Supplementary Information

Design and Synthesis of Pyrrolidine-Based Fragments that Sample Three Dimensional Molecular Space

Philip Garner,*,† Philip B. Cox,*,¶ Upendra Rathnayake,† Nicholas Holloran† and Paul Erdman¶

†Department of Chemistry, Washington State University, Pullman, WA 99164-4630

¶Discovery Chemistry and Technology, AbbVie Inc., 1 North Waukegan Road, North Chicago, IL 60064

Table of contents

I. General considerations. All moisture sensitive reactions were performed in flame dried glassware under an inert, dry atmosphere of argon (Ar). Air sensitive liquids were transferred via syringe or cannula through rubber septa. Reagent grade solvents were used for extraction and flash chromatography. Anhydrous solvents were prepared as follows: THF was distilled from Na/benzophenone under Ar; Methanol was distilled from magnesium methoxide onto 4Å molecular sieves. All other reagents and solvents were purchased from commercial sources and used directly without further purification. The progress of reactions was monitored by analytical thin layer chromatography (TLC, silica gel F-254 plates) and ^{1}H NMR. TLC plates were visualized first with UV illumination (254 nm) followed by Dragendorff stain. Flash column chromatography was performed on flash grade (230-400 mesh) silica gel. The solvent compositions reported for all chromatographic separations are on a volume/volume (v/v) basis. High performance liquid chromatography (HPLC) was carried out using Diacel Chiracel OD (4.6 x 250 mm) chiral column (enantiomeric ratio of **7b** and **ent-7b**). Eluent A was HPLC grade hexanes and Eluent B HPLC grade i-PrOH. HPLC analysis was monitored at the 254 nm wavelength. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 or 600 MHz and are reported in parts per million (ppm) on the δ scale relative to residual nondeuterated solvent peaks of $CDCl_3$ as an internal standard (δ 7.26), $(CD_3)_2CO$ as an internal standard (δ 2.05) or CD_3OD as an internal standard (δ 3.31). ^{13}C-NMR spectra were recorded at 100.5 MHz or 150.8 MHz and are reported in parts per million (ppm) on the δ scale relative to $CDCl_3$ as an internal standard (δ 77.16), $(CD_3)_2CO$ as an internal standard (δ 206.26) or DMSO-d6 as an internal standard (δ 39.52). Assignment of pyrrolidine ring protons and carbons is based on gCOSY and HSQCAD (compounds **4b**, **8b** and **7b**). The relative stereochemistry of the pyrrolidine ring protons is assigned based on 2D NOESY (compounds **4a**, **5a**, **4b**, **5b**, **4c**, **5c**, **4d**, **5d**, **4e**, **5e**, **4f**, **5f**). NMR spectra were acquired at ambient temperature. High resolution mass spectrometry (HRMS) was performed with ESI and MALDI using either α-cyano-4-hydroxycinnamic acid or 3,5-dimethoxy-4-hydroxycinnamic acid matrices.

II. Synthetic procedures for key compounds

1. **General procedure for *endo*-selective cycloaddition reactions (4a, 4b, 4c, 4d, 4e and 4f).** A mixture of Oppolzer's glycyl sultam (1.21 mmol, 1.3 equiv) and aldehyde (0.93 mmol, 1.0 equiv) in dry THF (3 mL) was stirred under argon at room temperature (50 °C for 4f). The reaction

was monitored by ^{1}H NMR for the completion of the corresponding imine formation, at which point AgOAc (10 mol %) was added to the reaction mixture followed by acrylonitrile (2.79 mmol, 3.0 equiv). The reaction was further stirred in the dark under argon at room temperature, until the formation of cycloadduct was complete (monitored by ^{1}H NMR for the complete disappearance of the corresponding imine). The reaction mixture was partitioned between saturated aq. NH_4Cl (15 mL) and DCM (5 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude cycloadducts were purified by flash chromatography.

2. General procedure for *exo*-selective cycloaddition reactions (5a, 5b, 5c, 5d, 5e and 5f)

A mixture of Oppolzer's glycyl sultam (1.21 mmol, 1.3 equiv), aldehyde (0.93 mmol, 1.0 equiv) in DMSO (6 mL) was stirred under argon at room temperature (50 °C for 5f). The reaction was monitored by ^{1}H NMR for the completion of the corresponding imine formation. To the reaction mixture was added a mixture of $Cu(MeCN)_4PF_6$ (5.0 mol%) and dppb (5.5 mol%) in DMSO (5 mL) which had been stirred in the dark at room temperature for 1hour under argon. The combined mixture was treated with the acrylonitrile (2.79 mmol, 3.0 equiv) and allowed to stir in the dark at room temperature until the formation of cycloadduct is completed (monitored by ^{1}H NMR for the complete disappearance of the corresponding imine). Upon the completion of the reaction, saturated aqueous NH_4Cl (50 mL) was added and the aqueous layer was extracted with DCM (3 x 300 mL). The combined organic layers were washed with water (2 x 300 mL) and brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude cycloadducts were purified by flash chromatography.

3. General procedure for the methanolysis reaction using $Sm(OTf)_3$ (for methyl esters 6a, 6b, 6d, 6e, 8a, 8b, 8d and 8e)

To a solution of cycloadduct (0.12 mmol, 1 equiv) in dry MeOH (2 mL), $Sm(OTf)_3$ (0.12 mmol, 1 equiv) was added and the resulting mixture was stirred at room temperature for 12 hours (monitored by TLC for the complete disappearance of the cycloadduct). Then the reaction mixture was concentrated under reduced pressure and purified by flash chromatography.

NOTE - The water solubility of the methyl esters is high. Hence, purification of above methyl esters was done directly without an aqueous workup.

4. Methanolysis of cycloadducts 4c and 5c (for methyl esters 6c and 8c)

To a solution of cycloadduct (0.12 mmol, 1 equiv) in dry MeOH (2 mL), $Sm(OTf)_3$ (0.12 mmol, 1 equiv) was added and the resulting mixture was stirred at room temperature for 12 hours (monitored by TLC for the complete disappearance of the cycloadduct). Then the reaction mixture was concentrated under reduced pressure, portioned between EtOAc (2 mL) and EDTA (0.5M) and vigorously stirred for 30 minutes. Organic layer was separated and washed with saturated aqueous NaCl and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude methyl esters were purified by flash chromatography.

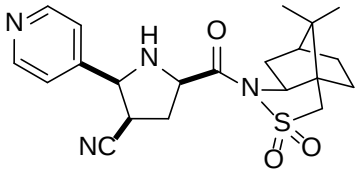
5. Methanolysis of cycloadducts 4f and 5f (for methyl esters 6f and 8f)

Cycloadduct (0.055 mmol, 1 equiv) was refluxed with K_2HPO_4 (0.005 mmol,10% mol) in MeOH (0.5 mL), for 36 hours (monitored by TLC for the complete disappearance of the cycloadduct). Then the reaction mixture was concentrated under reduced pressure and purified by flash chromatography.

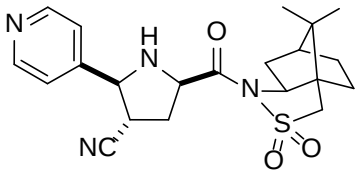
6. General procedure for the reduction reaction using $NaBH_4$

To a solution of cycloadduct (0.059 mmol, 1 equiv) in dry MeOH (1 mL) was added $NaBH_4$ (0.12 mmol, 2 equiv) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 1 hour and further stirred at room temperature until the reaction was complete (monitored by TLC for the complete disappearance of the cycloadduct). The crude reaction mixture was concentrated under reduced pressure and purified by flash chromatography.

III. Characterization of compounds

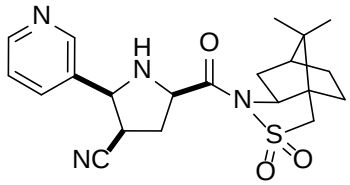


2S,3R,5R)-5-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-2-(pyridin-4-yl)pyrrolidine-3-carbonitrile (4a). Yellow solid, total yield: 54% (endo:exo = 67:33). Rf 0.25 (9:1 EtOAc/hexanes); mp 84-87 °C; ^{1}H NMR (600 MHz, Chloroform-d) δ 8.64 (d, J = 4.6 Hz, 2H), 7.45 (d, J = 5.0 Hz, 2H), 4.53 (dd, J = 8.6, 6.3 Hz, 1H), 4.45 (d, J = 6.6 Hz, 1H), 3.98 (t, J = 6.4 Hz, 1H), 3.54 (d, J = 13.9 Hz, 1H), 3.49 (d, J = 13.8 Hz, 1H), 3.37 (q, J = 6.2 Hz, 1H), 2.73 (dt, J = 13.2, 8.1 Hz, 1H), 2.45 (dt, J = 12.8, 5.6 Hz, 1H), 2.20 – 2.09 (m, 2H), 1.98 – 1.86 (m, 3H), 1.45 (t, J = 10.7 Hz, 1H), 1.41 – 1.34 (m, 1H), 1.16 (s, 3H), 0.99 (s, 3H).^{13}C NMR (151 MHz, Chloroform-d) δ 171.2, 150.3, 147.1, 122.3, 118.6, 65.7, 63.7, 59.4 53.2, 49.1, 48.0, 44.7, 38.3, 35.9, 35.6, 32.9, 26.6, 21.0, 20.0; HRMS (MALDI) *m/z* calcd for $C_{21}H_{27}N_4O_3S$ $[M+H]^+$ 415.1798; found, 415.1803.

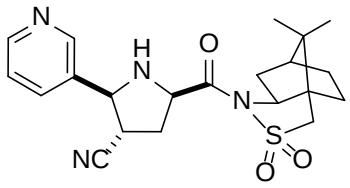


(2S,3S,5R)-5-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-2-(pyridin-4-yl)pyrrolidine-3-carbonitrile (5a). Pale yellow solid, total yield: 38% (endo:exo = 29:71). Rf 0.37 (9:1 EtOAc/hexanes); mp 153-157 °C; ^{1}H NMR (600 MHz, Chloroform-d) δ 8.66 – 8.56 (m, 2H), 7.50 – 7.44 (m, 2H), 4.69 (dd, J =

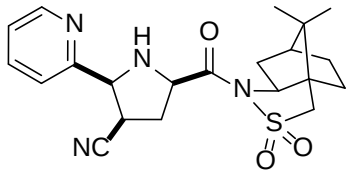
9.0, 4.0 Hz, 1H), 4.40 (d, J = 9.5 Hz, 1H), 3.94 (t, J = 6.4 Hz, 1H), 3.54 (d, J = 13.8 Hz, 1H), 3.48 (d, J = 13.8 Hz, 1H), 2.90 (td, J = 9.9, 8.4 Hz, 1H), 2.61 – 2.49 (m, 2H), 2.15 – 2.07 (m, 2H), 1.98 – 1.86 (m, 4H), 1.44 (t, J = 10.7 Hz, 1H), 1.41 – 1.33 (m, 1H), 1.15 (s, 3H), 0.99 (s, 3H).^{13}C NMR (151 MHz, Chloroform-d) δ 172.2, 150.4, 148.3, 121.8, 119.1, 65.9, 65.6, 58.3, 53.1, 49.0, 48.0, 44.8, 38.4, 36.7, 35.3, 33.0, 26.5, 21.1, 20.0; HRMS (MALDI) *m/z* calcd for $C_{21}H_{27}N_4O_3S$ $[M+H]^+$ 415.1798; found, 415.1804.



(2S,3R,5R)-5-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-2-(pyridin-3-yl)pyrrolidine-3-carbonitrile (4b). Pale yellow solid, total yield: 71% (endo:exo = 88:11). Rf 0.28 (9:1 EtOAc/hexanes); mp 79-82 °C; ^{1}H NMR (600 MHz, Chloroform-d) δ 8.65 (d, J = 2.3 Hz, 1H), 8.59 (dd, J = 4.8, 1.6 Hz, 1H), 8.01 (dt, J = 7.9, 2.0 Hz, 1H), 7.36 (ddd, J = 7.9, 4.9, 0.8 Hz, 1H), 4.53 (dd, J = 8.8, 5.9 Hz, 1H), 4.49 (d, J = 6.4 Hz, 1H), 3.98 (dd, J = 7.7, 5.0 Hz, 1H), 3.54 (d, J = 13.8 Hz, 1H), 3.49 (d, J = 13.8 Hz, 1H), 3.34 (ddd, J = 7.8, 6.4, 4.4 Hz, 1H), 2.75 (ddd, J = 13.6, 8.8, 7.8 Hz, 1H), 2.49 (ddd, J = 13.6, 5.9, 4.5 Hz, 1H), 2.20 – 2.10 (m, 2H), 1.98 – 1.87 (m, 3H), 1.49 – 1.43 (m, 1H), 1.42 – 1.35 (m, 1H), 1.17 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d) δ 171.3, 150.1, 149.1, 135.0, 133.8, 123.8, 118.9, 65.7, 62.6, 59.4, 53.2, 49.1, 48.0, 44.7, 38.3, 36.3, 35.8, 32.9, 26.6, 21.0, 20.0; HRMS (MALDI) *m/z* calcd for $C_{21}H_{27}N_4O_3S$ $[M+H]^+$ 415.1798; found, 415.1810.

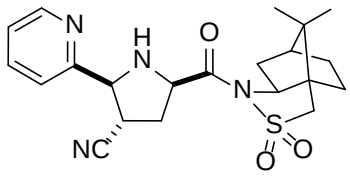


(2S,3S,5R)-5-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-2-(pyridin-3-yl)pyrrolidine-3-carbonitrile (5b). Pale yellow solid, total yield: 54% (endo:exo = 17:83). Rf 0.40 (9:1 EtOAc/hexanes); mp 178-180 °C; ^{1}H NMR (600 MHz, Chloroform-d) δ 8.77 (s, 1H), 8.61 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.32 (s, 1H), 4.68 (dd, J = 9.3, 3.9 Hz, 1H), 4.43 (d, J = 9.6 Hz, 1H), 3.94 (t, J = 6.4 Hz, 1H), 3.55 (d, J = 13.8 Hz, 1H), 3.48 (d, J = 13.8 Hz, 1H), 2.99 – 2.89 (m, 1H), 2.63 – 2.51 (m, 2H), 2.15 – 2.06 (m, 2H), 1.98 – 1.87 (m, 3H), 1.48 – 1.41 (m, 1H), 1.41 – 1.34 (m, 1H), 1.16 (s, 3H), 1.00 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d) δ 172.3, 150.2, 148.8, 134.6, 123.9, 119.0, 65.6, 65.1, 58.3, 53.2, 49.0, 48.0, 44.8, 38.5, 36.9, 35.4, 33.0, 26.5, 21.1, 20.0; HRMS (MALDI) *m/z* calcd for $C_{21}H_{27}N_4O_3S$ $[M+H]^+$ 415.1798; found, 415.1797.



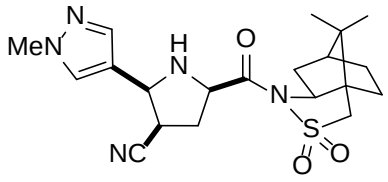
(2S,3R,5R)-5-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-2-(pyridin-2-yl)pyrrolidine-3-carbonitrile (4c). Yellow solid, isolated yield: 19% (desired stereoisomer with small amount of the staring glycyl-sultam). The compound streaks badly on TLC and during column chromatography and complete isolation of the desired product is not possible. Hence, the Rf value and the diastereomeric ratio are not reported. Flash chromatography was performed using EtOAc: Hexane: – 75:25 to 90:10;

^{1}H NMR (600 MHz, Chloroform-d) δ 8.66 – 8.61 (m, 1H), 7.74 (td, J = 7.7, 1.8 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.26 – 7.24 (m, 1H, signal peak is buried under the solvent peak), 4.56 (d, J = 7.0 Hz, 1H), 4.52 (t, J = 7.6 Hz, 1H), 3.98 (dd, J = 7.6, 5.0 Hz, 1H), 3.54 (d, J = 13.7 Hz, 1H), 3.51 – 3.46 (m, 2H), 2.81 (dt, J = 13.4, 8.2 Hz, 1H), 2.36 (ddd, J = 13.3, 6.7, 5.2 Hz, 1H), 2.20 – 2.11 (m, 2H), 1.92 (td, J = 14.7, 13.6, 11.1 Hz, 3H), 1.50 – 1.44 (m, 1H), 1.41 – 1.35 (m, 1H), 1.17 (s, 3H), 0.99 (s, 4H). ^{13}C NMR (151 MHz, Chloroform-d) δ 171.2, 157.2, 149.6, 137.0, 123.4, 122.0, 119.3, 66.1, 65.6, 60.5, 53.2, 49.1, 48.1, 44.7, 38.3, 36.9, 35.8, 32.9, 26.6, 20.9, 20.0; HRMS (MALDI) *m/z* calcd for $C_{21}H_{27}N_4O_3S$ $[M+H]^+$ 415.1798; found, 415.1809.

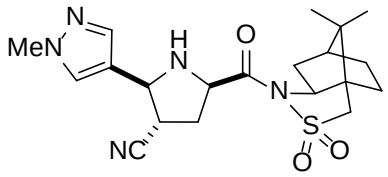


(2S,3S,5R)-5-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-2-(pyridin-2-yl)pyrrolidine-3-carbonitrile (5c). Yellow solid, isolated yield: 34% (desired stereoisomer with minor amounts of additional products) The compound streaks badly on TLC and during column chromatography and complete isolation of the desired product is not possible. Hence, the Rf value and the diastereomeric ratio are not reported. Flash chromatography was performed using acetone: hexane – 25:75 to 50:50; mp 168-171 °C; ^{1}H NMR (600 MHz, Chloroform-d) δ 8.61 (d, J = 4.5 Hz, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.28 – 7.24 (m, 1H, signal peak is buried under the solvent peak), 4.65 (dd, J = 9.7, 5.4 Hz, 1H), 4.35 (d, J = 9.0 Hz, 1H), 3.93 (t, J = 6.4 Hz, 1H), 3.53 (d, J = 13.8 Hz, 1H), 3.48 (d, J = 13.9 Hz, 1H), 3.03 (q, J = 9.2 Hz, 1H), 2.75 – 2.68 (m, 1H), 2.37 (ddd, J = 14.1, 9.2, 5.4 Hz, 1H), 2.10 (d, J = 6.2 Hz, 2H), 1.98 – 1.86 (m, 3H), 1.44 (t, J = 10.6 Hz, 1H), 1.36

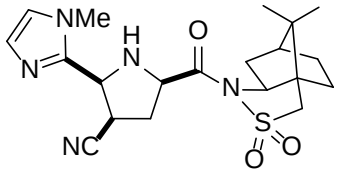
(ddd, J = 12.1, 9.6, 3.0 Hz, 1H), 1.14 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d) δ 171.7, 156.2, 150.0, 137.0, 123.7, 123.2, 119.8, 68.8, 65.3, 60.0, 53.1, 49.0, 48.0, 44.7, 38.3, 37.0, 35.5, 32.8, 26.5, 20.9, 20.0; HRMS (MALDI) *m/z* calcd for $C_{21}H_{27}N_4O_3S$ $[M+H]^+$ 415.1798; found, 415.1802.



(2S,3R,5R)-5-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)pyrrolidine-3-carbonitrile (4d). White solid, total yield: 81% (endo:exo = 93:7). Rf 0.23 (9:1 EtOAc/hexanes); mp 65-68 °C; ^{1}H NMR (600 MHz, Chloroform-d) δ 7.61 (s, 1H), 7.54 (d, J = 0.9 Hz, 1H), 4.43 (dd, J = 9.1, 5.6 Hz, 1H), 4.35 (d, J = 6.0 Hz, 1H), 3.94 (dd, J = 7.8, 4.9 Hz, 1H), 3.89 (s, 3H), 3.52 (d, J = 13.8 Hz, 1H), 3.47 (d, J = 13.8 Hz, 1H), 3.22 – 3.18 (m, 1H), 2.72 (ddd, J = 13.7, 9.1, 7.6 Hz, 1H), 2.38 (ddd, J = 13.8, 5.6, 4.0 Hz, 1H), 2.19 – 2.13 (m, 1H), 2.11 (dd, J = 14.0, 7.8 Hz, 1H), 1.96 – 1.86 (m, 3H), 1.47 – 1.41 (m, 1H), 1.41 – 1.34 (m, 1H), 1.16 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d) δ 171.8, 138.3, 128.8, 119.7, 118.9, 65.6, 59.6, 57.7, 53.1, 49.1, 48.0, 44.6, 39.3, 38.2, 36.5, 36.4, 32.8, 26.6, 20.9, 20.0; HRMS (MALDI) *m/z* calcd for $C_{20}H_{28}N_5O_3S$ $[M+H]^+$ 418.1907; found, 418.1908.

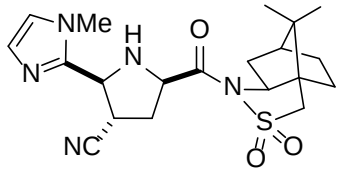


(2S,3S,5R)-5-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)pyrrolidine-3-carbonitrile (5d). White solid, total yield: 66% (endo:exo = 20:80). Rf 0.31 (9:1 EtOAc/hexanes); mp 192-195 °C; ^{1}H NMR (600 MHz, Chloroform-d) δ 7.57 (s, 1H), 7.47 (s, 1H), 4.57 (dd, J = 9.6, 4.1 Hz, 1H), 4.30 (d, J = 9.6 Hz, 1H), 3.90 (t, J = 6.4 Hz, 1H), 3.88 (s, 3H), 3.53 (d, J = 13.8 Hz, 1H), 3.47 (d, J = 13.8 Hz, 1H), 2.74 – 2.68 (m, 1H), 2.61 (dd, J = 13.5, 10.0 Hz, 1H), 2.40 (ddd, J = 13.1, 8.4, 4.2 Hz, 1H), 2.08 (d, J = 5.7 Hz, 2H), 1.97 – 1.87 (m, 3H), 1.46 – 1.40 (m, 1H), 1.36 (t, J = 10.2 Hz, 1H), 1.14 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d) δ 172.4, 137.3, 128.5, 119.7, 119.5, 65.4, 59.8, 59.1, 53.1, 49.0, 48.0, 44.7, 39.2, 38.3, 36.6, 36.1, 32.9, 26.5, 21.0, 20.0; HRMS (MALDI) *m/z* calcd for $C_{20}H_{28}N_5O_3S$ $[M+H]^+$ 418.1907; found, 418.1918.



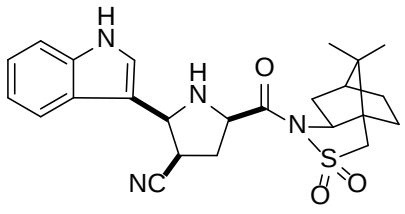
(2S,3R,5R)-5-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-2-(1-methyl-1H-imidazol-2-yl)pyrrolidine-3-carbonitrile (4e). Yellow solid, isolated yield: 32% (desired stereoisomer with small amount of the staring glycyl-sultam). The compound streaks badly on TLC and during column chromatography and complete isolation of the desired product is not possible. Hence, the Rf value

and the diastereomeric ratio are not reported. Flash chromatography was performed using EtOAc: hexane: MeOH – 50:50:1 to 90:10:1; 1H NMR (600 MHz, Chloroform-d) δ 7.05 (d, J = 1.3 Hz, 1H), 6.88 (d, J = 1.3 Hz, 1H), 4.55 (d, J = 7.2 Hz, 1H), 4.38 (t, J = 7.7 Hz, 1H), 3.94 (dd, J = 7.7, 5.0 Hz, 1H), 3.74 (s, 3H), 3.51 (d, J = 13.7 Hz, 1H), 3.47 (d, J = 13.8 Hz, 1H), 3.40 (q, J = 7.6 Hz, 1H), 2.79 (ddd, J = 12.8, 8.1, 6.9 Hz, 1H), 2.33 (dt, J = 12.6, 7.8 Hz, 1H), 2.16 – 2.07 (m, 2H), 1.92 – 1.87 (m, 3H), 1.44 (t, J = 9.8 Hz, 1H), 1.38 – 1.35 (m, 1H), 1.14 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d) δ 170.3, 144.2, 128.2, 122.4, 118.8, 65.5, 60.9, 57.5, 53.2, 49.0, 48.0, 44.6, 38.2, 36.7, 34.7, 33.3, 32.8, 26.6, 20.9, 20.0; HRMS (MALDI) *m/z* calcd for $C_{20}H_{28}N_5O_3S$ $[M+H]^+$ 418.1907; found, 418.1926.

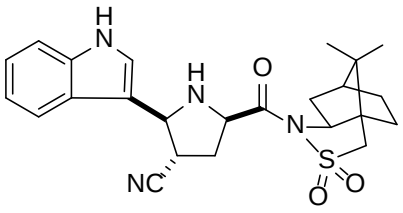


(2S,3S,5R)-5-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-2-(1-methyl-1H-imidazol-2-yl)pyrrolidine-3-carbonitrile (5e). White solid, isolated yield: 32%. The compound streaks badly on TLC and during column chromatography and complete isolation of the desired product is not possible. Hence, the Rf value and the diastereomeric ratio are not reported. Flash chromatography was performed using EtOAc: hexane: MeOH – 50:50:1 to 90:10:1; mp 185-187 °C; ^{1}H NMR (600 MHz, Chloroform-d) δ 6.99 (d, J = 1.4 Hz, 1H), 6.87 (d, J = 1.6 Hz, 1H), 4.56 (dd, J = 9.6, 6.0 Hz, 1H), 4.34 (d, J = 8.9 Hz, 1H), 3.91 – 3.86 (m, 1H), 3.73 (s, 2H), 3.52 (d, J = 13.8 Hz, 1H), 3.49 – 3.44 (m, 2H), 2.73 (dt, J = 13.3, 9.4 Hz, 1H), 2.39 – 2.30 (m, 1H), 2.07 – 2.02 (m, 2H), 1.94 – 1.86 (m, 3H), 1.42 (t, J = 10.6 Hz, 1H), 1.37 – 1.31 (m, 1H), 1.13 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (151

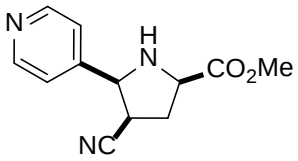
MHz, Chloroform-d) δ 170.9, 143.8, 128.0, 122.4, 119.9, 65.2, 60.5, 60.2, 53.0, 49.0, 48.0, 44.6, 38.1, 36.6, 33.7, 32.9, 32.8, 26.5, 20.9, 20.0; HRMS (MALDI) *m/z* calcd for $C_{20}H_{28}N_5O_3S$ $[M+H]^+$ 418.1907; found, 418.1921.



(2S,3R,5R)-5-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-2-(1H-indol-3-yl)pyrrolidine-3-carbonitrile (4f). Pale yellow solid, total yield: 53% (endo:exo = 80:20). Rf 0.56 (75:25 EtOAc/hexanes); mp 93-96 °C; ^{1}H NMR (600 MHz, Chloroform-d) δ 7.61 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 2.5 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 4.72 (d, J = 5.8 Hz, 1H), 4.54 (dd, J = 9.4, 5.3 Hz, 1H), 3.96 (dd, J = 7.9, 4.9 Hz, 1H), 3.51 (q, J = 13.8 Hz, 2H), 3.42 (ddd, J = 8.5, 5.9, 3.2 Hz, 1H), 2.83 (dt, J = 13.9, 8.6 Hz, 1H), 2.51 – 2.45 (m, 1H), 2.19 (dt, J = 12.5, 3.9 Hz, 1H), 2.11 (dd, J = 14.2, 7.9 Hz, 1H), 1.96 – 1.86 (m, 3H), 1.44 (t, J = 10.7 Hz, 1H), 1.39 – 1.33 (m, 1H), 1.18 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d) δ 172.0, 136.3, 126.4, 122.6, 122.5, 120.1, 119.9, 118.6, 112.9, 111.7, 65.6, 59.5, 58.9, 53.2, 49.1, 48.0, 44.6, 38.2, 37.0, 36.2, 32.8, 26.6, 20.9, 20.0; HRMS (ESI) *m/z* calcd for $C_{24}H_{29}N_4O_3S$ $[M+H]^+$ 453.1955; found, 453.1961.

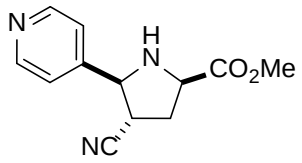


(2S,3S,5R)-5-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-2-(1H-indol-3-yl)pyrrolidine-3-carbonitrile (5f). Pale pink solid, total yield: 62% (endo:exo = 23:77). Rf 0.56 (75:25 EtOAc/hexanes); mp 204-206 °C; 1H NMR (600 MHz, Chloroform-d) δ 7.87 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 4.69 (dd, J = 9.6, 4.7 Hz, 1H), 4.65 (d, J = 9.5 Hz, 1H), 3.93 (t, J = 6.4 Hz, 1H), 3.54 (d, J = 13.8 Hz, 1H), 3.47 (d, J = 13.8 Hz, 1H), 3.14 (q, J = 9.4 Hz, 1H), 2.68 (dt, J = 13.6, 9.8 Hz, 1H), 2.49 (ddd, J = 13.5, 8.7, 4.7 Hz, 1H), 2.14 (d, J = 6.9 Hz, 2H), 1.98 – 1.86 (m, 3H), 1.42 (t, J = 9.0 Hz, 1H), 1.39 – 1.34 (m, 1H), 1.18 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d) δ 172.5, 136.9, 125.7, 122.9, 122.7, 120.2, 120.2, 119.8, 113.2, 111.6, 65.4, 62.0, 59.1, 53.1, 49.0, 48.0, 44.8, 38.4, 36.1, 35.1, 32.9, 26.5, 21.1, 20.0; HRMS (ESI) *m/z* calcd for $C_{24}H_{29}N_4O_3S$ $[M+H]^+$ 453.1955; found, 453.1958.

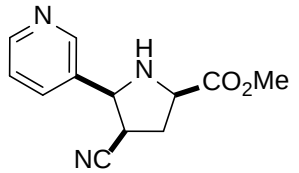


methyl (2R,4R,5S)-4-cyano-5-(pyridin-4-yl)pyrrolidine-2-carboxylate (6a). Yellow oil, yield: 50%. Rf 0.20 (95:5 EtOAc:MeOH); ^{1}H NMR (400 MHz, Acetone-d6) δ 8.60 – 8.55 (m, 2H), 7.54 (d, J = 4.9 Hz, 2H), 4.63 (d, J = 6.7 Hz, 1H), 4.09 (dd, J = 8.9, 6.6 Hz, 1H), 3.75 (s, 3H), 3.70 (ddd, J = 8.1, 6.7, 4.9 Hz, 1H), 2.70 (ddd, J = 13.3, 8.9, 8.1 Hz, 1H), 2.40 (ddd, J = 13.3, 6.6, 4.9 Hz,

1H). ^{13}C NMR (101 MHz, Acetone-d6) δ 173.7, 150.4, 149.8, 123.7, 123.3, 120.5, 120.1, 63.4, 58.9, 52.3, 35.8, 34.0; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_3O_2$ $[M+H]^+$ 232.1081; found, 232.1084.

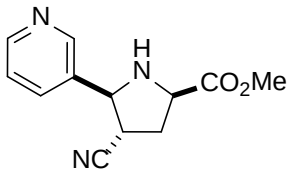


methyl (2R,4S,5S)-4-cyano-5-(pyridin-4-yl)pyrrolidine-2-carboxylate (8a). yellow oil, yield: 60%. Rf 0.50 (90:10 EtOAc:MeOH); ^{1}H NMR (600 MHz, Acetone-d6) δ 8.70 – 8.63 (m, 2H), 7.68 (d, J = 4.6 Hz, 2H), 4.58 (d, J = 8.8 Hz, 1H), 4.21 (dd, J = 8.9, 4.8 Hz, 1H), 3.73 (s, 3H), 3.11 (q, J = 8.7 Hz, 1H), 2.57 (ddd, J = 12.8, 8.0, 4.8 Hz, 1H), 2.50 (dt, J = 13.0, 9.1 Hz, 1H). ^{13}C NMR (151 MHz, Acetone-d6) δ 174.4, 152.7, 149.8, 123.3, 122.8, 120.7, 120.4, 66.1, 59.2, 52.3, 37.0, 34.7; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_3O_2$ $[M+H]^+$ 232.1081; found, 232.1082.

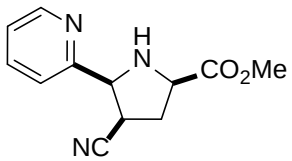


methyl (2R,4R,5S)-4-cyano-5-(pyridin-3-yl)pyrrolidine-2-carboxylate (6b). Colorless semi solid, yield: 94%. Rf 0.34 (90:10 EtOAc:MeOH); ^{1}H NMR (400 MHz, Methanol-d4) δ 8.79 (s, 1H), 8.56 (d, J = 4.8 Hz, 1H), 8.20 (dt, J = 8.0, 1.8 Hz, 1H), 7.59 (dd, J = 8.0, 5.0 Hz, 1H), 4.65 (d, J = 6.7 Hz, 1H), 4.08 (dd, J = 9.0, 6.4 Hz, 1H), 3.81 (s, 3H), 3.64 (ddd, J = 8.1, 6.7, 4.8 Hz, 1H), 2.69 (ddd, J = 13.4, 8.f9, 8.1 Hz, 1H), 2.45 (ddd, J = 13.4, 6.4, 4.8 Hz, 1H). 13C NMR (101 MHz,

DMSO-d6) δ 173.13, 148.04, 147.82, 136.31, 136.10, 123.78, 120.26, 60.76, 57.65, 52.07, 34.79, 32.72; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_3O_2$ $[M+H]^+$ 232.1081; found, 232.1078.

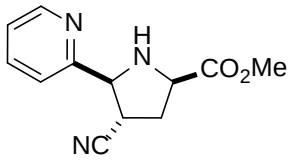


methyl (2R,4S,5S)-4-cyano-5-(pyridin-3-yl)pyrrolidine-2-carboxylate (8b). Color less semi solid, yield: 55%. Rf 0.34 (90:10 EtOAc:MeOH); ^{1}H NMR (600 MHz, Acetone-d6) δ 8.73 (d, J = 2.4 Hz, 1H), 8.54 (dd, J = 4.8, 1.7 Hz, 1H), 7.96 (dt, J = 7.8, 0.7 Hz, 1H), 7.40 – 7.36 (m, 1H), 4.50 (d, J = 9.2 Hz, 1H), 4.18 (dd, J = 9.1, 4.5 Hz, 1H), 3.73 (s, 3H), 3.14 – 3.08 (m, 1H), 2.63 – 2.58 (m, 1H), 2.51 (dt, J = 12.9, 9.3 Hz, 1H). ^{13}C NMR (151 MHz, Acetone-d6) δ 174.5, 150.5, 149.8, 137.1, 135.3, 124.5, 120.6, 65.5, 59.2, 52.5, 37.3, 34.8; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_3O_2$ $[M+H]^+$ 232.1081; found, 232.1081.

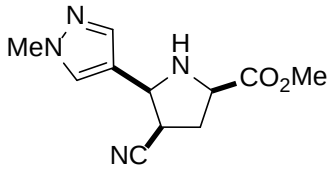


methyl (2R,4R,5S)-4-cyano-5-(pyridin-2-yl)pyrrolidine-2-carboxylate (6c). Yellow oil, isolated yield 20%. The compound streaks badly on TLC and during column chromatography. Hence, the Rf value is not reported. Flash chromatography was performed using EtOAc: MeOH – 90:10 to 80:20; ^{1}H NMR (400 MHz, Acetone-d6) δ 8.59 – 8.55 (m, 1H), 7.80 (dd, J = 7.7, 1.8 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.31 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 4.60 (d, J = 7.0 Hz, 1H), 4.02 (dd, J = 8.6, 6.8 Hz, 1H), 3.76 (s, 3H), 3.65 (ddd, J = 8.1, 7.0, 5.4 Hz, 1H), 2.72 (dt, J = 13.1, 8.3

Hz, 1H), 2.35 (ddd, J = 13.1, 6.8, 5.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d6) δ 173.3, 158.5, 148.8, 136.9, 123.1, 122.0, 120.2, 64.7, 58.3, 52.2, 34.4, 34.0; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_3O_2$ $[M+H]^+$ 232.1081; found, 232.1086.

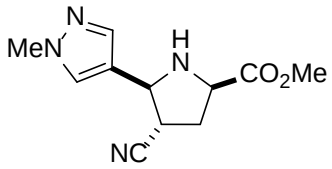


methyl(2R,4S,5S)-4-cyano-5-(pyridin-2-yl)pyrrolidine-2-carboxylate (8c). Pale yellow oil, isolated yield 20%. The compound streaks badly on TLC and during column chromatography. Hence, the Rf value is not reported. Flash chromatography was performed using EtOAc: MeOH – 90:10 to 80:20; ^{1}H NMR (400 MHz, Acetone-d6) δ 8.61 – 8.57 (m, 1H), 7.83 (td, J = 7.7, 1.8 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.35 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 4.47 – 4.40 (m, 1H), 4.13 (q, J = 7.3 Hz, 1H), 3.73 (s, 3H), 3.14 (q, J = 8.6 Hz, 1H), 2.55 – 2.49 (mz, 2H). ^{13}C NMR (101 MHz, DMSO-d6) δ 173.5, 158.5, 149.2, 137.2, 123.4, 122.2, 121.0, 67.1, 58.7, 52.2, 34.5, 34.1; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_3O_2$ $[M+H]^+$ 232.1081; found, 232.1079.

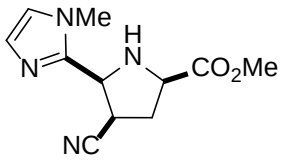


methyl (2R,4R,5S)-4-cyano-5-(1-methyl-1H-pyrazol-4-yl)pyrrolidine-2-carboxylate (6d). White solid, yield: 57%. Rf 0.20 (95:5 EtOAc:MeOH); mp 46-48 °C; ^{1}H NMR (400 MHz, Acetone-d6) δ 7.64 (s, 1H), 7.46 (s, 1H), 4.39 (t, J = 6.6 Hz, 1H), 3.93 (dt, J = 9.0, 6.6 Hz, 1H),

3.86 (s, 3H), 3.74 (s, 3H), 3.42 (ddd, J = 7.9, 6.0, 4.5 Hz, 1H), 2.63 (ddd, J = 13.4, 9.2, 8.0 Hz, 1H), 2.34 (ddd, J = 13.4, 6.3, 4.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d6) δ 173.3, 137.4, 129.2, 120.9, 119.8, 57.5, 56.3, 52.1, 38.6, 35.1, 33.2; HRMS (ESI) *m/z* calcd for $C_{11}H_{15}N_4O_2$ $[M+H]^+$ 235.1190; found, 235.1190.

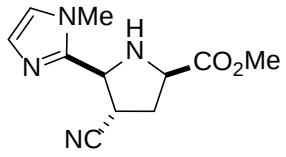


methyl (2R,4S,5S)-4-cyano-5-(1-methyl-1H-pyrazol-4-yl)pyrrolidine-2-carboxylate (8d). Pale yellow solid, yield: 77%. Rf 0.56 (90:10 EtOAc:MeOH); mp 69-72 °C; ^{1}H NMR (600 MHz, Acetone-d6) δ 7.65 (s, 1H), 7.48 (s, J = 0.9 Hz, 1H), 4.28 (d, J = 9.3 Hz, 1H), 4.02 (dd, J = 9.3, 5.0 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 2.94 (tdd, J = 9.3, 8.7, 0.5 Hz, 1H), 2.53 (ddd, J = 13.5, 8.7, 5.0 Hz, 1H), 2.44 (dt, J = 13.1, 9.5 Hz, 1H). ^{13}C NMR (151 MHz, Acetone-d6) δ 174.6, 137.8, 129.5, 121.6, 121.0, 60.3, 59.5, 52.6, 39.2, 37.0, 35.1; HRMS (ESI) *m/z* calcd for $C_{11}H_{15}N_4O_2$ $[M+H]^+$ 235.1190; found, 235.1194.

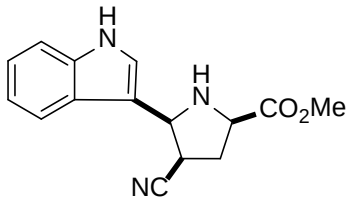


methyl (2R,4S,5S)-4-cyano-5-(1-methyl-1H-imidazol-2-yl)pyrrolidine-2-carboxylaten (6e). Yellow oil, isolated yield: 77% (with a small amount of uncharacterized impurities). The compound streaks badly on TLC and during column chromatography. Hence, the Rf value is not reported. Flash chromatography was performed using EtOAc: MeOH –90:10 to 75:25; ^{1}H NMR

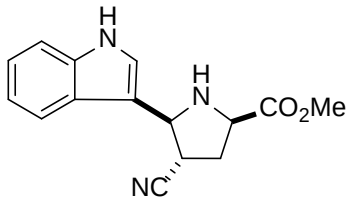
(400 MHz, Acetone-d6) δ 7.76 (d, J = 1.5 Hz, 2H), 5.53 (d, J = 7.9 Hz, 1H), 4.32 (dd, J = 8.1, 6.7 Hz, 1H), 4.17 – 4.09 (m, 4H), 3.78 (s, 3H), 2.87 (dt, J = 13.2, 8.1 Hz, 1H), 2.43 (dt, J = 13.5, 6.9 Hz, 1H). ^{13}C NMR (101 MHz, Acetone-d6) δ 175.8, 148.2, 125.6, 119.6, 118.8, 59.4, 56.4, 52.9, 35.6, 34.7, 33.9; HRMS (ESI) *m/z* calcd for $C_{11}H_{15}N_4O_2$ $[M+H]^+$ 235.1190; found, 235.1191.



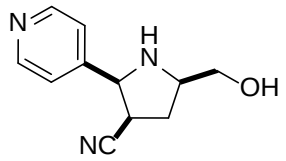
(2S,3S,5R)-5-((6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-2-(1-methyl-1H-imidazol-2-yl)pyrrolidine-3-carbonitrile (6e). Colorless oil, isolated yield: 95%. The compound streaks badly on TLC and during column chromatography. Hence, the Rf value is not reported. Flash chromatography was performed using (EtOAc: MeOH –90:10); ^{1}H NMR (400 MHz, Methanol-d4) δ 7.13 (d, J = 1.3 Hz, 1H), 6.96 (d, J = 1.3 Hz, 1H), 4.62 (d, J = 8.5 Hz, 1H), 4.14 – 4.09 (m, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.56 – 3.48 (m, 1H), 2.66 – 2.52 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d6) δ 173.1, 144.7, 126.4, 122.9, 121.0, 58.8, 58.4, 52.1, 33.7, 32.5, 32.4; HRMS (ESI) *m/z* calcd for $C_{11}H_{15}N_4O_2$ $[M+H]^+$ 235.1190; found, 235.1188.



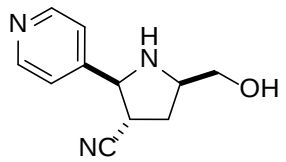
methyl (2R,4R,5S)-4-cyano-5-(1H-indol-3-yl)pyrrolidine-2-carboxylate (6f). Yellow oil, yield: 60%. Rf 0.29 (75:25 EtOAc:Hexane); ^{1}H NMR (600 MHz, Acetone-d6) δ 7.69 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 1.0 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.12 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.03 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 4.75 (dd, J = 6.0, 1.0 Hz, 1H), 4.01 (dd, J = 9.4, 6.0 Hz, 1H), 3.77 (s, 3H), 3.67 (ddd, J = 8.1, 6.0, 3.6 Hz, 1H), 2.75 (ddd, J = 13.4, 9.4, 8.2 Hz, 1H), 2.45 (ddd, J = 13.4, 6.0, 3.6 Hz, 1H). ^{13}C NMR (151 MHz, Acetone-d6) δ 174.3, 137.6, 127.6, 123.6, 122.5, 121.2, 119.9, 119.7, 114.2, 112.4, 59.3, 58.9, 52.6, 36.2, 35.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{16}N_3O_2$ $[M+H]^+$ 270.1237; found, 270.1240.



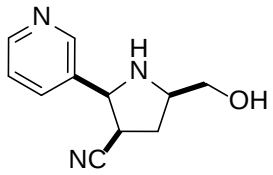
methyl (2R,4S,5S)-4-cyano-5-(1H-indol-3-yl)pyrrolidine-2-carboxylate (8f). Orange yellow oil, yield: 53%. Rf 0.65 (75:25 EtOAc:Hexane); ^{1}H NMR (600 MHz, Acetone-d6) δ 7.83 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 4.65 (d, J = 9.3 Hz, 1H), 4.12 (dd, J = 9.5, 5.1 Hz, 1H), 3.75 (s, 3H), 3.26 (q, J = 9.2 Hz, 1H), 2.62 (td, J = 8.2, 4.3 Hz, 1H), 2.54 (dt, J = 13.0, 9.5 Hz, 1H). ^{13}C NMR (151 MHz, Acetone-d6) δ 174.9, 138.3, 127.0, 124.2, 122.8, 121.4, 120.4, 120.1, 114.5, 112.7, 62.4, 59.5, 52.6, 35.6, 35.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{16}N_3O_2$ $[M+H]^+$ 270.1237; found, 270.1240.



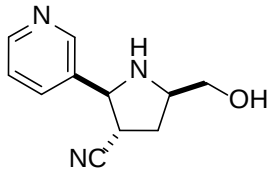
(2S,3R,5R)-5-(hydroxymethyl)-2-(pyridin-4-yl)pyrrolidine-3-carbonitrile (7a). Yellow solid, yield: 62%. Rf 0.09 (90:10 EtOAc:MeOH); mp 86-88 °C; ^{1}H NMR (600 MHz, Acetone-d6) δ 8.57 – 8.52 (m, 2H), 7.51 – 7.47 (m, 2H), 4.54 (d, J = 6.7 Hz, 1H), 3.65 (tt, J = 10.7, 5.2 Hz, 2H), 3.59 (ddd,z J = 8.6, 6.7, 4.3 Hz, 1H), 3.50 (ddt, J = 8.4, 6.6, 5.5 Hz, 1H), 2.46 (dt, J = 13.2, 8.5 Hz, 1H), 1.99 (ddd, J = 13.2, 6.5, 4.3 Hz, 1H). ^{13}C NMR (151 MHz, Acetone-d6) δ 150.6, 150.2, 123.3, 121.2, 66.4, 63.6, 59.6, 35.9, 33.7; HRMS (ESI) *m/z* calcd for $C_{11}H_{13}N_3ONa$ $[M+Na]^+$ 226.0951; found, 226.0952.



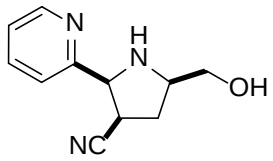
(2S,3S,5R)-5-(hydroxymethyl)-2-(pyridin-4-yl)pyrrolidine-3-carbonitrile (9a). Pale yellow solid, yield: 73%. Rf 0.19 (90:10 EtOAc:MeOH); mp 77-79 °C; ^{1}H NMR (600 MHz, Acetone-d6) δ 8.57 – 8.53 (m, 2H), 7.53 – 7.48 (m, 2H), 4.40 (d, J = 8.9 Hz, 1H), 3.63 – 3.52 (m, 3H), 2.94 (q, J = 8.8 Hz, 1H), 2.28 – 2.19 (m, 2H). ^{13}C NMR (151 MHz, Acetone-d6) δ 151.3, 150.9, 122.7, 121.5, 66.4, 66.2, 59.6, 36.9, 33.7; HRMS (ESI) *m/z* calcd for $C_{11}H_{14}N_3O$ $[M+H]^+$ 204.1131; found, 204.1132.



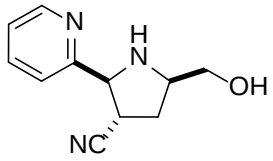
(2S,3R,5R)-5-(hydroxymethyl)-2-(pyridin-3-yl)pyrrolidine-3-carbonitrile (7b). Pale yellow solid, yield: 87%. Rf 0.16 (90:10 EtOAc:MeOH); mp 83-85 °C; 1H NMR (600 MHz, Acetone-d6) δ 8.69 (d, J = 2.1 Hz, 1H), 8.50 (dd, J = 4.7, 1.7 Hz, 1H), 7.93 (dddd, J = 7.9, 2.4, 1.7, 0.7 Hz, 1H), 7.34 (ddd, J = 7.9, 4.7, 0.9 Hz, 1H), 4.57 (d, J = 6.5 Hz, 1H), 3.67 (dd, J = 10.7, 5.3 Hz, 1H), 3.63 (dd, J = 10.6, 5.7 Hz, 1H), 3.55 (ddd, J = 8.6, 6.6, 4.2 Hz, 1H), 3.49 (ddt, J = 8.4, 6.5, 5.5 Hz, 1H), 2.47 (dt, J = 13.2, 8.5 Hz, 1H), 2.01 (ddd, J = 13.2, 6.6, 4.2 Hz, 1H).^{13}C NMR (151 MHz, Acetone-d6) δ 150.2, 150.0, 136.8, 135.7, 124.0, 121.5, 66.4, 62.5, 59.5, 36.2, 33.7; HRMS (ESI) *m/z* calcd for $C_{11}H_{14}N_3O$ $[M+H]^+$ 204.1131; found, 204.1132.



(2S,3S,5R)-5-(hydroxymethyl)-2-(pyridin-3-yl)pyrrolidine-3-carbonitrile (9b). Pale yellow solid, yield: 87%. Rf 0.15 (90:10 EtOAc:MeOH); mp 100-102 °C; ^{1}H NMR (600 MHz, Acetone-d6) δ 8.72 (d, J = 2.2 Hz, 1H), 8.52 (dd, J = 4.8, 1.7 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.36 (dd, J = 7.9, 4.8 Hz, 1H), 4.41 (d, J = 9.3 Hz, 1H), 3.63 – 3.52 (m, 3H), 2.99 (q, J = 9.1 Hz, 1H), 2.25 (dd, J = 9.0, 6.8 Hz, 2H). ^{13}C NMR (151 MHz, Acetone-d6) δ 150.4, 149.7, 137.5, 135.2, 124.4, 121.4, 66.1, 65.5, 59.4, 37.0, 33.6; HRMS (ESI) *m/z* calcd for $C_{11}H_{14}N_3O$ $[M+H]^+$ 204.1131; found, 204.1132.

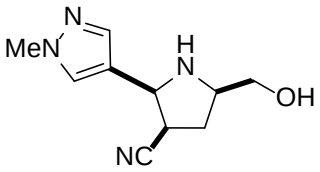


(2S,3R,5R)-5-(hydroxymethyl)-2-(pyridin-2-yl)pyrrolidine-3-carbonitrile (7c). Brown solid, isolated yield 46%. The compound streaks badly on TLC and during column chromatography. Hence, the Rf value is not reported. Flash chromatography was performed using EtOAc: MeOH – 90:10; mp 78-82 °C; 1H NMR (600 MHz, Acetone-d6) δ 8.55 – 8.52 (m, 1H), 7.78 (td, J = 7.7, 1.8 Hz, 1H), 7.61 (dq, J = 7.9, 0.9 Hz, 1H), 7.27 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 4.58 (d, J = 7.2 Hz, 1H), 3.70 (dd, J = 10.7, 4.9 Hz, 1H), 3.65 (dd, J = 10.8, 5.0 Hz, 1H), 3.56 (ddd, J = 8.5, 7.2, 5.6 Hz, 1H), 3.48 (tt, J = 7.6, 5.0 Hz, 1H), 2.42 (dt, J = 12.9, 8.1 Hz, 1H), 2.09 – 2.02 (m, 1H, signal peak is buried under the solvent peak). ^{13}C NMR (151 MHz, Acetone-d6) δ 161.0, 149.8, 137.4, 123.6, 122.7, 121.4, 66.3, 65.6, 60.5, 35.7, 33.9; HRMS (ESI) *m/z* calcd for C11H16N3O2 $[M+H+H_2O]^+$ 222.1237; found, 222.1239.

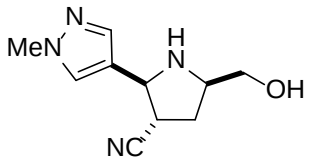


(2S,3S,5R)-5-(hydroxymethyl)-2-(pyridin-2-yl)pyrrolidine-3-carbonitrile (9c). Brown solid, isolated yield 77 %. The compound streaks badly on TLC and during column chromatography. Hence, the Rf value is not reported. Flash chromatography was performed using EtOAc: MeOH – 90:10; mp 67-69 °C; ^{1}H NMR (600 MHz, Acetone-d6) δ 8.59 – 8.53 (m, 1H), 7.80 (td, J = 7.7, 1.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.31 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 4.43 (d, J = 7.9 Hz, 1H), 3.66 – 3.53 (m, 3H), 3.20 (dt, J = 9.2, 7.8 Hz, 1H), 2.27 – 2.16 (m, 2H). ^{13}C NMR (151 MHz,

Acetone-d6) δ 160.7, 150.3, 137.8, 124.0, 123.2, 122.2, 69.2, 65.0, 61.1, 36.0, 34.5; HRMS (ESI) *m/z* calcd for $C_{11}H_{14}N_3O$ $[M+H]^+$ 204.1131; found, 204.1132.

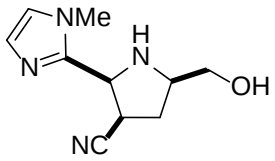


(2S,3R,5R)-5-(hydroxymethyl)-2-(1-methyl-1H-pyrazol-4-yl)pyrrolidine-3-carbonitrile (7d). Colorless oil, yield: 75%. Rf 0.67 (90:10 EtOAc:MeOH); ^{1}H NMR (600 MHz, Acetone-d6) δ 7.60 (s, 1H), 7.44 (s, 1H), 4.36 (d, J = 6.2 Hz, 1H), 3.84 (s, 3H), 3.61 (dd, J = 10.6, 5.1 Hz, 1H), 3.56 (dd, J = 10.7, 5.3 Hz, 1H), 3.35 (ddt, J = 8.5, 6.7, 5.2 Hz, 1H), 3.33 – 3.29 (m, 1H), 2.37 (dt, J = 13.2, 8.5 Hz, 1H), 1.95 (ddd, J = 13.2, 6.6, 4.2 Hz, 1H). ^{13}C NMR (151 MHz, Acetone-d6) δ 138.5, 129.6, 122.1, 121.6, 65.9, 59.4, 57.6, 39.1, 36.6, 33.9; HRMS (ESI) *m/z* calcd for $C_{20}H_{29}N_8O_2$ $[2M+H]^+$ 413.2408; found, 413.2411.

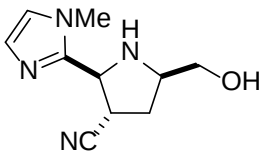


(2S,3S,5R)-5-(hydroxymethyl)-2-(1-methyl-1H-pyrazol-4-yl)pyrrolidine-3-carbonitrile (9d). Yellow oil, yield: 94%. Rf 0.27 (90:10 EtOAc:MeOH); 1H NMR (600 MHz, Acetone-d6) δ 7.61 (s, 1H), 7.45 (s, 1H), 4.23 (d, J = 9.3 Hz, 1H), 3.84 (s, 3H), 3.54 (dd, J = 10.7, 4.7 Hz, 1H), 3.50 (dd, J = 10.7, 4.6 Hz, 1H), 3.46 (ddt, J = 9.4, 6.3, 4.7 Hz, 1H), 2.83 (q, J = 9.1 Hz, 1H), 2.21 – 2.12

(m, 2H). ^{13}C NMR (151 MHz, Acetone-d6) δ 137.7, 129.2, 122.5, 122.0, 65.3, 60.3, 59.7, 39.1, 37.1, 33.8; HRMS (ESI) *m/z* calcd for $C_{10}H_{15}N_4O$ $[M+H]^+$ 207.1240; found, 207.1241.

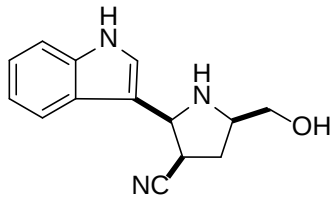


(2S,3R,5R)-5-(hydroxymethyl)-2-(1-methyl-1H-imidazol-2-yl)pyrrolidine-3-carbonitrile (7e). Yellow solid, isolated yield: 53%. The compound streaks badly on TLC and during column chromatography. Hence, the Rf value is not reported. Flash chromatography was performed using EtOAc: MeOH – 90:10; mp 64-67 °C; ^{1}H NMR (600 MHz, Acetone-d6) δ 7.03 (d, J = 1.3 Hz, 1H), 6.83 (d, J = 1.2 Hz, 1H), 4.50 (d, J = 7.5 Hz, 1H), 3.78 (s, 3H), 3.61 – 3.55 (m, 2H), 3.53 – 3.48 (m, 2H), 2.30 (ddd, J = 12.7, 9.6, 6.4 Hz, 1H), 2.17 (dt, J = 12.8, 7.3 Hz, 1H). ^{13}C NMR (151 MHz, Acetone-d6) δ 147.1, 127.6, 123.1, 122.2, 64.0, 61.4, 60.4, 34.3, 34.1, 33.0; HRMS (ESI) *m/z* calcd for $C_{10}H_{15}N_4O$ $[M+H]^+$ 207.1240; found, 207.1241.

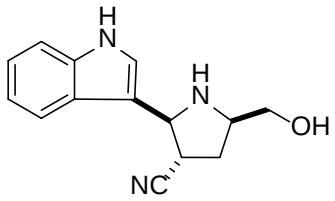


(2S,3S,5R)-5-(hydroxymethyl)-2-(1-methyl-1H-imidazol-2-yl)pyrrolidine-3-carbonitrile (9e). Yellow oil, isolated yield: 73%. The compound streaks badly on TLC and during column chromatography. Hence, the Rf value is not reported. Flash chromatography was performed using EtOAc: MeOH – 90:10; 1H NMR (600 MHz, Acetone-d6) δ 7.02 (d, J = 1.2 Hz, 1H), 6.85 (d, J =

1.2 Hz, 1H), 4.81 (d, J = 7.7 Hz, 1H), 3.76 (s, 3H), 3.73 (dd, J = 11.1, 3.5 Hz, 1H), 3.57 (dd, J = 11.1, 3.5 Hz, 1H), 3.53 (dt, J = 10.1, 7.9 Hz, 1H), 3.44 (ddd, J = 9.1, 7.1, 3.6 Hz, 1H), 2.32 – 2.23 (m, 2H). ^{13}C NMR (151 MHz, Acetone-d6) δ 148.5, 127.4, 122.6, 120.5, 64.0, 61.1, 56.8, 35.1, 33.2, 32.5; HRMS (ESI) *m/z* calcd for $C_{10}H_{15}N_4O$ $[M+H]^+$ 207.1240; found, 207.1241.

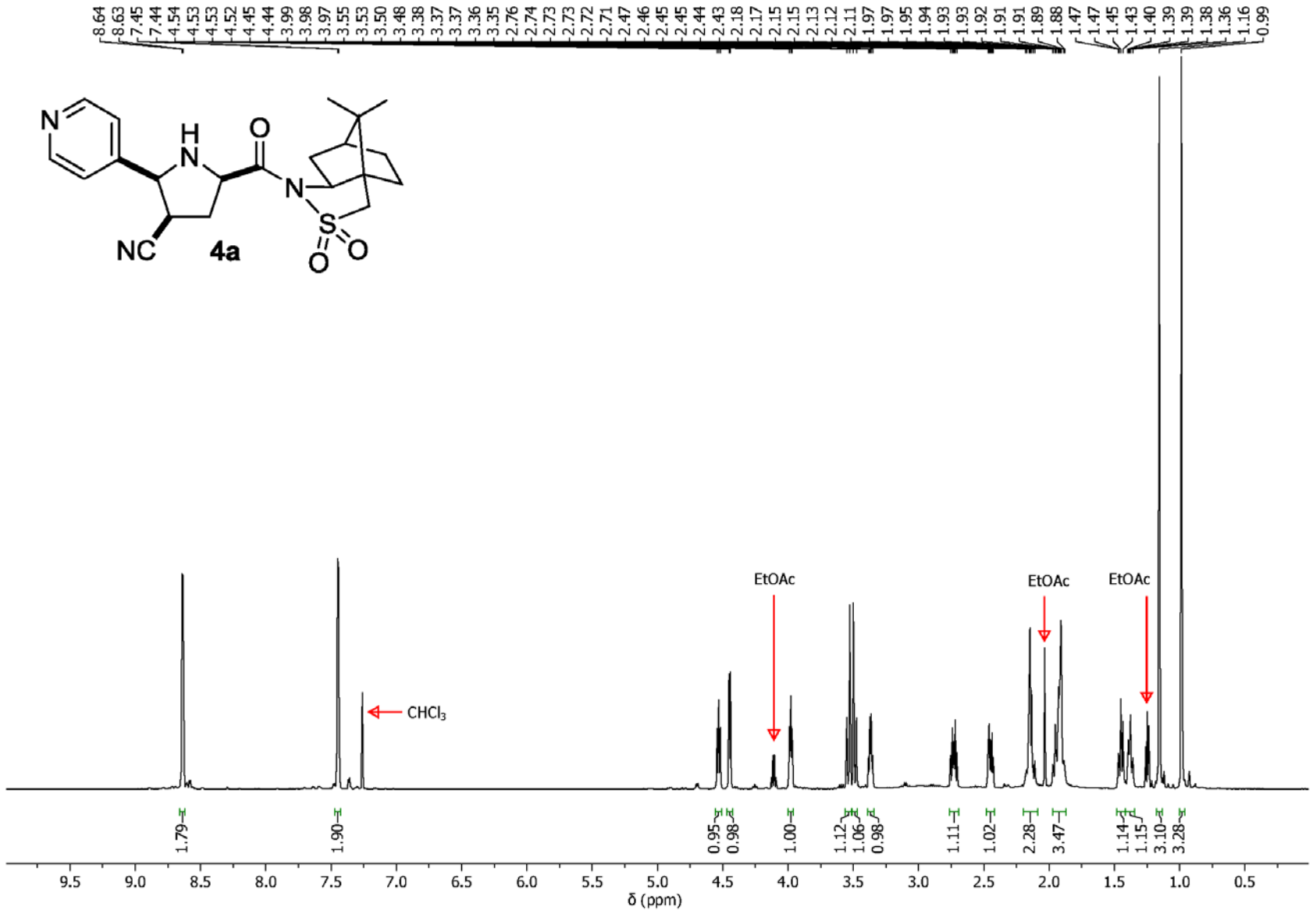


(2S,3R,5R)-5-(hydroxymethyl)-2-(1H-indol-3-yl)pyrrolidine-3-carbonitrile (7f). Yellow oil, yield: 100%. Rf 0.18 (90:10 EtOAc:MeOH); 1H NMR (600 MHz, Acetone-d6) δ 7.67 (d, J = 8.2 Hz, 1H), 7.49 (s, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.11 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.01 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 4.74 (dd, J = 6.2, 0.9 Hz, 1H), 3.68 (dd, J = 10.6, 5.1 Hz, 1H), 3.64 (dd, J = 10.6, 5.3 Hz, 1H), 3.58 (ddd, J = 8.8, 6.2, 3.6 Hz, 1H), 3.45 (ddt, J = 8.7, 6.4, 5.2 Hz, 1H), 2.49 (dt, J = 13.2, 8.7 Hz, 1H), 2.09 – 2.03 (m, 1H, signal peak is buried under the solvent peak). ^{13}C NMR (151 MHz, Acetone-d6) δ 137.6, 127.6, 123.7, 122.3, 122.2, 119.7, 119.6, 115.0, 112.3, 65.9, 59.1, 58.9, 36.1, 34.1; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}N_3O$ $[M+H]^+$ 242.1288; found, 242.1289.

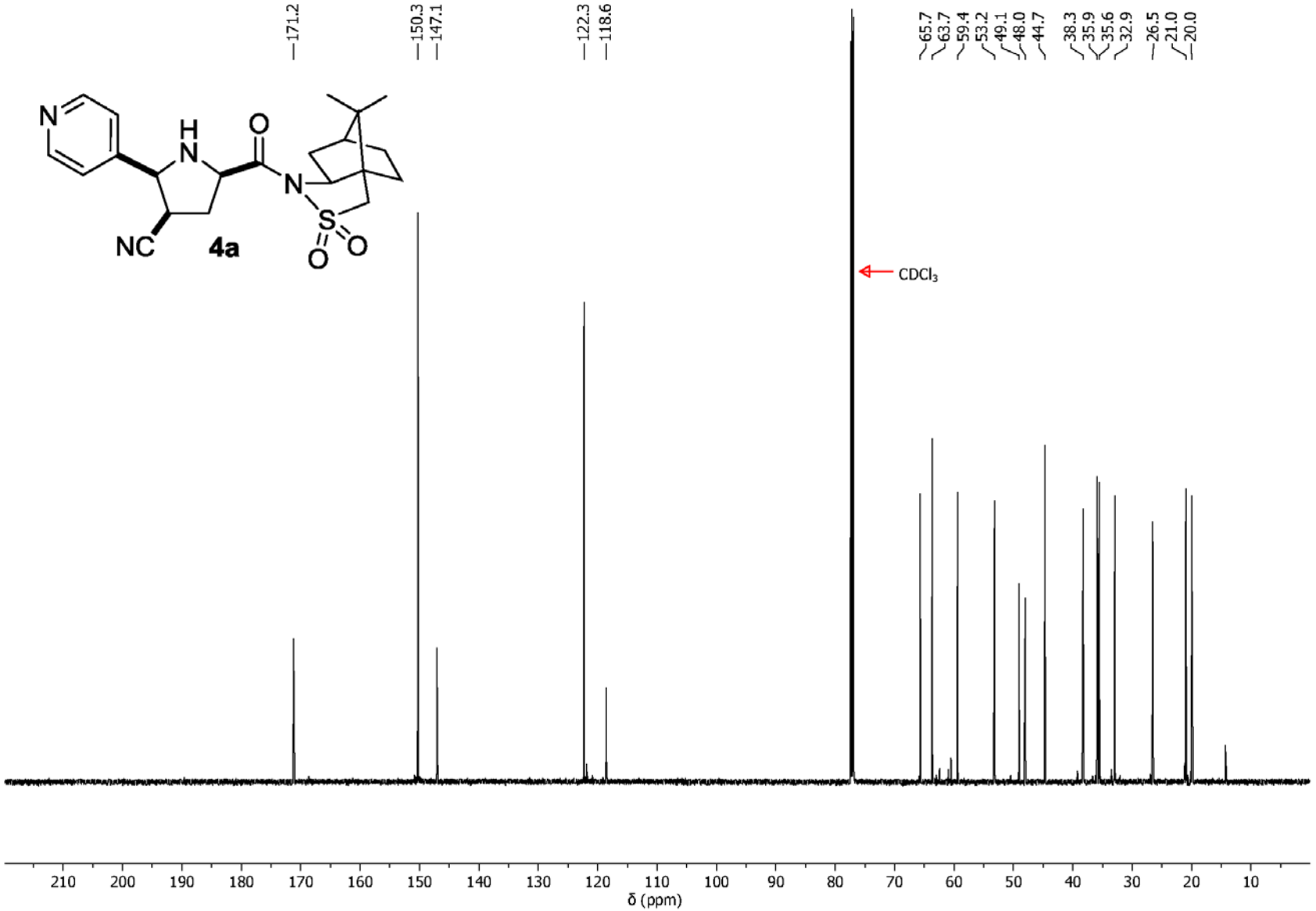


(2S,3S,5R)-5-(hydroxymethyl)-2-(1H-indol-3-yl)pyrrolidine-3-carbonitrile (9f). Yellow oil, yield: 100%. Rf 0.20 (90:10 EtOAc:MeOH); ^{1}H NMR (600 MHz, Acetone-d6) δ 7.81 (dd, J = 8.0, 1.1 Hz, 1H), 7.43 (s, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.12 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.03 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 4.61 (d, J = 9.1 Hz, 1H), 3.63 (qd, J = 10.7, 4.6 Hz, 2H), 3.55 (ddt, J = 9.1, 6.6, 4.6 Hz, 1H), 3.16 (td, J = 9.4, 8.1 Hz, 1H), 2.32 – 2.20 (m, 2H). ^{13}C NMR (151 MHz, Acetone-d6) δ 138.0, 127.0, 123.6, 122.5, 122.4, 120.5, 119.8, 115.4, 112.4, 65.1, 62.3, 59.9, 35.7, 34.0; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}N_3O$ $[M+H]^+$ 242.1288; found, 242.1290.

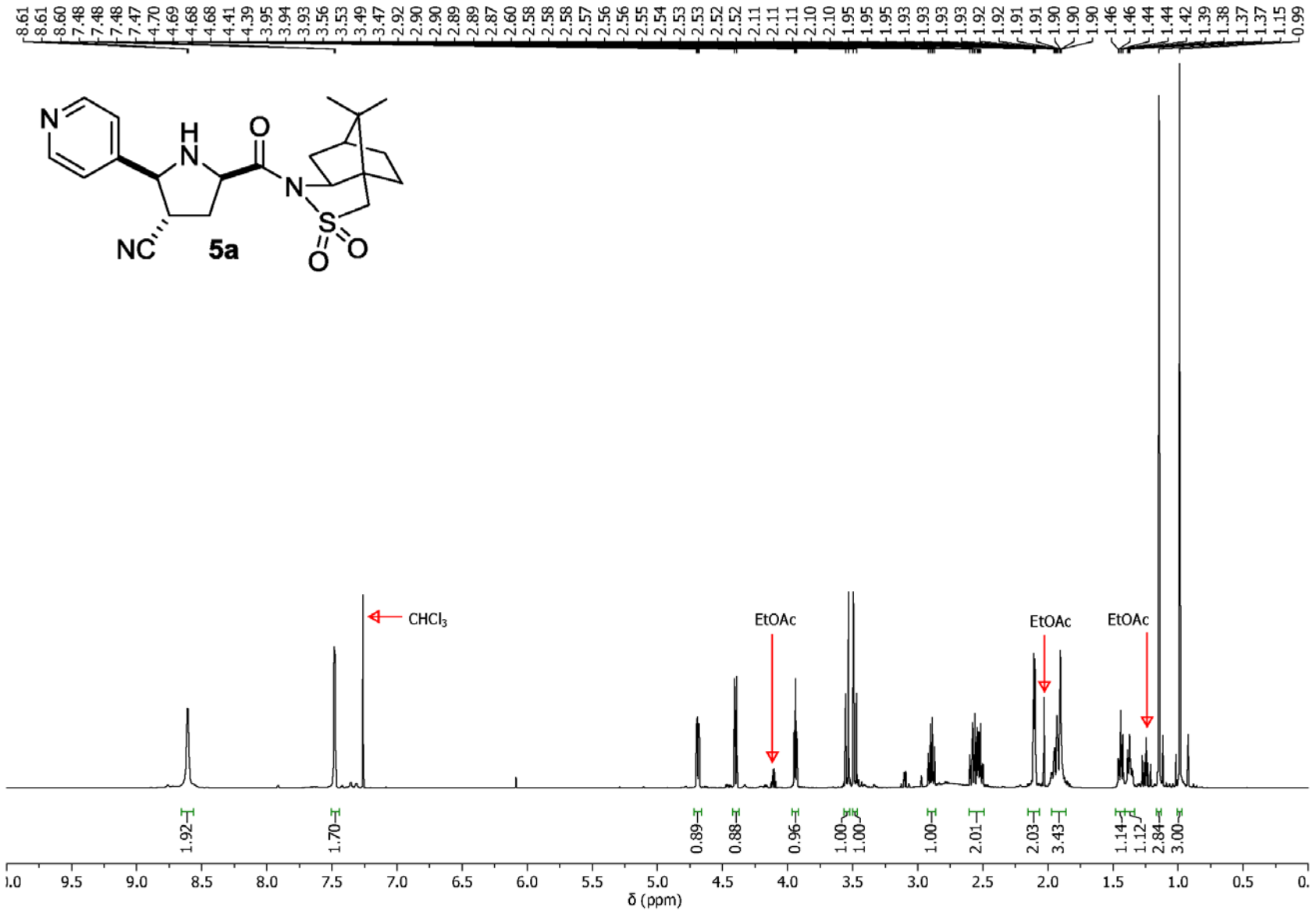
600 MHz ^{1}H NMR, $CDCl_3$



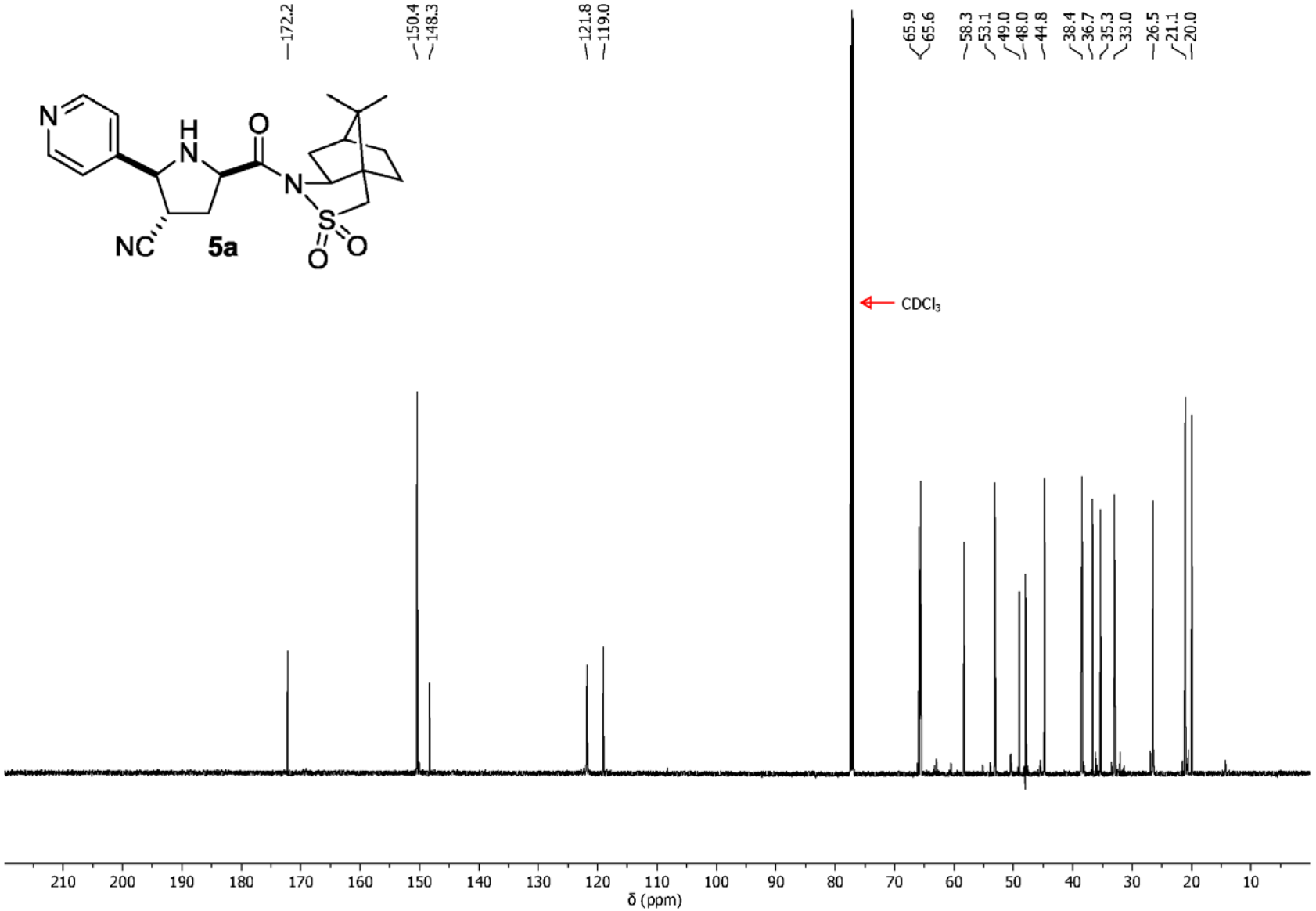
150.8 MHz ^{13}C NMR, $CDCl_3$



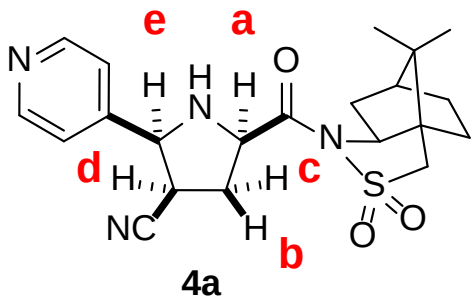
600 MHz ^{1}H NMR, $CDCl_3$



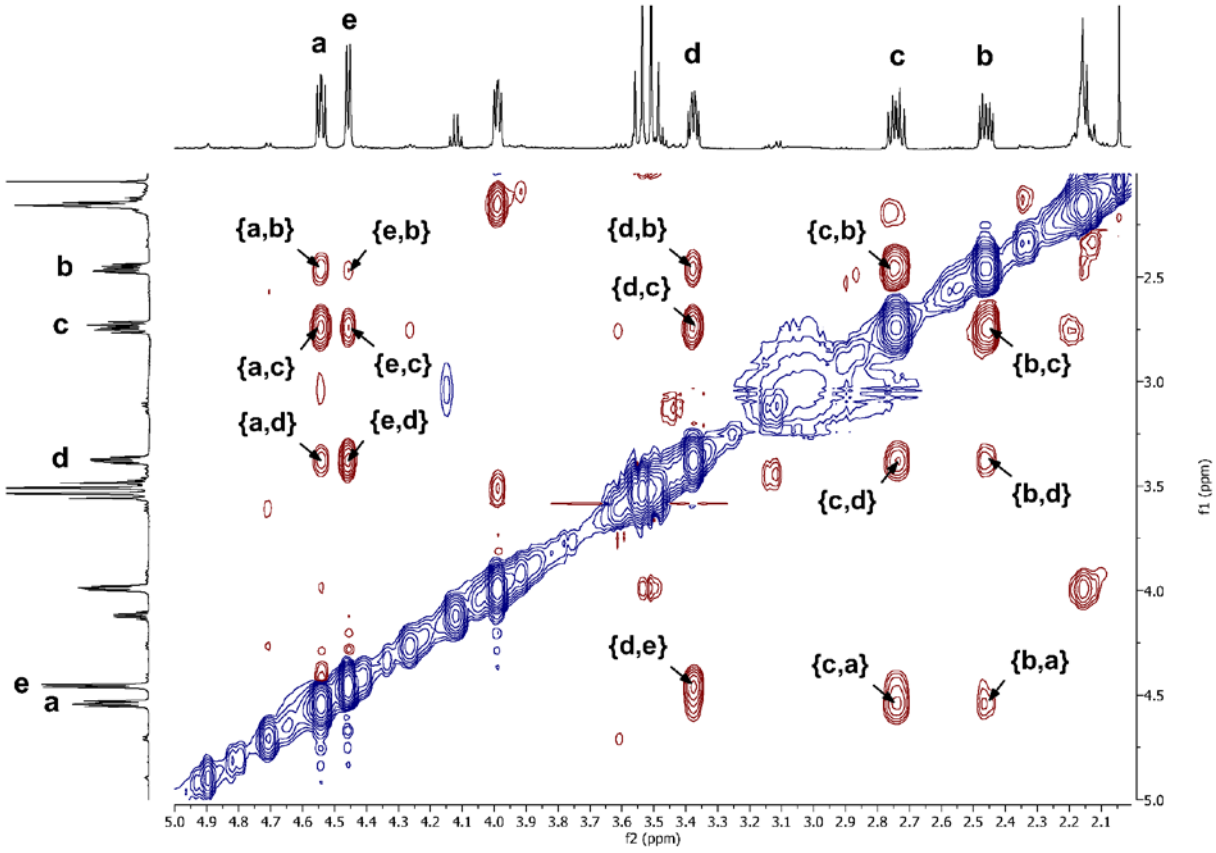
150.8 MHz ^{13}C NMR, $CDCl_3$



600 MHz 2D NOESY NMR, $CDCl_3$

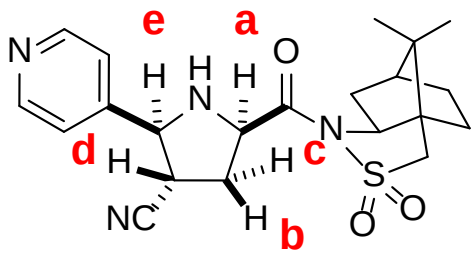


4a

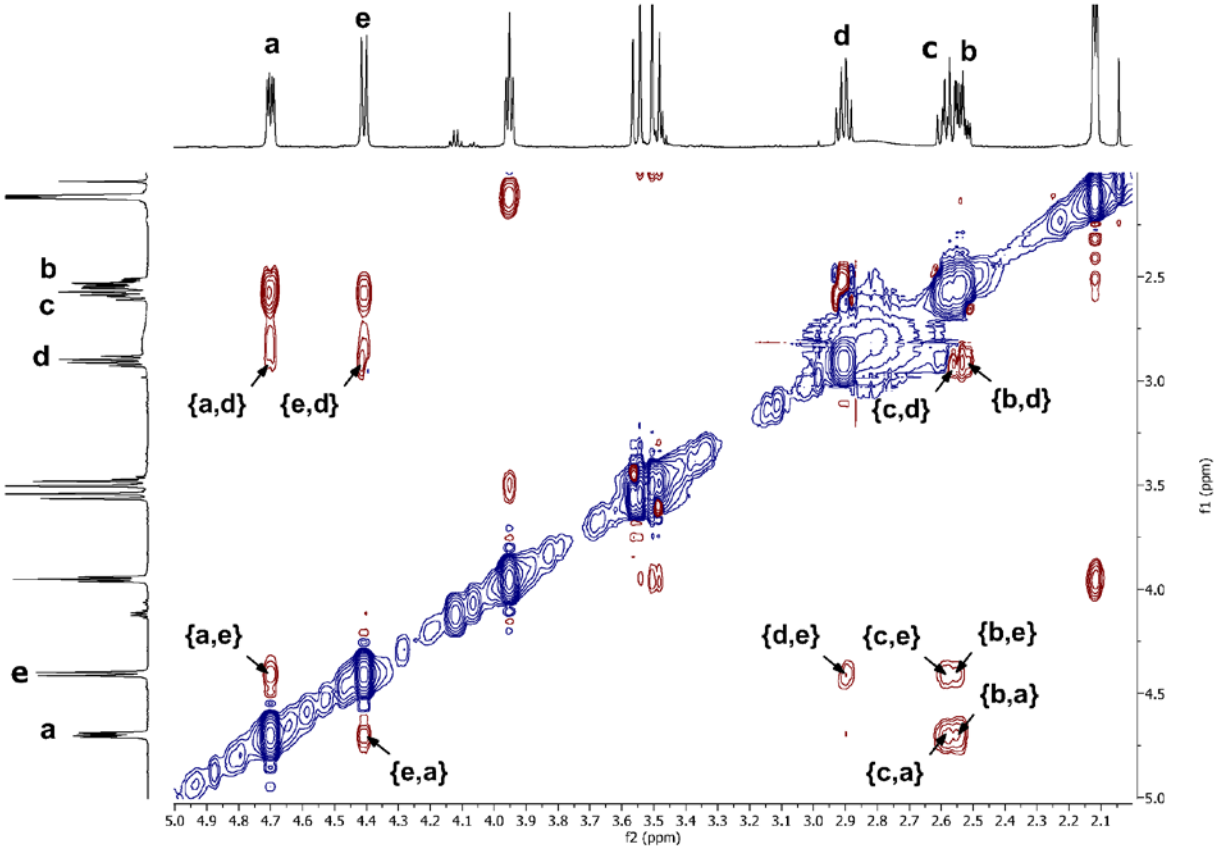


Relevant portion of the 600 MHz 2D NOESY ^{1}H NMR spectra obtained for compound **4a** in $CDCl_3$ showing interactions between **a-b, a-c, a-d, c-b, c-d, c-e, b-d, b-e** and **d-e** in the pyrrolidine ring. The data were collected at ambient T with a 700 ms mixing time, scans per t1 increment = 16, t1 increments = 128 and 1.5 s relaxation time.

600 MHz 2D NOESY NMR, $CDCl_3$

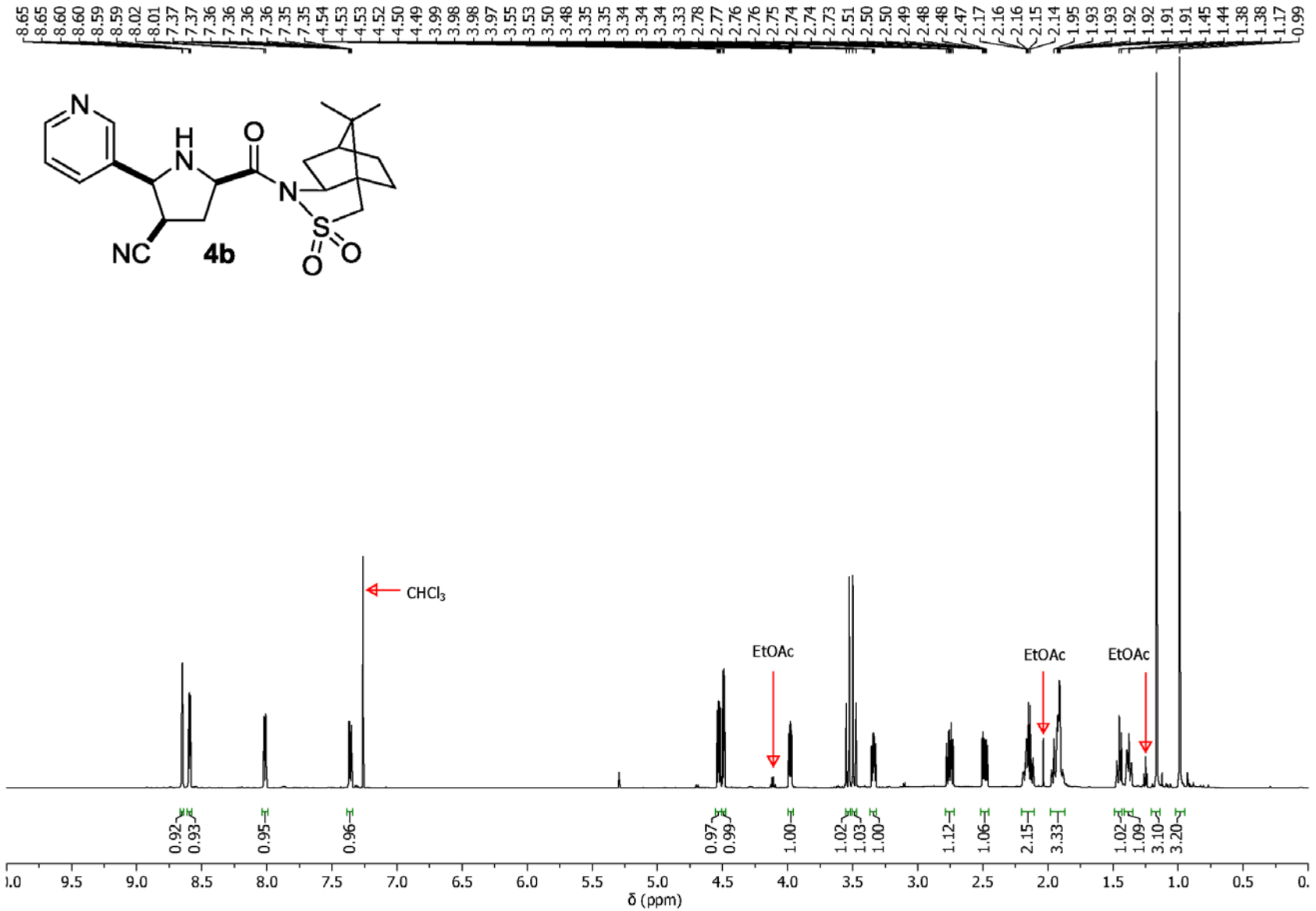


5a

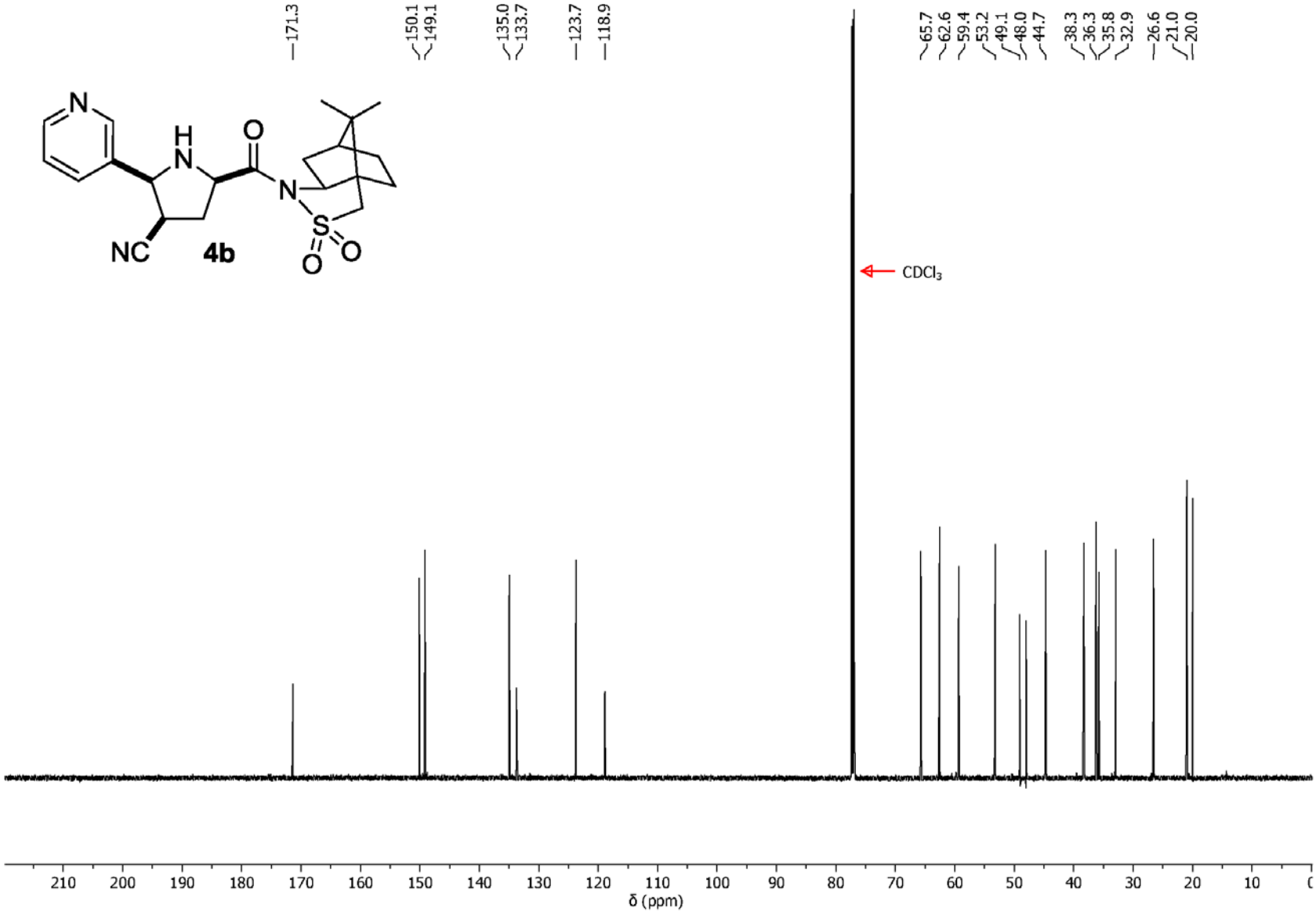


Relevant portion of the 600 MHz 2D NOESY ^{1}H NMR spectra obtained for compound **5a** in $CDCl_3$ showing interactions between **a-b, a-c, a-d, a-e, c-d, c-e, b-d, b-e** and **d-e** in the pyrrolidine ring. The data were collected at ambient T with a 700 ms mixing time, scans per t1 increment = 16, t1 increments = 128 and 1.5 s relaxation time.

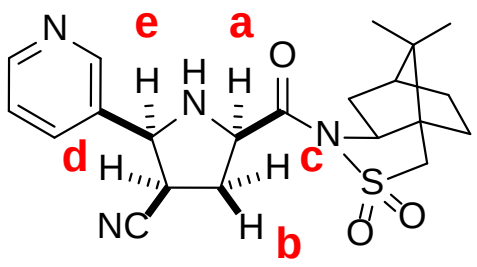
600 MHz ^{1}H NMR, $CDCl_3$



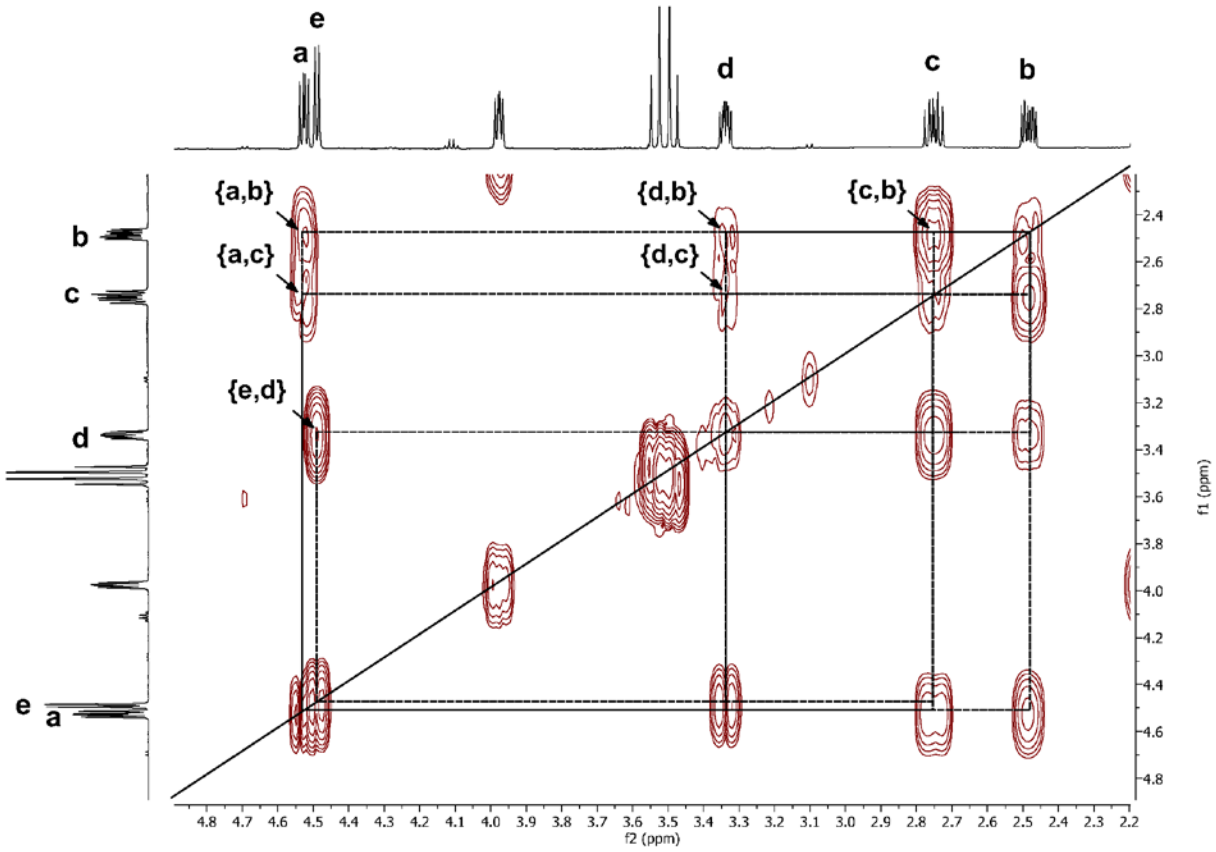
150.8 MHz ^{13}C NMR, $CDCl_3$



600 MHz gCOSY ^{1}H NMR, $CDCl_3$

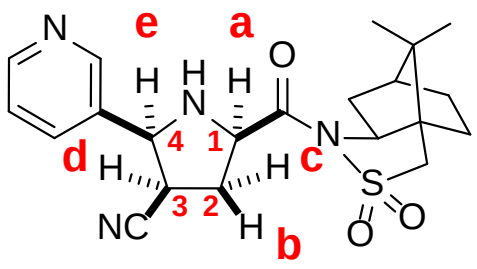


4b

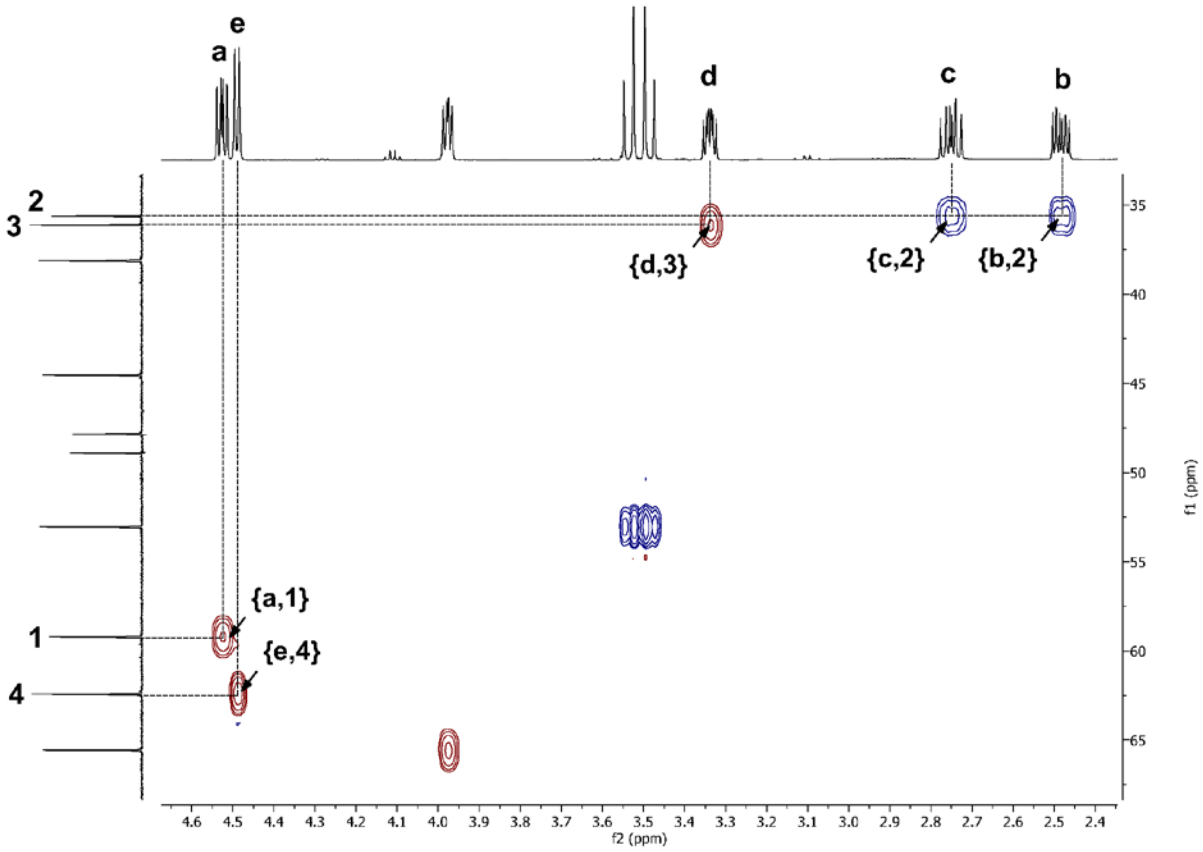


Relevant portion of the 600 MHz 2D gCOSY ^{1}H NMR spectra obtained for compound **4b** in $CDCl_3$ showing interactions between **a-b, a-c, e-d, d-b, d-c** and **c-b** in the pyrrolidine ring.

600 MHz HSQCAD NMR, $CDCl_3$

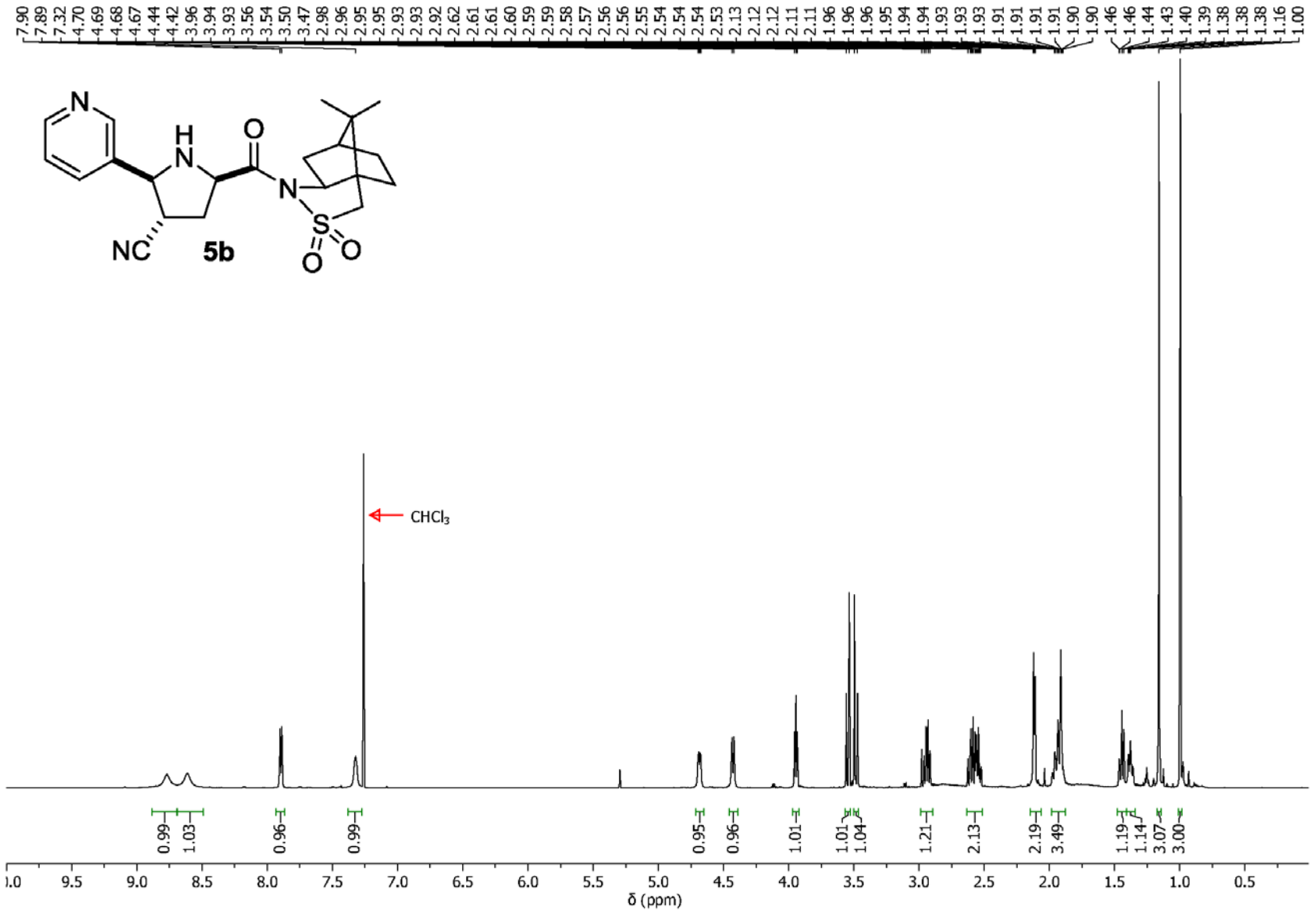


4b

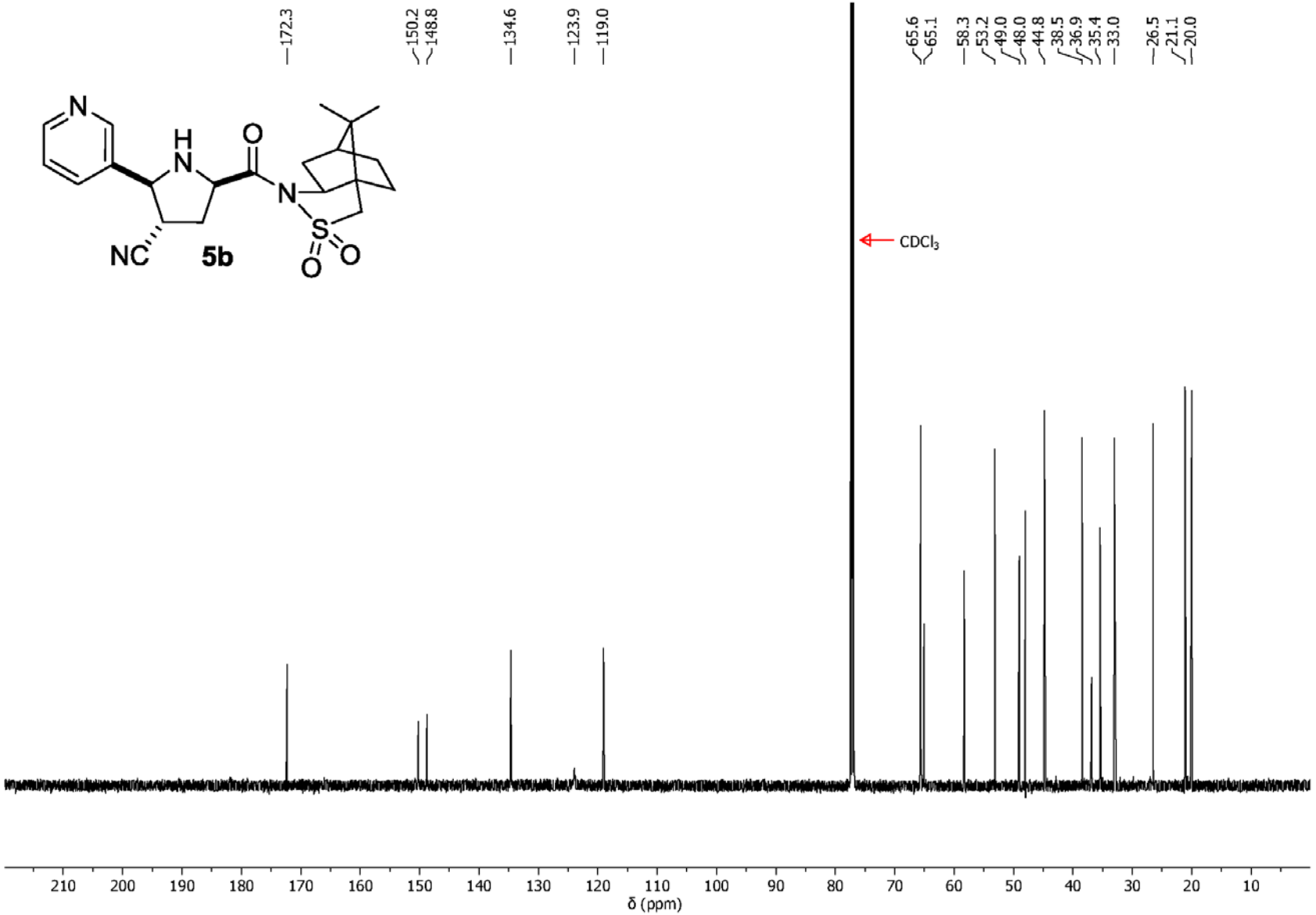


Relevant portion of the 600 MHz HSQCAD NMR spectra obtained for compound **4b** in $CDCl_3$ showing interactions between **a-1, e-4, d-3, c-2** and **b-2.** Blue color contours stand for -CH_2 group and red color contours stand for -CH and CH_3 groups.

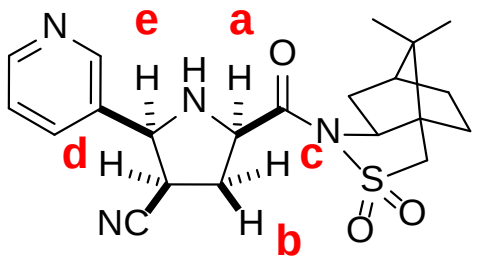
600 MHz ^{1}H NMR, $CDCl_3$



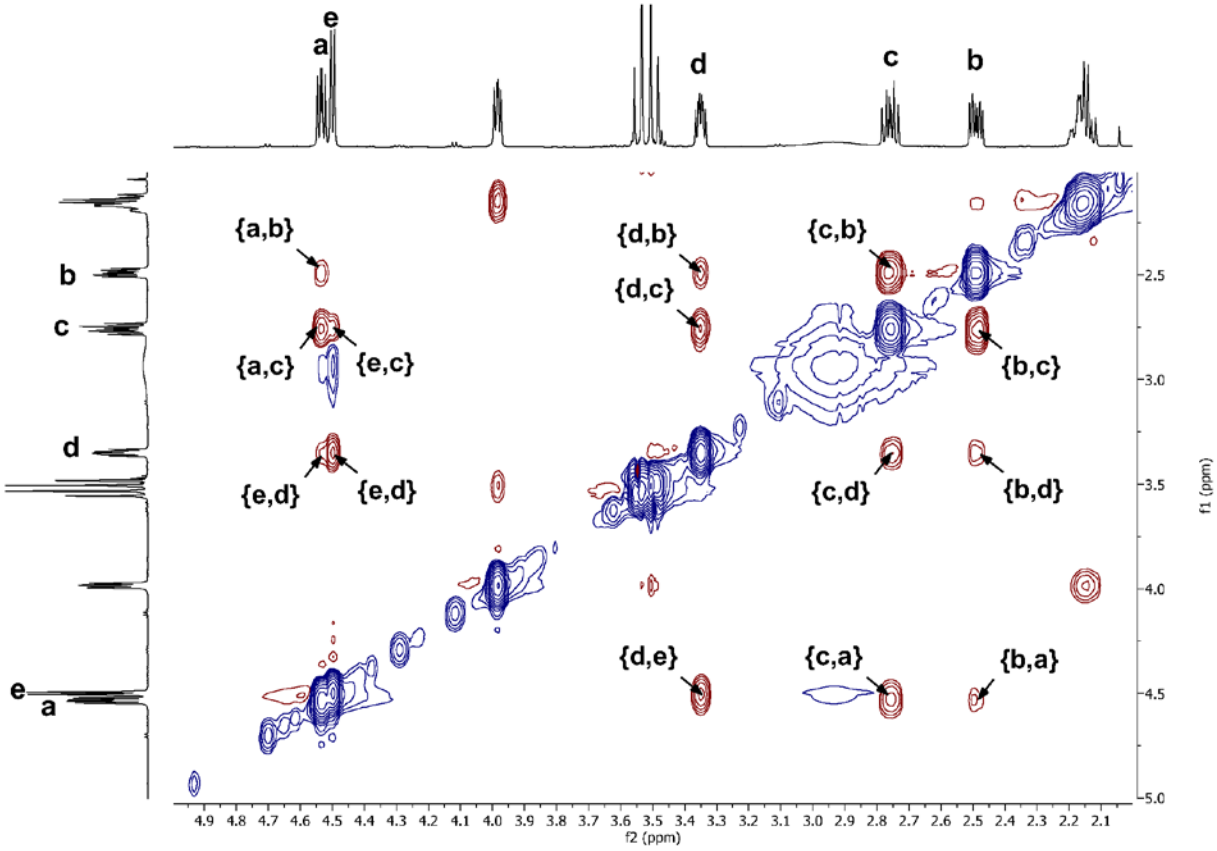
150.8 MHz ^{13}C NMR, $CDCl_3$



600 MHz 2D NOESY ^{1}H NMR, $CDCl_3$

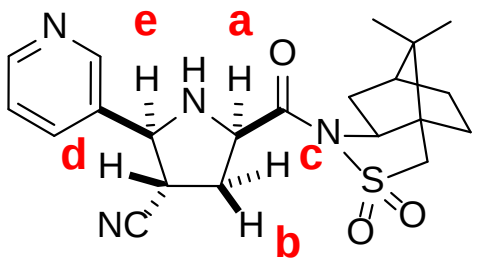


4b

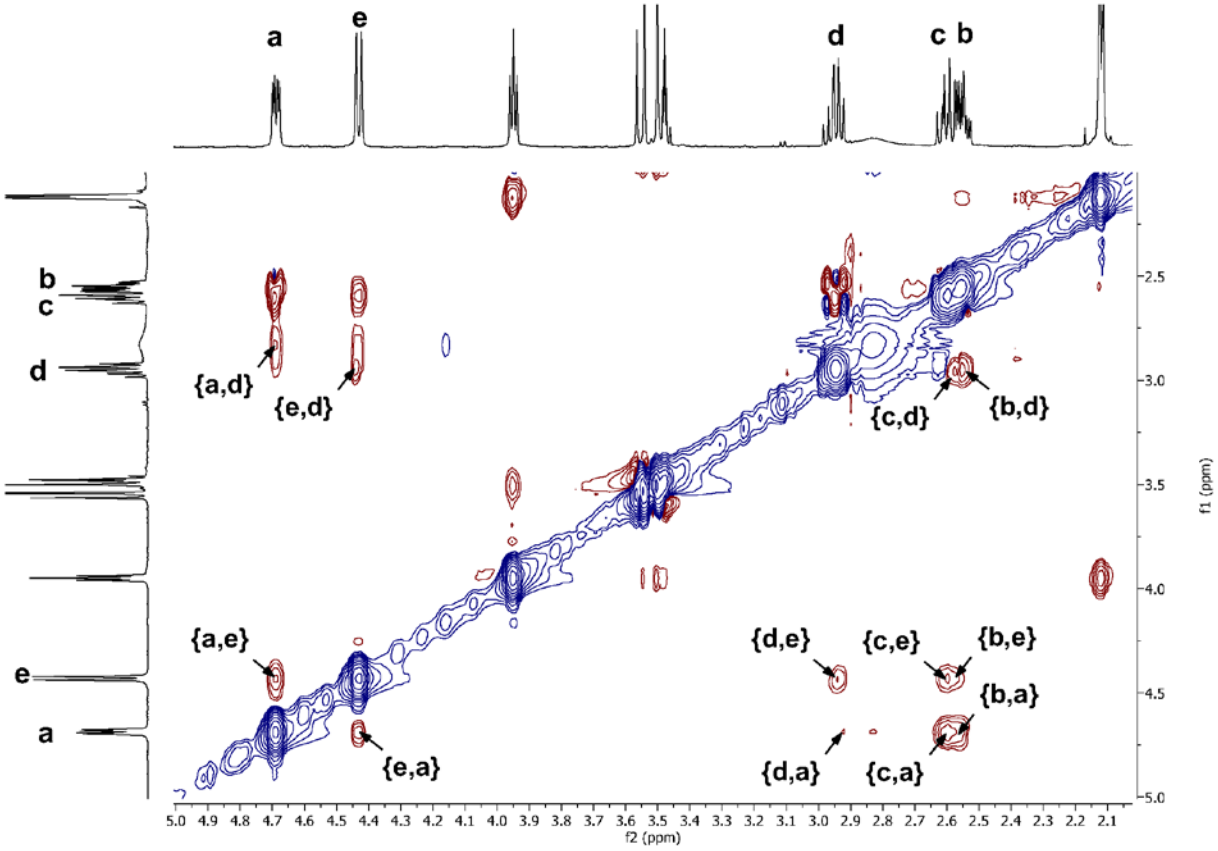


Relevant portion of the 600 MHz 2D NOESY ^{1}H NMR spectra obtained for compound **4b** in $CDCl_3$ showing interactions between **a-b, a-c, a-d, a-e, c-b, c-d, c-e, b-d, b-e** and **d-e** in the pyrrolidine ring. The data were collected at ambient T with a 700 ms mixing time, scans per t1 increment = 16, t1 increments = 128 and 1.5 s relaxation time.

600 MHz 2D NOESY ^{1}H NMR, $CDCl_3$

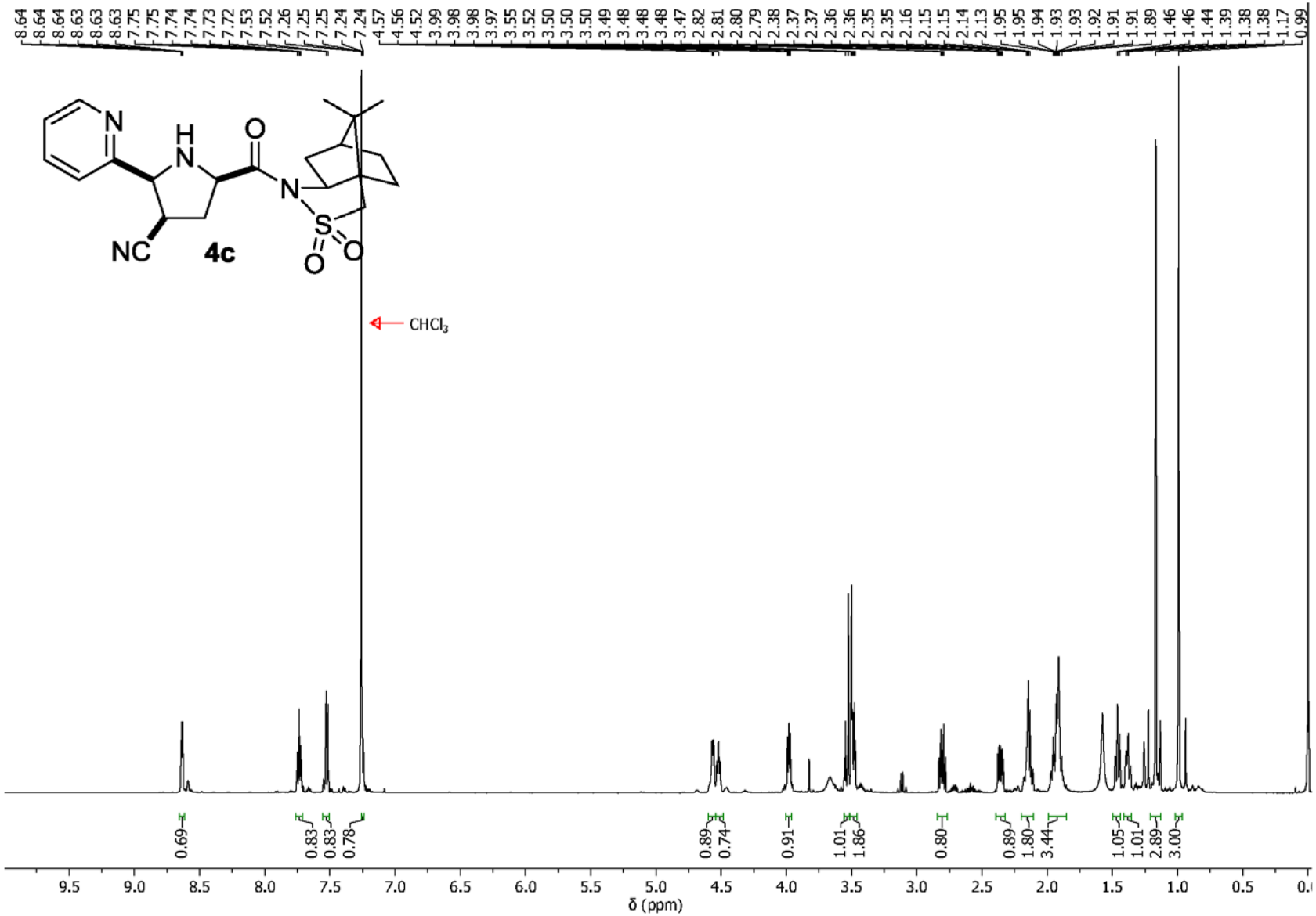


5b

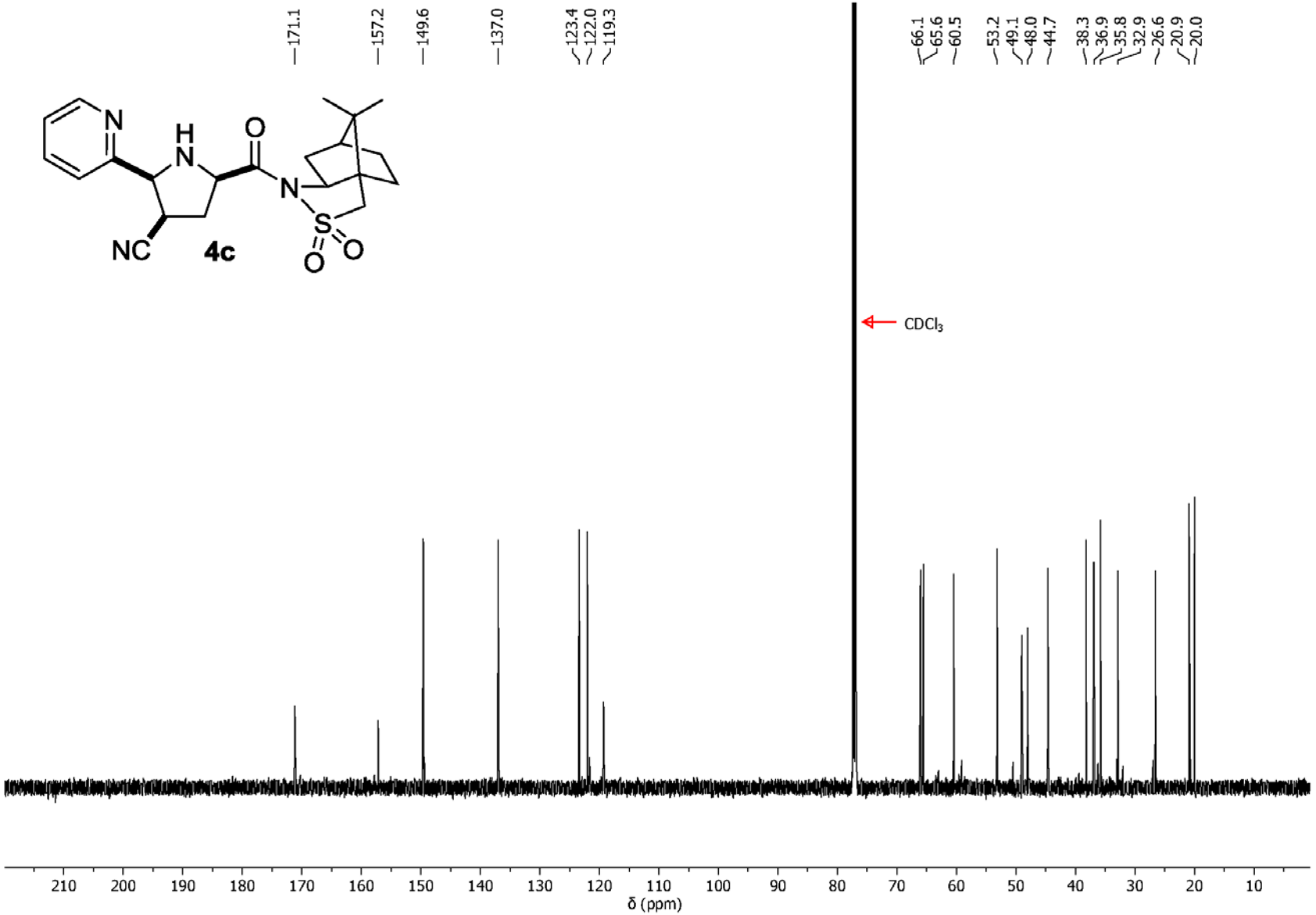


Relevant portion of the 600 MHz 2D NOESY ^{1}H NMR spectra obtained for compound **5b** in $CDCl_3$ showing interactions between **a-b, a-c, a-d, a-e, c-d, c-e, b-d, b-e** and **d-e** in the pyrrolidine ring. The data were collected at ambient T with a 700 ms mixing time, scans per t1 increment = 16, t1 increments = 128 and 1.5 s relaxation time.

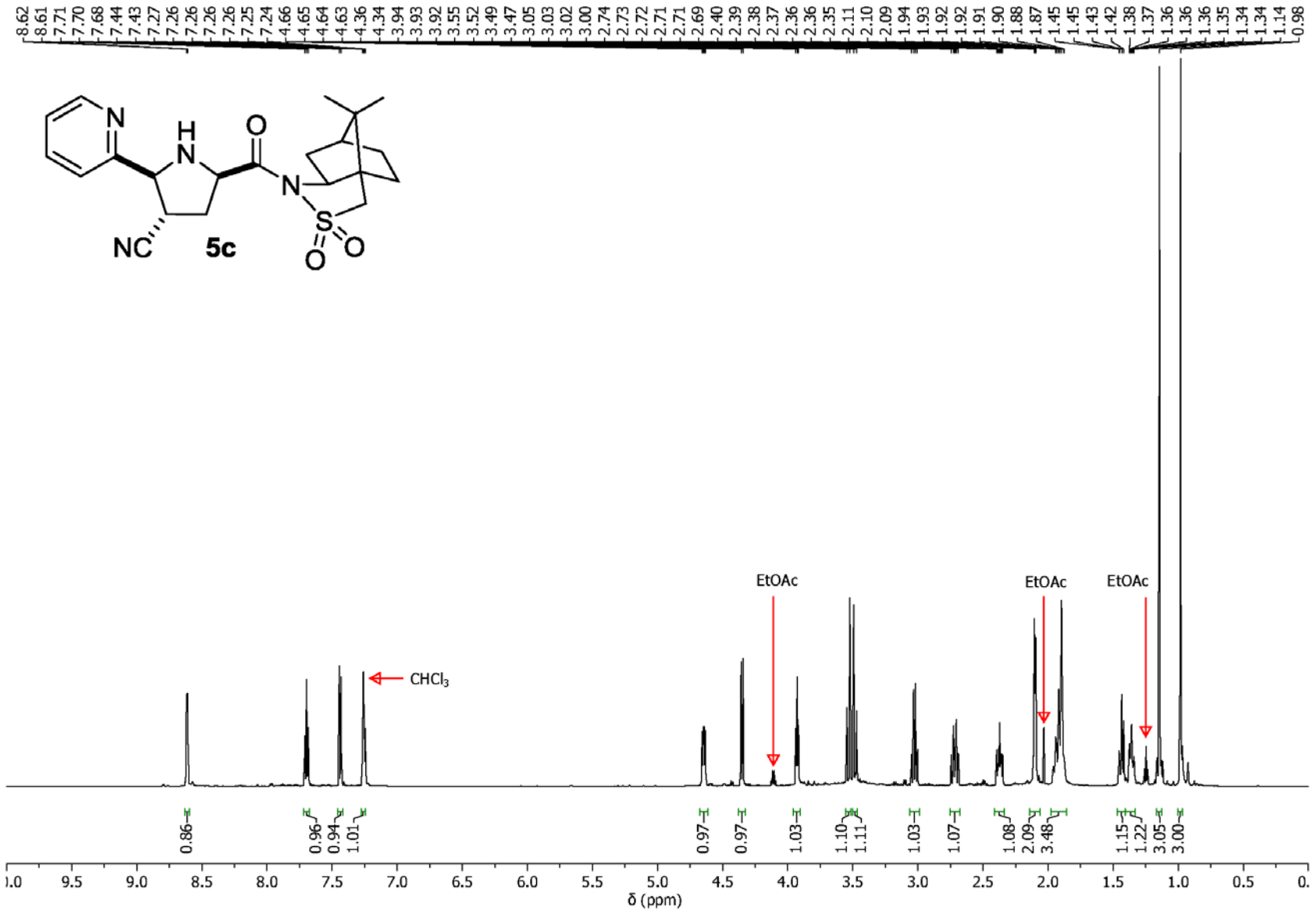
600 MHz ^{1}H NMR, $CDCl_3$



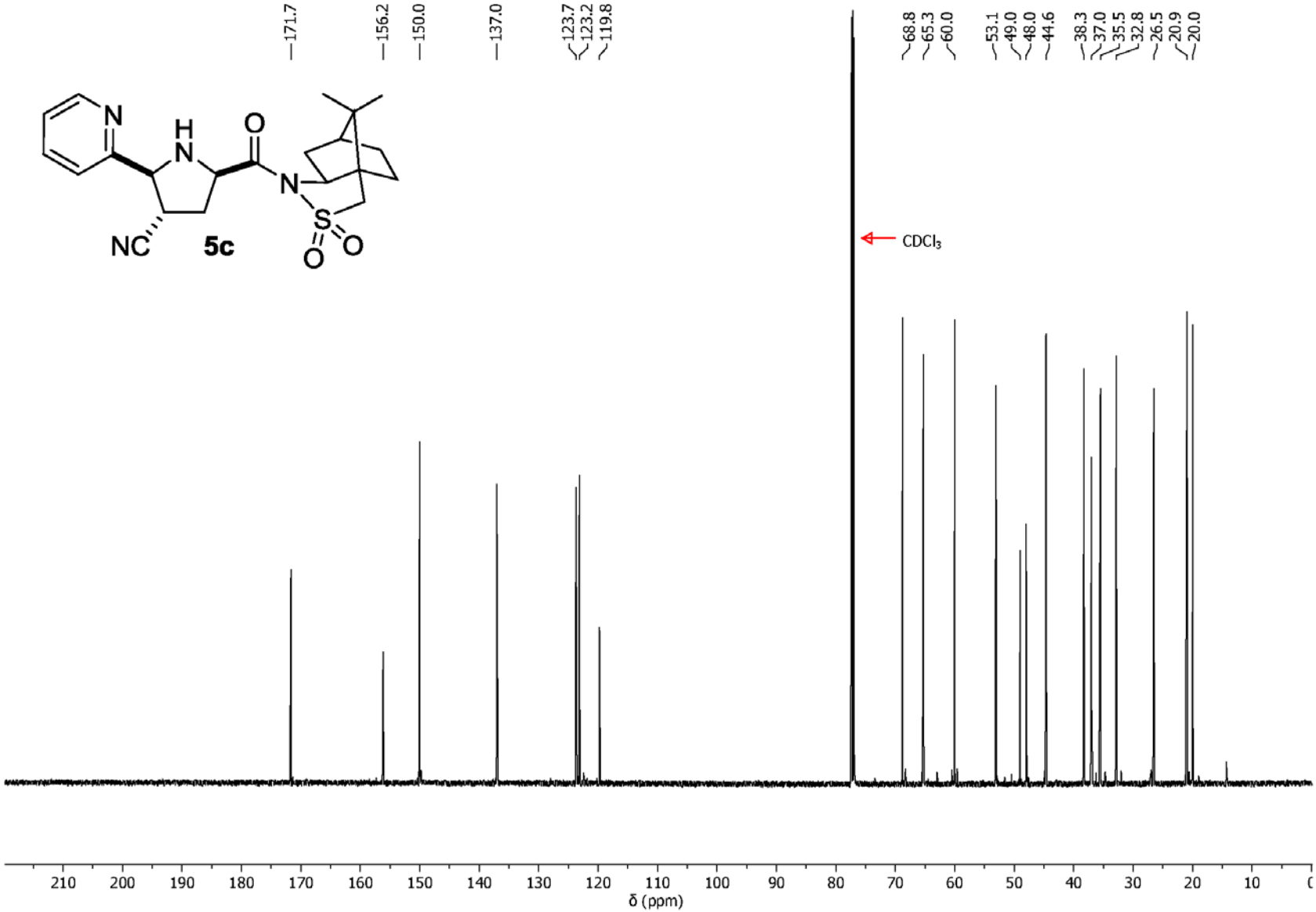
150.8 MHz ^{13}C NMR, $CDCl_3$



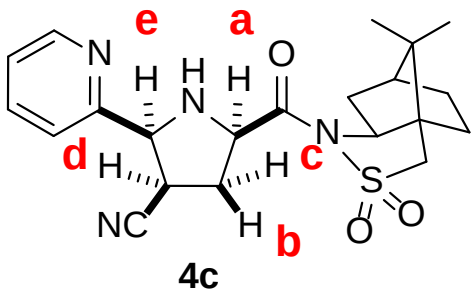
600 MHz ^{1}H NMR, $CDCl_3$



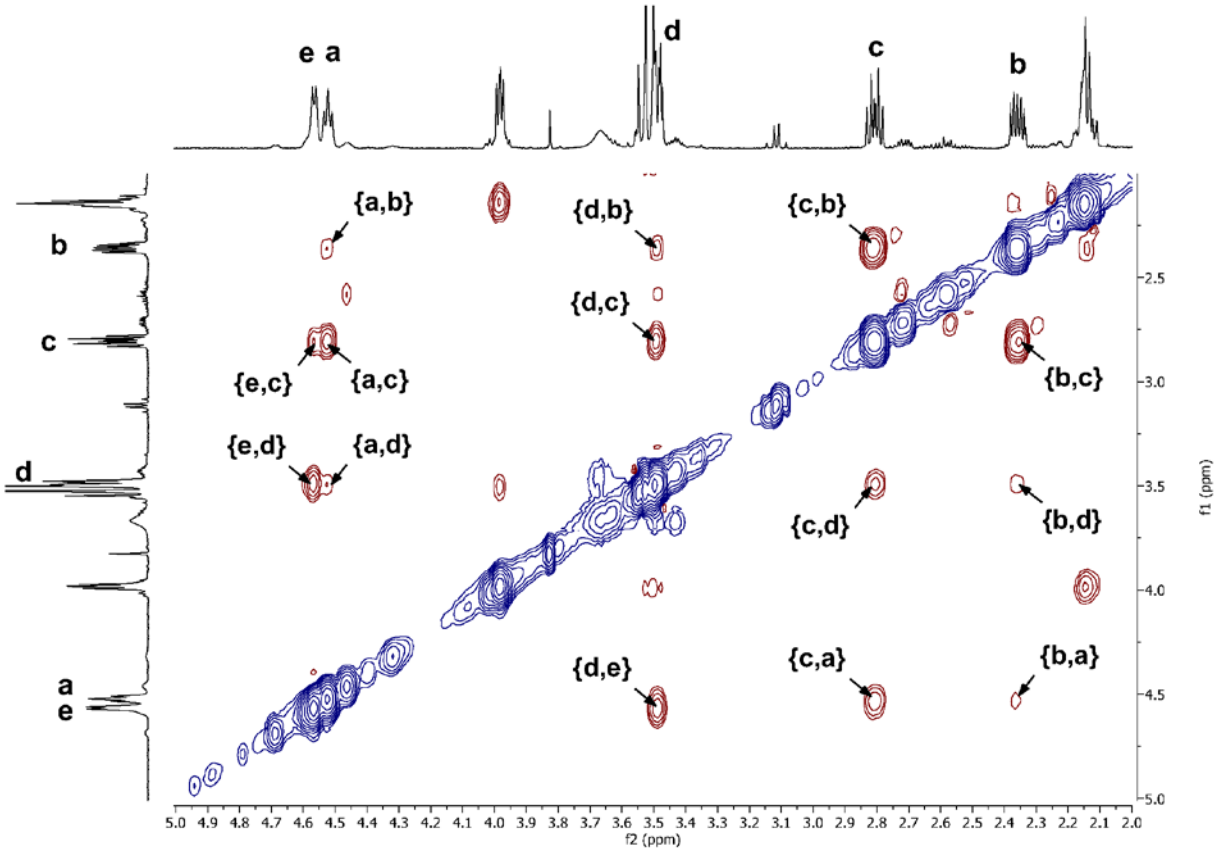
150.8 MHz ^{13}C NMR, $CDCl_3$



600 MHz 2D NOESY ^{1}H NMR, $CDCl_3$

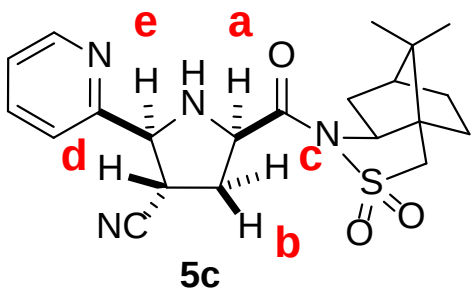


4c

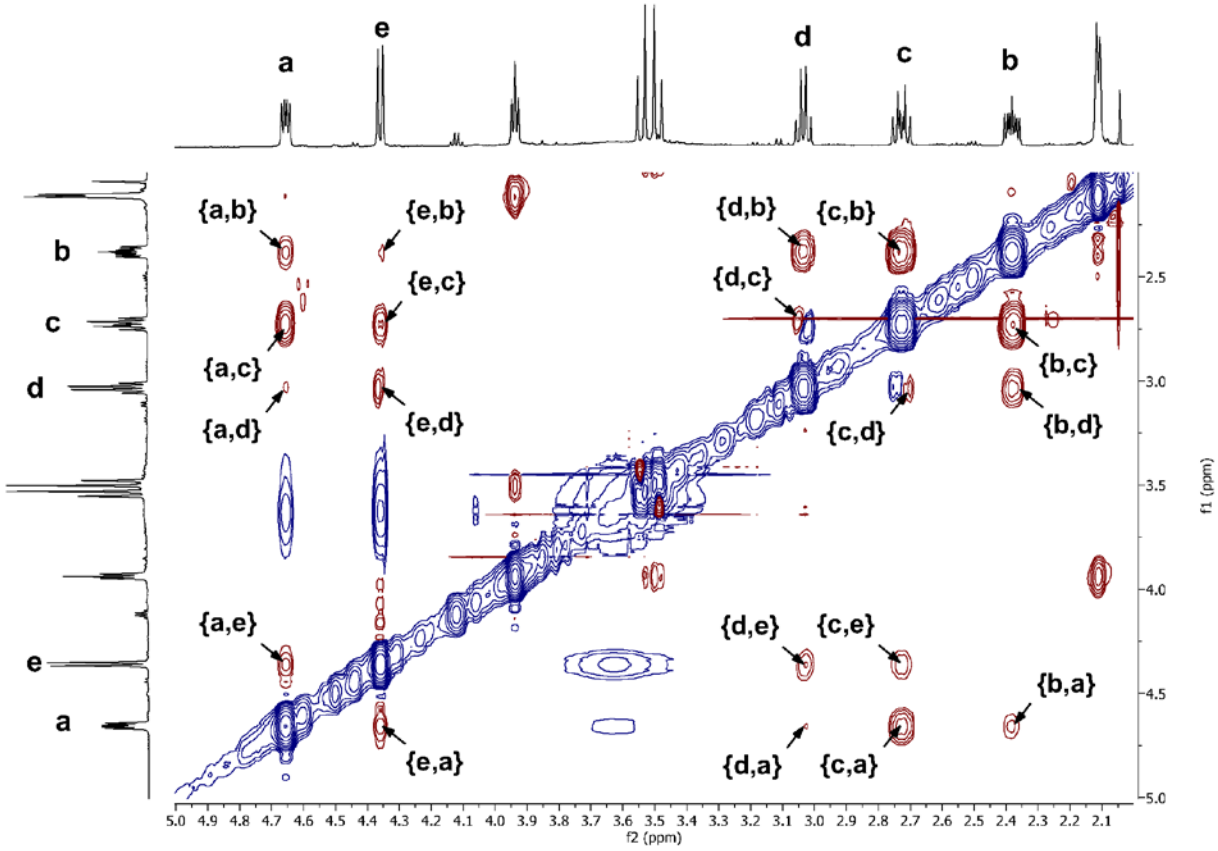


Relevant portion of the 600 MHz 2D NOESY ^{1}H NMR spectra obtained for compound **4c** in $CDCl_3$ showing interactions between **a-b, a-c, a-d, c-b, c-d, c-e, b-d,** and **d-e** in the pyrrolidine ring. The data were collected at ambient T with a 700 ms mixing time, scans per t1 increment = 16, t1 increments = 128 and 1.5 s relaxation time.

600 MHz 2D NOESY ^{1}H NMR, $CDCl_3$

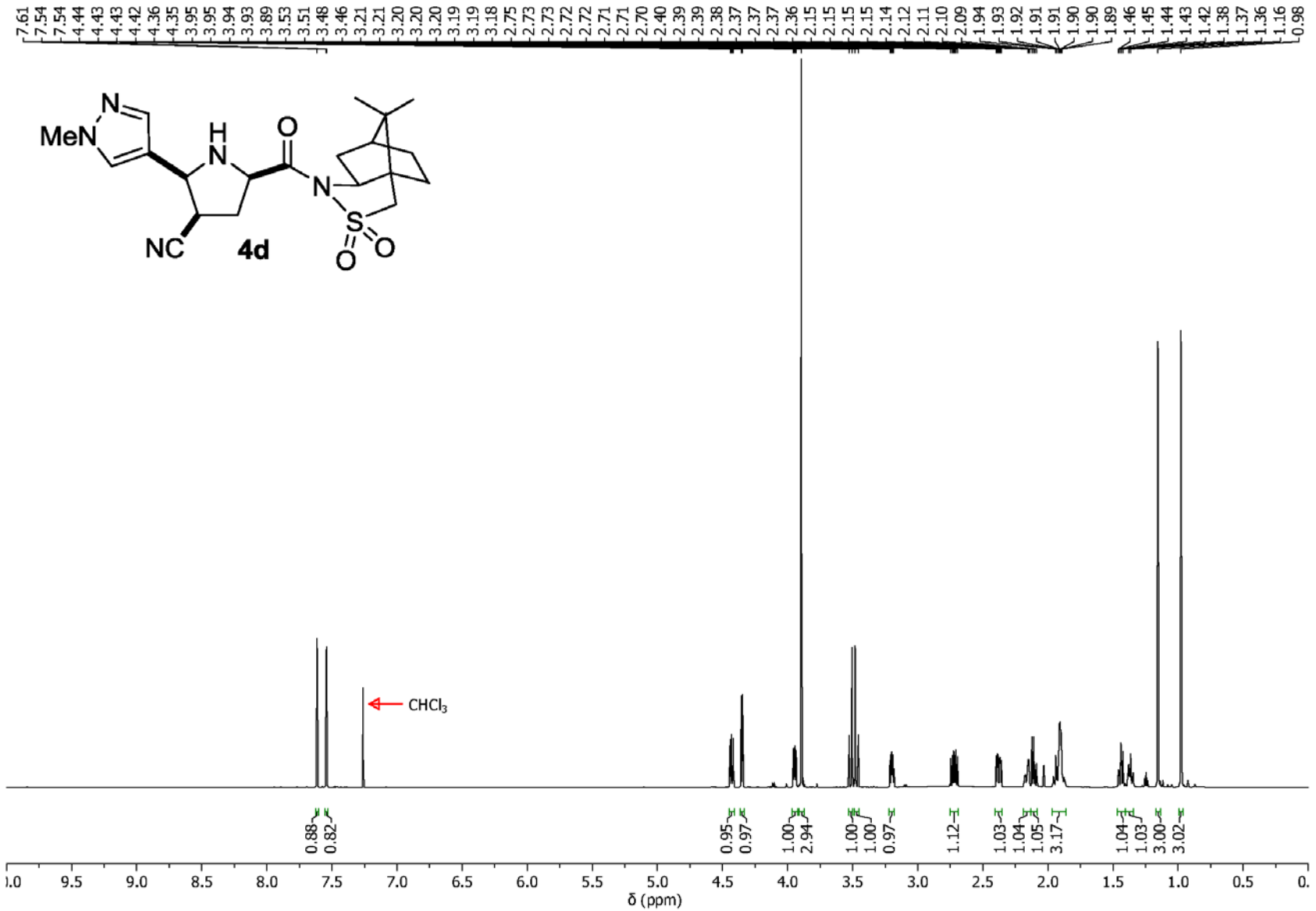


5c

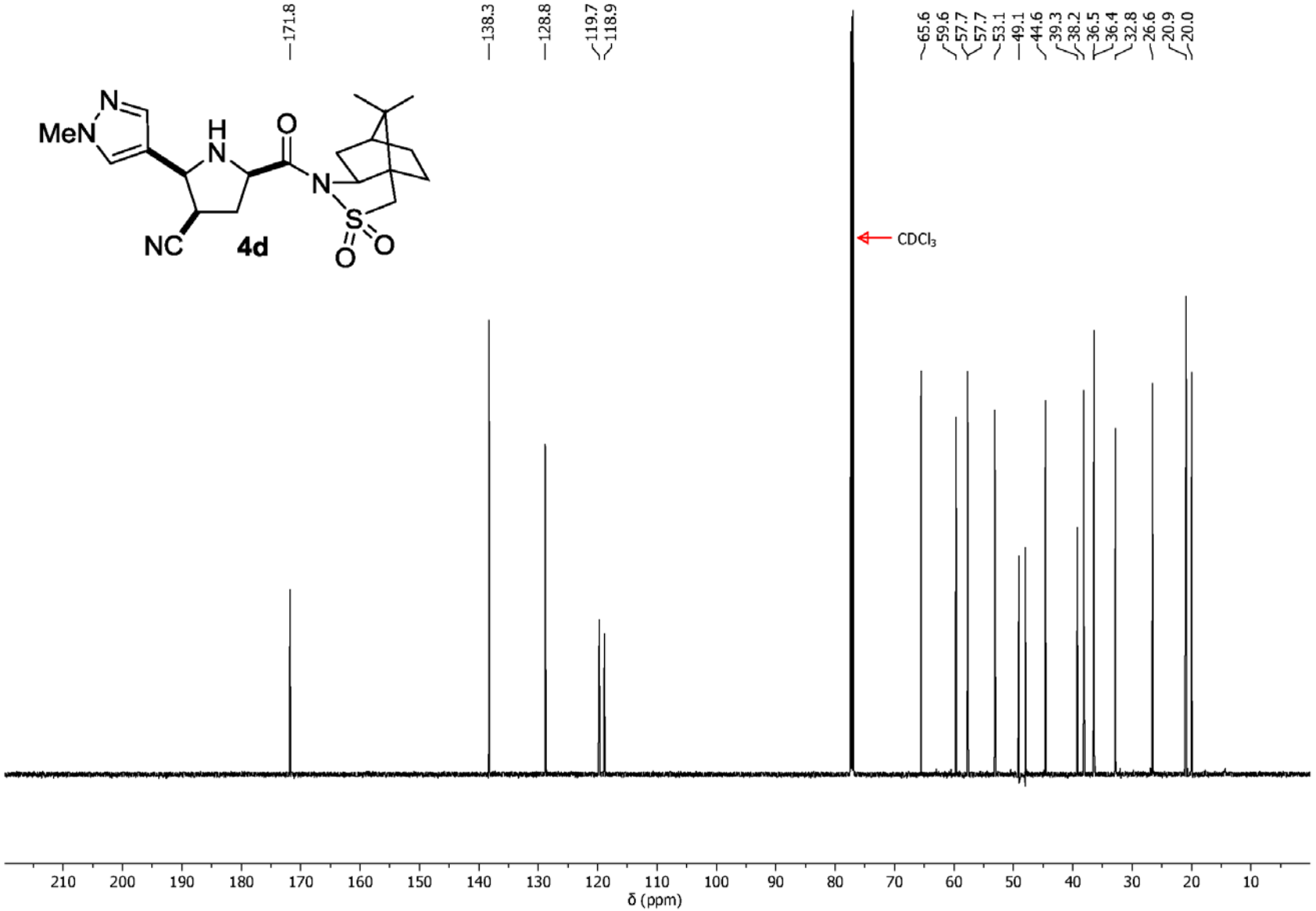


Relevant portion of the 600 MHz 2D NOESY ^{1}H NMR spectra obtained for compound **5c** in $CDCl_3$ showing interactions between **a-b, a-c, a-d, a-e, c-b, c-d, c-e, b-d, b-e** and **d-e** in the pyrrolidine ring. The data were collected at ambient T with a 700 ms mixing time, scans per t1 increment = 16, t1 increments = 128 and 1.5 s relaxation time.

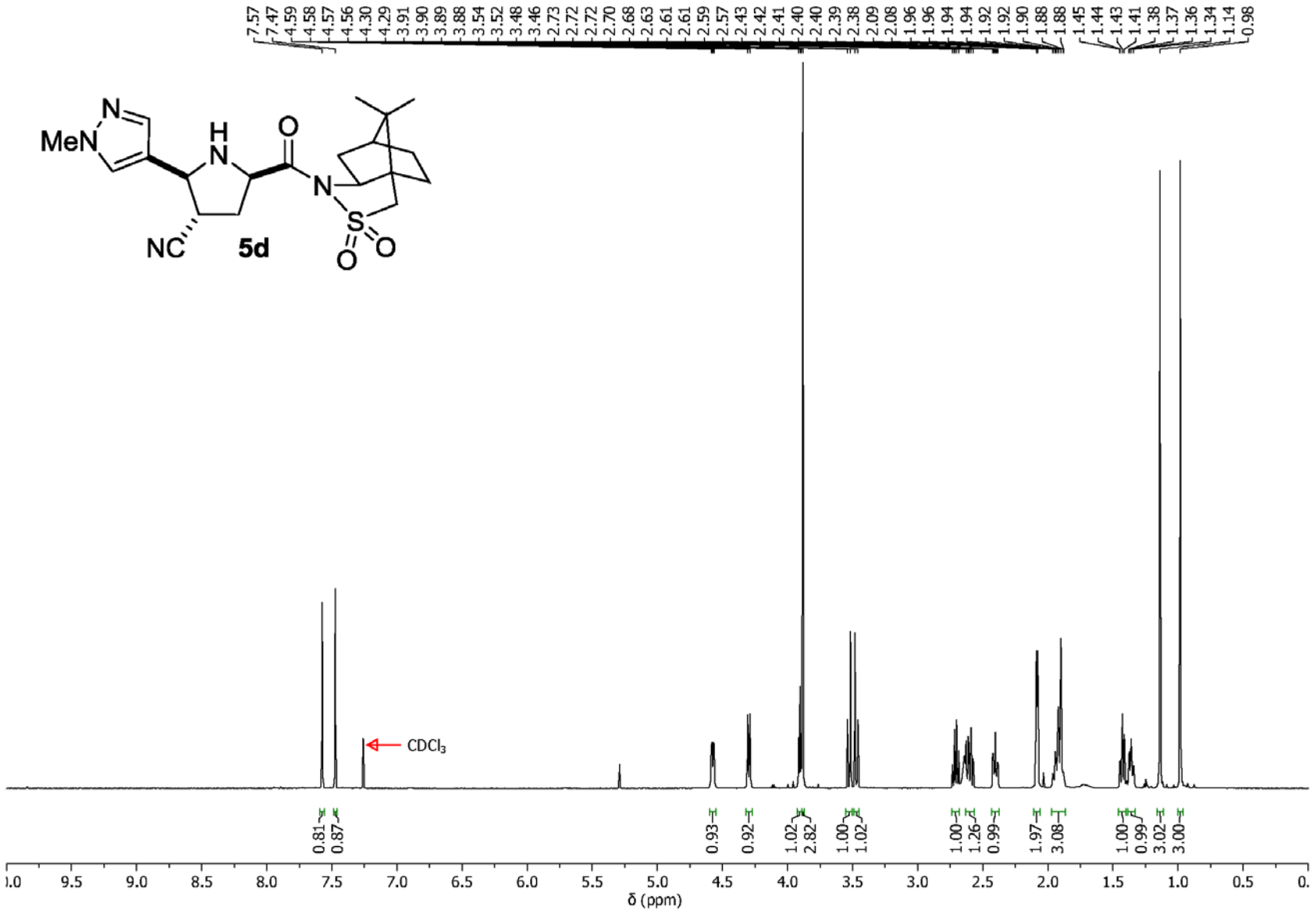
600 MHz ^{1}H NMR, $CDCl_3$



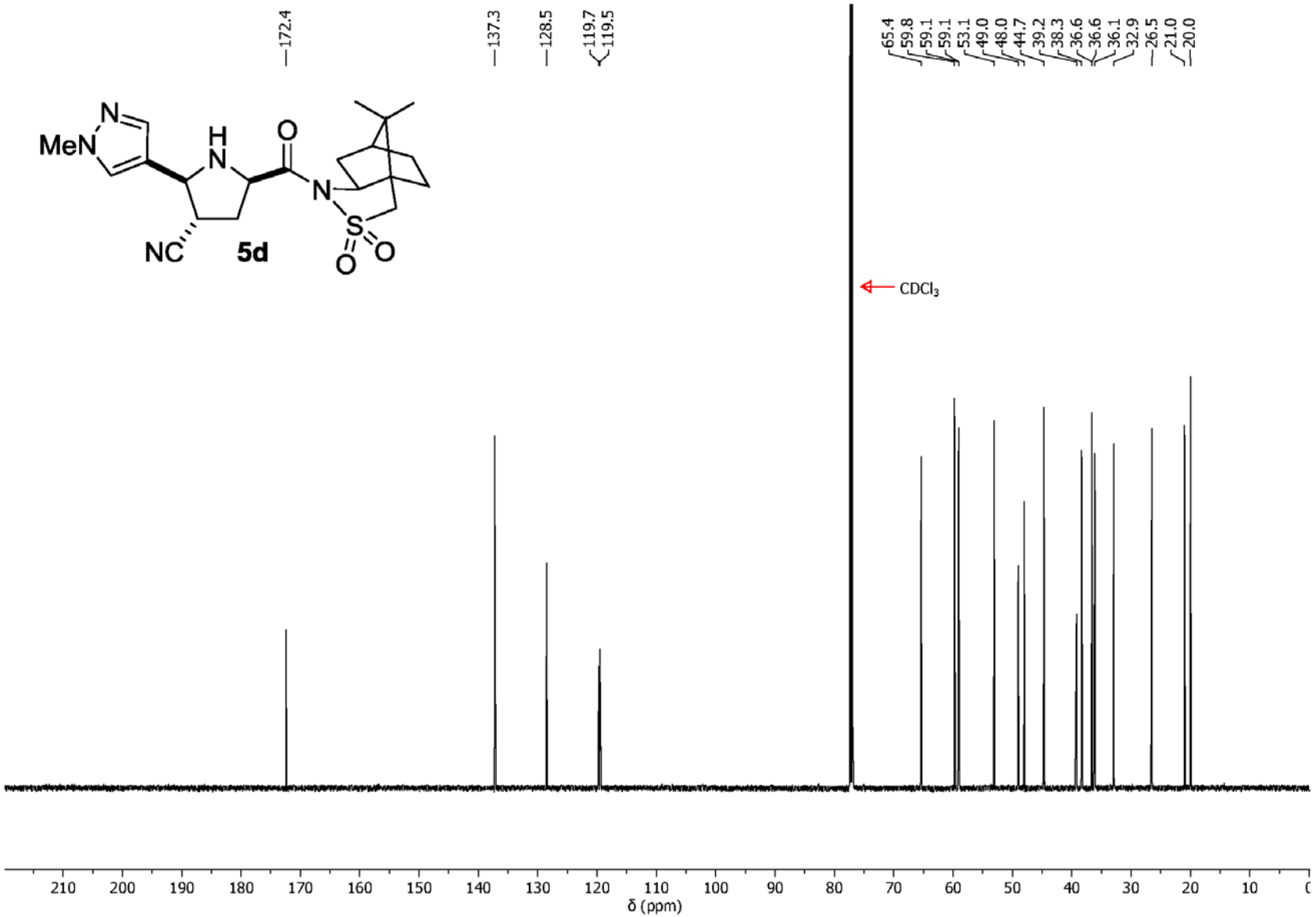
150.8 MHz ^{13}C NMR, $CDCl_3$



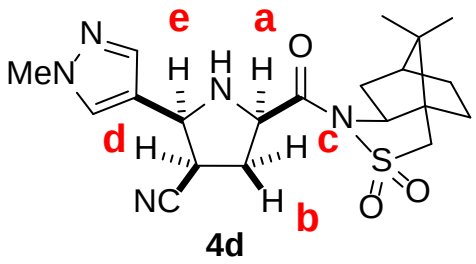
600 MHz ^{1}H NMR, $CDCl_3$



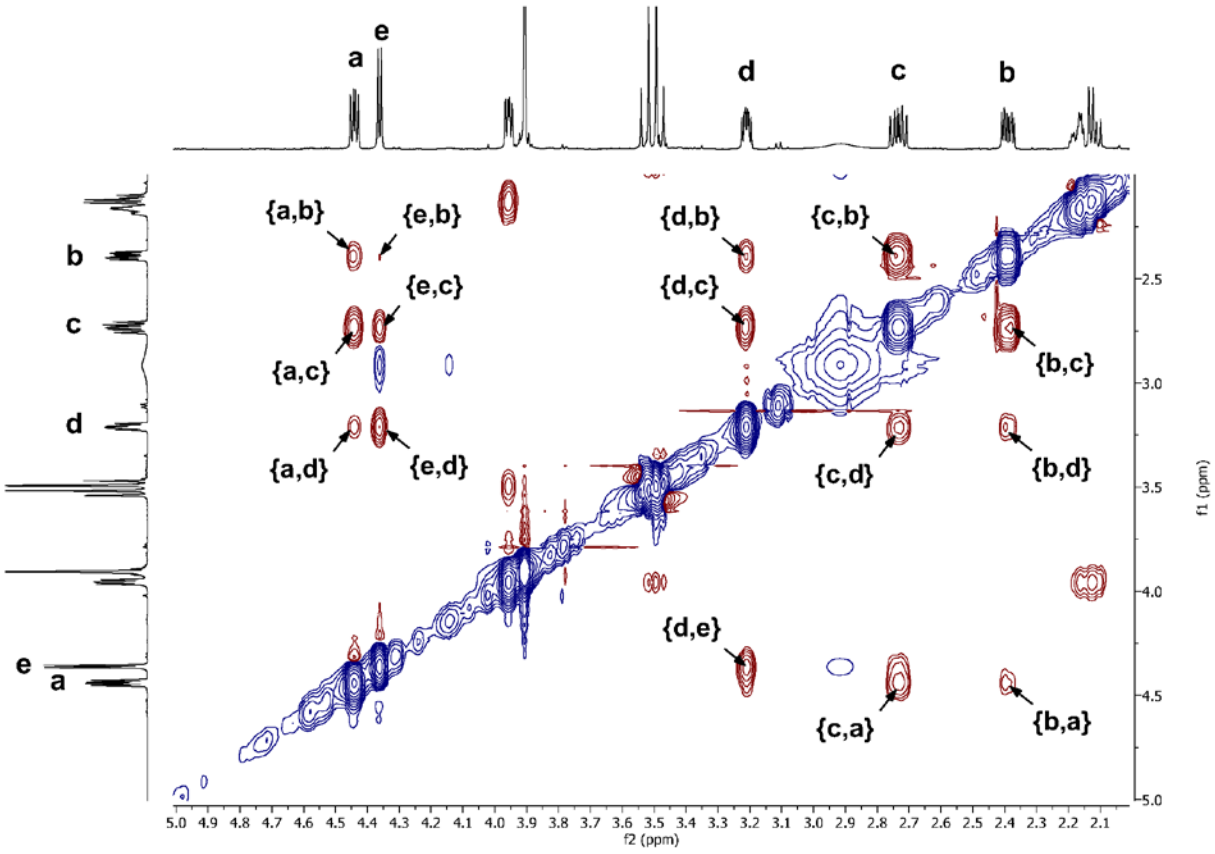
150.8 MHz ^{13}C NMR, $CDCl_3$



600 MHz 2D NOESY ^{1}H NMR, $CDCl_3$

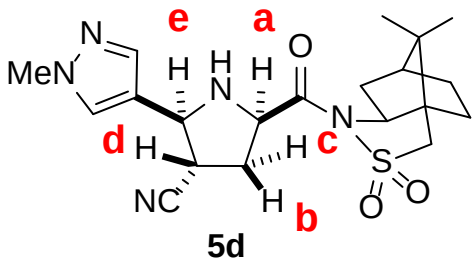


4d

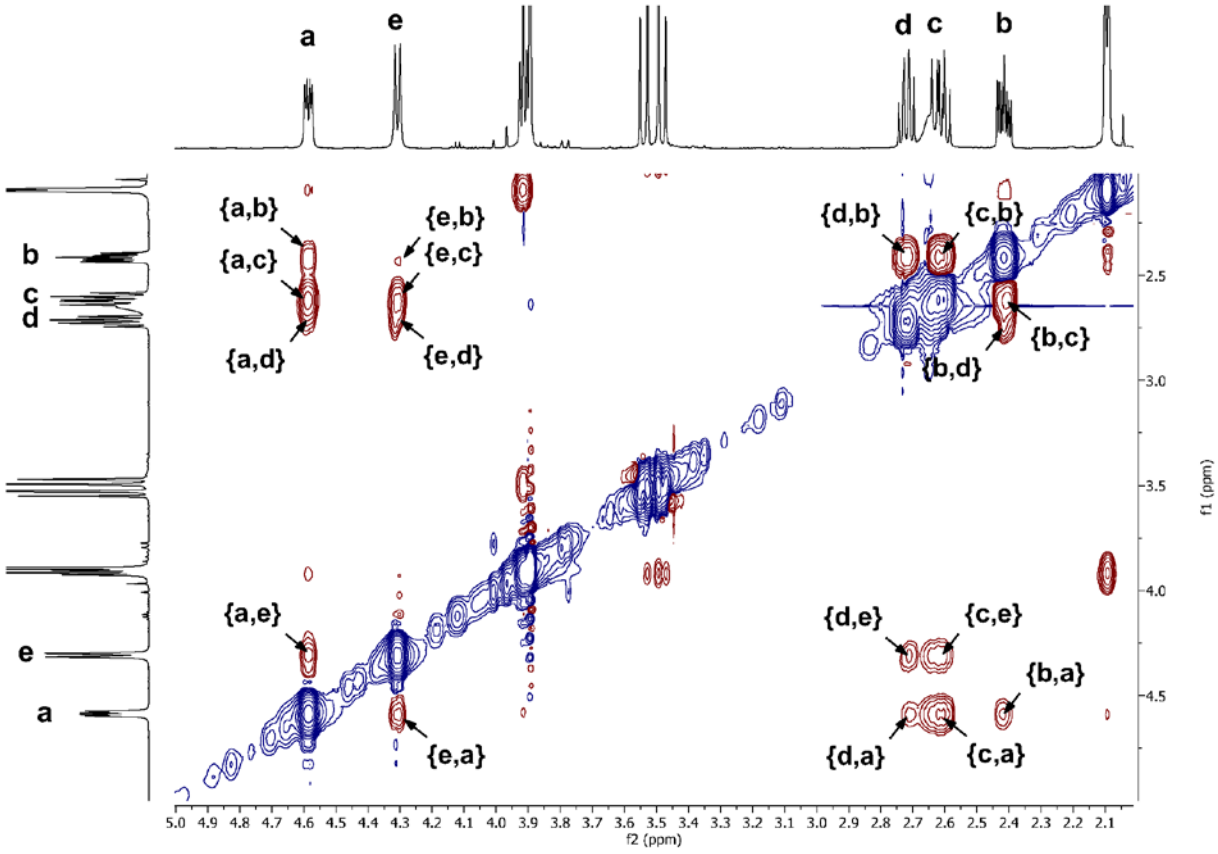


Relevant portion of the 600 MHz 2D NOESY ^{1}H NMR spectra obtained for compound **4d** in $CDCl_3$ showing interactions between **a-b, a-c, a-d, c-b, c-d, c-e, b-d, b-e** and **d-e** in the pyrrolidine ring. The data were collected at ambient T with a 700 ms mixing time, scans per t1 increment = 16, t1 increments = 128 and 1.5 s relaxation time.

600 MHz 2D NOESY ^{1}H NMR, $CDCl_3$

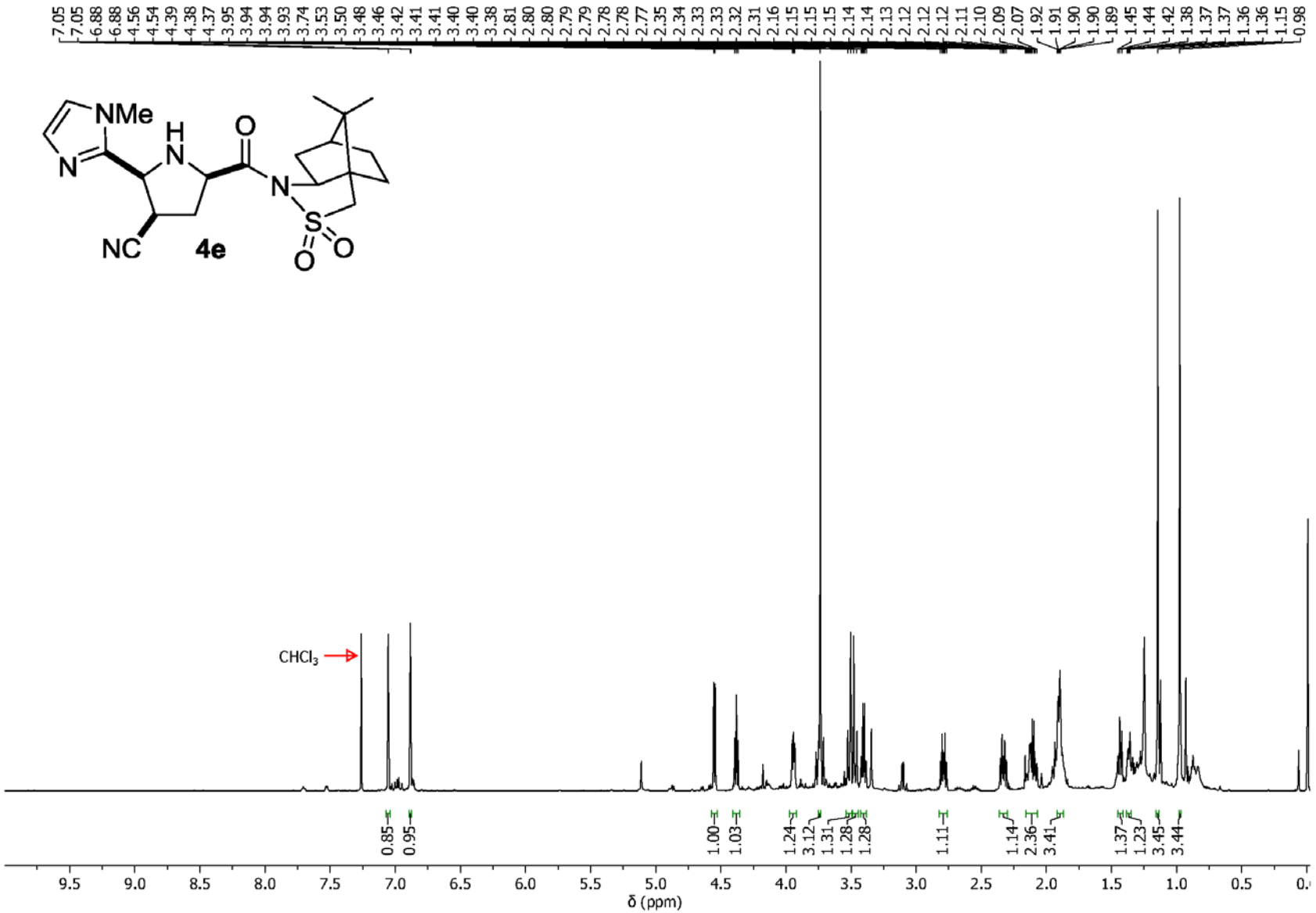


5d

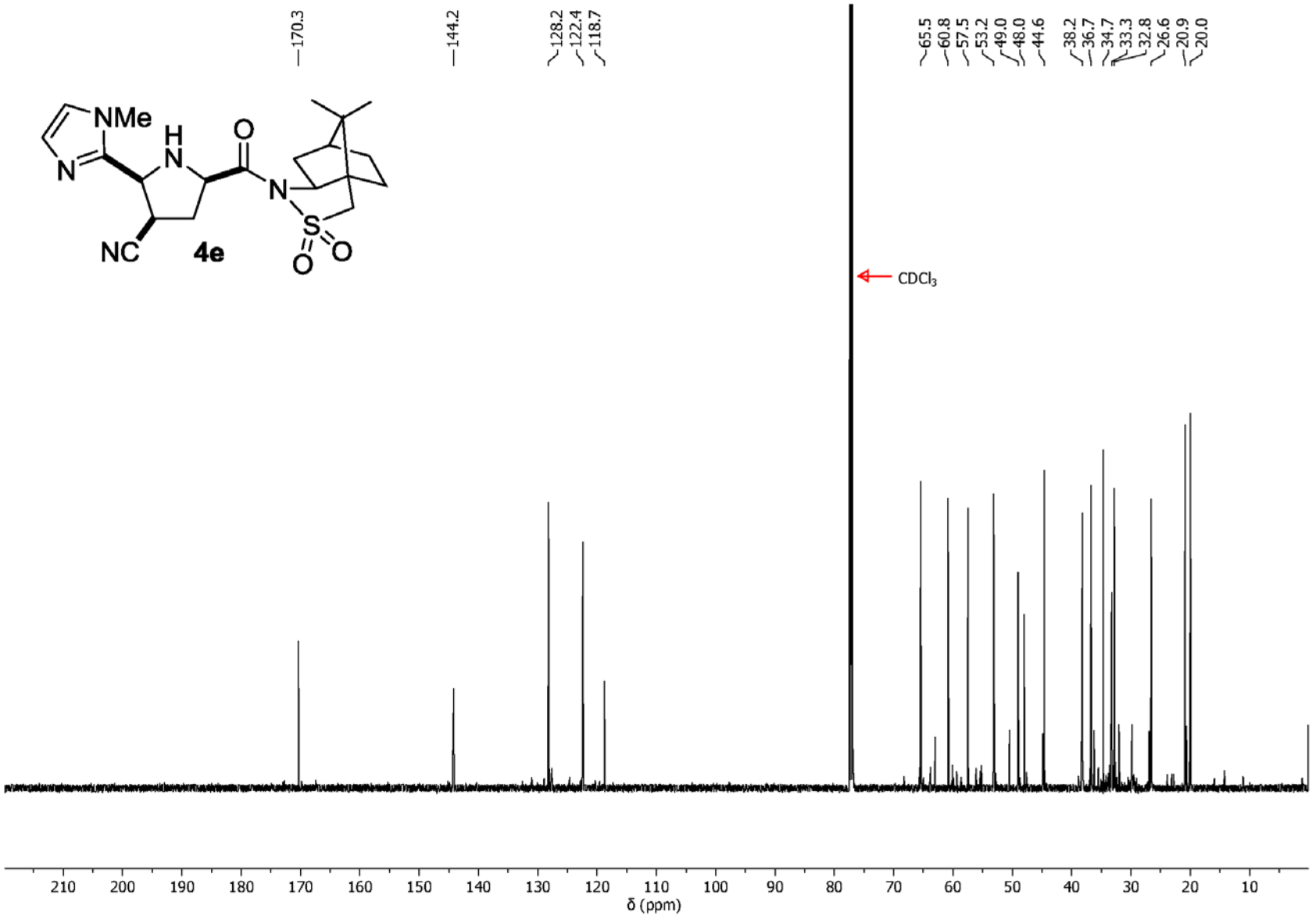


Relevant portion of the 600 MHz 2D NOESY ^{1}H NMR spectra spectra obtained for compound **5d** in $CDCl_3$ showing interactions between **a-b, a-c, a-d, a-e, c-b, c-e, b-d, b-e** and **d-e** in the pyrrolidine ring. The data were collected at ambient T with a 700 ms mixing time, scans per t1 increment = 16, t1 increments = 128 and 1.5 s relaxation time.

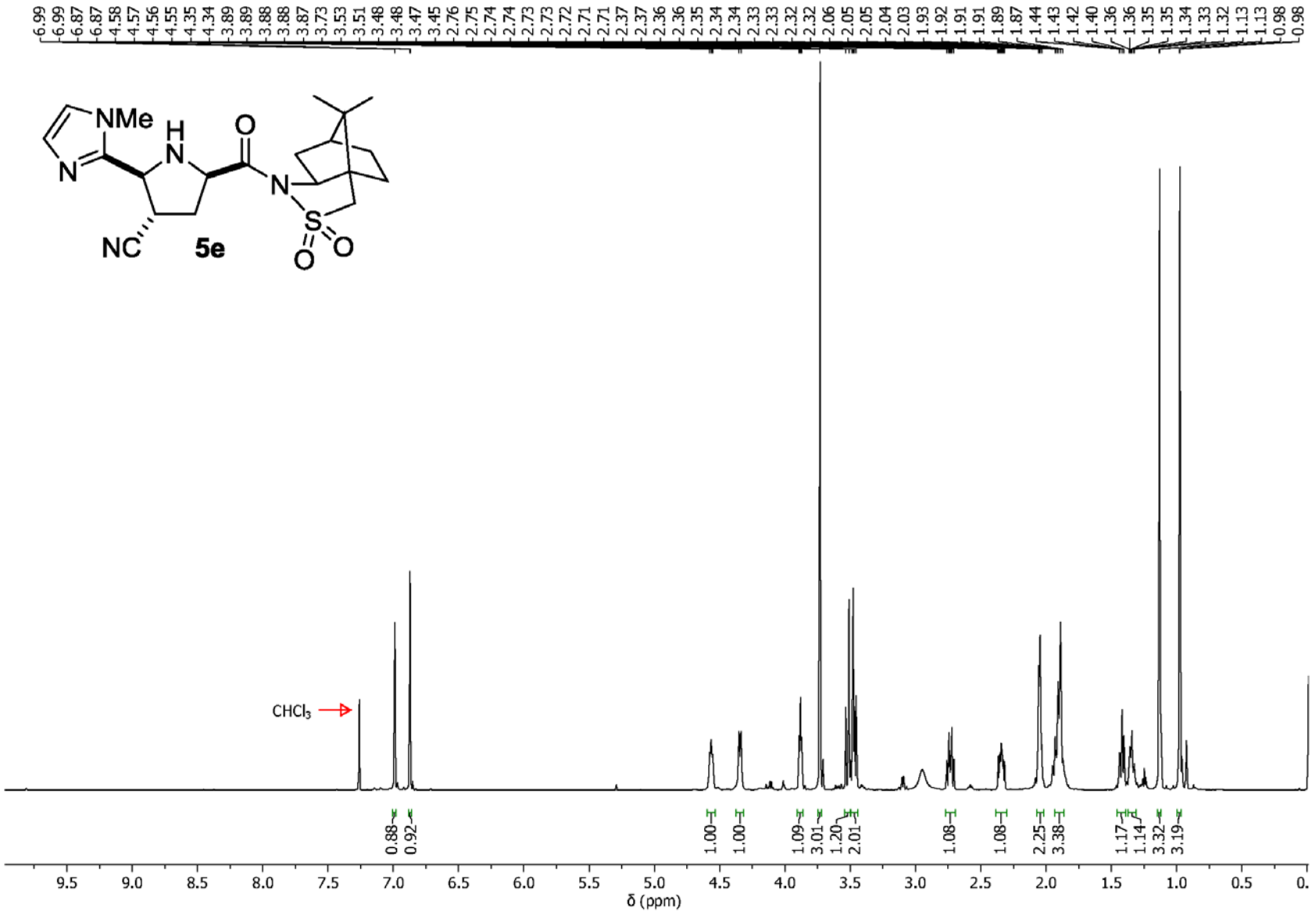
600 MHz ^{1}H NMR, $CDCl_3$



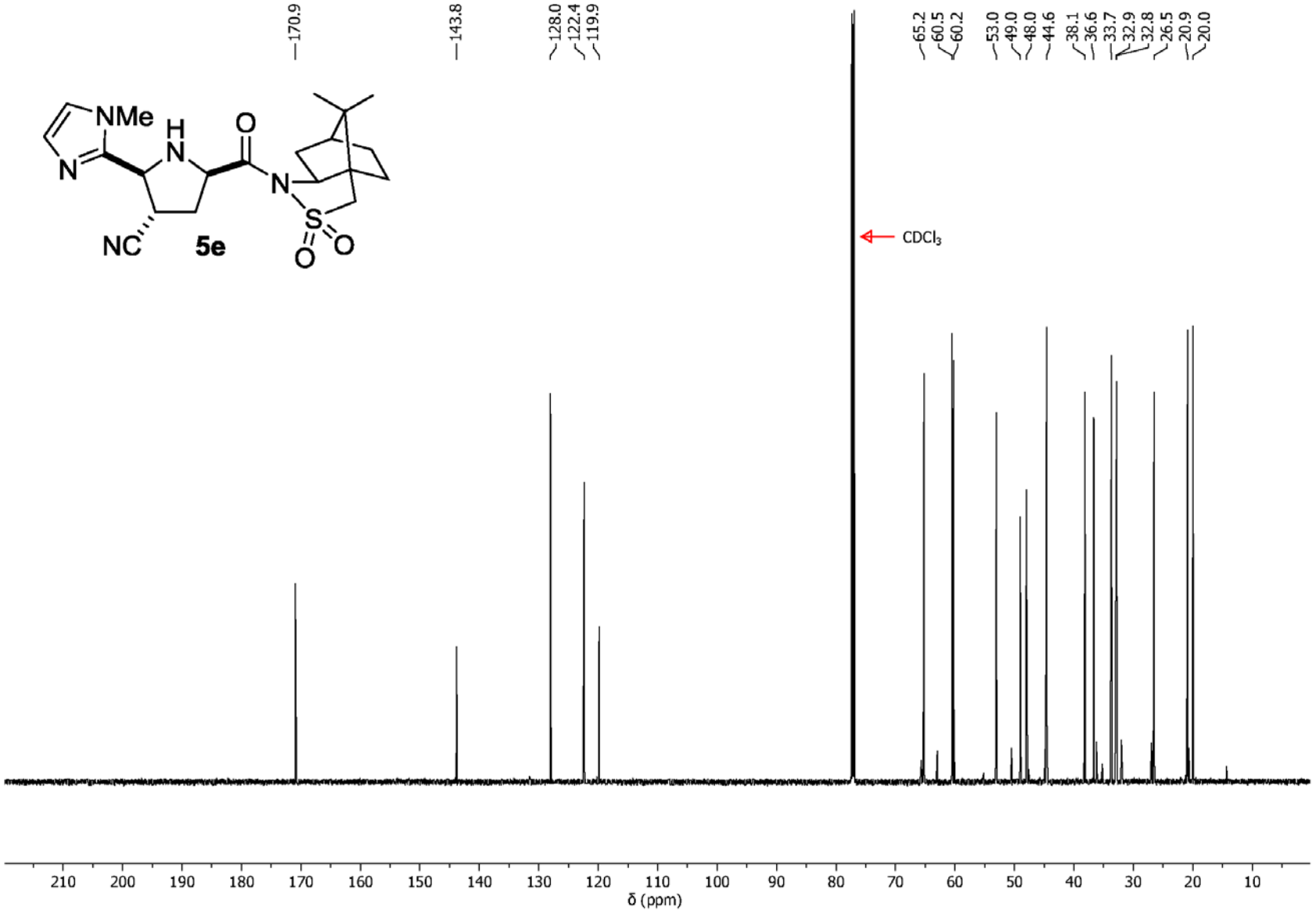
150.8 MHz ^{13}C NMR, $CDCl_3$



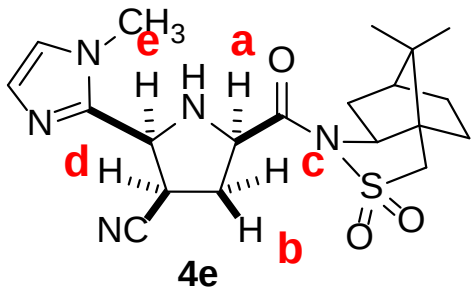
600 MHz ^{1}H NMR, $CDCl_3$



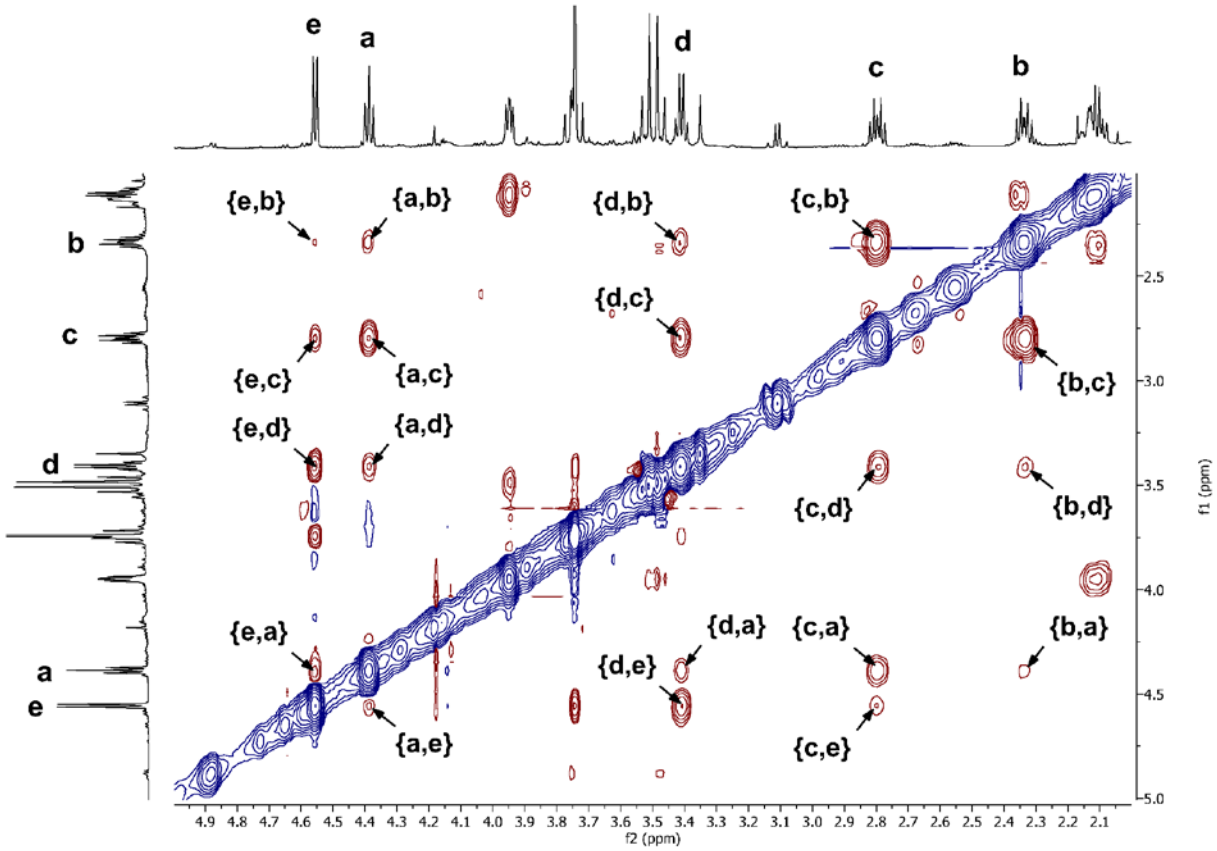
150.8 MHz ^{13}C NMR, $CDCl_3$



600 MHz 2D NOESY ^{1}H NMR, $CDCl_3$

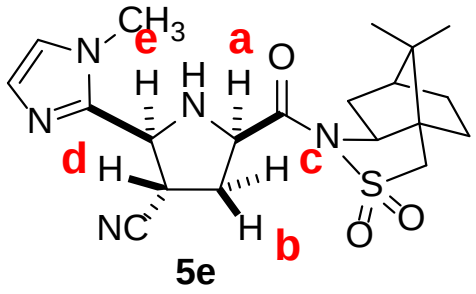


4e

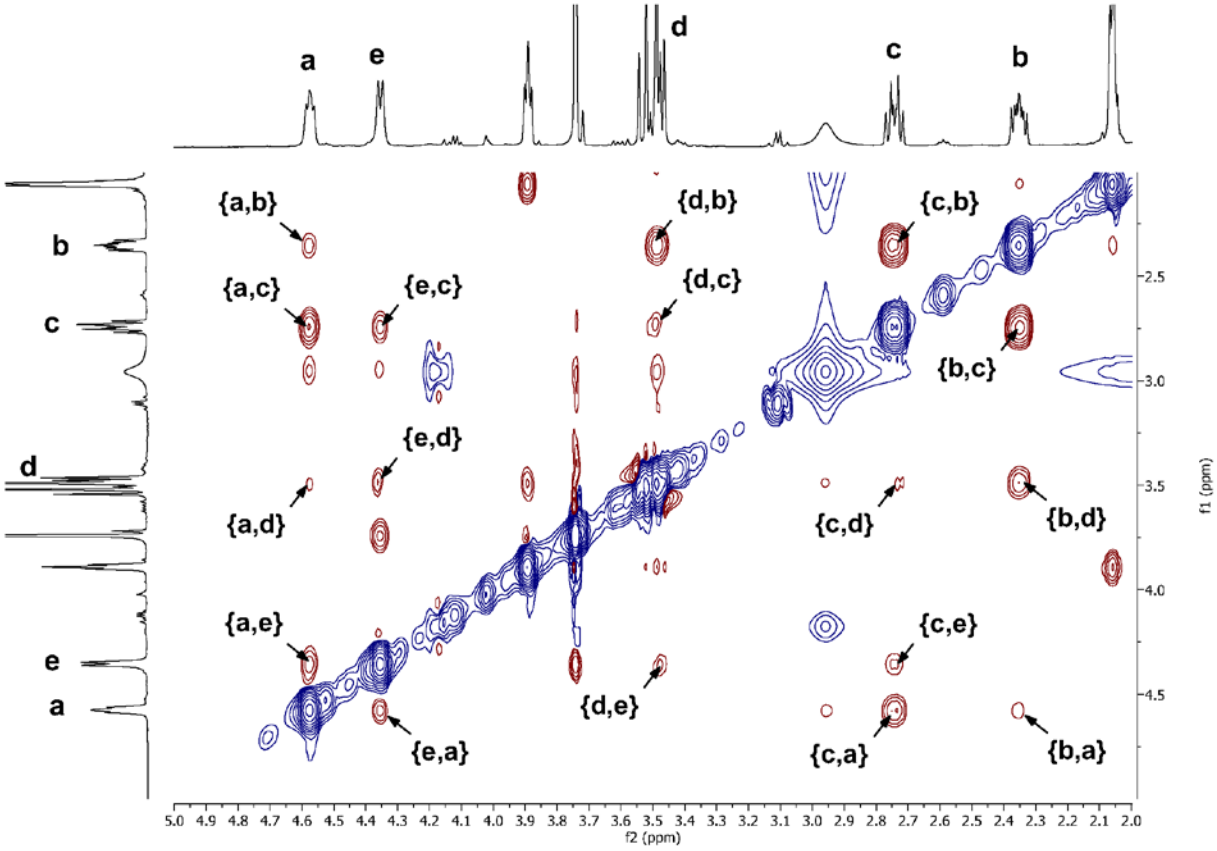


Relevant portion of the 600 MHz 2D NOESY ^{1}H NMR spectra obtained for compound **4e** in $CDCl_3$ showing interactions between **a-b, a-c, a-d, a-e, c-b, c-d, c-e, b-d, b-e** and **d-e** in the pyrrolidine ring. The data were collected at ambient T with a 700 ms mixing time, scans per t1 increment = 16, t1 increments = 128 and 1.5 s relaxation time.

600 MHz 2D NOESY ^{1}H NMR, $CDCl_3$

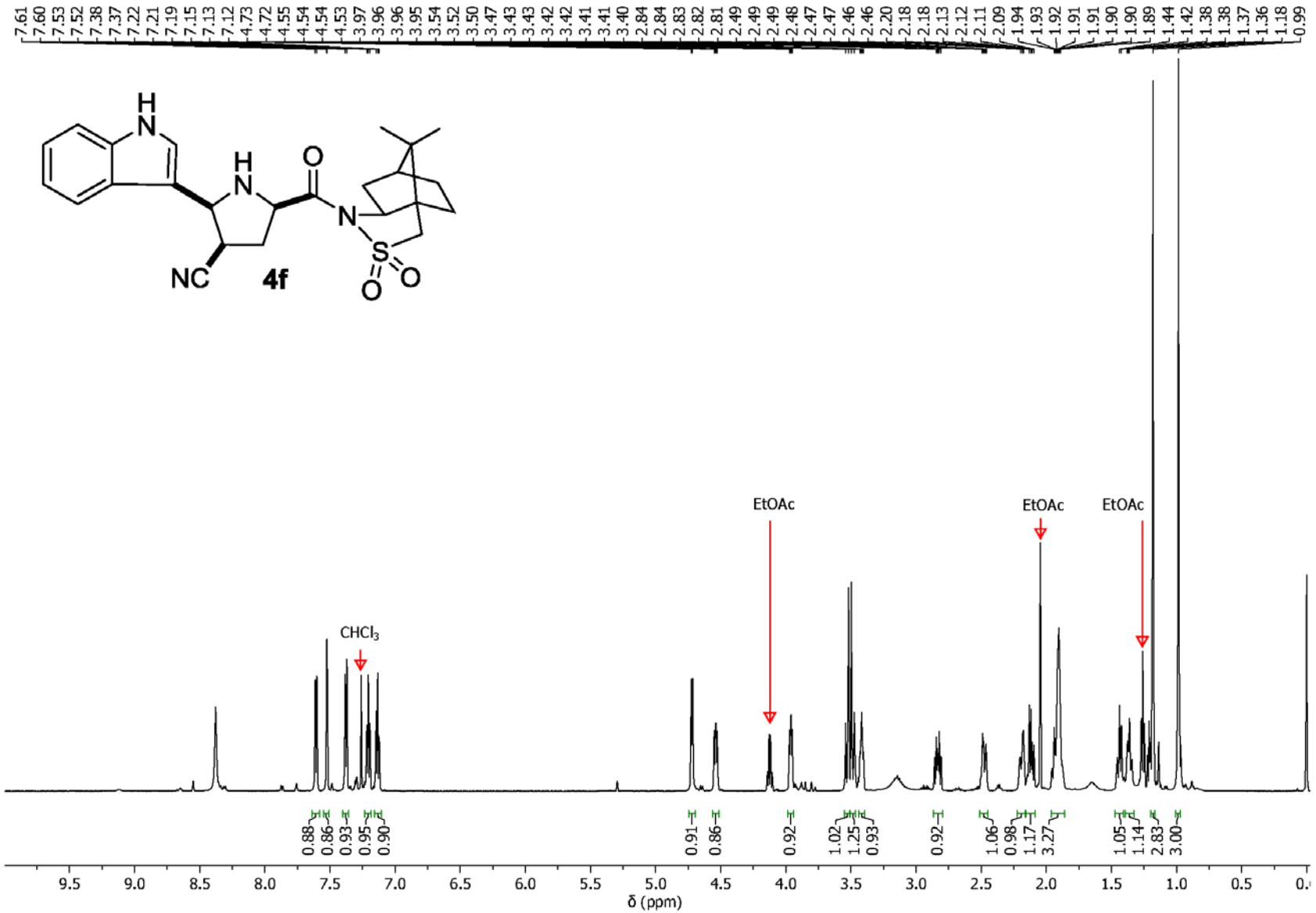


5e

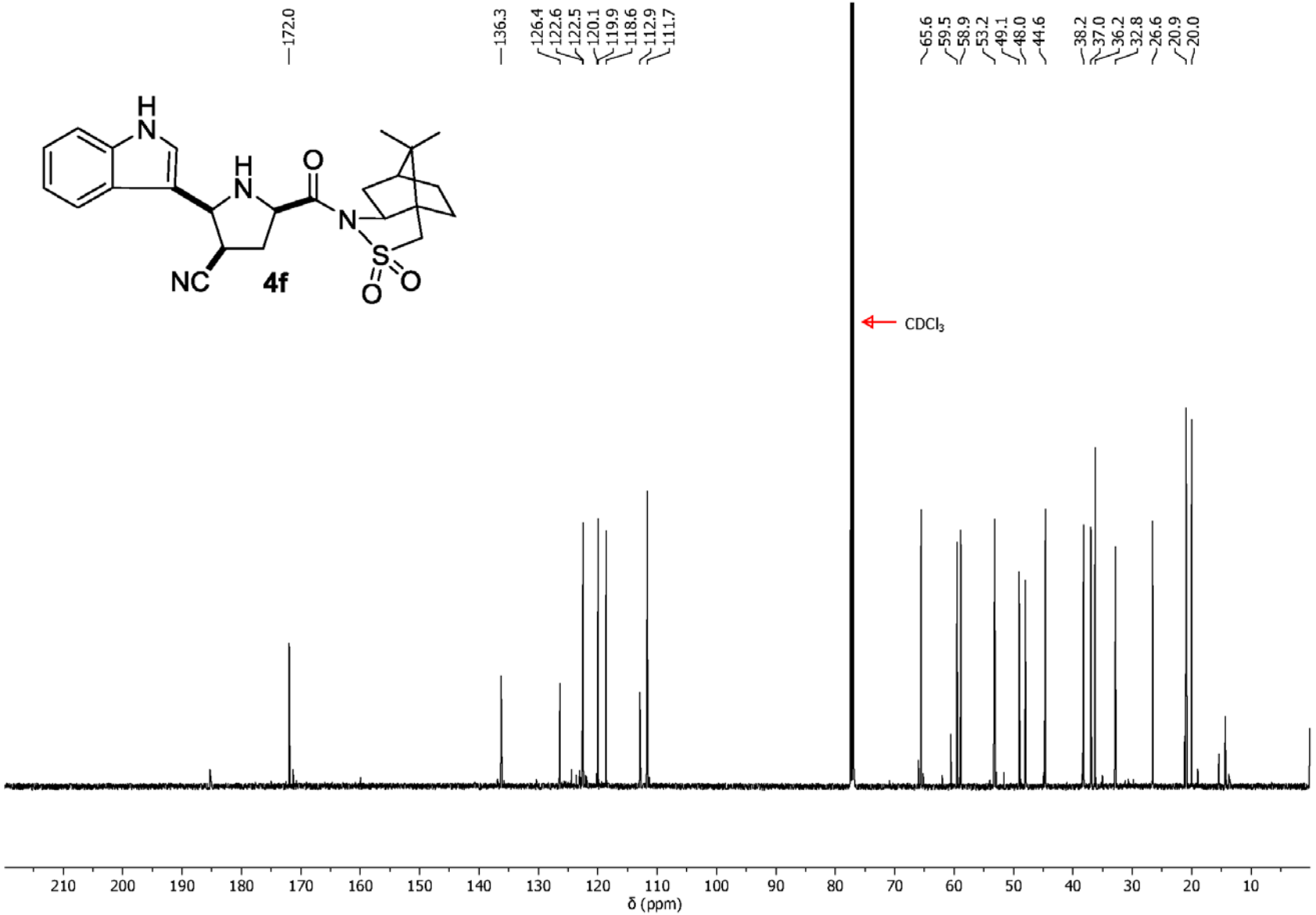


Relevant portion of the 600 MHz 2D NOESY ^{1}H NMR spectra obtained for compound **5e** in $CDCl_3$ showing interactions between **a-b, a-c, a-d, a-e, c-b, c-d, c-e, b-d** and **d-e** in the pyrrolidine ring. The data were collected at ambient T with a 700 ms mixing time, scans per t1 increment = 16, t1 increments = 128 and 1.5 s relaxation time.

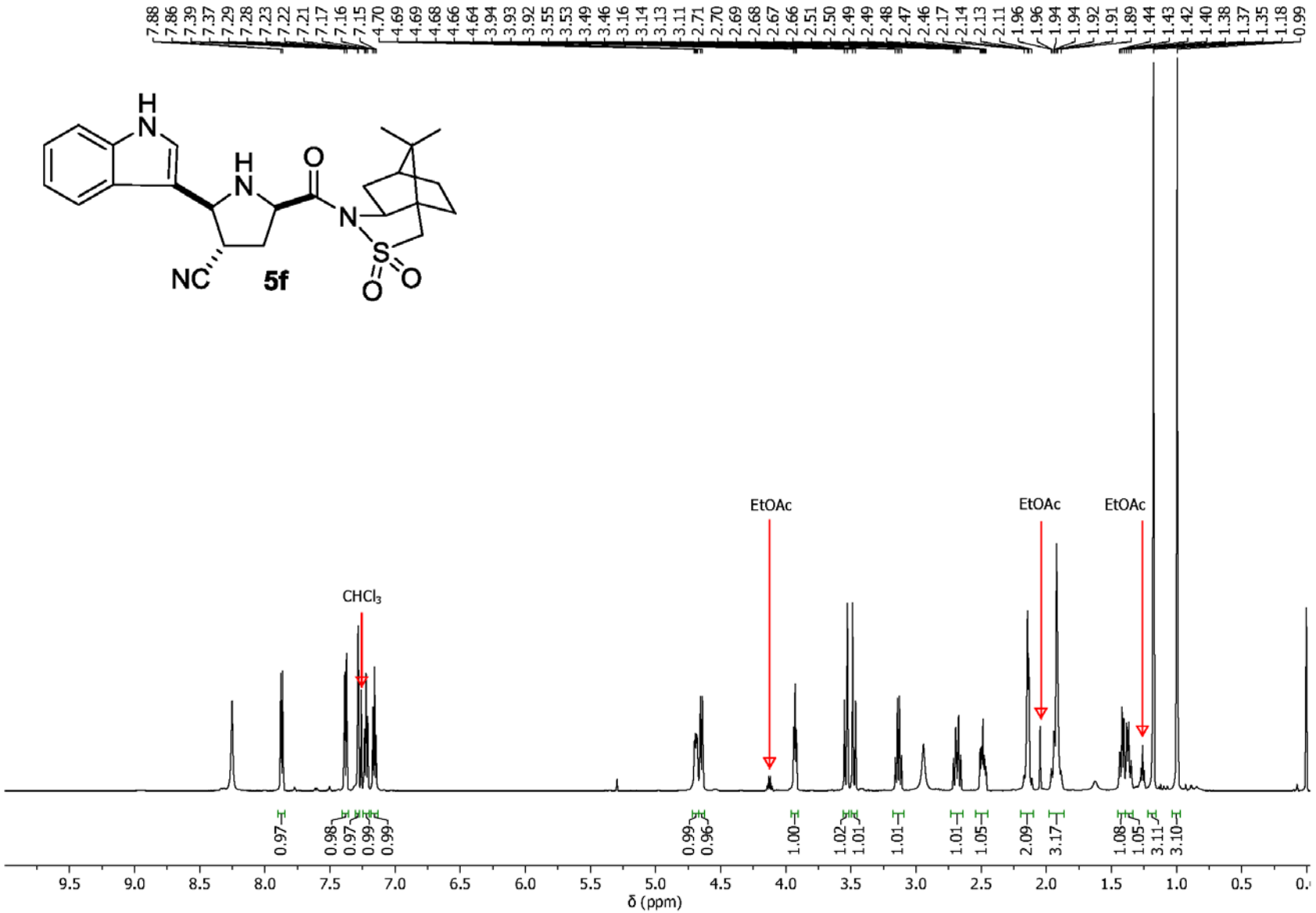
600 MHz ^{1}H NMR, $CDCl_3$



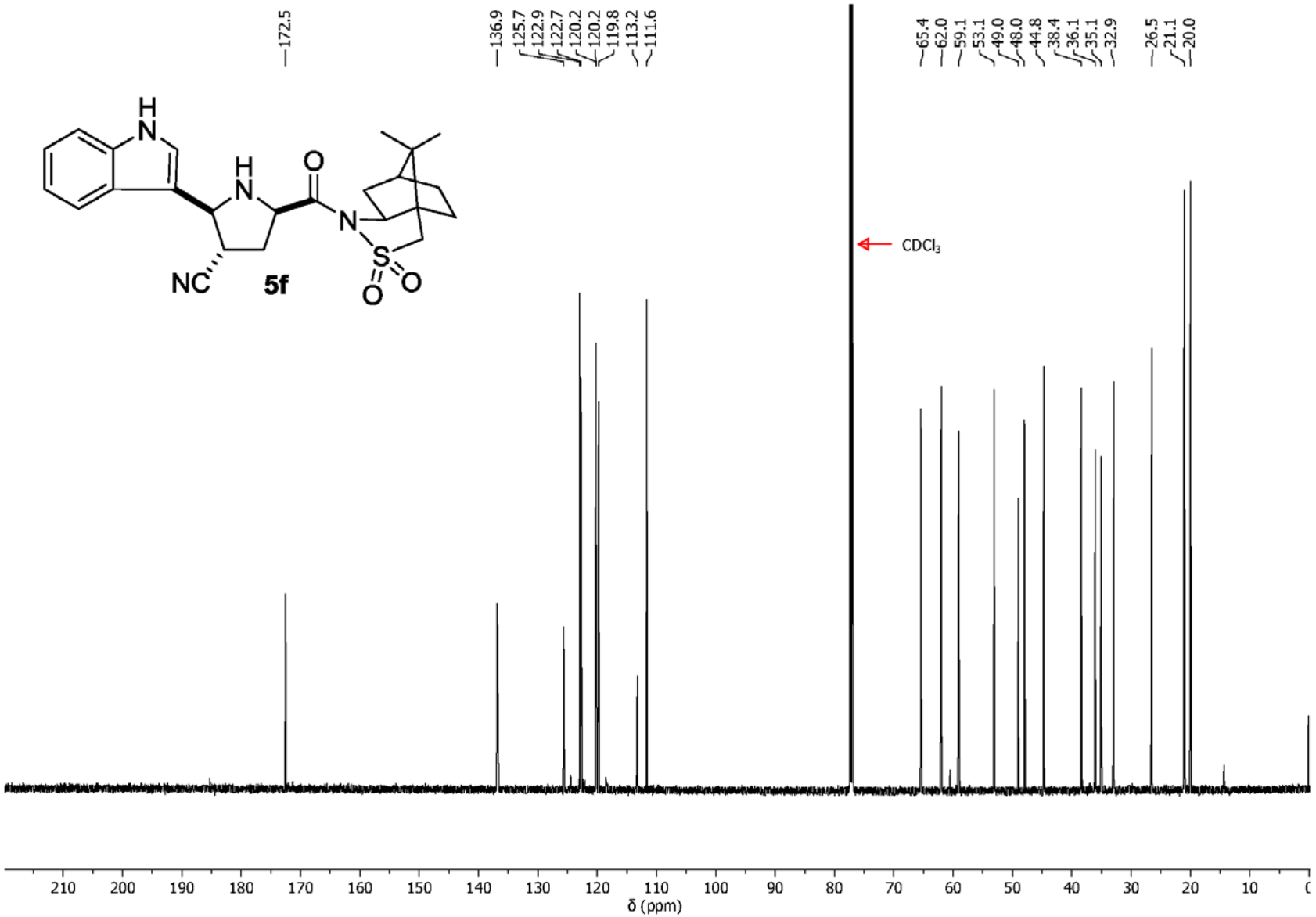
150.8 MHz ^{13}C NMR, $CDCl_3$



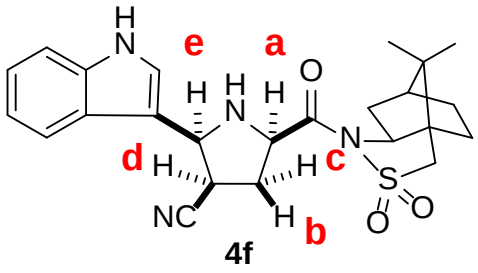
600 MHz ^{1}H NMR, $CDCl_3$



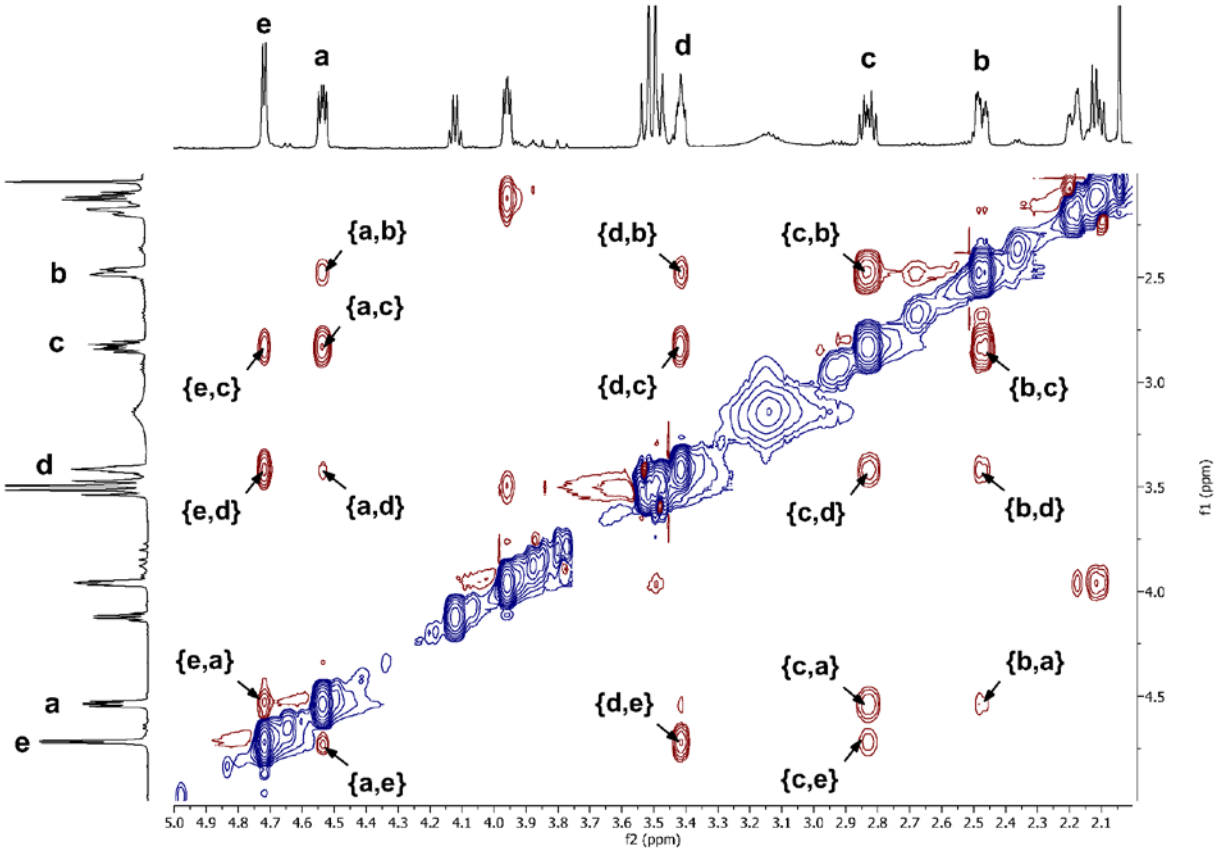
150.8 MHz ^{13}C NMR, $CDCl_3$



600 MHz 2D NOESY ^{1}H NMR, $CDCl_3$

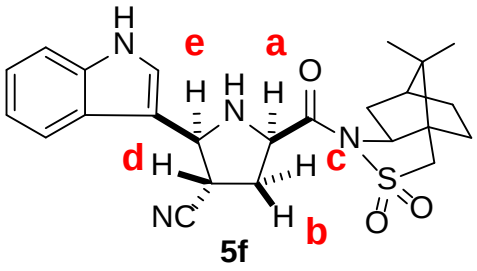


4f

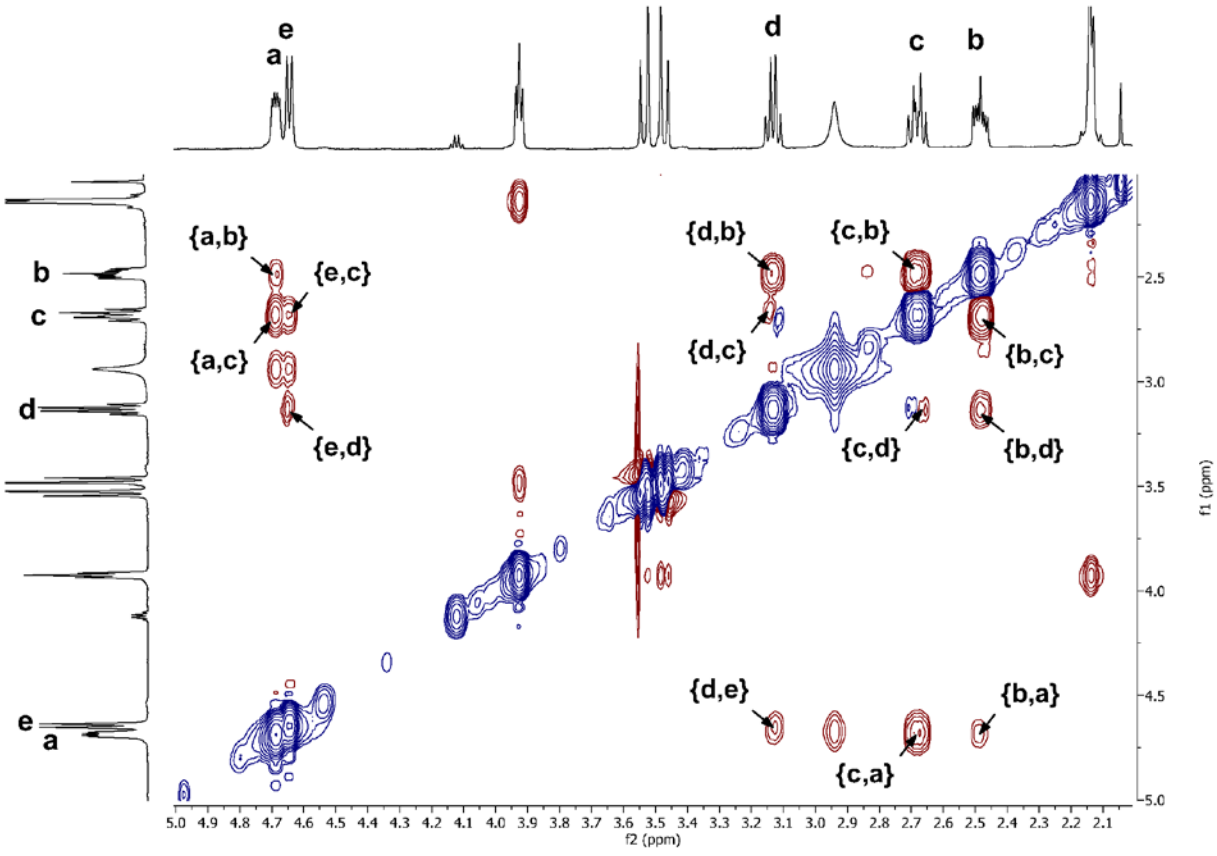


Relevant portion of the 600 MHz 2D NOESY ^{1}H NMR spectra obtained for compound **4f** in $CDCl_3$ showing interactions between **a-b, a-c, a-d, a-e, c-b, c-d, c-e, b-d** and **d-e** in the pyrrolidine ring. The data were collected at ambient T with a 700 ms mixing time, scans per t1 increment = 16, t1 increments = 128 and 1.5 s relaxation time.

600 MHz 2D NOESY ^{1}H NMR, $CDCl_3$

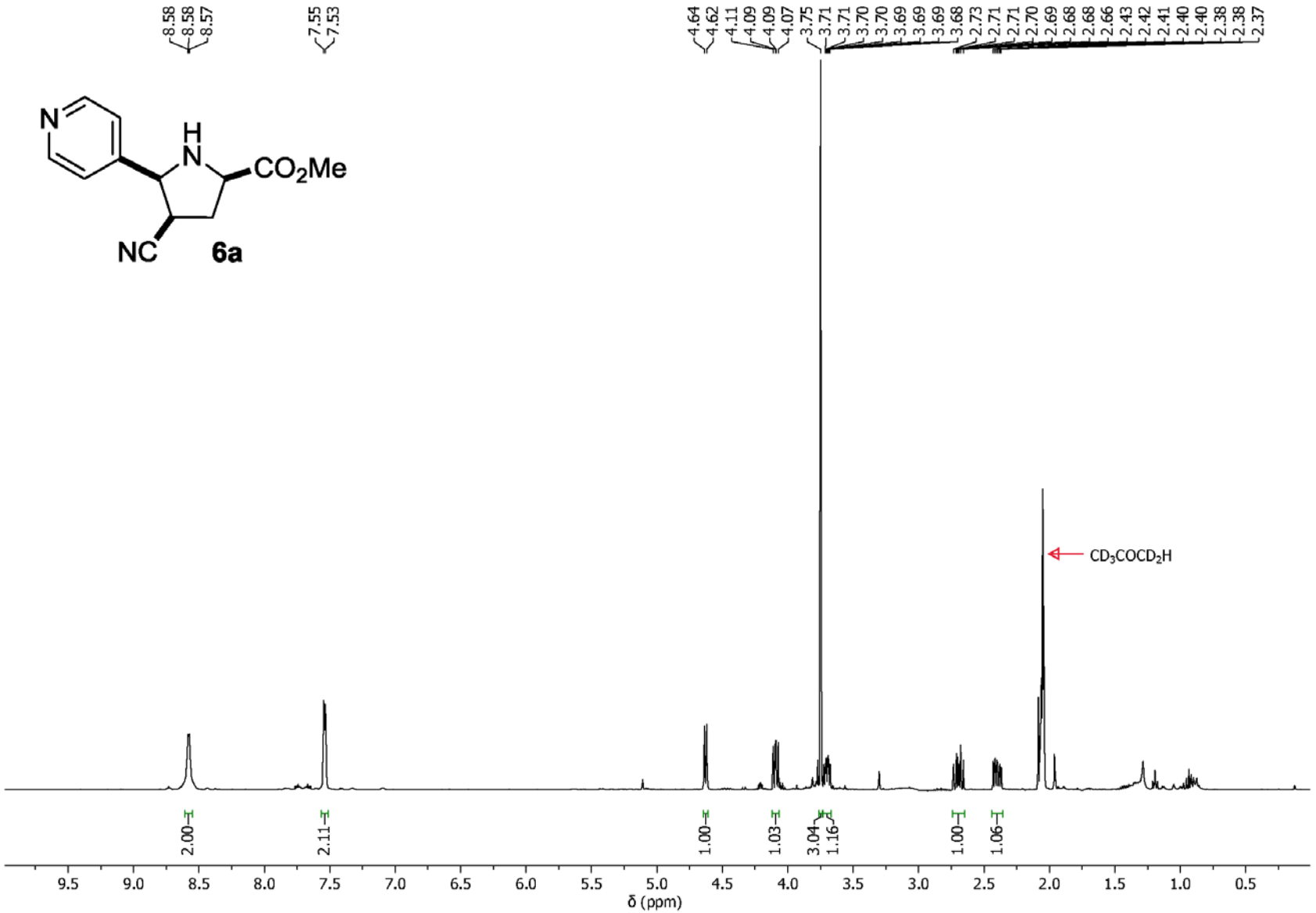


5f

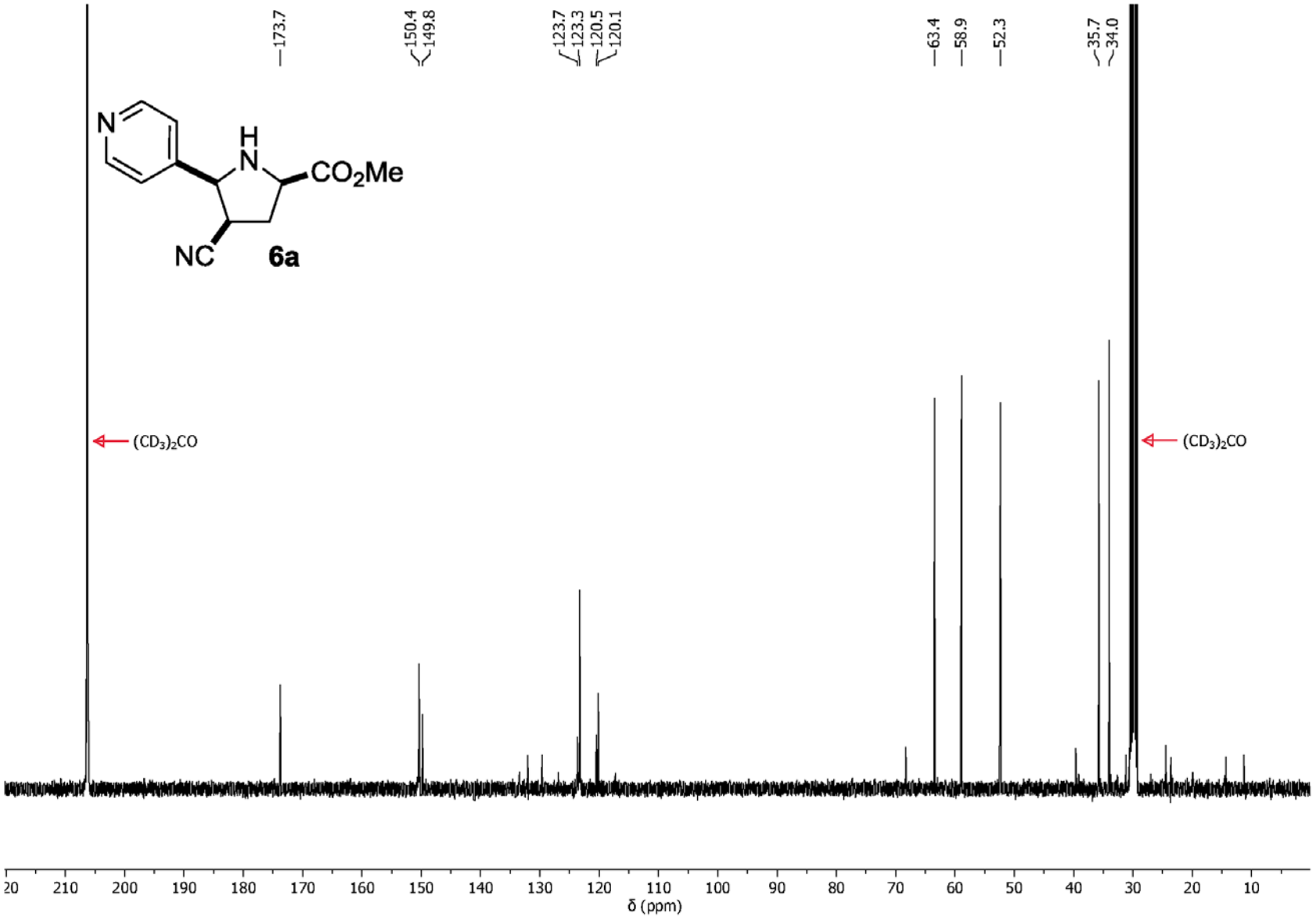


Relevant portion of the 600 MHz 2D NOESY ^{1}H NMR spectra obtained for compound **5f** in $CDCl_3$ showing interactions between **a-b, a-c, c-b, c-d, c-e, b-d, b-e** and **d-e** in the pyrrolidine ring. The data were collected at ambient T with a 700 ms mixing time, scans per t1 increment = 16, t1 increments = 128 and 1.5 s relaxation time.

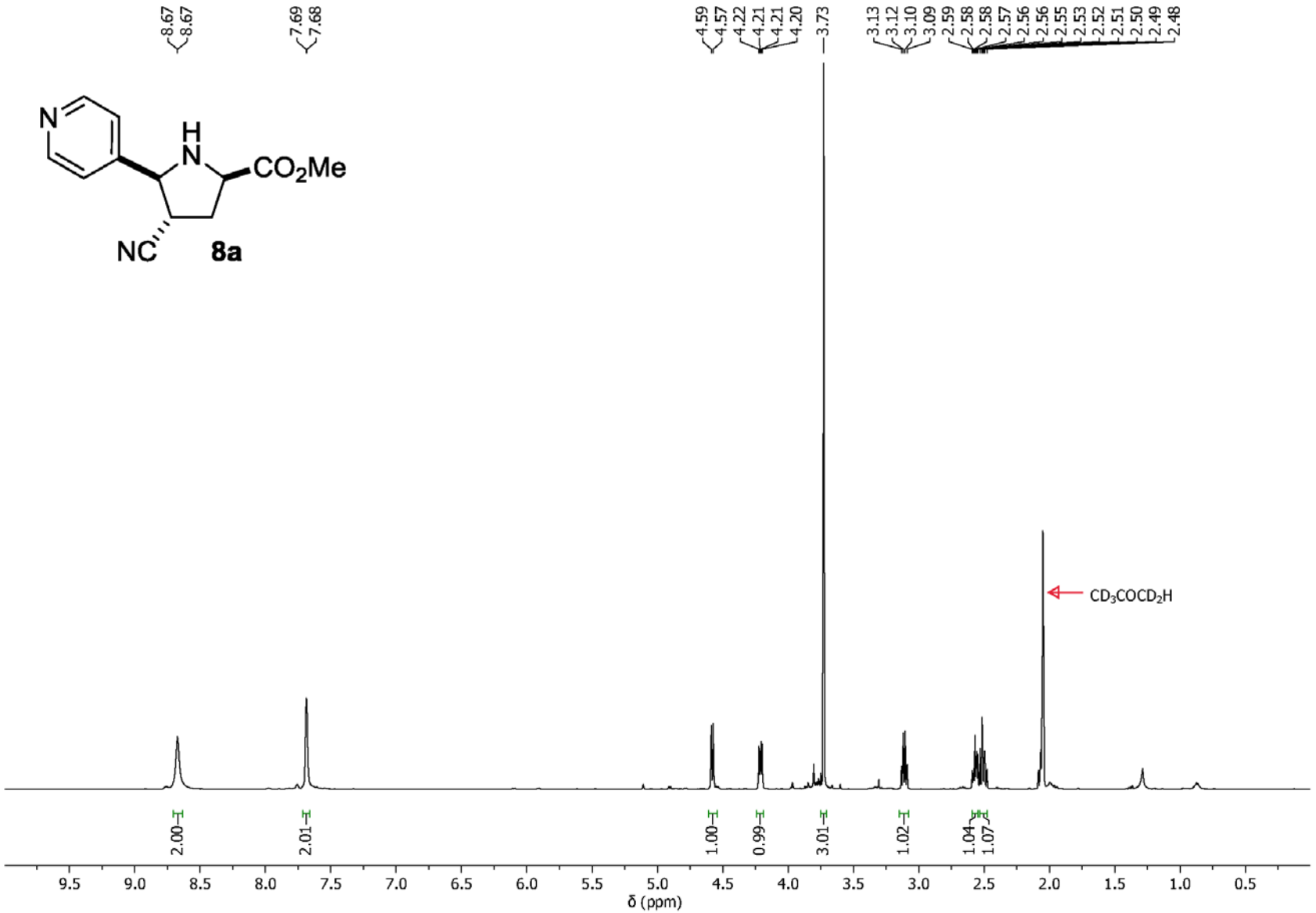
400 MHz ^{1}H NMR, $(CD_3)_2CO$



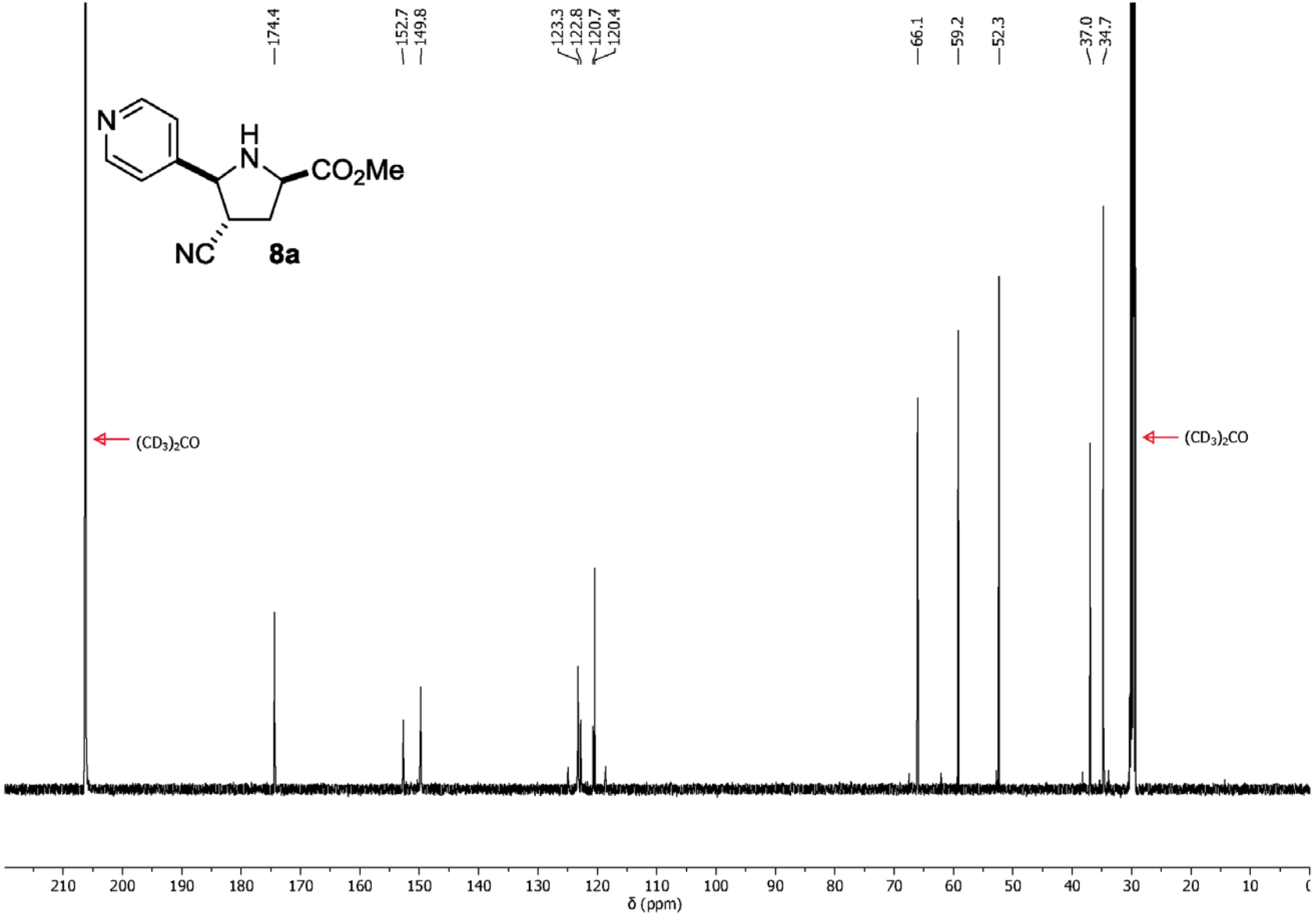
100.5 MHz ^{13}C NMR, $(CD_3)_2CO$



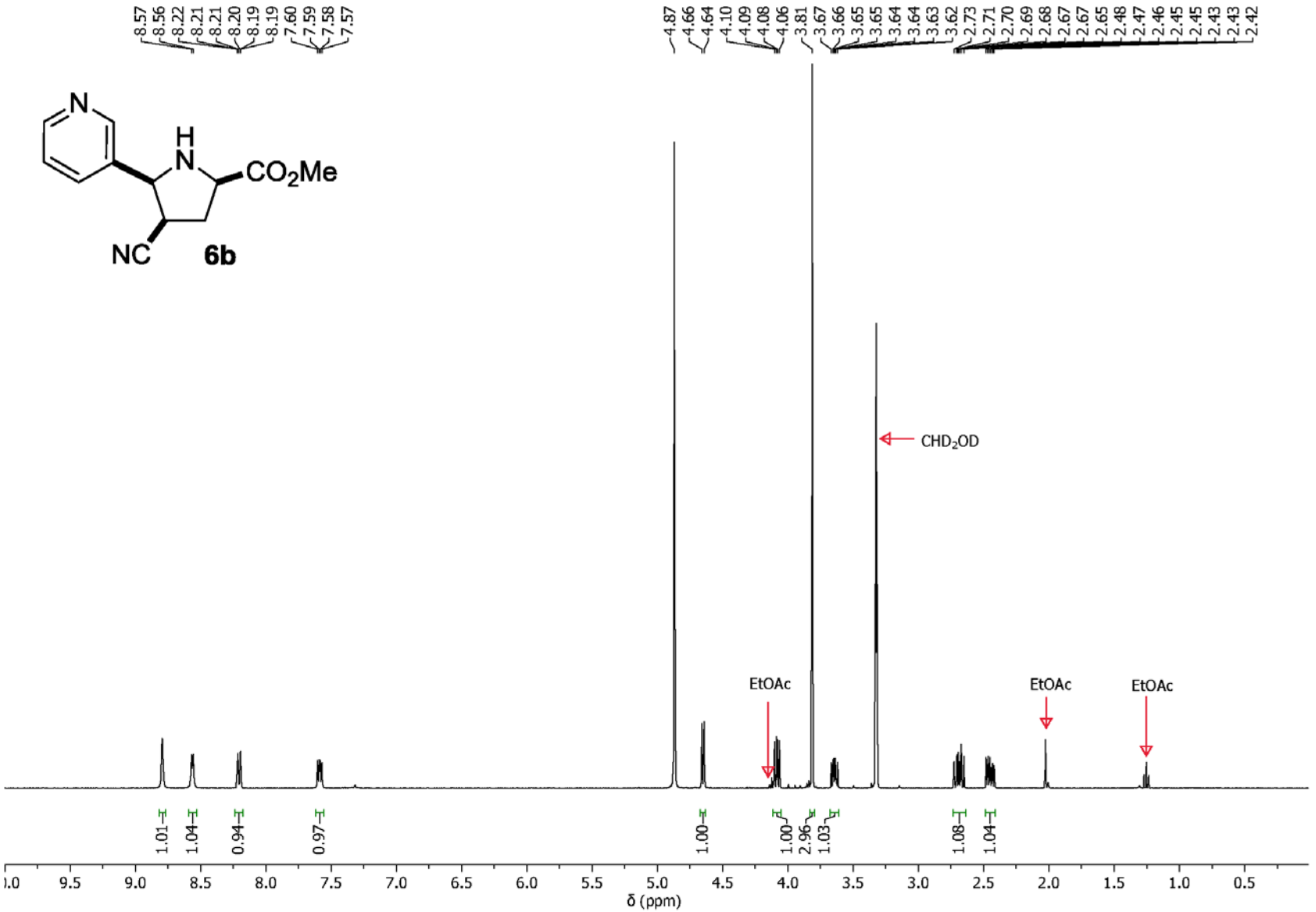
600 MHz ^{1}H NMR, $(CD_3)_2CO$



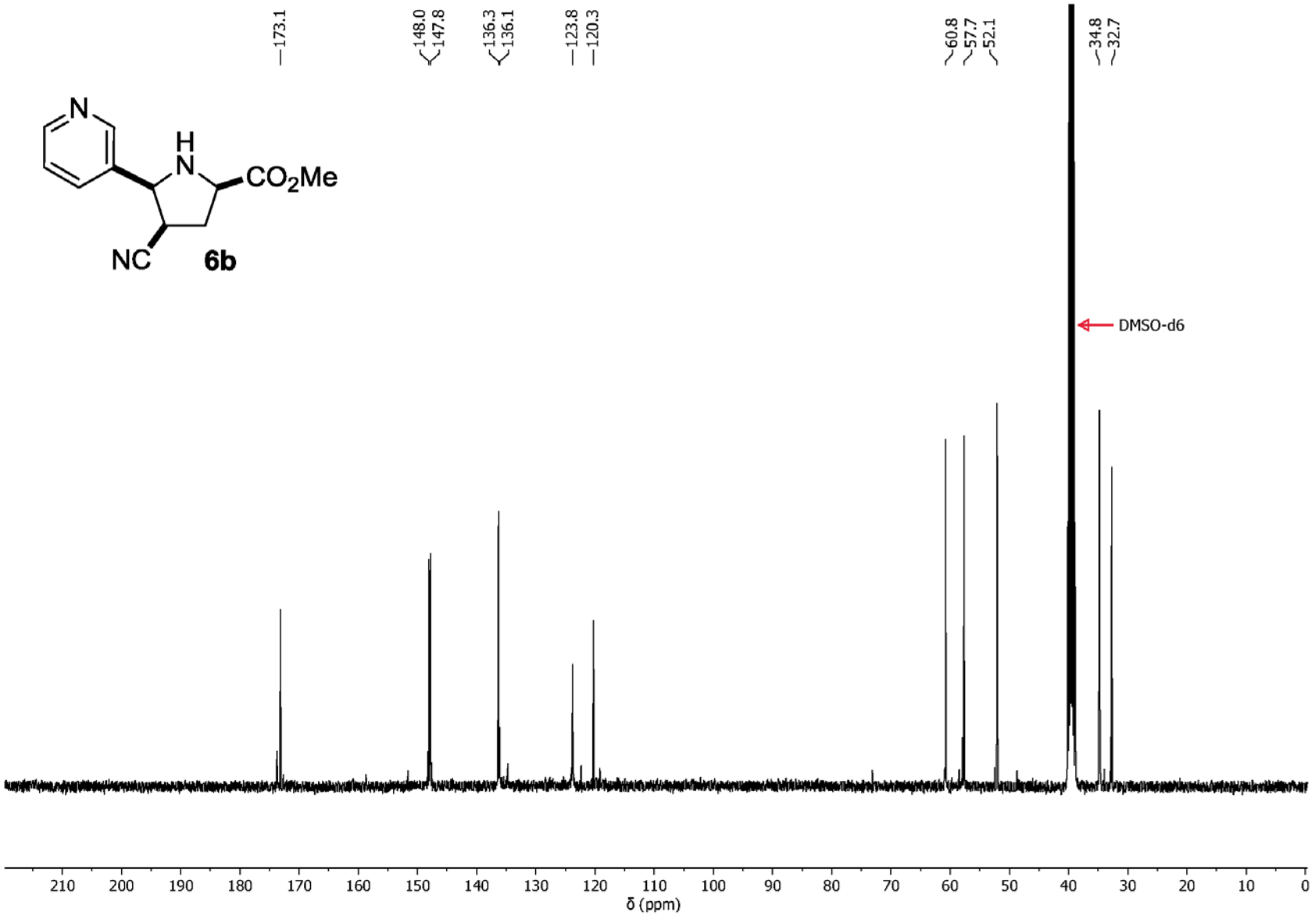
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



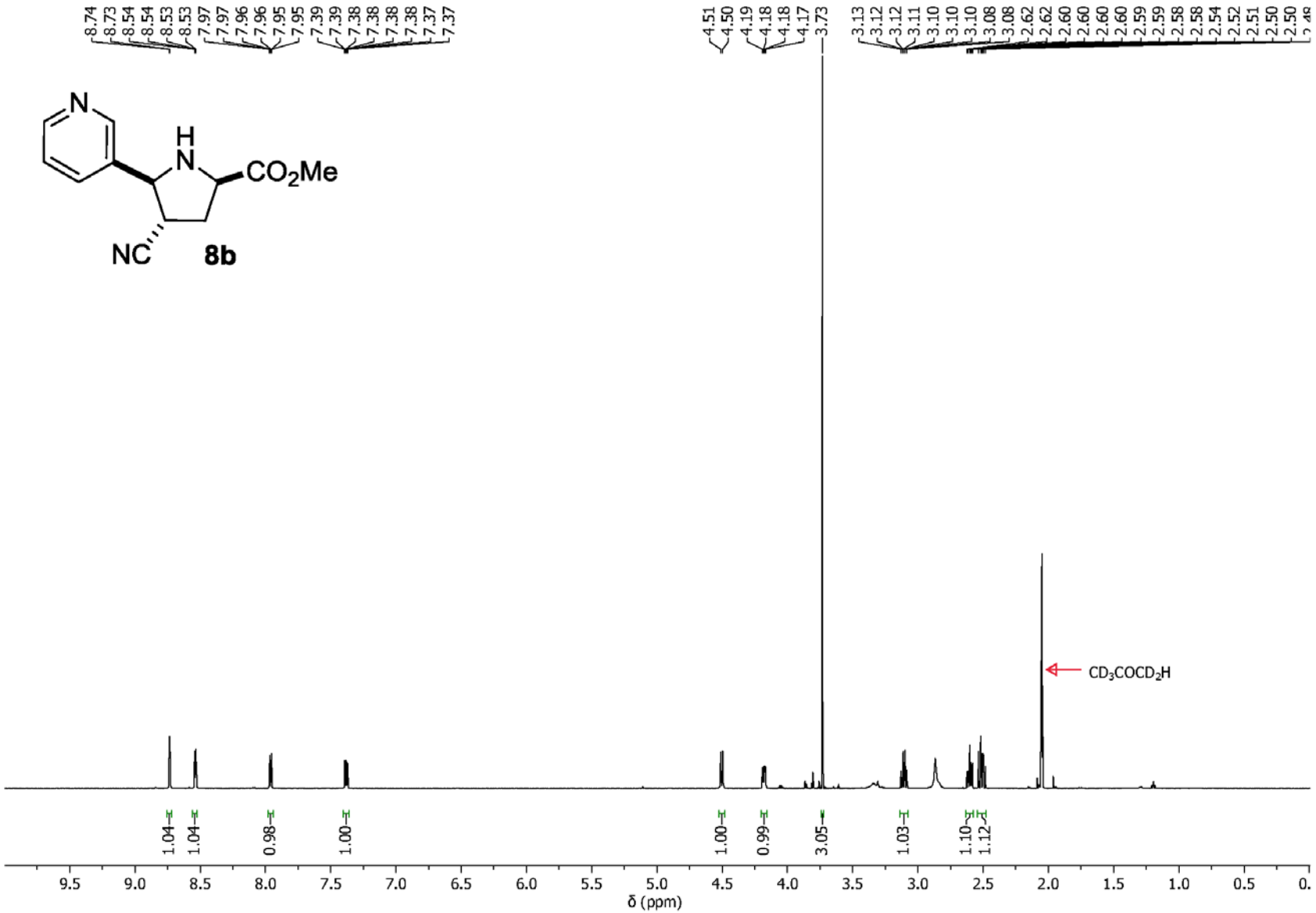
400 MHz ^{1}H NMR, CD_3OD



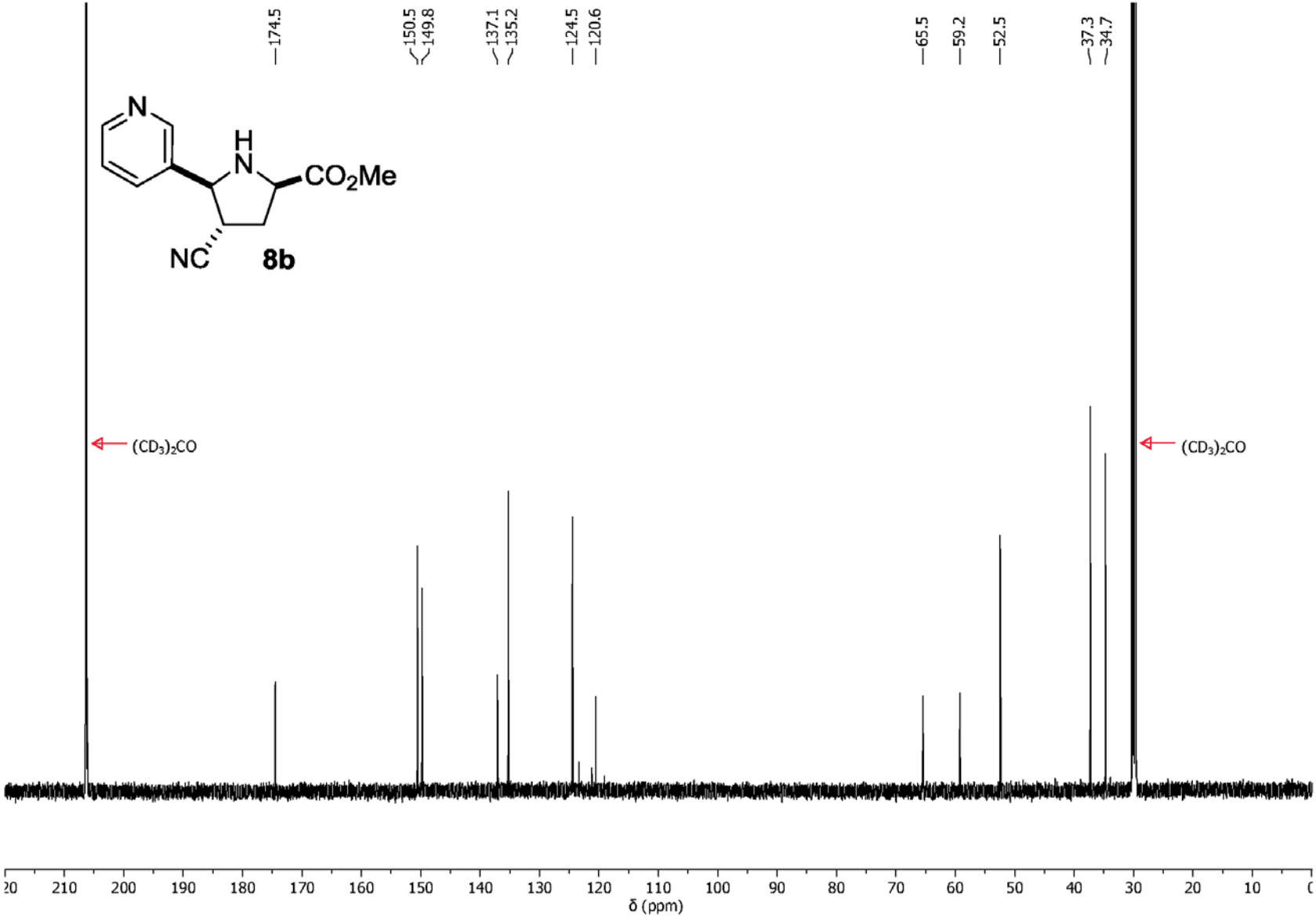
100.5 MHz ^{13}C NMR, DMSO-d6



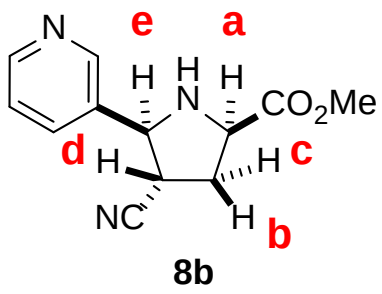
600 MHz ^{1}H NMR, $(CD_3)_2CO$



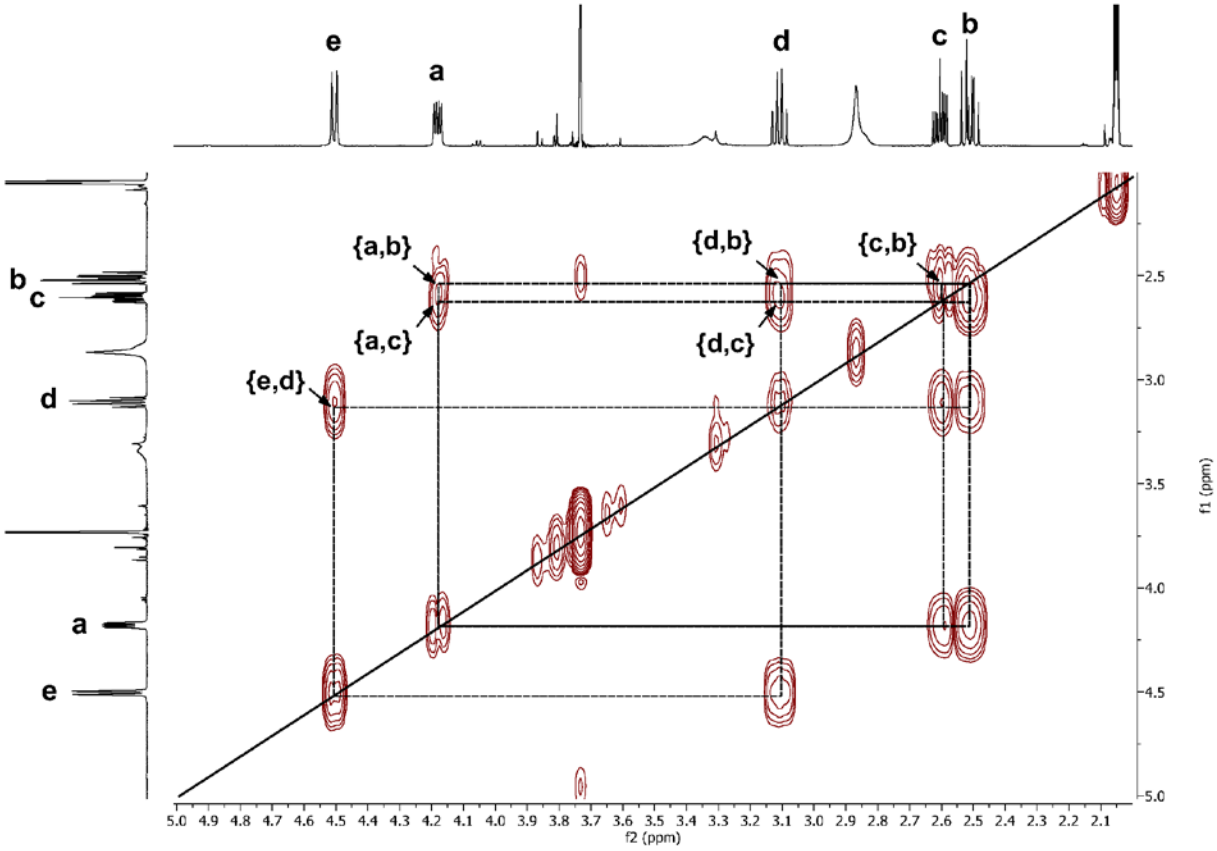
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



600 MHz gCOSY 1H NMR, $(CD_3)_2CO$

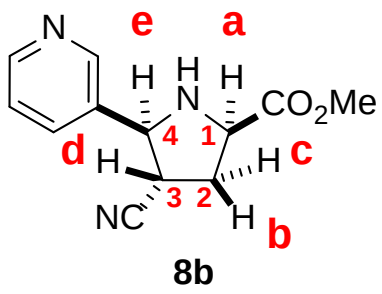


8b

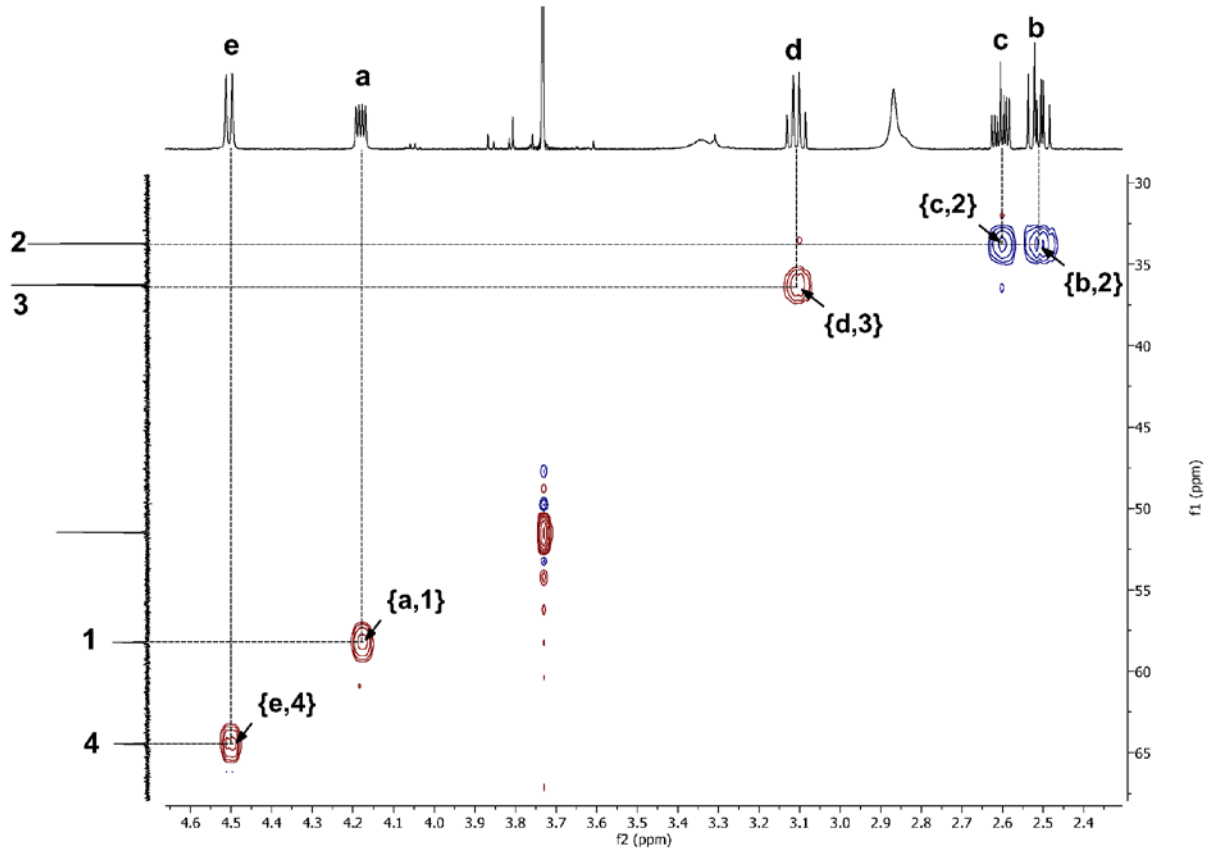


Relevant portion of the 600 MHz 2D gCOSY ^{1}H NMR spectra obtained for compound **8b** in $CDCl_3$ showing interactions between **a-b, a-c, e-d, d-b, d-c** and **c-b** in the pyrrolidine ring.

600 MHz HSQCAD NMR, $(CD_3)_2CO$

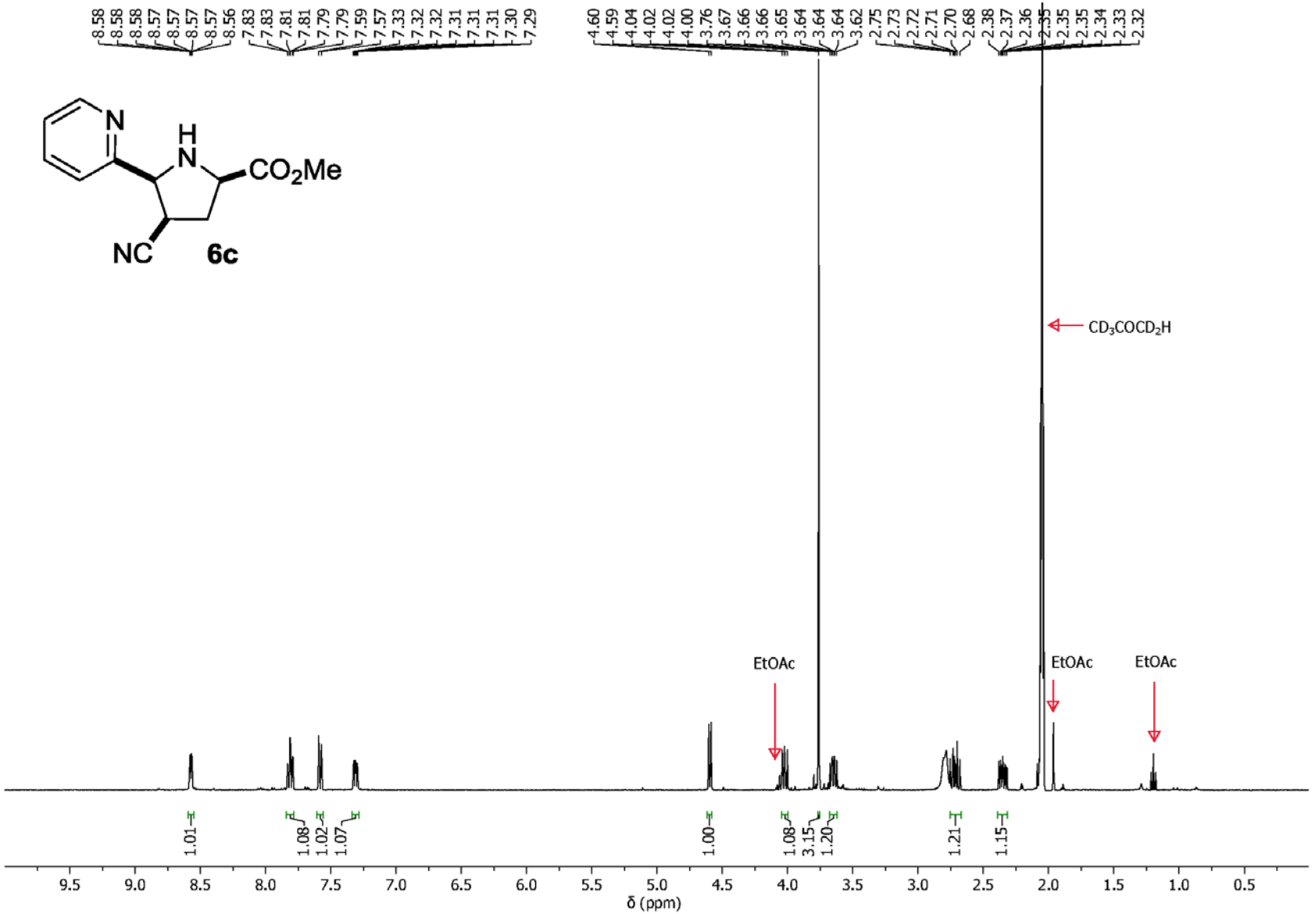


8b

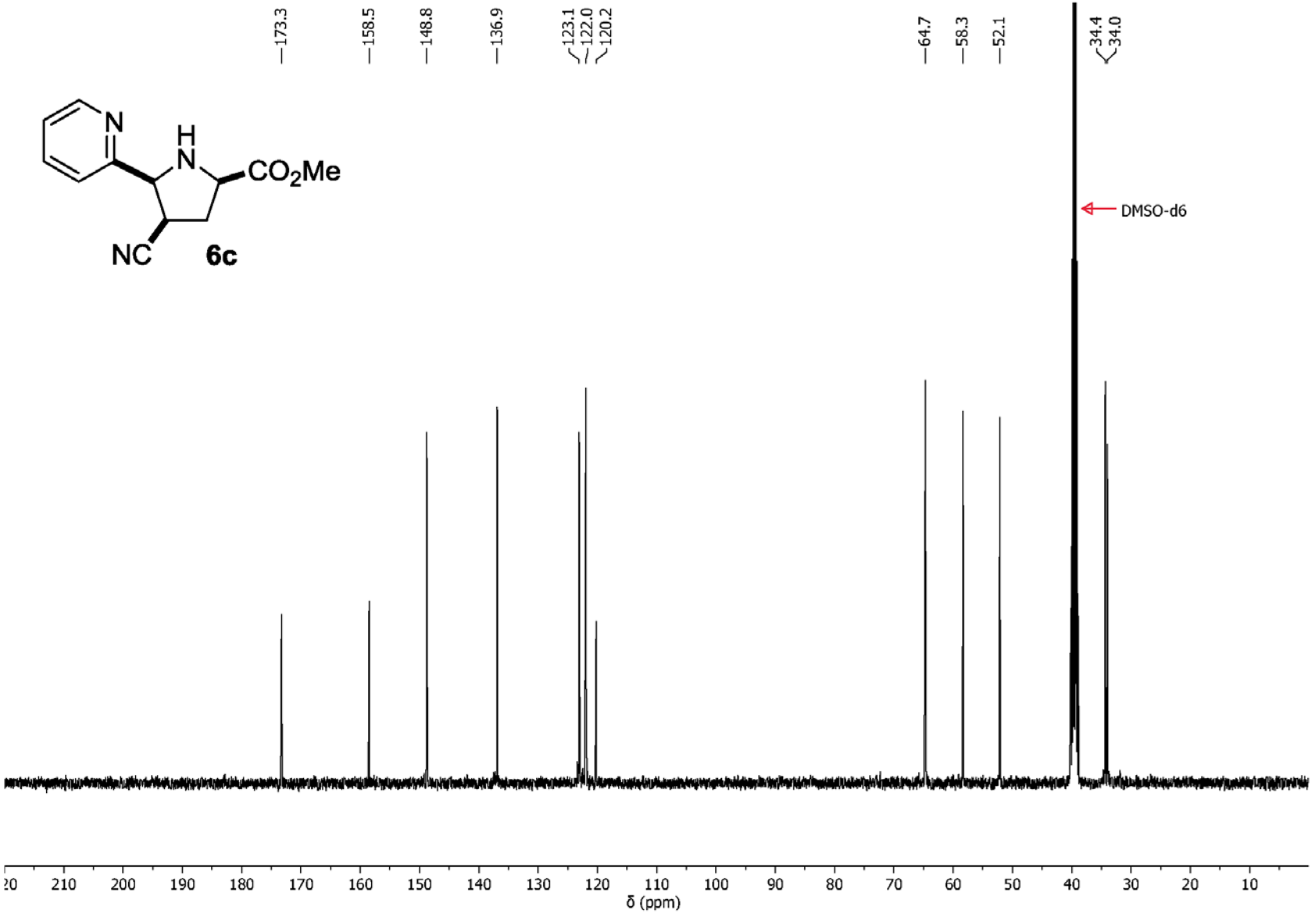


Relevant portion of the 600 MHz HSQCAD NMR spectra obtained for compound **8b** in $CDCl_3$ showing interactions between **a-1, e-4, d-3, c-2** and **b-2.** Blue color contours stand for -CH_2 group and red color contours stand for -CH and CH_3 groups.

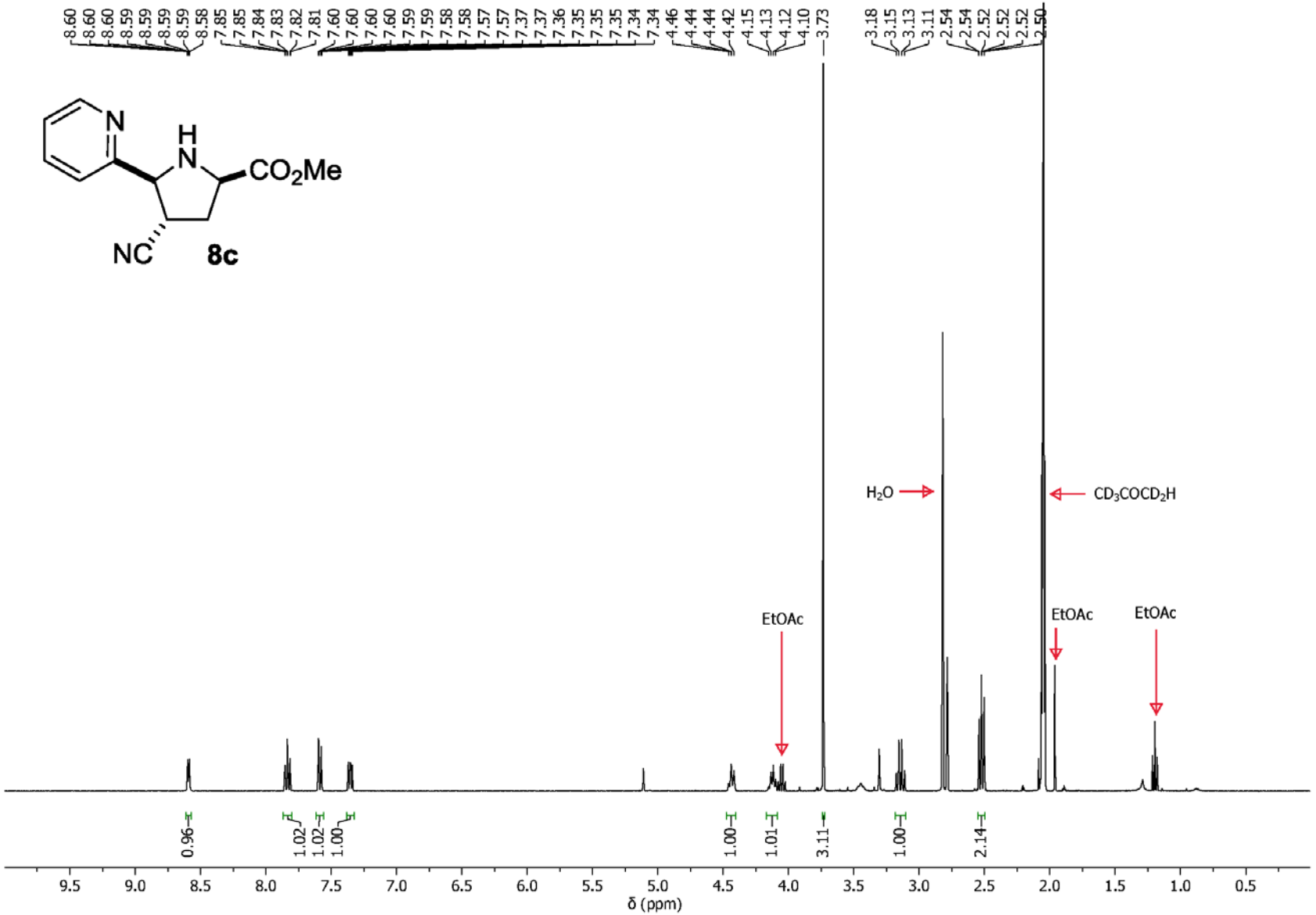
400 MHz ^{1}H NMR, $(CD_3)_2CO$



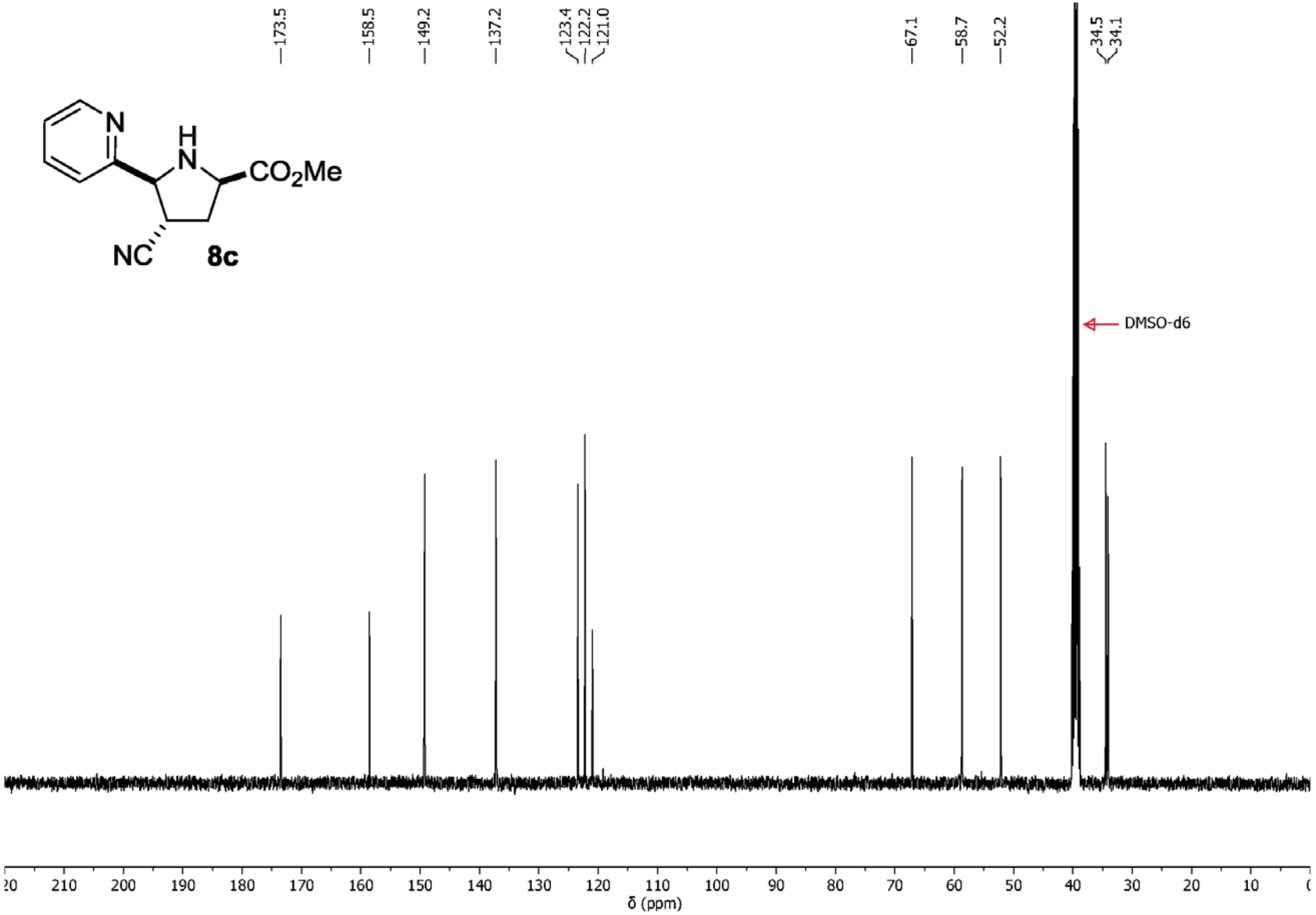
100.5 MHz ^{13}C NMR, DMSO-d6



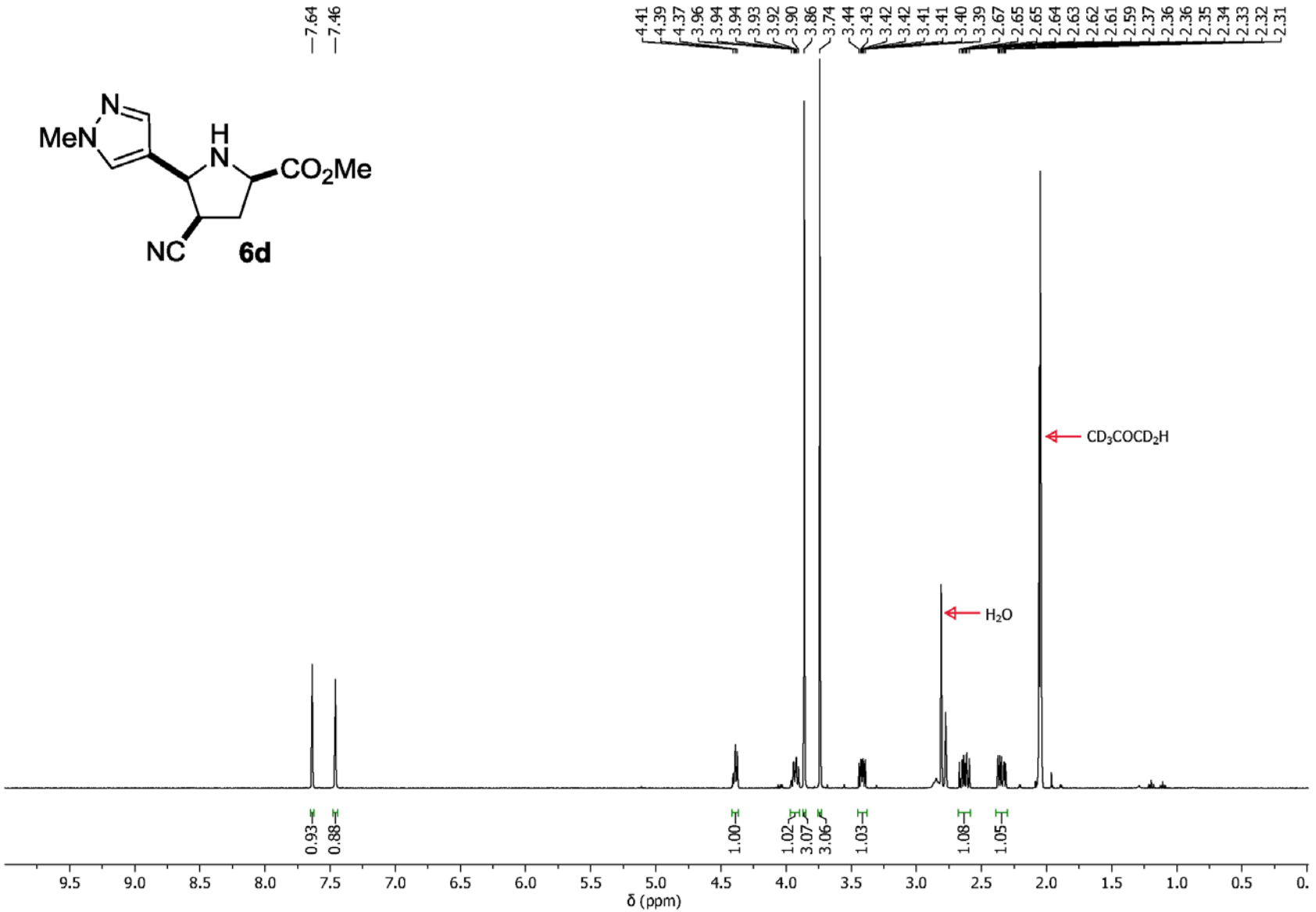
400 MHz ^{1}H NMR, $(CD_3)_2CO$



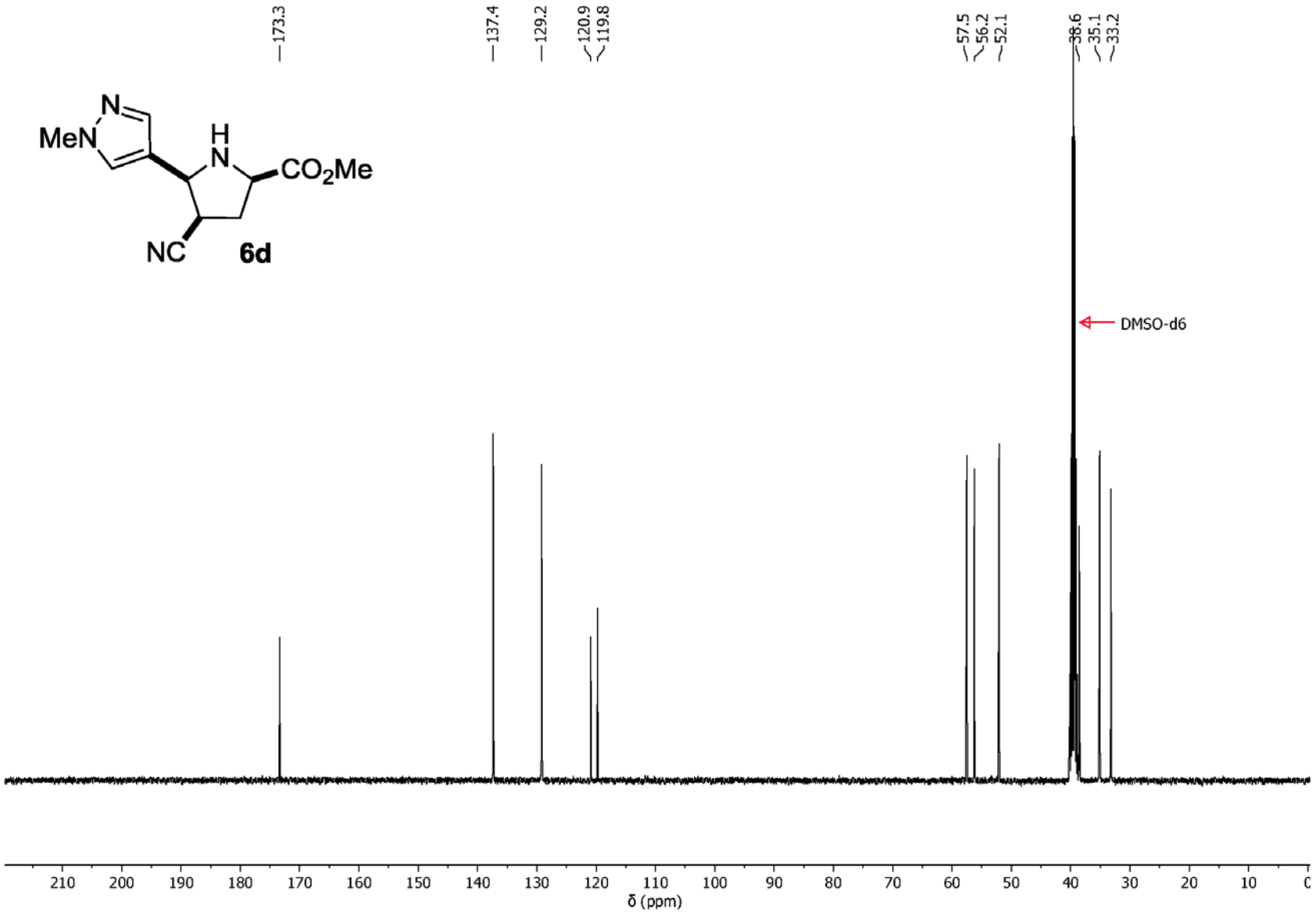
100.5 MHz ^{13}C NMR, DMSO-d6



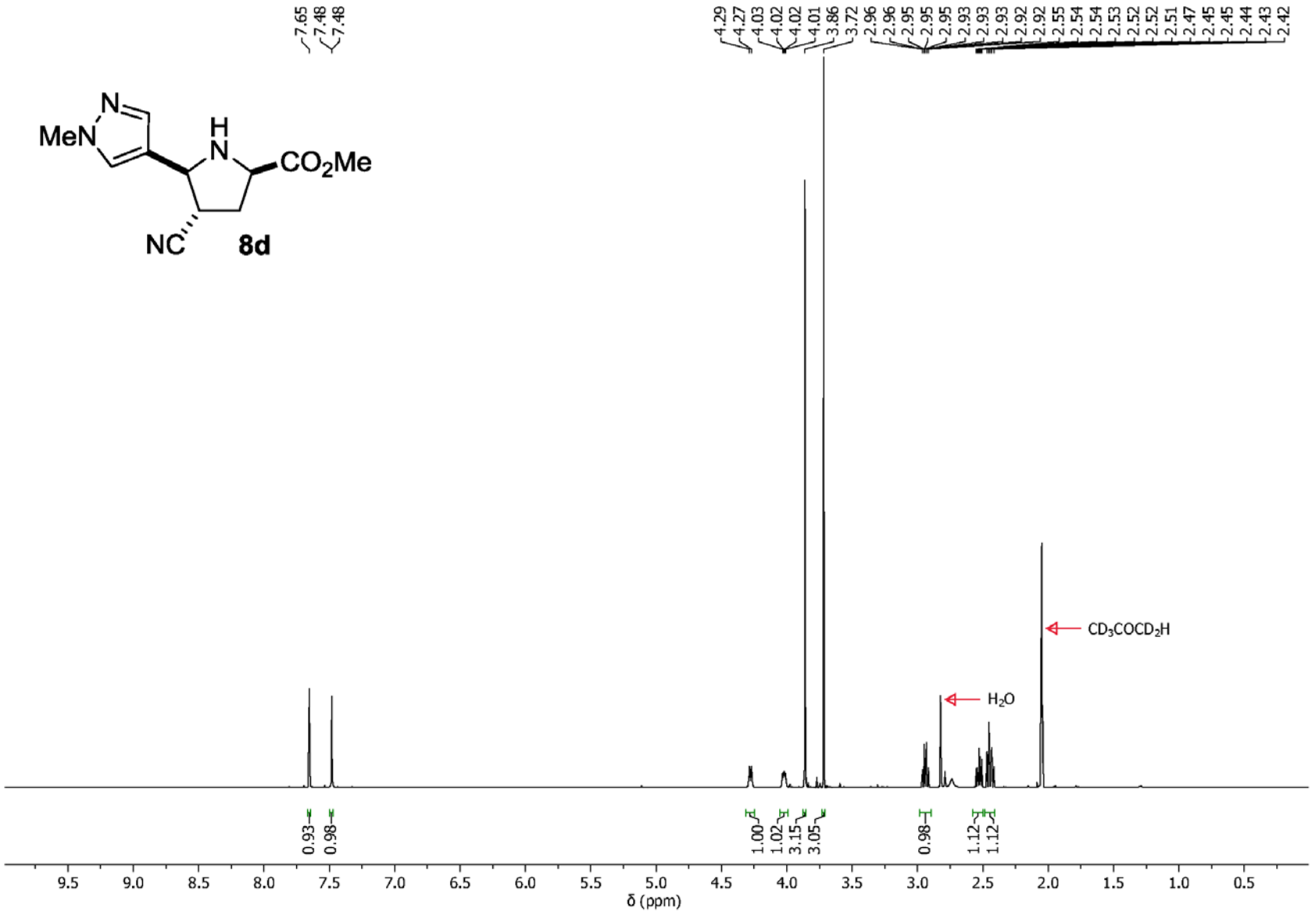
400 MHz ^{1}H NMR, $(CD_3)_2CO$



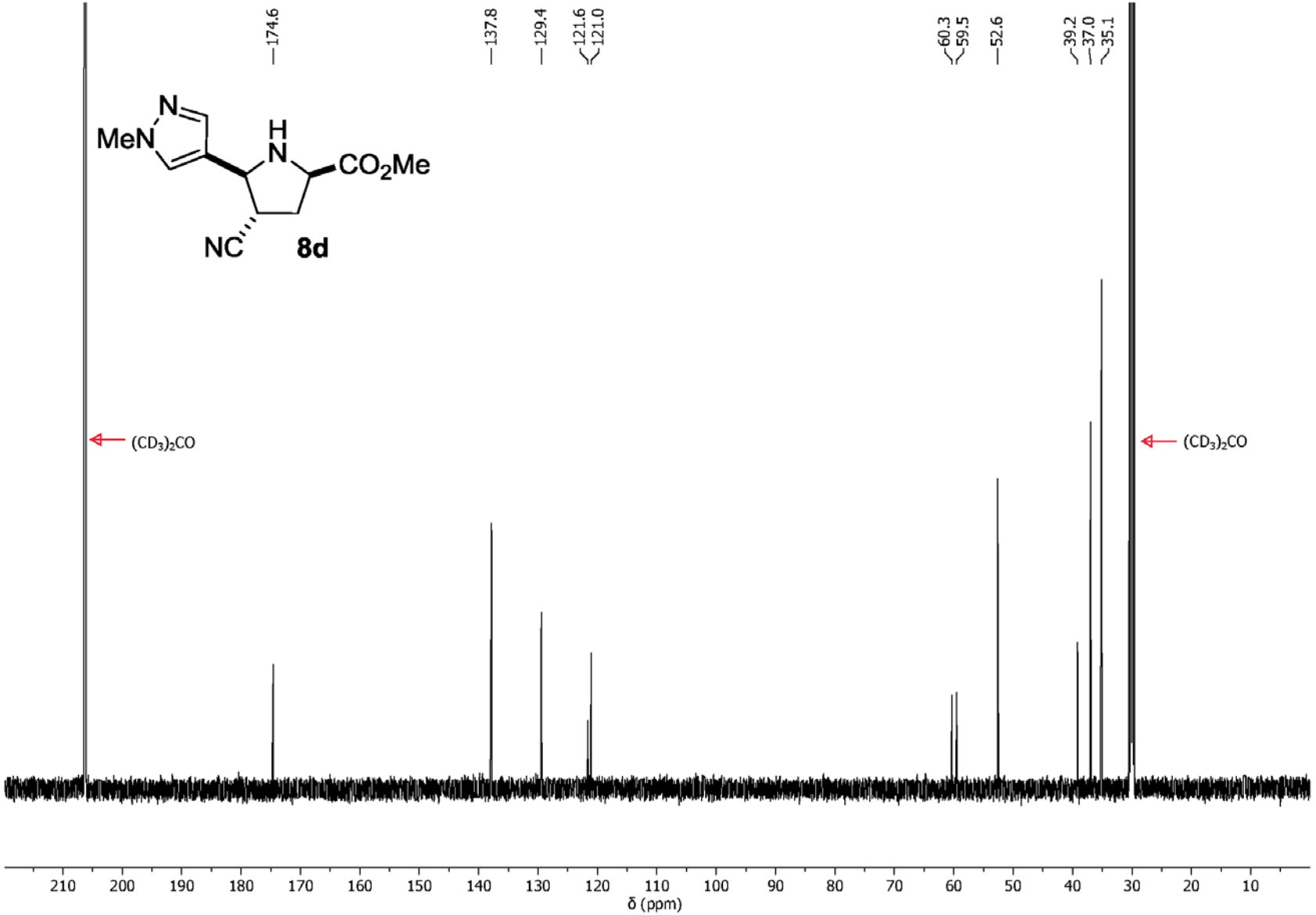
100.5 MHz ^{13}C NMR, DMSO-d6



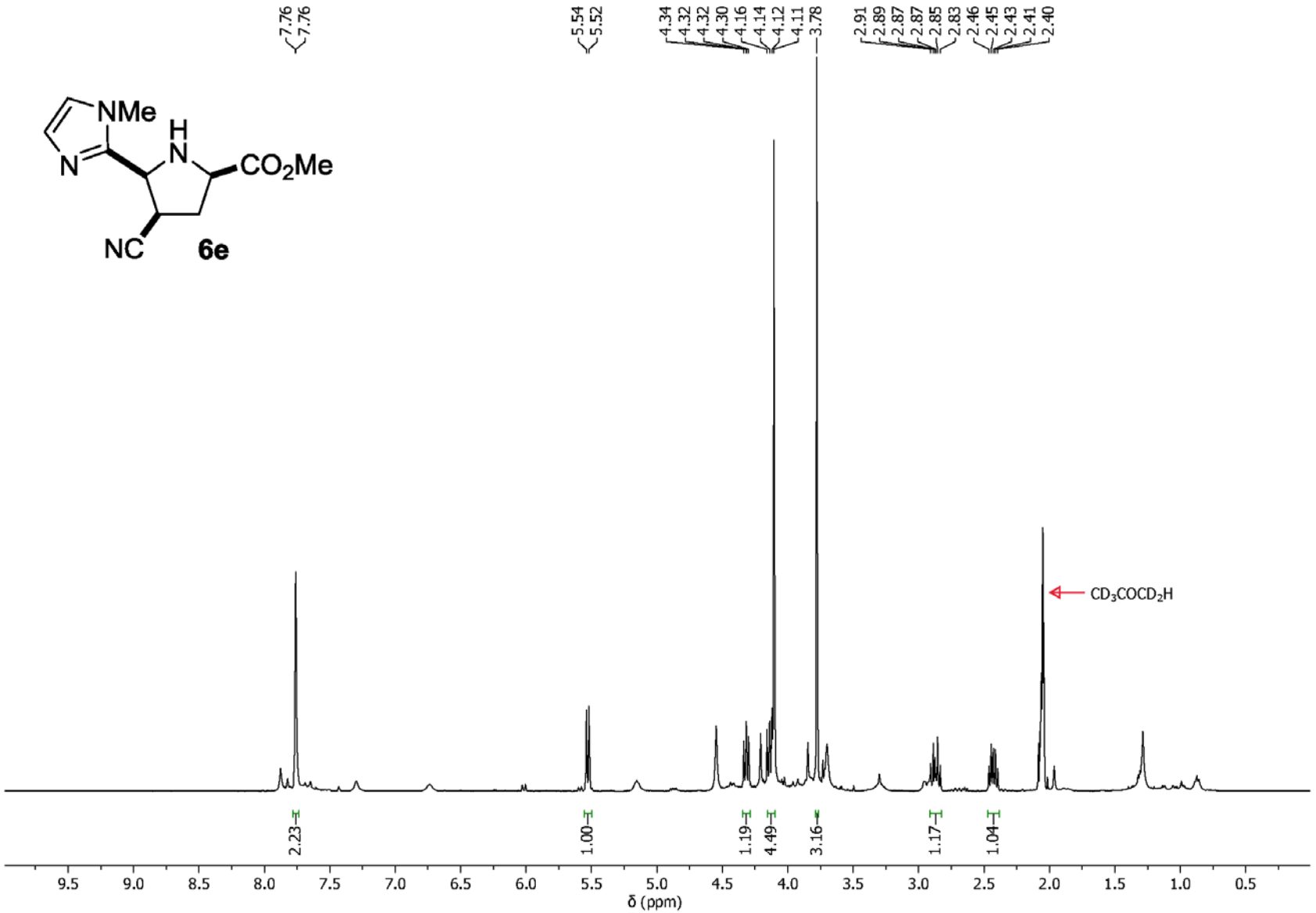
600 MHz ^{1}H NMR, $(CD_3)_2CO$



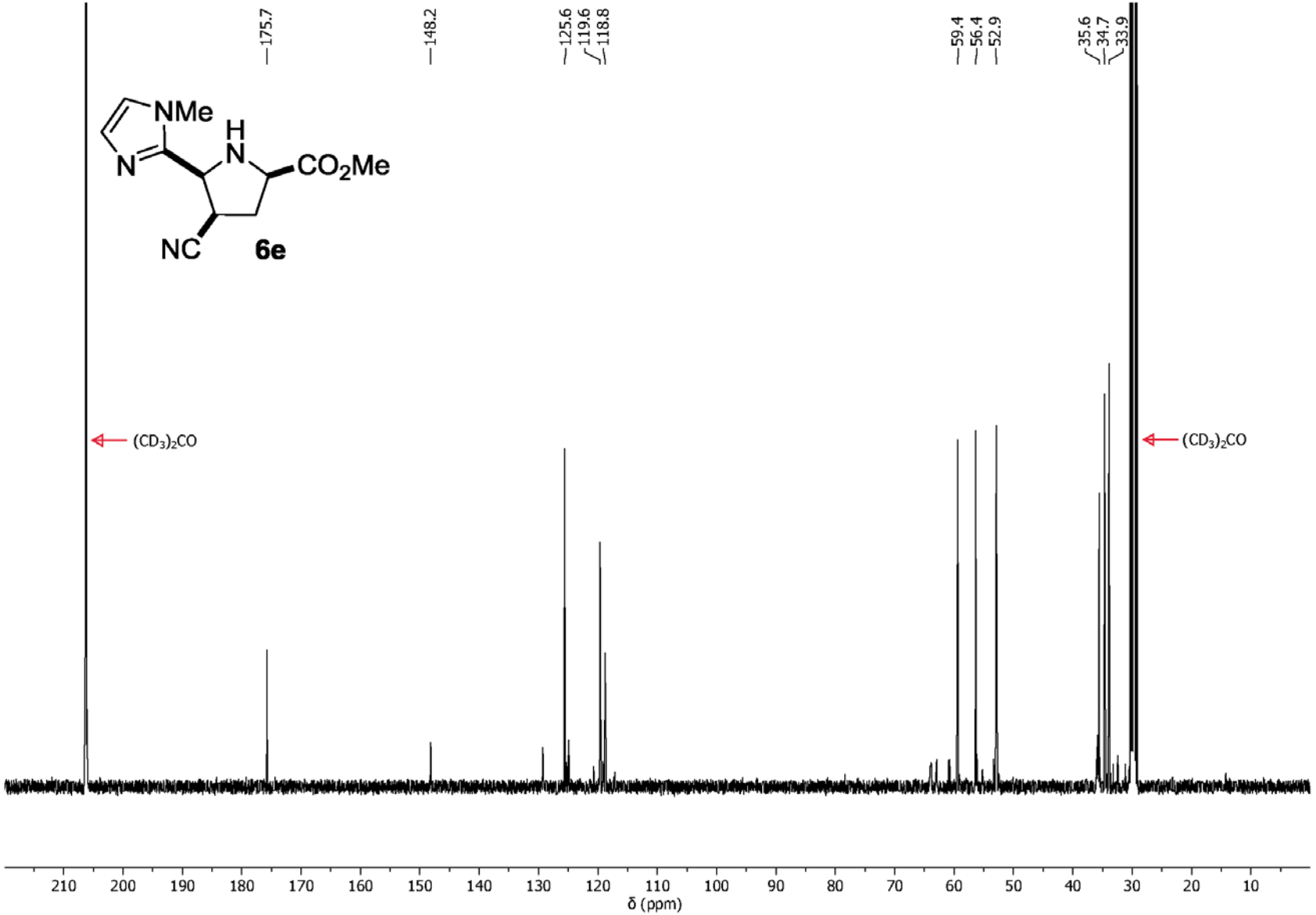
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



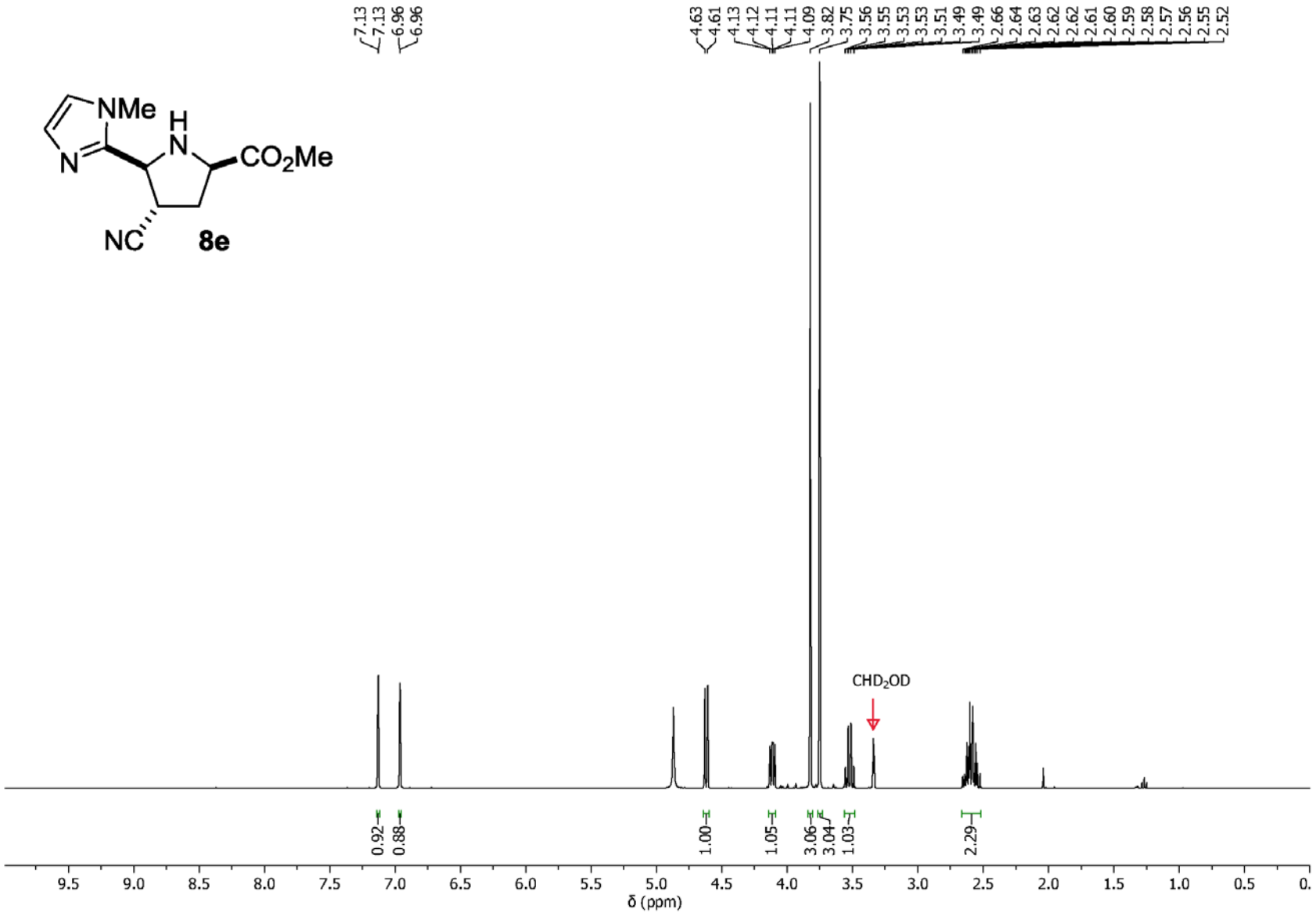
400 MHz ^{1}H NMR, $(CD_3)_2CO$



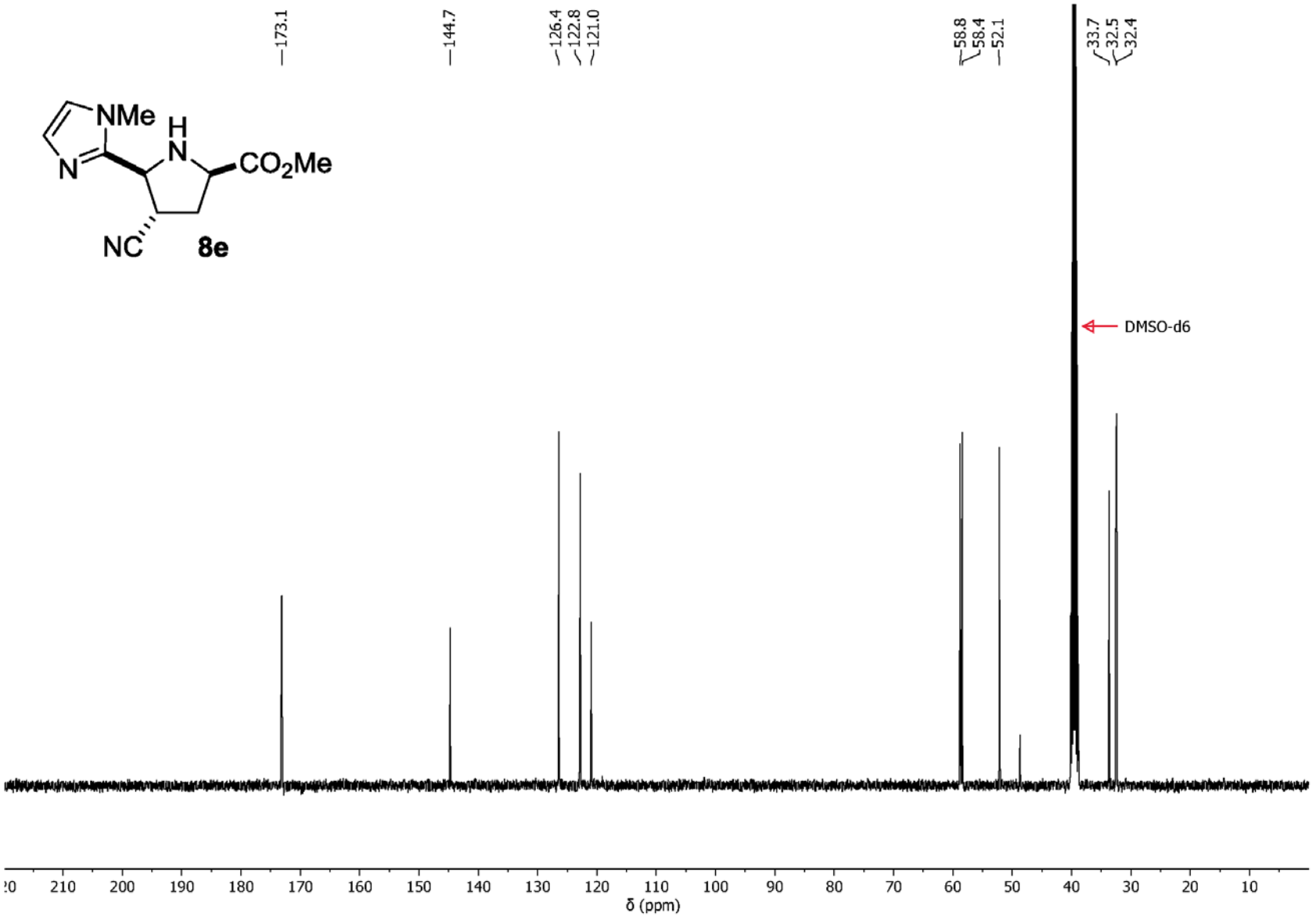
100.5 MHz ^{13}C NMR, $(CD_3)_2CO$



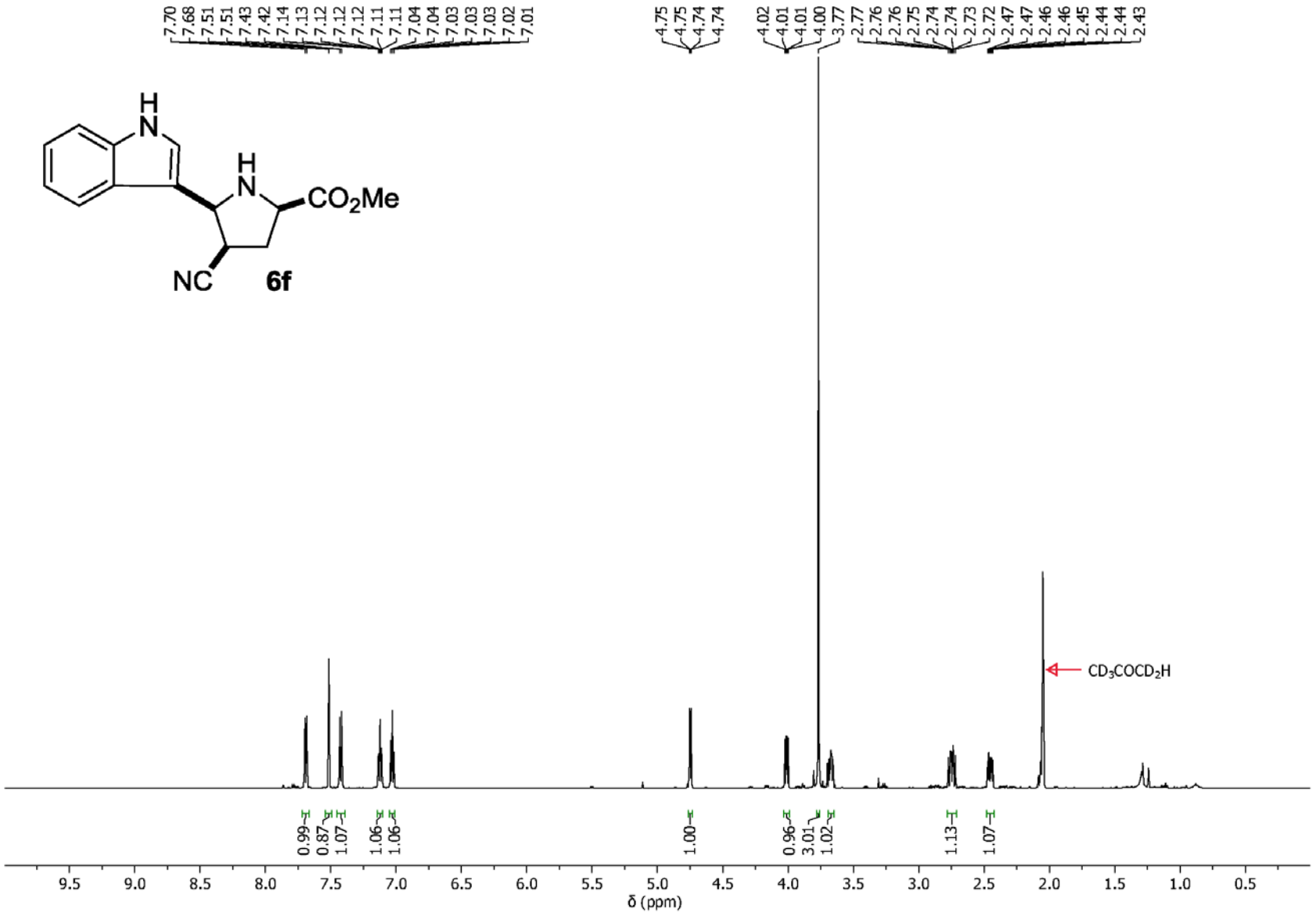
400 MHz ^{1}H NMR, CD_3OD



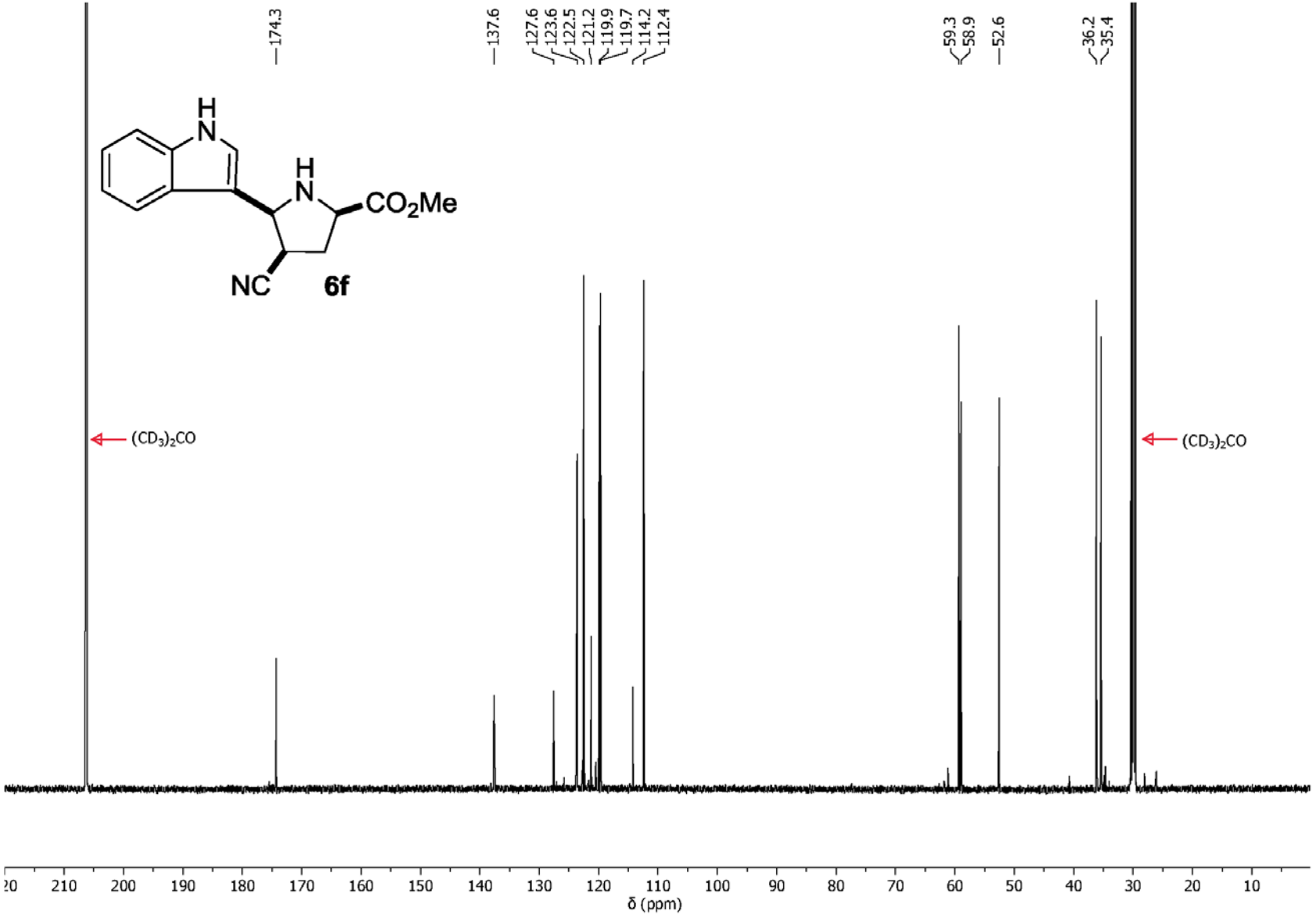
100.5 MHz ^{13}C NMR, DMSO-d6



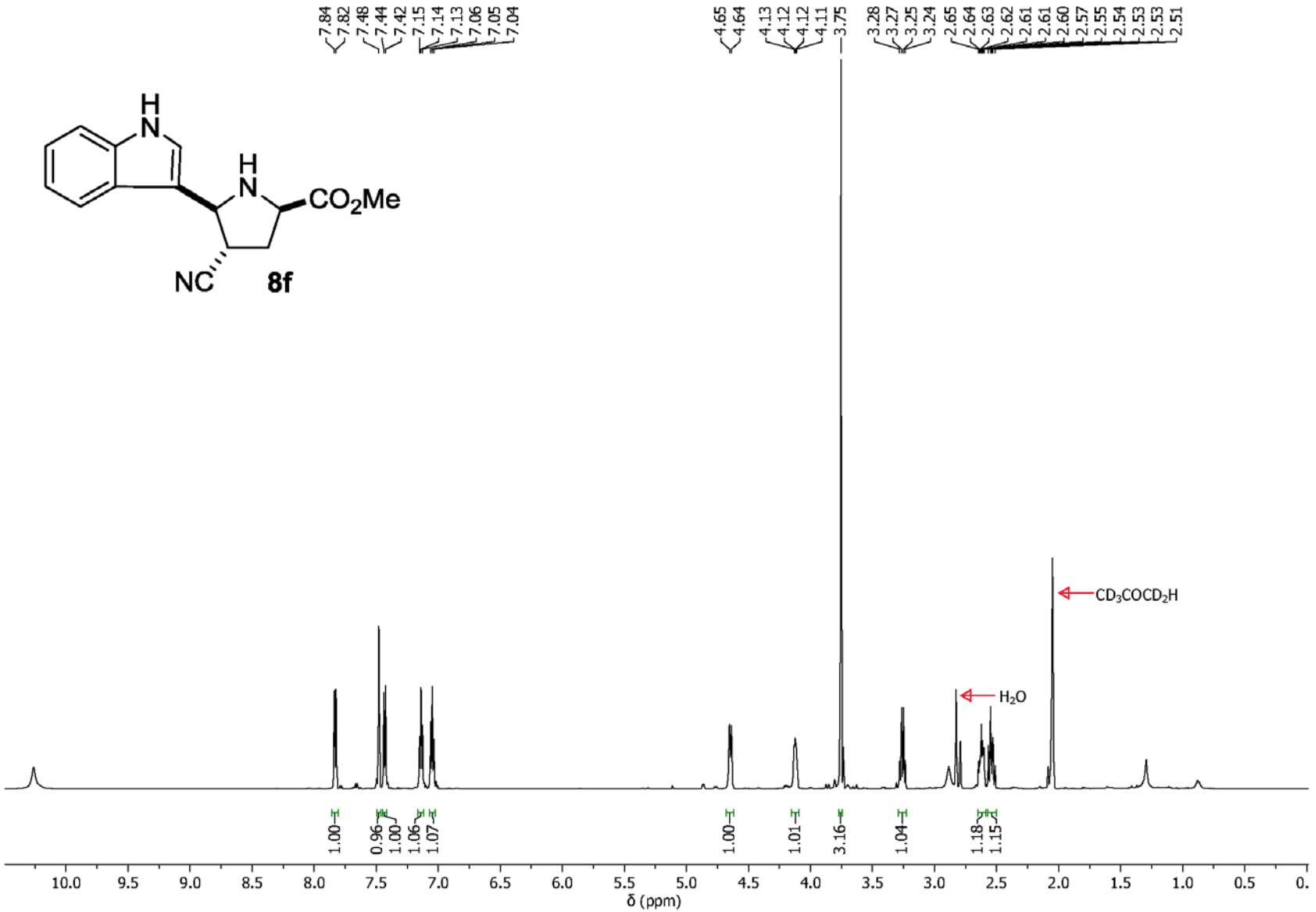
600 MHz ^{1}H NMR, $(CD_3)_2CO$



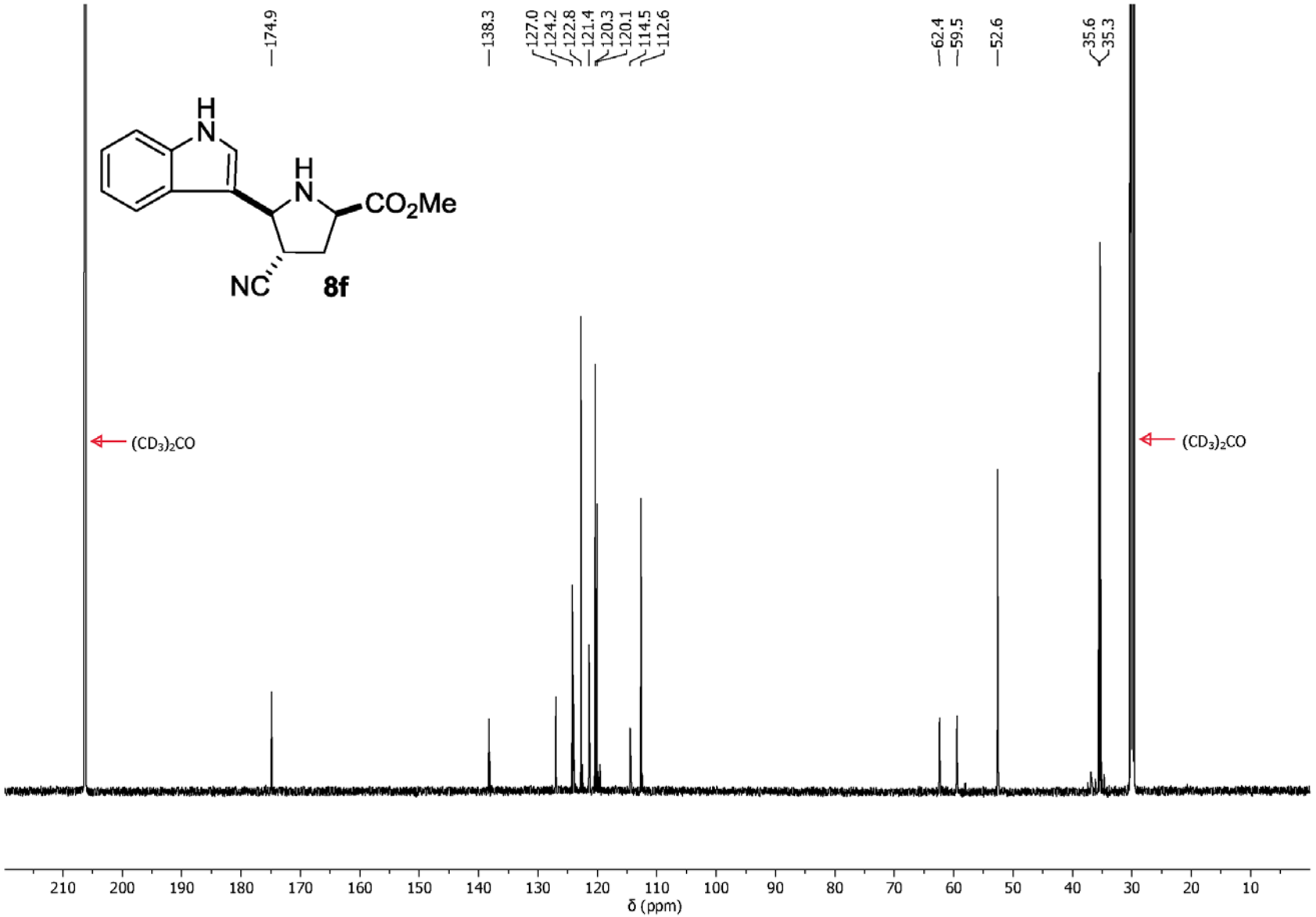
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



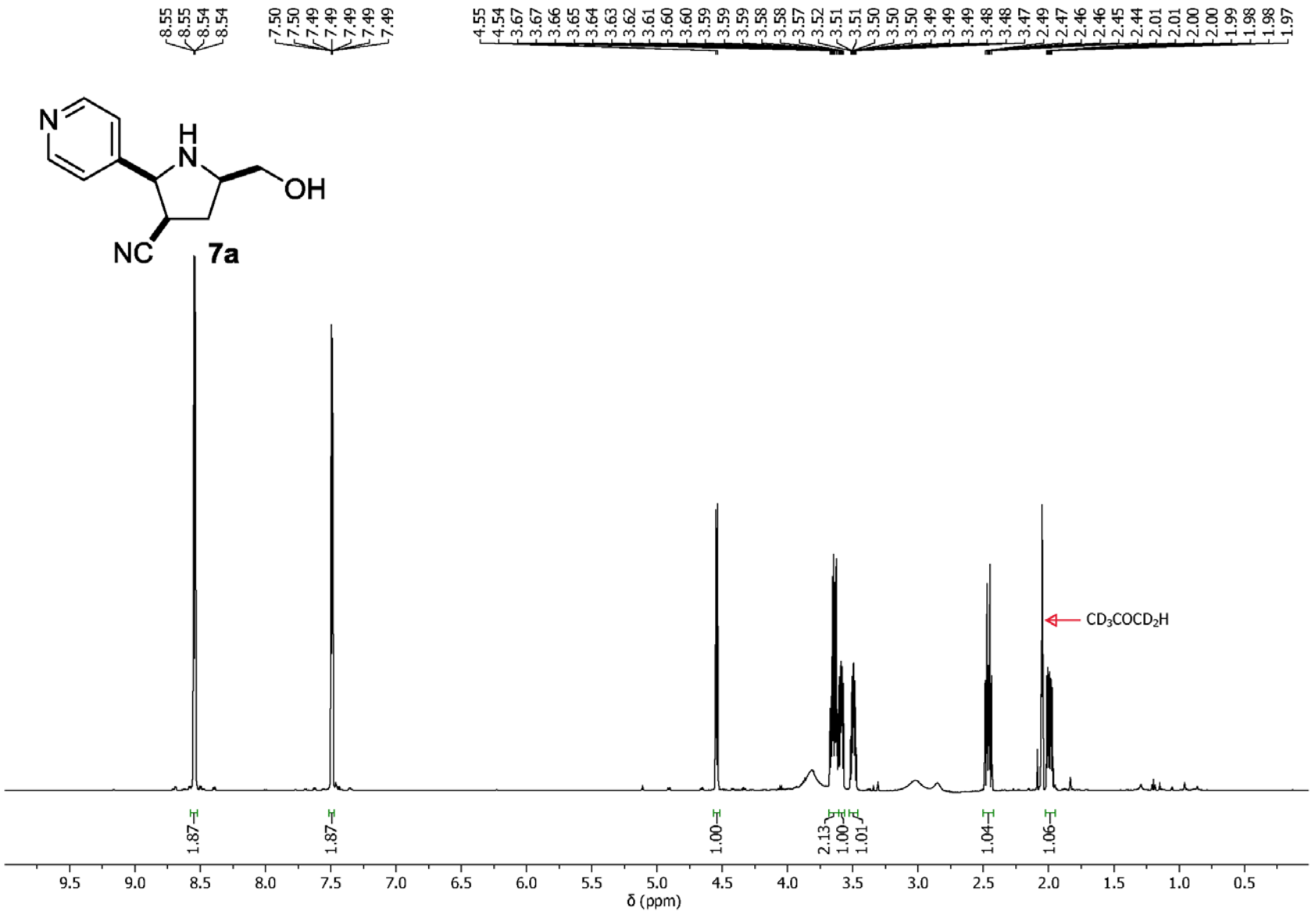
600 MHz ^{1}H NMR, $(CD_3)_2CO$



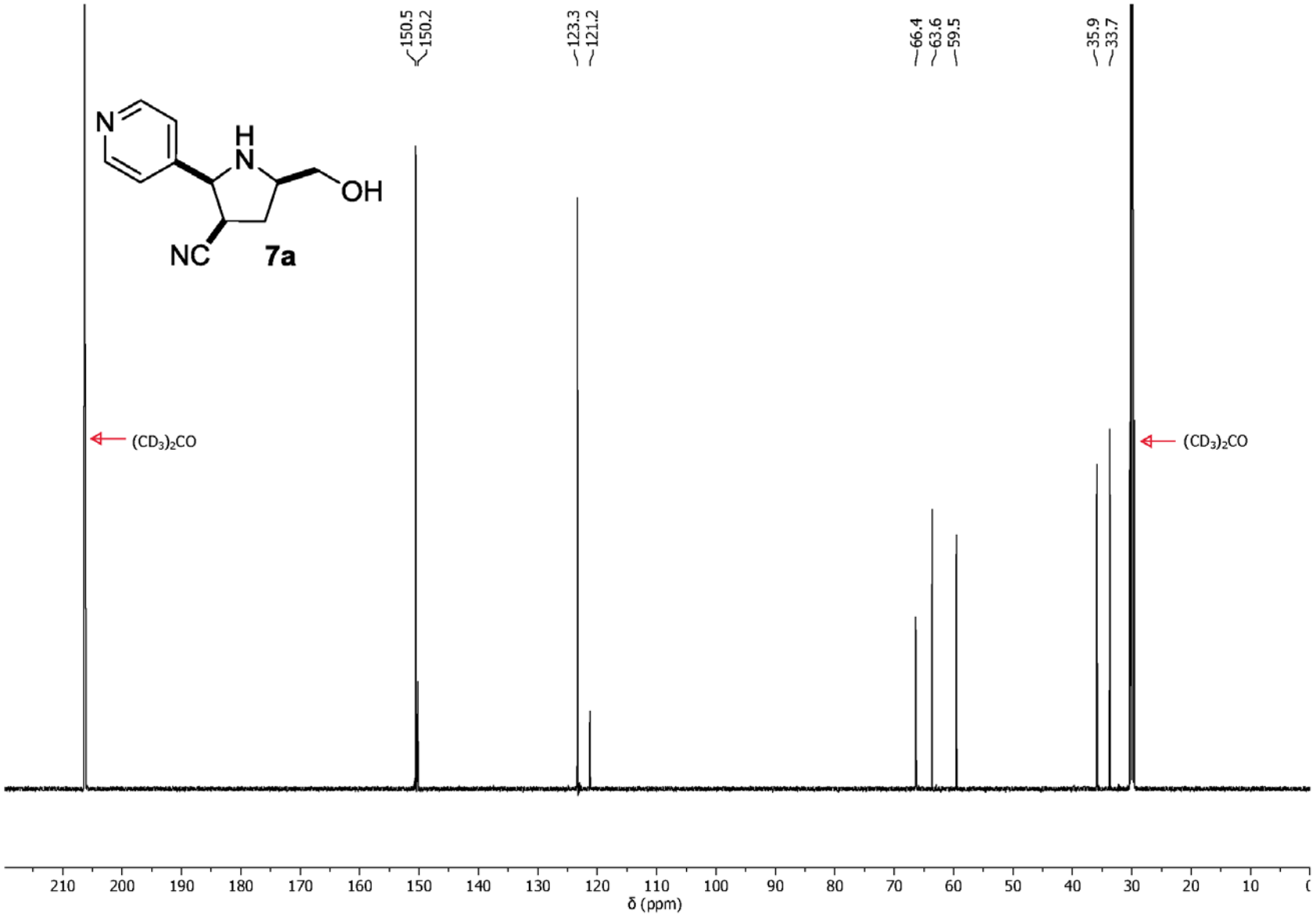
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



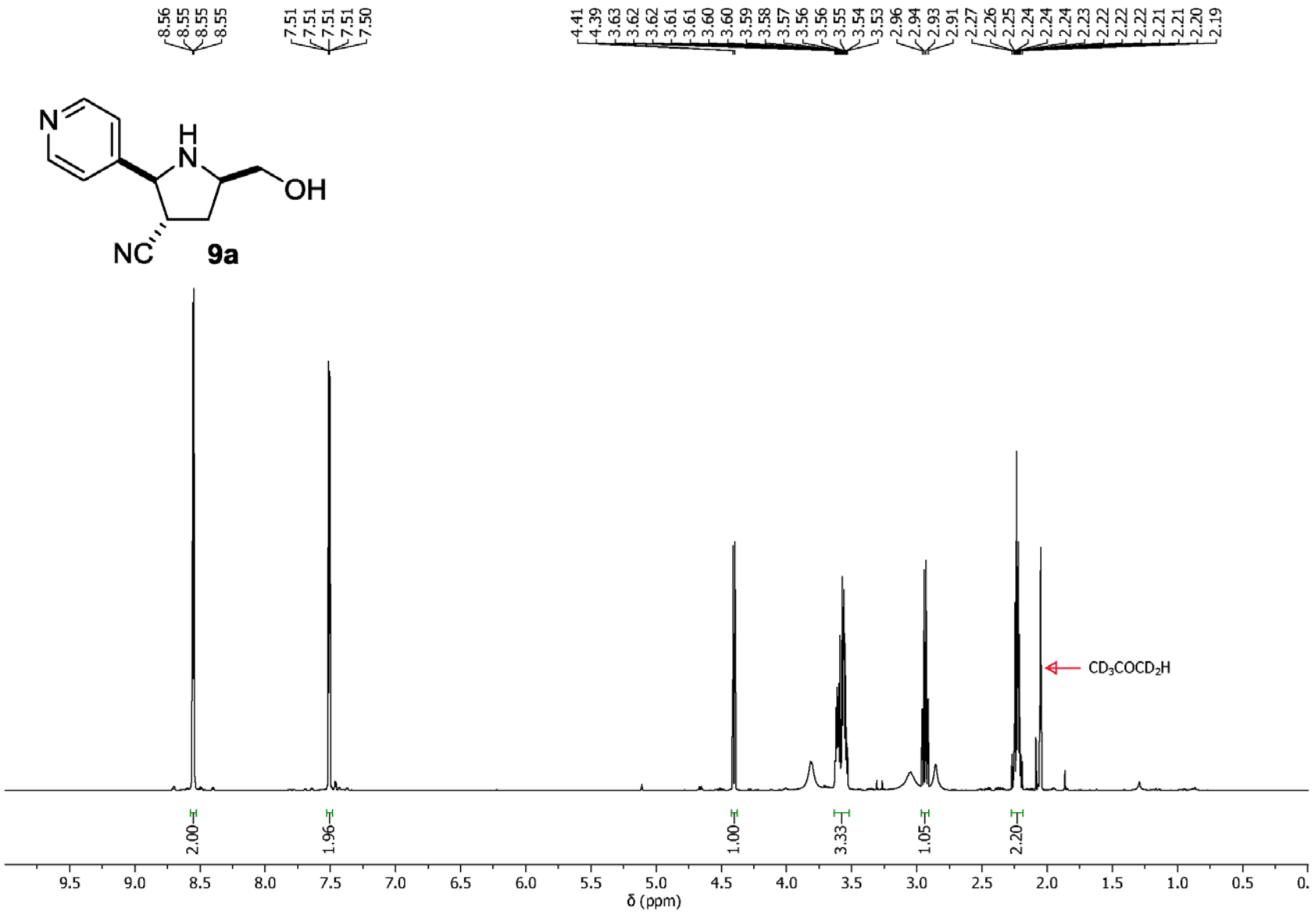
600 MHz ^{1}H NMR, $(CD_3)_2CO$



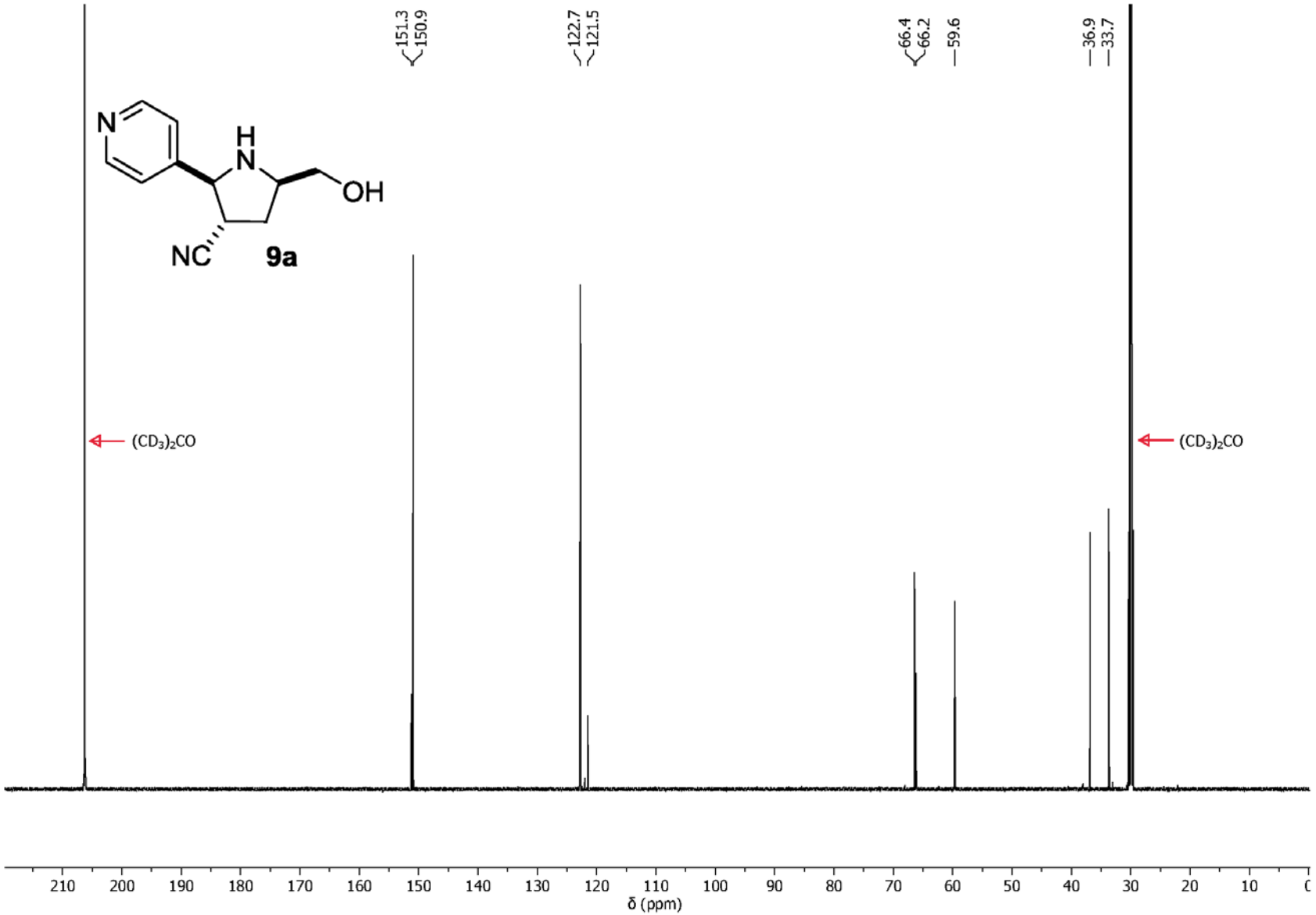
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



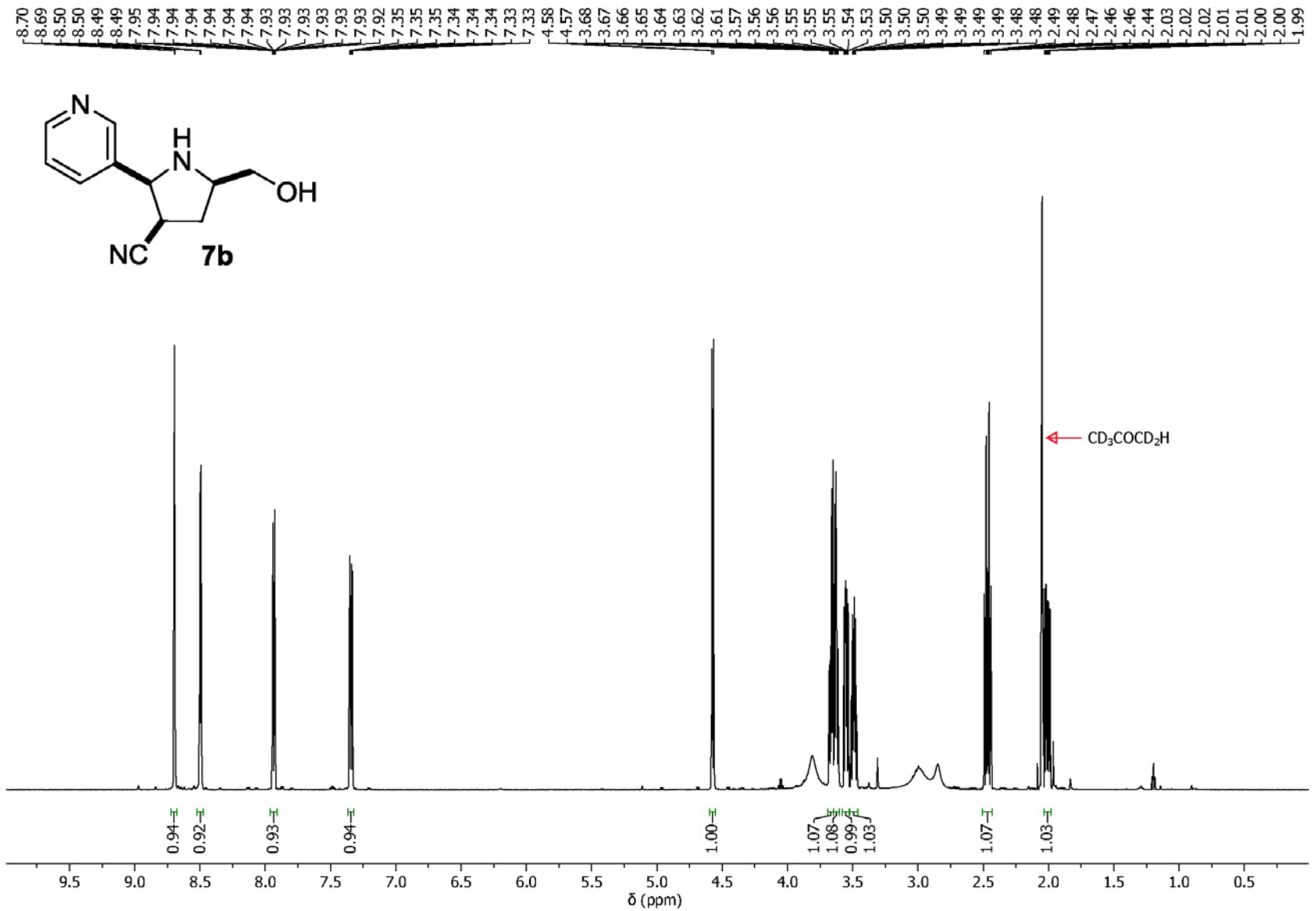
600 MHz ^{1}H NMR, $(CD_3)_2CO$



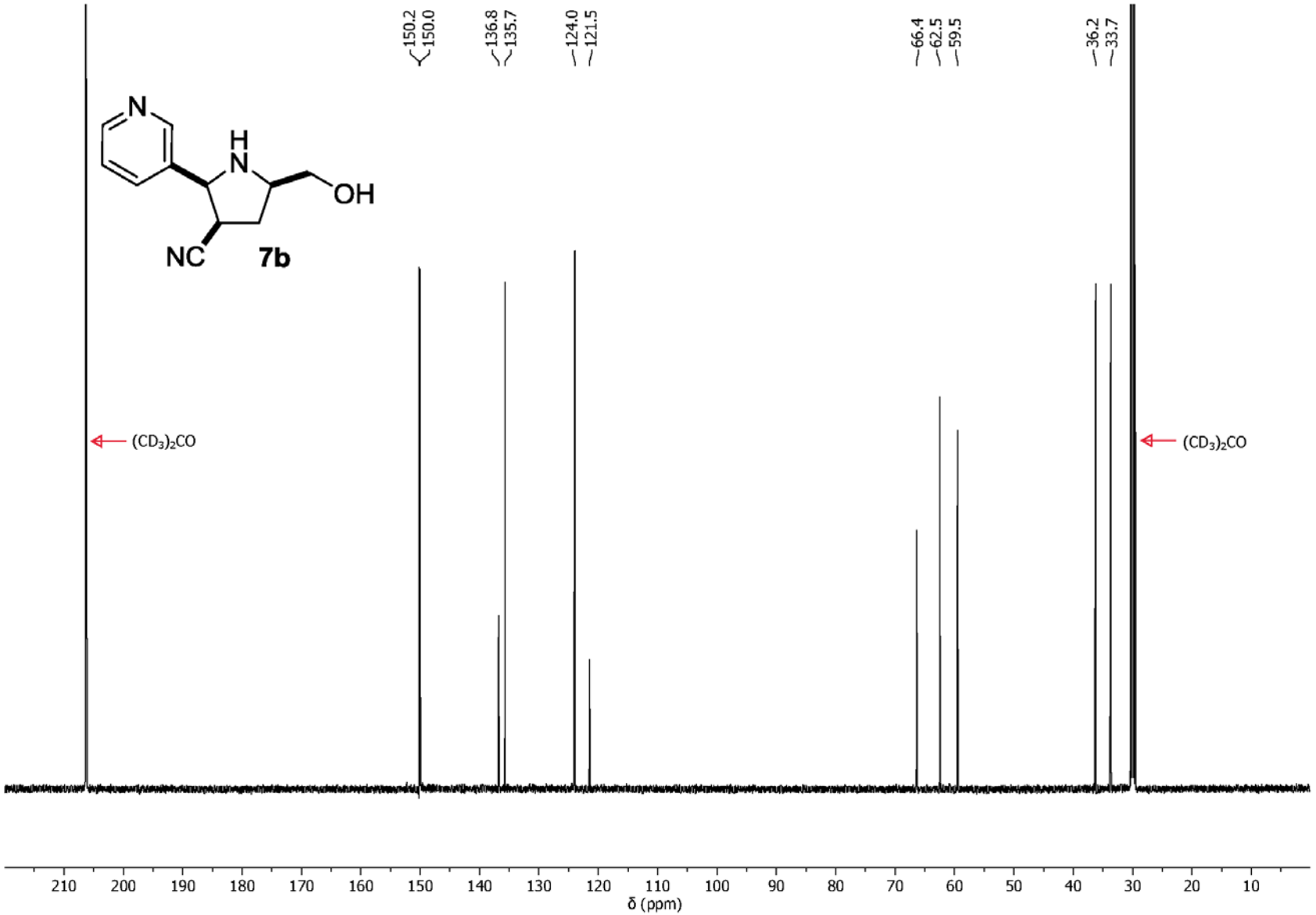
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



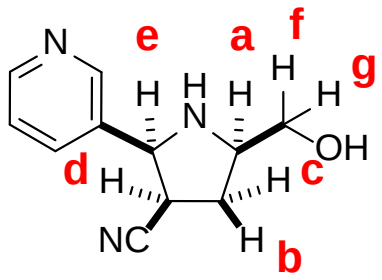
600 MHz ^{1}H NMR, $(CD_3)_2CO$



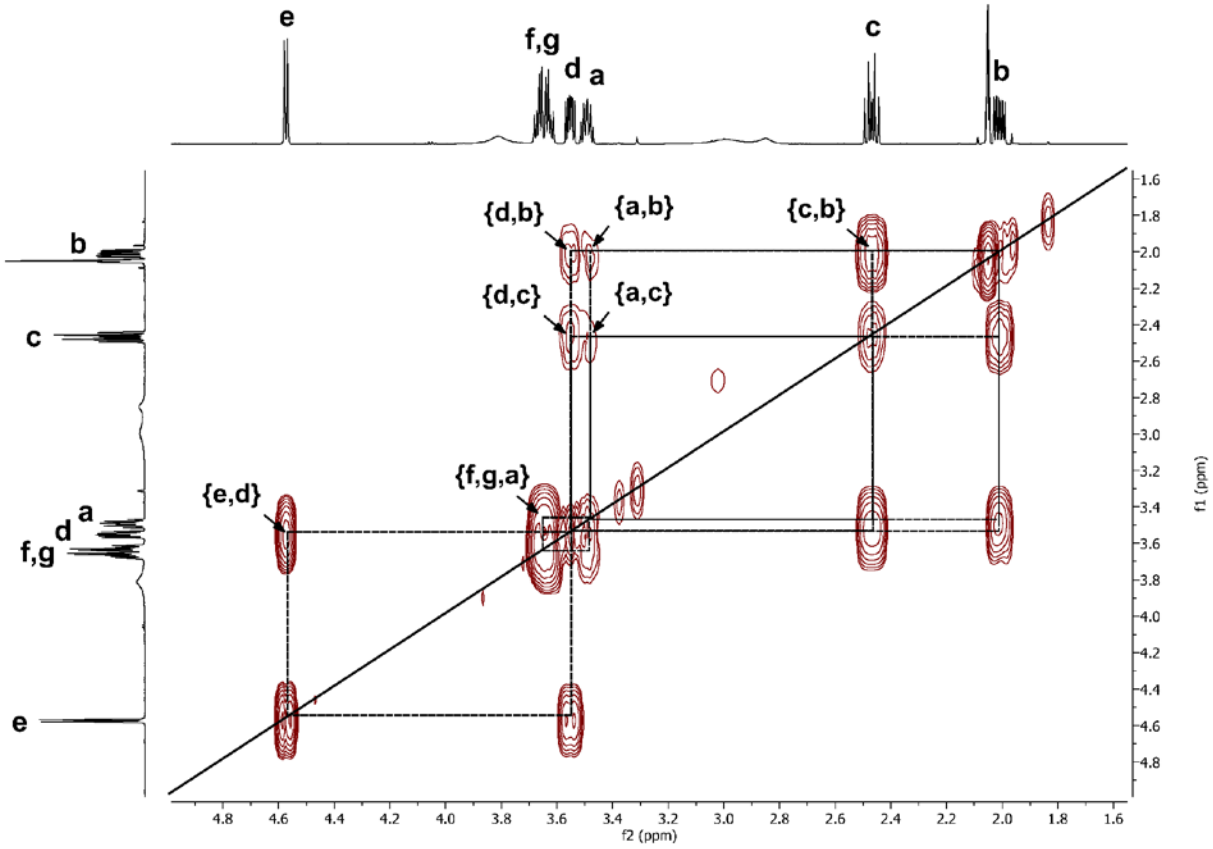
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



600 MHz gCOSY ^{1}H NMR, $(CD_3)_2CO$

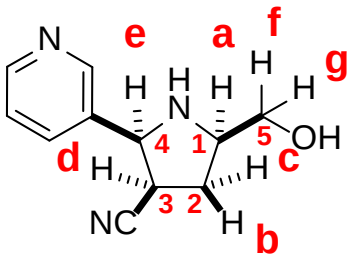


7b

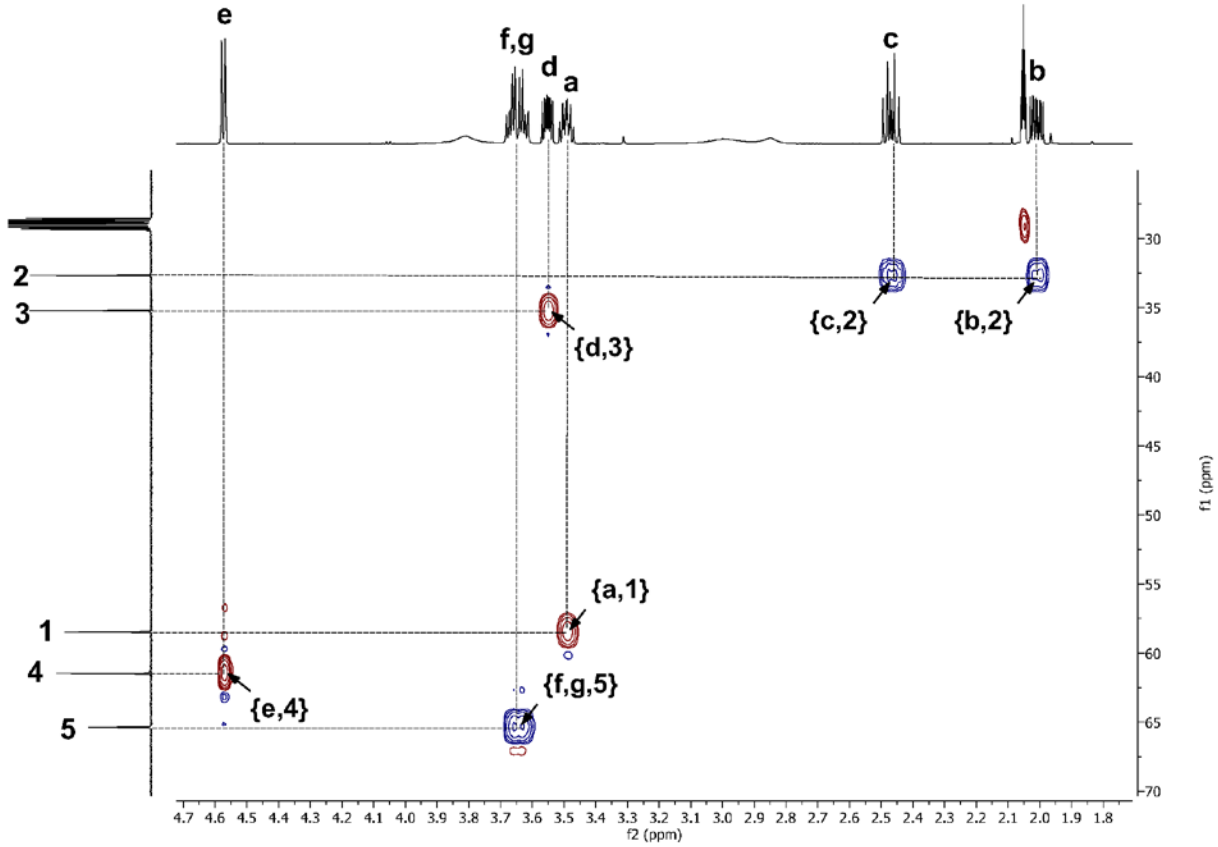


Relevant portion of the 600 MHz 2D gCOSY ^{1}H NMR spectra obtained for compound **7b** in $CDCl_3$ showing interactions between **e-d**, **d-b, d-c, f-g-a, a-b, a-c** and **c-b** in the molecule.

600 MHz HSQCAD NMR, $(CD_3)_2CO$

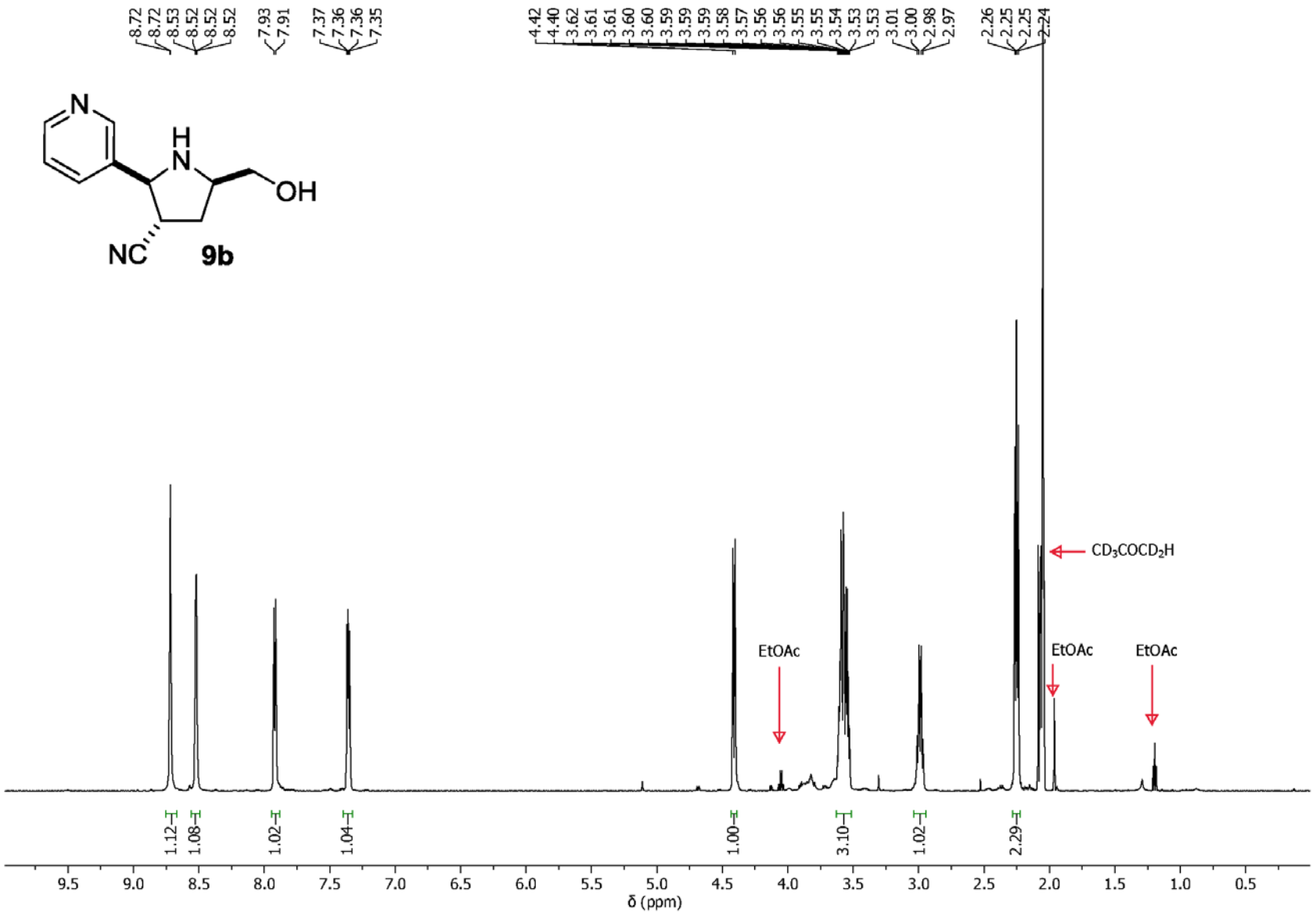


7b

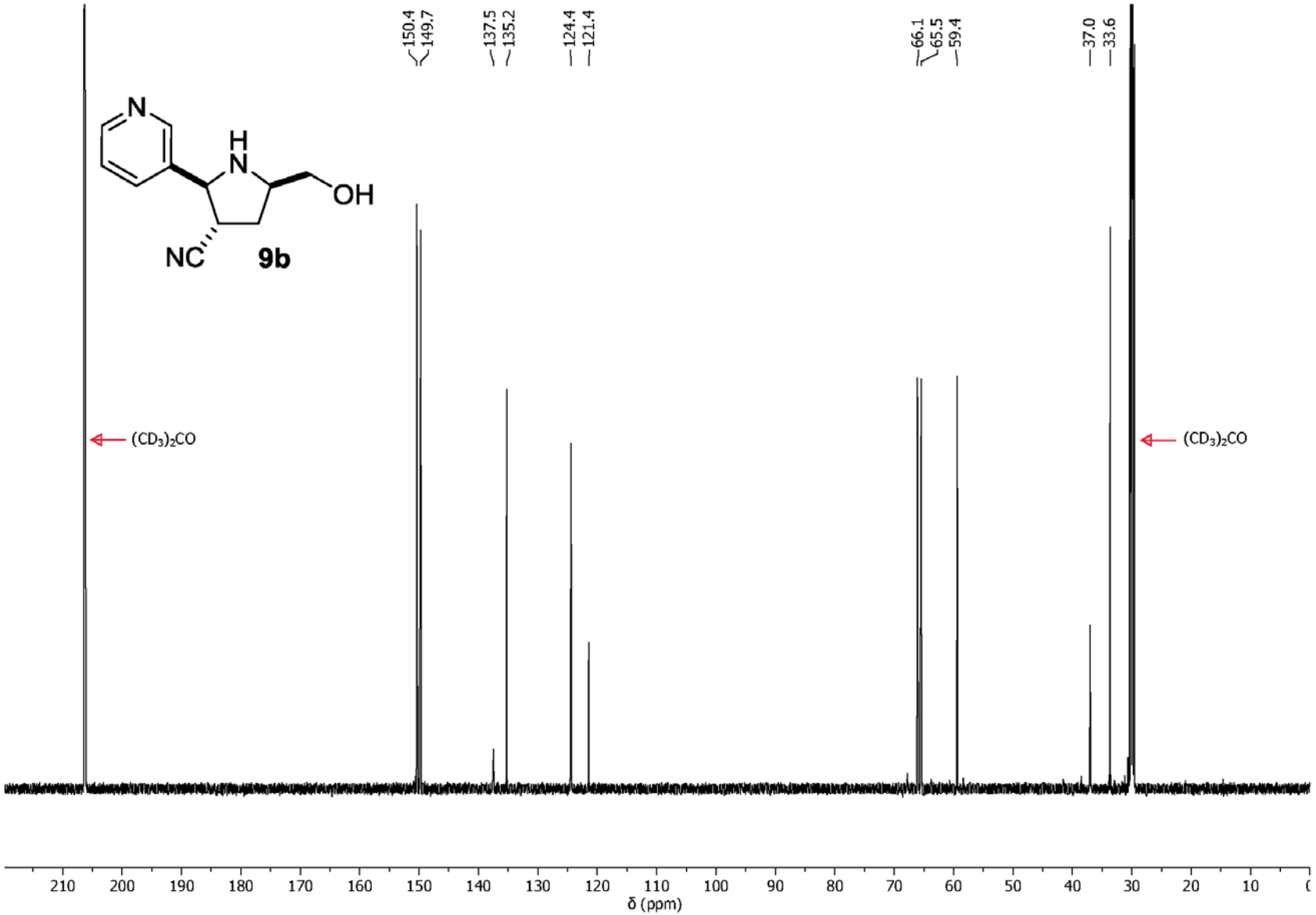


Relevant portion of the 600 MHz HSQCAD NMR spectra obtained for compound **7b** in $CDCl_3$ showing interactions between **a-1, e-4, d-3, f-g-5, c-2** and **b-2.** Blue color contours stand for -CH_2 group and red color contours stand for -CH and CH_3 groups.

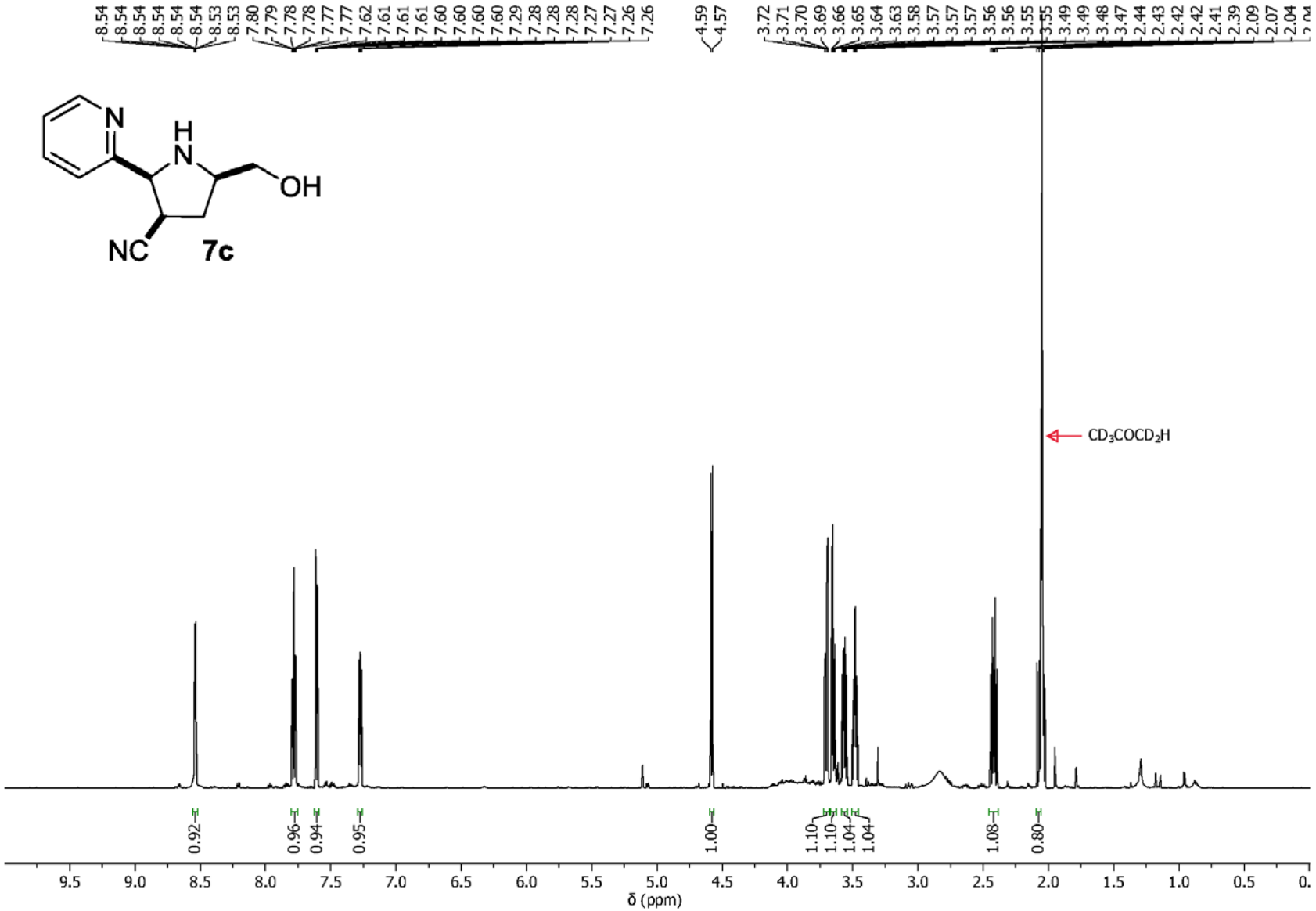
600 MHz ^{1}H NMR, $(CD_3)_2CO$



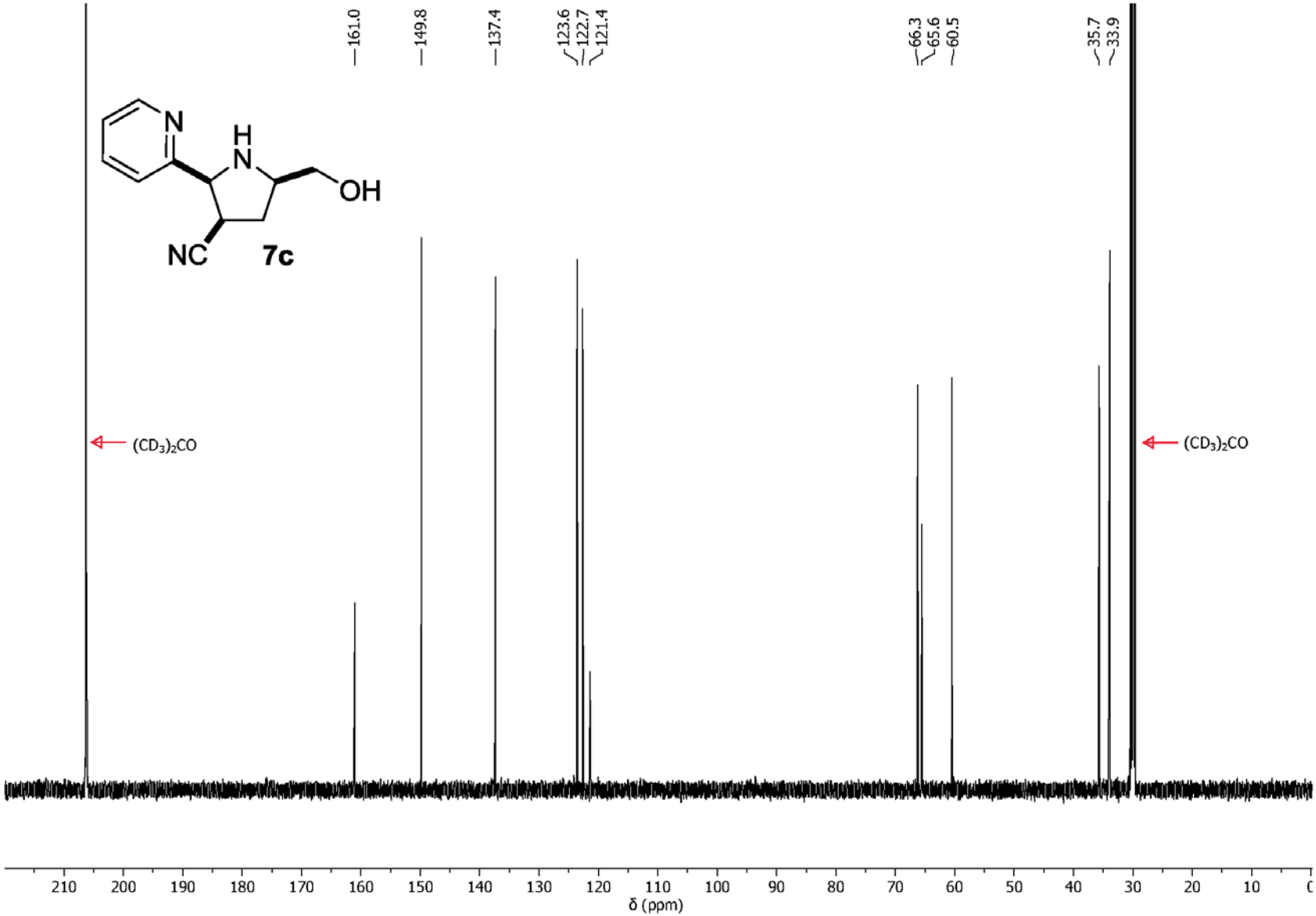
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



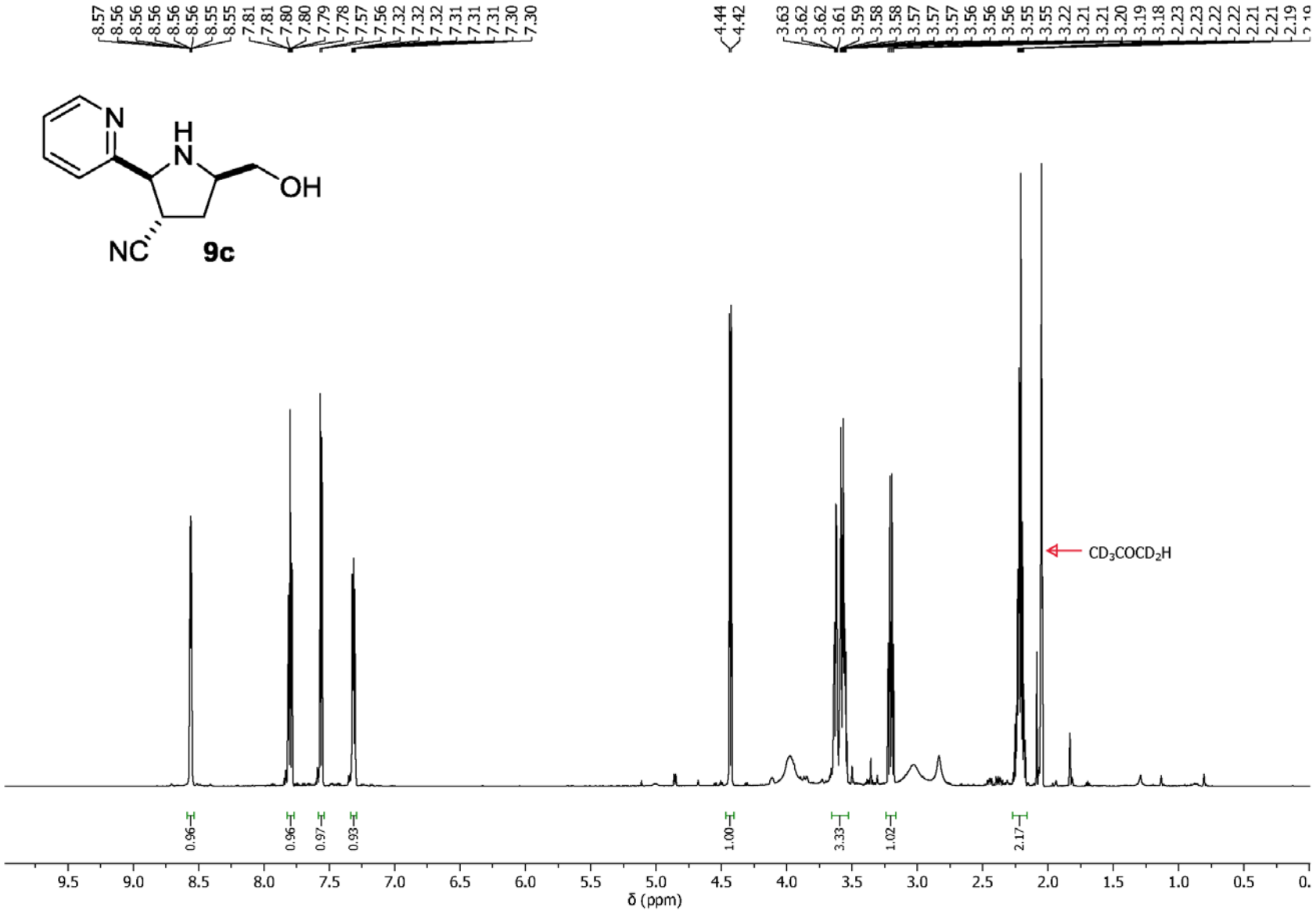
600 MHz ^{1}H NMR, $(CD_3)_2CO$



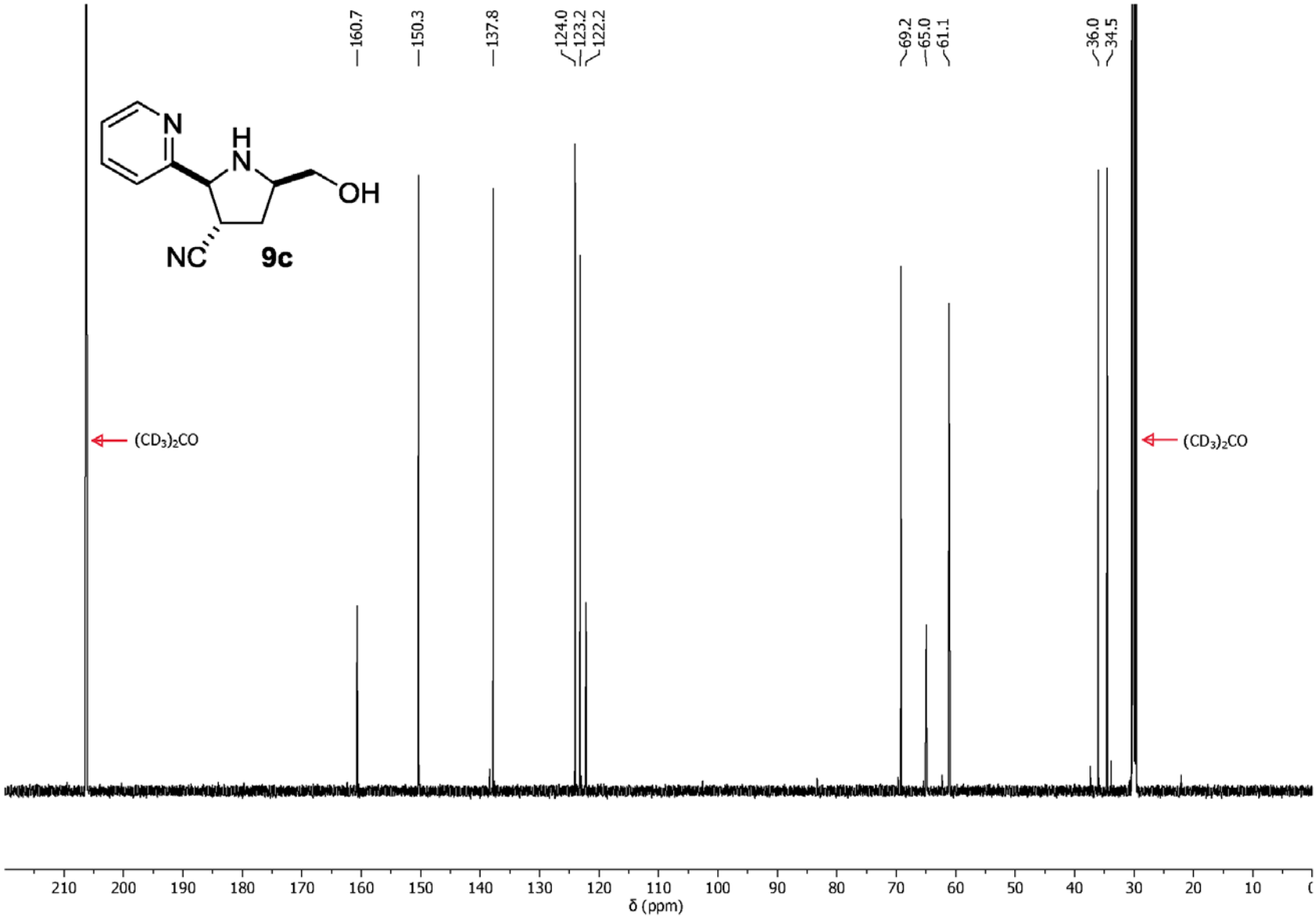
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



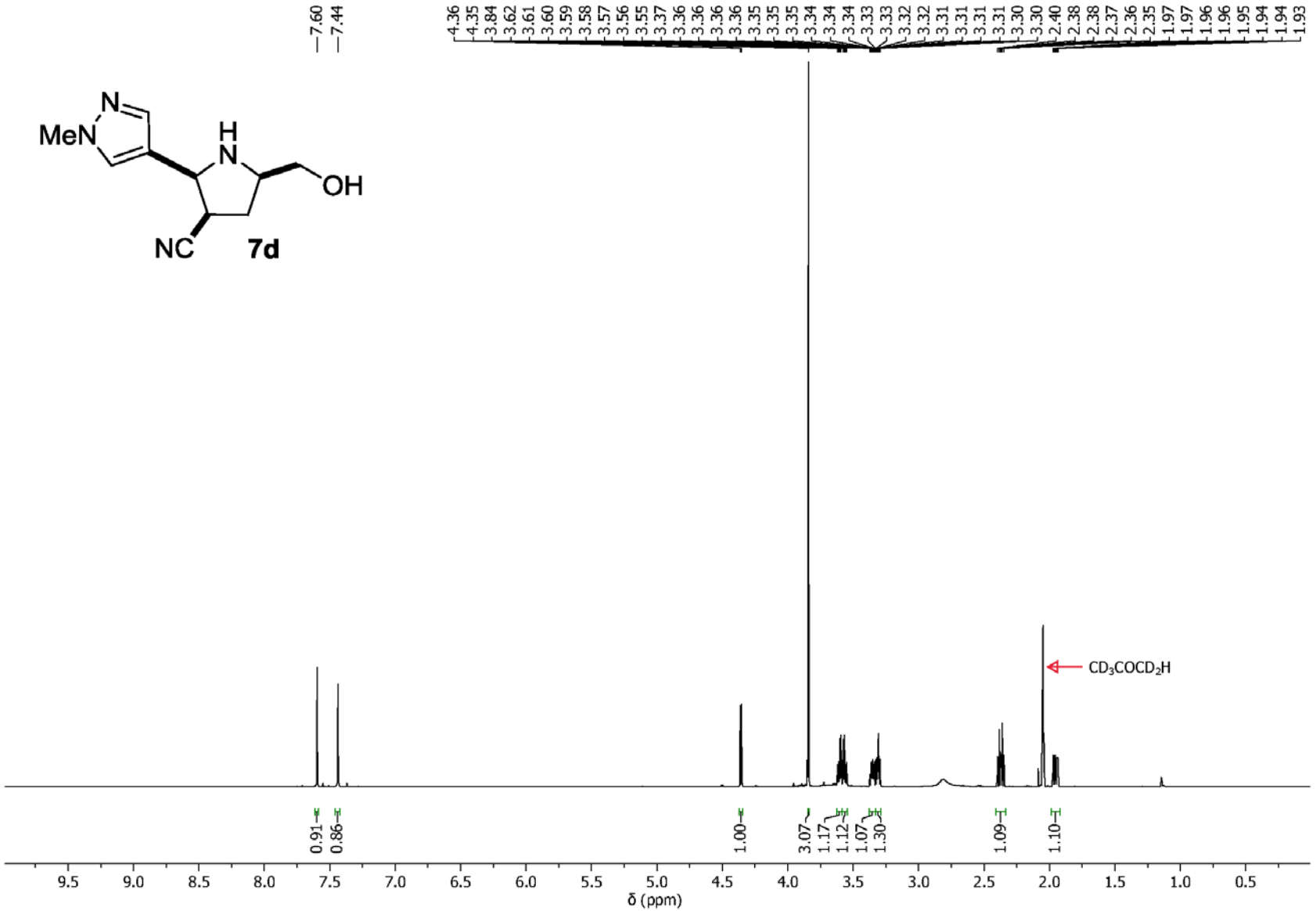
600 MHz ^{1}H NMR, $(CD_3)_2CO$



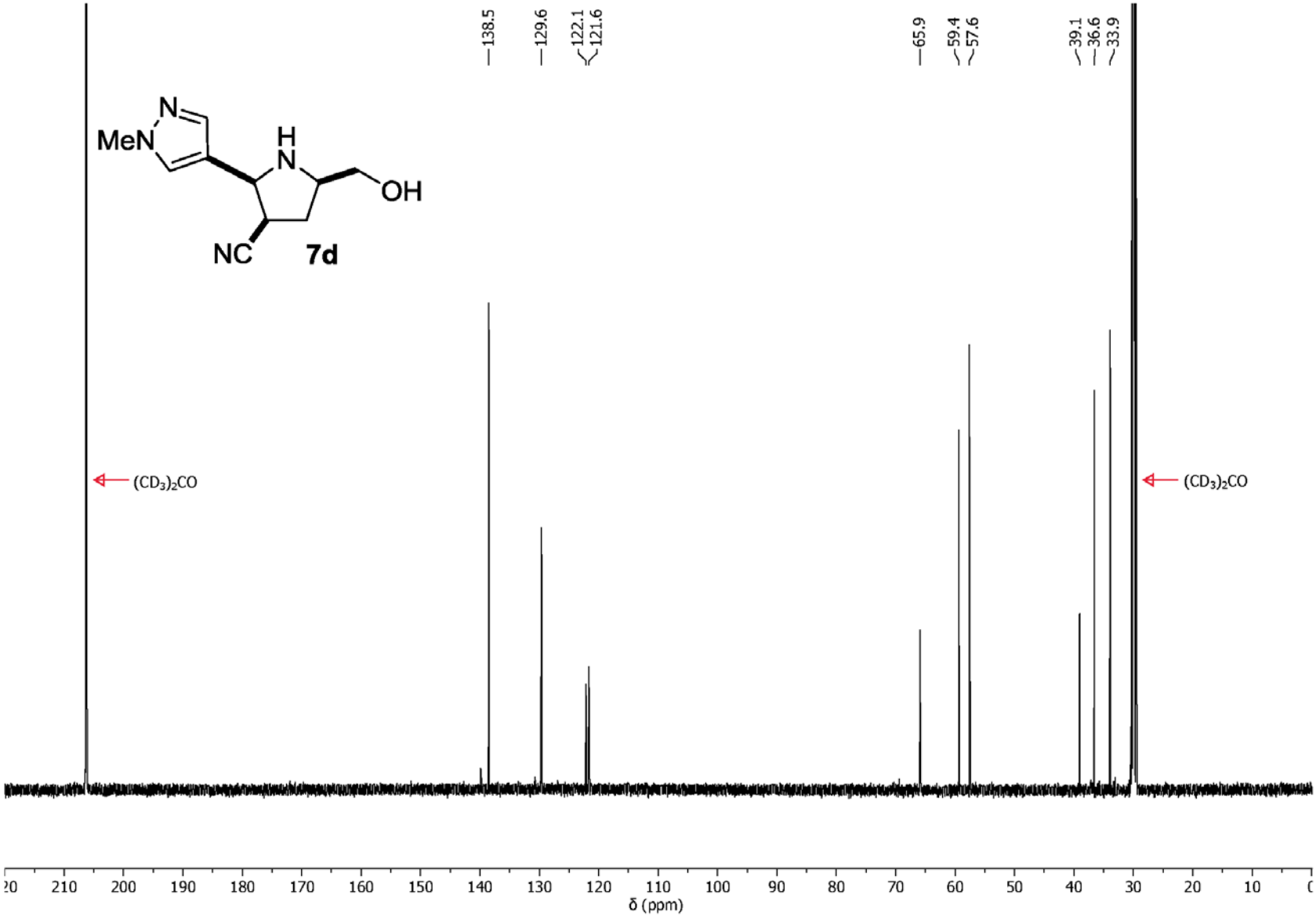
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



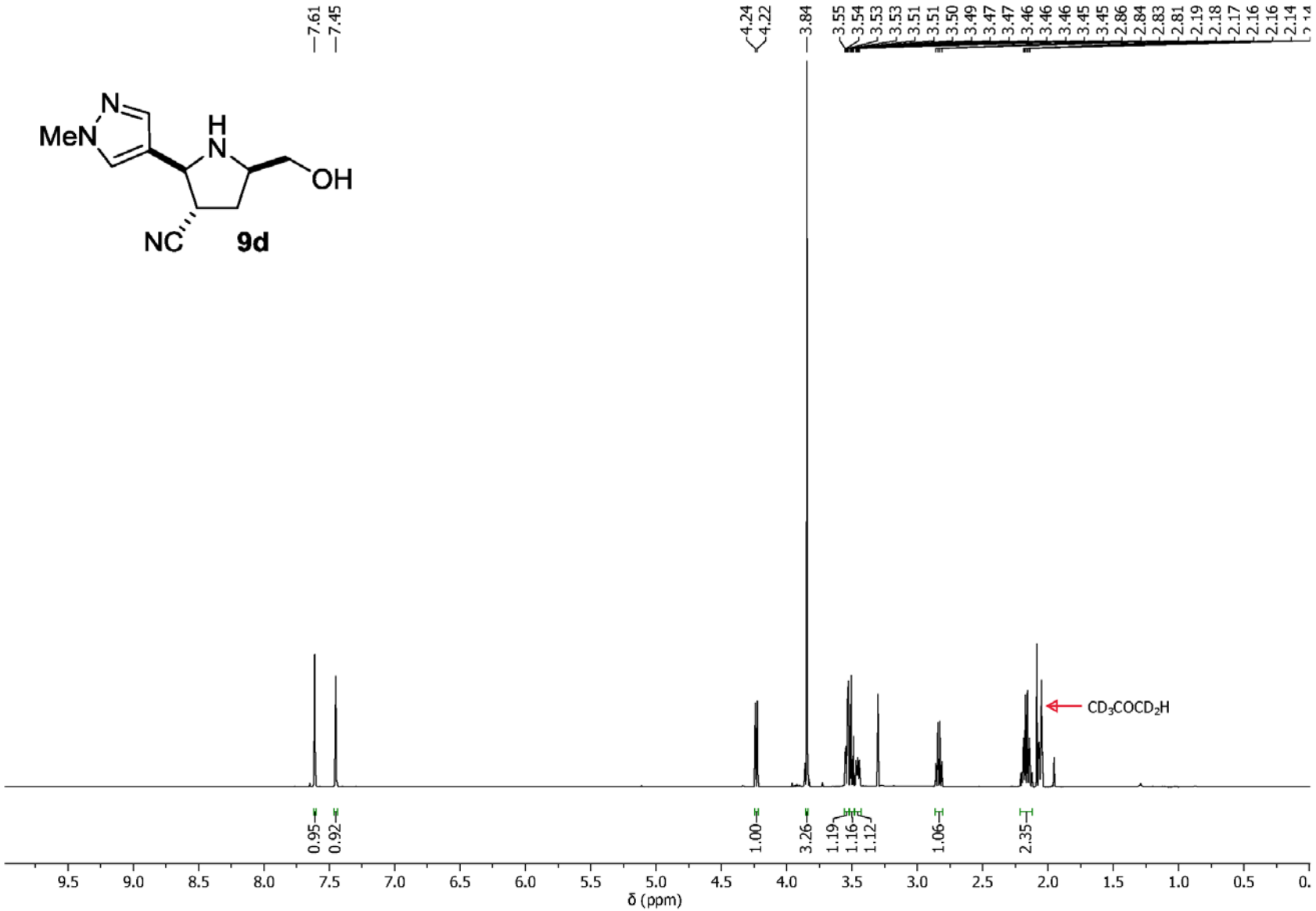
600 MHz ^{1}H NMR, $(CD_3)_2CO$



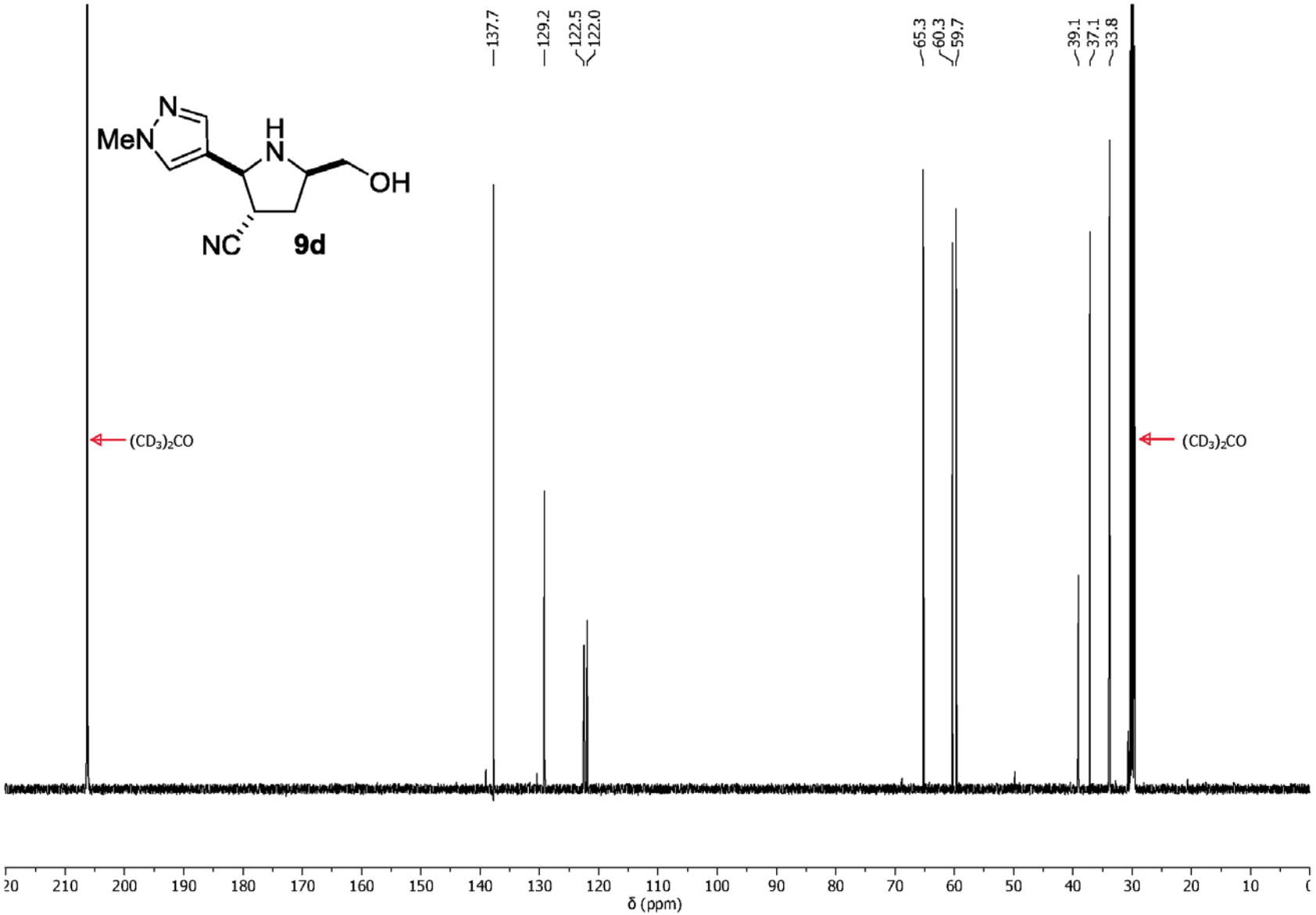
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



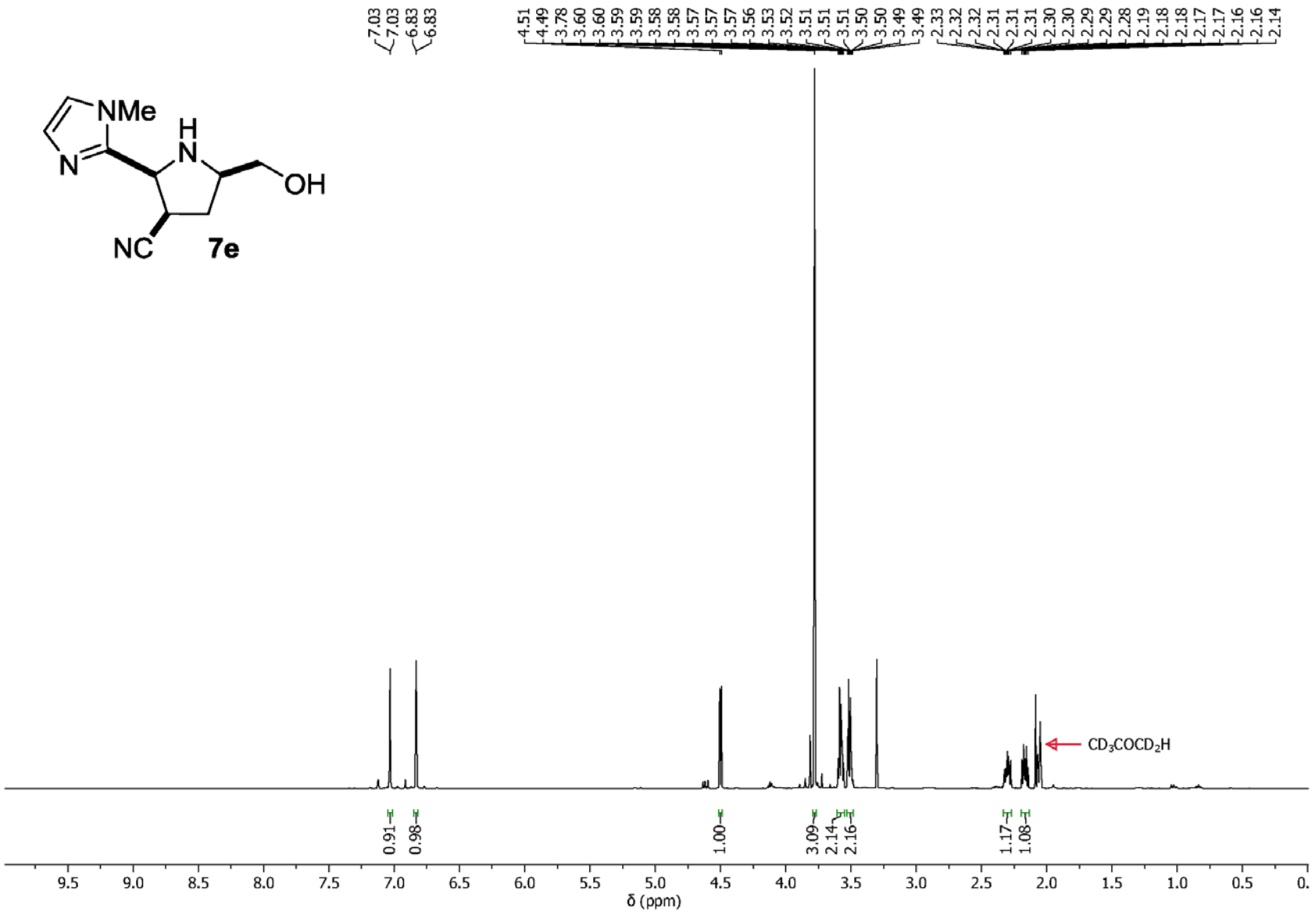
600 MHz ^{1}H NMR, $(CD_3)_2CO$



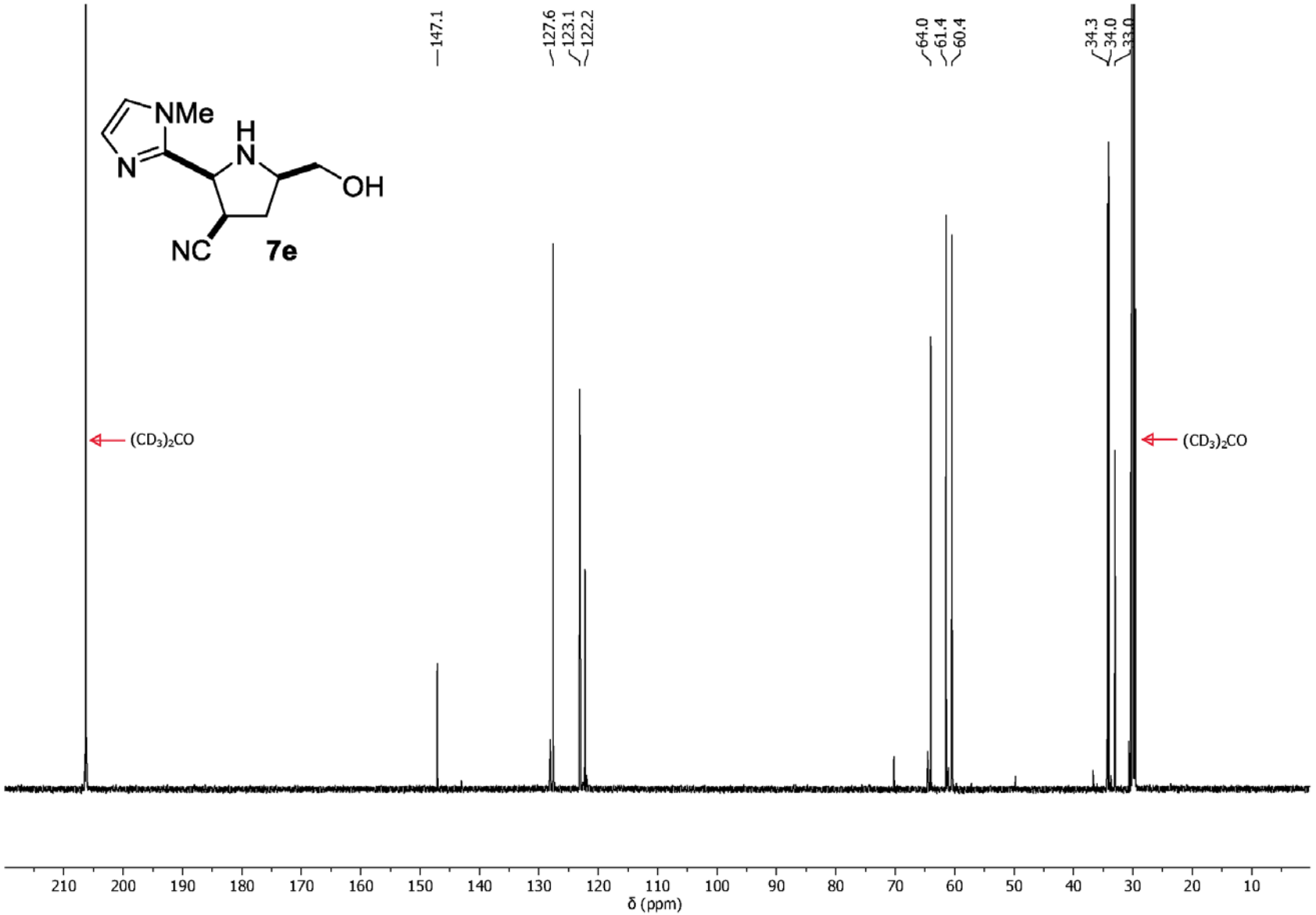
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



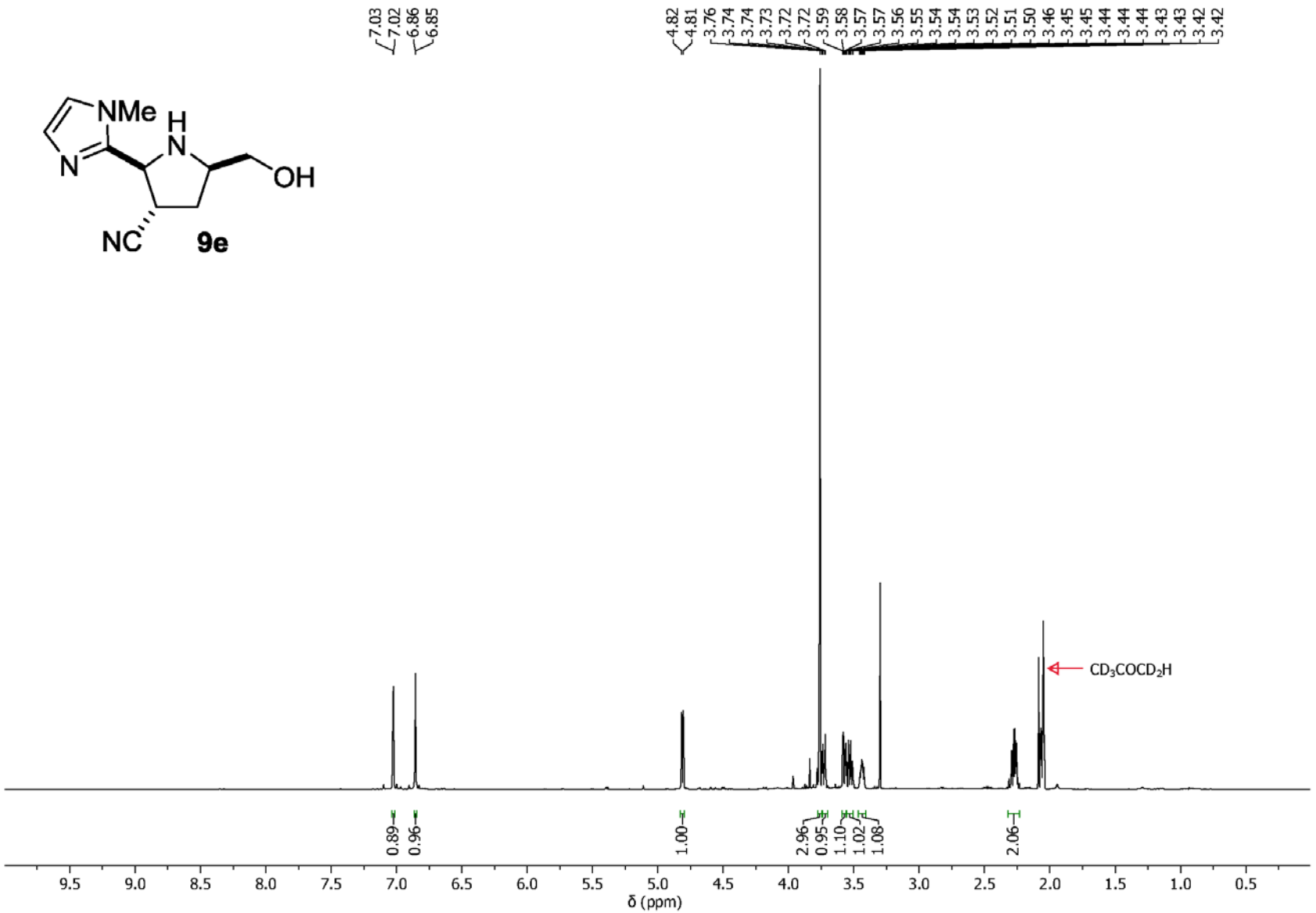
600 MHz ^{1}H NMR, $(CD_3)_2CO$



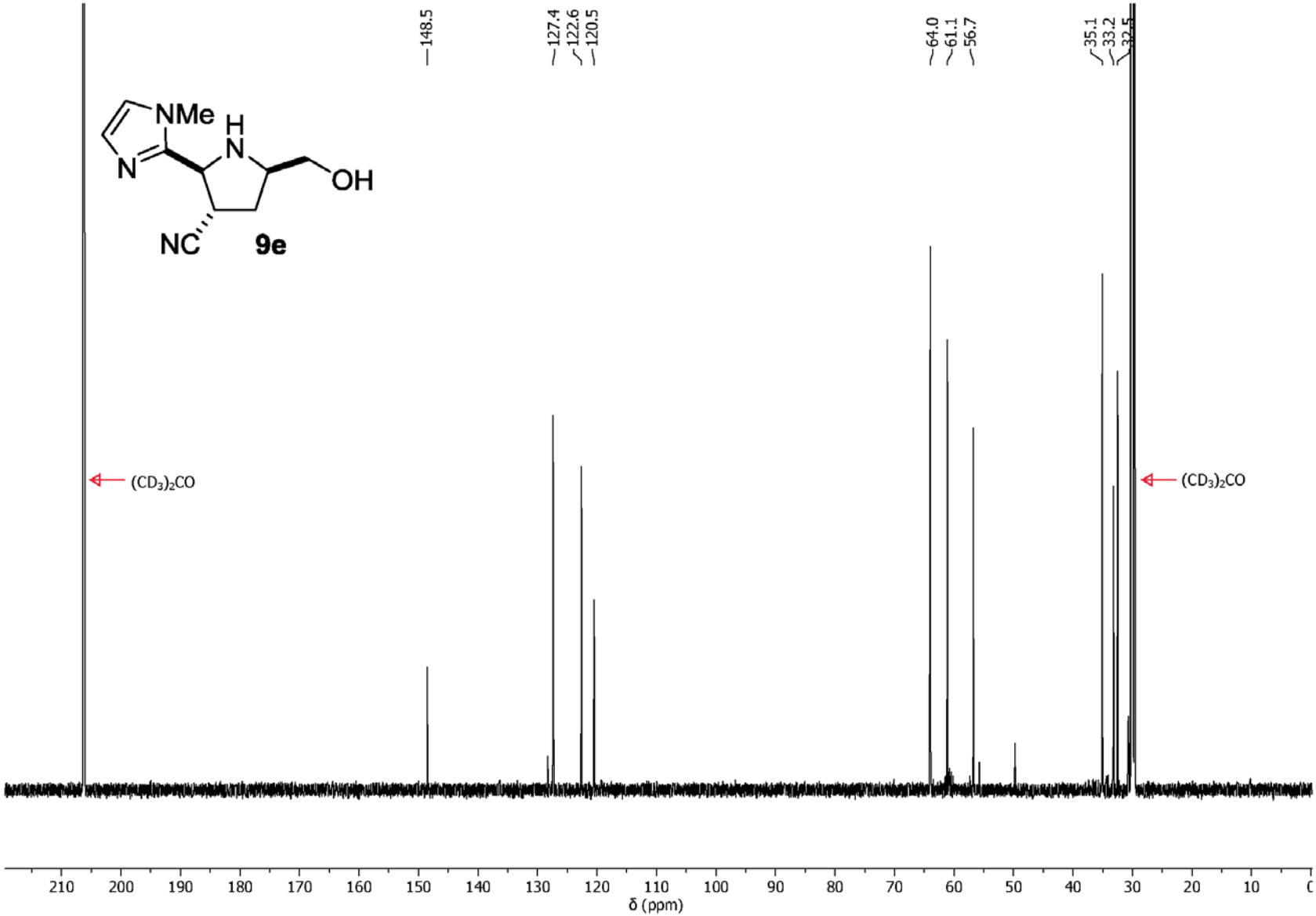
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



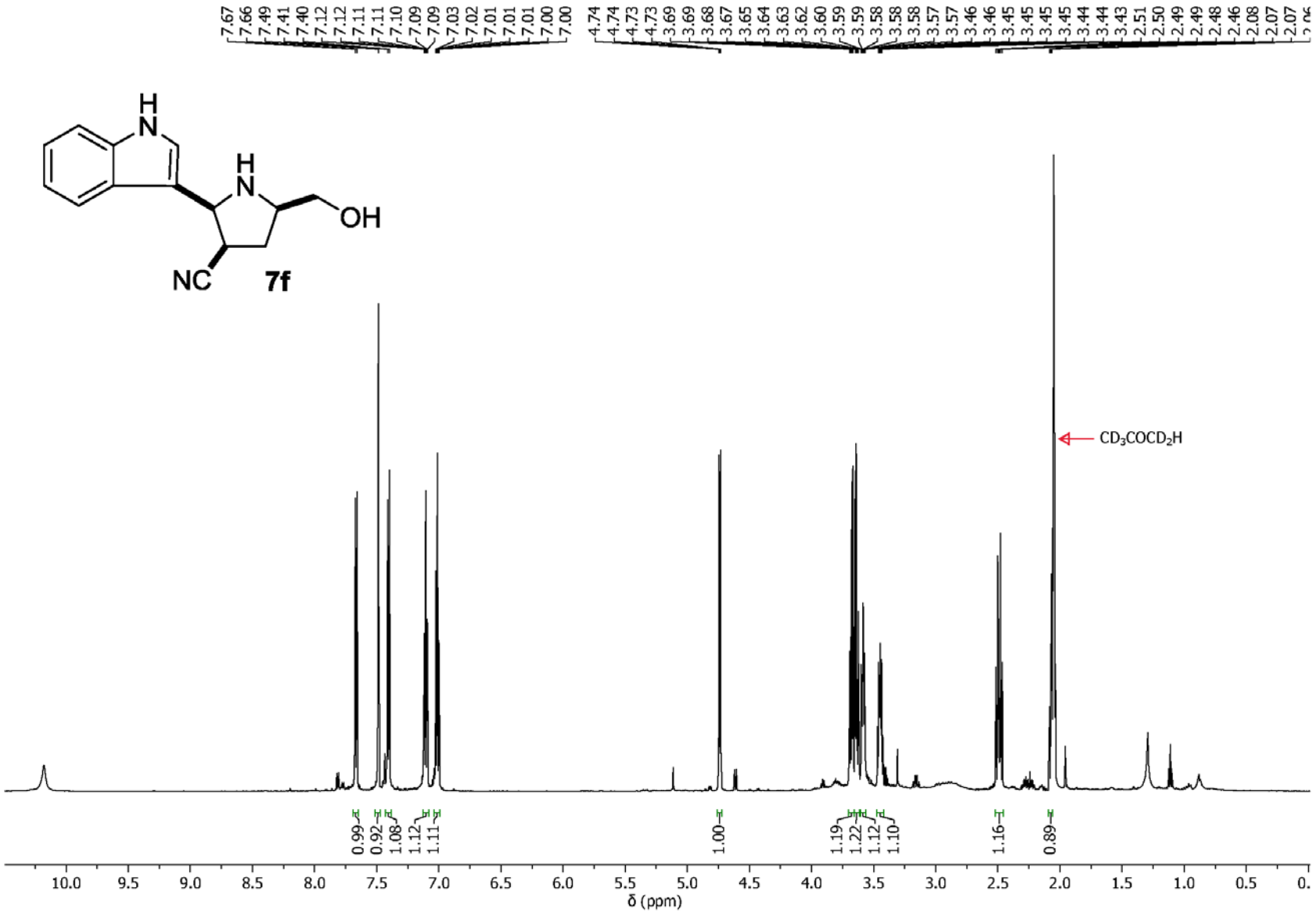
600 MHz ^{1}H NMR, $(CD_3)_2CO$



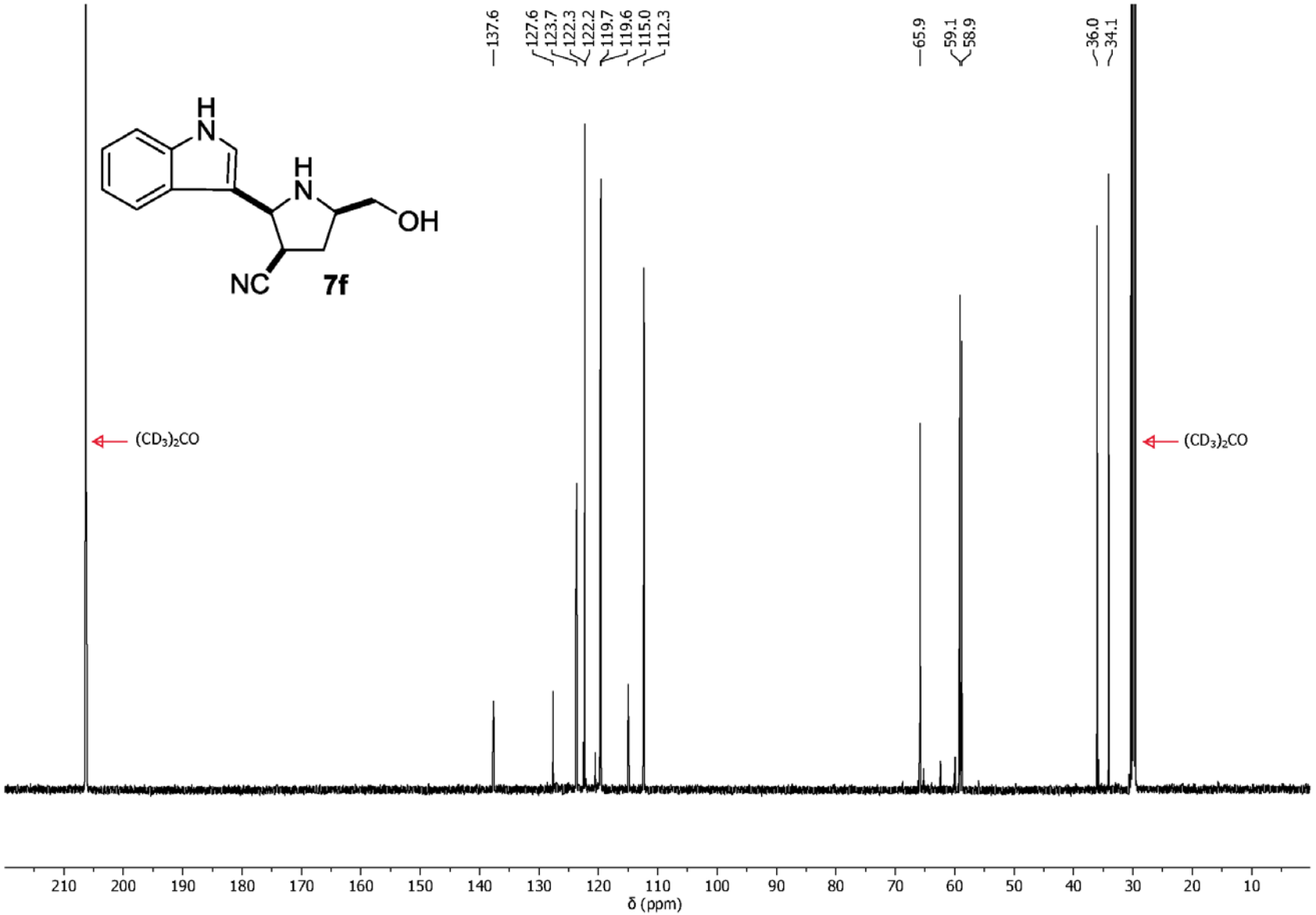
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



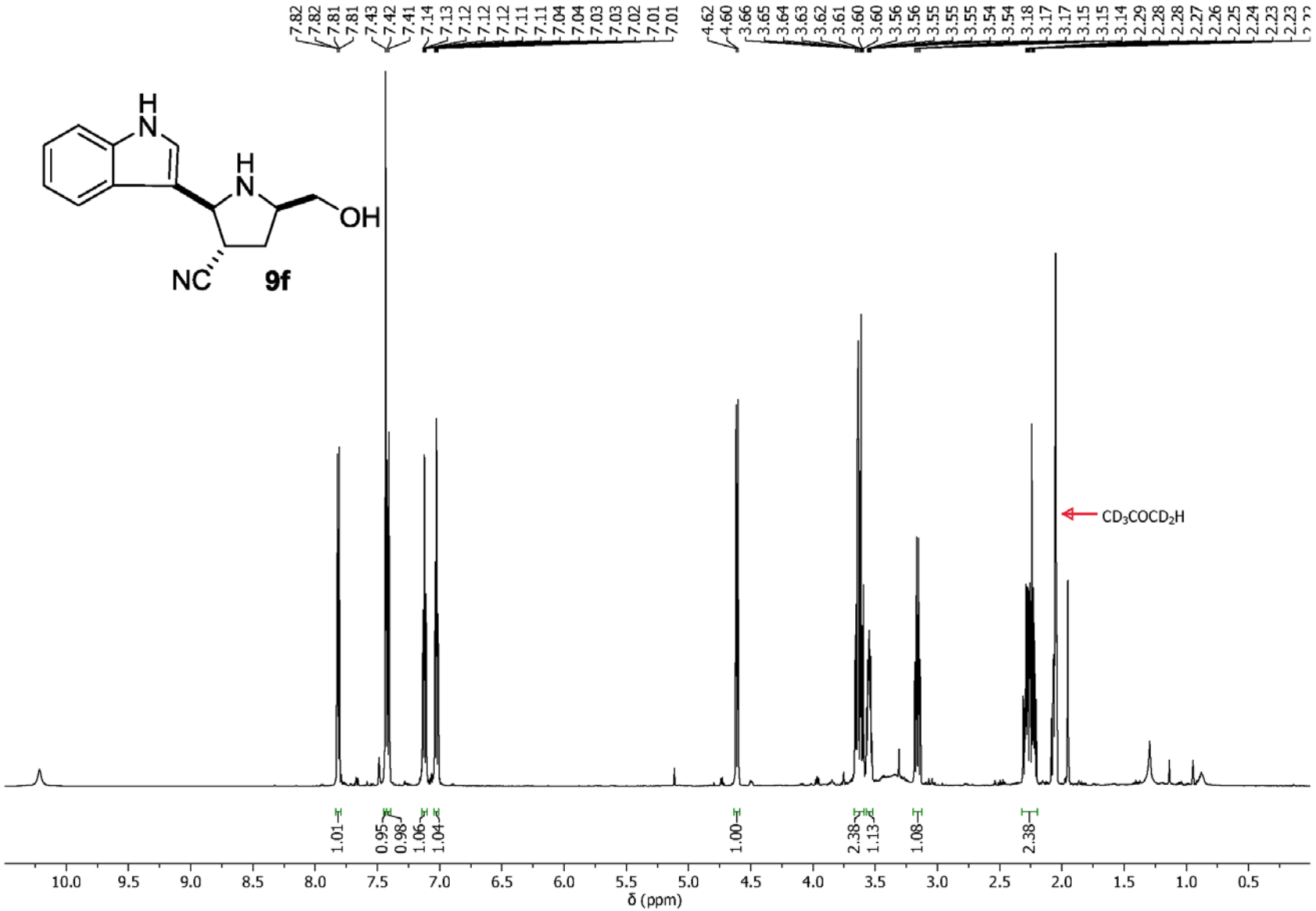
600 MHz ^{1}H NMR, $(CD_3)_2CO$



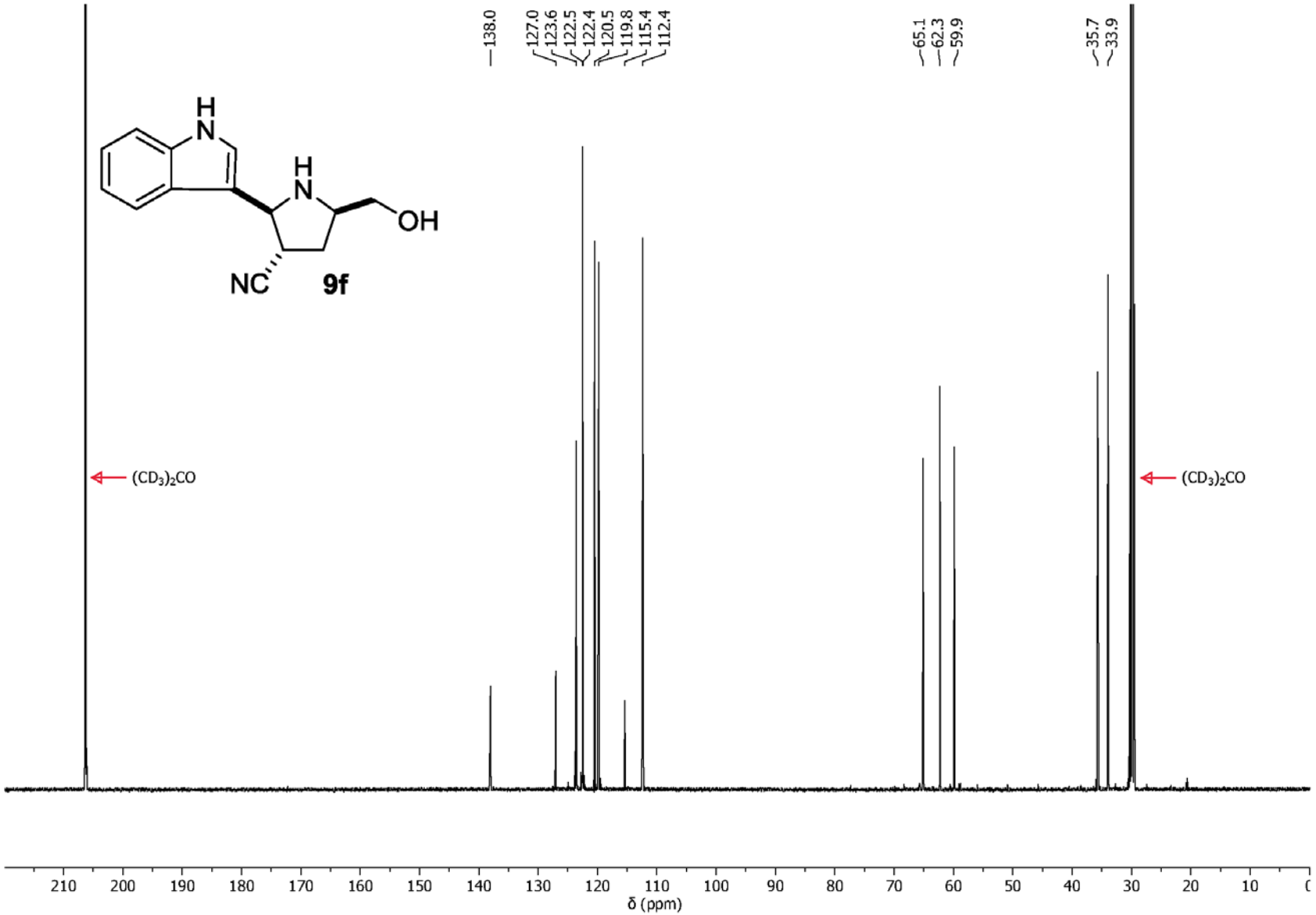
150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



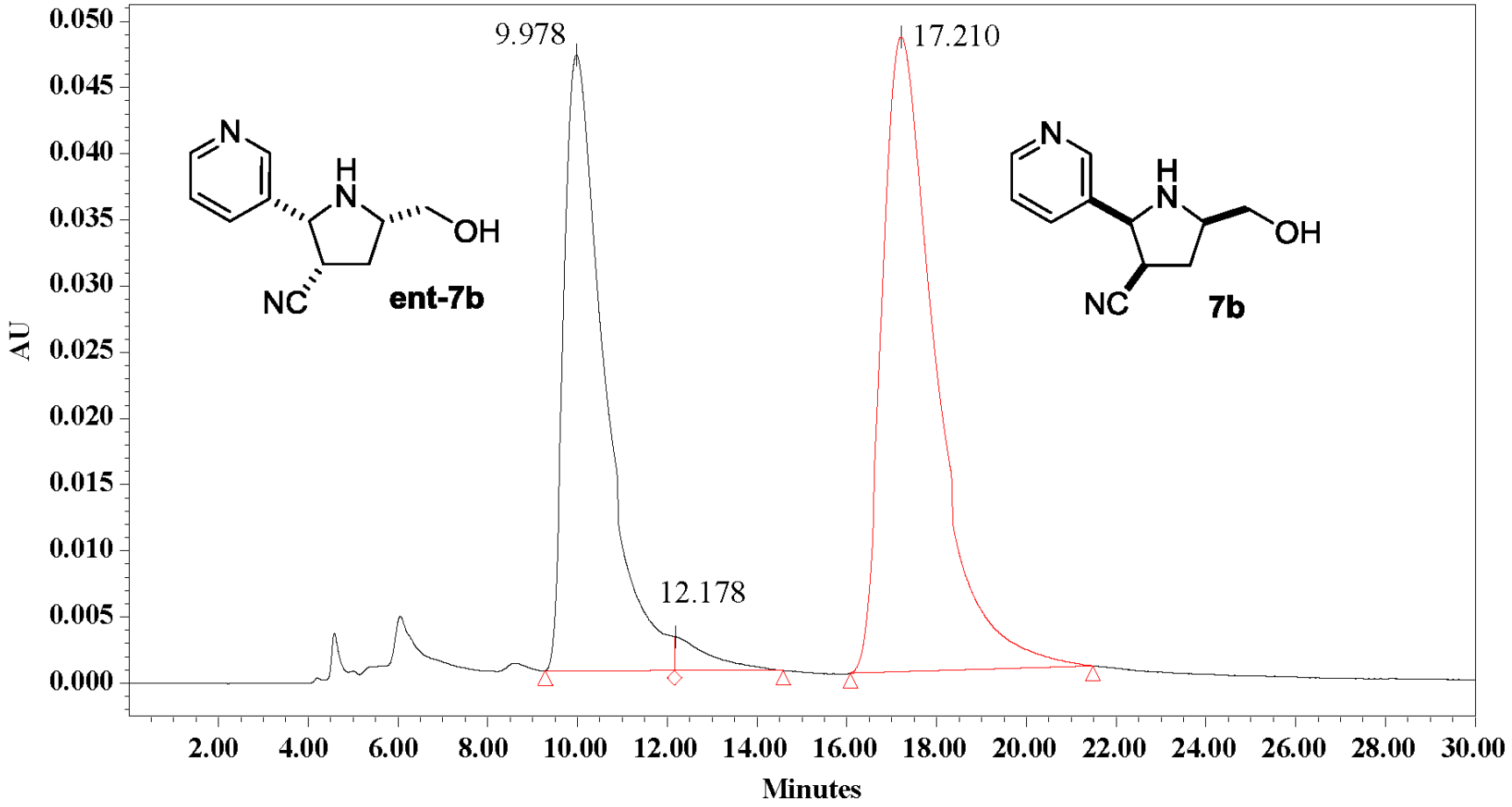
600 MHz ^{1}H NMR, $(CD_3)_2CO$



150.8 MHz ^{13}C NMR, $(CD_3)_2CO$



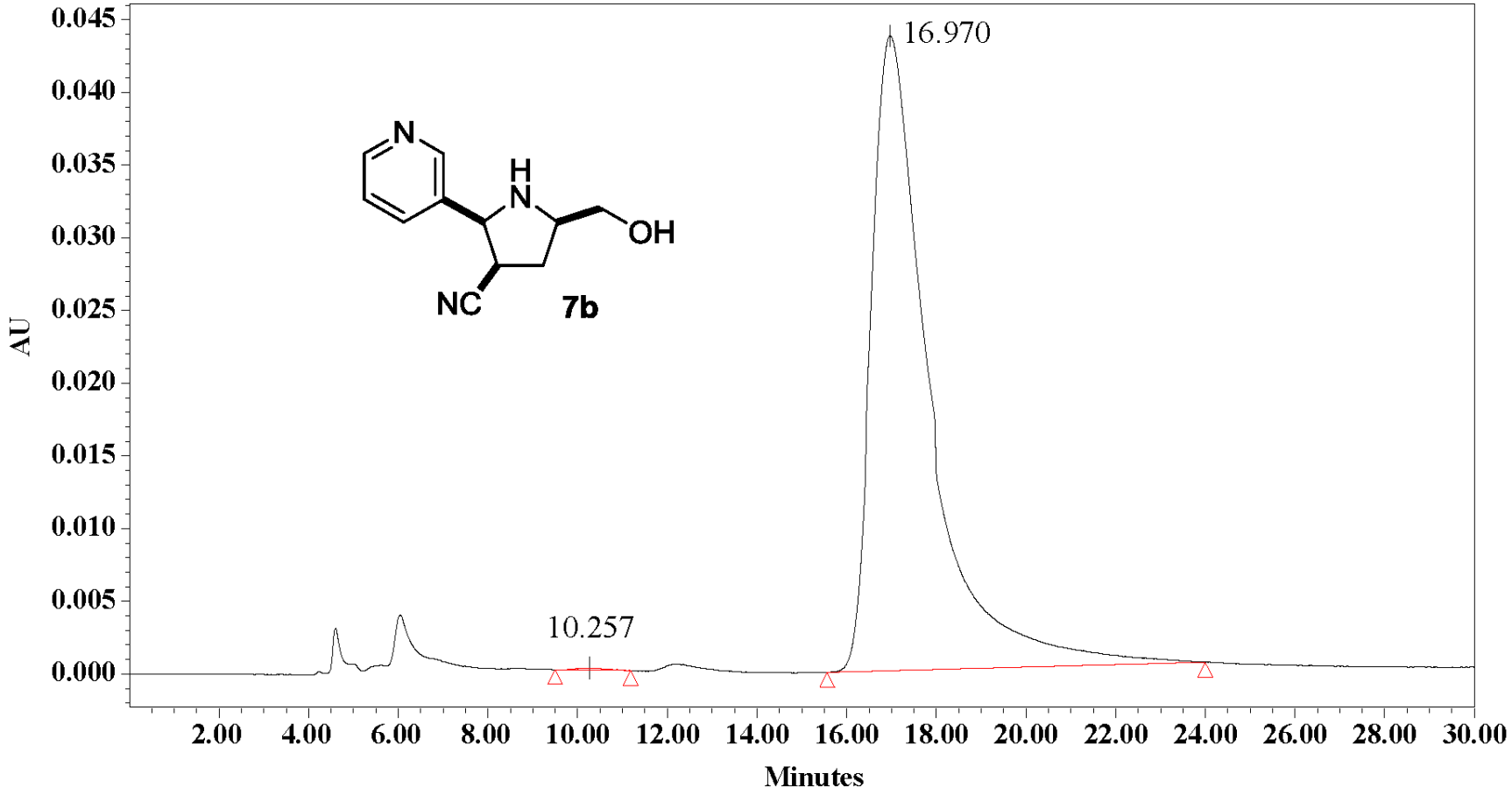
HPLC chromatograph of 7b and ent-7b



	RT	Area	% Area	Height
1	9.978	2920676	41.46	46511
2	12.178	131991	1.87	2549
3	17.210	3991869	56.67	47958

Diacel Chiral OD (4.6 x 250 nm) column, 75% iPrOH in hex over 30 min at 0.8 mL/min, 254 nm, **ent-7b**, t_R: 9.98; **7b**, t_R: 17.21.

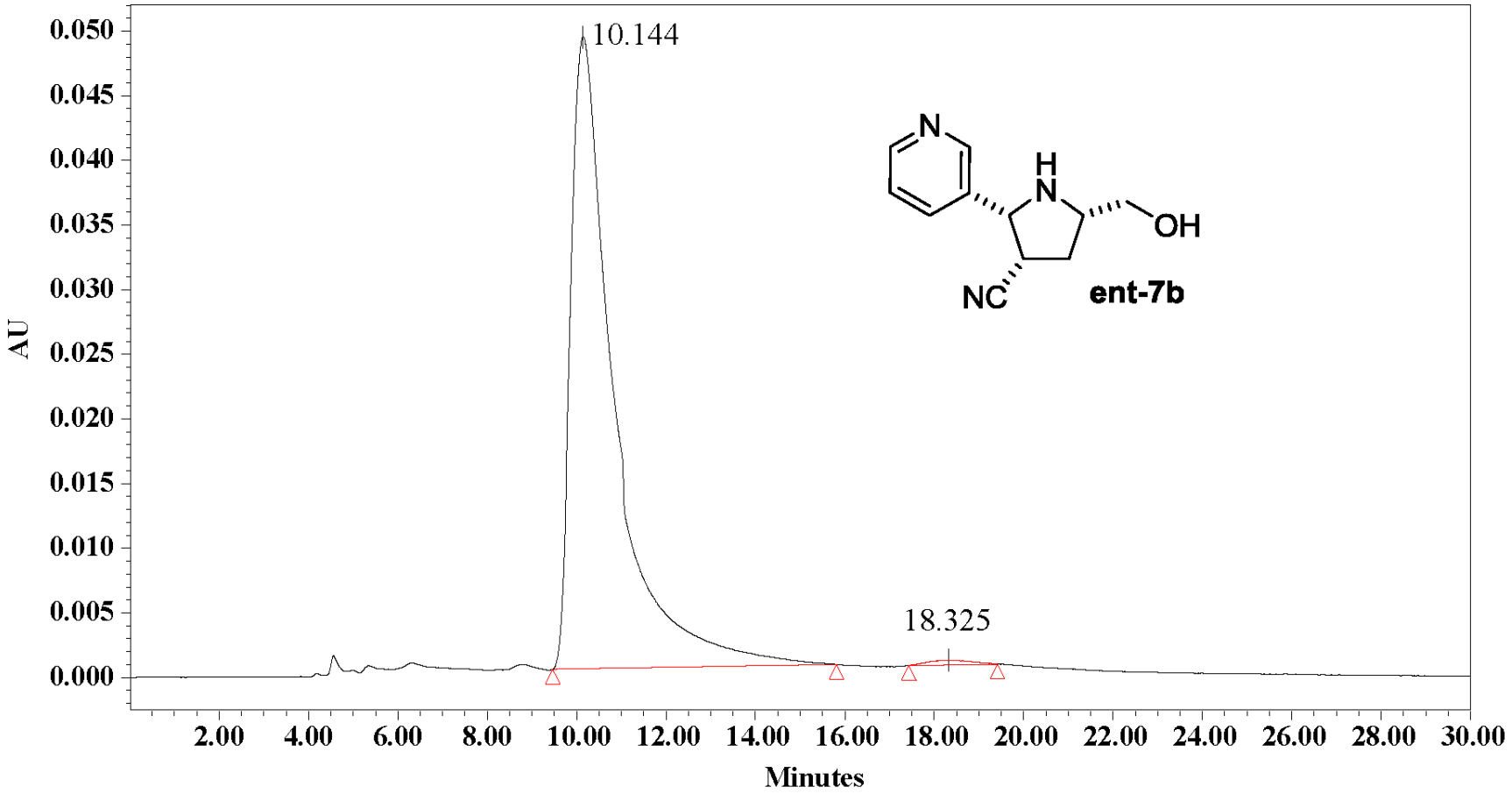
HPLC chromatograph of 7b



	RT	Area	% Area	Height
1	10.257	6071	0.15	135
2	16.970	3931668	99.85	43675

Diacel Chiral OD (4.6 x 250 nm) column, 75% iPrOH in hex over 30 min at 0.8 mL/min, 254 nm, **7b**, t_R: 16.97.

HPLC chromatograph of ent-7b



	RT	Area	% Area	Height
1	10.144	3307281	99.25	48868
2	18.325	25130	0.75	362

Diacel Chiral OD (4.6 x 250 nm) column, 75% iPrOH in hex over 30 min at 0.8 mL/min, 254 nm, **ent-7b**, t_R: 10.14.