Supporting Information for:

A rapid and efficient assay for the characterization of substrates and inhibitors of nicotinamide *N*-methyltransferase

Matthijs J. van Haren,[a] Javier Sastre Toraño,[a] Davide Sartini,[b] Monica Emanuelli,[b] Richard B. Parsons[c], Nathaniel I. Martin[a,*]

[a]Department of Chemical Biology & Drug Discovery, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands
[b]Department of Clinical Sciences, Universitá Politecnica delle Marche, Ancona, Italy
[c]Institute of Pharmaceutical Science, King's College London, London SE1 9NH, UK

Department of Chemical Biology & Drug Discovery,
Utrecht Institute for Pharmaceutical Sciences, Utrecht University,
David de Wied Building, Office: 5.64, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands.

n.i.martin@uu.nl

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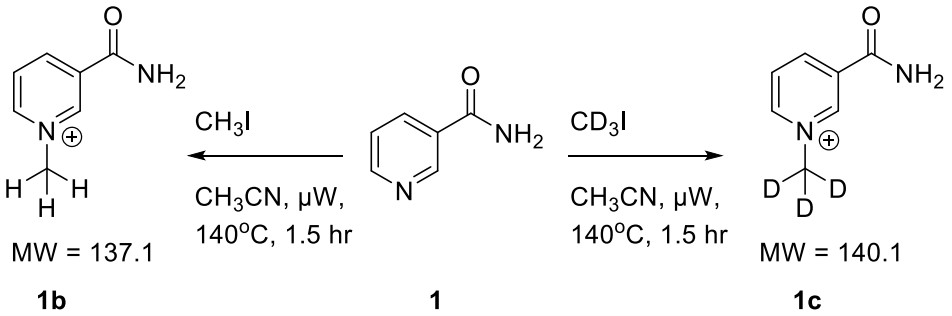
General procedures

Reagents and Instrumentation for characterization

All reagents employed were of American Chemical Society (ACS) grade or finer and were used without further purification unless otherwise stated. For compound characterization ^{1}H NMR spectra were recorded at 400 MHz with chemical shifts reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS), H_2O (δ 4.79) or DMSO (δ 2.50). ^{1}H NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet and m, multiplet), coupling constant (J) in hertz (Hz) and the number of protons. Where appropriate, the multiplicity is preceded by br, indicating that the signal was broad. ^{13}C NMR spectra were recorded at 101 MHz with chemical shifts reported relative to $CDCl_3$ (δ 77.16) or DMSO (δ 39.52). The ^{13}C NMR spectra of the compounds recorded in D_2O could not be referenced. High-resolution mass spectrometry (HRMS) analysis was performed using a Q-TOF instrument.

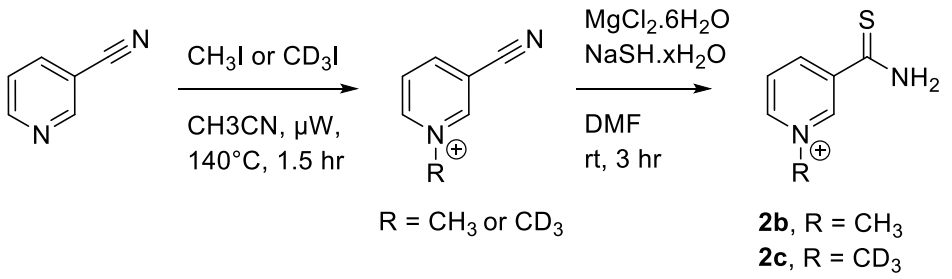
General procedure for the synthesis of reference standards and internal standards



Scheme S1. General procedure used for the synthesis of reference standards (using methyl iodide), and internal standards (using trideuteromethyl iodide).

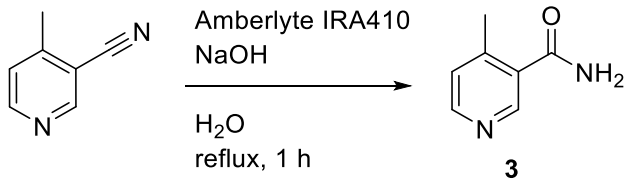
Substrate (1.0 eq, 1.0 mmol) is dissolved in 2 mL dry CH_3CN and methyl iodide (2.2 eq, 2.2 mmol, 312 mg) or d_3-methyl iodide (2.2 eq, 2.2 mmol, 319 mg) is added. The tube is sealed and reacted in a microwave for 90 minutes at 140°C. If necessary, the product is precipitated with dry diethyl ether. The precipitate is filtered off and washed with dry diethyl ether.

Standards prepared via alternate procedures



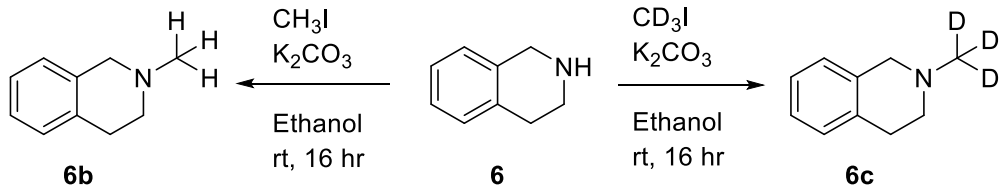
Scheme S2. Synthesis of thionicotinamide from *N'*-methyl-3-pyridinecarbonitrile

N'-methyl-thionicotinamide **2b** and *N'*-d_3-methyl-thionicotinamide **2c** were synthesized from 3-pyridinecarbonitrile, which was first methylated using the general procedure and subsequently thionated using sodium hydrosulphide following a literature procedure.[2]



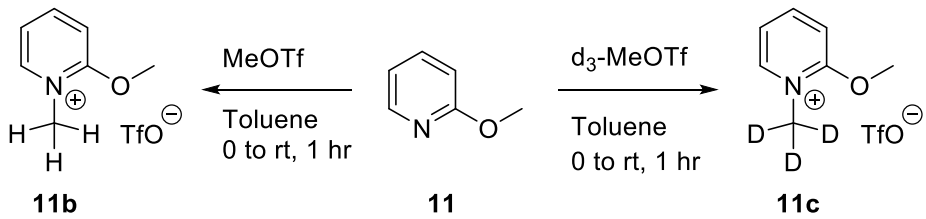
Scheme S3. Synthesis of 4-methylnicotinamide by alkaline hydrogenolysis using Amberlyte IRA410 resin

4-methylnicotinamide **3** is prepared by alkaline hydrogenolysis of 4-methyl-3-cyanopyridine using alkaline ion-exchange resin Amberlite IRA 410 as previously described.[1] The standards of **3** are prepared using the general procedure.



Scheme S4. Synthesis of the standards of 1,2,3,4-tetrahydroisoquinoline

1,2,3,4-tetrahydroisoquinoline **6** is methylated using methyl iodide or d_3-methyl iodide and potassium carbonate in ethanol at room temperature overnight and subsequent purification by column chromatography.

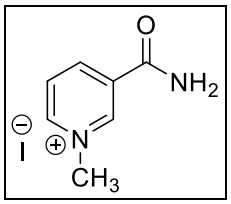


Scheme S5. Synthesis of the standards of 2-methoxypyridine using methyltriflate

N-methyl-2-methoxypyridine **11b** was synthesized by reaction with methyl triflate as previously described.[3] *N*-d_3-methyl-2-methoxypyridine **11c** was synthesized in a similar manner by reaction with d_3-methyl triflate, which was freshly prepared from d_3-methyl iodide and silver triflate.

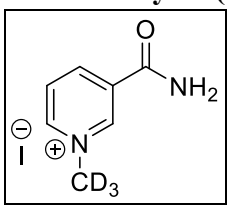
Experimental details and analytical data for compounds 1-11

3-carbamoyl-1-methylpyridin-1-ium iodide 1b



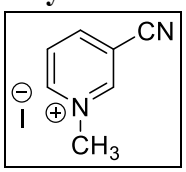
Obtained from commercial sources.

3-carbamoyl-1-(methyl-d3)pyridin-1-ium iodide 1c



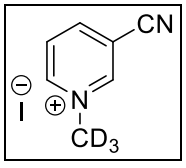
Synthesized according to the general procedure.
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 9.07 (d, J = 5.9 Hz, 1H), 8.87 (d, J = 8.0 Hz, 1H), 8.47 (s, 1H), 8.21 (t, J = 7.0 Hz, 1H), 8.10 (s, 1H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 163.26, 147.60, 146.10, 143.26, 133.70, 127.83
HRMS (ESI): calculated for $C_7H_6D_3N_2O^+$ 140.0898, found 140.0883.

3-cyano-1-methylpyridin-1-ium iodide



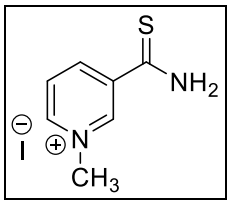
Synthesized according to the general procedure.
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 9.25 (d, J = 5.4 Hz, 1H), 9.07 (d, J = 7.9 Hz, 1H), 8.34 (t, J = 6.7 Hz, 1H), 4.37 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 149.69, 149.08, 148.07, 127.95, 113.87, 112.11, 48.61.
HRMS (ESI): calculated for $C_7H_7N_2^+$ 119.0604, found 119.0615.

3-cyano-1-(methyl-d3)pyridin-1-ium iodide



Synthesized according to the general procedure.
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 9.25 (d, J = 5.3 Hz, 1H), 9.07 (d, J = 7.6 Hz, 1H), 8.34 (t, J = 6.4 Hz, 1H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 149.73, 149.08, 148.09, 127.95, 113.87, 112.11.
HRMS (ESI): calculated for $C_7H_4D_3N_2^+$ 122.0792, found 122.0810.

3-carbamothioyl-1-methylpyridin-1-ium iodide 2b



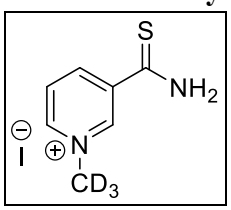
1-methyl-3-cyanopyridinium iodide (246 mg, 1.0 mmol, 1.0 eq) is added to a slurry of $NaSH.xH_2O$ (240 mg, 3.0 mmol, 3.0 eq, 70% NaSH) and $MgCl_2.6H_2O$ (305 mg, 1.5 mmol, 1.5 eq) in DMF (3 mL). The mixture is stirred for 3 hours at room temperature. The precipitate is filtered off and the mixture is concentrated under vacuum. The residue is dissolved in water, filtered and freeze dried yielding the **2b** as an orange red solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75-10.05 (m, 2H), 9.44 (s, 1H), 9.05 (d, J = 5.9 Hz, 1H), 8.83 (d, J = 8.4 Hz, 1H), 8.16 (t, J = 7.1 Hz, 1H), 4.39 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 192.72, 146.44, 144.69, 141.95, 138.27, 126.91, 48.21.

HRMS (ESI): calculated for $C_7H_9N_2S^+$ 153.0481, found 153.0449.

3-carbamothioyl-1-(methyl-d3)pyridin-1-ium iodide 2c



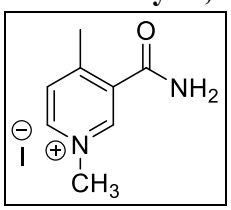
Prepared as described for compound **2b**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75-10.05 (m, 2H), 9.43 (s, 1H), 9.05 (d, J = 6.1 Hz, 1H), 8.83 (d, J = 8.4 Hz, 1H), 8.16 (dd, J = 8.0, 6.3 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 192.70, 146.44, 144.75, 141.95, 138.31, 126.92.

HRMS (ESI): calculated for $C_7H_6D_3N_2S^+$ 156.0669, found 156.0626.

3-carbamoyl-1,4-dimethylpyridin-1-ium iodide 3b



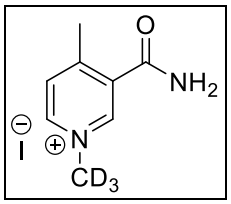
Synthesized according to the general procedure.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.87 (d, J = 6.2 Hz, 1H), 8.19 (s, 1H), 8.11 (s, 1H), 8.05 (d, J = 6.3 Hz, 1H), 4.29 (s, 2H), 2.63 (s, 2H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 164.74, 155.59, 144.77, 143.43, 135.46, 129.12, 47.23, 19.85.

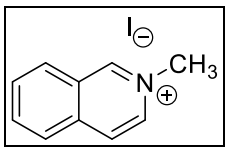
HRMS (ESI): calculated for $C_8H_{11}N_2O^+$ 151.0866, found 151.0910.

3-carbamoyl-4-methyl-1-(methyl-d3)pyridin-1-ium iodide 3c



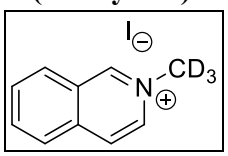
Synthesized according to the general procedure.
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.87 (d, J = 6.3 Hz, 1H), 8.20 (s, 1H), 8.11 (s, 1H), 8.05 (d, J = 6.3 Hz, 1H), 2.63 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 164.74, 155.61, 144.75, 143.42, 135.43, 129.11, 19.85.
HRMS (ESI): calculated for $C_8H_8D_3N_2O^+$ 154.1054, found 154.1077.

2-methylisoquinolin-2-ium iodide 4b



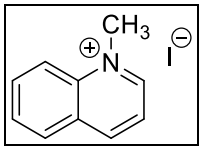
Synthesized according to the general procedure.
^{1}H NMR (400 MHz, d_2o) δ 9.61 (s, 1H), 8.42 (d, J = 6.6 Hz, 1H), 8.38 – 8.27 (m, 2H), 8.28 – 8.09 (m, 2H), 7.99 (t, J = 7.1 Hz, 1H), 4.52 (s, 3H).
^{13}C NMR (101 MHz, d_2o) δ 149.70, 137.02, 136.84, 134.79, 131.22, 129.80, 127.33, 127.04, 126.04, 47.94.
HRMS (ESI): calculated for $C_{10}H_{10}N^+$ 144.0808, found 144.0785.

2-(methyl-d3)isoquinolin-2-ium iodide 4c



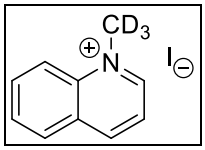
Synthesized according to the general procedure.
^{1}H NMR (400 MHz, d_2o) δ 9.62 (s, 1H), 8.43 (d, J = 6.7 Hz, 1H), 8.40 – 8.32 (m, 2H), 8.25 – 8.13 (m, 2H), 8.01 (t, J = 7.4 Hz, 1H).
^{13}C NMR (101 MHz, d_2o) δ 149.73, 137.09, 136.85, 134.74, 131.22, 129.81, 127.38, 127.06, 126.04.
HRMS (ESI): calculated for $C_{10}H_7D_3N^+$ 147.0996, found 147.0978.

1-methylquinolin-1-ium iodide 5b



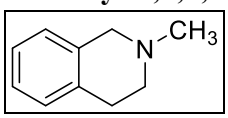
Synthesized according to the general procedure.
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (d, J = 5.2 Hz, 1H), 9.30 (d, J = 8.3 Hz, 1H), 8.56 – 8.45 (m, 2H), 8.29 (t, J = 7.9 Hz, 1H), 8.19 (t, J = 6.9 Hz, 1H), 8.07 (t, J = 7.5 Hz, 1H), 4.65 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 150.09, 146.94, 138.21, 135.38, 130.22, 129.87, 129.08, 121.95, 119.11, 45.43.
HRMS (ESI): calculated for $C_{10}H_{10}N^+$ 144.0808, found 144.0766.

1-(methyl-d3)quinolin-1-ium iodide 5c



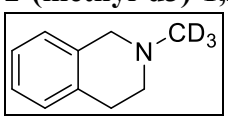
Synthesized according to the general procedure.
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (d, J = 5.3 Hz, 1H), 9.30 (d, J = 8.3 Hz, 1H), 8.56 – 8.45 (m, 2H), 8.29 (t, J = 7.8 Hz, 1H), 8.19 (d, J = 7.0 Hz, 1H), 8.07 (t, J = 7.5 Hz, 1H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 150.10, 146.98, 138.24, 135.40, 130.24, 129.90, 129.11, 121.97, 119.12.
HRMS (ESI): calculated for $C_{10}H_7D_3N^+$ 147.0996, found 147.0967.

2-methyl-1,2,3,4-tetrahydroisoquinoline 6b



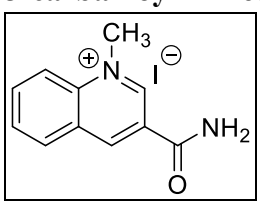
1,2,3,4-Tetrahydroisoquinoline **6** (533 mg, 1.0 eq, 4 mmol) was dissolved in ethanol (20 mL) and potassium carbonate (1106 mg, 2.0 eq, 6 mmol) was added followed by methyl iodide (852 mg, 1.5 eq, 8 mmol). The mixture was stirred overnight at room temperature, concentrated, redissolved in water (25 mL) and extracted with $CHCl_3$ (3 x 25 mL). The crude product was purified by column chromatography (5% MeOH in DCM) yielding the product as a slightly brown oil (106 mg, 18%)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 2H), 7.18 (d, J = 7.4 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 4.32 (s, 2H), 3.48 (t, J = 6.3 Hz, 2H), 3.28 (t, J = 6.3 Hz, 2H), 2.92 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 130.21, 129.04, 128.63, 127.53, 126.81, 126.57, 54.53, 51.40, 42.77, 24.94.
HRMS (ESI): calculated for $C_{10}H_{13}N$ $(M+H)^+$ 148.1121, found 148.1160

2-(methyl-d3)-1,2,3,4-tetrahydroisoquinoline 6c



Prepared as described for compound **6b** using d_3-methyl iodide yielding a slightly brown oil (226 mg, 38 %)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 2H), 7.20 – 7.14 (m, 2H), 4.44 (s, 2H), 3.55 (t, J = 6.2 Hz, 2H), 3.23 (t, J = 6.0 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 131.24, 129.13, 128.32, 127.42, 126.91, 126.68, 44.13, 41.77, 25.04.
HRMS (ESI): calculated for $C_{10}H_{11}D_3N$ $(M+H)^+$ 151.1309, found 151.1323

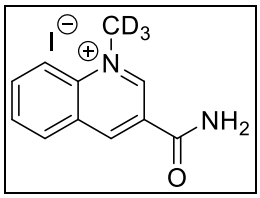
3-carbamoyl-1-methylquinolin-1-ium iodide 7b



Synthesized according to the general procedure.

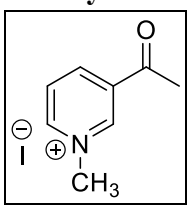
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 9.69 (s, 1H), 8.59 (br s, 1H), 8.57 (d, J = 9.1 Hz, 1H), 8.51 (d, J = 7.9 Hz, 1H), 8.37 (t, J = 7.6 Hz, 1H), 8.17 (br s, 1H), 8.13 (t, J = 7.6 Hz, 1H), 4.69 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 163.27, 149.95, 145.11, 138.74, 136.78, 131.33, 130.58, 128.14, 127.52, 119.32, 45.65.
HRMS (ESI): calculated for $C_{11}H_{11}N_2O^+$ 187.0866, found 187.0841.

3-carbamoyl-1-(methyl-d3)quinolin-1-ium iodide 7c



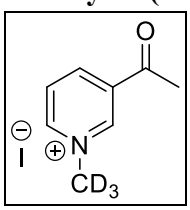
Synthesized according to the general procedure.
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 9.68 (s, 1H), 8.59 (br s, 1H), 8.56 (d, J = 9.0 Hz, 1H), 8.51 (d, J = 8.2 Hz, 1H), 8.37 (t, J = 7.9 Hz, 1H), 8.17 (br s, 1H), 8.13 (t, J = 7.6 Hz, 1H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 163.28, 149.92, 145.12, 138.73, 136.77, 131.32, 130.58, 128.13, 127.50, 119.32.
HRMS (ESI): calculated for $C_{11}H_8D_3N_2O^+$ 190.1054, found 190.1030.

3-acetyl-1-methylpyridin-1-ium iodide 8b



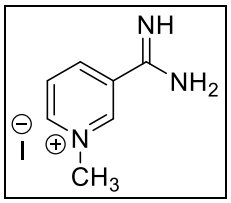
Synthesized according to the general procedure.
^{1}H NMR (400 MHz, d_2o) δ 9.43 (s, 1H), 9.16 – 8.92 (m, 2H), 8.25 (t, J = 6.9 Hz, 1H), 4.53 (s, 3H), 2.82 (s, 3H).
^{13}C NMR (101 MHz, d_2o) δ 196.43, 147.91, 145.81, 144.24, 135.51, 128.23, 48.63, 26.61.
HRMS (ESI): calculated for $C_8H_{10}NO^+$ 136.0757, found 136.0731.

3-acetyl-1-(methyl-d3)pyridin-1-ium iodide 8c



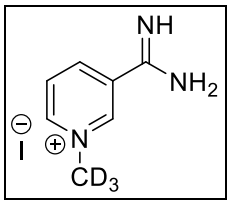
Synthesized according to the general procedure.
^{1}H NMR (400 MHz, d_2o) δ 9.43 (s, 1H), 9.14 – 8.93 (m, 2H), 8.26 (t, J = 7.1 Hz, 1H), 2.82 (s, 3H).
^{13}C NMR (101 MHz, d_2o) δ 196.44, 147.89, 145.80, 144.26, 135.51, 128.24, 26.63.
HRMS (ESI): calculated for $C_8H_7D_3NO^+$ 139.0945, found 139.0914.

3-carbamimidoyl-1-methylpyridin-1-ium iodide 9b



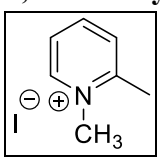
Synthesized according to the general procedure.
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (br s, 3H), 9.65 (s, 1H), 9.25 (d, J = 6.1 Hz, 1H), 8.93 (d, J = 8.2 Hz, 1H), 8.36 (dd, J = 7.9, 6.4 Hz, 1H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 160.90, 148.90, 146.11, 144.77, 127.50, 127.17, 48.40.
HRMS (ESI): calculated for $C_7H_{10}N_3^+$ 136.0869, found 136.0814.

3-carbamimidoyl-1-(methyl-d3)pyridin-1-ium iodide 9c



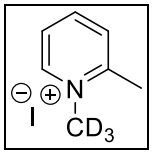
Synthesized according to the general procedure.
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (br s, 3H), 9.63 (s, 1H), 9.25 (d, J = 6.1 Hz, 1H), 8.93 (d, J = 8.3 Hz, 1H), 8.36 (dd, J = 8.0, 6.3 Hz, 1H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 160.90, 148.90, 146.09, 144.79, 127.54, 127.18.
HRMS (ESI): calculated for $C_7H_7D_3N_3^+$ 139.1058, found 139.1012.

1,2-dimethylpyridin-1-ium iodide 10b



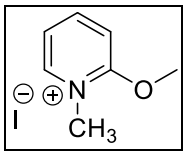
Synthesized according to the general procedure.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (d, J = 6.1 Hz, 1H), 8.47 (t, J = 7.8 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.94 (t, J = 6.8 Hz, 1H), 4.24 (s, 3H), 2.79 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 155.84, 145.97, 144.93, 129.05, 125.15, 45.53, 20.02.
HRMS (ESI): calculated for $C_7H_{10}N^+$ 108.0808, found 108.0820.

2-methyl-1-(methyl-d3)pyridin-1-ium iodide 10c



Synthesized according to the general procedure.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (d, J = 5.8 Hz, 1H), 8.47 (t, J = 7.5 Hz, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.94 (t, J = 6.4 Hz, 1H), 2.78 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 155.85, 145.97, 144.95, 129.04, 125.14, 19.91.
HRMS (ESI): calculated for $C_7H_7D_3N^+$ 111.0996, found 111.1017.

2-methoxy-1-methylpyridin-1-ium iodide 11b



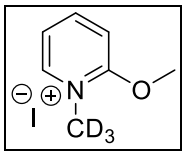
To a cold (0°C) solution of 2-methoxypyridine **11** (445 mg, 4 mmol) in toluene (4 mL) was added methyl trifluoromethanesulfonate (464 µL (673 mg), 4.1 mmol). The mixture was allowed to warm to room temperature, which resulted in the formation of a white crystalline precipitate. After 1 hour, the white solid was collected by filtration of the crude reaction mixture through a fritted glass funnel, followed by drying under vacuum yielding 984 mg (91%) of the product as the triflate salt.

^{1}H NMR (400 MHz, d_2o) δ 8.54-8.32 (m, 2H), 7.59 (d, J = 6.9 Hz, 1H), 7.54-7.40 (br m, 1H), 4.31 (s, 3H), 4.06 (s, 3H)

^{13}C NMR (101 MHz, d_2o) δ 160.65, 147.74, 143.05, 121.13 (triflate), 118.30, 117.98 (triflate), 110.59, 58.70, 41.14.

HRMS (ESI): calculated for $C_7H_{10}NO^+$ 124.0757, found 124.0721.

2-methoxy-1-(methyl-d3)pyridin-1-ium iodide 11c



Deuterated methyl triflate was freshly prepared by mixing silver triflate (900 mg, 3.5 mmol) and methyl-d3-iodide (507 mg, 3.5 mmol) in CCl_4 (6 mL) at room temperature overnight. After filtration over cotton and flushing with 1 mL CCl_4, 7 mL of a 0.5 M CD_3OTf solution was obtained and used as is.

2-methoxypyridine **11** (110 mg, 1 mmol) in CCl_4 (0.5 mL) was added to 2.2 mL of the CD_3OTf solution at 0°C and the mixture was stirred for 1.5 hours at room temperature. The product was filtered off and flushed with dry diethyl ether yielding 140 mg (51%) white product as the triflate salt.

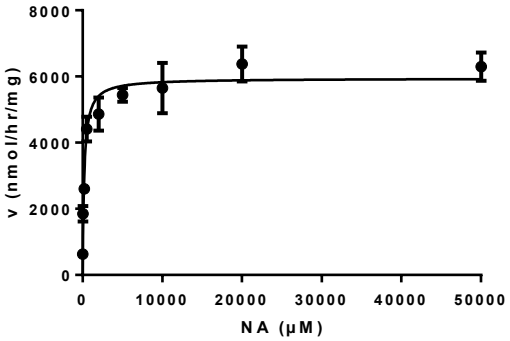
^{1}H NMR (400 MHz, d_2o) δ 8.44 (t, J = 7.9 Hz, 1H), 8.39 (d, J = 6.3 Hz, 1H), 7.59 (d, J = 8.9 Hz, 1H), 7.48 (t, J = 6.8 Hz, 1H), 4.30 (s, 3H).

^{13}C NMR (101 MHz, d_2o) δ 160.65, 147.75, 143.01, 121.12 (triflate), 118.29, 117.97 (triflate), 110.57, 58.68.

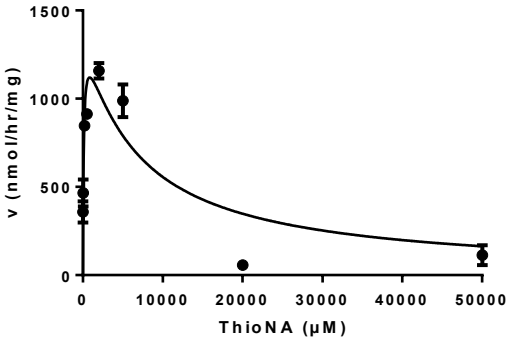
HRMS (ESI): calculated for $C_7H_7D_3NO^+$ 127.0945, found 127.0911.

Curves of the Michaelis-Menten and substrate inhibition kinetics for compounds 1-11

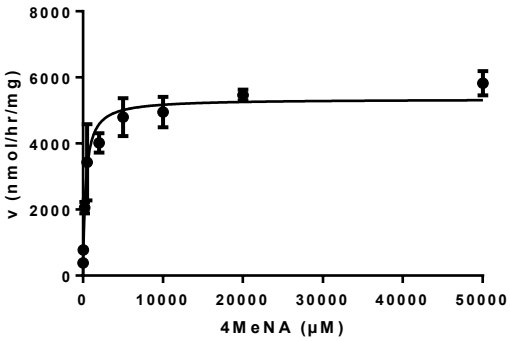
Nicotinamide (Compound 1)



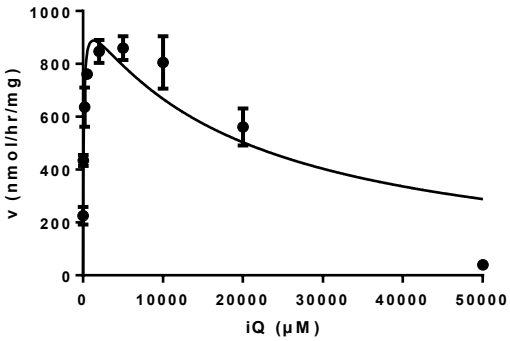
Thionicotinamide (Compound 2)



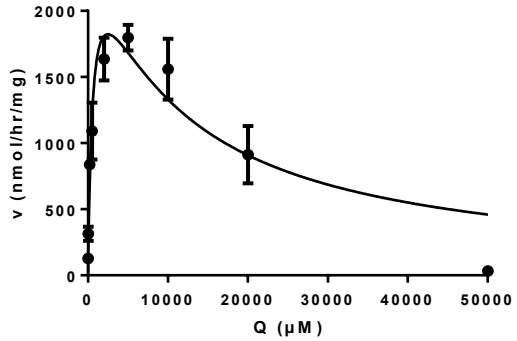
4-Methylnicotinamide (Compound 3)



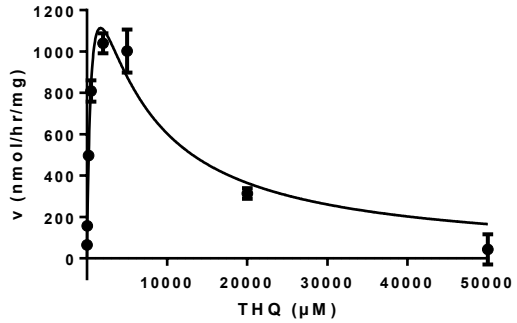
Isoquinoline (Compound 4)



Quinoline (Compound 5)

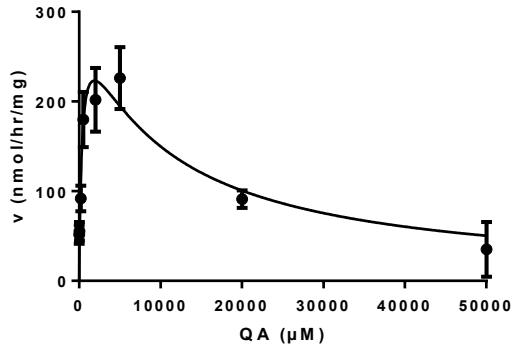


1,2,3,4-Tetrahydroisoquinoline (Compound 6)[a]

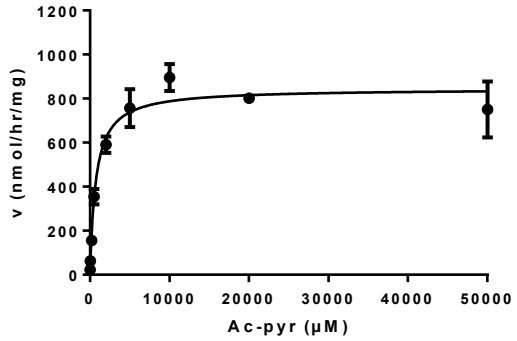


[a] Data corrected for an impurity in the substrate (about 0.005%) that exhibited the same retention time and *m/z* as the measured product.

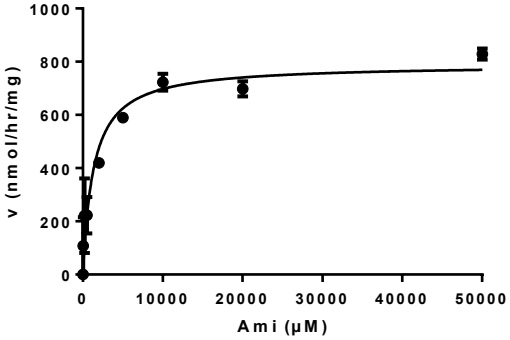
Quinoline-3-carboxamide (Compound 7)



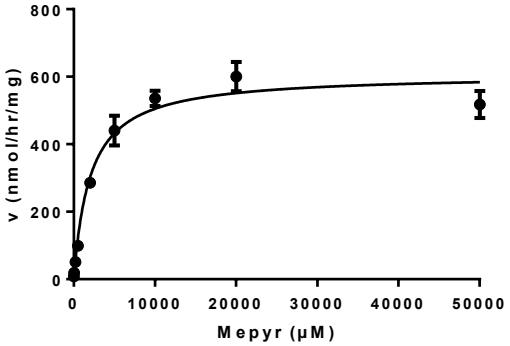
3-Acetylpyridine (Compound 8)



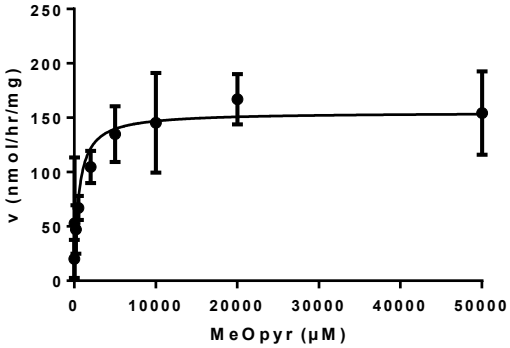
Nicotinimidamide (Compound 9)



2-Methylpyridine (Compound 10)

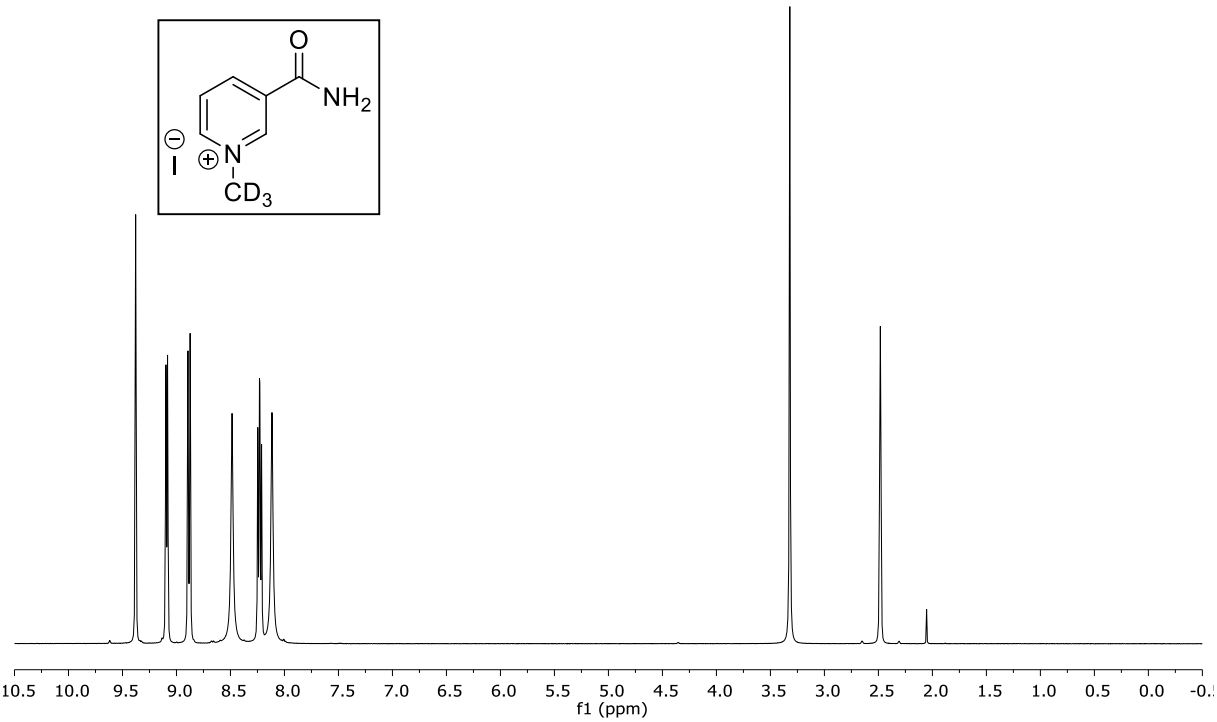


2-Methoxypyridine (Compound 11)

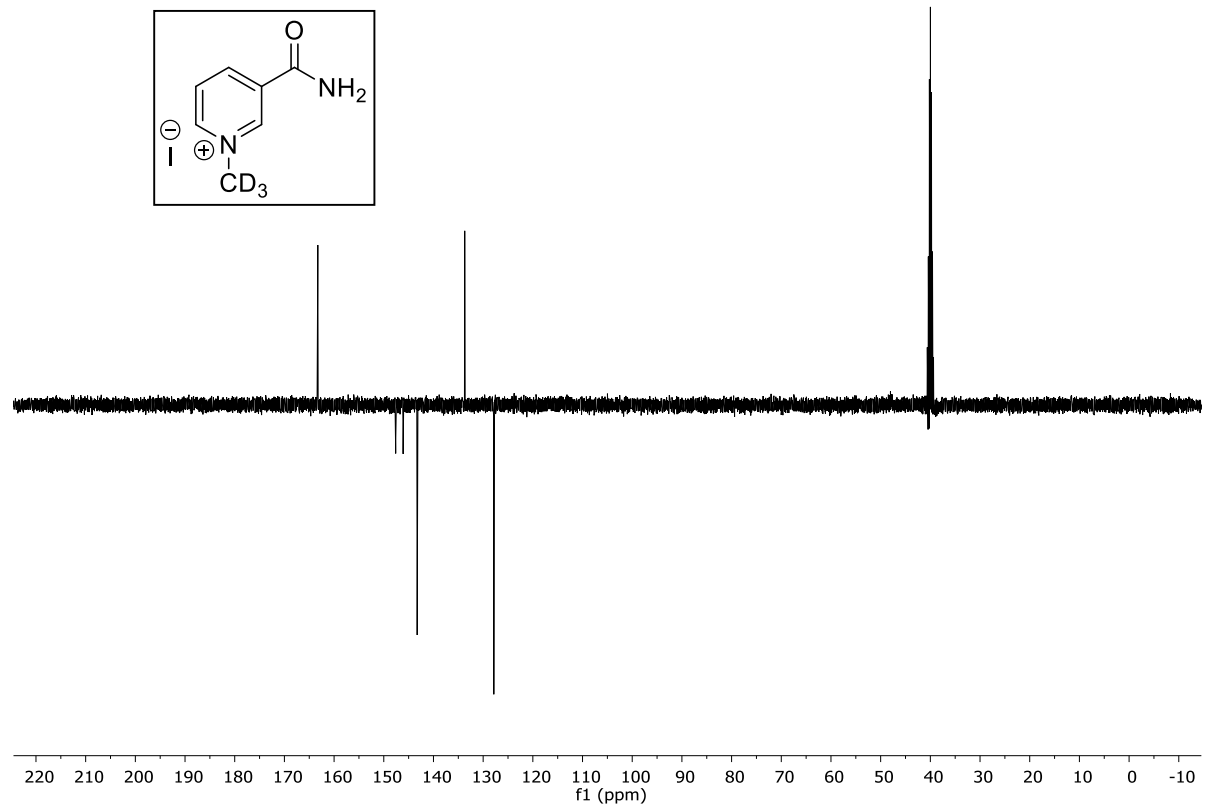


^{1}H and ^{13}C NMR spectra for compounds 1-11

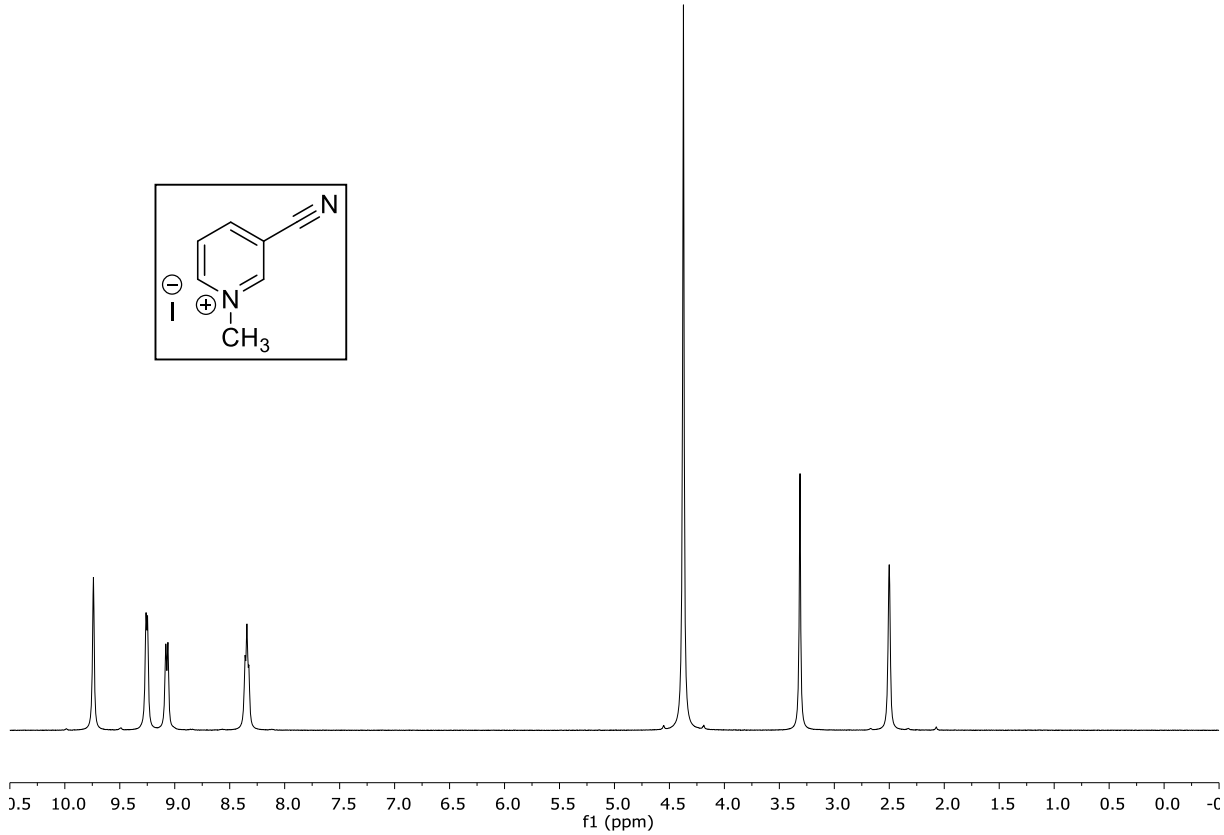
Compound 1c: ^{1}H NMR (400 MHz, DMSO-d_6)



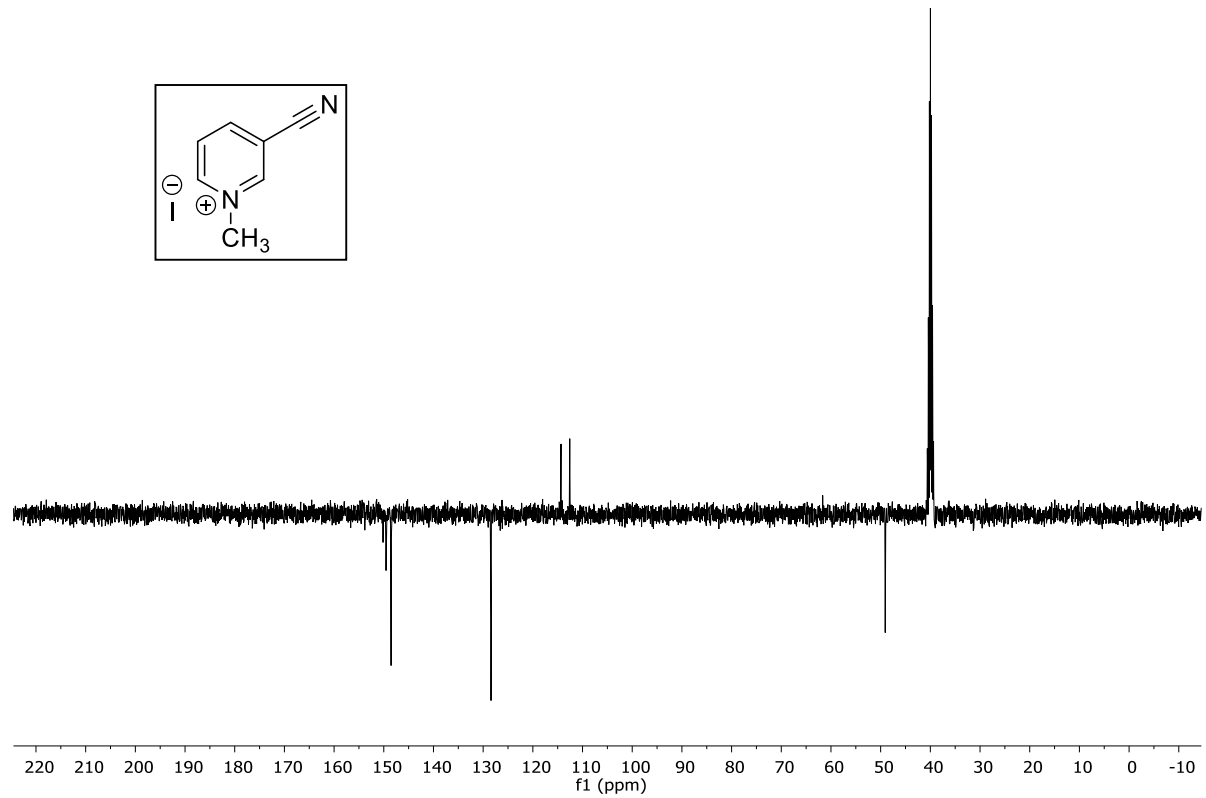
Compound 1c: ^{13}C NMR (101 MHz, DMSO-d_6)



3-cyano-1-methylpyridin-1-ium iodide: ^{1}H NMR (400 MHz, DMSO-d_6)

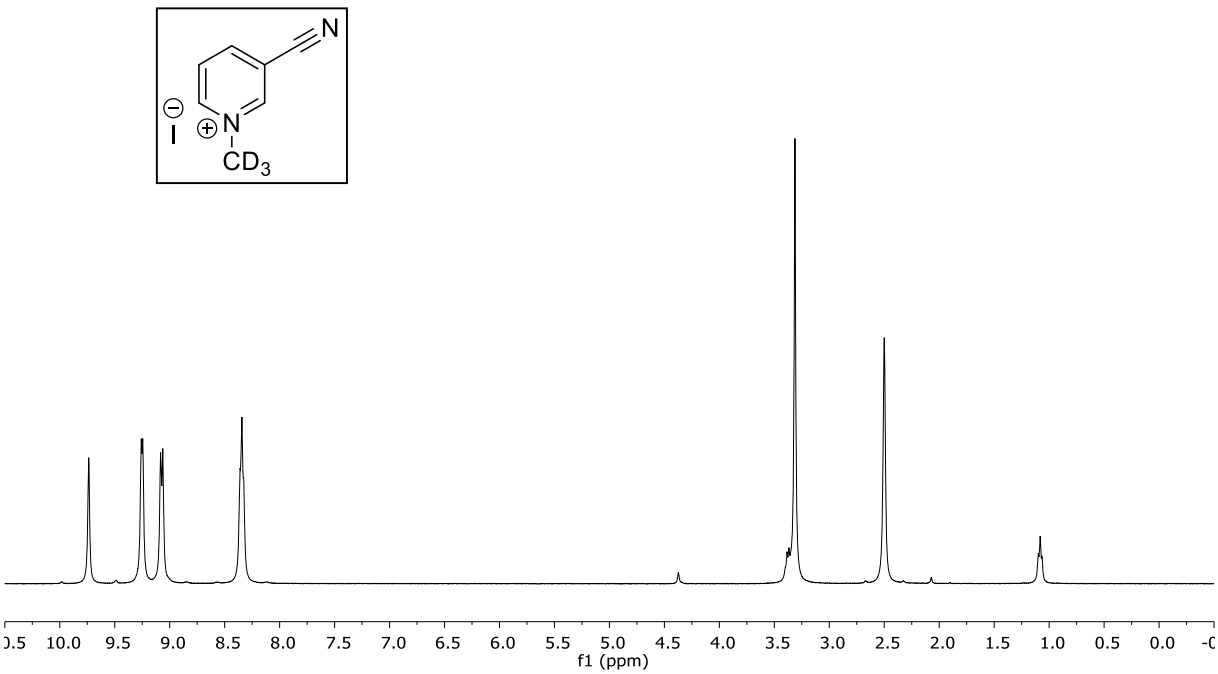


3-cyano-1-methylpyridin-1-ium iodide: ^{13}C NMR (101 MHz, DMSO-d_6)

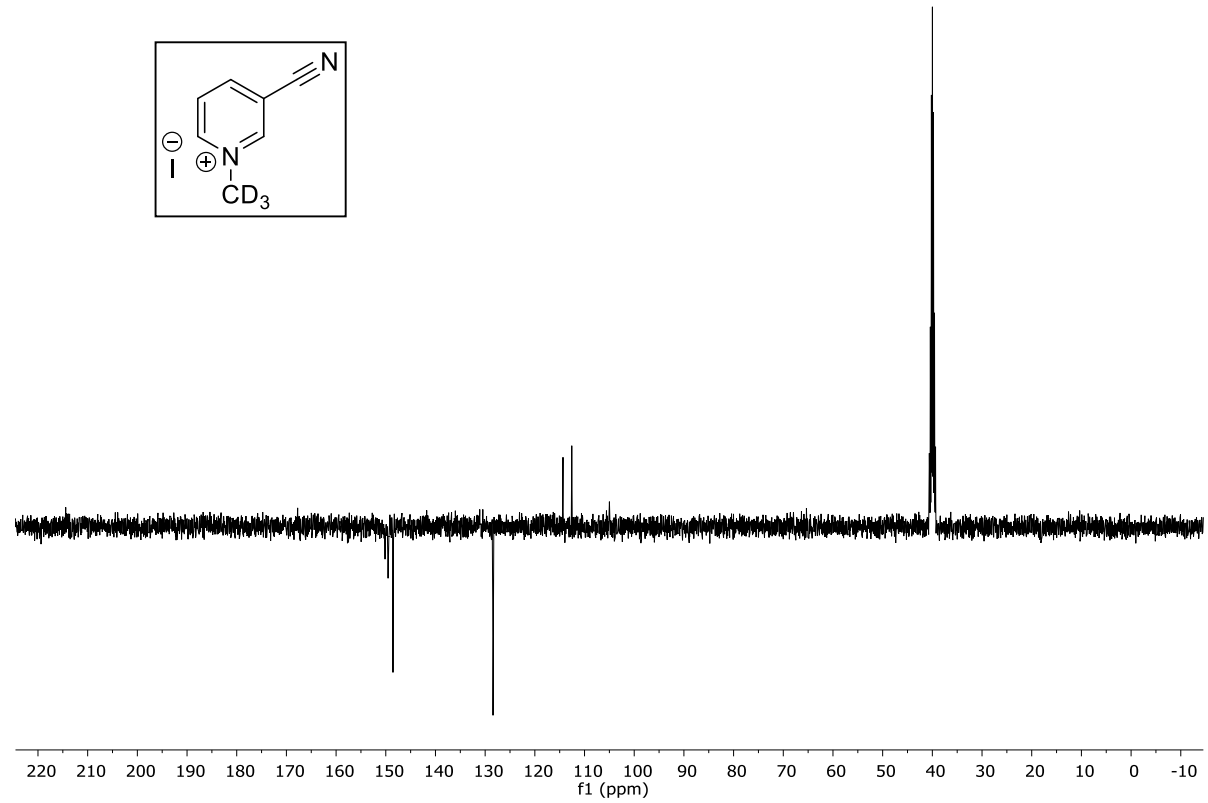


3-cyano-1-(methyl-d3)pyridin-1-ium iodide

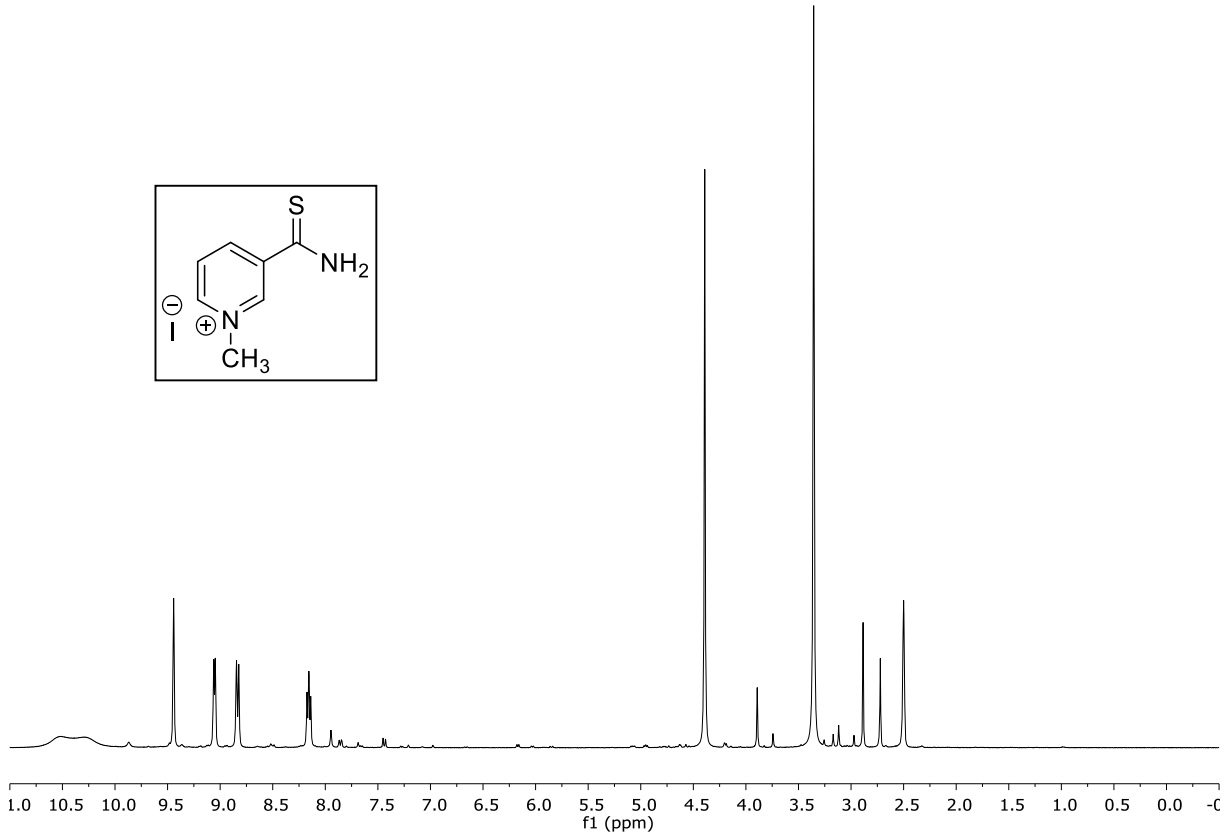
3-cyano-1-(methyl-d3)pyridin-1-ium iodide: ^{1}H NMR (400 MHz, DMSO-d$_6$)



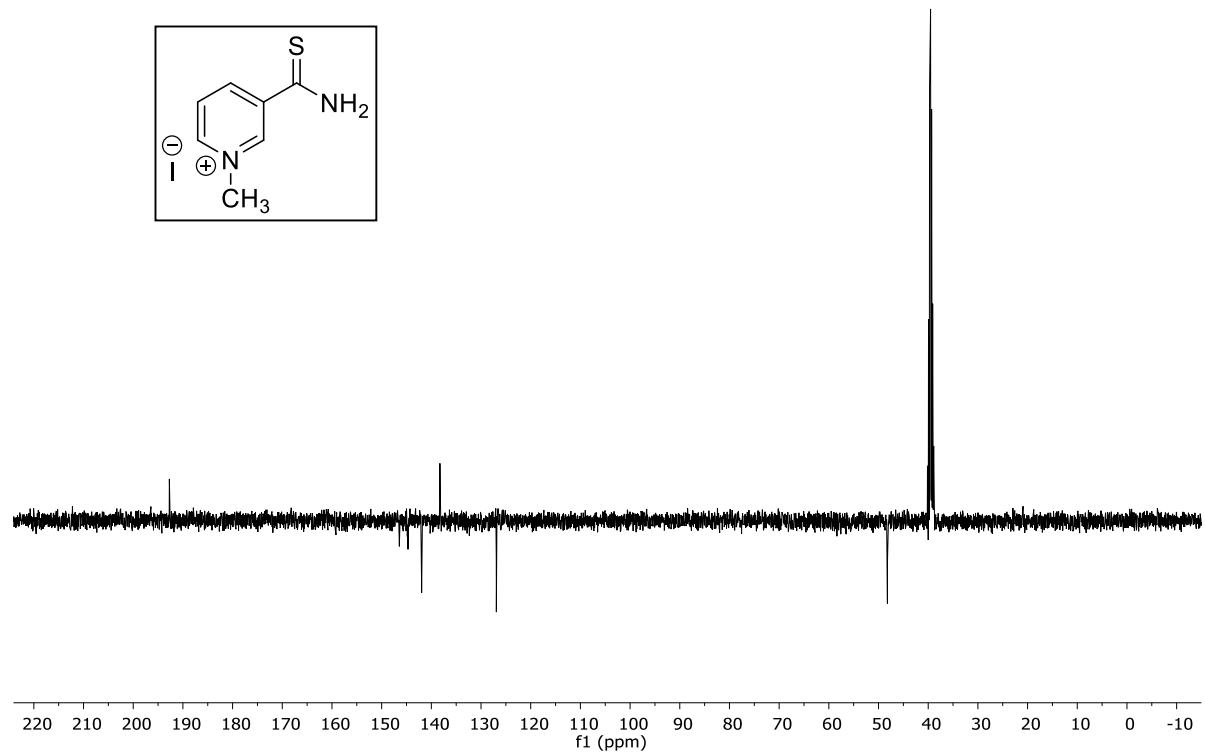
3-cyano-1-(methyl-d3)pyridin-1-ium iodide: ^{13}C NMR (101 MHz, DMSO-d$_6$)



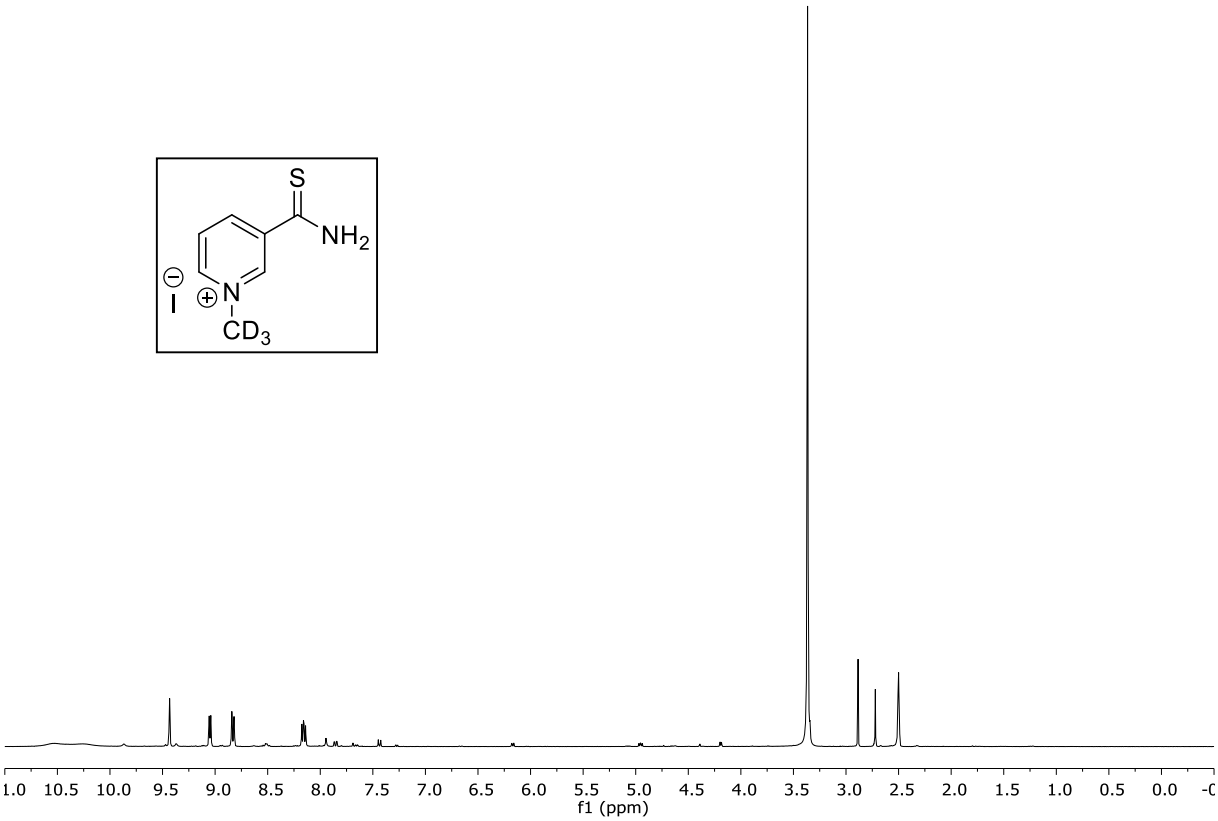
Compound 2b: ^{1}H NMR (400 MHz, DMSO-d_6)



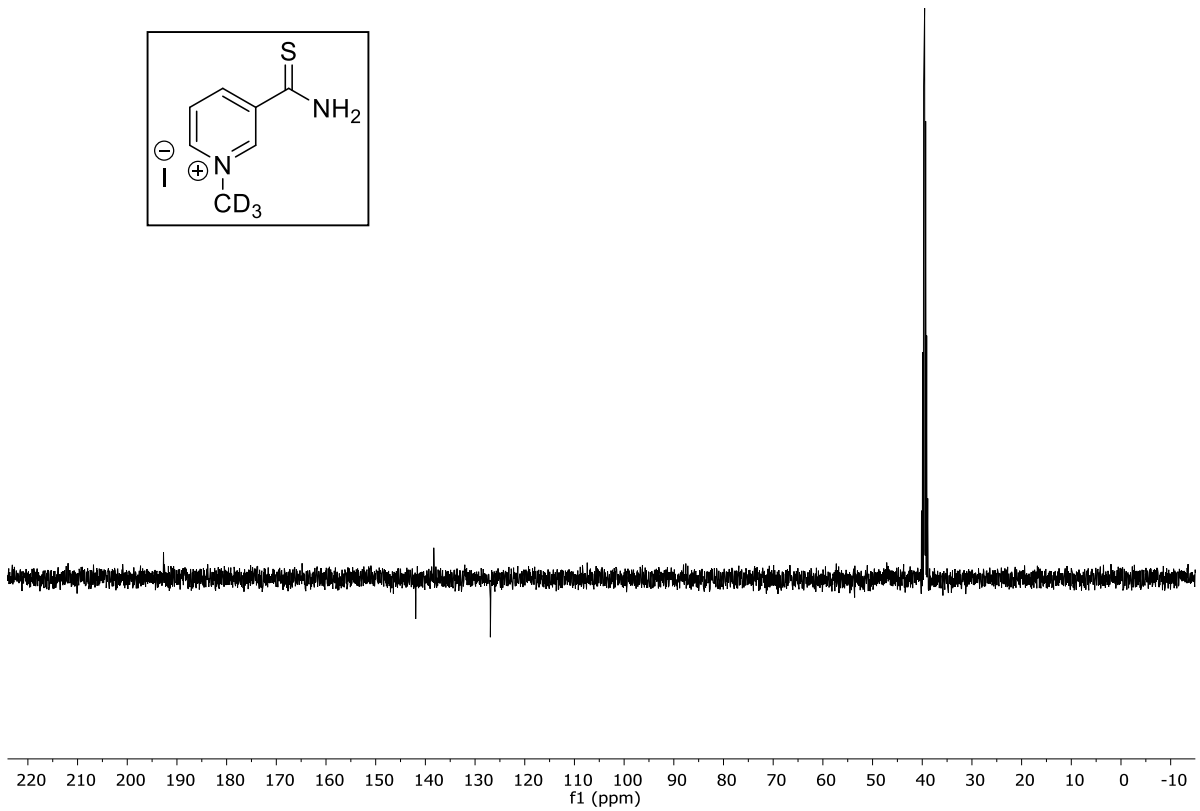
Compound 2b: ^{13}C NMR (101 MHz, DMSO-d_6)



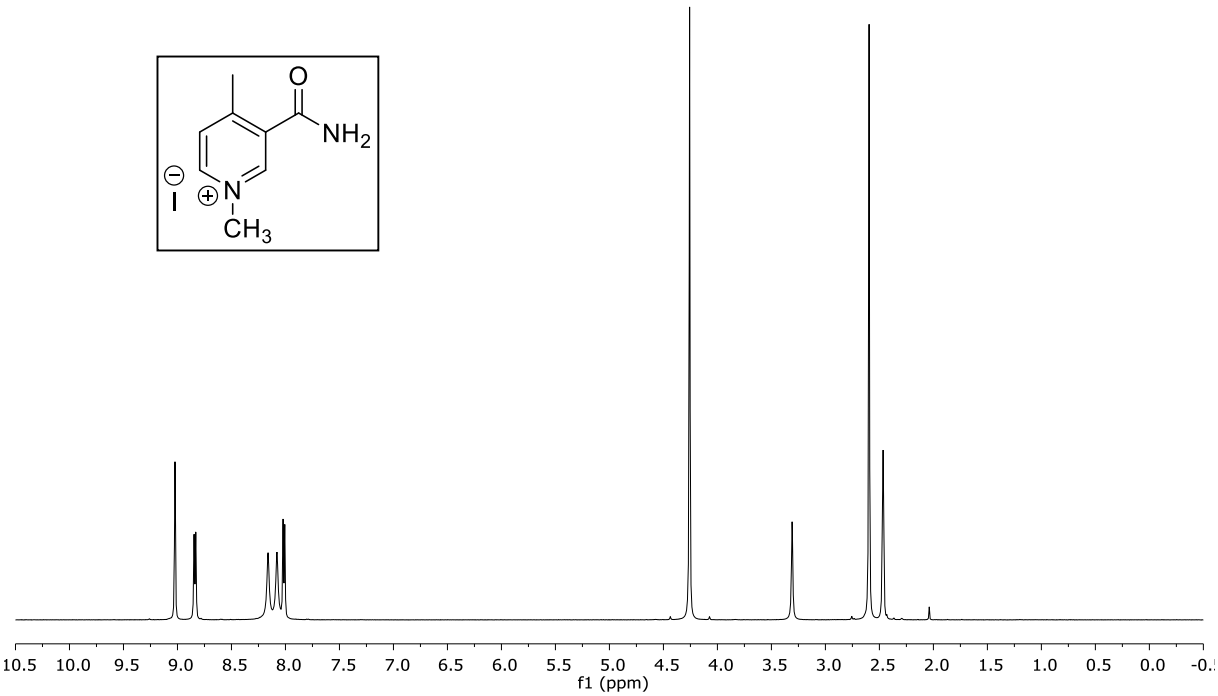
Compound 2c: ^{1}H NMR (400 MHz, DMSO-d_6)



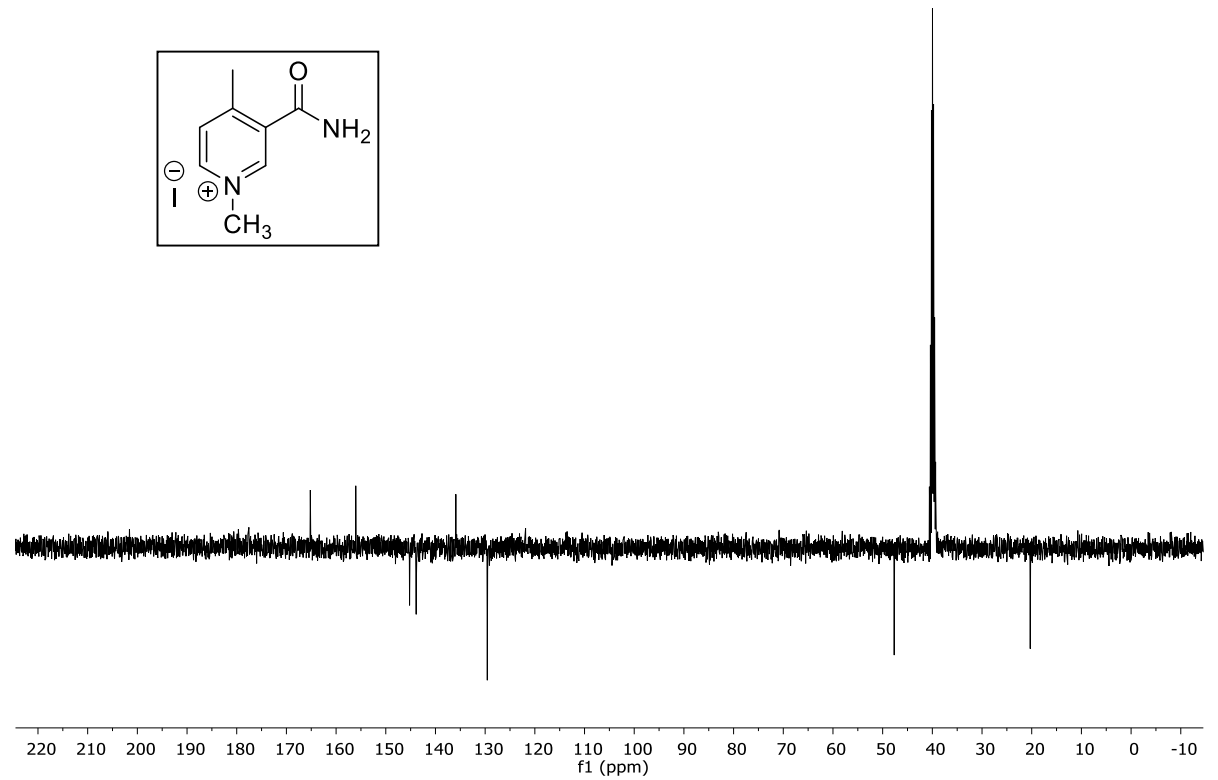
Compound 2c: ^{13}C NMR (101 MHz, DMSO-d_6)



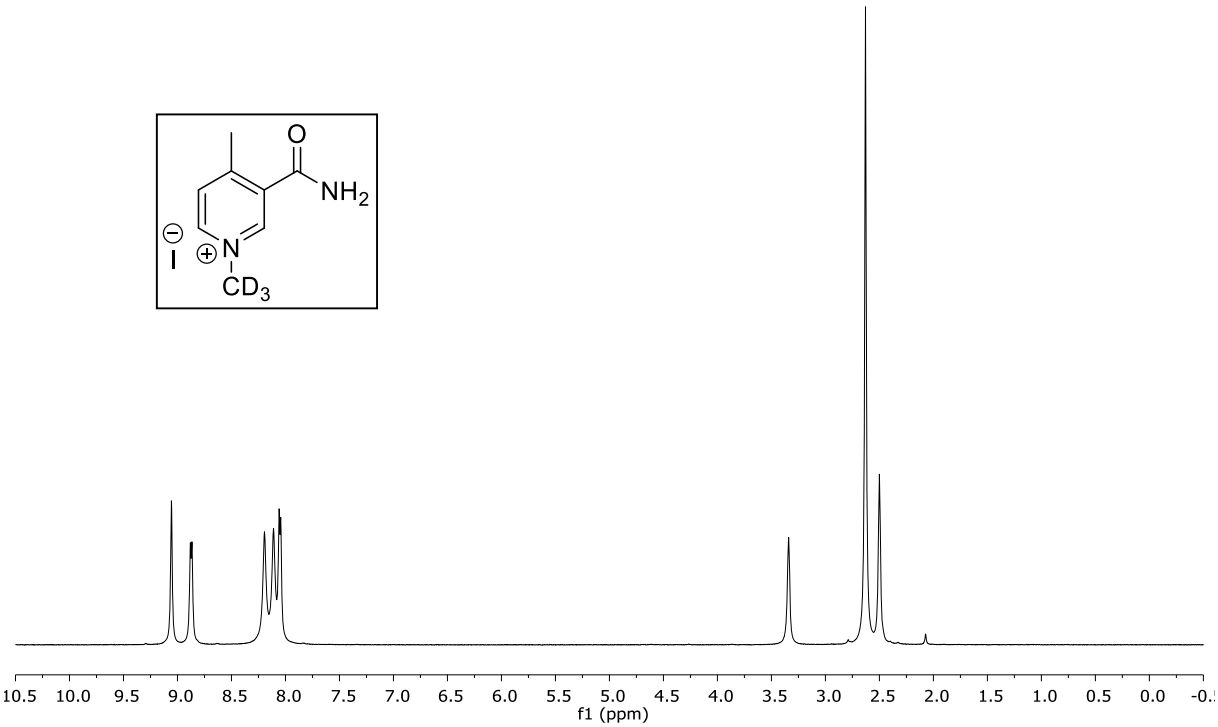
Compound 3b: ^{1}H NMR (400 MHz, DMSO-d_6)



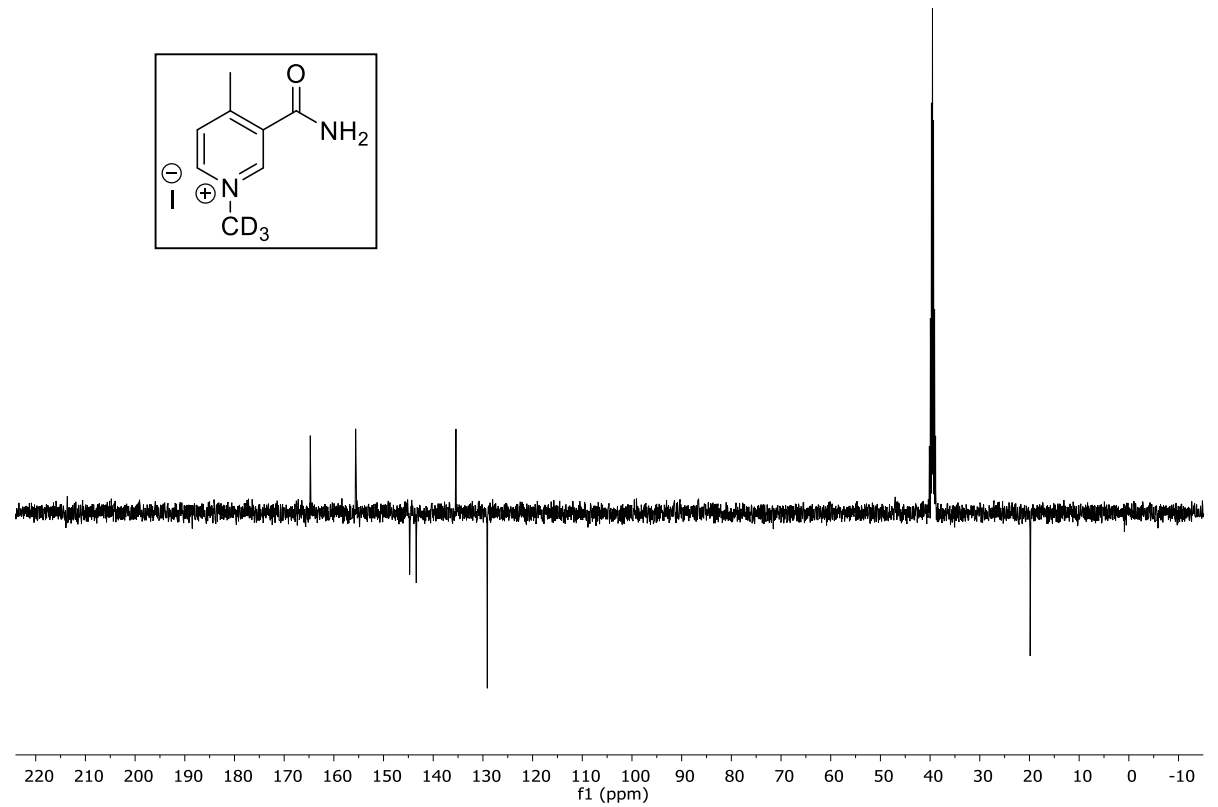
Compound 3b: ^{13}C NMR (101 MHz, DMSO-d_6)



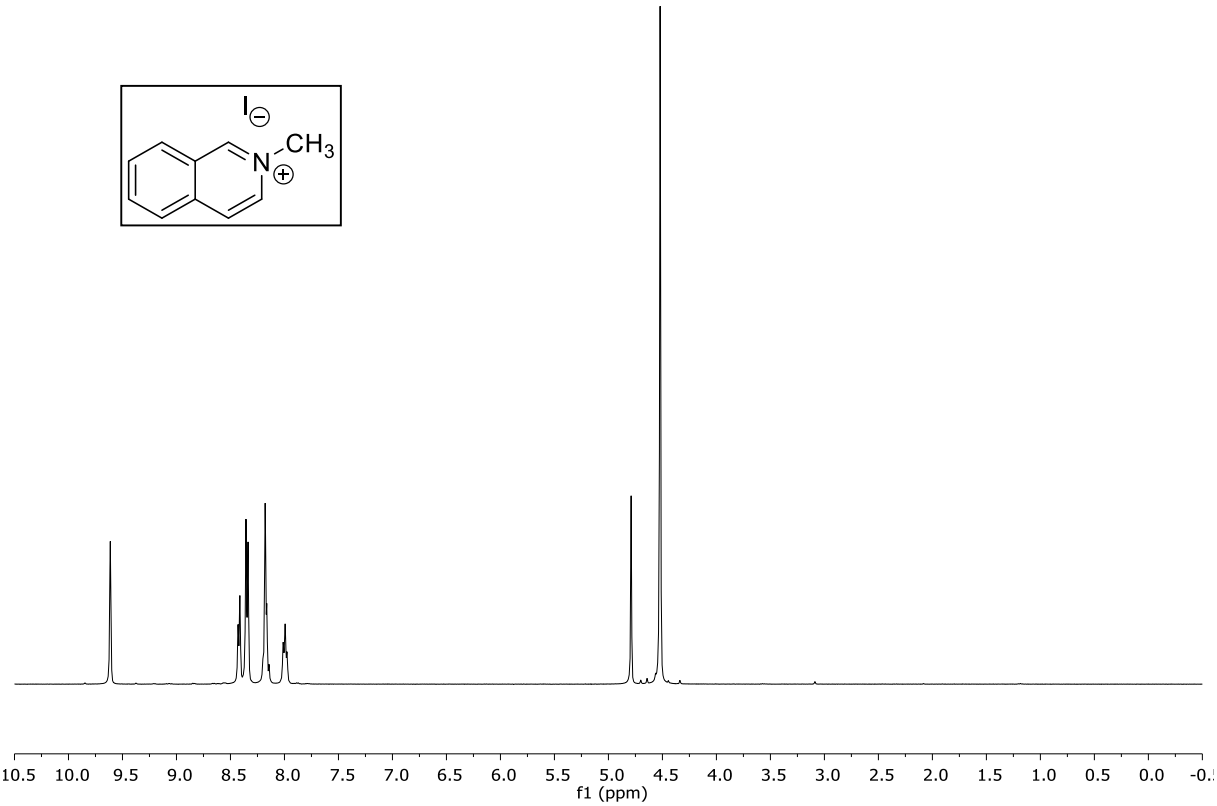
Compound 3c: ^{1}H NMR (400 MHz, DMSO-d_6)



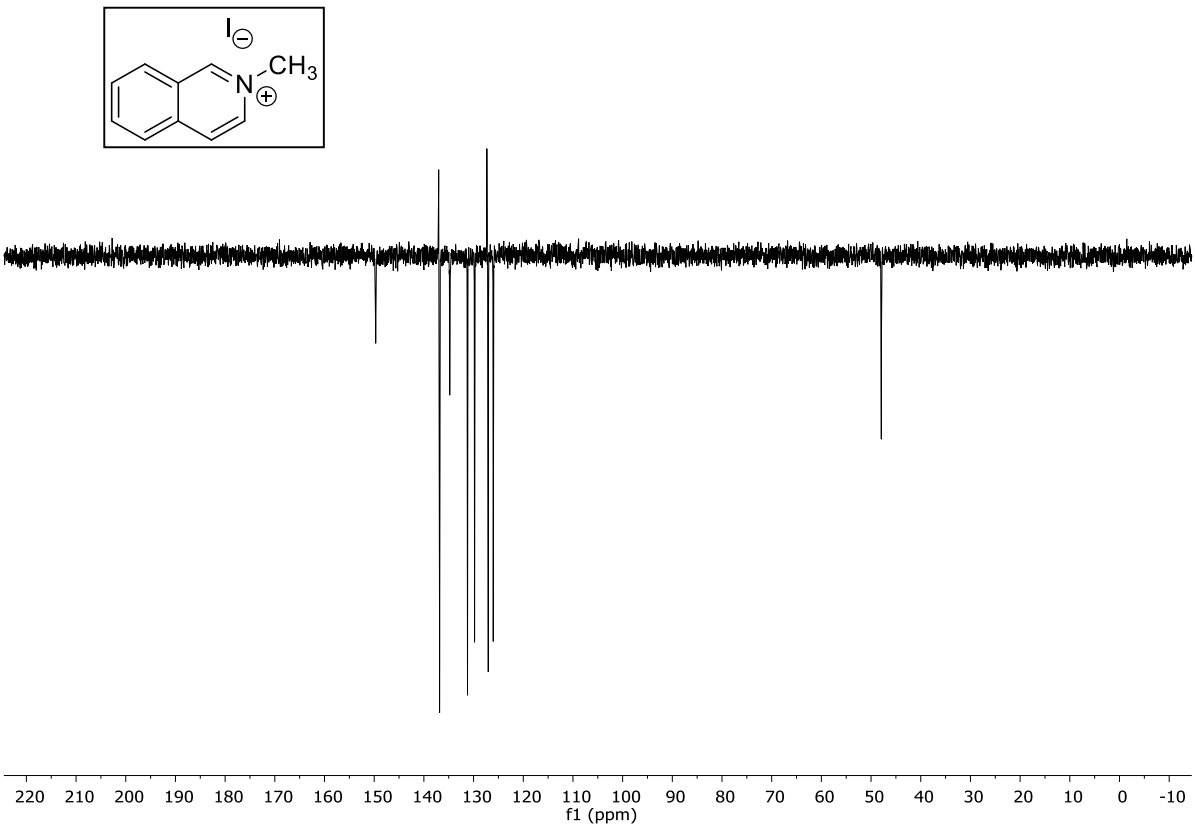
Compound 3c: ^{13}C NMR (101 MHz, DMSO-d_6)



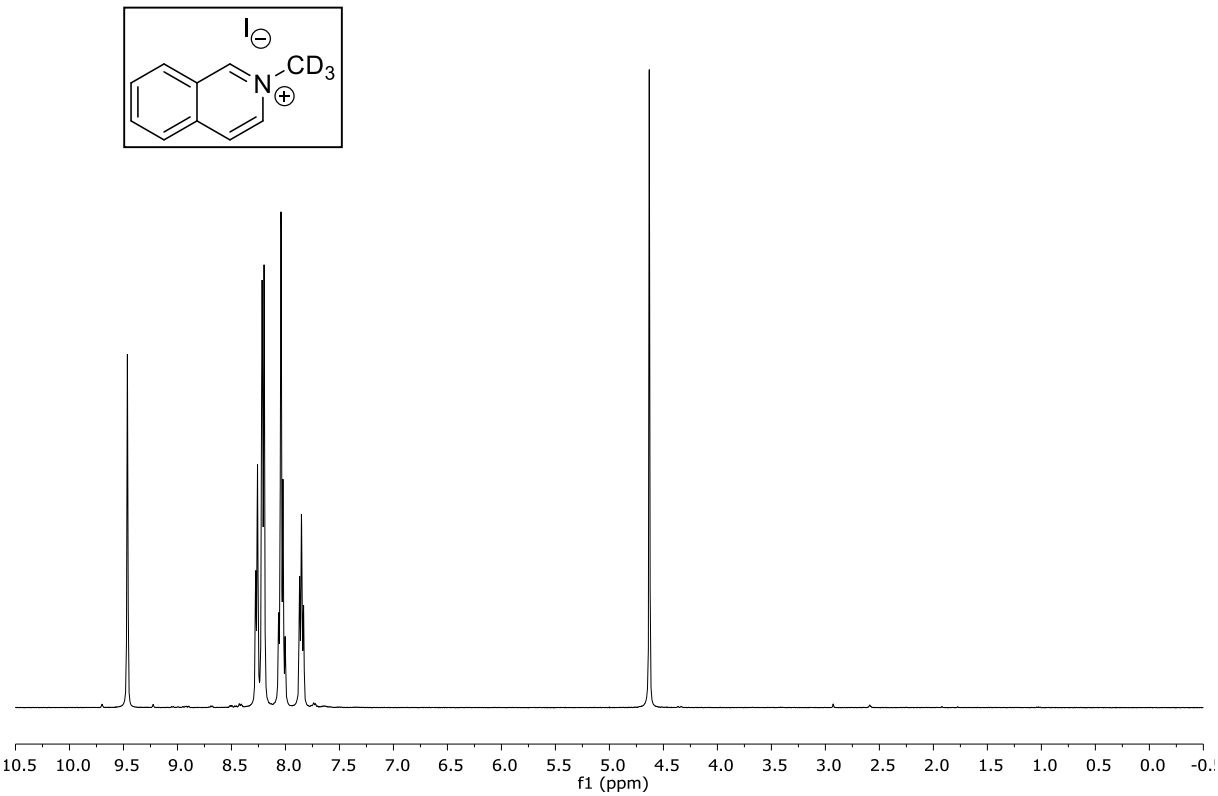
Compound 4b: ^{1}H NMR (400 MHz, D_2O)



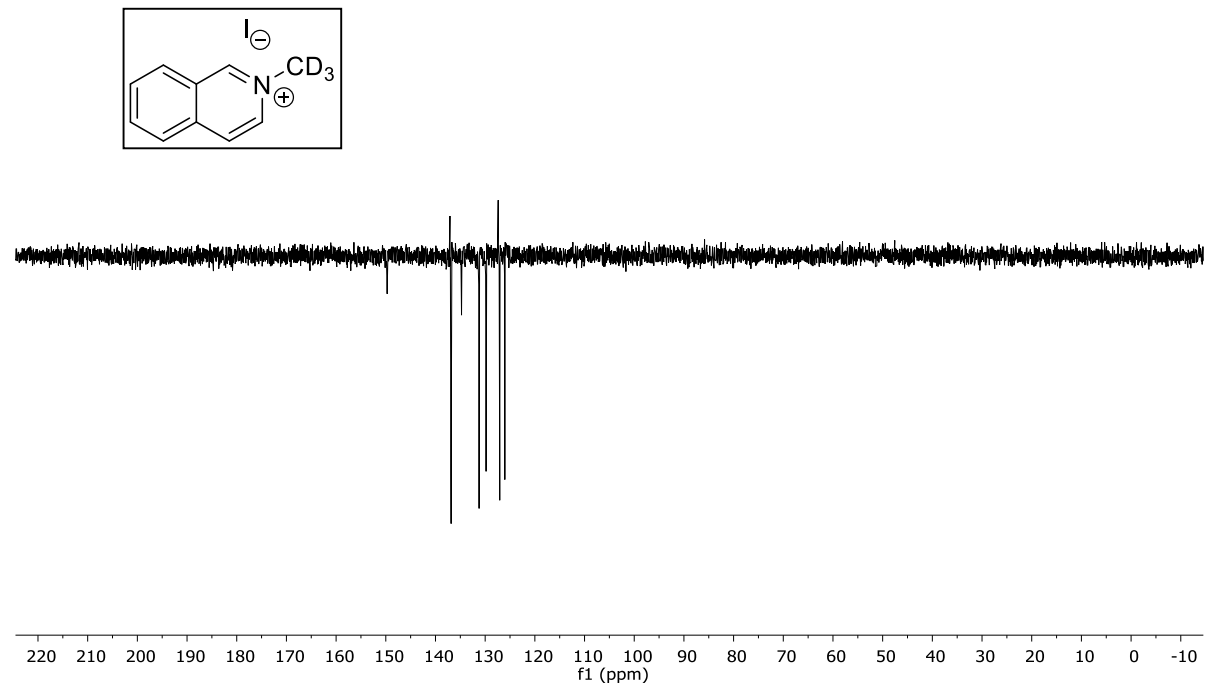
Compound 4b: ^{13}C NMR (101 MHz, D_2O)



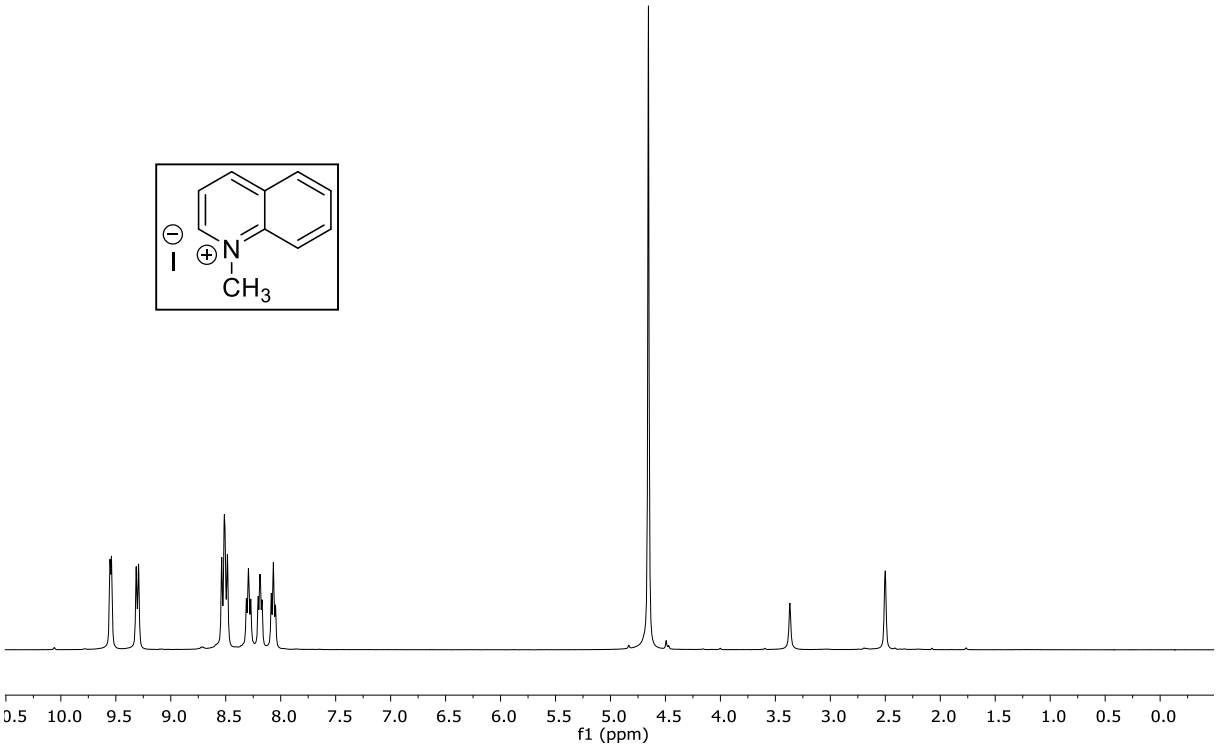
Compound 4c: ^{1}H NMR (400 MHz, D_2O)



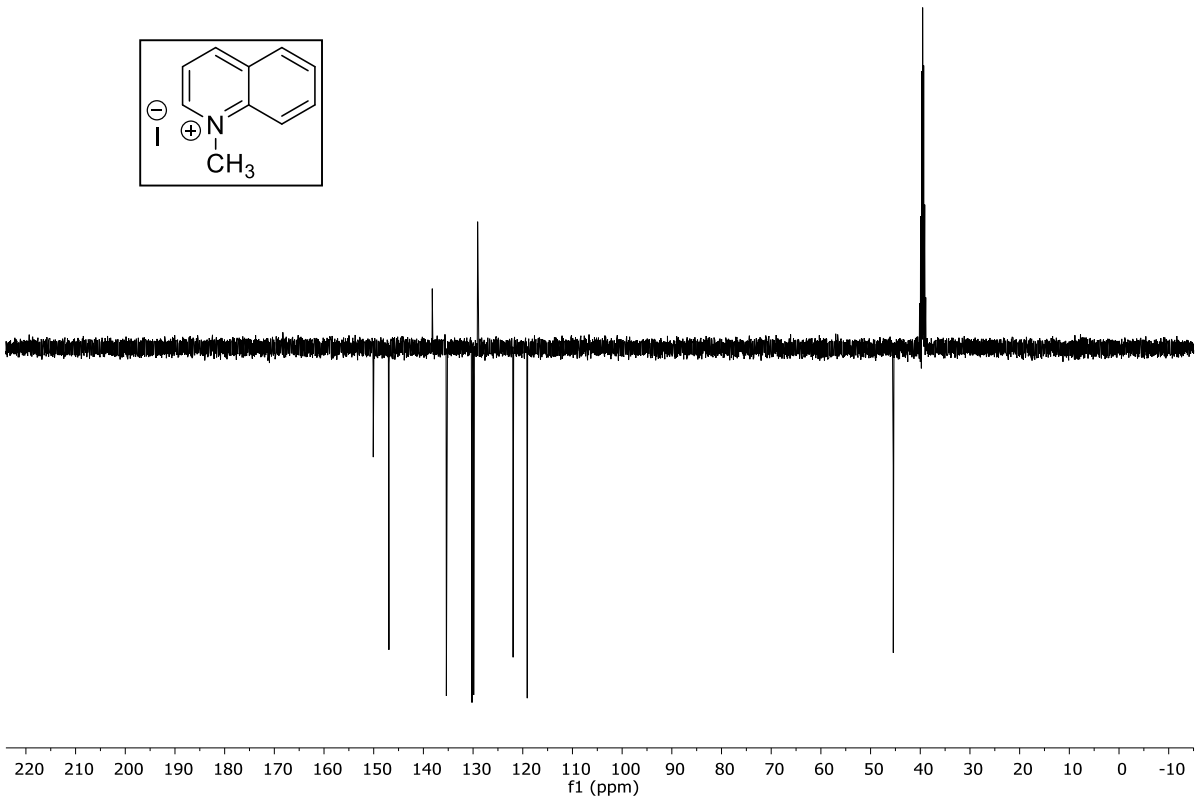
Compound 4c: ^{13}C NMR (101 MHz, D_2O)



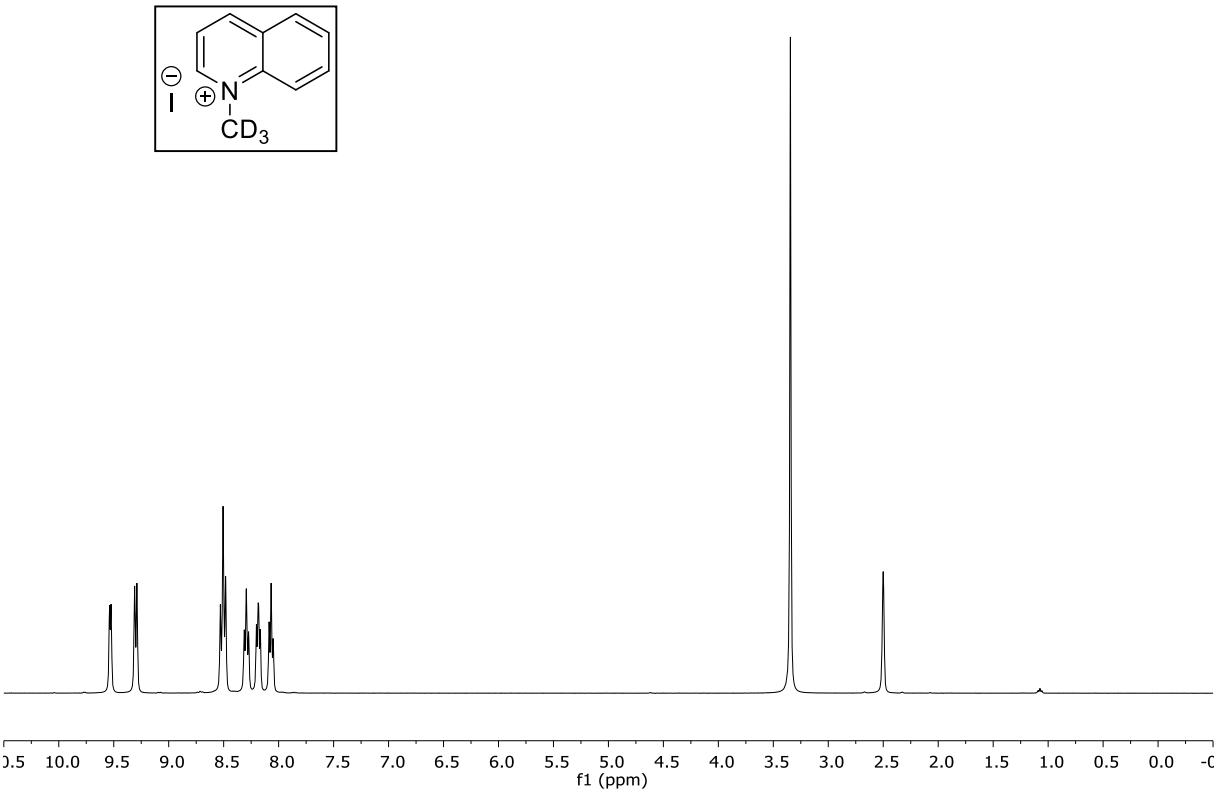
Compound 5b: ^{1}H NMR (400 MHz, DMSO-d_6)



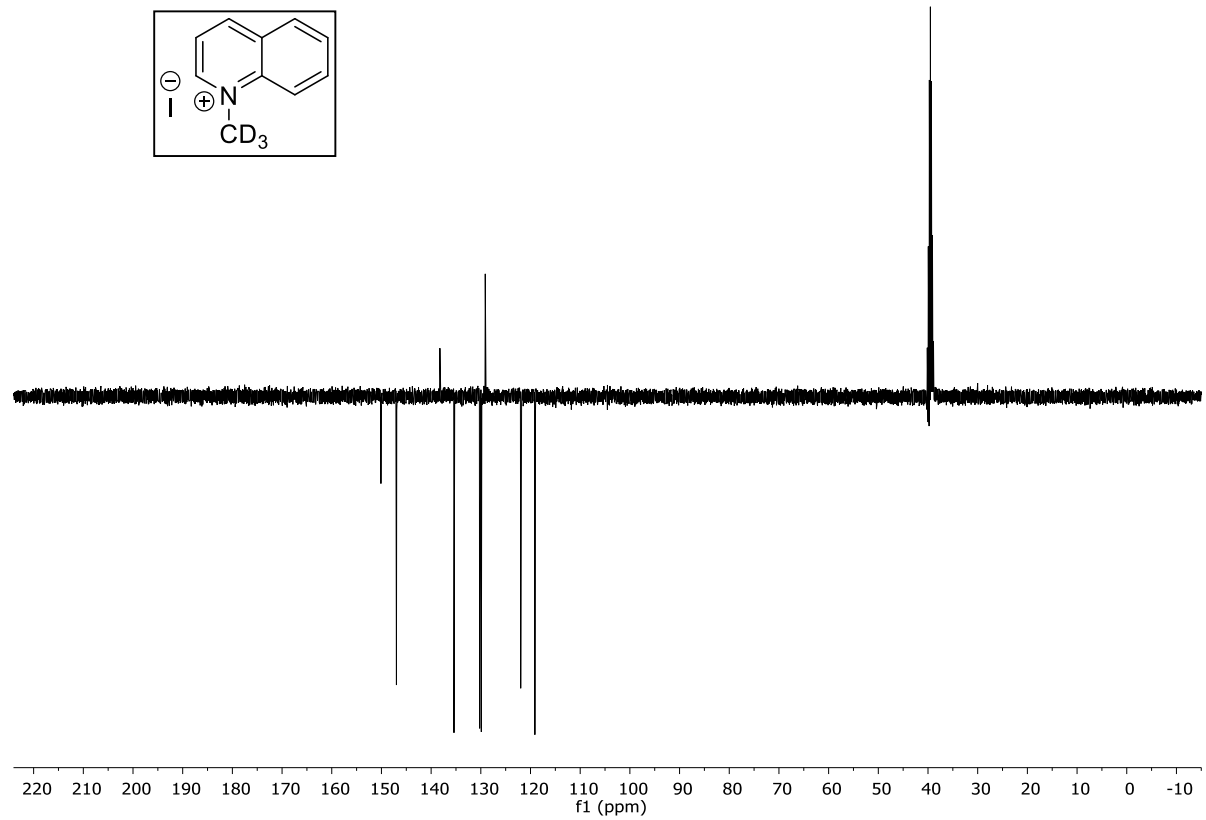
Compound 5b: ^{13}C NMR (101 MHz, DMSO-d_6)



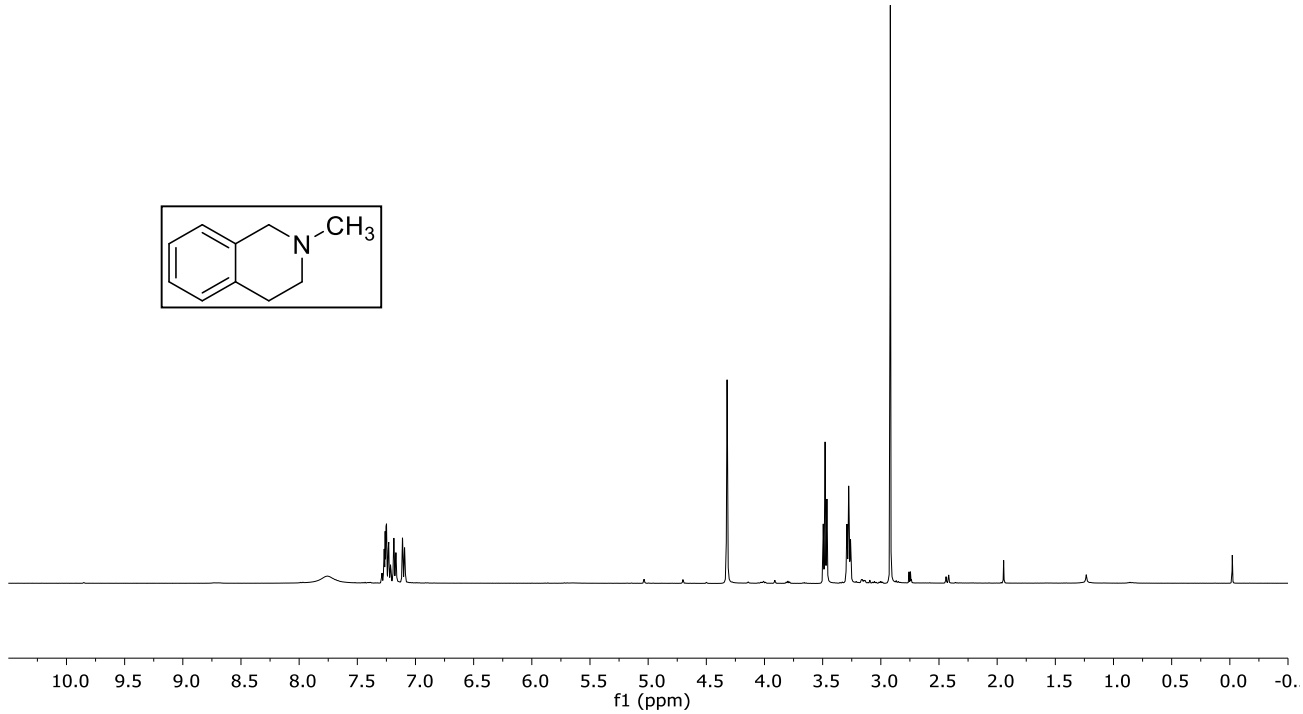
Compound 5c: ^{1}H NMR (400 MHz, DMSO-d_6)



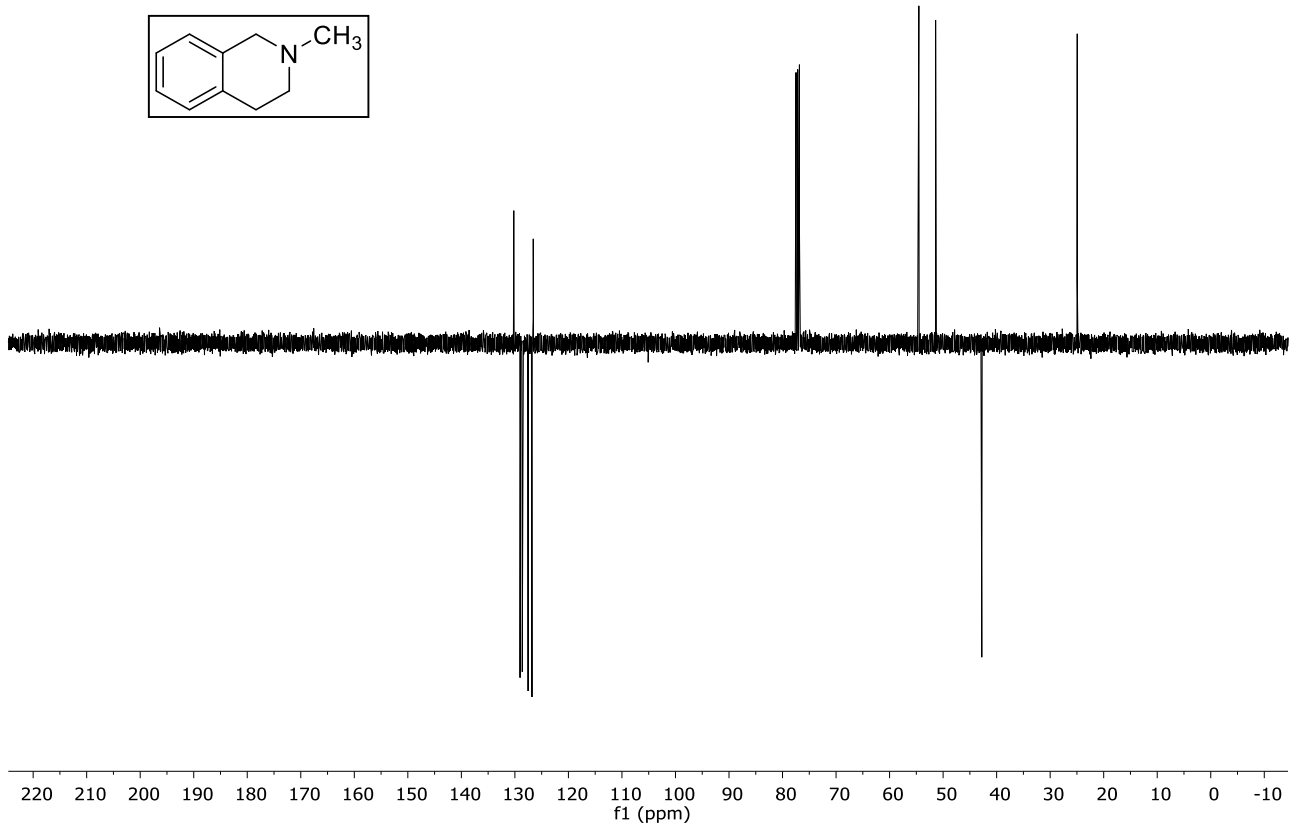
Compound 5c: ^{13}C NMR (101 MHz, DMSO-d_6)



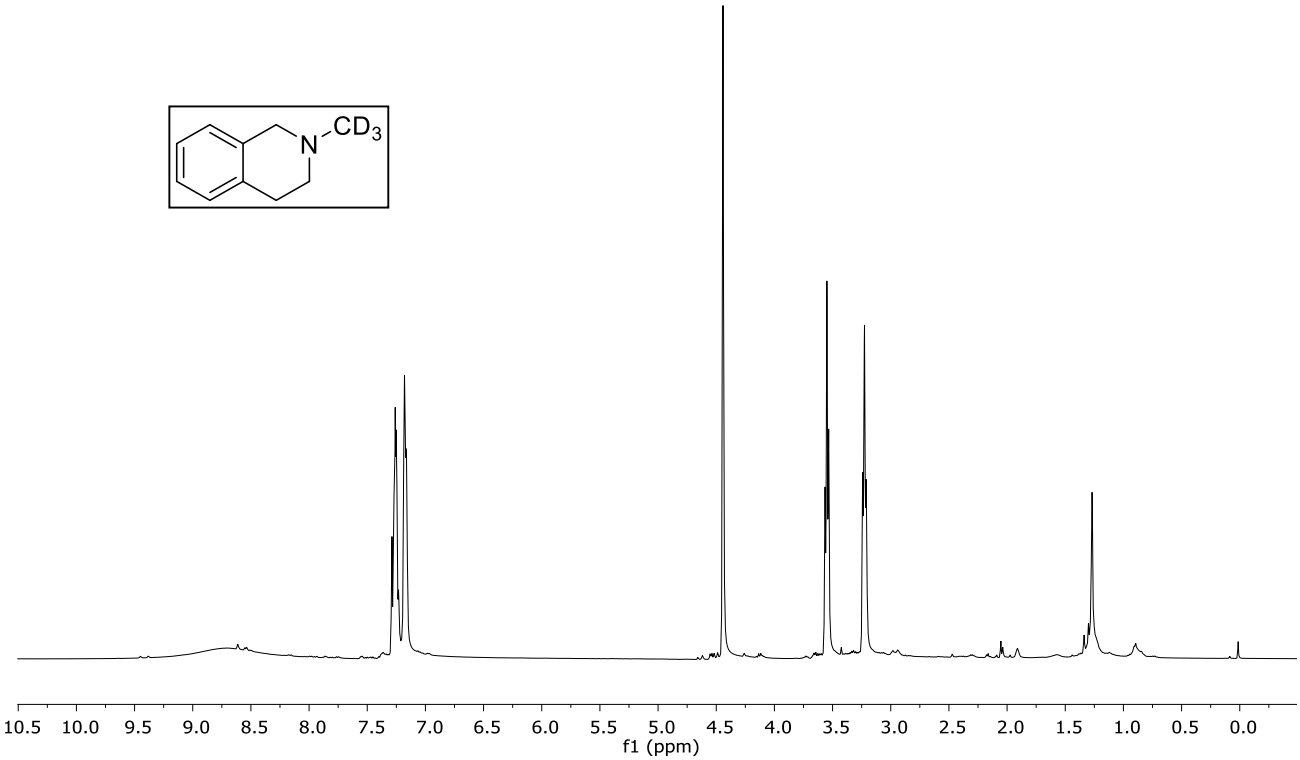
Compound 6b ^{1}H NMR (400 MHz, $CDCl_3$)



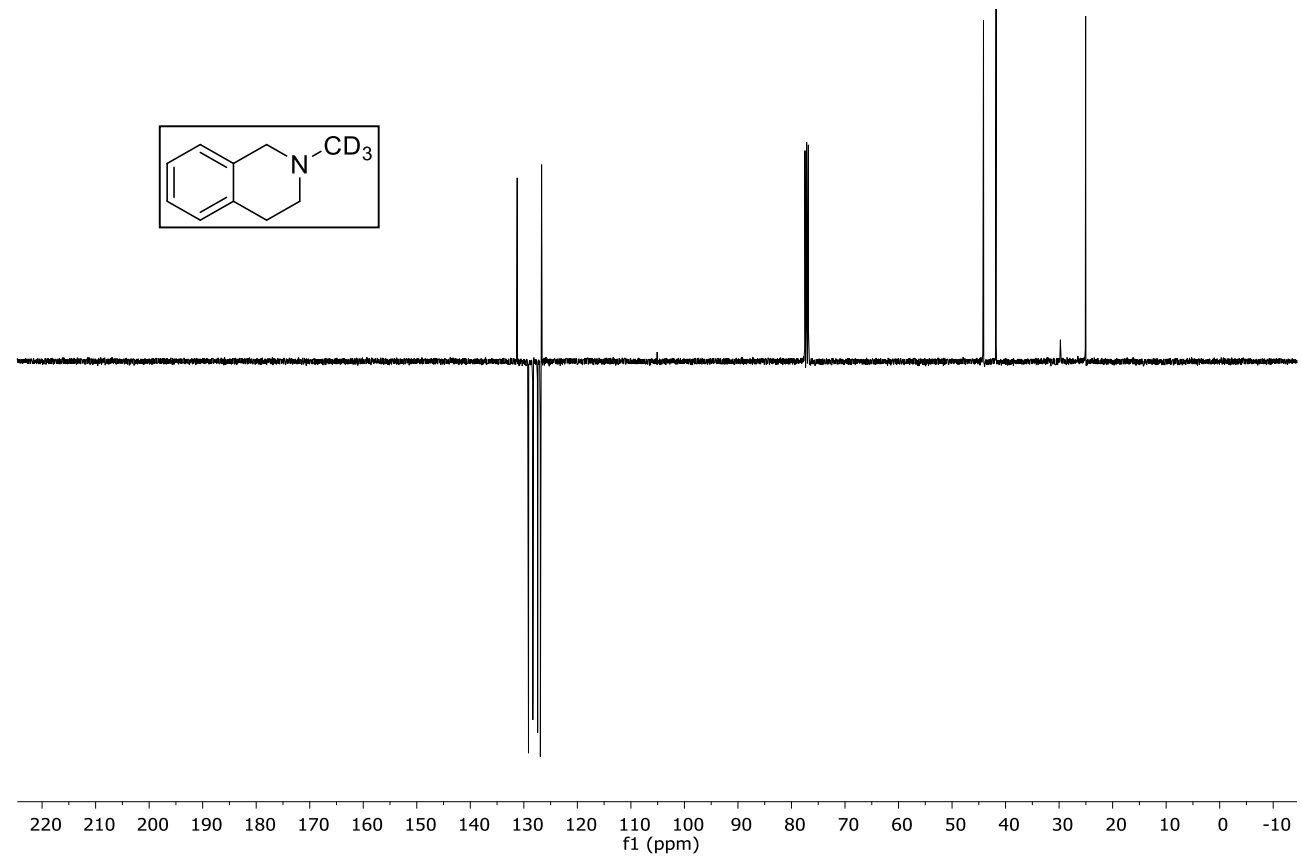
Compound 6b ^{13}C NMR (101 MHz, $CDCl_3$)



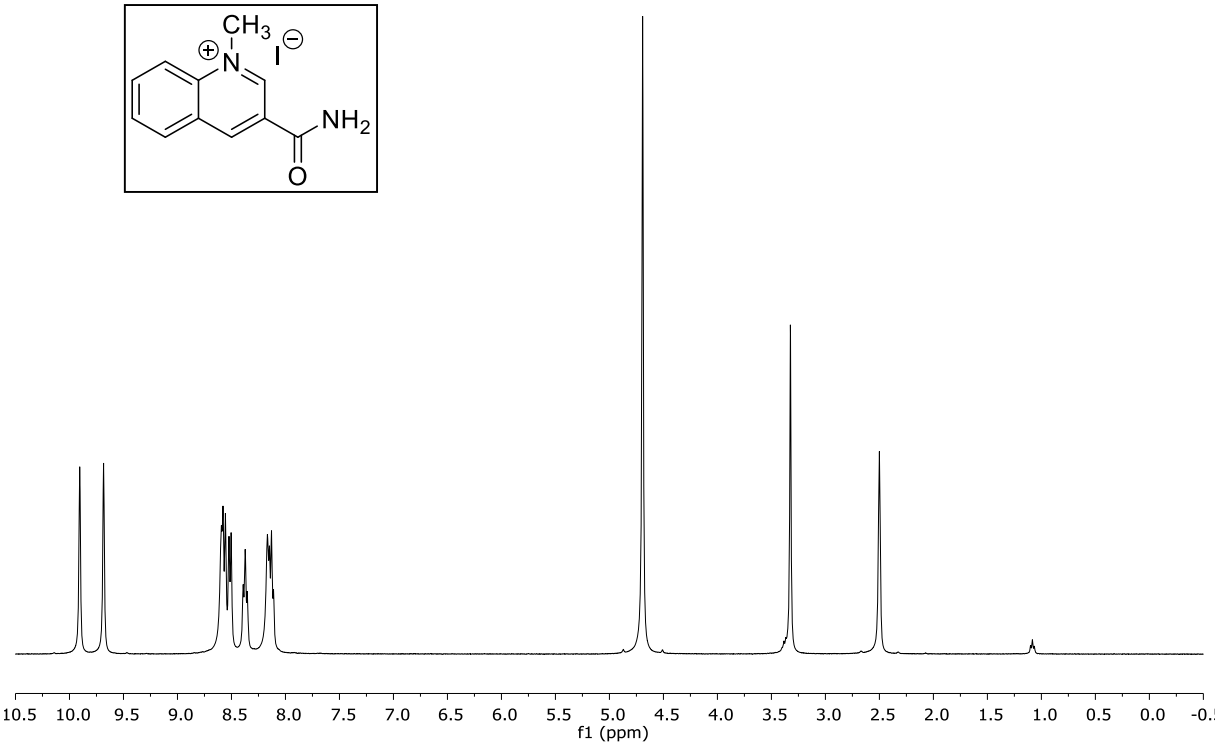
Compound 6c ^{1}H NMR (400 MHz, $CDCl_3$)



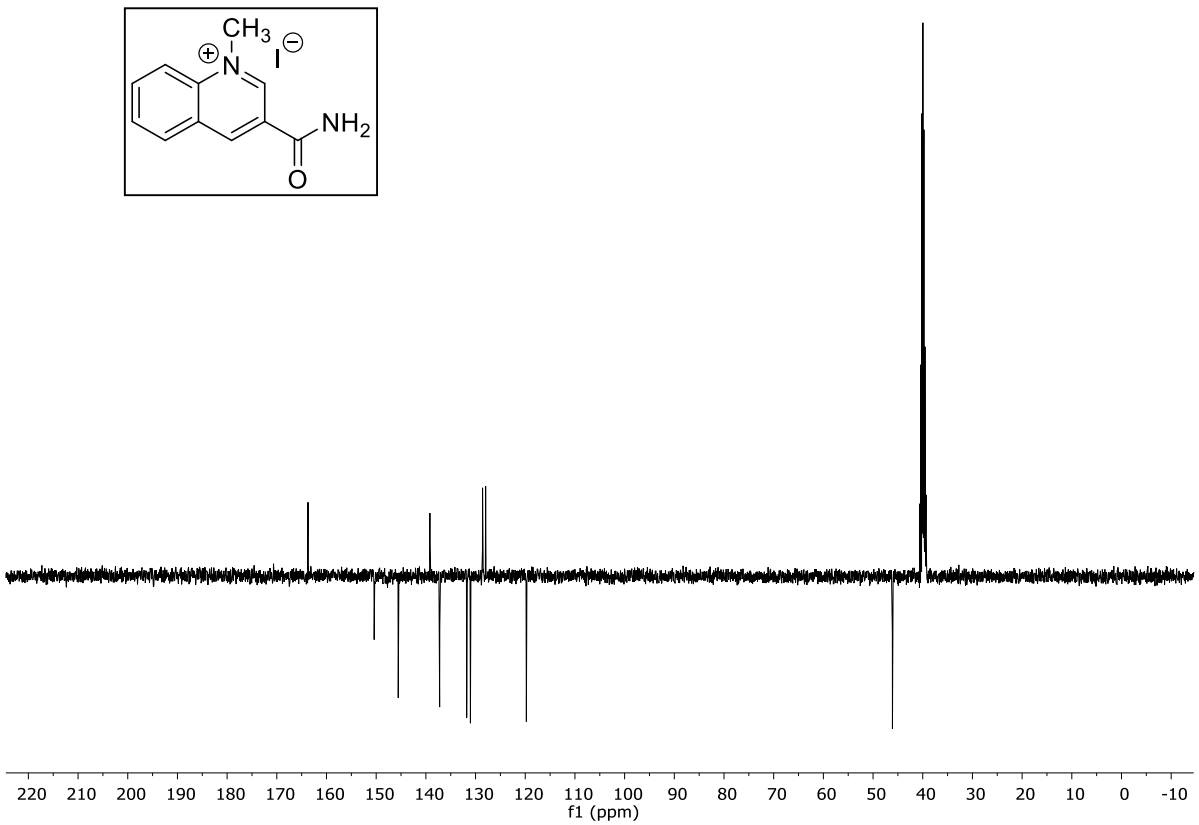
Compound 6c ^{13}C NMR (101 MHz, $CDCl_3$)



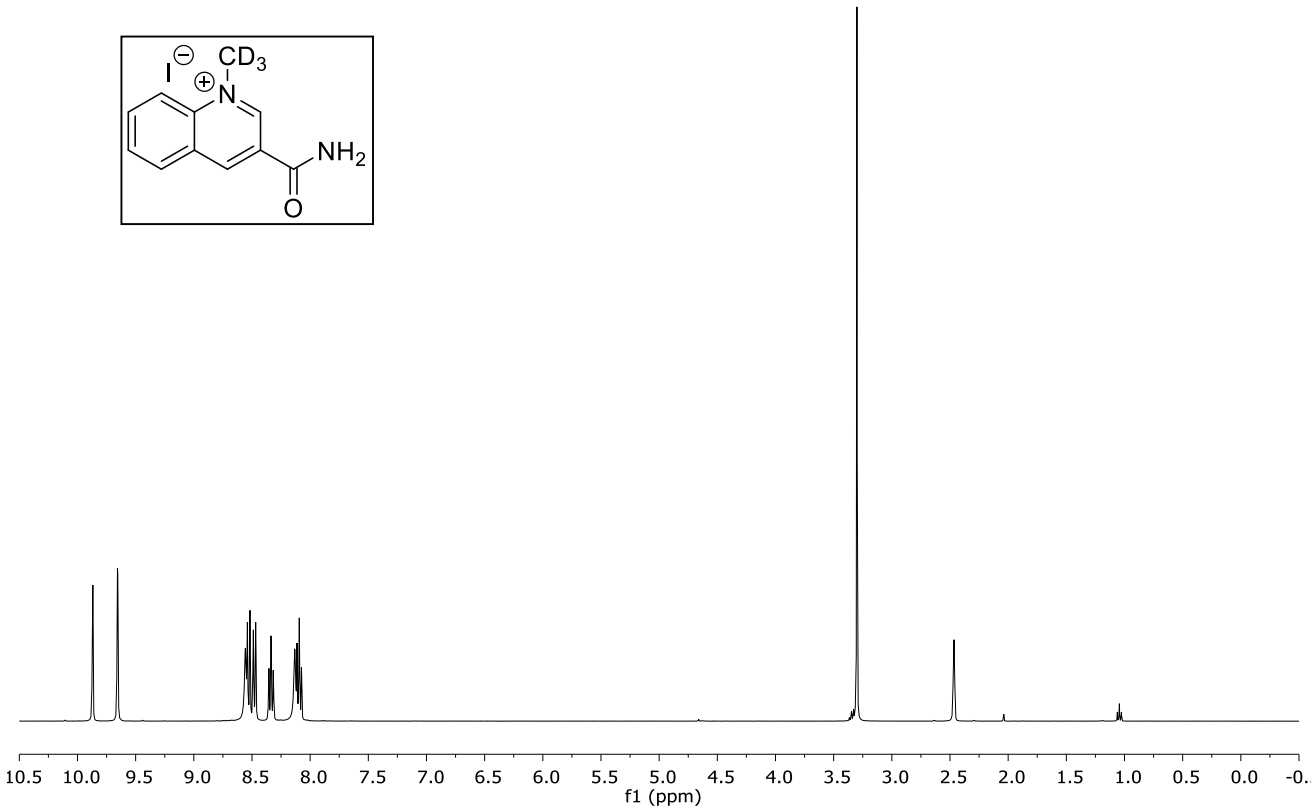
Compound 7b: ^{1}H NMR (400 MHz, DMSO-d_6)



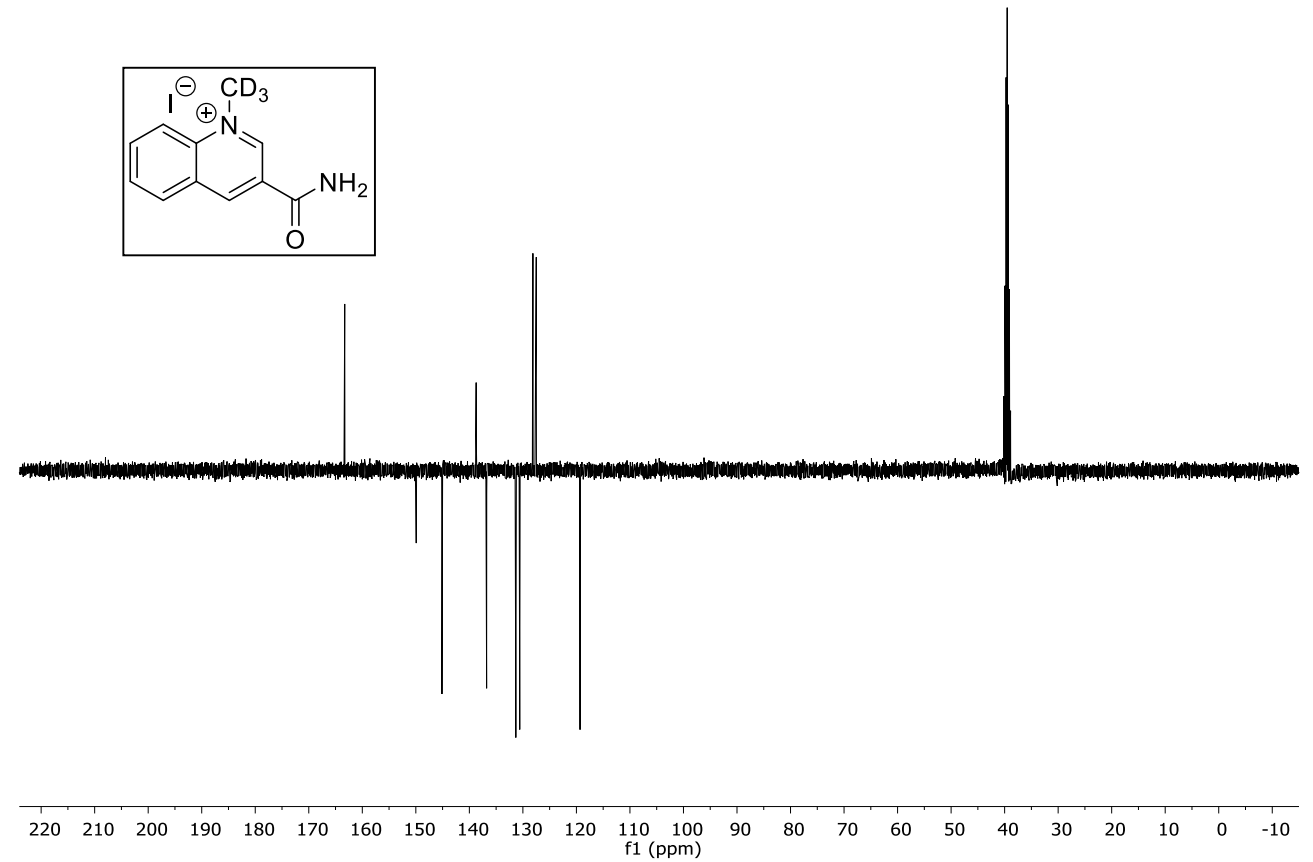
Compound 7b: ^{13}C NMR (101 MHz, DMSO-d_6)



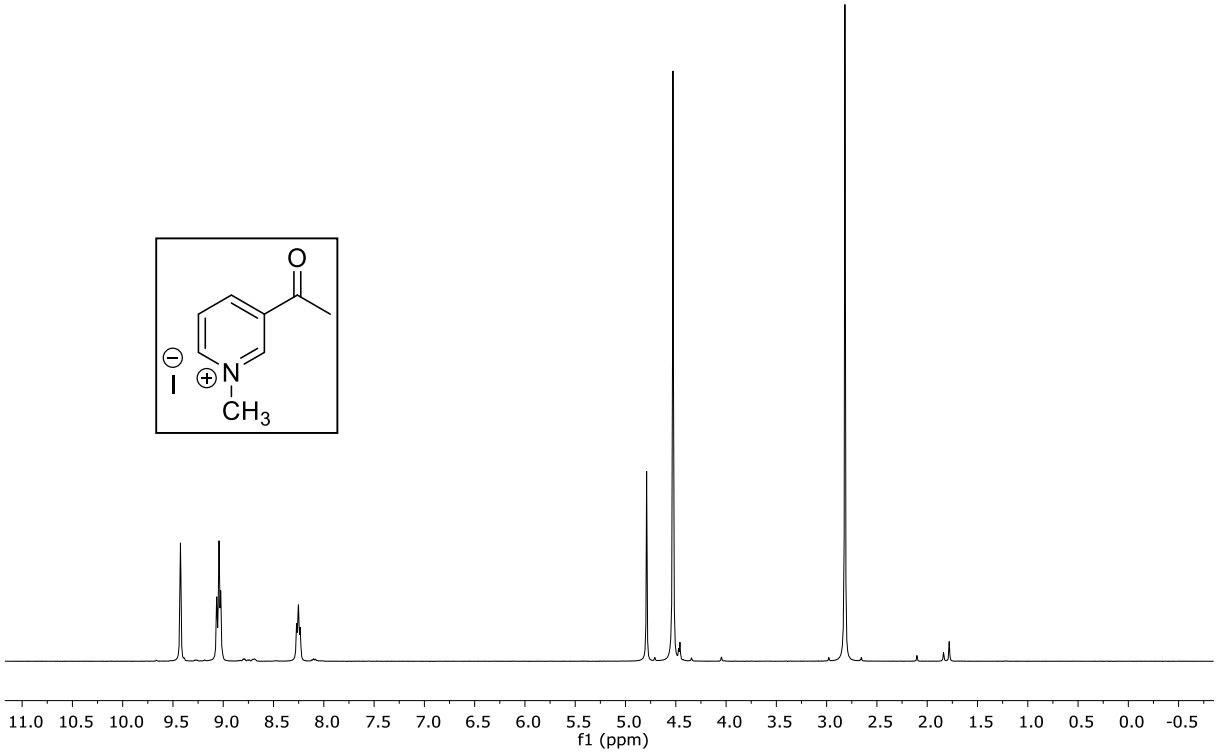
Compound 7c: ^{1}H NMR (400 MHz, DMSO-d_6)



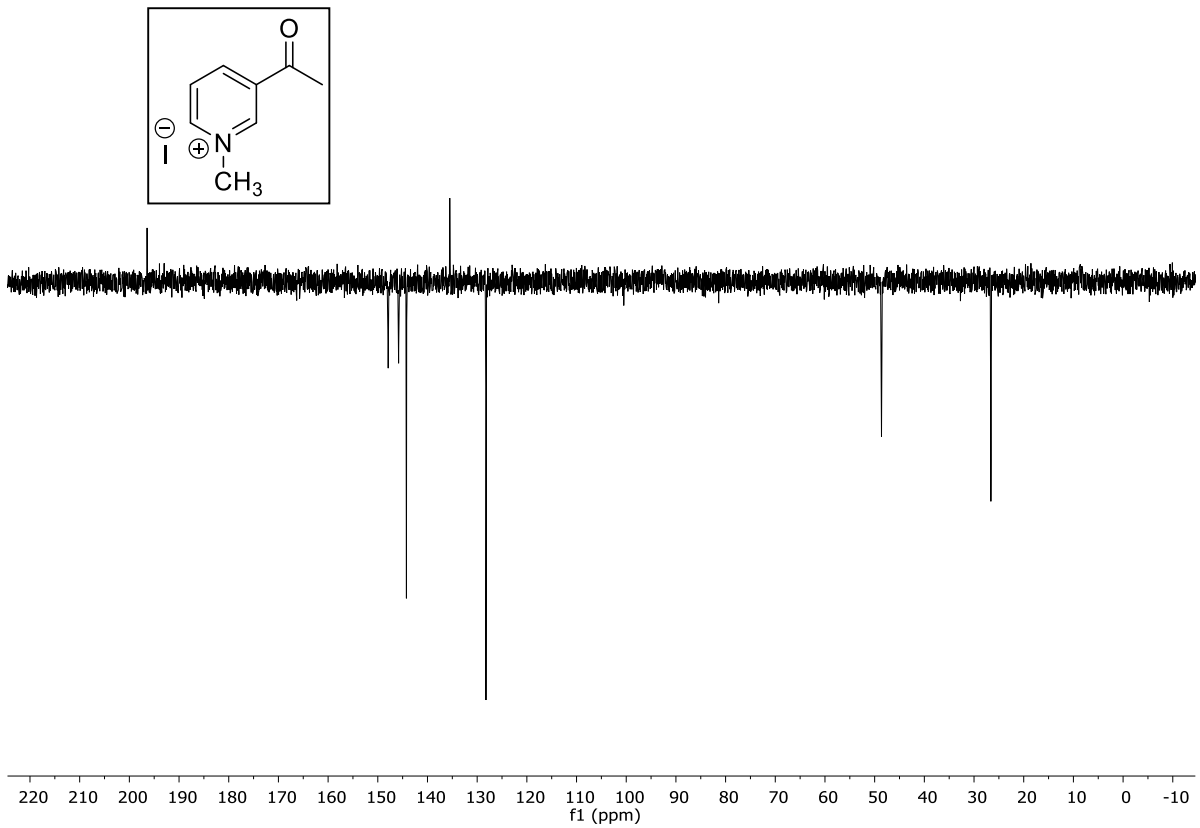
Compound 7c: ^{13}C NMR (101 MHz, DMSO-d_6)



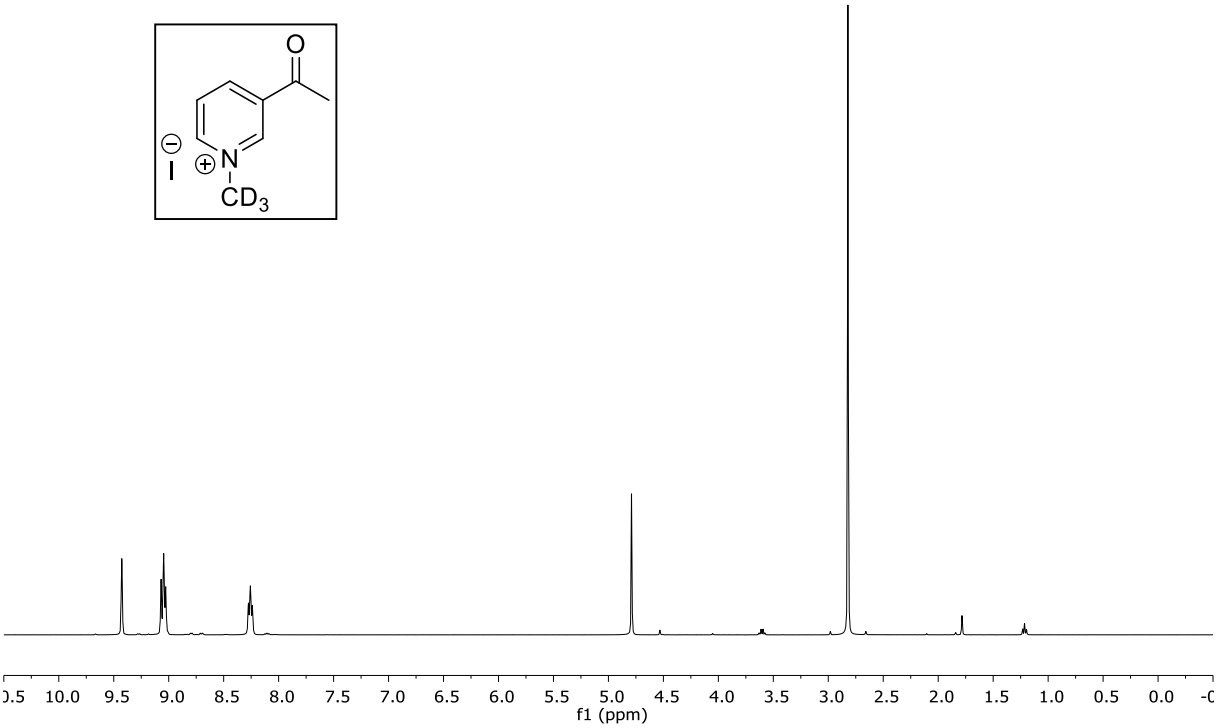
Compound 8b: ^{1}H NMR (400 MHz, D_2O)



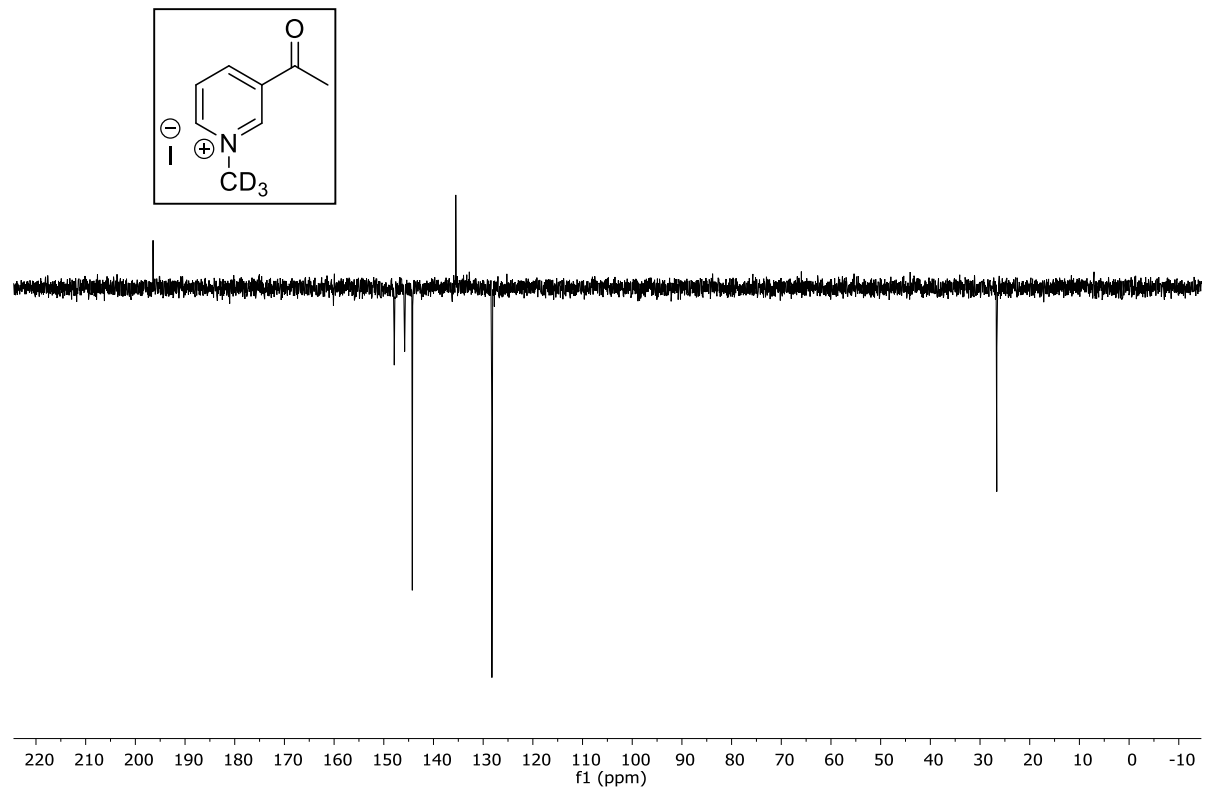
Compound 8b: ^{13}C NMR (101 MHz, D_2O)



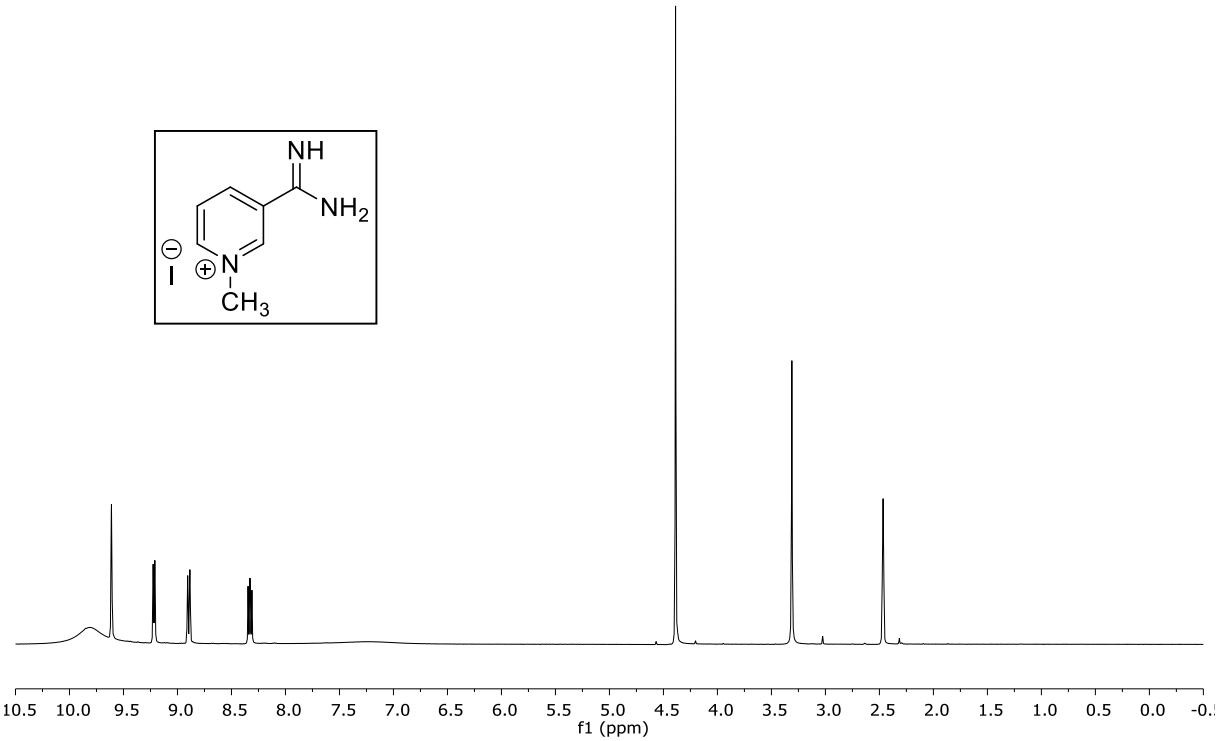
Compound 8c: ^{1}H NMR (400 MHz, D_2O)



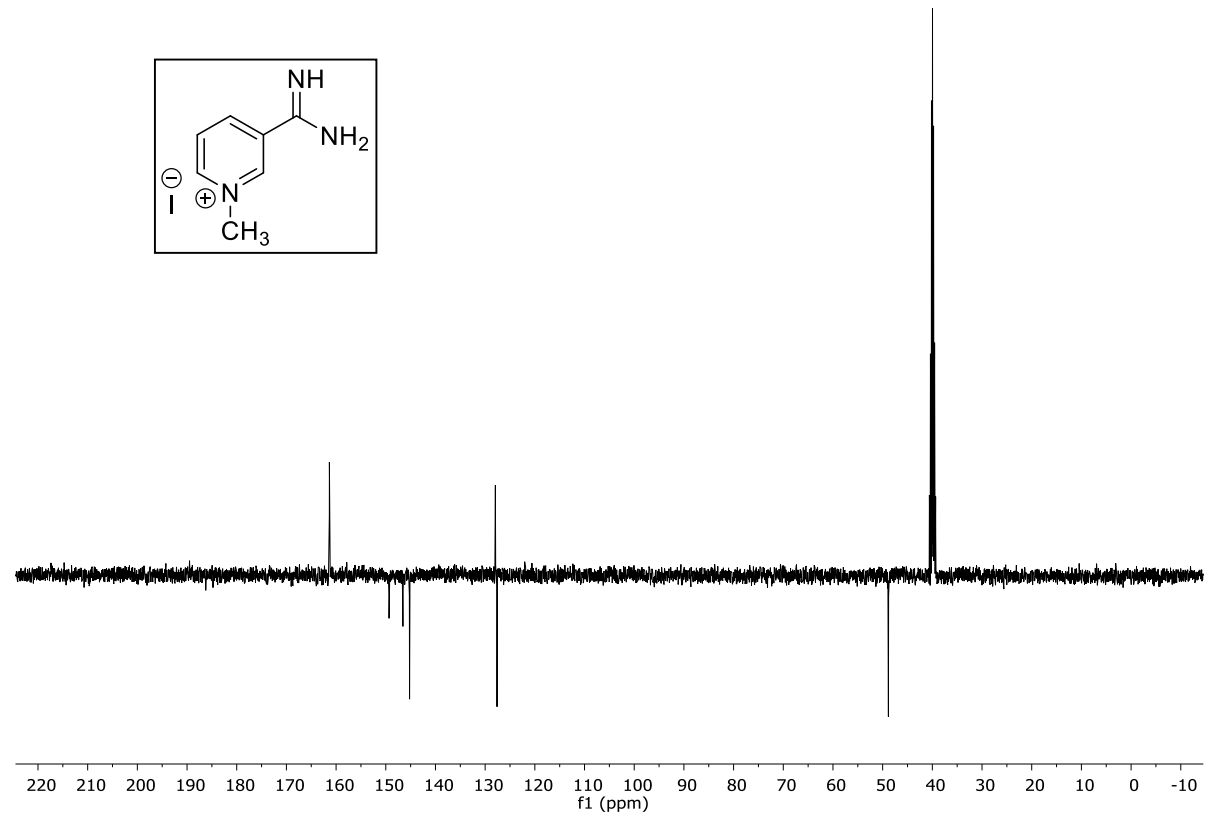
Compound 8c: ^{13}C NMR (101 MHz, D_2O)



Compound 9b: ^{1}H NMR (400 MHz, DMSO-d_6)



Compound 9b: ^{13}C NMR (101 MHz, DMSO-d_6)



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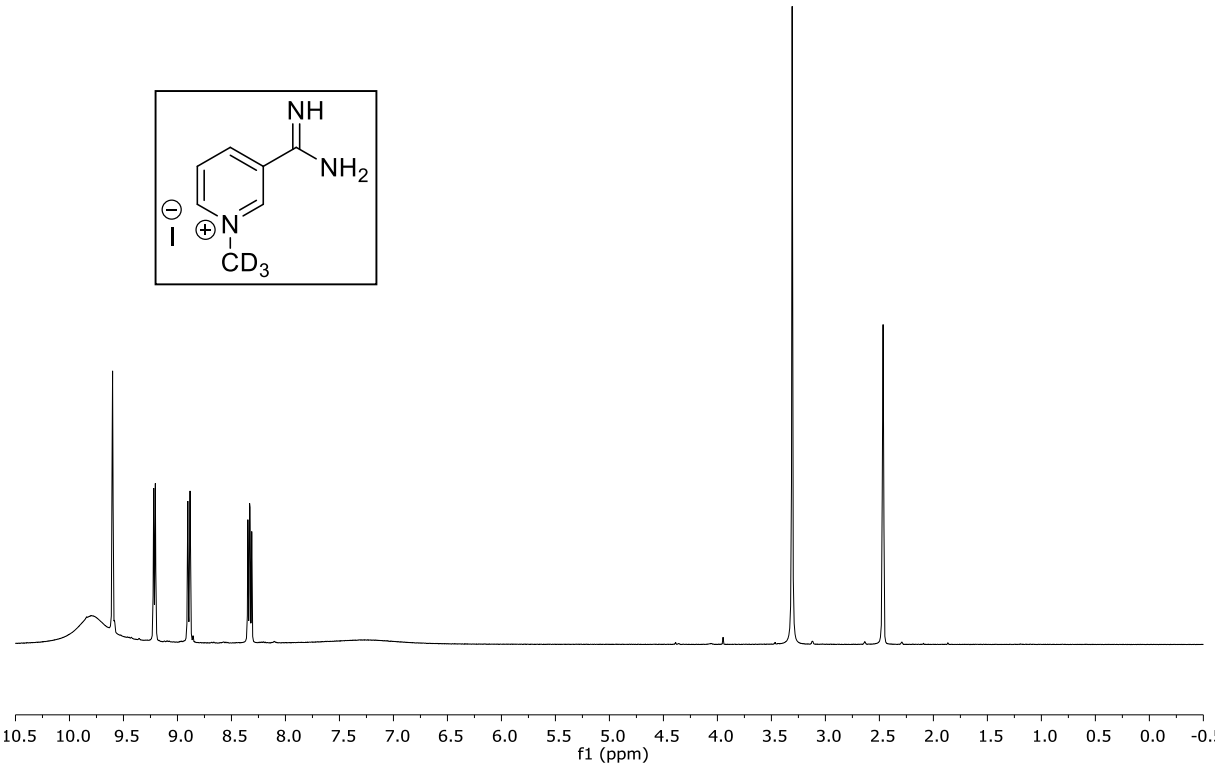

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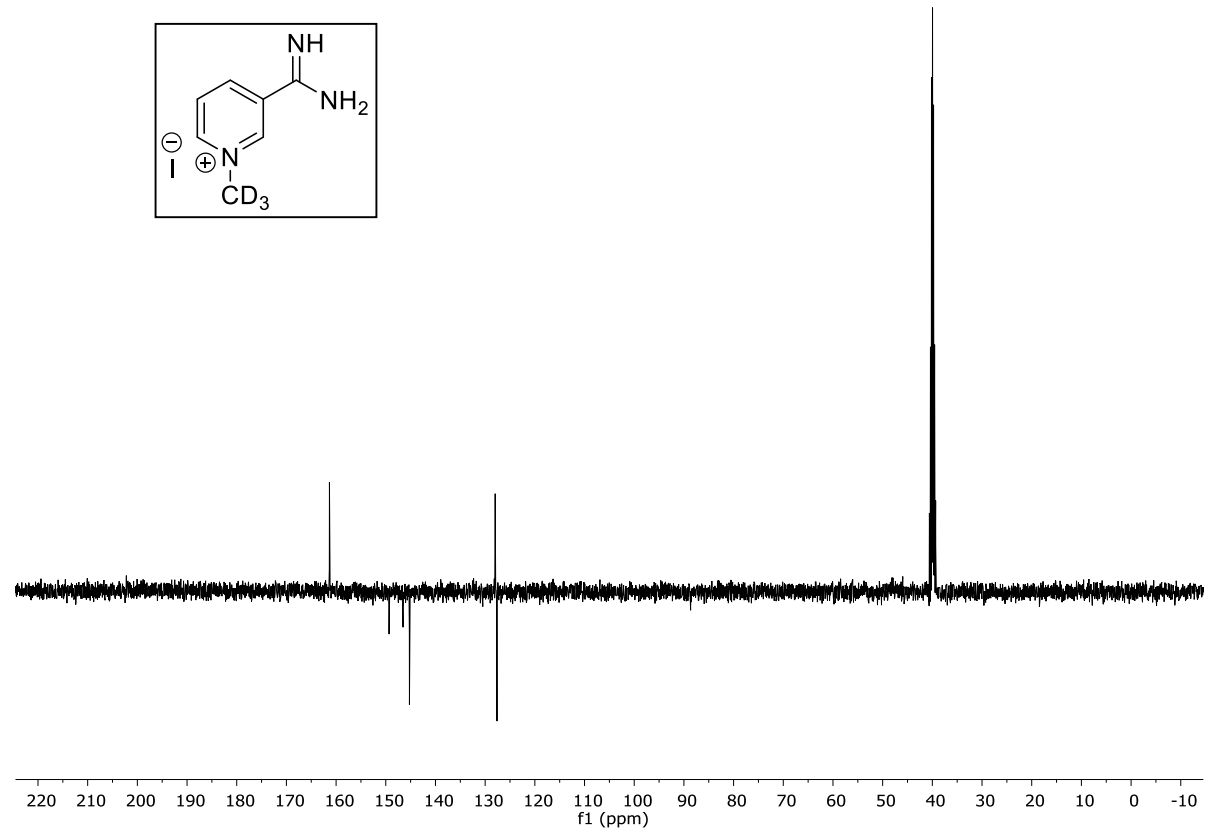

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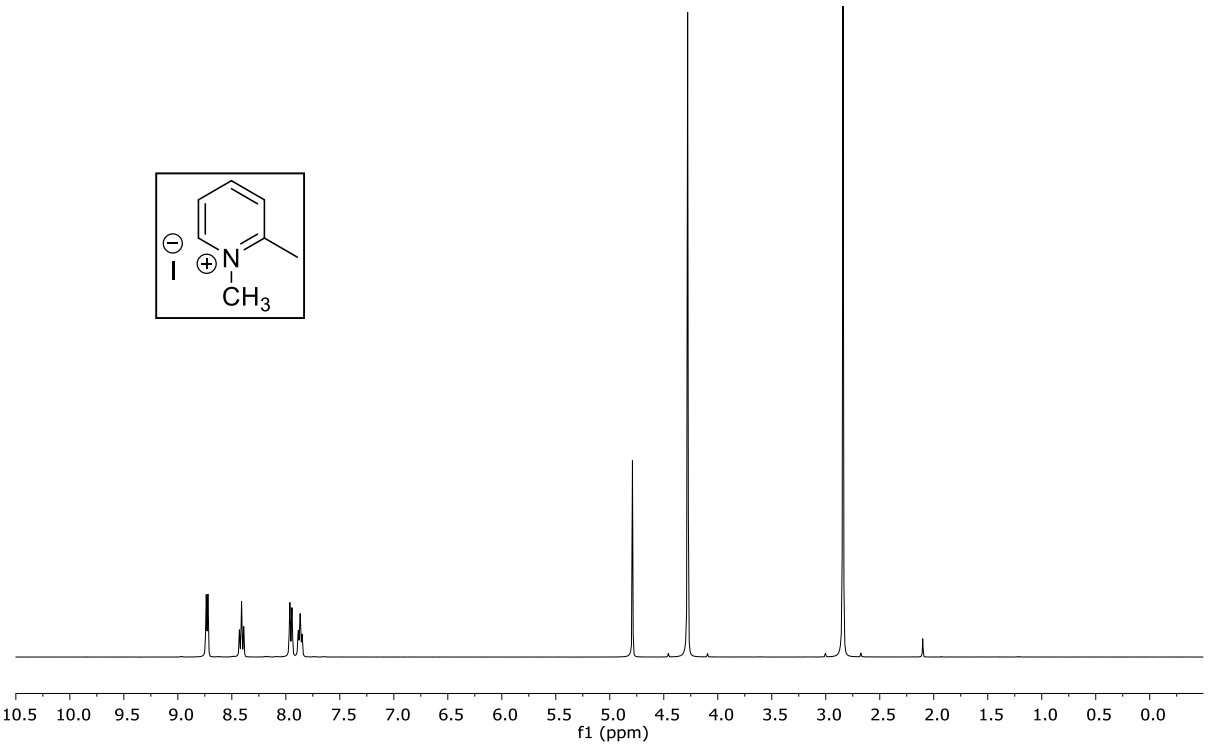

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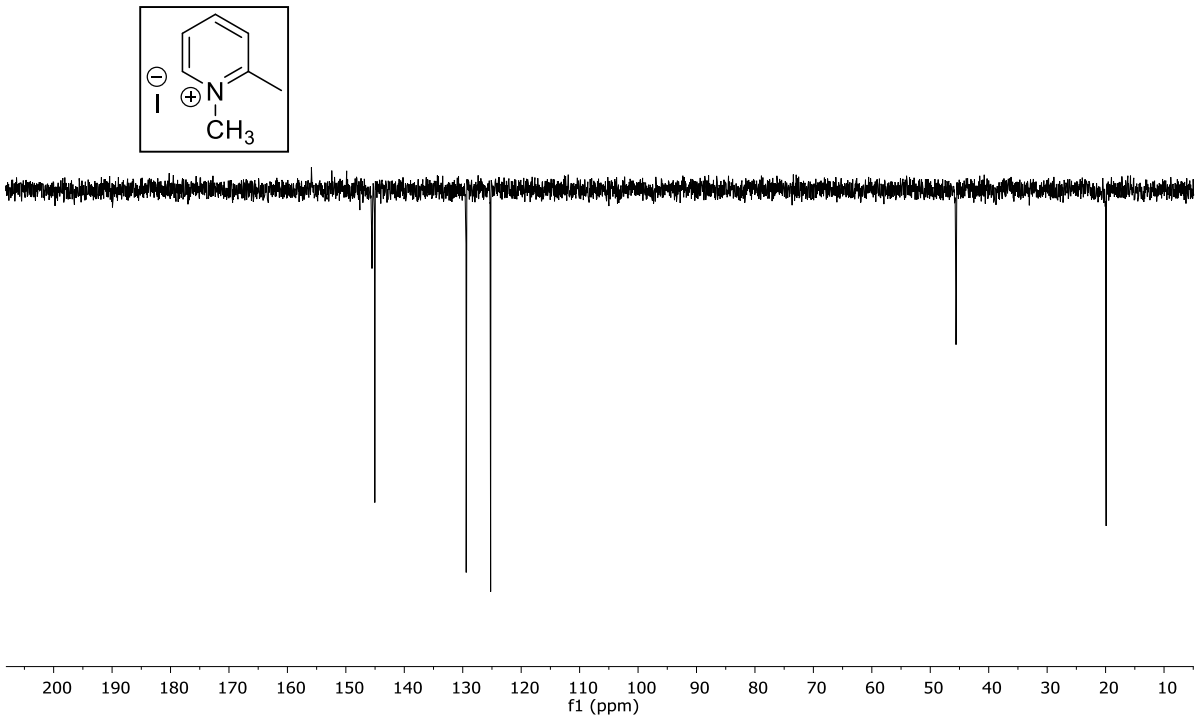
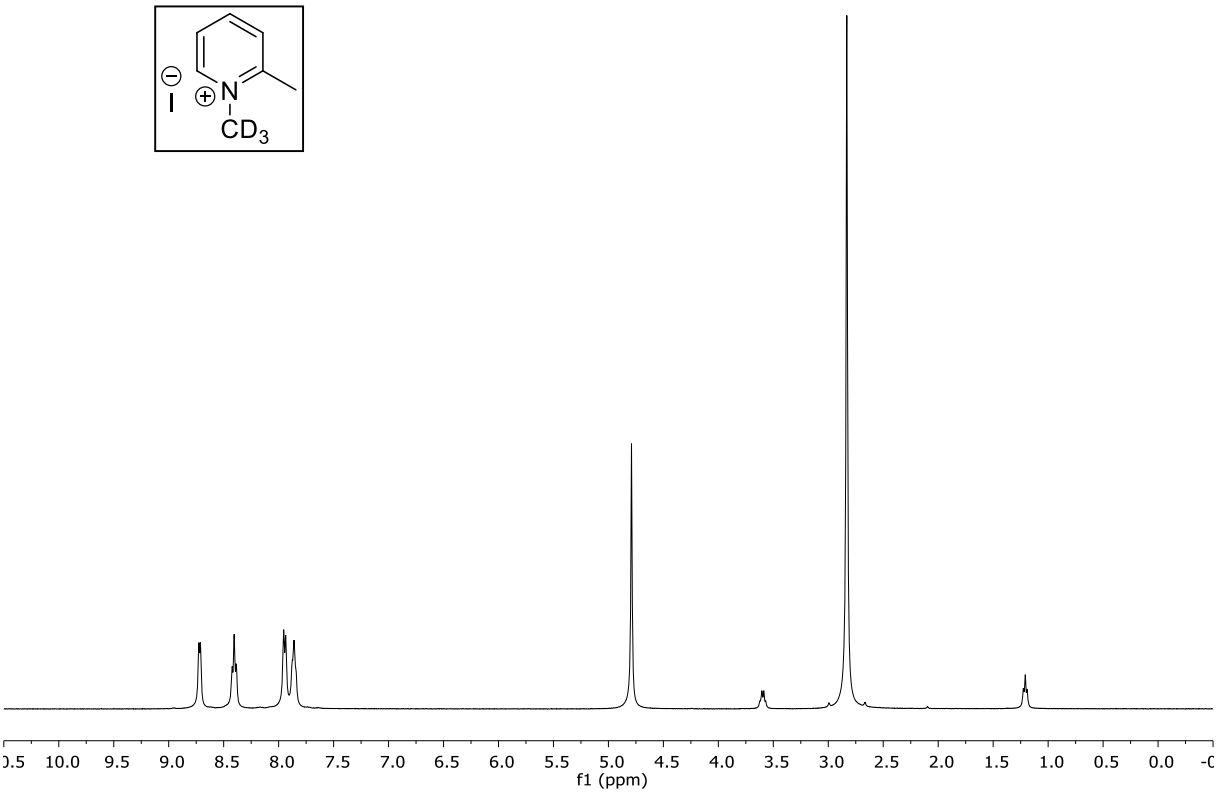
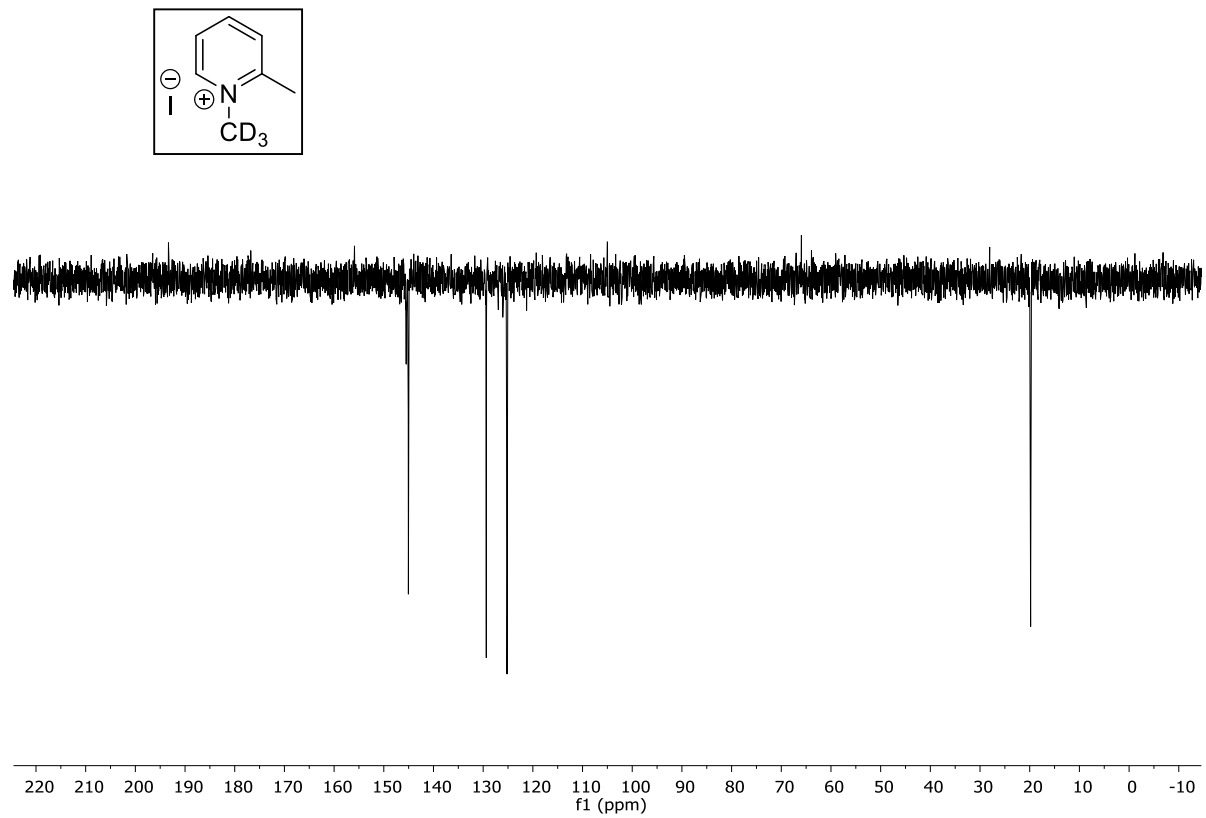


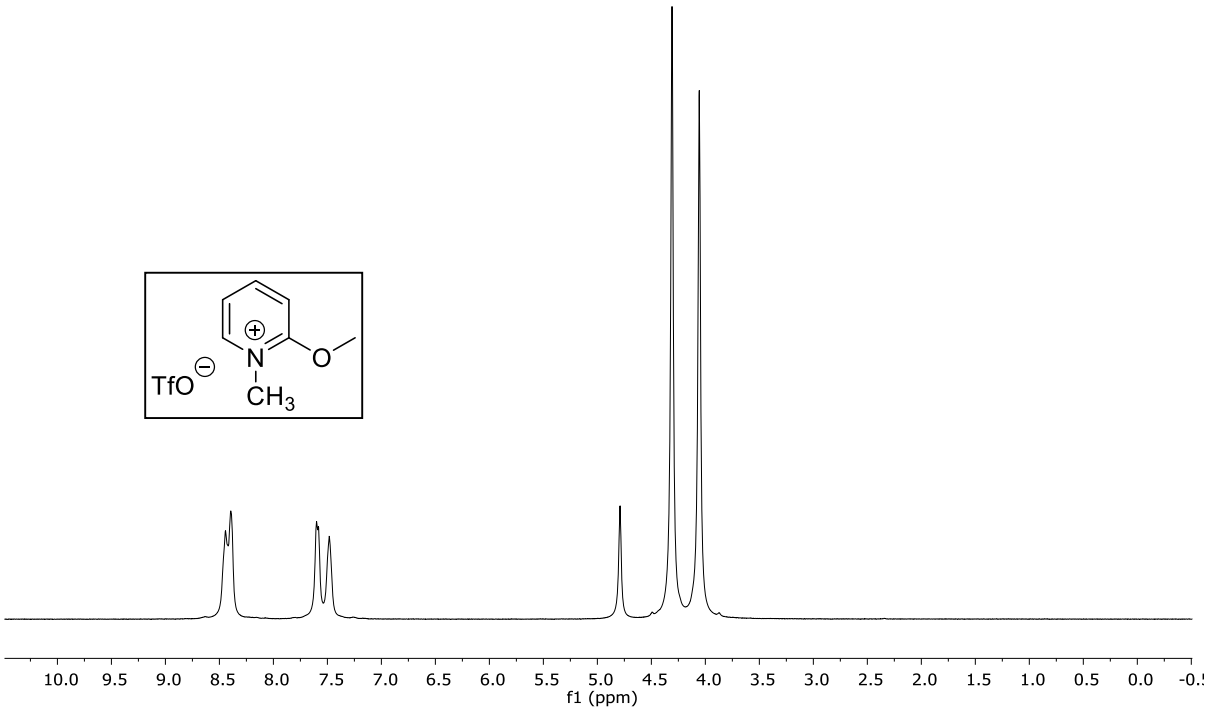
Compound 10c: ^{1}H NMR (400 MHz, D_2O)



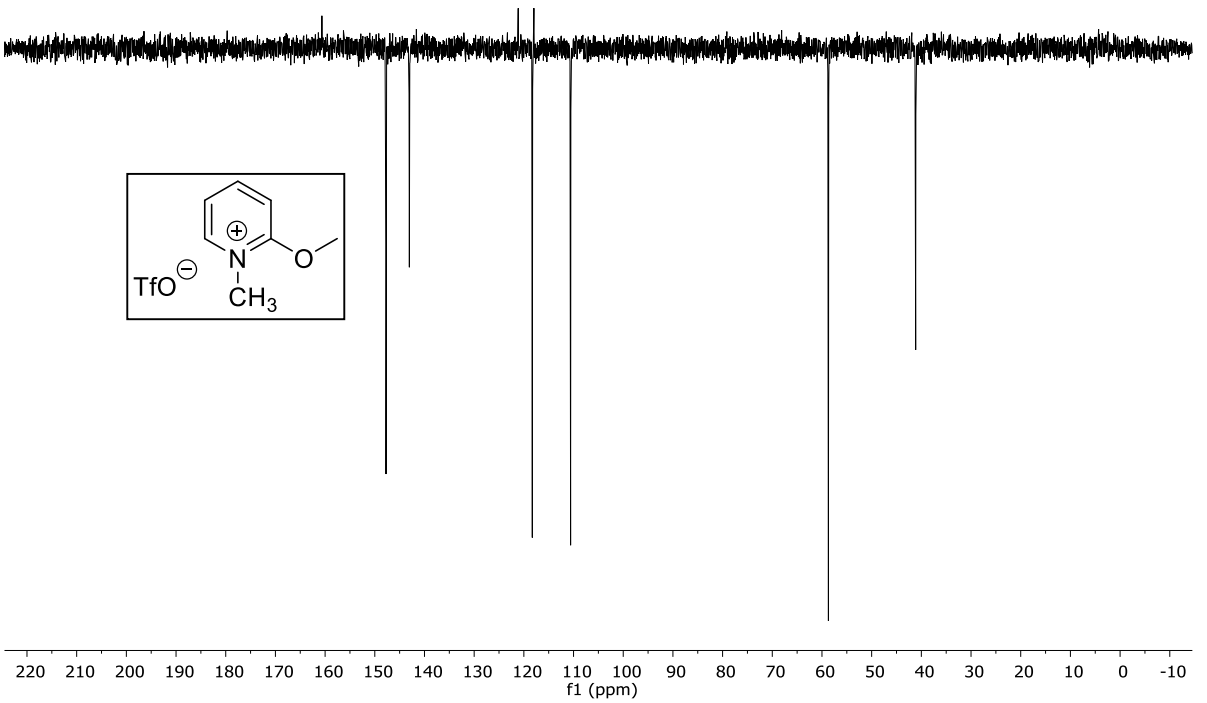
Compound 10c: ^{13}C NMR (101 MHz, D_2O)



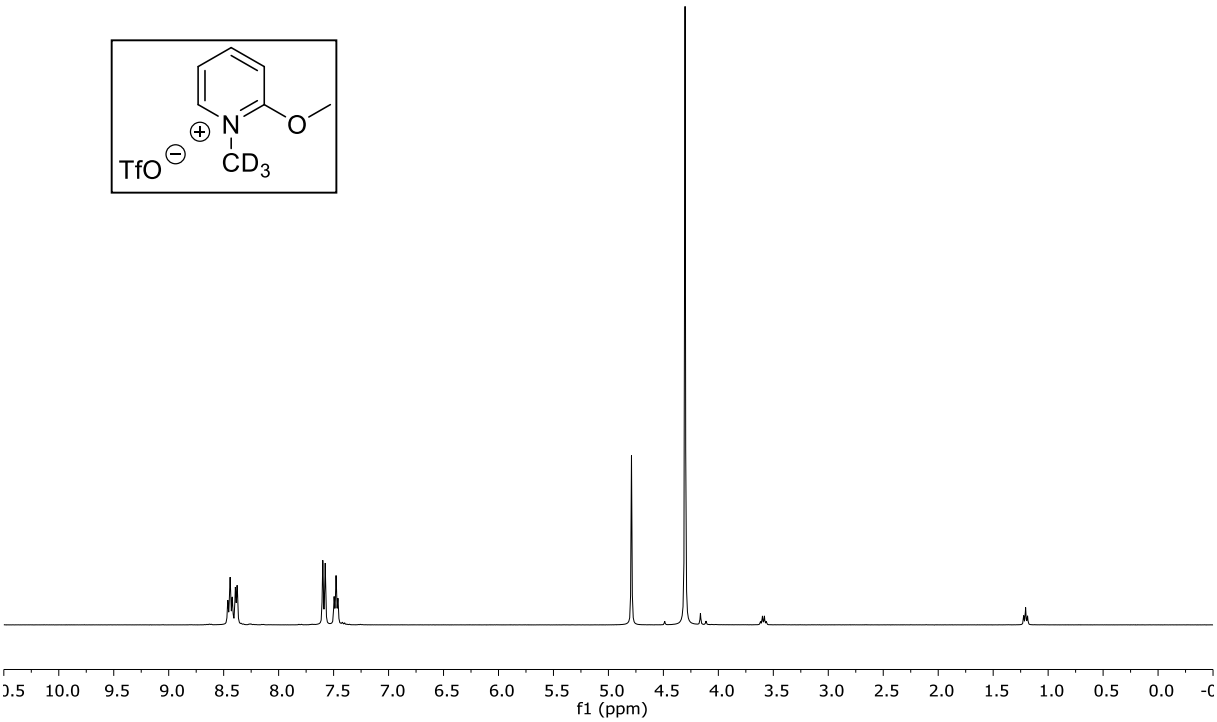
Compound 11b: ^{1}H NMR (400 MHz, D_2O)



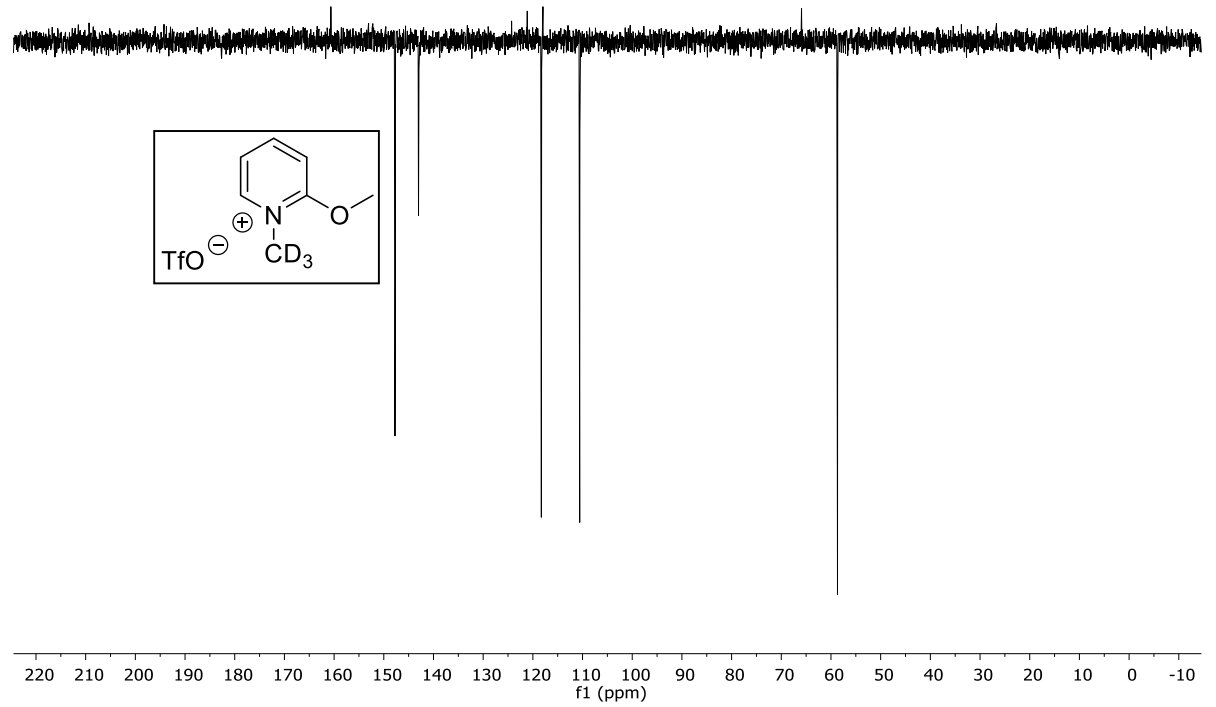
Compound 11b: ^{13}C NMR (101 MHz, D_2O)



Compound 11c: ^{1}H NMR (400 MHz, D_2O)



Compound 11c: ^{13}C NMR (101 MHz, D_2O)



References

(1) Di Rienzo, B., Mellini, P., Tortorella, S., De Vita, D., and Scipione, L. (2010) Facile and Efficient Synthesis of 4-Alkyl Derivatives of 3-Carbamoyl- and 3,5-Dicarbamoylpyridines as Nicotinamide Mimetics. *Synthesis (Stuttg). 2010*, 3835–3838.

(2) Manaka, A., and Sato, M. (2005) Synthesis of Aromatic Thioamide from Nitrile Without Handling of Gaseous Hydrogen Sulfide. *Synth. Commun. 35*, 761–764.

(3) Poon, K. W. C., and Dudley, G. B. (2006) Mix-and-heat benzylation of alcohols using a bench-stable pyridinium salt. *J. Org. Chem. 71*, 3923–3927.