

Base controlled diastereoselective synthesis of either *anti*- or *syn*- β -aminonitriles

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Supplementary Information

General experimental, experimental procedures and data

X-ray structure

Copies of ^1H and ^{13}C NMR spectra:

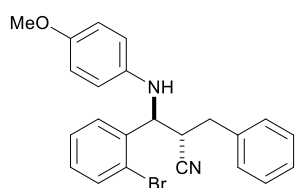
General experimental. Reactions were performed under N_2 atmosphere unless otherwise stated. Unless otherwise stated, all reagents and solvents were obtained from commercial sources and used without further purifications. All temperatures are in $^\circ\text{C}$. Proton and ^{13}C NMR were recorded using a Bruker AVANCE III 400 MHz, Bruker AVANCE 500 MHz or Bruker AVANCE III 600 MHz and referenced to residual CHCl_3 . Data was manipulated directly using Bruker XwinNMR (version 2.6) or TopSpin (version 2.1). All J values are in Hz and if not specifically stated, the NMR experiments were run at 20°C . Mass spectroscopy data was collected on a Thermo Finnigan Mat900xp (EI/CI) VG-70se (FAB) and Waters LCT Premier XE (ES) instruments. Infrared data was collected using a Perkin-Elmer 1600 FTIR machine as a thin film unless otherwise stated. Thin layer chromatography (TLC) was performed on using Polygram[®] SIL G/UV254 0.25 mm silica gel pre-coated plastic plates with fluorescent indicator. The plates were visualised by the use of a combination of ultraviolet light (254 and 366 nm) and/or aqueous potassium permanganate with heating. Flash column chromatography was performed either by automated (Flashmaster) techniques or manual chromatography on pre-packed cartridges (SPE) or manually-packed flash columns using Apollo Scientific ZEOprep silica gel. Melting points were recorded on Stuart Automatic Melting Point, SMP40.

General Procedure for the Synthesis of β -Amino nitrile 3 (Table 2)

To nitrile **1** (0.5 mmol) in dry THF (5 mL) stirred under nitrogen at -78 °C was added the appropriate base nBuLi (1.6 M in hexanes) or LHMDS (1.0 M in hexanes) (0.55 mmol) and stirred for 10 min. Then a solution of imine **2** (0.55 mmol) in THF (1 mL) was added and stirred for 1 h at -78 °C and then quenched with saturated aq NaHCO₃ (10 mL). The layers were separated, the aqueous phase was extracted with Et₂O (2 x 20 mL), the combined organics were washed with brine (10 mL), dried (MgSO₄), and solvent was removed *in vacuo* to provide crude β-amino nitrile. The diastereoselectivities were calculated by comparison of the ¹H NMR signals for the CH₂CHCN protons (δ 2.5-3.5 ppm) of the crude isolates. The crude isolate was then purified by flash column chromatography to yield the diastereomerically β-amino nitrile (except for Entry 19 which was isolated as a 40:60 anti:syn ratio, see Table 2).

Representative procedure for the Synthesis of β-Amino nitrile **3** (Table 2)

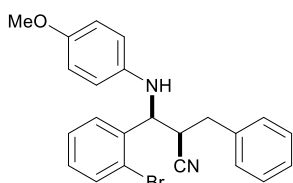
(2*S**, 3*S**)-2-benzyl-3-(2-bromophenyl)-3-((4-methoxyphenyl)amino)propanenitrile (Entry 1)



To 3-phenylpropanenitrile **1** (R¹=PhCH₂)(200 mg, 1.52 mmol) in dry THF (10 mL) stirred under nitrogen at -78 °C was added nBuLi (1.05 mL of a 1.6 M solution in hexanes, 1.68 mmol, 1.1 equiv) and stirred for 10 min. Then a solution of imine **2** (R²=2-Br-C₆H₅)(487 mg, 1.68 mmol, 1.1 equiv) in THF (2 mL) was added and stirred for 1 h at -78 °C and then quenched with saturated aq NaHCO₃ (20 mL). The layers were separated, the aqueous phase was extracted with Et₂O (2 x 30 mL), the combined organics were washed with brine (20 mL), dried (MgSO₄), and solvent was removed *in vacuo* to provide crude β-amino nitrile which was purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 1 (397 mg, 62%) as a white solid, mp 107-109 °C; ¹H NMR (400 MHz; CDCl₃) 2.84 (1H, dd, *J*=13.6, 10.8, CH_{2a}), 3.16 (1H, dd, *J*=13.6, 4.2, CH_{2b}), 3.55 (1H, ddd, *J*=10.8, 6.0, 4.3, CHCN), 3.76 (3H, s, OCH₃), 4.23 (1H, br. s, CHNH), 5.20 (1H, d, *J*=6.0, CHNH), 6.53-6.68 (2H, m, ArH), 6.71-6.86 (2H, m, ArH), 7.21-7.30 (3H, m, ArH), 7.30-7.43 (4H, m, ArH), 7.67 (1H, dd, *J*=7.9, 1.4, ArH), 7.51 (1H, dd, *J*=8.0, 1.0, ArH); ¹³C NMR (101 MHz; CDCl₃) 34.5 (CH₂), 40.4 (CHCN), 55.6 (OCH₃), 57.9 (CHNH), 114.9 (2C,

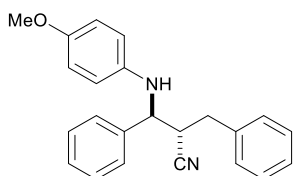
Ar), 115.7 (2C, Ar), 119.4 (C=N), 124.1 (Ar), 127.4 (Ar), 128.2 (Ar), 128.8 (Ar), 128.8 (2C, Ar), 129.0 (2C, Ar), 129.9 (Ar), 133.5 (Ar), 136.5 (q), 137.5 (q), 139.4 (q), 153.2 (q); IR (neat) 3366, 3030, 2932, 2243, 1511; Mass Spec (ES, M + H) Theoretical: 421.0910, Measured: 421.0905.

(2R*, 3S*)-2-benzyl-3-(2-bromophenyl)-3-((4-methoxyphenyl)amino)propanenitrile (Entry 2)



Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 2 (160 mg, 76%) as a white solid, mp 154-156 °C; ¹H NMR (400 MHz; CDCl₃) 3.16-3.32 (3H, m, CH₂ and CHCN), 3.69 (3H, s, OCH₃), 4.33 (1H, br. s, CHNH), 4.88 (1H, br. s, CHNH), 6.39-6.50 (2H, m, ArH), 6.64-6.78 (2H, m, ArH), 7.05-7.17 (1H, m, ArH), 7.22-7.39 (6H, m, ArH), 7.45 (1H, dd, *J*=7.9, 1.6, ArH), 7.51 (1H, dd, *J*=8.0, 1.0, ArH); ¹³C NMR (101 MHz; CDCl₃) 37.1 (CH₂), 40.8 (CHCN), 55.6 (OCH₃), 56.2 (CHNH), 115.0 (4C, Ar), 119.0 (C=N), 123.0 (Ar), 127.5 (Ar), 127.8 (Ar), 128.2 (Ar), 128.8 (2C, Ar), 129.3 (2C, Ar), 129.7 (Ar), 133.1 (Ar), 136.3 (q), 138.5 (q), 139.4 (q), 152.8 (q); IR (neat) 3355, 3030, 2932, 2242, 1511; Mass Spec (ES, M + H) Theoretical: 421.0910, Measured: 421.0909.

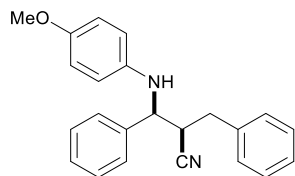
(2S*, 3R*)-2-benzyl-3-((4-methoxyphenyl)amino)-3-phenylpropanenitrile (Entry 3)



Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 3 (75 mg, 44%) as a white solid, mp 80-82 °C; ¹H NMR (400 MHz; CDCl₃) 2.87 (1H, dd, *J*=13.8, 9.3, CH_{2a}), 2.96 (1H, dd, *J*=13.8, 5.8, CH_{2b}), 3.50 (1H, app. dt, *J*=9.2, 5.7, CHCN), 3.76 (3H, s, OCH₃), 4.54 (1H, d, *J*=5.3, CHNH), 6.60 (2H, d, *J*=8.5, ArH), 6.77 (2H, d, *J*=9.0, ArH), 7.25-7.52 (10H, m, ArH); ¹³C NMR (101 MHz; CDCl₃) 35.5 (CH₂), 40.7 (CHCN), 55.7 (OCH₃), 59.5 (CHNH), 114.9 (2C, Ar), 116.0 (2C, Ar), 119.7 (C=N), 127.4 (Ar), 127.5 (2C, Ar), 128.6 (Ar), 128.9 (2C, Ar), 128.9 (2C, Ar),

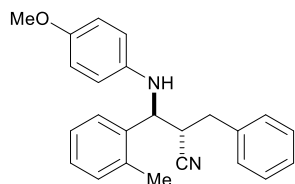
129.0 (2C, Ar), 136.5 (q), 138.1 (q), 138.1 (q), 153.2 (q); IR (neat) 3366, 3030, 2933, 2241, 1511; Mass Spec (ES, M + H) Theoretical: 343.1810, Measured: 343.1796.

(2R*, 3R*)-2-benzyl-3-((4-methoxyphenyl)amino)-3-phenylpropanenitrile (Entry 4)



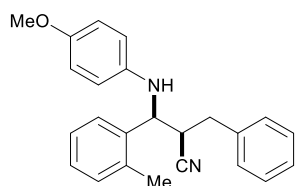
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 4 (116 mg, 68%) as a white solid, mp 50-52 °C; ¹H NMR (400 MHz; CDCl₃) 3.07-3.29 (3H, m, CH₂ and CHCN), 3.74 (3H, s, OCH₃), 4.21 (1H, br, s, CHNH), 4.53 (1H, d, J=3.0 CHNH), 6.57 (2H, d, J=8.8, ArH), 6.68-6.82 (2H, m, ArH), 7.21-7.43 (10H, m, ArH); ¹³C NMR (101 MHz; CDCl₃) 36.4 (CH₂), 42.9 (CHCN), 55.6 (OCH₃), 58.0 (CHNH), 114.9 (2C, Ar), 115.6 (2C, Ar), 119.5 (C=N), 126.4 (2C, Ar), 127.4 (Ar), 128.1 (Ar), 128.9 (2C, Ar), 129.0 (2C, Ar), 129.0 (2C, Ar), 136.7 (q), 139.9 (q), 140.0 (q), 152.9 (q); IR (neat) 3385, 3030, 2933, 2241, 1511; Mass Spec (ES, M + H) Theoretical: 343.1810, Measured: 343.1803.

(2S*, 3R*)-2-benzyl-3-(4-methoxyphenylamino)-3-o-tolylpropanenitrile (Entry 5)



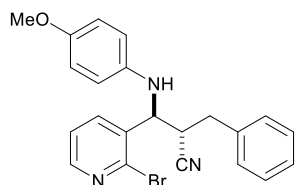
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 5 (119 mg, 67%) as a white solid, mp 109-111 °C; ¹H NMR (400 MHz; CDCl₃) 2.37 (3H, s, CH₃), 3.01 (1H, dd, J=13.7, 9.4, CH_{2a}), 3.10 (1H, dd, J=13.7, 5.1, CH_{2b}), 3.43 (1H, app. ddd, J=9.4, 6.5, 5.6, CHCN), 3.79 (3H, s, OCH₃), 3.96 (1H, br. s, CHNH), 4.86 (1H, br. d, J= 4.0, CHNH), 6.60 (2H, d, J=7.5, ArH), 6.77-6.85 (2H, m, ArH), 7.24-7.43 (8H, m, ArH), 7.63-7.74 (1H, m, ArH); ¹³C NMR (101 MHz; CDCl₃) 19.9 (CH₃), 35.3 (CH₂), 40.4 (CHCN), 55.1 (CHNH), 56.0 (OCH₃), 115.3 (2C, Ar), 115.8 (2C, Ar), 120.3 (C=N), 125.9 (Ar), 127.2 (Ar), 127.7 (Ar), 128.4 (Ar), 129.1 (2C, Ar), 129.2 (2C, Ar), 131.4 (Ar), 136.4 (q), 136.9 (q), 137.4 (q), 140.4 (q), 153.3 (q); IR (neat) 3369, 3030, 2931, 2241, 1511; Mass Spec (ES, M + H) Theoretical: 357.1967, Measured: 357.1958.

(2R*, 3R*)-2-benzyl-3-(4-methoxyphenylamino)-3-o-tolylpropanenitrile (Entry 6)



Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 6 (143 mg, 80%) as a white solid, mp 125-127 °C; ¹H NMR (400 MHz; CDCl₃) 2.03 (3H, s, CH₃), 3.03 (1H, app. td, *J*=7.7, 3.3, CHCN), 3.18-3.29 (2H, m, CH₂), 3.73 (3H, s, OCH₃), 4.28 (1H, br. s, CHNH), 4.67 (1H, d, *J*= 3.0, CHNH), 6.49 (2H, d, *J*=9.0, ArH), 6.69-6.79 (2H, m, ArH), 7.10-7.29 (5H, m, ArH), 7.31-7.40 (3H, m, ArH), 7.41-7.50 (1H, m, ArH); ¹³C NMR (101 MHz; CDCl₃) 18.5 (CH₃), 36.7 (CH₂), 41.6 (CHCN), 52.8 (CHNH), 55.6 (OCH₃), 114.9 (2C, Ar), 115.2 (2C, Ar), 119.5 (C=N), 125.3 (Ar), 126.8 (Ar), 127.5 (Ar), 127.8 (Ar), 128.9 (2C, Ar), 129.2 (2C, Ar), 130.8 (Ar), 134.5 (q), 136.7 (q), 137.8 (q), 140.0 (q), 152.7 (q); IR (neat) 3388, 3029, 2933, 2240, 1510; Mass Spec (ES, M + H) Theoretical: 357.1967, Measured: 357.1951.

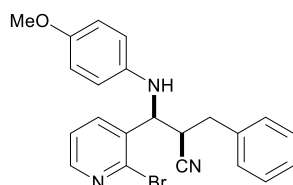
(2S*, 3S*)-2-benzyl-3-(2-bromopyridin-3-yl)-3-(4-methoxyphenylamino)propanenitrile (Entry 7)



Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 7 (137 mg, 65%) as an off white solid, mp 164-166 °C; ¹H NMR (400 MHz; CDCl₃) 3.21-3.39 (3H, m, CH₂ and CHCN), 3.71 (3H, s, OCH₃), 4.28 (1H, br. s, CHNH), 4.81 (1H, br. d, *J*= 1.5, CHNH), 6.44 (2H, d, *J*=8.8, ArH), 6.70-6.78 (2H, m, ArH), 7.23-7.39 (6H, m, ArH), 7.77 (1H, dd, *J*=7.8, 1.8, ArH), 8.29 (1H, dd, *J*=4.5, 1.8, ArH); ¹³C NMR (101 MHz; CDCl₃) 36.9 (CH₂), 40.2 (CHCN), 55.4 (CHNH), 55.6 (OCH₃), 114.9 (2C, Ar), 115.1 (2C, Ar), 118.6 (C=N), 123.5 (Ar), 127.7 (Ar), 128.9 (2C, Ar), 129.3 (2C, Ar), 135.8 (q), 136.1 (q), 136.6 (Ar), 138.7 (q), 142.7 (q), 149.7 (Ar), 153.1 (q); IR (neat) 3381, 3029, 2970, 2241, 1512; Mass Spec (ES, M + H) Theoretical: 422.0868, Measured: 422.0858.

(2R*, 3S*)-2-benzyl-3-(2-bromopyridin-3-yl)-3-(4-methoxyphenylamino)propanenitrile

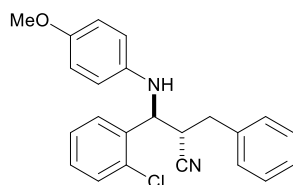
(Entry 8,9)



Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 8 (84 mg, 40%) or Entry 9 (131 mg, 62%) as an off white solid, mp 165-167 °C; ¹H NMR (400 MHz; CDCl₃) 2.83 (1H, dd, *J*=13.6, 11.0, CH_{2a}), 3.19 (1H, dd, *J*=13.6, 4.3, CH_{2b}), 3.53-3.68 (1H, m, CHCN), 3.77 (3H, s, OCH₃), 4.25 (1H, br. s, CHNH), 5.16 (1H, br. s, CHNH), 6.60 (2H, d, *J*=7.0, ArH), 6.79 (2H, d, *J*=9.0 ArH), 7.17-7.46 (6H, m, ArH), 7.87-8.05 (1H, m, ArH), 8.41 (1H, dd, *J*=4.6, 1.9, ArH); ¹³C NMR (101 MHz; CDCl₃) 35.0 (CH₂), 40.7 (CHCN), 56.0 (OCH₃), 57.9 (CHNH), 115.4 (2C, Ar), 116.2 (2C, Ar), 119.4 (C=N), 123.9 (Ar), 128.0 (2C, Ar), 129.4 (3C, Ar), 135.5 (q), 136.4 (Ar), 138.1 (q), 139.2 (q), 144.1 (q), 150.4 (Ar), 153.9 (q); IR (neat) 3379, 3032, 2930, 2241, 1511; Mass Spec (ES, M + H) Theoretical: 422.0868, Measured: 422.0862.

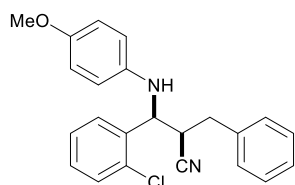
(2S*, 3S*)-2-benzyl-3-(2-chlorophenyl)-3-(4-methoxyphenylamino)propanenitrile (Entry

10)



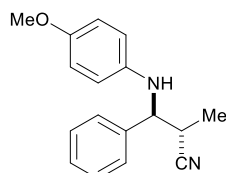
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 10 (109 mg, 58%) as a white solid, mp 133-134 °C; ¹H NMR (400 MHz; CDCl₃) 3.16 (3H, m, CH₂ and CHCN), 3.69 (3H, s, OCH₃), 4.32 (1H, br. s, CHNH), 4.92 (1H, br. d, *J*= 1.8, CHNH), 6.39-6.53 (2H, d, *J*=7.5, ArH), 6.66-6.77 (2H, m, ArH), 7.15-7.39 (8H, m, ArH), 7.46 (1H, dd, *J*=7.3, 2.0, ArH); ¹³C NMR (101 MHz; CDCl₃) 37.4 (CH₂), 41.1 (CHCN), 54.3 (CHNH), 56.1 (OCH₃), 115.4 (2C, Ar), 115.5 (2C, Ar), 119.6 (C=N), 127.9 (Ar), 128.0 (2C, Ar), 129.3 (2C, Ar), 129.7 (2C, Ar), 129.8 (Ar), 130.3 (Ar), 131.4 (q), 136.8 (q), 137.5 (q), 139.9 (q), 153.3 (q); IR (neat) 3382, 3030, 2931, 2242, 1511; Mass Spec (EI) Theoretical: 376.1337, Measured: 376.1334.

(2R*, 3S*)-2-benzyl-3-(2-chlorophenyl)-3-(4-methoxyphenylamino)propanenitrile (Entry 11)



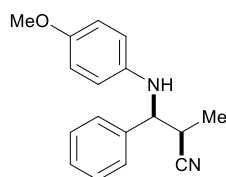
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 11 (132 mg, 70%) as a white solid, mp 165-167 °C; ¹H NMR (400 MHz; CDCl₃) 2.83 (1H, dd, *J*=13.6, 10.8, CH_{2a}), 3.19 (1H, dd, *J*=13.6, 4.1, CH_{2b}), 3.55 (1H, ddd, *J*= 10.7, 6.0, 4.1, CHCN), 3.75 (3H, s, OCH₃), 4.24 (1H, br. s, CHNH), 5.21 (1H, d, *J*= 5.9, CHNH), 6.61 (2H, d, *J*=8.8, ArH), 6.72-6.85 (2H, m, ArH), 7.23-7.42 (7H, m, ArH), 7.47 (1H, dd, *J*=7.5, 1.8, ArH), 7.63 (1H, dd, *J*=7.4, 1.9, ArH); ¹³C NMR (101 MHz; CDCl₃) 34.6 (CH₂), 40.4 (CHCN), 55.6 (OCH₃), 55.7 (CHNH), 114.9 (2C, Ar), 115.6 (2C, Ar), 119.4 (C=N), 127.4 (Ar), 127.6 (Ar), 128.6 (Ar), 128.8 (2C, Ar), 129.0 (2C, Ar), 129.6 (Ar), 130.1 (Ar), 133.6 (q), 135.9 (q), 136.5 (q), 139.4 (q), 153.1 (q); IR (neat) 3379, 3030, 2930, 2241, 1511; Mass Spec (EI) Theoretical: 376.1337, Measured: 376.1340.

(2S*, 3R*)-3-((4-methoxyphenyl)amino)-2-methyl-3-phenylpropanenitrile (Entry 12)



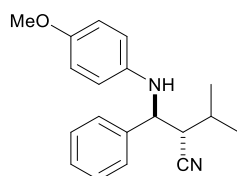
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 12 (67 mg, 50%) as a clear oil; ¹H NMR (400 MHz; CDCl₃) 1.27 (3H, d, *J*=7.0, CH₃), 3.17-3.33 (1H, m, CHCN), 3.72 (3H, s, OCH₃), 4.02 (1H, br. s, CHNH), 4.42 (1H, d, *J*=5.3, CHNH), 6.50-6.65 (2H, m, ArH), 6.67-6.82 (2H, m, ArH), 7.30-7.48 (5H, m, ArH); ¹³C NMR (101 MHz; CDCl₃) 14.9 (CH₃), 32.6 (CHCN), 55.7 (OCH₃), 60.7 (CHNH), 114.9 (2C, Ar), 115.8 (2C, Ar), 120.7 (C=N), 127.3 (2C, Ar), 128.4 (Ar), 128.9 (2C, Ar), 138.2 (q), 139.9 (q), 153.0 (q); IR (neat) 3373, 2932, 2242, 1511; Mass Spec (ES, M + H) Theoretical: 267.1492, Measured: 267.1492.

(2R*, 3R*)-3-((4-methoxyphenyl)amino)-2-methyl-3-phenylpropanenitrile (Entry 13)



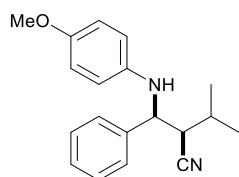
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 13 (100 mg, 75%) as a clear oil; ^1H NMR (400 MHz; CDCl_3) 1.43 (3H, d, $J=7.3$, CH_3), 2.97-3.16 (1H, m, CHCN), 3.73 (3H, s, OCH_3), 4.45 (1H, d, $J=5.5$, CHNH), 6.54-6.65 (2H, m, ArH), 6.70-6.79 (2H, m, ArH), 7.28-7.46 (5H, m, ArH); ^{13}C NMR (101 MHz; CDCl_3) 16.4 (CH_3), 34.5 (CHCN), 56.1 (OCH_3), 61.5 (CHNH), 115.3 (2C, Ar), 116.1 (2C, Ar), 121.3 ($\text{C}=\text{N}$), 127.1 (2C, Ar), 128.7 (Ar), 129.4 (2C, Ar), 140.2 (q), 140.7 (q), 153.3 (q); IR (neat) 3375, 2935, 2242, 1512; Mass Spec (ES, $\text{M} + \text{H}$) Theoretical: 267.1492, Measured: 267.1491.

(2S*, 3R*)-2-(((4-methoxyphenyl)amino)(phenyl)methyl)-3-methylbutanenitrile (Entry 14)



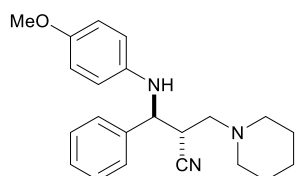
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 14 (74 mg, 50%) as a yellow solid, mp 89-91 °C; ^1H NMR (400 MHz; CDCl_3) 1.09 (3H, d, $J=6.8$, CH_3), 1.17 (3H, d, $J=7.3$, CH_3), 1.96 (1H, m, CH), 2.63-2.76 (1H, m, CHCN), 3.68 (3H, s, OCH_3), 4.07 (1H, d, $J=6.6$, CHNH), 4.54 (1H, app. t, $J=5.9$, CHNH), 6.47-6.60 (2H, m, ArH), 6.64-6.73 (2H, m, ArH), 7.23-7.40 (5H, m, ArH); ^{13}C NMR (101 MHz; CDCl_3) 19.9 (CH_3), 21.3 (CH_3), 28.3 (CCH_3), 48.8 (CHCN), 55.7 (OCH_3), 57.7 (CHNH), 114.8 (2C, Ar), 115.5 (2C, Ar), 119.2 ($\text{C}=\text{N}$), 126.5 (2C, Ar), 128.1 (Ar), 129.0 (2C, Ar), 140.3 (q), 140.6 (q), 152.8 (q); IR (neat) 3377, 2964, 2238, 1510; Mass Spec (ES, $\text{M} + \text{H}$) Theoretical: 295.1805, Measured: 295.1803.

(2R*, 3R*)-2-(((4-methoxyphenyl)amino)(phenyl)methyl)-3-methylbutanenitrile (Entry 15)



Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 15 (69 mg, 47%) as a colourless oil; ^1H NMR (400 MHz; CDCl_3) 1.08 (3H, d, $J=6.8$, CH_3), 1.14 (3H, d, $J=6.8$, CH_3), 1.92-2.00 (1H, m, CH), 2.78-3.01 (1H, m, CHCN), 3.70 (3H, br. s, OCH_3), 4.52 (1H, br. s, $J=5.9$, CHNH), 6.50-6.67 (2H, m, ArH), 6.67-6.77 (2H, m, ArH), 7.28-7.39 (3H, m, ArH), 7.40-7.47 (2H, m, ArH); ^{13}C NMR (101 MHz; CDCl_3) 19.5 (CH_3), 21.4 (CH_3), 27.3 (CCH_3), 47.0 (CHCN), 55.7 (OCH_3), 57.8 (CHNH), 114.9 (2C, Ar), 115.6 (2C, Ar), 119.1 ($\text{C}=\text{N}$), 127.2 (2C, Ar), 128.4 (Ar), 128.9 (2C, Ar), 139.3 (q), 140.0 (q), 152.9 (q); IR (neat) 3377, 2964, 2238, 1510; Mass Spec (ES, M + H) Theoretical: 295.1805, Measured: 295.1805.

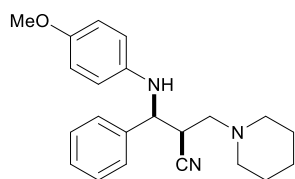
(2S*, 3R*)-3-(4-methoxyphenylamino)-3-phenyl-2-(piperidin-1-ylmethyl)propanenitrile (Entry 16)



Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 16 (94 mg, 54%) as a colourless oil; ^1H NMR (400 MHz; CDCl_3) 1.44-1.53 (2H, m, CH_2), 1.60-1.71 (4H, m, CH_2), 2.31-2.48 (2H, m, CH_2), 2.49-2.56 (2H, m, CH_2), 2.59 (1H, dd, $J=13.1$, 4.8, NCH_{2a}), 2.73 (1H, dd, $J=13.1$, 9.3, NCH_{2b}), 3.19-3.32 (1H, m, CHCN), 3.68 (3H, s, OCH_3), 4.84 (1H, dd, $J=9.0$, 3.0, CHNH), 5.39 (1H, d, $J=9.0$, CHNH), 6.47-6.57 (2H, m, ArH), 6.64-6.75 (2H, m, ArH), 7.23-7.43 (5H, m, ArH); ^{13}C NMR (101 MHz; CDCl_3) 24.1 (CH_2), 26.2 (2 CH_2), 37.1 (CHCN), 54.7 (2 CH_2), 55.7 (OCH_3), 57.8 (NCH_2), 58.0 (CHNH), 114.9 (2C, Ar), 115.0 (2C, Ar), 119.5 ($\text{C}=\text{N}$), 126.9 (2C, Ar), 128.0 (Ar), 128.8 (2C, Ar), 139.3 (q), 140.6 (q), 152.4 (q); IR (neat) 3366, 3030, 2934, 2241, 1510; Mass Spec (ES, M + H) Theoretical: 350.2232, Measured: 350.2216.

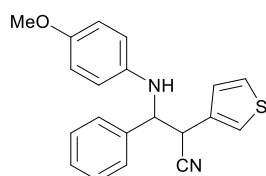
(2R*, 3R*)-3-(4-methoxyphenylamino)-3-phenyl-2-(piperidin-1-ylmethyl)propanenitrile

(Entry 17)



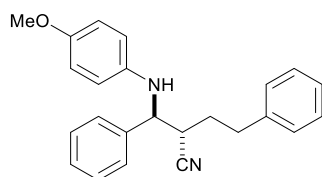
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 17 (103 mg, 59%) as a colourless oil; ^1H NMR (400 MHz; CDCl_3) 1.42-1.56 (2H, m, CH_2), 1.58-1.74 (4H, m, CH_2), 2.33-2.47 (2H, m, CH_2), 2.48-2.68 (4H, m, CH_2 and NCH_2), 3.14-3.29 (1H, m, CHCN), 3.68 (3H, s, OCH_3), 4.63 (1H, d, $J=6.5$, CHNH), 5.58 (1H, br. s, CHNH), 6.43-6.56 (2H, m, ArH), 6.62-6.74 (2H, m, ArH), 7.24-7.41 (3H, m, ArH), 7.41-7.50 (2H, m, ArH); ^{13}C NMR (101 MHz; CDCl_3) 24.0 (CH_2), 26.1 (2CH_2), 36.3 (CHCN), 54.7 (2CH_2), 55.7 (OCH_3), 58.5 (NCH_2), 59.7 (CHNH), 114.9 (2C, Ar), 115.0 (2C, Ar), 119.6 ($\text{C}=\text{N}$), 127.3 (2C, Ar), 128.3 (Ar), 128.3 (2C, Ar), 139.3 (q), 140.7 (q), 152.5 (q); IR (neat) 3273, 3030, 2934, 2240, 1511; Mass Spec (ES, M + H) Theoretical: 350.2232, Measured: 350.2221.

3-(4-methoxyphenylamino)-3-phenyl-2-(thiophen-3-yl)propanenitrile (Entry 19)



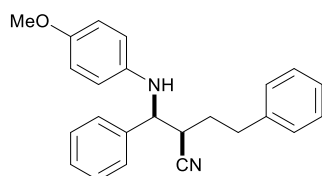
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 19 (105 mg, 63%) as a colourless oil; ^1H NMR (400 MHz; CDCl_3) 3.69 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 4.05 (2H, br. s, NH), 4.35 (1H, d, $J=4.5$, CHCN), 4.49 (1H, d, $J=5.3$, CHCN), 4.72 (1H, d, $J=5.3$, CHNH), 4.75 (1H, d, $J=4.5$, CHNH), 6.47-6.58 (4H, m, ArH), 6.66-6.75 (4H, m, ArH), 6.77 (1H, dd, $J=5.1$, 1.0, ArH), 6.92 (1H, dd, $J=4.9$, 1.1, ArH), 7.04-7.07 (1H, m, ArH), 7.17-7.36 (13H, m, ArH); ^{13}C NMR (101 MHz; CDCl_3) 40.5 (CHCN), 40.8 (CHCN), 55.7 (OCH_3 , 2C), 61.6 (CHNH), 61.8 (CHNH), 114.9 (2C, Ar), 114.9 (2C, Ar), 115.8 (2C, Ar), 116.0 (2C, Ar), 118.6 ($\text{C}=\text{N}$), 118.7 ($\text{C}=\text{N}$), 124.4 (Ar), 124.4 (Ar), 126.9 (2C, Ar), 126.9 (2C, Ar), 127.0 (2C, Ar), 127.0 (2C, Ar), 127.3 (2C, Ar), 128.4 (Ar), 128.6 (2C, Ar), 128.8 (Ar), 132.1 (q), 132.5 (q), 137.9 (q), 138.8 (q), 139.7 (q), 139.9 (q), 153.0 (q), 153.2 (q); IR (neat) 3377, 2929, 2238, 1510; Mass Spec (ES, M + H) Theoretical: 335.1218, Measured: 335.1207.

(2S*, 3R*)-2-((4-methoxyphenylamino)(phenyl)methyl)-4-phenylbutanenitrile (Entry 20)



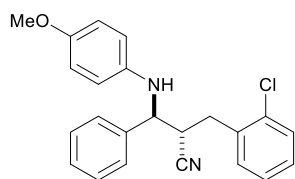
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 20 (100 mg, 56%) as a colourless oil; ^1H NMR (400 MHz; CDCl_3) 1.75-1.95 (2H, m, CH_2CN), 2.69 (1H, app. dt, $J=14.1, 8.3$, PhCH_{2a}), 2.89 (1H, ddd, $J=14.1, 8.7, 5.3$, PhCH_{2b}), 3.12 (1H, app. dt, $J=10.4, 5.1$, CHCN), 3.69 (3H, s, OCH_3), 4.41 (1H, d, $J=5.5$, CHNH), 6.46-6.54 (2H, m, ArH), 6.65-6.71 (2H, m, ArH), 7.12-7.17 (2H, m, ArH), 7.21-7.25 (1H, m, ArH), 7.27-7.40 (7H, m, ArH); ^{13}C NMR (101 MHz; CDCl_3) 31.0 (CH_2), 33.2 (PhCH_2), 38.0 (CHCN), 55.6 (OCH_3), 59.9 (CHNH), 114.9 (2C, Ar), 115.7 (2C, Ar), 119.8 ($\text{C}=\text{N}$), 126.6 (Ar), 127.3 (2C, Ar), 128.4 (2C, Ar), 128.5 (Ar), 128.7 (2C, Ar), 128.9 (2C, Ar), 138.3 (q), 139.7 (q), 139.7 (q), 153.0 (q); IR (neat) 3382, 3030, 2931, 2240, 1512; Mass Spec (EI) Theoretical: 356.1883, Measured: 356.1887.

(2R*, 3R*)-2-((4-methoxyphenylamino)(phenyl)methyl)-4-phenylbutanenitrile (Entry 21)



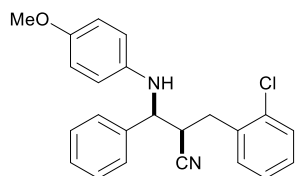
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 21 (146 mg, 82%) as a colourless oil; ^1H NMR (400 MHz; CDCl_3) 1.94-2.11 (1H, m, CH_2CN), 2.13-2.27 (1H, m, CH_2CN), 2.78 (1H, app. dt, $J=14.1, 8.0$, PhCH_{2a}), 2.86-3.05 (2H, m, PhCH_{2b} and CHCN), 3.72 (3H, s, OCH_3), 4.51 (1H, d, $J=4.5$, CHNH), 6.54-6.61 (2H, m, ArH), 6.66-6.78 (2H, m, ArH), 7.19 (2H, d, $J=7.0$, ArH), 7.22-7.40 (8H, m, ArH); ^{13}C NMR (101 MHz; CDCl_3) 31.7 (CH_2), 33.2 (PhCH_2), 39.8 (CHCN), 55.7 (OCH_3), 59.6 (CHNH), 114.8 (2C, Ar), 115.7 (2C, Ar), 119.8 ($\text{C}=\text{N}$), 126.5 (2C, Ar), 126.6 (Ar), 128.2 (Ar), 128.4 (2C, Ar), 128.7 (2C, Ar), 129.0 (2C, Ar), 139.7 (q), 139.8 (q), 140.1 (q), 152.9 (q); IR (neat) 3377, 3028, 2931, 2239, 1510; Mass Spec (ES, M + H) Theoretical: 357.1967, Measured: 357.1956.

(2*S, 3*R**)-2-(2-chlorobenzyl)-3-(4-methoxyphenylamino)-3-phenylpropanenitrile (Entry 22)**



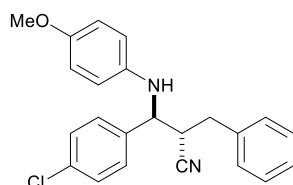
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 22 (66 mg, 35%) as a white solid, mp 102-104 °C; ¹H NMR (400 MHz; CDCl₃) 2.68 (1H, dd, *J*=13.6, 11.0, CH_{2a}), 3.26 (1H, dd, *J*=13.6, 4.3, CH_{2b}), 3.57-3.68 (1H, ddd, *J*=13.6, 5.3, 4.3, CHCN), 3.76 (3H, s, OCH₃), 4.63 (1H, d, *J*=5.3, CHNH), 6.63-6.68 (2H, m, ArH), 6.72-6.84 (2H, m, ArH), 7.22-7.31 (3H, m, ArH), 7.38-7.50 (4H, m, ArH), 7.56 (2H, d, *J*=7.3 ArH); ¹³C NMR (101 MHz; CDCl₃) 33.8 (CH₂), 38.8 (CHCN), 55.7 (OCH₃), 60.1 (CHNH), 115.0 (2C, Ar), 115.8 (2C, Ar), 119.3 (C=N), 127.3 (Ar), 127.4 (2C, Ar), 128.7 (2C, Ar), 129.0 (2C, Ar), 129.8 (Ar), 131.5 (Ar), 133.9 (q), 134.4 (q), 138.1 (q), 139.6 (q), 153.1 (q); IR (neat) 3371, 3061, 2927, 2241, 1511; Mass Spec (ES, M + H) Theoretical: 377.1421, Measured: 377.1429.

(2*R, 3*R**)-2-(2-chlorobenzyl)-3-(4-methoxyphenylamino)-3-phenylpropanenitrile (Entry 23)**



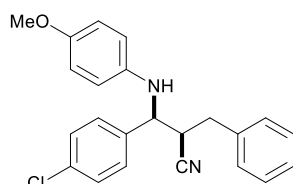
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 23 (170 mg, 90%) as a white solid, mp 100-102 °C; ¹H NMR (500 MHz; CDCl₃) 3.20 (1H, dd, *J*=13.6, 9.1, CH_{2a}), 3.31 (1H, dd, *J*=13.6, 6.5, CH_{2b}), 3.38-3.46 (1H, m, CHCN), 3.71 (3H, s, OCH₃), 4.53 (1H, d, *J*=3.8, CHNH), 6.57 (2H, d, *J*=8.5, ArH), 6.69-6.76 (2H, m, ArH), 7.20-7.43 (9H, m, ArH); ¹³C NMR (126 MHz; CDCl₃) 34.9 (CH₂), 40.7 (CHCN), 55.7 (OCH₃), 58.7 (CHNH), 115.0 (2C, Ar), 115.7 (2C, Ar), 119.3 (C=N), 126.6 (2C, Ar), 127.4 (Ar), 128.3 (Ar), 129.1 (2C, Ar), 129.2 (Ar), 129.9 (Ar), 132.0 (Ar), 134.0 (q), 134.4 (q), 139.6 (q), 139.9 (q), 153.0 (q); IR (neat) 3386, 3060, 2935, 2242, 1510; Mass Spec (ES, M + H) Theoretical: 377.1421, Measured: 377.1420.

(2*S, 3*R**)-2-benzyl-3-(4-chlorophenyl)-3-(4-methoxyphenylamino)propanenitrile (Entry 24)**



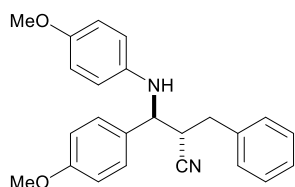
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 24 (81 mg, 43%) as a white solid, mp 133-135 °C; ¹H NMR (500 MHz; CDCl₃) 2.83 (1H, dd, *J*=13.9, 9.1, CH_{2a}), 2.89 (1H, dd, *J*=13.9, 6.0, CH_{2b}), 3.40 (1H, app. dt, *J*=9.0, 5.8, CHCN), 3.72 (3H, s, OCH₃), 4.47 (1H, d, *J*=5.4, CHNH), 6.46-6.54 (2H, m, ArH), 6.68-6.77 (2H, m, ArH), 7.17-7.24 (2H, m, ArH), 7.27-7.40 (7H, m, ArH); ¹³C NMR (126 MHz; CDCl₃) 35.5 (CH₂), 40.8 (CHCN), 55.7 (OCH₃), 58.7 (CHNH), 115.0 (2C, Ar), 115.9 (2C, Ar), 119.5 (C=N), 127.6 (Ar), 128.9 (2C, Ar), 129.0 (2C, Ar), 129.0 (2C, Ar), 129.3 (2C, Ar), 134.5 (q), 136.3 (q), 136.9 (q), 139.4 (q) 153.2 (q); IR (neat) 3365, 3030, 2933, 2241, 1510; Mass Spec (EI) Theoretical: 376.1337, Measured: 376.1339.

(2*R, 3*R**)-2-benzyl-3-(4-chlorophenyl)-3-(4-methoxyphenylamino)propanenitrile (Entry 25)**



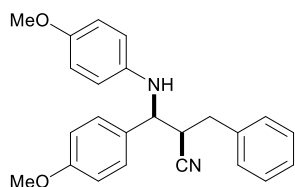
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 25 (132 mg, 70%) as a white solid, mp 133-135 °C; ¹H NMR (500 MHz; CDCl₃) 2.99-3.22 (3H, m, CH₂ and CHCN), 3.71 (3H, s, OCH₃), 4.14 (1H, br. s, CHNH), 4.45 (1H, br. s, CHNH), 6.38-6.57 (2H, m, ArH), 6.64-6.80 (2H, m, ArH), 7.21-7.37 (9H, m, ArH); ¹³C NMR (126 MHz; CDCl₃) 36.4 (CH₂), 42.9 (CHCN), 55.7 (OCH₃), 57.2 (CHNH), 115.0 (2C, Ar), 115.6 (2C, Ar), 119.3 (C=N), 127.7 (Ar), 127.9 (2C, Ar), 129.1 (4C, Ar), 129.3 (2C, Ar), 134.0 (q), 136.5 (q), 138.6 (q), 139.7 (q), 153.0 (q); IR (neat) 3381, 3030, 2930, 2242, 1511; Mass Spec (ES) Theoretical: 377.1421, Measured: 377.1401.

(2*S, 3*R**)-2-benzyl-3-(4-methoxyphenyl)-3-(4-methoxyphenylamino)propanenitrile (Entry 26)**



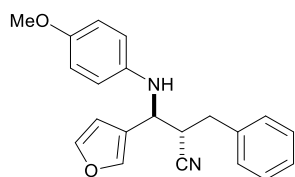
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 26 (89 mg, 48%) as a white solid, mp 133-135 °C; ¹H NMR (500 MHz; CDCl₃) 2.81 (1H, dd, *J*=13.8, 9.1, CH_{2a}), 2.87 (1H, dd, *J*=13.8, 5.9, CH_{2b}), 3.31-3.54 (2H, m, CHCN and NH), 3.71 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 4.44 (1H, br. s, CHNH), 6.38-6.62 (2H, m, ArH), 6.63-6.80 (2H, m, ArH), 6.84-7.01 (2H, m, ArH), 7.19-7.42 (7H, m, ArH); ¹³C NMR (126 MHz; CDCl₃) 35.6 (CH₂), 40.9 (CHCN), 55.4 (OCH₃), 55.7 (OCH₃), 58.7 (CHNH), 114.4 (2C, Ar), 114.9 (2C, Ar), 115.8 (2C, Ar), 119.9 (C=N), 127.5 (2C, Ar), 128.6 (Ar), 128.9 (2C, Ar), 129.0 (2C, Ar), 130.2 (q), 136.7 (q), 139.8 (q), 153.0 (q), 159.7 (q); IR (neat) 3367, 3030, 2933, 2241, 1510; Mass Spec (CI) Theoretical: 373.1916, Measured: 373.1915.

(2*R, 3*R**)-2-benzyl-3-(4-methoxyphenyl)-3-(4-methoxyphenylamino)propanenitrile (Entry 27)**



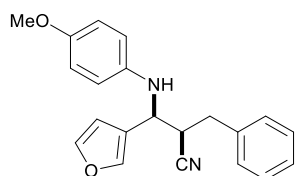
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 29 (99 mg, 53%) as a white solid, mp 115-117 °C; ¹H NMR (500 MHz; CDCl₃) 2.98-3.11 (3H, m CHCN and CH₂), 3.63 (3H, s, OCH₃), 3.69 (3H, s, OCH₃), 4.37 (1H, br. s, CHNH), 6.39-6.51 (2H, m, ArH), 6.58-6.69 (2H, m, ArH), 6.72-6.83 (2H, m, ArH), 7.12-7.28 (7H, m, ArH); ¹³C NMR (126 MHz; CDCl₃) 34.2 (CH₂), 41.0 (CHCN), 53.1 (OCH₃), 53.5 (OCH₃), 55.3 (CHNH), 112.2 (2C, Ar), 112.7 (2C, Ar), 113.5 (2C, Ar), 117.6 (C=N), 125.3 (Ar), 125.4 (2C, Ar), 126.8 (2C, Ar), 126.9 (2C, Ar), 129.7 (q), 134.6 (q), 137.9 (q), 150.7 (q), 157.2 (q); IR (neat) 3384, 3030, 2933, 2240, 1509; Mass Spec (CI) Theoretical: 373.1916, Measured: 373.1909.

(2R*, 3S*)-2-benzyl-3-(furan-3-yl)-3-(4-methoxyphenylamino)propanenitrile (Entry 28)



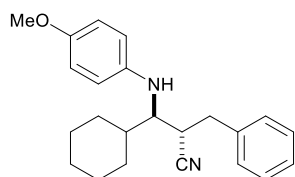
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 28 (71 mg, 43%) as a white solid, mp 102-104 °C; ¹H NMR (500 MHz; CDCl₃) 3.06-3.16 (2H, m, CH₂), 3.21 (1H, app. td, *J*=7.9, 4.4, CHCN), 3.75 (3H, s, OCH₃), 4.51 (1H, d, *J*=3.8, CHNH), 6.37-6.43 (1H, m, ArH), 6.55-6.64 (2H, m, ArH), 6.72-6.81 (2H, m, ArH), 7.18-7.24 (2H, m, ArH), 7.27-7.36 (3H, m, ArH), 7.38 (2H, d, *J*=1.6, ArH); ¹³C NMR (126 MHz; CDCl₃) 35.7 (CH₂), 41.3 (CHCN), 51.3 (CHNH), 55.7 (OCH₃), 108.6 (Ar), 115.0 (2C, Ar), 116.0 (2C, Ar), 120.0 (C=N), 125.0 (q), 127.5 (Ar), 129.0 (2C, Ar), 129.1 (2C, Ar), 136.8 (q), 136.8 (q), 140.1 (Ar), 143.9 (Ar), 153.3 (q); IR (neat) 3361, 3030, 2934, 2234, 1510; Mass Spec (ES) Theoretical: 333.1603, Measured: 333.1604.

(2S*, 3S*)-2-benzyl-3-(furan-3-yl)-3-(4-methoxyphenylamino)propanenitrile (Entry 29)



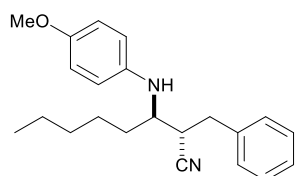
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 29 (83 mg, 50%) as a white solid, mp 117-119 °C; ¹H NMR (500 MHz; CDCl₃) 2.82 (1H, d, *J*=13.9, 7.1, CH_{2a}), 2.95 (1H, d, *J*=13.9, 8.2, CH_{2a}), 3.42 (1H, ddd, *J*= 8.2, 7.1, 4.9, CHCN), 3.73 (3H, s, OCH₃), 4.43 (1H, d, *J*=4.7, CHNH), 6.47-6.57 (2H, m, ArH), 6.64 (1H, dd, *J*= 1.8, 0.9, ArH), 6.70-6.79 (2H, m, ArH), 7.18-7.24 (2H, m, ArH), 7.28-7.38 (3H, m, ArH), 7.48 (1H, t, *J*=1.7, ArH), 7.55 (1H, s, ArH); ¹³C NMR (126 MHz; CDCl₃) 35.6 (CH₂), 39.3 (CHCN), 51.5 (CHNH), 55.7 (OCH₃), 109.0 (Ar), 115.0 (2C, Ar), 115.9 (2C, Ar), 120.2 (C=N), 122.6 (q), 127.6 (Ar), 128.9 (2C, Ar), 129.0 (2C, Ar), 136.4 (q), 139.3 (q), 140.7 (Ar), 144.0 (Ar), 153.3 (q); IR (neat) 3385, 3030, 2933, 2242, 1509; Mass Spec (ES) Theoretical: 333.1603, Measured: 333.1586.

(2S*, 3R*)-2-benzyl-3-cyclohexyl-3-(4-methoxyphenylamino)propanenitrile (Entry 30, 31)



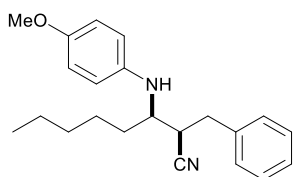
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 30 (92 mg, 53%) or Entry 31 (87 mg, 50%) as a white solid, mp 80-82 °C; ^1H NMR (600 MHz; CDCl_3) 1.05-1.21 (2H, m, CH_2), 1.23-1.37 (3H, m, CH_2), 1.60-1.72 (2H, m, CH_2), 1.75 (1H, d, $J=9.4$, CH), 1.81 (1H, d, $J=13.2$, CH), 1.87-1.98 (2H, m, CH), 2.86-2.99 (2H, m, CHCN and CH_{2a}), 3.06 (1H, d, $J=12.2$, 3.6, CH_{2b}) 3.29-3.49 (2H, m, NH and CHNH), 3.75 (3H, s, OCH_3), 6.45-6.64 (2H, m, ArH), 6.67-6.83 (2H, m, ArH), 7.23-7.34 (5H, m, ArH); ^{13}C NMR (151 MHz; CDCl_3) 26.1 (CH_2), 26.3 (CH_2), 26.3 (CH_2) 27.1 (CH_2), 31.5 (CH_2), 35.7 (PhCH_2), 38.6 (CHCN), 41.3 (CHCHNH), 55.9 (OCH_3), 59.9 (CHNH), 114.6 (2C, Ar), 115.1 (2C, Ar), 121.0 ($\text{C}=\text{N}$), 127.3 (Ar), 128.9 (2C, Ar), 129.1 (2C, Ar), 137.4 (q), 141.9 (q) 152.4 (q); IR (neat) 3381, 3029, 2927, 2238, 1511; Mass Spec (EI) Theoretical: 348.2196, Measured: 348.2190.

(2S*, 3R*)-2-benzyl-3-(4-methoxyphenylamino)octanenitrile (Entry 32)



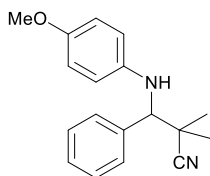
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 32 (81 mg, 48%) as a yellow oil; ^1H NMR (600 MHz; CDCl_3) 0.89 (3H, t, $J=6.8$, CH_3), 1.23-1.41 (5H, m, CH_2), 1.51-1.69 (2H, m, CH_2), 1.81-1.92 (1H, m, CH), 2.86 (1H, dd, $J=13.8$, 7.3, CH_{2a}), 3.04 (1H, dd, $J=13.8$, 8.3, CH_{2b}), 3.17 (1H, app. td, $J=7.8$, 3.2, CHCN), 3.28-3.44 (2H, m, NH and CHNH), 3.73 (3H, s, OCH_3), 6.30-6.40 (2H, m, ArH), 6.65-6.76 (2H, m, ArH), 7.20-7.24 (2H, m, ArH), 7.27-7.32 (1H, m, ArH), 7.33-7.38 (2H, m, ArH); ^{13}C NMR (151 MHz; CDCl_3) 14.1 (CH_3), 22.7 (CH_2), 26.0 (CH_2) 31.3 (CH_2), 31.8 (CH_2), 35.8 (PhCH_2), 38.7 (CHCN), 53.9 (CHNH), 55.9 (OCH_3), 114.8 (2C, Ar), 115.2 (2C, Ar), 120.3 ($\text{C}=\text{N}$), 127.5 (Ar), 128.9 (2C, Ar), 129.0 (2C, Ar), 136.9 (q), 140.1 (q) 152.6 (q); IR (neat) 3391, 3029, 2931, 2237, 1512; Mass Spec (EI) Theoretical: 336.2196, Measured: 336.2200.

(2*R**, 3*R**)-2-benzyl-3-(4-methoxyphenylamino)octanenitrile (Entry 33)



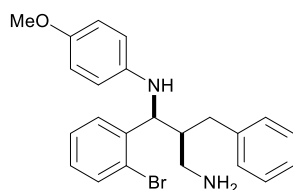
Purified by flash chromatography (0-25% TBME/cyclohexane) to give Entry 33 (29 mg, 17%) as a yellow oil; ^1H NMR (600 MHz; CDCl_3) 0.85 (3H, t, $J=7.0$, CH_3), 1.16-1.30 (4H, m, CH_2), 1.30-1.40 (2H, m, CH_2), 1.67 (2H, app. q, $J=7.4$, CH), 2.94-3.09 (3H, m, CH_2 and CHCN), 3.33 (1H, br. s, NH), 3.48 (1H, td, $J=6.7$, 2.4, CHNH), 3.76 (3H, s, OCH_3), 6.48-6.58 (2H, m, ArH), 6.75-6.81 (2H, m, ArH), 7.13-7.19 (2H, m, ArH), 7.23-7.28 (1H, m, ArH), 7.29-7.34 (2H, m, ArH); ^{13}C NMR (151 MHz; CDCl_3) 14.1 (CH_3), 22.6 (CH_2), 26.2 (CH_2), 31.6 (CH_2), 34.2 (CH_2), 35.2 (PhCH_2), 39.4 (CHCN), 54.8 (CHNH), 55.9 (OCH_3), 115.0 (2C, Ar), 115.1 (2C, Ar), 120.4 ($\text{C}=\text{N}$), 127.3 (Ar), 128.9 (2C, Ar), 129.1 (2C, Ar), 137.4 (q), 141.0 (q), 152.6 (q); IR (neat) 3381, 3029, 2930, 2237, 1511; Mass Spec (EI) Theoretical: 336.2196, Measured: 336.2193.

3-(4-methoxyphenylamino)-2,2-dimethyl-3-phenylpropanenitrile



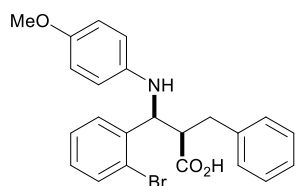
Purified by flash chromatography (0-25% TBME/cyclohexane) to give a white solid (10 mg, 7%), mp 84-86 °C; ^1H NMR (400 MHz; CDCl_3) 1.22 (3H, s, CH_3), 1.58 (3H, s, CH_3), 3.67 (3H, s, OCH_3), 4.11 (1H, s, CHNH), 6.50-6.57 (2H, m, ArH), 6.64-6.71 (2H, m, ArH), 7.26-7.41 (5H, m, ArH); ^{13}C NMR (101 MHz; CDCl_3) 24.2 (CH_3), 25.8 (CH_3), 38.8 (CCN), 55.3 (OCH_3), 65.5 (CHNH), 114.5 (2C, Ar), 115.3 (2C, Ar), 123.2 ($\text{C}=\text{N}$), 127.5 (2C, Ar), 128.2 (Ar), 128.2 (2C, Ar), 138.1 (q), 140.2 (q), 152.4 (q); IR (neat) 3391, 2990, 2937, 2233, 1511; Mass Spec (ES, M + H) Theoretical: 281.1654, Measured: 281.1653.

(2*S, 3*S**)-2-benzyl-1-(2-bromophenyl)-N1-(4-methoxyphenyl)propane-1,3-diamine**



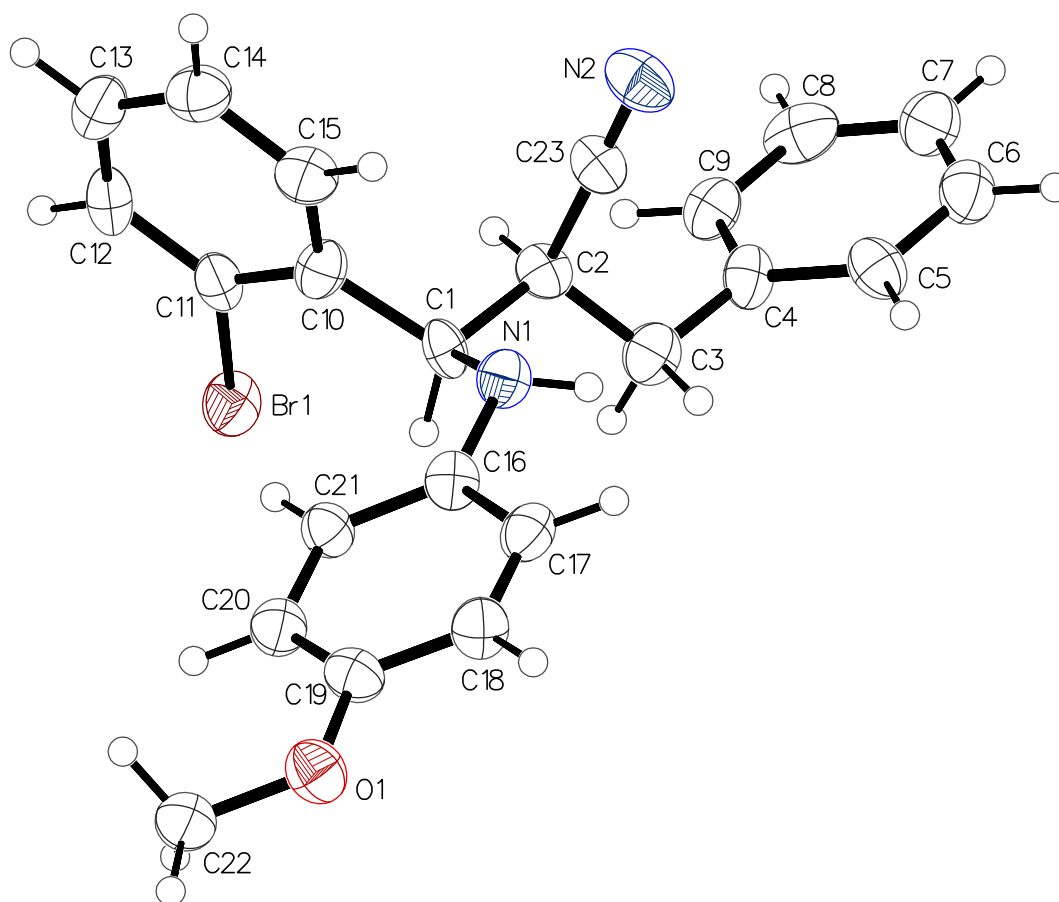
To LiAlH₄ in ether (1.994 mL, 1.994 mmol) in a 100 mL 3-neck flask under nitrogen at -5 °C was added concentrated H₂SO₄ (0.055 mL, 1.092 mmol). A vigorous evolution of gas was observed and the solution became slightly cloudy and was stirred for 1 h at 0 °C and then 2-benzyl-3-(2-bromophenyl)-3-((4-methoxyphenyl)amino)propanenitrile (400 mg, 0.949 mmol) in THF (10 mL) was added over 3 min. After 40 min at 0 °C water (5 mL) was added slowly (vigorous reaction) and to the resulting thick white mixture was added 2 M sodium hydroxide (5 mL). The two phases were separated and the aqueous phase extracted with ether (2 x 20 mL). The organics were combined and washed with brine, dried and evaporated to give an oil. This oil was dissolved in Et₂O (5 mL) and HCl (1 M in Et₂O, 2 mL) was added to give an off white solid, which was filter off. The White solid was dissolved in NaOH (2 M, 5 mL) and extracted with EtOAc (3 x 20 mL). Organics combined and washed with brine, dried and concentrated to give 2-benzyl-1-(2-bromophenyl)-N1-(4-methoxyphenyl)propane-1,3-diamine (375 mg, 0.882 mmol, 93 % yield) as a white solid. mp 54-56 °C; ¹H NMR (400 MHz; CDCl₃) 2.19-2.27 (1H, m, CH), 2.75-2.85 (2H, m, CH₂NH₂), 2.96 (1H, dd, *J*=13.6, 8.5, PhCH_{2a}), 3.05 (1H, dd, *J*=13.6, 7.0, PhCH_{2b}), 3.74 (3H, s, OCH₃), 4.83 (1H, dd, *J*=4.0, CHNH), 6.36-6.48 (2H, m, ArH), 6.64-6.78 (2H, m, ArH), 7.06-7.15 (1H, m, ArH), 7.19-7.41 (6H, m, ArH), 7.53 (1H, dd, *J*=7.8, 1.5, ArH), 7.56 (1H, dd, *J*=8.0, 1.0, ArH); ¹³C NMR (101 MHz; CDCl₃) 35.9 (PhCH₂), 40.1 (CH₂NH), 44.3 (CH₂CH), 55.5 (OCH₃), 60.3 (CHNH), 113.2 (2C, Ar), 114.6 (2C, Ar), 123.4 (q), 125.8 (Ar), 127.1 (Ar), 128.0 (Ar), 128.0 (2C, Ar), 128.5 (Ar), 128.9 (2C, Ar), 132.7 (Ar), 139.9 (q), 141.4 (q), 141.8 (q), 151.0 (q); IR (neat) 3305, 3026, 2908, 1512; Mass Spec (ES, M + H) Theoretical: 425.1228, Measured: 425.1211.

(2*R, 3*S**)-2-benzyl-3-(2-bromophenyl)-3-(4-methoxyphenylamino)propanoic acid**



2-benzyl-3-(2-bromophenyl)-3-((4-methoxyphenyl)amino)propanenitrile (100 mg, 0.237 mmol) was dissolved in a mixture of THF (3 mL), ethanol (3 mL) and sodium hydroxide (2.5 mL, 1 M). Then the reaction mixture was cooled to 0 °C and hydrogen peroxide (0.202 mL, 1.780 mmol) was added. The reaction mixture was allowed to warm to RT and stirred at room temperature overnight. Then 2 M HCl and CH₂Cl₂ (20 mL) were added and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL), then combined and dried over Na₂SO₄ and solvent was removed under reduced pressure. The oil residue was dissolved in 1:1 MeOH:MeCN 1 mL and purified by Open Access Mass Directed AutoPrep on Xbridge column using Acetonitrile/Water with an ammonium carbonate modifier. The solvent was evaporated in vacuo to give the required product 2-benzyl-3-(2-bromophenyl)-3-(4-methoxyphenylamino)propanoic acid (68 mg, 65%) as a white solid, mp 130-132 °C; ¹H NMR (400 MHz; CDCl₃) 2.93 (1H, ddd, *J*=8.7, 6.5, 3.0, CHCO₂H), 3.14 (1H, dd, *J*=13.4, 6.4, CH_{2a}), 3.30 (1H, dd, *J*=13.4, 8.7, CH_{2b}), 3.70 (3H, s, OCH₃), 4.88 (1H, d, *J*=3.0 CHNH), 5.13 (1H, br. s, NH or OH), 5.84 (1H, br. s, NH or OH), 6.35-6.46 (2H, m, ArH), 6.64-6.75 (2H, m, ArH), 7.08 (1H, td, *J*=7.6, 1.6, ArH), 7.16-7.34 (6H, m, ArH), 7.38 (1H, dd, *J*=7.8, 1.5, ArH), 7.53 (1H, dd, *J*=7.8, 1.0, ArH); ¹³C NMR (101 MHz; CDCl₃) 37.4 (CH₂), 51.8 (CHCO₂H), 55.7 (OCH₃), 58.0 (CHNH), 113.7 (2C, Ar), 114.9 (2C, Ar), 123.0 (q), 126.6 (Ar), 127.8 (Ar), 128.5 (2C, Ar), 128.6 (Ar), 128.9 (Ar), 129.2 (2C, Ar), 132.9 (Ar), 138.8 (q), 140.3 (q), 140.8 (q), 151.6 (q), 175.2 (q, CO); IR (neat) 3371, 3028, 2908, 1669, 1512; Mass Spec (EI) Theoretical: 439.0778, Measured: 439.0779.

X-ray structure of *syn*-3 R¹=Bn, R²=2-Br-C₆H₅

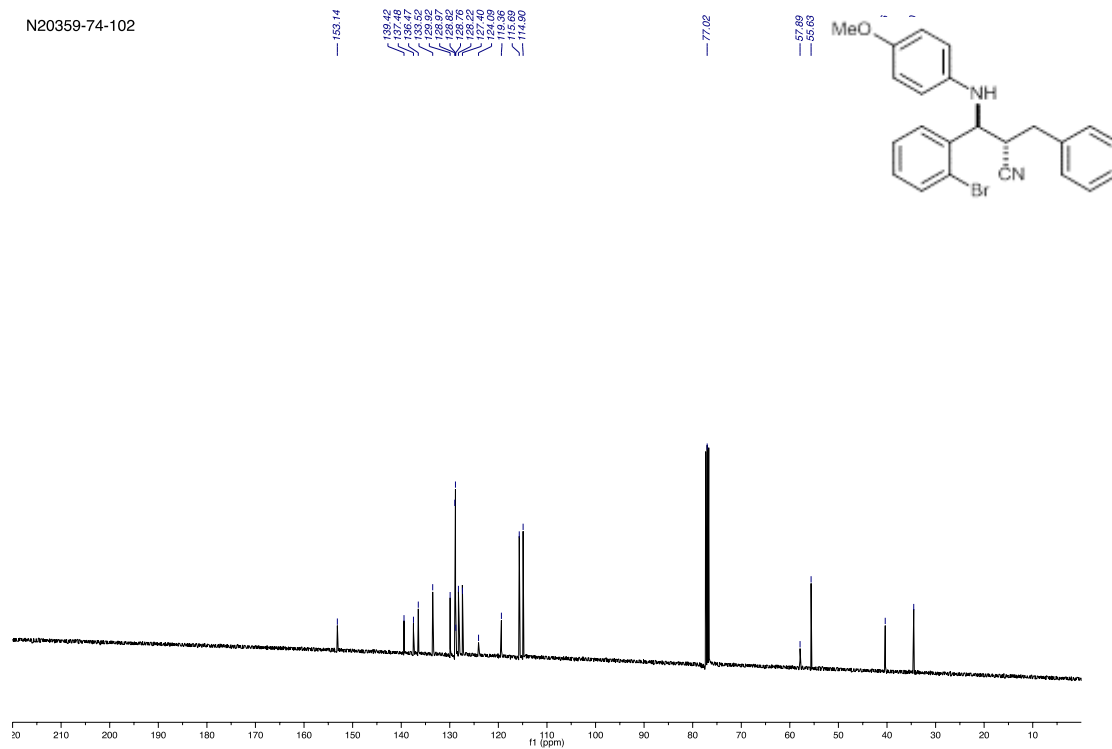
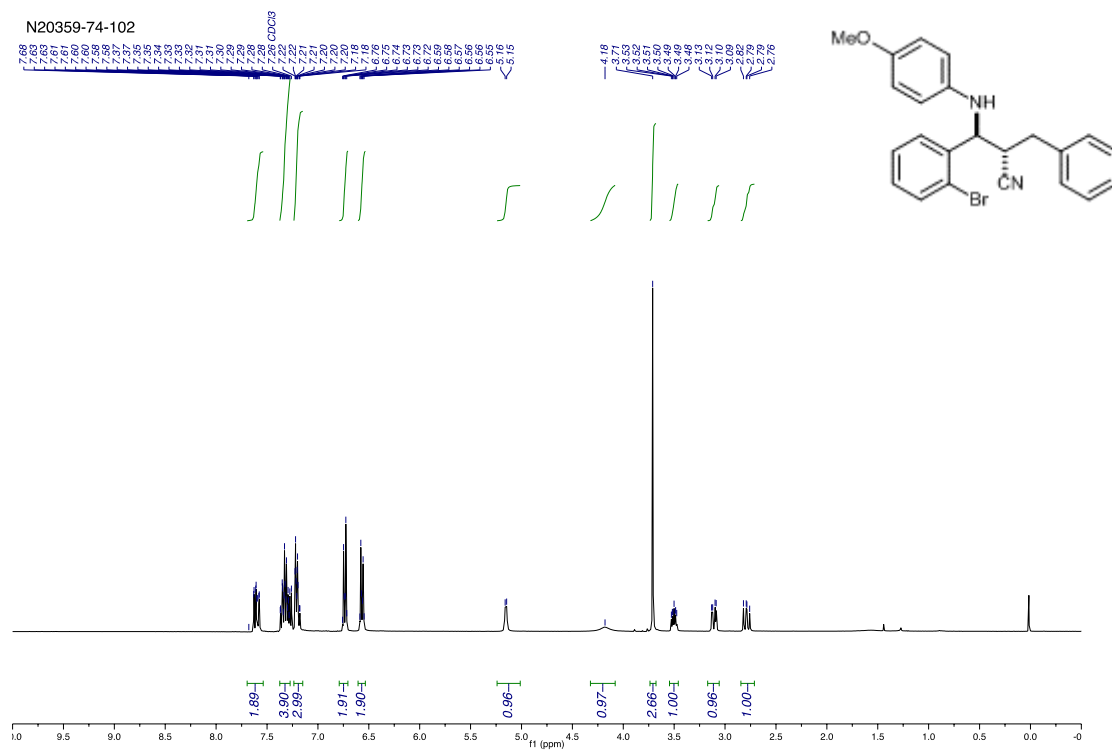


Crystallographic data (excluding structure factors) for this structure has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1531946. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

| | | |
|------------------------|--|-----------------------|
| Empirical formula | C ₂₃ H ₂₁ BrN ₂ O | |
| Formula weight | 421.33 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54187 Å | |
| Crystal system | Monoclinic | |
| Space group | <i>P</i> 2 ₁ / <i>n</i> | |
| Unit cell dimensions | <i>a</i> = 9.5441(2) Å | <i>α</i> = 90° |
| | <i>b</i> = 7.5459(2) Å | <i>β</i> = 96.595(7)° |
| | <i>c</i> = 27.2946(19) Å | <i>γ</i> = 90° |
| Volume | 1952.72(15) Å ³ | |
| <i>Z</i> | 4 | |
| Density (calculated) | 1.433 Mg / m ³ | |
| Absorption coefficient | 2.977 mm ⁻¹ | |
| <i>F</i> (000) | 864 | |

| | |
|--|--|
| Crystal | Block; colourless |
| Crystal size | 0.10 × 0.08 × 0.01 mm ³ |
| θ range for data collection | 6.37 – 66.56° |
| Index ranges | $-11 \leq h \leq 11, -8 \leq k \leq 7, -32 \leq l \leq 27$ |
| Reflections collected | 11530 |
| Independent reflections | 3395 [$R_{int} = 0.1017$] |
| Completeness to $\theta = 66.56^\circ$ | 98.4 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9708 and 0.7551 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 3395 / 1 / 249 |
| Goodness-of-fit on F^2 | 1.169 |
| Final R indices [$F^2 > 2\sigma(F^2)$] | $R1 = 0.0863, wR2 = 0.2246$ |
| R indices (all data) | $R1 = 0.1007, wR2 = 0.2443$ |
| Extinction coefficient | 0.0039(8) |
| Largest diff. peak and hole | 1.884 and $-1.168 \text{ e } \text{\AA}^{-3}$ |

Table 2, Entry 1



N20359-74-102

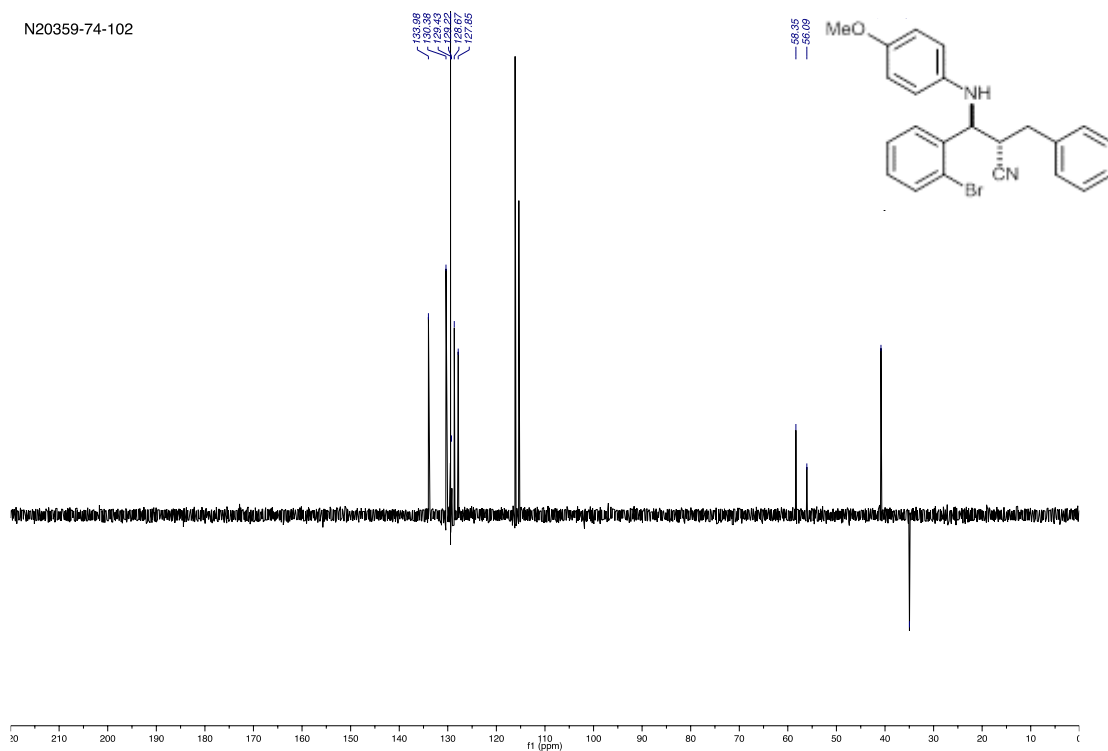
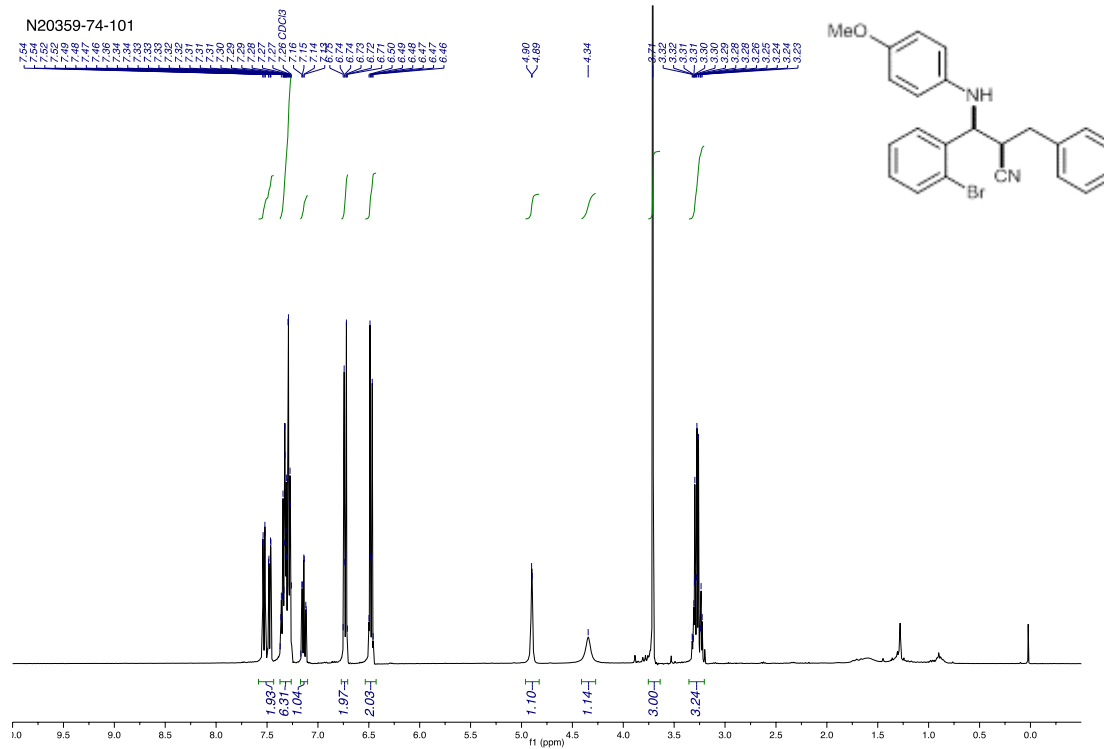
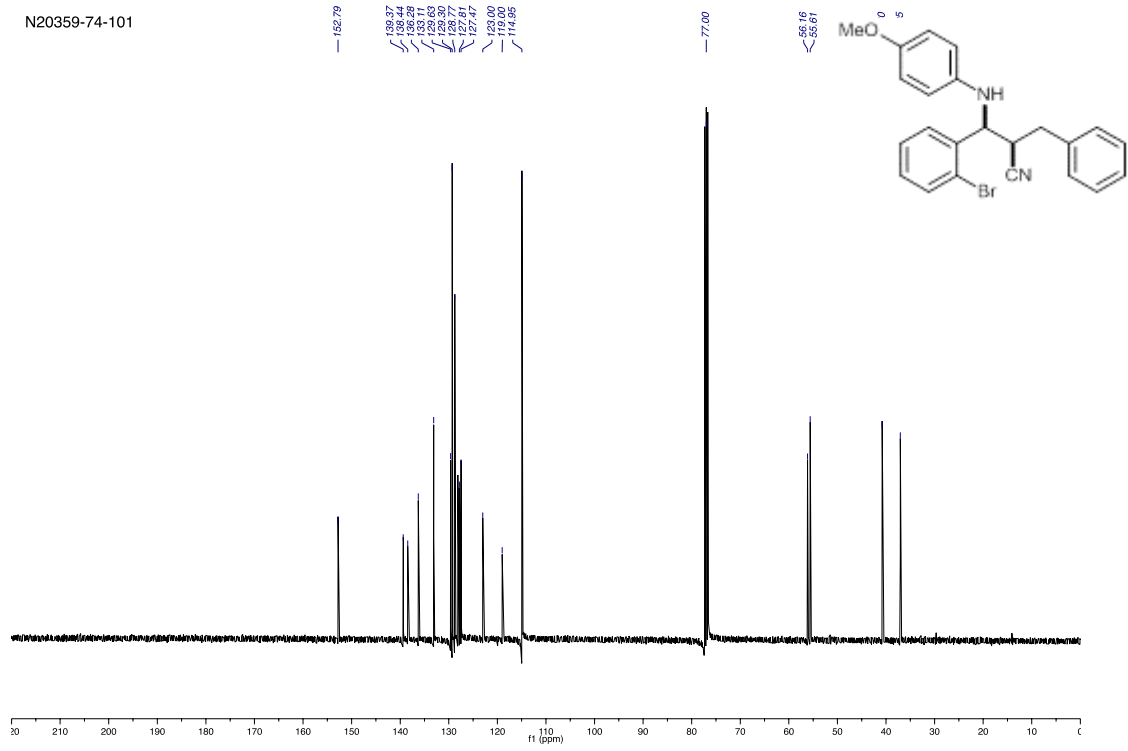


Table 2, Entry 2



N20359-74-101



N20359-74-101

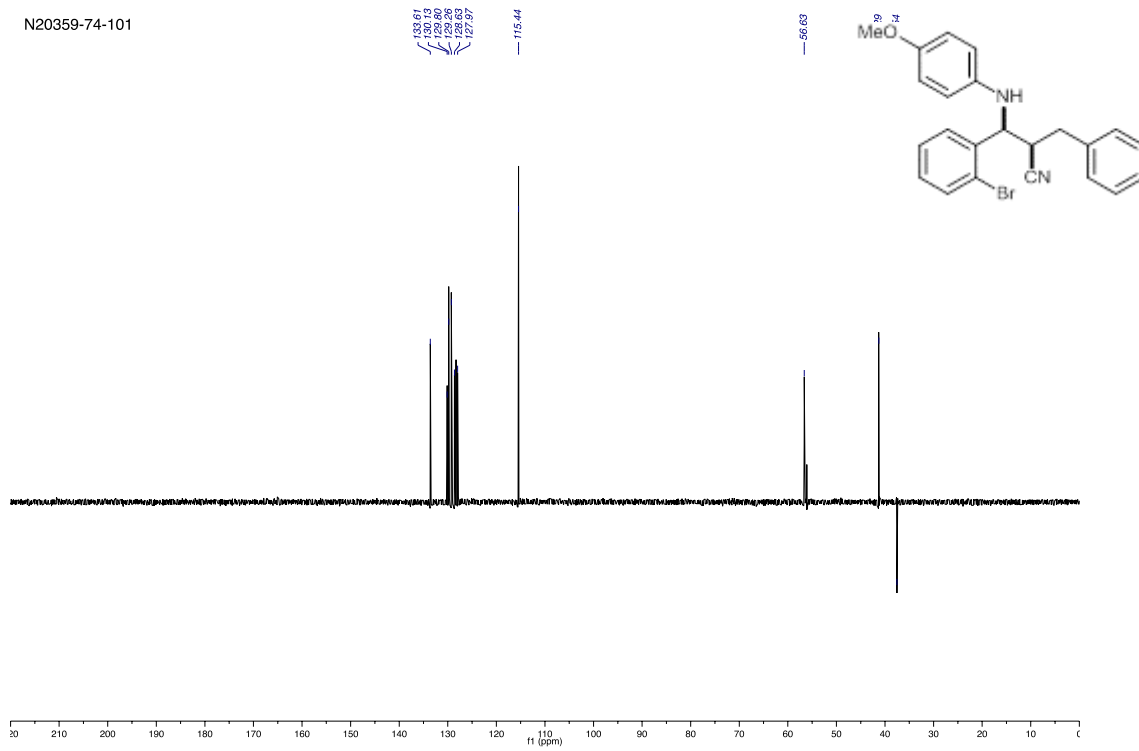
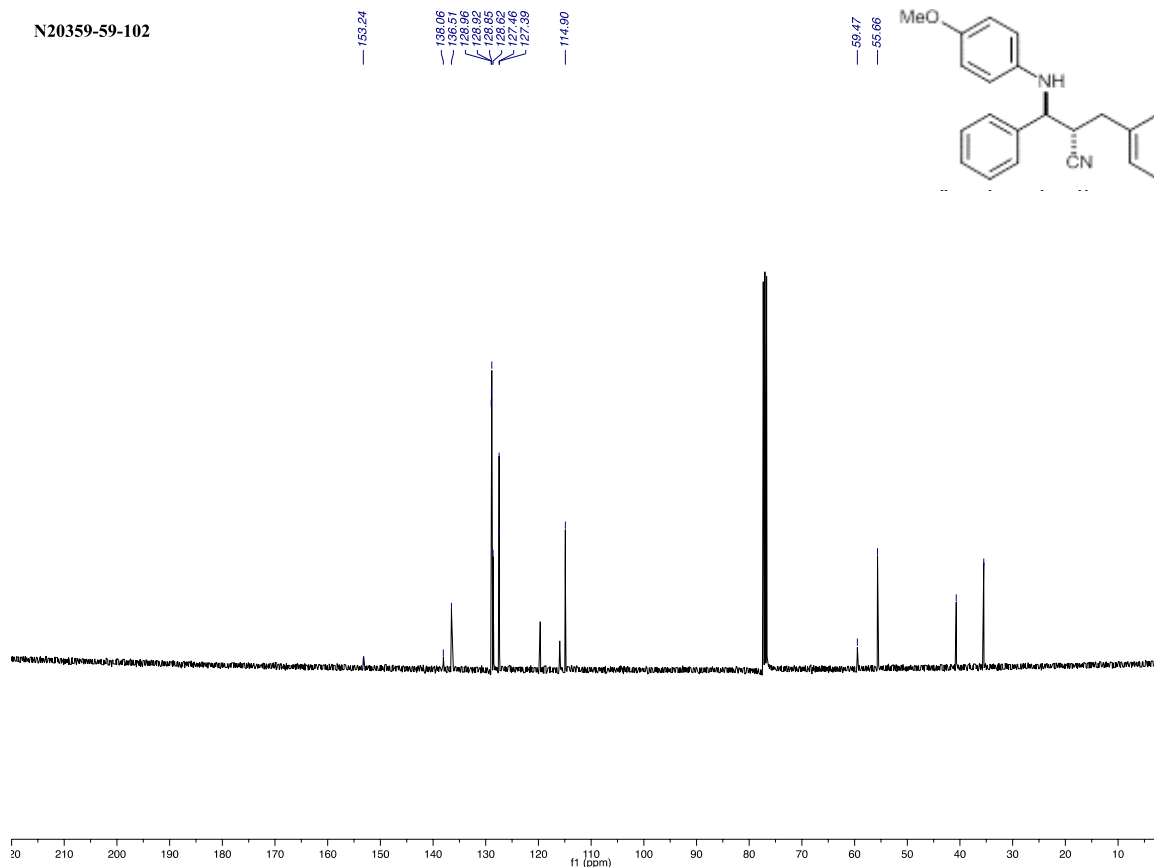
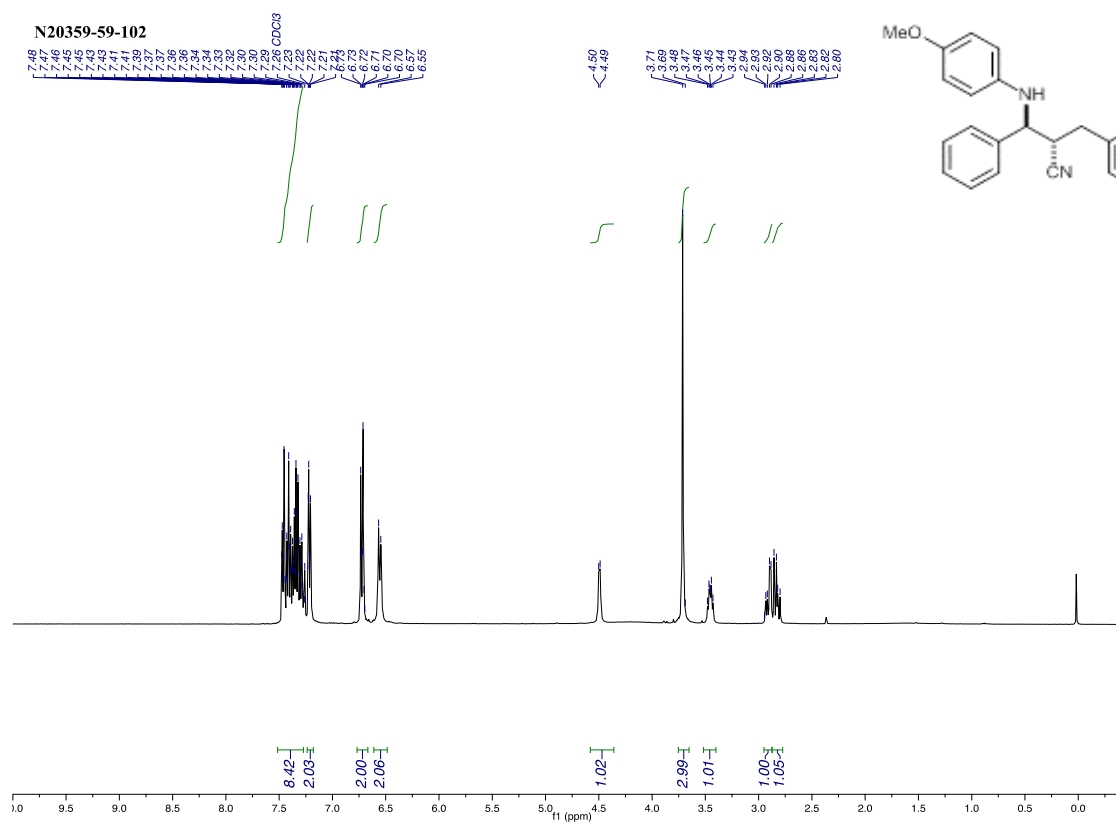


Table 2, Entry 3



N20359-59-102

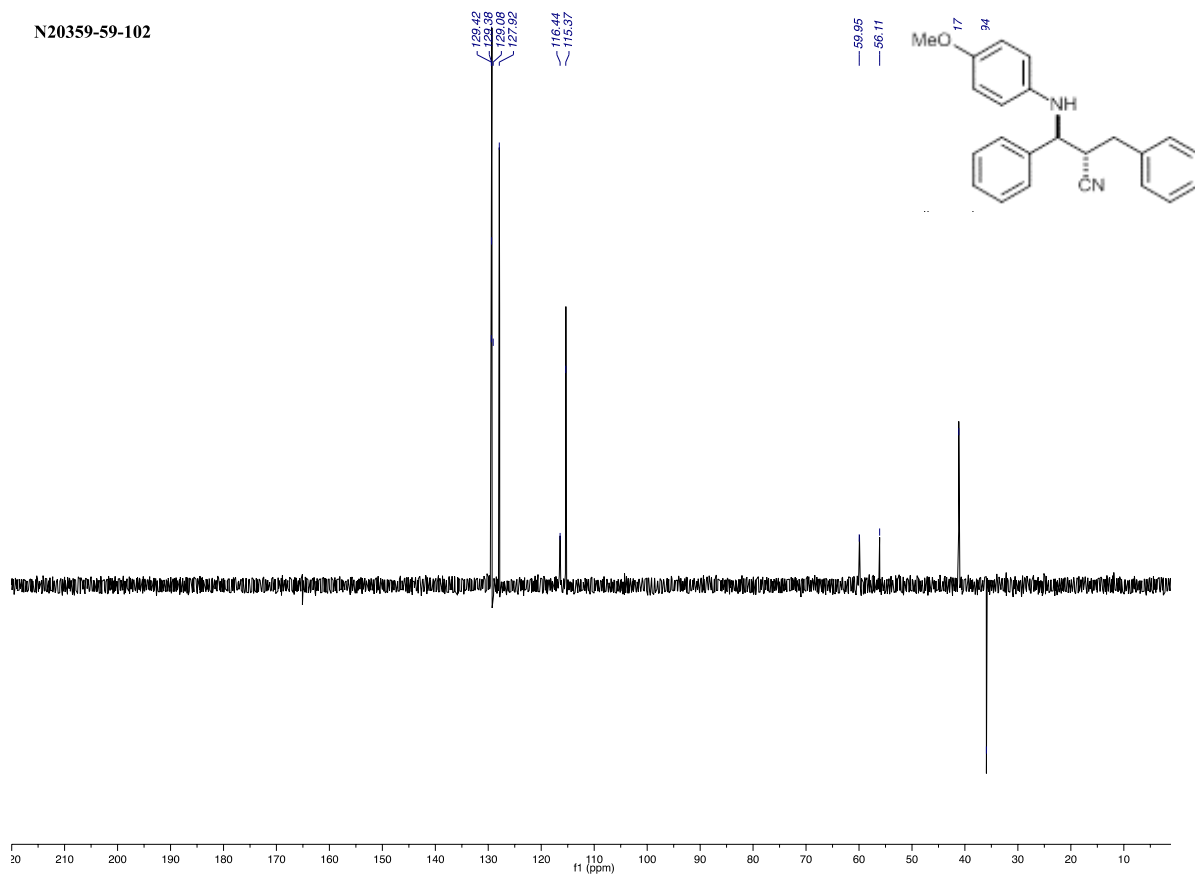
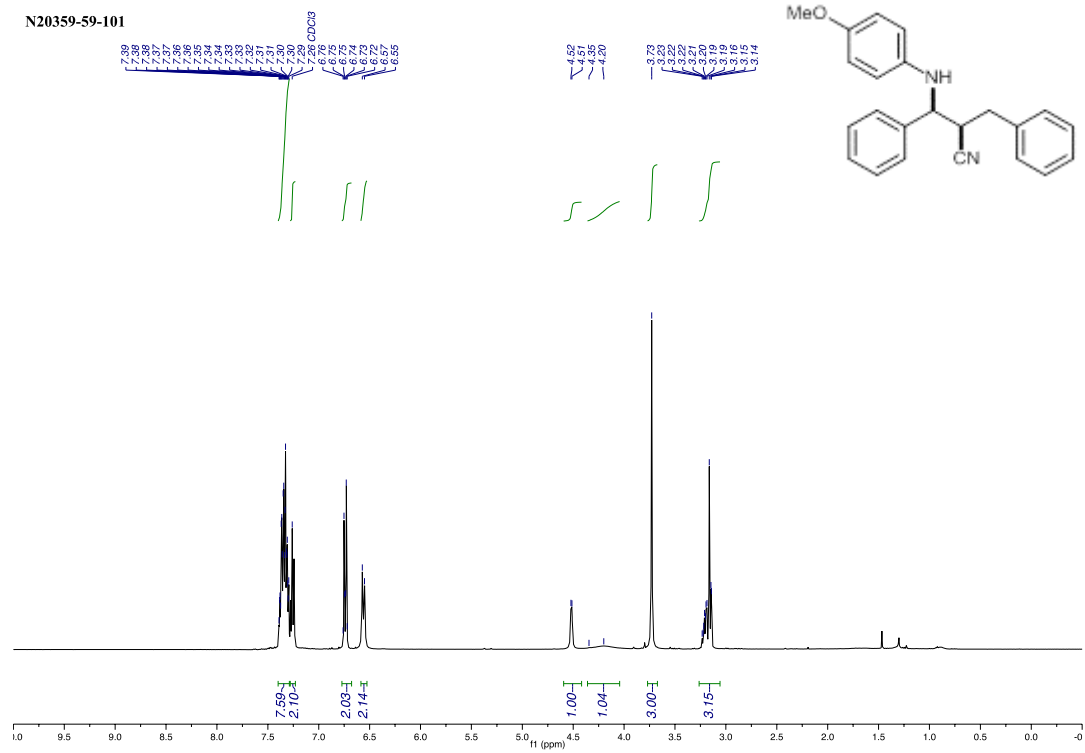
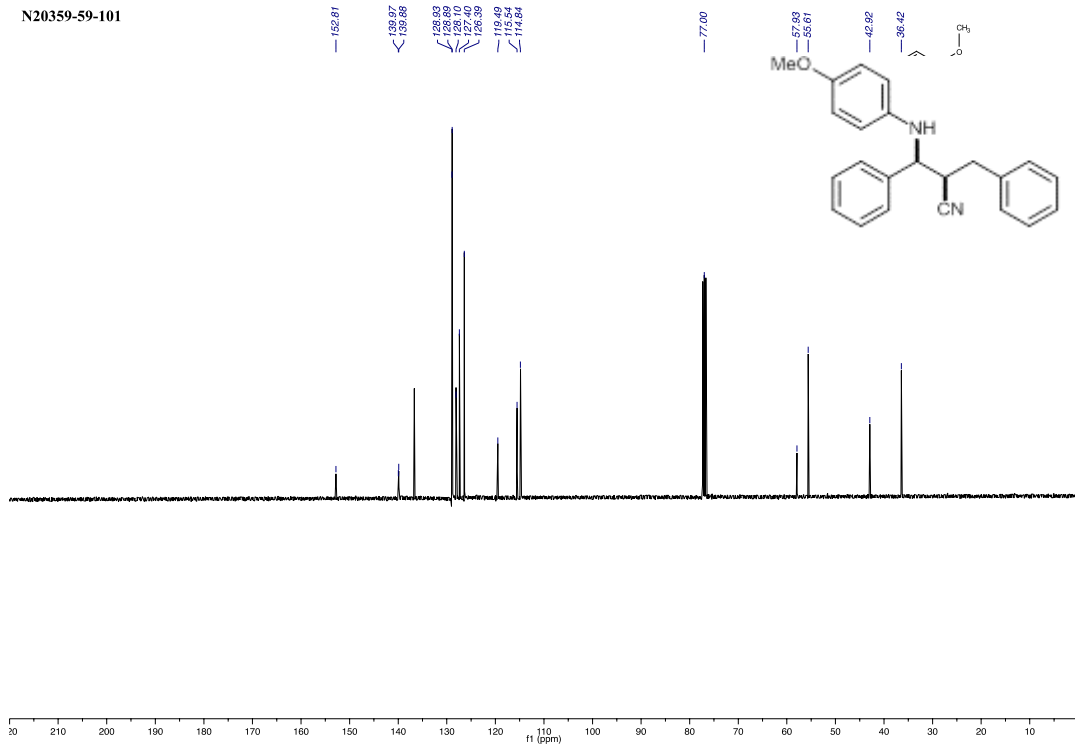


Table 2, Entry 4

N20359-59-101



N20359-59-101



N20359-59-101

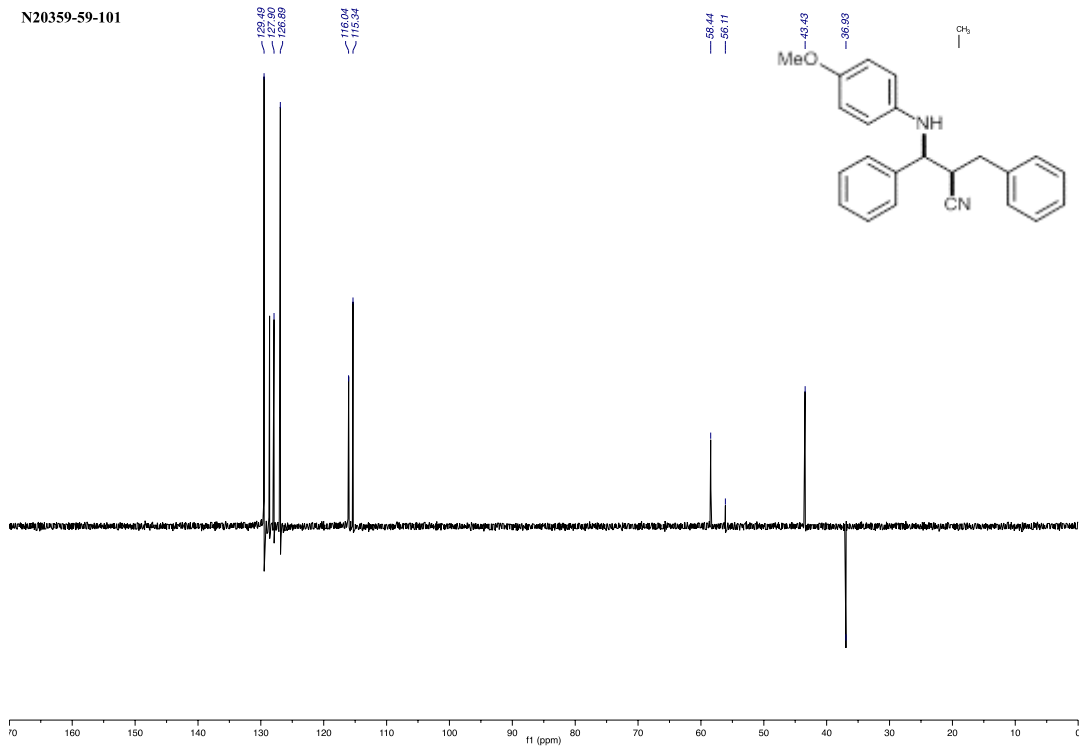
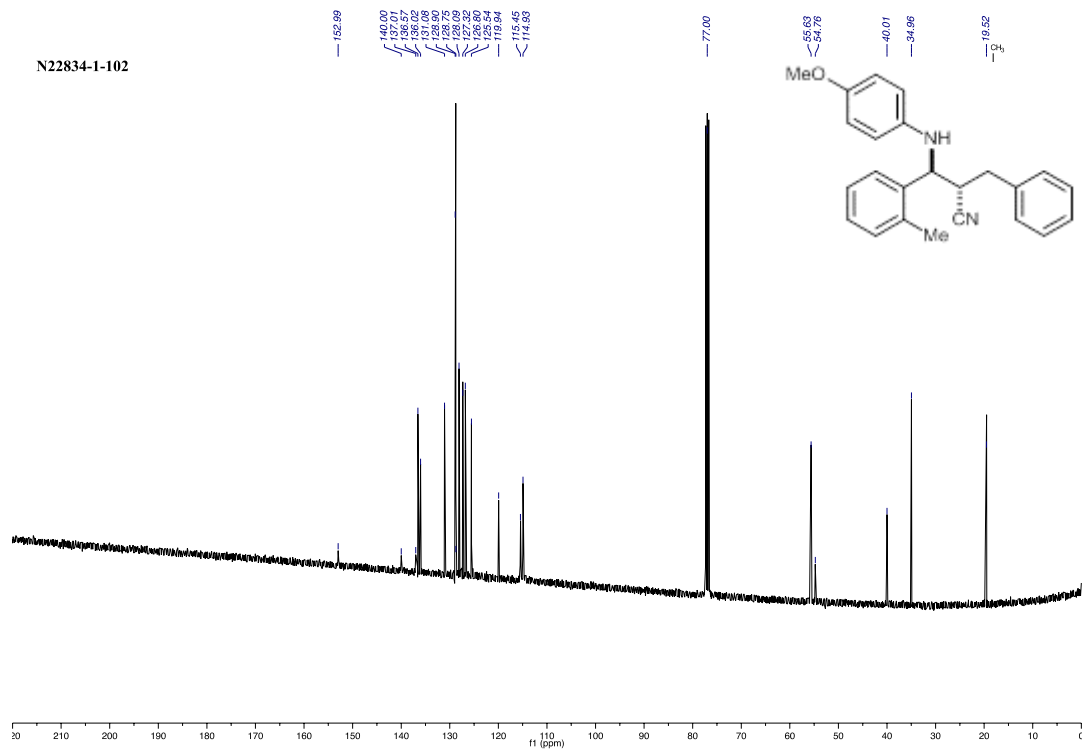
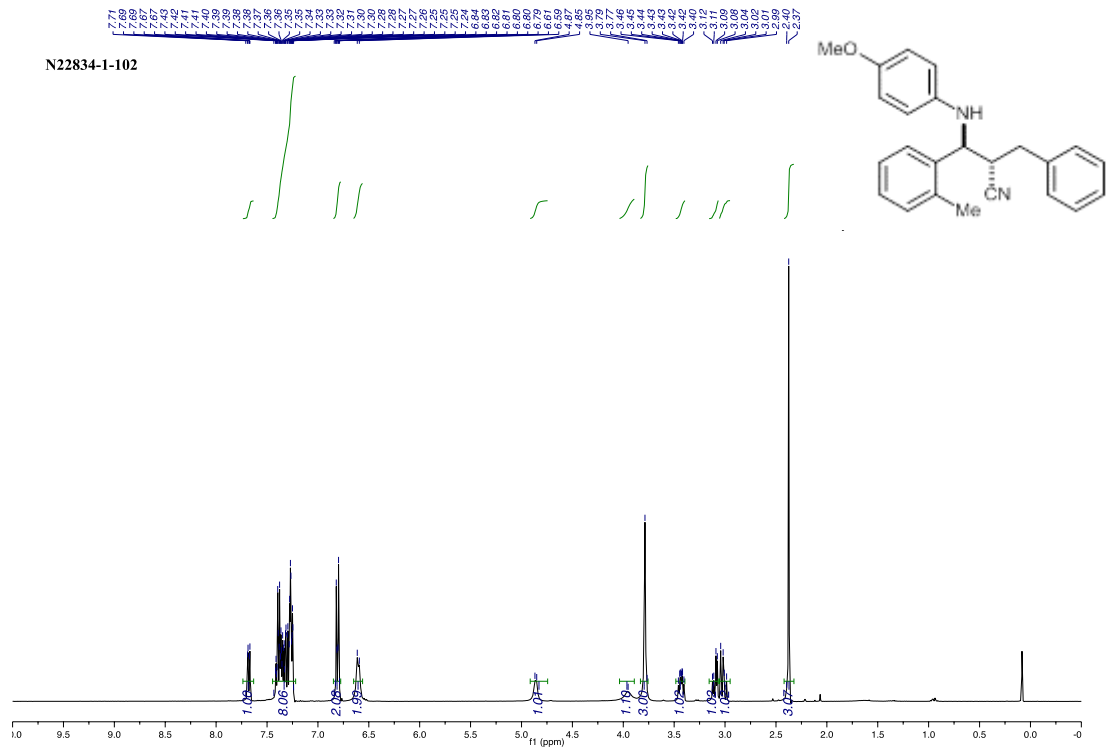


Table 2, Entry 5



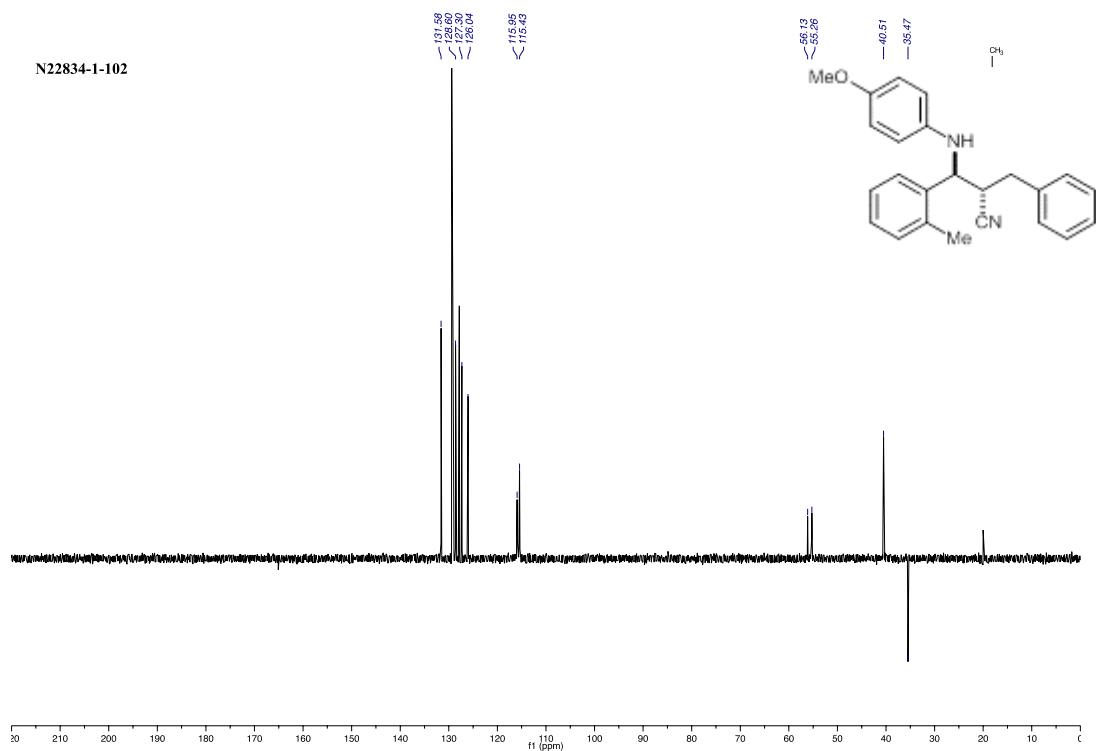
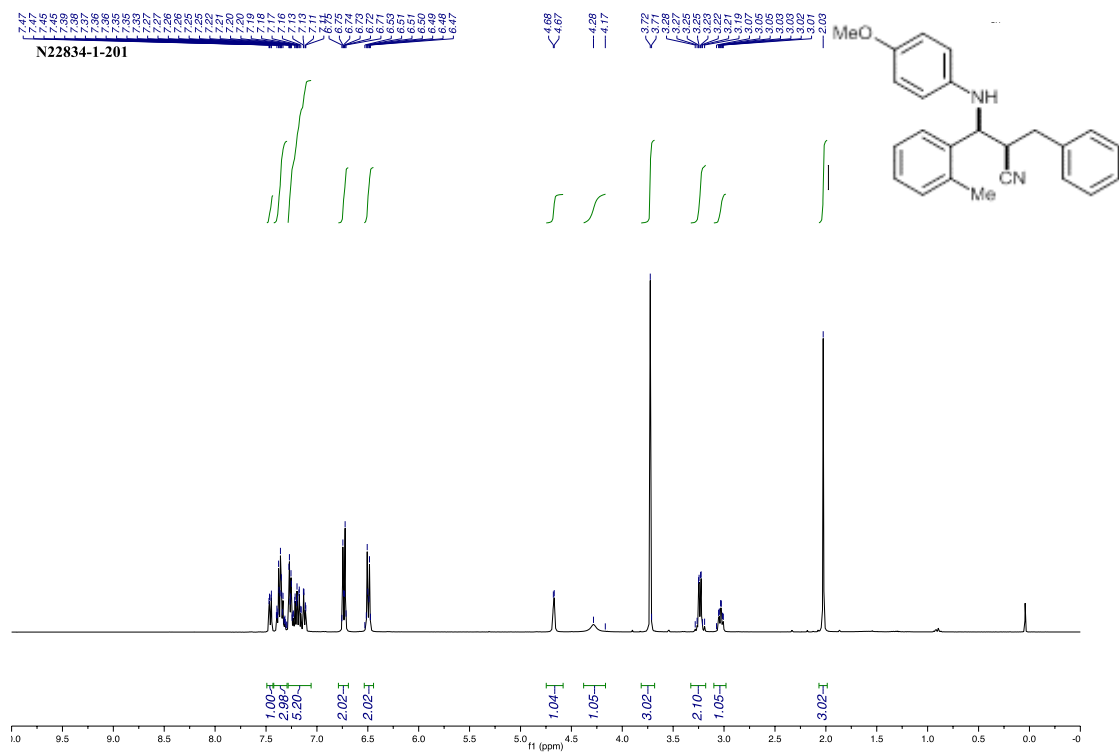
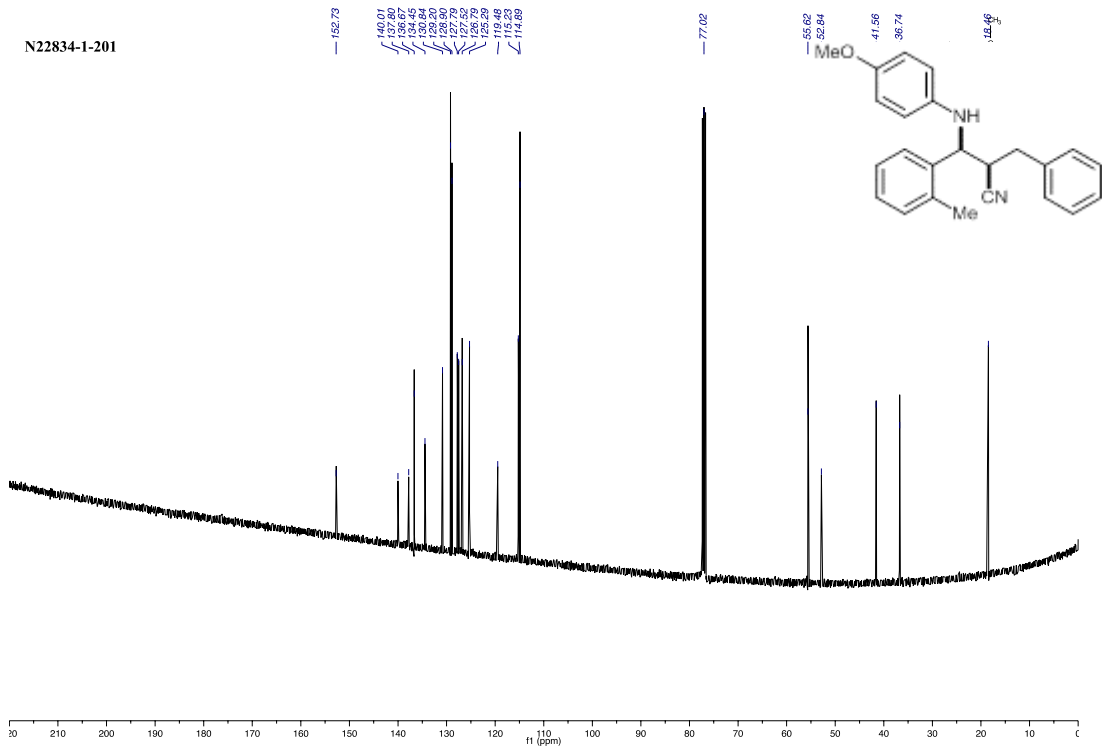


Table 2, Entry 6



N22834-1-201



N22834-1-201

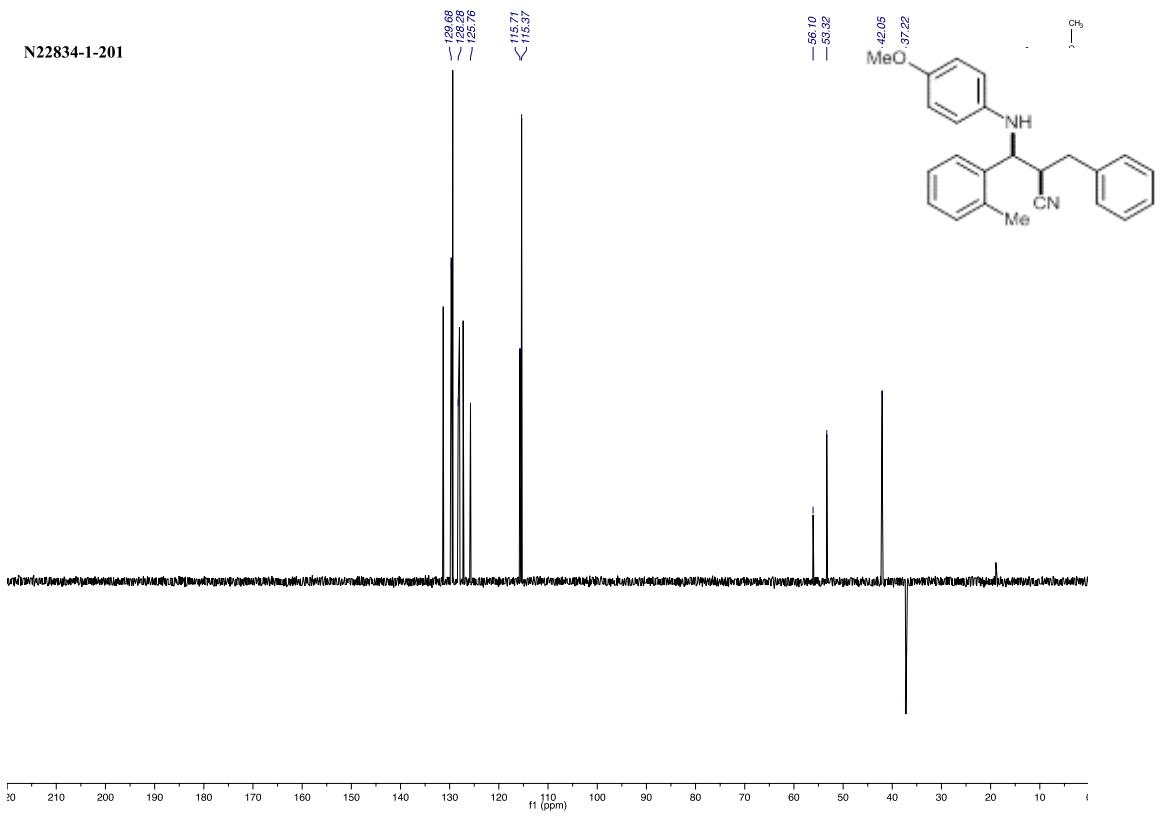
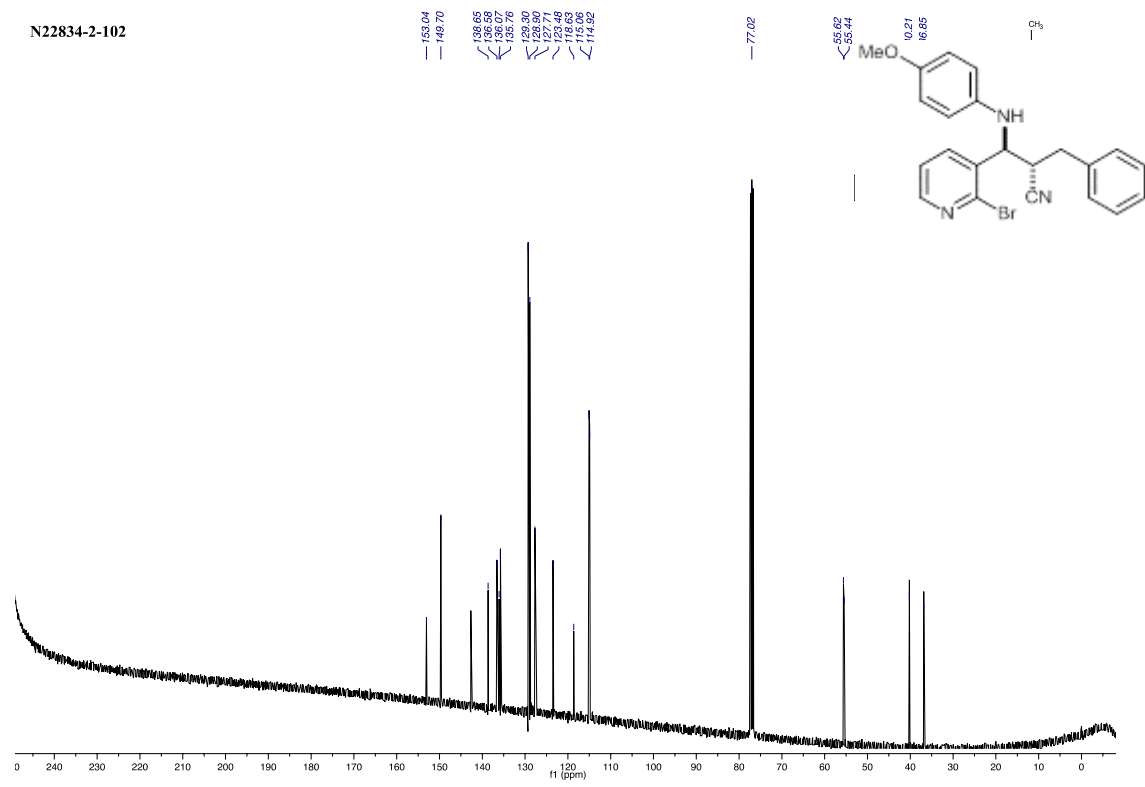
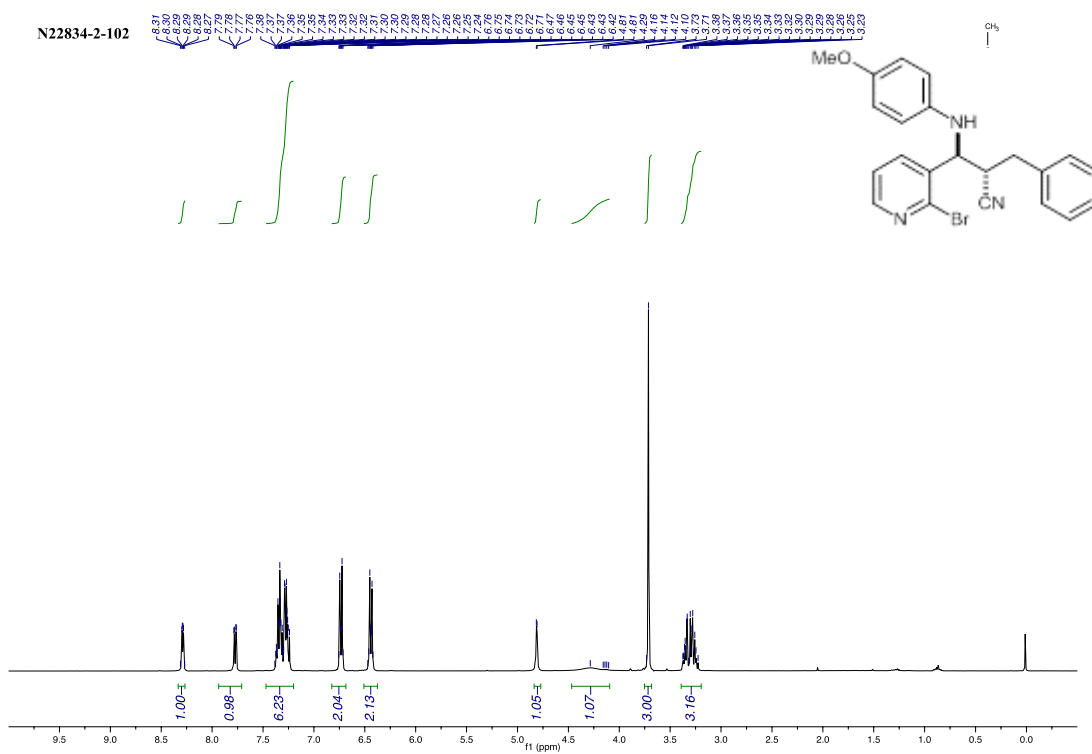


Table 2, Entry 7



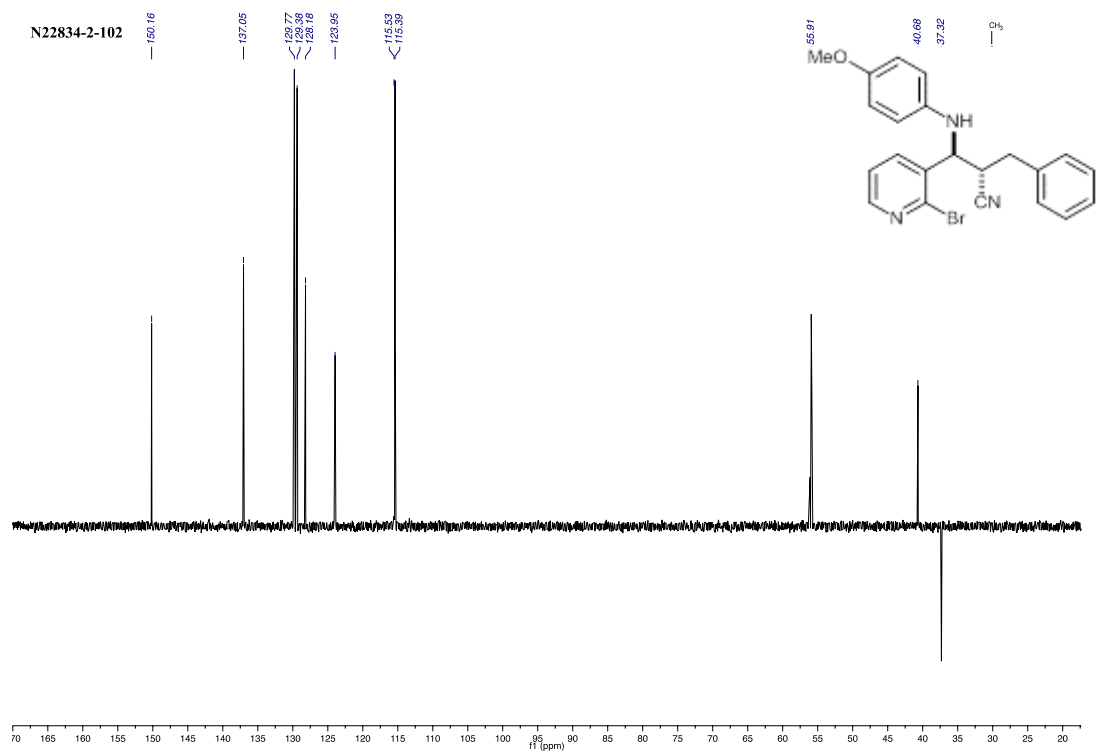
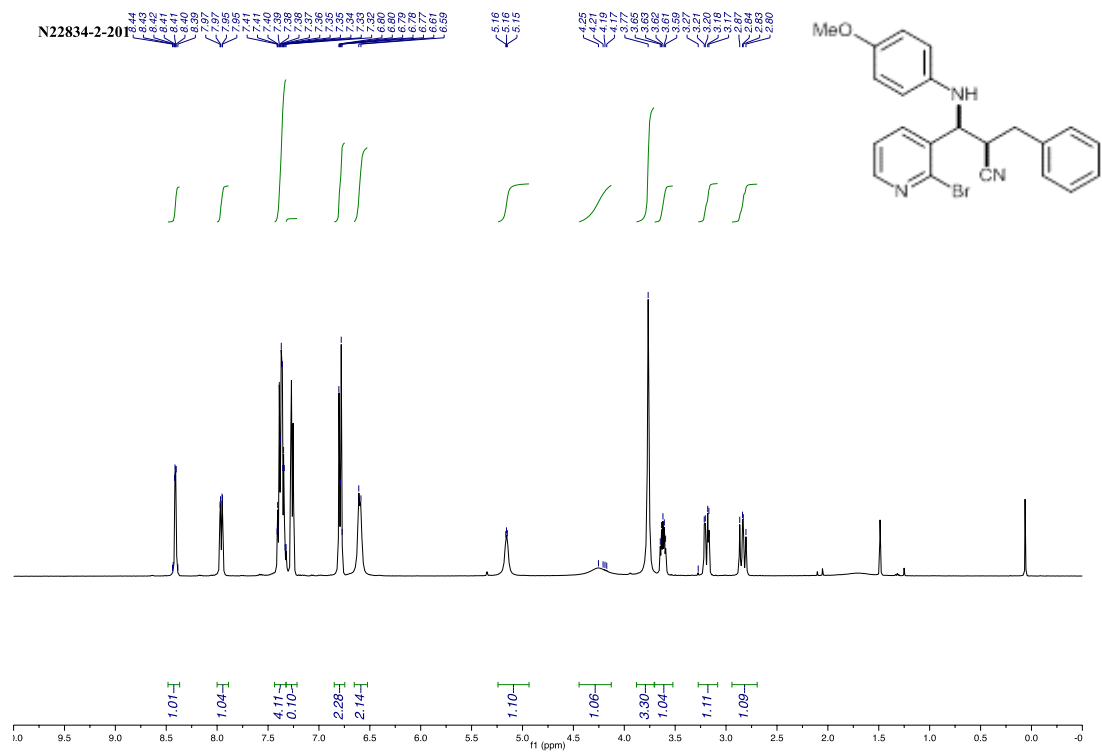
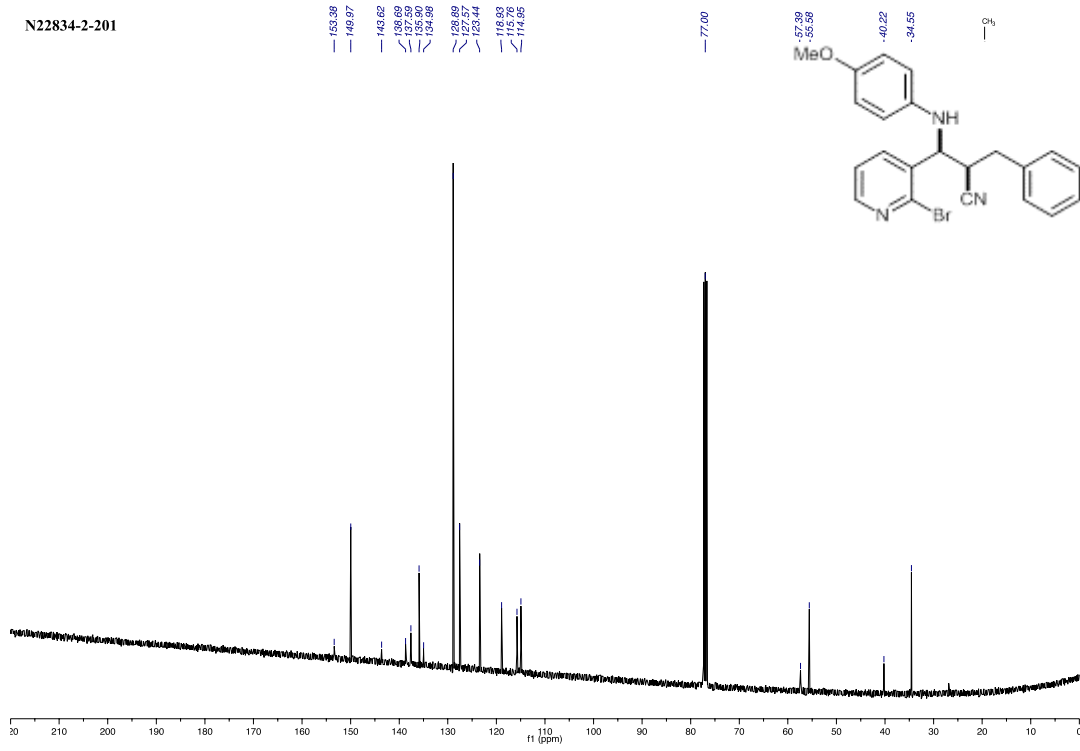


Table 2, Entry 9



N22834-2-201



N22834-2-201

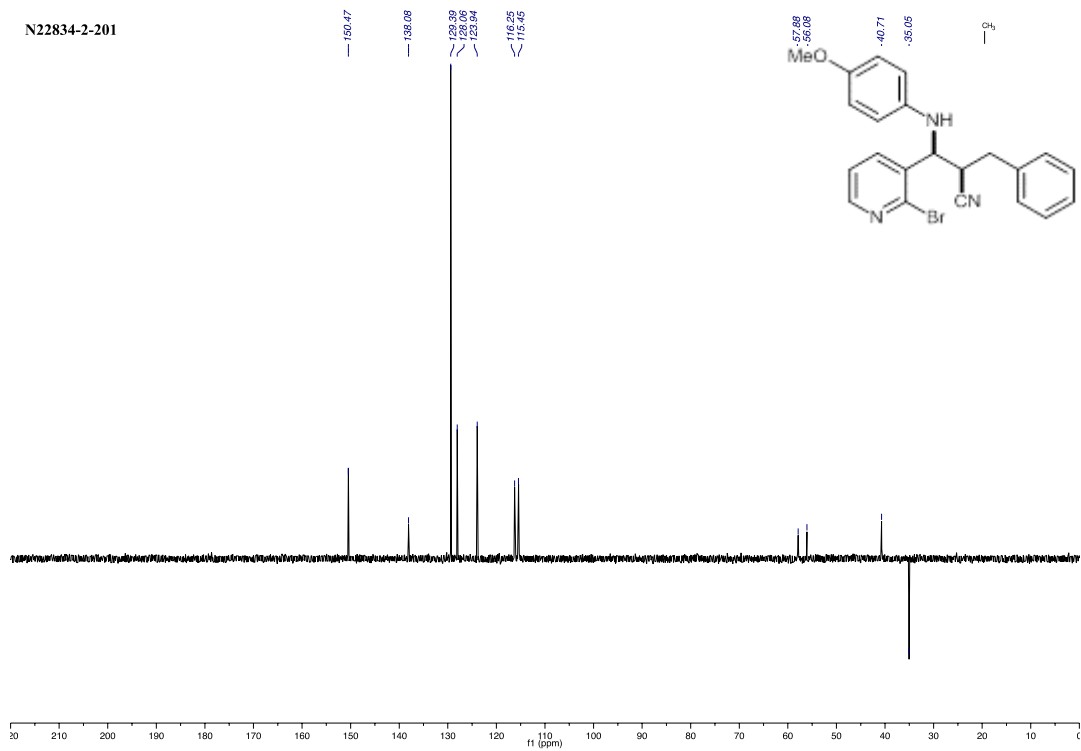
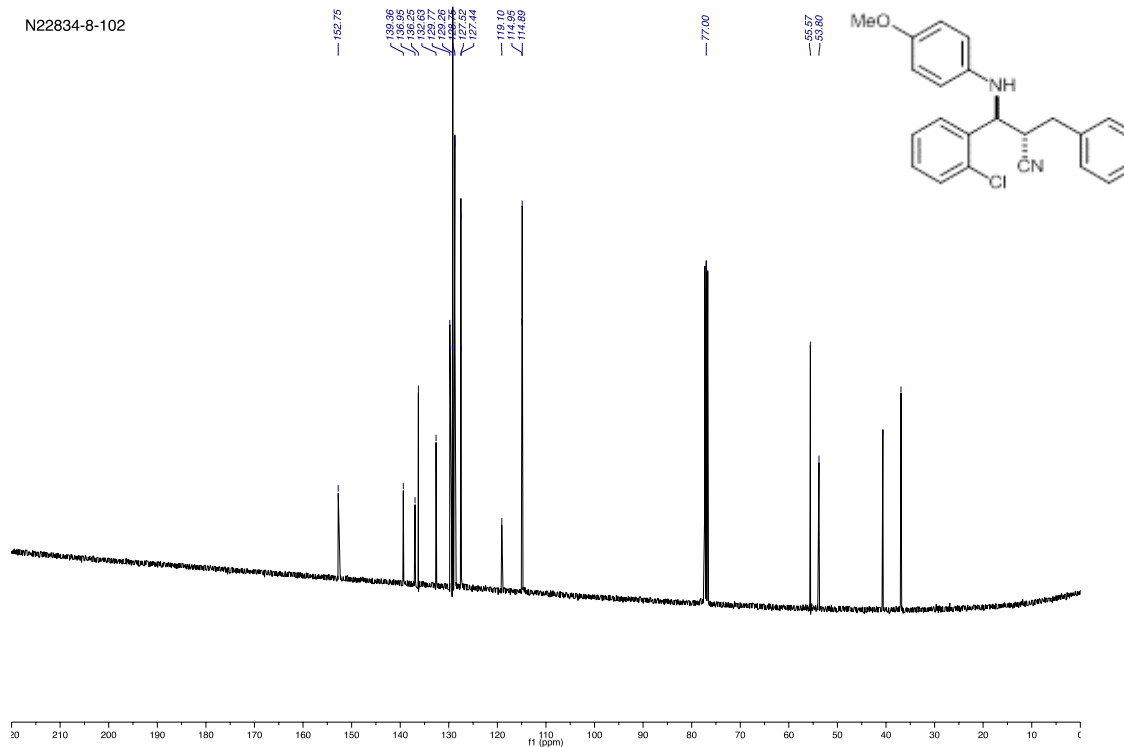
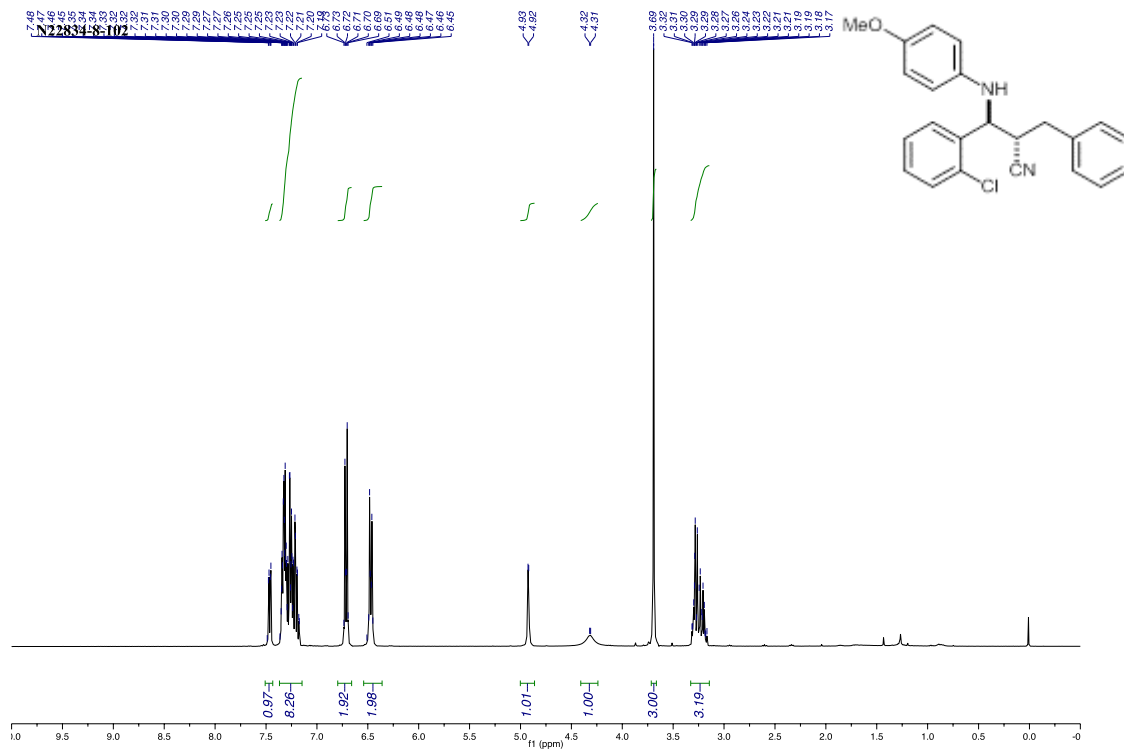


Table 2, Entry 10



N22834-8-102

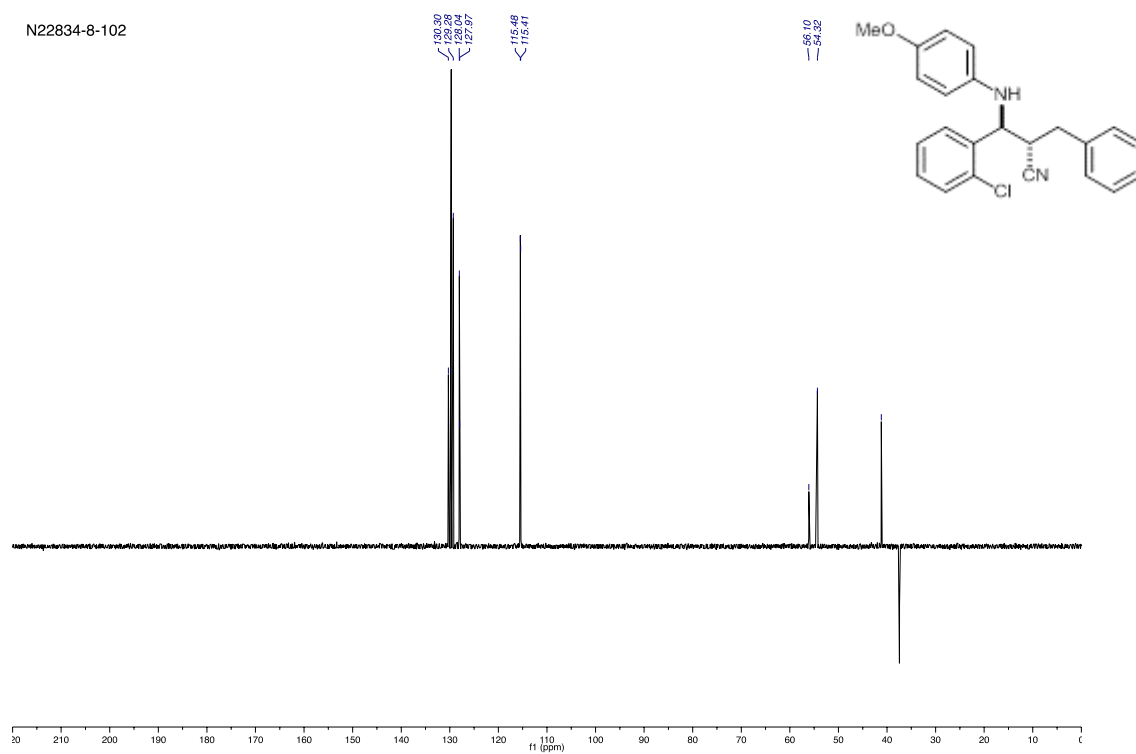
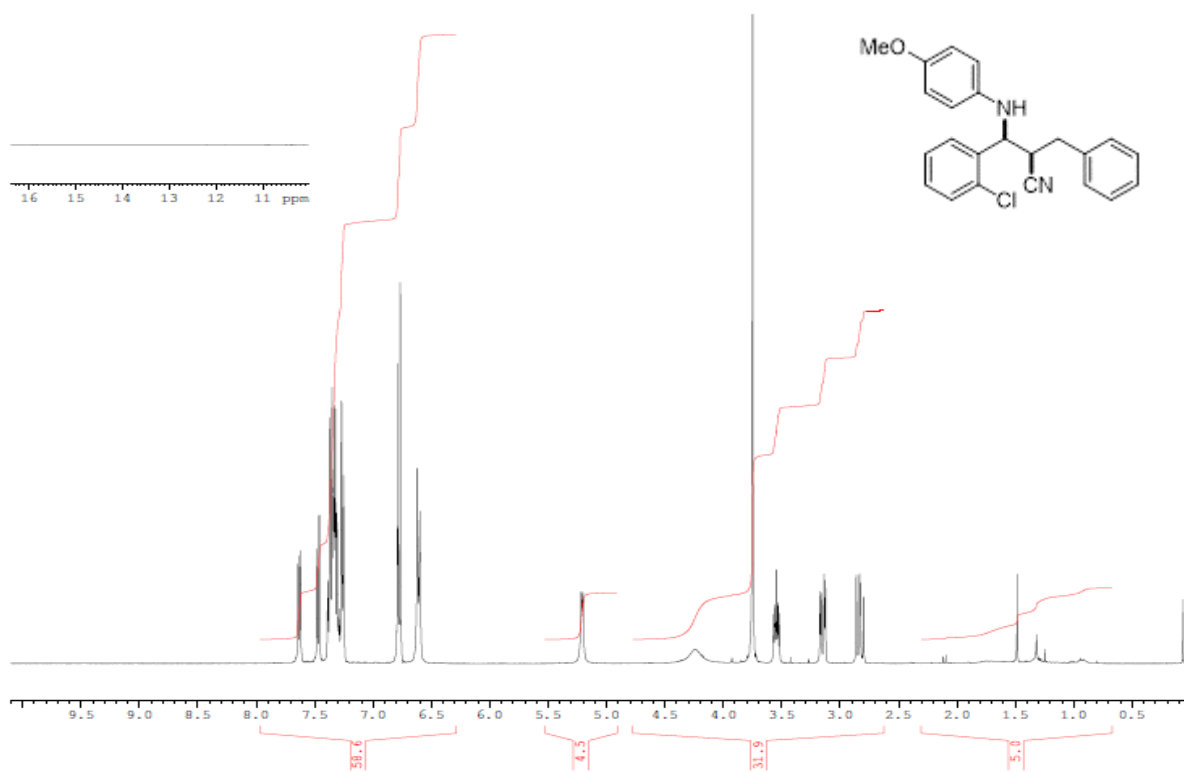


Table 2, Entry 11



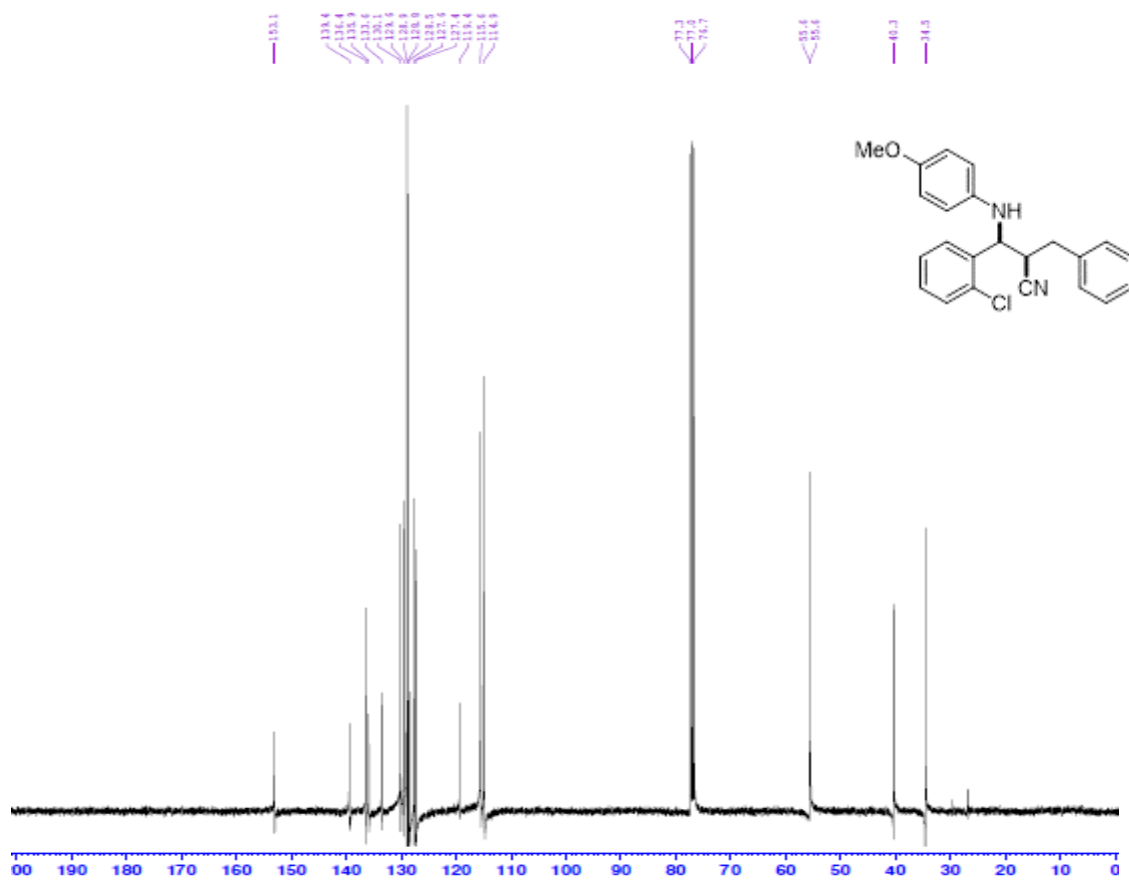
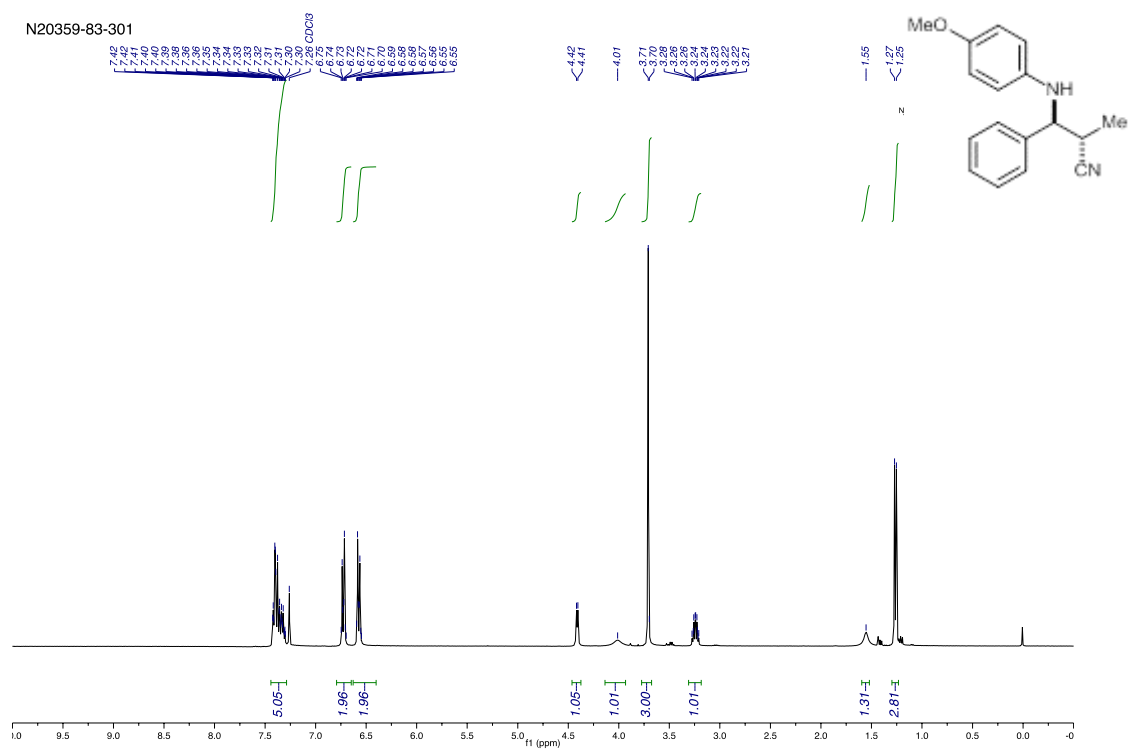
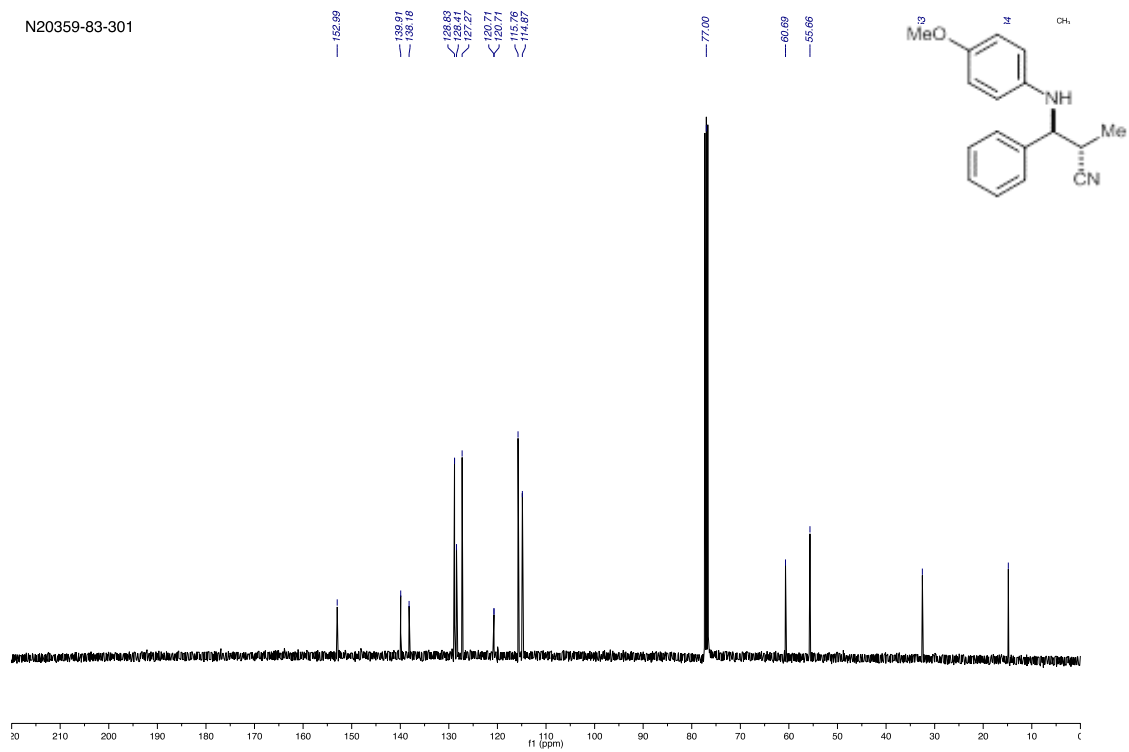


Table 2, Entry 12



N20359-83-301



N20359-83-301

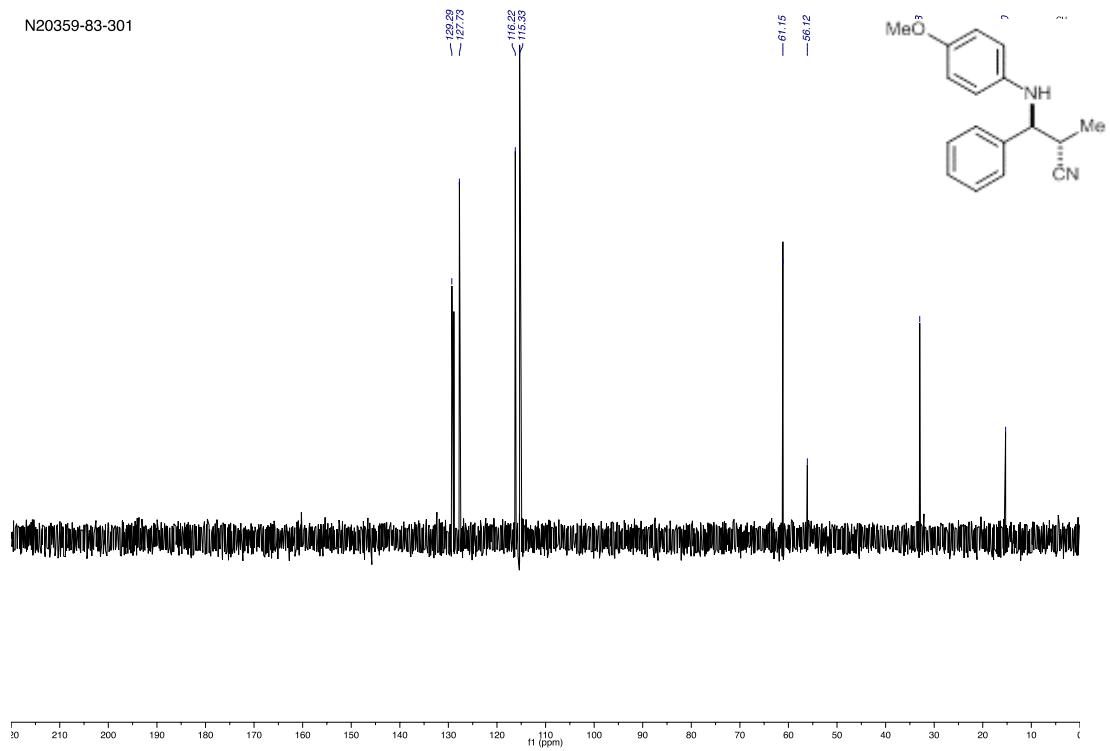
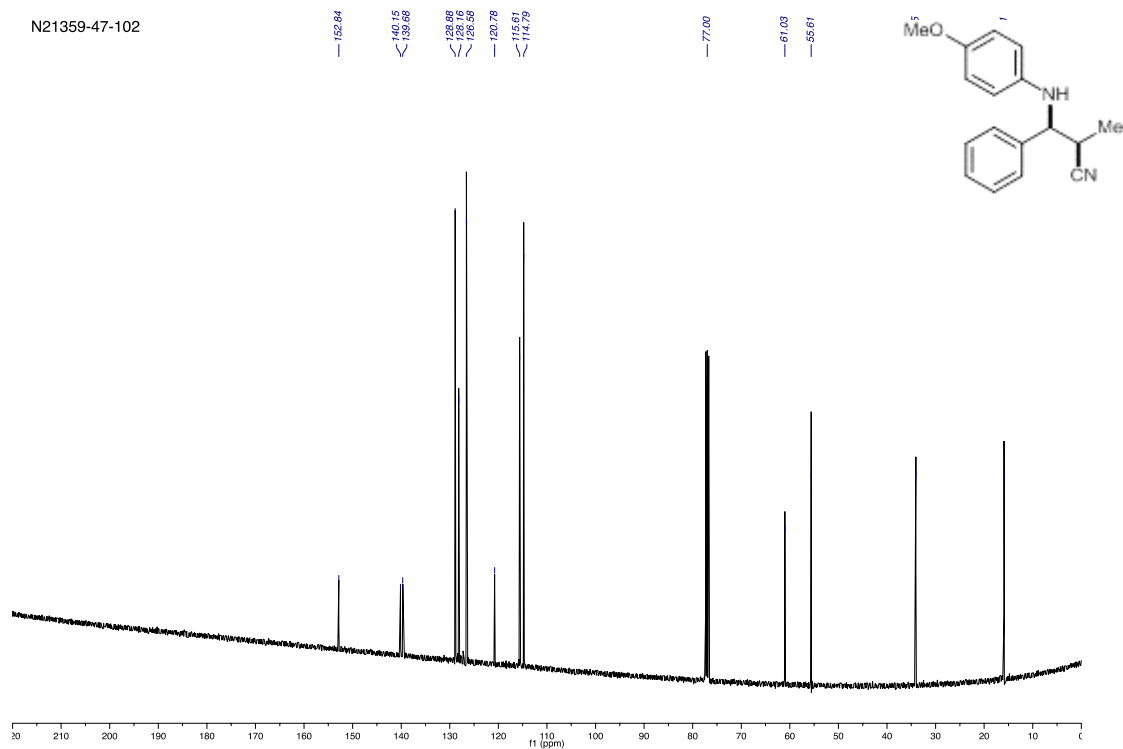
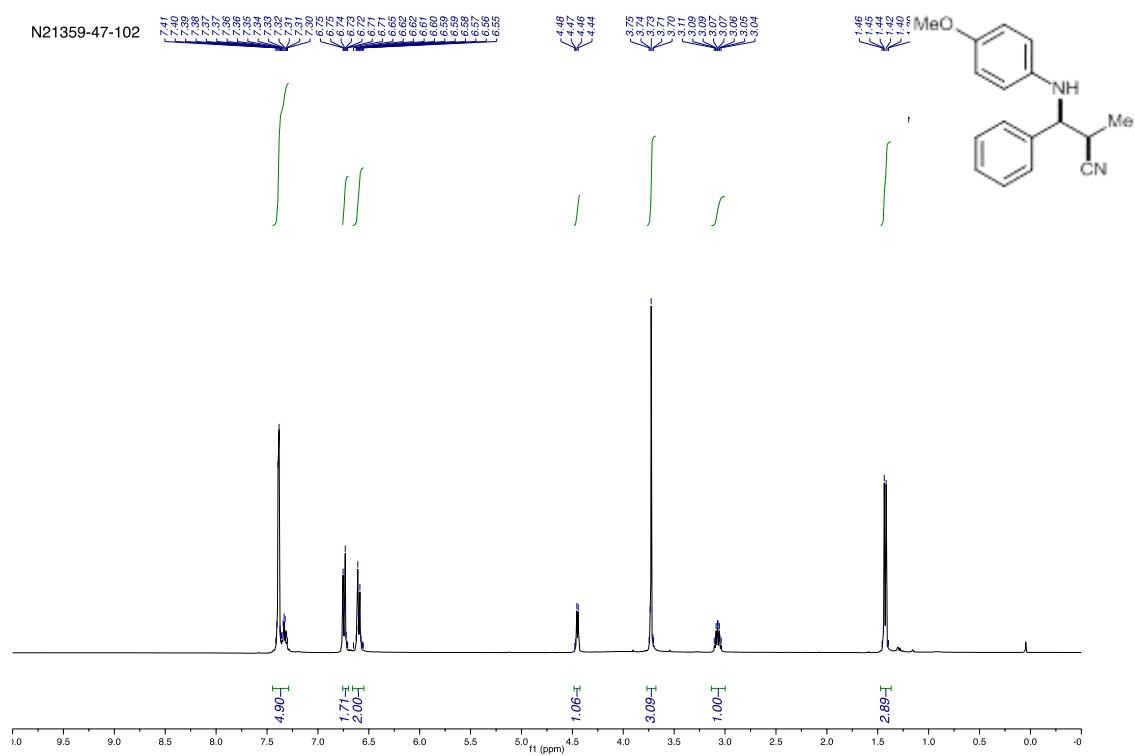


Table 2, Entry 13



N21359-47-102

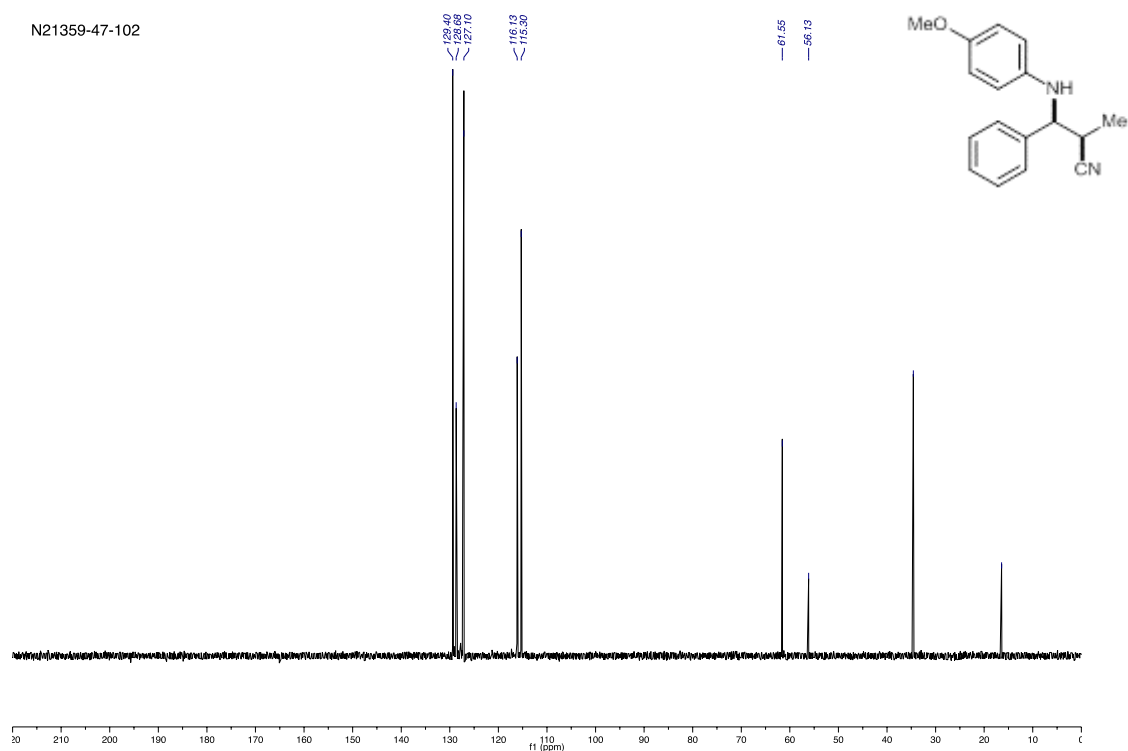
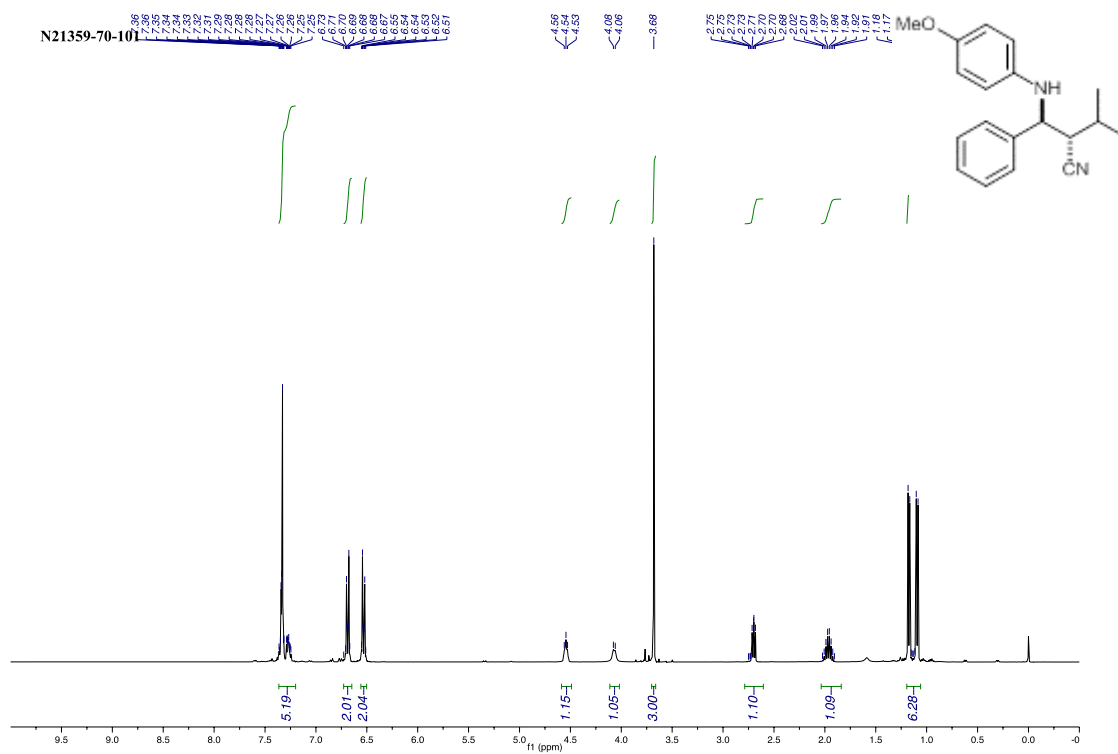
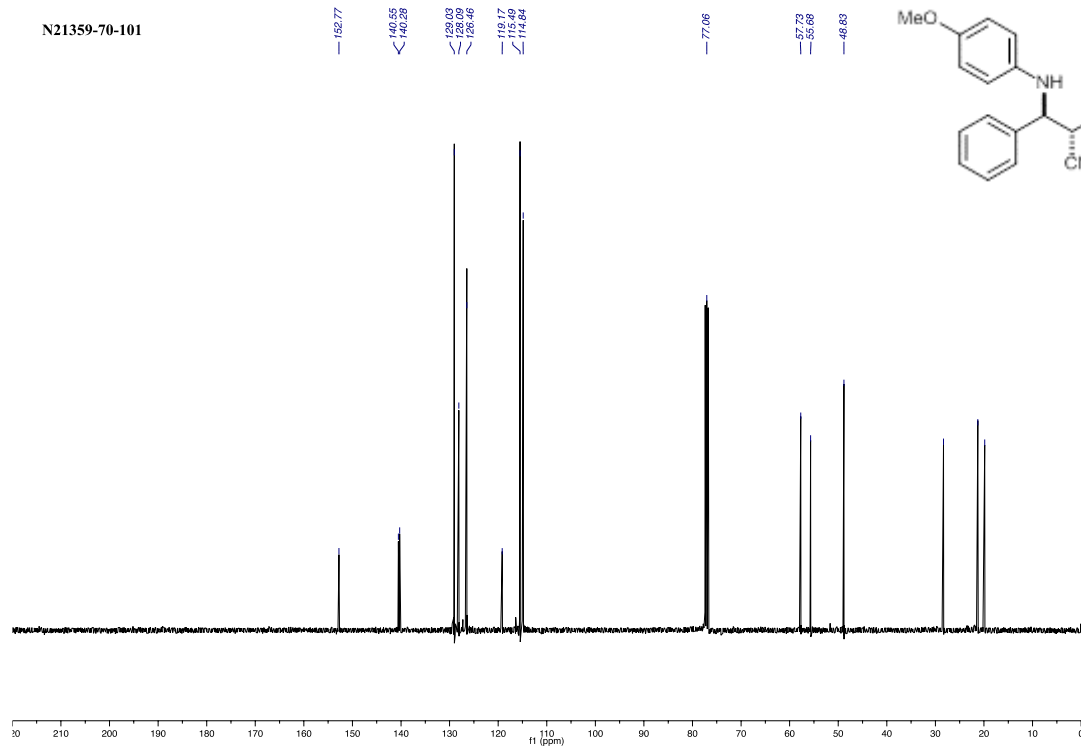


Table 2, Entry 14



N21359-70-101



N21359-70-101

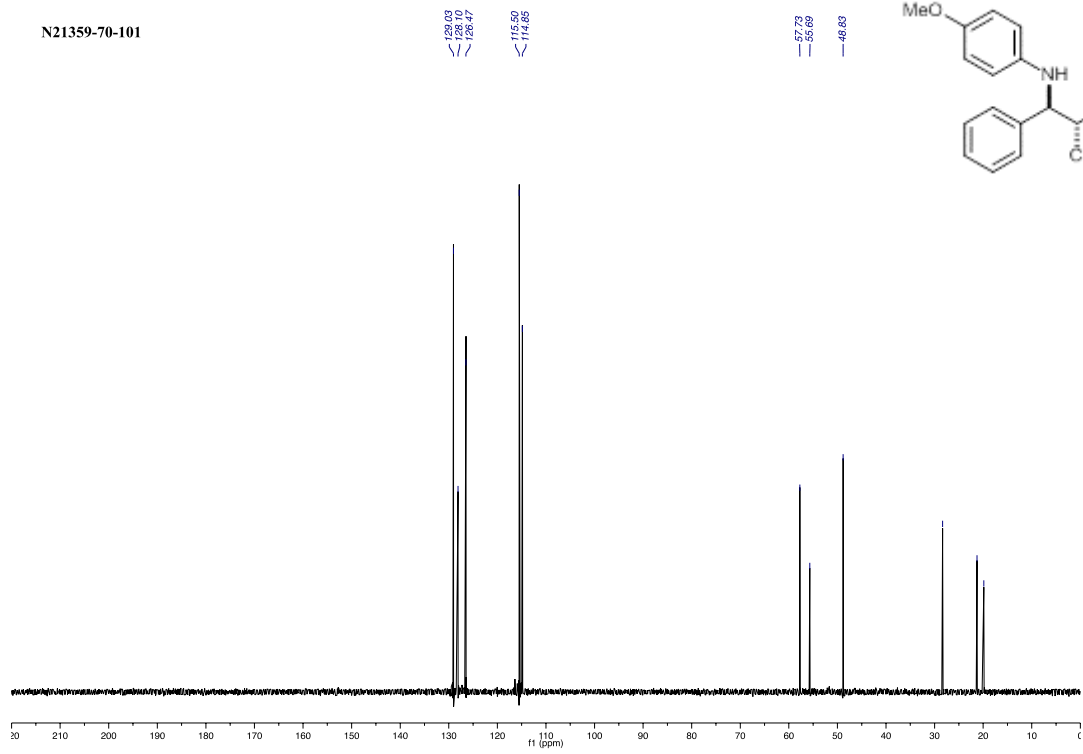
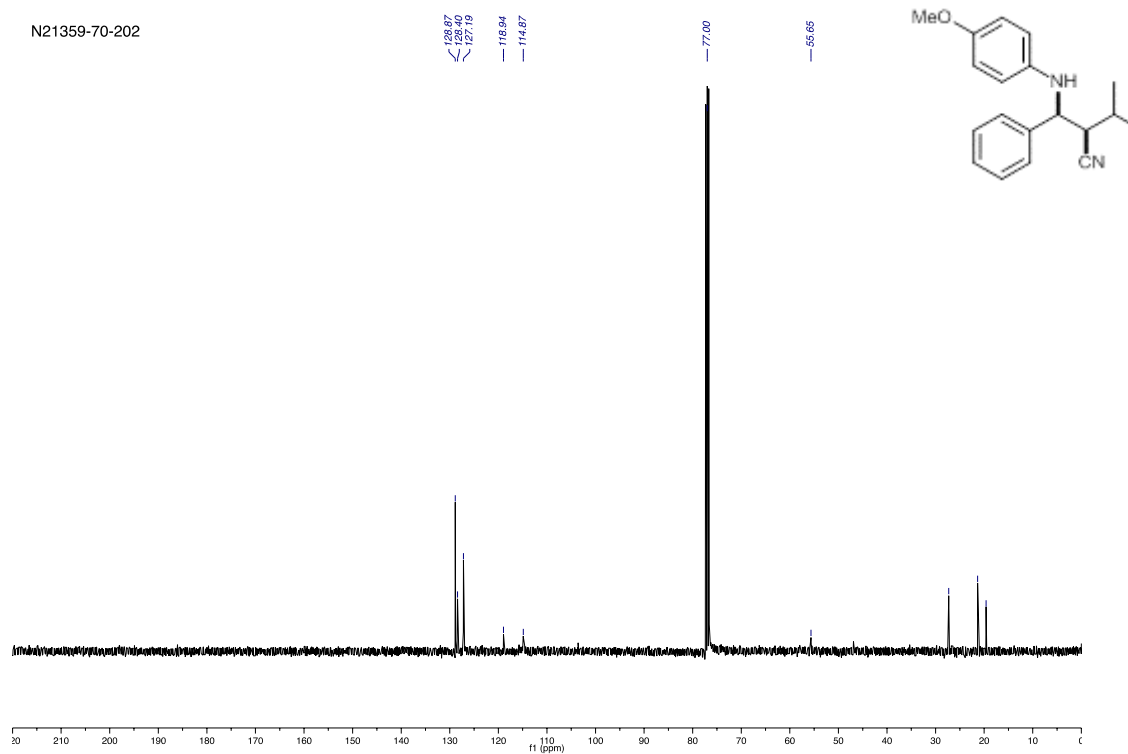
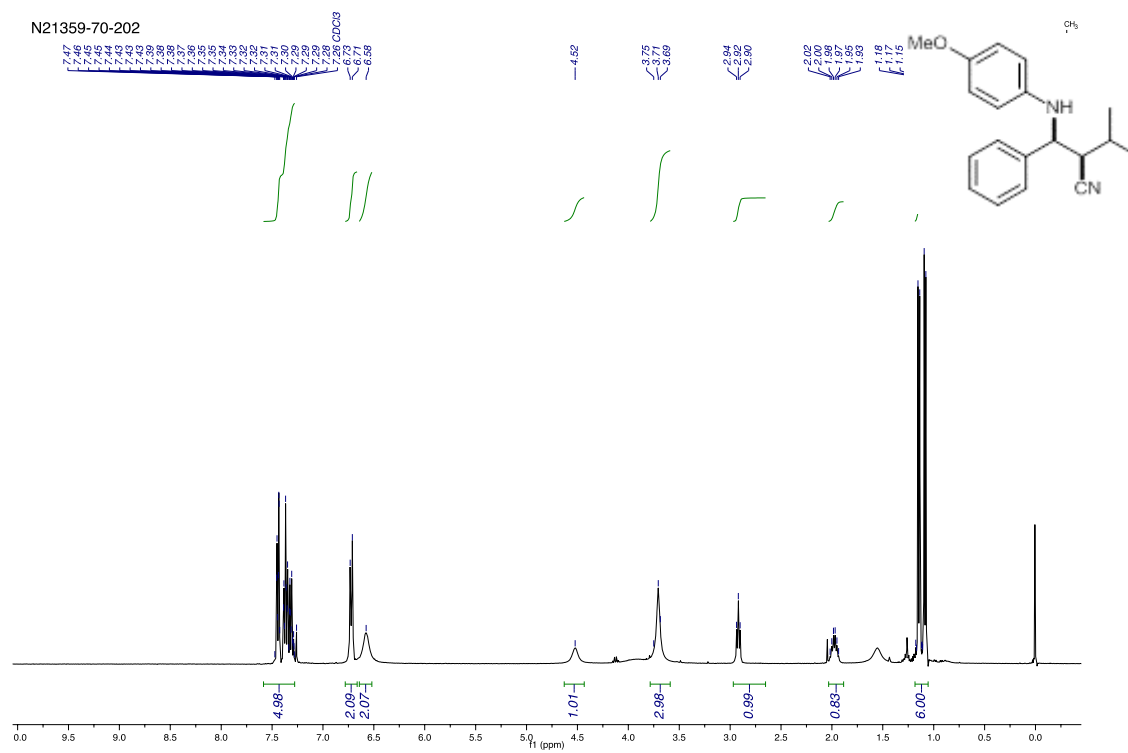


Table 2, Entry 15



N21359-70-202

128.90
127.25

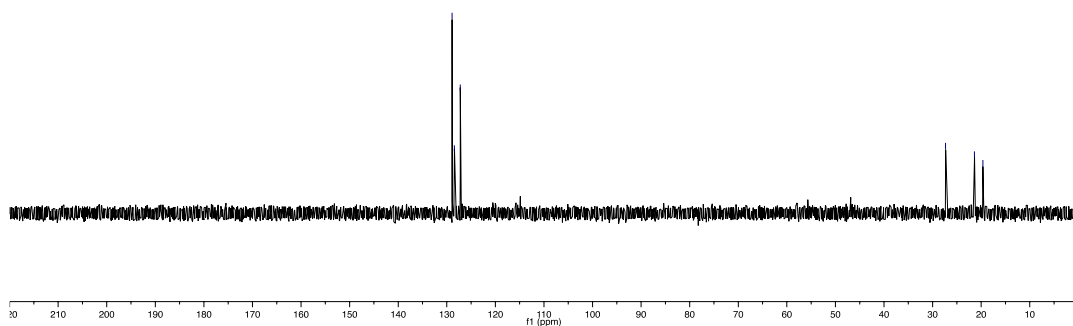
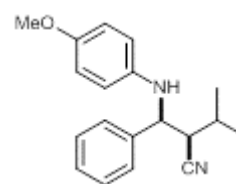
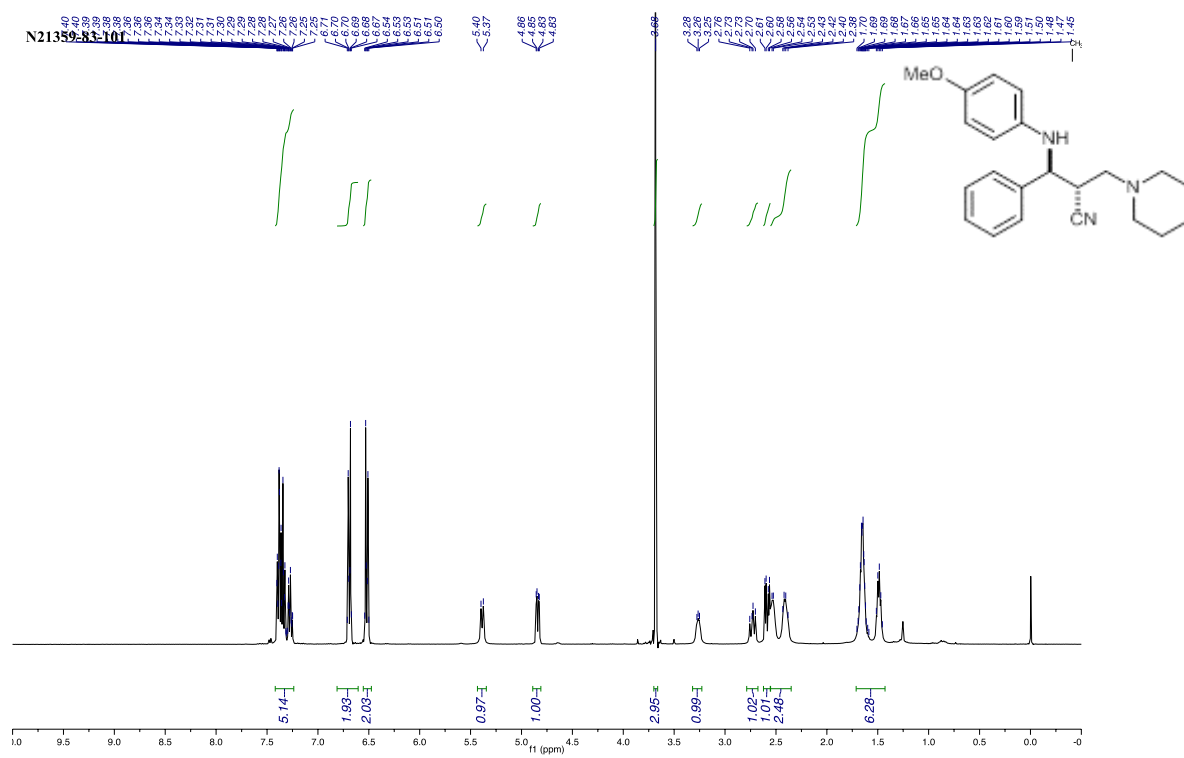
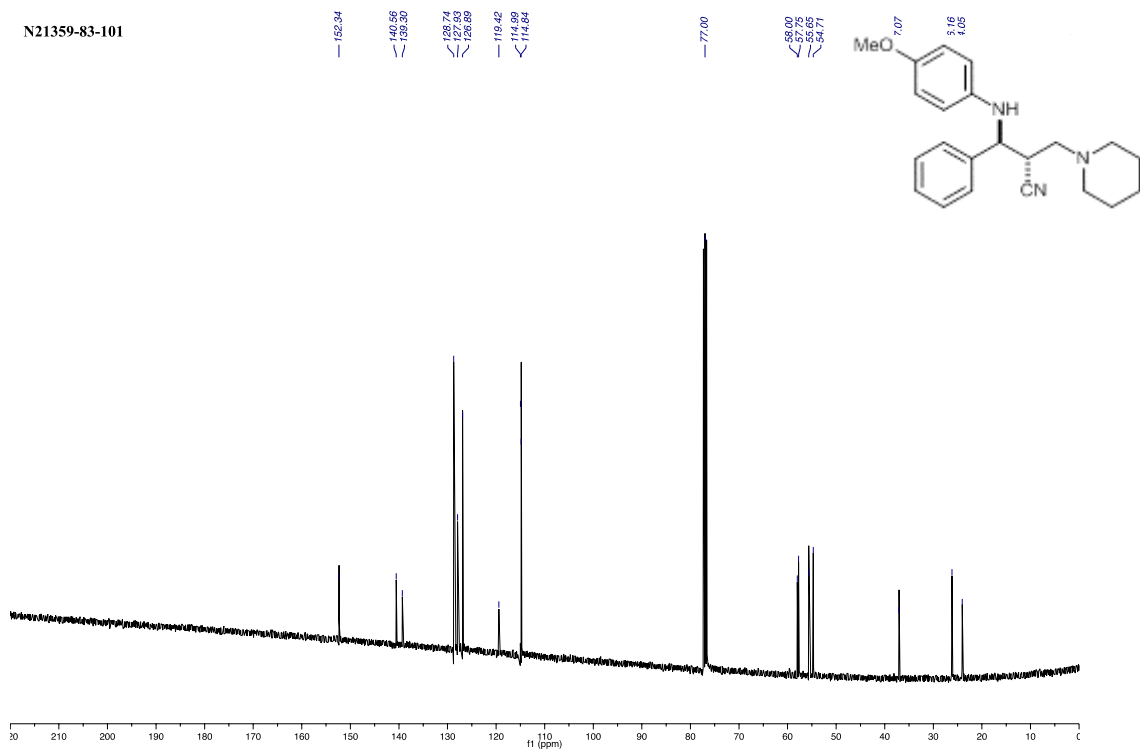


Table 2, Entry 16



N21359-83-101



N21359-83-101

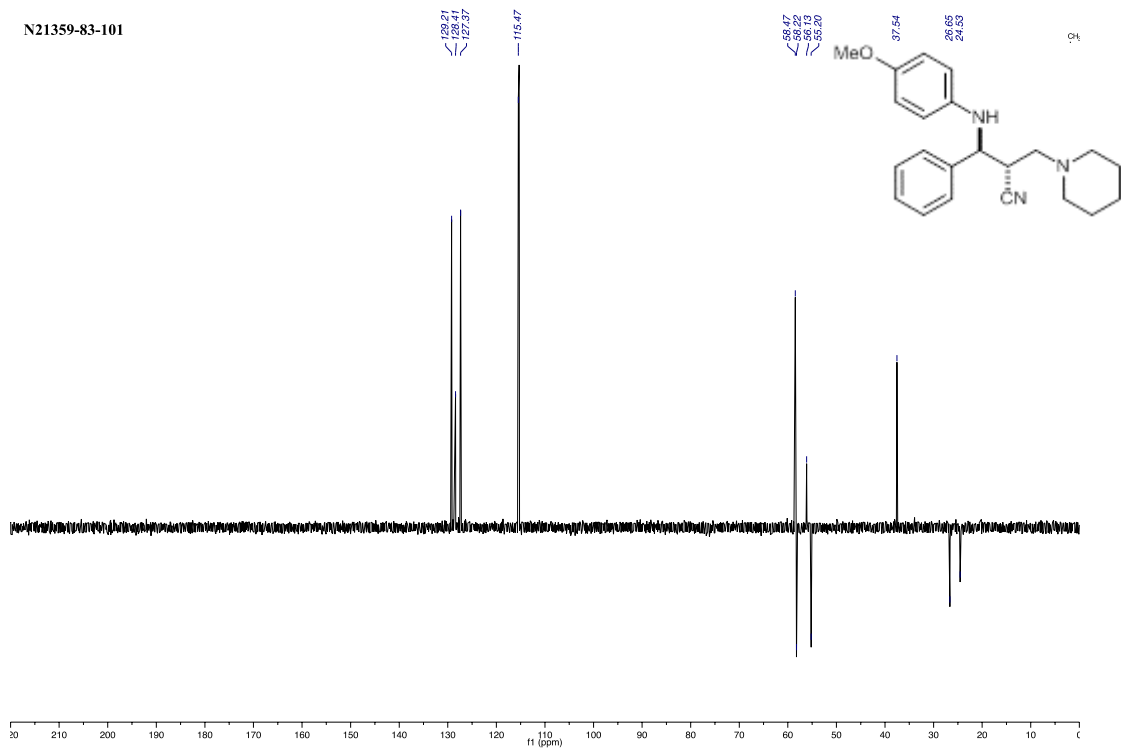
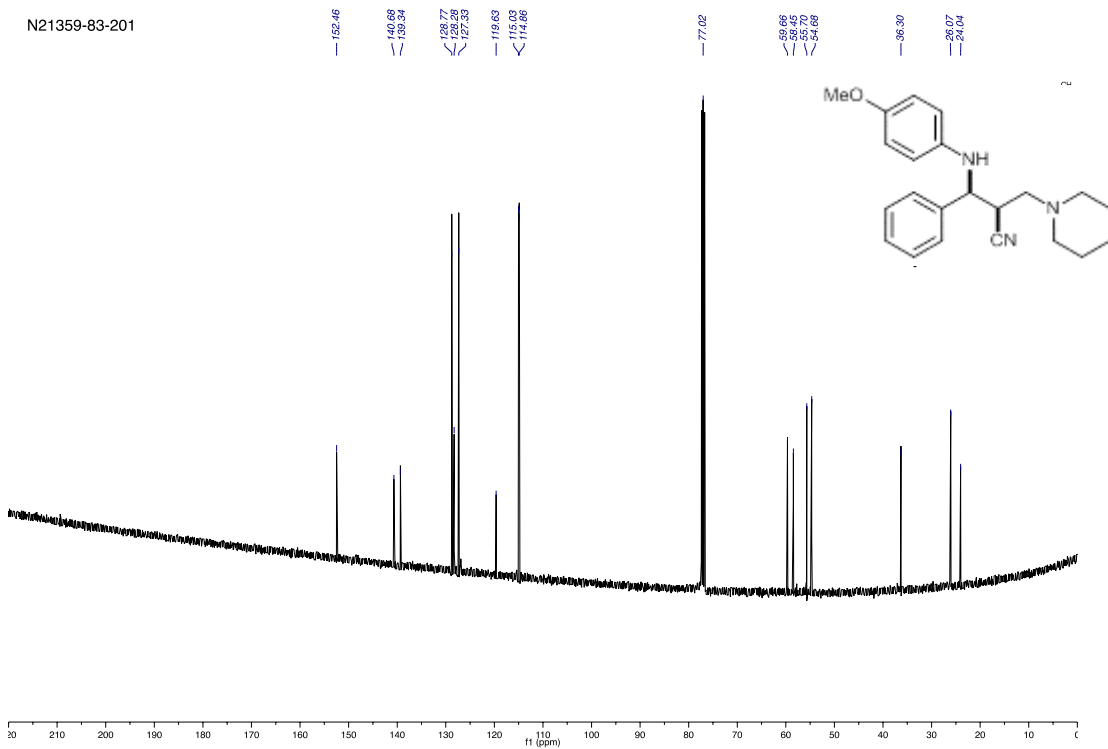
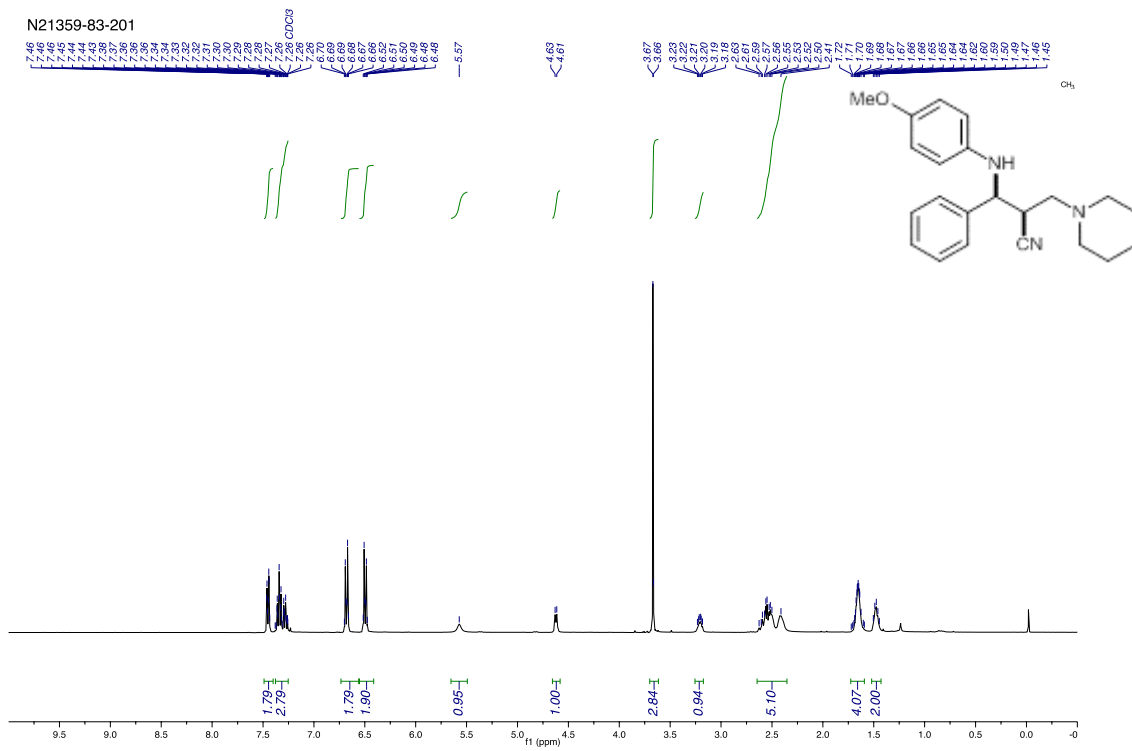


Table 2, Entry 17



N21359-83-201

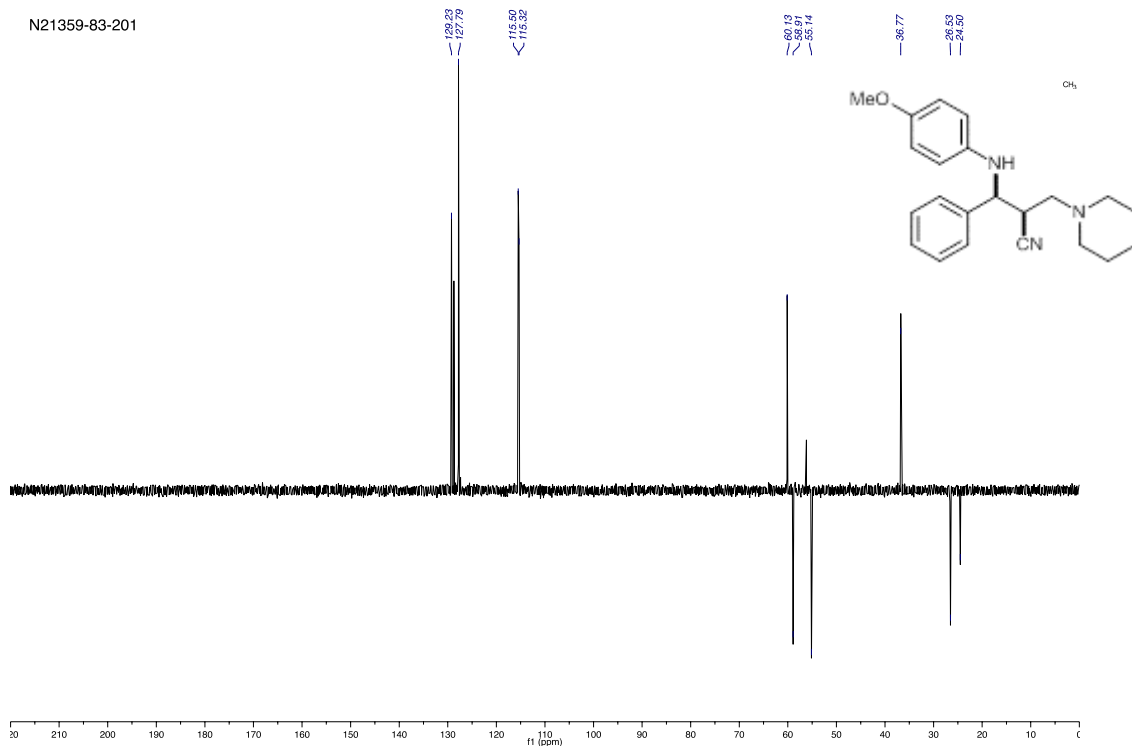
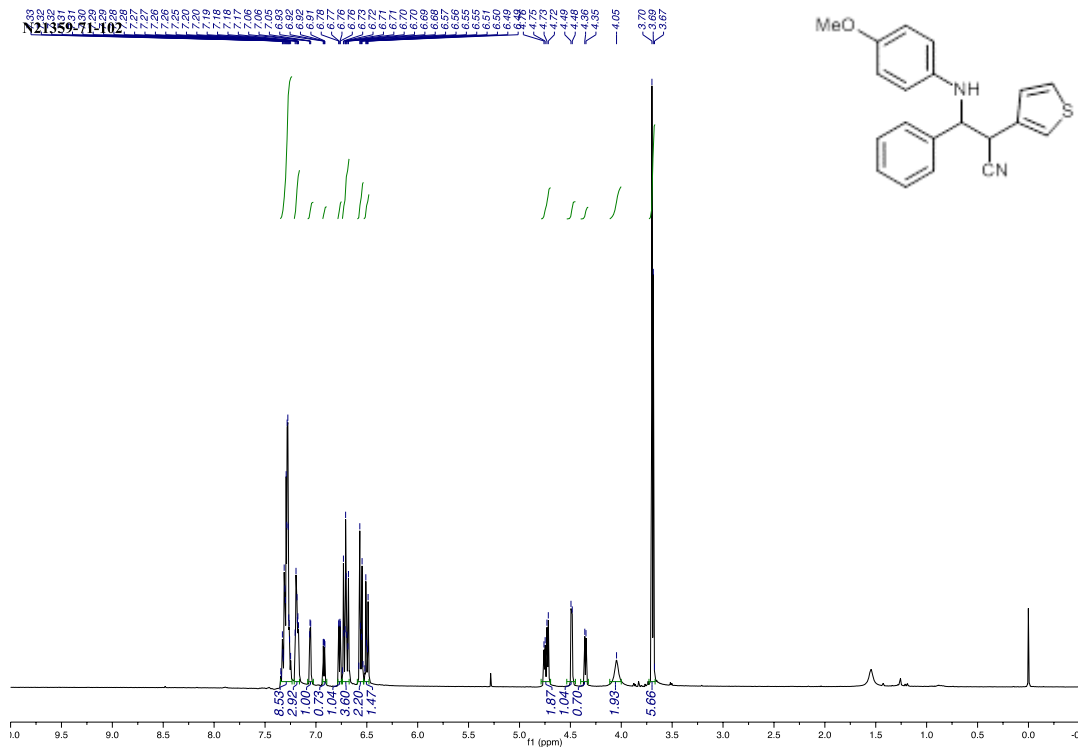
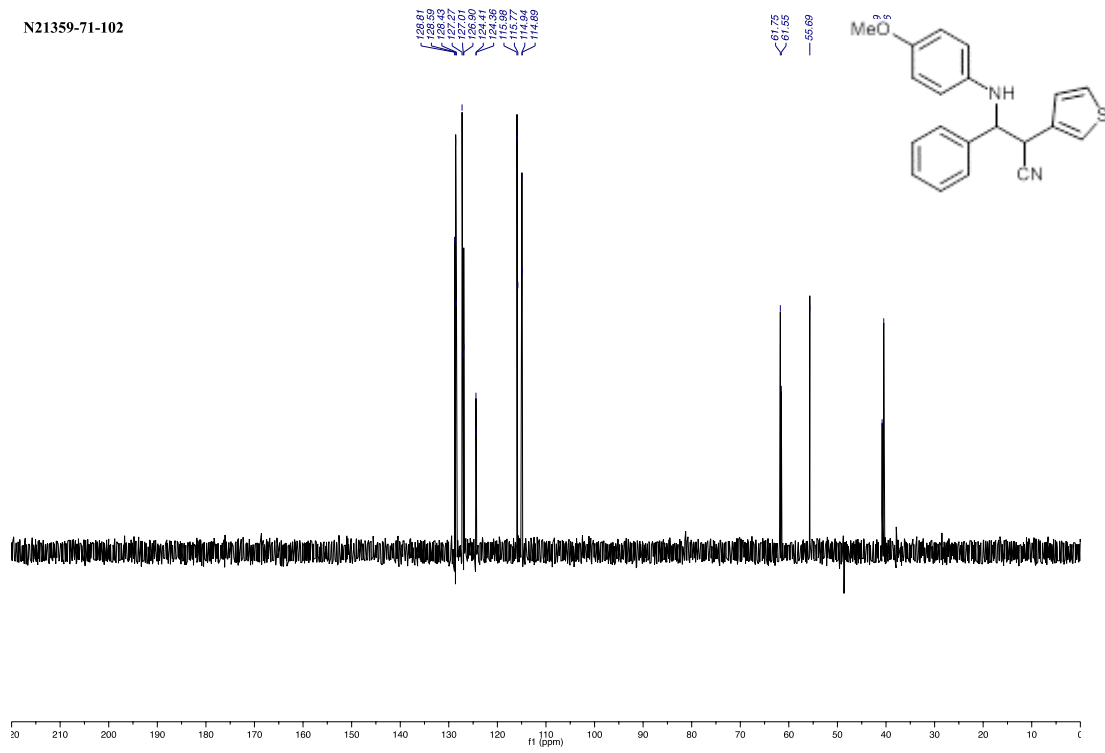


Table 2, Entry 19



N21359-71-102



N21359-71-102

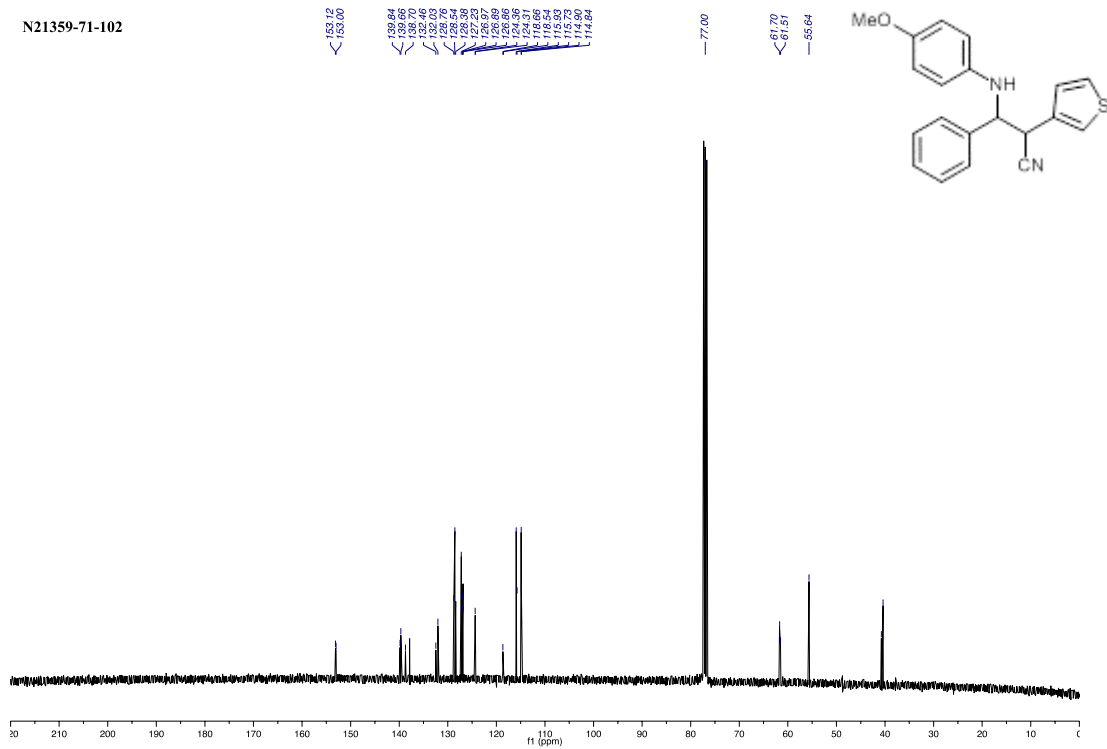
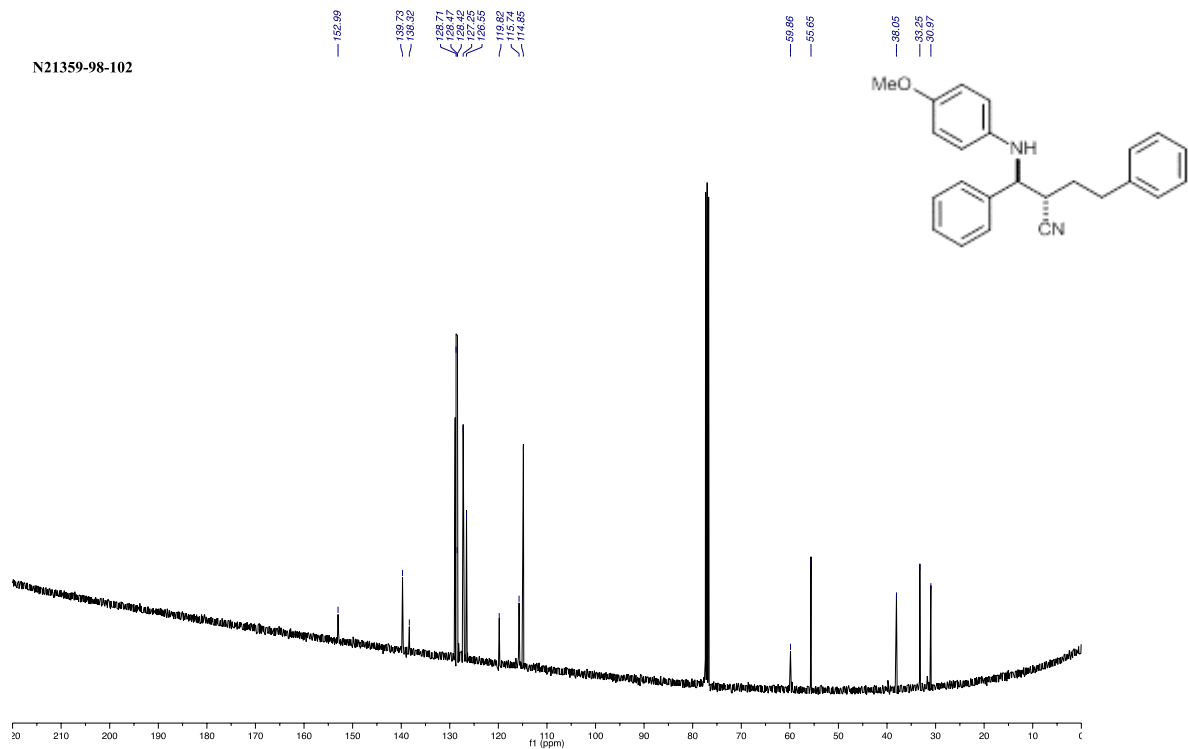
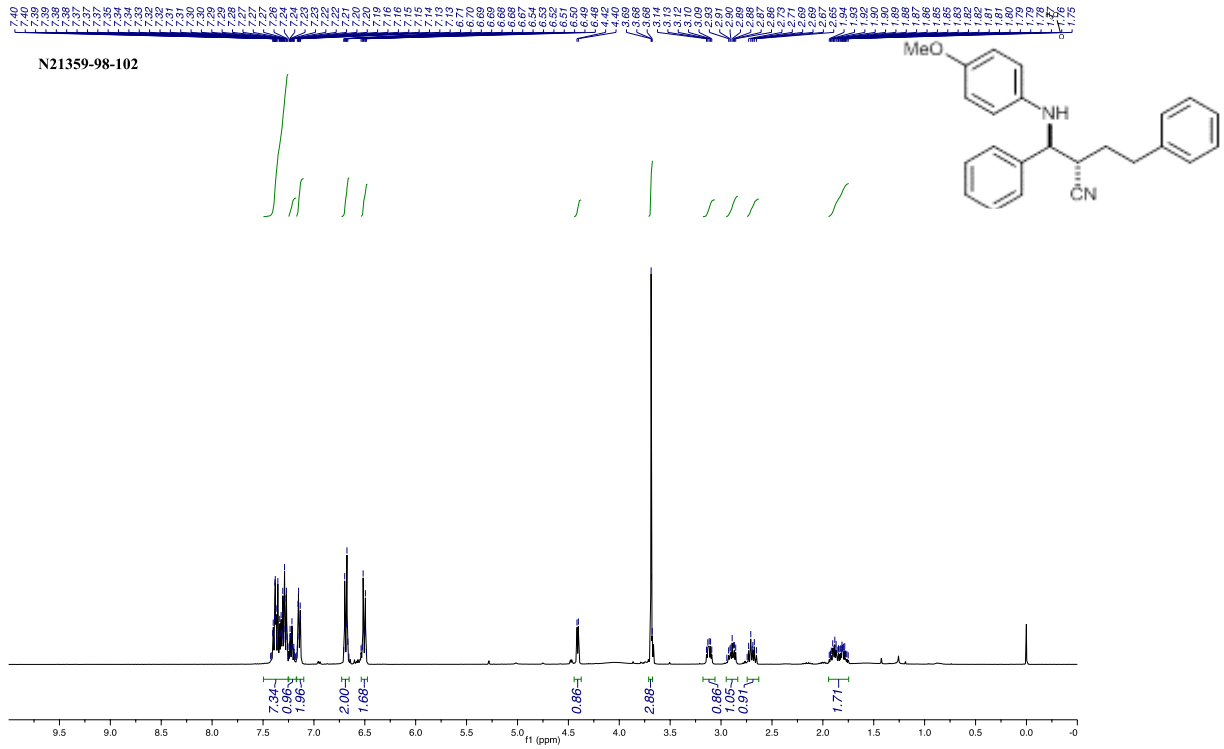


Table 2, Entry 20



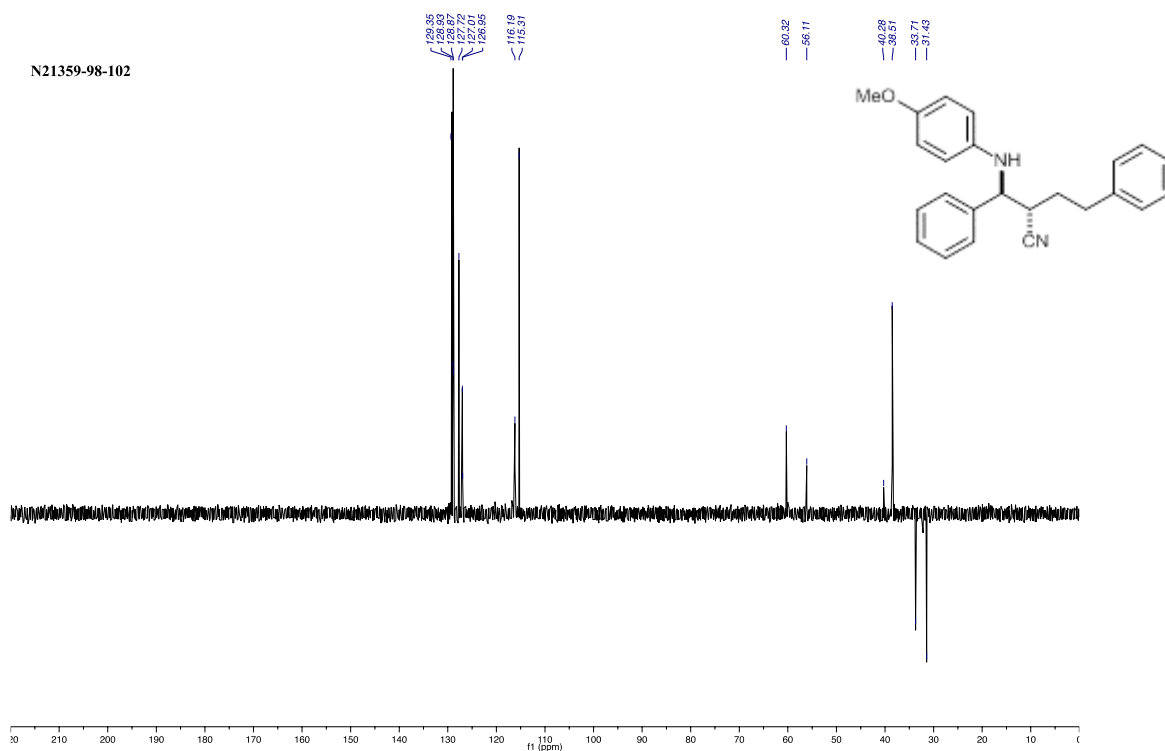
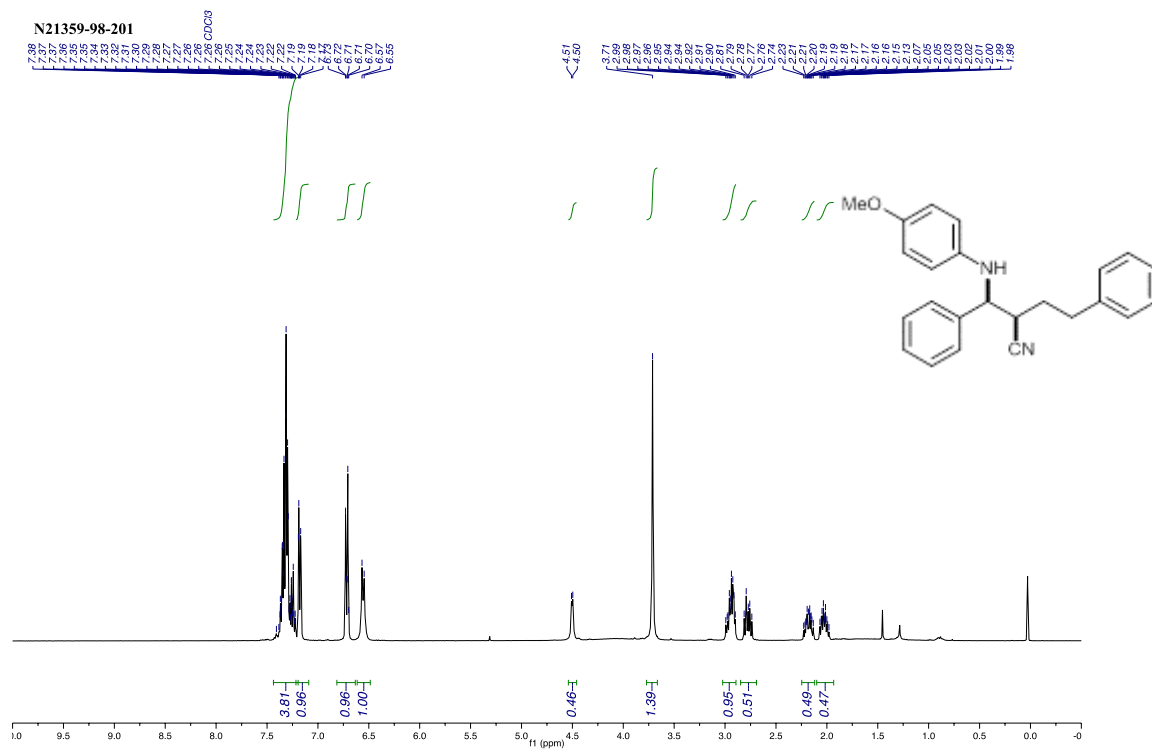
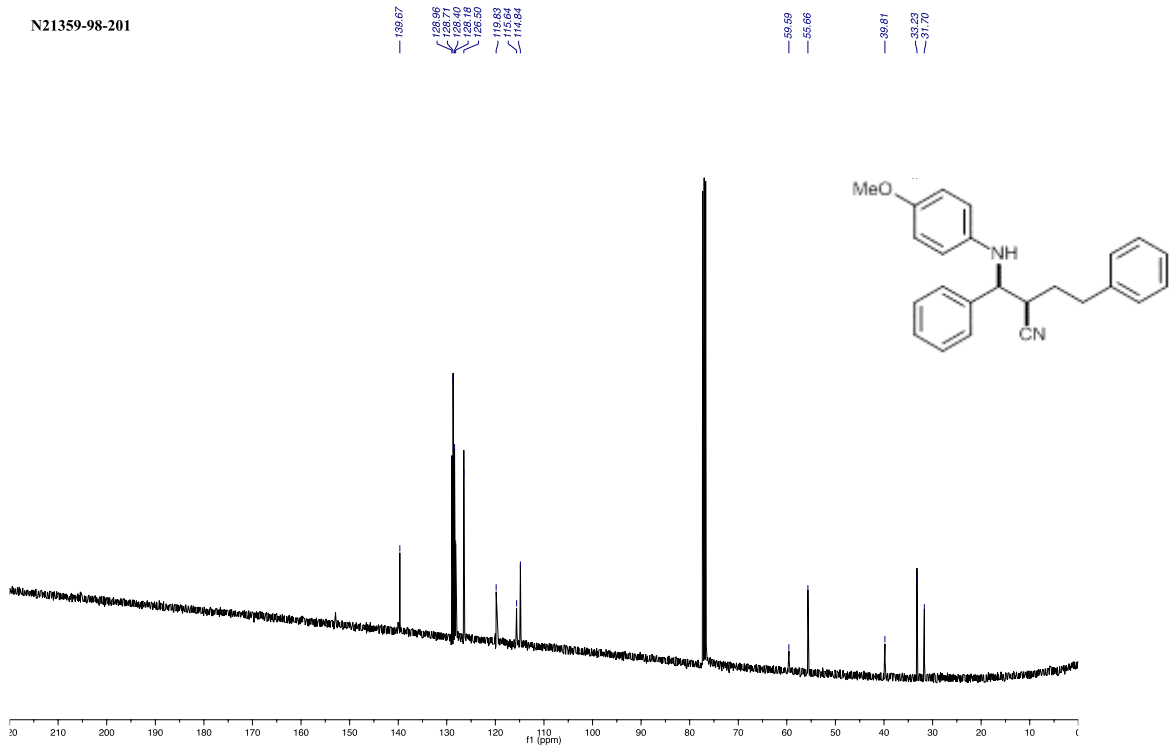


Table 2, Entry 21



N21359-98-201



N21359-98-201

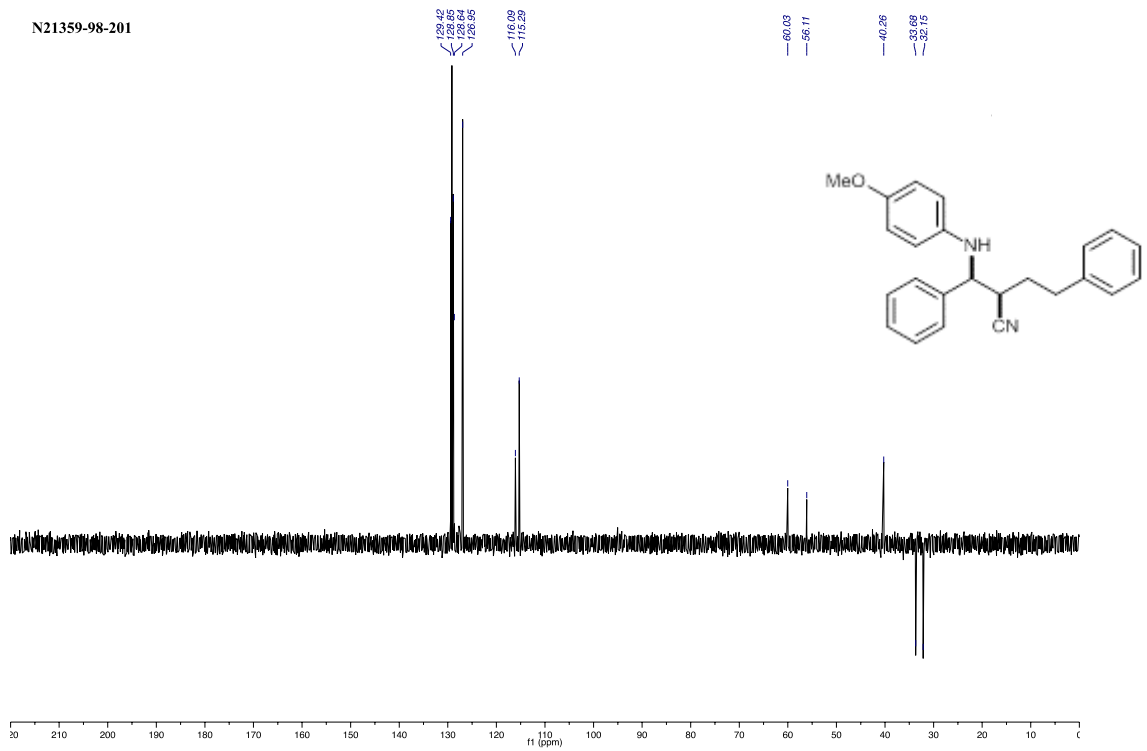


Table 2, Entry 22

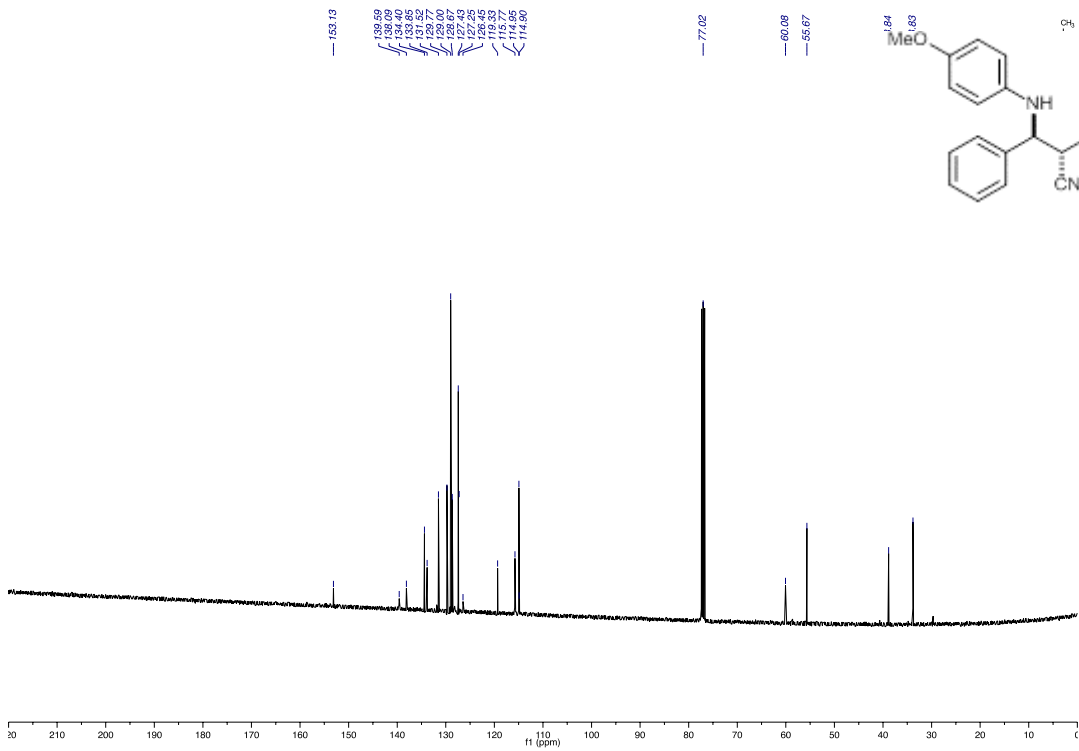
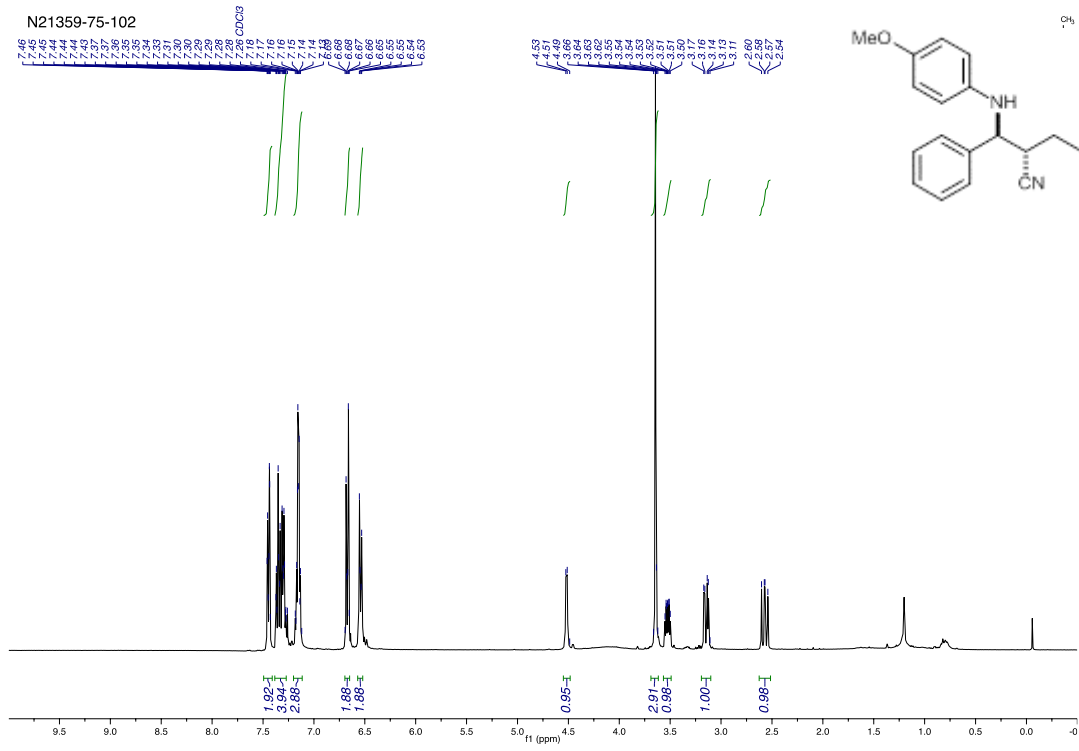
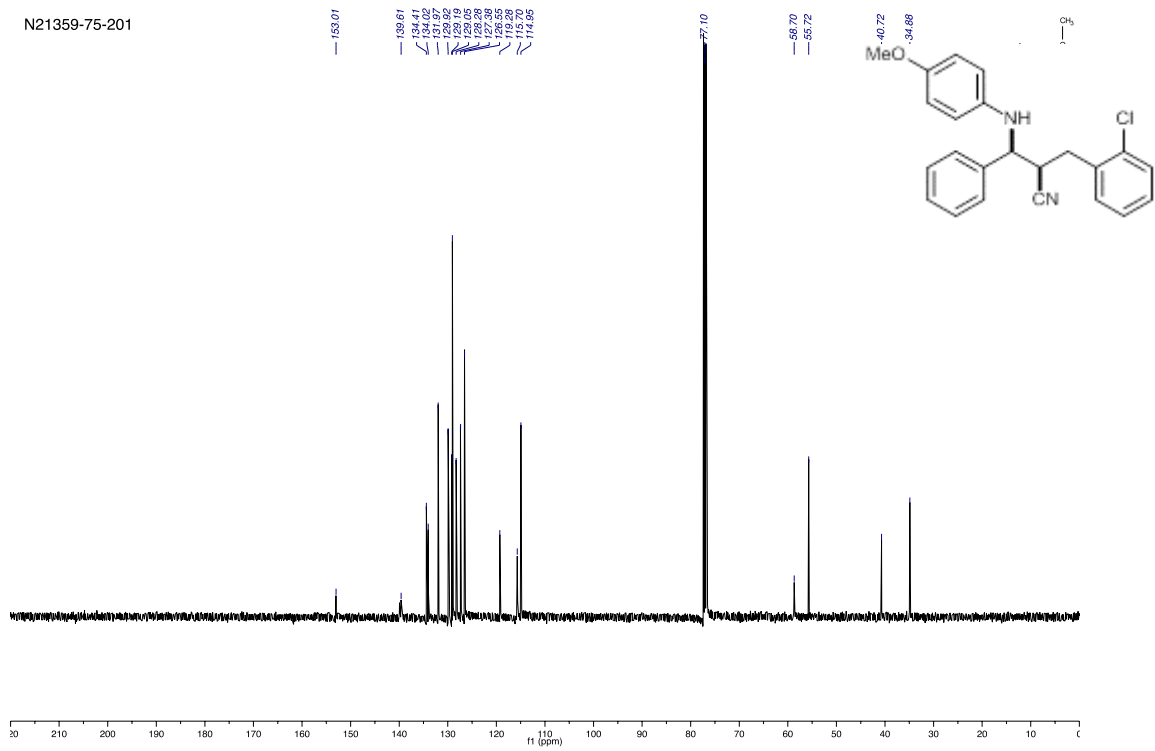
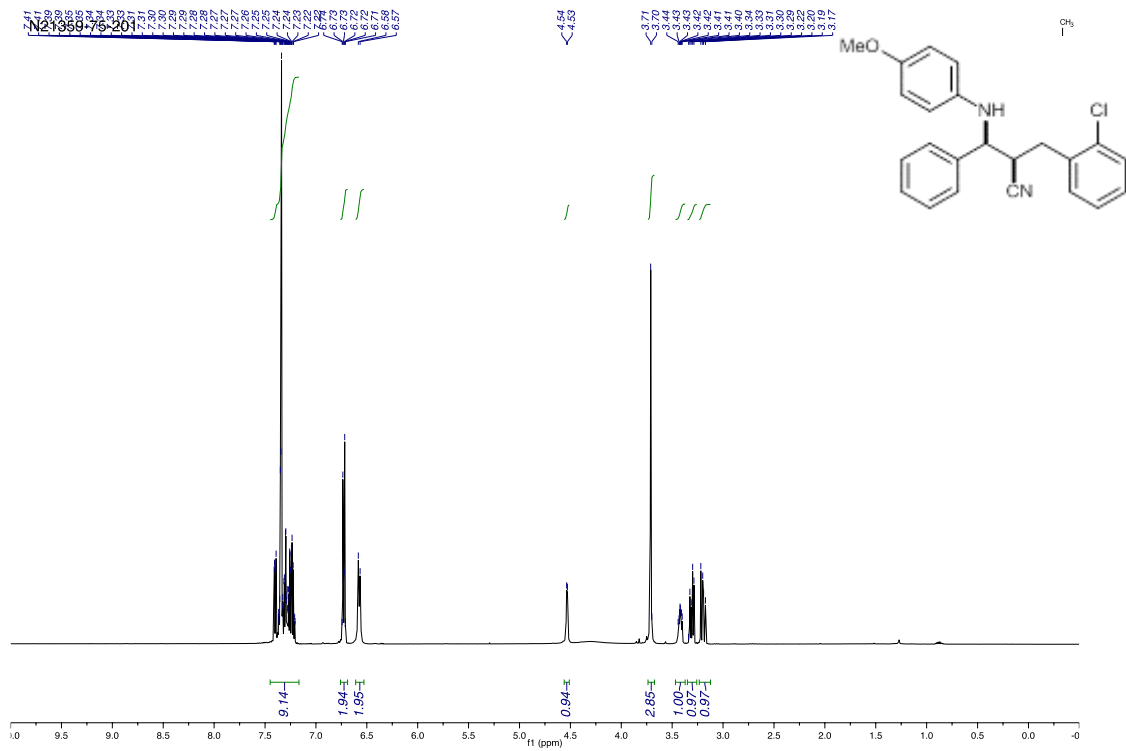


Table 2, Entry 23



N21359-75-201

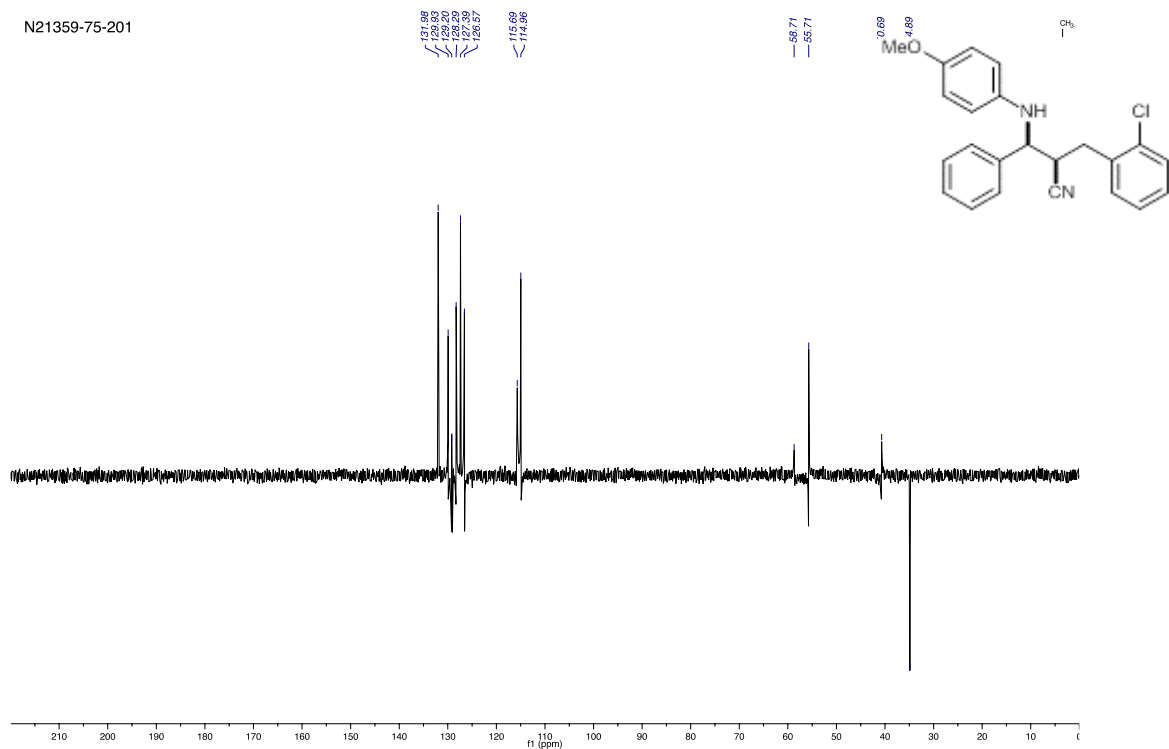
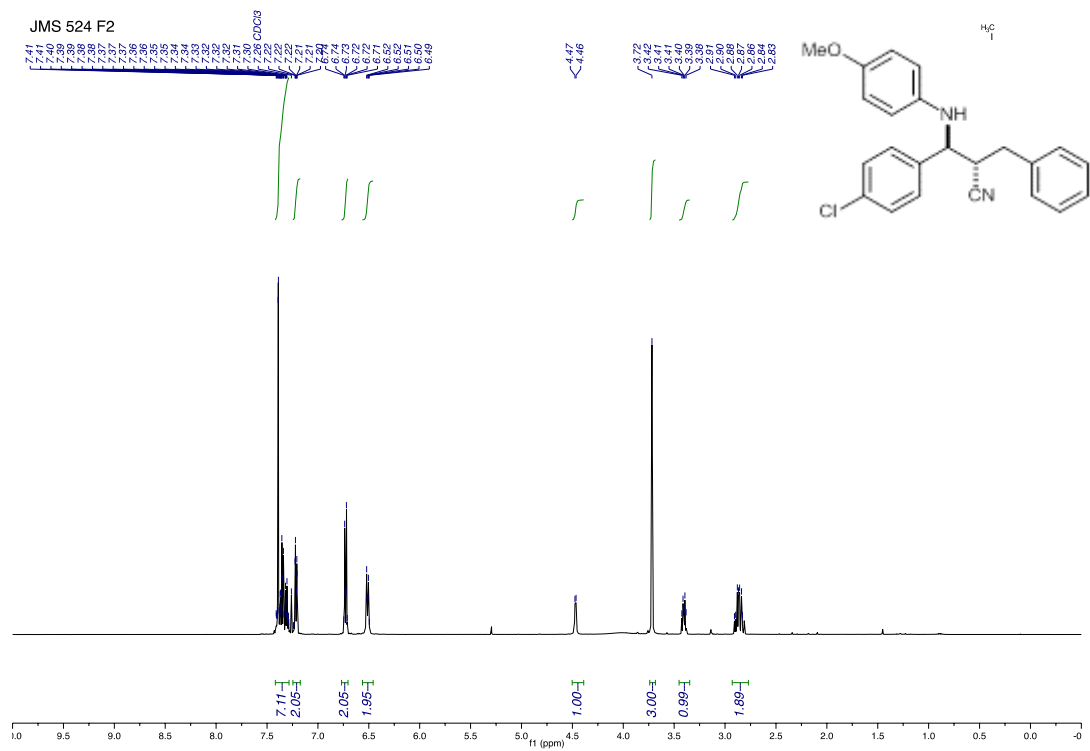
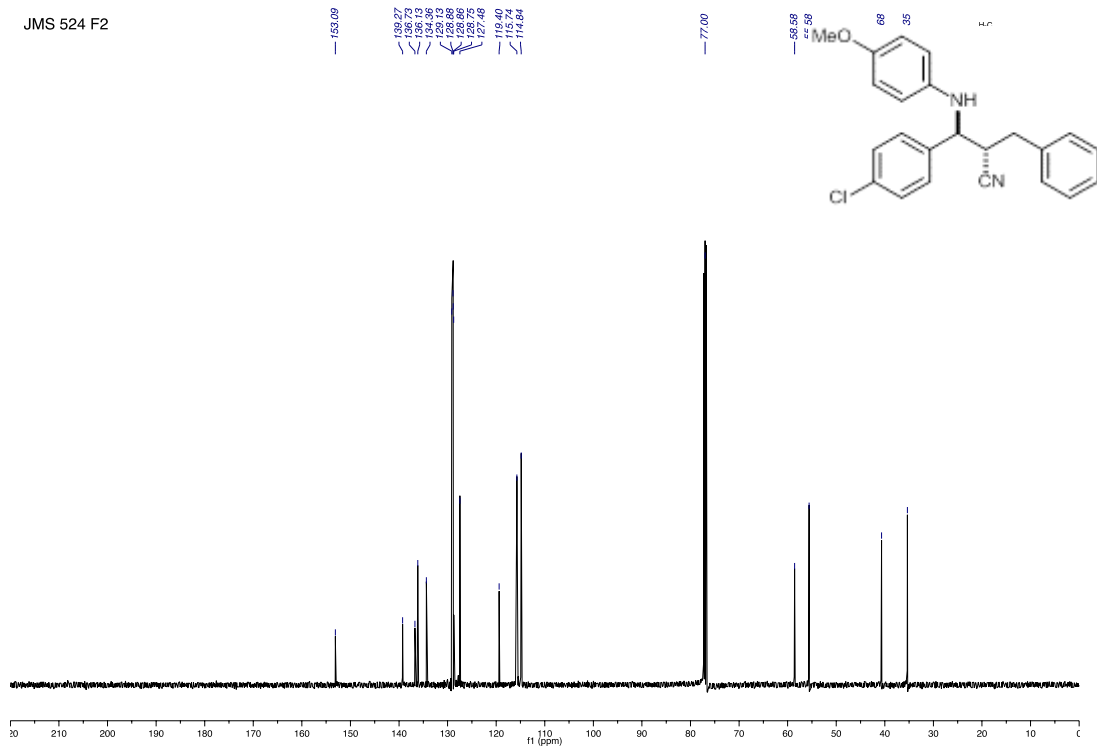


Table 2, Entry 24



JMS 524 F2



JMS 524 F2

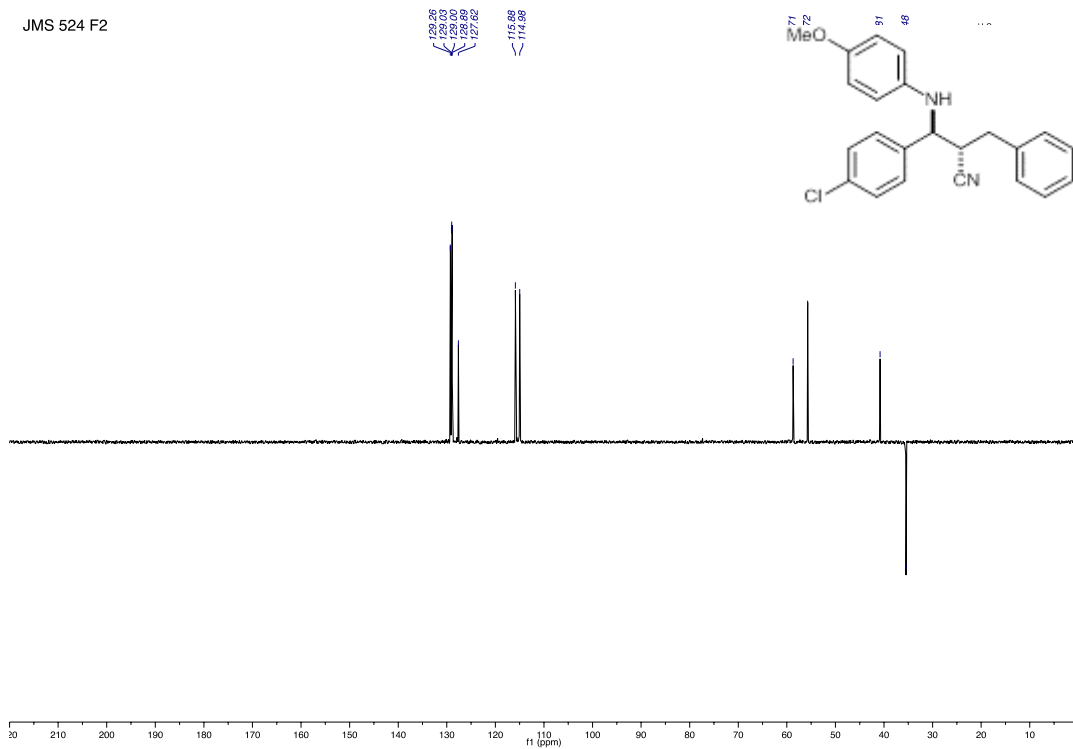
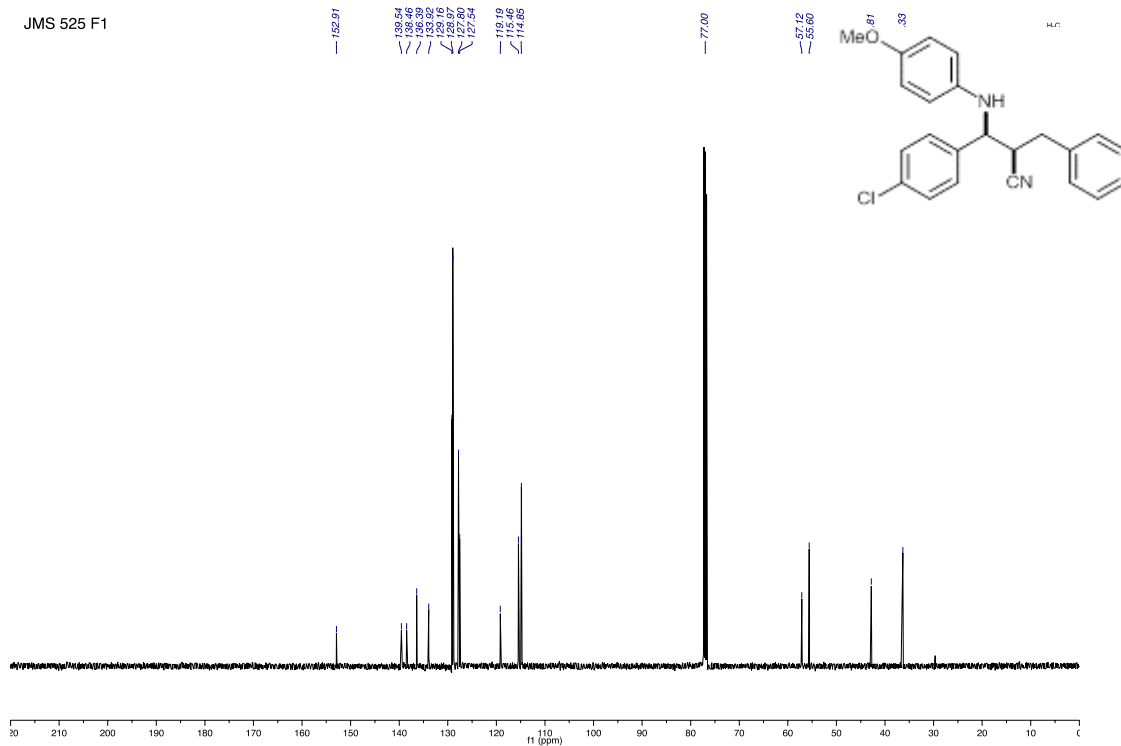
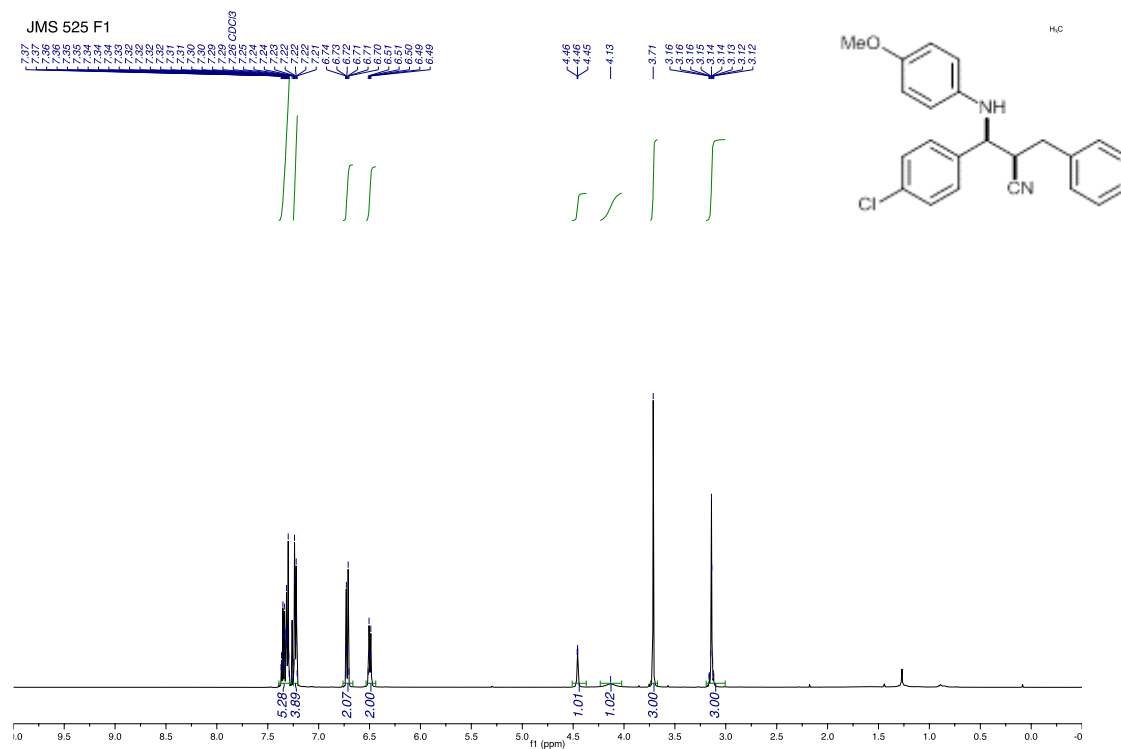


Table 2, Entry 25



JMS 525 F1

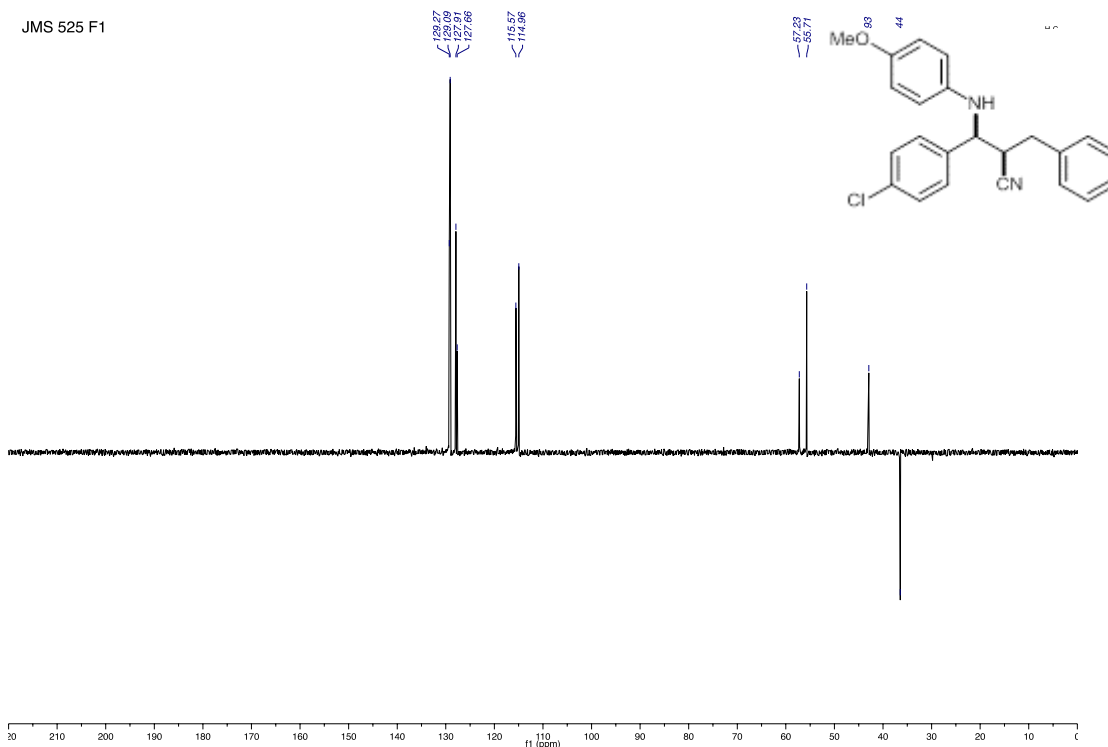
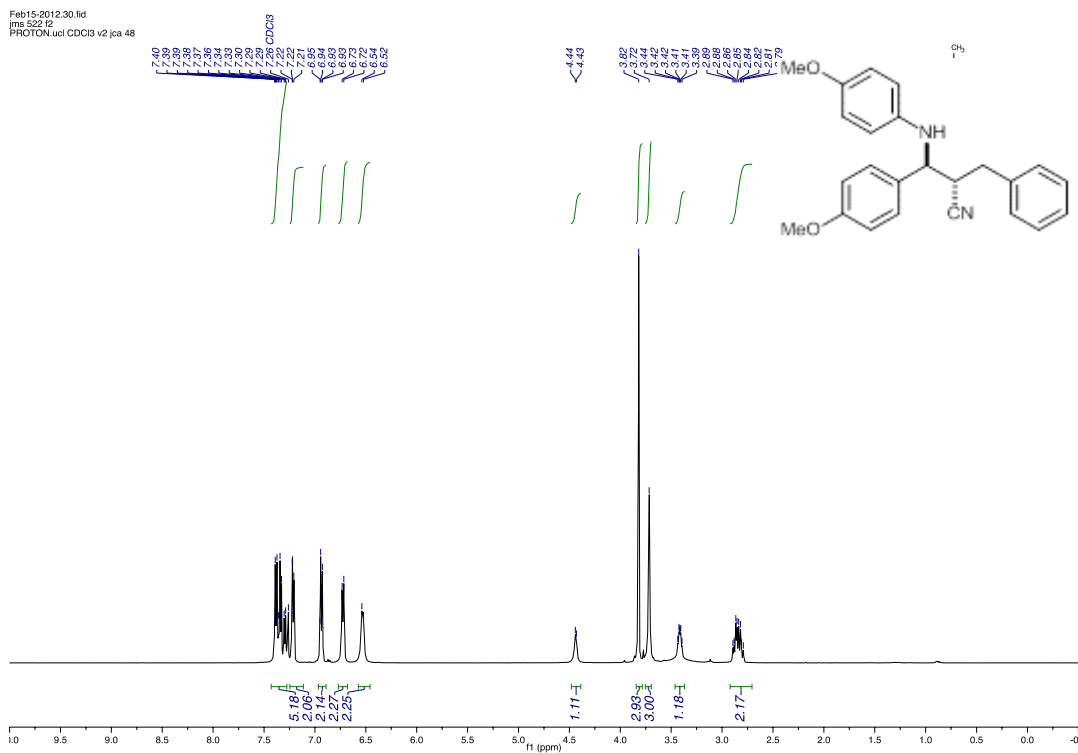
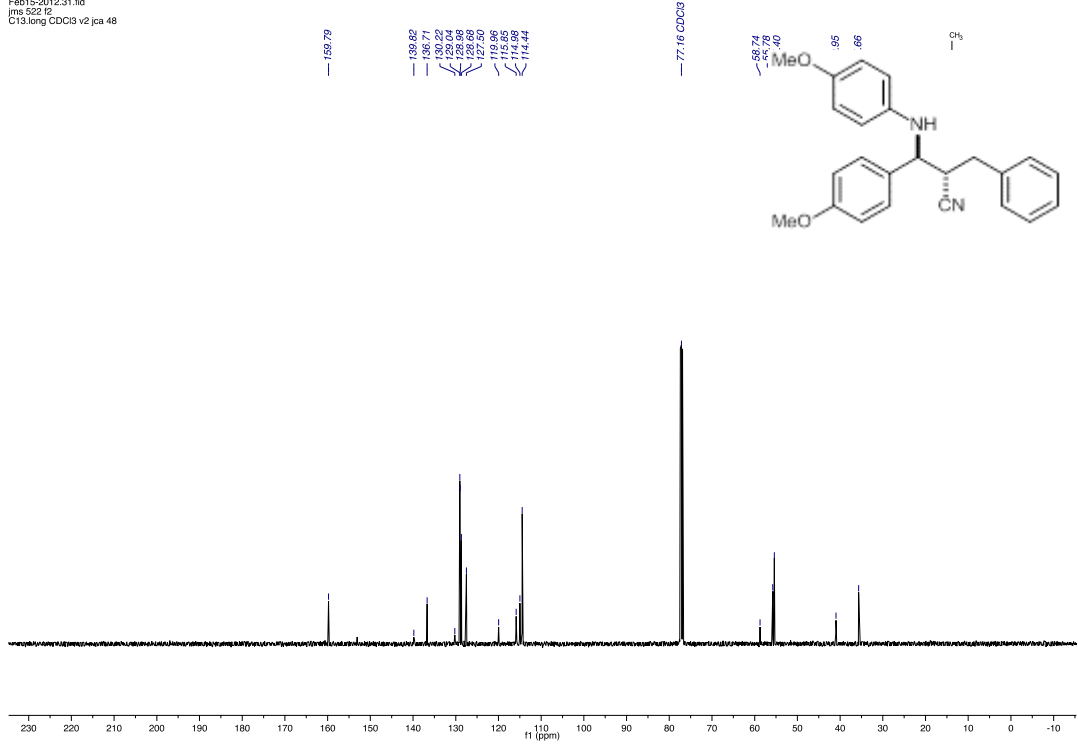


Table 2, Entry 26



Feb15-2012.31.fid
jms 522.f2
C13.lmg CDCl3 v2 jca 48



JMS 522 - F2.32.fid
jms 522.f2
depl lmg CDCl3 v2 jca 48

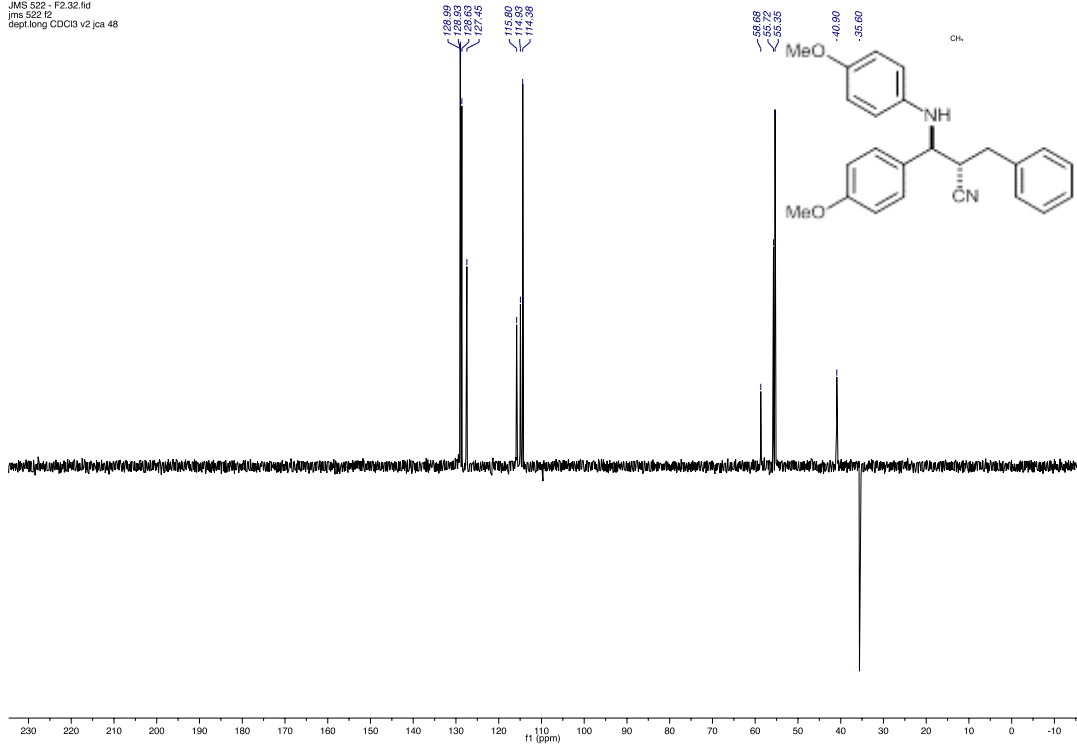
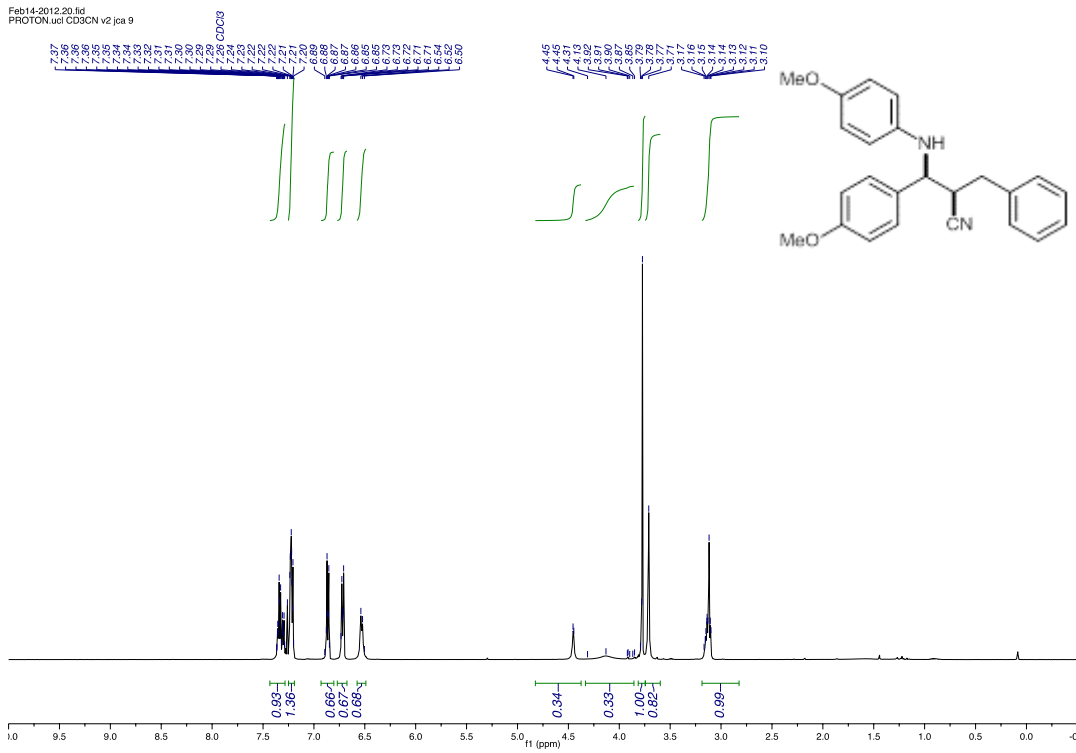
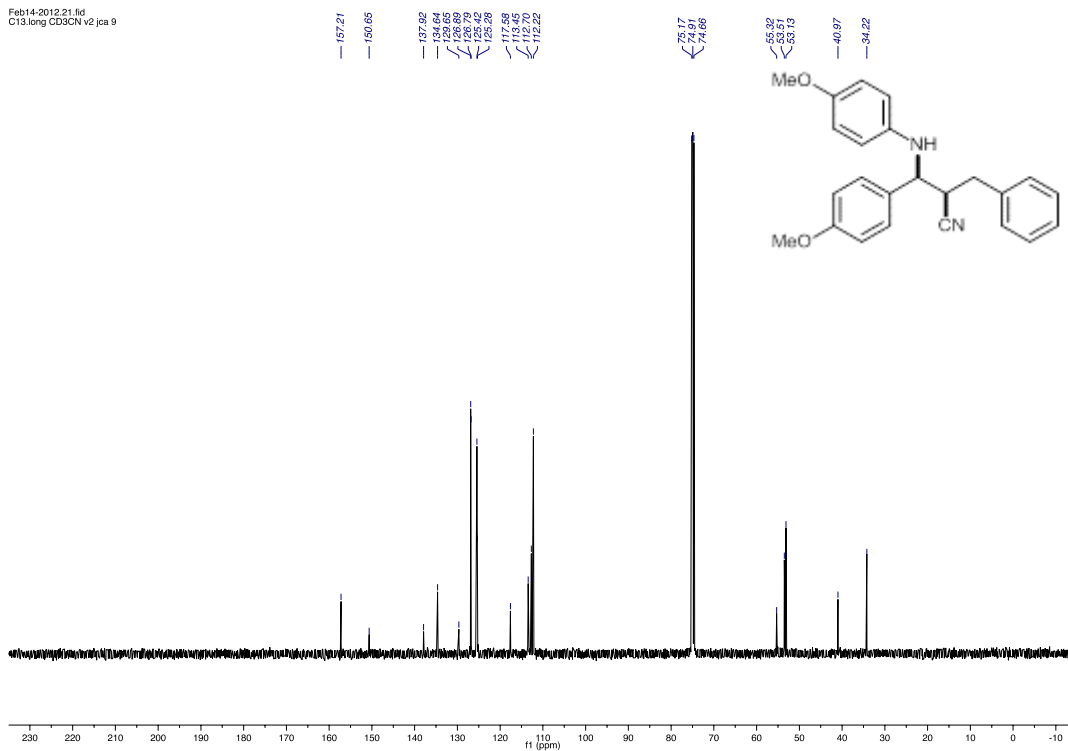


Table 2, Entry 27

Feb14-2012.20.fid
PROTON.ucf CD3CN v2 jca 9



Feb14-2012.21.fid
C13.long CD3CN v2 jca 9



JMS 523 F1.22.fid
dept.long CD3CN v2.jca 9

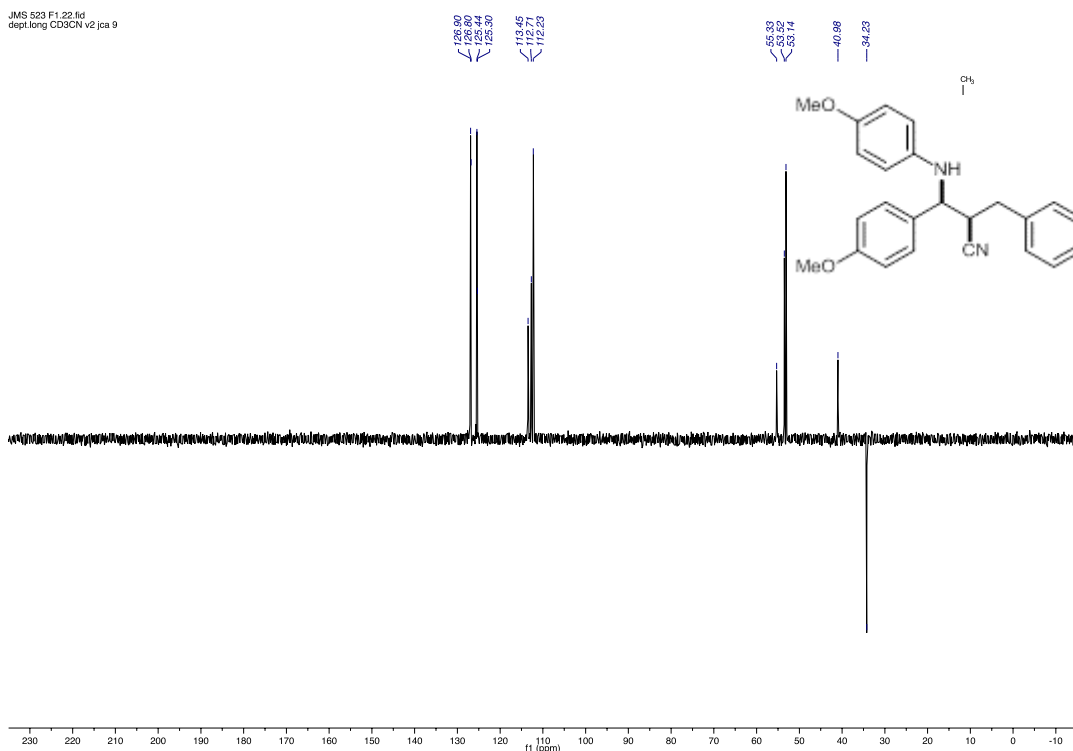
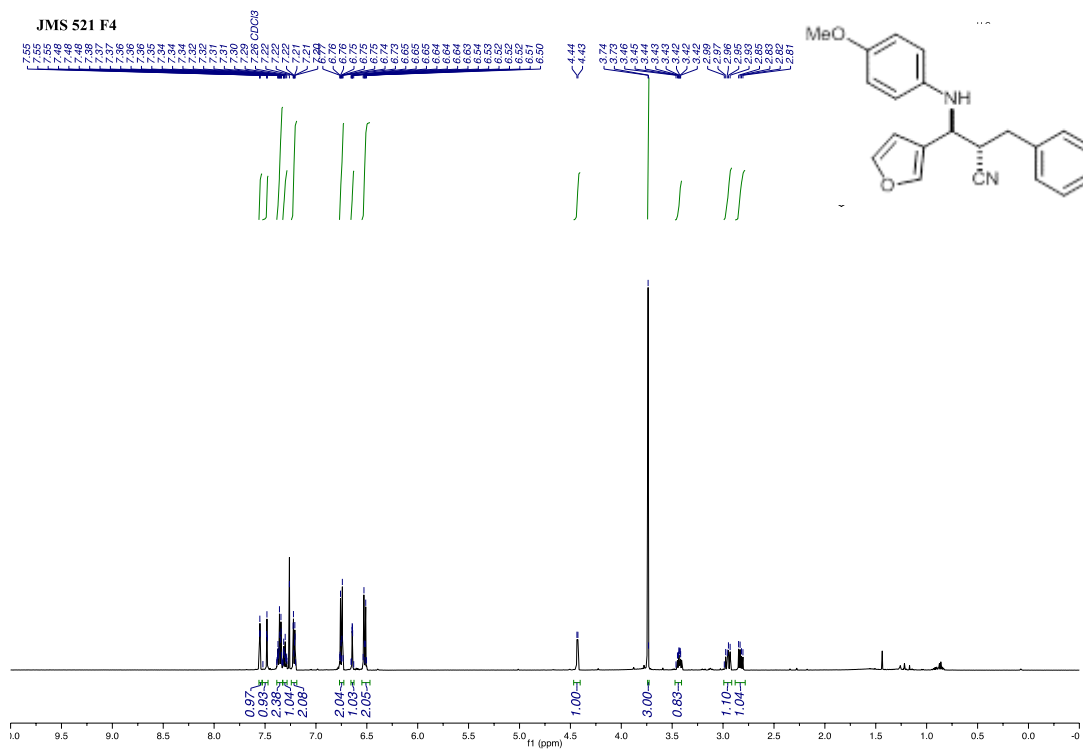


Table 2, Entry 28



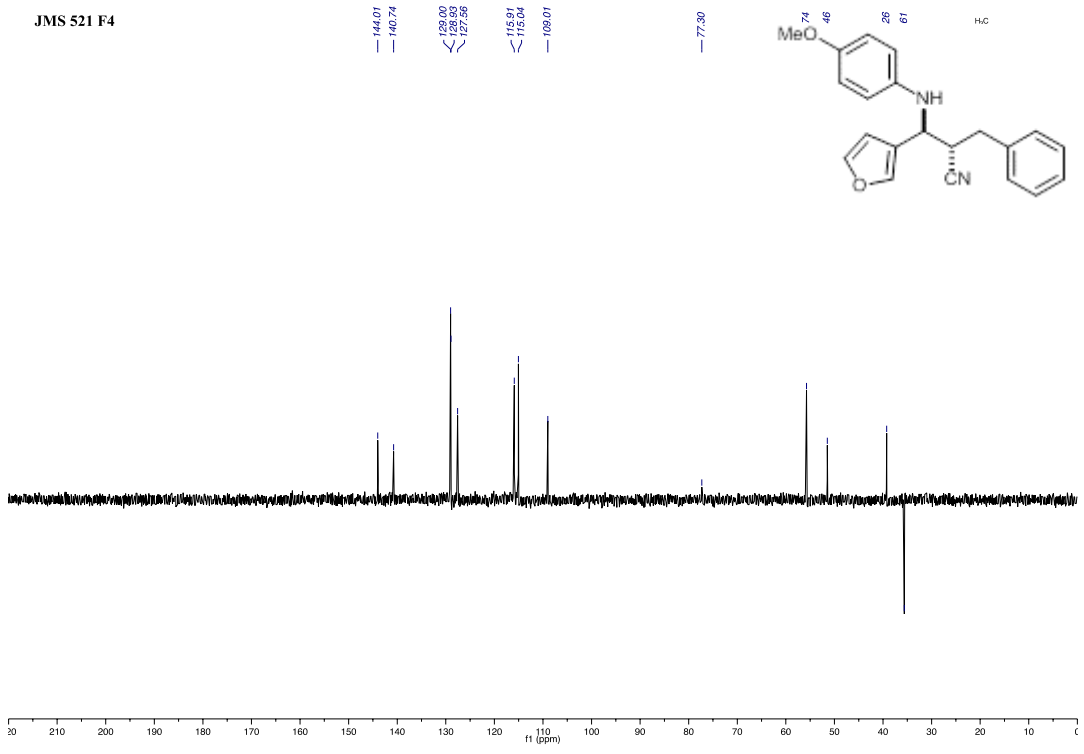
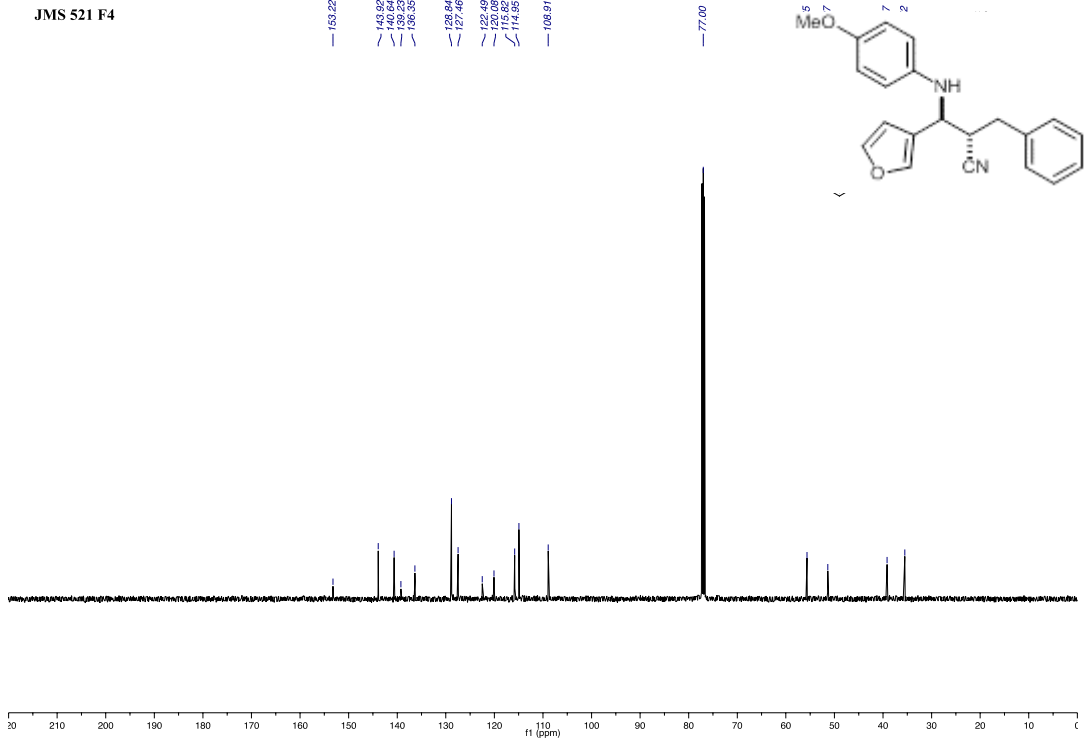
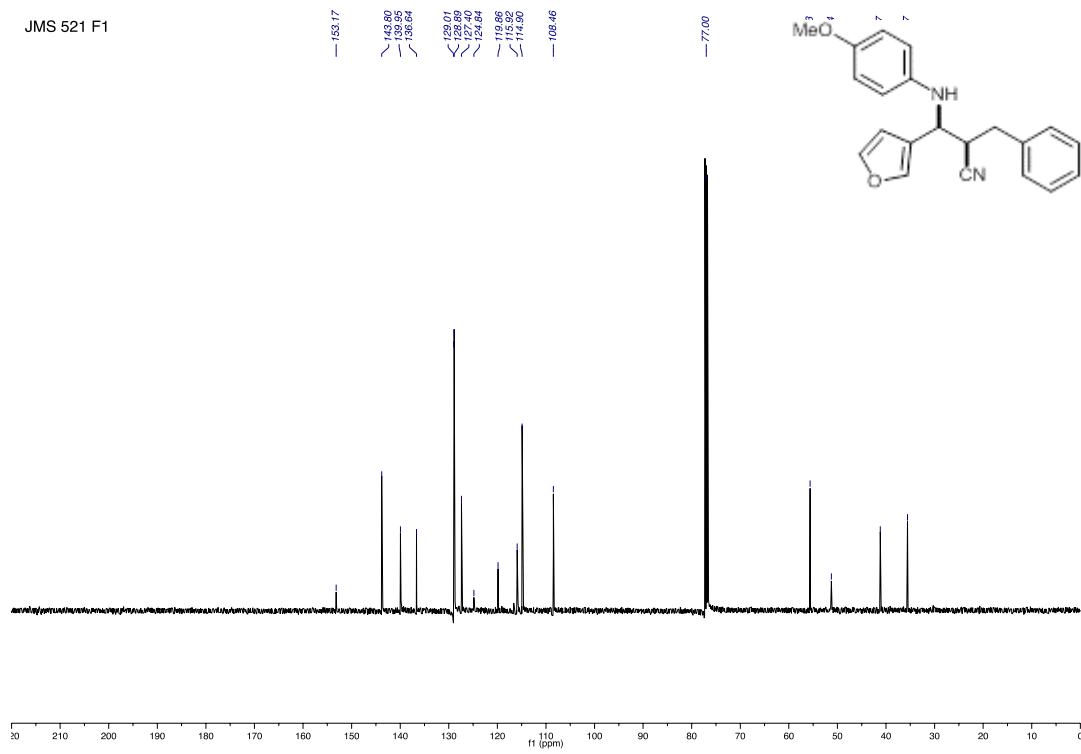
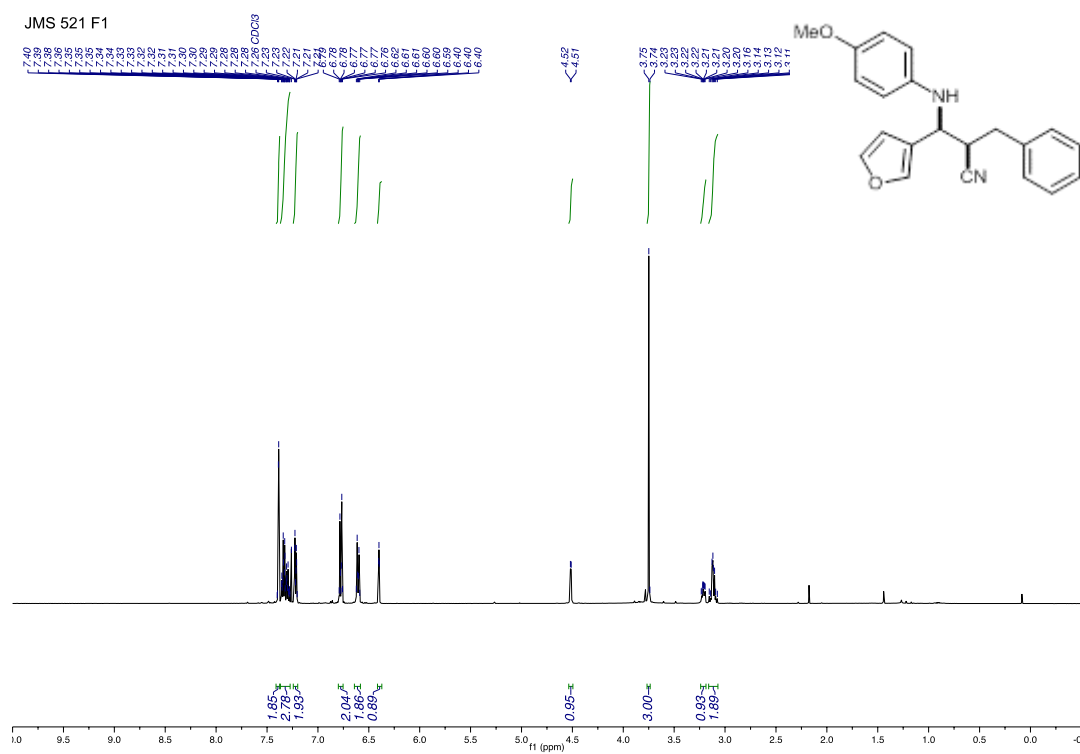


Table 2, Entry 29



JMS 521 F1

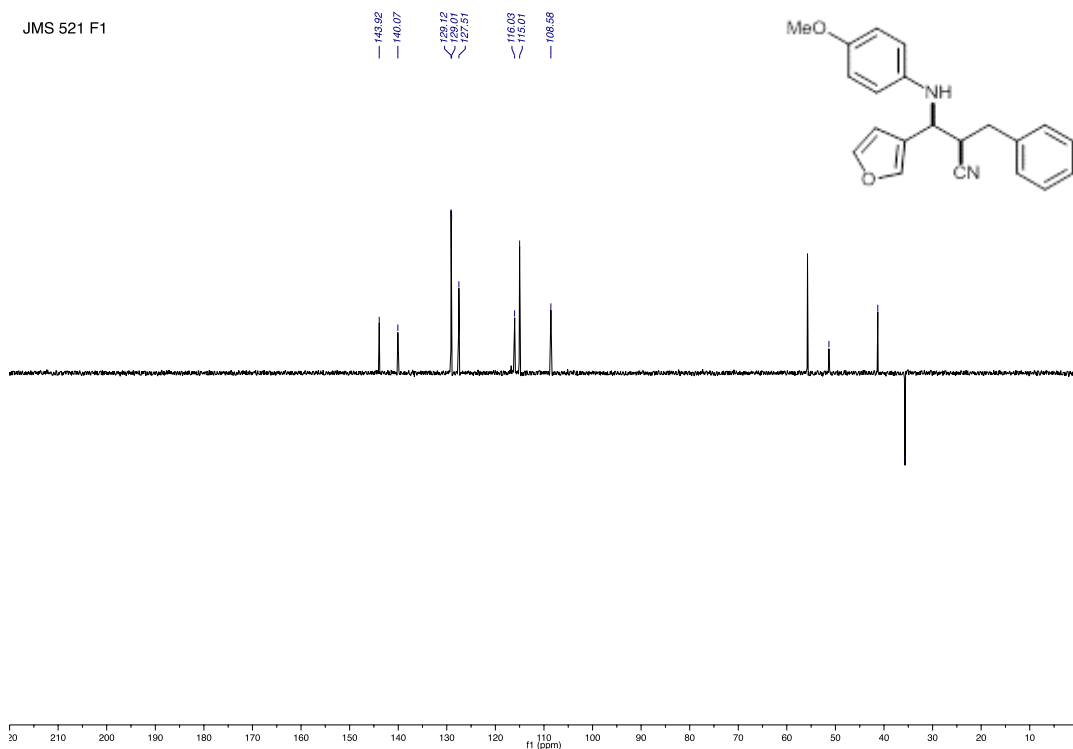
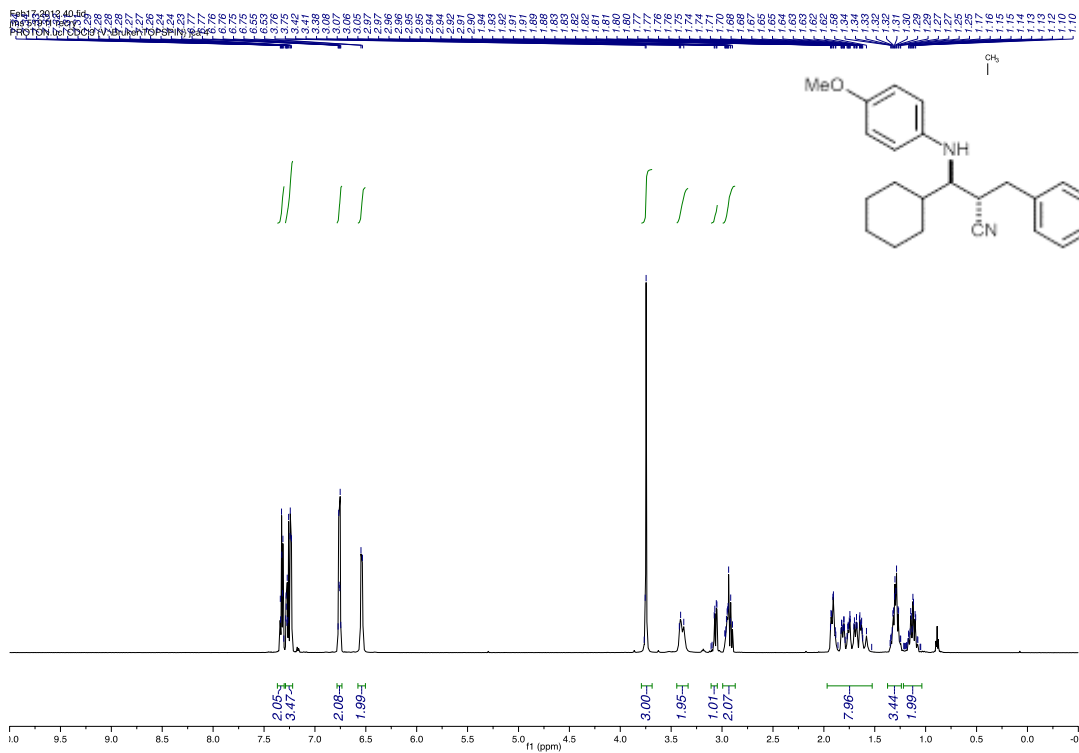
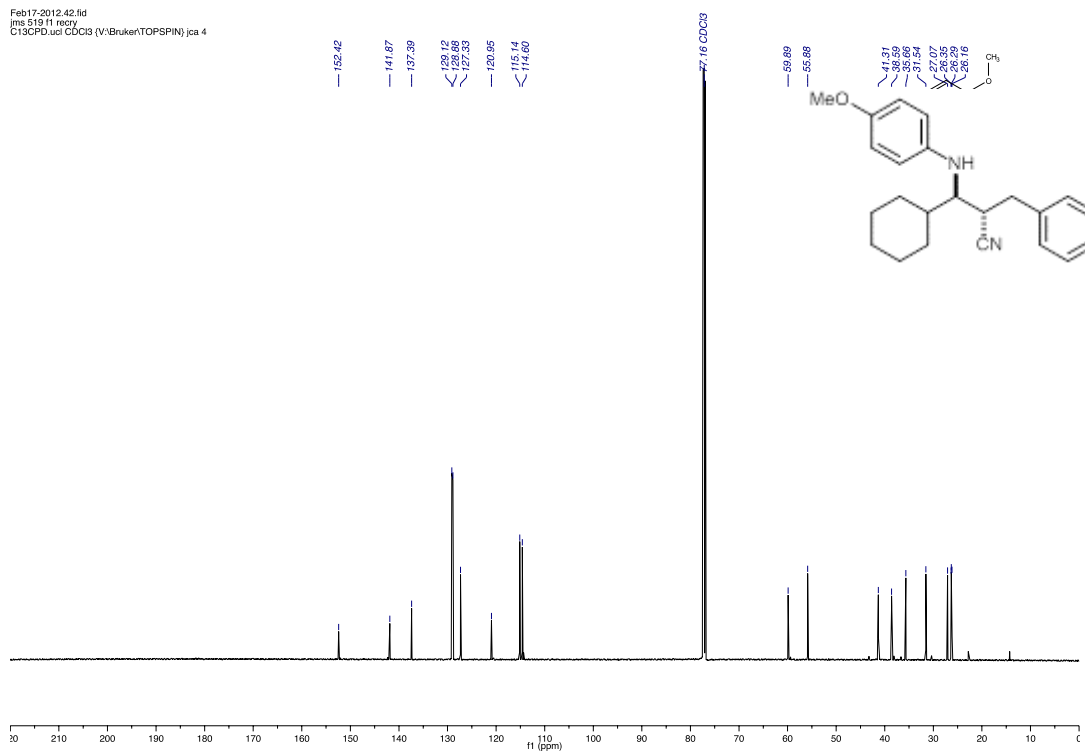


Table 2, Entry 30



Feb17-2012.42.fid
jms 519 f1 recy
C13CPD.ucl CDC13 (V1:Bruker/TOPSPIN) jca 4



Feb17-2012.43.fid
jms 519 f1 recy
C13DEPT135.ucl CDC13 (V1:Bruker/TOPSPIN) jca 4

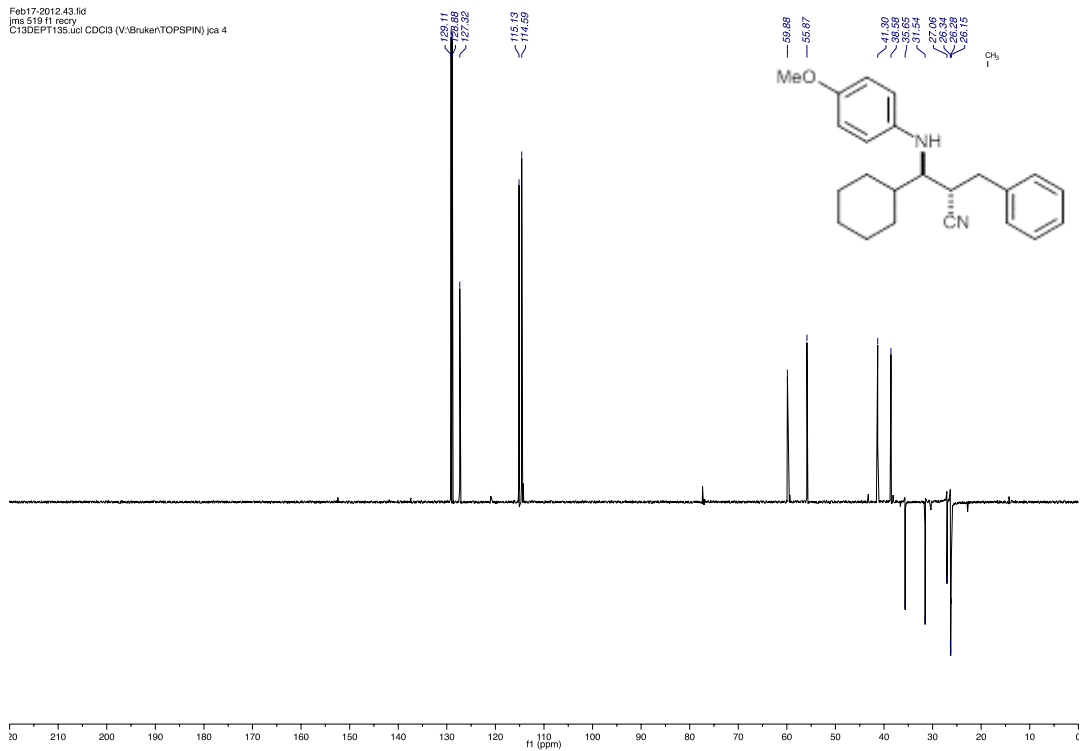
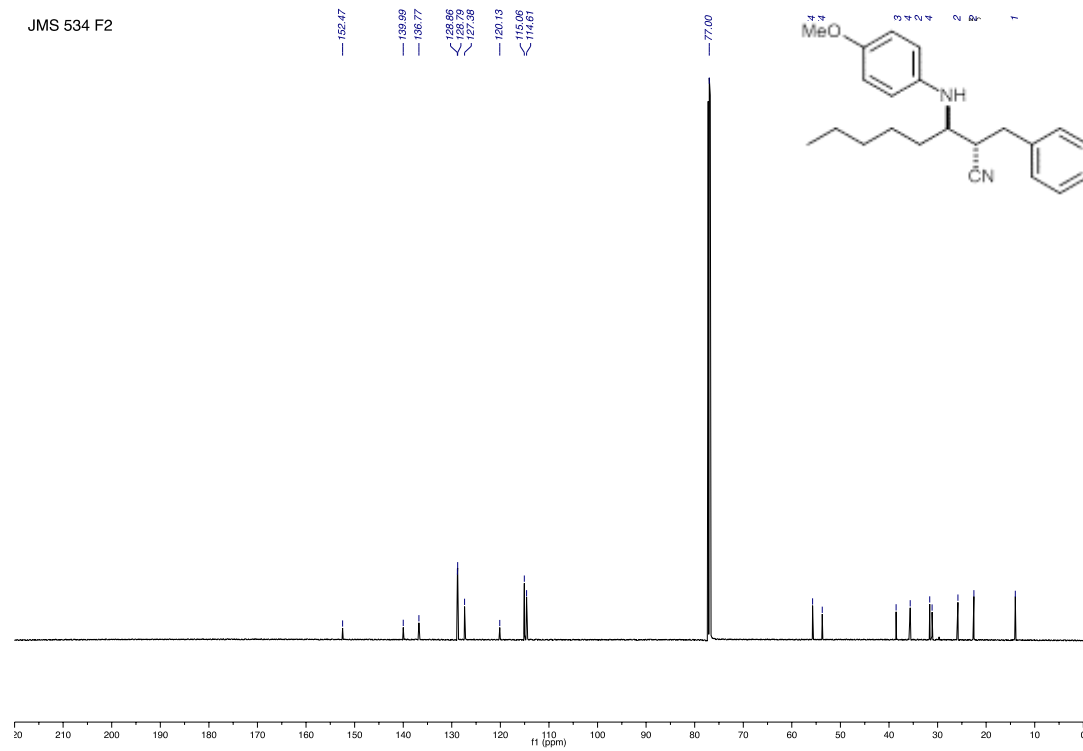
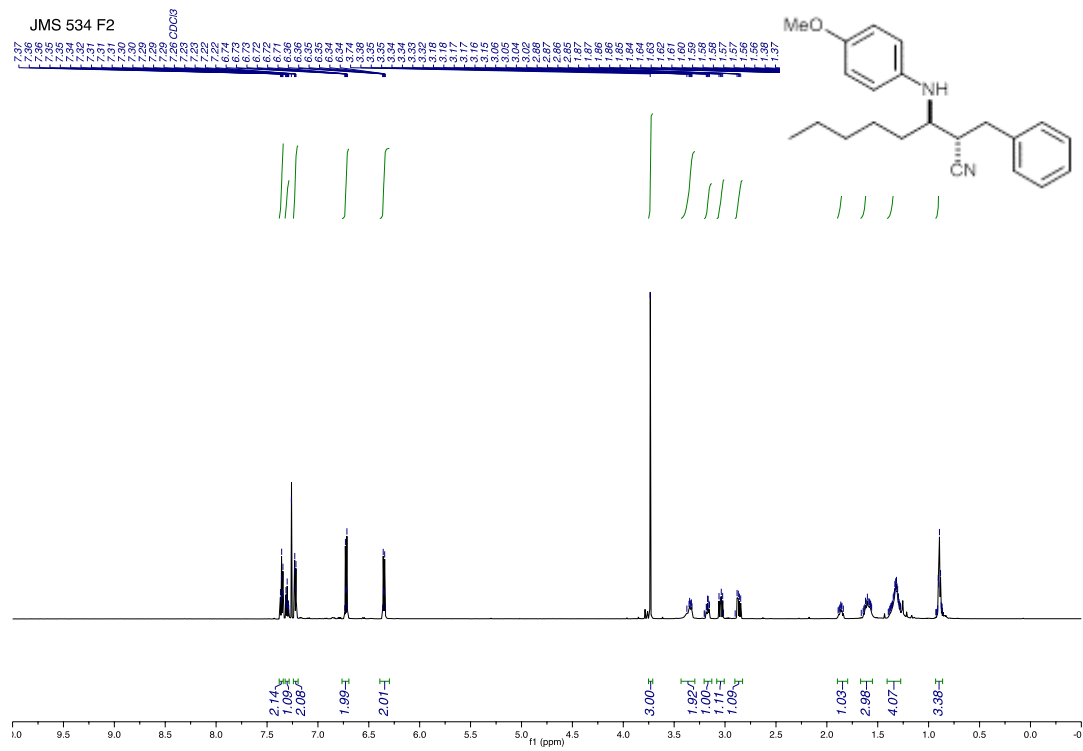


Table 2, Entry 32



JMS 534 F2

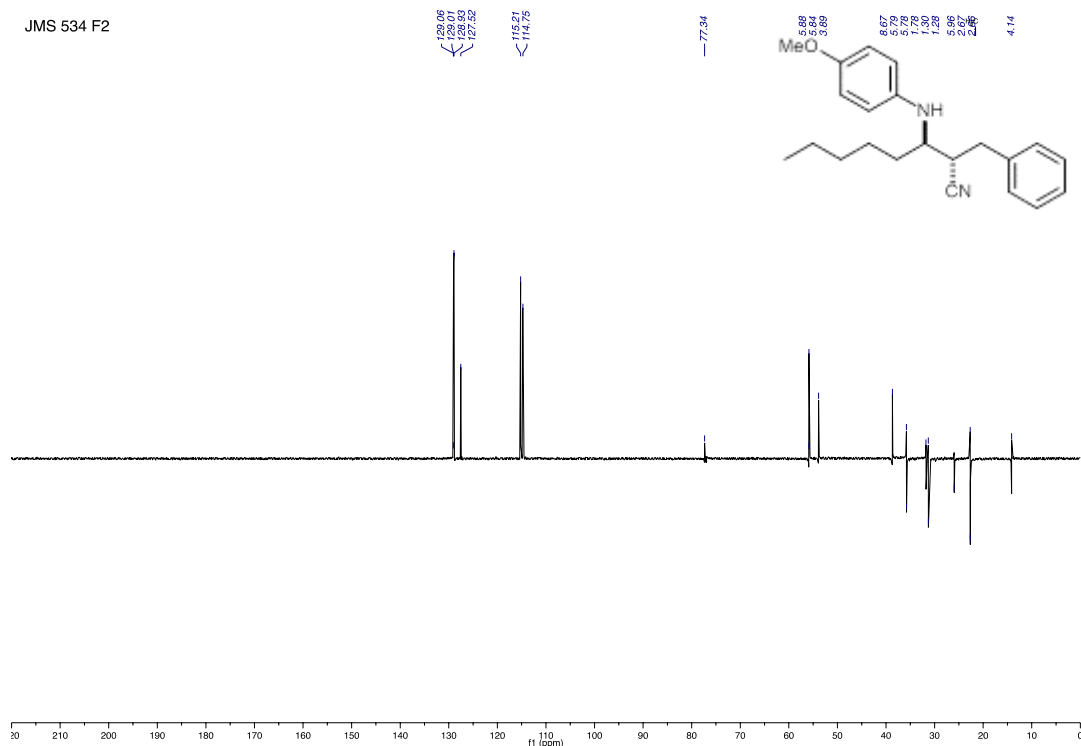
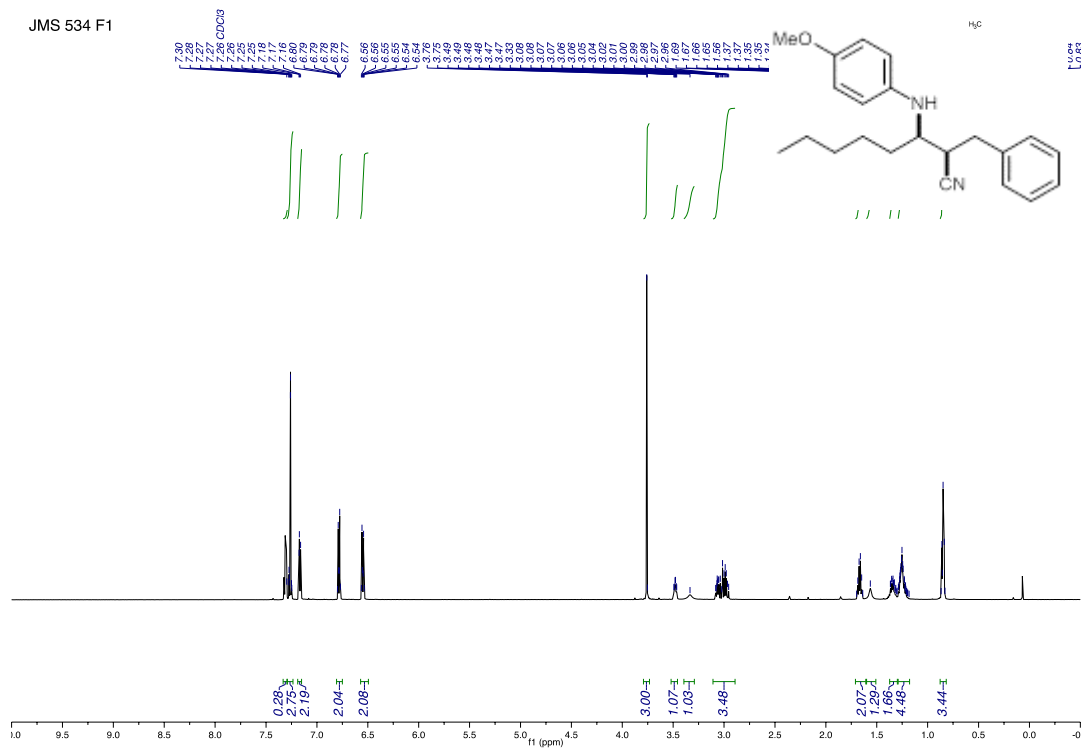
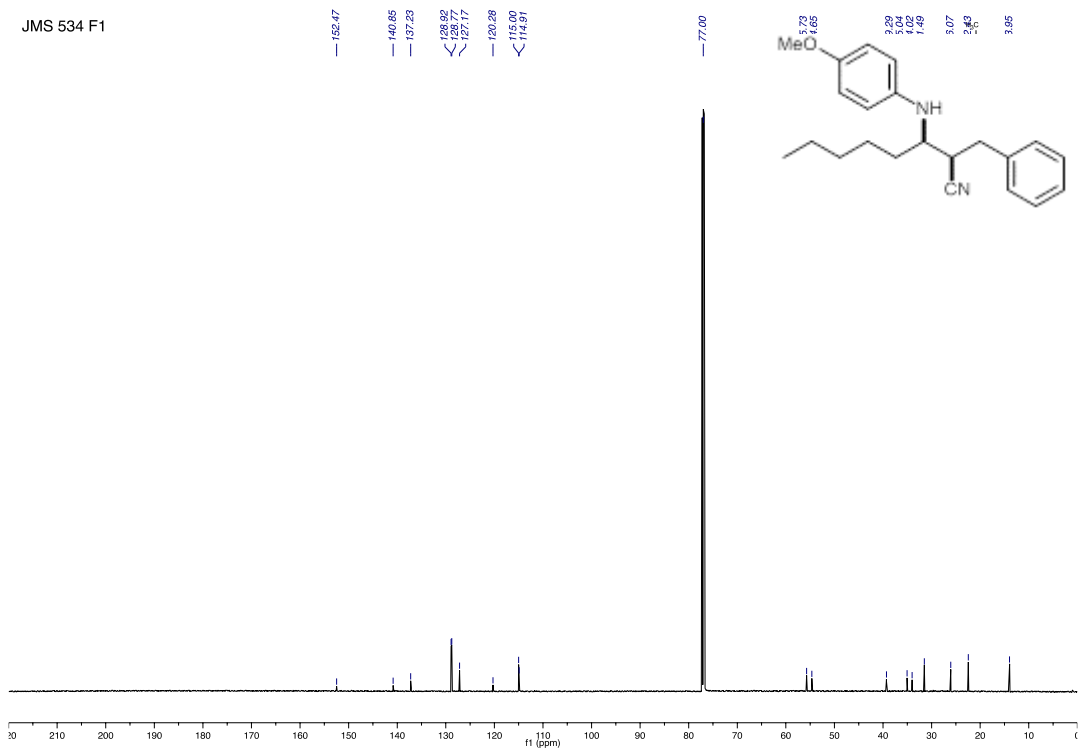


Table 2, Entry 33

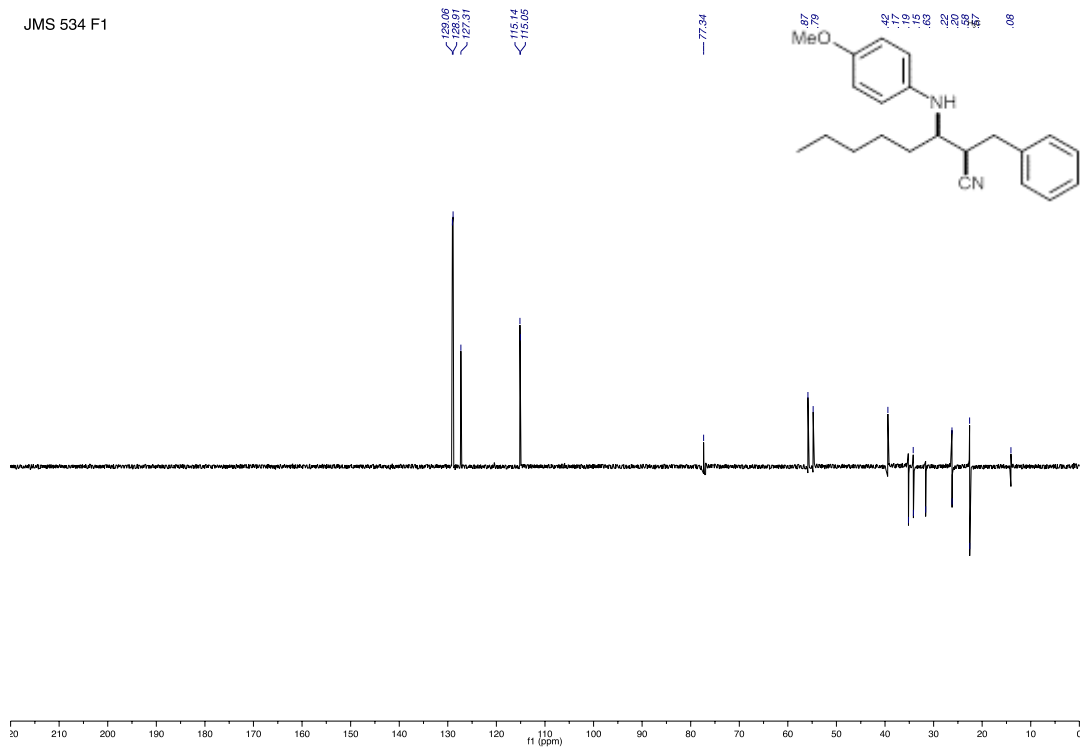
JMS 534 F1



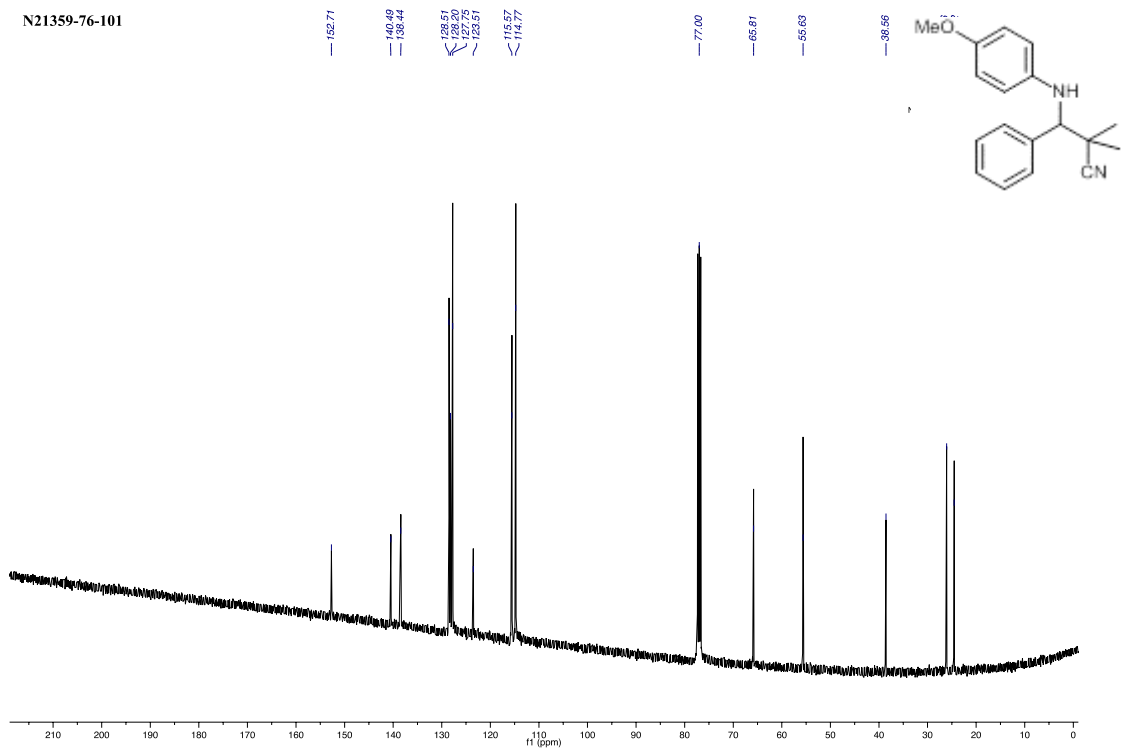
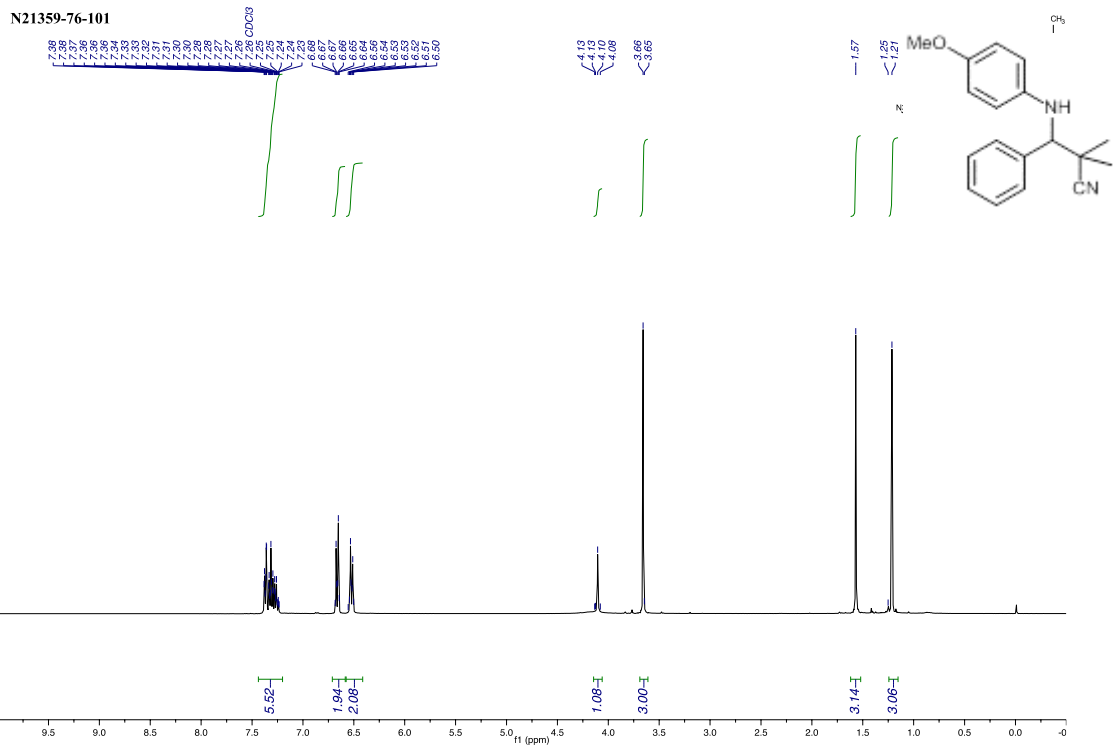
JMS 534 F1



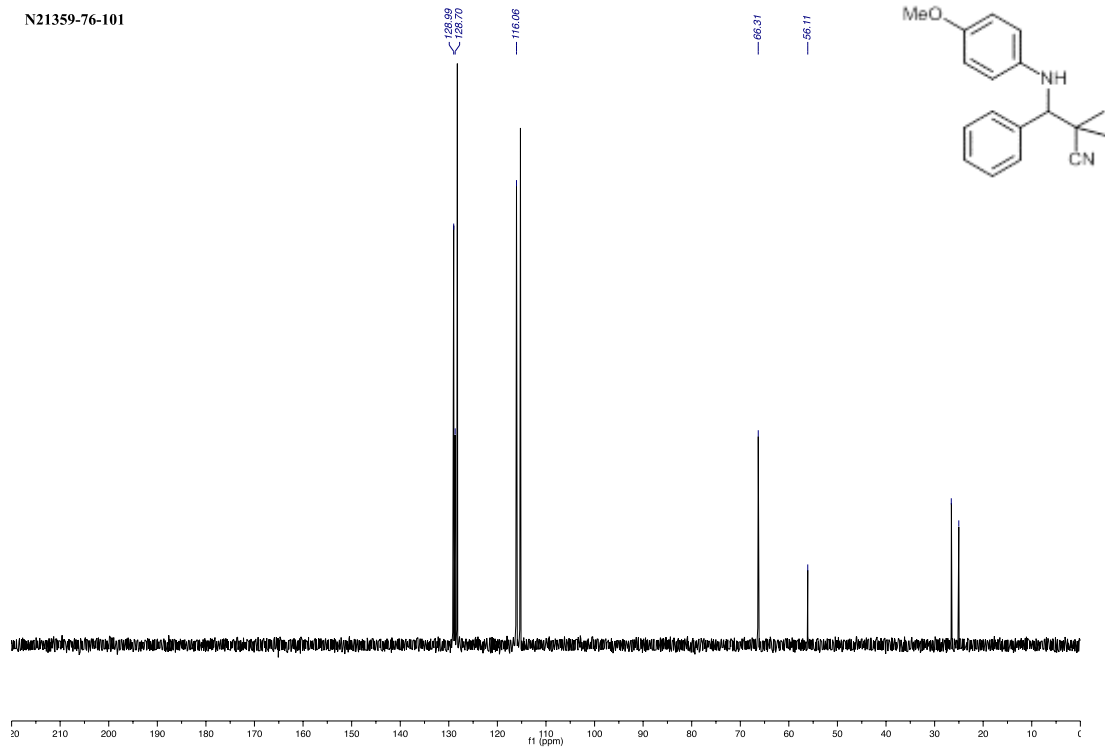
JMS 534 F1



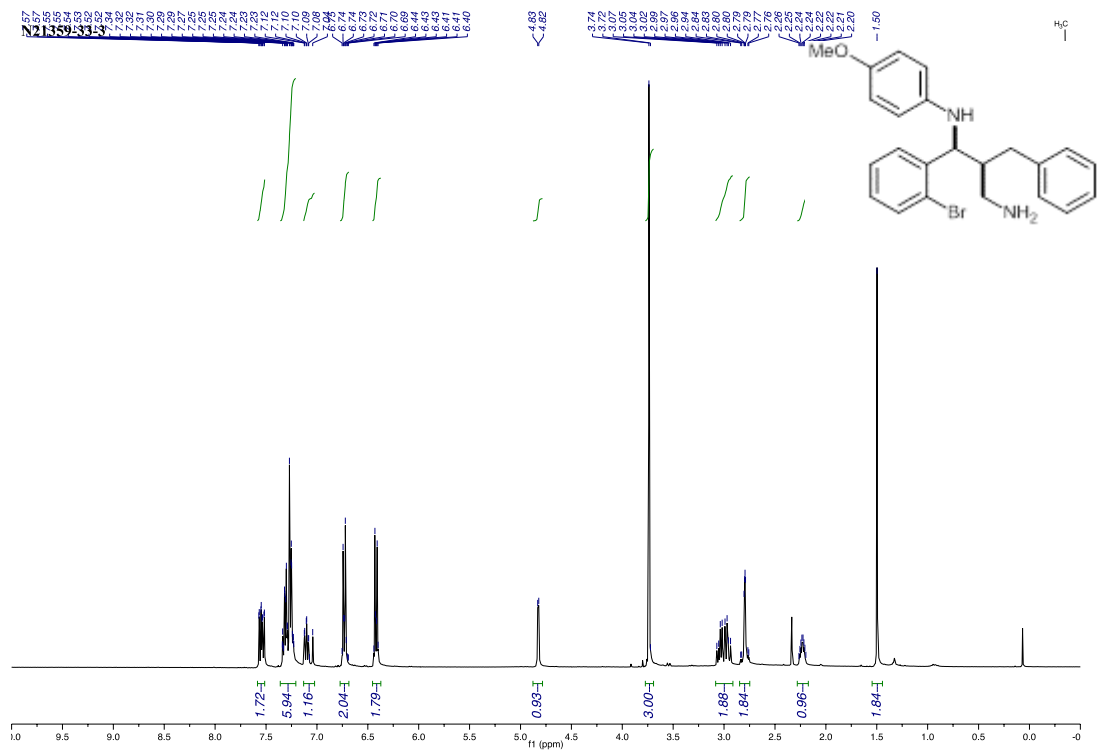
Reaction with *iso*-butyronitrile



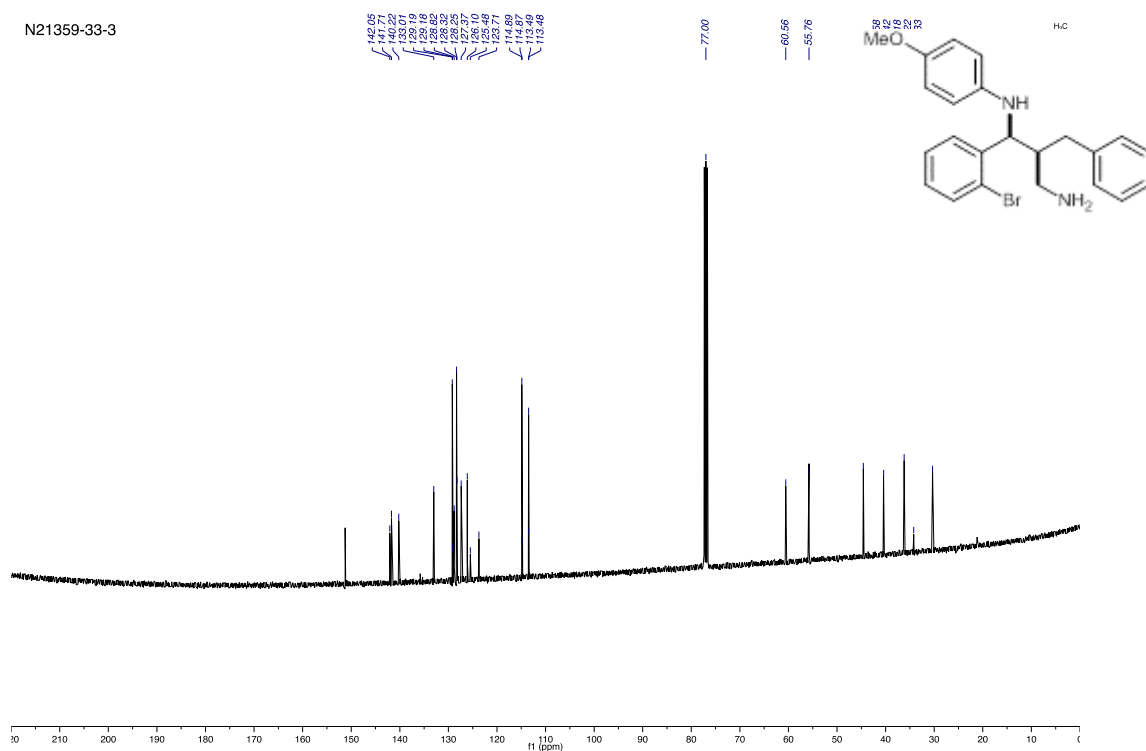
N21359-76-101



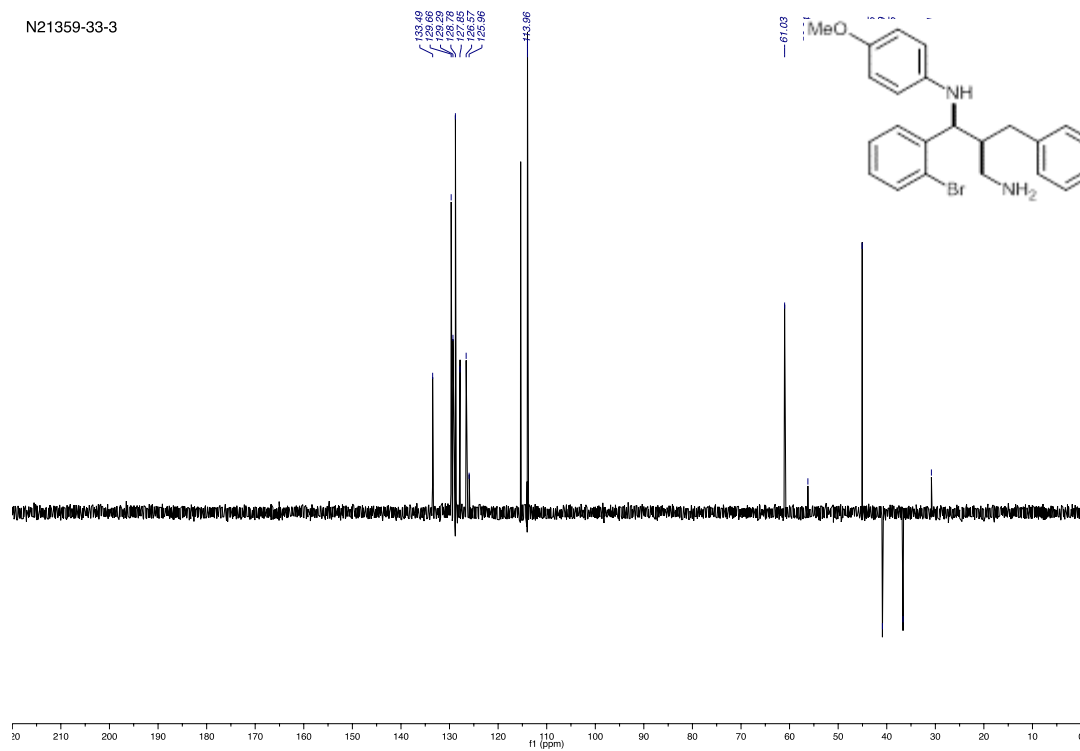
1,3-diamine from syn-3 (R¹=Bn, R²=2-Br-C₆H₅)



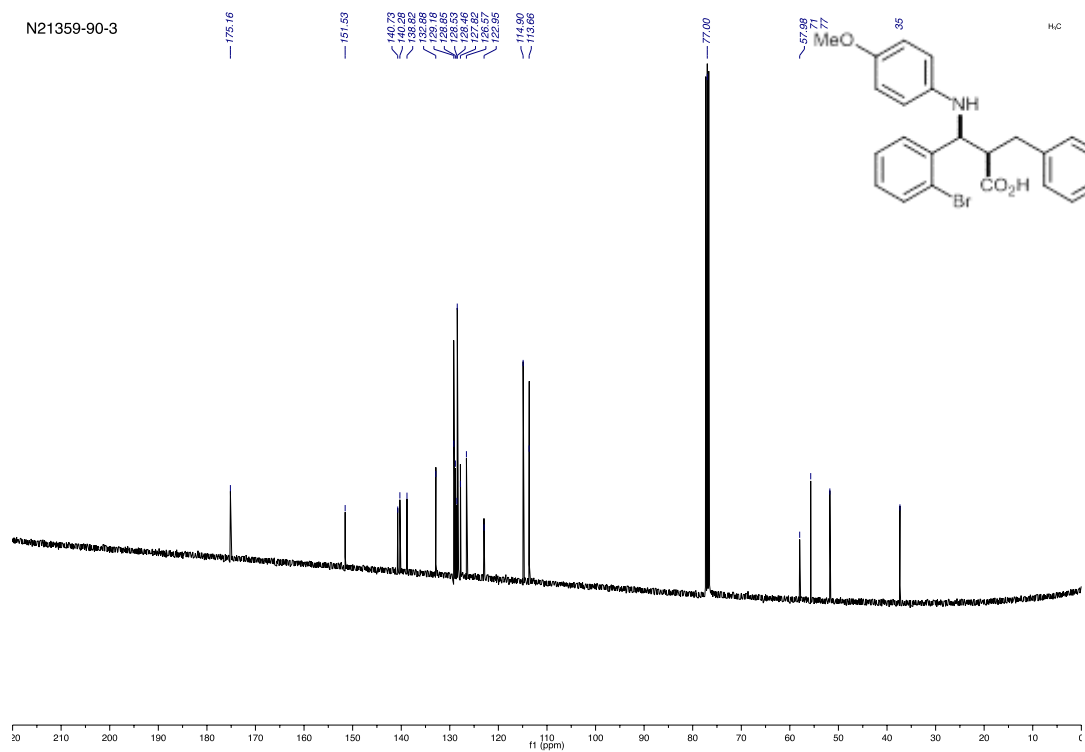
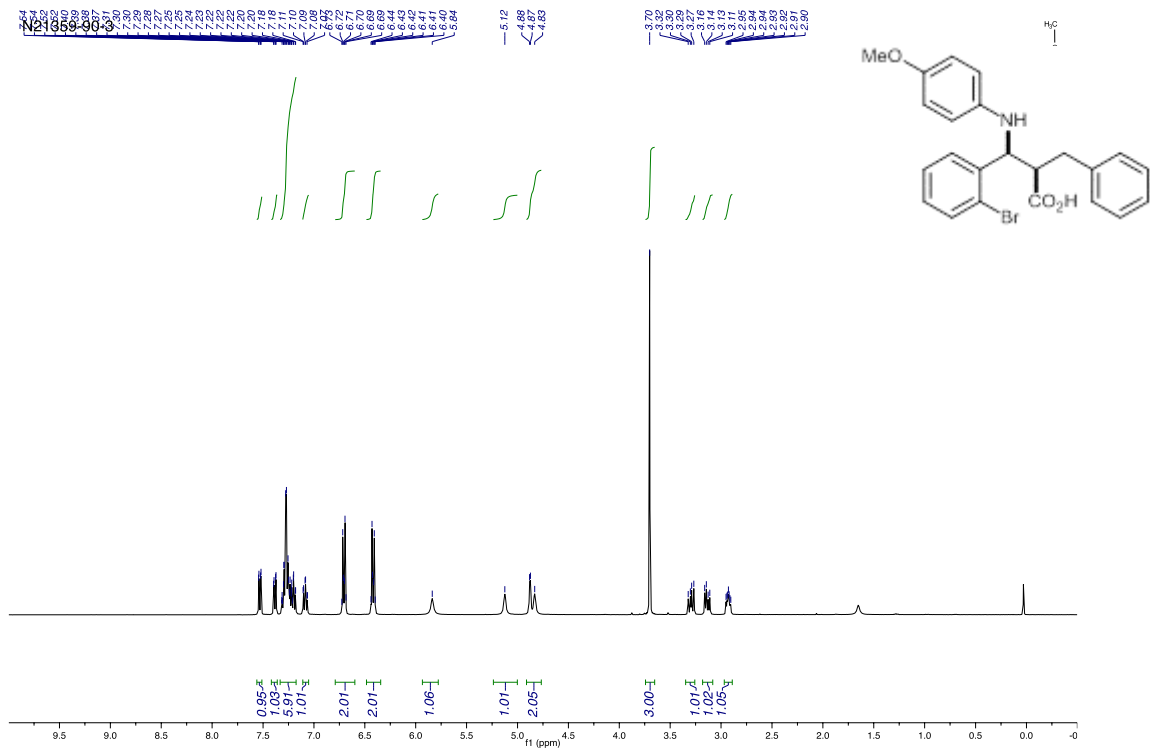
N21359-33-3



N21359-33-3



β -amino acid from syn-3 (R¹=Bn, R²=2-Br-C₆H₅)



N21359-90-3

