

SUPPORTING INFORMATION

Synthesis of trifluoromethyl *N,N*-aminals from nitrogen containing heterocycles by using a plasma flow microreactor

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General Methods

All the plasma reactions were carried in a gas/liquid biphasic microreactor Biflow 2.7. For more details concerning the flow reactor description and the biphasic flow and the plasma discharge characterizations see Supporting Information (SI) in *Chem. Commun.*, 2022, **58**, 7281–7284.¹ All chemicals obtained from commercially available sources were used without any further purification unless stated. The solvents (Et₂O, pentane) used for column chromatography were purified by distillation. Column chromatography was performed on neutral alumina (Al₂O₃, 150 mesh) under air pressure. Analytical thin layer chromatography (TLC) was performed on aluminum oxide plates (Merck – TLC Aluminum oxide 60 F₂₅₄, neutral). TLC plates were visualized at 254 nm and/or KMnO₄ staining solution followed by heating. ¹H-, ¹³C-, ¹⁹F-NMR spectra were recorded at room temperature on a Bruker Avance III™ HD 400 MHz. Chemical shifts (δ scale, in ppm) were referenced as follows: CDCl₃ referenced to solvent signal: 7.26 ppm for ¹H NMR and 77.16 ppm for ¹³C NMR. The multiplicities of the signals are reported as s (singlet), d (doublet), brd (broad doublet), t (triplet), brt (broad triplet), t_{app} (apparent triplet), brt_{app} (broad apparent triplet), q (quartet), q_{app} (apparent quartet), pent_{app} (apparent pentuplet), m (multiplet or overlap). Coupling constants (J) are given in Hz. GC/MS spectra were obtained using Agilent GC system 7890B and mass spectra from Agilent 5977B equipped with electron impact ionization source (EI). Infrared spectra (ATR) were recorded using a Thermo Fischer SCIENTIFIC Nicolet iS5 – iD7 ATR FTIR spectrometer. Wavenumbers (ν^{max}) are reported in cm⁻¹.

Device:

A biflow 2.7 microreactor equipped with a planar copper electrode was used. For the device see ref 1.

Plasma generation:

A sine (sinusoid) wave signal (AC) was sent from a function generator RS PRO (AFG-21025) to a voltage amplifier (TREK 20/20c high voltage amplifier ×2000) which multiplies the input voltage by 2000. This high voltage was applied to the microreactor and a 14 nF capacitor in series and was monitored with an oscilloscope (PicoScope 5000 Series) through the 2000:1 output monitor of the amplifier. The capacitor mounted, in a series circuit with the reactor is necessary to calculate the discharge power, and the capacitance voltage was measured by a low voltage probe (Teledyne LeCroy PP024 500 MHz 10:1). The frequency used was 2 kHz, and the high voltage was set at 25 kVpp.

TMSCF₃ recycling:

TMSCF₃ was distilled by using a Kugelrohr like apparatus. Up to 90% of TMSCF₃ was recovered by distillation and the recovered TMSCF₃ was used to perform the *N,N*-aminolization. Four recyclings were realized without any significant decrease in the aminol yield. In the case of the piperidine the average yield over 4 cycles is 73%. The purity of distilled TMSCF₃ was evaluated by ¹H NMR, ¹⁹F NMR and GC/MS measurements.

General procedure (GP1) for the preparation of trifluoromethyl *N,N*-amines 2 using TMSCF₃.

In a Biflow 2.7 microreactor equipped with a planar copper electrode and maintained at 30 °C, a solution of amine in TMSCF₃ ($c = 0.1$ M) was pumped in the reactor using a syringe pump with a flow rate of 12 $\mu\text{L}/\text{min}$, and simultaneously argon (Ar) gas was introduced using a Mass Flow Controller (MFC) at a 1.3 sccm flow rate. At these flow rates (12 $\mu\text{L}/\text{min}$ and 1.3 sccm), biphasic laminar flow was obtained (the control was made using a CCD camera).

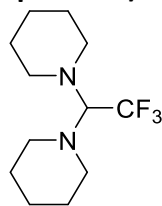
Once the biphasic laminar flow was obtained, the plasma discharge was initiated by using an alternative function generator (AFG – sinusoidal wave at 2 kHz) and a voltage amplifier (Trek 20/20C). The voltage was adjusted slowly until it reached 25 kV_{pp}. Once 25 kV_{pp} was reached, 5 min were necessary to reach the equilibrium. The reaction mixture was collected over a period of 5 h to 8 h. TMSCF₃ was then distilled for recycling using a Kugelrohr like apparatus and the purification of the products was realized by column chromatography on neutral alumina.

Post-functionalization procedure (GP2) for the preparation of 1-dialkylamine-2,2,2-trifluoroethanes.

In a dry round bottom flask equipped with a stirring bar, under an argon atmosphere, ZnCl₂ (1.2 equiv) and NaBH₃CN (1.2 equiv) were added to a solution of 1,1-bis(dialkylamine)-2,2,2-trifluoroethanes (1 equiv) in dry THF (3 mL). The reaction mixture was heated at reflux. After 4 h, the solvent was then evaporated, a solution of NaOH (3M) was added to the residue to reach pH = 11. The aqueous phase was extracted with Et₂O (3 x 25 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated to afford the trifluoroethylamines as a pale-yellow oil. No further purification was made.

Spectral Data

1,1-Bis(piperidine)-2,2,2-trifluoroethane (**2a**)²



2a

Chemical Formula: C₁₂H₂₁F₃N₂

Molecular Weight: 250.31

Compound **2a** was prepared according to the general procedure **GP1**. A solution of piperidine **1a** (43 mg, 0.5 mmol) in TMSCF₃ (5 mL) was subjected to an argon plasma. After 7 h, TMSCF₃ was distilled, and the crude was purified by flash column chromatography on neutral alumina (Et₂O/pentane = 5:95) providing **2a** as a colorless oil (47 mg, yield = 75%).

Compound **2a** was also prepared from **1a** using TESCf₃. A solution of piperidine **1a** (43 mg, 0.5 mmol) in TESCf₃ (5 mL) was subjected to an argon plasma. After 7 h, TESCf₃ was evaporated, and the crude was purified by flash column chromatography on neutral alumina (Et₂O/pentane = 5:95) providing **2a** as a colorless oil (45 mg, yield = 74%).

R_f = 1 (Et₂O/pentane = 5:95)

IR (neat): 2933, 2852, 2818, 1792, 1453, 1442, 1391, 1353, 1257, 1151, 1122, 1109, 1066, 1006 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 3.33 (q, *J* = 7.8 Hz, 1H), 2.70 (t_{app}, 8H), 1.58 – 1.49 (m, 8H), 1.48 – 1.40 (m, 4H).

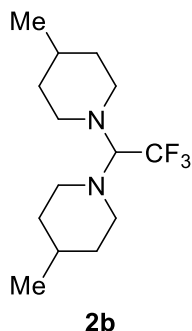
¹³C NMR (101 MHz, CDCl₃): δ = 125.9 (q, *J* = 293.5 Hz), 84.6 (q, *J* = 26.4 Hz), 51.0 (4C), 26.5 (4C), 24.8 (2C).

¹⁹F NMR (376 MHz, CDCl₃): δ = -65.9.

GC/MS - EI *m/z*: 250 (M⁺, 1), 211 (1), 181 (9), 166 (100), 138 (1), 110 (6), 86 (6), 69 (11), 41 (6).

HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₂H₂₂F₃N₂: 251.1730. Found: 251.1726

1,1-Bis(4-methylpiperidine)-2,2,2-trifluoroethane (**2b**)



Chemical Formula: C₁₄H₂₅F₃N₂

Molecular Weight: 278.36

Compound **2b** was prepared according to the general procedure **GP1**. A solution of 4-methylpiperidine **1b** (49 mg, 0.5 mmol) in TMSCF₃ (5 mL) was subjected to an argon plasma. After 7 h, TMSCF₃ was distilled, and the crude was purified by flash column chromatography on neutral alumina (Et₂O/pentane = 5:95) providing **2b** as a colorless oil (45mg, yield = 65%).

R_f = 1 (Et₂O/pentane = 5:95)

IR (neat): 2949, 2919, 2871, 2819, 1455, 1443, 1393, 1377, 1345, 1252, 1194, 1146, 1109, 1080, 975 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 3.38 (q, *J* = 7.7 Hz, 1H), 2.99 (brt, *J* = 12.1 Hz, 4H), 2.51 – 2.31 (pent_{app}, *J* = 12.0 Hz, 4H), 1.65 – 1.50 (m, 4H), 1.43 – 1.28 (m, 2H), 1.24 – 1.08 (m, 4H), 0.91 (d, *J* = 6.5 Hz, 6H).

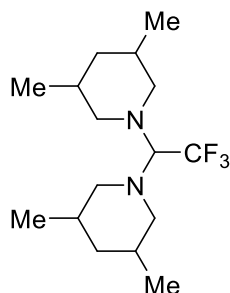
¹³C NMR (101 MHz, CDCl₃): δ = 126.0 (q, *J* = 293.3 Hz), 84.0 (q, *J* = 26.5 Hz), 51.3 (2C), 49.2 (2C), 35.1 (2C), 34.7 (2C), 31.2 (2C), 22.1 (2C).

¹⁹F NMR (376 MHz, CDCl₃): δ = -66.0.

GC/MS - EI *m/z*: 278 (M⁺, 1), 239 (1), 209 (11), 193 (1), 180 (100), 164 (1), 138 (9), 112 (13), 100 (5), 83 (1), 69 (11), 57 (3), 41 (2).

HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₄H₂₆F₃N₂: 279.2043. Found: 279.2039

1,1-Bis(3,5-dimethylpiperidine)-2,2,2-trifluoroethane (**2c**)



2c

Chemical Formula: C₁₆H₂₉F₃N₂

Molecular Weight: 306.42

Compound **2c** was prepared according to the general procedure **GP1**. A solution of 3,5-dimethylpiperidine **1c** (40 mg, 0.35 mmol, isomers ratio 85:15) in TMSCF₃ (3.5 mL) was subjected to an argon plasma. After 5 h, TMSCF₃ was distilled, and the crude was purified by flash column chromatography on neutral alumina (Et₂O/pentane = 5:95) providing **2c** as a colorless oil (35 mg, yield = 65%). Two isomers are present in a ratio = 85:15.

R_f = 1 (Et₂O/pentane = 5:95)

IR (neat): 2952, 2928, 2908, 2872, 2831, 1459, 1377, 1349, 1330, 1254, 1194, 1150, 1129, 1109, 1073, 969 cm⁻¹.

¹H NMR (400 MHz, CDCl₃):

Major isomer δ = 3.42 (q, *J* = 7.7 Hz, 1H), 3.01 – 2.88 (m, 4H), 1.94 (pent_{app}, *J* = 8.0 Hz, 4H), 1.69 – 1.54 (m, 4H), 1.38 – 1.17 (m, 2H), 0.84 (d, *J* = 2.7 Hz, 6H), 0.82 (d, *J* = 2.7 Hz, 6H), 0.54 (q, *J* = 12.0 Hz, 2H).

Minor isomer δ = 3.36 (q, *J* = 7.7 Hz, 1H), 2.78 – 2.66 (m, 4H), 1.94 (pent_{app}, *J* = 8.0 Hz, 4H), 1.69 – 1.54 (m, 4H), 1.38 – 1.17 (m, 2H), 0.94 (d, *J* = 0.9 Hz, 6H), 0.93 (d, *J* = 0.8 Hz, 6H), 0.54 (q, *J* = 12.0 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃):

Major isomer δ = 125.8 (q, *J* = 293.1 Hz), 83.6 (q, *J* = 26.4 Hz), 58.7 (2C), 56.6 (2C), 42.5 (2C), 31.6 (2C), 31.3 (2C), 19.6 (2C), 19.5 (2C).

Minor isomer δ = 125.8 (q, *J* = 293.1 Hz), 83.6 (q, *J* = 26.4 Hz), 58.4 (2C), 57.2 (2C), 39.4 (2C), 27.8 (2C), 27.7 (2C), 18.9 (2C), 18.9 (2C).

¹⁹F NMR (376 MHz, CDCl₃):

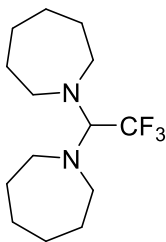
Major isomer δ = -65.9.

Minor isomer δ = -65.8.

GC/MS - EI *m/z*: 265 (1), 208 (100), 178 (1), 152 (4), 126 (19), 112 (15), 96 (1), 70 (5), 55 (11).

HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₆H₃₀F₃N₂: 307.2283. Found: 307.2281

1,1-Bis(azepane)-2,2,2-trifluoroethane (2d)²



2d

Chemical Formula: C₁₄H₂₅F₃N₂

Molecular Weight: 278.36

Compound **2d** was prepared according to the general procedure **GP1**. A solution of azepane **1d** (39 mg, 0.4 mmol) in TMSCF₃ (4 mL) was subjected to an argon plasma. After 5.5 h, TMSCF₃ was distilled, and the crude was purified by flash column chromatography on neutral alumina (Et₂O/pentane = 5:95) providing **2d** as a colorless oil (42 mg, yield = 75%).

R_f = 1 (Et₂O/pentane = 5:95)

IR (neat): 2923, 2852, 1451, 1360, 1254, 1143, 1111, 1008, 967 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 3.76 (q, *J* = 7.4 Hz, 1H), 2.91 – 2.84 (m, 8H), 1.76 – 1.39 (m, 16H).

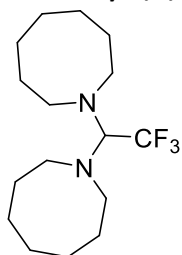
¹³C NMR (101 MHz, CDCl₃): δ = 126.2 (q, *J* = 292.7 Hz), 83.6 (q, *J* = 26.7 Hz), 51.3 (4C), 29.6 (4C), 27.3 (4C).

¹⁹F NMR (376 MHz, CDCl₃): δ = -66.8.

GC/MS - EI *m/z*: 278 (M⁺, 1), 258 (1), 209 (9), 180 (100), 164 (1), 126 (11), 112 (23), 100 (3), 83 (1), 69 (1), 55 (11), 41 (7).

HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₄H₂₆F₃N₂: 279,3632. Found: 279,3635

1,1-Bis(azocane)-2,2,2-trifluoroethane (**2e**)



2e

Chemical Formula: C₁₆H₂₉F₃N₂

Molecular Weight: 306.42

Compound **2e** was prepared according to the general procedure **GP1**. A solution of azocane **1e** (45 mg, 0.4 mmol) in TMSCF₃ (4 mL) was subjected to an argon plasma. After 5.5 h, TMSCF₃ was distilled, and the crude was purified by flash column chromatography on neutral alumina (Et₂O/pentane = 5:95) providing **2e** as a colorless oil (45 mg, yield = 80%).

R_f = 1 (Et₂O/pentane = 5:95)

IR (neat): 2919, 2850, 1484, 1461, 1443, 1381, 1261, 1155, 1123, 1107, 1045, 1021, 1003 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 3.77 (q, *J* = 8.4 Hz, 1H), 2.90 – 2.74 (m, 8H), 1.65 – 1.56 (m, 8H), 1.51 – 1.44 (m, 12H).

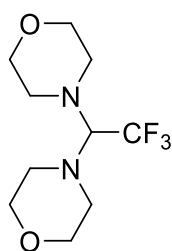
¹³C NMR (101 MHz, CDCl₃): δ = 126.0 (q, *J* = 292.1 Hz), 78.5 (q, *J* = 26.6 Hz), 49.6 (4C), 26.1 (4C), 24.8 (4C), 21.1 (2C).

¹⁹F NMR (376 MHz, CDCl₃): δ = -67.0

GC/MS - EI *m/z*: 295 (1), 265 (1), 223 (1), 208 (100), 178 (1), 152 (3), 126 (22), 109 (17), 82 (1), 70 (8), 55 (10), 41 (4).

HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₆H₃₀F₃N₂: 307,4172. Found: 307,4168

1,1-Bis(morpholine)-2,2,2-trifluoroethane (**2f**)²



2f

Chemical Formula: C₁₀H₁₇F₃N₂O₂

Molecular Weight: 254.25

Compound **2f** was prepared according to the general procedure **GP1**. A solution of morpholine **1f** (44 mg, 0.5 mmol) in TMSCF₃ (5 mL) was subjected to an argon plasma. After 7 h, TMSCF₃ was distilled, and the crude was purified by flash column chromatography on neutral alumina (Et₂O/pentane = 2:8) providing **2f** as a colorless oil (47 mg, yield = 73%).

R_f = 0.5 (Et₂O/pentane = 1:1)

IR (neat): 2959, 2916, 2893, 2851, 1795, 1453, 1360, 1271, 1249, 1151, 1110, 1072, 1019, 1005, 951, 933 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 3.68 (t_{app}, J = 4.4 Hz, 8H), 3.28 (q, J = 7.1 Hz, 1H), 2.77 (t_{app}, J = 4.4 Hz, 8H).

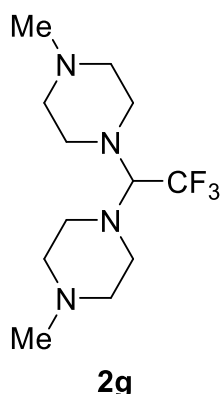
¹³C NMR (101 MHz, CDCl₃): δ = 125.4 (q, J = 293.2 Hz), 83.7 (q, J = 26.7 Hz), 67.4 (4C), 49.8 (4C).

¹⁹F NMR (376 MHz, CDCl₃): δ = -65.5.

GC/MS - EI *m/z*: 254 (M⁺, 1), 185 (5), 168 (100), 147 (3), 124 (38), 110 (4), 74 (7), 56 (1), 41 (1).

HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₀H₁₈F₃N₂O₂: 255.1315. Found: 255.1311

1,1-Bis(1-methylpiperazine)-2,2,2-trifluoroethane (**2g**)



Chemical Formula: C₁₂H₂₃F₃N₄

Molecular Weight: 280.34

Compound **2g** was prepared according to the general procedure **GP1**. A solution of 1-methylpiperazine **1g** (50 mg, 0.5 mmol) in TMSCF₃ (5 mL) was subjected to an argon plasma. After 7 h, TMSCF₃ was distilled, and the crude was purified by flash column chromatography on neutral alumina (Et₂O/pentane = 8:2) providing **2g** as a colorless oil (51 mg, yield = 73%).

R_f = 0.35 (Et₂O/pentane = 8:2)

IR (neat): 2936, 2840, 2793, 1681, 1456, 1371, 1358, 1288, 1258, 1204, 1156, 1140, 1110, 1007, 958, 945 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 3.37 (q, *J* = 7.3 Hz, 1H), 2.80 (brt_{app}, *J* = 4.4 Hz, 8H), 2.45 – 2.34 (m, 8H), 2.27 (s, 6H).

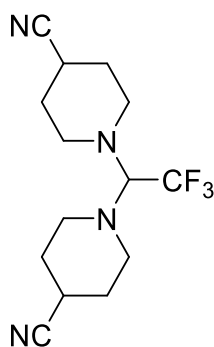
¹³C NMR (101 MHz, CDCl₃): 125.6 (q, *J* = 286.2 Hz), 83.1 (q, *J* = 26.9 Hz), 55.6 (4C), 49.3 (4C), 46.2 (2C).

¹⁹F NMR (376 MHz, CDCl₃): δ = -66.0.

GC/MS - EI *m/z*: 280 (M⁺, 1), 260 (1), 240 (1), 211 (3), 196 (1), 181 (100), 166 (7), 160 (7), 151 (1), 138 (51), 112 (17), 99 (95), 83 (4), 70 (49), 56 (25), 42 (25).

HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₂H₂₄F₃N₄: 281.1948. Found: 281.1945

1,1-Bis(4-cyanopiperidine)-2,2,2-trifluoroethane (2h)



2h

Chemical Formula: C₁₄H₁₉F₃N₄

Molecular Weight: 300.33

Compound **2h** was prepared according to the general procedure **GP1**. A solution of 4-cyanopiperidine **1h** (50 mg, 0.45 mmol) in TMSCF₃ (4.5 mL) was subjected to an argon plasma. After 6 h, TMSCF₃ was distilled, and the crude was purified by flash column chromatography on neutral alumina (Et₂O/pentane = 7:3) providing **2h** as a colorless oil (57 mg, yield = 85%).

R_f = 0.25 (Et₂O/pentane = 1:1)

IR (neat): 2931, 2829, 2240, 1447, 1395, 1268, 1253, 1156, 1126, 1110, 1044, 1005, 989, 944 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 3.38 (q, *J* = 7.3 Hz, 1H), 3.02 – 2.91 (m, 4H), 2.73 – 2.61 (m, 6H), 1.97 – 1.88 (m, 4H), 1.88 – 1.76 (m, 4H).

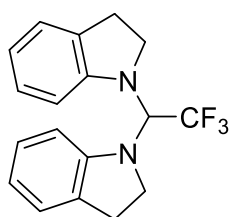
¹³C NMR (101 MHz, CDCl₃): 125.2 (q, *J* = 292.5 Hz), 121.6 (2C), 83.4 (q, *J* = 27.4 Hz), 48.1 (2C), 47.2 (2C), 29.3 (2C), 29.2 (2C), 26.5 (2C).

¹⁹F NMR (376 MHz, CDCl₃): δ = -66.0.

GC/MS - EI *m/z*: 280 (1), 231 (3), 207 (1), 191 (100), 164 (1), 141 (1), 110 (10), 67 (3), 41 (1).

HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₁₄H₁₉F₃N₄Na: 323.1454. Found: 323.1454

1,1-Bis(indoline)-2,2,2-trifluoroethane (**2i**)



2i

Chemical Formula: $C_{18}H_{17}F_3N_2$

Molecular Weight: 318.34

Compound **2i** was prepared according to the general procedure **GP1**. A solution of indoline **1i** (53 mg, 0.45 mmol) in $TMSCF_3$ (4.5 mL) was subjected to an argon plasma. After 6 h, $TMSCF_3$ was distilled, and the crude was purified by flash column chromatography on neutral alumina (Et_2O /pentane = 5:95) providing **2j** as a colorless oil (56 mg, yield = 78%).

R_f = 1 (Et_2O /pentane = 5:95)

IR (neat): 2950, 2853, 1606, 1492, 1491, 1457, 1387, 1364, 1329, 1300, 1254, 1163, 1130, 1026, 1000 cm^{-1} .

1H NMR (400 MHz, $CDCl_3$): δ = 7.08 (brd, J = 7.2 Hz, 2H), 7.03 (t_{app} , J = 7.7 Hz, 2H), 6.75 – 6.67 (t_{app} , 7.6 Hz, 2H), 6.38 (d, J = 7.9 Hz, 2H), 5.43 (q, J = 7.5 Hz, 1H), 3.78 – 3.68 (m, 2H), 3.61 (d, J = 12.0 Hz, 2H), 3.16 – 2.96 (m, 4H).

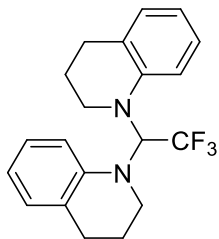
^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.7 (2C), 128.7 (2C), 127.7 (2C), 124.9 (2C), 124.5 (q, J = 286.2 Hz), 118.7 (2C), 106.5 (2C), 67.8 (q, J = 32.5 Hz), 48.4 (2C), 28.7 (2C).

^{19}F NMR (376 MHz, $CDCl_3$) : δ = -72.3.

GC/MS - EI m/z : 318 (M^+ , 12), 249 (1), 219 (1), 200 (100), 180 (2), 160 (1), 130 (17), 117 (4), 91 (1); 103 (1), 77 (4), 51 (1).

HRMS (ESI) m/z : [$M+H$] $^+$ Calcd for $C_{18}H_{18}F_3N_2$: 319.1417. Found: 319.1413

1,1-Bis(1,2,3,4-tetrahydroquinoline)-2,2,2-trifluoroethane (2j)



2j

Chemical Formula: C₂₀H₂₁F₃N₂

Molecular Weight: 346.40

Compound **2j** was prepared according to the general procedure **GP1**. A solution of 1,2,3,4-tetrahydroquinoline **1j** (47 mg, 0.35 mmol) in TMSCF₃ (3.5 mL) was subjected to an argon plasma. After 5 h, TMSCF₃ was distilled, and the crude was purified by flash column chromatography on neutral alumina (pentane) providing **2j** as a white solid (45 mg, yield = 75%).

R_f = 0.4 (pentane)

IR (neat): 2933, 2846, 1603, 1493, 1455, 1378, 1343, 1312, 1286, 1268, 1201, 1186, 1159, 1143, 1131, 1111, 1056, 928, 907 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.05 – 6.97 (m, 4H), 6.71 (t, *J* = 7.3 Hz, 2H), 6.44 (d, *J* = 8.2 Hz, 2H), 5.63 (q, *J* = 7.5 Hz, 1H), 3.59 – 3.48 (m, 2H), 3.45 – 3.33 (m, 2H), 2.85 – 2.61 (m, 4H), 2.08 – 1.79 (m, 4H).

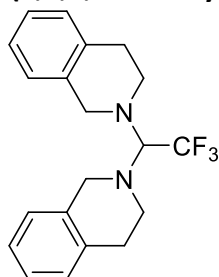
¹³C NMR (101 MHz, CDCl₃): δ = 143.7 (2C), 129.7 (2C), 127.4 (2C), 124.8 (q, *J* = 278.4 Hz), 123.8 (2C), 118.1 (2C), 112.2 (2C), 72.7 (q, *J* = 31.8 Hz), 44.7 (2C), 28.1 (2C), 22.0 (2C).

¹⁹F NMR (376 MHz, CDCl₃): δ = -69.5.

GC/MS - EI *m/z*: 346 (M⁺, 9), 277 (1), 247 (1), 214 (100), 186 (6), 166 (5), 144 (6), 130 (9), 117 (13), 91 (9), 65 (1), 39 (1).

HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₂₀H₂₂F₃N₂: 347.1657. Found: 347.1655

1,1-Bis(1,2,3,4-tetrahydroisoquinoline)-2,2,2-trifluoroethane (2k)



2k

Chemical Formula: $C_{20}H_{21}F_3N_2$

Molecular Weight: 346.40

Compound **2k** was prepared according to the general procedure **GP1**. A solution of 1,2,3,4-tetrahydroisoquinoline **1k** (47 mg, 0.35 mmol) in $TMSCF_3$ (3.5 mL) was subjected to an argon plasma. After 5 h, $TMSCF_3$ was distilled, and the crude was purified by flash column chromatography on neutral alumina (pentane) providing **2k** as a colorless oil (40 mg, yield = 70%).

R_f = 0.4 (pentane)

IR (neat): 2920, 2830, 1497, 1453, 1427, 1389, 1256, 1144, 1107, 1039, 933, cm^{-1} .

1H NMR (400 MHz, $CDCl_3$): 7.19 – 7.08 (m, 6H), 7.06 – 6.99 (m, 2H), 4.11 (d, $J_{AB} = 15.0$ Hz, 2H), 3.97 (d, $J_{AB} = 15.0$ Hz, 2H), 3.81 (q, $J = 7.0$ Hz, 1H), 3.27 – 3.04 (m, 4H), 3.01 – 2.73 (m, 4H).

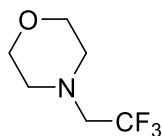
^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 134.9$ (2C), 134.6 (2C), 129.0 (2C), 126.7 (2C), 126.2 (2C), 125.9 (q, $J = 293.8$ Hz), 125.8 (2C), 82.3 (q, $J = 27.1$ Hz), 51.8 (2C), 46.8 (2C), 29.5 (2C).

^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -65.4$.

GC/MS - EI m/z : 307 (1), 277 (1), 241 (1), 214 (100), 174 (2), 132 (5), 117 (13), 103 (7) 91 (4), 79 (3), 39 (1).

HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{20}H_{22}F_3N_2$: 347.1657. Found: 347.1661

1-Morpholine-2,2,2-trifluoroethane (**4f**)³



4f

Chemical Formula: C₆H₁₀F₃NO

Molecular Weight: 169.15

Compound **4f** was prepared according to the general procedure **GP2** by reducing 1,1-bis(morpholine)-2,2,2-trifluoroethane **2f** (130 mg, 0.5 mmol) in THF using anhydrous ZnCl₂ (82 mg, 0.6 mmol, 1.2 equiv) and NaBH₃CN (38 mg, 0.6 mmol, 1.2 equiv). Compound **4f** was obtained as a pale-yellow oil (32 mg, yield = 39%).

IR (neat): 2958, 2924, 2854, 1455, 1319, 1272, 1196, 1146, 1119, 1100, 1015, 959 cm⁻¹.

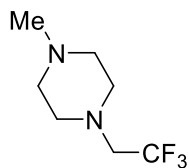
¹H NMR (400 MHz, CDCl₃): 3.72 – 3.67 (m, 4H), 2.94 (q, *J* = 9.5 Hz, 2H), 2.67 – 2.61 (m, 4H).

¹³C NMR (101 MHz, CDCl₃): δ = 125.4 (q, *J* = 279.7 Hz), 67.0 (2C), 59.0 (q, *J* = 30.4 Hz), 54.1 (2C).

¹⁹F NMR (376 MHz, CDCl₃): δ = -69.1.

GC/MS - EI *m/z*: 169 (M⁺, 35), 139 (3), 124 (1), 111 (51), 100 (100), 83 (11), 70 (17), 56 (13), 42 (77).

1-(1-Methylpiperazine)-2,2,2-trifluoroethane (**4g**)³



4g

Chemical Formula: C₇H₁₃F₃N₂

Molecular Weight: 182,19

Compound **4g** was prepared according to the general procedure **GP2** by reducing 1,1-bis(1-methylpiperazine)-2,2,2-trifluoroethane **2g** (150 mg, 0.53 mmol) in THF using anhydrous ZnCl₂ (87 mg, 0.64 mmol, 1.2 equiv) and NaBH₃CN (40 mg, 0.64 mmol, 1.2 equiv). Compound **4g** was obtained as a pale-yellow oil (42 mg, yield = 44%).

IR (neat): 2938, 2857, 2790, 1315, 1270, 1238, 1166, 1137, 1120, 1094, 1060, 1040, 1003, 966, 949 cm⁻¹.

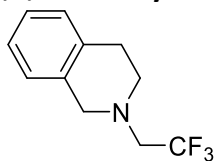
¹H NMR (400 MHz, CDCl₃): 2.96 (q, *J* = 9.6 Hz, 2H), 2.83 – 2.61 (m, 4H), 2.51 – 2.39 (m, 4H), 2.28 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 126.1 (q, *J* = 228.0 Hz), 58.6 (q, *J* = 30.4 Hz), 55.1 (2C), 53.8 (2C), 46.2.

¹⁹F NMR (376 MHz, CDCl₃) : δ = -69.1.

GC/MS - EI *m/z*: 182 (M⁺, 100), 162 (37), 138 (12), 124 (8), 108 (25), 99 (30), 83 (9), 70 (40), 56 (30), 43 (65).

1-(1,2,3,4-Tetrahydroisoquinoline)-2,2,2-trifluoroethane (4k)⁴



4k

Chemical Formula: C₁₁H₁₂F₃N

Molecular Weight: 215.22

Compound **4k** was prepared according to the general procedure **GP2** by reducing 1,1-bis(1-methylpiperazine)-2,2,2-trifluoroethane **2k** (350 mg, 1 mmol) in THF using anhydrous ZnCl₂ (164 mg, 1.2 mmol, 1.2 equiv) and NaBH₃CN (75 mg, 1.2 mmol, 1.2 equiv). Compound **4k** was obtained as a pale-yellow oil (129 mg, yield = 60%).

IR (neat): 2923, 2797, 1498, 1451, 1413, 1317, 1268, 1134, 1094, 1055, 1038, 1011, 942 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 7.22 – 7.11 (m, 3H), 7.08 – 7.00 (m, 1H), 3.92 (s, 2H), 3.18 (q, *J* = 9.5 Hz, 2H), 3.04 – 2.98 (m, 2H), 2.97 – 2.91 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ = 134.1, 133.8, 128.9, 126.6, 126.5, 125.9, 125.7 (q, *J* = 280.1 Hz), 58.1 (q, *J* = 30.6 Hz), 56.1, 51.6, 28.8.

¹⁹F NMR (376 MHz, CDCl₃): δ = -69.2.

GC/MS - EI *m/z*: 214 (M⁺, 100), 199 (15), 186 (4), 146 (53), 130 (13), 115 (19), 104 (100), 91 (11), 78 (21), 51 (7).

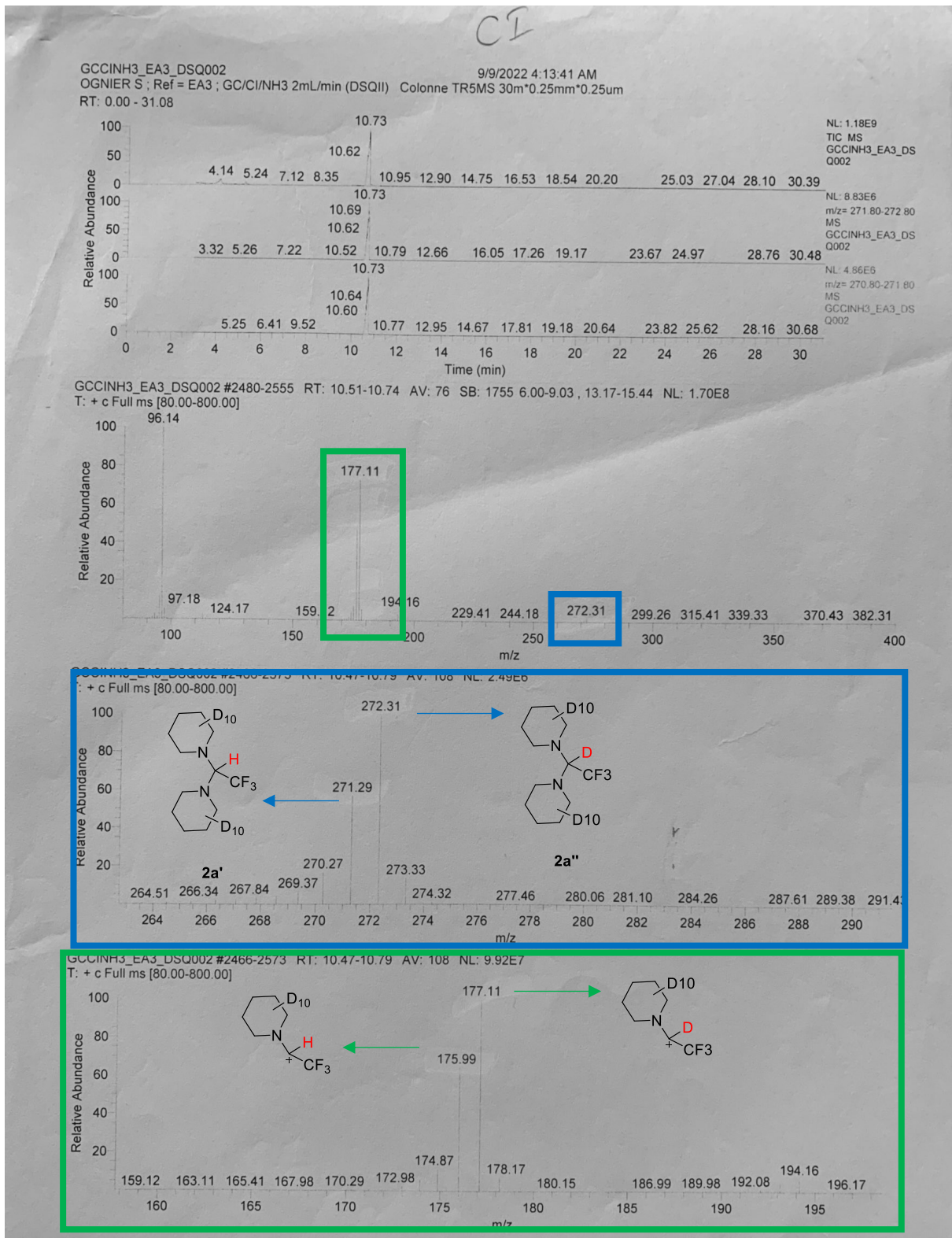
References

- 1 E. Abdelnour, S. Ognier, M. Zhang, L. Schio, O. Venier, J. Cossy and M. Tatoulian, *Chem. Commun.*, 2022, **58**, 7281–7284.
- 2 Y. Xu, Dolbier William R. and X. X. Rong, *J. Org. Chem.*, 1997, **62**, 1576–1577.
- 3 K. G. Andrews, R. Faizova and R. M. Denton, *Nat. Commun.*, 2017, **8**, 15913.
- 4 H. Mimura, K. Kawada, T. Yamashita, T. Sakamoto and Y. Kikugawa, *J. Fluorine Chem.*, 2010, **131**, 477–486.

GC/MS (EI and CI) chromatograms and spectra for compounds 2a' and 2a''.

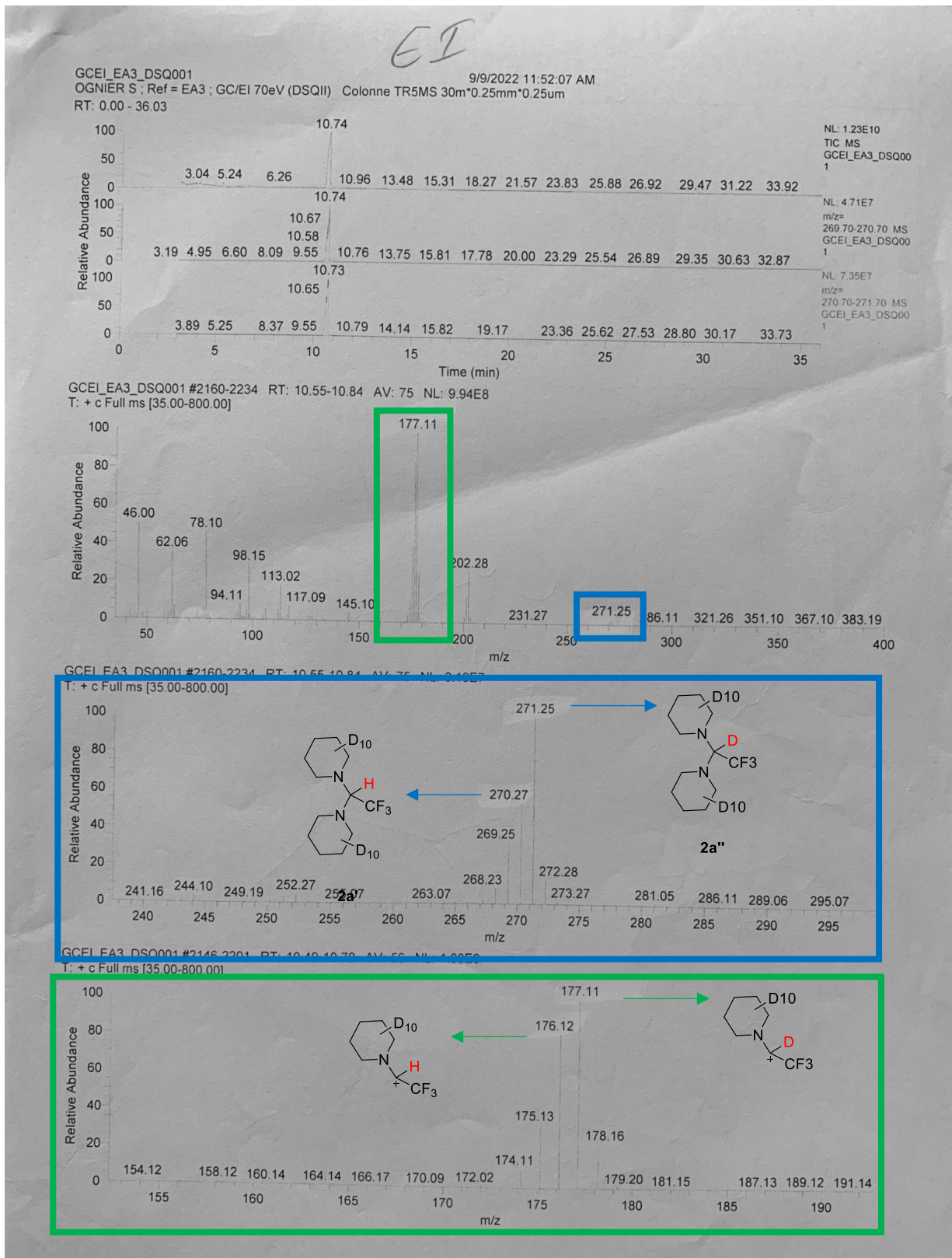
GC/MS IC

The compounds 2a' and 2a'' are co-eluting at 10.73 min.



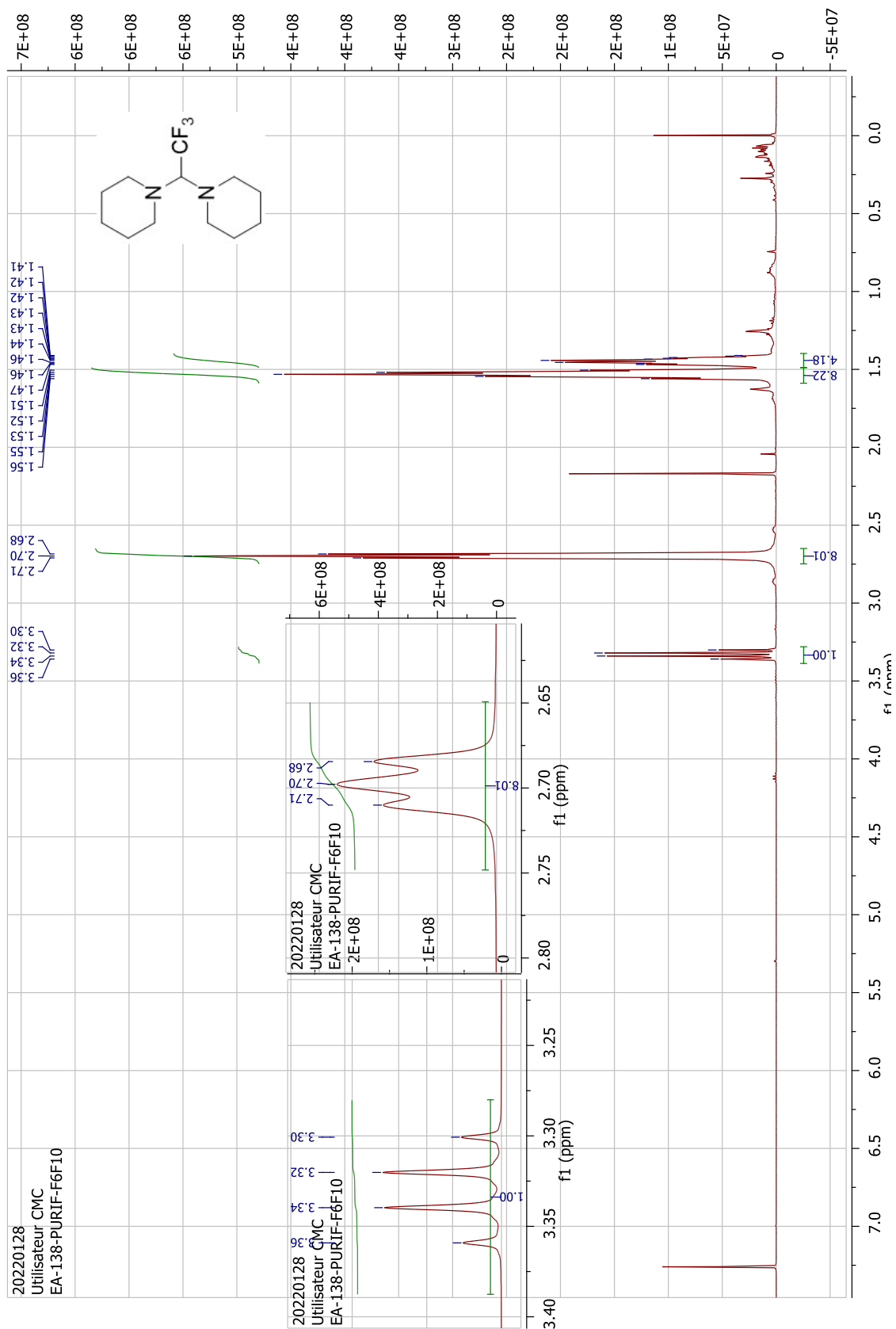
GC/MS EI

The compounds 2a' and 2a'' are co-eluting at 10.74 minutes.

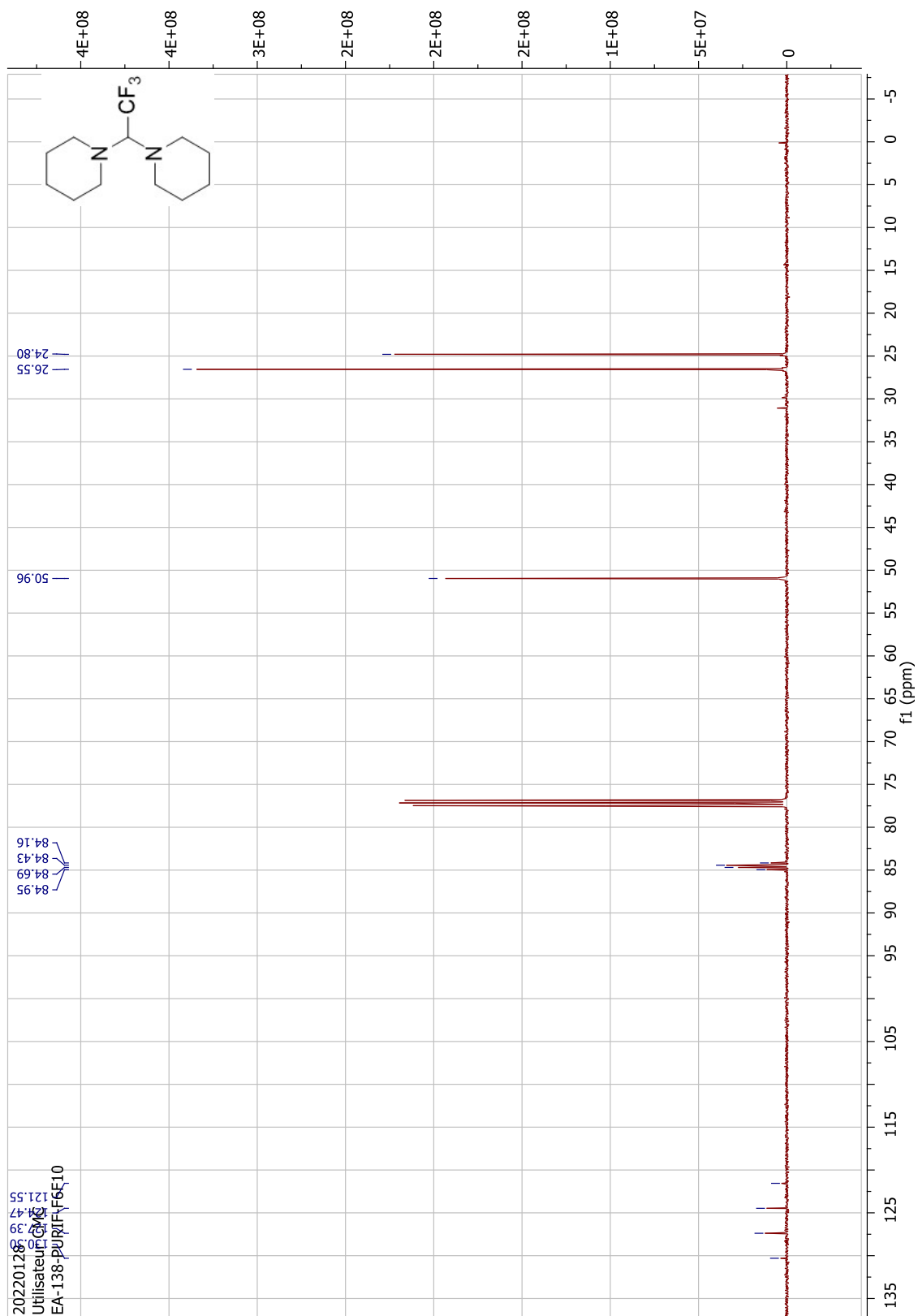


^1H NMR, ^{13}C NMR and ^{19}F NMR Spectra of the prepared compounds.

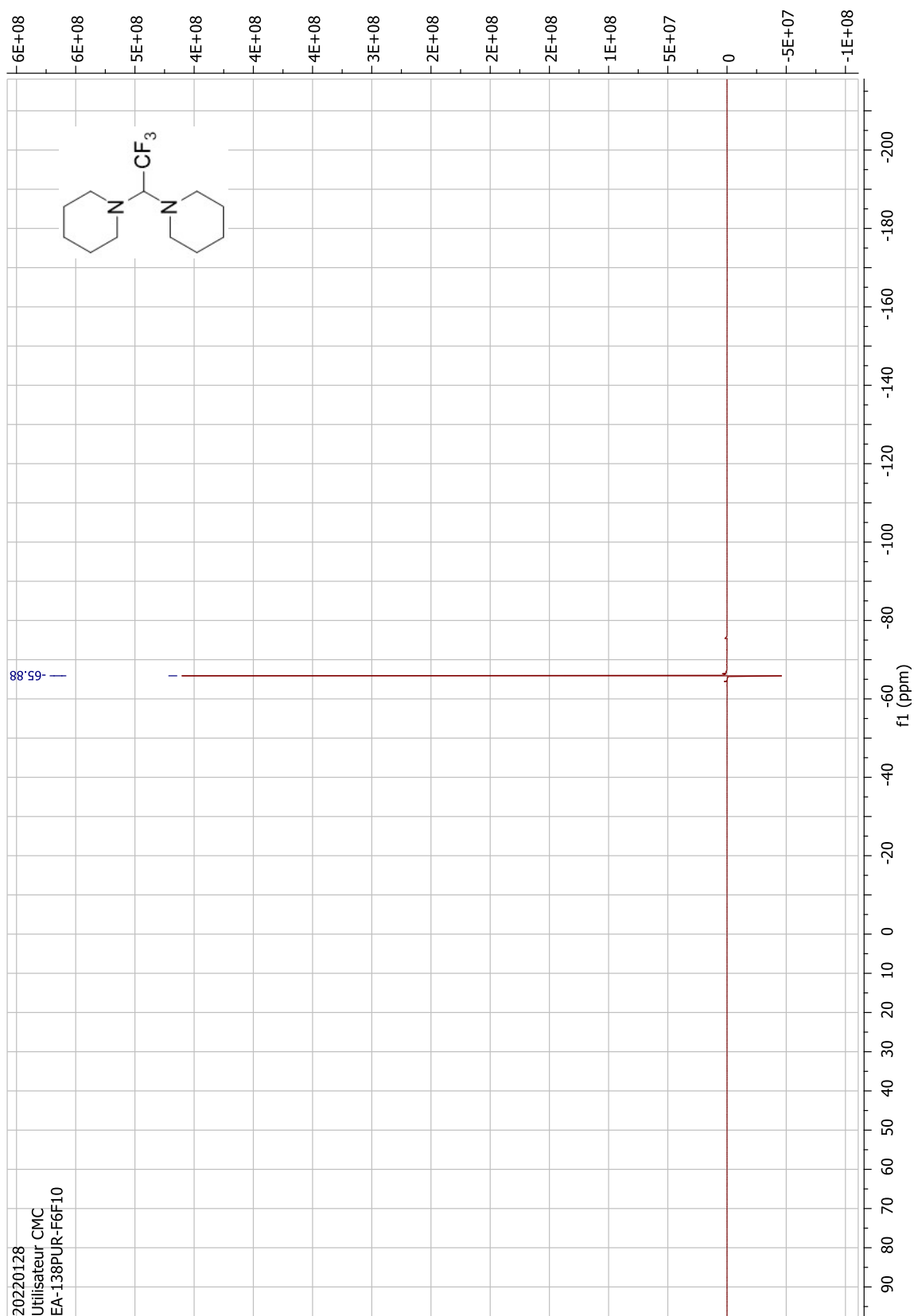
1,1-Bis(piperidine)-2,2,2-trifluoroethane (2a)² - ¹H NMR



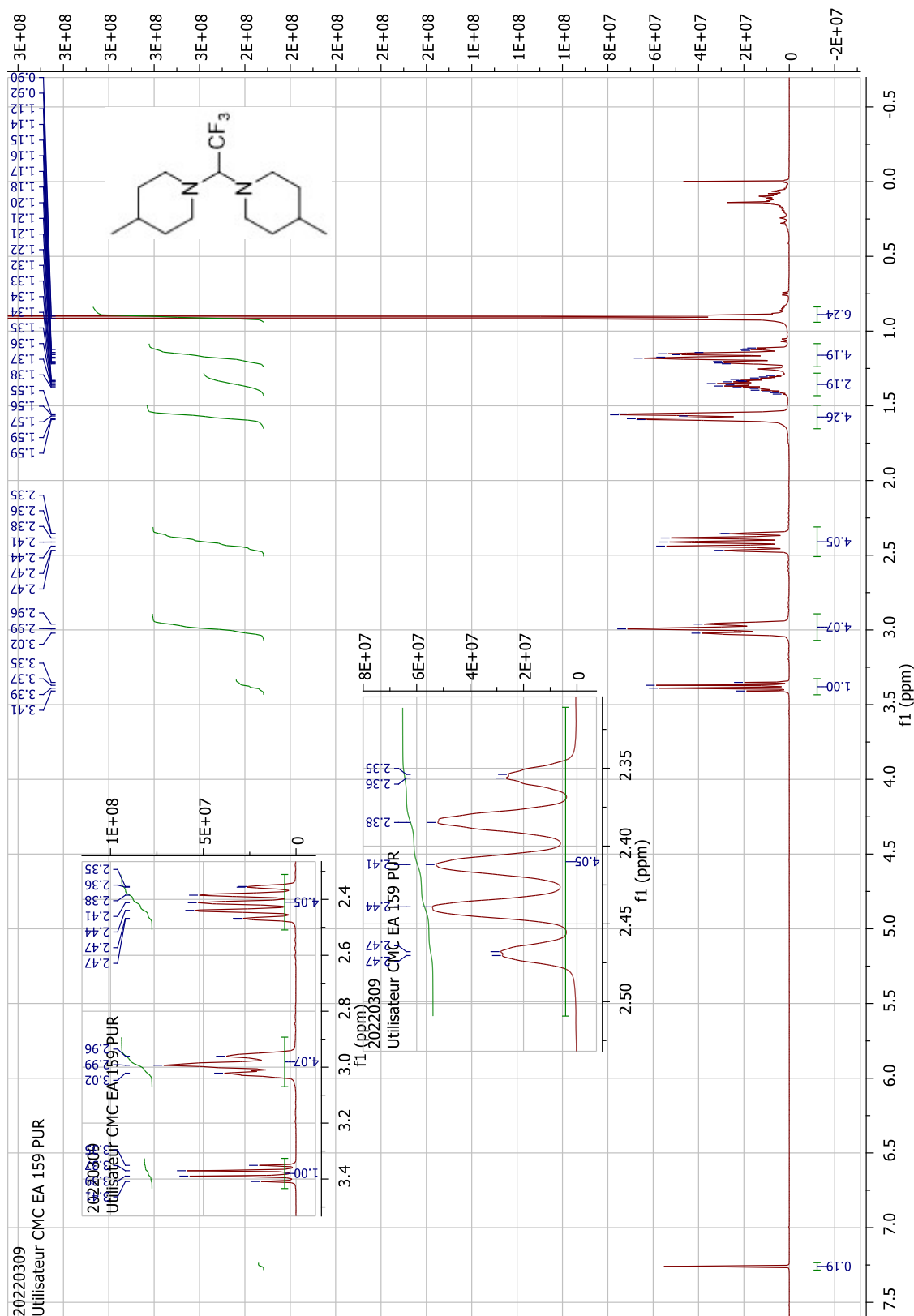
1,1-Bis(piperidine)-2,2,2-trifluoroethane (2a)² - ¹³C NMR



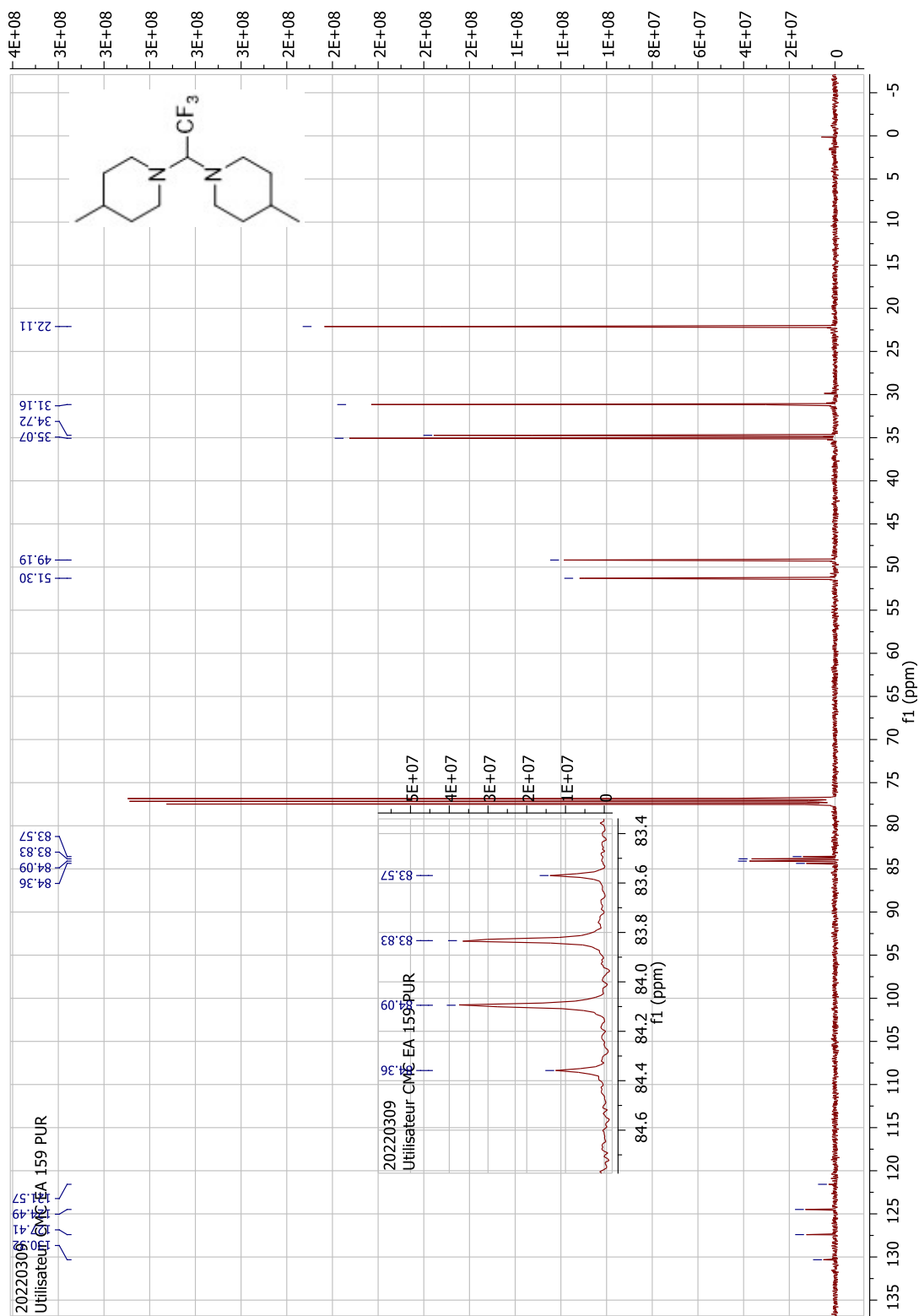
1,1-Bis(piperidine)-2,2,2-trifluoroethane (2a)² - ¹⁹F NMR



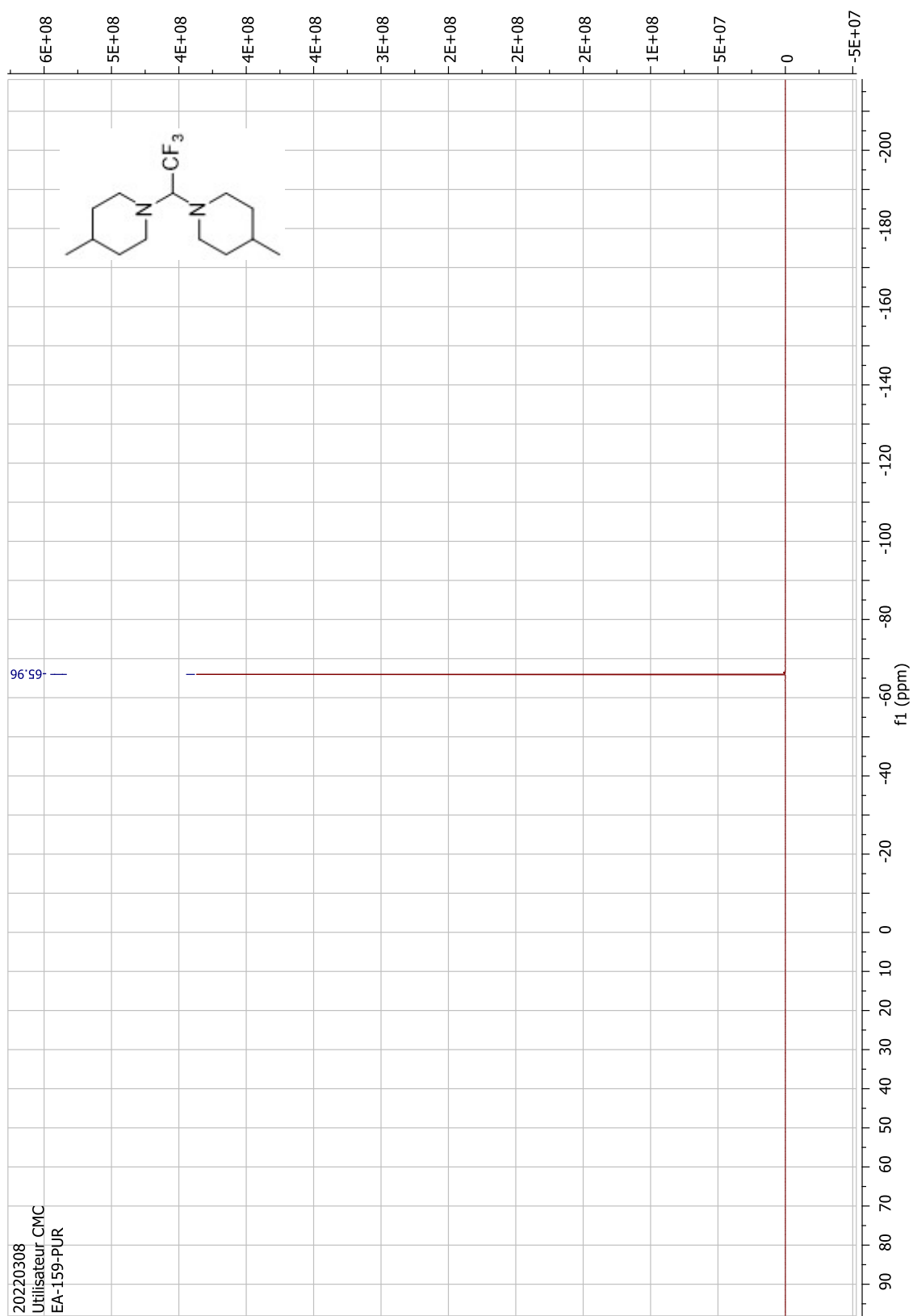
1,1-Bis(4-methylpiperidine)-2,2,2-trifluoroethane (2b) - ¹H NMR



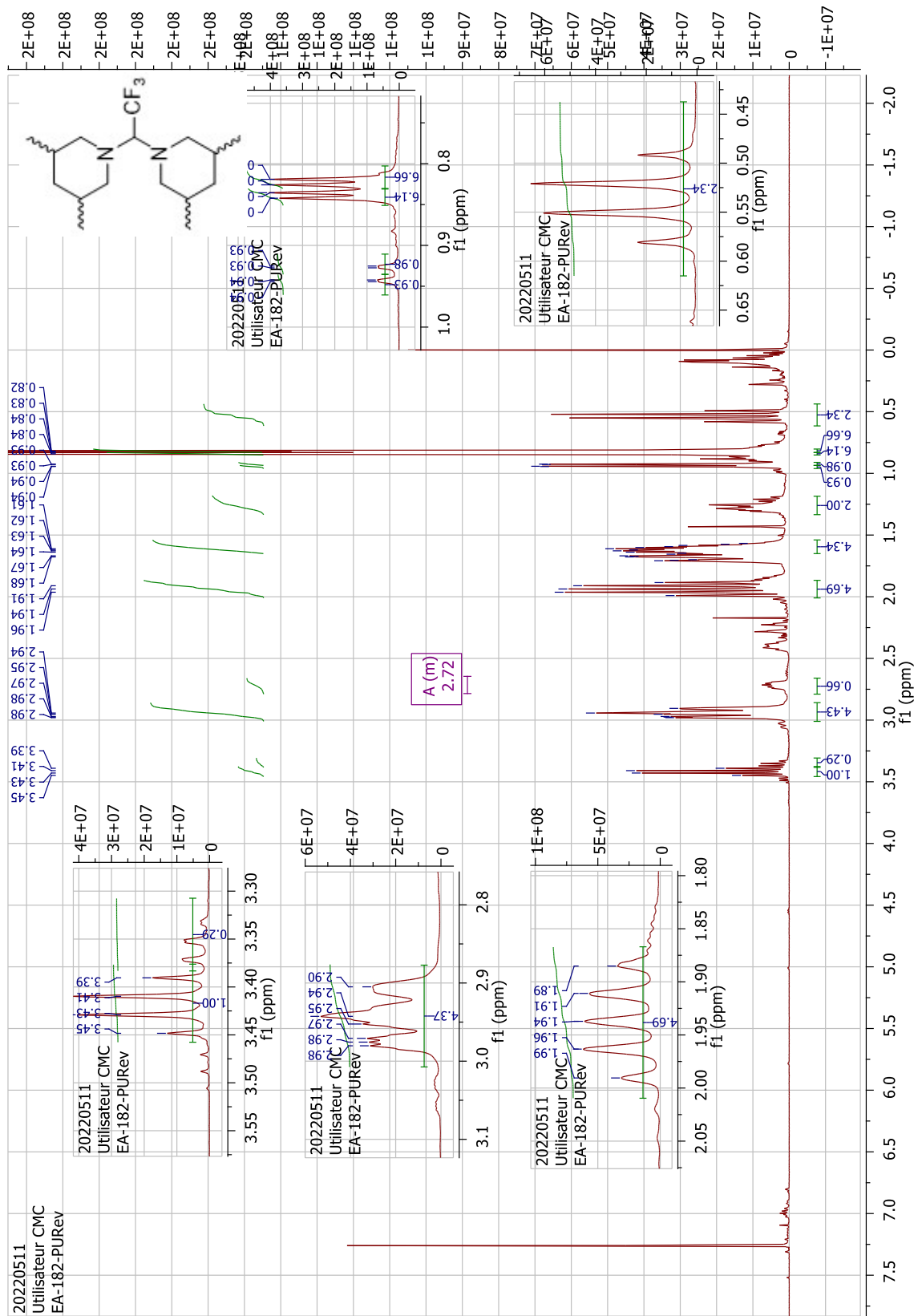
1,1-Bis(4-methylpiperidine)-2,2,2-trifluoroethane (2b) - ^{13}C NMR



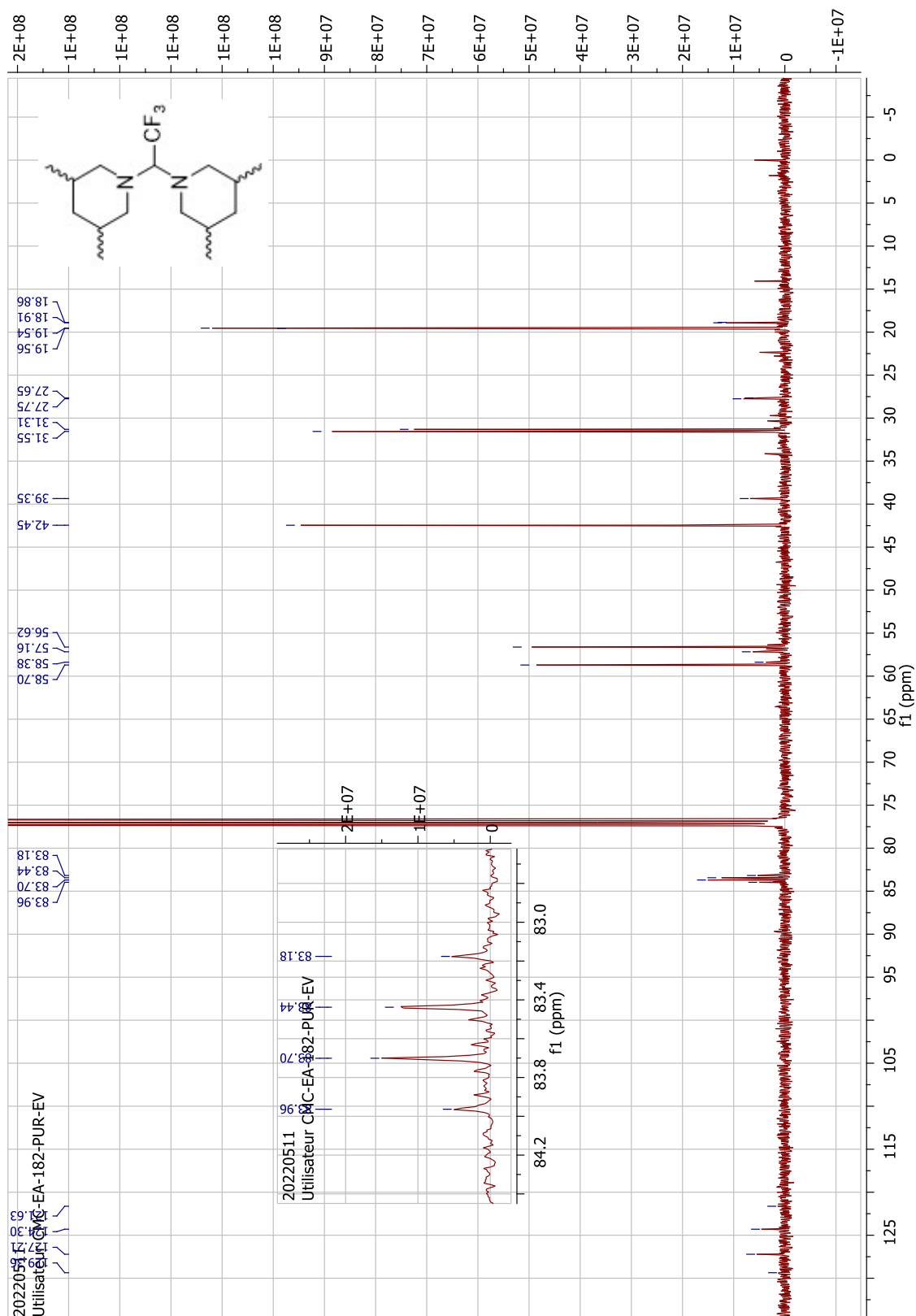
1,1-Bis(4-methylpiperidine)-2,2,2-trifluoroethane (2b) - ^{19}F NMR



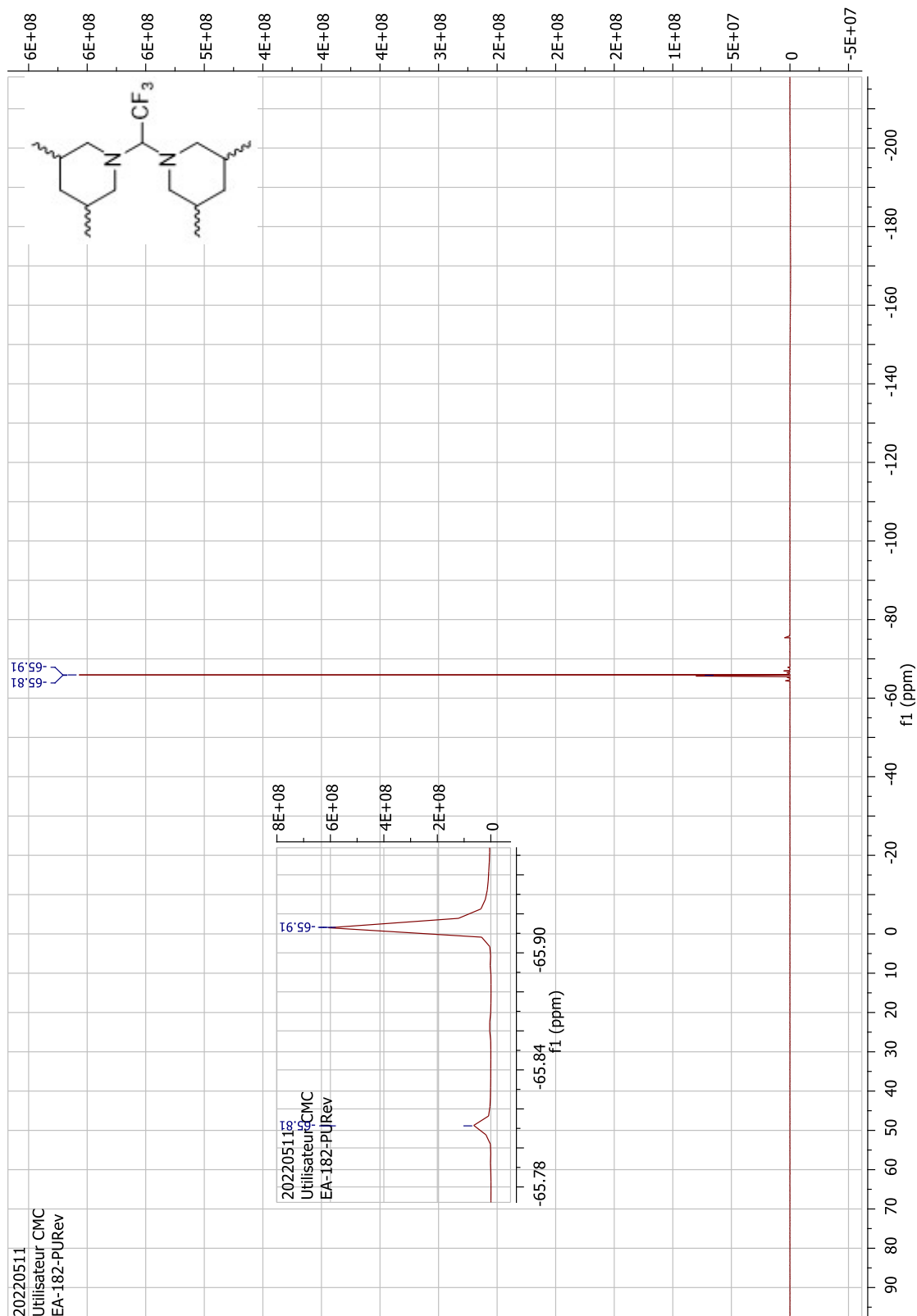
1,1-Bis(3,5-dimethylpiperidine)-2,2,2-trifluoroethane (2c) - ¹H NMR



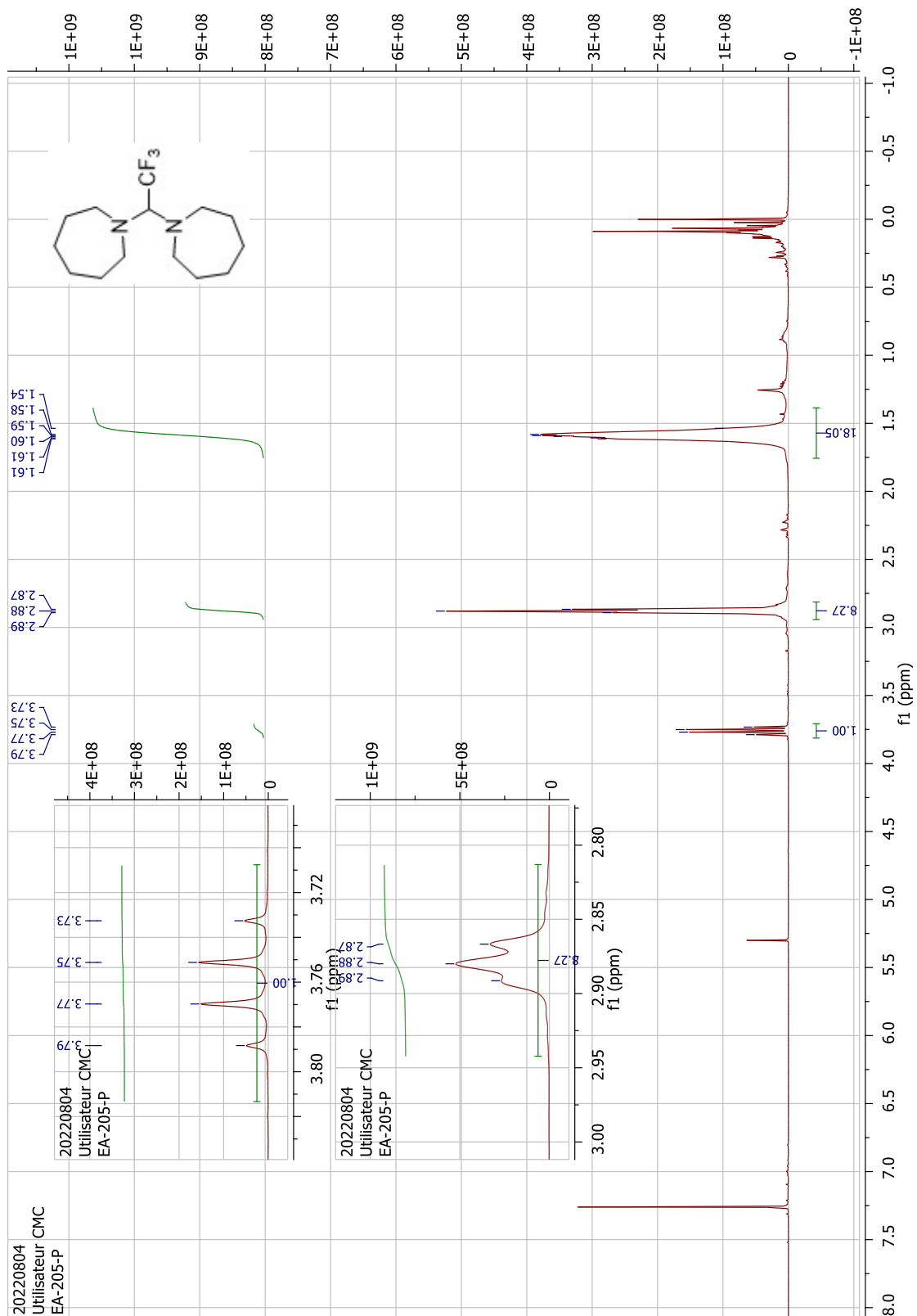
1,1-Bis(3,5-dimethylpiperidine)-2,2,2-trifluoroethane (2c) - ¹³C NMR



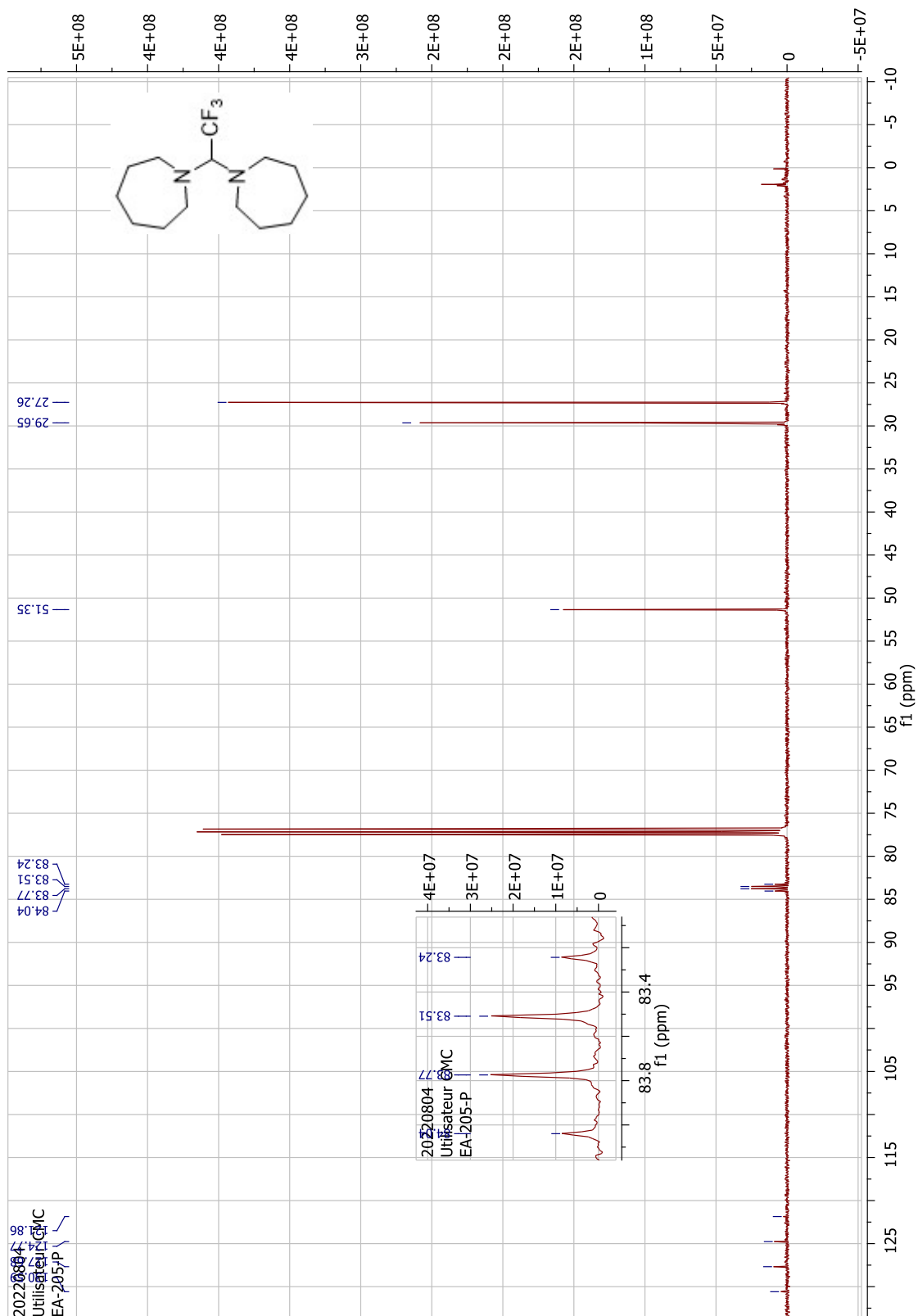
1,1-Bis(3,5-dimethylpiperidine)-2,2,2-trifluoroethane (2c) - ¹⁹F NMR



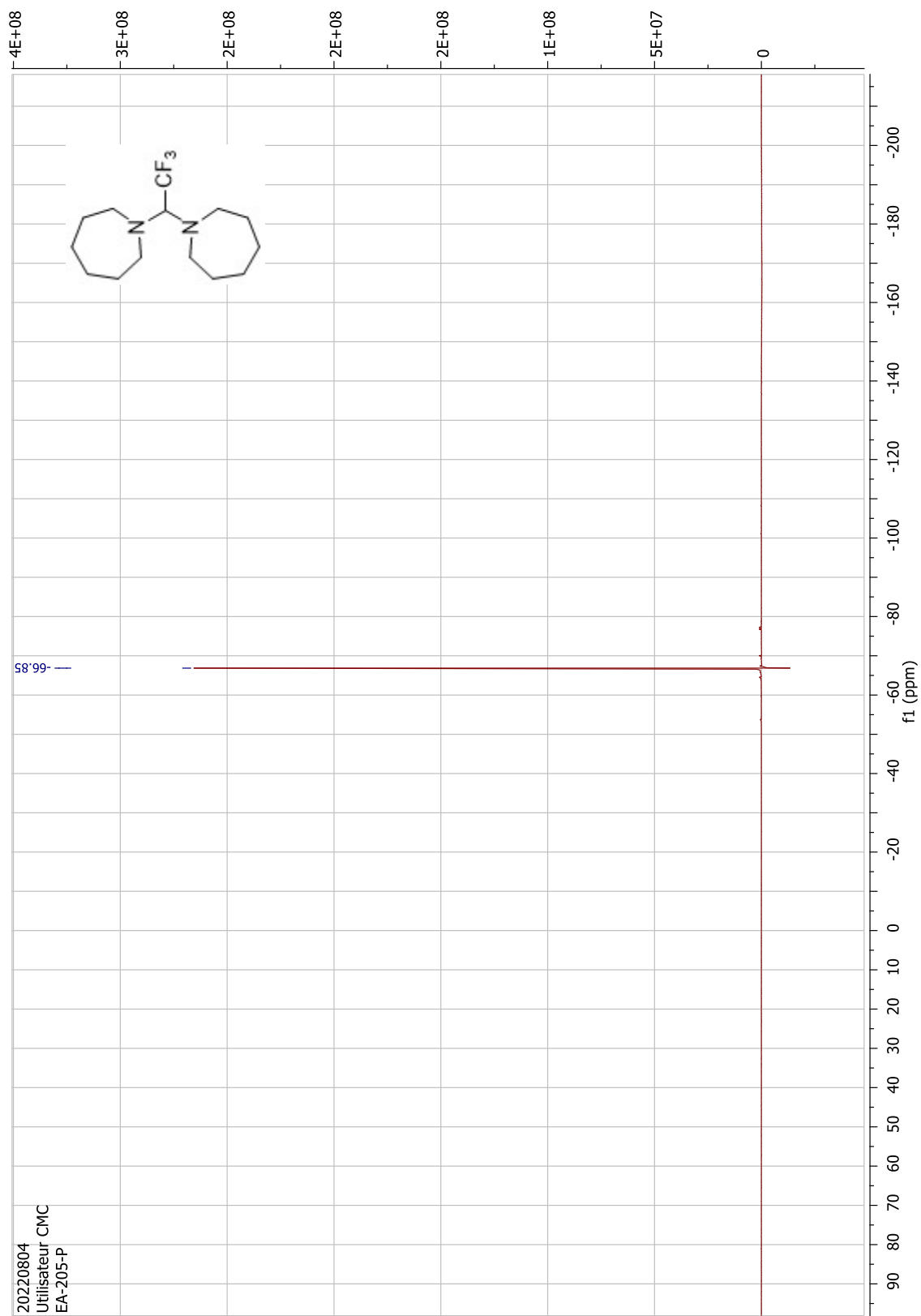
1,1-Bis(azepane)-2,2,2-trifluoroethane (2d)² - ¹H NMR



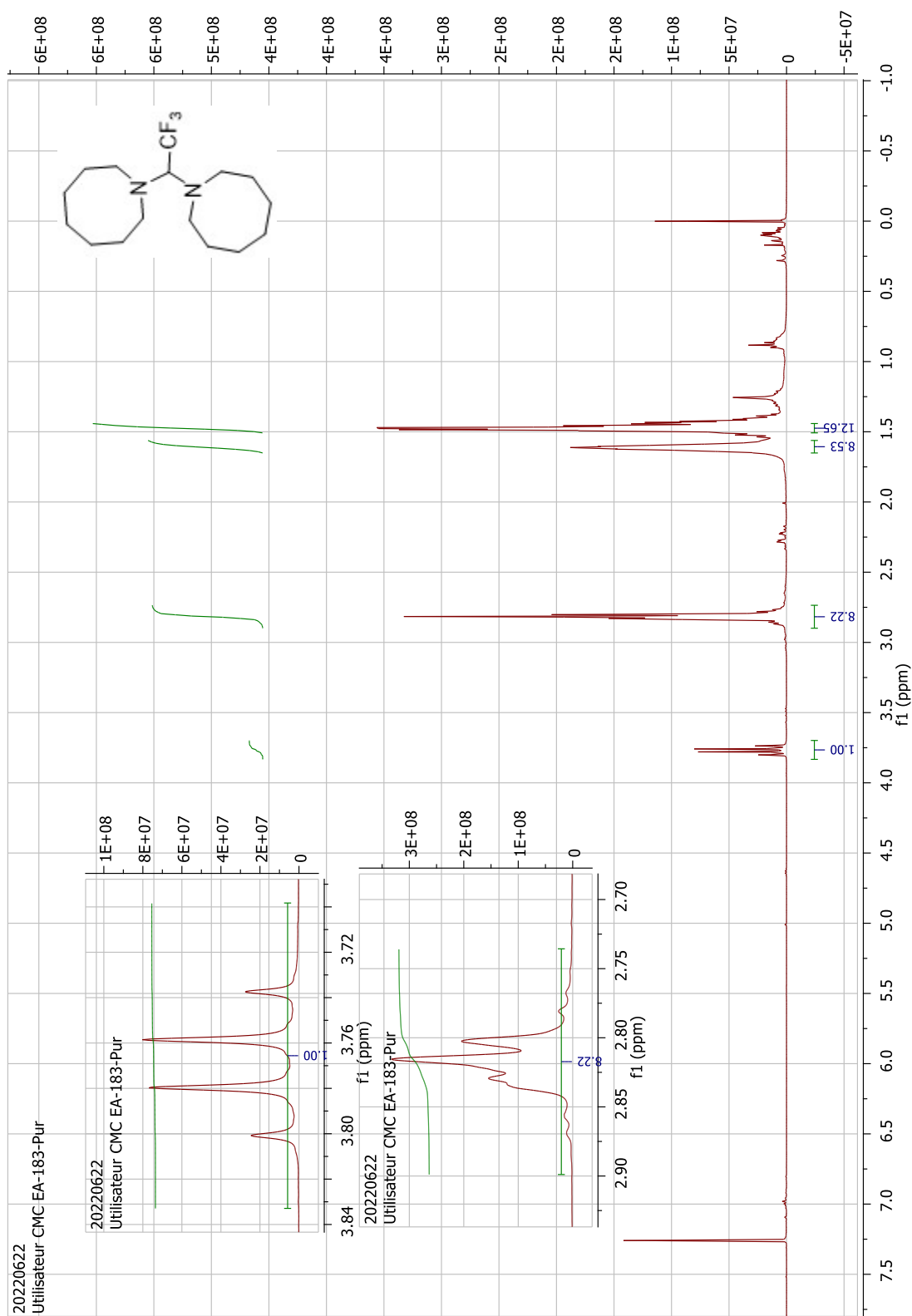
1,1-Bis(azepane)-2,2,2-trifluoroethane (2d)² – ¹³C NMR



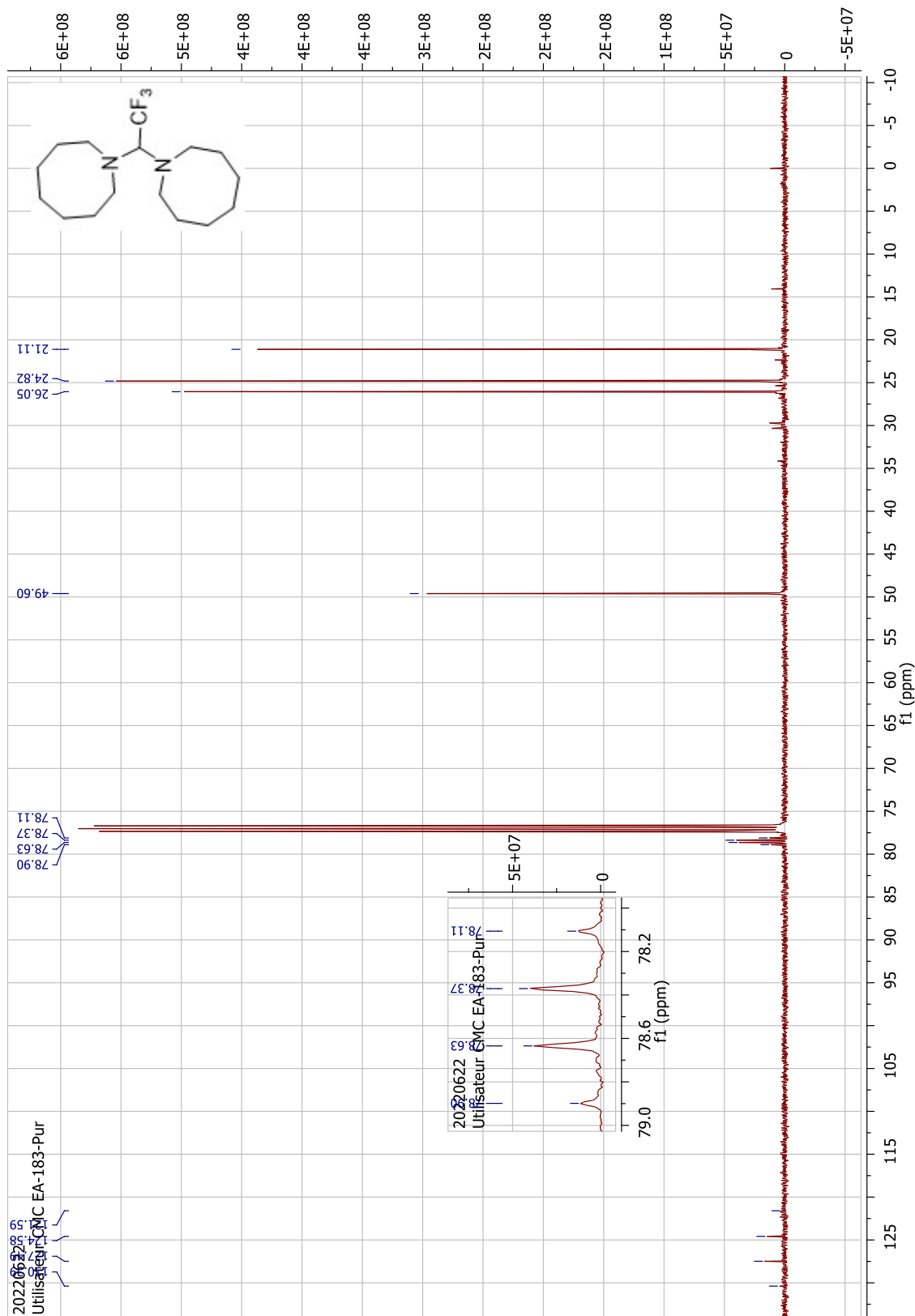
1,1-Bis(azepane)-2,2,2-trifluoroethane (2d)² – ¹⁹F NMR



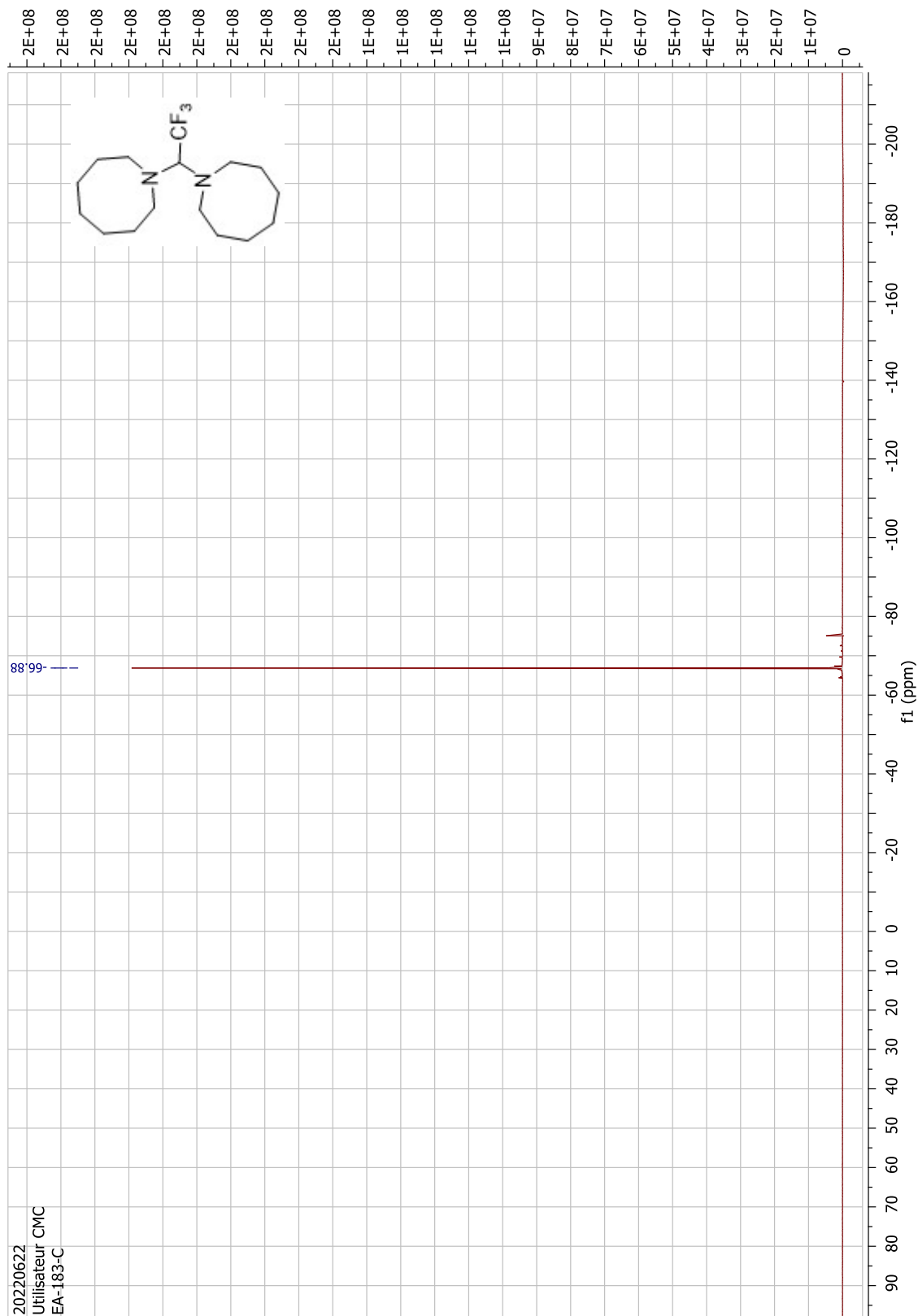
1,1-Bis(azocane)-2,2,2-trifluoroethane (2e) - ¹H NMR



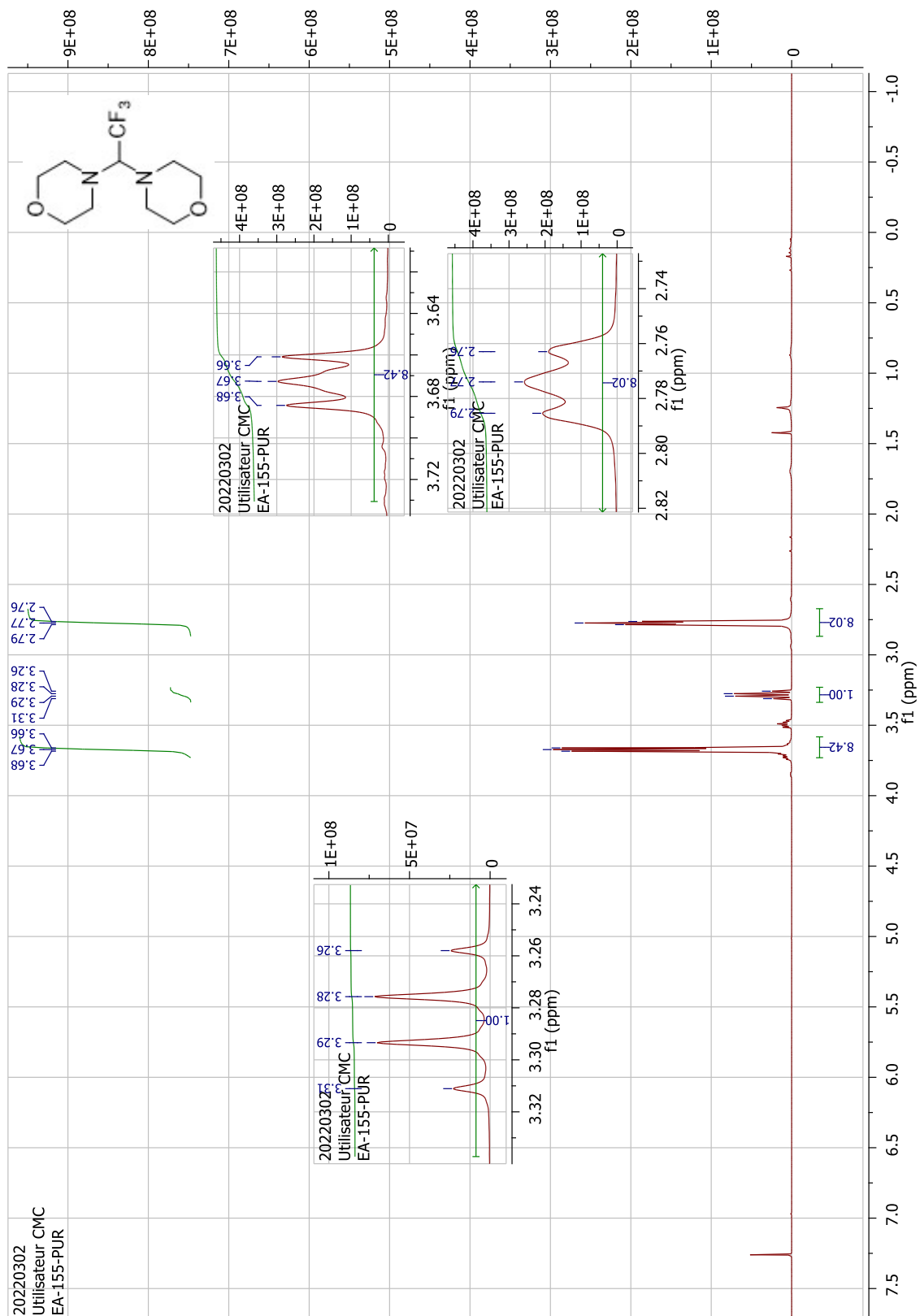
1,1-Bis(azocane)-2,2,2-trifluoroethane (2e) - ^{13}C NMR



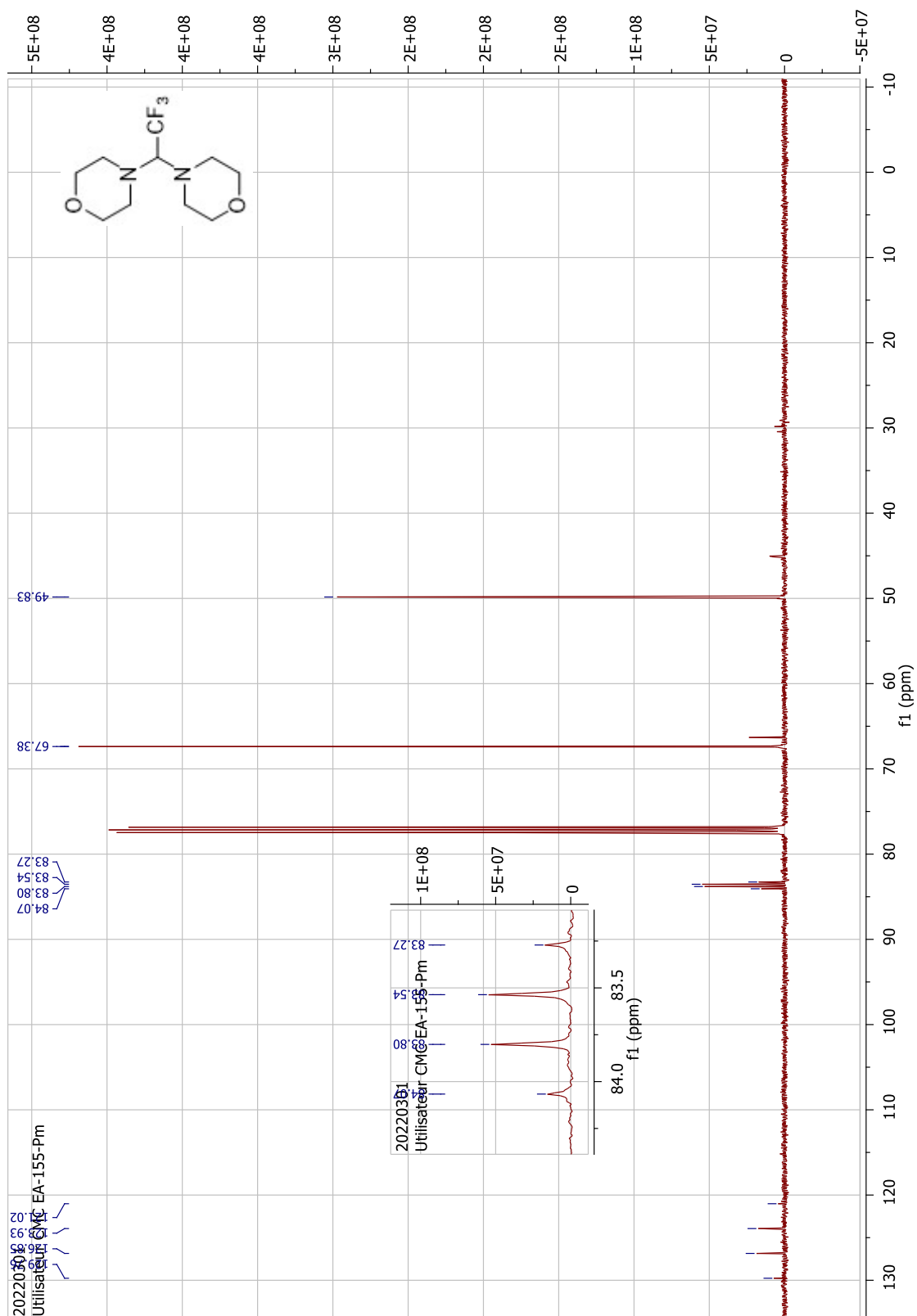
1,1-Bis(azocane)-2,2,2-trifluoroethane (2e) – ¹⁹F NMR



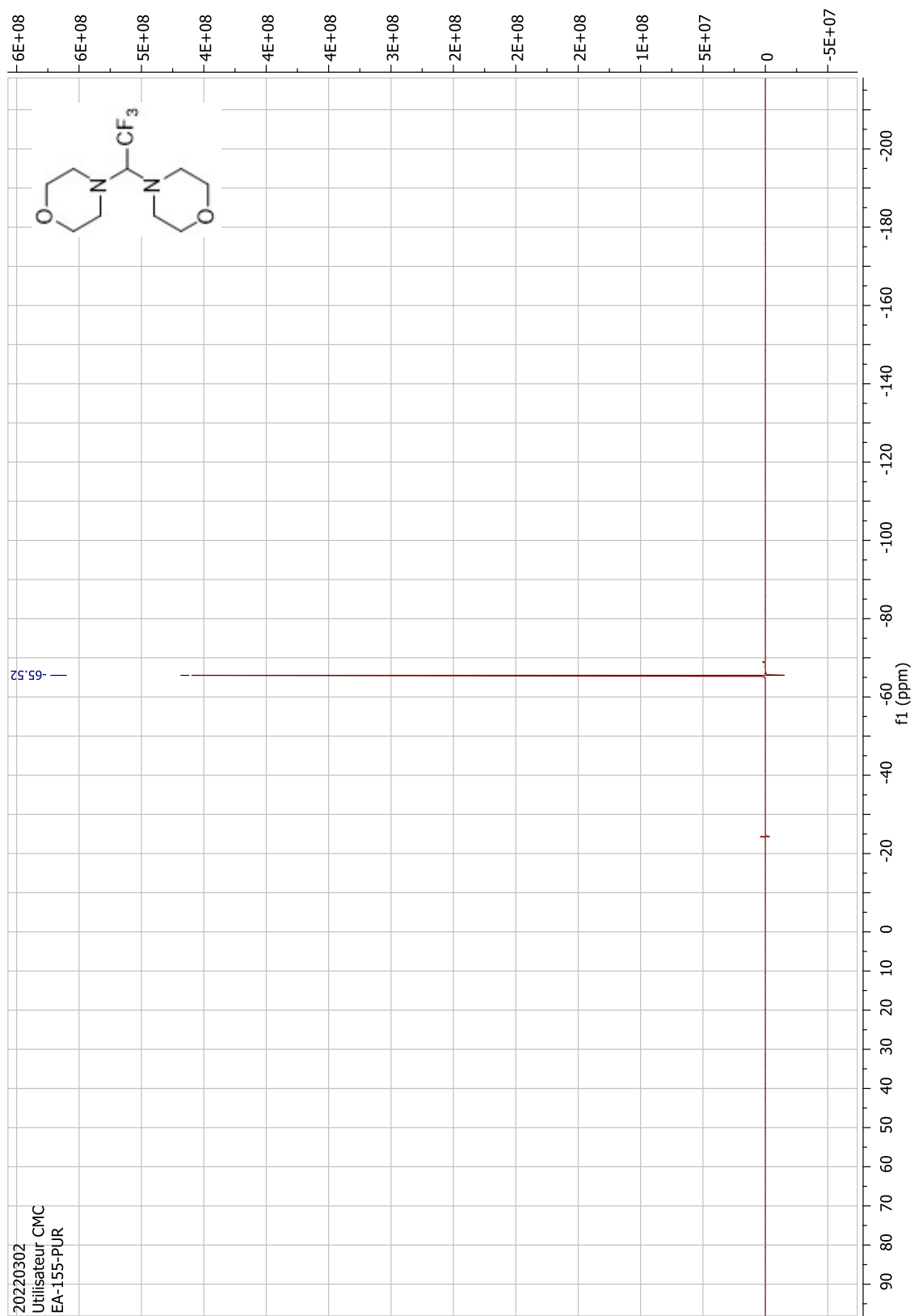
1,1-Bis(morpholine)-2,2,2-trifluoroethane (2f)² - ¹H NMR



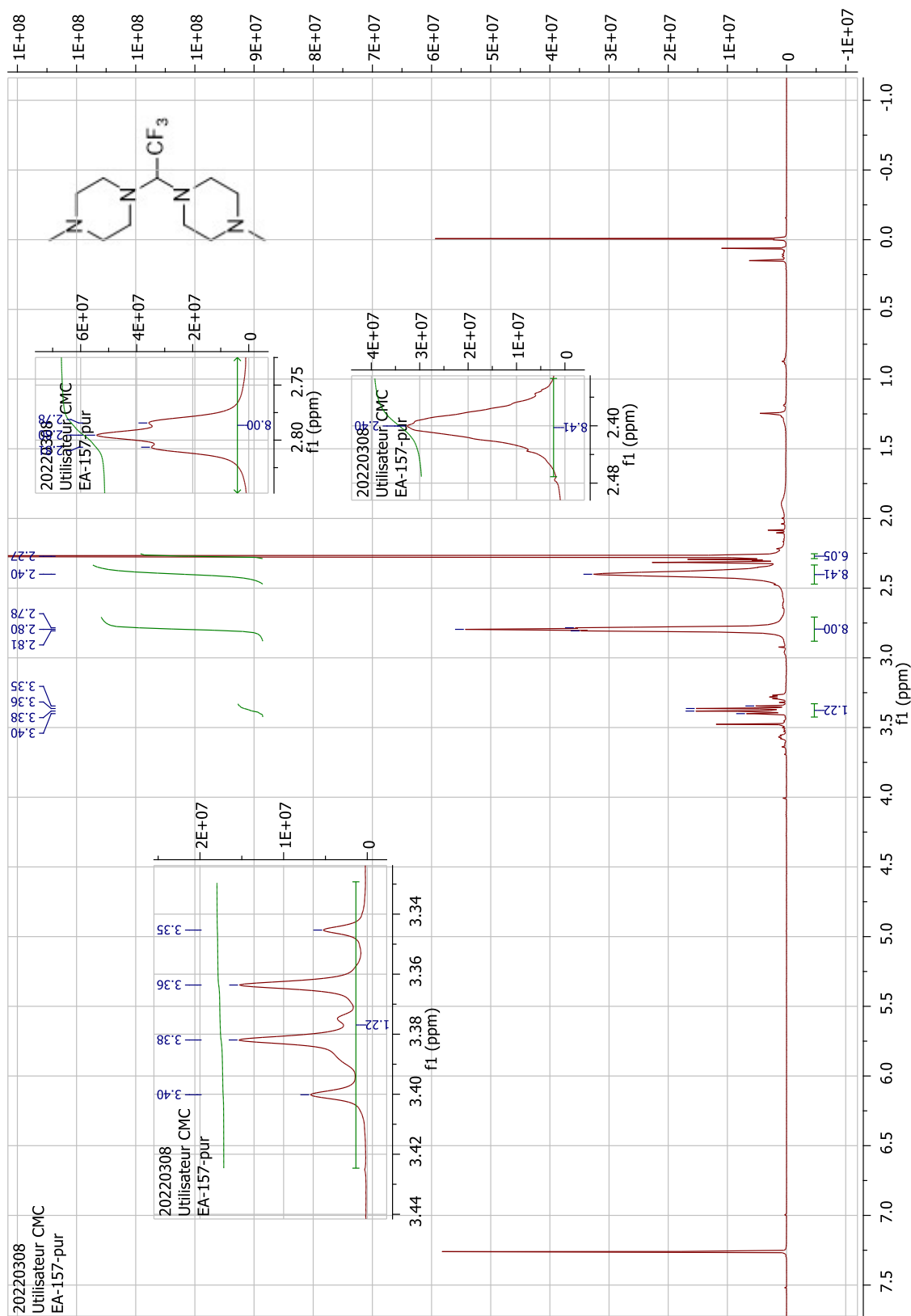
1,1-Bis(morpholine)-2,2,2-trifluoroethane (2f)² – ¹³C NMR



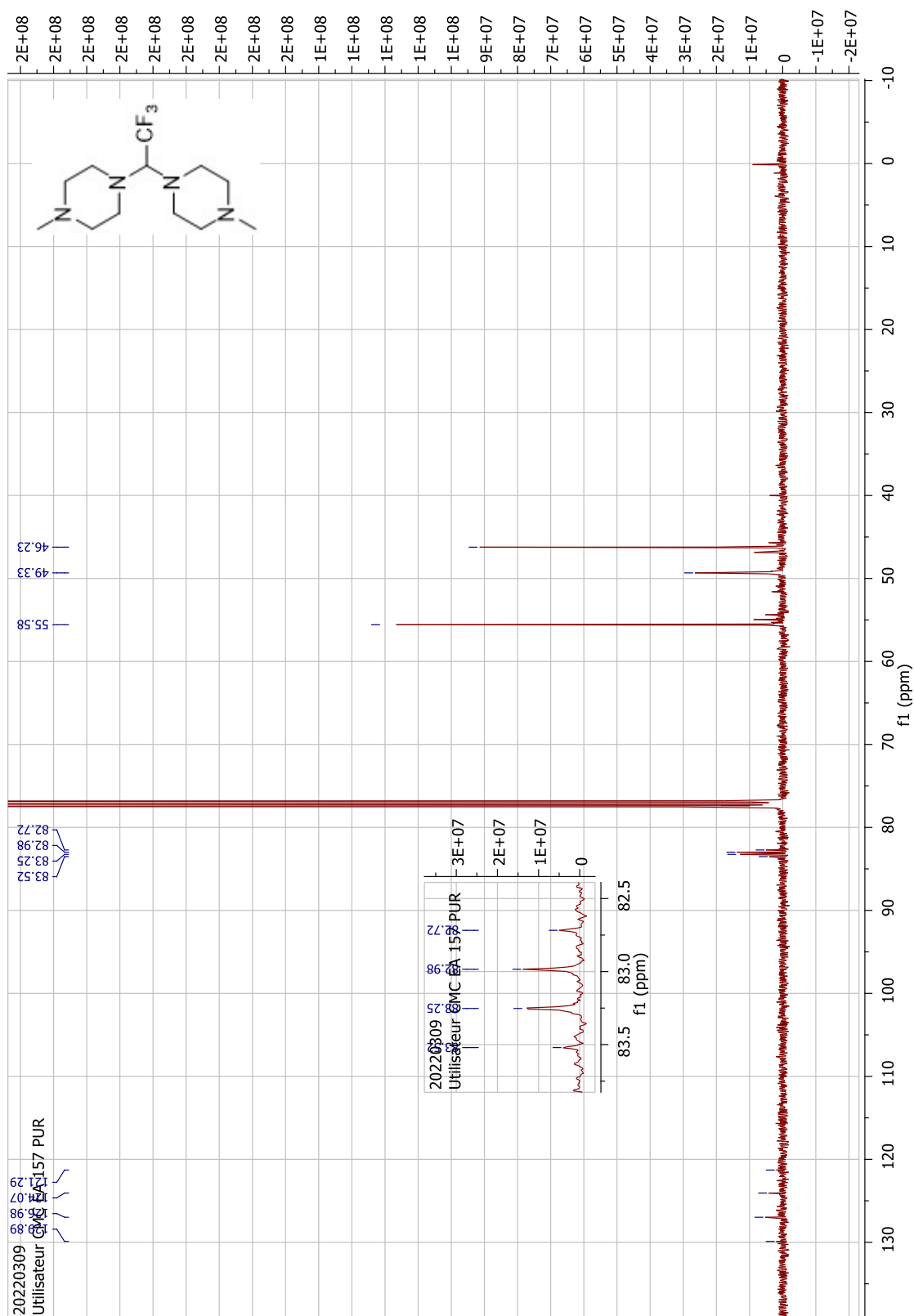
1,1-Bis(morpholine)-2,2,2-trifluoroethane (2f)² - ¹⁹F NMR



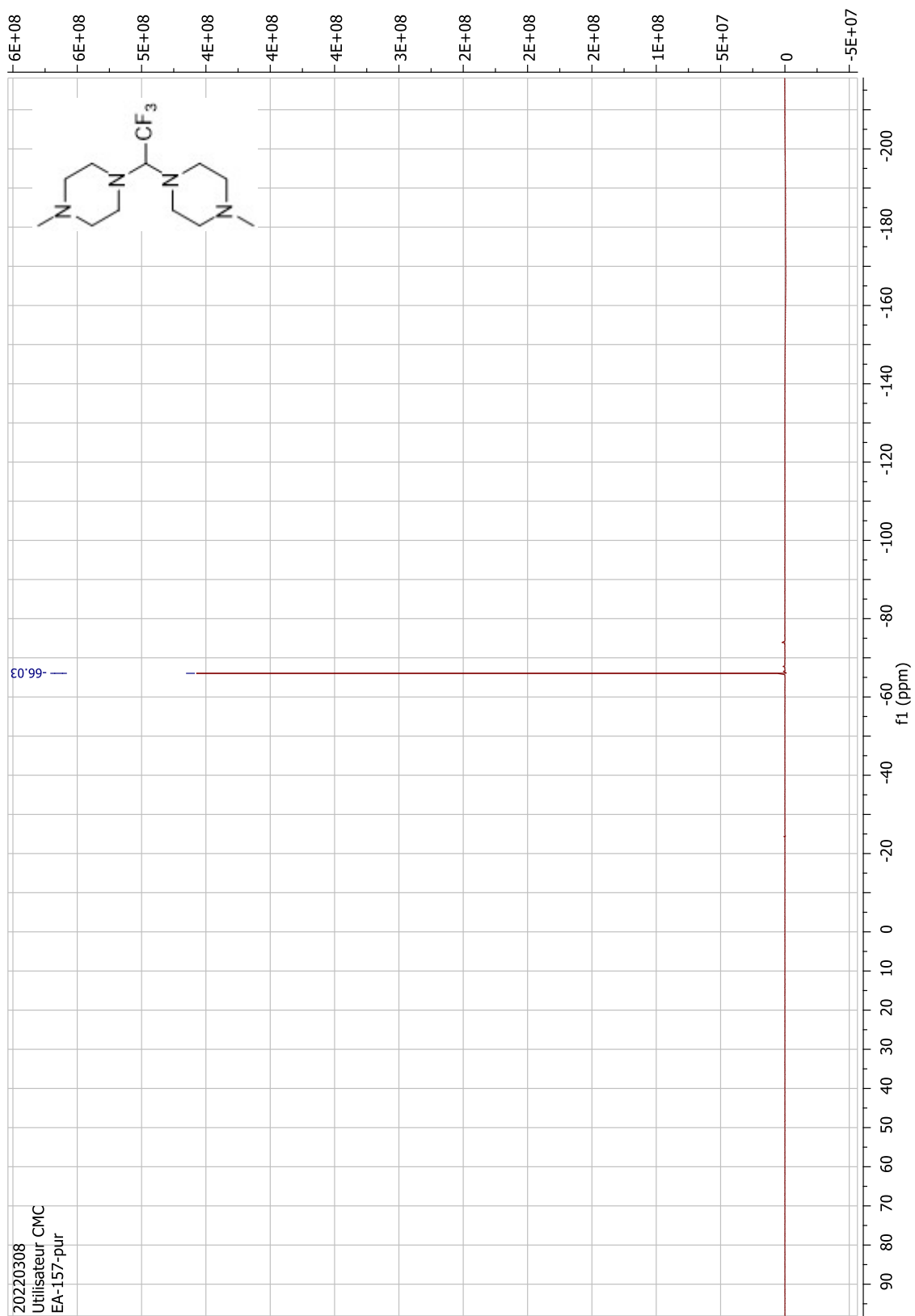
1,1-Bis(1-methylpiperazine)-2,2,2-trifluoroethane (2g) - ¹H NMR



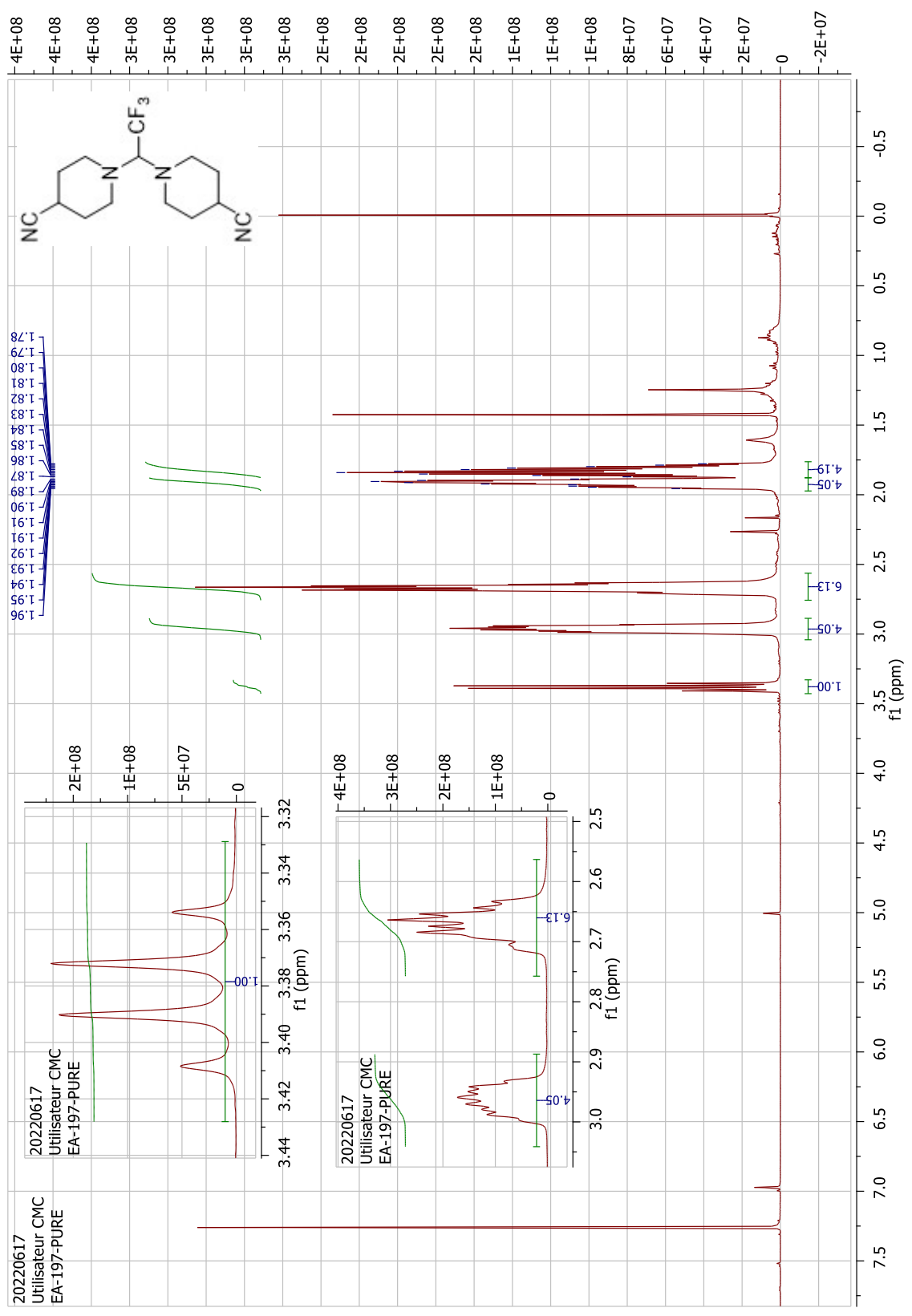
1,1-Bis(1-methylpiperazine)-2,2,2-trifluoroethane (2g) - ¹³C NMR



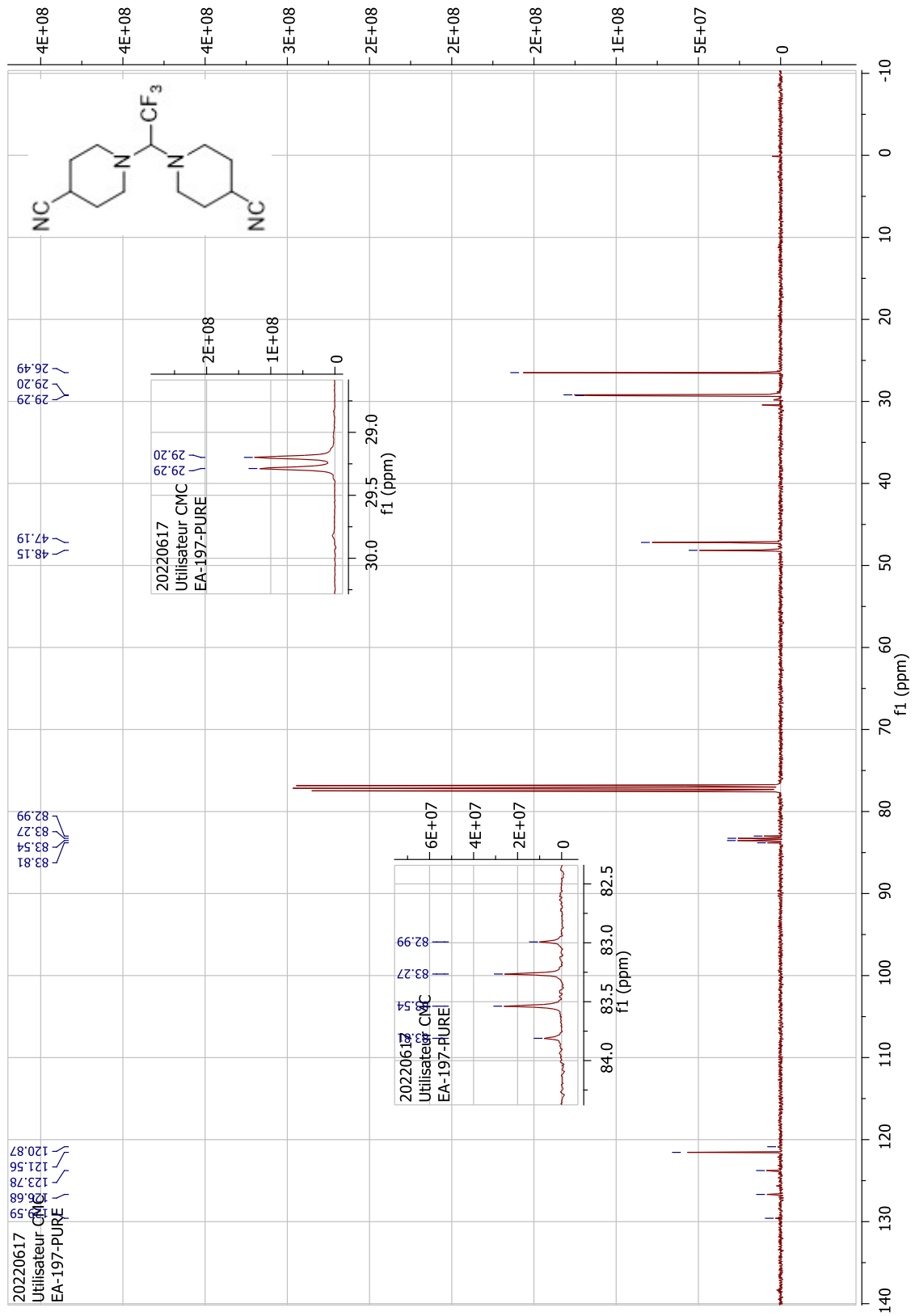
1,1-Bis(1-methylpiperazine)-2,2,2-trifluoroethane (2g) - ^{19}F NMR



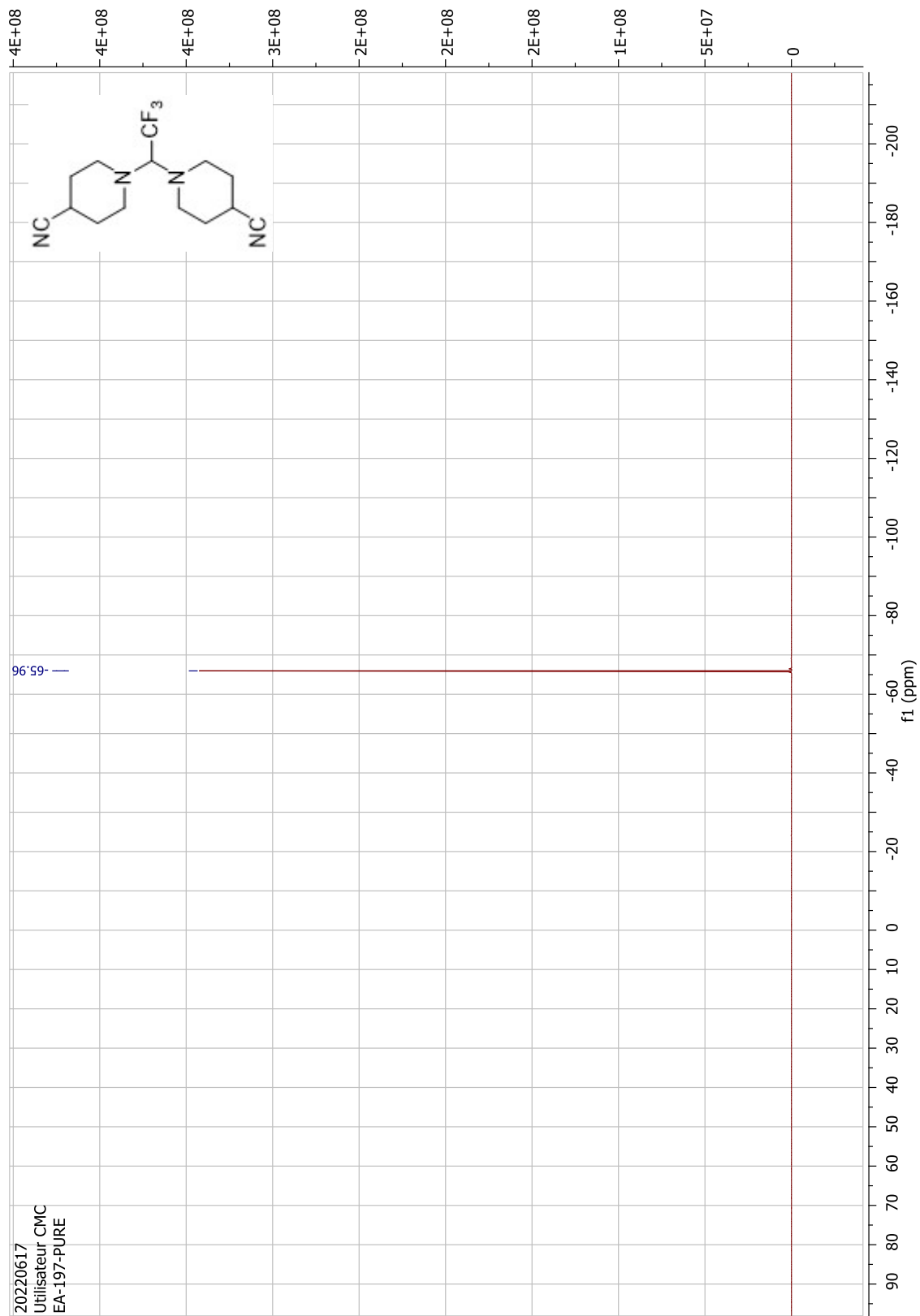
1,1-Bis(4-cyanopiperidine)-2,2,2-trifluoroethane (2h) - ¹H NMR



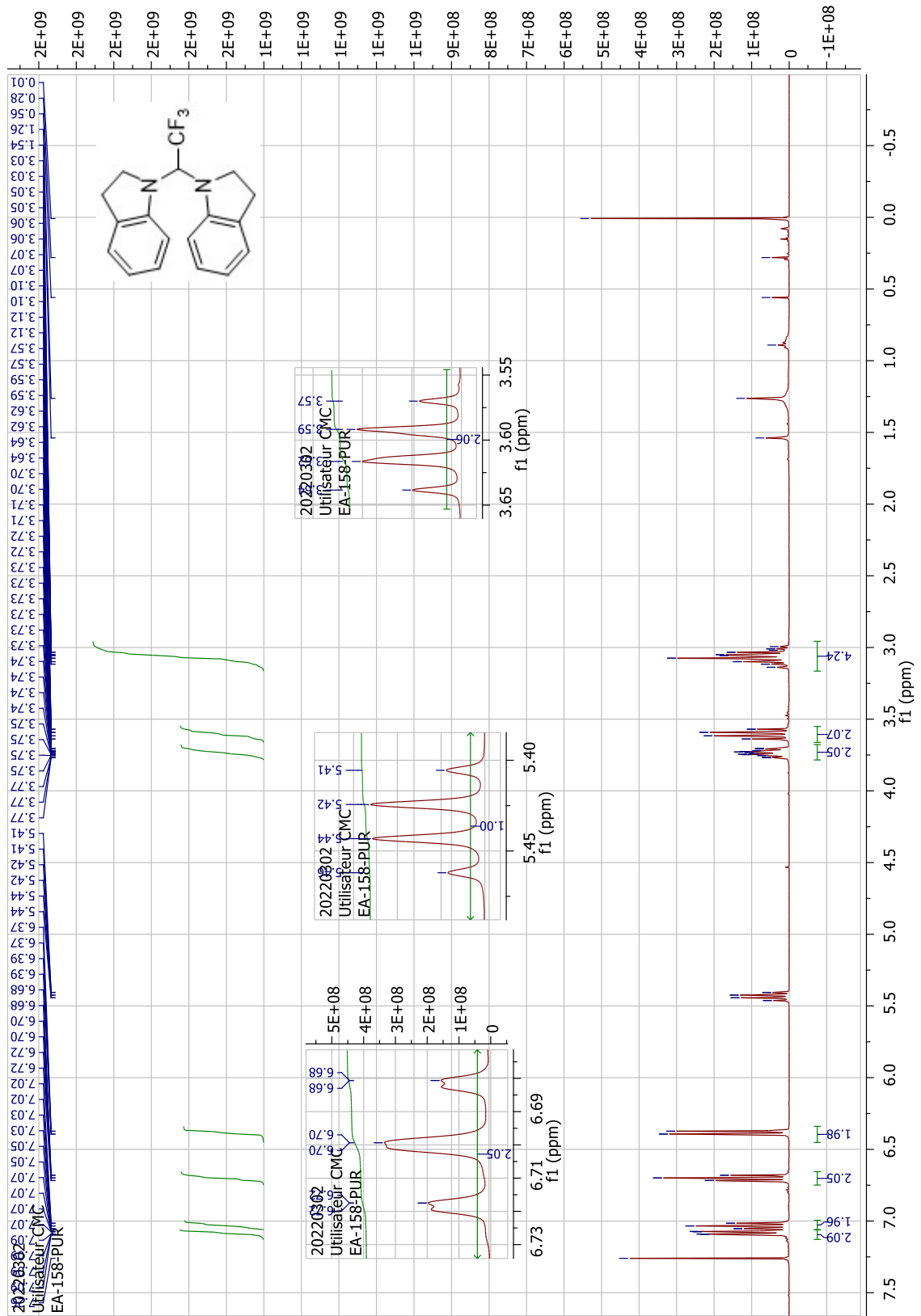
1,1-Bis(4-cyanopiperidine)-2,2,2-trifluoroethane (2h) - ¹³C NMR



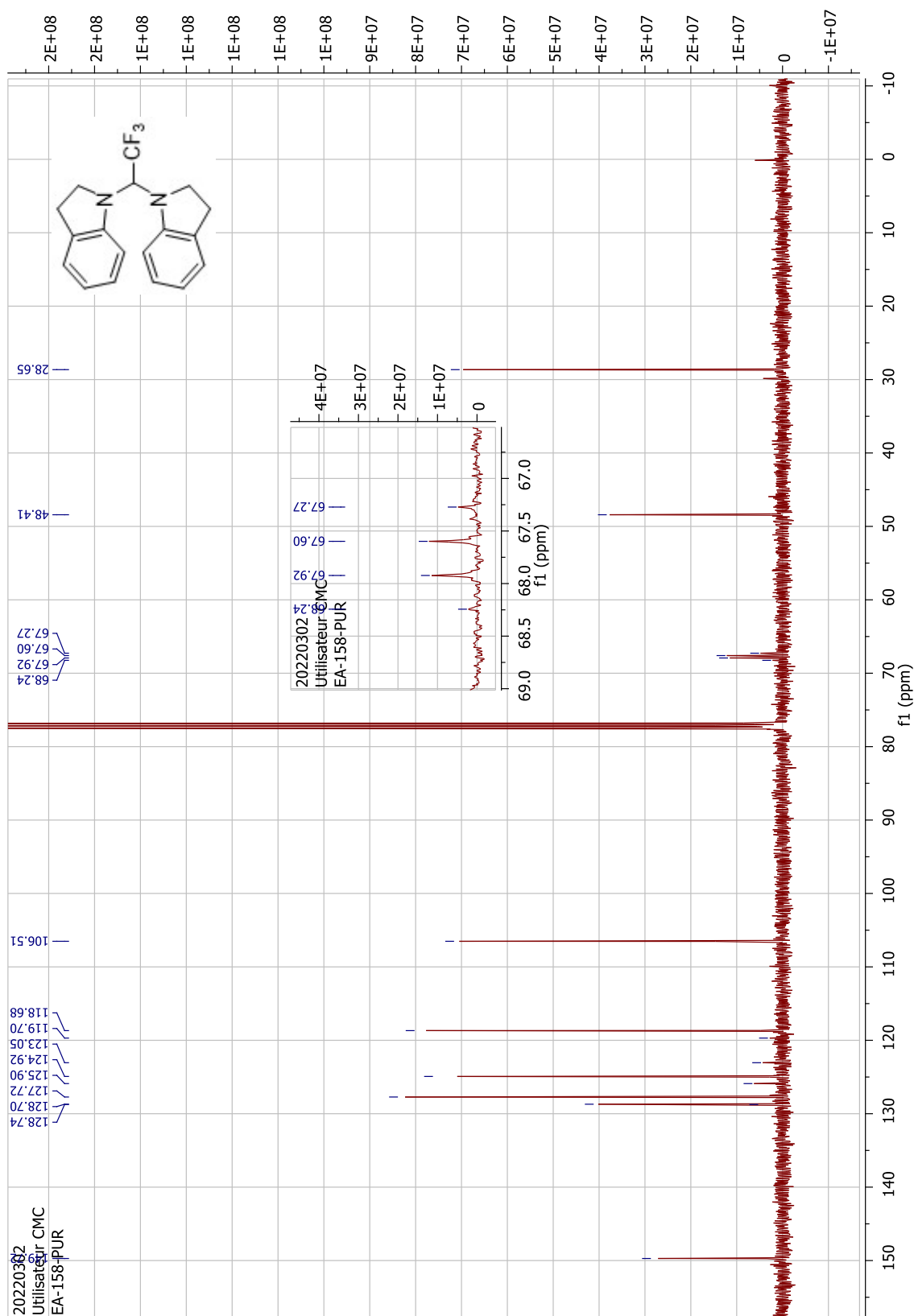
1,1-Bis(4-cyanopiperidine)-2,2,2-trifluoroethane (2h) - ¹⁹F NMR



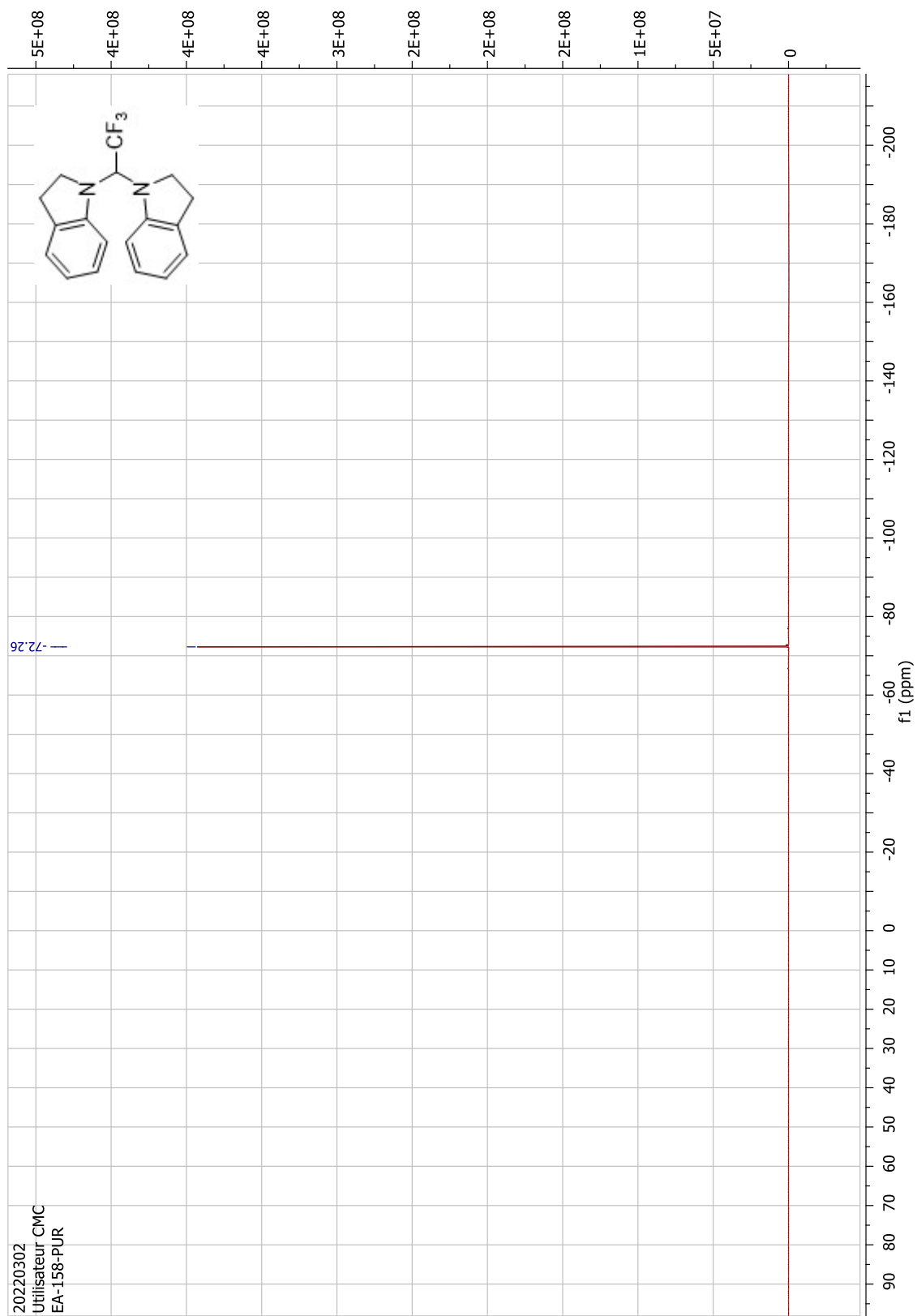
1,1-Bis(indoline)-2,2,2-trifluoroethane (2i) - ¹H NMR



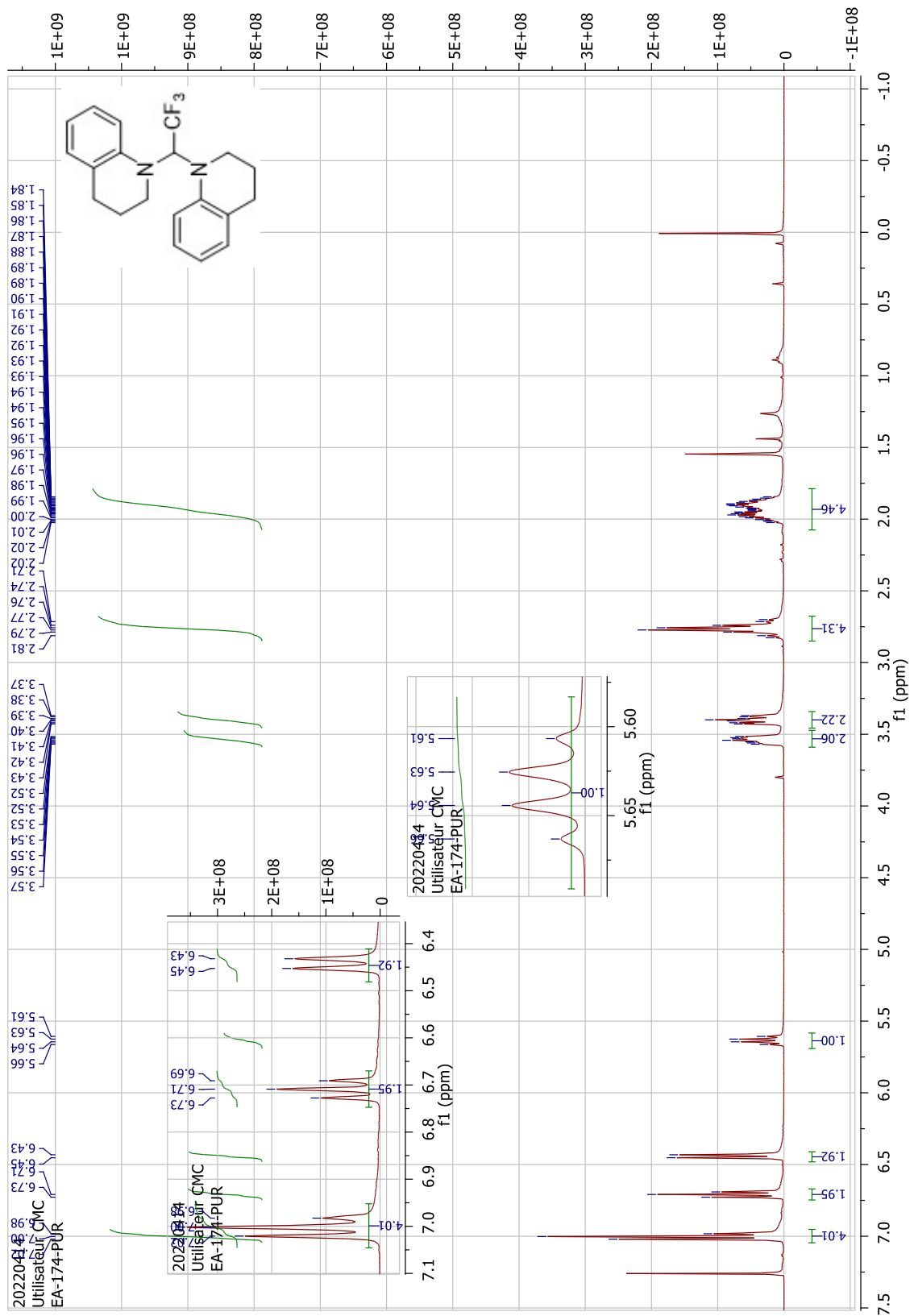
1,1-Bis(indoline)-2,2,2-trifluoroethane (2i) - ¹³C NMR



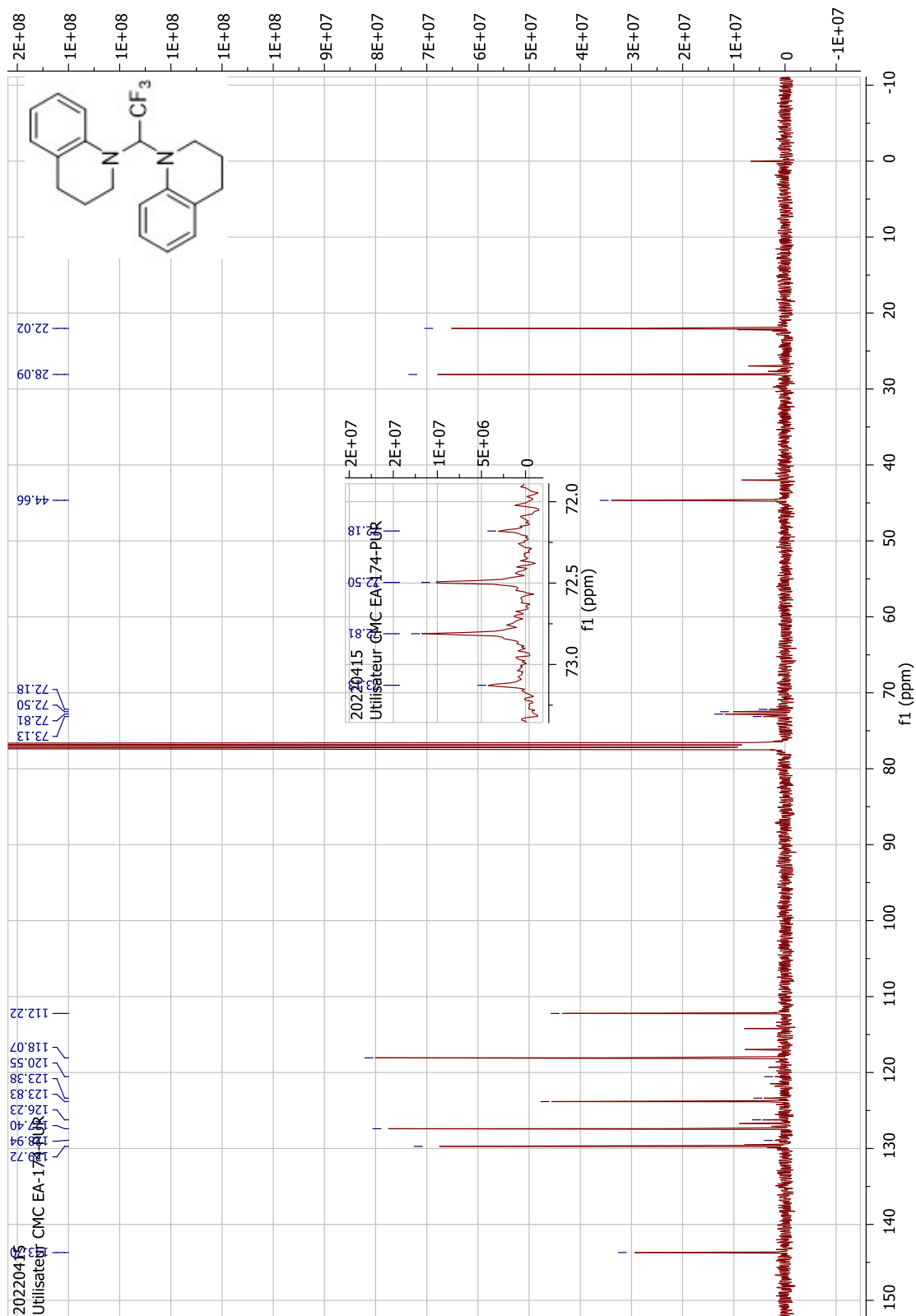
1,1-Bis(indoline)-2,2,2-trifluoroethane (2i) - ¹⁹F NMR



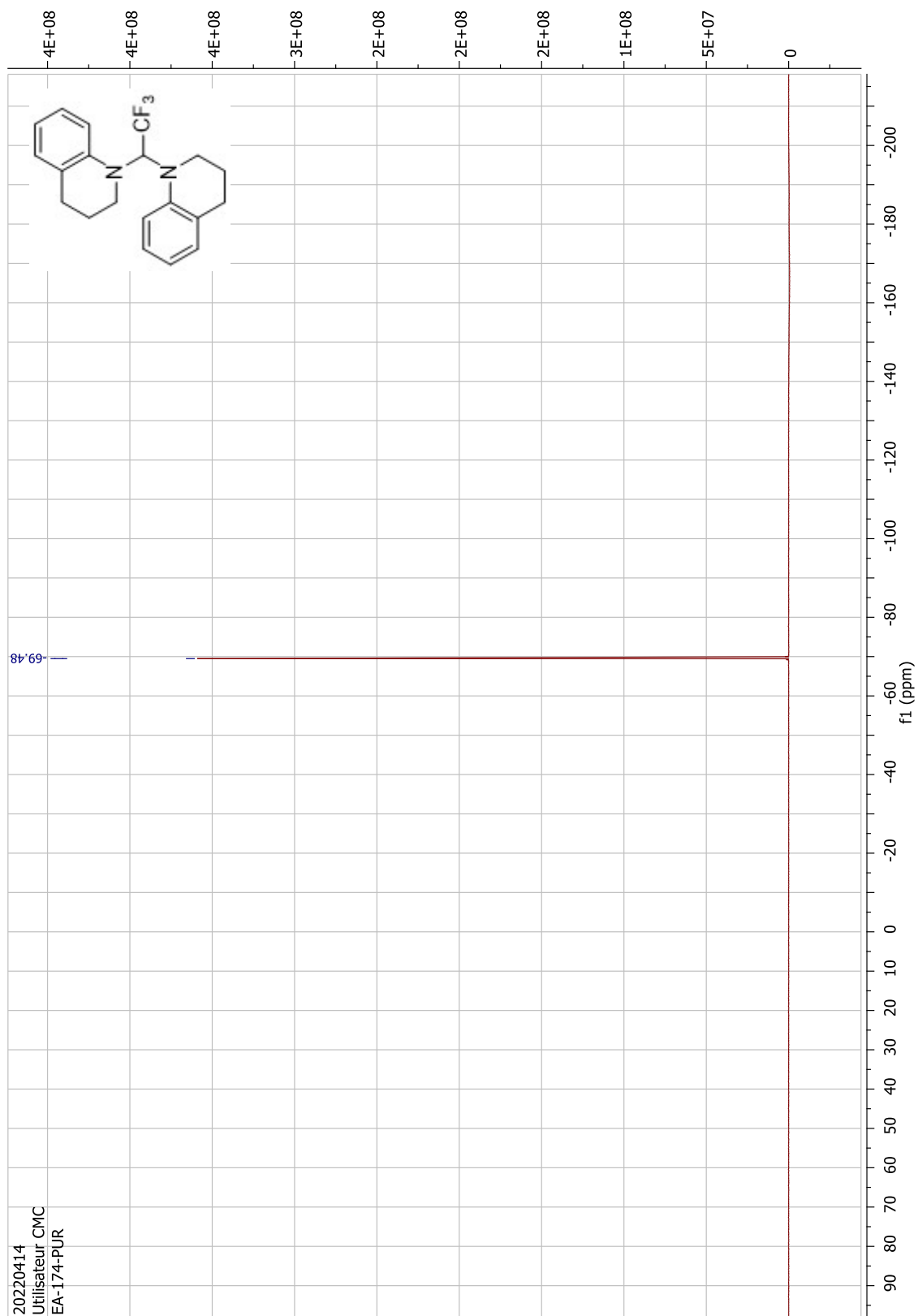
1,1-Bis(1,2,3,4-tetrahydroquinoline)-2,2,2-trifluoroethane (2j) - ¹H NMR



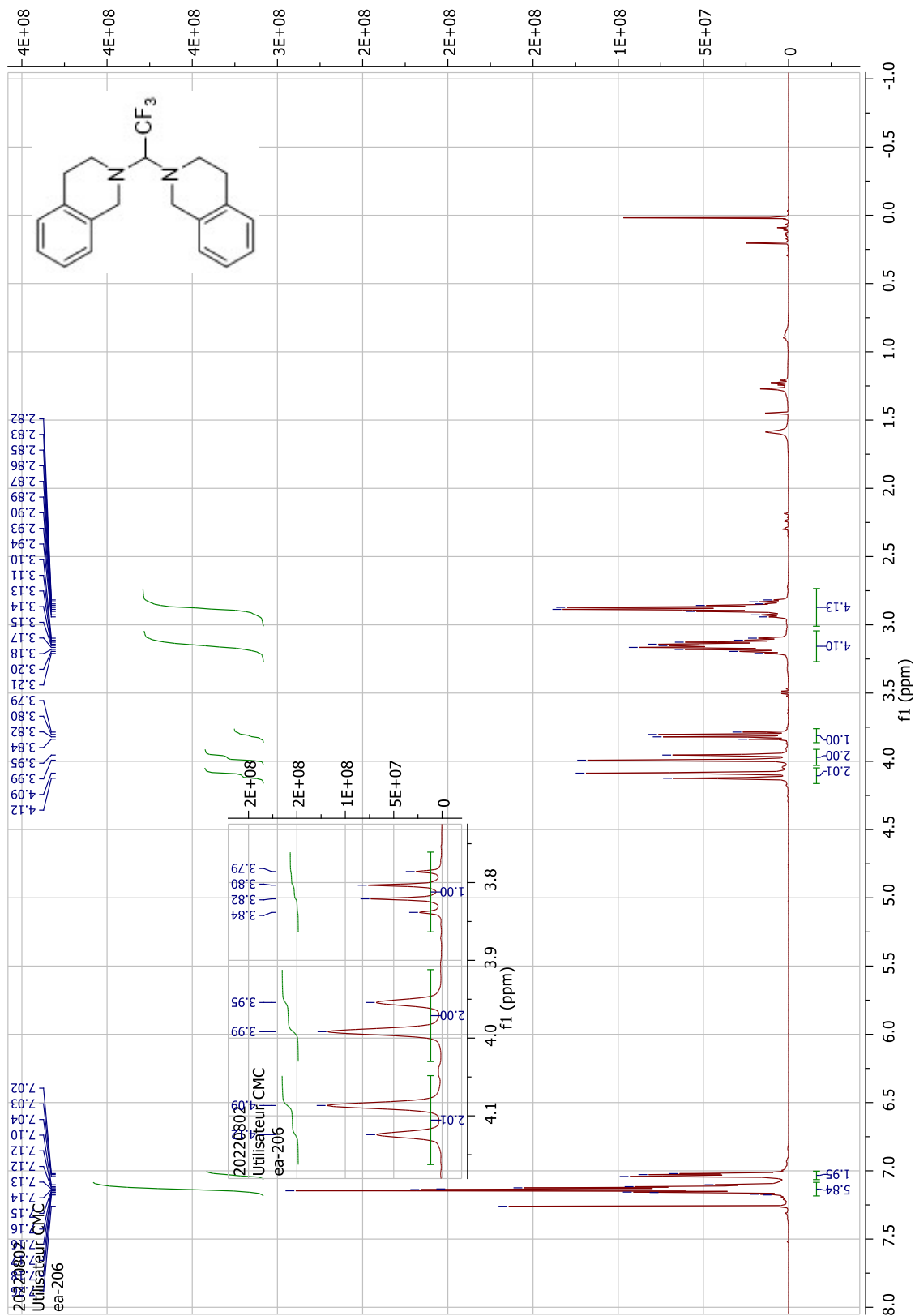
1,1-Bis(1,2,3,4-tetrahydroquinoline)-2,2,2-trifluoroethane (2j) - ^{13}C NMR



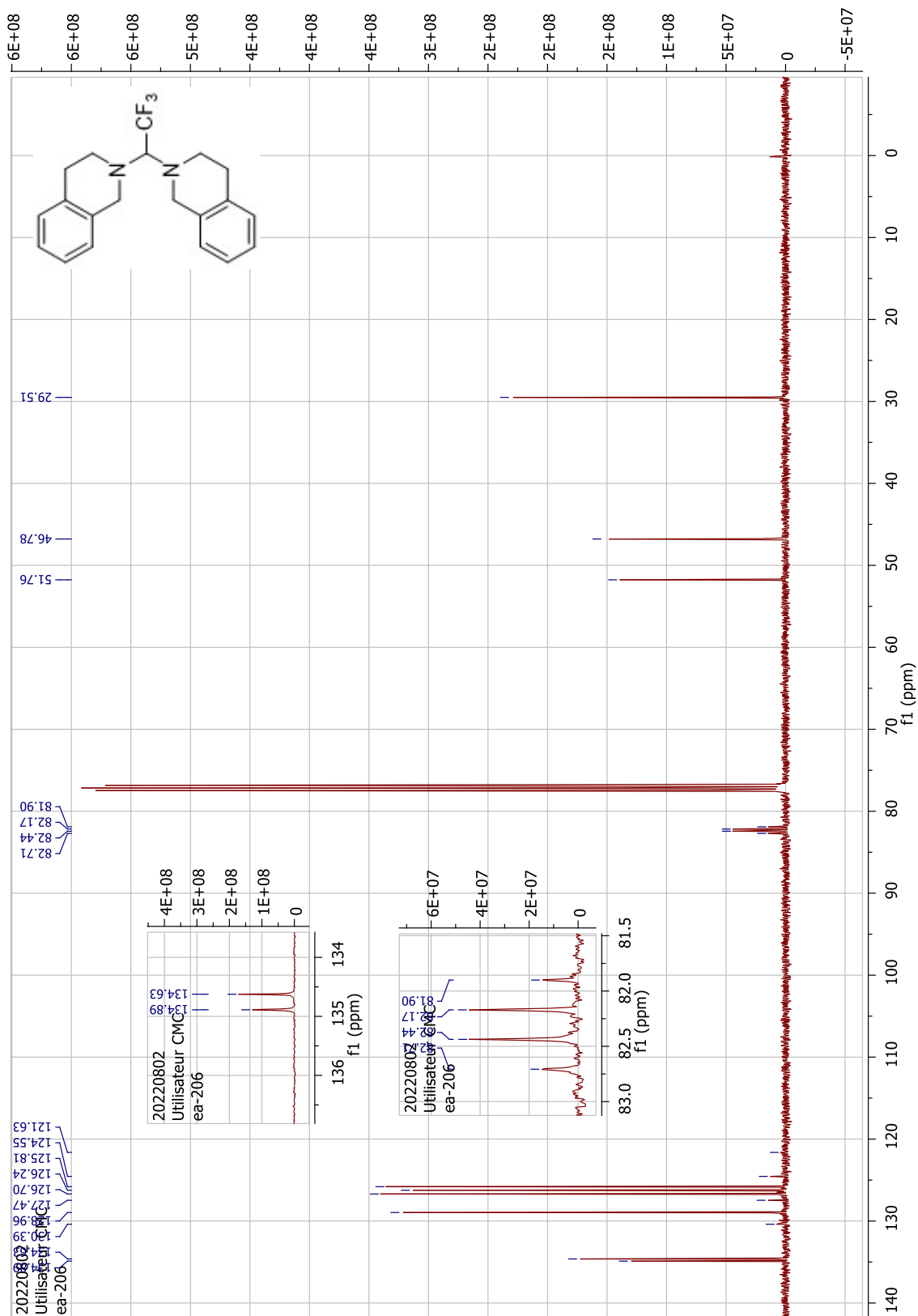
1,1-Bis(1,2,3,4-tetrahydroquinoline)-2,2,2-trifluoroethane (2j) - ^{19}F NMR



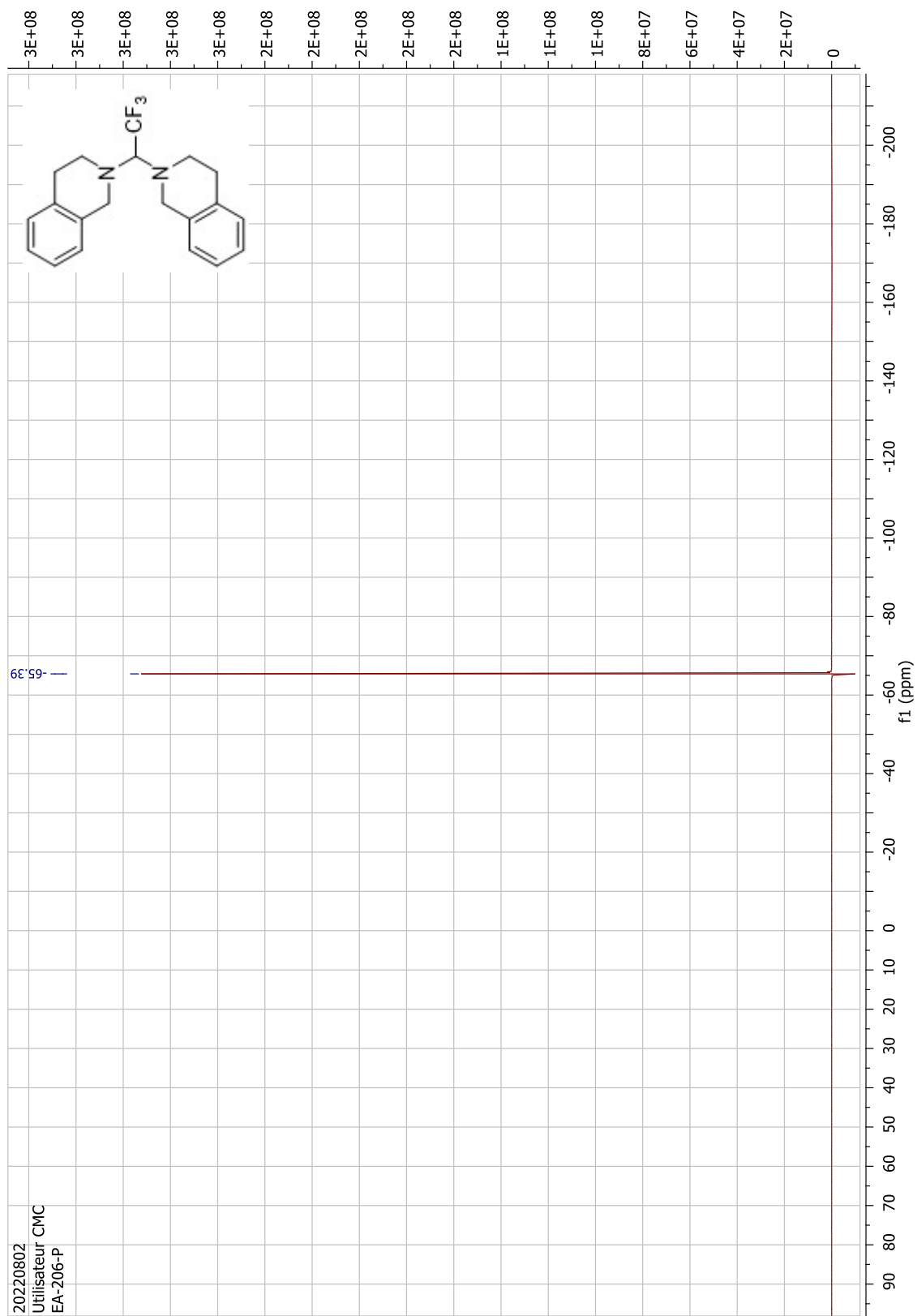
1,1-Bis(1,2,3,4-tetrahydroisoquinoline)-2,2,2-trifluoroethane (2k) - ¹H NMR



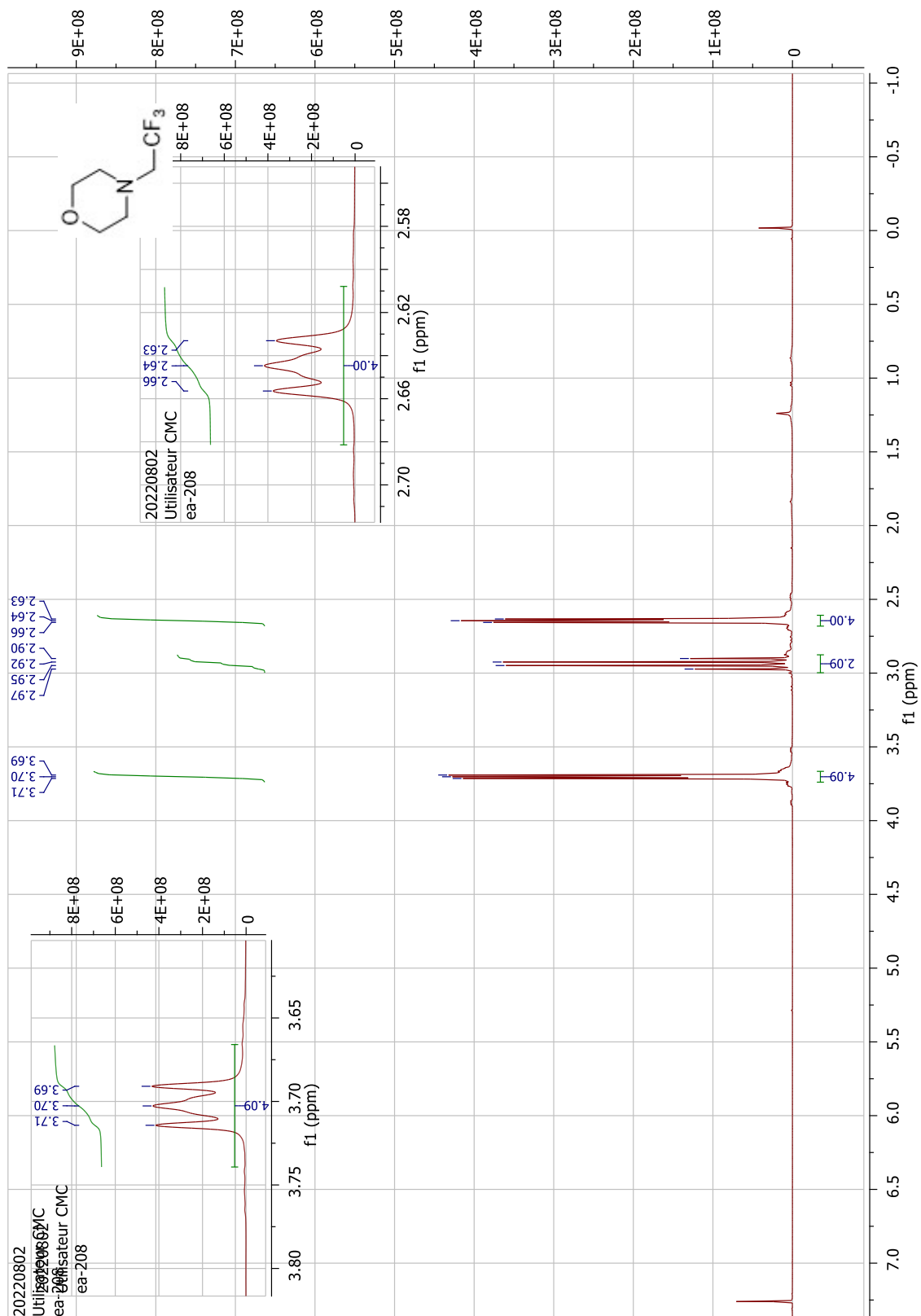
1,1-Bis(1,2,3,4-tetrahydroisoquinoline)-2,2,2-trifluoroethane (2k) - ¹³C NMR



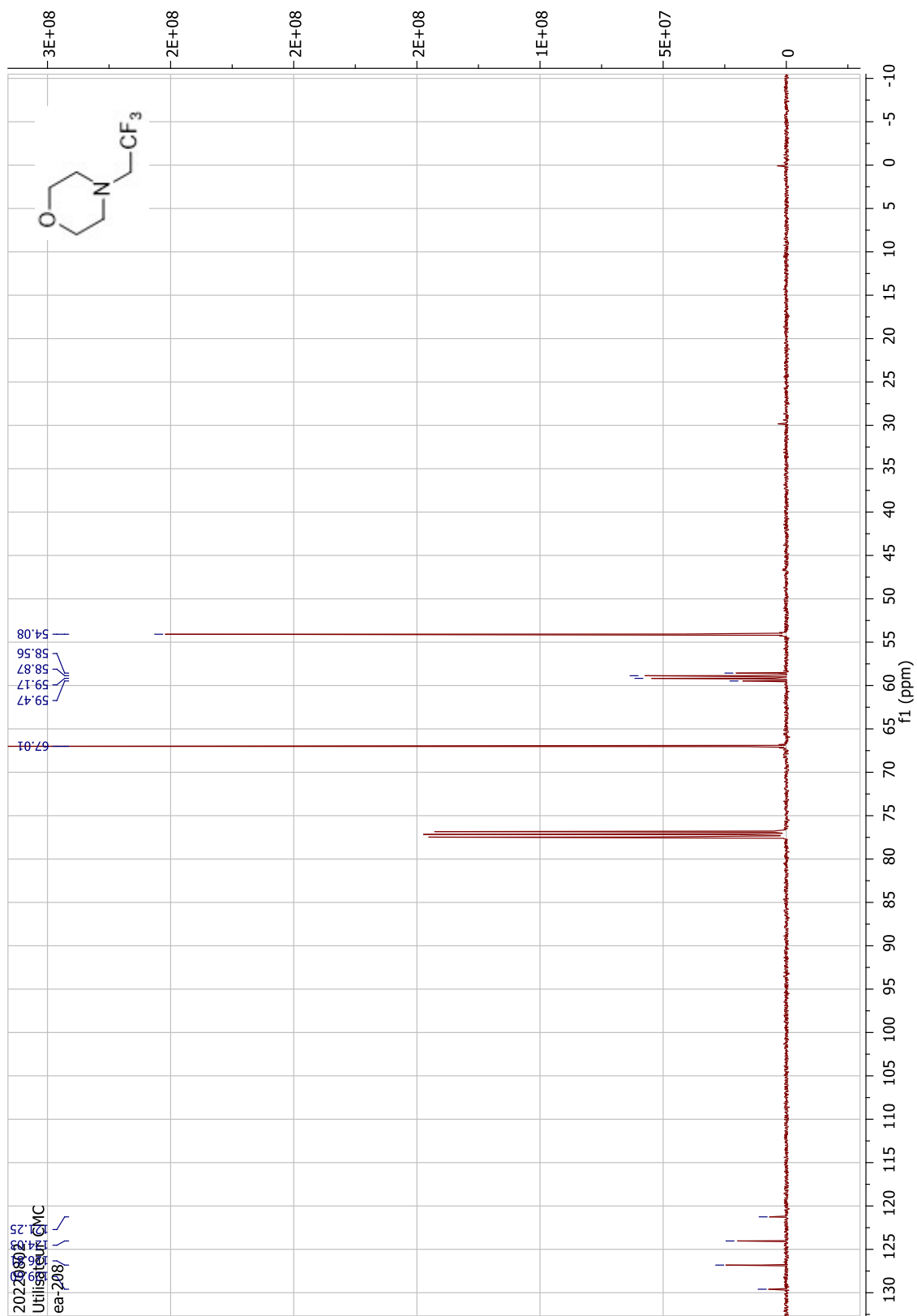
1,1-Bis(1,2,3,4-tetrahydroisoquinoline)-2,2,2-trifluoroethane (2k) - ¹⁹F NMR



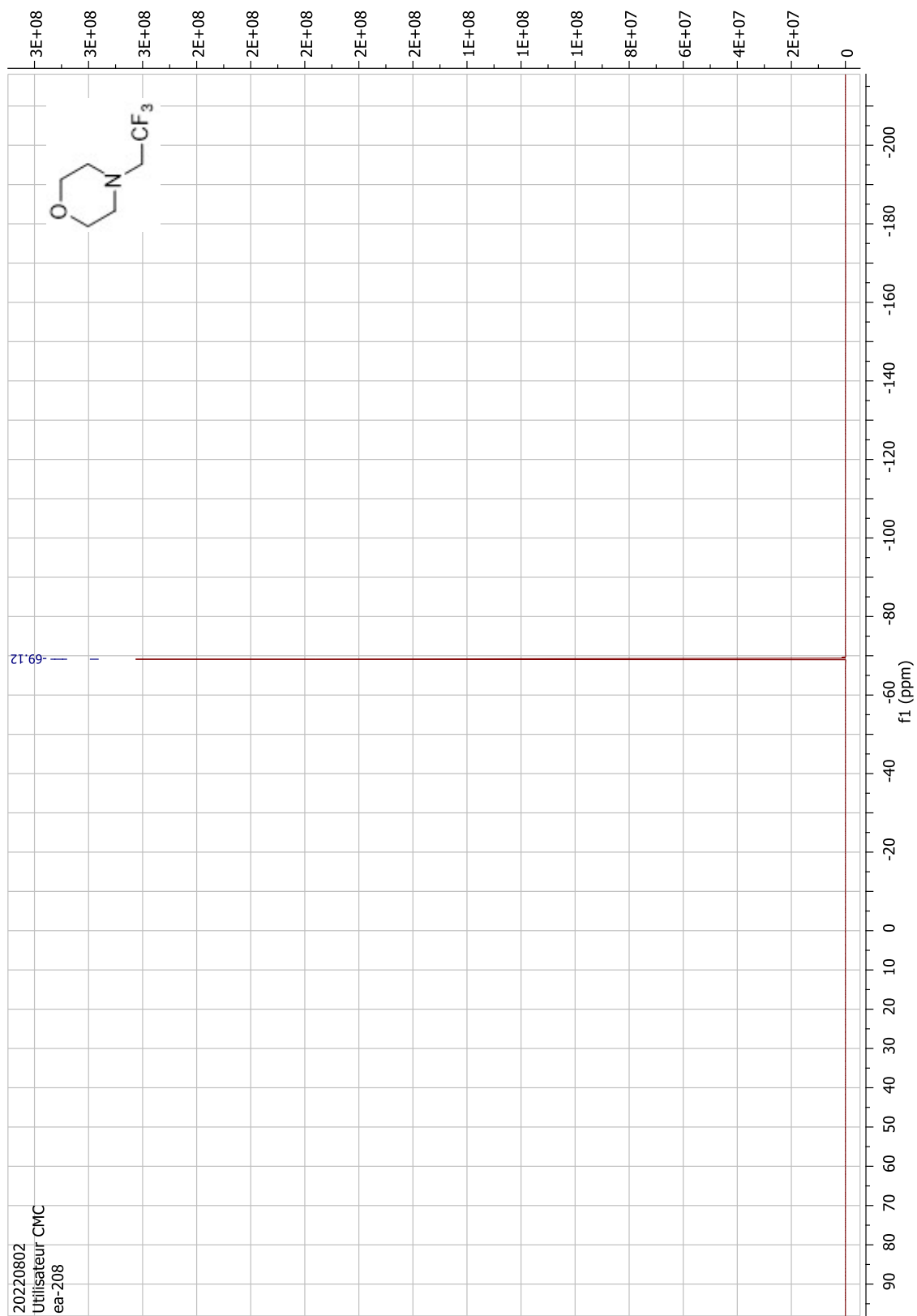
1-Morpholine-2,2,2-trifluoroethane (4f)³ - ¹H NMR



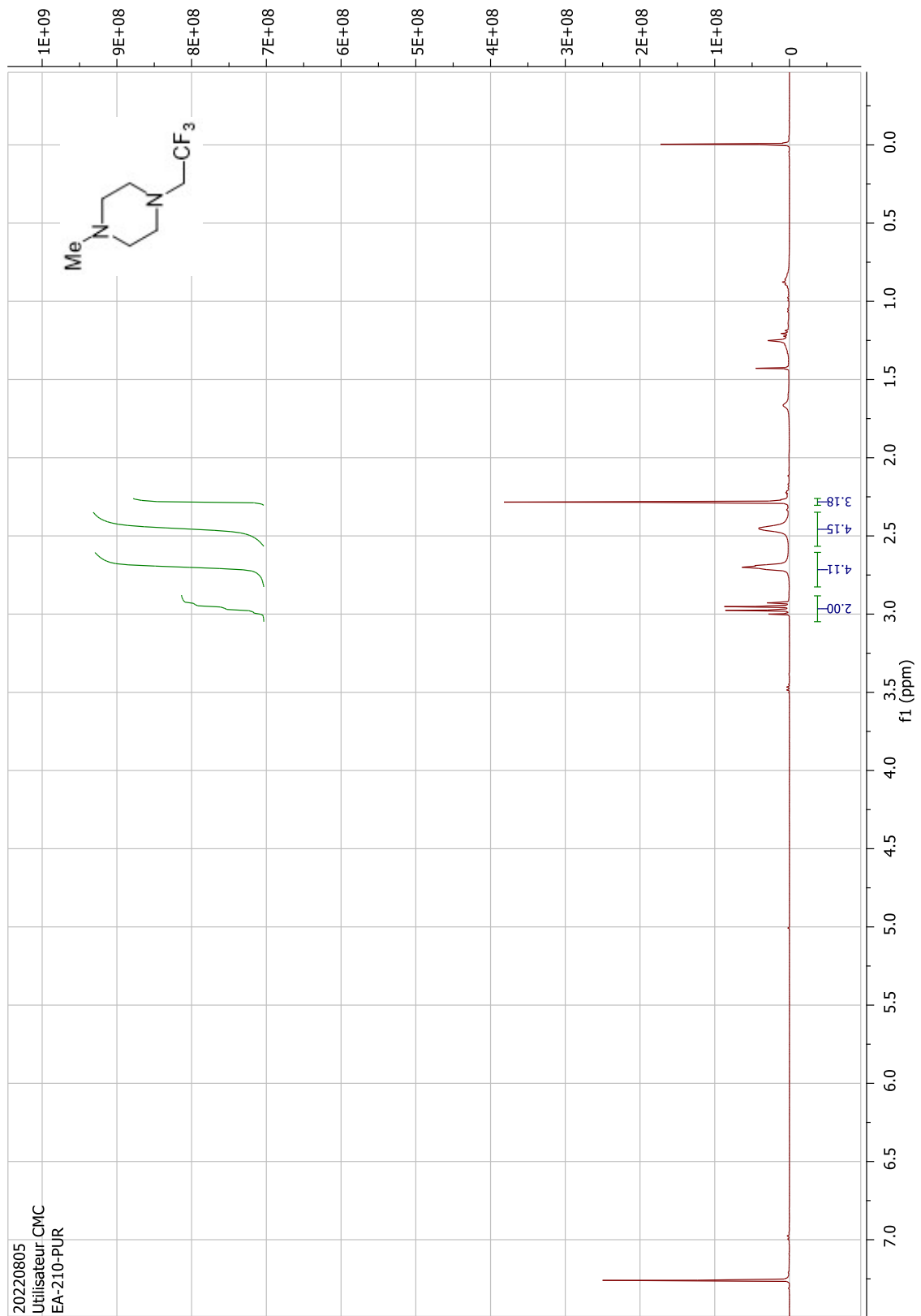
1-Morpholine-2,2,2-trifluoroethane (4f)³ - ¹³C NMR



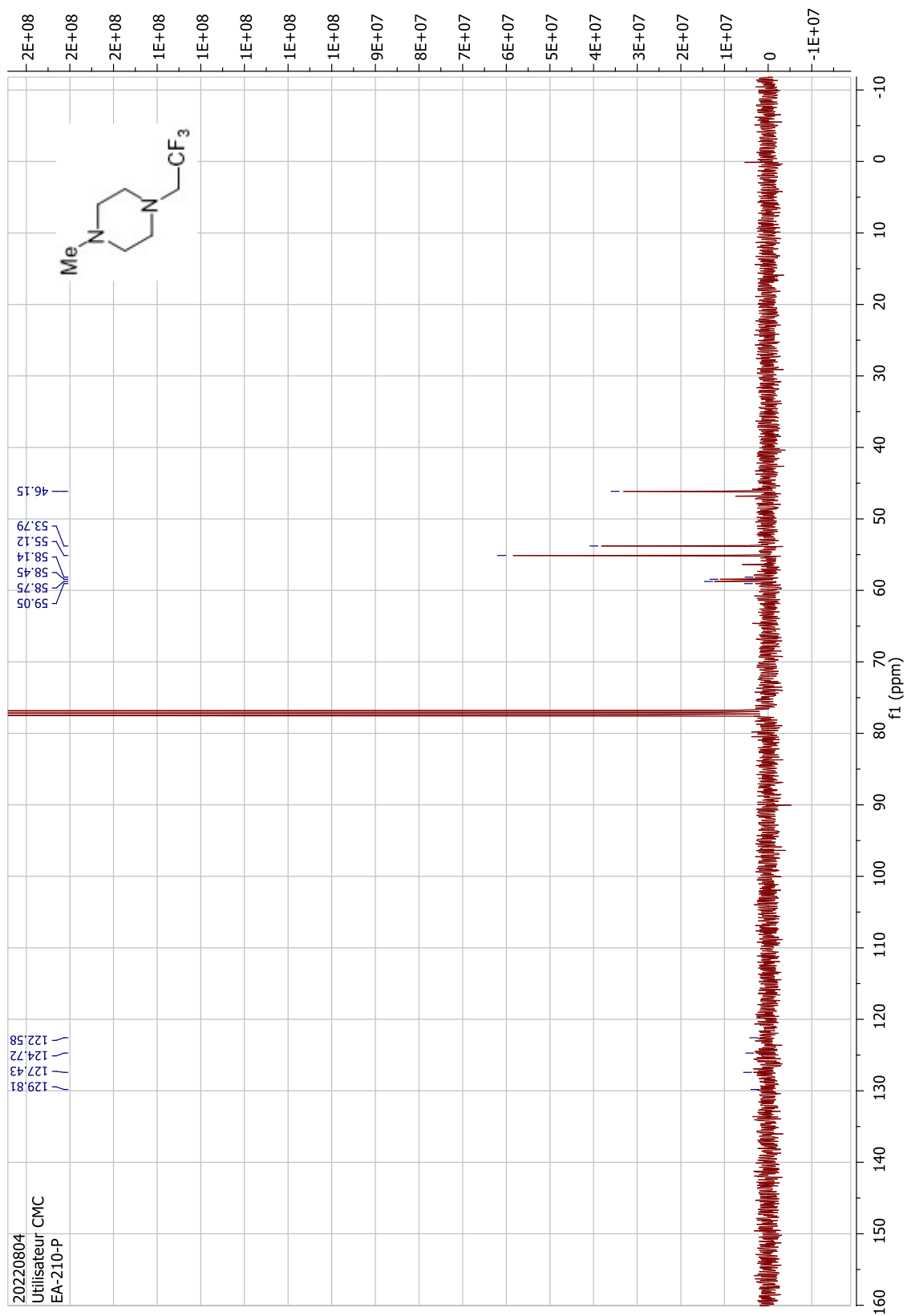
1-Morpholine-2,2,2-trifluoroethane (4f)³ - ¹⁹F NMR



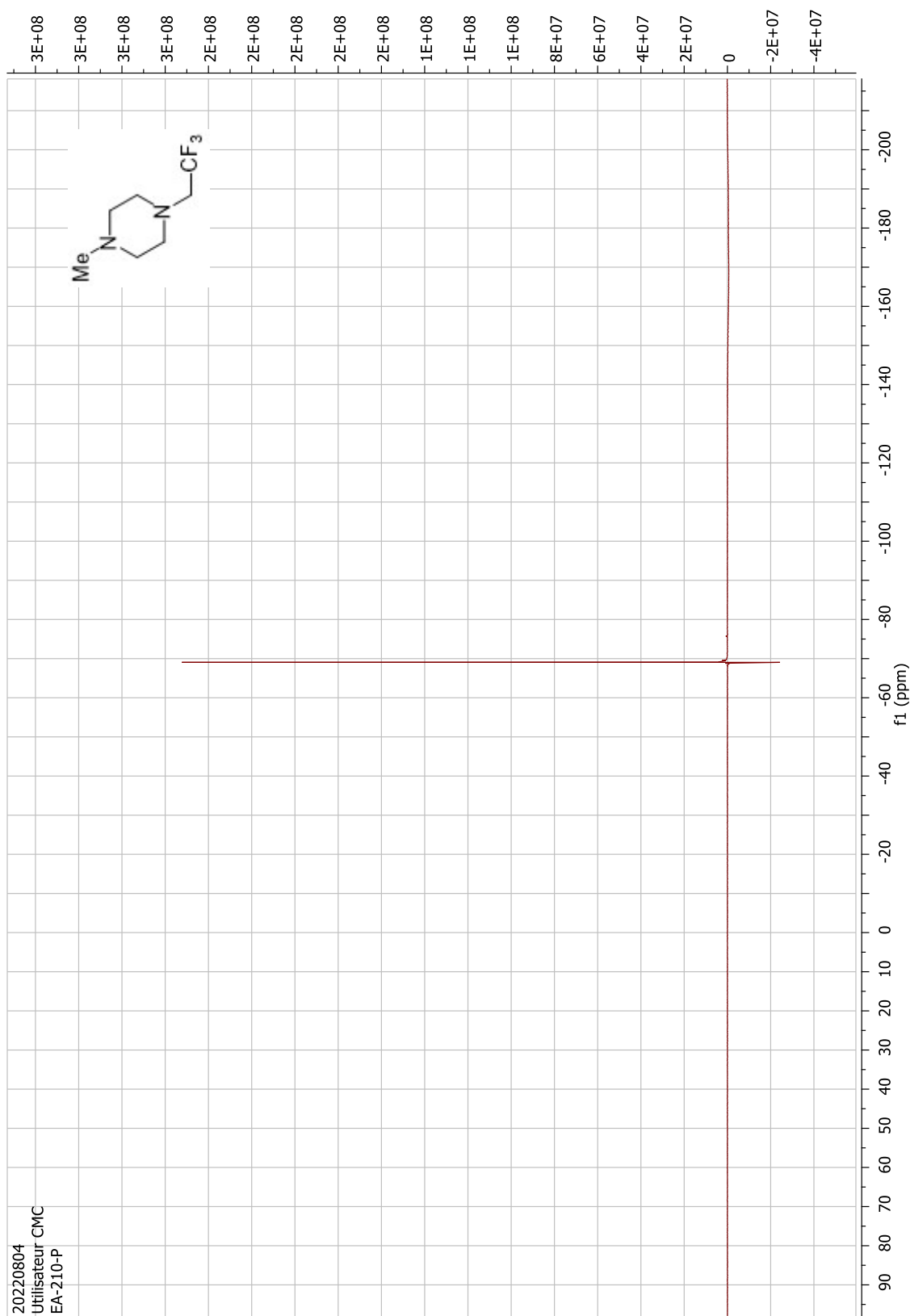
1-(1-Methylpiperazine)-2,2,2-trifluoroethane (4g)³ - ¹H NMR



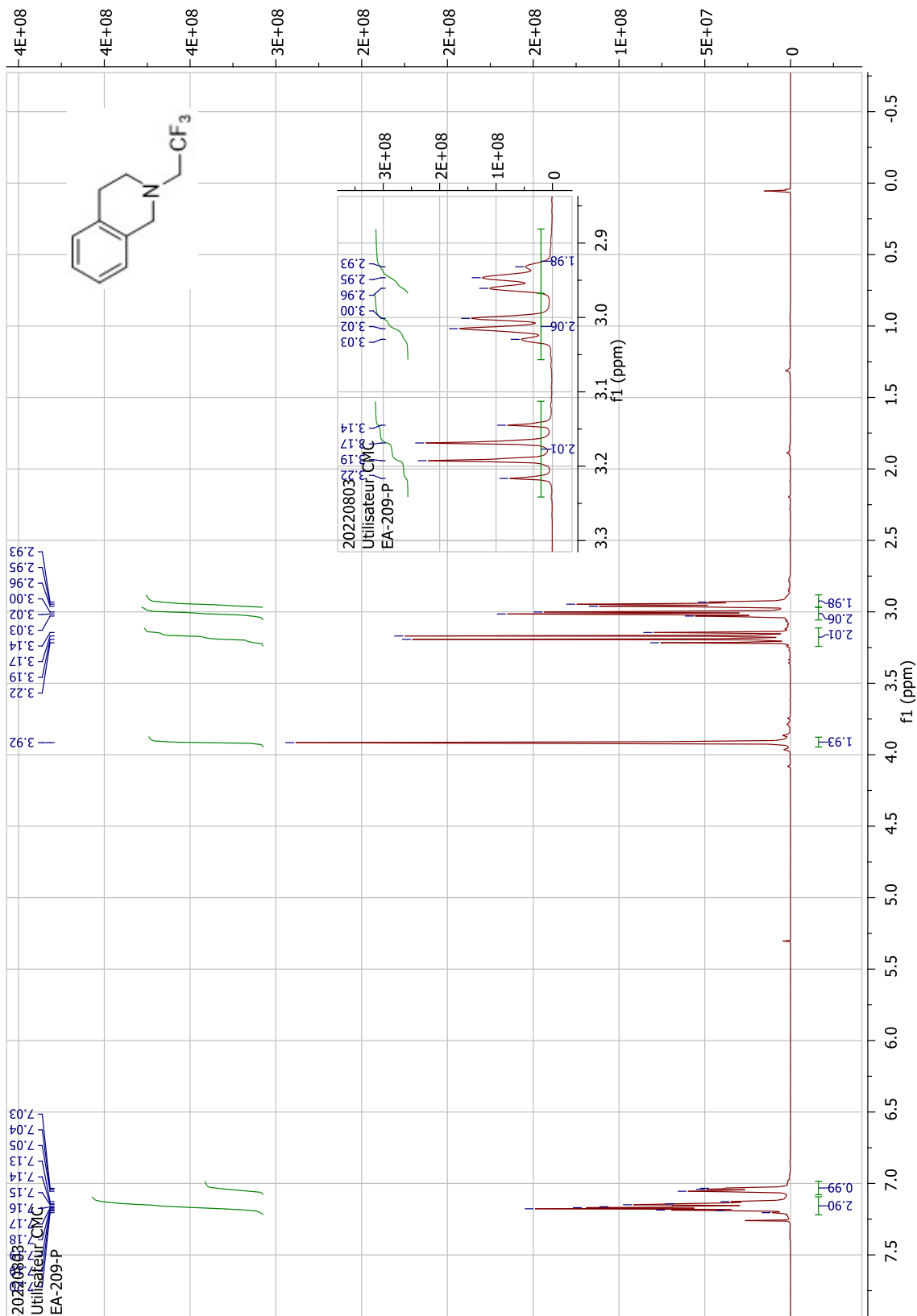
1-(1-Methylpiperazine)-2,2,2-trifluoroethane (4g)³ - ¹³C NMR



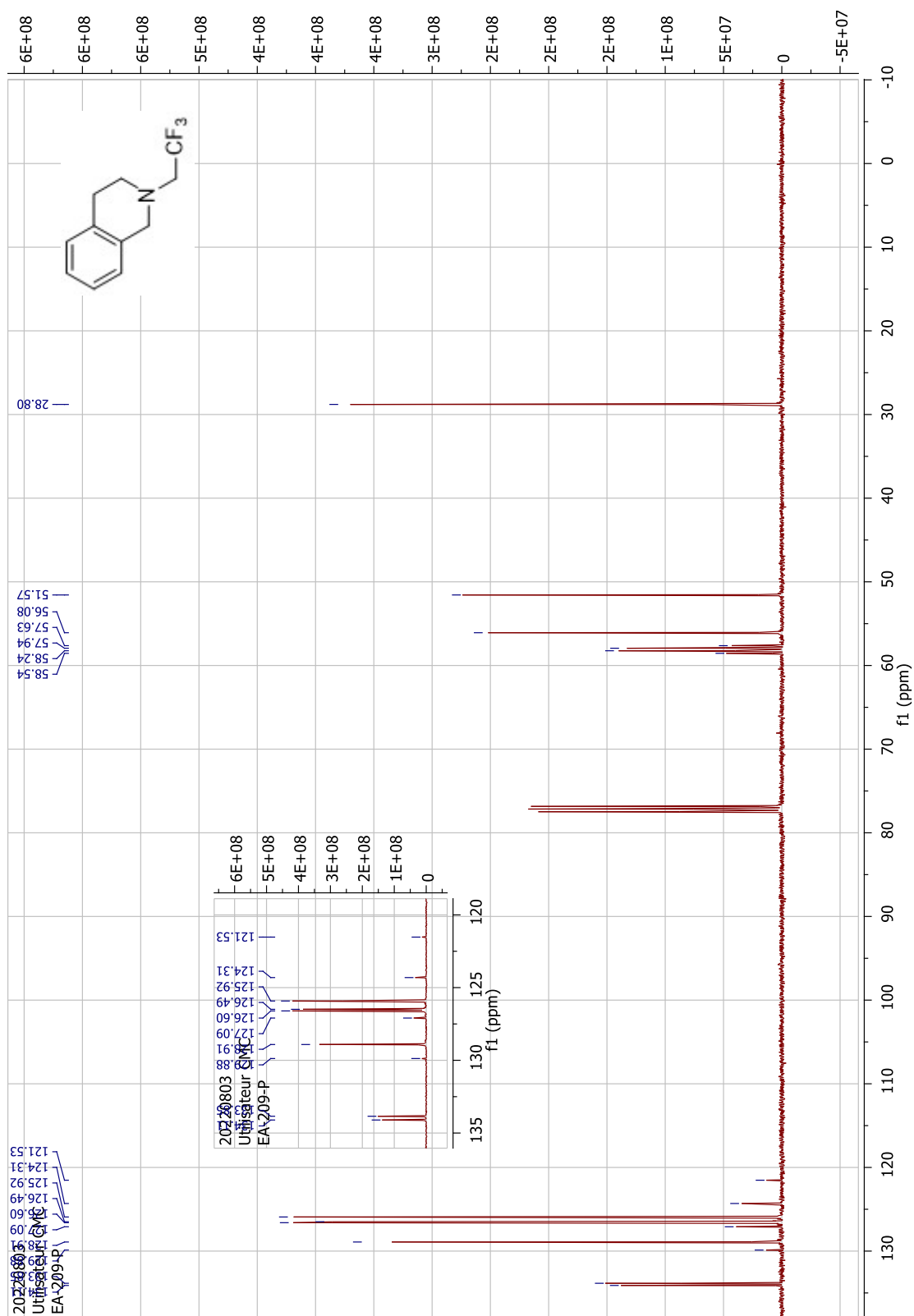
1-(1-Methylpiperazine)-2,2,2-trifluoroethane (4g)³ - ¹⁹F NMR



1-(1,2,3,4-Tetrahydroisoquinoline)-2,2,2-trifluoroethane (4k)⁴ - ¹H NMR



1-(1,2,3,4-Tetrahydroisoquinoline)-2,2,2-trifluoroethane (4k)⁴ - ¹³C NMR



1-(1,2,3,4-Tetrahydroisoquinoline)-2,2,2-trifluoroethane (4k)⁴ - ¹⁹F NMR

