SUPPORTING INFORMATION

HDAC6 Brain Mapping with [^{18}F]Bavarostat Enabled by a Ru-Mediated Dexoyfluorination

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MATERIALS AND METHODS

All air- and/or moisture-sensitive reactions were performed under an inert atmosphere of nitrogen or argon with standard Schlenk and glovebox techniques.[1]

Solvents

Tetrahydrofuran was distilled from deep purple sodium benzophenone ketyl. Dry DMF and dry DMSO were purchased from Acros Organics. Other anhydrous solvents (acetonitrile, diethyl ether, dichloromethane, pentane, and toluene) were obtained by filtration through drying columns[2] on an mBraun system.

Chromatography

Thin layer chromatography (TLC) was performed by EMD TLC plates pre-coated with 250 μm thickness silica gel 60 F_{254} plates and visualized by fluorescence quenching under UV light and $KMnO_4$ stain. Flash chromatography was performed with silica gel (230-400 mesh) purchased from Silicycle Inc., or, where stated, with spherical silica gel cartridges (ZIP sphere) from Biotage with an Isolera purification system.

Spectroscopy and Instruments

NMR spectra were recorded on either a Varian Unity/Inova 600 spectrometer operating at 600 MHz for ^{1}H acquisitions, a Bruker 500 spectrometer or a Varian Unity/Inova 500 spectrometer, both operating at 500 MHz, 471 MHz and 126 MHz for ^{1}H, ^{19}F and ^{13}C acquisitions, respectively, or a Varian Mercury 400 spectrometer operating at 375 MHz for ^{19}F acquisitions. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (^{1}H: Chloroform-d, δ 7.26; DMSO-d_6, δ 2.50), (^{13}C: $CDCl_3$, δ 77.16; DMSO-d_6, δ 39.52). Data is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz; integration.

Starting materials

All substrates and reagents were used as received from commercial suppliers unless otherwise stated.

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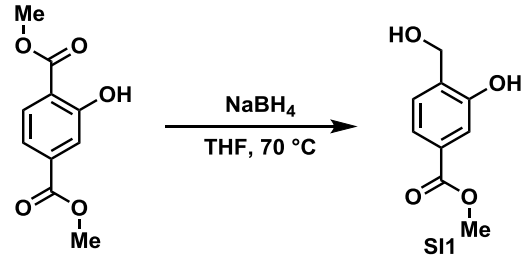
[1] Shriver, D. F.; Drezdon, M. A. Inert-Atmosphere Glove Boxes. *The Manipulation of Air-Sensitive Compounds*, 2nd ed.; John Wiley & Sons: New York, **1986**; pp. 45–67.

[2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

EXPERIMENTAL DATA

Synthesis of Bavarostat Standard, Labeling Precursor and [CpRu(COD)Cl]

Methyl-3-hydroxy-4-(hydroxymethyl)benzoate (SI1)



To a solution of dimethyl hydroxyterephthalate (500 mg, 2.38 mmol, 1.00 eq) in 5 mL THF was added sodium borohydride (180 mg, 4.76 mmol, 2.00 eq) and the suspension was heated at reflux (70 °C) for 2 h. The solvent was removed in vacuo and 5 mL of water were added to the residue. The solution was acidified with 1M HCl and stored at 0 °C until crystallization was observed. The solid was isolated by filtration. The product was purified by column chromatography. The product (368 mg, 2.02 mmol, 84.9%) was obtained as a white solid.

R_f = 0.11 (EtOAc in hexanes = 25%).

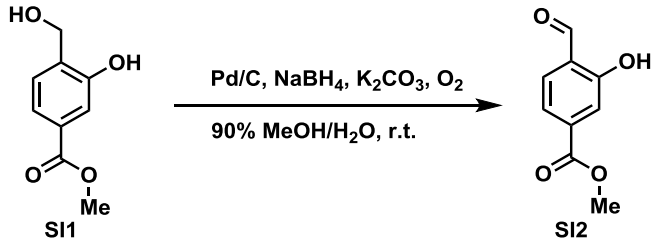
NMR Spectroscopy:

^{1}H NMR (600 MHz, DMSO-d_6) δ 9.83 (s, 1H), 7.42 (dt, J = 3.3, 1.9 Hz, 2H), 7.36 (q, J = 1.6 Hz, 1H), 5.16 (s, 1H), 4.51 (s, 2H), 3.81 (dd, J = 2.2, 1.1 Hz, 3H).

^{13}C NMR (600 MHz, DMSO-d_6) δ 9.83 (s, 1H), 7.42 (dt, J = 3.3, 1.9 Hz, 2H), 7.36 (q, J = 1.6 Hz, 1H), 5.16 (s, 1H), 4.51 (s, 2H), 3.81 (dd, J = 2.2, 1.1 Hz, 3H).

HRMS-FIA(m/z) calc'd for $C_9H_{10}O_4$ $[M+Na]^+$, 205.0471; found, 205.0471.

Methyl-4-formyl-3-hydroxybenzoate (SI2)



To a solution of **SI1** (250 mg, 1.37mmol, 1.00 eq) in 3 mL 10% aqueous methanol was added Pd/C (73 mg, 10% loading, 0.034 mmol, 2.5 mol%), potassium carbonate (567 mg, 4.11 mmol, 3.00 eq) and sodium borohydride (5.2 mg, 0.14 mmol, 0.10 eq) and the mixture was stirred under an atmosphere of oxygen over night. Then, the mixture was diluted with dichloromethane and filtered. The solution was concentrated *in vacuo*, partitioned between ethyl acetate and water, the aqueous layer extracted two more times with ethyl acetate and the combined organic phases were dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography. Aldehyde **SI2** (92 mg, 0.51 mmol, 37%) was obtained as a white solid

R_f = 0.50 (EtOAc in hexanes = 25%).

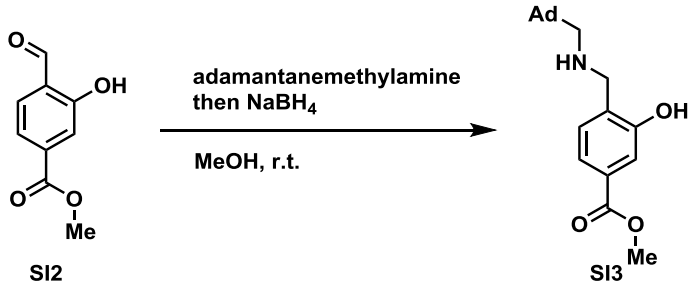
NMR Spectroscopy:

^{1}H NMR(600 MHz, Chloroform-d) δ 10.94 (s, 1H), 9.98 (s, 1H), 7.69 – 7.63 (m, 3H), 3.94 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 196.44, 165.67, 161.24, 137.30, 133.62, 122.86, 120.40, 119.12, 52.69.

HRMS-FIA(m/z) calc'd for $C_9H_8O_4$ $[M+H]^+$, 181.0495; found, 181.0494.

Secondary adamantylmethylamine SI3



A solution of aldehyde **SI2** (100 mg, 556 µmol, 1.00 eq) and adamantanemethylamine (96.4 mg, 0.583 mmol, 1.05 eq) in 2 mL methanol was stirred for 30 min at room temperature. Then, 378 mg (10.0 mmol, 18.0 eq) sodium borohydride was added portionwise and the reaction was stirred until no starting material remained, approximately 3h. The mixture was concentrated *in vacuo*, partitioned between ethyl acetate and water, the aqueous layer extracted two more times with ethyl acetate and the combined organic phases were dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography. Secondary amine **SI3** (136 mg, 0.413 mmol, 74.3%) was obtained as a clear oil that solidified upon standing.

R_f = 0.46 (EtOAc in hexanes = 25%).

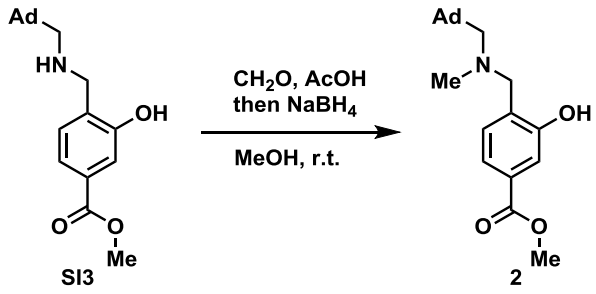
NMR Spectroscopy:

^{1}H NMR (600 MHz, Chloroform-d) δ 7.52 – 7.37 (m, 1H), 7.01 (d, J = 7.8 Hz, 0H), 3.98 (s, 1H), 3.86 (s, 1H), 2.30 (s, 1H), 1.99 – 1.93 (m, 2H), 1.70 (d, J = 12.6 Hz, 1H), 1.62 (d, J = 12.3 Hz, 1H), 1.56 – 1.44 (m, 3H).

^{13}C NMR (600 MHz, DMSO-d_6) δ 9.83 (s, 1H), 7.42 (dt, J = 3.3, 1.9 Hz, 2H), 7.36 (q, J = 1.6 Hz, 1H), 5.16 (s, 1H), 4.51 (s, 2H), 3.81 (dd, J = 2.2, 1.1 Hz, 3H).

HRMS-FIA(m/z) calc'd for $C_{20}H_{27}NO_3$ $[M+H]^+$, 330.2064; found, 330.1910.

Labeling Precursor 2



A solution of amine **SI3** (100 mg, 0.303 mmol, 1.00 eq) in 3 mL methanol, 0.5 mL formalin and a drop of acetic acid were stirred for 2h, then sodium borohydride (22.9 mg, 0.606 mmol, 2.00 eq) were added and the mixture stirred for another hour. The mixture was concentrated in vacuo, partitioned between ethyl acetate and water, the aqueous layer extracted two more times with ethyl acetate and the combined organic phases were dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography. The labeling precursor **2** (67.7 mg, 0.197 mmol, 65.0%) was obtained as a clear oil that solidified upon standing.

R_f = 0.64 (EtOAc in hexanes = 25%).

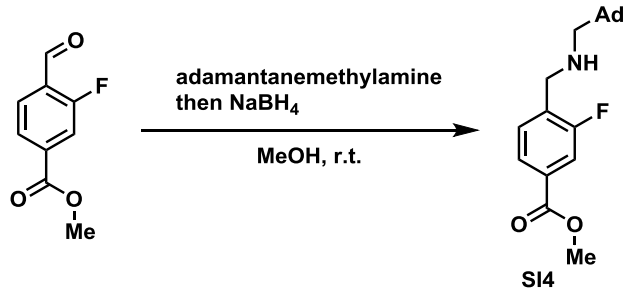
NMR Spectroscopy:

^{1}H NMR (600 MHz, Chloroform-d) δ 7.46 (s, 1H), 7.43 (dd, J = 7.8, 1.7 Hz, 2H), 6.99 (d, J = 7.8 Hz, 2H), 3.87 (s, 7H), 3.76 (s, 4H), 2.26 (s, 7H), 2.23 (s, 4H), 1.76 – 1.68 (m, 6H), 1.69 – 1.60 (m, 7H), 1.56 (d, J = 3.0 Hz, 12H).

^{13}C NMR (600 MHz, DMSO-d_6) δ 9.83 (s, 1H), 7.42 (dt, J = 3.3, 1.9 Hz, 2H), 7.36 (q, J = 1.6 Hz, 1H), 5.16 (s, 1H), 4.51 (s, 2H), 3.81 (dd, J = 2.2, 1.1 Hz, 3H).

HRMS-FIA(m/z) calc'd for $C_{21}H_{29}NO_3$ $[M+H]^+$, 344.2220; found, 344.2230.

Secondary Adamantylmethylamine SI4



A solution of methyl 3-fluoro-4-formylbenzoate (250 mg, 1.37 mmol, 1.00 eq) and adamantanemethylamine (238 mg, 1.44 mmol, 1.05 eq) in 2 mL methanol was stirred for 30 min at room temperature. Then, sodium borohydride (104 mg, 2.74 mmol, 2.00 eq) was added and the reaction was stirred until no starting material remained, approximately 3h. The mixture was concentrated *in vacuo*, partitioned between ethyl acetate and water, the aqueous layer extracted two more times with ethyl acetate and the combined organic phases were dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography. The secondary amine **SI4** (372 mg, 1.12 mmol, 81.8%) was obtained as a clear oil that solidified upon standing.

R*f* = 0.49 (EtOAc in hexanes = 25%).

NMR Spectroscopy:

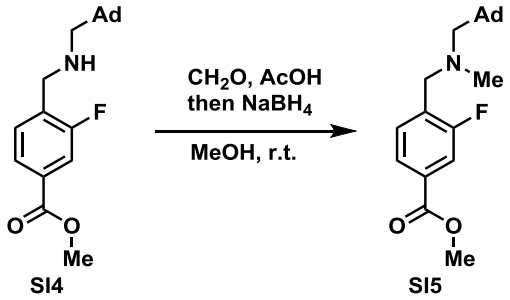
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.79 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.66 (dd, *J* = 10.5, 1.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 2H), 2.22 (s, 2H), 1.94 (d, *J* = 3.1 Hz, 2H), 1.80 – 1.65 (m, 3H), 1.65 – 1.57 (m, 3H), 1.51 (d, *J* = 3.0 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.49, 160.85 (d, *J*= 247.4 Hz), 132.34, 131.35, 129.58 (d, *J* = 13.3 Hz), 122.45, 114.22 (d, *J* = 24.8 Hz), 70.83, 56.96, 45.36, 40.88, 37.10, 34.97, 28.42.

^{19}F NMR (471 MHz, Chloroform-d) δ -118.66.

HRMS-FIA(m/z) calc'd for $C_{20}H_{26}FNO_2$ $[M+H]^+$, 332.2020; found, 332.2068.

Tertiary Adamantanemethylamine SI5



A solution of of amine **SI4** (350 mg, 1.06 mmol, 1.00 eq) in 3 mL methanol, 0.5 mL formalin and a drop of acetic acid were stirred for 2h, then sodium borohydride (80.2 mg, 2.12 mmol, 2.00 eq) were added and the mixture stirred for another hour. The mixture was concentrated in vacuo, partitioned between ethyl acetate and water, the aqueous layer extracted two more times with ethyl acetate and the combined organic phases were dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography. The tertiary amine **SI5** (227 mg, 0.657 mmol, 62.0%) was obtained as a clear oil that solidified upon standing.

$\mathbf{R_f}$ = 0.75 (EtOAc in hexanes = 25%).

NMR Spectroscopy:

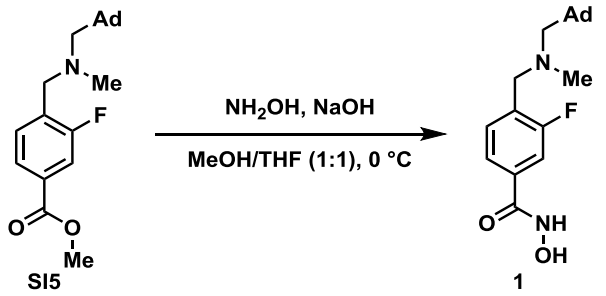
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.73 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.64 – 7.44 (m, 2H), 3.83 (s, 3H), 3.56 (s, 2H), 2.16 (s, 3H), 2.06 (s, 2H), 1.90 – 1.80 (m, 3H), 1.63 (dd, *J* = 12.2, 3.3 Hz, 3H), 1.59 – 1.52 (m, 4H), 1.46 – 1.35 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-d) δ 165.75, 160.66 (d, *J* = 245.8 Hz), 132.49 (d, *J* = 14.3 Hz), 130.62, 130.26, 124.94, 116.06 (d, *J* = 24.0 Hz), 71.00, 57.15, 51.98, 45.52, 40.91, 37.12, 35.06, 28.42.

^{19}F NMR (471 MHz, Chloroform-d) δ -117.42.

HRMS-FIA(m/z) calc'd for $C_{21}H_{28}FNO_2$ $[M+H]^+$, 346.2177; found, 346.2158.

Bavarostat (1)



To a solution of ester **SI5** (200 mg, 0.580 mmol, 1.00 eq) in 2mL 1:1 THF/MeOH at 0 °C was added 0.50 mL hydroxylamine (50% aq, 0.25g, 3.6 mmol, 6.2 eq) and aqueous NaOH (5.0 M, 0.10 mL, 0.50 mmol, 0.86 eq). The reaction mixture was stirred for 2h, then partitioned between DCM and water. The aqueous layer was extracted another three times with DCM, the combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The product was purified by preparative HPLC with a gradient of water and acetonitrile buffered with formic acid. Upon drying *in vacuo* Bavarostat (123 mg, 0.355 mmol, 61.2 %) was obtained as a light orange, foamy solid.

NMR Spectroscopy:

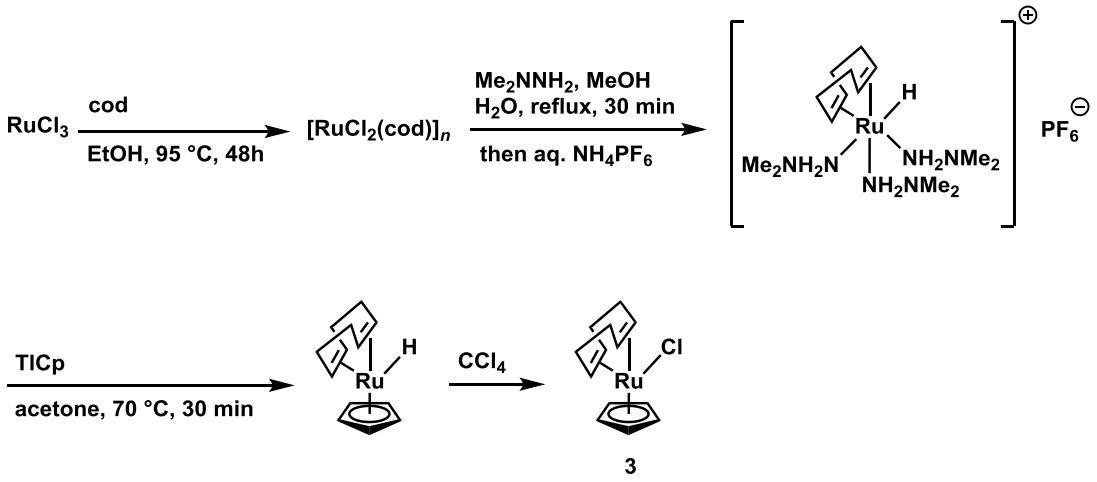
^{1}H NMR (600 MHz, DMSO-d_6) δ 11.21 (s, 1H), 9.11 (s, 1H), 7.59 – 7.50 (m, 2H), 7.47 (dd, *J* = 10.9, 1.6 Hz, 1H), 3.56 (s, 2H), 2.16 (s, 3H), 2.08 (s, 2H), 1.88 (s, 3H), 1.63 (d, *J* = 12.3 Hz, 3H), 1.55 (d, *J* = 12.2 Hz, 3H), 1.43 (s, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.49, 160.85 (d, *J* = 247.4 Hz), 132.34, 131.35, 129.63, 122.45, 114.22 (d, *J* = 24.8 Hz), 70.83, 56.96, 45.36, 40.88, 37.10, 34.97, 28.42.

^{19}F NMR (471 MHz, Chloroform-d) δ -116.71.

HRMS-FIA(m/z) calc'd for $C_{20}H_{27}FN_2O_2$ $[M+H]^+$, 347.2129; found: 347.2560.

[CpRu(cod)Cl] (3)



$[RuCl_2(cod)]_n$

A two-neck round bottom flask was flame-dried and purged with N_2. Ruthenium trichloride hydrate ($RuCl_3 \cdot \times H_2O$, 7.4 g, 0.03 mol, 1 eq) was added to the flask. The flask was evacuated and kept under vacuum for 1 h and then was purged with N_2. To the flask were added 1,5-cyclooctadiene (20 mL, 18 g, 0.16 mol, 5 equiv.) and ethanol (0.14 L, c = 0.2 M) to give a dark brown solution. The reaction mixture was stirred and heated at reflux at 95 °C for 48 h and subsequently cooled to 23 °C. The resulting brown precipitate was filtered off through a sintered glass funnel under air, and washed thoroughly with ethanol (50 mL). The brown solid was dried under vacuum for 48 h to afford $[RuCl_2(cod)]_n$ (8.2 g). The material was used in subsequent steps without further purification.

Note: Commercial $RuCl \cdot \times H_2O$ has variable water content, the total ruthenium content is 40–43%.

$[(cod)RuH(NH_2NMe_2)_3]PF_6$

To an oven dried 250 mL two-neck round bottom flask equipped with a magnetic stir bar was added $[RuCl_2(cod)]_n$ (5.50 g) under N_2. To the flask were added degassed methanol (55 mL), degassed water (13.8 mL) and freshly distilled degassed *N*,*N*'-dimethyl hydrazine (55 mL, 43 g, 0.72 mol). The mixture was heated at 95 °C and stirred at the same temperature for 45 min. The resulting mixture was subsequently cooled to 23 °C over 60 min with stirring.

Under N_2, to the above reaction mixture was added a degassed solution of NH_4PF_6 (5.5 g, 34 mmol) in H_2O (55 mL). The slurry was kept at –20 °C for 12 h under N_2.

The resulting colorless precipitate was filtered through a sintered glass funnel under air. Then the filtrate was concentrated under reduced pressure to half of the volume and was kept at –20 °C for 60 min. The resulting colorless precipitate was filtered through a sintered glass funnel to afford a second crop of product, which was combined with the previous fraction. The combined colorless precipitate was washed thoroughly with ice-cold water (200 mL) and dried under vacuum for 48 h to afford $[(cod)RuH(NH_2NMe_2)_3]PF_6$ (4.9 g). The material was used in subsequent steps without further purification.

[CpRu(cod)Cl] (3)

Caution: This step involves the use of toxic CpTl reagent. Proper care is essential to safely carry out this reaction, and the appropriate disposal of the thallium-contaminated flask, celite, gloves, needles and other materials is of the utmost importance for the safety of the chemist, staff, and other personnel.

Inside a nitrogen-filled glovebox, a 250 mL two necked round bottom flask equipped with a magnetic stir-bar and a rubber septum was charged with $[(cod)RuH(Me_2NNH_2)_3]PF_6$ (5.00 g) and thallium cyclopentadienide (2.78 g, 10.3 mmol). The flask was sealed with a second rubber septum and was brought outside the glovebox. Degassed acetone (88 mL) was added to the flask under N_2. The mixture was heated at 65 °C and stirred at the same temperature for 30 min. The resulting mixture was subsequently cooled to 23 °C over 20 min. The mixture was transferred with a cannula into a Schlenck flask, sealed, and brought inside a glovebox (Note: a rubber septum alone can not withstand the pressure difference inside the antechamber and presents a significant spill hazard). The mixture was filtered through a pad of celite under vacuum. The resulting filtrate was concentrated *in vacuo* to afford a brown solid. Pentane (30 mL) was added to the brown solid and the mixture was shaken vigorously for 10 min. The resulting mixture was drawn into a syringe and filtered through a 0.2 nm PTFE syringe filter into a separate 50 mL flask containing CCl_4 (1.93 mL). A yellow precipitate was immediately observed. The above sequence of pentane (30 mL) addition to the brown solid was repeated. The supernatant was filtered again and added to the CCl_4 containing flask. The mixture was stirred inside a glove box for 30 min. Then the flask was removed from the glove box, and the mixture was filtered through a sintered glass funnel under air. The resulting solid was washed with pentane (30 mL) and dried under vacuum to afford [CpRu(cod)Cl] (1.21 g, 3.27 mmol, 16 ± 1 % from $RuCl_3$) as a dark yellow solid.

NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 ºC, δ): 5.32–5.29 (m, 2H), 4.95 (s, 5H), 4.41–4.38 (m, 2H), 2.62–2.59 (m, 2H), 2.10–2.03 (m, 4H), 2.00–1.93 (m, 2H).[3]

^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 128.8, 87.1, 85.9, 78.7, 32.6, 28.1, 28.0.

HRMS (m/z) calc'd for $C_{13}H_{17}ClRu$ $[M\text{-}Cl]^+$, 275.0374; found, 275.0367.

[3] The ^{1}H NMR spectroscopic data correspond to the data reported in the literature. See: *Chem. Eur. J.* **2014**, *20*, 11101–11110.

RADIOCHEMISTRY

Semipreparative HPLC for [^{18}F]Bavarostat purification

Agilent Eclipse C-18, 9.4 x 250 mm, 5 µm;

flow ramp 0.5 mL·min^{-1} to 5 mL·min^{-1} from 0-4 min, then 5 mL·min^{-1}, 5 % ACN in 0.01 N NaOH from 0 - 4 min, then ramp to 70 % ACN in 0.01 NaOH at 45 min.

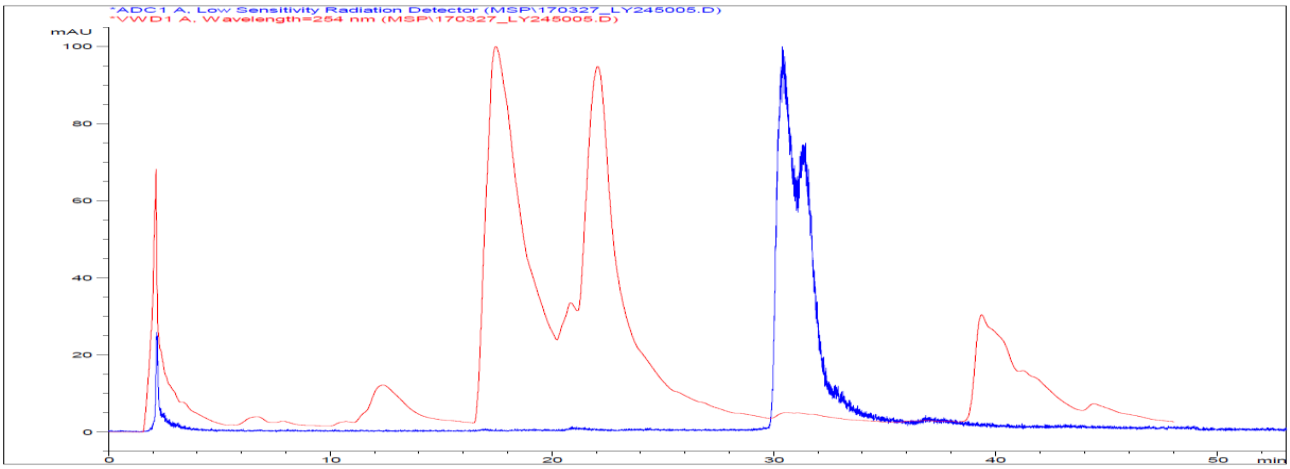


Fig SI1. Semipreparative HPLC of injected dose UV(254nm) shown in red, low-sensitivity γ-trace shown in blue.

Analytical HPLC of injected [^{18}F]Bavarostat dose

Agilent Eclipse C-18, 4.6 x 10 mm, 5 µm, flow 2 mL·min^{-1}, gradient from 5 % ACN/H_2O, 0.1 % TFA at 0 min to 95 % ACN/H_2O, 0.1% TFA at 10 min.

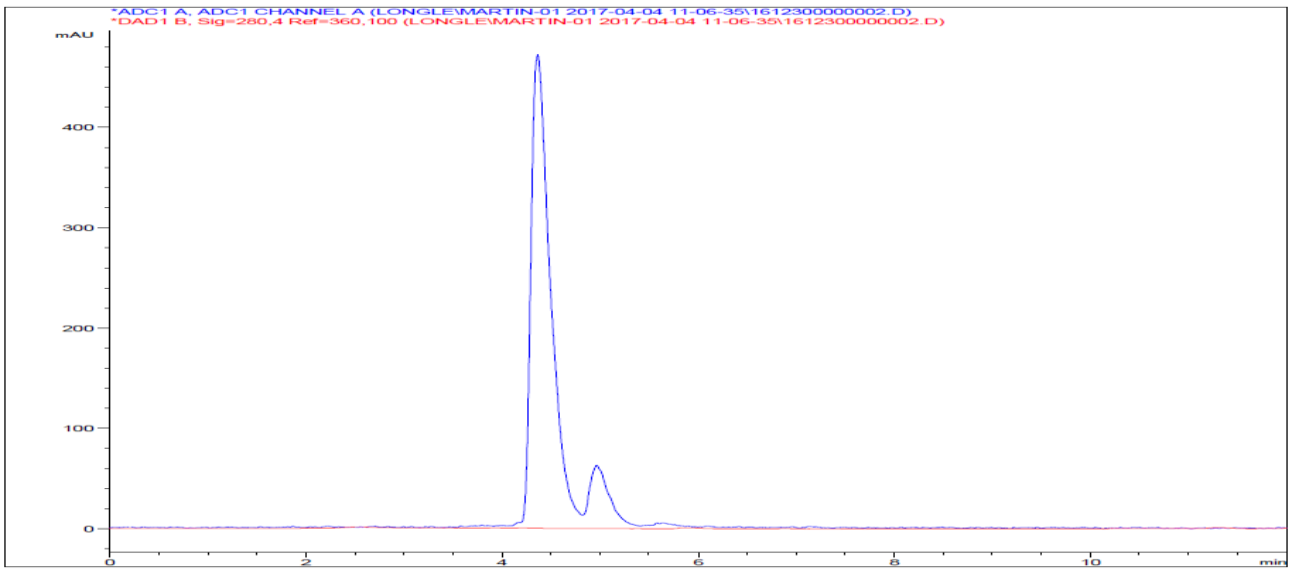
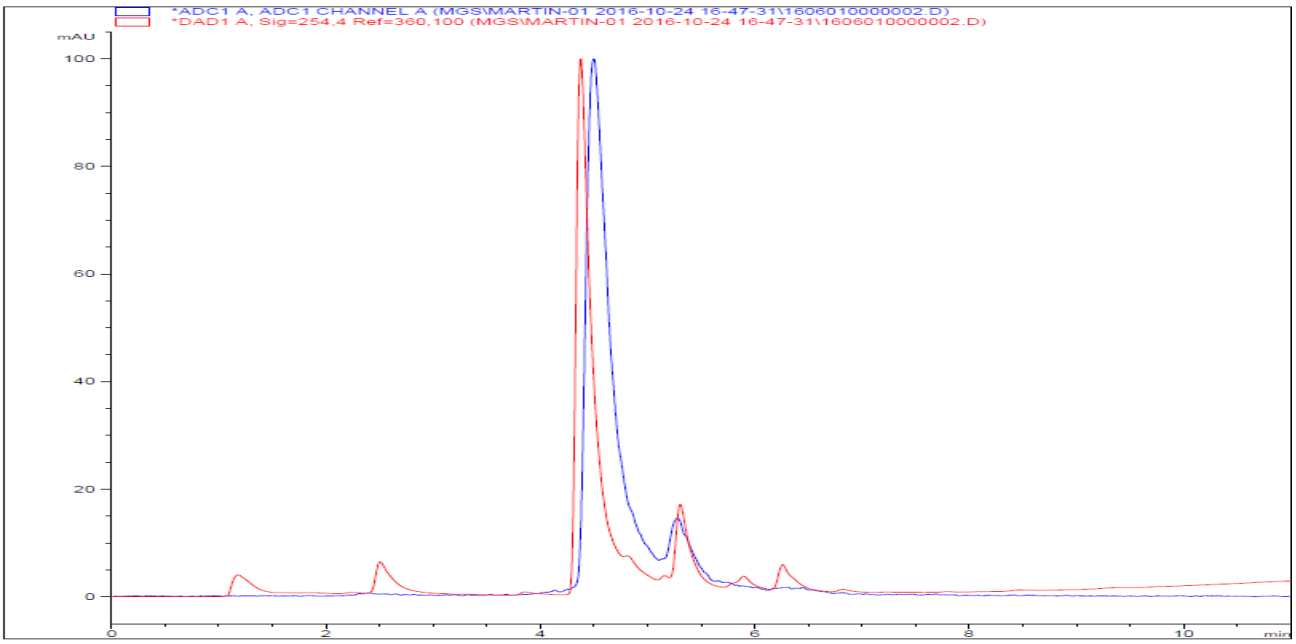


Fig SI2. Analytical HPLC of injected dose UV(280nm) shown in red, γ-trace shown in blue

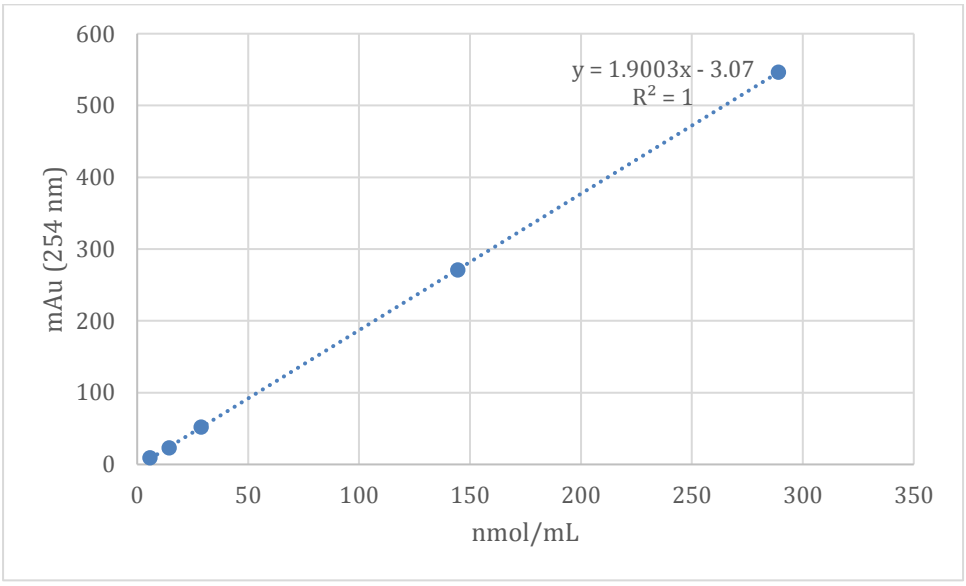
Analytical HPLC of [^{18}F]Bavarostat coinjected with standard

Agilent Eclipse C-18, 4.6 x 10 mm, 5 µm, flow 2 mL·min^{-1}, gradient from 5 % ACN/H_2O, 0.1 % TFA at 0 min to 95 % ACN/H_2O, 0.1% TFA at 10 min.



Calibration curve for determination of specific activity of [^{18}F]Bavarostat

Each point measured in triplicate; Agilent Eclipse C-18, 4.6 x 10 mm, 5 µm, flow 2 mL·min^{-1}, gradient from 5 % ACN/H_2O, 0.1 % TFA at 0 min to 95 % ACN/H_2O, 0.1% TFA at 10 min.



DOCKING STUDIES

Additional interactions contributing to HDAC6 selectivity

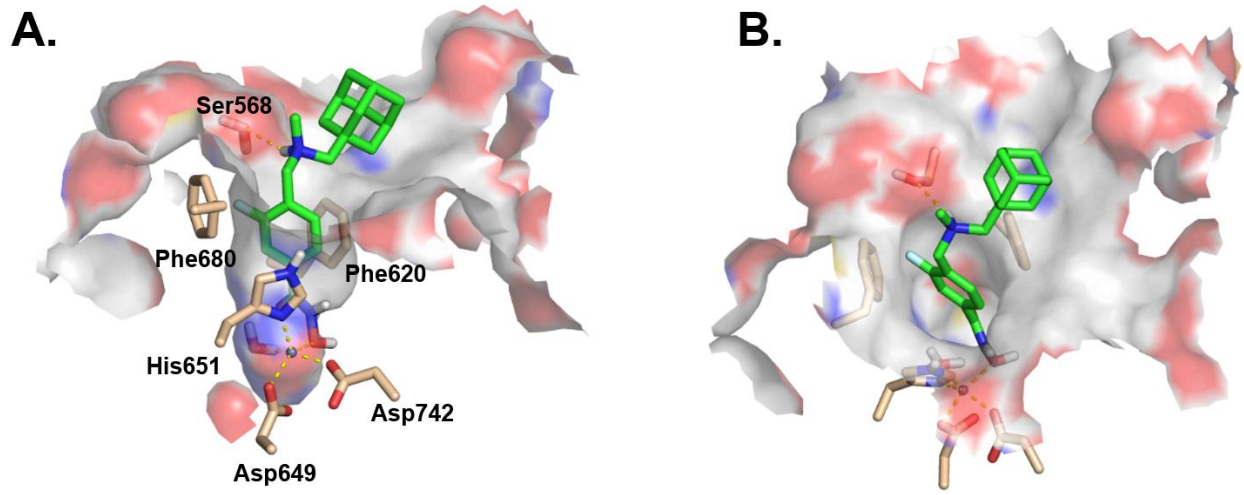


Fig SI3. Bavarostat docked into the CD2 *hHDAC6 complex* described in the methods section. A. The complex hydrogen bond network between the catalytic zinc (purple sphere), the protein and the ligand are shown as yellow dashed lines. B. Bavarostat's fluorine substituent on the linker phenyl ring is modelled to vector in a hollow divot/cleft in the hHDAC6 10Å channel leading to the protein surface.

BIOCHEMICAL EXPERIMENTS

Western blotting

Protein separation was accomplished on a Criterion Stain-Free 4-20% gel (Biorad 567-8095) at 200 V for 50 min. Protein transfer onto a low fluorescence PVDF membrane (Biorad 162-0264) was performed at 0.14 A for 60 min. Gel and membrane imaging for quality control was conducted with a Chemidoc XRS system (Biorad 170-8264). Membranes after transfer were treated with Tris buffered saline/Tween 20 (TBST, 0.1% Tween 20) with 5% blocker (Biorad 170-6404) overnight at 4 °C. The following steps were then carried out at room temperature. The membrane was washed with TBST, incubated with primary antibody solutions (1% blocker in TBST with appropriate dilution of antibody: acetyl histone H3 lysine 9: EMD Millipore 06-942-S 1:4000, acetyl histone H4 lysing 12: EMD Millipore 07-595 1:4000, acetyl-α-tubulin: EMD Millipore ABT241 1:4000) for 1 h, washed with TBST, incubated with secondary antibody (1% blocker in TBST with appropriate dilution of antibody: anti-rabbit-HRP: Cell Signaling #7074S 1:5000) for 1h, washed with TBST and TBS and developed with ECL prime western blotting reagent (GE RPN2232) and imaged with a Chemidoc XRS system with Image Lab 5.2.1. (Figure SI4)

Images were exported as 600 dpi Tif files and processed in Image J as 8-bit images. Background was substracted and Gaussian smooting with a 50 pixel radius was applied. Images were inverted and the

measurement tool was used to quantify band intensity.

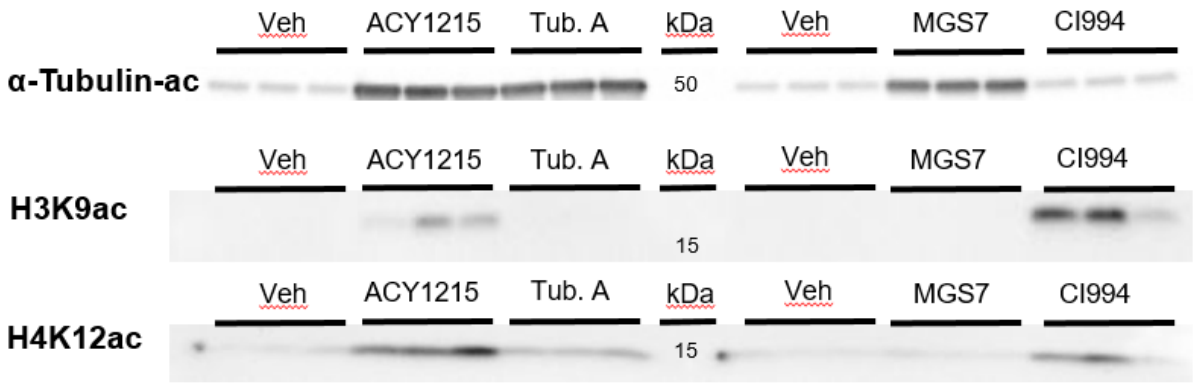


Fig SI4. Western blots to determine HDAC substrate acetylation levels

Statistical Analysis

Statistical Analysis was performed with GraphPad Prism (Prism6, GraphPad Software Inc.). Differences in protein acetylation levels between treatment conditions were evaluated with a one-way ANOVA (a=0.05 with Dunnett's multiple comparisons correction) (Fig. 2). In autoradiographic assays, differences between [^{18}F]Bavarostat baseline and blocking intensity values were evaluated with a two-tailed student's t-test (Fig. 4).

IMAGING

Regional analysis of [^{18}F]Bavarostat binding in baboon brain

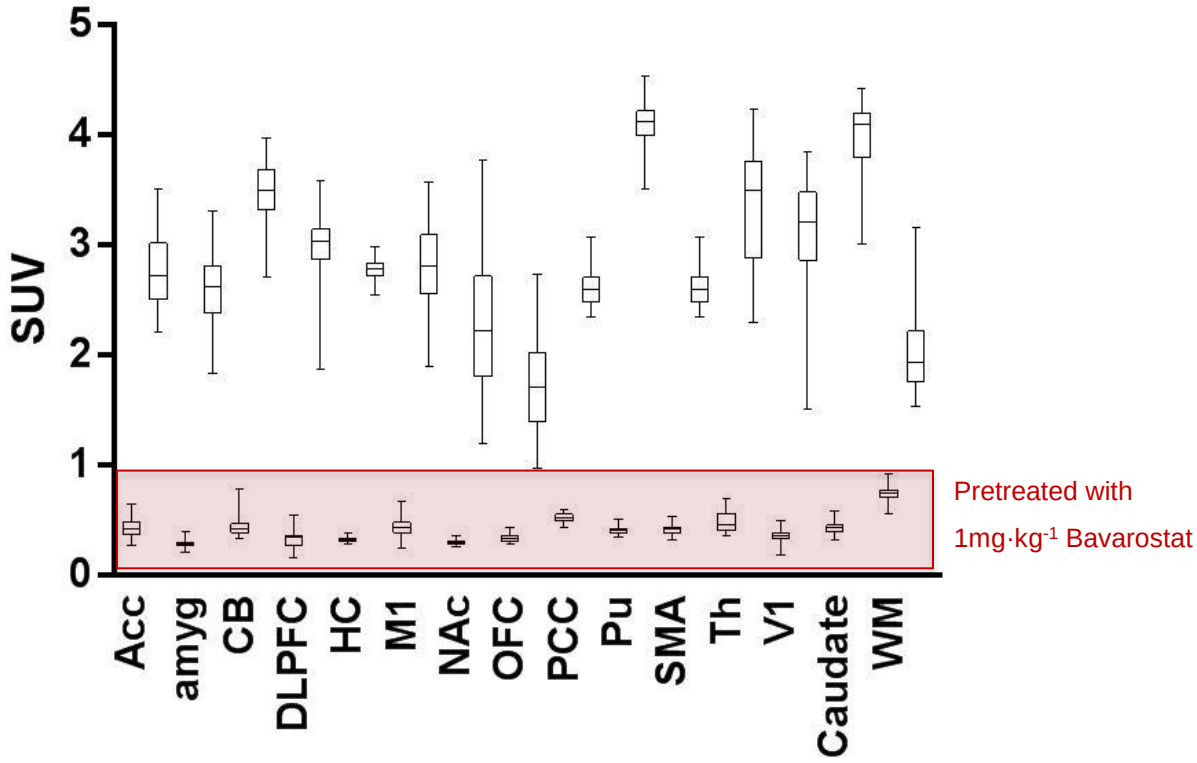


Fig SI5. SUV analysis of voxel SUV distribution within ROIs Analysis of 15 regions within the baboon brain using the black baboon atlas, comparison of baseline and pretreated distribution. Each region of interest (ROI) is shown as a distribution of SUV values (averaged 60-120 min) of each voxel within the ROI. ACC = Anterior cingulate cortex, amgyg = amygdala, CB = cerebellum, DLPFC = dorsolateral prefrontal cortex, HC = hippocampus, M1 = primary motor area, NAc = Nucleus accumbens, OFC = orbitofrontal cortex, PCC = posterior cingulate cortex, Pu = putamen, SMA = supplementary motor area, Th = Thalamus, V1 = primary visual cortex, WM = white matter

Comparison of SUV and kinetic modeling

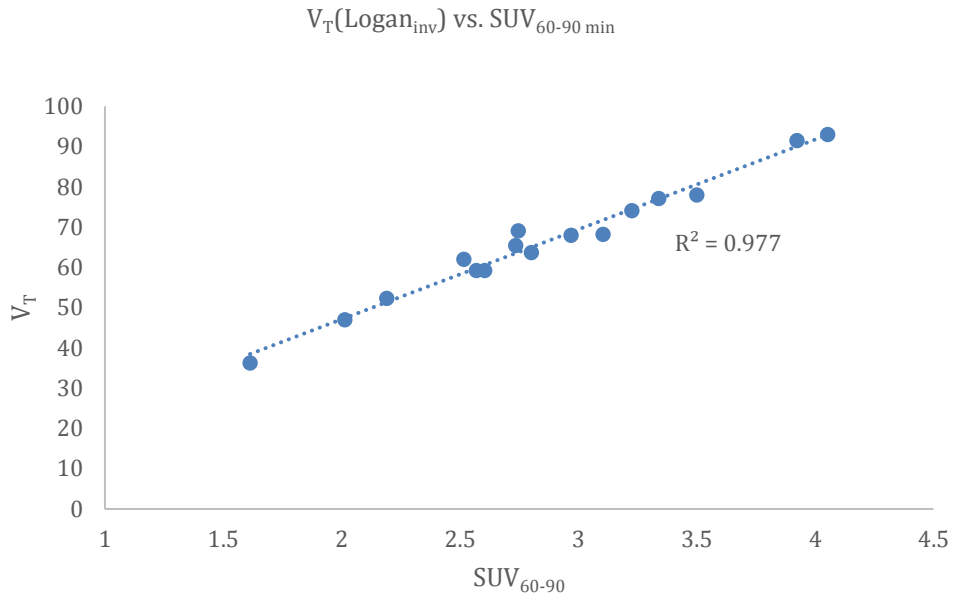
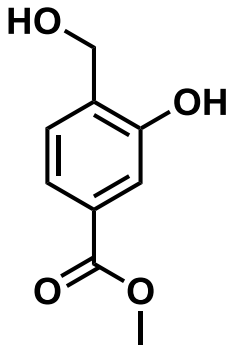


Figure SI6. SUV and V_T comparison V_T was derived from a metabolite corrected arterial plasma input function (Feng interpolation) and calculated via an invasive Logan plot.

SPECTROSCOPIC DATA

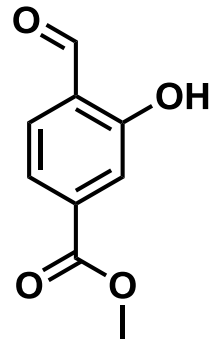
^{1}H-NMR of Methyl-3-hydroxy-4-(hydroxymethyl)benzoate (SI1)

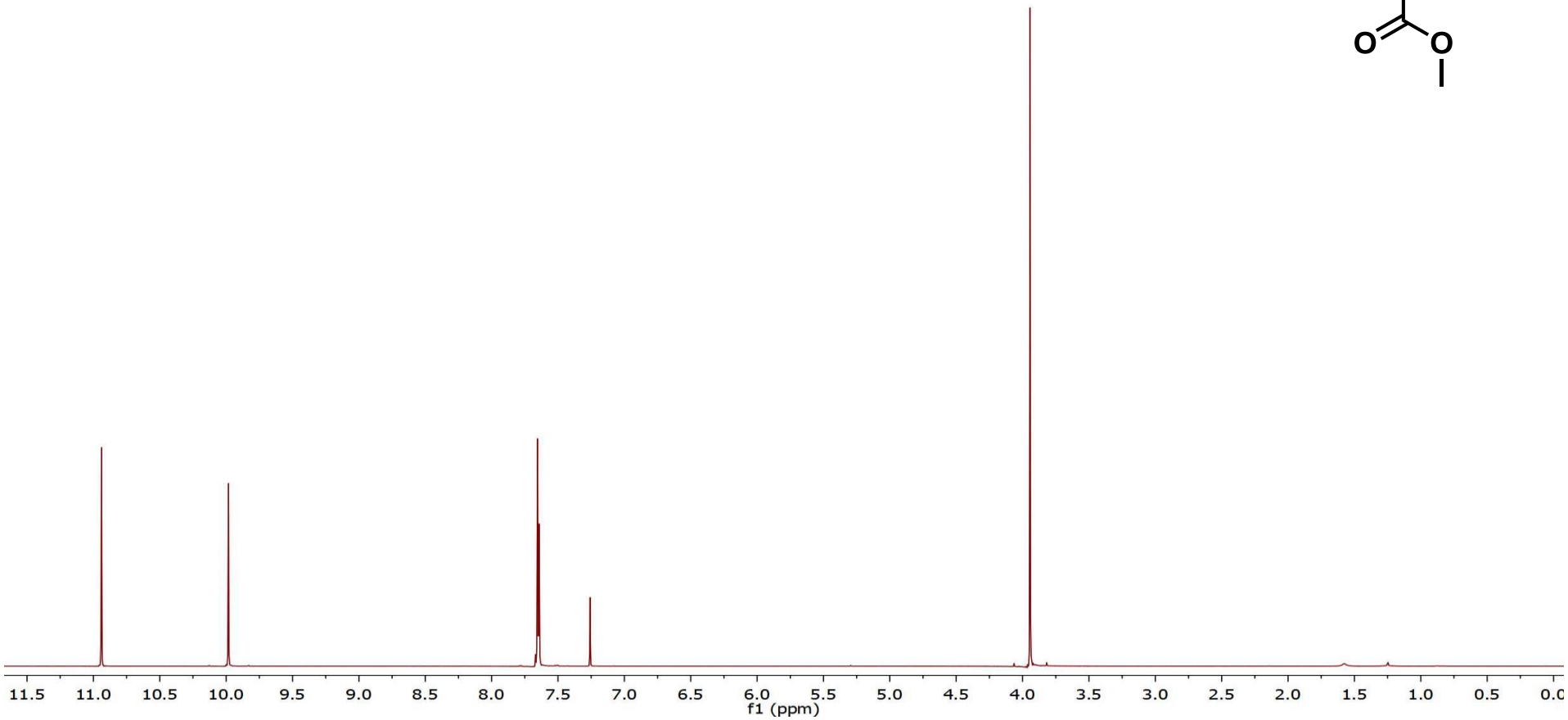
DMSO-d_6, 23 ºC



^{1}H-NMR of Methyl-4-formyl-3-hydroxybenzoate (SI2)

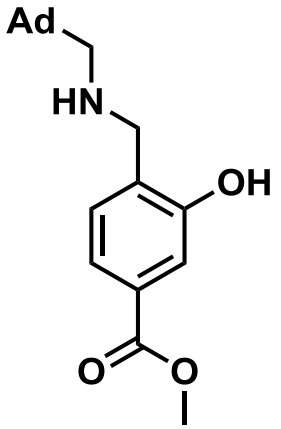
Chloroform-d, 23 ºC

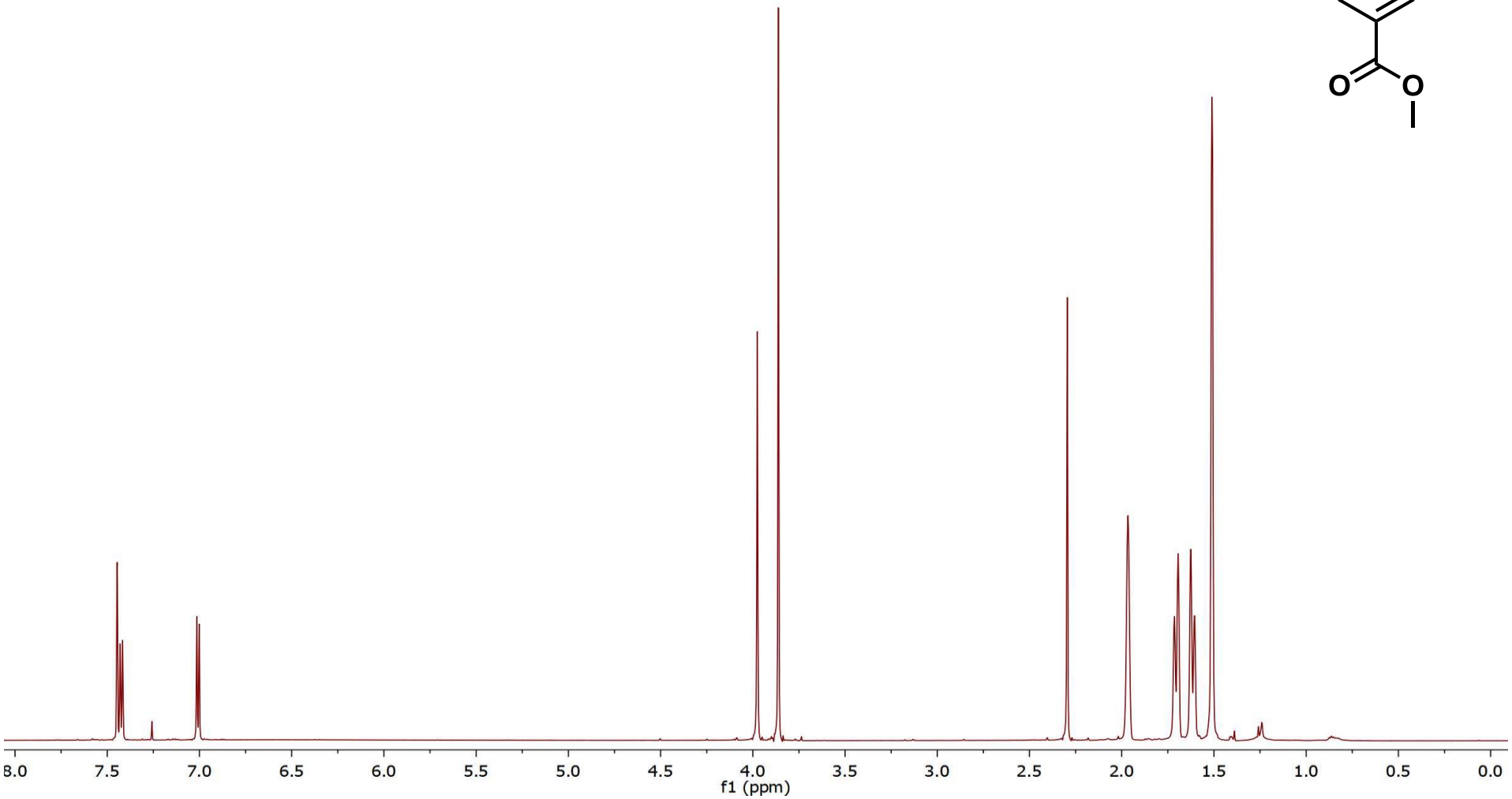




^{1}H-NMR of Secondary adamantanemetylamine SI3

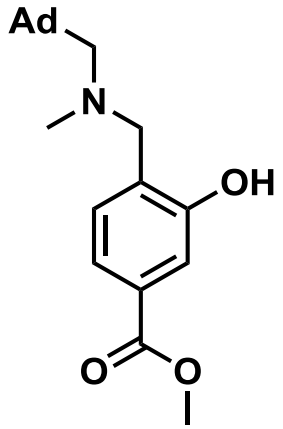
Chloroform-d, 23 ºC

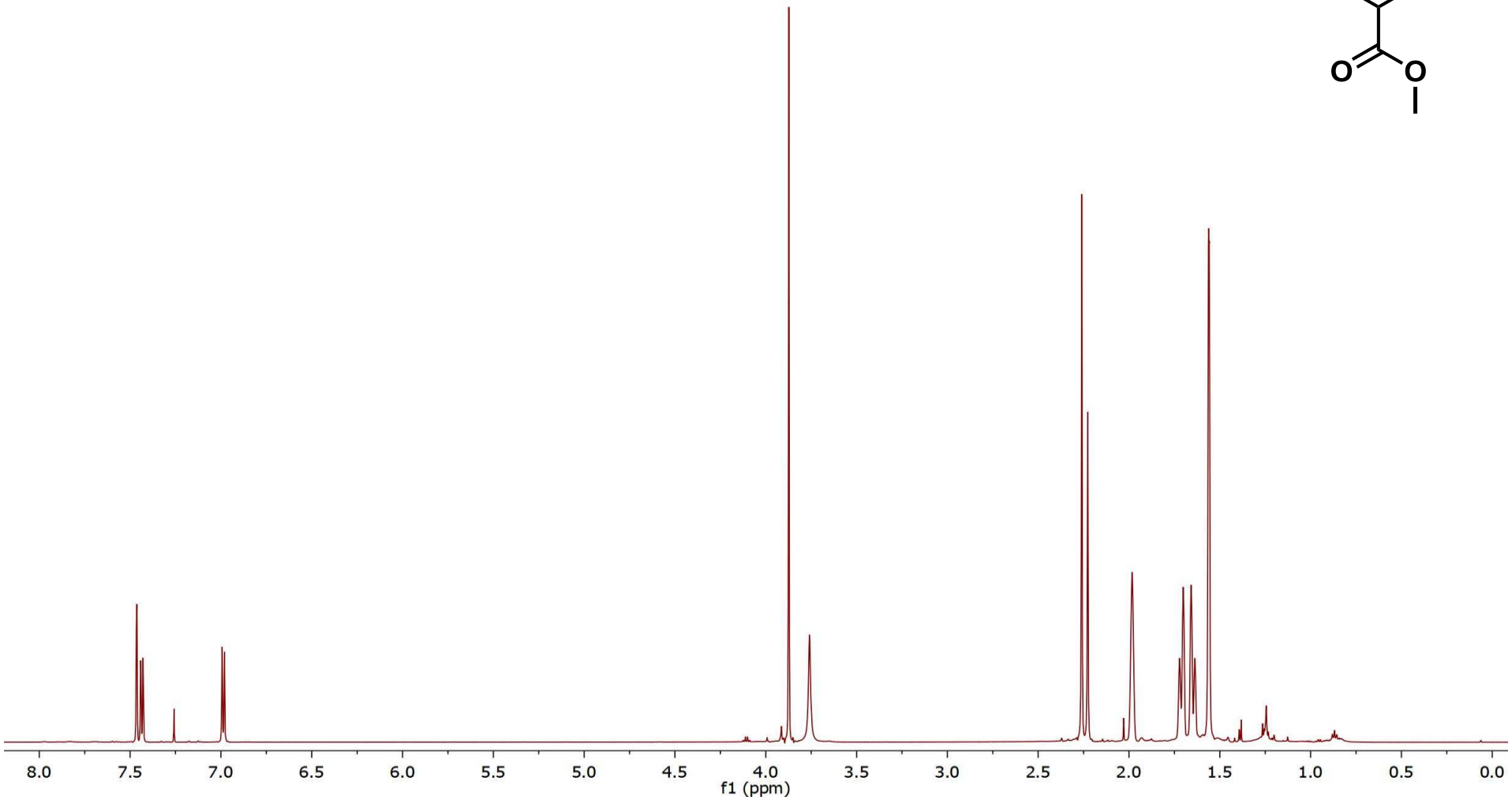




^{1}H-NMR of labeling precursor 2

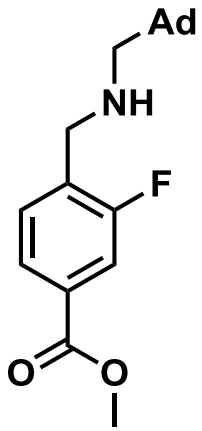
Chloroform-d, 23 ºC

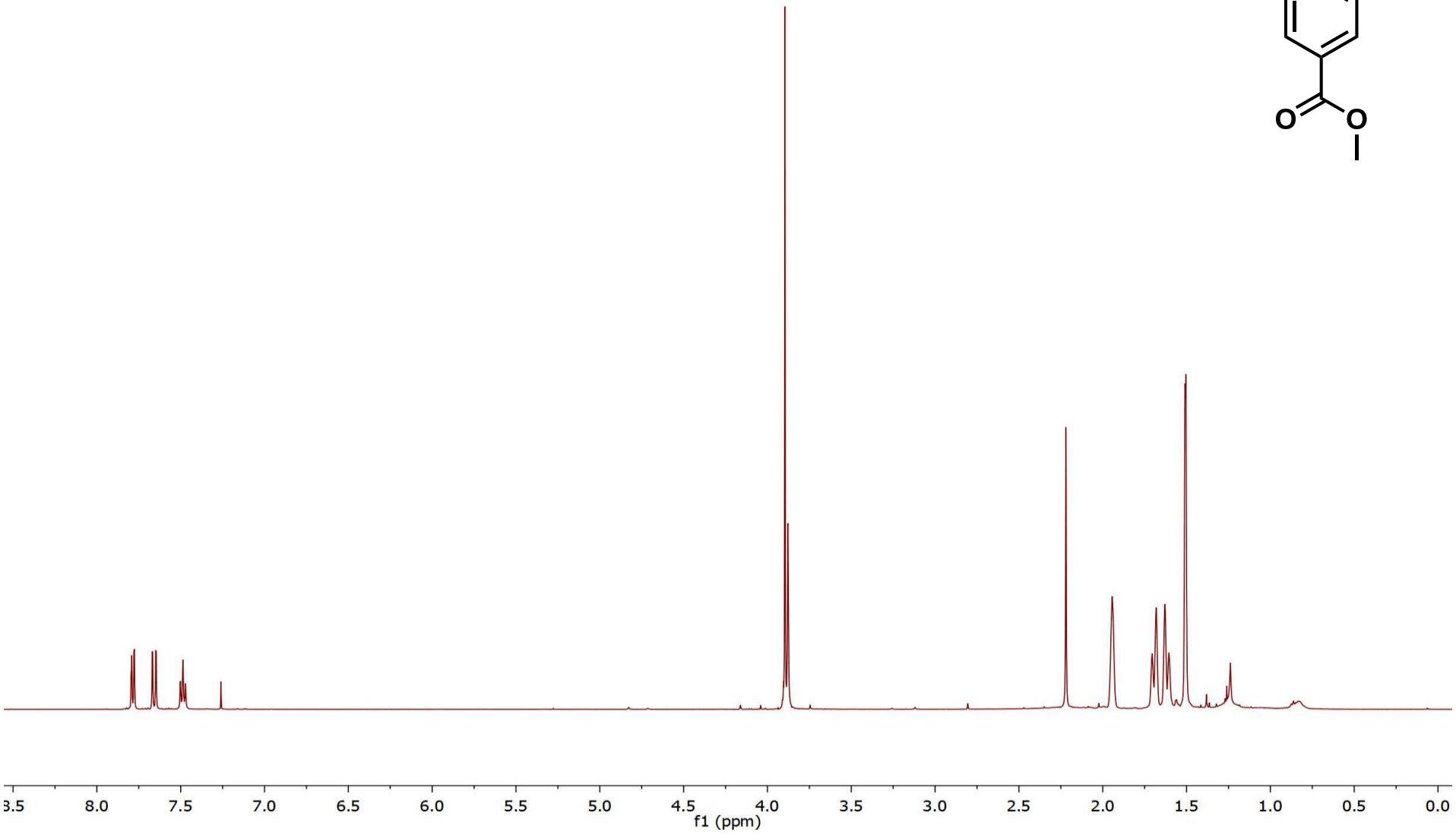




^{1}H-NMR of Secondary adamantanemetylamine SI4

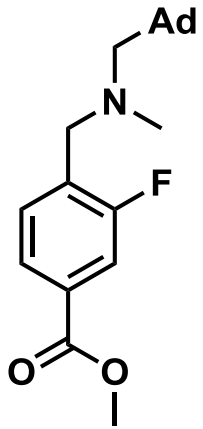
Chloroform-d, 23 ºC

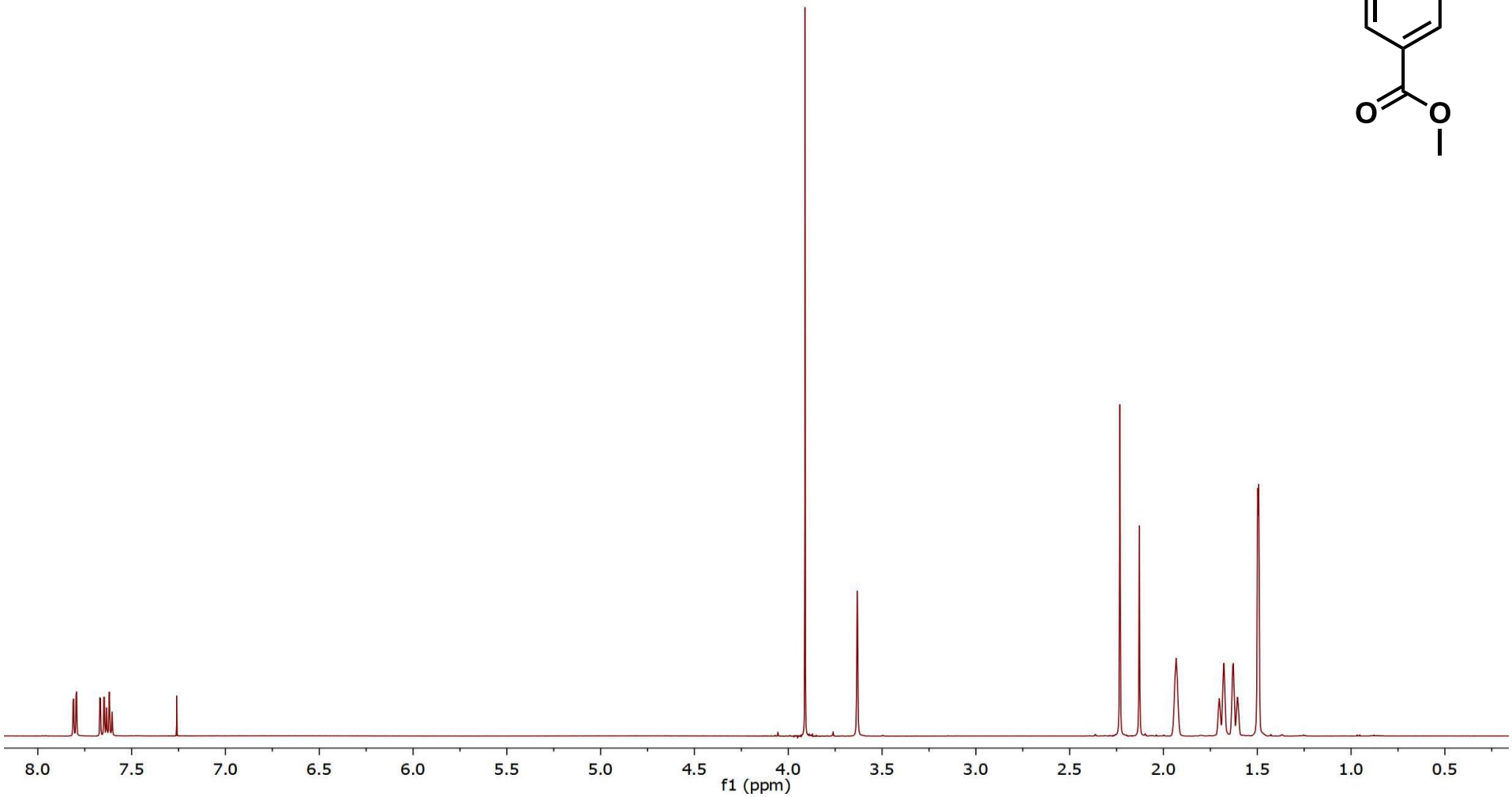




^{1}H-NMR of Tertiary adamantanemetylamine SI5

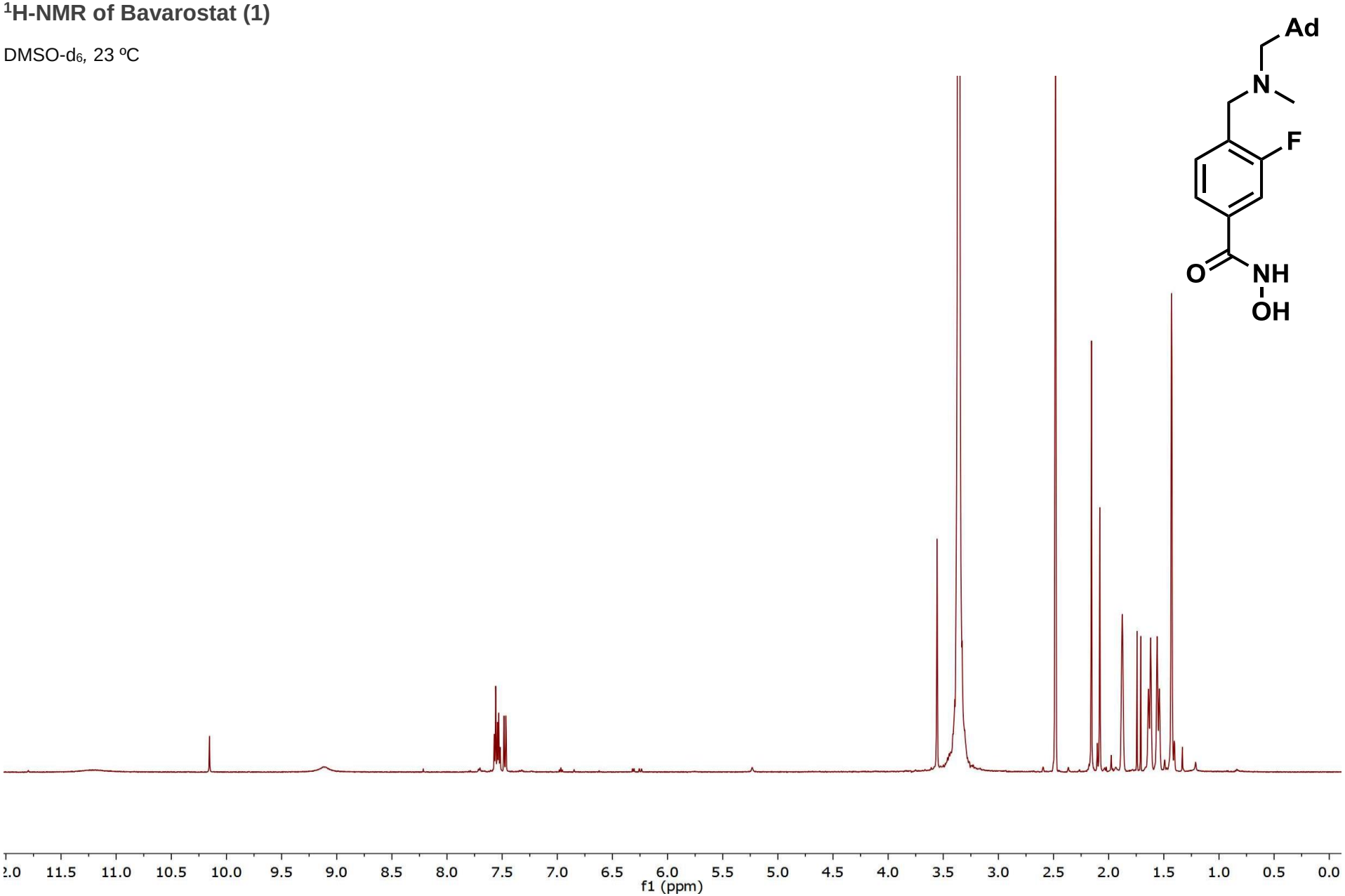
Chloroform-d, 23 ºC





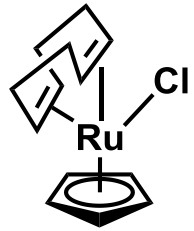
^{1}H-NMR of Bavarostat (1)

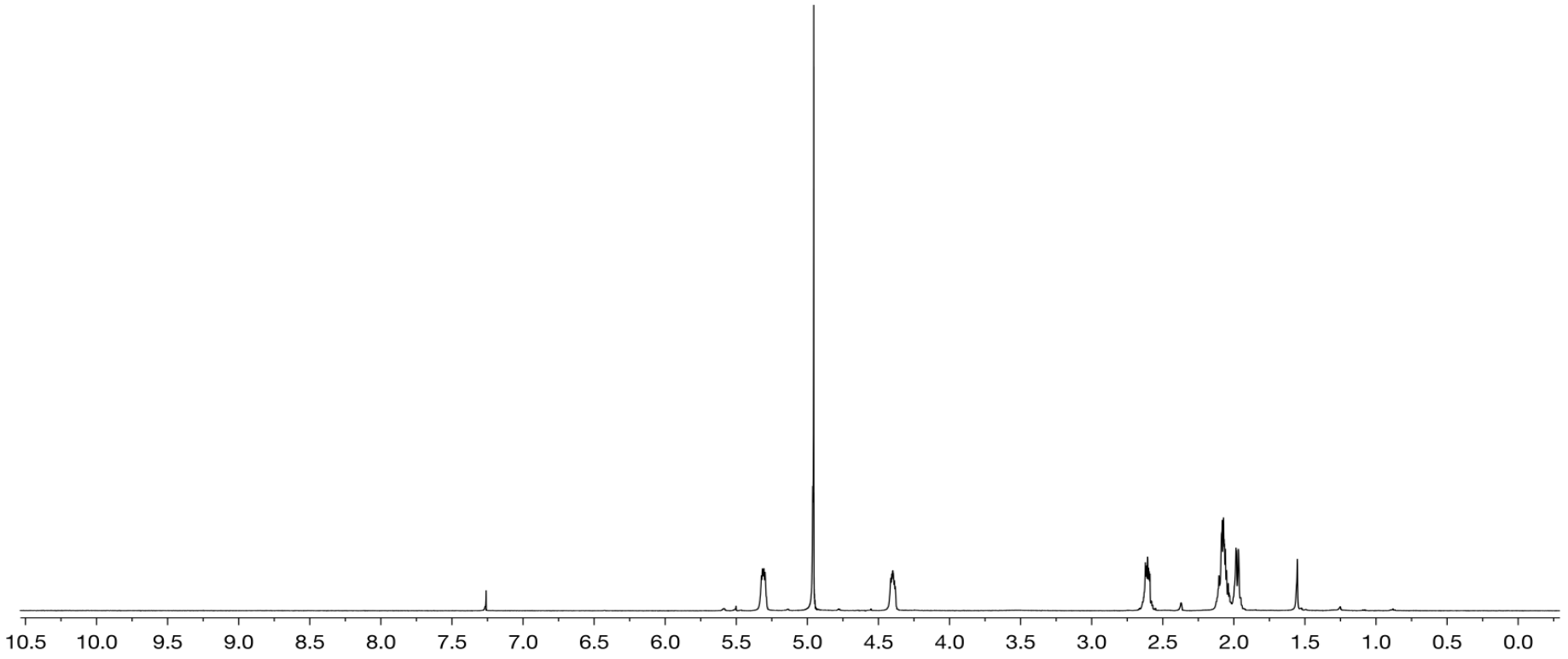
DMSO-d_6, 23 ºC



^{1}H-NMR of [CpRu(COD)Cl] (3)

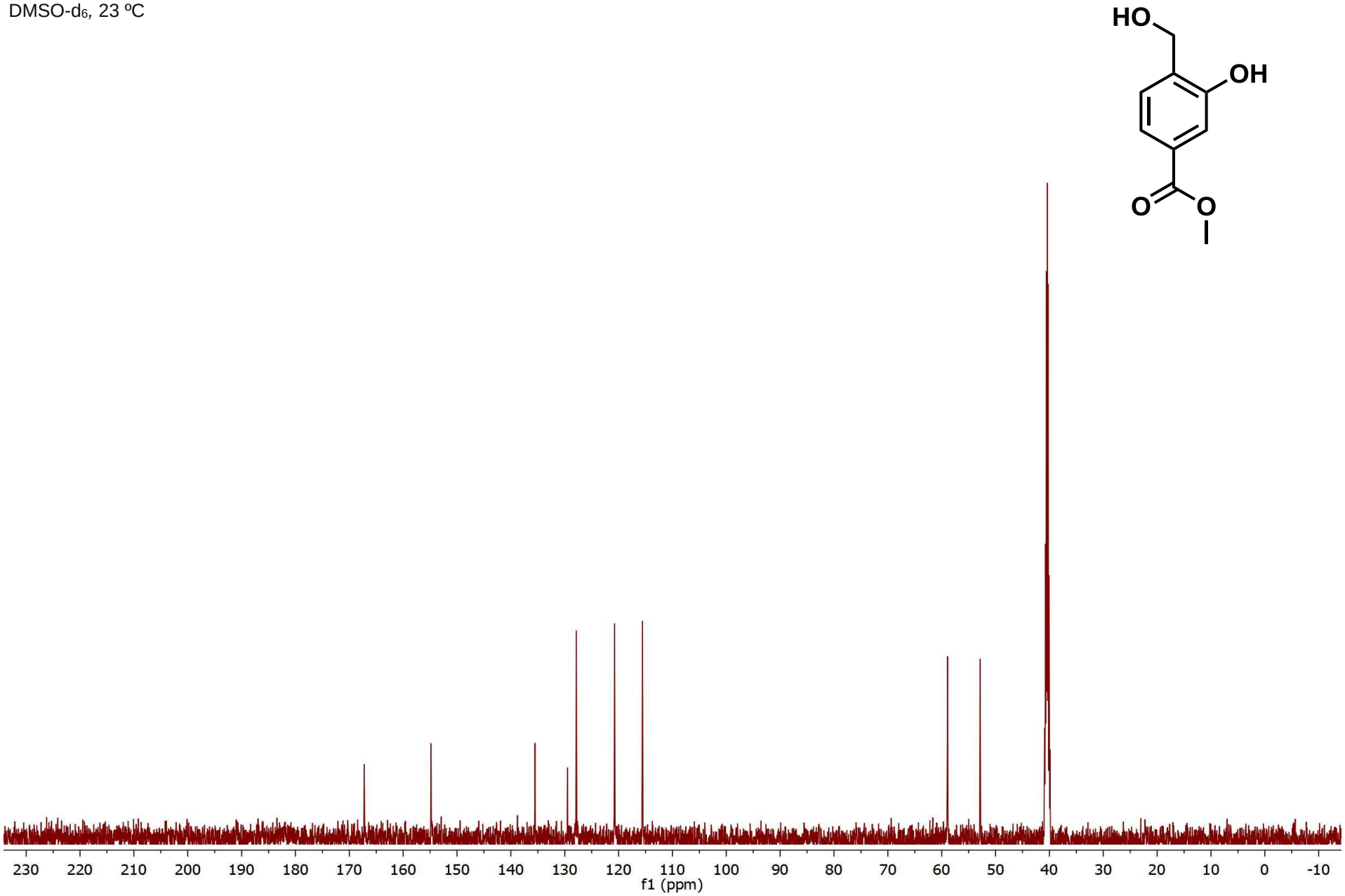
Chloroform-d, 23 ºC





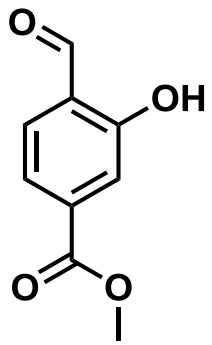
^{13}C NMR of Methyl-3-hydroxy-4-(hydroxymethyl)benzoate (SI1)

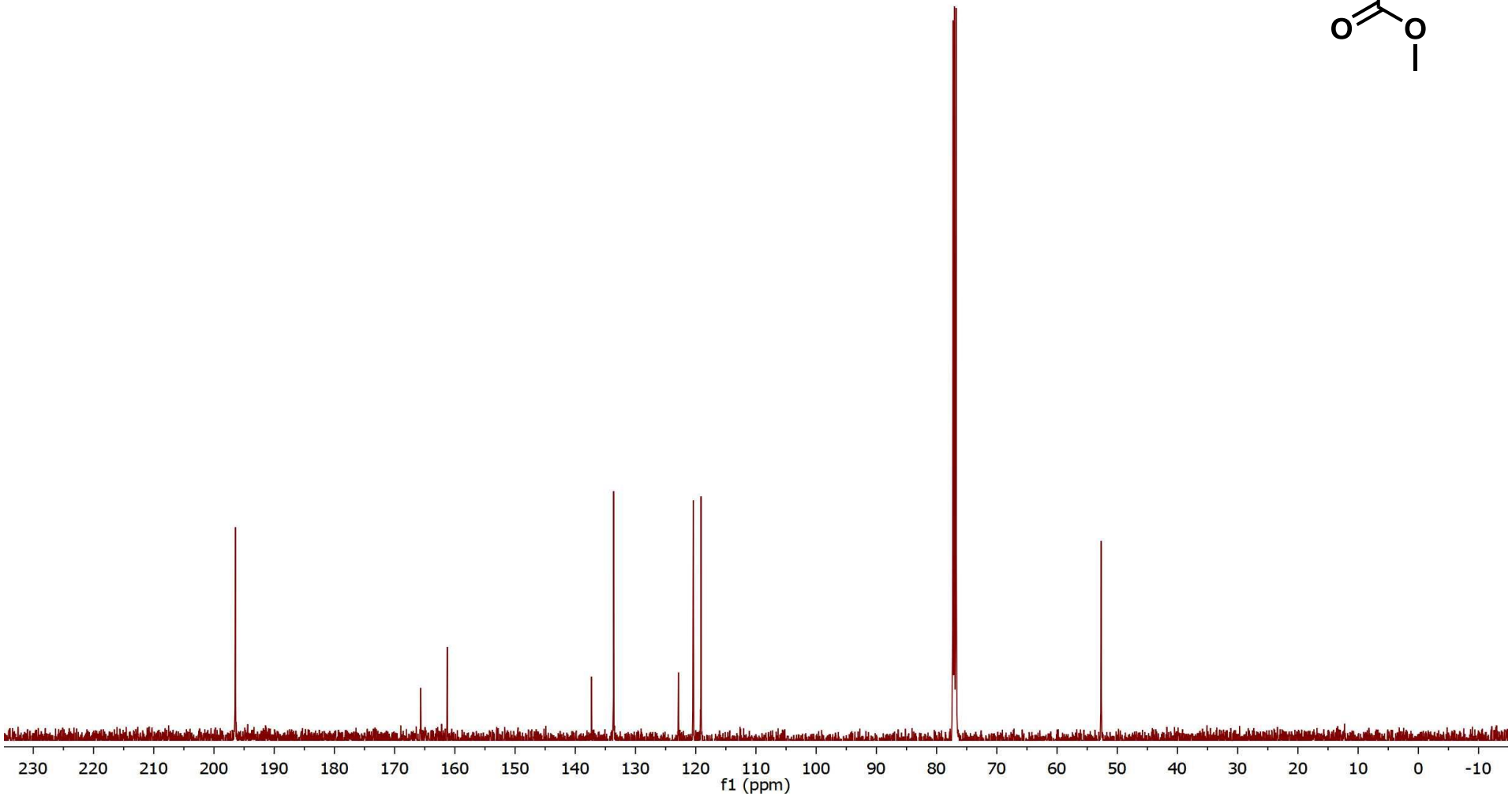
DMSO-d_6, 23 ºC



^{13}C-NMR of Methyl-4-formyl-3-hydroxybenzoate (SI2)

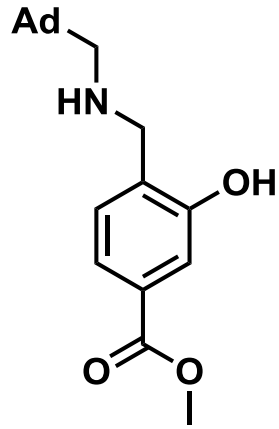
Chloroform-d, 23 ºC

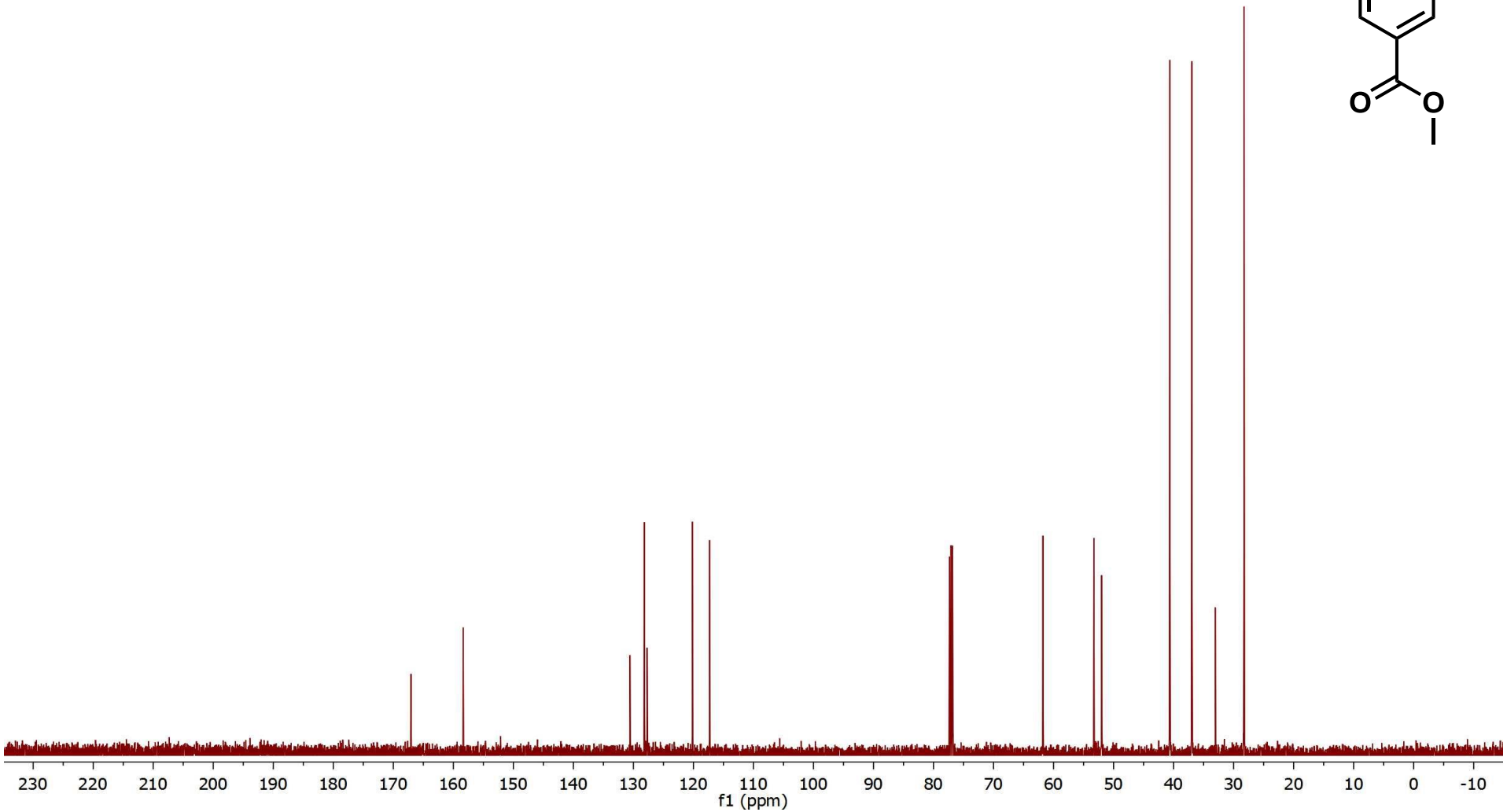




^{13}C-NMR of Secondary adamantanemetylamine SI3

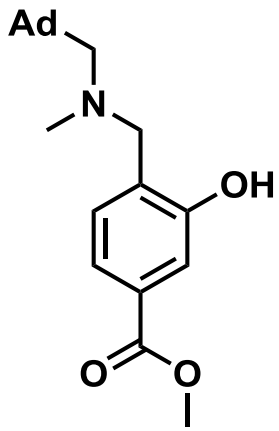
Chloroform-d, 23 ºC

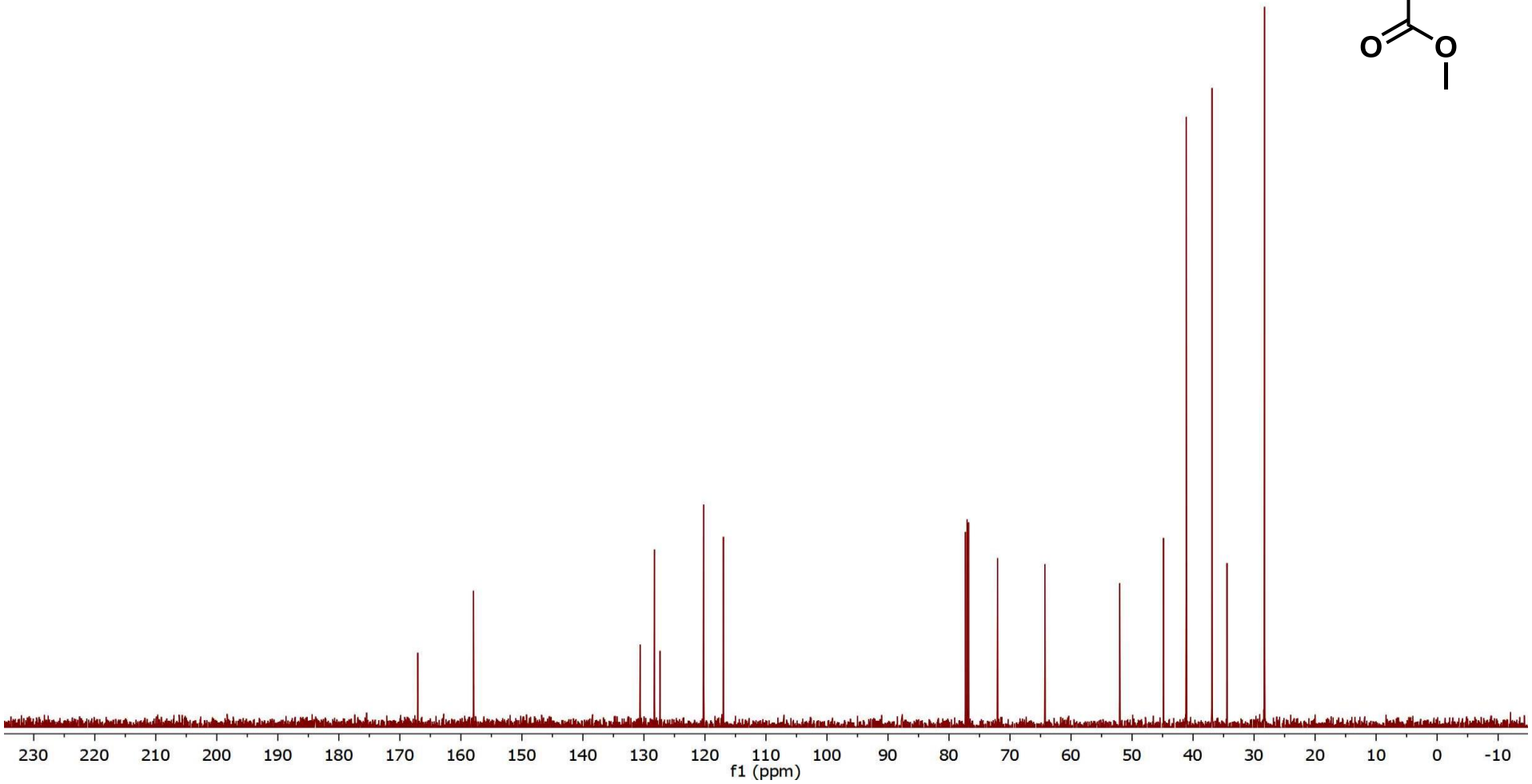




^{13}C-NMR of labeling precursor 2

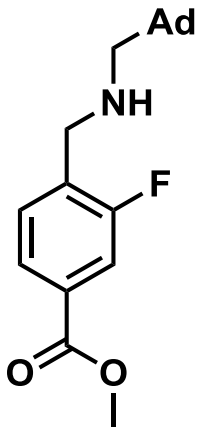
Chloroform-d, 23 ºC

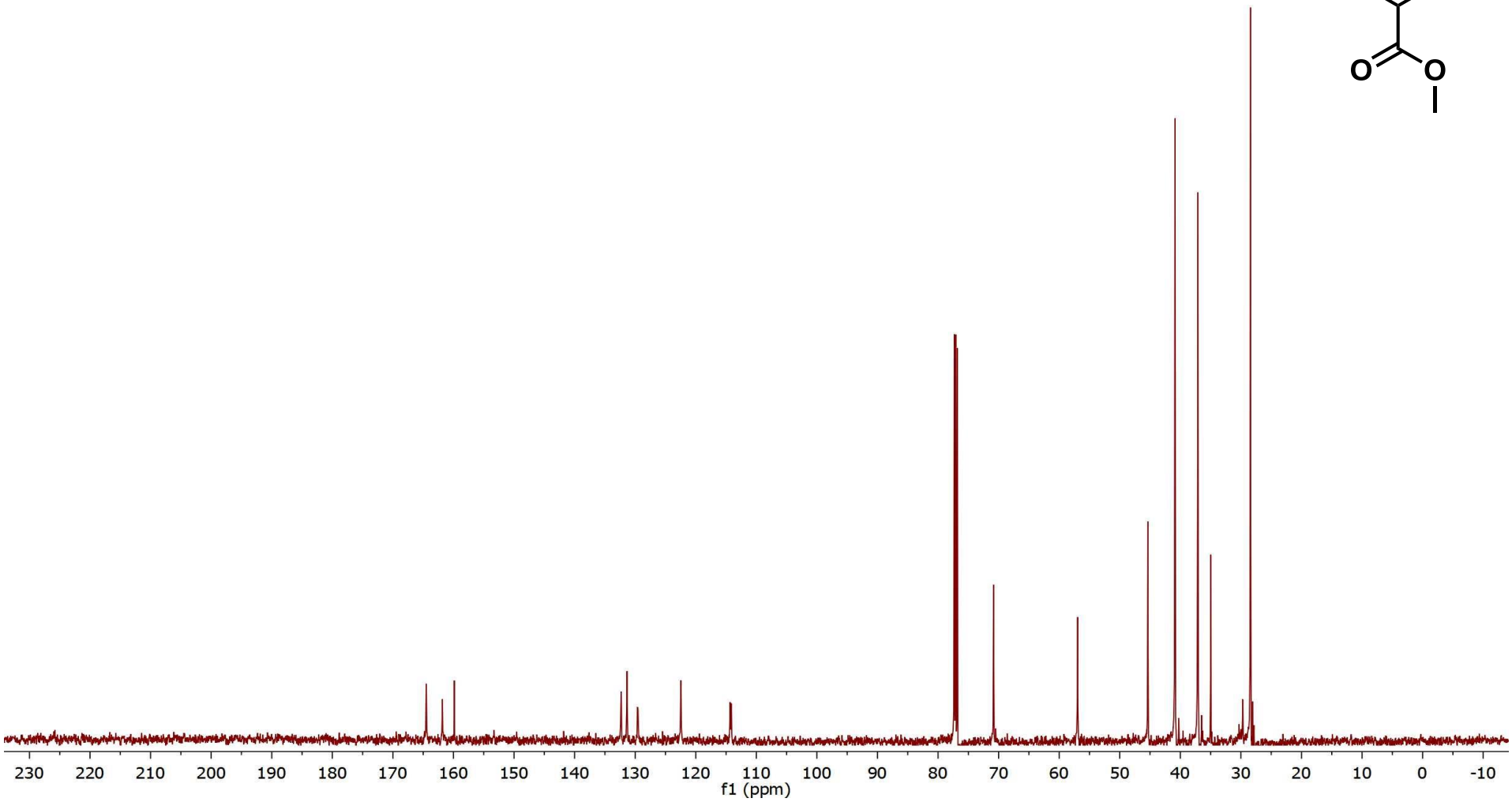




^{13}C-NMR of Secondary adamantanemetylamine SI4

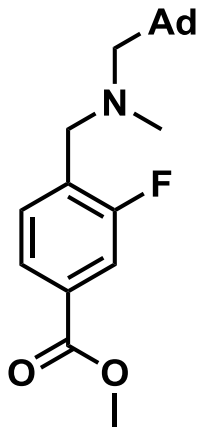
Chloroform-d, 23 ºC

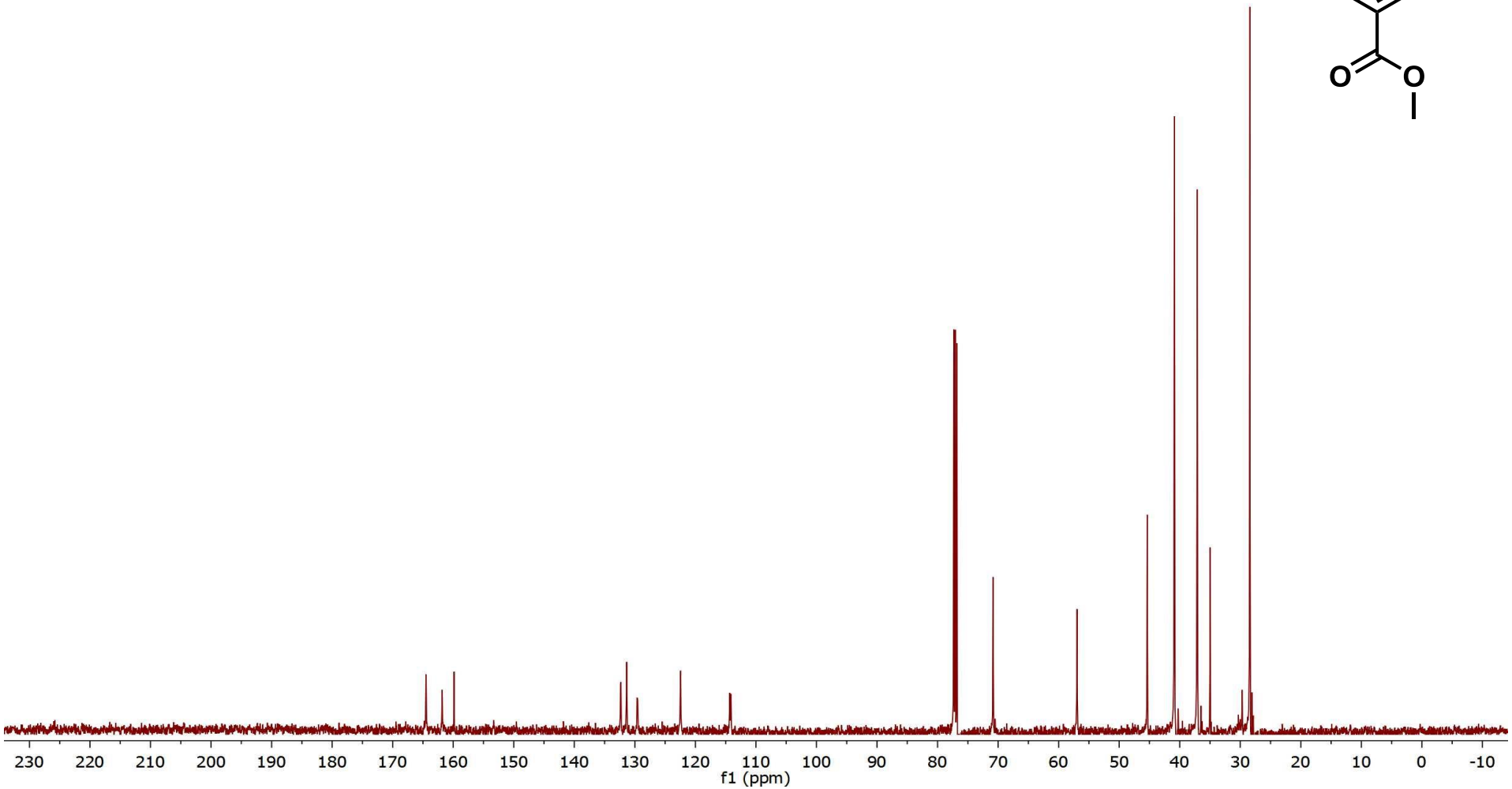




^{13}C-NMR of Tertiary adamantanemetylamine SI5

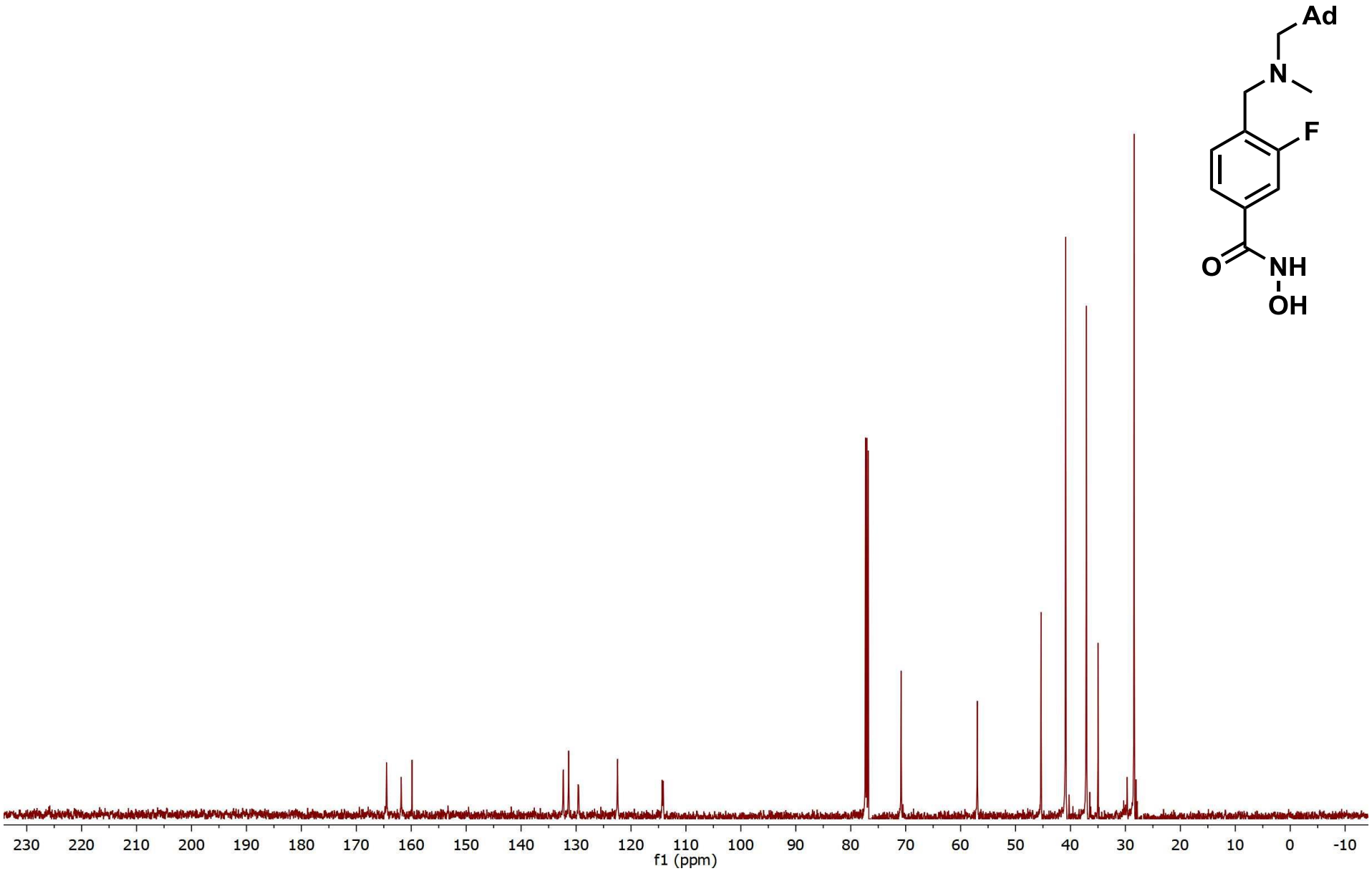
Chloroform-d, 23 ºC





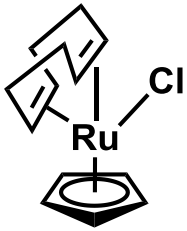
^{13}C-NMR of Bavarostat (1)

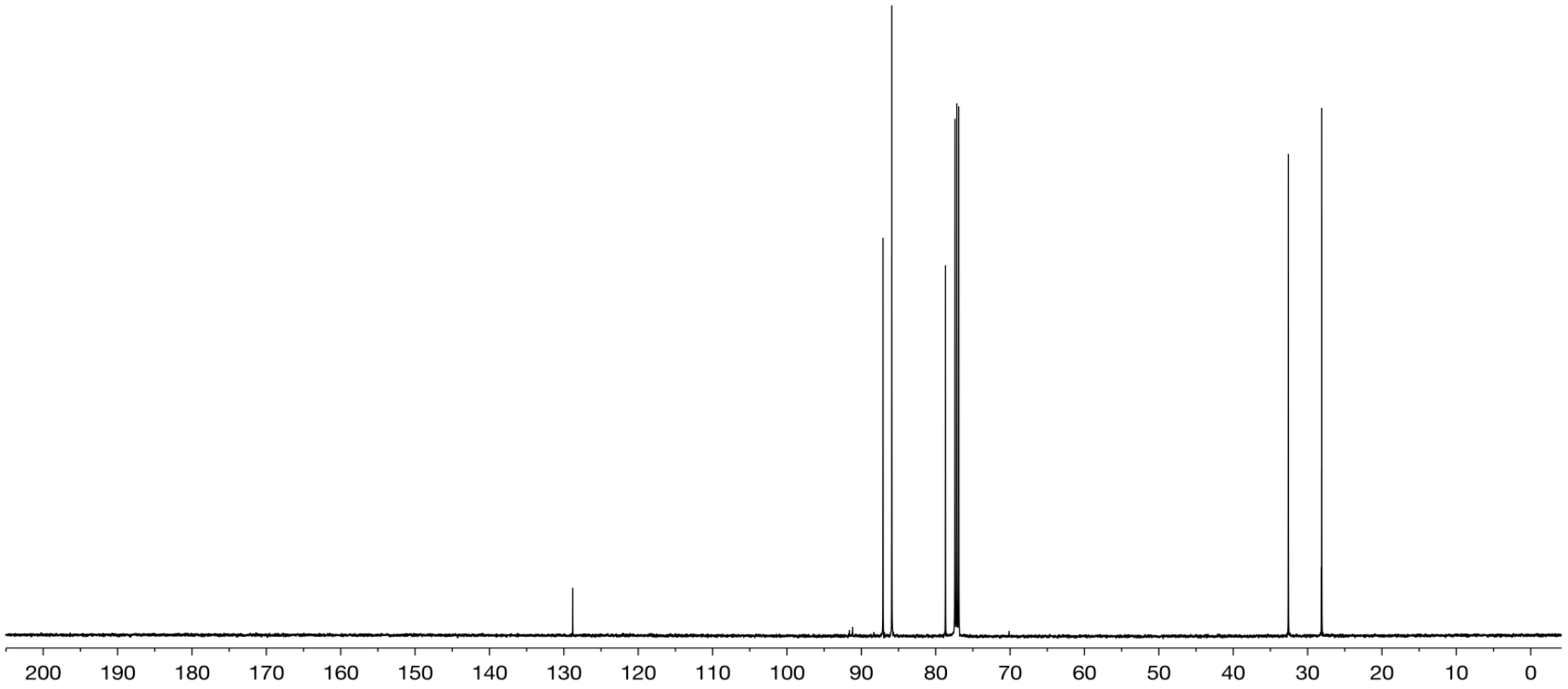
DMSO-d_6, 23 ºC



^{13}C-NMR of [CpRu(COD)Cl] (3)

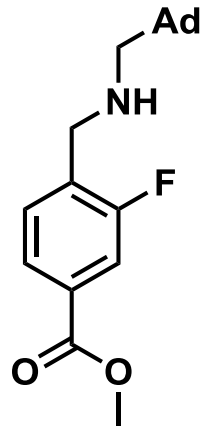
Chloroform-d, 23 ºC

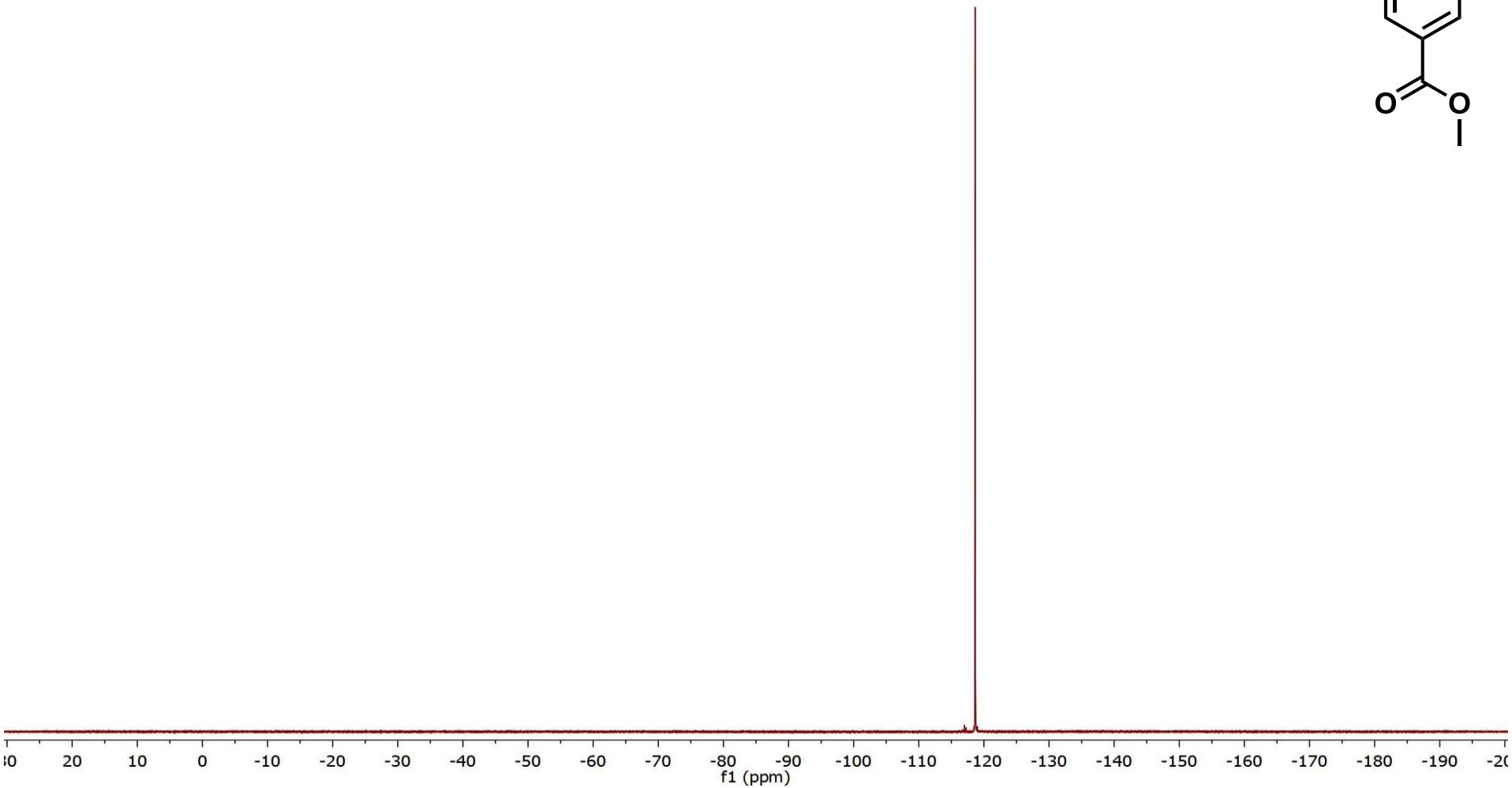




^{19}F-NMR of Secondary adamantanemetylamine SI4

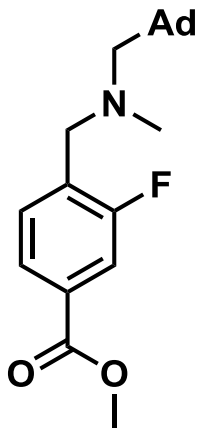
Chloroform-d, 23 ºC

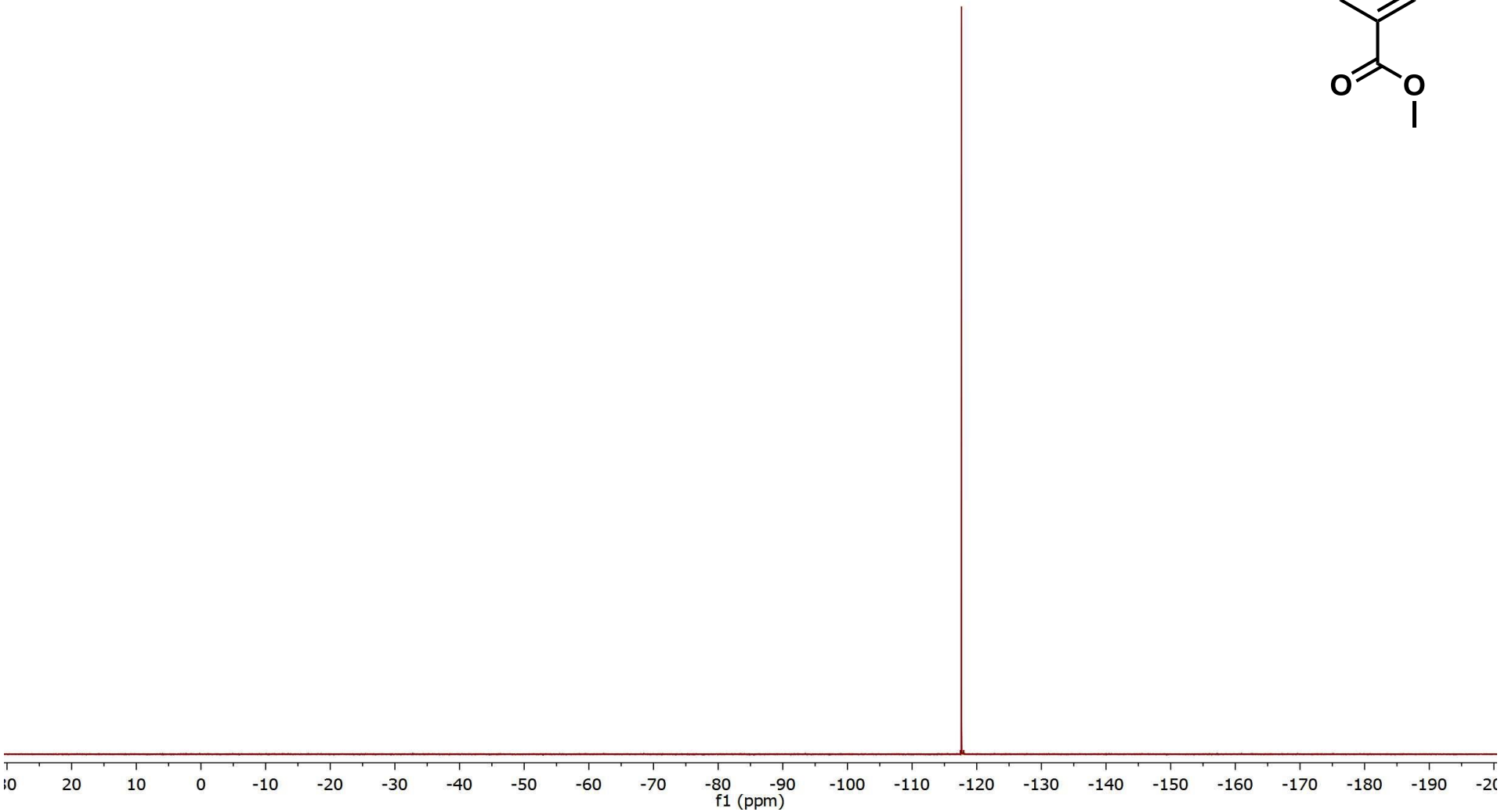




^{19}F-NMR of Tertiary adamantanemetylamine SI5

Chloroform-d, 23 ºC





^{19}F-NMR of Bavarostat (1)

DMSO-d_6, 23 ºC