Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Visible-Light-Driven Photoredox-Catalyzed C(sp^3)-C(sp^3) Cross-Coupling of N-arylamines with Cycloketone Oxime Esters

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(A) Typical Experimental Procedure

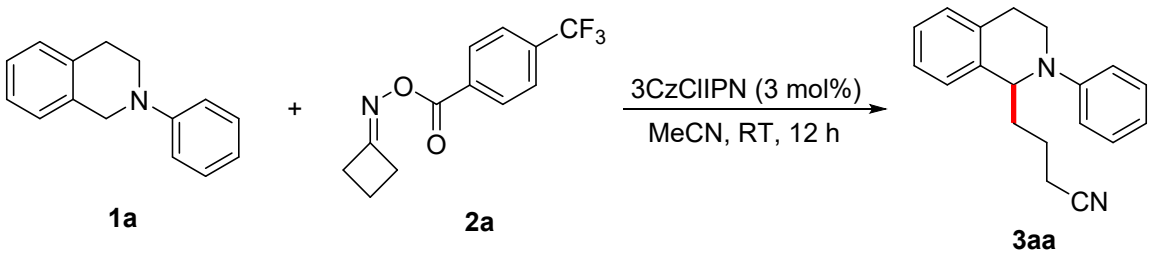
(a) General information

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker 500 (500, 125, and 471 MHz) advance spectrometer at room temperature in $CDCl_3$ (solvent signals, δ 7.26 and 77.0 ppm) using TMS as internal standard. Low-resolution mass spectra (LRMS) data were measured on GCMS-QP2010 Ultra. High-resolution mass spectra (HRMS) was recorded on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry. Melting Points were recorded on Hanon MP100 Apparatus. Unless otherwise noted, all reactions were carried out using standard Schlenk techniques, and all starting materials and solvents were commercially available and were used without further purification. Column chromatography was performed on silica gel (300-400 mesh) using petroleum ether (PE)/ethyl acetate (EA). The light source were used 5 W Blue LEDs (manufacturer: liang yuan ligbting, model: LY-PD001**,** wavelength range: 450-460 nm, λ_{max} = 455 nm), with wrap in foil, less than 5cm from the light source to the irradiation vessel.

(b) General procedure for the synthesis of starting compounds 1a & 2a:

Cycloketone Oxime Esters, [1] amides of N-aryl-substituted glycine,[2] dipeptides,[3] were all prepared according to previous reports.

(c) General procedure for synthesis of compound 3aa.



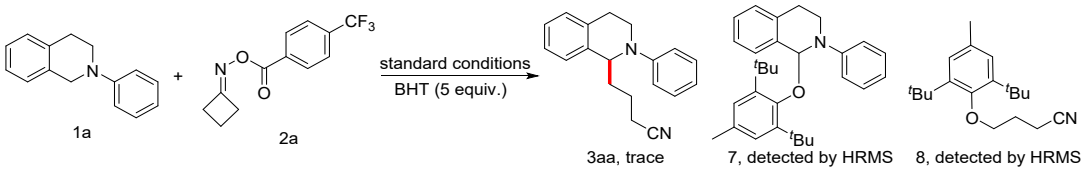
1a **2a** **3aa**

To a Schlenk tube were added 2-phenyl-1,2,3,4-tetrahydroisoquinoline **1a** (0.2 mmol, 41.8 mg), cyclobutanone O-(4-(trifluoromethyl)phenyl) oxime **2a** (1.2 equiv., 55.0 mg), 3CzClIPN (3 mol%, 4.7 mg), and MeCN (2.0 mL). Then the mixture was stirred at room temperature under argon atmosphere for indicated time until complete consumption of starting material as monitored by TLC and/or GC-MS analysis. The residue was purified by silica gel flash column chromatography (hexane/ethyl acetate) to afford the compound **3aa** (47.0 mg, 0.17 mmol, 86% yeild).

One gram reaction: To a Schlenk tube were added 2-phenyl-1,2,3,4-tetrahydroisoquinoline **1a** (4.8mmol, 1 g), cyclobutanone cyclobutanone O-(4-(trifluoromethyl)phenyl) oxime **2a** (1.2 equiv., 1.32 g), 3CzClIPN (3 mol%, 112.8 mg), and MeCN (10.0 mL). Then the mixture was stirred at room temperature under argon atmosphere for indicated time until complete consumption of starting material as monitored by TLC and/or GC-MS analysis. The residue was purified by silica gel flash column chromatography (hexane/ethyl acetate) to afford the compound **3aa** (1.06 g, 3.84 mmol, 80% yeild).

(B) The mechanistic studies

(a) BHT redical trapping expriments.



To a Schlenk tube were added 2-phenyl-1,2,3,4-tetrahydroisoquinoline **1a** (0.2 mmol, 41.8 mg), cyclobutanone O-(4-(trifluoromethyl)phenyl) oxime **2a** (1.2 equiv., 55.0 mg), 3CzClIPN (3 mol%, 4.7 mg), Butylated Hydroxytoluene (220 mg, 1 mmol, 5 equiv.) and MeCN (2.0 mL). The mixture was bubbled with Ar for 1 min, and the reaction excuted under argon atmosphere. The reaction was then stirred and photolyzed with 5 W blue LEDs at distances to the vial of approximately 1 cm for 12 h. The reaction mixture was then analyzed by HRMS. The HRMS spectrum (Figure S1 and S2) showed evidence for the formation of **7** (an adduct of BHT and tetrahydroisoquinoline radical) and **8** (an adduct of BHT and butyronitrile radical).

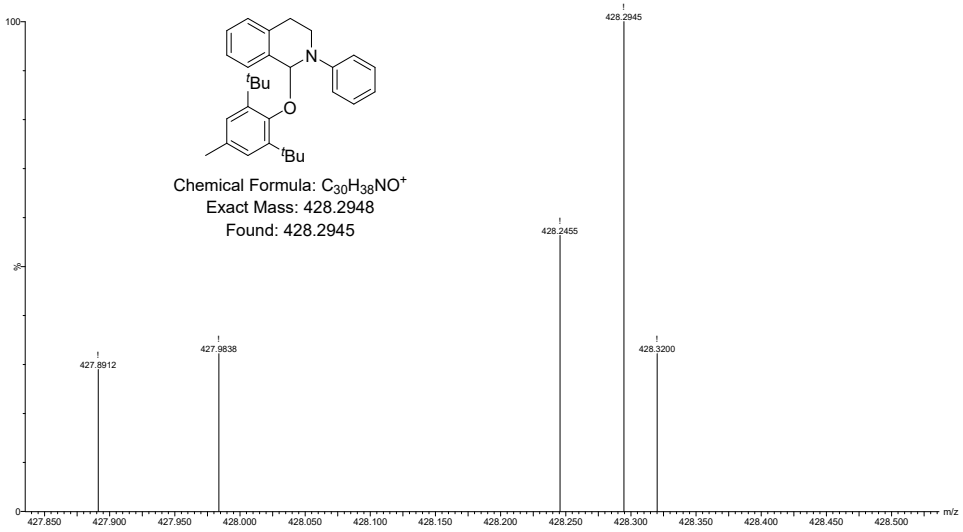


Figure S1

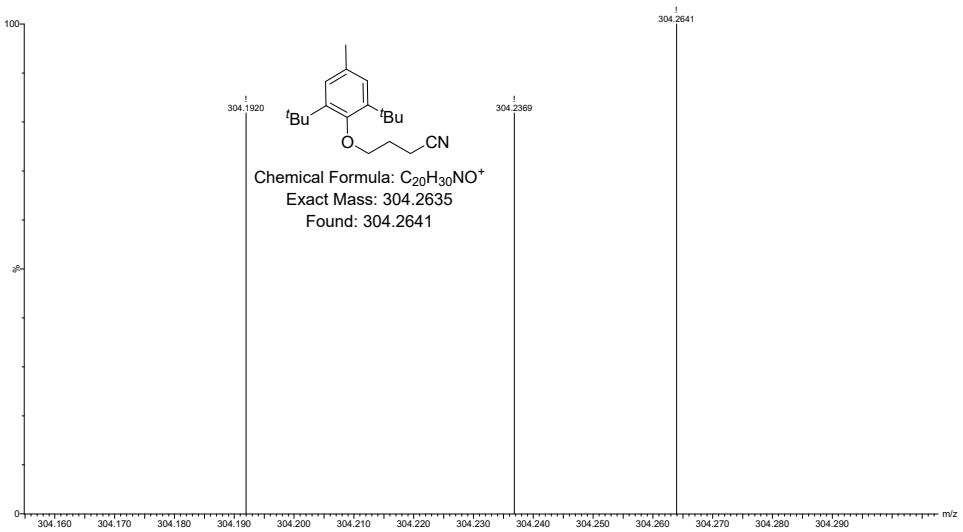


Figure S2

(b) Stern-Volmer fluorescence quenching study

Emission intensities were recorded using a HITACHI spectrofluorophotometer F-7000. All 3CzClIPN solutions were excited at 350 nm and the emission intensity at 552 nm was observed. MeCN was degassed with a stream of argon for 30 min. In a typical experiment, the emission spectrum of the sample was collected after the sample was degassed with a stream of argon for 15 minutes. First, the emission spectrum of a 2.0×10^{-4} M solution of 3CzClIPN in MeCN was collected. Then, the appropriate amount of quencher was added to the measured solution and the emission spectrum of the sample was collected.

As shown on Fig. 3-4, Stern-Volmer studies resulted in linear dependence between I_0/I and the concentration of quenchers. The results indicates that the N-phenyl THIQ quenches the excited state of 3CzClIPN, where it presumably engages in SET event with the photoexcited 3CzClIPN complex.

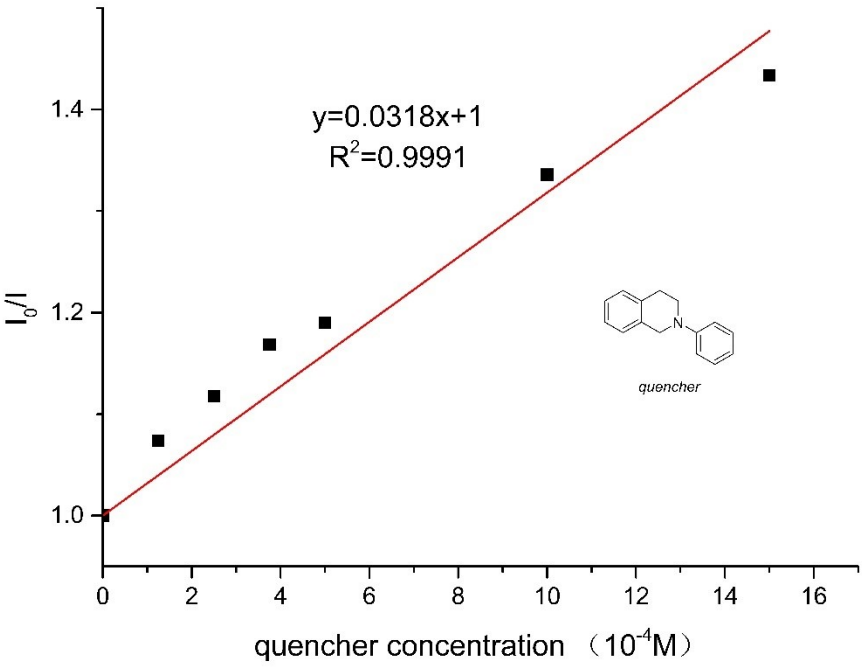


Figure S3 Stern-Volmer plot for the emission quenching of 3CzClIPN by various concentrations of THIQ

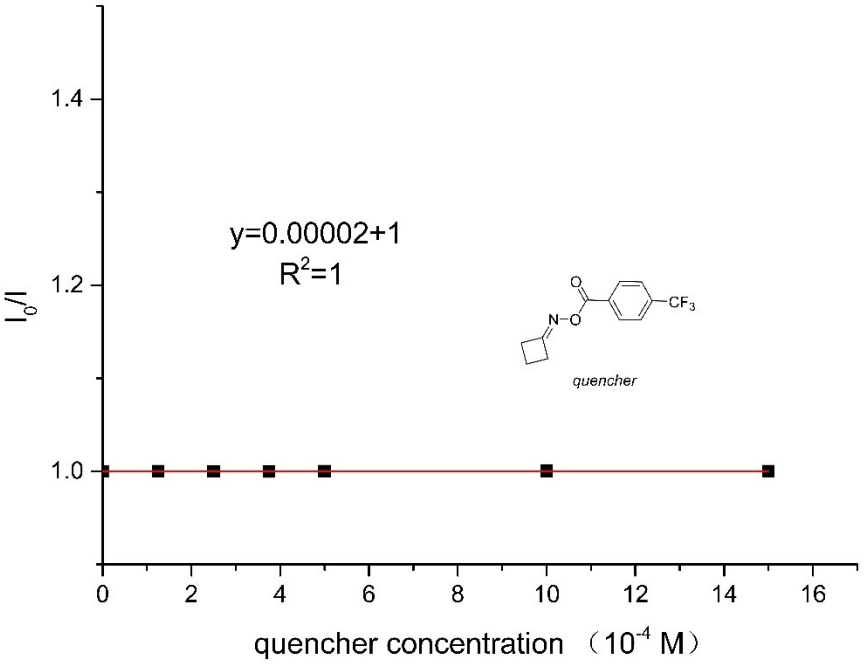
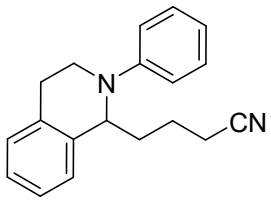


Figure S4 Stern-Volmer plot for the emission quenching of 3CzClIPN by various concentrations of cyclobutanone O-(4-(trifluoromethyl)phenyl) oxime

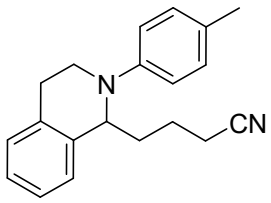
(C) Analytical data

4-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3aa),47.5 mg, 86% yield;



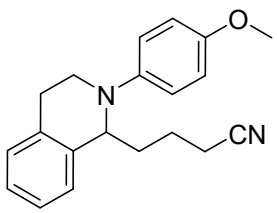
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.5 Hz, 2H), 7.16 (d, *J* = 6.5 Hz, 2H), 7.11 (d, *J* = 6.5 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 7.5 Hz, 1H), 4.67 (t, *J* = 6.5 Hz, 1H), 3.66-3.57 (m, 2H), 3.02-2.96 (m, 1H), 2.76 (d, *J* = 16 Hz, 1H), 2.33 (t, *J* = 7.0 Hz, 2H), 2.09-2.04 (m, 1H), 1.93-1.83 (m, 2H), 1.80–1.75 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 137.9, 134.9, 129.3, 128.8, 127.0, 126.7, 126.0, 119.5, 118.0, 114.8, 58.3, 42.0, 35.5, 26.5, 22.8, 17.1; LRMS (EI, 70 eV) m/z (%): 276 (M^+, 4), 193 (5),208 (100), 165 (3); HRMS m/z (ESI) calcd for $C_{19}H_{20}N_2$ $[M+H]^+$ 277.1699, found 277.1694.

4-(2-(p-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ba), 47.1 mg, 81% yield;



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18-7.14 (m, 2H), 7.11–7.07 (m, 2H), 7.03 (d, *J* = 7.5 Hz, 2H), 6.80 (t, *J* = 6.0 Hz,, 2H), 4.62-4.58 (m, 1H), 3.62–3.52 (m, 2H), 2.98-2.91 (m, 1H), 2.73-2.68 (m, 1H), 2.34-2.31 (m, 2H), 2.24 (d, *J* = 4.0 Hz, 3H), 2.08–2.01 (m, 1H), 1.92-1.81 (m, 2H), 1.79–1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 138.0, 134.8, 129.8, 128.8, 127.6, 127.0, 126.5, 125.9, 119.6, 115.6, 58.3, 42.3, 35.4, 26.1, 22.8, 20.2, 17.0; LRMS (EI, 70 eV) m/z (%): 290 (M^+, 3), 115 (17), 222 (100), 91 (30); HRMS m/z (ESI) calcd for $C_{20}H_{22}N_2$ $[M+H]^+$ 291.1856, found 291.1860.

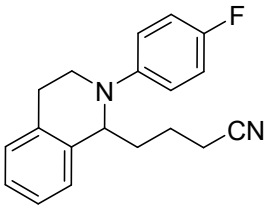
4-(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ca), 51.4 mg, 84% yield;



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18-7.12 (m, 3H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.88-6.85 (m, 2H), 6.81–6.79 (m, 2H),

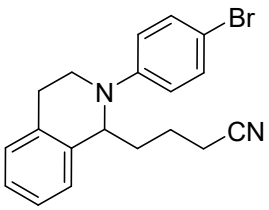
4.50-4.47 (m, 1H), 3.74 (d, J = 3,0 Hz, 3H), 3.54-3.51 (m, 2H), 2.93-2.86 (m, 1H), 2.68-2.64 (m, 1H), 2.34-2.32 (m, 2H), 2.04-1.99 (m, 1H), 1.90–1.78 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 144.5, 138.1, 134.9, 129.0, 127.0, 126.4, 126.0, 119.6, 118.7, 114.6, 58.9, 55.6, 43.6, 35.3, 26.0, 22.7, 17.0; LRMS (EI, 70 eV) m/z (%): 306 (M^+, 4), 223 (6), 238 (100), 115 (13); HRMS m/z (ESI) calcd for $C_{20}H_{22}N_2O$ $[M+H]^+$ 307.1805, found 307.1803.

4-(2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3da), 58.3 mg, 74% yield;



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19-7.14 (m, 2H), 7.10 (t, J = 10.5 Hz, 2H), 6.93–6.89 (m, 2H), 6.83-6.80 (m, 2H), 4.54-4.50 (m, 1H), 3.55–3.53 (m, 2H), 2.94-2.88 (m, 1H), 2.73-2.67 (m, 1H), 2.31 (t, J = 7.5 Hz, 2H), 2.05–2.00 (m, 1H), 1.91–1.80 (m, 2H), 1.78-1.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3 (d, J_{CF} = 236.3 Hz), 146.5 (d, J_{CF} = 2.1 Hz), 137.7, 134.6, 128.9, 127.0, 126.6, 126.0, 119.5, 117.3 (d, J_{CF} = 7.4 Hz), 115.6 (d, J_{CF} = 21.8 Hz), 58.7, 43.0, 35.4, 26.0, 22.7, 17.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ -125.9; LRMS (EI, 70 eV) m/z (%): 294 (M^+, 3), 115 (11), 226 (100), 95 (10); HRMS m/z (ESI) calcd for $C_{19}H_{19}FN_2$ $[M+H]^+$ 295.1605, found 295.1600.

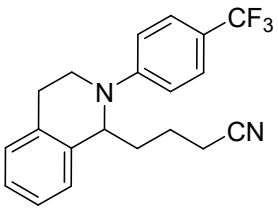
4-(2-(4-bromophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ea), 51.0 mg, 72% yield;



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.27 (m, 2H), 7.18-7.15 (m, 2H), 7.12-7.08 (m, 2H), 6.73-6.71 (m, 2H), 4.61-4.58 (m, 1H), 3.57-3.54 (m, 2H), 2.98-2.92 (m, 1H), 2.80-2.74 (m, 1H), 2.32-2.29 (m, 2H), 2.09–2.01 (m, 1H), 1.90–1.78 (m, 2H), 1.76–1.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 137.4, 134.5, 131.9, 128.7, 127.0, 126.8, 126.1, 119.4, 116.1, 109.6, 58.2, 42.0, 35.3, 26.4, 22.7, 17.0;

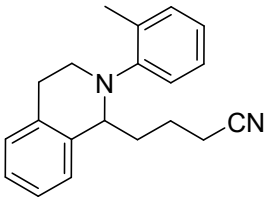
LRMS (EI, 70 eV) m/z (%): 354 (M^+, 17), 253 (38), 207 (100), 281 (32); HRMS m/z (ESI) calcd for $C_{19}H_{19}BrN_2$ $[M+H]^+$ 355.0804, found 355.0799.

4-(2-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3fa), 33.0 mg, 48% yield;



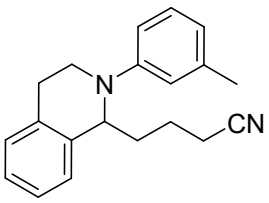
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 8.5 Hz, 2H), 7.21–7.15 (m, 3H),7.11 (d, J = 5.5 Hz, 1H), 6.86 (d, J = 8.5 Hz, 2H), 4.75 (t, J = 7.5 Hz, 1H), 3.65 (t, J = 7.0 Hz, 2H), 3.06-3.00 (m, 1H), 2.92-2.87 (m, 1H), 2.35 (t, J = 7.5 Hz, 2H), 2.15-2.08 (m, 1H), 1.96–1.88 (m, 1H), 1.85–1.72 (m, 1H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 151.4, 137.2, 134.5, 128.7, 127.2, 127.1, 126.7 (q, J_{CF} = 3.8 Hz), 126.3, 124.8 (d, J_{CF} = 268.2 Hz), 119.3, 118.7 (d, J_{CF} = 32.5 Hz), 112.5, 58.2, 41.9, 35.4, 26.9, 22.7, 17.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ -61.1; LRMS (EI, 70 eV) m/z (%): 344 (M^+, 4), 172 (8), 276 (100), 145 (11); HRMS m/z (ESI) calcd for $C_{20}H_{19}F_3N_2$ $[M+H]^+$ 345.1573, found 345.1574.

4-(2-(o-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ga), 51.0 mg, 88% yield;



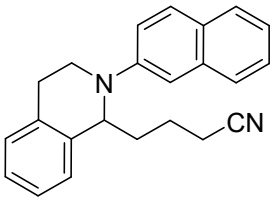
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.16 (m, 4H), 7.09 (d, J = 7.5 Hz, 1H), 7.04–6.96 (m, 2H), 6.85 (d, J = 7.5 Hz, 1H), 4.33 (d, J = 9.0 Hz, 1H), 3.41-3.35 (m, 1H), 3.17-3.12 (m, 1H), 2.75-2.68 (m, 1H), 2.63-2.59 (m, 1H), 2.36 (s, 3H), 2.31-2.23 (m, 2H), 2.04-1.97 (m, 1H), 1.89–1.75 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 138.7, 135.5, 133.4, 131.1, 129.1, 126.6, 126.4, 126.2, 123.5, 122.5, 119.7, 59.5, 44.4, 35.3, 25.9, 22.4, 18.1, 16.9; LRMS (EI, 70 eV) m/z (%): 290 (M^+, 2), 223 (17), 222 (100), 220 (10); HRMS m/z (ESI) calcd for $C_{20}H_{22}N_2$ $[M+H]^+$ 291.1856, found 291.1857.

4-(2-(m-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ha), 52.2mg, 90% yield;



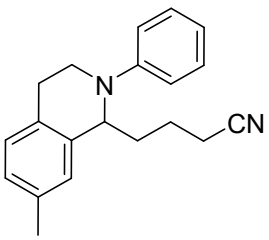
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15-7.08 (m, 5H), 6.68 (d, *J* = 13.0 Hz, 2H), 6.58 (d, *J* = 7.5 Hz, 1H), 4.67 (t, *J* = 7.0 Hz, 1H), 3.66-3.54 (m, 2H), 3.01-2.94 (m, 1H), 2.76– 2.71 (m, 1H), 2.31 (d, *J* = 9.0 Hz, 5H), 2.08-2.02 (m, 1H), 1.91-1.73 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 138.9, 138.0, 134.8, 129.1, 128.8, 127.0, 126.6, 125.9, 119.5, 118.9, 115.5, 111.9, 58.1, 41.8, 35.4, 26.4, 22.7, 21.8, 17.0; LRMS (EI, 70 eV) m/z (%): 290 (M^+, 12), 207 (37), 83 (100), 276 (35); HRMS m/z (ESI) calcd for $C_{20}H_{22}N_2$ $[M+H]^+$ 291.1856, found 291.1858.

4-(2-(naphthalen-2-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ia), 47.6 mg, 73% yield;



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73–7.67 (m, 2H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.25-7.17 (m, 5H), 7.11 (d, *J* = 6.5 Hz, 1H), 7.06 (s, 1H), 4.84-4.81 (m, 1H), 3.82-3.78 (m, 1H), 3.69-3.64 (m, 1H), 3.05-2.99 (m, 1H), 2.80-2.76 (m, 1H), 2.35-2.32 (m, 2H), 2.14-2.10 (m, 1H), 1.97-1.91 (m, 1H), 1.89-1.78 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 137.8, 134.7, 129.0, 128.9, 127.6, 127.3, 127.1, 126.7, 126.3, 126.1, 122.8, 119.6, 118.2, 109.4, 58.2, 42.1, 35.5, 26.4, 22.8, 17.1; LRMS (EI, 70 eV) m/z (%): 326 (M^+, 29), 173 (38), 207 (100), 168 (70); HRMS m/z (ESI) calcd for $C_{23}H_{22}N_2$ $[M+H]^+$ 327.1856, found 327.1858.

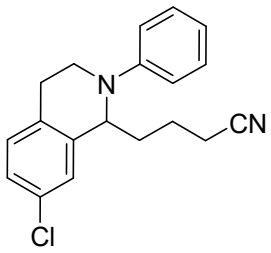
4-(7-methyl-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ka), 46.4 mg, 80% yield;



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, *J* = 8.5 Hz, 2H), 6.97 (t, *J* = 11.0 Hz, 2H), 6.92 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.74 (t, *J* = 8.0 Hz, 1H), 4.62 (t, *J* = 7.0 Hz, 1H), 3.63-3.53 (m, 2H), 2.95-2.89 (m, 1H), 2.72–2.67 (m, 1H), 2.32 (d, *J* = 8.0

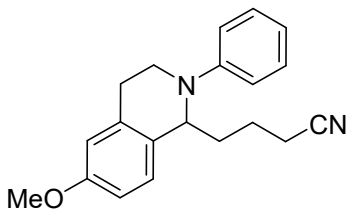
Hz, 5H), 2.06–2.03 (m, 1H), 1.92–1.81 (m, 2H), 1.79–1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 137.7, 135.4, 131.7, 129.2, 128.6, 127.5, 127.4, 119.5, 117.9, 114.8, 58.2, 42.0, 35.5, 25.9, 22.8, 21.0, 17.0; LRMS (EI, 70 eV) m/z (%): 290 (M^+, 4), 115 (6), 222 (100), 104 (9); HRMS m/z (ESI) calcd for $C_{20}H_{22}N_2$ $[M+H]^+$ 291.1856, found 291.1859.

4-(7-chloro-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3la), 44.6 mg, 72% yield;



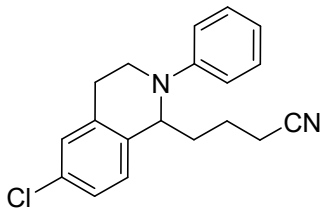
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.21 (m, 2H), 7.12 (d, *J* = 6.5 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.78 (t, *J* = 8.0 Hz, 1H), 4.63-4.61 (m, 1H), 3.71-3.65 (m, 1H), 3.58-3.51 (m, 1H), 2.95-2.88 (m, 1H), 2.69-2.64 (m, 2H), 2.40-2.34 (m, 2H), 2.10-2.01 (m, 1H), 1.93–1.81 (m, 3H), 1.81–1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 139.8, 133.2, 131.4, 130.3, 129.3, 126.8, 126.8, 119.4, 118.6, 115.4, 58.0, 41.6, 35.3, 25.5, 22.8, 17.0; LRMS (EI, 70 eV) m/z (%): 310 (M^+, 2), 206 (9), 242 (100), 173 (16); HRMS m/z (ESI) calcd for $C_{19}H_{19}ClN_2$ $[M+H]^+$ 311.1310, found 311.1310.

4-(6-methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ma), 49.6 mg, 81% yield;



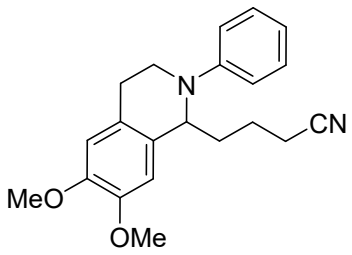
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.21 (m, 2H), 7.04-7.01 (m, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.77-6.72 (m, 2H), 6.65 (s, 1H), 4.62 (t, *J* = 4.5 Hz, 1H), 3.77 (s, 3H), 3.63-3.55 (m, 2H), 2.98-2.92 (m, 1H), 2.72-2.70 (m, 1H), 2.34-2.31 (m, 2H), 2.05–2.02 (m, 1H), 1.89-1.81 (m, 2H), 1.79–1.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 149.6, 136.2, 130.1, 129.3, 128.0, 119.5, 118.0, 114.8, 113.5, 112.1, 57.7, 55.2, 41.9, 35.6, 26.8, 22.8, 17.1; LRMS (EI, 70 eV) m/z (%): 306 (M^+, 13), 207 (43), 242 (100), 196 (16); HRMS m/z (ESI) calcd for $C_{20}H_{22}N_2O$ $[M+H]^+$ 307.1805, found 307.1800.

4-(6-chloro-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3na), 44.6 mg, 72% yield;



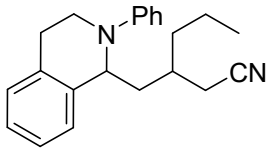
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 7.06 (t, *J* = 7.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.79 (t, *J* = 7.5 Hz, 1H), 4.64 (t, *J* = 4.5 Hz, 1H), 3.68-3.63 (m, 1H), 3.59-3.52 (m, 1H), 2.98-2.92 (m, 1H), 2.73-2.68 (m, 1H), 2.37-2.34 (m, 2H), 2.09-2.03 (m, 1H), 1.91-1.82 (m, 2H), 1.81–1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 136.8, 136.5, 132.2, 129.4, 128.8, 128.3, 126.2, 119.4, 118.6, 115.3, 57.8, 41.6, 35.4, 26.1, 22.7, 17.1; LRMS (EI, 70 eV) m/z (%): 310 (M^+, 3), 244 (35), 242 (100), 243 (19); HRMS m/z (ESI) calcd for $C_{19}H_{19}ClN_2$ $[M+H]^+$ 311.1310, found 311.1298.

4-(6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3oa), 62.5 mg, 93% yield;



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.5 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.62-6.58 (m, 2H), 4.62-4.59 (m, 1H), 3.88 (d, *J* = 3.0 Hz, 3H), 3.85 (d, *J* = 3.0 Hz, 3H), 3.71-3.66 (m, 1H), 3.59–3.52 (m, 1H), 2.94–2.88 (m, 1H), 2.64-2.60 (m, 1H), 2.40-2.37 (m, 2H), 2.11–2.04 (m, 1H), 1.97–1.86 (m, 2H), 1.84–1.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 147.7, 147.2, 129.8, 129.3, 126.8, 119.6, 118.3, 115.3, 111.5, 109.8, 57.9, 56.0, 55.8, 41.9, 35.4, 25.6, 22.8, 17.1; LRMS (EI, 70 eV) m/z (%): 336 (M^+, 5), 244 (34), 242 (100), 243 (25); HRMS m/z (ESI) calcd for $C_{21}H_{24}N_2O_2$ $[M+H]^+$ 337.1911, found 337.1915.

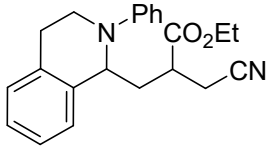
3-((2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)hexanenitrile (3ab), 45.8 mg, 72% yield; (dr = 1:1):



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.13 (m, 5H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.78 (t, *J* = 8.0 Hz, 1H), 4.70 (t, *J* = 7.0 Hz, 1H), 3.74 (t, *J* = 5.5 Hz, 1H), 3.60–3.54 (m, 1H), 2.96-2.89 (m, 1H), 2.63 (d, *J* = 16.0 Hz, 1H), 2.37 (t, *J* = 3.5 Hz, 2H), 2.15 (t, *J* = 13.0 Hz, 1H), 1.96 (t, *J* = 7.5 Hz, 1H), 1.78–1.72 (m, 1H), 1.47 (t, *J* = 8.5 Hz, 2H), 1.40-1.34 (m, 2H), 0.93 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 138.2, 134.7, 129.4, 129.1, 127.1, 126.6, 126.1, 118.8, 118.6, 116.1, 55.4, 42.0, 39.9, 36.1, 31.6, 25.4, 21.3, 19.9, 14.0; LRMS (EI, 70 eV) m/z (%): 318 (M^+, 2), 216 (2), 208 (100), 193 (5); HRMS m/z (ESI) calcd for $C_{22}H_{26}N_2$ $[M+H]^+$ 319.2169, found 319.2173.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, *J* = 8.0 Hz, 2H), 7.17-7.09 (m, 3H), 7.06 (d, *J* = 7.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.77 (t, *J* = 7.5 Hz, 1H), 4.73 (d, *J* = 10.0 Hz, 1H), 3.79-3.75 (m, 1H), 3.65 (t, *J* = 12.5 Hz, 1H), 2.98-2.93 (m, 1H), 2.63 (d, *J* = 16.5 Hz, 1H), 2.56-2.51 (m, 1H), 2.38-2.34 (m, 1H), 2.15–2.10 (m, 1H), 2.00-1.96 (m, 1H), 1.80-1.75 (m, 1H), 1.53 (d, *J* = 13.5 Hz, 1H), 1.43-1.35 (m, 2H), 1.30-1.26 (m, 1H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 138.4, 134.8, 129.3, 129.1, 127.0, 126.5, 126.0, 119.0, 118.6, 116.0, 57.3, 41.6, 40.8, 36.0, 33.2, 25.4, 22.1, 19.6, 14.0.

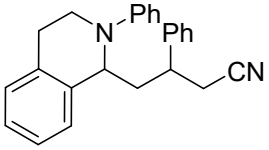
ethyl 3-cyano-2-((2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)propanoate (3ac), 56.4 mg, 81% yield; (dr = 4:1):



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.13 (m, 5H), 7.10–7.05 (m, 1H), 6.90 (t, *J* = 8.5 Hz, 2H), 6.79 (t, *J* = 7.5 Hz, 1H), 4.88–4.85 (m, 0.8H), 4.75–4.72 (m, 0.2H), 4.23-4.18 (m, 2H), 3.79-3.75 (m, 0.8H), 3.62-3.55 (m, 1.2H), 3.05–2.90 (m, 2H), 2.75-2.67 (m, 1H), 2.64-2.57 (m, 2H), 2.37-2.27 (m, 1H), 1.38 (t, *J* = 6.5 Hz, 0.8H), 1.29–1.24 (m, 3.22H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 172.5, 150.0, 149.4, 137.4, 137.0, 134.9, 134.8, 129.3, 129.2, 127.2, 127.1, 126.9, 126.7, 126.2, 126.1, 119.1, 118.9, 117.9, 117.6, 116.5, 115.9, 61.5, 56.4, 42.2, 41.6, 39.4, 38.7, 37.7, 37.5, 36.2, 25.5, 24.9, 21.0, 20.0,

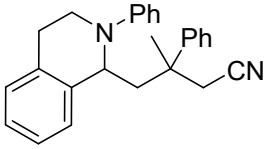
19.7, 16.7, 14.1, 14.0, 14.0; LRMS (EI, 70 eV) m/z (%): 348 (M^+, 3), 115 (13), 238 (100), 116 (11); HRMS m/z (ESI) calcd for $C_{22}H_{24}N_2O_2$ $[M+H]^+$ 349.1911, found 349.1913.

3-phenyl-4-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ad), 47.9 mg, 68% yield; (dr = 1:1):



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, *J* = 10.0 Hz, 1H), 7.34-7.29 (m, 3H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.21–7.08 (m, 5H), 7.01 (d, *J* = 6.5 Hz, 0.5H), 6.93 (d, *J* = 7.0 Hz, 0.5H), 6.75–6.63 (m, 3H),4.53 (t, *J* = 8.0 Hz, 0.5H), 4.44 (d, *J* = 11.5 Hz, 0.5H), 3.89-3.85 (m, 0.5H), 3.69-3.62 (m, 0.5H), 3.58-3.52 (m, 0.5H), 3.48-3.43 (m, 0.5H), 3.06-2.91 (m, 1.5H), 2.88-2.84 (m, 0.5H), 2.64–2.49 (m, 3.5H), 2.45-2.39 (m, 0.5H), 2.21-2.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 149.0, 141.2, 141.2, 138.2, 137.5, 134.9, 134.6, 129.2, 129.2, 129.0, 129.0, 128.7, 127.7, 127.6, 127.5, 127.1, 127.0, 126.8, 126.4, 125.9, 125.8, 118.6, 118.4, 118.3, 117.8, 115.9, 114.3, 56.1, 55.8, 42.5, 41.9, 40.8, 40.6, 39.4, 38.7, 26.6, 25.6, 24.9, 24.7; LRMS (EI, 70 eV) m/z (%): 352 (M^+, 23), 238 (66), 207 (100), 193 (33); HRMS m/z (ESI) calcd for $C_{25}H_{24}N_2$ $[M+H]^+$ 353.2012, found 353.2014.

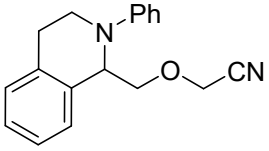
3-methyl-3-phenyl-4-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ae), 52.7 mg, 72% yield; (dr = 2:1):



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.37 (m, 1.73H), 7.33–7.29 (m, 3H), 7.25–7.17 (m, 2H), 7.13-7.07 (m, 3H), 6.97 (t, *J* = 4.5 Hz, 0.73H), 6.82-6.73 (m, 2.37H), 6.61 (t, *J* = 4.5 Hz, 1.37H), 5.04 (d, *J* = 4.0 Hz, 1H), 4.30 (d, *J* = 10.5 Hz, 1H), 3.87–3.67 (m, 1.73H), 3.47 (t, *J* = 5.5 Hz, 0.27H), 3.21 (d, *J* = 15.0 Hz, 0.73H), 3.07-2.90 (m, 1.27H), 2.86-2.77 (m, 1H), 2.74-2.66 (m, 1H), 2.48 (d, *J* = 16.5 Hz, 0.73H), 2.40-2.30 (m, 0.54H), 2.14 (d, *J* = 15.5 Hz, 0.73H), 1.57-1.52 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 149.0, 144.6, 138.3, 136.5, 135.9, 135.0, 130.9, 129.2, 129.2, 129.1, 128.9,

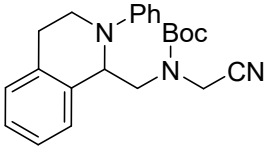
128.8, 128.5, 128.4, 127.4, 126.9, 126.9, 126.3, 125.9, 125.9, 125.7, 119.3, 119.1, 119.0, 118.7, 116.8, 115.8, 62.8, 55.1, 48.1, 45.9, 44.9, 44.5, 42.2, 40.8, 29.6, 27.8, 27.4, 25.9, 24.5, 22.8; LRMS (EI, 70 eV) m/z (%): 366 (M^+, 2), 193 (7), 208 (100), 165 (4); HRMS m/z (ESI) calcd for $C_{26}H_{26}N_2$ $[M+H]^+$ 367.2169, found 367.2170.

2-((2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methoxy)acetonitrile-d14 (3af), 45.6 mg, 82% yield;



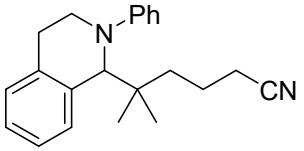
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.23 (m, 2H), 7.18 (t, *J* = 7.0 Hz, 3H), 7.13 (t, *J* = 4.5 Hz, 1H), 6.93 (t, *J* = 3.0 Hz, 2H), 6.79-6.75 (m, 1H), 4.92-4.89 (m, 1H), 4.17 (t, *J* = 4.0 Hz, 2H), 3.95–3.91 (m, 1H), 3.77-3.73 (m, 1H), 3.62-3.57 (m, 2H), 3.03-2.99 (m, 1H), 2.85-2.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 135.5, 134.5, 129.3, 128.5, 127.5, 127.2, 126.1, 118.1, 115.8, 114.2, 74.3, 59.0, 56.5, 42.3, 27.3; HRMS m/z (ESI) calcd for $C_{18}H_{18}N_2O$ $[M+H]^+$ 279.1492, found 279.1489.

tert-butyl (cyanomethyl)((2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)carbamate (3ag), 52.8 mg, 70% yield; (dr = 1:1):



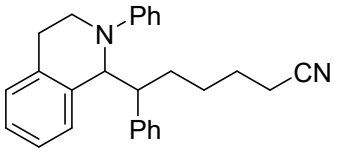
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, *J* = 9.0 Hz, 5H), 7.14 (s, 0.5H)7.07 (d, *J* = 7.0 Hz, 0.5H), 6.90 (t, *J* = 10.5 Hz, 2H), 6.80-6.75 (m, 1H), 5.12 (t, *J* = 5.5 Hz, 0.5H), 4.96 (t, *J* = 8.0 Hz, 0.5H), 4.68 (d, *J* = 3.0 Hz, 0.5H), 4.10 (d, *J* = 12.5 Hz, 0.5H), 4.00–3.85 (m, 1H), 3.74 (d, *J* = 16.0 Hz, 1H), 3.66 (s, 1H), 3.63-3.54 (m, 2H), 3.09-3.02 (m, 1H), 2.89-2.79 (m, 1H), 1.56 (d, *J* = 19.5 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 154.1, 149.4, 149.2, 135.6, 135.3, 135.0, 134.9, 129.4, 128.7, 128.7, 127.5, 127.4, 127.2, 127.1, 126.5, 126.3, 118.2, 118.1, 116.0, 115.9, 114.2, 113.9, 82.2, 82.0, 80.9, 58.8, 58.3, 51.8, 51.0, 42.2, 41.4, 37.3, 36.3, 28.3, 28.2, 26.9, 26.5; LRMS (EI, 70 eV) m/z (%): 377 (M^+, 5), 244 (30), 242 (100), 243 (17); HRMS m/z (ESI) calcd for $C_{23}H_{27}N_3O_2$ $[M+H]^+$ 378.2176, found 378.2175.

5-methyl-5-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)hexanenitrile (3ah), 41.3 mg, 65% yield;



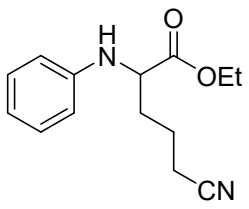
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21-7.11 (m, 6H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.72 (t, *J* = 7.5 Hz, 1H), 4.63 (s, 1H), 3.89-3.83 (m, 1H), 3.62-3.56 (m, 1H), 2.96 (t, *J* = 7.0 Hz, 2H), 2.19 (t, *J* = 6.5 Hz, 2H), 1.63 (d, *J* = 10.5 Hz, 2H), 1.51 (t, *J* = 6.5 Hz, 2H), 1.01 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 136.2, 135.6, 129.1, 128.7, 128.6, 126.7, 125.2, 119.7, 117.9, 115.9, 65.0, 44.8, 41.3, 39.9, 26.8, 25.5, 20.8, 17.8; LRMS (EI, 70 eV) m/z (%): 318 (M^+, 9), 317 (20), 207 (100), 267 (30); HRMS m/z (ESI) calcd for $C_{22}H_{26}N_2$ $[M+H]^+$ 319.2169, found 319.2168.

6-phenyl-6-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)hexanenitrile (3ai), 40.3 mg, 53% yield; (dr = 1:1):



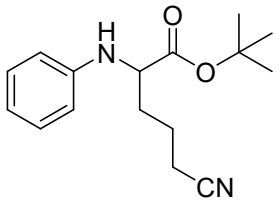
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 8.5 Hz, 1H), 7.22–7.15 (m, 3.5H), 7.13-7.07 (m, 3.5H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.93-6.89 (m, 1.5H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1.5H), 6.64 (t, *J* = 8.0 Hz, 0.5H), 6.50 (d, *J* = 8.0 Hz, 0.5H), 4.87 (d, *J* = 7.0 Hz, 0.5H), 4.82 (d, *J* = 7.0 Hz, 0.5H), 3.62-3.56 (m, 0.5H), 3.52-3.47 (m, 0.5H), 3.41-3.31 (m, 1H), 3.19-3.12 (m, 1H), 2.97-2.91 (m, 0.5H), 2.85-2.79 (m, 0.5H), 2.73-2.67 (m, 0.5H), 2.22-2.11 (m, 2H), 2.10-2.00(m, 1H), 1.86-1.75 (m, 1.5H), 1.58-1.47 (m, 2H), 1.21-1.15 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 149.4, 141.5, 141.3, 136.8, 135.9, 135.7 135.3, 129.3, 129.2, 129.2, 128.9, 128.6, 128.6, 128.5, 128.1, 128.0, 127.8, 126.8, 126.7, 126.7, 126.5, 125.2, 125.0, 119.6, 118.8, 117.2, 116.7, 114.3, 112.7, 64.4, 64.0, 51.7, 51.3, 43.0, 42.7, 31.6, 31.4, 27.0, 26.9, 26.7, 25.4, 17.0, 16.9; HRMS m/z (ESI) calcd for $C_{27}H_{28}N_2$ $[M+H]^+$ 381.2325, found 381.2325.

ethyl 5-cyano-2-(phenylamino)pentanoate (5aa), 44.8 mg, 91% yield;



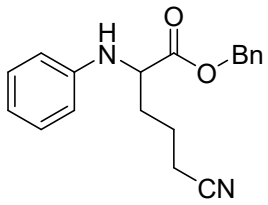
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.5 Hz, 2H), 6.76 (t, *J* = 7.0 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 2H), 4.21-4.17 (m, 3H), 4.08 (t, *J* = 6.5 Hz, 1H), 2.40-2.36 (m, 2H), 2.04-1.98 (m, 1H), 1.93-1.86 (m, 1H), 1.84-1.78 (m, 2H), 1.25 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 146.4, 129.3, 119.1, 118.6, 113.5, 61.4, 55.9, 31.6, 21.7, 16.9, 14.1; LRMS (EI, 70 eV) m/z (%): 246 (M^+, 9), 132 (25), 173 (100), 120 (30); HRMS m/z (ESI) calcd for $C_{14}H_{18}N_2O_2$ $[M+H]^+$ 247.1441, found 247.1438.

tert-butyl 5-cyano-2-(phenylamino)pentanoate (5ba), 47.7 mg, 87% yield;



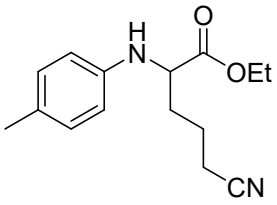
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, *J* = 8.0 Hz, 2H), 6.75 (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 2H), 4.17 (s, 1H), 3.99 (t, *J* = 5.0 Hz, 1H), 2.42-2.37 (m, 2H), 2.01–1.95 (m, 1H), 1.91-1.88 (m, 1H), 1.84-1.78 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 146.6, 129.3, 119.2, 118.4, 113.5, 82.2, 56.4, 31.6, 27.9, 21.6, 17.0; LRMS (EI, 70 eV) m/z (%): 274 (M^+, 4), 118 (23), 173 (100), 104 (10); HRMS m/z (ESI) calcd for $C_{16}H_{22}N_2O_2$ $[M+H]^+$ 275.1754, found 275.1759.

benzyl 5-cyano-2-(phenylamino)pentanoate (5ca), 37.6 mg, 61% yield;



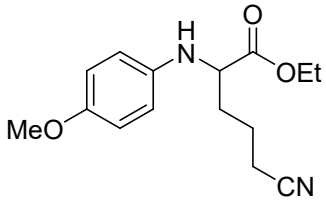
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.5 Hz, 3H), 7.28 (d, *J* = 7.0 Hz, 2H), 7.17 (t, *J* = 7.5 Hz, 2H), 6.76 (t, *J* = 7.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 2H), 5.18-5.12 (m, 2H), 4.30-4.09 (m, 2H), 2.36-2.28 (m, 2H), 2.04–1.97 (m, 1H), 1.93-1.85 (m, 1H), 1.77-1.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 146.4, 135.2, 129.4, 128.6, 128.5, 128.3, 119.0, 118.8, 113.6, 67.1, 56.0, 31.6, 21.6, 16.9; LRMS (EI, 70 eV) m/z (%): 308 (M^+, 5), 120 (23), 173 (100), 91 (59); HRMS m/z (ESI) calcd for $C_{19}H_{20}N_2O_2$ $[M+H]^+$ 309.1598, found 309.1593.

ethyl 5-cyano-2-(p-tolylamino)pentanoate (5da), 44.2 mg, 85% yield;



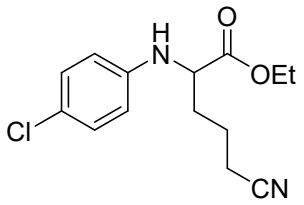
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, *J* = 7.5 Hz, 2H), 6.54 (d, *J* = 7.5 Hz, 2H), 4.20-4.15 (m, 2H), 4.04 (d, *J* = 9.0 Hz, 2H), 2.40–2.33 (m, 2H), 2.22 (s, 3H), 2.02-1.95 (m, 1H), 1.90-1.84 (m, 1H), 1.83–1.76 (m, 2H), 1.24 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 144.1, 129.7, 127.8, 119.1, 113.7, 61.2, 56.2, 31.6, 21.7, 20.2, 16.8, 14.1; LRMS (EI, 70 eV) m/z (%): 260 (M^+, 13), 134 (18), 187 (100), 146 (14); HRMS m/z (ESI) calcd for $C_{15}H_{20}N_2O_2$ $[M+H]^+$ 261.1598, found 261.1601.

ethyl 5-cyano-2-((4-methoxyphenyl)amino)pentanoate (5ea), 49.1 mg, 89% yield;



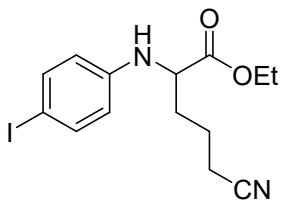
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78–6.75 (m, 2H), 6.61–6.59 (m, 2H), 4.19–4.15 (m, 2H), 3.99-3.93 (m, 2H), 3.73 (d, *J* = 2.0 Hz, 3H), 2.40-2.36 (m, 2H), 1.99–1.94 (m, 1H), 1.88–1.79 (m, 3H), 1.25-1.22 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 152.8, 140.5, 119.1, 115.2, 114.7, 61.1, 57.0, 55.5, 31.7, 21.7, 16.8, 14.1; LRMS (EI, 70 eV) m/z (%): 276 (M^+, 18), 162 (12), 203 (100), 134 (22); HRMS m/z (ESI) calcd for $C_{15}H_{20}N_2O_3$ $[M+H]^+$ 277.1547, found 277.1544.

ethyl 2-((4-chlorophenyl)amino)-5-cyanopentanoate (5fa), 34.7 mg, 62% yield;



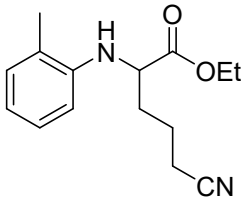
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14-7.11 (m, 2H), 6.55 (d, *J* = 9.0 Hz, 2H), 4.21–4.18 (m, 3H), 4.05-4.01 (m, 1H), 2.45-2.35 (m, 2H), 2.04-1.97 (m, 1H), 1.93–1.86 (m, 1H), 1.83-1.77 (m, 2H), 1.28-1.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 145.1, 129.2, 123.3, 119.0, 114.7, 61.5, 56.0, 31.5, 21.6, 16.9, 14.1; LRMS (EI, 70 eV) m/z (%): 280 (M^+, 10), 203 (24), 207 (100), 209 (32); HRMS m/z (ESI) calcd for $C_{14}H_{17}ClN_2O_2$ $[M+H]^+$ 281.1051, found 281.1048.

ethyl 5-cyano-2-((4-iodophenyl)amino)pentanoate (5ga), 53.6 mg, 72% yield;



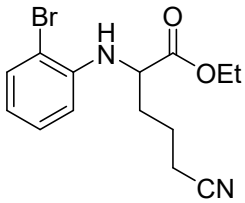
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.0 Hz, 2H), 6.40 (d, J = 8.0 Hz, 2H), 4.28 (d, J = 9.0 Hz, 1H), 4.22-4.17 (m, 2H), 4.05-4.01 (m, 1H), 2.40-2.36 (m, 2H), 2.02-1.96 (m, 1H), 1.1.92-1.84 (m, 1H), 1.81-1.75 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 146.1, 137.8, 119.0, 115.6, 79.4, 61.5, 55.6, 31.3, 21.5, 16.8, 14.1; LRMS (EI, 70 eV) m/z (%): 372 (M^+, 28), 230 (11), 299 (100), 119 (27); HRMS m/z (ESI) calcd for $C_{14}H_{17}IN_2O_2$ $[M+H]^+$ 373.0407, found 373.0405.

ethyl 5-cyano-2-(o-tolylamino)pentanoate (5ha), 44.2 mg, 85% yield;



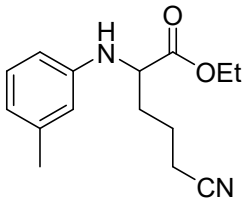
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11-7.07 (m, 2H), 6.72-6.69 (m, 1H), 6.54 (t, J = 3.0 Hz, 1H), 4.23–4.18 (m, 2H), 4.14 (t, J = 7.5 Hz, 1H), 2.42–2.37 (m, 2H), 2.21 (d, J = 3.0 Hz, 3H), 2.07–2.01 (m, 1H), 1.99–1.93 (m, 1H), 1.86-1.79 (m, 2H), 1.29-1.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 144.5, 130.4, 127.0, 123.0, 119.1, 118.2, 110.4, 61.4, 55.8, 31.7, 21.7, 17.4, 16.9, 14.1; LRMS (EI, 70 eV) m/z (%): 260 (M^+, 10), 188 (14), 187 (100), 146 (16); HRMS m/z (ESI) calcd for $C_{15}H_{20}N_2O_2$ $[M+H]^+$ 261.1598, found 261.1593.

ethyl 2-((2-bromophenyl)amino)-5-cyanopentanoate (5ia), 38.9 mg, 60% yield;



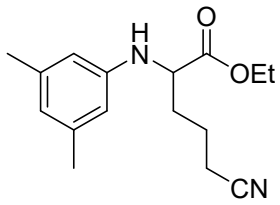
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 6.63 (t, J = 8.0 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 4.83 (d, J = 8.5 Hz, 1H), 4.25-4.20 (m, 2H), 4.14 (d, J = 7.0 Hz, 1H), 2.44-2.40 (m, 2H), 2.11-2.05 (m, 1H), 2.03-1.95 (m, 1H), 1.86-1.80 (m, 2H), 1.28 (d, J = 8.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 143.4, 132.8, 128.5, 119.1, 119.0, 111.8, 110.6, 61.7, 55.9, 31.4, 21.6, 17.0, 14.2; LRMS (EI, 70 eV) m/z (%): 324 (M^+, 10), 210 (15), 251 (100), 184 (22); HRMS m/z (ESI) calcd for $C_{14}H_{17}BrN_2O_2$ $[M+H]^+$ 325.0546, found 325.0544.

ethyl 5-cyano-2-(m-tolylamino)pentanoate (5ja), 48.4 mg, 93% yield;



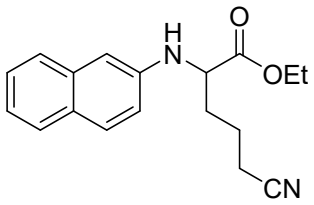
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (t, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 7.5 Hz, 1H), 6.44 (t, *J* = 7.5 Hz, 2H), 4.22-4.18 (m, 2H), 4.13-4.07 (m, 2H), 2.41-2.37 (m, 2H), 2.27 (s, 3H), 2.02–1.98 (m, 1H), 1.91–1.87 (m, 1H), 1.84-1.80 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 146.5, 139.2, 129.2, 119.6, 119.1, 114.4, 110.6, 61.4, 55.9, 31.7, 21.7, 21.5, 16.9, 14.2; LRMS (EI, 70 eV) m/z (%): 260 (M^+, 10), 146 (16), 187 (100), 118 (23); HRMS m/z (ESI) calcd for $C_{15}H_{20}N_2O_2$ $[M+H]^+$ 261.1598, found 261.1599.

ethyl 5-cyano-2-((3,5-dimethylphenyl)amino)pentanoate (5ka), 49.3 mg, 90% yield;



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (s, 1H), 6.26 (s, 2H), 4.22-4.17 (m, 2H), 4.11–4.06 (m, 2H), 2.40-2.36 (m, 2H), 2.22 (d, *J* = 2.5 Hz, 6H), 2.02–1.96 (m, 1H), 1.91-1.85 (m, 1H), 1.83-1.77 (m, 2H), 1.28-1.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 146.5, 139.0, 120.6, 119.1, 111.4, 61.3, 55.8, 31.7, 21.7, 21.4, 16.9, 14.1; LRMS (EI, 70 eV) m/z (%): 274 (M^+, 16), 160 (14), 201 (100), 148 (13); HRMS m/z (ESI) calcd for $C_{16}H_{22}N_2O_2$ $[M+H]^+$ 275.1754, found 275.1759.

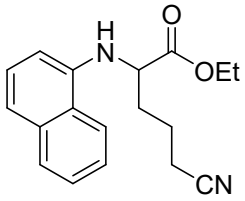
ethyl 5-cyano-2-(naphthalen-2-ylamino)pentanoate (5la), 45.6 mg, 77% yield;



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.59 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 6.79 (s, 1H), 4.38 (d, *J* = 7.5 Hz, 1H), 4.23-4.18 (m, 3H), 2.39-2.31 (m, 2H), 2.08-2.02 (m, 1H), 1.97-1.90 (m, 1H), 1.84-1.78 (m, 2H), 1.25 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 144.1, 134.8, 129.2, 127.9, 127.5, 126.4, 126.0, 122.5, 119.1, 118.1, 105.5, 61.4, 55.8, 31.4, 21.6, 16.9, 14.1; LRMS (EI, 70 eV) m/z (%): 296 (M^+, 14), 168

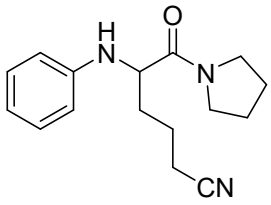
(25), 223 (100), 173 (40); HRMS m/z (ESI) calcd for $C_{18}H_{20}N_2O_2$ $[M+H]^+$ 297.1598, found 297.1593.

ethyl 5-cyano-2-(naphthalen-1-ylamino)pentanoate (5ma), 43.8 mg, 74% yield;



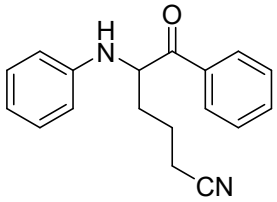
Yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92-7.90 (m, 1H), 7.79 (t, *J* = 6.0 Hz, 1H), 7.49-7.46 (m, 2H), 7.33-7.28 (m, 2H), 6.56 (d, *J* = 6.5 Hz, 1H), 4.94 (d, *J* = 8.0 Hz, 1H), 4.31-4.22 (m, 3H), 2.46–2.37 (m, 2H), 2.18-2.12 (m, 1H), 2.10-2.03 (m, 1H), 1.91–1.84 (m, 2H), 1.30-1.27 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 141.6, 134.4, 128.6, 126.2, 126., 125.1, 123.9, 120.0, 119.1, 118.8, 105.3, 61.6, 55.9, 31.4, 21.8, 17.0, 14.2; LRMS (EI, 70 eV) m/z (%): 296 (M^+, 20), 224 (19), 223 (100), 182 (17); HRMS m/z (ESI) calcd for $C_{18}H_{20}N_2O_2$ $[M+H]^+$ 297.1598, found 297.1599.

6-oxo-5-(phenylamino)-6-(pyrrolidin-1-yl)hexanenitrile (5na), 36.3 mg, 67% yield;



Yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, *J* = 8.0 Hz, 2H), 6.73 (t, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 2H), 4.56 (d, *J* = 8.0 Hz, 1H), 4.22 (d, *J* = 7.5 Hz, 1H), 3.61-3.56 (m, 1H), 3.54-3.49 (m, 2H), 3.46 (t, *J* = 7.5 Hz, 1H), 2.42-2.36 (m, 2H), 2.03-1.97 (m, 3H), 1.89-1.80 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 146.9 129.4, 119.4, 118.2, 113.6, 54.5, 46.4, 46.1, 30.9, 26.1, 24.0, 21.2, 17.0; LRMS (EI, 70 eV) m/z (%): 271 (M^+, 5), 120 (24), 173 (100), 132 (19); HRMS m/z (ESI) calcd for $C_{16}H_{21}N_3O$ $[M+H]^+$ 272.1757, found 272.1758.

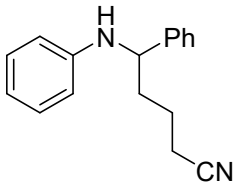
6-oxo-6-phenyl-5-(phenylamino)hexanenitrile (5oa), 48.9 mg, 88% yield;



Yellow oil; Yellow oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 2H), 6.74 (t, *J* = 7.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 2H), 5.11 (t, *J* = 5.0 Hz, 1H), 4.70 (s, 1H), 2.31 (t, *J*

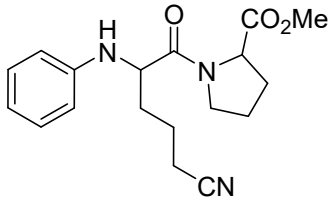
= 6.5 Hz, 2H), 2.17-2.12 (m, 1H), 1.84-1.77 (m, 2H), 1.75–1.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 146.6, 134.6, 134.0, 129.4, 129.0, 128.3, 119.1, 118.4, 113.6, 57.1, 31.8, 21.1, 17.0; HRMS m/z (ESI) calcd for $C_{18}H_{18}N_2O$ $[M+H]^+$ 279.1492, found 279.1496.

5-phenyl-5-(phenylamino)pentanenitrile (5pa), 20.5 mg, 41% yield;



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 4.0 Hz, 4H), 7.24 (d, *J* = 4.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 2H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 2H), 4.36 (t, *J* = 6.9 Hz, 1H), 4.04 (s, 1H), 2.37-2.33 (m, 2H), 2.02–1.91 (m, 2H), 1.84-1.78 (m, 1H), 1.72-1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9, 142.9, 129.2, 128.8, 127.4, 126.3, 119.3, 117.7, 113.4, 57.4, 37.3, 22.4, 17.1; HRMS m/z (ESI) calcd for $C_{17}H_{18}N_2$ $[M+H]^+$ 251.1543, found 251.1538.

methyl (5-cyano-2-(phenylamino)pentanoyl)prolinate (5ra), 49.4 mg, 75% yield; (dr = 1:1):

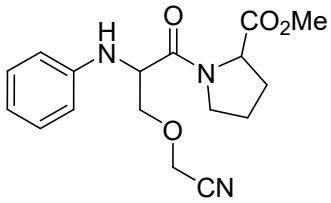


Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.62-6.55 (m, 2H), 4.54-4.50 (m, 2H), 4.28 (s, 1H), 3.73 (s, 3H), 3.69 (t, *J* = 5.0 Hz, 2H), 2.43-2.34 (m, 2H), 2.26-2.19 (m, 1H), 2.12–2.02 (m, 2H), 2.02–1.97 (m, 2H), 1.89–1.78 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 171.1, 146.7, 129.4, 119.4, 118.3, 113.7, 113.6, 58.9, 54.3, 52.2, 46.9, 30.7, 28.7, 24.9, 20.8, 17.0; LRMS (EI, 70 eV) m/z (%): 329 (M^+, 1), 244 (31), 242 (100), 173 (20); HRMS m/z (ESI) calcd for $C_{18}H_{23}N_3O_3$ $[M+H]^+$ 330.1812, found 330.1809.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.0 Hz, 2H), 6.78-6.72 (m, 1H), 6.62 (d, *J* = 8.0 Hz, 2H), 4.50-4.43 (m, 2H), 4.26 (d, *J* = 7.5 Hz, 1H), 3.84-3.78 (m, 1H), 3.65 (d, *J* = 3.0 Hz, 3H), 3.62–3.54 (m, 1H), 2.43–2.34 (m, 2H), 2.25–2.18 (m, 1H), 2.13-2.07 (m, 1H), 2.03 (t, *J* = 8.5 Hz, 3H), 1.86-1.77 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

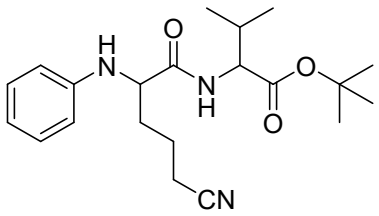
δ 172.2, 171.0, 146.5, 129.3, 119.3, 118.2, 113.4, 59.2, 54.5, 52.1, 46.8, 30.4, 28.8, 24.7, 21.1, 16.9.

methyl O-(cyanomethyl)-N-phenylserylprolinate (5rf), 43.0 mg, 65% yield; (dr = 3:1):



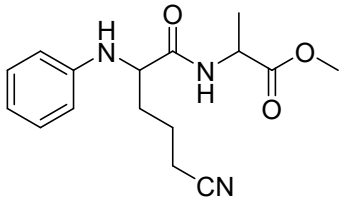
Yellow oil; 1H NMR (500 MHz, CDCl3) δ 7.18 (d, J = 8.0 Hz, 2H), 6.78-6.74 (m, 1H), 6.66 (d, J = 8.0 Hz, 2H), 4.54–4.44 (m, 2H), 4.40–4.28 (m, 2H), 3.93-3.89 (m, 1H), 3.85-3.80 (m, 2H), 3.74 (t, J = 2.0 Hz, 3H), 3.70–3.59 (m, 2H), 2.24-2.18 (m, 1H), 2.12–2.07 (m, 1H), 2.03-1.96 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 172.3, 172.1, 169.7, 169.6, 146.2, 146.0, 129.4, 129.4, 118.7, 118.5, 115.8, 115.6, 113.7, 113.4, 72.0, 71.5, 59.2, 59.0, 56.9, 56.8, 55.2, 55.0, 52.3, 52.2, 47.1, 47.0, 29.0, 28.9, 24.8, 24.7; HRMS m/z (ESI) calcd for C17H21N3O4 [M+H]+ 332.1605, found 332.1601.

tert-butyl (5-cyano-2-(phenylamino)pentanoyl)valinate (5sa), 53.7 mg, 72% yield; (dr = 1:1):



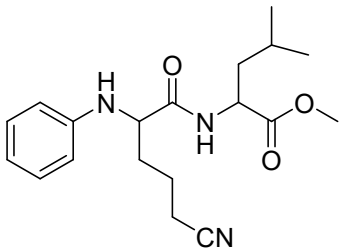
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21-7.15 (m, 2H), 6.80 (t, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 7.5 Hz, 2H), 4.42-4.36 (m, 1H), 4.14-4.04 (m, 1H), 3.81-3.75 (m, 1H), 2.44-2.37 (m, 2H), 2.13-2.07 (m, 2H), 2.04-1.91 (m, 2H), 1.89-1.82 (m, 2H), 1.45 (s, 5H), 1.32 (s, 4H), 1.26 (t, *J* = 7.5 Hz, 1H), 0.90-0.86 (m, 3H), 0.80 (d, *J* = 6.5 Hz, 1H), 0.69 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 172.2, 170.8, 170.0, 146.3, 146.1, 129.3, 119.3, 119.2, 119.2, 113.8, 113.5, 82.0, 81.9, 58.9, 58.5, 57.6, 57.0, 32.5, 32.3, 31.4, 31.1, 27.9, 27.7, 22.2, 22.1, 18.9, 18.8, 17.7, 17.1, 16.9, 16.9; LRMS (EI, 70 eV) m/z (%): 373 (M^+, 2), 242 (13), 173 (100), 222 (10); HRMS m/z (ESI) calcd for $C_{21}H_{31}N_3O_3$ $[M+H]^+$ 374.2438, found 374.2435.

methyl (5-cyano-2-(phenylamino)pentanoyl)alaninate (5ta), 43.0 mg, 71% yield; (dr = 1:1):



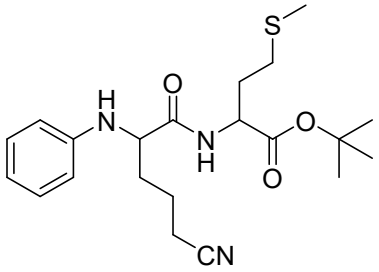
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.5 Hz, 2H), 6.81 (t, *J* = 7.5 Hz, 1H), 6.66-6.61 (m, 2H), 4.62-4.53 (m, 1H), 4.11–4.05 (m, 1H), 3.77–3.72 (m, 3H), 3.67 (d, *J* = 2.5 Hz, 1H), 2.45-2.36 (m, 2H), 2.11–2.07 (m, 1H), 1.97-1.90 (m, 2H), 1.88-1.83 (m, 2H), 1.39 (d, *J* = 7.5 Hz, 1H), 1.33 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 172.7, 172.5, 172.3, 146.3, 146.3, 129.4, 129.3, 119.3, 119.3, 119.2, 119.1, 113.8, 113.5, 60.3, 58.6, 52.4, 52.3, 47.9, 47.7, 32.3, 22.1, 21.9, 18.0, 17.9, 16.9, 16.9; HRMS m/z (ESI) calcd for $C_{16}H_{21}N_3O_3$ $[M+H]^+$ 304.1656, found 304.1652.

methyl (5-cyano-2-(phenylamino)pentanoyl)leucinate (5ua), 51.7 mg, 75% yield; (dr = 1:1):



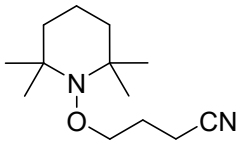
Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.18 (m, 2H), 7.04-6.97 (m, 1H), 6.85-6.81 (m, 1H), 6.66-6.61 (m, 2H), 4.61-4.57 (m, 1H), 3.95 (d, *J* = 20.5 Hz, 1H), 3.78–3.72 (m, 3H), 3.64 (d, *J* = 3.0 Hz, 1H), 2.46-2.38 (m, 2H), 2.12–2.06 (m, 1H), 1.98–1.92 (m, 1H), 1.90-1.82 (m, 2H), 1.60-1.50 (m, 2H), 1.46–1.34 (m, 1H), 0.93-0.90 (m, 3H), 0.85-0.78 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 172.6, 172.4, 171.2, 146.3, 146.1, 129.4, 129.4, 119.6, 119.5, 119.2, 119.2, 114.0, 113.6, 58.9, 58.5, 52.3, 52.2, 50.6, 50.3, 41.0, 32.4, 32.4, 24.9, 24.6, 22.8, 22.7, 22.2, 22.0, 21.7, 21.4, 17.0; LRMS (EI, 70 eV) m/z (%): 345 (M^+, 3), 207 (7), 173 (100), 120 (24); HRMS m/z (ESI) calcd for $C_{19}H_{27}N_3O_3$ $[M+H]^+$ 346.2125, found 346.2130.

tert-butyl (5-cyano-2-(phenylamino)pentanoyl)methioninate (5va), 51.0 mg, 63% yield; (dr = 1.2:1):



Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.18 (m, 2H), 6.84-6.79 (m, 1H), 6.665-6.60 (m, 2H), 4.64–4.52 (m, 1H), 4.06–4.02 (m, 1H), 3.79-3.74 (m, 1H), 2.45-2.38 (m, 3H), 2.28–2.24 (m, 1H), 2.14–2.08 (m, 2H), 2.06 (d, J = 3.5 Hz, 2H), 1.96-1.92 (m, 3H), 1.89-1.83 (m, 3H), 1.45 (d, J = 3.0 Hz, 5H), 1.36 (d, J = 3.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 172.2, 170.6, 160.0, 146.3, 146.1, 129.4, 129.4, 119.3, 119.2, 113.7, 113.4, 82.4, 82.3, 58.6, 58.4, 52.2, 51.6, 32.3, 31.8, 31.4, 29.9, 29.6, 27.9, 27.7, 22.2, 22.1, 17.0, 16.9, 15.4, 15.2, 14.1; LRMS (EI, 70 eV) m/z (%): 405 (M^+, 22), 281 (43), 207 (100), 177 (44); HRMS m/z (ESI) calcd for $C_{21}H_{31}N_3O_3S$ $[M+H]^+$ 406.2159, found 406.2157.

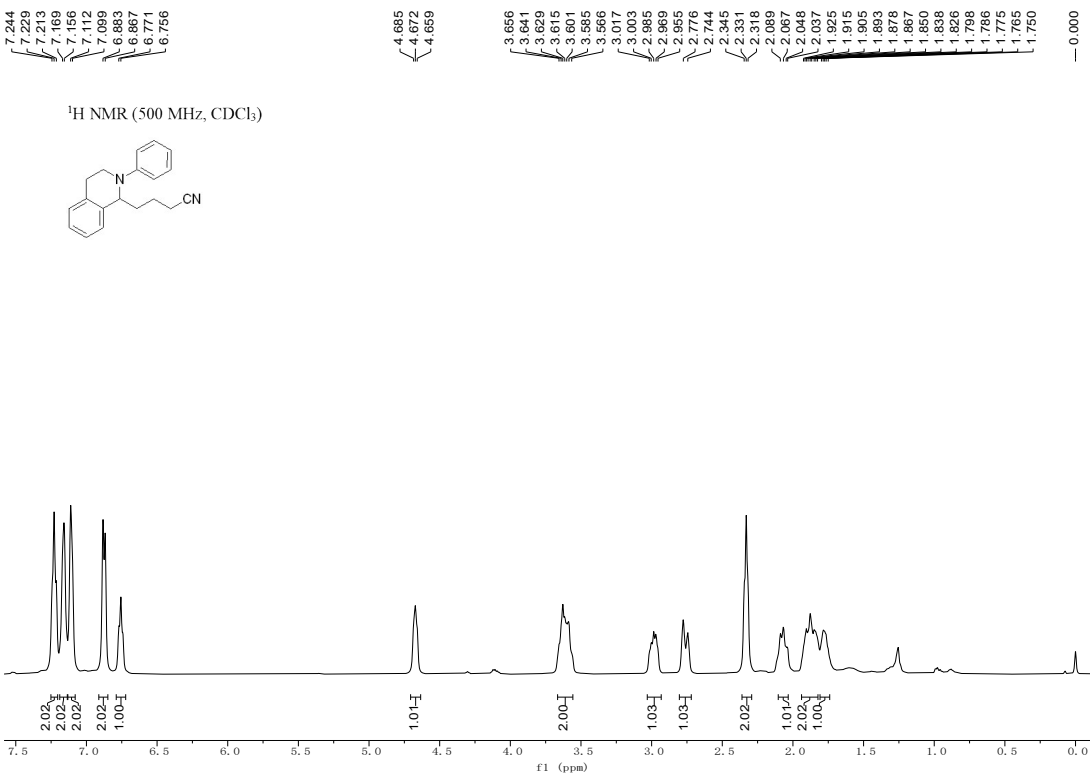
4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)butanenitrile (6)

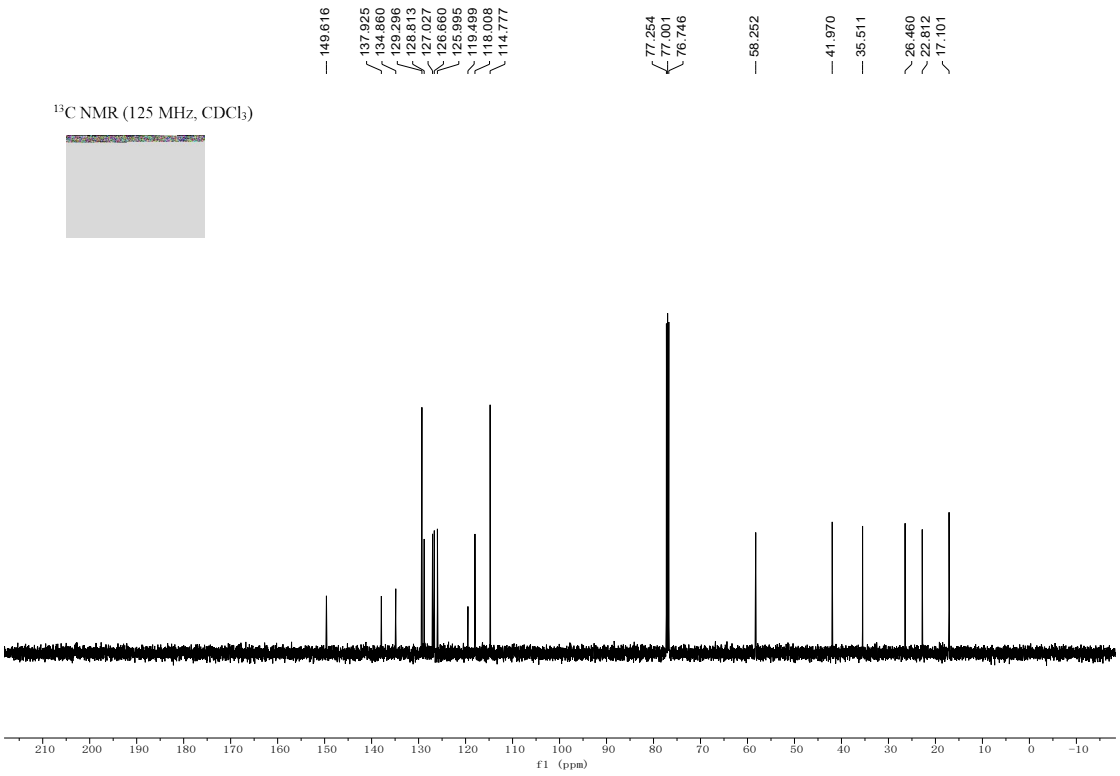


Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (d, J = 4.0 Hz, 2H), 2.49 (t, J = 7.5 Hz, 2H), 1.89 (t, J = 7.5 Hz, 2H), 1.47–1.43 (m, 4H), 1.32 (d, J = 2.0 Hz, 2H), 1.15 (s, 6H), 1.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 119.6, 73.5, 59.7, 39.5, 33.0, 25.0, 20.0, 16.9, 14.4; LRMS (EI, 70 eV) m/z (%): 224 (M^+, 3), 155 (23), 209 (100), 109 (31).

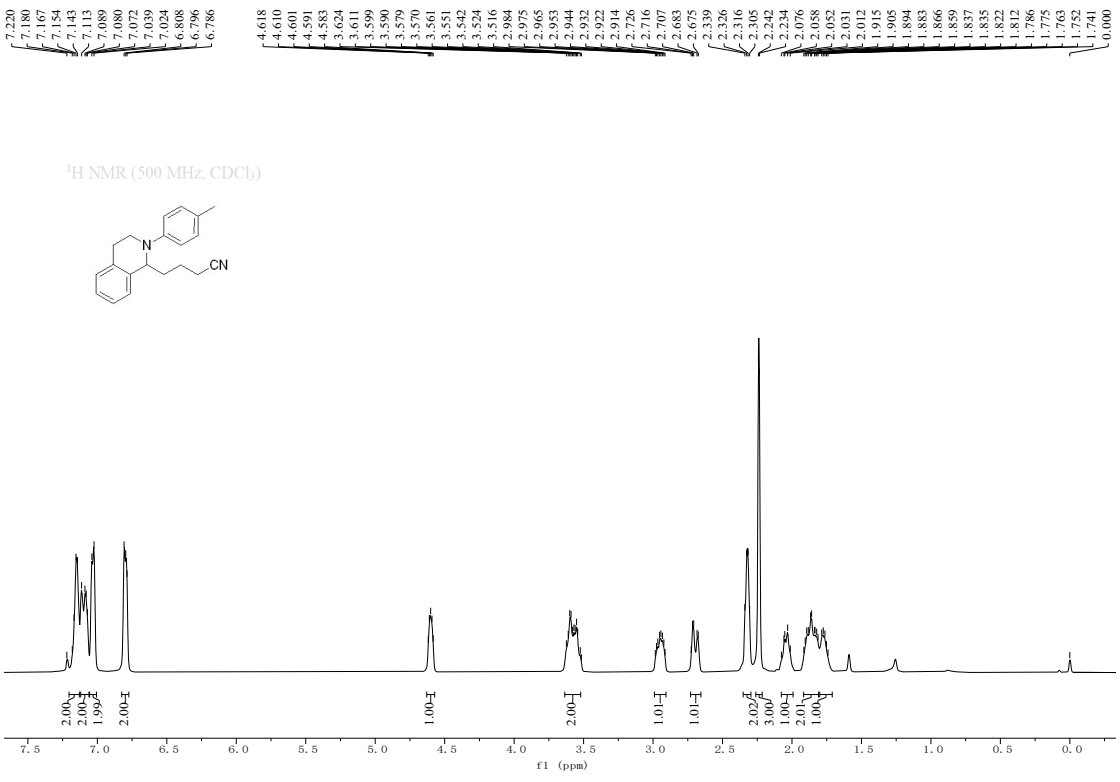
(C) Spectra

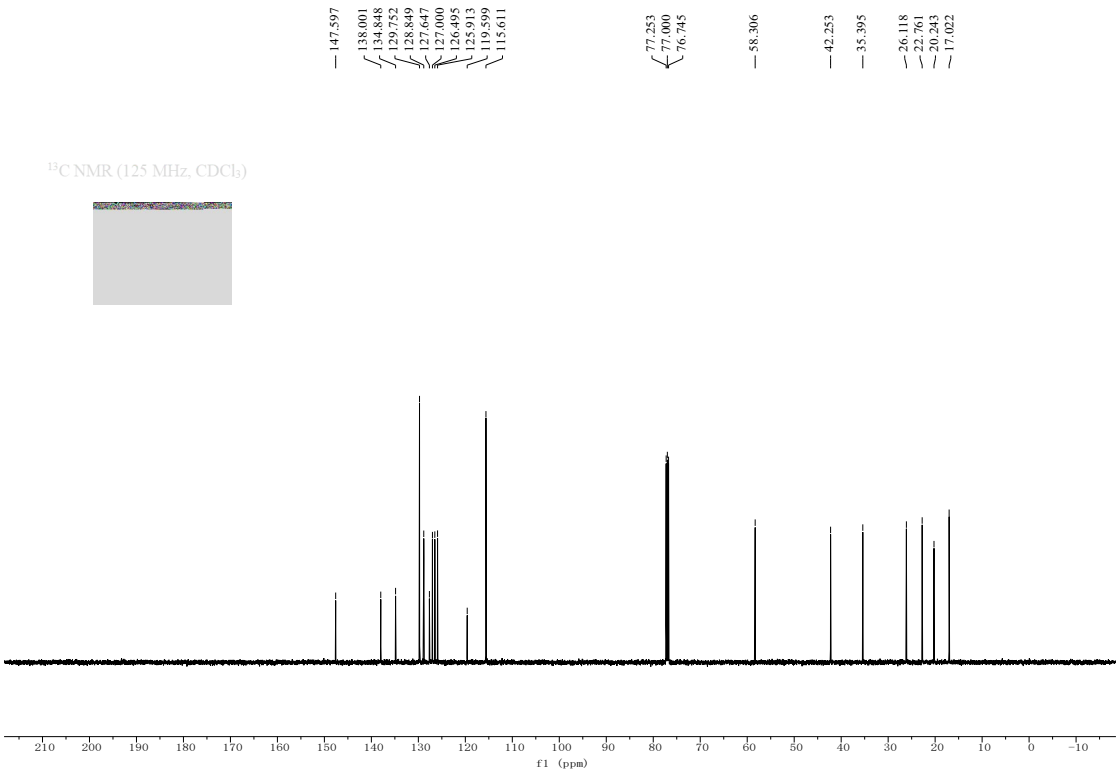
4-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3aa)



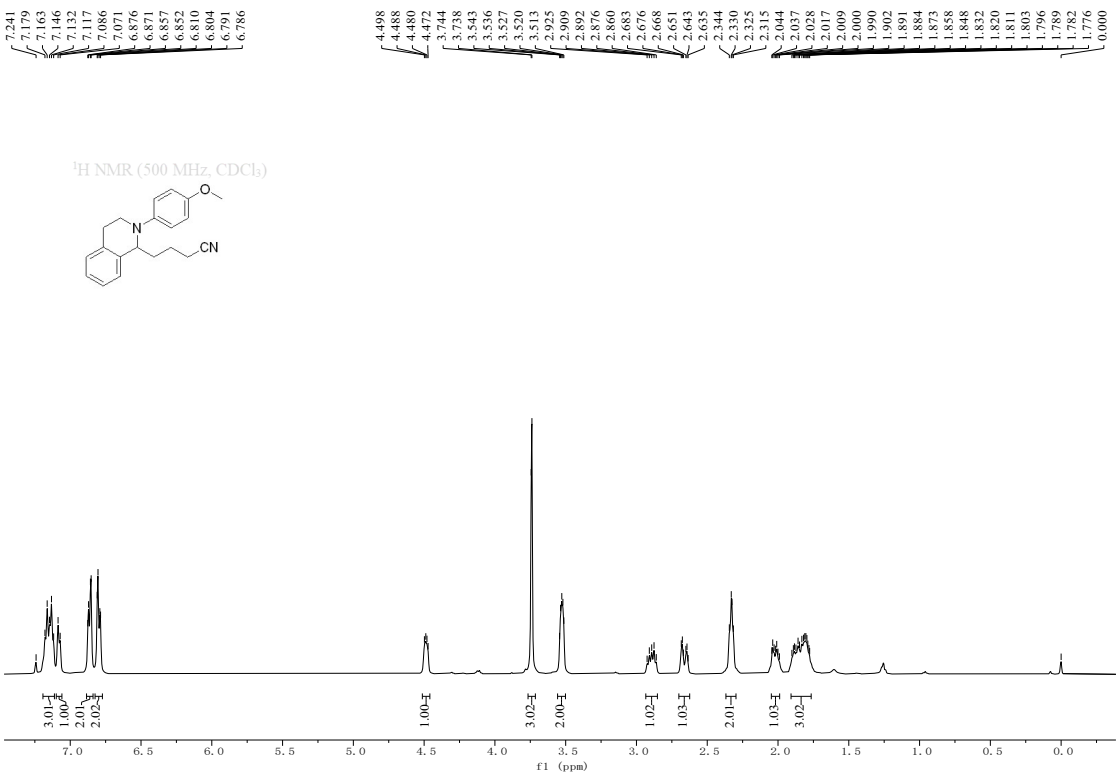


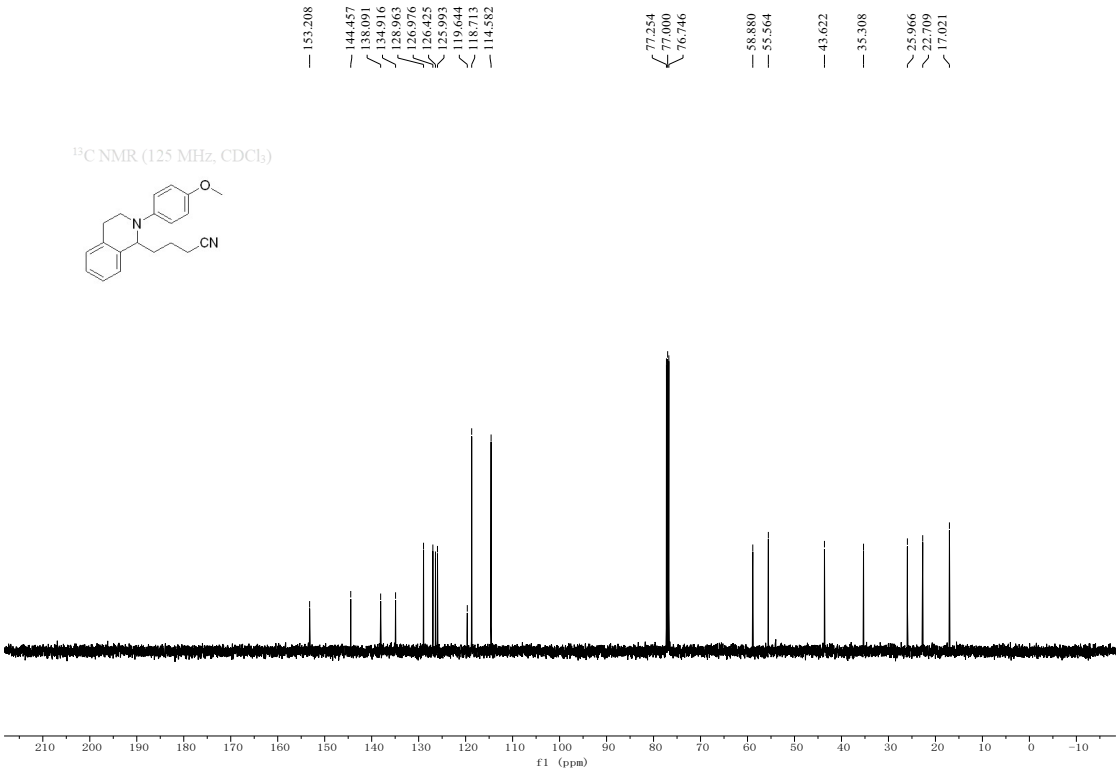
4-(2-(p-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ba)



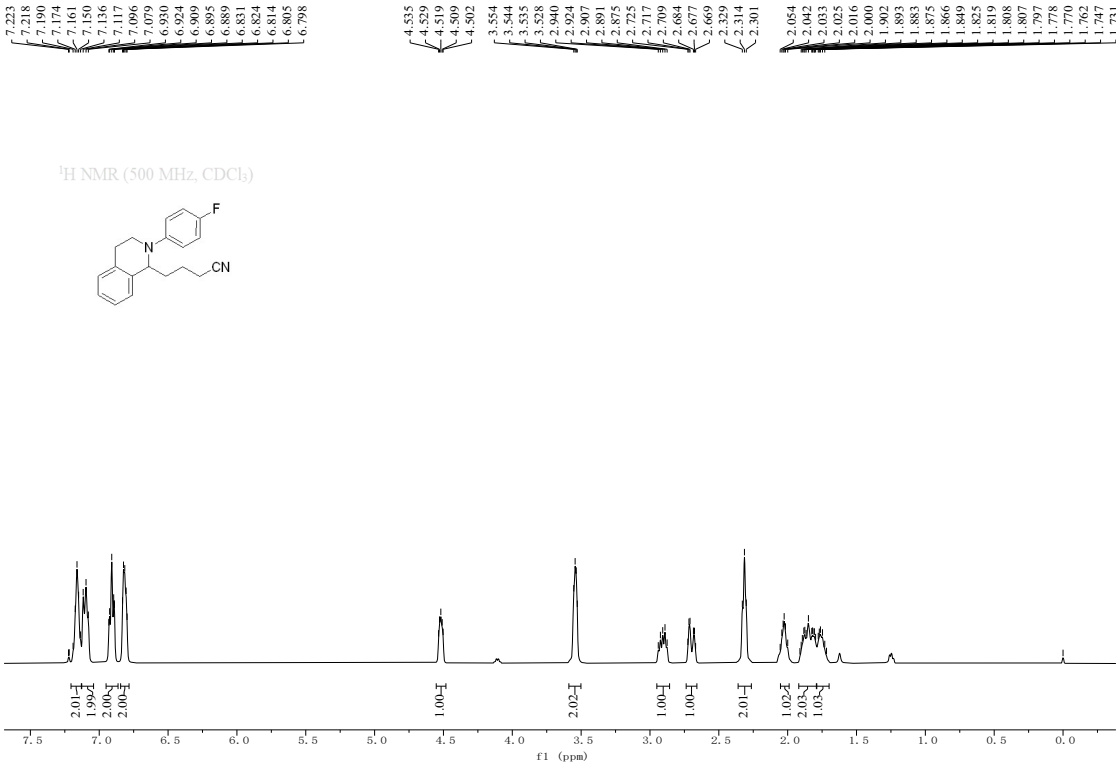


4-(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ca)


7.241
7.179
7.163
7.146
7.132
7.117
7.086
7.071
6.876
6.871
6.857
6.852
6.810
6.804
6.791
6.786
4.498
4.488
4.480
4.472
3.744
3.738
3.543
3.536
3.527
3.520
3.513
2.925
2.909
2.892
2.876
2.860
2.683
2.676
2.668
2.651
2.643
2.635
2.344
2.330
2.325
2.315
2.044
2.037
2.028
2.017
2.009
2.000
1.990
1.902
1.891
1.884
1.873
1.858
1.848
1.832
1.820
1.811
1.803
1.796
1.789
1.782
1.776
0.000
^{1}H NMR (500 MHz, CDCl$_3$)
O
N
CN
3.01
1.00
2.01
2.02
1.00
3.02
2.00
1.02
1.03
2.01
1.03
3.02
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

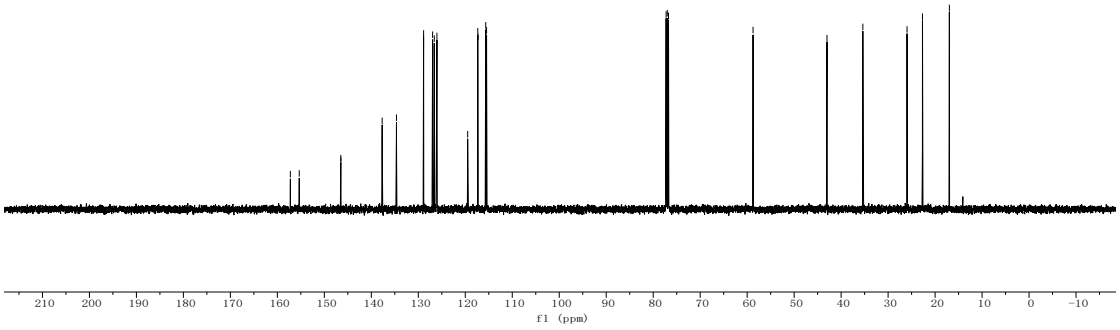

153.208
144.457
138.091
134.916
128.963
126.976
126.425
125.993
119.644
118.713
114.582
77.254
77.000
76.746
58.880
55.564
43.622
35.308
25.966
22.709
17.021
^{13}C NMR (125 MHz, CDCl$_3$)
O
N
CN
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

4-(2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3da)



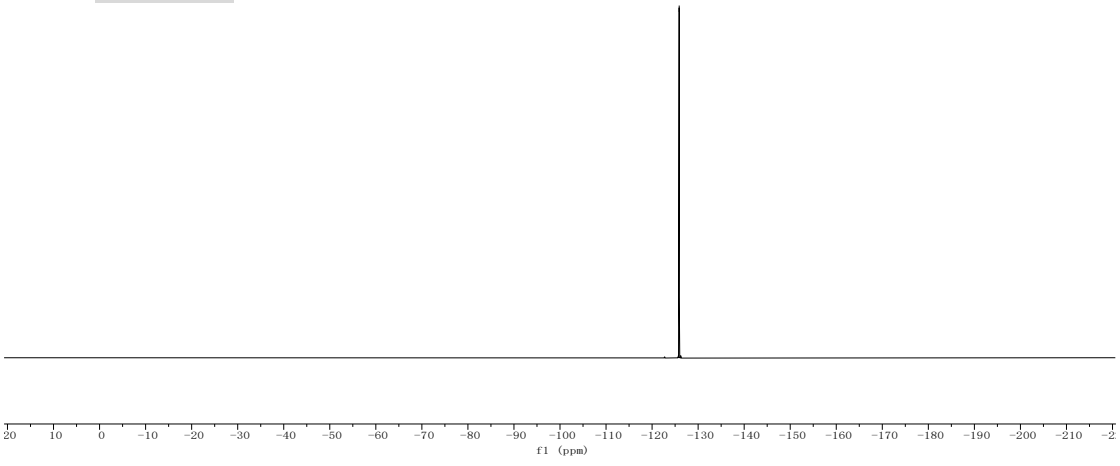
157.230
155.340
146.494
146.477
137.690
134.644
128.872
126.957
126.600
126.034
119.493
117.340
117.281
115.647
115.473
77.253
77.000
76.744
58.745
43.005
35.377
25.969
22.684
16.961

^{13}C NMR (125 MHz, $CDCl_3$)

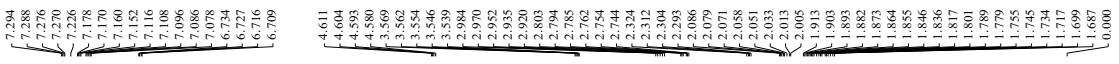


-125.887

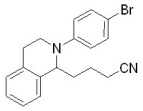
^{19}F NMR (471 MHz, $CDCl_3$)

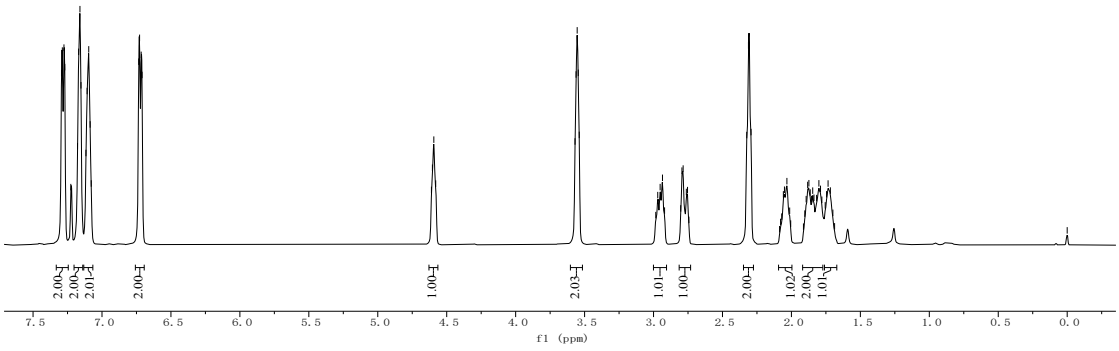


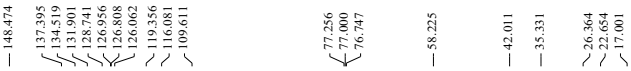
4-(2-(4-bromophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ea)



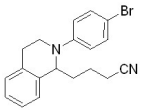
^{1}H NMR (500 MHz, $CDCl_3$)

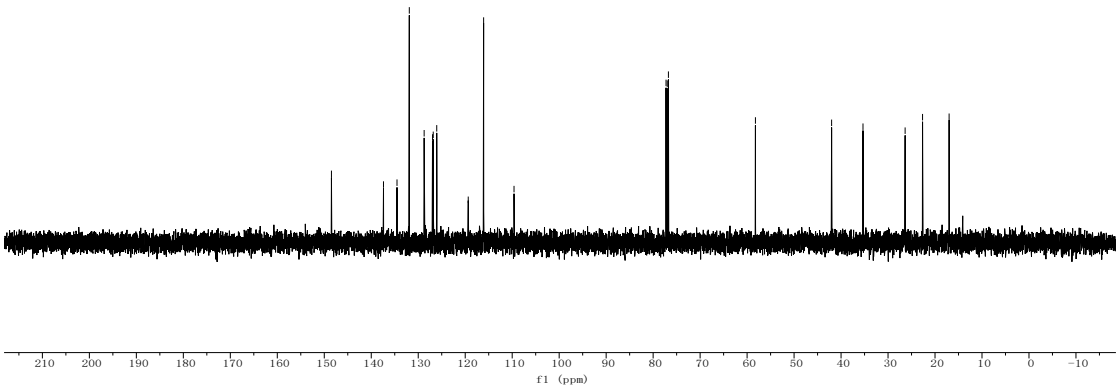




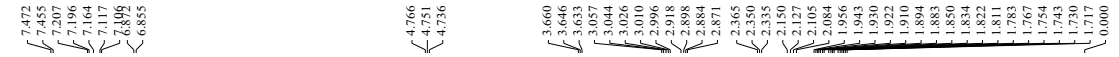


^{13}C NMR (125 MHz, $CDCl_3$)

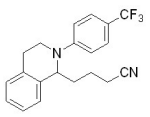


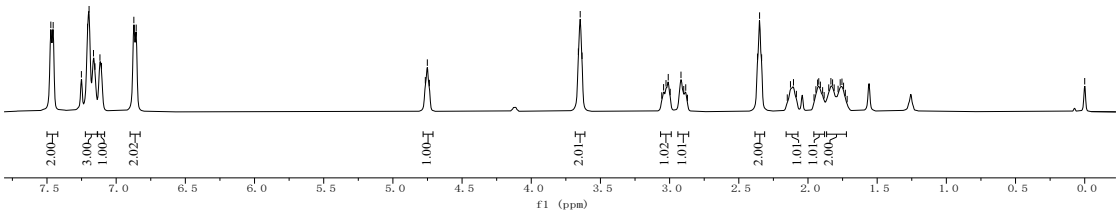


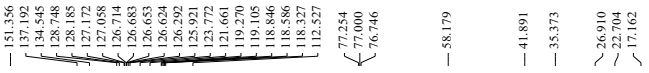
4-(2-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3fa)



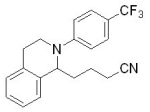
^{1}H NMR (500 MHz, $CDCl_3$)

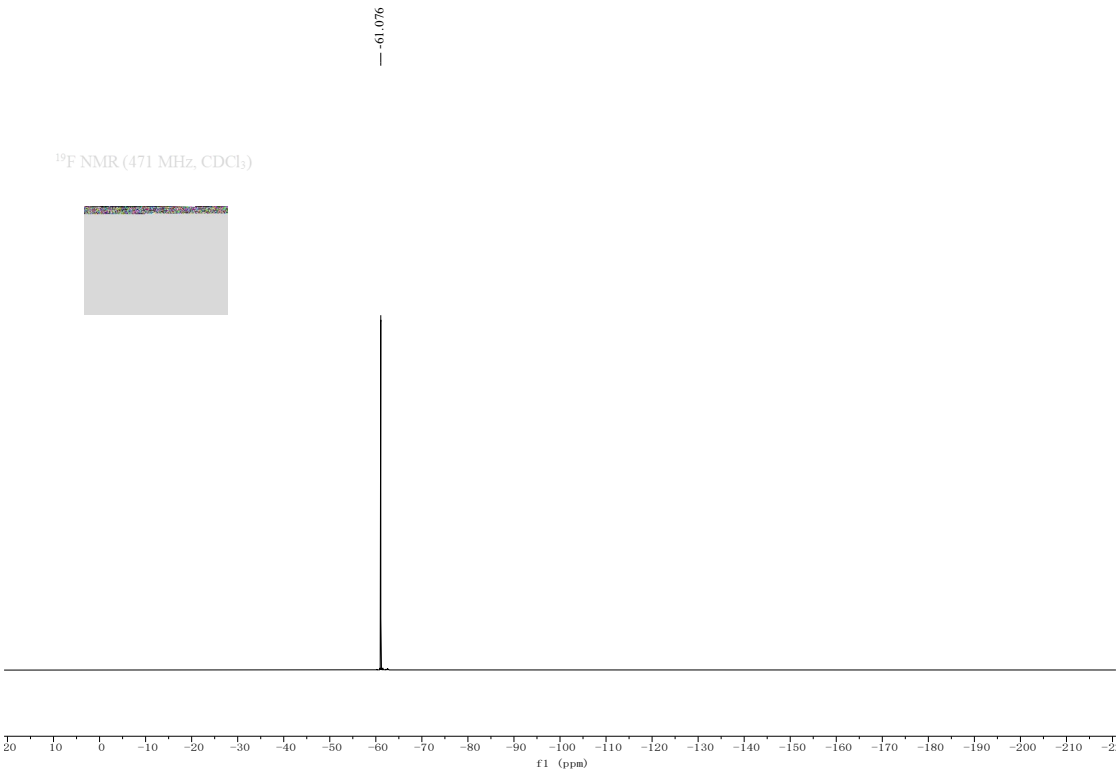






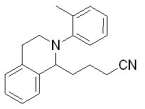
^{13}C NMR (125 MHz, $CDCl_3$)

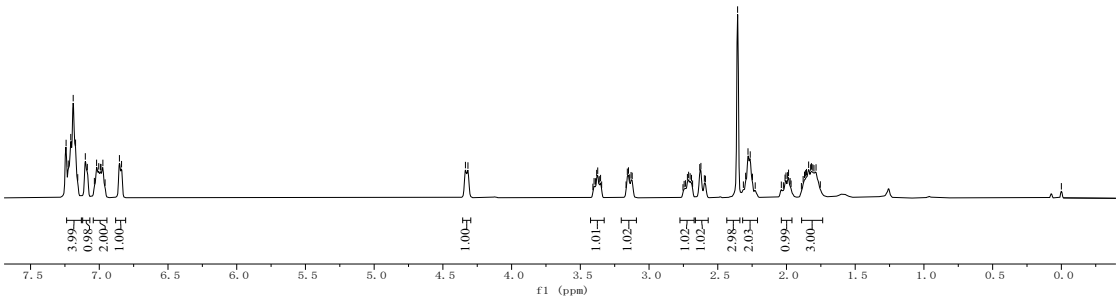




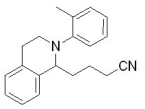
4-(2-(o-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ga)

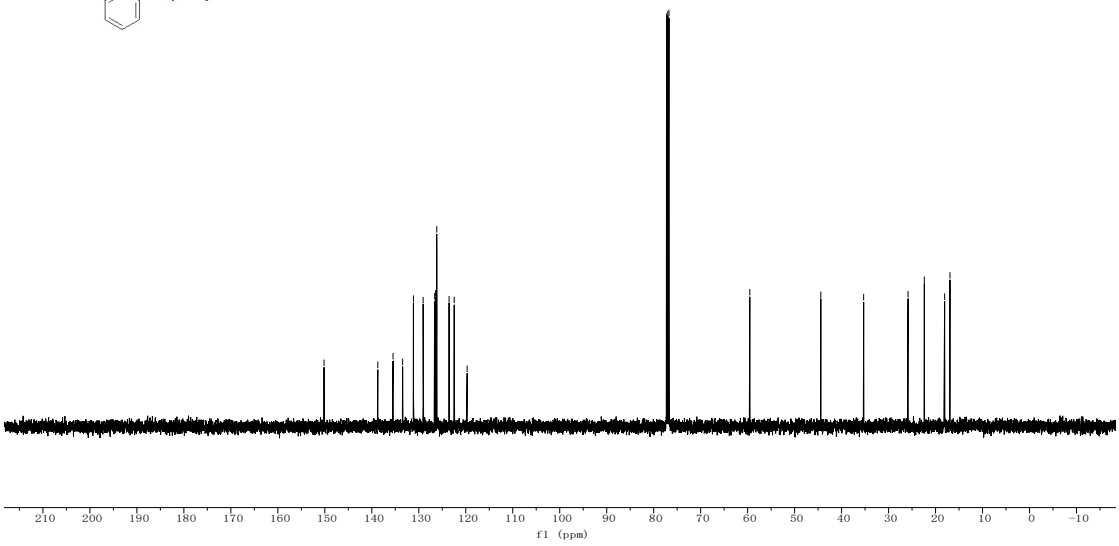
^{1}H NMR (500 MHz, $CDCl_3$)



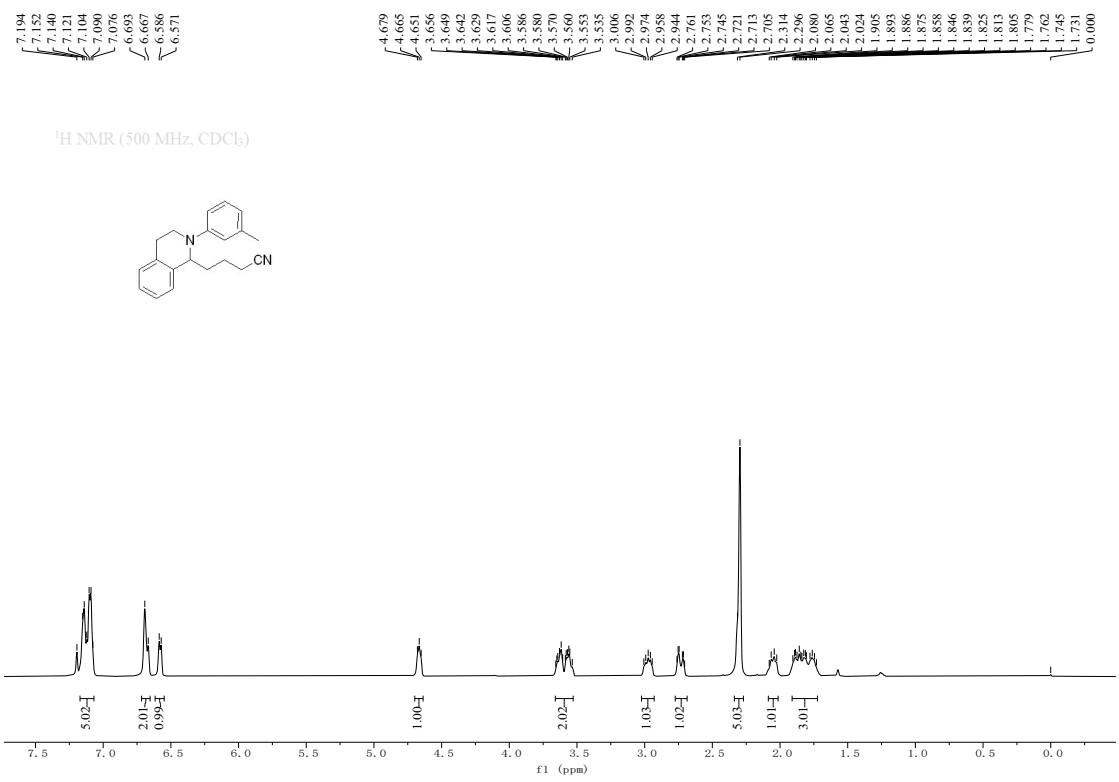


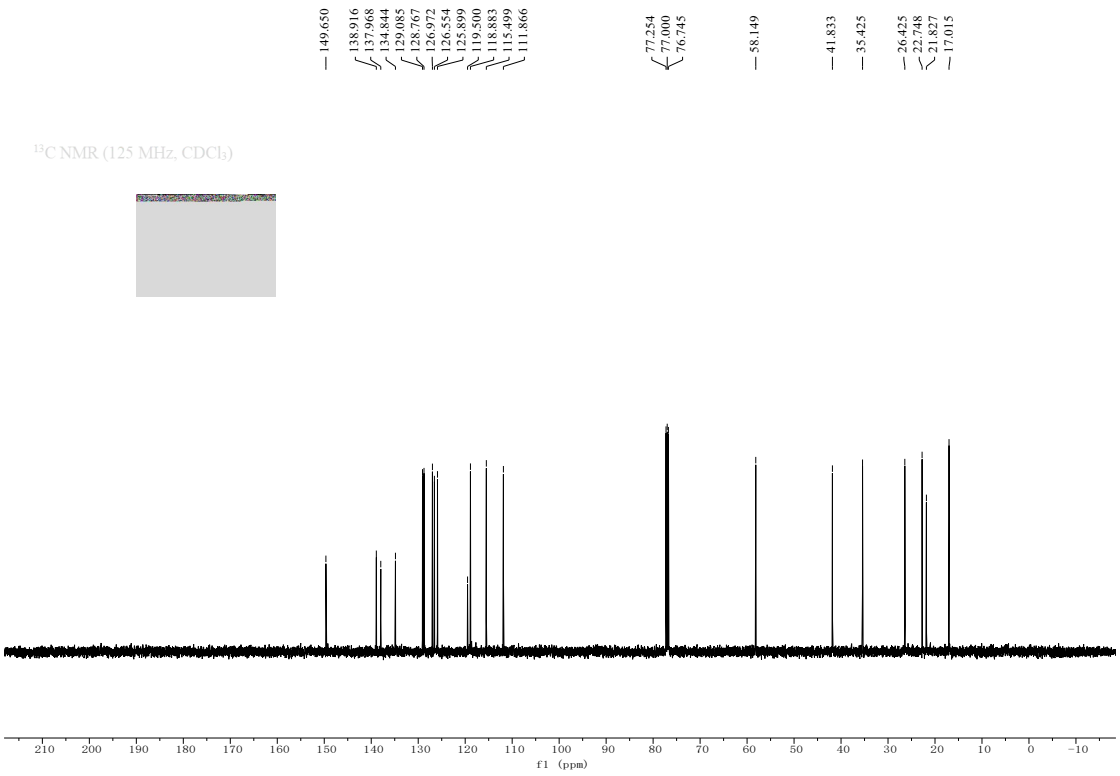
^{13}C NMR (125 MHz, $CDCl_3$)



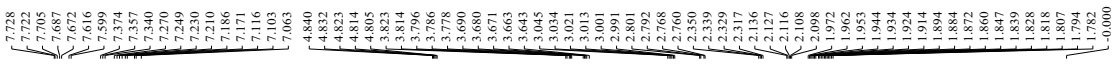


4-(2-(m-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ha)

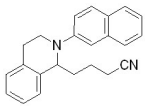


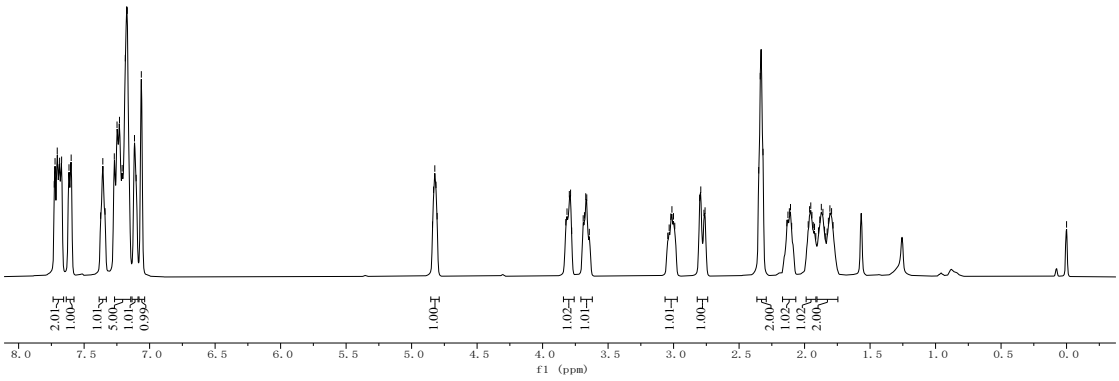


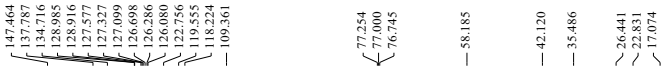
4-(2-(naphthalen-2-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ia)



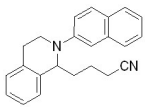
^{1}H NMR (500 MHz, $CDCl_3$)

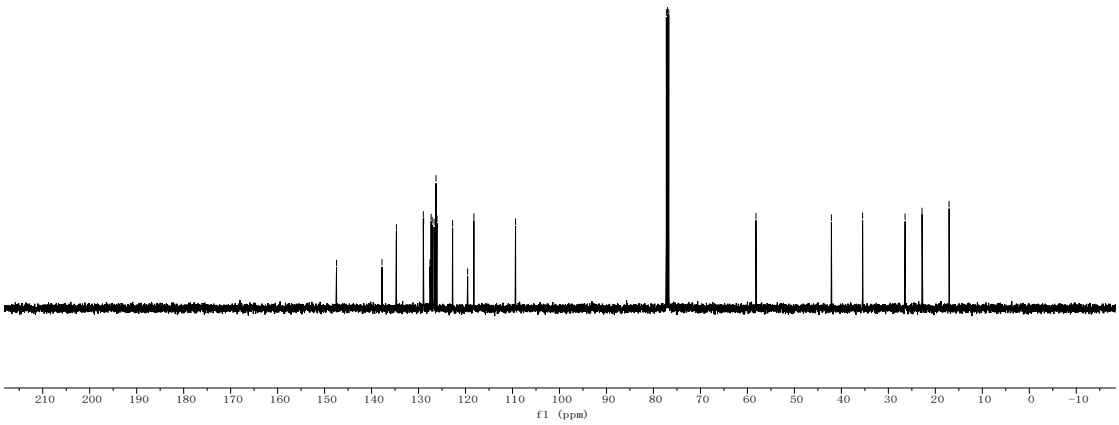




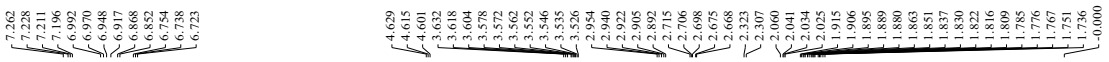


^{13}C NMR (125 MHz, $CDCl_3$)

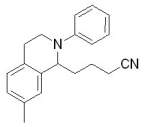


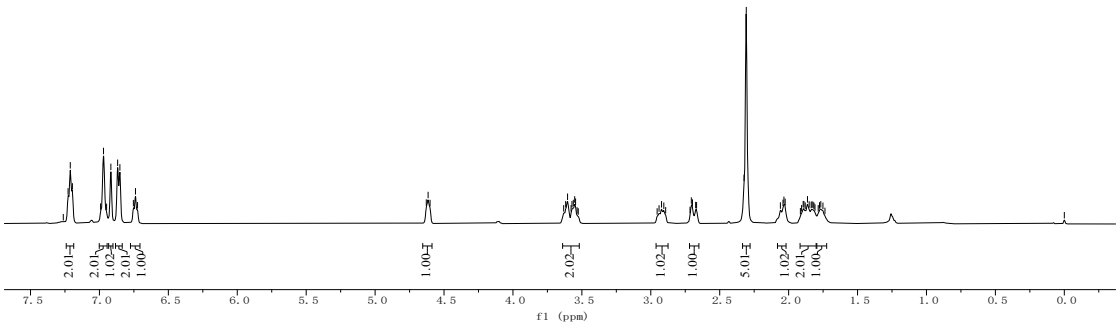


4-(7-methyl-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ka)

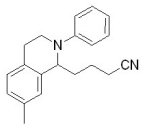


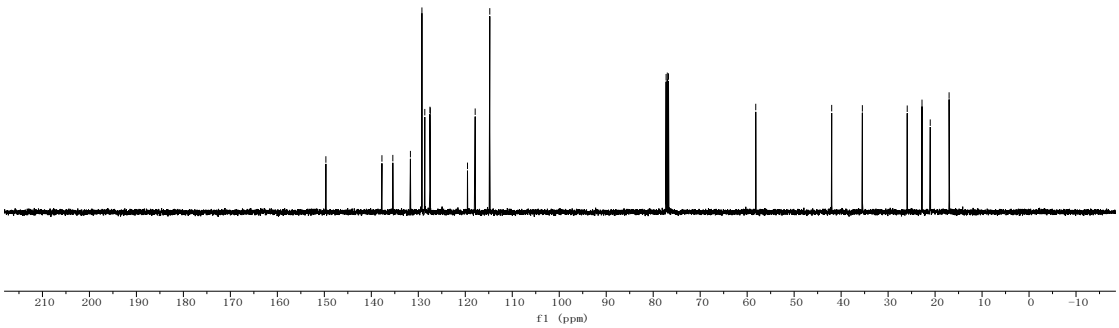
^{1}H NMR (500 MHz, $CDCl_3$)



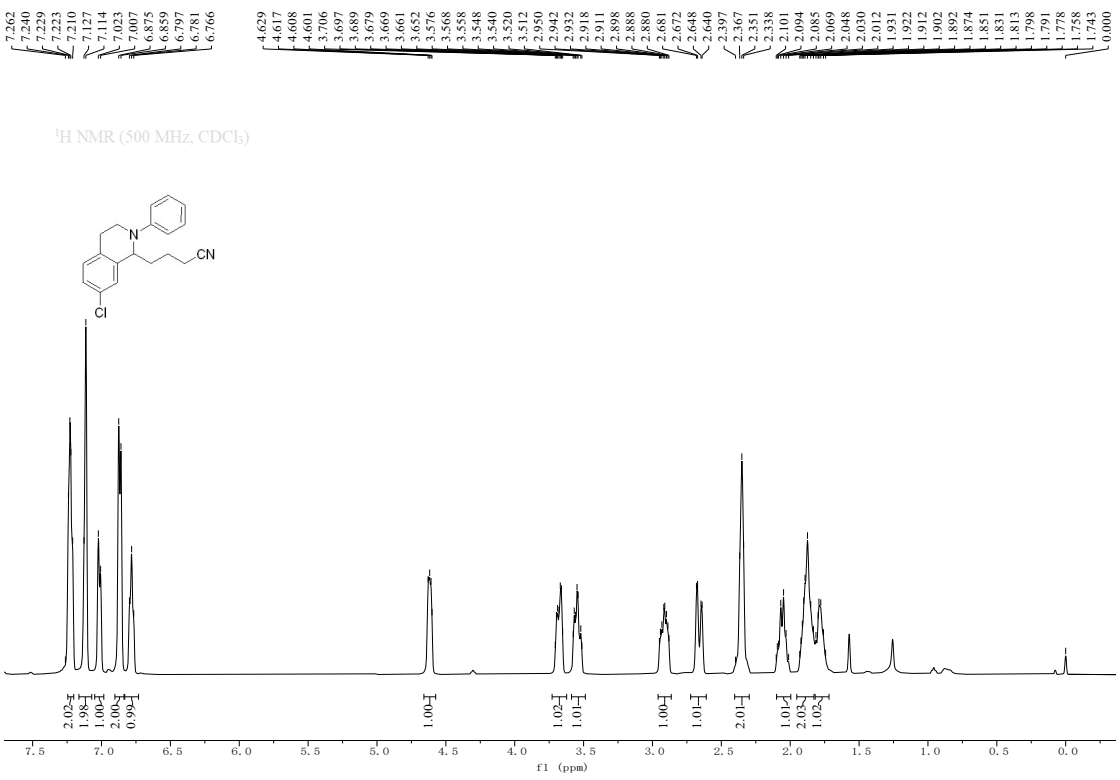


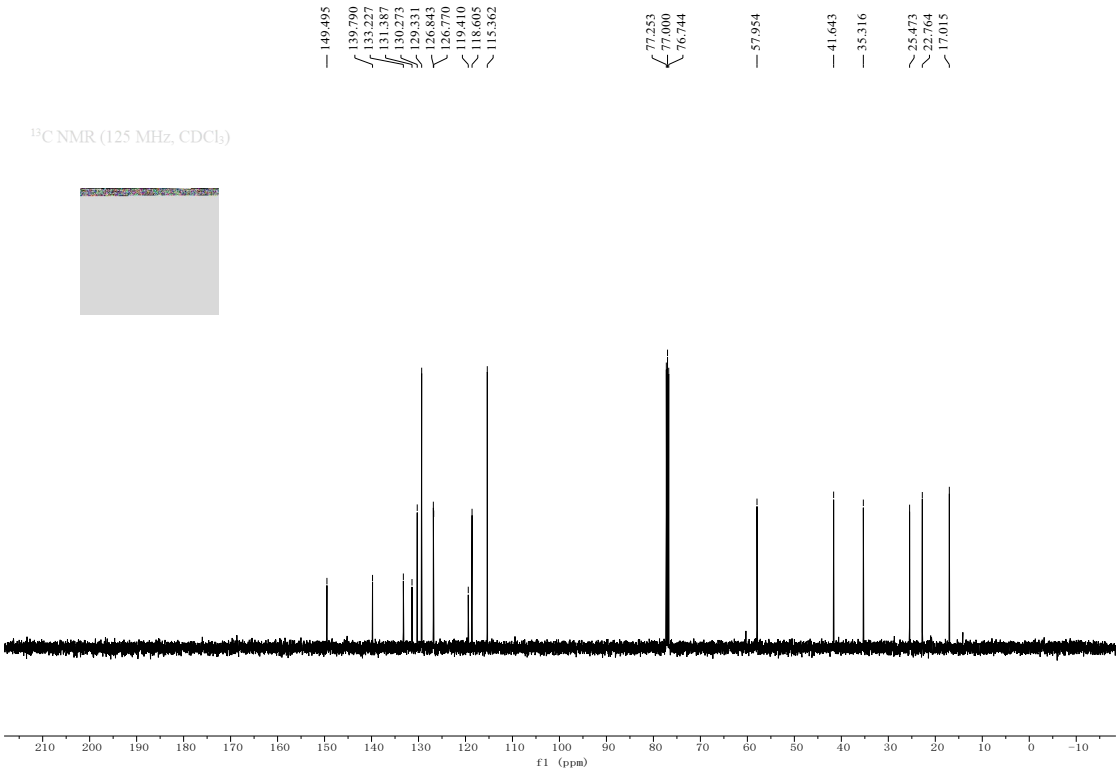
^{13}C NMR (125 MHz, $CDCl_3$)



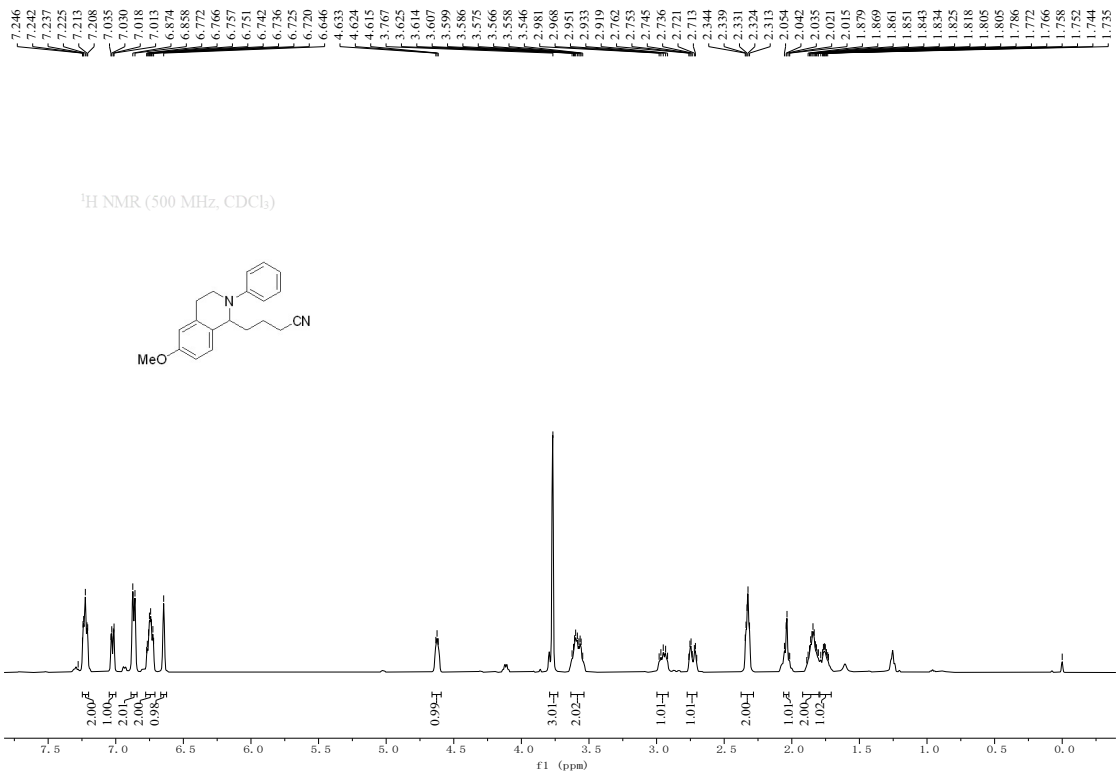


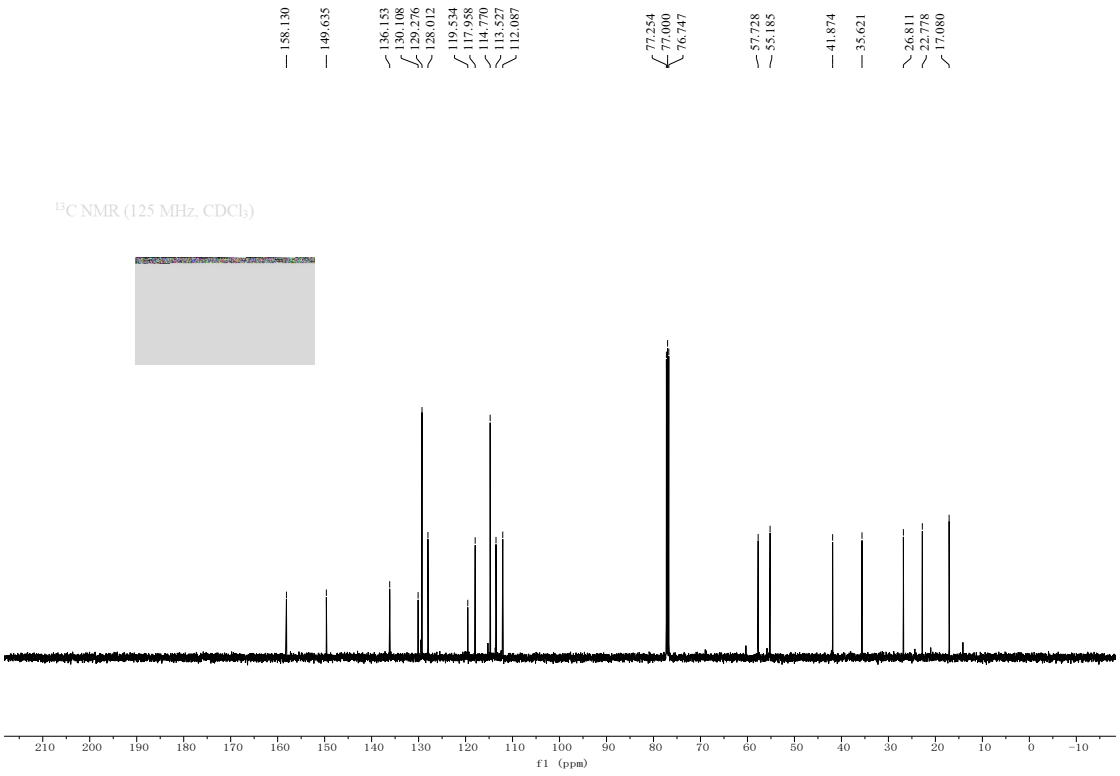
4-(7-chloro-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3la)





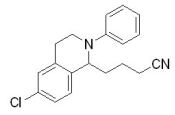
4-(6-methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ma)

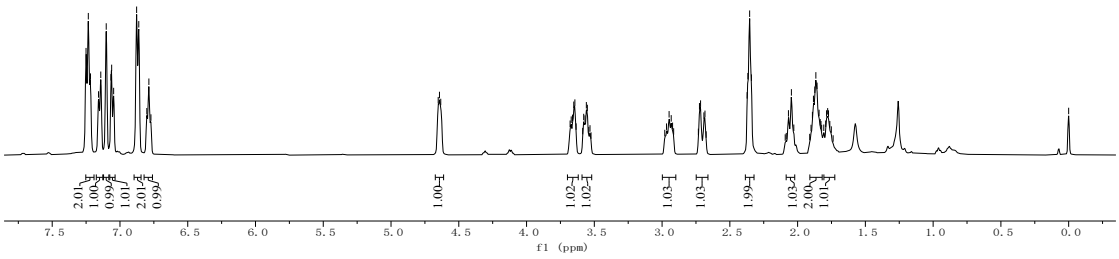




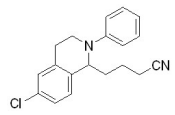
4-(6-chloro-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3na)

^{1}H NMR (500 MHz, $CDCl_3$)



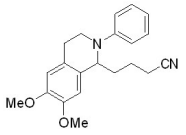


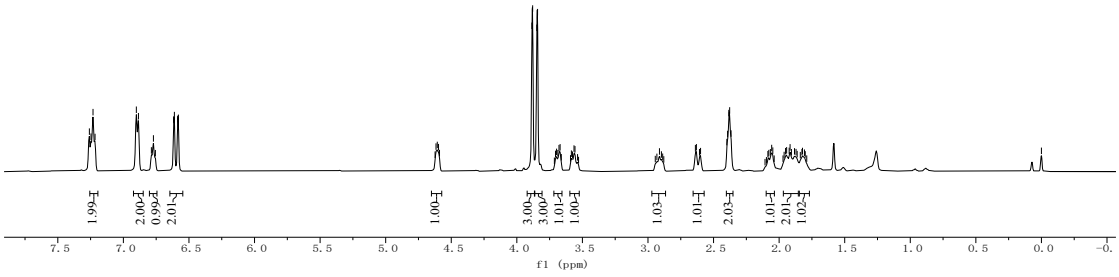
^{13}C NMR (125 MHz, $CDCl_3$)

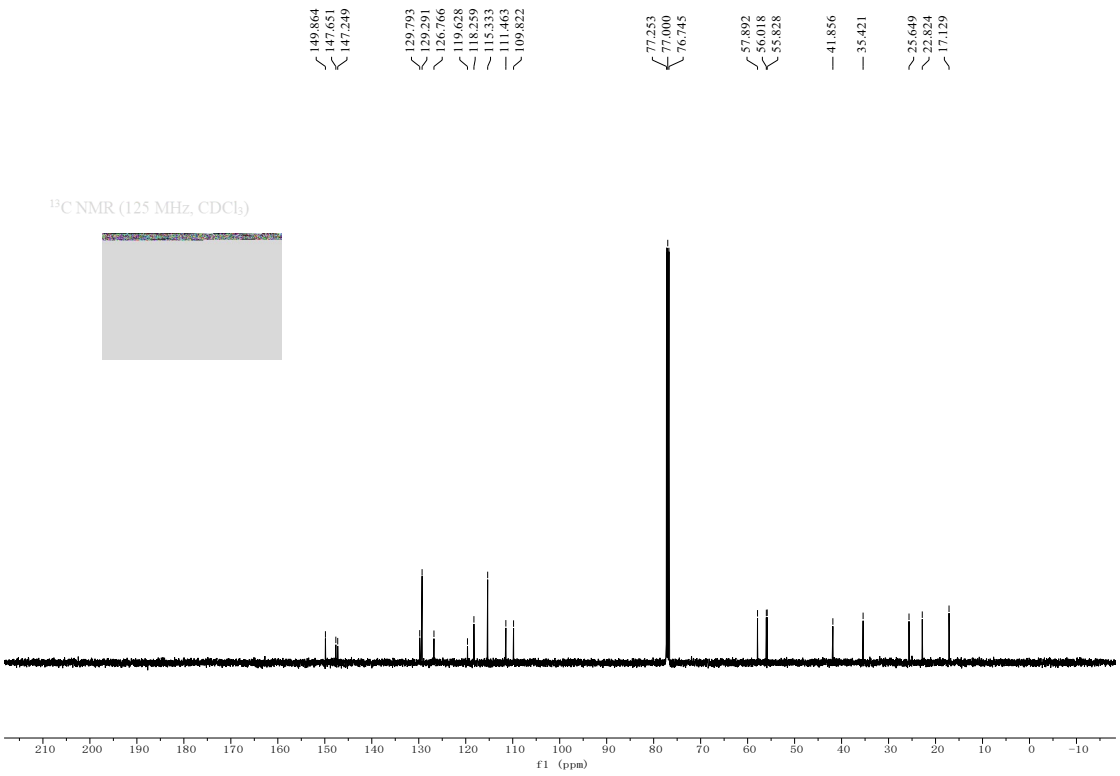


4-(6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3oa)

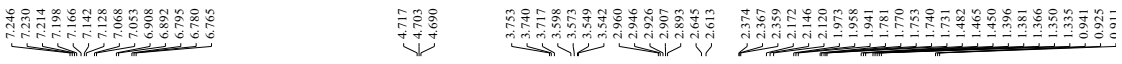
^{1}H NMR (500 MHz, $CDCl_3$)



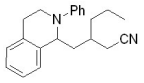


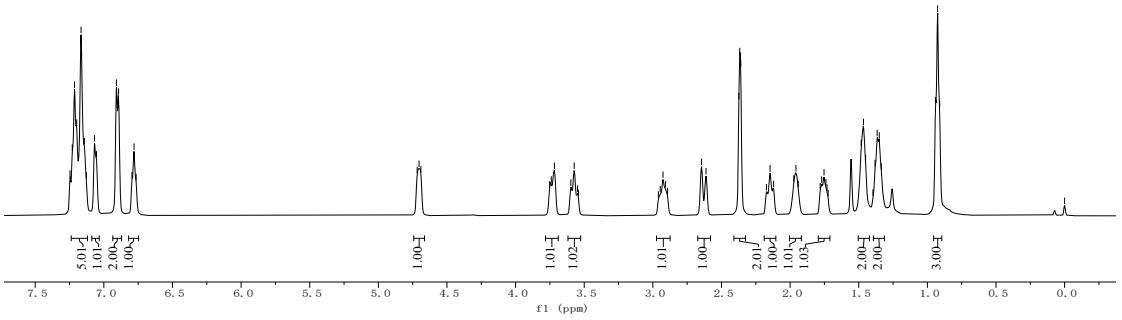


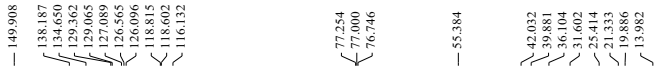
3-((2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)hexanenitrile (3ab)
(dr = 1:1)



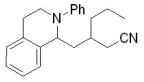
^{1}H NMR (500 MHz, $CDCl_3$)

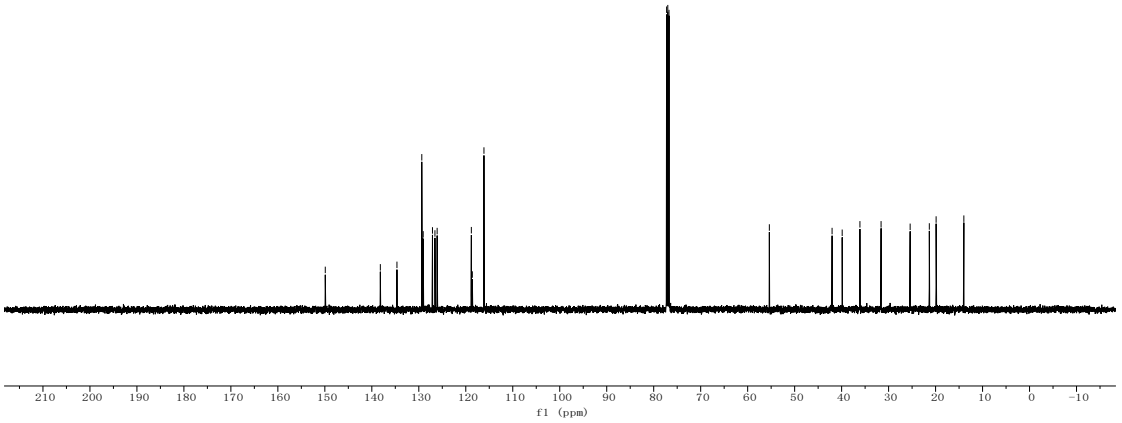


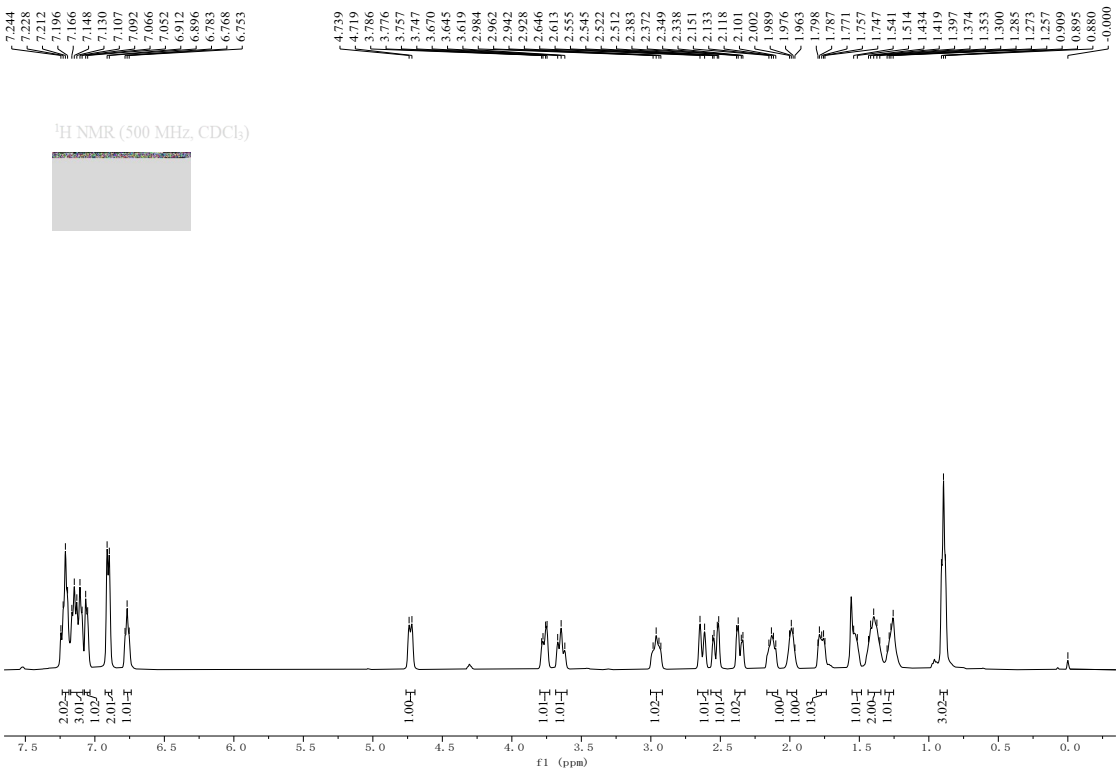




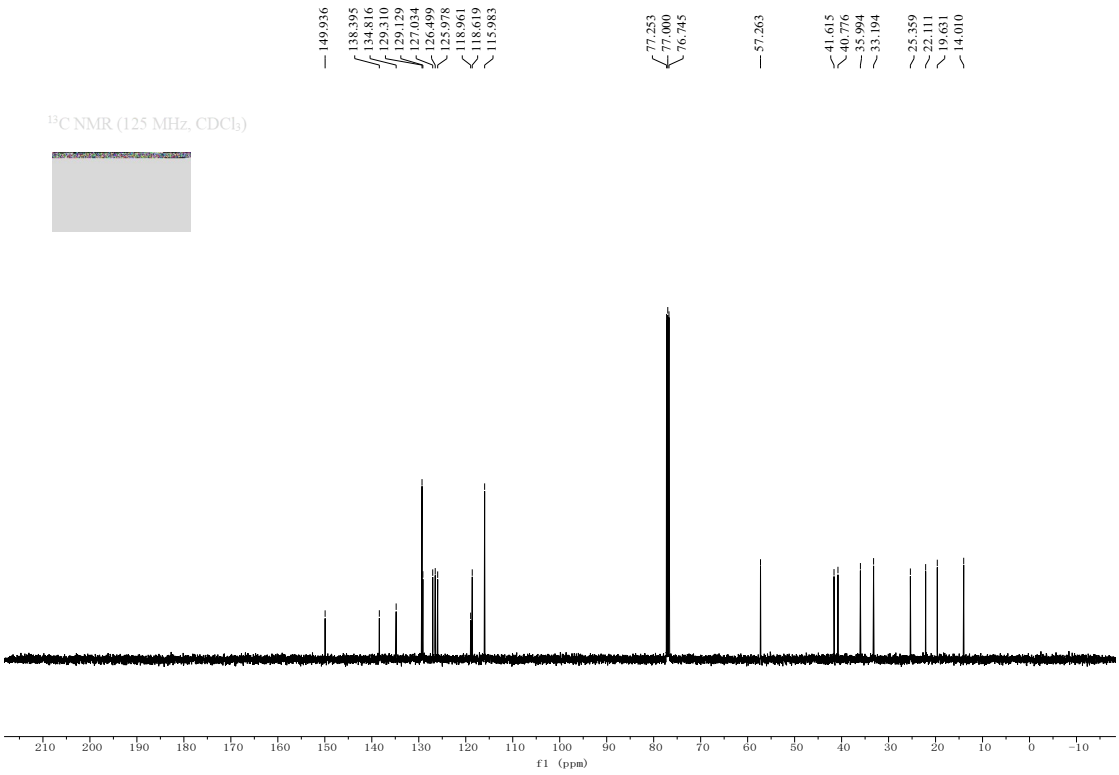
^{13}C NMR (125 MHz, $CDCl_3$)





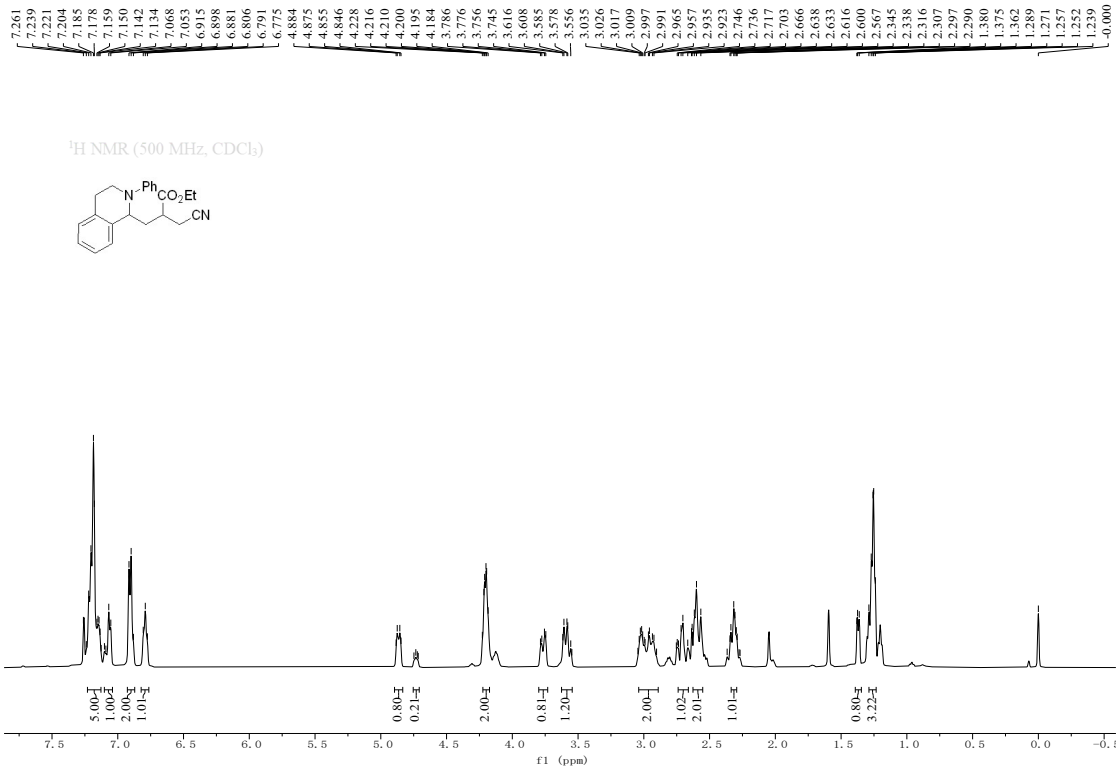


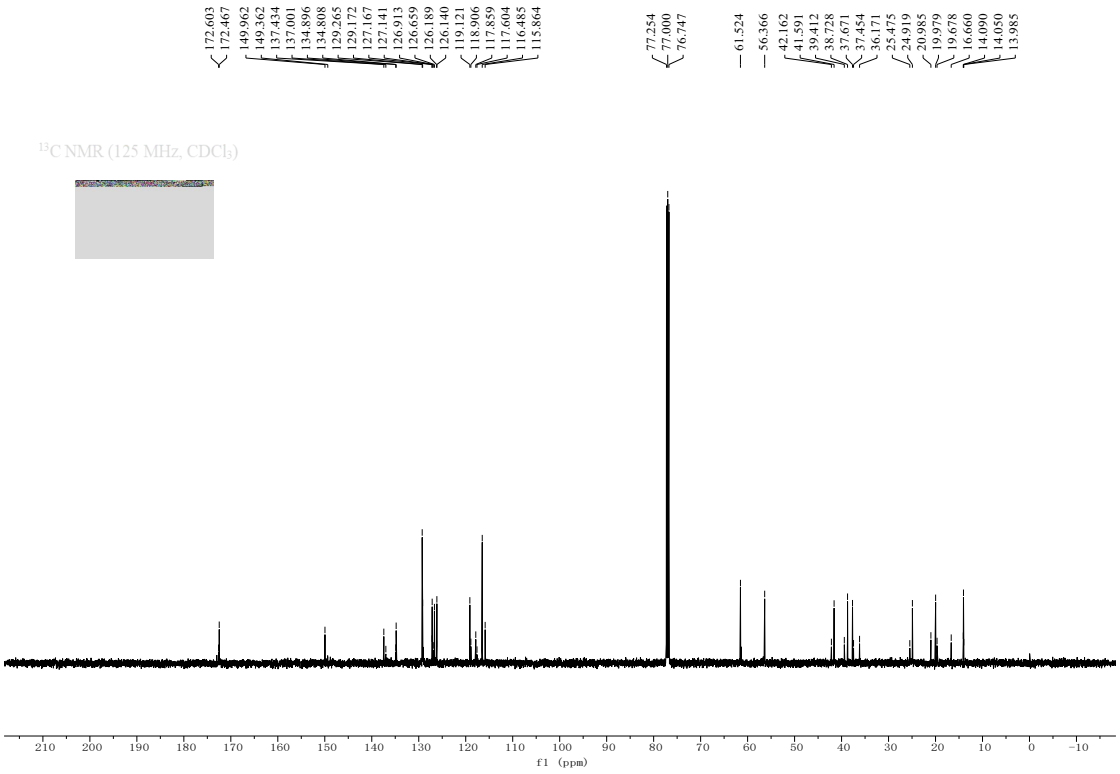
^{1}H NMR (500 MHz, $CDCl_3$)



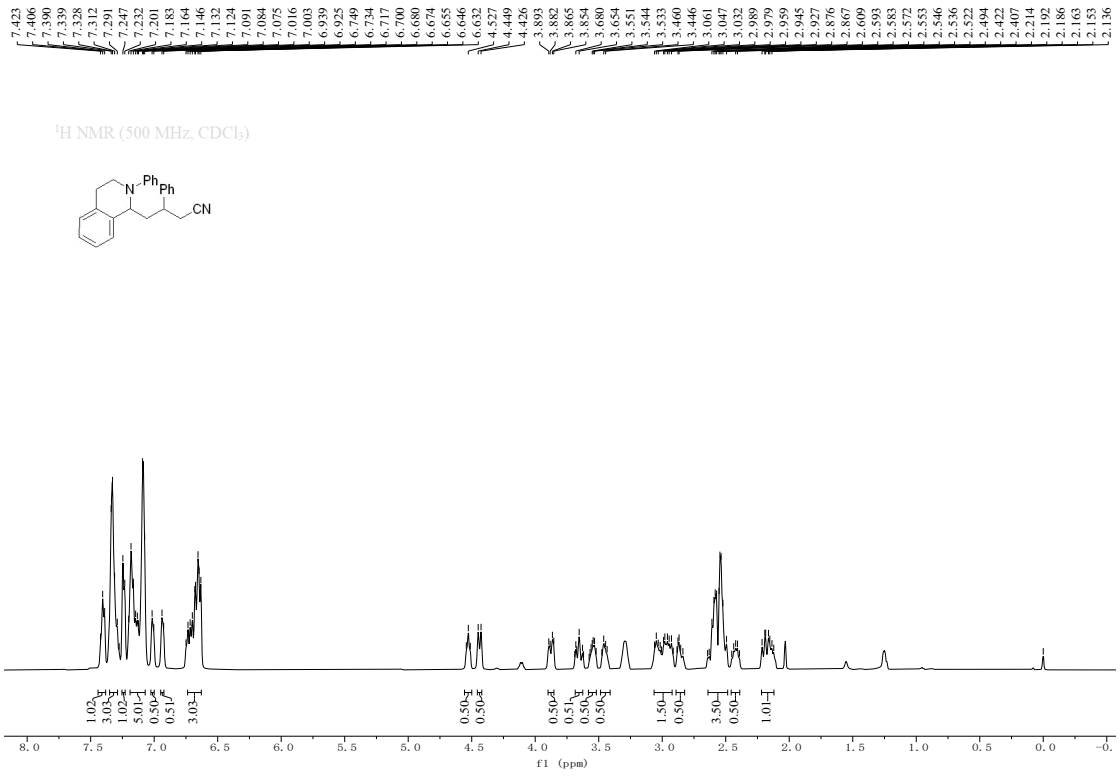
^{13}C NMR (125 MHz, $CDCl_3$)

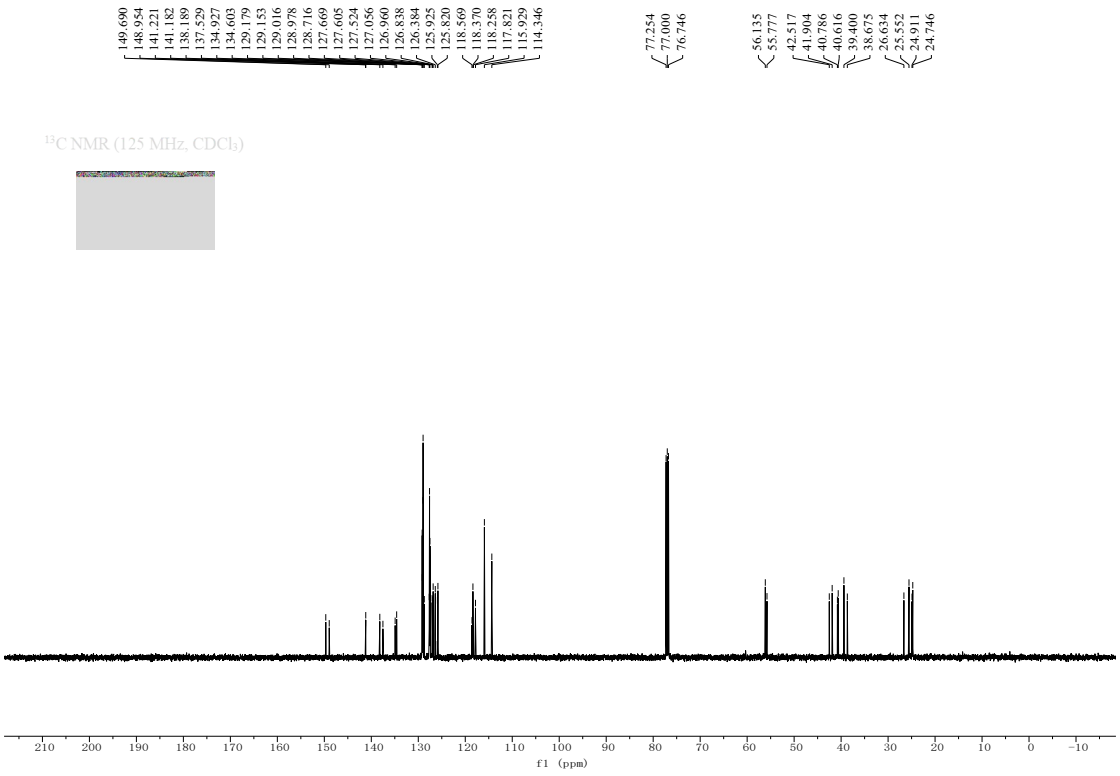
ethyl 3-cyano-2-((2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)propanoate (3ac) (dr = 4:1)



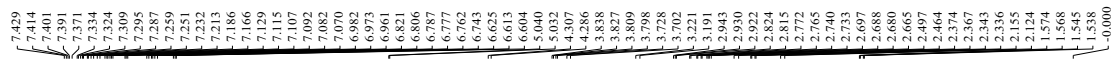


3-phenyl-4-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ad) (dr = 1:1)

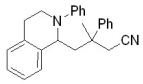


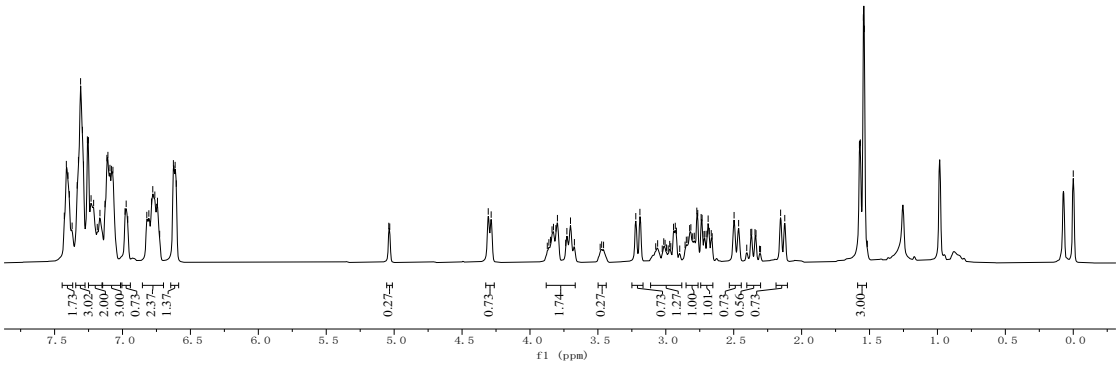


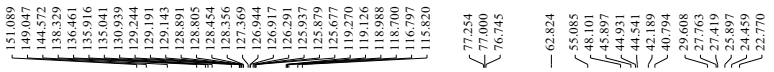
3-methyl-3-phenyl-4-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile (3ae) (dr = 2:1)



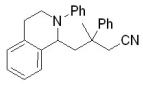
^{1}H NMR (500 MHz, $CDCl_3$)

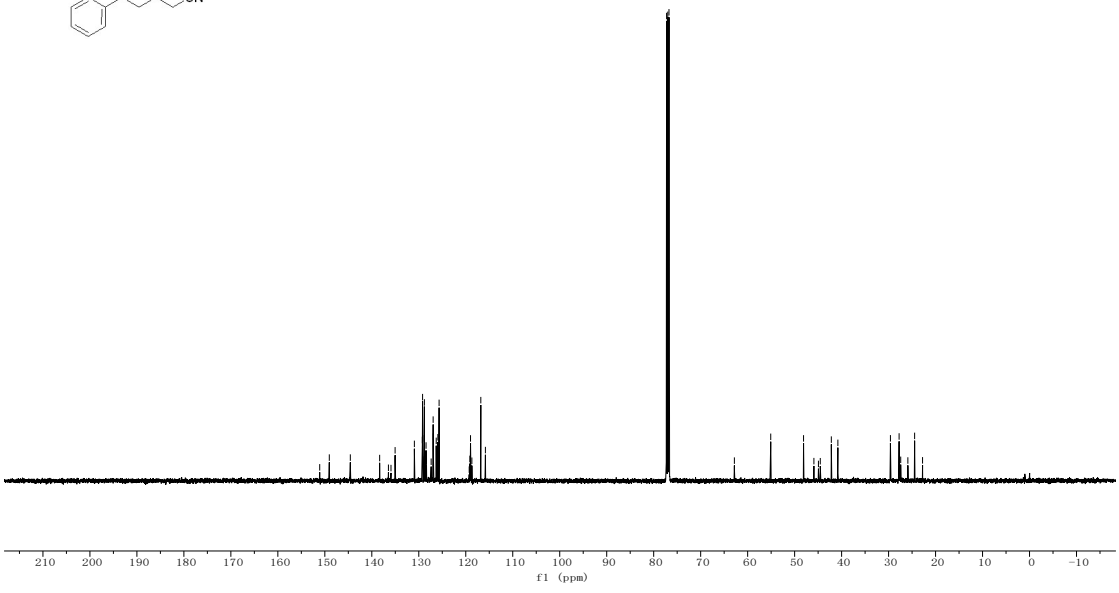






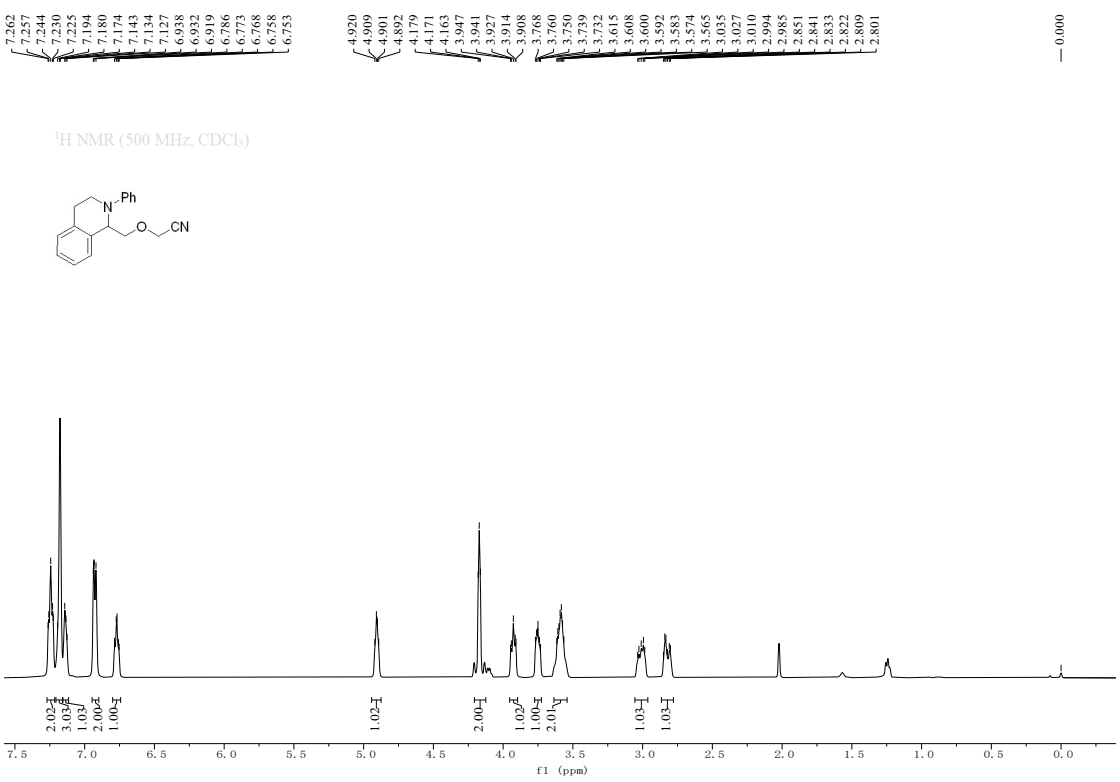
^{13}C NMR (125 MHz, $CDCl_3$)



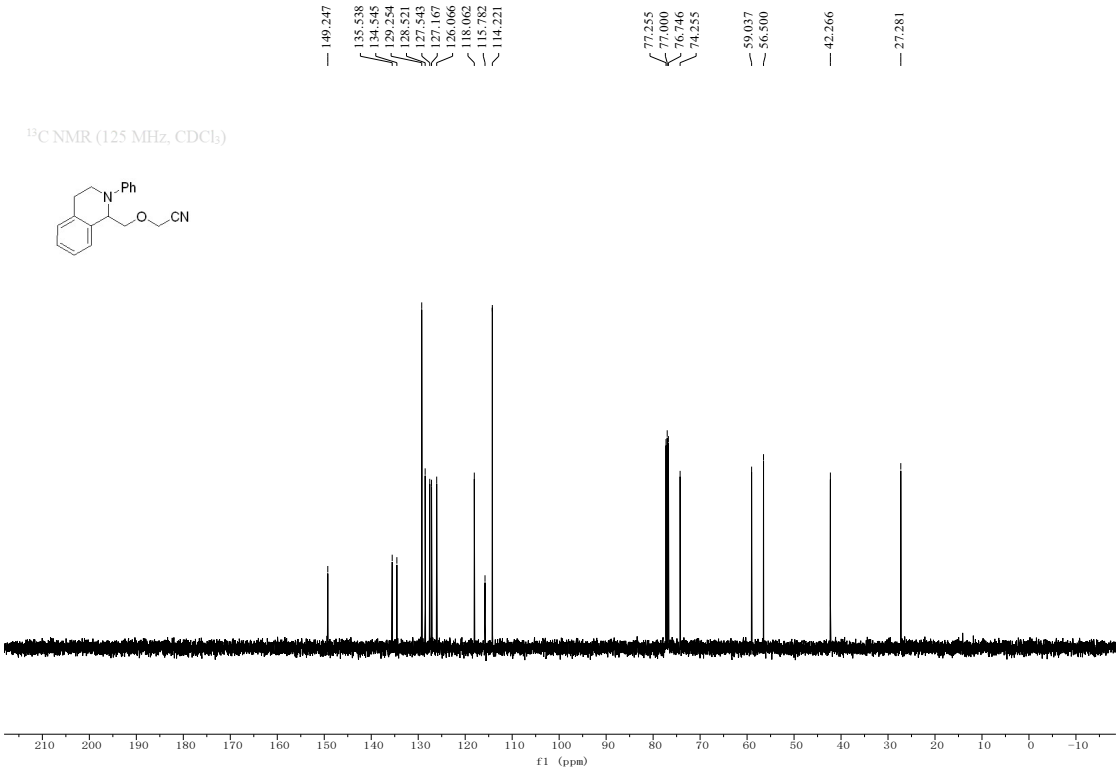


2-((2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methoxy)acetonitrile (3af)

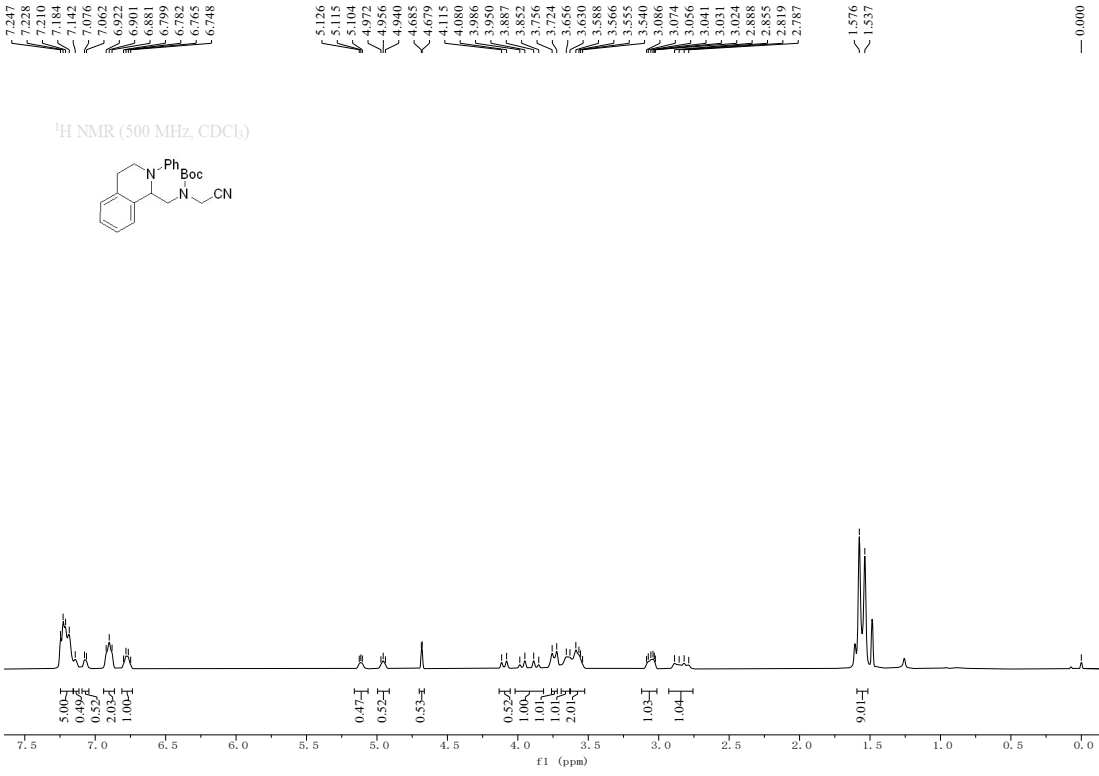
^{1}H NMR (500 MHz, $CDCl_3$)

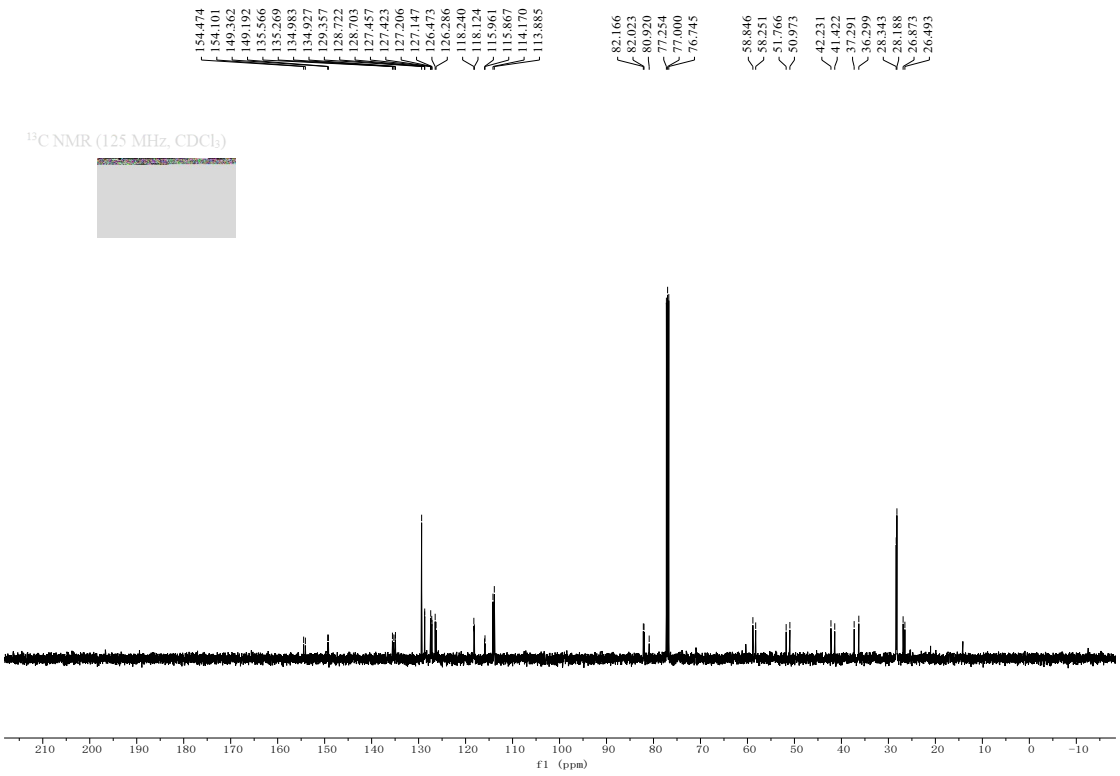


^{13}C NMR (125 MHz, $CDCl_3$)

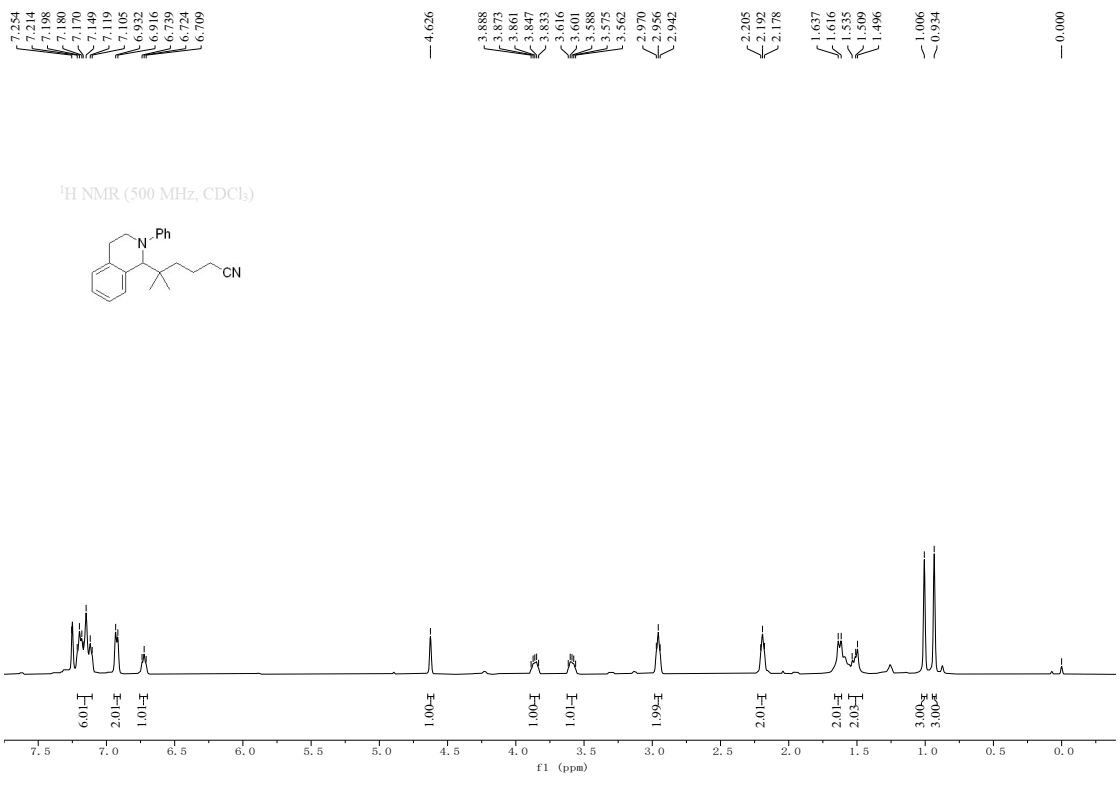


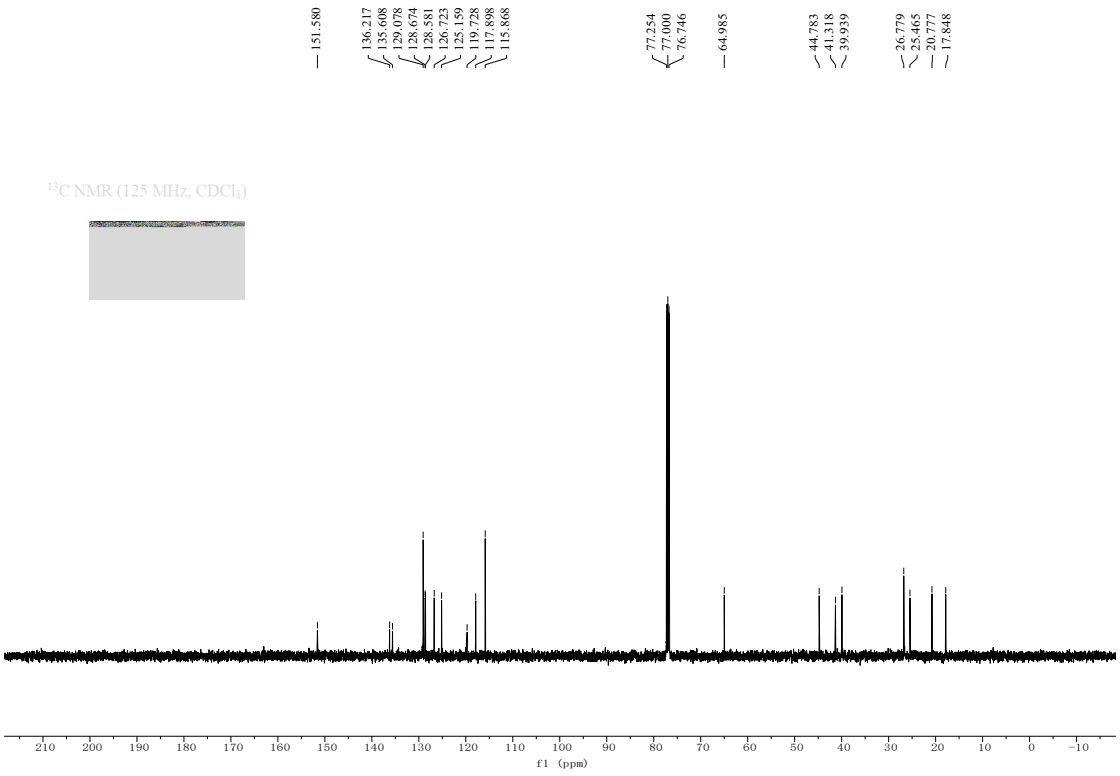
tert-butyl (cyanomethyl)((2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)carbamate (3ag) (dr = 1:1)



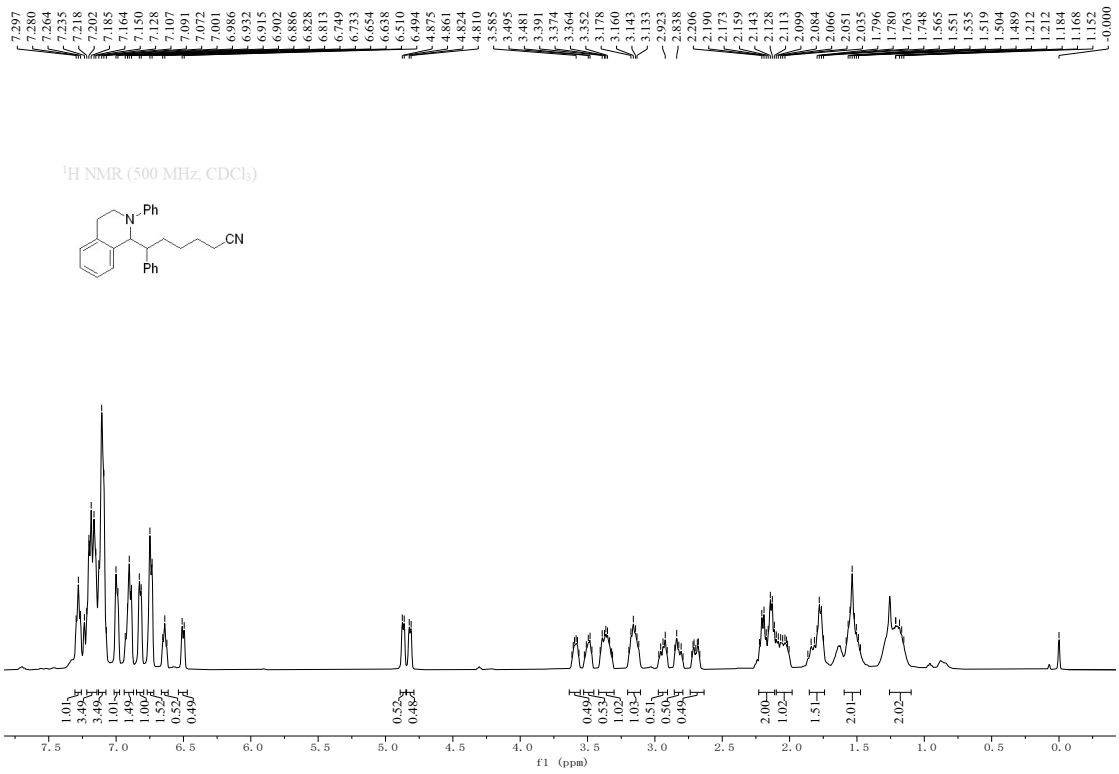


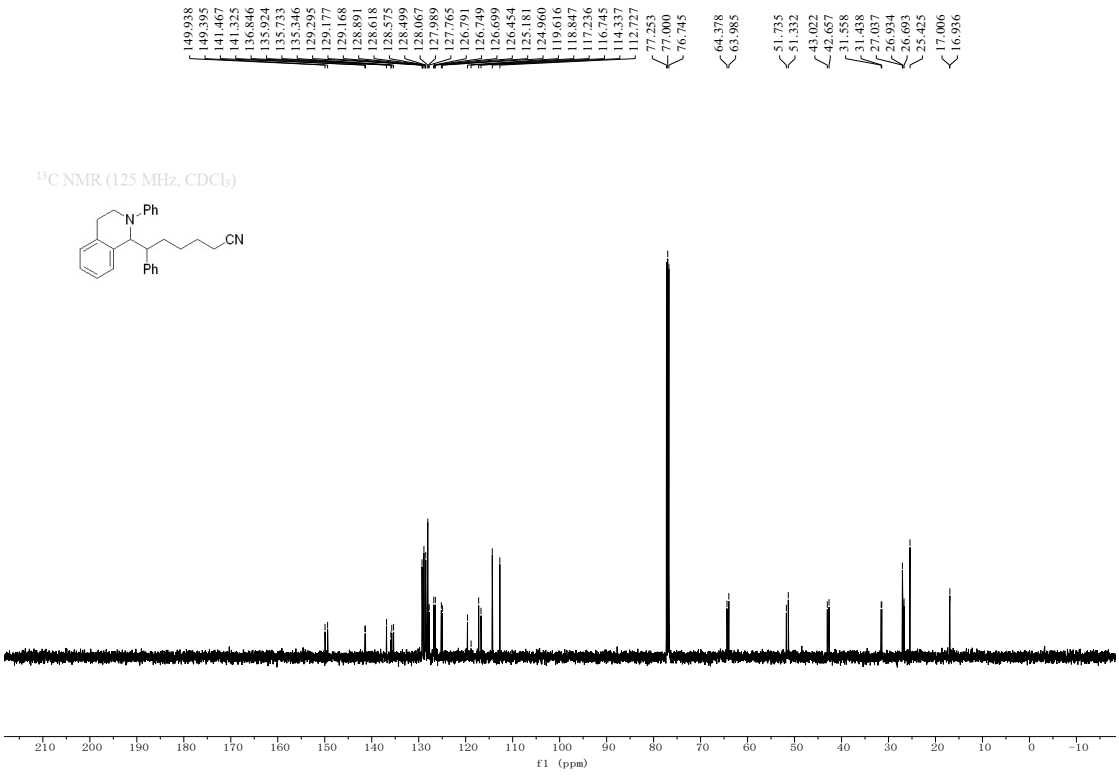
5-methyl-5-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)hexanenitrile (3ah)





6-phenyl-6-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)hexanenitrile (3ai) (dr = 1:1)

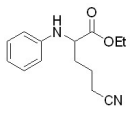


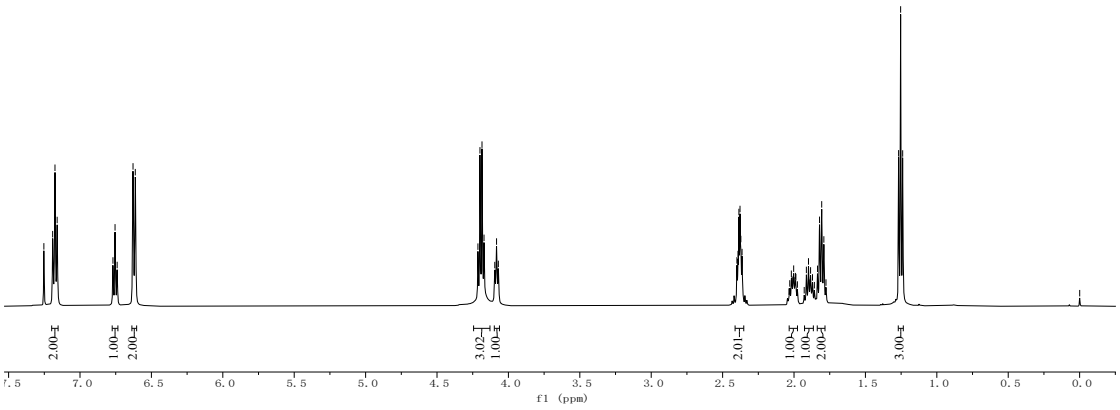


ethyl 5-cyano-2-(phenylamino)pentanoate (5aa)

7.253
7.192
7.175
7.160
6.769
6.755
6.740
6.629
6.613
4.213
4.199
4.185
4.171
4.096
4.083
4.070
2.400
2.392
2.386
2.378
2.372
2.364
2.035
2.030
2.019
2.014
2.008
2.002
1.994
1.990
1.987
1.976
1.929
1.913
1.899
1.889
1.884
1.871
1.858
1.835
1.821
1.806
1.791
1.776
1.268
1.253
1.239
0.000

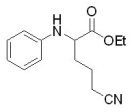
^{1}H NMR (500 MHz, $CDCl_3$)

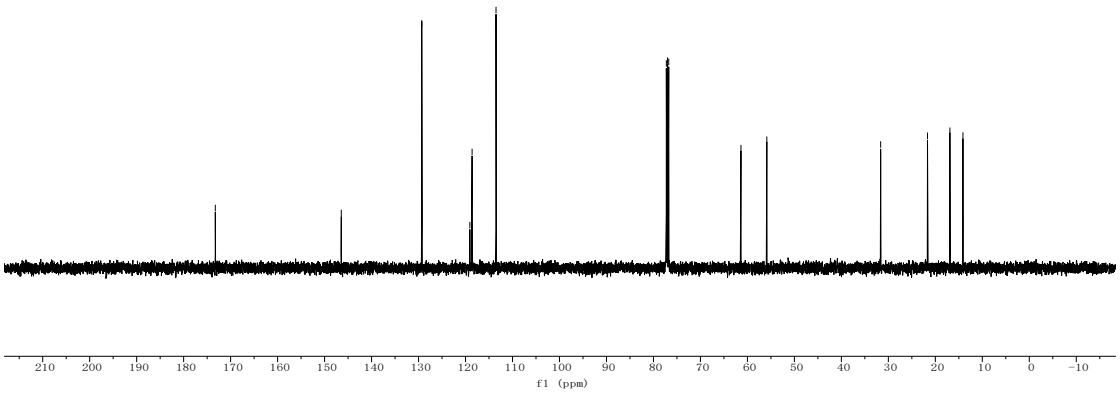




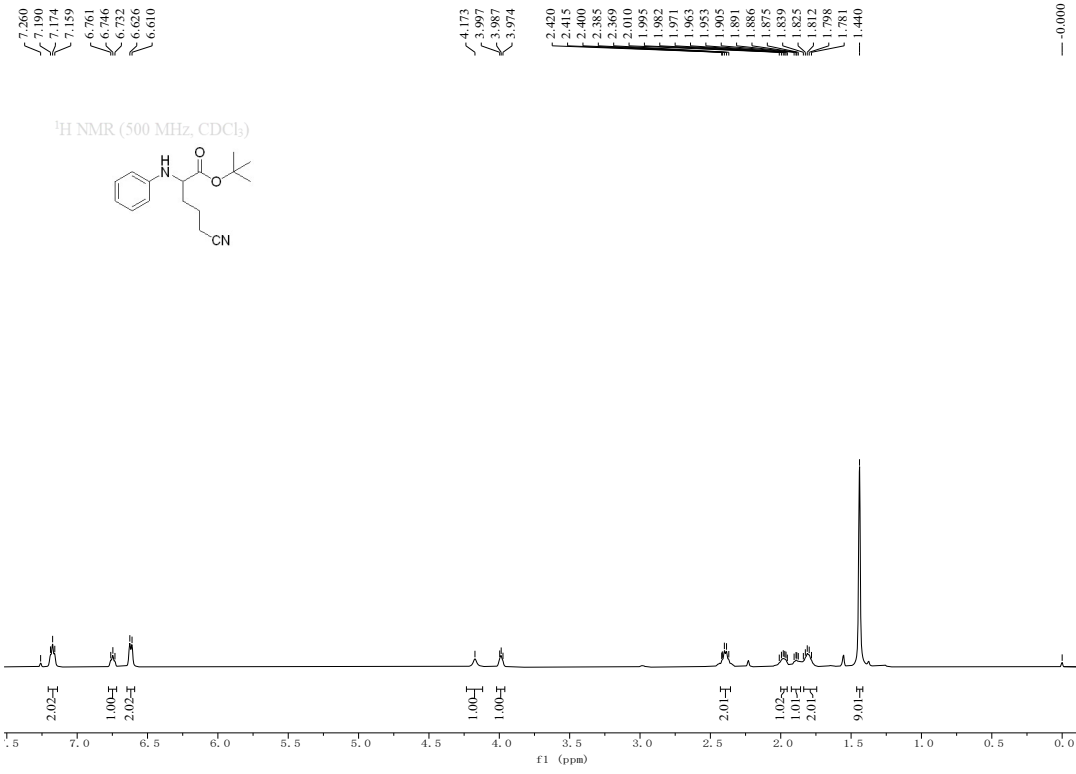
173.259
146.447
129.320
119.079
118.603
113.511
77.255
77.000
76.745
61.376
55.868
31.638
21.667
16.901
14.124

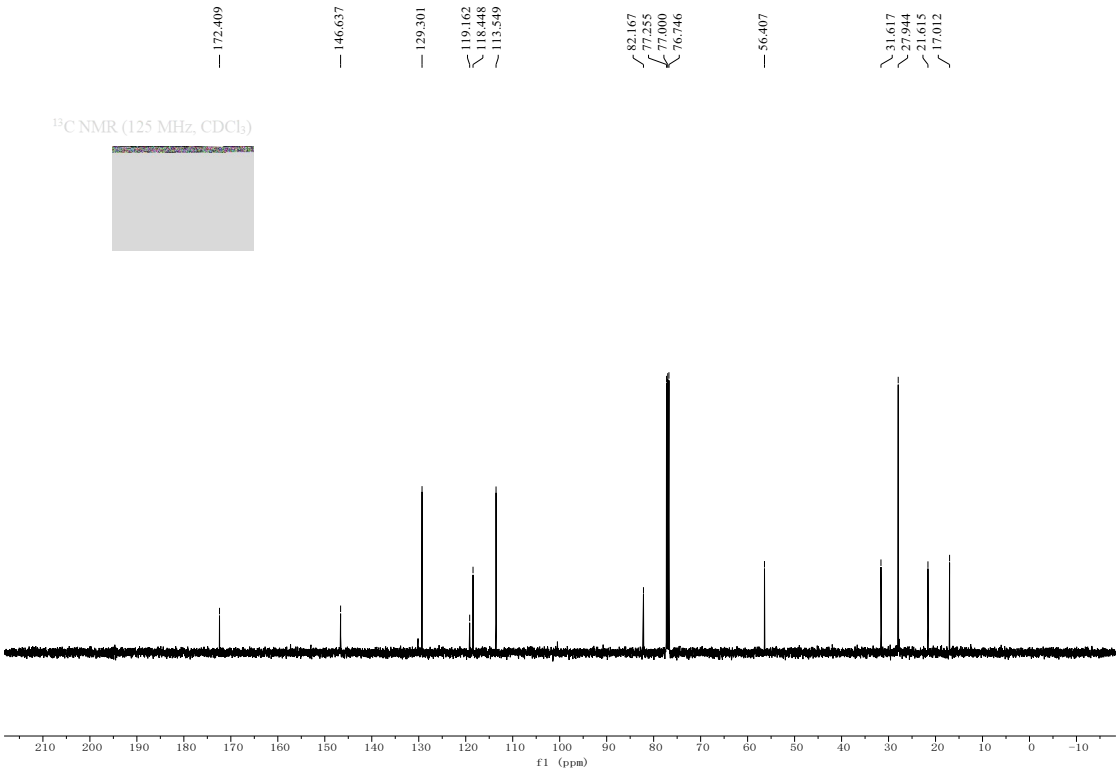
^{13}C NMR (125 MHz, $CDCl_3$)



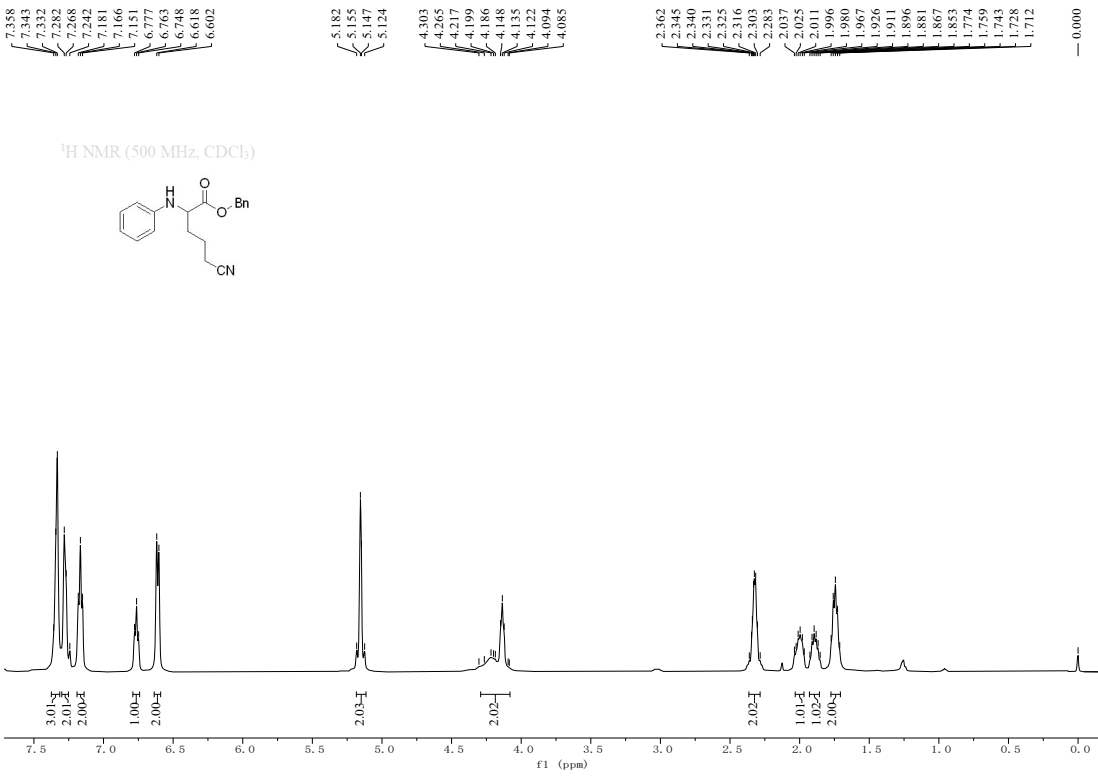


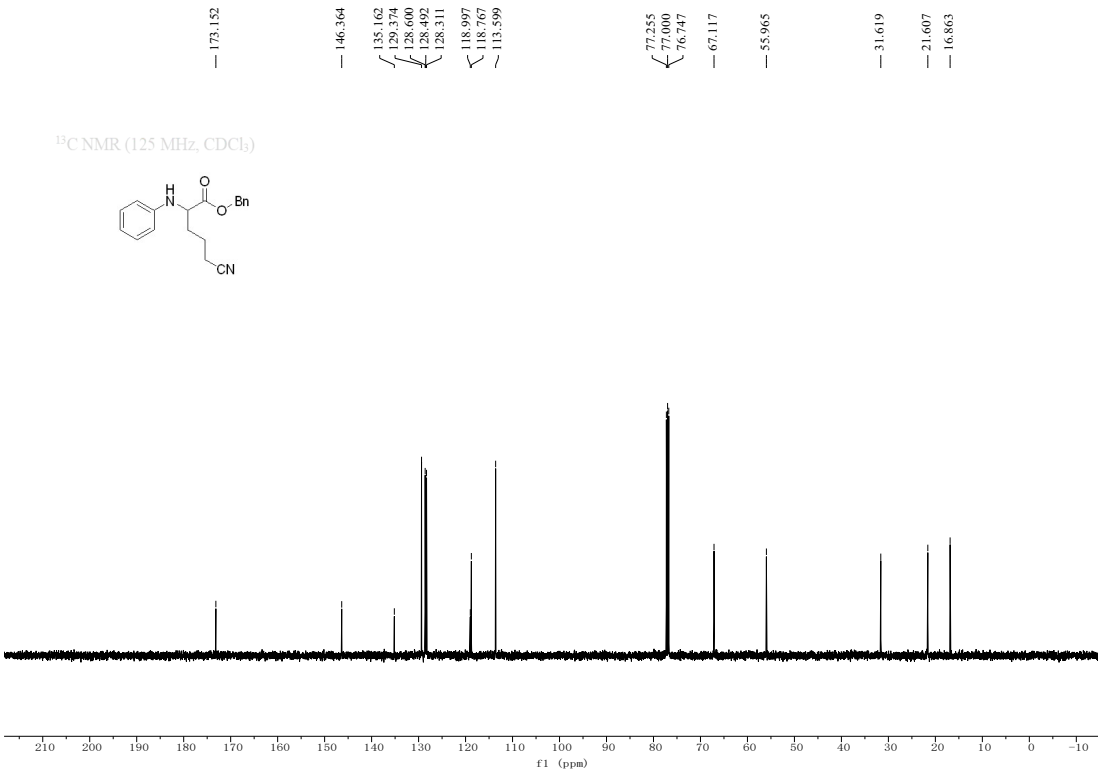
tert-butyl 5-cyano-2-(phenylamino)pentanoate (5ba)



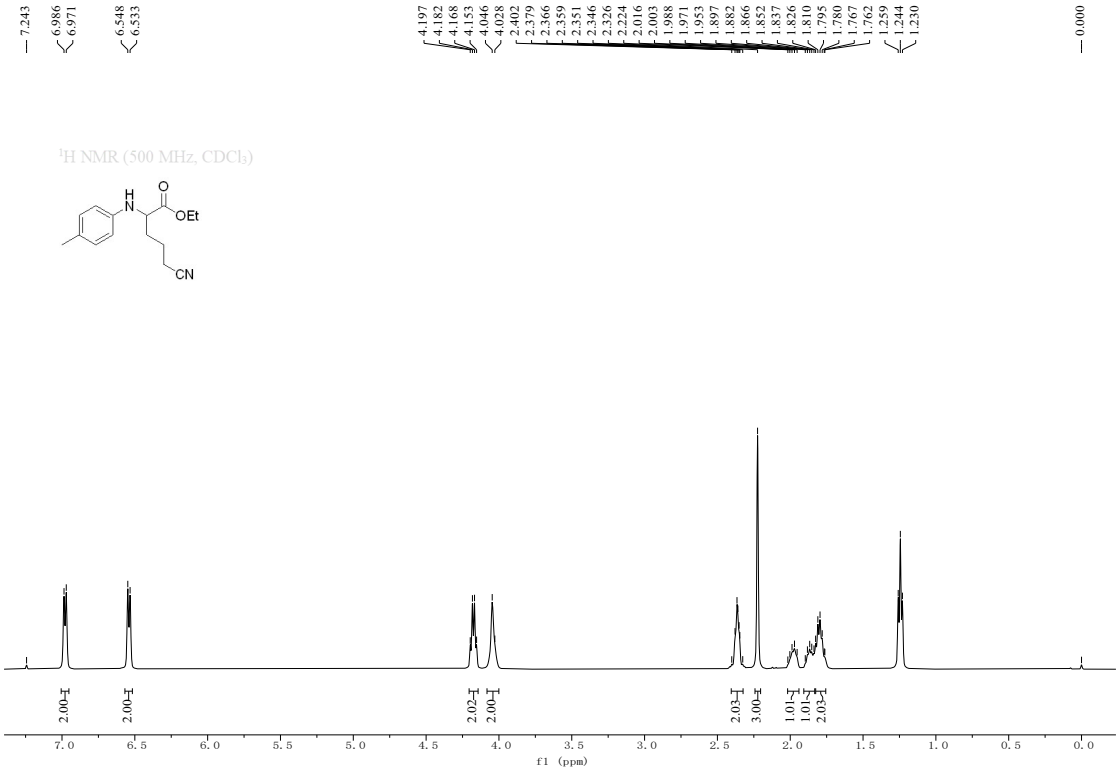


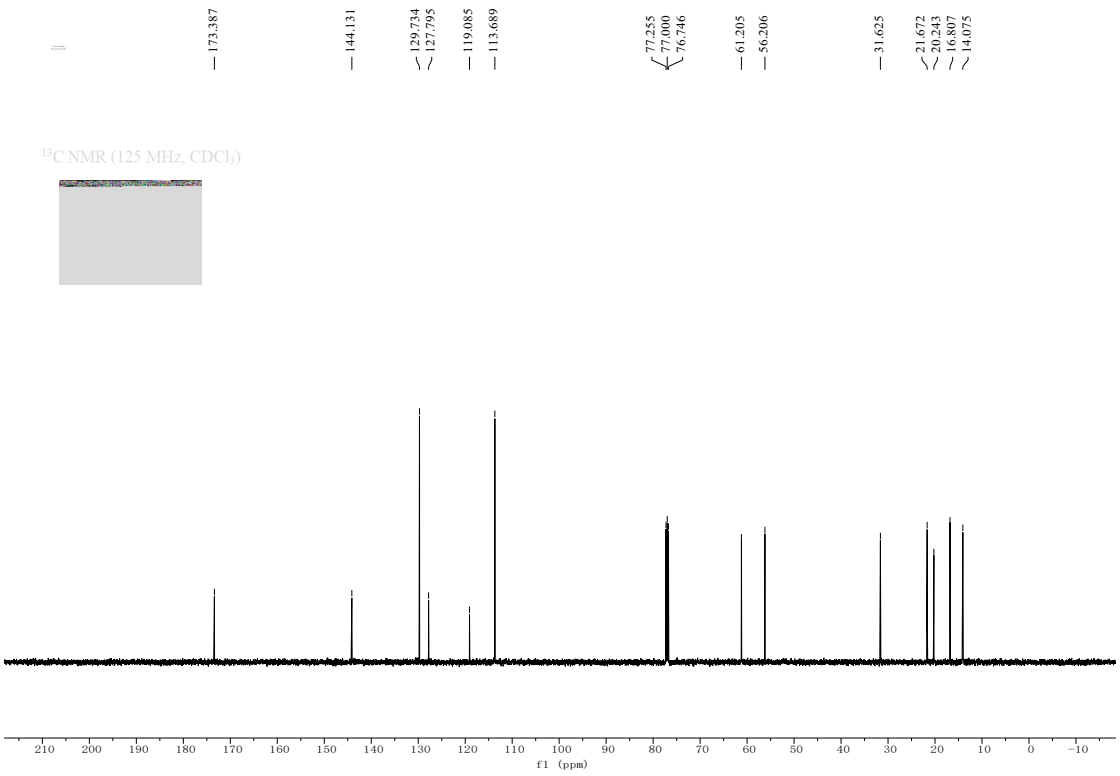
benzyl 5-cyano-2-(phenylamino)pentanoate (5ca)


7.358
7.343
7.332
7.282
7.268
7.242
7.181
7.166
7.151
6.777
6.763
6.748
6.618
6.602
5.182
5.155
5.147
5.124
4.303
4.265
4.217
4.199
4.186
4.148
4.135
4.122
4.094
4.085
2.362
2.345
2.340
2.331
2.325
2.316
2.303
2.283
2.037
2.025
2.011
1.996
1.980
1.967
1.926
1.911
1.896
1.881
1.867
1.853
1.774
1.759
1.743
1.728
1.712
0.000
^{1}H NMR (500 MHz, CDCl$_3$)
Bn
CN
3.01
2.01
2.00
1.00
2.00
2.03
2.02
2.02
1.01
1.02
2.00
f1 (ppm)

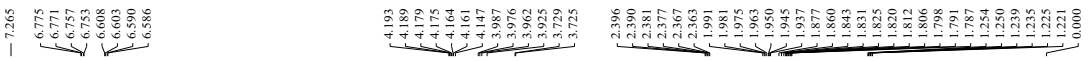

173.152
146.364
135.162
129.374
128.600
128.492
128.311
118.997
118.767
113.599
77.255
77.000
76.747
67.117
55.965
31.619
21.607
16.863
^{13}C NMR (125 MHz, CDCl$_3$)
Bn
CN
f1 (ppm)

ethyl 5-cyano-2-(p-tolylamino)pentanoate (5da)

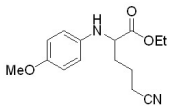


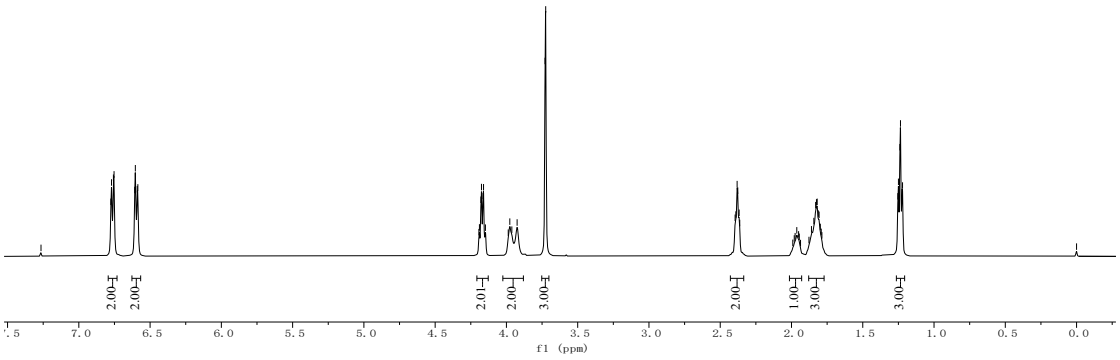


ethyl 5-cyano-2-((4-methoxyphenyl)amino)pentanoate (5ea)

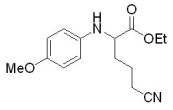


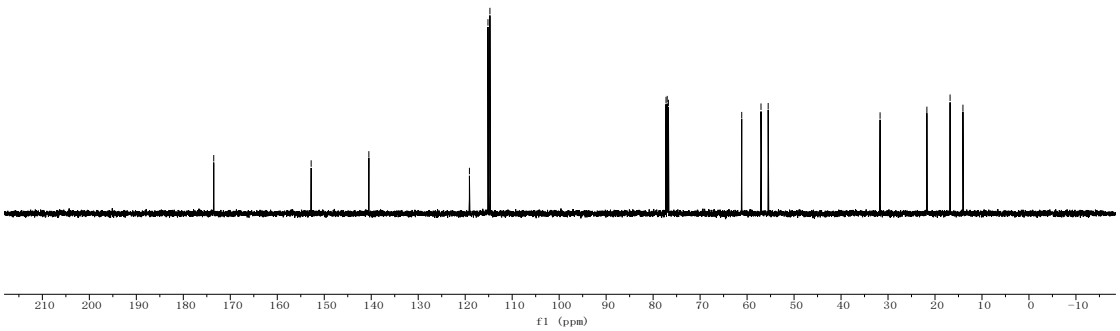
^{1}H NMR (500 MHz, $CDCl_3$)



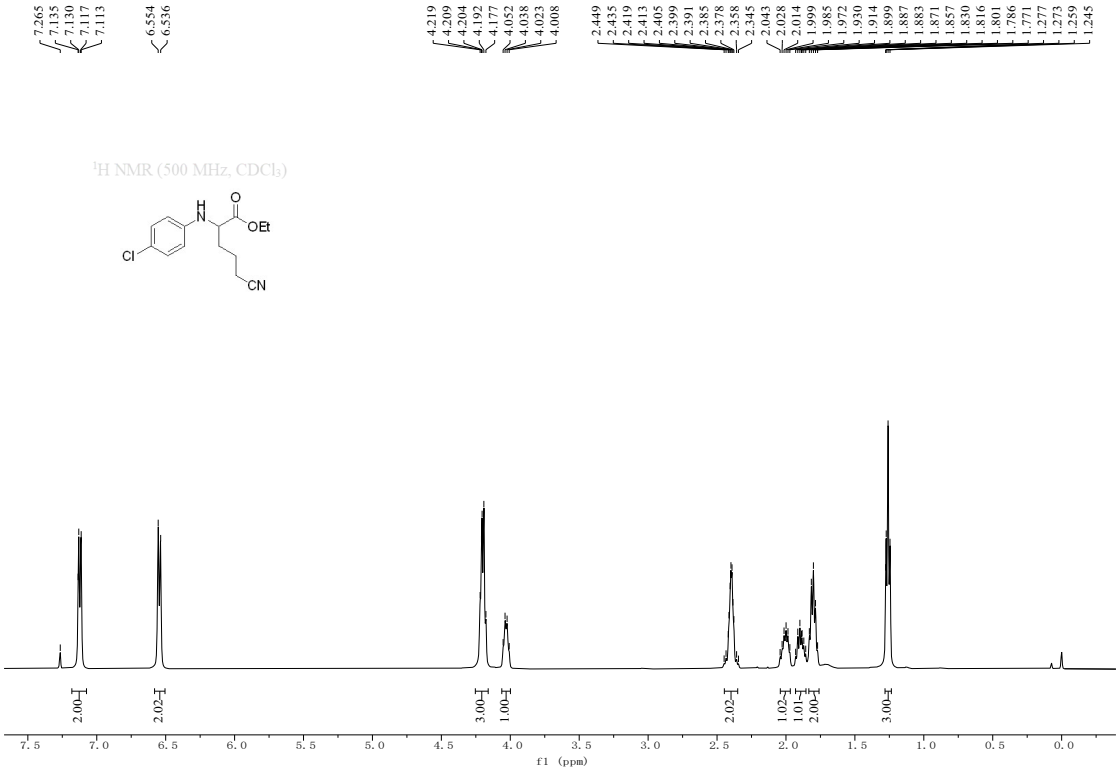


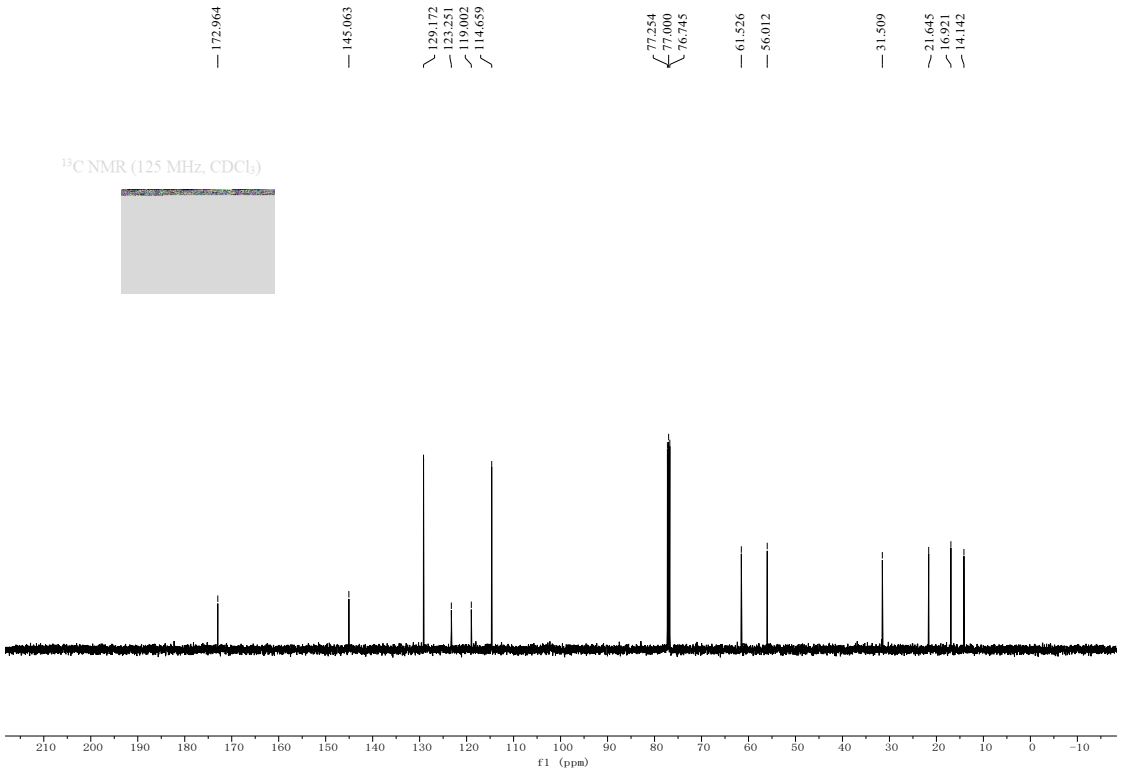
^{13}C NMR (125 MHz, $CDCl_3$)



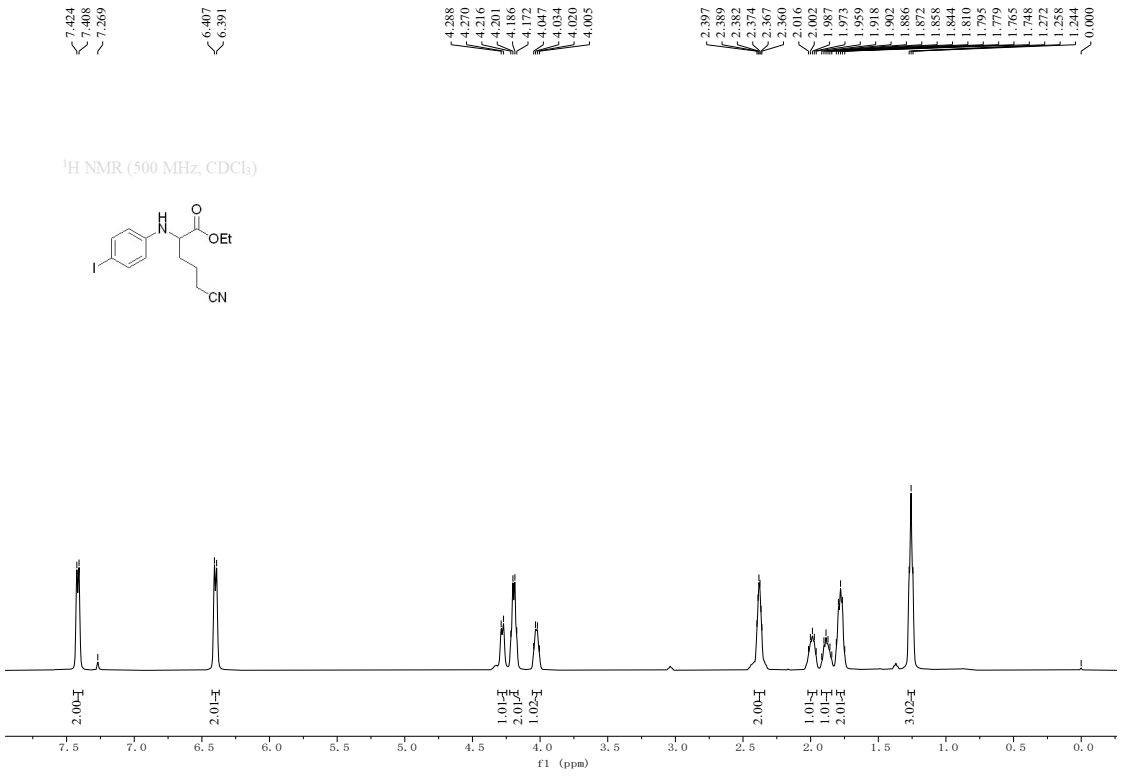


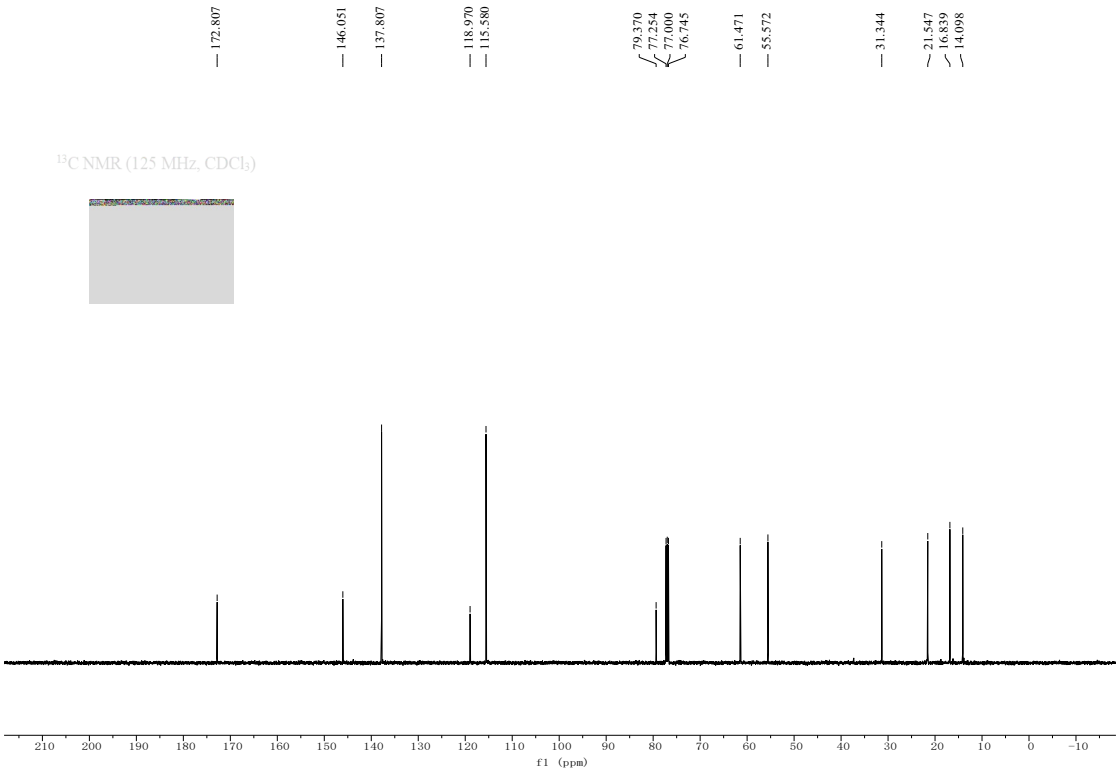
ethyl 2-((4-chlorophenyl)amino)-5-cyanopentanoate (5fa)



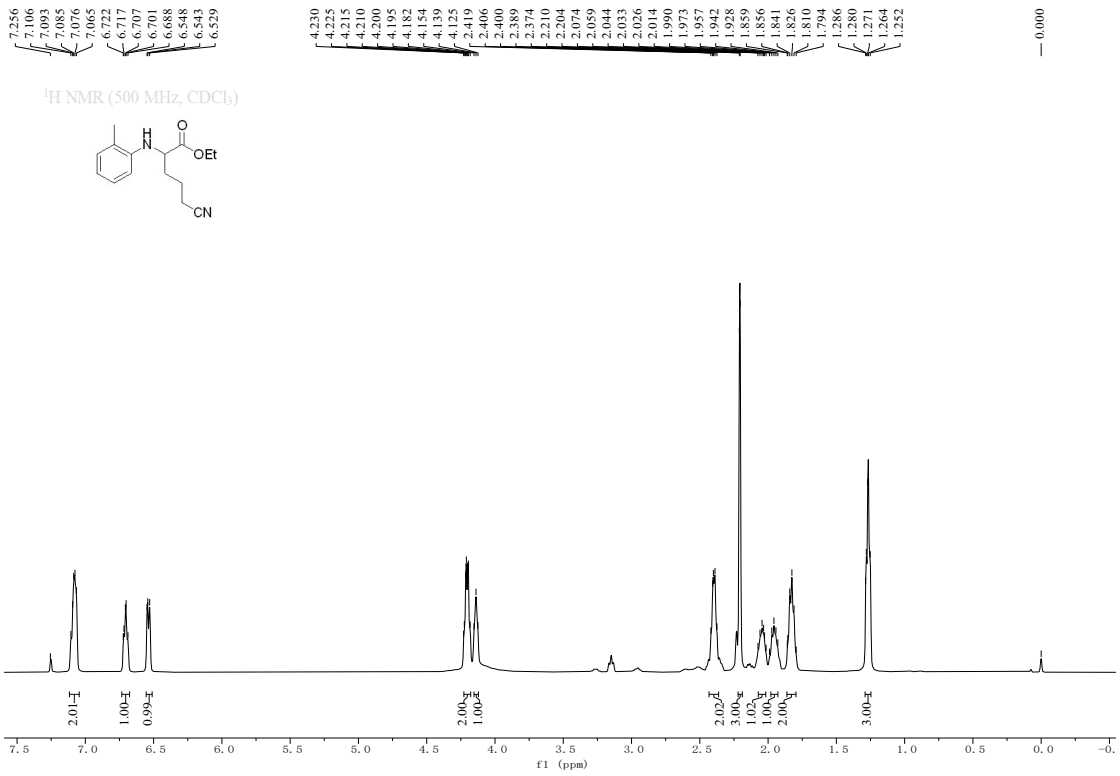


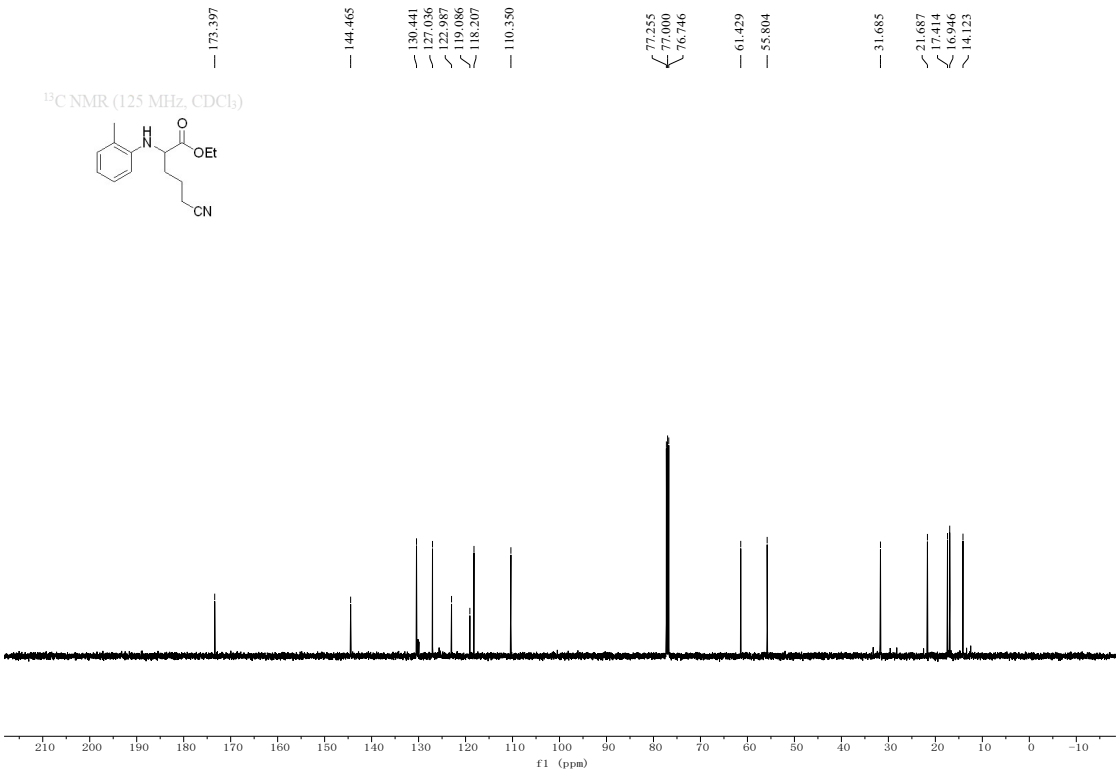
ethyl 5-cyano-2-((4-iodophenyl)amino)pentanoate (5ga)



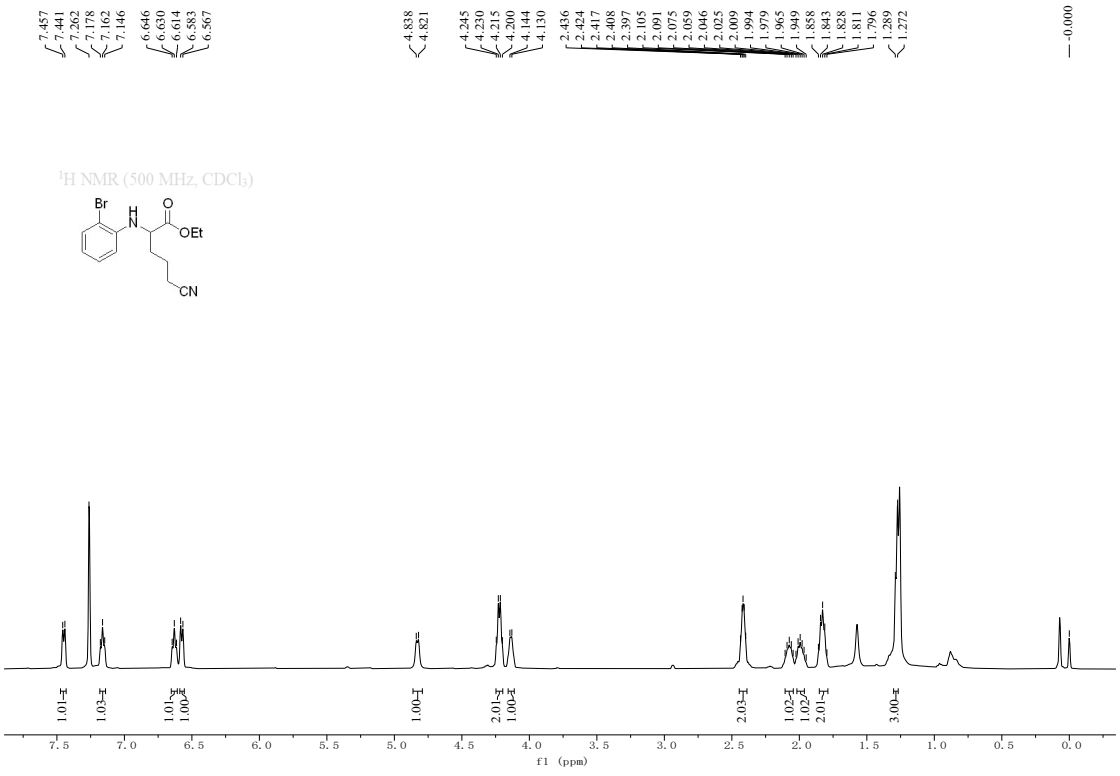


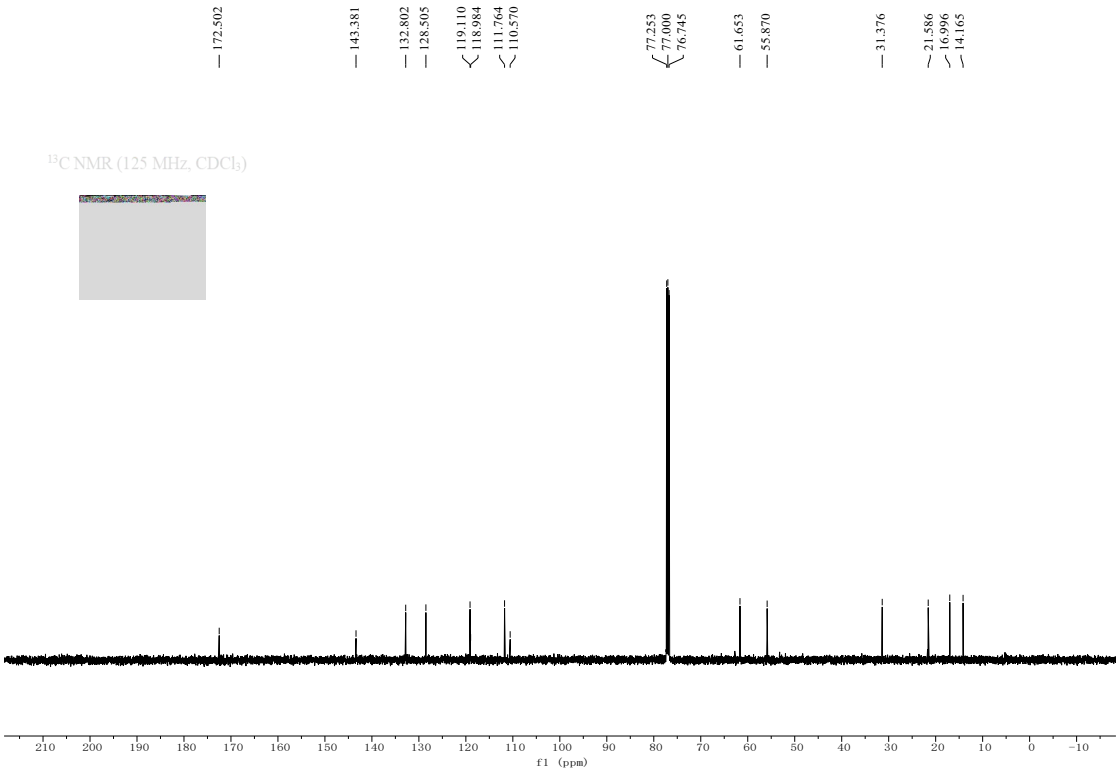
ethyl 5-cyano-2-(o-tolylamino)pentanoate (5ha)


7.256
7.106
7.093
7.085
7.076
7.065
6.722
6.717
6.707
6.701
6.688
6.548
6.543
6.529
4.230
4.225
4.215
4.210
4.200
4.195
4.182
4.154
4.139
4.125
2.419
2.406
2.400
2.389
2.374
2.210
2.204
2.074
2.059
2.044
2.033
2.026
2.014
1.990
1.973
1.957
1.942
1.928
1.859
1.856
1.841
1.826
1.810
1.794
1.286
1.280
1.271
1.264
1.252
0.000
1H NMR (500 MHz, CDCl3)
O
H
N
OEt
CN
2.01
1.00
0.99
2.00
1.00
2.02
3.00
1.02
1.00
2.00
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.
f1 (ppm)

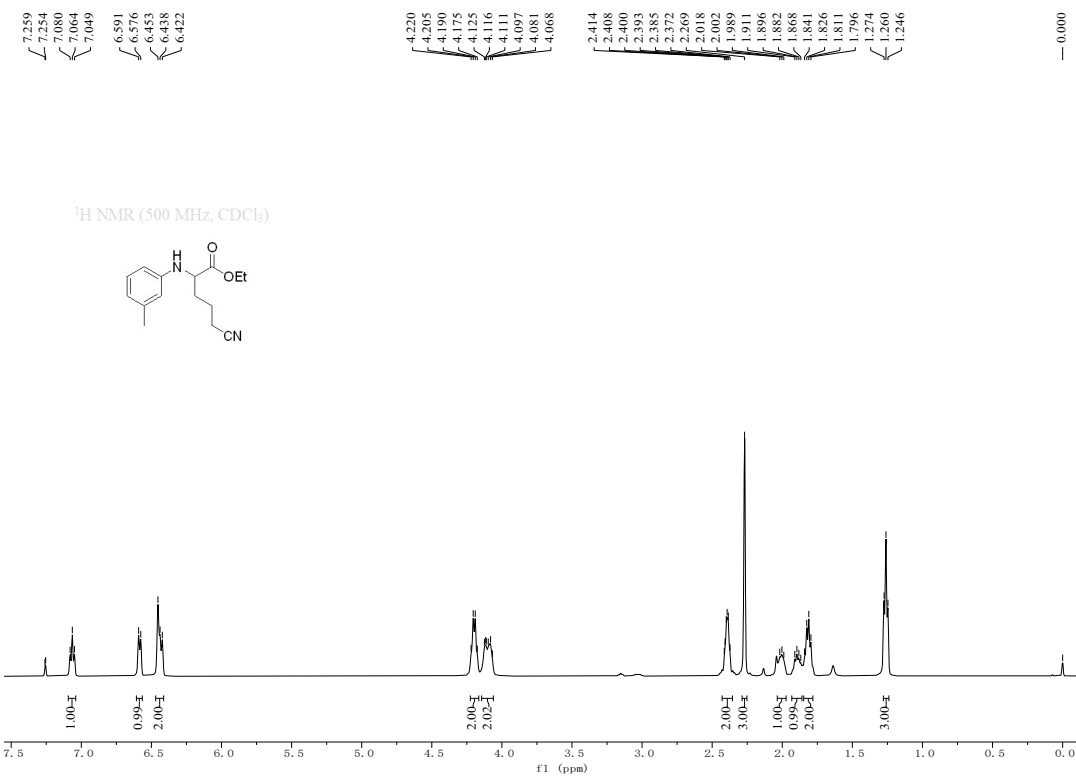

173.397
144.465
130.441
127.036
122.987
119.086
118.207
110.350
77.255
77.000
76.746
61.429
55.804
31.685
21.687
17.414
16.946
14.123
13C NMR (125 MHz, CDCl3)
O
H
N
OEt
CN
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

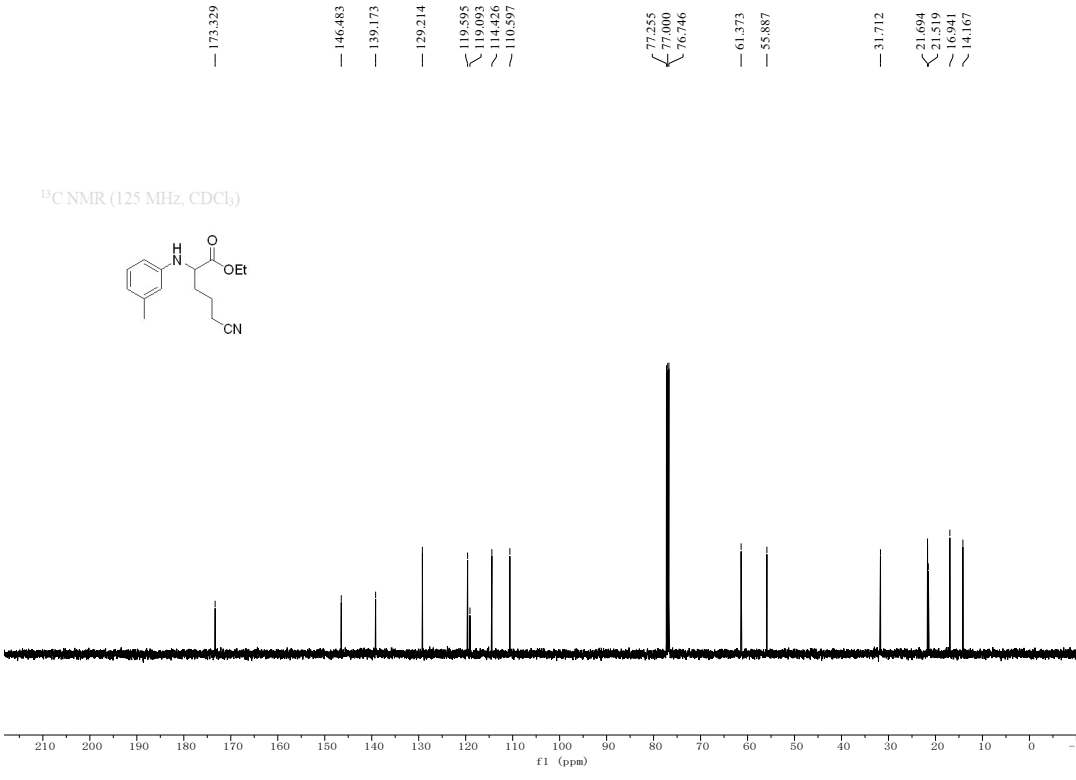
ethyl 2-((2-bromophenyl)amino)-5-cyanopentanoate (5ia)



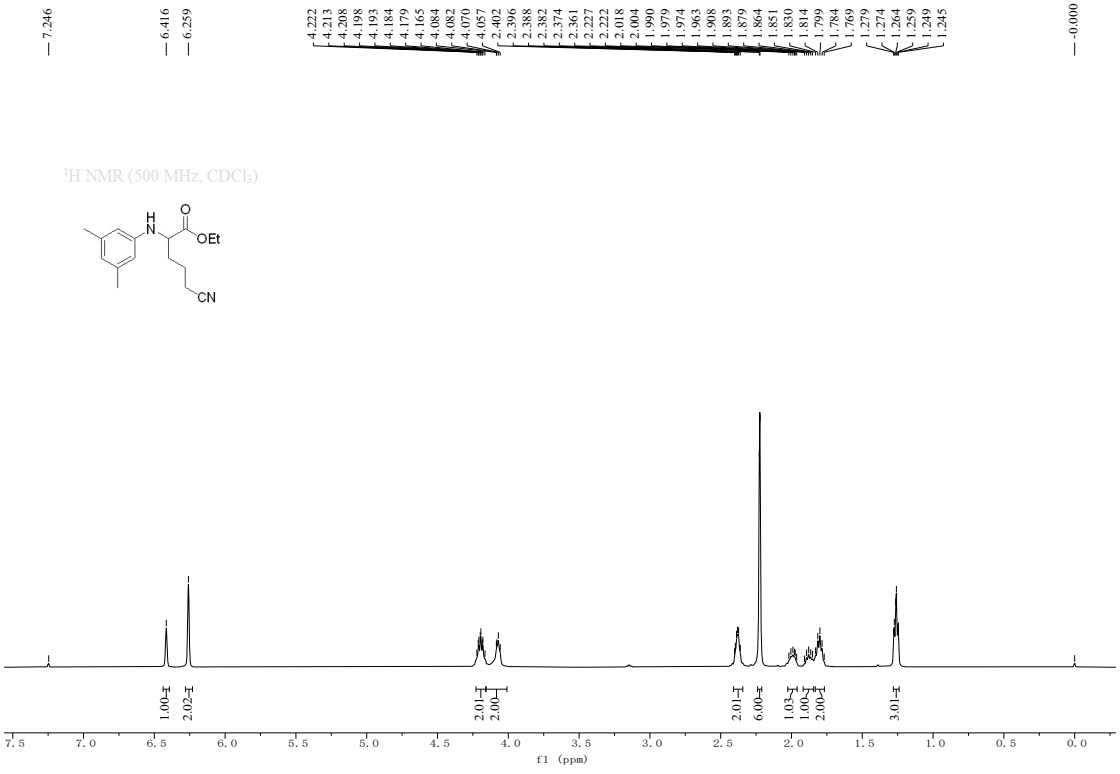


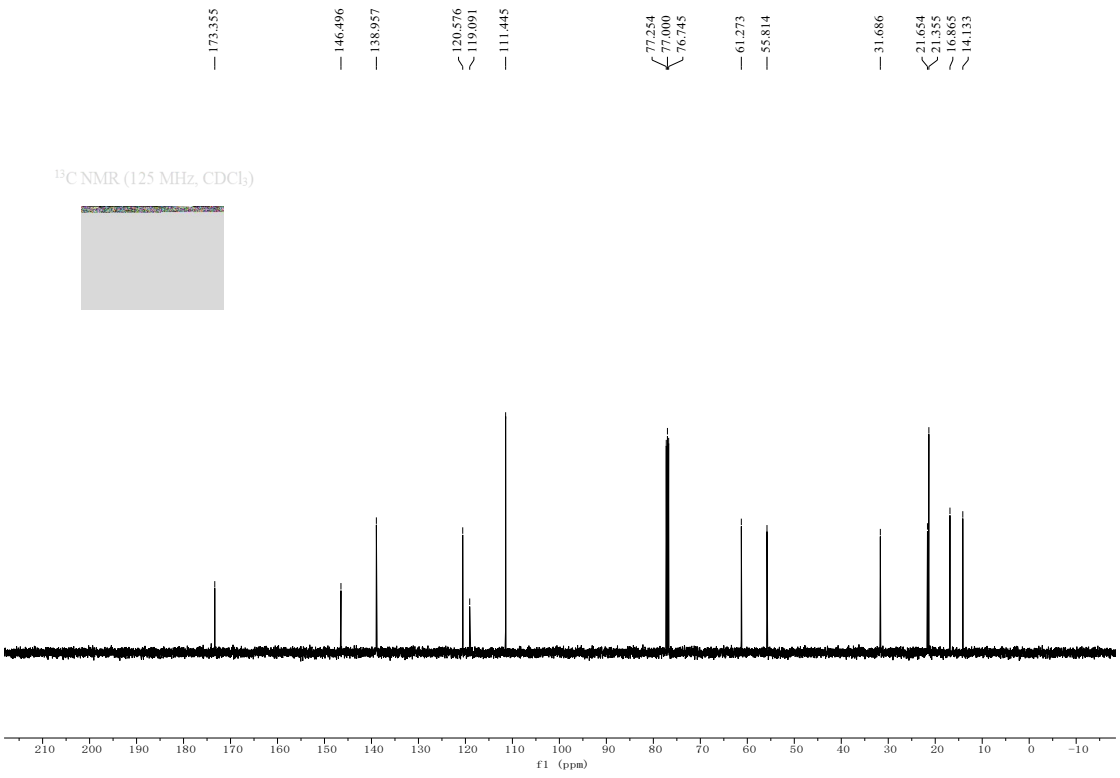
ethyl 5-cyano-2-(m-tolylamino)pentanoate (5ja)


7.259
7.254
7.080
7.064
7.049
6.591
6.576
6.453
6.438
6.422
4.220
4.205
4.190
4.175
4.125
4.116
4.111
4.097
4.081
4.068
2.414
2.408
2.400
2.393
2.385
2.372
2.269
2.018
2.002
1.989
1.911
1.896
1.882
1.868
1.841
1.826
1.811
1.796
1.274
1.260
1.246
0.000
1H NMR (500 MHz, CDCl3)
H
N
O
OEt
CN
1.00
0.99
2.00
2.00
2.02
2.00
3.00
1.00
0.99
2.00
3.00
f1 (ppm)


173.329
146.483
139.173
129.214
119.595
119.093
114.426
110.597
77.255
77.000
76.746
61.373
55.887
31.712
21.694
21.519
16.941
14.167
13C NMR (125 MHz, CDCl3)
H
N
O
OEt
CN
f1 (ppm)

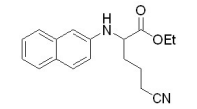
ethyl 5-cyano-2-((3,5-dimethylphenyl)amino)pentanoate (5ka)

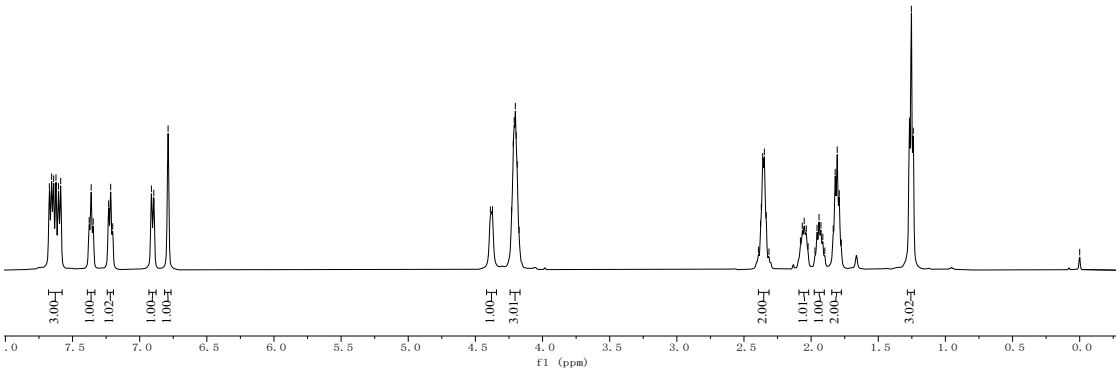




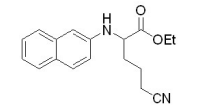
ethyl 5-cyano-2-(naphthalen-2-ylamino)pentanoate (5la)

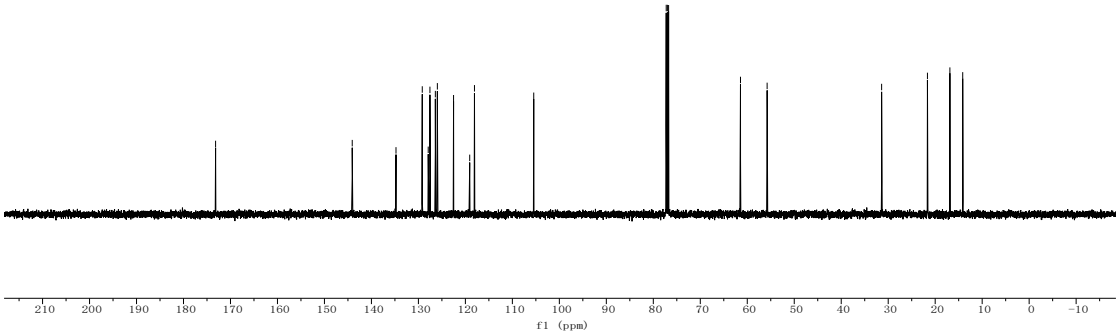
^{1}H NMR (500 MHz, $CDCl_3$)



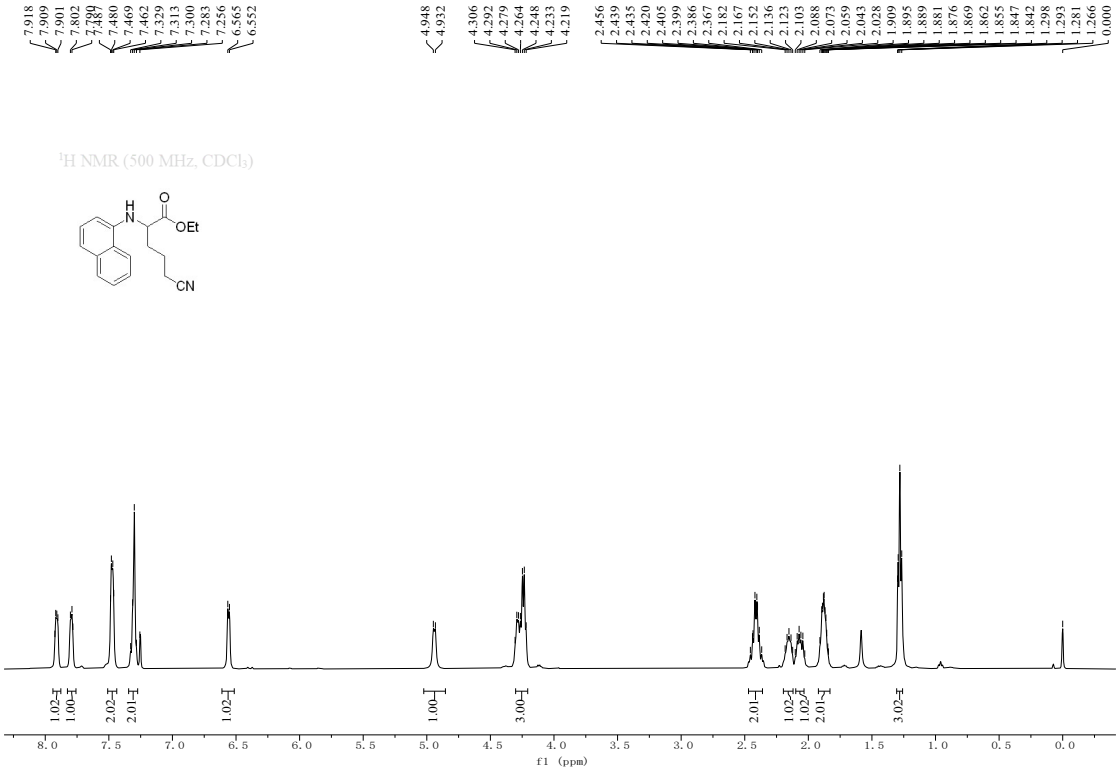


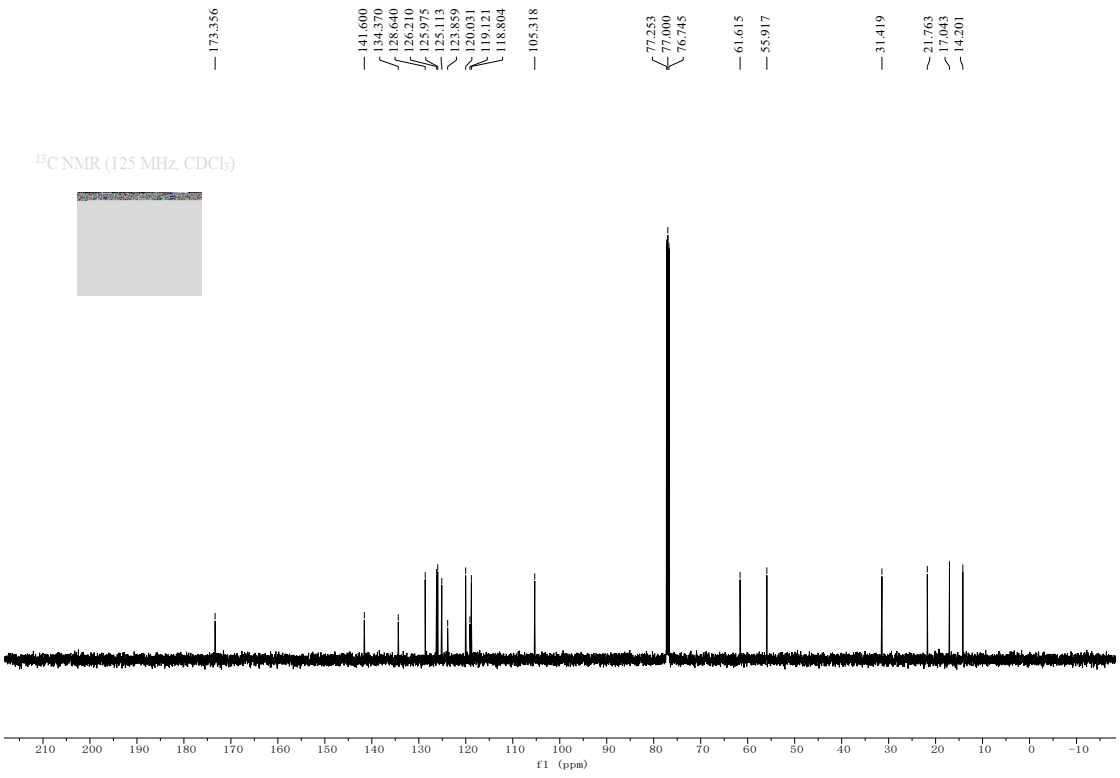
^{13}C NMR (125 MHz, $CDCl_3$)



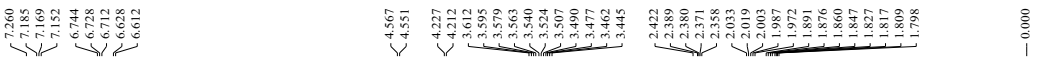


ethyl 5-cyano-2-(naphthalen-1-ylamino)pentanoate (5ma)

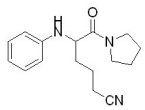


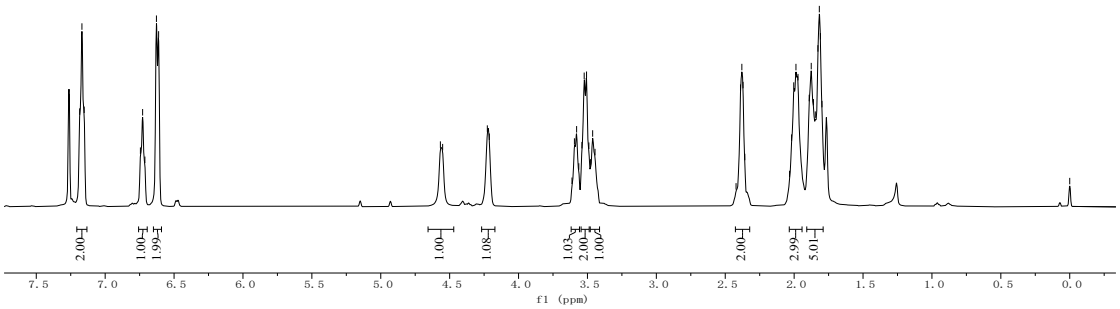


6-oxo-5-(phenylamino)-6-(pyrrolidin-1-yl)hexanenitrile (5na)

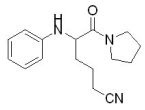


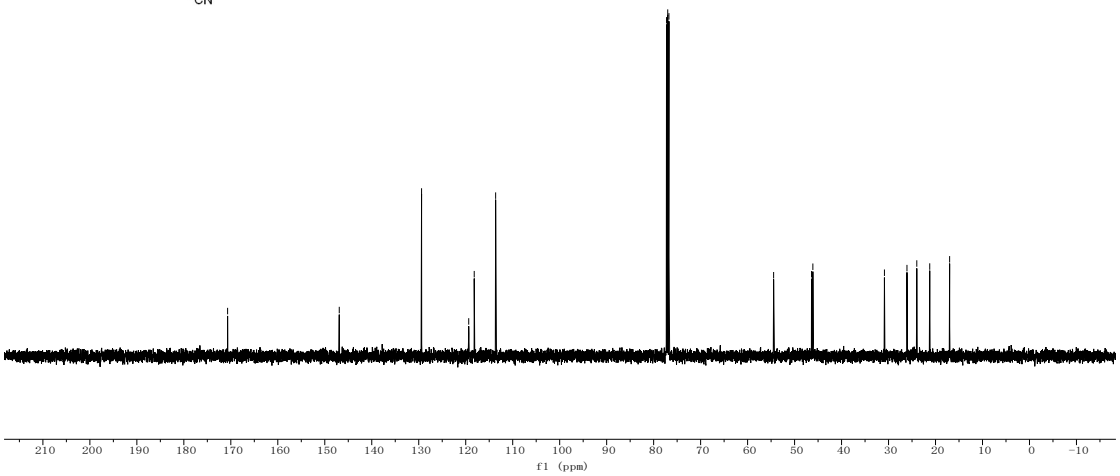
^{1}H NMR (500 MHz, $CDCl_3$)



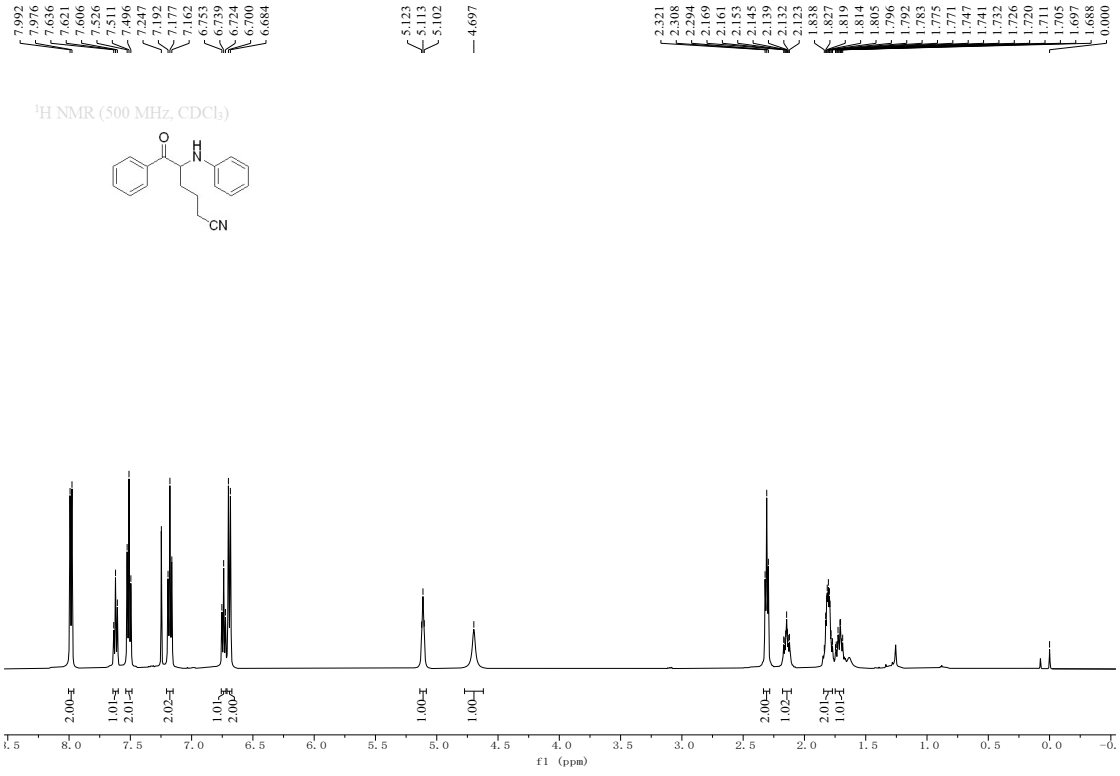


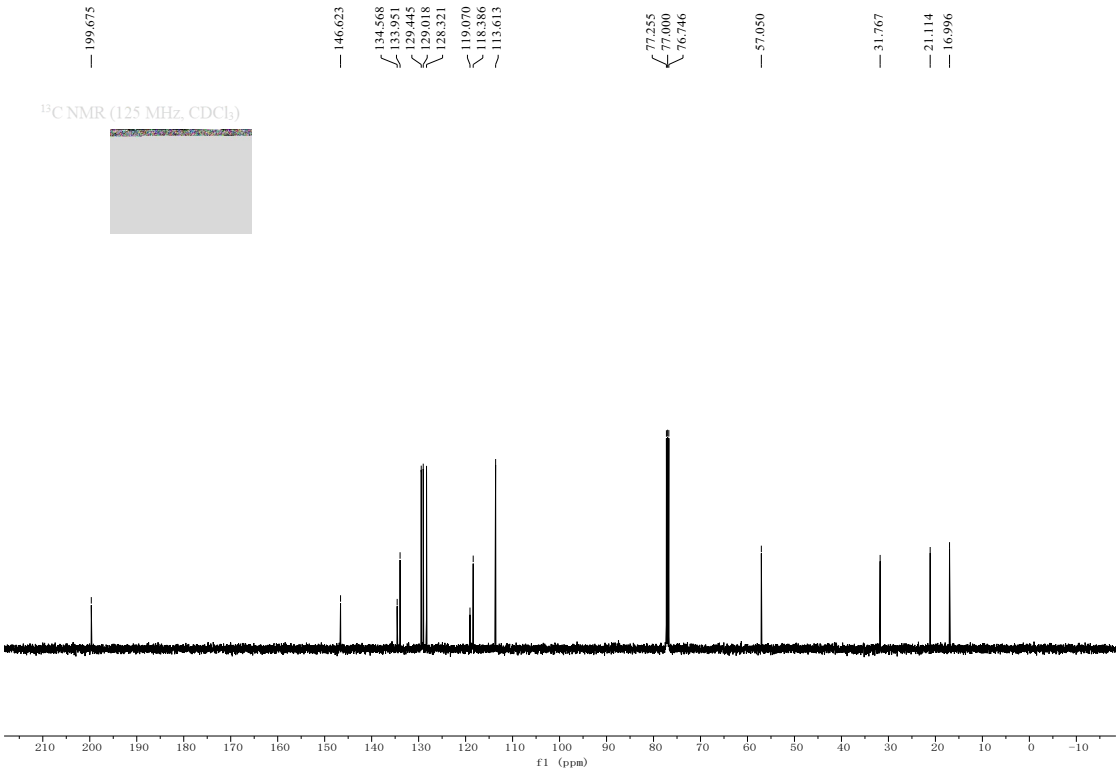
^{13}C NMR (125 MHz, $CDCl_3$)



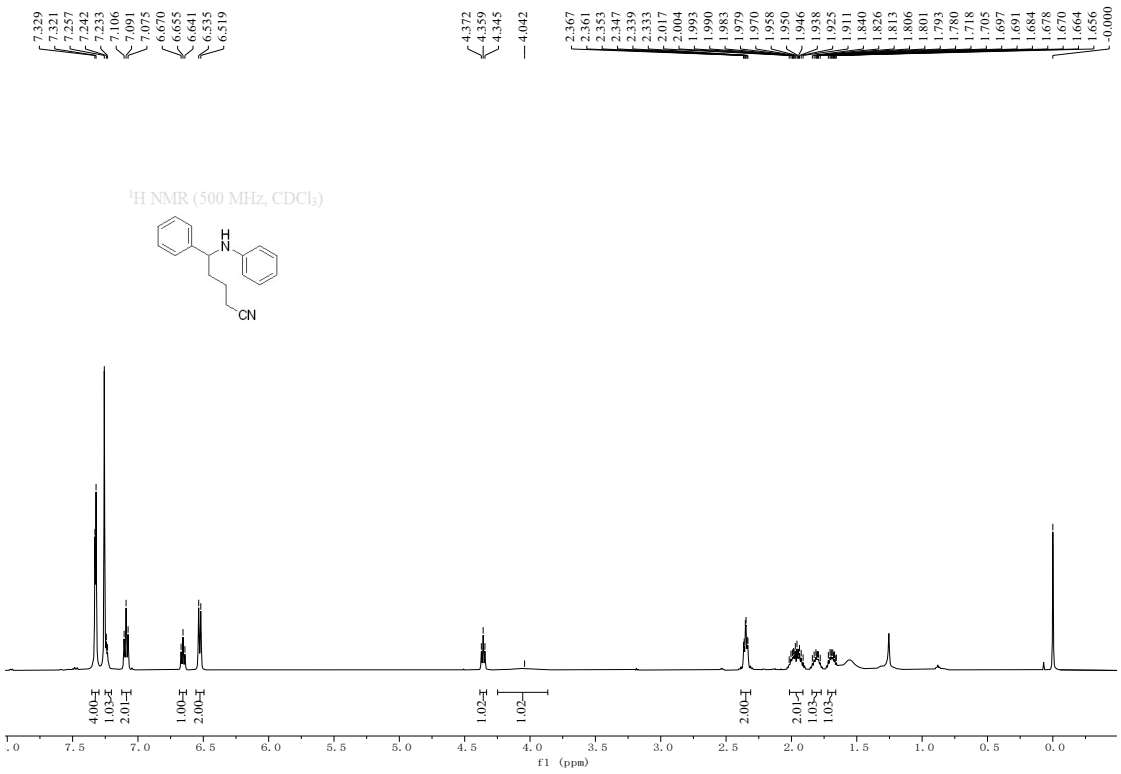


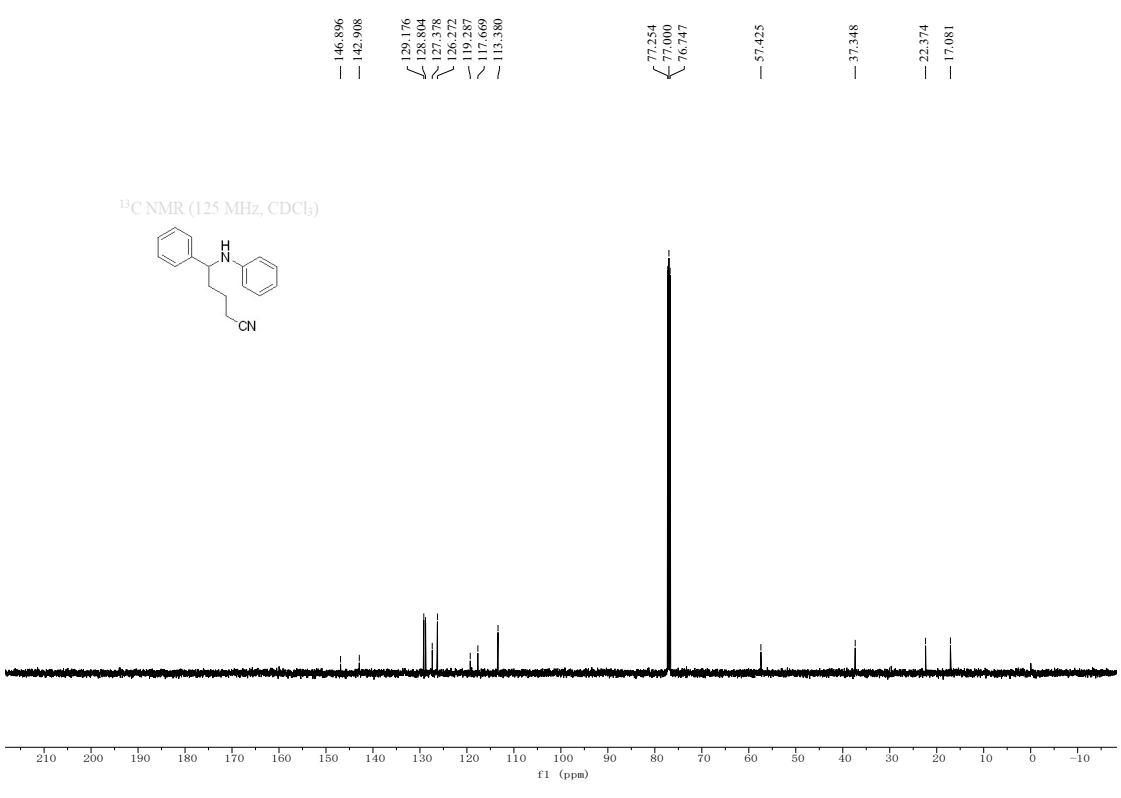
6-oxo-6-phenyl-5-(phenylamino)hexanenitrile (5oa)



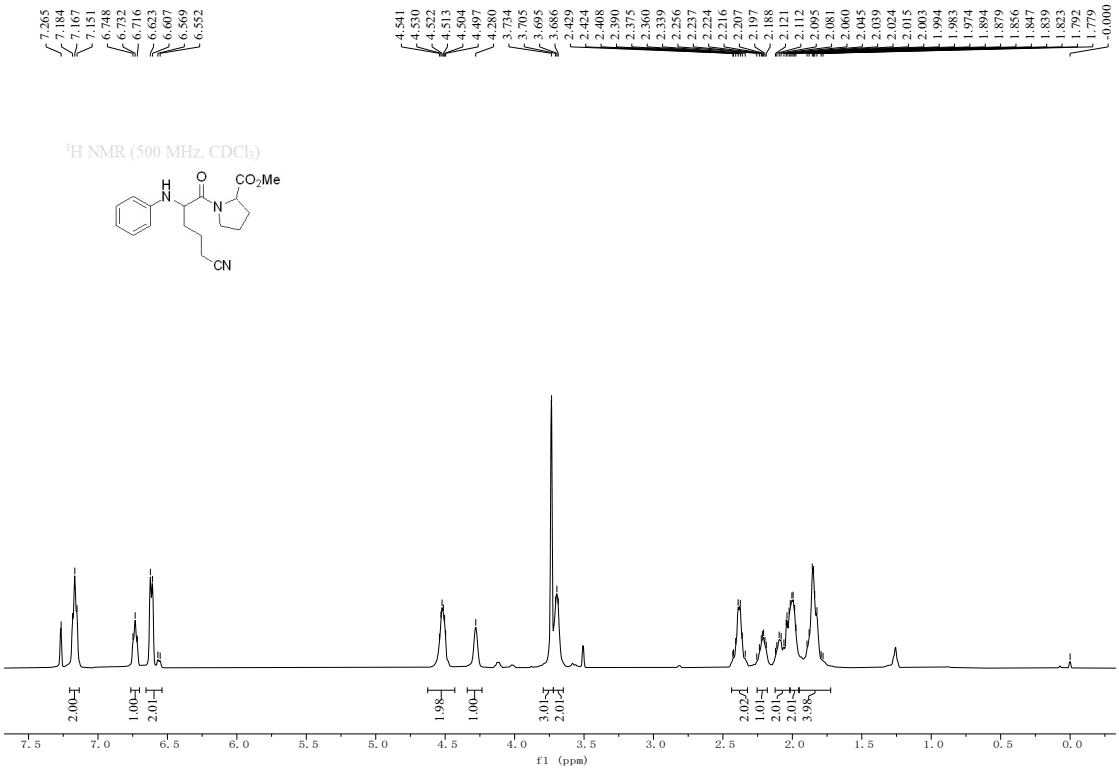


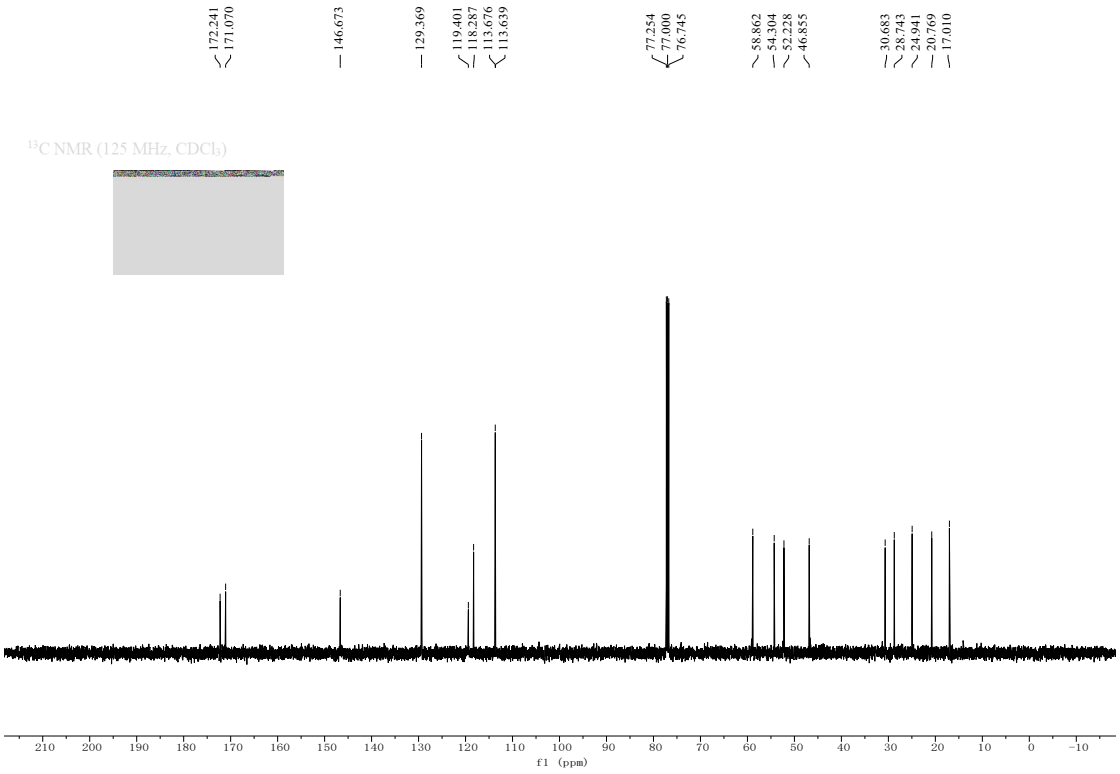
5-phenyl-5-(phenylamino)pentanenitrile (5pa)

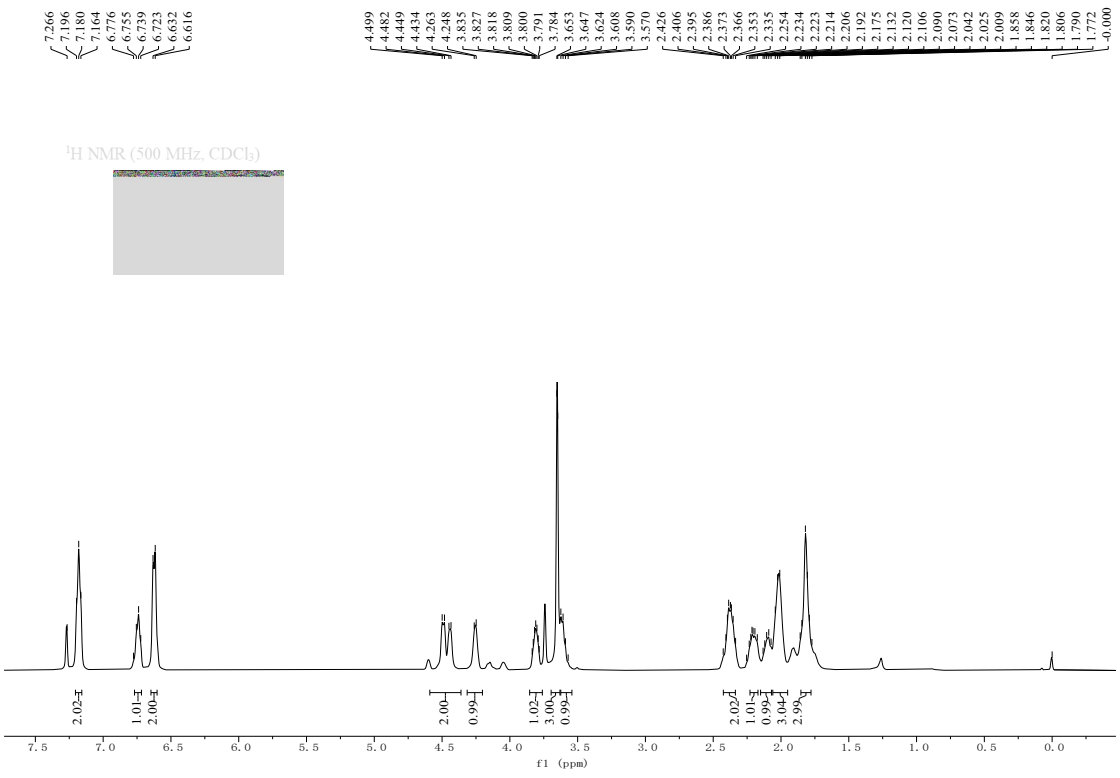

7.329
7.321
7.257
7.242
7.233
7.106
7.091
7.075
6.670
6.655
6.641
6.535
6.519
4.372
4.359
4.345
4.042
2.367
2.361
2.353
2.347
2.339
2.333
2.017
2.004
1.993
1.990
1.983
1.979
1.970
1.958
1.950
1.946
1.938
1.925
1.911
1.840
1.826
1.813
1.806
1.801
1.793
1.780
1.718
1.705
1.697
1.691
1.684
1.678
1.670
1.664
1.656
0.000
1H NMR (500 MHz, CDCl3)
H
N
CN
4.00
1.03
2.01
1.00
2.00
1.02
1.02
2.00
2.01
1.03
1.03
f1 (ppm)

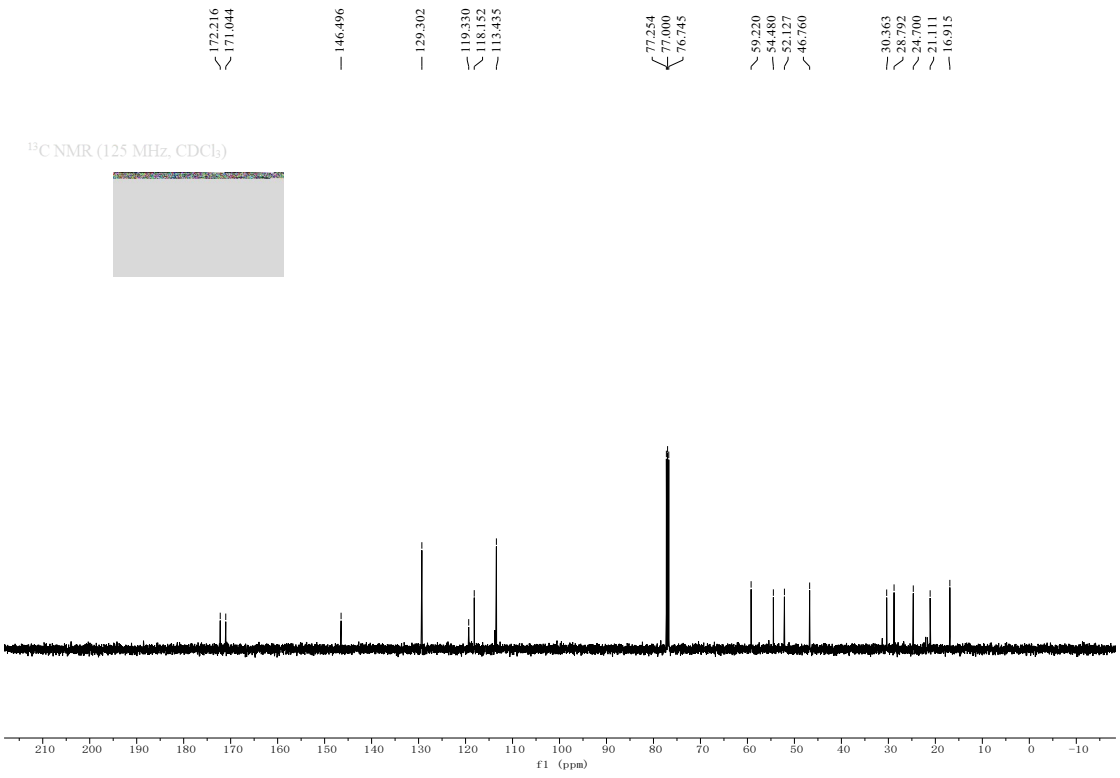

146.896
142.908
129.176
128.804
127.378
126.272
119.287
117.669
113.380
77.254
77.000
76.747
57.425
37.348
22.374
17.081
13C NMR (125 MHz, CDCl3)
H
N
CN
f1 (ppm)

methyl (5-cyano-2-(phenylamino)pentanoyl)prolinate (5ra) (dr = 1:1)



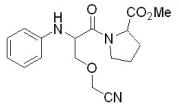

172.241
171.070
146.673
129.369
119.401
118.287
113.676
113.639
77.254
77.000
76.745
58.862
54.304
52.228
46.855
30.683
28.743
24.941
20.769
17.010
13C NMR (125 MHz, CDCl3)
f1 (ppm)

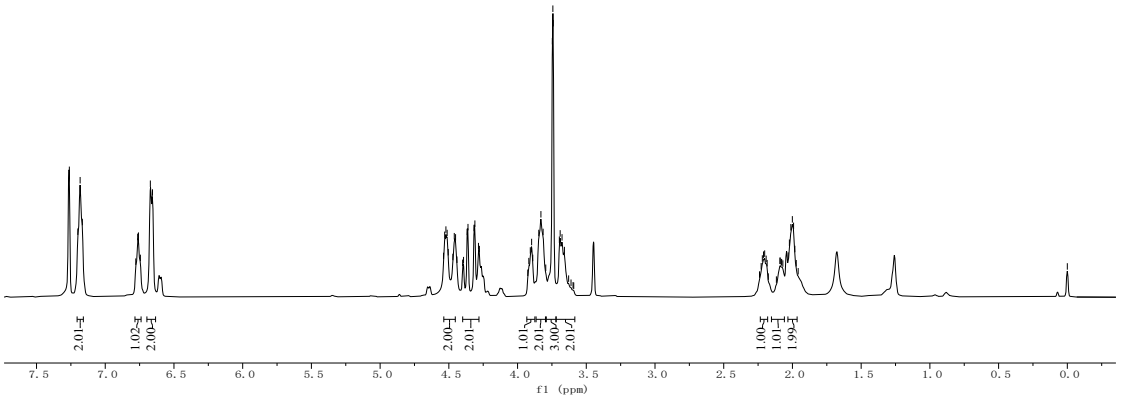

7.266
7.196
7.180
7.164
6.776
6.755
6.739
6.723
6.632
6.616
4.499
4.482
4.449
4.434
4.263
4.248
3.835
3.827
3.818
3.809
3.800
3.791
3.784
3.653
3.647
3.624
3.608
3.590
3.570
2.426
2.406
2.395
2.386
2.373
2.366
2.353
2.335
2.254
2.234
2.223
2.214
2.206
2.192
2.175
2.132
2.120
2.106
2.090
2.073
2.042
2.025
2.009
1.858
1.846
1.820
1.806
1.790
1.772
-0.000
1H NMR (500 MHz, CDCl3)
2.02
1.01
2.00
2.00
0.99
1.02
3.00
0.99
2.02
1.01
0.99
3.04
2.99
f1 (ppm)



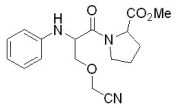
methyl O-(cyanomethyl)-N-phenylserylprolinate (5rf) (dr = 3:1)

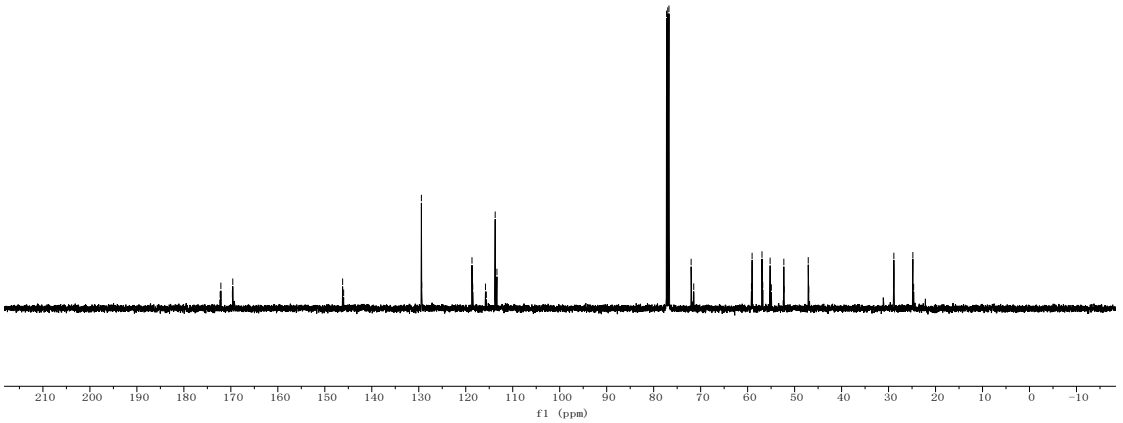
^{1}H NMR (500 MHz, $CDCl_3$)



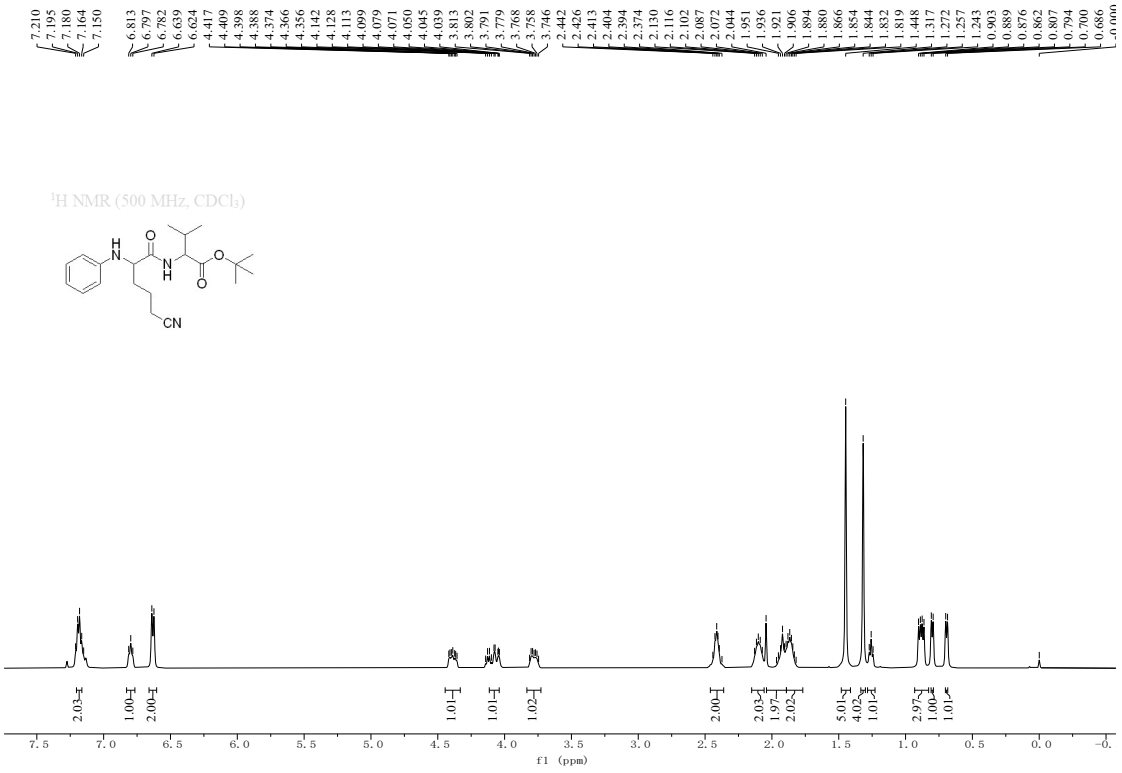


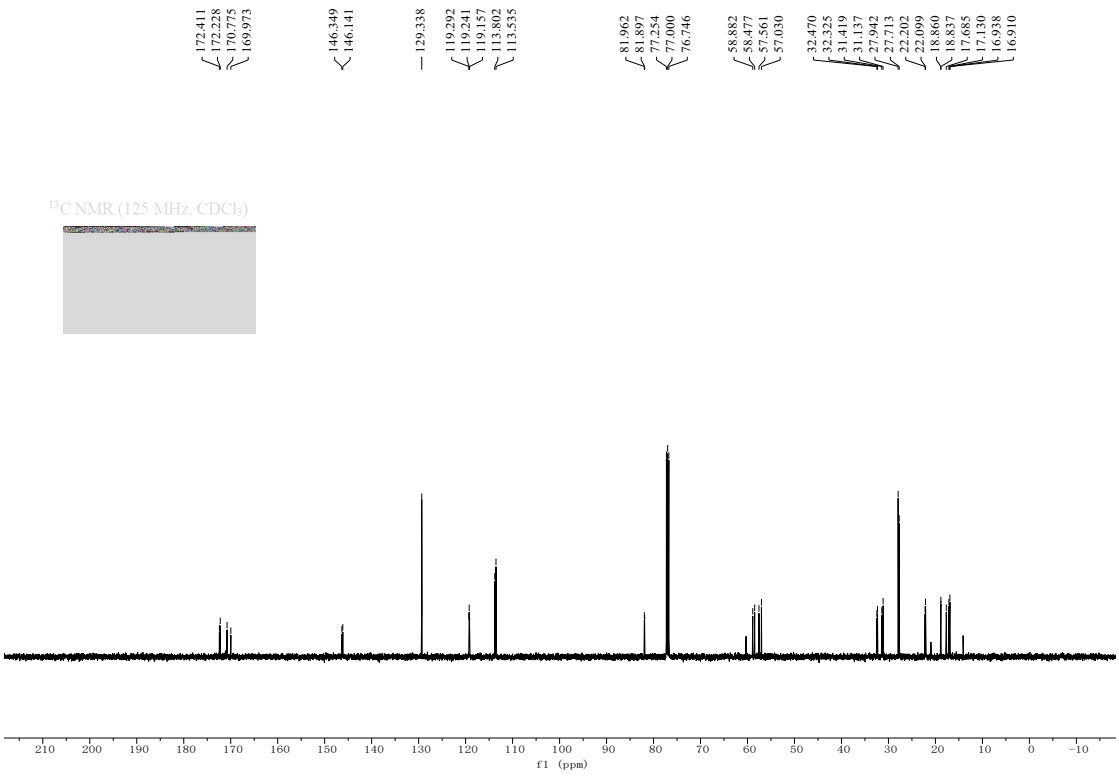
^{13}C NMR (125 MHz, $CDCl_3$)



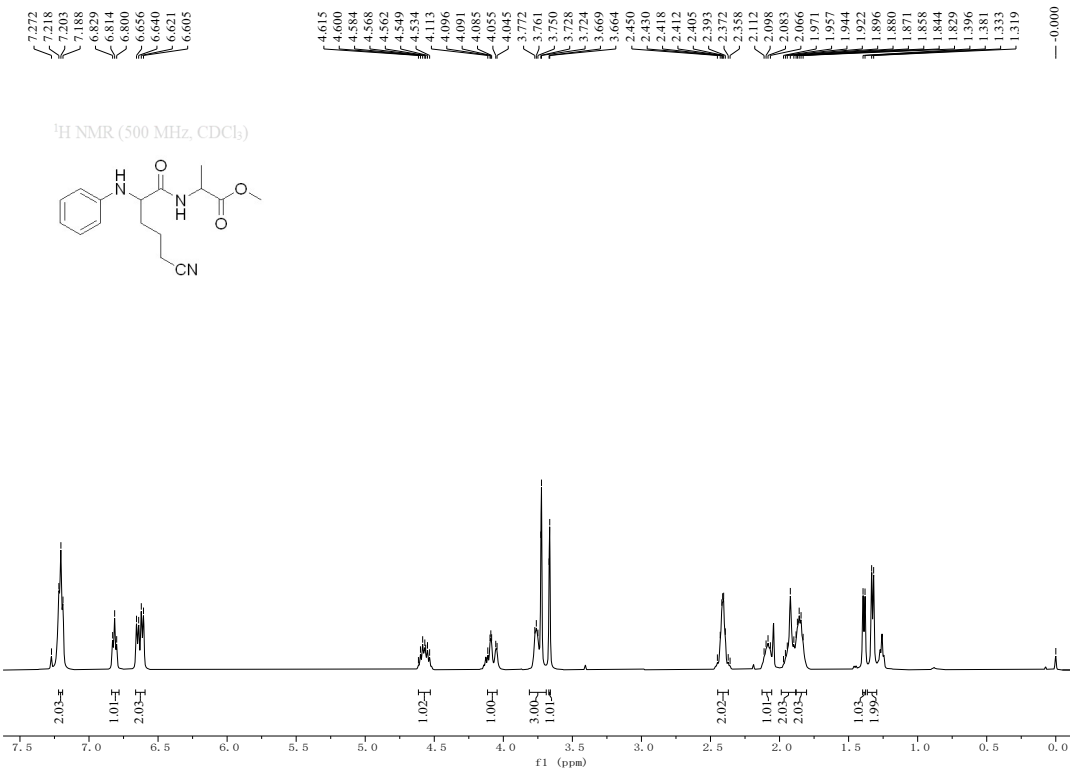


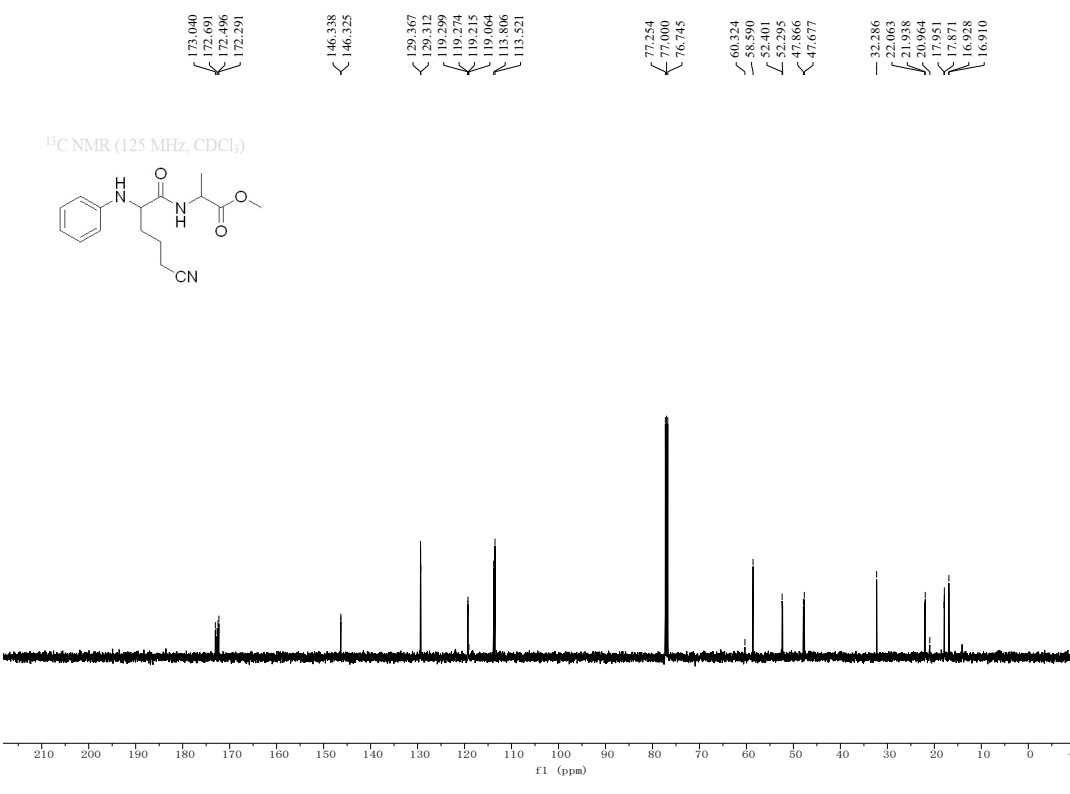
tert-butyl (5-cyano-2-(phenylamino)pentanoyl)valinate (5sa) (dr = 1:1)



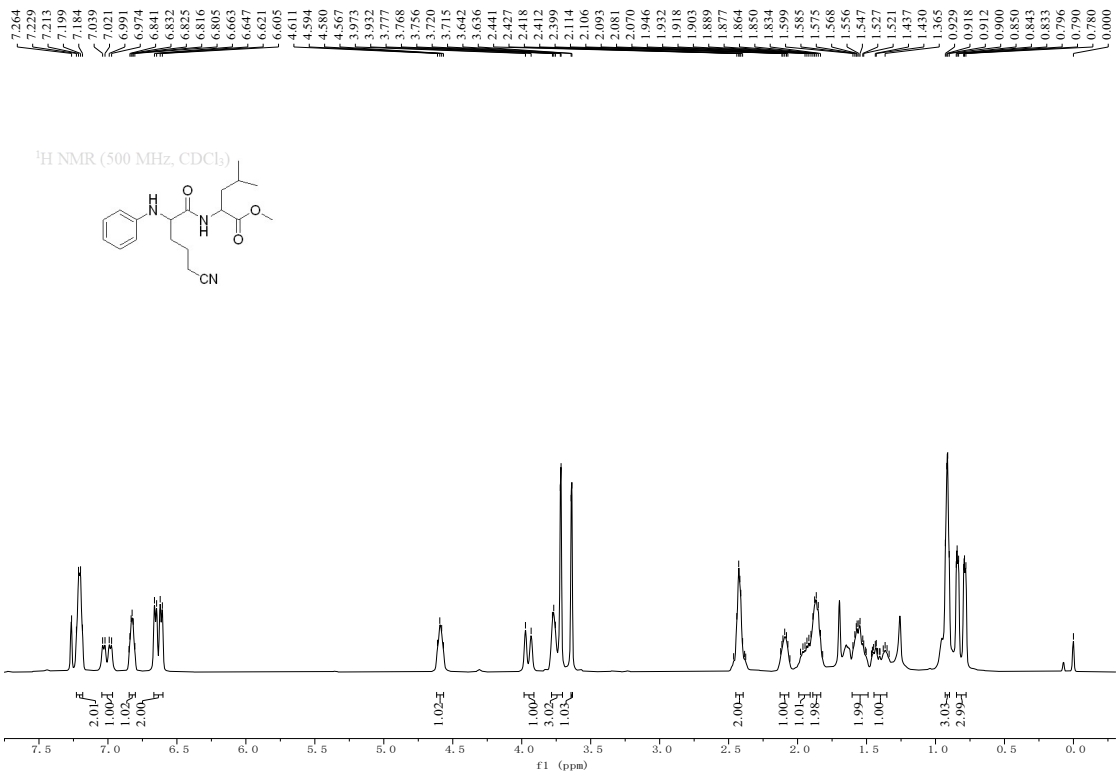


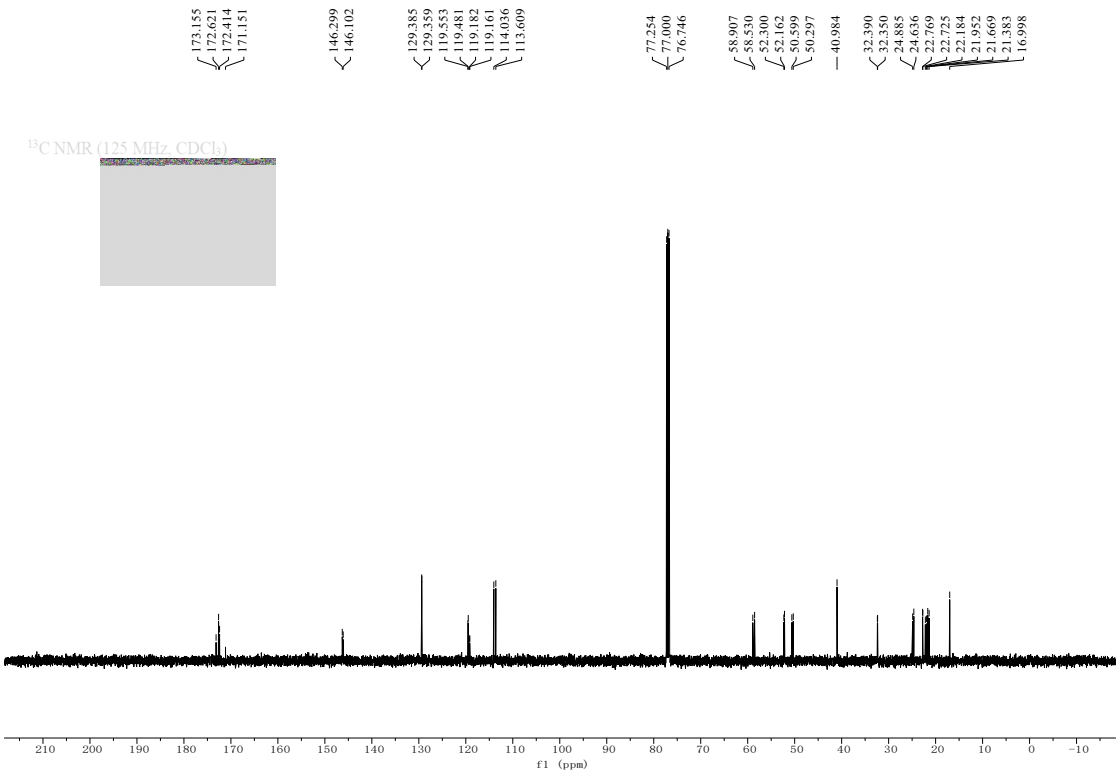
methyl (5-cyano-2-(phenylamino)pentanoyl)alaninate (5ta) (dr = 1:1)


7.272
7.218
7.203
7.188
6.829
6.814
6.800
6.656
6.640
6.621
6.605
4.615
4.600
4.584
4.568
4.562
4.549
4.534
4.113
4.096
4.091
4.085
4.055
4.045
3.772
3.761
3.750
3.728
3.724
3.669
3.664
2.450
2.430
2.418
2.412
2.405
2.393
2.372
2.358
2.112
2.098
2.083
2.066
1.971
1.957
1.944
1.922
1.896
1.880
1.871
1.858
1.844
1.829
1.396
1.381
1.333
1.319
-0.000
^{1}H NMR (500 MHz, CDCl$_3$)
2.03
1.01
2.03
1.02
1.00
3.00
1.01
2.02
1.01
2.03
2.03
1.03
1.99
f1 (ppm)

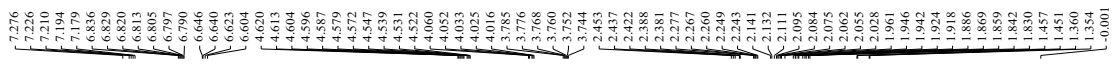

173.040
172.691
172.496
172.291
146.338
146.325
129.367
129.312
119.299
119.274
119.215
119.064
113.806
113.521
77.254
77.000
76.745
60.324
58.590
52.401
52.295
47.866
47.677
32.286
22.063
21.938
20.964
17.951
17.871
16.928
16.910
^{13}C NMR (125 MHz, CDCl$_3$)
f1 (ppm)

methyl (5-cyano-2-(phenylamino)pentanoyl)leucinate (5ua) (dr = 1:1)

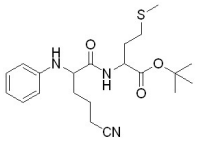


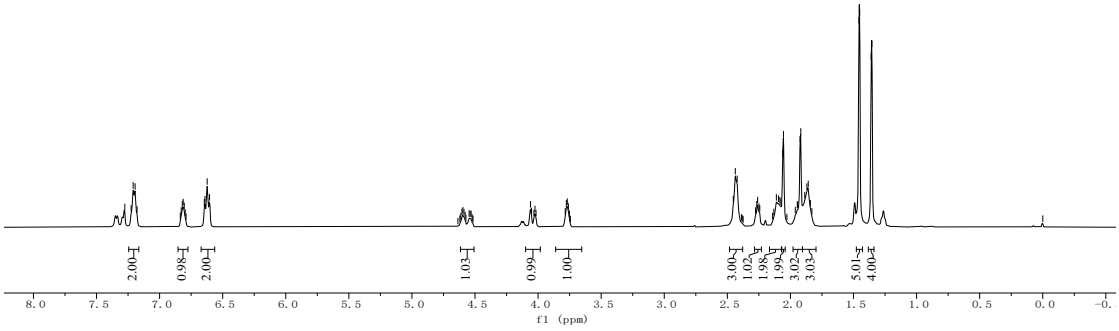


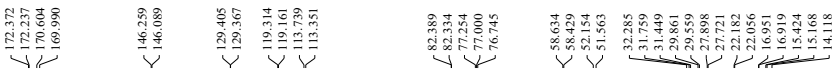
tert-butyl (5-cyano-2-(phenylamino)pentanoyl)methioninate (5va) (dr = 1.2:1)



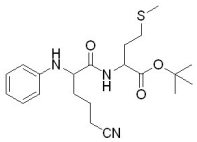
^{1}H NMR (500 MHz, $CDCl_3$)

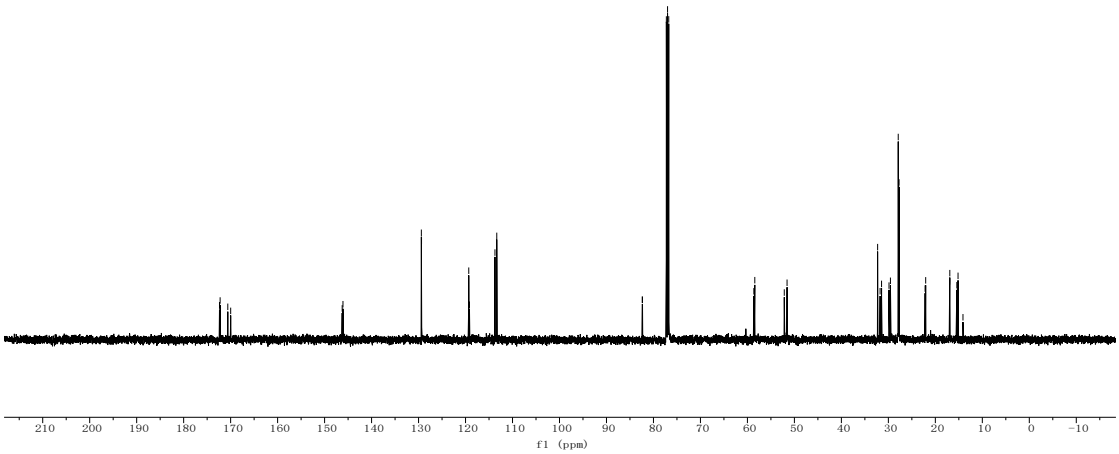




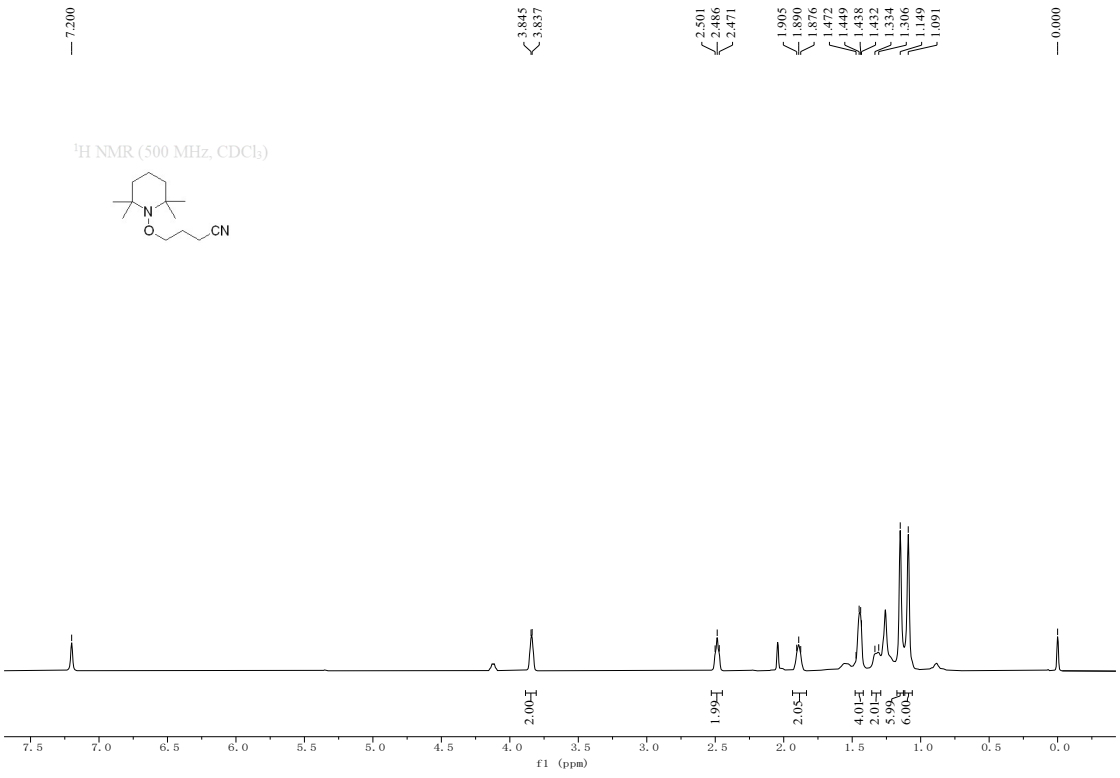


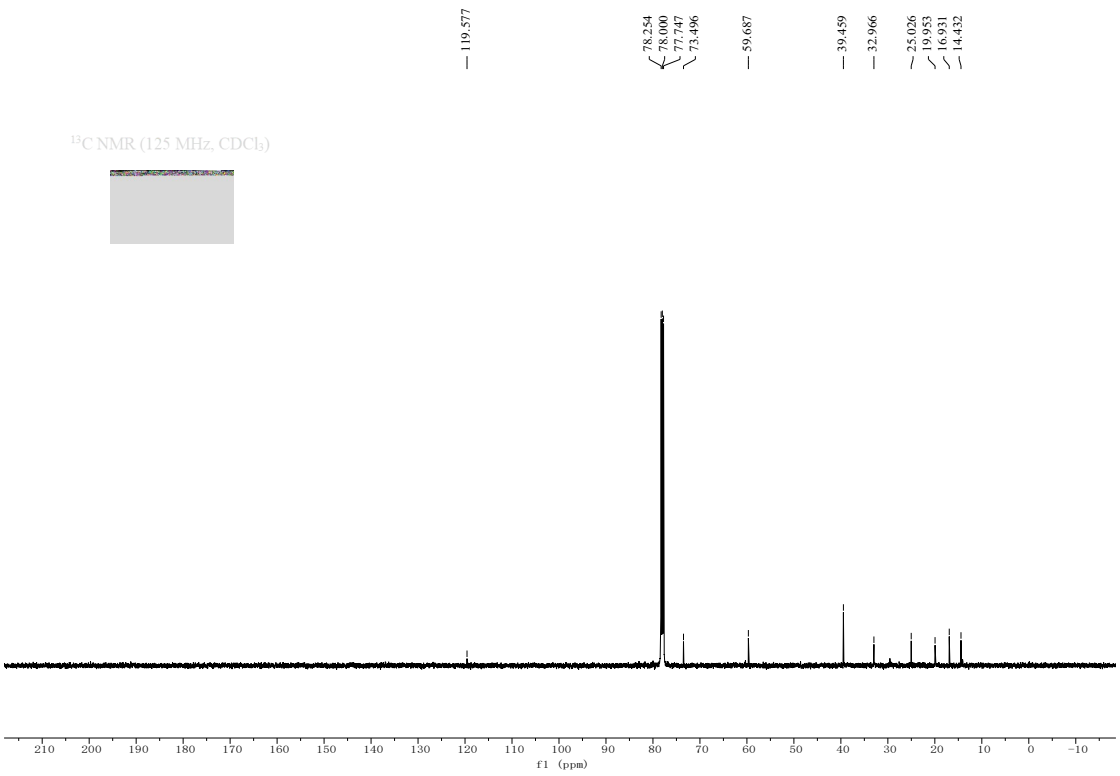
^{13}C NMR (125 MHz, $CDCl_3$)





4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)butanenitrile (6)




119.577
78.254
78.000
77.747
73.496
59.687
39.459
32.966
25.026
19.953
16.931
14.432
13C NMR (125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

(D) References

1. Y. Deng, C. Zhao, Y. Zhou, H. Wang, X. Li, G.-J. Cheng and J. Fu, Directing-Group-Based Strategy Enabling Intermolecular Heck-Type Reaction of Cycloketone Oxime Esters and Unactivated Alkenes, *Org. Lett.*, 2020, **22**, 3524-3530.

2. H. Zhi, S. P.-M. Ung, Y. Liu, L. Zhao and C.-J. Li, Phosphorylation of Glycine Derivatives via Copper(I)-Catalyzed Csp^3−H Bond Functionalization, *Adv. Synth. Catal.*, 2016, **358**, 2553-2557.

3. M. San Segundo and A. Correa, Site-Selective Cu-Catalyzed Alkylation of α-Amino Acids and Peptides toward the Assembly of Quaternary Centers, *ChemSusChem*, 2018, **11**, 3893-3898.