Supplementary Information

Divergent and chemoselective deuteration of *N*-unsubstituted imidazoles enabled by precise acid/base control

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1. Author contributions and acknowledgements

1.1. Author contributions

Atsushi Kaga: conceptualization; direction; performing the syntheses; data curation; writing – manuscript.

Hayate Saito: computational study; writing – manuscript.

Mitsuhisa Yamano: supervision; writing – review.

1.2. Acknowledgements

The authors would like to thank Mr. Naoyuki Higuchi (HRMS).

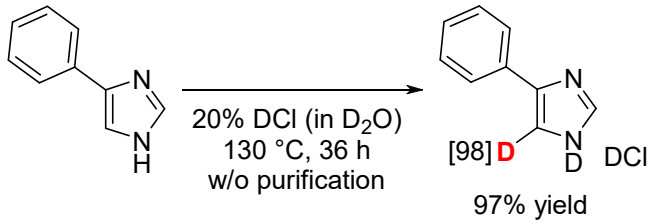
2. General

NMR spectra were recorded at 500 MHz (^{1}H) and 126 MHz (^{13}C) on a Bruker ULTRASHIELD™ 500 PLUS spectrometer. Chemical shifts are given in ppm (δ) and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Preparative flash chromatography was performed using Biotage® Sfär Silica HC D High Capacity Duo 20 μm. HRMS were obtained with a Thermo Fisher Scientific Orbitrap Elite spectrometer (H_2O/MeCN/HCO_2H conditions). LCMS was performed using a SHIMADZU LC-MS-2020 (H_2O/MeCN/NH_4OAc conditions). Due to the labile nature of N-D bonds in deuterated products under HRMS and LCMS conditions, their rapid reverse deuterium exchange to N-H bonds was observed during the analysis.

All substrates were commercially available compounds. 20 w/w% DCl (in D_2O) and CD_3OD were purchased from FUJIFILM Wako Pure Chemical Corporation. D_2O and 40 w/w% NaOD (in D_2O) were purchased from Cambridge Isotope Laboratories, Inc. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers.

3. C5-selective deuteration of imidazoles under acidic conditions

3.1. Synthesis of 4-phenyl-1*H*-imidazole-1,5-d_2 deuterochloride (2a) (Scheme 2a: typical procedure A)



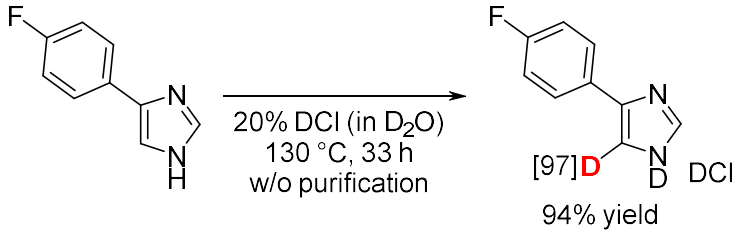
A test tube was charged with imidazole **1a** (57.8 mg, 0.401 mmol), 20 w/w% DCl (in D_2O) (4.0 mL). The tube was sealed and heated at 130 °C (bath temp.) for 36 h. Deuterium incorporation was monitored using ^{1}H NMR analysis [Preparation of ^{1}H NMR sample: Aliquot of the mixture (50 μL) was collected and diluted with CD_3OD (0.70 mL)]. The mixture was cooled to room temperature and transferred to the flask with CD_3OD. The mixture was concentrated under reduced pressure. The residue was dissolved in CD_3OD and concentrated under reduced pressure to provide imidazole **2a** (71.8 mg, 0.391 mmol, 97% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.47 – 7.52 (m, 1H), 7.53 – 7.57 (m, 2H), 7.70 – 7.82 (m, 2H), 7.94 – 7.96 (m, 0.02H), 9.03 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.2 (t, J = 30.2 Hz), 126.9, 128.1, 130.7, 131.0, 135.3, 135.9.

HRMS (*m/z*, ESI): Found: 146.0820. Calculated for $C_9H_8DN_2$: $(M+H)^+$ 146.0823.

3.2. Synthesis of 4-(4-fluorophenyl)-1*H*-imidazole-1,5-d_2 deuterochloride (2b) (Scheme 3)



Prepared using imidazole **1b** (65.1 mg, 0.401 mmol) for 33 h by typical procedure A.

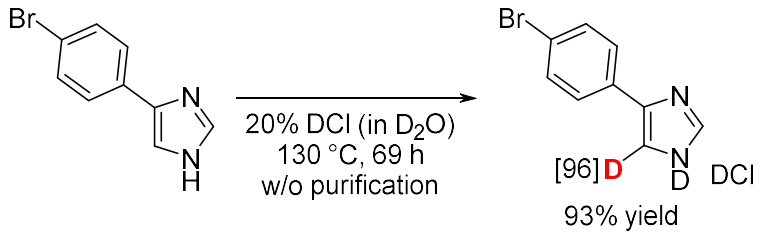
Yield: 75.8 mg (0.376 mmol, 94% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.28 – 7.31 (m, 2H), 7.79 – 7.83 (m, 2H), 7.91 – 7.95 (m, 0.03H), 9.03 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.2 (t, J = 30.2 Hz), 117.6 (d, J = 22.7 Hz), 124.5 (d, J = 3.8 Hz), 129.4 (d, J = 8.8 Hz), 134.4, 135.9, 165.0 (d, J = 249 Hz).

HRMS (*m/z*, ESI): Found: 164.0725. Calculated for $C_9H_7DN_2F$: $(M+H)^+$ 164.0729.

3.3. Synthesis of 4-(4-bromophenyl)-1*H*-imidazole-1,5-d_2 deuterochloride (2c) (Scheme 3)



Prepared using imidazole **1c** (89.0 mg, 0.399 mmol) for 69 h by typical procedure A.

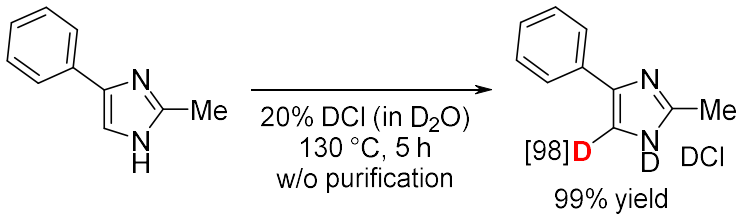
Yield: 97.4 mg (0.371 mmol, 93% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.67 – 7.73 (m, 4H), 7.97 – 8.00 (m, 0.04H), 9.04 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.7 (t, J = 30.9 Hz), 124.9, 127.3, 128.7, 133.8, 134.3, 136.2.

HRMS (*m/z*, ESI): Found: 223.9884. Calculated for $C_9H_7D^{79}BrN_2$: $(M+H)^+$ 223.9928.

3.4. Synthesis of 2-methyl-4-phenyl-1*H*-imidazole-1,5-d_2 deuterochloride (2d) (Scheme 3)



Prepared using imidazole **1d** (63.6 mg, 0.402 mmol) for 5 h by typical procedure A.

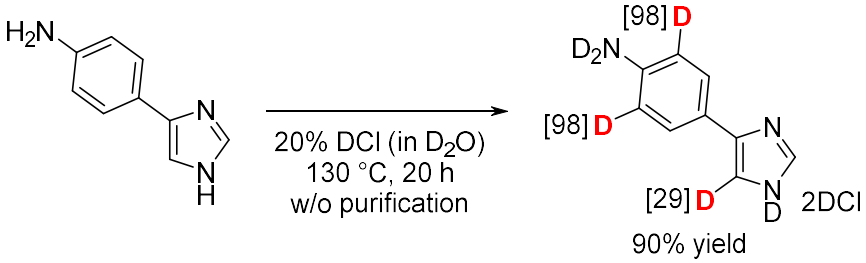
Yield: 78.6 mg (0.398 mmol, 99% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ 2.63 (s, 3H), 7.40 (t, J = 7.6 Hz, 1H), 7.49 (dd, J = 7.6, 7.6 Hz, 2H), 7.86 (d, J = 7.6 Hz, 2H), 8.00 – 8.04 (m, 0.02H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 11.9, 114.7 (t, J = 29.0 Hz), 125.4, 128.3, 129.0, 129.5, 132.6, 145.4.

HRMS (*m/z*, ESI): Found: 160.0976. Calculated for $C_{10}H_{10}DN_2$: $(M+H)^+$ 160.0980.

3.5. Synthesis of 4-(1*H*-imidazol-4-yl-1,5-d_2)benzen-2,6-d_2-amine-*d* dideuterochloride (2e) (Scheme 3)



Prepared using imidazole **1e** (63.3 mg, 0.398 mmol) for 20 h by typical procedure A.

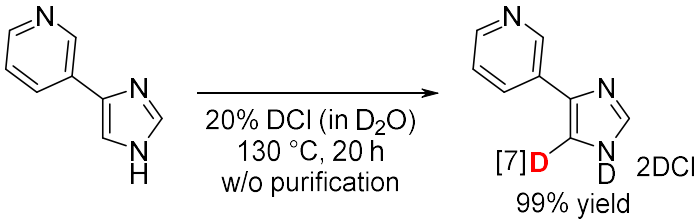
Yield: 86.0 mg (0.360 mmol, 90% yield) as an orange solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ 7.65 – 7.70 (m, 0.02H × 2), 7.85 (s, 2H), 8.09 (d, J = 1.3 Hz, 0.71H), 9.21 – 9.24 (m, 1H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 114.4, 119.8 – 120.1 (m), 121.6, 126.6, 132.3 – 132.4 (m), 134.4, 139.1.

HRMS (*m/z*, ESI): Found: 162.0991. Calculated for $C_9H_8D_2N_3$: $(M+H)^+$ 162.0995.

3.6. Synthesis of 3-(1*H*-imidazol-4-yl-1,5-*d*)pyridine dideuterochloride (2f) (Scheme 3)



Prepared using imidazole **1f** (58.1 mg, 0.400 mmol) for 20 h by typical procedure A.

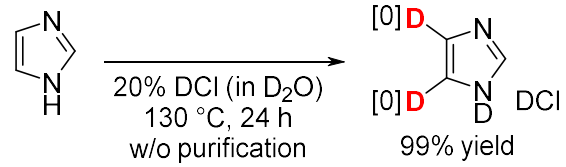
Yield: 88.5 mg (0.400 mmol, 99% yield) as an orange solid.

^{1}H NMR (500 MHz, CD_3OD): δ 8.16 (dd, *J* = 8.0, 5.8 Hz, 1H), 8.33 (d, *J* = 1.3 Hz, 0.93H), 8.87 (d, *J* = 8.5 Hz, 1H), 8.91 (d, *J* = 5.5 Hz, 1H), 9.20 (d, *J* = 1.3 Hz, 1H), 9.32 (d, *J* = 1.9 Hz, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 120.0, 128.6, 128.7, 129.9, 137.9, 142.0, 142.5, 144.7.

HRMS (*m/z*, ESI): Found: 146.0709. Calculated for $C_8H_8N_3$: $(M+H)^+$ 146.0713.

3.7. Synthesis of 1*H*-imidazole-1-*d* deuterochloride (2g) (Scheme 3)



Prepared using imidazole **1g** (27.1 mg, 0.398 mmol) for 24 h by typical procedure A.

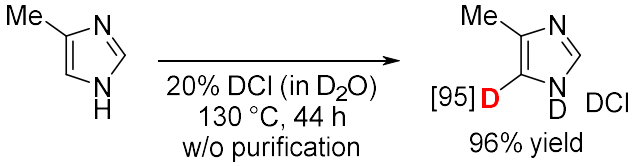
Yield: 42.3 mg (0.397 mmol, 99% yield) as a pale-yellow oil.

^{1}H NMR (500 MHz, D_2O): δ 7.40 (s, 2H), 8.62 (s, 1H).

^{13}C NMR (126 MHz, D_2O): δ 119.0, 133.4.

All the resonances in ^{1}H and ^{13}C NMR spectra were consistent with those of 1*H*-imidazole hydrochloride (**1g·HCl**).

3.8. Synthesis of 4-methyl-1*H*-imidazole-1,5-d_2 deuterochloride (2h) (Scheme 3)



Prepared using imidazole **1h** (33.0 mg, 0.402 mmol) for 44 h by typical procedure A.

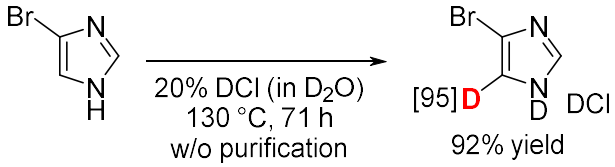
Yield: 46.8 mg (0.385 mmol, 96% yield) as a white solid.

^{1}H NMR (500 MHz, CD_3OD): δ 2.39 (s, 3H), 7.30 (m, 0.05H), 8.79 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 9.8, 117.0 (t, *J* = 30.9 Hz), 131.2, 134.5.

HRMS (*m/z*, ESI): Found: 84.0663. Calculated for $C_4H_6DN_2$: $(M+H)^+$ 84.0667.

3.9. Synthesis of 4-bromo-1*H*-imidazole-1,5-d_2 deuterochloride (2i) (Scheme 3)



Prepared using imidazole **1i** (58.5 mg, 0.398 mmol) for 71 h by typical procedure A.

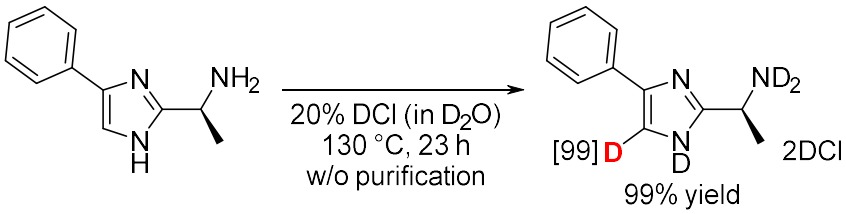
Yield: 68.5 mg (0.367 mmol, 92% yield) as a white solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.68 (s, 0.05H), 8.91 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 105.9, 120.9 (t, J = 30.9 Hz), 137.2.

HRMS (*m/z*, ESI): Found: 147.9615. Calculated for $C_3H_3D^{79}BrN_2$: $(M+H)^+$ 147.9615.

3.10. Synthesis of (*S*)-1-(4-phenyl-1*H*-imidazol-2-yl-1,5-d_2)ethan-1-amine-d_2 dideuterochloride (2j) (Scheme 3)



Prepared using imidazole **1j** (75.5 mg, 0.403 mmol) for 23 h by typical procedure A.

Yield: 106 mg (0.398 mmol, 99% yield) as a pale-yellow oil.

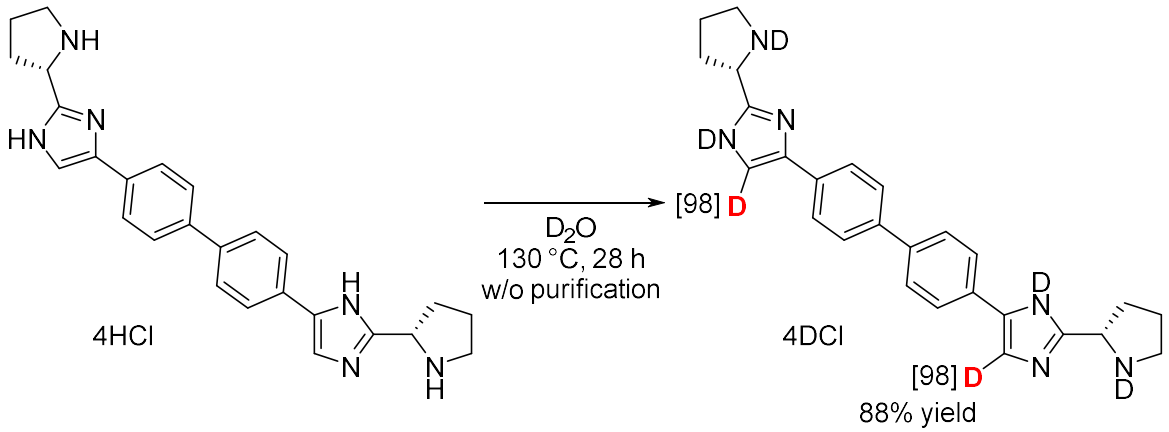
^{1}H NMR (500 MHz, D_2O): δ 1.81 (d, J = 6.6 Hz, 3H), 5.02 (q, J = 6.6 Hz, 1H), 7.41 – 7.50 (m, 2H), 7.62 (d, J = 6.9 Hz, 2H), 7.69 – 7.73 (m, 0.01H).

^{13}C NMR (126 MHz, D_2O): δ 16.0, 42.4, 115.9 (t, J = 31.8 Hz), 125.9, 126.0, 129.4, 130.1, 134.6, 141.3.

HRMS (*m/z*, ESI): Found: 172.0978. Calculated for $C_{11}H_{10}DN_2$: $(M - NH_2)^+$ 172.0980.

LCMS (*m/z*, ESI): Found: 189.05. Calculated for $C_{11}H_{13}DN_3$: $(M+H)^+$ 189.12.

3.11. Synthesis of 4,4'-bis(2-((*S*)-pyrrolidin-2-yl-1-*d*)-1*H*-imidazol-4-yl-1,5-d_2)-1,1'-biphenyl tetradeuterochloride (2k) (Scheme 3)



Prepared using imidazole **1k** (229 mg, 0.401 mmol) in D_2O (4.0 mL) instead of 20 w/w% DCl (in D_2O) for 28 h by typical procedure A.

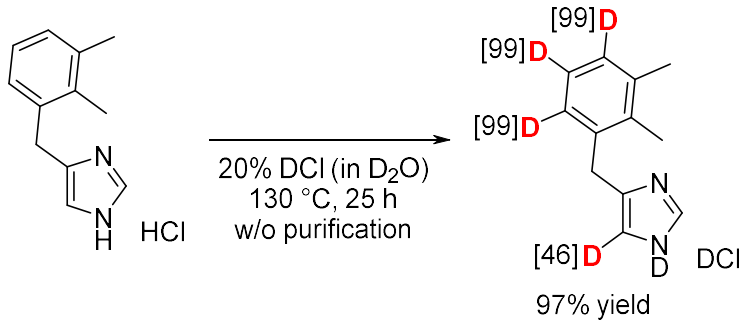
Yield: 205 mg (0.353 mmol, 88% yield) as a beige solid.

^{1}H NMR (500 MHz, CD_3OD): δ 2.20 – 2.31 (m, 2H), 2.42 (m, 2H), 2.54 – 2.63 (m, 2H), 2.70 – 2.78 (m, 2H), 3.61 (t, J = 6.6 Hz, 4H), 5.23 (t, J = 8.5 Hz, 2H), 7.90 (d, J = 7.9 Hz, 4H), 7.97 (d, J = 7.9 Hz, 4H), 8.09 – 8.13 (m, 0.02H×2).

^{13}C NMR (126 MHz, D_2O): δ 23.9, 28.9, 46.7, 53.1, 116.6 (t, J = 30.2 Hz), 125.9, 126.5, 127.6, 134.7, 139.8, 140.3.

HRMS (*m/z*, ESI): Found: 427.2564. Calculated for $C_{26}H_{27}D_2N_6$: $(M+H)^+$ 427.2574.

3.12. Synthesis of 4-(dimethylbenzyl)-1*H*-imidazole-1,5-d_2 deuterochloride (2l) (Scheme 3)



Prepared using imidazole **1l** (88.6 mg, 0.398 mmol) for 25 h by typical procedure A.

Yield: 88.4 mg (0.386 mmol, 97% yield) as a pale-yellow oil.

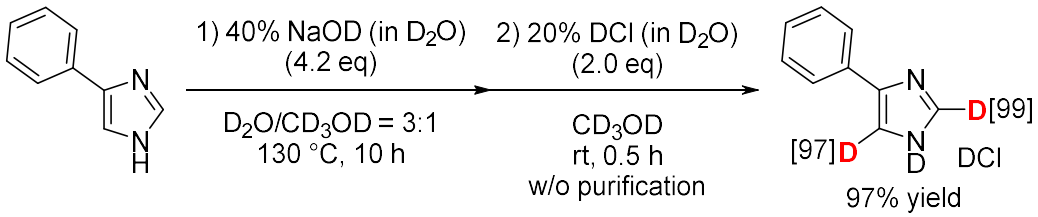
^{1}H NMR (500 MHz, D_2O): δ 2.03 (s, 3H), 2.15 (s, 3H), 3.95 (s, 2H), 6.93 (s, 0.54H), 6.98 – 7.17 (m, 0.01H×3), 8.47 (s, 1H).

^{13}C NMR (126 MHz, D_2O): δ 14.3, 19.5, 28.5, 115.4 – 115.8 (m), 125.5 (t, J = 24.6 Hz), 127.0 (t, J = 24.0 Hz), 128.7 (t, J = 23.9 Hz), 132.6 – 132.86 (m), 132.9, 134.6, 135.4, 137.9.

All the chemical shifts in ^{1}H and ^{13}C NMR spectra were consistent with those of Detomidine hydrochloride (**1l**).

4. Exhaustive deuteration of imidazoles under basic conditions

4.1. Synthesis of 4-phenyl-1*H*-imidazole-1,2,5-d_3 deuterochloride (3a) (Scheme 2b)



A test tube was charged with imidazole **1a** (57.8 mg, 0.401 mmol), CD_3OD (1.0 mL), D_2O (3.0 mL) and 40 w/w% NaOD (in D_2O) (0.12 mL, 1.68 mmol). The tube was sealed and heated at 130 °C (bath temp.) for 10 h. Deuterium incorporation was monitored using ^{1}H NMR analysis [Preparation of ^{1}H NMR sample: Aliquot of the mixture (25 μL) was collected and diluted with DMSO-d_6 (0.70 mL)]. The mixture was cooled to room temperature and neutralized with 20 w/w% DCl (in D_2O) (0.30 mL) at 0 °C. The resulting mixture was extracted four times with EtOAc (4 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure.

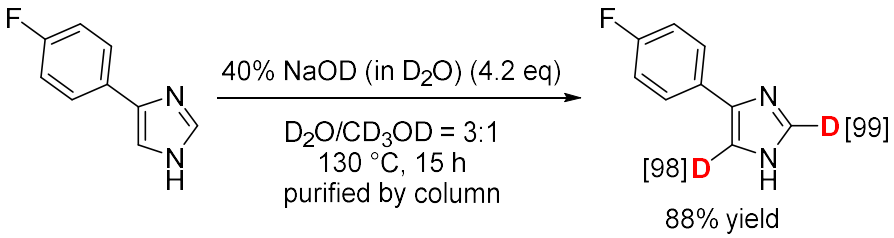
The flask including the crude obtained above was charged with CD_3OD (2.0 mL). 20 w/w% DCl (in D_2O) (133 μL, 0.798 mmol) was added and the mixture was stirred at room temperature for 0.5 h. The mixture was transferred to the flask with CD_3OD and concentrated under reduced pressure. The residue was dissolved in CD_3OD and concentrated under reduced pressure to provide imidazole **3a** (71.7 mg, 0.388 mmol, 97% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.49 (t, J = 7.5 Hz, 1H), 7.55 (dd, J = 7.7, 7.5 Hz, 2 H), 7.77 (d, J = 7.7 Hz, 2H), 7.95 (s, 0.03H), 9.01 – 9.06 (m, 0.01H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.1 (t, J = 30.2 Hz), 127.0, 128.1, 130.7, 131.0, 135.3, 135.8 (t, J = 32.8 Hz).

HRMS (*m/z*, ESI): Found: 147.0884. Calculated for $C_9H_7D_2N_2$: $(M+H)^+$ 147.0886.

4.2. Synthesis of 4-(4-fluorophenyl)-1*H*-imidazole-2,5-d_2 (3b) (Scheme 4: typical procedure B)



A test tube was charged with imidazole **1b** (65.1 mg, 0.401 mmol), CD_3OD (1.0 mL), D_2O (3.0 mL) and 40 w/w% NaOD (in D_2O) (0.12 mL, 1.68 mmol). The tube was sealed and heatad at 130 °C (bath temp.) for 15 h. Deuterium incorporation was monitored using ^{1}H NMR analysis [Preparation of ^{1}H NMR sample: Aliquot of the mixture (30 μL) was collected and diluted with DMSO-d_6 (0.70 mL)]. The mixture was cooled to room temperature and neutralized with 20 w/w% DCl (in D_2O) (0.30 mL) at 0 °C. The resulting mixture was extracted four times with EtOAc (4 mL). The combined organic layer was

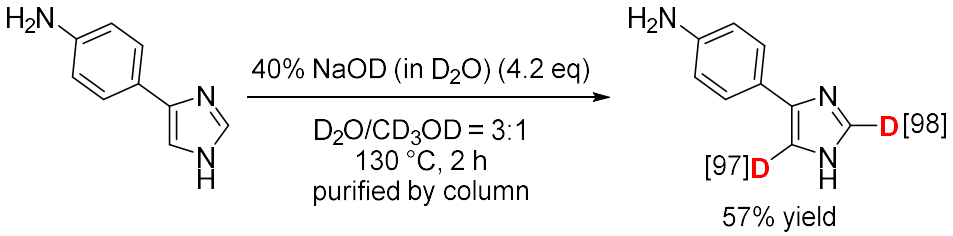
dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: $CHCl_3$/MeOH = 88:12) to provide imidazole **3b** (58.1 mg, 0.354 mmol, 88% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, CD_3CN): δ 7.12 – 7.16 (m, 2H), 7.39 – 7.41 (m, 0.02H), 7.64 – 7.66 (m, 0.01H), 7.79 – 7.82 (m, 2H).

^{13}C NMR (126 MHz, CD_3CN): δ 114.4 (t, *J* = 30.2 Hz), 116.6 (d, *J* = 22.7 Hz), 127.7 (d, *J* = 7.6 Hz), 132.3 (d, *J* = 2.5 Hz), 137.0 (t, *J* = 30.2 Hz), 140.0, 163.0 (d, *J* = 243 Hz).

HRMS (*m/z*, ESI): Found: 165.0790. Calculated for $C_9H_6D_2FN_2$: $(M+H)^+$ 165.0792.

4.3. Synthesis of 4-(1*H*-imidazol-4-yl-2,5-*d*$_2$)aniline (3e) (Scheme 4)



Prepared using imidazole **1e** (63.7 mg, 0.400 mmol) for 2 h by typical procedure B.

Yield: 36.9 mg (0.229 mmol, 57% yield) as an orange oil.

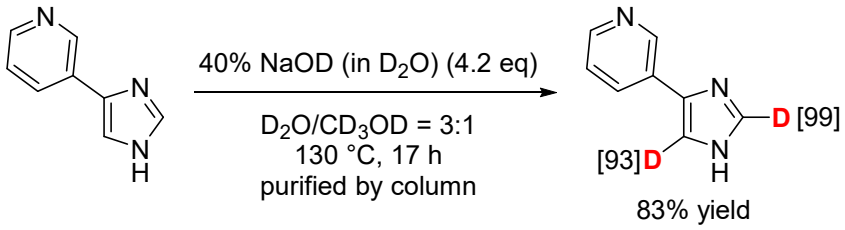
Eluent: $CHCl_3$/MeOH = 85:15

^{1}H NMR (500 MHz, CD_3OD): δ 6.76 (d, *J* = 7.7 Hz, 2H), 7.21 (s, 0.03H), 7.44 (d, *J* = 7.7 Hz, 2H), 7.68 (s, 0.02H).

^{13}C NMR (126 MHz, CD_3OD): δ 115.9 (t, *J* = 32.2 Hz), 116.8, 124.0, 127.1, 136.1 (t, *J* = 34.0 Hz), 139.0, 148.2.

HRMS (*m/z*, ESI): Found: 162.0991. Calculated for $C_9H_8D_2N_3$: $(M+H)^+$ 162.0995.

4.4. Synthesis of 3-(1*H*-imidazol-4-yl-2,5-*d*$_2$)pyridine (3f) (Scheme 4)



Prepared using imidazole **1f** (58.4 mg, 0.402 mmol) for 17 h by procedure B.

Yield: 49.2 mg (0.334 mmol, 83% yield) as an orange oil.

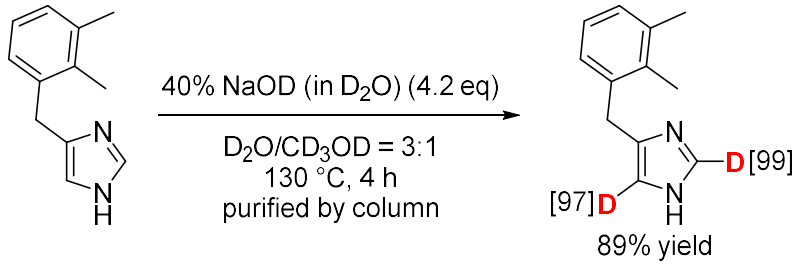
Eluent: $CHCl_3$/MeOH = 89:11

^{1}H NMR (500 MHz, CD_3OD): δ 7.42 – 7.45 (m, 1H), 7.63 (s, 0.07H), 7.80 – 7.84 (m, 0.01H), 8.16 (dt, *J* = 7.9, 1.9 Hz, 1H), 8.40 (dd, *J* = 5.0, 1.6 Hz, 1H), 8.93 (d, *J* = 1.6 Hz, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.4 (t, *J* = 24.0 Hz), 125.5, 131.8, 134.2, 137.3, 137.9 (t, *J* = 32.1 Hz), 146.7, 148.1.

HRMS (*m/z*, ESI): Found: 148.0835. Calculated for $C_8H_6D_2N_3$: $(M+H)^+$ 148.0838.

4.5. Synthesis of 4-(2,3-dimethylbenzyl)-1*H*-imidazole-2,5-d_2 (3l-free) (Scheme 4)



Prepared using imidazole **1l**-free (74.1 mg, 0.398 mmol) for 4 h by typical procedure B.

Yield: 66.5 mg (0.353 mmol, 89% yield) as a pale-yellow solid.

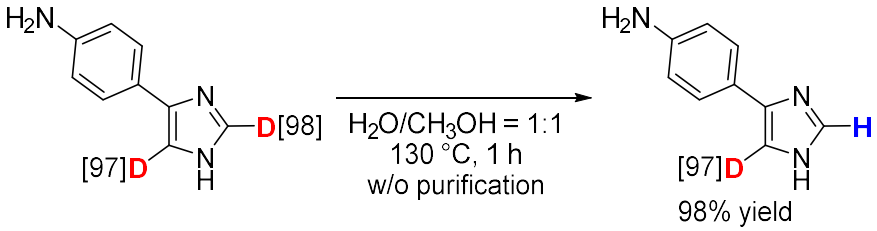
^{1}H NMR (500 MHz, CD_3OD): δ 2.18 (s, 3H), 2.28 (s, 3H), 3.94 (s, 2H), 6.47 – 6.54 (m, 0.03H), 6.98 – 7.04 (m, 3H), 7.56 – 7.60 (m, 0.01H).

^{13}C NMR (126 MHz, CD_3OD): δ 13.9, 19.3, 31.0, 117.0 (m), 125.1, 127.1, 127.9, 134.3 (t, J = 34.7 Hz), 134.4, 136.0, 136.5, 137.3.

All the chemical shifts in ^{1}H and ^{13}C NMR spectra were consistent with those of Detomidine free base (**1l**-free).

5. Synthesis of C5-deuterated imidazole 3e (C2-H) by C2-reverse deuterium exchange

5.1. Synthesis of 4-(1*H*-imidazol-4-yl-5-*d*)aniline (3e (C2-H)) (Scheme 5)



A test tube was charged with imidazole **3e** (27.1 mg, 0.168 mmol), CH_3OH (1.7 mL), and H_2O (1.7 mL). The tube was sealed and heated at 130 °C (bath temp.) for 1 h. After cooling the mixture to room temperature, the mixture was transferred to the flask with CH_3OH and concentrated under reduced pressure. The residue was dissolved with CH_3OH and concentrated under reduced pressure to provide imidazole **3e (C2-H)** (26.3 mg, 0.164 mmol, 98% yield) as a red oil.

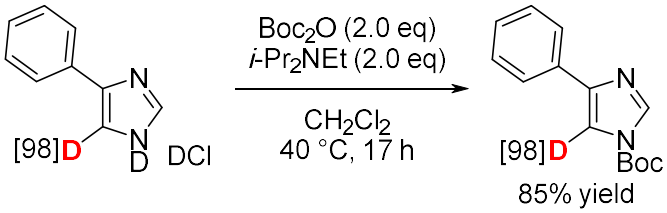
^{1}H NMR (500 MHz, CD_3OD): δ 6.76 (d, J = 7.9 Hz, 2H), 7.18 – 7.24 (m, 0.03H), 7.44 (d, J = 7.9 Hz, 2H), 7.67 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.0 (t, J = 29.0 Hz), 116.8, 124.0, 127.1, 136.3, 139.0, 148.2.

HRMS (*m/z*, ESI): Found: 161.0931. Calculated for $C_9H_9DN_3$: $(M+H)^+$ 161.0932.

6. Retention of deuterium incorporation in acylation of products

6.1. Synthesis of *tert*-butyl 4-phenyl-1*H*-imidazole-1-carboxylate-5-*d* (2a-Boc) (Scheme 6a: typical procedure C)



A test tube was charged with imidazole **2a** (36.7 mg, 0.200 mmol) and CH_2Cl_2 (2.0 mL). *i*-Pr_2NEt (68 µL, 0.400 mmol) and Boc_2O (92 µL, 0.400 mmol) were added at 0 °C. The mixture was stirred at 40 °C for 17 h and then cooled to room temperature. CH_2Cl_2 (15 mL) was added to the mixture and the resulting solution was washed with 20 w/w% NaCl aq. (15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: Hexane/EtOAc = 82:18) to provide *N*-Boc imidazole **2a-Boc** (41.9 mg, 0.171 mmol, 85% yield) as a pale-yellow solid.

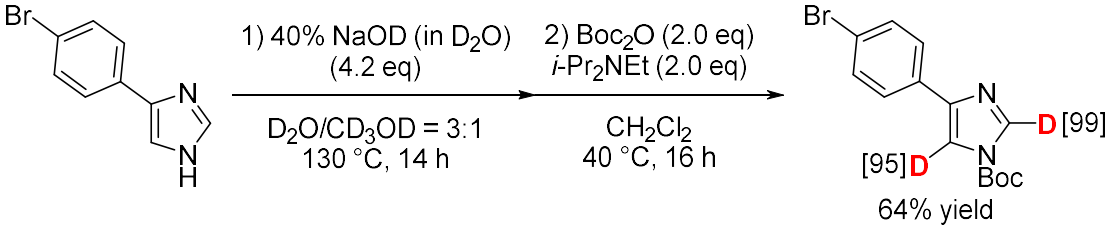
^{1}H NMR (500 MHz, CD_3OD): δ 1.68 (s, 9H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.41 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.80 (d, *J* = 7.4 Hz, 2H), 7.84 – 7.86 (m, 0.02H), 8.26 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 28.2, 87.5, 113.7 (t, *J* = 30.2 Hz), 126.5, 129.0, 129.9, 134.0, 139.0, 143.8, 148.4.

HRMS (*m/z*, ESI): Found: 146.0821. Calculated for $C_9H_8DN_2$: $(M - Boc + 2H)^+$ 146.0823.

LCMS (*m/z*, ESI): Found: 246.05. Calculated for $C_{14}H_{16}DN_2O_2$: $(M+H)^+$ 246.13.

6.2. Synthesis of *tert*-butyl 4-(4-bromophenyl)-1*H*-imidazole-1-carboxylate-2,5-d_2 (3c-Boc) (Scheme 6b)



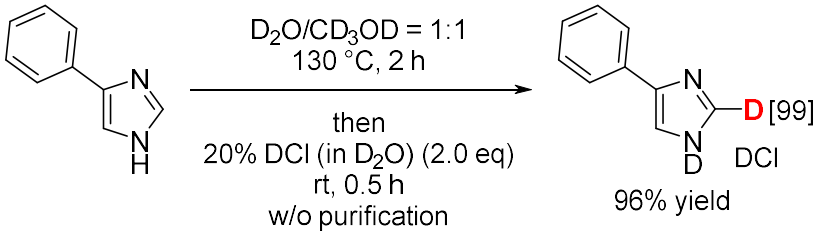
A test tube was charged with imidazole **1c** (89.0 mg, 0.399 mmol), CD_3OD (1.0 mL), D_2O (3.0 mL), and 40 w/w% NaOD (in D_2O) (0.12 mL, 1.68 mmol). The tube was sealed and heated at 130 °C (bath temp.) for 14 h. Deuterium incorporation was monitored using ^{1}H NMR analysis [Preparation of ^{1}H NMR sample: Aliquot of the mixture (25 µL) was collected and diluted with DMSO-d_6 (0.70 mL)]. The mixture was cooled to room temperature and neutralized with 20 w/w% DCl (in D_2O) (0.30 mL) at 0 °C. The resulting mixture was extracted four times with EtOAc (4 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was passed through a plug of silica gel with elusion of $CHCl_3$/MeOH = 90:10 before it was subjected to the next step.

The flask containing the crude obtained above was charged with CH_2Cl_2 (4.0 mL) and *i*-Pr_2NEt (136 µL, 0.800 mmol) at 0 °C. Boc_2O (184 µL, 0.801 mmol) was added at 0 °C and the mixture was stirred at 40 °C for 16 h. The mixture was cooled to room temperature and CH_2Cl_2 (5 mL) was added to the mixture. The mixture was washed with 20 w/w% NaCl aq. (10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: Hexane/EtOAc = 88:12) to provide *N*-Boc imidazole **3c-Boc** (83.3 mg, 0.256 mmol, 64% yield) as a white solid.

^{1}H NMR (500 MHz, CD_3OD): δ 1.68 (s, 9H), 7.56 (d, *J* = 7.7 Hz, 2H), 7.72 (d, *J* = 7.7 Hz, 2H), 7.91 (s, 0.05H), 8.26 (s, 0.01H).
^{13}C NMR (126 MHz, CD_3OD): δ 28.2, 87.6, 114.2 (t, *J* = 30.2 Hz), 122.6, 128.3, 133.0, 133.3, 138.9 (t, *J* = 32.1 Hz), 142.7, 148.3.
HRMS (*m/z*, ESI): Found: 268.9884. Calculated for $C_{10}H_6D_2{}^{79}BrN_2O_2$: $(M - tBu + 2H)^+$ 268.9889.
LCMS (*m/z*, ESI): Found: 324.95. Calculated for $C_{14}H_{14}D_2{}^{79}BrN_2O_2$: $(M+H)^+$ 325.05.

7. C2-selective deuteration of imidazoles under neutral conditions

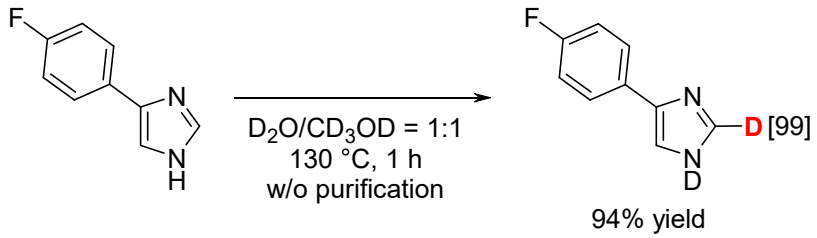
7.1. Synthesis of 4-phenyl-1*H*-imidazole-1,2-*d*$_2$ deuterochloride (4a) (Scheme 2c)



A test tube was charged with imidazole **1a** (57.9 mg, 0.399 mmol), CD_3OD (2.0 mL), and D_2O (2.0 mL). The tube was sealed and heatad at 130 °C (bath temp.) for 2 h. Deuterium incorporation was monitored using ^{1}H NMR analysis [Preparation of ^{1}H NMR sample: Aliquot of the mixture (30 µL) was collected and diluted with CD_3OD (0.70 mL) in the presence of 20 w/w% DCl (in D_2O) (30 µL)]. After cooling the mixture to room temperature, 20 w/w% DCl (in D_2O) (133 µL, 0.798 mmol) was added. The mixture was stirred at room temperature for 0.5 h. The mixture was transferred to the flask with CD_3OD and concentrated under reduced pressure. The residue was dissolved in CD_3OD and concentrated under reduced pressure to provide imidazole **4a** (70.7 mg, 0.385 mmol, 96% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.47 – 7.52 (m, 1H), 7.53 – 7.58 (m, 2H), 7.77 (d, *J* = 7.6 Hz, 2H), 7.95 (s, 1H), 9.02 – 9.07 (m, 0.01H).
^{13}C NMR (126 MHz, CD_3OD): δ 116.3, 127.0, 128.1, 130.7, 131.0, 135.4, 135.8 (t, *J* = 34.0 Hz).
HRMS (*m/z*, ESI): Found: 146.0823. Calculated for $C_9H_8DN_2$: $(M+H)^+$ 146.0823.

7.2. Synthesis of 4-(4-fluorophenyl)-1*H*-imidazole-1,2-d_2 (4b) (Scheme 7: typical procedure D)



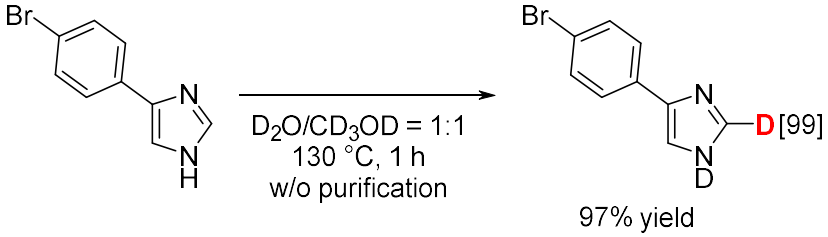
A test tube was charged with imidazole **1b** (64.9 mg, 0.400 mmol), CD_3OD (2.0 mL), and D_2O (2.0 mL). The tube was sealed and heatad at 130 °C (bath temp.) for 1 h. Deuterium incorporation was monitored using ^{1}H NMR analysis [Preparation of ^{1}H NMR sample: Aliquot of the mixture (25 μL) was collected and diluted with CD_3OD (0.70 mL)]. The mixture was cooled to room temperature and transferred to the flask with CD_3OD. The mixture was concentrated under reduced pressure. The residue was dissolved with CD_3OD and concentrated under reduced pressure to provide imidazole **4b** (61.5 mg, 0.375 mmol, 94% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, CD_3CN): δ 7.11 – 7.16 (m, 2H), 7.41 (s, 1H), 7.64 – 7.68 (m, 0.01H), 7.78 – 7.83 (m, 2H).

^{13}C NMR (126 MHz, CD_3CN): δ 114.6, 116.6 (d, J = 21.4 Hz), 127.7 (d, J = 7.6 Hz), 132.3 (d, J = 2.5 Hz), 137.0 (t, J = 31.5 Hz), 140.1, 163.0 (d, J = 243 Hz).

HRMS (*m/z*, ESI): Found: 164.0728. Calculated for $C_9H_7DFN_2$: $(M+H)^+$ 164.0729.

7.3. Synthesis of 4-(4-bromophenyl)-1*H*-imidazole-1.2-d_2 (4c) (Scheme 7)



Prepared using imidazole **1c** (88.9 mg, 0.399 mmol) for 1 h by typical procedure D.

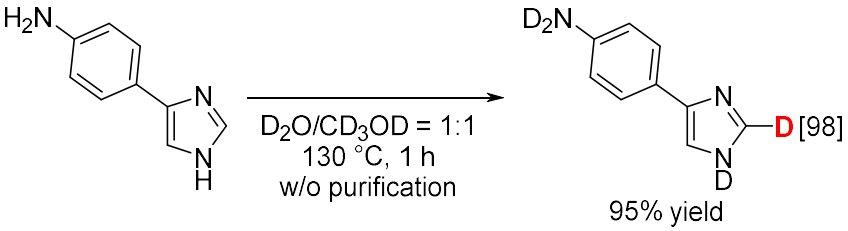
Yield: 86.8 mg (0.386 mmol, 97% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.50 (s, 1H), 7.53 (d, J = 7.4 Hz, 2H), 7.65 (d, J = 7.4 Hz, 2 H), 7.79 – 7.81 (m, 0.01H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.4, 121.5, 127.8, 133.0, 133.8, 137.3 (t, J = 32.1 Hz), 139.2.

HRMS (*m/z*, ESI): Found: 223.9928. Calculated for $C_9H_7D^{79}BrN_2$: $(M+H)^+$ 223.9928.

7.4. Synthesis of 4-(1*H*-imidazol-4-yl-1,2-d_2)aniline-d_2 (4e) (Scheme 7)



Prepared using imidazole **1e** (63.5 mg, 0.399 mmol) for 1 h by typical procedure D.

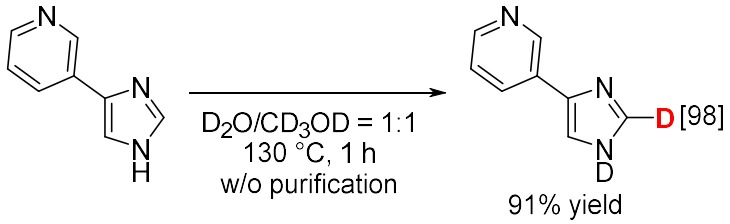
Yield: 62.2 mg (0.381 mmol, 95% yield) as an orange solid.

^{1}H NMR (500 MHz, CD_3OD): δ 6.74 – 6.78 (m, 2H), 7.20 (s, 1H), 7.43 – 7.46 (m, 2H), 7.63 – 7.67 (m, 0.02H).

^{13}C NMR (126 MHz, CD_3OD): δ 114.5, 115.3, 122.7, 125.5, 134.7 (t, J = 31.5 Hz), 137.7, 146.5.

HRMS (*m/z*, ESI): Found: 161.0930. Calculated for $C_9H_9DN_3$: $(M+H)^+$ 161.0932.

7.5. Synthesis of 3-(1*H*-imidazol-4-yl-1,2-d_2)pyridine (4f) (Scheme 7)



Prepared using imidazole **1f** (58.2 mg, 0.401 mmol) for 1 h by typical procedure D.

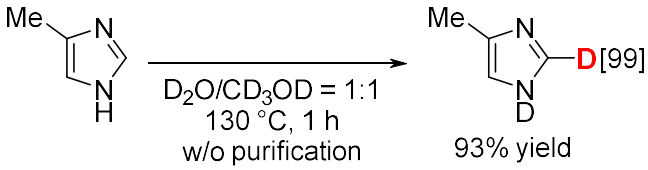
Yield: 54.0 mg (0.367 mmol, 91% yield) as an orange solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.44 – 7.49 (m, 1H), 7.64 (s, 1H), 7.81 – 7.84 (m, 0.02H), 8.17 (dt, J = 8.2, 1.9 Hz, 1H), 8.41 (dd, J = 4.9, 1.4 Hz, 1H), 8.94 (d, J = 1.6 Hz, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.5, 125.5, 131.9, 134.2, 137.5, 137.9 (t, J = 32.1 Hz), 146.7, 148.1.

HRMS (*m/z*, ESI): Found: 147.0774. Calculated for $C_8H_7DN_3$: $(M+H)^+$ 147.0776.

7.6. Synthesis of 4-methyl-1*H*-imidazole-1,2-d_2 (4h) (Scheme 7)



Prepared using imidazole **1h** (32.9 mg, 0.401 mmol) for 1 h by typical procedure D.

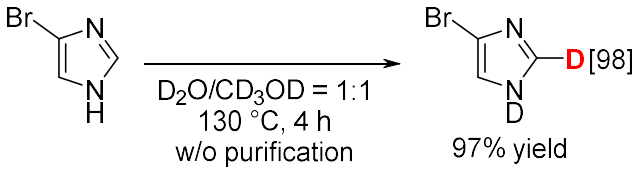
Yield: 31.5 mg (0.374 mmol, 93% yield) as a pale-yellow oil.

^{1}H NMR (500 MHz, CD_3OD): δ 2.20 (s, 3H), 6.72 (s, 1H), 7.49 – 7.56 (m, 0.01H).

^{13}C NMR (126 MHz, CD_3OD): δ 11.7, 118.8, 133.1, 135.5 (t, J = 31.5 Hz).

HRMS (*m/z*, ESI): Found: 84.0664. Calculated for $C_4H_6DN_2$: $(M+H)^+$ 84.0667.

7.7. Synthesis of 4-bromo-1*H*-imidazole-1,2-d_2 (4i) (Scheme 7)



Prepared using imidazole **1i** (58.6 mg, 0.399 mmol) for 4 h by typical procedure D.

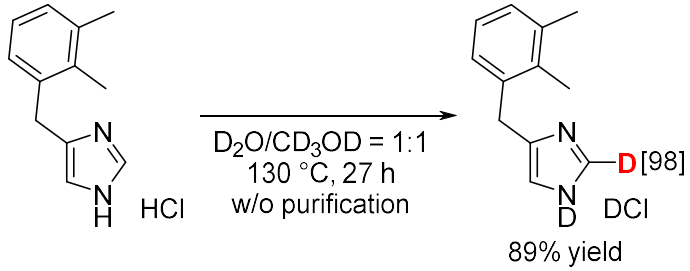
Yield: 57.4 mg (0.385 mmol, 97% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.13 (s, 1H), 7.63 (s, 0.02H).

^{13}C NMR (126 MHz, CD_3OD): δ 114.7, 117.3, 137.1 (t, J = 31.5 Hz).

HRMS (*m/z*, ESI): Found: 147.9614. Calculated for $C_3H_3D^{79}BrN_2$: $(M+H)^+$ 147.9615.

7.8. Synthesis of 4-(2,3-dimethylbenzyl)-1*H*-imidazole-1,2-d_2 deuterochloride (4l) (Scheme 7)



Prepared using imidazole **1l** (89.1 mg, 0.400 mmol) for 27 h by typical procedure D.

Yield: 80.5 mg (0.357 mmol, 89% yield) as a white solid.

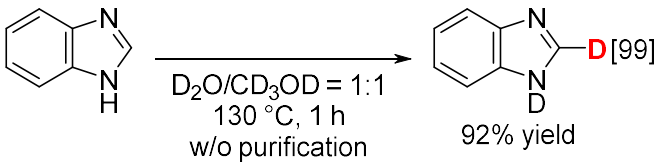
^{1}H NMR (500 MHz, D_2O): δ 2.07 (s, 3H), 2.19 (s, 3H), 4.00 (s, 2H), 6.95 (s, 1H), 7.01 – 7.05 (m, 1H), 7.05 – 7.13 (m, 2H), 8.43 – 8.52 (m, 0.02H).

^{13}C NMR (126 MHz, D_2O): δ 14.4, 19.6, 28.6, 115.8, 126.0, 127.5, 129.2, 132.8, 132.8 (t, J = 32.8 Hz), 134.8, 135.6, 138.1.

HRMS (*m/z*, ESI): Found: 82.0508. Calculated for $C_4H_4DN_2$: $(M - C_8H_9)^+$ 82.0510.

LCMS (*m/z*, ESI): Found: 188.10. Calculated for $C_{12}H_{14}DN_2$: $(M+H)^+$ 188.13.

7.9. Synthesis of 1*H*-benzo[*d*]imidazole-1,2-d_2 (4m) (Scheme 7)



Prepared using imidazole **1m** (47.4 mg, 0.401 mmol) for 1 h by typical procedure D.

Yield: 44.3 mg (0.369 mmol, 92% yield) as a white solid.

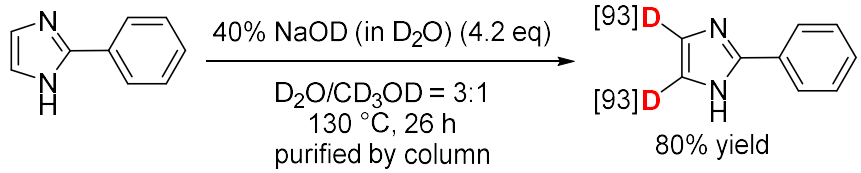
^{1}H NMR (500 MHz, CD_3OD): δ 7.24 – 7.28 (m, 2H), 7.62 (dd, J = 6.0, 3.2 Hz, 2H), 8.13 – 8.18 (m, 0.01H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.4, 123.9, 142.4 (t, J = 31.5 Hz).

HRMS (*m/z*, ESI): Found: 120.0665. Calculated for $C_7H_6DN_2$: $(M+H)^+$ 120.0667.

8. Imidazole-selective deuteration of 2-arylimidazoles under basic conditions

8.1. Synthesis of 2-phenyl-1*H*-imidazole-4,5-d_2 (5n) (Scheme 8a)



Prepared using imidazole **1n** (57.9 mg, 0.402 mmol) for 26 h by typical procedure B.

Yield: 47.2 mg (0.323 mmol, 80% yield) as a pale-yellow solid.

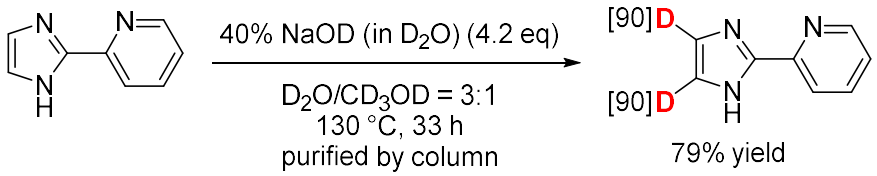
Eluent: $CHCl_3$/MeOH = 95:5

^{1}H NMR (500 MHz, acetone-d_6): δ 7.14 (s, 0.075H×2), 7.33 – 7.34 (m, 1H), 7.40 – 7.43 (m, 2H), 7.98 – 8.01 (m, 2H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 117.7 (m), 124.7, 127.8, 128.7, 129.0 (m), 130.8, 145.4.

HRMS (*m/z*, ESI): Found: 147.0885. Calculated for $C_9H_7D_2N_2$: $(M+H)^+$ 147.0886.

8.2. Synthesis of 2-(1*H*-imidazol-2-yl-4,5-d_2)pyridine (5o) (Scheme 8b)



Prepared using imidazole **1o** (58.0 mg, 0.400 mmol) for 33 h by typical procedure B.

Yield: 46.3 mg (0.315 mmol, 79% yield) as a pale-orange solid.

Eluent: $CHCl_3$/MeOH = 89:11

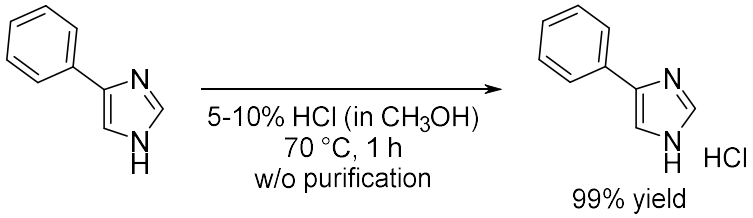
^{1}H NMR (500 MHz, DMSO-d_6): δ 7.08 (br s, 0.10H), 7.23 (br s, 0.10H), 7.36 (m, 1H), 7.87 – 7.88 (m, 1H), 8.04 (d, J = 7.9 Hz, 1H), 8.60 (m, 1H), 12.78 (br s, 1H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 118.3 – 118.5 (m), 119.4, 122.9, 129.1 – 129.3 (m), 137.2, 145.5, 148.9, 149.0.

HRMS (*m/z*, ESI): Found: 148.0837. Calculated for $C_8H_6D_2N_3$: $(M+H)^+$ 148.0838.

9. Synthesis and characterization of unlabeled compounds

9.1. Synthesis of 4-phenyl-1*H*-imidazole hydrochloride (1a·HCl) (typical procedure E)



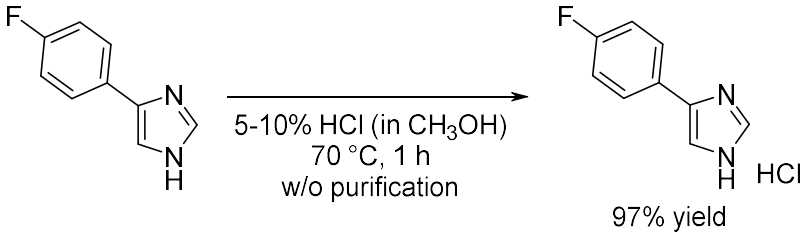
A test tube was charged with imidazole **1a** (57.5 mg, 0.399 mmol) and 5-10% HCl in CH_3OH (4.0 mL). The tube was sealed and heated at 70 °C (bath temp.) for 1 h. After cooling the mixture to room temperature, the mixture was transferred to the flask with CH_3OH and concentrated under reduced pressure to provide imidazole hydrochloride **1a·HCl** (71.3 mg, 0.395 mmol, 99% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.47 – 7.52 (m, 1H), 7.53 – 7.57 (m, 2H), 7.74 – 7.80 (m, 2H), 7.95 (d, J = 1.3 Hz, 1H), 9.04 (d, J = 1.3 Hz, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.4, 127.0, 128.0, 130.7, 131.0, 135.4, 135.9.

HRMS (*m/z*, ESI): Found: 145.0759. Calculated for $C_9H_9N_2$: $(M+H)^+$ 145.0760.

9.2. Synthesis of 4-(4-fluorophenyl)-1*H*-imidazole hydrochloride (1b·HCl)



Prepared using imidazole **1b** (64.0 mg, 0.395 mmol) for 1 h by typical procedure E.

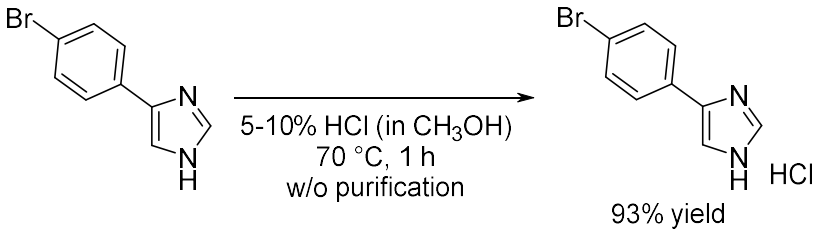
Yield: 76.2 mg (0.384 mmol, 97% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.27 – 7.32 (m, 2H), 7.79 – 7.83 (m, 2H), 7.93 (d, J = 1.6 Hz, 1H), 9.05 (d, J = 1.3 Hz, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.4, 117.6 (d, J = 22.7 Hz), 124.5 (d, J = 3.8 Hz), 129.4 (d, J = 8.8 Hz), 134.5, 136.0, 165.0 (d, J = 249 Hz).

HRMS (*m/z*, ESI): Found: 163.0664. Calculated for $C_9H_8FN_2$: $(M+H)^+$ 163.0666.

9.3. Synthesis of 4-(4-bromophenyl)-1*H*-imidazole hydrochloride (1c·HCl)



Prepared using imidazole **1c** (88.9 mg, 0.399 mmol) in for 1 h by typical procedure E.

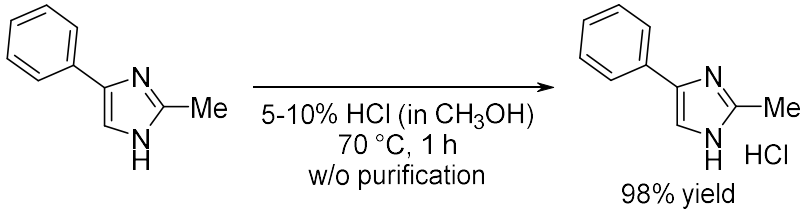
Yield: 96.5 mg (0.372 mmol, 93% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.68 – 7.74 (m, 4H), 8.00 (d, J = 1.3 Hz, 1H), 9.07 (d, J = 1.3 Hz, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.9, 124.9, 127.2, 128.7, 133.9, 134.3, 136.3.

HRMS (*m/z*, ESI): Found: 222.9777. Calculated for $C_9H_8{}^{79}BrN_2$: $(M+H)^+$ 222.9865.

9.4. Synthesis of 2-methyl-4-phenyl-1*H*-imidazole hydrochloride (1d·HCl)



Prepared using imidazole **1d** (63.0 mg, 0.398 mmol) for 1 h by typical procedure E.

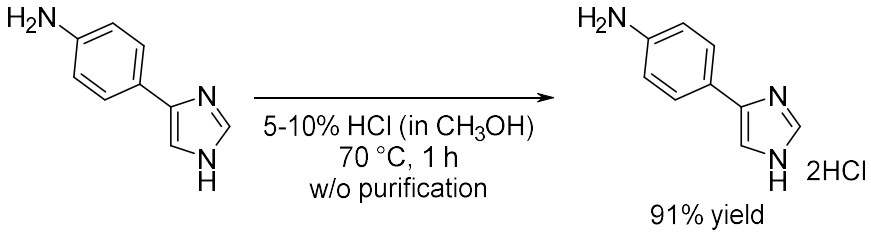
Yield: 75.8 mg (0.389 mmol, 98% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ 2.66 (s, 3H), 7.41 (t, J = 7.6 Hz, 1H), 7.50 (dd, J = 7.6, 7.4 Hz, 2H), 7.89 (d, J = 7.6 Hz, 2H), 8.03 (s, 1H), 14.55 – 15.05 (br s, 1H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 11.6, 114.8, 125.5, 127.6, 129.3, 129.6, 132.2, 145.5.

HRMS (*m/z*, ESI): Found: 159.0916. Calculated for $C_{10}H_{11}N_2$: $(M+H)^+$ 159.0917.

9.5. Synthesis of 4-(1*H*-imidazol-4-yl)aniline dihydrochloride (1e·HCl)



Prepared using imidazole **1e** (64.3 mg, 0.404 mmol) in for 1 h by typical procedure E.

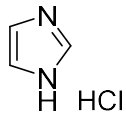
Yield: 85.5 mg (0.368 mmol, 91% yield) as a brown solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ 7.43 (d, J = 7.9 Hz, 2H), 7.99 (d, J = 7.9 Hz, 2H), 8.19 (s, 1H), 9.26 (s, 1H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 115.5, 122.7, 124.9, 126.7, 131.9, 134.9, 135.0.

HRMS (*m/z*, ESI): Found: 160.0867. Calculated for $C_9H_{10}N_3$: $(M+H)^+$ 160.0869.

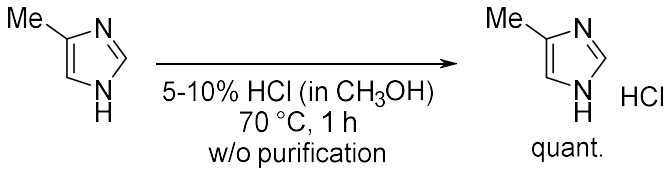
9.6. Characterization data of 1*H*-imidazole hydrochloride (1g·HCl) (CAS No. 1467-16-9)



^{1}H NMR (500 MHz, D_2O): δ 7.43 (s, 2H), 8.65 (s, 1H).

^{13}C NMR (126 MHz, D_2O): δ 119.0, 133.4.

9.7. Synthesis of 4-methyl-1*H*-imidazole hydrochloride (1h·HCl)



Prepared using imidazole **1h** (33.7 mg, 0.410 mmol) for 1 h by typical procedure E.

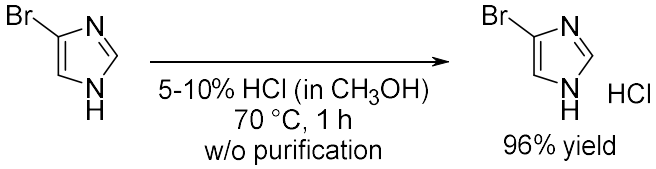
Yield: 54.7 mg (0.461 mmol, quant.) as a white solid.

^{1}H NMR (500 MHz, CD_3OD): δ 2.39 (s, 3 H), 7.30 (s, 1H), 8.79 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 9.76, 117.2, 131.3, 134.5.

HRMS (*m/z*, ESI): Found: 83.0601. Calculated for $C_4H_7N_2$: $(M+H)^+$ 83.0604.

9.8. Synthesis of 4-bromo-1*H*-imidazole hydrochloride (1i·HCl)



Prepared using imidazole **1i** (58.8 mg, 0.400 mmol) in for 1 h by typical procedure E.

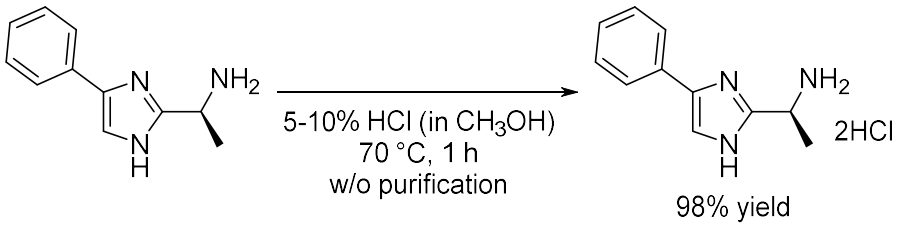
Yield: 70.2 mg (0.383 mmol, 96% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.72 (s, 1H), 9.00 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 105.5, 121.3, 137.3.

HRMS (*m/z*, ESI): Found: 146.9552. Calculated for $C_3H_4{}^{79}BrN_2$: $(M+H)^+$ 146.9552.

9.9. Synthesis of (*S*)-1-(4-phenyl-1*H*-imidazol-2-yl)ethan-1-amine dihydrochloride (1j·HCl)



Prepared using imidazole **1j** (75.2 mg, 0.402 mmol) for 1 h by typical procedure E.

Yield: 103 mg (0.394 mmol, 98% yield) as a yellow oil.

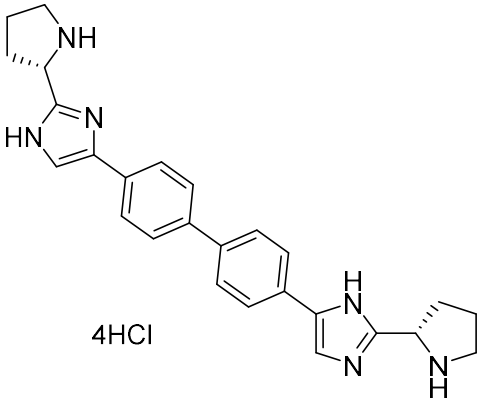
^{1}H NMR (500 MHz, D_2O): δ 1.83 (d, J = 6.9 Hz, 3H), 5.03 (q, J = 6.9 Hz, 1H), 7.45 – 7.52 (m, 3H), 7.64 (d, J = 7.3 Hz, 2 H), 7.72 (s, 1H).

^{13}C NMR (126 MHz, D_2O): δ 16.1, 42.5, 116.2, 126.0, 126.1, 129.4, 130.0, 134.8, 141.5.

HRMS (*m/z*, ESI): Found: 171.0916. Calculated for $C_{11}H_{11}N_2$: $(M - NH_2)^+$ 171.0917.

LCMS (*m/z*, ESI): Found: 188.10. Calculated for $C_{11}H_{14}N_3$: $(M+H)^+$ 188.12.

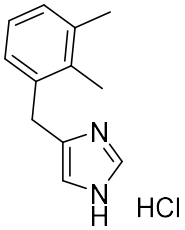
9.10. Characterization data of 4,4'-bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-4-yl)-1,1'-biphenyl tetrahydrochloride (1k) (CAS No. 1009119-83-8)



^{1}H NMR (500 MHz, CD_3OD): δ 2.27 (m, 2H), 2.39 – 2.47 (m, 2H), 2.54 – 2.63 (m, 2H), 2.71 – 2.79 (m, 2H), 3.59 – 3.66 (m, 4H), 5.22 (t, *J* = 8.7 Hz, 2H), 7.91 (m, 4H), 7.99 (m, 4H), 8.11 (s, 2H).

^{13}C NMR (126 MHz, D_2O): δ 23.9, 29.0, 46.7, 53.2, 116.8, 126.2, 126.5, 127.7, 135.0, 140.0, 140.6.

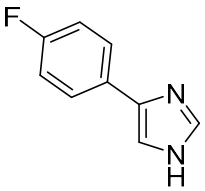
9.11. Characterization data of Detomidine Hydrochloride (1l) (CAS No. 90038-01-0)



^{1}H NMR (500 MHz, D_2O): δ 2.09 (s, 3H), 2.22 (s, 3H), 4.03 (s, 2H), 6.97 (s, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.10 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 8.49 (s, 1H).

^{13}C NMR (126 MHz, D_2O): δ 14.4, 19.6, 28.6, 115.9, 126.0, 127.5, 129.2, 132.8, 133.0, 134.8, 135.6, 138.1.

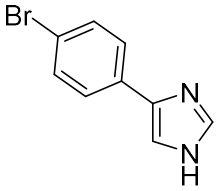
9.12. Characterization data of 4-(4-fluorophenyl)-1*H*-imidazole (1b) (CAS: 65020-70-4)



^{1}H NMR (500 MHz, CD_3CN): δ 7.12 – 7.16 (m, 2H), 7.41 (d, *J* = 0.95 Hz, 1H), 7.66 (d, *J* = 0.95 Hz, 1H), 7.79 – 7.82 (m, 2H).

^{13}C NMR (126 MHz, CD_3CN): δ 114.7, 116.6 (d, *J* = 21.4 Hz), 127.7 (d, *J* = 7.6 Hz), 132.3 (d, *J* = 3.8 Hz), 137.2, 140.2, 163.0 (d, *J* = 243 Hz).

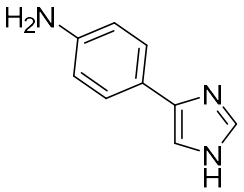
9.13. Characterization data of 4-(4-bromophenyl)-1*H*-imidazole (1c) (CAS No. 13569-96-5)



^{1}H NMR (500 MHz, CD_3OD): δ 7.50 (d, *J* = 1.3 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 1.0 Hz, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.4, 121.5, 127.8, 133.0, 133.8, 137.5, 139.2.

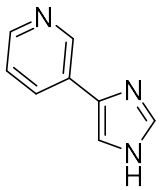
9.14. Characterization data of 4-(1*H*-imidazol-4-yl)aniline (1e) (CAS No. 29528-28-7)



^{1}H NMR (500 MHz, CD_3OD): δ 6.74 – 6.78 (m, 2H), 7.20 (d, *J* = 1.3 Hz, 1H), 7.42 – 7.46 (m, 2H), 7.65 (d, *J* = 0.95 Hz, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.2, 116.8, 124.2, 127.1, 136.4, 139.3, 148.1.

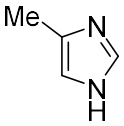
9.15. Characterization data of 3-(1*H*-imidazol-4-yl)pyridine (1f) (CAS No. 51746-85-1)



^{1}H NMR (500 MHz, CD_3OD): δ 7.45 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.64 (s, 1H), 7.83 (s, 1H), 8.17 (dt, *J* = 8.0, 1.9 Hz, 1H), 8.40 (dd, *J* = 4.7, 1.0 Hz, 1H), 8.91 – 8.97 (m, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.5, 125.5, 131.9, 134.2, 137.5, 138.1, 146.7, 148.1.

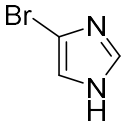
9.16. Characterization data of 4-methyl-1*H*-imidazole (1h) (CAS No. 822-36-6)



^{1}H NMR (500 MHz, CD_3OD): δ 2.22 (d, *J* = 0.95 Hz, 3H), 6.74 (s, 1H), 7.54 (d, *J* = 0.95 Hz, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 11.7, 118.8, 133.2, 135.7.

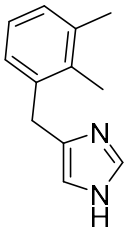
9.17. Characterization data of 4-bromo-1*H*-imidazole (1i) (CAS No. 2302-25-2)



^{1}H NMR (500 MHz, CD_3OD): δ 7.13 (s, 1H), 7.63 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 114.6, 117.4, 137.1.

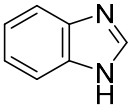
9.18. Characterization data of Detomidine free base (1l-free) (CAS No. 76631-46-4)



^{1}H NMR (500 MHz, CD_3OD): δ 2.18 (s, 3H), 2.28 (s, 3H), 3.93 (s, 2H), 6.52 (s, 1H), 6.98 – 7.04 (m, 3H), 7.58 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 13.9, 19.3, 31.1, 117.2, 125.1, 127.1, 127.9, 134.4, 134.5, 136.2, 136.5, 137.3.

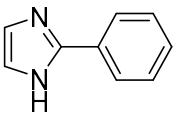
9.19. Characterization data of 1*H*-benzo[*d*]imidazole (1m) (CAS No. 51-17-2)



^{1}H NMR (500 MHz, CD_3OD): δ 7.23 – 7.24 (m, 2 H), 7.59 (m, 2H), 8.13 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.3, 123.9, 142.6.

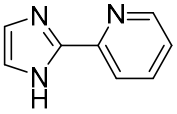
9.20. Characterization data of 2-phenyl-1*H*-imidazole (1n) (CAS No. 670-96-2)



^{1}H NMR (500 MHz, acetone-d_6): δ 7.06 – 7.22 (m, 2H), 7.33 (t, J = 7.5 Hz, 1H), 7.42 (d, J = 7.8, 7.5 Hz, 2H), 7.99 (d, J = 7.8 Hz, 2H), 11.29 – 12.31 (br s, 1H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 117.6, 124.7, 127.9, 128.7, 129.0, 130.9, 145.5.

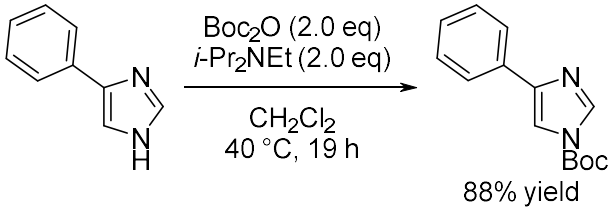
9.21. Characterization data of 2-(1*H*-imidazol-2-yl)pyridine (1o) (CAS No. 18653-75-3)



^{1}H NMR (500 MHz, DMSO-d_6): δ 7.09 (br s, 1H), 7.24 (br s, 1H), 7.36 – 7.37 (m, 1H), 7.87 – 7.88 (m, 1H), 8.05 (d, J = 7.9 Hz, 1H), 8.60 (m, 1H), 12.79 (br s, 1H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 118.7, 119.4, 122.9, 129.5, 137.2, 145.6, 148.9, 149.0.

9.22. Synthesis of *tert*-butyl 4-phenyl-1*H*-imidazole-1-carboxylate (1a-Boc)



88% yield

Prepared using imidazole **1a** (43.4 mg, 0.301 mmol) by typical procedure C.

Yield: 65.0 mg (0.266 mmol, 88% yield) as a pale-yellow solid.

Eluent: Hexane/EtOAc = 82:18

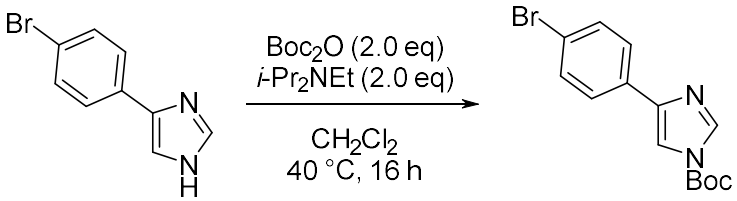
^{1}H NMR (500 MHz, CD_3OD): δ 1.68 (s, 9H), 7.31 (t, J = 7.2 Hz, 1H), 7.41 (dd, J = 7.2, 7.2 Hz, 2H), 7.80 (d, J = 7.2 Hz, 2H), 7.84 – 7.87 (m, 1H), 8.23 – 8.27 (m, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 28.2, 87.5, 113.9, 126.5, 129.0, 129.9, 134.0, 139.0, 144.0, 148.4.

HRMS (*m/z*, ESI): Found: 145.0759. Calculated for $C_9H_9N_2$: $(M - Boc + 2H)^+$ 145.0760.

LCMS (*m/z*, ESI): Found: 245.05. Calculated for $C_{14}H_{17}N_2O_2$: $(M+H)^+$ 245.13.

9.23. Synthesis of *tert*-butyl 4-(4-bromophenyl)-1*H*-imidazole-1-carboxylate (1c-Boc)



87% yield

Prepared using imidazole **1c** (89.1 mg, 0.399 mmol) by typical procedure C.

Yield: 112 mg (0.346 mmol, 87% yield) as a white solid.

Eluent: Hexane/EtOAc = 88:12

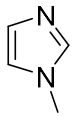
^{1}H NMR (500 MHz, CD_3OD): δ 1.68 (s, 9H), 7.55 (d, J = 7.6 Hz, 2H), 7.73 (d, J = 7.6 Hz, 2H), 7.91 (d, J = 1.3 Hz, 1H), 8.26 (d, J = 1.3 Hz, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 28.2, 87.6, 114.4, 122.6, 128.3, 133.0, 133.3, 139.2, 142.8, 148.3.

HRMS (*m/z*, ESI): Found: 266.9762. Calculated for $C_{10}H_8{}^{79}BrN_2O_2$: $(M - t\text{Bu} + 2H)^+$ 266.9764.

LCMS (*m/z*, ESI): Found: 322.95. Calculated for $C_{14}H_{16}{}^{79}BrN_2O_2$: $(M+H)^+$ 323.04.

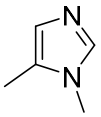
9.24. Characterization data of 1-methyl-1*H*-imidazole (1g-Me) (CAS No. 616-47-7)



^{1}H NMR (500 MHz, CD_3OD): δ 3.72 (s, 3H), 6.94 (s, 1H), 7.06 (s, 1H), 7.57 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 32.1, 120.4, 127.6, 137.7.

9.25. Characterization data of 1,5-dimethyl-1*H*-imidazole (1p) (CAS No. 10447-93-5)

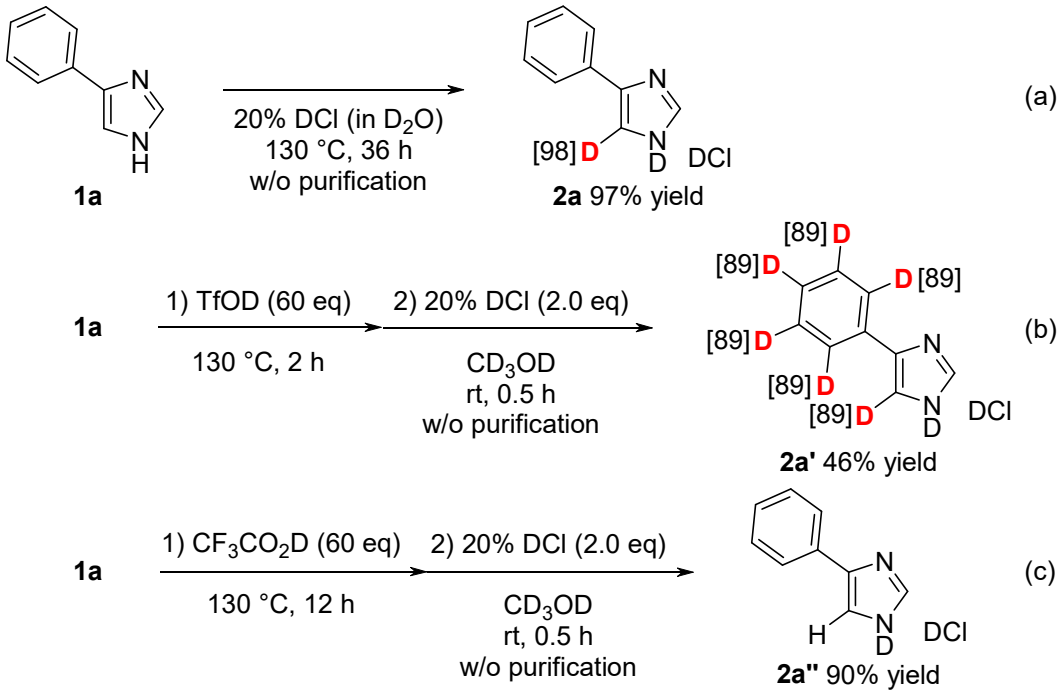


^{1}H NMR (500 MHz, CD_3OD): δ 2.21 – 2.23 (m, 3H), 3.61 (s, 3H), 6.69 (s, 1H), 7.52 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 7.3, 30.0, 124.7, 128.2, 137.0.

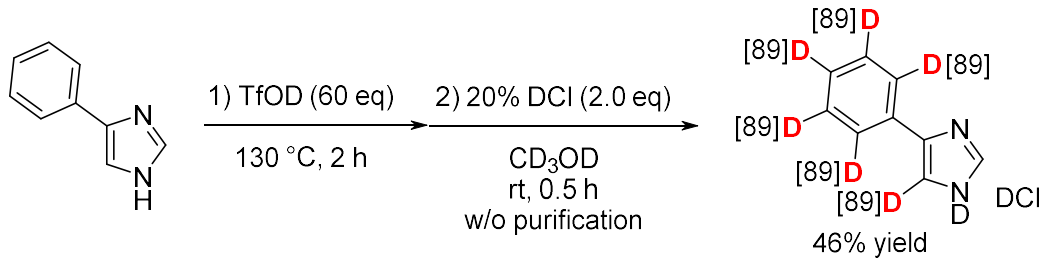
10. Investigation of acid strength for C5-deuteration of 4-phenylimidazole (1a)

To achieve the C5-selective deuteration of 4-phenylimidazole (**1a**), the effect of acidity was investigated. The treatment of **1a** with superacid TfOD[1] instead of DCl (in D_2O) promoted concurrent deuteration of the aromatic ring along with that of C5 position on the imidazole (Scheme S1a and S1b). On the other hand, the use of TFA-*d* which is weaker than DCl resulted in no deuteration of C-H bonds on the imidazole at all (Scheme S1c). To determine the degree of deuteration incorporation onto **1a**, products were converted to DCl salts **2a'** and **2a"**. These results indicated that the choice of an appropriate acid is the key for achieving the C5-deuteration of the imidazole as well as the imidazole-selectivity.



Scheme S1. Effect of acidity for C5-deuteration of **1a** using a) DCl (in D_2O), b) TfOD, c) CF_3CO_2D.

10.1. Synthesis of 4-(phenyl-d_5)-1*H*-imidazole-1,5-d_2 deuterochloride (2a')



A test tube was charged with imidazole **1a** (33.1 mg, 0.230 mmol) and TfOD (2.07 g, 13.7 mmol) at 0 °C. The tube was sealed and heated at 130 °C (bath temp.) for 2 h. Deuterium incorporation was monitored using ^{1}H NMR analysis [Preparation of ^{1}H NMR sample: Aliquot of the mixture (15 μL) was collected and diluted with CD_3OD (0.70 mL)]. The mixture was cooled to room temperature and quenched with D_2O (2.0 mL), 40 w/w% NaOD (in D_2O) (0.70 mL), and 20 w/w% DCl (in D_2O) (50 μL) at 0 °C. The resulting mixture was extracted thrice with EtOAc (10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting mixture was suspended with $CHCl_3$ (25 mL) and then filtered and concentrated under reduced pressure.

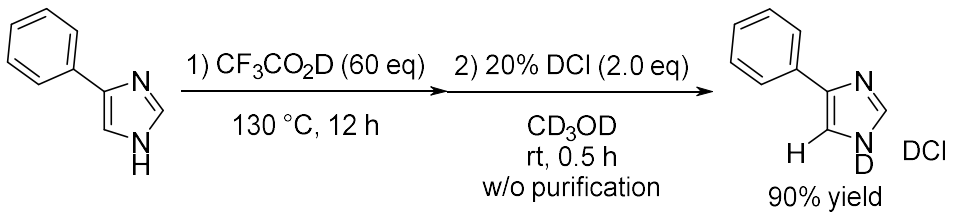
The flask including the crude obtained above was charged with CD_3OD (1.1 mL). 20 w/w% DCl (in D_2O) (76 μL, 0.456 mmol) was added and the mixture was stirred at room temperature for 0.5 h. The mixture was concentrated under reduced pressure. The residue was dissolved in CD_3OD and concentrated under reduced pressure to provide imidazole **2a'** (20.0 mg, 0.106 mmol, 46% yield) as a brown solid.

^{1}H NMR (500 MHz, CD_3OD): δ 7.37 (s, 0.11H), 7.43 (s, 0.11H×2), 7.64 (s, 0.11H×2), 7.82 (d, J = 1.3 Hz, 0.11H), 8.90 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 115.9 – 116.4 (m), 126.5 – 126.8 (m), 127.8, 130.2 – 130.8 (m, 2C), 135.2, 135.9.

HRMS (*m/z*, ESI): Found: 151.1135. Calculated for $C_9H_3D_6N_2$: $(M+H)^+$ 151.1137.

10.2. Synthesis of 4-phenyl-1*H*-imidazole-1-*d* deuterochloride (2a")



A test tube was charged with imidazole **1a** (28.7 mg, 0.199 mmol), TFA-*d* (0.92 mL, 12.0 mmol). The tube was sealed and heated at 130 °C (bath temp.) for 12 h. Deuterium incorporation was monitored using ^{1}H NMR analysis [Preparation of ^{1}H NMR sample: Aliquot of the mixture (15 μL) was collected and diluted with CD_3OD (0.70 mL)]. The mixture was cooled to room temperature and quenched with D_2O (2.0 mL), 40 w/w% NaOD (in D_2O) (1.0 mL) at 0 °C. The resulting mixture was extracted five

times with EtOAc (5 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting mixture was suspended with $CHCl_3$ (25 mL) and then filtered and concentrated under reduced pressure.

The flask including the crude obtained above was charged with CD_3OD (1.0 mL). 20 w/w% DCl (in D_2O) (66.8 μL, 0.401 mmol) was added and the mixture was stirred at room temperature for 0.5 h. The mixture was concentrated under reduced pressure. The residue was dissolved in CD_3OD and concentrated under reduced pressure to provide imidazole **2a"** (32.7 mg, 0.180 mmol, 90% yield) as a brown solid.

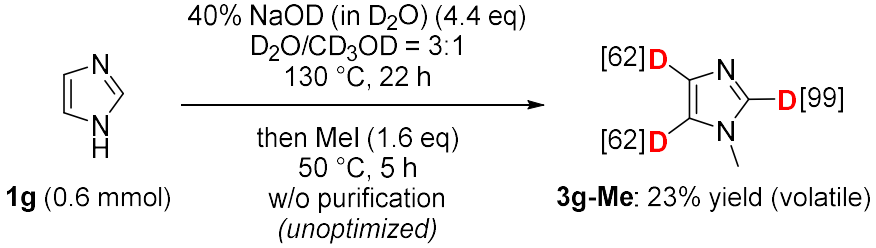
^{1}H NMR (500 MHz, CD_3OD): δ 7.36 – 7.40 (m, 1H), 7.41 – 7.45 (m, 2H), 7.65 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 1.3 Hz, 1H), 8.92 (d, J = 1.3 Hz, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 116.4, 127.0, 128.0, 130.7, 131.0, 135.4, 135.9.

HRMS (*m/z*, ESI): Found: 145.0758. Calculated for $C_9H_9N_2$: $(M+H)^+$ 145.0760.

11. Exhaustive deuteration of parent imidazole (1g)

The reaction of parent imidazole (**1g**) under basic conditions provided C2-, C4- and C5-deuterated imidazole **3g** of which the deuterium incorporation was determined via *N*-methylation (Scheme S2). The deuteration and the derivatization conditions are unoptimized yet.



Scheme S2. Exhaustive deuteration of parent imidazole (**1g**).

A test tube was charged with imidazole **1g** (41.0 mg, 0.602 mmol), CD_3OD (1.5 mL), D_2O (4.5 mL) and 40 w/w% NaOD (in D_2O) (0.19 mL, 2.66 mmol). The tube was sealed and heated at 130 °C (bath temp.) for 22 h. After cooling the mixture to 0 °C, MeI (0.06 mL, 0.964 mmol) was added at the same temperature. The mixture was heated at 50 °C for 5 h. After cooling the mixture to room temperature, the mixture was diluted with CH_2Cl_2 (12 mL) and 20 w/w% NaCl aq. (10 mL). The organic phase was collected, and the aqueous phase was extracted twice with CH_2Cl_2 (10 mL). The combined organic extracts were washed twice with water (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide imidazole **3g-Me** (11.6 mg, 0.136 mmol, 23% yield) as a pale-yellow oil.

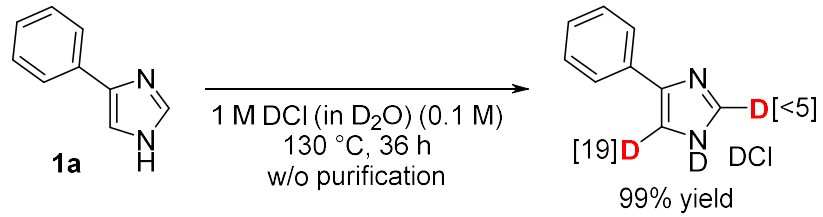
^{1}H NMR (500 MHz, CD_3OD): δ 3.73 (s, 3H), 6.94 (s, 0.38H), 7.06 (s, 0.38H), 7.57 – 7.60 (m, 0.01H).

^{13}C NMR (126 MHz, CD_3OD): δ 32.1, 120.3 – 120.4 (m), 127.4 – 127.6 (m), 137.1 – 137.7 (m).

All the chemical shifts in ^{1}H and ^{13}C NMR spectra were consistent with those of 1-methyl-1*H*-imidazole (**1g-Me**).

12. Evaluation of classical acidic conditions in ref 23

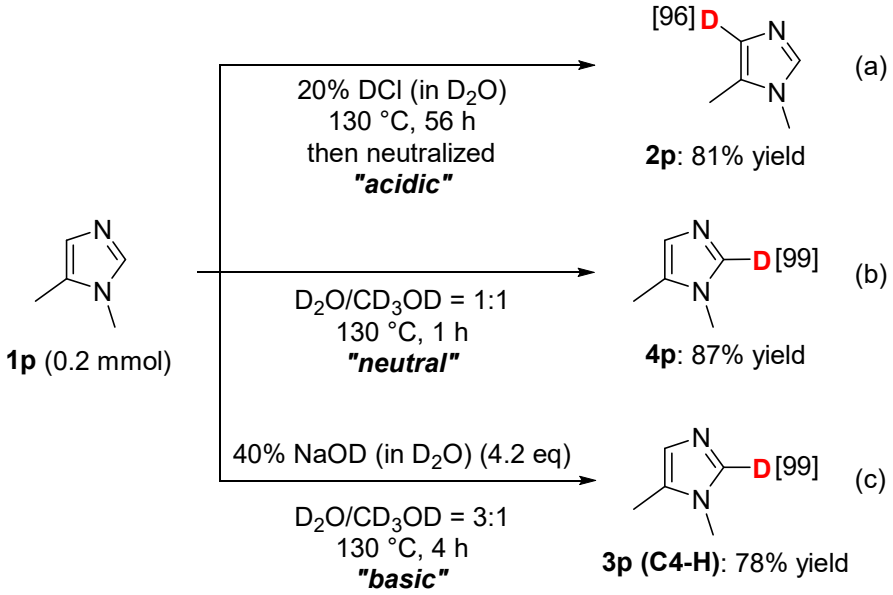
The least reactivity of C2-hydrogen in the imidazole ring under acidic conditions has been suggested by Cohen *et al.* in 1979 as ref 23 in manuscript[2]. However, their conditions using 1 M DCl (in D_2O) seems not to be complete C5-selectivity and the degree of deuterium incorporation has not been described. We also tested the use of 1 M DCl (in D_2O) for the deuteration of 4-phenylimidazole (**1a**) at 130 °C for 36 h (Scheme S3), which resulted in inefficient C5-deuteration (19%D at C5) with trace C2-deuteration (<5%D at C2). In this context, efficient C5-selective deuteration of the imidazoles still remains elusive.



Scheme S3. Deuteration of 4-phenylimidazole (**1a**) using 1 M DCl (in D_2O).

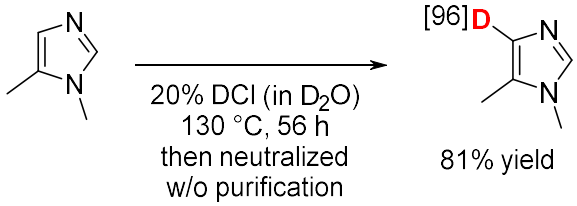
13. Deuteration of *N*-substituted imidazoles under acid/base conditions

We examined the deuteration of 1,5-dimethyl imidazole (**1p**) under each condition. As similar to the results of *N*-unsubstituted imidazoles, C5- or C2-selective deuteration of *N*-substituted imidazole **1p** was observed under acidic (Scheme S4a) or neutral conditions (Scheme S4b). In contrast, base-mediated deuteration of **1p** resulted in C2-selective deuteration without labelling C4-hydrogen (Scheme 4c), which is distinct from the exhaustive deuteration of *N*-unsubstituted imidazoles under the same conditions. The mechanism of deuterating *N*-substituted imidazoles under basic conditions is currently under investigation.



Scheme S4. Deuteration of 1,5-dimethyl imidazole (**1p**) under acid/base conditions.

13.1. Synthesis of 1,5-dimethyl-1*H*-imidazole-4-*d* (2p)



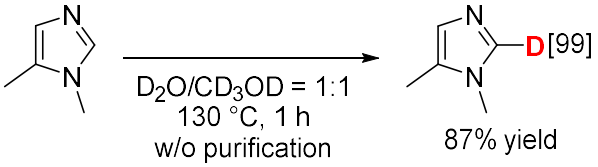
A test tube was charged with imidazole **1p** (20.4 mg, 0.212 mmol), 20 w/w% DCl (in D_2O) (2.1 mL). The tube was sealed and heated at 130 °C (bath temp.) for 56 h. Deuterium incorporation was monitored using ^{1}H NMR analysis [Preparation of ^{1}H NMR sample: Aliquot of the mixture (20 μL) was collected and diluted with CD_3OD (0.70 mL)]. The mixture was cooled to room temperature and neutralized with 40 w/w% NaOD (in D_2O) (1.0 mL) at 0 °C. The resulting mixture was diluted with CH_2Cl_2 (13 mL) and 20 w/w% NaCl aq. (10 mL). The organic phase was collected, and the aqueous phase was extracted thrice with CH_2Cl_2 (8 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide imidazole **2p** (16.6 mg, 0.171 mmol, 81% yield) as a pale-yellow oil.

^{1}H NMR (500 MHz, CD_3OD): δ 2.22 (s, 3H), 3.61 (s, 3H), 6.67 – 6.70 (m, 0.04H), 7.51 (s, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 7.3, 30.0, 124.6 (t, J = 29.0 Hz), 128.1, 137.0.

All the chemical shifts in ^{1}H and ^{13}C NMR spectra were consistent with those of 1,5-dimethyl-1*H*-imidazole (**1p**).

13.2. Synthesis of 1,5-dimethyl-1*H*-imidazole-2-*d* (4p)



Prepared using imidazole **1p** (19.7 mg, 0.205 mmol) for 1 h by typical procedure D.

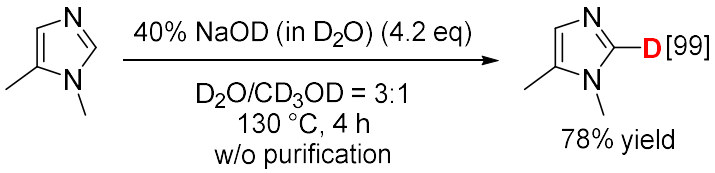
Yield: 17.4 mg (0.179 mmol, 87% yield) as a pale-yellow oil.

^{1}H NMR (500 MHz, CD_3OD): δ 2.22 (s, 3H), 3.61 (s, 3H), 6.70 (s, 1H), 7.51 – 7.55 (m, 0.01H).

^{13}C NMR (126 MHz, CD_3OD): δ 7.4, 30.0, 124.6, 128.2, 136.8 (t, J = 32.2 Hz).

All the chemical shifts in ^{1}H and ^{13}C NMR spectra were consistent with those of 1,5-dimethyl-1*H*-imidazole (**1p**).

13.3. Synthesis of 1,5-dimethyl-1*H*-imidazole-2-*d* (3p (C4-H))



A test tube was charged with imidazole **1p** (19.3 mg, 0.201 mmol), CD_3OD (0.5 mL), D_2O (1.5 mL) and 40 w/w% NaOD (in D_2O) (0.06 mL, 0.84 mmol). The tube was sealed and heated at 130 °C (bath temp.) for 4 h. After cooling the mixture to room temperature, the resulting mixture was extracted four times with CH_2Cl_2 (3 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide imidazole **3p (C4-H)** (15.2 mg, 0.156 mmol, 78% yield) as a pale-yellow oil.

^{1}H NMR (500 MHz, CD_3OD): δ 2.22 (s, 3H), 3.60 (s, 3H), 6.68 (s, 1H), 7.47 – 7.52 (m, 0.01H).

^{13}C NMR (126 MHz, CD_3OD): δ 7.3, 29.9, 124.8, 128.1, 136.8 (t, J = 31.5 Hz).

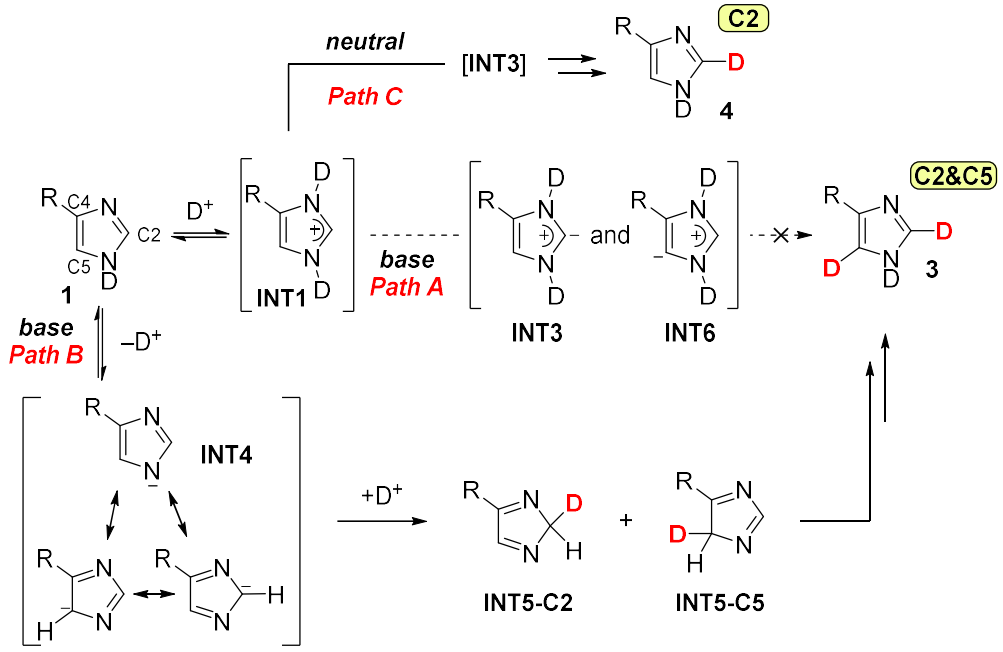
All the chemical shifts in ^{1}H and ^{13}C NMR spectra were consistent with those of 1,5-dimethyl-1*H*-imidazole (**1p**).

14. Details of computational study

All calculations were performed with GAMESS 2023 R1 program.[3] Structure optimizations were conducted at the ωB97X-D/def2-SVP level and free energies of all optimized structures were obtained at the ωB97X-D/6-31G(df,p) level at 403.15 K in H_2O modeled by SMD method.[4] For all calculations, parameters of NRAD and NLEB in the $DFT section were set to 96 and 590, respectively. To simplify the calculation and the comparison of energies, deuterium was replaced to proton in all calculations.

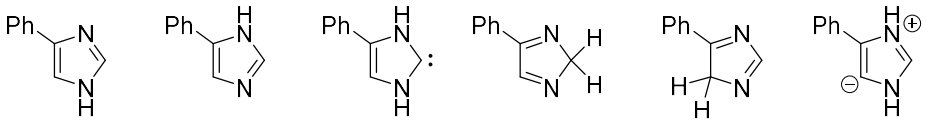
Our calculations revealed that the generation of ylide **INT6** is not feasible due to the higher energy (Δ*G* at 130 °C: +41.5 kcal/mol from **1a**) (Scheme S5, Path A). Alternatively, we speculated another mechanism to achieve H/D exchange via **INT4** and **INT5-C2**/**INT5-C5** in Scheme S5, Path B. First, the deprotonation of the *N*-H moiety on the imidazole ring gives anionic species **INT4**, which is assumed to be easily generated under basic and thermal conditions since the pK_a value of the *N*-H proton of simple imidazole is only 14.2. The resulting **INT4** has resonance structures bearing a negative charge on the C2 or C5-position. We suppose that iterative C2- and C5-deuteration of **INT4** enable the exhaustive deuteration of the imidazoles via **INT5-C2** and **INT5-C5**. Our calculation revealed that relative free energies of proton analogues of **INT5-C2** and **INT5-C5** were estimated to be +16.0 and +13.5 kcal/mol from **1a**, which means that the generation of **INT4** bearing a C2- or C5-negative charge in an equilibrium would be possible enough.

Compared to basic conditions, it would be difficult to form **INT5-C2** and **INT5-C5** under neutral conditions since their anionic precursor **INT4** hardly form without a base. Thus we propose the mechanism of intermediate **INT3** for the neutral conditions (Scheme S5, Path C) while the formation of **INT3** was expected to be slightly up-hill process (Δ*G* at 130 °C: +30.0 kcal/mol from **1a**).



Scheme S5. Proposed mechanism under basic and neutral conditions.

Table S1. Free energies for each structure (deuterium was replaced to proton)



1a **1a-iso** **INT3** **INT5-C2** **INT5-C5** **INT6**

Compounds	Free energies at 403.15 K (in Hartree)	$\Delta G_{403.15\,K}$ from **1a** (in kcal/mol)
1a	-457.0682038	–
1a-iso	-457.0676584	+0.3
INT3	-457.0204280	+30.0
INT5-C2	-457.0426669	+16.0
INT5-C5	-457.0467649	+13.5
INT6	-457.0020699	+41.5

Cartesian coordinates for optimized structures

1a

C	0.000000	0.000000	0.000000
H	1.089719	0.000000	0.000000
N	-0.768572	1.056058	0.000000
N	-0.727661	-1.150033	-0.000052
C	-2.052306	-0.792179	-0.000040
C	-2.061261	0.587244	-0.000012
H	-0.363887	-2.093075	-0.000095
H	-2.849095	-1.530330	-0.000092
C	-3.213401	1.506322	-0.000039
C	-2.993227	2.890258	-0.000054
C	-4.533791	1.035122	-0.000018
C	-5.606262	1.924183	-0.000017
C	-4.066316	3.778367	-0.000028
C	-5.377275	3.300656	0.000014
H	-4.732077	-0.039881	0.000020
H	-6.629171	1.539123	0.000033
H	-1.962820	3.250899	-0.000045
H	-3.876859	4.854831	-0.000027
H	-6.218649	3.997989	0.000021

1a-iso

C	0.000000	0.000000	0.000000
H	1.089889	0.000000	0.000000
N	-0.724916	1.152027	0.000000
N	-0.769677	-1.059107	0.002887
C	-2.048941	-0.577183	0.014472
C	-2.058193	0.802946	0.016536
H	-2.912366	-1.240925	-0.004315
C	-3.153698	1.777799	0.014690
C	-2.994931	3.058535	-0.536394
C	-4.400128	1.435246	0.561820
C	-5.454230	2.344379	0.553021
C	-4.047094	3.972385	-0.532134
C	-5.281901	3.618734	0.010295
H	-4.534303	0.449244	1.012706
H	-6.416897	2.058935	0.984112
H	-2.045680	3.341277	-1.000252
H	-3.903362	4.964324	-0.967463
H	-6.108126	4.333448	0.009903
H	-0.357303	2.092274	0.055470

INT3

C	-3.137824	-0.744383	0.256296
N	-1.803233	-0.995439	0.332082
N	-3.125353	0.546812	-0.175177
C	-1.857630	1.074952	-0.348786
C	-0.989697	0.078184	-0.018421
H	-3.979746	1.058435	-0.347473
H	-1.669603	2.081727	-0.710953
H	-1.447154	-1.878748	0.671692
C	0.477142	0.036273	-0.012217
C	1.165928	-1.166081	-0.231277
C	1.221783	1.204493	0.211623
C	2.613460	1.171109	0.211117
C	2.559084	-1.200237	-0.218316
C	3.288438	-0.032343	0.001204
H	0.699902	2.144305	0.407605
H	3.176340	2.090541	0.389476
H	0.609785	-2.084438	-0.437829
H	3.077926	-2.146301	-0.390647
H	4.380525	-0.059535	0.010604

INT5-C2

C	0.000000	0.000000	0.000000
N	1.450081	0.000000	0.000000
N	-0.488583	1.361136	0.000000
C	0.556423	2.087098	-0.090053
C	1.780668	1.235031	-0.153400
C	3.175431	1.703164	-0.261196
C	4.214799	0.763924	-0.309635
C	3.479720	3.067814	-0.315968
C	4.804794	3.489153	-0.417799
C	5.535104	1.186409	-0.411163
C	5.833142	2.550275	-0.465490
H	2.682305	3.811378	-0.279371
H	5.033373	4.554860	-0.459948
H	3.957247	-0.295009	-0.265652
H	6.339565	0.450471	-0.448431
H	6.870042	2.880280	-0.545183
H	-0.444847	-0.558186	-0.841353
H	-0.323296	-0.514552	0.920898
H	0.512146	3.178755	-0.114029

INT5-C5

C	0.000000	0.000000	0.000000
H	1.093920	0.000000	0.000000
N	-0.690229	1.230092	0.000000
N	-0.699405	-1.072758	-0.000001
C	-2.066916	-0.605760	0.000002
C	-1.938798	0.896076	0.000004
C	-3.043947	1.864445	0.000002
C	-2.763836	3.239205	-0.000006
C	-4.378599	1.436582	0.000055
C	-5.416673	2.366163	0.000046
C	-3.801317	4.165294	-0.000010
C	-5.129302	3.731009	-0.000017
H	-4.613545	0.369023	0.000099
H	-6.453993	2.023628	0.000096
H	-1.718963	3.556162	-0.000010
H	-3.575954	5.234345	-0.000020
H	-5.943202	4.460190	-0.000018
H	-2.609142	-0.982004	-0.884852
H	-2.609138	-0.982012	0.884854

INT6

C	0.000000	0.000000	0.000000
N	1.329045	0.000000	0.000000
N	-0.367823	1.286663	0.000000
C	0.689598	2.194006	0.000000
C	1.776742	1.320059	0.000000
H	-1.339389	1.574203	0.000000
H	1.898210	-0.837850	0.000048
C	3.207237	1.643622	-0.000020
C	4.213677	0.667831	-0.000040
C	3.587007	2.995906	0.000160

C	4.929756	3.353146	0.000167
C	5.560338	1.029254	-0.000031
C	5.925628	2.373050	-0.000002
H	2.794160	3.745089	0.000307
H	5.205470	4.409082	0.000311
H	3.963662	-0.396417	-0.000041
H	6.326977	0.252644	-0.000045
H	6.978997	2.656496	-0.000003
H	-0.639279	-0.878003	0.000015

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[4] A. V. Marenich, C. J. Cramer and D. G. Truhlar, *J. Phys. Chem. B,* 2009, **113**, 6378.

16. NMR spectra

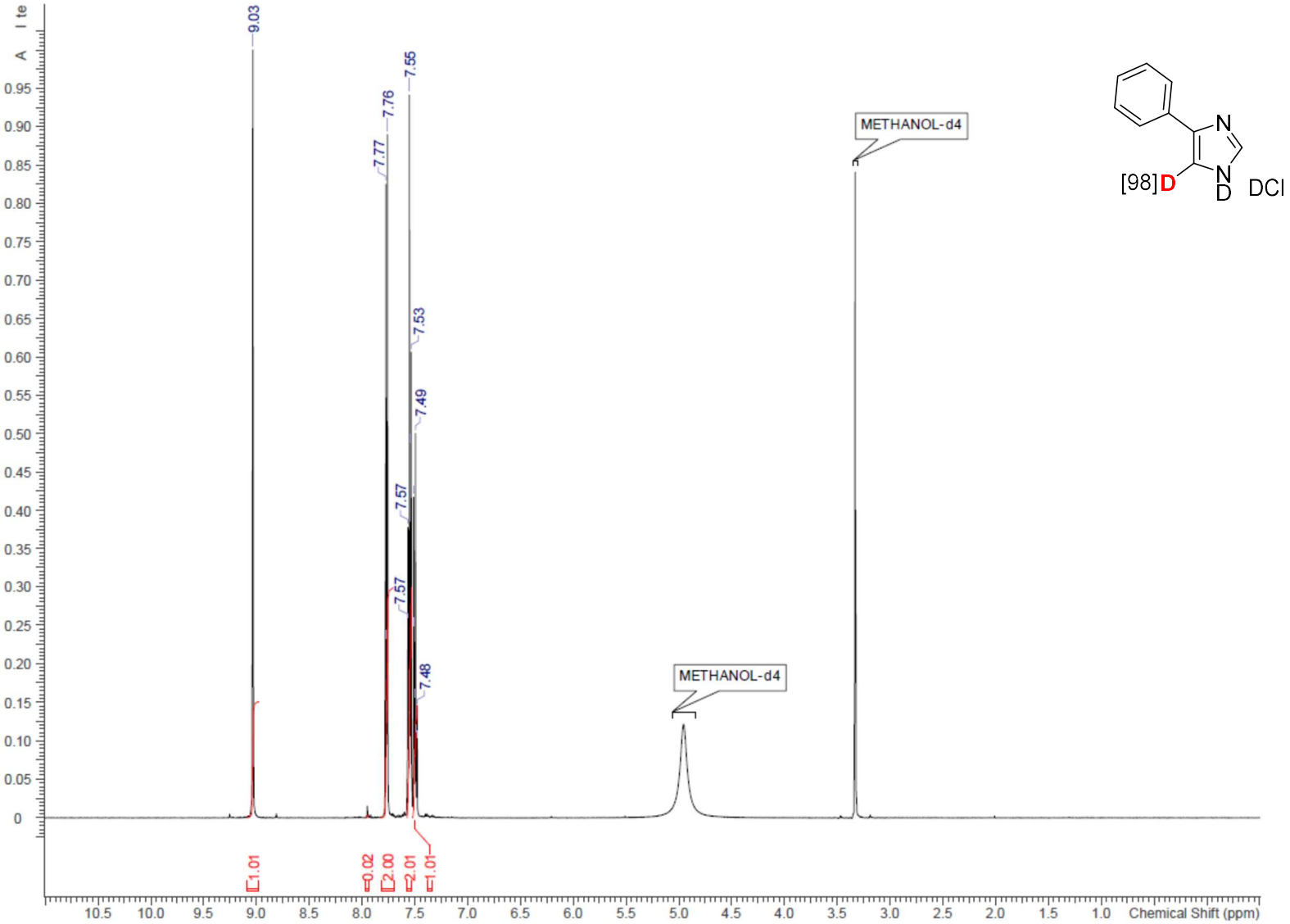

Figure S 1. ^{1}H NMR spectrum of **2a** (CD_3OD)

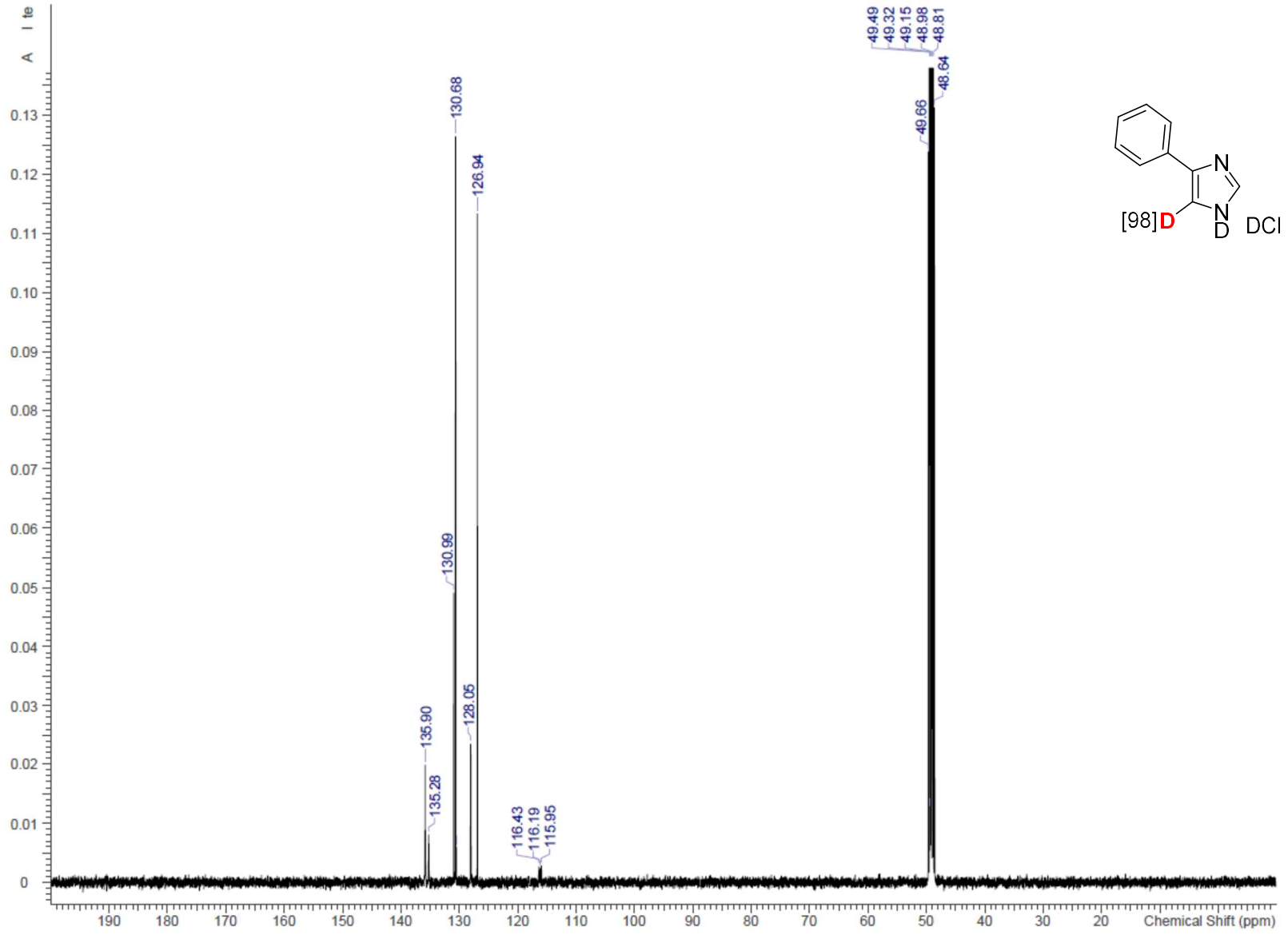

Figure S 2. ^{13}C NMR spectrum of **2a** (CD_3OD)

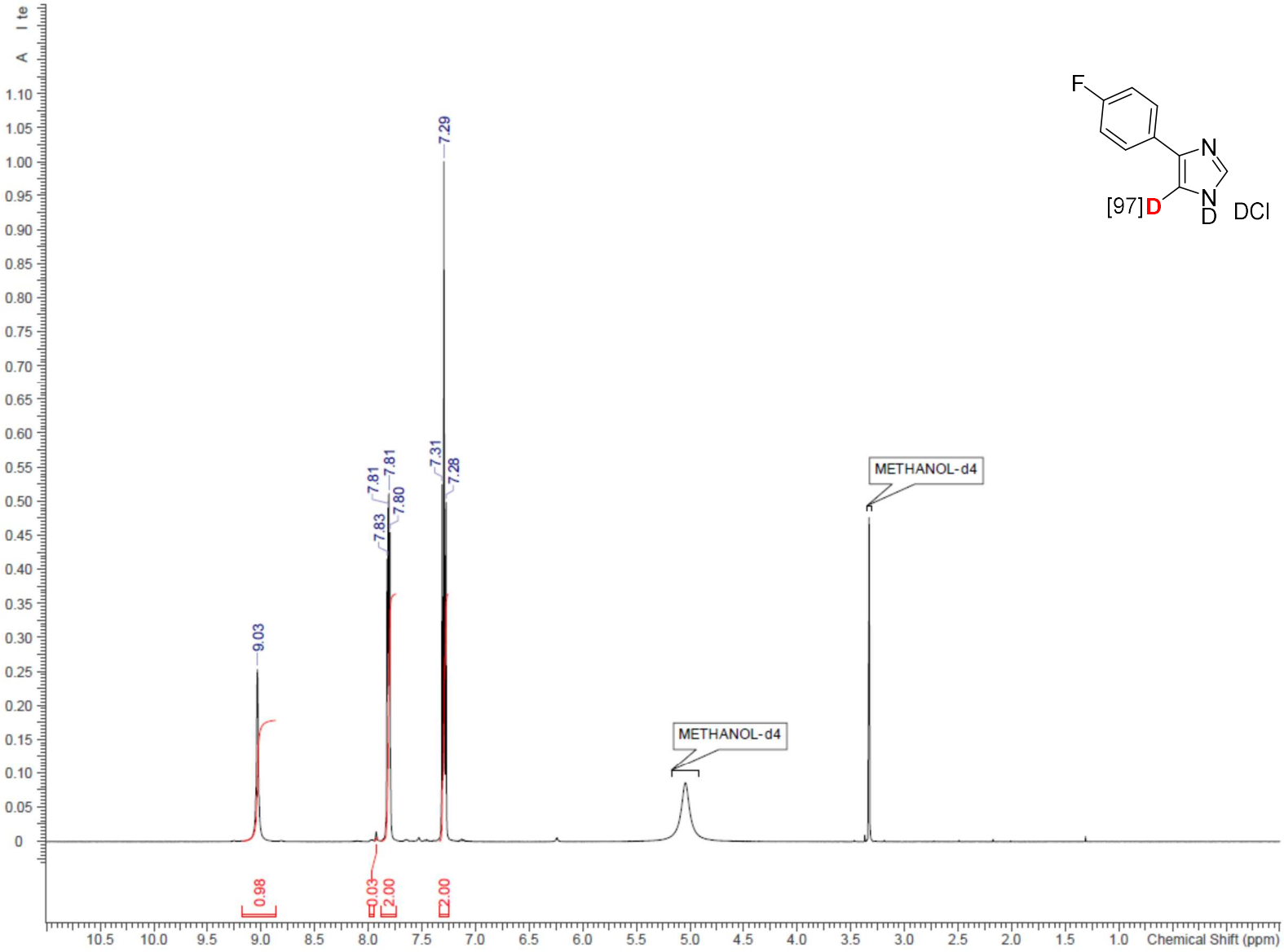

Figure S 3. ^{1}H NMR spectrum of **2b** (CD_3OD)

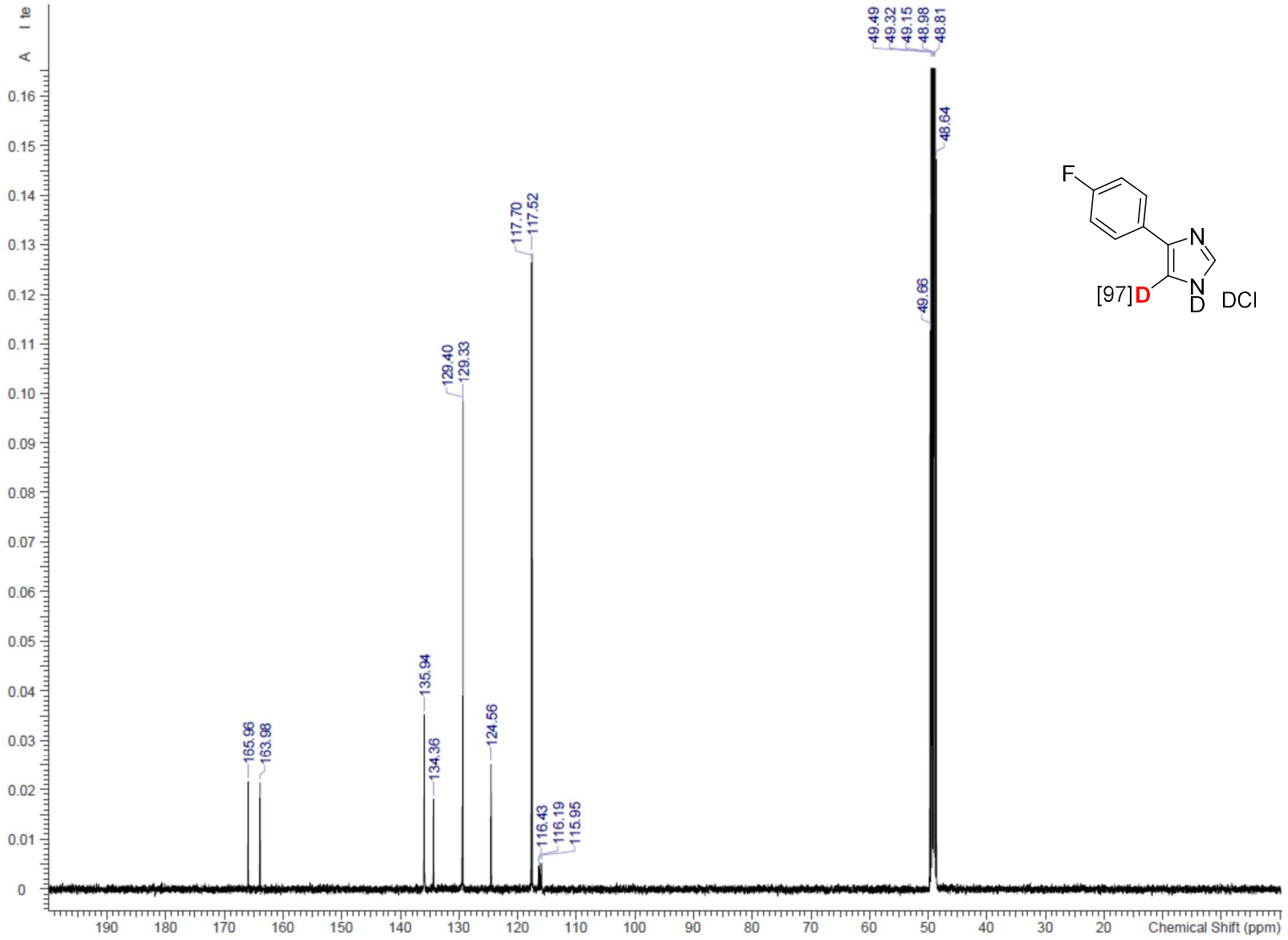

Figure S 4. ^{13}C NMR spectrum of **2b** (CD_3OD)

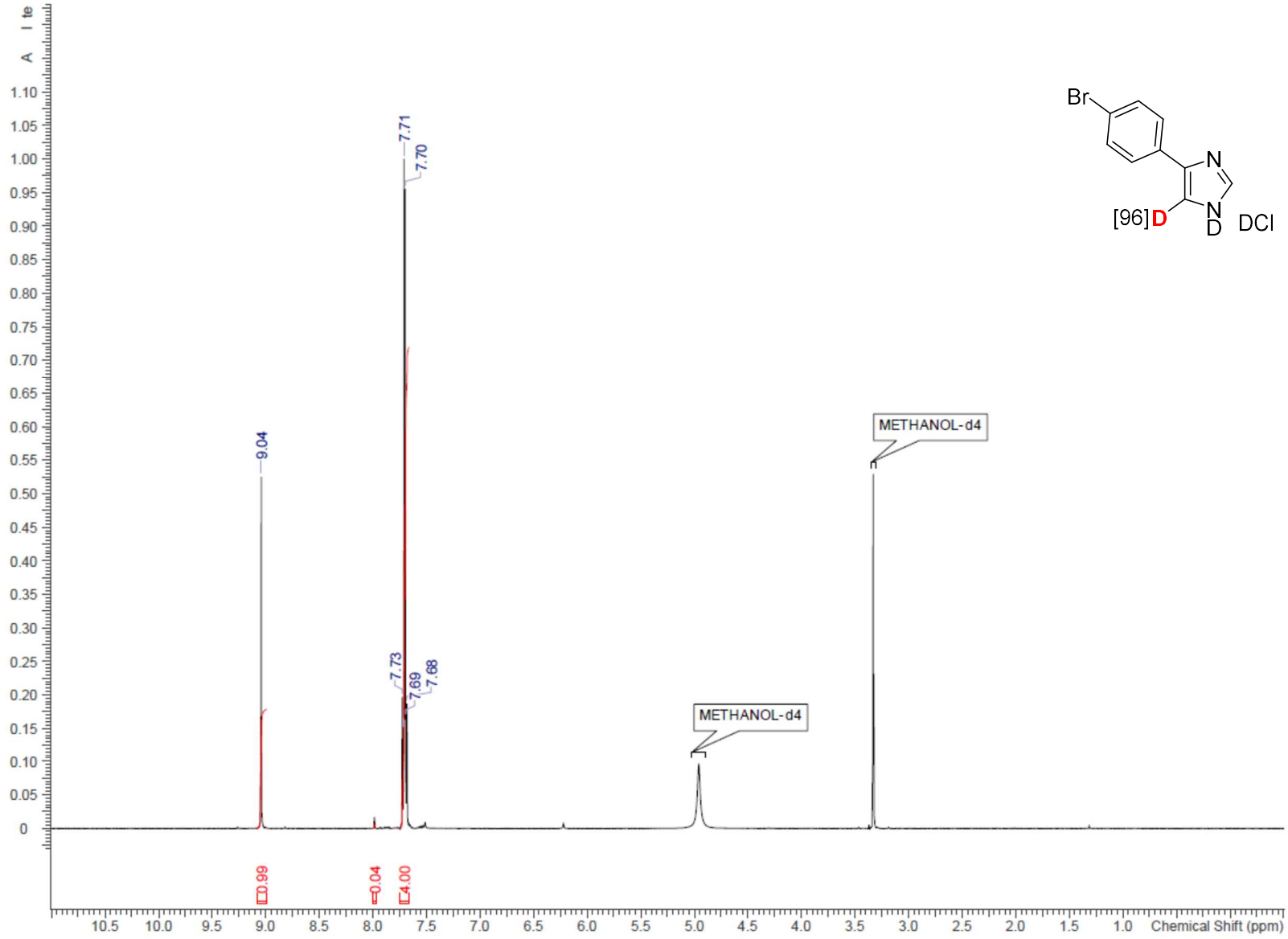

Figure S 5. ^{1}H NMR spectrum of **2c** (CD_3OD)

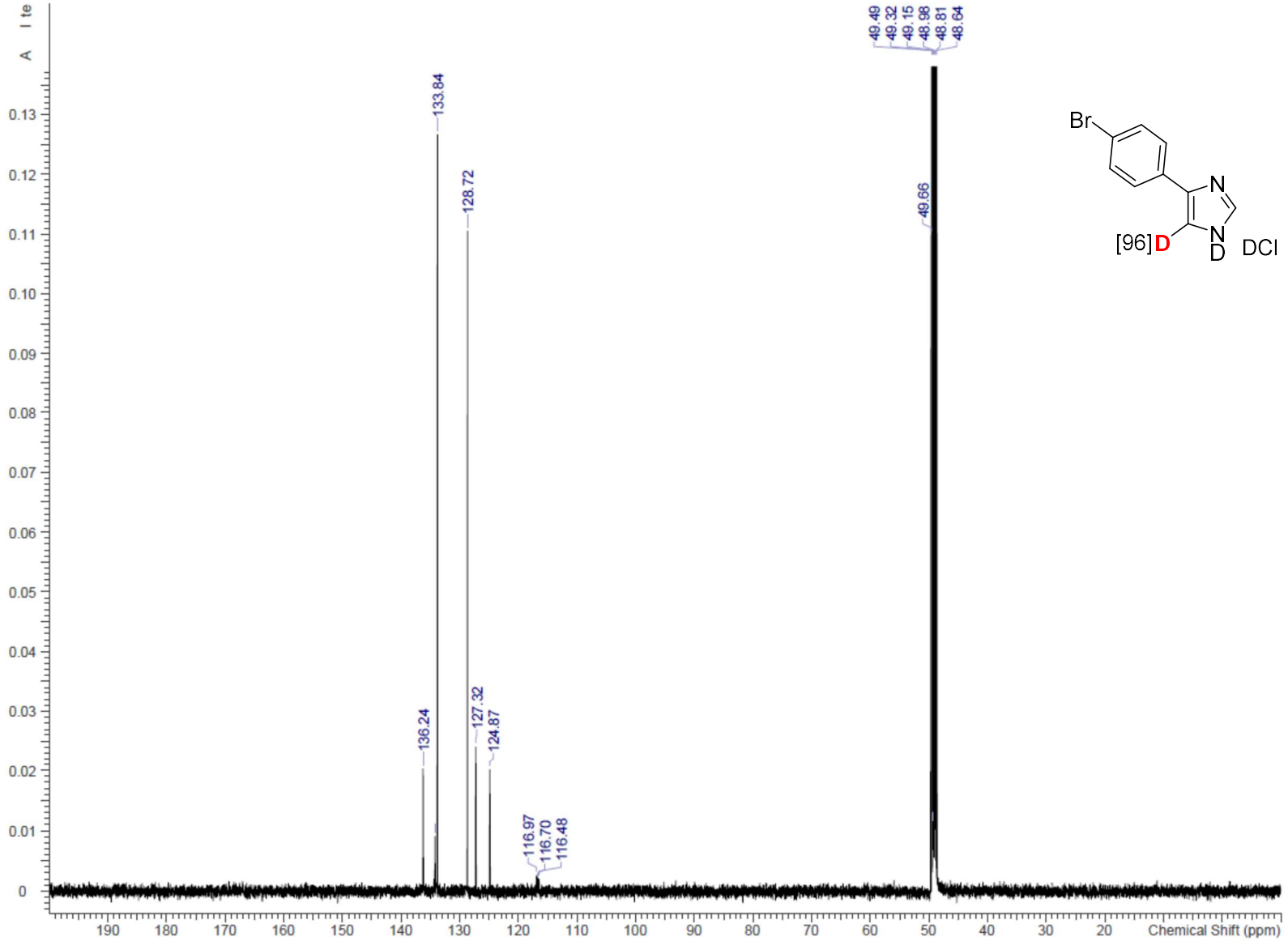

Figure S 6. ^{13}C NMR spectrum of **2c** (CD_3OD)

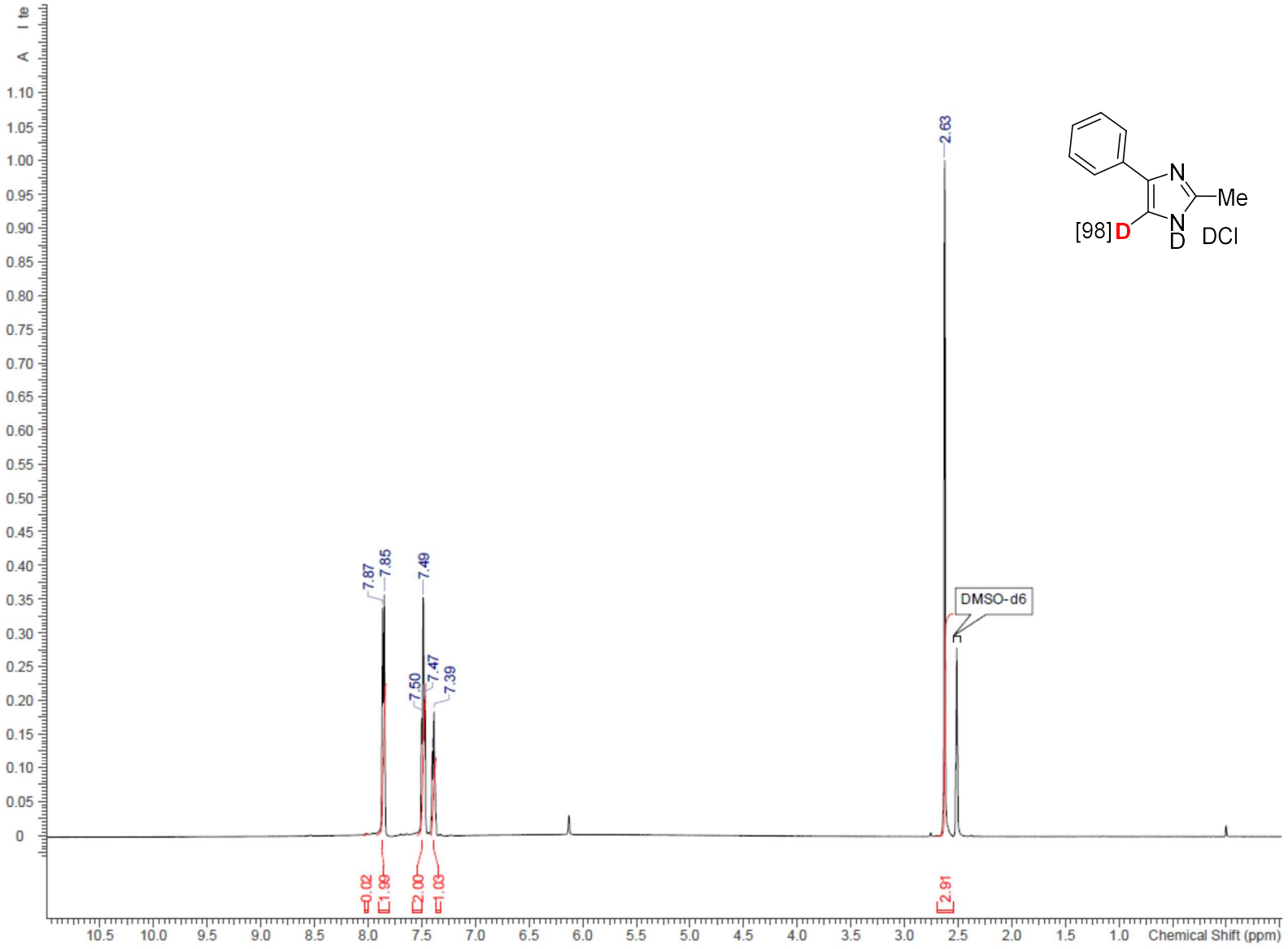

Figure S 7. ^{1}H NMR spectrum of **2d** (DMSO-d_6)

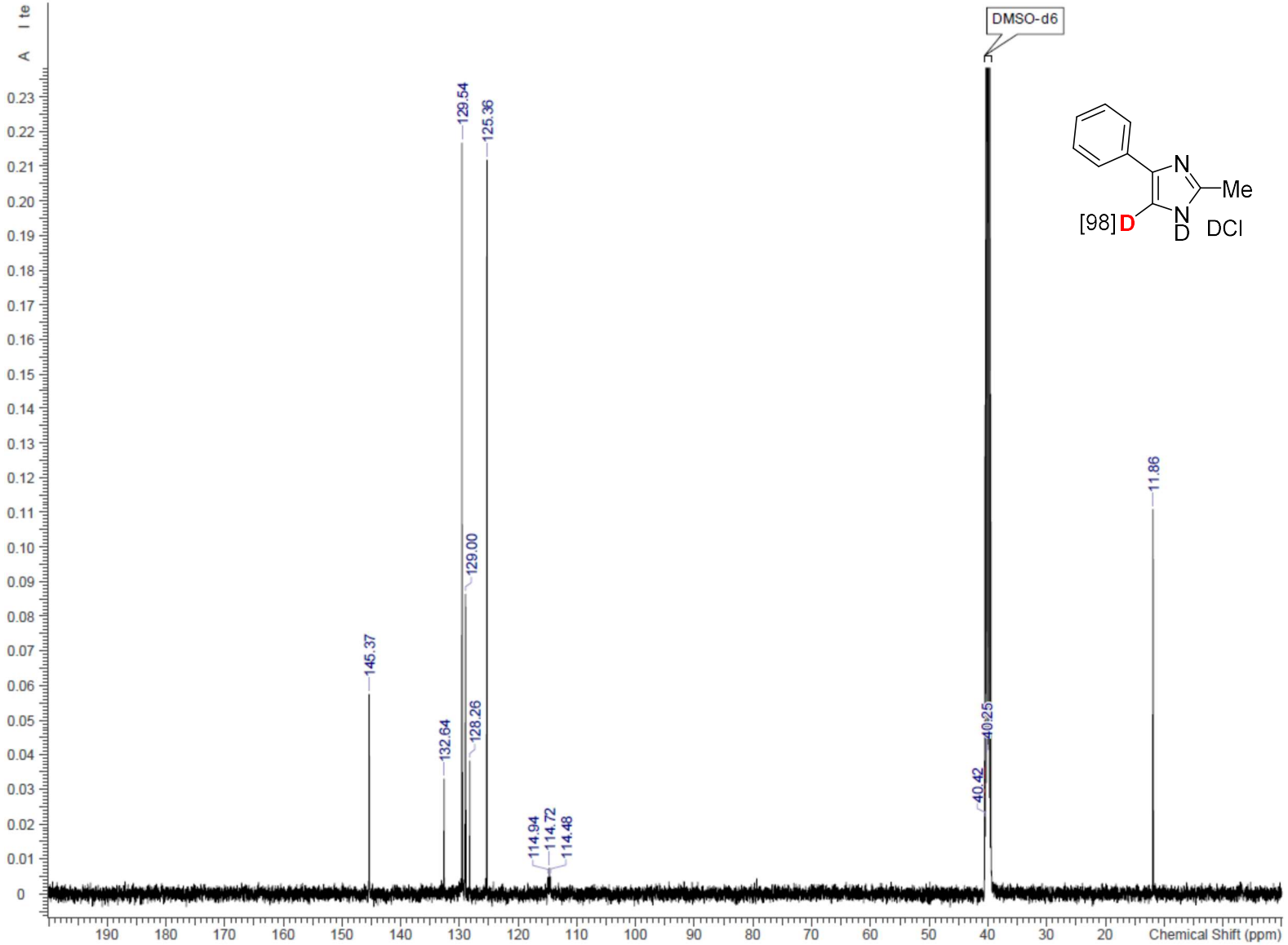

Figure S 8. ^{13}C NMR spectrum of **2d** (DMSO-d_6)

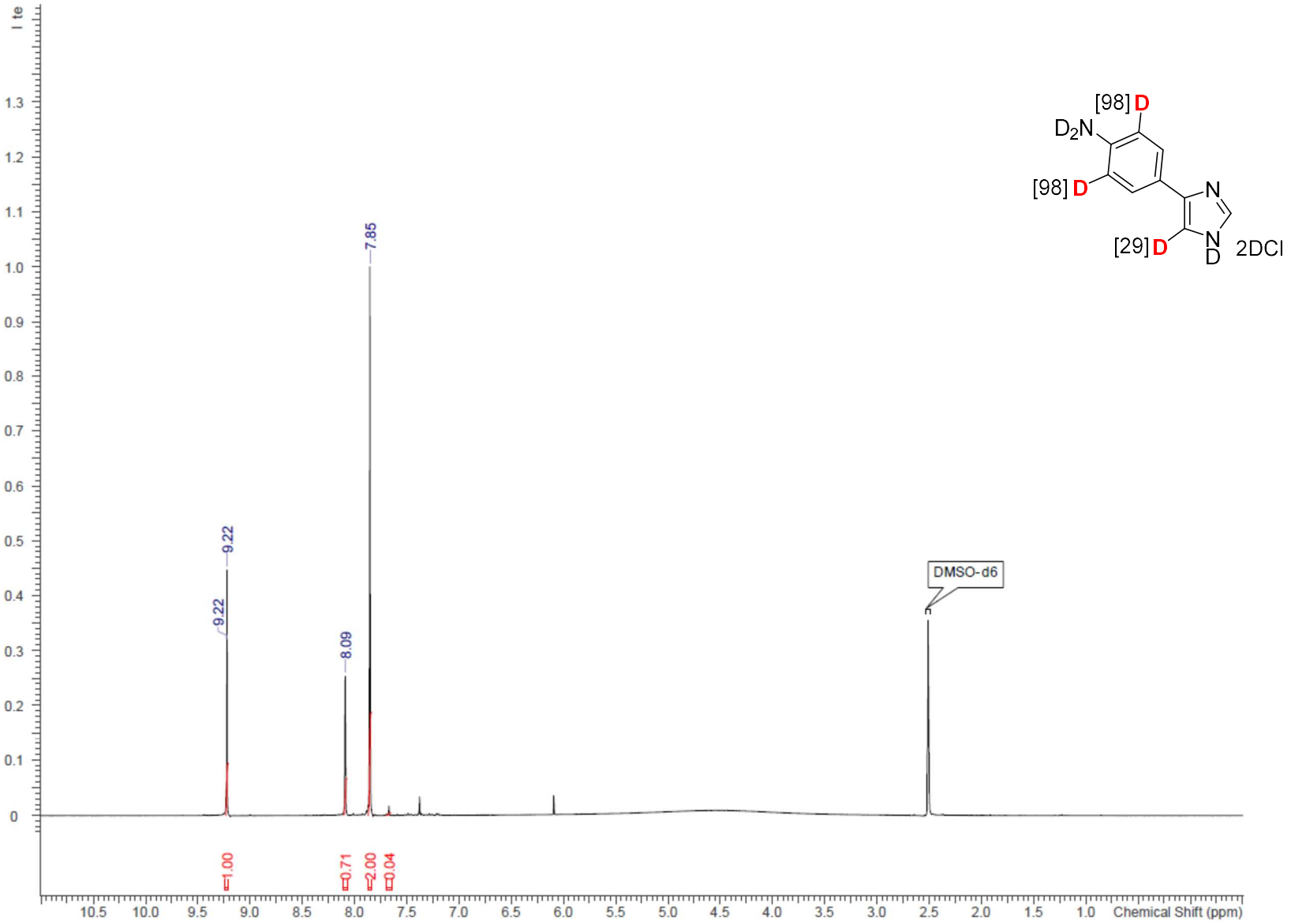

Figure S 9. ^{1}H NMR spectrum of **2e** (DMSO-d_6)

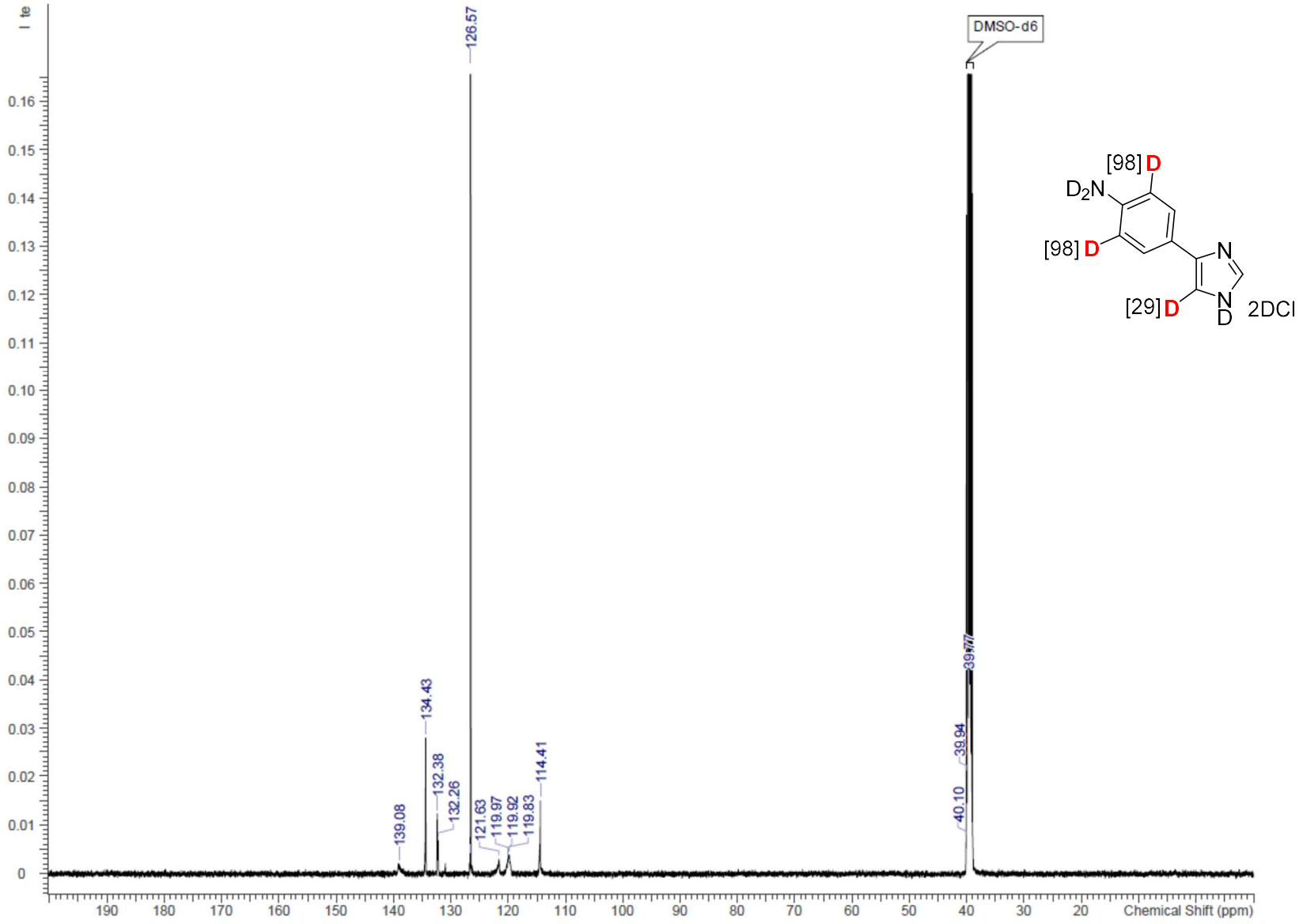

Figure S 10. ^{13}C NMR spectrum of **2e** (DMSO-d_6)

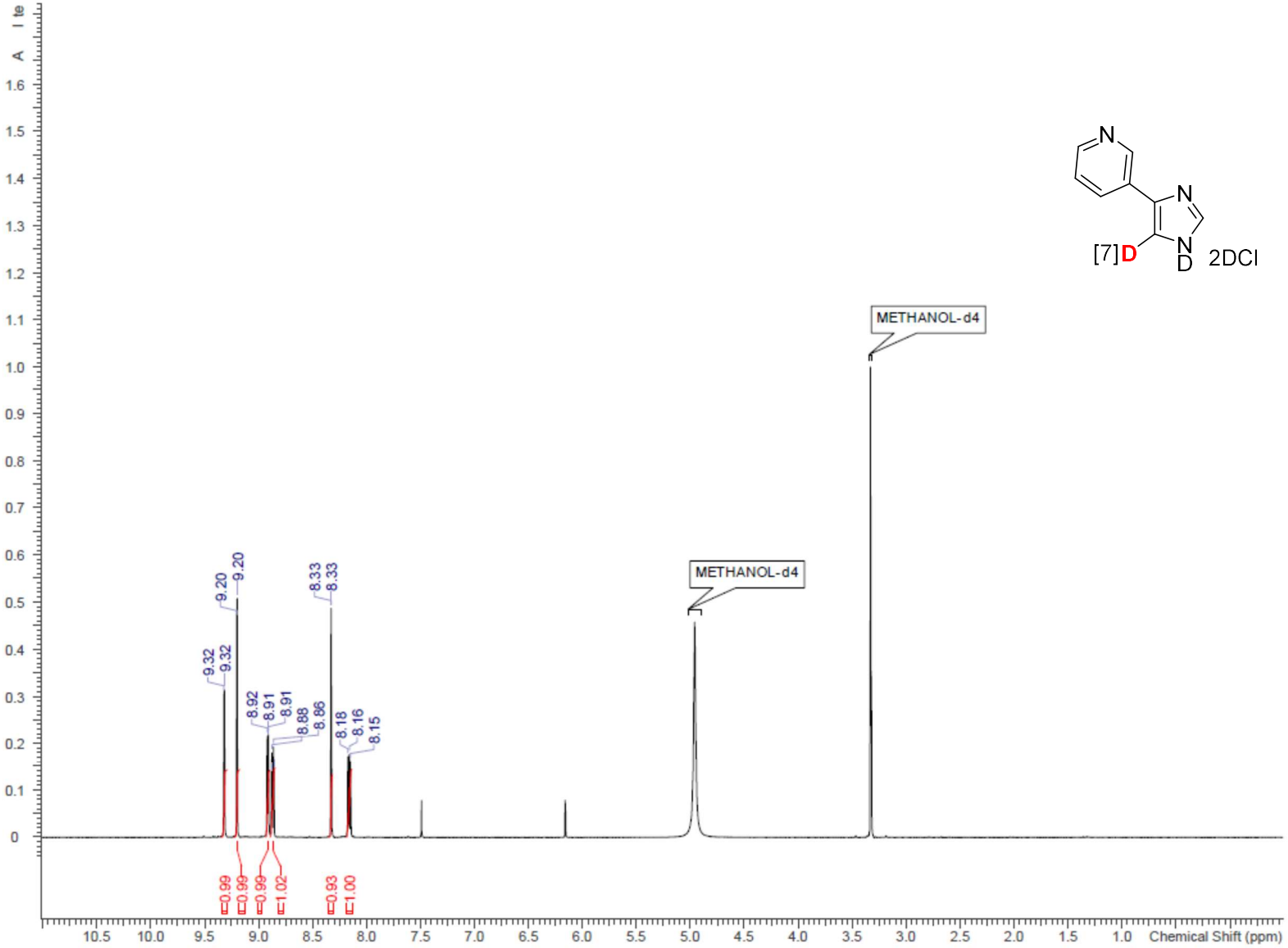

Figure S 11. ^{1}H NMR spectrum of **2f** (CD_3OD)

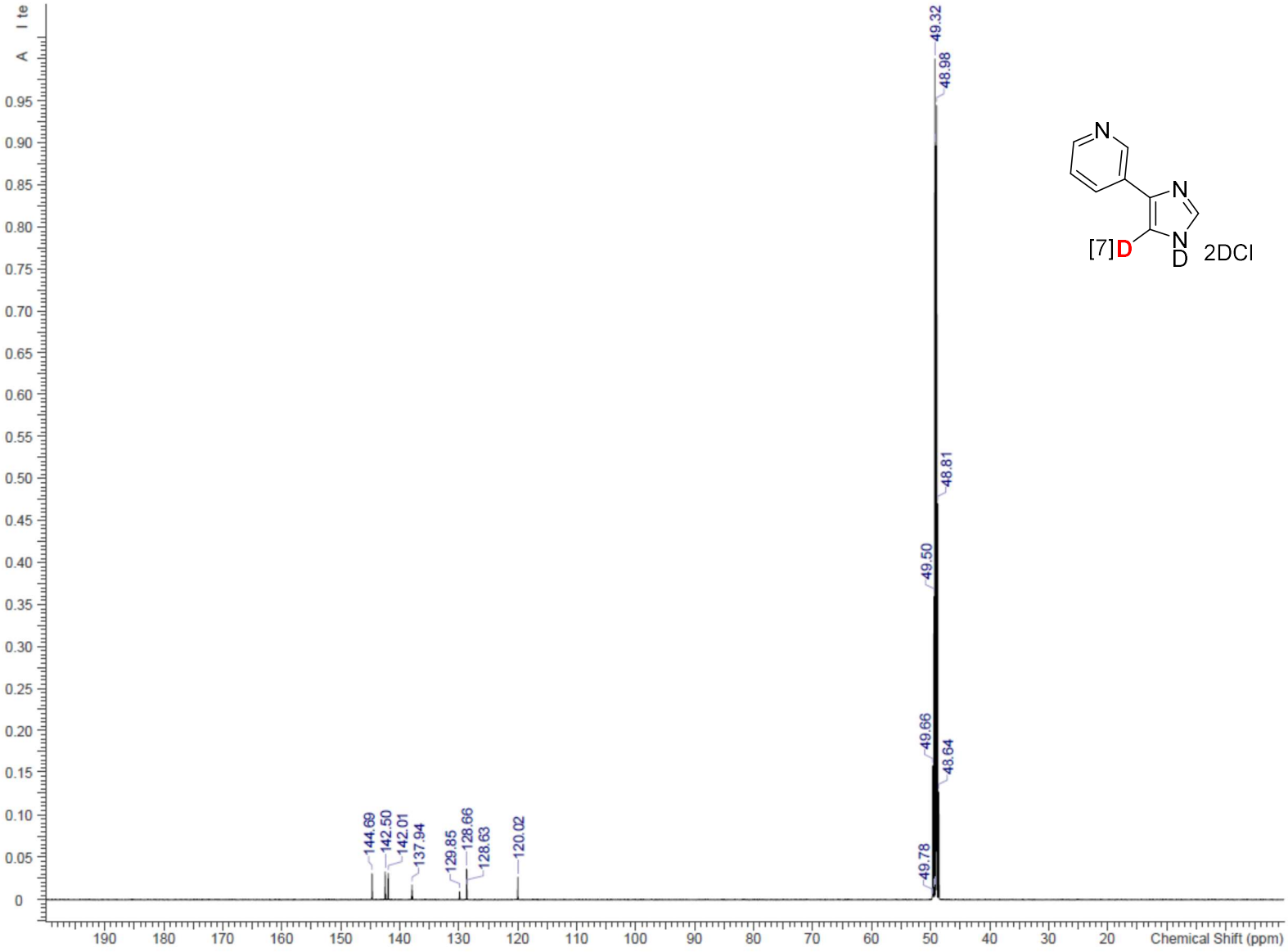

Figure S 12. ^{13}C NMR spectrum of **2f** (CD_3OD)

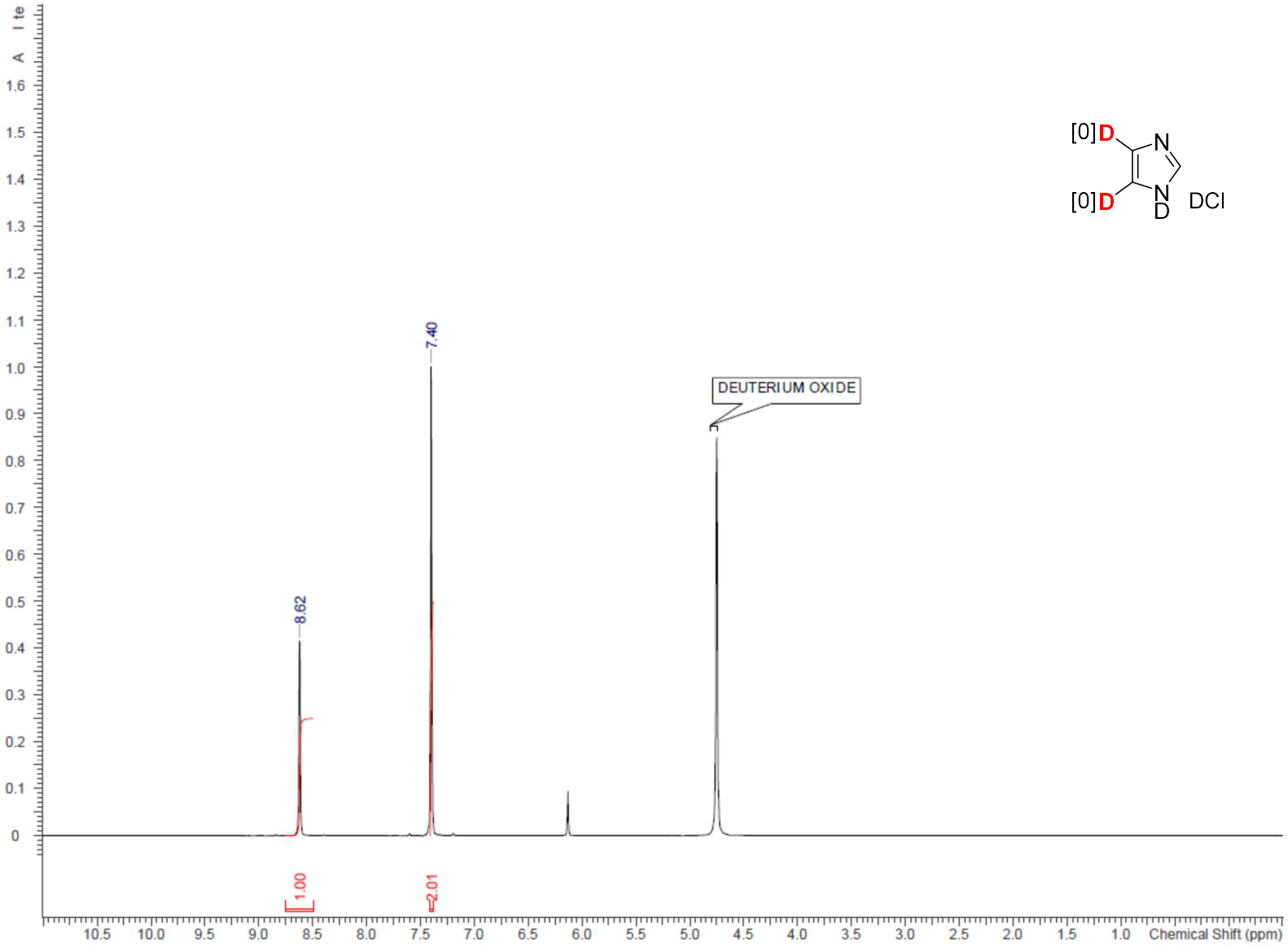

Figure S 13. ^{1}H NMR spectrum of **2g** (D_2O)

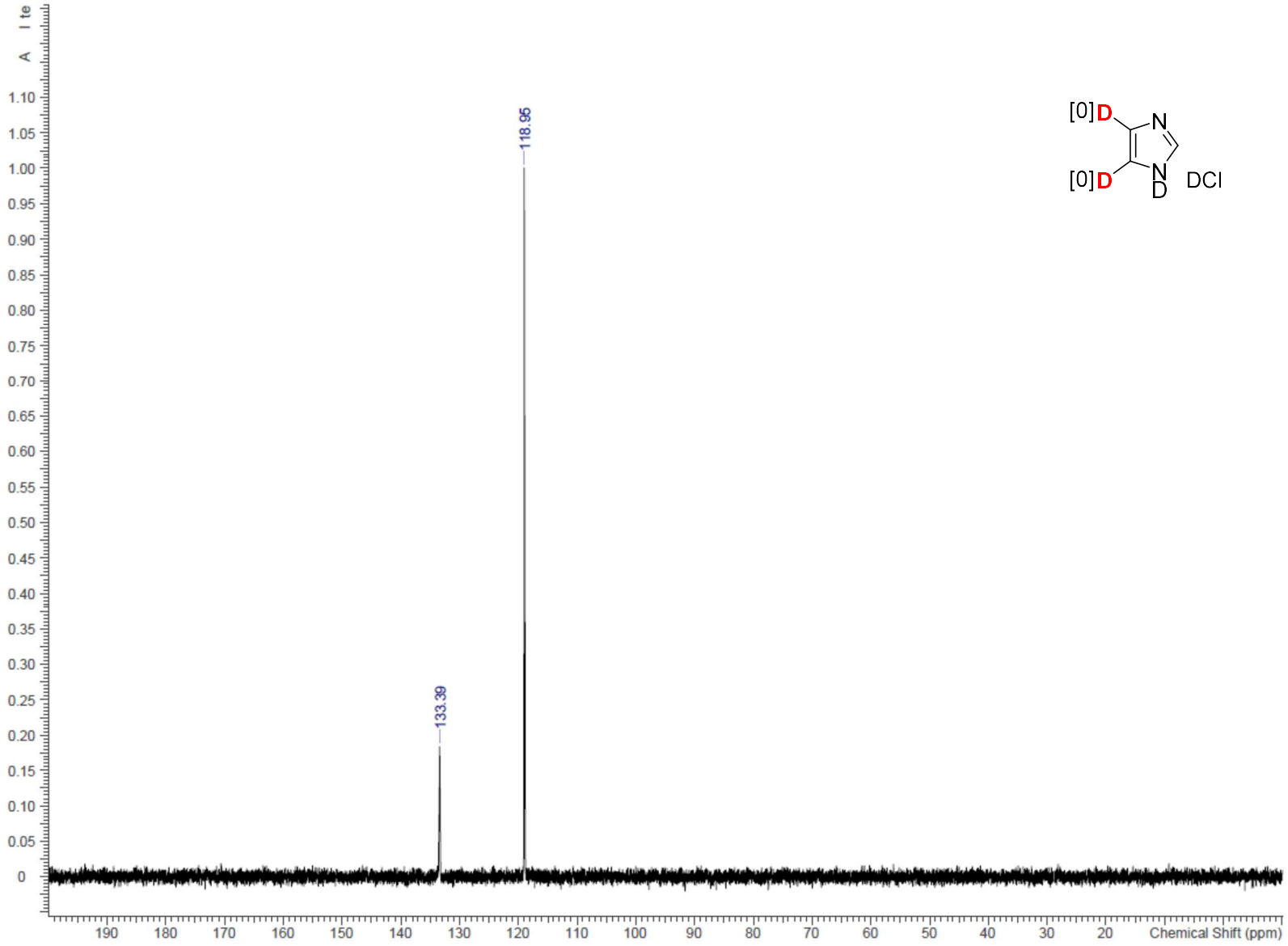

Figure S 14. ^{13}C NMR spectrum of **2g** (D_2O)

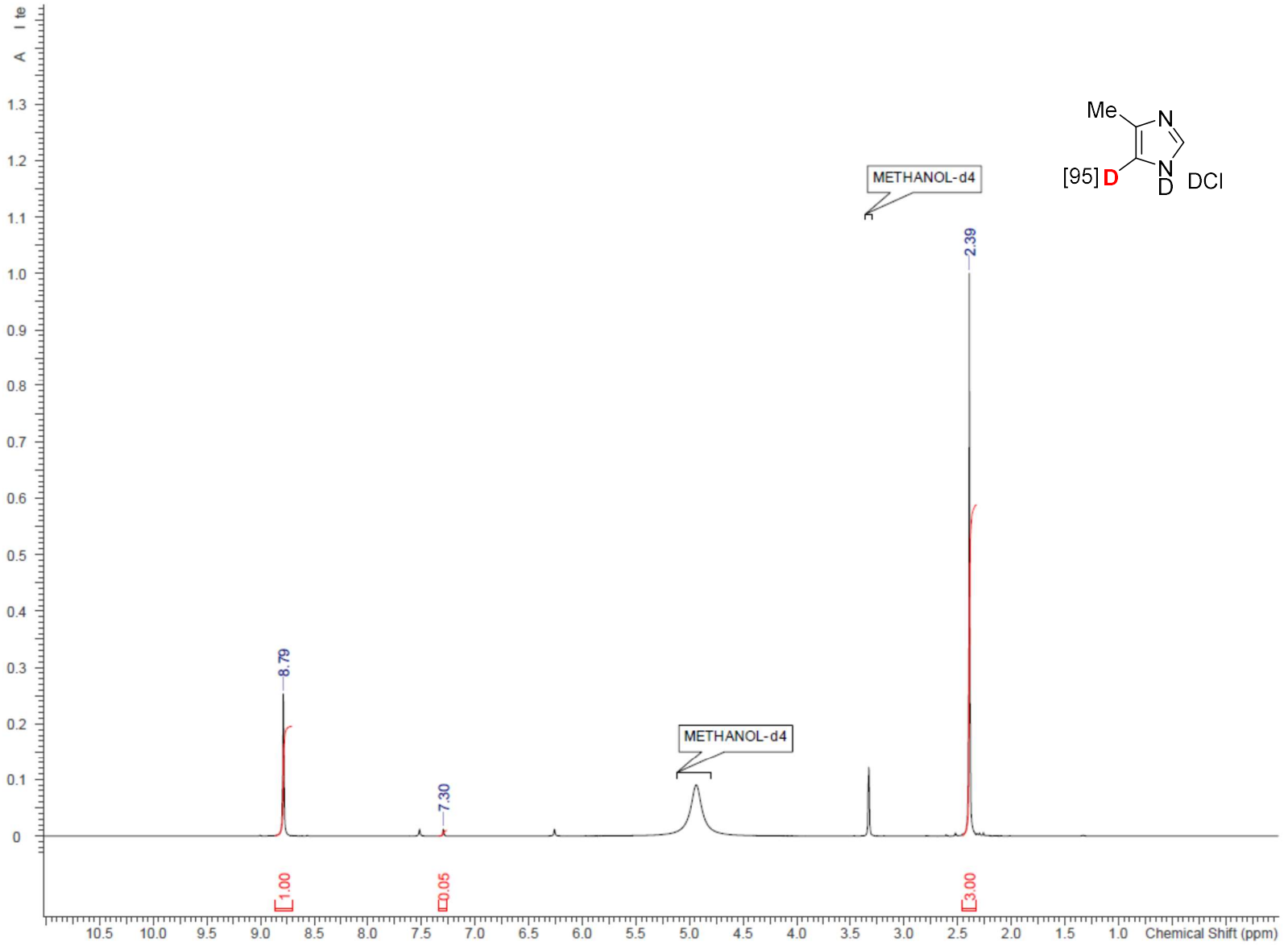

Figure S 15. ^{1}H NMR spectrum of **2h** (CD_3OD)

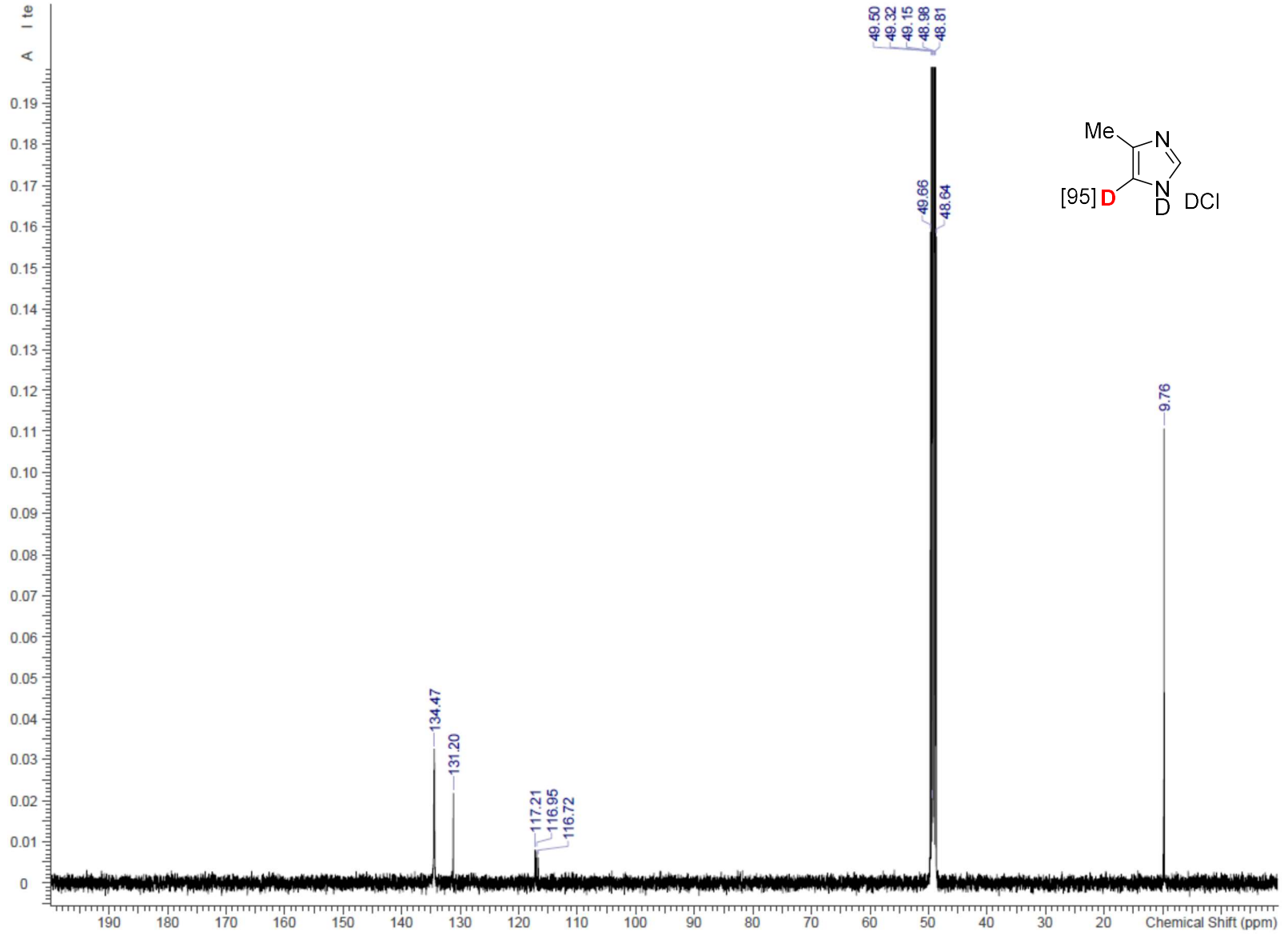

Figure S 16. ^{13}C NMR spectrum of **2h** (CD_3OD)

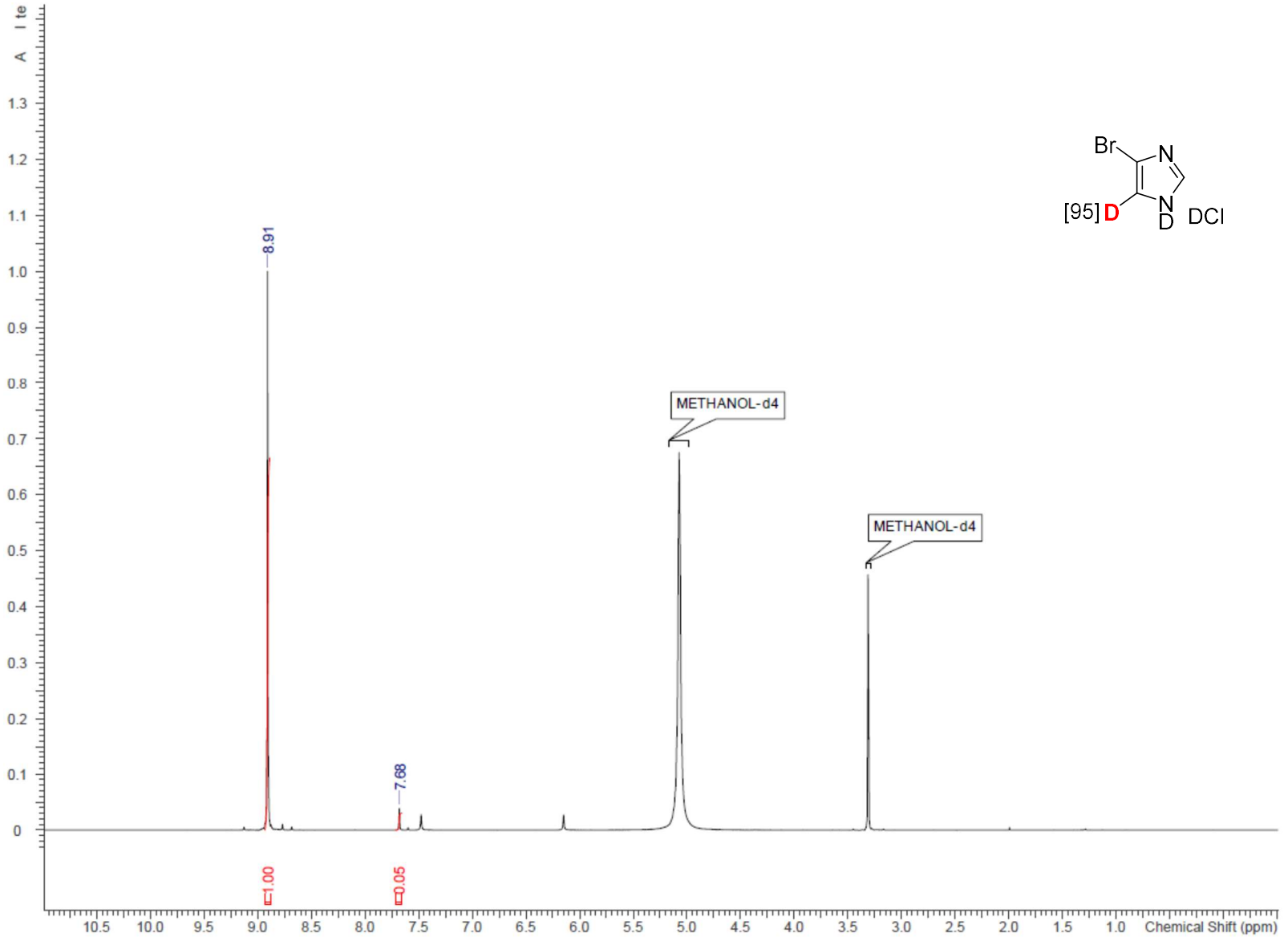

Figure S 17. ^{1}H NMR spectrum of **2i** (CD_3OD)

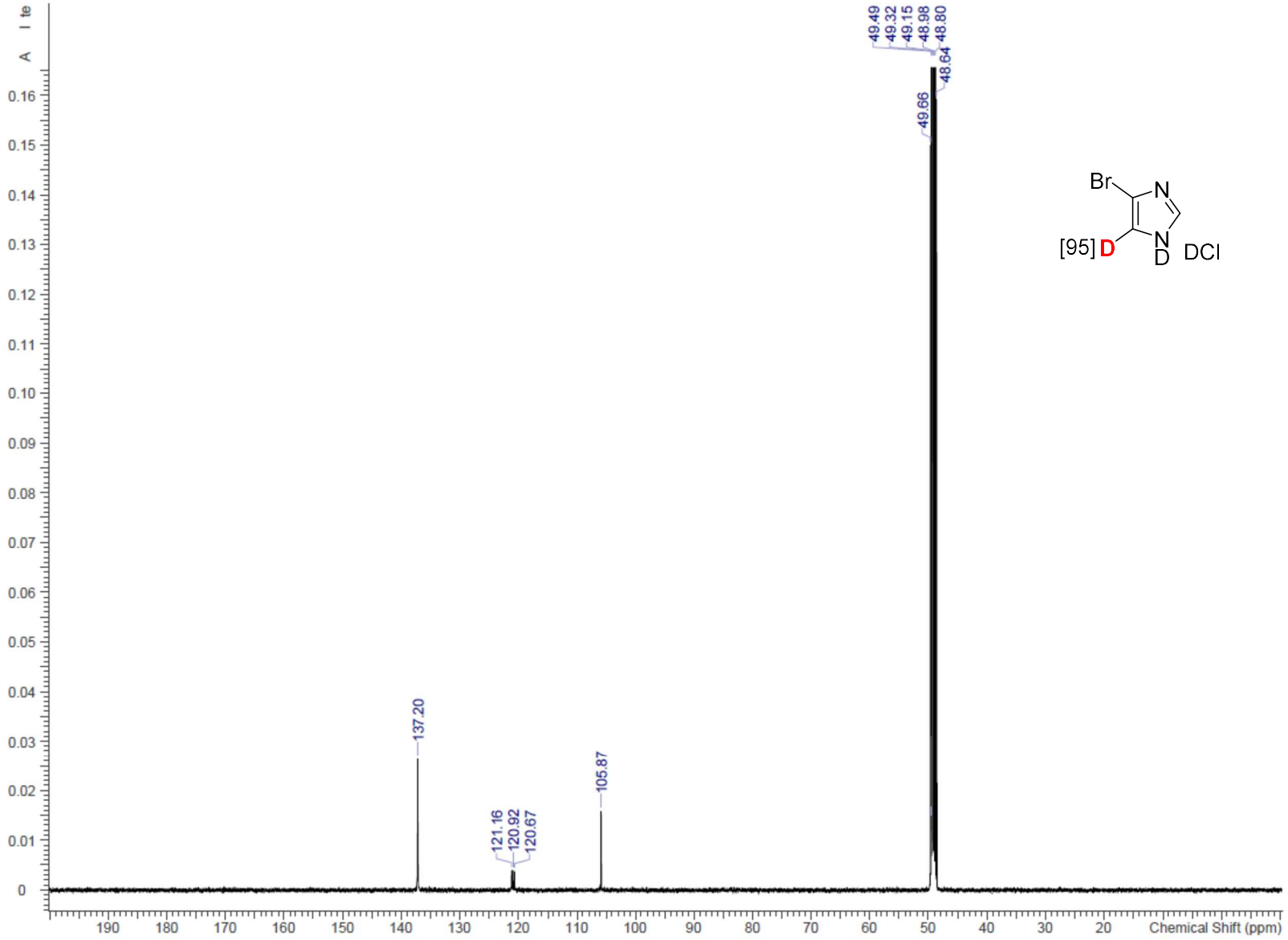

Figure S 18. ^{13}C NMR spectrum of **2i** (CD_3OD)

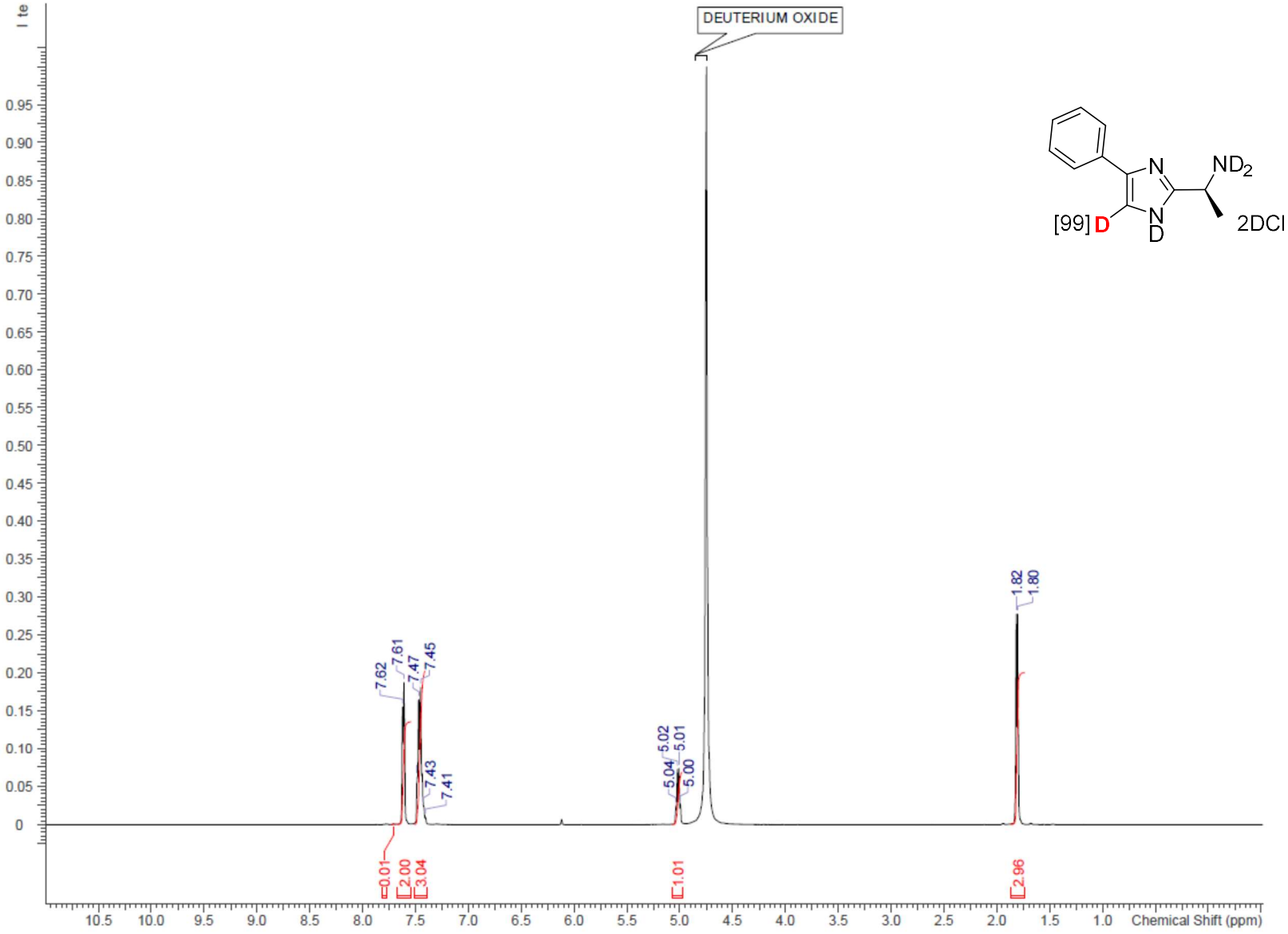

Figure S 19. ^{1}H NMR spectrum of **2j** (D_2O)

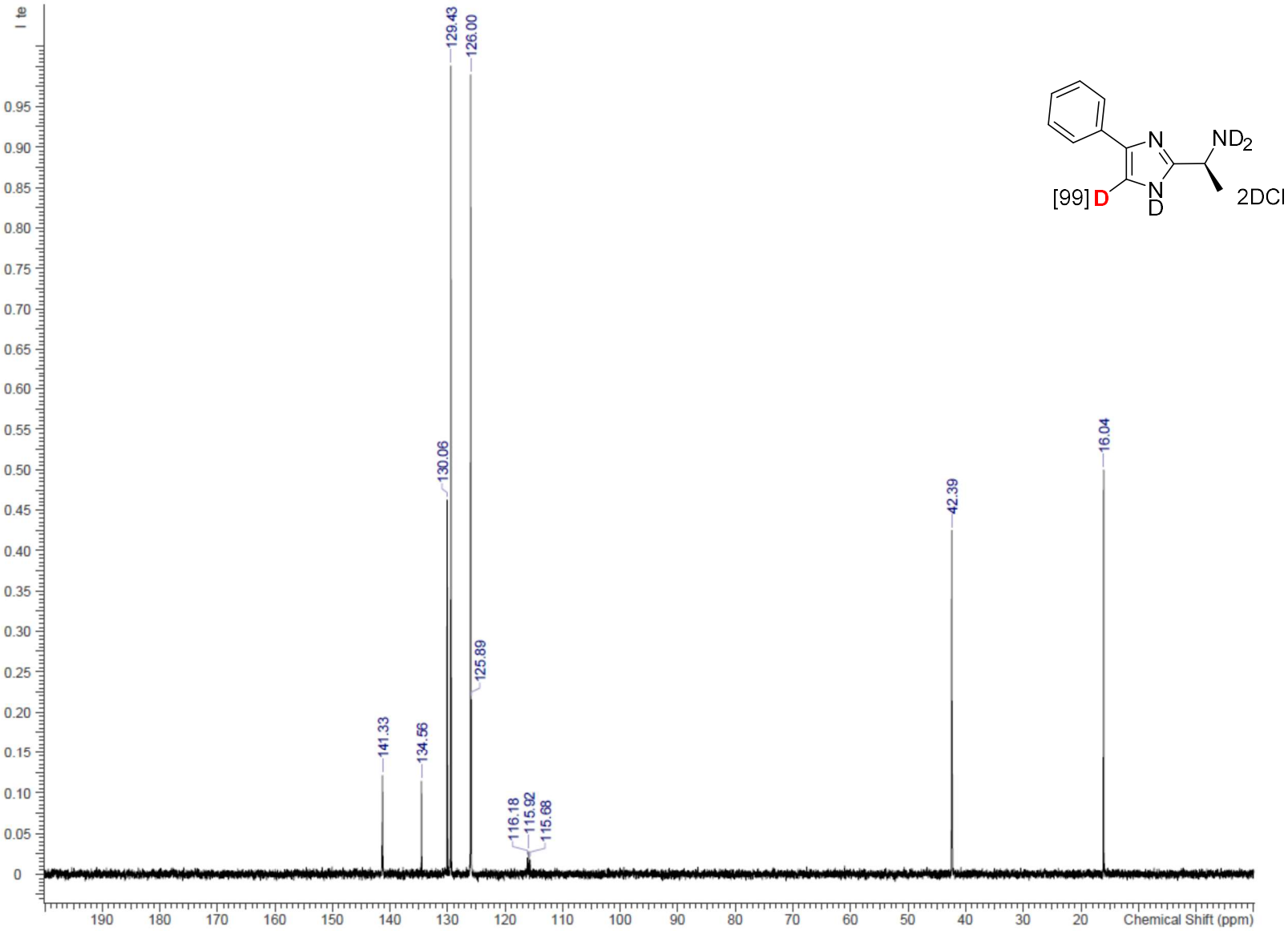

Figure S 20. ^{13}C NMR spectrum of **2j** (D_2O)

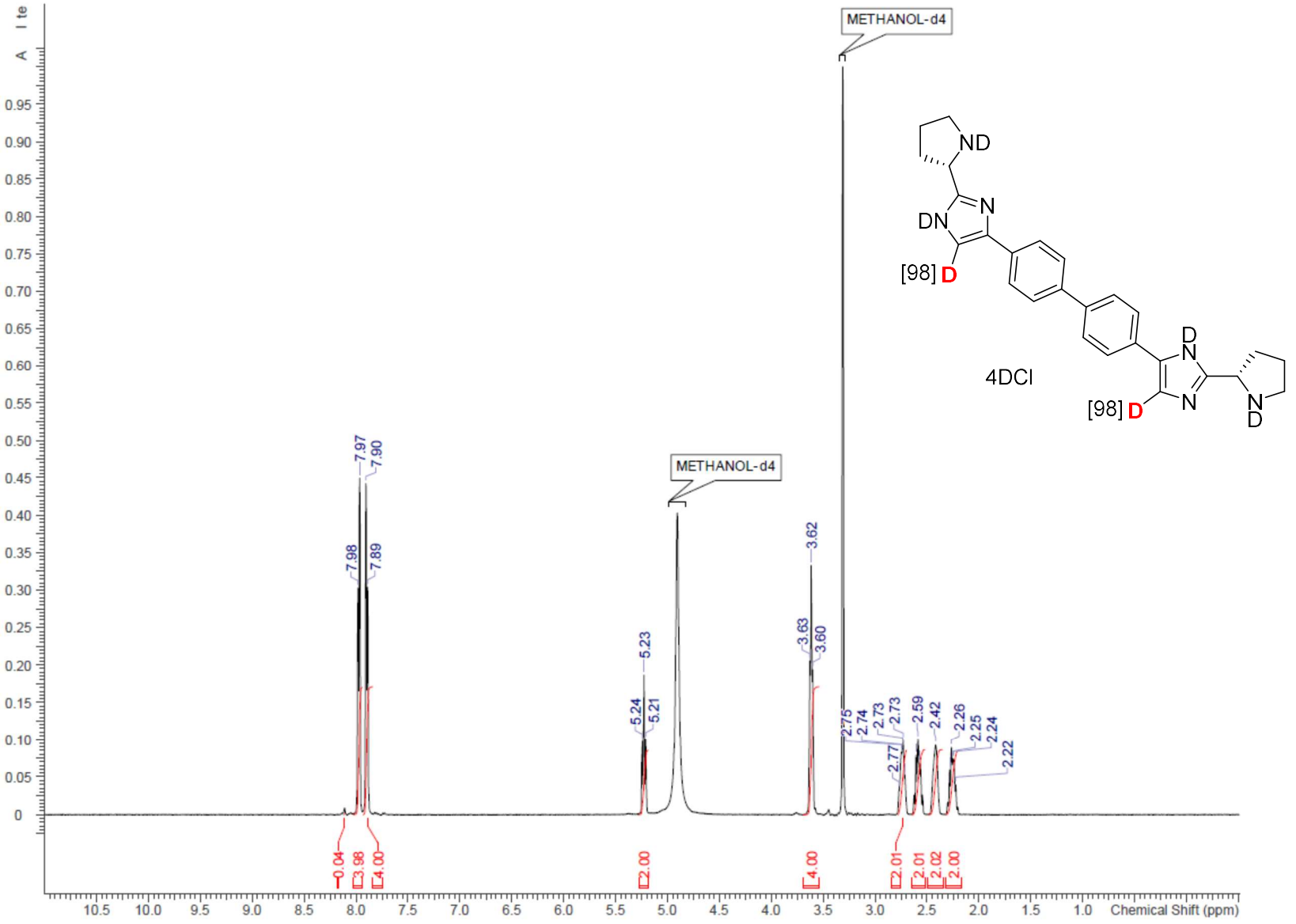

Figure S 21. ^{1}H NMR spectrum of **2k** (CD_3OD)

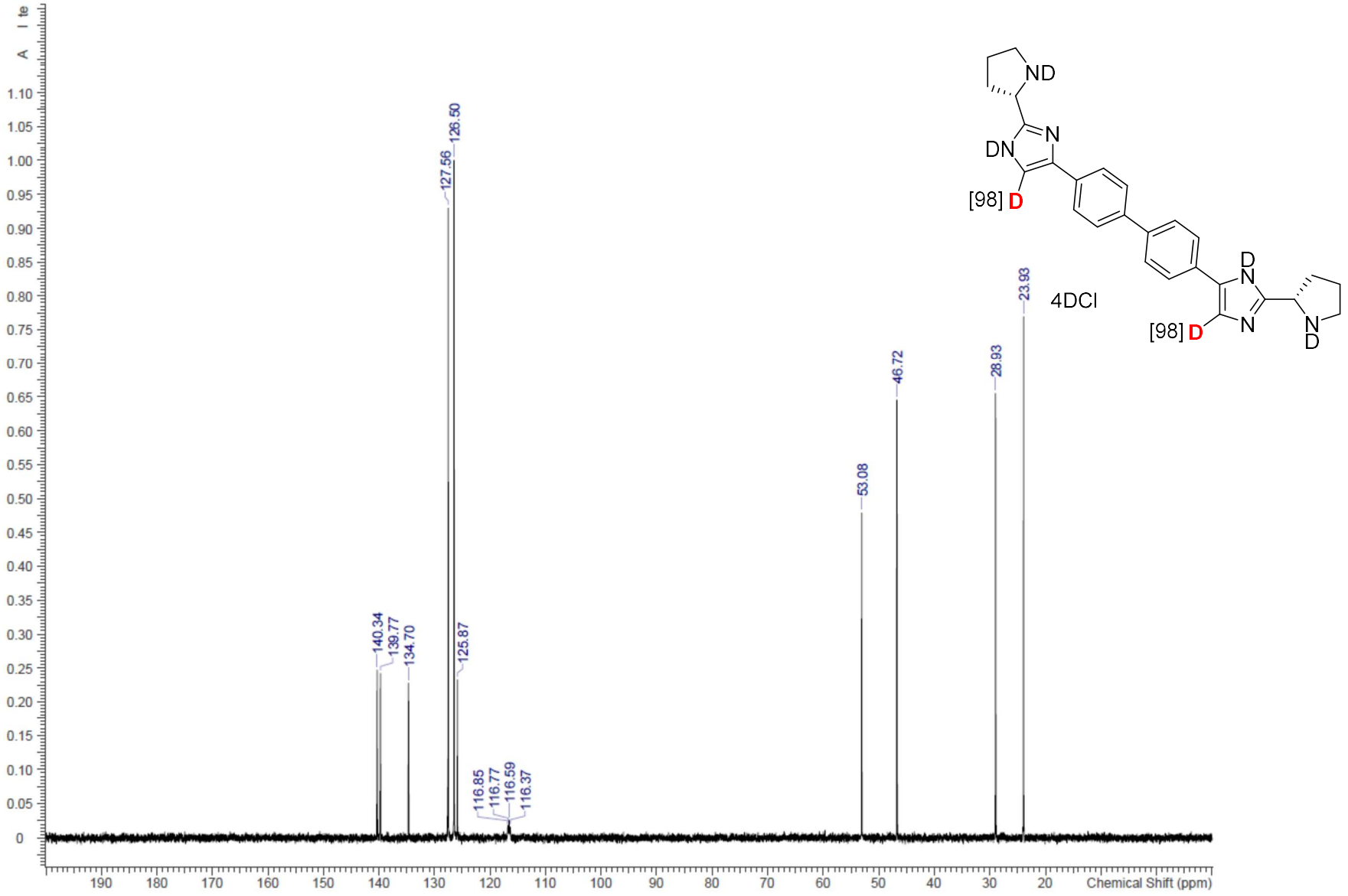

Figure S 22. ^{13}C NMR spectrum of **2k** (D_2O)

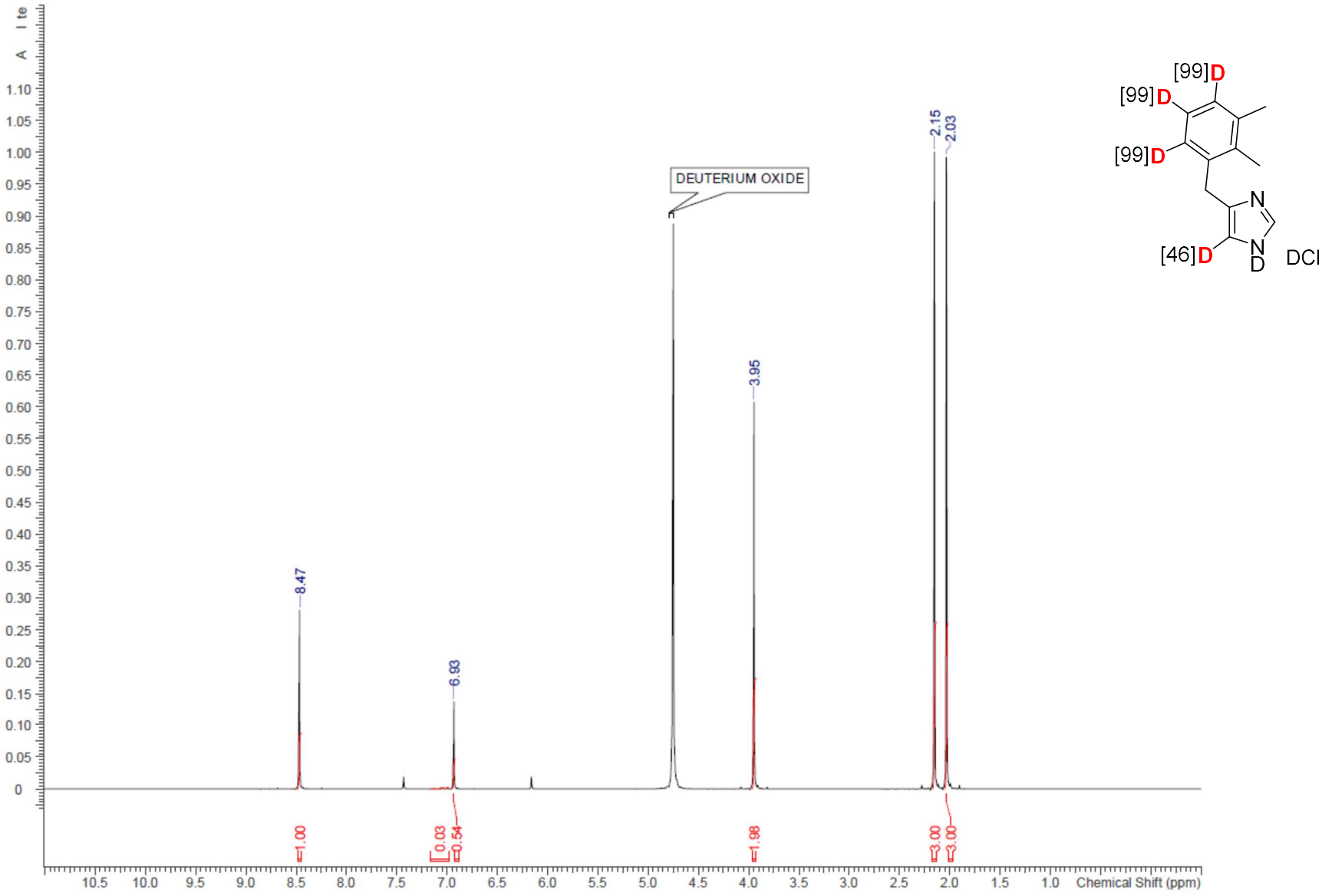

Figure S 23. ^{1}H NMR spectrum of **2l** (D_2O)

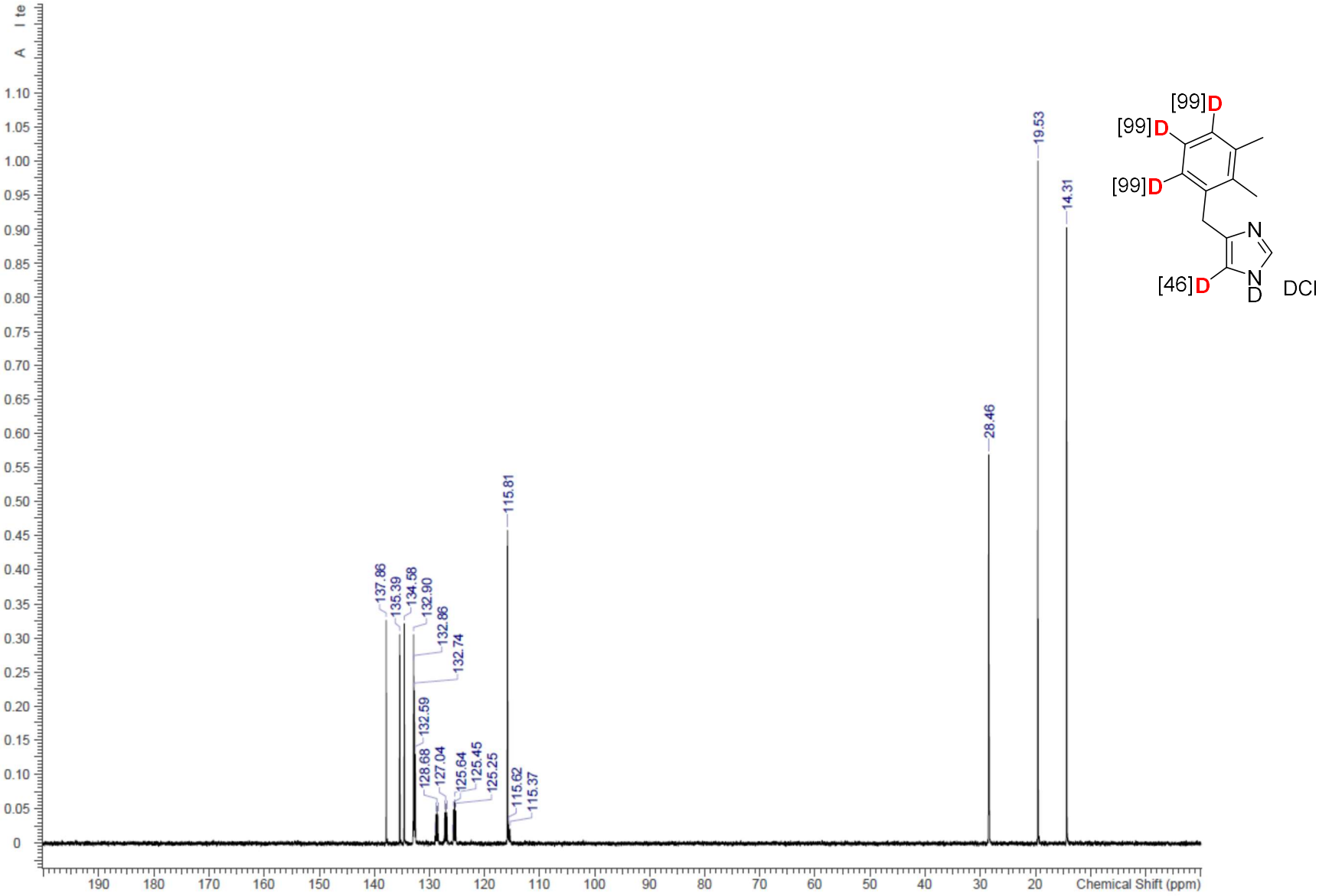

Figure S 24. ^{13}C NMR spectrum of **2l** (D_2O)

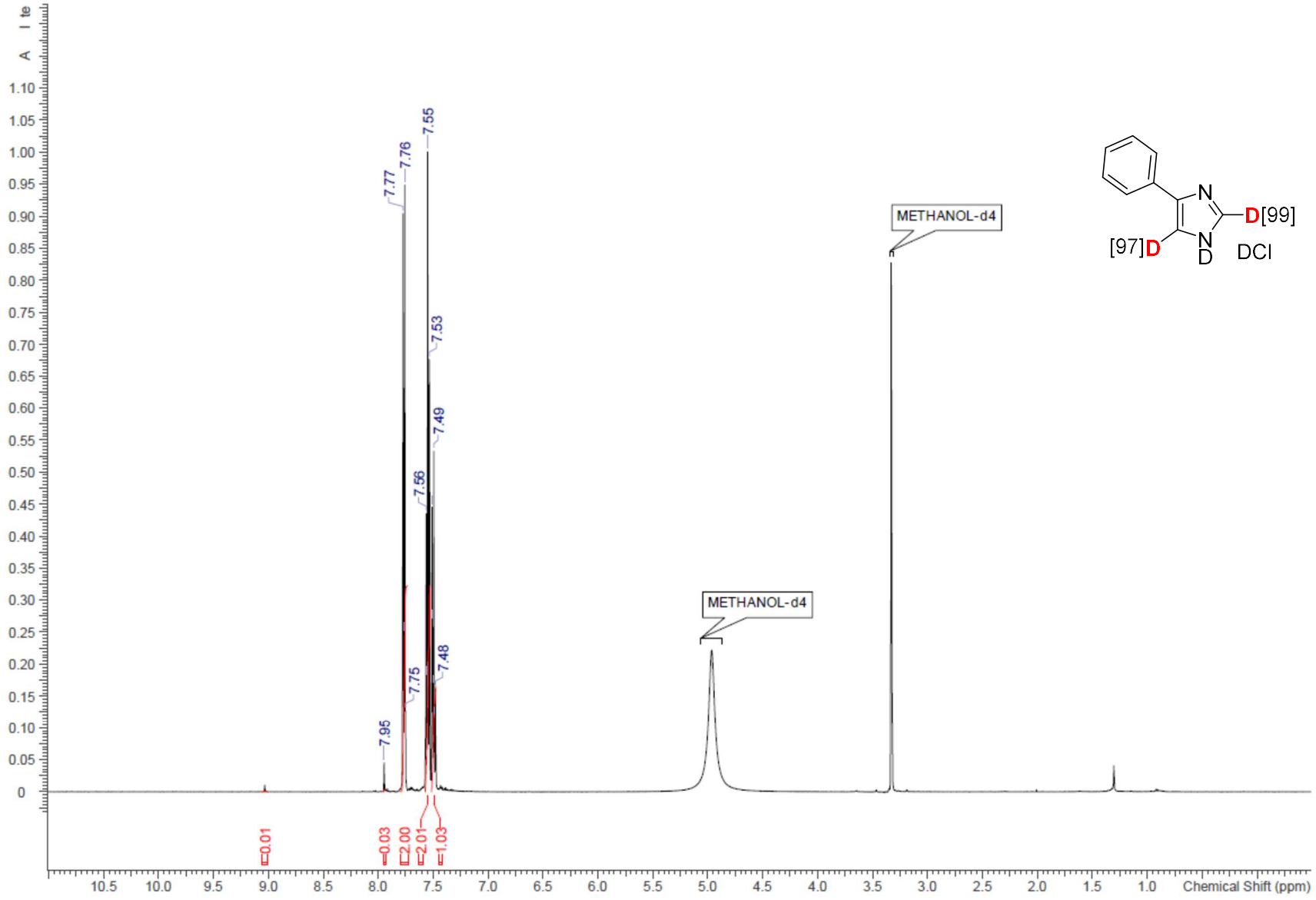

Figure S 25. ^{1}H NMR spectrum of **3a** (CD_3OD)

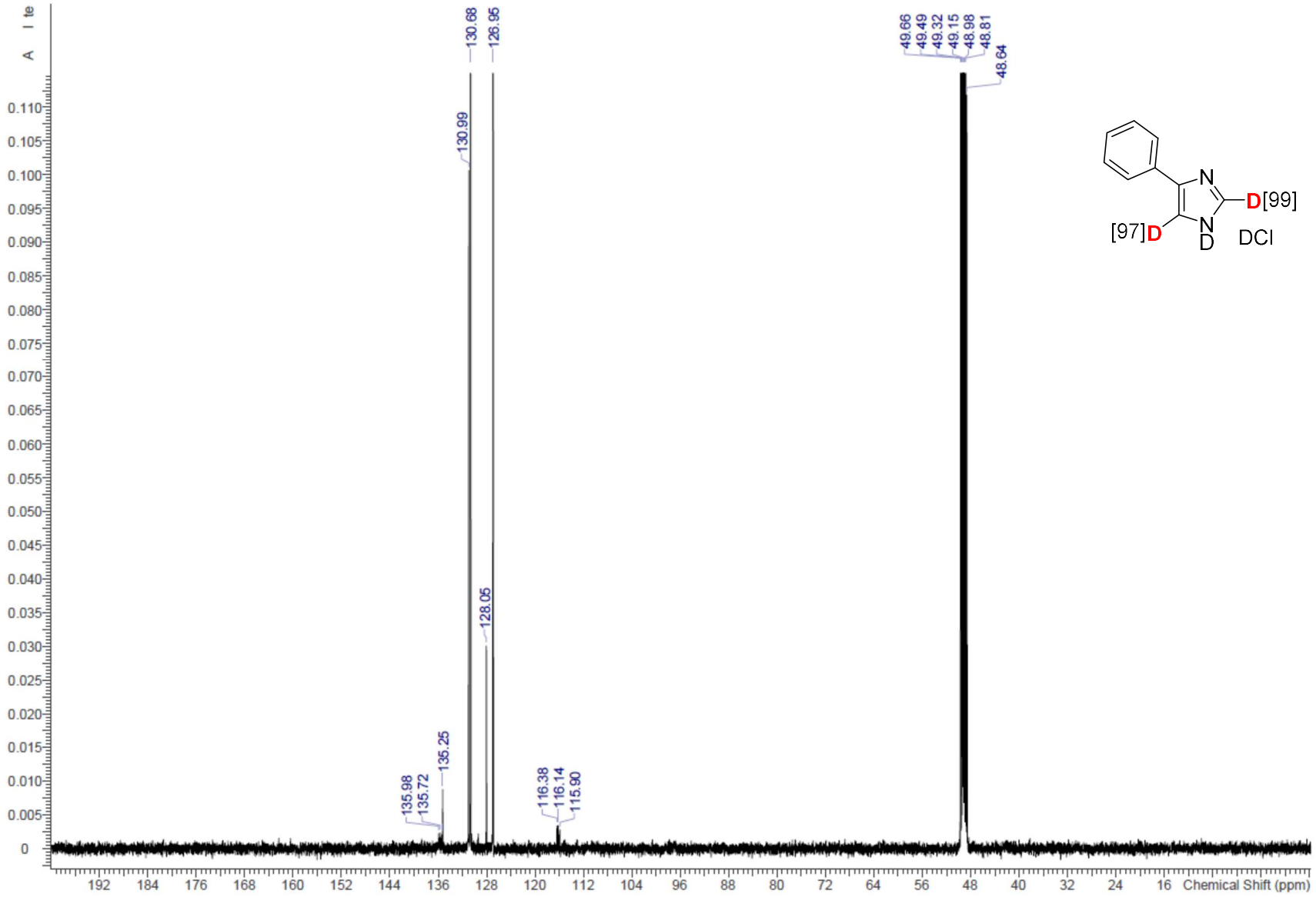

Figure S 26. ^{13}C NMR spectrum of **3a** (CD_3OD)

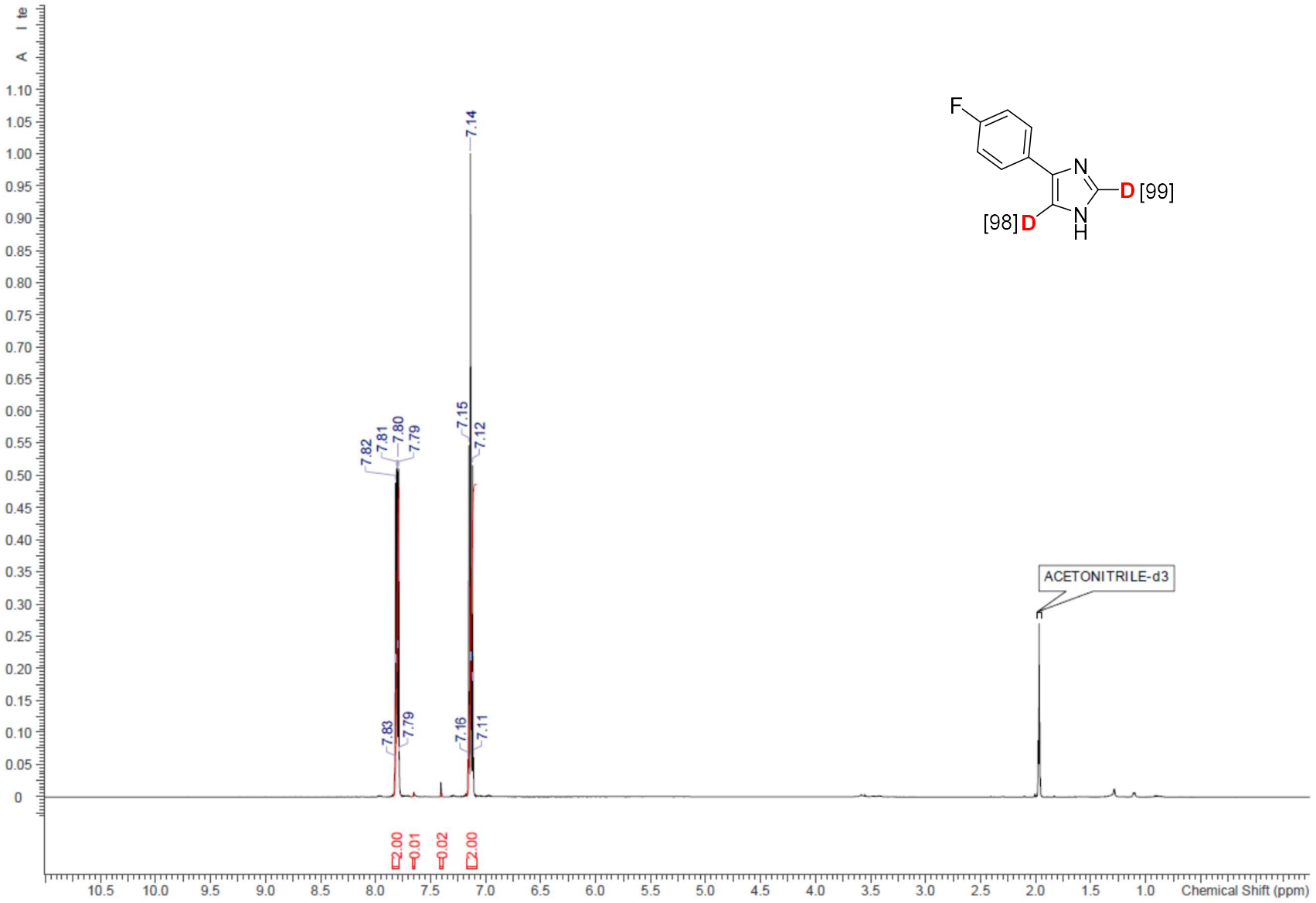

Figure S 27. ^{1}H NMR spectrum of **3b** (CD_3CN)

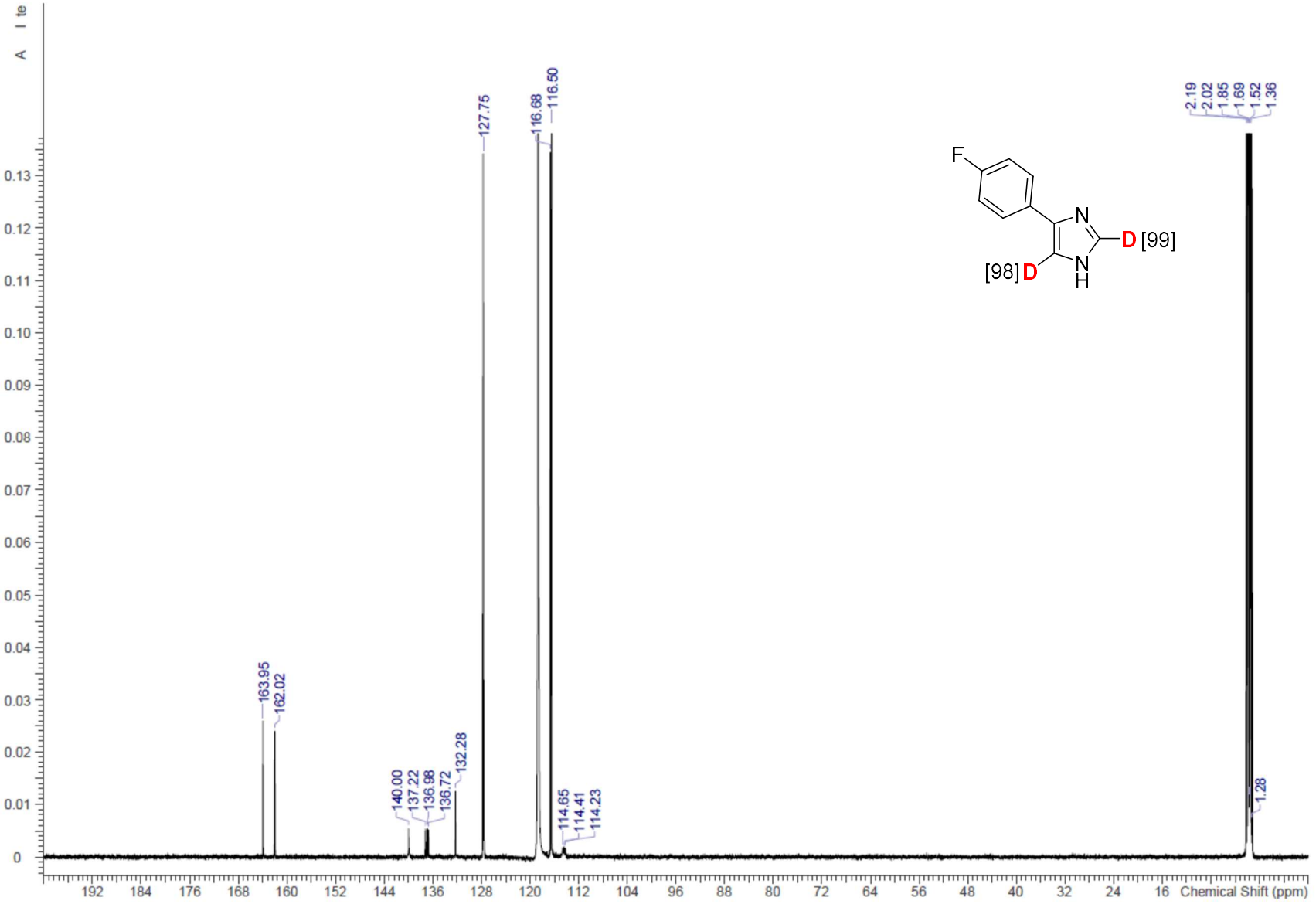

Figure S 28. ^{13}C NMR spectrum of **3b** (CD_3CN)

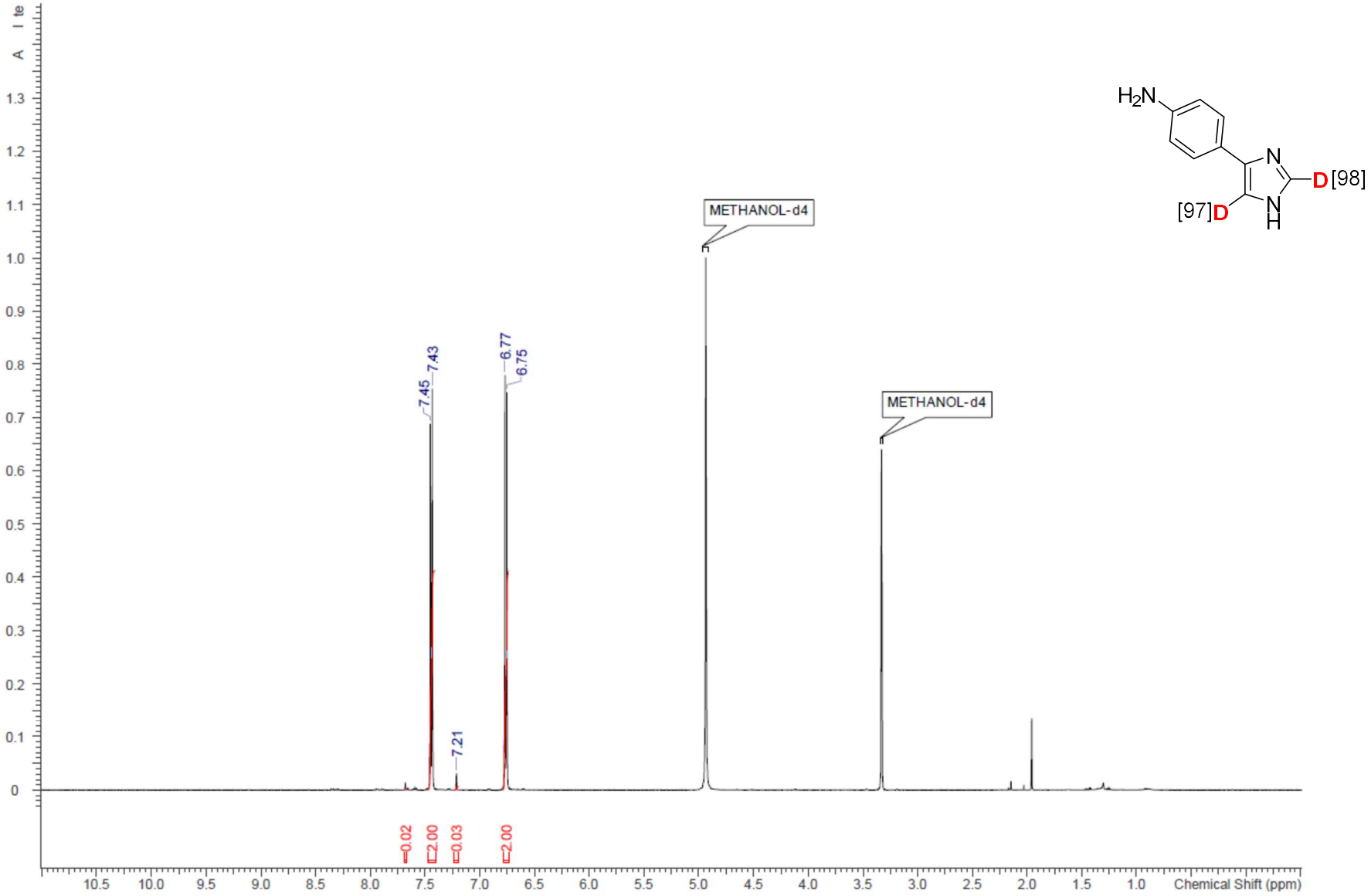

Figure S 29. ^{1}H NMR spectrum of **3e** (CD_3OD)

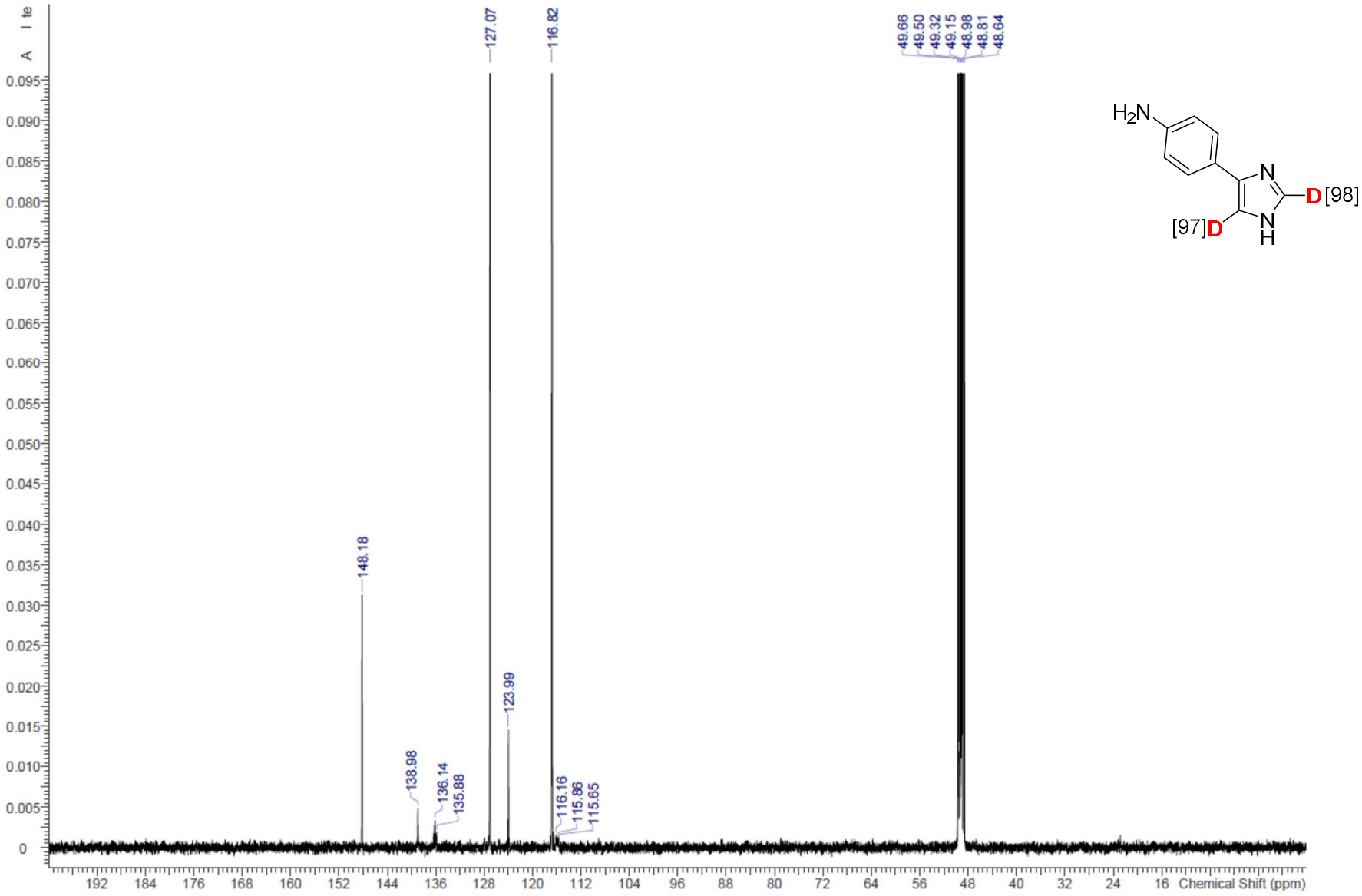

Figure S 30. ^{13}C NMR spectrum of **3e** (CD_3OD)

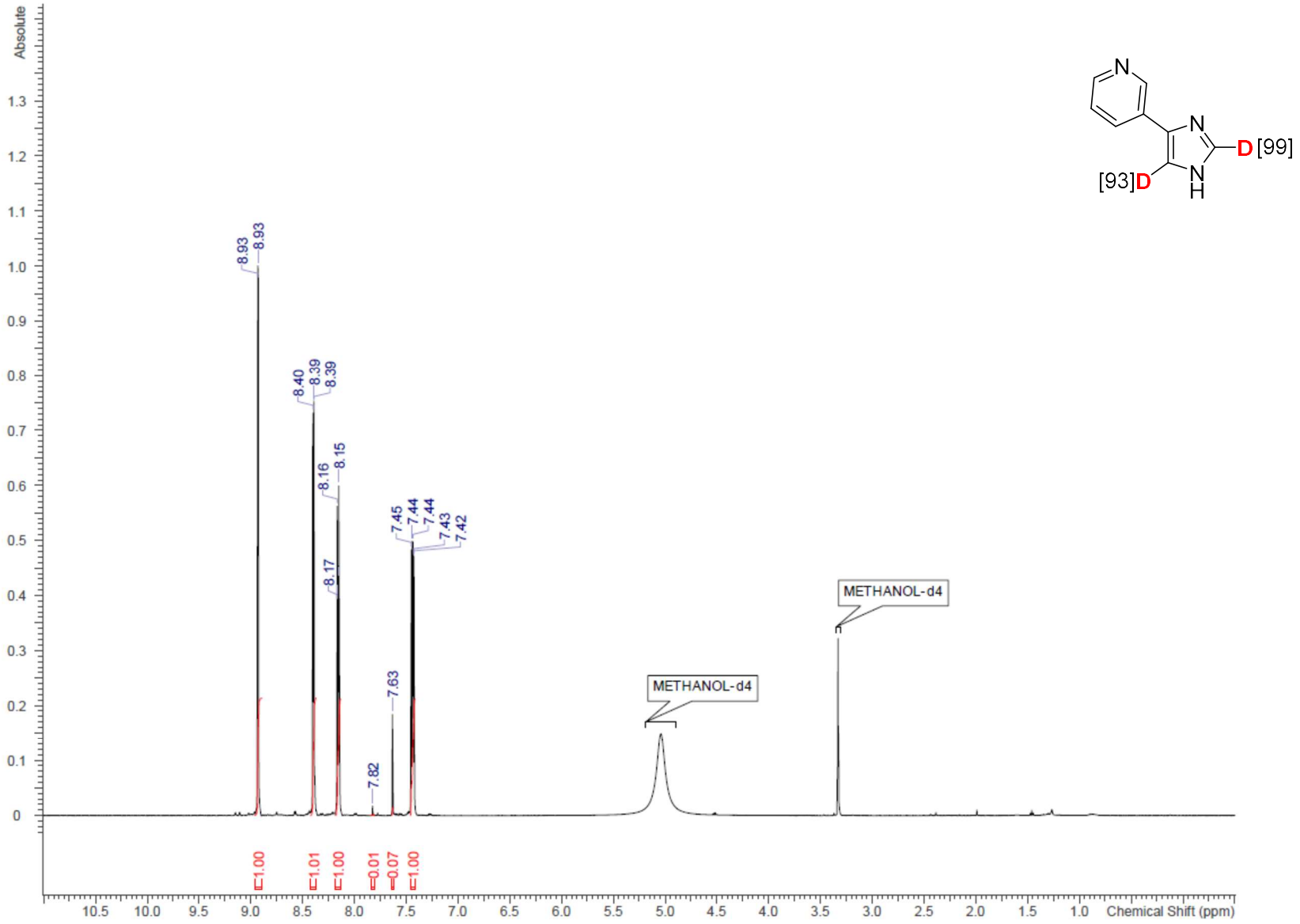

Figure S 31. ^{1}H NMR spectrum of **3f** (CD_3OD)

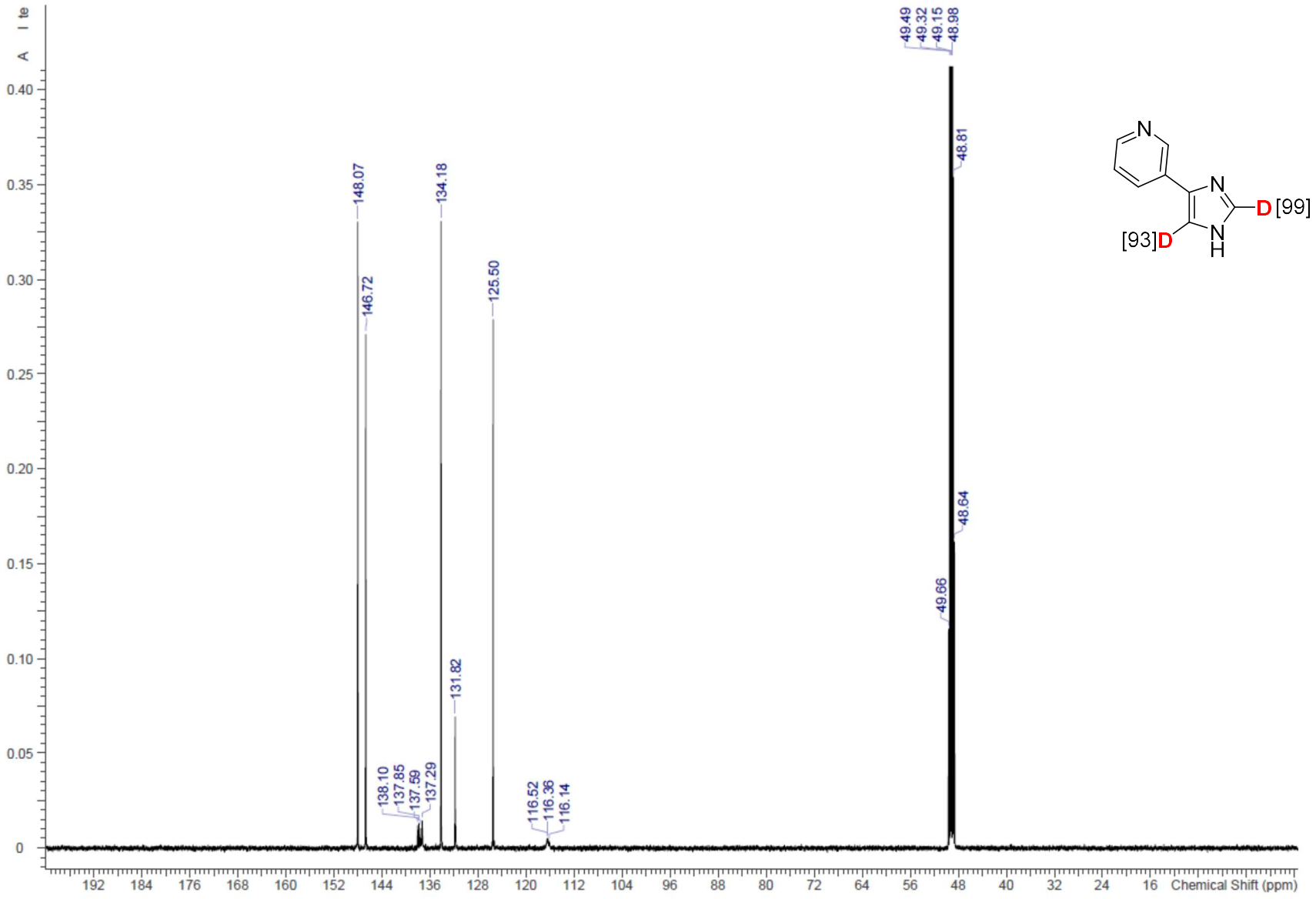

Figure S 32. ^{13}C NMR spectrum of **3f** (CD_3OD)

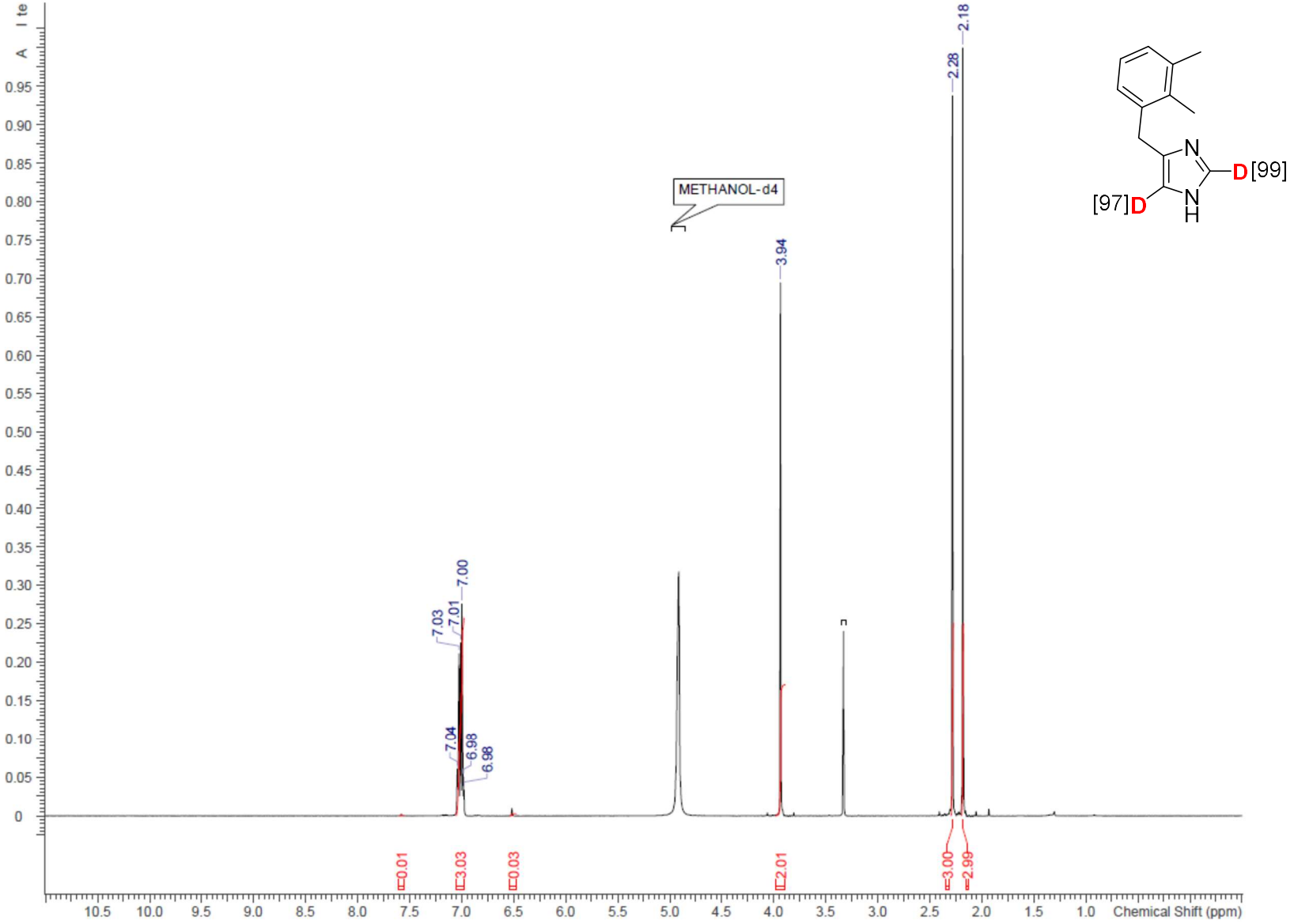

Figure S 33. ^{1}H NMR spectrum of **3l**-free (CD_3OD)

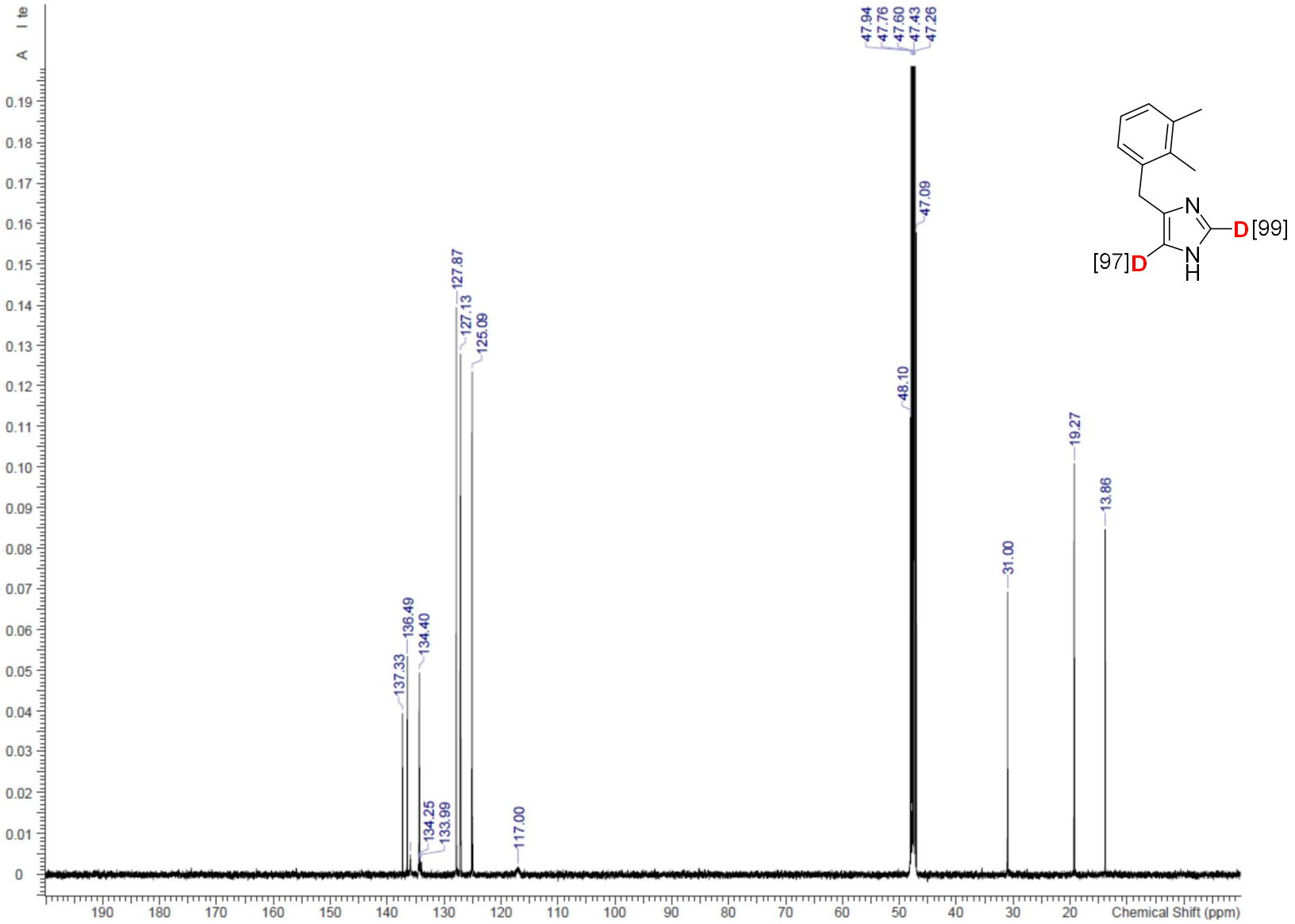

Figure S 34. ^{13}C NMR spectrum of **3l**-free (CD_3OD)

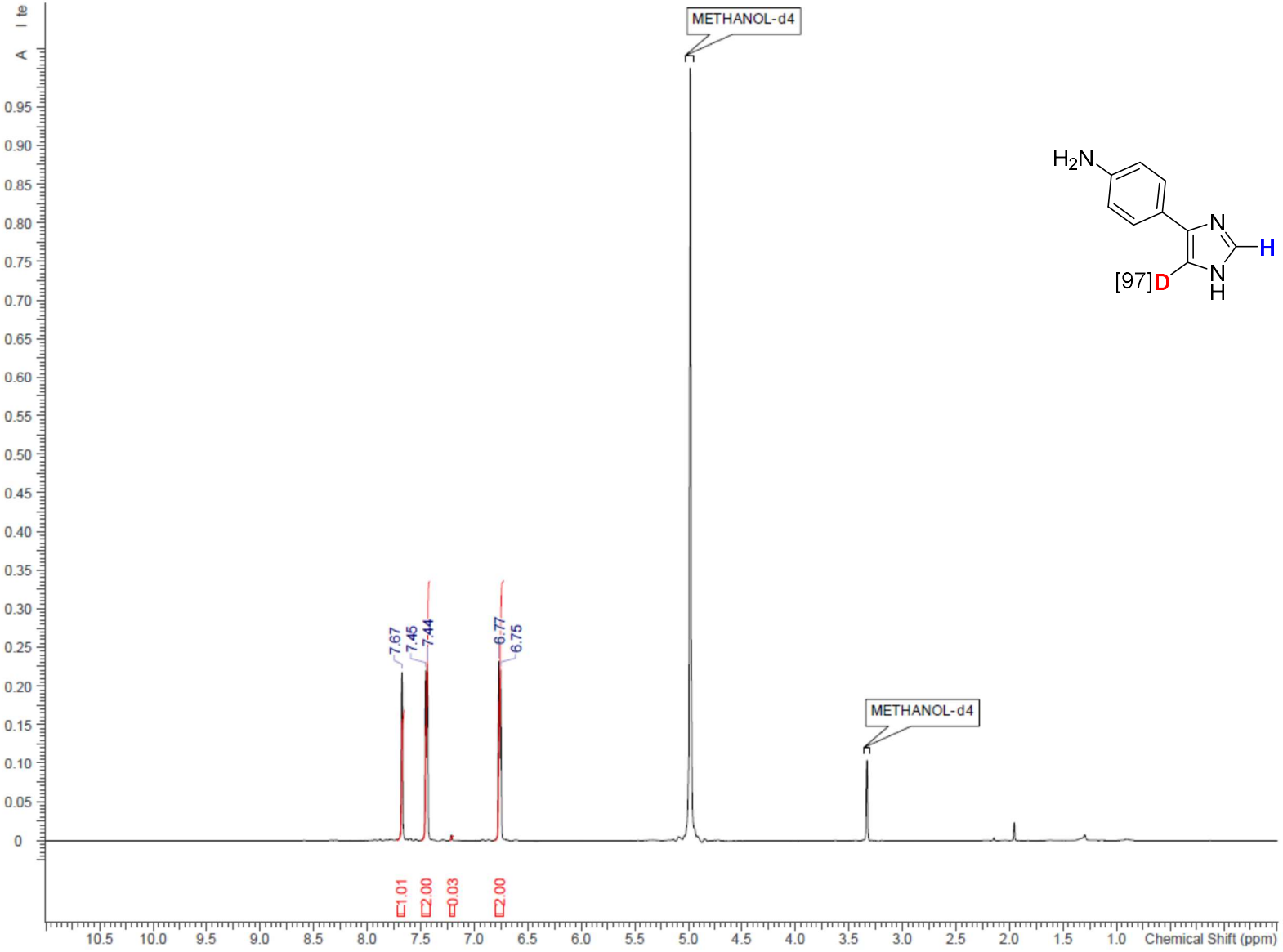

Figure S 35. ^{1}H NMR spectrum of **3e (C2-H)** (CD_3OD)

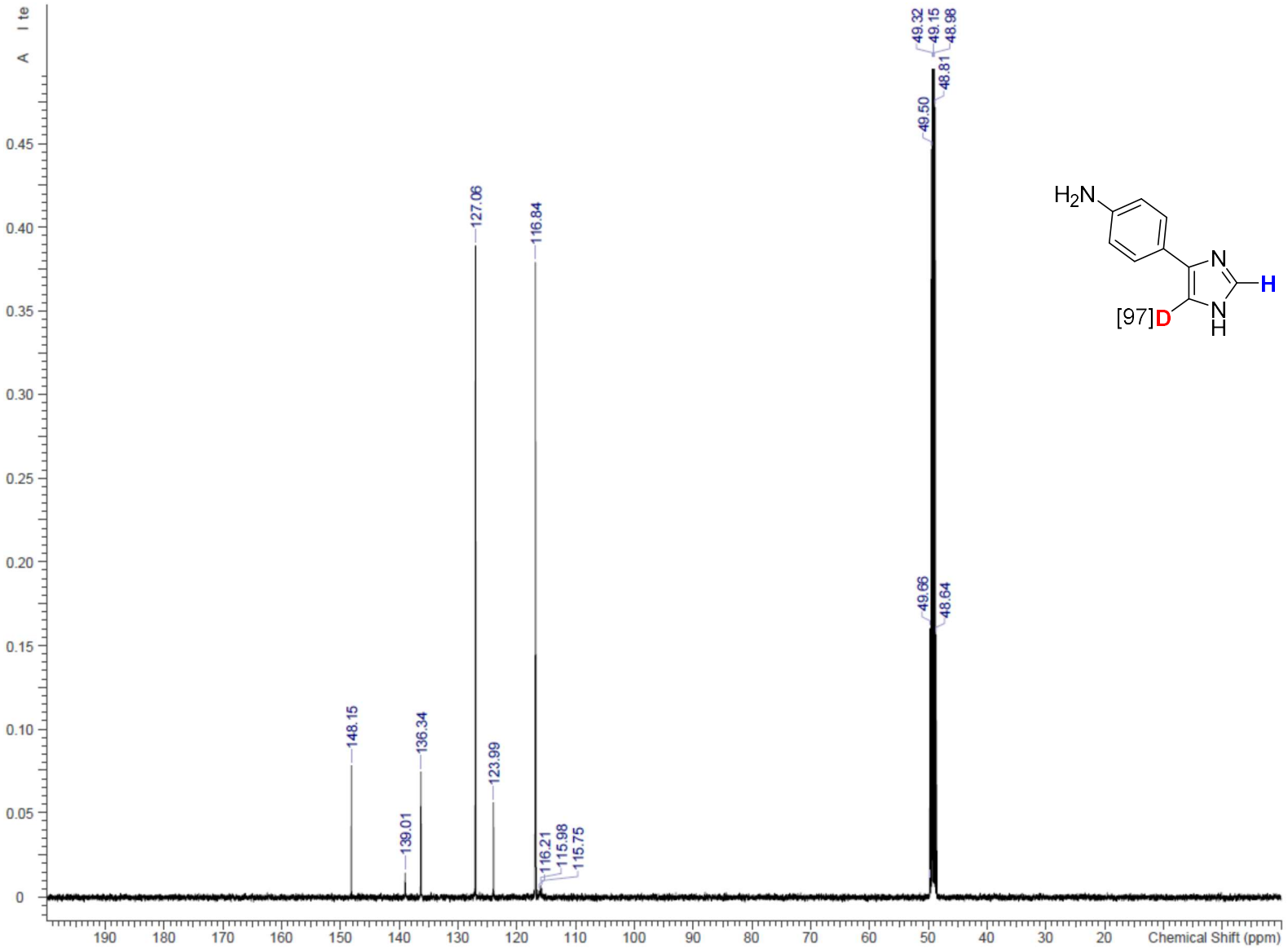

Figure S 36. ^{13}C NMR spectrum of **3e (C2-H)** (CD_3OD)

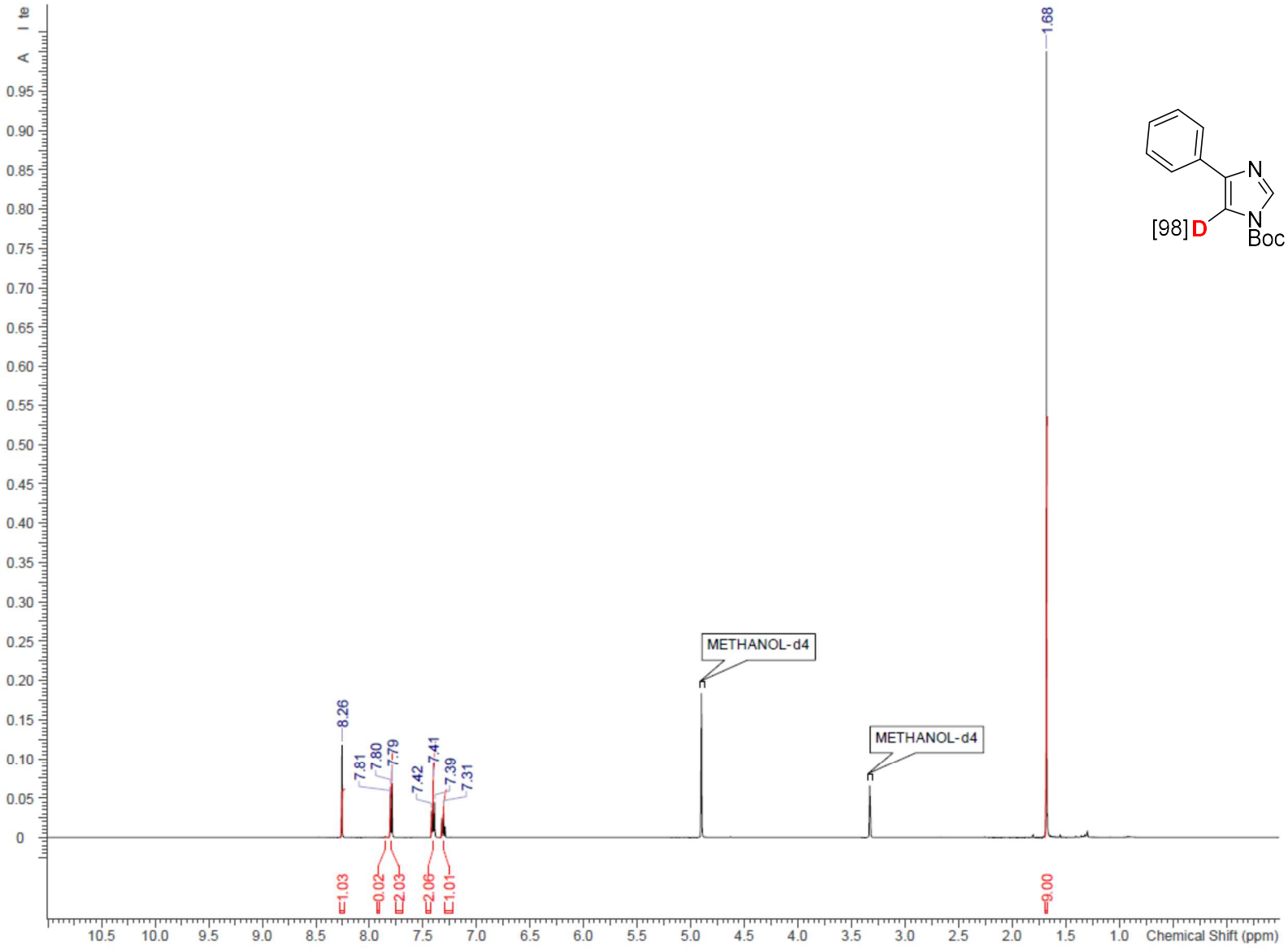

Figure S 37. ^{1}H NMR spectrum of **2a-Boc** (CD_3OD)

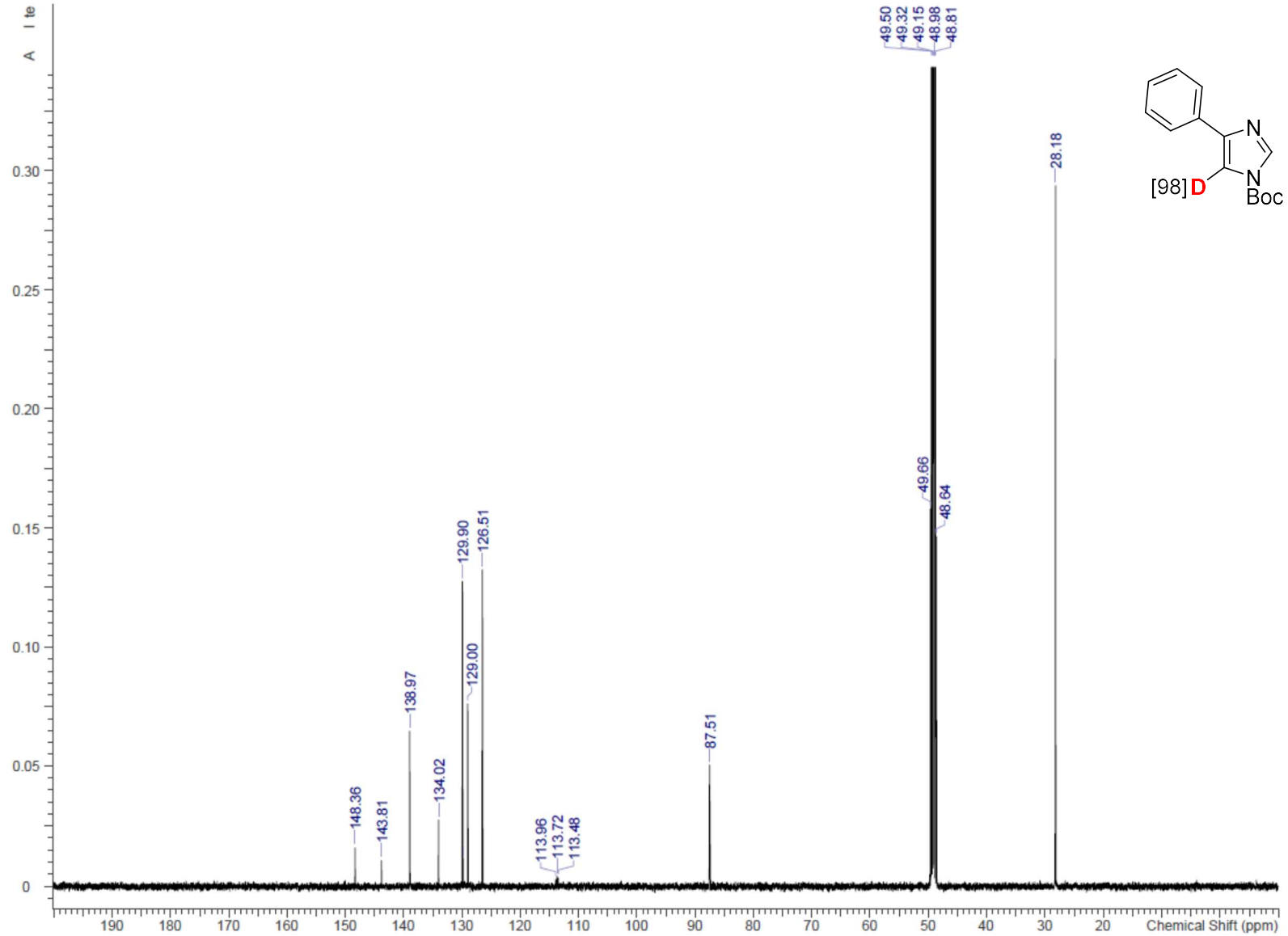

Figure S 38. ^{13}C NMR spectrum of **2a-Boc** (CD_3OD)

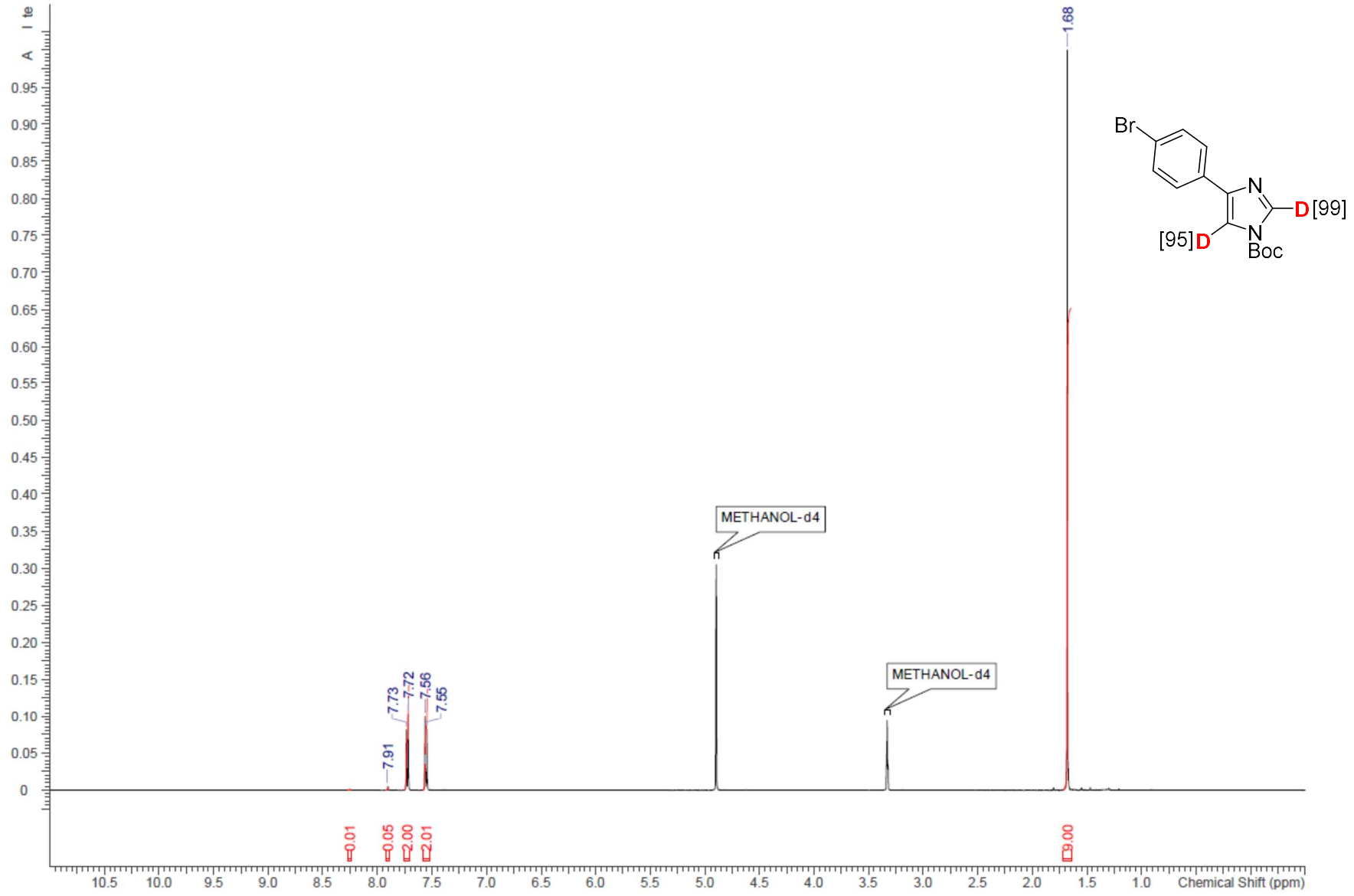

Figure S 39. ^{1}H NMR spectrum of **3c-Boc** (CD_3OD)

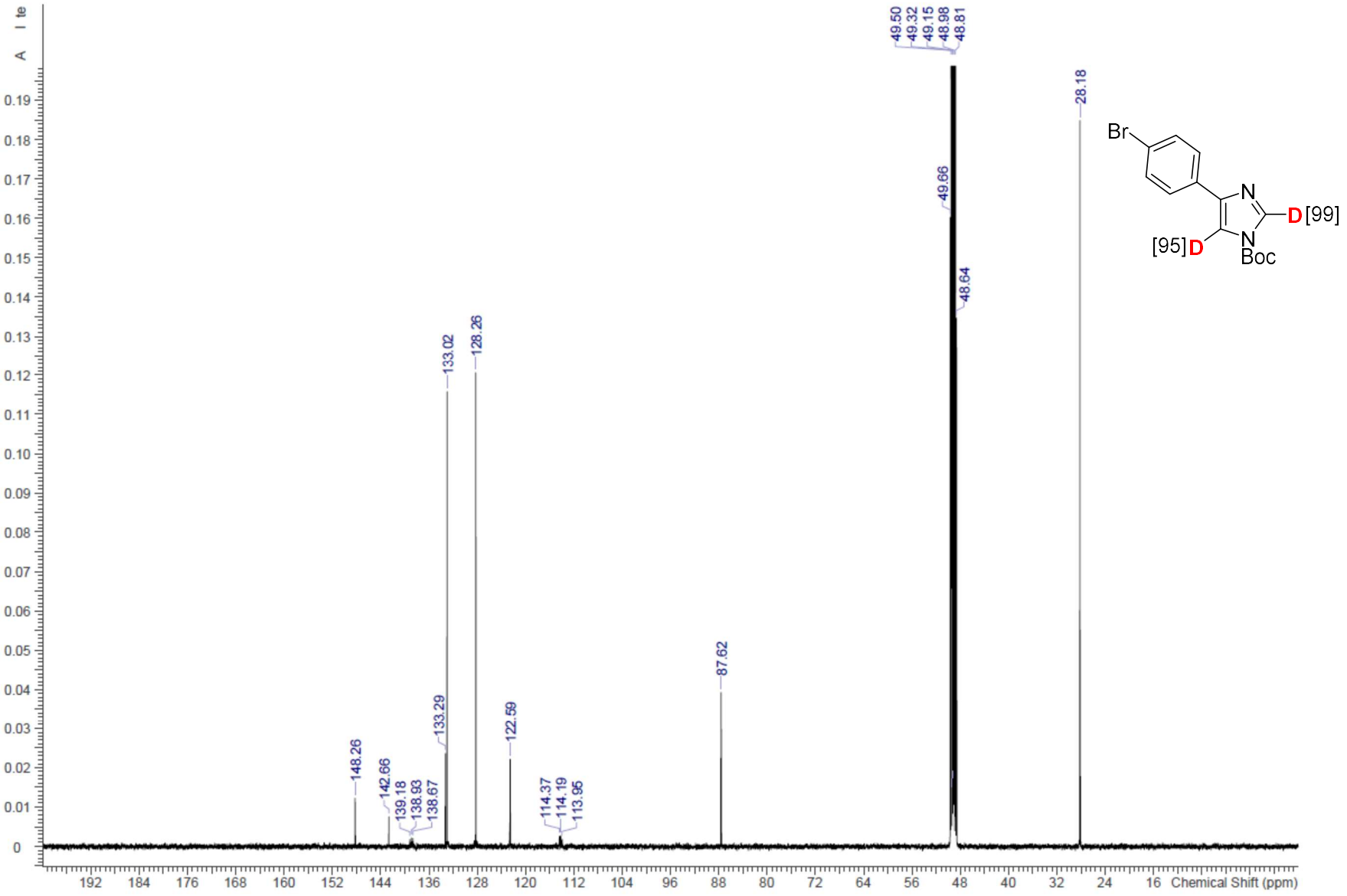

Figure S 40. ^{13}C NMR spectrum of **3c-Boc** (CD_3OD)

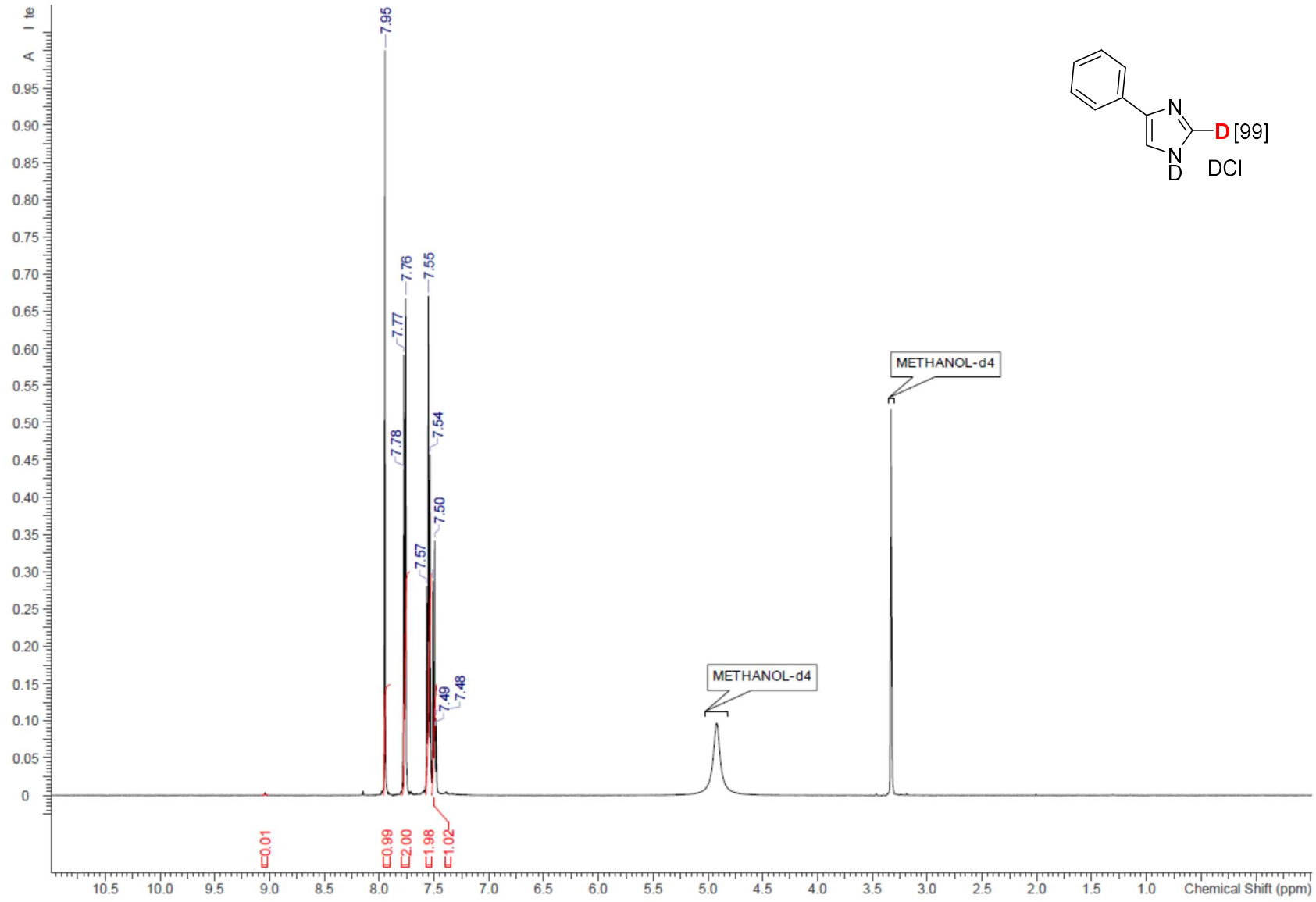

Figure S 41. ^{1}H NMR spectrum of **4a** (CD_3OD)

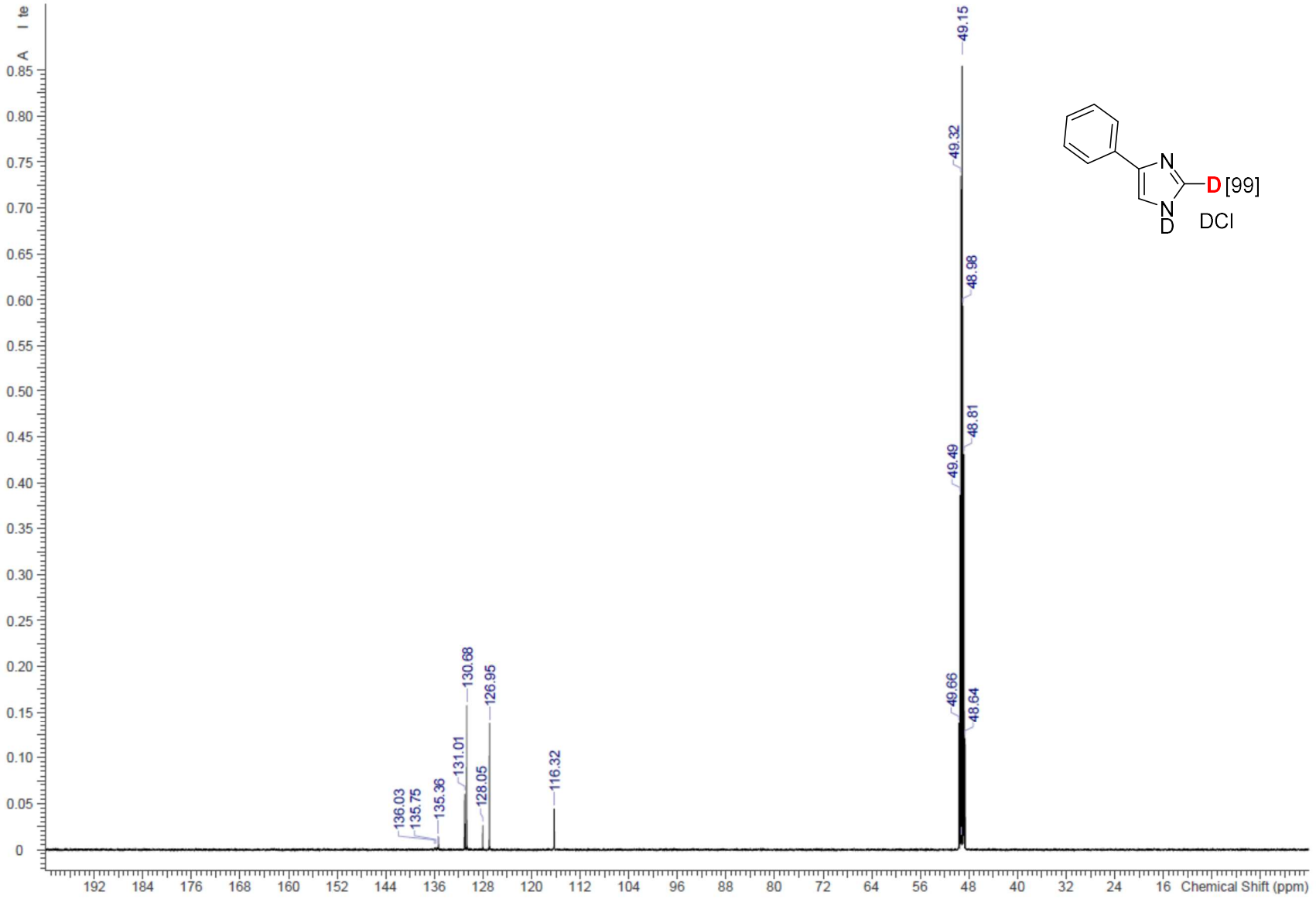

Figure S 42. ^{13}C NMR spectrum of **4a** (CD_3OD)

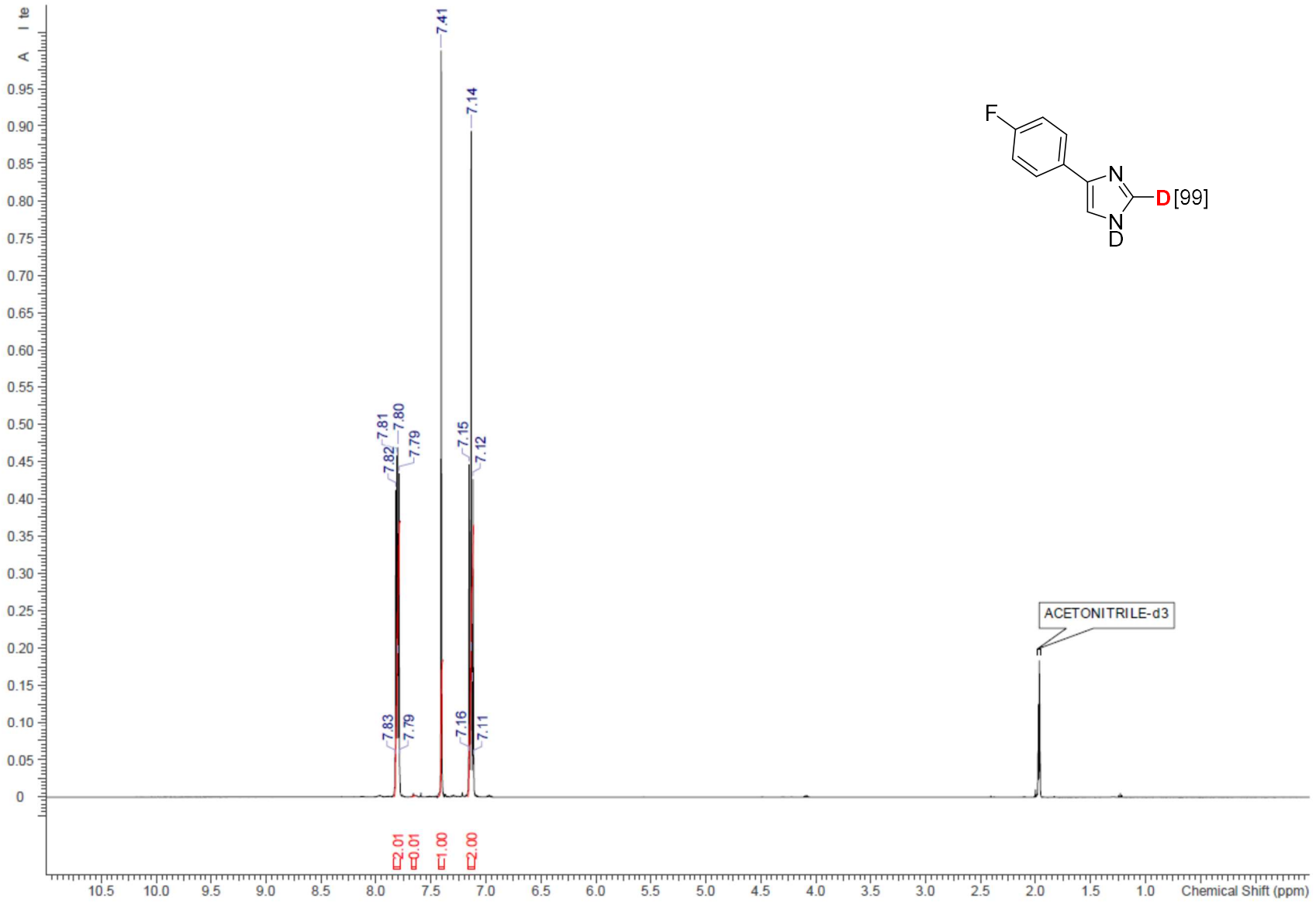

Figure S 43. ^{1}H NMR spectrum of **4b** (CD_3CN)

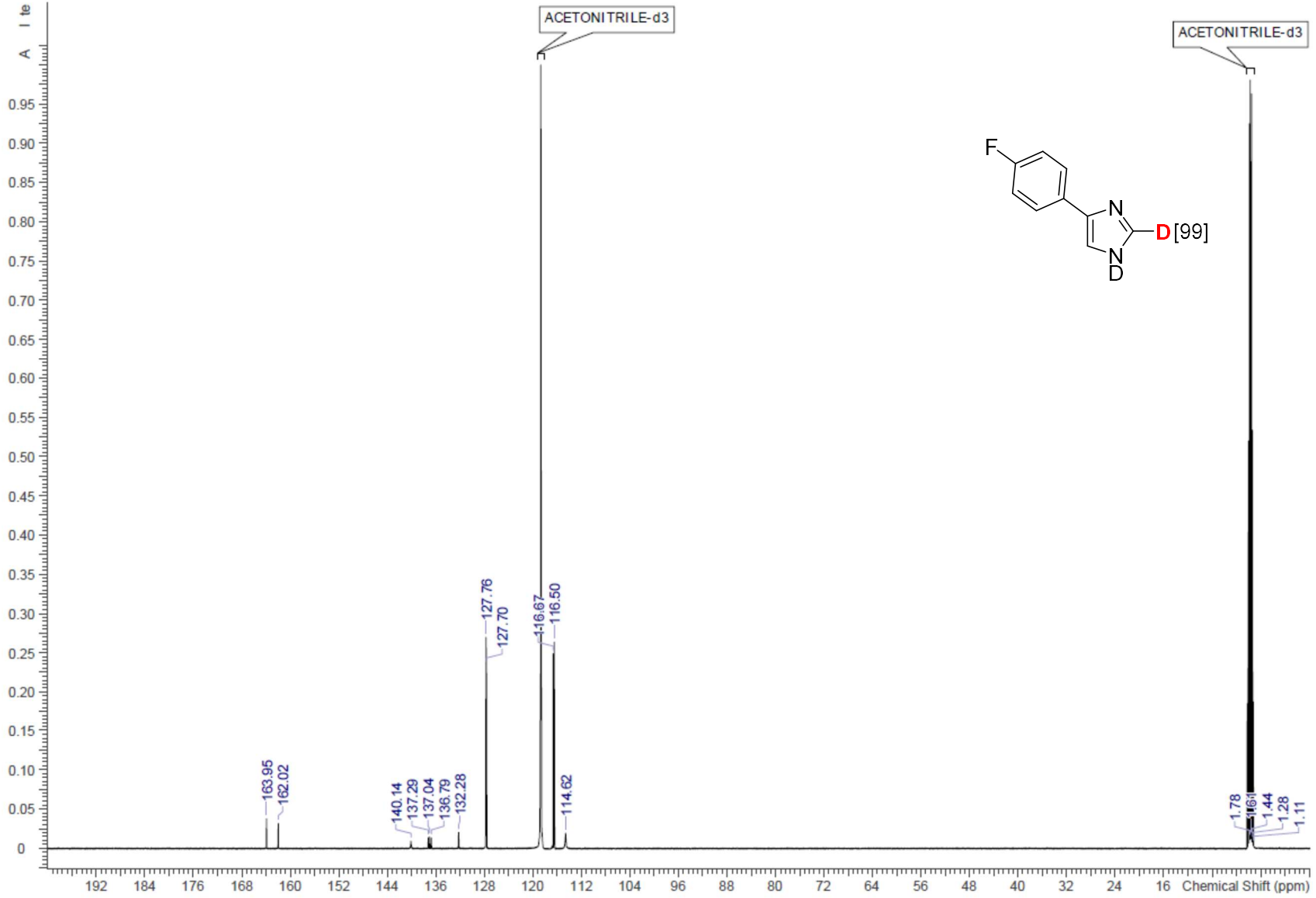

Figure S 44. ^{13}C NMR spectrum of **4b** (CD_3CN)

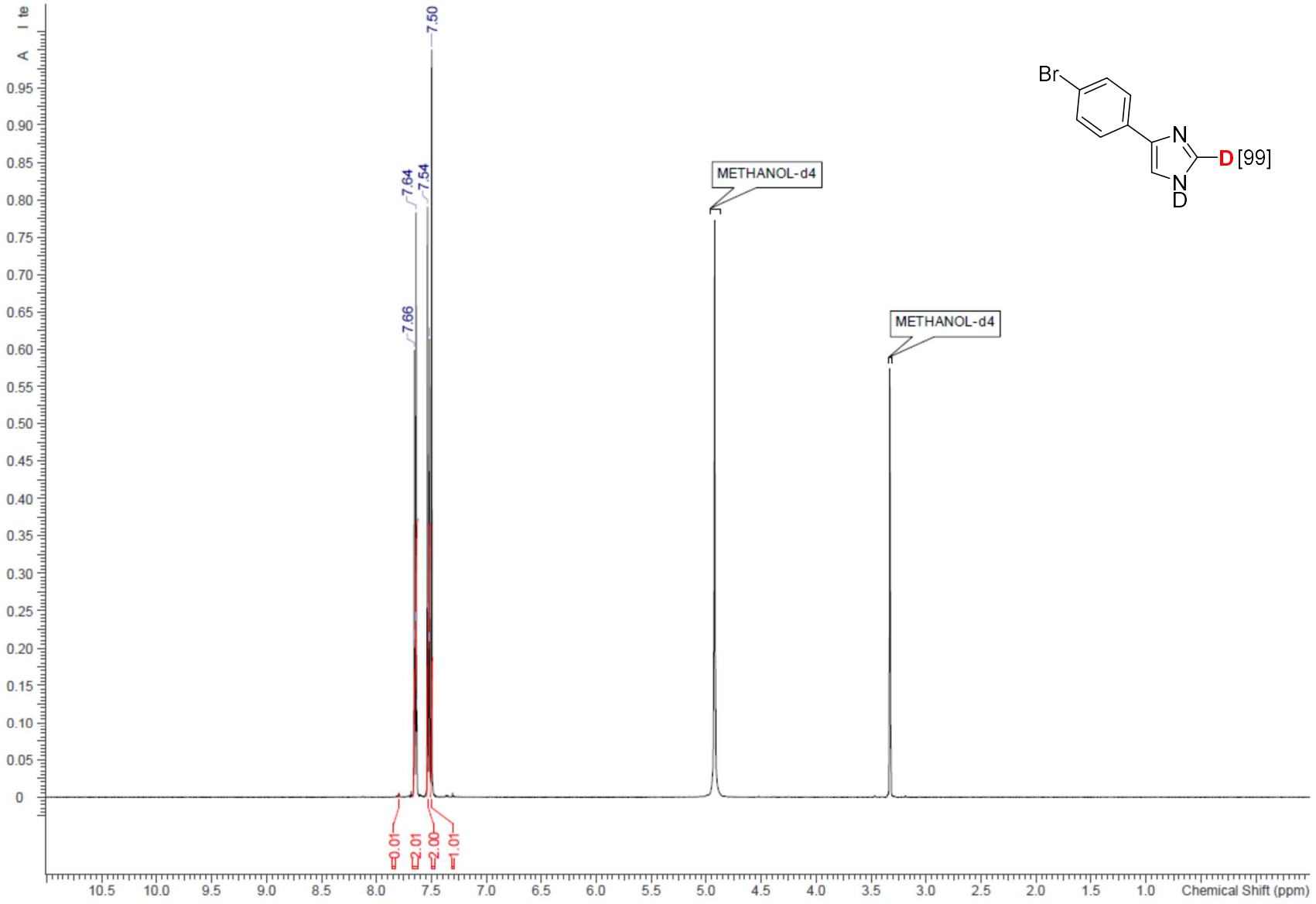

Figure S 45. ^{1}H NMR spectrum of **4c** (CD_3OD)

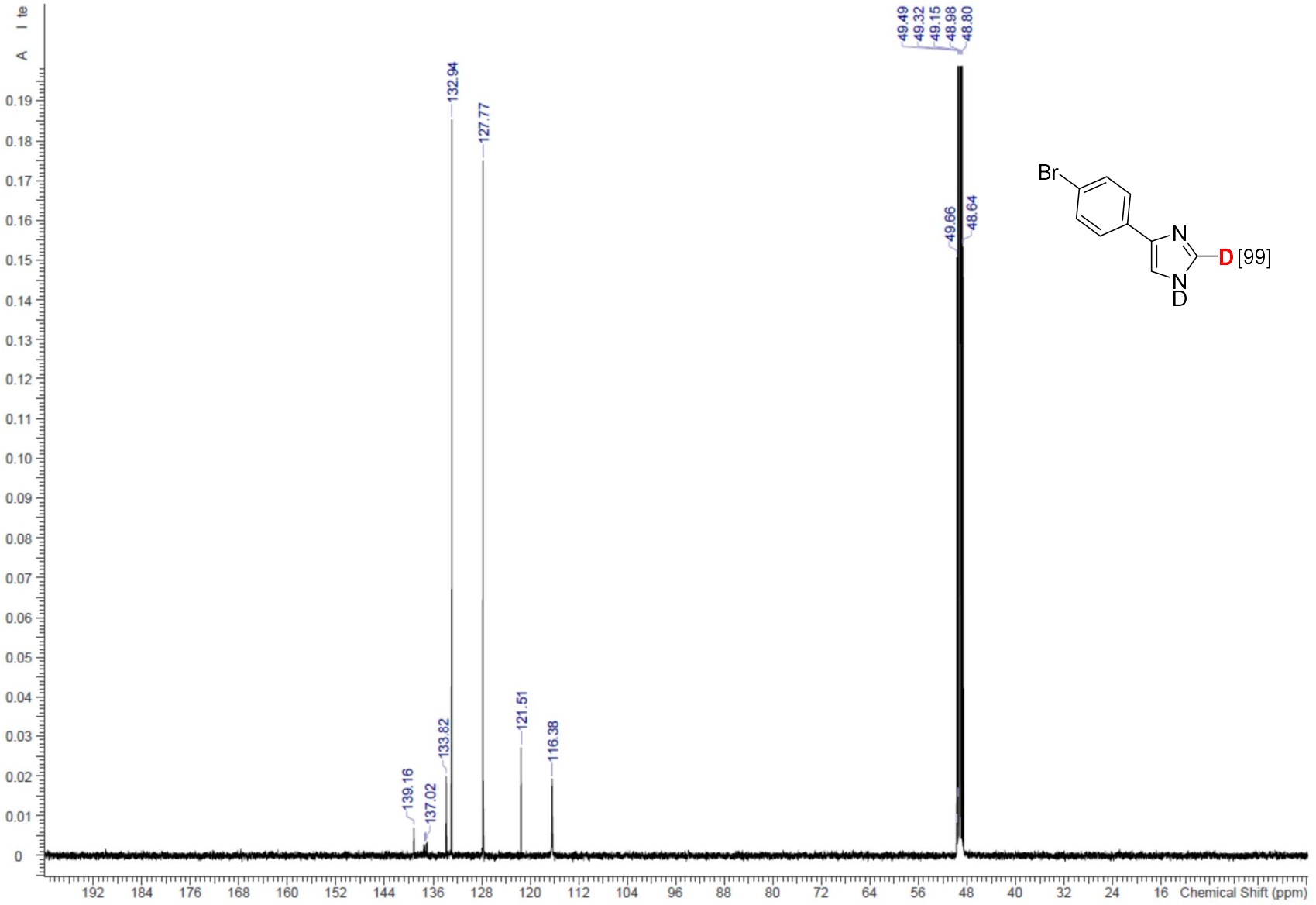

Figure S 46. ^{13}C NMR spectrum of **4c** (CD_3OD)

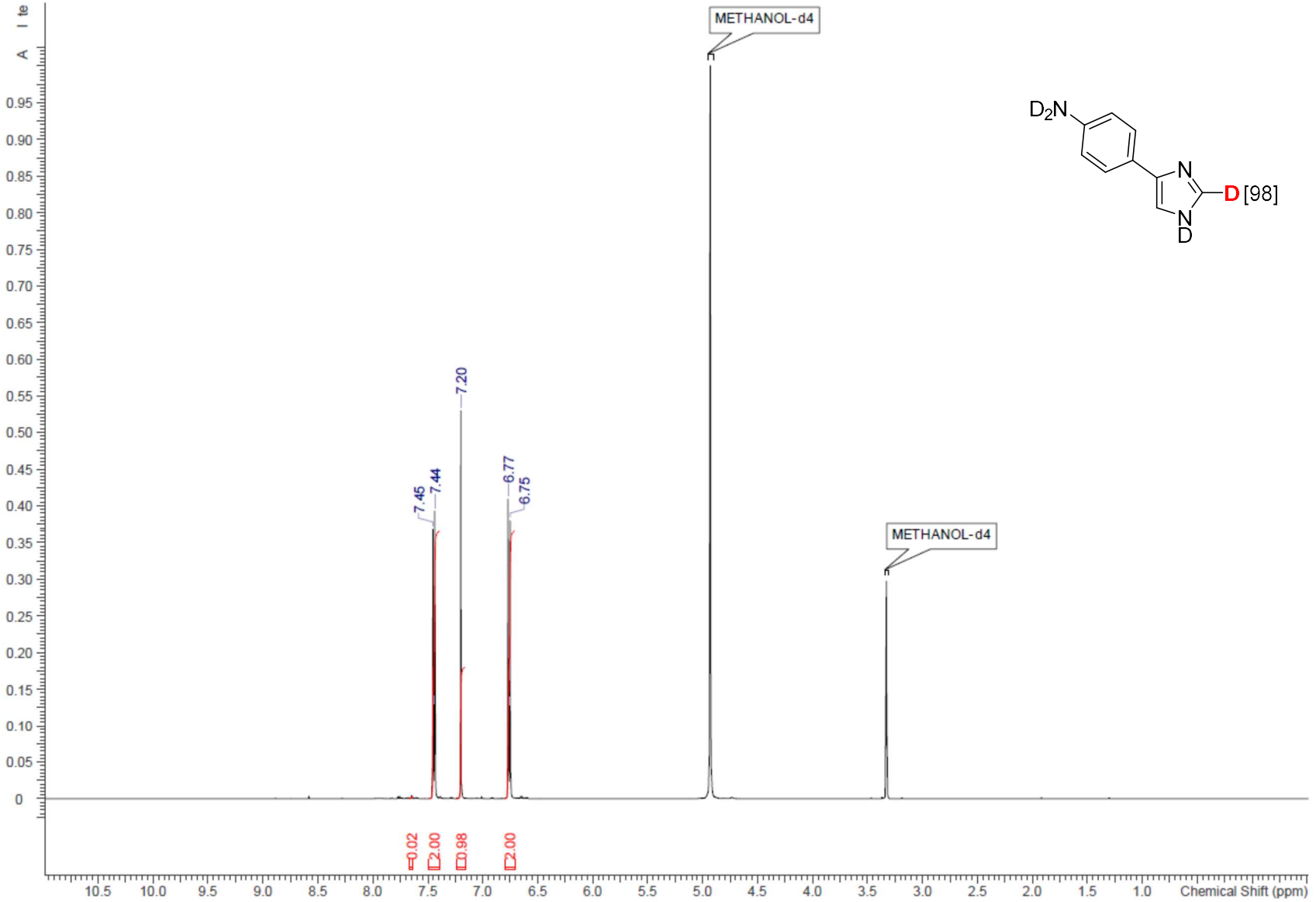

Figure S 47. ^{1}H NMR spectrum of **4e** (CD_3OD)

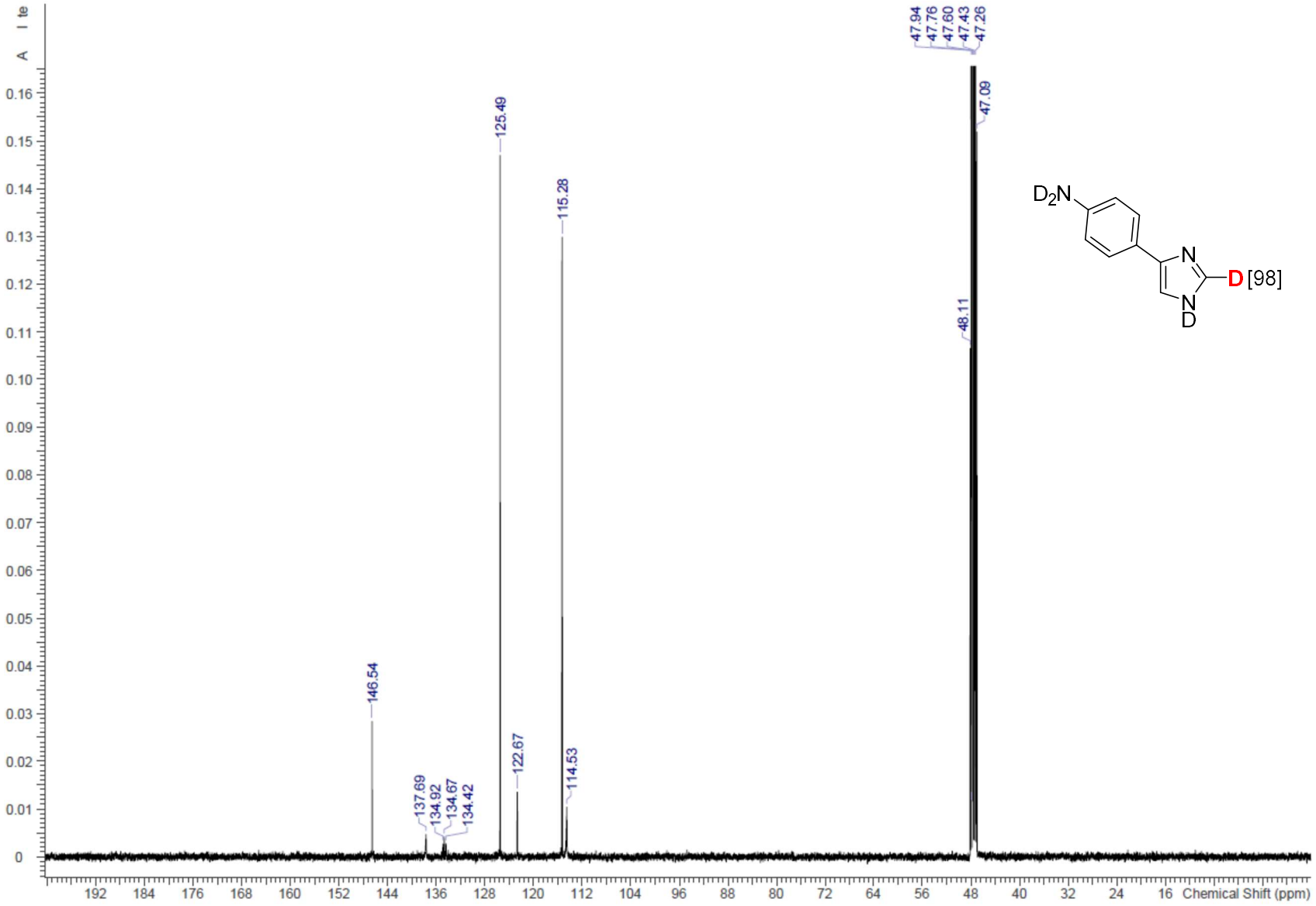

Figure S 48. ^{13}C NMR spectrum of **4e** (CD_3OD)

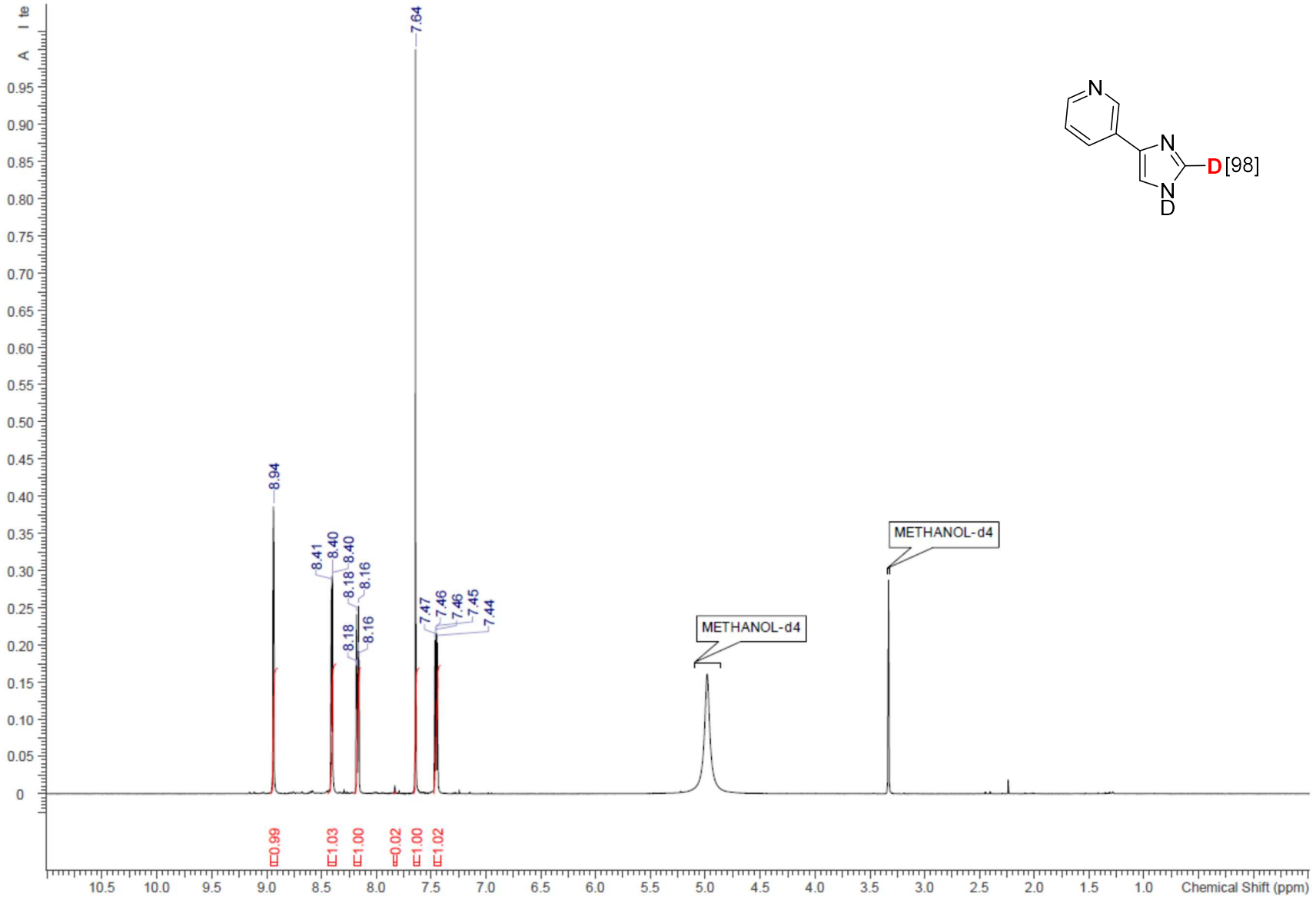

Figure S 49. ^{1}H NMR spectrum of **4f** (CD_3OD)

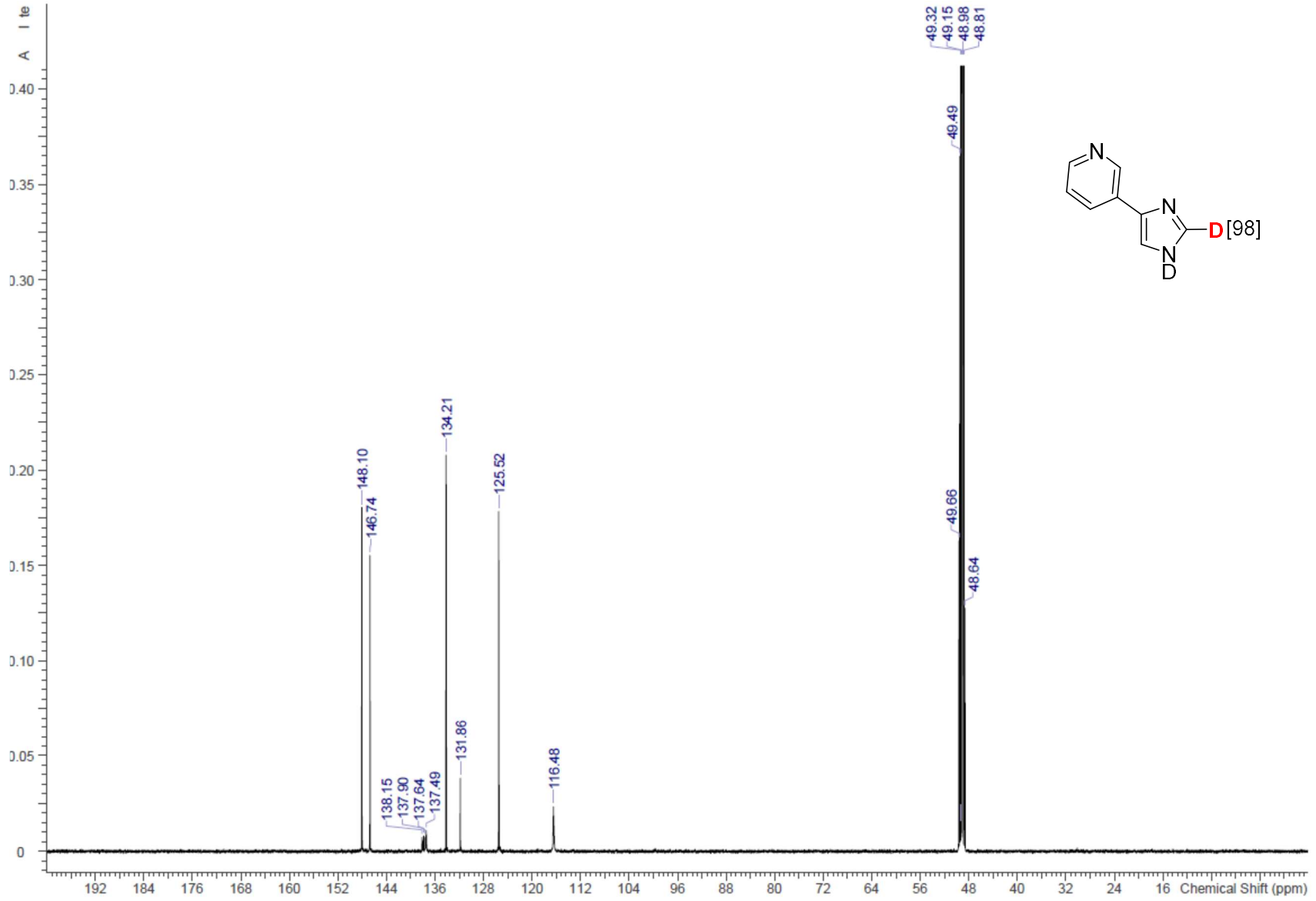

Figure S 50. ^{13}C NMR spectrum of **4f** (CD_3OD)

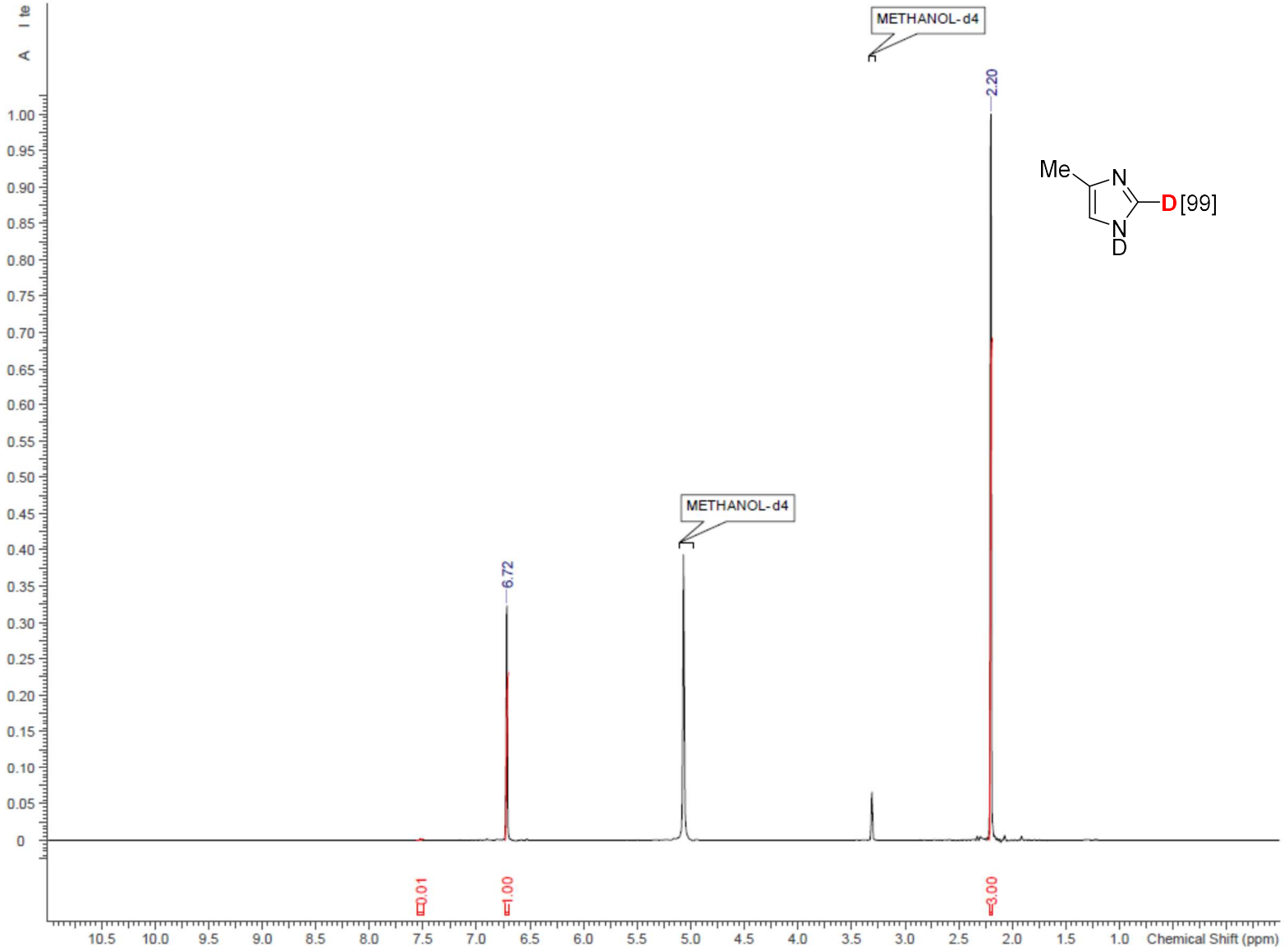

Figure S 51. ^{1}H NMR spectrum of **4h** (CD_3OD)

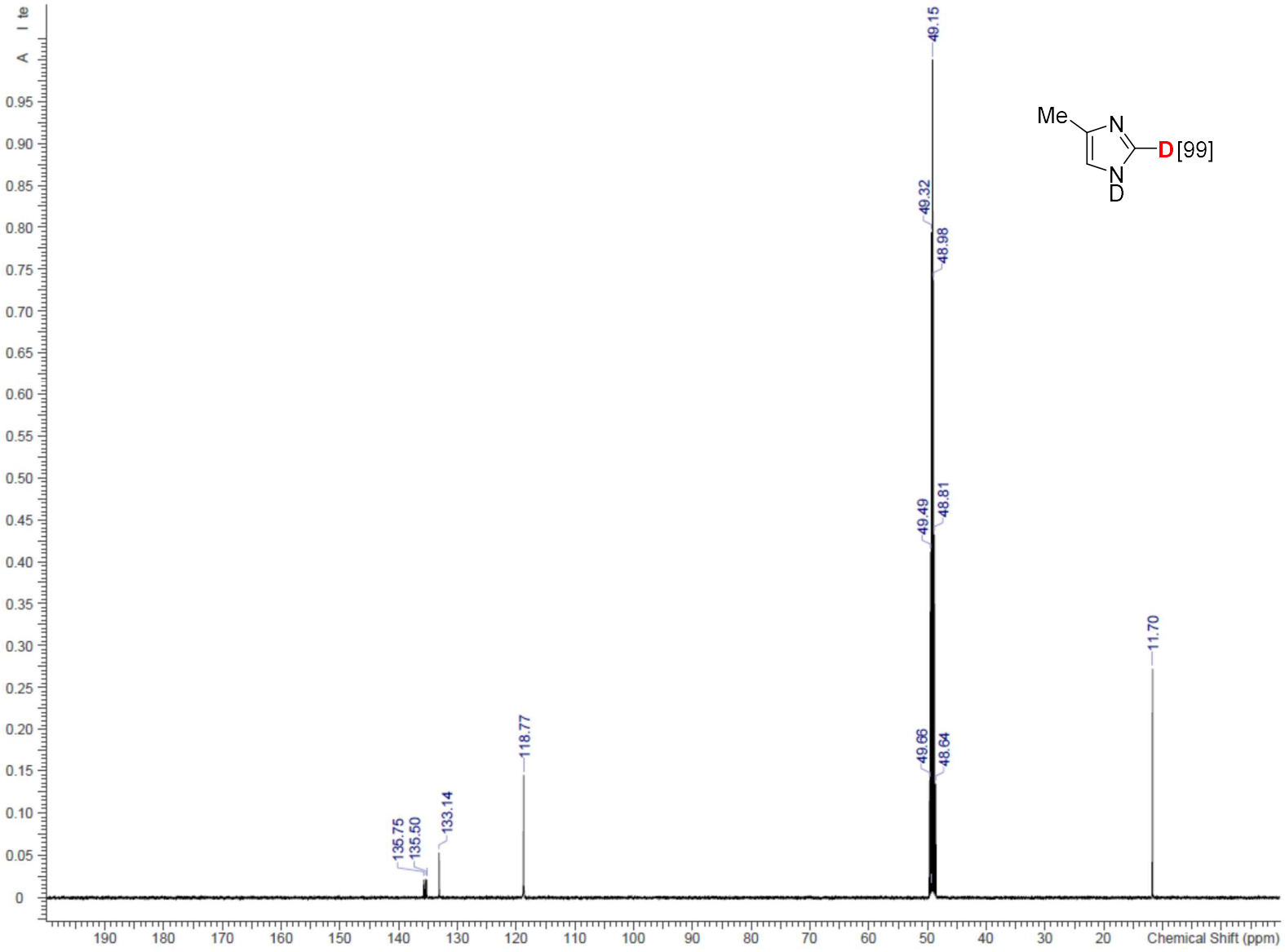

Figure S 52. ^{13}C NMR spectrum of **4h** (CD_3OD)

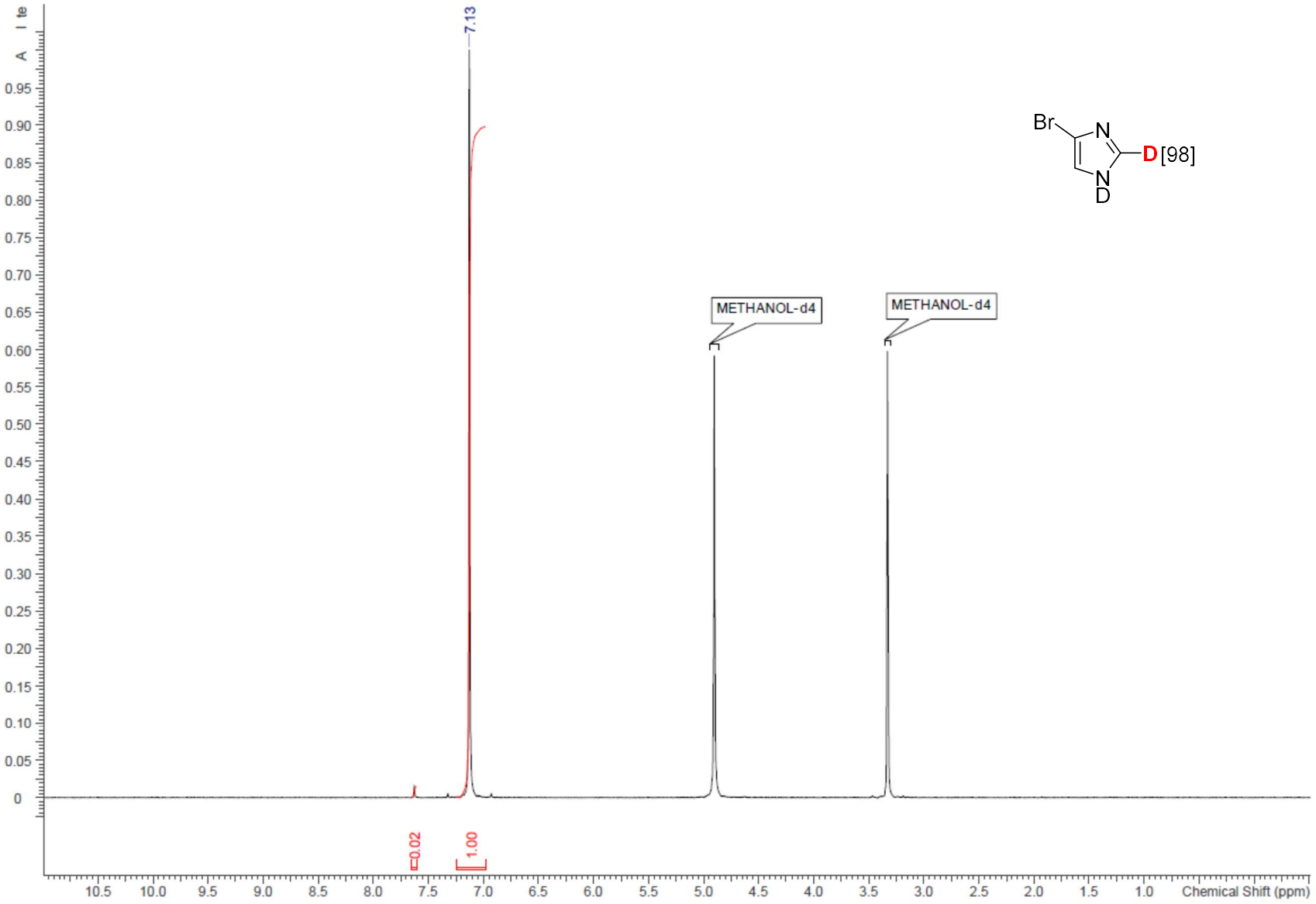

Figure S 53. ^{1}H NMR spectrum of **4i** (CD_3OD)

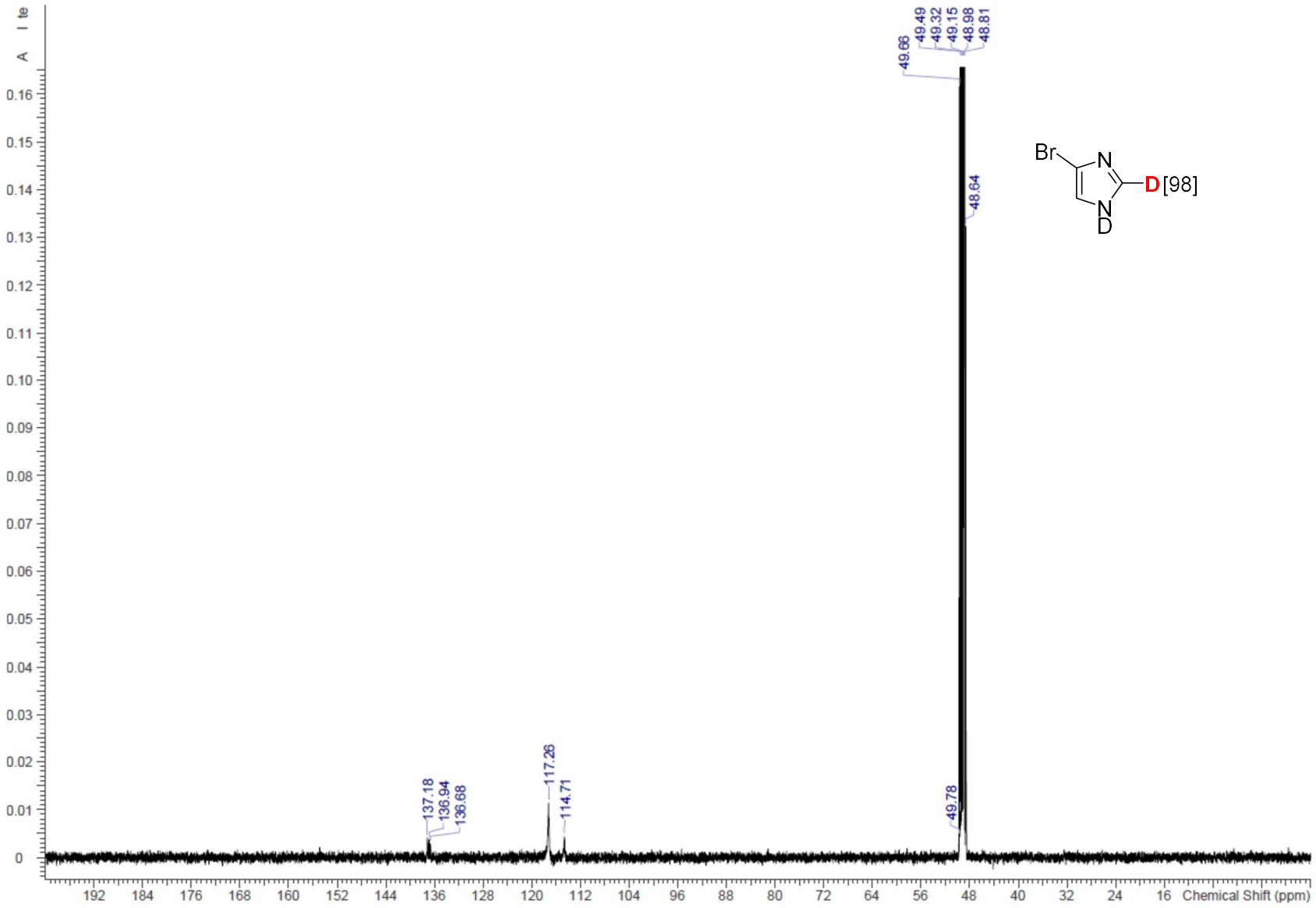

Figure S 54. ^{13}C NMR spectrum of **4i** (CD_3OD)

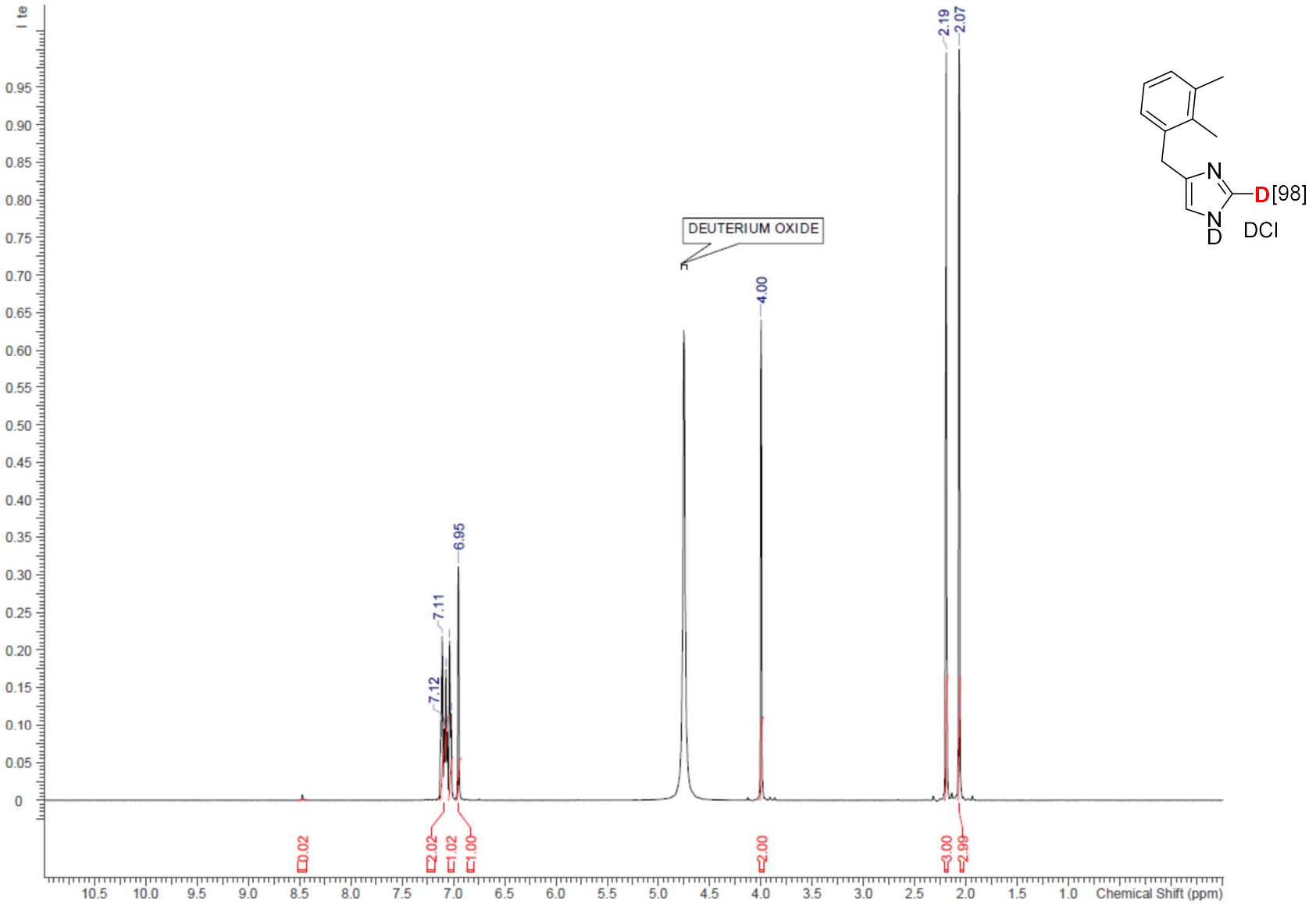

Figure S 55. ^{1}H NMR spectrum of **4l** (D_2O)

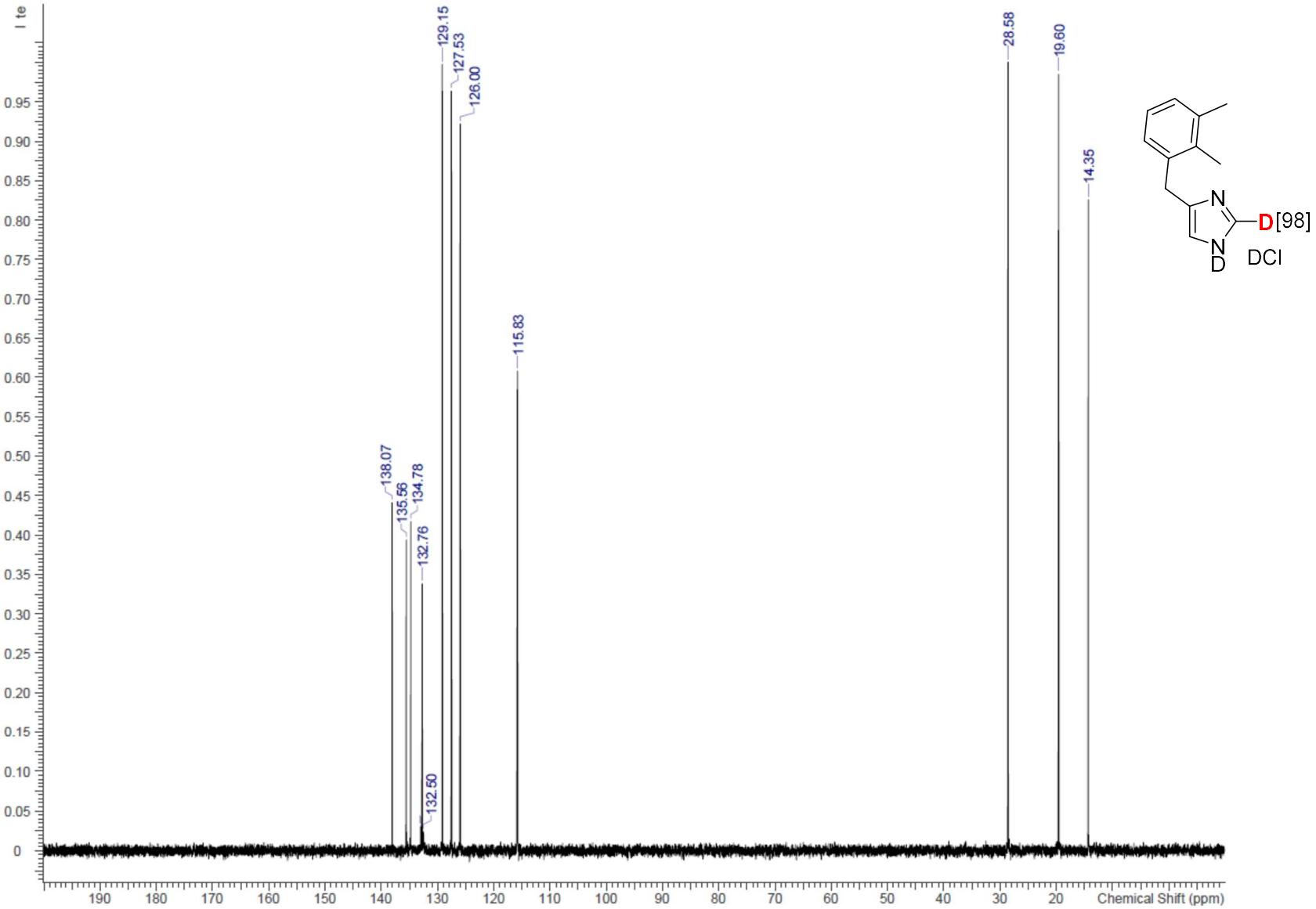

Figure S 56. ^{13}C NMR spectrum of **4l** (D_2O)

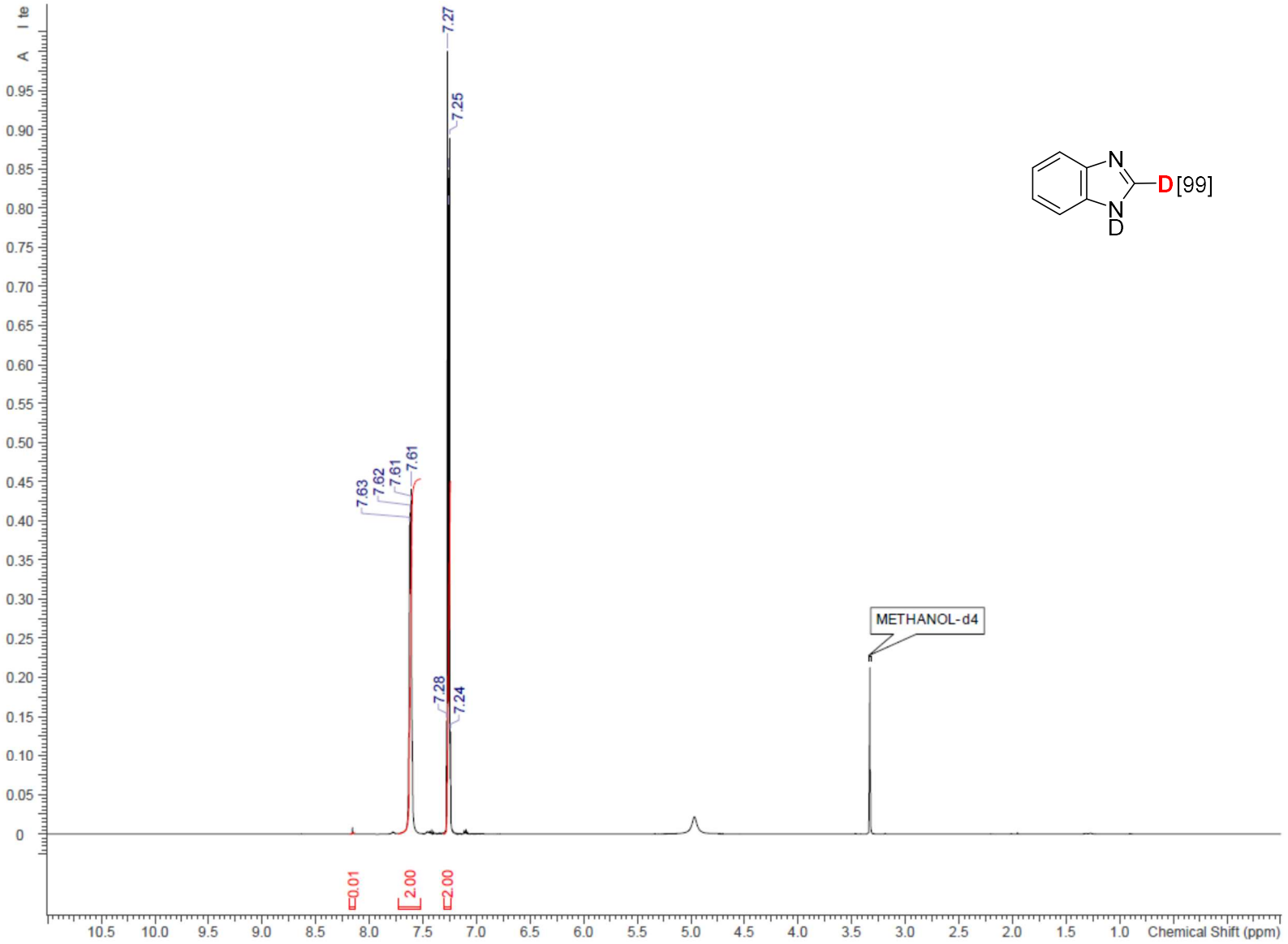

Figure S 57. ^{1}H NMR spectrum of **4m** (CD_3OD)

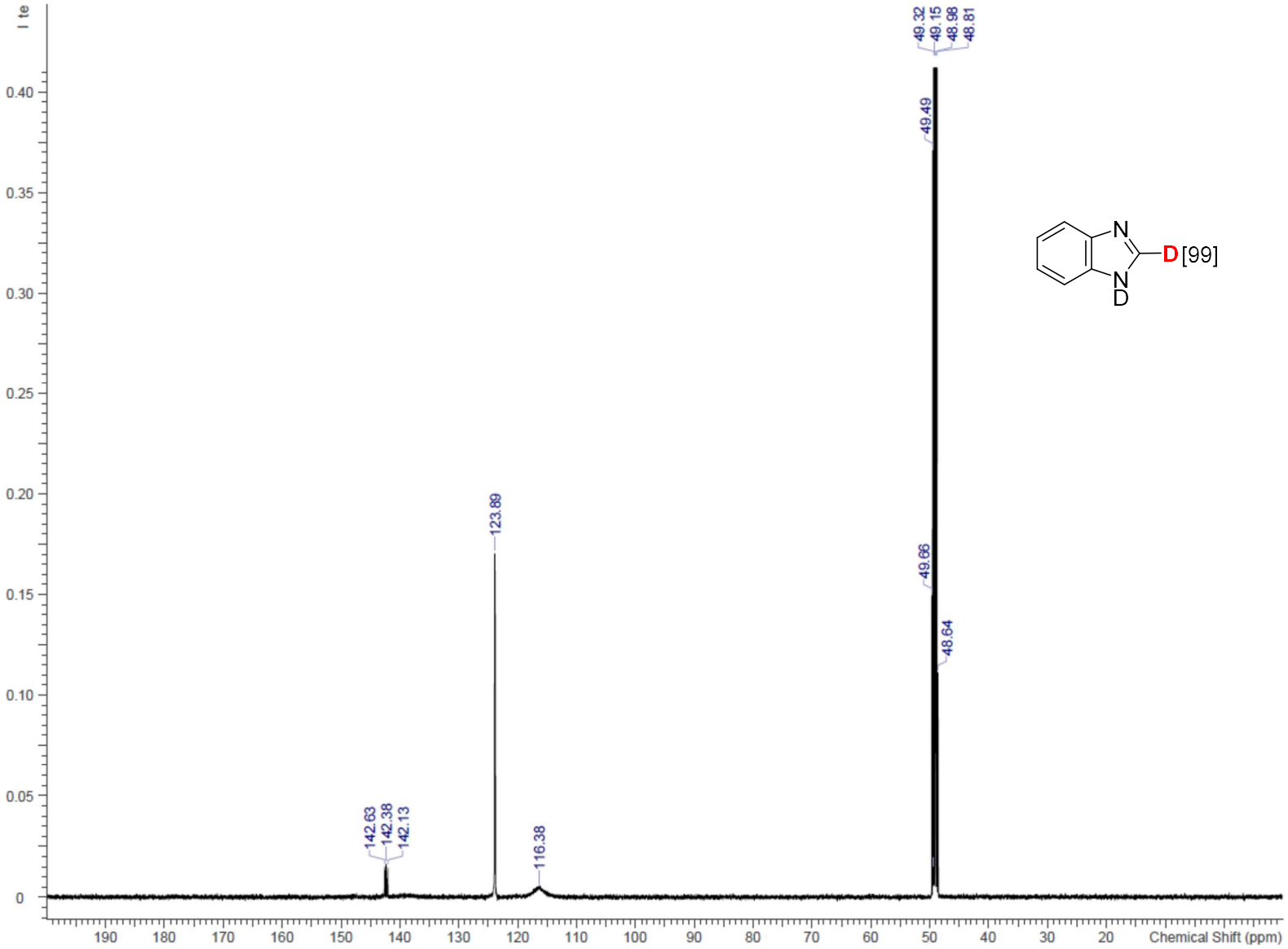

Figure S 58. ^{13}C NMR spectrum of **4m** (CD_3OD)

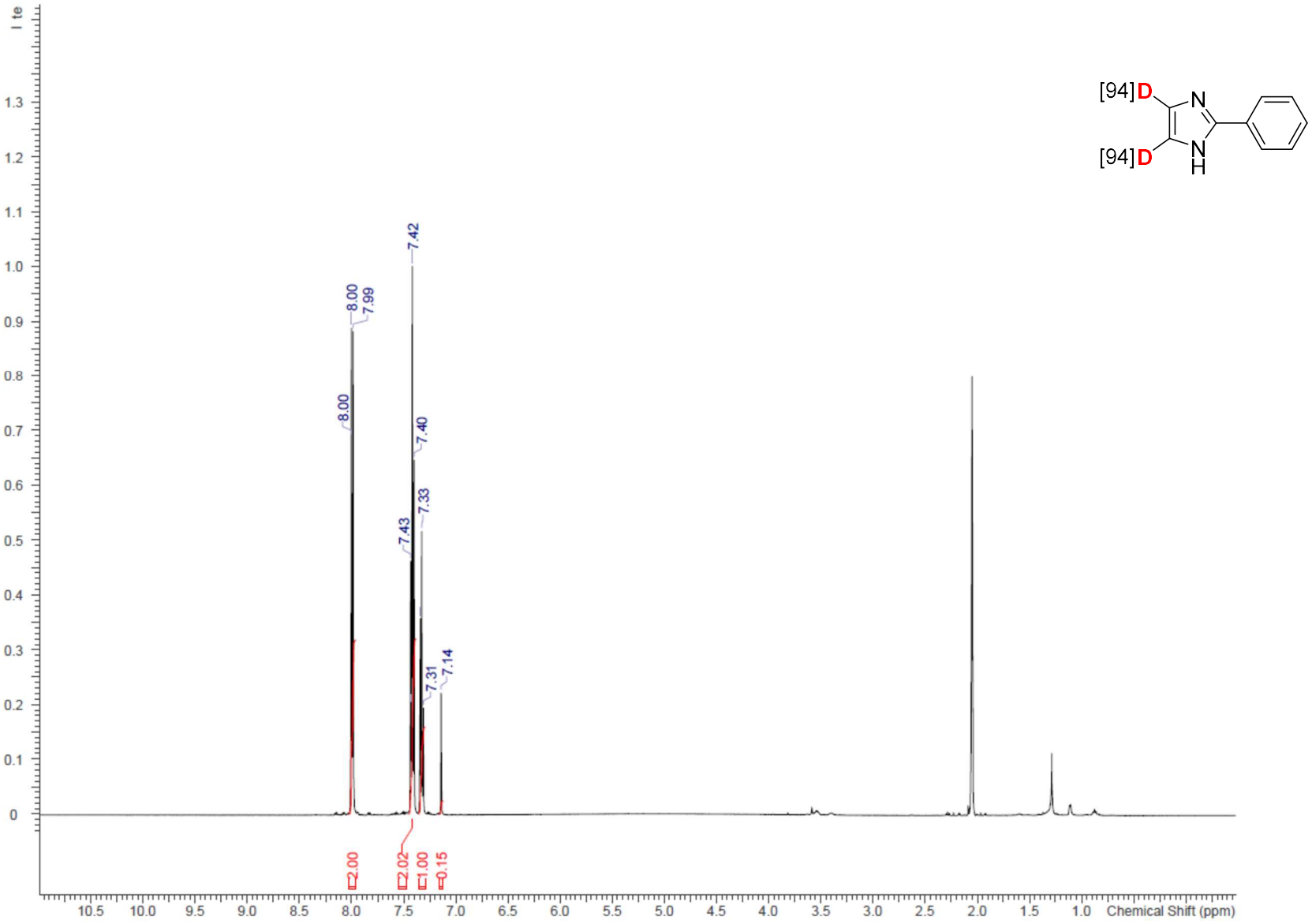

Figure S 59. ^{1}H NMR spectrum of **5n** (acetone-d_6)

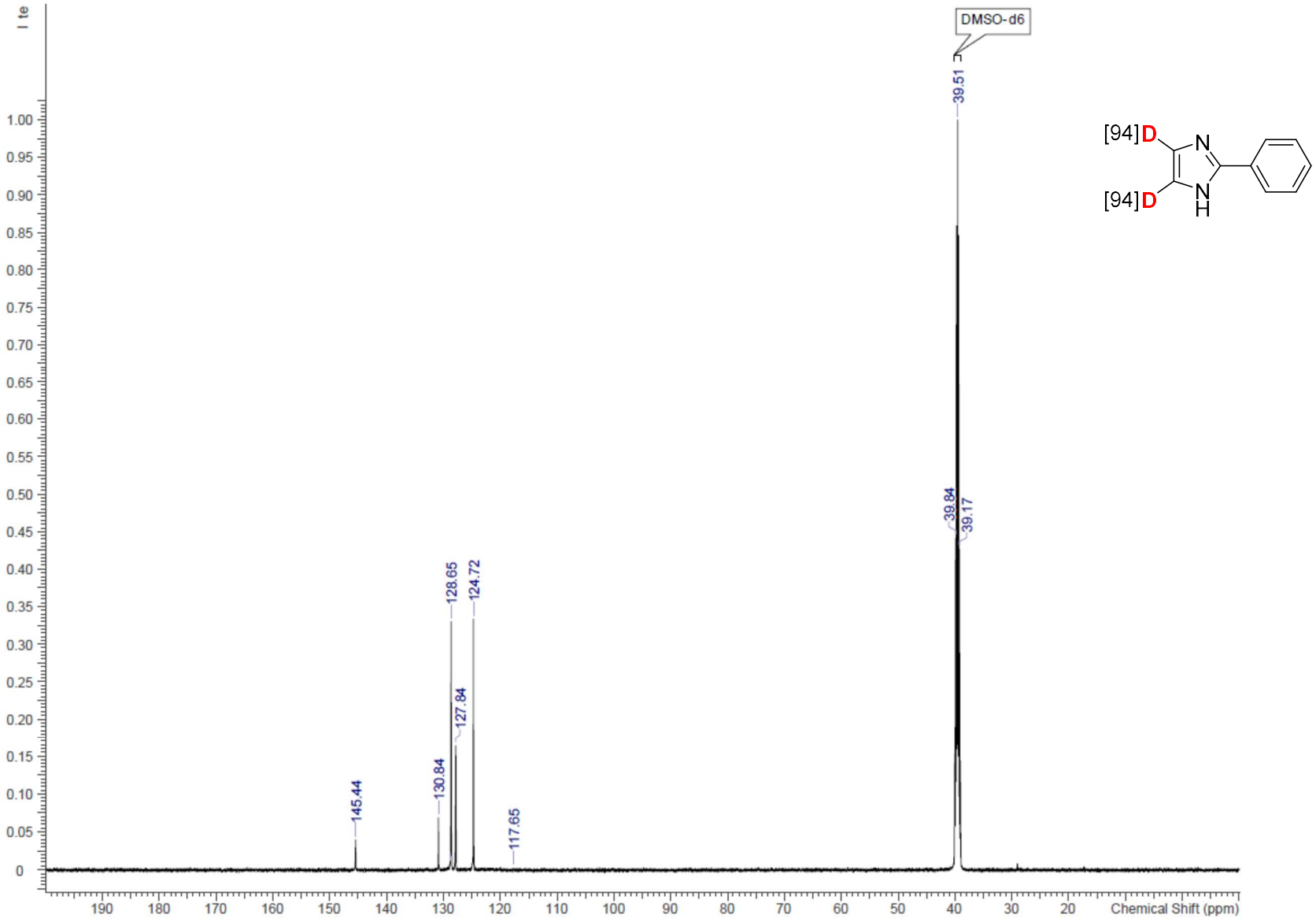

Figure S 60. ^{13}C NMR spectrum of **5n** (DMSO-d_6)

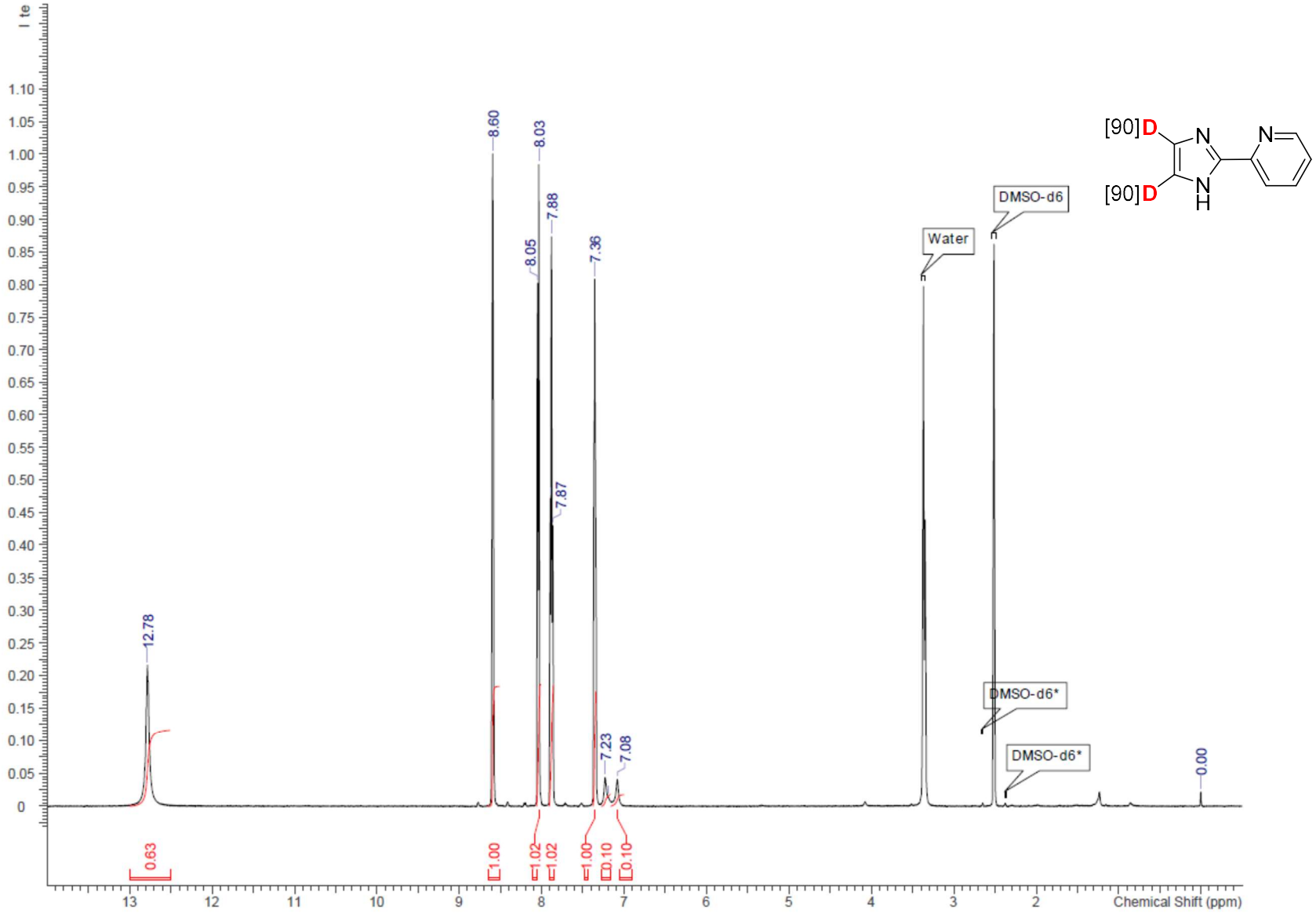

Figure S 61. ^{1}H NMR spectrum of **5o** (DMSO-d_6)

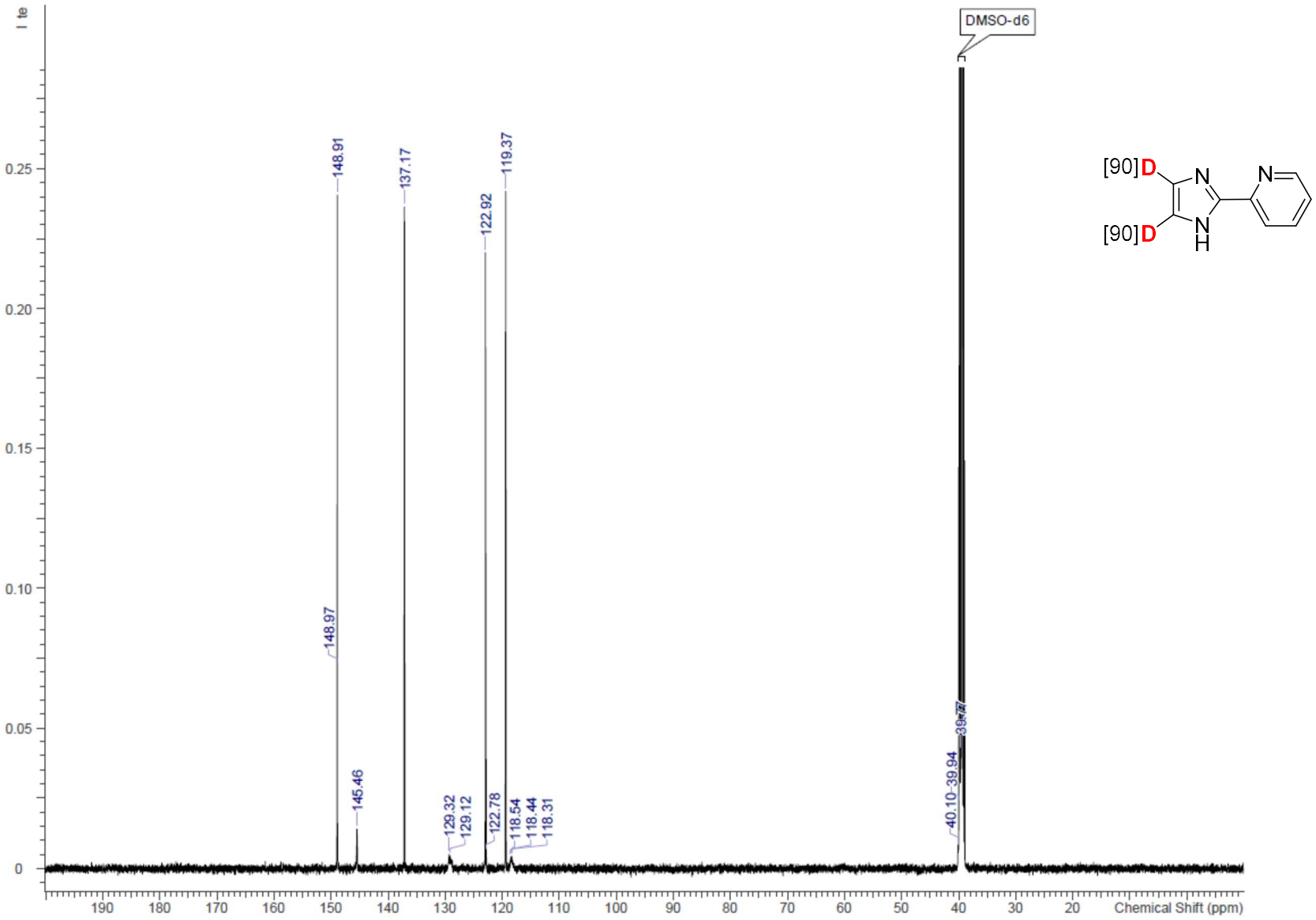

Figure S 62. ^{13}C NMR spectrum of **5o** (DMSO-d_6)

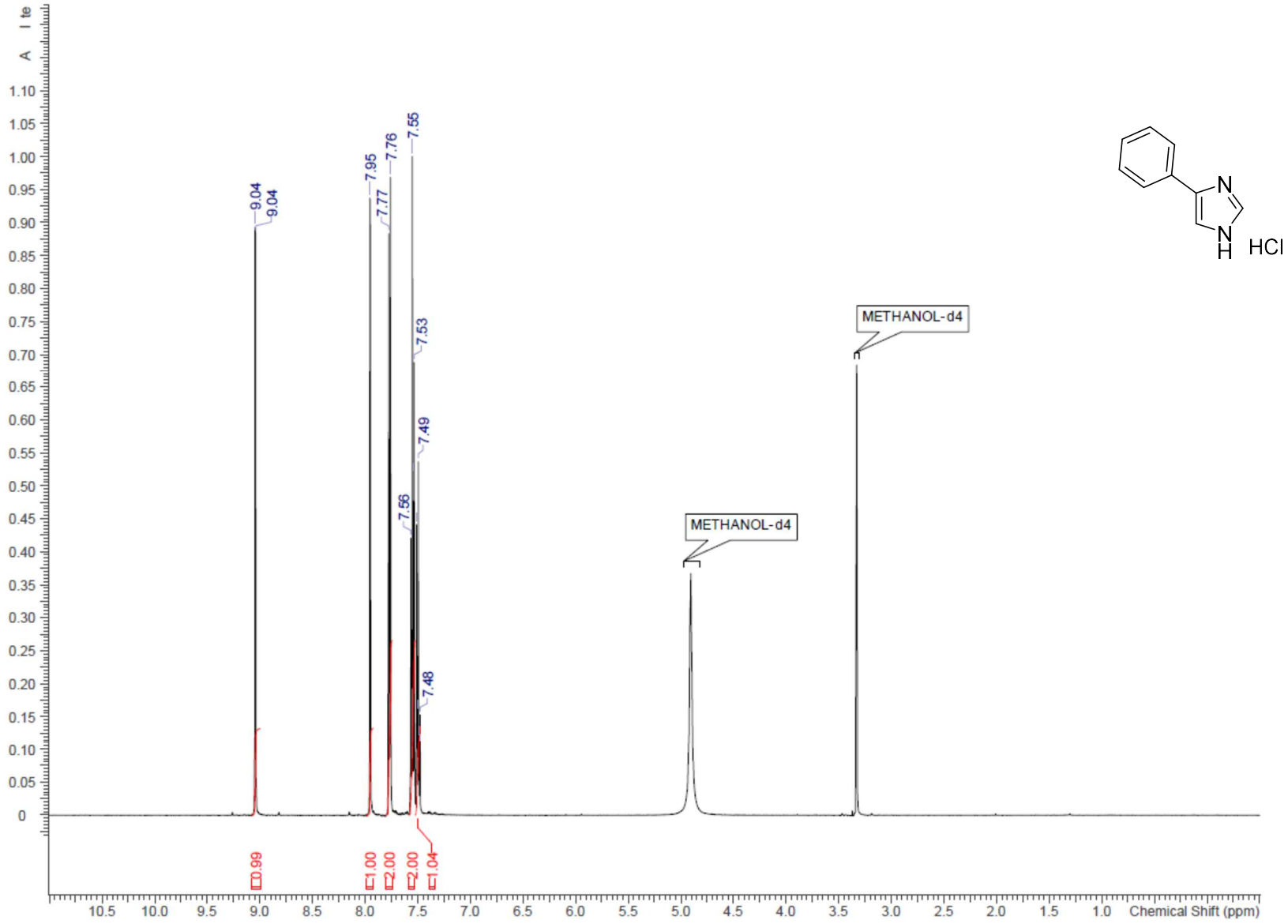

Figure S 63. ^{1}H NMR spectrum of **1a·HCl** (CD_3OD)

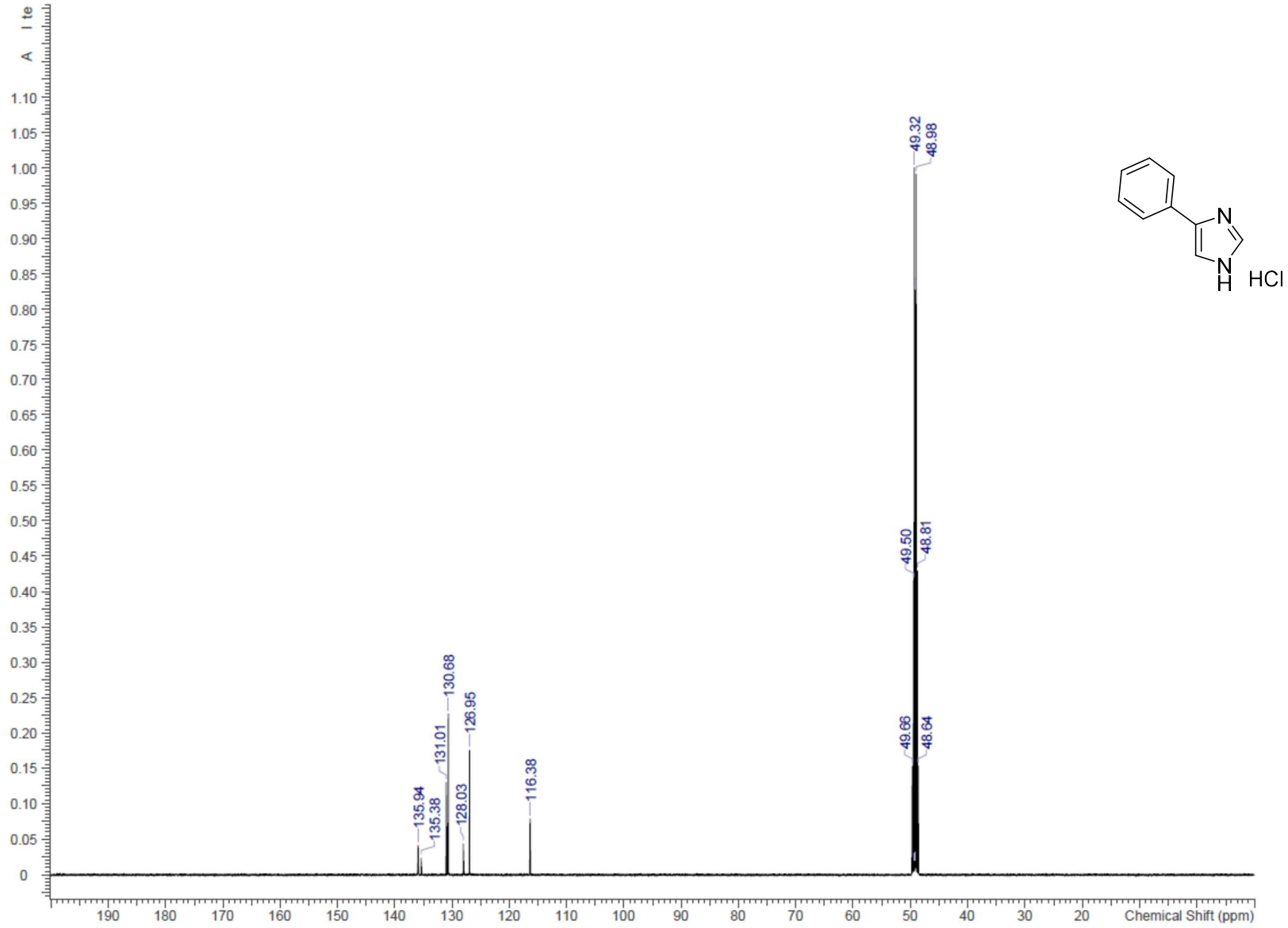

Figure S 64. ^{13}C NMR spectrum of **1a·HCl** (CD_3OD)

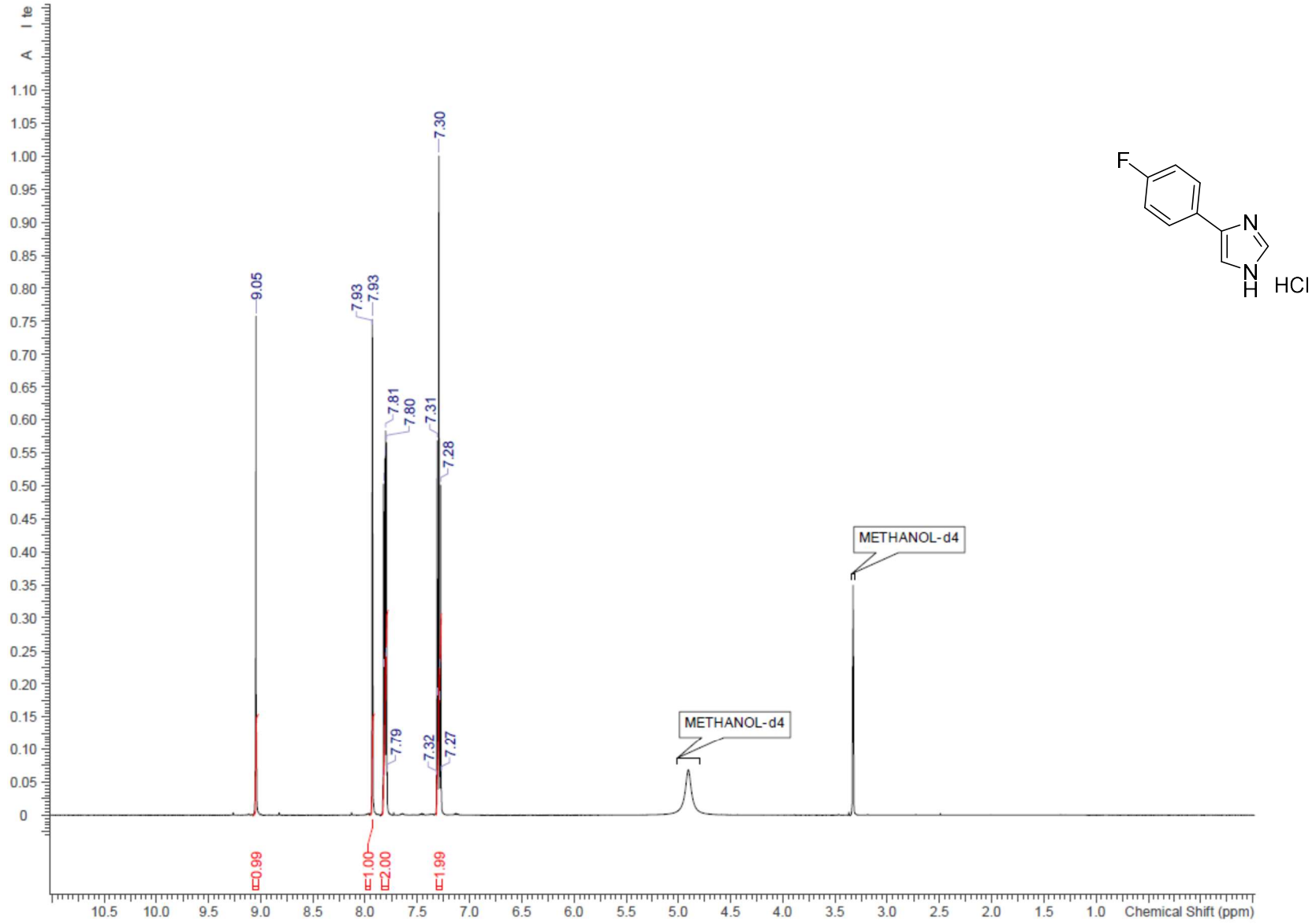

Figure S 65. ^{1}H NMR spectrum of **1b·HCl** (CD_3OD)

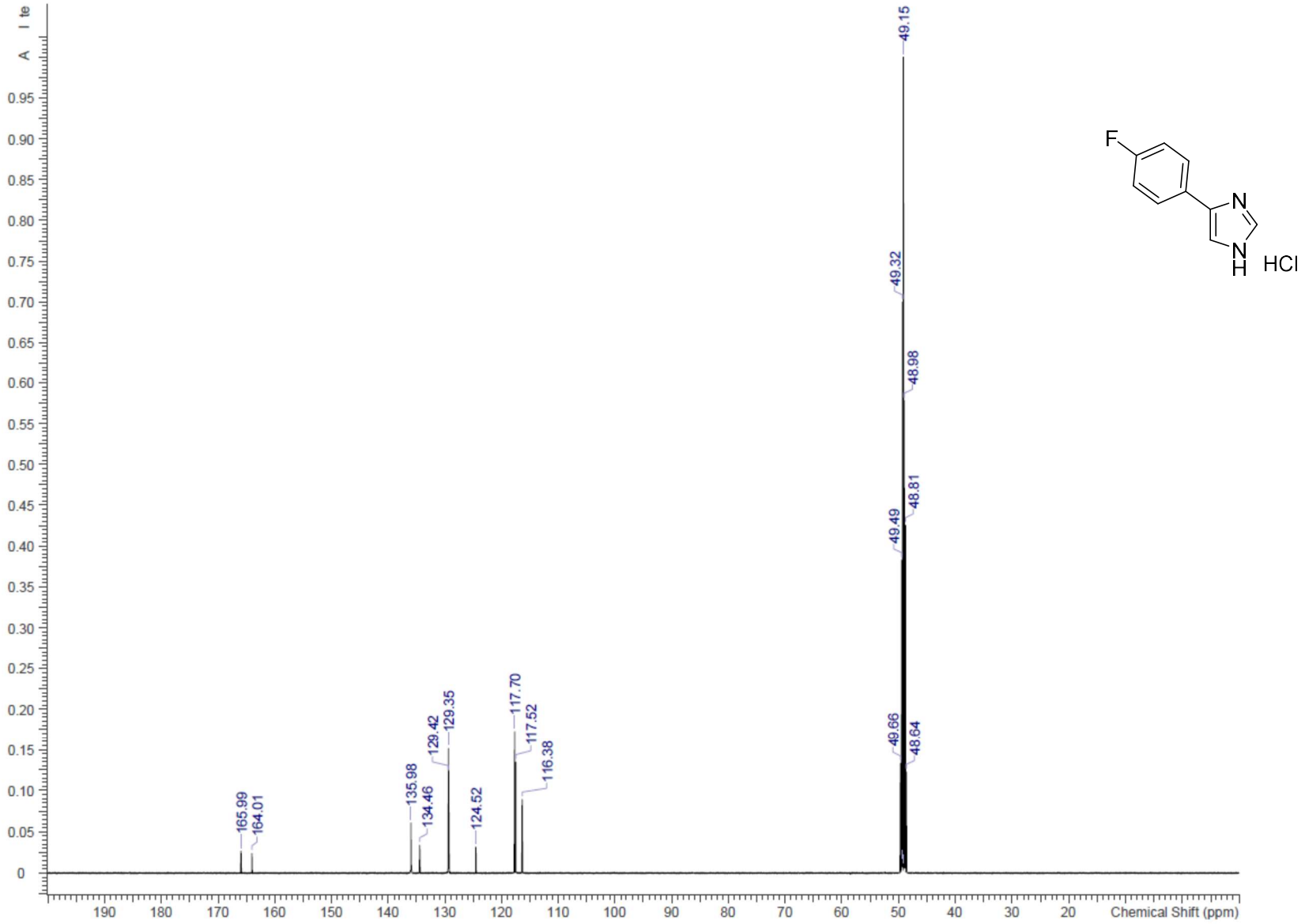

Figure S 66. ^{13}C NMR spectrum of **1b·HCl** (CD_3OD)

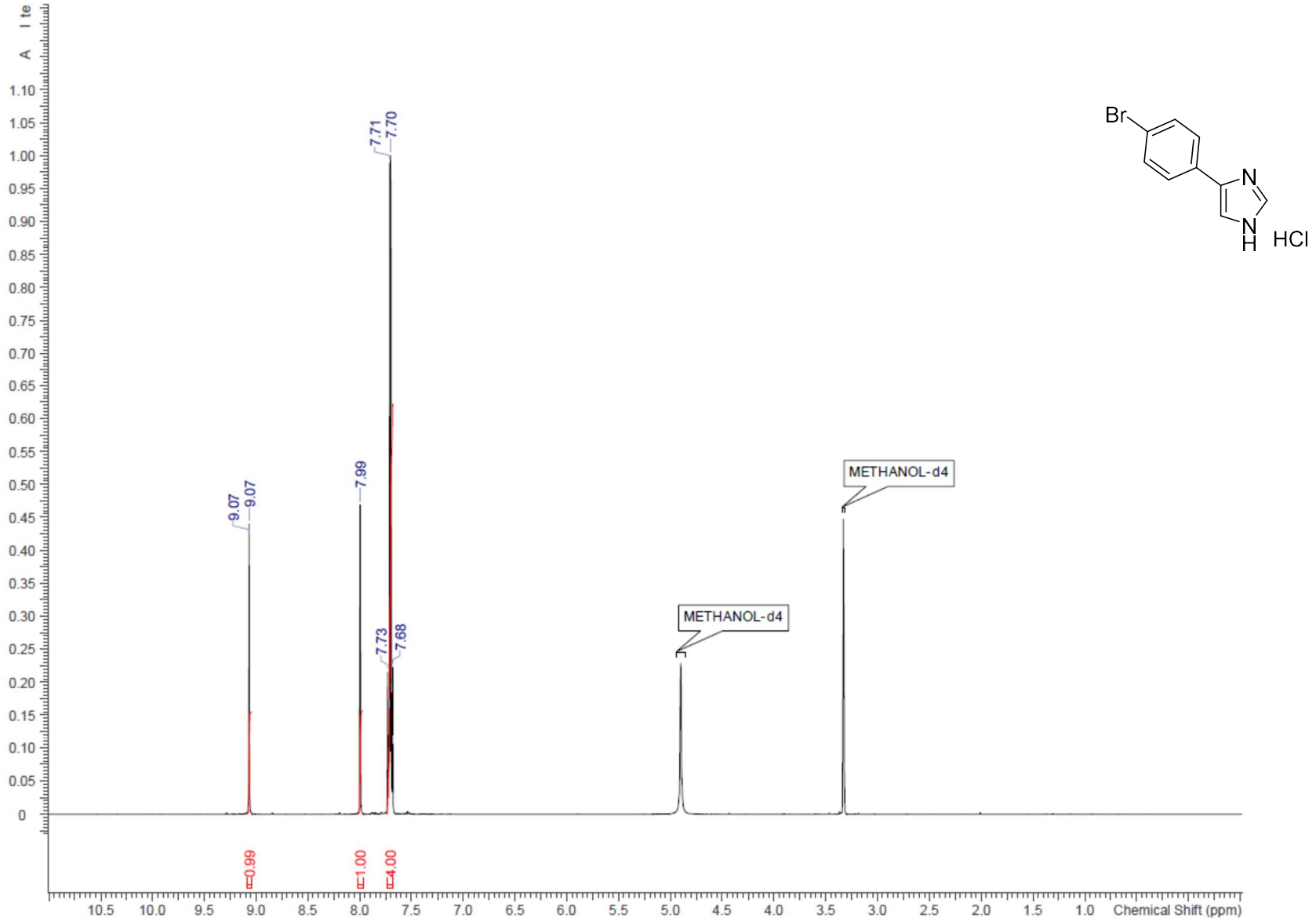

Figure S 67. ^{1}H NMR spectrum of **1c·HCl** (CD_3OD)

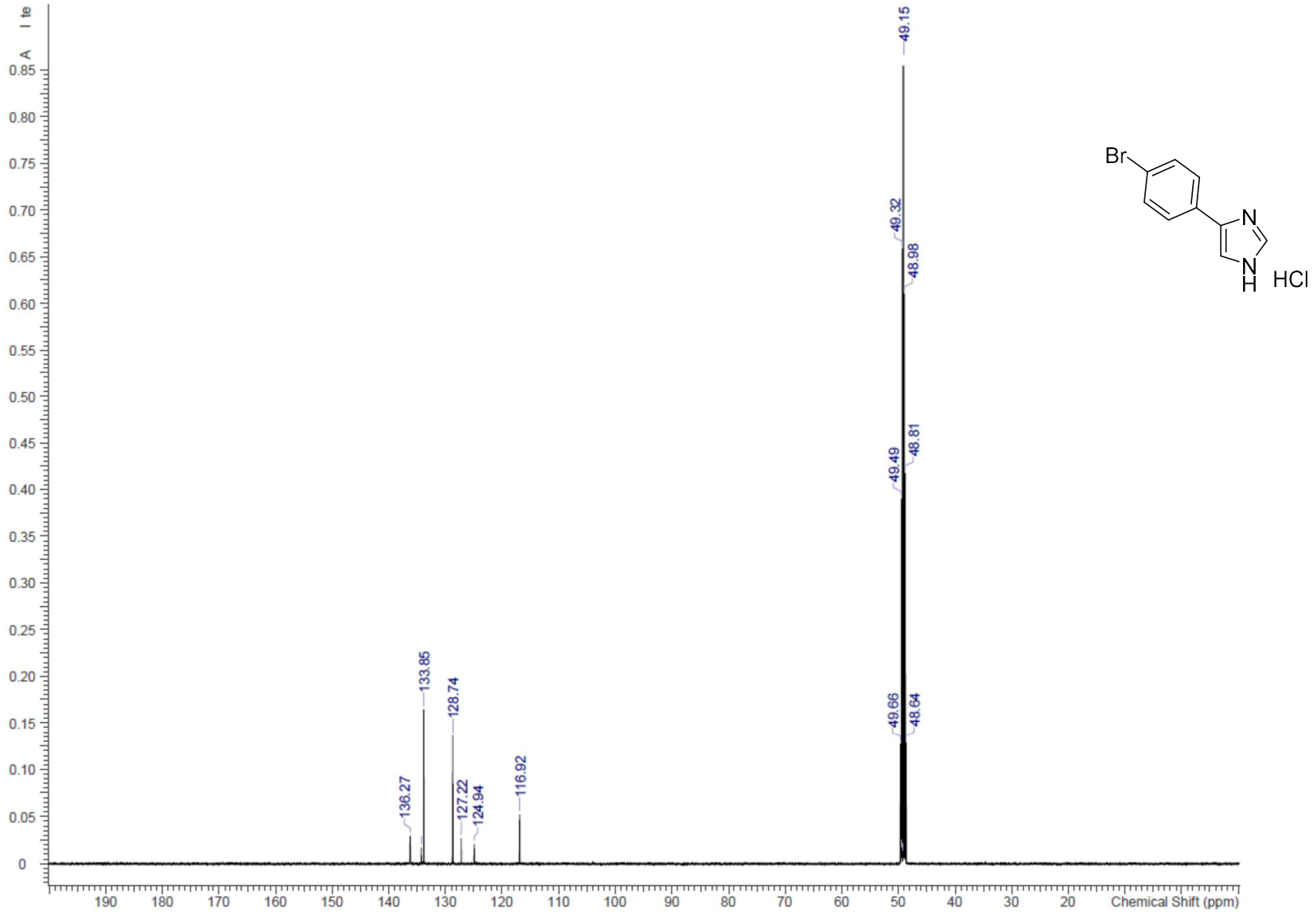

Figure S 68. ^{13}C NMR spectrum of **1c·HCl** (CD_3OD)

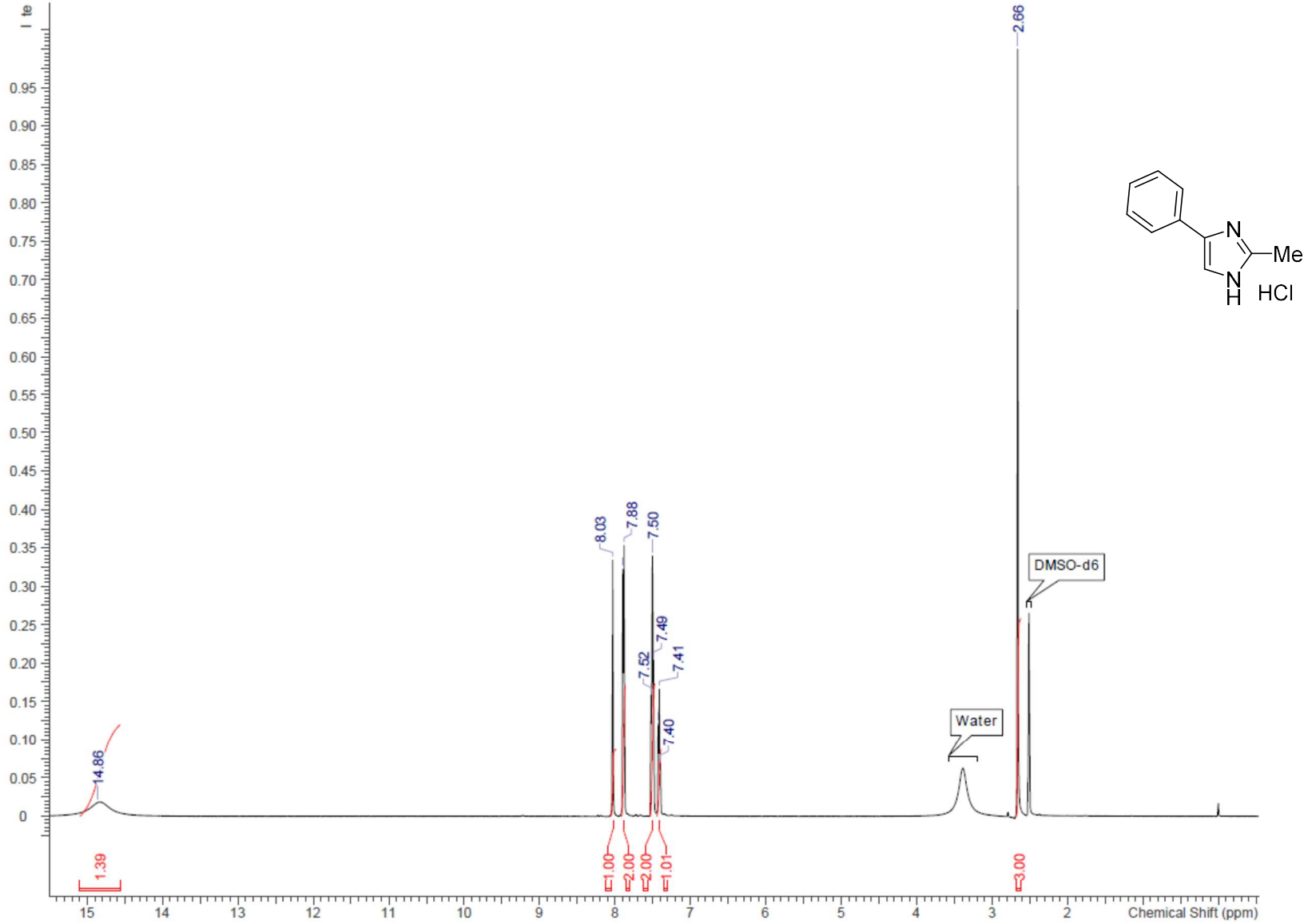

Figure S 69. ^{1}H NMR spectrum of **1d·HCl** (DMSO-d_6)

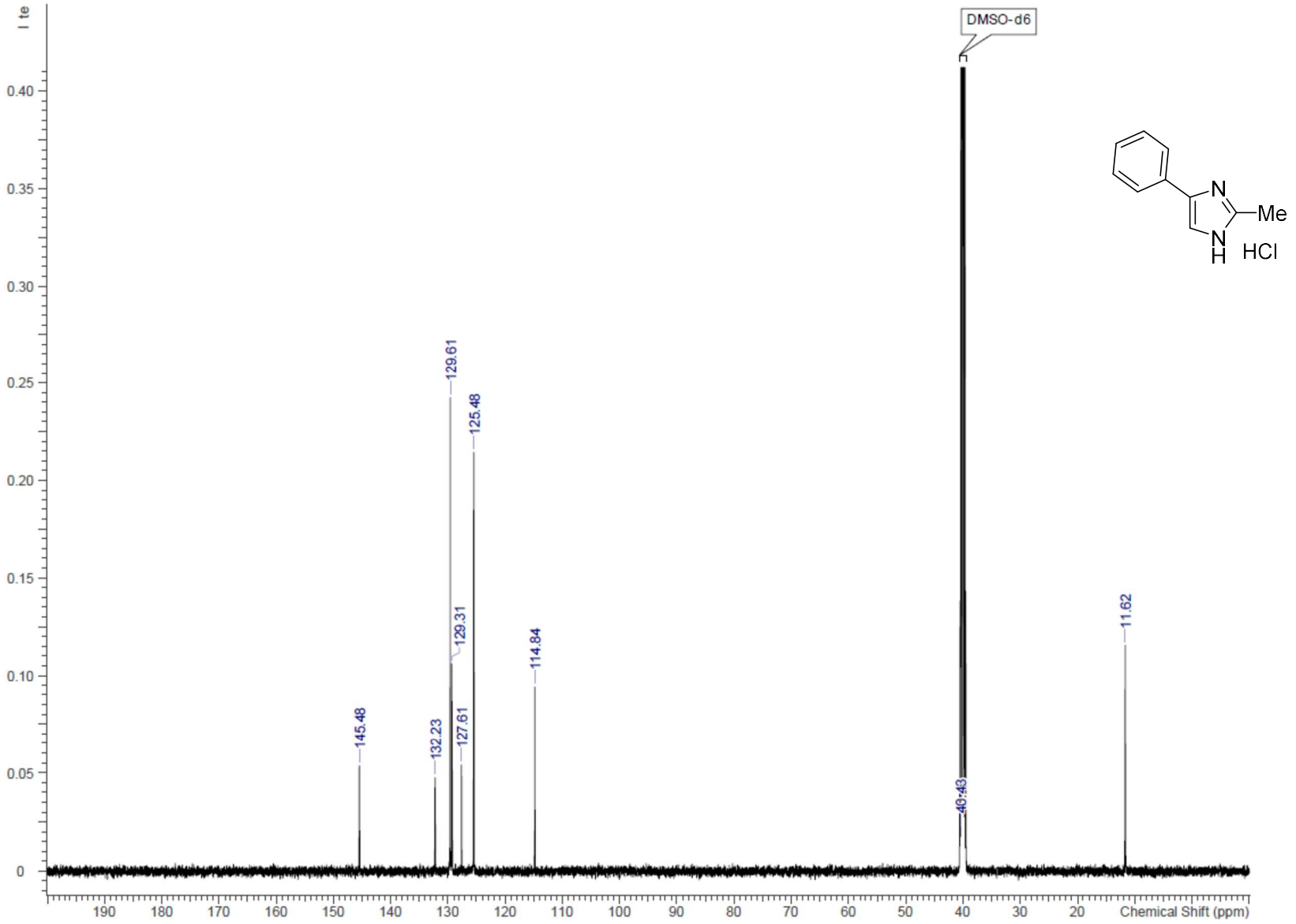

Figure S 70. ^{13}C NMR spectrum of **1d·HCl** (DMSO-d_6)

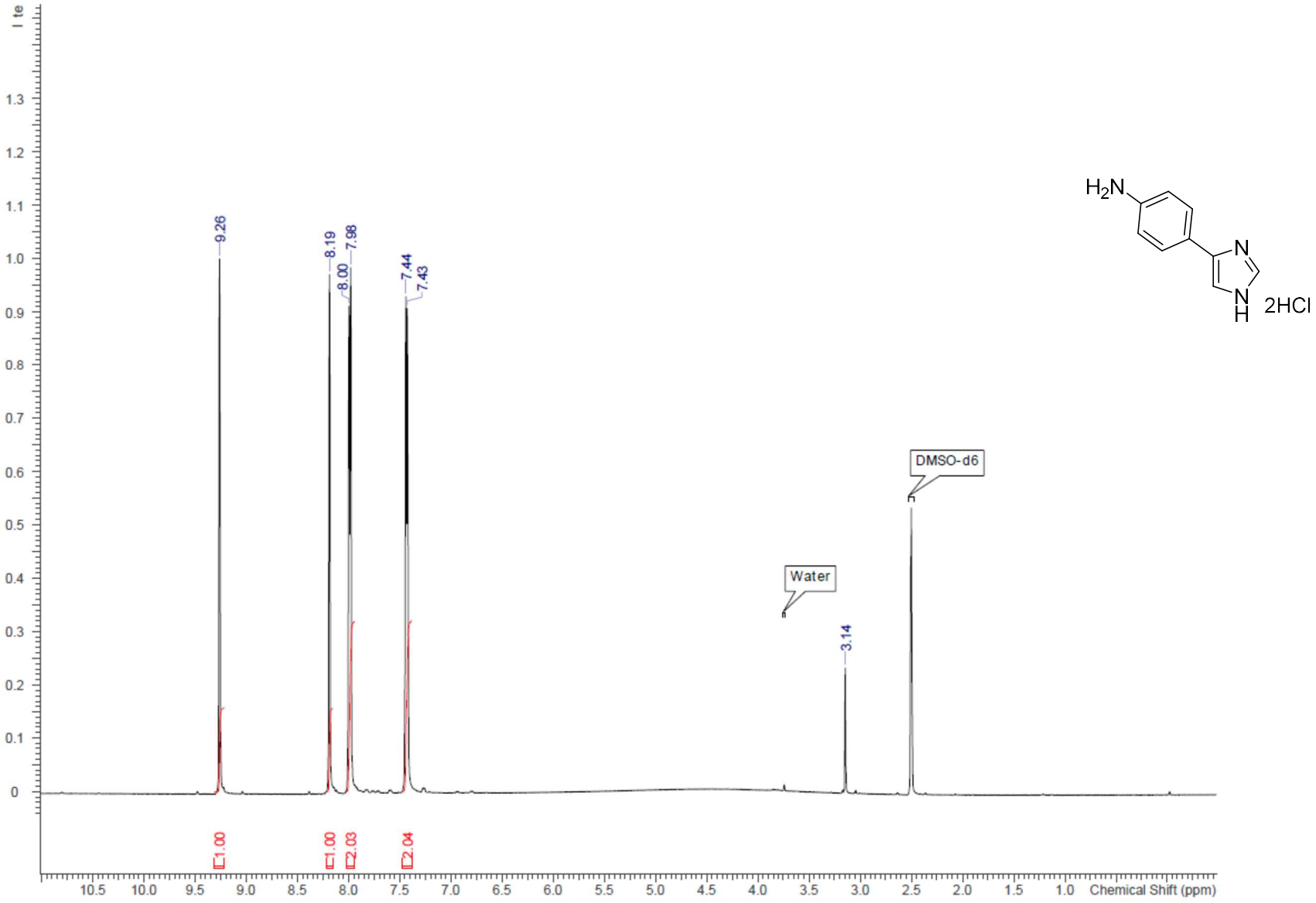

Figure S 71. ^{1}H NMR spectrum of **1e·HCl** (DMSO-d_6)

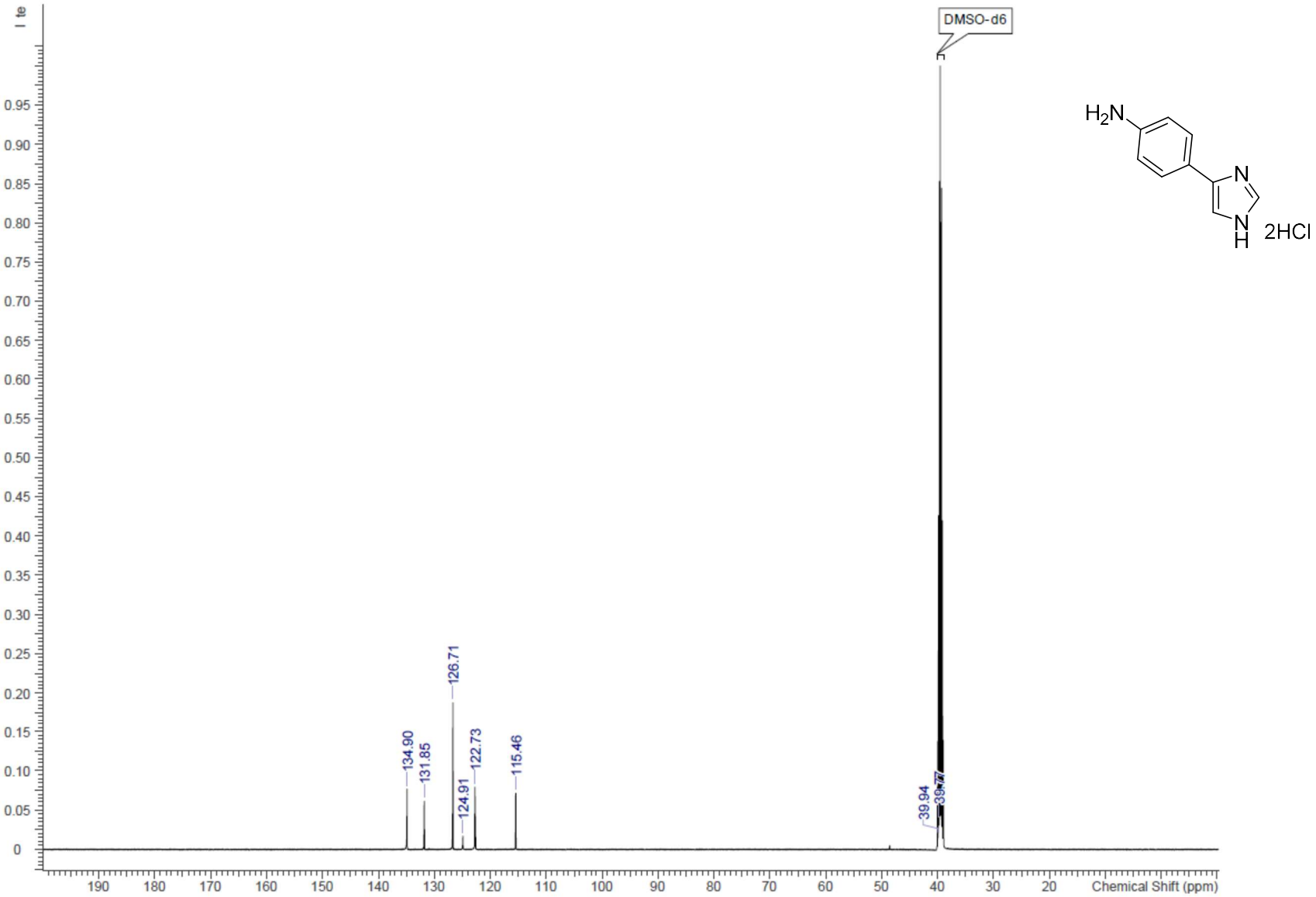

Figure S 72. ^{13}C NMR spectrum of **1e·HCl** (DMSO-d_6)

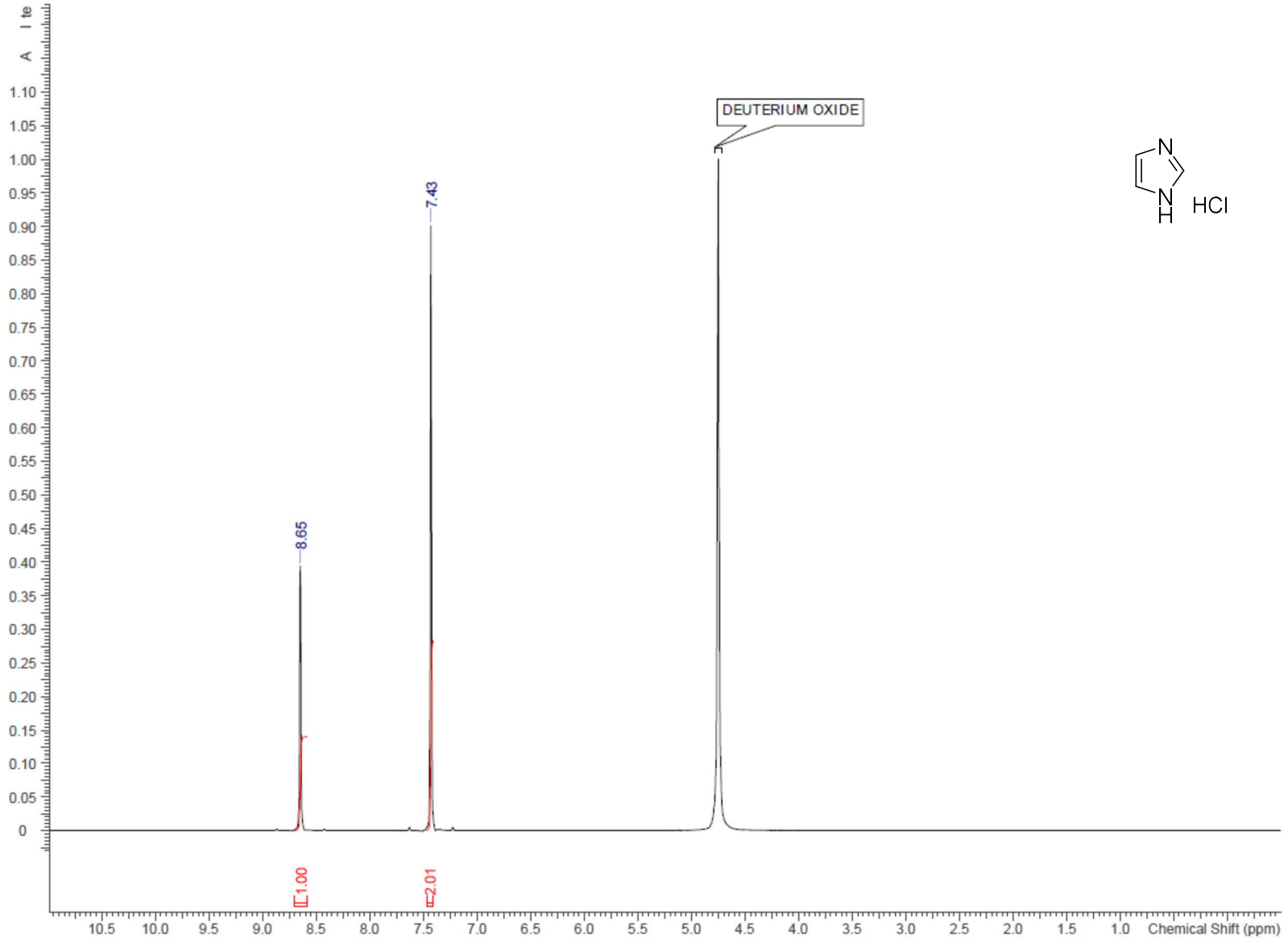

Figure S 73. ^{1}H NMR spectrum of **1g·HCl** (D_2O)

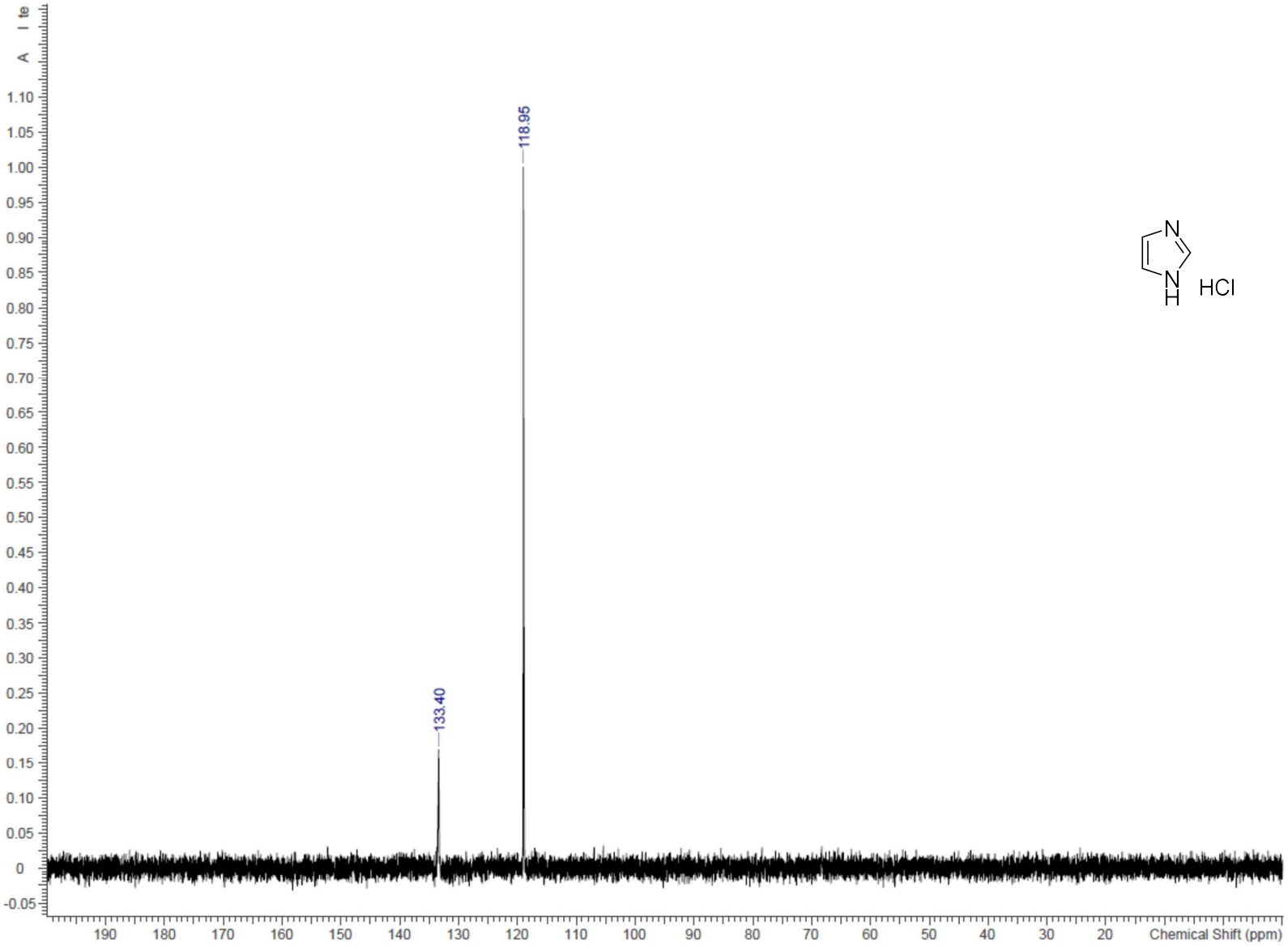

Figure S 74. ^{13}C NMR spectrum of **1g·HCl** (D_2O)

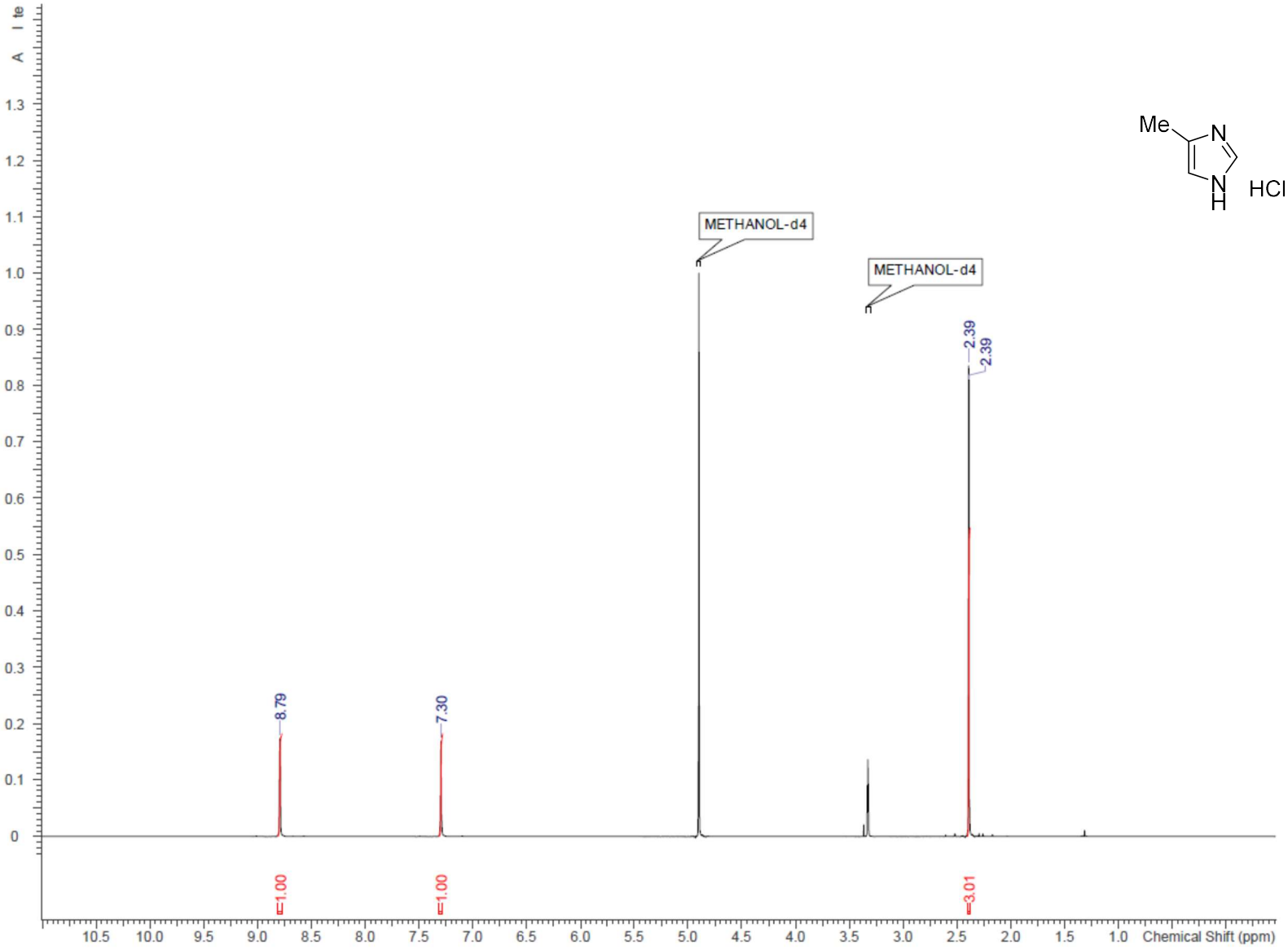

Figure S 75. ^{1}H NMR spectrum of **1h·HCl** (CD_3OD)

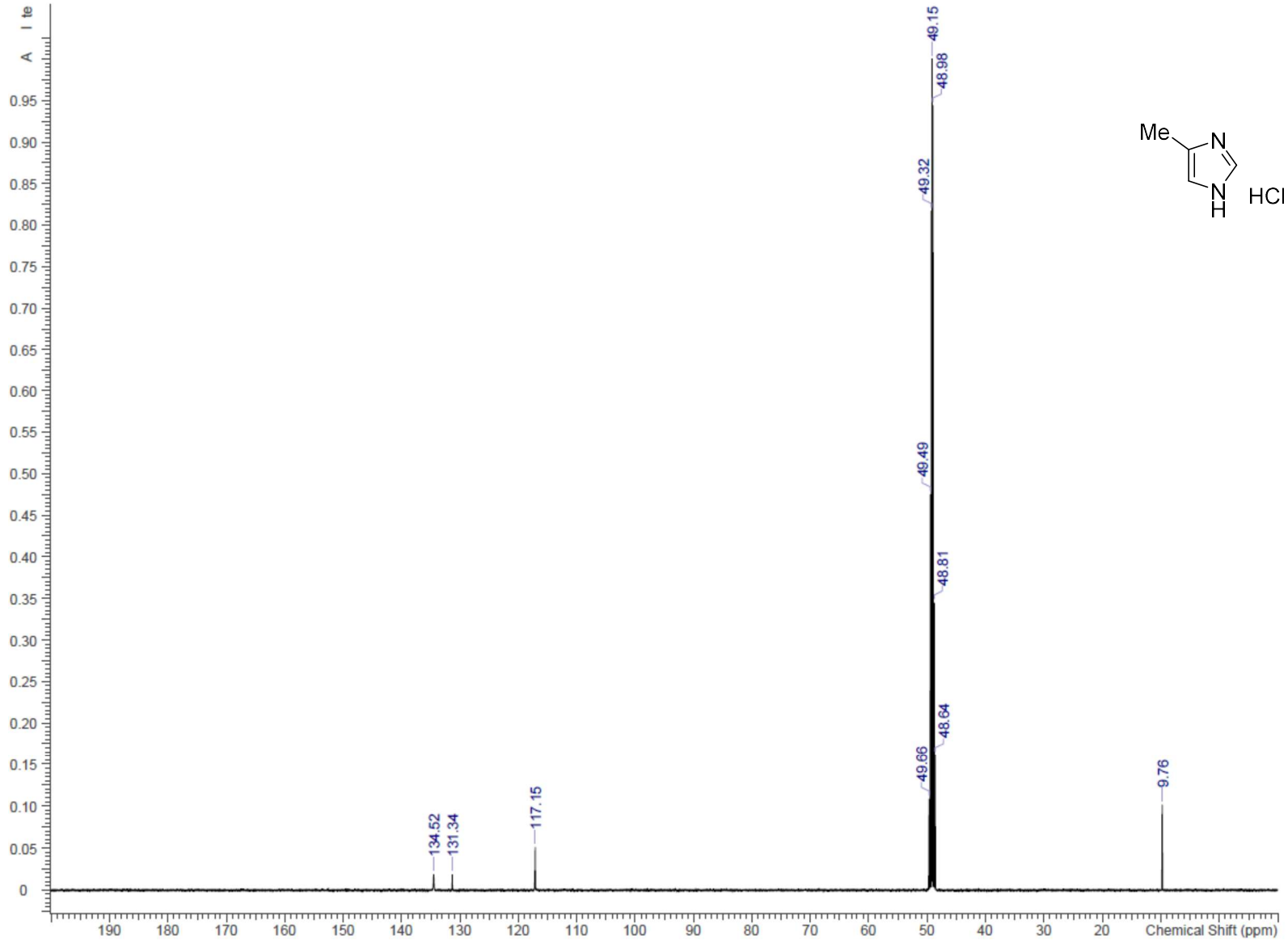

Figure S 76. ^{13}C NMR spectrum of **1h·HCl** (CD_3OD)

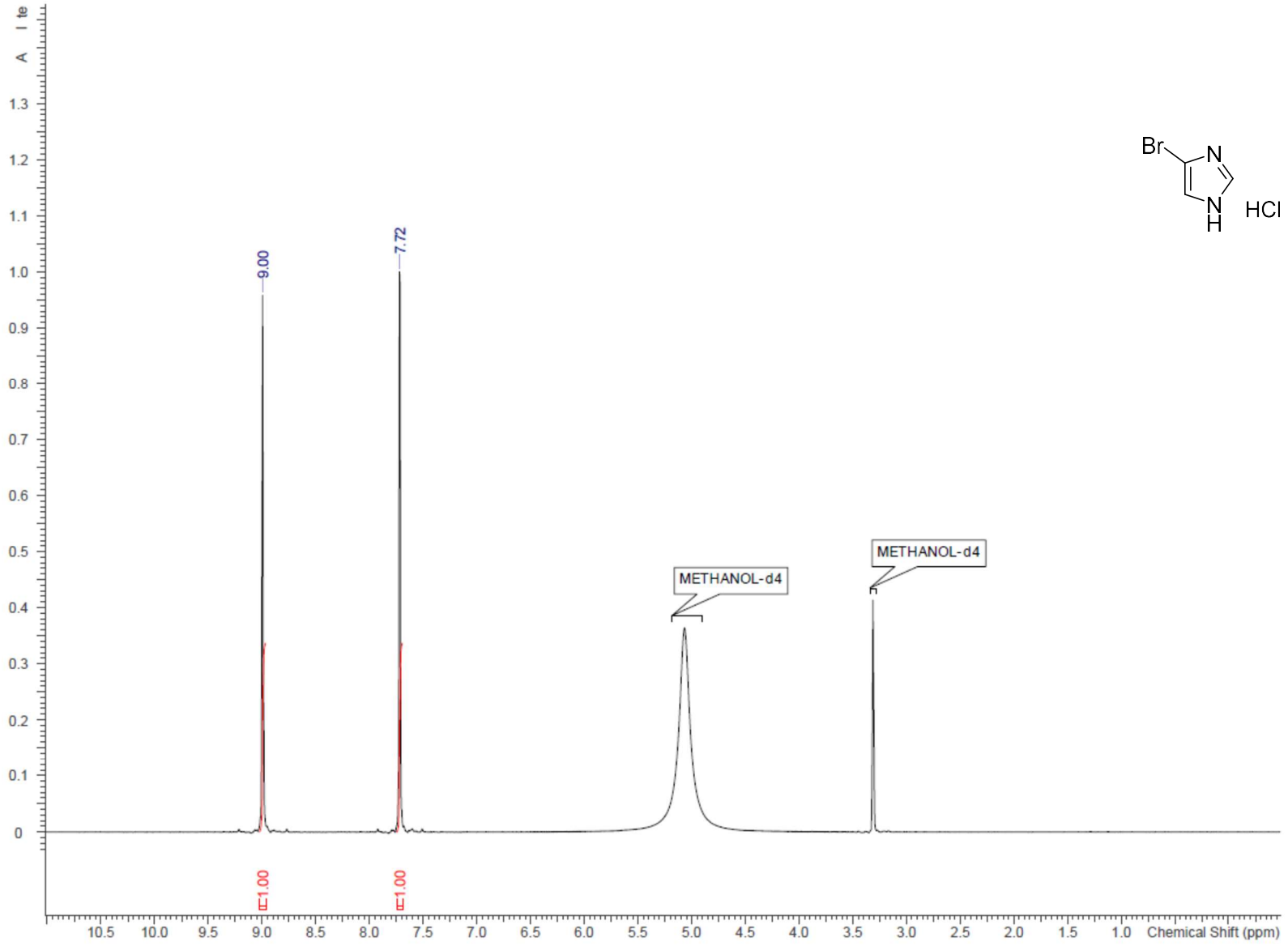

Figure S 77. ^{1}H NMR spectrum of **1i·HCl** (CD_3OD)

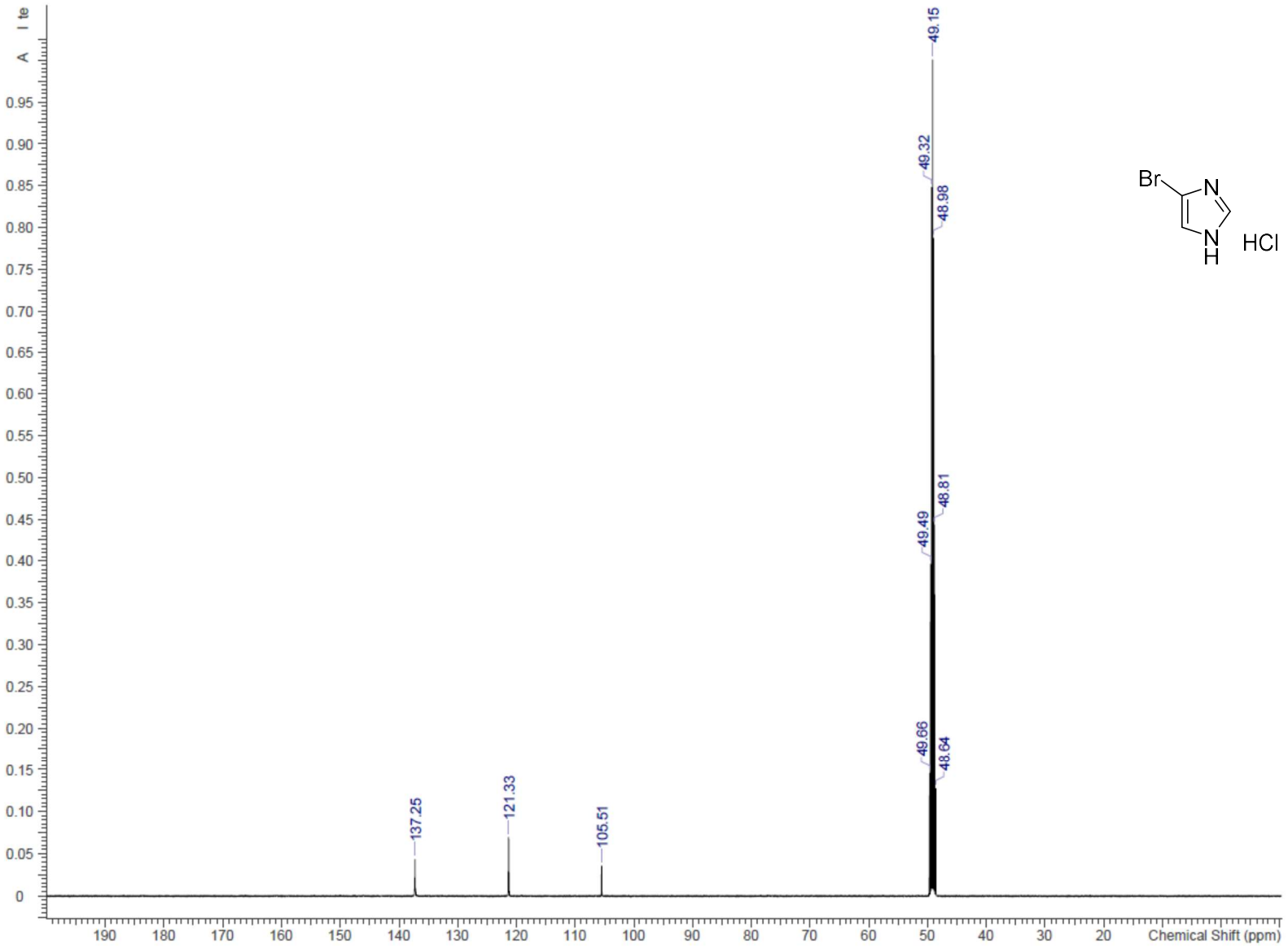

Figure S 78. ^{13}C NMR spectrum of **1i·HCl** (CD_3OD)

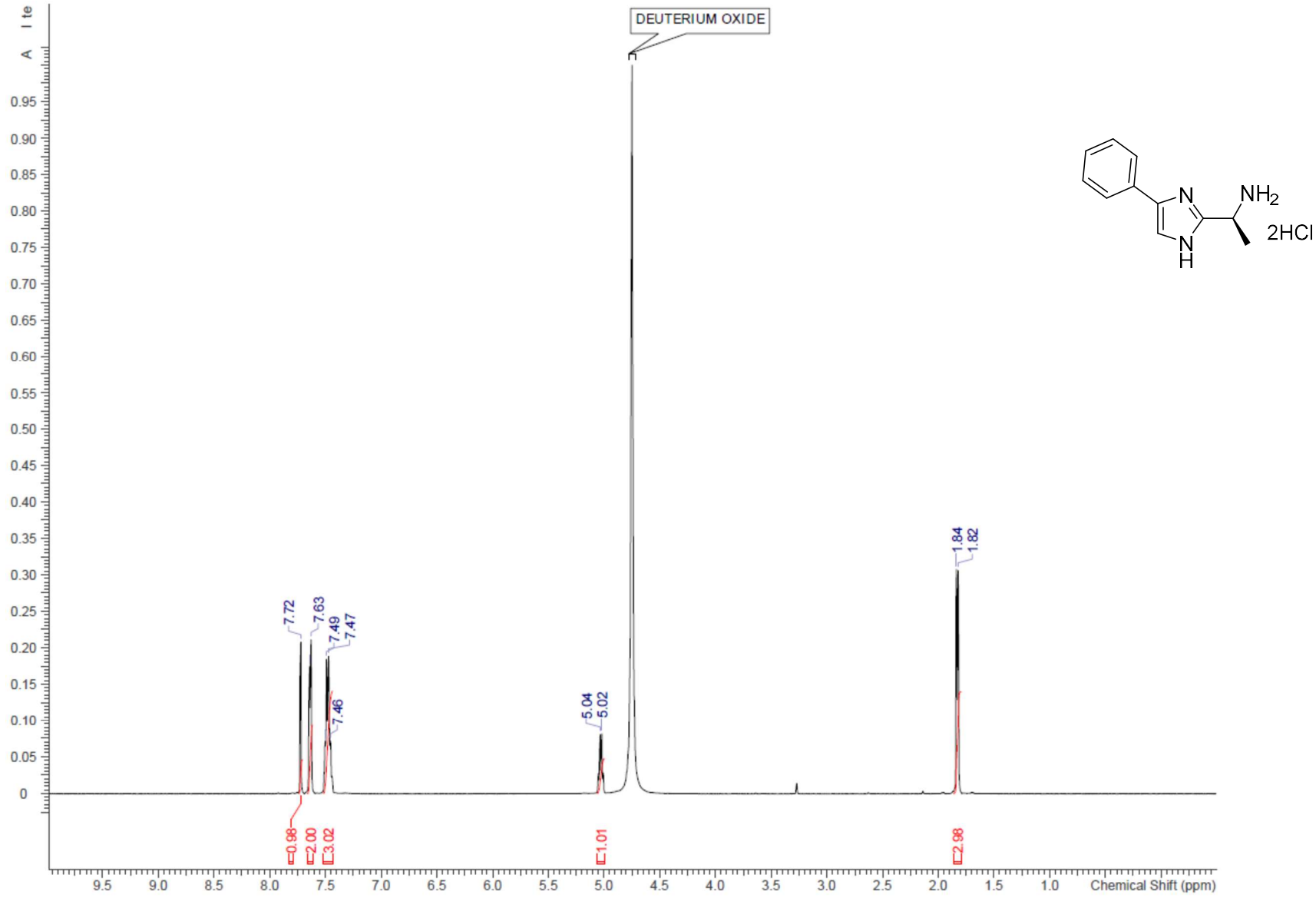

Figure S 79. ^{1}H NMR spectrum of **1j·HCl** (D_2O)

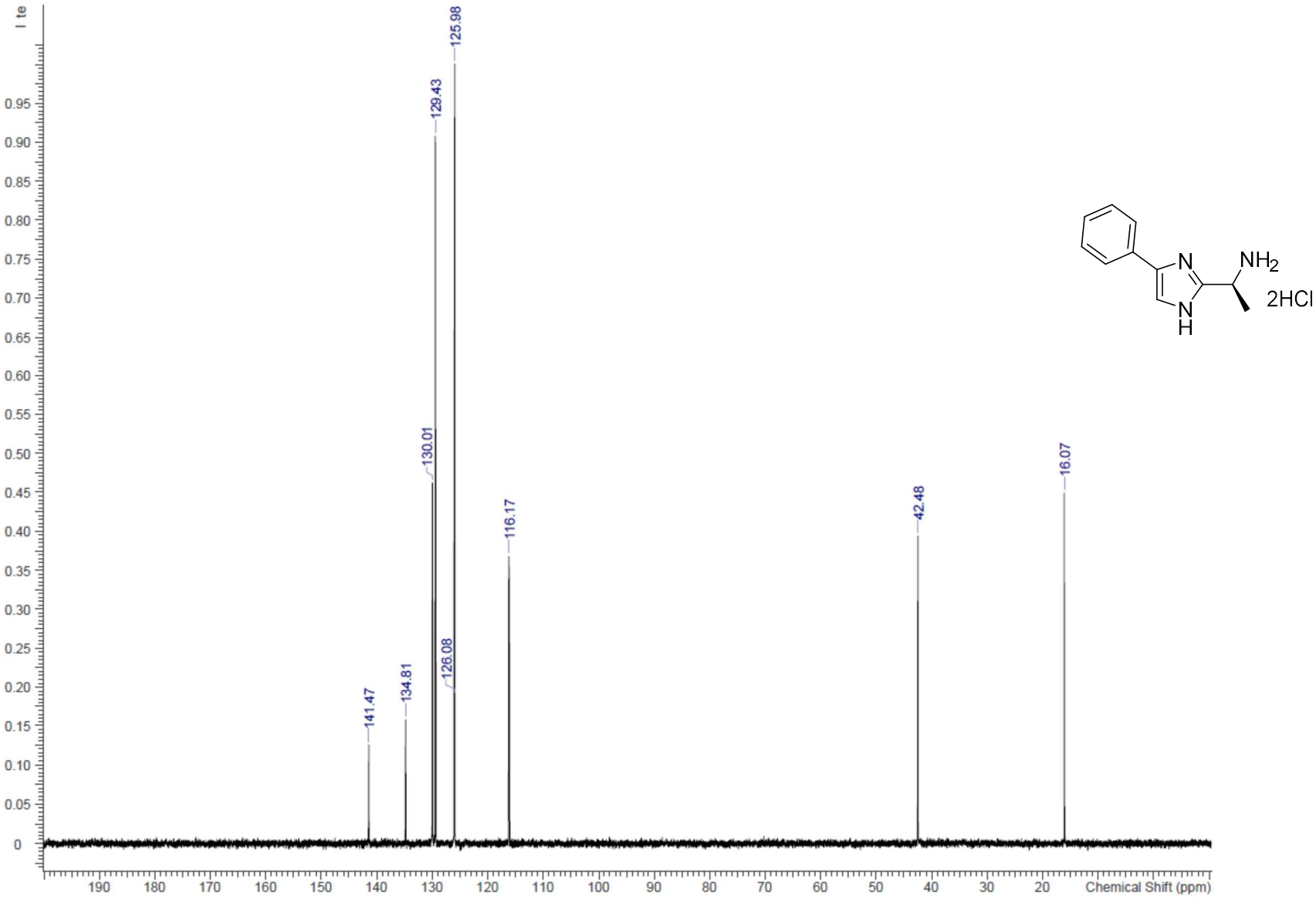

Figure S 80. ^{13}C NMR spectrum of **1j·HCl** (D_2O)

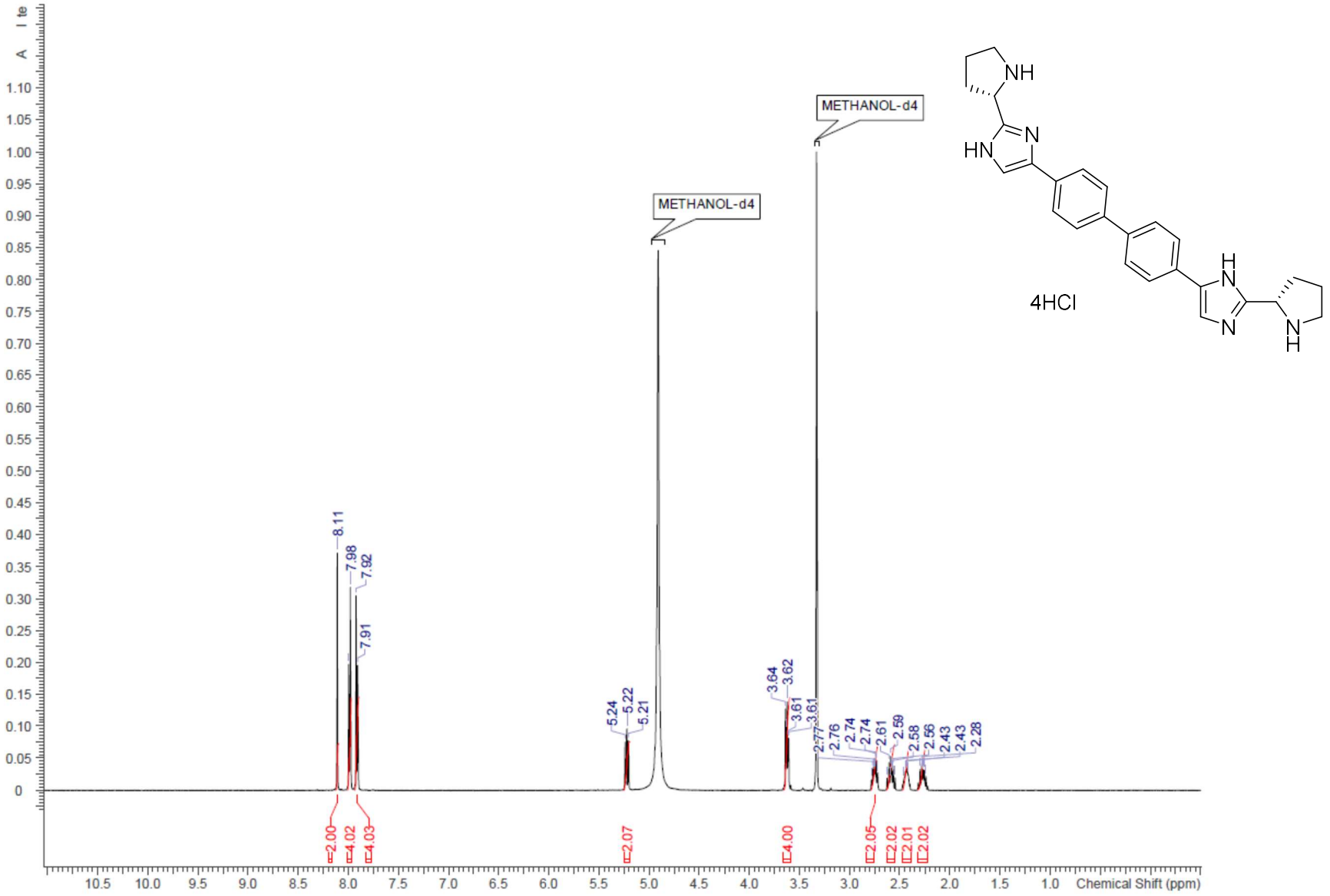

Figure S 81. ^{1}H NMR spectrum of **1k** (CD_3OD)

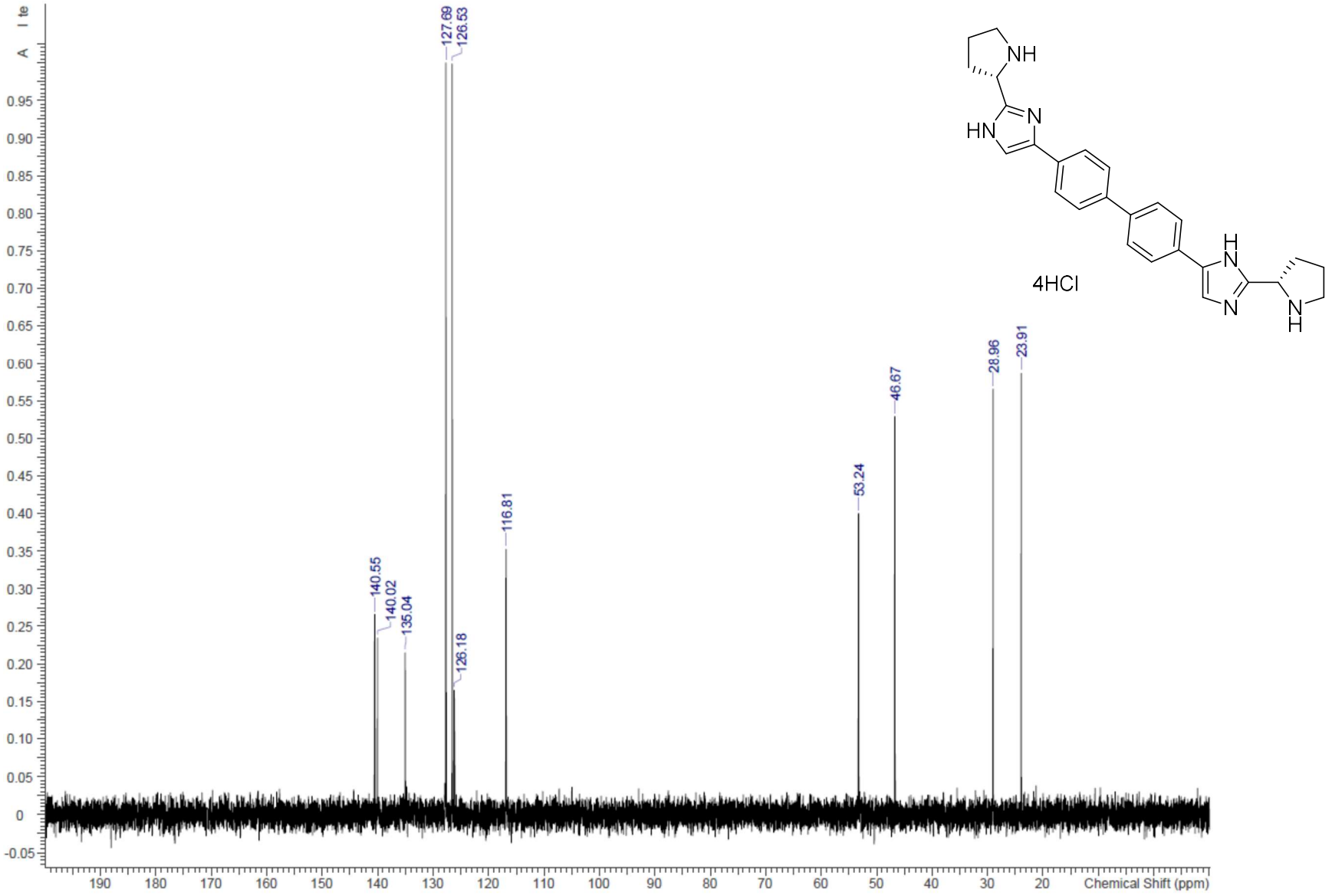

Figure S 82. ^{13}C NMR spectrum of **1k** (D_2O)

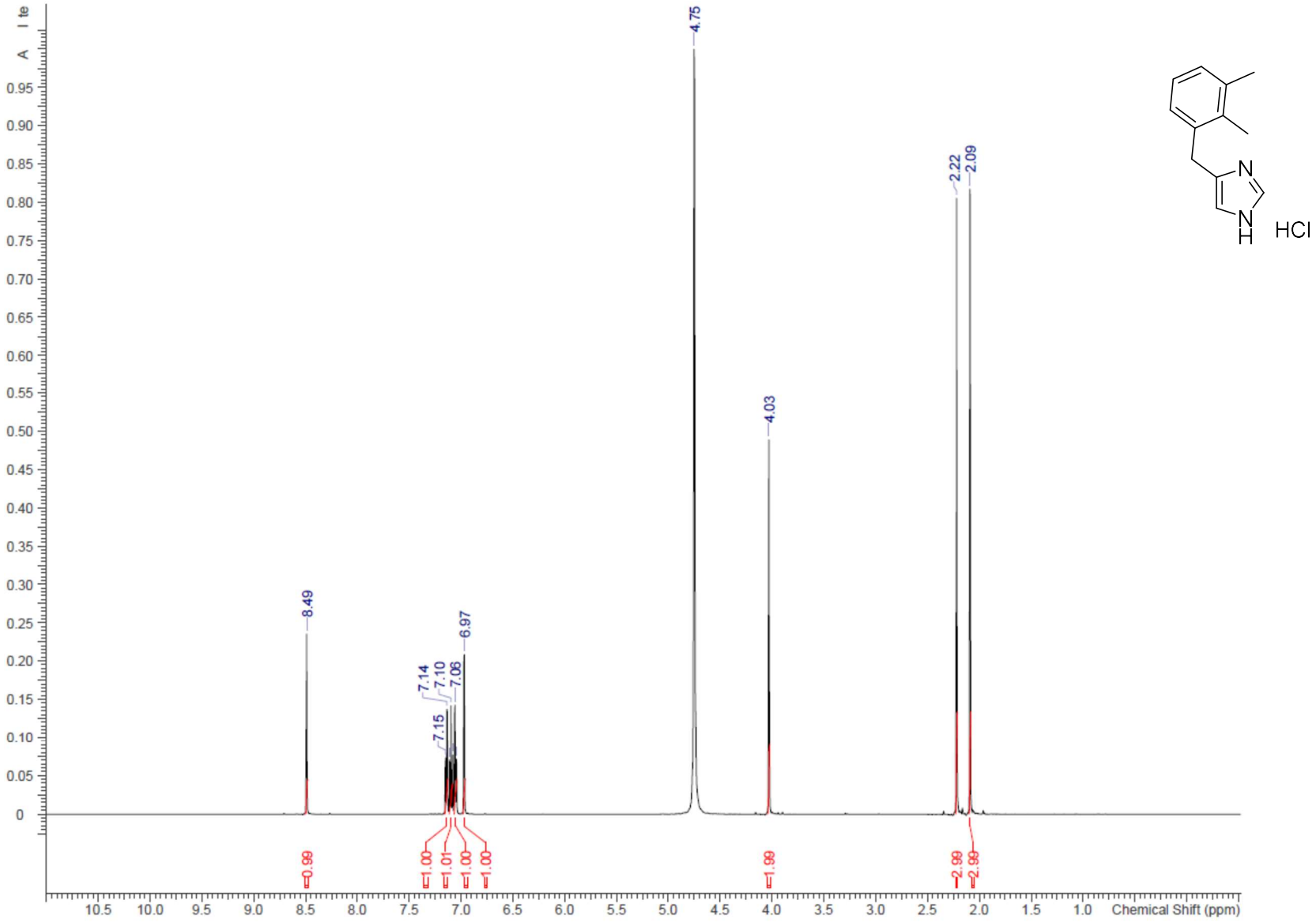

Figure S 83. ^{1}H NMR spectrum of **1l** (D_2O)

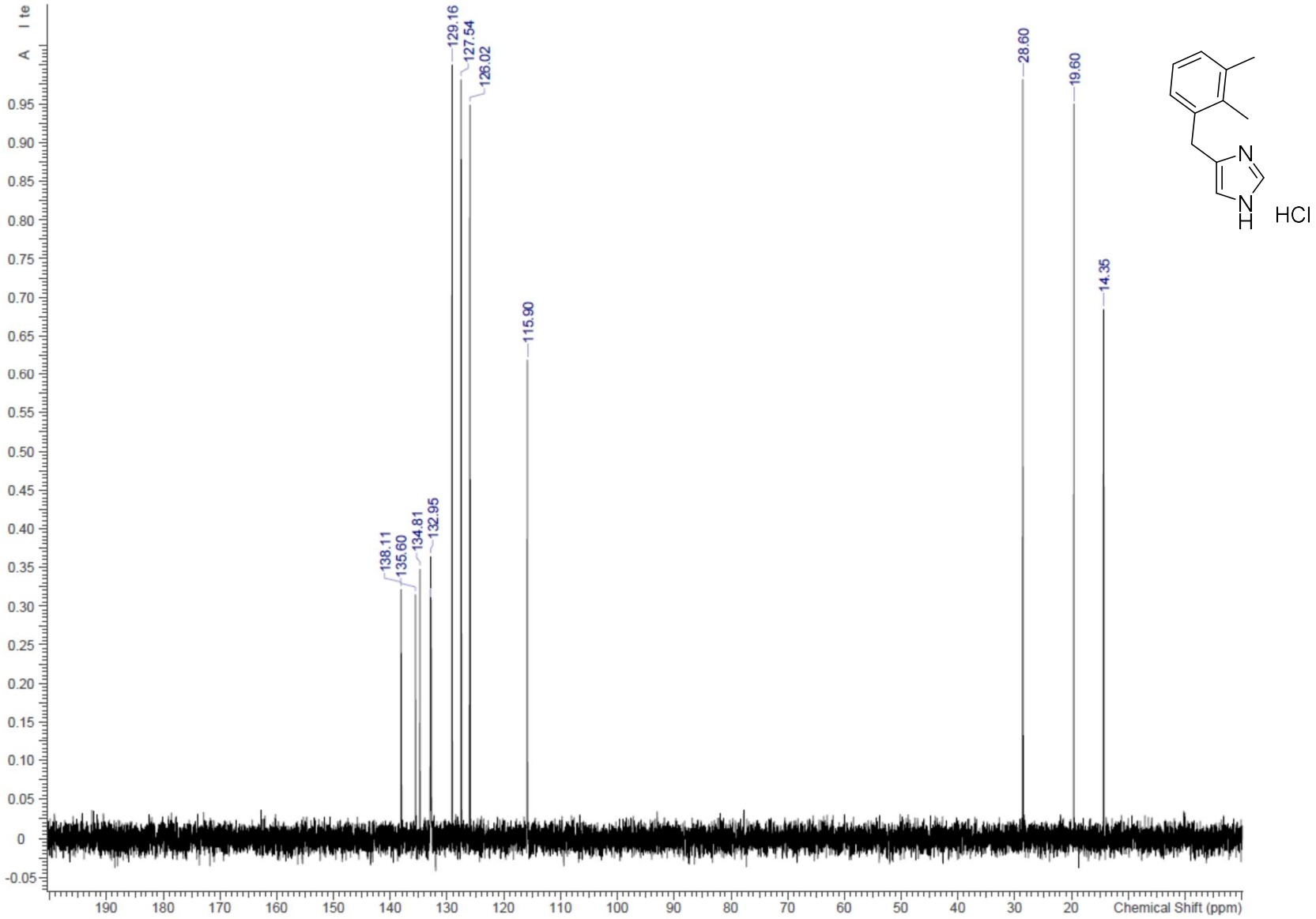

Figure S 84. ^{13}C NMR spectrum of **1l** (D_2O)

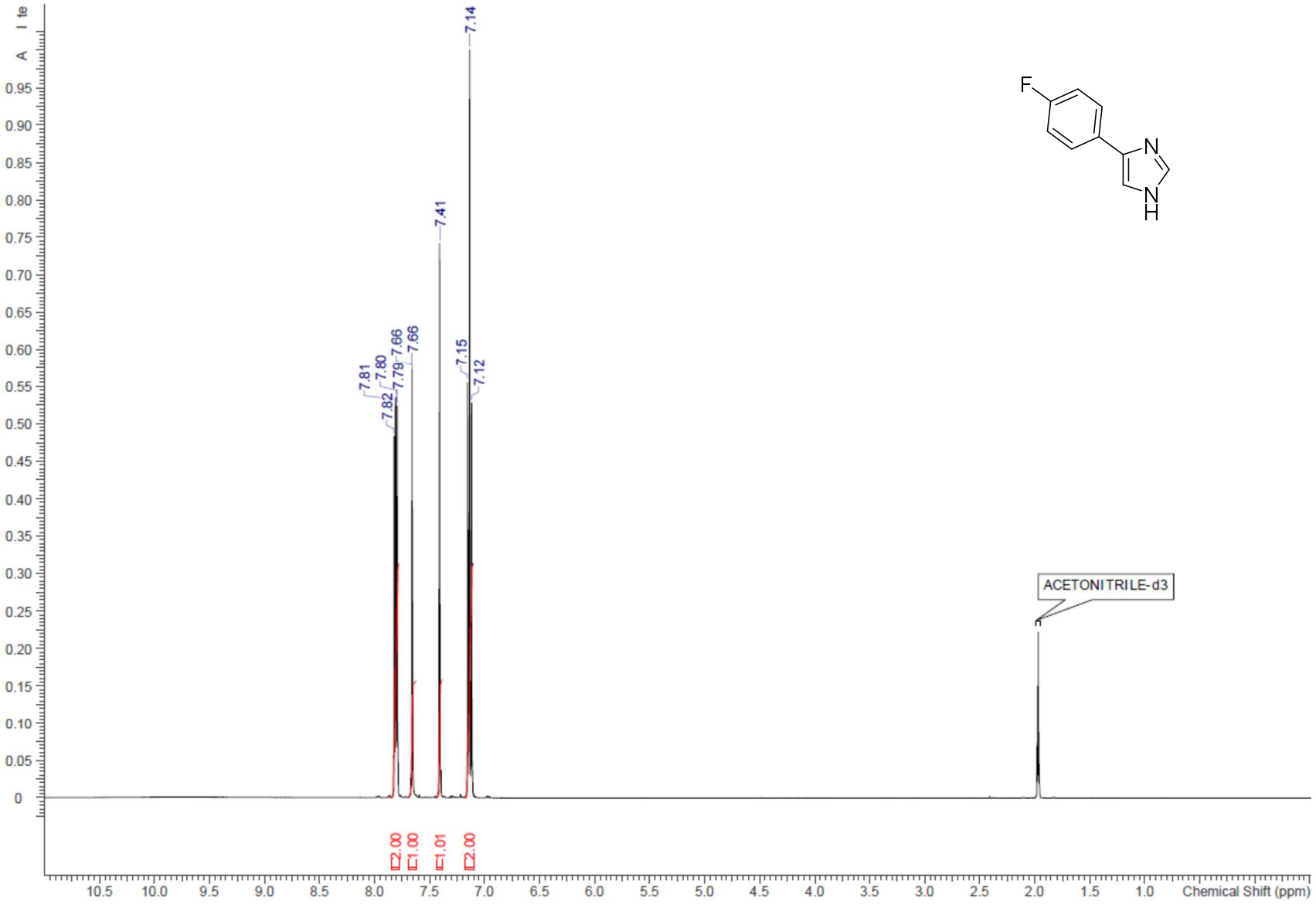

Figure S 85. ^{1}H NMR spectrum of **1b** (CD_3CN)

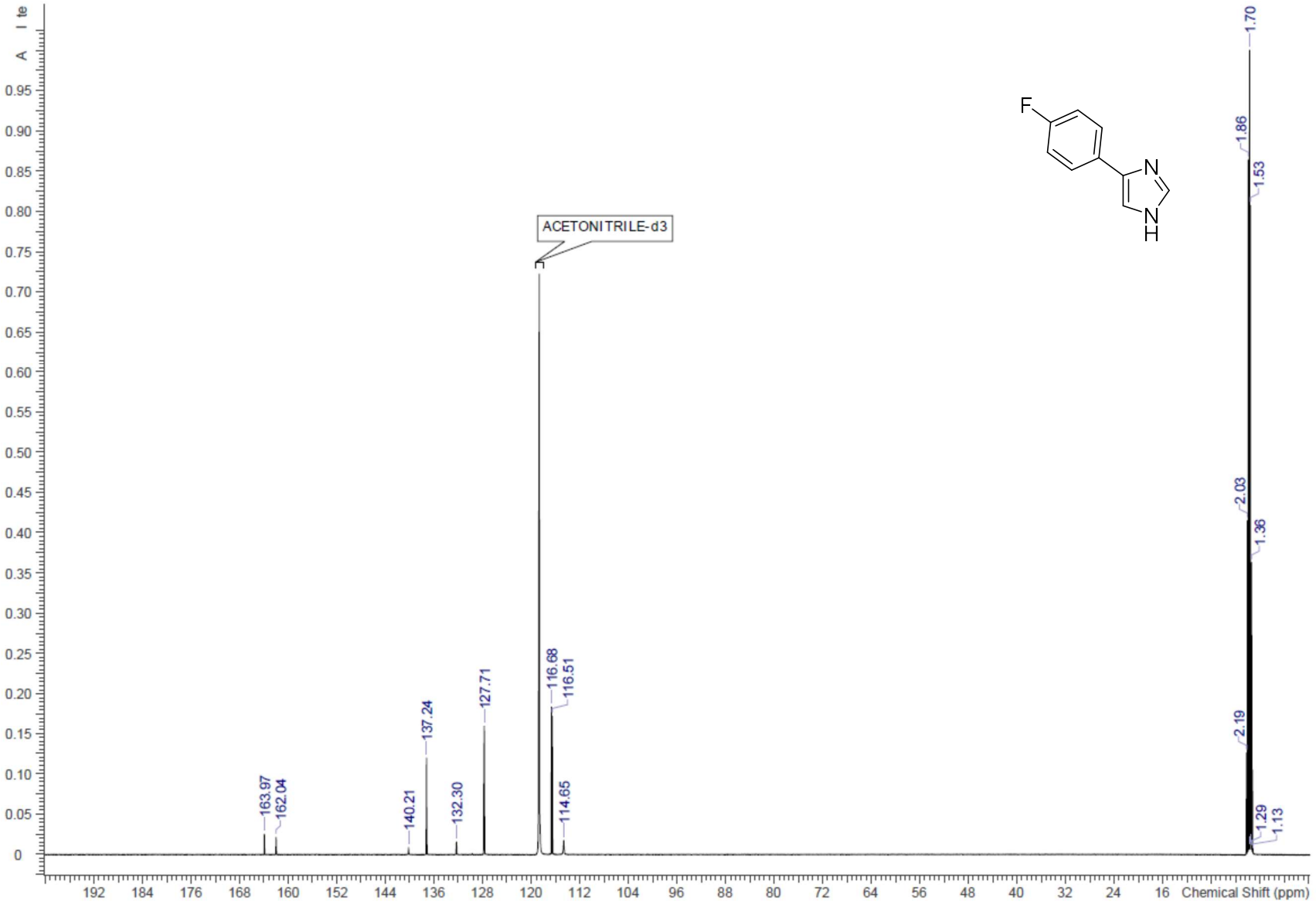

Figure S 86. ^{13}C NMR spectrum of **1b** (CD_3CN)

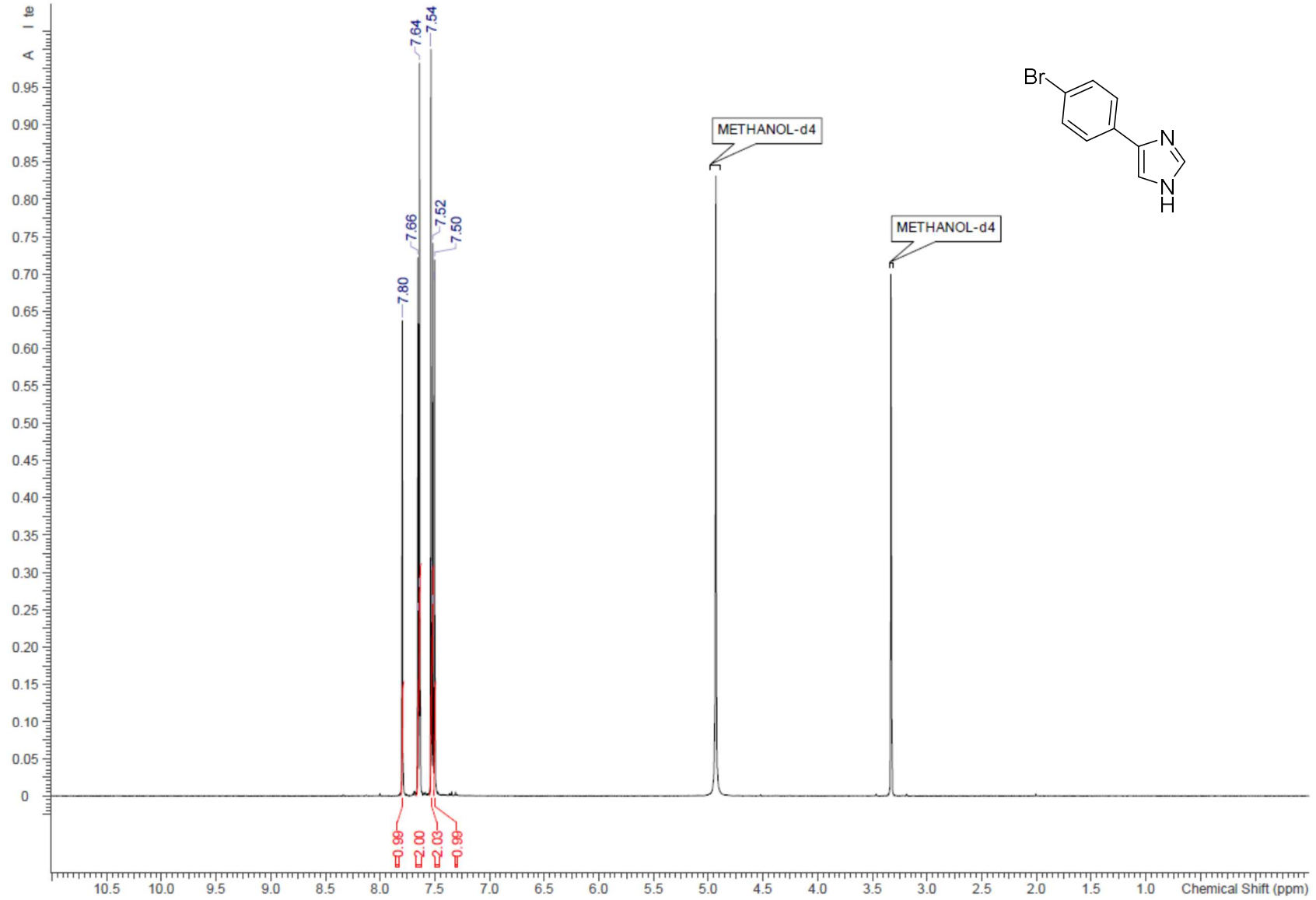

Figure S 87. ^{1}H NMR spectrum of **1c** (CD_3OD)

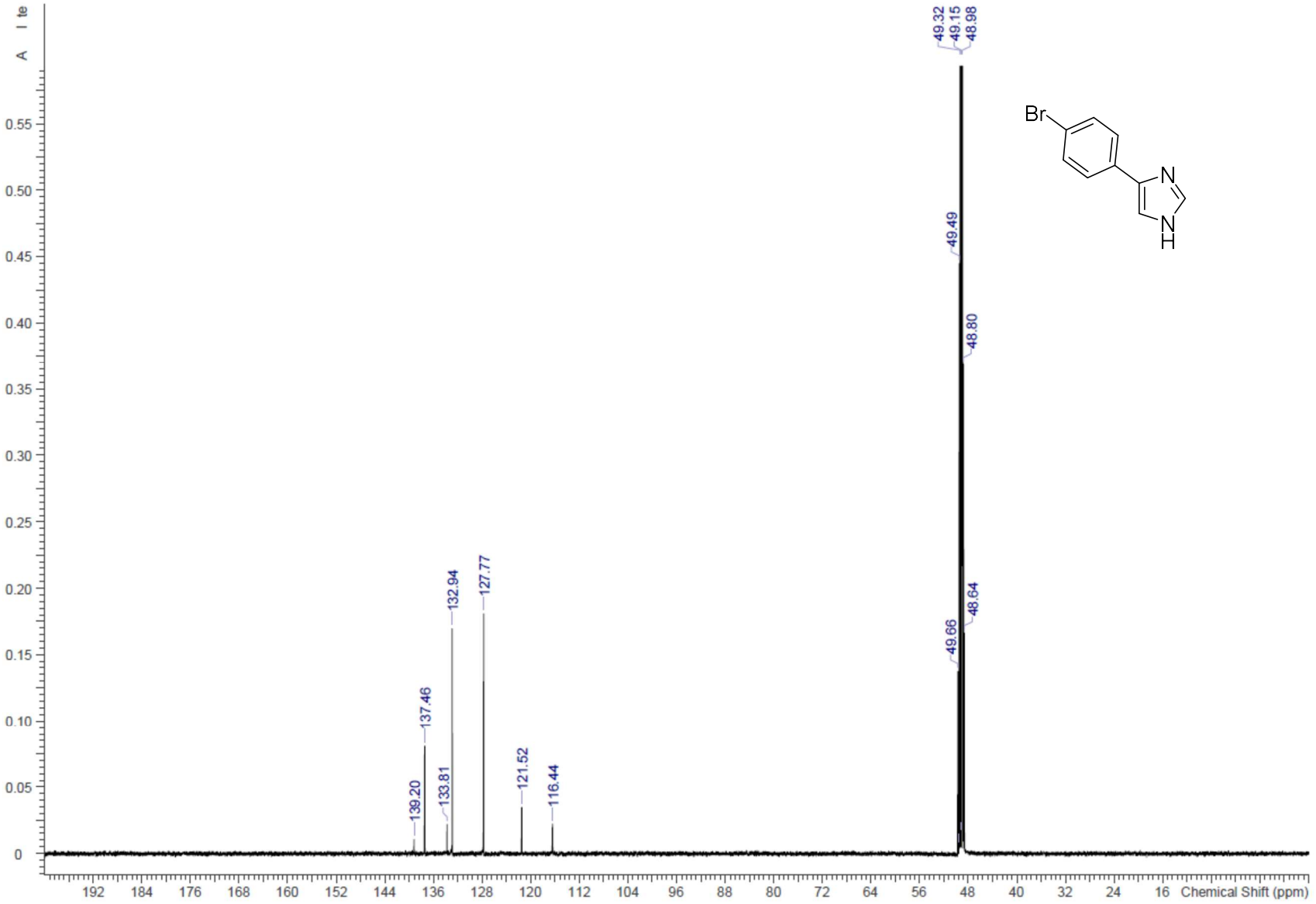

Figure S 88. ^{13}C NMR spectrum of **1c** (CD_3OD)

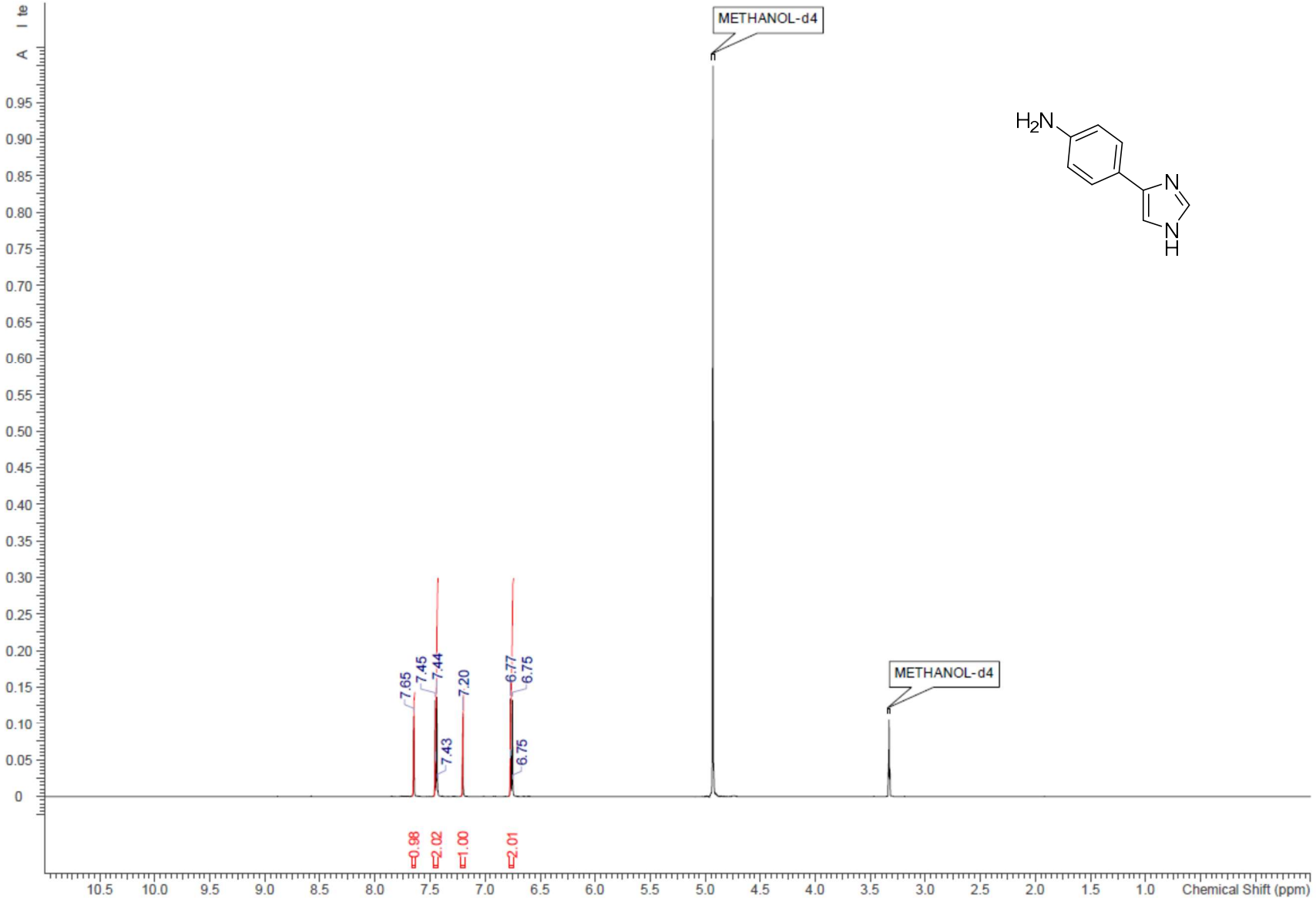

Figure S 89. ^{1}H NMR spectrum of **1e** (CD_3OD)

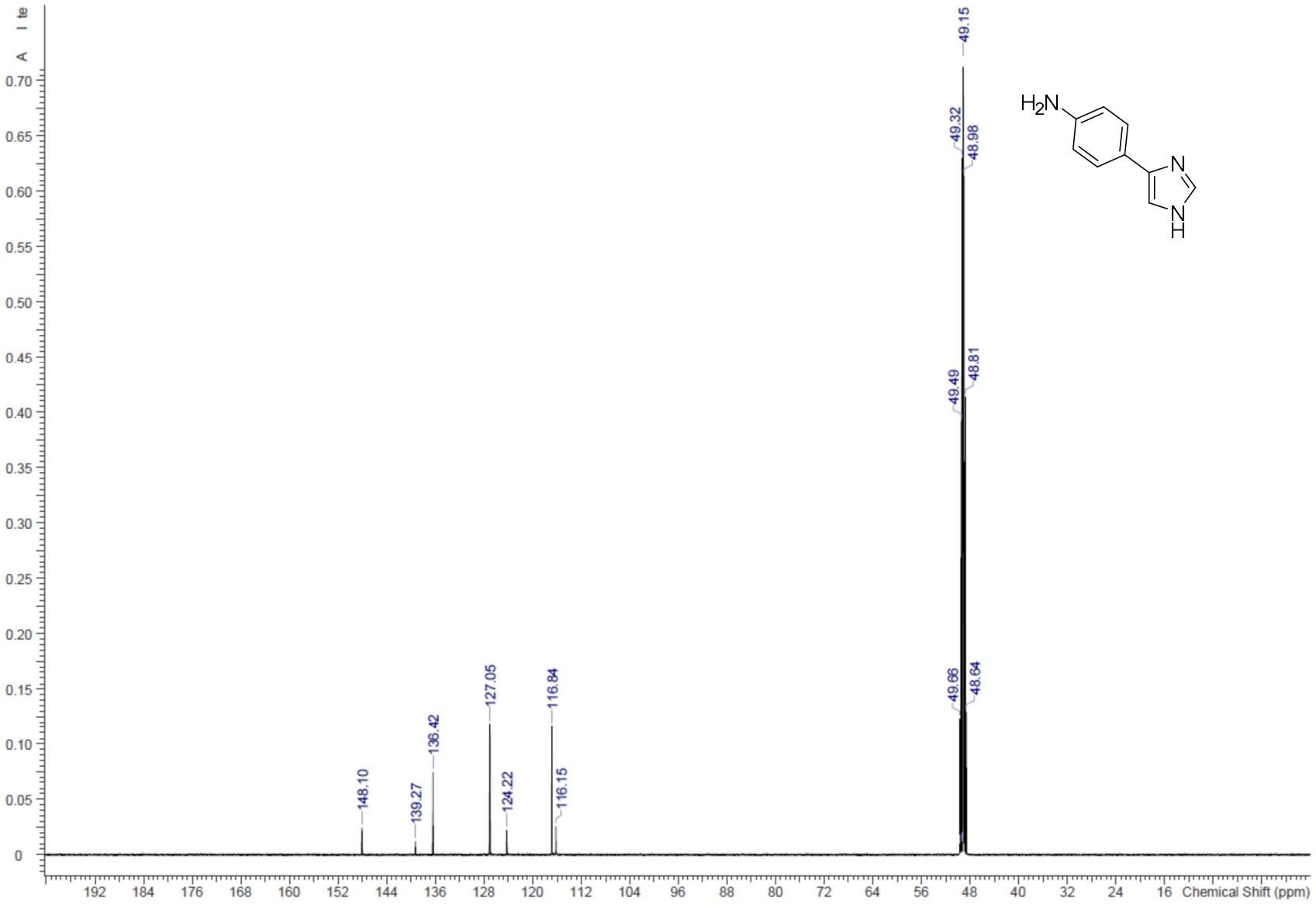

Figure S 90. ^{13}C NMR spectrum of **1e** (CD_3OD)

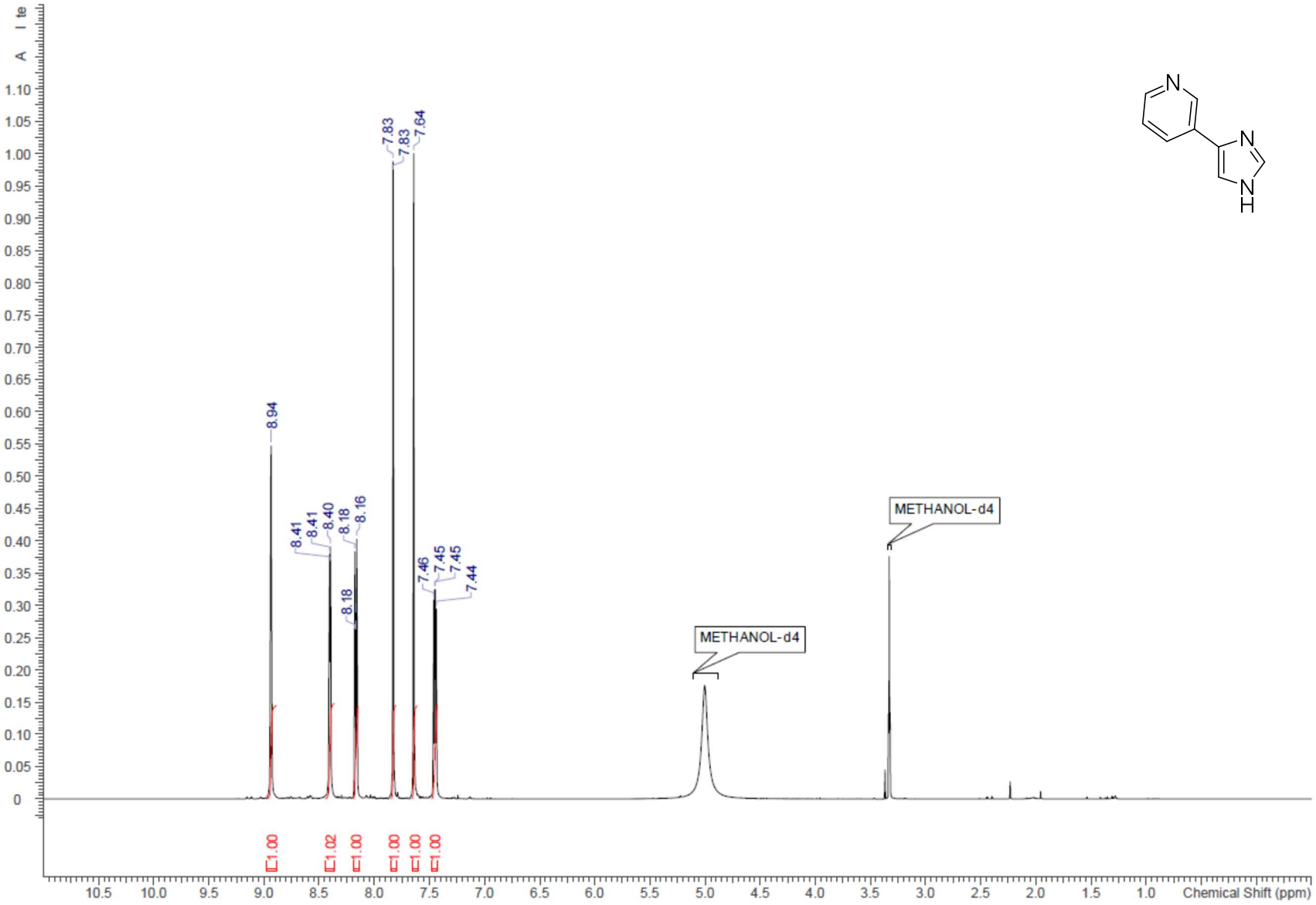

Figure S 91. ^{1}H NMR spectrum of **1f** (CD_3OD)

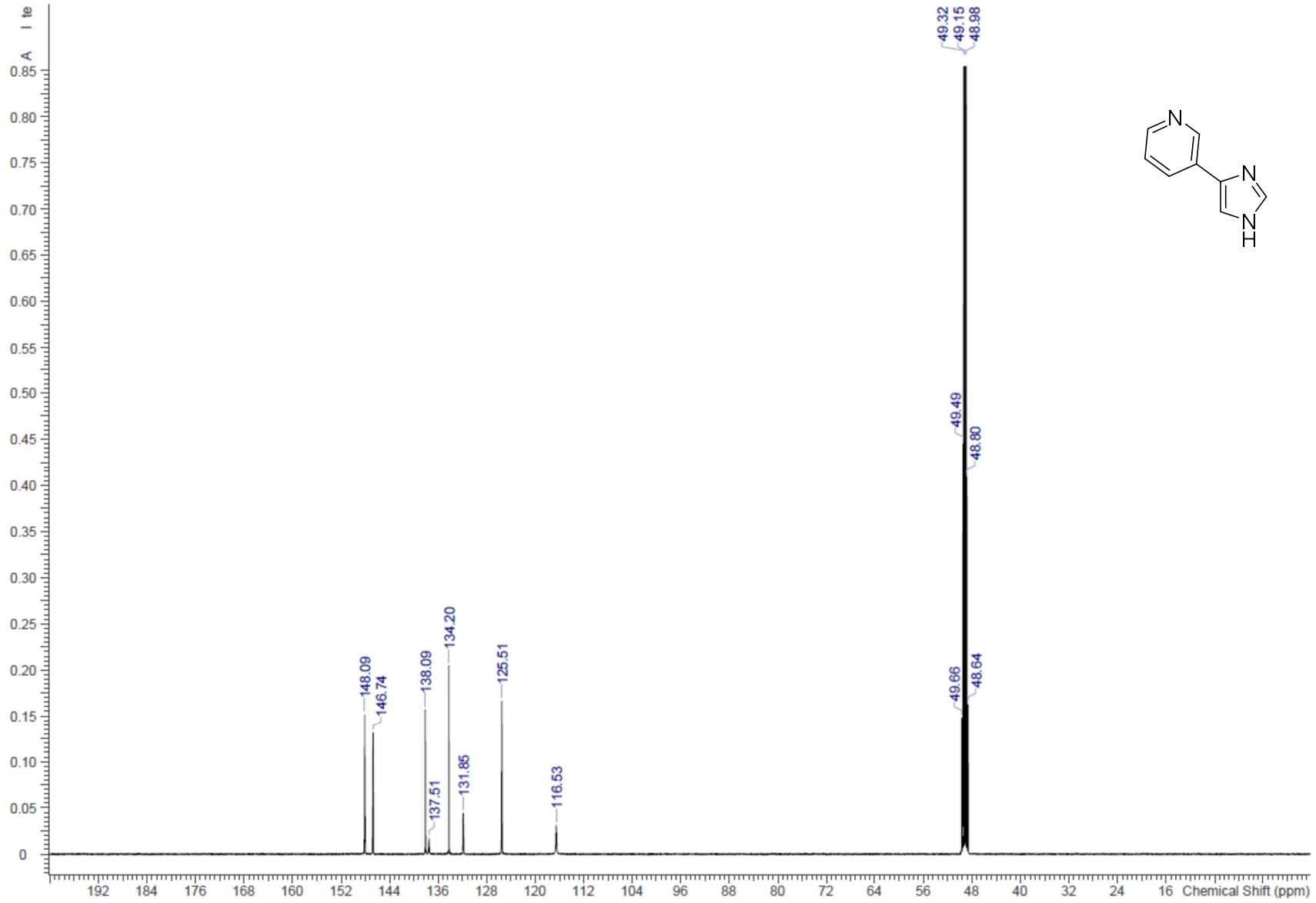

Figure S 92. ^{13}C NMR spectrum of **1f** (CD_3OD)

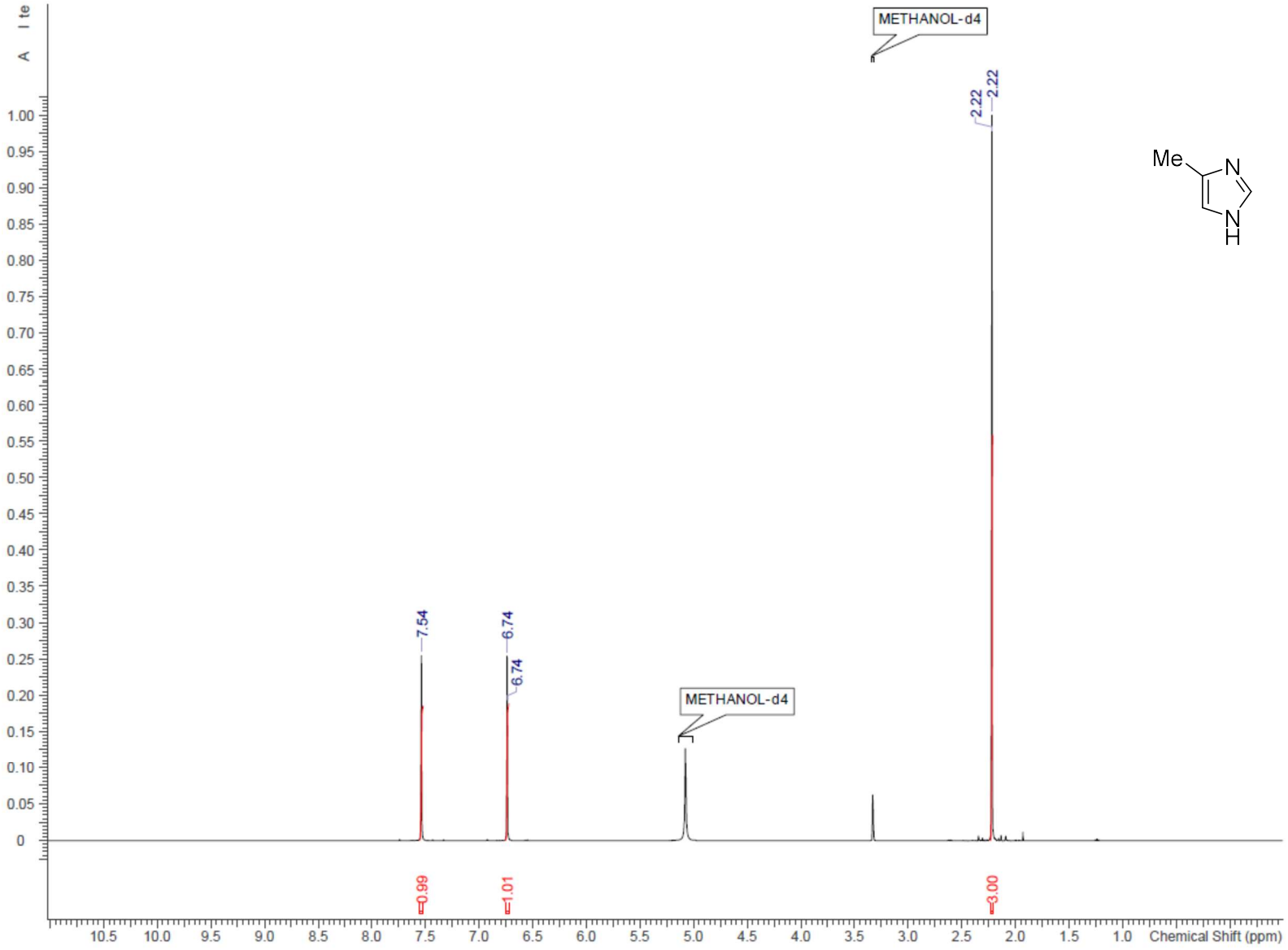

Figure S 93. ^{1}H NMR spectrum of **1h** (CD_3OD)

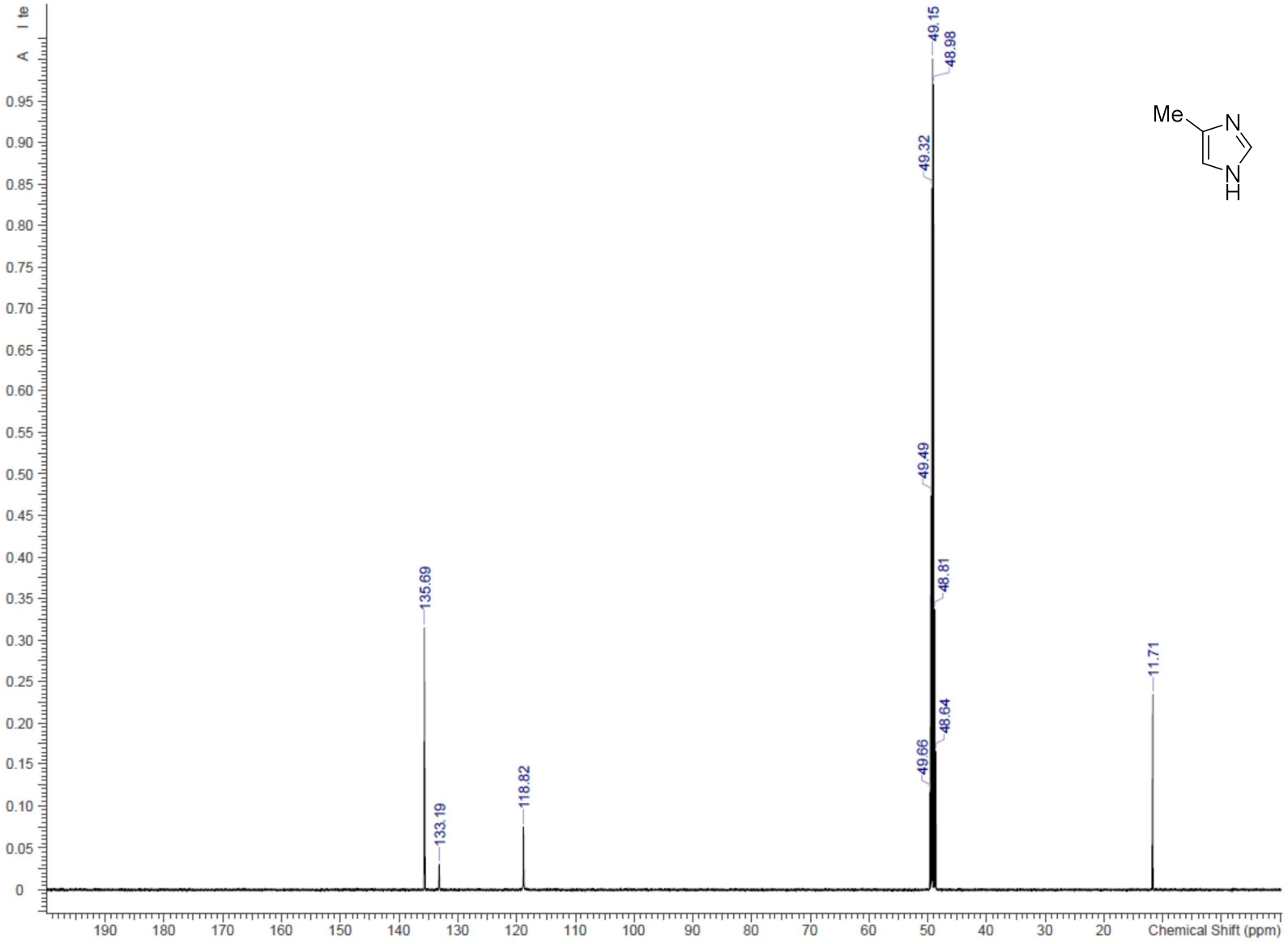

Figure S 94. ^{13}C NMR spectrum of **1h** (CD_3OD)

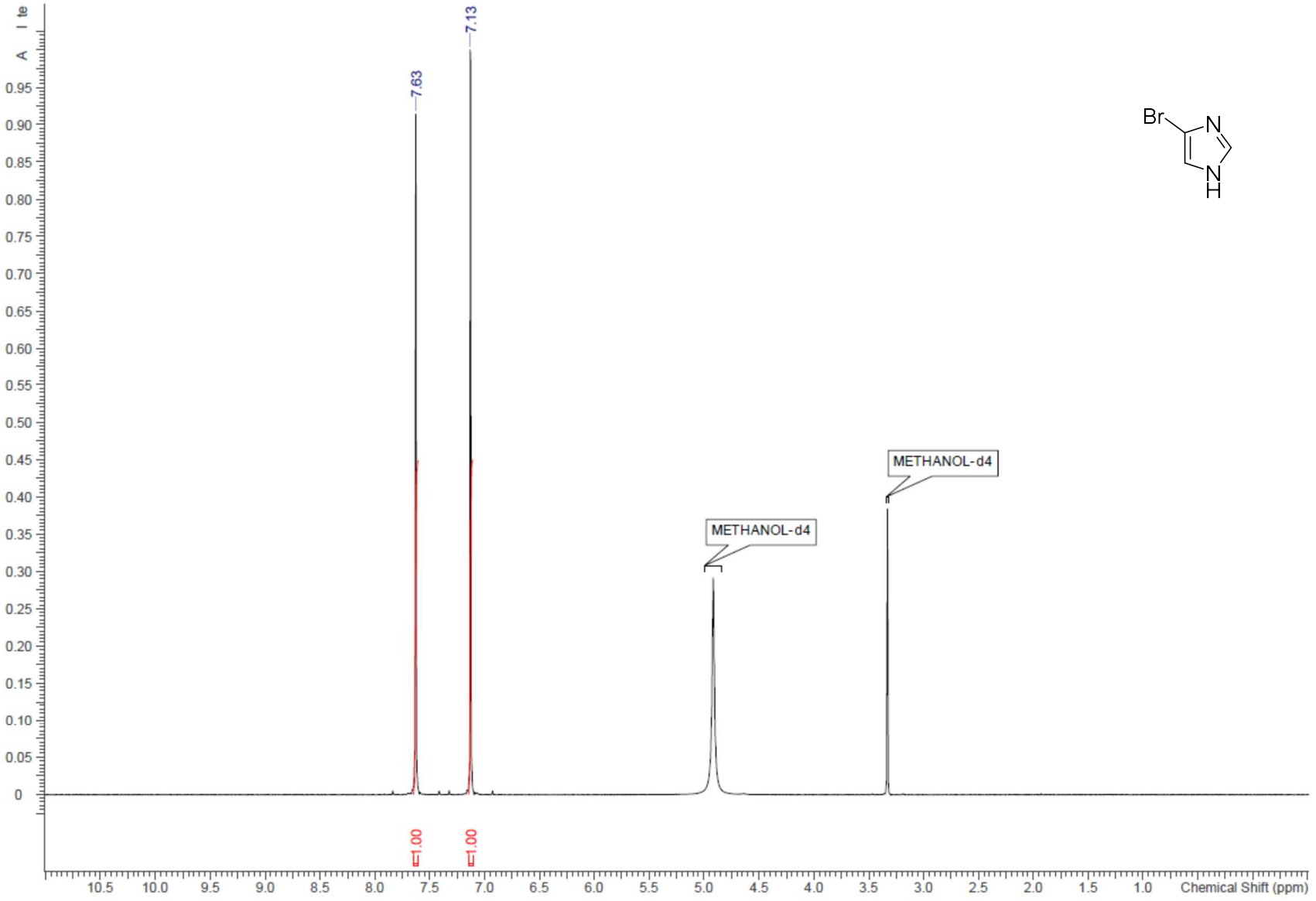

Figure S 95. ^{1}H NMR spectrum of **1i** (CD_3OD)

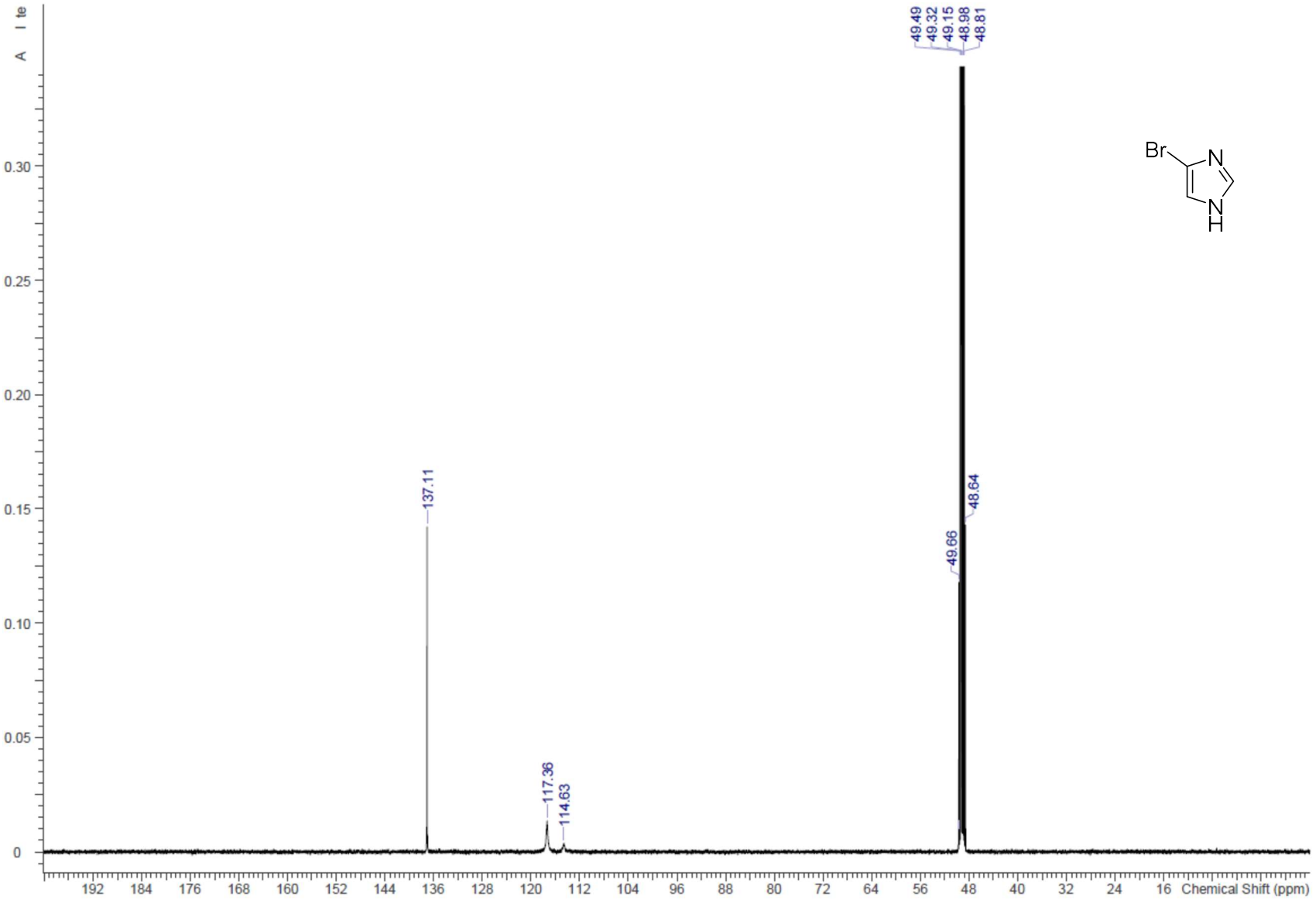

Figure S 96. ^{13}C NMR spectrum of **1i** (CD_3OD)

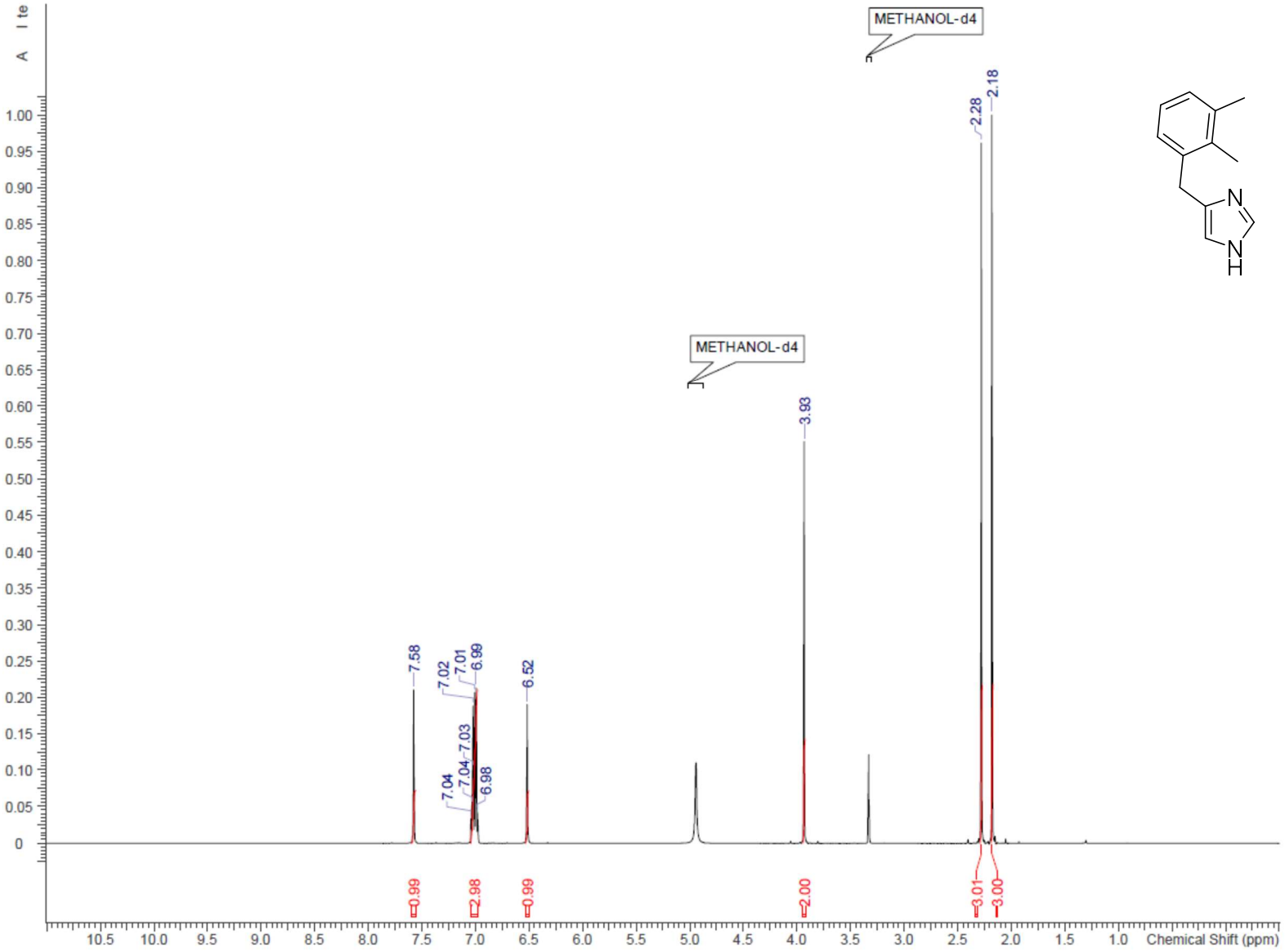

Figure S 97. ^{1}H NMR spectrum of **1l**-free (CD_3OD)

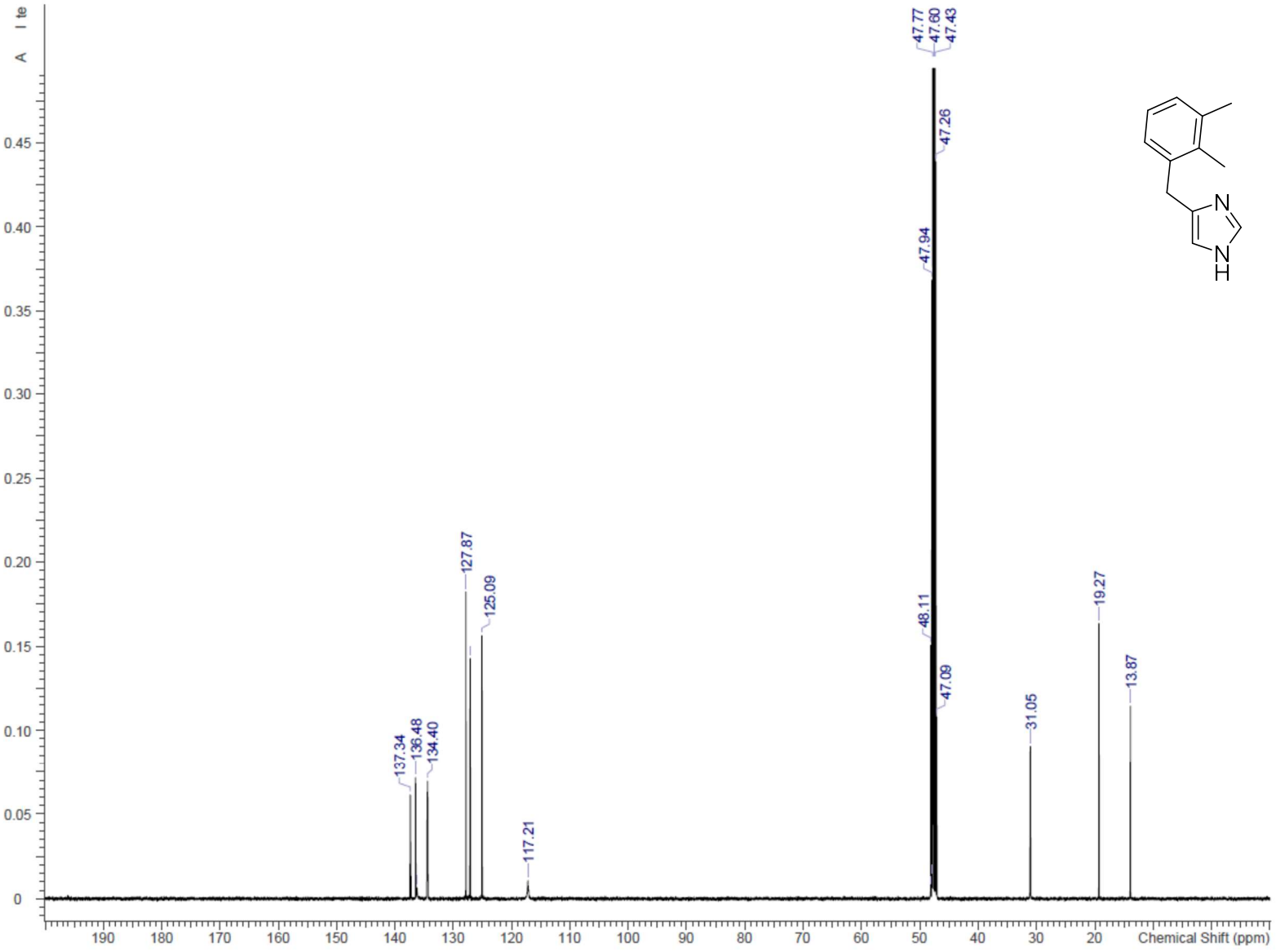

Figure S 98. ^{13}C NMR spectrum of **1l**-free (CD_3OD)

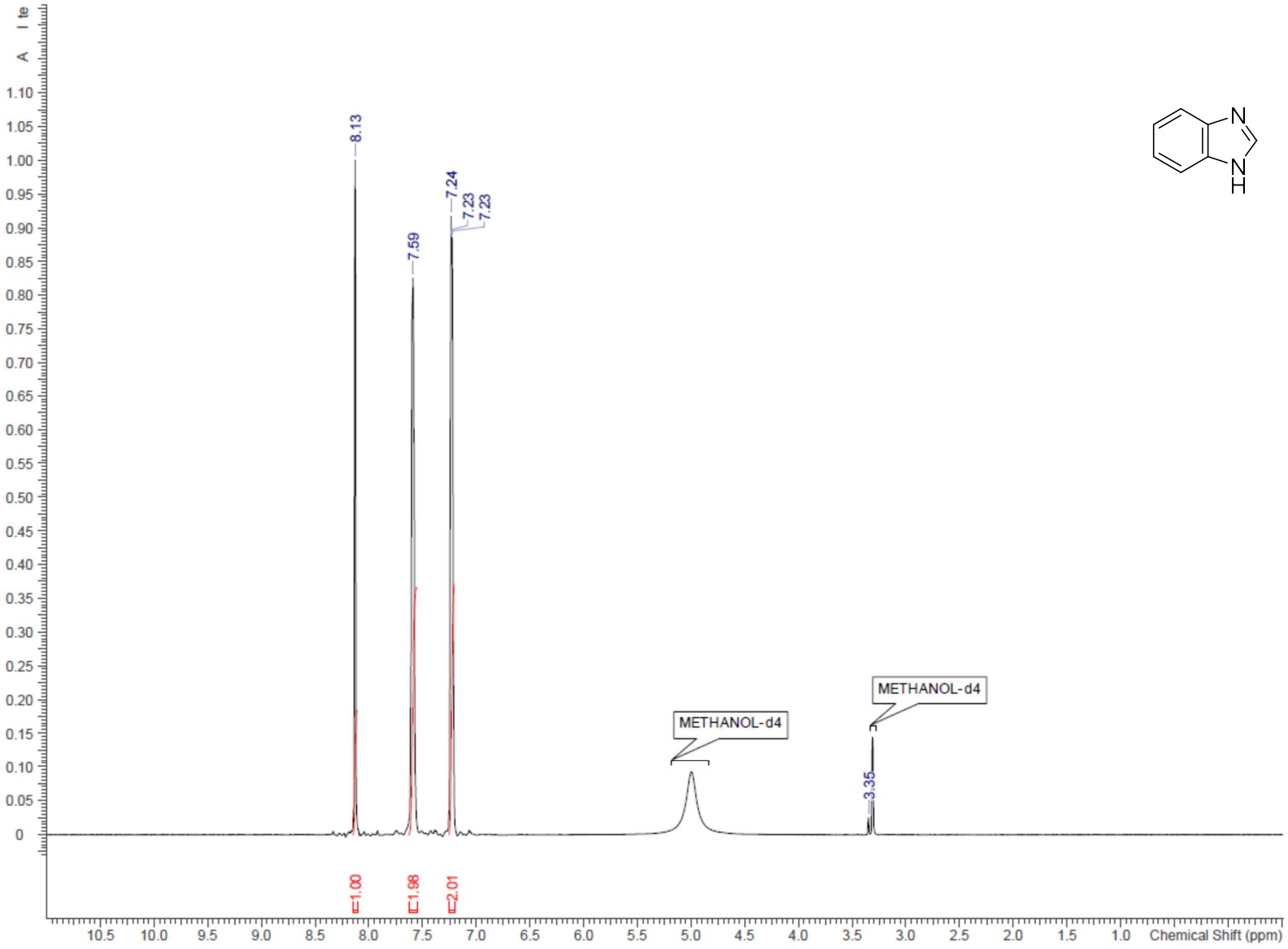

Figure S 99. ^{1}H NMR spectrum of **1m** (CD_3OD)

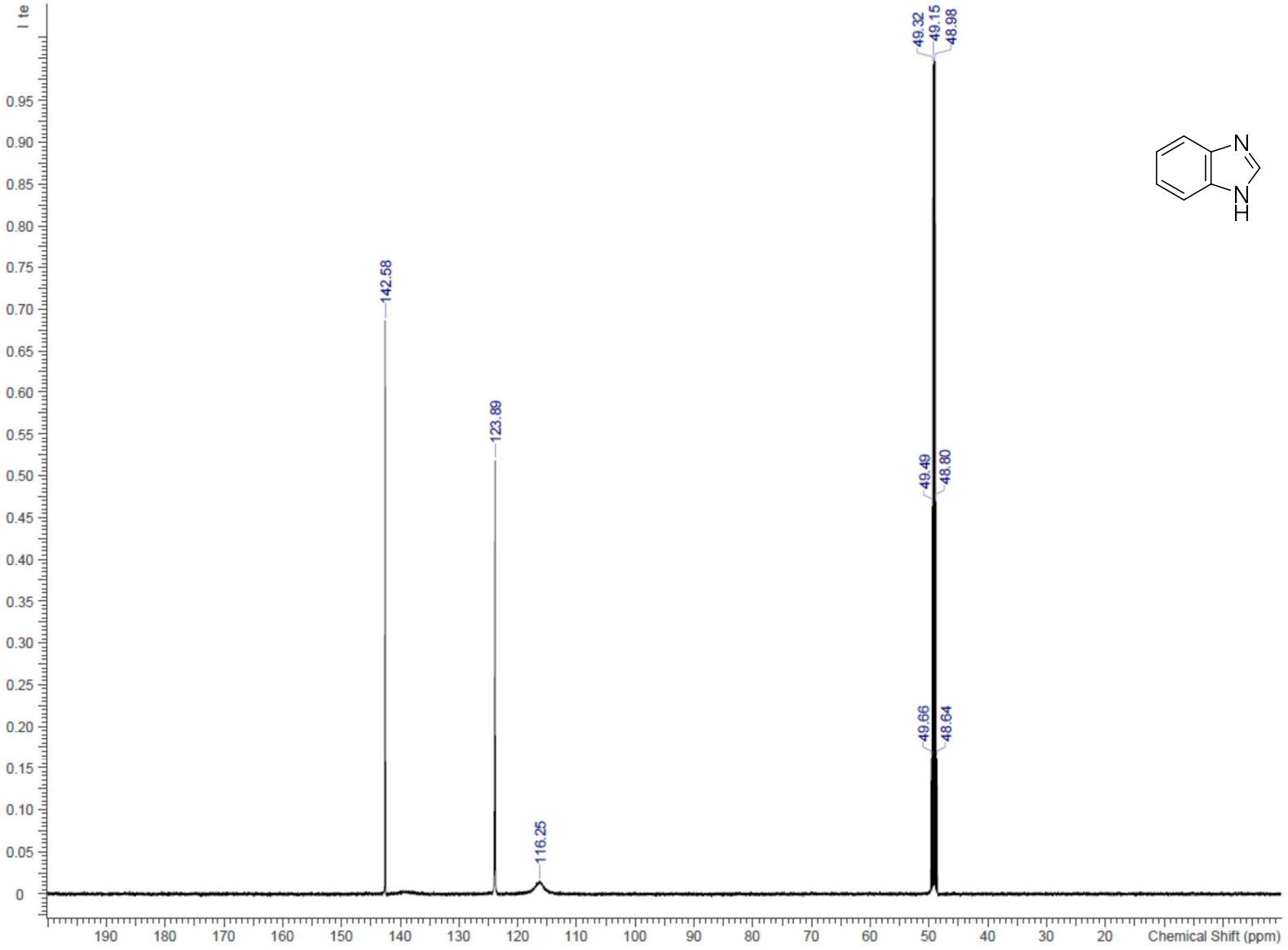

Figure S 100. ^{13}C NMR spectrum of **1m** (CD_3OD)

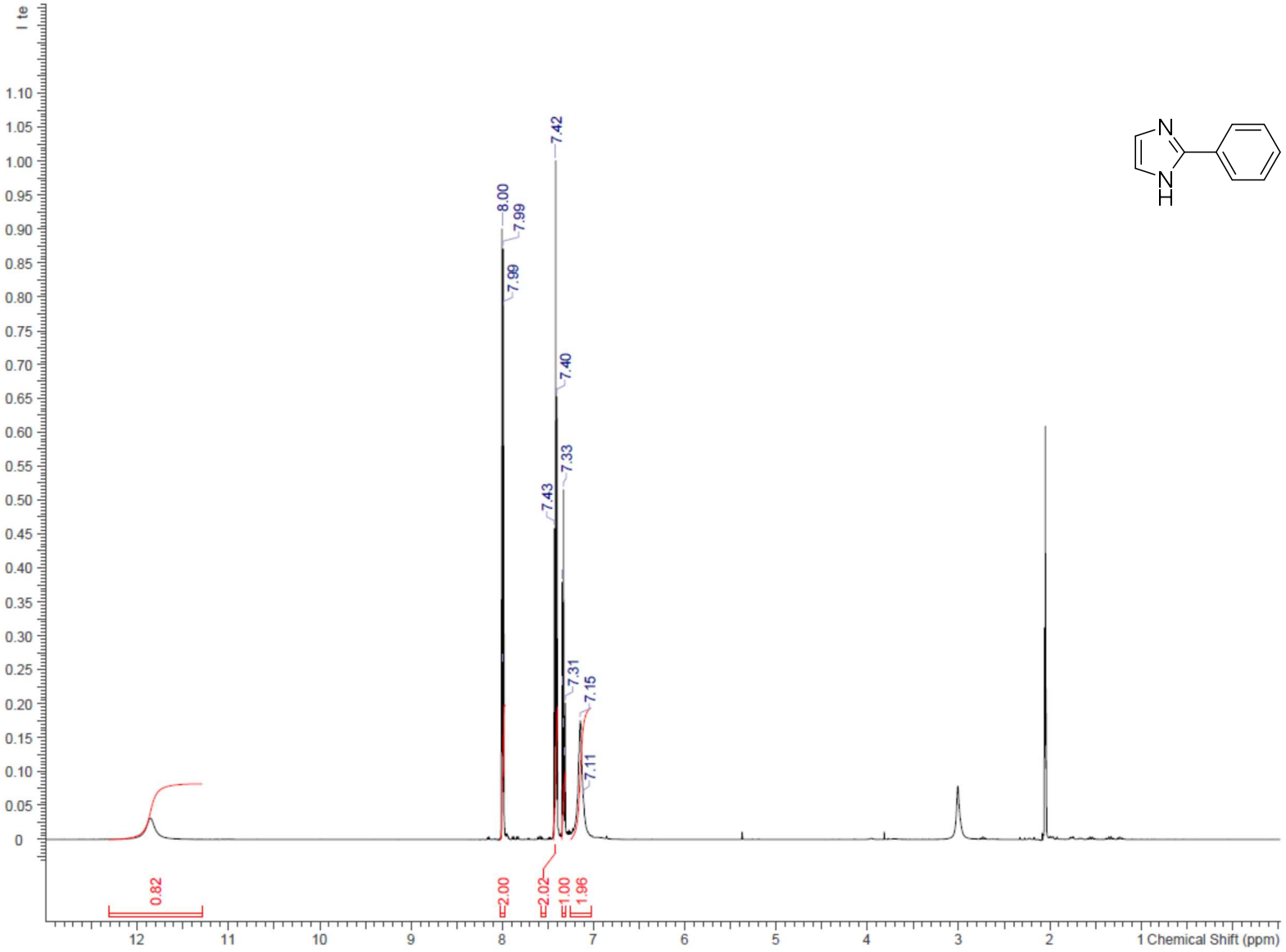

Figure S 101. ^{1}H NMR spectrum of **1n** (acetone-d_6)

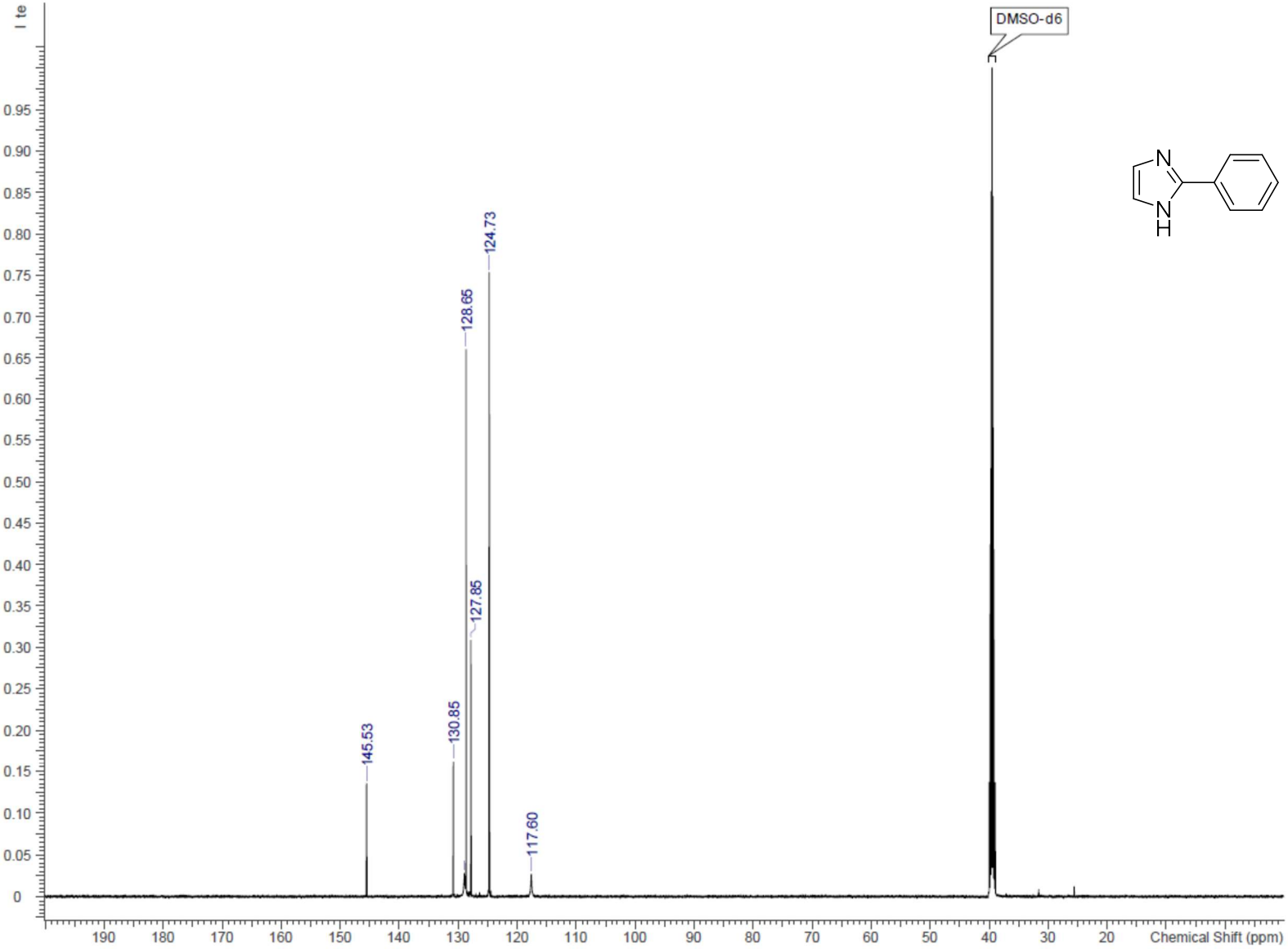

Figure S 102. ^{13}C NMR spectrum of **1n** (DMSO-d_6)

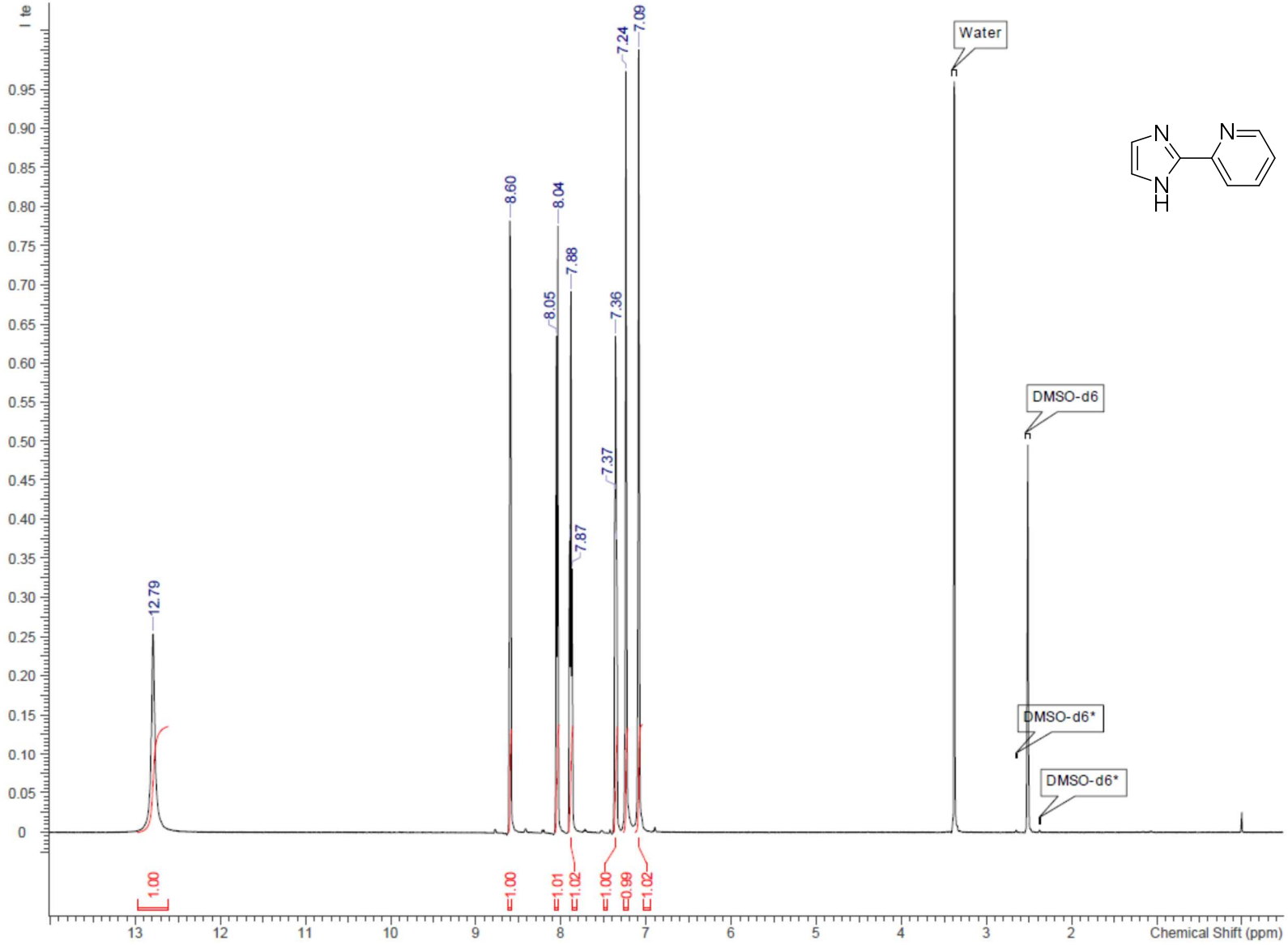

Figure S 103. ^{1}H NMR spectrum of **1o** (DMSO-d_6)

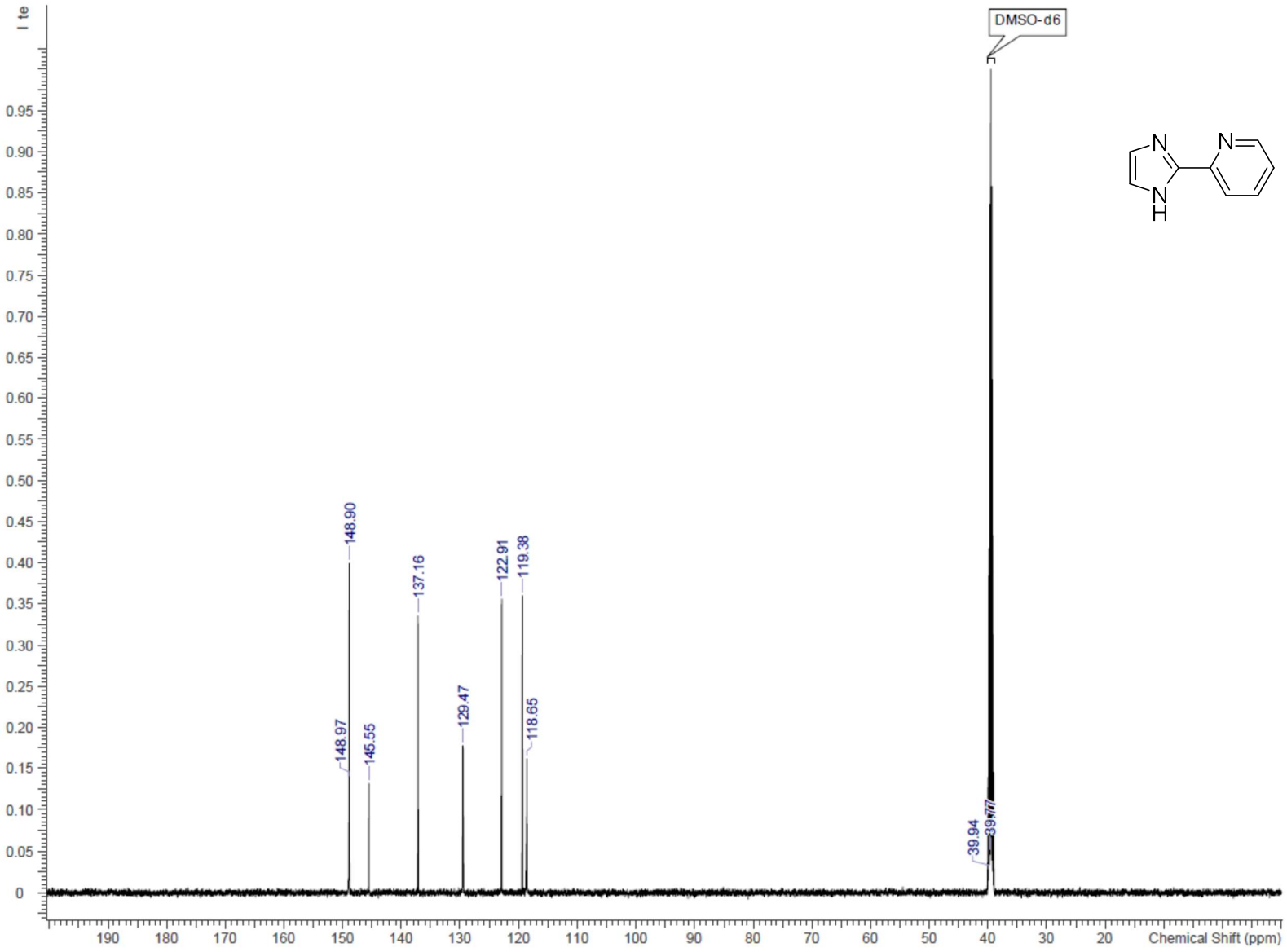

Figure S 104. ^{13}C NMR spectrum of **1o** (DMSO-d_6)

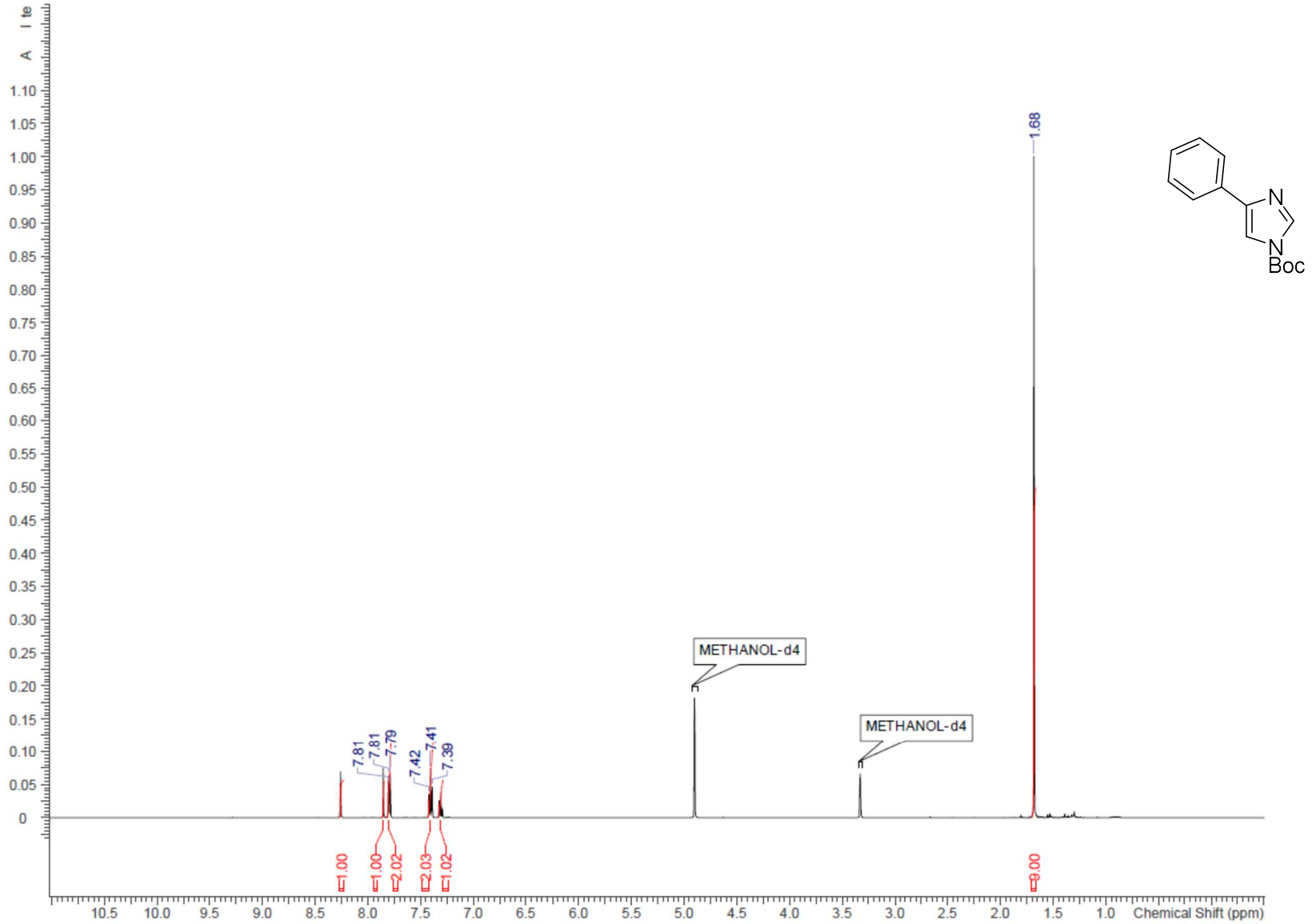

Figure S 105. ^{1}H NMR spectrum of **1a-Boc** (CD_3OD)

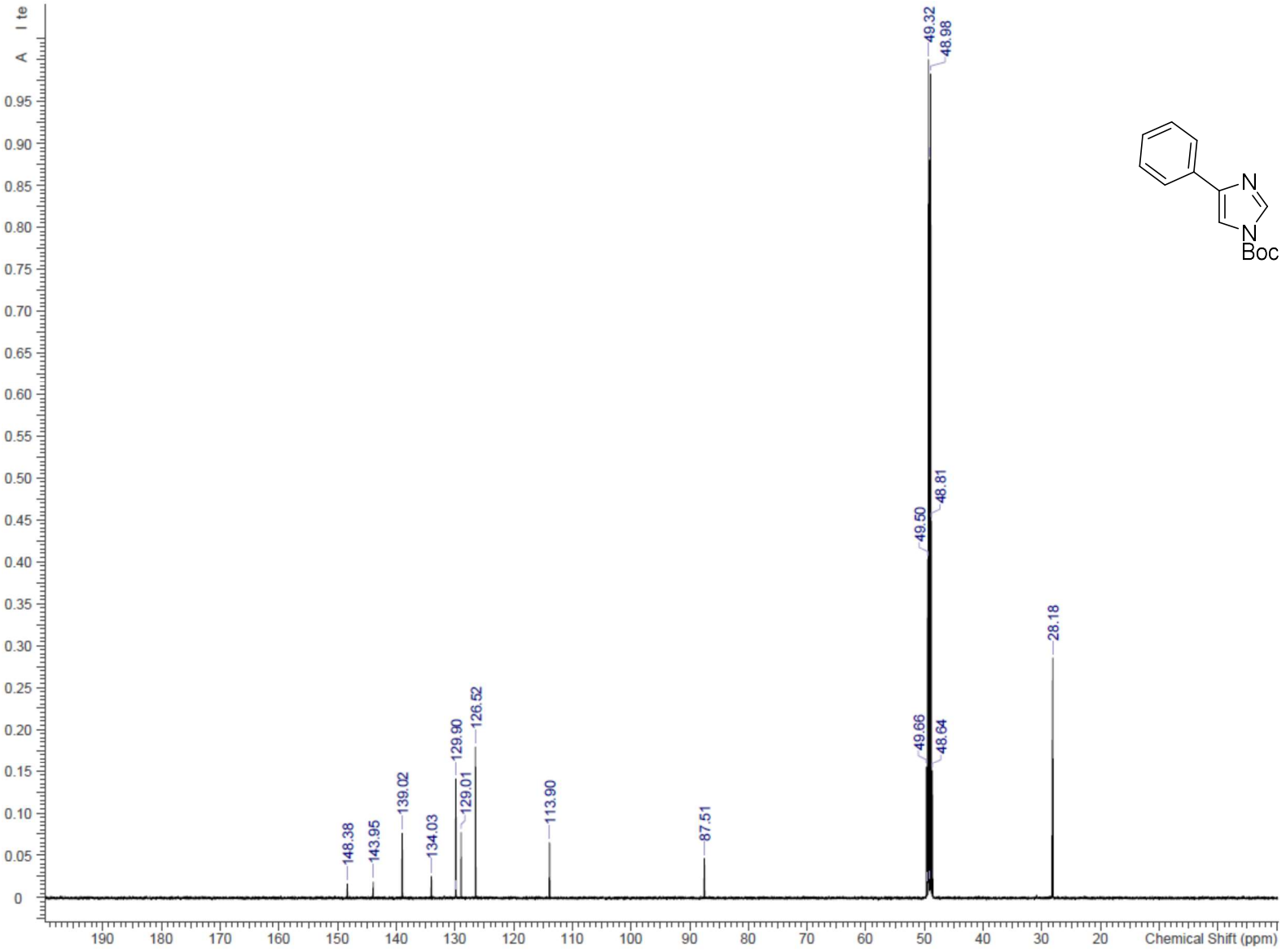

Figure S 106. ^{13}C NMR spectrum of **1a-Boc** (CD_3OD)

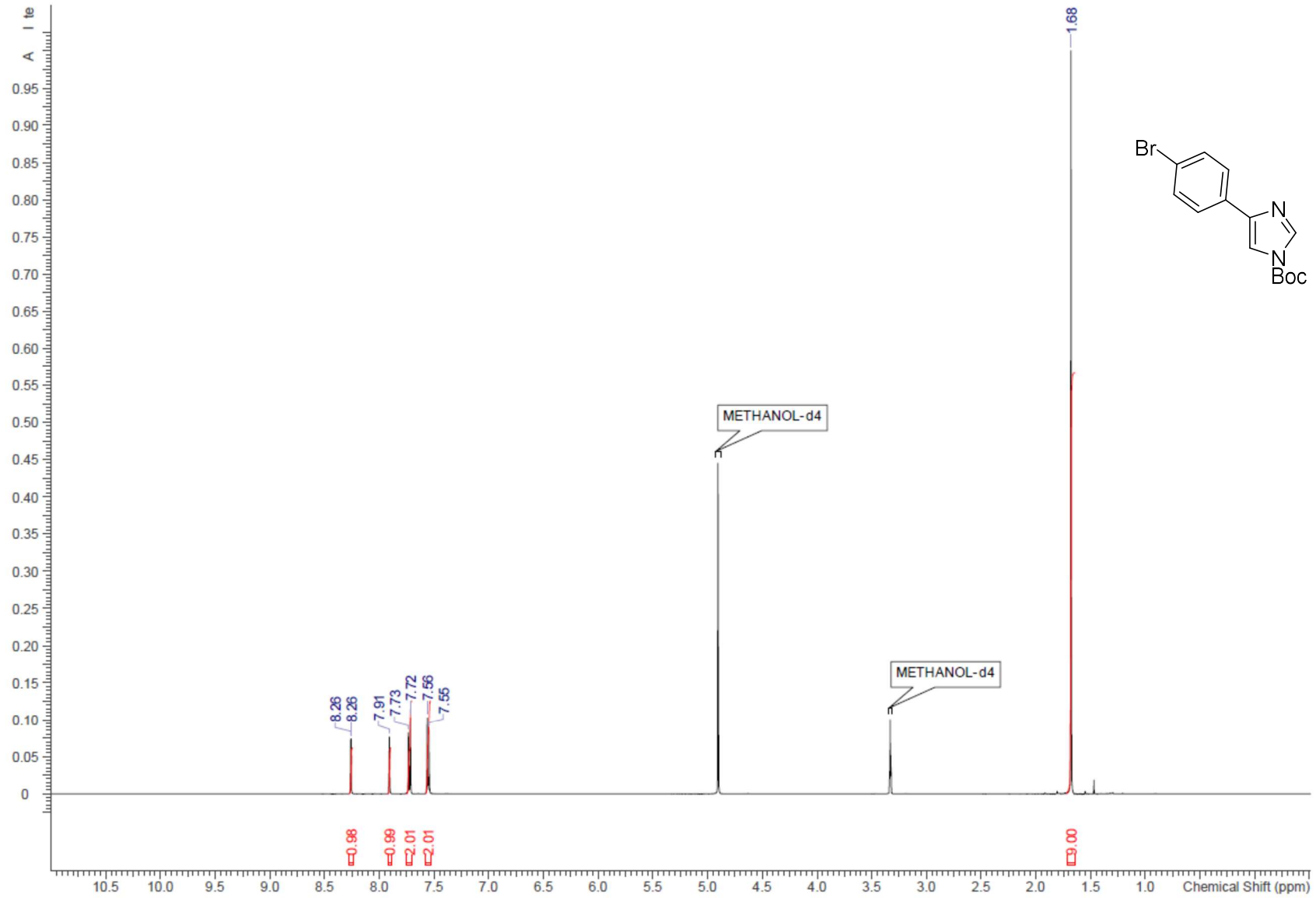

Figure S 107. ^{1}H NMR spectrum of **1c-Boc** (CD_3OD)

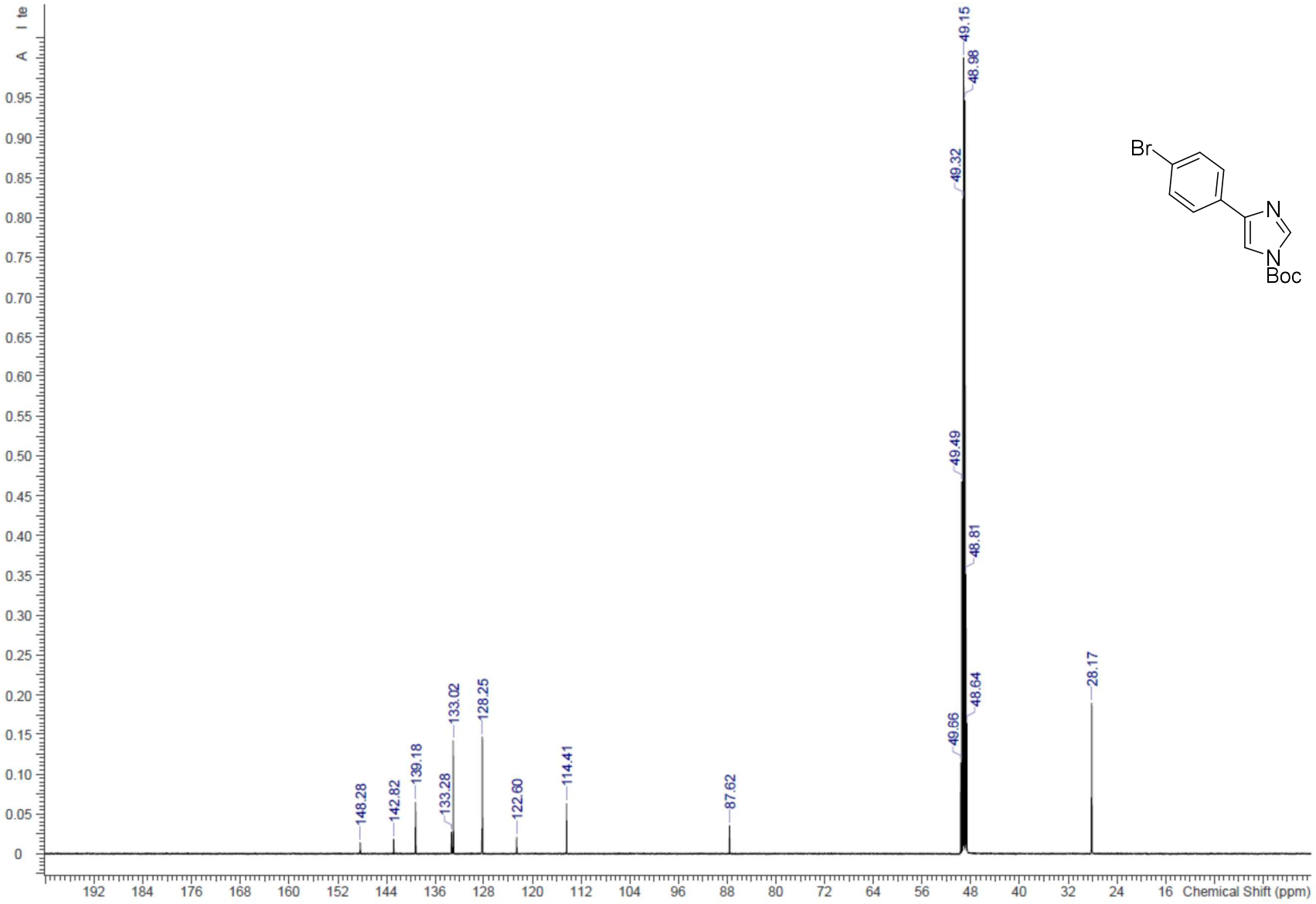

Figure S 108. ^{13}C NMR spectrum of **1c-Boc** (CD_3OD)

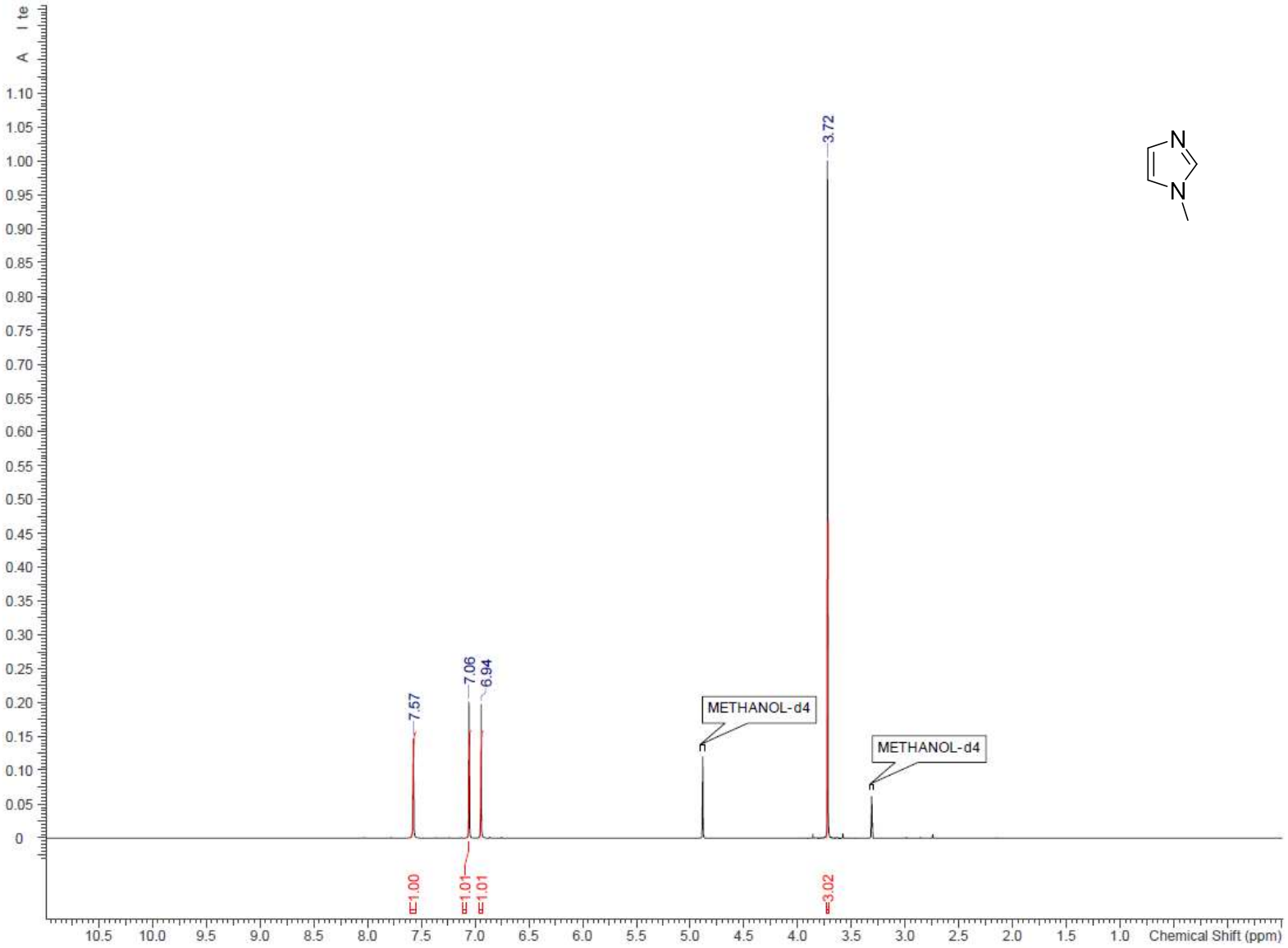

Figure S 109. ^{1}H NMR spectrum of **1g-Me** (CD_3OD)

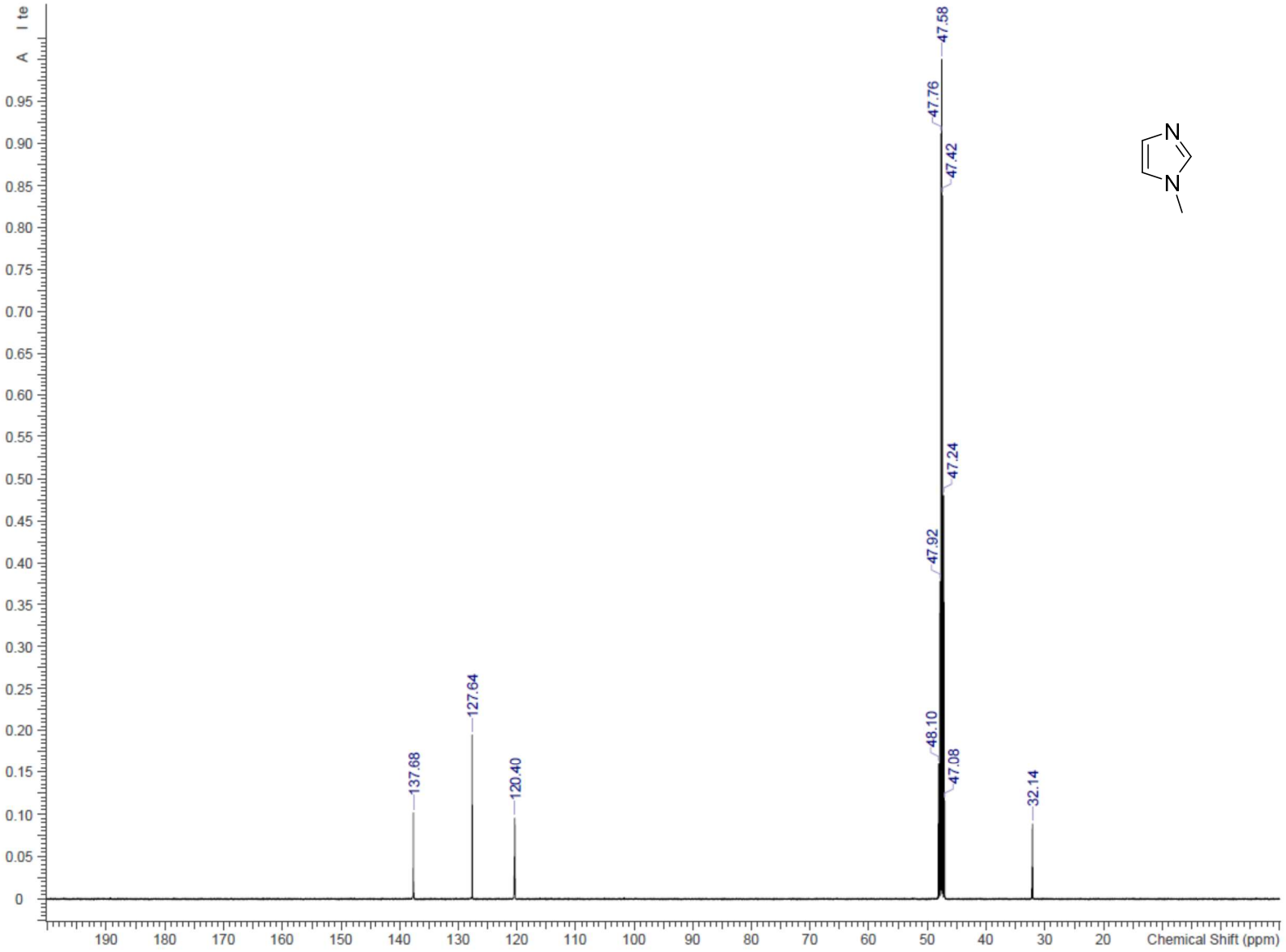

Figure S 110. ^{13}C NMR spectrum of **1g-Me** (CD_3OD)

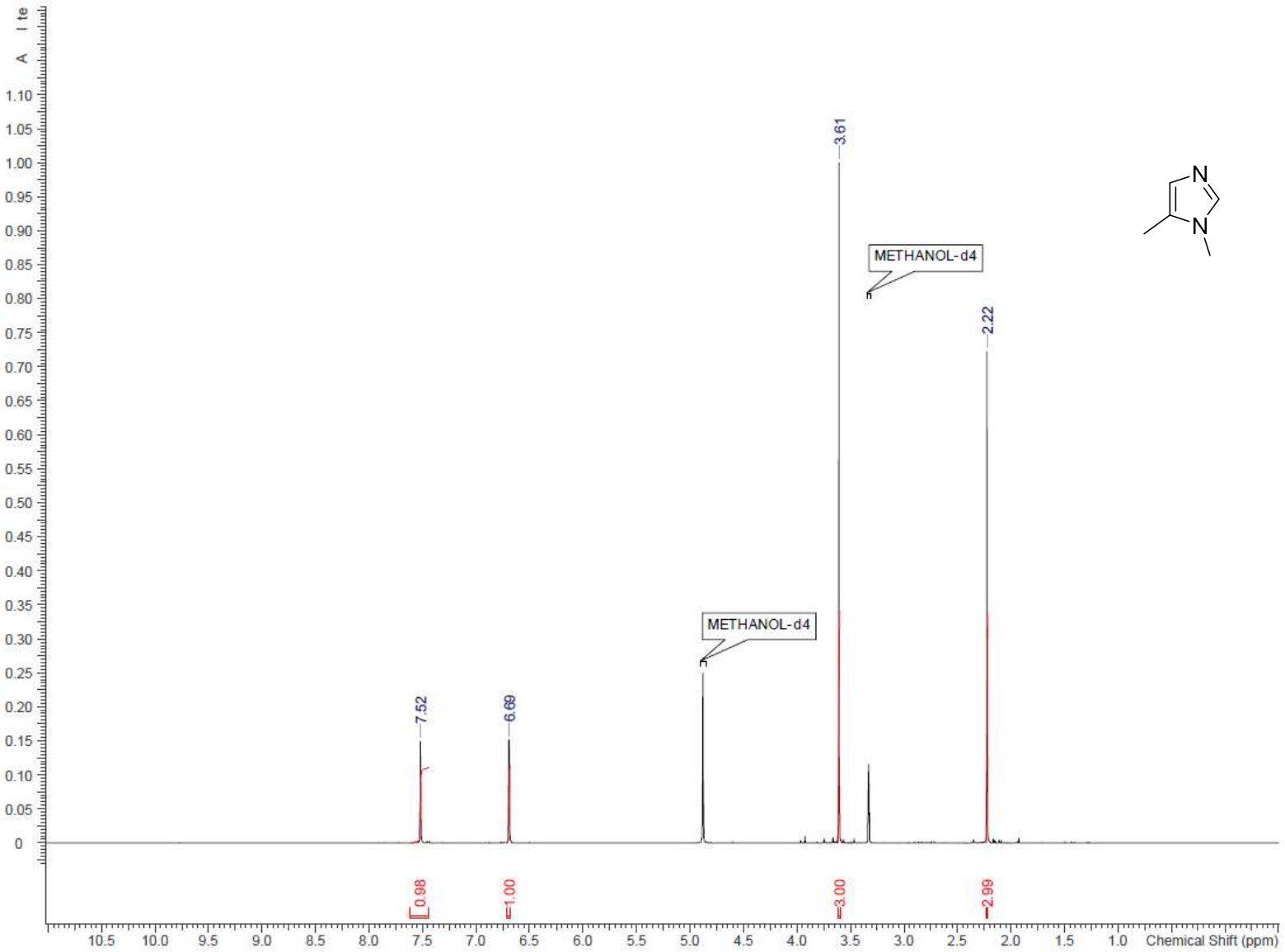

Figure S 111. ^{1}H NMR spectrum of **1p** (CD_3OD)

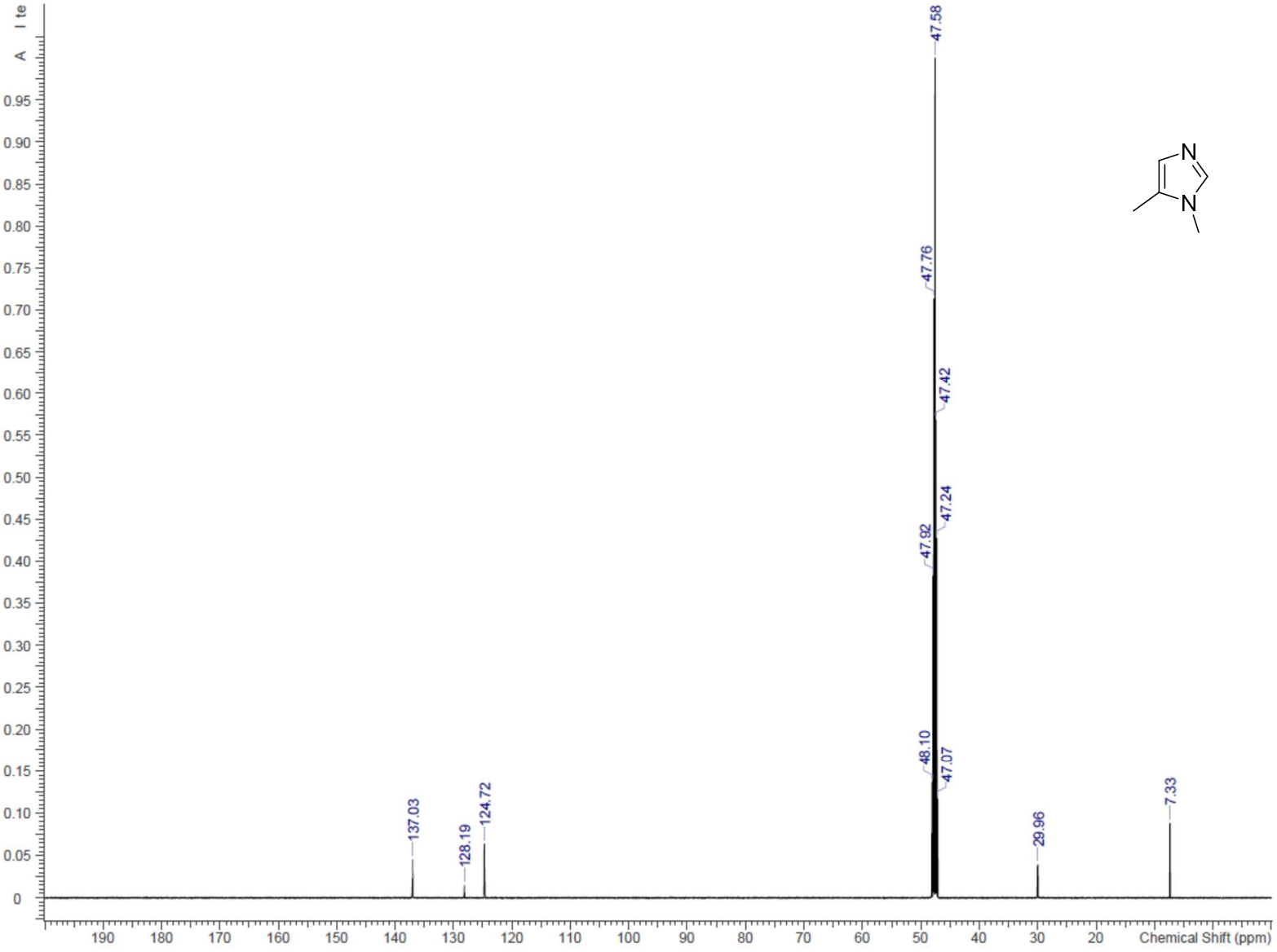

Figure S 112. ^{13}C NMR spectrum of **1p** (CD_3OD)

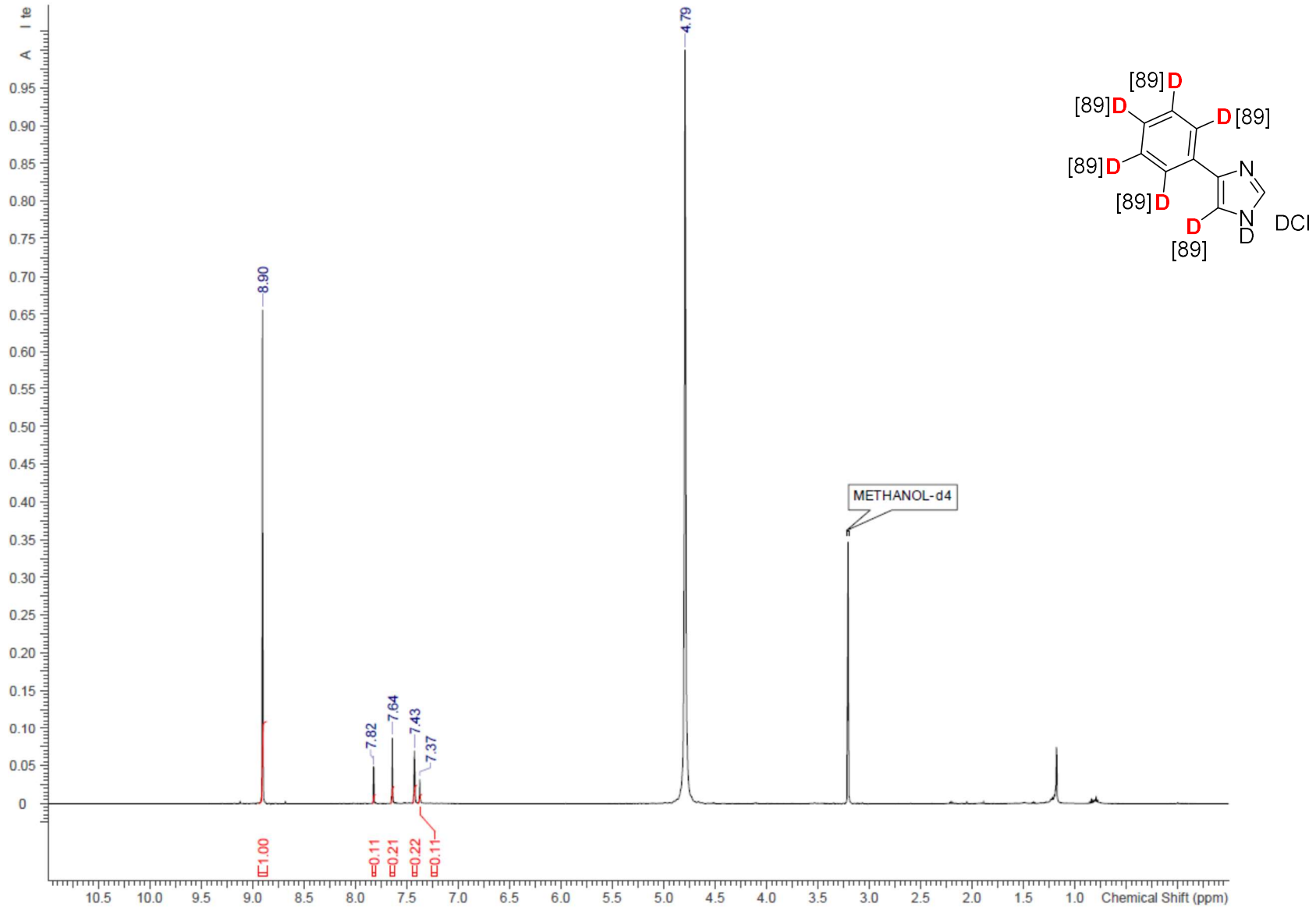

Figure S 113. ^{1}H NMR spectrum of **2a'** (CD_3OD)

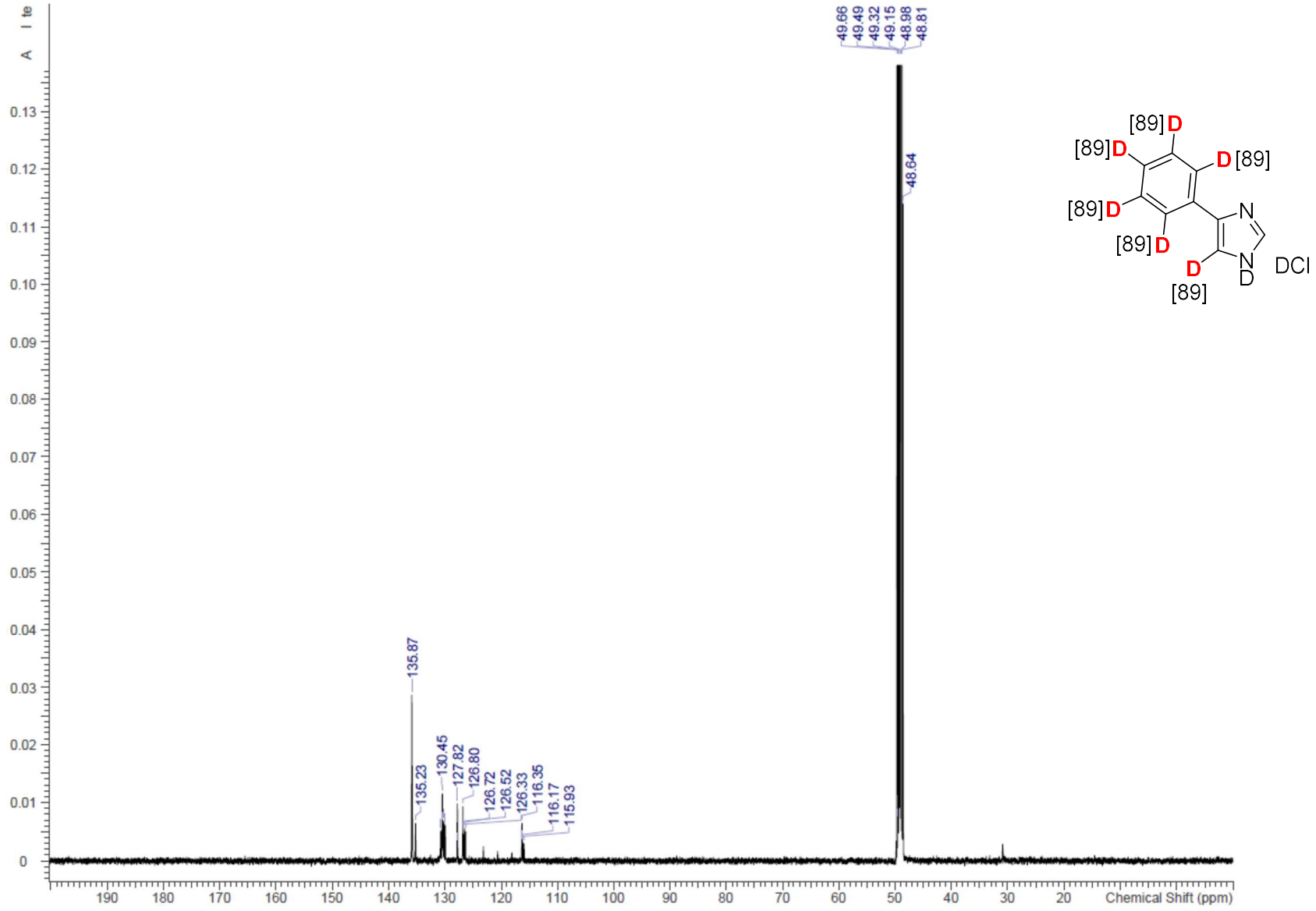

Figure S 114. ^{13}C NMR spectrum of **2a'** (CD_3OD)

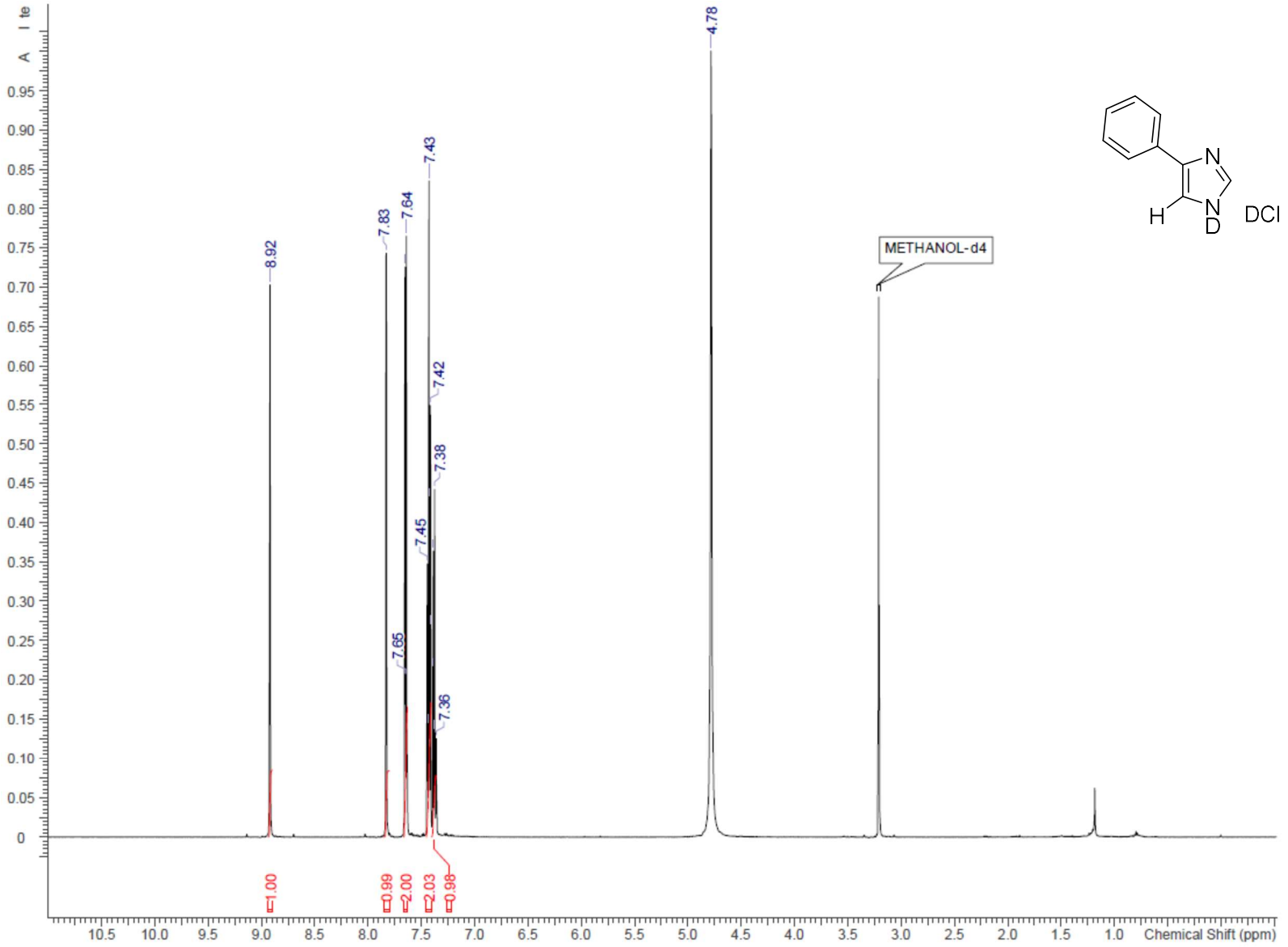

Figure S 115. ^{1}H NMR spectrum of **2a"** (CD_3OD)

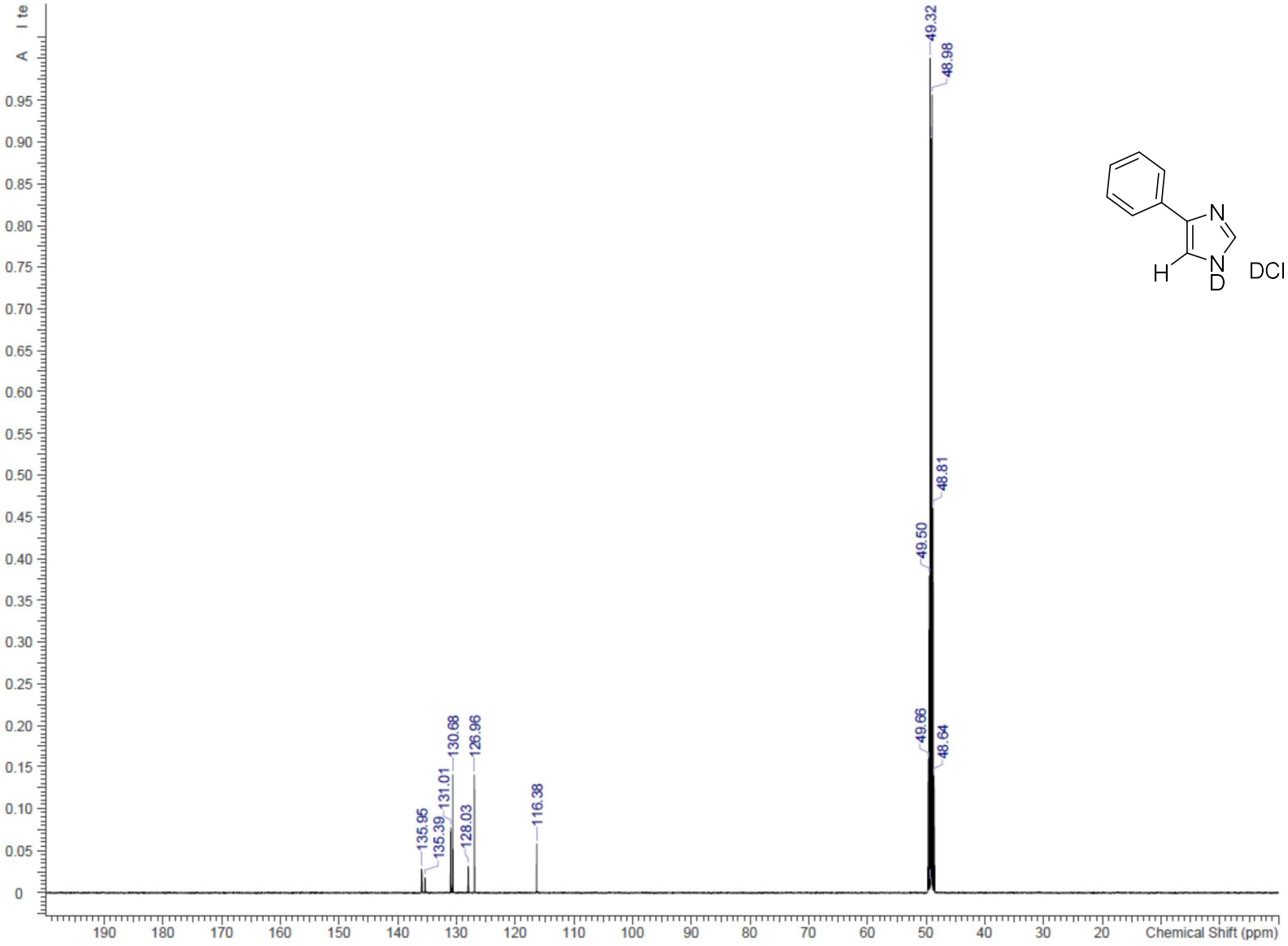

Figure S 116. ^{13}C NMR spectrum of **2a"** (CD_3OD)

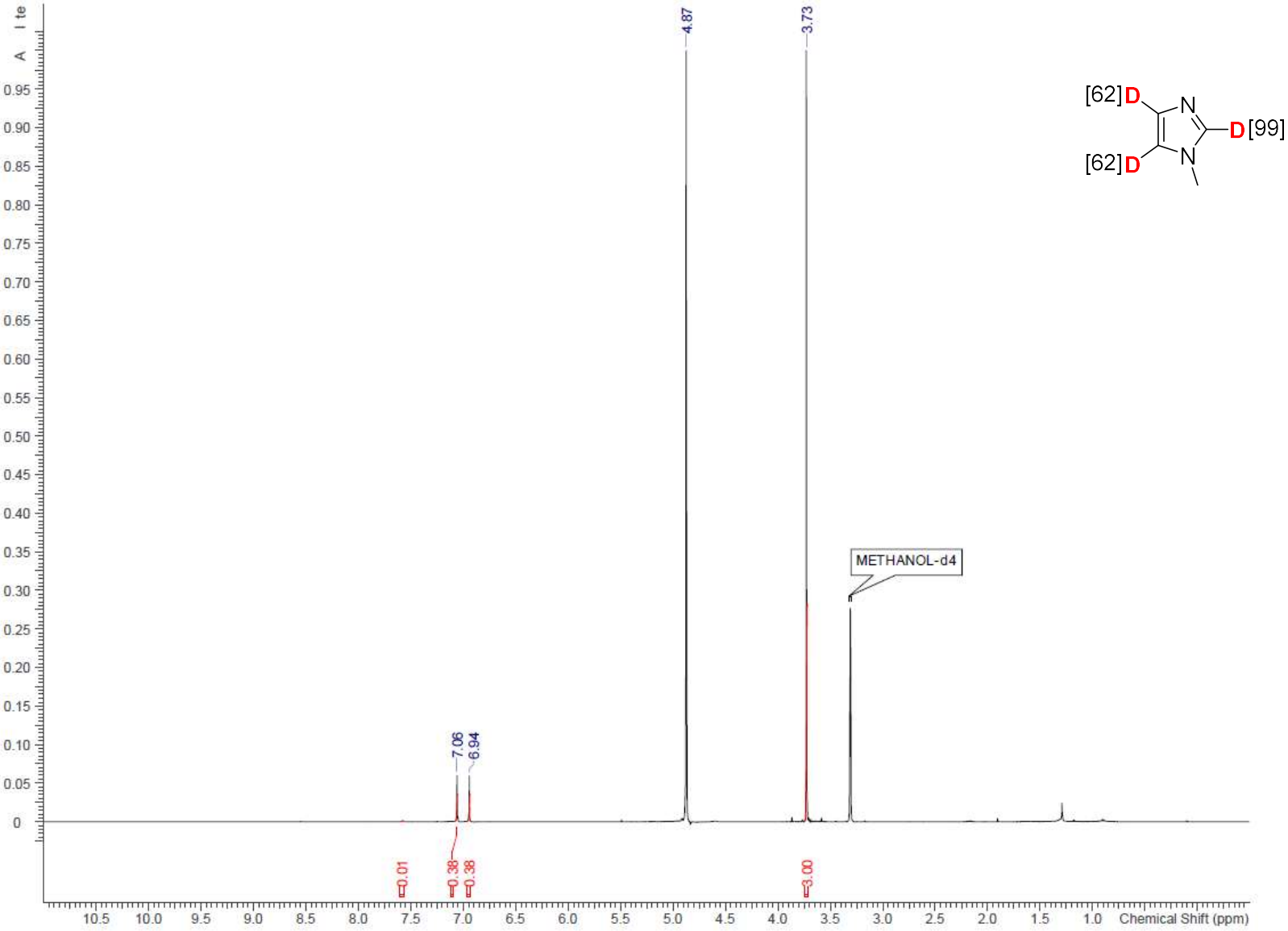

Figure S 117. ^{1}H NMR spectrum of **3g-Me** (CD_3OD)

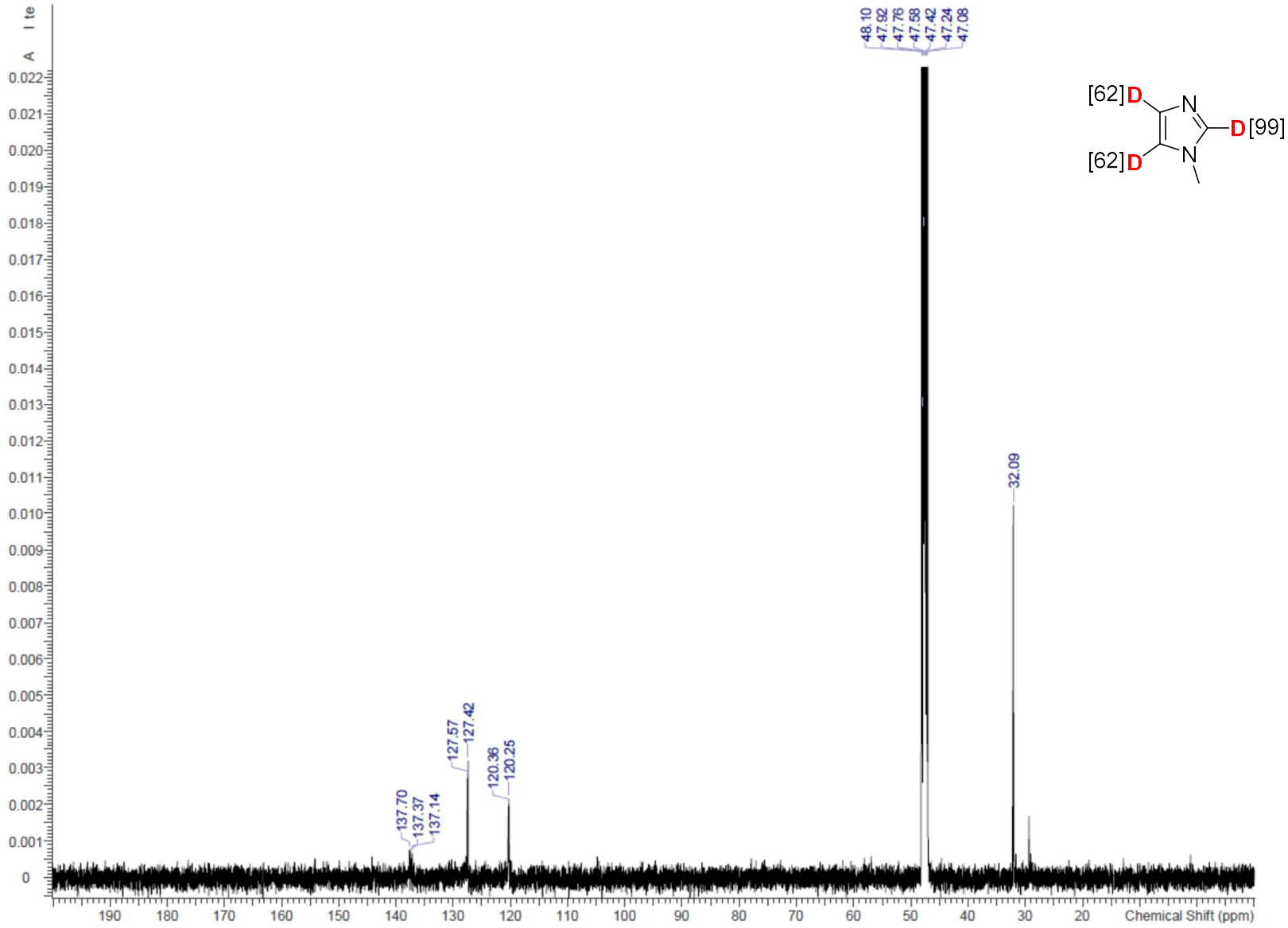

Figure S 118. ^{13}C NMR spectrum of **3g-Me** (CD_3OD)

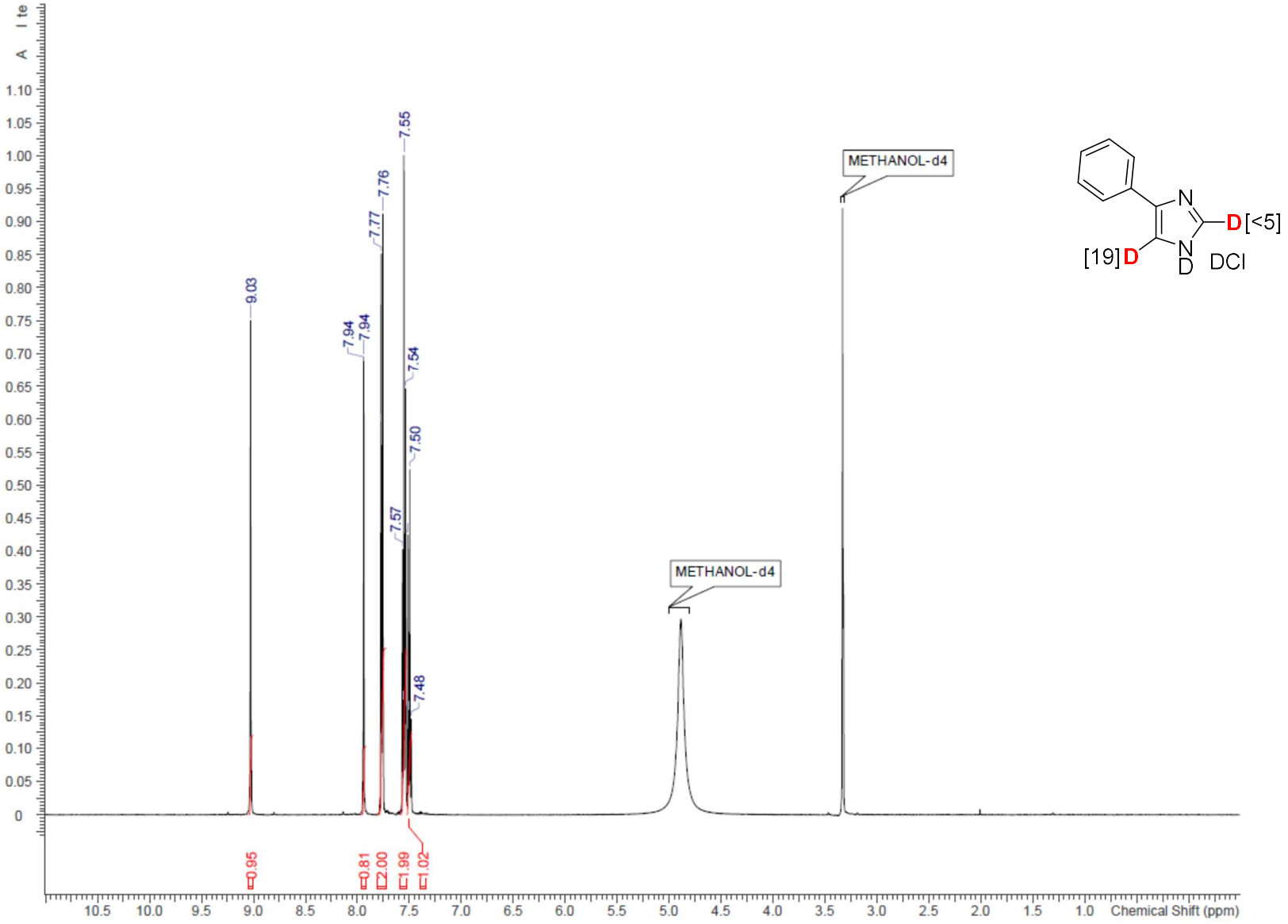

Figure S 119. ^{1}H NMR spectrum from the reaction of **1a** using 1 M DCl (in D_2O) (Scheme S3) (CD_3OD)

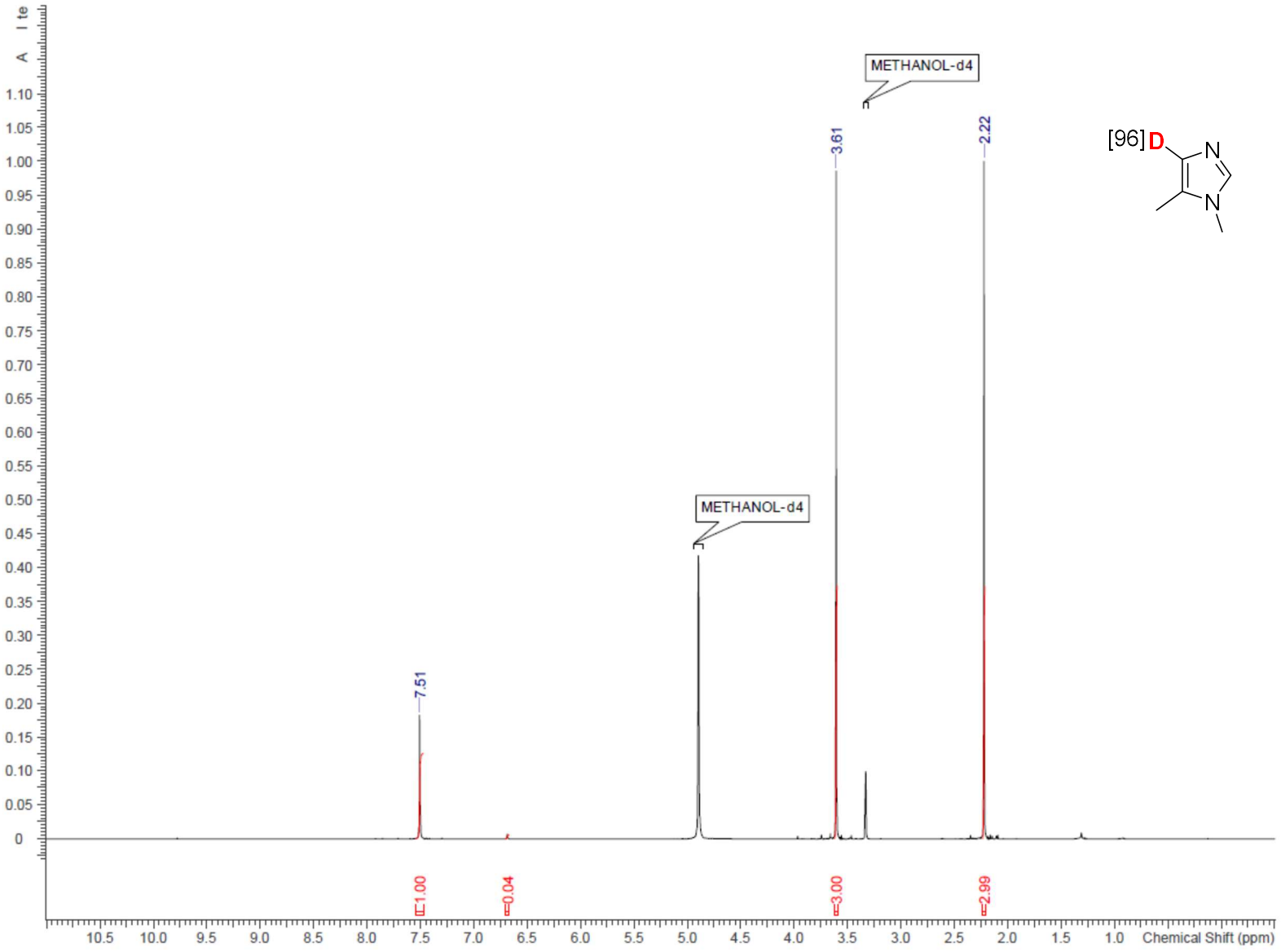

Figure S 120. ^{1}H NMR spectrum of **2p** (CD_3OD)

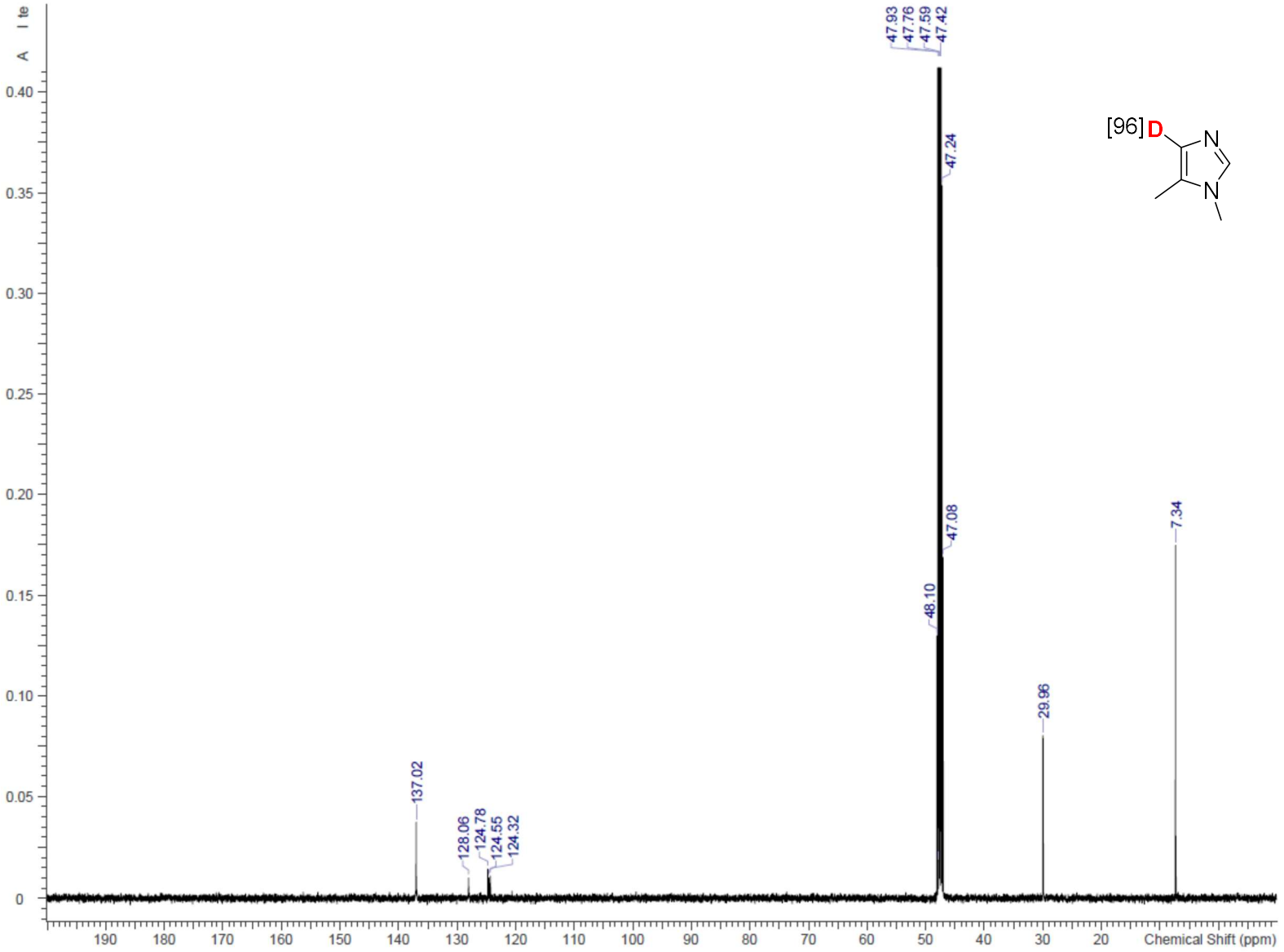

Figure S 121. ^{13}C NMR spectrum of **2p** (CD_3OD)

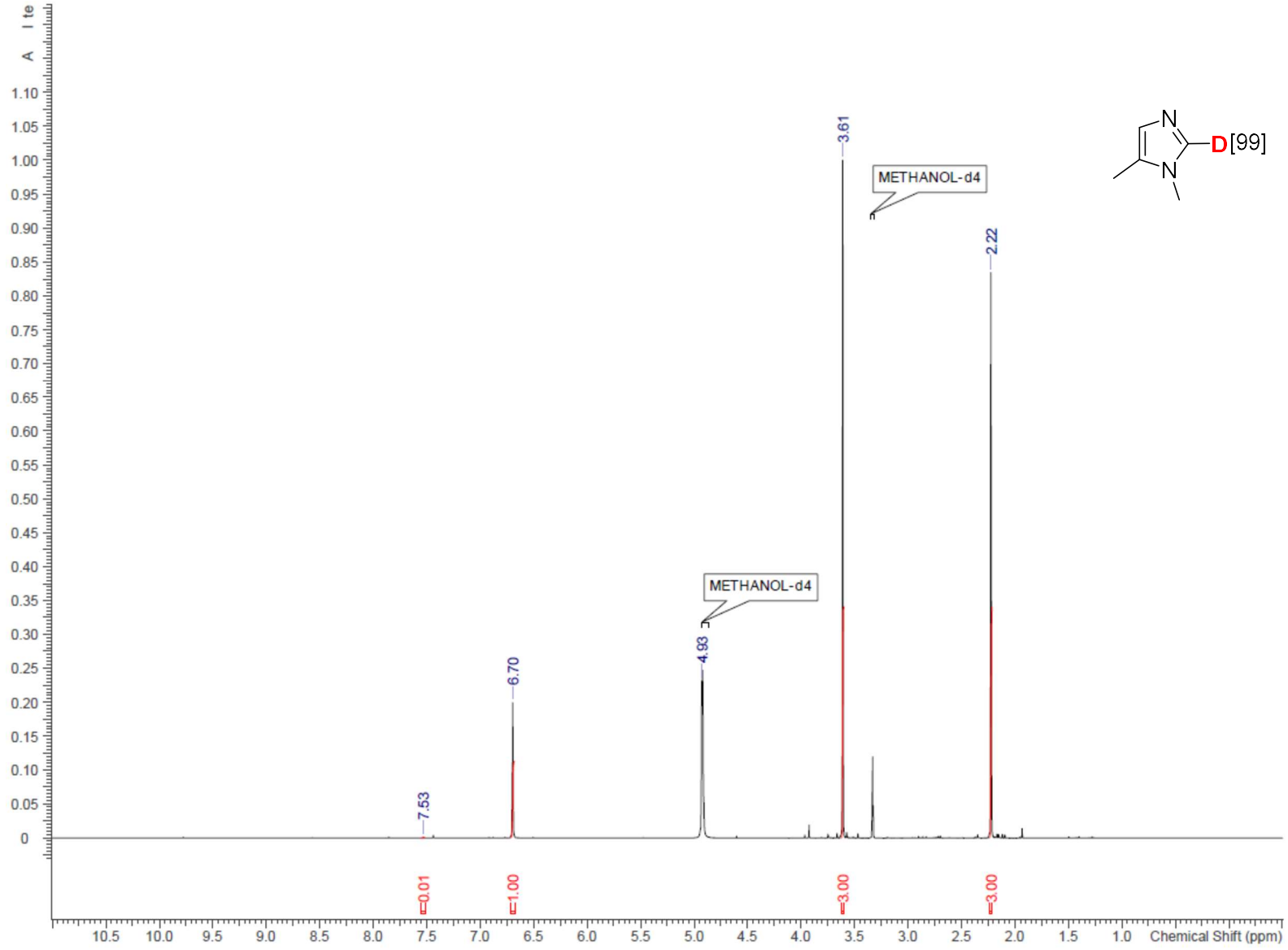

Figure S 122. ^{1}H NMR spectrum of **4p** (CD_3OD)

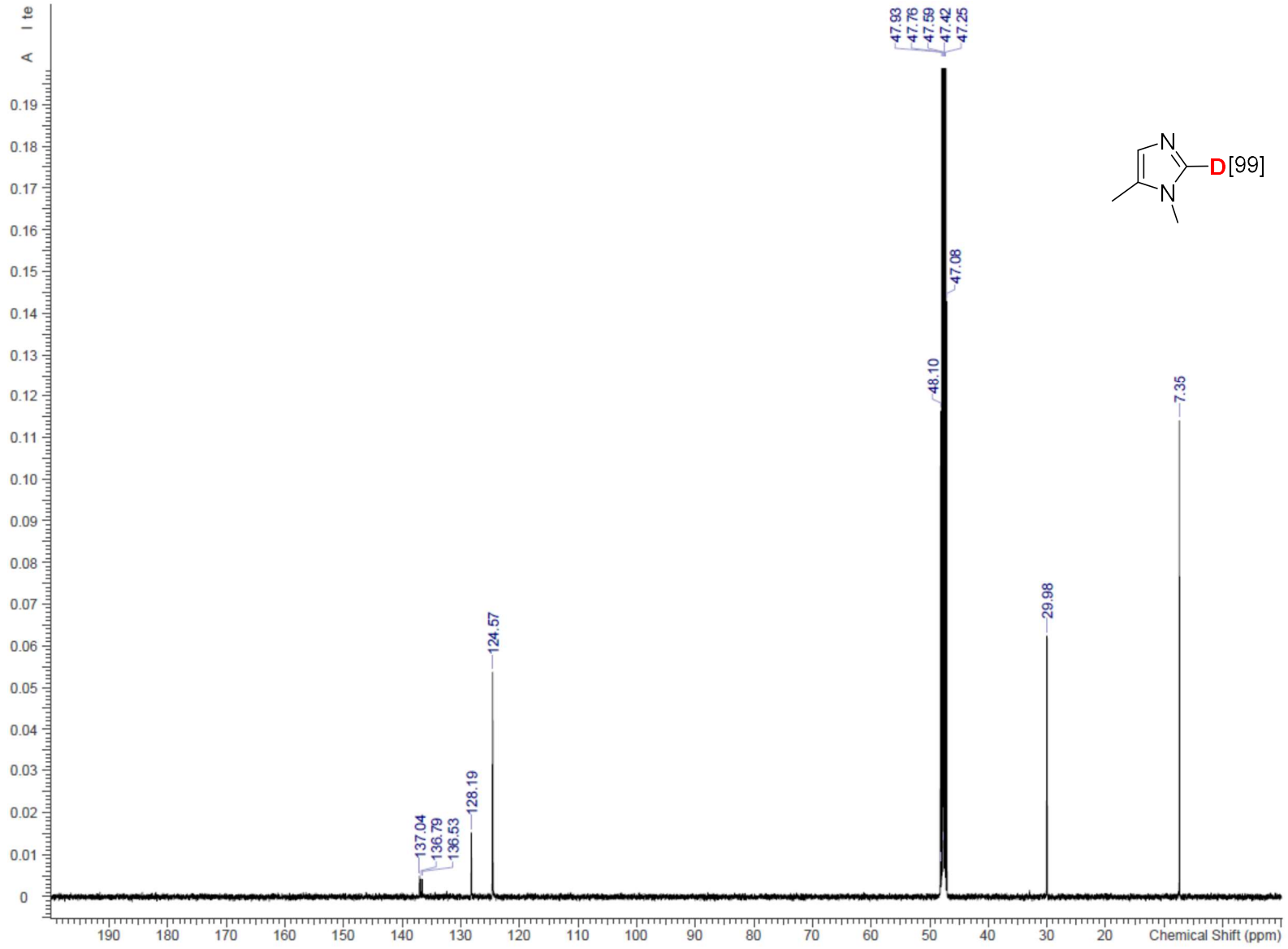

Figure S 123. ^{13}C NMR spectrum of **4p** (CD_3OD)

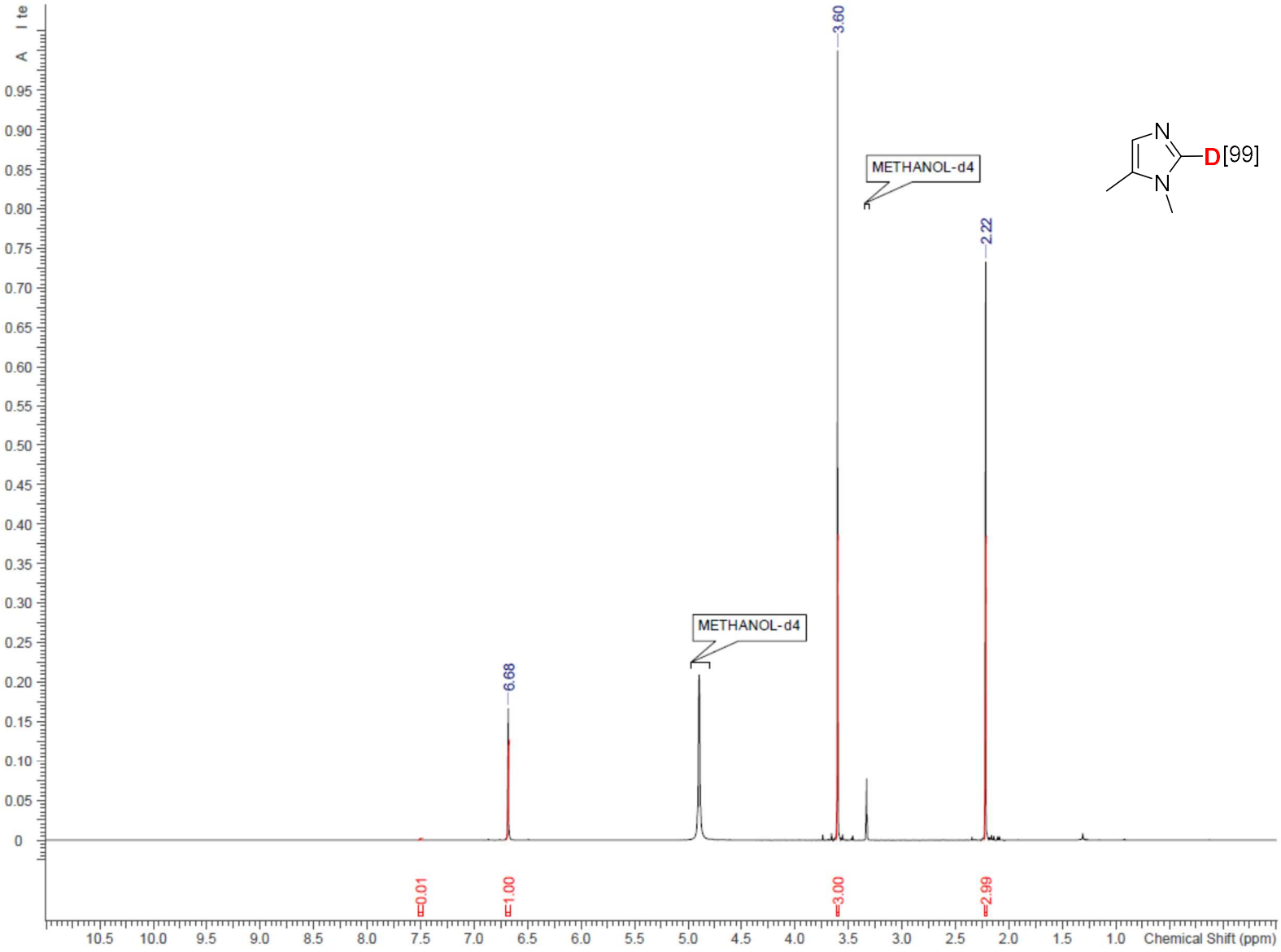

Figure S 124. ^{1}H NMR spectrum of **3p (C4-H)** (CD_3OD)

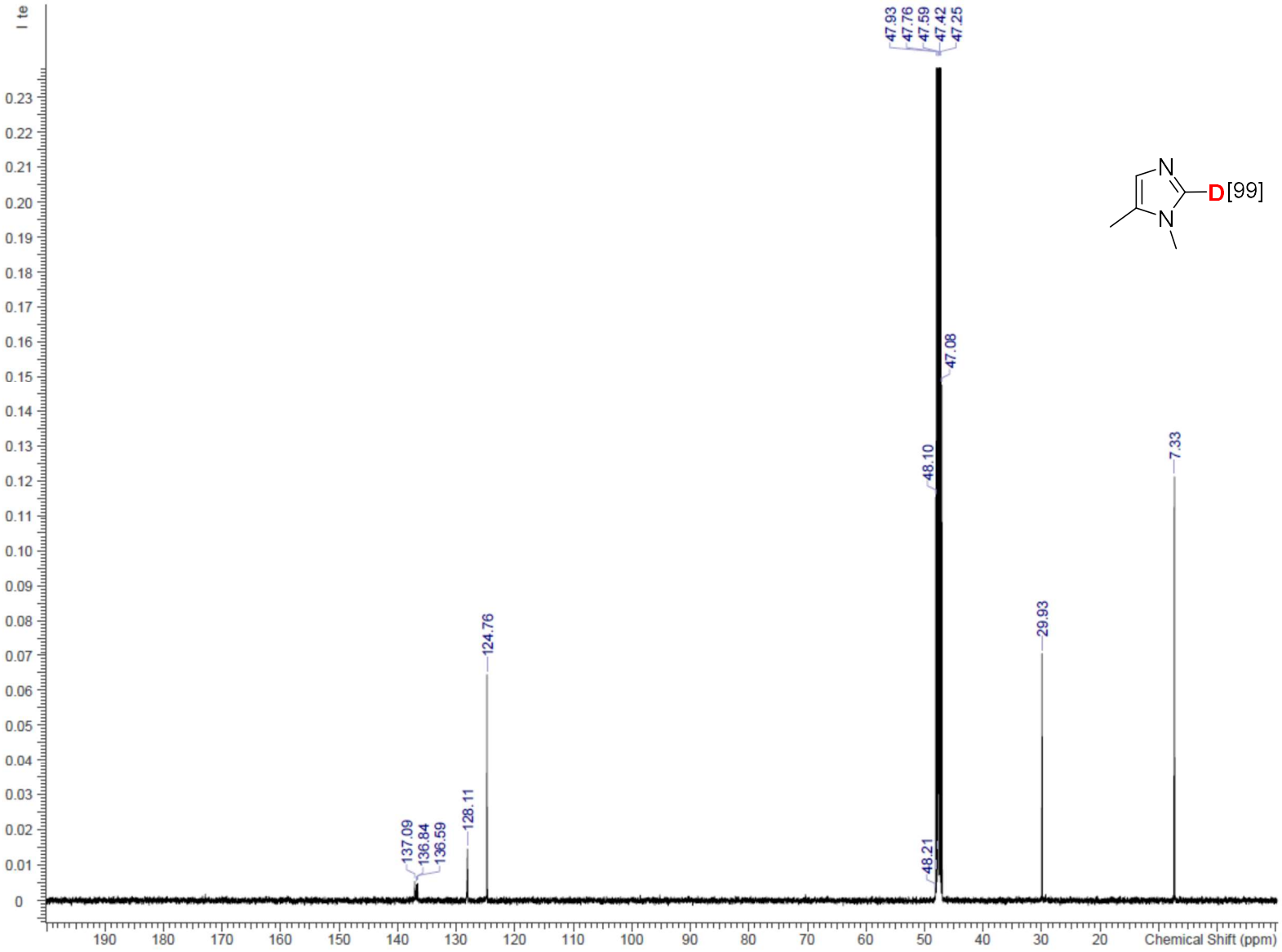

Figure S 125. ^{13}C NMR spectrum of **3p (C4-H)** (CD_3OD)