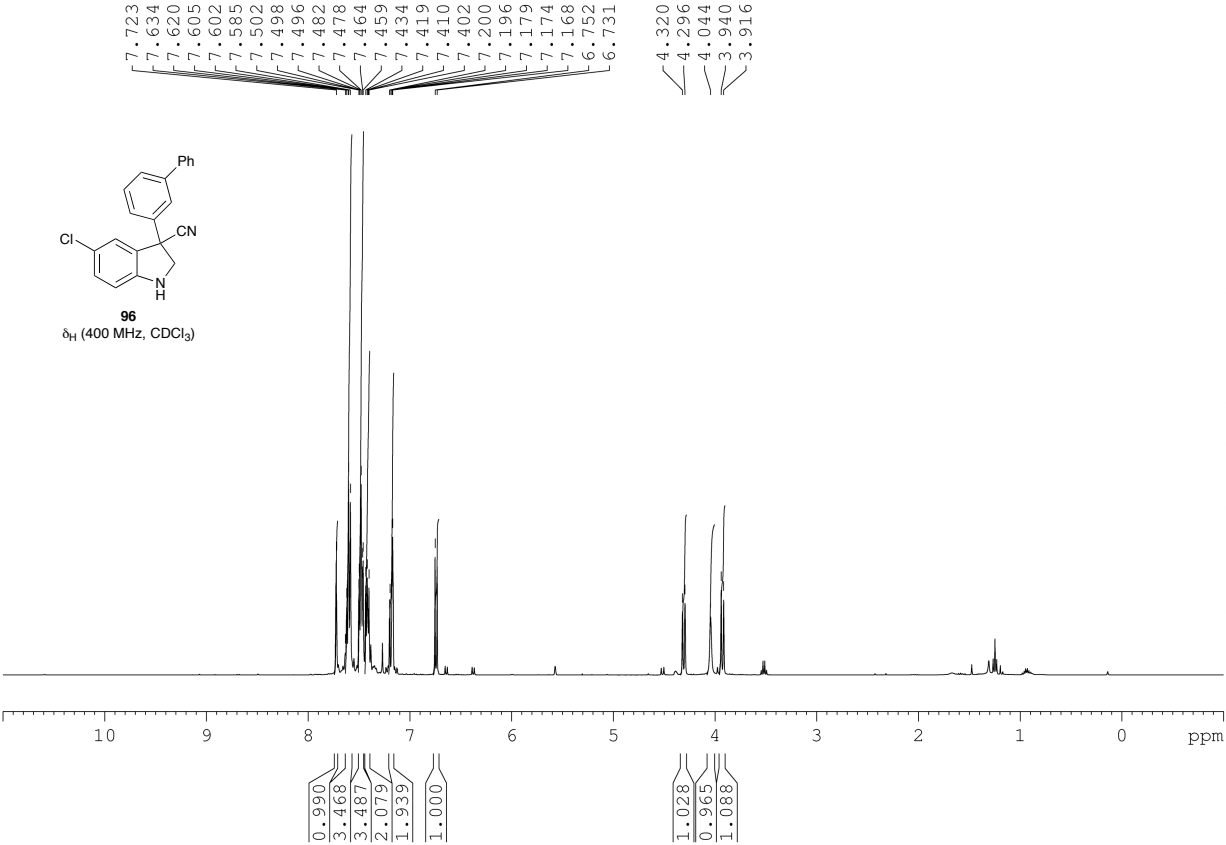


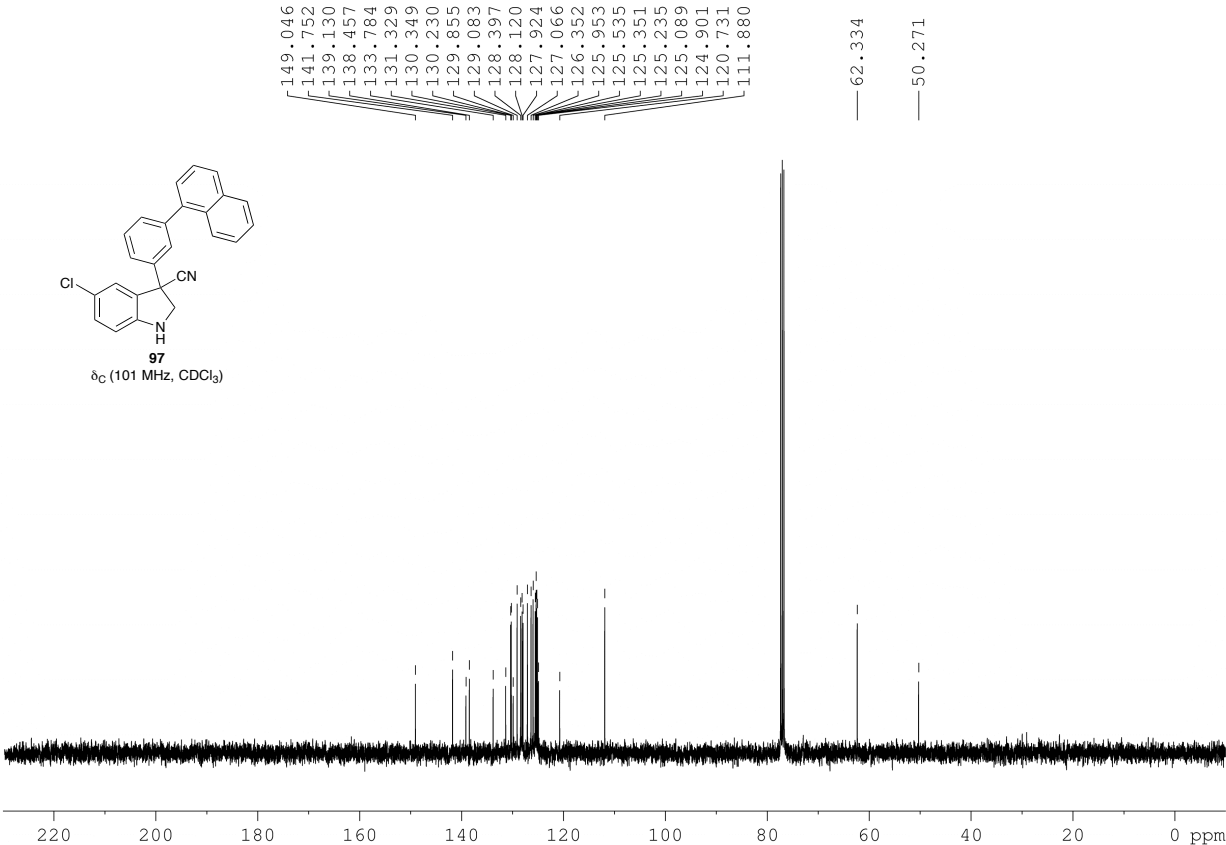
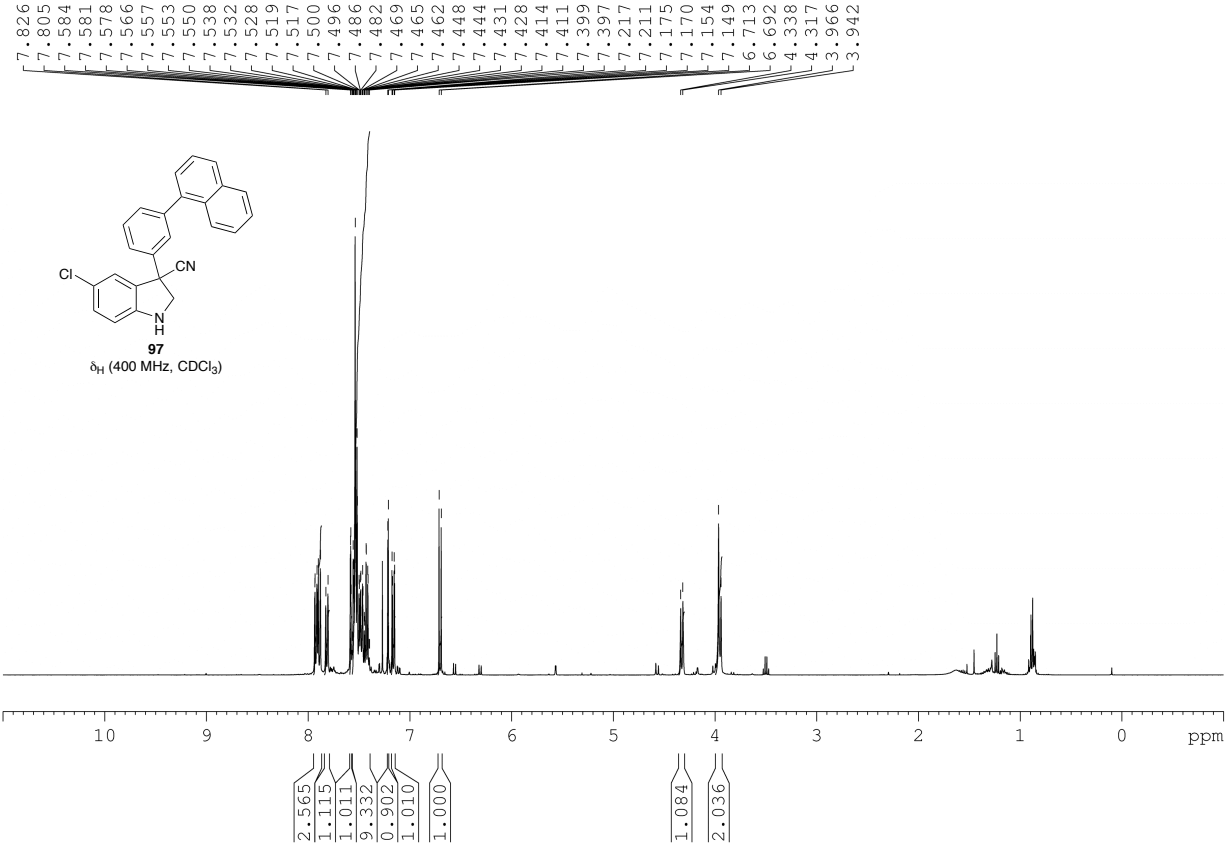


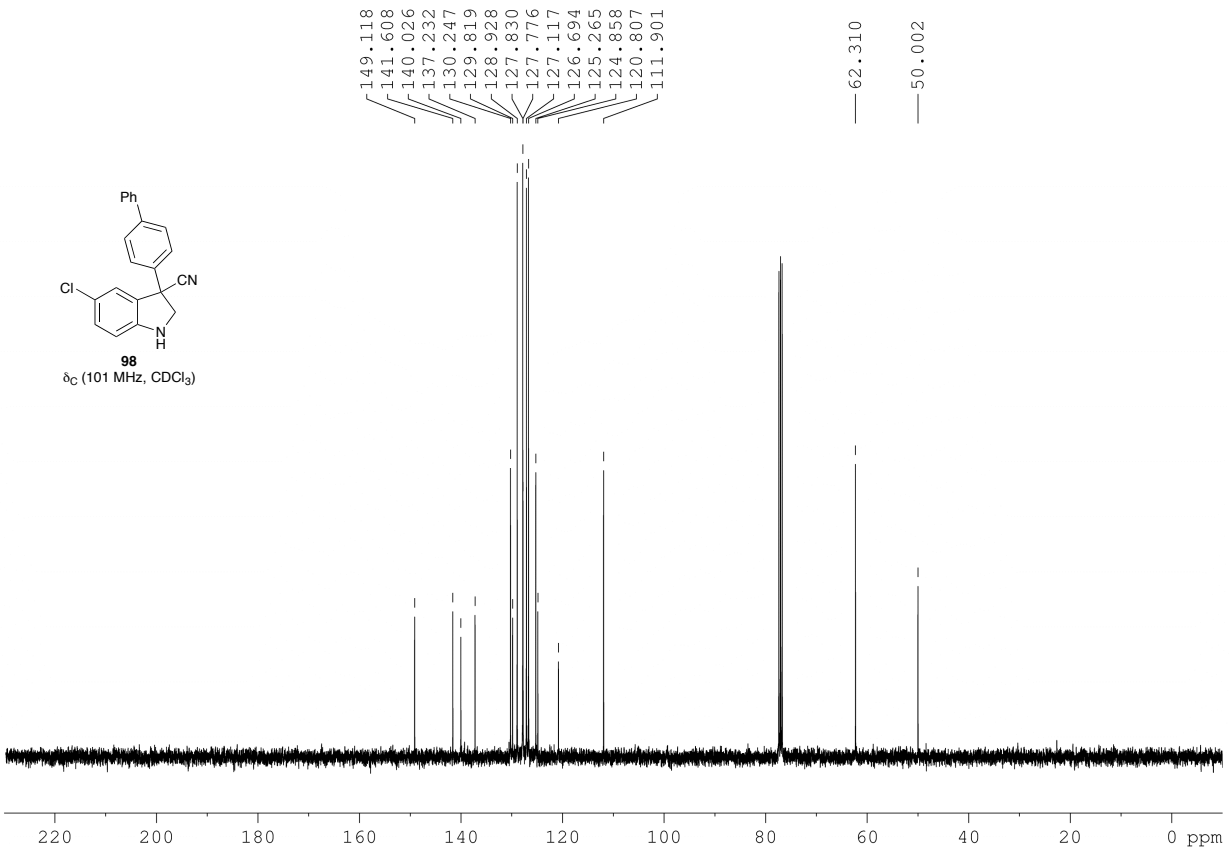
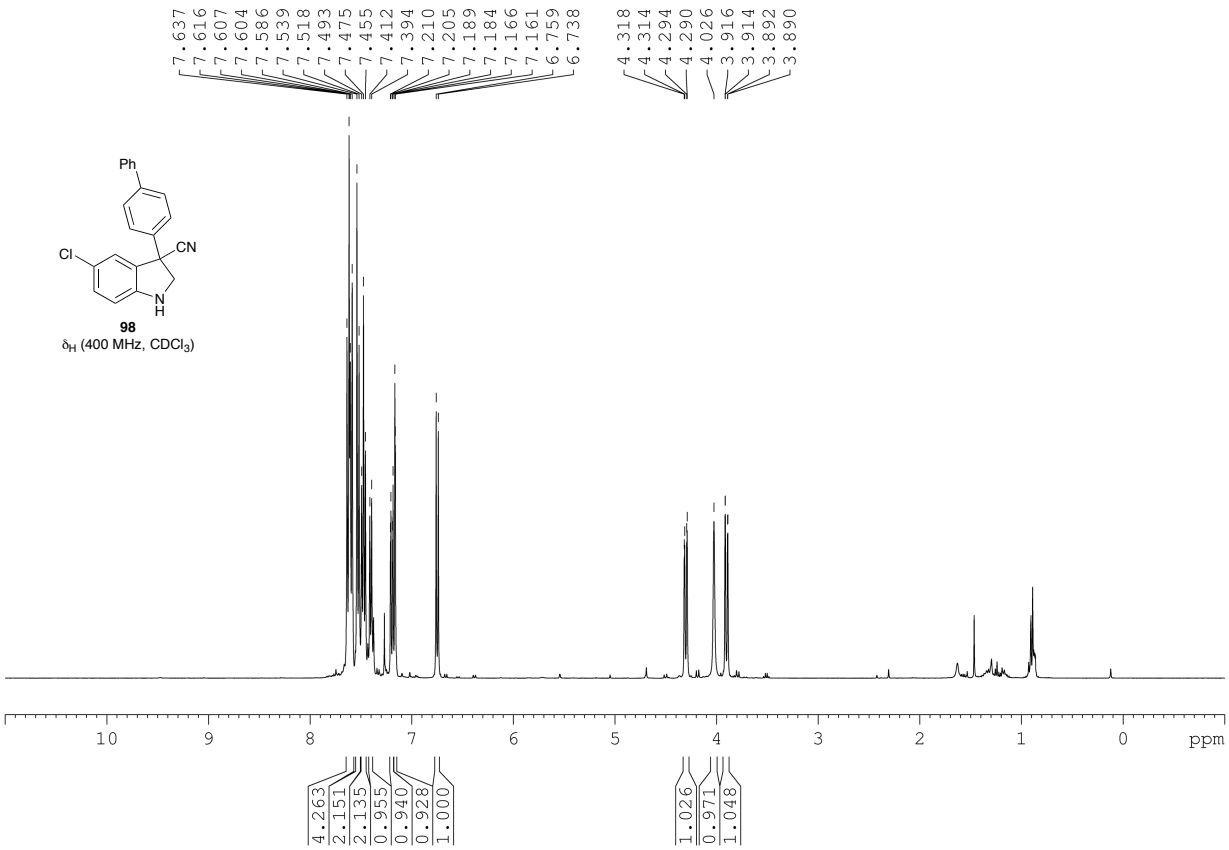


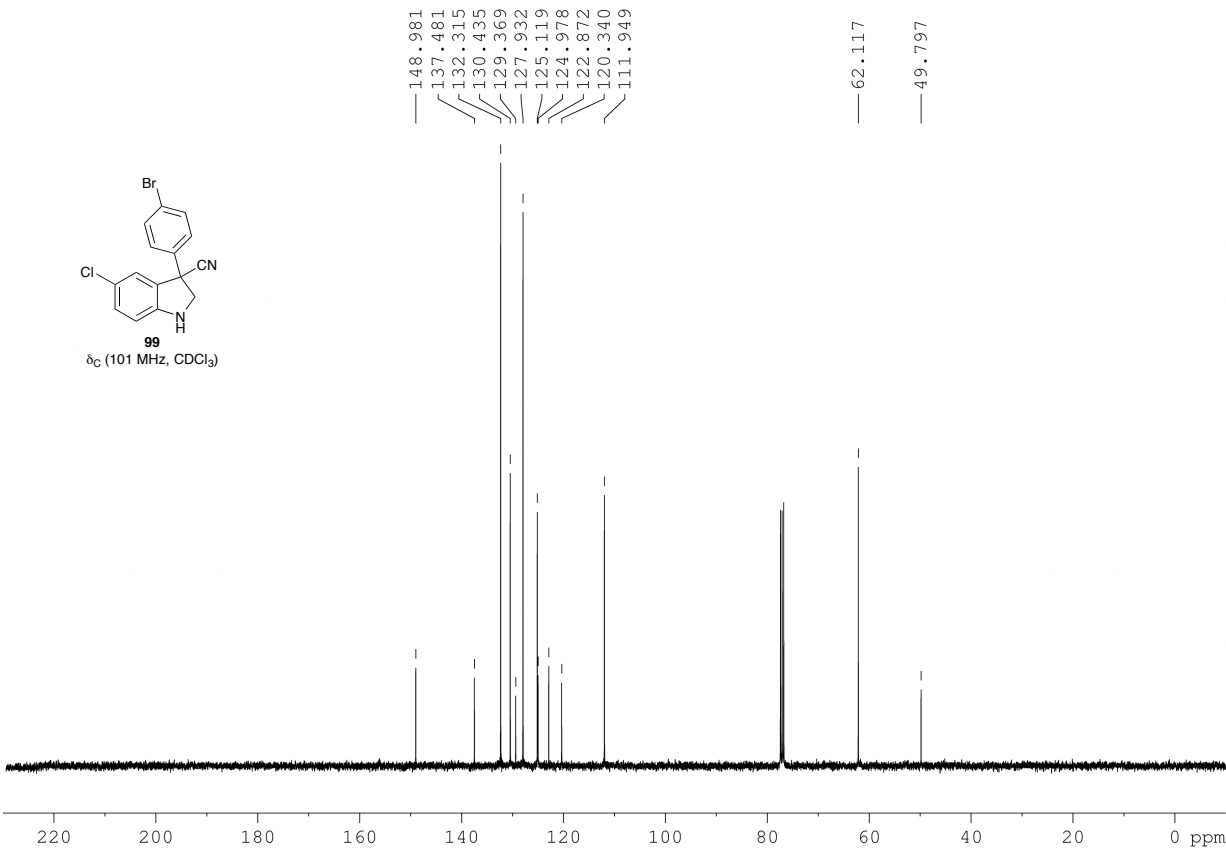
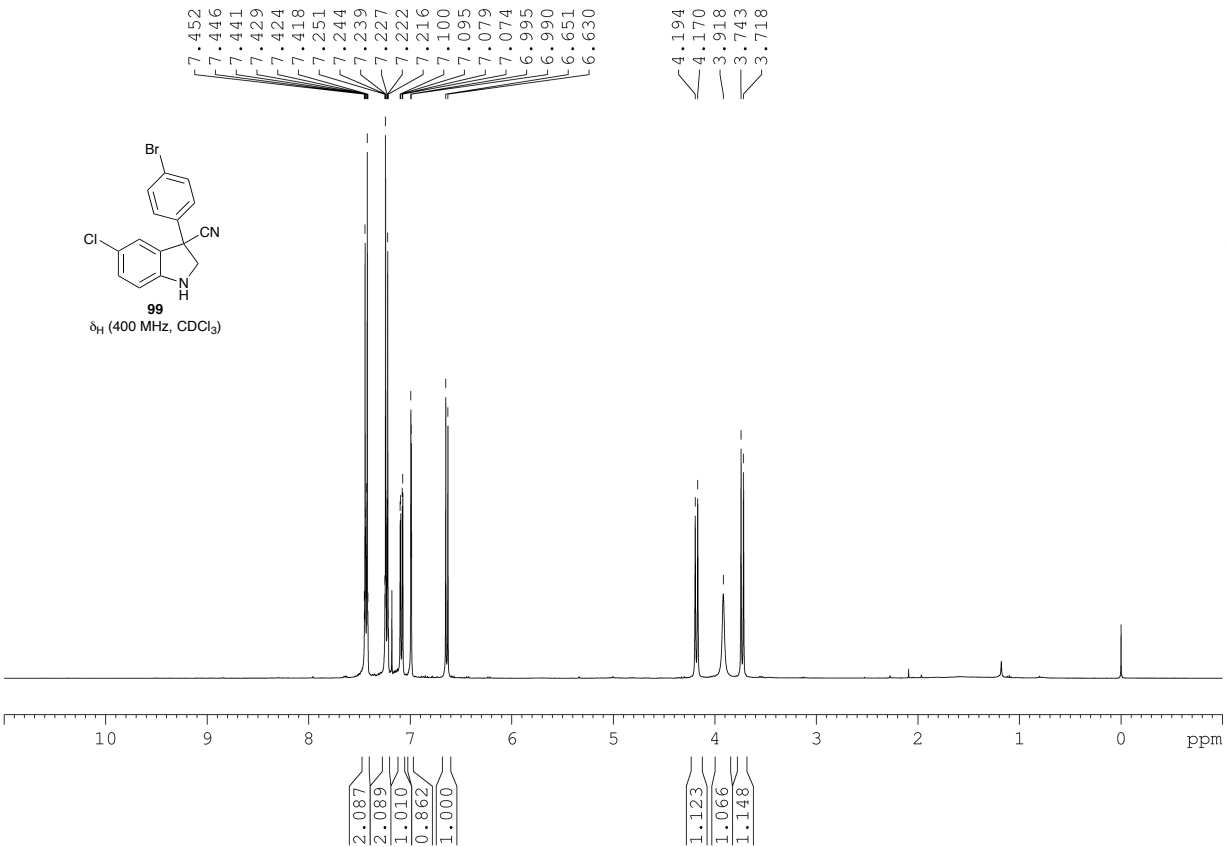


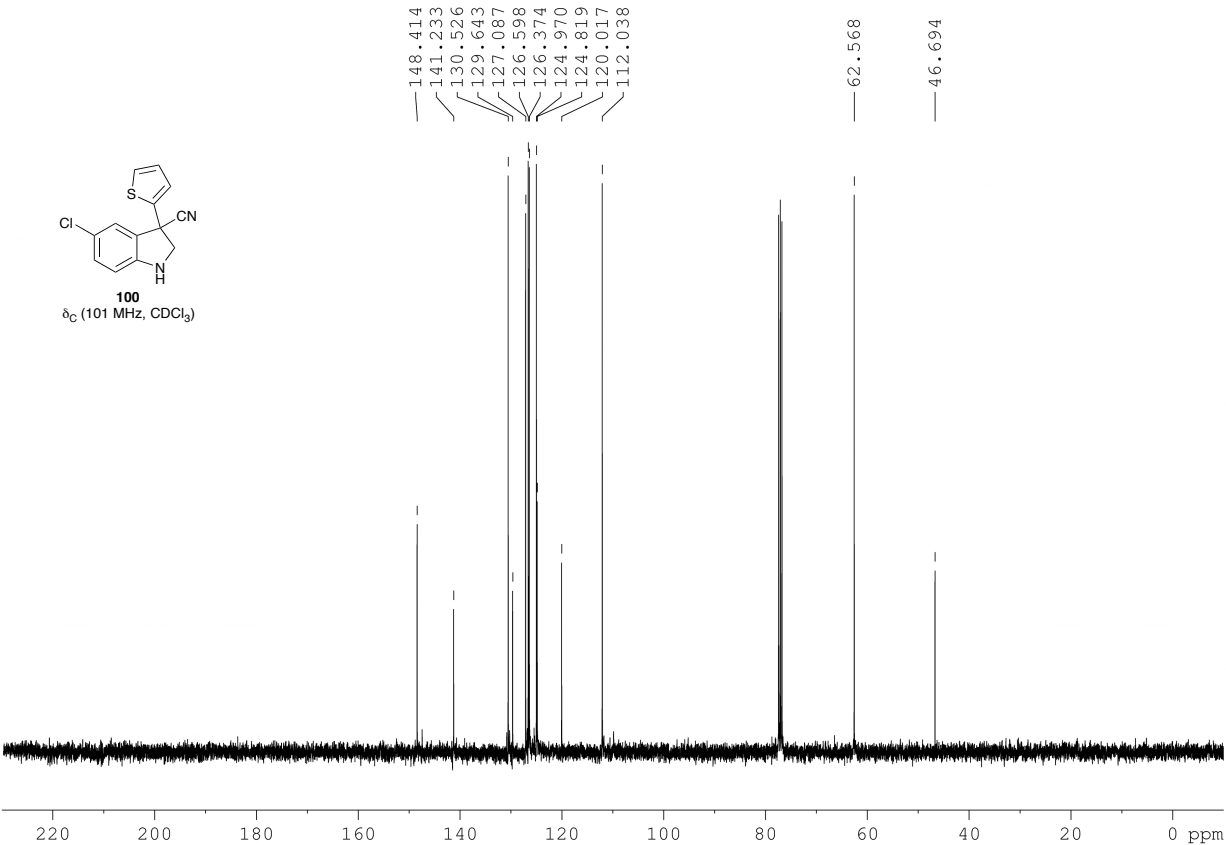
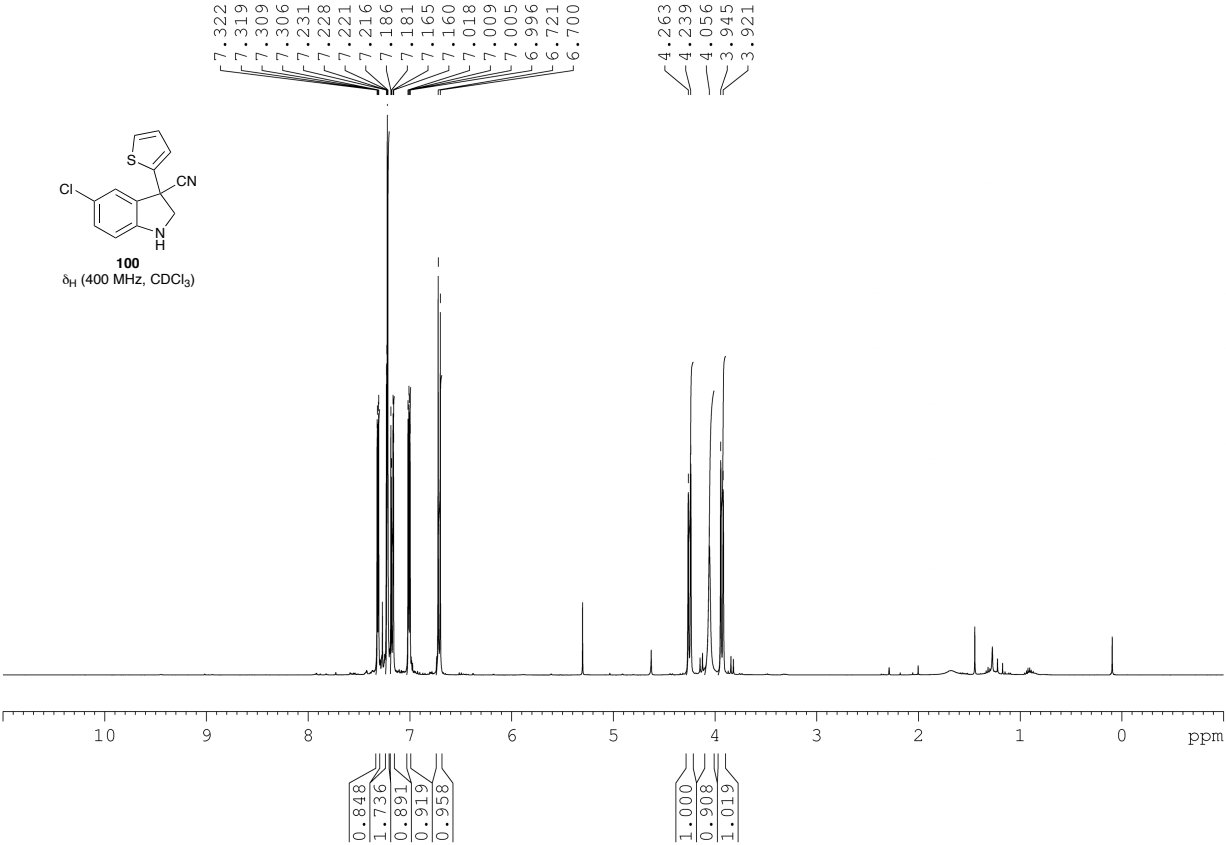


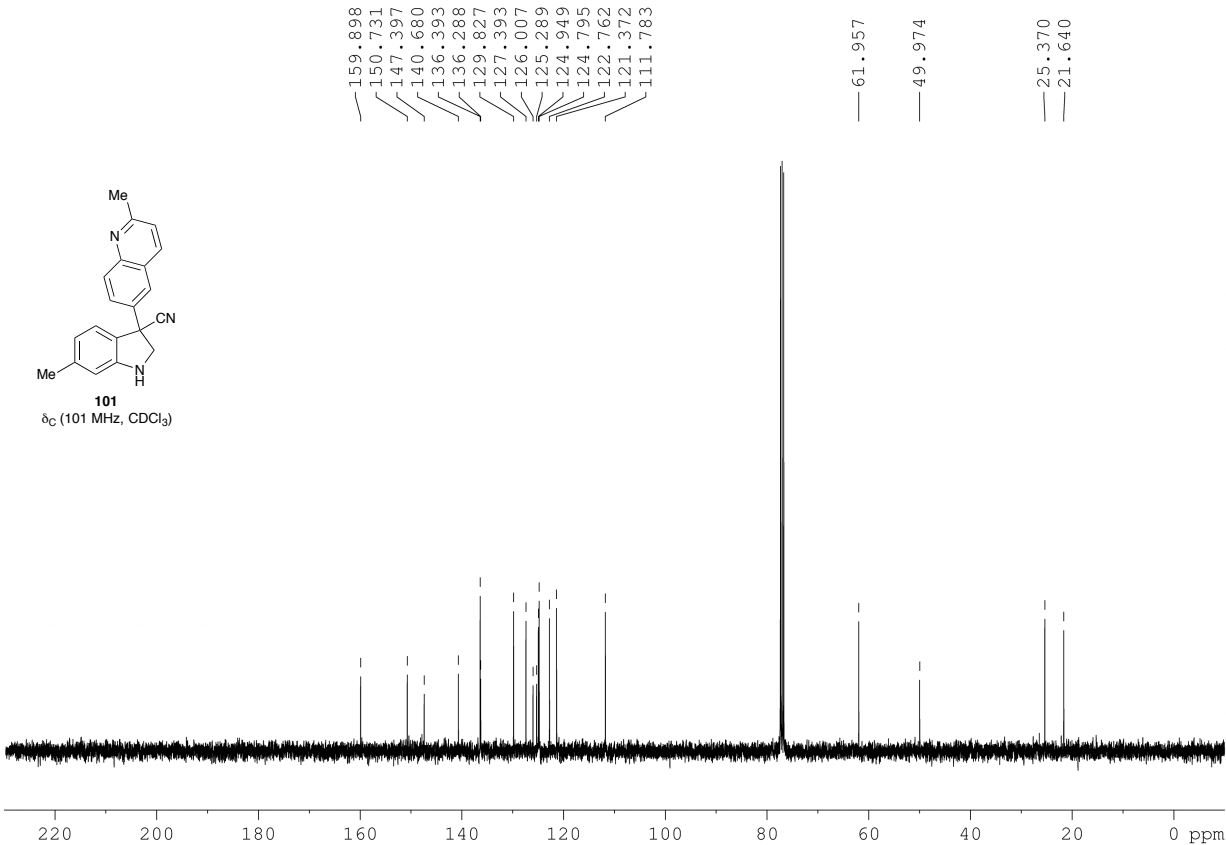
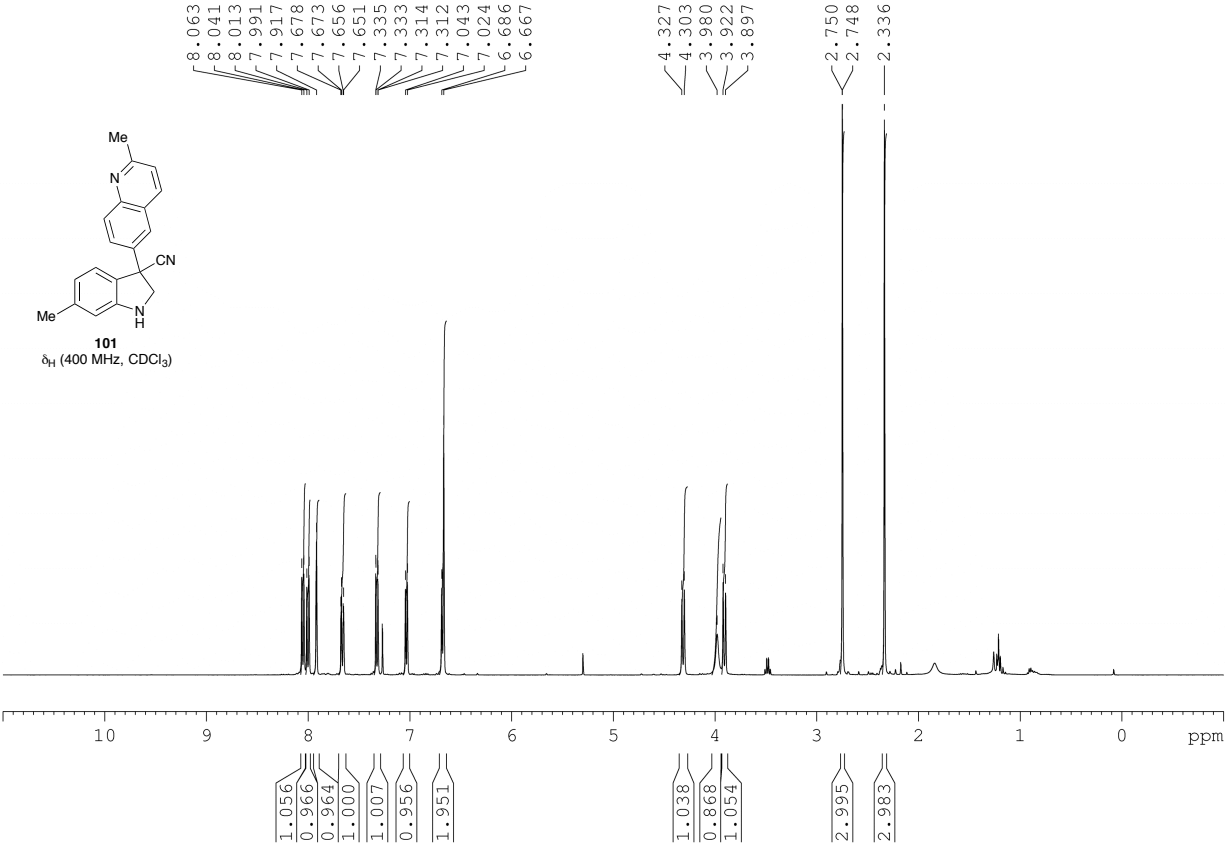


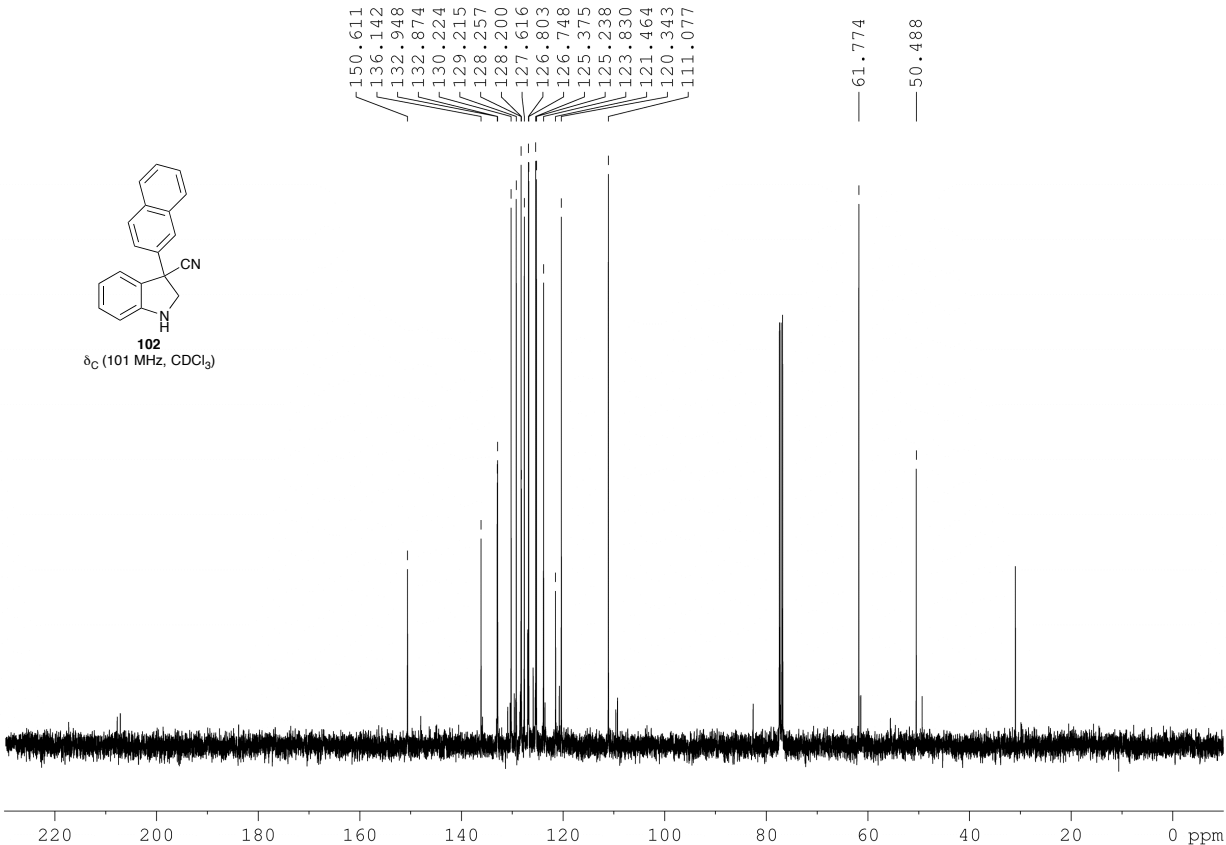
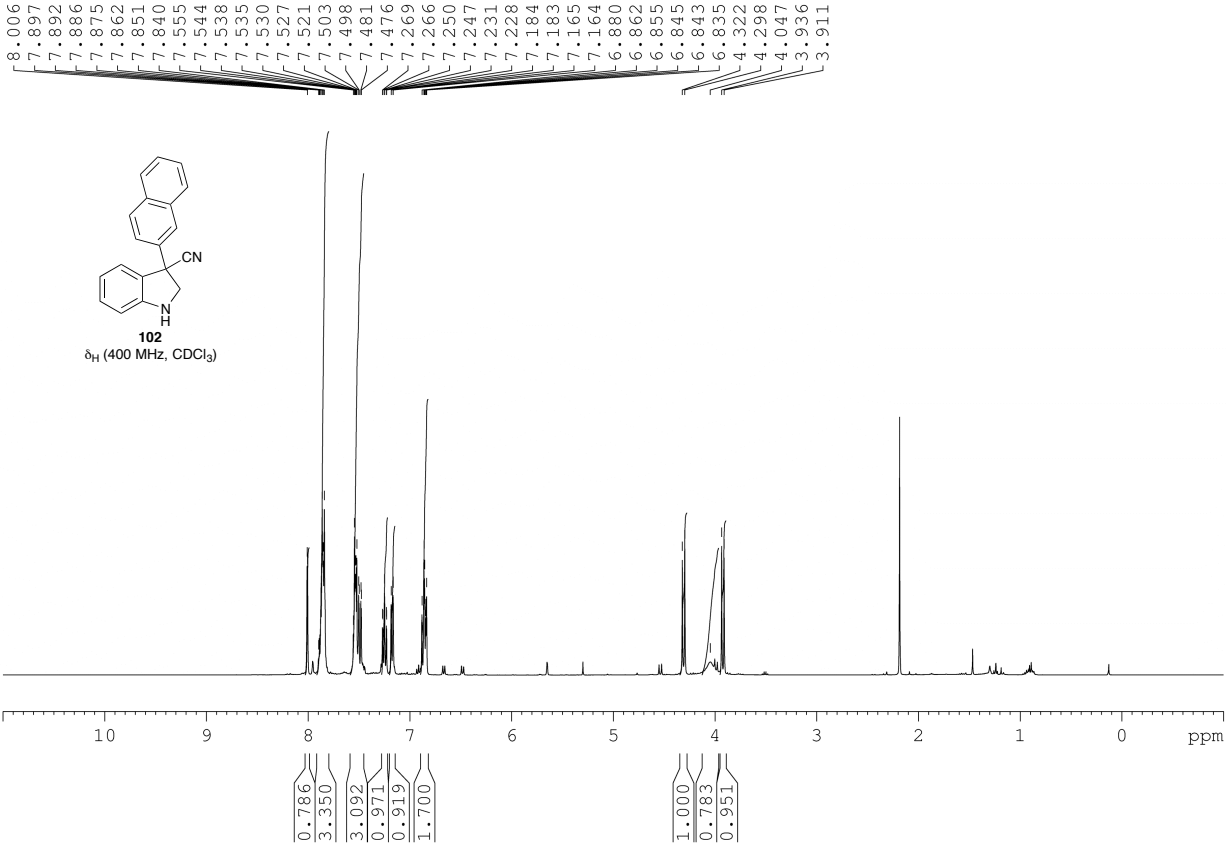


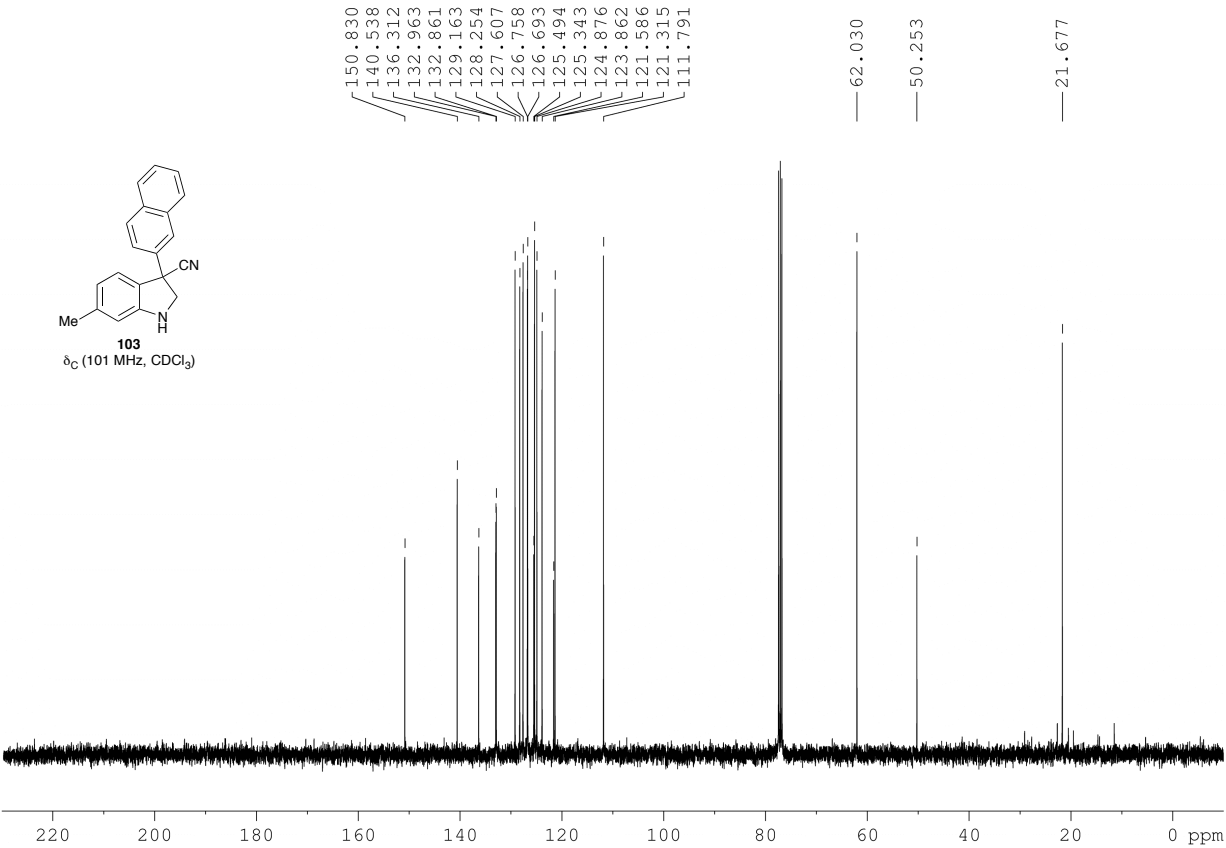
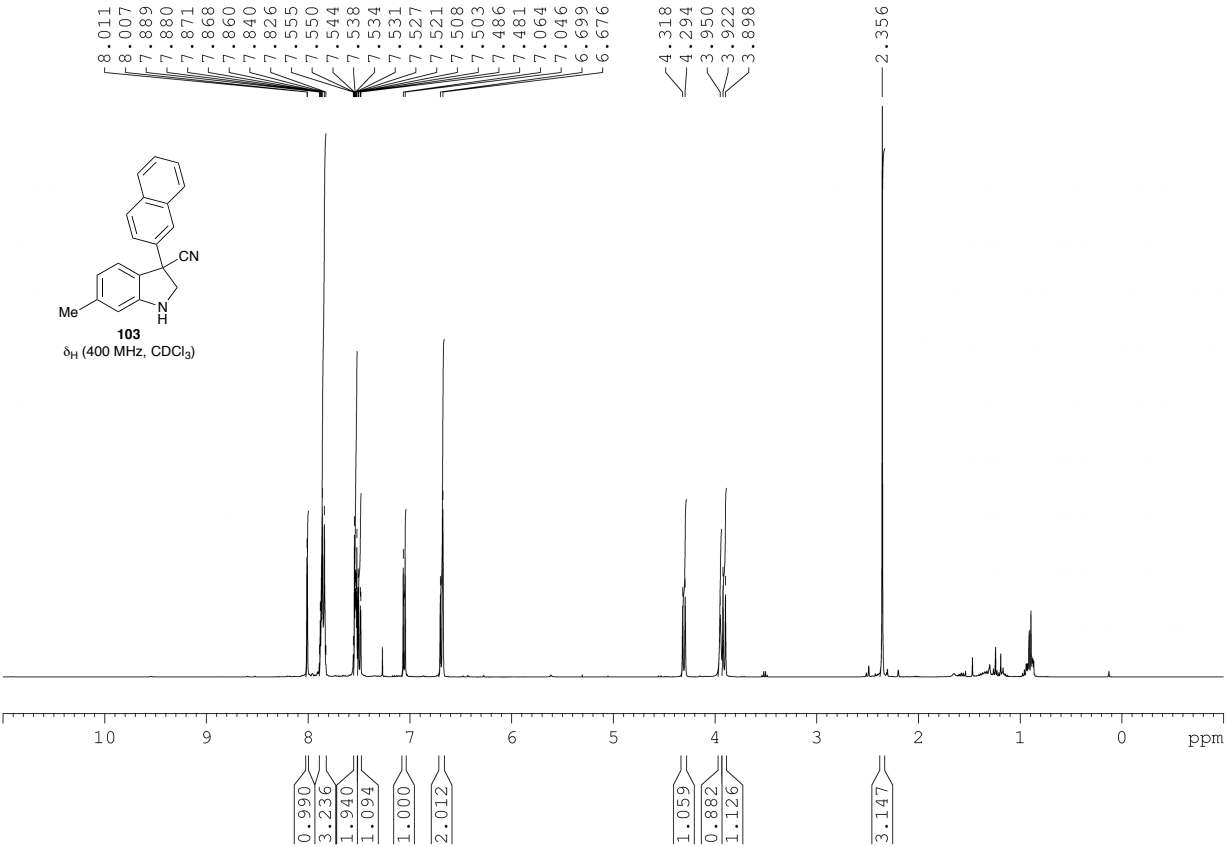


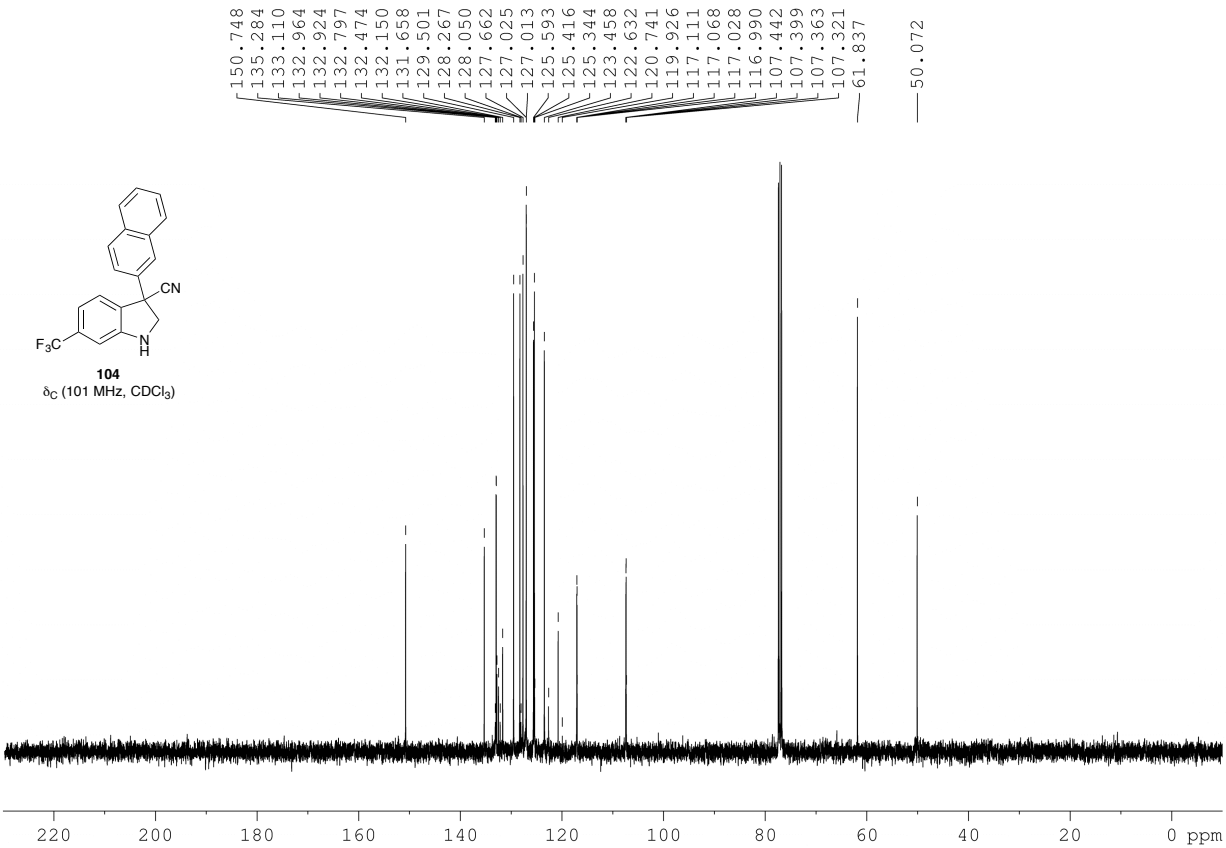
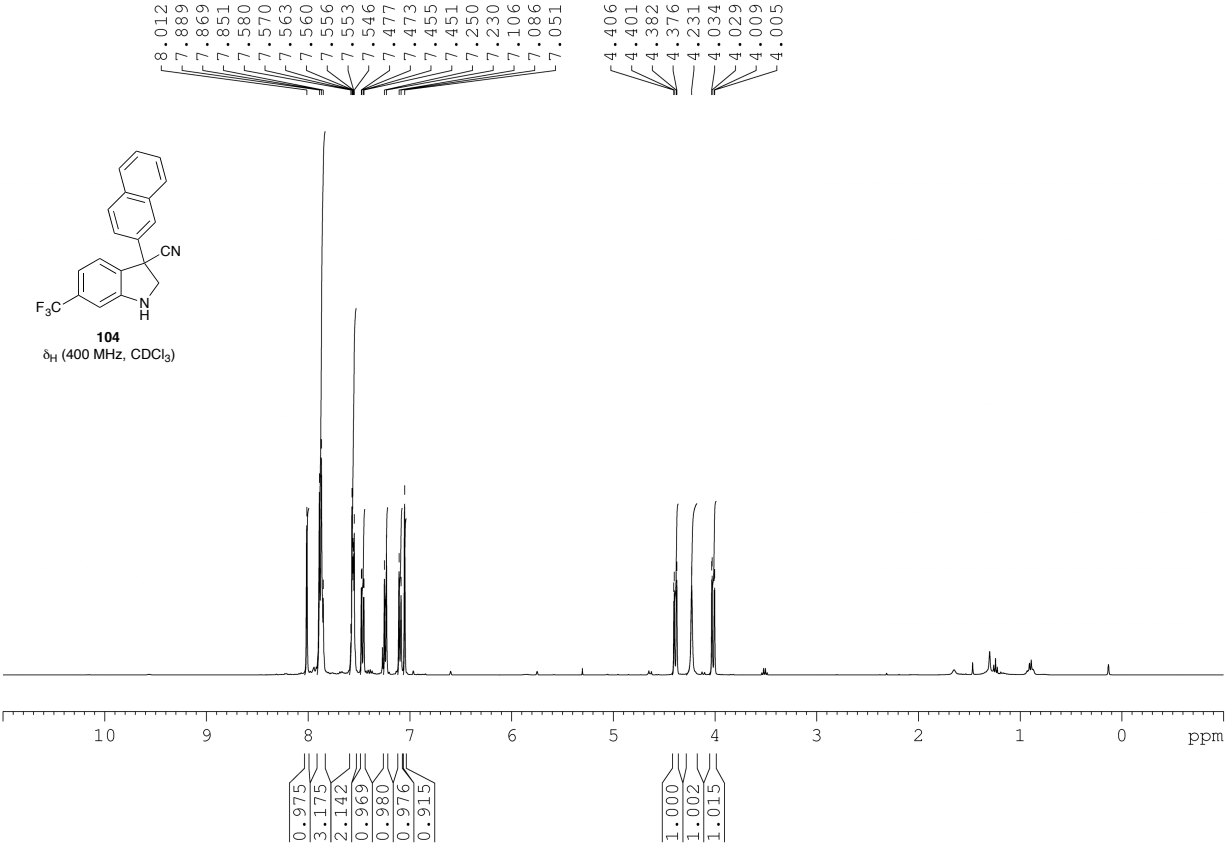


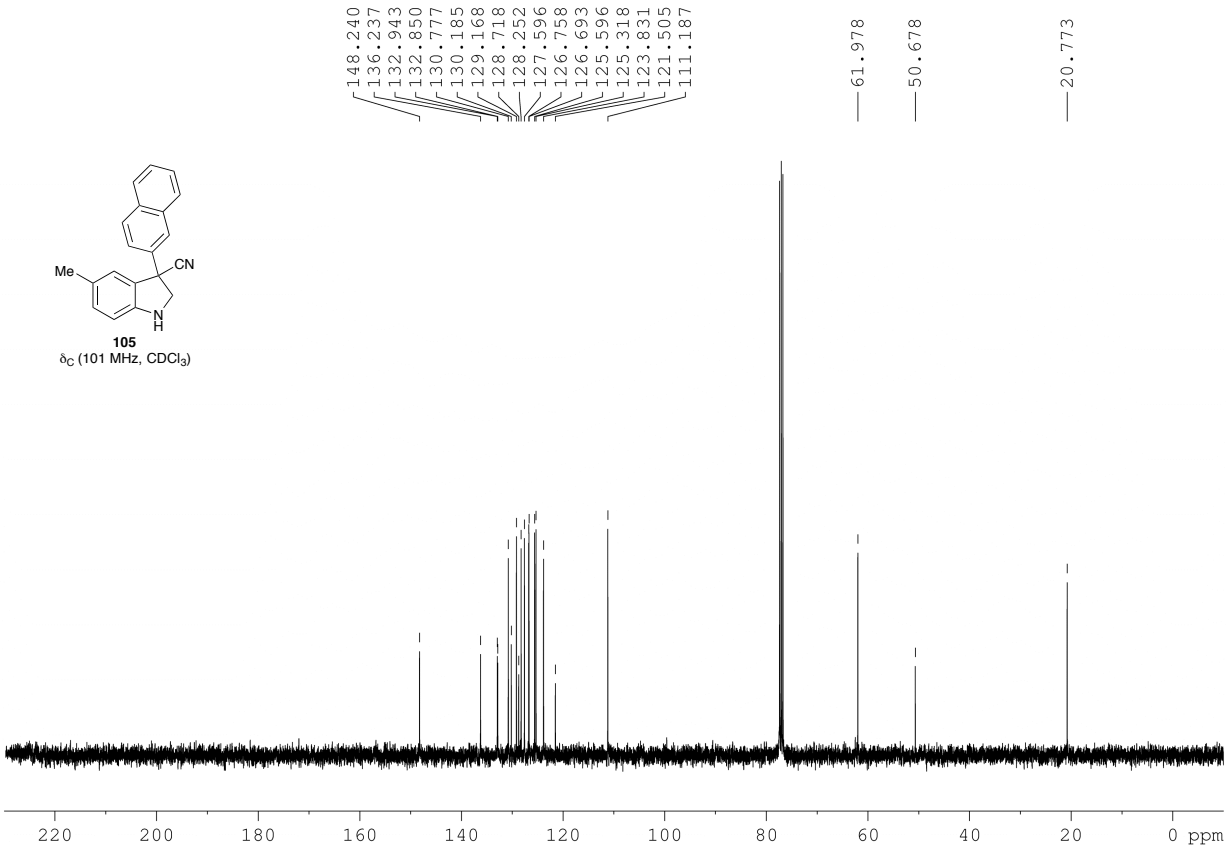
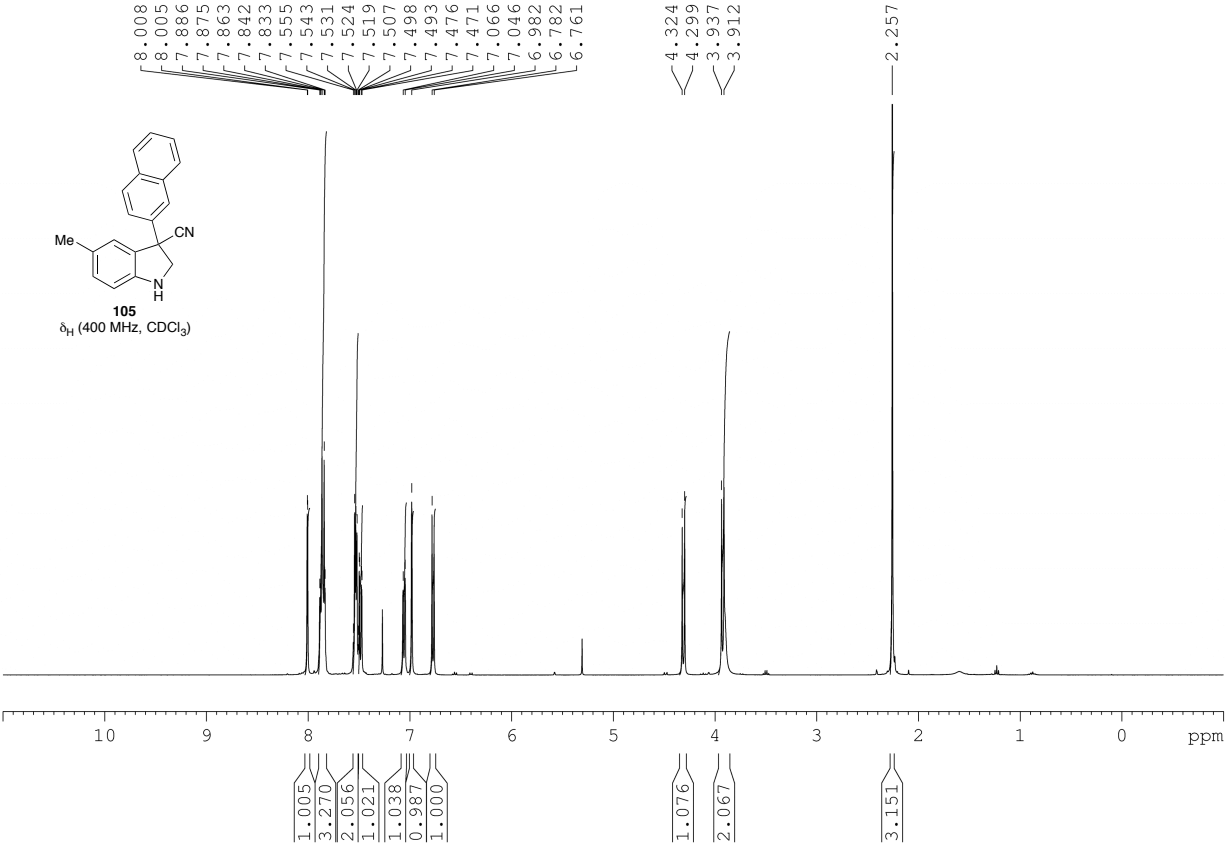


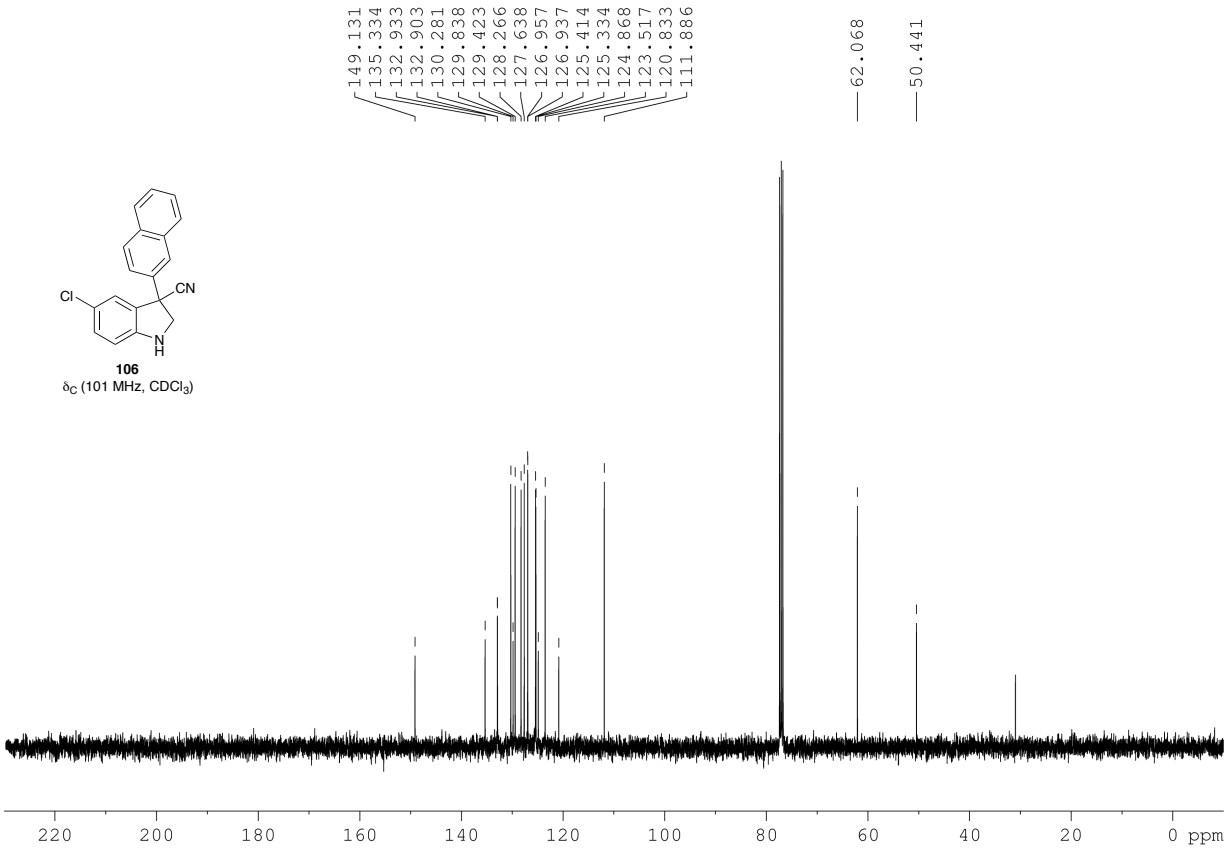
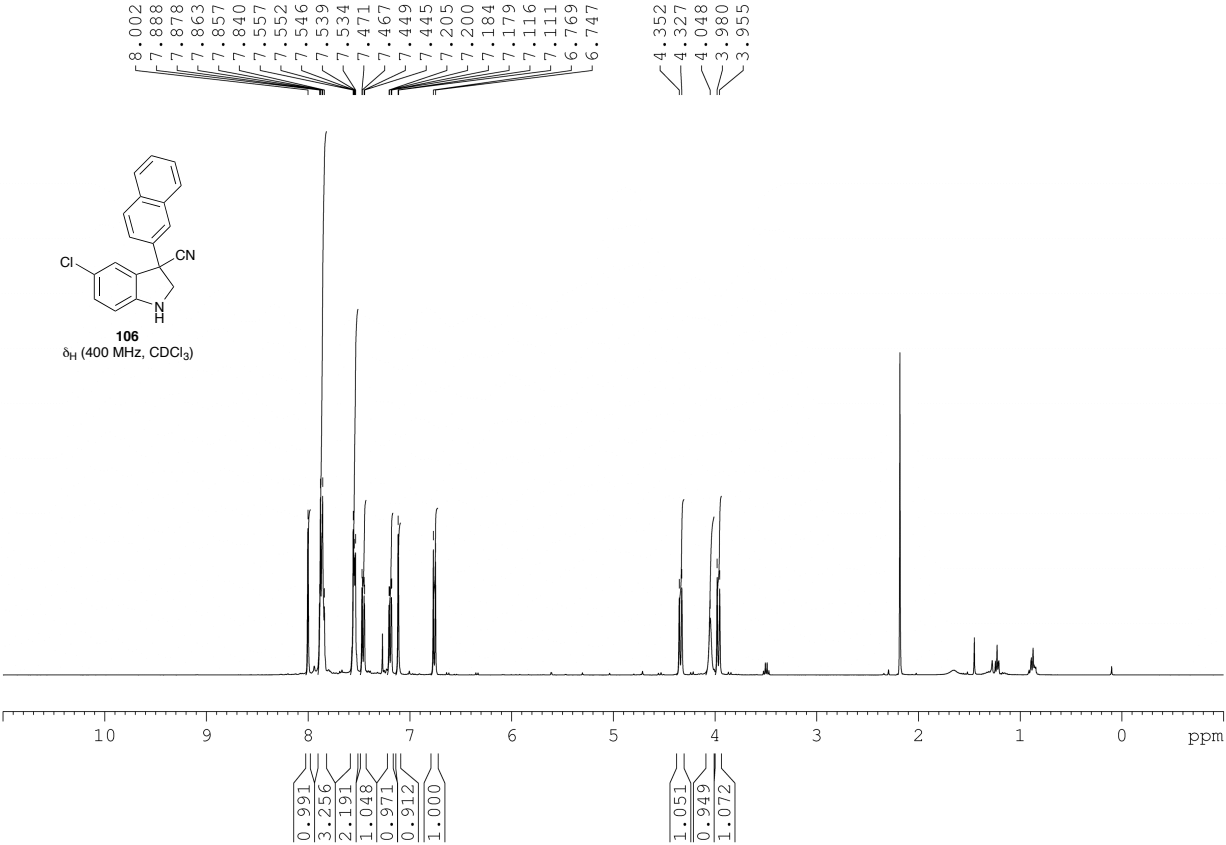


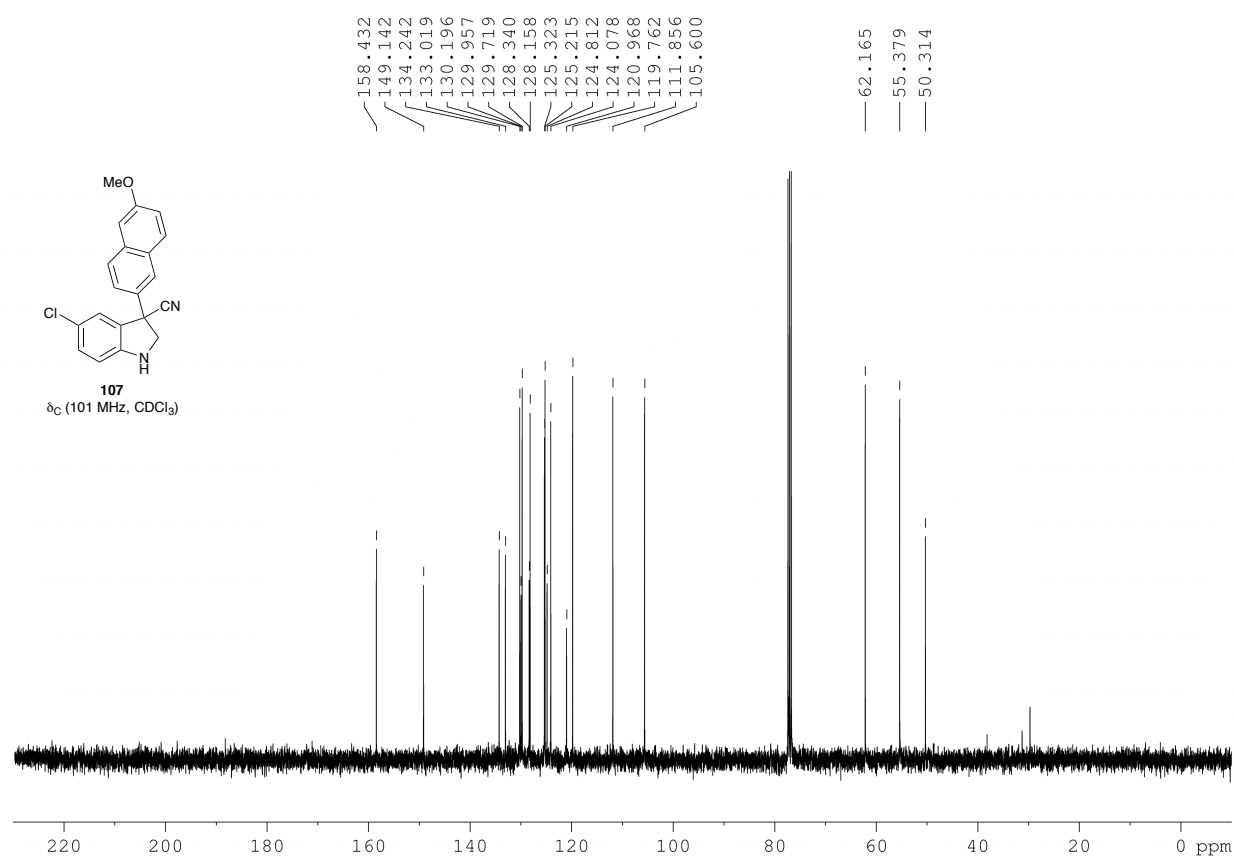
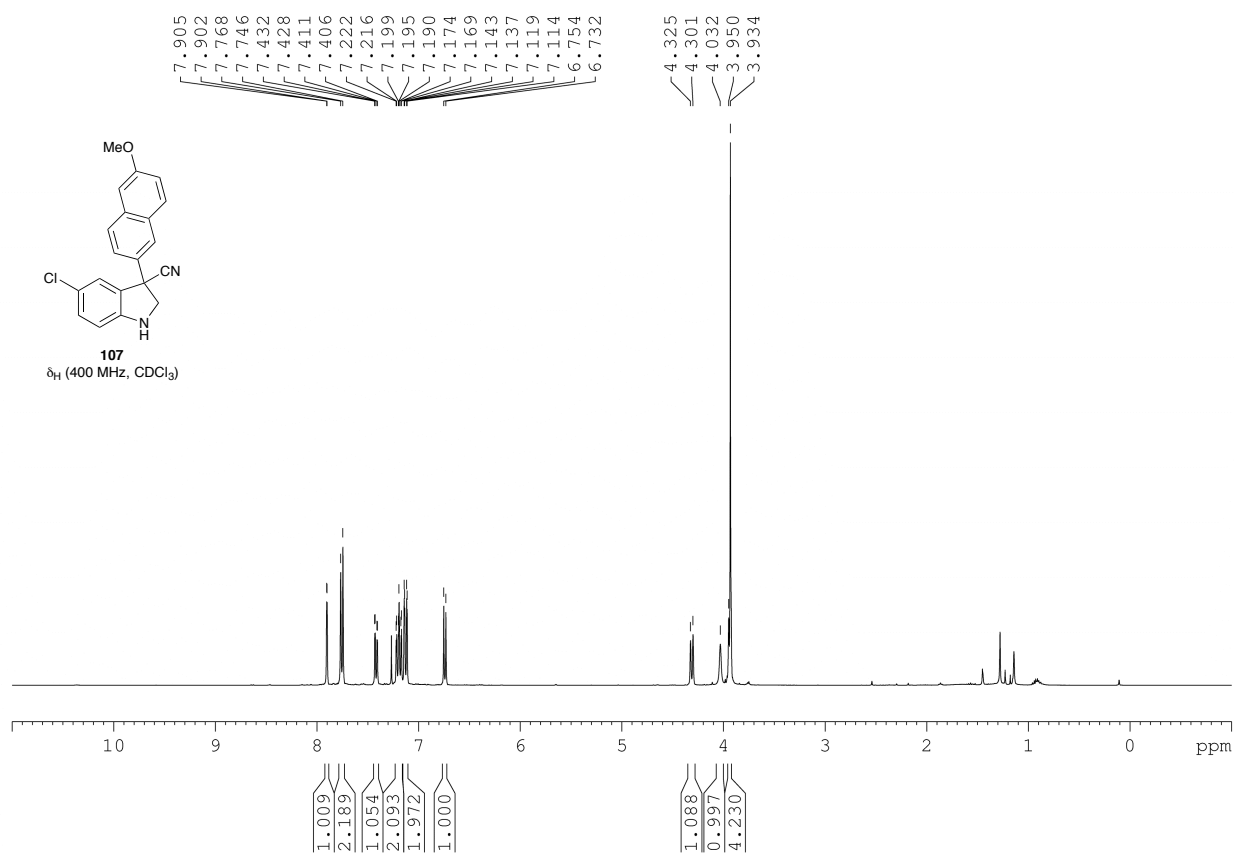


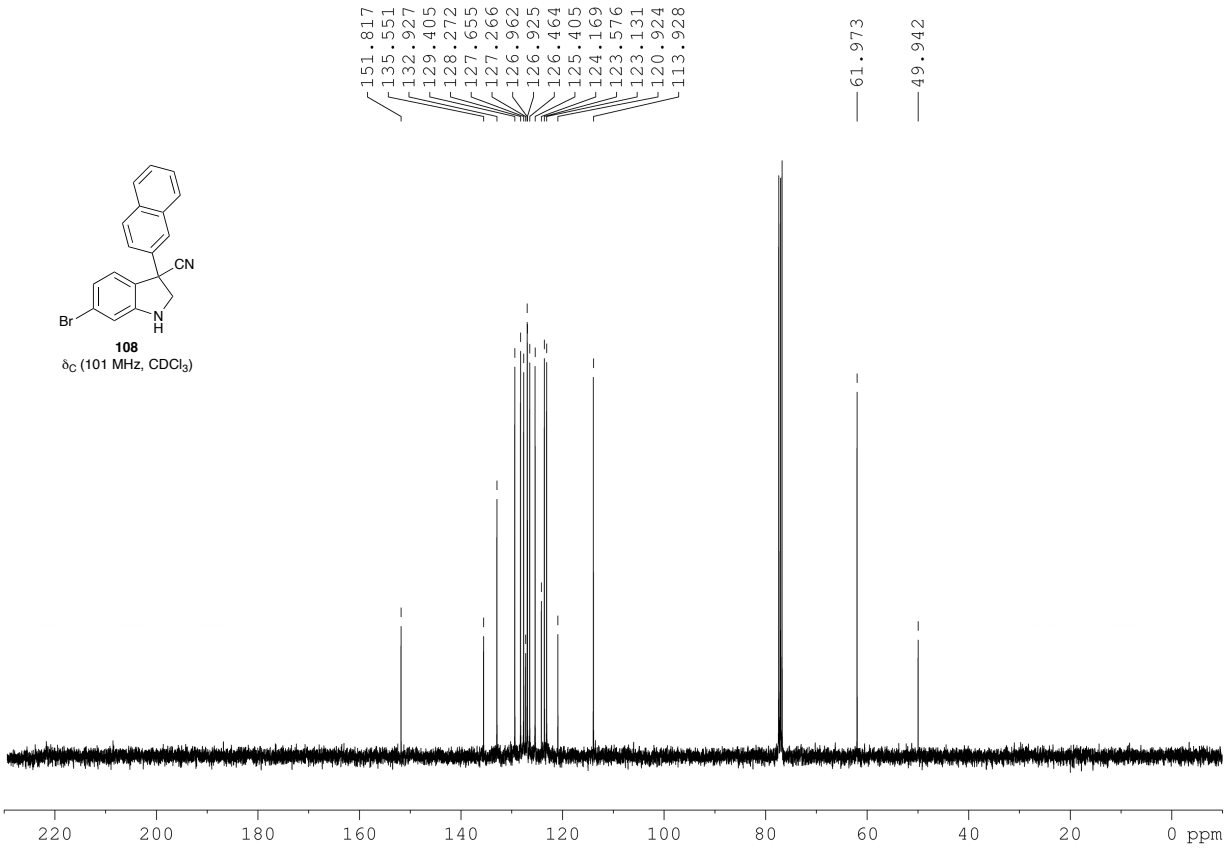
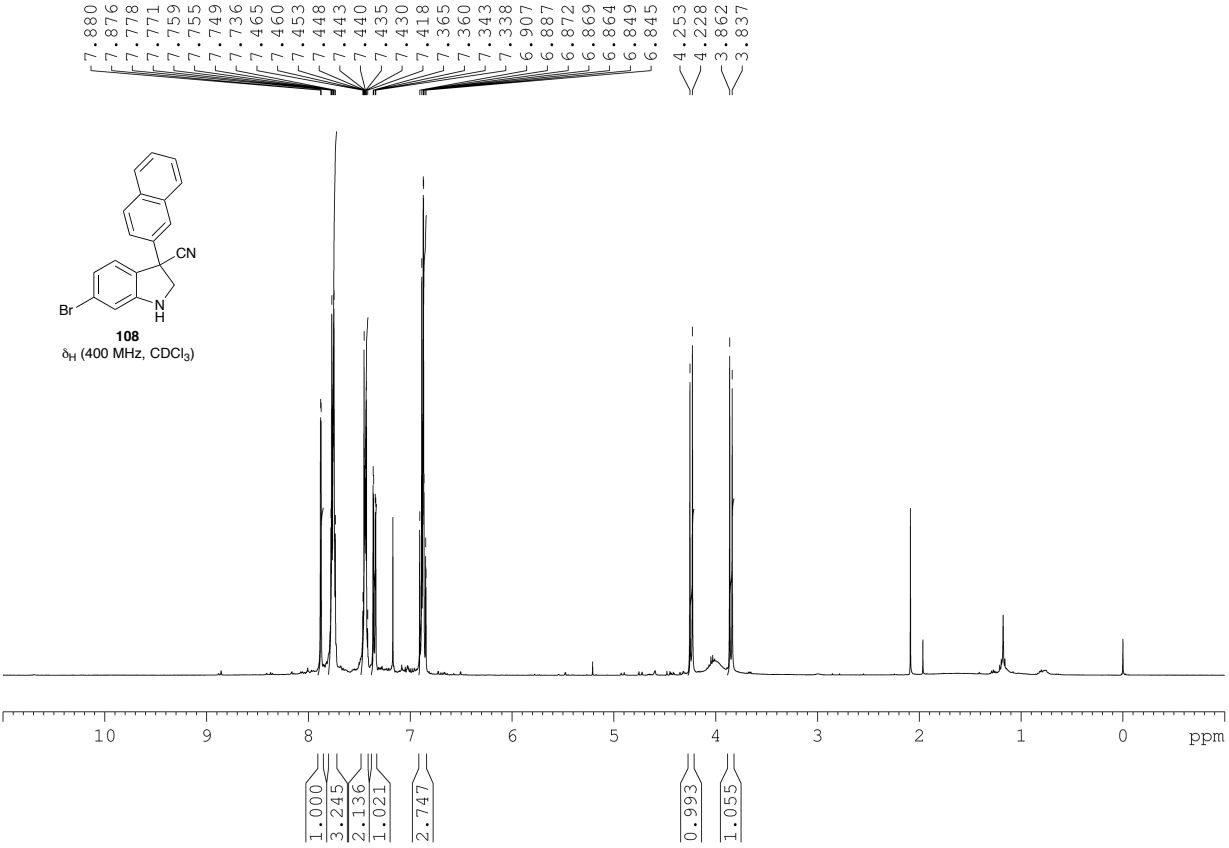


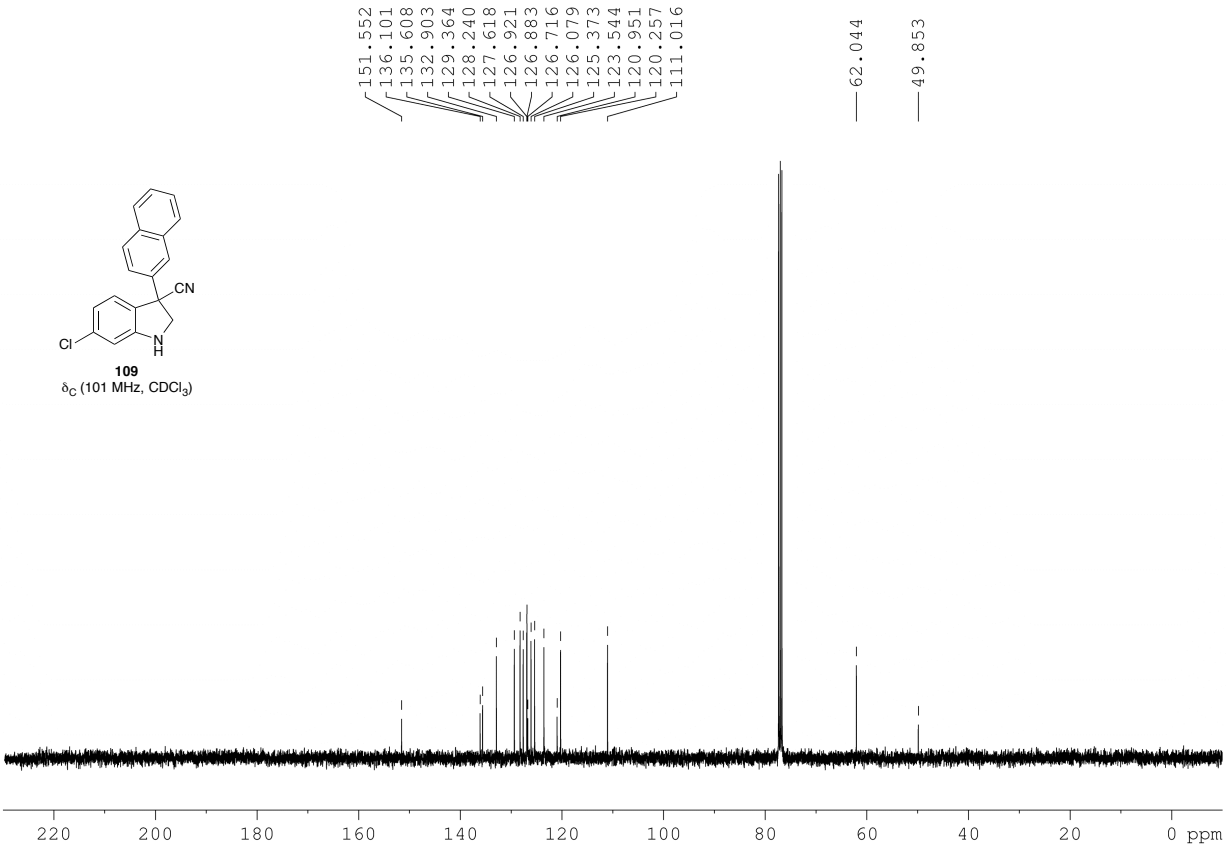
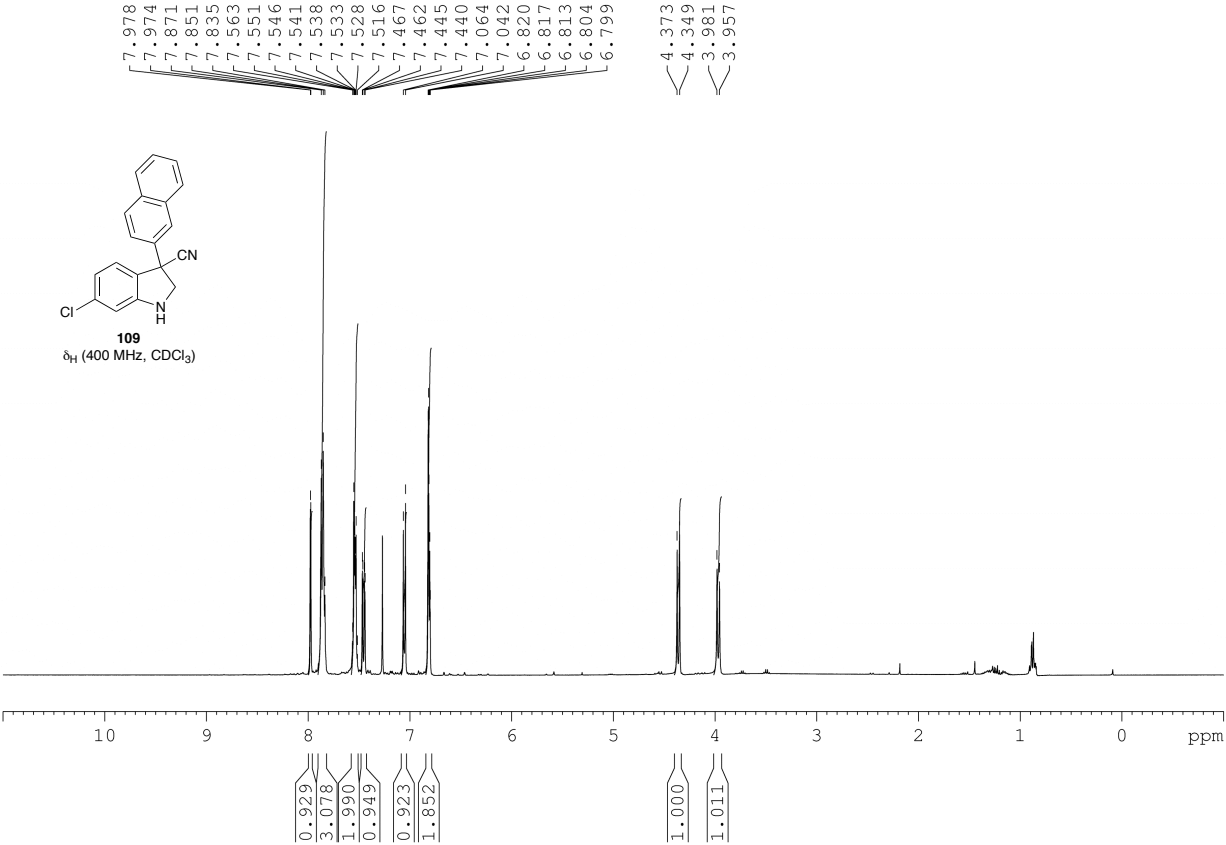


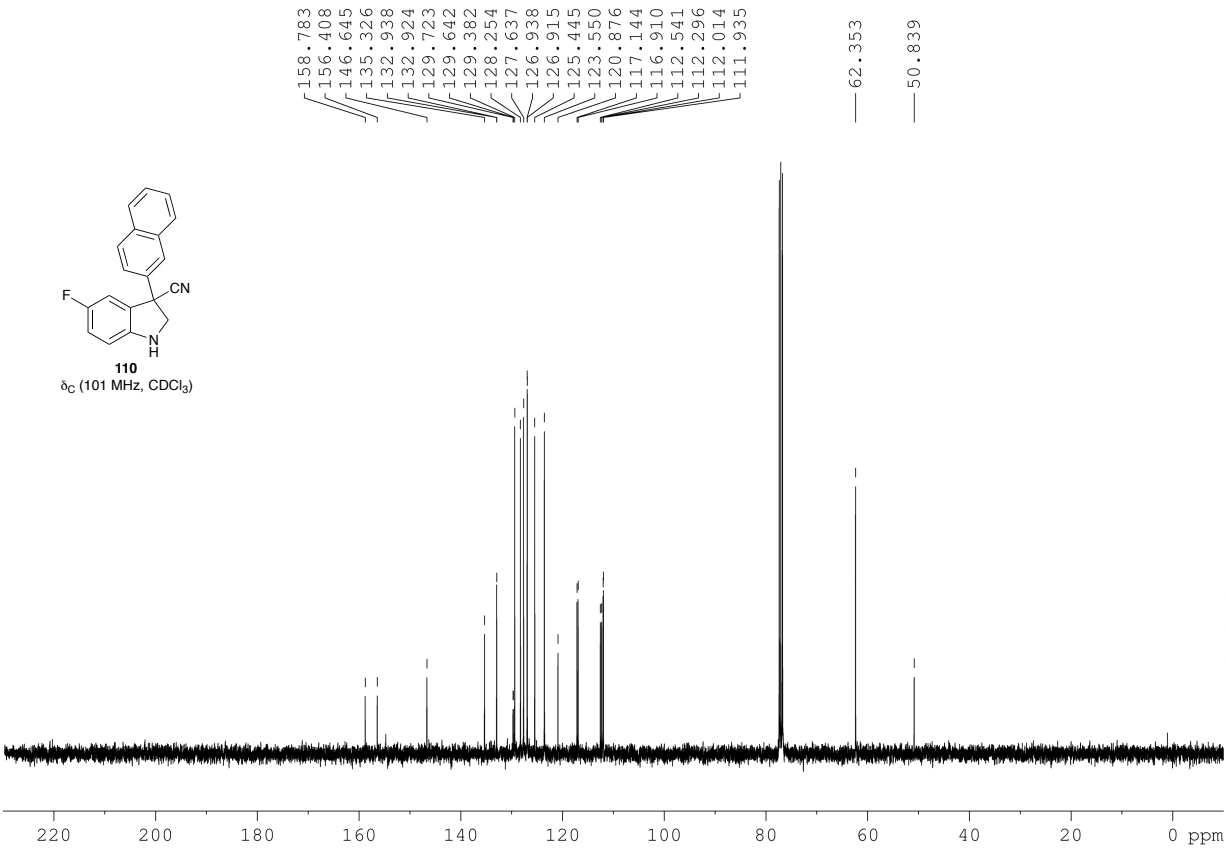
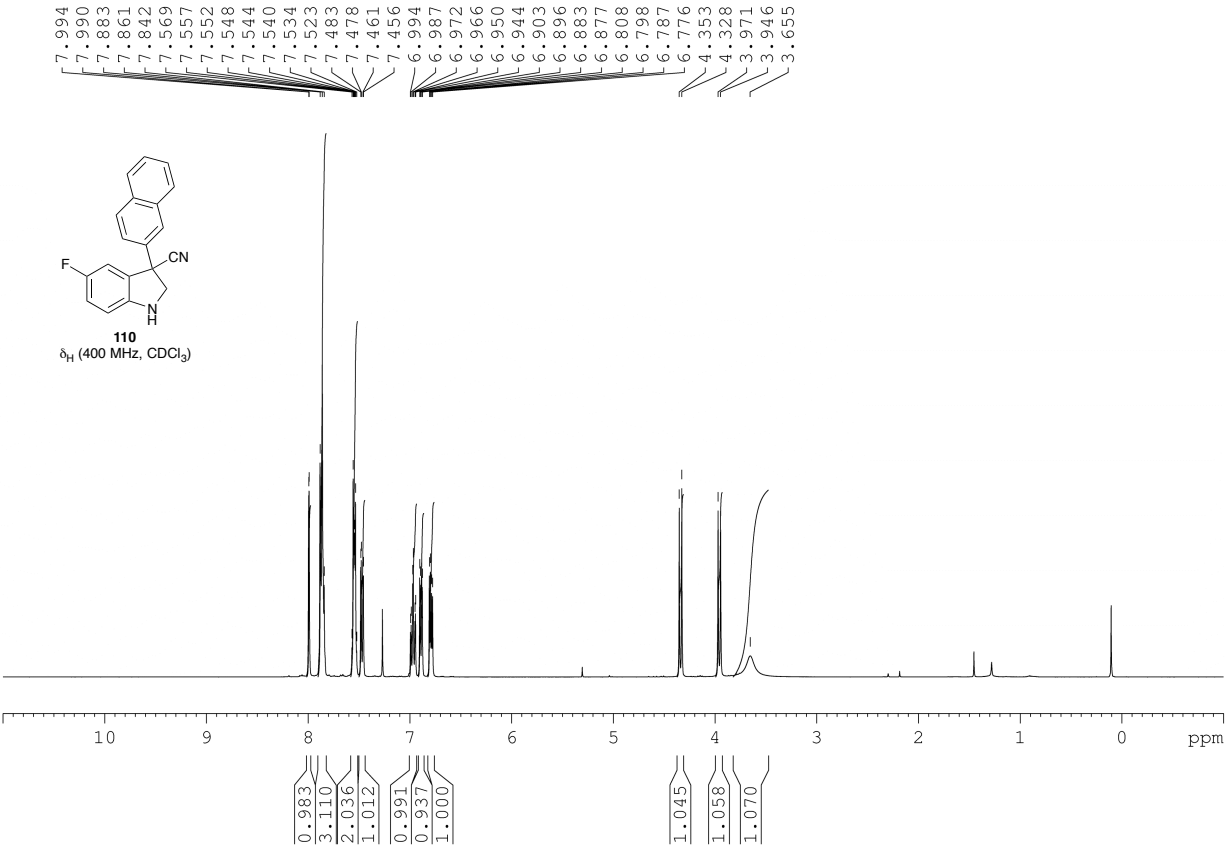


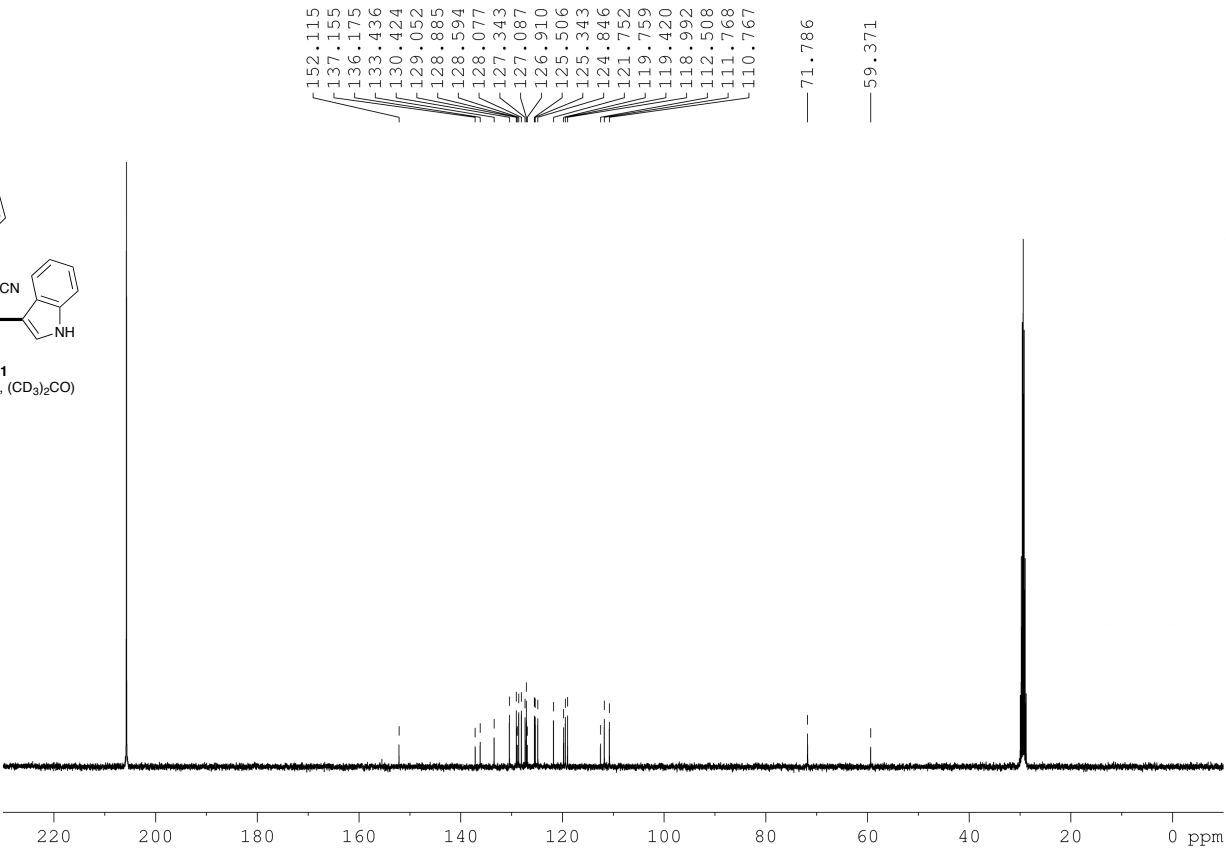
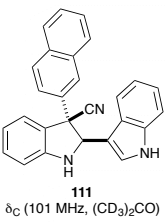
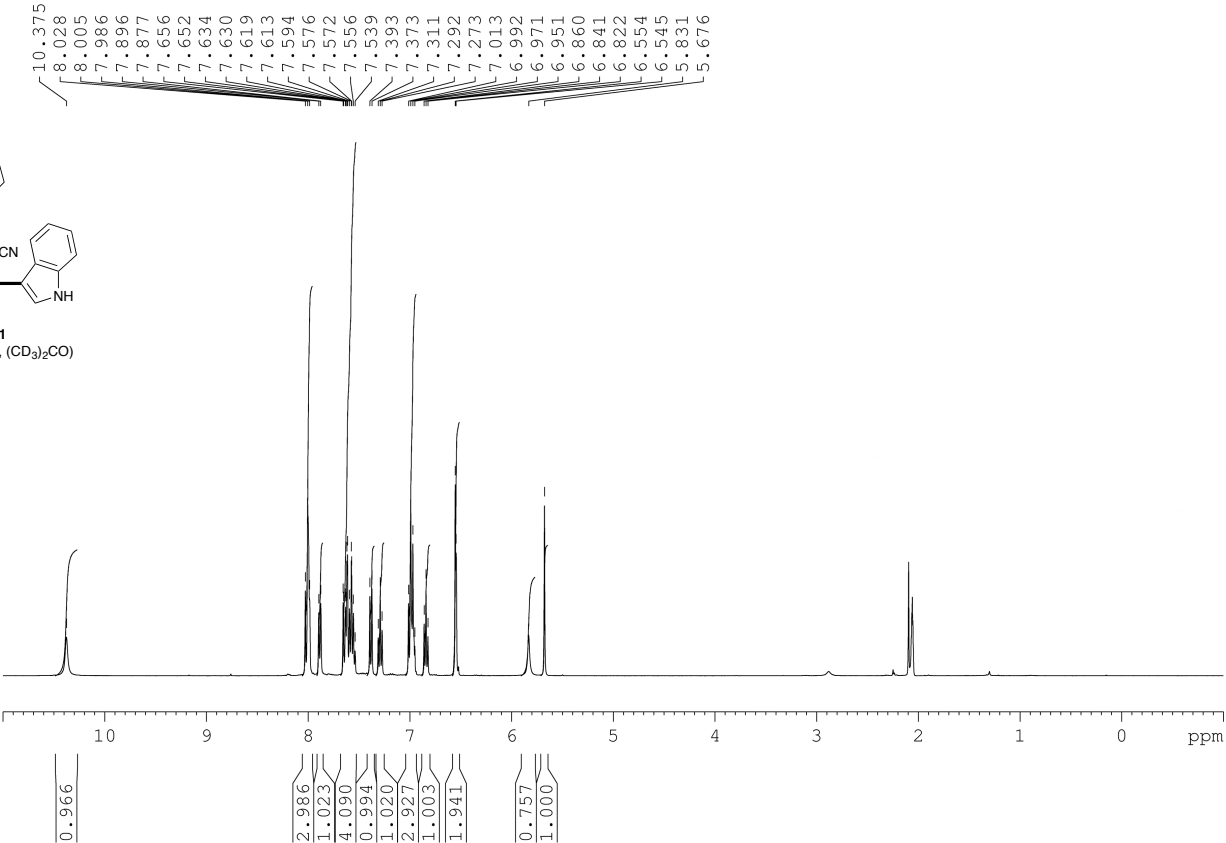
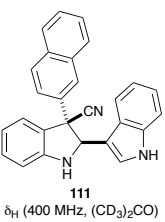


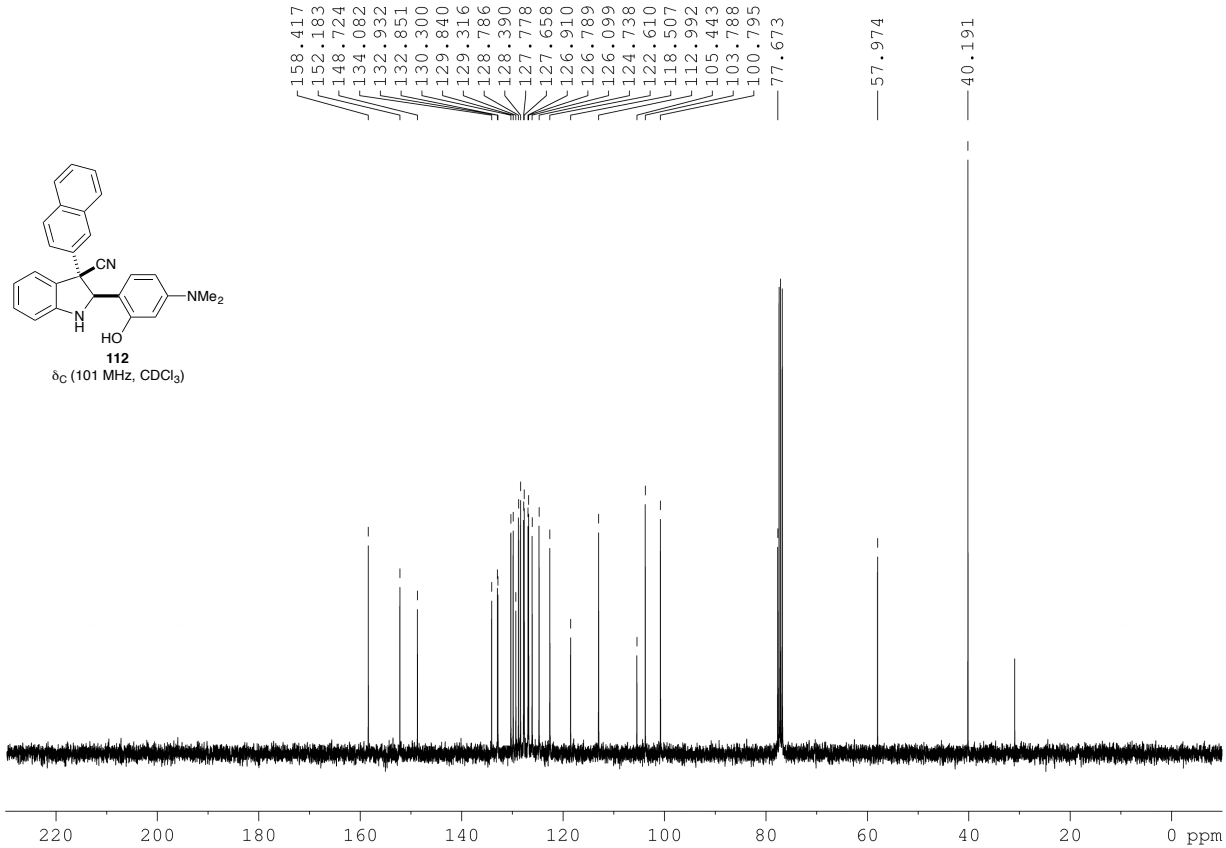
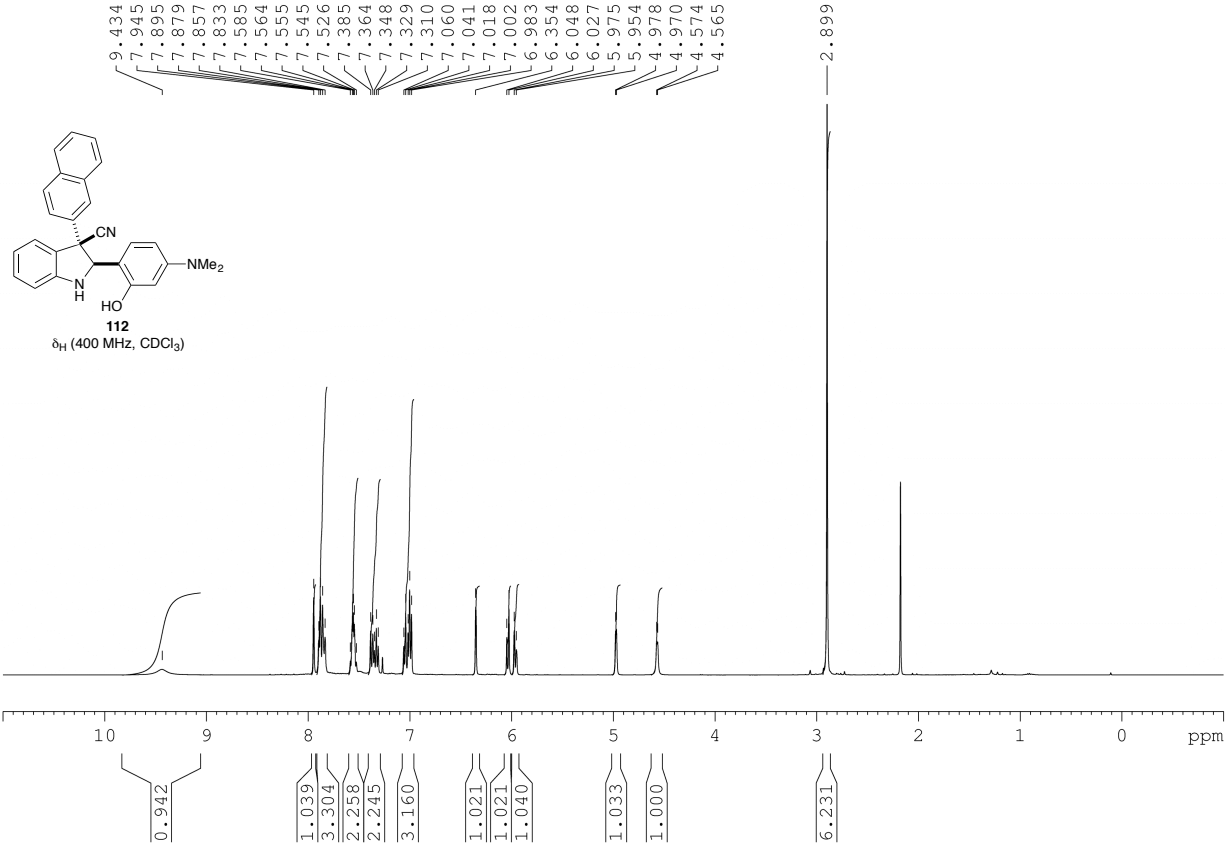


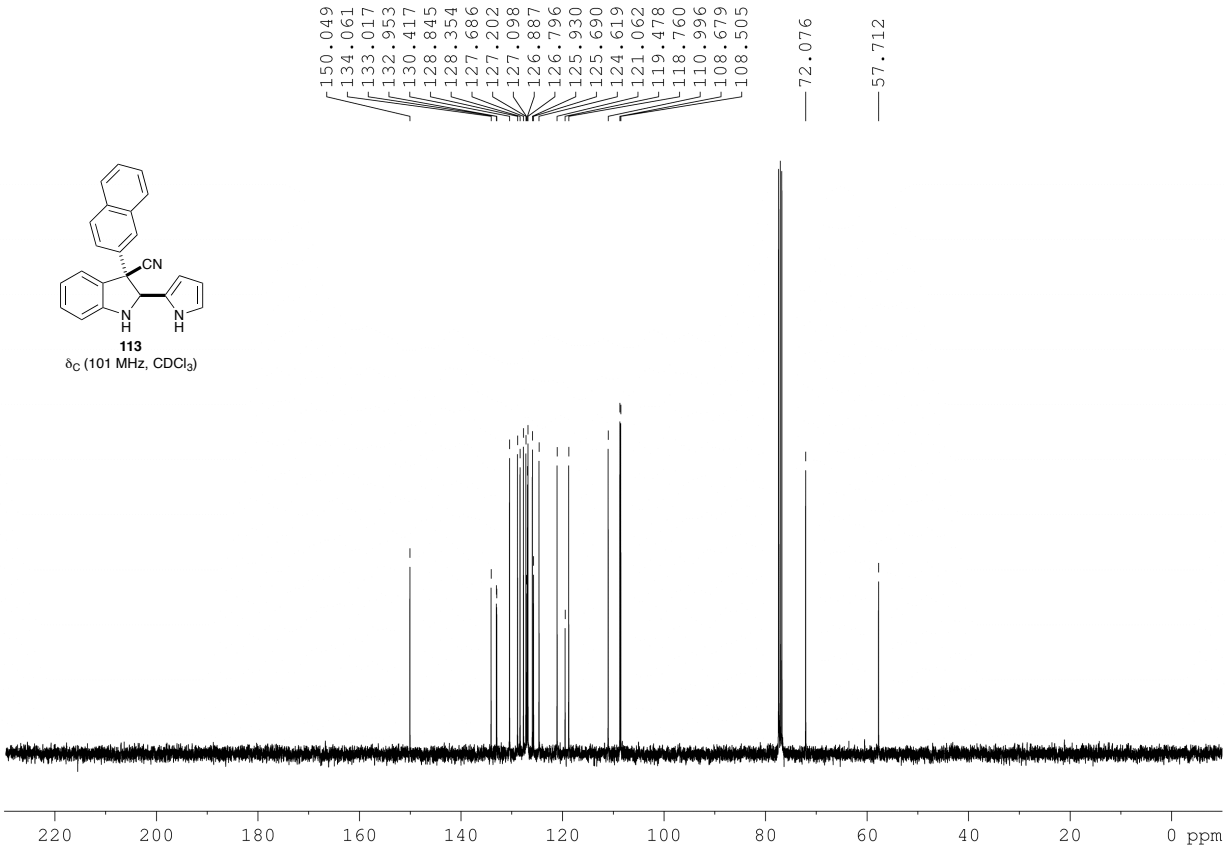
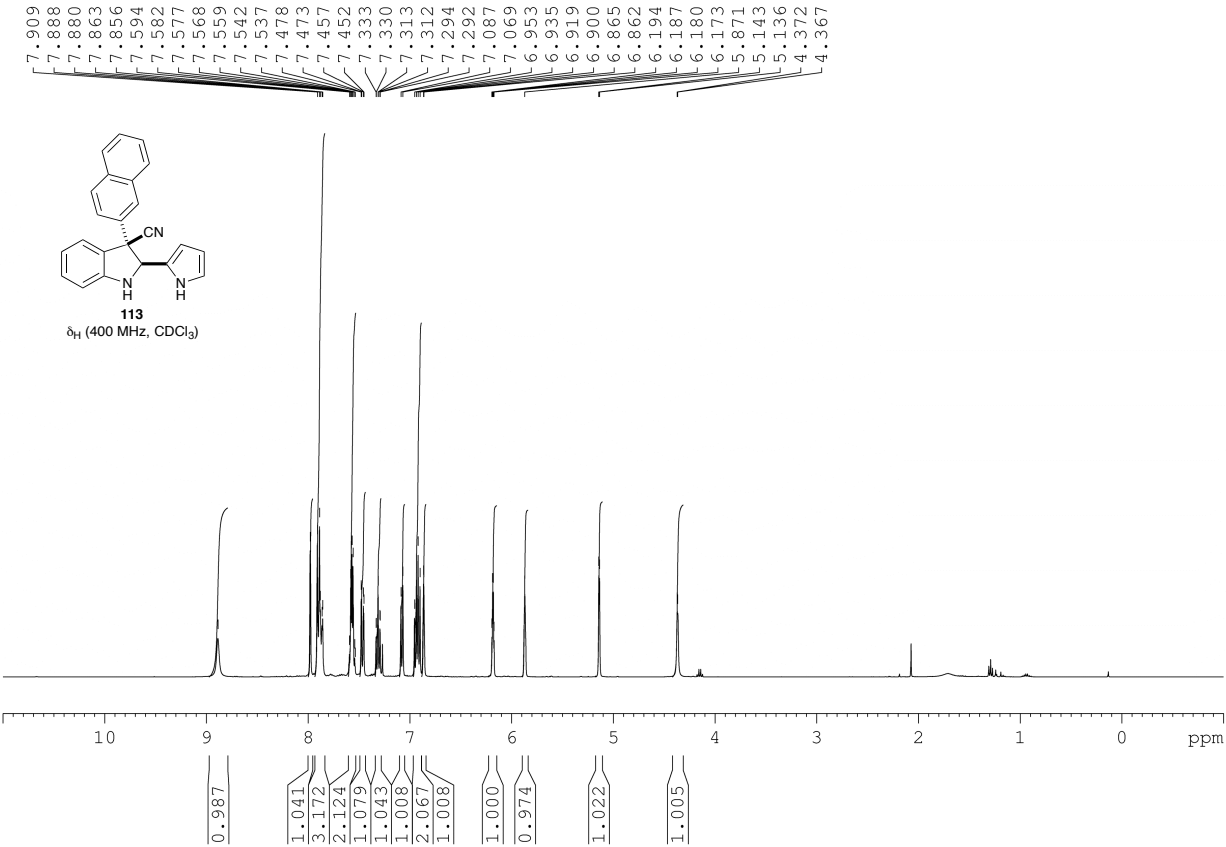


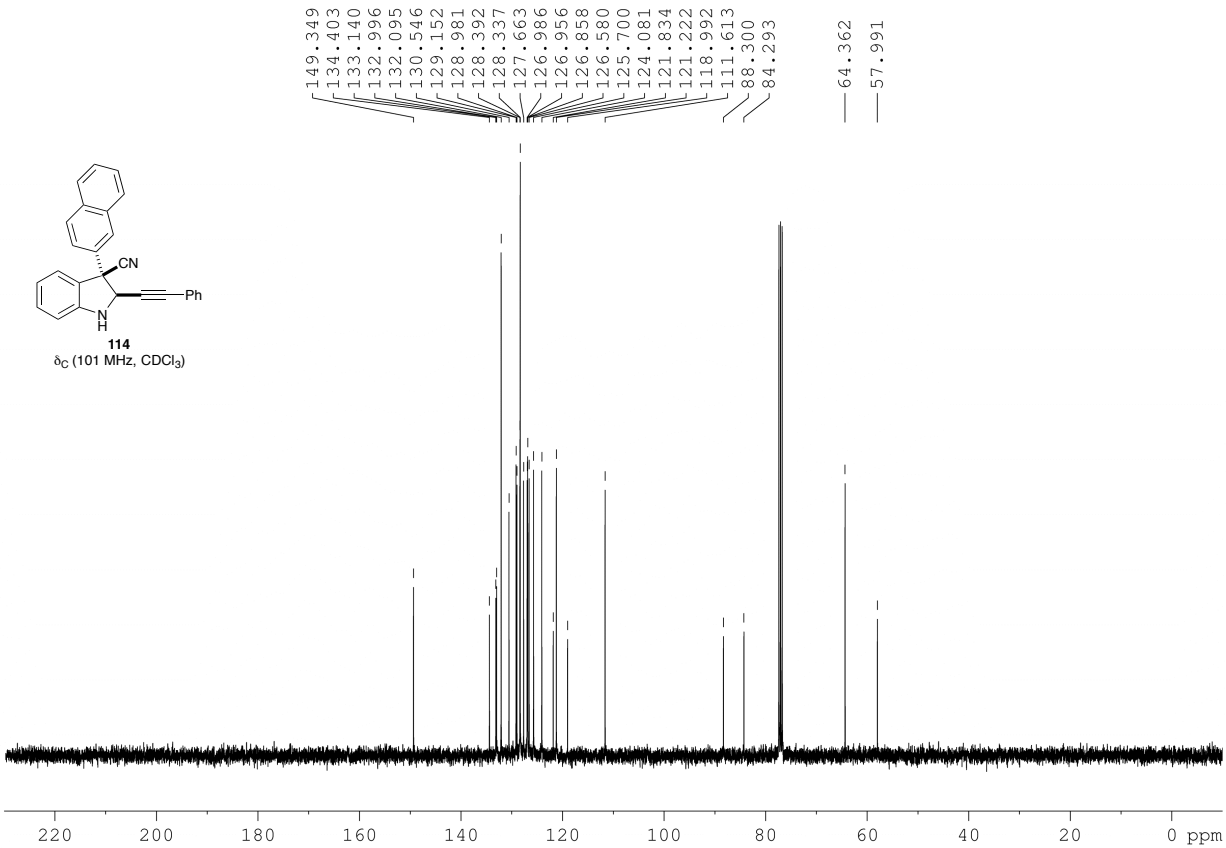
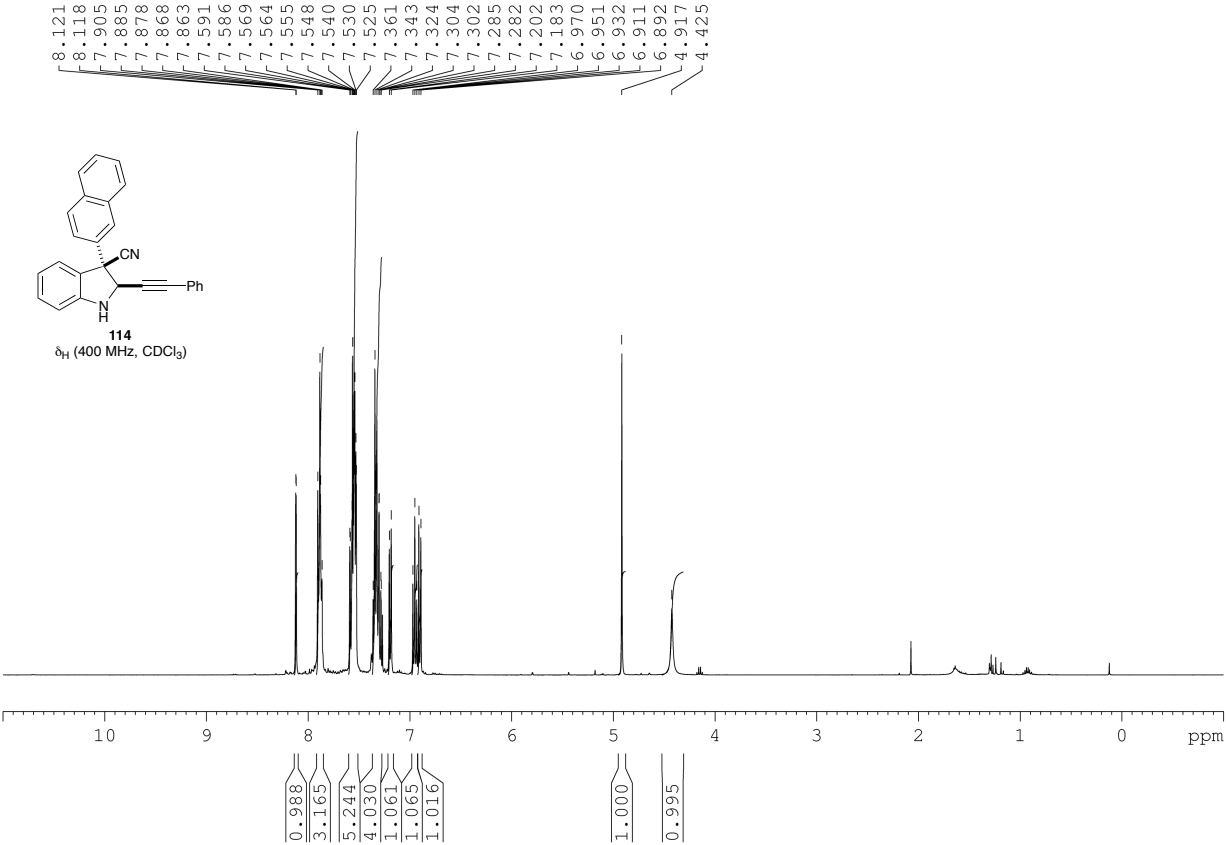


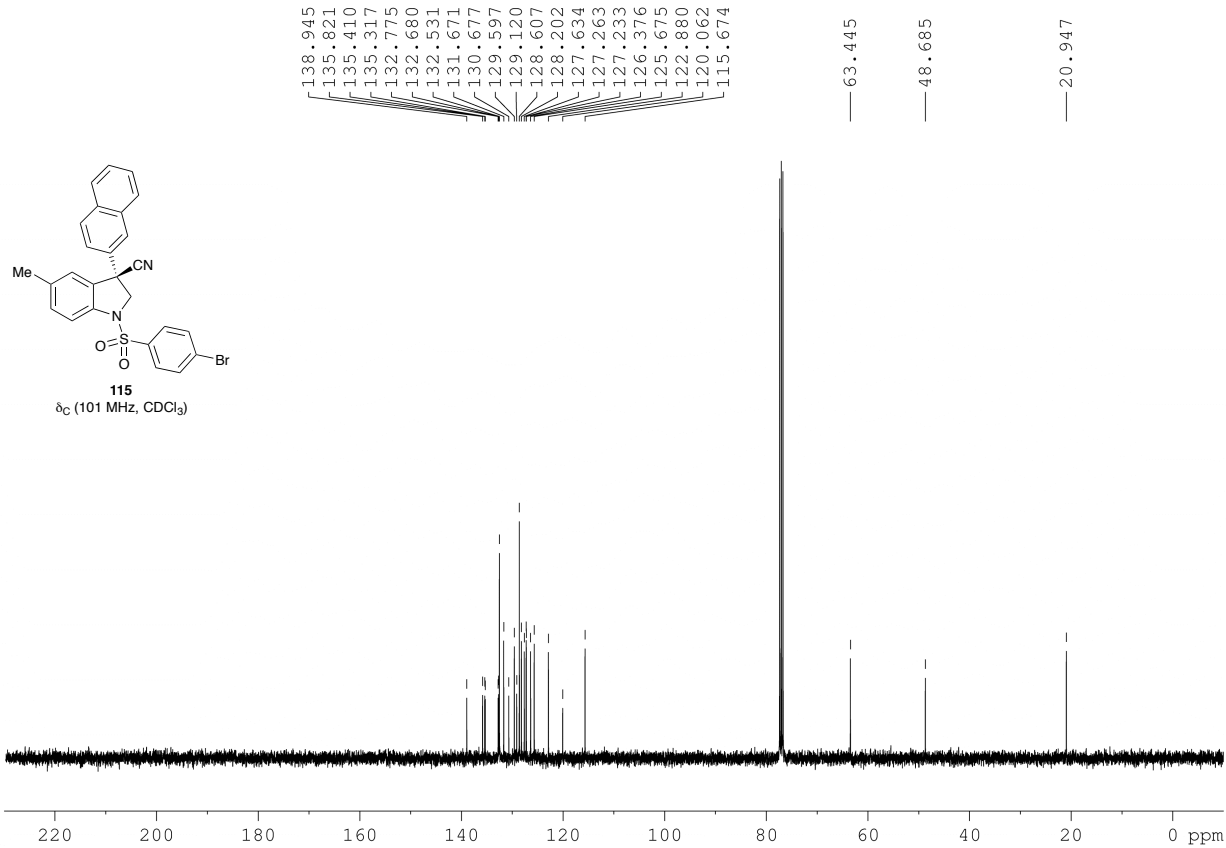
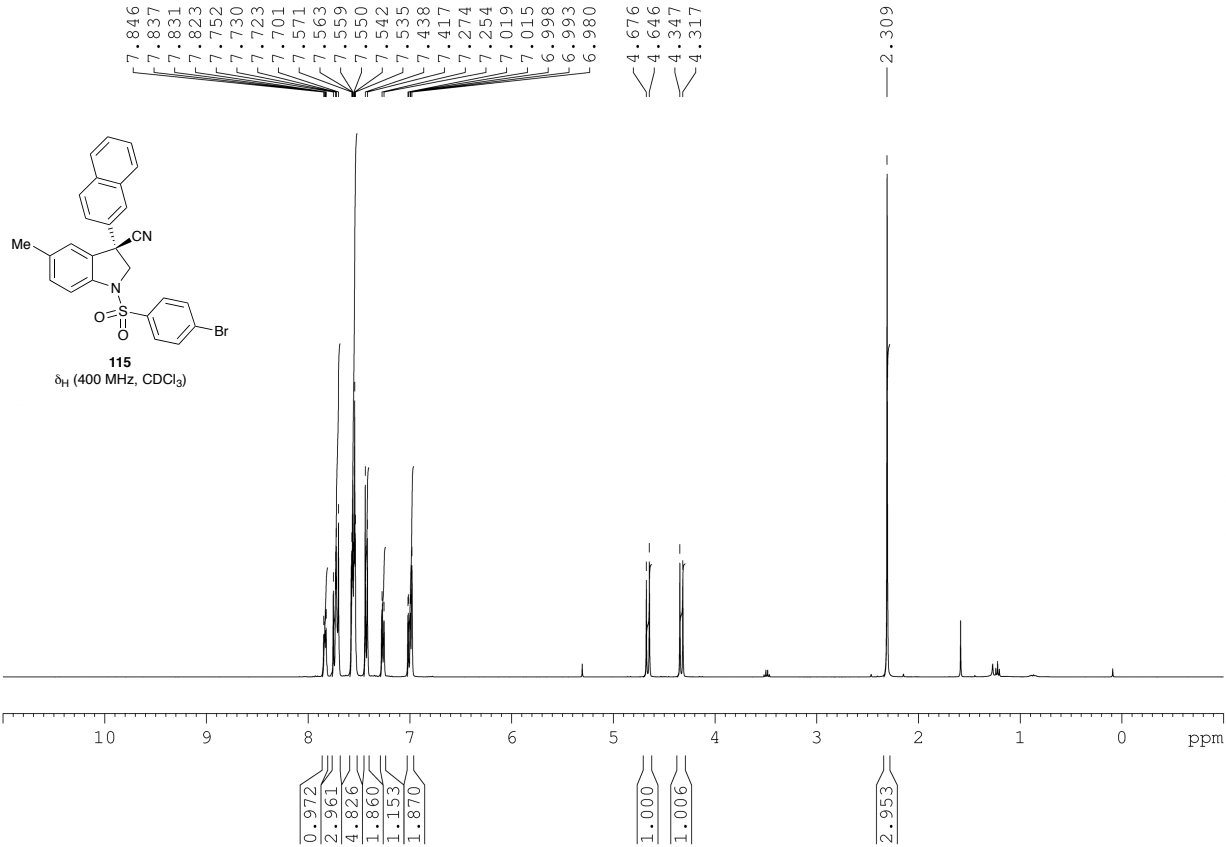




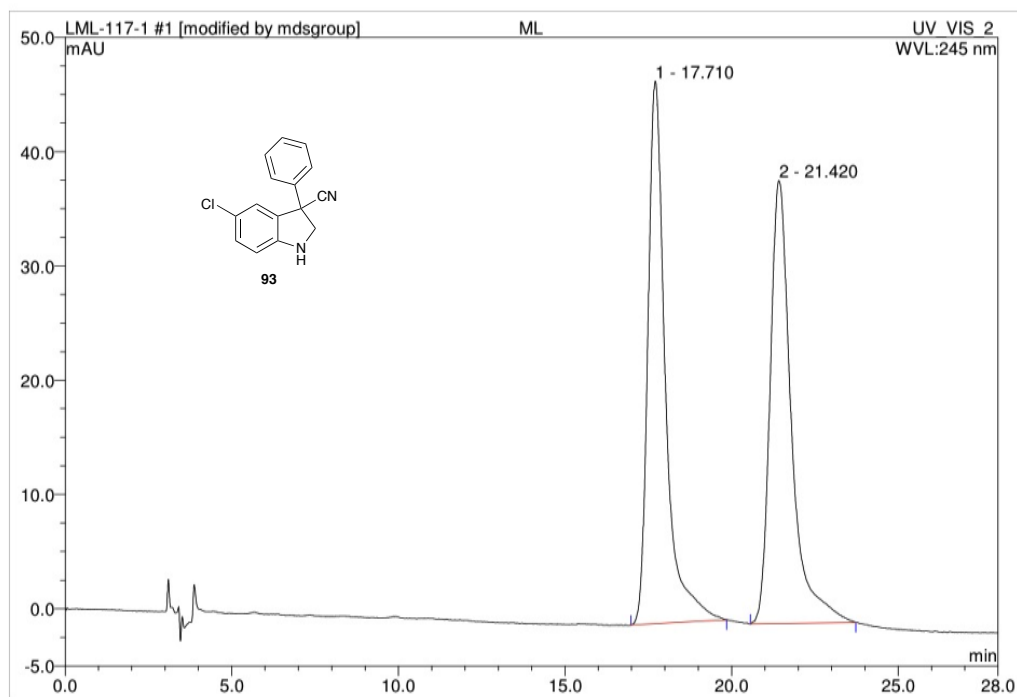




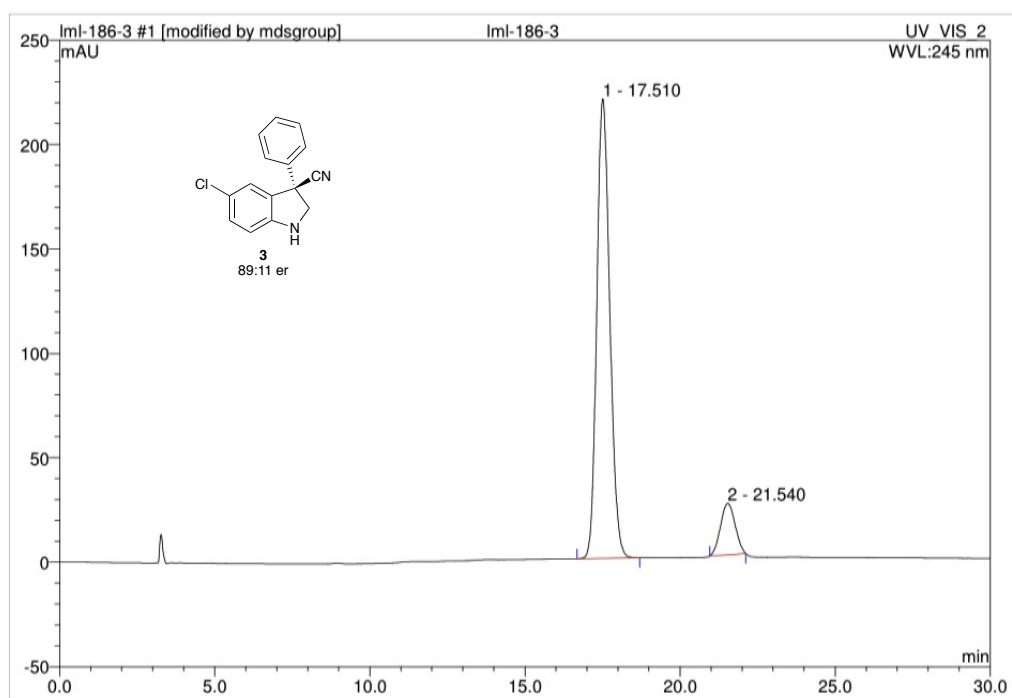




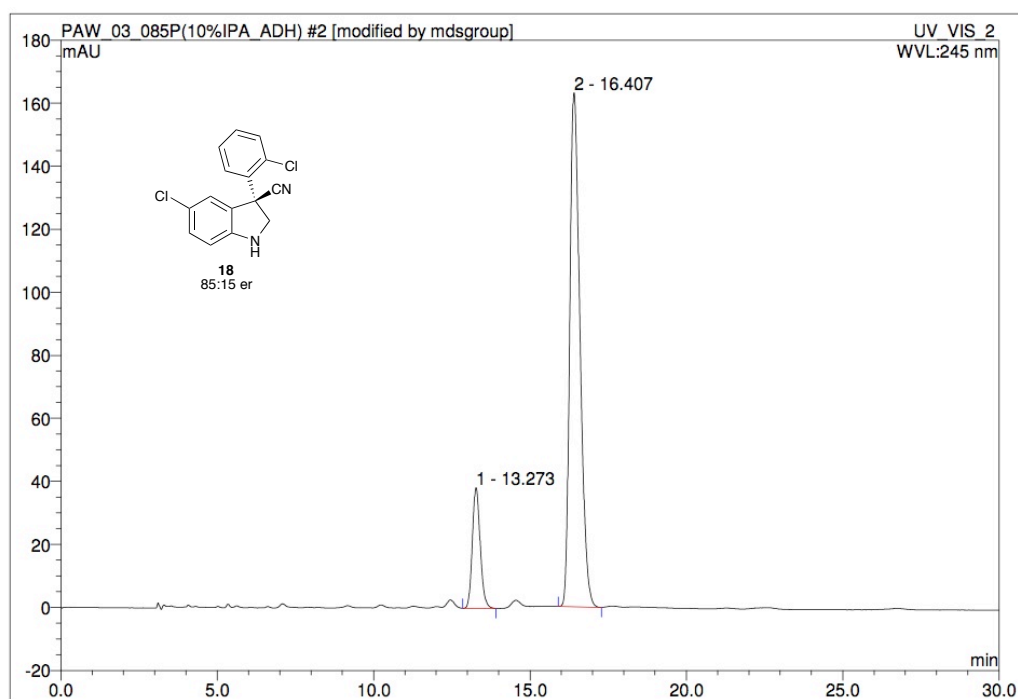
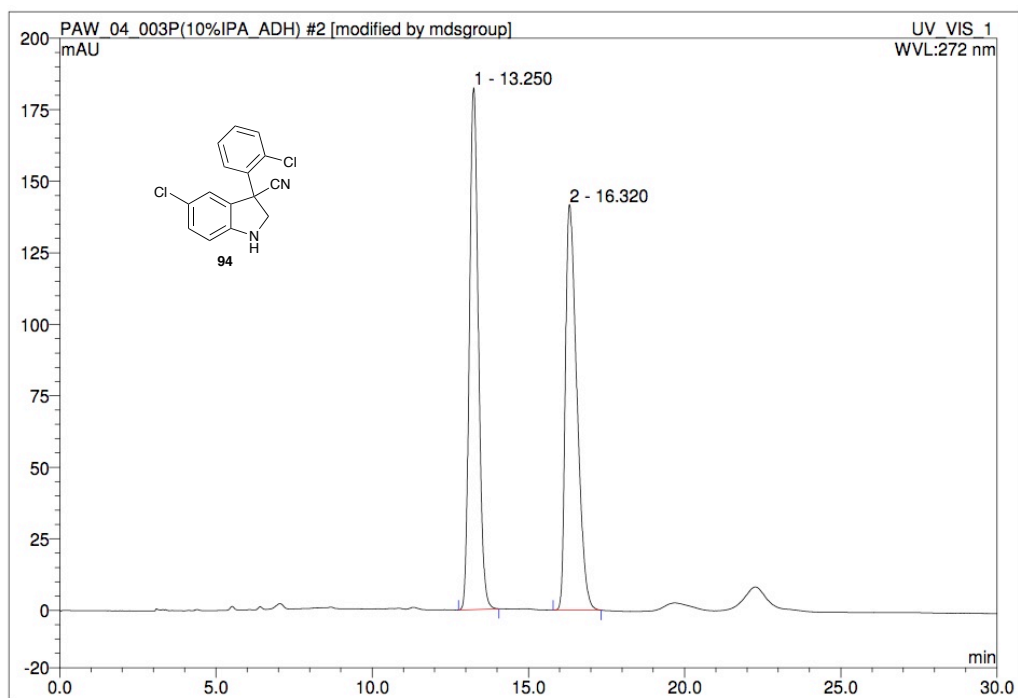
Appendix III: HPLC Data

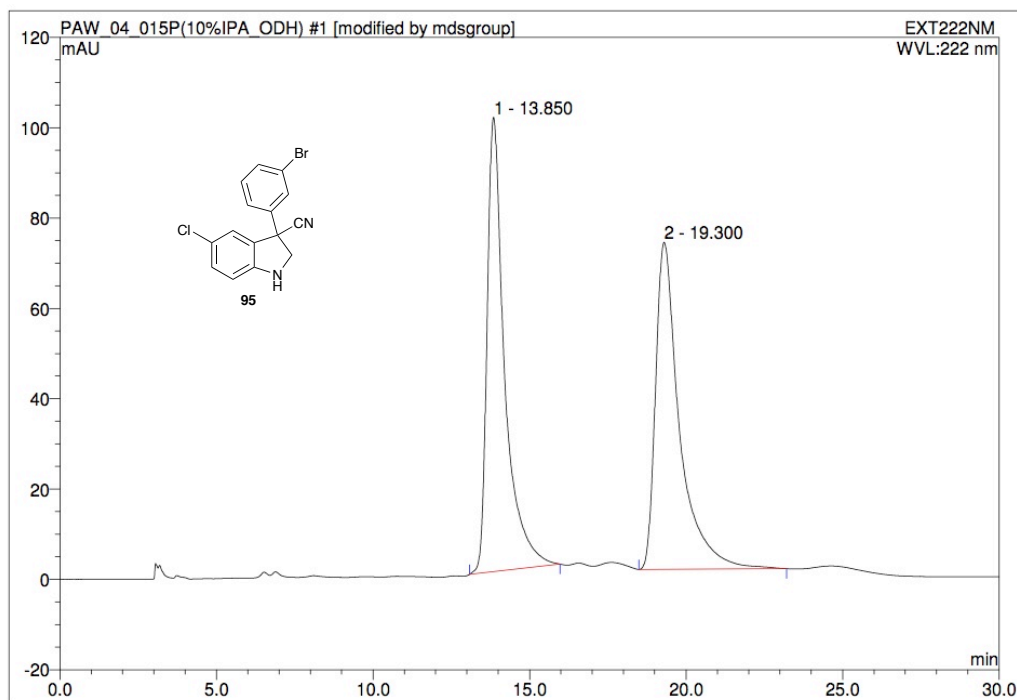


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17.71	n.a.	47.474	28.863	50.19	n.a.	BMB
2	21.42	n.a.	38.758	28.650	49.81	n.a.	BMB
Total:			86.232	57.512	100.00	0.000	

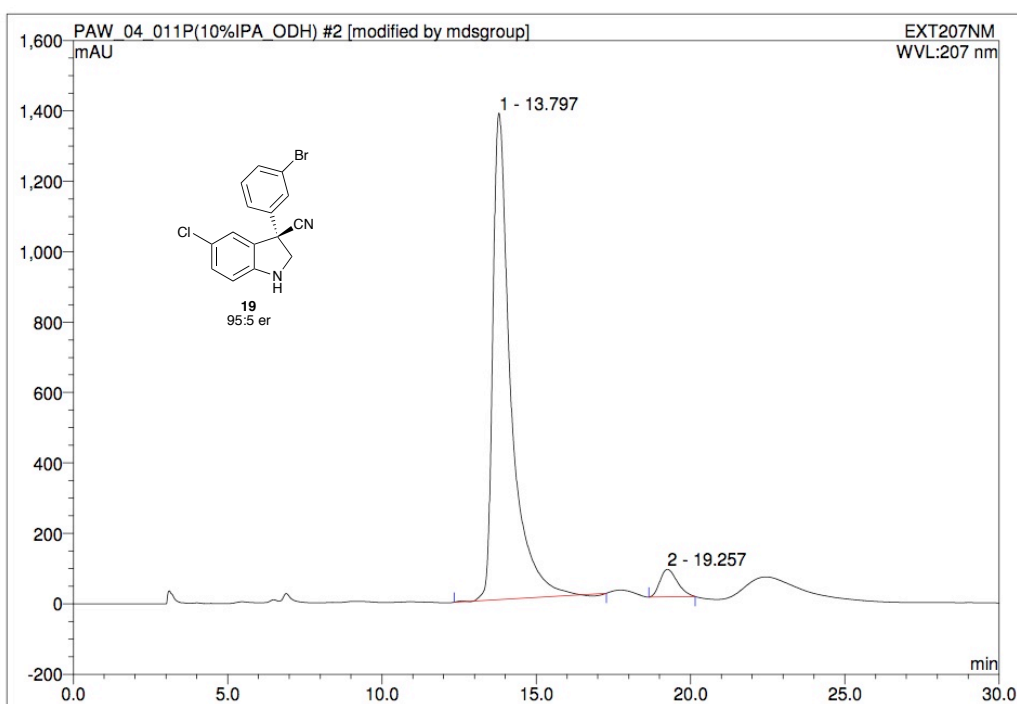


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17.51	n.a.	220.200	106.490	88.80	n.a.	BMB*
2	21.54	n.a.	24.656	13.429	11.20	n.a.	BMB*
Total:			244.856	119.919	100.00	0.000	

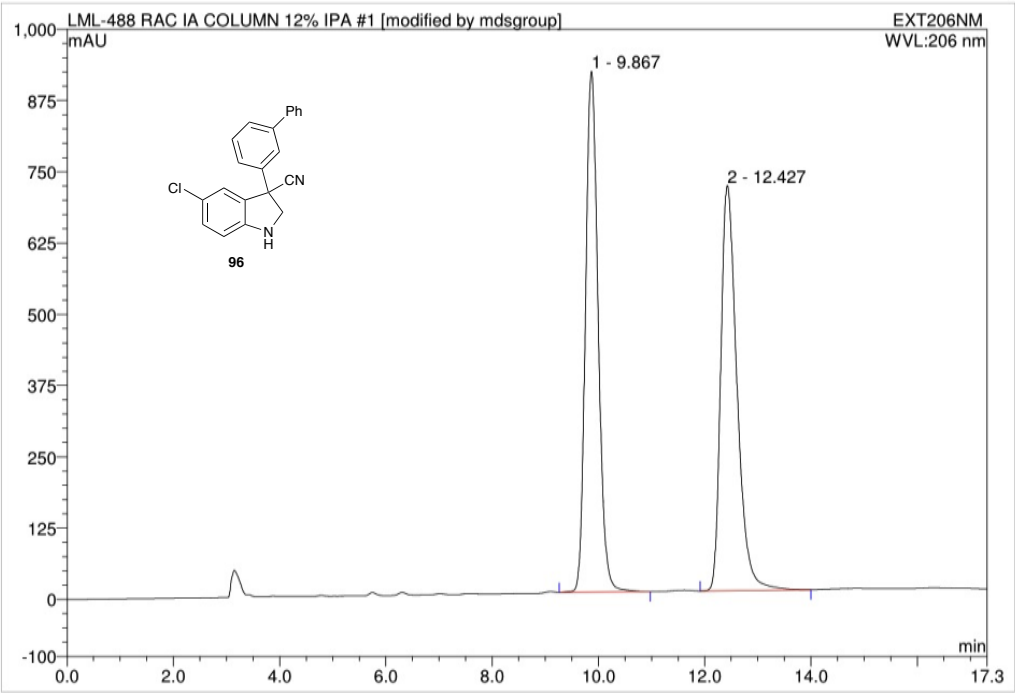




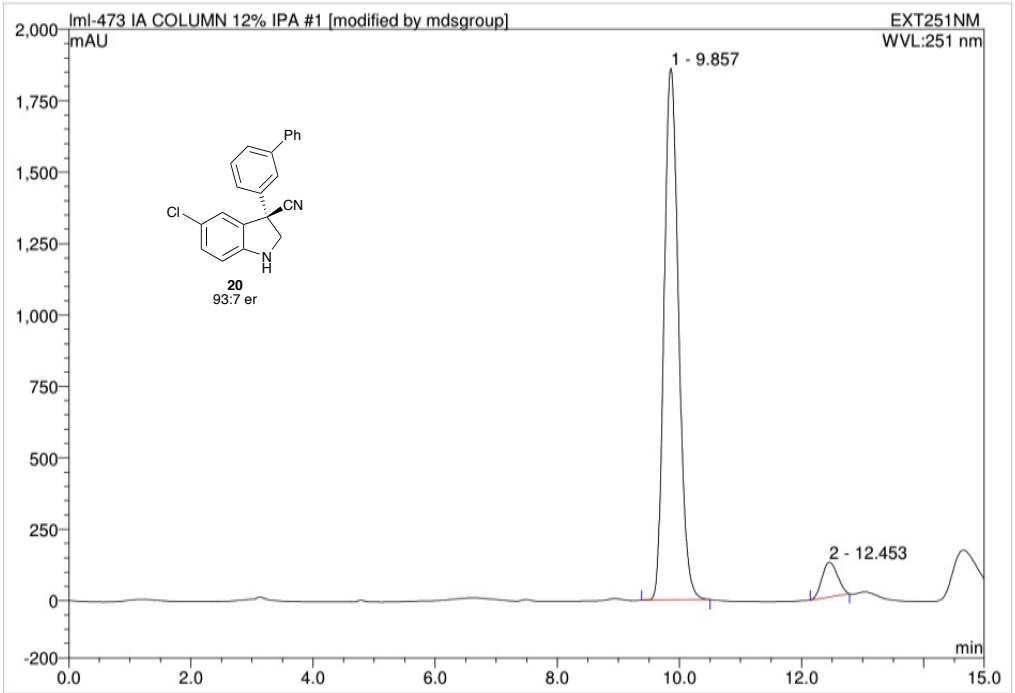
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.85	n.a.	100.587	65.284	50.37	n.a.	BMB*
2	19.30	n.a.	72.402	64.326	49.63	n.a.	BMB
Total:			172.989	129.610	100.00	0.000	



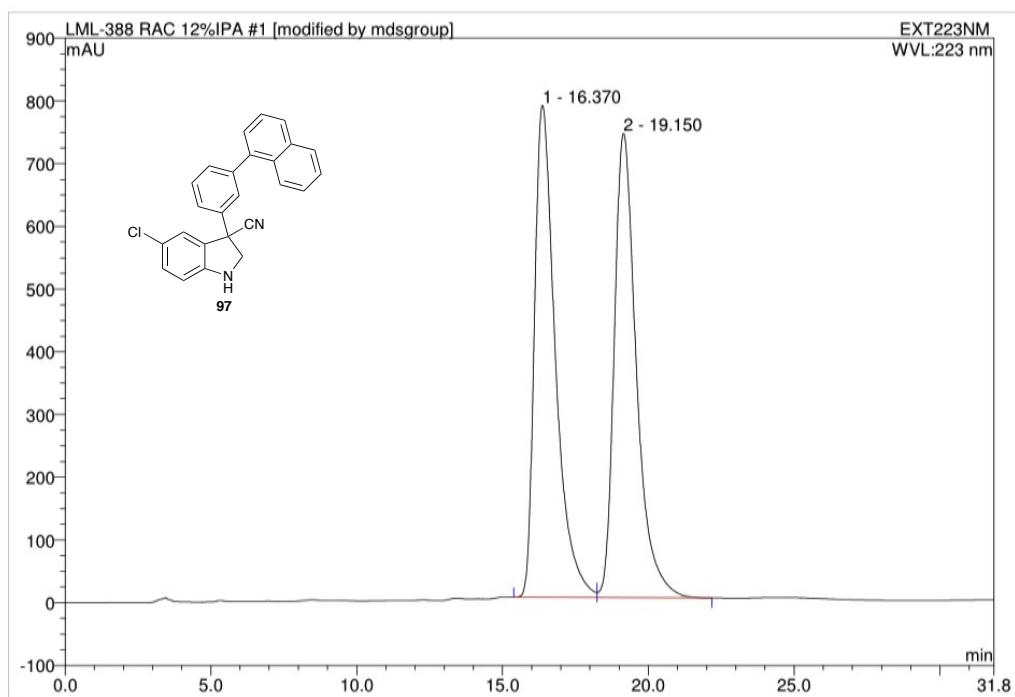
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.80	n.a.	1381.854	932.730	94.82	n.a.	BMB*
2	19.26	n.a.	78.214	50.905	5.18	n.a.	BMB*
Total:			1460.068	983.635	100.00	0.000	



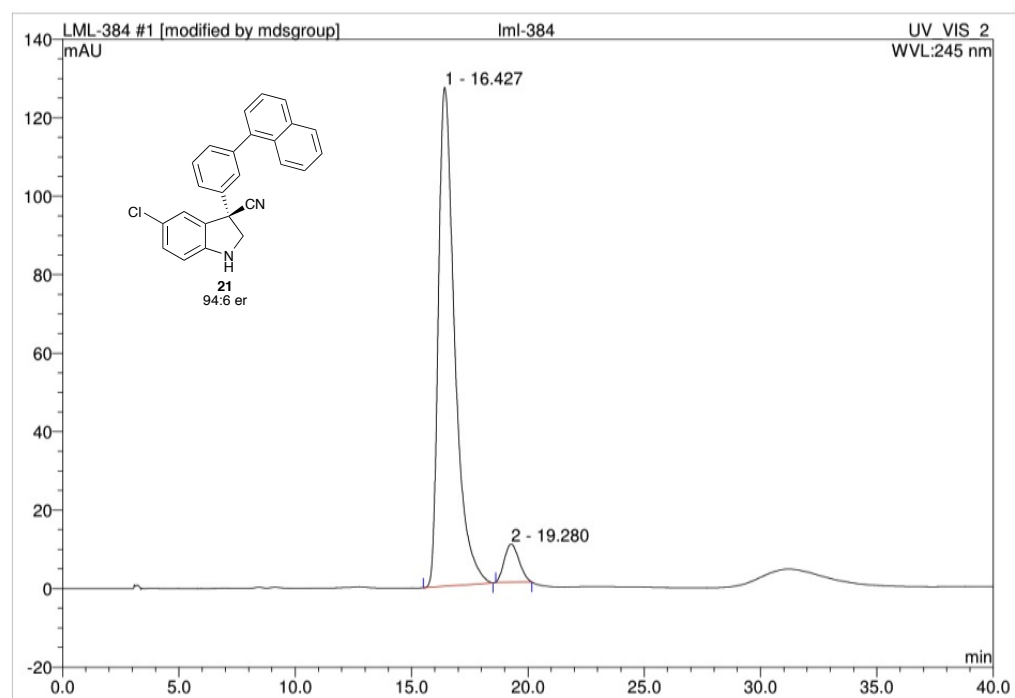
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.87	n.a.	913.938	251.508	50.03	n.a.	BMB*
2	12.43	n.a.	710.624	251.186	49.97	n.a.	BMB
Total:			1624.562	502.694	100.00	0.000	



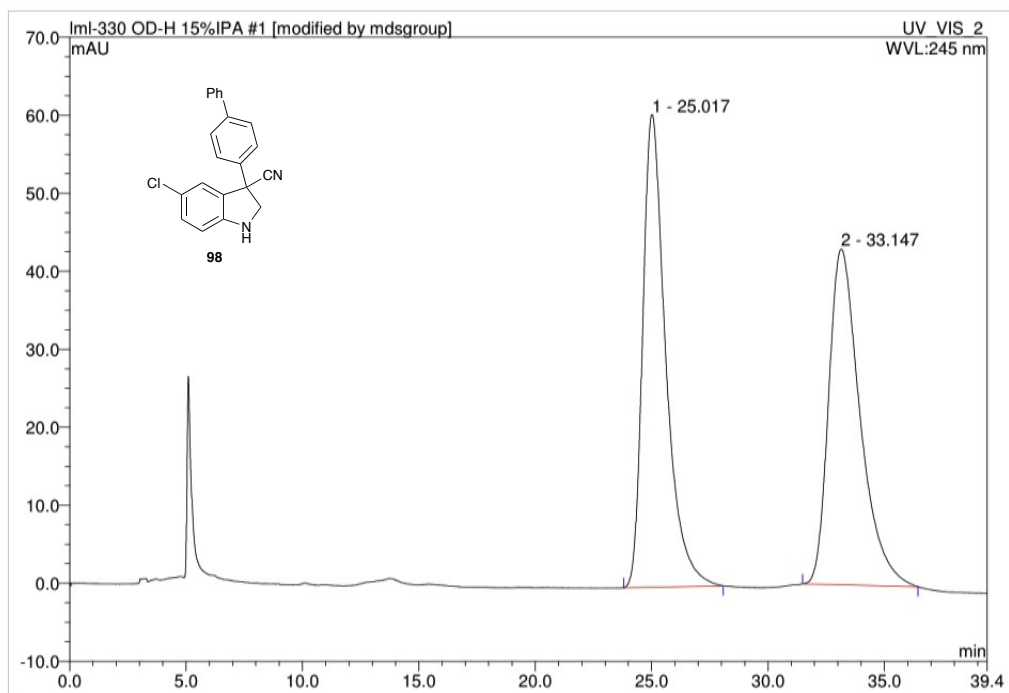
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.86	n.a.	1860.600	510.436	93.45	n.a.	BMB*
2	12.45	n.a.	121.593	35.779	6.55	n.a.	BMB*
Total:			1982.193	546.215	100.00	0.000	



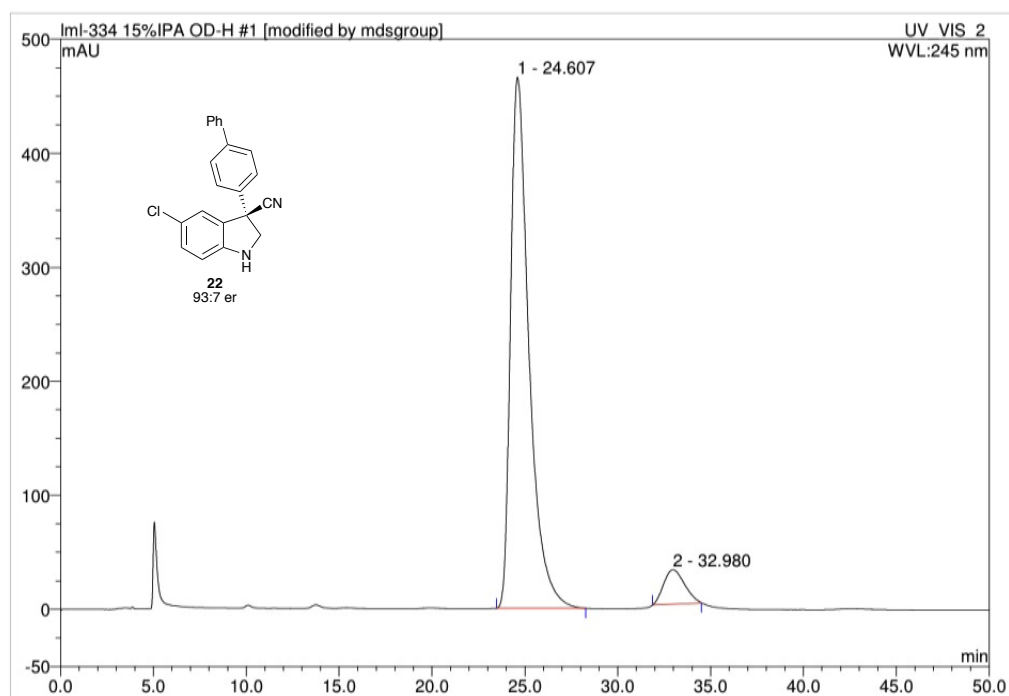
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16.37	n.a.	784.391	650.923	49.98	n.a.	BM *
2	19.15	n.a.	740.108	651.543	50.02	n.a.	MB
Total:			1524.499	1302.466	100.00	0.000	



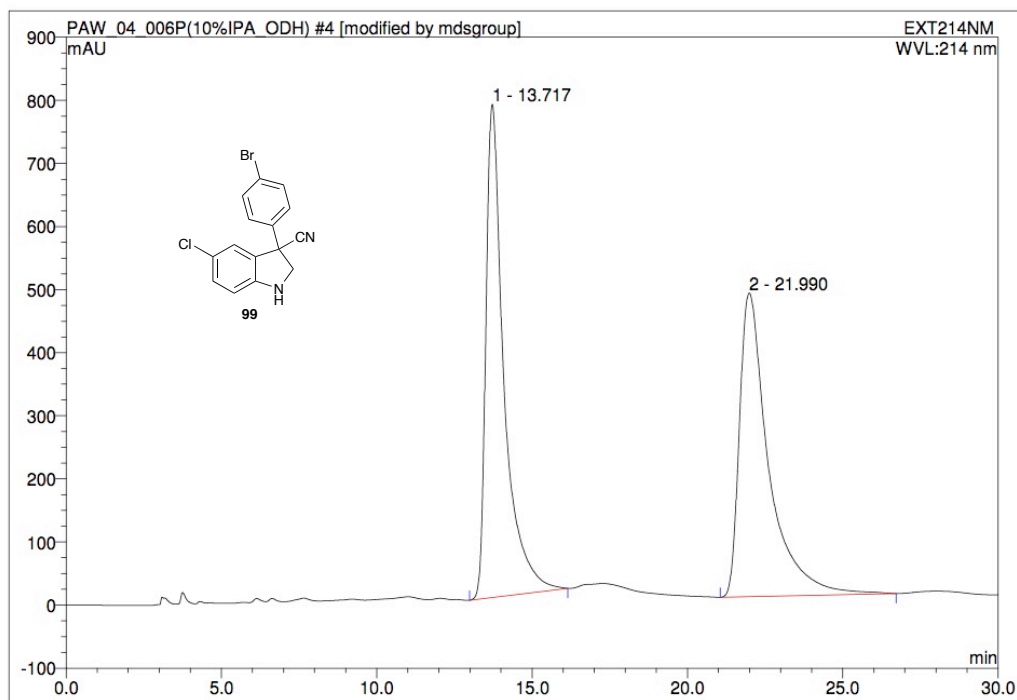
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16.43	n.a.	127.129	103.377	93.54	n.a.	BMB*
2	19.28	n.a.	9.709	7.139	6.46	n.a.	BMB*
Total:			136.838	110.516	100.00	0.000	



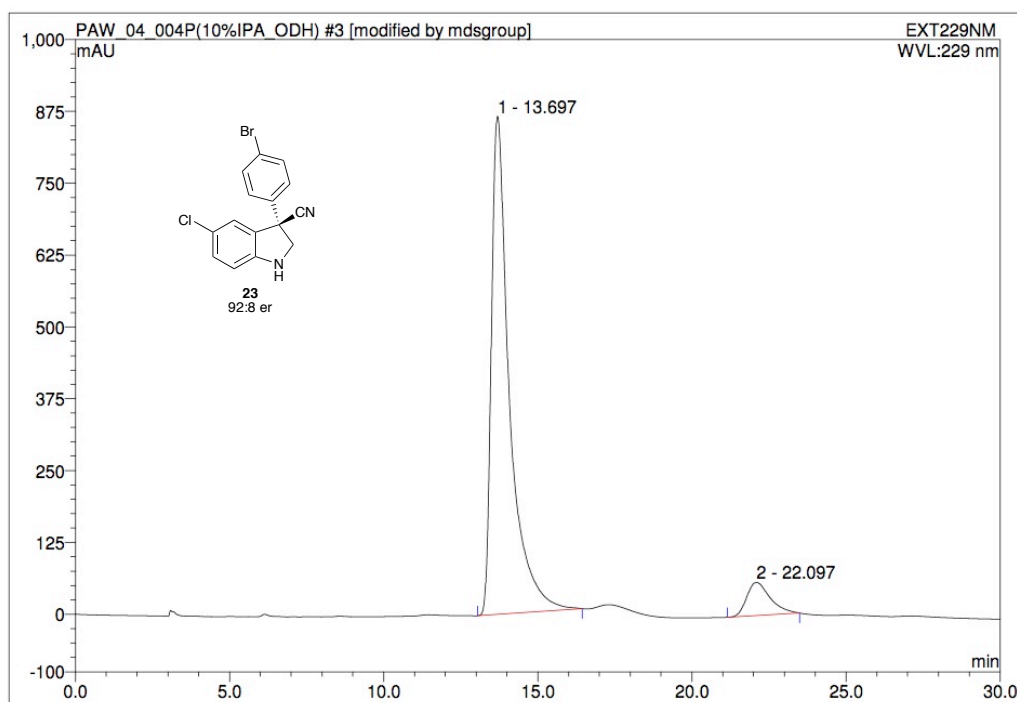
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25.02	n.a.	60.580	69.225	50.73	n.a.	BMB
2	33.15	n.a.	43.047	67.236	49.27	n.a.	BMB
Total:			103.627	136.460	100.00	0.000	



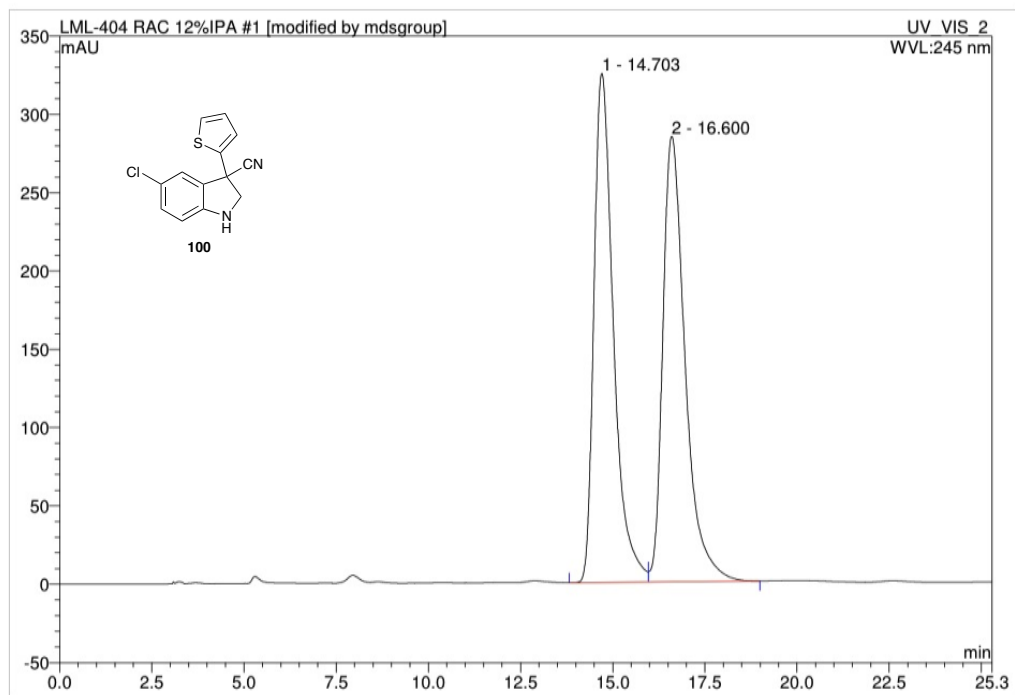
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	24.61	n.a.	465.785	534.897	93.17	n.a.	BMB*
2	32.98	n.a.	30.025	39.196	6.83	n.a.	BMB*
Total:			495.809	574.093	100.00	0.000	



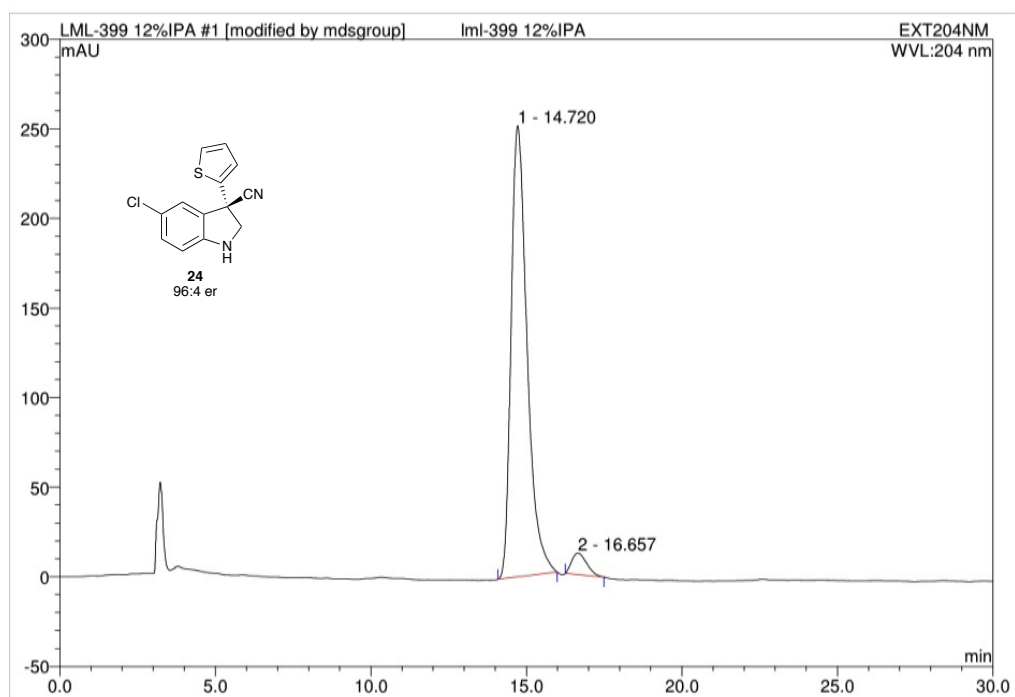
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.72	n.a.	781.971	526.820	50.15	n.a.	BMB*
2	21.99	n.a.	481.601	523.566	49.85	n.a.	BMB*
Total:			1263.572	1050.386	100.00	0.000	



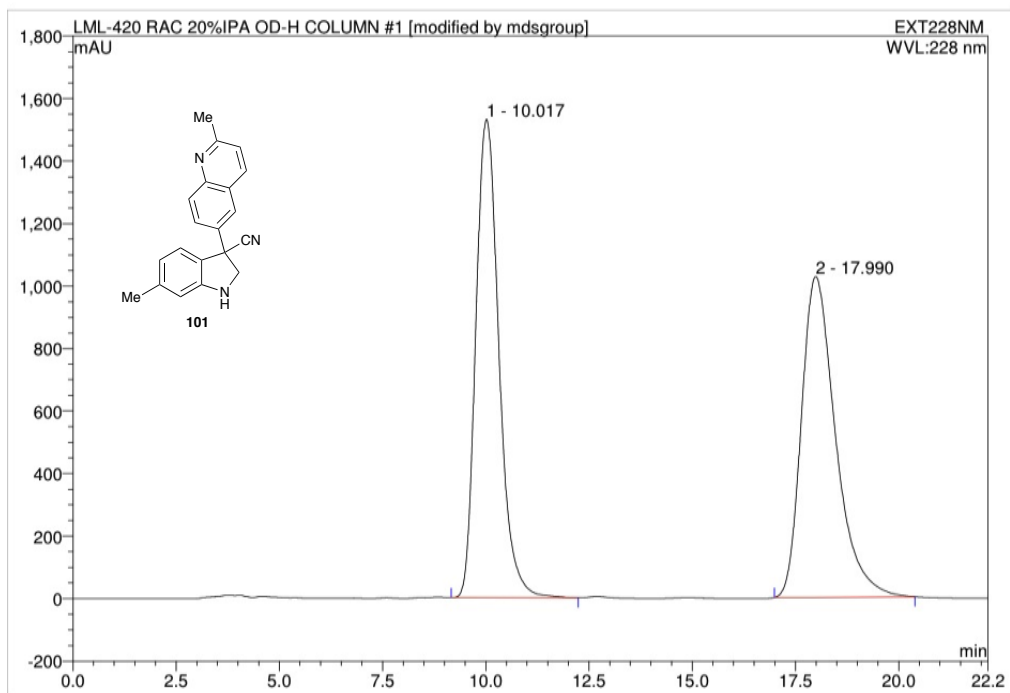
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.70	n.a.	866.418	588.474	92.01	n.a.	BMB*
2	22.10	n.a.	57.816	51.107	7.99	n.a.	BMB*
Total:			924.233	639.581	100.00	0.000	



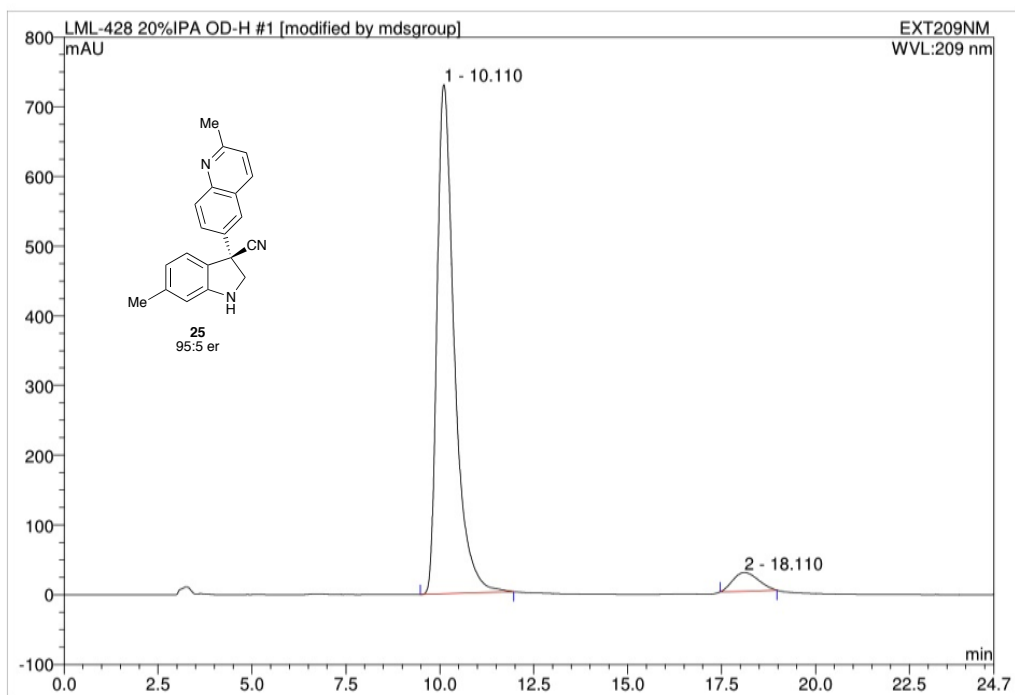
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.70	n.a.	324.959	198.431	49.90	n.a.	BM
2	16.60	n.a.	284.367	199.219	50.10	n.a.	MB
Total:			609.326	397.650	100.00	0.000	



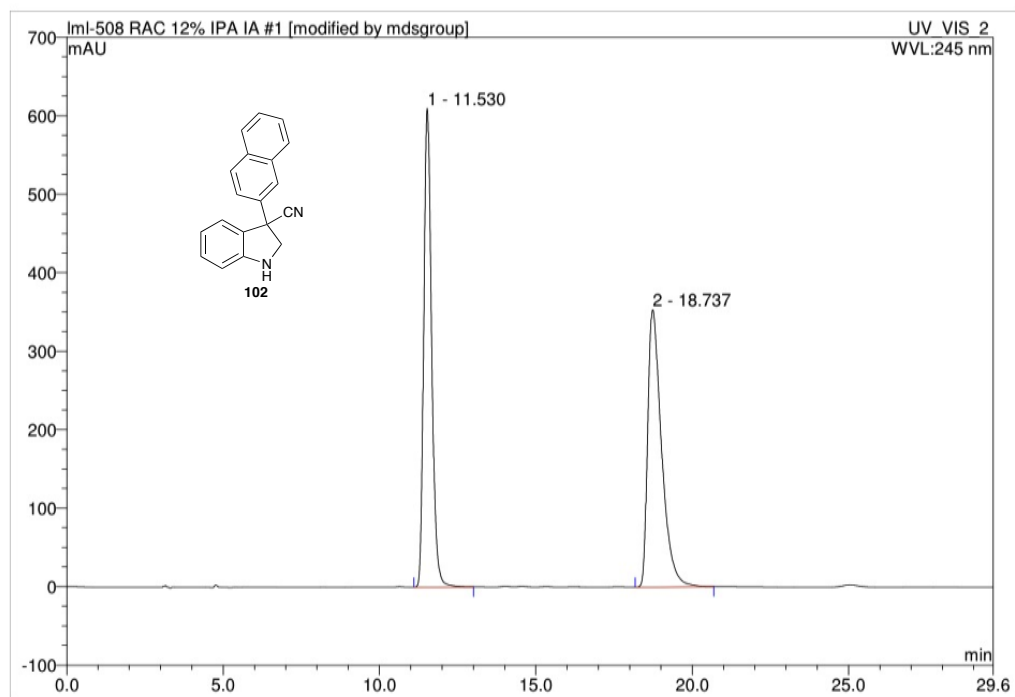
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.72	n.a.	251.785	149.531	95.68	n.a.	BMB*
2	16.66	n.a.	12.018	6.756	4.32	n.a.	BMB*
Total:			263.803	156.287	100.00	0.000	



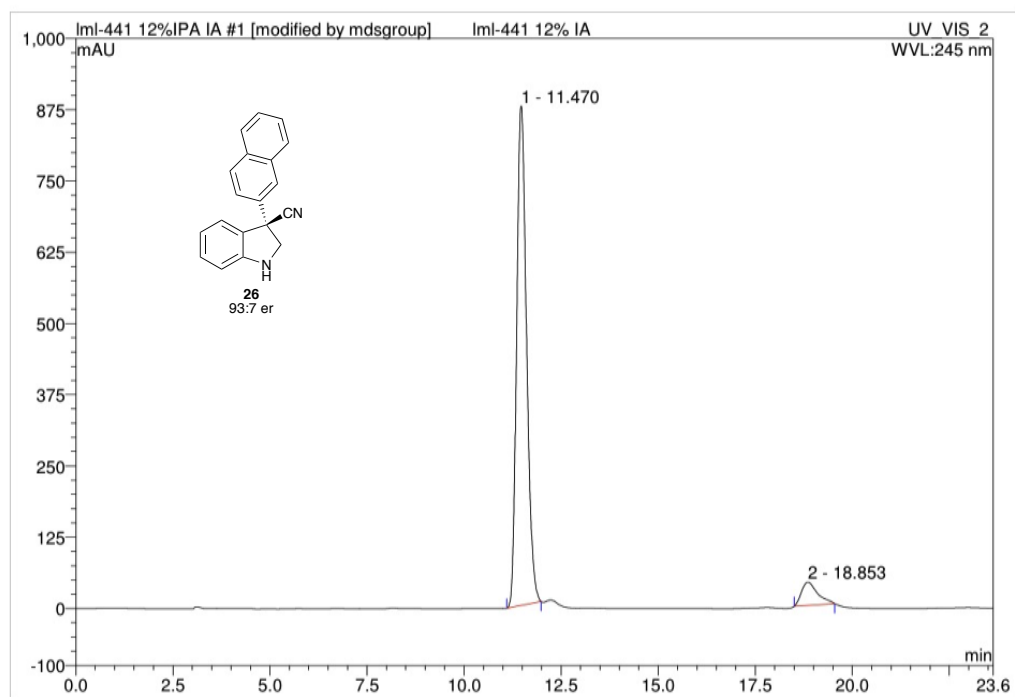
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.02	n.a.	1531.331	989.796	50.22	n.a.	BMB*
2	17.99	n.a.	1026.223	981.213	49.78	n.a.	BMB*
Total:			2557.554	1971.009	100.00	0.000	



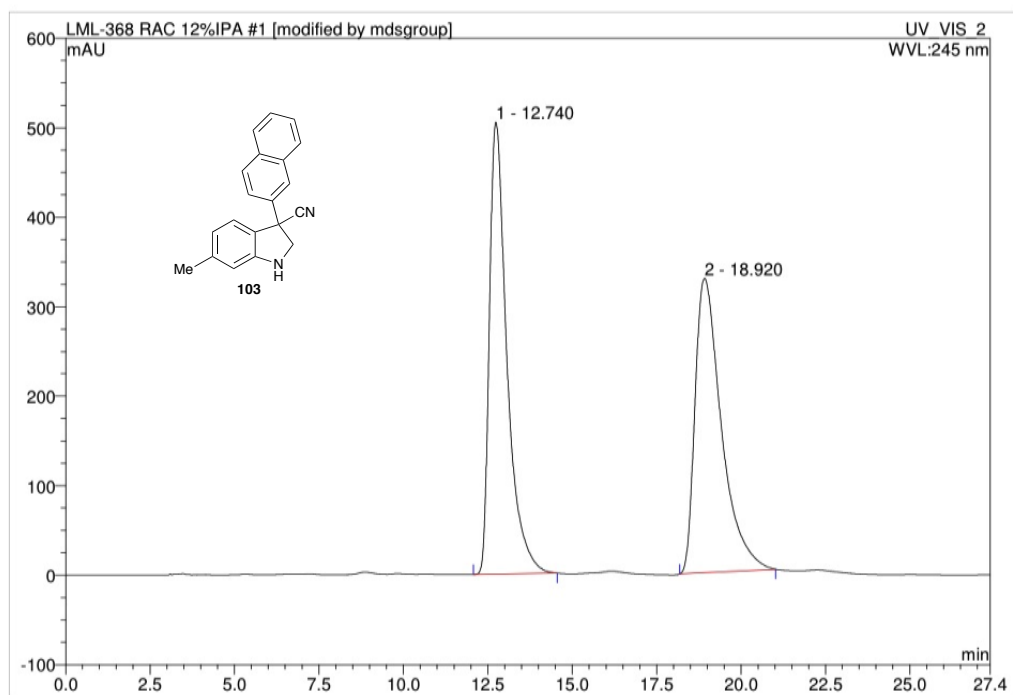
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.11	n.a.	730.502	389.478	94.87	n.a.	BMB*
2	18.11	n.a.	26.905	21.043	5.13	n.a.	BMB*
Total:			757.408	410.521	100.00	0.000	



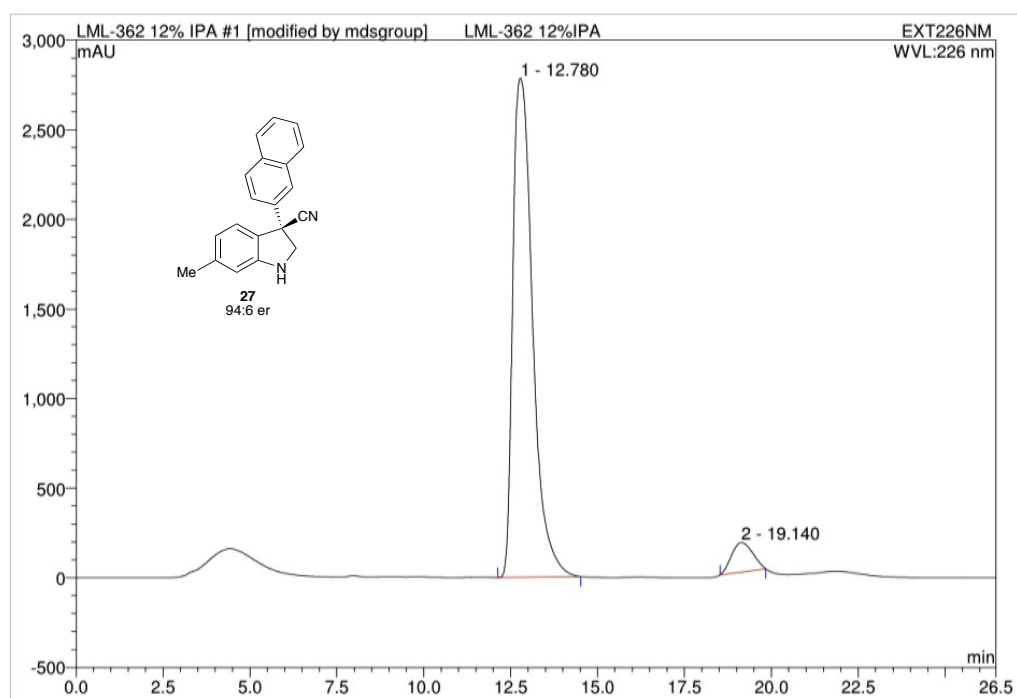
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.53	n.a.	610.022	178.255	49.56	n.a.	BMB
2	18.74	n.a.	353.557	181.449	50.44	n.a.	BMB
Total:			963.579	359.704	100.00	0.000	



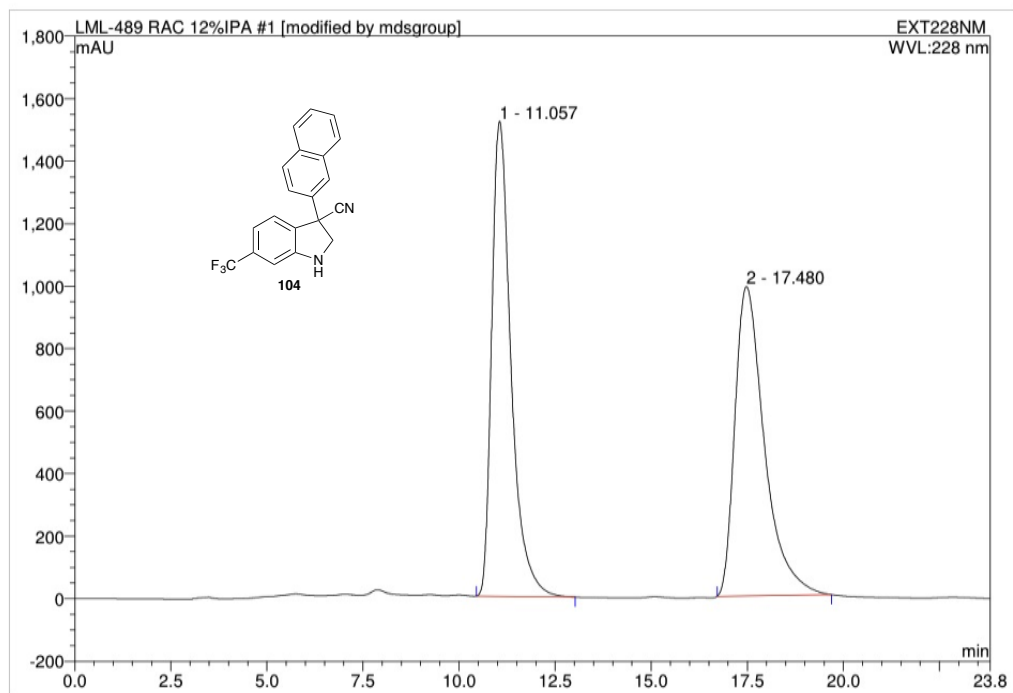
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.47	n.a.	876.011	257.216	92.92	n.a.	BMB*
2	18.85	n.a.	40.840	19.593	7.08	n.a.	BMB*
Total:			916.850	276.809	100.00	0.000	



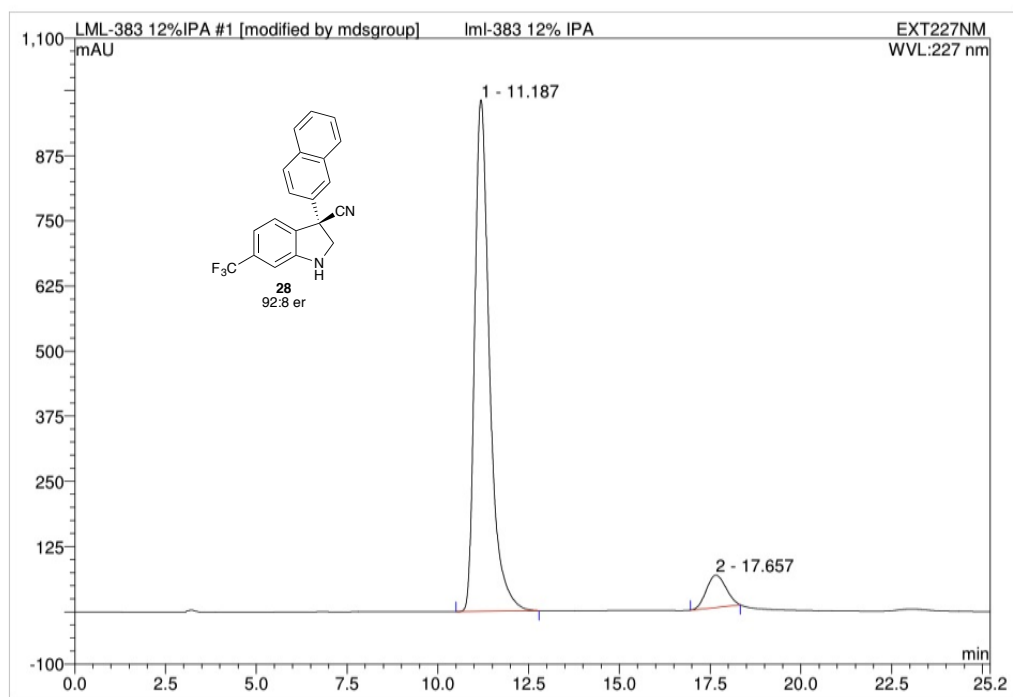
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.74	n.a.	505.012	303.444	50.49	n.a.	BMB*
2	18.92	n.a.	329.079	297.550	49.51	n.a.	BMB*
Total:			834.091	600.994	100.00	0.000	



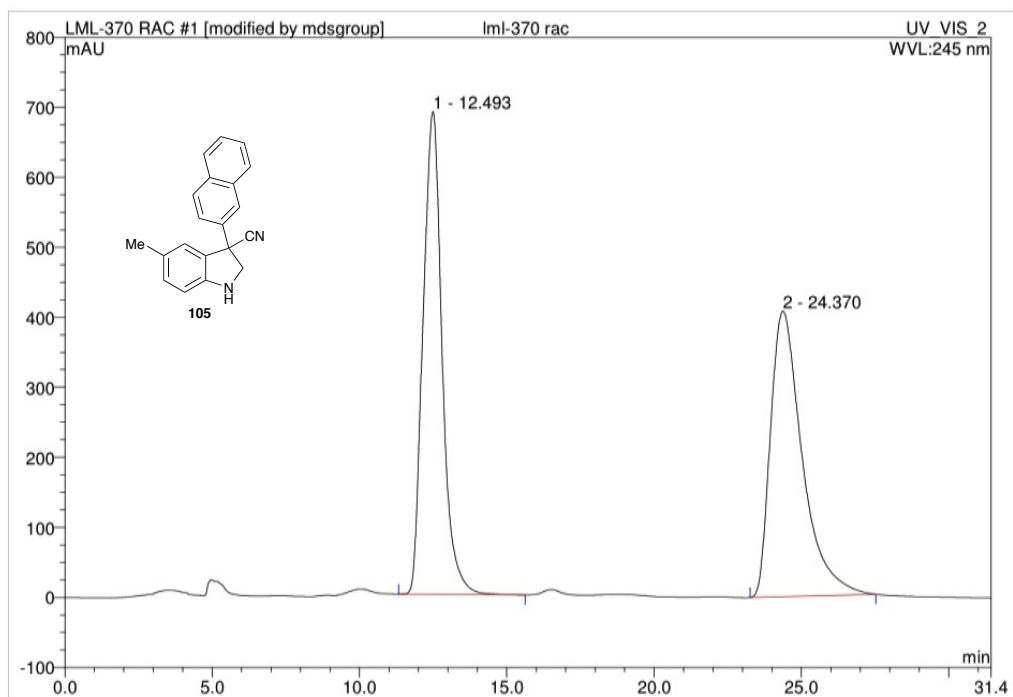
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.78	n.a.	2785.052	1838.705	94.05	n.a.	BMB*
2	19.14	n.a.	164.857	116.280	5.95	n.a.	BMB*
Total:			2949.910	1954.984	100.00	0.000	



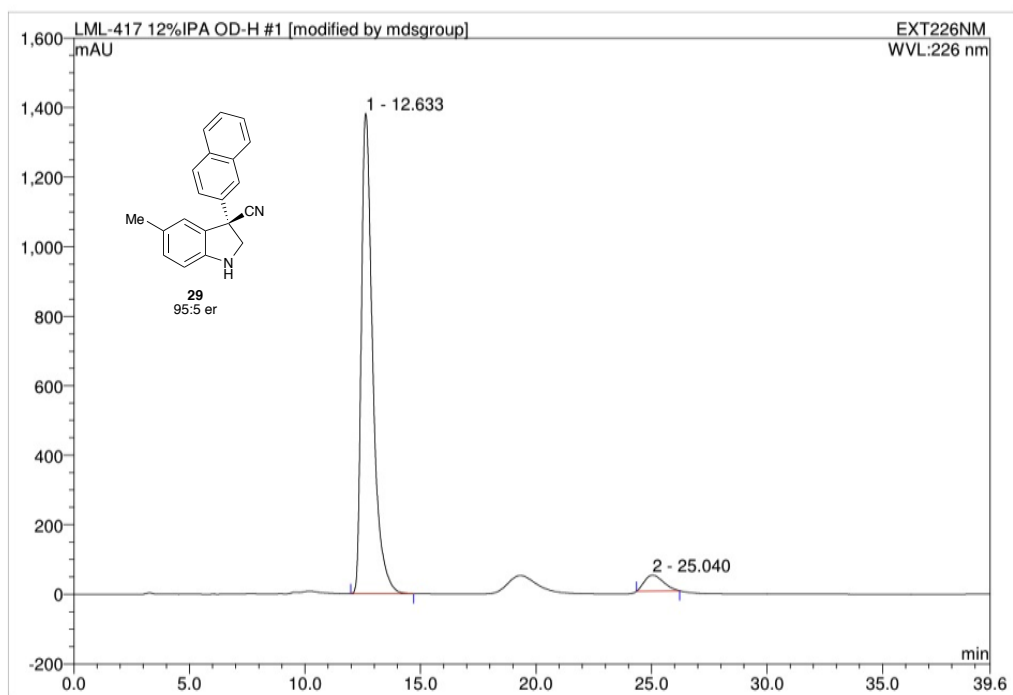
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.06	n.a.	1520.712	882.389	50.05	n.a.	BMB*
2	17.48	n.a.	989.742	880.688	49.95	n.a.	BMB*
Total:			2510.454	1763.076	100.00	0.000	



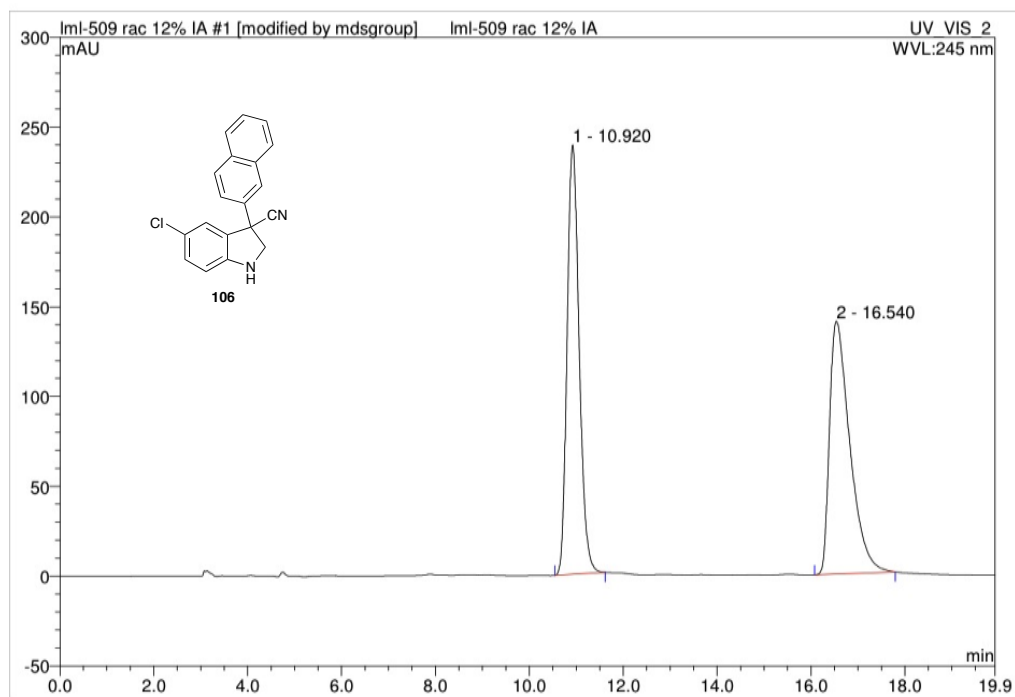
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.19	n.a.	980.846	465.297	92.34	n.a.	BMB*
2	17.66	n.a.	61.903	38.610	7.66	n.a.	BMB*
Total:			1042.749	503.906	100.00	0.000	



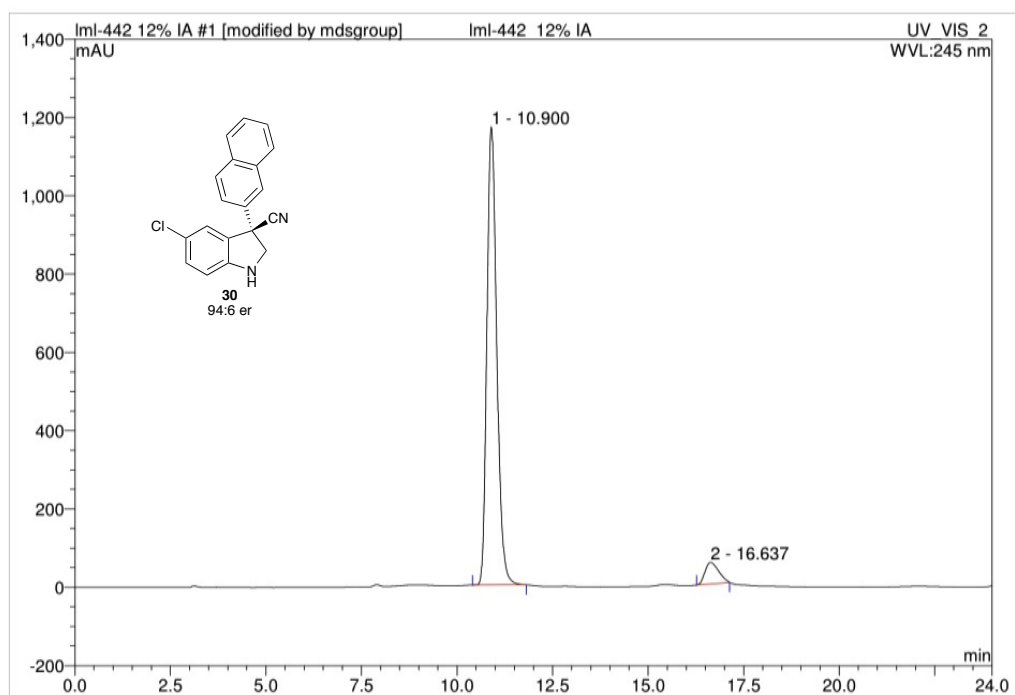
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.49	n.a.	689.531	515.360	50.35	n.a.	BMB*
2	24.37	n.a.	407.933	508.275	49.65	n.a.	BMB*
Total:			1097.464	1023.635	100.00	0.000	



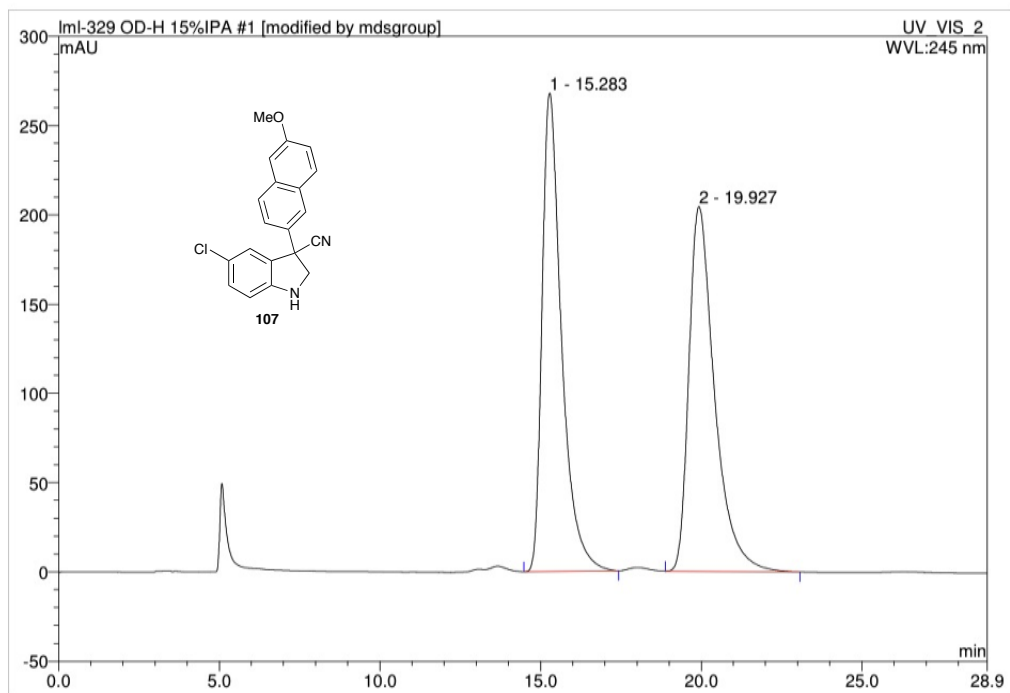
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.63	n.a.	1381.770	787.017	94.80	n.a.	BMB*
2	25.04	n.a.	45.722	43.187	5.20	n.a.	BMB*
Total:			1427.492	830.204	100.00	0.000	



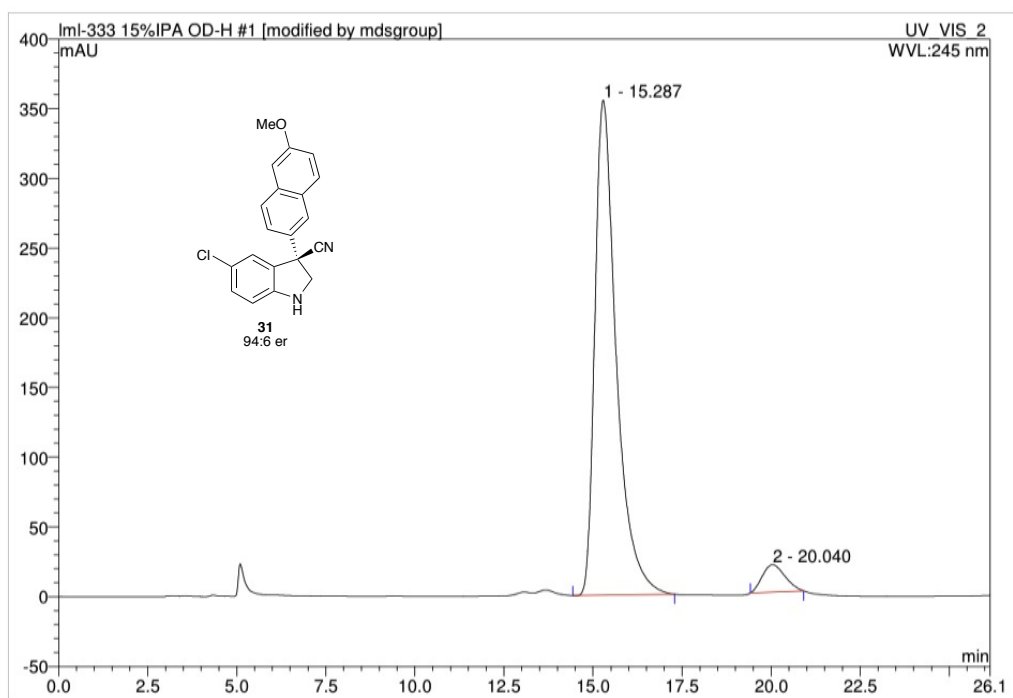
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.92	n.a.	239.071	70.882	50.13	n.a.	BMB*
2	16.54	n.a.	140.819	70.507	49.87	n.a.	BMB*
Total:			379.890	141.389	100.00	0.000	



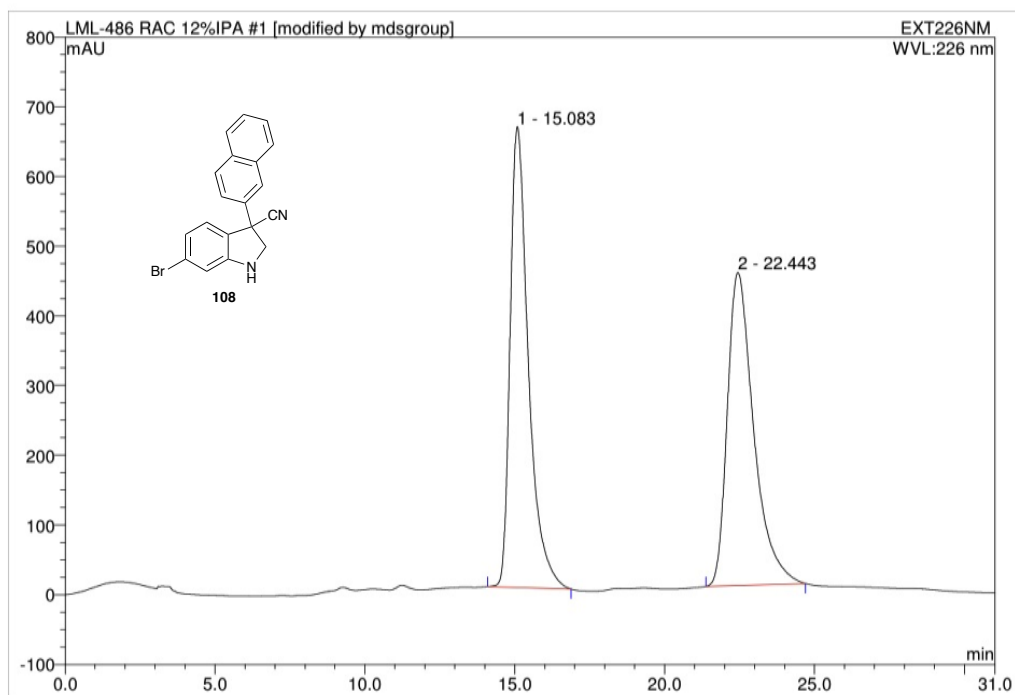
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.90	n.a.	1169.779	349.869	93.95	n.a.	BMB*
2	16.64	n.a.	54.684	22.530	6.05	n.a.	BMB*
Total:			1224.463	372.399	100.00	0.000	



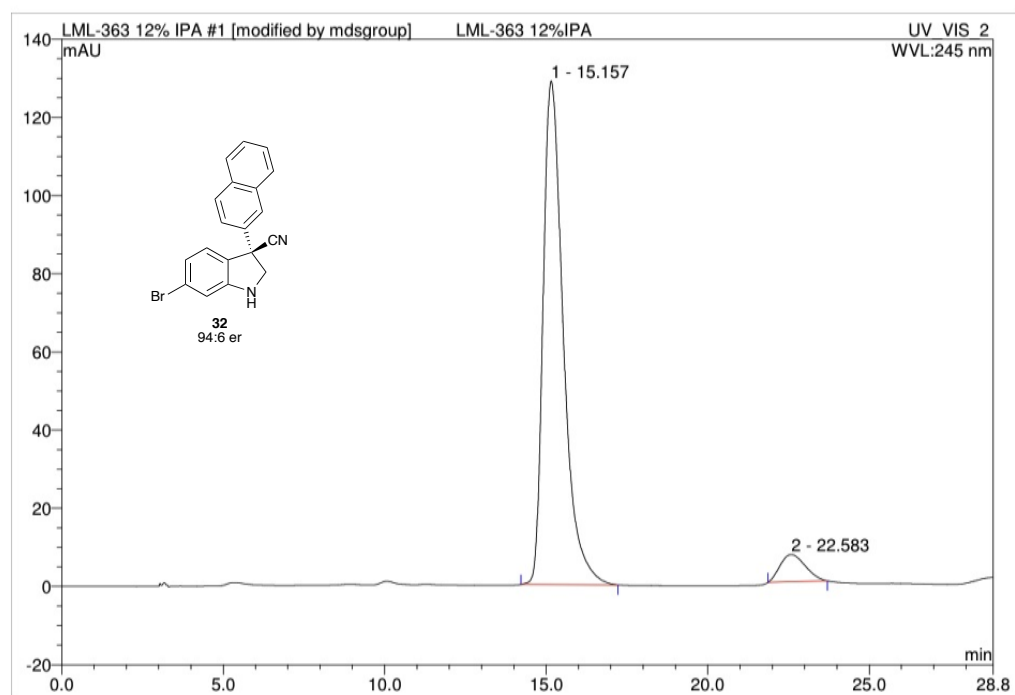
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15.28	n.a.	267.917	187.825	49.81	n.a.	BMB*
2	19.93	n.a.	204.330	189.238	50.19	n.a.	BMB*
Total:			472.247	377.062	100.00	0.000	



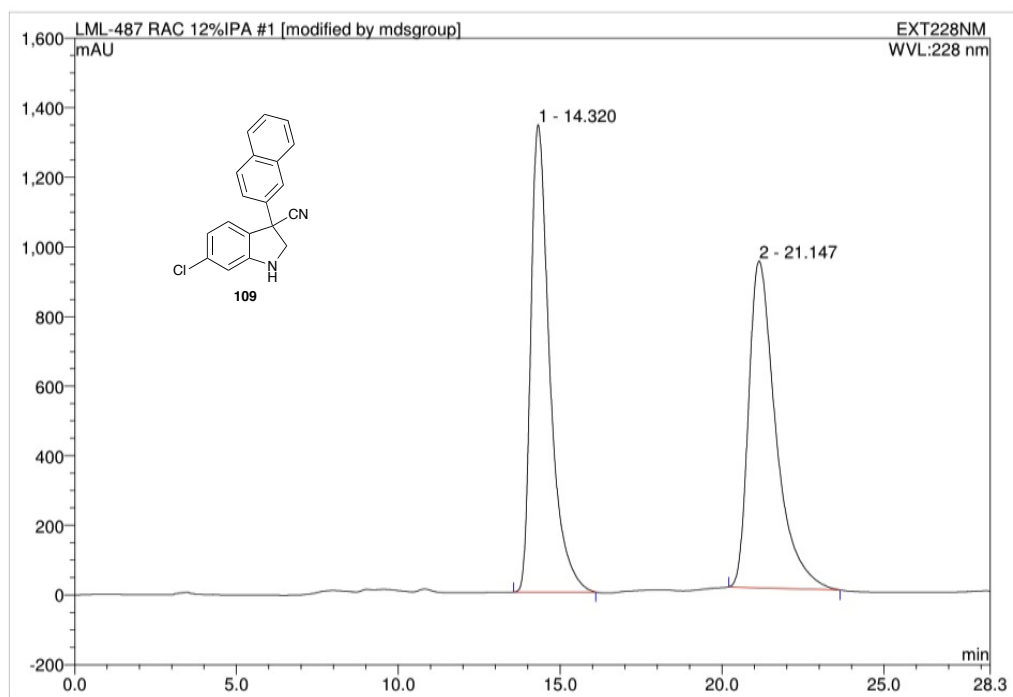
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15.29	n.a.	355.185	246.781	94.45	n.a.	BMB*
2	20.04	n.a.	19.634	14.514	5.55	n.a.	BMB*
Total:			374.819	261.294	100.00	0.000	



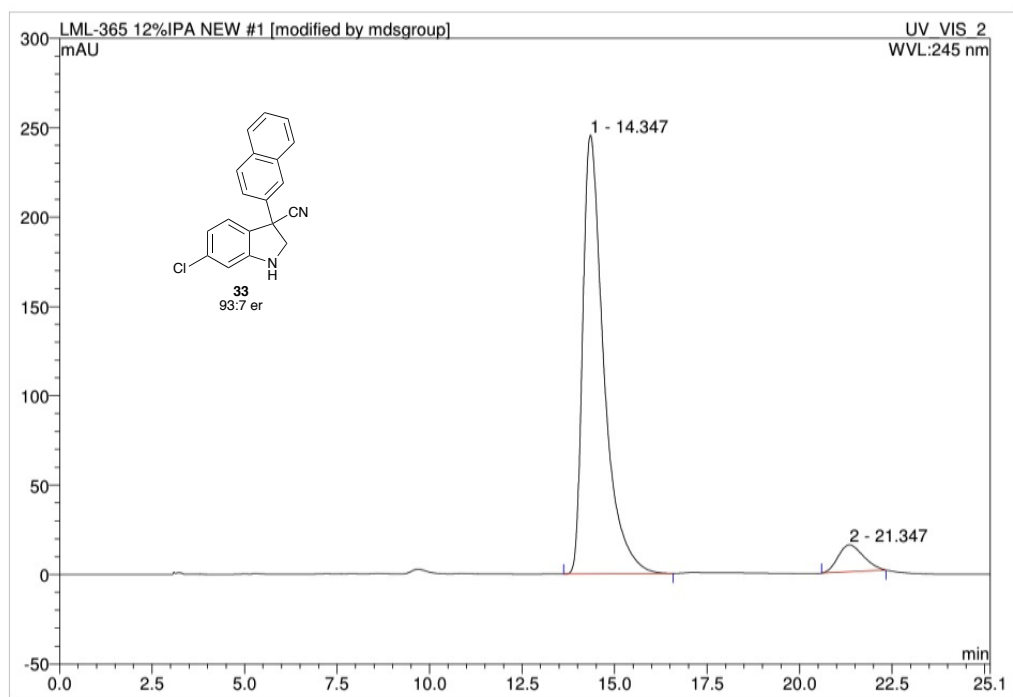
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15.08	n.a.	661.319	466.528	50.47	n.a.	BMB*
2	22.44	n.a.	449.253	457.760	49.53	n.a.	BMB*
Total:			1110.572	924.288	100.00	0.000	



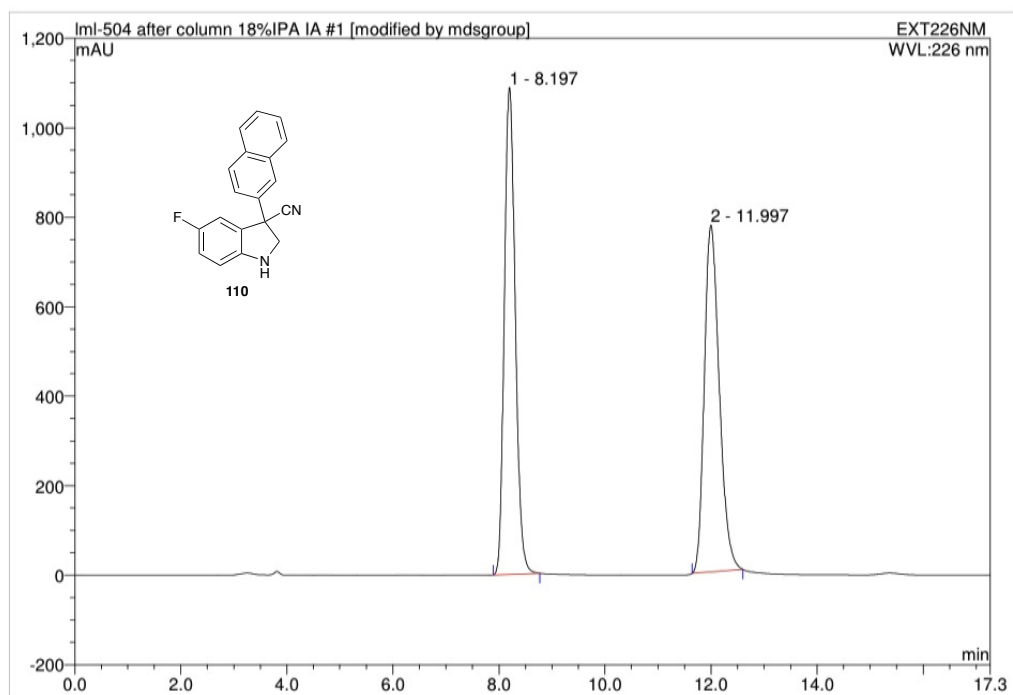
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15.16	n.a.	128.758	93.110	93.65	n.a.	BMB*
2	22.58	n.a.	6.982	6.317	6.35	n.a.	BMB*
Total:			135.740	99.428	100.00	0.000	



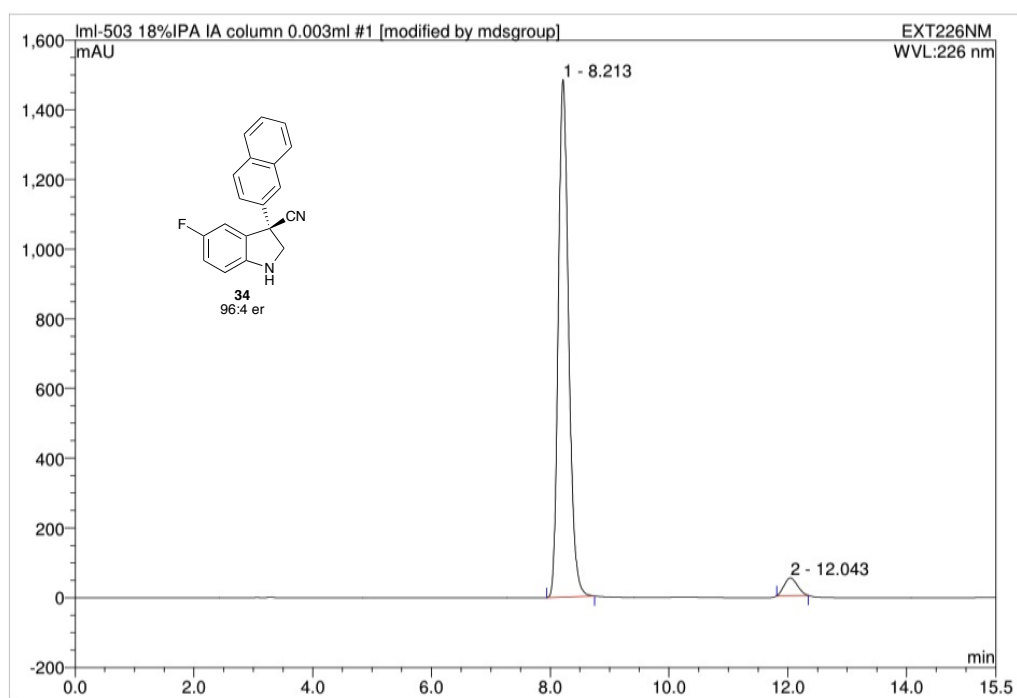
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.32	n.a.	1343.118	911.487	49.90	n.a.	BMB*
2	21.15	n.a.	939.381	915.142	50.10	n.a.	BMB*
Total:			2282.499	1826.630	100.00	0.000	



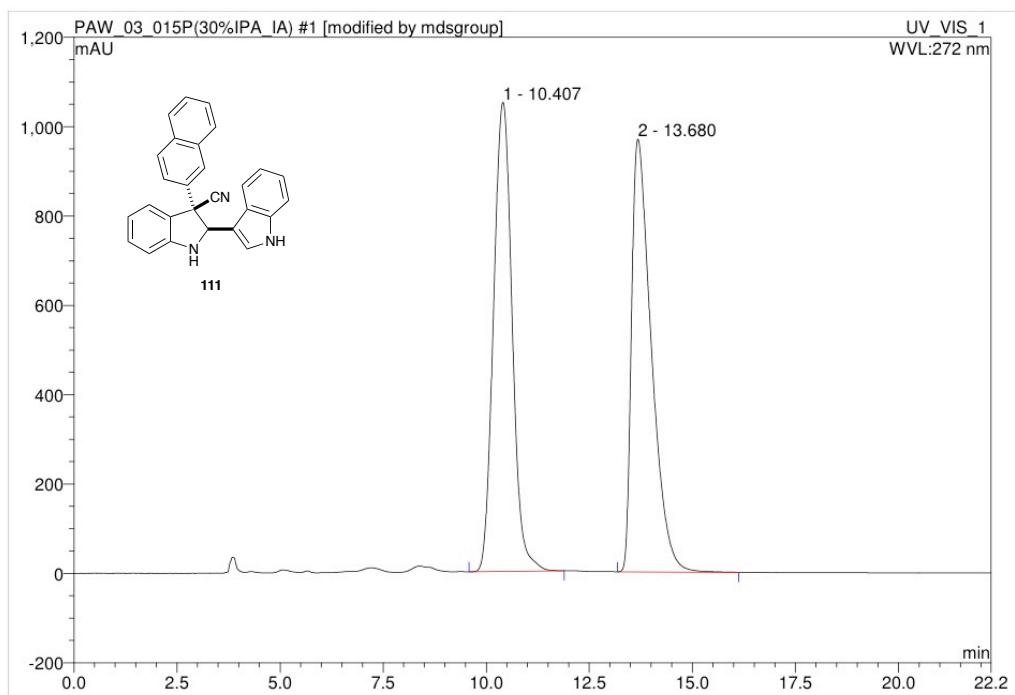
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.35	n.a.	245.431	161.217	93.11	n.a.	BMB
2	21.35	n.a.	14.971	11.932	6.89	n.a.	BMB*
Total:			260.402	173.149	100.00	0.000	



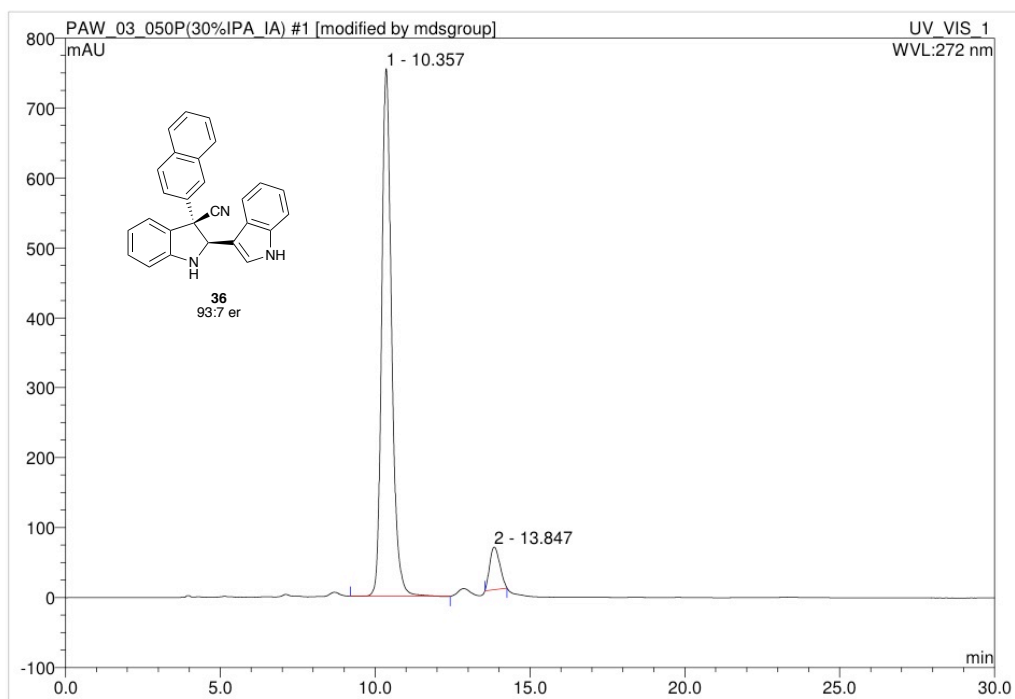
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.20	n.a.	1088.706	259.497	50.62	n.a.	BMB*
2	12.00	n.a.	775.197	253.176	49.38	n.a.	BMB*
Total:			1863.902	512.672	100.00	0.000	



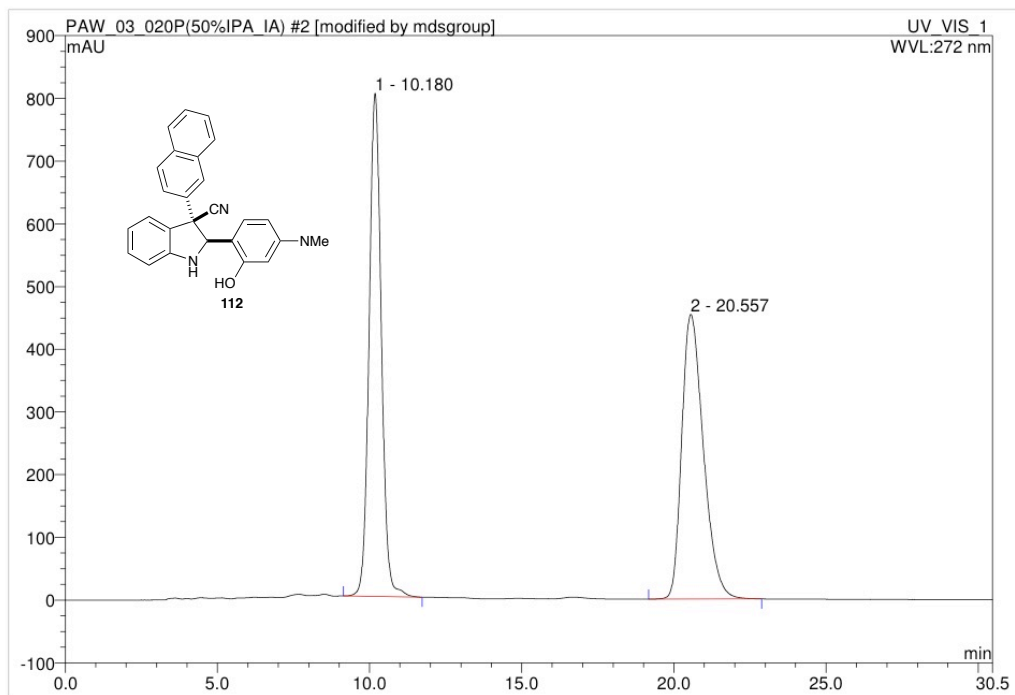
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.21	n.a.	1485.503	299.895	95.80	n.a.	BMB*
2	12.04	n.a.	50.448	13.154	4.20	n.a.	BMB*
Total:			1535.951	313.049	100.00	0.000	



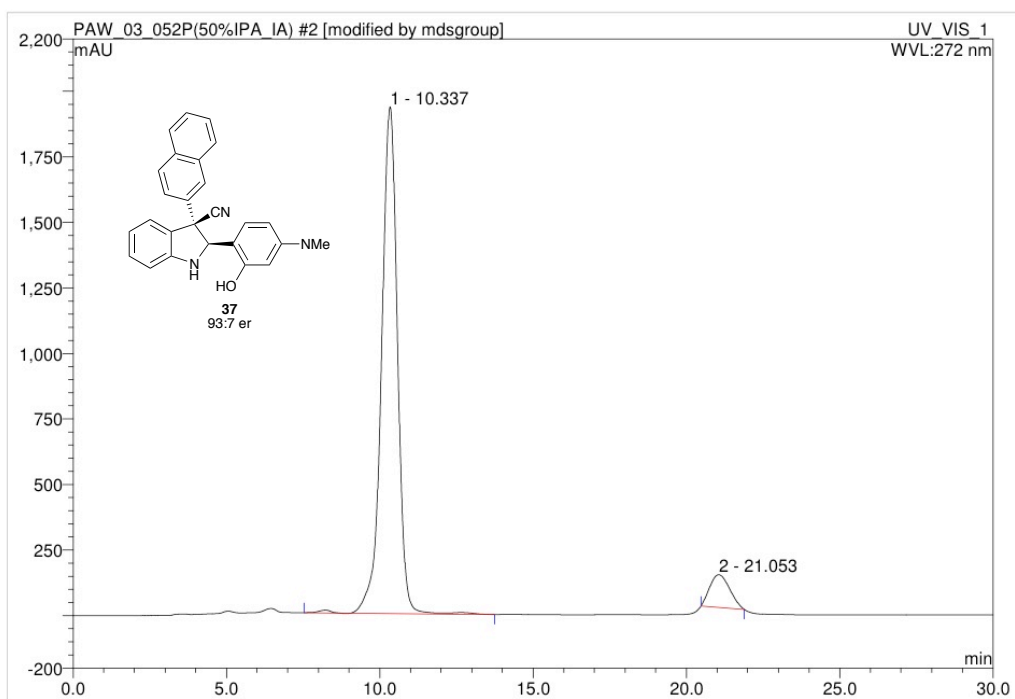
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.41	n.a.	1050.103	547.783	50.37	n.a.	BMB*
2	13.68	n.a.	968.632	539.691	49.63	n.a.	BMB
Total:			2018.734	1087.474	100.00	0.000	



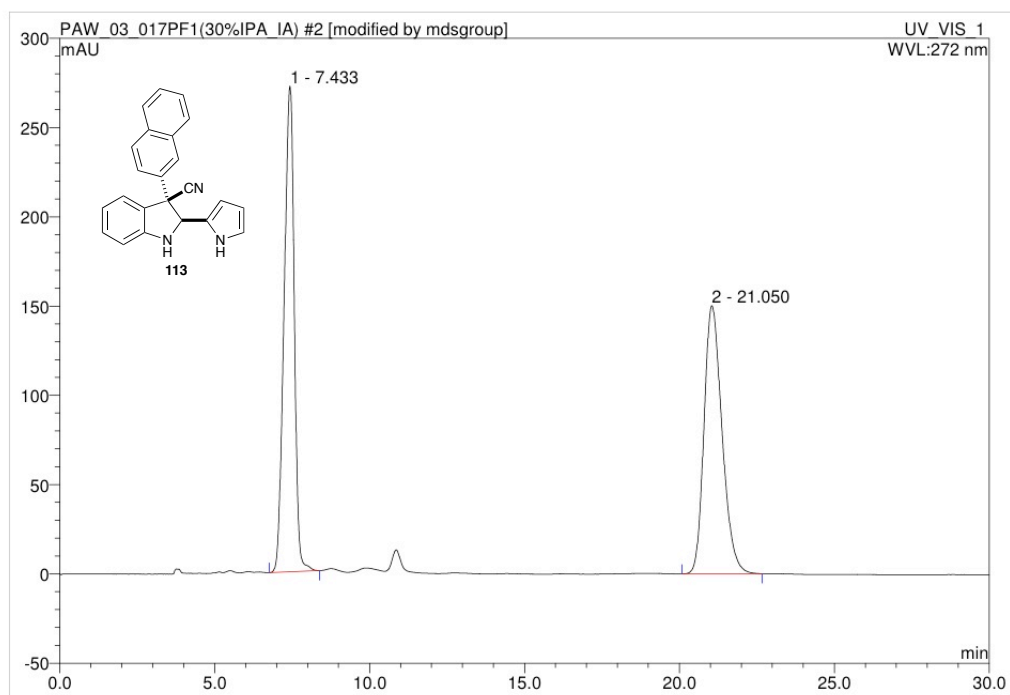
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.36	n.a.	754.518	280.622	92.50	n.a.	BMB*
2	13.85	n.a.	60.821	22.742	7.50	n.a.	BMB*
Total:			815.339	303.364	100.00	0.000	



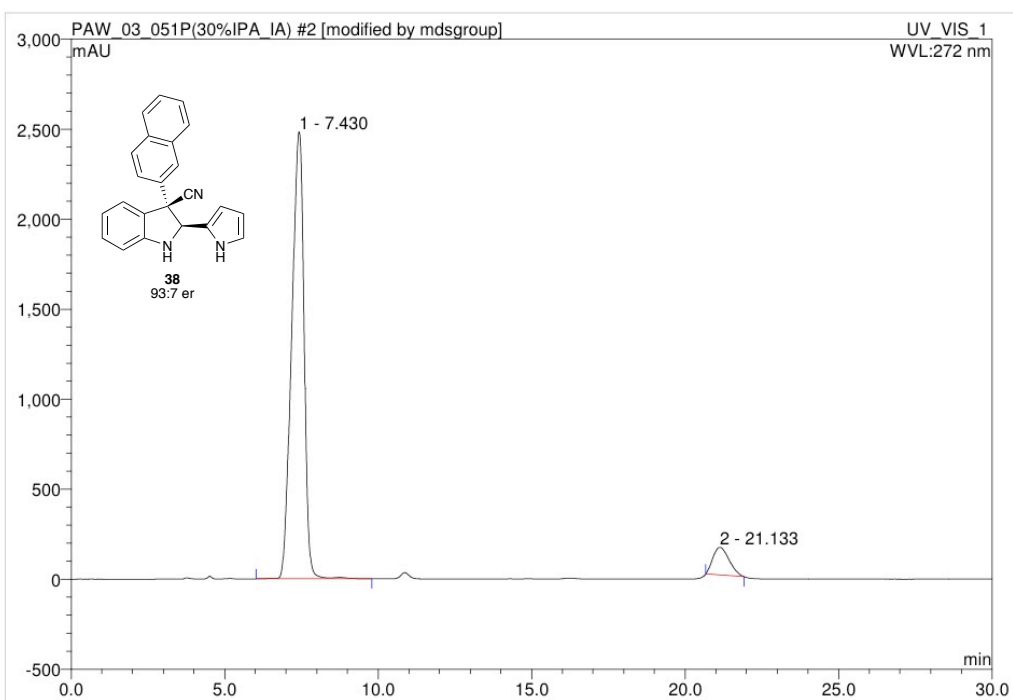
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.18	n.a.	802.352	373.586	49.91	n.a.	BMB
2	20.56	n.a.	454.361	374.997	50.09	n.a.	BMB
Total:			1256.713	748.583	100.00	0.000	



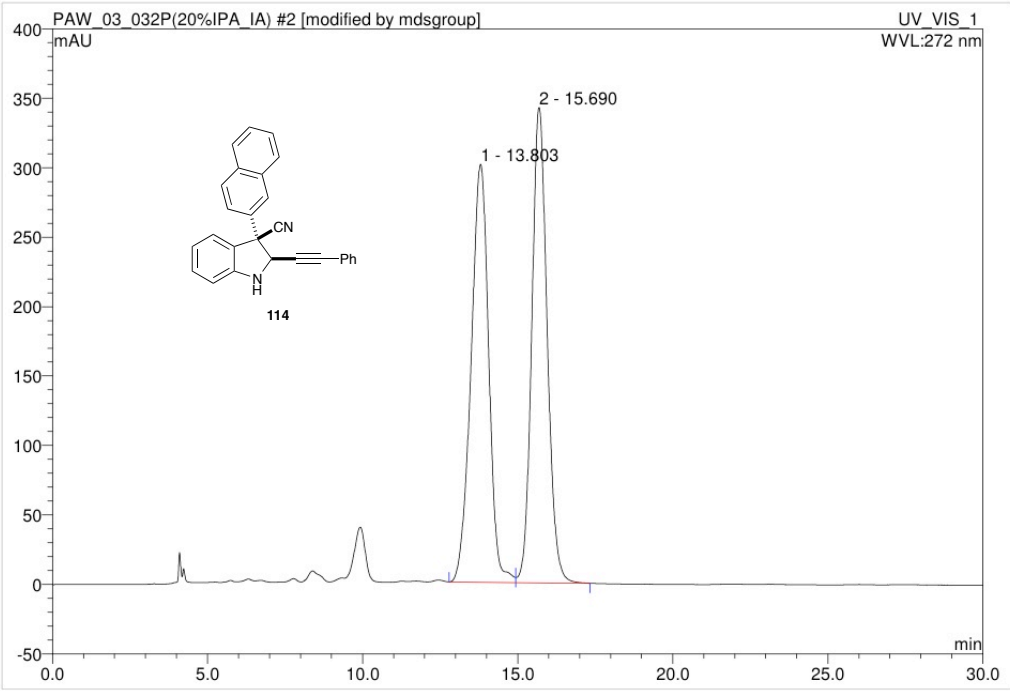
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.34	n.a.	1932.441	1167.859	92.56	n.a.	BMB*
2	21.05	n.a.	124.837	93.921	7.44	n.a.	BMB*
Total:			2057.278	1261.780	100.00	0.000	



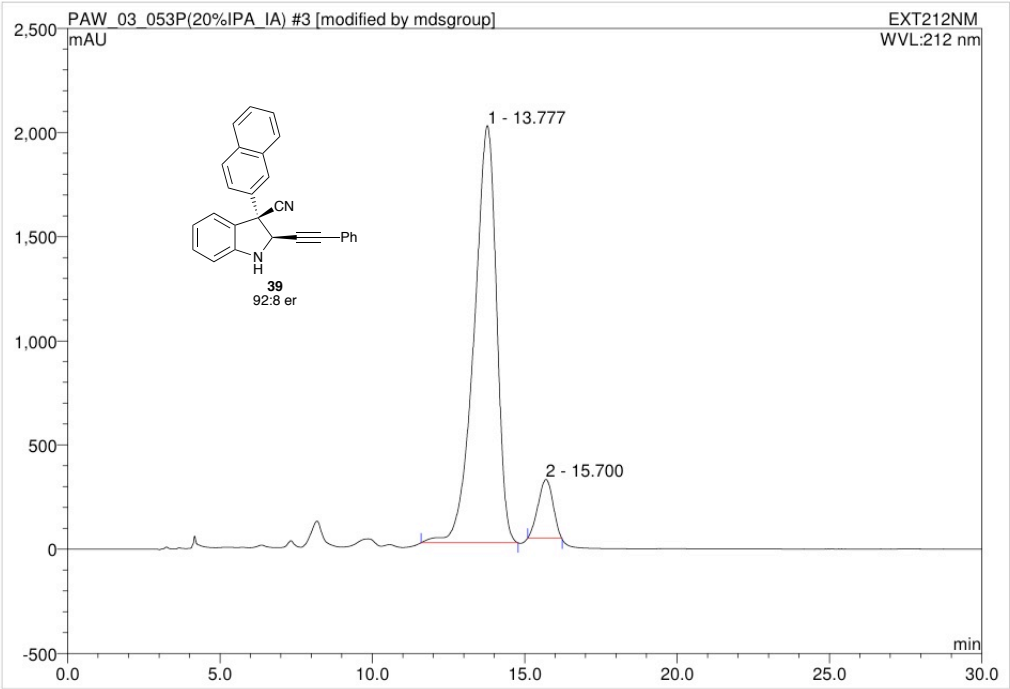
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.43	n.a.	271.952	103.314	50.43	n.a.	BMB*
2	21.05	n.a.	150.295	101.544	49.57	n.a.	BMB
Total:			422.247	204.858	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.43	n.a.	2483.460	1155.738	92.51	n.a.	BMB*
2	21.13	n.a.	153.096	93.513	7.49	n.a.	BMB*
Total:			2636.557	1249.252	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.80	n.a.	300.951	198.754	50.24	n.a.	BM *
2	15.69	n.a.	342.225	196.866	49.76	n.a.	MB*
Total:			643.176	395.620	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.78	n.a.	2002.147	1709.394	91.57	n.a.	BMB*
2	15.70	n.a.	280.784	157.404	8.43	n.a.	BM *
Total:			2282.931	1866.799	100.00	0.000	