

# Supporting Information

**A Practical Route to Substituted 7-Aminoindoles from Pyrrole-3-carboxaldehydes**

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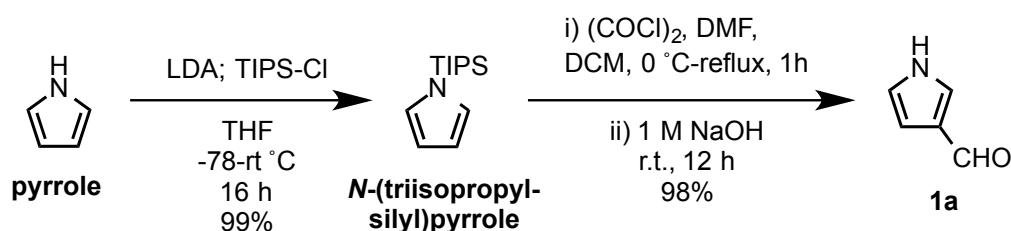
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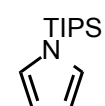
# 1 Experimental Section

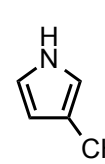
## 1.1 General Information

Reactions requiring anhydrous conditions were conducted under an inert atmosphere of argon using anhydrous solvents.  $\text{CH}_2\text{Cl}_2$ , toluene and MeOH were distilled over  $\text{CaH}_2$ .  $\text{Et}_2\text{O}$  and THF were distilled over Na and benzophenone. All reactions were monitored by analytical thin-layer chromatography (TLC) using indicated solvent systems on Analtech Uniplate Silica Gel TLC plates (250 microns). Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on either Bruker Avance 400 MHz or 300 MHz spectrometers as indicated. Chemical shifts ( $\delta$ ) are quoted in parts per million (ppm) and referenced to the following residual solvent signals:  $^1\text{H}$   $\delta$  = 7.26 ( $\text{CDCl}_3$ ), 2.50 ( $\text{DMSO-d}_6$ ), 3.31 (MeOD), 2.05 (acetone- $\text{d}_6$ );  $^{13}\text{C}$   $\delta$  = 77.0 ( $\text{CDCl}_3$ ), 39.43 ( $\text{DMSO-d}_6$ ), 49.05 (MeOD), 29.84 (acetone- $\text{d}_6$ ). Coupling constants ( $J$ ) are given in Hz. Pyrrole and ethyl 4-formylpyrrole-2-carboxylate (**2c**) were obtained from Sigma-Aldrich.

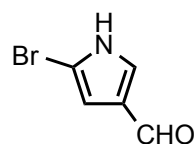
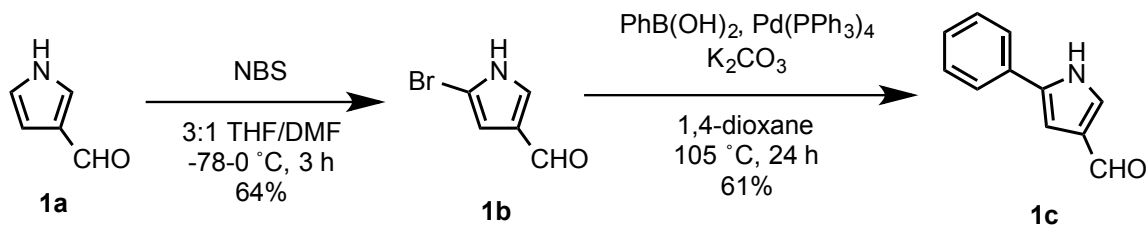
## 1.2 Preparation of Aldehydes 1a-g



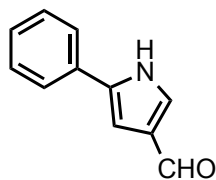
 **N-(Triisopropylsilyl)pyrrole.** To a 1.0 M solution of freshly prepared LDA (72.43 mmol) in THF at -78 °C was added pyrrole (5.0 mL, 72.07 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 30 min before cooling to -78 °C, followed by the slow addition of chlorotriisopropylsilane (16.96 mL, 79.27 mmol). The reaction solution was allowed to warm to room temperature and stirred overnight, then quenched with  $\text{NaHCO}_3$  (200 mL) and extracted with DCM (3 x 150 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. Purification by silica gel chromatography (2% EtOAc in hexanes) afforded the TIPS-protected pyrrole as a clear oil (15.9 g, 71.48 mmol, 99%). All spectral data matched literature values.<sup>1</sup>

 **Pyrrole-3-carboxaldehyde (1a).** To a 0.18 M solution of oxalyl chloride (5.99 mL, 69.82 mmol) in DCM at 0 °C was added dropwise a 2 M solution of DMF (5.41 mL, 69.82 mmol) in DCM. The reaction mixture was stirred at 0 °C for 30 min before rapid addition of a 1.15 M solution of *N*-triisopropylsilylpyrrole (12.00 g, 53.71 mmol) in DCM. The reaction mixture was heated to reflux and stirred for 30 min. The solvent was removed *in vacuo* and the crude reaction mixture was resuspended in 1 M NaOH (300 mL) and stirred at room temperature for

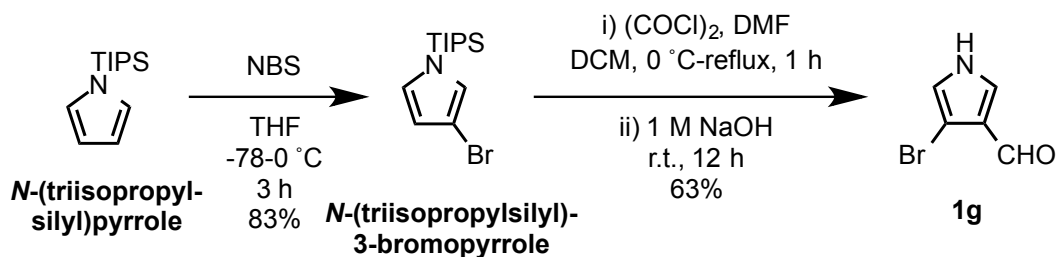
12 h. The aqueous mixture was extracted with DCM (3 × 150 mL) and the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by silica gel chromatography (40% EtOAc in hexanes) afforded pyrrole-3-carboxaldehyde as a light brown solid (5.00 g, 98%). All spectral data matched literature values.<sup>1</sup>

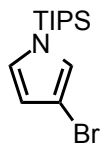


**5-Bromo-1H-pyrrole-3-carboxaldehyde (1b).** To a stirring solution of pyrrole-3-carboxaldehyde (250 mg, 2.63 mmol) in THF (3.9 mL) at -78 °C was added slowly *N*-bromosuccinimide (473 mg, 2.66 mmol) as a solution in DMF (2.0 mL). The reaction mixture was stirred at -78 °C for 1 h, then warmed to -10 °C over 2 h. The reaction was quenched with ice water, and the product was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with NaHCO<sub>3</sub> and brine, then dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The reaction mixture was purified by silica gel chromatography (30% EtOAc/hexanes) to afford 5-bromopyrrole-3-carboxaldehyde (293 mg, 1.68 mmol, 64%). All spectral data matched literature values.<sup>2</sup>

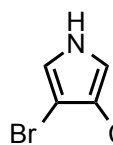


**5-Phenyl-1H pyrrole-3-carboxaldehyde (1c).** 5-Bromopyrrole-3-carboxaldehyde (50 mg, 0.29 mmol), phenyl boronic acid (42 mg, 0.34 mmol), and potassium carbonate (95 mg, 0.69 mmol) were suspended in dioxane (2.6 mL), and the mixture was degassed with argon. Tetrakis(triphenylphosphine)palladium (0) (17 mg, 5 mol %) was added, then the suspension was degassed again with argon and heated to 105 °C for 24 h. The crude product mixture was concentrated, partitioned between EtOAc and water, and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification by silica gel chromatography (30% EtOAc/Hexanes) afforded 5-Phenyl-1H pyrrole-3-carboxaldehyde (30 mg, 0.18 mmol, 61%). Spectral data matched literature values.<sup>2</sup>

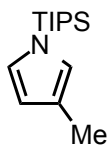
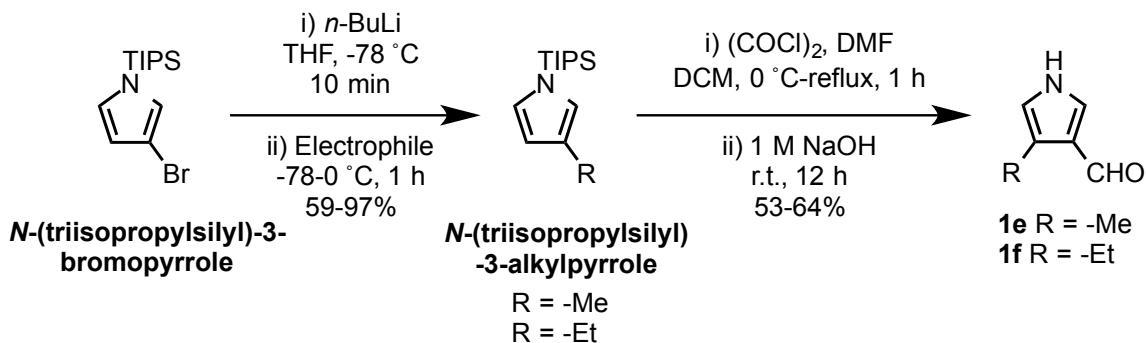




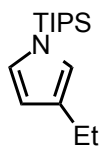
**N-(Triisopropylsilyl)-3-bromopyrrole.** To a stirred solution of *N*-(triisopropylsilyl)pyrrole (214 mg, 0.96 mmol) in anhydrous THF (2.1 mL) at  $-78\text{ }^{\circ}\text{C}$  was added *N*-bromosuccinimide (170 mg, 0.96 mmol). The reaction mixture was kept at  $-78\text{ }^{\circ}\text{C}$  for 2 h and then warmed to room temperature. The reaction was quenched with  $\text{NaHCO}_3$ , extracted with  $\text{Et}_2\text{O}$  ( $3 \times 20$  mL), and the combined organic extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The crude product was filtered through a short plug of silica gel, which was eluted with 2% EtOAc in hexanes. Concentration afforded the desired product as a clear oil (238 mg, 78.7 mmol, 82%). Spectral data matched literature values.<sup>1</sup>



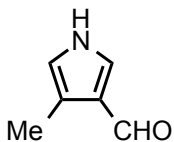
**4-Bromo-1H-pyrrole-3-carboxaldehyde (1g).** To a 0.18 M solution of oxalyl chloride (333  $\mu\text{L}$ , 4.3 mmol) in DCM (24 mL) at  $0\text{ }^{\circ}\text{C}$  was added dropwise a 2 M solution of DMF (333  $\mu\text{L}$ , 4.3 mmol) in DCM (2.2 mL). The reaction mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 30 min before rapid addition of a 1.15 M solution of 3-bromo-*N*-(triisopropylsilyl)pyrrole (1000 mg, 3.3 mmol) in DCM (2.88 mL). The reaction mixture was heated to reflux and stirred for 30 min. The solvent was removed under reduced pressure, and the crude mixture was resuspended in 1 M NaOH (20 mL) and stirred at room temperature overnight. The reaction was quenched with saturated  $\text{NH}_4\text{Cl}$ , and the product was extracted with EtOAc ( $3 \times 25$  mL). The combined organic extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. Purification by recrystallization from hot EtOAc and hexanes afforded the aldehyde as a white solid (359 mg, 2.06 mmol, 62%).  $^1\text{H-NMR}$  (400 MHz; acetone- $d_6$ ):  $\delta$  11.12 (s, 1H), 9.80 (s, 1H), 7.59 (d,  $J = 2.1$  Hz, 1H), 7.04 (d,  $J = 2.1$  Hz, 1H);  $^{13}\text{C-NMR}$  (101 MHz, acetone- $d_6$ ):  $\delta$  184.87, 127.62, 123.83, 121.89, 96.66; HRMS (FAB) calcd for  $\text{C}_5\text{H}_4\text{BrNO}$  [ $M$ ] $^+$ , 172.9476; found, 172.9473.



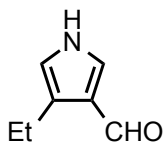
**N-(Triisopropylsilyl)-3-methylpyrrole.** To a solution of 3-bromo-*N*-(triisopropylsilyl)pyrrole (400 mg, 1.32 mmol) in THF (6.6 mL) was added *n*-butyllithium (1.85 M, 1.46 mmol) at  $-78\text{ }^{\circ}\text{C}$ . The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 10 min then MeI (107  $\mu\text{L}$ , 1.72 mmol) was added, and the mixture was warmed to  $0\text{ }^{\circ}\text{C}$  over 1 h. The reaction mixture was quenched by addition of saturated  $\text{NH}_4\text{Cl}$  and extracted with EtOAc ( $3 \times 25$  mL). The combined organic extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated to dryness to afford the desired alkyl pyrrole as a yellow oil (306 mg, 97%), which was used without purification. Spectral data matched literature values.<sup>3</sup>



**N-(Triisopropylsilyl)-3-ethylpyrrole.** To a solution of 3-bromo-*N*-(triisopropylsilyl)pyrrole (400 mg, 1.32 mmol) in THF (6.6 mL) was added *n*-butyllithium (1.85 M, 1.46 mmol) at  $-78\text{ }^{\circ}\text{C}$ . The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 10 min then iodoethane (118  $\mu\text{L}$ , 1.72 mmol) was added and the mixture was warmed to  $0\text{ }^{\circ}\text{C}$  over 1 h. The reaction mixture was quenched using saturated  $\text{NH}_4\text{Cl}$  and extracted with EtOAc ( $3 \times 25\text{ mL}$ ). The combined organic extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated to dryness. The residue was purified by silica gel chromatography (1% EtOAc in hexanes) to afford the desired alkyl pyrrole as a clear oil (180 mg, 54%). Spectral data matched literature values.<sup>4</sup>

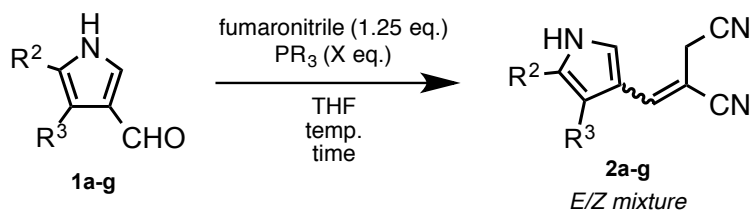


**4-Methyl-1H-pyrrole-3-carboxaldehyde (1e).** To a 0.18 M solution of oxalyl chloride (136  $\mu\text{L}$ , 1.58 mmol) in DCM (8.8 mL) at  $0\text{ }^{\circ}\text{C}$  was added dropwise a 2 M solution of DMF (122  $\mu\text{L}$ , 1.58 mmol) in DCM (800  $\mu\text{L}$ ). The reaction mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 30 min before rapid addition of a 1.15 M solution of 3-methyl-*N*-(triisopropylsilyl)pyrrole (300 mg, 1.26 mmol) in DCM (1.1 mL). The reaction mixture was heated to reflux and stirred for 30 min. The solvent was removed *in vacuo*. The crude product mixture was resuspended in 1 M NaOH (15 mL) and stirred at room temperature overnight, then quenched with  $\text{NH}_4\text{Cl}$  and extracted with EtOAc ( $3 \times 15\text{ mL}$ ). The combined organic extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. Purification by silica gel chromatography (20% acetone in petroleum ether) afforded the aldehyde as an off-white solid (88 mg, 0.81 mmol, 64%). Spectral data matched literature values.<sup>5</sup>

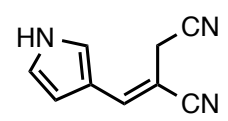


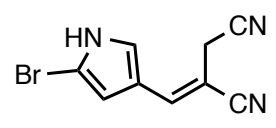
**4-Ethyl-1H-pyrrole-3-carboxaldehyde (1f).** To a 0.18 M solution of oxalyl chloride (77  $\mu\text{L}$ , 0.89 mmol) in DCM (5 mL) at  $0\text{ }^{\circ}\text{C}$  was added dropwise a 2 M solution of DMF (69  $\mu\text{L}$ , 0.89 mmol) in DCM (450  $\mu\text{L}$ ). The reaction mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 30 min before rapid addition of a 1.15 M solution of 3-ethyl-*N*-(triisopropylsilyl)pyrrole (180 mg, 0.72 mmol) in DCM (650  $\mu\text{L}$ ). The reaction mixture was heated to reflux and stirred for 30 min. The solvent was removed *in vacuo*. The crude mixture was resuspended in 1 M NaOH (5 mL) and stirred at room temperature overnight, then quenched with  $\text{NH}_4\text{Cl}$  and extracted with EtOAc ( $3 \times 15\text{ mL}$ ). The combined organic extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. Purification by silica gel chromatography (20% acetone in petroleum ether) afforded the aldehyde as an off-white solid (47 mg, 0.38 mmol, 53%). Spectral data matched literature values.<sup>4</sup>

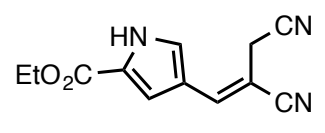
### 1.3 One-Pot, Three-Component Wittig Reaction

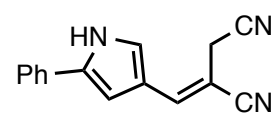


**General Procedure.** To a stirring solution of the pyrrole-3-carboxaldehyde (1.0 equiv.) in THF (0.25 M) at room temperature was added fumaronitrile (1.25 equiv.) followed by phosphine (X equiv.) dropwise. The reaction mixture was stirred at the denoted temperature until the starting material was no longer visible by TLC, then quenched with aqueous  $NaHCO_3$  and extracted with EtOAc ( $\times 3$ ). The combined organic extracts were washed with brine, dried over  $Na_2SO_4$ , and concentrated *in vacuo*. Generally, purification by silica gel chromatography afforded a mixture of the *E* and *Z* olefin Wittig products due to the similar  $R_f$  values of the two isomers. Alternatively, crystallization from EtOAc and hexanes afforded the pure *E* isomer. Spectral data shown below are for the pure *E* isomers.

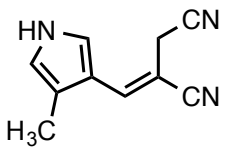
 **2-((1H-Pyrrol-3-yl)methylene)succinonitrile (2a)**. yield: 97%, 3:1 *E/Z*; mp 119-120 °C;  $^1H$ -NMR (400 MHz;  $CDCl_3$ ):  $\delta$  8.73 (s, 1H), 7.34 (s, 1H), 7.11 (q,  $J = 2.1$  Hz, 1H), 6.92 (q,  $J = 2.1$  Hz, 1H), 6.41 (q,  $J = 2.1$  Hz, 1H), 3.52 (s, 2H);  $^{13}C$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  1423.11, 125.20, 121.69, 120.75, 118.89, 117.10, 109.58, 95.26, 19.42; HRMS (FAB) calcd for  $C_9H_7N_3$   $[M]^+$ , 157.0640; found, 157.0637.

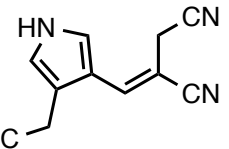
 **2-((5-Bromo-1H-pyrrol-3-yl)methylene)succinonitrile (2b)**. yield: 97%, 3:1 *E/Z*; mp 108-109 °C;  $^1H$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  11.26 (s, 1H), 7.37 (s, 1H), 7.34 (s, 1H), 6.54 (s, 1H), 3.82 (s, 2H);  $^{13}C$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  141.65, 126.21, 120.31, 120.25, 116.85, 111.16, 102.25, 96.86, 19.32; HRMS (FAB) calcd for  $C_9H_6(^{79}Br)N_3$   $[M]^+$ , 234.9745; found, 234.9743.

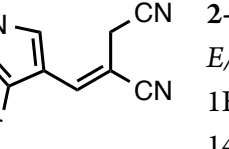
 **Ethyl 4-(2,3-dicyanoprop-1-en-1-yl)-1H-pyrrole-2-carboxylate (2c)**. yield: 96%, 5:1 *E/Z*; mp 134-135 °C;  $^1H$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  11.62 (s, 1H), 7.56 (s, 1H), 7.46 (s, 1H), 7.15 (s, 1H), 4.30 (q,  $J = 7.1$  Hz, 2H), 3.90 (s, 2H), 1.32 (t,  $J = 7.1$  Hz, 3H);  $^{13}C$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  160.80, 141.91, 128.59, 126.05, 120.13, 119.90, 116.84, 115.70, 98.57, 61.11, 19.57, 14.66; HRMS (EI): Exact mass calcd for  $C_{12}H_{11}N_3O_2$   $[M]^+$ , 229.0851. Found 229.0854.

 **2-((5-Phenyl-1H-pyrrol-3-yl)methylene)succinonitrile (2d)**. yield: 88%, 3:1 *E/Z*; mp 197-198 °C;  $^1H$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  11.26 (s, 1H), 7.72 (dd,  $J = 8.5, 1.2$  Hz, 2H), 7.43-7.41 (m, 4H), 7.27 (tt,  $J = 1.2$  Hz, 1H), 6.95

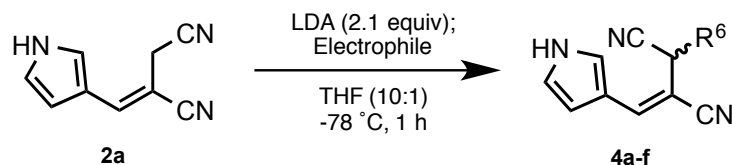
(t,  $J = 2.1$  Hz, 1H), 3.92 (d,  $J = 1.2$  Hz, 2H);  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  142.59, 135.55, 132.70, 129.76, 127.81, 126.55, 125.07, 120.66, 120.44, 117.13, 106.63, 96.18, 19.54; HRMS (FAB): Exact mass calcd for  $\text{C}_{15}\text{H}_{11}\text{N}_3$   $[\text{M}]^+$ , 233.0953. Found 233.0954.

 **2-((4-Methyl-1H-pyrrol-3-yl)methylene)succinonitrile (2e)**. yield: 85%, 4:1 *E/Z*; mp 109-111 °C;  $^1\text{H}$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  10.59 (s, 1H), 7.38 (d,  $J = 1.3$  Hz, 1H), 7.26 (t,  $J = 1.2$  Hz, 1H), 6.75 (s, 1H), 3.75 (d,  $J = 1.3$  Hz, 2H), 2.14 (s, 3H);  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  141.32, 122.30, 120.68, 120.56, 118.51, 117.64, 116.98, 95.82, 19.89, 9.90; HRMS (FAB) calcd for  $\text{C}_{10}\text{H}_9\text{N}_3$   $[\text{M}]^+$ , 171.0797; found, 171.0793.

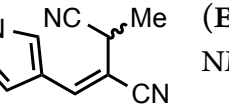
 **2-((4-Ethyl-1H-pyrrol-3-yl)methylene)succinonitrile (2f)**. yield: 85%, 4:1 *E/Z*; mp 108-109 °C;  $^1\text{H}$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  10.63 (s, 1H), 7.40 (s, 1H), 7.26 (s, 1H), 6.77 (s, 1H), 3.76 (s, 2H), 2.59 (q,  $J = 7.5$  Hz, 2H), 1.18 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  141.23, 127.62, 122.33, 120.67, 117.34, 117.00, 116.71, 95.92, 19.93, 18.57, 14.90; HRMS (FAB) calcd for  $\text{C}_{11}\text{H}_{11}\text{N}_3$   $[\text{M}]^+$ , 185.0953; found, 185.0950.

 **2-((4-Bromo-1H-pyrrol-3-yl)methylene)succinonitrile (2g)**. yield: 93%, 5:3 *E/Z*; mp 124-125 °C  $^1\text{H}$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  11.17 (s, 1H), 7.42 (s, 1H), 7.28 (s, 1H), 7.13 (s, 1H), 3.82 (s, 2H);  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  140.01, 122.67, 120.84, 119.94, 117.01, 116.62, 100.06, 99.00, 19.93; HRMS (FAB) calcd for  $\text{C}_9\text{H}_6(^{79}\text{Br})\text{N}_3$   $[\text{M}]^+$ , 234.9745; found, 234.9739.

#### 1.4 Dianionic Alkylation of 2a

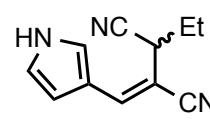


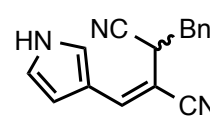
**General Procedure.** To a stirring 0.3 M solution of alkene **2a** in THF at  $-78$  °C was added 2.2 eq. of LDA dropwise. The reaction mixture was stirred for 20 min and the electrophile (1.05 equiv.) was quickly added. The reaction mixture was allowed to warm to  $0$  °C over 1 h, then quenched with  $\text{NH}_4\text{Cl}$  and extracted with  $\text{EtOAc}$  ( $\times 3$ ), and the combined organic extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. Purification by silica gel chromatography afforded the alkylated products **4a-f**.

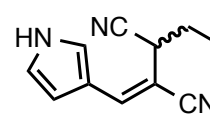
 **(E)-2-((1H-Pyrrol-3-yl)methylene)-3-methylsuccinonitrile (4a)**. yield: 77%;  $^1\text{H}$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  10.81 (s, 1H), 7.37 (s, 1H), 7.36 (dd,  $J = 2.8, 2.2$

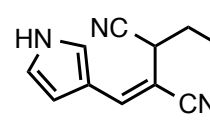


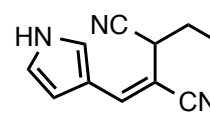
Hz, 1H), 7.00 (q,  $J = 2.2$  Hz, 1H), 6.50 (dd,  $J = 2.8, 2.2$  Hz, 1H), 4.33 (q,  $J = 7.0$  Hz, 1H), 1.61 (d,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  142.08, 125.50, 121.87, 120.47, 119.34, 118.63, 109.49, 102.61, 25.97, 18.04; HRMS (FAB): Exact mass calcd for  $\text{C}_{10}\text{H}_9\text{N}_3$   $[\text{M}]^+$ , 171.0797. Found 171.0799.

 (E)-2-((1H-Pyrrol-3-yl)methylene)-3-ethylsuccinonitrile (**4b**). yield: 80%;  $^1\text{H}$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  10.79 (s, 1H), 7.41 (s, 1H), 7.36 (m, 1H), 7.00 (m, 1H), 6.50 (m, 1H), 4.15 (t,  $J = 7.5$  Hz, 1H), 1.97 (m, 2H), 1.14 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  142.86, 125.62, 121.87, 119.58, 119.54, 118.62, 109.41, 101.29, 32.98, 26.32, 11.57; HRMS (FAB): Exact mass calcd for  $\text{C}_{11}\text{H}_{11}\text{N}_3$   $[\text{M}]^+$ , 185.0953. Found 185.0954.

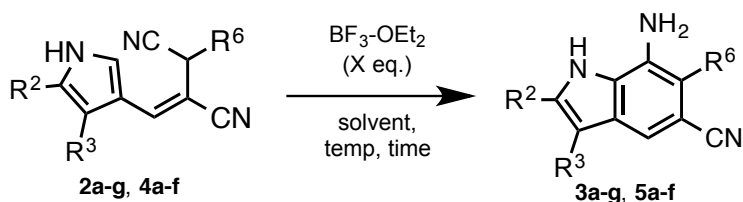
 (E)-2-((1H-Pyrrol-3-yl)methylene)-3-benzylsuccinonitrile (**4c**). yield: 75%;  $^1\text{H}$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  10.77 (s, 1H), 7.43-7.24 (m, 7H), 6.98 (q,  $J = 2.5$  Hz, 1H), 6.48 (q,  $J = 2.2$  Hz, 1H), 4.51 (t,  $J = 7.9$  Hz, 1H), 3.34 (dd,  $J = 13.7, 7.9$  Hz, 1H), 3.22 (dd,  $J = 13.7, 7.9$  Hz, 1H);  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  143.17, 136.90, 129.96, 129.38, 128.14, 125.60, 121.89, 119.55, 119.26, 118.47, 109.25, 100.80, 38.13, 33.43; HRMS (FAB): Exact mass calcd for  $\text{C}_{16}\text{H}_{13}\text{N}_3$   $[\text{M}]^+$ , 247.1110. Found 247.1107.

 (E)-2-((1H-Pyrrol-3-yl)methylene)-3-allylsuccinonitrile (**4d**). yield: 67%;  $^1\text{H}$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  10.82 (s, 1H), 7.41 (s, 1H), 7.36 (dt,  $J = 3.1, 1.6$  Hz, 1H), 7.00 (q,  $J = 2.3$  Hz, 1H), 6.51-6.49 (m, 1H), 5.90 (ddt,  $J = 17.1, 10.2, 6.9$  Hz, 1H), 5.31 (dq,  $J = 17.1, 1.4$  Hz, 1H), 5.20 (dq,  $J = 10.2, 1.4$  Hz, 1H), 4.31 (t,  $J = 7.6$  Hz, 1H), 2.80-2.63 (m, 2H);  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  142.93, 133.43, 125.68, 121.94, 119.75, 119.50, 119.21, 118.59, 109.39, 100.91, 36.67, 31.45; HRMS (FAB): Exact mass calcd for  $\text{C}_{12}\text{H}_{11}\text{N}_3$   $[\text{M}]^+$ , 197.0953. Found 197.0958.

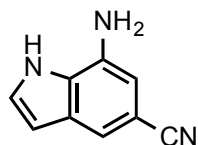
 (E)-2-((1H-Pyrrol-3-yl)methylene)-3-(prop-2-yn-1-yl)succinonitrile (**4e**). yield: 72%;  $^1\text{H}$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  10.83 (s, 1H), 7.47 (s, 1H), 7.38 (q,  $J = 2.3$  Hz, 1H), 7.01 (q,  $J = 2.3$  Hz, 1H), 6.51 (q,  $J = 2.3$  Hz, 1H), 4.48 (t,  $J = 7.4$  Hz, 1H), 3.00-2.85 (m, 2H), 2.67 (t,  $J = 2.7$  Hz, 1H);  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  143.62, 125.92, 122.07, 119.15, 118.53, 118.49, 109.37, 99.99, 79.11, 73.81, 31.48, 22.52; HRMS (FAB): Exact mass calcd for  $\text{C}_{12}\text{H}_9\text{N}_3$   $[\text{M}]^+$ , 195.0797. Found 195.0793.

 Ethyl (E)-3,4-dicyano-5-(1H-pyrrol-3-yl)pent-4-enoate (**4f**). yield: 80%;  $^1\text{H}$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  10.85 (s, 1H), 7.44 (s, 1H), 7.39 (t,  $J = 1.4$  Hz, 1H), 7.03 (d,  $J = 2.4$  Hz, 1H), 6.52 (q,  $J = 2.2$  Hz, 1H), 4.60 (t,  $J = 7.4$  Hz, 1H), 4.17 (q,  $J = 7.1$  Hz, 2H), 3.15-2.98 (m, 2H), 1.23 (t,  $J = 7.1$  Hz, 4H);  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  169.54, 143.25, 125.90, 122.06, 119.19, 118.84, 118.61, 109.45, 99.85, 61.88, 36.63, 28.06, 14.34; HRMS (FAB): Exact mass calcd for  $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_2$   $[\text{M}]^+$ , 243.1008. Found 243.1004.

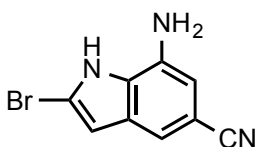
## 1.5 Intramolecular Houben-Hoesch Annulation to Indoles



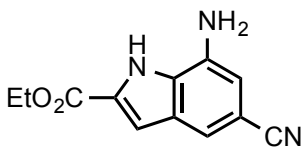
**General Procedure.** To a stirring 0.1 M solution of alkene **2a-g** or **4a-4f** (1.0 equiv.) in the 1,2-dichloroethane at room temperature was added  $\text{BF}_3 \cdot \text{OEt}_2$  (2.5 equiv.). The reaction mixture was heated to 90 °C and stirred until completion (8-12 h), then cooled to room temperature and quenched with  $\text{NaHCO}_3$ . The reaction mixture was extracted with EtOAc ( $\times 3$ ), and the combined organic extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. Crystallization from hot EtOAc and hexanes afforded the desired indoles.



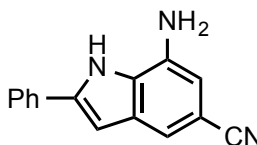
**7-Amino-5-cyano-1H-indole (3a).** yield: 91%; mp 158-159 °C;  $^1\text{H-NMR}$  (400 MHz; acetone- $d_6$ ):  $\delta$  10.48 (s, 1H), 7.42 (d,  $J = 3.1$  Hz, 1H), 7.37 (d,  $J = 1.3$  Hz, 1H), 6.70 (d,  $J = 1.3$  Hz, 1H), 6.53 (d,  $J = 3.1$  Hz, 1H), 5.12 (s, 2H);  $^{13}\text{C-NMR}$  (101 MHz, acetone- $d_6$ ):  $\delta$  134.59, 128.53, 127.84, 125.96, 120.91, 115.53, 106.71, 103.08, 103.00; HRMS (FAB) calcd for  $\text{C}_9\text{H}_7\text{N}_3$   $[\text{M}]^+$ , 157.0640; found, 157.0637.



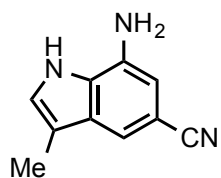
**7-Amino-2-bromo-5-cyano-1H-indole (3b).** yield: 67%; mp 179-180 °C;  $^1\text{H-NMR}$  (400 MHz; acetone- $d_6$ ):  $\delta$  7.30 (s, 1H), 6.72 (s, 1H), 6.61 (s, 1H), 5.15 (s, 1H);  $^{13}\text{C-NMR}$  (101 MHz, acetone- $d_6$ ):  $\delta$  137.84, 130.19, 120.79, 120.54, 114.97, 113.95, 106.15, 106.10, 104.53; HRMS (FAB) calcd for  $\text{C}_9\text{H}_6(^{79}\text{Br})\text{N}_3$   $[\text{M}]^+$ , 234.9745; found, 234.9743.



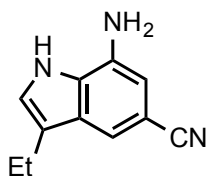
**Ethyl 7-amino-5-cyano-1H-indole-2-carboxylate (3c).** yield: 62%; mp 202-203 °C;  $^1\text{H-NMR}$  (400 MHz; acetone- $d_6$ ):  $\delta$  11.02 (s, 1H), 7.46 (d,  $J = 1.4$  Hz, 1H), 7.21 (d,  $J = 1.6$  Hz, 1H), 6.78 (d,  $J = 1.4$  Hz, 1H), 5.48 (s, 2H), 4.38 (q,  $J = 7.1$  Hz, 2H), 1.37 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C-NMR}$  (101 MHz, acetone- $d_6$ ):  $\delta$  161.84, 136.40, 130.05, 129.75, 128.70, 121.09, 117.44, 109.69, 108.83, 105.67, 61.61, 14.63; HRMS (FAB): Exact mass calcd for  $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_2$   $[\text{M}]^+$ , 229.0851. Found 229.0855.



**7-Amino-5-cyano-2-phenyl-1H-indole (3d).** yield: 87%; mp 209-210 °C;  $^1\text{H-NMR}$  (400 MHz; acetone- $d_6$ ):  $\delta$  10.72 (s, 1H), 7.86 (dd,  $J = 8.3, 1.2$  Hz, 2H), 7.47 (dd,  $J = 8.3, 7.1$  Hz, 2H), 7.37-7.35 (m, 2H), 6.94 (d,  $J = 1.4$  Hz, 1H), 6.71 (d,  $J = 1.4$  Hz, 1H), 5.23 (s, 2H);  $^{13}\text{C-NMR}$  (101 MHz, acetone- $d_6$ ):  $\delta$  140.13, 135.44, 132.85, 130.50, 129.43, 128.82, 126.13, 121.64, 116.02, 108.06, 104.57, 101.09; HRMS (FAB): Exact mass calcd for  $\text{C}_{15}\text{H}_{11}\text{N}_3$   $[\text{M}]^+$ , 233.0953. Found 233.0953.

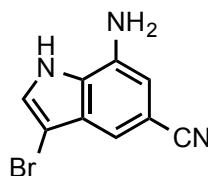


**7-Amino-5-cyano-3-methyl-1H-indole (3e).** yield: 94%; mp 181-182 °C; <sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 10.15 (s, 1H), 7.31 (s, 1H), 7.18 (s, 1H), 6.69 (s, 1H), 5.04 (s, 2H), 2.28 (s, 3H); <sup>13</sup>C-NMR (101 MHz, acetone-d<sub>6</sub>): δ 135.32, 129.66, 128.99, 124.31, 121.90, 114.72, 112.78, 107.66, 103.28, 9.65; HRMS (FAB) calcd for C<sub>10</sub>H<sub>9</sub>N<sub>3</sub> [M]<sup>+</sup>, 171.0797; found, 171.0795.

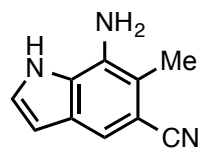


**7-Amino-5-cyano-3-ethyl-1H-indole (3f).** yield: 92%; mp 139-140 °C; <sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 10.16 (s, 1H), 7.35 (s, 1H), 7.20 (s, 1H), 6.69 (s, 1H), 5.05 (s, 2H), 2.74 (q, *J* = 7.5 Hz, 2H), 1.29 (t, *J* = 7.5 Hz, 3H); <sup>13</sup>C-NMR (101 MHz, acetone-d<sub>6</sub>): δ 135.39, 129.12, 128.78, 123.17, 121.91, 114.81, 113.23, 107.65, 103.26, 18.82, 14.96; HRMS (FAB) calcd for C<sub>11</sub>H<sub>11</sub>N<sub>3</sub> [M]<sup>+</sup>, 185.0953; found,

185.0960.

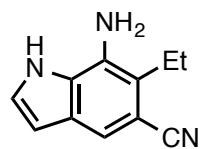


**7-Amino-3-bromo-5-cyano-1H-indole (3g).** yield: 75%; mp 187-189 °C; <sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 10.76 (s, 1H), 7.57 (d, *J* = 1.3 Hz, 1H), 7.22 (d, *J* = 1.3 Hz, 1H), 6.78 (d, *J* = 1.3 Hz, 1H), 5.27 (s, 2H); <sup>13</sup>C-NMR (101 MHz, acetone-d<sub>6</sub>): δ 135.98, 128.22, 128.10, 126.58, 121.11, 113.83, 108.50, 105.26, 91.80; HRMS (FAB) calcd for C<sub>9</sub>H<sub>6</sub>(<sup>79</sup>Br)N<sub>3</sub> [M]<sup>+</sup>, 236.9745; found, 236.9747.



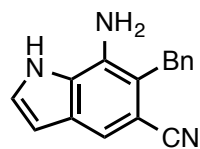
**7-Amino-5-cyano-6-methyl-1H-indole (5a).** yield: 88%; mp 161-162 °C; <sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 10.32 (s, 1H), 7.39 (s, 1H), 7.37 (d, *J* = 3.2 Hz, 1H), 6.47 (d, *J* = 3.2 Hz, 1H), 4.90 (s, 2H), 2.42 (s, 3H); <sup>13</sup>C-NMR (101 MHz, acetone-d<sub>6</sub>): δ 132.77, 129.17, 127.61, 126.49, 121.20, 116.62, 114.06, 105.67, 103.58, 14.92;

HRMS (FAB): Exact mass calcd for C<sub>10</sub>H<sub>9</sub>N<sub>3</sub> [M], 171.0797. Found 171.0793.



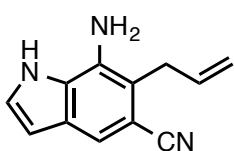
**7-Amino-5-cyano-6-ethyl-1H-indole (5b).** yield: 95%; mp 165-166 °C; <sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 10.34 (s, 1H), 7.40 (s, 1H), 7.37 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.47 (t, *J* = 1.8 Hz, 1H), 4.93 (s, 2H), 2.91 (q, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H); <sup>13</sup>C-NMR (101 MHz, acetone-d<sub>6</sub>): δ 132.05, 129.45, 127.53, 126.54, 121.06,

120.62, 117.08, 105.01, 103.55, 23.02, 14.31; HRMS (FAB): Exact mass calcd for C<sub>11</sub>H<sub>11</sub>N<sub>3</sub> [M]<sup>+</sup>, 185.0953. Found 185.0955.



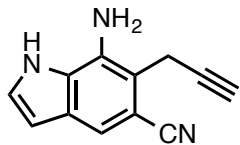
**7-Amino-6-benzyl-5-cyano-1H-indole (5c).** yield: 96%; mp 170-171 °C; <sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 10.45 (s, 1H), 7.50 (s, 1H), 7.40 (d, *J* = 3.2 Hz, 1H), 7.27-7.24 (m, 4H), 7.18-7.15 (m, 1H), 6.53 (d, *J* = 3.2 Hz, 1H), 4.87 (s, 2H), 4.30 (s, 2H); <sup>13</sup>C-NMR (101 MHz, acetone-d<sub>6</sub>): δ 140.55, 133.04, 129.43, 129.17, 128.98, 127.99,

126.89, 126.85, 121.34, 117.33, 117.02, 106.16, 103.71, 35.30; HRMS (FAB): Exact mass calcd for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub> [M]<sup>+</sup>, 247.1110. Found 247.1109.



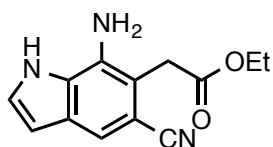
**6-Allyl-7-amino-5-cyano-1H-indole (5d).** yield: 93%; mp 113-115 °C; <sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 10.43 (s, 1H), 7.43 (s, 1H), 7.39 (d, *J* = 3.1 Hz,

1H), 6.50 (d,  $J = 3.1$  Hz, 1H), 5.98 (ddt,  $J = 17.1, 10.1, 6.0$  Hz, 1H), 5.09-5.00 (m, 2H), 4.88 (s, 2H), 3.65 (dt,  $J = 6.0, 1.7$  Hz, 2H);  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  136.08, 132.84, 129.75, 129.03, 127.87, 126.72, 121.00, 117.24, 115.64, 105.66, 103.65, 33.99; HRMS (FAB): Exact mass calcd for  $\text{C}_{12}\text{H}_{11}\text{N}_3$   $[\text{M}]^+$ , 197.0953. Found 197.0960.



**7-Amino-5-cyano-6-(prop-2-yn-1-yl)-1H-indole (5e).** yield: 92%; mp 182-183;  $^1\text{H}$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  10.52 (s, 1H), 7.45 (s, 1H), 7.43 (m, 1H), 6.52 (m, 1H), 5.08 (s, 2H), 3.80 (d,  $J = 2.8$  Hz, 2H), 2.52 (t,  $J = 2.8$  Hz, 1H);  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  133.06, 129.30, 128.18, 127.09, 120.61, 117.30,

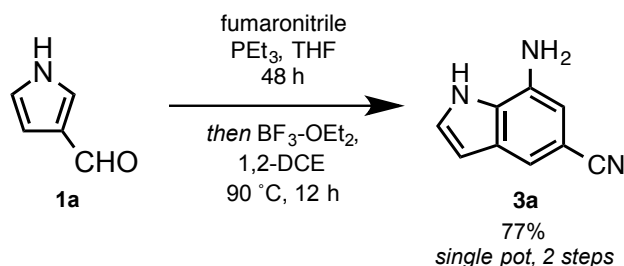
112.97, 105.01, 103.77, 81.35, 70.97, 19.32; HRMS (FAB): Exact mass calcd for  $\text{C}_{12}\text{H}_9\text{N}_3$   $[\text{M}]^+$ , 195.0797. Found 195.0796.



**Ethyl 2-(7-amino-5-cyano-1H-indol-6-yl)acetate (5f).** yield: 72%; mp 177-178  $^\circ\text{C}$ ;  $^1\text{H}$ -NMR (400 MHz; acetone- $d_6$ ):  $\delta$  10.51 (s, 1H), 7.46 (s, 1H), 7.42 (t,  $J = 2.3$  Hz, 1H), 6.52 (t,  $J = 2.0$  Hz, 1H), 5.07 (s, 2H), 4.12 (q,  $J = 7.0$  Hz, 2H), 3.91 (s, 2H), 1.21 (t,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):

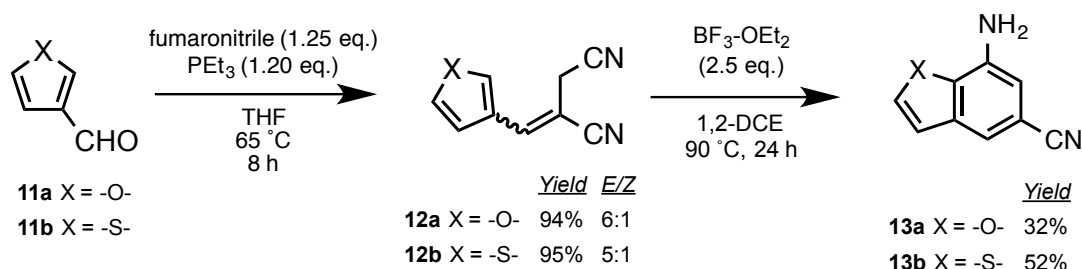
$\delta$  171.32, 133.88, 129.43, 128.24, 127.05, 120.73, 117.41, 111.71, 106.22, 103.81, 61.39, 35.72, 14.49; Exact mass calcd for  $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_2$   $[\text{M}]^+$ , 243.1008. Found 243.1007.

## 1.6 One-Pot Wittig/Houben-Hoesch Indole Synthesis



**Procedure.** To a stirring solution of pyrrole-3-carboxaldehyde (100 mg, 1.05 mmol) in THF (2.1 mL) at room temperature was added fumaronitrile (103 mg, 1.31 mmol) followed by trimethylphosphine (131  $\mu\text{L}$ , 1.26 mmol) dropwise. The reaction mixture was stirred for 48 h, then concentrated on a rotary evaporator. The residue was then taken up in 1,2-DCE (10.5 mL) and  $\text{BF}_3 \cdot \text{OEt}_2$  (324  $\mu\text{L}$ , 2.63 mmol) was added dropwise. The reaction mixture was heated to 90  $^\circ\text{C}$  and stirred for 12 h, then cooled to room temperature and quenched with  $\text{NaHCO}_3$ . The crude product mixture was extracted with EtOAc (3  $\times$  20 mL), and the combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was run through a short plug of silica gel, which was eluted with 30% acetone/petroleum ether, then recrystallized from hot EtOAc and hexanes to afford indole **3a** (128 mg, 0.81 mmol, 77%).

## 1.7 Preparation of Benzofuran 13a and Benzothiophene 13b



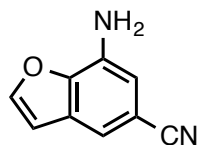
**General Procedure for Wittig Olefination.** To a stirring solution of the heteroaryl-3-carboxaldehyde (1.0 equiv.) in THF (0.25 M) at room temperature was added fumaronitrile (1.25 equiv.) followed by triethylphosphine (1.20 equiv.) dropwise. The reaction mixture was stirred at 65 °C until the starting material was no longer visible by TLC (typically 8 h), then quenched with NaHCO<sub>3</sub> and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification by silica gel chromatography afforded a mixture of the *E*- and *Z*-olefin Wittig products due to the similar R<sub>f</sub> values of the two isomers. Crystallization was unable to separate the two isomers which were used as an *E/Z* mixture (6:1 for **12a**, 5:1 for **12b**) for the cyclization reaction. The spectroscopic data is given for the *E*-isomer.

**2-(Furan-3-ylmethylene)succinonitrile (12a).** <sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 8.10 (s, 1H), 7.77 (d, *J* = 1.4 Hz, 1H), 7.47 (s, 1H), 6.87 (d, *J* = 1.4 Hz, 1H), 3.91 (d, *J* = 1.2 Hz, 2H); <sup>13</sup>C-NMR (101 MHz, acetone-d<sub>6</sub>): δ 147.62, 146.04, 139.13, 120.97, 119.42, 116.56, 110.56, 102.43, 19.60; HRMS (EI): Exact mass calcd for C<sub>9</sub>H<sub>6</sub>N<sub>2</sub>O [M]<sup>+</sup>, 158.0480. Found 158.0483.

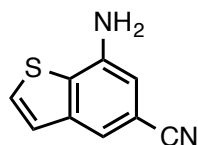
**2-(Thiophen-3-ylmethylene)succinonitrile (12b).** <sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 7.93 (d, *J* = 2.8 Hz, 1H), 7.68 (dd, *J* = 5.1, 2.8 Hz, 1H), 7.61 (s, 1H), 7.40 (dd, *J* = 5.1, 1.3 Hz, 1H), 3.96 (d, *J* = 1.3 Hz, 2H); <sup>13</sup>C-NMR (101 MHz, acetone-d<sub>6</sub>): δ 142.24, 135.29, 131.58, 128.88, 128.44, 119.50, 116.60, 102.85, 19.75; HRMS (EI): Exact mass calcd for C<sub>9</sub>H<sub>6</sub>N<sub>2</sub>S [M]<sup>+</sup>, 174.0252; Found 174.0257.

### General Procedure for Houben-Hoesch Annulation to Benzofuran 13a and Benzothiophene 13b.

To a stirring 0.1 M solution of alkene **12a-b** (1.0 equiv.) in 1,2-dichloroethane at room temperature was added BF<sub>3</sub>·OEt<sub>2</sub> (2.5 equiv.). The reaction mixture was heated to 90 °C and stirred for 24 h. The reaction stalled around 24 h and did not progress further even with addition of excess Lewis acid or extended reaction time. The reaction mixture was then cooled to room temperature and quenched with NaHCO<sub>3</sub>. The reaction mixture was extracted with EtOAc (×3), and the combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Recrystallization from hot EtOAc and hexanes afforded the desired heterocycles **13a-b**.

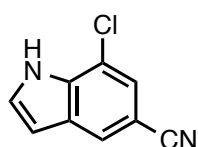
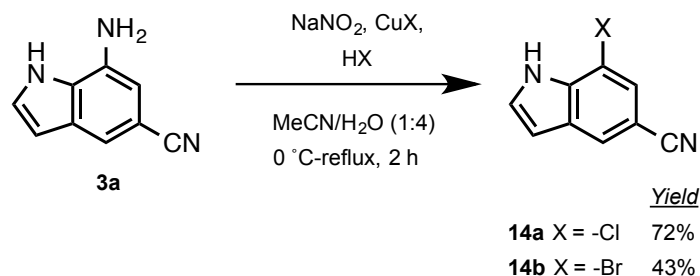


**7-Amino-5-cyanobenzofuran (13a).** yield: 32%; mp 197-198 °C; <sup>1</sup>H-NMR (400 MHz; MeOD): δ 8.09 (d, *J* = 2.2 Hz, 1H), 8.03 (d, *J* = 1.3 Hz, 1H), 7.55 (d, *J* = 1.3 Hz, 1H), 7.11 (d, *J* = 2.2 Hz, 1H); <sup>13</sup>C-NMR (101 MHz, MeOD): δ 150.02, 149.94, 131.47, 125.69, 122.07, 122.04, 120.74, 119.32, 108.61; HRMS (FAB) calcd for C<sub>9</sub>H<sub>6</sub>N<sub>2</sub>O [M]<sup>+</sup>, 158.0480; found, 158.0479.

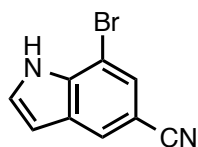


**7-Amino-5-cyanobenzothiophene (13b).** yield: 52%; mp 123-124 °C; <sup>1</sup>H-NMR (300 MHz; acetone-d<sub>6</sub>): δ 7.77 (d, *J* = 5.4 Hz, 1H), 7.63 (d, *J* = 1.4 Hz, 1H), 7.48 (d, *J* = 5.4 Hz, 1H), 6.92 (d, *J* = 1.4 Hz, 1H), 5.50 (s, 2H); <sup>13</sup>C-NMR (101 MHz, acetone-d<sub>6</sub>): δ 144.62, 141.81, 130.72, 128.82, 125.73, 120.43, 117.85, 109.78, 109.60; HRMS (FAB) calcd for C<sub>9</sub>H<sub>6</sub>N<sub>2</sub>S [M]<sup>+</sup>, 174.0252; found, 174.0258.

### 1.8 Elaboration of 3a: Sandmeyer Reaction



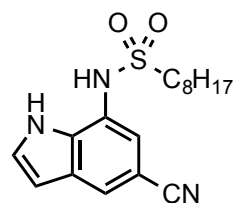
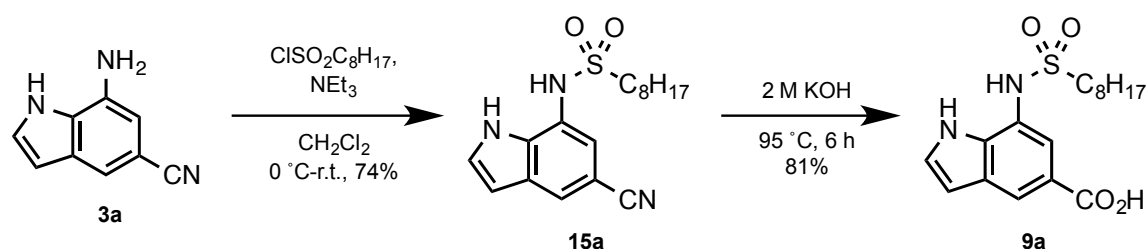
**7-Chloro-5-cyano-1H-indole (14a).** To a stirring solution of 7-amino-5-cyano[1H]indole•HCl (100 mg, 0.52 mmol) in 4.3 mL MeCN and 4.3 mL water at 0 °C was added 0.3 mL concentrated HCl. Sodium nitrite (71 mg, 1.03 mmol) was then added as a solution in 4.3 mL water. The reaction mixture was allowed to warm to room temperature over 30 min before addition of CuCl (256 mg, 2.58 mmol) as a solution in 8.6 mL water. The reaction mixture was heated to reflux for 3 h, then the MeCN was evaporated. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (3 × 30). The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Crystallization from hot EtOAc and hexanes afforded the chlorinated indole (71 mg, 0.40 mmol, 72%). <sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 11.15 (s, 1H), 8.06 (s, 1H), 7.64 (t, *J* = 3.0 Hz, 1H), 7.53 (d, *J* = 1.6 Hz, 1H), 6.76 (dd, *J* = 3.0, 1.6 Hz, 1H); <sup>13</sup>C-NMR (101 MHz, acetone-d<sub>6</sub>): δ 135.10, 129.50, 128.53, 124.94, 122.90, 118.96, 117.25, 103.99, 103.32; HRMS (FAB) calcd for C<sub>9</sub>H<sub>5</sub>ClN<sub>2</sub> [M]<sup>+</sup>, 176.0141; found, 176.0153.



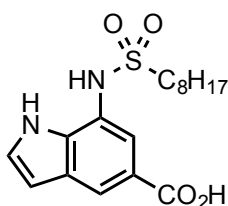
**7-Bromo-5-cyano-1H-indole (14b).** To a stirring solution of the 7-amino-5-cyano[1H]indole•HCl (100 mg, 0.52 mmol) in 4.3 mL MeCN and 4.3 mL water at 0 °C was added the HBr (48% solution in water, 0.3 mL). Sodium nitrite (72 mg, 1.03 mmol) was then added as a solution in 4.3 mL water. The reaction mixture was allowed to warm to room temperature over 30 min before addition of CuBr (370 mg, 2.58 mmol) as a

solution in 8.6 mL water. The reaction mixture was heated to reflux for 3 h, then the MeCN was evaporated. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Purification by recrystallization from EtOAc and hexanes afforded the pure bromoindole (49 mg, 0.22 mmol, 43%). <sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 11.01 (s, 1H), 8.09 (s, 1H), 7.66 (s, 1H), 7.63 (s, 1H), 6.79 (s, 1H); <sup>13</sup>C-NMR (101 MHz, acetone-d<sub>6</sub>): δ 136.62, 129.01, 128.51, 125.89, 125.37, 118.85, 104.73, 104.11, 103.66; HRMS (FAB) calcd for C<sub>9</sub>H<sub>5</sub><sup>79</sup>BrN<sub>2</sub> [M]<sup>+</sup>, 219.9636; found, 219.9637; C<sub>9</sub>H<sub>5</sub><sup>81</sup>BrN<sub>2</sub> [M]<sup>+</sup>, 221.9616; found, 221.9615.

### 1.9 Elaboration of 3a: Preparation of GPAT Inhibitor Analog 9a.



**N-(5-cyano-1H-indol-7-yl)octane-1-sulfonamide (15a).** To a stirring solution of indole **3a** (68 mg, 0.43 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at 0 °C was added octanesulfonyl chloride (101 μL, 0.52 mmol) followed by NEt<sub>3</sub> (121 μL, 0.87 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched by addition of 20 mL NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc/Hexanes) afforded the pure sulfonamide (106 mg, 0.32 mmol, 74%). <sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 10.71 (s, 1H), 8.73 (s, 1H), 7.95 (d, *J* = 1.1 Hz, 1H), 7.60 (t, *J* = 2.8 Hz, 1H), 7.46 (d, *J* = 1.2 Hz, 1H), 6.70 (dd, *J* = 3.2, 1.9 Hz, 1H), 3.24-3.20 (m, 2H), 1.84-1.76 (m, 2H), 1.39 (quintet, *J* = 7.1 Hz, 2H), 1.24 (m, *J* = 11.5 Hz, 8H), 0.85 (t, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (100 MHz; acetone-d<sub>6</sub>): δ 132.4, 130.0, 128.0, 123.6, 123.2, 119.7, 117.5, 103.3, 102.7, 51.0, 31.5, 28.76, 28.74, 27.8, 23.3, 22.3, 13.4; HRMS (EI) calcd for C<sub>17</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>S [M]<sup>+</sup>, 333.1511; found, 333.1510.

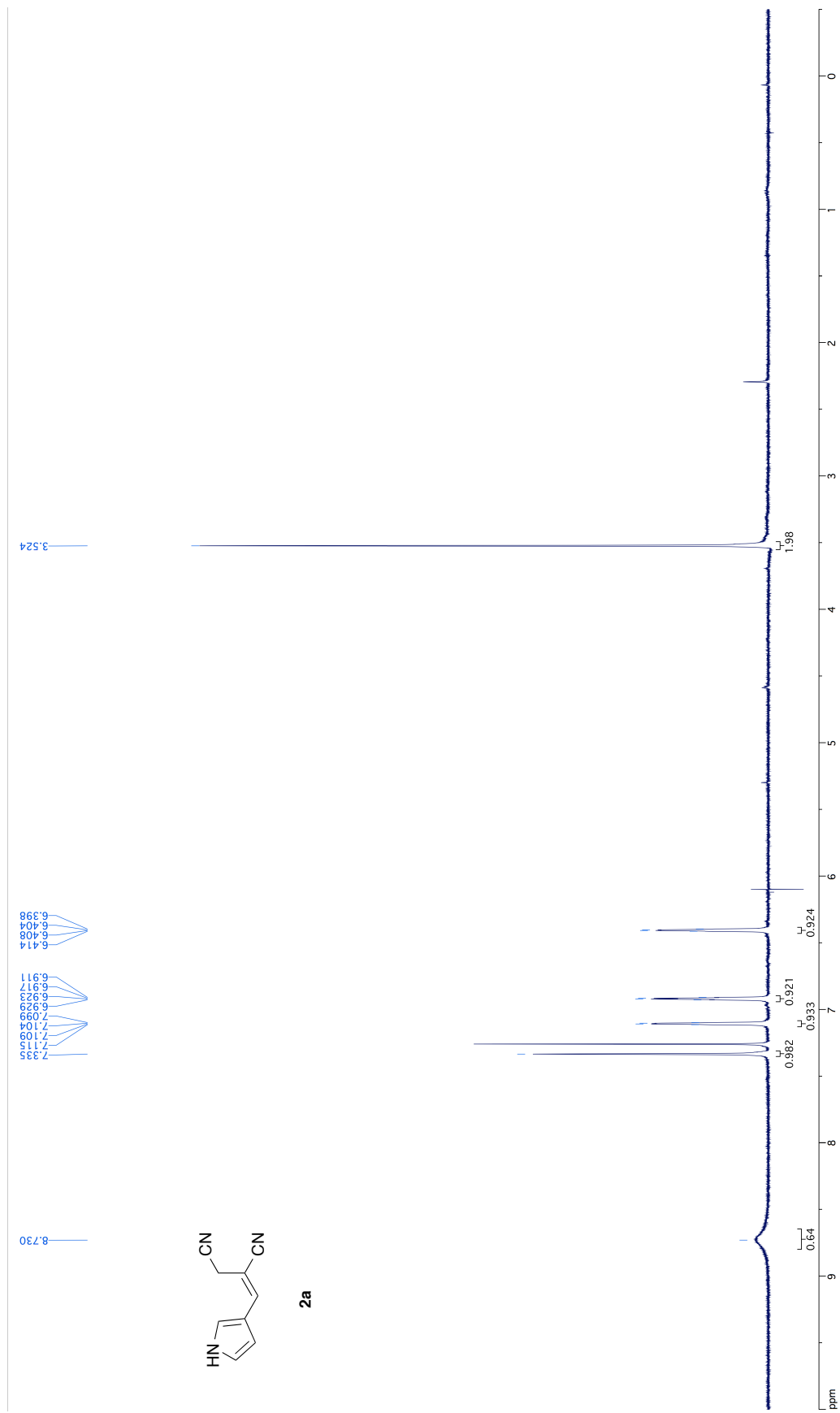


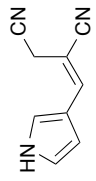
**7-(octylsulfonamido)-1H-indole-5-carboxylic acid (9a).** To a stirring solution the cyanoindole **15a** (33 mg, 0.10 mmol) at room temperature was added 2 M KOH (1 mL). The reaction mixture was stirred at 95 °C for 6 h, then quenched with 1 M HCl (3 mL). The white precipitate was filtered, washed with cold water, and dried. Purification by flash chromatography (20% acetone/77% petroleum ether/3% AcOH) afforded the pure carboxylic acid **9a** (28 mg, 0.080 mmol, 81%). <sup>1</sup>H-NMR (400 MHz; acetone-d<sub>6</sub>): δ 10.60 (s, 1H), 8.28 (s, 1H), 7.90 (s, 1H), 7.50 (s,

1H), 6.67 (s, 1H), 3.15 (m, 2H), 1.81 (m, 2H), 1.37 (m, 2H), 1.22 (m, 8H), 0.84 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$ -NMR (101 MHz, acetone- $d_6$ ):  $\delta$  168.62, 134.35, 130.56, 127.86, 127.70, 122.73, 122.23, 118.15, 104.44, 51.52, 32.41, 30.09, 29.89, 28.75, 24.23, 23.22, 14.31; HRMS (EI) calcd for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$   $[\text{M}]^+$ , 352.1457; found, 352.1456.



## 2 NMR Spectra





2a

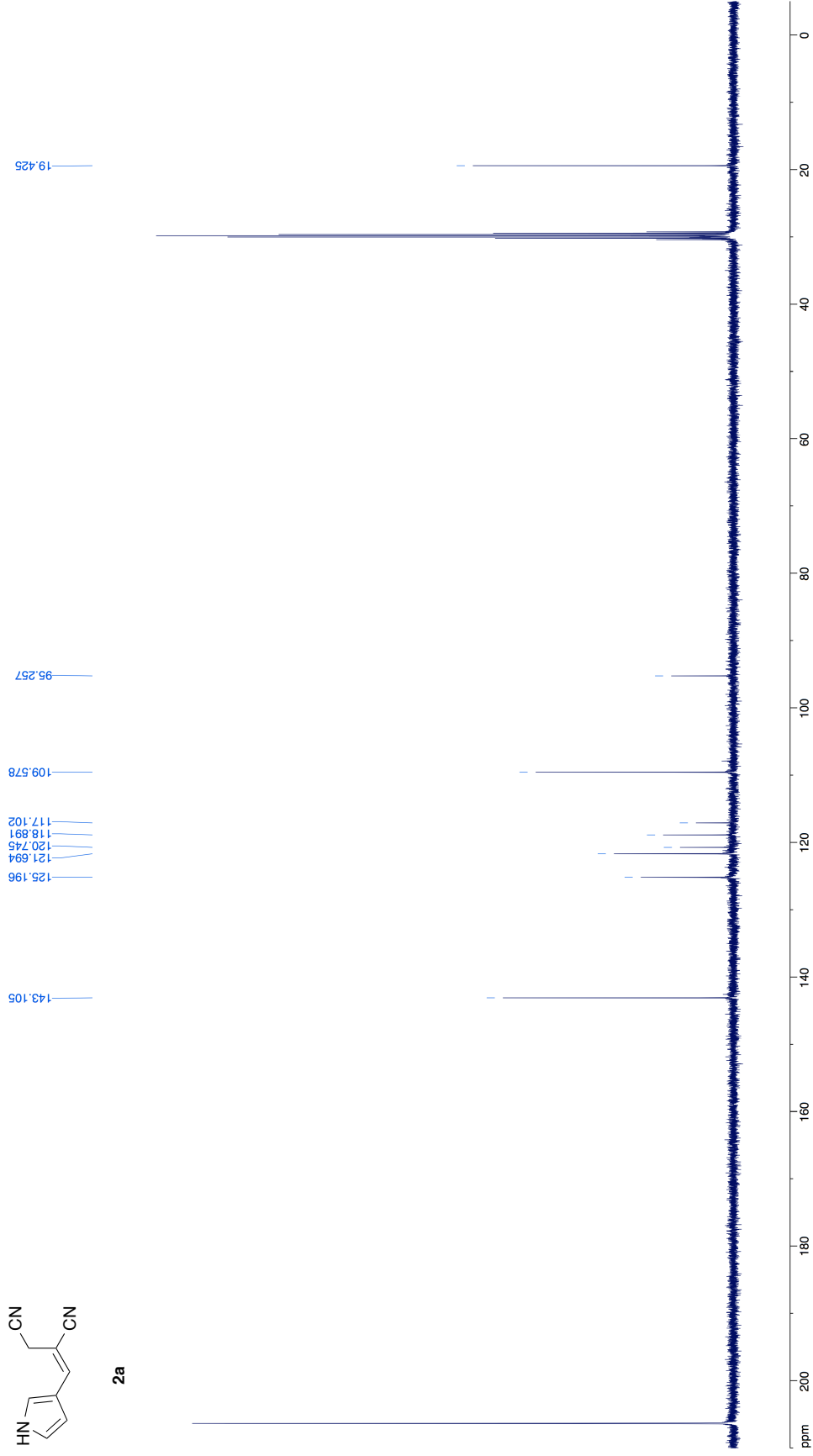


Figure 2 13C-NMR spectrum for compound 2a (acetone-d<sub>6</sub>, 100 MHz)

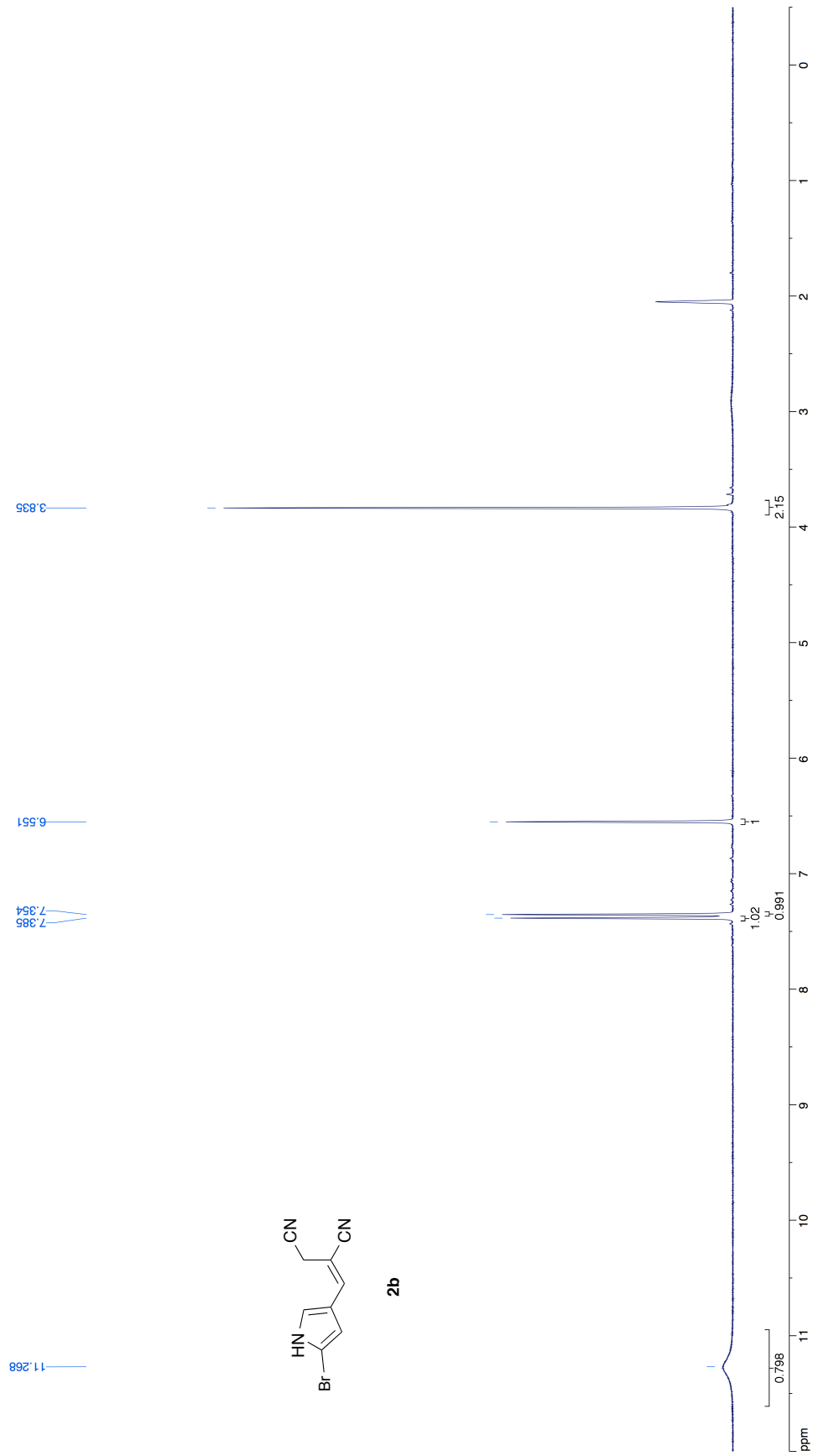
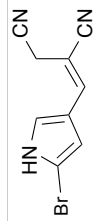


Figure 3 <sup>1</sup>H-NMR spectrum for compound 2b (Acetone-d<sub>6</sub>, 400 MHz)



2b

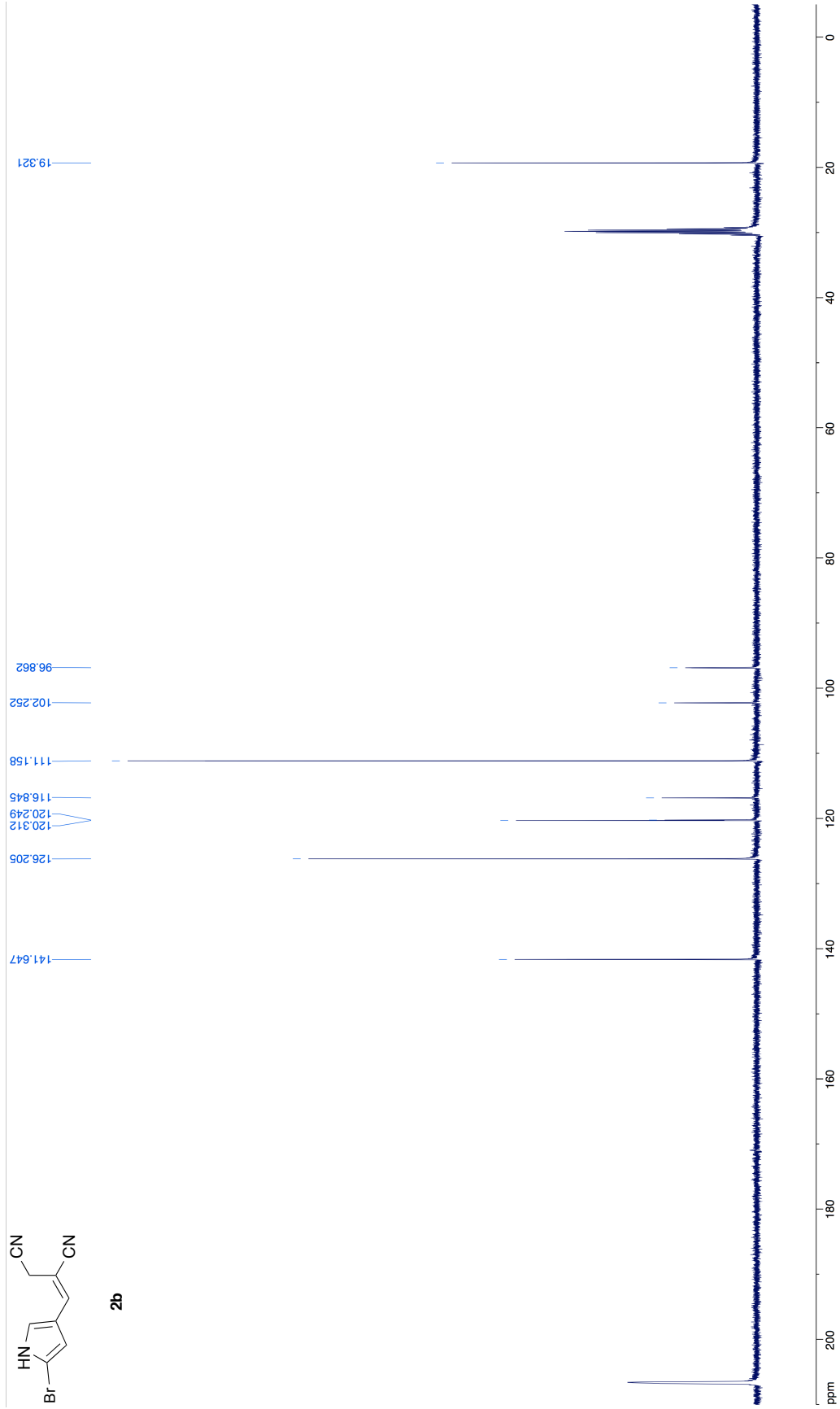


Figure 4 13C-NMR spectrum for compound 2b (Acetone-d<sub>6</sub>, 100 MHz)

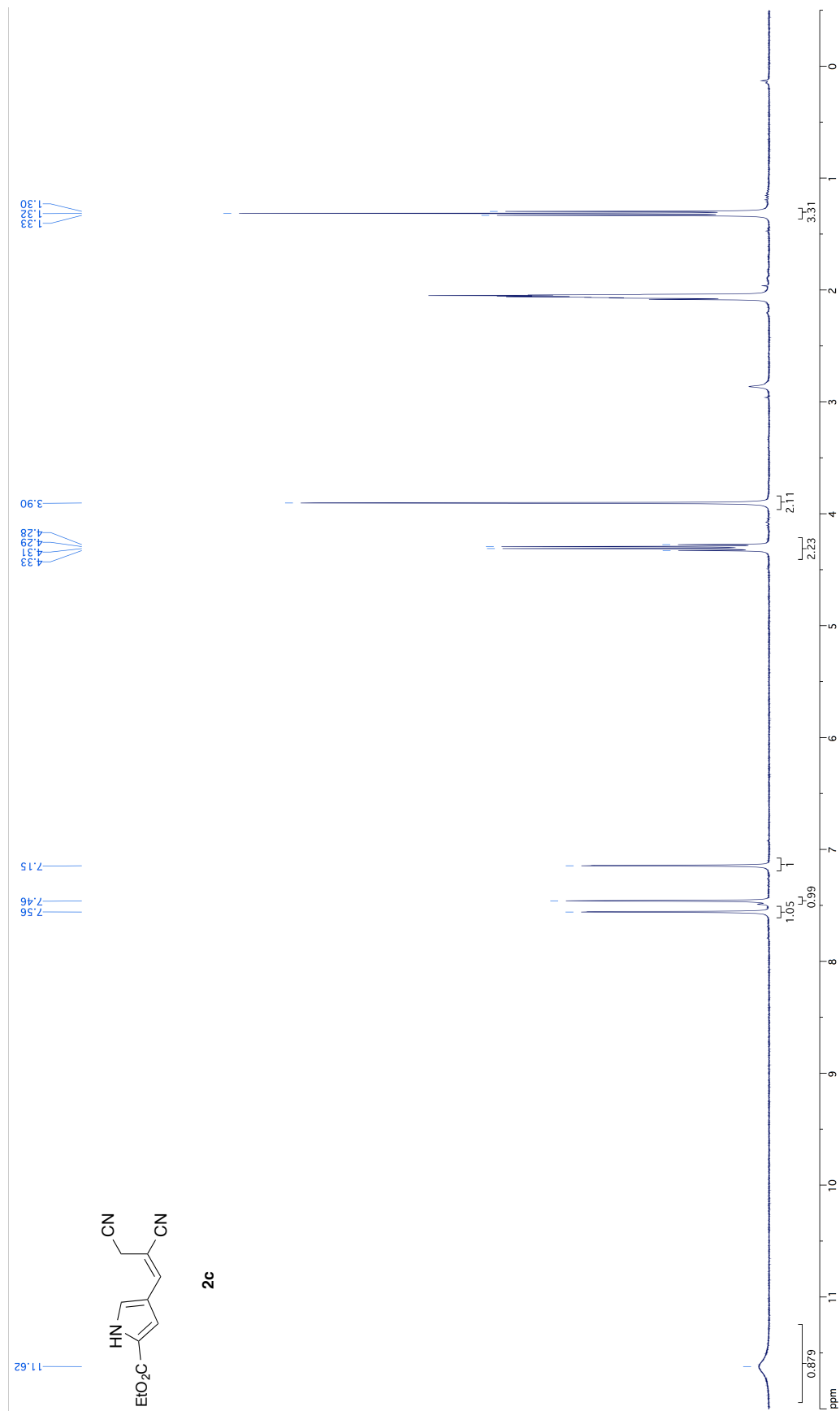


Figure 5 <sup>1</sup>H-NMR spectrum for compound **2c** (Acetone-d<sub>6</sub>, 400 MHz)

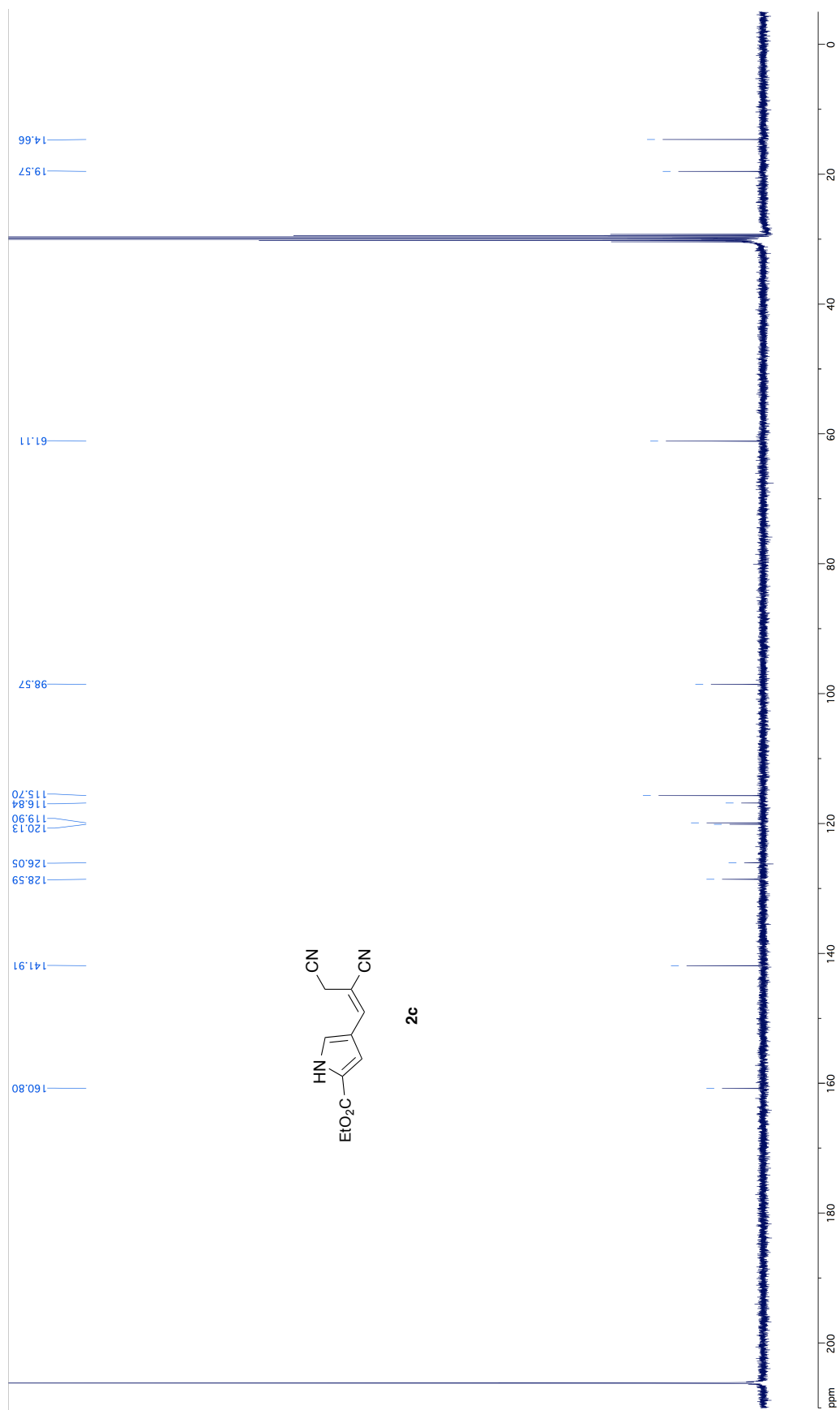


Figure 6 <sup>13</sup>C-NMR spectrum for compound **2c** (Acetone-d<sub>6</sub>, 100 MHz)

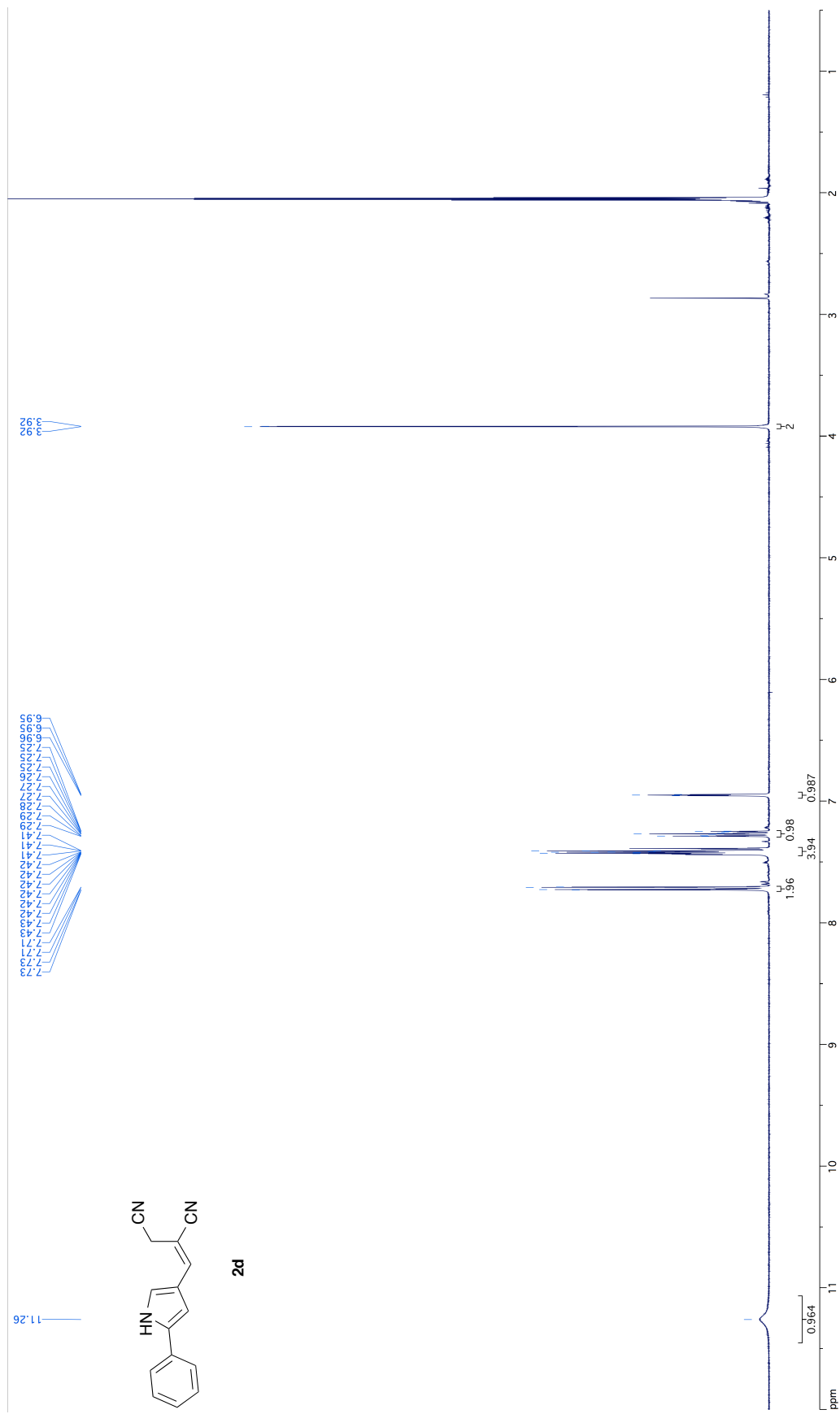


Figure 7 <sup>1</sup>H-NMR spectrum for compound 2d (Acetone-d<sub>6</sub>, 400 MHz)



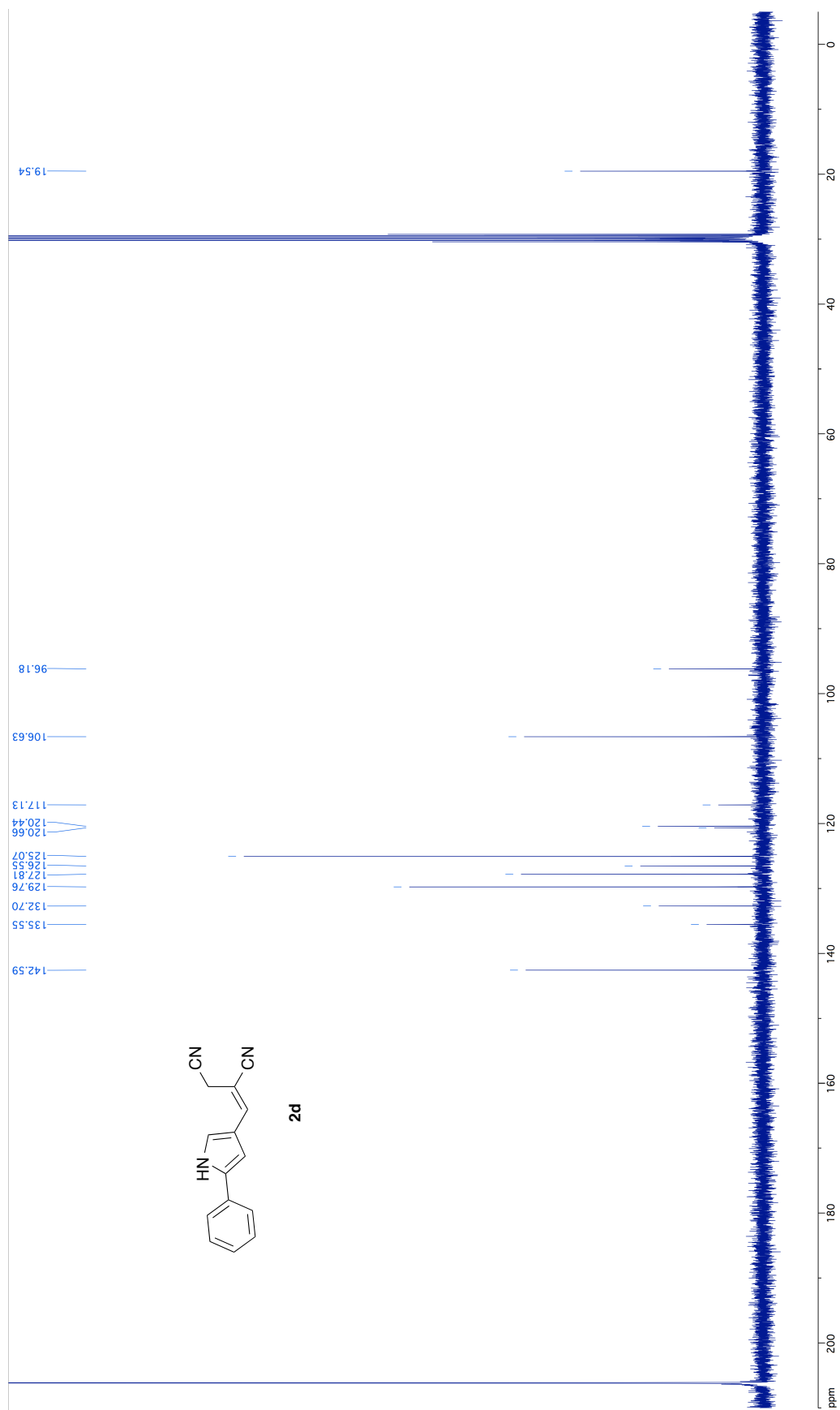


Figure 8 13C-NMR spectrum for compound 2d (Acetone-d<sub>6</sub>, 100 MHz)

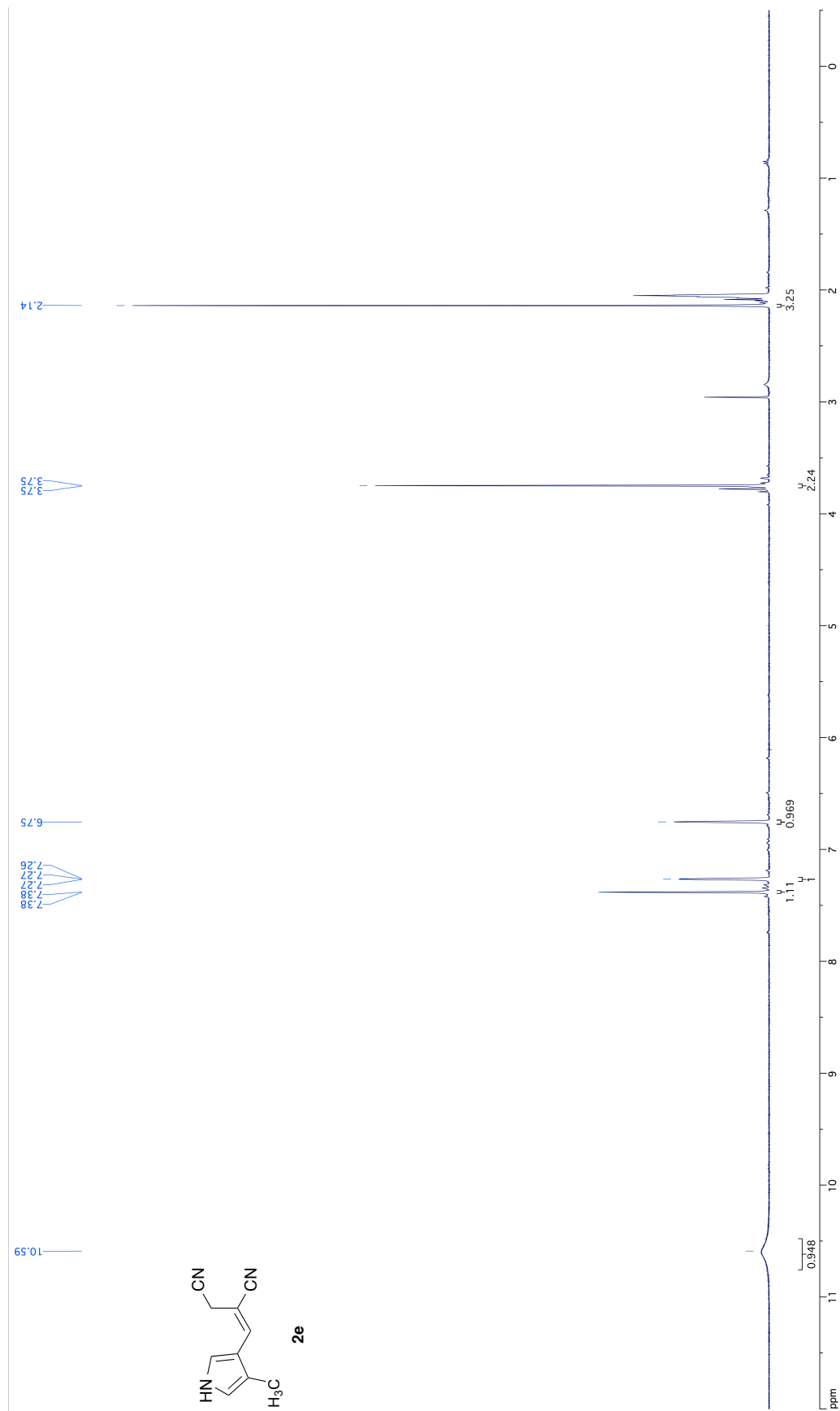


Figure 9 <sup>1</sup>H-NMR spectrum for compound **2e** (Acetone-d<sub>6</sub>, 400 MHz)

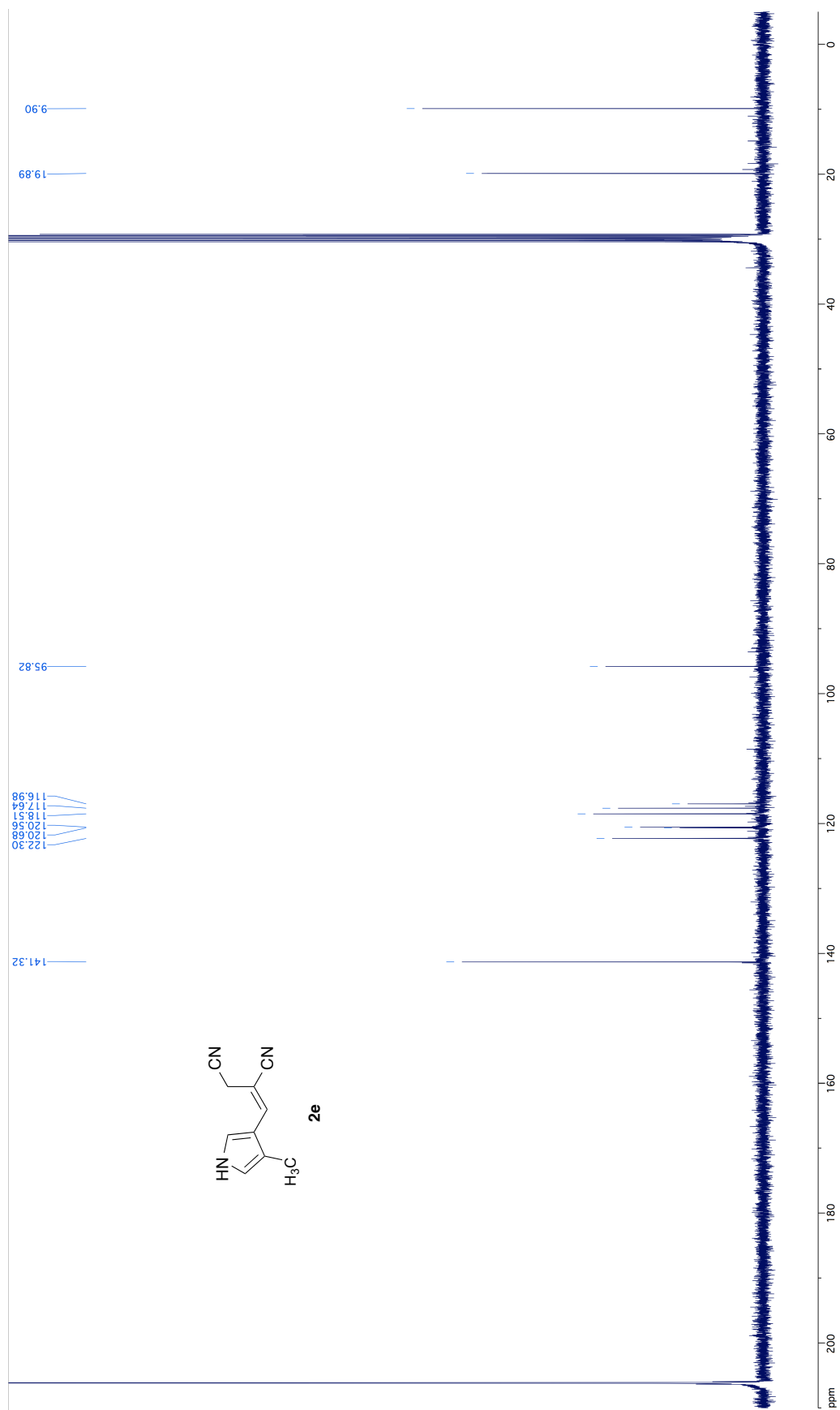
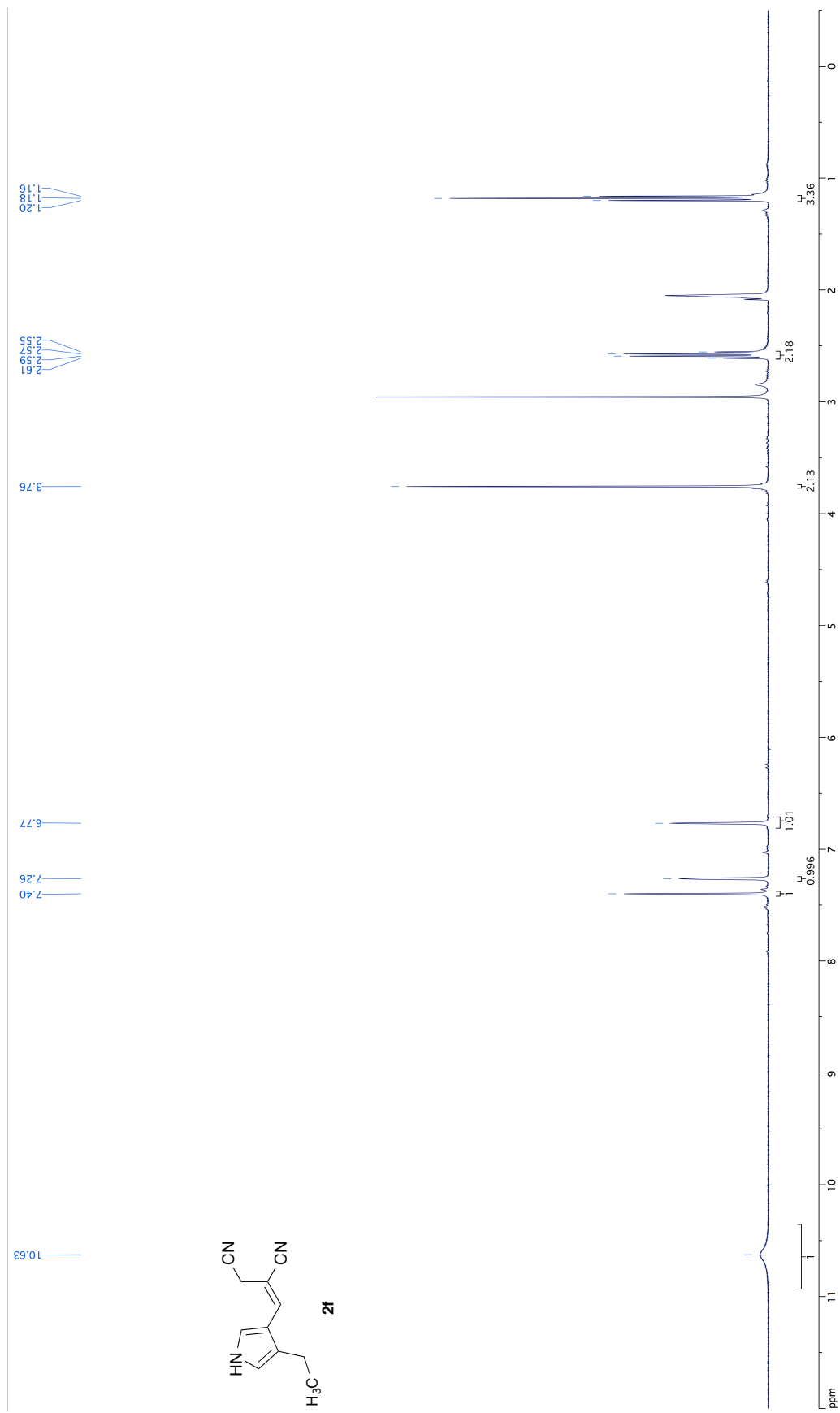
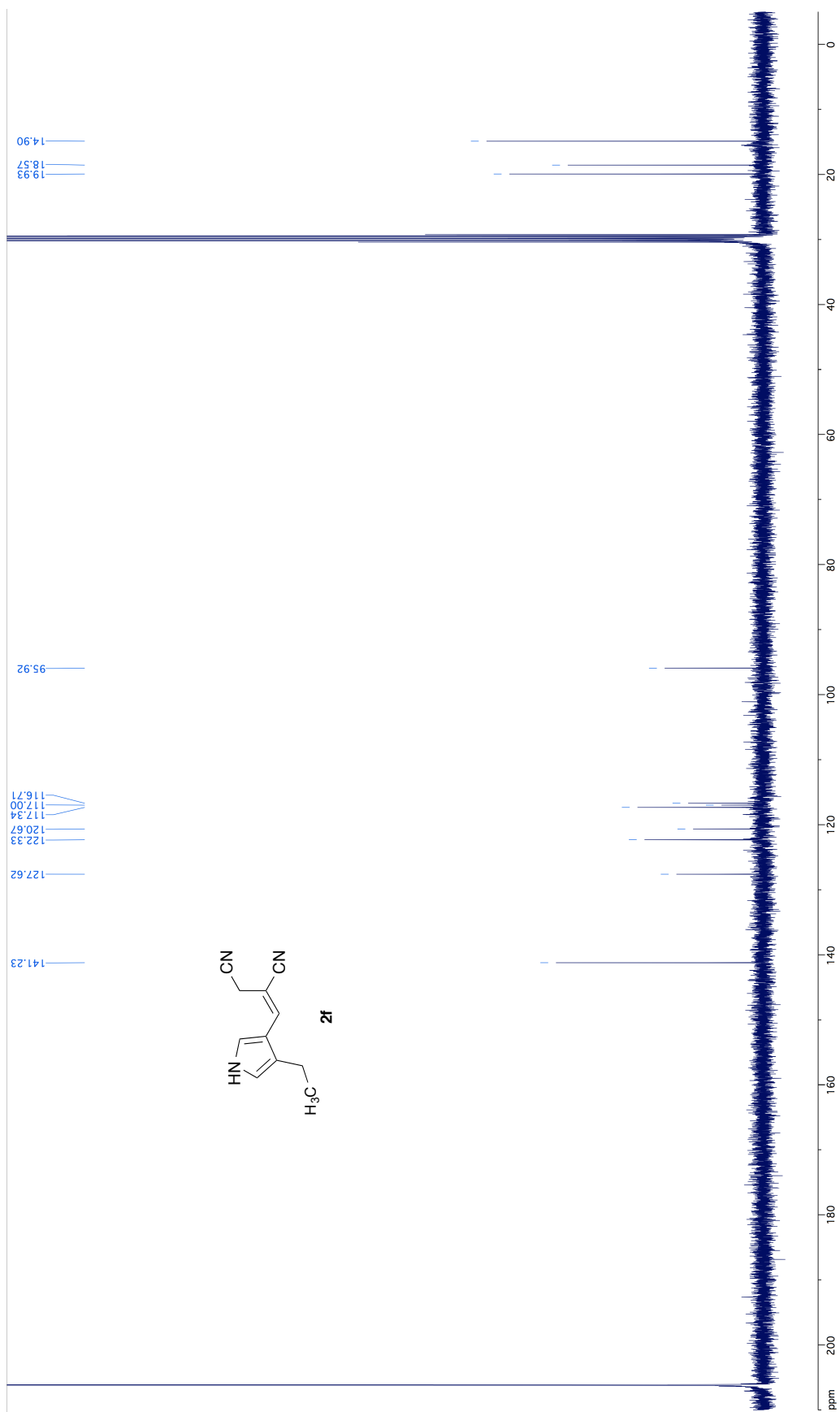


Figure 10 <sup>13</sup>C-NMR spectrum for compound **2e** (Acetone-d<sub>6</sub>, 100 MHz)





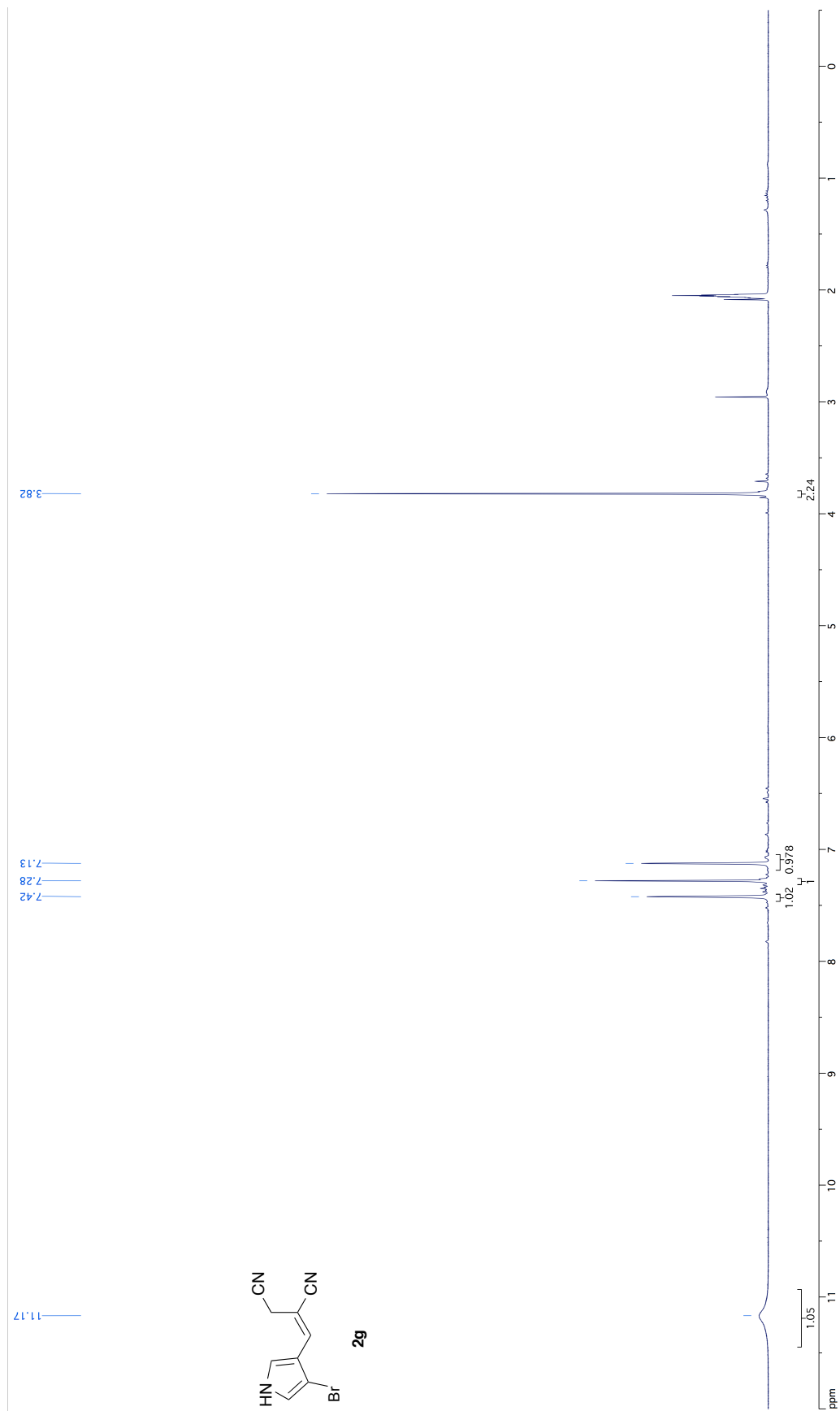


Figure 13 <sup>1</sup>H-NMR spectrum for compound 2g (Acetone-d<sub>6</sub>, 400 MHz)

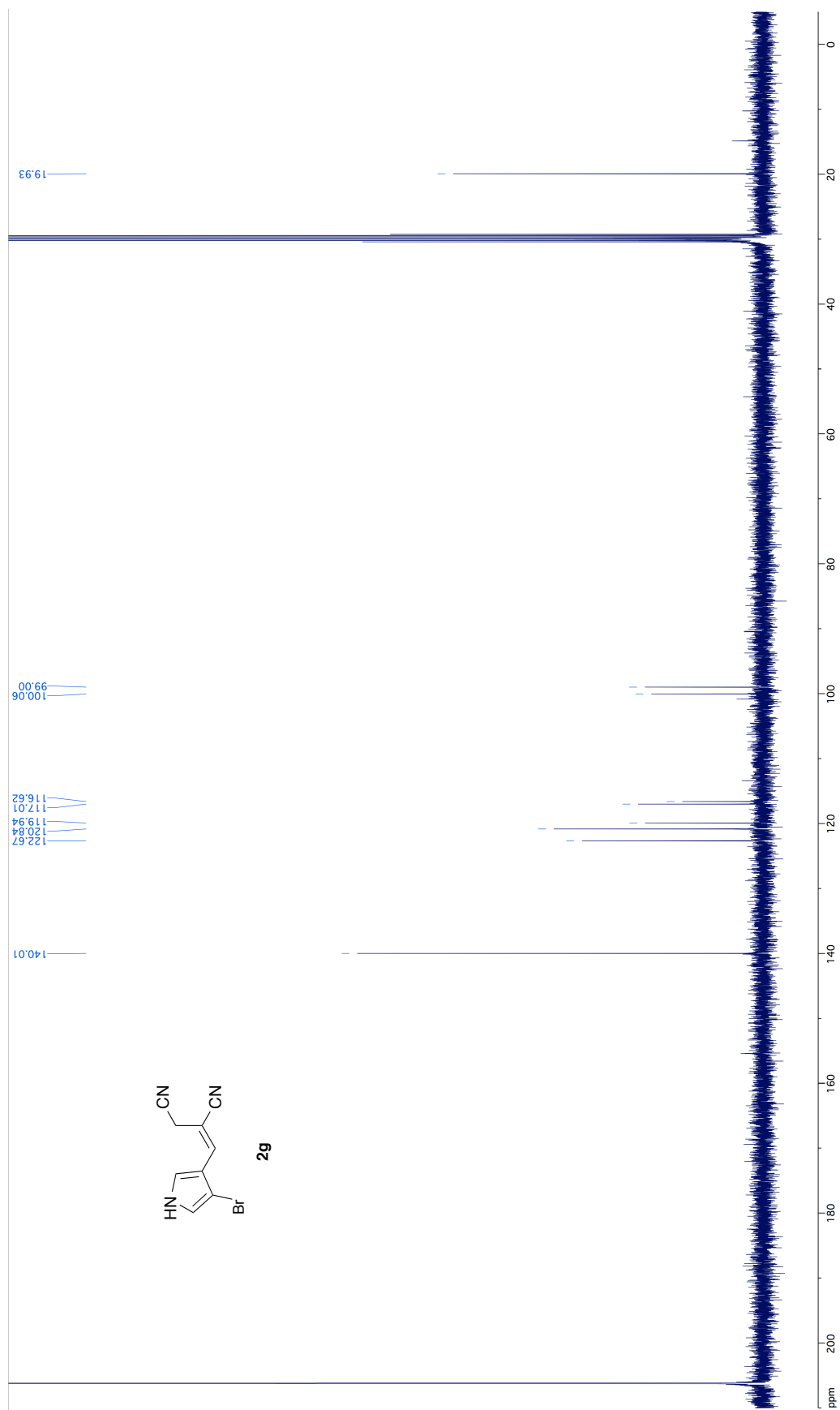
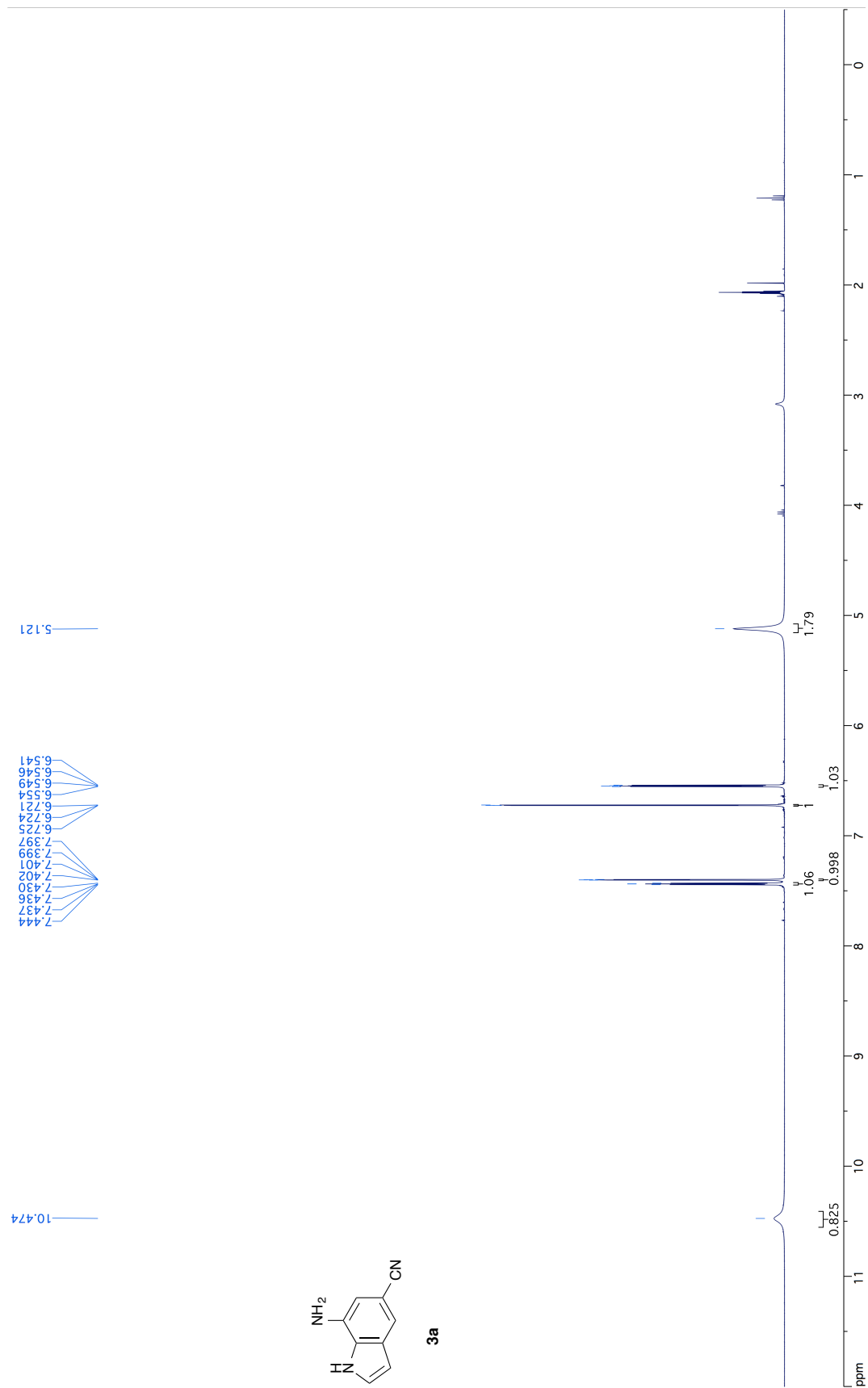
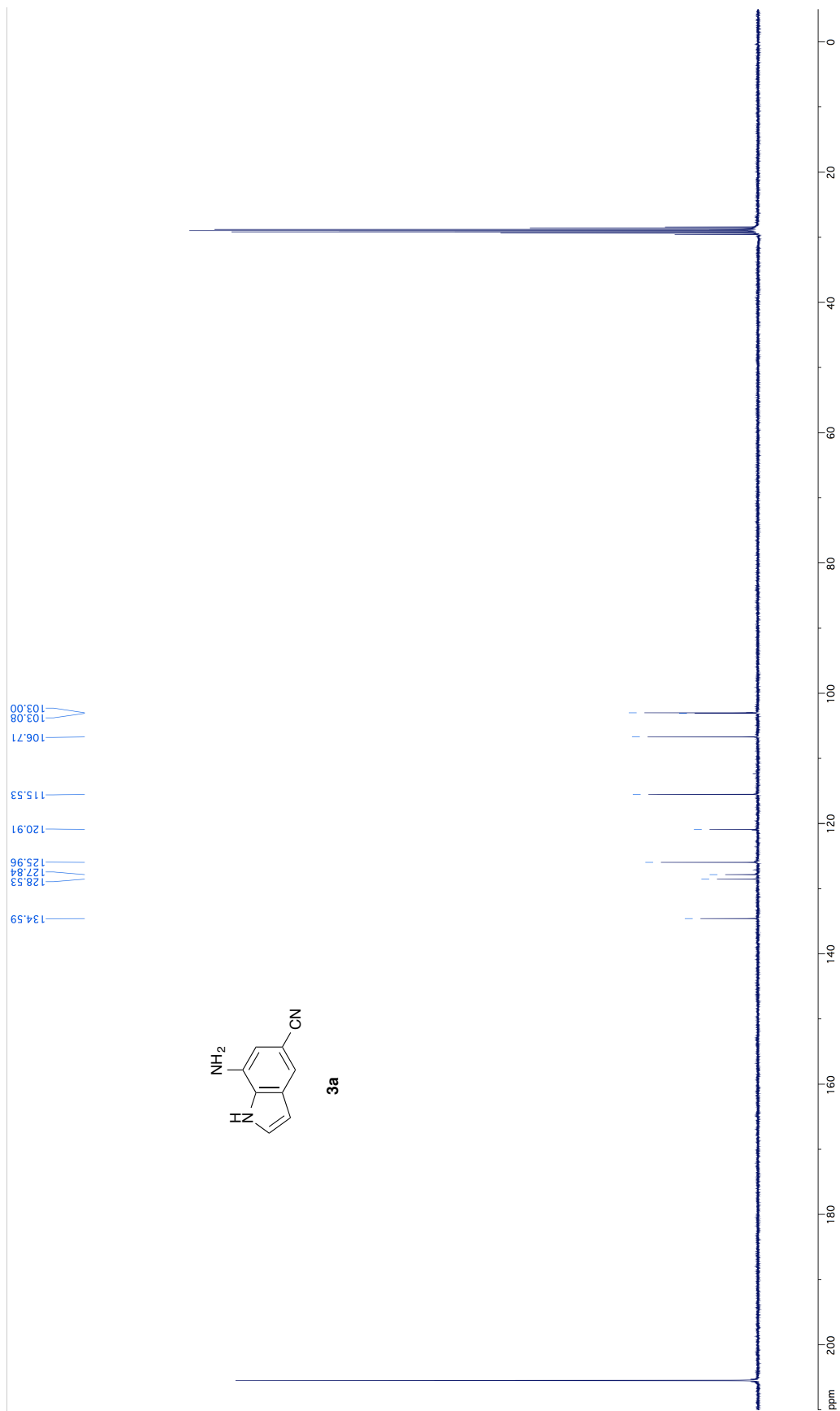


Figure 14 <sup>13</sup>C-NMR spectrum for compound **2g** (Acetone-d<sub>6</sub>, 100 MHz)







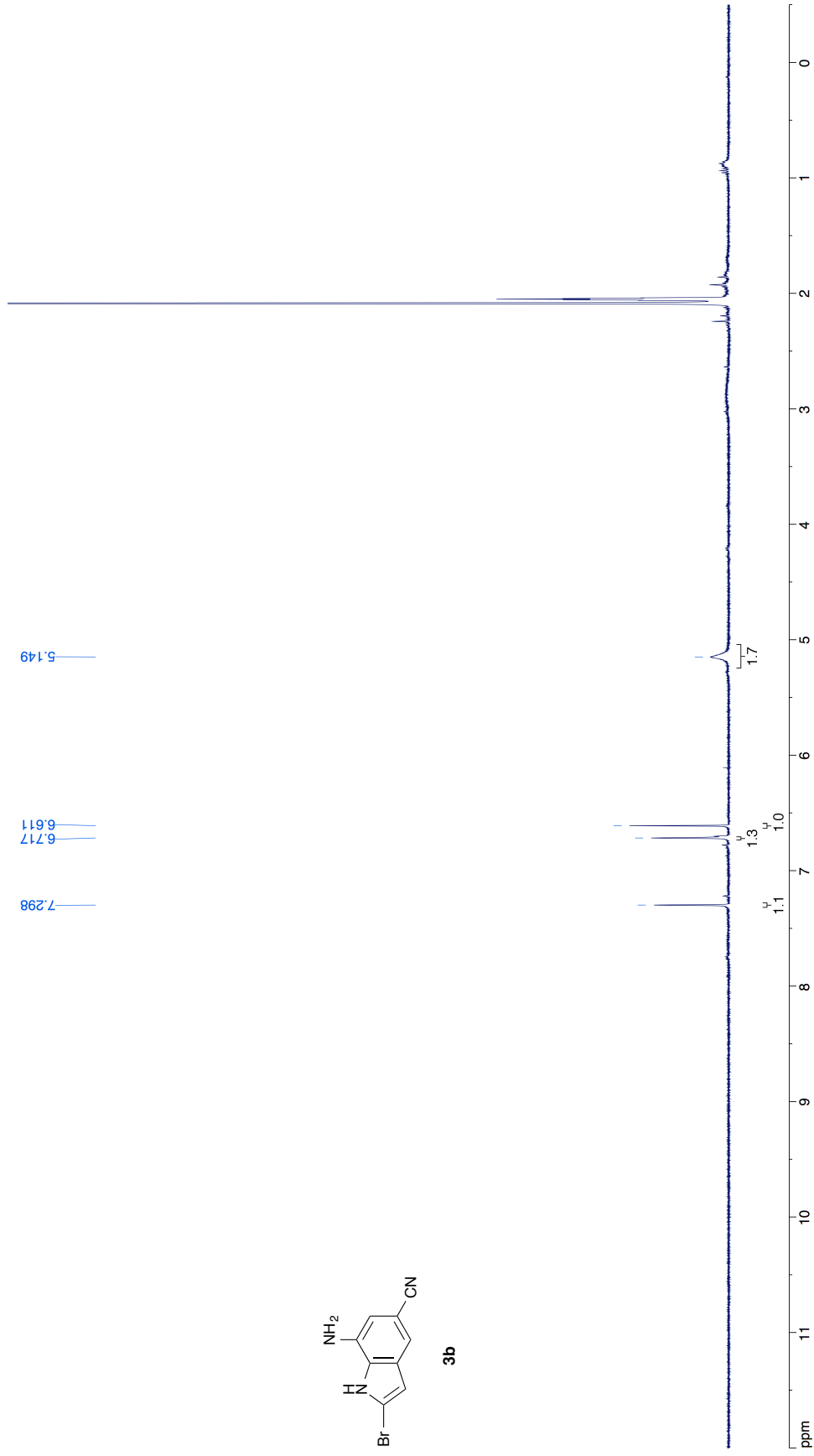
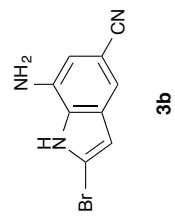


Figure 17 1H-NMR spectrum for compound 3b (Acetone-d<sub>6</sub>, 400 MHz)

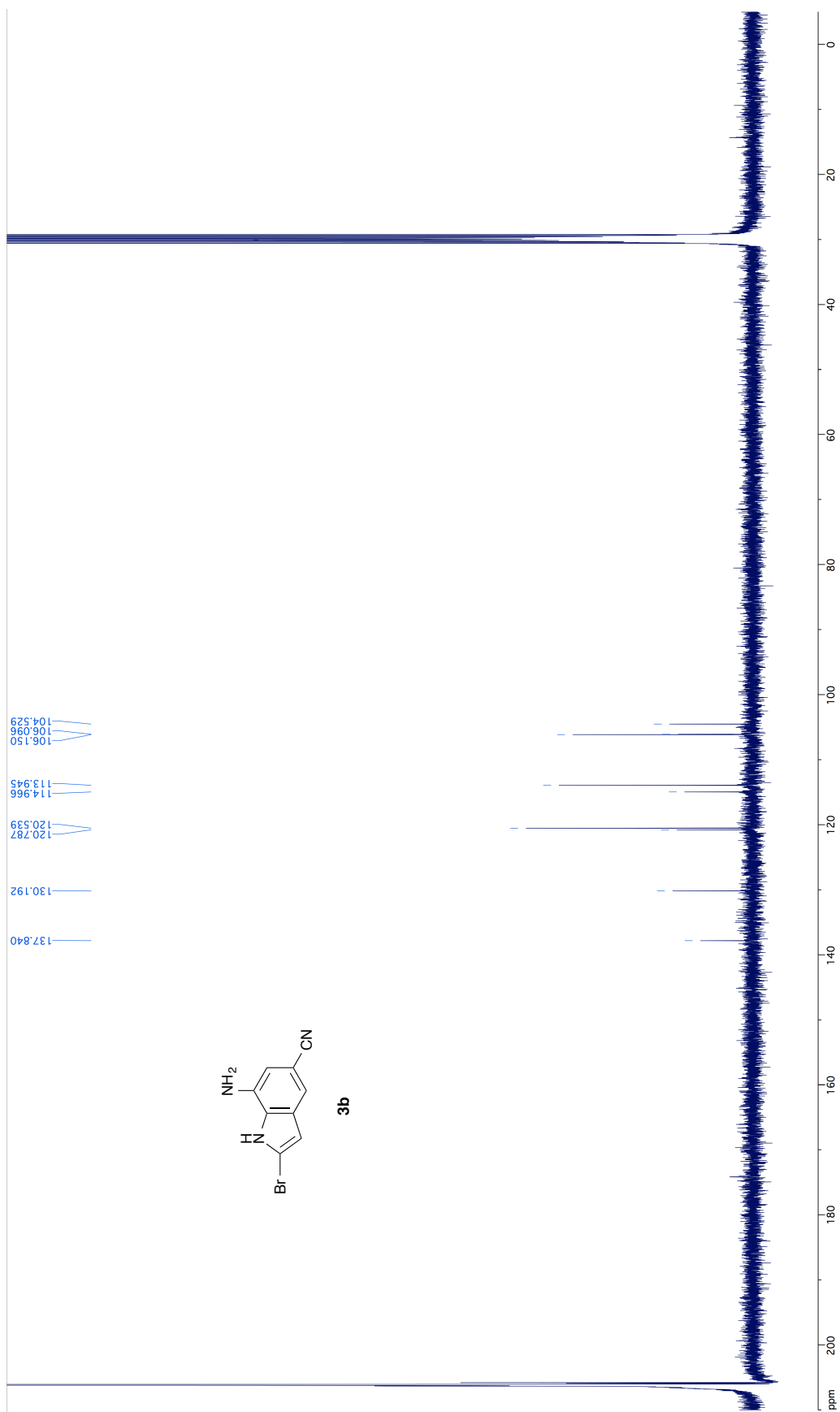


Figure 18 <sup>13</sup>C-NMR spectrum for compound **3b** (Acetone-d<sub>6</sub>, 100 MHz)

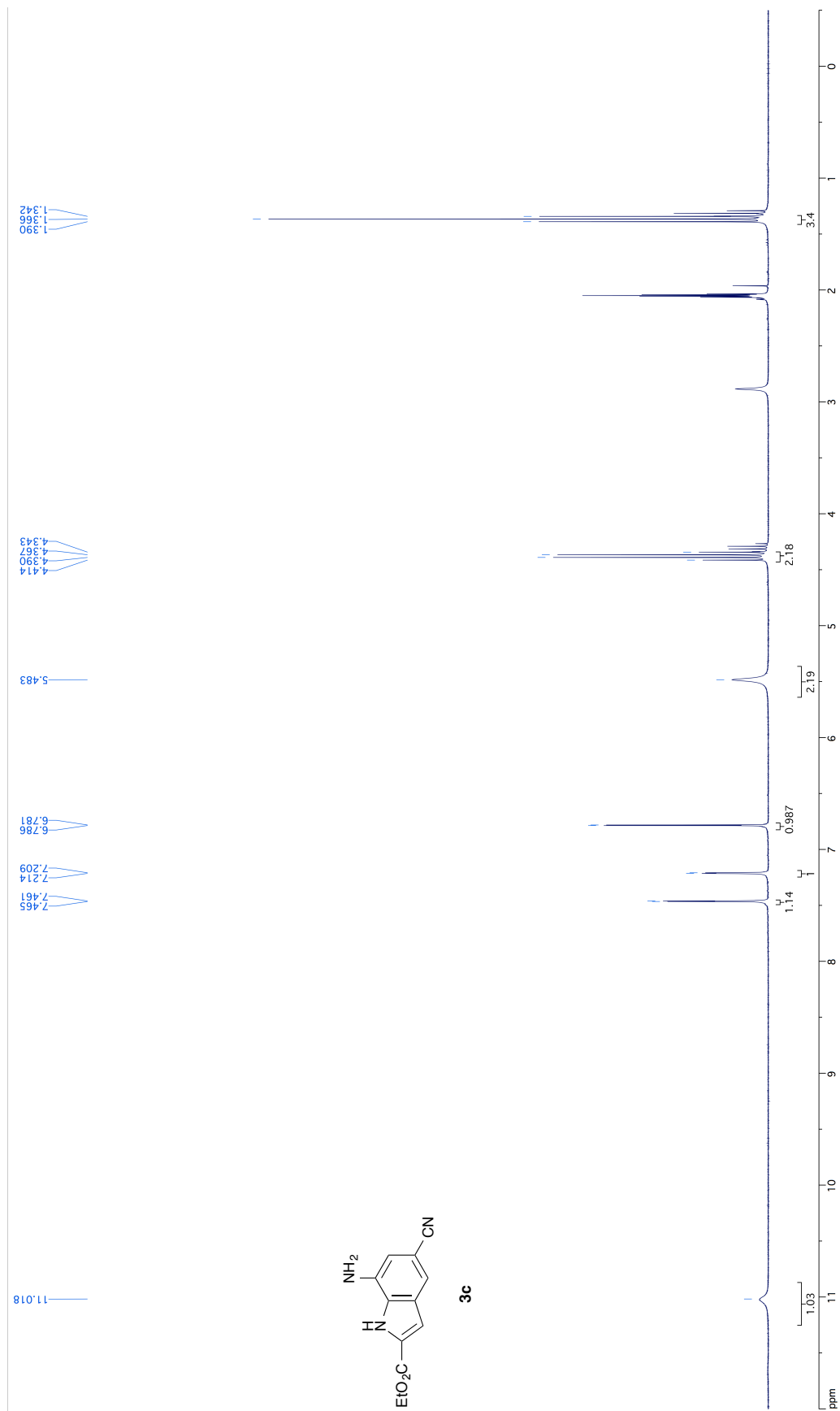


Figure 19 <sup>1</sup>H-NMR spectrum for compound **3c** (Acetone-d<sub>6</sub>, 400 MHz)

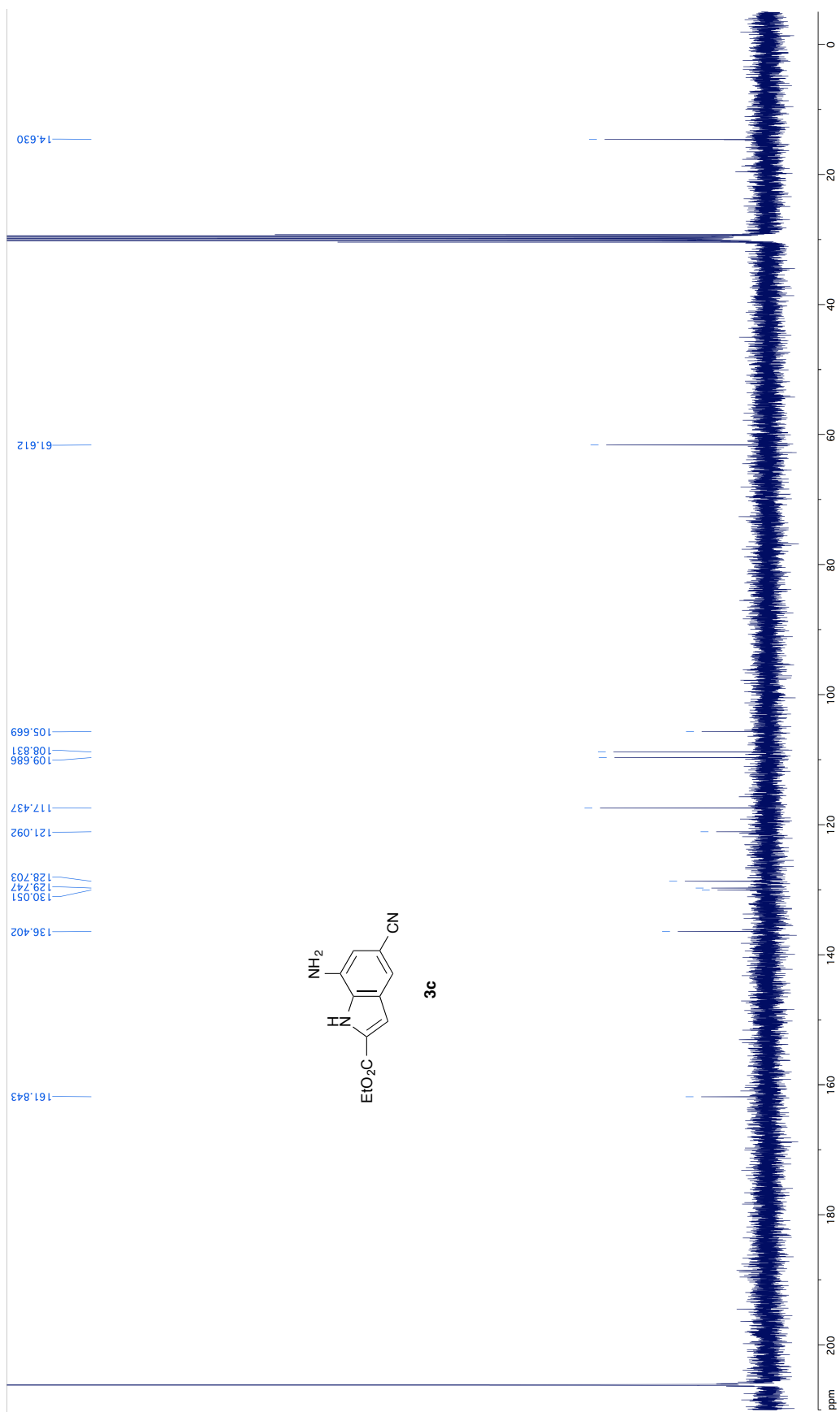


Figure 20 <sup>13</sup>C-NMR spectrum for compound **3c** (Acetone-d<sub>6</sub>, 100 MHz)

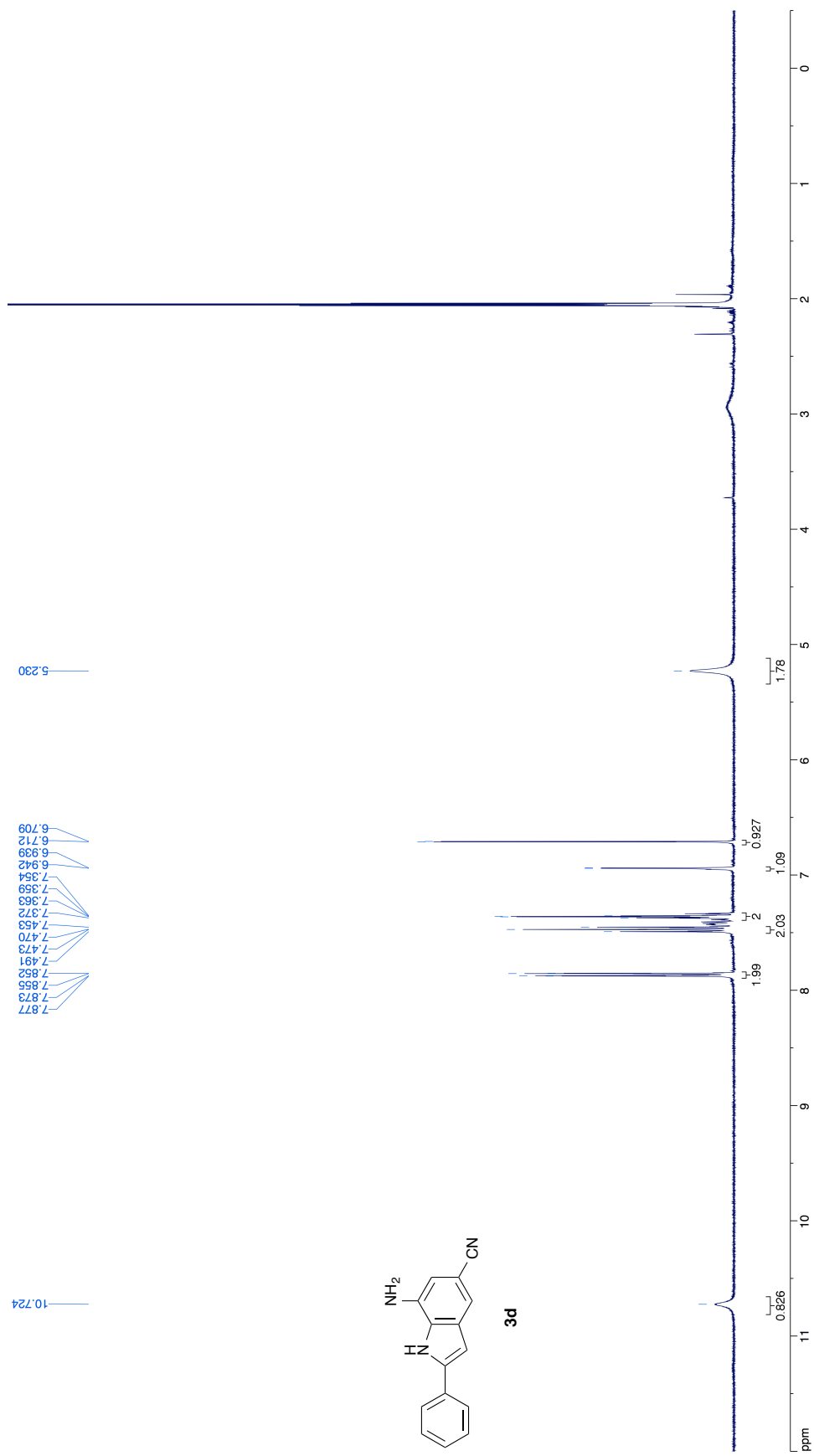


Figure 21 1H-NMR spectrum for compound 3d (Acetone-d<sub>6</sub>, 400 MHz)

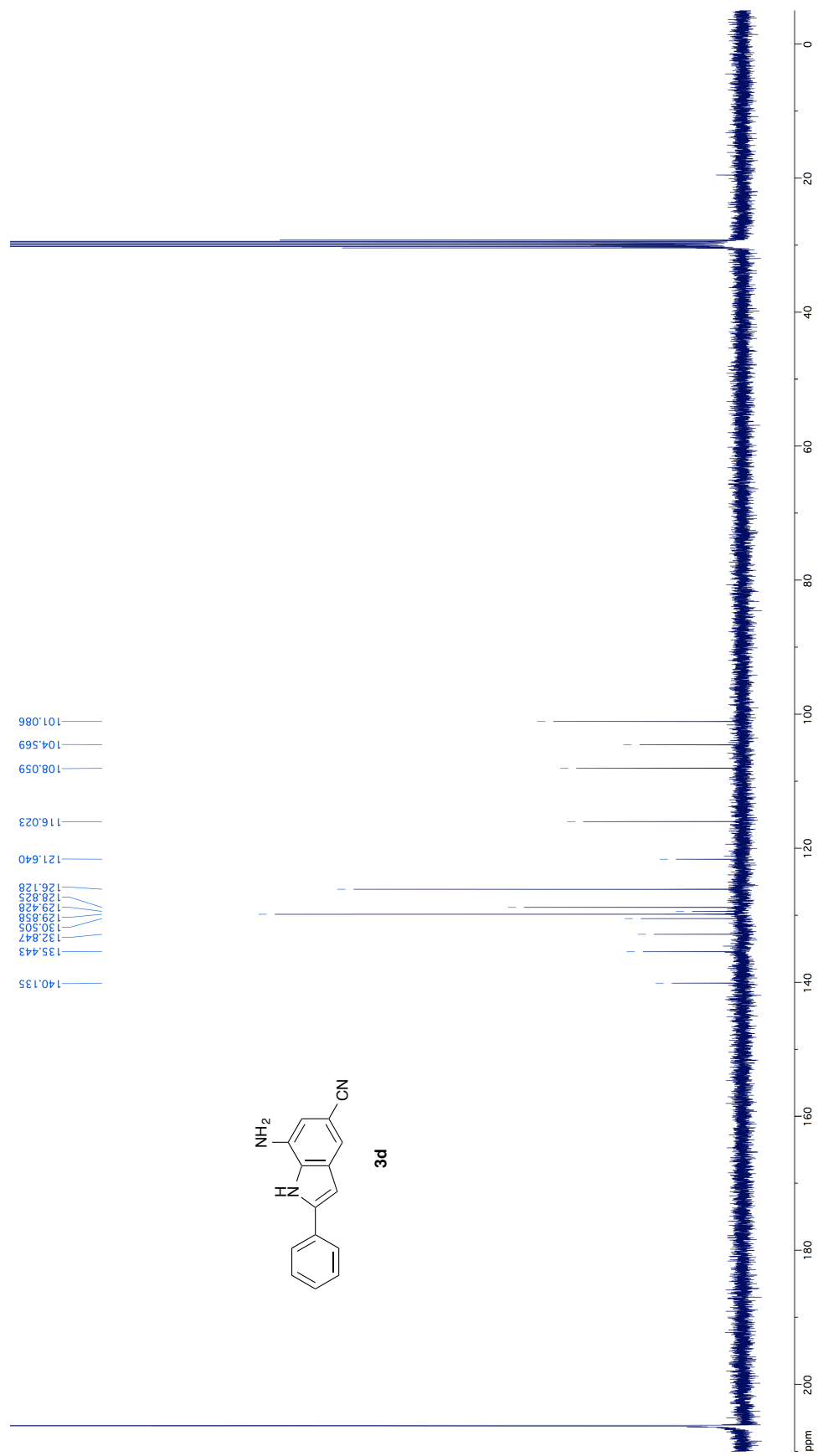
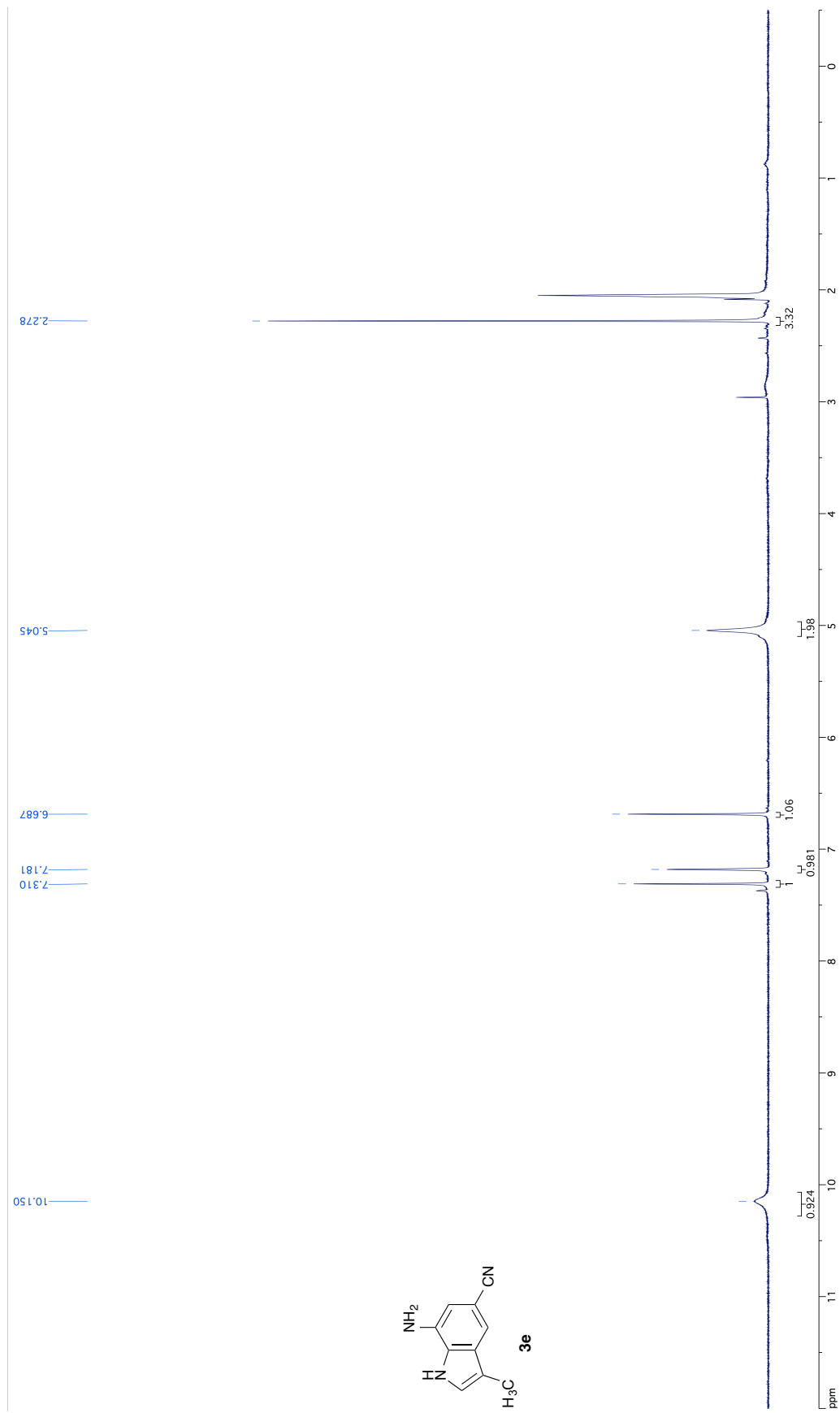
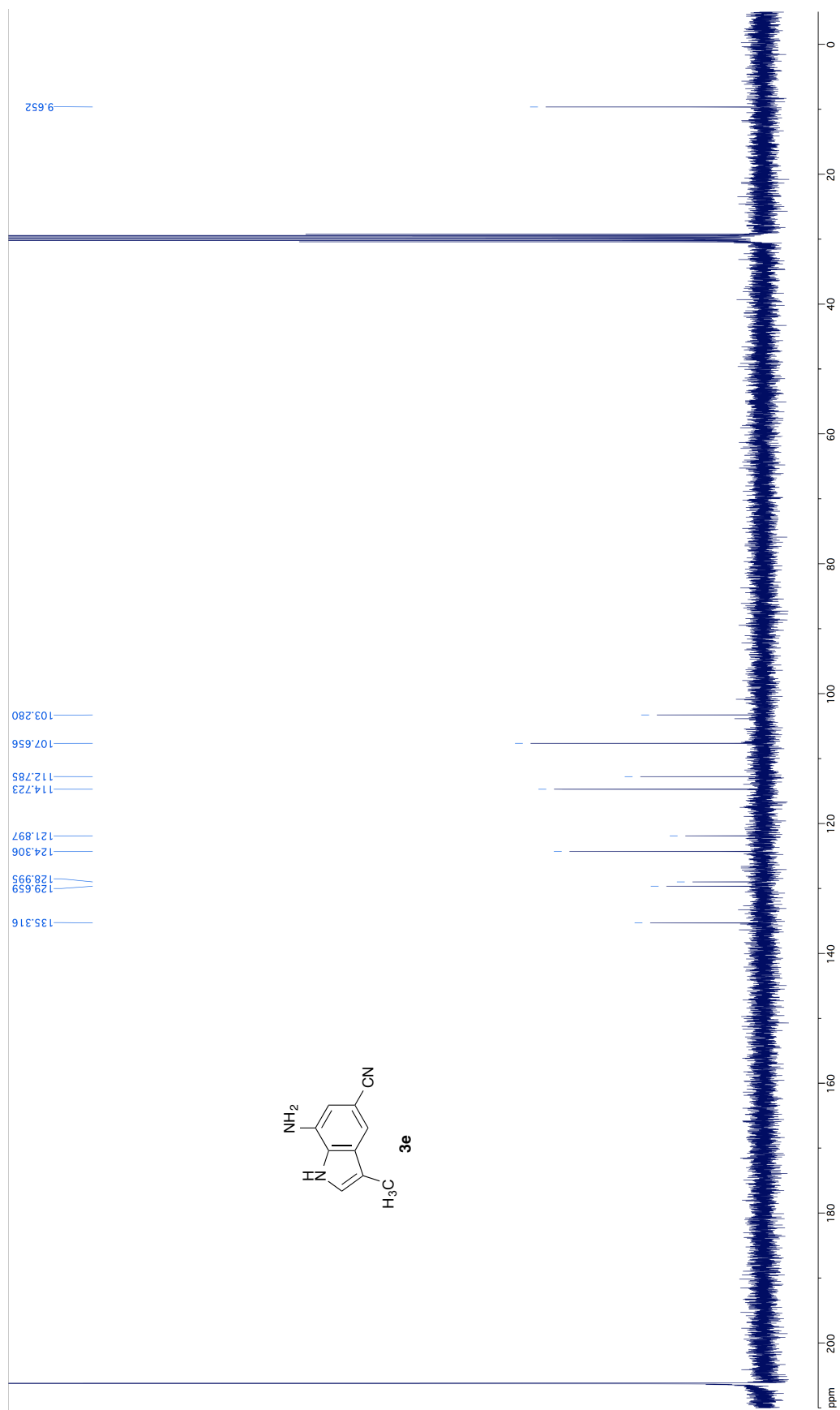
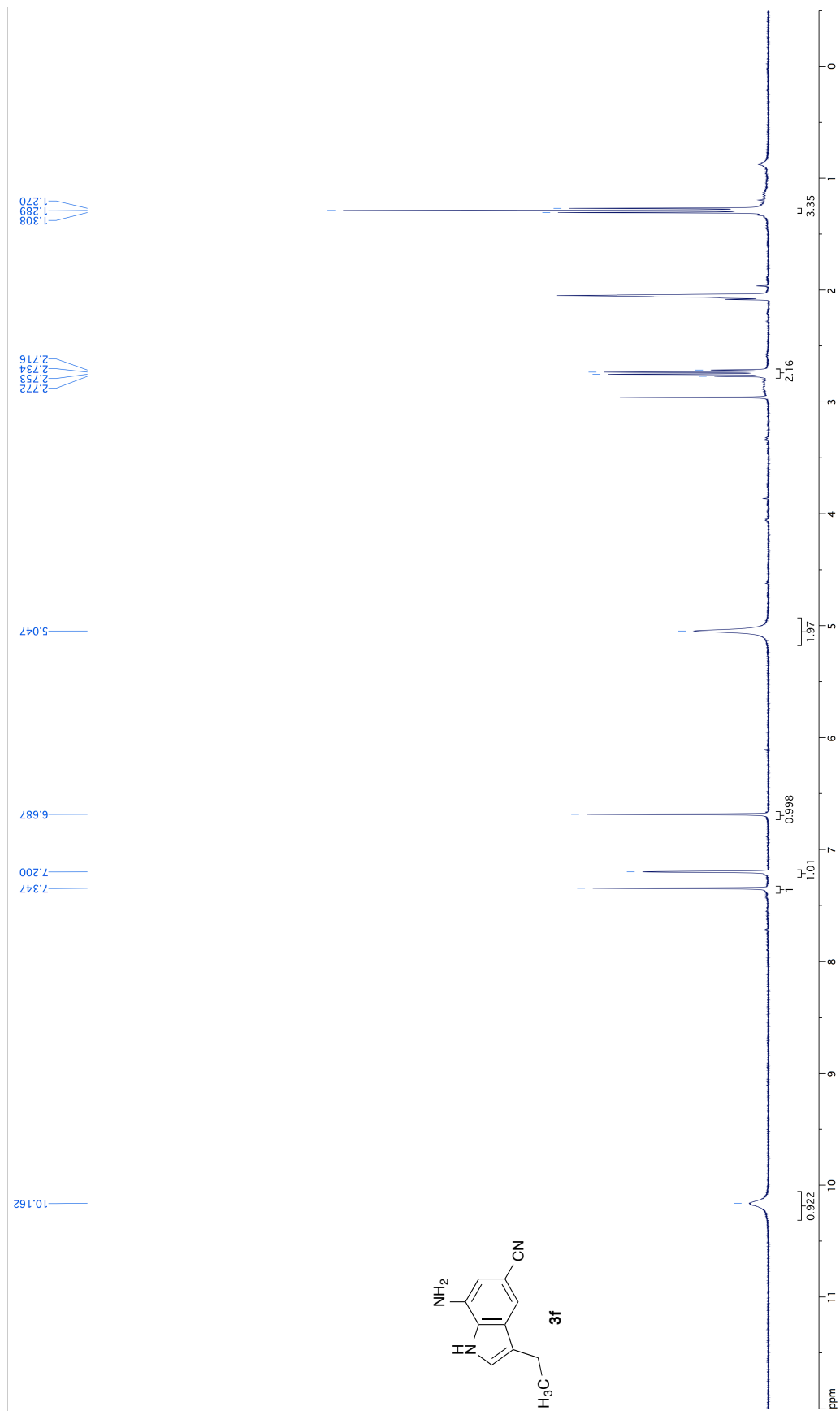


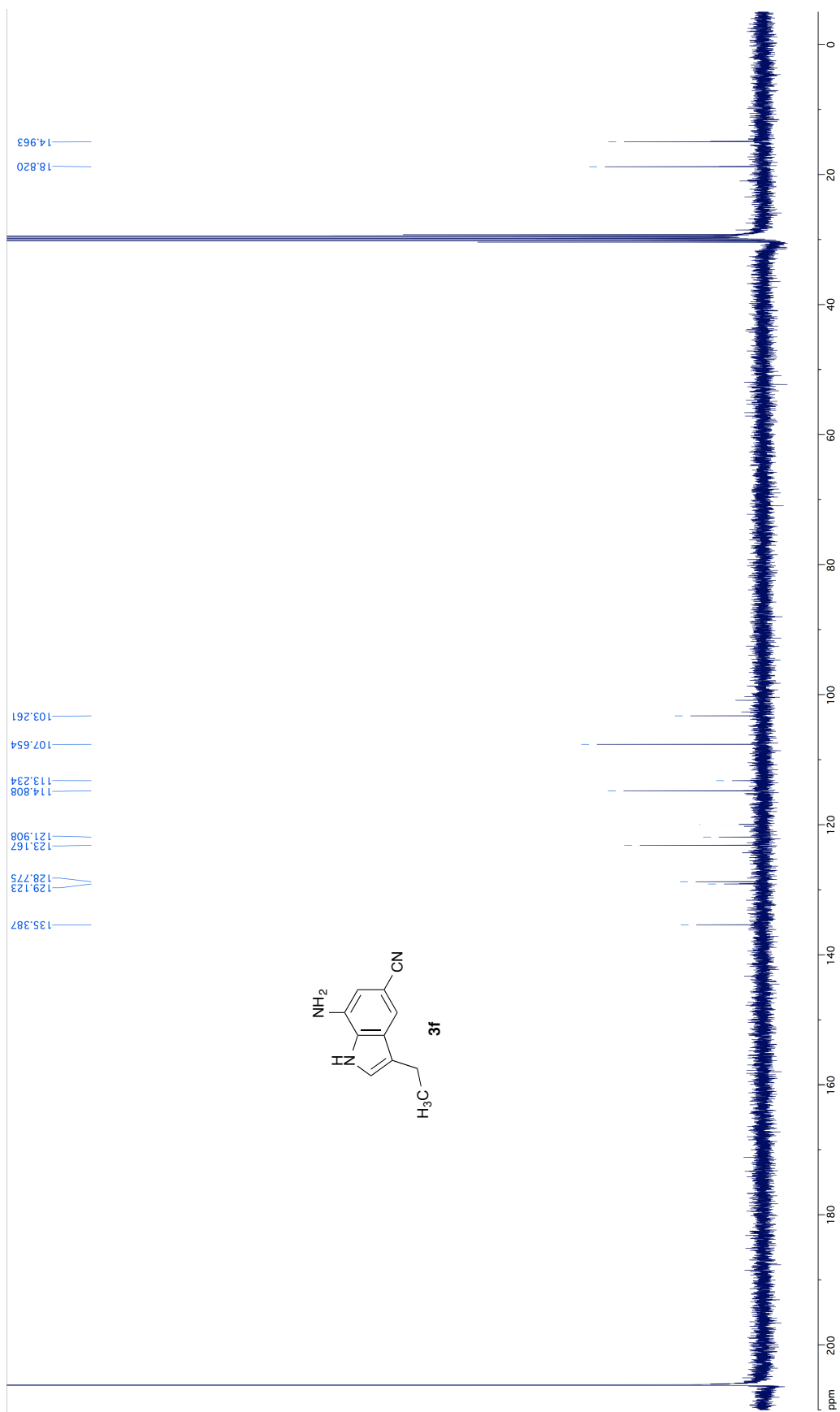
Figure 22 <sup>13</sup>C-NMR spectrum for compound **3d** (Acetone-d<sub>6</sub>, 100 MHz)











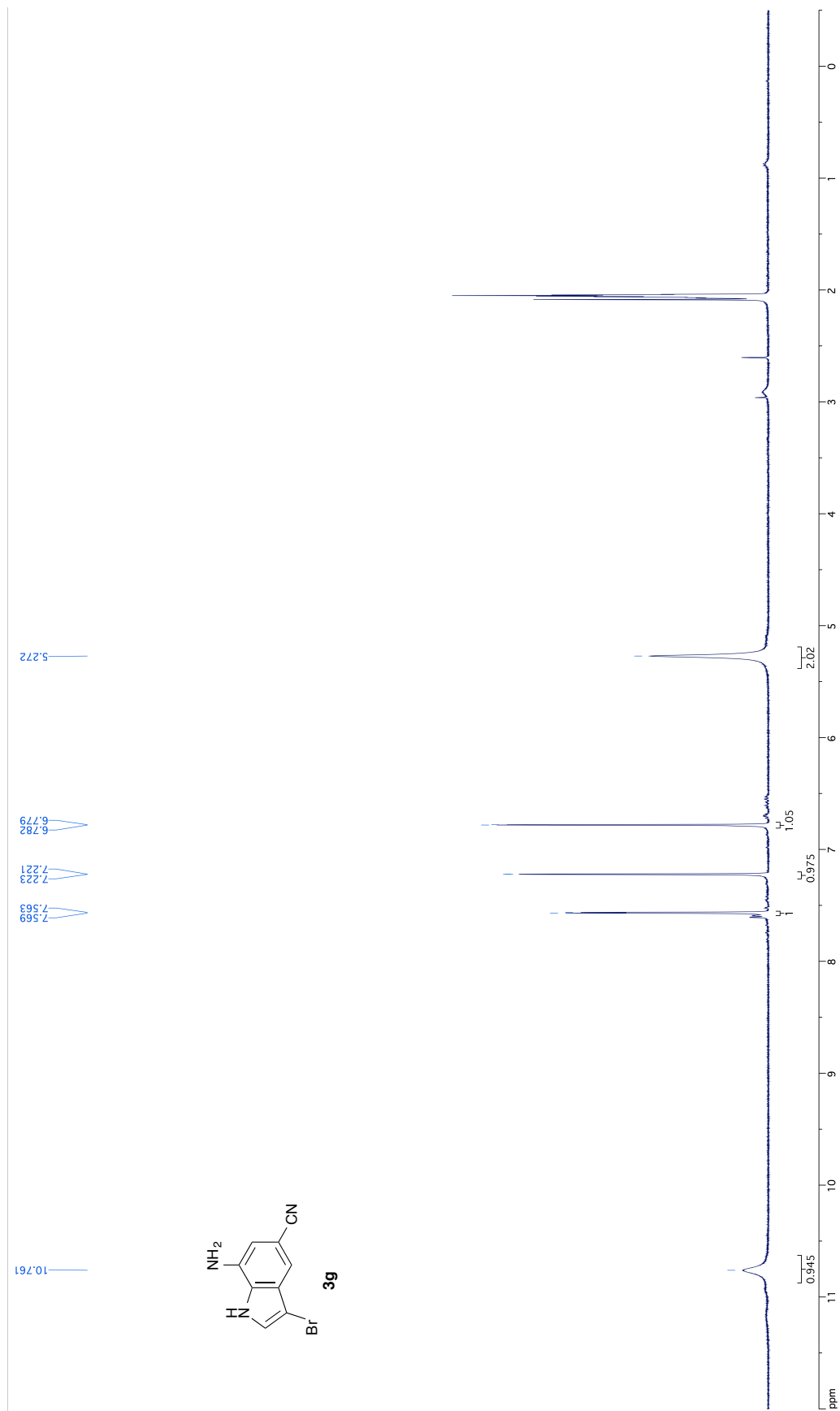
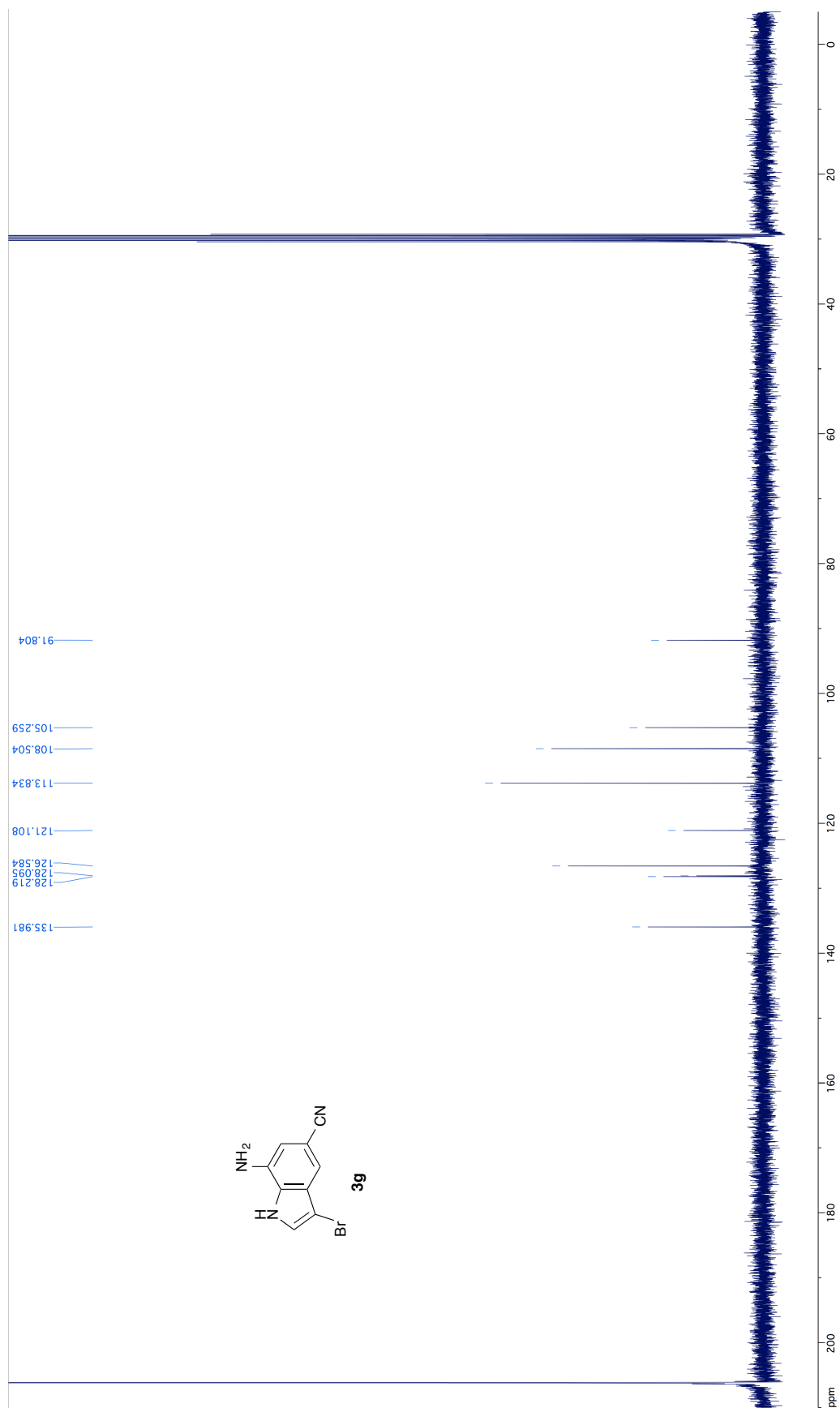
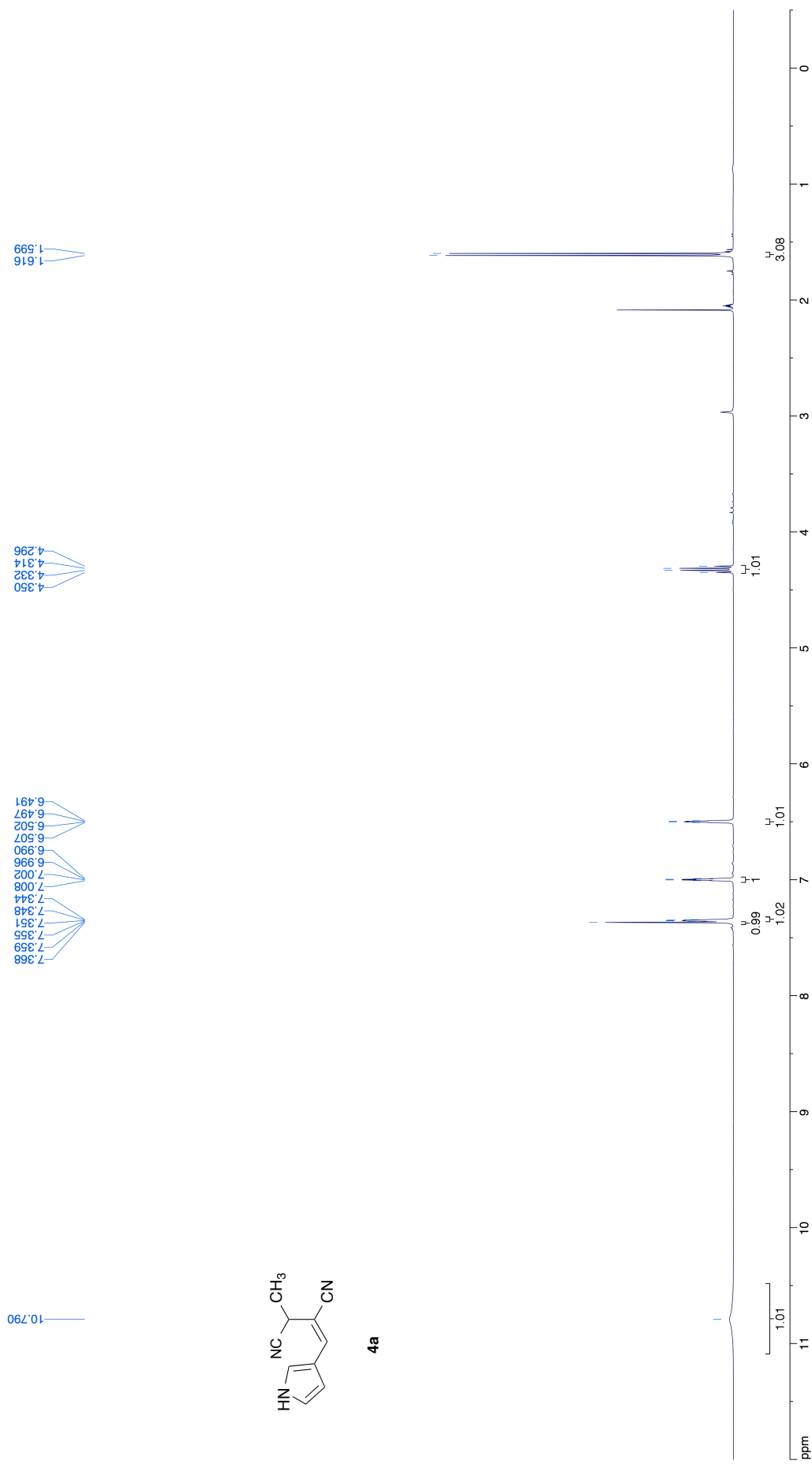


Figure 27 <sup>1</sup>H-NMR spectrum for compound **3g** (Acetone-d<sub>6</sub>, 400 MHz)





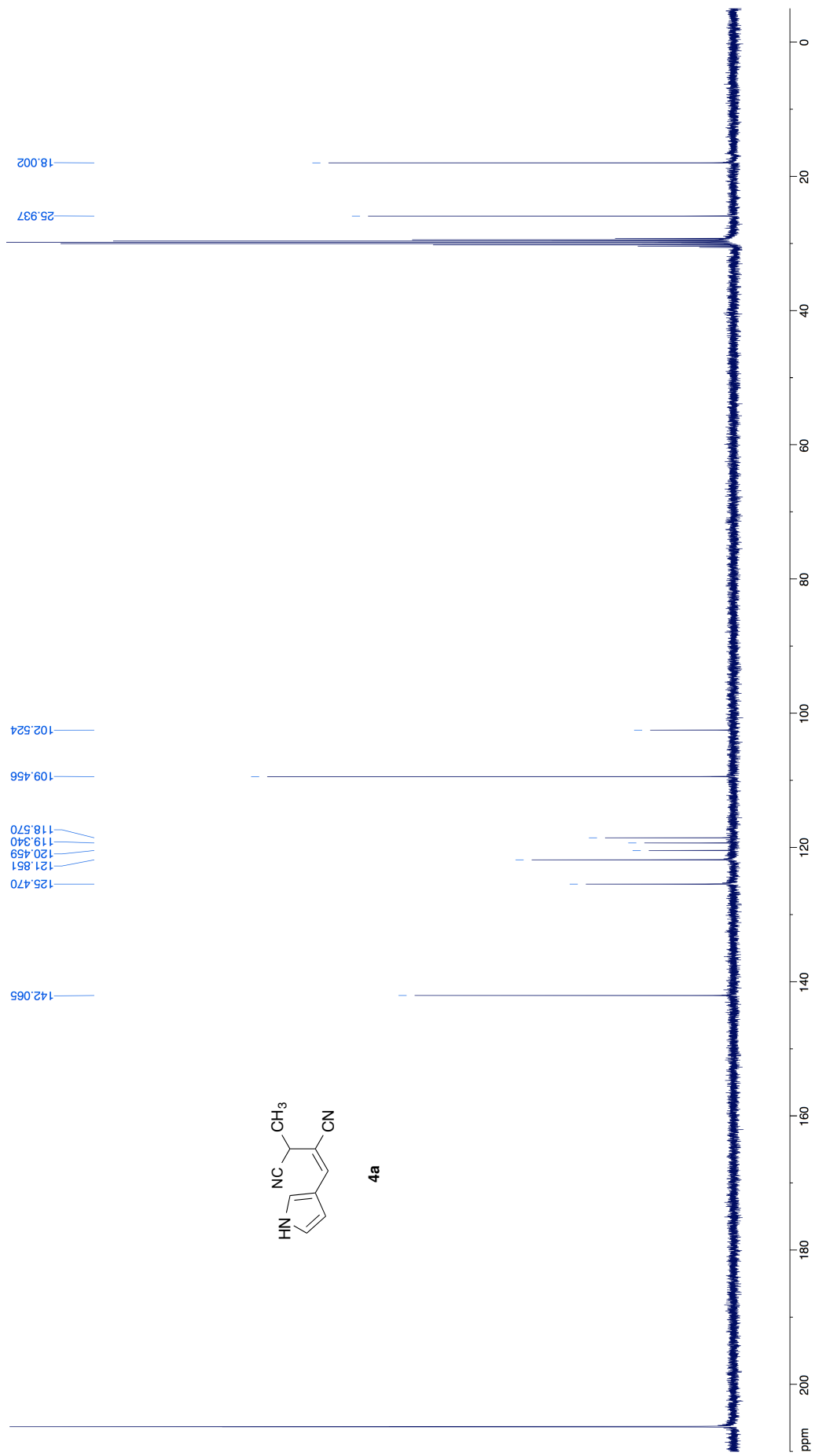


Figure 30 <sup>13</sup>C-NMR spectrum for compound 4a (Acetone-d<sub>6</sub>, 100 MHz)

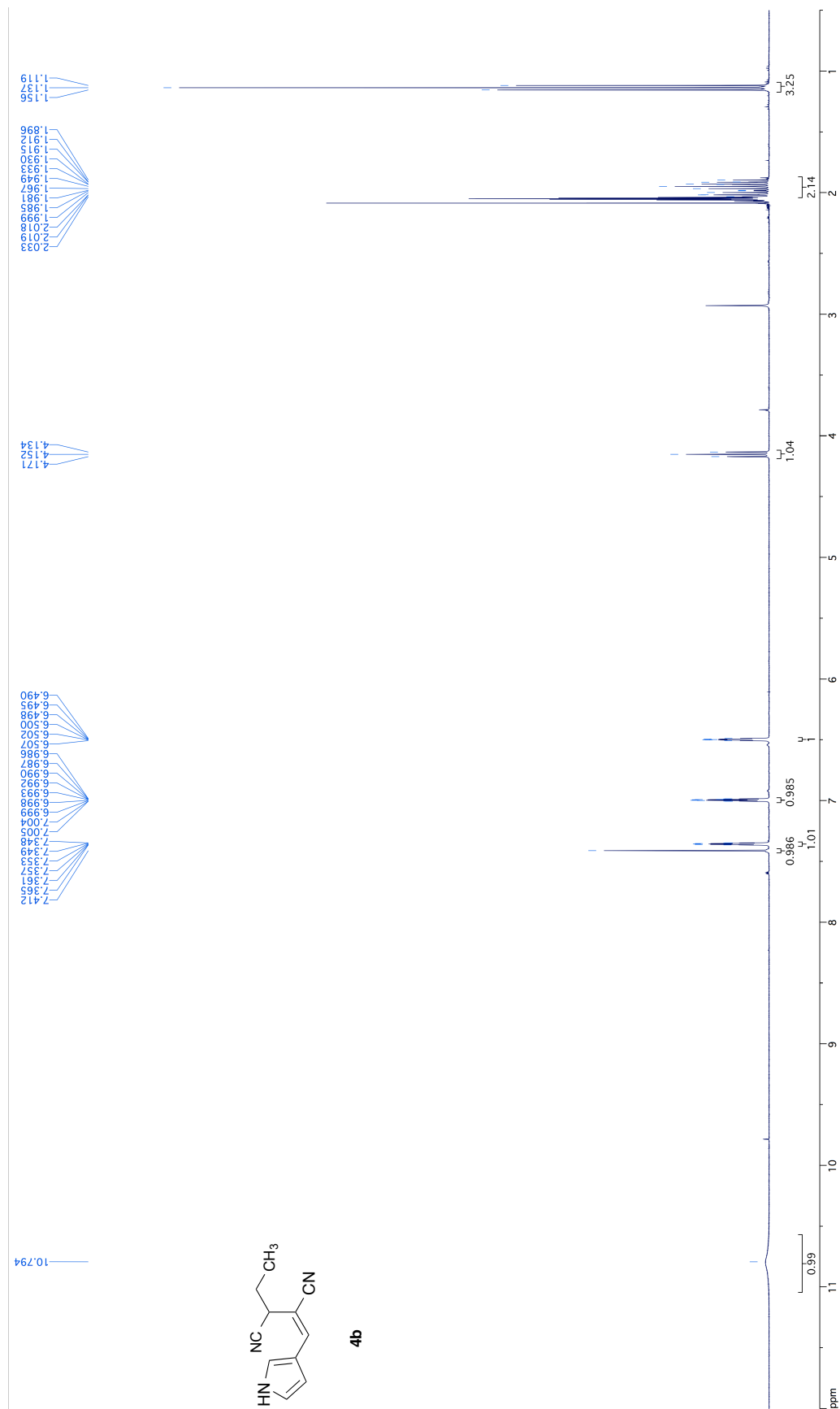
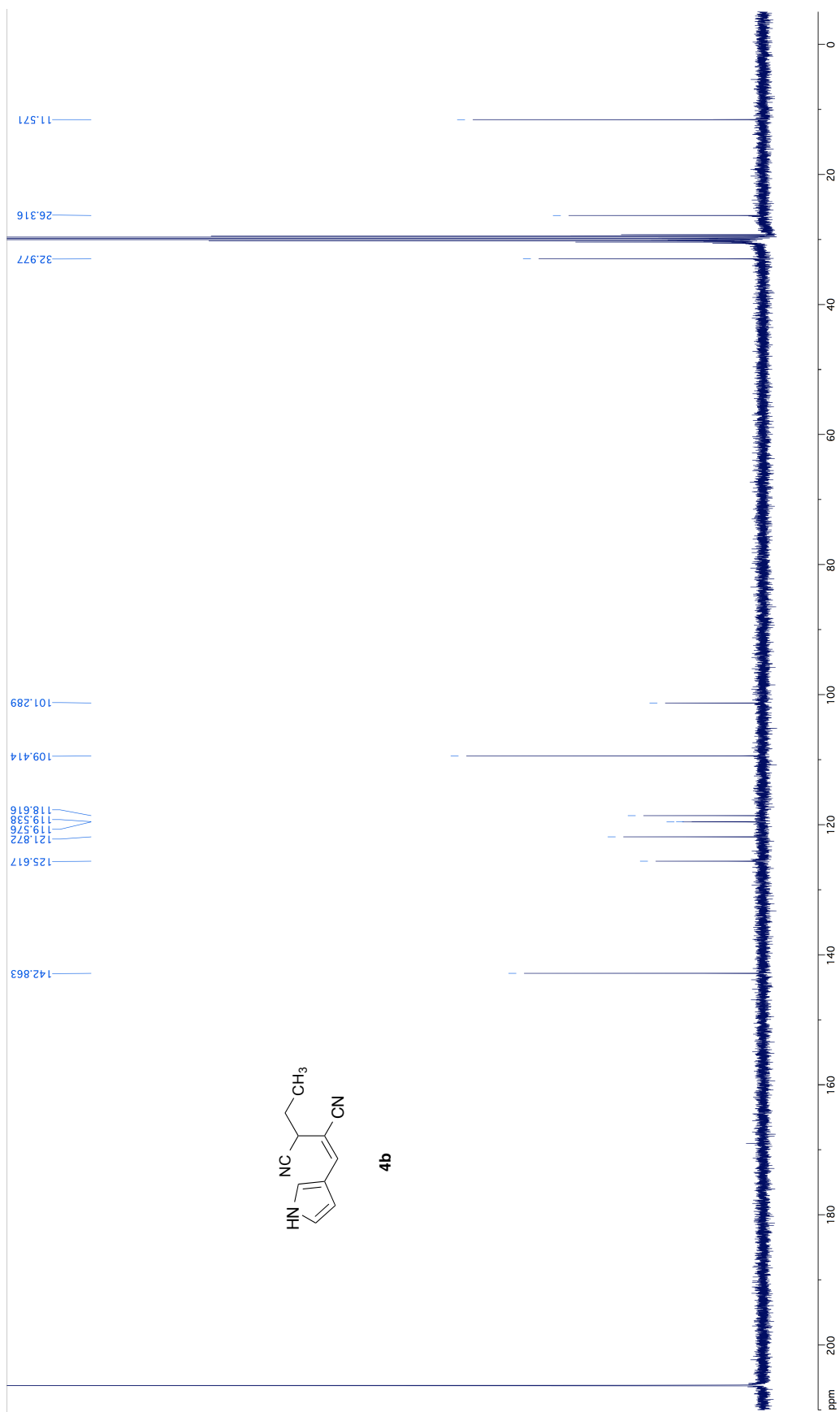
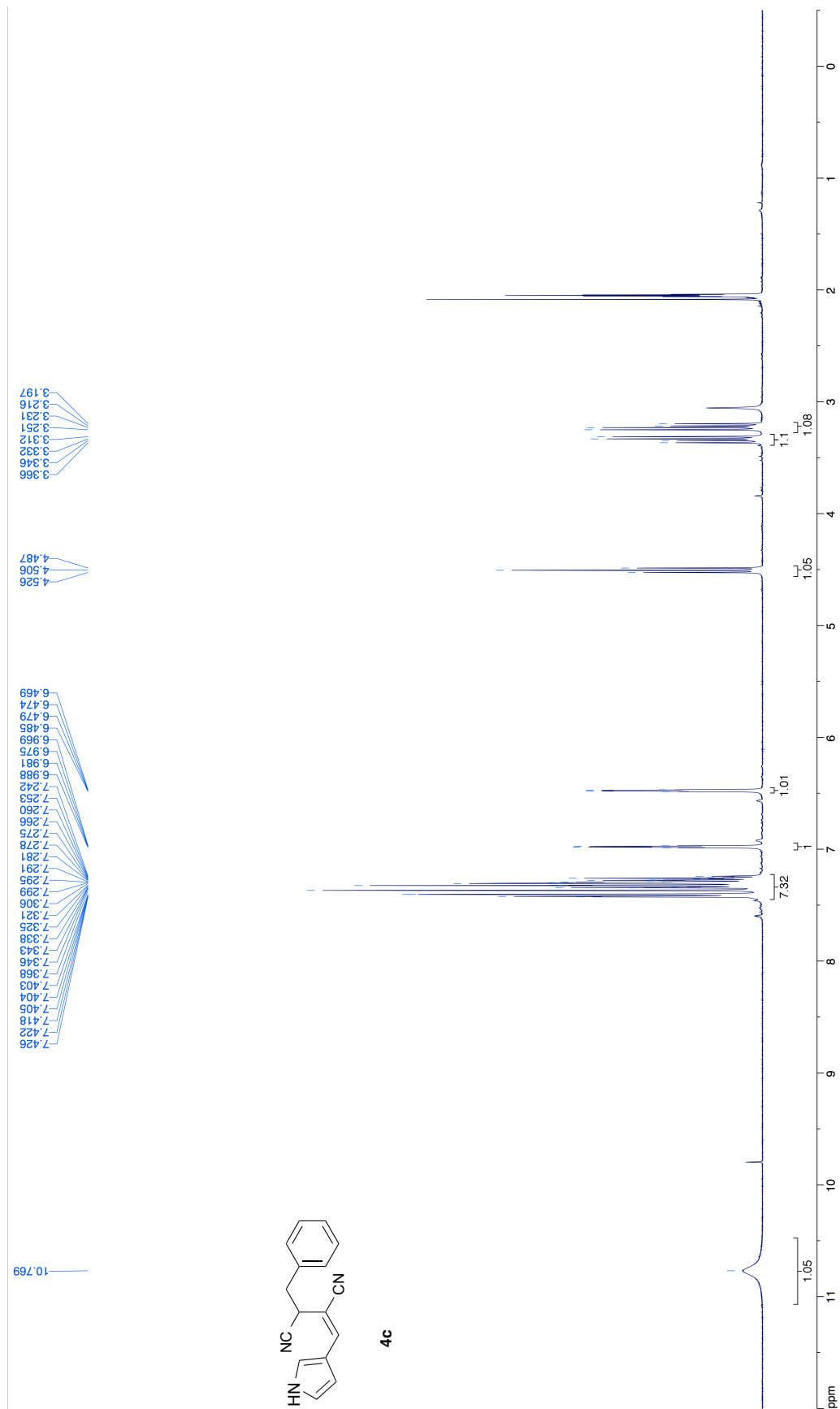


Figure 31 <sup>1</sup>H-NMR spectrum for compound 4b (Acetone-d<sub>6</sub>, 400 MHz)







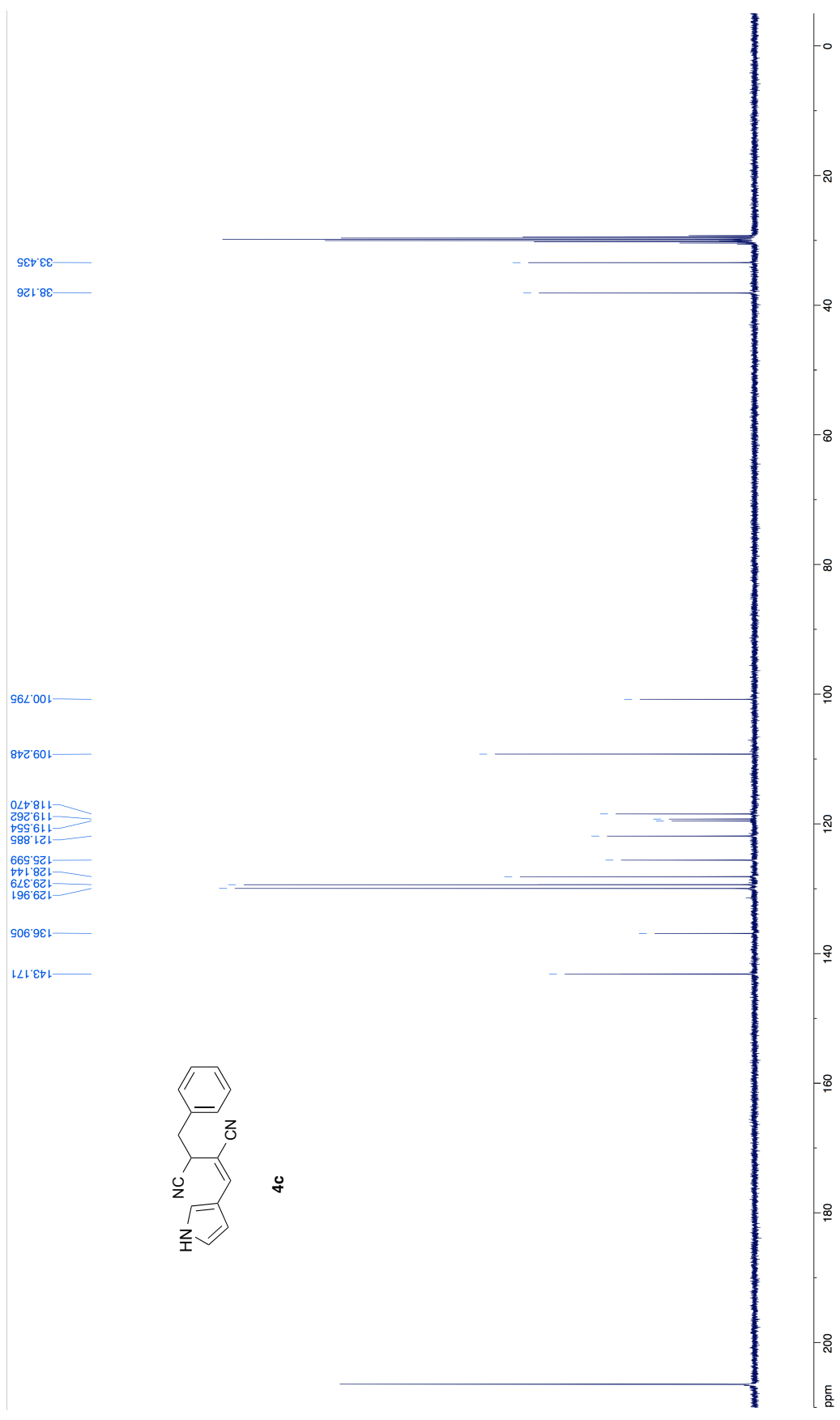


Figure 34 <sup>13</sup>C-NMR spectrum for compound 4c (Acetone-d<sub>6</sub>, 100 MHz)

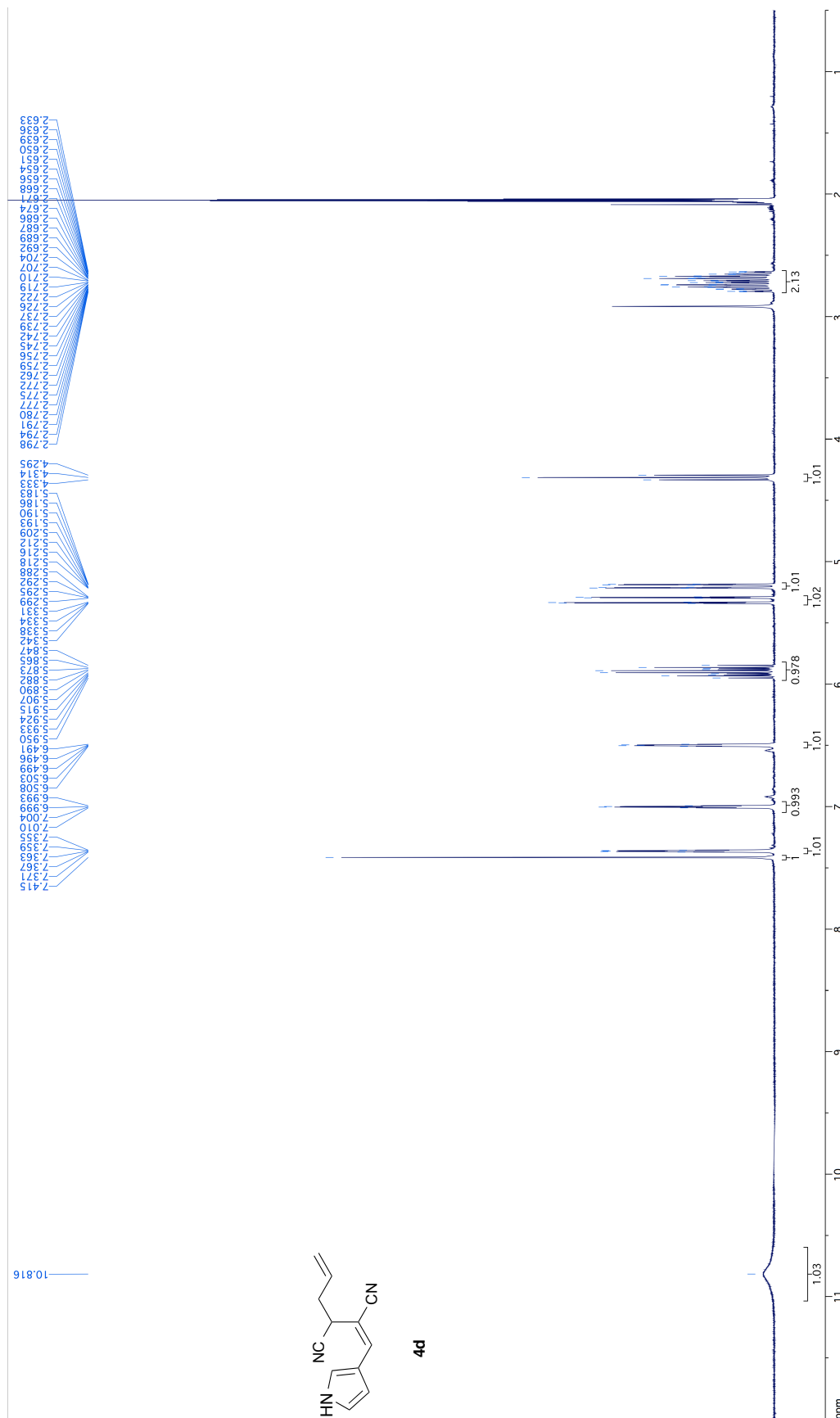


Figure 35 1H-NMR spectrum for compound 4d (Acetone-d<sub>6</sub>, 400 MHz)

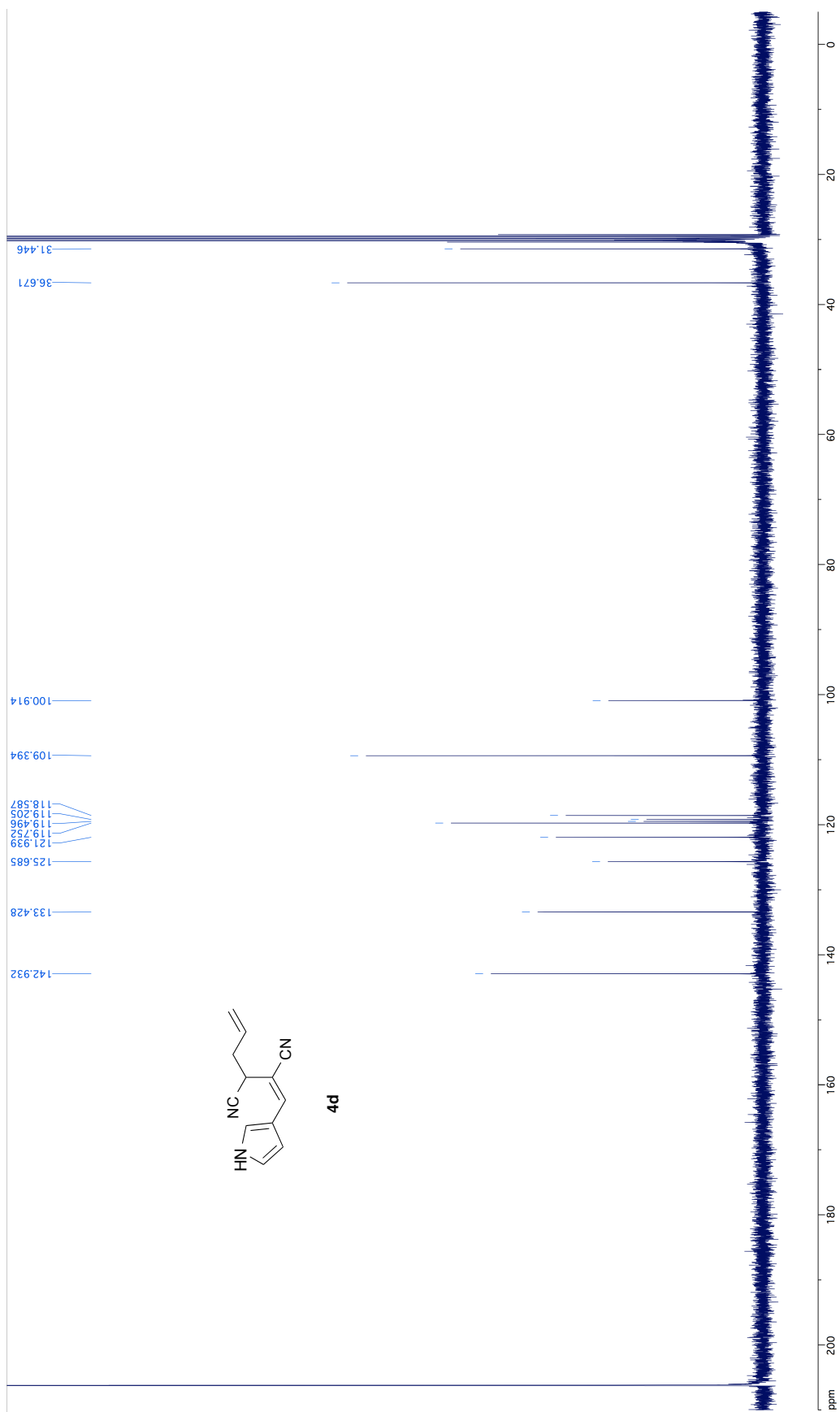


Figure 36 <sup>13</sup>C-NMR spectrum for compound 4d (Acetone-d<sub>6</sub>, 100 MHz)

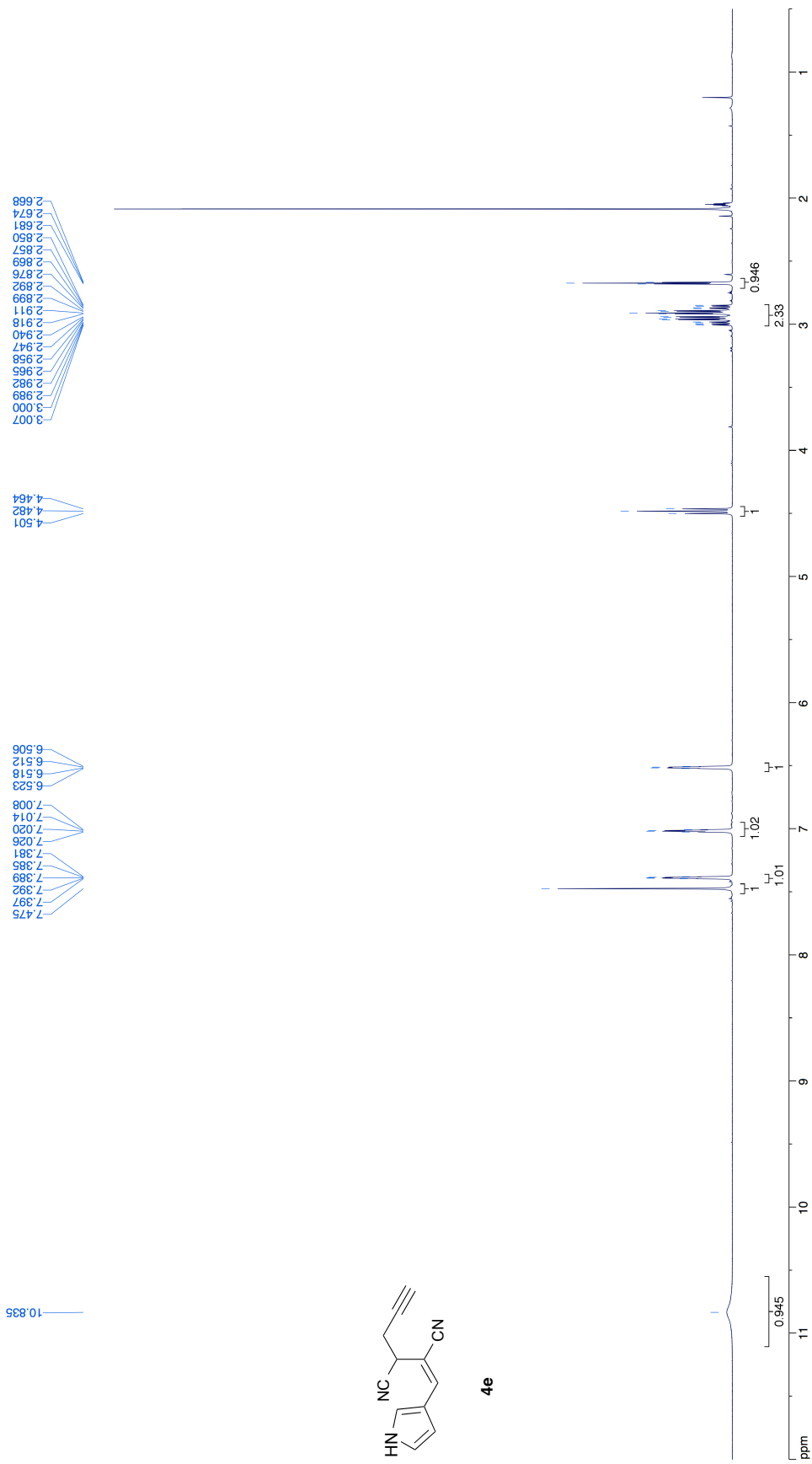


Figure 37 <sup>1</sup>H-NMR spectrum for compound **4e** (Acetone-d<sub>6</sub>, 400 MHz)

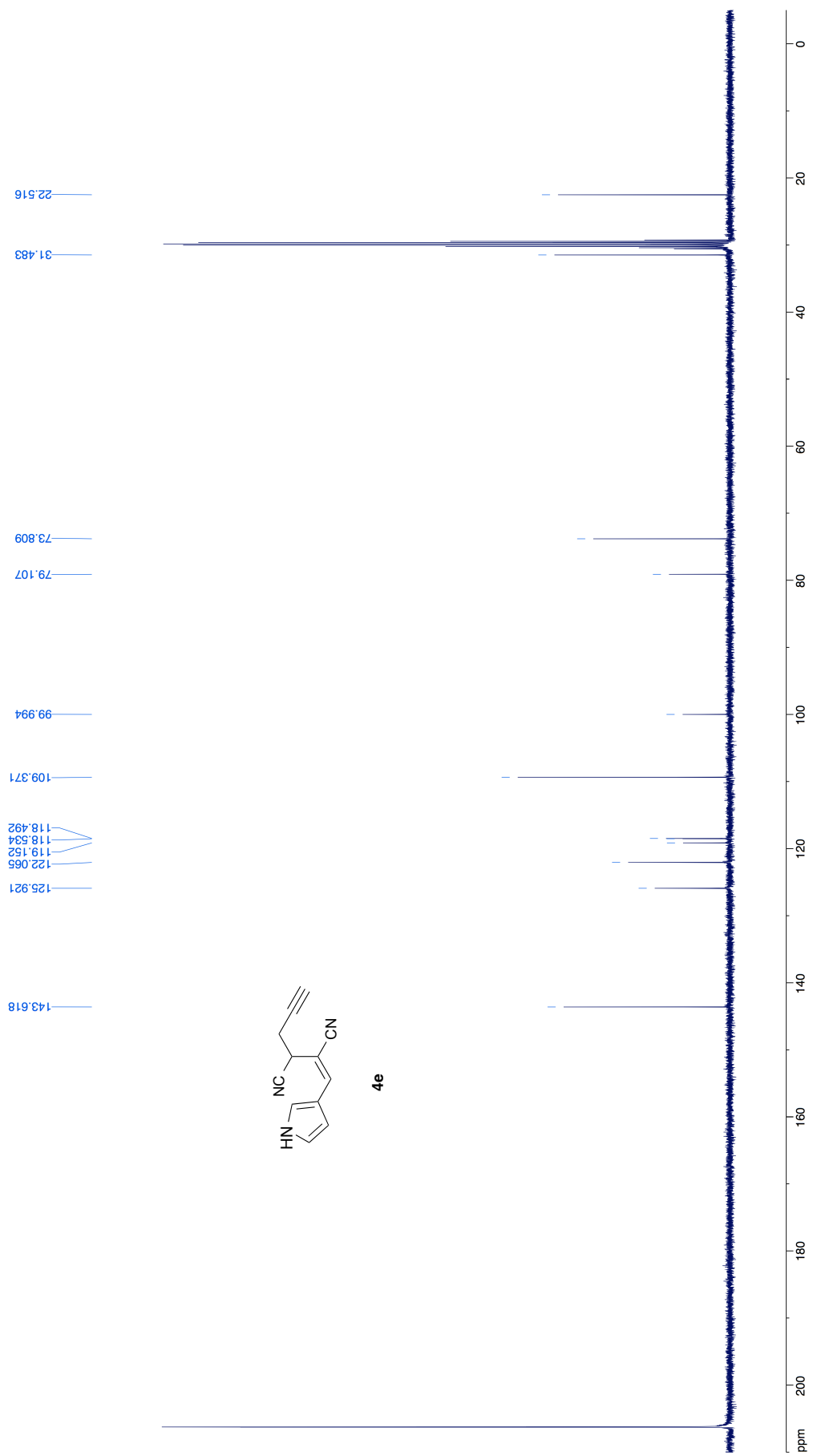


Figure 38  $^{13}\text{C}$ -NMR spectrum for compound 4e (Acetone- $d_6$ , 100 MHz)

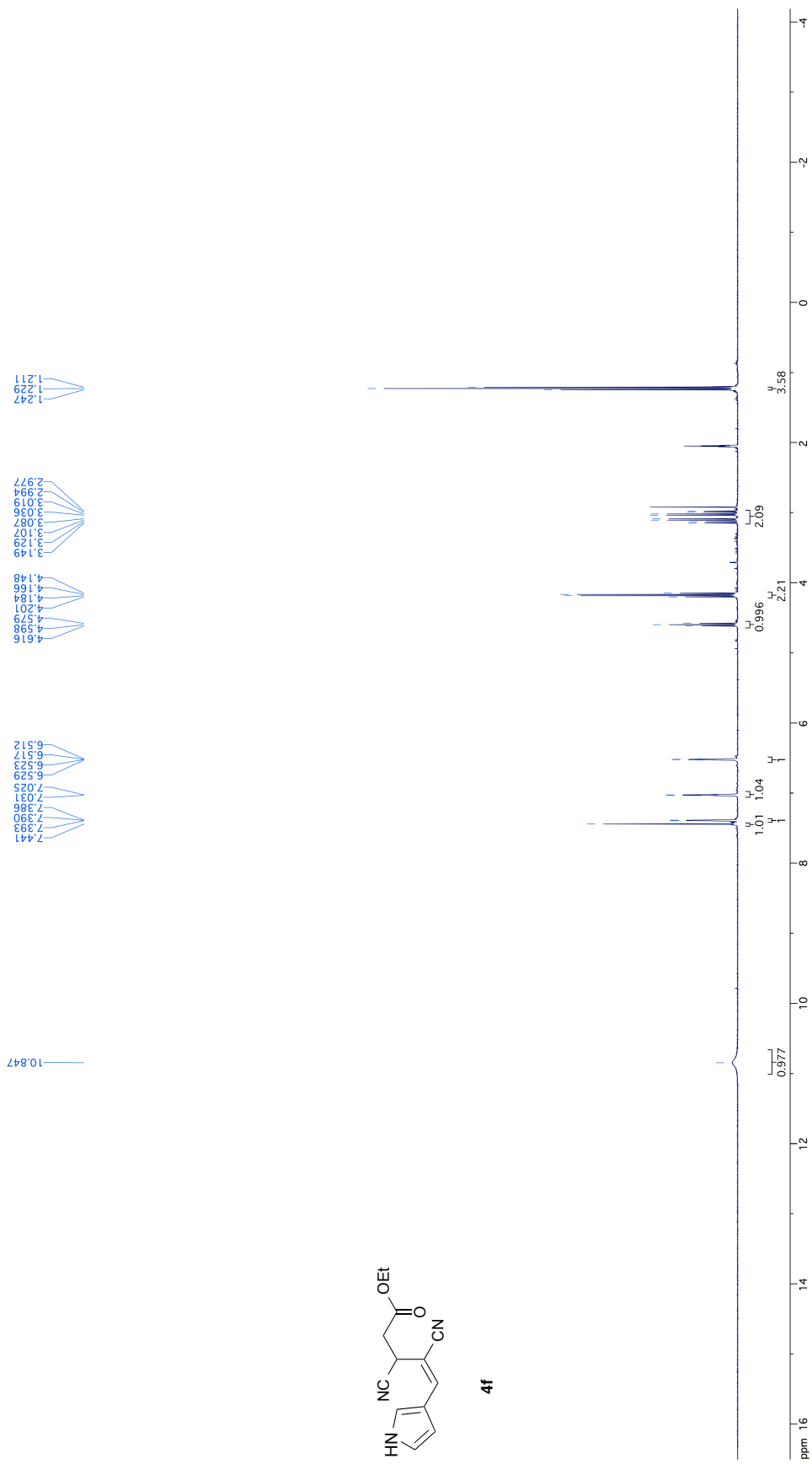


Figure 39 <sup>1</sup>H-NMR spectrum for compound 4f (Acetone-d<sub>6</sub>, 400 MHz)



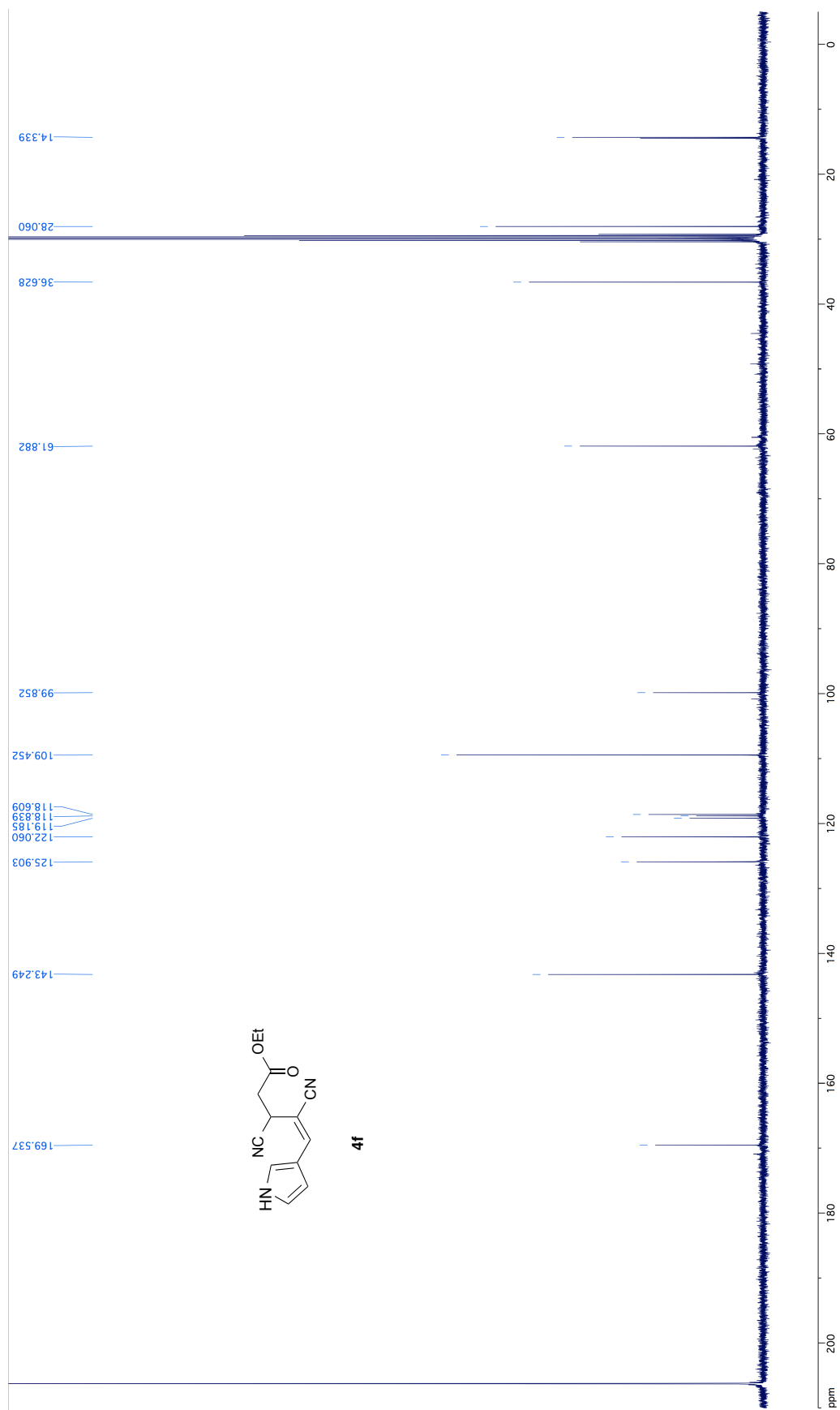


Figure 40 <sup>13</sup>C-NMR spectrum for compound 4f (Acetone-d<sub>6</sub>, 100 MHz)

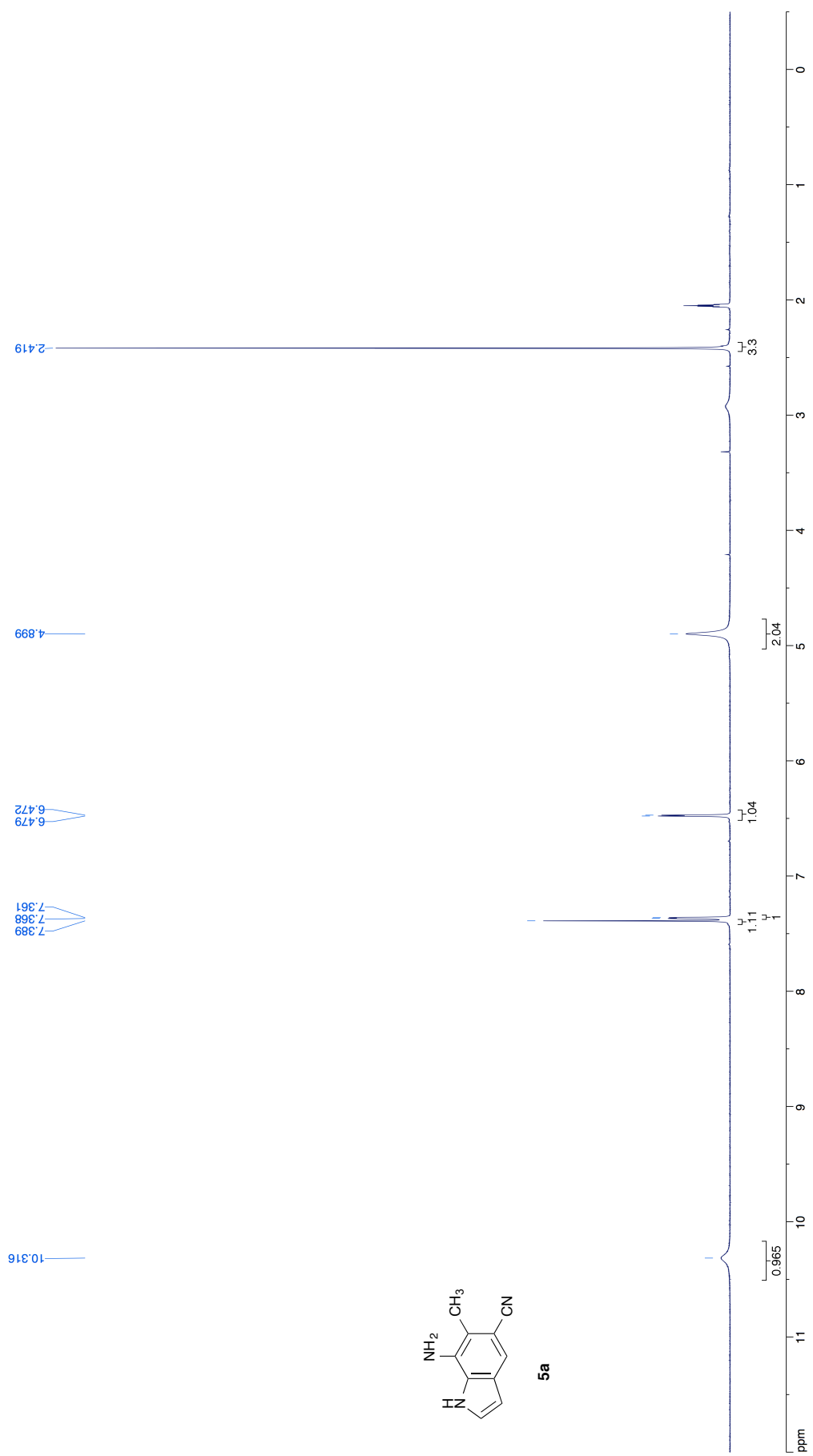


Figure 41 <sup>1</sup>H-NMR spectrum for compound 5a (Acetone-d<sub>6</sub>, 400 MHz)

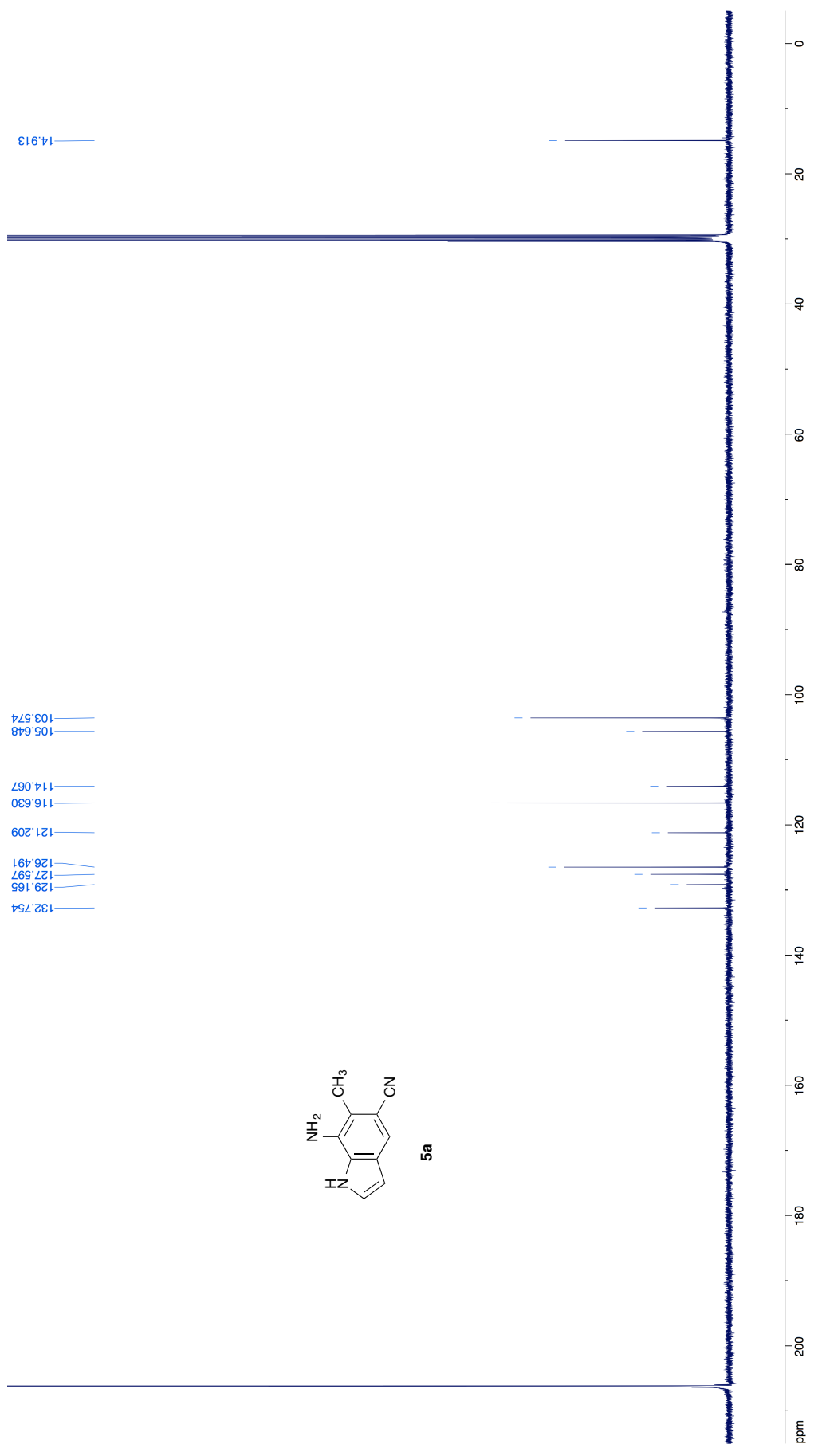
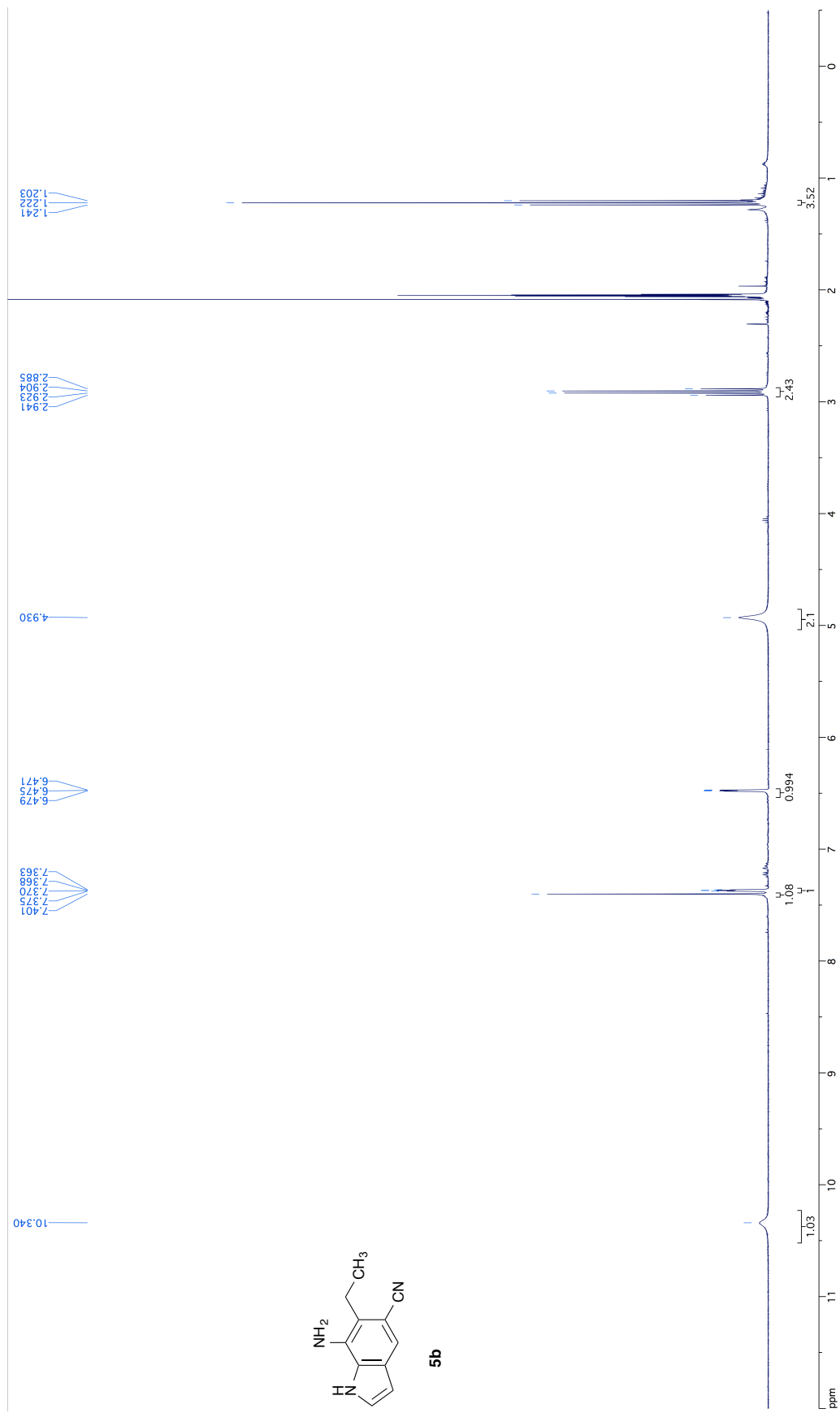


Figure 42 <sup>13</sup>C-NMR spectrum for compound 5a (Acetone-d<sub>6</sub>, 100 MHz)



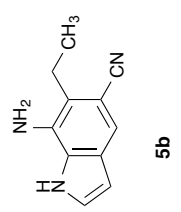
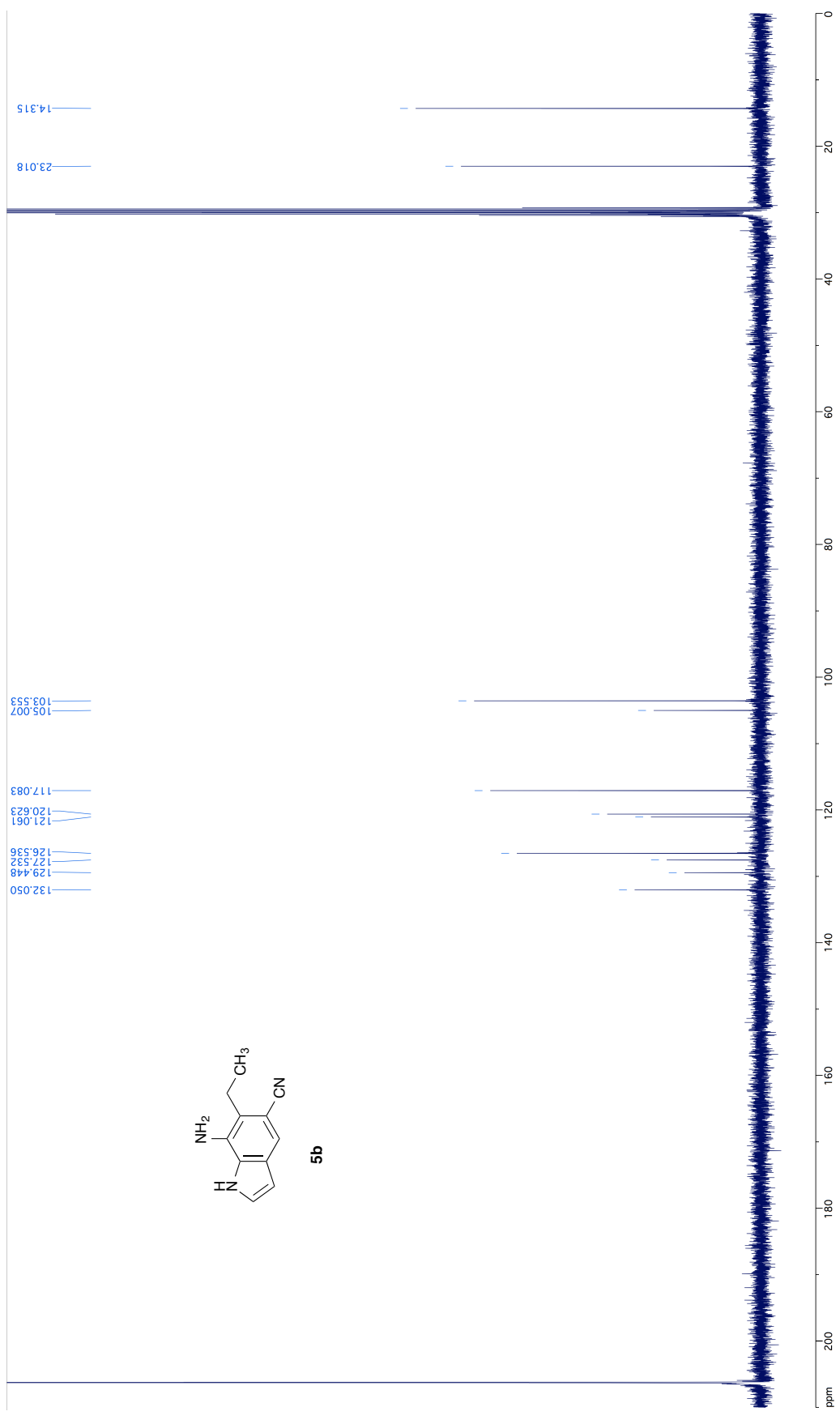
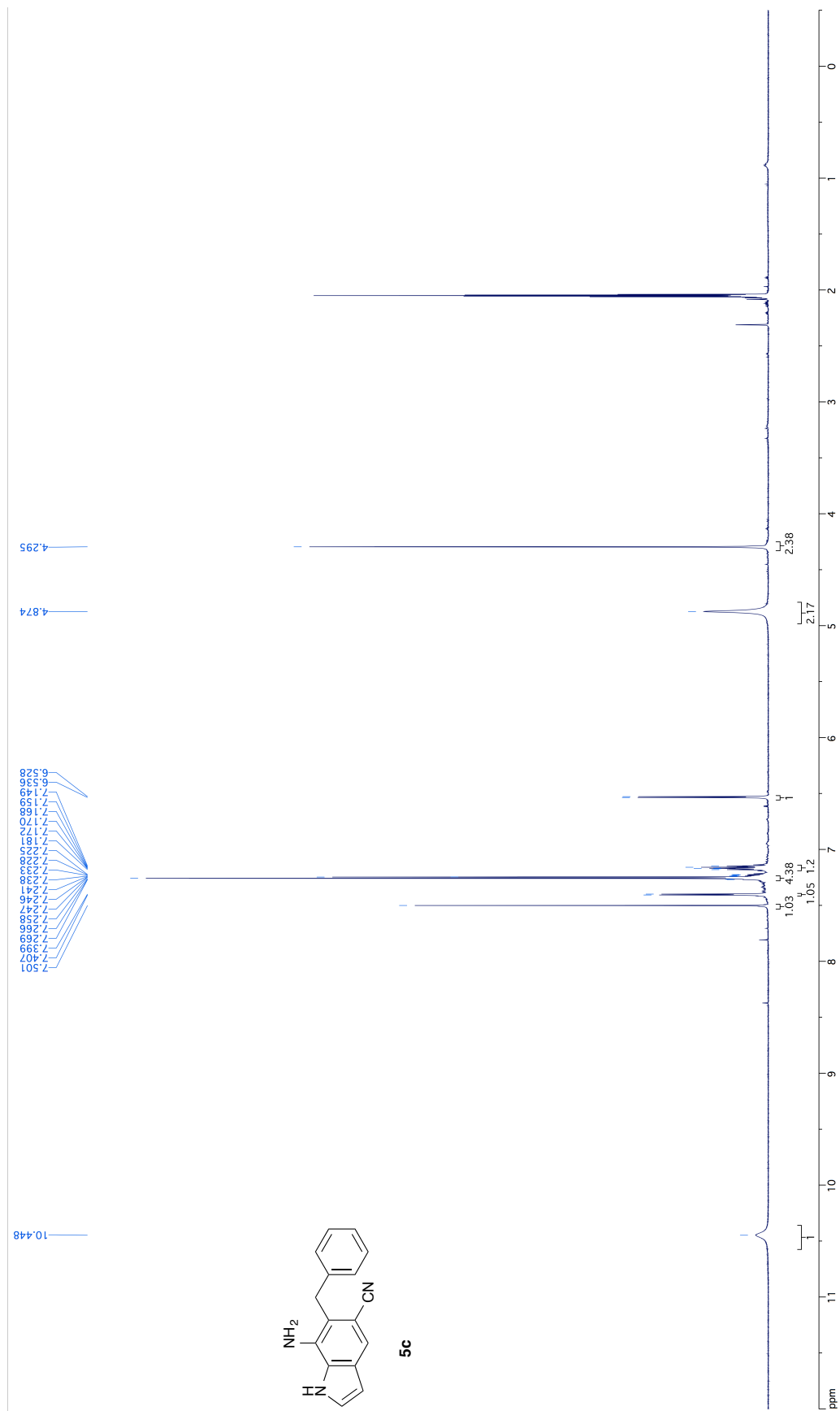


Figure 44 <sup>13</sup>C-NMR spectrum for compound 5b (Acetone-d<sub>6</sub>, 100 MHz)



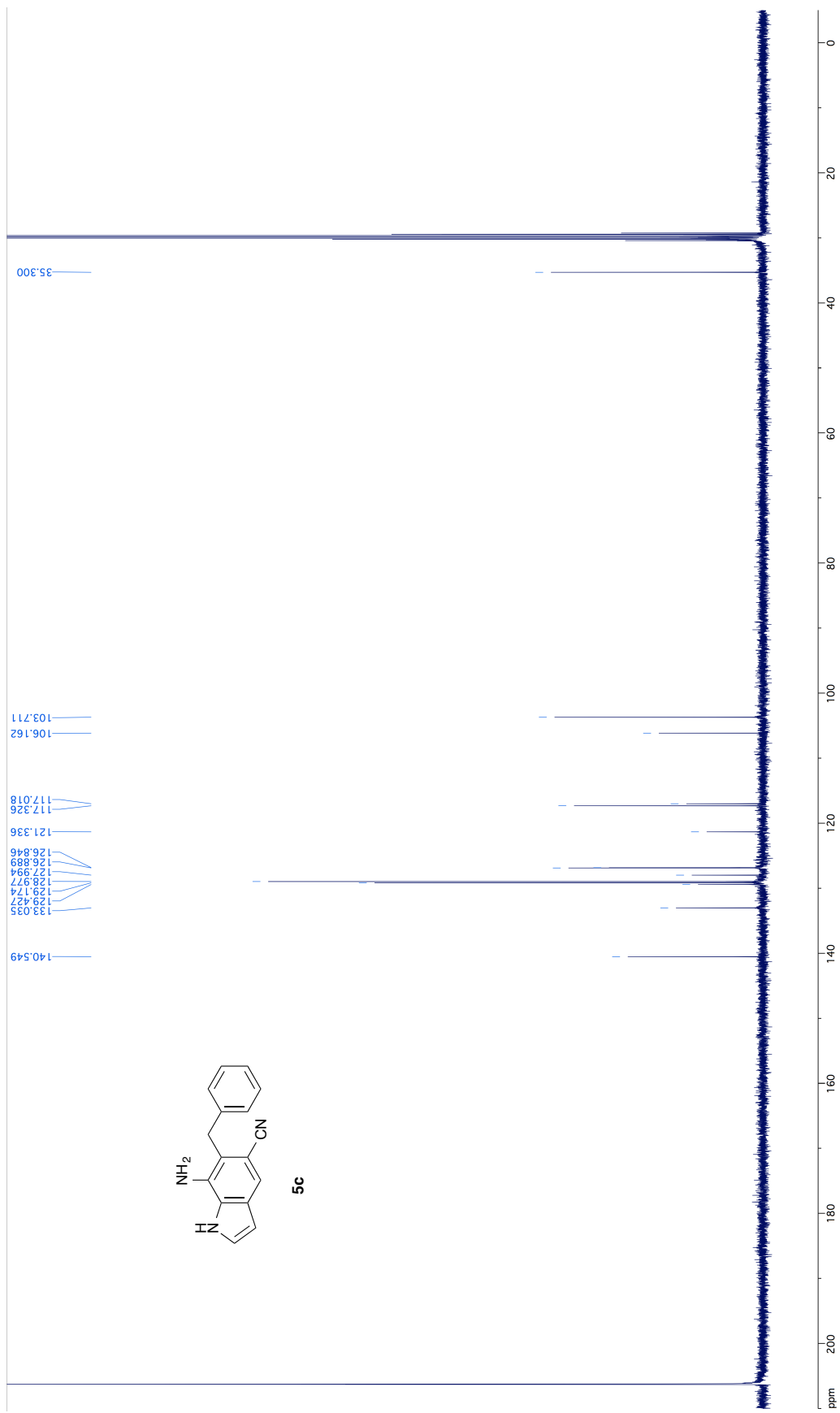
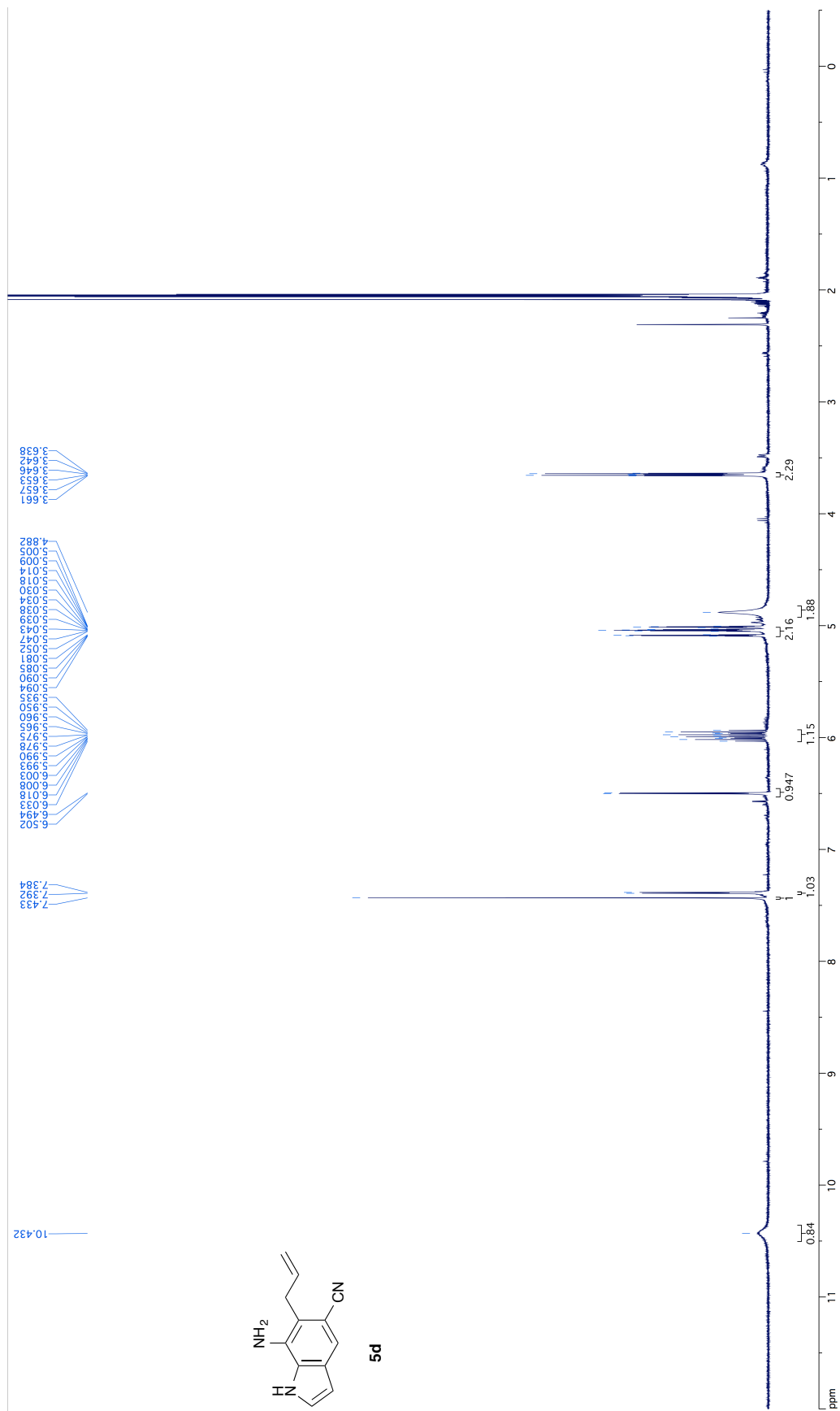
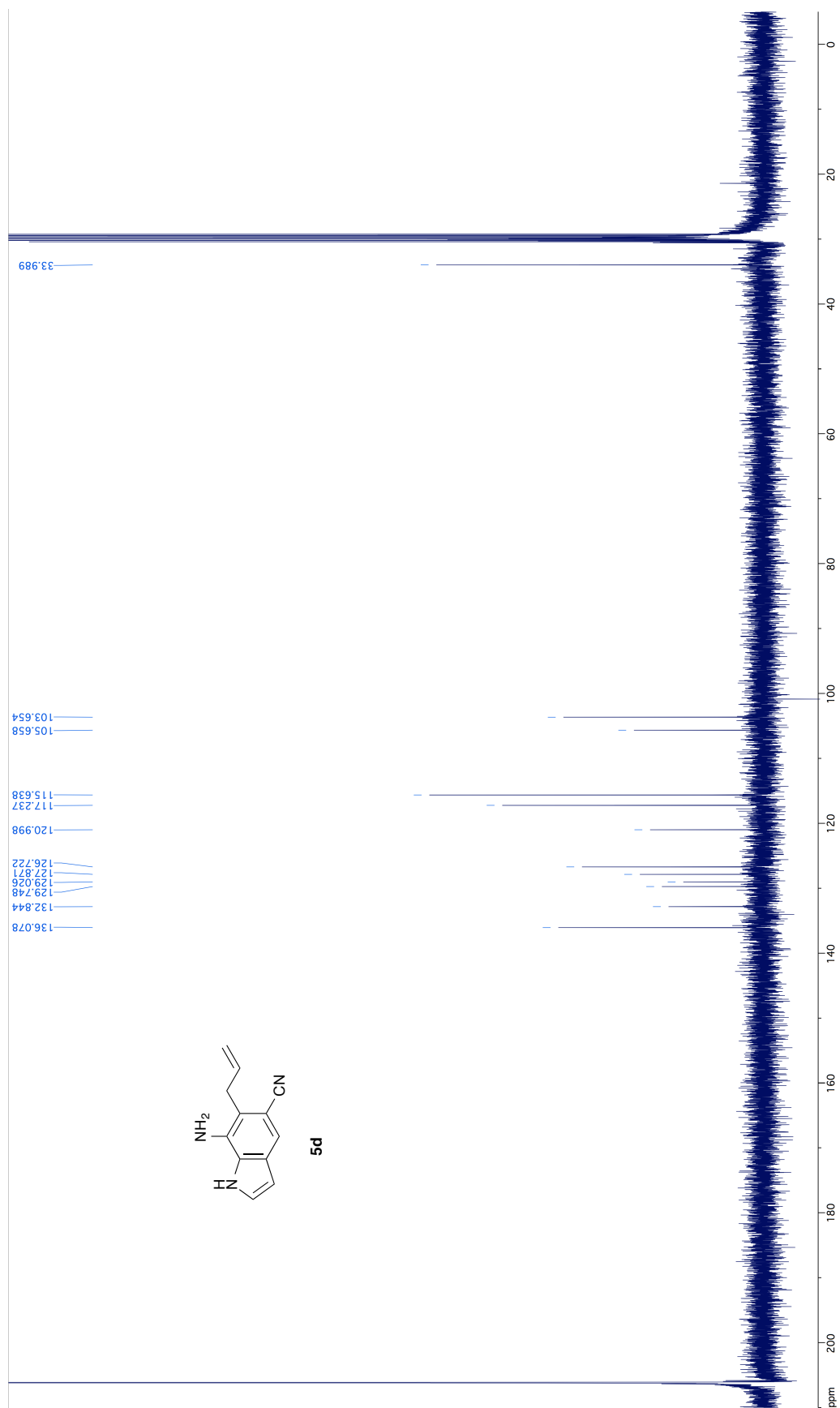


Figure 46 <sup>13</sup>C-NMR spectrum for compound **5c** (Acetone-d<sub>6</sub>, 100 MHz)







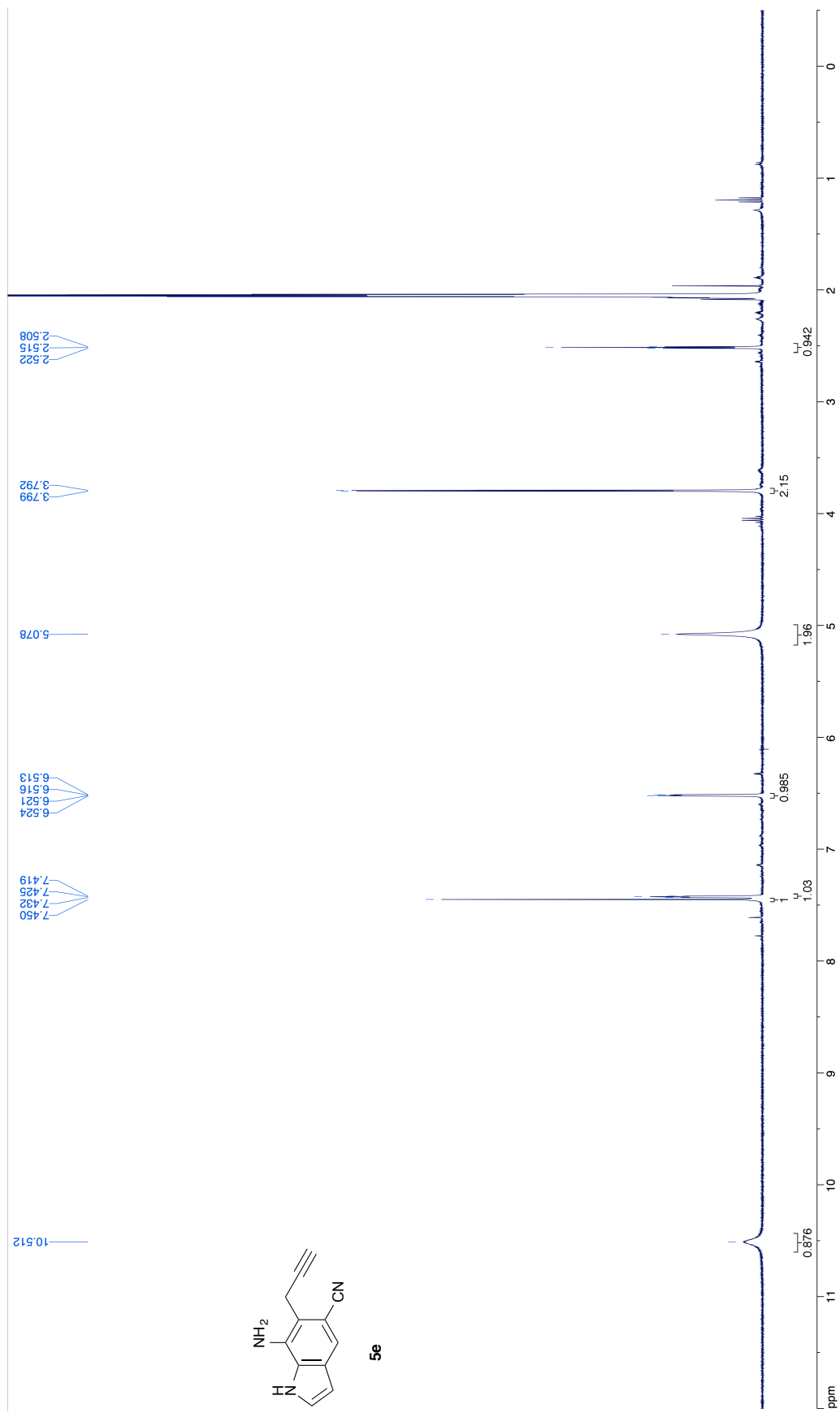


Figure 49  $^1\text{H-NMR}$  spectrum for compound 5e (Acetone- $d_6$ , 400 MHz)

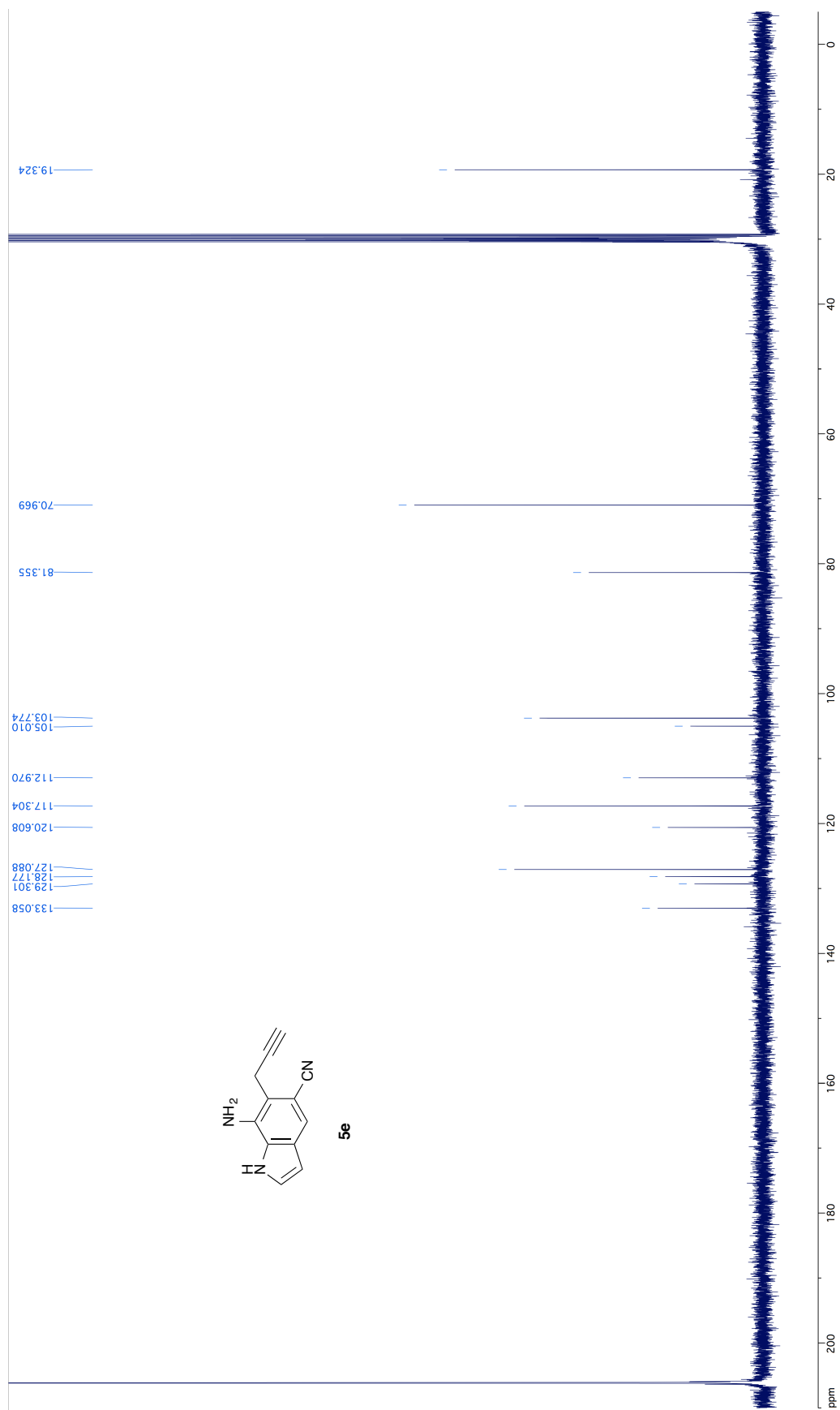


Figure 50  $^{13}\text{C}$ -NMR spectrum for compound **5e** (Acetone- $d_6$ , 100 MHz)

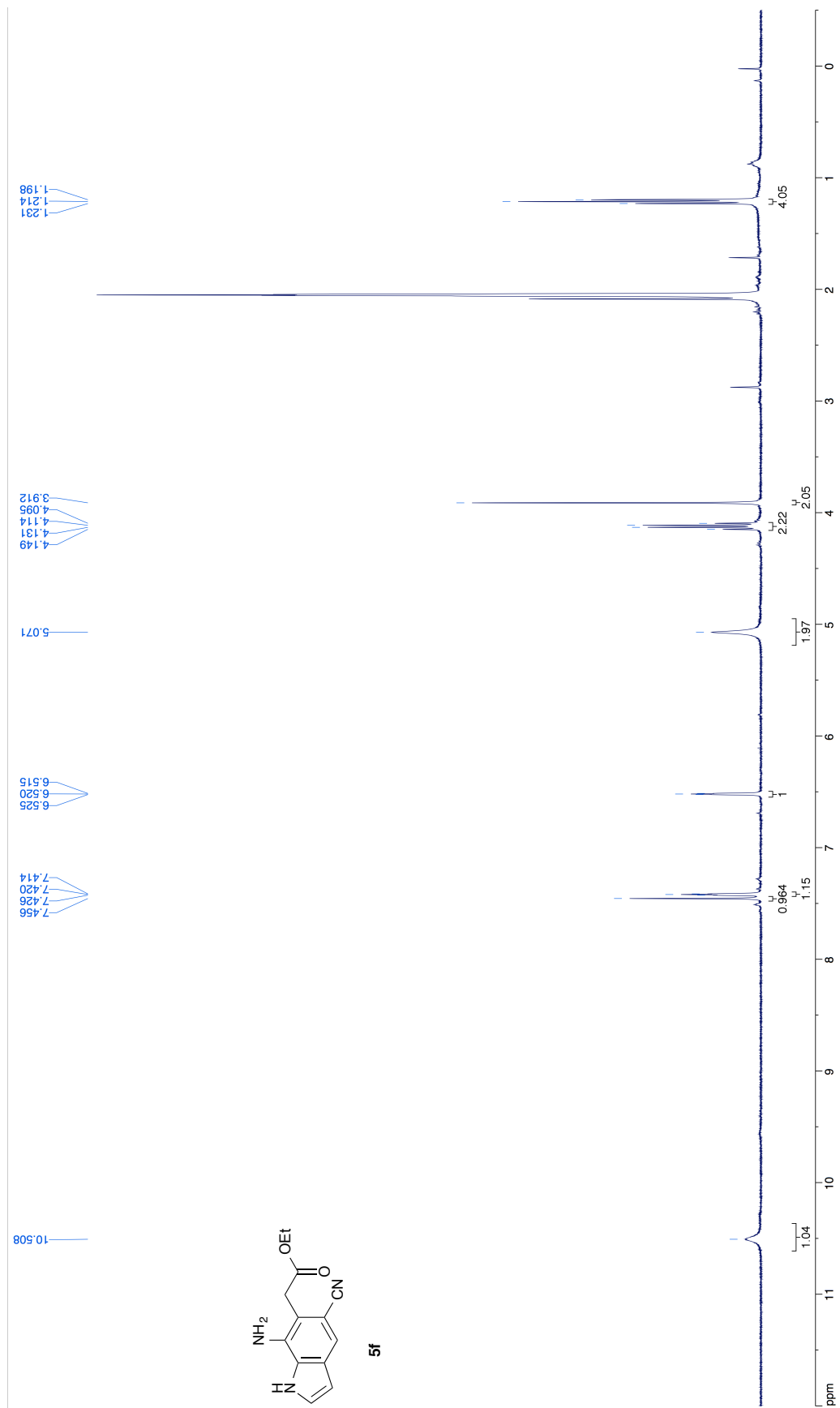


Figure S1 1H-NMR spectrum for compound **5f** (Acetone-d<sub>6</sub>, 400 MHz)

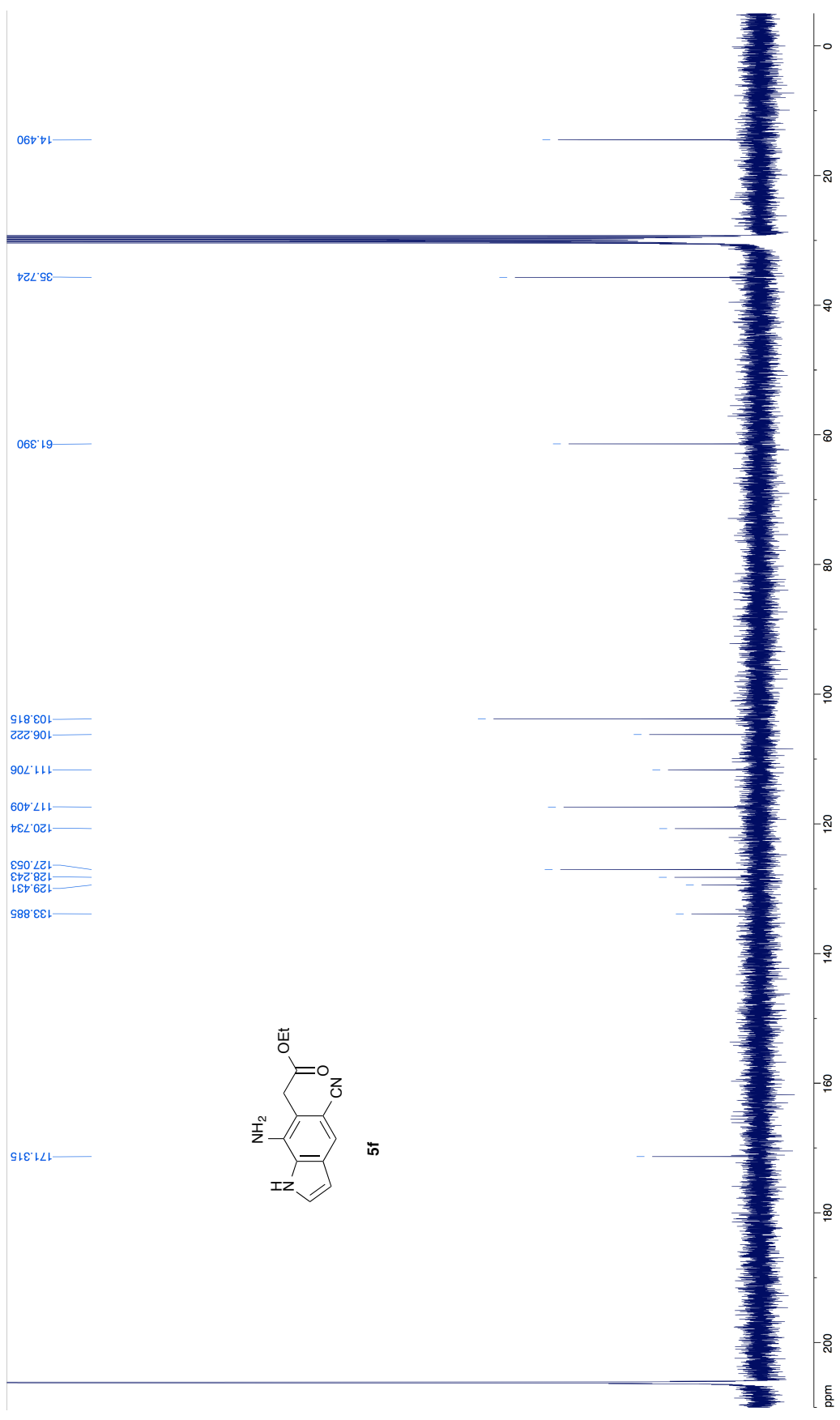
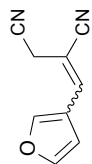


Figure S2 <sup>13</sup>C-NMR spectrum for compound 5f (Acetone-d<sub>6</sub>, 100 MHz)



**12a**  
(6:1 E/Z)

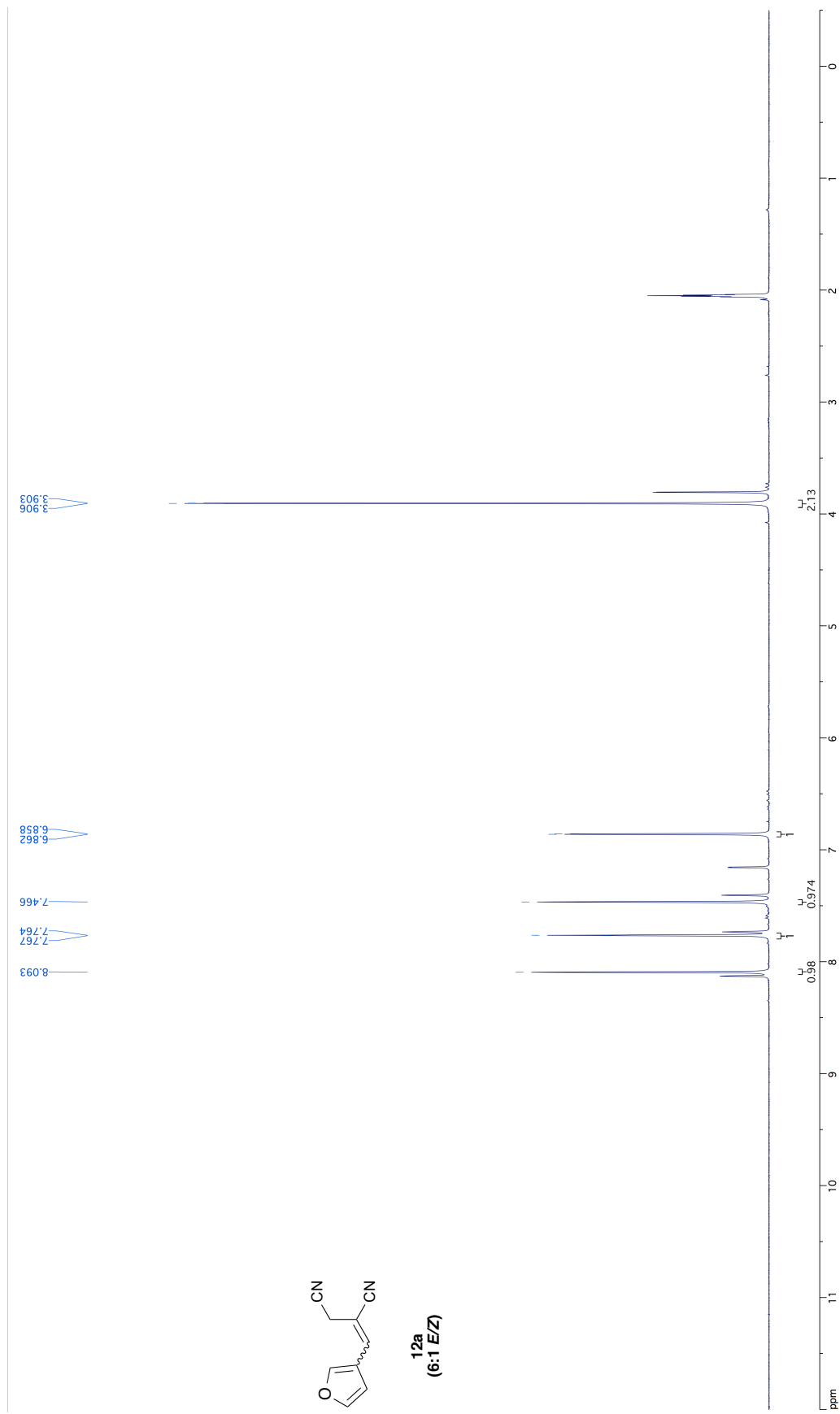


Figure S3  $^1\text{H-NMR}$  spectrum for compound 12a (Acetone- $d_6$ , 400 MHz)

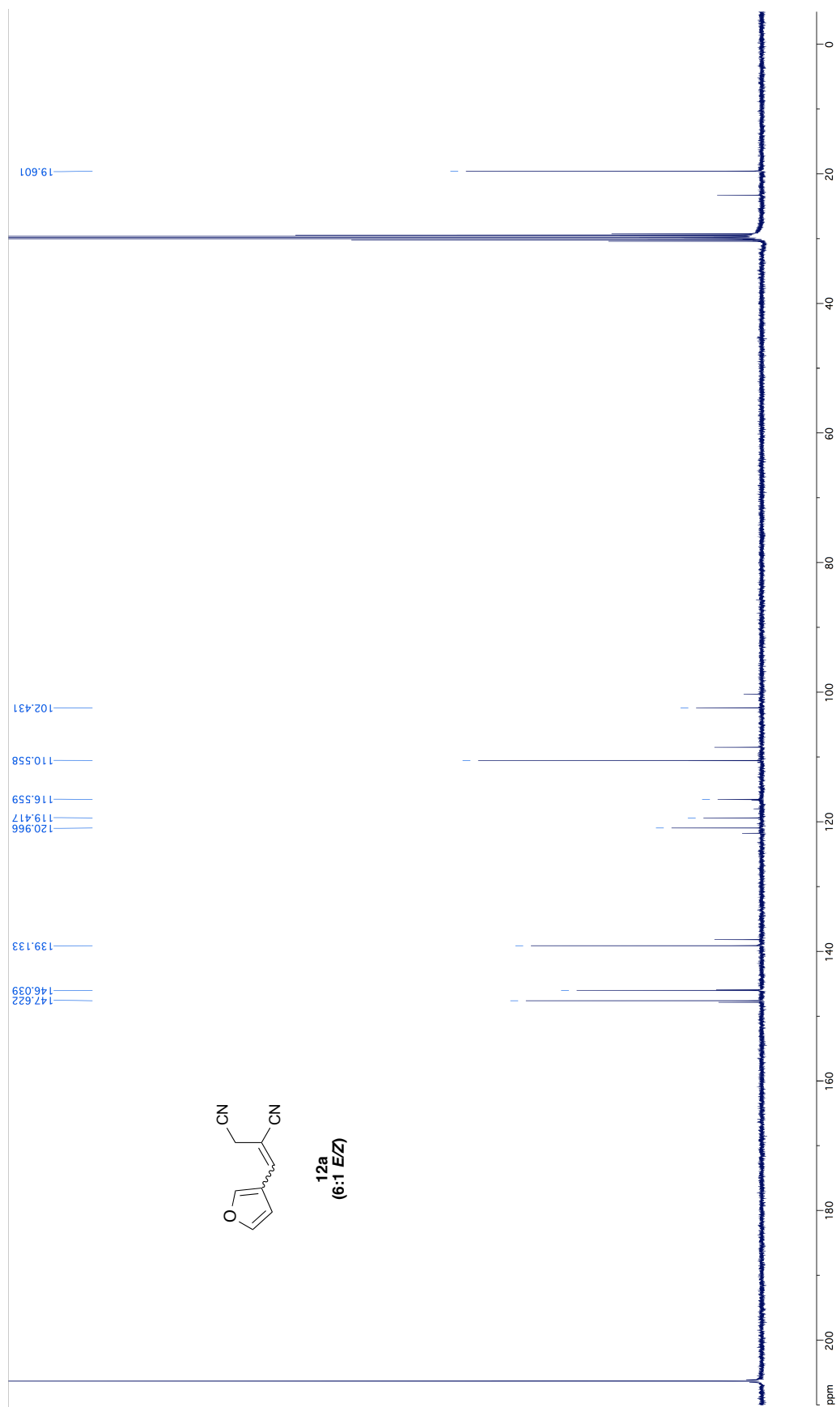


Figure S4 <sup>13</sup>C-NMR spectrum for compound 12a (Acetone-d<sub>6</sub>, 100 MHz)

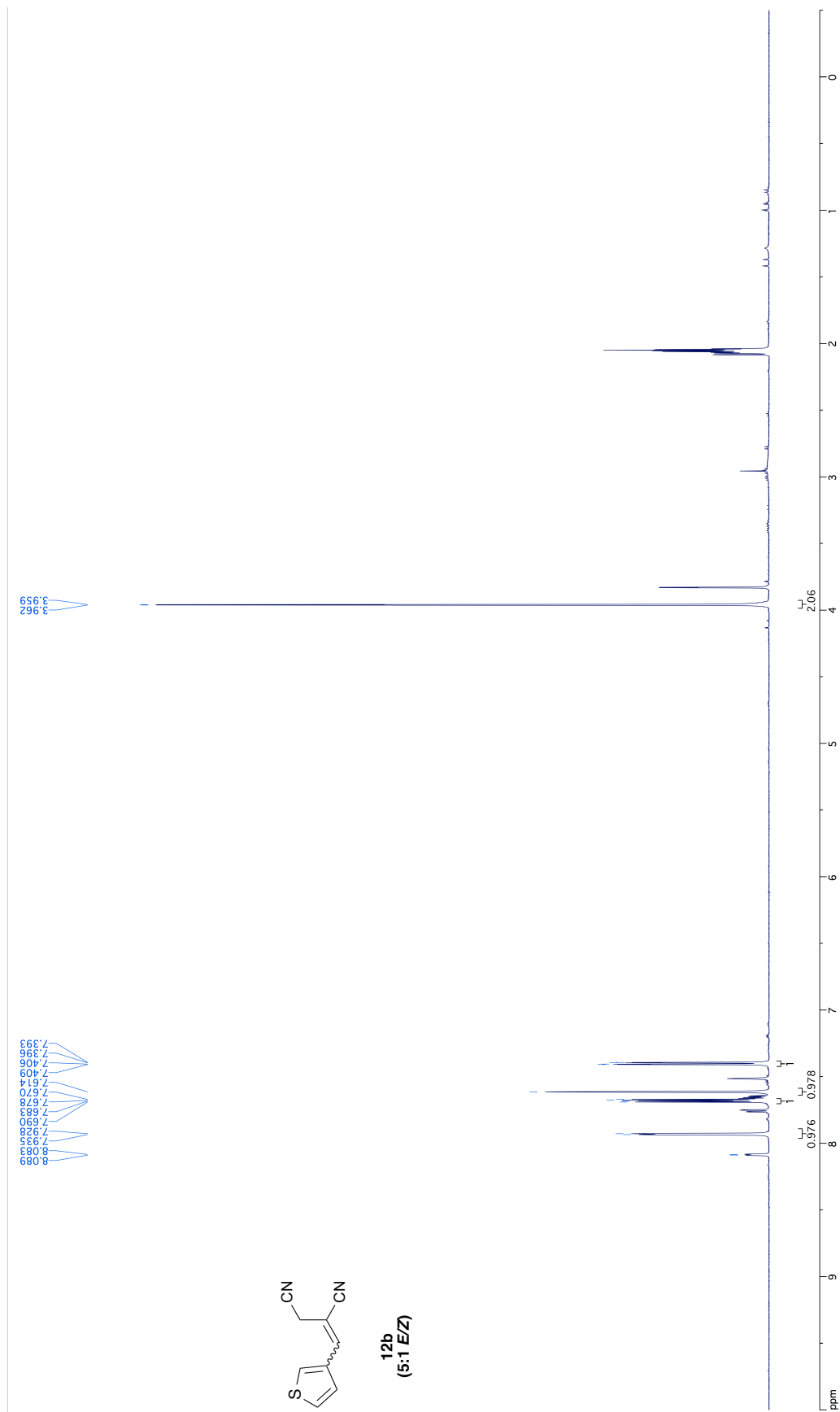


Figure S5 1H-NMR spectrum for compound 12b (Acetone-d<sub>6</sub>, 400 MHz)



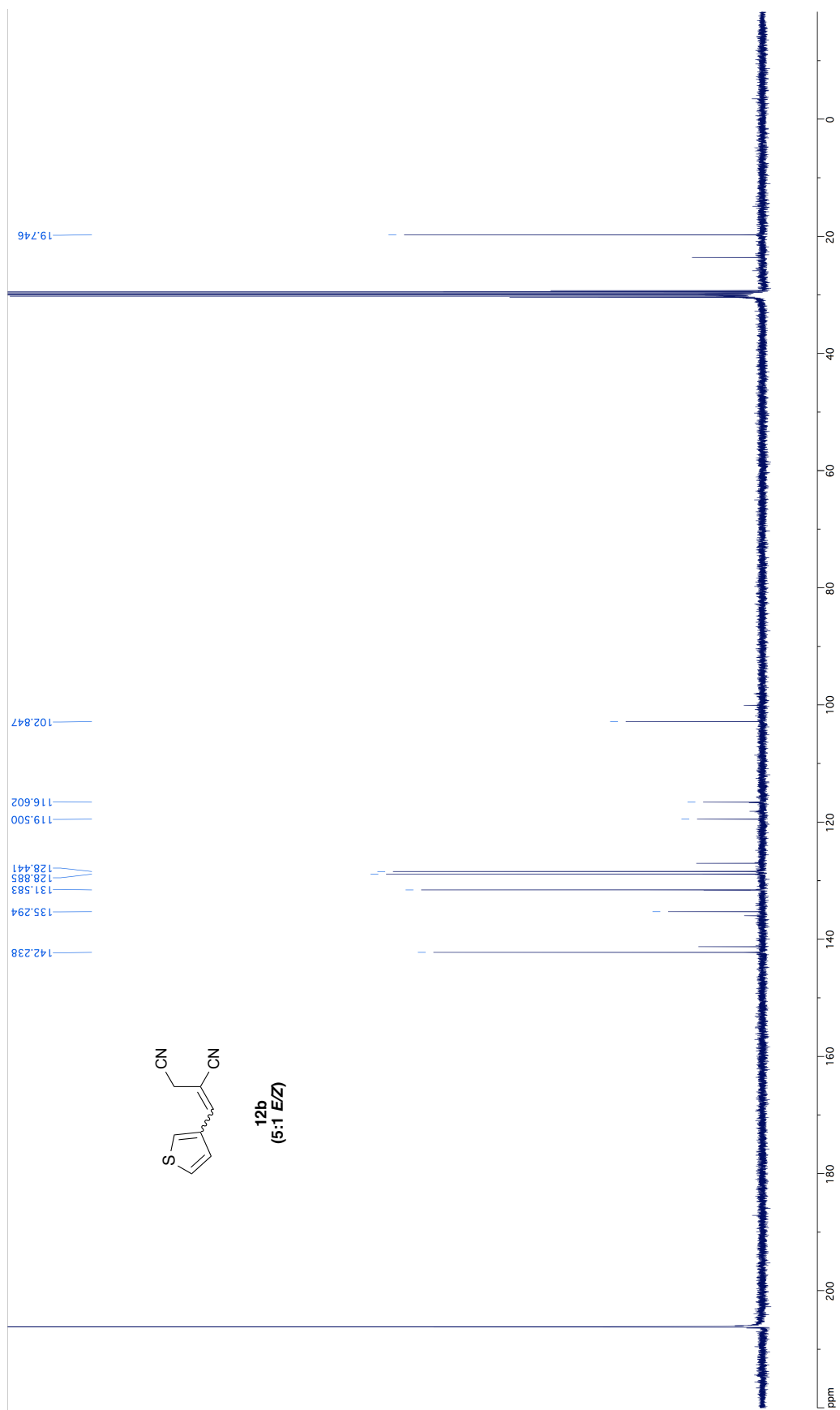


Figure S6 <sup>13</sup>C-NMR spectrum for compound 12b (Acetone-d<sub>6</sub>, 100 MHz)

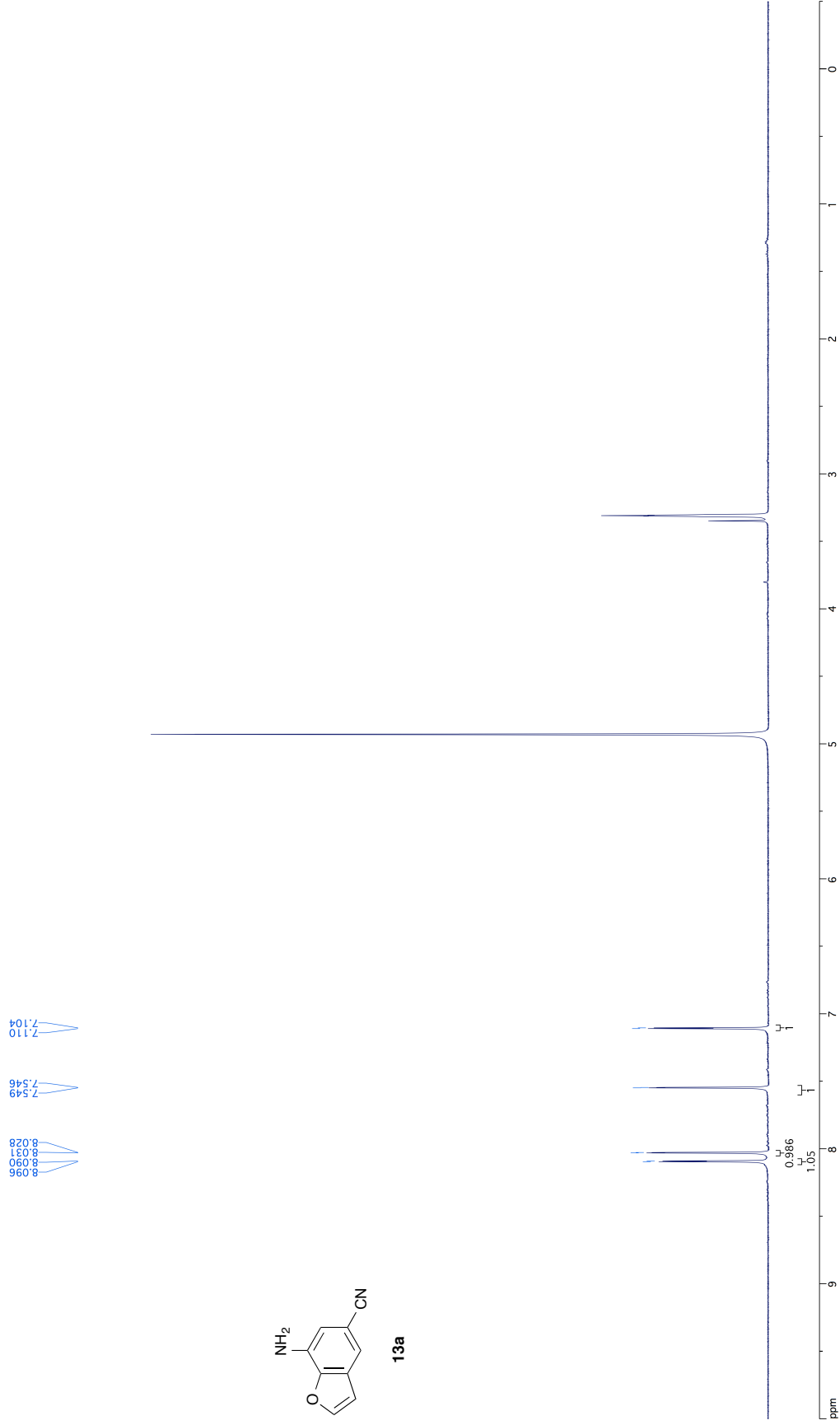
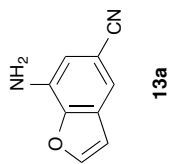


Figure S7 <sup>1</sup>H-NMR spectrum for compound 13a (MeOD, 400 MHz)

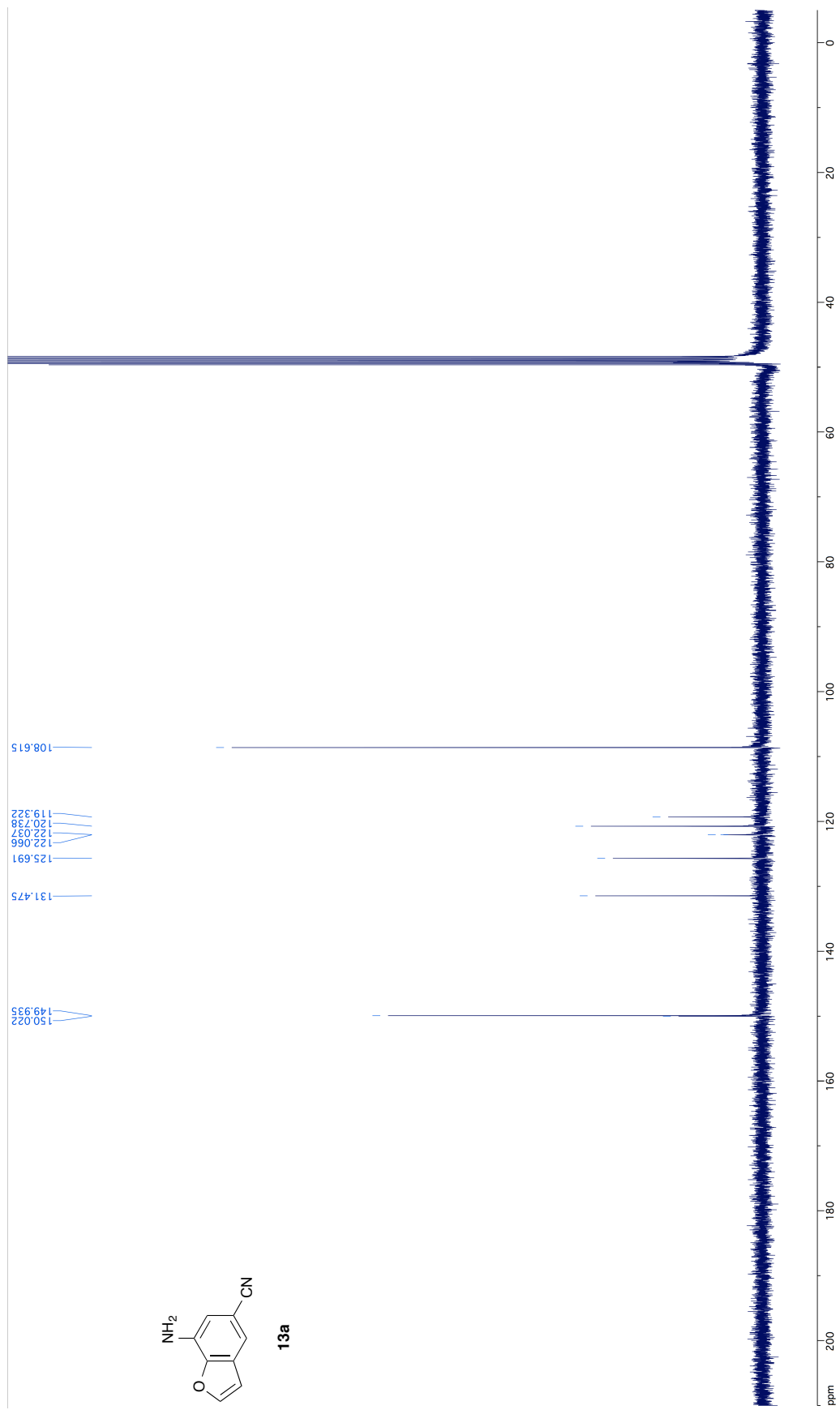
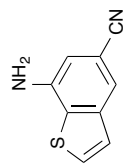


Figure 58 <sup>13</sup>C-NMR spectrum for compound 13a (MeOD, 100 MHz)



13b

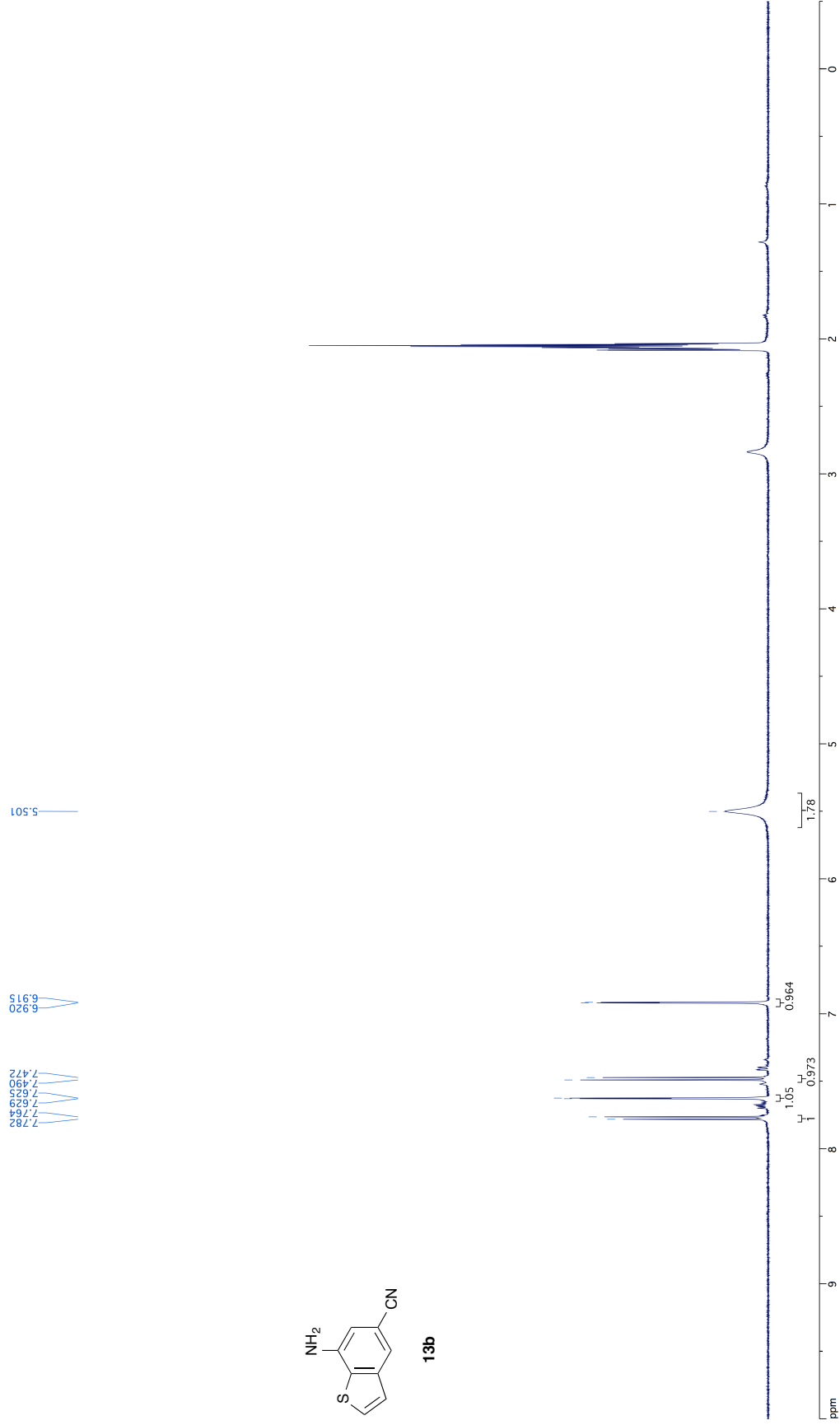


Figure S9 <sup>1</sup>H-NMR spectrum for compound 13b (Acetone-d<sub>6</sub>, 400 MHz)

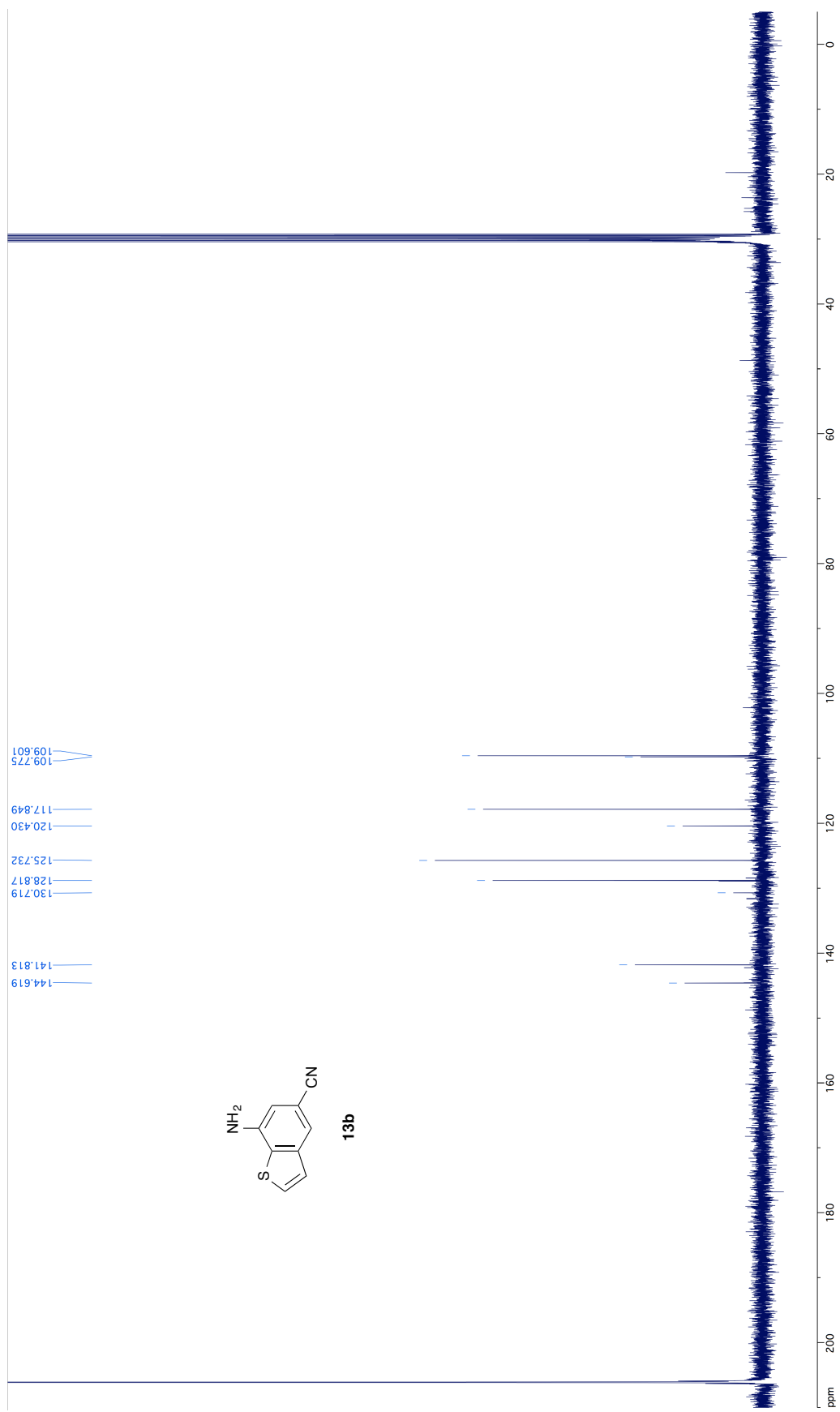


Figure 60 <sup>13</sup>C-NMR spectrum for compound 13b (Acetone-d<sub>6</sub>, 100 MHz)

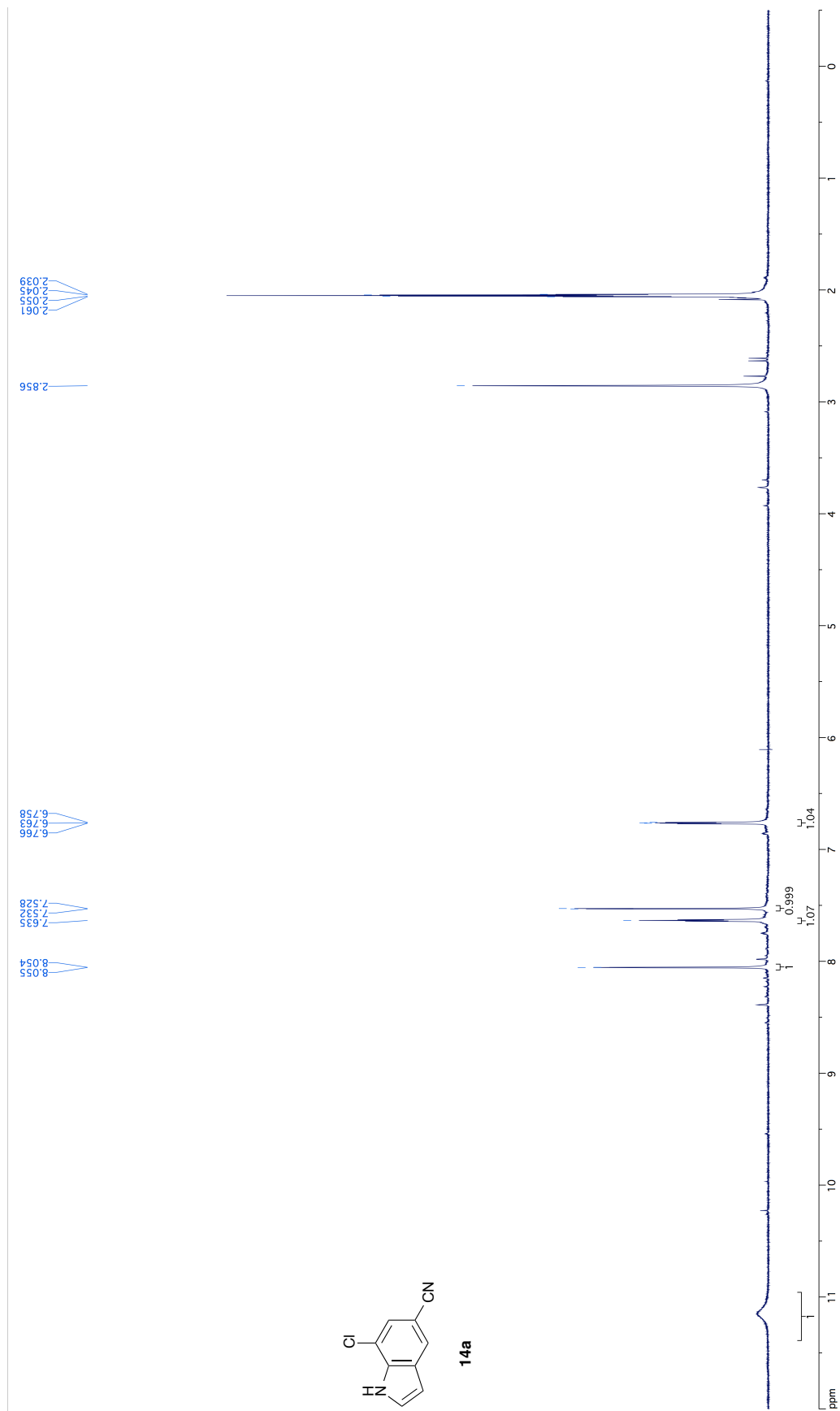


Figure 61 <sup>1</sup>H-NMR spectrum for compound 14a (Acetone-d<sub>6</sub>, 400 MHz)

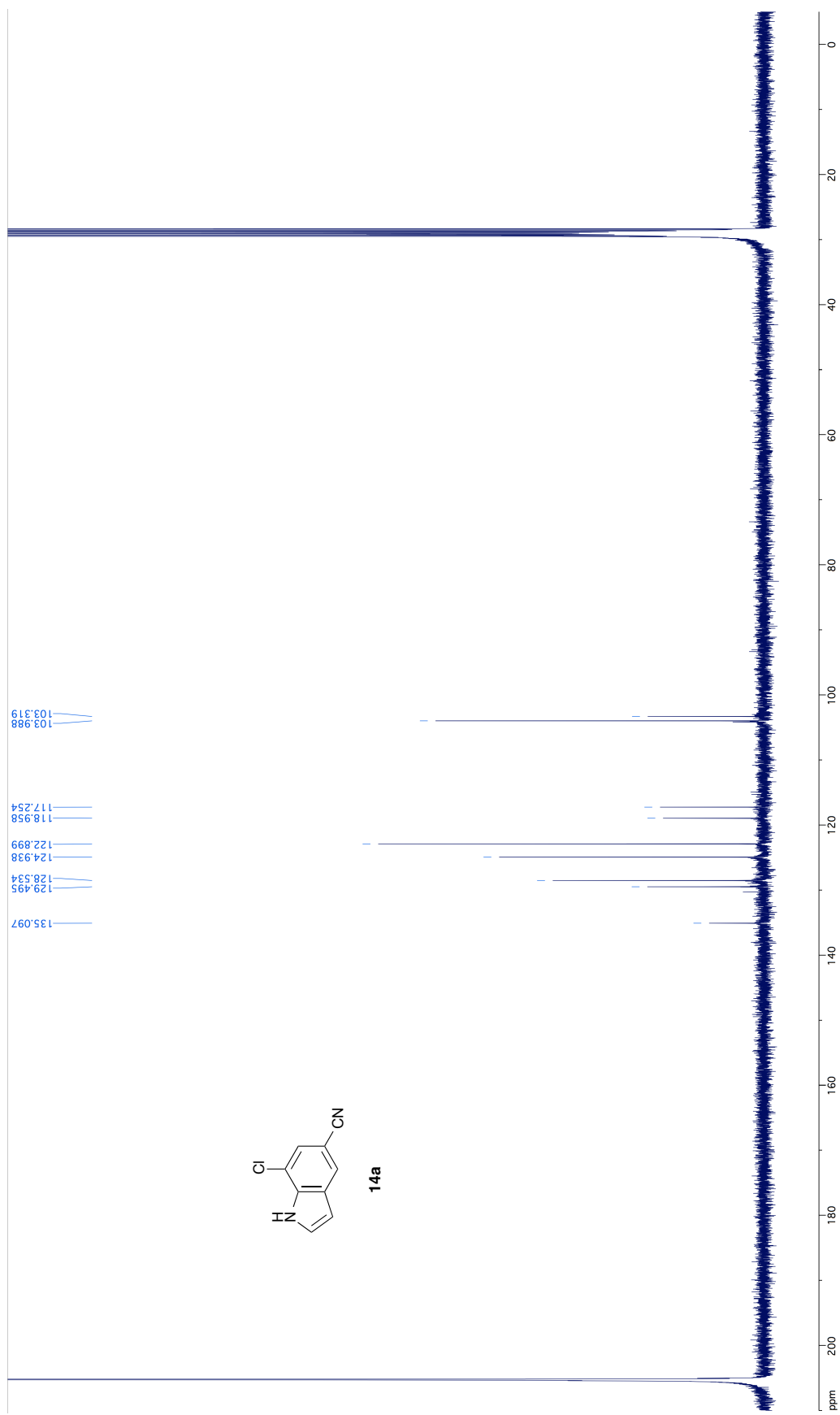
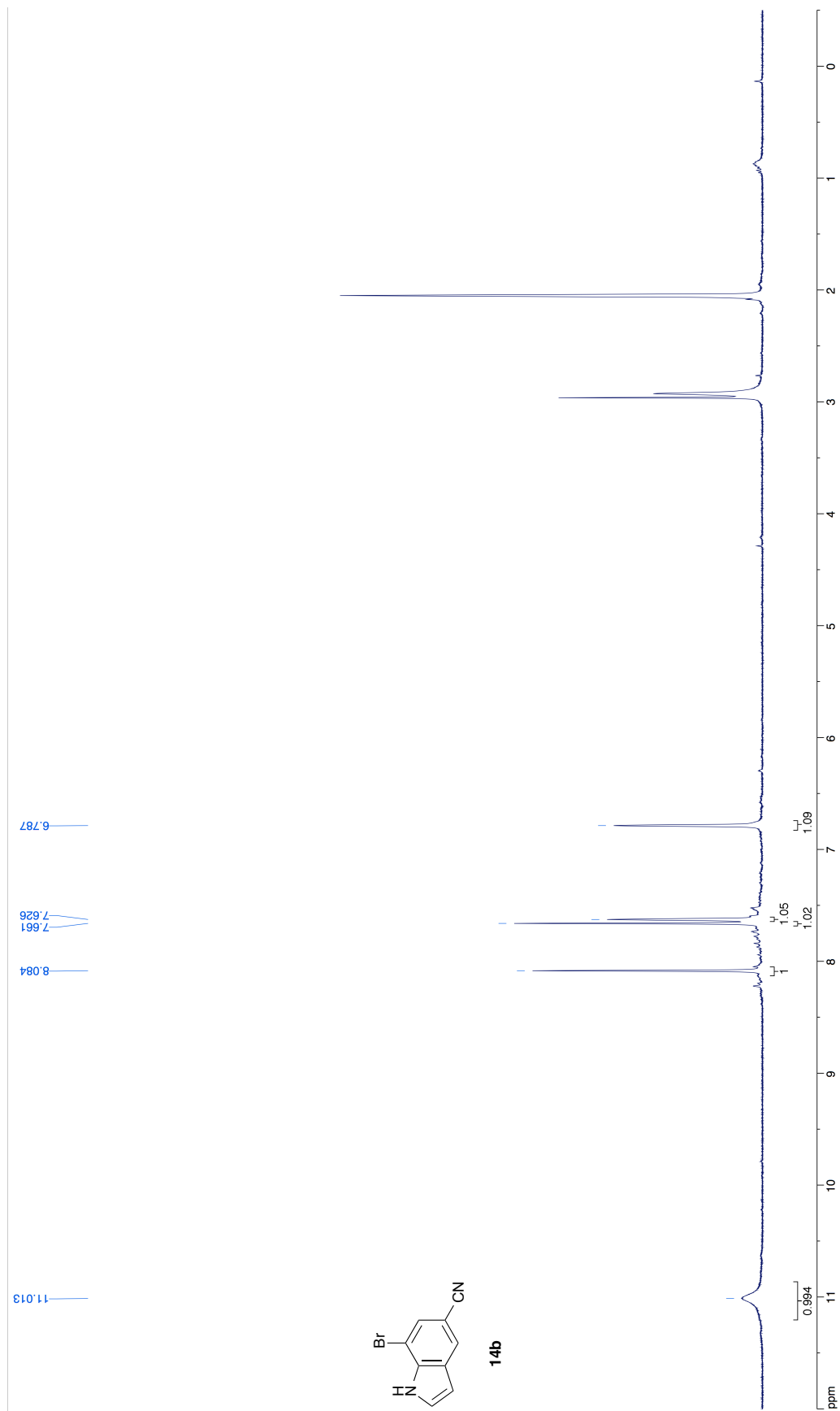


Figure 62 <sup>13</sup>C-NMR spectrum for compound 14a (Acetone-d<sub>6</sub>, 100 MHz)





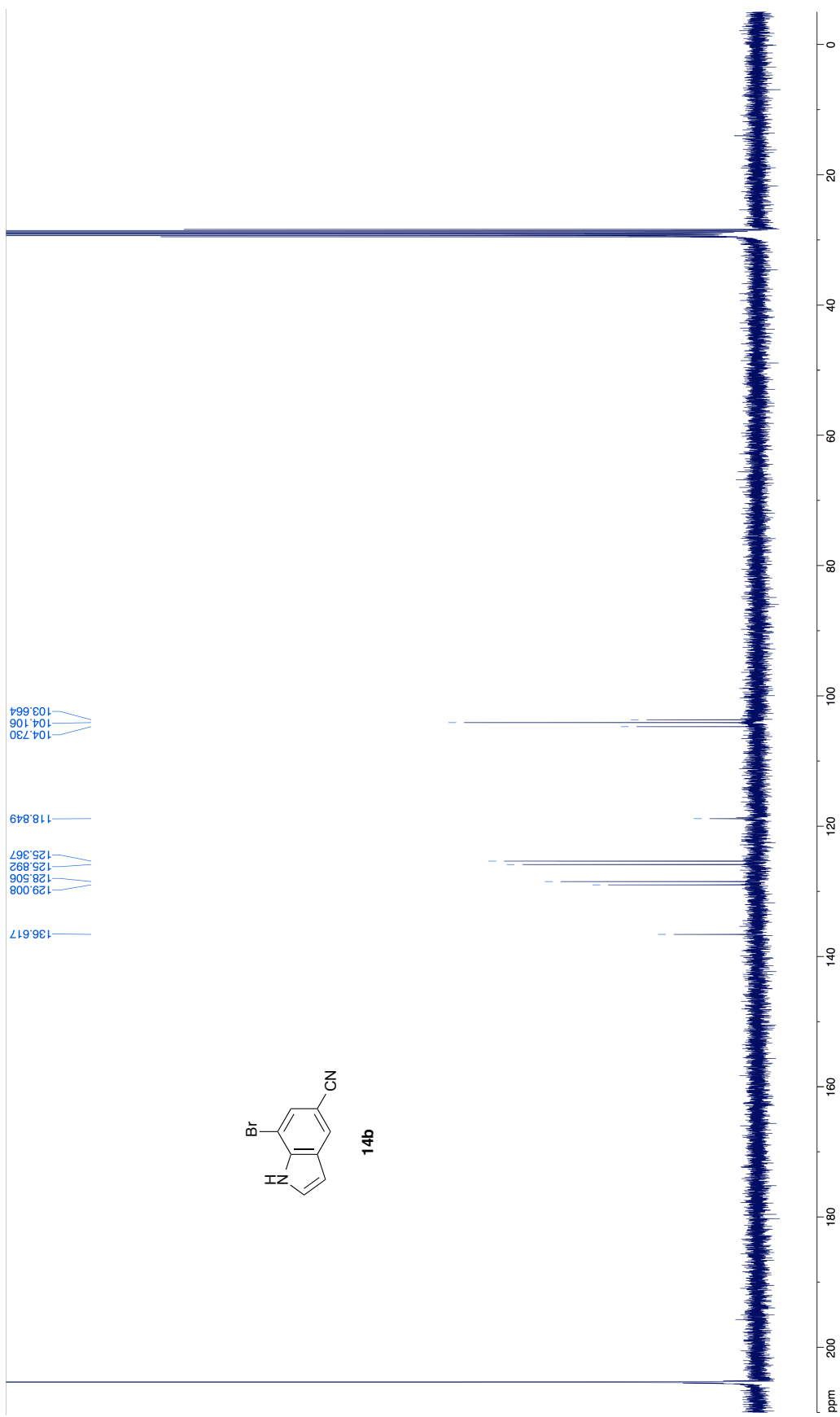
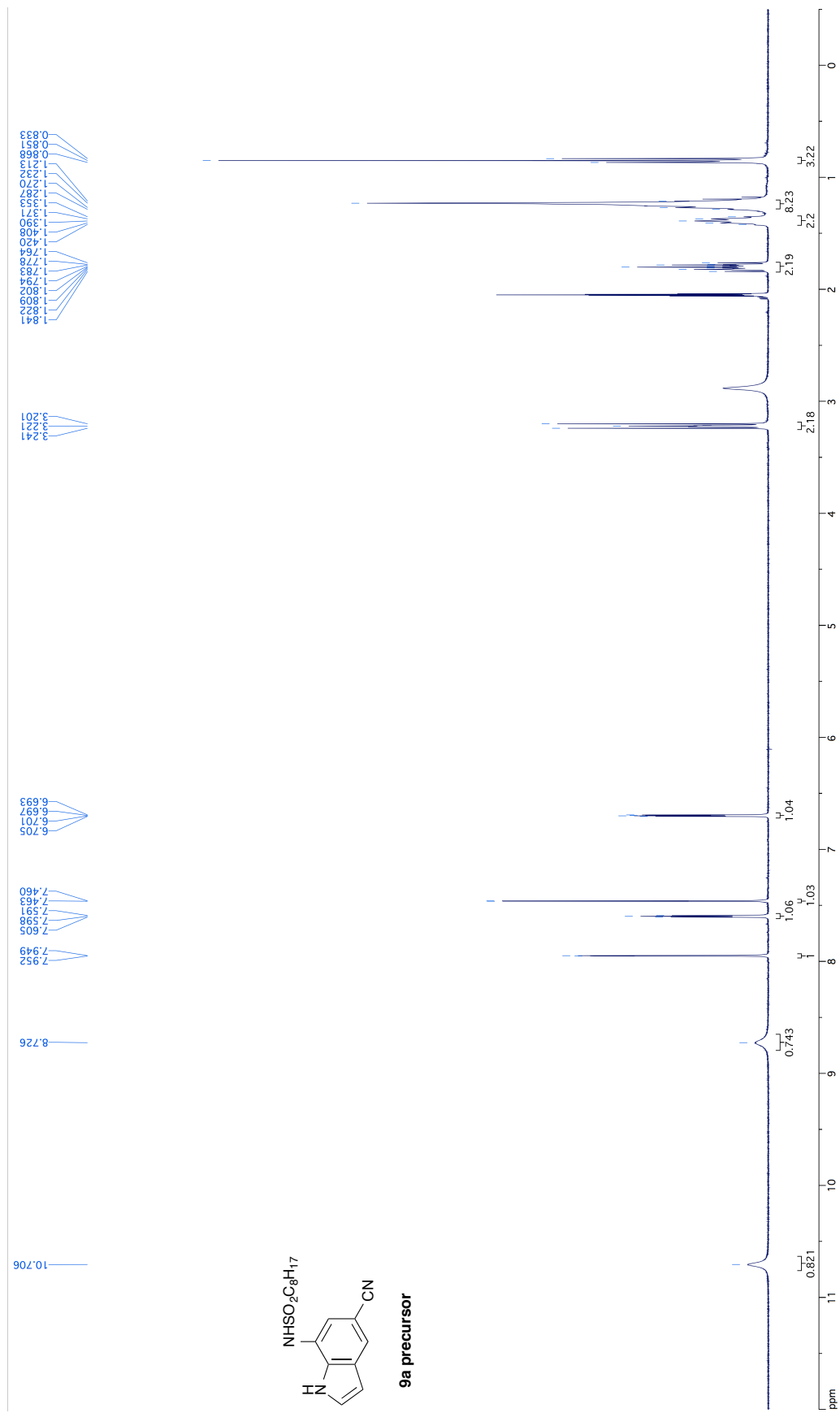


Figure 64 <sup>13</sup>C-NMR spectrum for compound 14b (Acetone-d<sub>6</sub>, 100 MHz)



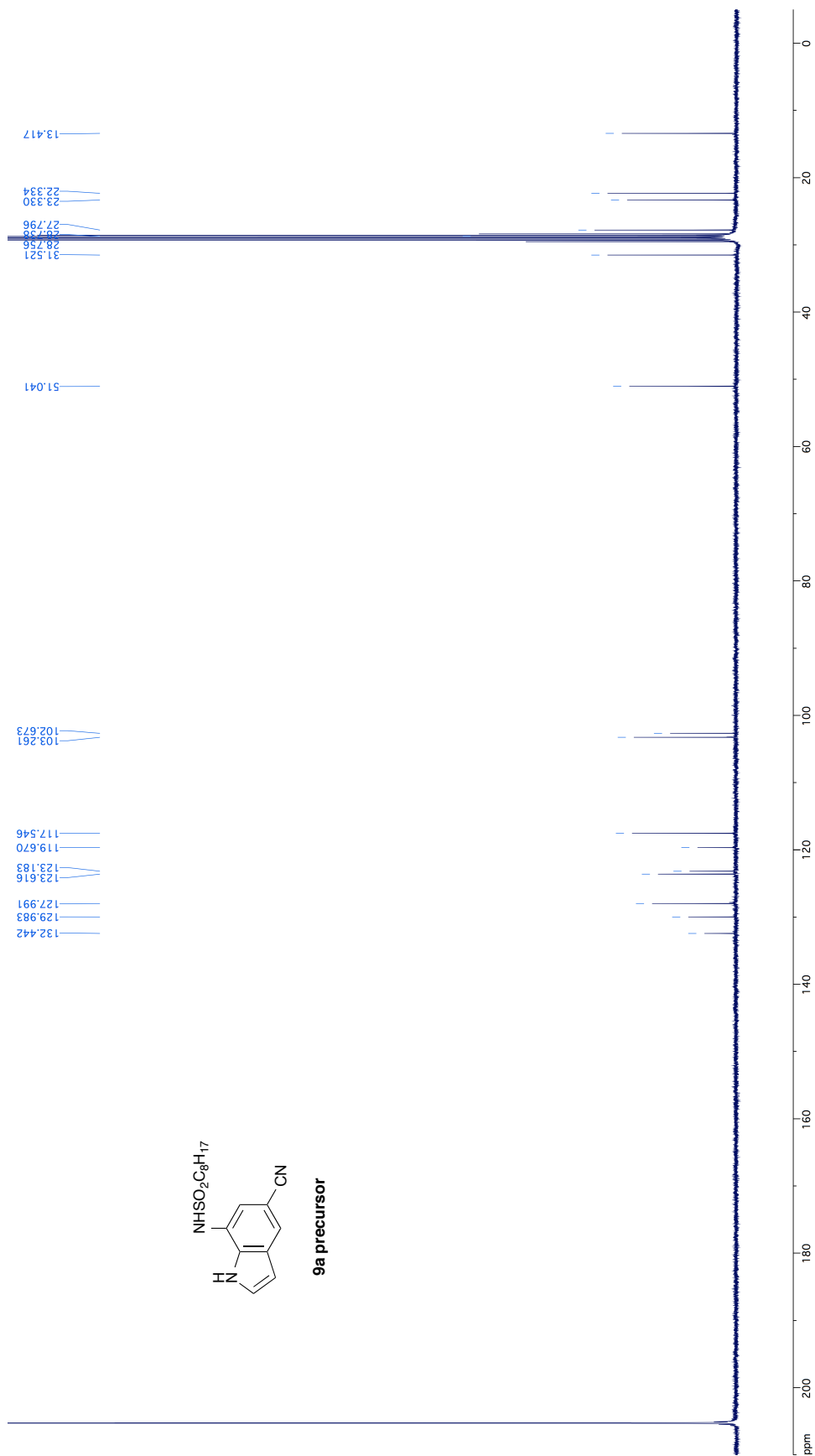


Figure 66  $^{13}\text{C}$ -NMR spectrum for compound **9a precursor** (Acetone- $d_6$ , 100 MHz)

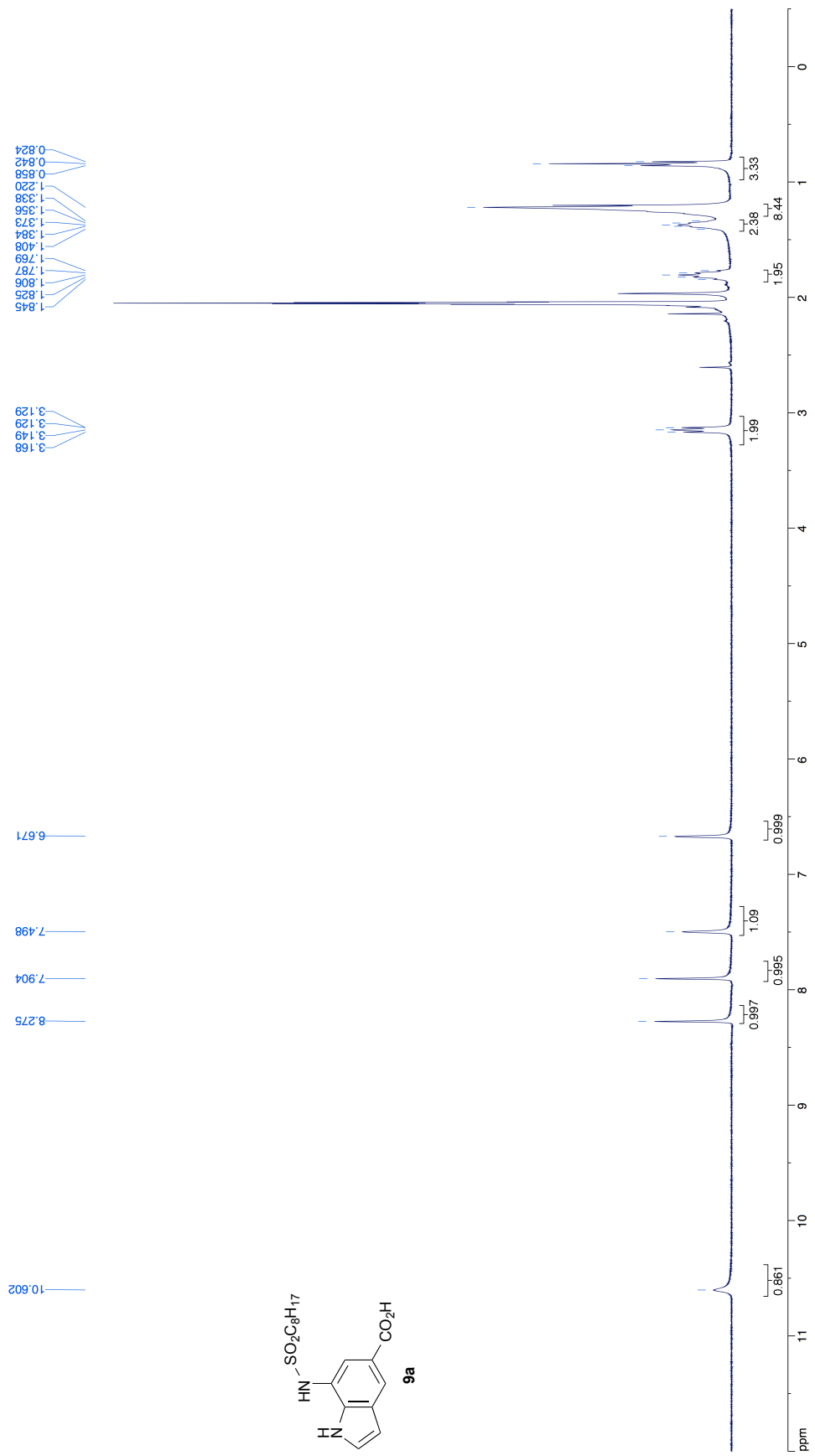


Figure 67 <sup>1</sup>H-NMR spectrum for compound **9a** (Acetone-d<sub>6</sub>, 400 MHz)

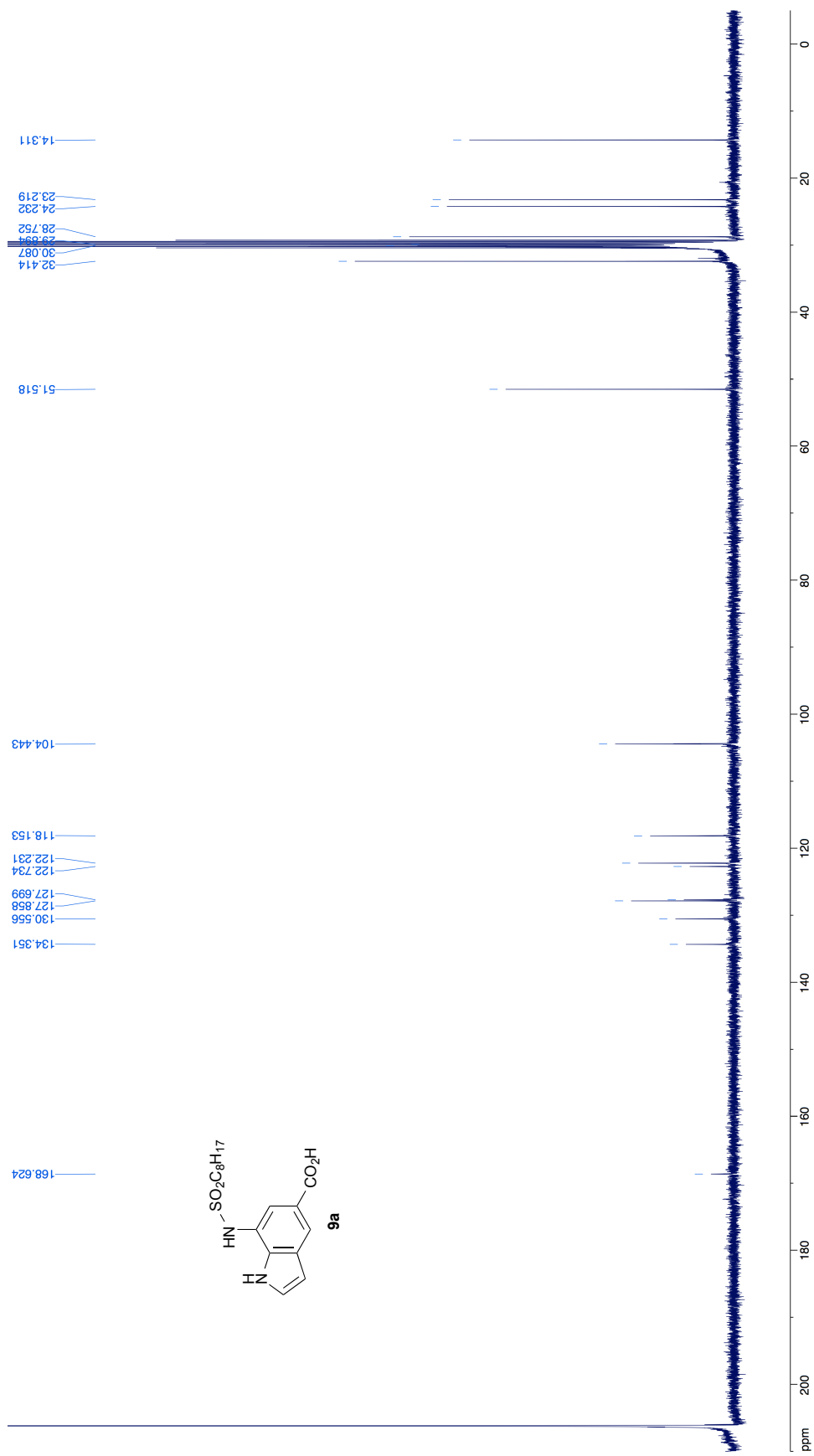


Figure 68 <sup>13</sup>C-NMR spectrum for compound 9a (Acetone-d<sub>6</sub>, 100 MHz)

### 3 References

<sup>1</sup> Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317–6328.

<sup>2</sup> Arikawa, Y.; Nishida, H.; Kurasawa, O.; Hasuoka, A.; Hirase, K.; Inatomi, N.; Hori, Y.; Matsukawa, J.; Imanishi, A.; Kondo, M.; Tarui, N.; Hamada, T.; Takagi, T.; Takeuchi, T.; Kajino, M. *J. Med. Chem.* **2012**, *55*, 4446–4456.

<sup>3</sup> Muchowski, J. M.; Naef, R. *Helvetica Chimica Acta.* **1984**, *67*, 1168–1172.

<sup>4</sup> Stefan, K.-P.; Schuhmann, W.; Parlar, H.; Korte, F. *Chem. Ber.* **1989**, *122*, 169–174.

<sup>5</sup> Dawadi, P. B. S.; Lugtenburg, J. *Eur. J. Org. Chem.* **2008**, 2288–2292.