

## Supporting information

### Continuous Flow $\alpha$ -Arylation of *N,N*-dialkylhydrazones under Visible-Light Photoredox Catalysis

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## 1. General information

**Chemistry. General Methods.** Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates (Merck). Flash column chromatography was performed on silica gel, particle size 60 Å, mesh of 230–400 (Merck), under standard techniques. Ion exchange chromatography was performed using ISOLUTE® SCX-2 (Si-propylsulfonic acid) cartridges. Nuclear magnetic resonance (NMR) spectra were recorded on either a Bruker DPX-400 or a Bruker Avance II HD spectrometer with standard pulse sequences operating at 400 and 500 MHz, respectively, using CDCl<sub>3</sub>, C<sub>6</sub>D<sub>6</sub> and DMSO-*d*<sub>6</sub> as solvents. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) downfield from tetramethylsilane ( $\delta = 0$ ). Coupling constants are reported in hertz. Splitting patterns are defined by s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), or m (multiplet). High resolution mass spectra (HRMS) were recorded on a QToF mass spectrometer configured with an electrospray ionization source, maintained at 140 °C, using nitrogen as the nebulizer gas, argon as collision gas and Lockmass device for mass calibration using Leucine-Enkephaline as standard substance. Spectra were acquired either in positive or in negative ionization mode, by scanning from 50 to 1200 Da in 0.1 s. In positive mode, the capillary needle voltage could vary from 0.25 to 2.0 kV. In negative mode, the capillary needle voltage was 2.0 kV. Cone voltage was 25 V in both ionization modes. Reverse phase liquid chromatography (HPLC) was performed on a 1260 HPLC system (Agilent Technologies) comprising two preparative pumps, an autosampler, a diode array detector (DAD), and fraction collectors. Stationary phase: C18 XBridge 30 x 100 mm 5  $\mu$ m; Mobile phase: gradient from 80 % 10mM NH<sub>4</sub>CO<sub>3</sub>H pH 9 solution in water, 20 % MeOH to 0 % 10mM NH<sub>4</sub>CO<sub>3</sub>H pH 9 solution in water, 100 % MeOH). Data acquisition was performed with Chemstation software. Purities of all new compounds were determined by analytical RPHPLC using the area percentage method on the UV trace recorded at a wavelength of 254 nm and were found to have  $\geq 95\%$  purity unless otherwise specified. Flow photochemistry reactions were performed in a Vapourtec Easy-Medchem flow instrument, using the Photochemistry reactor module UV-150 from Vapourtec. For detailed information, visit the webpage: [www.vapourtec.com](http://www.vapourtec.com)

## 2. Preparation of starting materials: synthesis of hydrazones 1a-1j and analysis data

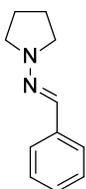
- a. Hydrazones **1b-g** and **1j** were synthesized using **general procedure A** from the respective hydrazine and aldehyde derivatives.

**General procedure A:** To a 0.3M solution of the corresponding aldehyde (1 equiv) in DCM, the corresponding hydrazine (1.3 equiv) and anhydrous MgSO<sub>4</sub> (2 equiv) were added and the mixture was stirred at rt until total consumption of starting material (TLC, 10-72H). The reaction mixture was then filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The residue thus obtained was purified by flash chromatography on silica gel (EtOAc in heptane from 0/100 to 10/90). The desired fractions were collected and concentrated in vacuo to yield the corresponding hydrazone derivative.

b. Hydrazones **1a**, **1h** and **1i** were synthesized using **general procedure B** from the respective hydrazine and aldehyde derivatives

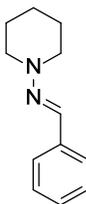
**Method B:** To a 0.3M solution of the corresponding aldehyde (1 equiv) in DCM, the corresponding hydrazine (1.3 equiv), *N,N*-diisopropylethylamine (1.3 equiv), and anhydrous MgSO<sub>4</sub> (2 equiv) were added and the mixture was stirred at rt until total consumption of starting material (TLC, 10-72H). The reaction mixture was then filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The residue thus obtained was purified by flash chromatography on silica gel (EtOAc in heptane from 0/100 to 10/90). The desired fractions were collected and concentrated in vacuo to yield the corresponding hydrazone derivative.

(*E*)-1-Phenyl-*N*-pyrrolidin-1-yl-methanimine (**1a**).



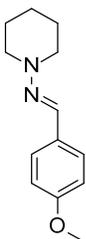
Prepared from 1-aminopyrrolidine hydrochloride (3.7 g, 30.18 mmol) following **general procedure B**: White solid; Yield: 3.94 g, (73 %). <sup>1</sup>H NMR data are in agreement with those reported in literature.<sup>i</sup>

(*E*)-1-Phenyl-*N*-(1-piperidyl)methanimine (**1b**).



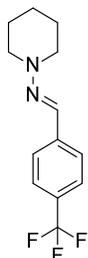
Prepared from 1-aminopiperidine (4 mL, 35.95 mmol) following **general procedure A**: White solid; Yield: 5 g (74%). <sup>1</sup>H NMR data are in agreement with those reported in literature.<sup>ii</sup>

(*E*)-1-(4-Methoxyphenyl)-*N*-(1-piperidyl)methanimine (**1c**).



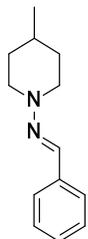
Prepared from 1-aminopiperidine (4 mL, 35.95 mmol) following **general procedure A**: White solid; Yield: 1.5 g (96%). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.49-7.58 (m), 6.87 (d, *J*=8.6 Hz), 3.81 (s), 3.12 (t, *J*=5.5 Hz), 1.75 (quin, *J*=5.7 Hz), 1.49-1.57 (m). **<sup>13</sup>C NMR** (10125 MHz, CDCl<sub>3</sub>) δ 159.56, 135.22, 129.57, 127.27 (2C), 113.92 (2C), 55.27, 52.36 (2C), 25.26 (2C), 24.17.

(*E*)-*N*-(1-Piperidyl)-1-[4-(trifluoromethyl)phenyl]methanimine (**1d**).



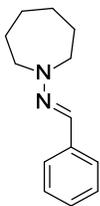
Prepared from 1-aminopiperidine (4 mL, 35.95 mmol) following **general procedure A**: Pale yellow solid; Yield: 1.47 g (97%). **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ 7.66 (d, *J*=8.1 Hz, 2H), 7.55 (d, *J*=8.1 Hz, 2H), 7.49 (s, 1H), 3.17-3.24 (m, 4H), 1.71-1.80 (m, 4H), 1.53-1.60 (m, 2H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>): δ 140.27 (d, *J*=1.8 Hz), 131.64, 129.04 (q, *J*=31.8 Hz), 125.74 (2C), 125.37 (q, *J*=3.9 Hz, 2 C), 124.31 (q, *J*=270.7 Hz), 51.77 (2C), 25.08 (2C), 24.03. **HRMS** (ESI) *m/z* calcd for C<sub>13</sub>H<sub>16</sub>F<sub>3</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 257.1266, found: 257.1268.

(*E*)-*N*-(4-methyl-1-piperidyl)-1-phenylmethanimine (**1e**).



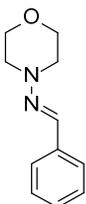
Prepared from 4-methyl-piperidin-1-ylamine (4 mL, 35.95 mmol) following **general procedure A**: Yellow solid; Yield: 0.42 g (78%). **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ 7.57-7.61 (m, 2H), 7.57 (br s, 1H), 7.32 (t, *J*=7.7 Hz, 2H), 7.21-7.27 (m, 1H), 3.69-3.77 (m, 2H), 2.62 (td, *J*=12.0, 2.6 Hz, 2H), 1.72-1.81 (m, 2H), 1.47-1.57 (m, 1H), 1.35-1.46 (m, 2H), 0.98 (d, *J*=6.4 Hz, 3H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>): δ 136.55, 133.28, 128.42 (2C), 127.82, 125.96 (2C), 51.41 (2C), 33.25 (2C), 30.57, 21.55. **HRMS** (ESI) *m/z* calcd for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 203.1470, found: 203.1474.

(*E*)-*N*-(Azepan-1-yl)-1-phenylmethanimine (**1f**).



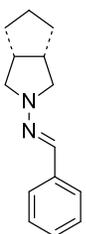
Prepared from 1-aminohomopiperidine (0.98 g, 8.55 mmol) following **general procedure A**: White solid; Yield: 0.91 g (70%). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.49-7.53 (m, 2H), 7.25-7.32 (m, 2H), 7.11-7.16 (m, 1H), 7.09 (s, 1H), 3.49-3.55 (m, 4H), 1.72-1.82 (m, 4H), 1.56-1.63 (m, 4H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 137.97, 128.36 (2C), 126.32, 126.13, 124.81 (2C), 53.44 (2C), 28.55 (2C), 27.63 (2C). **HRMS** (ESI) *m/z* calcd for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 203.1470, found: 203.1469.

(*E*)-*N*-Morpholino-1-phenylmethanimine (**1g**).



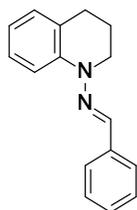
Prepared from 4-aminomorpholine (0.83 g, 8.55 mmol) following **general procedure A**: White solid; Yield: 1.5 g (92%). **<sup>1</sup>H NMR** data are in agreement with those reported in literature.<sup>iii</sup>

(*E*)-*N*-(3,3a,4,5,6,6a-Hexahydro-1*H*-cyclopenta[*c*]pyrrol-2-yl)-1-phenylmethanimine (**1h**).



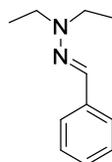
Prepared from 3-amino-3-azabicyclo[3.3.0]octane hydrochloride (1.39 g, 8.55 mmol) following **general procedure B**: White solid; Yield: 1.3 g (71%). **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ 7.52-7.60 (m, 2H), 7.29-7.35 (m, 2H), 7.27 (s, 1H), 7.19-7.25 (m, 1H), 3.35-3.44 (m, 2H), 3.06 (dd, *J*=9.7, 3.6 Hz, 2H), 2.64-2.79 (m, 2H), 1.80-1.94 (m, 2H), 1.66-1.78 (m, 1H), 1.48-1.61 (m, 3H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>): δ 136.83, 135.56, 128.41 (2C), 127.36, 125.56 (2C), 58.21 (2C), 40.34 (2C), 33.42 (2C), 26.08. **HRMS** (ESI) *m/z* calcd for C<sub>14</sub>H<sub>19</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 215.1548, found: 215.1547.

(*E*)-*N*-(3,4-Dihydro-2*H*-quinolin-1-yl)-1-phenyl-methanimine (**1i**).



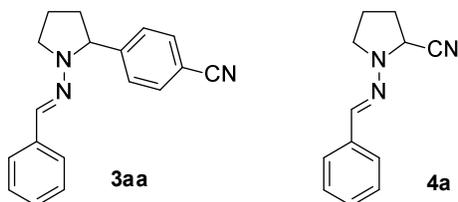
Prepared from 3,4-dihydro-2*H*-quinolin-1-ylamine hydrochloride (2 g, 10.83 mmol) following **general procedure B**: White solid; Yield: 2.42 g (95%).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.78 (d,  $J=8.1$  Hz, 1H), 7.67-7.72 (m, 2H), 7.51 (s, 1H), 7.34-7.39 (m, 2H), 7.23-7.27 (m, 1H), 7.18-7.22 (m, 1H), 7.01 (d,  $J=6.6$  Hz, 1H), 6.80 (td,  $J=7.3, 1.0$  Hz, 1H), 3.66 (t,  $J=6.2$  Hz, 2H), 2.73-2.78 (m, 2H), 2.14-2.20 (m, 2H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  142.96, 136.99, 130.45, 128.51 (2C), 128.18, 127.53, 127.38, 125.96 (2C), 123.57, 119.50, 114.39, 44.74, 27.05, 21.87.

*N*-[(*E*)-Benzylideneamino]-*N*-ethylethanamine (**1j**).



Prepared from 1,1-diethylhydrazine (0.50 g, 5.67 mmol) following **general procedure A**: Yellow solid; Yield: 0.6 g, (60%).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.54 (dd,  $J=8.2, 1.0$  Hz, 2 H), 7.26 - 7.32 (m, 3 H), 7.14 - 7.20 (m, 1 H), 3.34 (q,  $J=7.0$  Hz, 4 H), 1.17 (t,  $J=7.2$  Hz, 6 H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  137.45 (s, 1 C), 130.16 (br s, 1 C), 128.34 (s, 2 C), 126.72 (s, 1 C), 125.19 (s, 2 C), 46.65 (s, 2 C), 11.68 (s, 2 C). **HRMS** (ESI)  $m/z$  calcd for  $\text{C}_{11}\text{H}_{16}\text{N}_2$   $[\text{M}+\text{H}]^+$ : 177.1313, found: 177.1319.

### 3. Preparation of compounds **3a** and **4a** using a batch chemistry protocol.

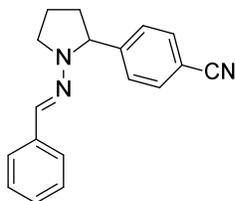


$\text{Ir}(\text{ppy})_3$  (3.76 mg, 0.006 mmol) was added solution of **1a** (0.15 g, 0.86 mmol.), **2a** (0.074 g, 0.57 mmol), and  $\text{LiOAc}$  (0.12 g, 1.15 mmol) in DMSO (2,3 mL) at rt. A stream of  $\text{N}_2$  was bubbled through the solution for 5 min. The mixture was stirred and irradiated with a LED lamp (450 nm wavelength) at 40 °C for 30 min. After cooling to rt

NaHCO<sub>3</sub> (aq. sat. soltn.) and EtOAc were added. The organic layer was separated and the volatiles were evaporated in vacuo. The residue The mixture was concentrated and purified by ion exchange chromatography on acidic resin (ISOLUTE® SCX-2 cartridge) eluting first with DCM/MeOH (1:1) (30 mL) to collect crude **4a** and then with 7N NH<sub>3</sub> in MeOH (10 mL) to give crude **3aa**. Crude compounds **3aa** and **4a** were further purified by RP HPLC (Stationary phase: C18 XBridge 30 x 100 mm 5 μm), mobile phase: gradient from 47 % 10 mM NH<sub>4</sub>CO<sub>3</sub>H pH 9 solution in water / 53 % CH<sub>3</sub>CN to 30 % 10 mM NH<sub>4</sub>CO<sub>3</sub>H pH 9 solution in water / 70 % CH<sub>3</sub>CN) to obtain **3aa** (74.9 mg, 68 % yield) and **4a** (11 mg, 7 % yield) both as white solids.

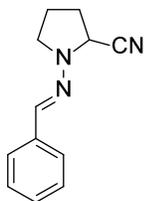
#### 4. Preparation of compounds **3aa** and **4a** using a flow chemistry protocol.

4-[1-[(*E*)-Benzylideneamino]pyrrolidin-2-yl]benzonitrile (**3aa**).



A to a stirred 0.25 M solution of 1,4-DCB **2a** (51.2 mg, 0.4 mmol), LiOAc (81.6 mg, 0.8 mmol) and Ir(ppy)<sub>3</sub> (2.62 mg, 1 mol%) in DMSO (1.6 mL) hydrazone **1a** (104.5 mg, 0.6 mmol) was added at rt. A stream of N<sub>2</sub> was bubbled through the solution for 5 min. The solution was then pumped through a Vapourtec photoreactor (UV-150 module, 10 mL volume coil with an internal bore of 1.3 mm and a wall thickness of 0.15 mm) at a flow of 1 mL/min (10 min residence time) at 40 °C under irradiation with a LED lamp (450 nm wavelength). After cooling to rt NaHCO<sub>3</sub> (aq. sat. soltn.) and EtOAc were added. The organic layer was separated and the volatiles were evaporated in vacuo. The residue was purified by ion exchange chromatography on acidic resin (ISOLUTE® SCX-2 cartridge) eluting first with DCM/MeOH (1:1) (30 mL) to collect crude **4a** (54% pure) and then with 7N NH<sub>3</sub> in MeOH (10 mL) to give crude **3a** (purity >91%). Crude compound **3a** was further purified by RP HPLC (Stationary phase: C18 XBridge 30 x 100 mm 5 μm), mobile phase: gradient from 47% 10 mM NH<sub>4</sub>CO<sub>3</sub>H pH 9 solution in water / 53% CH<sub>3</sub>CN to 30% 10 mM NH<sub>4</sub>CO<sub>3</sub>H pH 9 solution in water / 70% CH<sub>3</sub>CN). The product containing fractions were collected and the volatiles were evaporated under vacuum to yield product **3aa**. White solid; Yield: 82.6 mg (75%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.64 (d, *J*=8.3 Hz, 2H), 7.39-7.49 (m, 4H), 7.23-7.30 (m, 2H), 7.15-7.22 (m, 2H), 4.64 (dd, *J*=7.6, 6.0 Hz, 1H), 3.78 (dt, *J*=9.7, 6.0 Hz, 1H), 3.31-3.41 (m, 1H), 2.42 (dq, *J*=12.4, 7.7 Hz, 1H), 2.06 (quin, *J*=6.8 Hz, 2H), 1.85 (dq, *J*=12.7, 6.3 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 149.73, 136.66, 133.53, 132.26 (2C), 128.40 (2C), 127.33 (3C), 125.41 (2C), 119.02, 110.57, 66.55, 50.74, 33.85, 22.33. HRMS (ESI) *m/z* calcd for C<sub>18</sub>H<sub>18</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 276.1501, found: 276.1500.

1-[(*E*)-Benzylideneamino]pyrrolidine-2-carbonirile (**4a**).

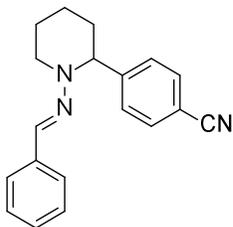


Crude compound **4a** was further purified by RP HPLC (Stationary phase: C18 XBridge 30 x 100 mm 5  $\mu$ m), mobile phase: gradient from 47% 10 mM  $\text{NH}_4\text{CO}_3\text{H}$  pH 9 solution in water / 53%  $\text{CH}_3\text{CN}$  to 30% 10 mM  $\text{NH}_4\text{CO}_3\text{H}$  pH 9 solution in water / 70%  $\text{CH}_3\text{CN}$ ). The product containing fractions were collected and the volatiles were evaporated under vacuum to yield product **4a**. White solid; Yield: 5.8 mg (7%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.58-7.63 (m, 2H), 7.33-7.39 (m, 3H), 7.27-7.32 (m, 1H), 4.55 (dd,  $J=6.6, 3.2$  Hz, 1H), 3.28-3.41 (m, 2H), 2.11-2.35 (m, 4H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  137.89, 135.70, 128.52 (2C), 128.37, 126.13 (2C), 119.06, 54.59, 47.83, 28.49, 22.14. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{14}\text{N}_3$   $[\text{M}+\text{H}]^+$ : 200.1188, found: 200.1190.

### 5. General procedure for the preparation of compounds **3** and **4** using a flow chemistry protocol.

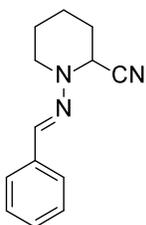
A to a stirred 0.25 M solution of cyanoaryl **2** (0.4 mmol), LiOAc (0.8 mmol) and  $\text{Ir}(\text{ppy})_3$  (1 mol%) in DMSO the corresponding hydrazone **1** (0.6 mmol) was added at rt. A stream of  $\text{N}_2$  was bubbled through the solution for 5 min. The solution was then pumped through a Vapourtec photoreactor (UV-150 module, 10 mL volume coil with an internal bore of 1.3 mm and a wall thickness of 0.15 mm) at a flow of 1 mL/min (10 min residence time) at 40  $^\circ\text{C}$  under irradiation with a LED lamp (450 nm wavelength). After cooling to rt  $\text{NaHCO}_3$  (aq. sat. soltn.) and EtOAc were added. The organic layer was separated and the volatiles were evaporated in vacuo. The residue was purified by ion exchange chromatography on acidic resin (ISOLUTE<sup>®</sup> SCX-2 cartridge) eluting first with DCM/MeOH (1:1) (30 mL) to collect crude **4** (46-67% pure) and then with 7N  $\text{NH}_3$  in MeOH (10 mL) to give crude **3** (purity >87%). When required crude compounds **3** were further purified by RP HPLC (Stationary phase: C18 XBridge 30 x 100 mm 5  $\mu$ m), mobile phase: gradient from 47% 10 mM  $\text{NH}_4\text{CO}_3\text{H}$  pH 9 solution in water / 53%  $\text{CH}_3\text{CN}$  to 30% 10 mM  $\text{NH}_4\text{CO}_3\text{H}$  pH 9 solution in water / 70%  $\text{CH}_3\text{CN}$ ). It should be noted that products **3** are neither stable in silica gel nor in alumina, and therefore the residence time in the chromatographic column should be kept to a minimum. In general, typical recoveries after HPLC chromatography are in the range of 80-85%. Isolated hydrazones **3** were stable at rt under  $\text{N}_2$  atmosphere for more than one month. In all cases crude products **4** had to be further purified by RP HPLC (Stationary phase: C18 XBridge 30 x 100 mm 5  $\mu$ m), mobile phase: gradient from 47% 10 mM  $\text{NH}_4\text{CO}_3\text{H}$  pH 9 solution in water / 53%  $\text{CH}_3\text{CN}$  to 30% 10 mM  $\text{NH}_4\text{CO}_3\text{H}$  pH 9 solution in water / 70%  $\text{CH}_3\text{CN}$ ).

4-[1-[(*E*)-Benzylideneamino]-2-piperidyl]benzonitrile (**3ba**).



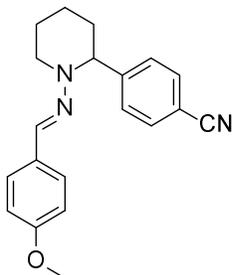
Reaction carried out starting from **1b** (3 g, 15.93 mmol.), **2a** (1.36 g, 10.6 mmol). White solid; Yield: 2.15 g (70%);  $^1\text{H NMR}$  (500 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  7.75-7.81 (m, 2H), 7.70 (s, 1H), 7.49-7.56 (m, 2H), 7.13-7.29 (m, 5H), 4.01 (dd,  $J=10.5, 3.0$  Hz, 1H), 3.80-3.90 (m, 1H), 2.63 (td,  $J=11.5, 3.3$  Hz, 1H), 1.82-1.94 (m, 2H), 1.62-1.81 (m, 3H), 1.36-1.51 (m, 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  150.62, 136.35, 136.17, 131.88 (2C), 128.54 (2C), 128.36 (2C), 127.83, 125.60 (2C), 119.06, 108.98, 67.42, 48.66, 34.51, 23.96, 22.76. **HRMS** (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{20}\text{N}_3$   $[\text{M}+\text{H}]^+$  290.1657, found: 290.1663.

1-[(*E*)-Benzylideneamino]piperidine-2-carbonitrile (**4b**).



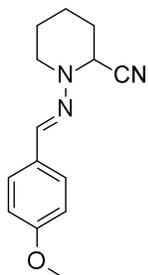
Reaction carried out starting from **1b** (3 g, 15.93 mmol.), **2a** (1.36 g, 10.6 mmol). White solid; Yield: 91 mg (4%);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.65 (s, 1H), 7.59-7.64 (m, 2H), 7.30-7.40 (m, 3H), 4.70 (t,  $J=3.8$  Hz, 1H), 3.57-3.70 (m, 1H), 2.73 (td,  $J=11.4, 3.5$  Hz, 1H), 1.99-2.13 (m, 2H), 1.88-1.98 (m, 1H), 1.60-1.85 (m, 3H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  139.24, 135.29, 128.99, 128.54 (2C), 126.69 (2C), 117.29, 54.97, 45.93, 28.67, 23.96, 20.29. **HRMS** (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{16}\text{N}_3$   $[\text{M}+\text{H}]^+$ : 214.2821, found: 214.2819.

4-[1-[(*E*)-(4-Methoxyphenyl)methyleneamino]-2-piperidyl]benzonitrile (**3ca**).



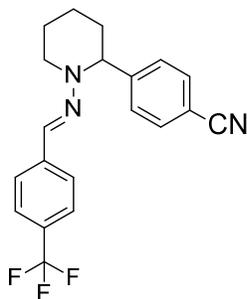
White solid; Yield: 92 mg (72%); **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ 7.64 (s, 1H), 7.60-7.63 (m, 2H), 7.48 (d, *J*=8.1 Hz, 2H), 7.20-7.25 (m, 2H), 6.75-6.81 (m, 2H), 3.85 (dd, *J*=11.3, 3.2 Hz, 1H), 3.78 (s, 3H), 3.73-3.80 (m, 1H), 2.61 (td, *J*=11.6, 3.5 Hz, 1H), 1.79-2.00 (m, 4H), 1.69-1.79 (m, 1H), 1.40-1.53 (m, 1H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>): δ 159.94, 150.65, 139.02, 131.88 (2C), 129.00, 128.47 (2C), 127.50 (2C), 119.32, 113.87 (2C), 109.99, 69.04, 55.25, 50.16, 35.17, 24.73, 23.63. **HRMS** (ESI) *m/z* calcd for C<sub>20</sub>H<sub>22</sub>N<sub>3</sub>O [M+H]<sup>+</sup>: 320.1763, found: 320.1766.

1-[(*E*)-(4-Methoxyphenyl)methyleneamino]piperidine-2-carbonitrile (**4c**).



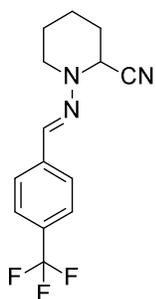
White solid; Yield: 10.7 mg (11%); **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ ppm 7.65 (s, 1H), 7.55-7.60 (m, 2H), 6.87-6.93 (m, 2H), 4.66 (t, *J*=3.9 Hz, 1H), 3.84 (s, 3H), 3.57-3.64 (m, 1H), 2.71 (td, *J*=11.4, 3.2 Hz, 1H), 2.00-2.10 (m, 2H), 1.90-1.97 (m, 1H), 1.66-1.83 (m, 3H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>): δ 160.43, 139.71, 128.13, 128.11 (2C), 117.40, 114.00 (2C), 55.32, 55.10, 46.25, 28.69, 24.05, 20.94. **HRMS** (ESI) *m/z* calcd for C<sub>14</sub>H<sub>18</sub>N<sub>3</sub>O [M+H]<sup>+</sup>: 244.1450, found: 244.1452.

4-[1-[(*E*)-[4-(Trifluoromethyl)phenyl]methyleneamino]-2-piperidyl]benzonitrile (**3da**).



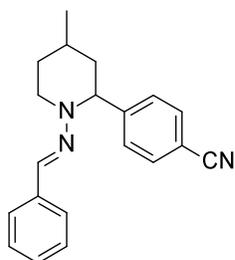
Yellow oil; Yield: 31.4 mg (22%); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.60-7.68 (m, 2H), 7.54 (s, 1H), 7.44-7.51 (m, 4H), 7.33 (d, *J*=8.1 Hz, 2H), 4.03 (dd, *J*=10.5, 3.4 Hz, 1H), 3.86 (dt, *J*=11.7, 4.0 Hz, 1H), 2.74 (td, *J*=11.4, 3.8 Hz, 1H), 1.92-2.04 (m, 2H), 1.75-1.92 (m, 3H), 1.44-1.58 (m, 1H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 149.77, 139.83 (br d, *J*=1.4 Hz), 133.44, 131.99 (2C), 129.43 (q, *J*=32.5 Hz), 128.40 (2C), 125.85 (2C), 125.34 (q, *J*=3.8 Hz, 2 C), 124.17 (q, *J*=274.8 Hz), 118.77, 110.35, 68.26, 48.56, 34.81, 24.38, 23.11. **HRMS** (ESI) *m/z* calcd for C<sub>20</sub>H<sub>19</sub>F<sub>3</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 358.1531, found: 358.1540.

1-[(*E*)-[4-(Trifluoromethyl)phenyl]methyleneamino]piperidine-2-carbonitrile (**4d**).



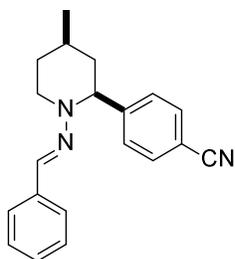
White solid; Yield: 11.2 mg (11%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.73 (d, *J*=8.1 Hz, 2H), 7.55-7.67 (m, 3H), 4.75 (t, *J*=3.7 Hz, 1H), 3.64-3.74 (m, 1H), 2.77 (td, *J*=11.6, 3.2 Hz, 1H), 2.00-2.19 (m, 2H), 1.90-2.00 (m, 1H), 1.63-1.89 (m, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 138.69, 136.57, 130.41 (q, *J*=32.1 Hz), 126.65 (2C), 125.48 (q, *J*=4.2 Hz, 2 C), 124.11 (q, *J*=272.0 Hz), 117.09, 54.85, 46.10, 28.64, 23.06, 20.18. HRMS (ESI) *m/z* calcd for C<sub>14</sub>H<sub>15</sub>F<sub>3</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 282.1218, found: 282.1222.

4-[1-[(*E*)-Benzylideneamino]-4-methyl-2-piperidyl]benzonitrile (**3ea**).



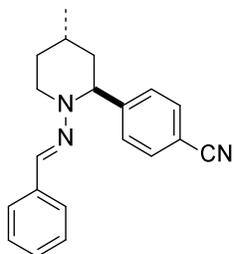
Yellow oil; Yield: 84.9 mg (70%); 1:1 mixture of diastereoisomers; The mixture of diastereomers was separated by chiral SFC (Stationary phase: Chiralpak AS-H 5μm 250\*20 mm, Mobile phase: 95% CO<sub>2</sub>, 5% MeOH) to get *cis*-**3ea** and *trans*-**3ea**:

*cis*-4-[1-[(*E*)-Benzylideneamino]-4-methyl-2-piperidyl]benzonitrile (*cis*-**3ea**).



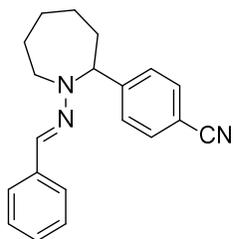
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.59-7.64 (m, 3H), 7.46-7.49 (m, 2H), 7.17-7.25 (m, 5H), 3.82-3.90 (m, 2H), 2.57 (td, *J*=12.0, 3.2 Hz, 1H), 1.91-1.97 (m, 1H), 1.86 (dq, *J*=13.3, 3.1 Hz, 1H), 1.63-1.73 (m, 1H), 1.51-1.60 (m, 1H), 1.39-1.48 (m, 1H), 1.01 (d, *J*=6.4 Hz, 3H) **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 150.52, 138.07, 136.20, 131.90 (2C), 128.47 (2C), 128.39 (2C), 128.29, 126.09 (2C), 119.34, 110.07, 68.98, 49.26, 43.93, 32.93, 30.57, 21.56. **HRMS** (ESI) *m/z* calcd for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 304.1735, found: 304.1698

*trans*-4-[-1-[(*E*)-Benzylideneamino]-4-methyl-2-piperidyl]benzonitrile (*trans*-**3ea**).



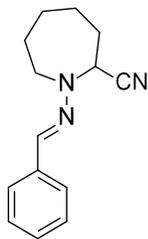
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.58-7.62 (m, 2H), 7.46 (s, 1H), 7.39-7.44 (m, 4H), 7.26-7.29 (m, 2H), 7.18-7.23 (m, 1H), 4.77 (t, *J*=4.8 Hz, 1H), 3.48-3.54 (m, 1H), 3.36 (ddd, *J*=12.6, 8.9, 4.2 Hz, 1H), 2.04-2.14 (m, 1H), 1.81-1.89 (m, 1H), 1.73-1.81 (m, 2H), 1.50-1.61 (m, 1H), 1.01 (d, *J*=6.4 Hz, 3H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 148.80, 136.58, 133.72, 132.07 (2C), 128.46 (2C), 128.20 (2C), 127.72, 125.72 (2C), 119.05, 110.18, 62.08, 44.94, 38.83, 31.15, 25.53, 20.06. **HRMS** (ESI) *m/z* calcd for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 304.1735, found: 304.1655

4-[1-[(*E*)-Benzylideneamino]azepan-2-yl]benzonitrile (**3fa**).



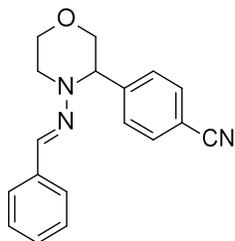
Off-white solid; Yield: 91 mg (75%); **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ 7.60-7.64 (m, 2H), 7.41-7.45 (m, 2H), 7.39 (d, *J*=8.1 Hz, 2H), 7.24-7.29 (m, 2H), 7.13-7.17 (m, 1H), 6.97 (br s, 1H), 4.71 (dd, *J*=11.4, 5.1 Hz, 1H), 3.95-4.03 (m, 1H), 3.57-3.66 (m, 1H), 2.28-2.38 (m, 1H), 1.91-1.99 (m, 1H), 1.71-1.89 (m, 4H), 1.47-1.55 (m, 1H), 1.34-1.45 (m, 1H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>): δ 149.09, 137.21, 132.51 (2C), 128.39 (2C), 126.95 (2C), 126.68 (2C), 125.03 (2C), 118.89, 110.66, 66.93, 51.48, 36.28, 29.22, 27.53, 26.93. **HRMS** (ESI) *m/z* calcd for C<sub>20</sub>H<sub>22</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 304.1814, found: 304.1815.

1-[(*E*)-Benzylideneamino]azepan-2-carbonitrile (**4f**).



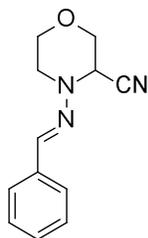
Cream solid; Yield: 20 mg (22%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.51-7.59 (m, 2H), 7.30-7.35 (m, 2H), 7.29 (s, 1H), 7.21-7.26 (m, 1H), 4.75 (dd,  $J=8.5, 5.1$  Hz, 1H), 3.59-3.67 (m, 1H), 3.42 (ddd,  $J=14.1, 6.9, 4.5$  Hz, 1H), 2.15-2.23 (m, 1H), 2.01-2.09 (m, 1H), 1.76-1.91 (m, 3H), 1.58-1.69 (m, 3H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  136.2, 131.6, 128.5 (2C), 127.7, 125.7 (2C), 118.9, 56.9, 48.3, 33.0, 28.0, 25.3, 25.2. **HRMS** (ESI)  $m/z$  calcd for  $\text{C}_{14}\text{H}_{18}\text{N}_3$   $[\text{M}+\text{H}]^+$ : 228.1501, found: 228.1500.

4-[4-[(*E*)-Benzylideneamino]morpholin-3-yl]benzonitrile (**3ga**).



White solid; Yield: 70 mg (60%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.59-7.70 (m, 3H), 7.55 (d,  $J=8.1$  Hz, 2H), 7.33 (dd,  $J=7.7, 1.9$  Hz, 2H), 7.21-7.29 (m, 3H), 4.10-4.20 (m, 2H), 3.90-4.00 (m, 2H), 3.63 (dd,  $J=11.8, 9.5$  Hz, 1H), 3.57 (dt,  $J=11.5, 2.5$  Hz, 1H), 2.90 (td,  $J=11.1, 3.9$  Hz, 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  144.75, 138.84, 135.52, 132.01 (2C), 129.12 (2C), 128.75, 128.47 (2C), 126.31 (2C), 118.94, 111.13, 72.64, 67.16, 66.33, 48.67. **HRMS** (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_3\text{O}$   $[\text{M}+\text{H}]^+$ : 292.1450, found: 292.1451.

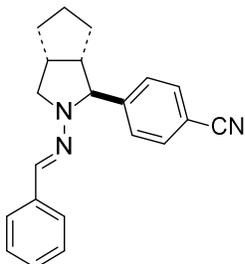
4-[(*E*)-Benzylideneamino]morpholine-3-carbonitrile (**4g**).



White solid; Yield: 14.6 mg (17%);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.70 (s, 1H), 7.61-7.67 (m, 2H), 7.32-7.42 (m, 3H), 4.49 (t,  $J=2.4$  Hz, 1H), 4.09-4.19 (m, 2H), 3.94 (dd,  $J=11.8, 2.8$  Hz, 1H), 3.78 (td,  $J=11.4, 3.0$  Hz, 1H), 3.45 (dt,  $J=12.0, 2.5$  Hz, 1H), 3.01 (td,  $J=11.3, 3.9$  Hz, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  140.60, 134.60, 129.46,

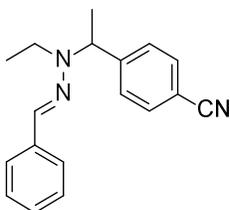
128.61 (2C), 126.87 (2C), 116.00, 67.82, 65.92, 54.53, 46.39. **HRMS** (ESI)  $m/z$  calcd for  $C_{12}H_{14}N_3O$   $[M+H]^+$ : 216.1137, found: 216.1136.

rac-4-[(3*S*,3*aS*,6*aR*)-2-[(*E*)-Benzylideneamino]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-3-yl]benzonitrile (**3ha**).



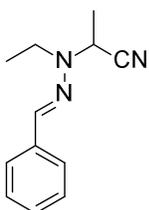
White solid; Yield: 100. mg (80%); **<sup>1</sup>H NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  7.61-7.69 (m, 2H), 7.44-7.51 (m, 2H), 7.36-7.43 (m, 2H), 7.22-7.29 (m, 3H), 7.16-7.22 (m, 1H), 3.94-4.07 (m, 2H), 2.84-2.97 (m, 1H), 2.77 (dd,  $J=9.6, 7.3$  Hz, 1H), 2.45-2.56 (m, 1H), 1.67-1.90 (m, 5H), 1.59-1.67 (m, 1H). **<sup>13</sup>C NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  149.48, 136.62, 136.42, 132.26 (2C), 128.38 (2C), 127.81 (2C), 127.74, 125.69 (2C), 118.89, 110.28, 74.55, 56.89, 51.29, 39.76, 32.33, 31.45, 25.21. **HRMS** (ESI)  $m/z$  calcd for  $C_{21}H_{22}N_3$   $[M+H]^+$ : 316.1814, found: 316.1895.

4-[1-[(*E*)-Benzylideneamino]ethyl-amino]ethyl]benzonitrile (**3ja**).



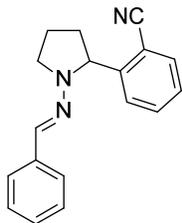
White solid; Yield: 77.6 mg (70%); **<sup>1</sup>H NMR** (500 MHz,  $CDCl_3$ ):  $\delta$  7.59-7.63 (m, 2H), 7.55-7.59 (m, 2H), 7.44-7.48 (m, 2H), 7.32-7.37 (m, 2H), 7.31 (s, 1H), 7.21-7.26 (m, 1H), 4.65 (q,  $J=6.9$  Hz, 1H), 3.26-3.36 (m, 1H), 3.14 (dq,  $J=14.4, 7.1$  Hz, 1H), 1.68 (d,  $J=6.9$  Hz, 3H), 1.13 (t,  $J=7.2$  Hz, 3H). **<sup>13</sup>C NMR** (126 MHz,  $CDCl_3$ ):  $\delta$  149.21, 137.43, 132.16 (2C), 129.66, 128.48 (2C), 127.79 (2C), 127.00, 125.30 (2C), 118.91, 110.76, 63.44, 43.39, 19.97, 11.68. **HRMS** (ESI)  $m/z$  calcd for  $C_{18}H_{20}N_3$   $[M+H]^+$ : 278.1657, found: 278.1660.

2-[(*E*)-Benzylideneamino]-ethyl-amino]propanenitrile (**4j**).



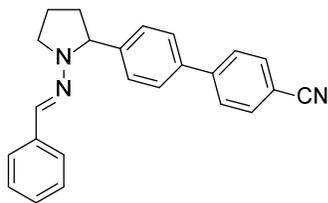
Cream solid; Yield: 8.3 mg (6%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.60-7.65 (m, 2H), 7.57 (s, 1H), 7.34-7.39 (m, 2H), 7.28-7.33 (m, 1H), 4.38 (q,  $J=7.1$  Hz, 1H), 3.41 (dq,  $J=14.3$ , 7.3 Hz, 1H), 3.29 (dq,  $J=14.2$ , 7.1 Hz, 1H), 1.69 (d,  $J=7.2$  Hz, 3H), 1.29 (t,  $J=7.2$  Hz, 3H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  137.49, 135.80, 128.49 (3C), 126.29 (2C), 119.24, 51.65, 44.34, 18.15, 11.86. **HRMS** (ESI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{16}\text{N}_3$   $[\text{M}+\text{H}]^+$ : 202.1344, found: 202.1350.

2-[1-[(*E*)-Benzylideneamino]pyrrolidin-2-yl]benzonitrile (**3ab**).



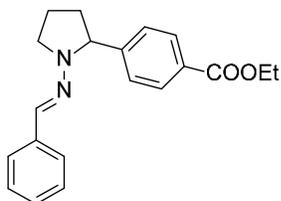
Yellow solid; Yield: 77.1 mg (70%);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.67 (dd,  $J=7.6$ , 0.9 Hz, 1H), 7.51-7.57 (m, 1H), 7.45-7.50 (m, 1H), 7.41-7.45 (m, 2H), 7.33 (td,  $J=7.6$ , 1.3 Hz, 1H), 7.21-7.28 (m, 2H), 7.13-7.19 (m, 2H), 4.95 (dd,  $J=7.9$ , 6.0 Hz, 1H), 3.81 (dt,  $J=9.8$ , 6.1 Hz, 1H), 3.33-3.41 (m, 1H), 2.55 (dq,  $J=12.5$ , 7.6 Hz, 1H), 2.07 (quin,  $J=6.9$  Hz, 2H), 1.89 (dq,  $J=13.0$ , 6.4 Hz, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.36, 136.69, 133.55, 133.26, 132.87, 128.35 (2C), 127.33, 127.26, 127.23, 125.48 (2C), 117.87, 110.72, 65.26, 50.72, 33.29, 22.41. **HRMS** (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_3$   $[\text{M}+\text{H}]^+$ : 276.1501, found: 276.1503.

4-[4-[1-[(*E*)-Benzylideneamino]pyrrolidin-2-yl]phenyl]benzonitrile (**3ac**).



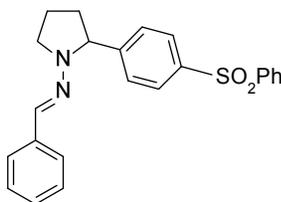
White solid; Yield: 102.6 mg (73%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.67-7.76 (m, 4H), 7.57 (d,  $J=8.4$  Hz, 2H), 7.45 (dd,  $J=12.7$ , 7.8 Hz, 4H), 7.23-7.29 (m, 2H), 7.14-7.20 (m, 2H), 4.67 (dd,  $J=7.8$ , 5.8 Hz, 1H), 3.83 (ddd,  $J=9.8$ , 7.6, 4.6 Hz, 1H), 3.39-3.46 (m, 1H), 2.45 (dq,  $J=12.3$ , 7.7 Hz, 1H), 2.00-2.16 (m, 2H), 1.90-1.98 (m, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  145.48, 144.82, 137.60, 136.99, 132.71, 132.56 (2C), 128.36 (2C), 127.57 (2C), 127.29 (2C), 127.24 (2C), 127.05, 125.33 (2C), 119.00, 110.66, 66.15, 51.32, 34.23, 22.41. **HRMS** (ESI)  $m/z$  calcd for  $\text{C}_{24}\text{H}_{22}\text{N}_3$   $[\text{M}+\text{H}]^+$ : 352.1814, found: 352.1808.

(*E*)-1-Phenyl-*N*-[2-(*p*-tolyl)pyrrolidin-1-yl]methanimine (**3ad**).



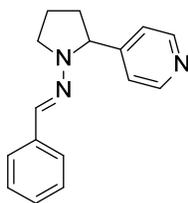
Reaction carried out starting from **1a** (4 g, 23 mmol.), **2d** (2.68 g, 15.3 mmol). White solid; Yield: 3.11 g (63%); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 8.01 (d, *J*=8.3 Hz, 2H), 7.42 (d, *J*=7.2 Hz, 2H), 7.37 (d, *J*=8.6 Hz, 2H), 7.20-7.28 (m, 2H), 7.16 (d, *J*=7.4 Hz, 1H), 7.12 (s, 1H), 4.63 (dd, *J*=7.7, 5.9 Hz, 1H), 4.37 (q, *J*=7.2 Hz, 2H), 3.79 (ddd, *J*=9.8, 7.1, 5.1 Hz, 1H), 3.33-3.45 (m, 1H), 2.41 (dq, *J*=12.3, 7.7 Hz, 1H), 1.94-2.11 (m, 2H), 1.81-1.92 (m, 1H), 1.38 (t, *J*=7.1 Hz, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 166.58, 149.32, 136.90, 132.85, 129.77 (2C), 129.09, 128.35 (2C), 127.08, 126.41 (2C), 125.34 (2C), 66.34, 60.80, 51.30, 34.17, 22.36, 14.34. **HRMS** (ESI) *m/z* calcd for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 323.1681, found: 323.1758

(*E*)-*N*-[2-[4-(Benzenesulfonyl)phenyl]pyrrolidin-1-yl]-1-phenyl-methanimine (**3af**).



White solid; Yield: 106.2 mg (68%); **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ 7.94-8.01 (m, 2H), 7.88-7.93 (m, 2H), 7.54-7.60 (m, 1H), 7.48-7.54 (m, 2H), 7.45 (d, *J*=8.1 Hz, 2H), 7.39-7.43 (m, 2H), 7.22-7.27 (m, 2H), 7.15-7.20 (m, 1H), 7.15 (s, 1H), 4.65 (dd, *J*=7.9, 5.6 Hz, 1H), 3.77 (dt, *J*=9.7, 6.0 Hz, 1H), 3.31-3.37 (m, 1H), 2.39 (dq, *J*=12.4, 7.8 Hz, 1H), 1.99-2.07 (m, 2H), 1.82 (dq, *J*=12.3, 6.2 Hz, 1H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 150.21, 141.73, 139.83, 136.64, 133.39, 133.05, 129.21 (2C), 128.37 (2C), 127.86 (2C), 127.63 (2C), 127.39 (2C), 127.27, 125.40 (2C), 66.39, 50.81, 33.85, 22.32. **HRMS** (ESI) *m/z* calcd for C<sub>23</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>S [M+H]<sup>+</sup>: 391.1480, found: 391.1469.

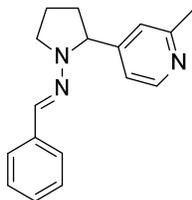
(*E*)-1-Phenyl-*N*-[2-(4-pyridyl)pyrrolidin-1-yl]methanimine (**3ag**).



Yellow oil; Yield: 70.4 mg (70%); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 8.51-8.59 (m, 2H), 7.40-7.49 (m, 2H), 7.22-7.29 (m, 4H), 7.13-7.20 (m, 2H), 4.58 (dd, *J*=8.1, 5.3 Hz, 1H), 3.76 (dt, *J*=9.8, 6.0 Hz, 1H), 3.30-3.39 (m, 1H), 2.40 (dq, *J*=12.3, 7.8 Hz, 1H), 1.98-2.08 (m, 2H), 1.85 (dq, *J*=12.4, 6.2 Hz, 1H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 153.12,

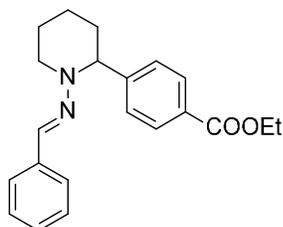
149.78 (2C), 136.67, 133.26, 128.37 (2C), 127.25, 125.37 (2C), 121.71 (2C), 65.77, 50.76, 33.47, 22.31. **HRMS** (ESI)  $m/z$  calcd for  $C_{16}H_{18}N_3$   $[M+H]^+$ : 252.1501, found: 252.1524.

(*E*)-*N*-[2-(2-Methyl-4-pyridyl)pyrrolidin-1-yl]-1-phenyl-methanimine (**3ah**).



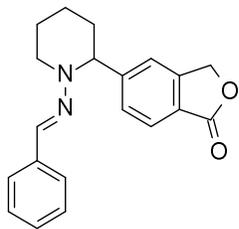
Residence time in coil was 40 min. Orange oil; Yield: 54.1 mg (51%);  **$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  8.43 (d,  $J=5.3$  Hz, 1H), 7.42-7.47 (m, 2H), 7.22-7.29 (m, 2H), 7.13-7.20 (m, 1H), 7.14 (s, 1H), 7.10 (s, 1H), 7.01-7.06 (m, 1H), 4.54 (dd,  $J=8.1, 5.5$  Hz, 1H), 3.77 (dt,  $J=9.7, 5.9$  Hz, 1H), 3.30-3.40 (m, 1H), 2.55 (s, 3H), 2.38 (dq,  $J=12.4, 7.8$  Hz, 1H), 1.97-2.06 (m, 2H), 1.79-1.88 (m, 1H).  **$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  158.40, 153.45, 149.11, 136.72, 133.13, 128.35 (2C), 127.19, 125.36 (2C), 121.06, 118.83, 65.72, 51.06, 33.57, 24.44, 22.34. **HRMS** (ESI)  $m/z$  calcd for  $C_{17}H_{20}N_3$   $[M+H]^+$ : 266.1657, found: 266.1660.

Ethyl 4-[1-[(*E*)-benzylideneamino]-2-piperidyl]benzoate (**3bd**).



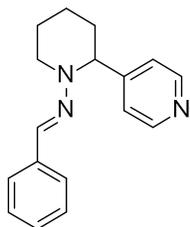
White solid; Yield: 75.4 mg (56%);  **$^1H$  NMR** (500 MHz,  $CDCl_3$ ):  $\delta$  7.98-8.06 (m, 2H), 7.60 (s, 1H), 7.44 (d,  $J=8.4$  Hz, 2H), 7.28-7.33 (m, 2H), 7.15-7.24 (m, 3H), 4.39 (q,  $J=7.2$  Hz, 2H), 4.00 (dd,  $J=10.3, 3.3$  Hz, 1H), 3.82 (dt,  $J=11.5, 3.9$  Hz, 1H), 2.74 (td,  $J=11.3, 3.6$  Hz, 1H), 1.91-2.00 (m, 2H), 1.75-1.91 (m, 3H), 1.44-1.56 (m, 1H), 1.41 (t,  $J=7.1$  Hz, 3H).  **$^{13}C$  NMR** (126 MHz,  $CDCl_3$ ):  $\delta$  166.80, 149.79, 136.86, 136.49, 129.39 (2C), 128.63, 128.32 (2C), 127.94, 127.60 (2C), 126.03 (2C), 68.30, 60.75, 49.51, 34.86, 24.64, 23.34, 14.36. **HRMS** (ESI)  $m/z$  calcd for  $C_{21}H_{25}N_2O_2$   $[M+H]^+$ : 337.1916, found: 337.1920.

5-[1-[(*E*)-Benzylideneamino]-2-piperidyl]-3*H*-isobenzofuran-1-one (**3be**).



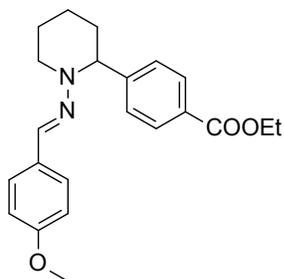
Yellow oil; Yield: 64.1 mg (50%);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.88 (d,  $J=7.9$  Hz, 1H), 7.62 (s, 1H), 7.54 (d,  $J=7.9$  Hz, 1H), 7.49 (s, 1H), 7.15-7.28 (m, 5H), 5.30 (s, 2H), 3.98 (dd,  $J=10.8$ , 3.4 Hz, 1H), 3.85 (dt,  $J=11.7$ , 3.6 Hz, 1H), 2.66 (td,  $J=11.5$ , 3.6 Hz, 1H), 1.73-2.03 (m, 5H), 1.41-1.59 (m, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.30, 152.14, 146.71, 137.37, 136.21, 129.00, 128.37 (2C), 128.20, 126.03 (2C), 125.29, 124.02, 120.95, 69.61, 68.95, 49.46, 35.39, 24.61, 23.48. **HRMS** (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 321.1603, found: 321.1630.

(*E*)-1-Phenyl-*N*-[2-(4-pyridyl)-1-piperidyl]methanimine (**3bg**).



Residence time in coil was 30 min. Cream solid; Yield: 54.1 mg (51%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.55 (d,  $J=5.5$  Hz, 2H), 7.60 (s, 1H), 7.28-7.32 (m, 4H), 7.16-7.24 (m, 3H), 3.92 (dd,  $J=10.3$ , 3.3 Hz, 1H), 3.80 (dt,  $J=11.4$ , 4.0 Hz, 1H), 2.70 (td,  $J=11.3$ , 3.6 Hz, 1H), 1.91-1.99 (m, 2H), 1.72-1.90 (m, 3H), 1.43-1.53 (m, 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  153.65, 149.50 (2C), 136.98, 136.31, 128.39 (2C), 128.15, 126.08 (2C), 123.00 (2C), 67.78, 49.09, 34.58, 24.53, 23.24. **HRMS** (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{20}\text{N}_3$   $[\text{M}+\text{H}]^+$ : 266.1657, found: 266.1670.

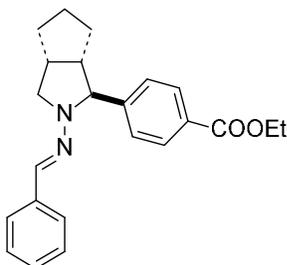
Ethyl 4-[1-[(*E*)-(4-methoxyphenyl)methyleneamino]-2-piperidyl]benzoate (**3cd**).



Colorless oil; Yield: 88 mg (60%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.96-8.03 (m, 2H), 7.62 (s, 1H), 7.39-7.46 (m, 2H), 7.19-7.25 (m, 2H), 6.71-6.78 (m, 2H), 4.37 (q,  $J=7.1$  Hz, 2H), 3.87-3.92 (m, 1H), 3.75 (s, 3H), 3.71-3.78 (m, 1H), 2.66 (td,  $J=11.3$ , 3.5 Hz, 1H), 1.89-1.97 (m, 2H), 1.73-1.88 (m, 3H), 1.41-1.52 (m, 1H), 1.39 (t,  $J=7.2$  Hz, 3H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.84, 159.80, 150.14, 138.81, 129.37 (2C), 129.27, 128.57, 127.64 (2C), 127.51

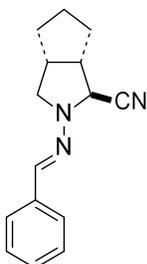
(2C), 113.83 (2C), 68.77, 60.74, 55.24, 50.38, 35.04, 24.81, 23.59, 14.37. **HRMS** (ESI)  $m/z$  calcd for  $C_{22}H_{26}N_2O_3$   $[M+H]^+$ : 367.19434, found: 367.2061

*rac*-Ethyl 4-[(3*S*,3*aS*,6*aR*)-2-[(*E*)-benzylideneamino]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-3-yl]benzoate (**3hd**).



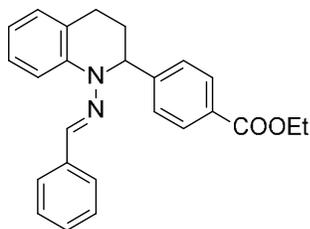
Reaction carried out starting from **1h** (2 g, 9.33 mmol.), **2d** (1.09 g, 6.22 mmol). Colorless oil; Yield: 1.29 g (57%); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.98-8.06 (m, 2H), 7.40-7.45 (m, 2H), 7.36-7.40 (m, 2H), 7.19-7.25 (m, 3H), 7.13-7.19 (m, 1H), 4.37 (q,  $J=7.2$  Hz, 2H), 4.04 (d,  $J=6.5$  Hz, 1H), 4.00 (t,  $J=9.0$  Hz, 1H), 2.84-2.95 (m, 1H), 2.75-2.84 (m, 1H), 2.48-2.59 (m, 1H), 1.57-1.88 (m, 6H), 1.39 (t,  $J=7.2$  Hz, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 166.67, 149.09, 136.66, 135.96, 129.75 (2C), 129.11, 128.33 (2C), 127.50, 126.93 (2C), 125.64 (2C), 74.37, 60.79, 56.95, 51.49, 39.70, 32.37, 31.26, 24.95, 14.36. **HRMS** (ESI)  $m/z$  calcd for  $C_{23}H_{26}N_2O_2$   $[M+H]^+$ : 363.1994, found: 363.2074.

*rac*-4-[(3*S*,3*aS*,6*aR*)-2-[(*E*)-Benzylideneamino]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrole-3-carbonitrile (**4h**).



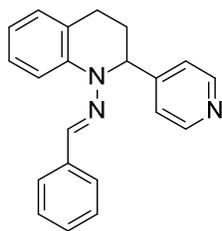
Reaction carried out starting from **1h** (2 g, 9.33 mmol.), **2d** (1.09 g, 6.22 mmol). White solid; Yield: 60 mg (4%); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.57-7.63 (m, 2H), 7.42 (s, 1H), 7.32-7.37 (m, 2H), 7.27-7.32 (m, 1H), 4.32 (d,  $J=1.2$  Hz, 1H), 3.14-3.26 (m, 2H), 2.83-2.97 (m, 2H), 1.90-2.08 (m, 2H), 1.70-1.80 (m, 1H), 1.46-1.62 (m, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 140.96, 135.41, 128.76, 128.52 (2C), 126.42 (2C), 118.51, 61.13, 54.47, 45.74, 39.85, 34.36, 33.03, 26.45. **HRMS** (ESI)  $m/z$  calcd for  $C_{15}H_{17}N_3$   $[M+H]^+$ : 240.1422, found: 240.1478.

(*E*)-1-Phenyl-*N*-[2-(*p*-tolyl)-3,4-dihydro-2*H*-quinolin-1-yl]methanimine (**3id**).



Residence time in coil was 60 min. Yellow oil; Yield: 84.5 mg (55%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.96-8.01 (m, 3H), 7.55 (dd,  $J=8.2, 1.0$  Hz, 2H), 7.26-7.32 (m, 5H), 7.23 (s, 1H), 7.19-7.23 (m, 1H), 7.04 (d,  $J=7.2$  Hz, 1H), 6.85 (td,  $J=7.3, 1.0$  Hz, 1H), 5.36-5.41 (m, 1H), 4.35 (q,  $J=7.1$  Hz, 2H), 2.48-2.63 (m, 2H), 2.42 (tt,  $J=12.7, 4.9$  Hz, 1H), 2.26 (dq,  $J=12.9, 3.4$  Hz, 1H), 1.36 (t,  $J=7.2$  Hz, 3H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.25, 145.47, 142.88, 136.43, 132.53, 130.22 (2C), 129.77, 128.62, 128.45 (2C), 127.89, 127.59, 126.14 (2C), 126.11 (2C), 122.67, 119.64, 114.07, 60.95, 57.30, 29.36, 22.78, 14.29. **HRMS** (ESI)  $m/z$  calcd for  $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 385.1837, found: 385.1913.

(*E*)-1-Phenyl-*N*-[2-(4-pyridyl)-3,4-dihydro-2*H*-quinolin-1-yl]methanimine (**3ig**).



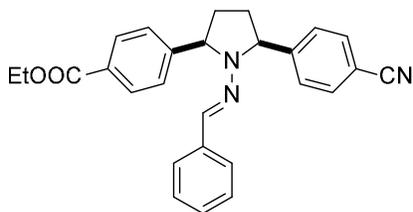
Residence time in coil was 60 min. Yellow solid; Yield: 75.2 mg (60%);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.51-8.58 (m, 2H), 7.98 (dd,  $J=8.4, 0.9$  Hz, 1H), 7.54-7.61 (m, 2H), 7.26-7.35 (m, 3H), 7.21-7.25 (m, 1H), 7.20 (s, 1H), 7.11-7.16 (m, 2H), 7.04 (d,  $J=7.5$  Hz, 1H), 6.87 (td,  $J=7.4, 1.2$  Hz, 1H), 5.30-5.37 (m, 1H), 2.57-2.65 (m, 1H), 2.39-2.53 (m, 2H), 2.23-2.30 (m, 1H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  150.42 (2C), 149.40, 142.64, 136.21, 132.46, 128.68, 128.52 (2C), 128.09, 127.71, 126.16 (2C), 122.36, 121.38 (2C), 119.86, 114.10, 56.40, 28.79, 22.73. **HRMS** (ESI)  $m/z$  calcd for  $\text{C}_{21}\text{H}_{19}\text{N}_3$   $[\text{M}+\text{H}]^+$ : 314.1579, found: 314.1651

## 6. General procedure for the preparation of $\alpha,\alpha'$ -diarylated hydrazones.

A to a stirred 0.25 M solution of cyanoaryl **2** (0.4 mmol), LiOAc (0.8 mmol) and  $\text{Ir}(\text{ppy})_3$  (2 mol%) in DMSO the corresponding hydrazone **3** (0.52 mmol) was added at rt. A stream of  $\text{N}_2$  was bubbled through the solution for 5 min. The solution was then pumped through a Vapourtec photoreactor (UV-150 module, 10 mL coil) at a flow of 0.25-050 mL/min (40-20 min residence time) at 50-75  $^\circ\text{C}$  under irradiation with a LED lamp (450 nm wavelength). After cooling to rt  $\text{NaHCO}_3$  (aq. sat. soltn.) and EtOAc were added. The organic layer was separated and the volatiles were evaporated in vacuo. The residue was purified by flash column chromatography (silica, DCM in heptane, from

0/100 to 50/50). The desired fractions were collected and concentrated in vacuo to yield final hydrazones. Separation of diastereoisomers was performed by RP HPLC (Stationary phase: C18 XBridge 30 x 100 mm 5  $\mu$ m), mobile phase: gradient from 47 % 10 mM  $\text{NH}_4\text{CO}_3\text{H}$  pH 9 solution in water / 53 %  $\text{CH}_3\text{CN}$  to 30 % 10 mM  $\text{NH}_4\text{CO}_3\text{H}$  pH 9 solution in water / 70 %  $\text{CH}_3\text{CN}$ ). The following  $\alpha,\alpha'$ -diarylhydrazones were obtained by this procedure:

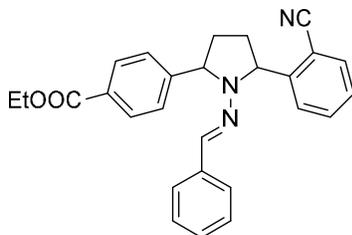
*rac-cis*-1-[(*E*)-Benzylideneamino]-5-(*p*-tolyl)pyrrolidin-2-yl]benzonitrile (*cis*-**3ada**).



Prepared according to the general procedure starting from hydrazone **3ad** (0.10 g, 0.31 mmol) and 1,4-DCB (**2a**, 0.031 g, 0.239 mmol) with a residence time of 20 min at 50  $^{\circ}\text{C}$ . Mixture of *cis/trans* isomers 9:1. Colorless oil; Yield: 61 mg (60%). The mixture was re-purified by RP HPLC as indicated in the general procedure to isolate *cis*-**3ada**:

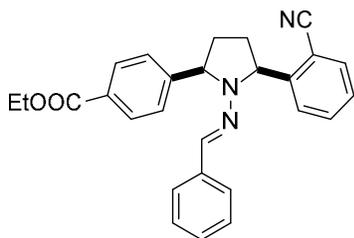
$^1\text{H NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  8.23-8.27 (m, 2H), 7.36-7.41 (m, 2H), 7.31 (d,  $J=8.1$  Hz, 2H), 7.09-7.12 (m, 2H), 7.06-7.09 (m, 2H), 7.04 (s, 1H), 6.99-7.03 (m, 2H), 6.93-6.97 (m, 1H), 4.29 (dd,  $J=7.9, 6.5$  Hz, 1H), 4.23 (t,  $J=7.2$  Hz, 1H), 4.15 (q,  $J=7.1$  Hz, 2H), 1.80-1.89 (m, 1H), 1.71-1.79 (m, 1H), 1.49 (dq,  $J=12.6, 6.4$  Hz, 1H), 1.36-1.44 (m, 1H), 1.03 (t,  $J=7.1$  Hz, 3H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  166.40, 149.08, 148.97, 137.05, 136.64, 132.81 (2C), 130.86 (2C), 130.73, 129.08 (2C), 128.64, 127.64 (2C), 126.93 (2C), 126.59 (2C), 119.21, 112.03, 68.23, 67.70, 61.24, 33.30, 32.86, 14.66. **HRMS** (ESI)  $m/z$  calcd for  $\text{C}_{27}\text{H}_{25}\text{N}_3\text{O}_2$   $[\text{M}+\text{H}]^+$ : 424.1946, found: 424.2018

2-[(*E*)-Benzylideneamino]-5-(*p*-tolyl)pyrrolidin-2-yl]benzonitrile (**3adb**).



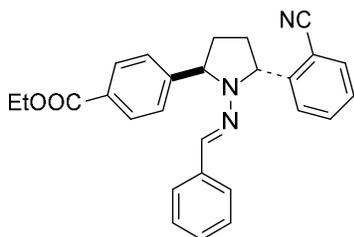
Prepared according to the general procedure starting from hydrazone **3ad** (0.09 g, 0.28 mmol) and 1,2-DCB (**2b**, 28 mg, 0.21 mmol) with a residence time of 20 min at 50  $^{\circ}\text{C}$ . Mixture of *cis/trans* isomers 9:1. Yellow oil; Yield: 52 mg (57%). The mixture was re-purified by RP HPLC as indicated in the general procedure to isolate *cis*-**3adb** and *cis*-**3adb**.

*cis*-2-[1-[(*E*)-Benzylideneamino]-5-(*p*-tolyl)pyrrolidin-2-yl]benzonitrile (*cis*-**3adb**).



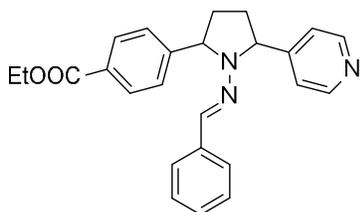
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.07-8.13 (m, 2H), 7.81 (d, *J*=7.9 Hz, 1H), 7.73 (dd, *J*=7.6, 0.9 Hz, 1H), 7.64 (td, *J*=7.6, 1.2 Hz, 1H), 7.58 (d, *J*=8.3 Hz, 2H), 7.40 (td, *J*=7.6, 1.2 Hz, 1H), 7.30-7.35 (m, 2H), 7.13-7.24 (m, 3H), 7.04 (s, 1H), 5.08 (t, *J*=7.2 Hz, 1H), 4.74 (dd, *J*=8.0, 6.1 Hz, 1H), 4.40 (q, *J*=7.2 Hz, 2H), 2.49-2.74 (m, 2H), 1.90-2.08 (m, 2H), 1.41 (t, *J*=7.1 Hz, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.46, 148.55, 147.46, 136.53, 135.99, 133.31, 133.18, 130.07 (2C), 129.51, 128.33 (2C), 127.97, 127.56, 126.91, 126.41 (2C), 125.94 (2C), 117.77, 111.00, 67.16, 66.12, 60.94, 32.85, 32.07, 14.36. **HRMS** (ESI) *m/z* calcd for for C<sub>27</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 424.1946, found: 424.1947.

*trans*-2-[1-[(*E*)-Benzylideneamino]-5-(*p*-tolyl)pyrrolidin-2-yl]benzonitrile (*trans*-**3adb**).



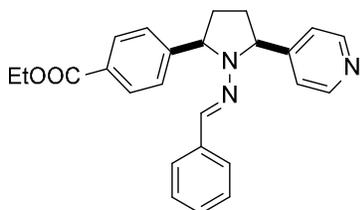
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 8.02-8.07 (m, 2H), 7.73 (dd, *J*=7.7, 1.0 Hz, 1H), 7.55 (td, *J*=7.7, 1.3 Hz, 1H), 7.29-7.41 (m, 4H), 7.23-7.27 (m, 2H), 7.15-7.21 (m, 2H), 7.09-7.14 (m, 1H), 6.80 (s, 1H), 5.53 (dd, *J*=8.2, 1.5 Hz, 1H), 5.22-5.29 (m, 1H), 4.38 (q, *J*=7.0 Hz, 2H), 2.62-2.74 (m, 1H), 2.49-2.62 (m, 1H), 1.87-2.00 (m, 2H), 1.39 (t, *J*=7.1 Hz, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 166.40, 147.73, 147.54, 136.49, 133.63, 132.95, 132.83, 130.00 (2C), 129.43, 128.28 (2C), 127.48, 127.21 (2C), 126.23 (2C), 125.35 (2C), 117.73, 110.46, 64.78, 64.00, 60.92, 31.57, 30.79, 14.34. **HRMS** (ESI) *m/z* calcd for for C<sub>27</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 424.1946, found: 424.1948

(*E*)-1-Phenyl-*N*-[2-(*p*-tolyl)-5-(4-pyridyl)pyrrolidin-1-yl]methanimine (**3adg**).



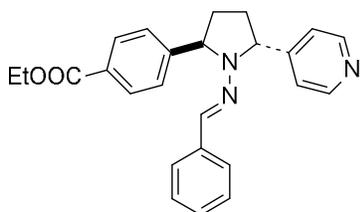
Prepared according to the general procedure starting from hydrazone **3ad** (0.10 g, 0.31 mmol) and 4-cyanopyridine (**2g**, 25 mg, 0.24 mmol) with a residence time of min 20 at 60 °C. Mixture of *cis/trans* isomers 1.3:1. Colorless oil; Yield: 55 mg (58%). The mixture was re-purified by RP HPLC as indicated in the general procedure to isolate *cis-3adg* and *cis-3adg*.

*cis-(E)*-1-phenyl-*N*-[2-(*p*-tolyl)-5-(4-pyridyl)pyrrolidin-1-yl]methanimine (*cis-3adg*).



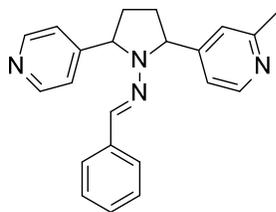
<sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>): δ 8.60-8.67 (m, 2H), 8.21-8.27 (m, 2H), 7.37-7.41 (m, 2H), 7.34 (d, *J*=8.1 Hz, 2H), 7.08-7.11 (m, 3H), 6.99-7.05 (m, 2H), 6.94-6.98 (m, 1H), 4.32 (t, *J*=7.1 Hz, 1H), 4.26 (t, *J*=7.1 Hz, 1H), 4.16 (q, *J*=7.0 Hz, 2H), 1.75-1.89 (m, 2H), 1.42-1.56 (m, 2H), 1.04 (t, *J*=7.1 Hz, 3H). <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>): δ 166.45, 152.58, 151.08 (2C), 149.12, 137.15, 136.50, 130.86 (2C), 130.65, 129.05 (2C), 128.52, 127.00 (2C), 126.63 (2C), 122.07 (2C), 67.93, 67.54, 61.19, 33.37, 32.64, 14.66. HRMS (ESI) *m/z* calcd for for C<sub>25</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 400.1946, found: 400.2020.

*trans-(E)*-1-phenyl-*N*-[2-(*p*-tolyl)-5-(4-pyridyl)pyrrolidin-1-yl]methanimine (*trans-3adg*).



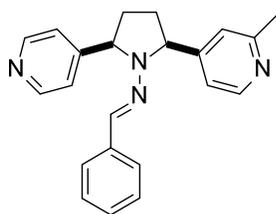
<sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>): δ 8.60 (br d, *J*=5.2 Hz, 2H), 8.19-8.23 (m, 2H), 7.34-7.40 (m, 2H), 7.05 (d, *J*=8.1 Hz, 2H), 6.98-7.03 (m, 2H), 6.90-6.96 (m, 1H), 6.80 (s, 1H), 6.77 (d, *J*=5.8 Hz, 2H), 4.73 (d, *J*=7.5 Hz, 1H), 4.64 (d, *J*=7.8 Hz, 1H), 4.16 (q, *J*=7.2 Hz, 2H), 1.86-2.00 (m, 2H), 1.27-1.32 (m, 1H), 1.19-1.25 (m, 1H), 1.05 (t, *J*=7.1 Hz, 3H). <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>): δ 166.45, 152.54, 150.88 (2C), 148.75, 137.60, 133.21, 130.70 (2C), 130.49, 129.07 (2C), 127.83, 126.85 (2C), 126.07 (2C), 121.92 (2C), 64.95, 64.85, 61.21, 31.62, 31.06, 14.67. HRMS (ESI) *m/z* calcd for for C<sub>25</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 400.1946, found: 400.2018.

(*E*)-*N*-[2-(2-Methyl-4-pyridyl)-5-(4-pyridyl)pyrrolidin-1-yl]-1-phenyl-methanimine (**3agh**).



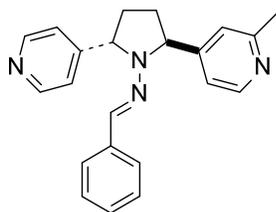
Prepared according to the general procedure starting from hydrazone **3ag** (0.10 g, 0.4 mmol) and 4-cyano-2-methylpyridine (**2h**, 36.2 mg, 0.31 mmol) with a residence time of min 40 at 75 °C. Mixture of *cis/trans* isomers 1.3:1. Colorless oil; Yield: 44 mg (42%). The mixture was re-purified by RP HPLC as indicated in the general procedure to isolate *cis-3agh* and *cis-3agh*.

*cis-(E)-N*-[2-(2-Methyl-4-pyridyl)-5-(4-pyridyl)pyrrolidin-1-yl]-1-phenyl-methanimine (*cis-3agh*).



<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 8.61-8.66 (m, 2H), 8.51 (d, *J*=5.2 Hz, 1H), 7.40-7.44 (m, 2H), 7.33-7.38 (m, 2H), 7.25 (s, 1H), 7.21-7.24 (m, 3H), 7.16-7.21 (m, 1H), 7.06 (s, 1H), 4.68 (t, *J*=6.8 Hz, 1H), 4.64 (t, *J*=6.6 Hz, 1H), 2.60 (s, 3H), 2.43-2.54 (m, 2H), 1.91-2.02 (m, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 158.87, 152.65, 152.34, 150.19 (2C), 149.59, 136.23, 135.93, 128.42 (2C), 128.08, 125.90 (2C), 121.66 (2C), 120.95, 118.67, 67.05, 66.78, 32.64, 32.42, 24.64. HRMS (ESI) *m/z* calcd for for C<sub>22</sub>H<sub>22</sub>N<sub>4</sub> [M+H]<sup>+</sup>: 343.1844, found:343.1963.

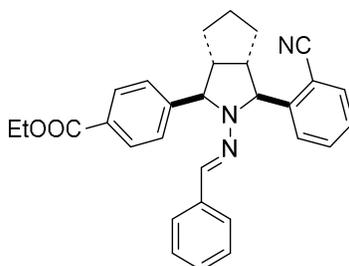
*trans-(E)-N*-[2-(2-Methyl-4-pyridyl)-5-(4-pyridyl)pyrrolidin-1-yl]-1-phenyl-methanimine (*trans-3agh*).



<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.54-8.62 (m, 2H), 8.46 (d, *J*=5.2 Hz, 1H), 7.27-7.31 (m, 2H), 7.18-7.23 (m, 2H), 7.16-7.18 (m, 2H), 7.12-7.16 (m, 1H), 7.04 (s, 1H), 6.98 (dd, *J*=5.2, 1.4 Hz, 1H), 6.82 (s, 1H), 5.15 (d, *J*=7.2 Hz, 1H), 5.08 (d, *J*=6.9 Hz, 1H), 2.56 (s, 3H), 2.47-2.55 (m, 2H), 1.82-1.92 (m, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 158.85, 152.27, 152.16, 150.07 (2C), 149.47, 136.38, 132.89, 128.39 (2C), 127.40, 125.37 (2C), 121.53 (2C),

120.80, 118.59, 64.40, 64.02, 30.99, 30.91, 24.59. **HRMS** (ESI)  $m/z$  calcd for for  $C_{22}H_{22}N_4$   $[M+H]^+$ :343.1844 , found: 343.1923.

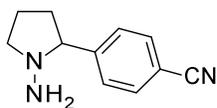
rac-2-[(1*S*,3*R*,3*aR*,6*aS*)-2-[(*E*)-Benzylideneamino]-1-(*p*-tolyl)-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrol-3-yl]benzotrile (**3hdb**).



Prepared according to the general procedure starting from hydrazone **3hd** (0.10 g, 0.28 mmol) and 2-cyanopyridine (**2b**, 27.8 mg, 0.21 mmol) with a residence time of min 20 at 50 °C. Yellow oil; Yield: 59 mg (61%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 8.06-8.13 (m, 2H), 7.82 (d,  $J=7.9$  Hz, 1H), 7.74 (dd,  $J=7.6$ , 0.9 Hz, 1H), 7.63-7.68 (m, 1H), 7.62 (d,  $J=8.1$  Hz, 2H), 7.40 (td,  $J=7.6$ , 1.2 Hz, 1H), 7.20-7.24 (m, 2H), 7.13-7.18 (m, 3H), 7.03 (s, 1H), 4.52-4.60 (m, 1H), 4.39 (q,  $J=7.2$  Hz, 2H), 4.11-4.19 (m, 1H), 2.62-2.75 (m, 2H), 1.96 (d,  $J=2.3$  Hz, 3H), 1.70-1.89 (m, 3H), 1.41 (t,  $J=7.1$  Hz, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 166.53, 148.54, 147.68, 139.27, 135.74, 133.37 (2C), 130.17 (2C), 129.53, 128.24 (3C), 127.73, 127.60, 126.54 (2C), 126.12 (2C), 118.21, 111.10, 74.07, 72.73, 60.90, 51.51, 51.06, 31.70, 30.50, 24.71, 14.36. **HRMS** (ESI)  $m/z$  calcd for for  $C_{30}H_{29}N_3O_2$   $[M+H]^+$ : 464.2259, found: 464.2342

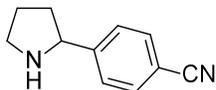
## 7. Preparation of 4-(1-aminopyrrolidin-2-yl)benzotrile (**10**) and analytical data.



A solution of **3aa** (0.1 g, 0.36 mmol) in aq. HCl (1 M, 8 mL) was refluxed at 120 °C for 1.5 h using a Dean-Stark apparatus to trap liberated benzaldehyde. The mixture was cooled to rt and extracted with EtOAc. The aqueous layer (containing the product) was evaporated in vacuo and the solid residue triturated with diisopropylether, filtered and dried in the vacuum oven (50 °C) to yield **5aa** (70 mg, 86 % yield, hydrochloride salt) as a pale yellow solid. Then 35 mg of the hydrochloride salt were treated with sat. NaHCO<sub>3</sub> and the free base thus obtained was purified by flash column chromatography (SiO<sub>2</sub>, methanol in dichloromethane 0/100 to 10/90) to collect compound **5aa** as a yellow solid which decomposes upon standing at rt for 24 h.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.60-7.68 (m, 2H), 7.50 (d, *J*=8.3 Hz, 2H), 3.42-3.50 (m, 1H), 3.32 (t, *J*=8.8 Hz, 1H), 2.52 (q, *J*=9.2 Hz, 1H), 2.25 (dddd, *J*=12.9, 9.8, 7.9, 5.2 Hz, 1H), 1.81-2.02 (m, 2H), 1.69 (dddd, *J*=12.8, 11.0, 9.5, 5.8 Hz, 1H); 2H exchanged. **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 148.47, 132.40 (2C), 128.20 (2C), 118.96, 110.99, 74.07, 59.56, 33.45, 20.88. **HRMS** (ESI) *m/z* calcd for C<sub>11</sub>H<sub>14</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 188.1188, found: 188.1187.

## 8. Preparation of 4-pyrrolidin-2-ylbenzonitrile (11) and analytical data.



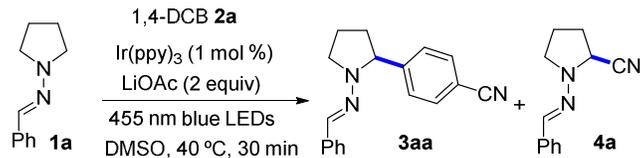
Sodium nitrite (14 mg, 0.203 mmol) was added to a suspension of **5aa** as hydrochloride (35 mg, 0.157 mmol) in acetic acid (0.53 mL, 9.171 mmol) and water (0.18 mL, 9.69 mmol) at 0 °C. After vigorous stirring for 30 min, CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and 2 M NaOH (1 mL) were added at 0 °C. The two phases were thoroughly mixed and then allowed to settle. The organic phase was separated, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (1 mL × 2). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography (SiO<sub>2</sub>, MeOH in DCM, from 0/100 to 10/90) to yield **6aa** (23 mg, 85 % yield) as a colorless oil.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.56-7.62 (m, 2H), 7.45-7.51 (m, 2H), 4.20 (t, *J*=7.8 Hz, 1H), 3.18 (ddd, *J*=10.0, 7.6, 5.5 Hz, 1H), 3.06 (br ddd, *J*=10.0, 8.1, 6.8 Hz, 1H), 2.23 (dtd, *J*=12.6, 7.8, 7.8, 4.9 Hz, 1H), 1.99 (br s, 1H), 1.80-1.95 (m, 2H), 1.56-1.66 (m, 1H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 151.03, 132.11 (2C), 127.17 (2C), 119.04, 110.29, 61.84, 47.00, 34.63, 25.52. **HRMS** (ESI) *m/z* calcd for C<sub>11</sub>H<sub>13</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 173.1079, found: 173.1081.

## 9. Comparison of batch and flow protocols.

In order to evaluate the added value of the flow protocol over the batch one space-time yield values<sup>iv,v</sup> were determined for the four experiments shown in Table 3. The preparation of compound **3aa** by the flow protocol at 0.4 mmol scale of **2a** (Table 3, entry 3) provided a 2.8 times better space-time yield than when the experiment was carried out in batch mode at the same reaction scale (Table 3, entry 1). Furthermore, a 1.8-fold decrease in space-time yield was also observed for a larger scale batch experiment (Table 3, entry 2), probably due to a suboptimal penetration of light in the reaction media. This scale-up detrimental effect was not observed in the case of the flow experiment, where 3.158 g of compound **3aa** could be obtained with a calculated space-time yield of 309.7 mg/h.mL (Table 3, entry 4), demonstrating the improved efficacy of flow protocols over the batch transformations.

**Table 3. Comparison between batch and flow protocols for the preparation of compound 3aa.**



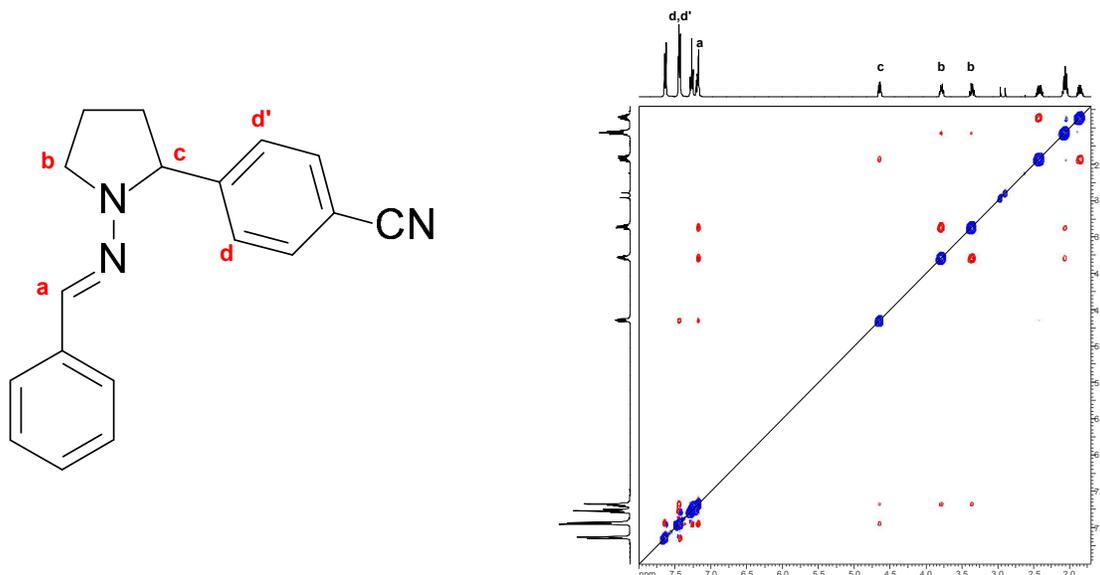
entry	method	<b>3aa</b> , yield (%) <sup>a</sup>	reaction time (min)	residence time (min)	<b>3aa</b> throughput (mg)	space-time yield (mg/h.mL)
1 <sup>b</sup>	batch	68	30	--	74.9	93.6
2 <sup>c</sup>	batch	38	30	--	313.9	52.3
3 <sup>d</sup>	flow	64	--	10	70.5	264.3
4 <sup>e</sup>	flow	75	--	10	3158	309.7

<sup>a</sup>Isolated yield. <sup>b</sup>Experiment carried out with 0.4 mmol of **2a** at 0.25 M concentration; reaction time 30 min. <sup>c</sup>Experiment carried out with 3 mmol of **2a** at 0.25 M concentration; reaction time 30 min. <sup>d</sup>Experiment carried out with 0.4 mmol of **2a** at 0.25 M concentration; residence time 10 min. <sup>e</sup>Experiment carried out with 15.3 mmol of **2a** at 0.25 M concentration; residence time 10 min.

## 10 Relative stereochemical configuration studies

### Stereochemical configuration of hydrazone **3aa**

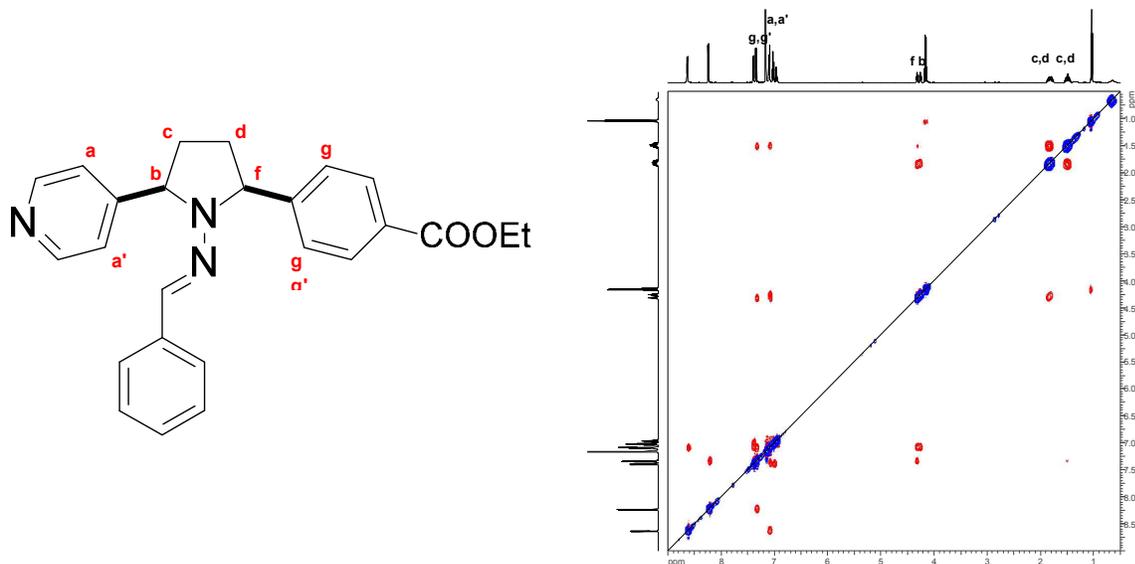
The relative configuration of the hydrazone **3aa** was determined as “*E*” on the basis of the strong NOE observed between proton H<sup>a</sup> and H<sup>b</sup> and the medium-size NOE seen between proton H<sup>a</sup> and protons H<sup>c</sup> and H<sup>d/d'</sup>. All other hydrazones described were assigned to be “*E*” isomers base on this determination.



### Relative stereochemical configuration of *cis*-**3adg**

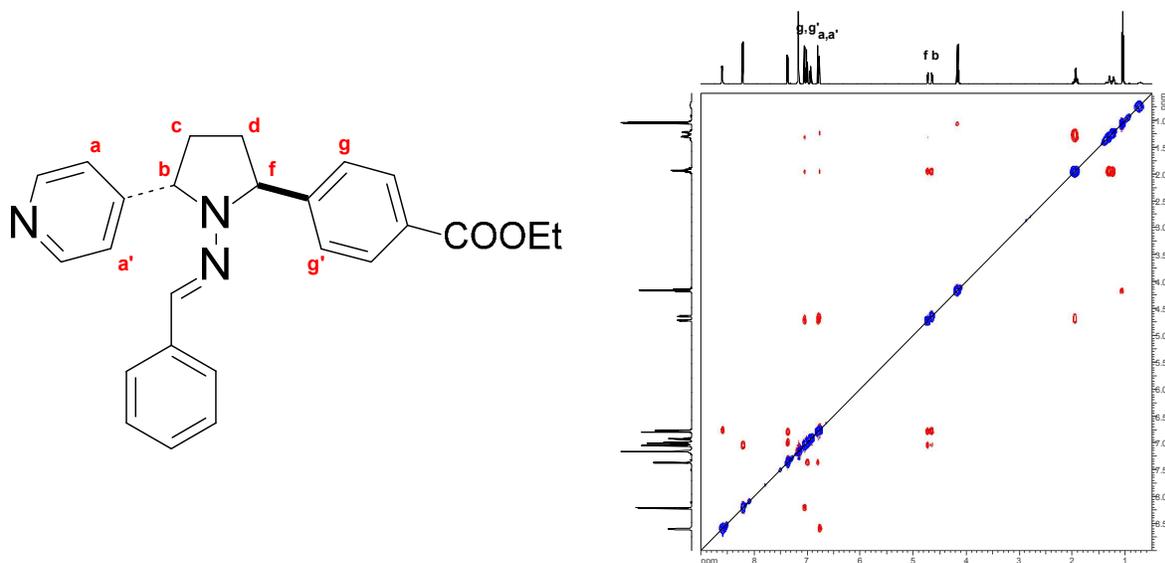
Strong NOE was observed between protons H<sup>a/a'</sup> and H<sup>g/g'</sup>. In addition, both proton H<sup>b</sup> and proton H<sup>f</sup> are coupled with their respective vicinal protons as triplet with a coupling constant  $J=7.1$  Hz, meaning that H<sup>b</sup> and H<sup>f</sup> have a

gauche relationship with both of their respective vicinal protons H<sup>c</sup> and H<sup>d</sup>. This finding is in a good agreement with the data predicted by molecular modelling calculations (MOE software, v 2014.09).



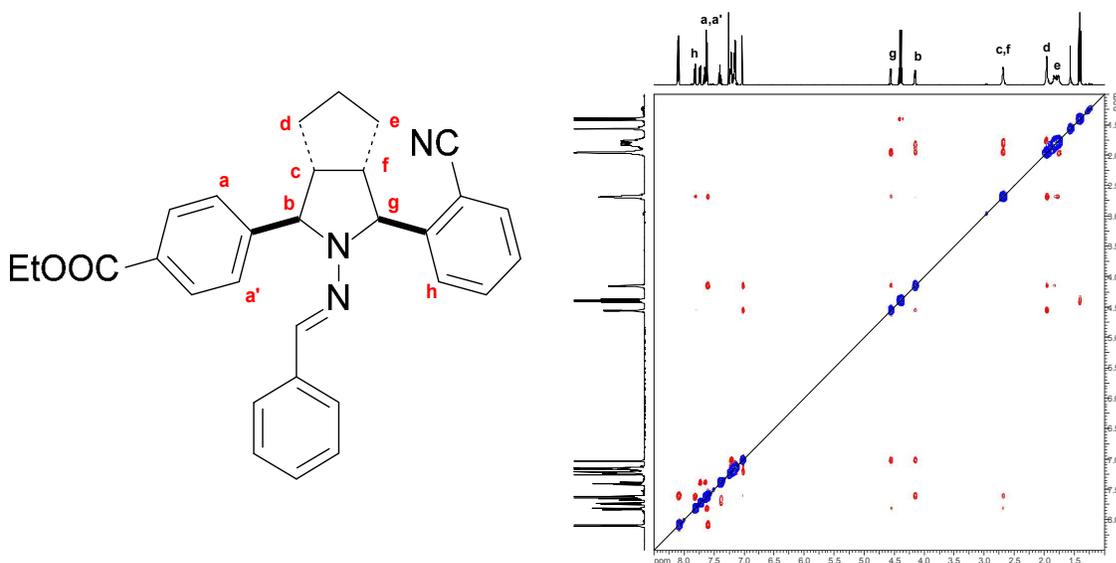
#### Relative stereochemical configuration of *trans*-3adg

In the case of its diastereomer we did not find any NOE between protons a,a' and g,g', as expected. In the <sup>1</sup>H-NMR spectrum both proton H<sup>b</sup> and H<sup>f</sup> appear as doublets with a coupling constant of  $J=7.8$  Hz and  $J=7.5$  Hz respectively. This means that proton H<sup>b</sup> is in a gauche relationship with one of their vicinal protons and a 90° dihedral angle with the other. The same can be said of proton f with respect to its vicinal protons. This is once again in full accordance with the theoretical dihedral angles provided by molecular modelling.



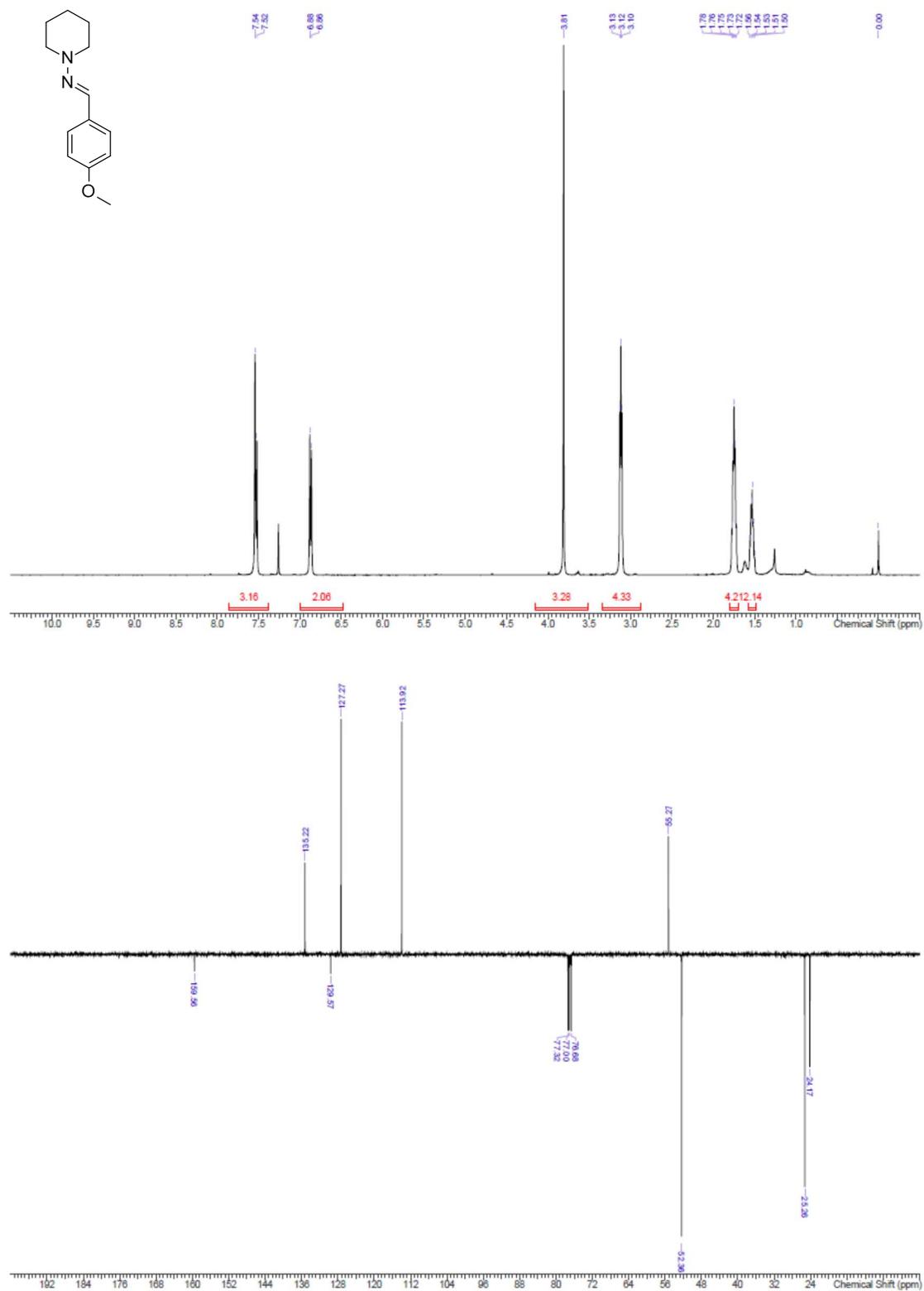
Relative stereochemical configuration of *cis-3hdb*

NOE information: strong cross-peaks can be seen between protons  $H^{a,a'}$  and proton  $H^b$ , between proton  $H^b$  and one of the  $H^d$  diastereotopic protons as well as between proton  $H^g$  and the corresponding  $H^c$  proton. These data are in accordance with theoretical distances extracted by molecular modelling calculations for this stereoisomer.

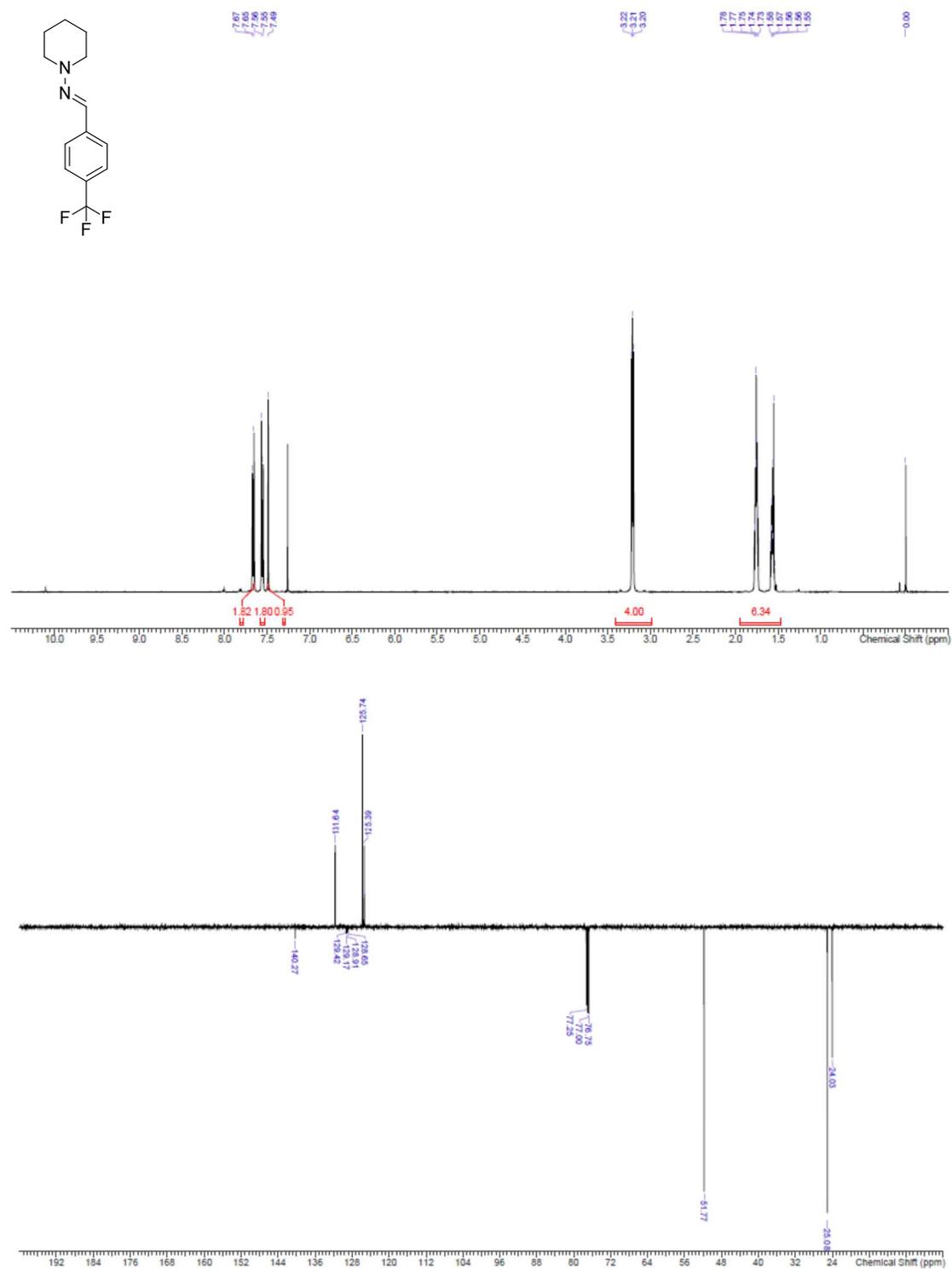


# 11 Copies of $^1\text{H}$ and $^{13}\text{C}$ NMR spectra

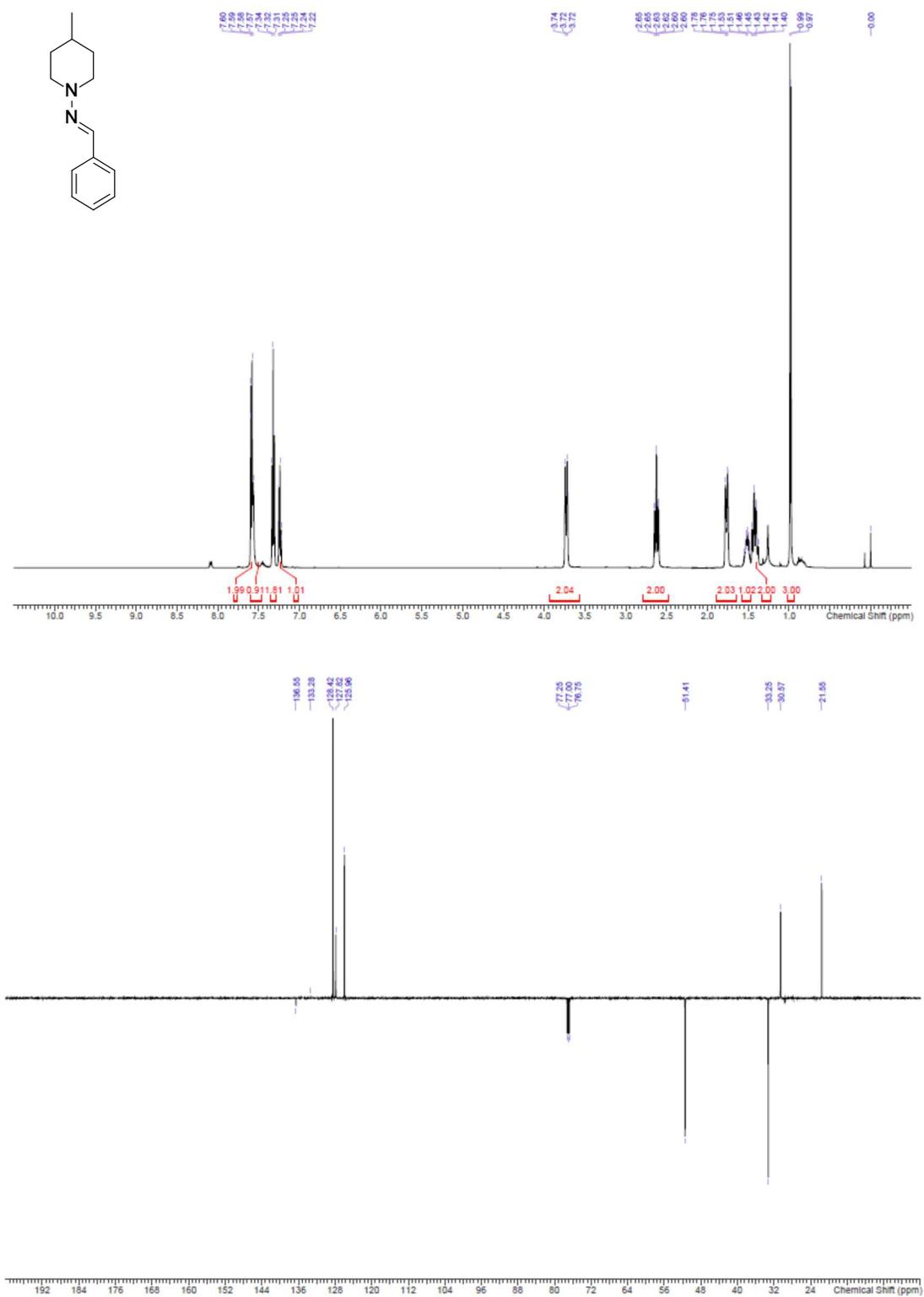
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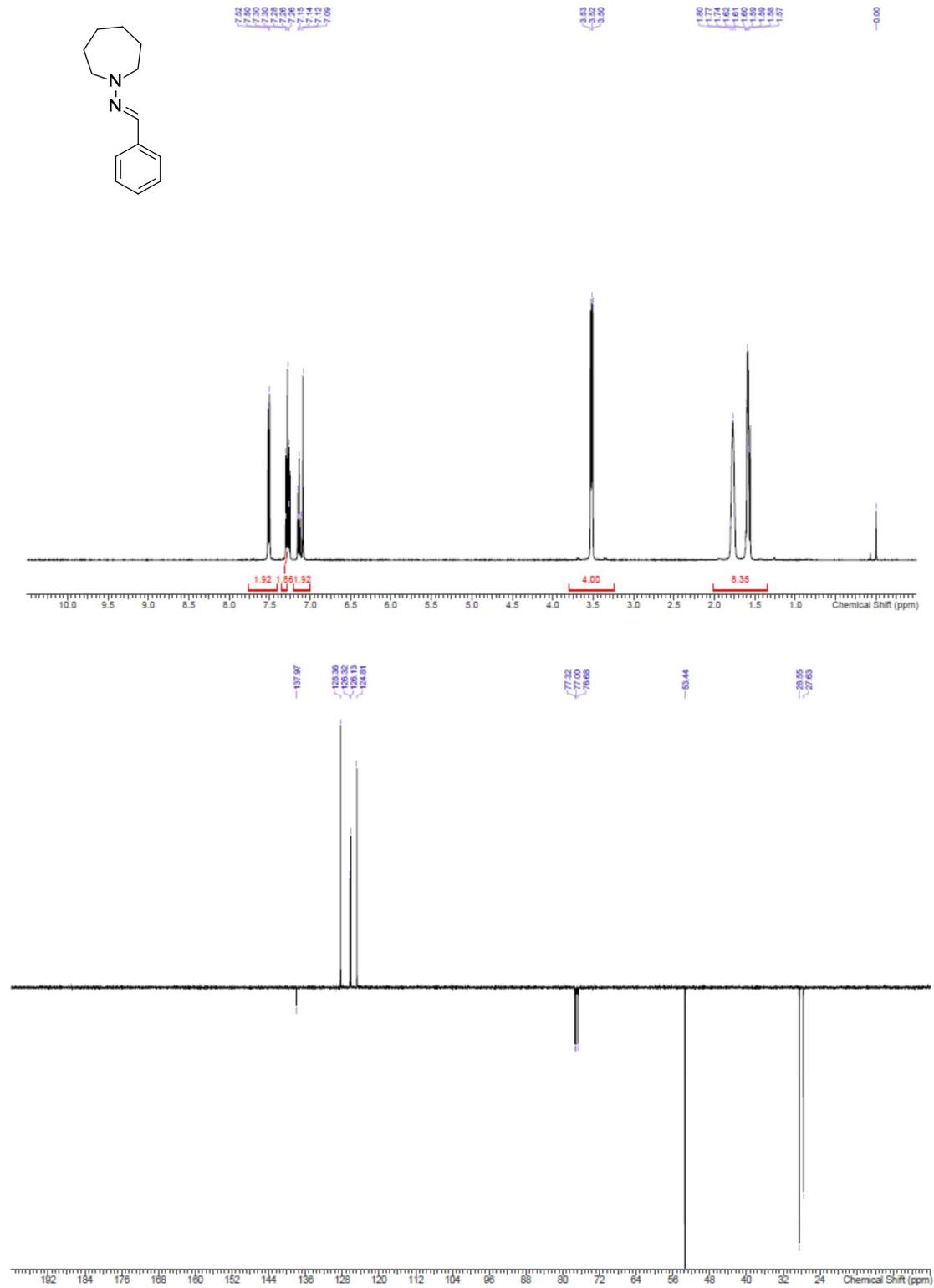
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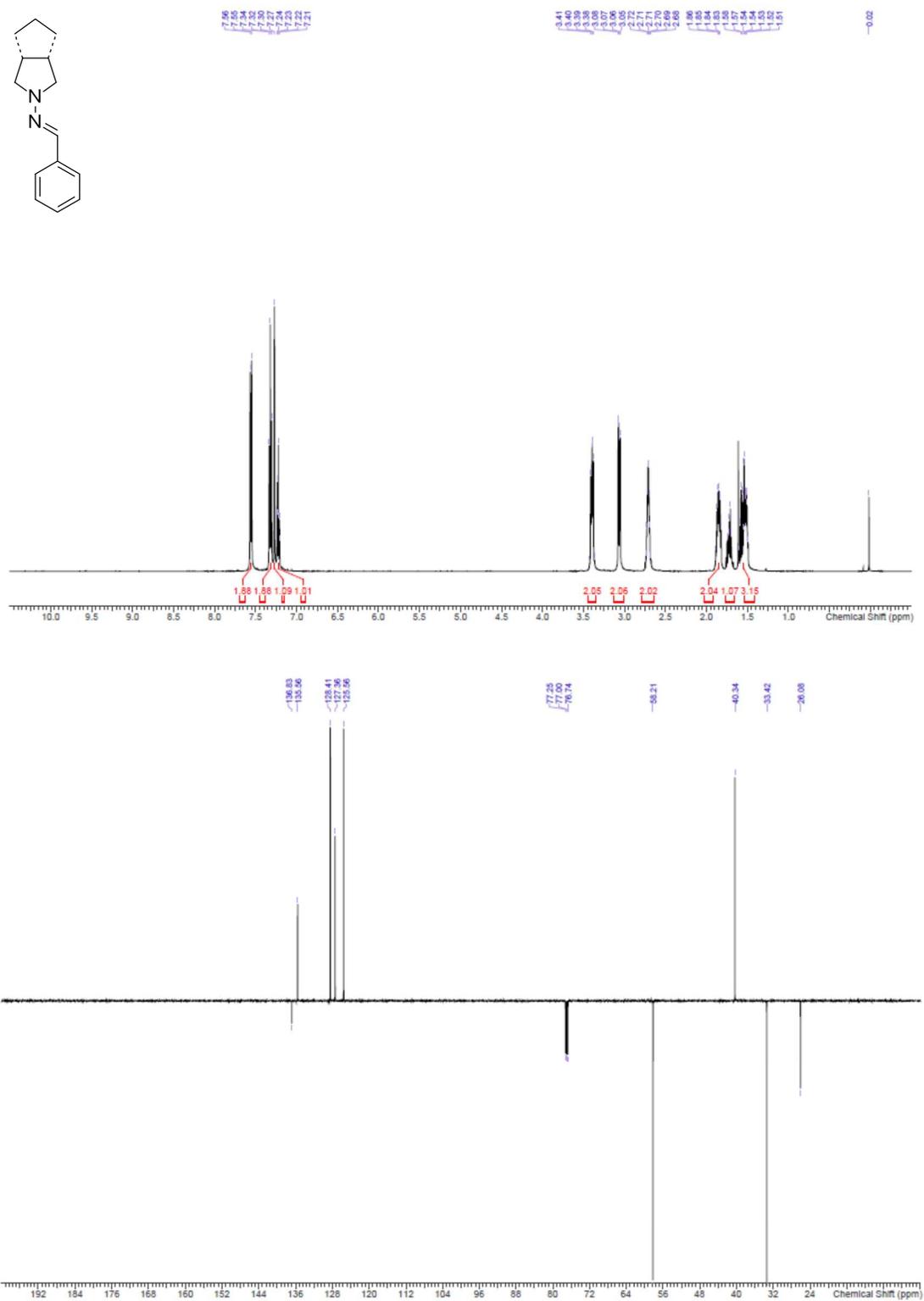
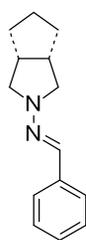
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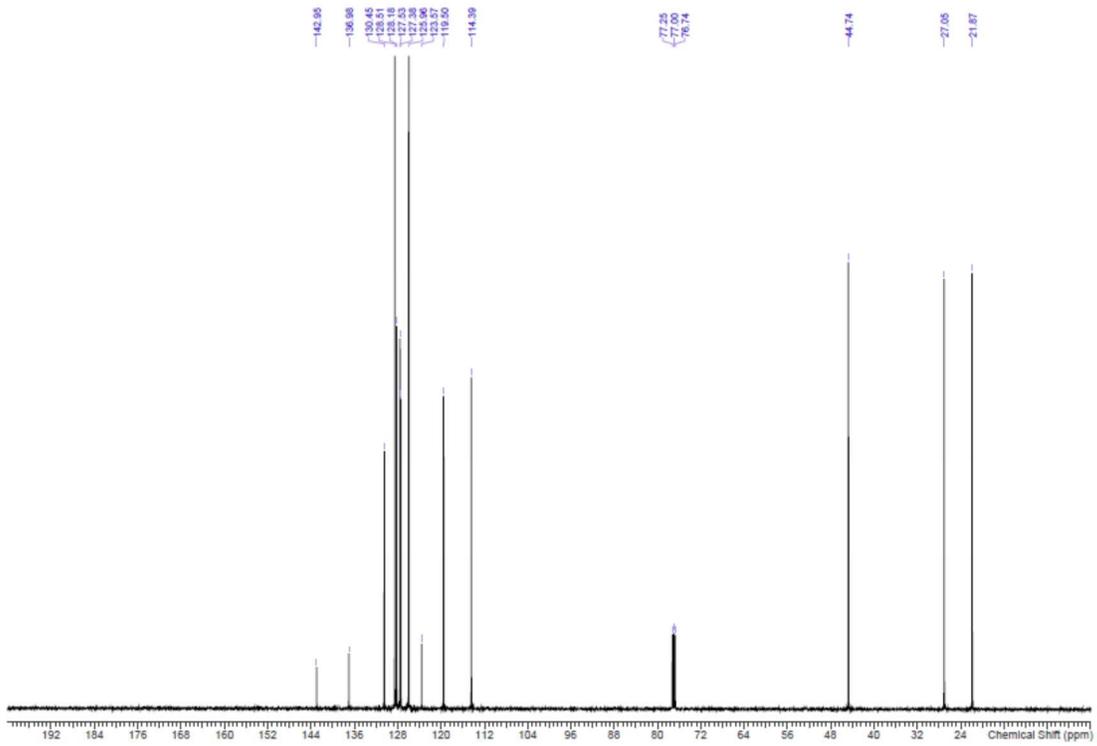
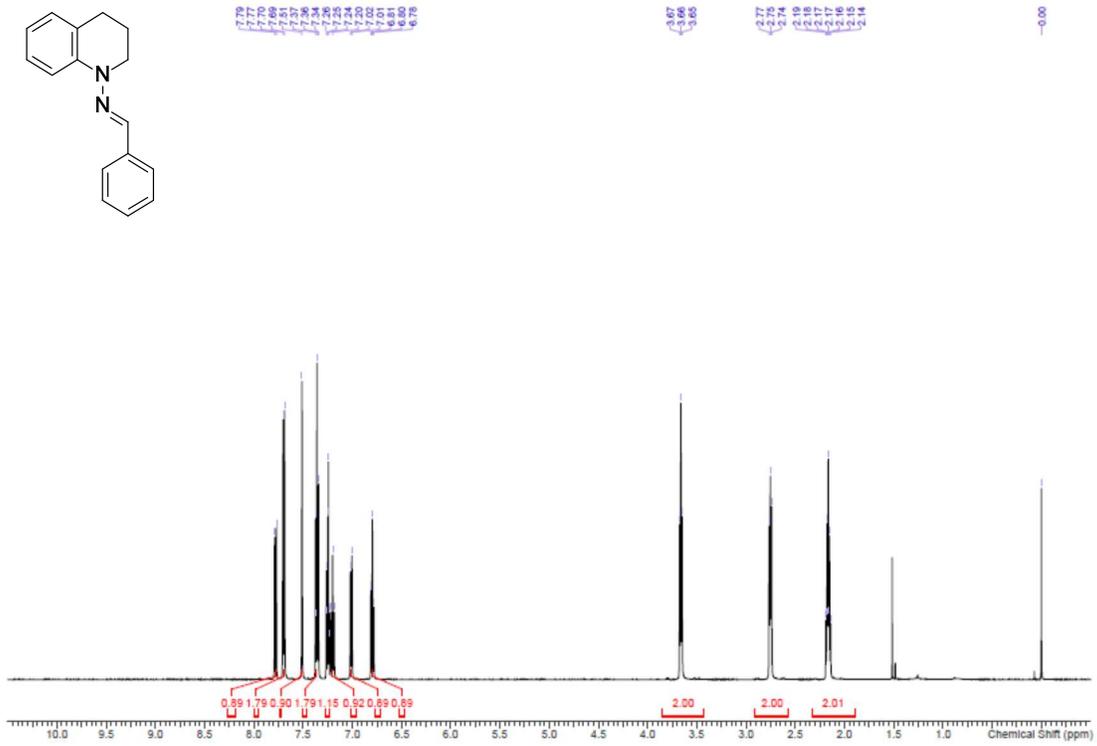
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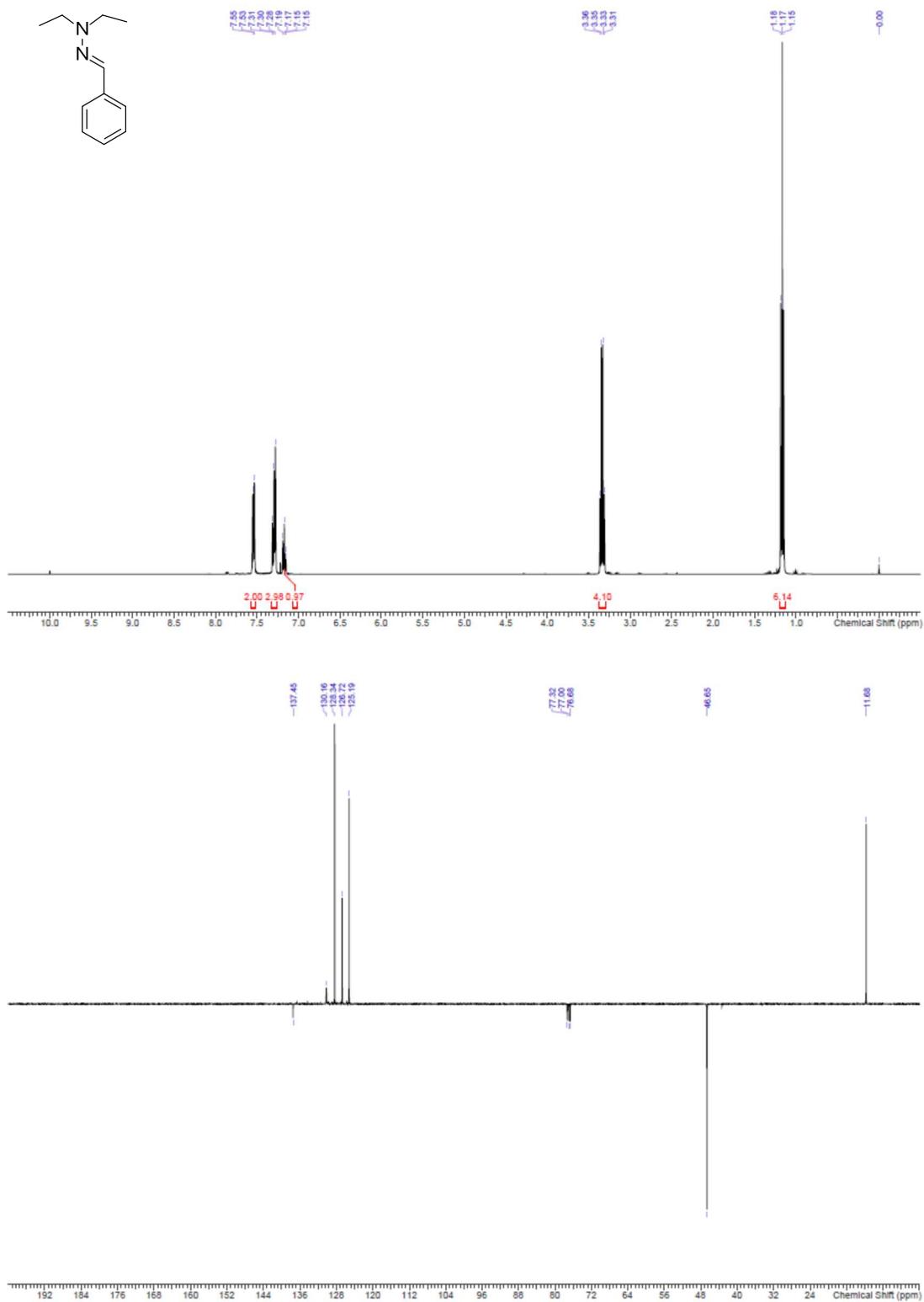
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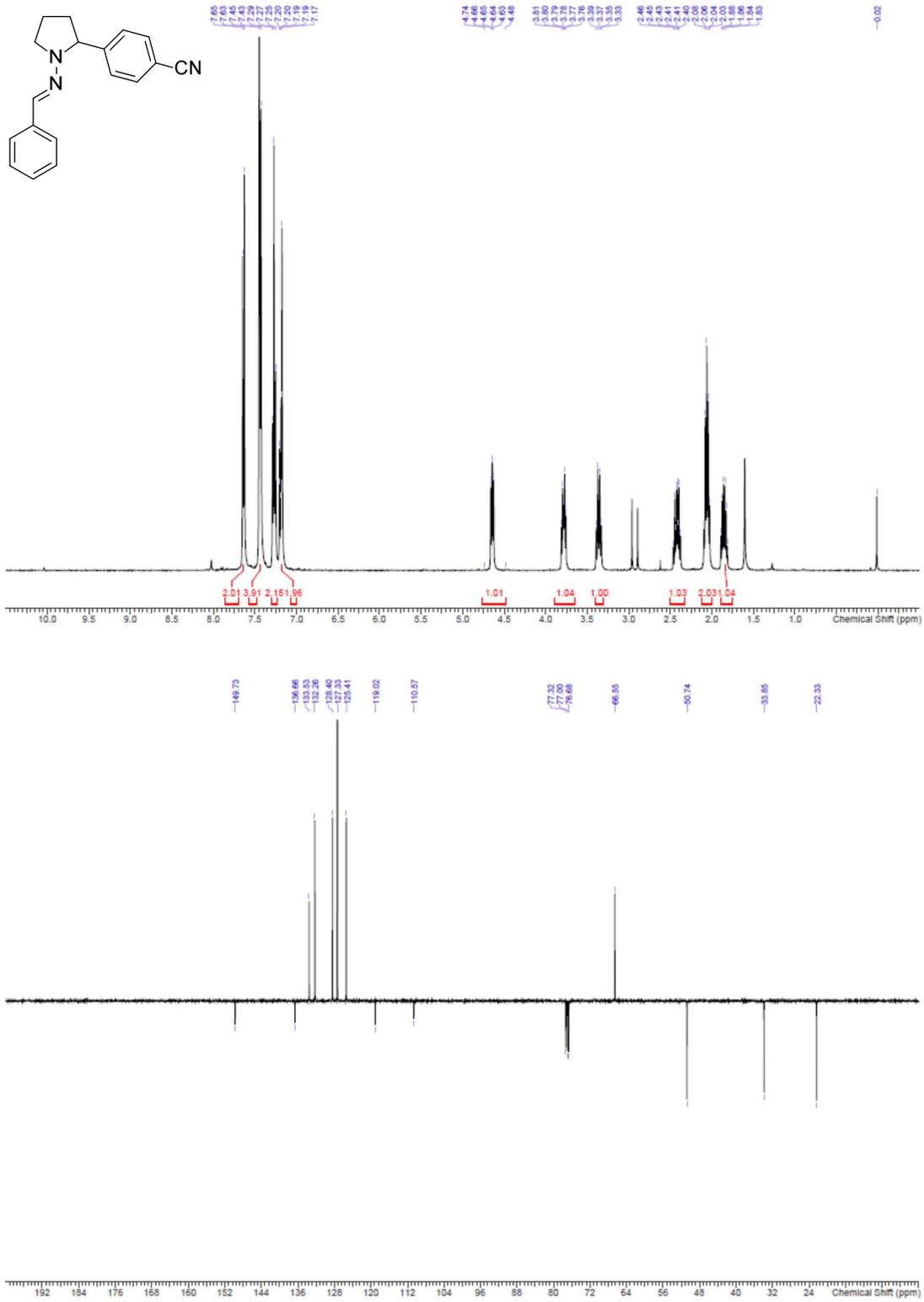
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1j

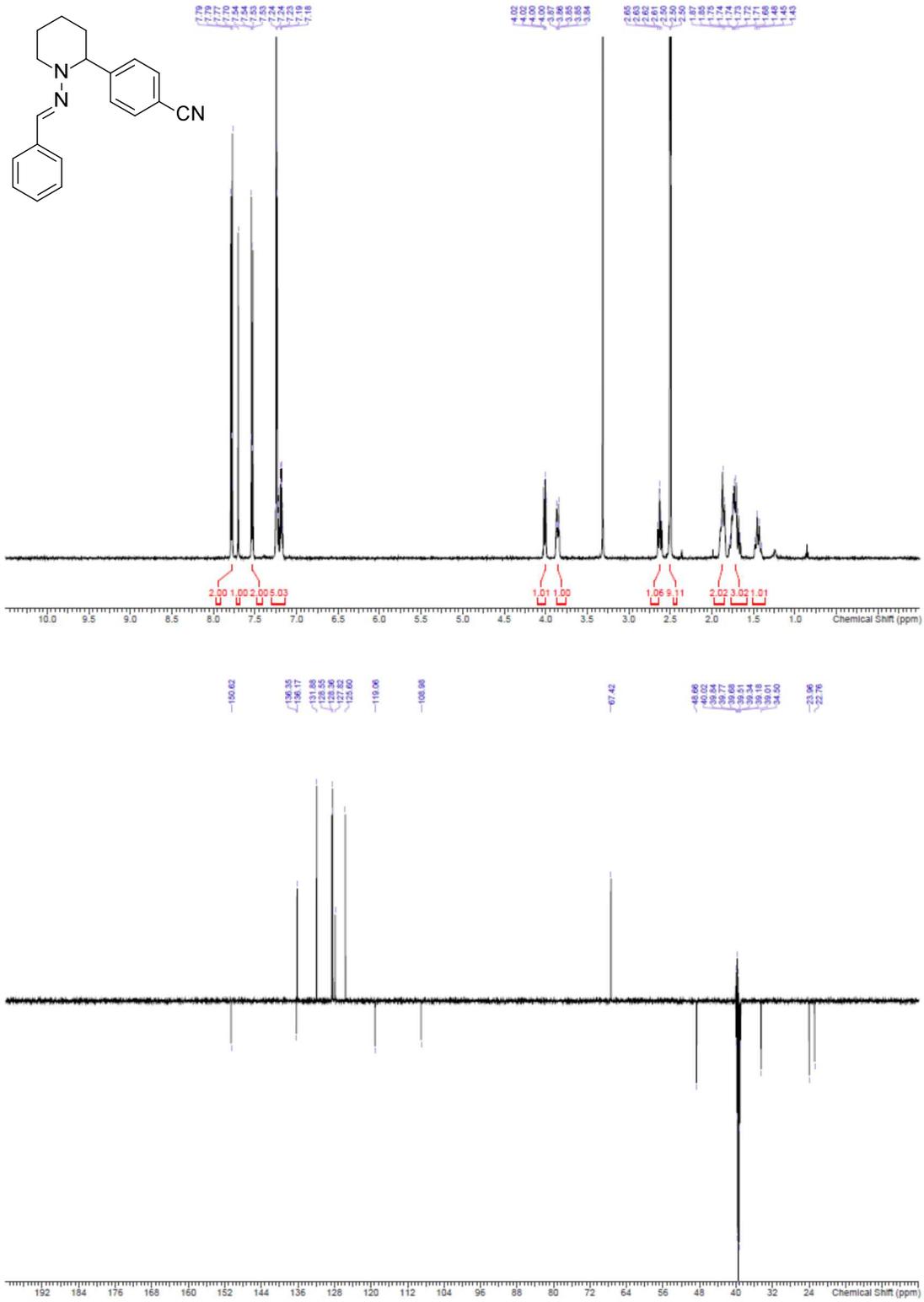


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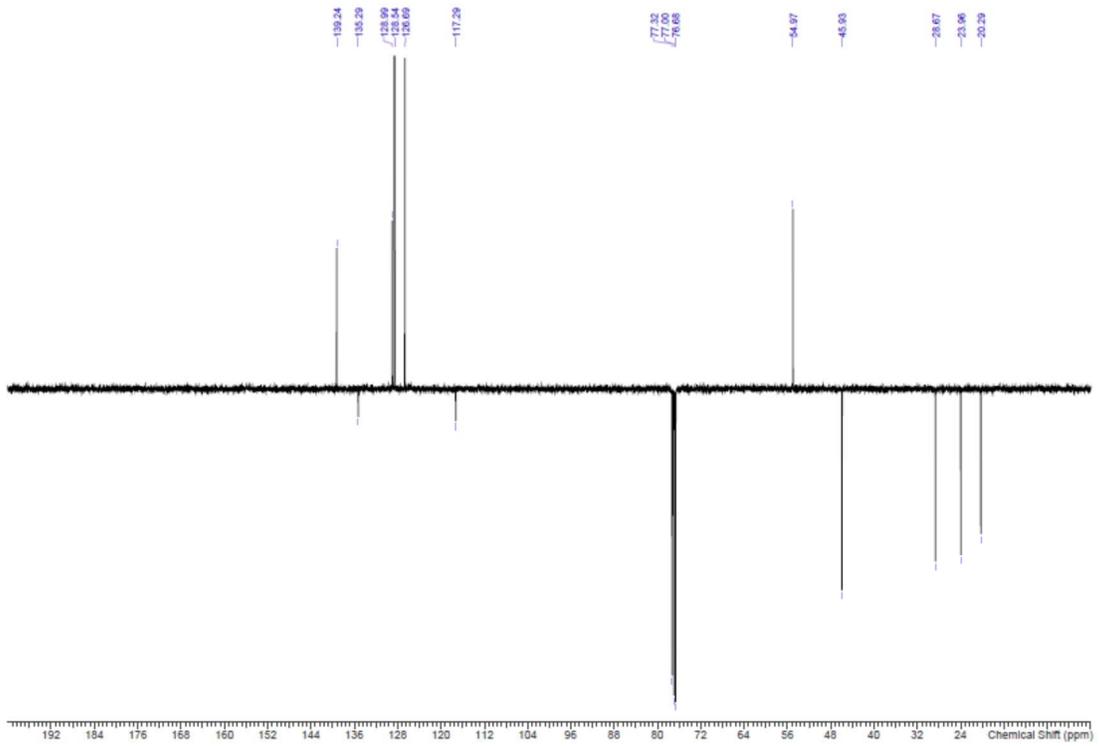
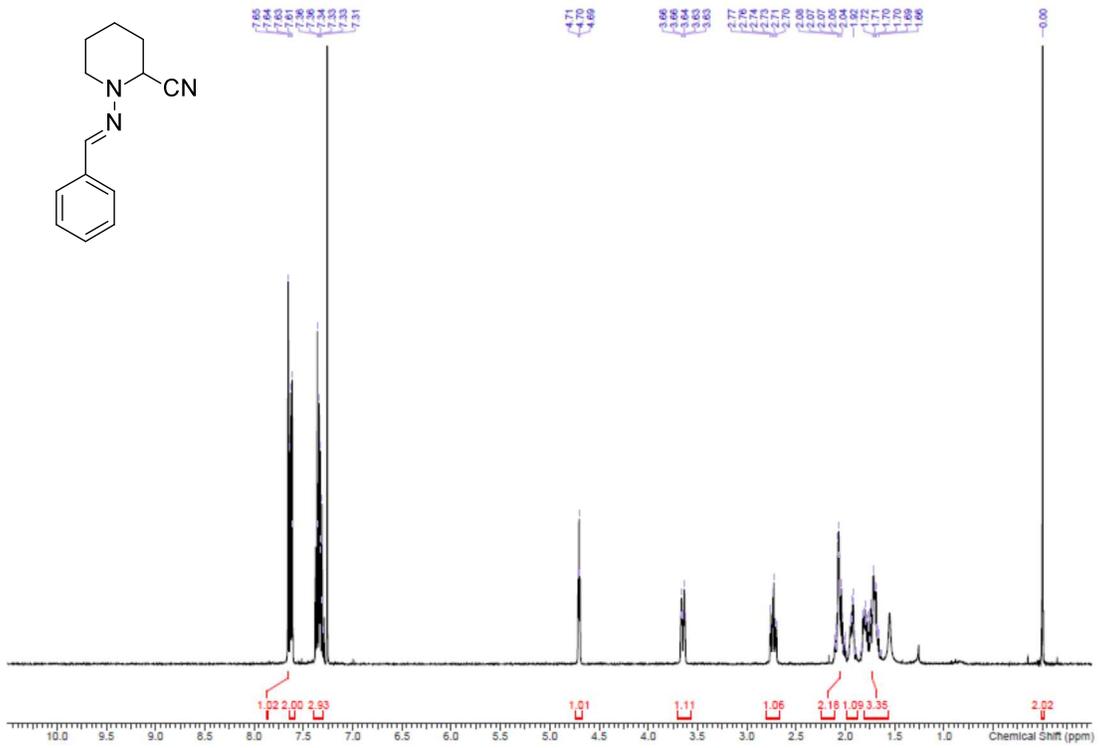




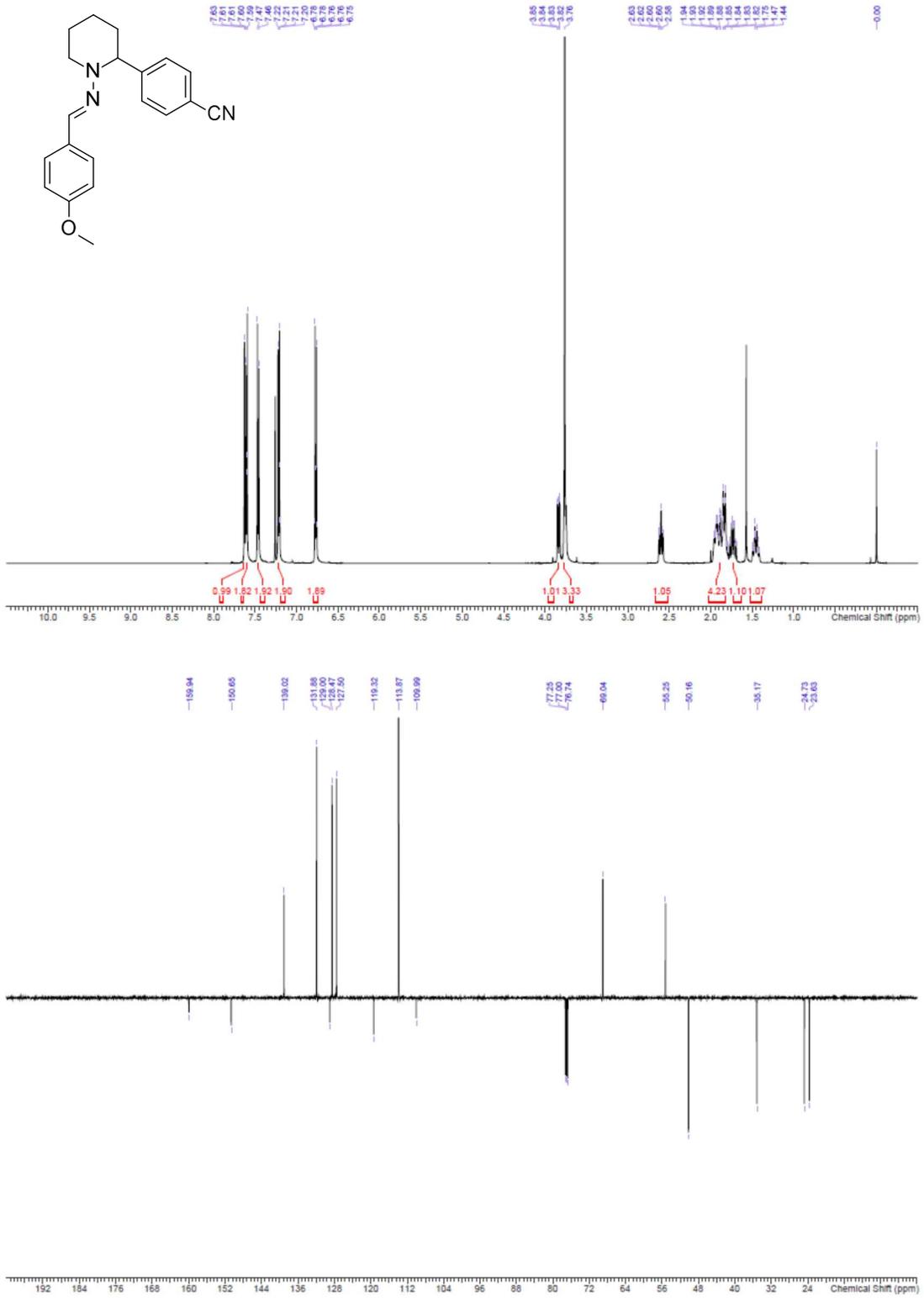
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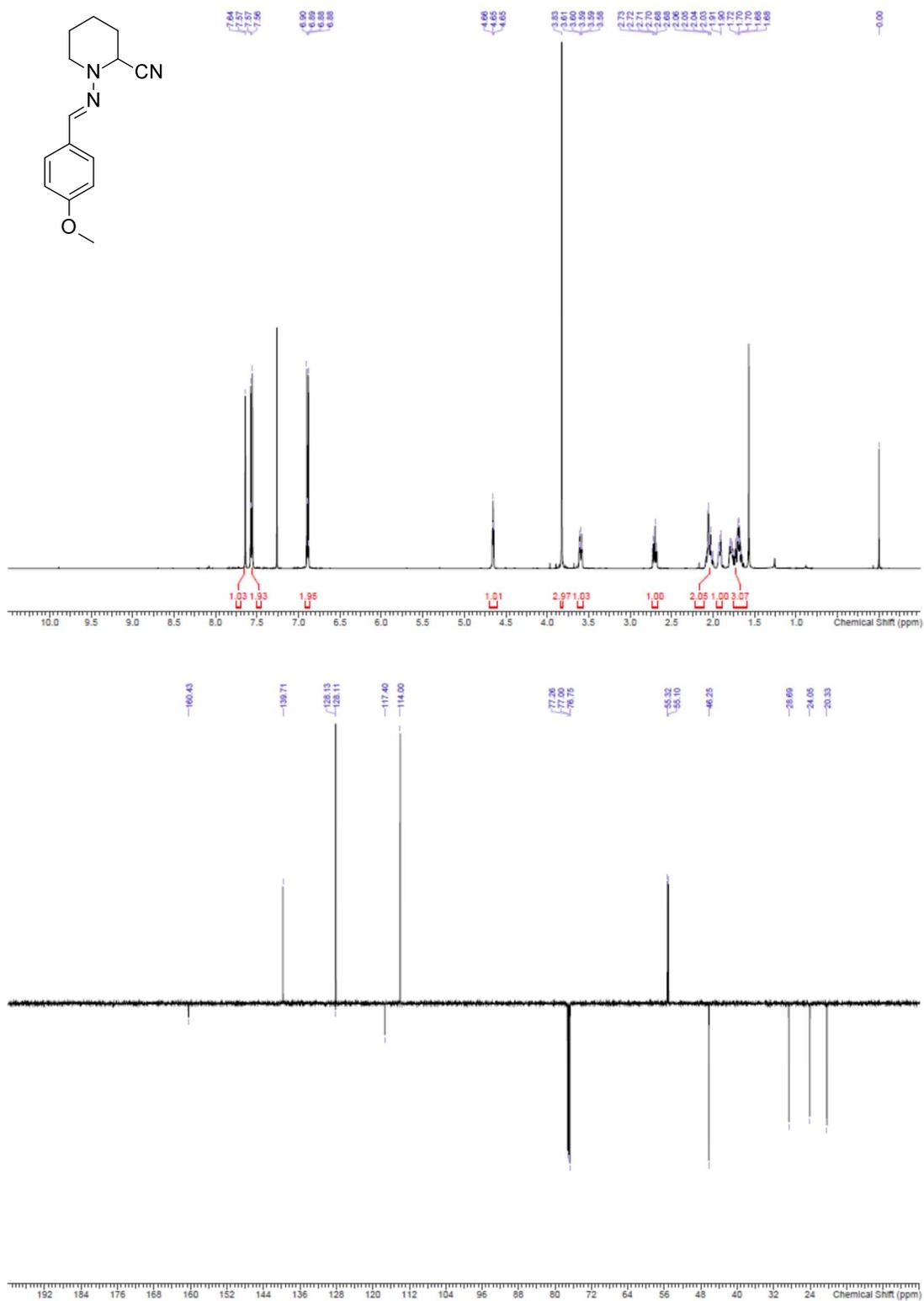
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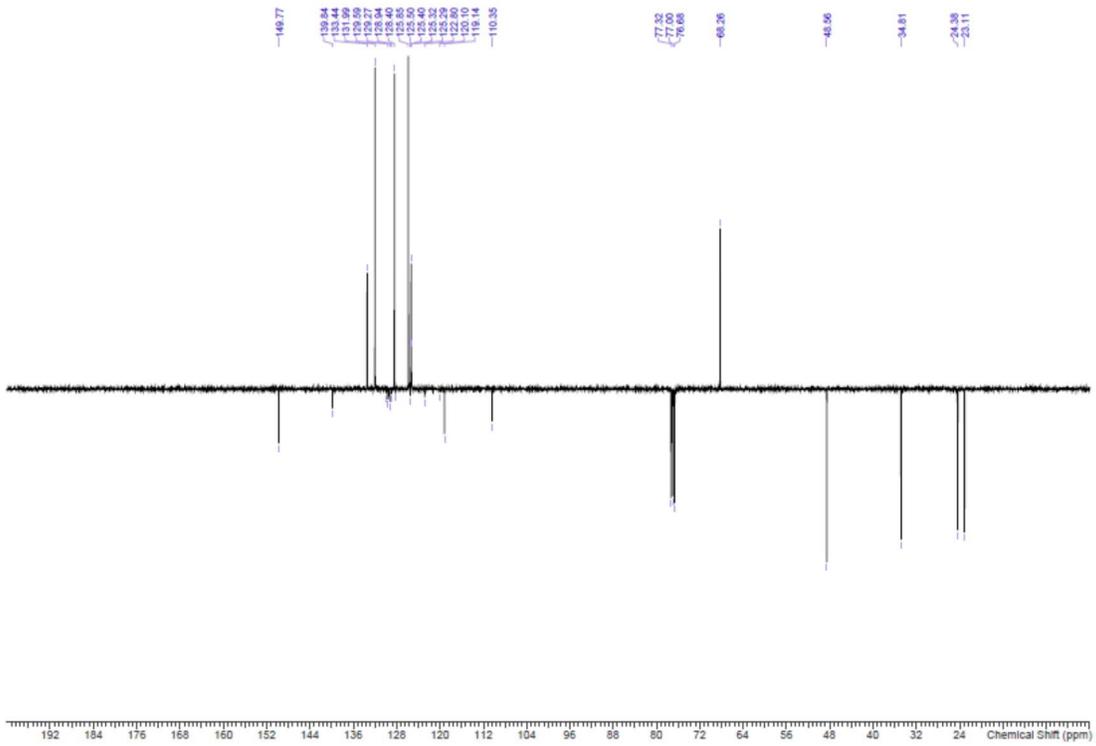
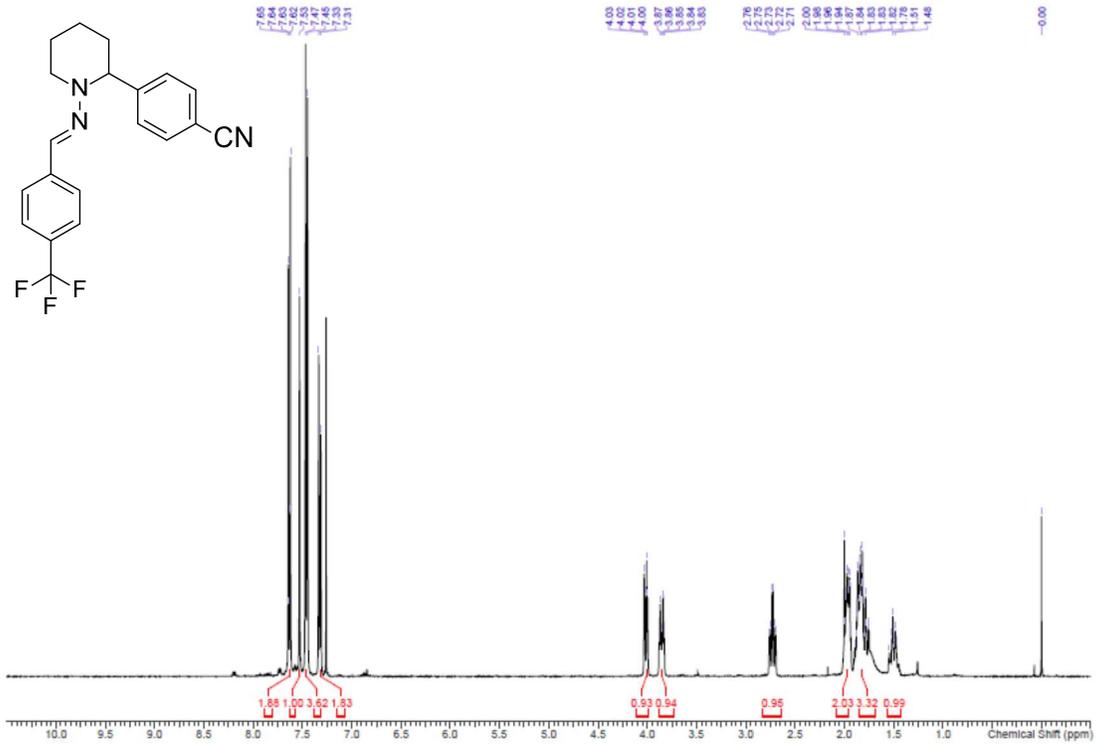
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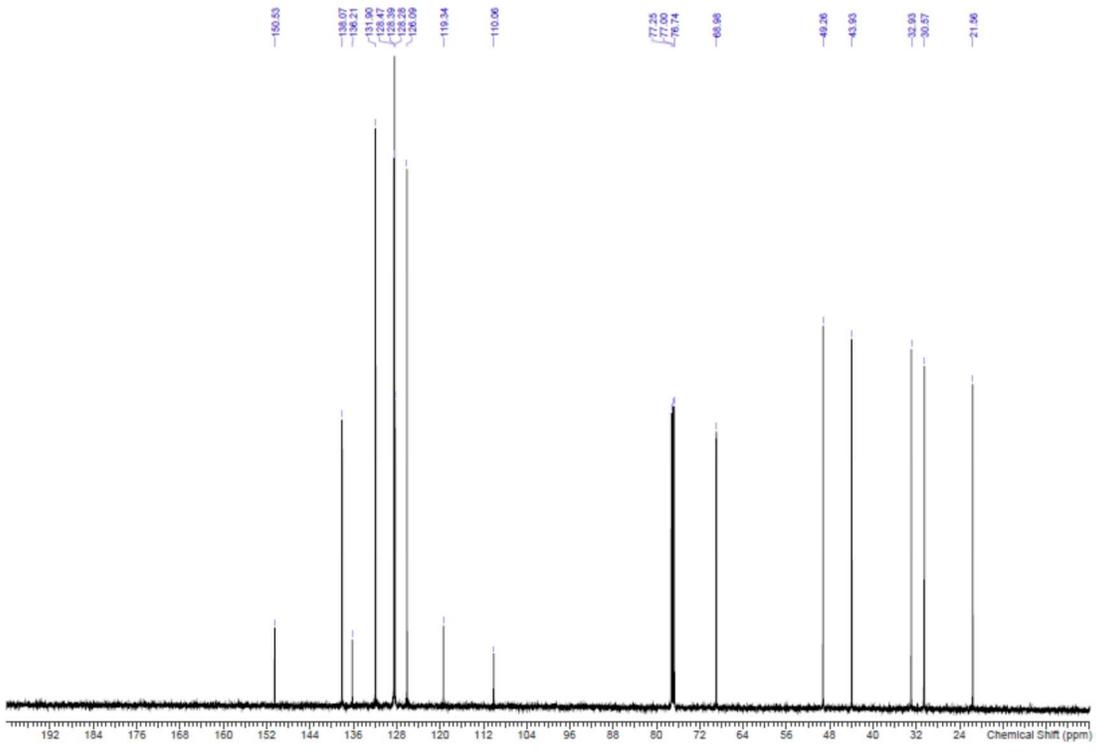
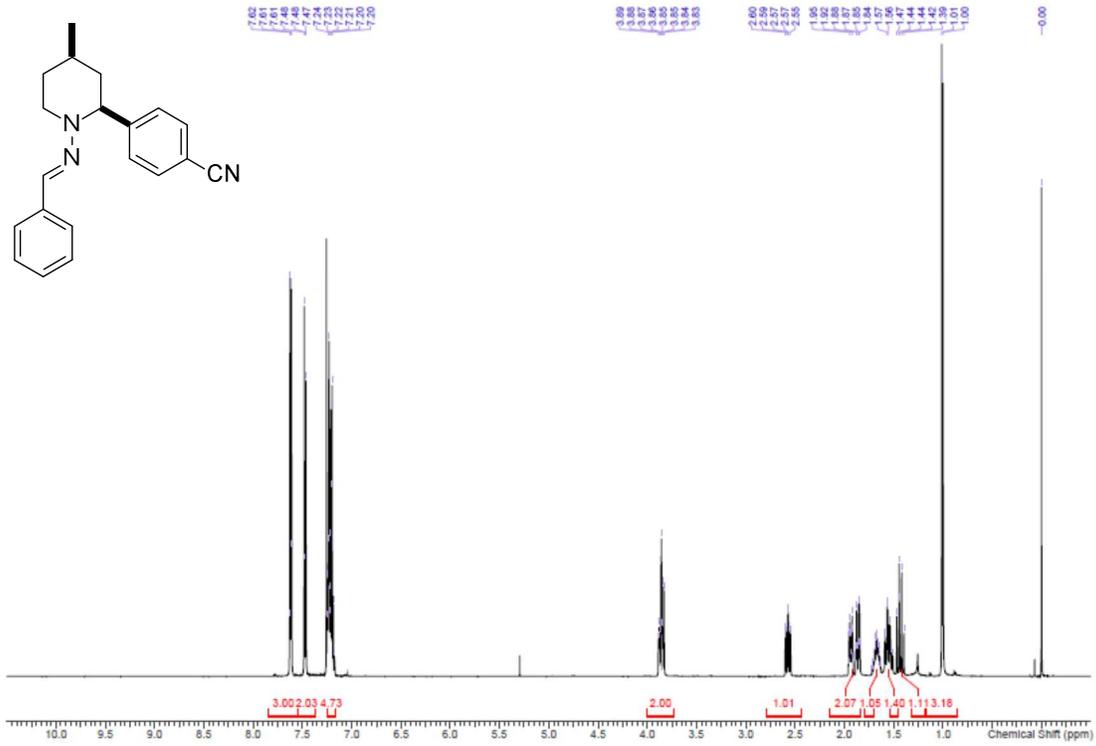


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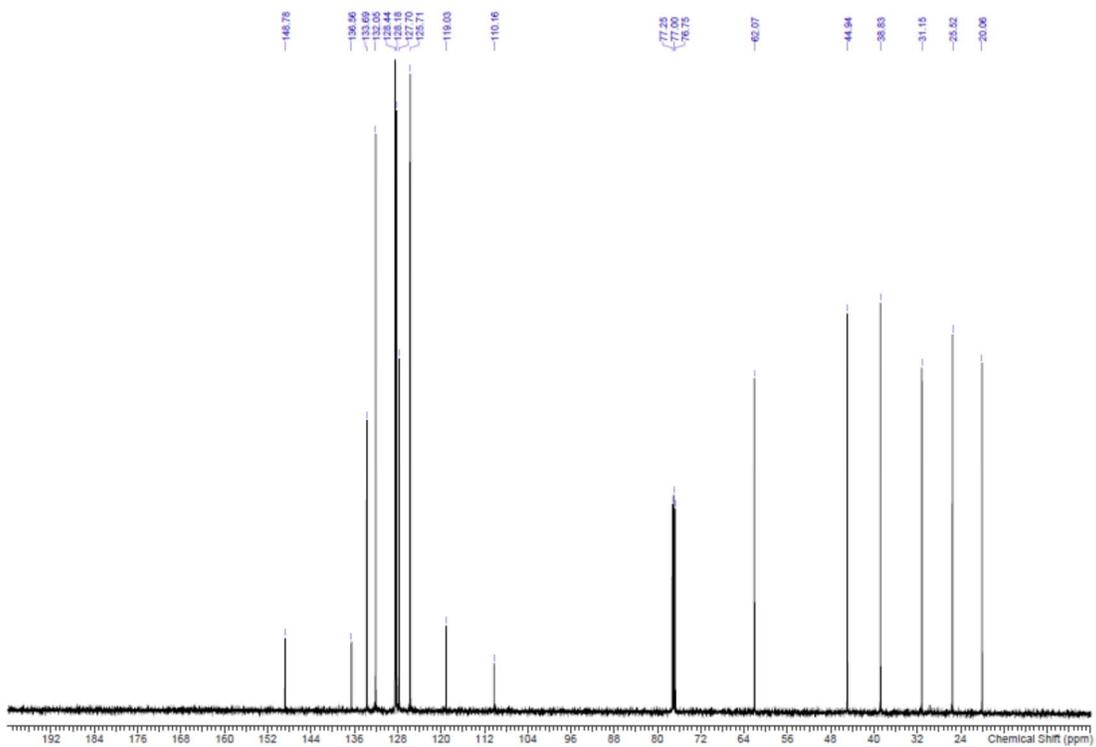
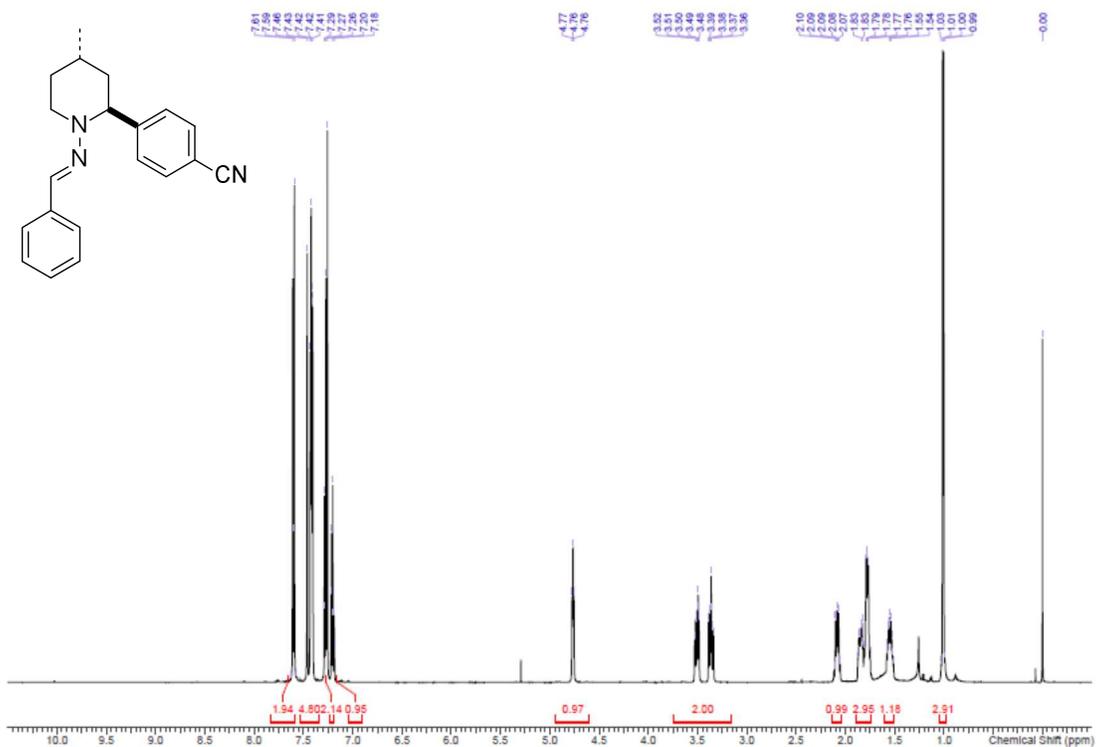




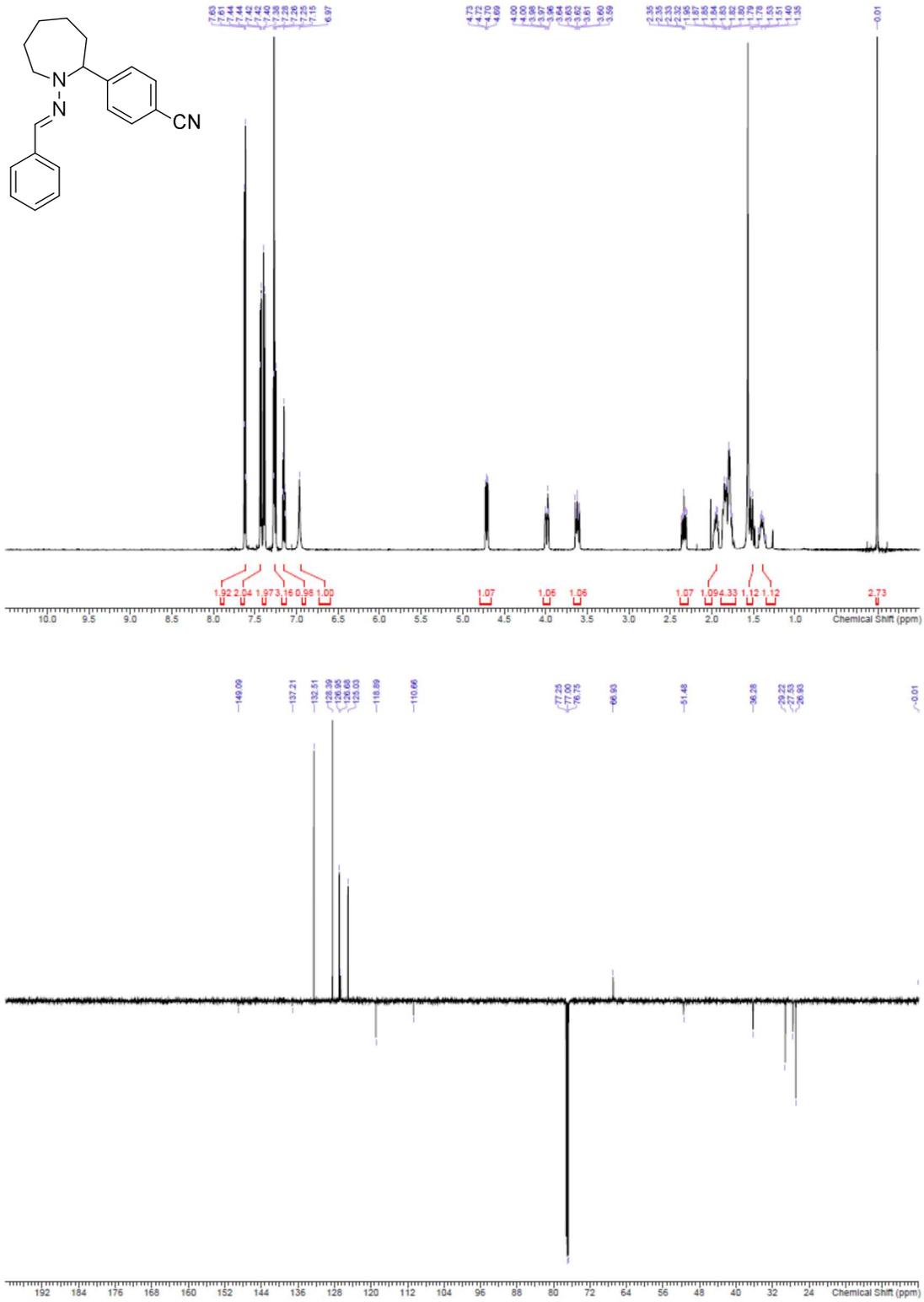
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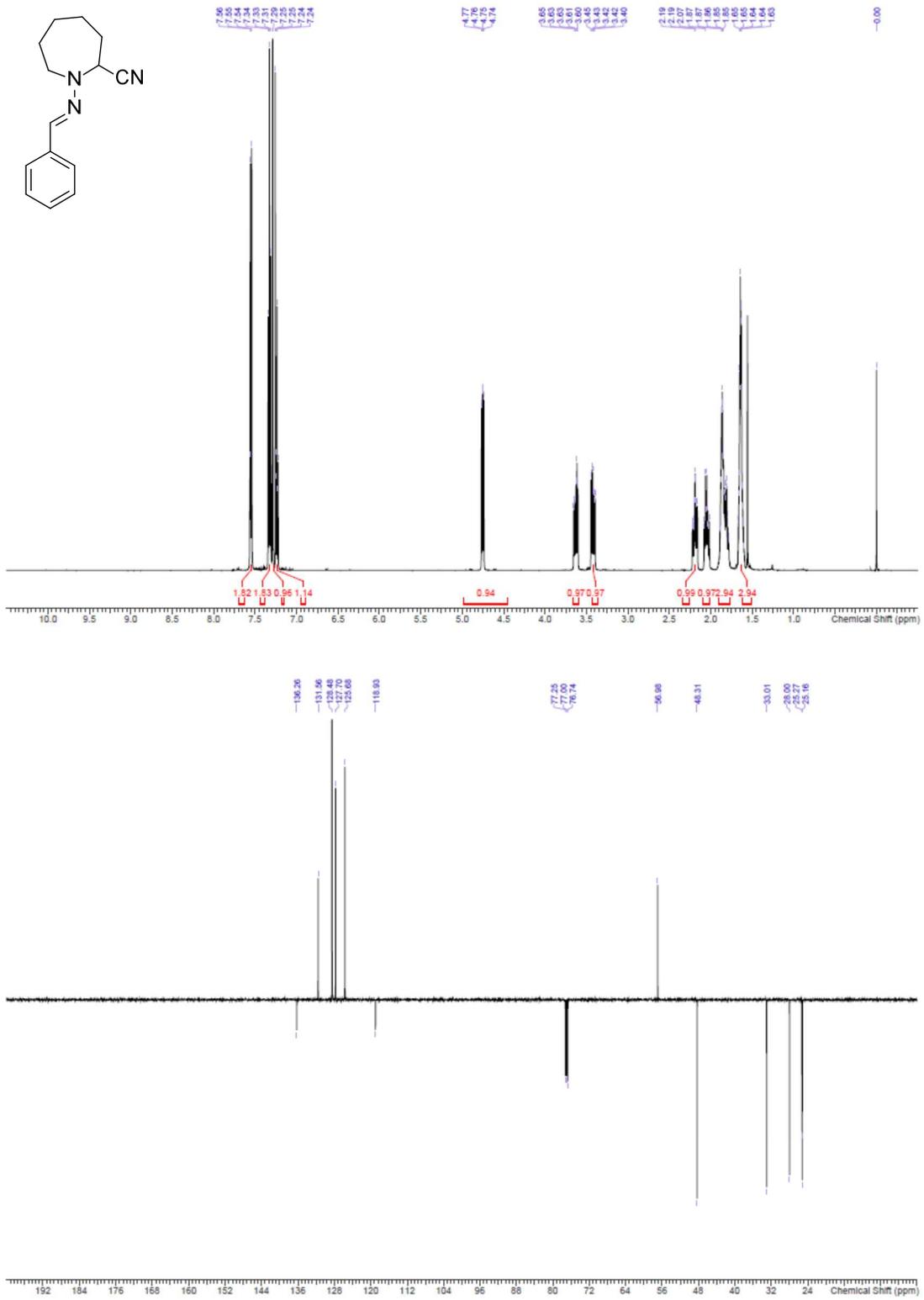
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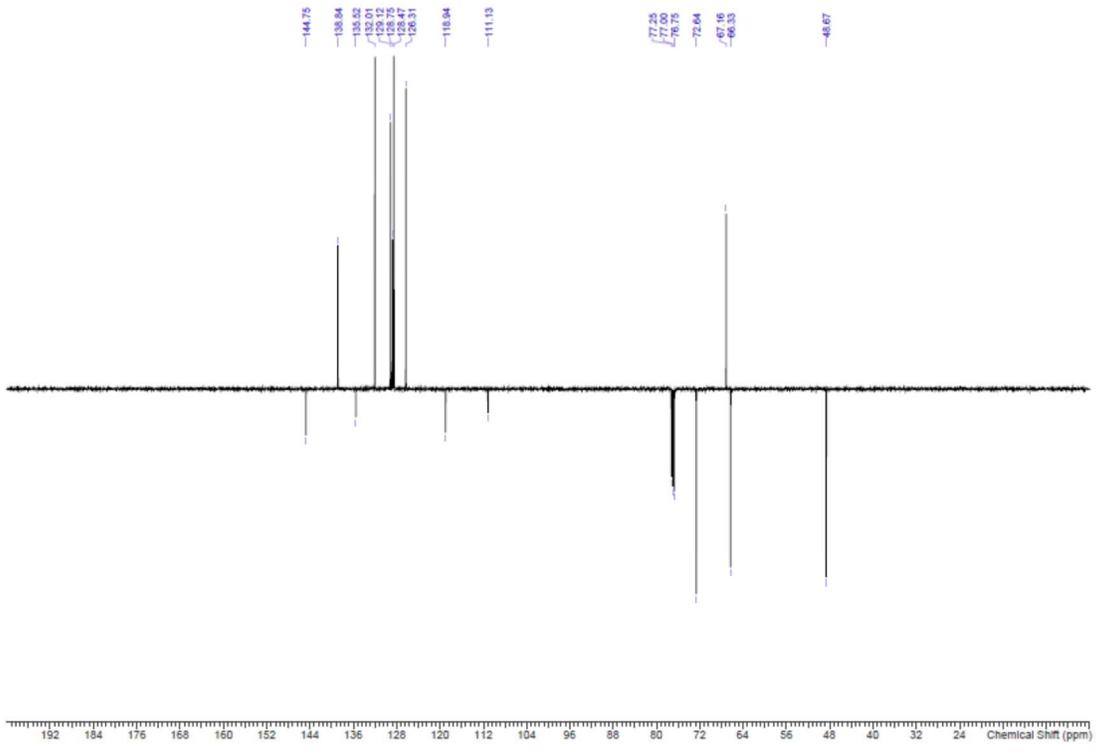
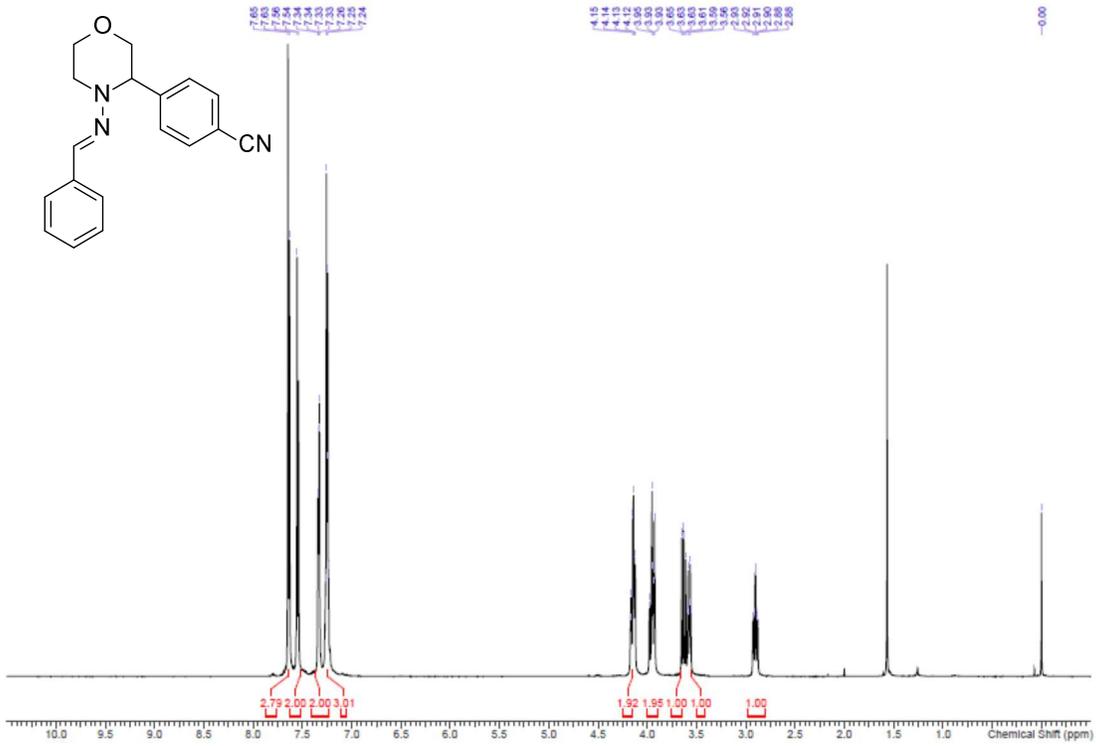
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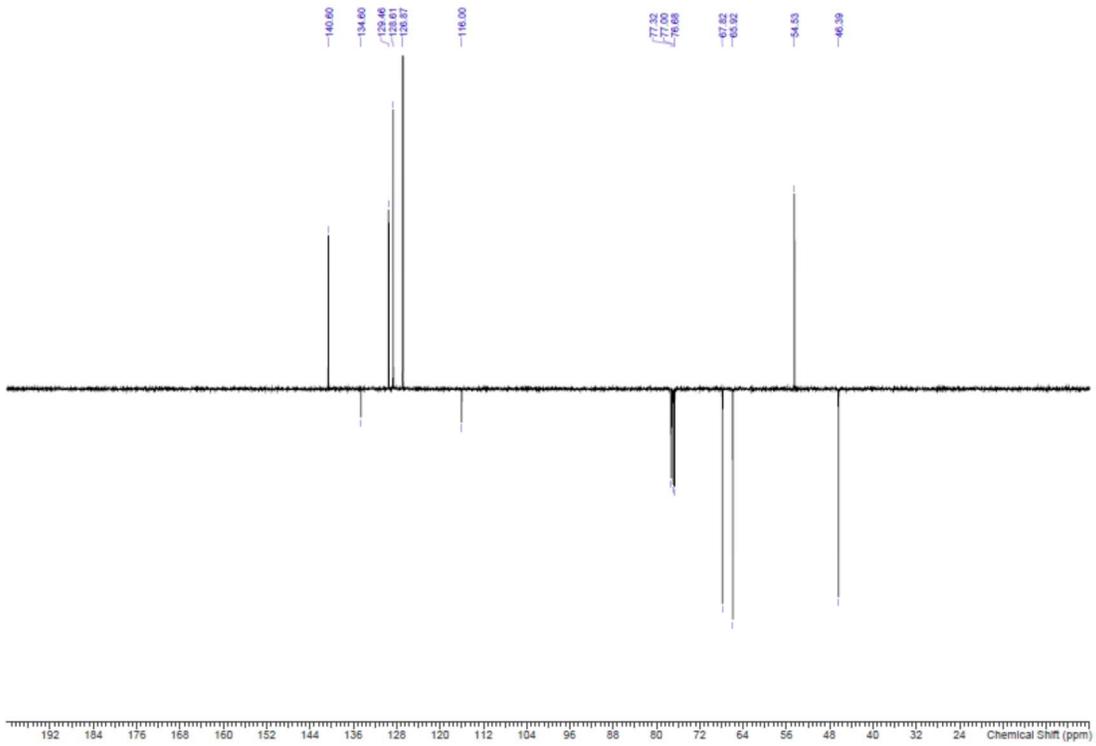
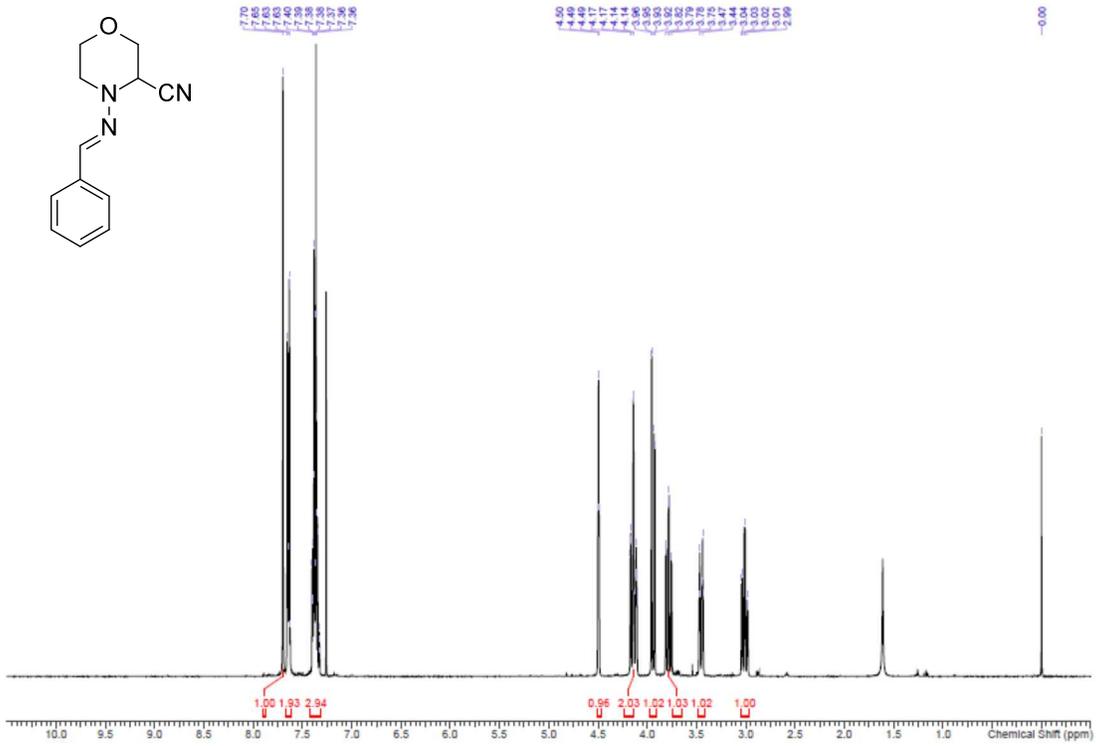
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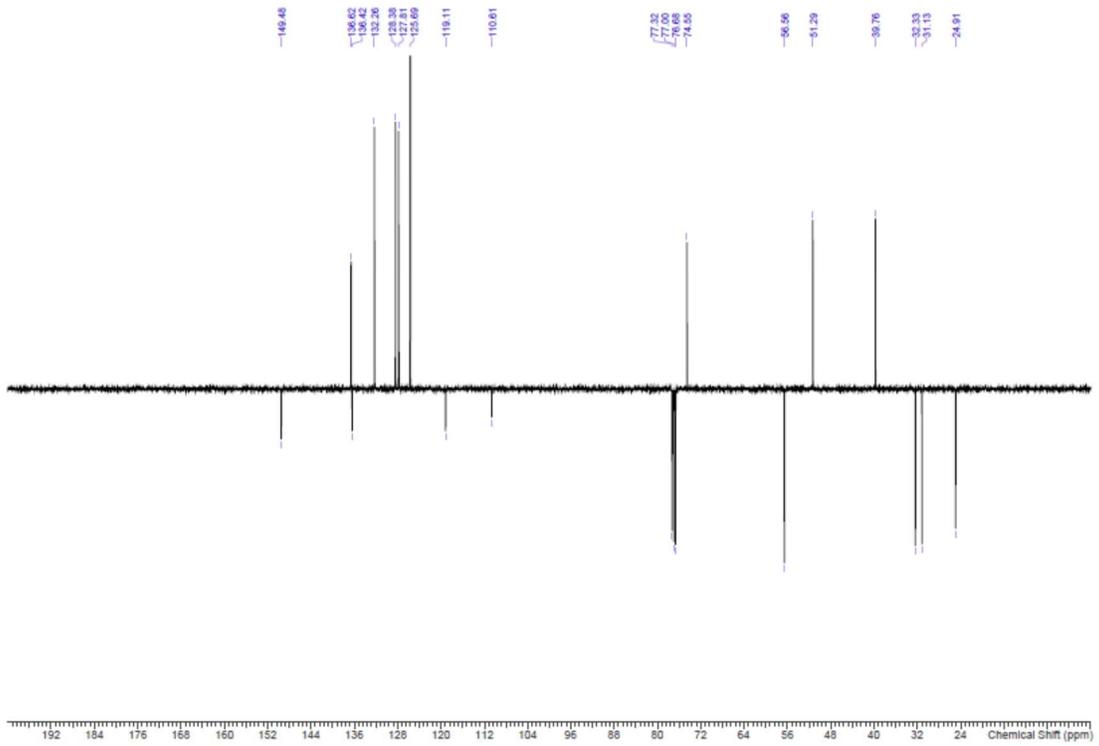
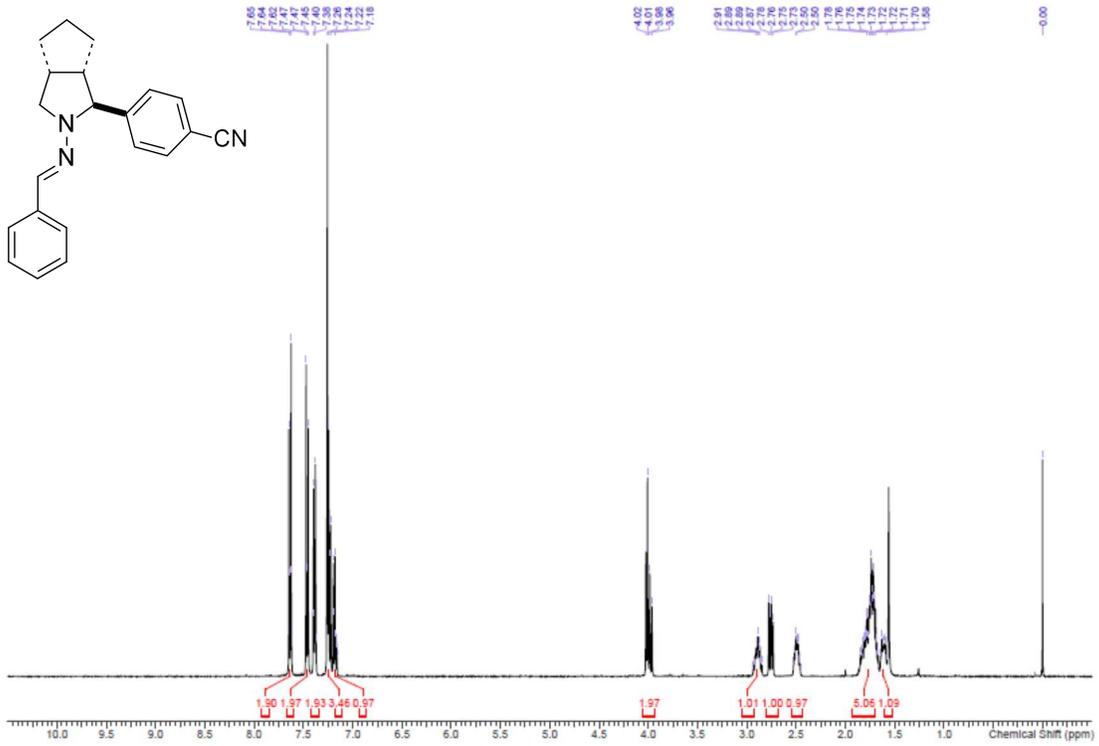
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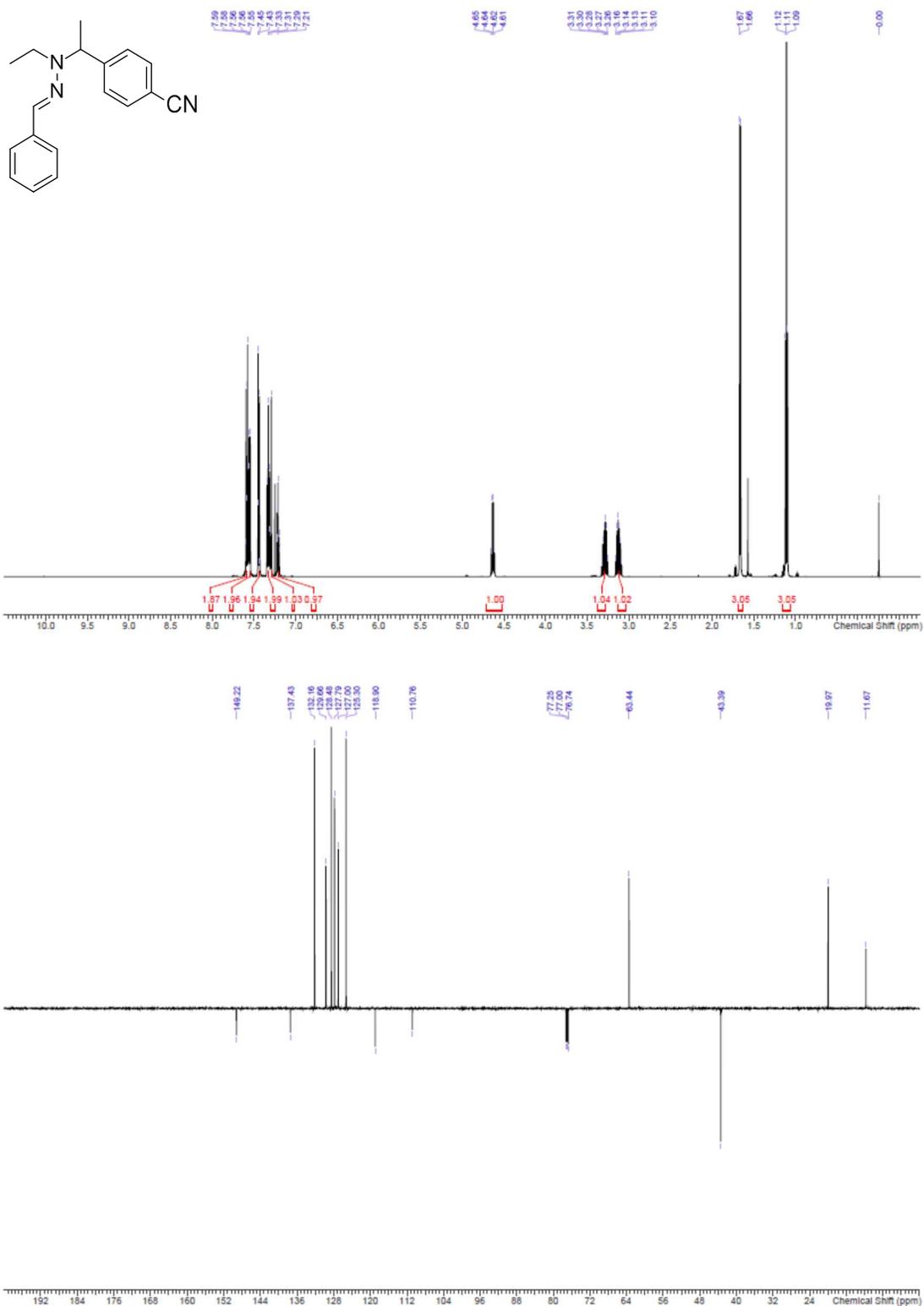
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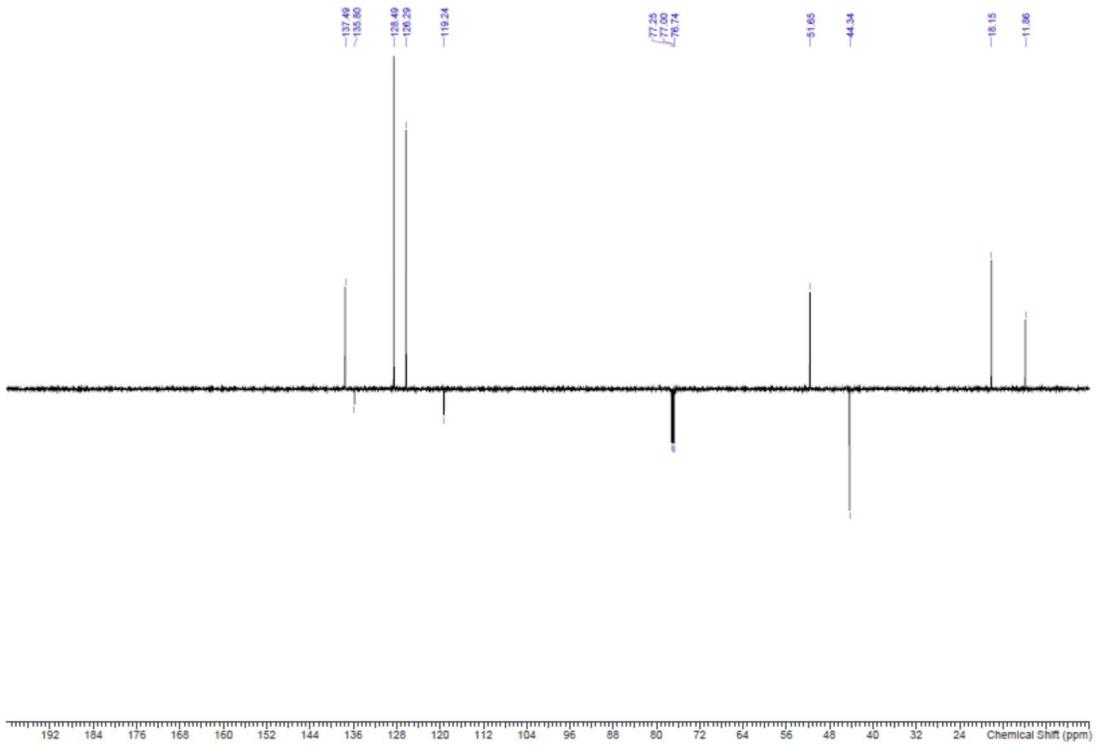
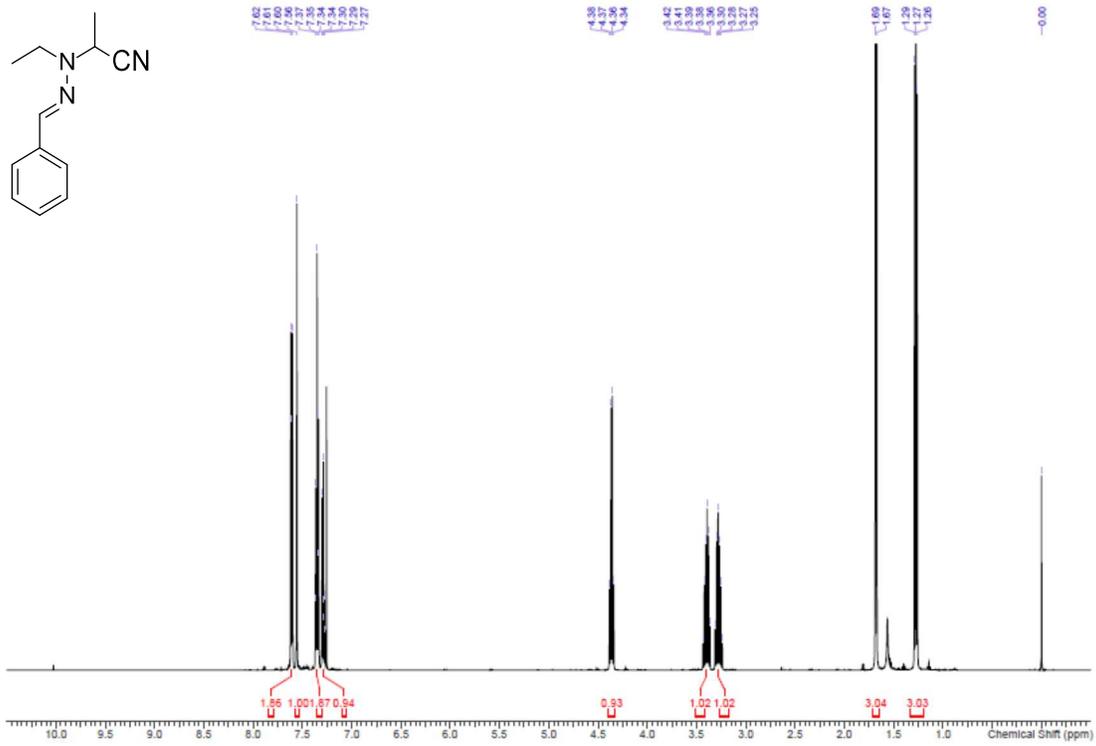
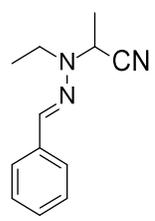
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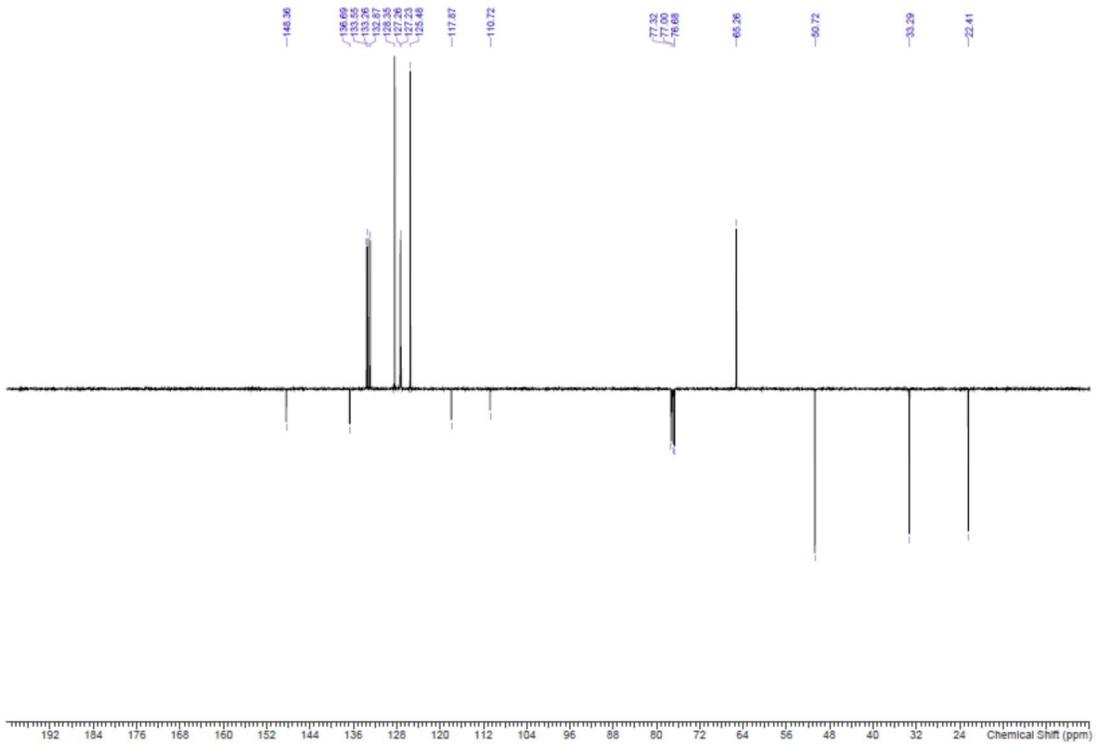
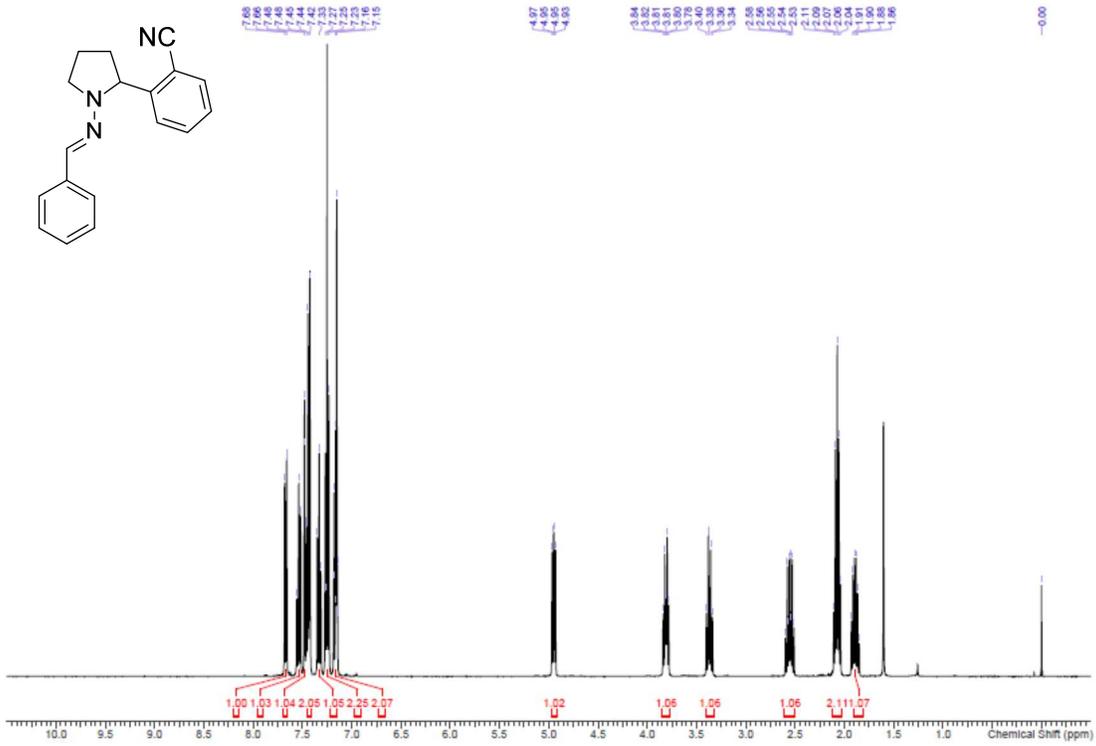
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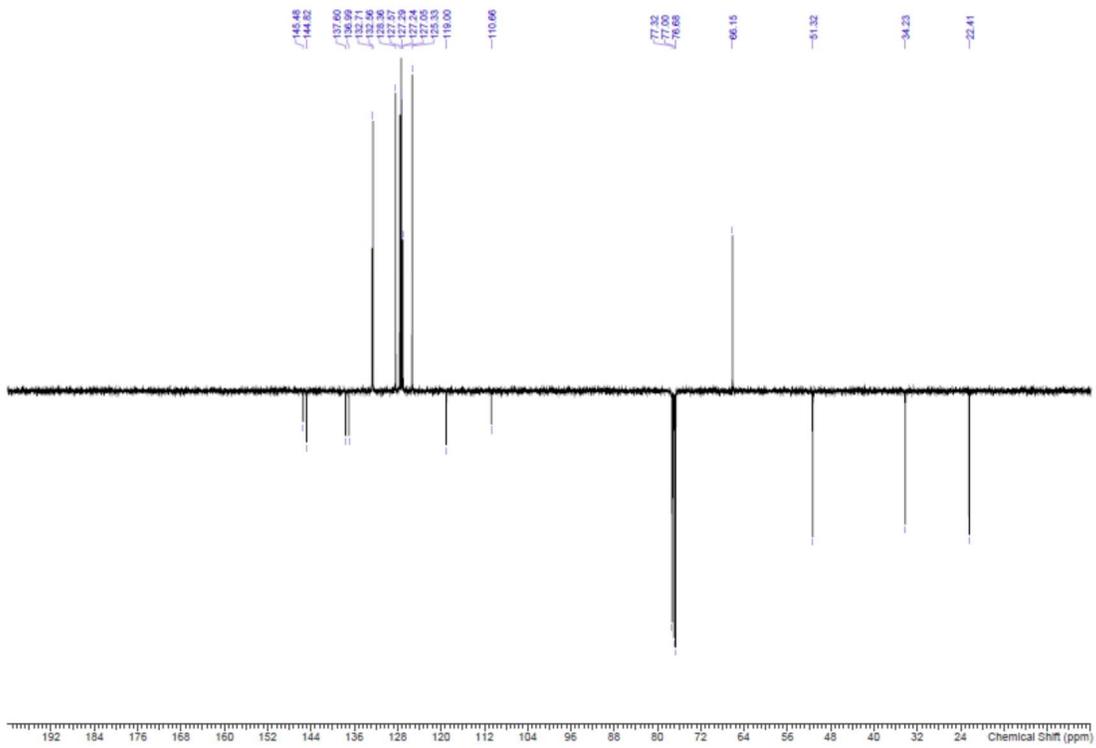
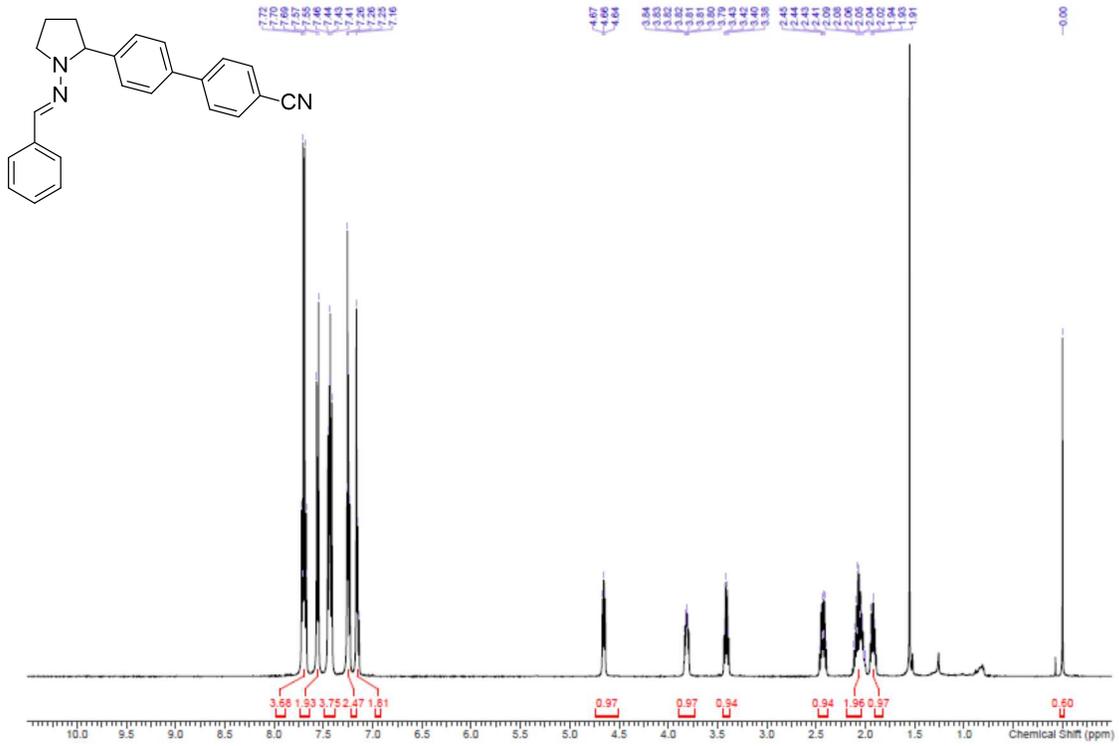
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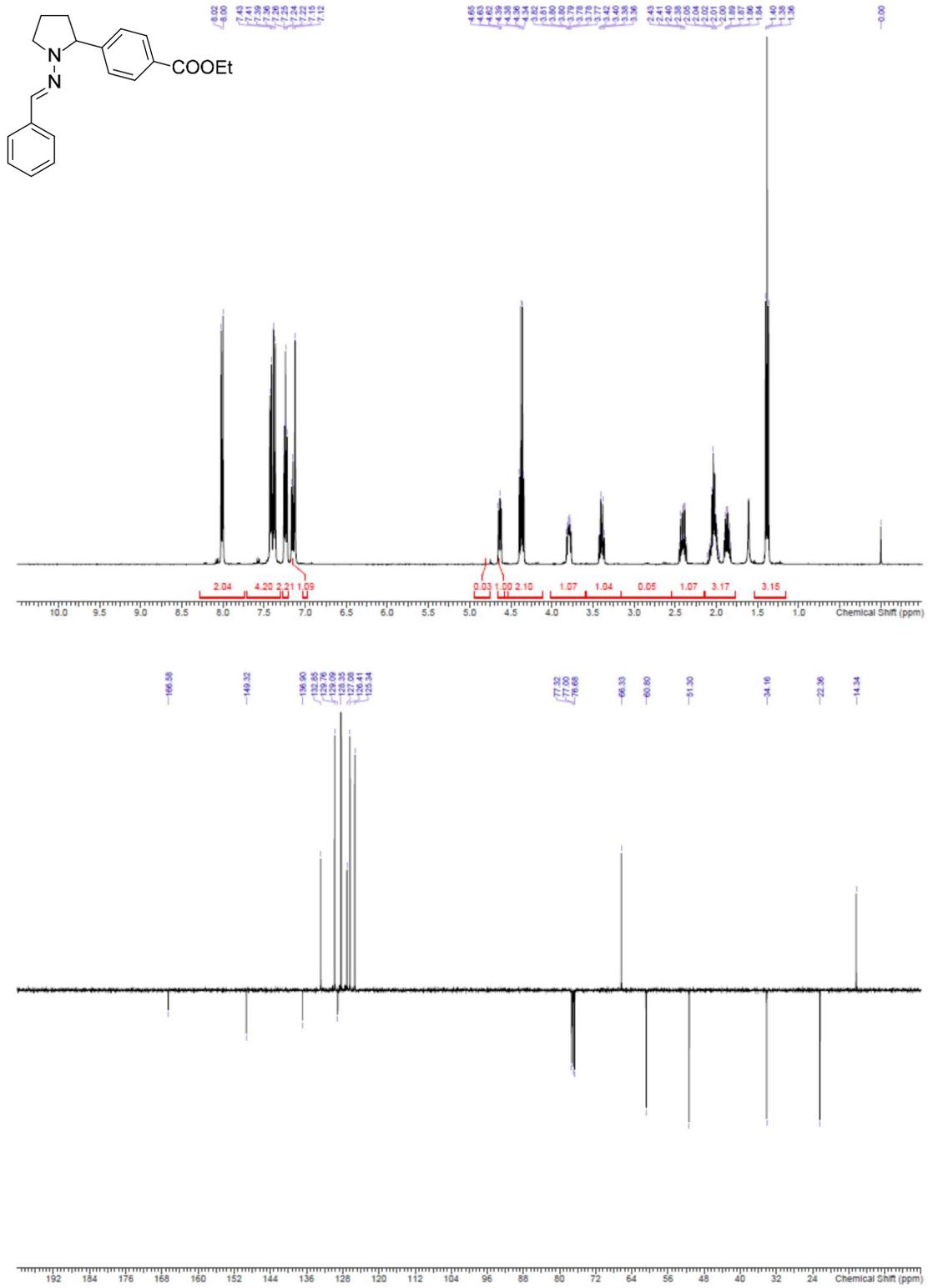
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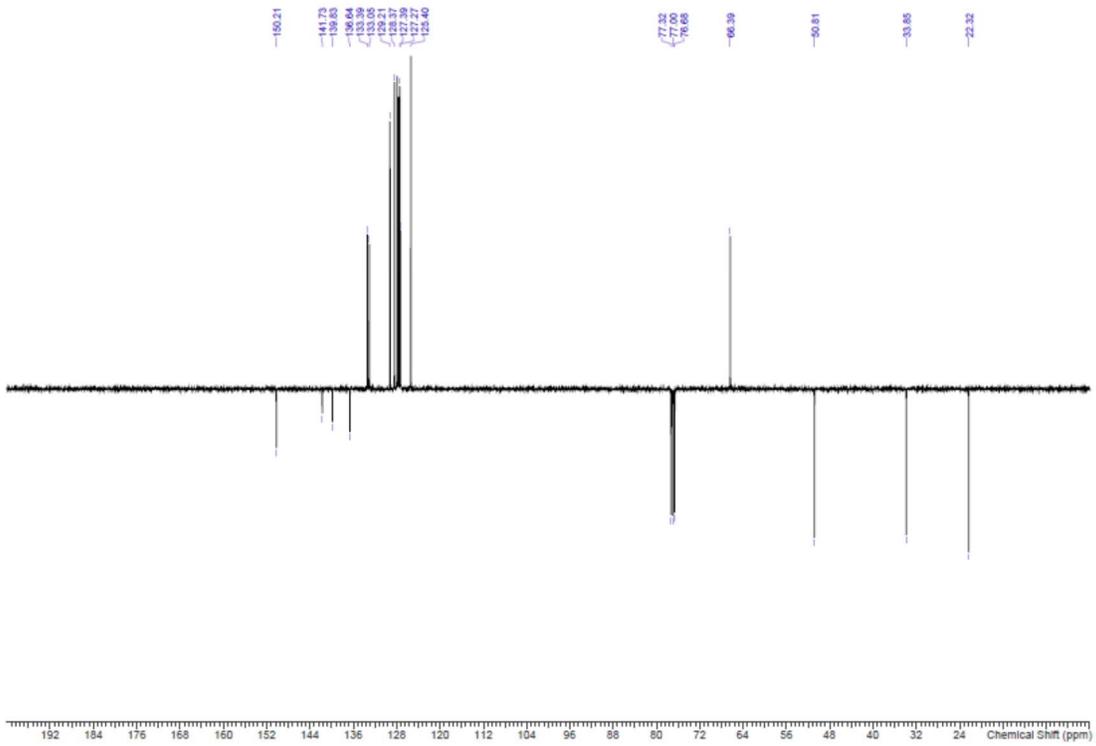
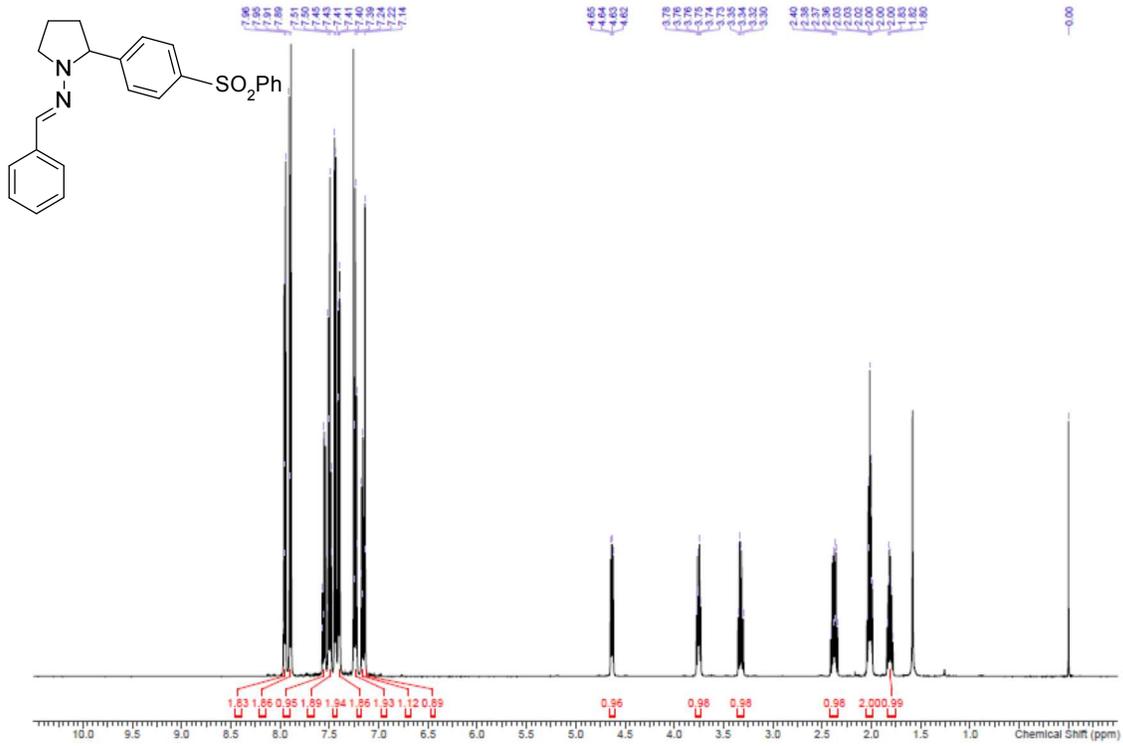
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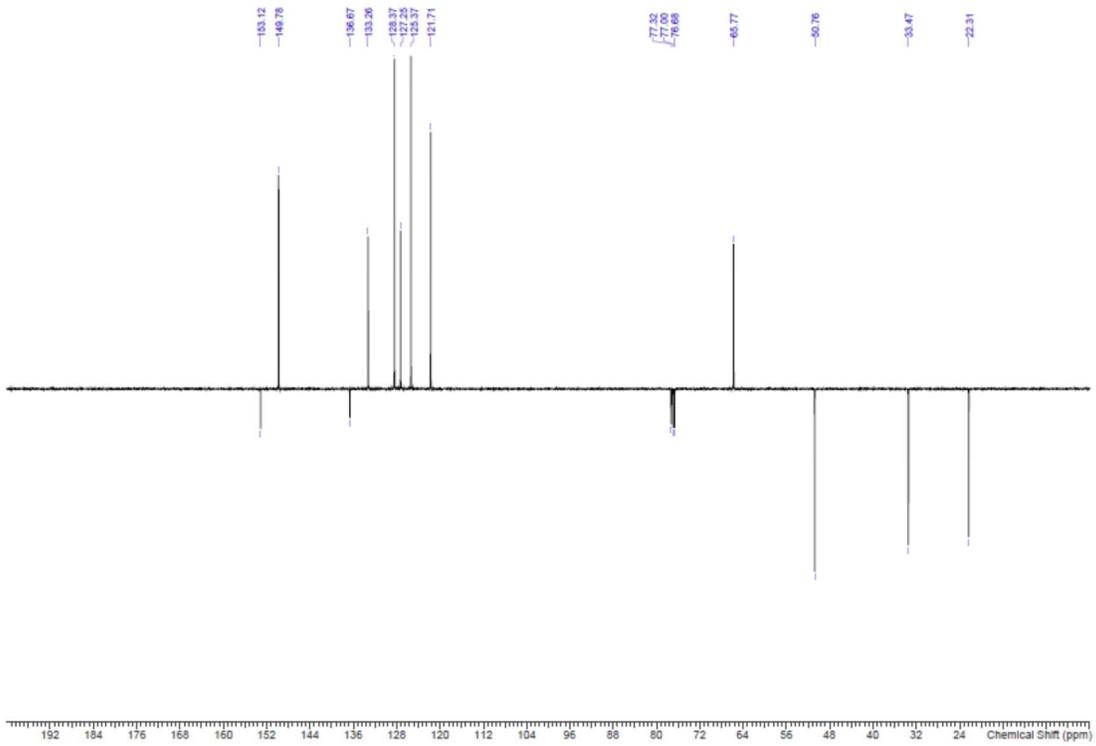
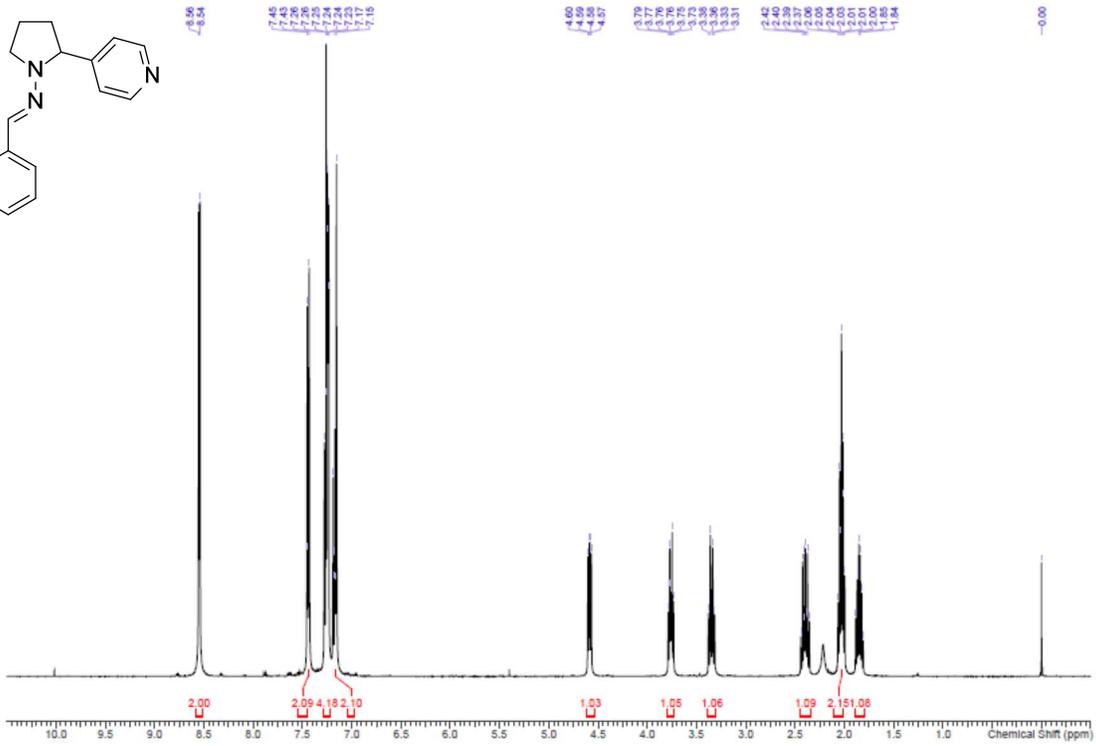
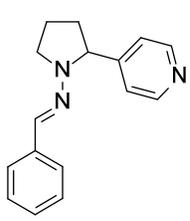
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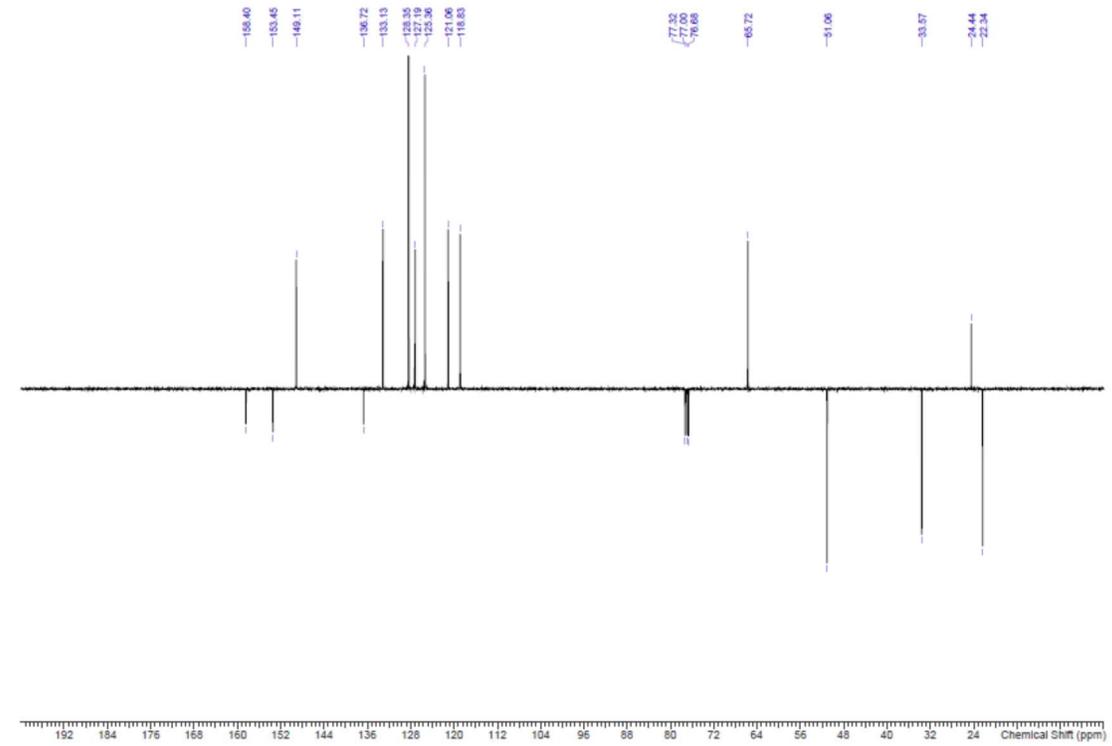
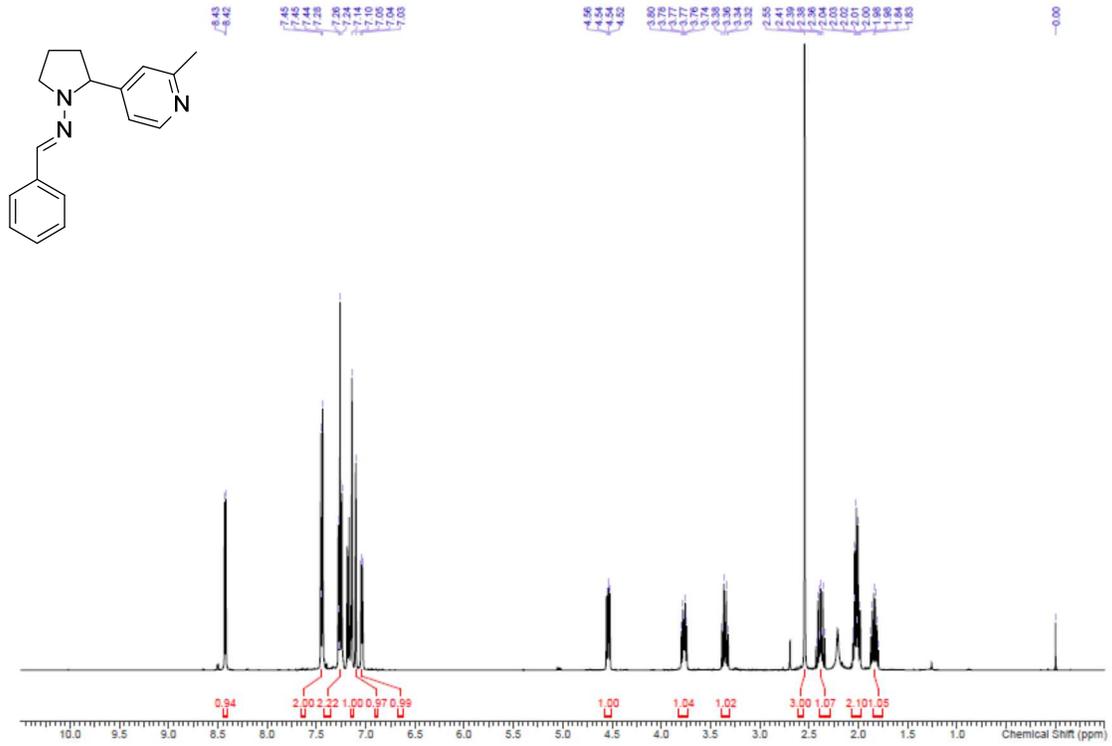
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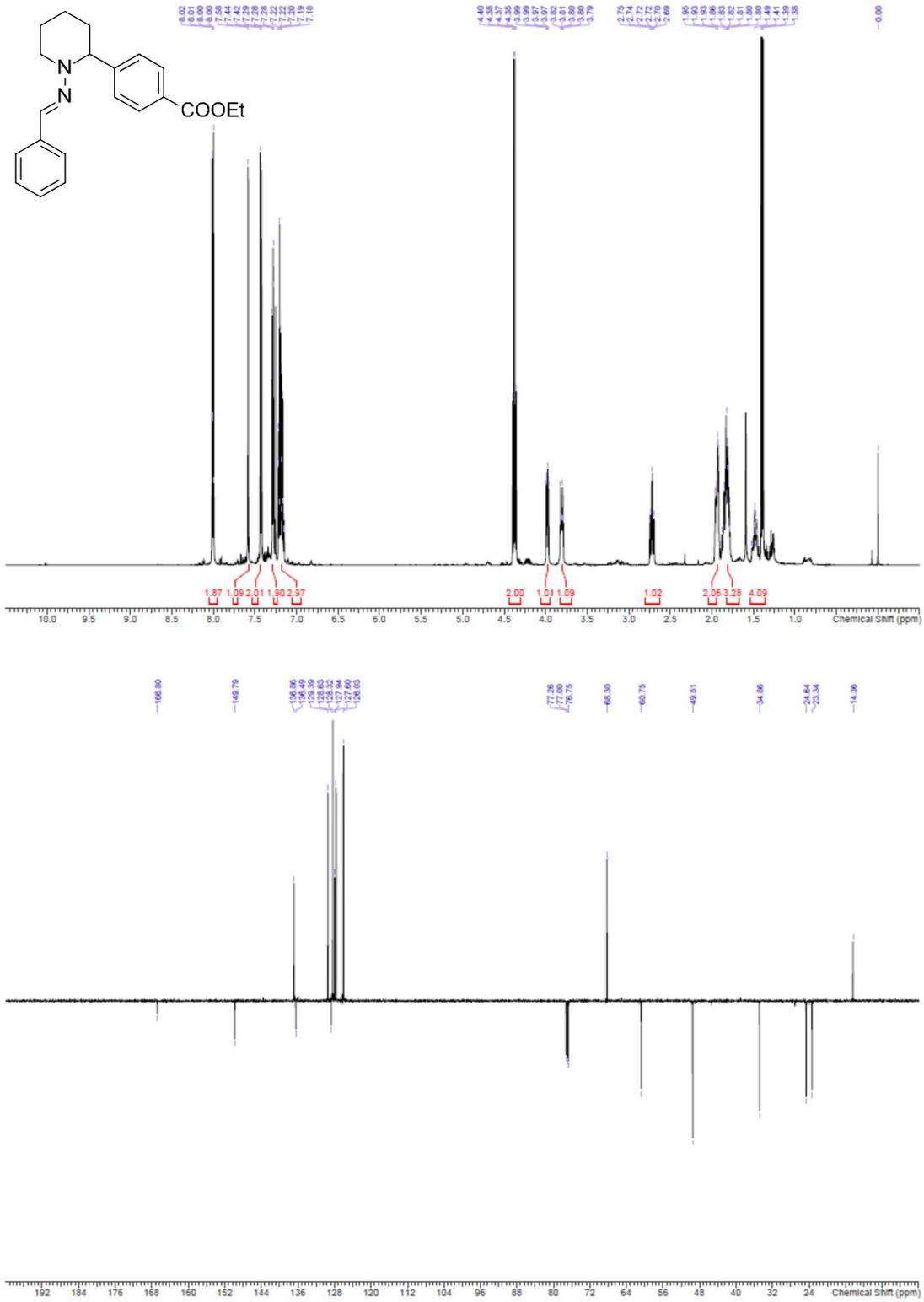
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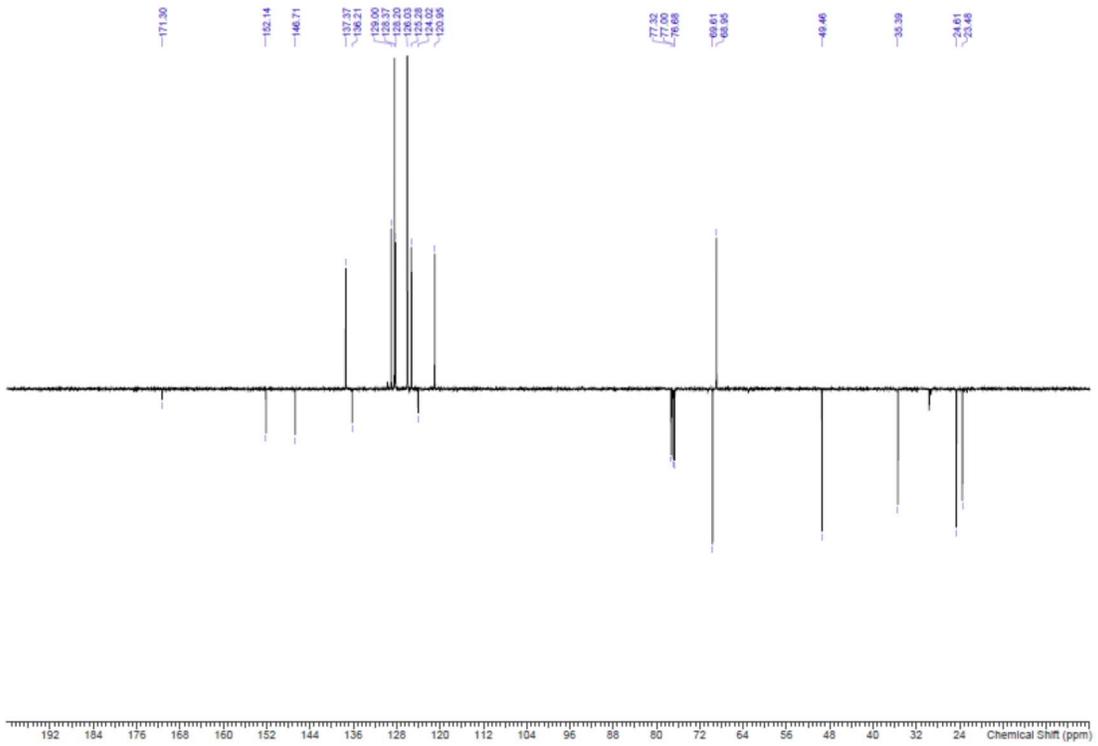
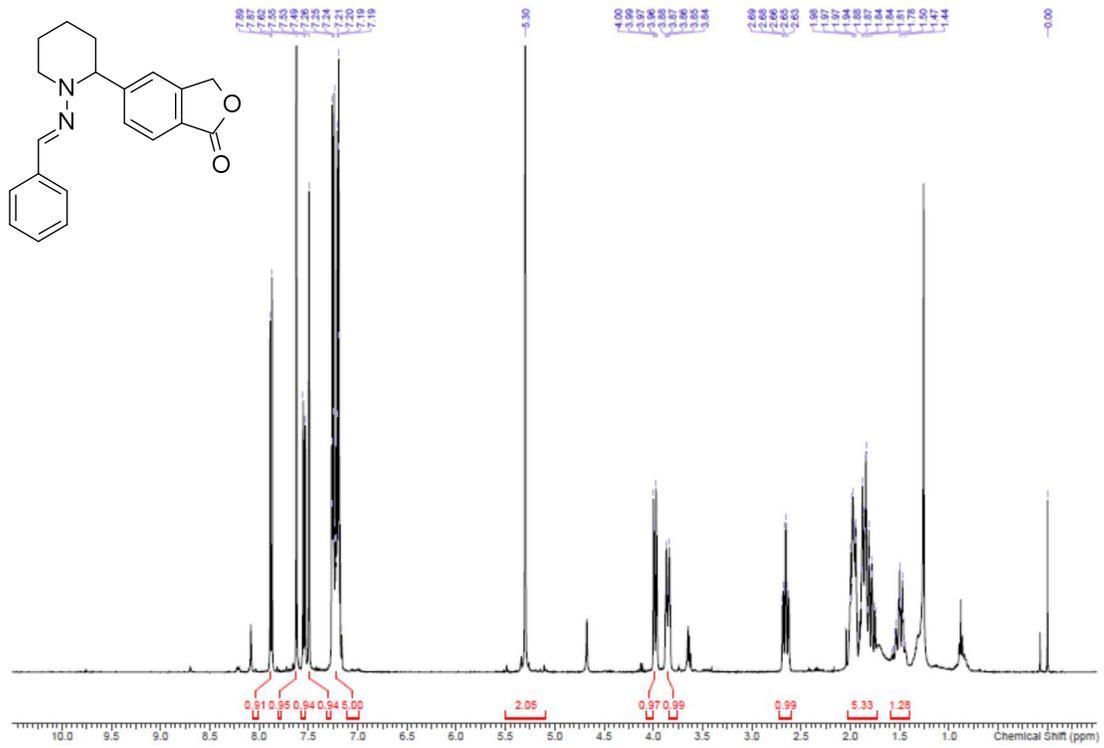
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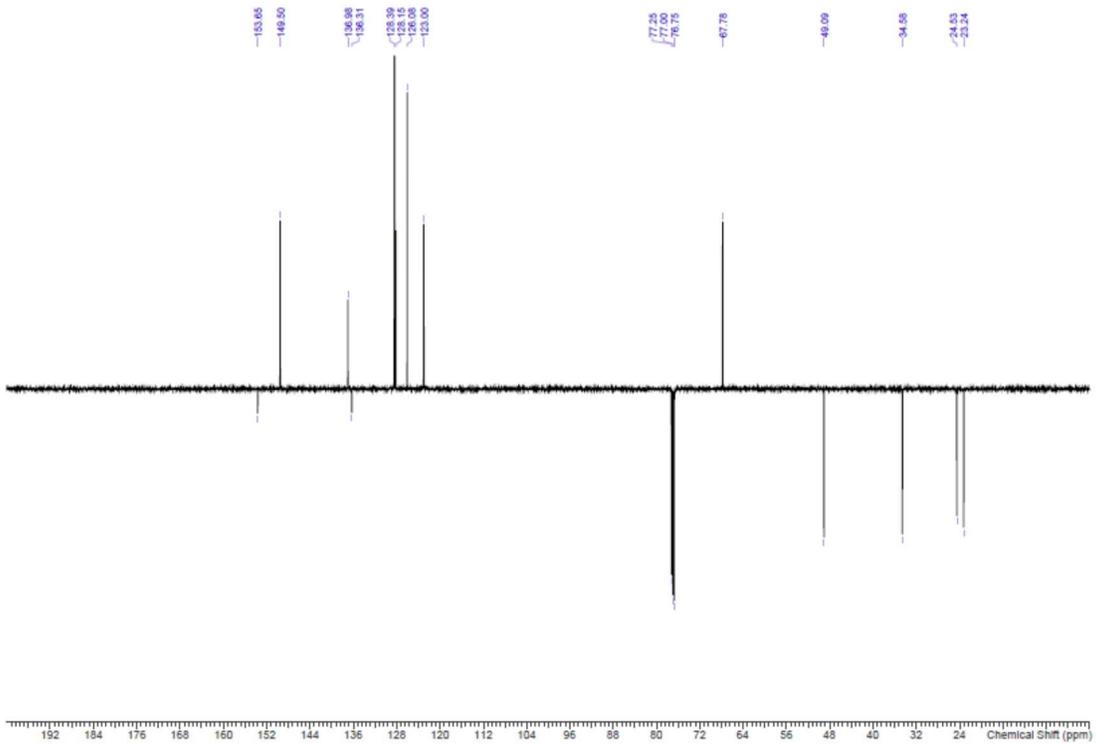
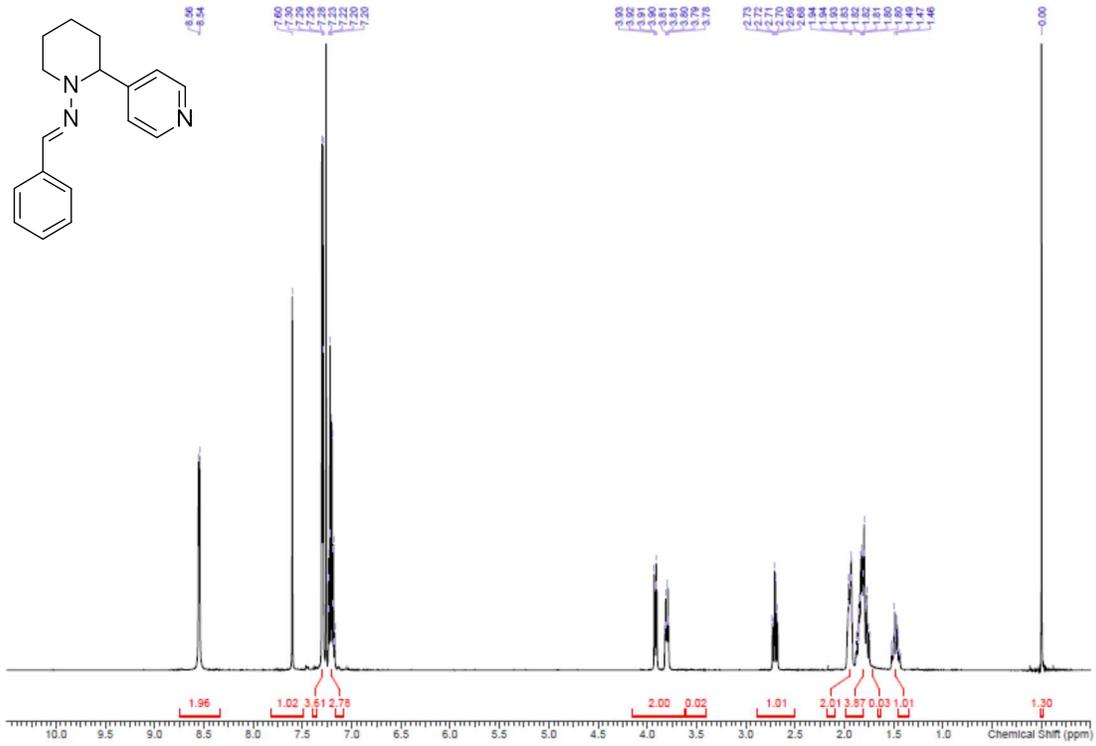
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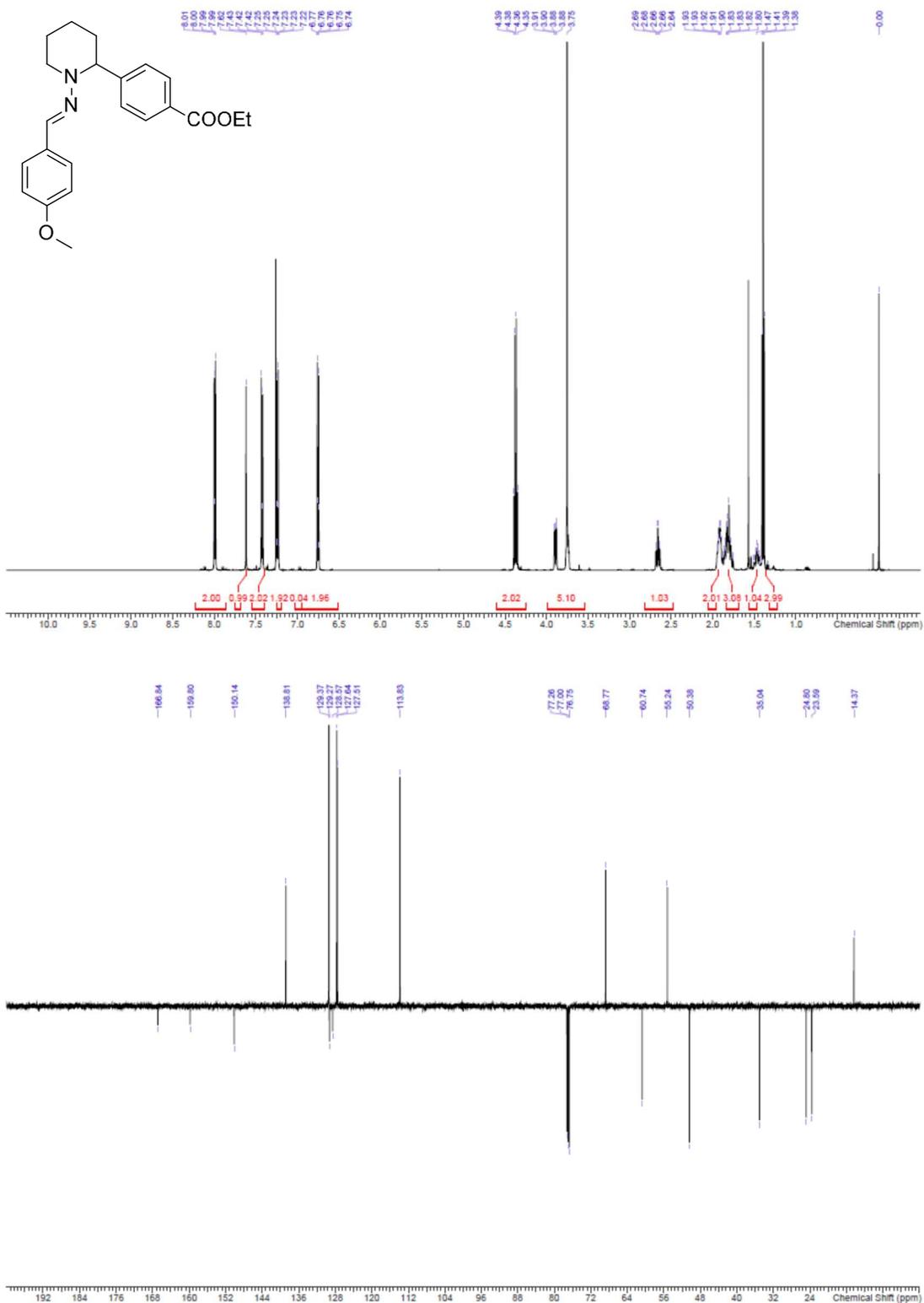
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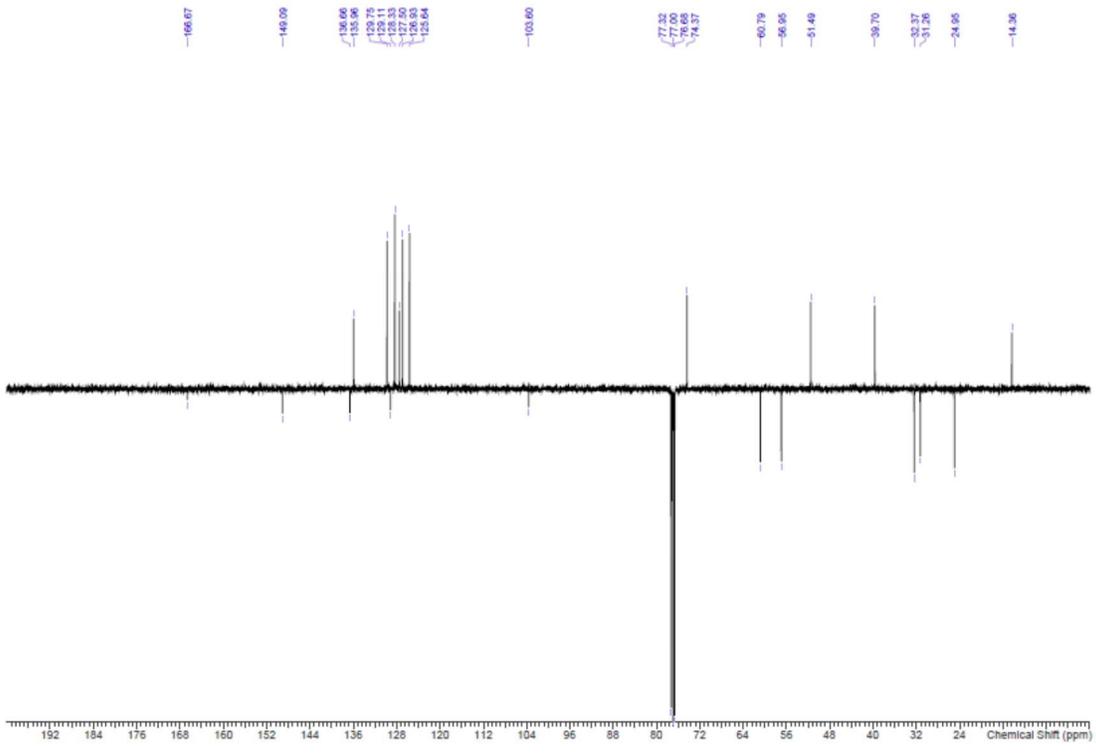
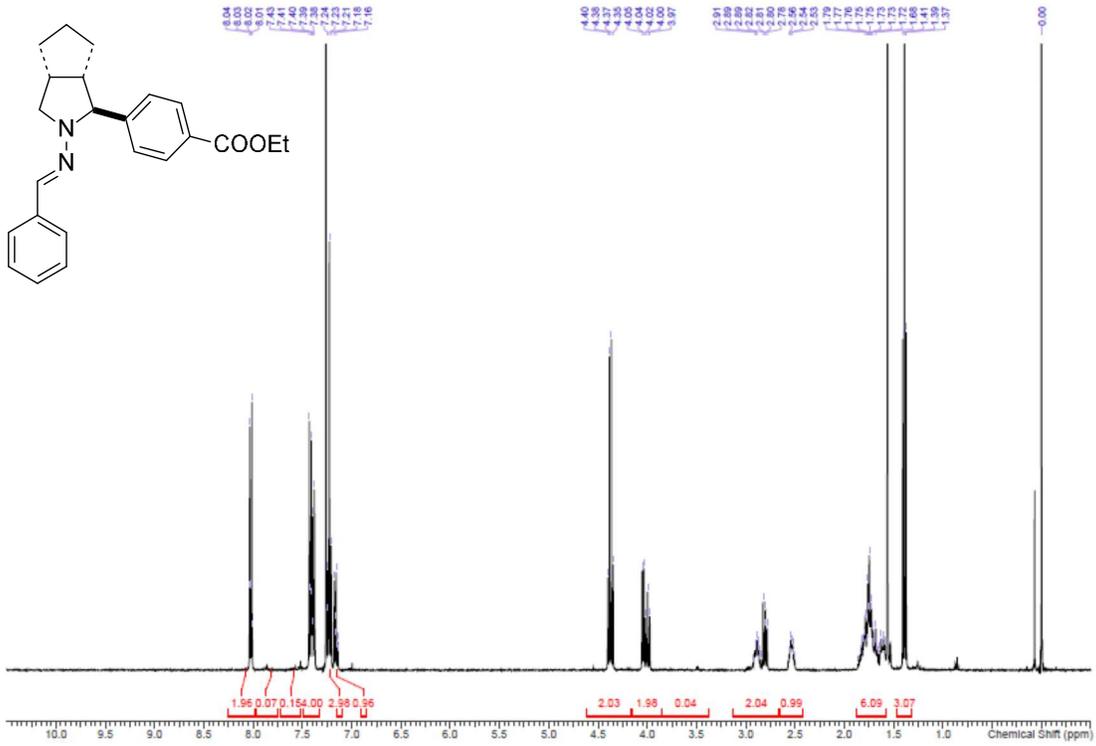
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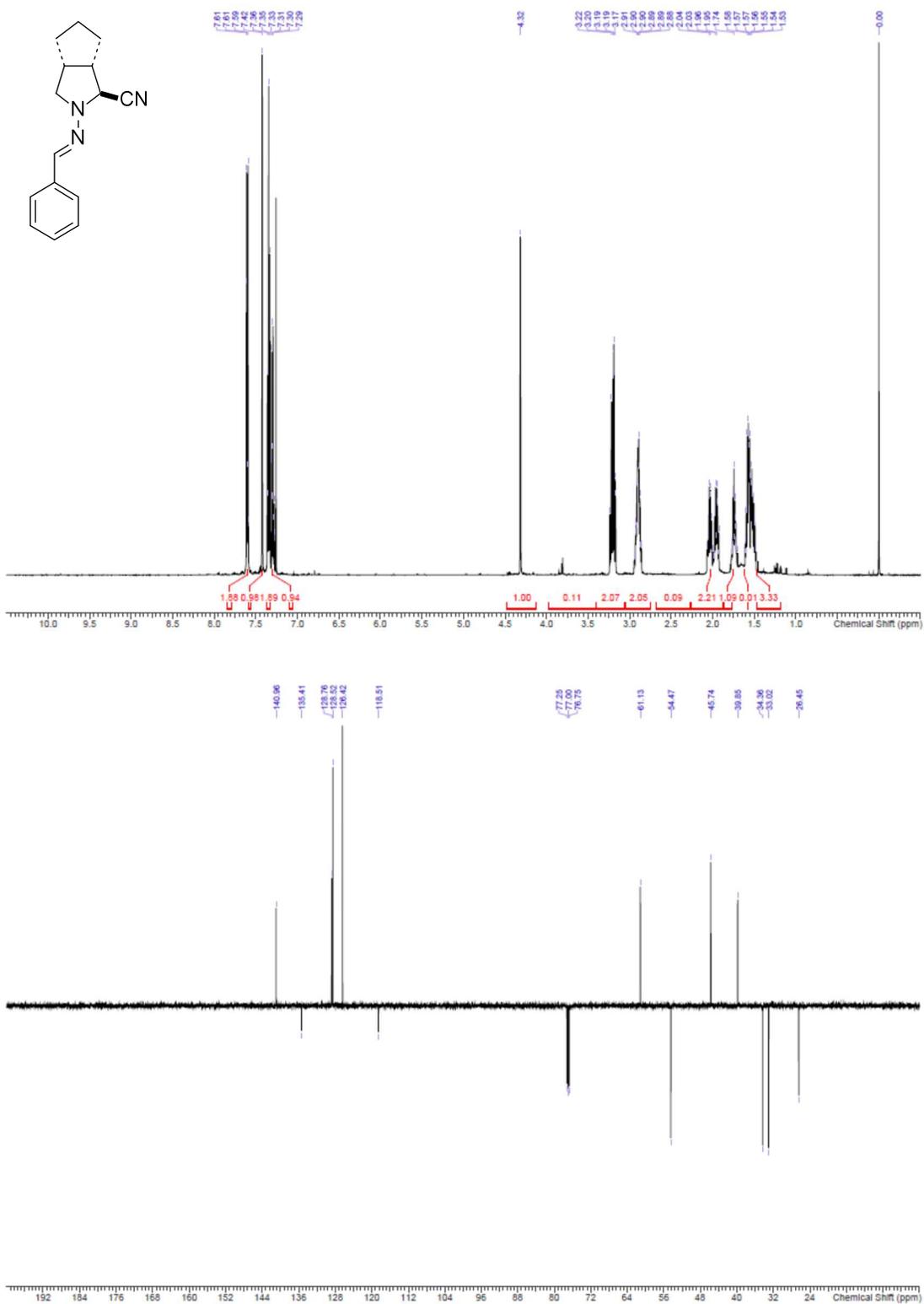
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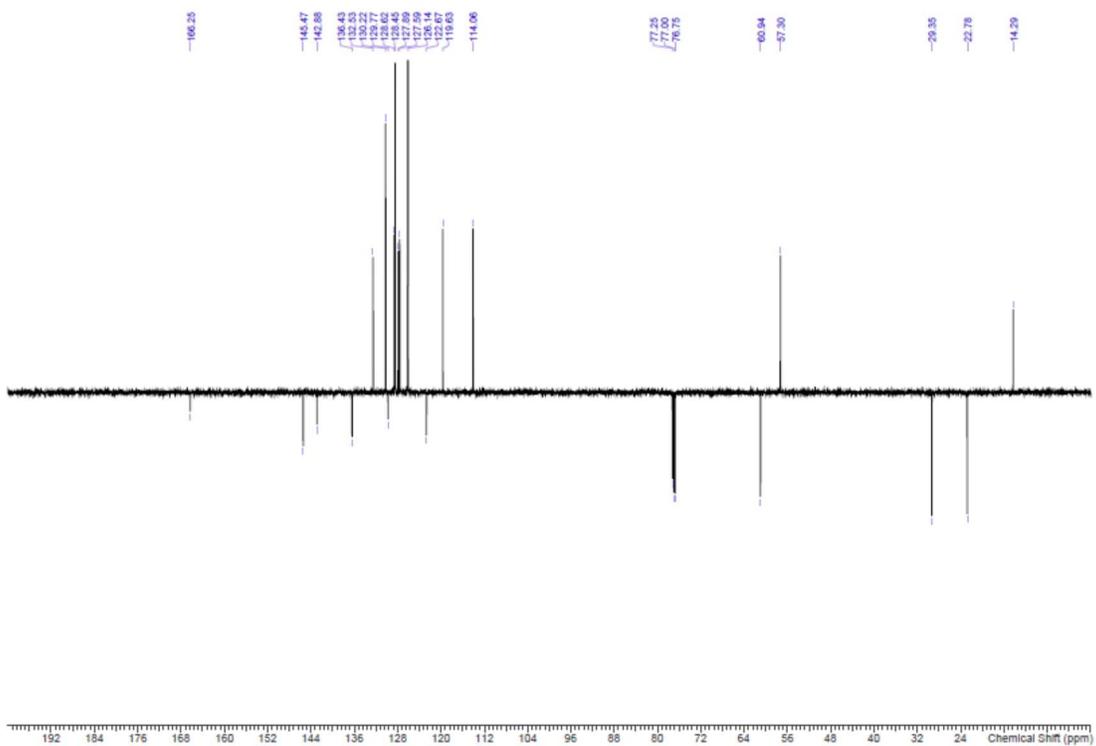
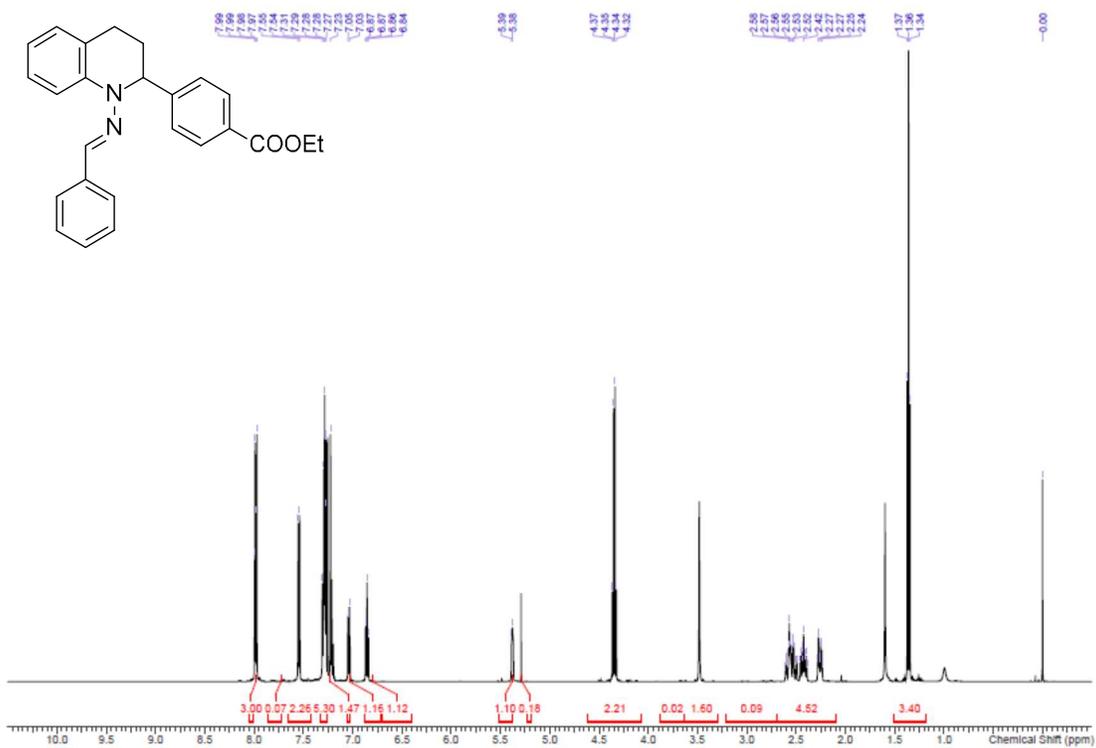
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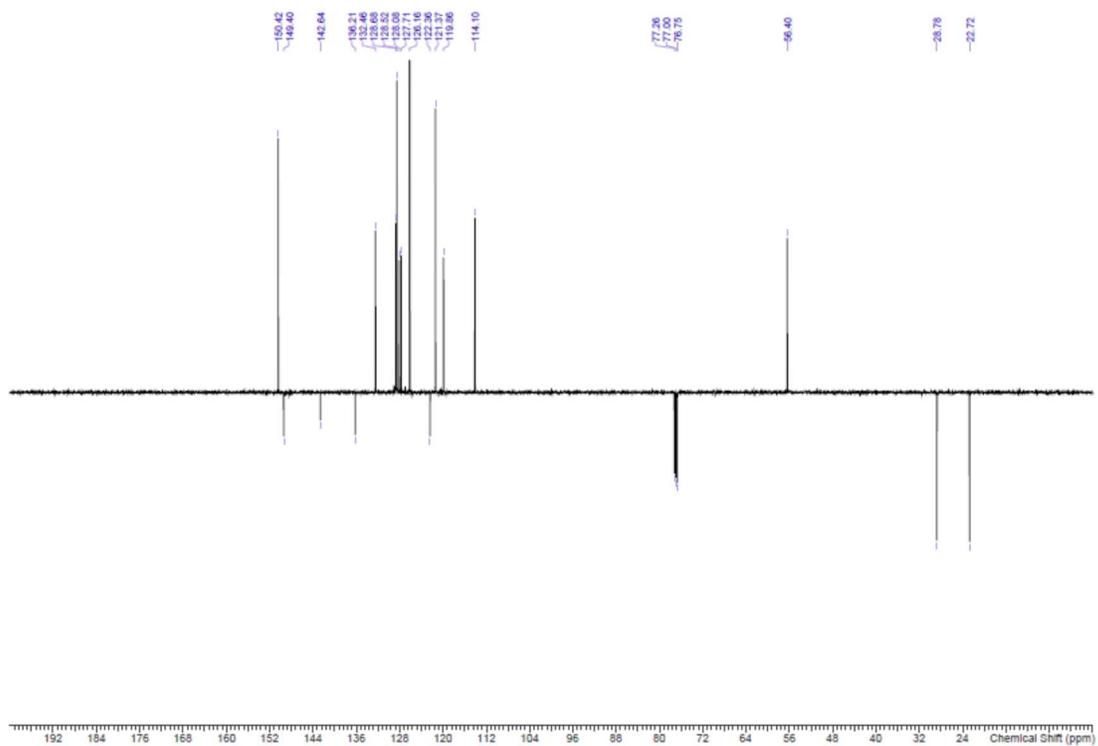
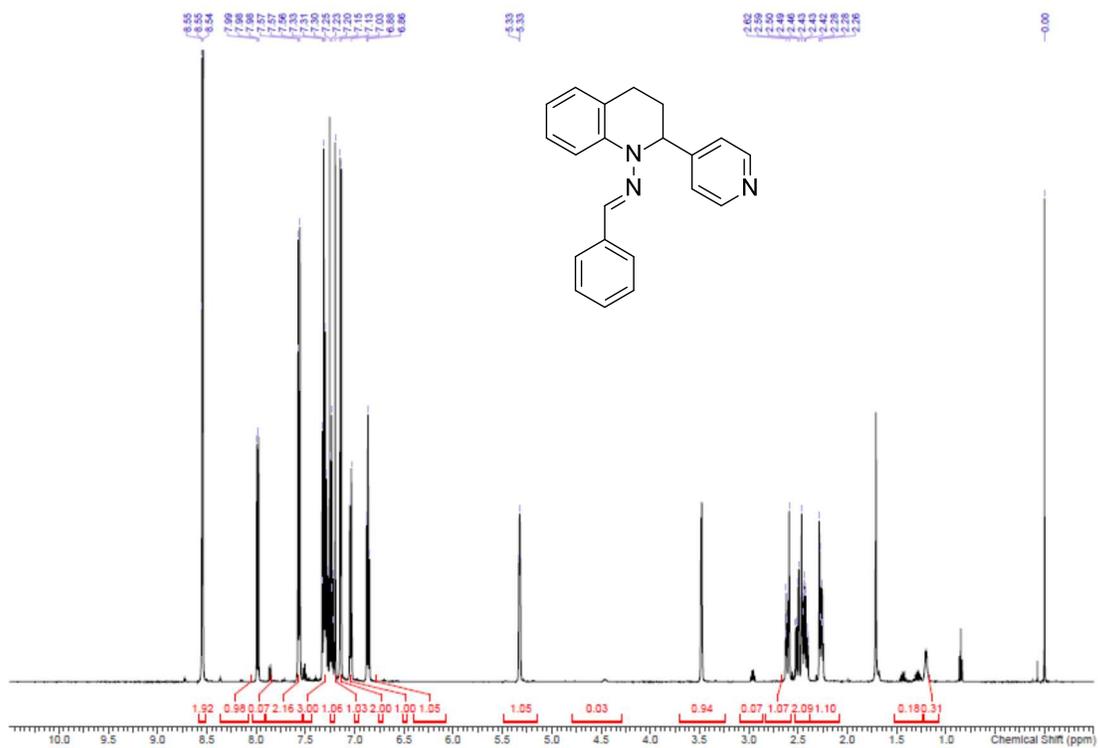
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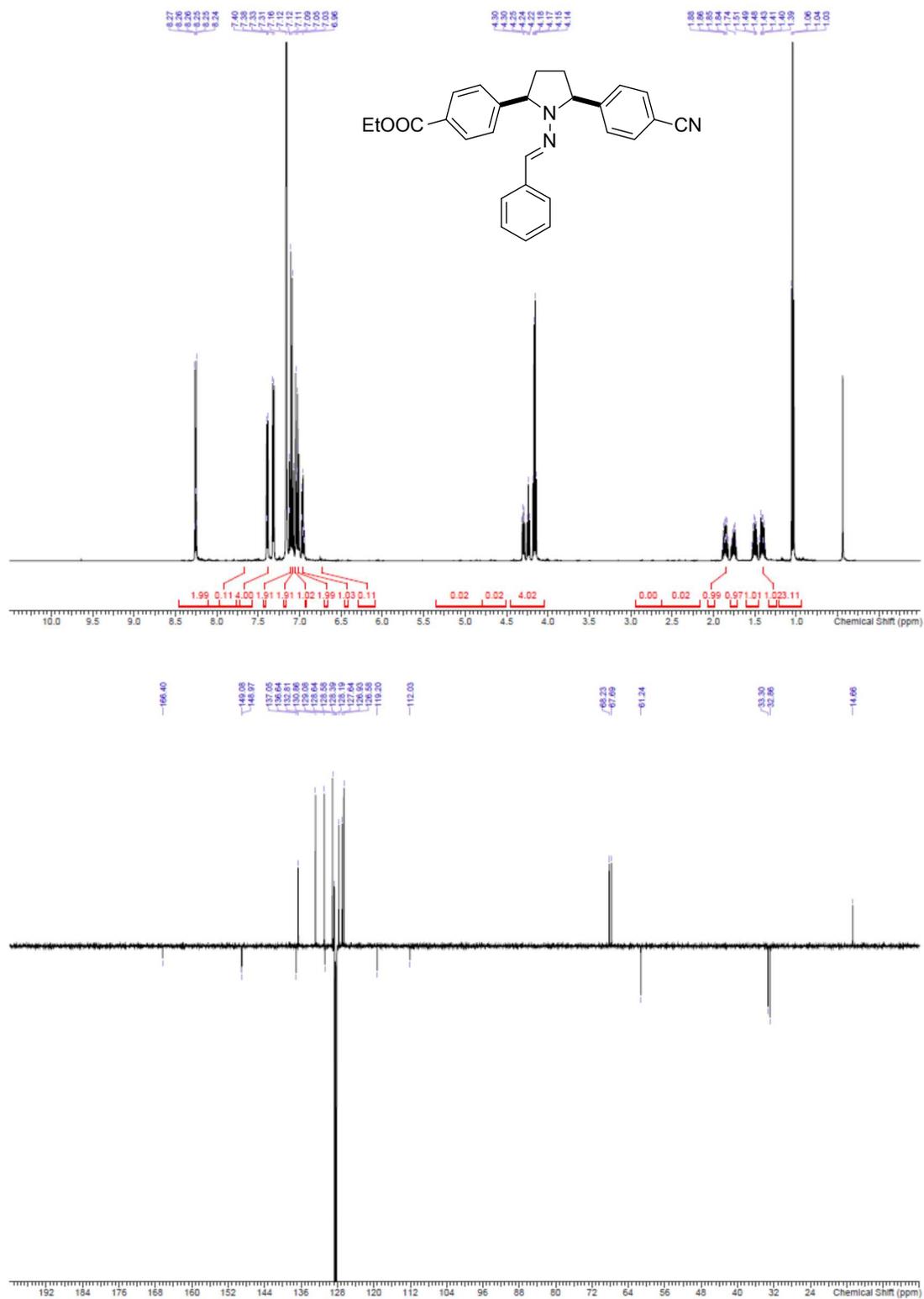
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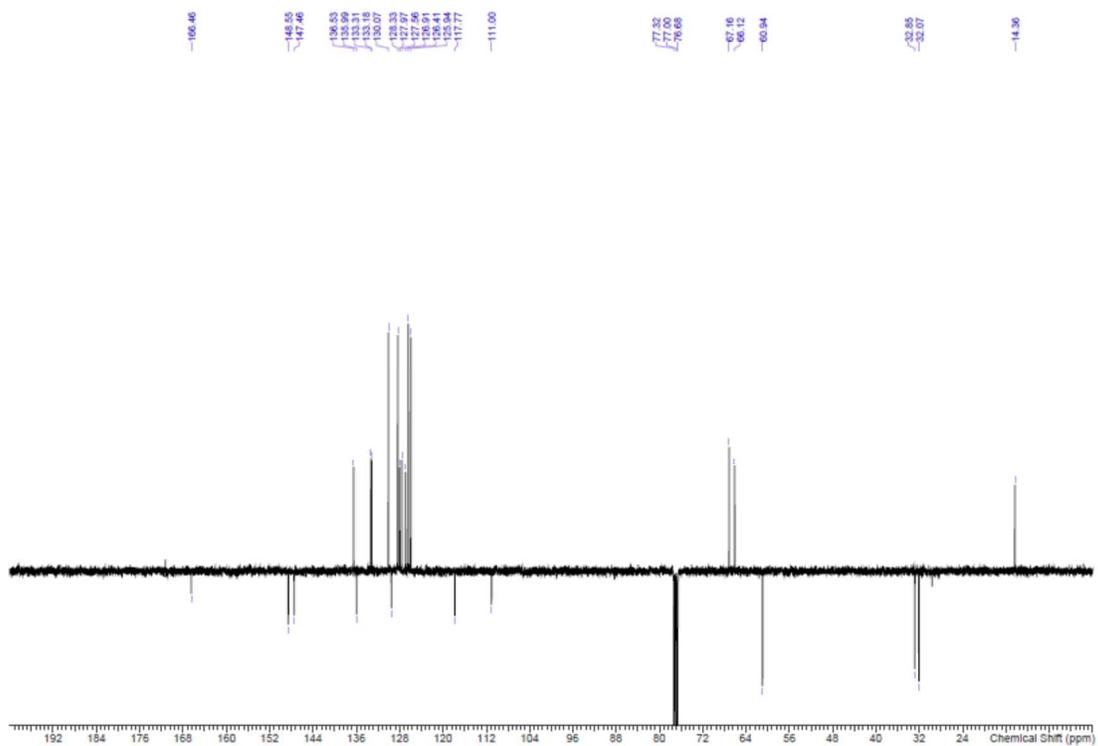
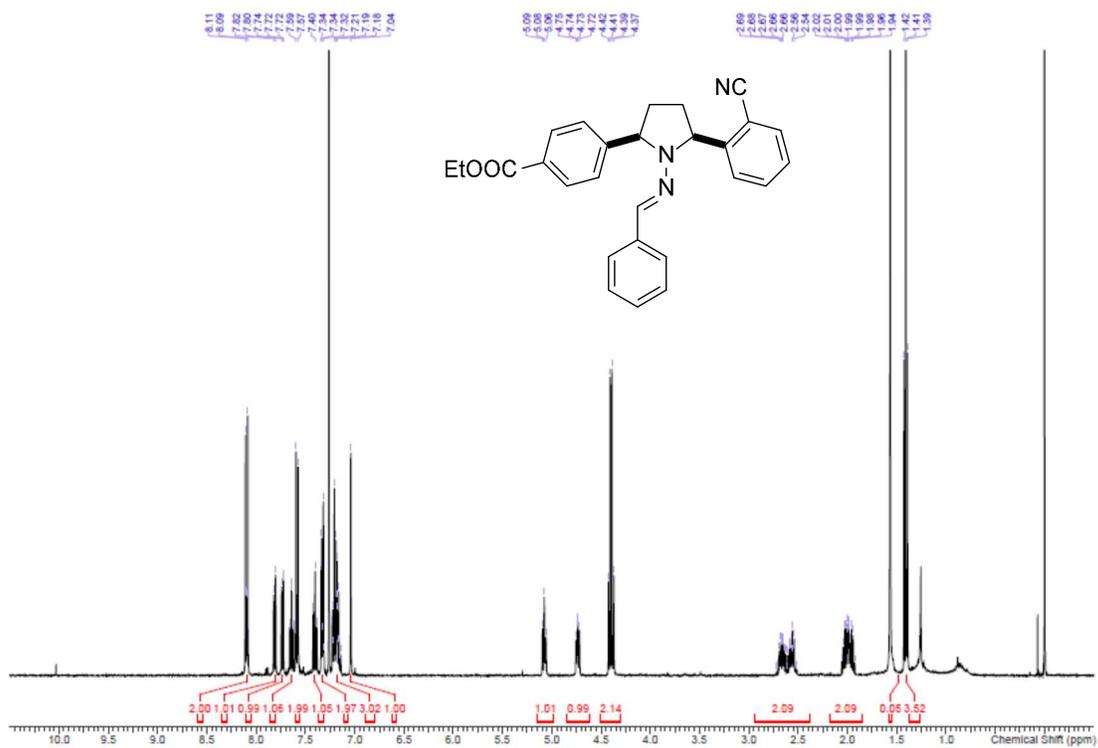
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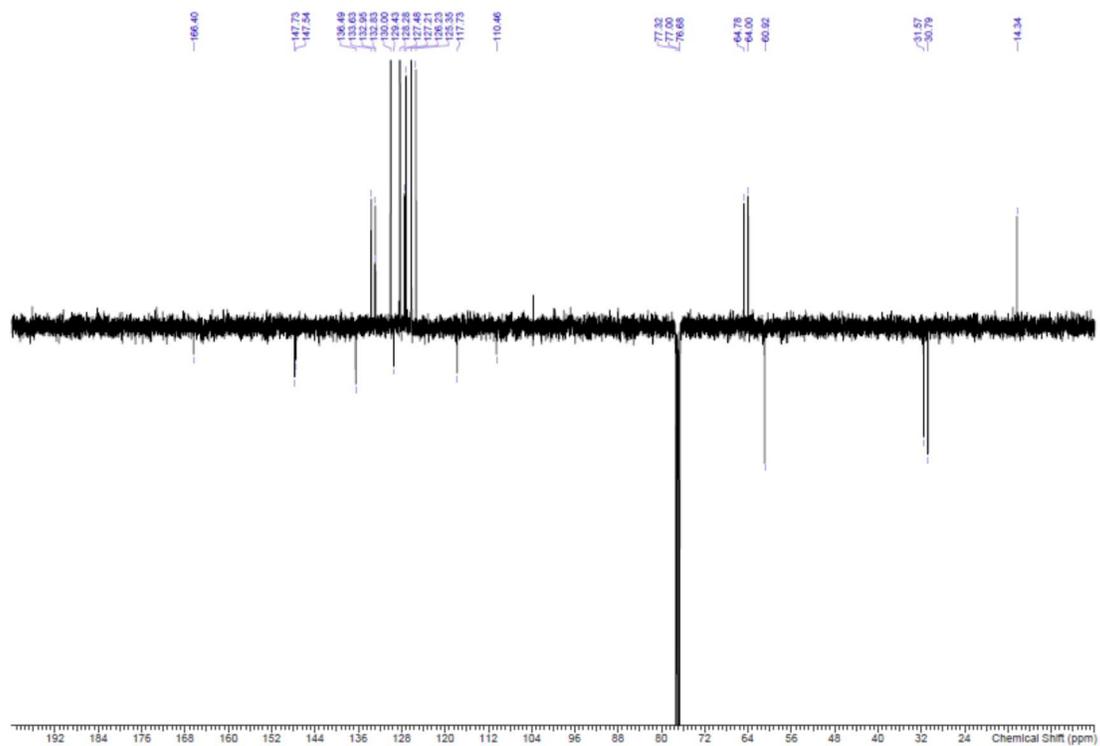
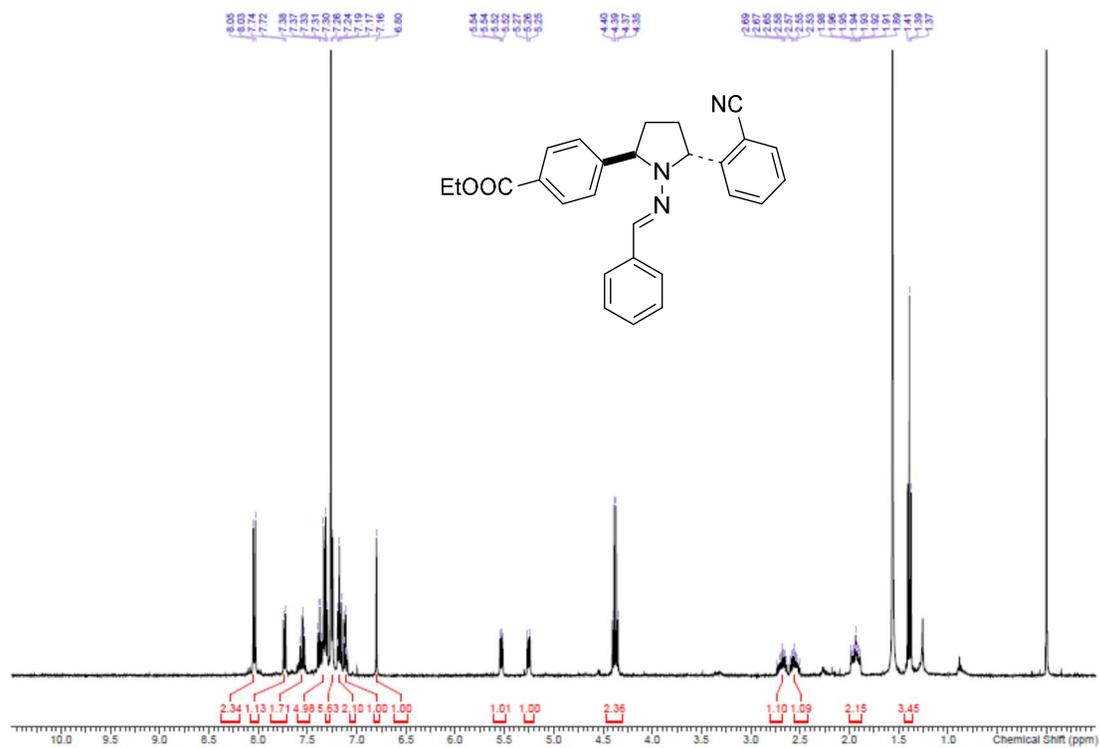
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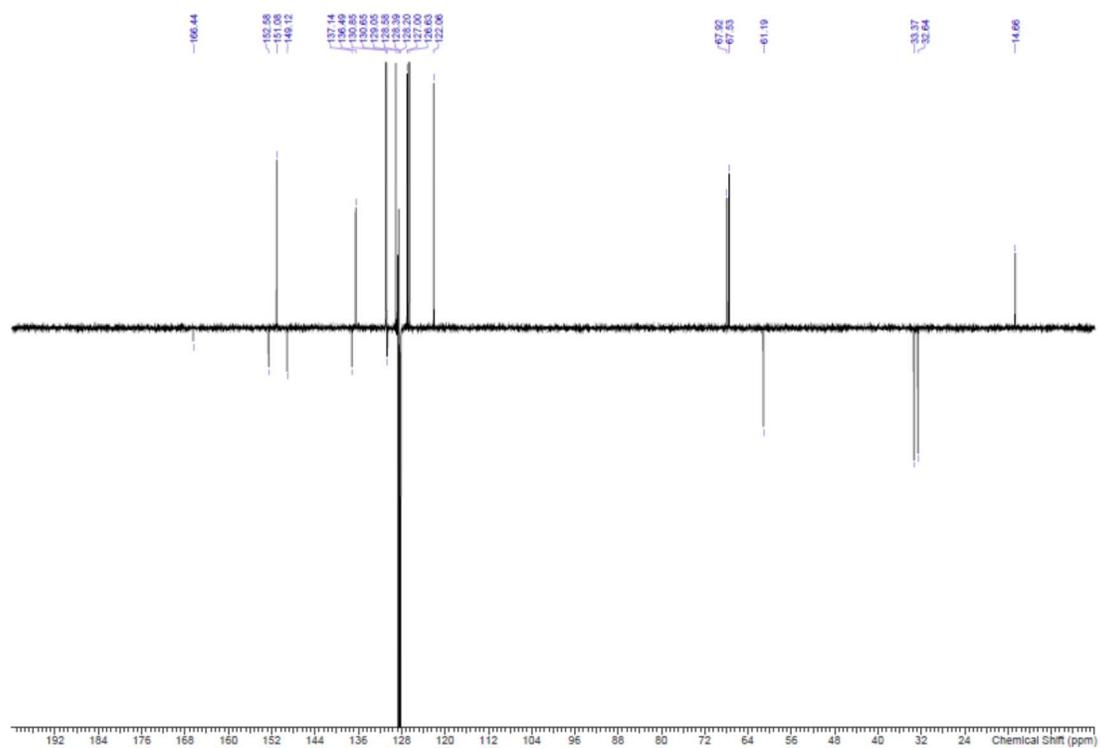
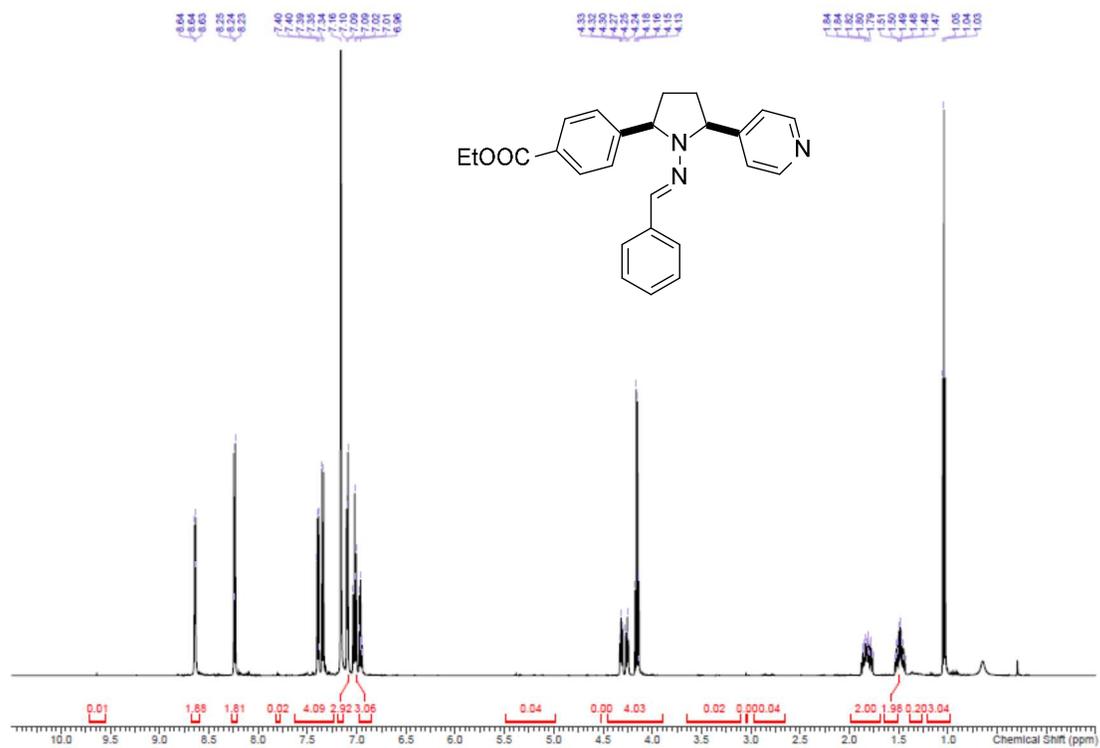
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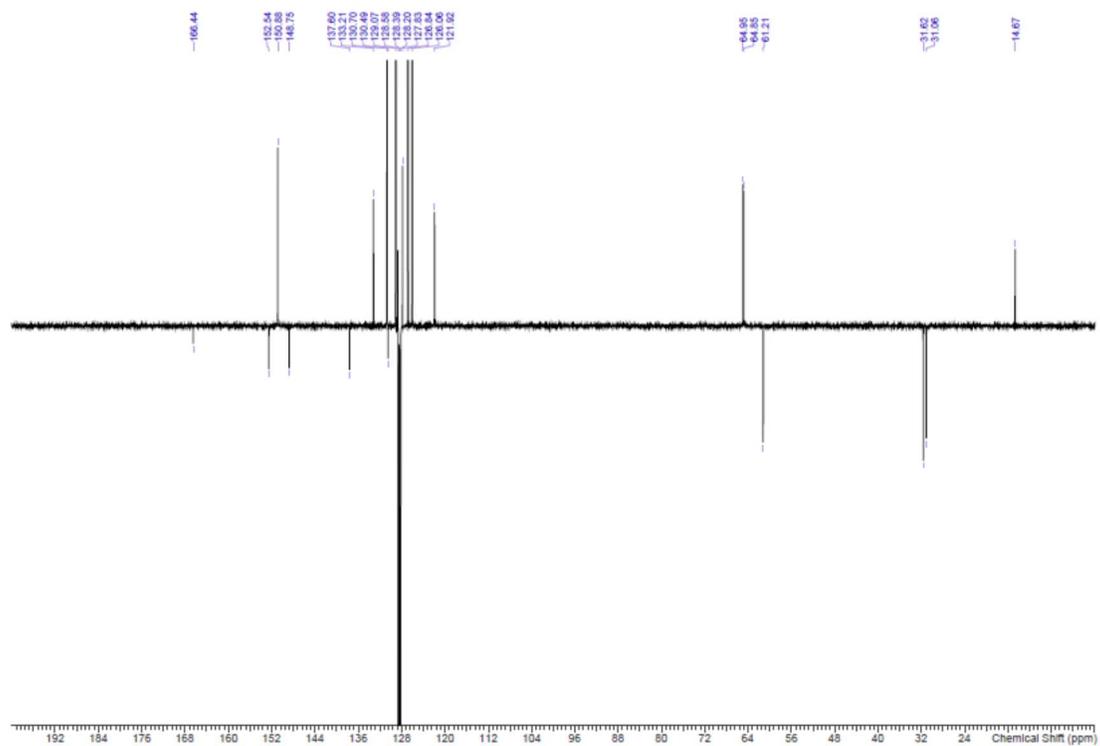
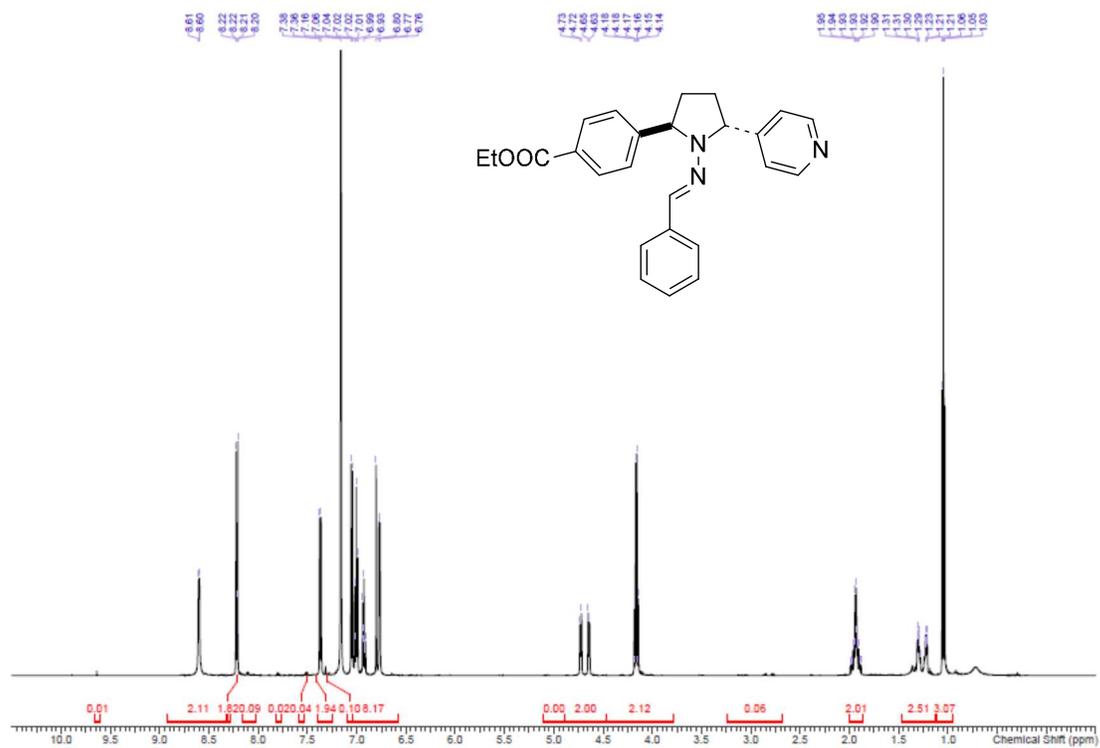
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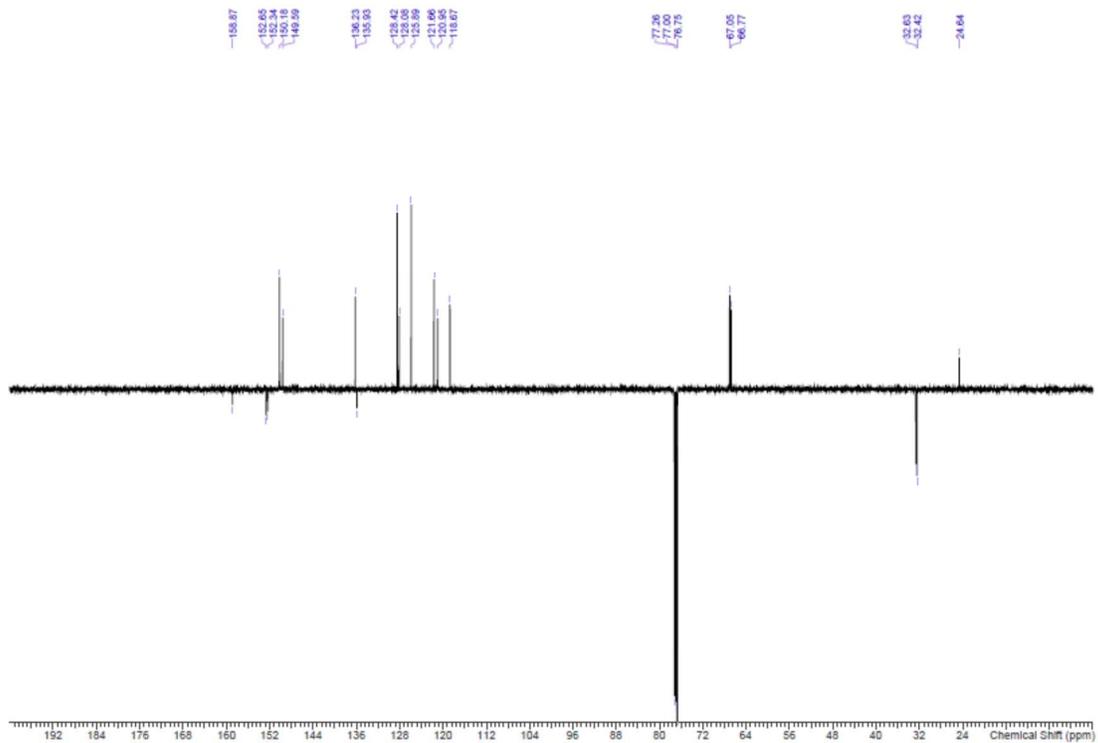
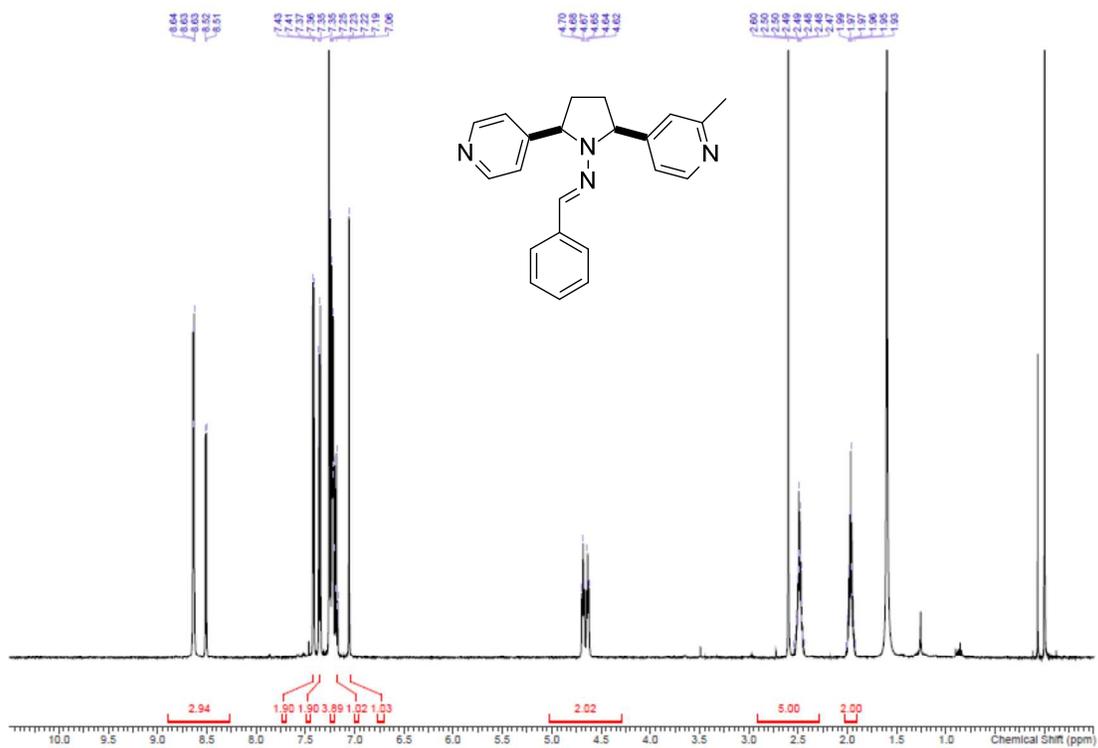
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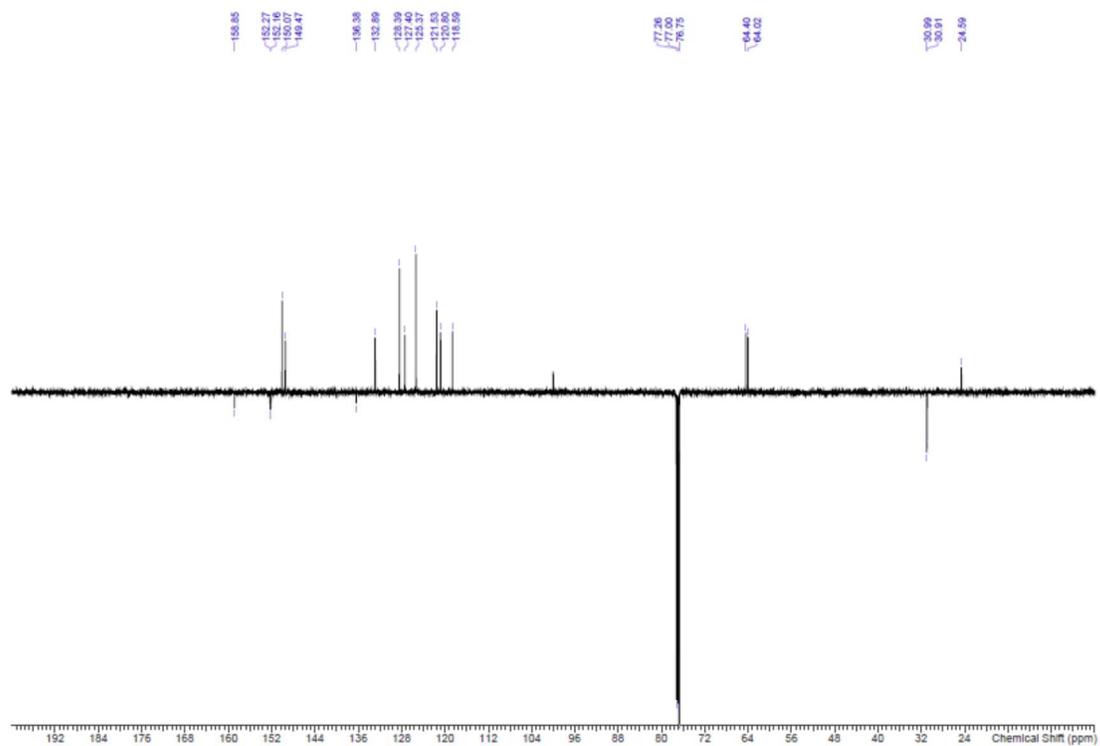
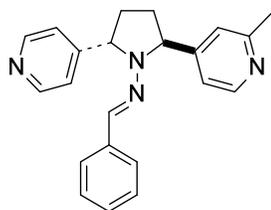
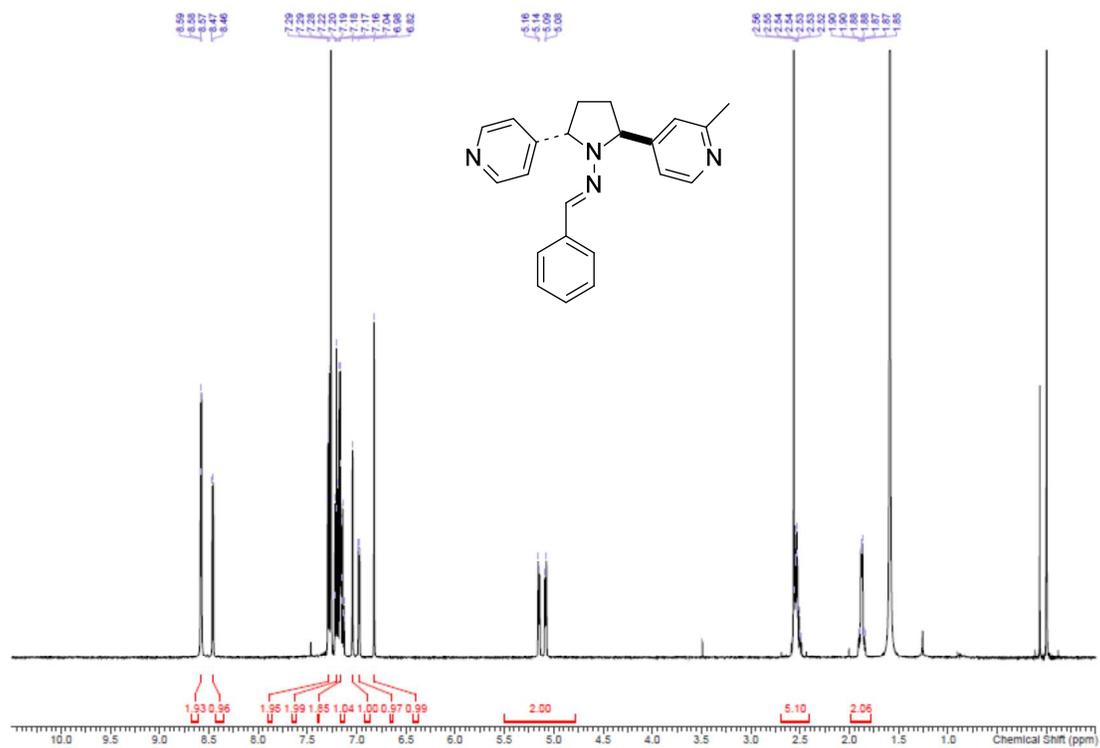
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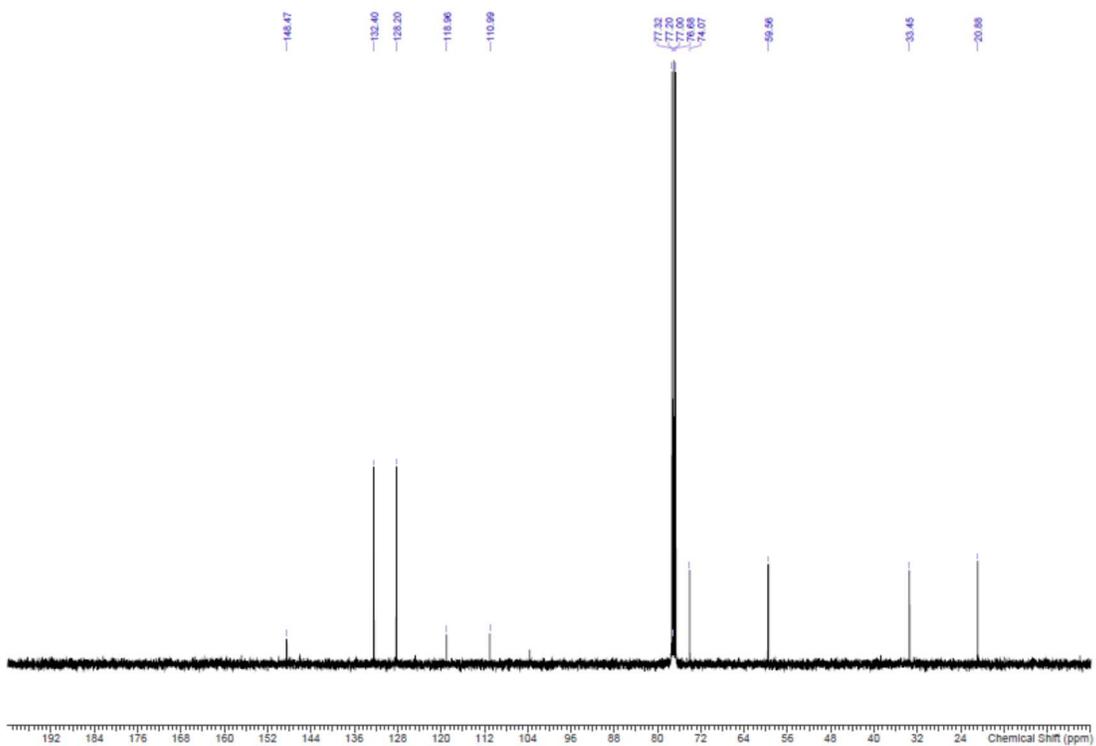
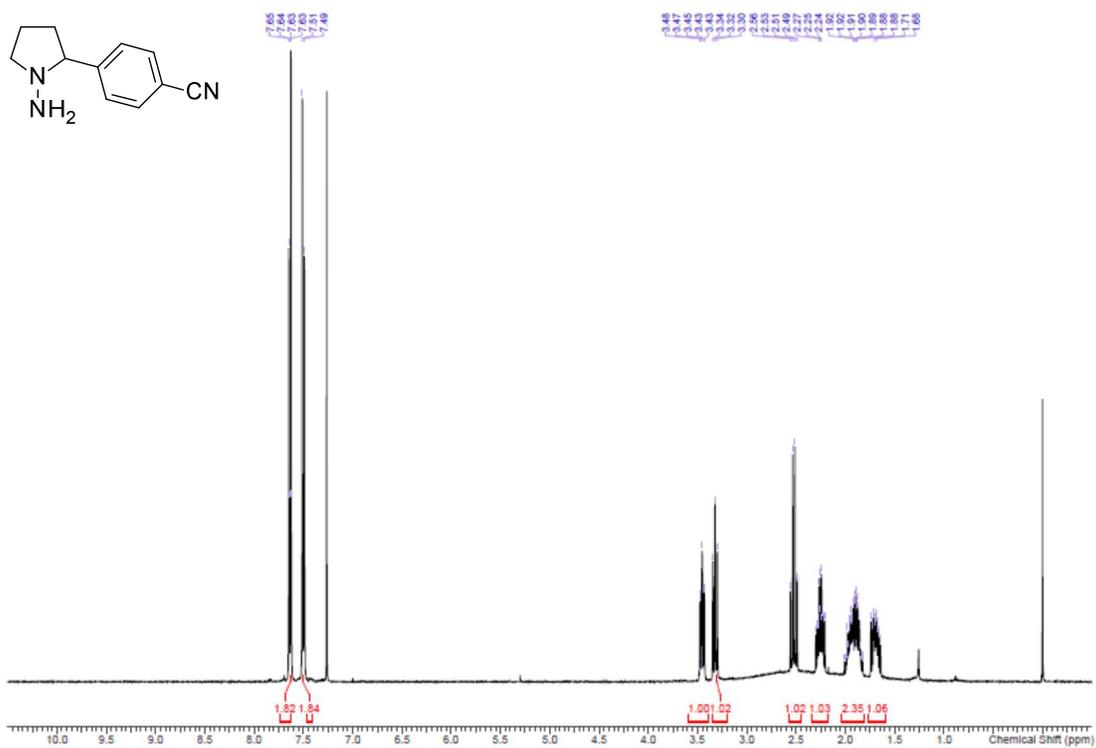


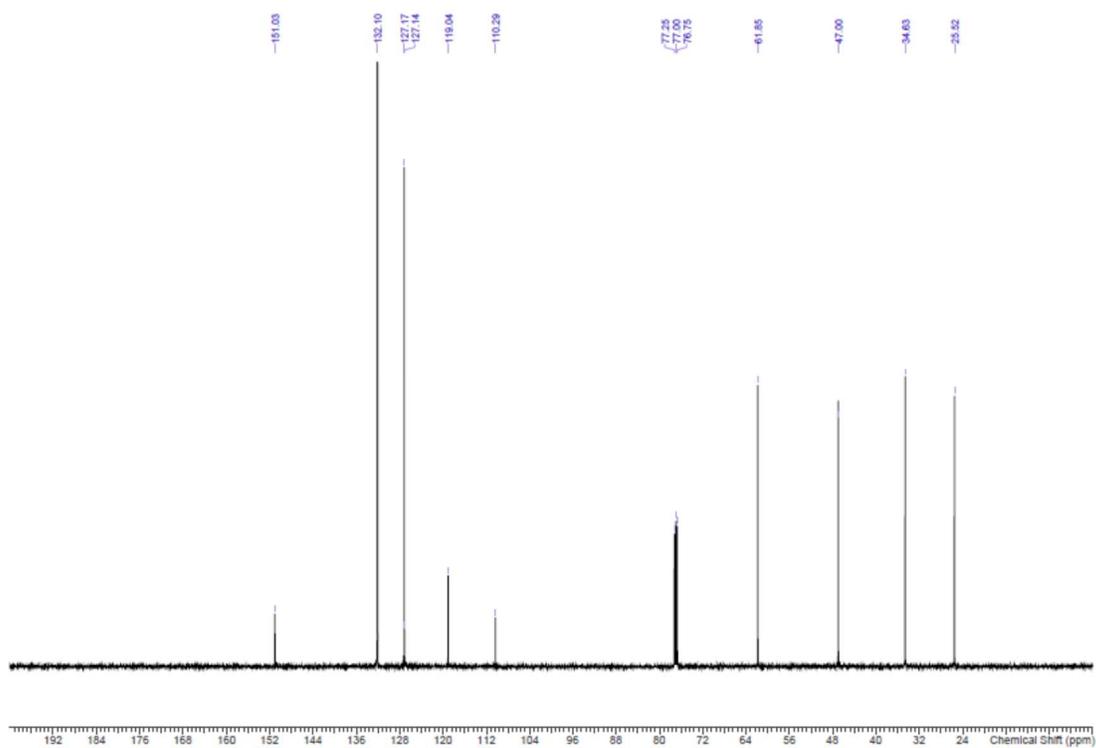
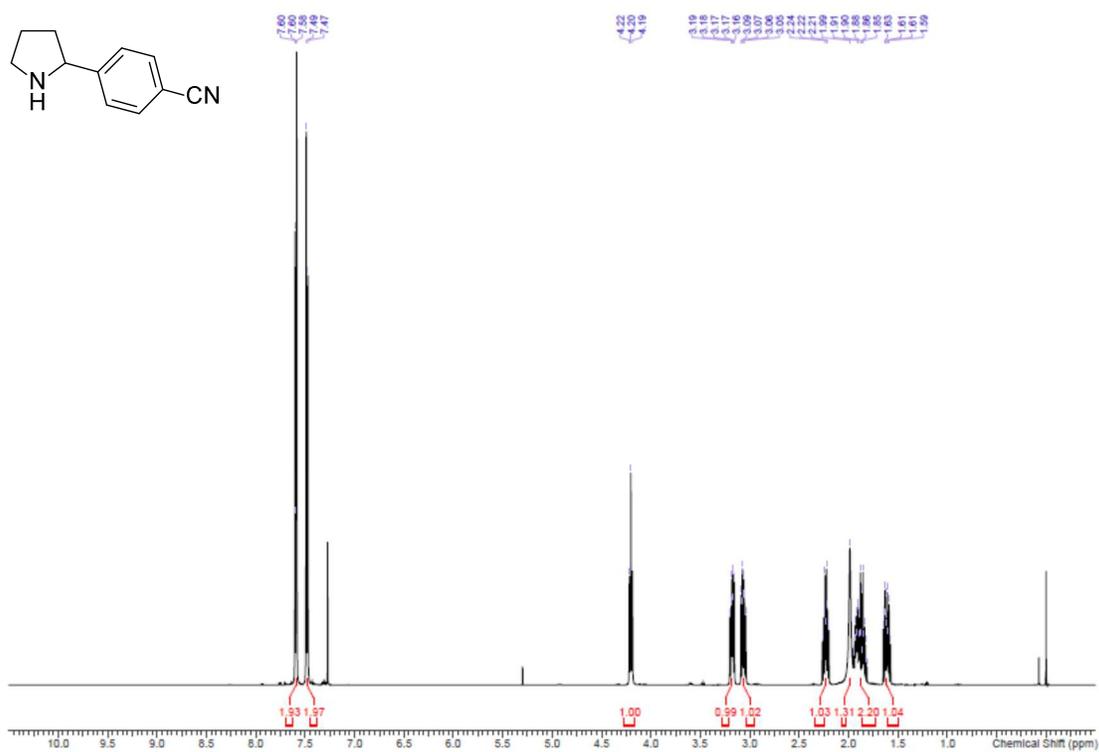
# Cis-3agh



# Trans-3agh







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- <sup>i</sup> Hashimoto, T.; Hirose, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 7556.
- <sup>ii</sup> Panda, A. K.; Das, U.; Quail, J. W.; Dimmock, J. R. *J. Het. Chem.*, **2014**, *51*, 219.
- <sup>iii</sup> Ke, M.; Song, Q. *J. Org. Chem.*, **2016**, *81*, 3654.
- <sup>iv</sup> Newman, S. G.; Jensen, K. F. *Green Chem.* **2013**, *15*, 1456.
- <sup>v</sup> Löwe, H.; Hessel, V.; Löbe, P.; Hubbard, S. *Org. Process Res. Dev.* **2006**, *10*, 1144.