Formation of Non-Natural α,α-Disubstituted Amino Esters via Catalytic Michael Addition

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Supporting Information

Table of contents

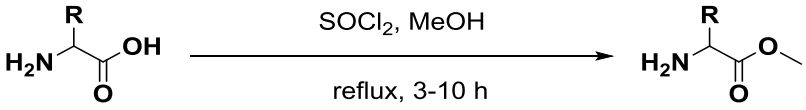
General Experimental:

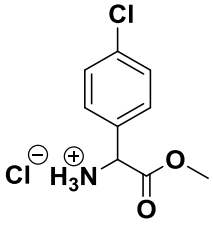
All reagents were obtained from commercial suppliers (Aldrich, VWR, TCI Chemicals, and Oakwood Chemicals) and used without further purification unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC), (obtained from sorbent technology Silica XHL TLC Plates, w/UV254, glass backed, 250 µm, 20 x 20 cm) and were visualized with ultraviolet light, potassium permanganate stain, GC-MS (QP 2010S, Shimadzu equipped with auto sampler) and ^{19}F and ^{1}H NMR.

Isolations were carried out using Teledyne Isco Combiflash Rf 200i flash chromatograph with Sorbtech normal phase silica (4 g, 12 g, 24 g, 40 g) with product detection at 254 and 288 nm and evaporative light scattering detection. NMR spectra were obtained on a 400 MHz Bruker Avance III spectrometer and 400 MHz Varian spectrometer. ^{1}H, ^{19}F and ^{13}C NMR chemical shifts are reported in ppm relative to the residual protio solvent peak or TMS signal. IR spectra were recorded on Varian 800 FT-IR. Mass spectra (HRMS) analysis was performed on LTQ-OrbitrapXL by Thermo Scientific ltd using a Heated-electrospray ionization (H-ESI) source.

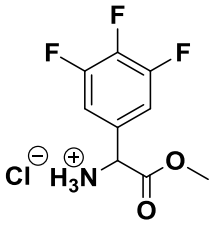
II. Synthesis of N-acyl/carbamate amino esters

II.i Procedures for the esterification of amino acids[1]





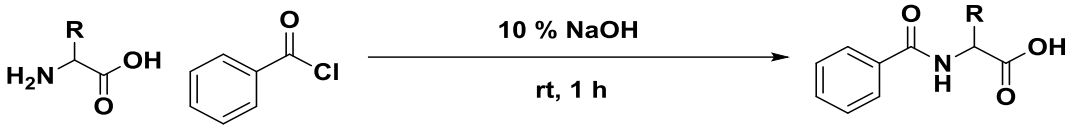
S-1: 1-(4-Chlorophenyl)-2-methoxy-2-oxoethanaminium chloride. *p*-Chlorophenylglycine (1 g, 5.39 mmol) was dissolved in MeOH (5 mL). The solution was cooled to 0 ˚C and thionyl chloride (0.78 mL, 10.8 mmol) was added dropwise. The reaction mixture was heated under reflux for 3 h. Cooling to rt followed by concentration in vacuo afforded the title compound as a white solid (1.27 g, quant.). Spectral data matched the literature values.[1]



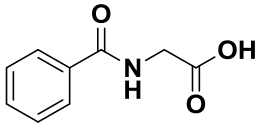
S-2: 1-(3,4,5-trifluoropheny)-2-methoxy-2-oxoethanaminium chloride. 3,4,5-trifluorophenylglycine (2.0 g, 9.7 mmol) was dissolved in MeOH (30 mL). The solution was cooled to 0 ◦C and thionyl chloride (1.4 mL, 19.5 mmol) was added dropwise. The reaction mixture was heated under reflux for 3 h. Cooling to rt followed by concentration in vacuo afforded the title compound as a crude semi-white solid (2.3 g, 93%). The crude compound was moved to next step without further purification.

II.ii ***N*-Acylation/protection of amino acids/esters**

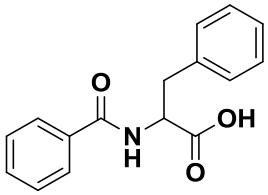
- General procedure A for the preparation of *N*-benzoyl-α-amino acids[2]



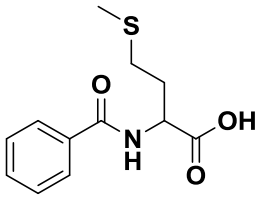
Benzoyl chloride **(1.2 equiv**) was added in 4 portions over **30** minutes to a **0 ºC** solution of the amino acid (**1 equiv)** and 10 % NaOH **(3.8 equiv**) in distilled water (open to air). After the addition was complete, the ice bath was removed, and the reaction was quenched by the dropwise addition of concentrated aqueous hydrochloric acid until **pH 1** was reached, which resulted in the precipitation of the product. The solid was isolated by filtration and then recrystallized from water. The resulting crystals were air dried to give the desired ***N*-**benzoyl amino acid, which showed no trace of benzoic acid by ^{1}H NMR. If benzoic acid was detected, the compound was stirred in cool (0 ºC) 1 M benzene (or toluene in relation to starting material)for 1 h,, and isolated by filtration.



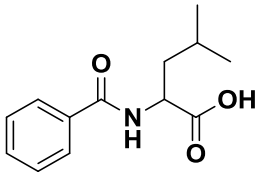
***N*-benzoyl glycine**: The **general procedure A** was followed using glycine (5.00 g, 66.6 mmol), benzoyl chloride (9.30 mL, 79.2 mmol), 10 % NaOH (100 mL, 251 mmol) to afford the title compound in 93% yield after isolation (10.86 g, 60.9 mmol) as a white solid. ^{1}H-NMR matched previous literature.[3]



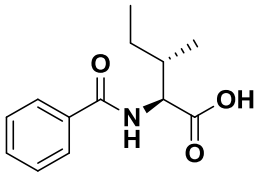
***N*-benzoyl phenyl alanine**: The **general procedure A** was followed using phenyl alanine (2.50 g, 15.1mmol), benzoyl chloride (2.11 mL, 18.1 mmol), 10 % NaOH (23.0 mL, 57.4 mmol) to afford the title compound in 79% yield after isolation (3.2 g, 11.9 mmol) as a white solid. ^{1}H-NMR matched previous literature.[4]



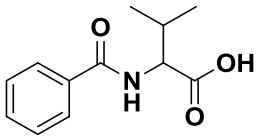
***N*-benzoyl methionine**: The **general procedure A** was followed using methionine (2.50 g, 16.8 mmol), benzoyl chloride (2.34 mL, 20.1 mmol), 10 % NaOH (25.5 ml, 63.8 mmol) to afford the title compound in 79% yield after isolation (3.2 g, 11.9 mmol) as a white solid.
^{1}H-NMR matched previous literature.[5]



***N*-benzoyl leucine**: The **general procedure A** was followed using leucine (2.00 g, 15.2 mmol), benzoyl chloride (2.12 mL, 18.3 mmol), 10 % NaOH (23.1 ml, 57.8 mmol) to afford the title compound in 67% yield after isolation (2.4 g, 10.2 mmol) as a white solid. ^{1}H-NMR matched previous literature.[4]

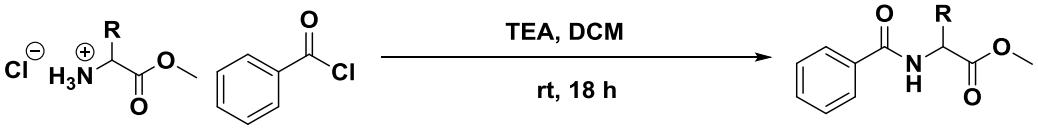


***N*-benzoyl L-isoleucine**: The **general procedure A** was followed using L-isoleucine (300 mg, 2.3 mmol), benzoyl chloride (0.32 mL, 2.7 mmol), 10 % NaOH (23.1 mL, 8.7 mmol) to afford the title compound in 43% yield after isolation (247 mg, 0.99 mmol) as a white solid. ^{1}H-NMR matched previous literature.[6]



***N*-benzoyl Valine**: The **general procedure A** was followed using leucine (1 g, 8.5 mmol), benzoyl chloride (1.2 mL, 10 mmol), 10 % NaOH (10 mL, 25.5 mmol) to afford the title compound in 88% yield after isolation (1.64 g, 7.5 mmol) as a white solid. ^{1}H-NMR matched previous literature.[4]

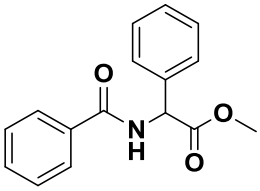
-General procedure B for the preparation of *N*-benzoyl-α-amino esters[7]



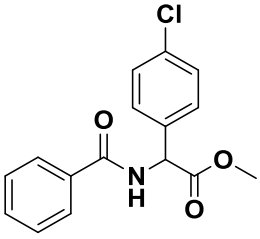
A solution of benzoyl chloride (**1 equiv**) in CH_2Cl_2 (**2 M**) was added dropwise to a suspension of the glycine methyl ester hydrochloride (**1 equiv**) and triethylamine (2.2 equiv) in CH_2Cl_2 (**0.5 M**) at 0 ^oC. The reaction mixture was stirred at room temperature for 18 h, it was washed with equal volumes of aq. HCl (**3 x 1 M**), saturated aq. $NaHCO_3$ (**3x**) and saturated aq. NaCl, successively. Next the organic extract was dried (over $MgSO_4$) and concentrated under reduced pressure. Then, the crude amide was purified via column chromatography.

- General procedure C for the preparation of *N*-benzoyl-α-amino esters[8]

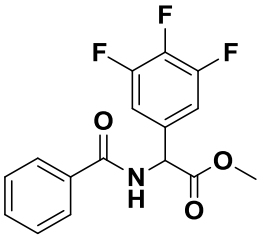
N-Benzoyl amino acid (**1 equiv**), alcohol (**3 equiv**), EDC (**1.5 equiv**), DMAP (**1 equiv**) were dissolved in anhydrous DCM (**0.2 M**) and the reaction was stirred for 16 h at room temperature under an argon atmosphere. The workup consisted of diluting solution with DCM and quenching with equal amount of water. The organic layer was separated and washed with equal amount of sat. $NaHCO_3$ (**3x**), 0.01 M HCl (**2x**) (this step was omitted when synthesizing trifluoroethyl esters), and water twice. The organic layer was separated, and the solution was concentrated under vacuum. Flash column chromatography was used to purify the desired compound.



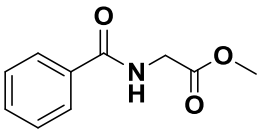
Methyl 2-benzamido-2-phenylacetate. The **general procedure B** was followed using the glycine methyl ester hydrochloride (1.00 g, 4.81 mmol), benzoyl chloride (0.560 mL, 4.81 mmol), triethylamine (1.48 mL, 10.6 mmol) to afford the title compound in 90% yield after isolation (1.17 g, 4.34 mmol) as a white solid. ^{1}H-NMR matched previous literature.[9]



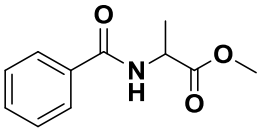
methyl 2-benzamido-2-(4-chlorophenyl)acetate. The **general procedure B** was followed using the 1-(4-Chlorophenyl)-2-methoxy-2-oxoethanaminium chloride (1.5 g, 6.35 mmol), benzoyl chloride (0.740 mL, 6.35 mmol), triethylamine (1.97 mL, 13.97 mmol) to afford the title compoound in 83% yield after isolation (1.6 g, 5.37 mmol) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 2H), 7.43 – 7.33 (m, 4H), 7.29 (d, *J* = 6.3 Hz, 1H), 5.77 (d, *J* = 6.7 Hz, 1H), 3.79 (s, 3H).^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.3, 166.6, 135.3, 134.6, 133.4, 132.1, 129.2, 128.8, 128.7, 127.3, 56.31, 53.2.



methyl 2-benzamido-2-(3,4,5-trifluorophenyl)acetate. The **general procedure B** was followed using the 1-(3,4,5-trifluoropheny)-2-methoxy-2-oxoethanaminium chloride. (0.700 mg, 2.74 mmol), benzoyl chloride (0.318 mL, 2.74 mmol), triethylamine (0.841 mL, 6.03 mmol) to afford the title compound in 71% yield after isolation (628 mg, 1.95 mmol) as a white solid. ^{1}H-NMR matched previous literature. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -131.81 – -134.40 (m), -160.07 (tt, *J* = 20.4, 6.4 Hz). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 7.1 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.41 (d, *J* = 6.2 Hz, 1H), 7.12 (dd, *J* = 7.9, 6.4 Hz, 2H), 5.72 (d, *J* = 6.4 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.5, 166.7, 151.5 (ddd, *J* = 251.4, 10.2, 3.9 Hz), 139.9 (dt, *J* = 253.0, 15.3 Hz), 133.1, 132.4, 128.9, 128.5, 127.8 – 126.4 (m), 113.3 – 110.1 (m), 55.9 (d, *J* = 1.8 Hz), 53.6.

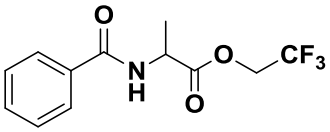


methyl benzoylglycinate. The **general procedure C** was followed using the *N*-benzoyl glycine (250 mg, 1.40 mmol), methanol (0.170 mL, 4.19 mmol), EDC (401 mg, 2.09 mmol), DMAP (170 mg, 1.40 mmol), and 7 mL of CH_2Cl_2 to afford the title compound in 73% yield after isolation (197 mg, 1.02 mmol) as a white solid. ^{1}H-NMR matched previous literature.[10]

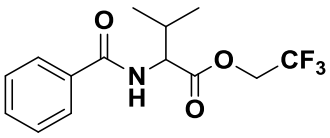


methyl benzoylalaninate. The **general procedure C** was followed using the *N*-benzoyl alanine (300 mg, 1.55 mmol), methanol (0.188 mL, 4.66 mmol), EDC (447 mg, 2.33 mmol), DMAP (190 mg, 1.55 mmol),

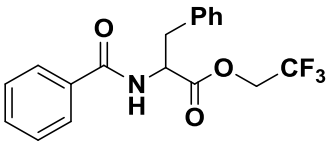
and 7.8 mL of CH_2Cl_2 to afford the title compound in 82% yield after isolation (264 mg, 1.27 mmol) as a white solid. ^{1}H-NMR matched previous literature.[11]



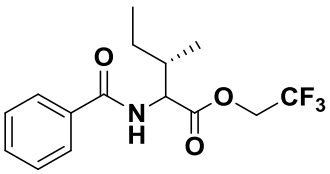
2,2,2-trifluoroethyl benzoylalaninate. The **general procedure C** was followed using the *N*-benzoyl alanine (500 mg, 2.59 mmol), trifluroethanol (0.586 mL, 7.76 mmol), EDC (744 mg, 3.88 mmol), DMAP (316 mg, 2.59 mmol), and 13 mL of CH_2Cl_2 to afford the title compound in 54% yield after isolation (290 m g, 1.40 mmol) as a white solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -73.85 (t, *J* = 8.3 Hz). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 7.0 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 2H), 6.58 (d, *J* = 6.9 Hz, 1H), 4.90 (p, *J* = 7.2 Hz, 1H), 4.67 (dq, *J* = 12.6, 8.3 Hz, 1H), 4.48 (dq, *J* = 12.6, 8.3 Hz, 1H), 1.58 (d, *J* = 7.3 Hz, 3H).^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.2, 167.6, 133.9, 132.3, 129.0, 127.9 – 127.3 (m), 123.1 (q, *J* = 277.3 Hz), 61.3 (q, *J* = 36.9 Hz), 48.8, 18.4.



2,2,2-trifluoroethyl benzoylvalinate. The **general procedure C** was followed using the *N*-benzoyl valine (600 mg, 2.71 mmol), trifluroethanol (0.614 mL, 8.13 mmol), EDC (780 mg, 4.07 mmol), DMAP (331 mg, 2.71 mmol), and 14 mL of CH_2Cl_2 to afford the title compound in 67% yield after isolation (551 mg, 1.82 mmol) as a white solid. ^{19}F NMR (376 MHz, Methylene Chloride-d_2) δ -74.05 (t, *J* = 8.5 Hz). ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 6.52 (d, *J* = 8.5 Hz, 1H), 4.79 (dd, *J* = 8.5, 5.1 Hz, 1H), 4.59 4.76 – 4.40 (m, 2H), 2.31 (hept, *J* = 6.9, 5.1 Hz, 1H), 1.03 (dd, *J* = 9.5, 6.9 Hz, 6H). ^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 171.2, 167.8, 134.6, 132.4, 129.2, 127.6, 123.5 (q, *J* = 277.2 Hz), 61.2 (d, *J* = 36.7 Hz), 58.1, 31.8, 19.3, 18.2.



2,2,2-trifluoroethyl benzoylphenylalaninate. The **general procedure C** was followed using the *N*-benzoyl phenylalanine (1000 mg, 3.71 mmol), trifluroethanol (0.841 mL, 11.1 mmol), EDC (1068 mg, 5.57 mmol), DMAP (454 mg, 3.71 mmol), and 14 mL of CH_2Cl_2 to afford the title compound in 61% yield after isolation (796 m g, 2.27 mmol) as a white solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -73.48 (t, *J* = 8.3 Hz). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 7.1 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.36 – 7.27 (m, 3H), 7.16 (d, *J* = 6.5 Hz, 2H), 6.46 (d, *J* = 7.7 Hz, 1H), 5.18 (dt, *J* = 7.8, 5.9 Hz, 1H), 4.66 – 4.41 (m, 2H), 3.39 – 3.20 (m, 2H).



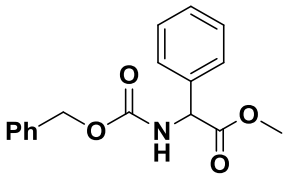
2,2,2-trifluoroethyl benzoyl-iso-leucinate. The **general procedure C** was followed using the *N*-benzoyl iso-leucine (250 mg, 1.06 mmol) as one diastereomer, trifluroethanol (0.319 mL, 3.19 mmol), EDC (306 mg, 1.59 mmol), DMAP (130 mg, 1.06 mmol), and 5.3 mL of CH_2Cl_2 to afford the title compound in 78% yield after isolation (263 mg, 0.83 mmol) as a white solid. ^{19}F NMR (376 MHz, Methylene Chloride-d_2) δ -74.03 (t, *J* = 8.3 Hz), -74.09 (d, *J* = 8.4 Hz). ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.78 (dt, *J* = 8.3, 1.2 Hz, 4H), 7.58 – 7.52 (m, 2H), 7.47 (tt, *J* = 8.3, 0.9 Hz, 4H), 6.54 (d, *J* = 7.9 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 1H),

4.96 (dd, *J* = 8.7, 4.2 Hz, 1H), 4.83 (dd, *J* = 8.4, 5.2 Hz, 1H), 4.68 (dqd, *J* = 12.7, 8.5, 1.4 Hz, 2H), 4.49 (dqd, *J* = 12.7, 8.5, 2.0 Hz, 2H), 2.17 – 1.98 (m, 2H), 1.61 – 1.44 (m, 5H), 1.38 – 1.23 (m, 2H), 1.06 – 0.93 (m, 12H). ^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 171.57, 171.18, 167.83, 167.65, 134.65, 134.59, 132.36, 129.18, 127.59 – 127.53 (m), 124.89, 122.14, 119.38, 61.16 (qd, *J* = 36.7, 6.0 Hz), 57.40, 56.23, 38.38, 38.16, 26.83, 25.84, 15.83, 15.00, 12.01, 11.82. d.r.-1.6/1.

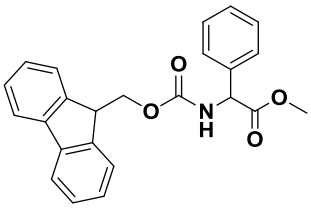
2,2,2-trifluoroethyl benzoylleucinate. The **general procedure C** was followed using the *N*-benzoyl leucine (1000 mg, 4.250 mmol), trifluroethanol (1.275 mL, 12.75 mmol), EDC (1222 mg, 6.37 mmol), DMAP (519 mg, 4.25 mmol), and 21 mL of CH_2Cl_2 to afford the title compound in 88% yield after isolation (1187 mg, 3.74 mmol) as a white solid. ^{19}F NMR (376 MHz, Methylene Chloride-d_2) δ -74.15 (t, *J* = 8.5 Hz). ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.79 (d, *J* = 7.1 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 2H), 6.57 (d, *J* = 8.1 Hz, 1H), 4 4.92 – 4.77 (m, 1H), 4.64 (dq, *J* = 12.7, 8.5 Hz, 1H), 2.00 – 1.53 (m, 3H), 1.06 – 0.94 (m, 6H). ^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 172.2, 167.7, 134.4, 132.4, 129.2, 127.6, 125.4 – 119.1 (m), 61.3 (q, *J* = 36.7 Hz), 51.7, 41.5, 25.6, 23.1, 22.1.

2,2,2-trifluoroethyl benzoylmethioninate. The **general procedure C** was followed using the *N*-benzoyl leucine (1000 mg, 3.95 mmol), trifluroethanol (0.894 mL, 11.84 mmol), EDC (1135 mg, 5.92 mmol), DMAP (482 mg, 3.95 mmol), and 20 mL of CH_2Cl_2 to afford the title compound in 61% yield after isolation (807 mg, 2.41 mmol) as a white solid. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -73.65 (t, *J* = 8.4 Hz). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 7.1 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 2H), 6.98 (d, *J* = 7.4 Hz, 1H), 5.03 (td, *J* = 7.4, 5.0 Hz, 1H), 4.49 (dq, *J* = 12.6, 8.3 Hz, 1H), 4.49 (dq, *J* = 12.6, 8.3 Hz, 1H), 2.69 – 2.56 (m, 2H), 2.32 (ddd, *J* = 14.5, 7.3, 5.0 Hz, 1H), 2.20 (dt, *J* = 14.4, 7.0 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.7, 167.3, 133.4, 132.0, 128.7, 127.1, 122.7 (q, *J* = 277.4 Hz), 61.0 (q, *J* = 36.9 Hz), 52.1, 30.9, 30.0, 15.5.

methyl 2-((tert-butoxycarbonyl)amino)-2-phenylacetate. To a solution of glycine methyl ester hydrochloride (500 mg, 2.48 mmol), triethylamine (0.864 mL, 6.20 mmol, 2.5 equiv), and a mixture of THF and H_2O (2.5/2.5 mL), Boc_2O (650 mg, 2.98 mmol, 1.2 equviv) was gradually added at 0 °C. After strirring for 15 h at rt, the mixture was concentrated in vacuo to a rid the mixture of THF. After extractions of ethyl acetate (3 x 50 mL), the combined organic layer was washed with aqueous HCl (0.1 M, 40 mL), water (40 mL), and saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford the title compound as a white solid (631 mg, 96%). The procedure and spectral data corresponds to that reported in the literature.[12,13]



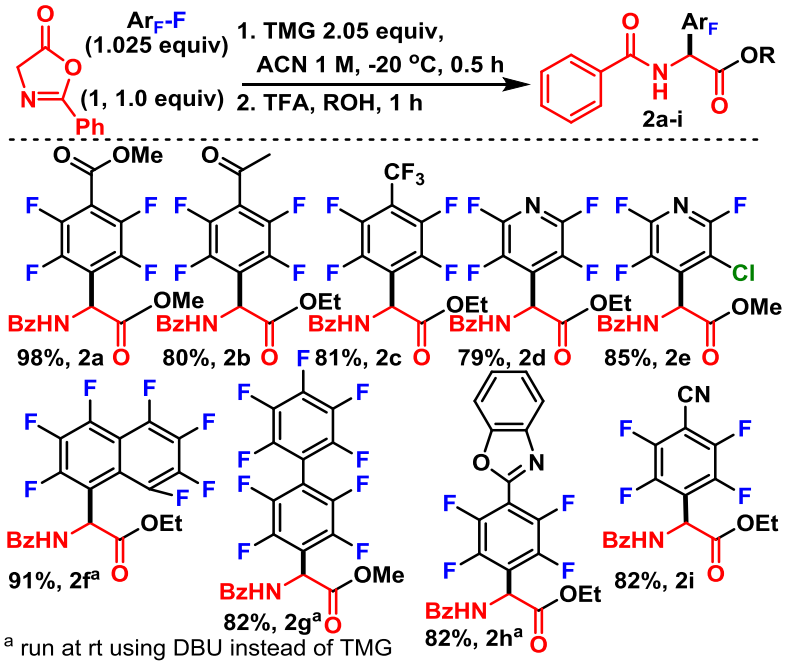
methyl 2-(((benzyloxy)carbonyl)amino)-2-phenylacetate A solution of glycine methyl ester hydrochloride (500 mg, 2.48 mmol) and Et_3N (0.864 mL, 6.20 mmol, 2.5 equiv) in CH_2Cl_2 (5 mL) was added dropwise to a solution of benzyl chloroformate (0.425 mL, 2.98 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL) at 0 °C. The solution was warmed to room temperature and stirred over night. Then, the reaction was quenched by the addition of water (20 mL). The organic layer was seperated and then dried over anhydrous $MgSO_4$. Evaporation and column chromatography on silica gel afforded corresponding the title compound as white solid (623 mg, 84%). The procedure and spectral data corresponds to that reported in the literature.[14,15]



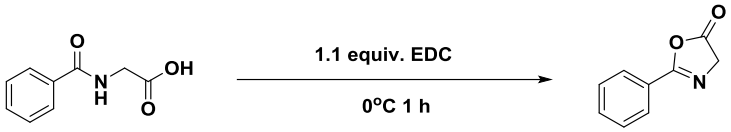
Methyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-phenylacetate. A solution of glycine methyl ester hydrochloride (300 mg, 1.49 mmol) and Et_3N (0.518 mL, 3.72 mmol, 2.5 equiv) in CH_2Cl_2 (5 mL) was added dropwise to a solution of fluorenyl chloroformate (0.463 mL, 1.79 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL) at 0 °C. The solution was warmed to room temperature and stirred overnight. Then, the reaction was quenched by the addition of water (20 mL). The organic layer was seperated and then dried over anhydrous $MgSO_4$. Evaporation and column chromatography on silica gel afforded corresponding the title compound as white solid (340 mg, 59%). The procedure and spectral data corresponds to that reported in the literature.[16]

Synthesis of perfluoro-*N*-benzoyl amino esters

(*see our previous work for more details in regards to synthesizing fluorinated non-natural amino acids via arylation of oxazolones*)[2]

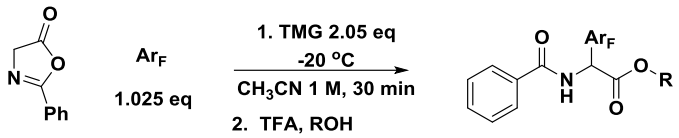


Synthesis of 5-(4H)-oxazolone



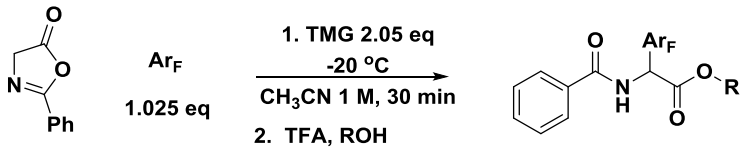
To a suspension of *N*-benzoyl glycine (2.50 g, 14.0 mmol) in dry CH_2Cl_2 (200 mL) under argon at 0 ºC was added EDC HCl (2.38 g, 15.3 mmol). The materials were stirred at 0 ºC for 1 hour. The reaction mixture was diluted with an equal volume of CH_2Cl_2, and washed successively with water, saturated aqueous $NaHCO_3$, and water (each 1/2 the volume of the organic phase), then dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compound in 80 % yield after isolation (1.80 g, 11.1 mmol) as a pale white solid. ^{1}H-NMR spectrum matched that previously reported in the literature.[2]

General procedure D for synthesis of *N*-benzoyl perfluoro-amino esters



Under an inert atmosphere oxazolone **(1 equiv**), Ar_{Fn} **(1.025 equiv),** CH_3CN **(1 M)** was added to small test tube and cooled to -20 ºC. Then a steady stream of tetramethylguandine **(2.05 equiv)** was added to mixture down the side of the test tube glass. The reaction was left to react for 30 min. After the reaction was complete, the cooling bath was removed, and the reaction was left to warm to room temperature, then quenched by the addition of a trifluoroacetic acid/alcohol solution (2 equiv and double the volume of the MeCN). The solution was concentrated and brought into $CHCl_3$ then the organic layer was washed with half volumes of a 1 M HCl brine solution (3x). The organic layer was dried with $MgSO_4$ and concentrated to give the crude product. The crude product was purified by column chromatography.

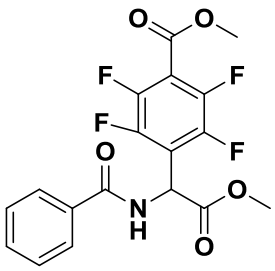
General procedure E for synthesis of *N*-benzoyl perfluoro-amino esters



Under an inert atmosphere oxazolone **(1 equiv**), Ar_F **(1.025 equiv),** CH_3CN **(1 M)** was added to small test tube at room temperature. Then a steady stream of 1,8-Diazabicyclo(5.4.0)undec-7-ene **(2.05 equiv)** was added to mixture down the side of the test tube glass. The reaction was left to react for 30 min. After the reaction was complete, the cooling bath was removed, and the reaction was left to warm to room temperature, then quenched by the addition of a trifluoroacetic acid/alcohol solution (2 equiv and

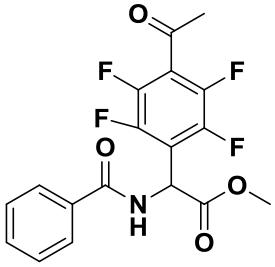
double the volume of the MeCN). The solution was concentrated and brought into $CHCl_3$ then the organic layer was washed with half volumes of a 1 M HCl brine solution (3x). The organic layer was dried with $MgSO_4$ and concentrated giving crude product. The crude product was purified by column chromatography.

2a methyl 4-(1-benzamido-2-ethoxy-2-oxoethyl)-2,3,5,6-tetrafluorobenzoate



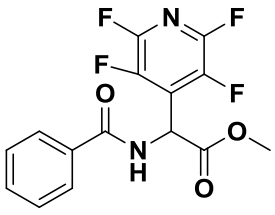
The **general procedure D** was followed using 2-phenyloxazol-5(4H)-one (300 mg, 1.86 mmol), 2,3,4,5,6 pentafluorobenzoate (431 mg, 1.91 mmol), tetramethylguanidine (0.487 ml, 3.81 mmol), 1.86 mL of MeCN and trifluoroacetic acid (0.284 mL, 3.72 mmol) in methanol (3.72 mL) was used to afford the titled compound in 90% yield (668 mg, 1.67 mmol). NMR data matched previous literature value.[2]

2b methyl 2-(4-acetyl-2,3,5,6-tetrafluorophenyl)-2-benzamidoacetate



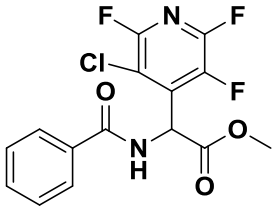
The **general procedure D** was followed using 2-phenyloxazol-5(4H)-one (150 mg, 0.931 mmol), 2',3',4',5',6' pentafluoroacetophenone (200 mg, 0.954 mmol), tetramethylguanidine (239 µL, 1.91 mmol), trifluoroacetic acid (142 µL, 1.86 mmol) in methanol (1.86 mL) and 0.931 mL of MeCN was used to afford the titled compound in 71 % yield (253 mg, 0.661 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -141.06 – -141.36 (m), -141.59 – -141.77 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 6.4 Hz, 1H), 6.21 (d, *J* = 6.5 Hz, 1H), 3.84 (s, 3H), 2.61 (t, *J* = 1.6 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 191.9, 168.6, 166.8, 146.8 – 144.8 (m), 143.9 (dt, *J* = 13.6, 4.7 Hz), 142.8 – 142.4 (m), 132.8, 132.5, 128.9, 127.3, 120.3 – 118.7 (m), 53.9, 47.2, 32.5.

2d methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate



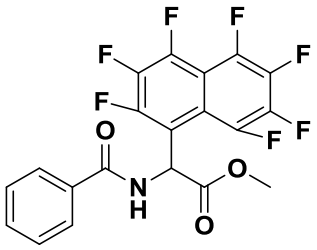
The **general procedure D** was followed using 2-phenyloxazol-5(4H)-one (300 mg, 1.86 mmol), pentafluoropyridine (323 mg, 1.91 mmol), tetramethylguanidine (0.487 µL, 3.81 mmol), trifluoroacetic acid (0.284 mL, 3.72 mmol) in methanol (3.72 mL) was used to afford the titled compound in 69% yield (439 mg, 1.28 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.79 – -90.87 (m), -142.46 – -145.85 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 7.1 Hz, 2H), 7.57 – 7.48 (m, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 6.22 (d, *J* = 6.3 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.7, 166.8, 143.4 (dddd, *J* = 246.3, 16.0, 12.6, 2.8 Hz), 141.9 – 138.9 (m), 132.5 (d, *J* = 11.1 Hz), 129.9 (tt, *J* = 14.1, 2.4 Hz), 128.8, 127.3, 54.7, 47.4.

2e methyl 2-benzamido-2-(3-chloro-2,5,6-trifluoropyridin-4-yl)acetate



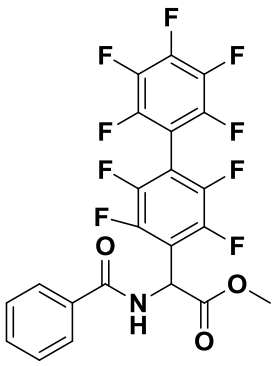
The **general procedure D** was followed using 2-phenyloxazol-5(4H)-one (100 mg, 0.621 mmol), 3-chloro-2,4,5,6 tetrafluoropyridine (118.0 mg, 0.636 mmol), tetramethylguanidine (145 mg, 1.27 mmol), trifluoroacetic acid (95 µL, 1.24 mmol) in methanol (1.24 mL) and 0.621 mL of MeCN was used to afford **2e** in 85% yield (178 mg, 0.487 mmol). NMR data matched previous literature values.[2]

2f methyl 2-benzamido-2-(perfluoronaphthalen-1-yl)acetate



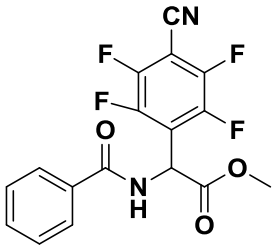
The **general procedure E** was followed using 2-phenyloxazol-5(4H)-one (50 mg, 0.310 mmol), octafluoronapalene (86 mg, 0.318 mmol), 1,8-diazabicyclo(5.4.0)undec-7-ene (96.7 mg, 0.636 mmol), trifluoroacetic acid (95 µL, 1.24 mmol) in ethanol (0.620 mL) and 0.310 mL of MeCN was used to afford **2f** in 82% yield (69.2 mg, 0.254 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -120.66 (dd, *J* = 68.1, 18.4 Hz), -138.68 – -139.91 (m), -142.74 – -143.82 (m), -145.84 (dtd, *J* = 57.6, 16.7, 4.6 Hz), -148.02 (dtt, *J* = 57.7, 18.1, 4.7 Hz), -152.03 – -153.02 (m), -154.60 – -155.85 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 7.1 Hz, 2H), 7.55 – 7.47 (m, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 6.36 (d, *J* = 6.6 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.9, 166.8, 150.9 (d, *J* = 260.5 Hz), 146.1 (d, *J* = 252.4 Hz), 142.8 (d, *J* = 41.3 Hz), 141.9, 141.4 (t, *J* = 15.1 Hz), 140.9 – 139.7 (m), 138.3 (dt, *J* = 118.8, 15.2 Hz), 132.8, 132.4, 128.8, 127.3, 115.2 (t, *J* = 17.7 Hz), 111.6, 108.0 (t, *J* = 13.7 Hz), 53.9, 47.2 (dt, *J* = 3.9, 2.1 Hz).

2g methyl 2-benzamido-2-(perfluoro-[1,1'-biphenyl]-4-yl)acetate



The **general procedure E** was followed using 2-phenyloxazol-5(4H)-one (100 mg, 0.621 mmol), decafluorobiphenyl (212.7 mg, 0.637 mmol), 1,8-diazabicyclo(5.4.0)undec-7-ene (193 mg, 1.27 mmol), trifluoroacetic acid (95 µL, 1.24 mmol) in methanol (1.24 mL) and 0.621 mL of MeCN was used to afford **2g** in 82% yield (265 mg, 0.508 mmol). NMR data matched previous literature values.[2]

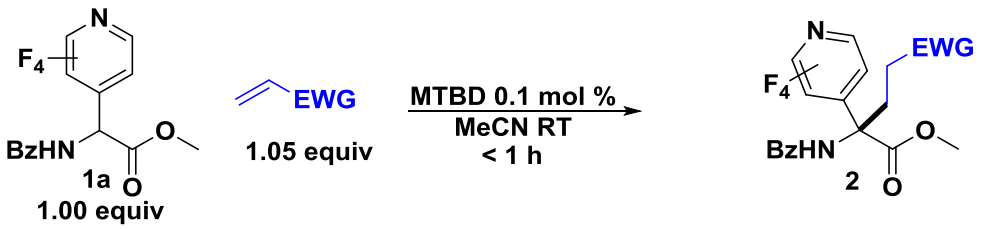
2i methyl 2-benzamido-2-(4-cyano-2,3,5,6-tetrafluorophenyl)acetic acid



The **general procedure D** was followed using 2-phenyloxazol-5(4H)-one (300 mg, 1.86 mmol), 2,3,4,5,6 pentaflurobenzonitrile (240 µL, 1.91 mmol), tetramethylguanidine (0.487 ml, 3.81 mmol), 1.86 mL of MeCN and trifluoroacetic acid (0.284 mL, 3.72 mmol) in methanol (3.72 mL) was used to afford the titled compound in 66% yield (668 mg, 1.67 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -128.70 – -134.21 (m), -139.47 (td, *J* = 16.5, 6.8 Hz). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 6.0 Hz, 1H), 6.18 (d, *J* = 6.1 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.9, 166.8, 148.8 – 145.4 (m), 146.6 – 143.2 (m), 132.6, 132.4, 128.9, 127.3, 123.2 (t, *J* = 15.3 Hz), 107.19 (t, *J* = 3.7 Hz), 94.65 (tt, *J* = 17.0, 2.8 Hz), 54.18, 47.46 (p, *J* = 2.1 Hz).

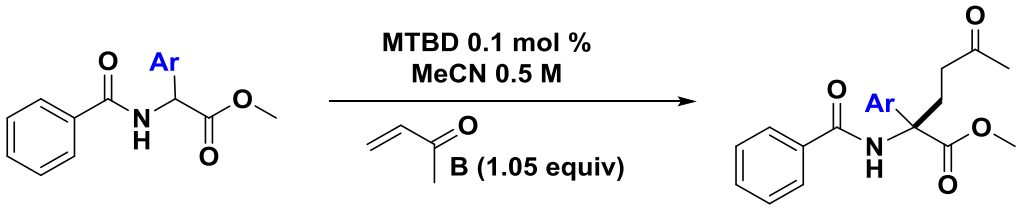
Michael reaction: synthesis of α,α-disubstituted amino acid derivatives

General procedure F for synthesis of Michael adducts



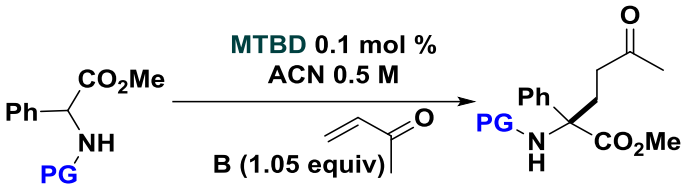
Under an inert atmosphere the methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate **(1 equiv**), Michael acceptor **(1.05 equiv),** CH_3CN **(0.5 M)** was added to a small test tube. Then MTBD **(0.001 equiv** made from a stock solution**)** was added to mixture and stirred vigorously. The reaction was monitored by ^{19}F NMR until the starting material was consumed. After the reaction was complete, the reaction was quenched with acetic acid (1 equiv). The solution was then concentrated and a half volume of brine solution was added. The salty water was extracted with CH_2Cl_2 (3x) and the combined organic extracts were washed with half volumes of a 1 M HCl brine solution (3x), and a final wash with tap water. The organic layer was dried with $MgSO_4$ and concentrated giving crude product. The crude product was purified further by column chromatography.

General procedure G for synthesis of *N*-benzoyl-Aryl-Michael adducts



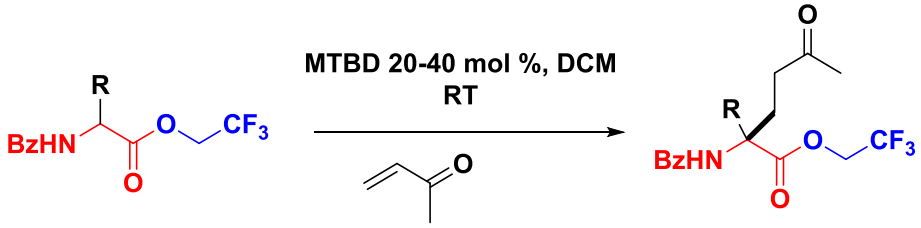
Under an inert atmosphere the amino ester substrate **(1 equiv**), methylvinyl ketone **(1.05 equiv),** CH_3CN **(0.5 M)** was added to a small test tube. Then MTBD **(0.001-0.01 equiv** made from a stock solution**)** was added to mixture and stirred vigorously. The reaction was monitored by ^{19}F NMR/^{1}H NMR until the starting material was consumed. After the reaction was complete, the reaction was quenched with acetic acid (1 equiv). The solution was then concentrated and a half volume of brine solution was added. The salty water was extracted with CH_2Cl_2 (3x) and the combined organic extracts were washed with half volumes of a 1 M HCl brine solution (3x) and a final wash with tap water. The organic layer was dried with $MgSO_4$ and concentrated giving crude/pure product. The crude product was purified further by column chromatography.

General procedure H for synthesis of *N*-boc/cbz-Aryl-Michael adducts



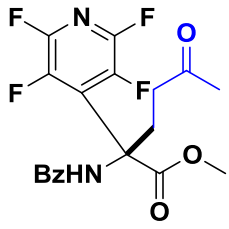
Under an inert atmosphere the protected phenyl glycine substrate **(1 equiv**), methylvinyl ketone **(1.05 equiv)**, CH_3CN **(0.5 M)** was added to a small test tube. Then MTBD **(0.001 equiv** made from a stock solution**)** was added to mixture and stirred vigorously. The reaction was monitored by ^{19}F NMR/^{1}H NMR until the starting material was consumed. After the reaction was complete, the reaction was quenched with acetic acid (1 equiv). The solution was then concentrated and a half volume of brine solution was added. The salty water was extracted with CH_2Cl_2 (3x) and the combined organic extracts were washed with half volumes of a 1 M HCl brine solution (3x) and a final wash with tap water. The organic layer was dried with $MgSO_4$ and concentrated giving crude/pure product. The crude product was purified further by column chromatography.

General procedure I for synthesis of *N*-benzoyl Michael adducts (natural amino esters)



Under a dry inert atmosphere, the amino ester substrate **(1 equiv**), methylvinyl ketone **(1.05 equiv)**, dry DCM **(0.5 M)** was added to a small test tube. Then MTBD **(0.10-0.40 equiv)** was added to mixture and stirred vigorously. The reaction was monitored by ^{19}F NMR/^{1}H NMR until the starting material was consumed. The organic solution was then dried with $MgSO_4$ and concentrated giving crude product. The crude product was purified further by column chromatography.

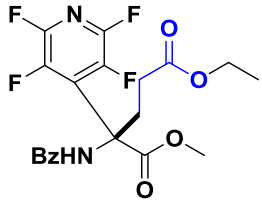
2a methyl-2-benzamido-5-oxo-2-(perfluoropyridin-4-yl)hexanoate



The **general procedure F** was followed using methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate (150 mg, 0.438 mmol), methyl vinyl ketone (38.4 µL, 0.460 mmol), 0.880 mL of a 0.0005 M MTBD/CH_3CN solution (0.0004383 mmol of MTBD) to afford the title compound in 99% yield (179 mg, 0.430 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -90.52 – -90.94 (m), -137.70 – -142.09 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 – 7.72 (m, 3H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 3.84 (s, 3H), 3.43 (dddt, *J* = 14.1, 6.9, 4.8, 2.1 Hz, 1H), 2.82 (dddt, *J* = 14.2, 6.9, 4.3, 2.2 Hz, 1H), 2.59 (dt, *J* = 18.2, 6.7 Hz, 1H), 2.47 (dt, *J* = 18.3, 7.0 Hz, 1H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.7, 170.8, 166.1, 144.4 (dt, *J* = 244.7, 18.2 Hz), 141.4 (dd, *J* = 261.2, 34.6 Hz), 133.2, 132.9, 132.4 – 131.9 (m), 129.3, 127.5, 54.9, 38.4, 30.4, 27.7, 2.4. FT-IR (neat) cm-1 1743, 1754, 1680, 1085. HRMS (ESI) $C_{19}H_{16}F_4N_2O_4$ calcd. $[M+Na]^+$ 435.0938 observed 435.0908.

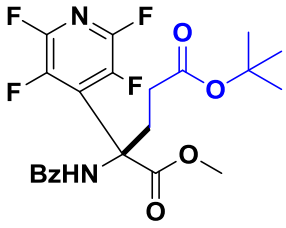
2a was also ran at a 1.46 mmol scale. The **general procedure F** was followed using methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate (0.500 mg, 1.46 mmol), methyl vinyl ketone (128 µL, 1.53 mmol), 2.92 mL of a 0.0005 M MTBD/CH_3CN solution (0.00146 mmol of MTBD) to afford the title compound in 97% yield (583 mg, 1.42 mmol). It is important to note that as the reaction progressed, the product slowly percipitated out of the soluton.

2b 5-ethyl 1-methyl-2-benzamido-2-(perfluoropyridin-4-yl)pentanedioate



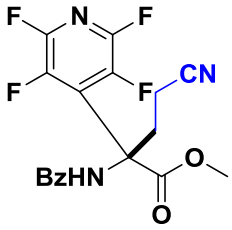
The **general procedure F** was followed using methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate (50 mg, 0.146 mmol), ethyl acrylate (18.0. µL, 0.153 mmol), 0.293 mL of a 0.0005 M MTBD/CH_3CN solution (0.0001463 mmol of MTBD) to afford the title compound in 97% yield (63 mg, 0.140 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.61 – -92.72 (m), -136.58 – -141.53 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.73 (m, 3H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.56 (dddd, *J* = 14.7, 8.6, 6.6, 2.1 Hz, 1H), 2.79 (dddd, *J* = 16.7, 8.6, 4.5, 2.2 Hz, 1H), 2.44 (ddd, *J* = 16.8, 7.9, 6.6 Hz, 1H), 2.29 (ddd, *J* = 16.7, 8.3, 6.7 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.4, 170.6, 166.1, 146.0 – 142.9 (m), 142.9 – 139.5 (m), 133.2, 132.9, 132.0 (t, *J* = 10.4 Hz), 129.3, 127.5, 62.9, 61.4, 54.9, 29.5, 29.1, 14.5. FT-IR (neat) cm-1 3412, 1748, 1730, 1508, 1270. HRMS (ESI) $C_{20}H_{18}F_4N_2O_5$ calcd. $[M+Na]^+$ 465.1044 observed 465.1027.

2c 5-(tert-butyl) 1-methyl-2-benzamido-2-(perfluoropyridin-4-yl)pentanedioate



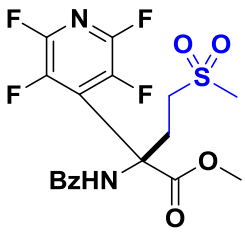
The **general procedure F** was followed using methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate (50 mg, 0.146 mmol), methyl vinyl ketone (22.5 µL, 0.153 mmol), 0.293 mL of a 0.0005 M MTBD/CH_3CN solution (0.000146 mmol of MTBD) to afford the title compound in 92% yield (63 mg, 0.130 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.33 – -93.28 (m), -139.54 (h, *J* = 13.8 Hz). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.43 (tt, *J* = 8.1, 1.4 Hz, 2H), 3.84 (s, 3H), 3.45 (dt, *J* = 14.7, 7.5 Hz, 1H), 2.75 (dt, *J* = 14.4, 7.1 Hz, 1H), 2.45 – 2.31 (m, 1H), 2.21 (dt, *J* = 16.9, 7.5 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.7, 170.5, 166.1, 144.3 (dt, *J* = 243.6, 15.7 Hz), 142.8 – 139.1 (m), 133.2, 132.8, 132.2 (t, *J* = 10.4 Hz), 129.2, 127.5, 81.6, 62.9, 54.8, 30.4, 28.9, 28.4. FT-IR (neat) cm-1 3430, 1727, 1702, 1595, 1310. HRMS (ESI) $C_{22}H_{22}F_4N_2O_5$ calcd. $[M+H]^+$ 471.1538 observed 471.1530.

2d methyl-2-benzamido-4-cyano-2-(perfluoropyridin-4-yl)butanoate



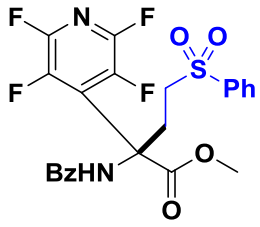
The **general procedure F** was followed using methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate (100 mg, 0.292 mmol), acrylonitrile (20.1 µL, 0.307 mmol), 0.584 mL of a 0.0005 M MTBD/CH_3CN solution (0.000292 mmol of MTBD) to afford the title compound in 99% yield (114 mg, 0.29 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -87.49 – -92.37 (m), -137.14 – -143.28 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 1.3 Hz, 3H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 3.95 (s, 3H), 3.72 (dtt, *J* = 14.2, 7.0, 2.0 Hz, 1H), 2.79 (dtd, *J* = 14.2, 8.3, 2.2 Hz, 1H), 2.50 (dt, *J* = 17.4, 6.7 Hz, 1H), 2.38 (dt, *J* = 17.4, 7.2 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.6, 166.1, 145.7 – 142.6 (m), 140.9 (dd, *J* = 261.4, 35.1 Hz), 132.9, 132.4, 130.9 (t, *J* = 11.2 Hz), 129.1, 127.2, 118.2, 62.1, 55.1, 29.5, 12.4. FT-IR (neat) cm-1 3270, 2248, 1762, 1515, 1295. HRMS (ESI) $C_{18}H_{13}F_4N_3O_3$ calcd. $[M+H]^+$ 396.0966 observed 396.0963.

2e methyl-2-benzamido-4-(methylsulfonyl)-2-(perfluoropyridin-4-yl)butanoate



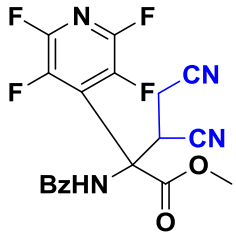
The **general procedure F** was followed using methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate (75 mg, 0.219 mmol), methyl vinyl sulfone (24 mg, 0.230 mmol), 0.438 mL of a 0.0005 M MTBD/CH_3CN solution (0.000219 mmol of MTBD) to afford the title compound in 99% yield (97 mg, 0.22 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -86.03 – -92.09 (m), -138.05 – -142.09 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 – 7.72 (m, 3H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 3.93 (s, 3H), 3.81 (td, *J* = 14.2, 13.0, 4.9 Hz, 1H), 3.16 (ddd, *J* = 14.0, 10.8, 5.1 Hz, 1H), 3.04 – 2.77 (m, 5H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.7, 166.1, 154.1 – 145.0 (m), 143.7 – 139.1 (m), 133.0, 132.3, 131.6 (t, *J* = 10.2 Hz), 129.2, 127.2, 62.0, 55.2, 49.9, 40.6, 27.3. FT-IR (neat) cm-1 3208, 1761, 1517, 1328, 1282. HRMS (ESI) $C_{18}H_{16}F_4N_2O_5S$ calcd. $[M+Na]^+$ 471.0608 observed 471.0597.

2f methyl-2-benzamido-2-(perfluoropyridin-4-yl)-4-(phenylsulfonyl)butanoate



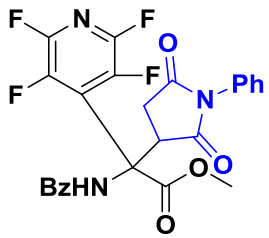
The **general procedure F** was followed using methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate (50 mg, 0.146 mmol), phenyl vinyl sulfone (26 mg, 0.153 mmol), 0.29 mL of a 0.0005 M MTBD/CH_3CN solution (0.0001461 mmol of MTBD) to afford the title compound in 99% yield (72 mg, 0.14 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -86.31 – -93.00 (m), -136.30 – -142.65 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 7.3 Hz, 2H), 7.70 – 7.61 (m, 4H), 7.59 – 7.51 (m, 3H), 7.45 (t, *J* = 7.6 Hz, 2H), 3.87 (s, 3H), 3.66 – 3.57 (m, 1H), 3.20 (ddd, *J* = 14.2, 10.8, 5.1 Hz, 1H), 3.03 – 2.90 (m, 1H), 2.81 (ddd, *J* = 15.5, 12.7, 3.5 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.9, 165.9, 150.0 – 145.2 (m), 143.7 – 139.6 (m), 138.8, 134.7, 133.1, 133.0, 132.0 – 130.9 (m), 130.0, 129.3, 128.1, 127.6, 60.9, 32.2, 23.2, 14.4. FT-IR (neat) cm^{-1} 3409, 1750, 1506, 1308, 1145. HRMS (ESI) $C_{23}H_{18}F_4N_2O_5S$ calcd. $[M+H]^+$ 511.0945 observed 511.0949.

2g methyl 2-benzamido-3,4-dicyano-2-(perfluoropyridin-4-yl)butanoate



The **general procedure F** was followed using methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate (50 mg, 0.146 mmol), fumanitrile (12 mg, 0.153 mmol), 0.29 mL of a 0.0005 M MTBD/CH_3CN solution (0.0001461 mmol of MTBD) to afford the title compound (d.r. 1.5:1) in 87% yield (53 mg, 0.130 mmol). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 (s, 1H), 7.81 – 7.72 (m, 8H), 7.64 – 7.57 (m, 3H), 7.49 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 6H), 5.39 (t, *J* = 5.8 Hz, 1H), 5.23 (t, *J* = 6.4 Hz, 2H), 4.08 (s, 6H), 4.06 (s, 3H), 3.16 – 2.67 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.2, 166.9, 166.6, 166.2, 145.9 – 142.5 (m), 142.4 – 138.8 (m), 133.6, 133.4, 131.7, 131.4, 129.3, 129.2, 128.1 – 127.5 (m), 127.4, 127.4, 115.2, 114.8, 114.6, 114.5, 62.5, 62.2, 55.9, 55.8, 34.1 (t, *J* = 4.7 Hz), 31.5 (t, *J* = 4.4 Hz), 18.8 (t, *J* = 3.5 Hz), 17.4. FT-IR (neat) cm-1 3376, 2999, 1752, 1505, 1316. HRMS (ESI) $C_{19}H_{12}F_4N_4O_3$ calcd. $[M+H]^+$ 421.0918 observed 421.0910.

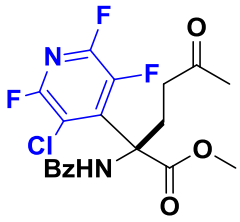
2h methyl 2-benzamido-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-(perfluoropyridin-4-yl)acetate



The **general procedure F** was followed using methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate (50 mg, 0.146 mmol), N-Phenylmaleimide (27 mg , 0.153 mmol), 0.29 mL of a 0.0005 M MTBD/CH_3CN solution (0.0001461 mmol of MTBD) to afford the title compound (d.r. 1.9:1 based on crude ^{19}F NMR) in 87% yield (66 mg, 0.130 mmol) when considering both diastermers, however we were able to separate one diastermer for characterization. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -86.86 – -93.28 (m), -139.58 (dt, *J* = 35.9, 17.9 Hz). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 (s, 1H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.54 – 7.37 (m, 5H), 7.20 (d, *J* = 7.1 Hz, 2H), 4.97 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.97 (s, 3H), 3.62 (dd, *J* = 19.0, 5.0 Hz, 1H),

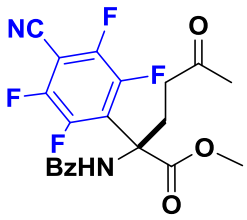
3.20 (dd, *J* = 19.0, 9.7 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 174.4, 174.1, 168.6, 167.6, 146.4 – 143.1 (m), 142.8 – 139.0 (m), 133.4, 132.7, 131.7, 129.7, 129.5, 129.4, 128.9 (d, *J* = 10.0 Hz), 127.6, 126.6, 63.4, 55.7, 46.9, 32.5. FT-IR (neat) cm^{-1} 3390, 1751, 1646, 1501, 1270. HRMS (ESI) $C_{25}H_{17}F_4N_3O_5$ calcd. $[M+H]^+$ 516.1177 observed 516.1184.

3a methyl-2-benzamido-2-(3-chloro-2,5,6-trifluoropyridin-4-yl)-5-oxohexanoate



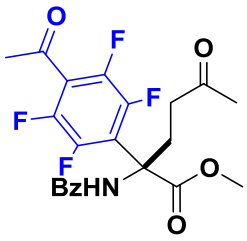
The **general procedure G** was followed using substrate (75 mg, 0.209 mmol), methyl vinyl ketone (18.3 µL, 0.220 mmol), 0.42 mL of a 0.005 M MTBD/CH_3CN solution (0.002094 mmol of MTBD) to afford the title compound in 94% yield (84 mg, 0.20 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -73.82 (dd, *J* = 26.5, 13.0 Hz), -87.39 (dd, *J* = 22.4, 13.0 Hz), -136.78 (ddt, *J* = 27.3, 22.2, 5.5 Hz). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.74 (m, 2H), 7.70 (s, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 3.80 (s, 3H), 3.47 (ddd, *J* = 12.0, 6.8, 5.1 Hz, 1H), 2.87 (ddd, *J* = 14.2, 12.7, 6.6 Hz, 1H), 2.55 (q, *J* = 6.9, 1.3 Hz, 2H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.5, 171.3, 165.7, 147.2 (d, *J* = 15.3 Hz), 145.4 (d, *J* = 16.5 Hz), 143.8 (dd, *J* = 183.2, 14.8 Hz), 133.3, 128.9, 127.2, 121.4 (t, *J* = 12.0 Hz), 119.4 – 119.0 (m), 62.6, 54.4, 38.3, 32.6, 30.1, 27.7. FT-IR (neat) cm-1 1754, 1739, 1676, 1100. HRMS (ESI) $C_{19}H_{16}ClF_3N_2O_4$ calcd. $[M+H]^+$ 429.0823 observed 429.0818.

3b methyl-2-benzamido-2-(4-cyano-2,3,5,6-tetrafluorophenyl)-5-oxohexanoate



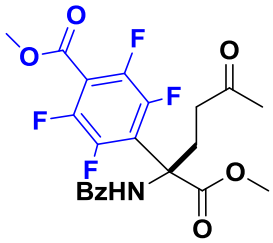
The **procedure G** was followed using substrate (75 mg, 0.205 mmol), methyl vinyl ketone (18.0 µL, 0.215 mmol), 0.41 mL of a 0.0005 M MTBD/CH_3CN solution (0.0002048 mmol of MTBD) to afford the title compound in 93% yield (83 mg, 0.20 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -132.44 (td, *J* = 15.1, 7.0 Hz), -135.22 (dq, *J* = 15.9, 6.9 Hz).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 – 7.64 (m, 3H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 3.76 (s, 3H), 3.34 (dtt, *J* = 14.0, 6.7, 2.1 Hz, 1H), 2.73 (dtt, *J* = 14.1, 6.9, 4.5, 2.2 Hz, 1H), 2.39 (dt, *J* = 18.3, 7.0 Hz, 1H), 2.39 (dt, *J* = 18.2, 7.0 Hz, 1H)2.07 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.6, 171.0, 166.1, 148.9 (dt, *J* = 18.1, 3.8 Hz), 147.7 – 144.5 (m), 133.2, 132.9, 129.3, 127.5, 125.7 (t, *J* = 11.7 Hz), 107.6 (t, *J* = 3.6 Hz), 94.5, 63.1 (d, *J* = 2.4 Hz), 54.9, 38.4 (t, *J* = 1.8 Hz), 30.4, 27.9 (t, *J* = 6.6 Hz). FT-IR (neat) cm-1 3412, 2246, 1747, 1718, 1581, 1303. HRMS (ESI) $C_{21}H_{16}F_4N_2O_4$ calcd. $[M+H]^+$ 437.1119 observed 437.1123.

3c methyl-2-(4-acetyl-2,3,5,6-tetrafluorophenyl)-2-benzamido-5-oxohexanoate



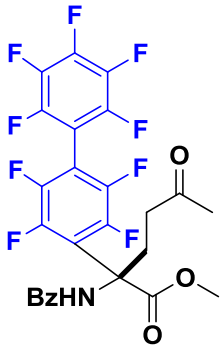
The **procedure G** was followed using substrate (90 mg, 0.235 mmol), methyl vinyl ketone (20.5 µL, 0.247 mmol), 0.47 mL of a 0.0005 M MTBD/CH_3CN solution (0.0002348 mmol of MTBD) to afford the title compound in 98% yield (104 mg, 0.230 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -137.37 (dd, *J* = 21.1, 11.4 Hz), -141.87 (dd, *J* = 21.2, 11.2 Hz). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 – 7.73 (m, 3H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 3.53 – 3.36 (m, 1H), 2.81 (dtt, *J* = 14.3, 7.0, 2.3 Hz, 1H), 2.60 (t, *J* = 1.7 Hz, 3H), 2.55 (m, 1H), 2.48 – 2.39 (m, 1H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 206.8, 192.4, 171.6, 165.9, 148.3 – 145.5 (m), 145.4 – 143.1 (m), 134.1, 132.6, 129.2 (d, *J* = 4.1 Hz), 127.6 (d, *J* = 4.2 Hz), 122.5 – 121.6 (m), 119.9 (d, *J* = 31.1 Hz), 63.1, 54.7, 38.6, 32.8, 30.3, 28.2. FT-IR (neat) cm-1 3306, 1762, 1715, 1533, 1184. HRMS (ESI) $C_{22}H_{19}F_4NO_5$ calcd. $[M+H]^+$ 454.1272 observed 454.1269.

3d methyl-4-(2-benzamido-1-methoxy-1,5-dioxohexan-2-yl)-2,3,5,6-tetrafluorobenzoate



The **procedure G** was followed using substrate (50 mg, 0.125 mmol), methyl vinyl ketone (11.0 µL, 0.131 mmol), 0.25 mL of a 0.0005 M MTBD/CH_3CN solution (0.0001252 mmol of MTBD) to afford the title compound in 99% yield (58 mg, 0.124 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -137.55 (dt, *J* = 16.2, 8.2 Hz), -139.33 – -139.83 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.73 (m, 3H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 3.95 (s, 3H), 3.80 (s, 3H), 3.43 (dddd, *J* = 16.3, 8.6, 6.1, 2.1 Hz, 1H), 2.88 – 2.72 (m, 1H), 2.57 (dt, *J* = 18.1, 6.8 Hz, 1H), 2.57 (dt, *J* = 18.1, 6.8 Hz, 1H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.5, 171.2, 165.7, 160.0, 146.6 (ddt, *J* = 98.8, 16.4, 5.2 Hz), 144.1 (ddt, *J* = 103.8, 16.7, 5.2 Hz), 133.3, 132.4, 128.9, 127.1, 121.8 (t, *J* = 12.0 Hz), 112.3 (t, *J* = 16.0 Hz), 62.6, 54.3, 53.4, 38.2, 30.0, 27.7 (t, *J* = 6.4 Hz).FT-IR (neat) cm^{-1} 2933, 2848, 1434, 1085. FT-IR (neat) cm-1 3240, 1744, 1732, 1709, 1517, 1250. HRMS (ESI) $C_{22}H_{19}F_4NO_6$calcd. $[M+H]^+$ 470.1221 observed 470.1214.

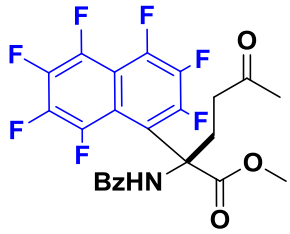
3e methyl-2-benzamido-5-oxo-2-(perfluoro-[1,1'-biphenyl]-4-yl)hexanoate



The **procedure G** was followed using substrate (62 mg, 0.122 mmol), methyl vinyl ketone (10.7 µL, 0.128 mmol), 0.24 mL of a 0.0005 M MTBD/CH_3CN solution (0.0001222 mmol of MTBD) to afford the title compound in 98% yield (69 mg, 0.120 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -136.42 – -136.89 (m), -137.52 (dt, *J* = 14.3, 7.6 Hz), -138.31 (dt, *J* = 19.3, 9.3 Hz), -150.13 (tt, *J* = 20.9, 3.2 Hz), -159.19 – -162.48 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.75 (m, 3H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 3.85 (s, 3H), 3.51 (dt, *J* = 14.2, 6.9 Hz, 1H), 2.85 (dddd, *J* = 16.3, 7.0, 4.4, 2.0 Hz, 1H), 2.46 (dt, *J* = 18.0, 7.1 Hz, 1H), 2.46 (dt, *J* = 18.0, 7.1 Hz, 1H), 2.15 (s, 3H).^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.6, 171.4, 165.7, 145.9 (d, *J* = 9.1 Hz), 145.6 – 144.5 (m), 145.3 – 142.8 (m), 141.3, 138.0 (d, *J* = 255.6 Hz), 133.4, 132.4, 128.9, 127.2, 120.9 (t, *J* = 12.0 Hz), 106.3 (t, *J* = 18.1 Hz), 102.3, 64.5 – 59.8 (m),

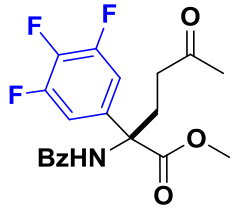
54.4, 38.3 (d, *J* = 1.8 Hz), 30.1, 27.7 (t, *J* = 6.4 Hz). FT-IR (neat) cm-1 3417, 1745, 1719, 1530, 1276. HRMS (ESI) $C_{26}H_{16}F_9NO_4$ calcd. $[M+H]^+$ 578.1008 observed 578.1000.

3f methyl-2-benzamido-5-oxo-2-(perfluoronaphthalen-1-yl)hexanoate



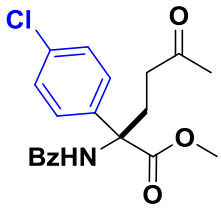
The **procedure G** was followed using substrate (69 mg, 0.155 mmol), methyl vinyl ketone (13.6 µL, 0.163 mmol), 0.31 mL of a 0.0005 M MTBD/CH_3CN solution (0.0001550 mmol of MTBD) to afford the title compound in 98% yield (78 mg, 0.152 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -115.07 (dd, *J* = 78.1, 17.1 Hz), -134.52 (d, *J* = 15.4 Hz), -142.70 (dtt, *J* = 77.8, 16.5, 4.3 Hz), -146.41 (dtd, *J* = 56.5, 16.9, 4.7 Hz), -148.46 (dtt, *J* = 56.5, 16.9, 4.7 Hz), -151.37 – -153.74 (m),153.74 – -158.34 (m). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.85 (s, 1H), 7.77 (d, *J* = 7.1 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 3.82 (s, 3H), 3.54 (dt, *J* = 12.0, 7.0 Hz, 1H), 2.90 (dddd, *J* = 16.3, 6.7, 4.5, 2.2 Hz, 1H), 2.69 – 2.41 (m, 2H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.6, 171.7, 165.7, 152.7, 150.2, 148.5, 146.1, 143.3, 142.4, 141.3, 140.6, 140.2, 138.8, 137.8, 133.4, 132.4, 128.9, 127.2, 118.1 – 116.5 (m), 62.8, 54.3, 38.4, 30.1, 27.9. FT-IR (neat) cm-1 3270, 1765, 1712, 1512, 1246. HRMS (ESI) $C_{24}H_{16}F_7NO_4$ calcd. $[M+H]^+$ 516.1040 observed 516.1031.

3g methyl-2-benzamido-5-oxo-2-(3,4,5-trifluorophenyl)hexanoate



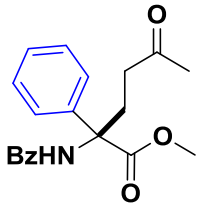
The **procedure G** was followed using substrate (100 mg, 0.309 mmol), methyl vinyl ketone (27.1 µL, 0.325 mmol), 0.62 mL of a 0.005 M MTBD/CH_3CN solution (0.003093 mmol of MTBD) to afford the title compound in 85% yield (103 mg, 0.263 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -130.73 – -135.68 (m), -160.84 (tt, *J* = 20.6, 6.3 Hz). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.01 (s, 1H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.14 (dd, *J* = 8.9, 6.4 Hz, 2H), 3.77 (s, 3H), 3.05 – 2.95 (m, 1H), 2.79 (ddd, *J* = 14.1, 8.1, 6.3 Hz, 1H), 2.62 (ddd, *J* = 17.9, 8.1, 6.0 Hz, 1H), 2.29 (ddd, *J* = 17.9, 8.5, 6.3 Hz, 1H), 2.14 (s, 3H).^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.5, 172.4, 165.8, 151.2 (ddd, *J* = 249.9, 10.0, 4.0 Hz), 139.4 (dt, *J* = 252.7, 15.3 Hz), 136.0 (td, *J* = 6.8, 4.4 Hz), 133.4, 132.4, 128.9, 127.2, 111.4 – 110.6 (m), 64.4, 54.1, 38.8, 30.1, 28.6. FT-IR (neat) cm-1 3405, 1739, 1717, 1530, 1239. HRMS (ESI) $C_{20}H_{18}F_3NO_4$ calcd. $[M+H]^+$ 394.1261 observed 394.1254.

3h methyl-2-benzamido-2-(4-chlorophenyl)-5-oxohexanoate



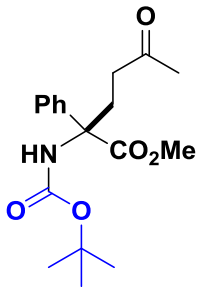
The **procedure G** was followed using substrate (100 mg, 0.329 mmol), methyl vinyl ketone (28.8 µL, 0.346 mmol), 0.66 mL of a 0.0005 M MTBD/CH_3CN solution (0.0003293 mmol of MTBD) to afford the title compound in 99% yield (122 mg, 0.326 mmol). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (s, 1H), 7.86 (d, *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.45 (dd, *J* = 21.0, 8.2 Hz, 4H), 7.30 (d, *J* = 8.7 Hz, 2H), 3.73 (s, 3H), 3.10 (ddd, *J* = 14.5, 9.2, 5.7 Hz, 1H), 3.10 (ddd, *J* = 14.5, 9.2, 5.7 Hz, 1H), 2.60 (ddd, *J* = 17.6, 8.8, 5.7 Hz, 1H), 2.28 (ddd, *J* = 17.6, 9.2, 5.9 Hz, 1H), 2.12 (s, 3H).^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.7, 173.1, 165.7, 137.9, 133.9, 133.8, 132.1, 128.8, 128.8, 127.6, 127.1, 64.8, 53.8, 38.9, 30.1, 28.3. FT-IR (neat) cm^{-1} 3315, 1737, 1702, 1525, 695. HRMS (ESI) $C_{20}H_{20}ClNO_4$ calcd. $[M+H]^+$ 374.1154 observed 374.1151.

3i methyl-2-benzamido-5-oxo-2-phenylhexanoate



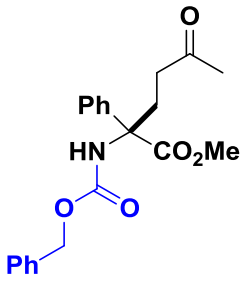
The **procedure G** was followed using substrate (25 mg, 0.093 mmol), methyl vinyl ketone (8.1 µL, 0.097 mmol), 0.19 mL of a 0.0005 M MTBD/CH_3CN solution (0.0000928 mmol of MTBD) to afford the title compound in 94% yield (30 mg, 0.087 mmol). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.81 (m, 3H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.50 – 7.42 (m, 4H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 3.72 (s, 3H), 3.18 (ddd, *J* = 14.9, 9.7, 5.5 Hz, 1H), 2.92 (ddd, *J* = 14.5, 9.4, 5.7 Hz, 1H), 2.60 (ddd, *J* = 17.4, 9.3, 5.5 Hz, 1H), 2.27 (ddd, *J* = 17.4, 9.7, 5.7 Hz, 1H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.9, 173.5, 165.7, 139.2, 134.2, 132.0, 128.8, 128.8, 128.1, 127.2, 126.1, 65.3, 53.7, 39.1, 30.0, 28.2. FT-IR (neat) cm^{-1} 3356, 1744, 1709, 1561. HRMS (ESI) $C_{20}H_{21}NO_4$ calcd. $[M+H]^+$ 340.1543 observed 340.1549.

4a methyl-2-((tert-butoxycarbonyl)amino)-5-oxo-2-phenylhexanoate



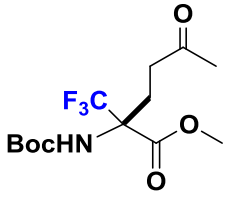
The **procedure G** was followed using substrate (150 mg, 0.565 mmol), methyl vinyl ketone (50.0 µL, 0.594 mmol), 1.13 mL of a 0.0005 M MTBD/CH_3CN solution (0.0005654 mmol of MTBD) to afford the title compound in 92% yield (174 mg, 0.520 mmol). ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.43 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 6.06 (s, 1H), 3.64 (s, 3H), 2.75 (m, 2H), 2.51 (ddd, *J* = 17.2, 9.7, 5.4 Hz, 1H), 2.26 (ddd, *J* = 17.2, 10.2, 5.6 Hz, 1H), 2.10 (s, 3H), 1.33 (s, 9H).^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 207.8, 173.4, 154.3, 140.9, 128.9, 128.3, 126.5, 80.2, 65.0, 53.7, 39.1, 30.2, 29.1, 28.5. FT-IR (neat) cm-1 3424, 2976, 1709. HRMS (ESI) $C_{18}H_{25}NO_5$ calcd. $[M+H]^+$ 336.1802 observed 336.1805.

4b methyl-2-(((benzyloxy)carbonyl)amino)-5-oxo-2-phenylhexanoate



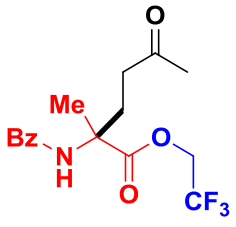
The **procedure G** was followed using substrate (25 mg, 0.084 mmol), methyl vinyl ketone (7.3 µL, 0.088 mmol), 0.17 mL of a 0.0005 M MTBD/CH_3CN solution (0.0000835 mmol of MTBD) to afford the title compound in 89% yield (27 mg, 0.074 mmol). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.40 (m, 2H), 7.37 – 7.28 (m, 8H), 6.37 (s, 1H), 5.02 (q, *J* = 12.3 Hz, 2H), 3.66 (s, 3H), 2.96 (s, 1H), 2.82 (td, *J* = 9.5, 9.0, 5.0 Hz, 1H), 2.38 (m, 2H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.5, 172.9, 154.1, 139.6, 136.5, 128.8, 128.6, 128.3, 128.2, 128.2, 125.9, 66.8, 64.7, 53.6, 38.8, 30.0, 28.1. FT-IR (neat) cm-1 3361, 3060, 3030, 1740, 1716. HRMS (ESI) $C_{21}H_{23}NO_5$ calcd. $[M+Na]^+$ 392.1468 observed 392.1462.

4d methyl-2-((tert-butoxycarbonyl)amino)-5-oxo-2-(trifluoromethyl)hexanoate



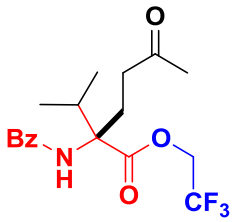
The **procedure G** was followed using substrate (100 mg, 0.389 mmol), methyl vinyl ketone (34.0 µL, 0.408 mmol), 0.78 mL of a 0.0005 M MTBD/CH_3CN solution (0.0003888 mmol of MTBD) to afford the title compound in 83% yield (106 mg, 0.323 mmol). ^{19}F NMR (376 MHz, Methylene Chloride-d_2) δ -74.70. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 5.61 (s, 1H), 3.80 (s, 3H), 2.72 – 2.52 (m, 2H), 2.49 – 2.38 (m, 1H), 2.31 (ddd, *J* = 14.9, 8.7, 6.2 Hz, 1H), 2.12 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 207.2, 167.6, 153.9, 124.9 (q, *J* = 287.5 Hz), 81.3, 65.2 (q, *J* = 28.1 Hz), 54.1, 37.9, 30.2, 28.4, 24.8. FT-IR (neat) cm-1 3425, 1740, 1723, 1537. HRMS (ESI) $C_{13}H_{20}F_3NO_5$calcd. $[M+H]^+$ 328.1366 observed 328.1366.

5b 2,2,2-trifluoroethyl-2-benzamido-2-methyl-5-oxohexanoate



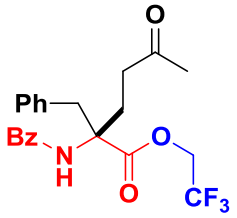
The **procedure H** was followed using substrate (40 mg, 0.145 mmol), methyl vinyl ketone (12.7 µL, 0.153 mmol), 0.290 mL of CH_2Cl_2, and MTBD (12.7 µL, 0.153 mmol, 20 mol %) to afford the title compound in 72% yield (36 mg, 0.100 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -73.69 (t, *J* = 8.4 Hz). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 7.1 Hz, 2H), 7.60 (s, 1H), 7.51 (d, *J* = 6.0 Hz, 1H), 7.45 (t, *J* = 7.3 Hz, 2H), 4.81 – 4.29 (m, 2H), 2.69 (qdd, *J* = 18.9, 7.6, 5.2 Hz, 2H), 2.36 (ddd, *J* = 14.8, 7.8, 5.2 Hz, 1H), 2.19 (s, 3H), 2.18 – 2.11 (m, 1H), 1.71 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.8, 172.2, 166.8, 133.8, 131.9, 128.8, 127.2, 123.0 (q, *J* = 277.4, 277.3 Hz), 61.2 (q, *J* = 36.6 Hz), 59.3, 38.7, 31.5, 30.1, 23.2. FT-IR (neat) cm-1 3445, 1733, 1718, 1598. HRMS (ESI) $C_{16}H_{18}F_3NO_4$ calcd. $[M+H]^+$ 346.1261 observed 346.1254.

5c 2,2,2-trifluoroethyl-2-benzamido-2-isopropyl-5-oxohexanoate



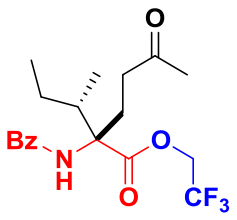
The **procedure H** was followed using substrate (150 mg, 0.495mmol), methyl vinyl ketone (43.3 µL, 0.519 mmol), 1.00 mL of CH_2Cl_2, and MTBD (21.3 µL, 0.148 mmol,30 mol %) to afford the title compound in 76% yield (140 mg, 0.376mmol). ^{19}F NMR (376 MHz, Methylene Chloride-d_2) δ -73.76 (t, J = 8.5 Hz). ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.76 (d, J = 7.2 Hz, 2H), 7.53 (t, J = 6.7 Hz, 1H), 7.45 (t, J = 7.4 Hz, 2H), 6.97 (s, 1H), 4.60 (qq, J = 8.6, 4.2 Hz, 2H), 2.79 – 2.58 (m, 2H), 2.57 – 2.45 (m, 1H), 2.45 – 2.27 (m, 2H), 2.05 (s, 3H), 1.07 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 208.2, 172.2, 166.8, 135.2, 132.2, 129.2, 127.4, 120.8 (q, J =277.3, 277.3 Hz), 67.4, 61.6 (q, J = 36.7 Hz), 39.2, 34.4, 30.2, 26.9, 18.2, 17.8. FT-IR (neat) cm-1 3423, 1741, 1720, 1560. HRMS (ESI) $C_{18}H_{22}F_3NO_4$ calcd. $[M+H]^+$ 374.1574 observed 374.1581.

5d 2,2,2-trifluoroethyl-2-benzamido-2-benzyl-5-oxohexanoate



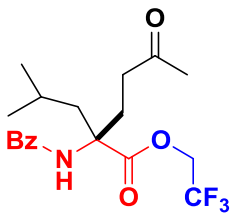
The **procedure H** was followed using substrate (120 mg, 0.342 mmol), methyl vinyl ketone (30.0 µL, 0.359 mmol), 1.00 mL of CH_2Cl_2, and MTBD (9.8 µL, 0.0684 mmol,20 mol %) to afford the title compound in 76% yield (115 mg, 0.273 mmol). ^{19}F NMR (376 MHz, Chloroform-d) δ -73.27 (t, J = 8.5 Hz). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.82 (d, J = 7.0 Hz, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.5 Hz, 2H), 7.34 – 7.29 (m, 3H), 7.17 – 7.13 (m, 2H), 7.12 (s, 1H), 4.68 (q, J = 8.4 Hz, 2H), 3.77 (d, J = 13.8 Hz, 1H), 3.58 (d, J = 13.8 Hz, 1H), 2.86 (dt, J = 14.2, 7.0 Hz, 1H), 2.64 (m, 2H), 2.36 (dt, J = 14.4, 6.7 Hz, 1H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 208.2, 171.9, 167.0, 135.7, 134.3, 132.0, 130.2, 128.9, 128.5, 127.3, 127.1, 122.9 (q, J =277.2, 277.3 Hz), 64.5, 61.7 (q, J = 36.8 Hz), 40.2, 38.5, 29.9, 29.6. FT-IR (neat) cm-1 3451, 1743, 1725, 1527. HRMS (ESI) $C_{22}H_{22}F_3NO_4$ calcd. $[M+H]^+$ 422.1574 observed 422.1570.

5e 2,2,2-trifluoroethyl-2-benzamido-2-isobutyl-5-oxohexanoate



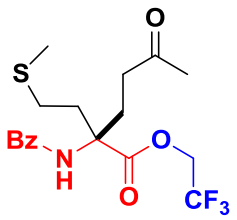
The **procedure H** was followed using substrate (100 mg, 0.315 mmol), methyl vinyl ketone (27.6 µL, 0.313 mmol), 0.600 mL of CH_2Cl_2, and MTBD (10.0 µL, 0.0894 mmol, 20 mol %) to afford the title compound (d.r. 1.5:1) in 52% yield (63 mg, 0.164 mmol). ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.68 (dt, J = 6.9, 1.3 Hz, 4H), 7.50 – 7.42 (m, 2H), 7.44 – 7.34 (m, 5H), 7.33 – 7.27 (m, 1H), 6.91 (s, 1H), 6.85 (s, 1H), 4.51 (qd, J = 8.5, 1.9 Hz, 4H), 2.77 – 2.61 (m, 3H), 2.57 – 2.37 (m, 3H), 2.37 – 2.15 (m, 6H), 1.98 (s, 6H), 0.98 (d, J = 6.9 Hz, 3H), 0.94 – 0.67 (m, 12H). ^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 208.2, 208.2, 172.4, 172.3, 166.7, 166.6, 135.2, 132.2, 129.5, 129.5, 129.2, 129.1, 127.4, 126.6 (d, J = 10.3 Hz), 125.7 (d, J = 162.6 Hz), 67.6, 67.4, 61.6 (qd, J = 36.8, 1.4 Hz, two carb ons), 46.8, 41.7, 41.3, 40.4, 39.3, 39.2, 30.2, 26.99, ,26.95, 26.3, 25.1, 24.7, 14.3, 13.9, 13.0. HRMS (ESI) $C_{19}H_{24}F_3NO_4$ calcd. $[M+H]^+$ 388.1730 observed 388.1722.

5f 2,2,2-trifluoroethyl-2-benzamido-2-isobutyl-5-oxohexanoate



The **procedure H** was followed using substrate (150 mg, 0..473 mmol), methyl vinyl ketone (41.4 µL, 0.496 mmol), 1.00 mL of CH_2Cl_2, and MTBD (27.2 µL, 0.189 mmol,20 mol %) to afford the title compound in 68% yield (125 mg, 0.321 mmol). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -73.27 (t, *J* = 8.5 Hz). ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.77 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.14 (s, 1H), 4.58 (q, *J* = 8.4 Hz, 2H), 2.74 (ddd, *J* = 14.5, 8.7, 6.0 Hz, 1H), 2.53 – 2.39 (m, 2H), 2.31 (ddd, *J* = 17.8, 8.7, 6.1 Hz, 1H), 2.17 (ddd, *J* = 14.5, 8.5, 6.1 Hz, 1H), 2.05 (s, 3H), 1.93 (dd, *J* = 14.4, 6.9 Hz, 1H), 1.72 – 1.55 (m, 1H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 208.0, 173.8, 166.6, 135.1, 132.2, 129.2, 127.4, 123.5(q, *J* =277.2, 277.3 Hz), 63.9, 61.9 (q, *J* = 36.8 Hz), 43.7, 38.6, 30.4, 30.2, 25.3, 24.1, 23.4. HRMS (ESI) $C_{19}H_{24}F_3NO_4$ calcd. $[M+H]^+$ 388.1730 observed 388.1738.

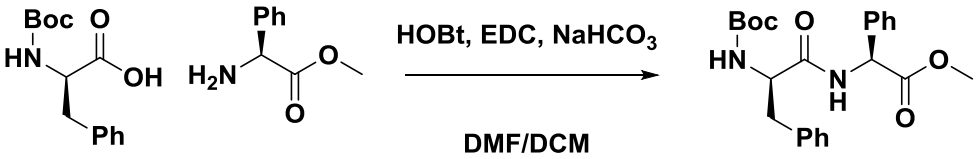
5g 2,2,2-trifluoroethyl-2-benzamido-2-(2-(methylthio)ethyl)-5-oxohexanoate



The **procedure H** was followed using substrate (100 mg, 0.298 mmol), methyl vinyl ketone (26.1 µL, 0.313 mmol), 0.600 mL of CH_2Cl_2, and MTBD (12.8 µL, 0.0894 mmol,30 mol %) to afford the title compound in 79% yield (96 mg, 0.235 mmol). ^{19}F NMR (376 MHz, Methylene Chloride-d_2) δ -73.85 (t, *J* = 8.5 Hz). ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.71 (d, *J* = 7.3 Hz, 2H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.24 (s, 1H), 4.52 (q, *J* = 8.4 Hz, 2H), 2.59 (ddd, *J* = 14.5, 10.1, 6.9 Hz, 2H), 2.52 – 2.23 (m, 5H), 2.15 – 2.06 (m, 1H), 2.01 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 208.4, 172.6, 166.8, 134.6, 132.4, 129.2, 127.5, 123.0 (q, *J* =277.2, 277.3 Hz), 63.5, 61.9 (q, *J* = 36.7 Hz), 38.6, 34.9, 30.2, 29.8, 29.1, 15.8. FT-IR (neat) cm-1 3421, 1752, 1726, 1608. HRMS (ESI) $C_{18}H_{22}F_3NO_4S$ calcd. $[M+H]^+$ 406.1294 observed 406.1303.

-Synthesis of peptides Boc-Phe-Phg-OMe and DAPT

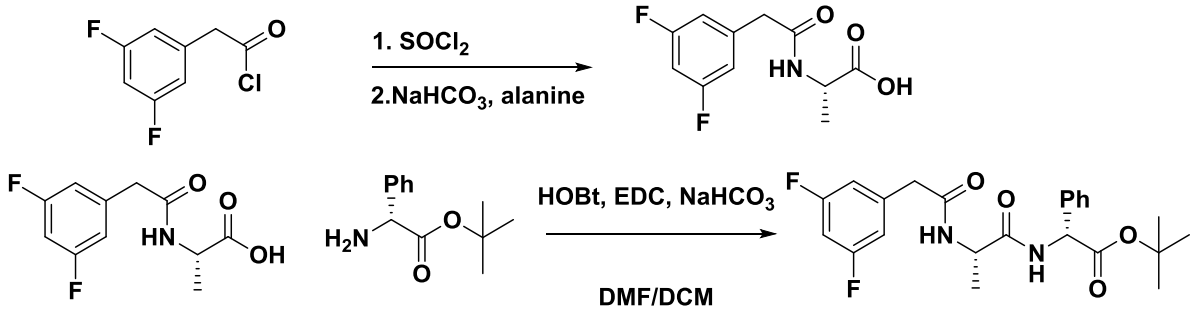
Boc-Phe-Phg-OMe (methyl 2-((R)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-2-phenylacetate)



N-Boc phenyl alanine (500 mg, 1.89 mmol), phenyl glycine methyl ester HCl (380 mg,1.89 mmol), EDC (432 mg, 2.26 mmol), HOBt (346 mg , 2.26 mmol) and $NaHCO_3$ (380 mg, 2.88 mmol) were dissolved in anhydrous DMF/DCM (9.43 mL 20/80 v/v) at 0 ºC and the reaction was stirred for 16 h at room temperature under inert atmosphere. The workup consisted of concentrating the solution, diluting with EtOAc 20 mL, and adding with an equal amount of water. The organic layer was separated and then washed with equal amount of sat. $NaHCO_3$ (x3), 1 M HCl (x2), and water. The organic layer was again separated and the solution was concentrated under vacuum. Flash column chromatography was used to purify the desired compound giving a yeild 60% (467 mg, 1.13 mmol). ^{1}H

NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.29 (m, 3H), 7.24 – 7.18 (m, 5H), 7.11 (dd, *J* = 7.3, 2.1 Hz, 2H), 6.88 – 6.71 (m, 1H), 5.50 (d, *J* = 7.1 Hz, 1H), 5.04 (s, 1H), 4.40 (s, 1H), 3.70 (s, 3H), 3.04 (d, *J* = 7.0 Hz, 2H), 1.40 (s, 9H).

DAPT, N-[N-(3,5-Difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester

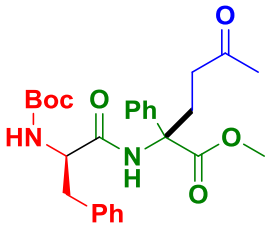


Synthesis of (3,5-difluorophenyl)acetyl chloride- 2-(3,5-difluorophenyl)acetic acid (3.00 g, 17.4 mmol) was added to 35 mL of DCM and 6 mL of $SOCl_2$ and left to react until by ^{19}F the starting material was consumed. Then the solution was concentrated and used without further purification.[17] Synthesis of (2-(3,5-difluorophenyl)acetyl)-L-alanine-2-(3,5-difluorophenyl)acetyl chloride (1.49 g, 16.8 mmol) was added alternately in 4 portions over 30 minutes to a solution of alanine (3.18 g, 16.8 mmol) in 20 mL of a 10 % $NaHCO_3$. After the addition was complete the reaction was left to react for 2 h. After 2 h, the reaction was quenched by the dropwise addition of concentrated aqueous hydrochloric acid until **pH 1,** which resulted in the formation of a precipitate. The solid was isolated by filtration and then trituration from DCM/Hexanes. The resulting crystals were filtered and air dried to give the desired acid in 62% (2.5 g, 10.3 mmol). Synthesis of DAPT, N-[N-(3,5-Difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester- 2-(3,5-difluorophenyl)acetyl)-L-alanine (300 mg, 1.23 mmol) from the above procedure, phenyl glycine tert-butyl ester HCl (331 mg,1.36 mmol), EDC (259 mg, 1.36 mmol), HOBt (208 mg , 1.36 mmol) and $NaHCO_3$ (155 mg, 1.85 mmol) were dissolved in anhydrous DMF/DCM (9.43 mL 20/80 v/v) at 0 ^oC and the reaction was stirred for 16 hr at room temperature under inert atmosphere. The workup consisted of concentrating solution, diluting with EtOAc 20 mL, and an equal amount of water. The organic layer was separated and washed with equal amount of sat. $NaHCO_3$ (x3), 1 M HCl (x2), and water. The organic layer was again separated and the solution was concentrated under vacuum. Flash column chromatography was used to purify the desired compound at 79% (421 mg, 0.973 mmol).Characterization data matched that was seen in literature.[17]

-Late stage functionliaztion of peptides Boc-Phe-Phg-OMe and DAPT

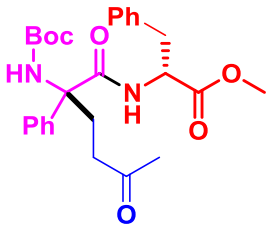
General Procedure A: Under an dry inert atmosphere the peptide (**1 equiv**), methylvinyl ketone **(1.05 equiv),** MeCN **(0.5 M)** was added to a small test tube. Then MTBD **(0.10-0.50 equiv)** was added to mixture and stirred vigorously. The reaction was monitored by ^{19}F NMR/^{1}H NMR until the starting material was consumed. The organic solution was then dried with $MgSO_4$ and concentrated giving crude product. The crude product was purified further by column chromatography.

6a Boc-Phe-Phg-OMe, methyl-2-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-5-oxo-2-phenylhexanoate



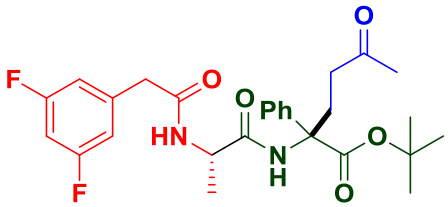
The **procedure A** was followed using substrate (25 mg, 0.0601 mmol), methyl vinyl ketone (5.3 µL, 0.0640 mmol), 0.120 mL of ACN, and MTBD (0.87 µL, 0.0060608 mmol, 20 mol %) to afford the title compound in 73% yield (21 mg, 0.044 mmol). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 (s, 1H), 7.29 – 7.15 (m, 19H), 7.14 – 7.10 (m, 3H), 4.88 (dd, *J* = 16.1, 7.1 Hz, 2H), 4.32 (p, *J* = 7.5 Hz, 2H), 3.58 (s, 3H), 3.56 (s, 3H), 3.07 – 2.85 (m, 6H), 2.65 (ddd, *J* = 14.5, 10.3, 5.2 Hz, 2H), 2.32 (ddd, *J* = 16.1, 10.4, 5.1 Hz, 1H), 2.15 (ddd, *J* = 15.7, 10.2, 5.1 Hz, 1H), 2.09 – 2.04 (m, 1H), 2.02 (s, 2H), 1.99 (s, 3H), 1.94 (ddd, *J* = 16.9, 10.6, 5.3 Hz, 1H), 1.39 (s, 9H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.6, 207.6, 172.9, 172.8, 169.9, 169.7, 139.1, 138.8, 136.7, 136.6, 129.6, 129.6, 128.9, 128.7, 128.7, 128.1, 128.1, 127.1, 125.9, 65.0, 64.9, 56.2, 53.5, 53.5, 38.7, 38.5, 37.6, 37.5, 30.1, 29.9, 28.4, 27.6, 27.3. FT-IR (neat) cm-1: 3327, 3061, 1760, 1635. HRMS (ESI) $C_{27}H_{34}N_2O_6$ calcd. $[M+H]^+$ 483.2490 observed 483.2499.

6b Boc-Phg-Phe-OMe derivative, methyl 2-((tert-butoxycarbonyl)amino)-5-oxo-2-phenylhexanoyl)-D-phenylalaninate



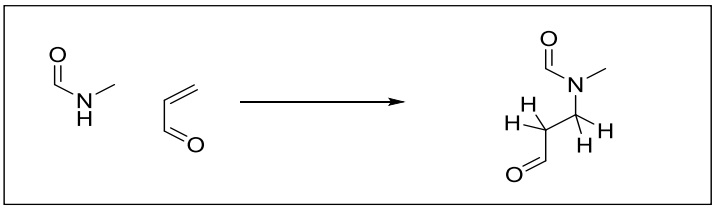
The **procedure A** was followed using substrate (135 mg, 0.328 mmol), methyl vinyl ketone (28.7 µL, 0.344 mmol), 0.655 mL of ACN, and MTBD (10.1 µL, 0.0655 mmol, 20 mol %) to afford the title compound in 33% yield (58 mg, 0.120 mmol). ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.42 – 7.27 (m, 10H), 7.21 (dq, J = 8.6, 2.9, 2.1 Hz, 2H), 7.17 – 7.12 (m, 1H), 7.08 (t, J = 7.4 Hz, 2H), 7.03 – 6.94 (m, 2H), 6.63 (s, 2H), 6.46 (s, 1H), 6.28 (s, 1H), 6.15 (s, 1H), 4.70 (ddd, J = 13.0, 7.8, 5.3 Hz, 2H), 3.85 – 3.67 (m, 1H), 3.66 (s, 3H), 3.57 (s, 2H), 3.17 – 3.01 (m, 1H), 2.89 (dd, J = 6.0, 3.5 Hz, 3H), 2.86 – 2.65 (m, 3H), 2.43 – 2.30 (m, 2H), 2.10 (s, 4H), 2.04 (s, 2H), 1.37 – 1.28 (m, 32H). ^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 208.4, 208.1, 172.3, 171.9, 171.7, 171.7, 154.4, 154.4, 142.1, 136.7, 135.9, 131.3, 129.7, 129.6, 129.4, 129.4, 129.2, 129.1, 128.3, 128.3, 127.5, 127.4, 126.4, 126.4, 80.2, 80.0, 64.7, 64.6, 52.8, 52.7, 38.8, 38.6, 38.2, 37.9, 30.4, 30.4, 30.3, 29.9, 29.9, 29.5, 28.8, 28.6, 28.6, 28.5. FT-IR (neat) cm-1: 3403, 3077, 1770, 1635. HRMS (ESI) $C_{27}H_{34}N_2O_6$ calcd. $[M+H]^+$ 483.2490 observed 483.2499.

6c DAPT deravative, tert-butyl-2-2-(2-(3,5-difluorophenyl)acetamido)propanamido)-5-oxo-2-phenylhexanoate



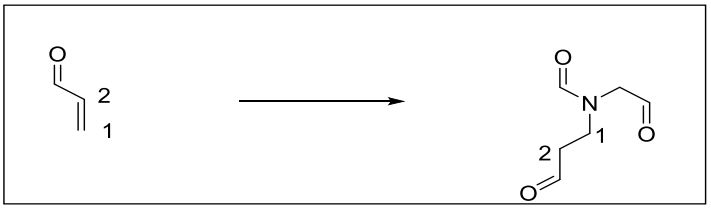
The **procedure A** was followed using substrate (100 mg, 0.231 mmol), methyl vinyl ketone (20.2 µL, 0.243 mmol), 0.120 mL of ACN, and MTBD (16.60 µL, 0.116 mmol, 50 mol %) to afford the title compound in 90% yield (105 mg, 0.208 mmol). ^{19}F NMR (376 MHz, Methylene Chloride-d_2) δ -110.39 – -110.46 (m), -110.47 – -110.53 (m). ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.52 (s, 1H), 7.46 (s, 1H), 7.40 – 7.18 (m, 9H), 6.84 (ddt, *J* = 6.7, 4.3, 2.1 Hz, 3H), 6.73 (tdd, *J* = 9.1, 5.2, 2.5 Hz, 2H), 6.34 (dd, *J* = 12.6, 7.0 Hz, 2H), 4.45 (td, *J* = 7.0, 3.6 Hz, 2H), 3.49 (s, 3H), 3.48 (s, 1H), 2.90 (dddd, *J* = 14.1, 10.8, 5.1, 3.3 Hz, 2H), 2.67 (ddd, *J* = 13.8, 10.5, 5.0 Hz, 2H), 2.43 (dddd, *J* = 17.5, 10.6, 5.1, 2.0 Hz, 2H), 2.23 – 2.11 (m, 3H), 2.08 (s, 1H), 2.06 (s, 1H), 1.32 (dd, *J* = 7.0, 4.8 Hz, 5H), 1.29 (d, *J* = 1.0 Hz, 16H). ^{13}C NMR (101 MHz, Methylene Chloride-d_2) δ 207.9, 207.7, 171.5, 171.5, 170.9, 170.9, 169.9, 169.8, 140.3, 140.3, 139.4 (td, *J* = 9.7, 5.5 Hz), 128.9, 128.1 (d, *J* = 1.3 Hz), 126.3, 113.6 – 112.1 (m), 103.0 (td, *J* = 25.3, 4.1 Hz), 83.8 (d, *J* = 3.3 Hz), 65.5 (d, *J* = 2.6 Hz), 50.1, 49.9, 43.2, 43.15, 4.99, 38.9, 30.2, 30.2, 27.9, 27.8, 27.7, 18.4 (d, *J* = 2.3 Hz). FT-IR (neat) cm-1 3431, 1502, 1254. HRMS (ESI) $C_{27}H_{32}F_2N_2O_5$ calcd. $[M+K]^+$ 541.1911 observed 541.1922.

Search 1



6224 Hits

Search 2



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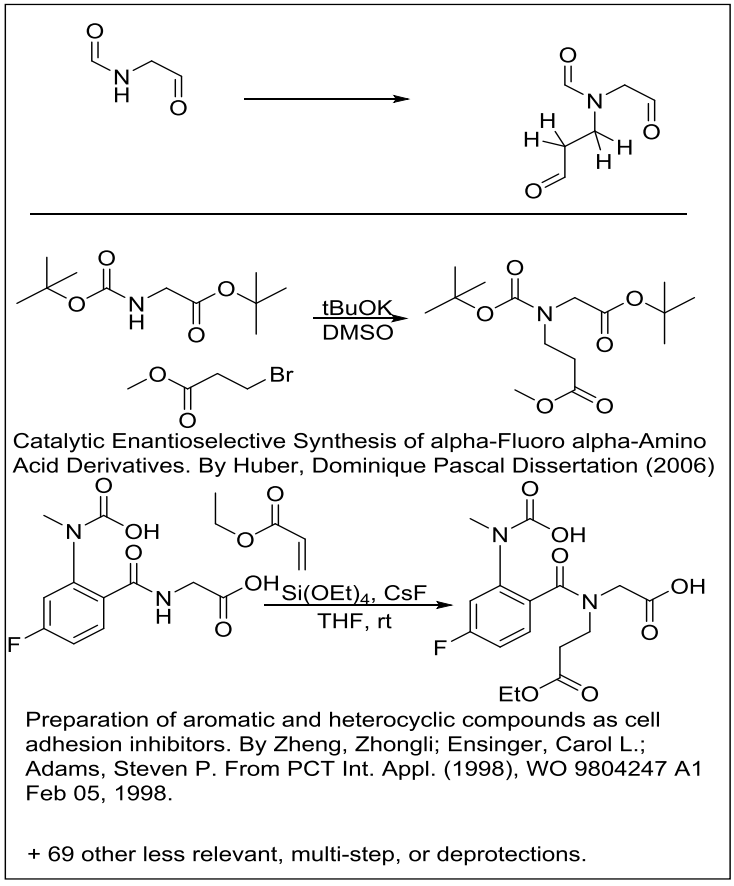


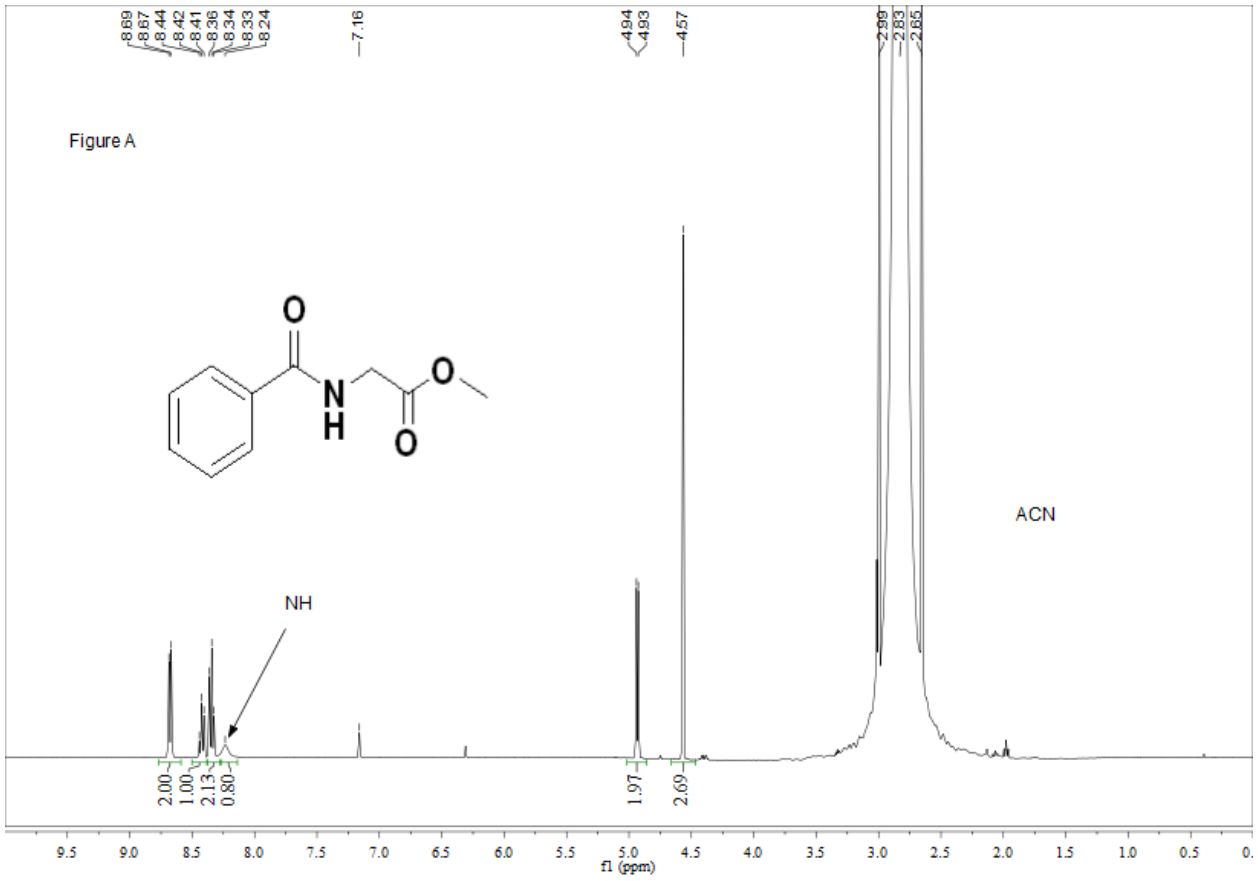
SciFinder Search

SciFinder searches were performed on the latest online version. Below are various searches (**Search 1-3**) conveying reactions of aza-michael type observed in literature. The first search (**Search 1**) clearly shows the aza-Micheal to form a tertiary nitrogen is possible. However looking the subset of products, no alpha-amino carbonyl compounds were found (**Search 2**). Moreover when starting with an alpha-amino carbonyl (**Search 3**) 71 hits were observed. Most of these examples were either irrelevant or unique multistep cases. These searches give support to the endothermic nature of N-alkylation products.

-Deuterium studies/experiments

Retro-Michael experiment

Phenyl glycine methyl ester substrate **(**10 mg, 0.0518 mmol,1 equiv) was added to a NMR tube fitted with a C_6D_6 capillary (for NMR locking purposes) and a ^{1}H NMR experiment was conducted as a baseline (**Figure A**). Then MTBD **(**7.9 mg, 0.0518 mmol, 1 equiv**)** was added to mixture and ^{1}H NMR experiment was conducted observing the N-H of the ester has been completely deprotonated (**Figure B**). Then MeOD **(**100 µL, 0.518 mmol,100 equiv) was added and the mixture was left to react for 1 h, then the solution was concentrated removing the excess MeOD. ^{1}H NMR indicated that the glycine ester nitrogen was either deutrerated, more likely bonded to MTBD-D which is indicated by the broadening of MTBD signal (**Figure C**). Next, methylvinyl ketone **(**4.3 µL, 0.0518 mmol, 1 equiv**)** was added and left to react for 6 h, and a final ^{1}HNMR was performed, which showed no incorporation of deuterium in the methylvinyl ketone nor a return of the ester's N-H (**Figure D**), indicating the lack of a transient N-alkylation event.



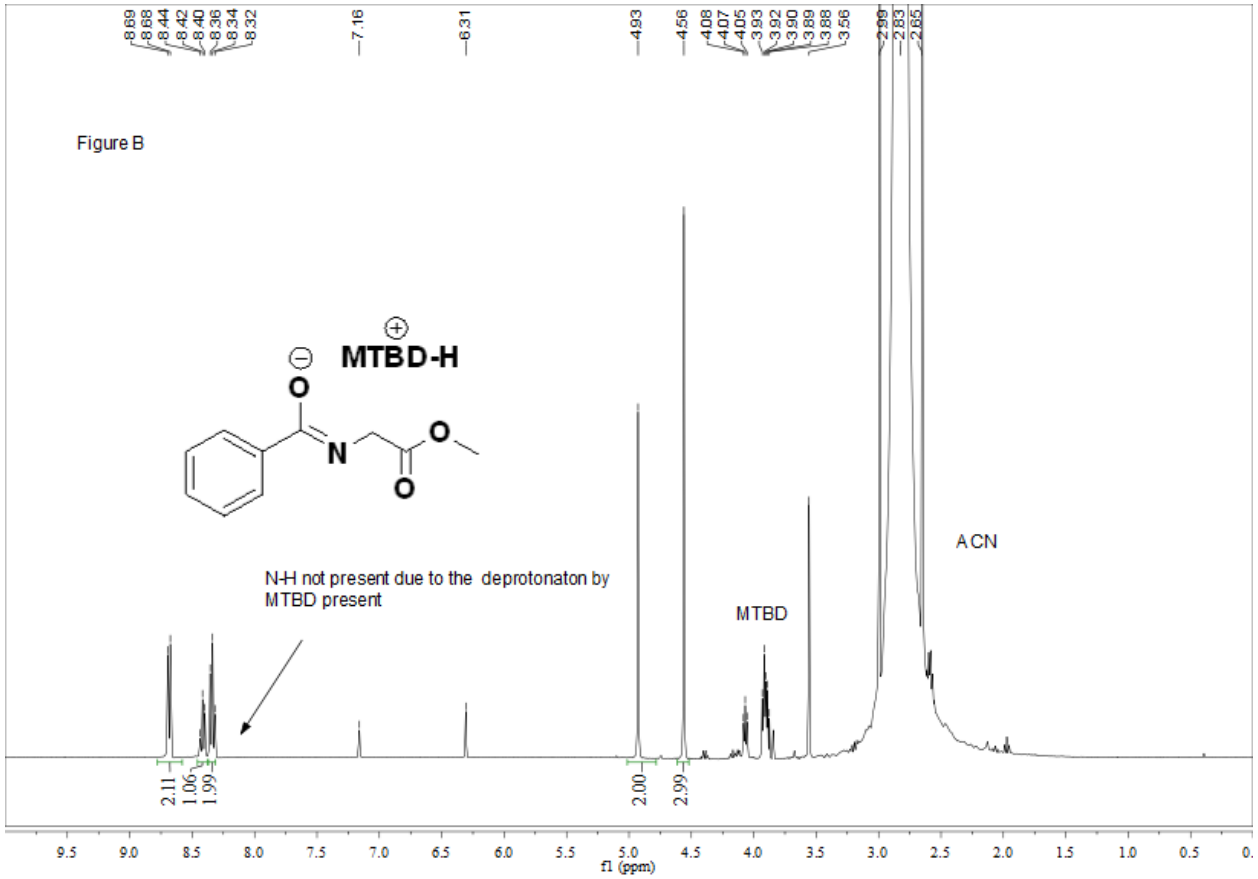


Figure B
MTBD-H
N-H not present due to the deprotonaton by MTBD present
MTBD
ACN
f1 (ppm)

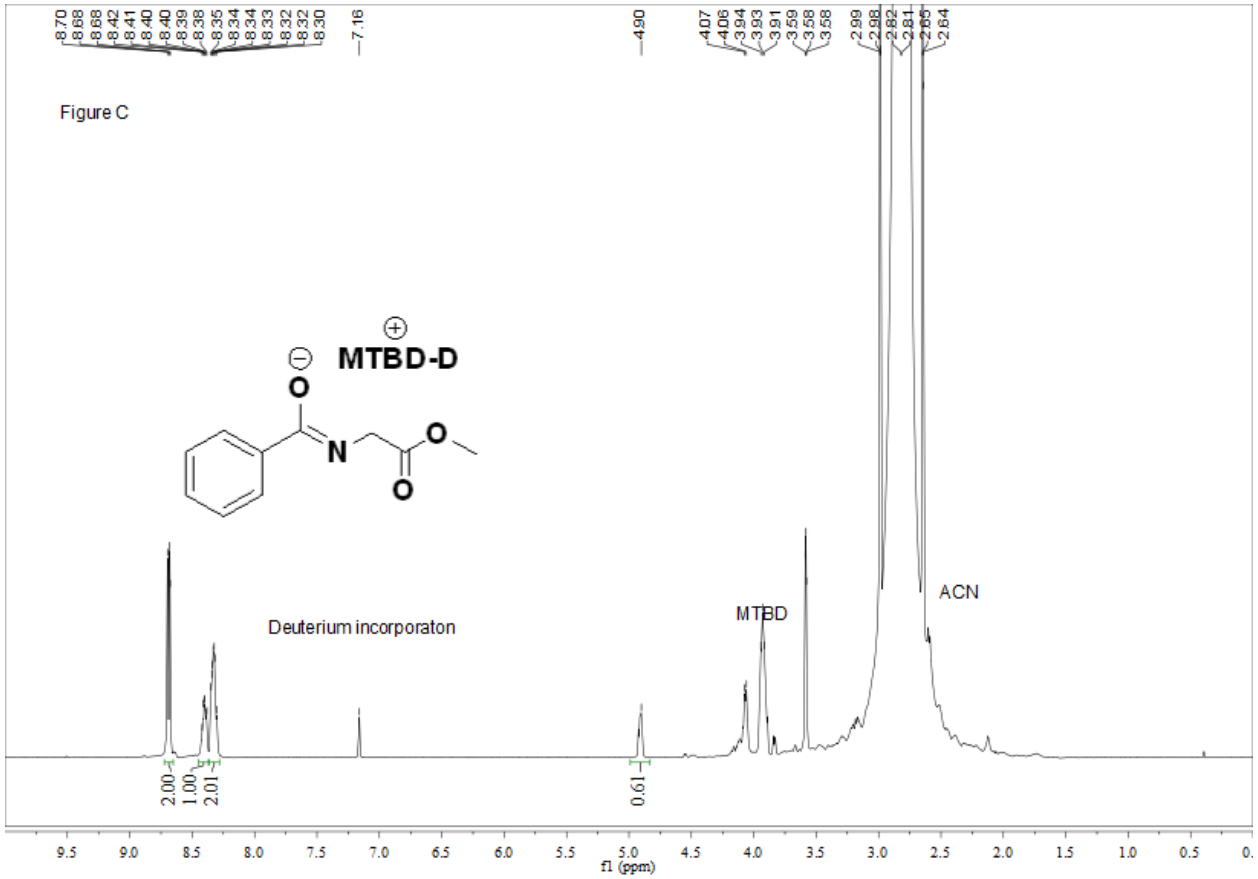
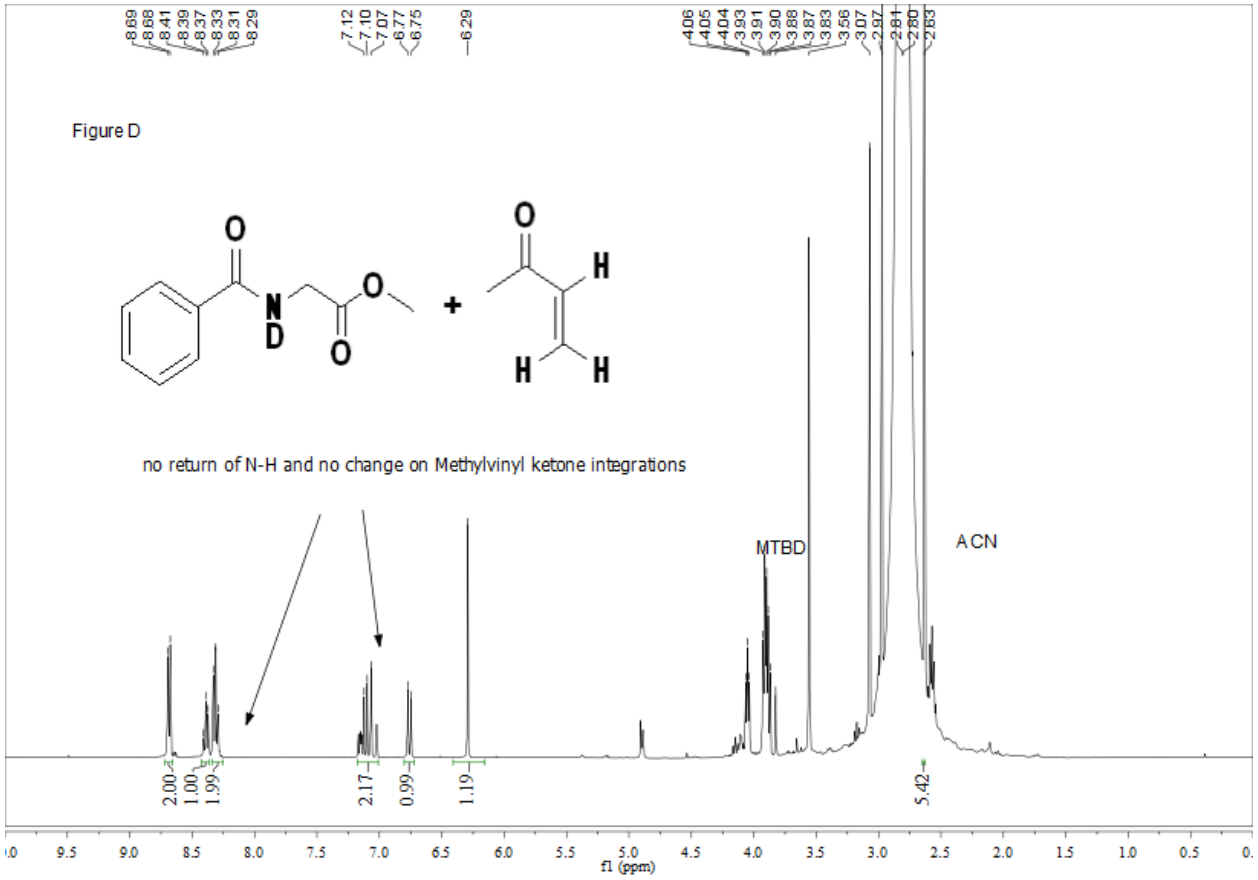
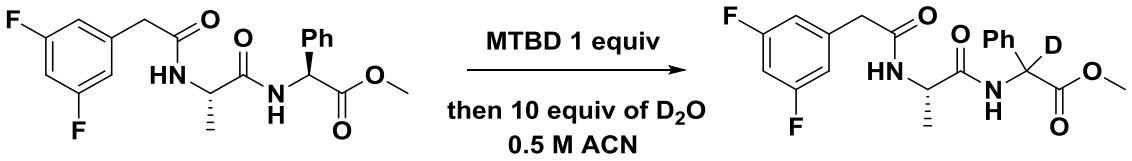


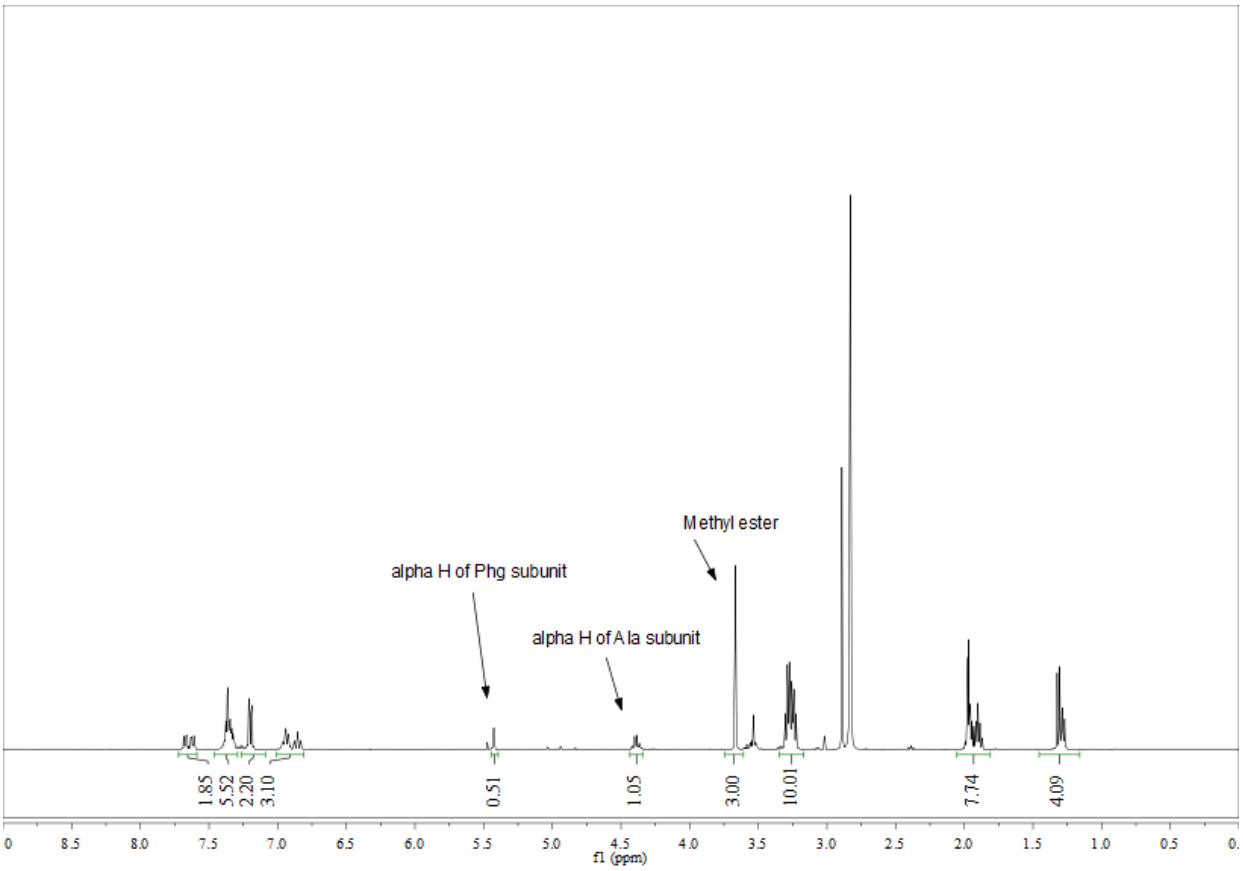
Figure C
MTBD-D
Deuterium incorporaton
MTBD
ACN
f1 (ppm)



Peptide deuterium experiment



To a dry NMR tube, MTBD (7.8 mg, 0.051 mmol) was added to a solution of the peptide (20 mg, 0.051 mmol) in acetonitrile (0.3 mL). Then D_2O (9.25 µL, 0.51 mmol) was added and the experiment was left to react for 24 h and monitored by ^1H NMR. The phenyl glycine methine integrations decreased displaying evidence of deuterium incorporation at the α-carbon of the phenyl glycine subunit. Integrations observed: **<u>0.49</u>**, 1.05, 3.00 (Phg-H, Ala-H, Phg-OMe) see the labeled spectrum below.



Failed experiments

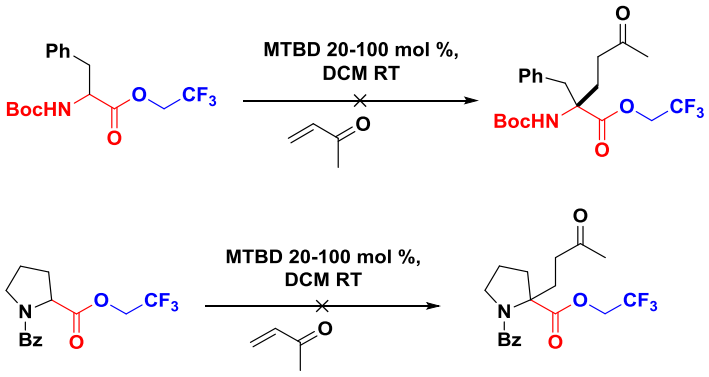
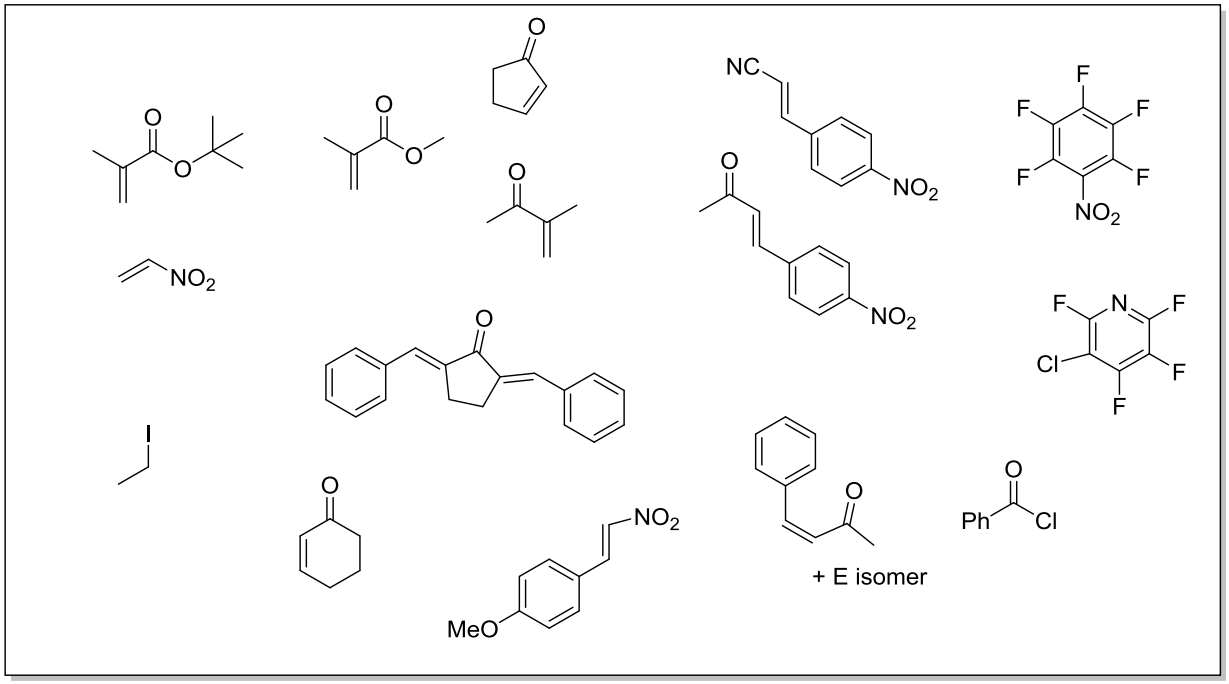


Table of failed Michael acceptors and other electrophiles.



DFT reference

M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria,
M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci,
G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian,
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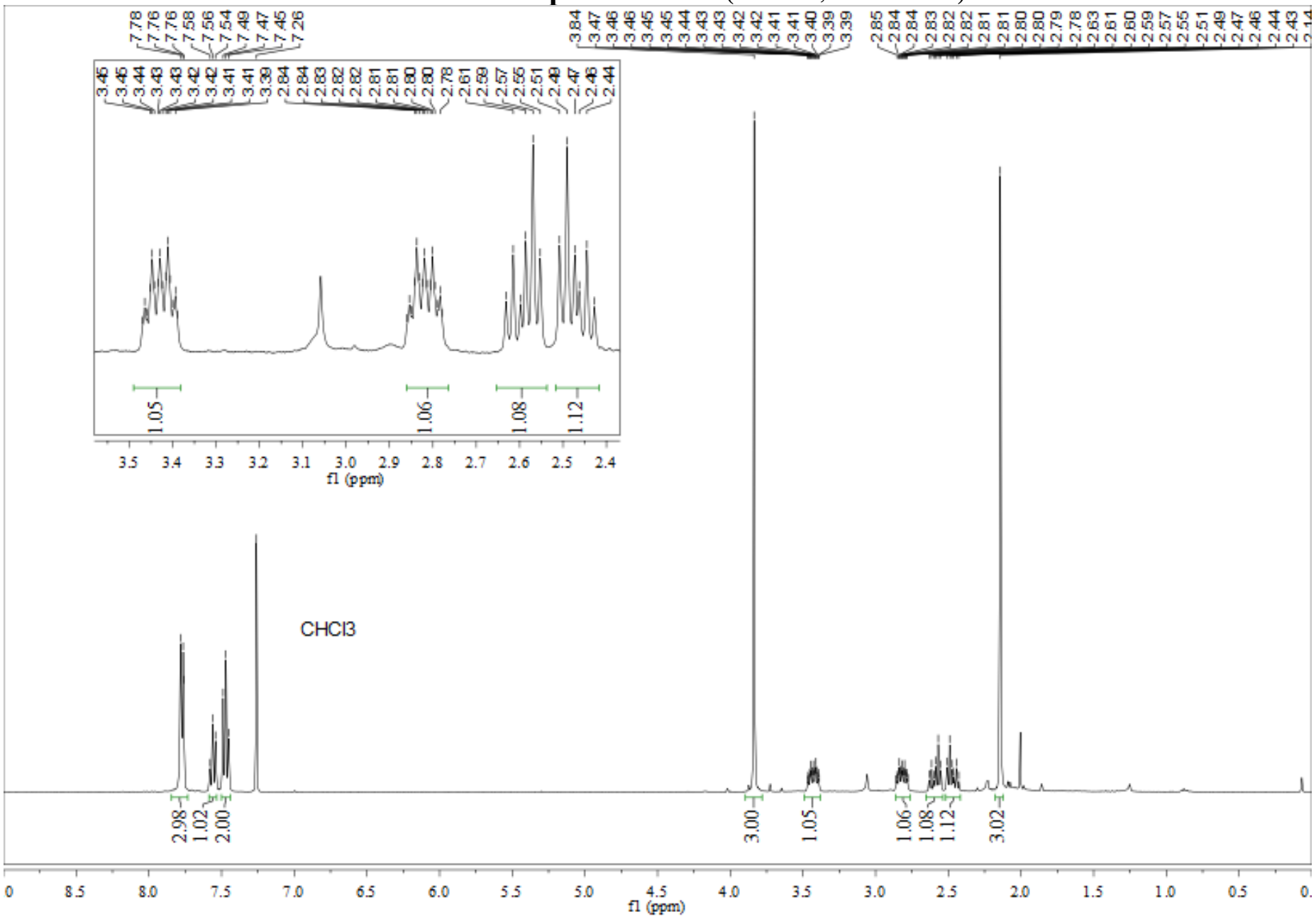
NMR spectra ^{1}H NMR (400 MHz, Chloroform-*d*) **2a**



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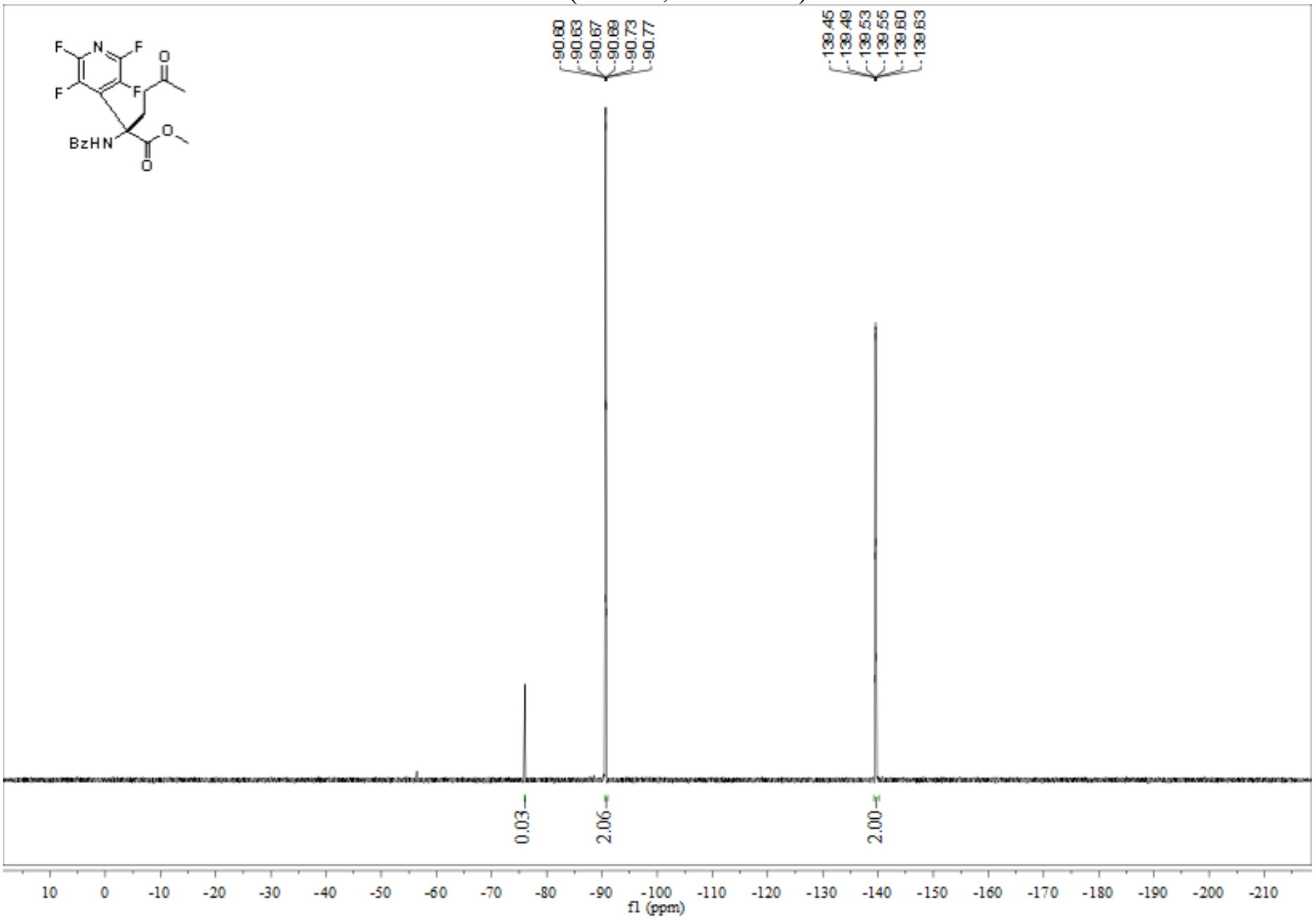

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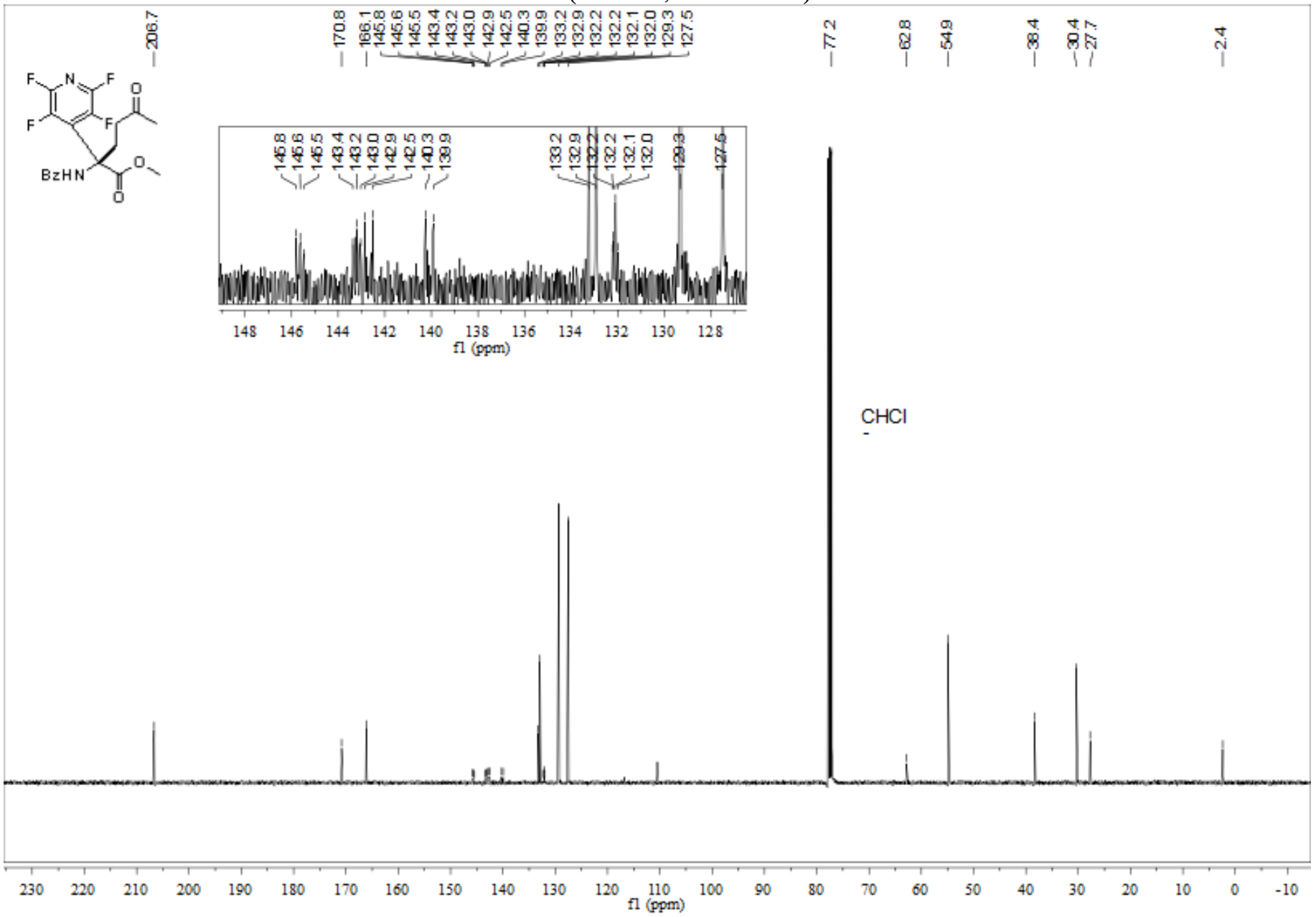

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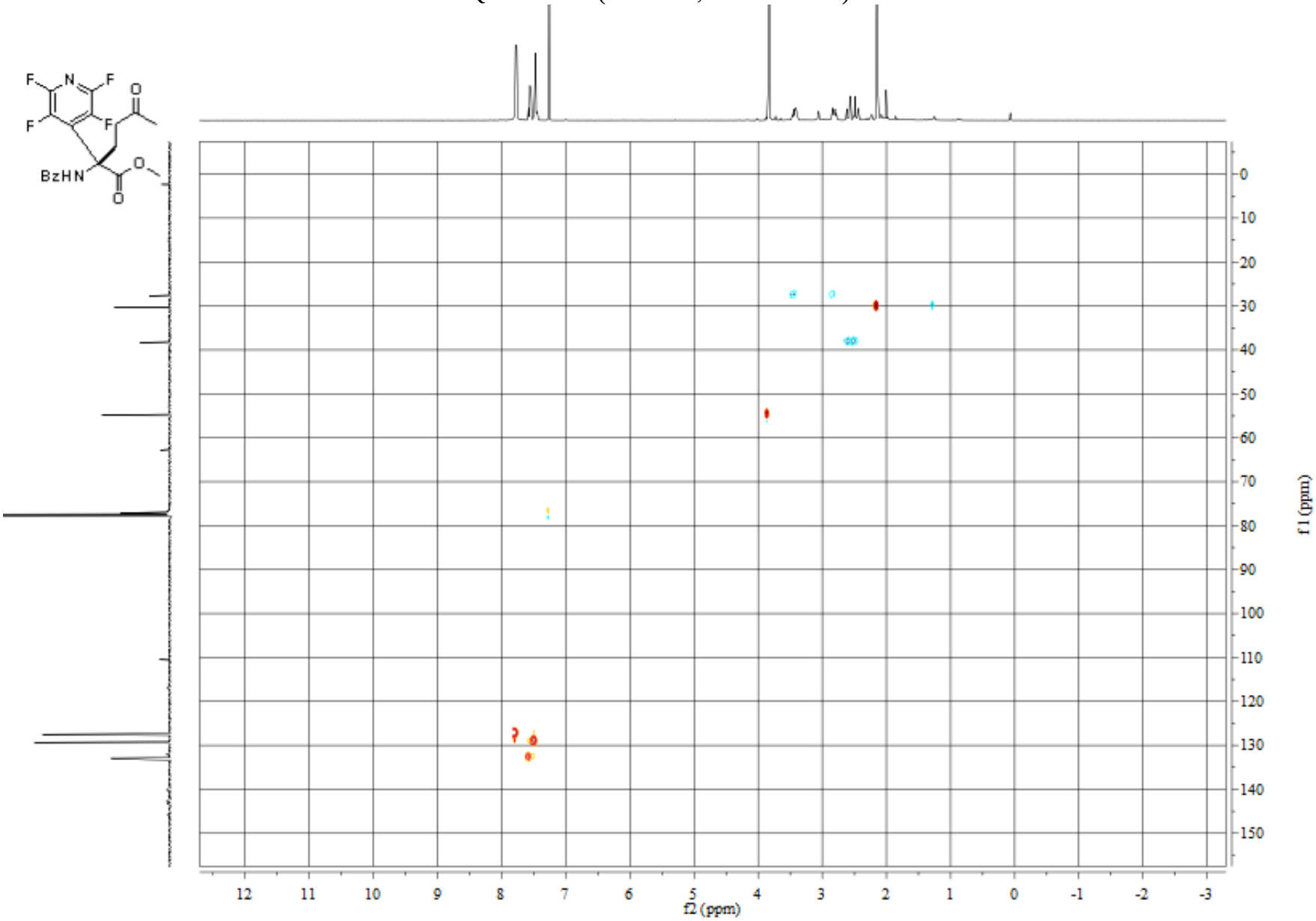

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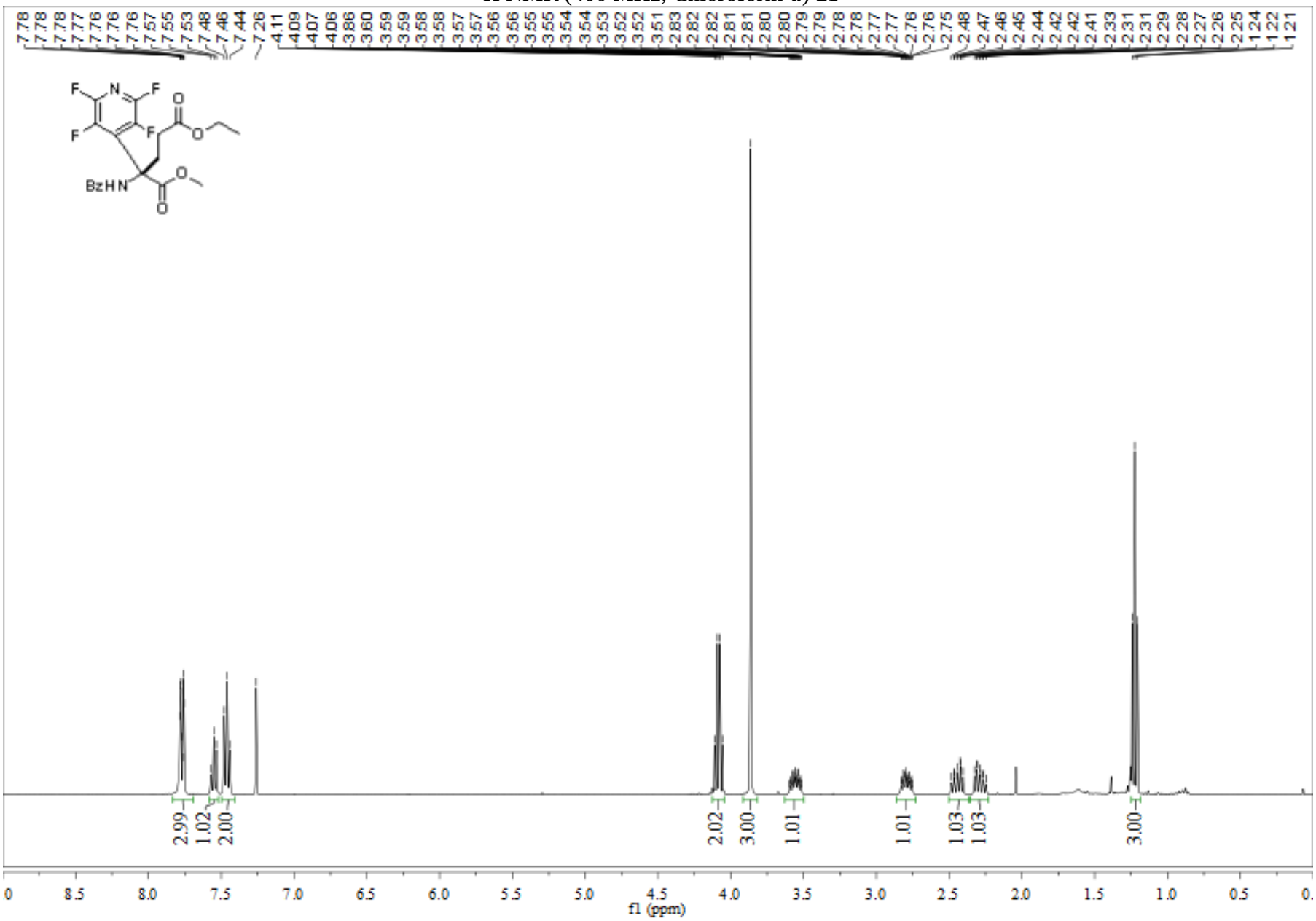

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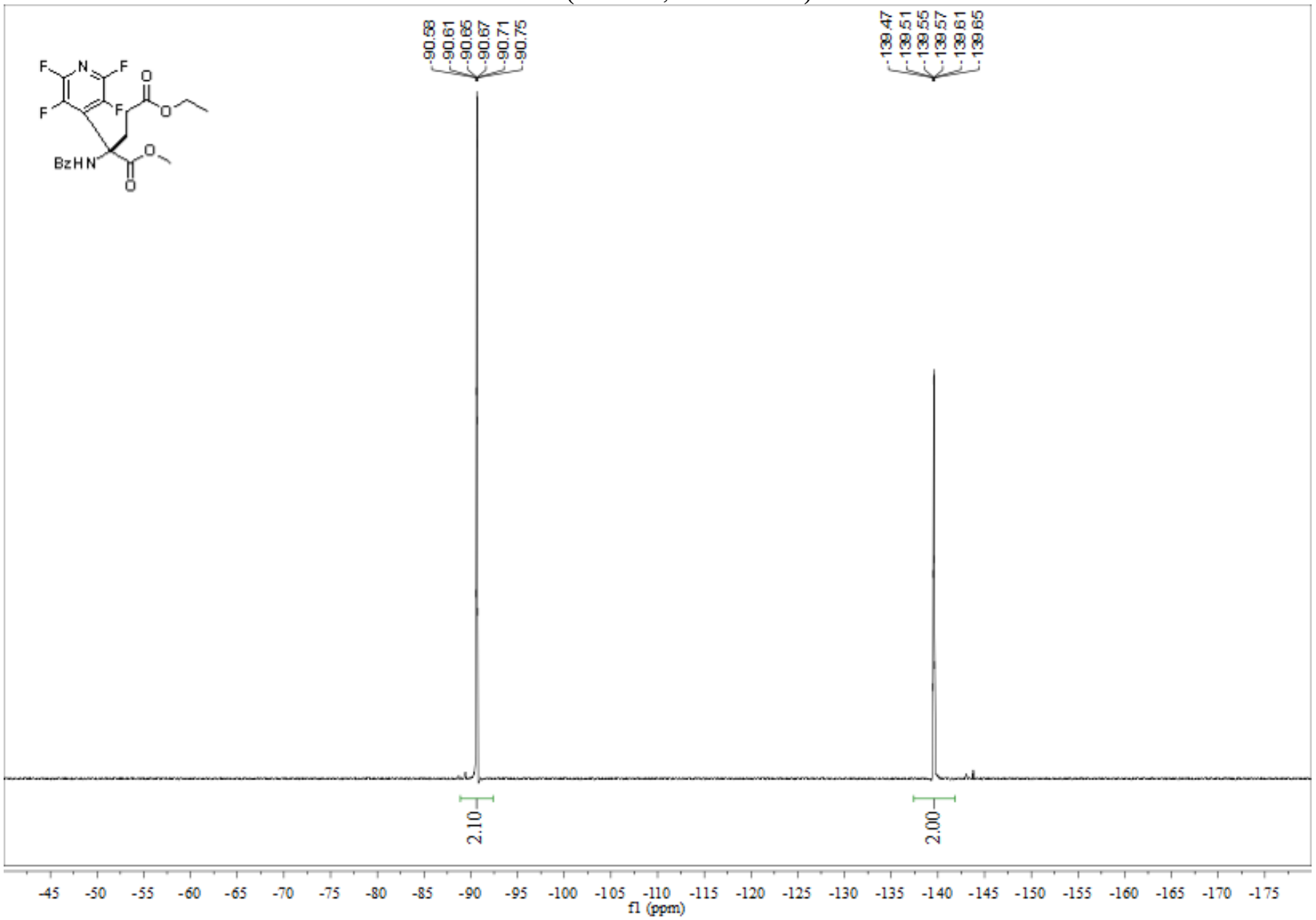

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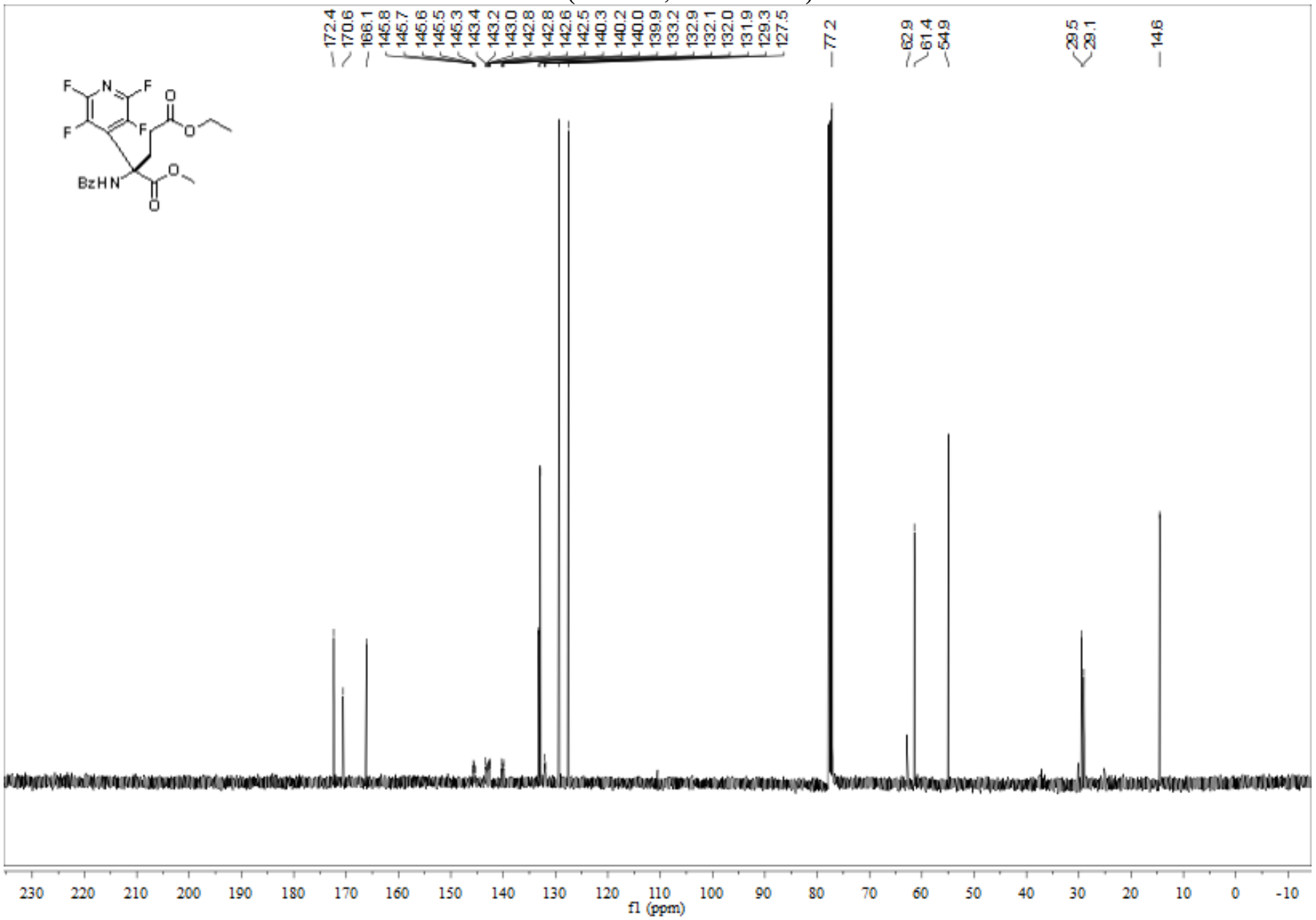

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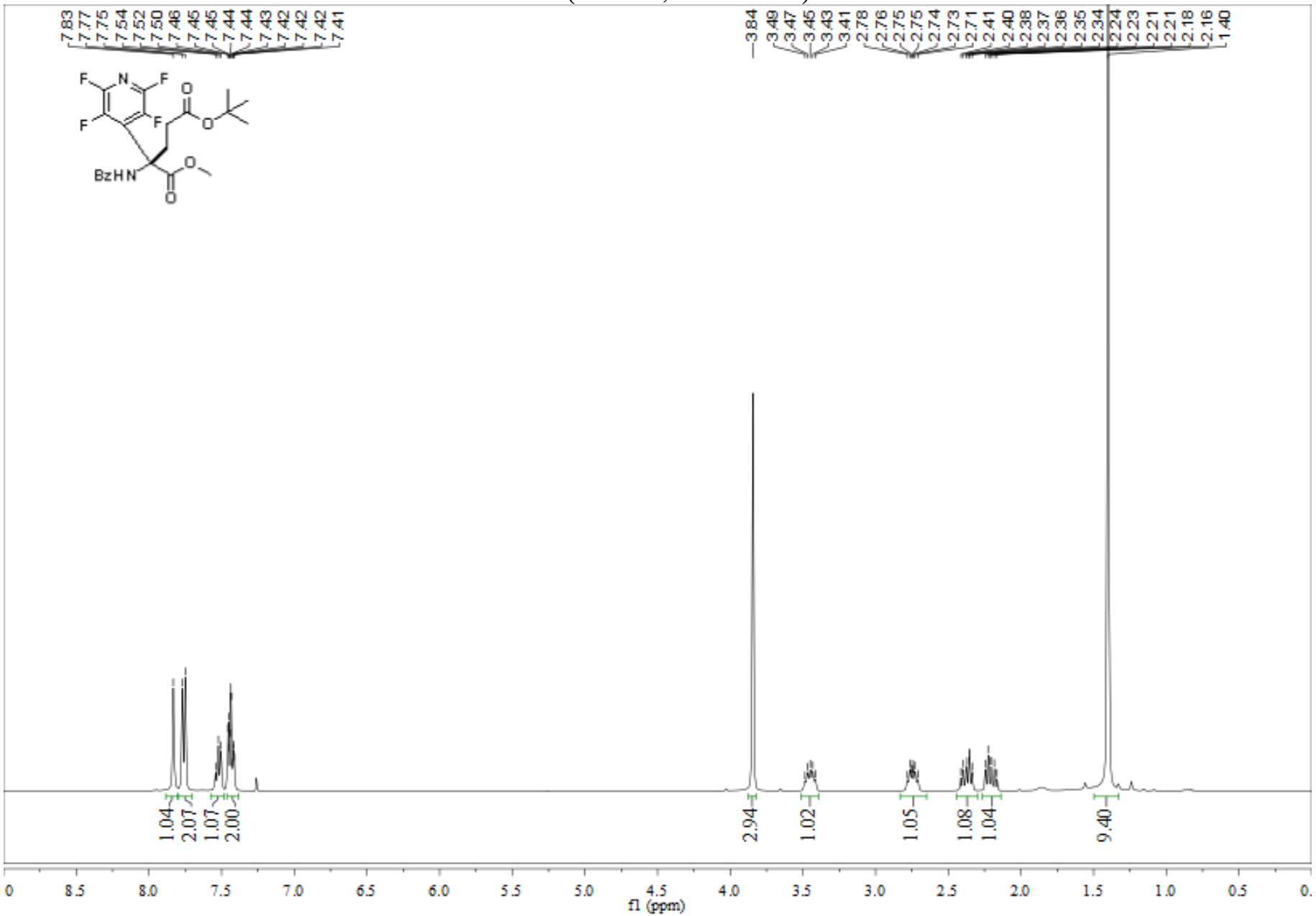

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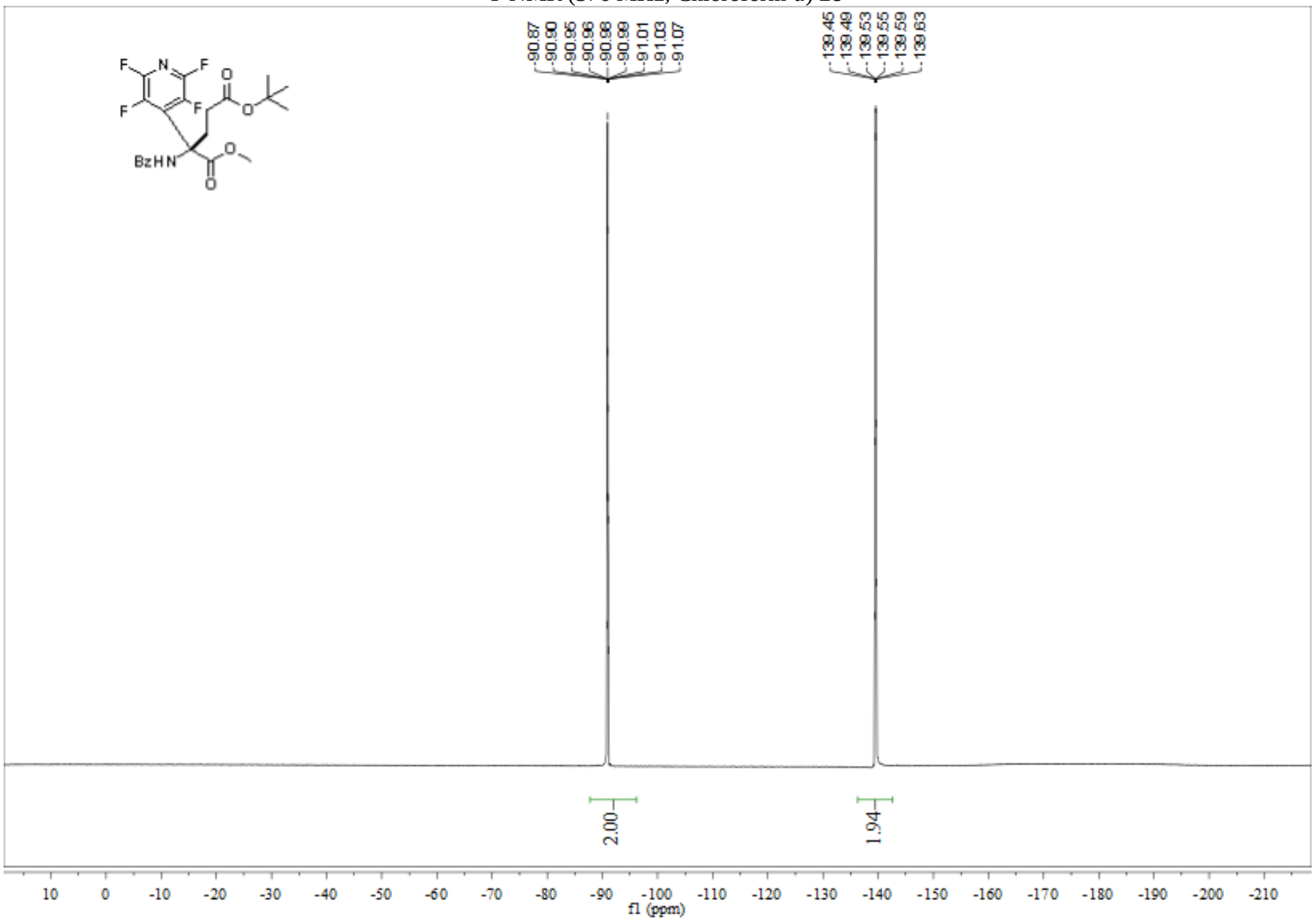

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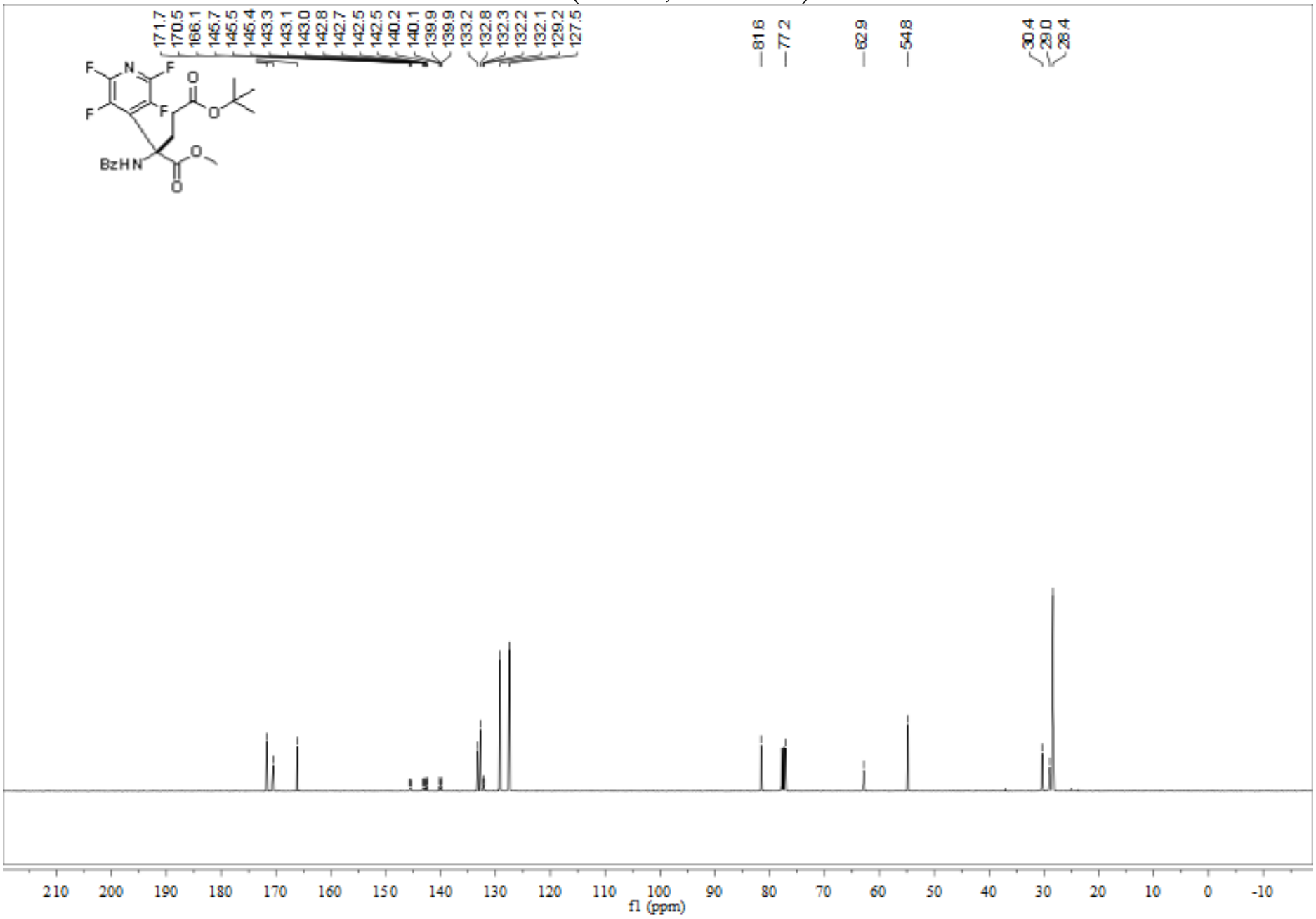

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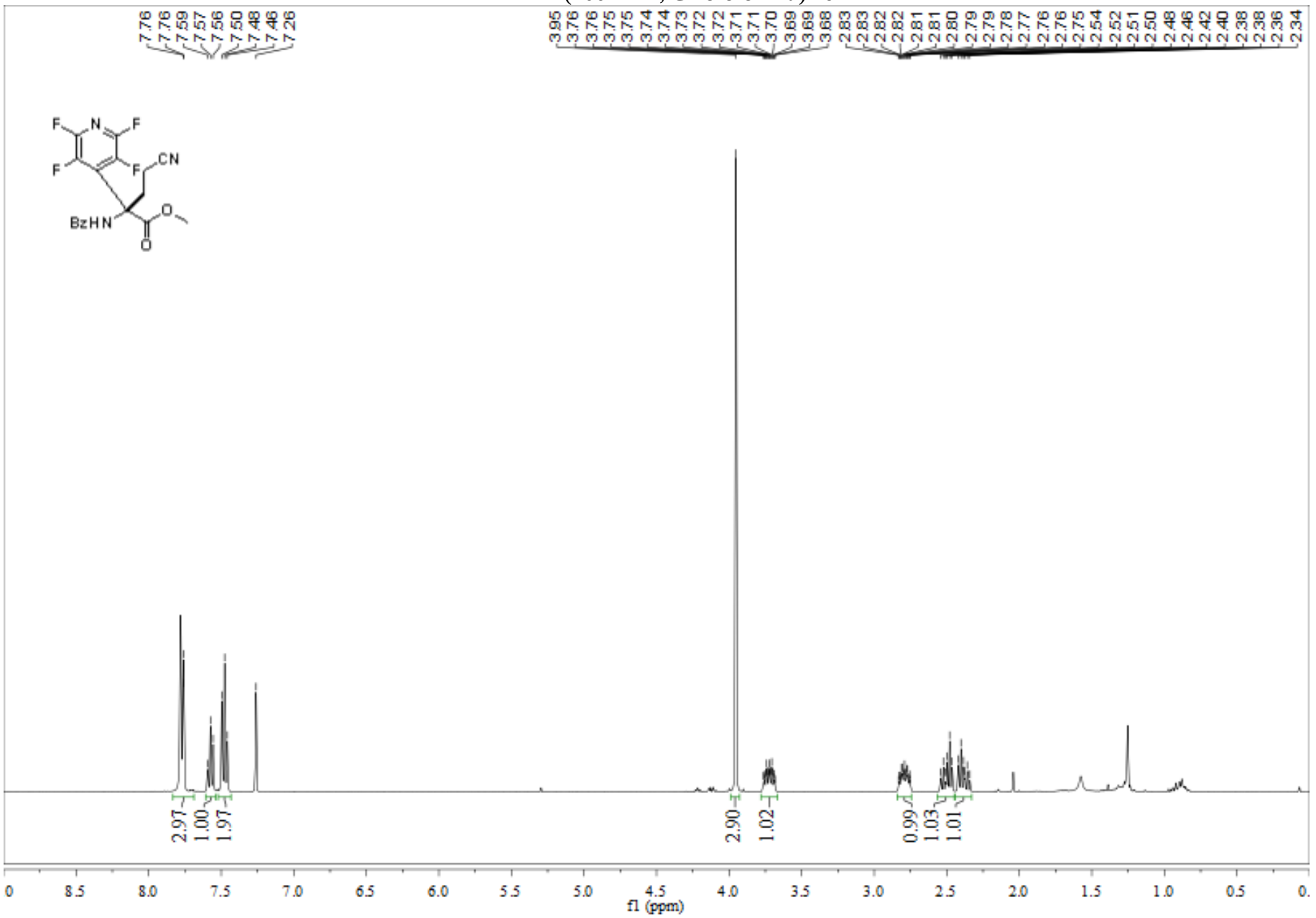

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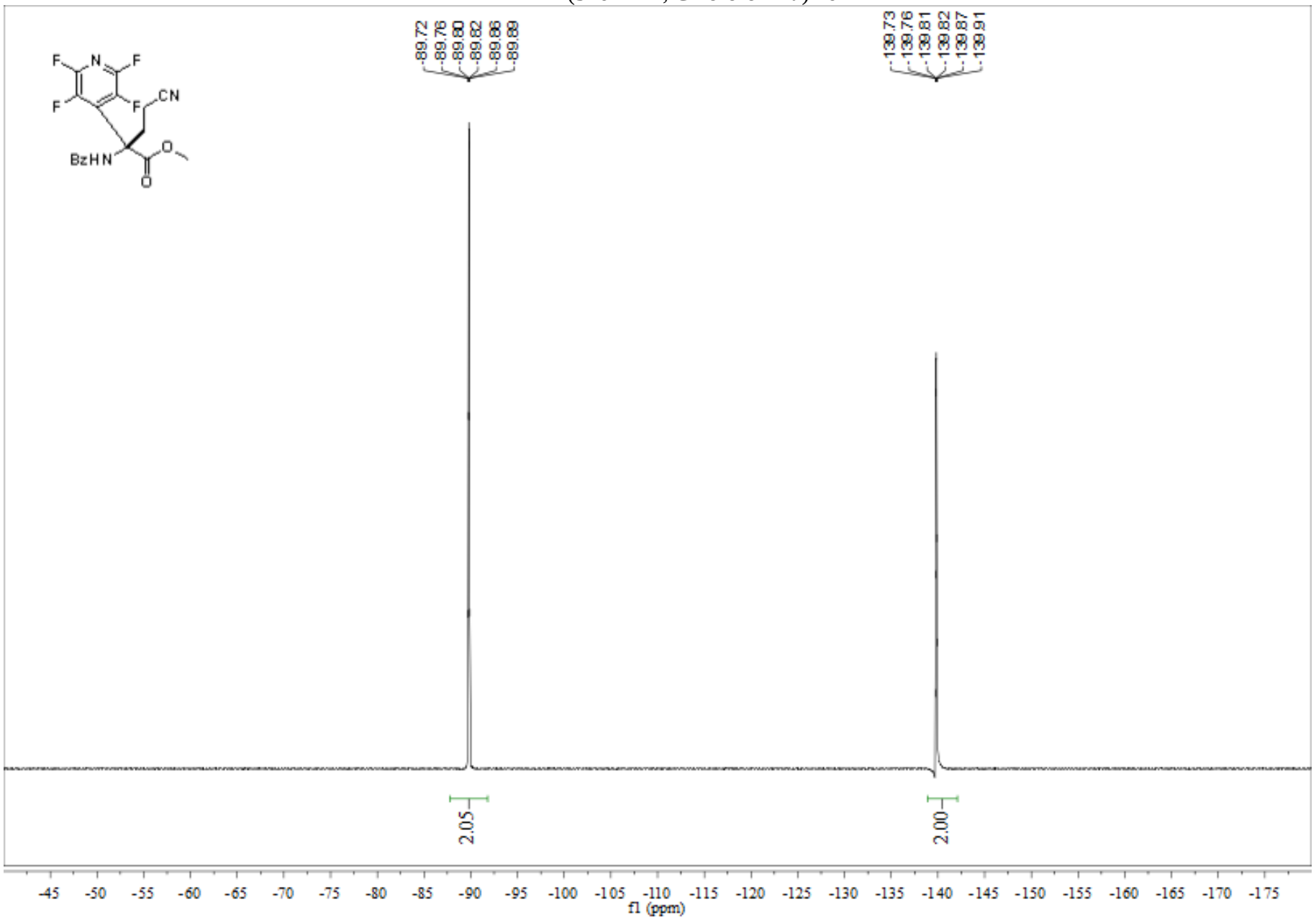

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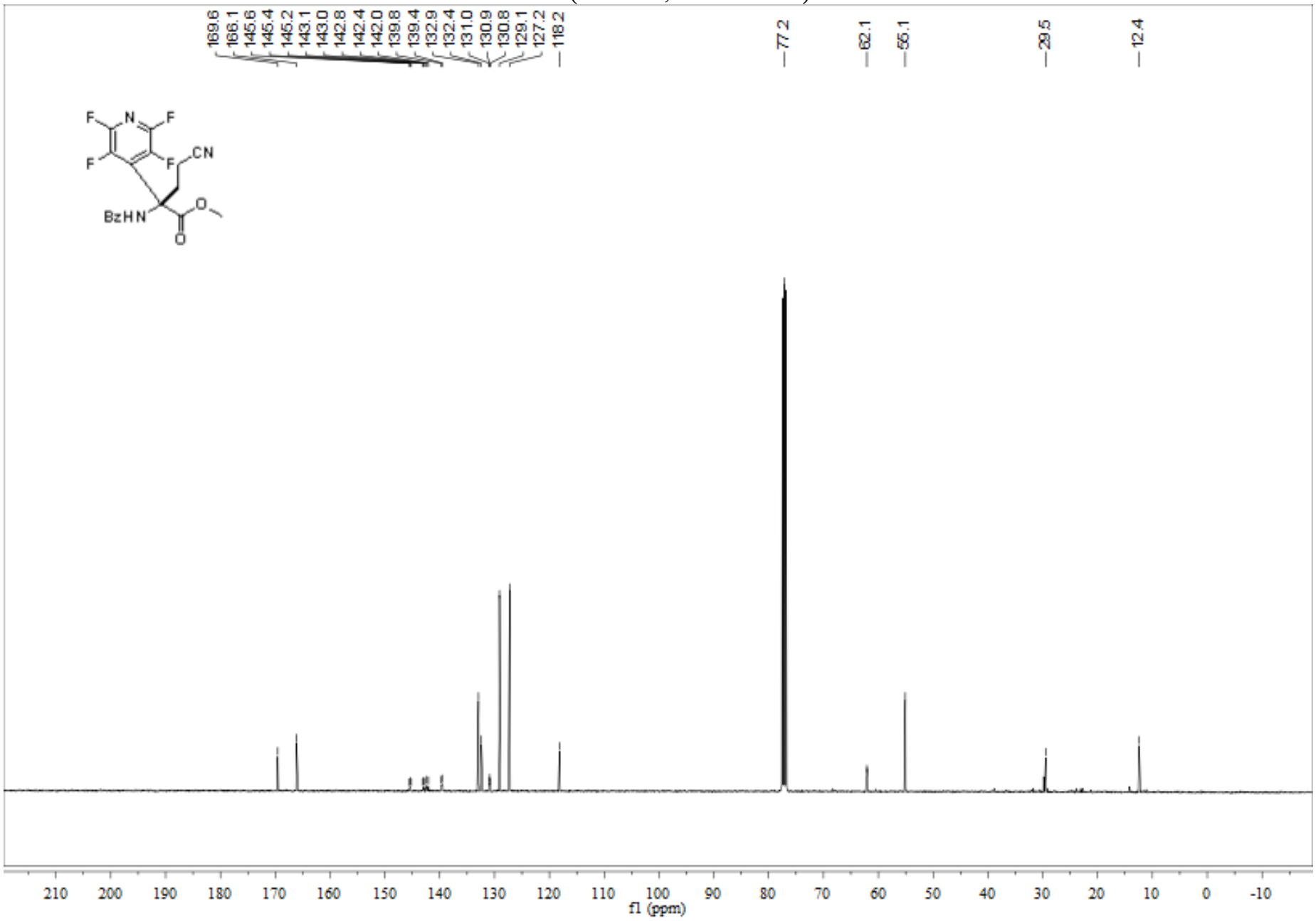

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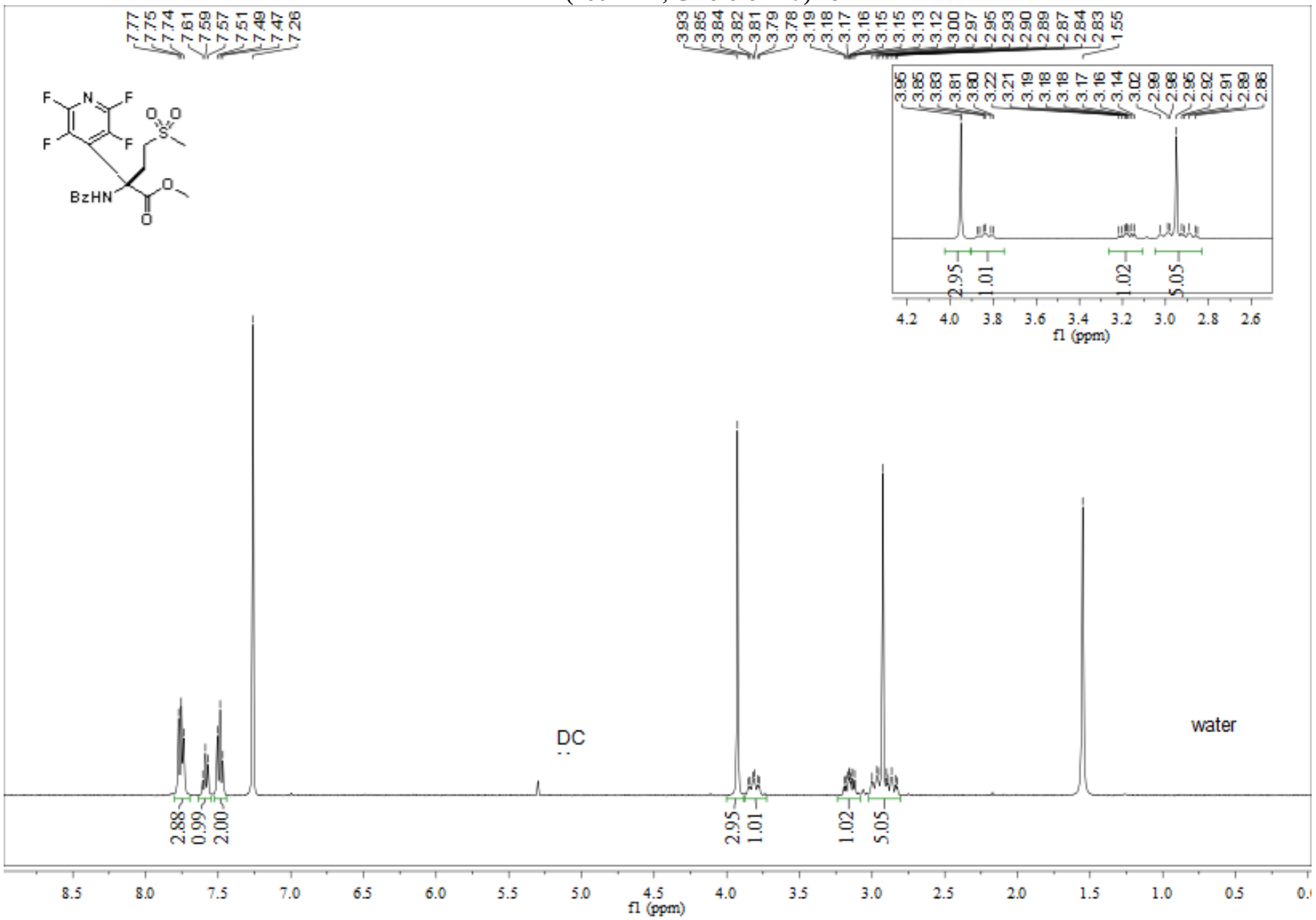

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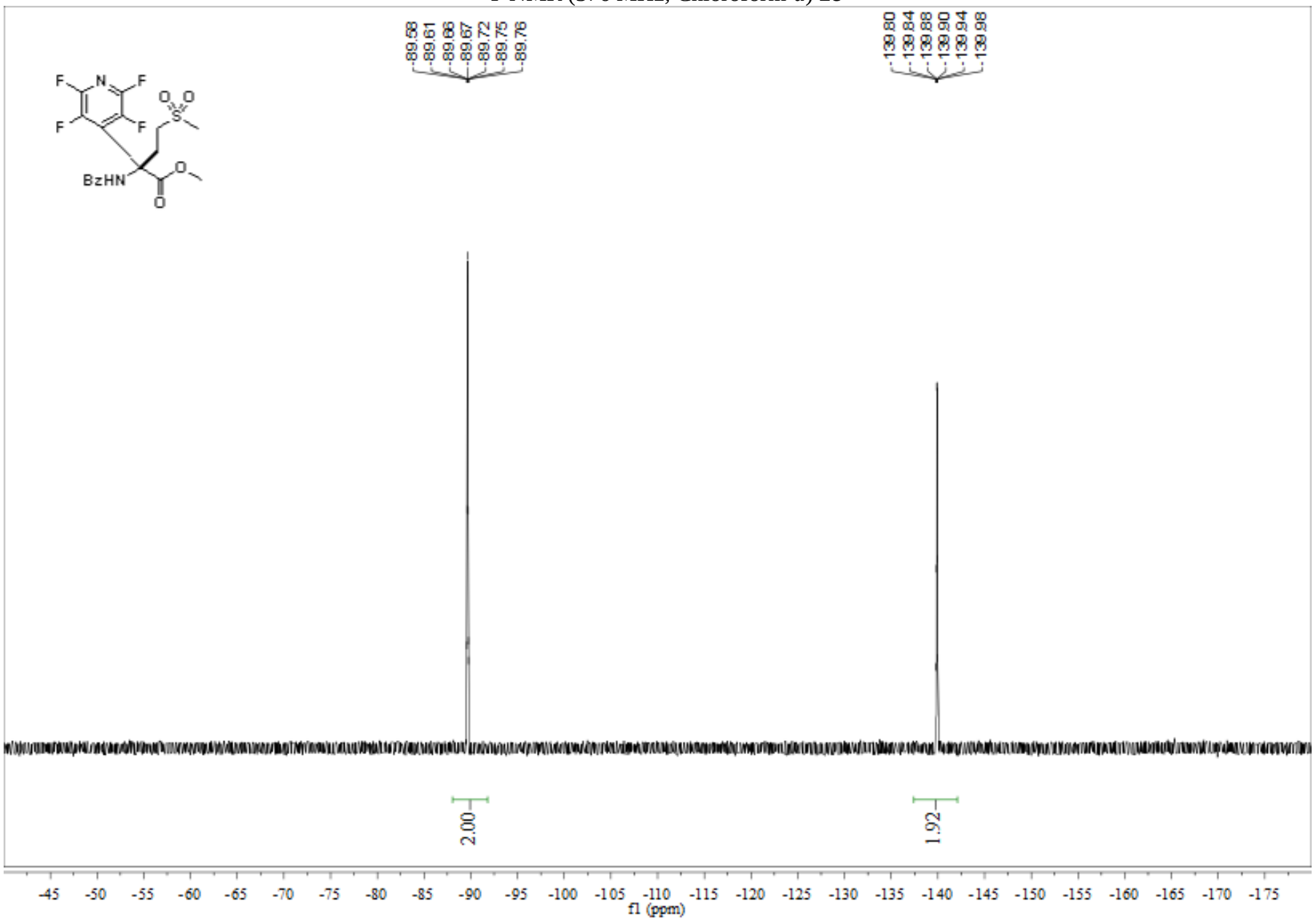

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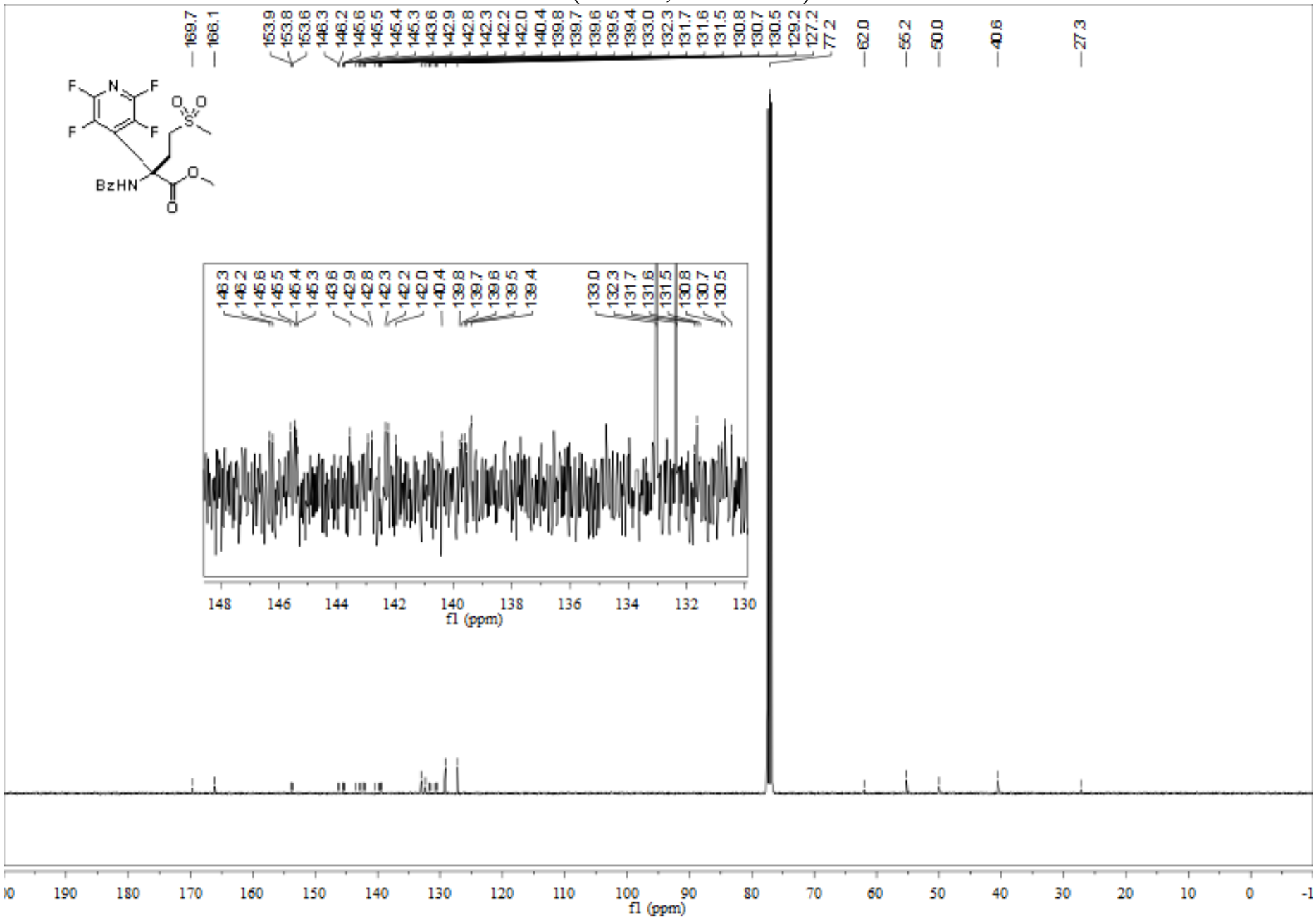

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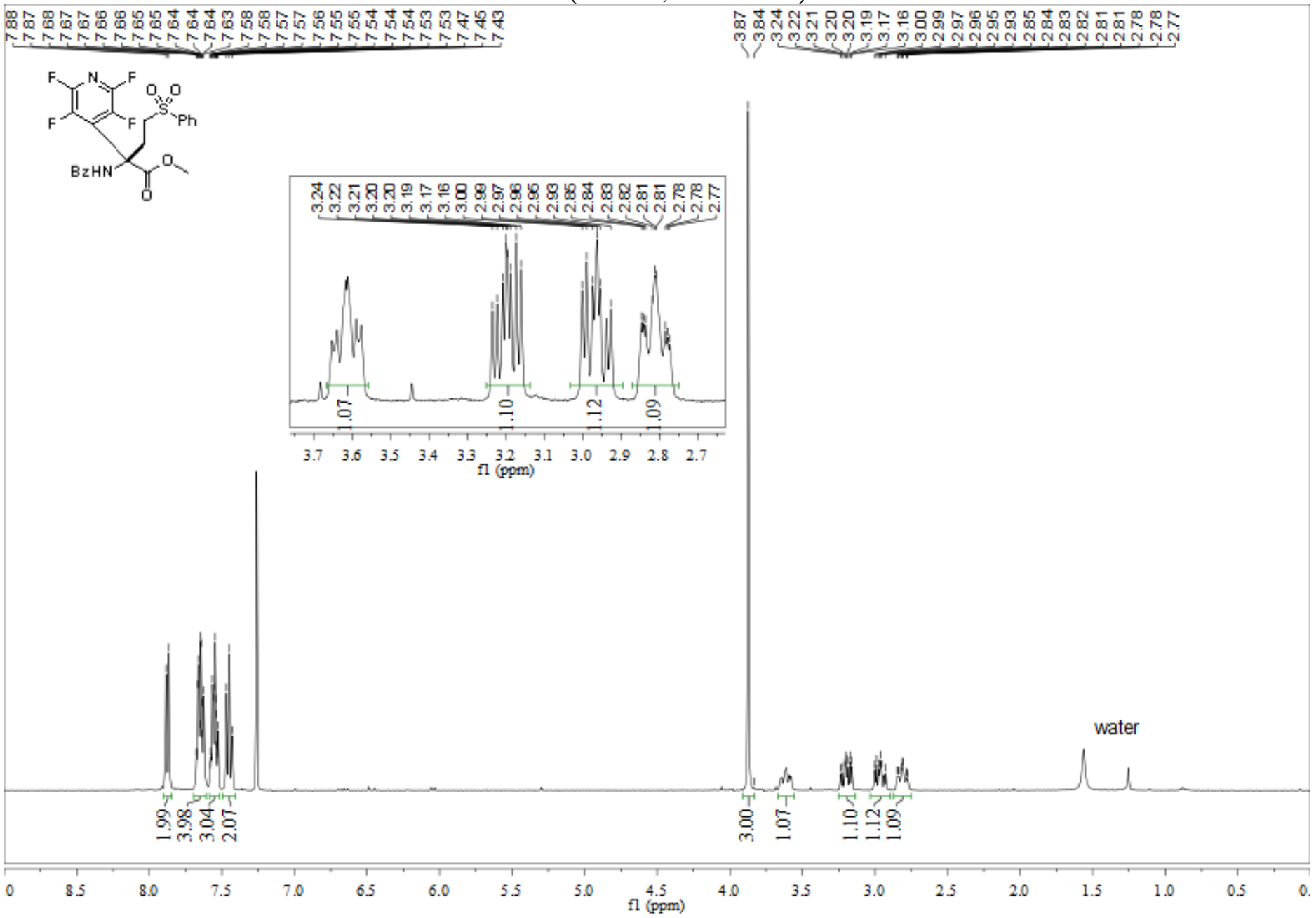

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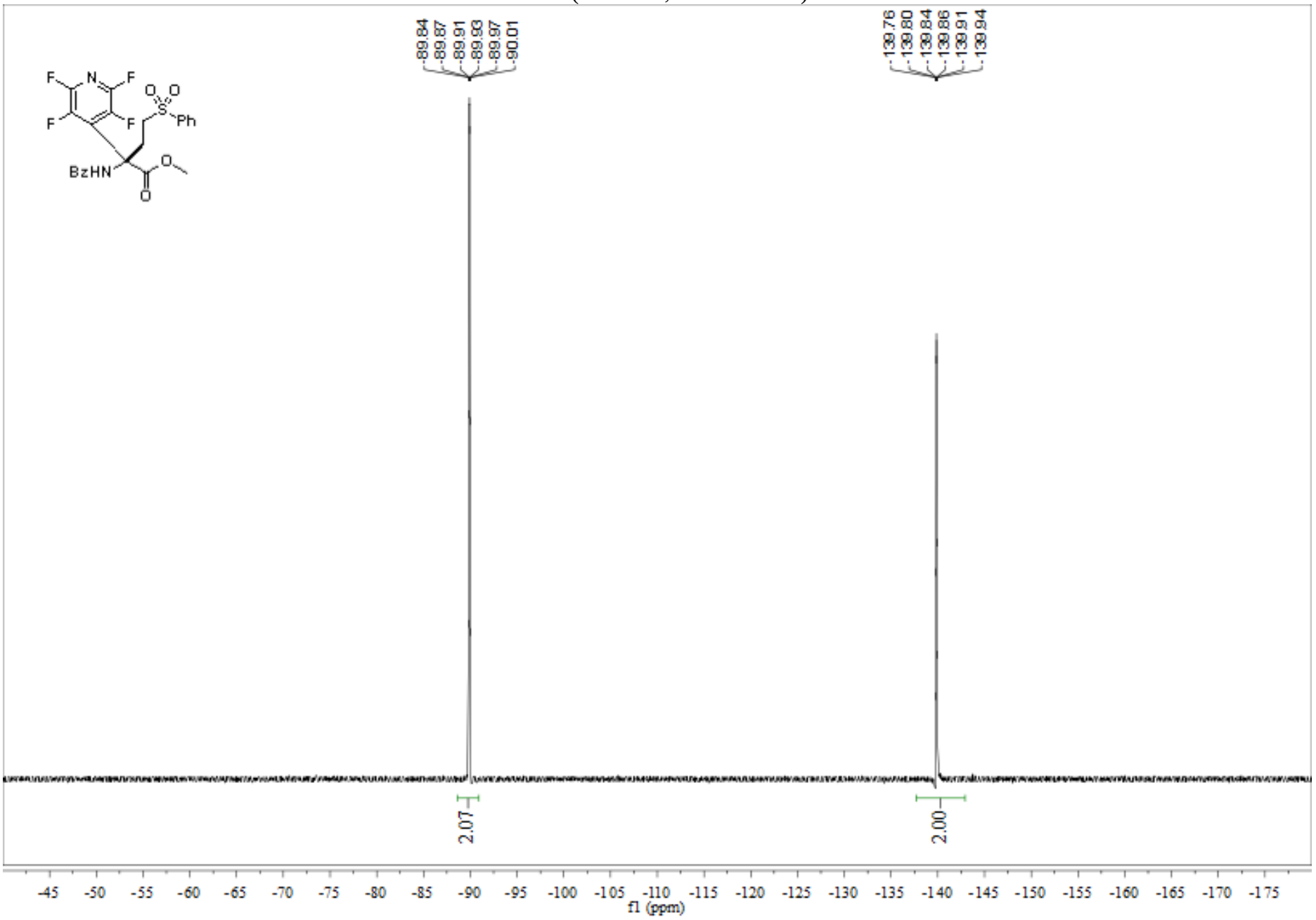

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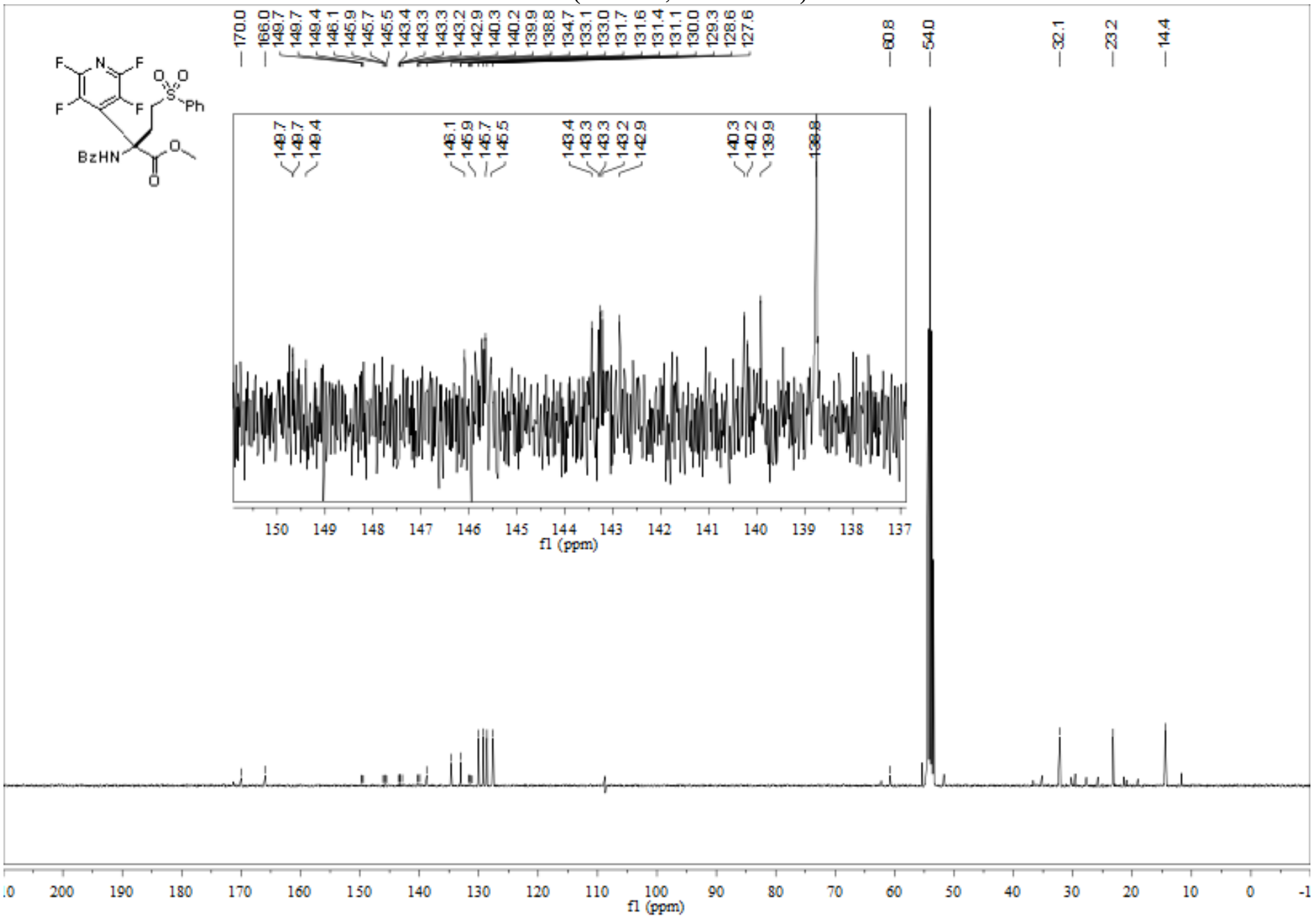

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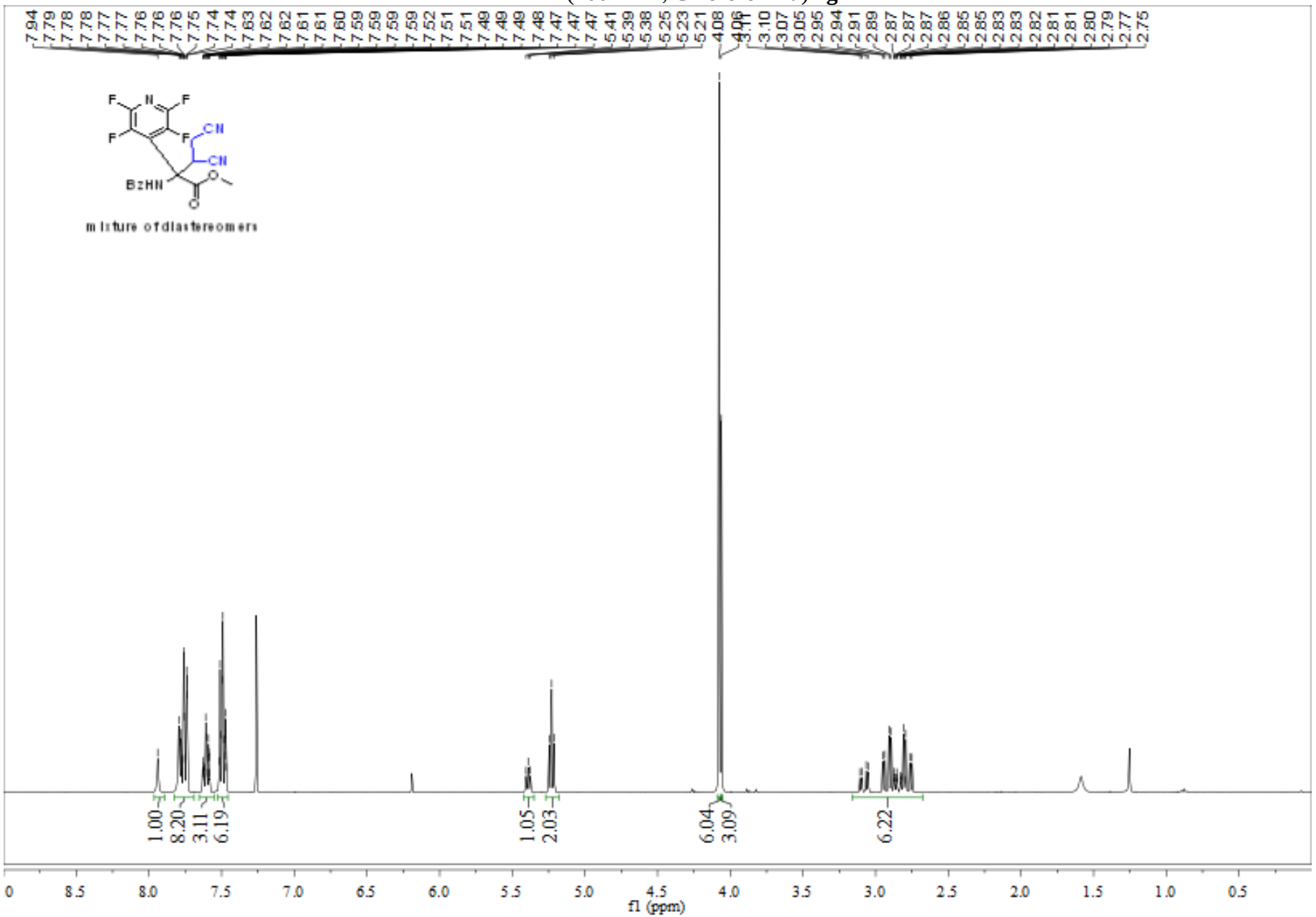

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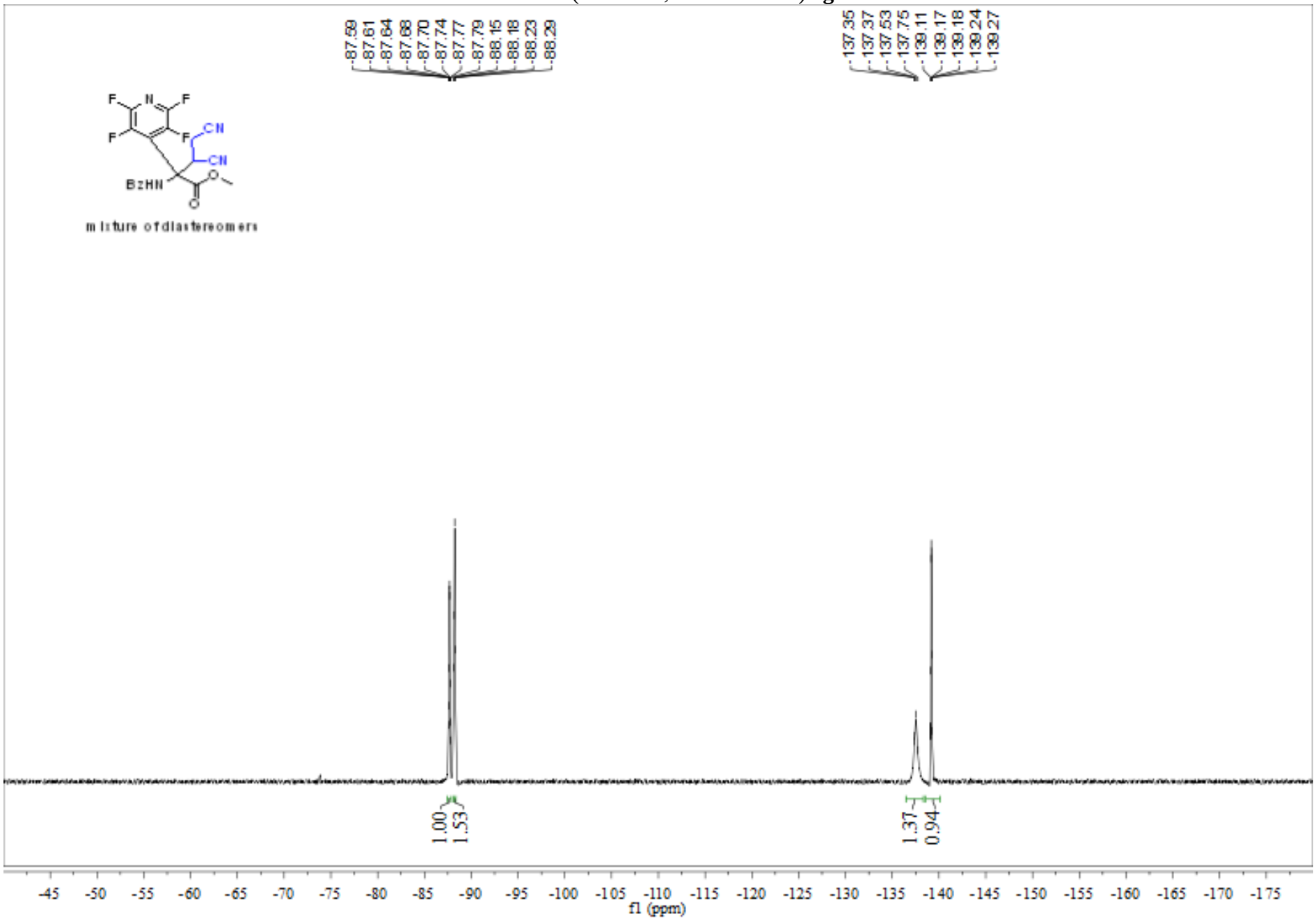

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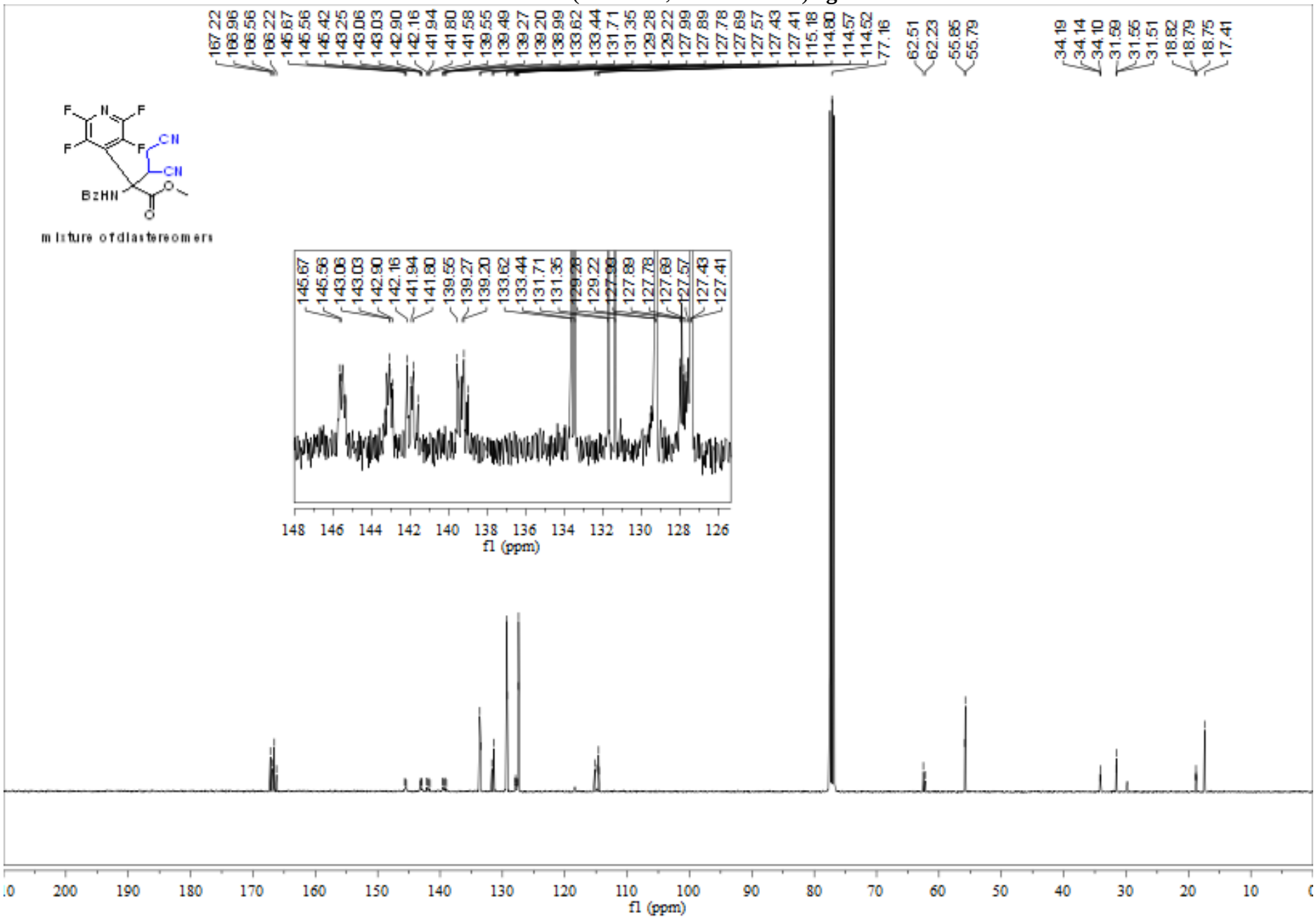

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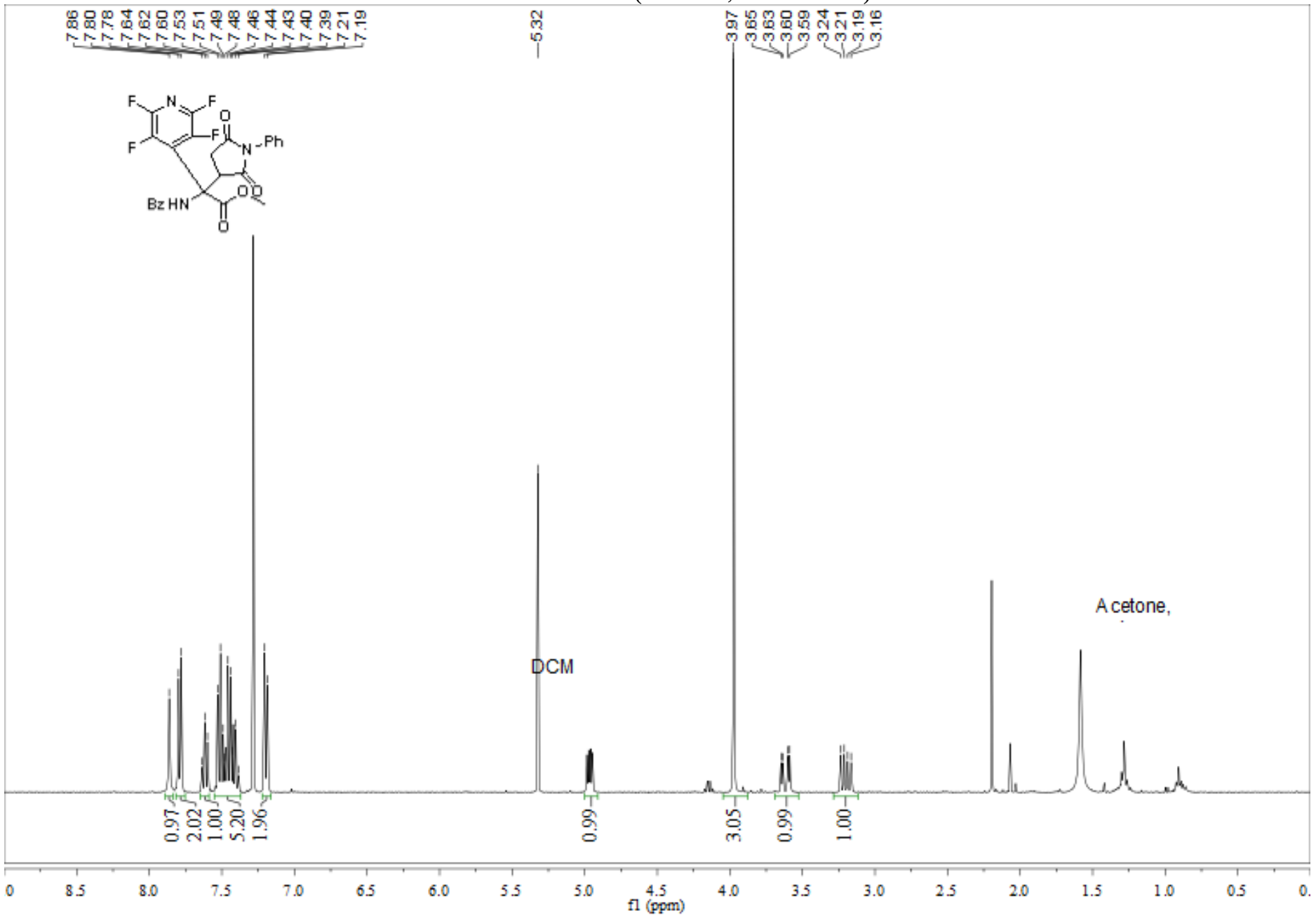

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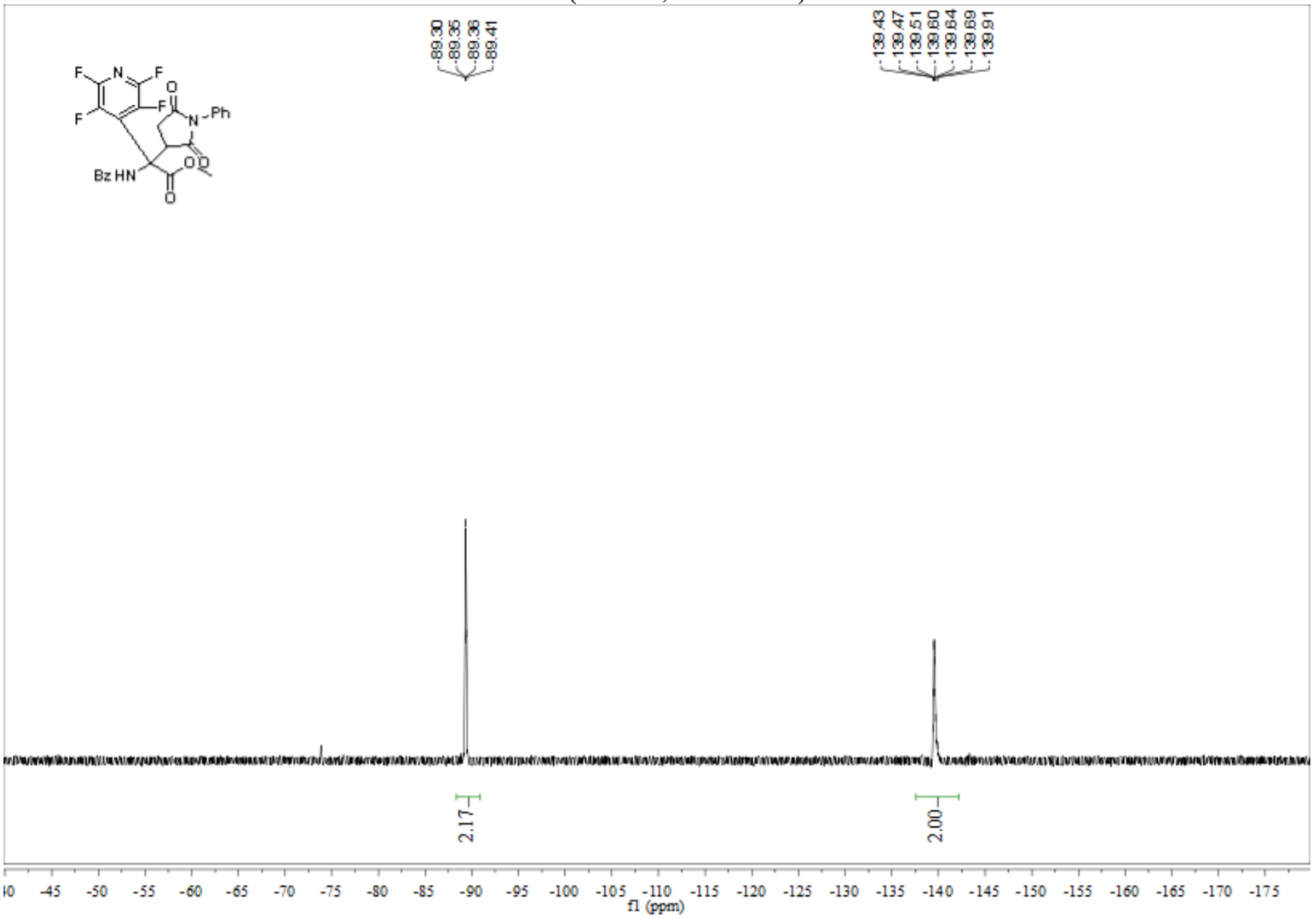

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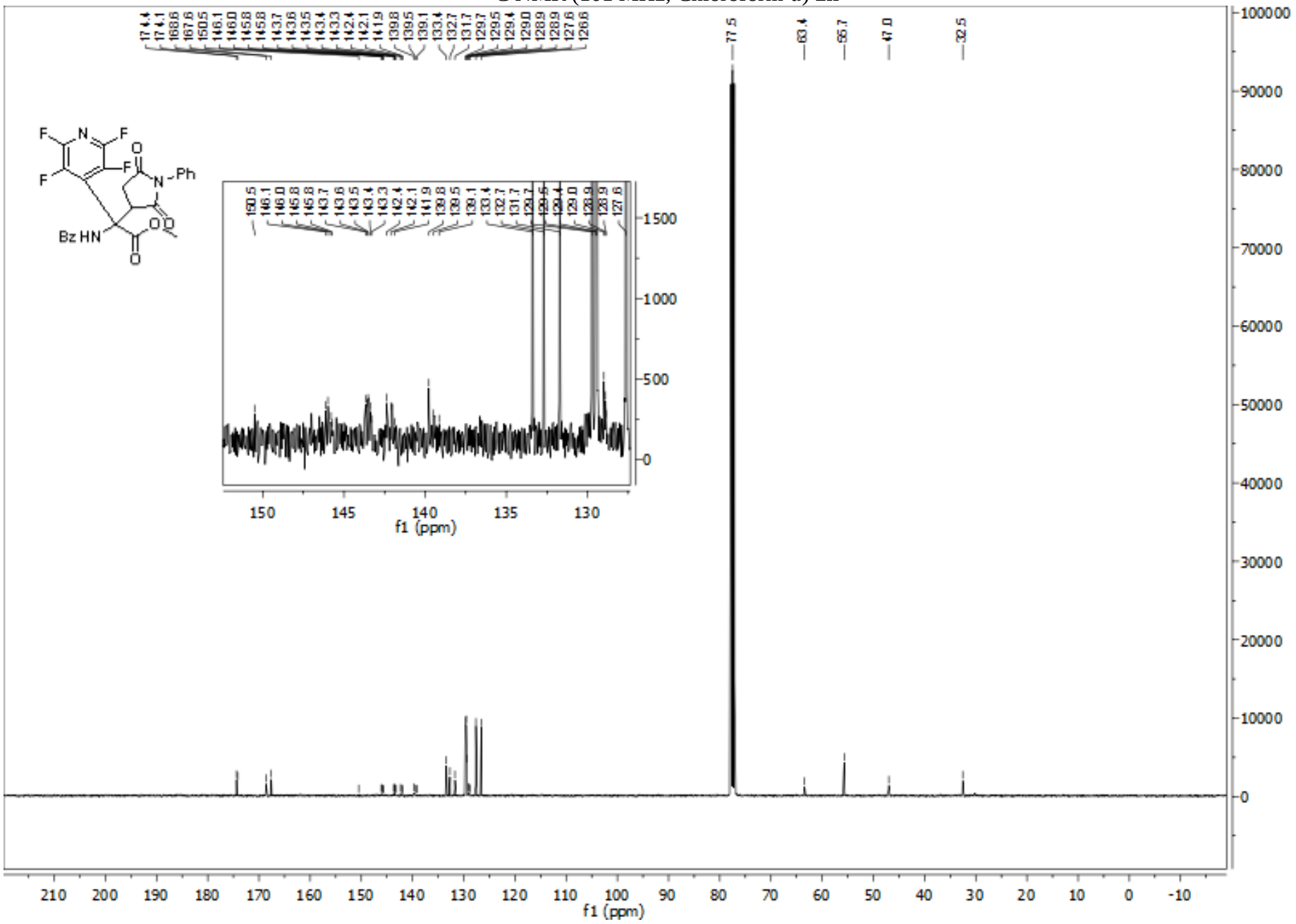

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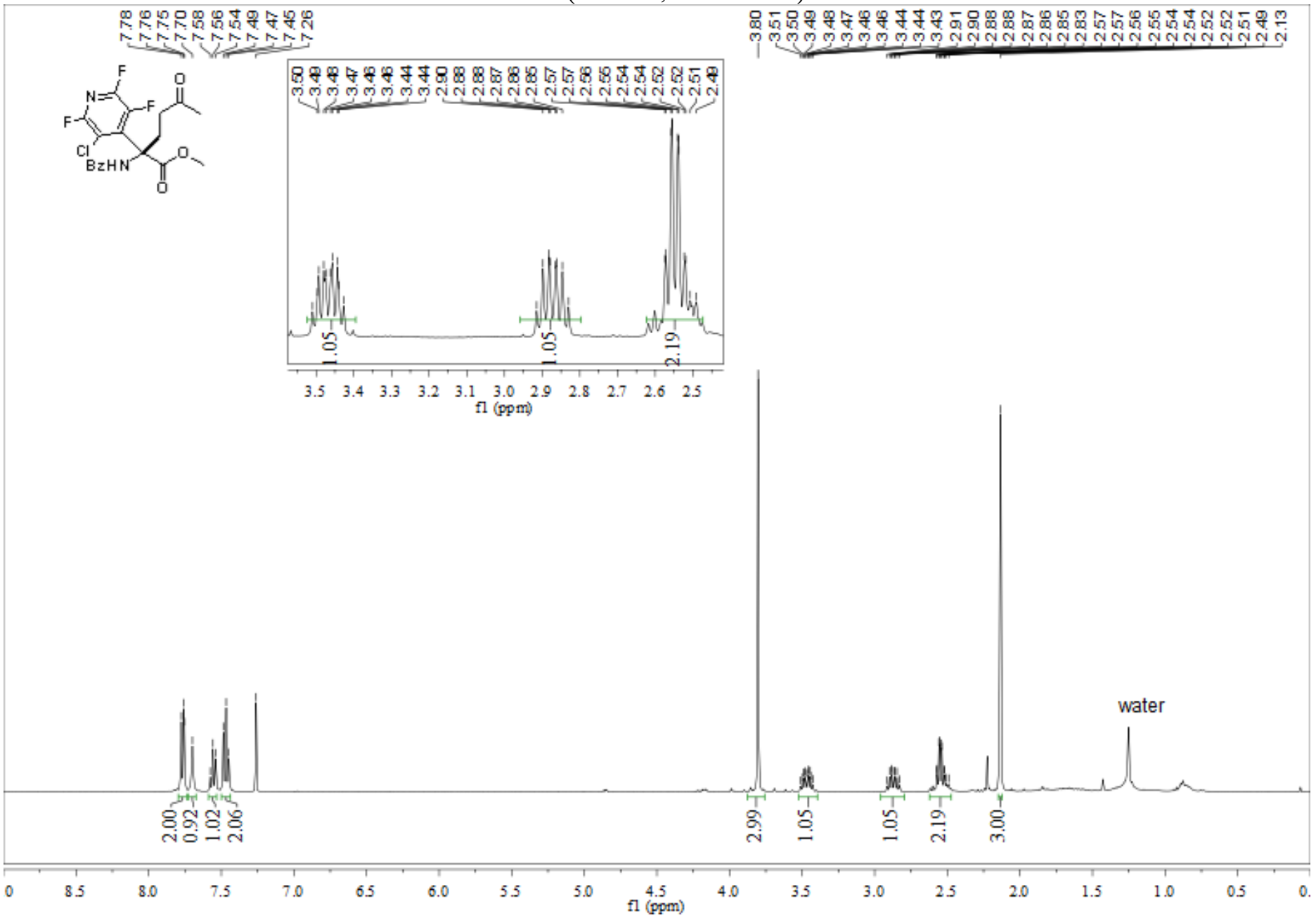

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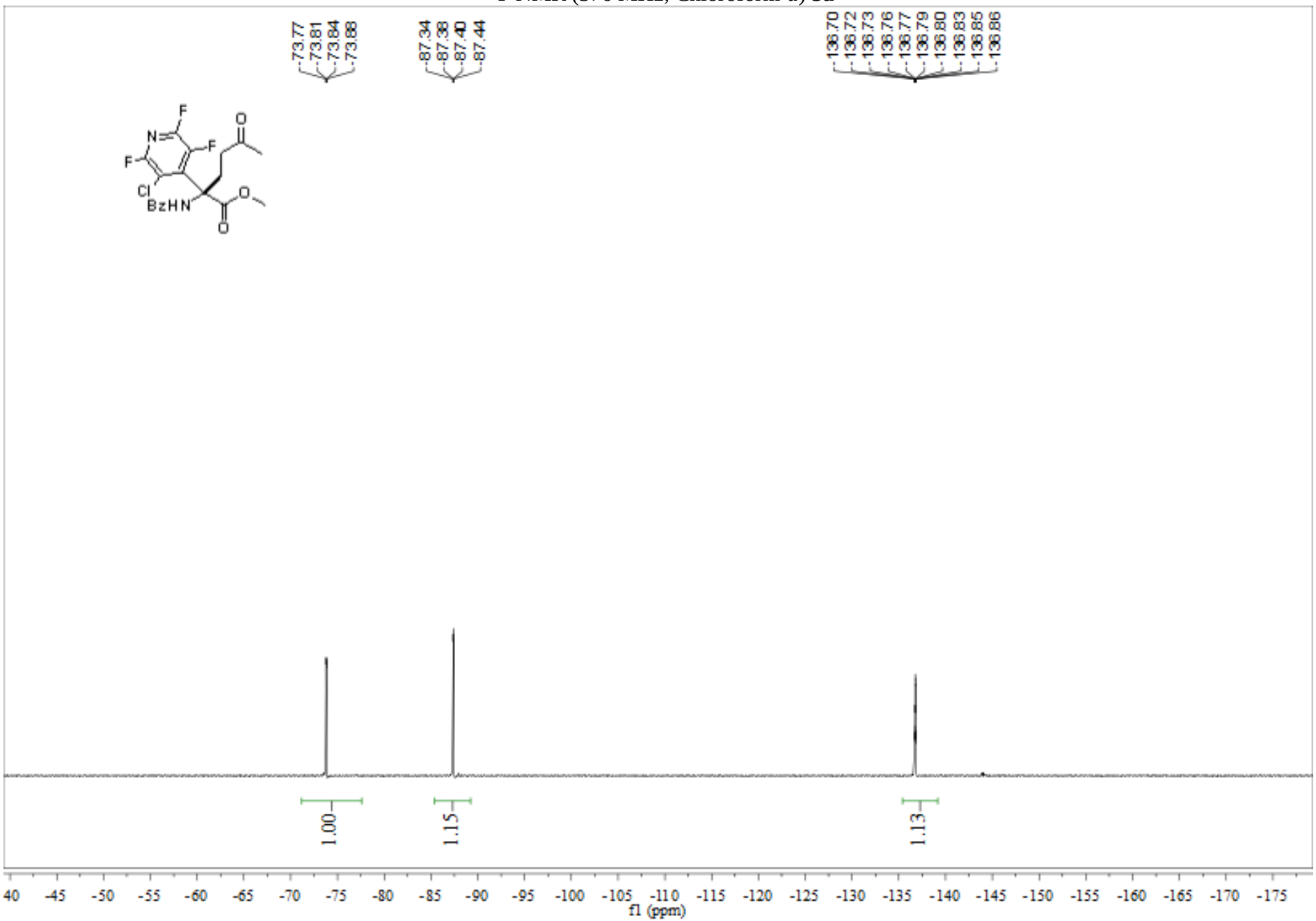

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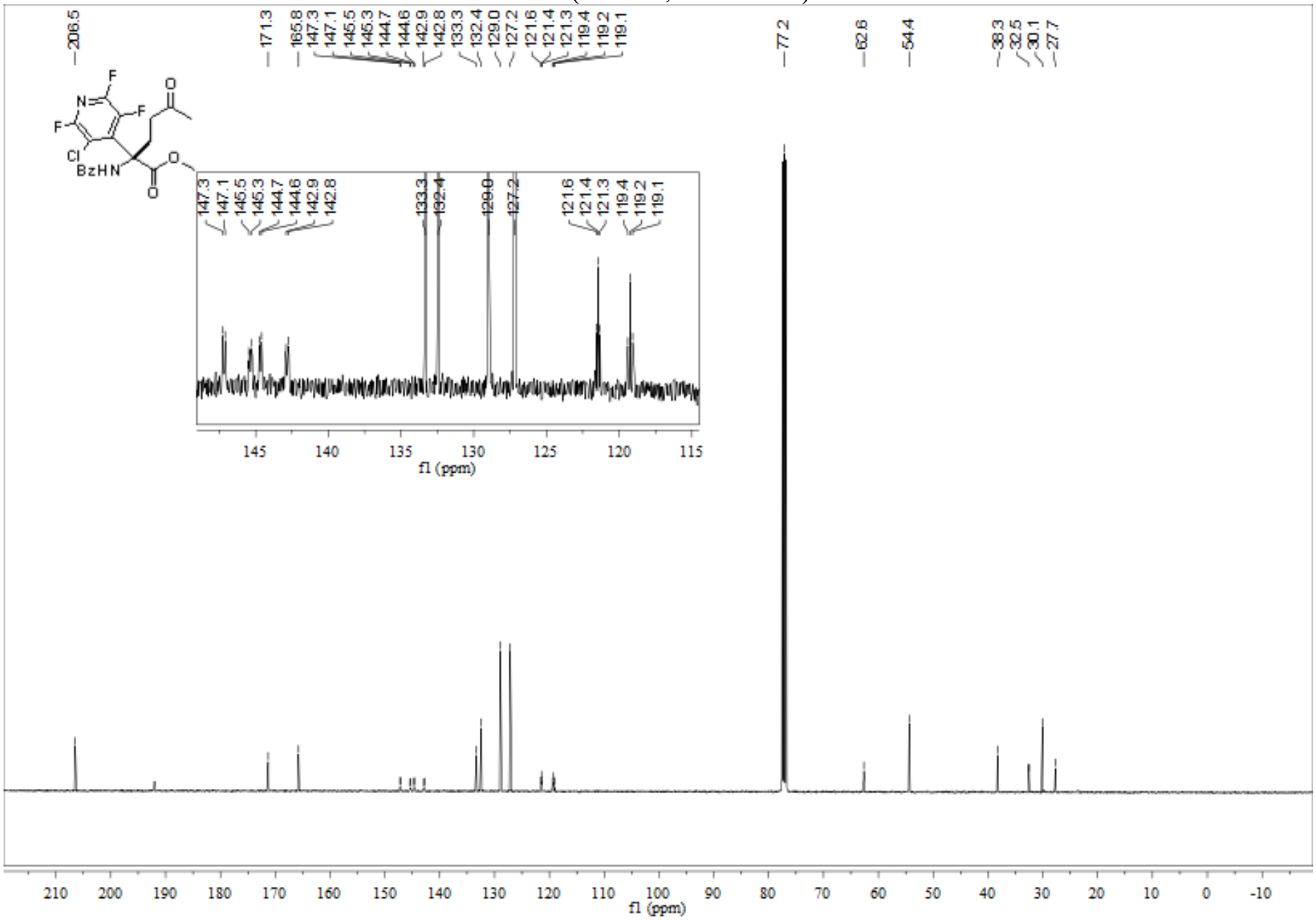

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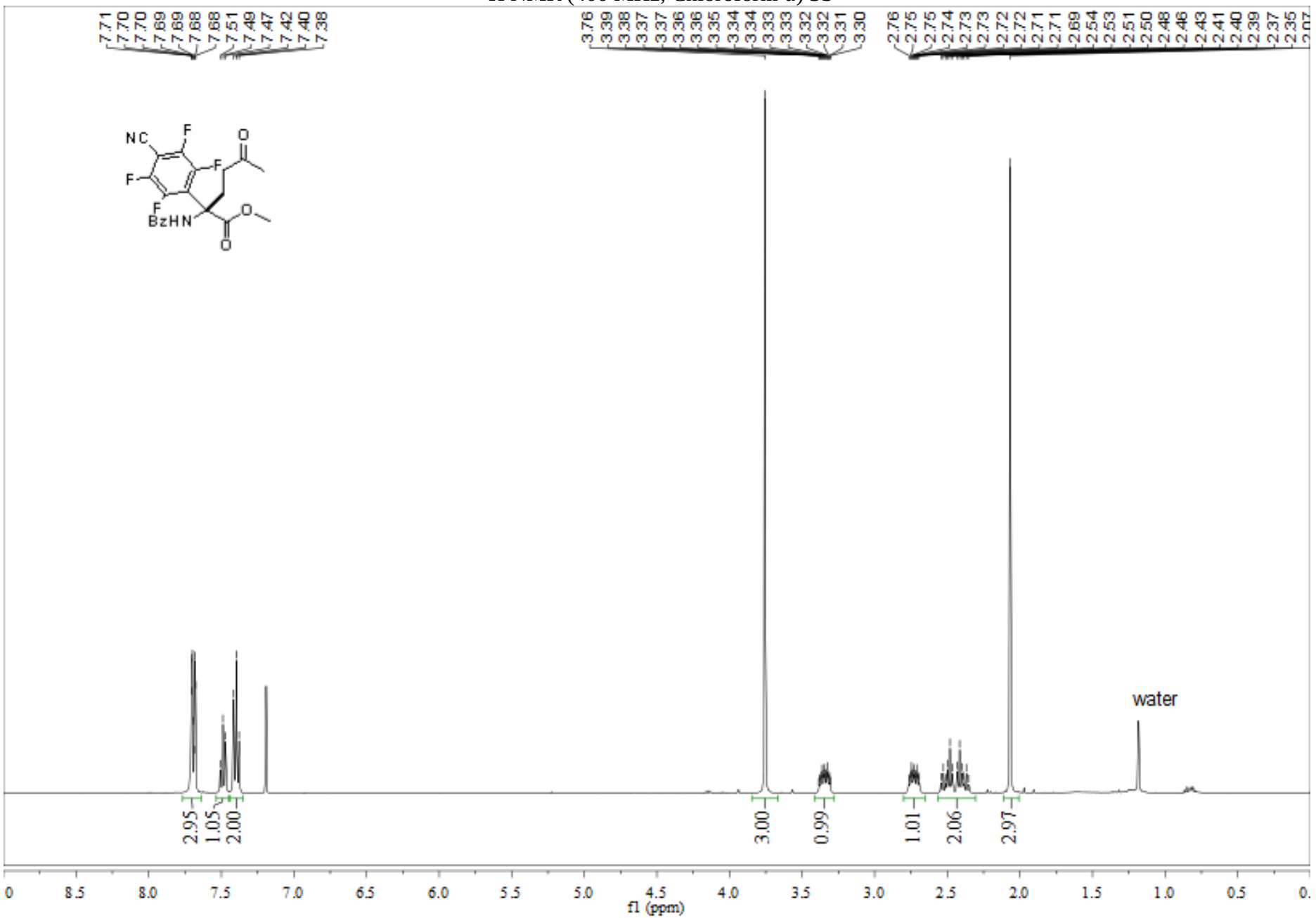

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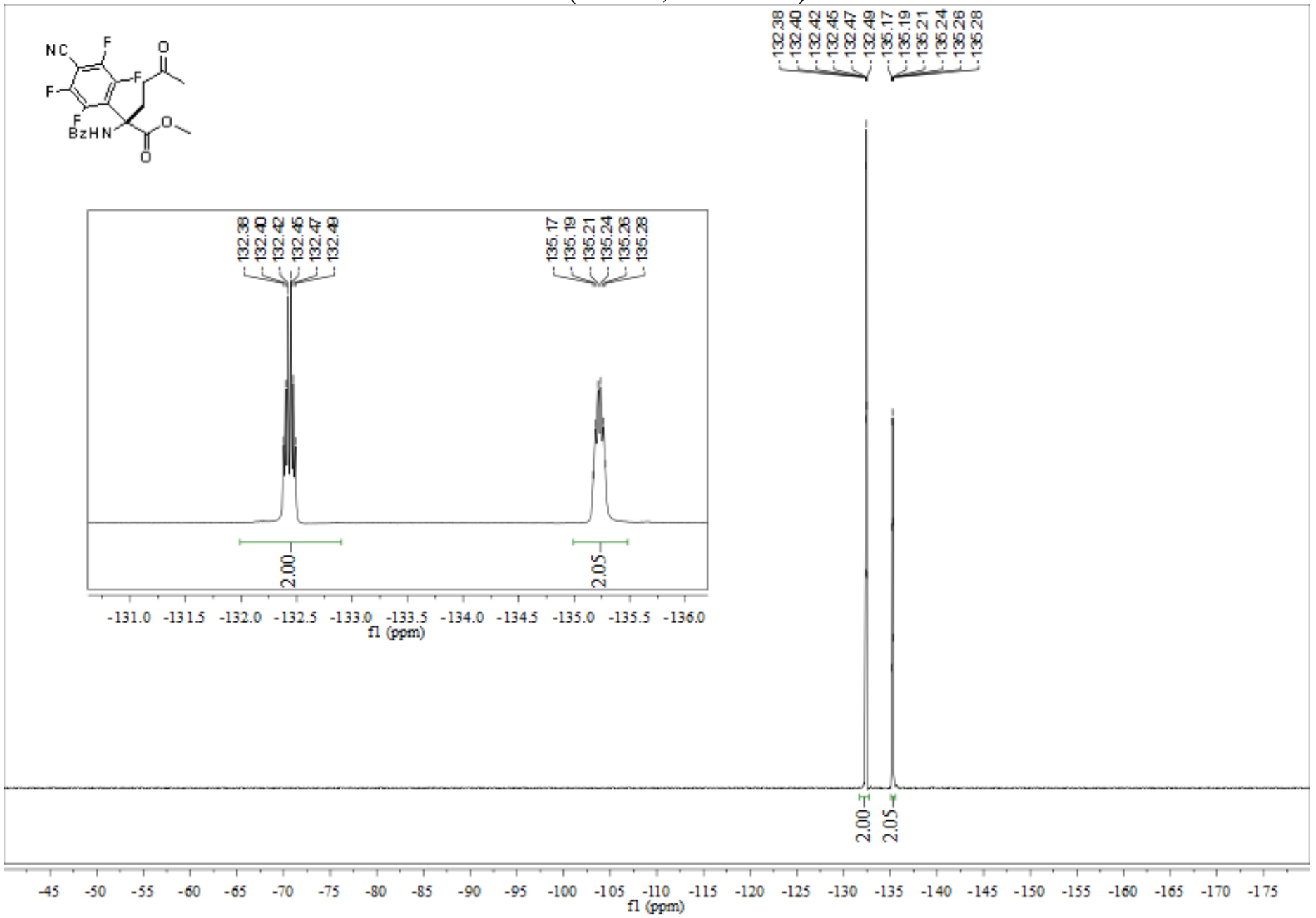

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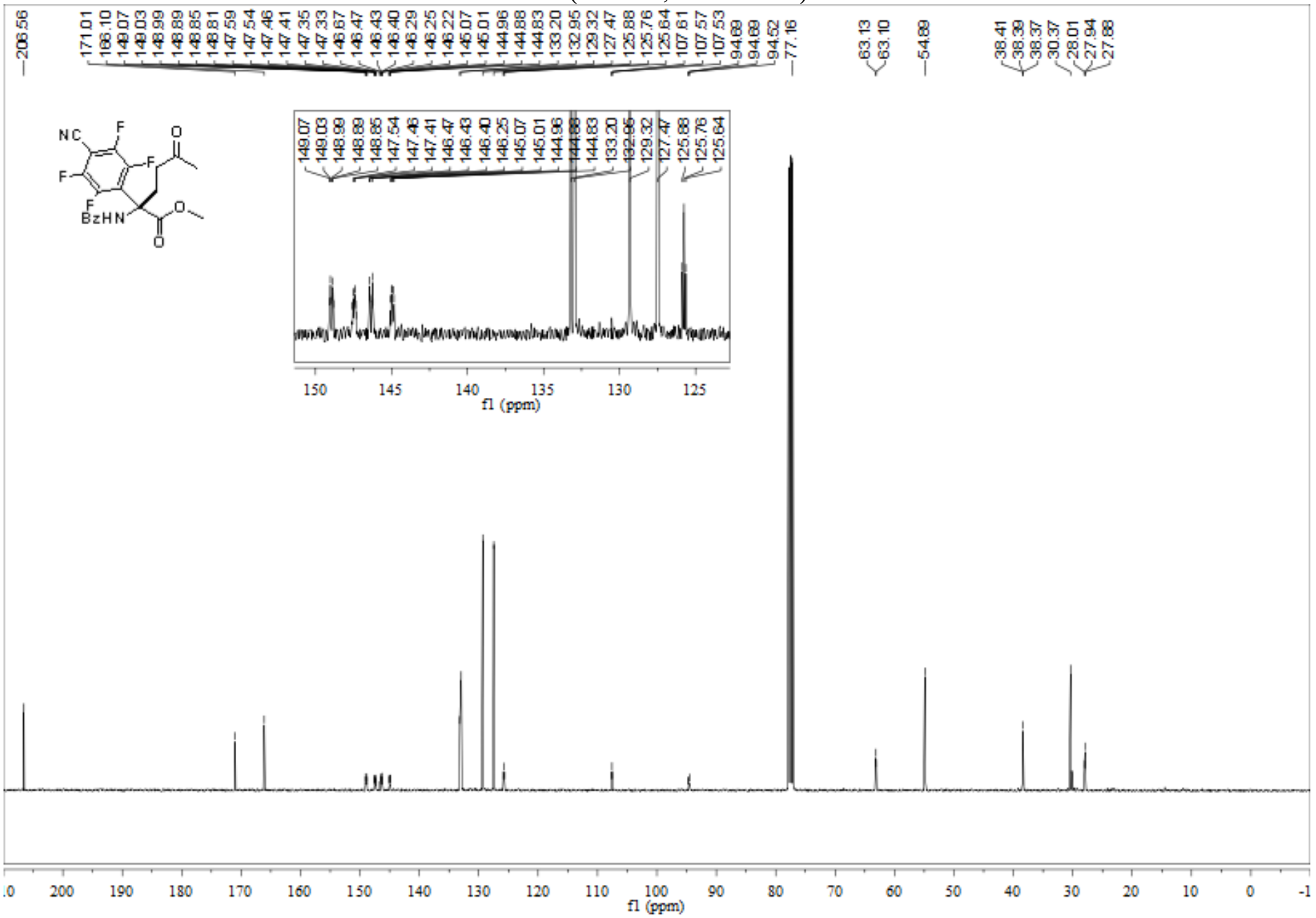

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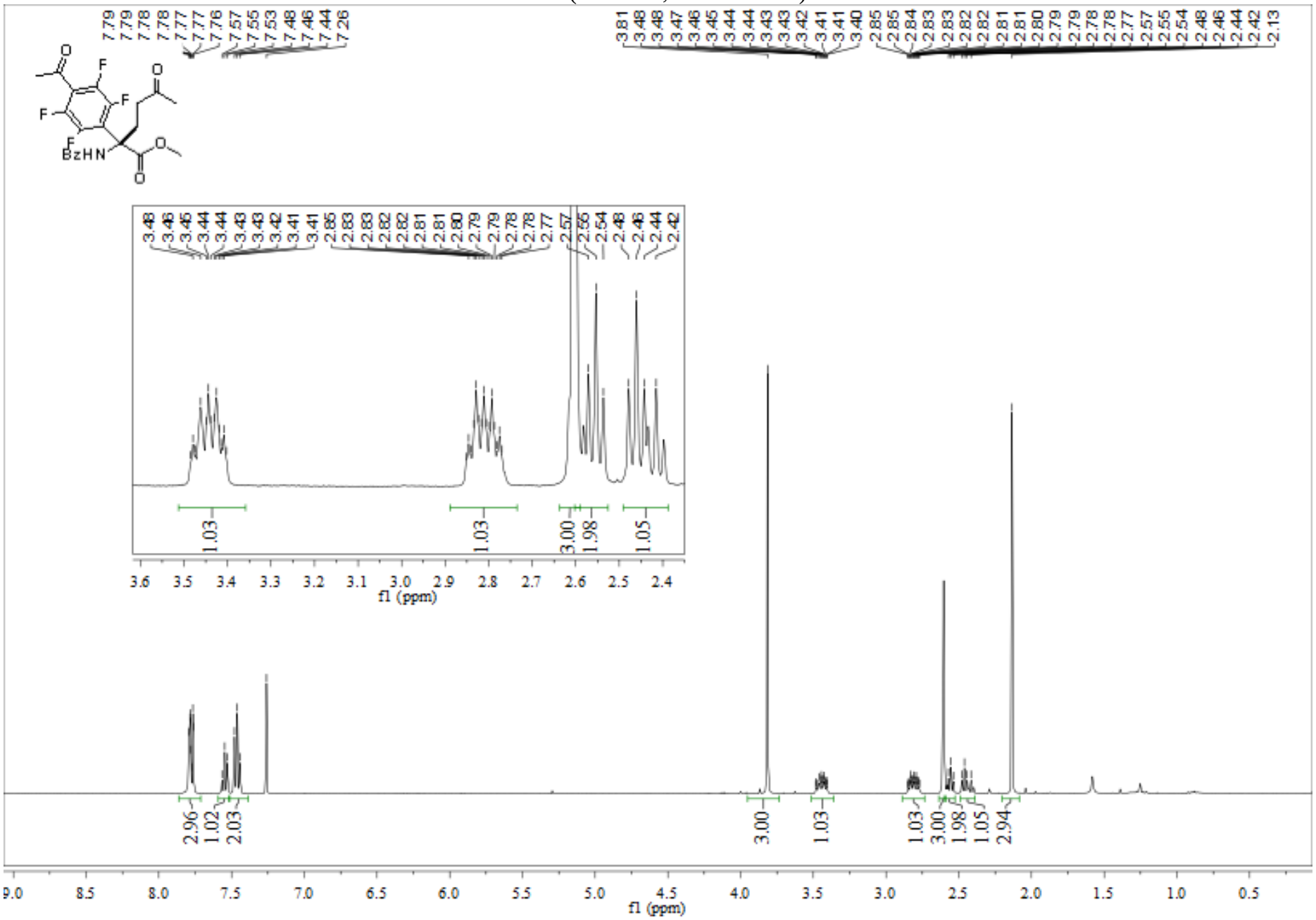

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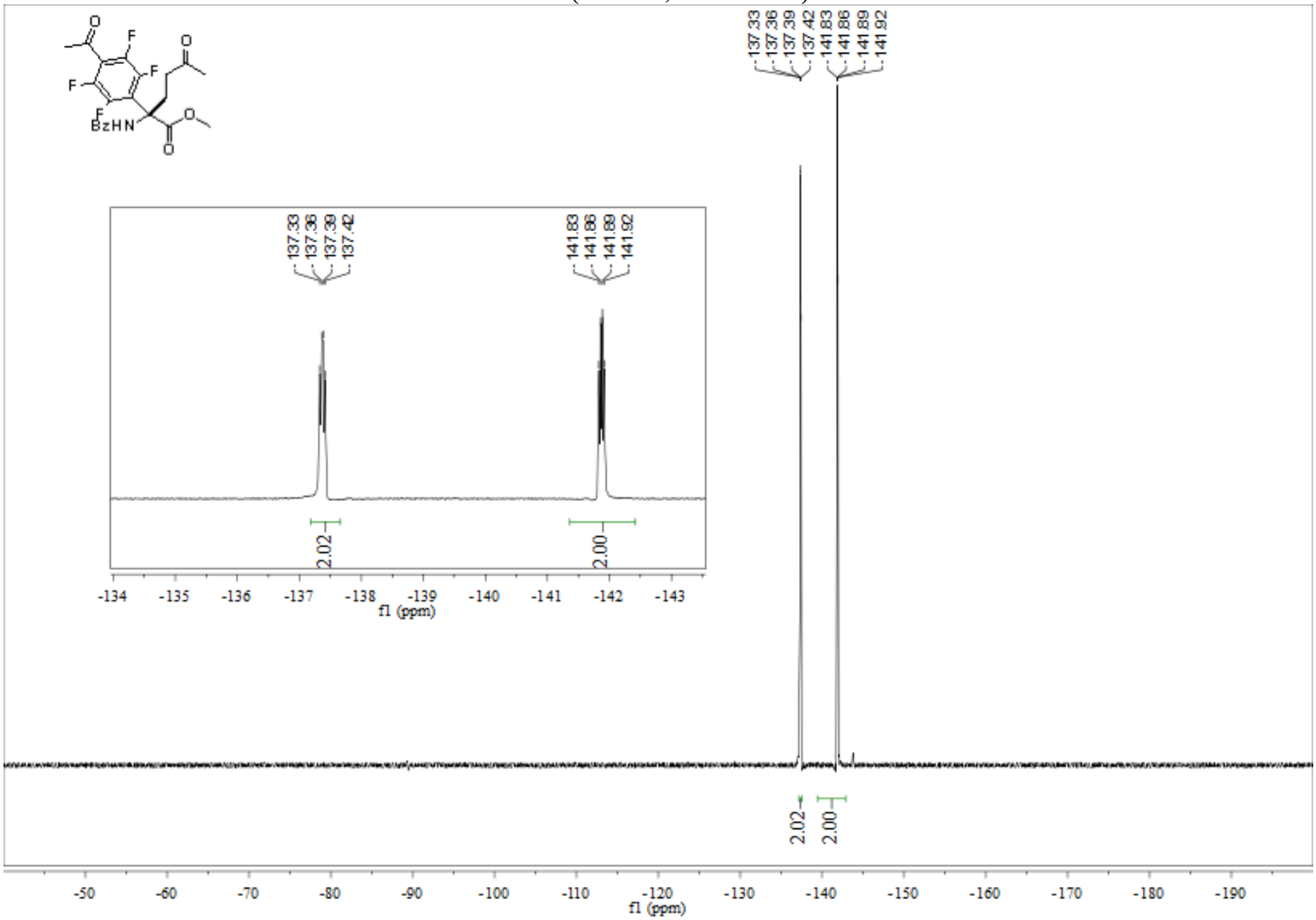

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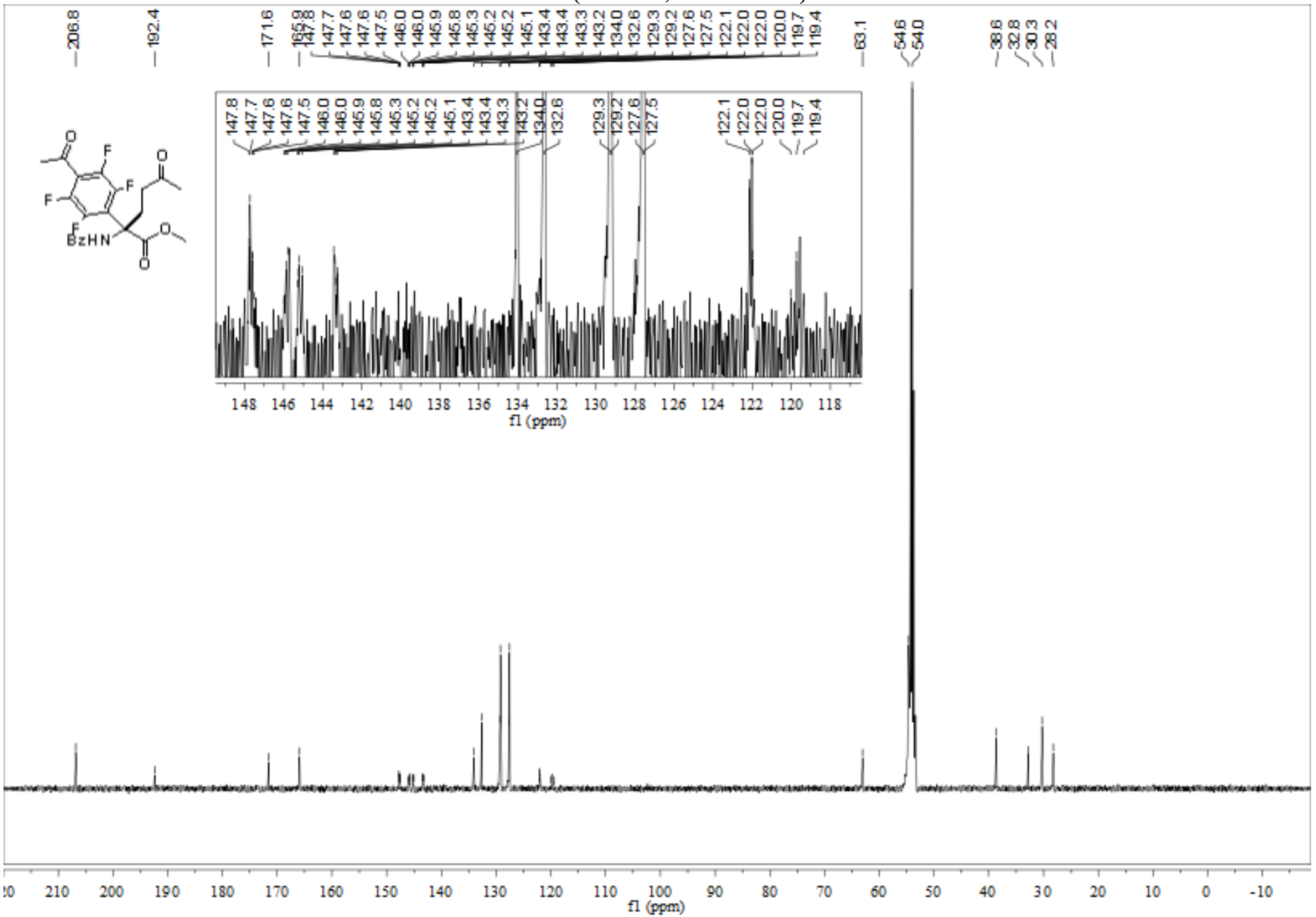

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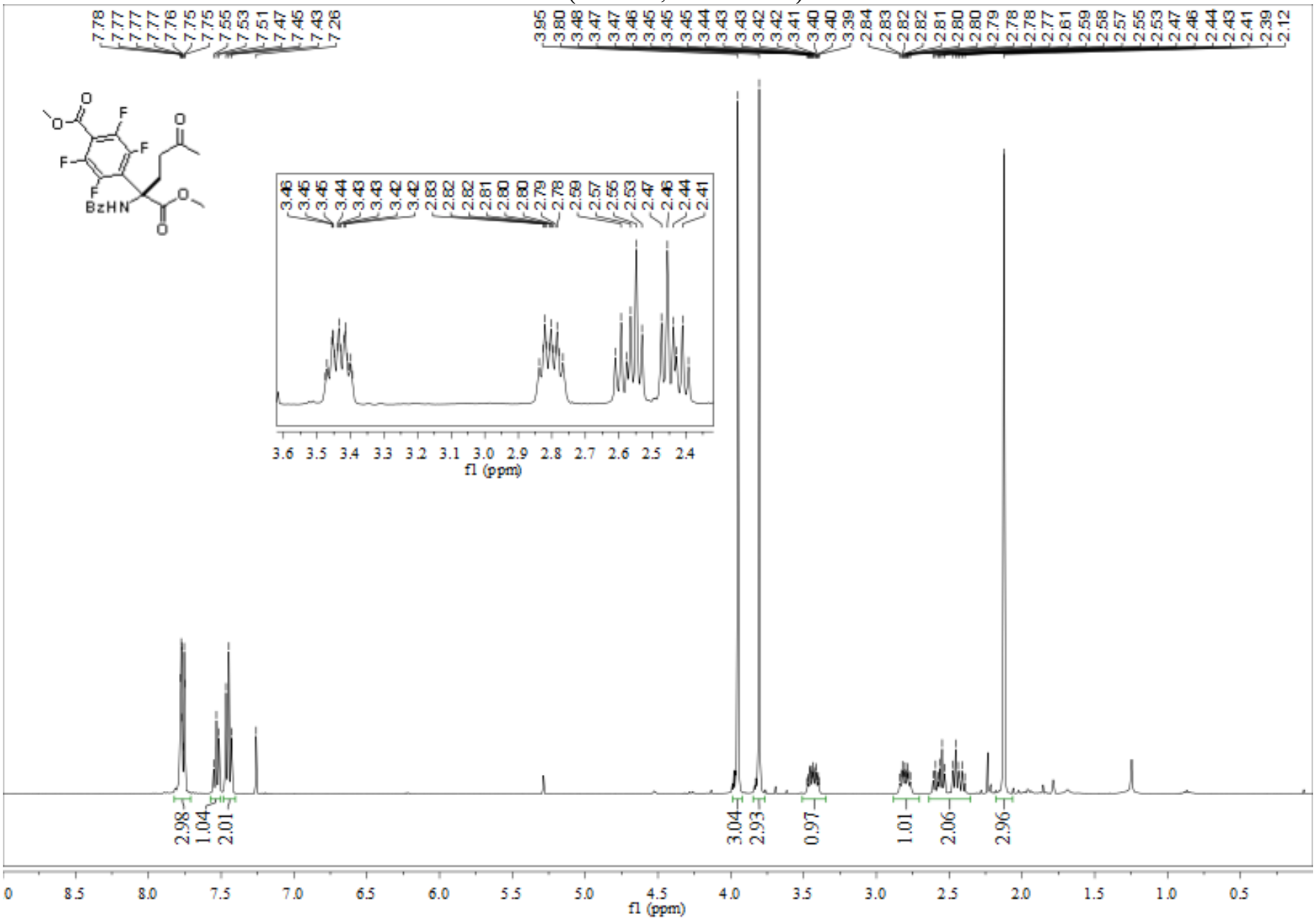

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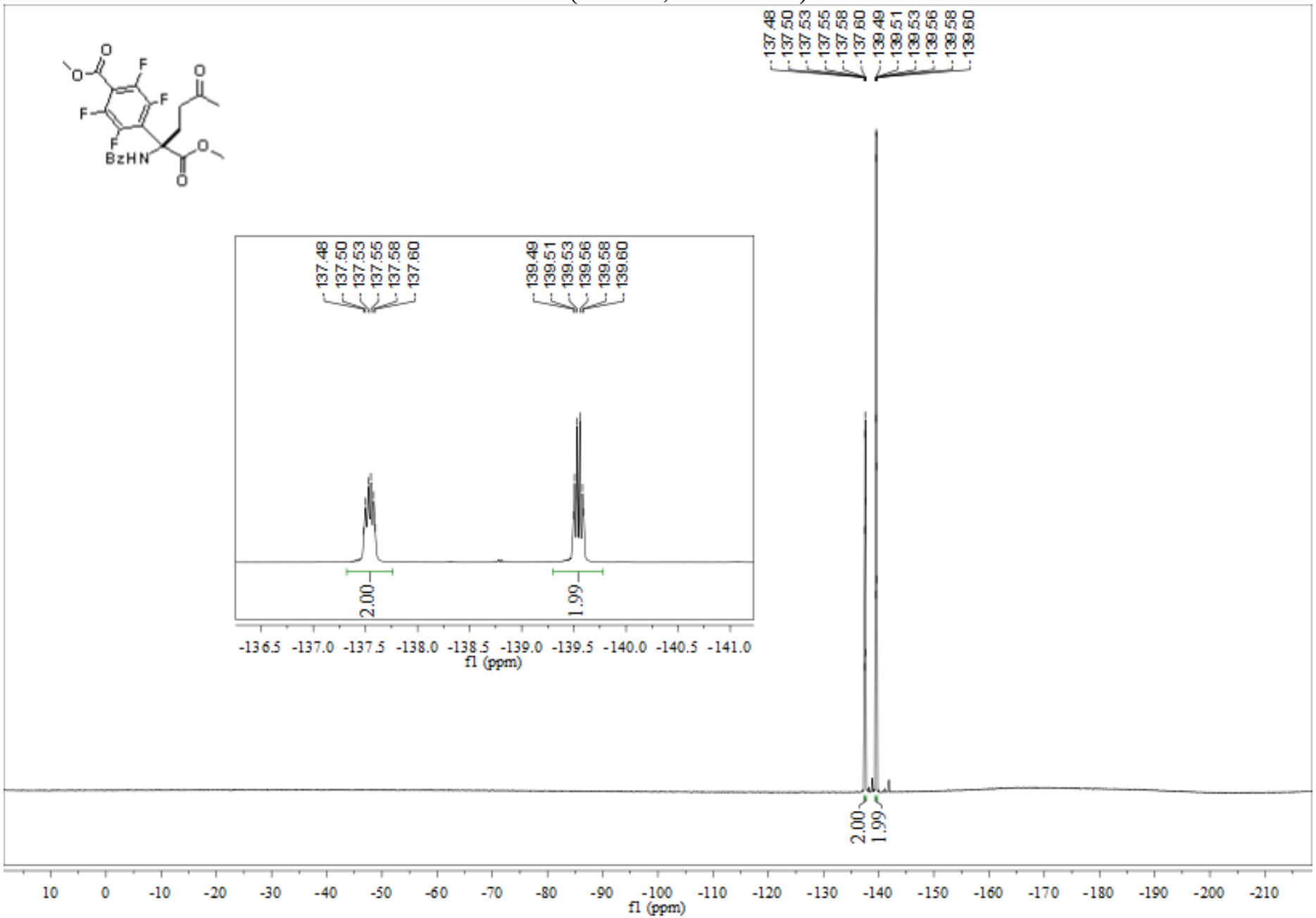

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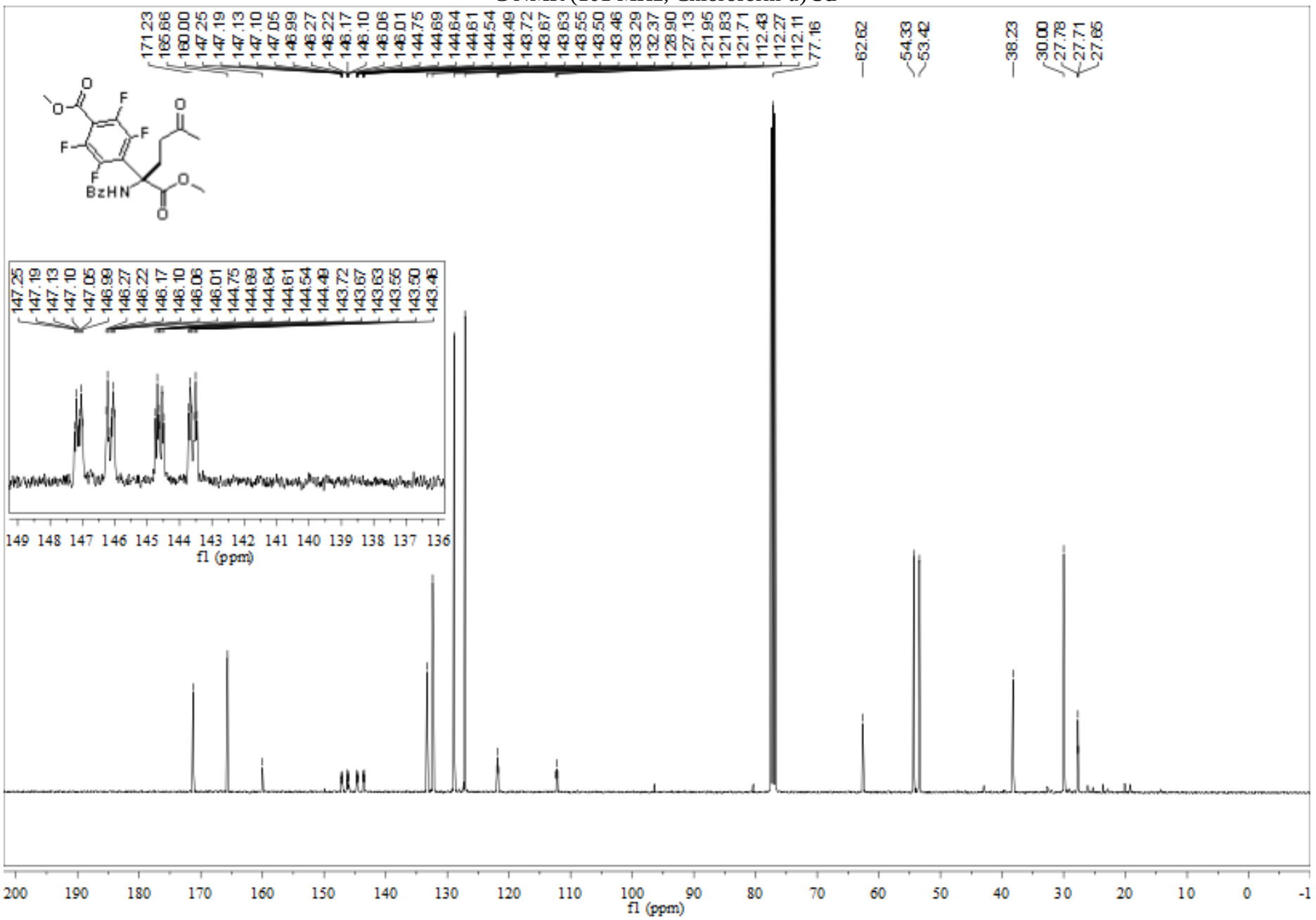

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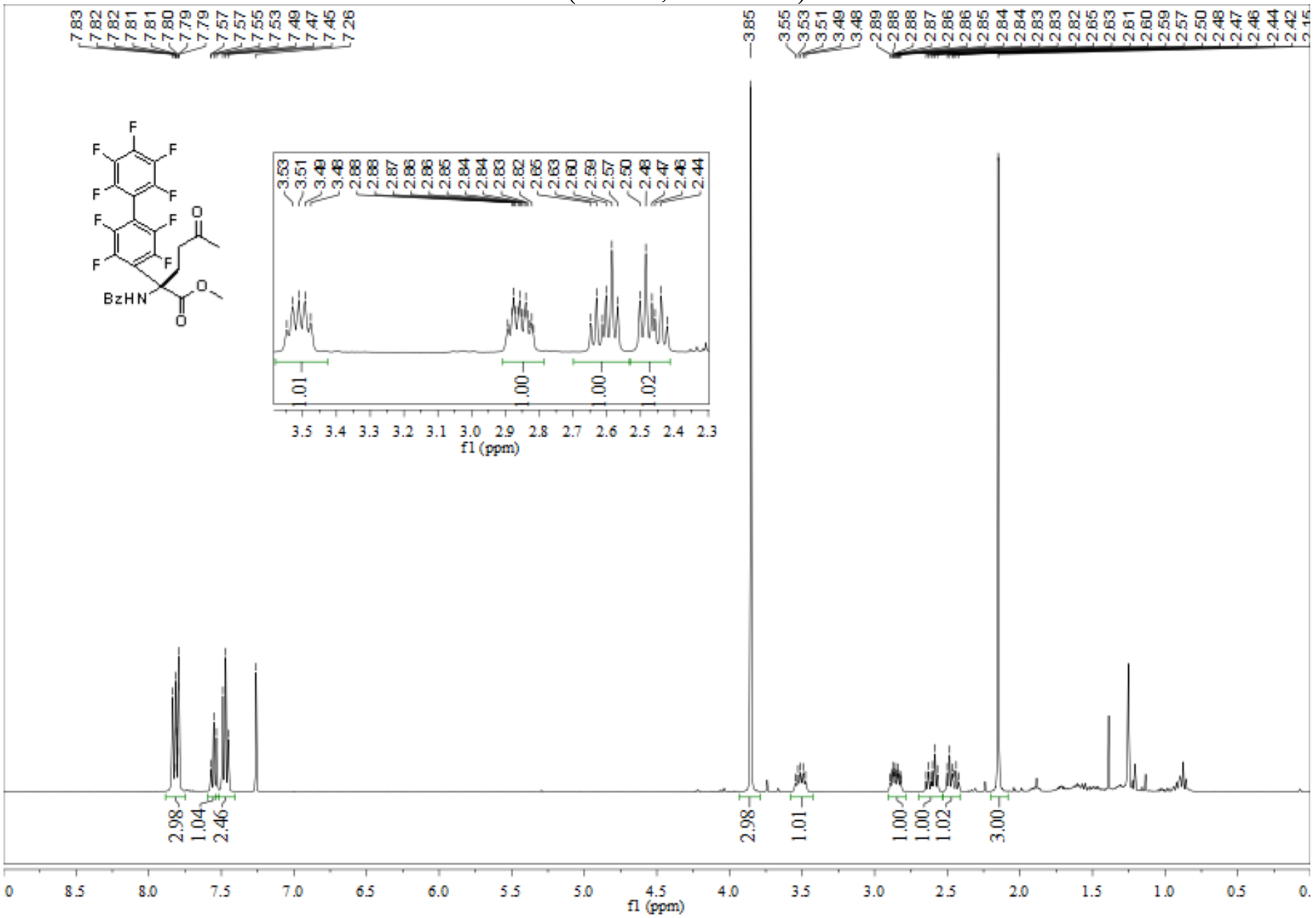

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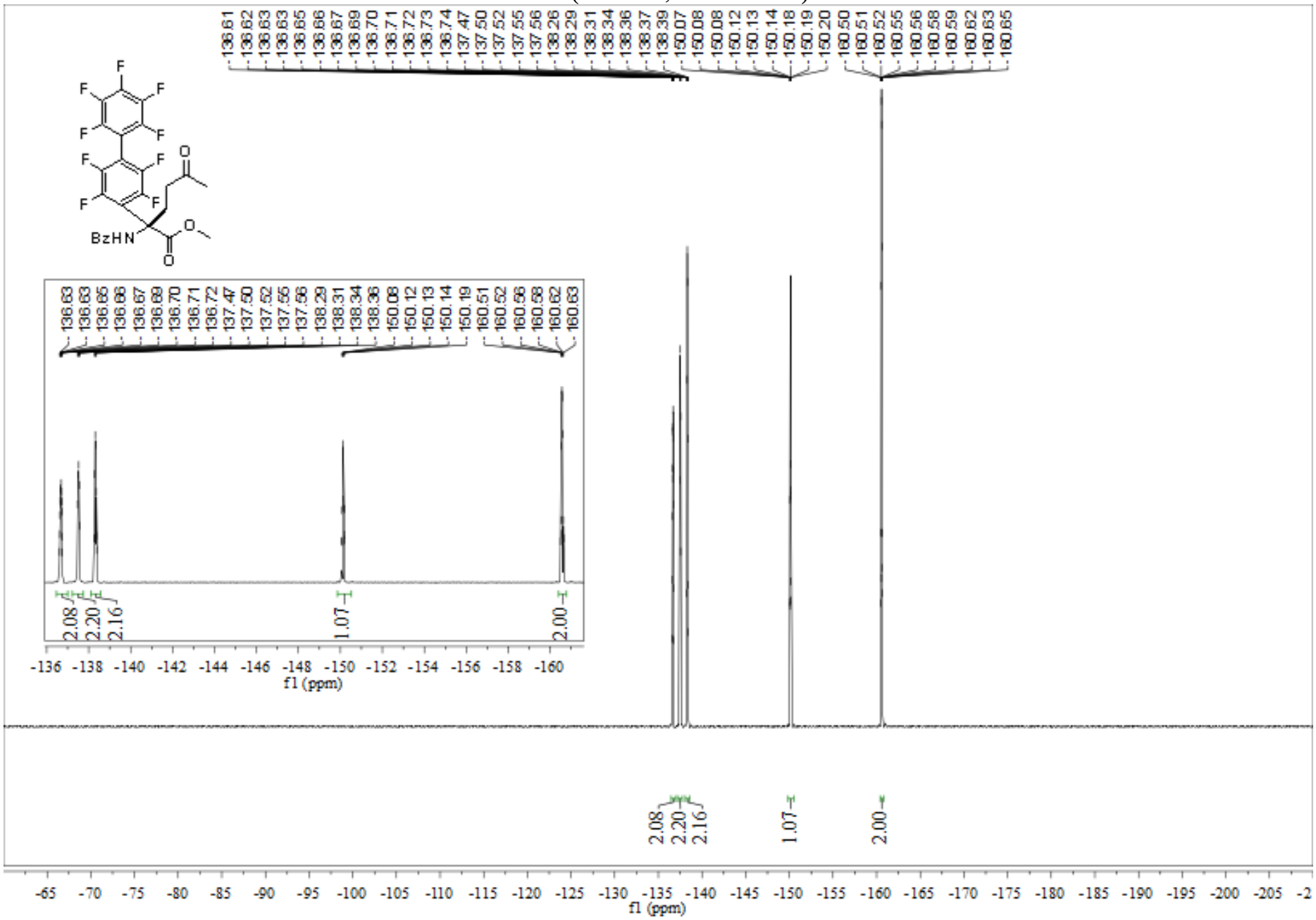

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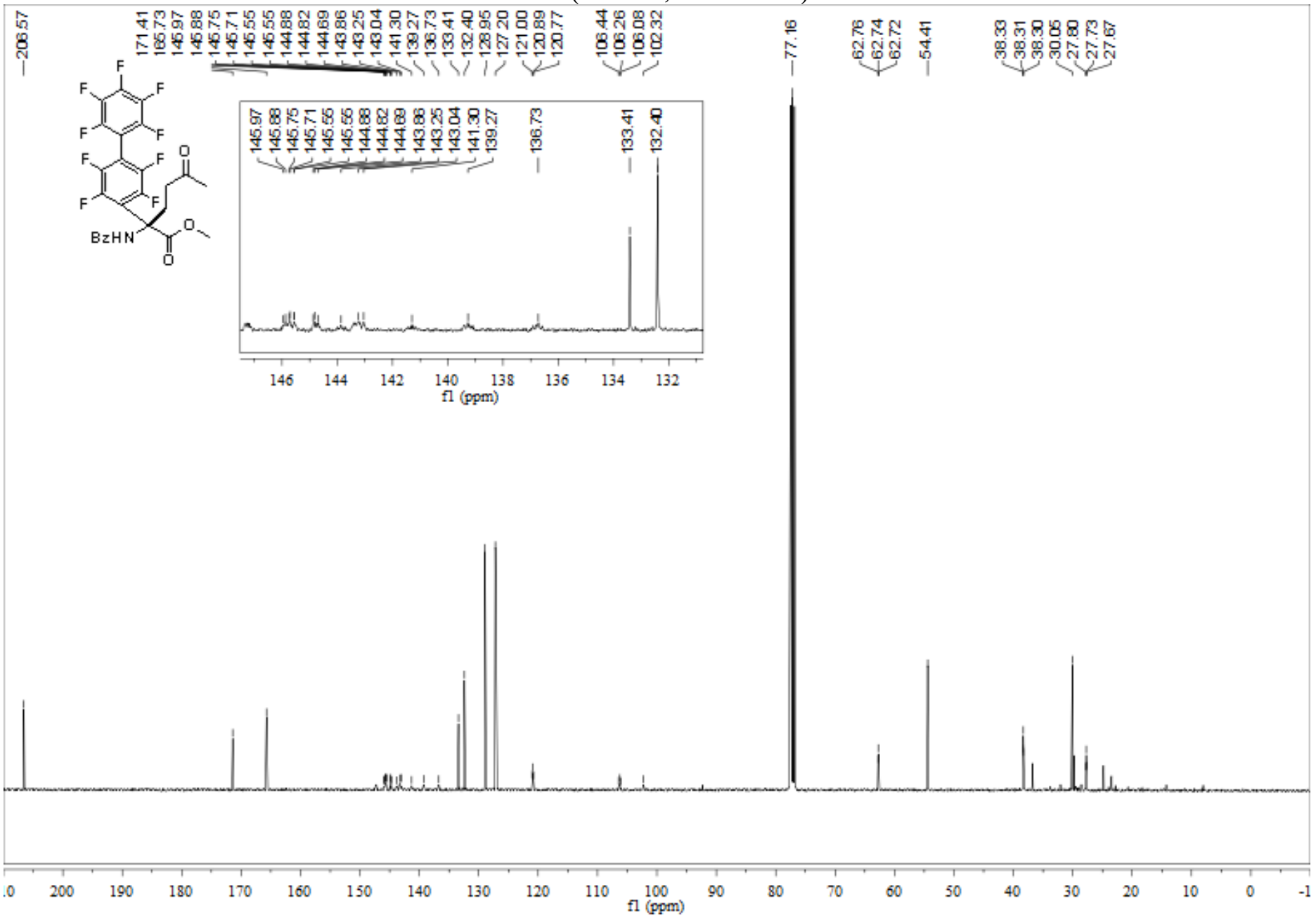
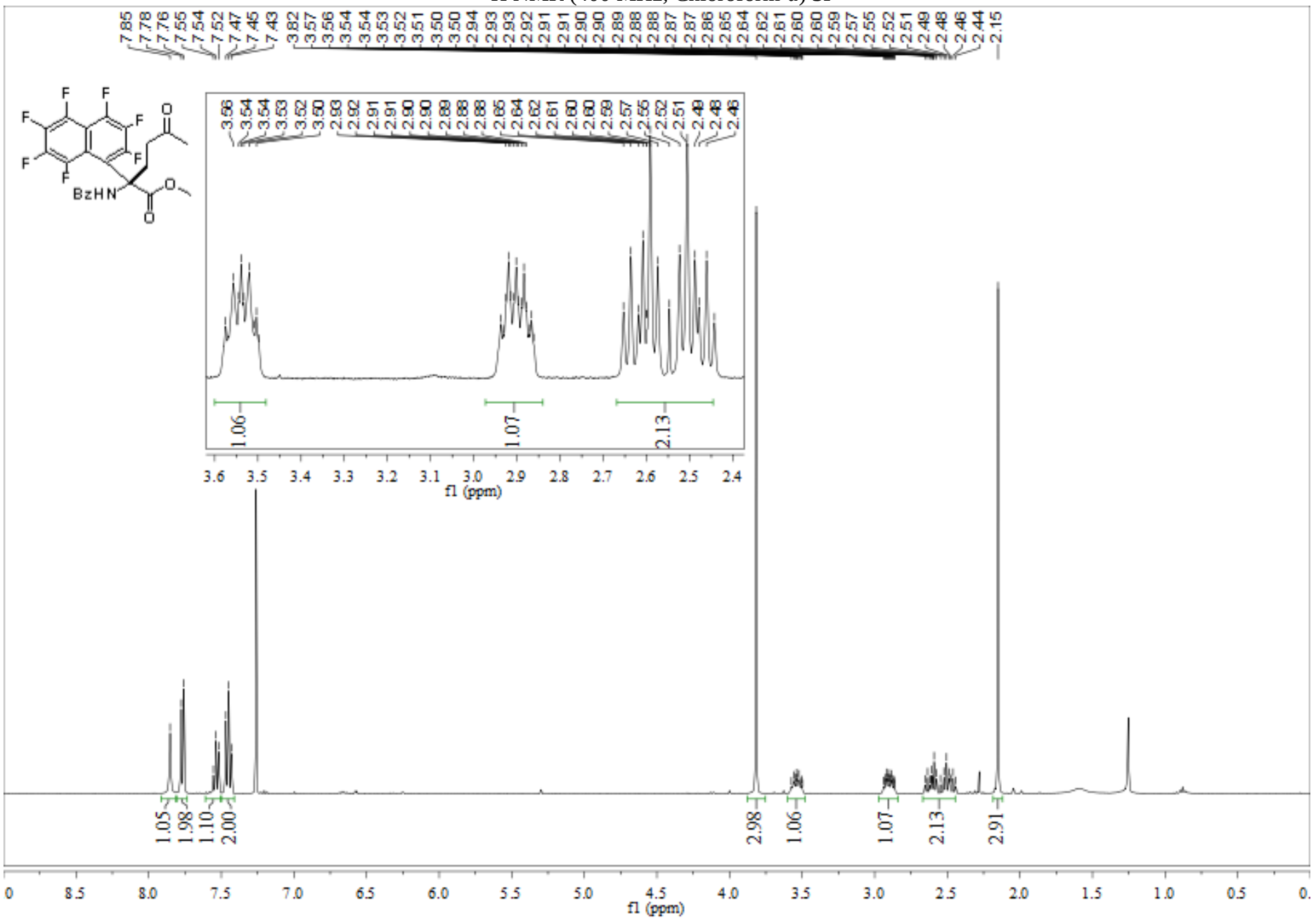
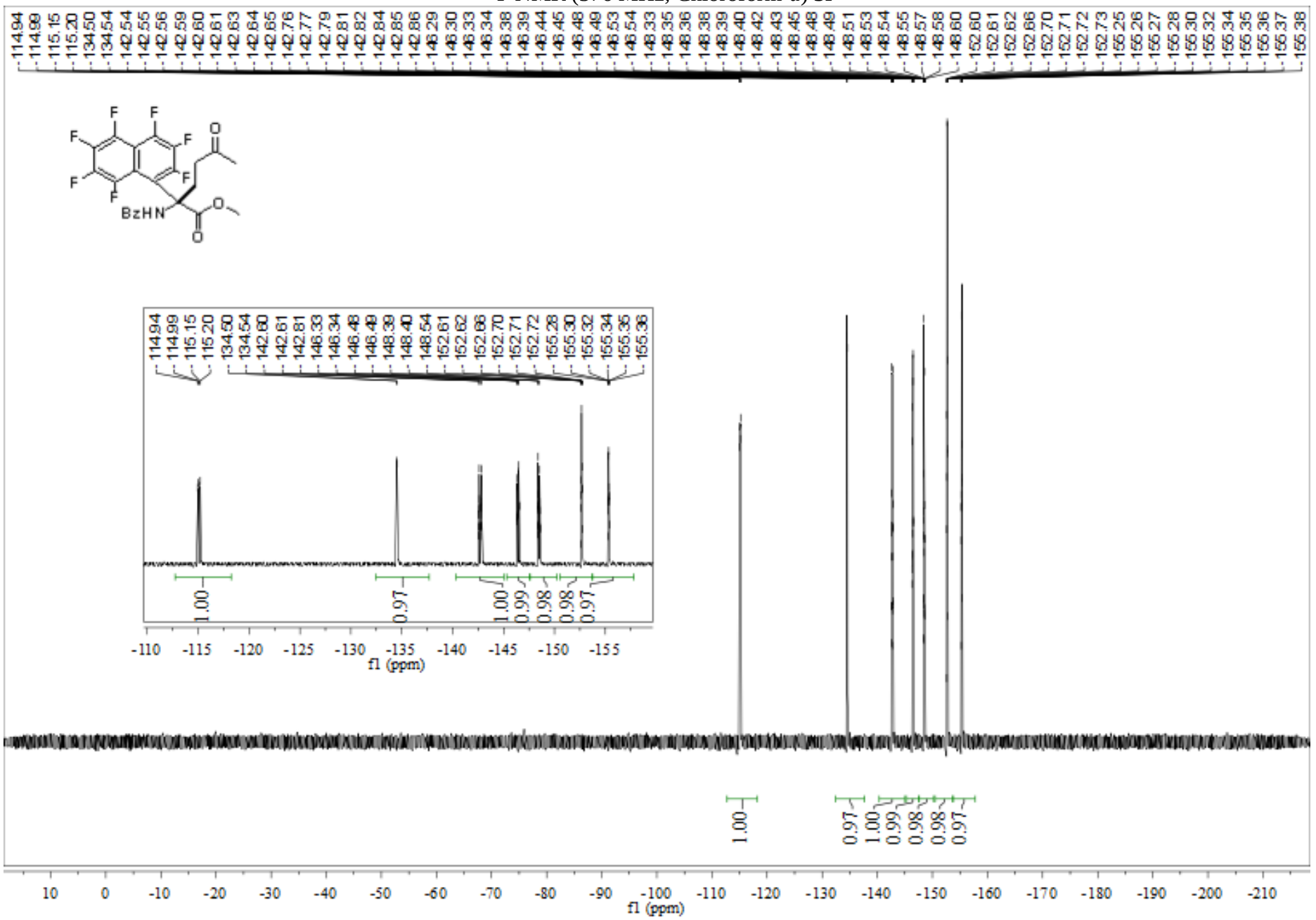


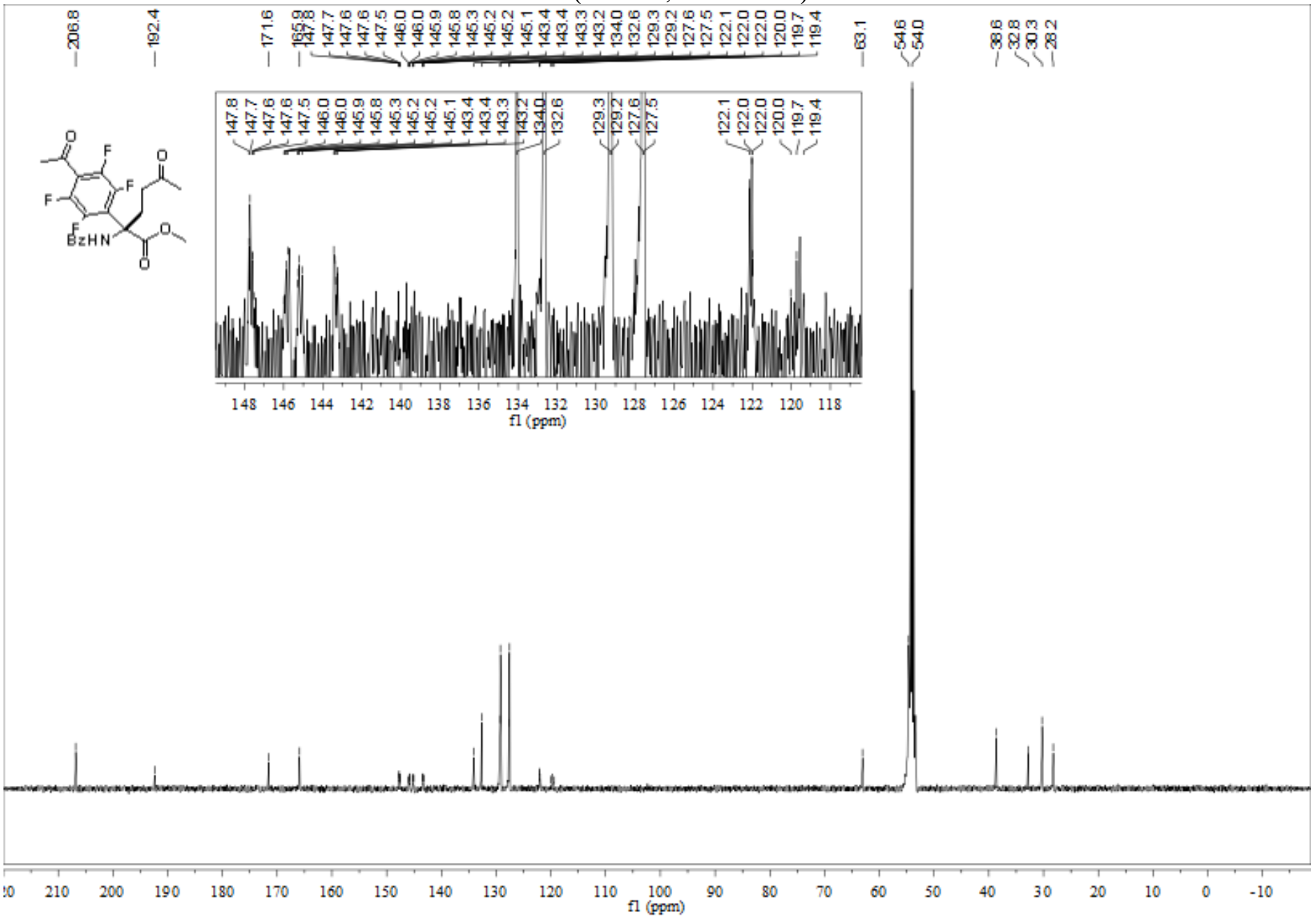
^{1}H NMR (400 MHz, Chloroform-*d*) **3f**



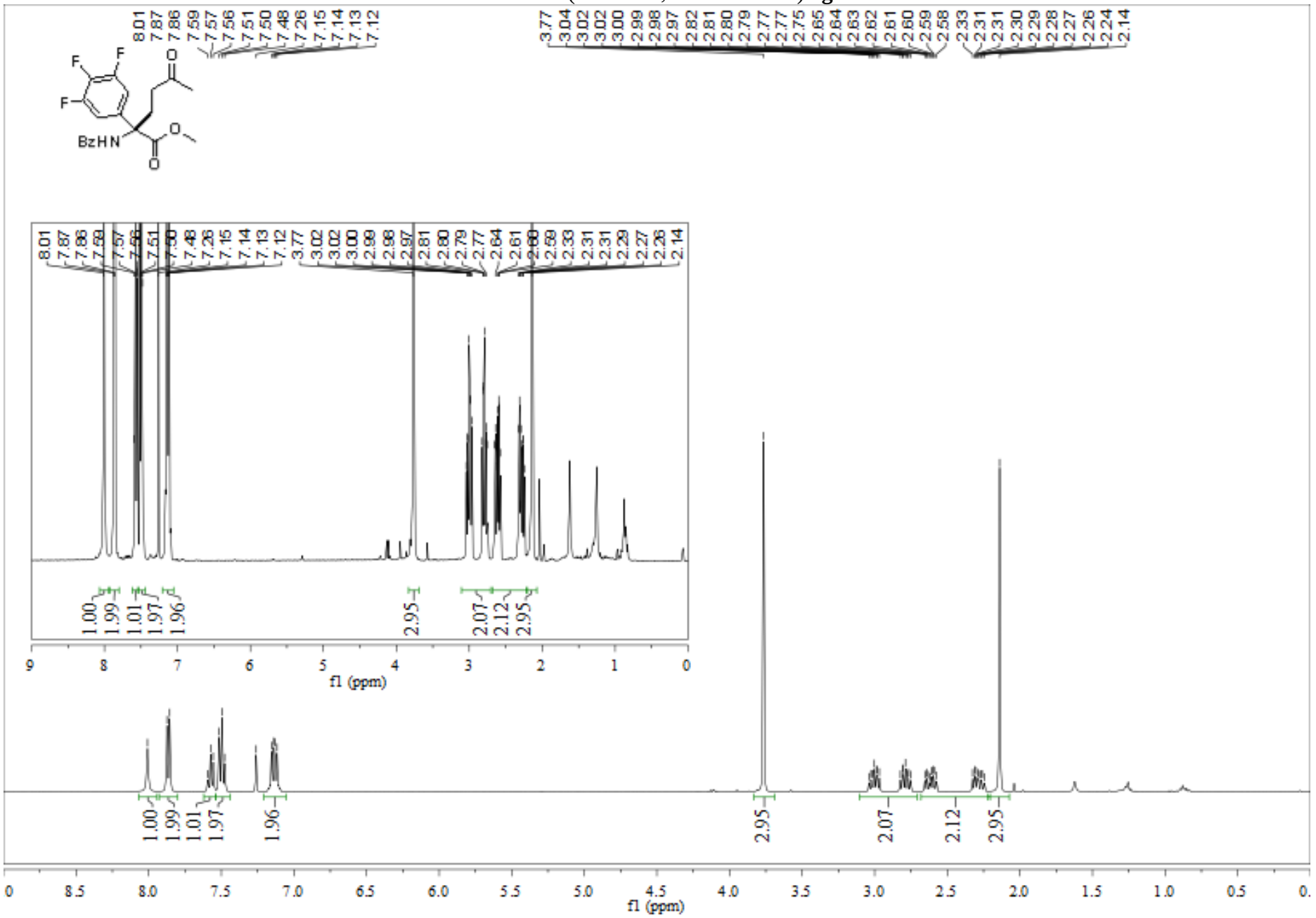
^{19}F NMR (376 MHz, Chloroform-*d*) **3f**



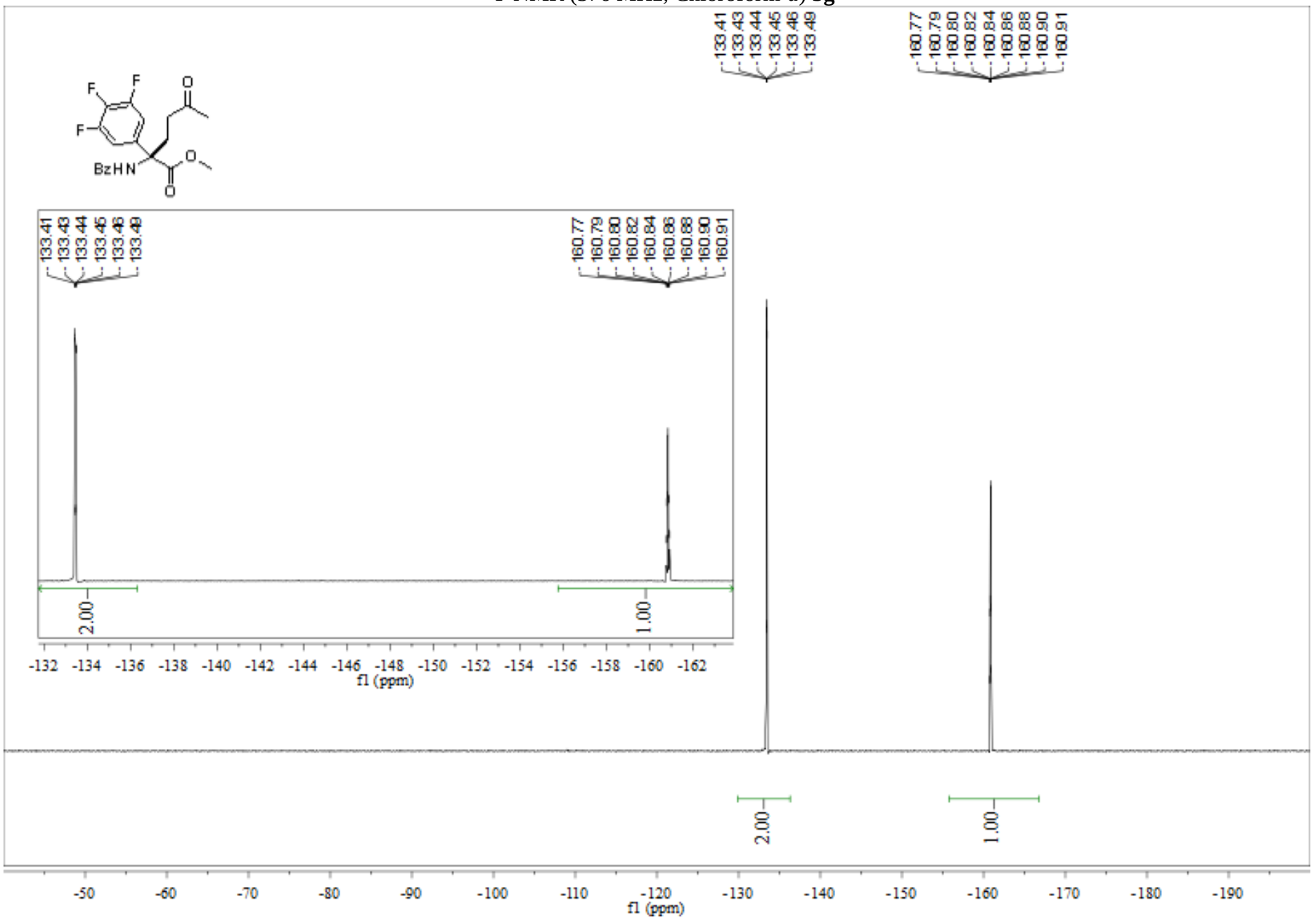
^{13}C NMR (101 MHz, Chloroform-*d*) **3f**



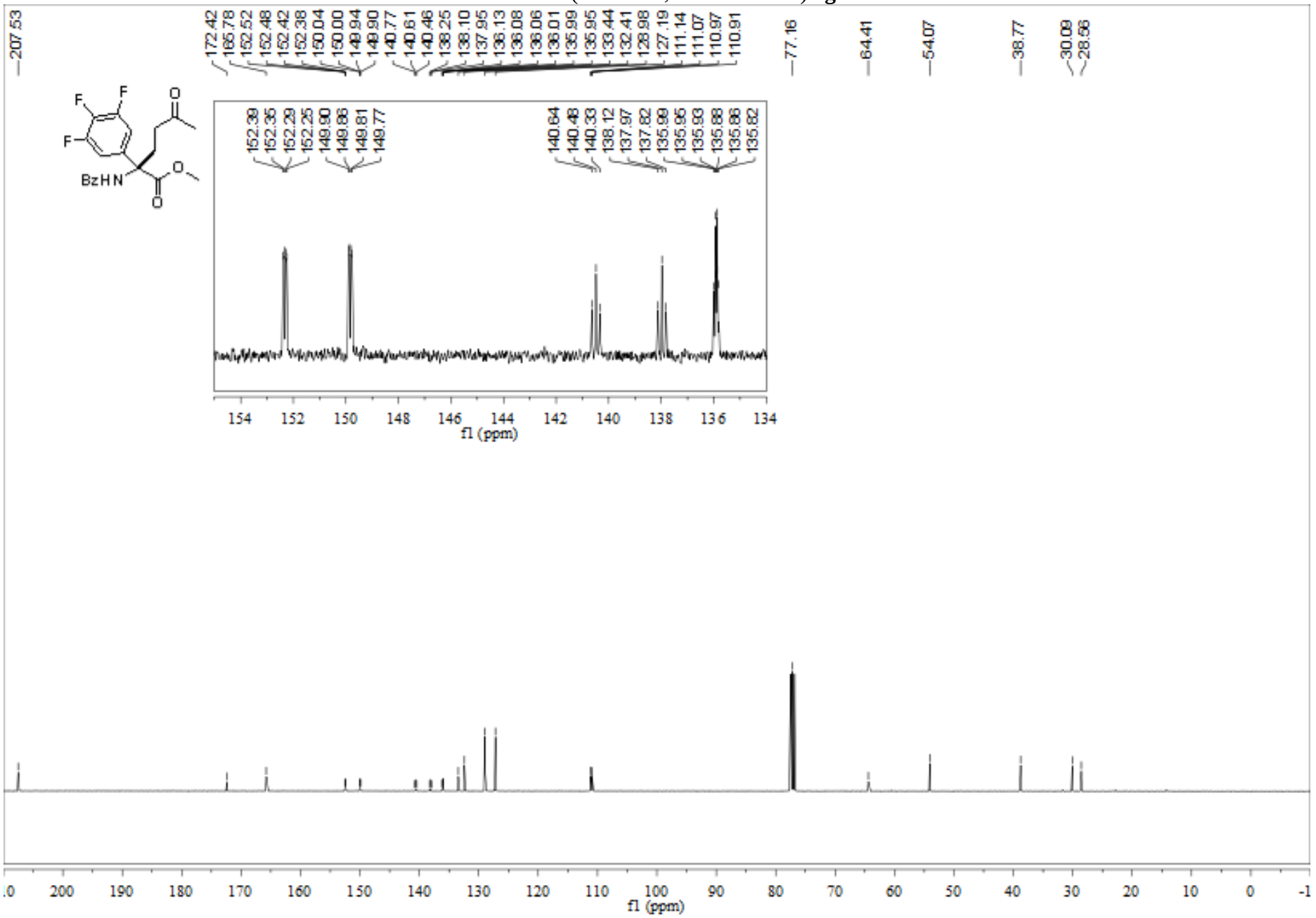
^{1}H NMR (400 MHz, Chloroform-*d*) **3g**



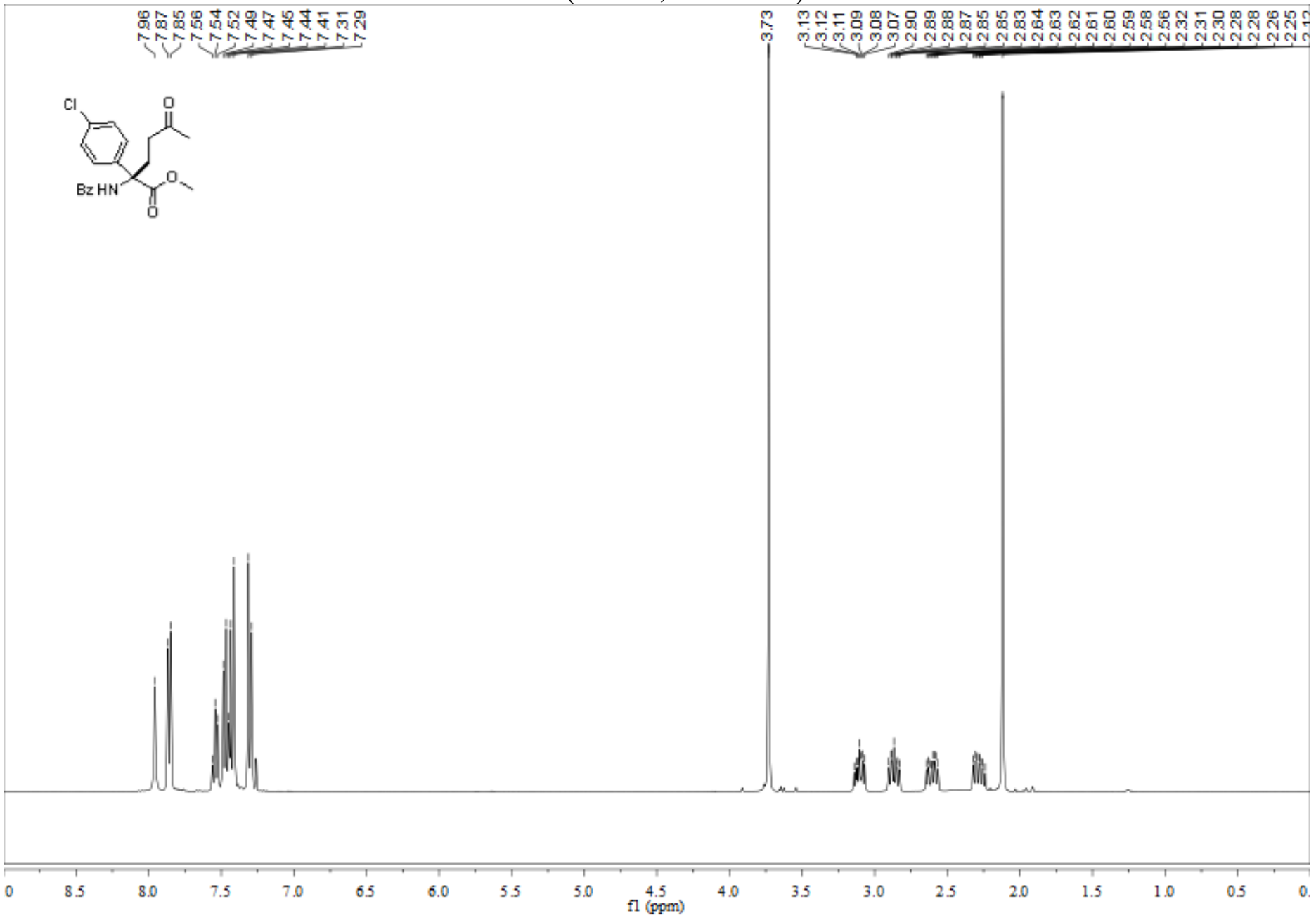
^{19}F NMR (376 MHz, Chloroform-*d*) **3g**



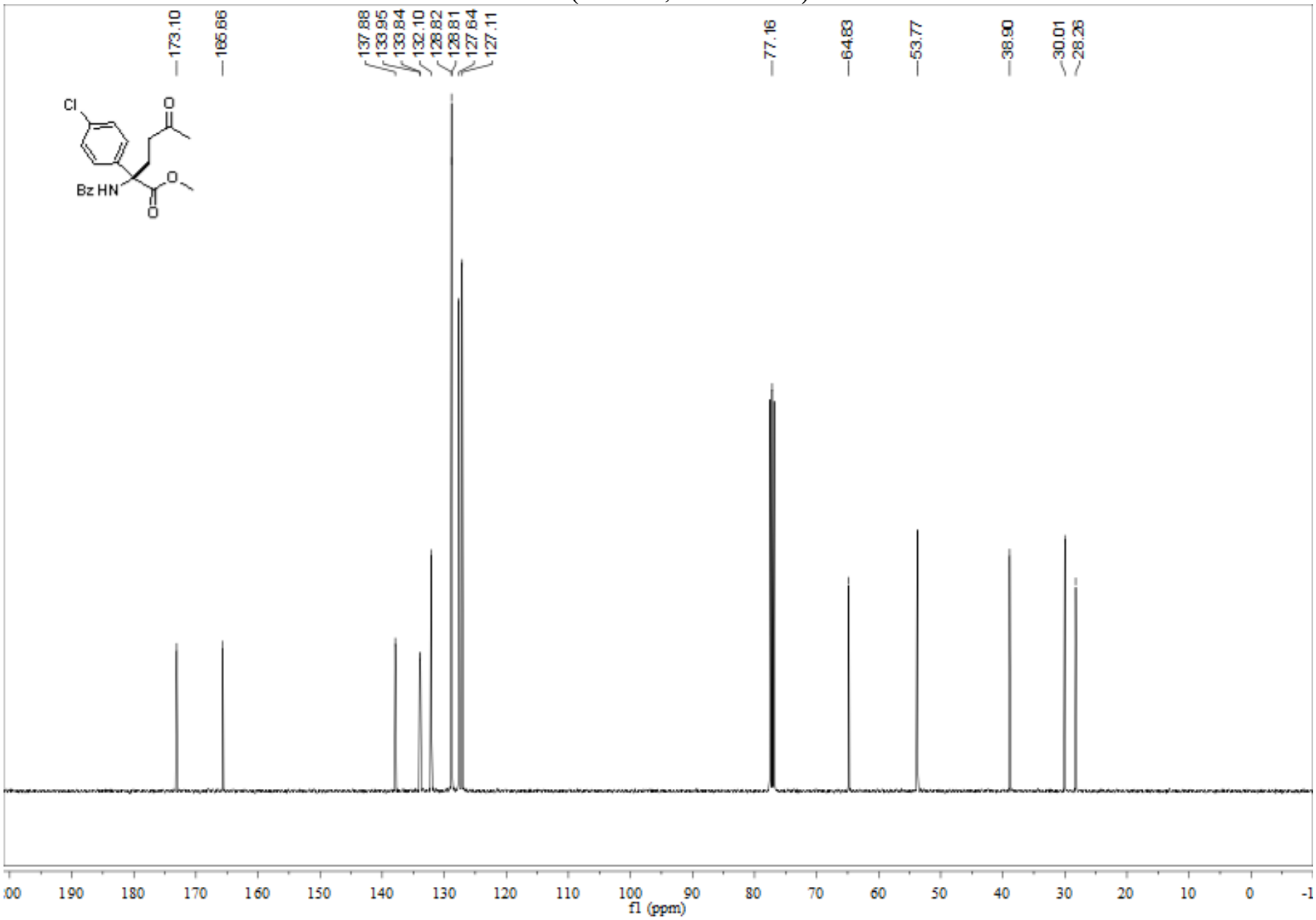
^{13}C NMR (101 MHz, Chloroform-*d*) **3g**



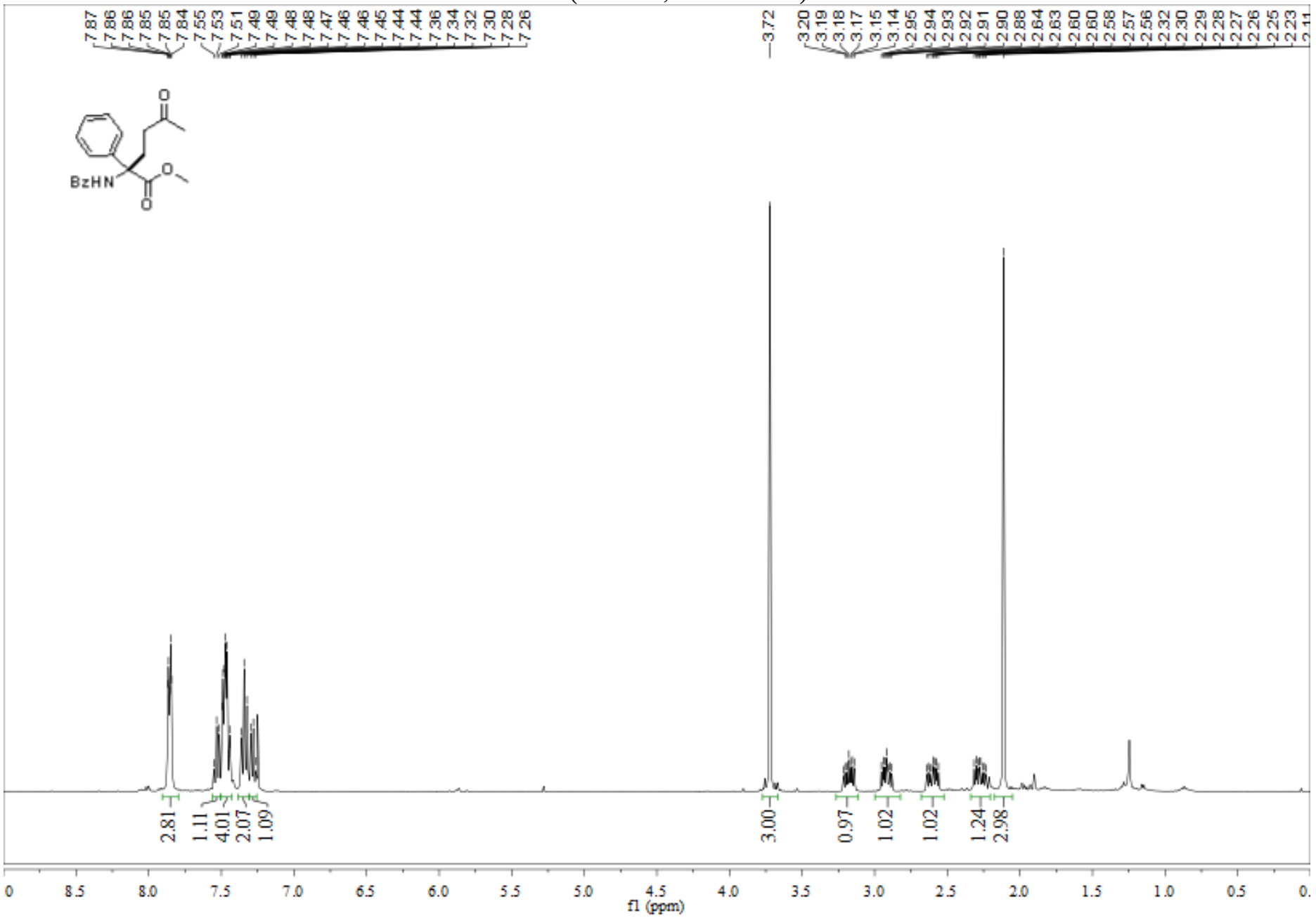
^{1}H NMR (400 MHz, Chloroform-*d*) **3h**



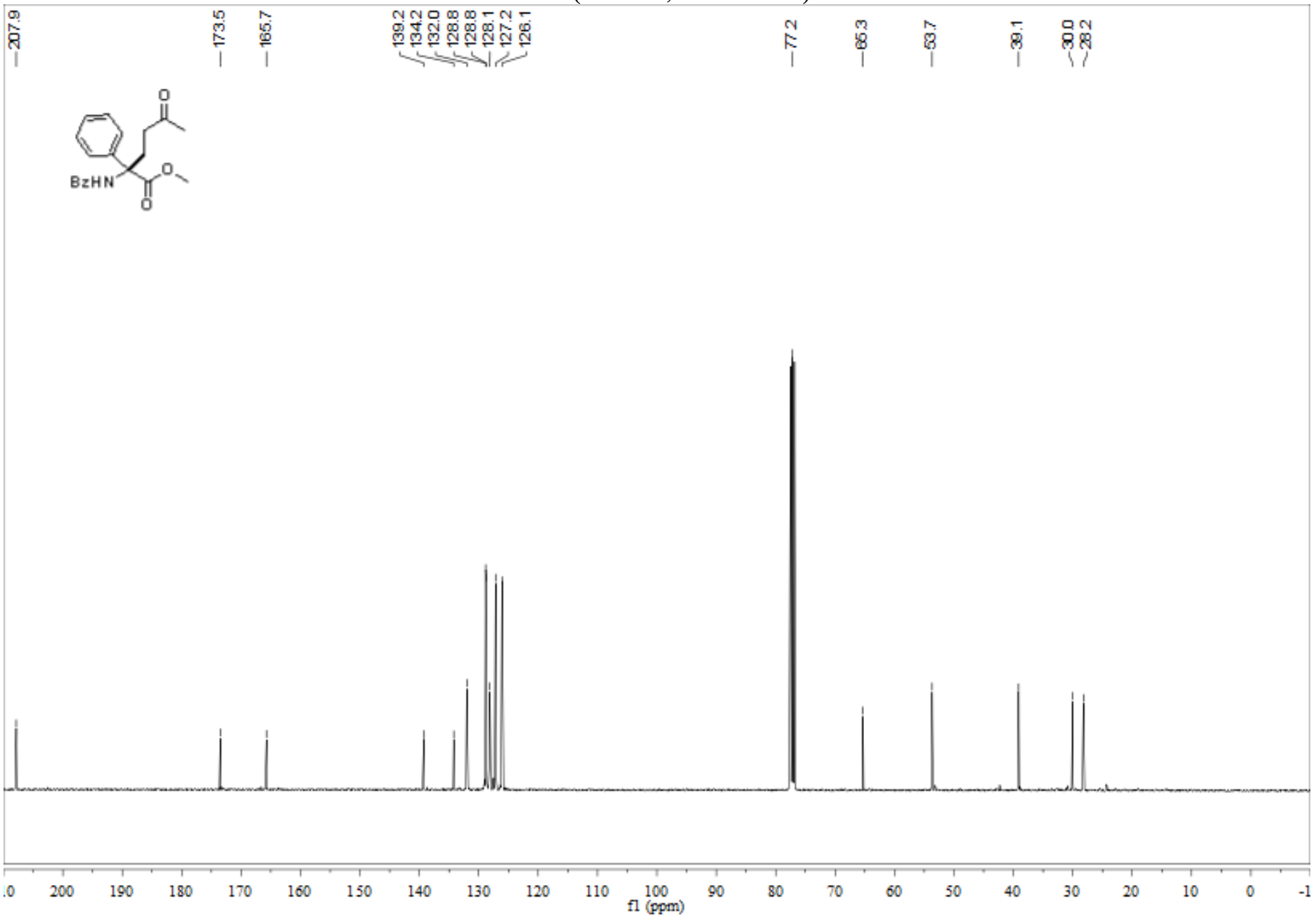
^{13}C NMR (101 MHz, Chloroform-*d*) **3h**



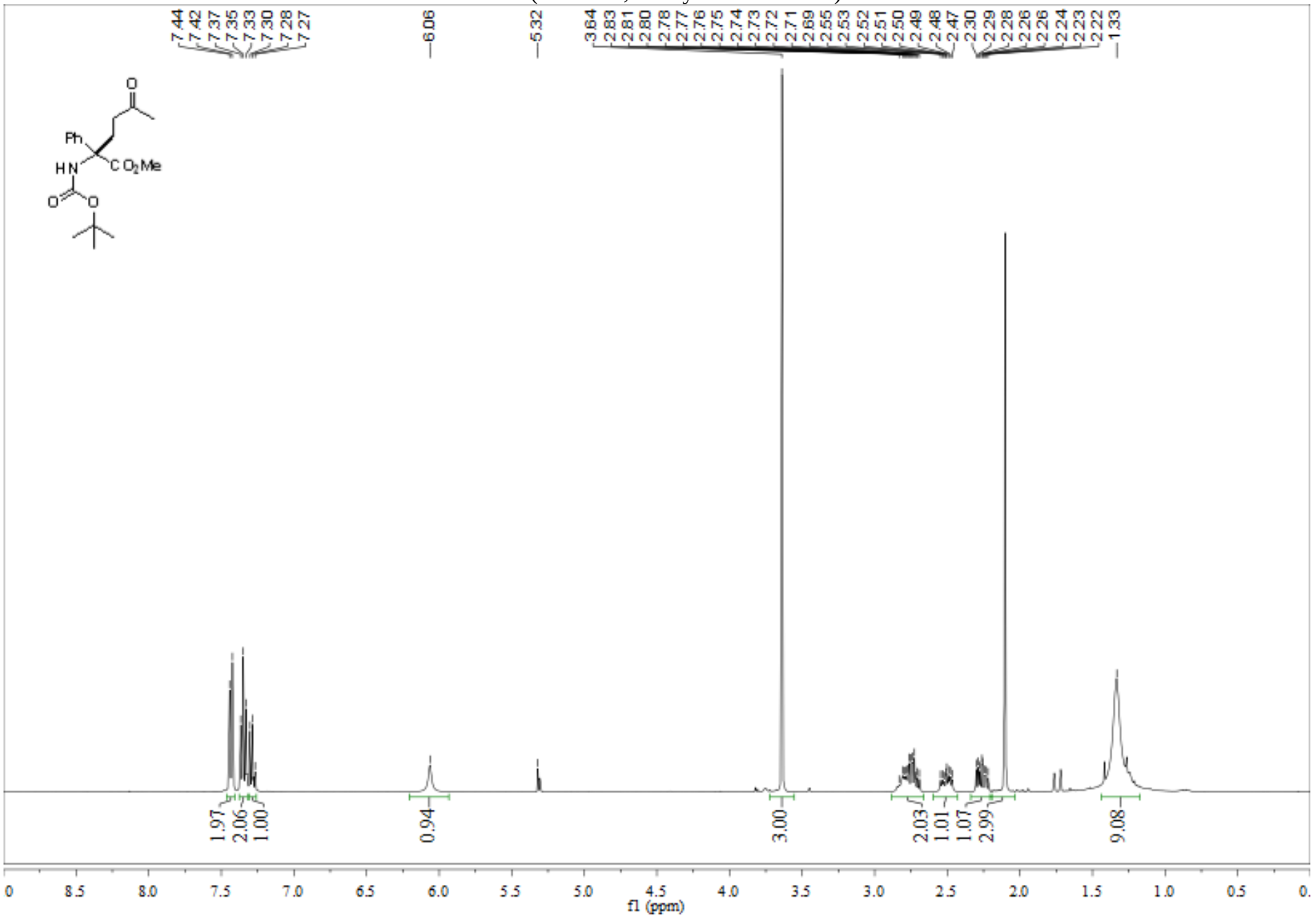
^{1}H NMR (400 MHz, Chloroform-*d*) **3i**



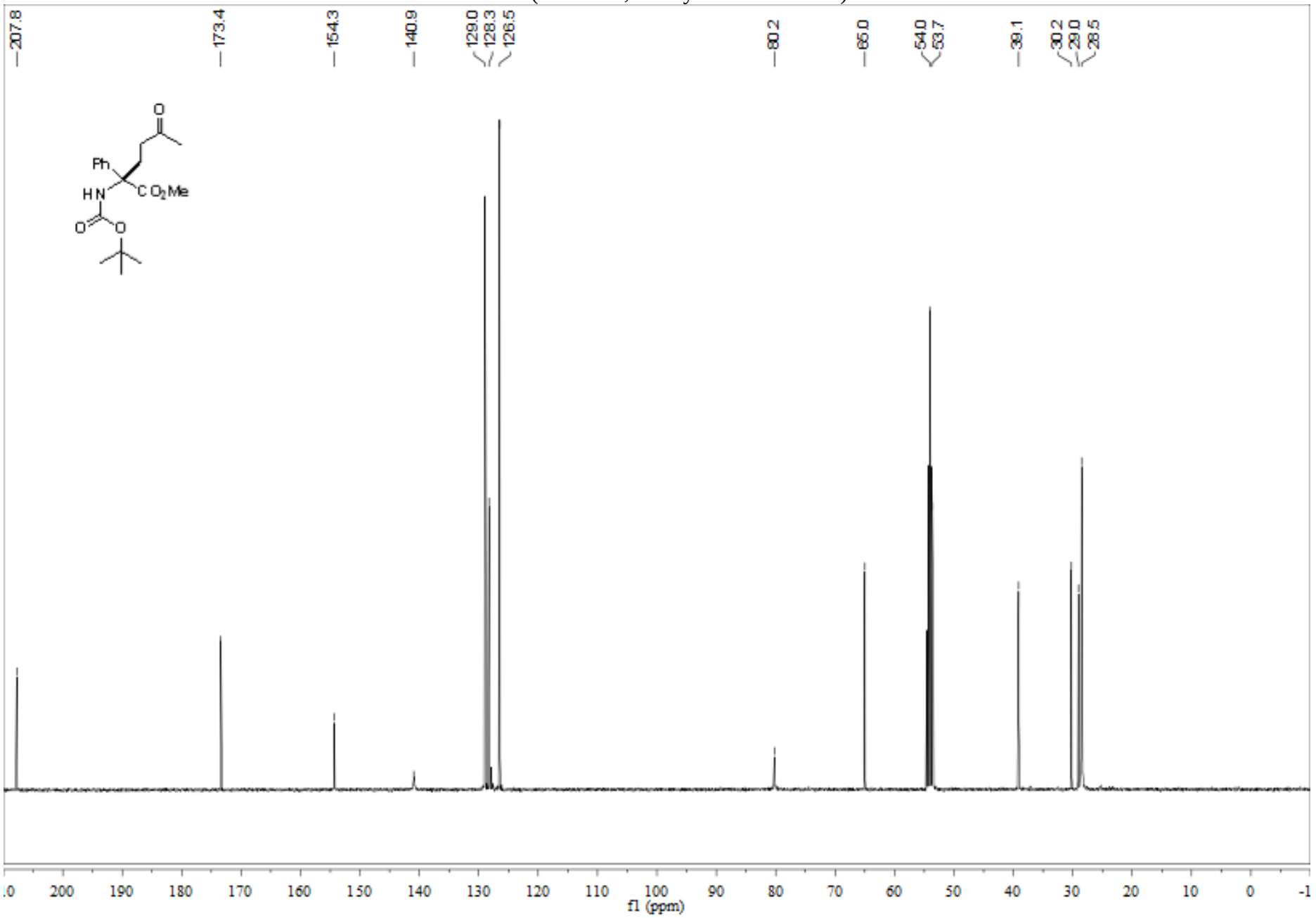
^{13}C NMR (101 MHz, Chloroform-*d*) **3i**



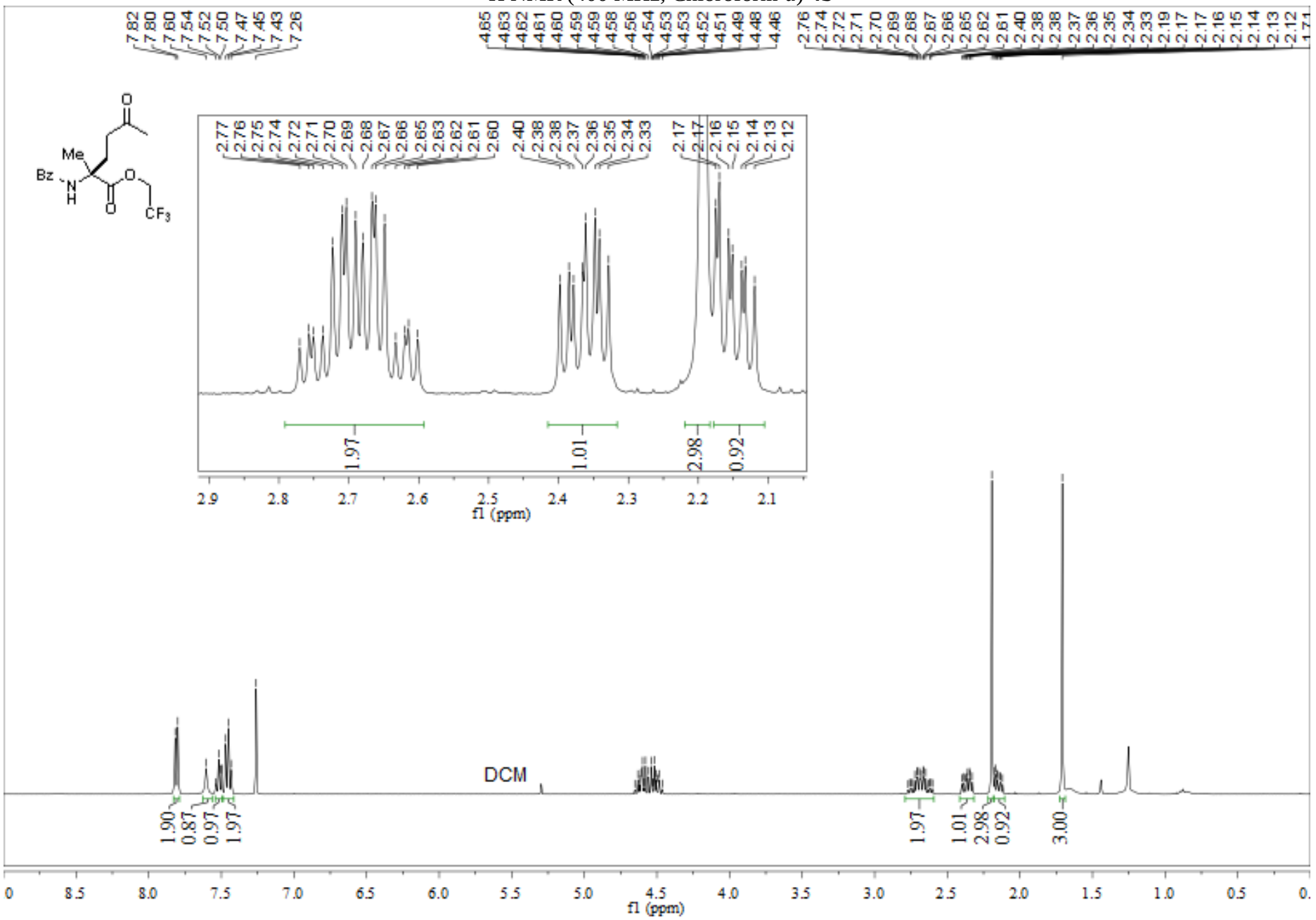
^{1}H NMR (400 MHz, Methylene Chloride-*d*) **4a**



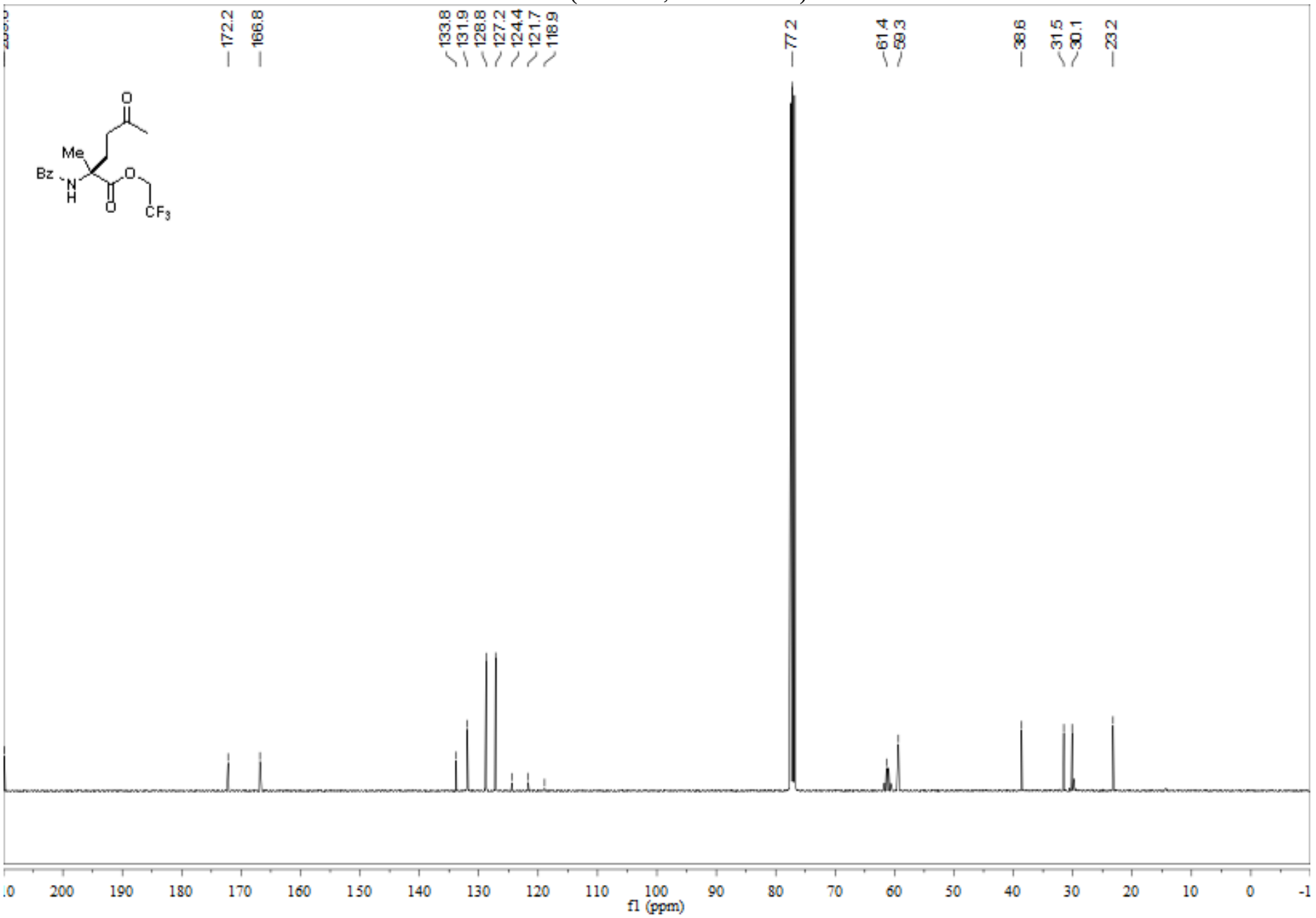
^{13}C NMR (101 MHz, Methylene Chloride -*d*) **4a**



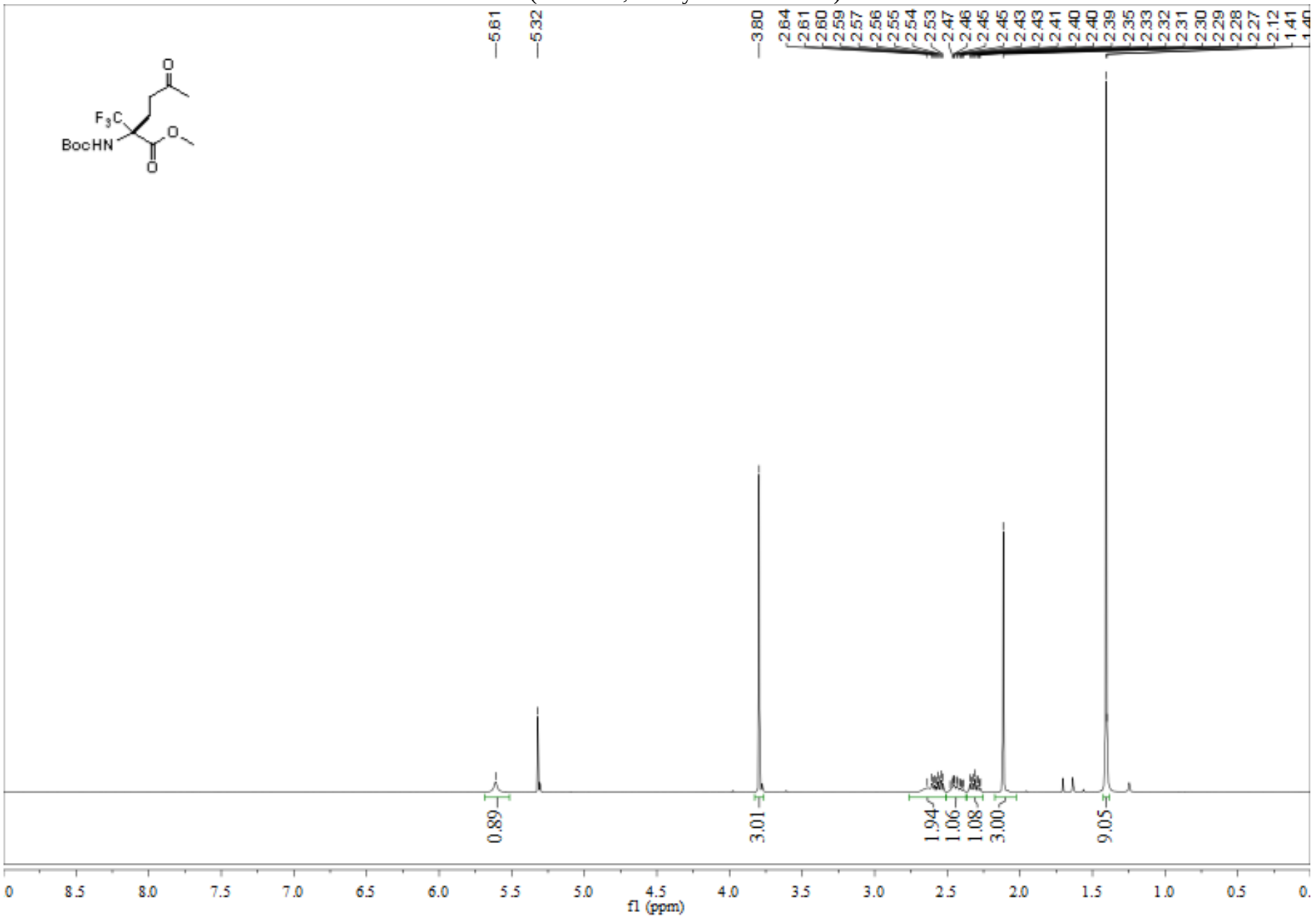
^{1}H NMR (400 MHz, Chloroform-*d*) **4b**



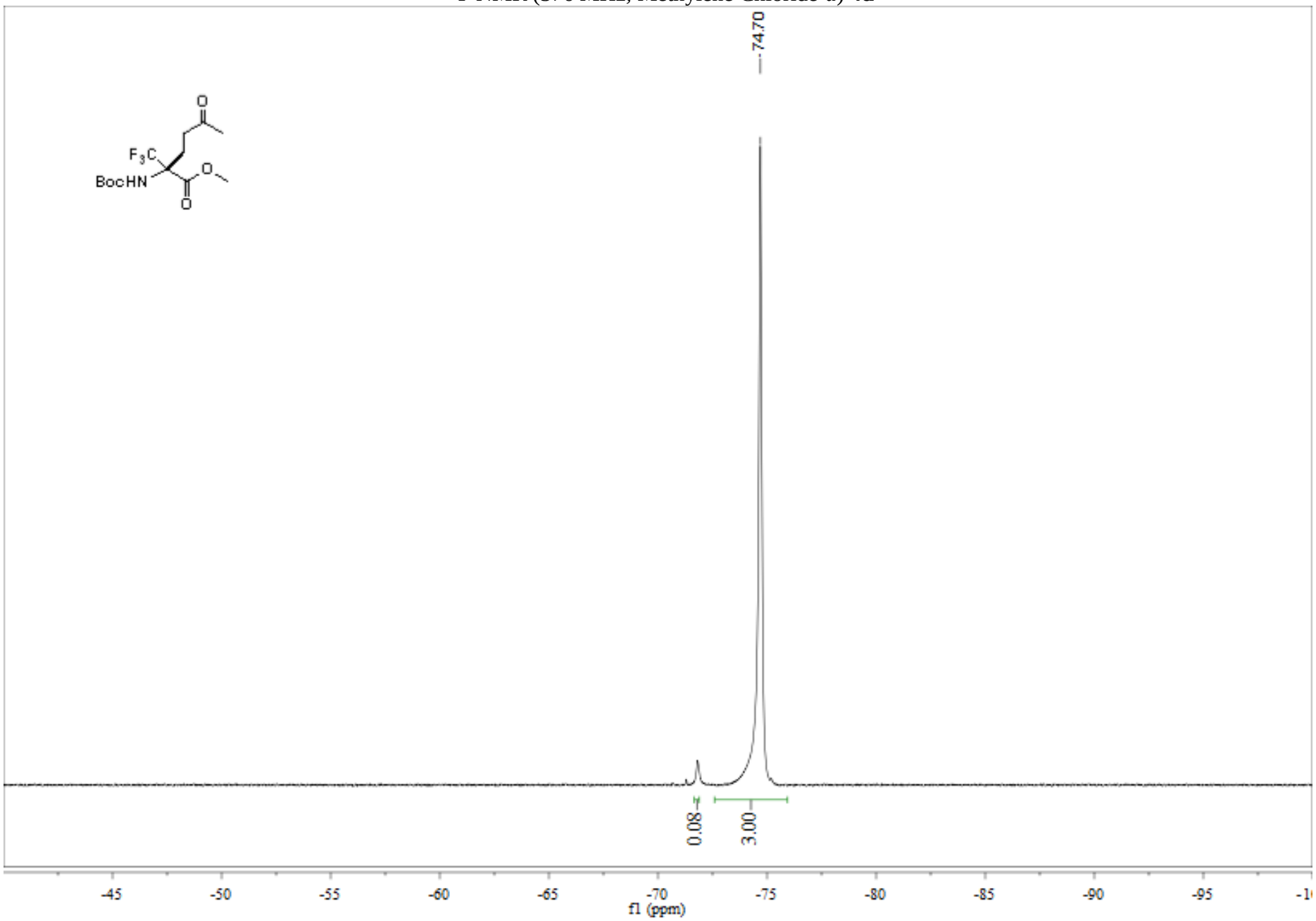
^{13}C NMR (101 MHz, Chloroform-*d*) **4b**



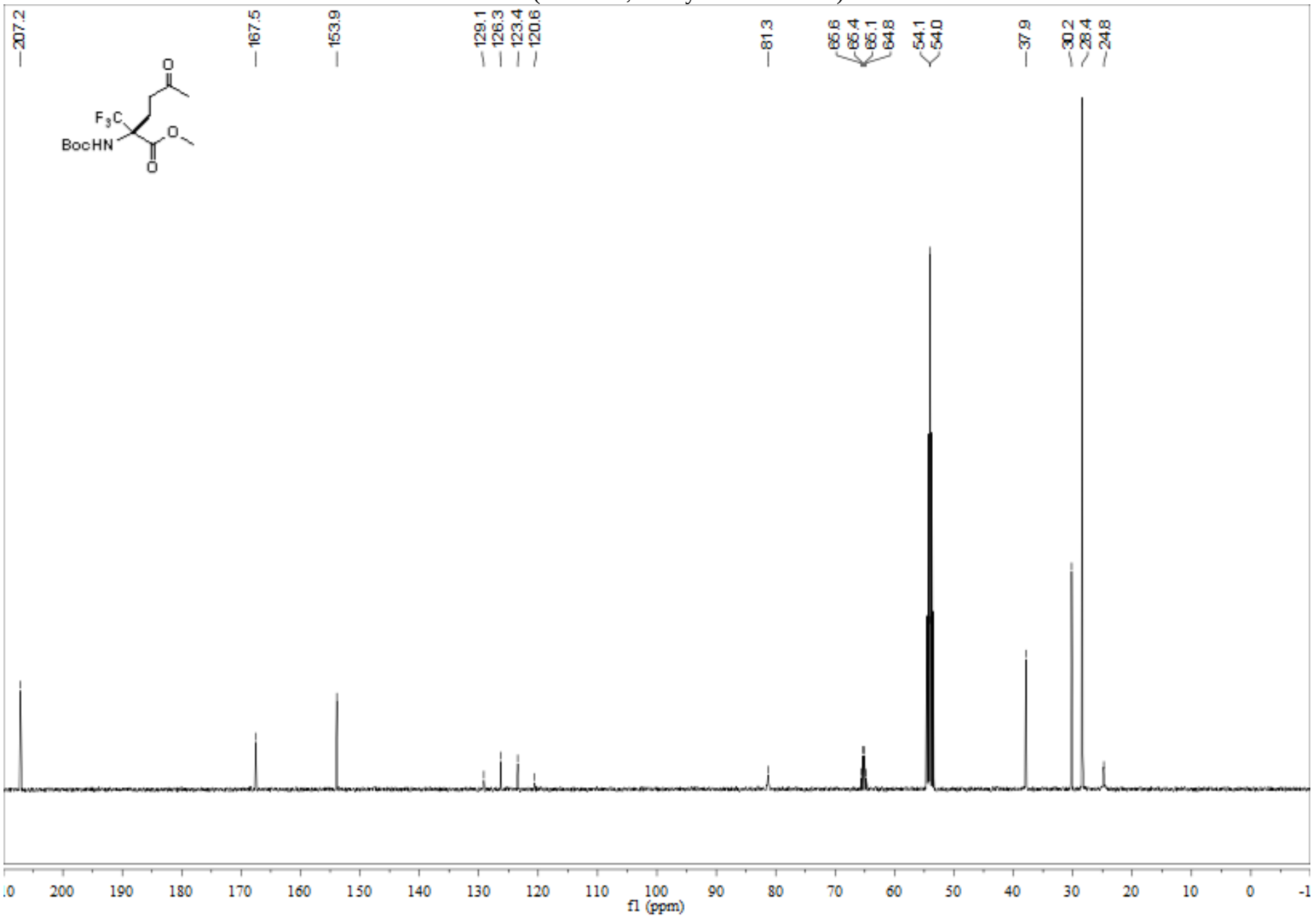
[1]H NMR (400 MHz, Methylene Chloride-*d*) **4d**



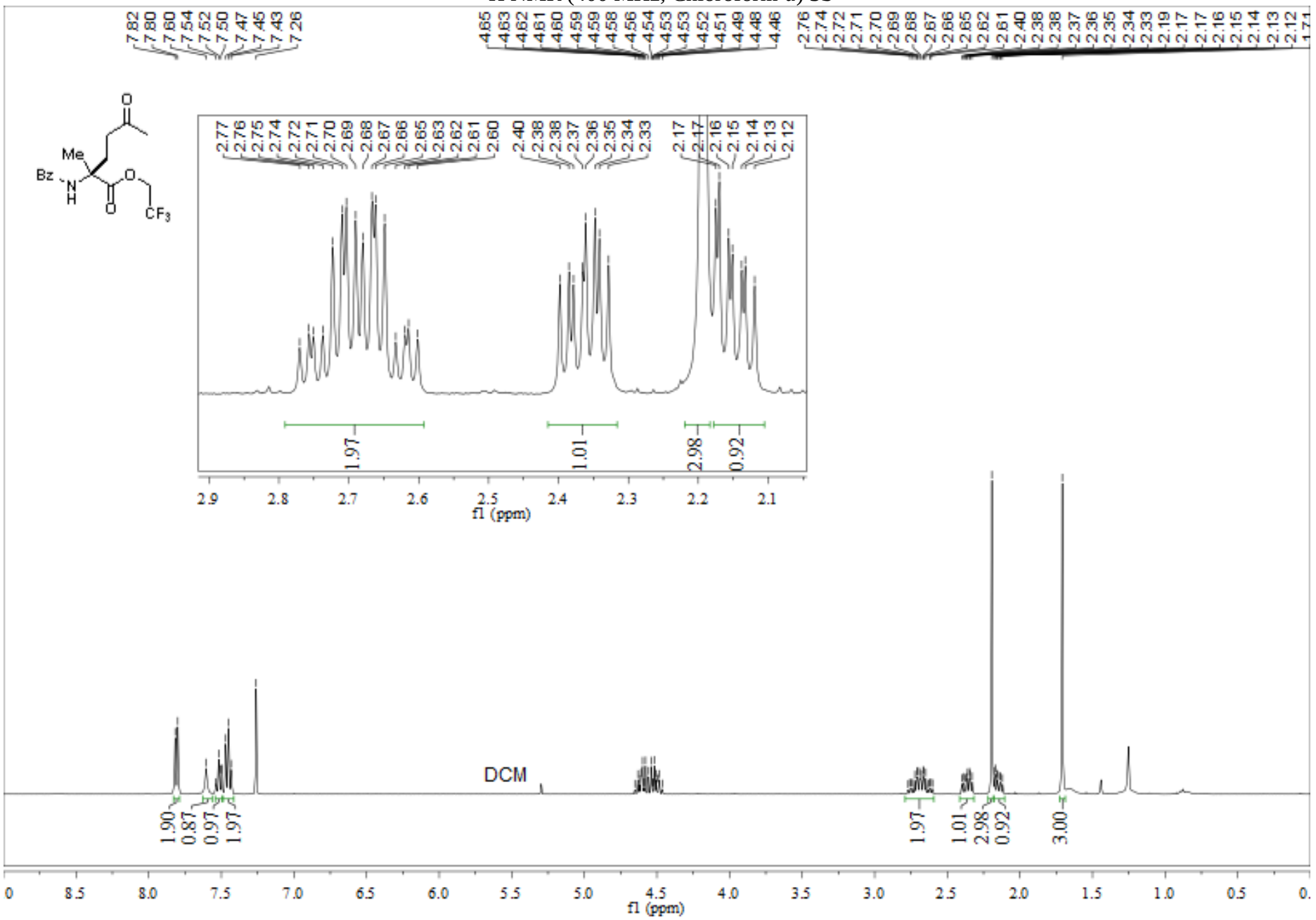
^{19}F NMR (376 MHz, Methylene Chloride-*d*) **4d**



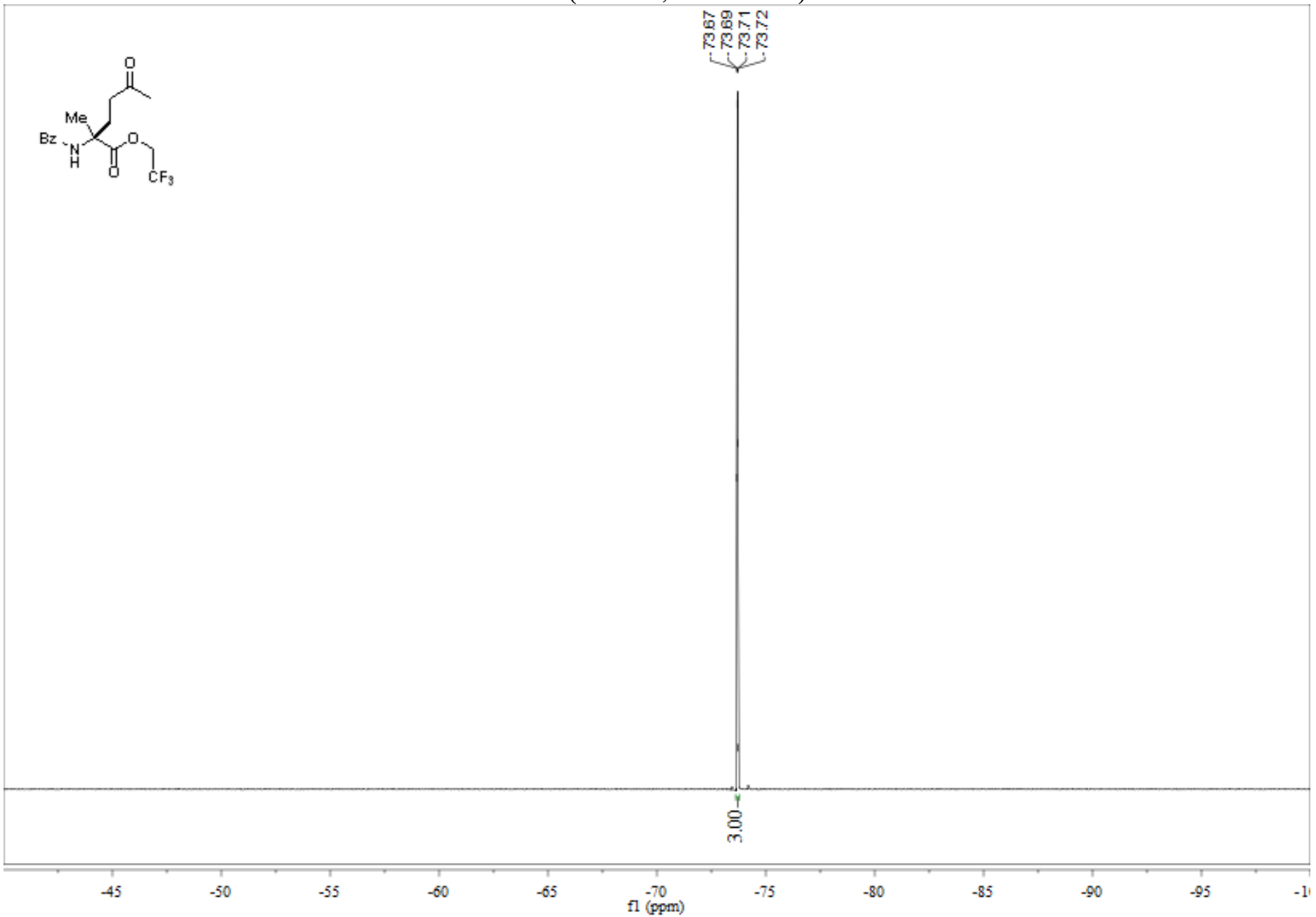
^{13}C NMR (101 MHz, Methylene Chloride-*d*) **4d**



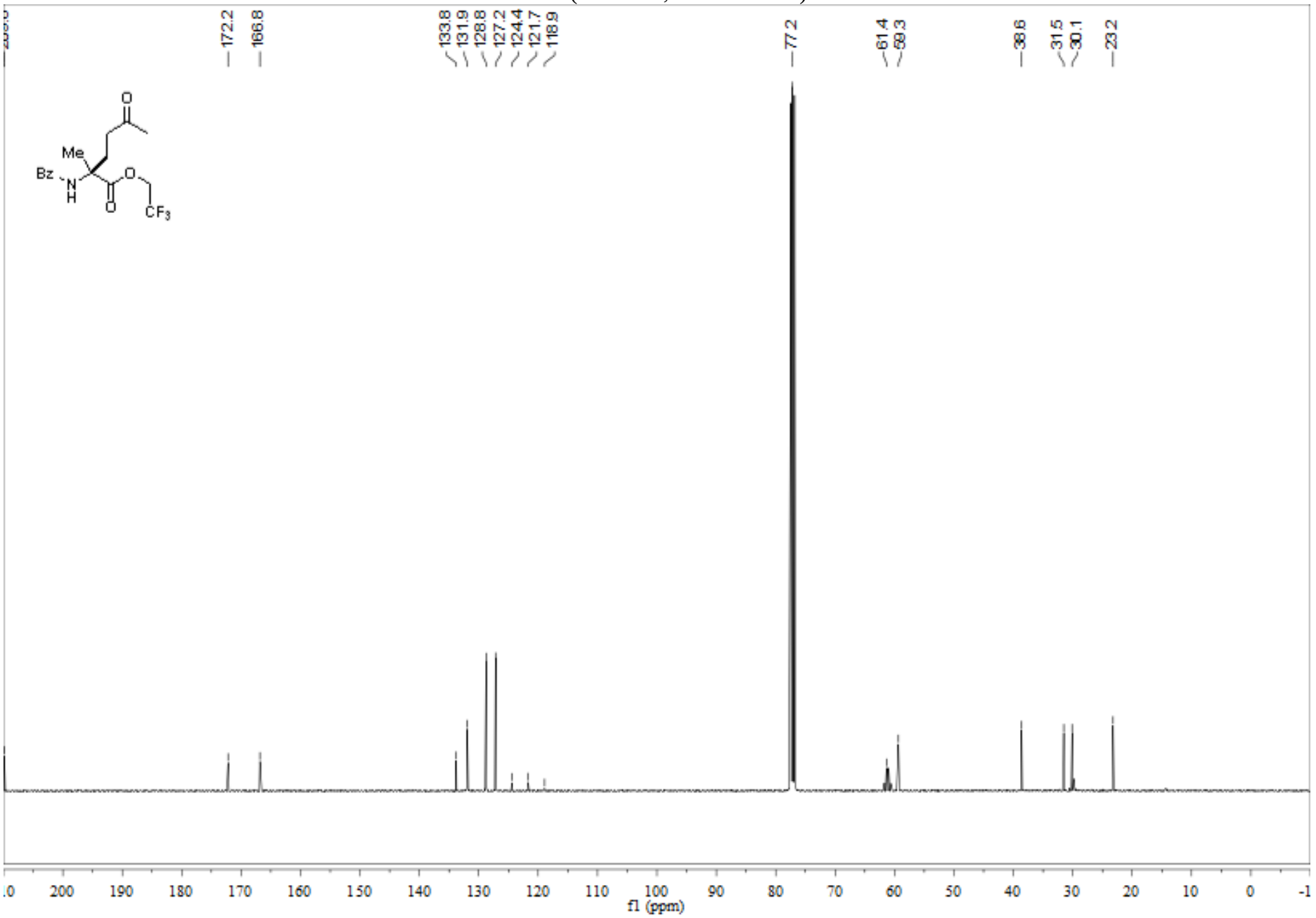
^{1}H NMR (400 MHz, Chloroform-*d*) **5b**



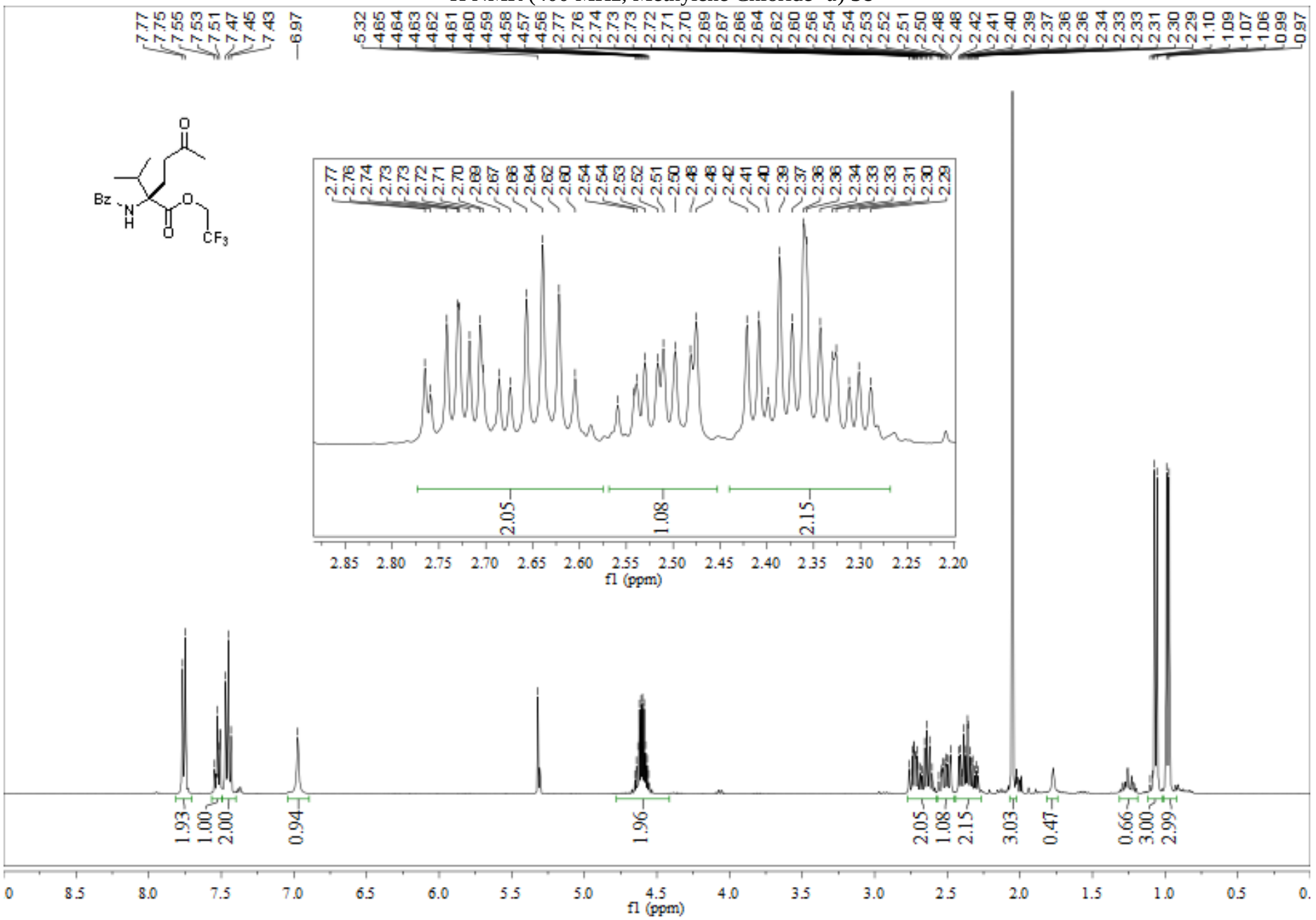
^{19}F NMR (376 MHz, Chloroform-*d*) **5b**



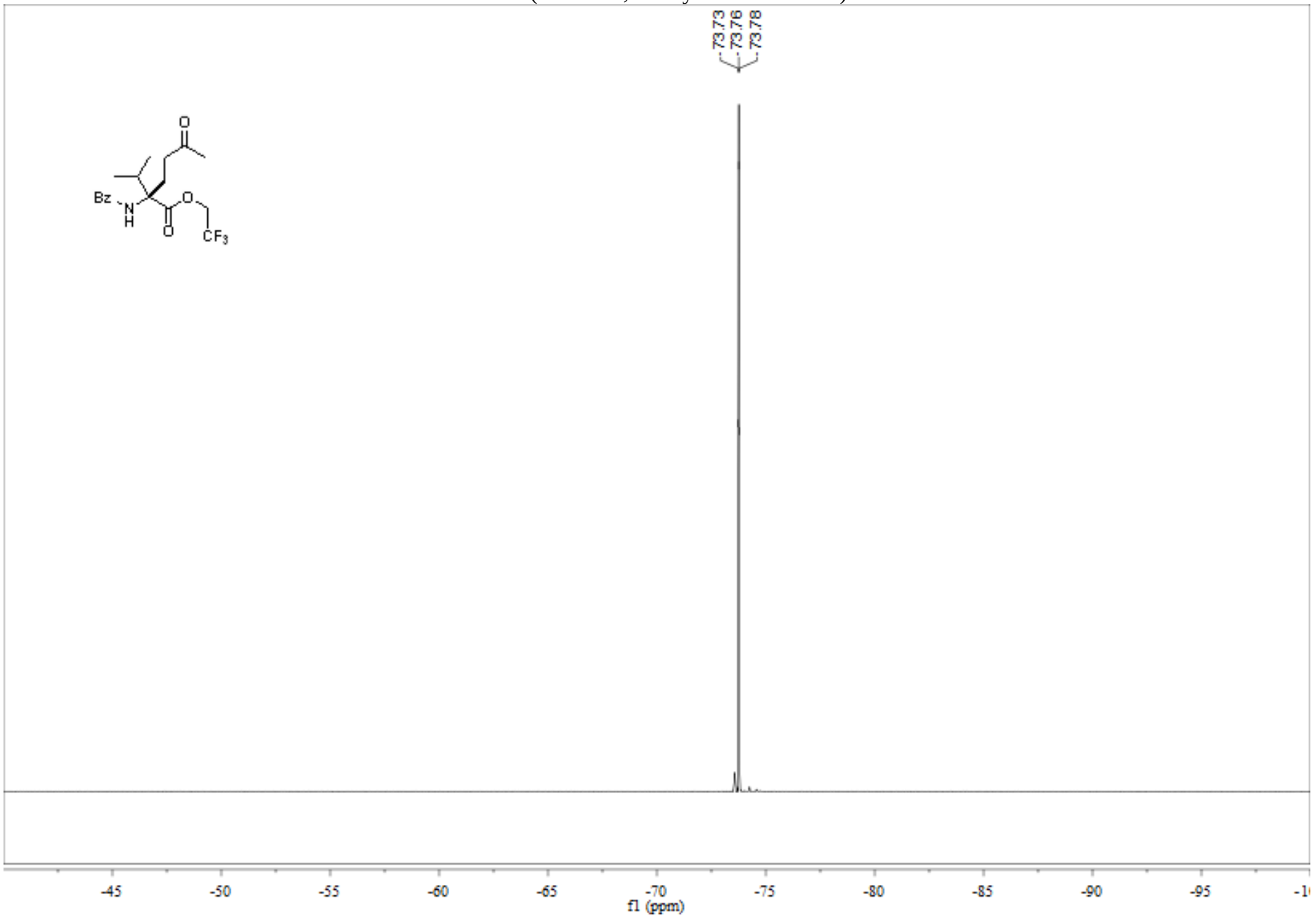
^{13}C NMR (101 MHz, Chloroform-*d*) **5b**



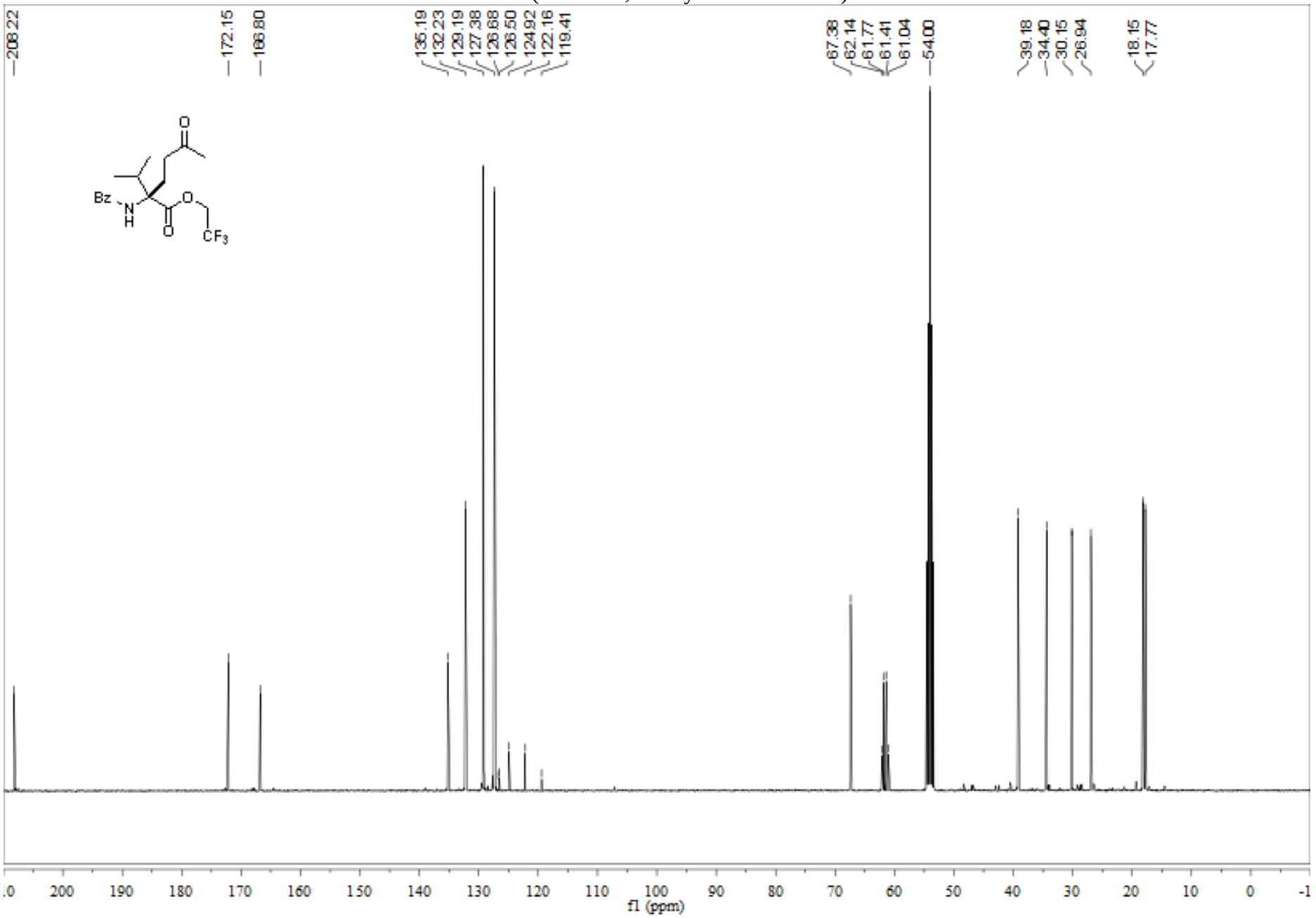
^{1}H NMR (400 MHz, Methylene Chloride -*d*) **5c**



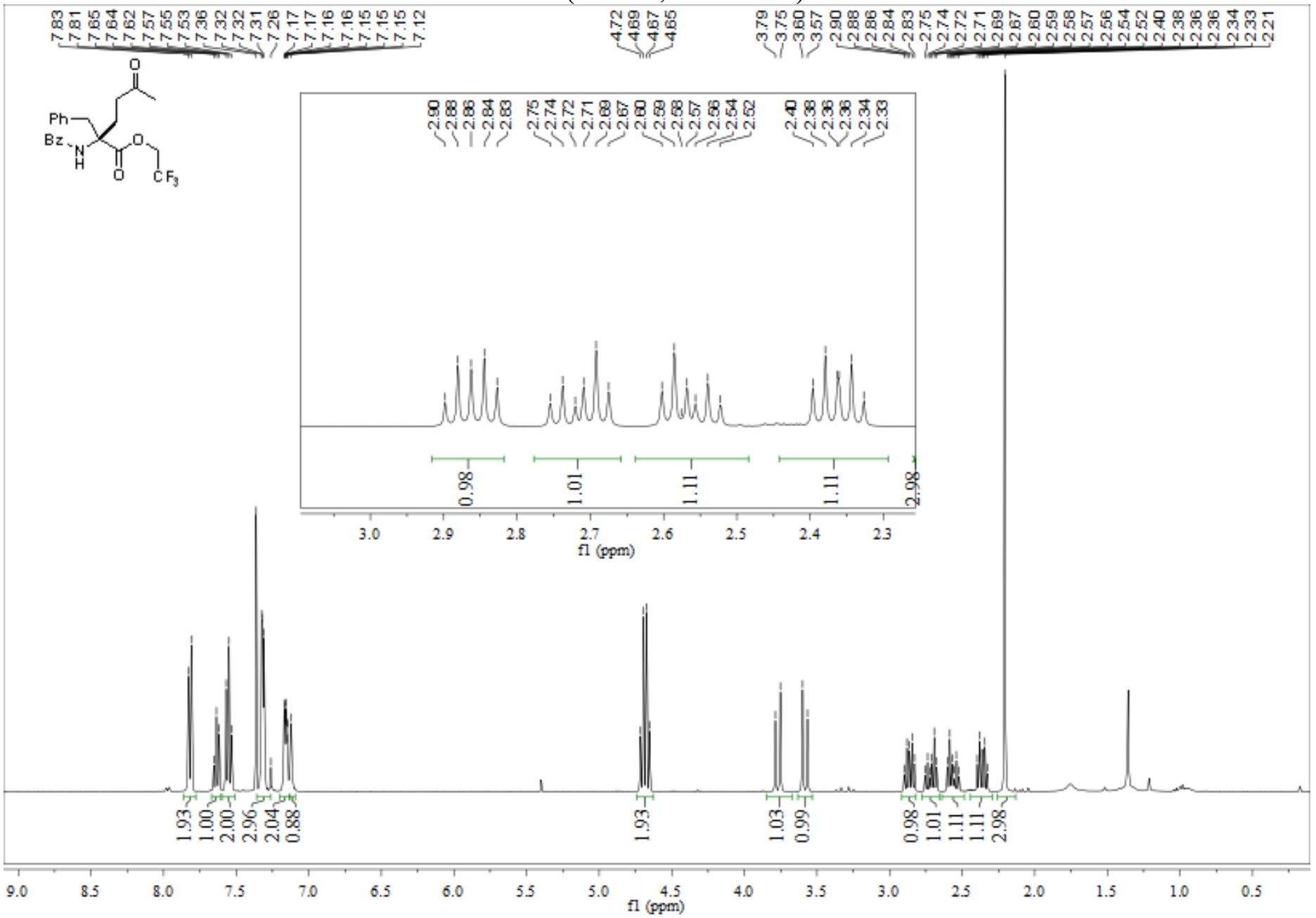
^{19}F NMR (376 MHz, Methylene Chloride -*d*) **5c**



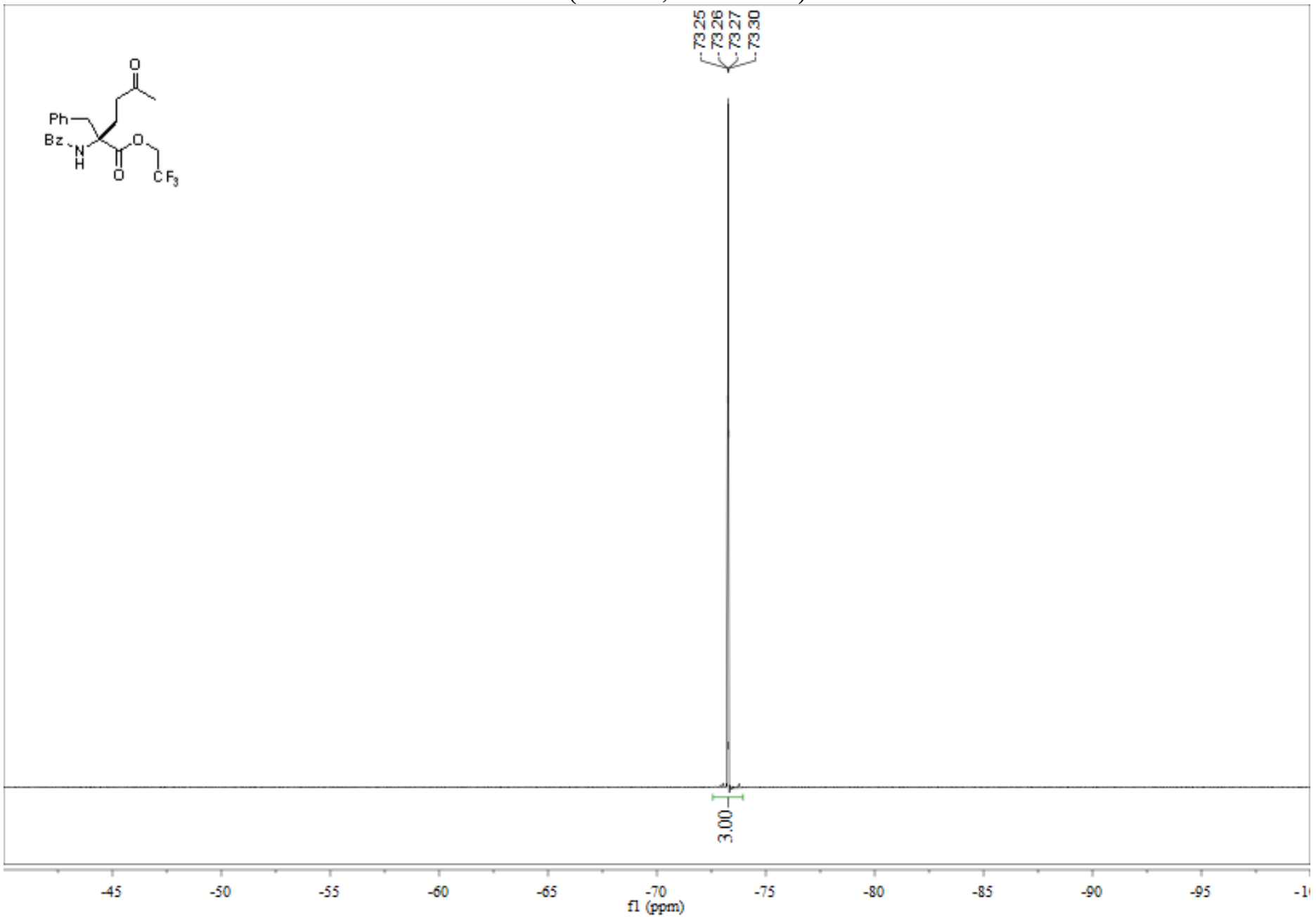
^{13}C NMR (101 MHz, Methylene Chloride -*d*) **5c**



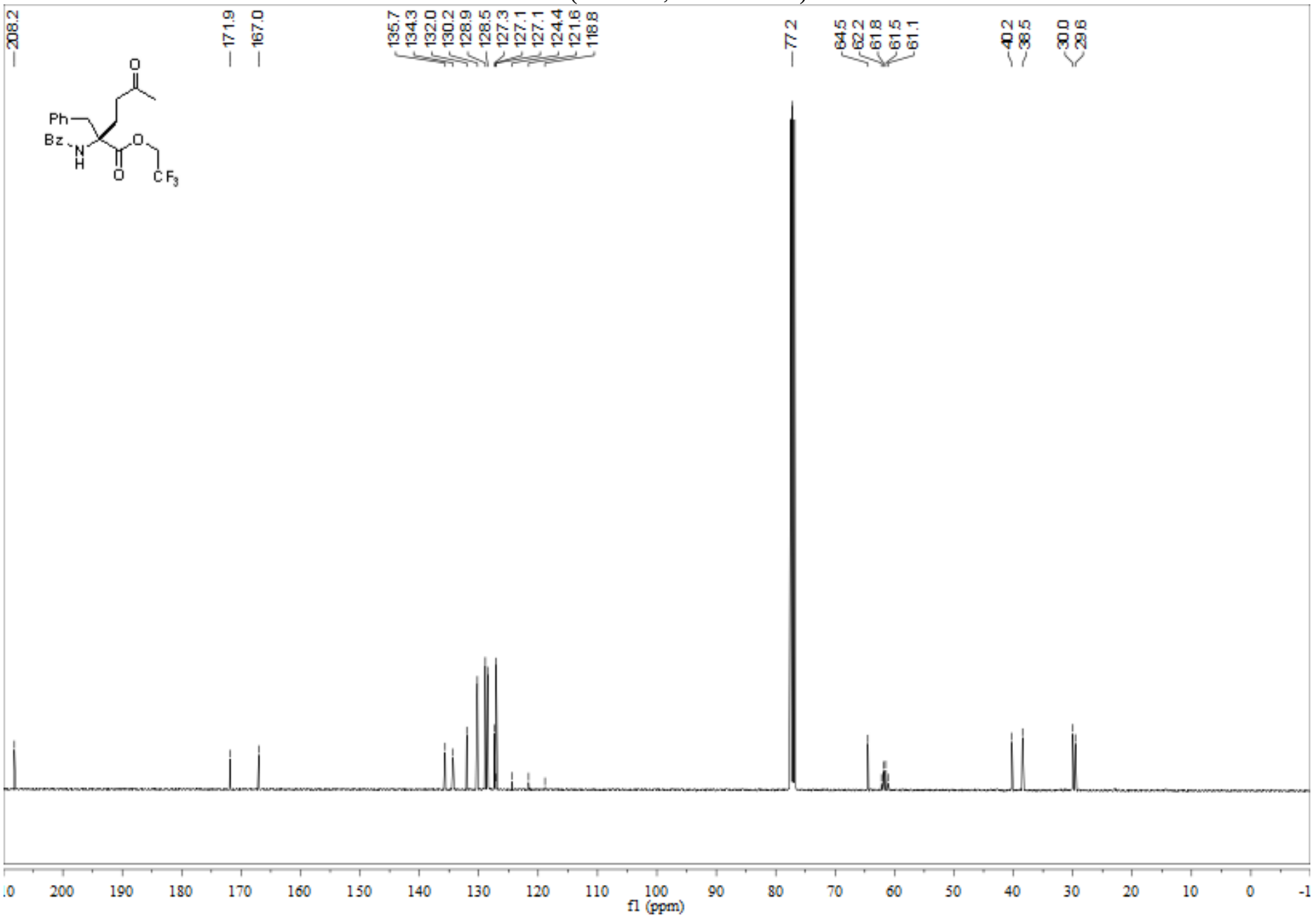
^{1}H NMR (400 MHz, Chloroform-*d*) **5d**



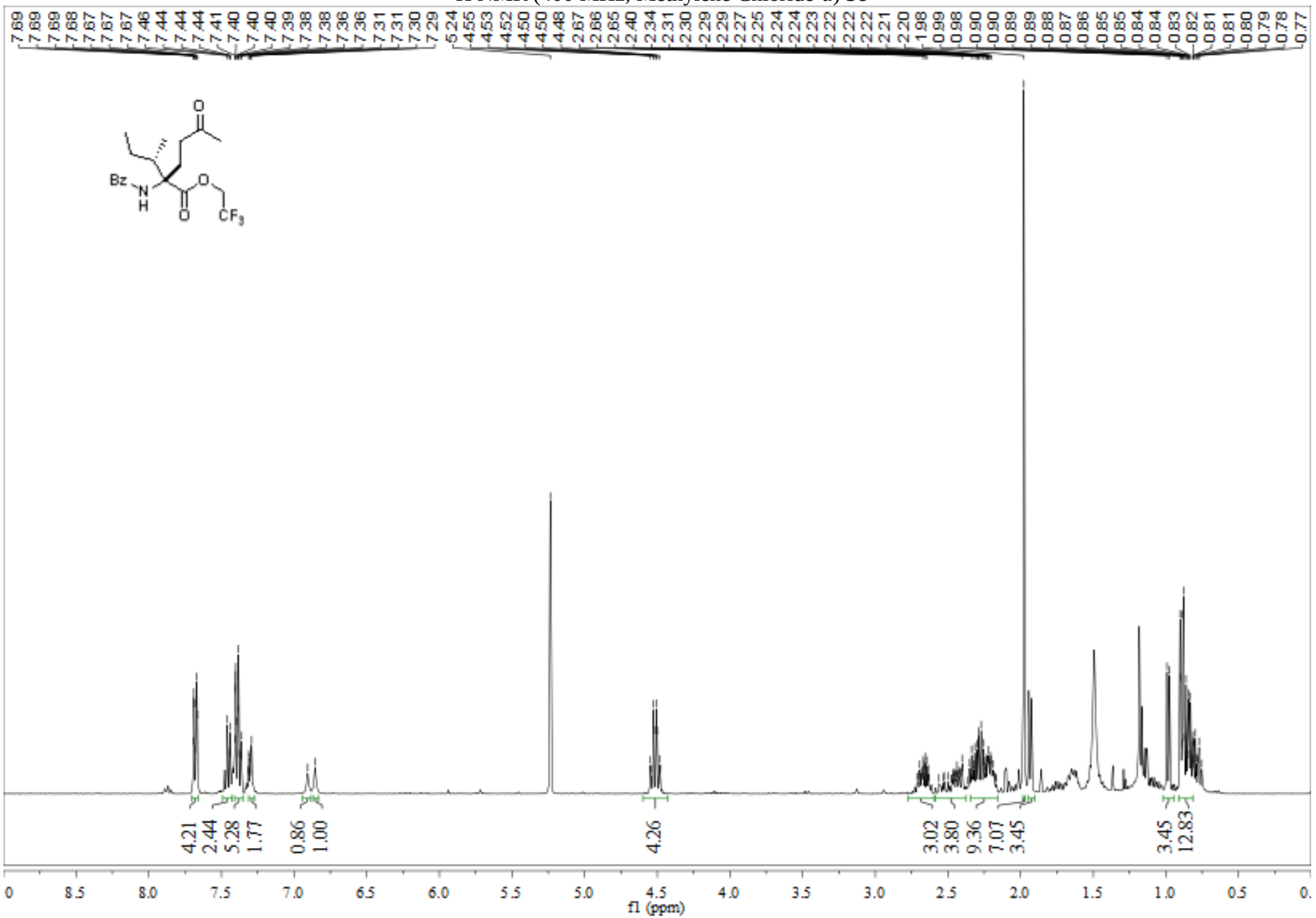
^{19}F NMR (376 MHz, Chloroform-*d*) **5d**



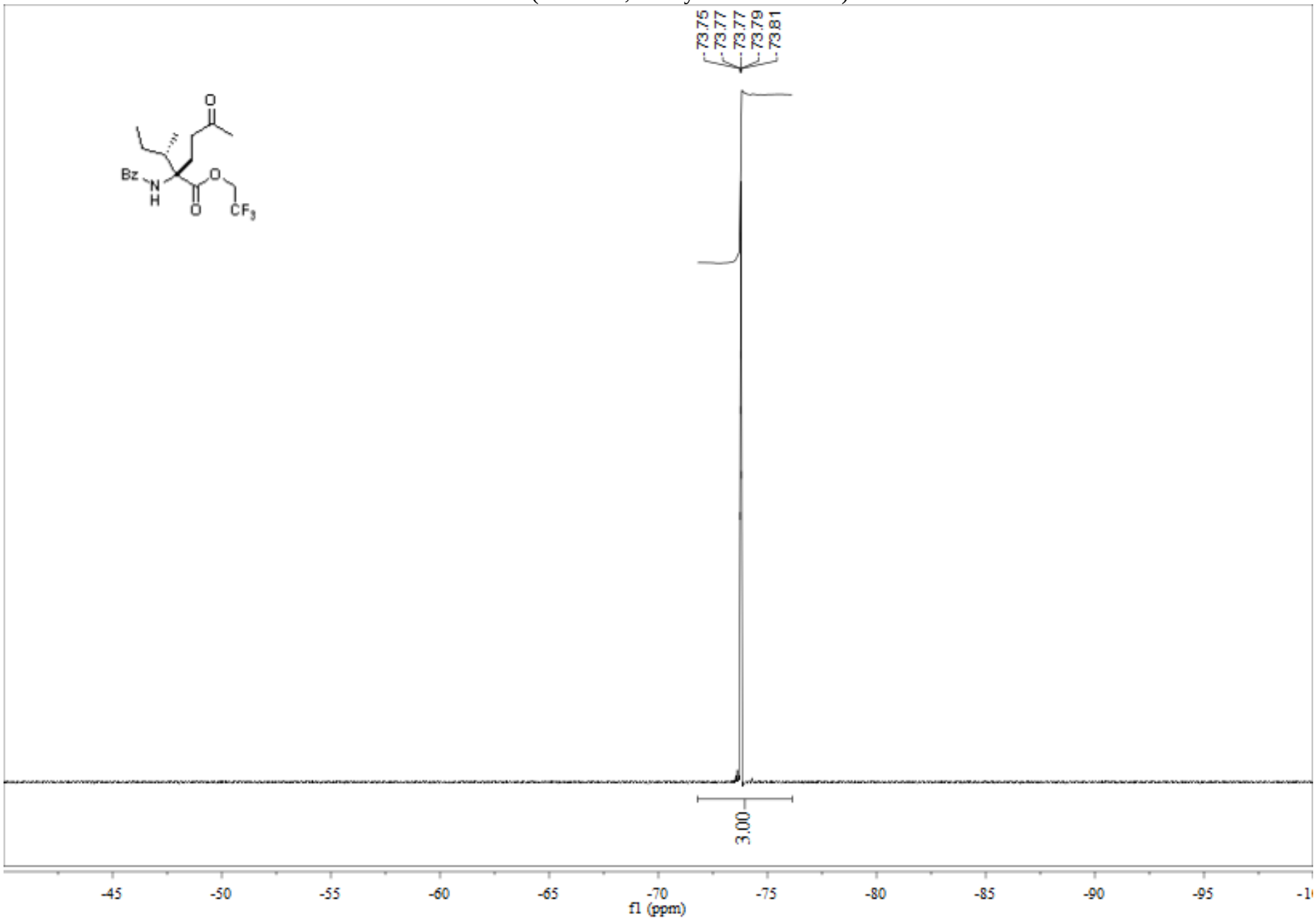
^{13}C NMR (101 MHz, Chloroform-*d*) **5d**



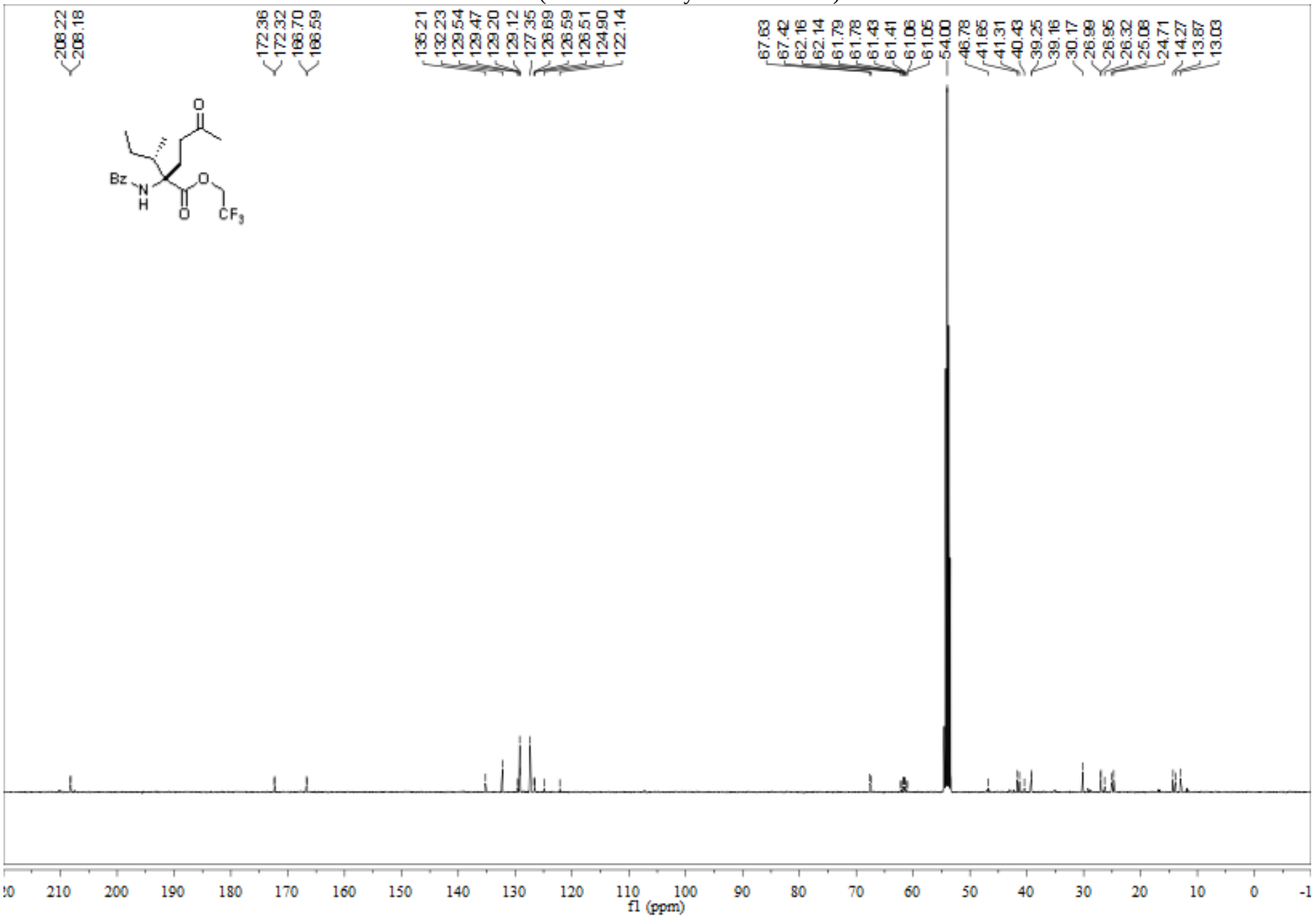
^{1}H NMR (400 MHz, Methylene Chloride-*d*) **5e**



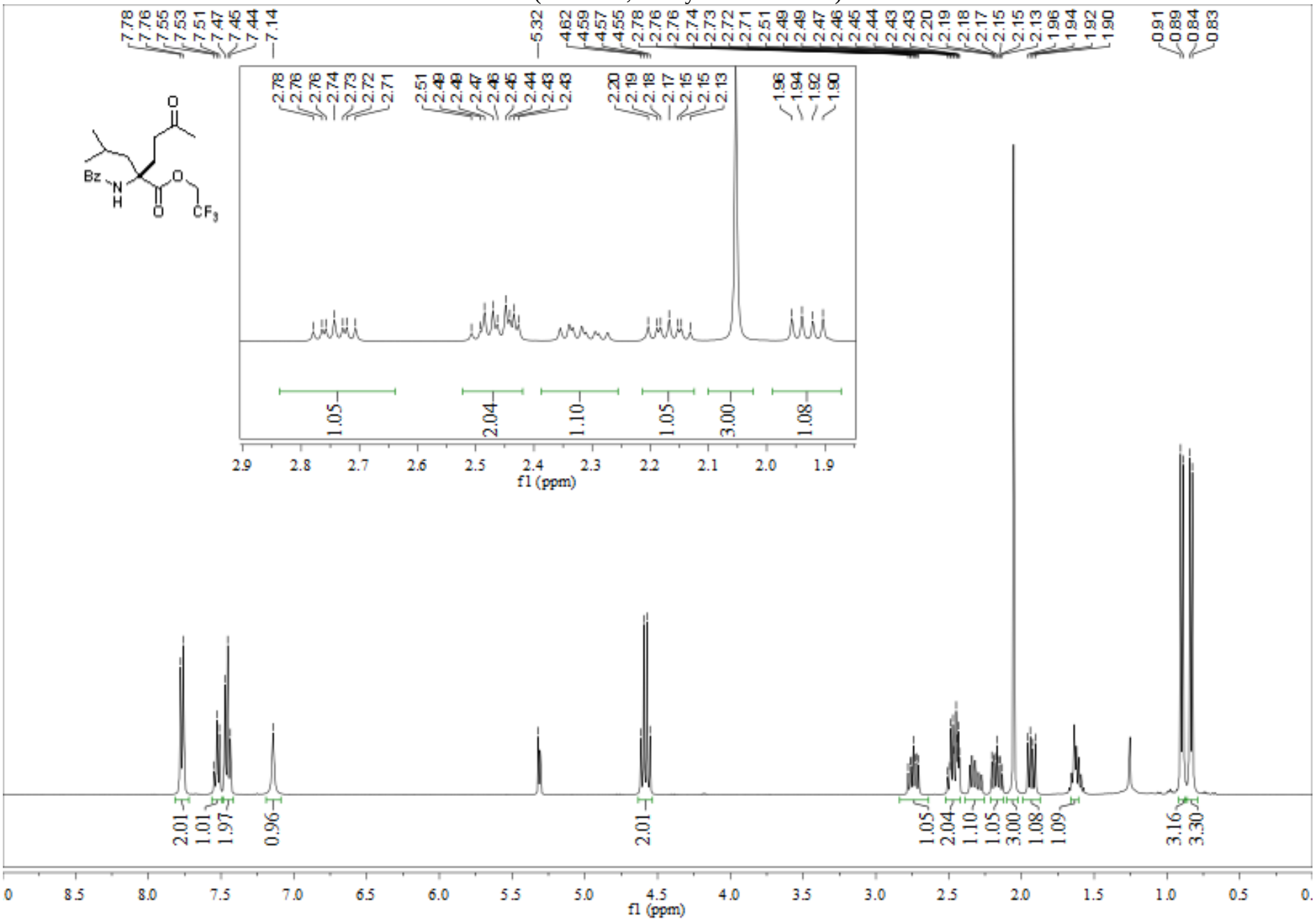
^{19}F NMR (376 MHz, Methylene Chloride -*d*) **5e**



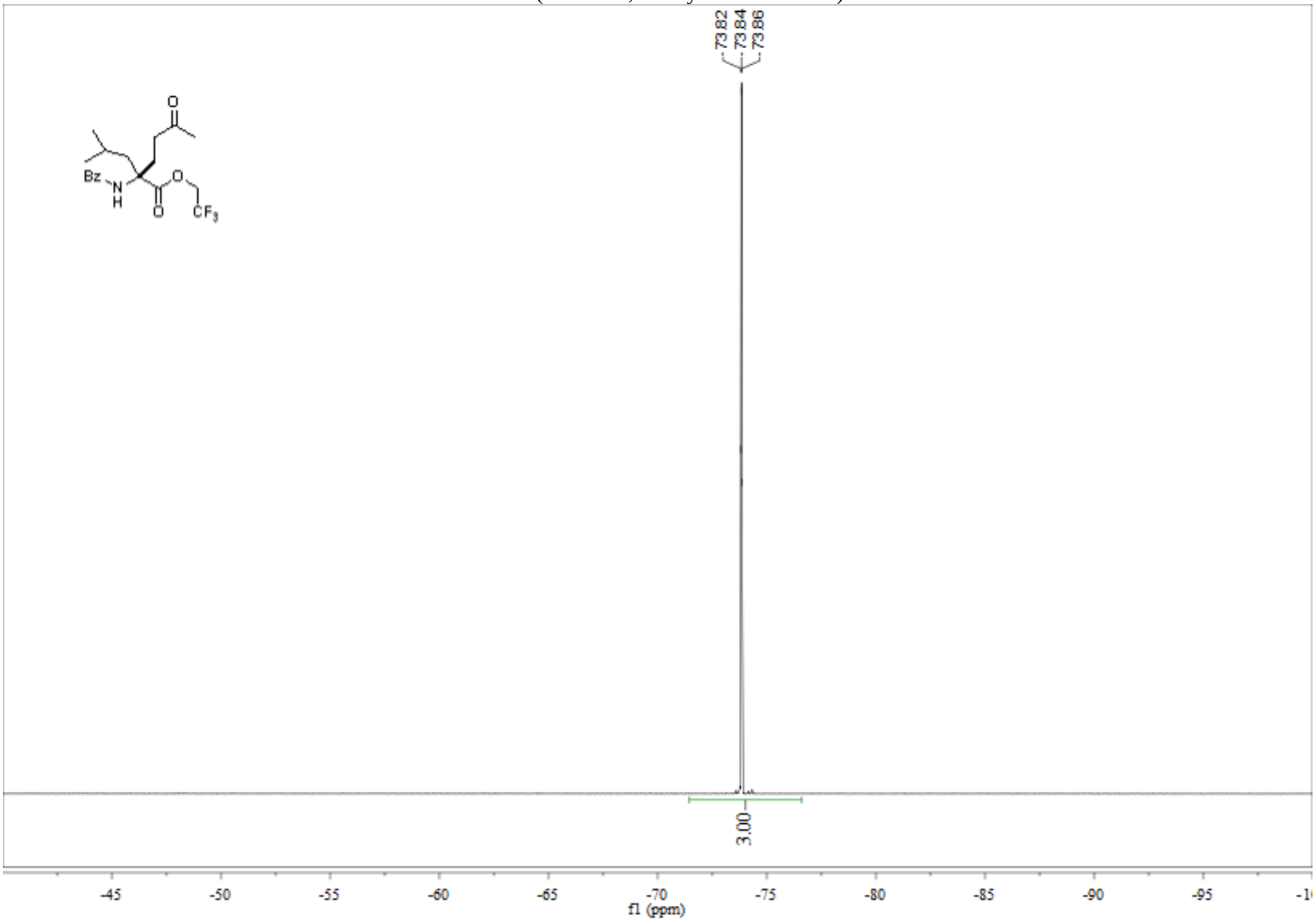
^{13}C NMR (101 MHz Methylene Chloride-*d*) **5e**



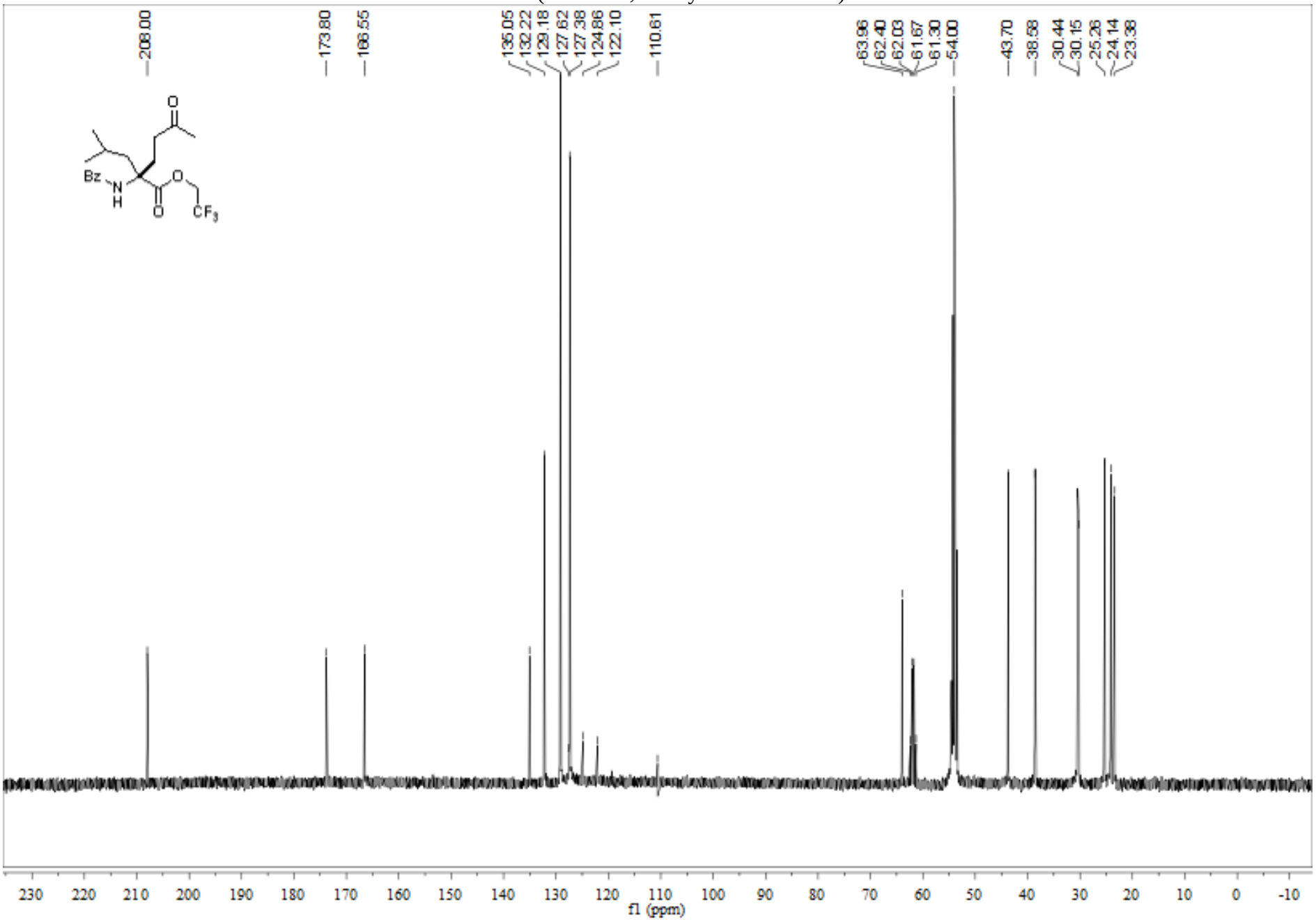
^{1}H NMR (400 MHz, Methylene Chloride-*d*) **5f**



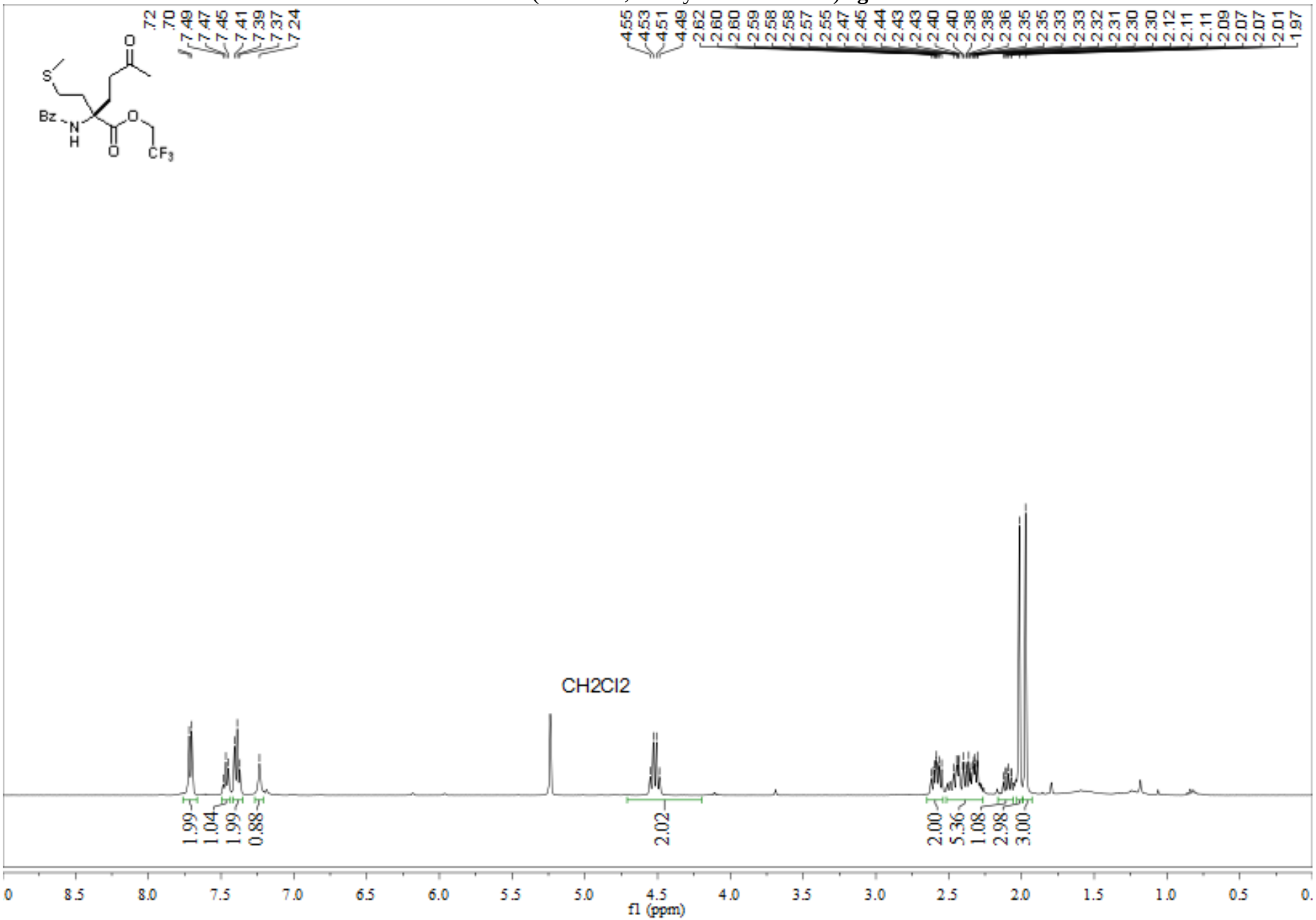
^{19}F NMR (376 MHz, Methylene Chloride-*d*) **5f**



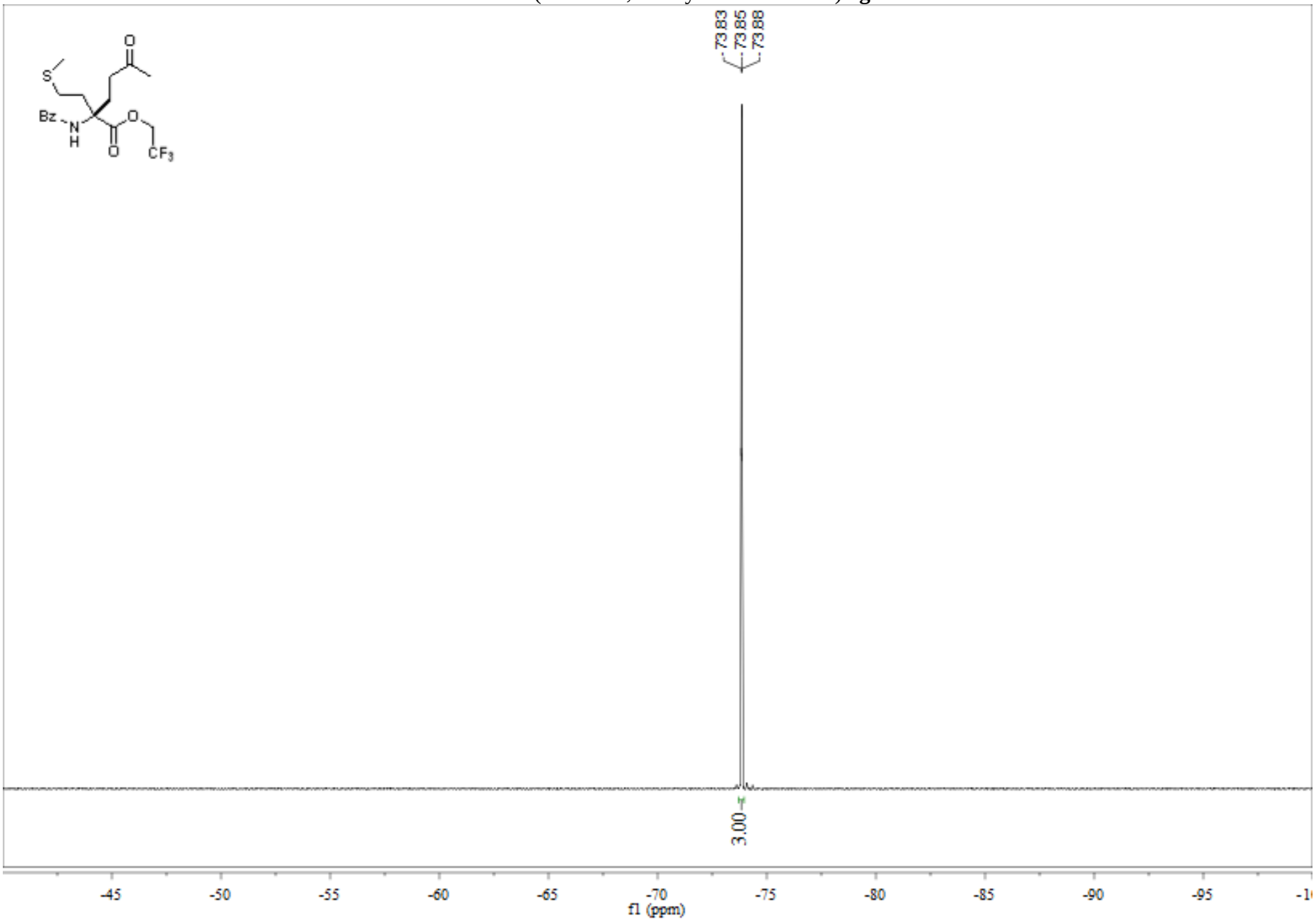
^{13}C NMR (101 MHz, Methylene Chloride-*d*) **5f**



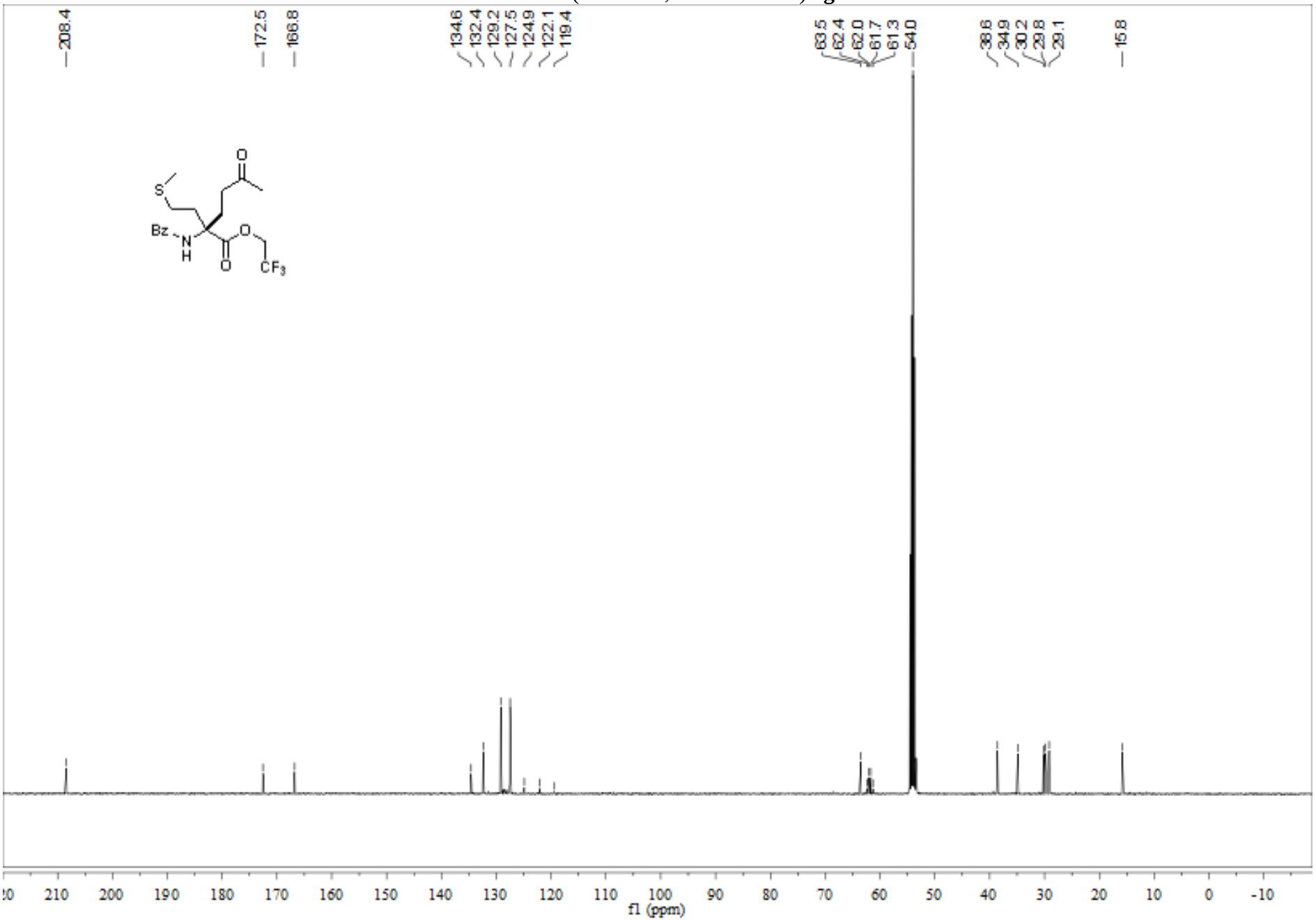
^{1}H NMR (400 MHz, Methylene Chloride-*d*) **5g**



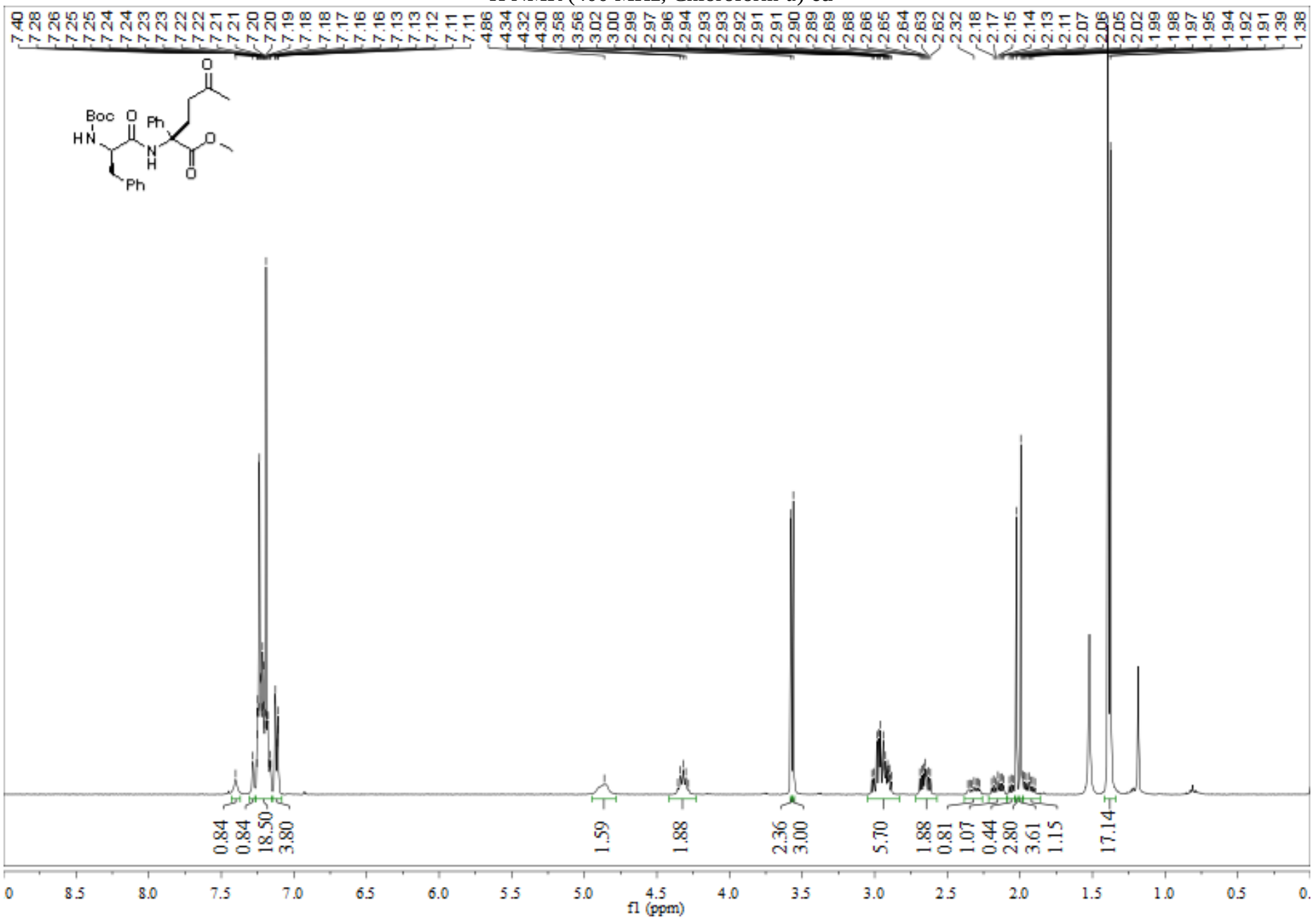
^{19}F NMR (376 MHz, Methylene Chloride-*d*) **5g**



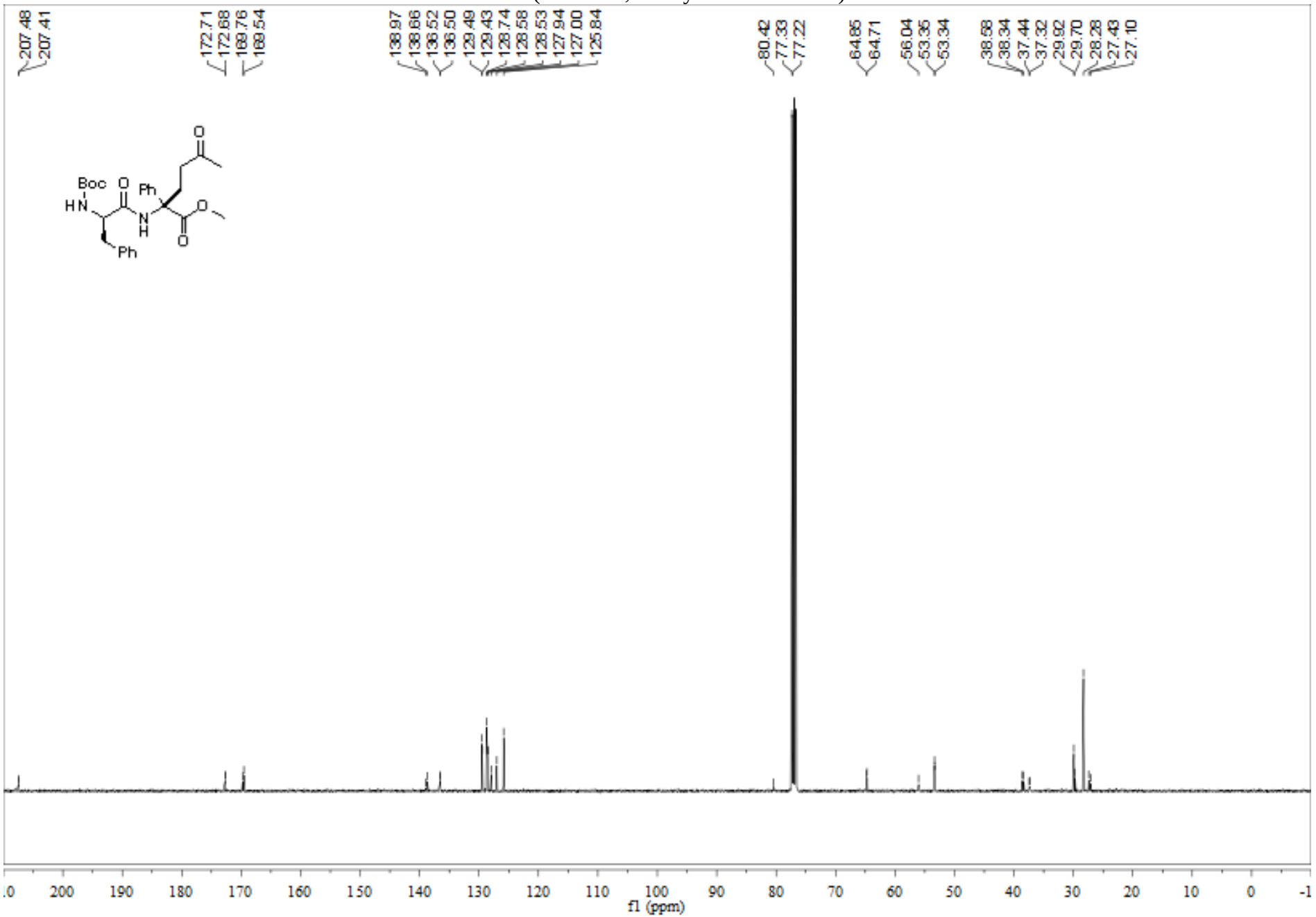
^{13}C NMR (101 MHz, Chloroform-*d*) **5g**



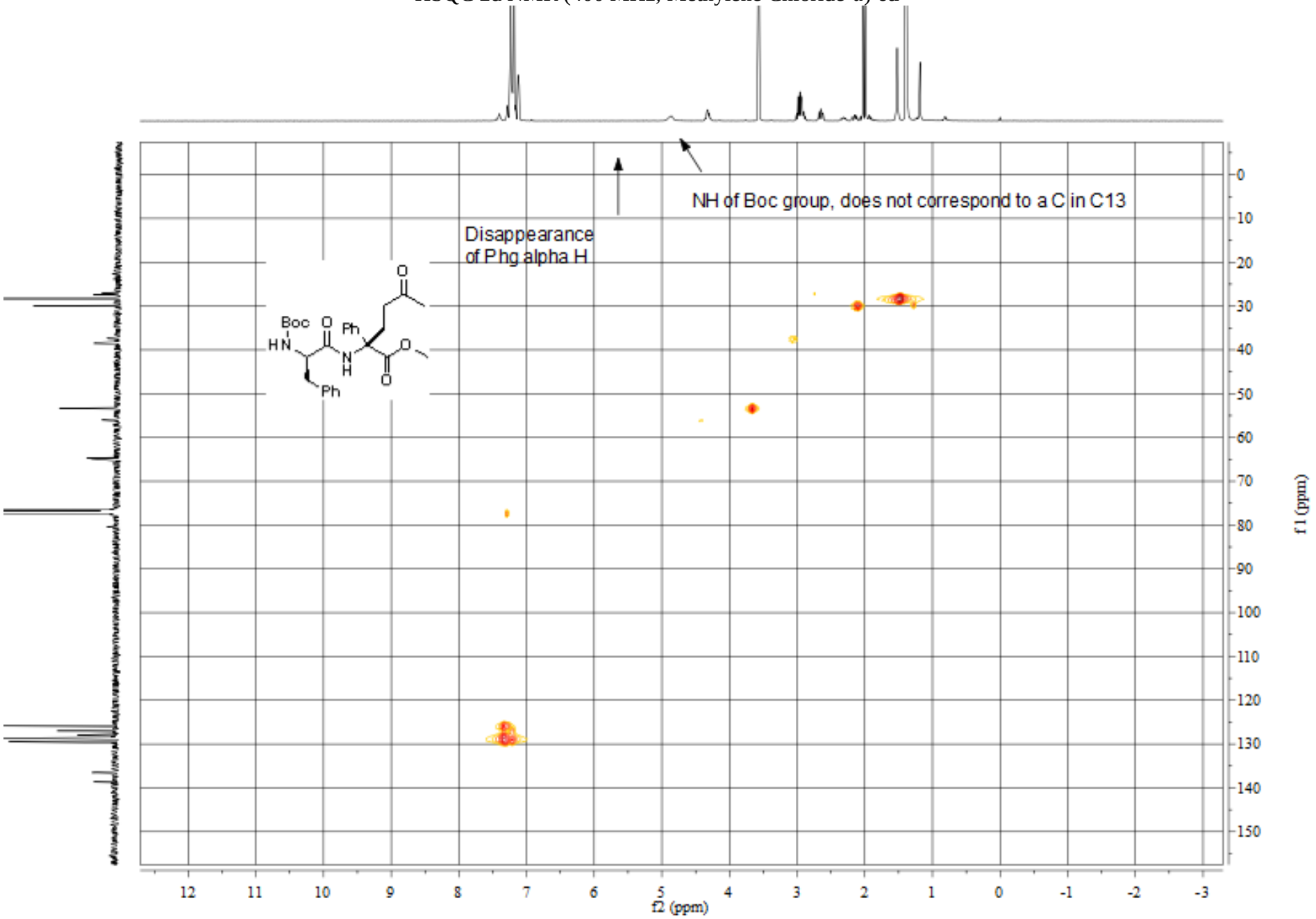
^{1}H NMR (400 MHz, Chloroform-*d*) **6a**



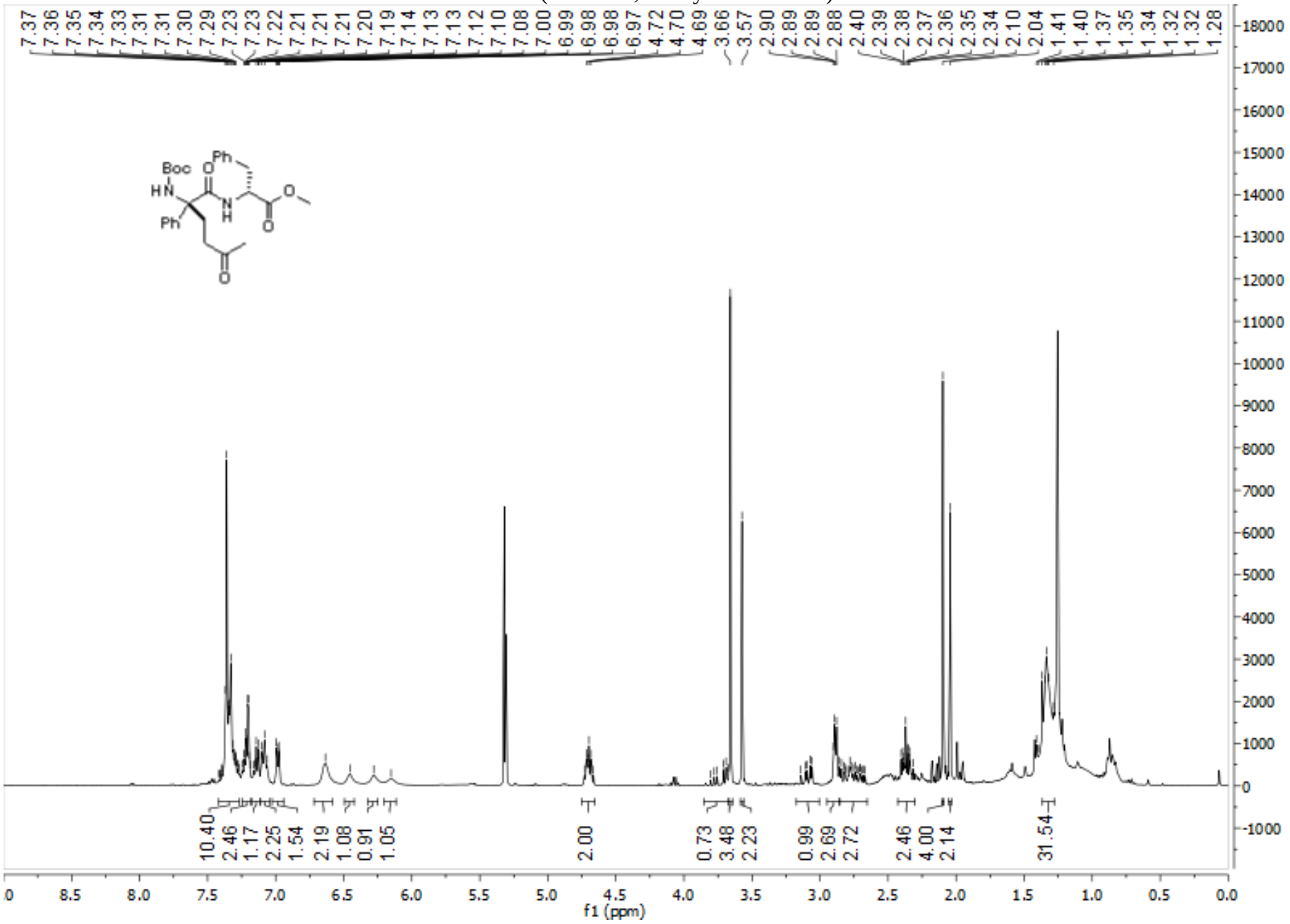
^{13}C NMR (101 MHz, Methylene Chloride -*d*) **6a**



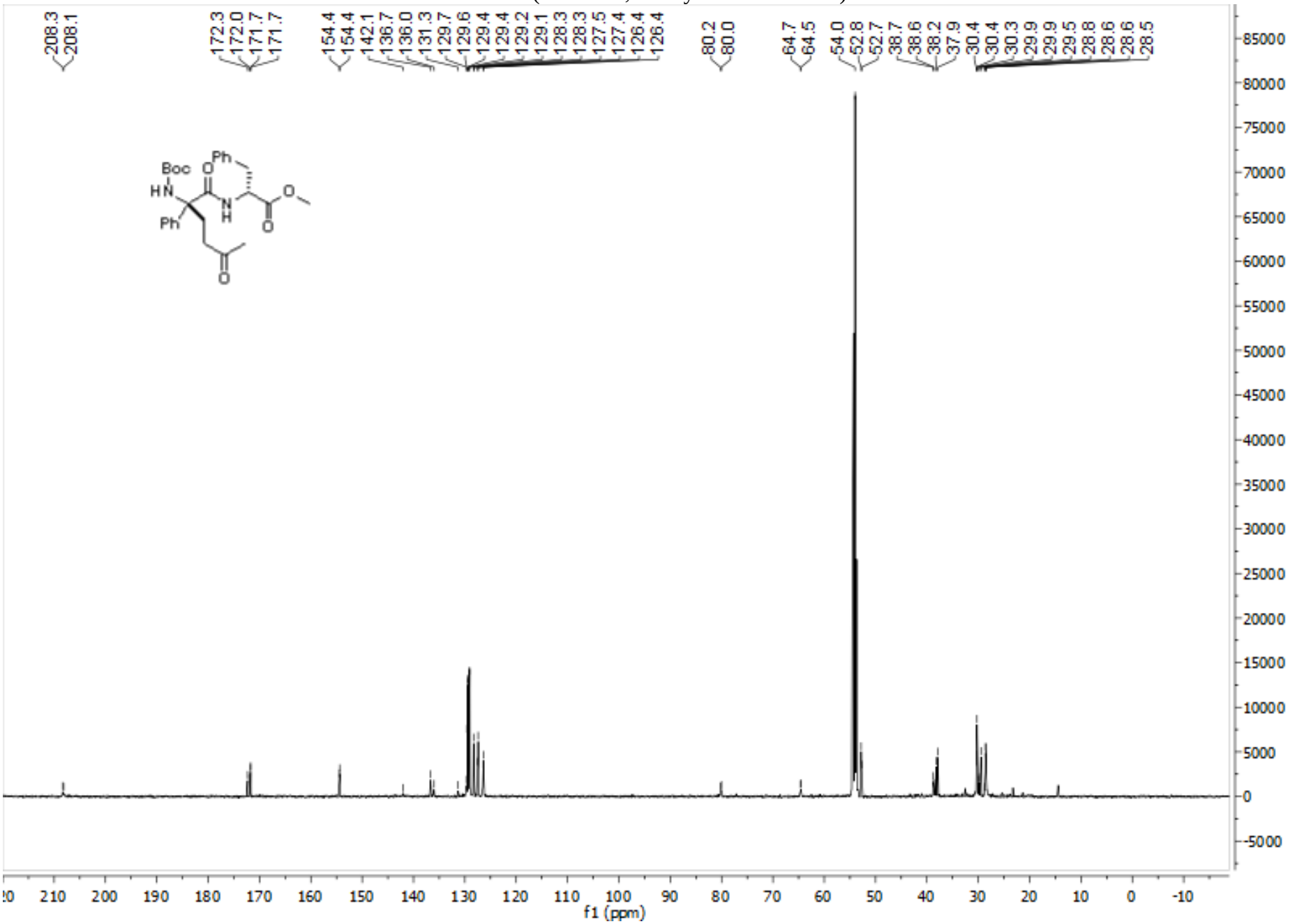
HSQC 2d NMR (400 MHz, Methylene Chloride-*d*) **6a**



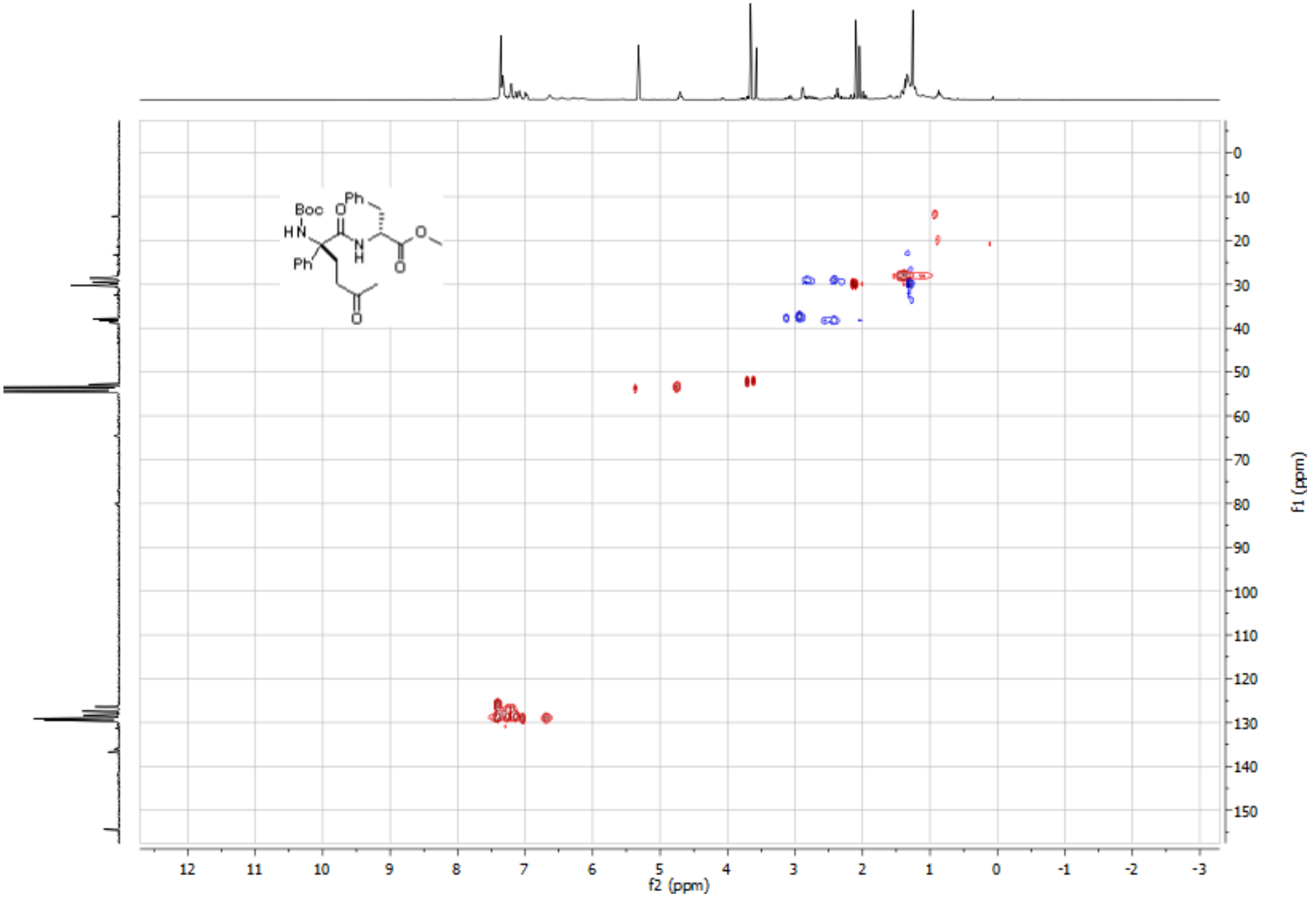
^{1}H NMR (400 MHz, Methylene Chloride) **6b**



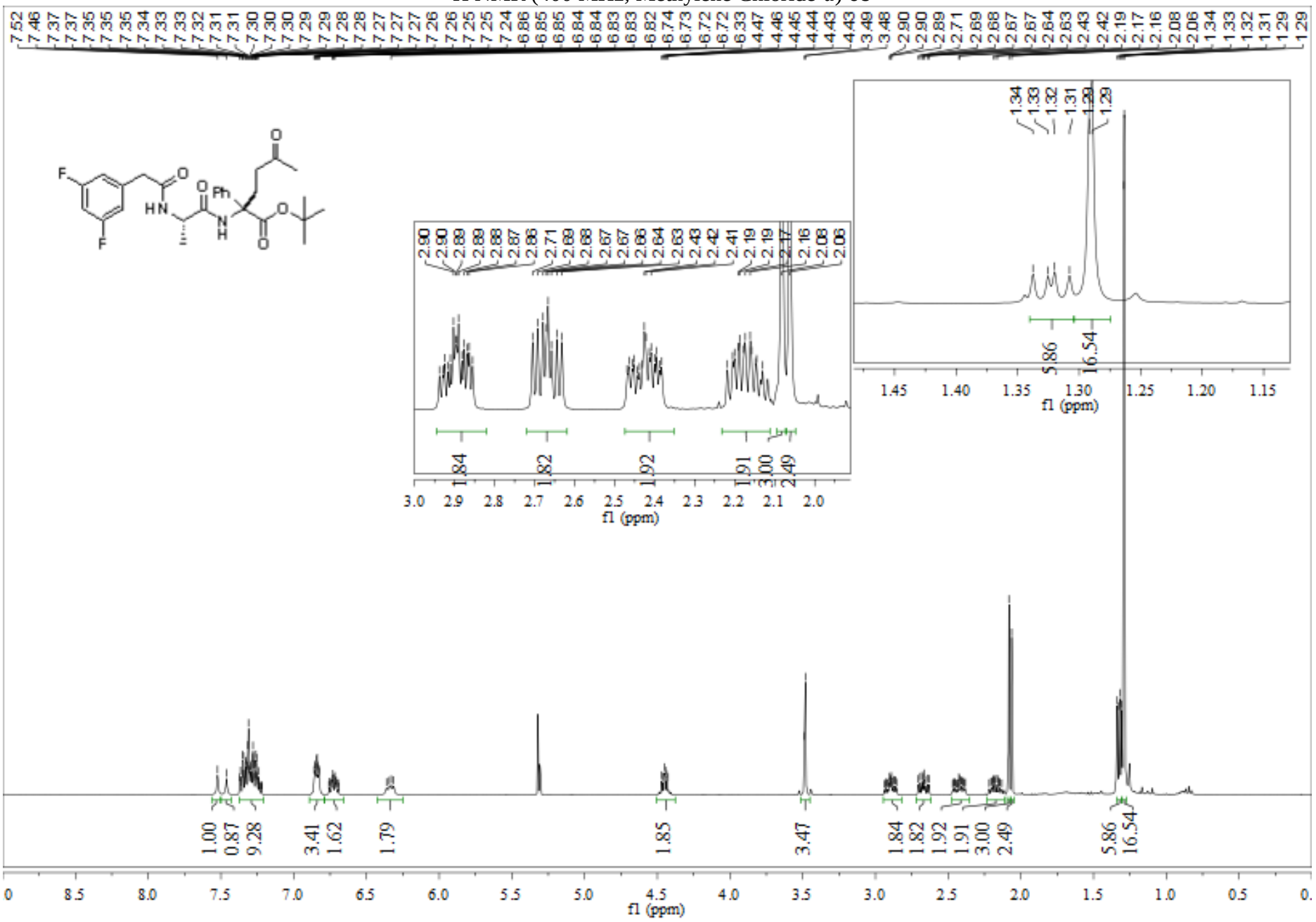
^{13}C NMR (101 MHz, Methylene Chloride -*d*) **6b**



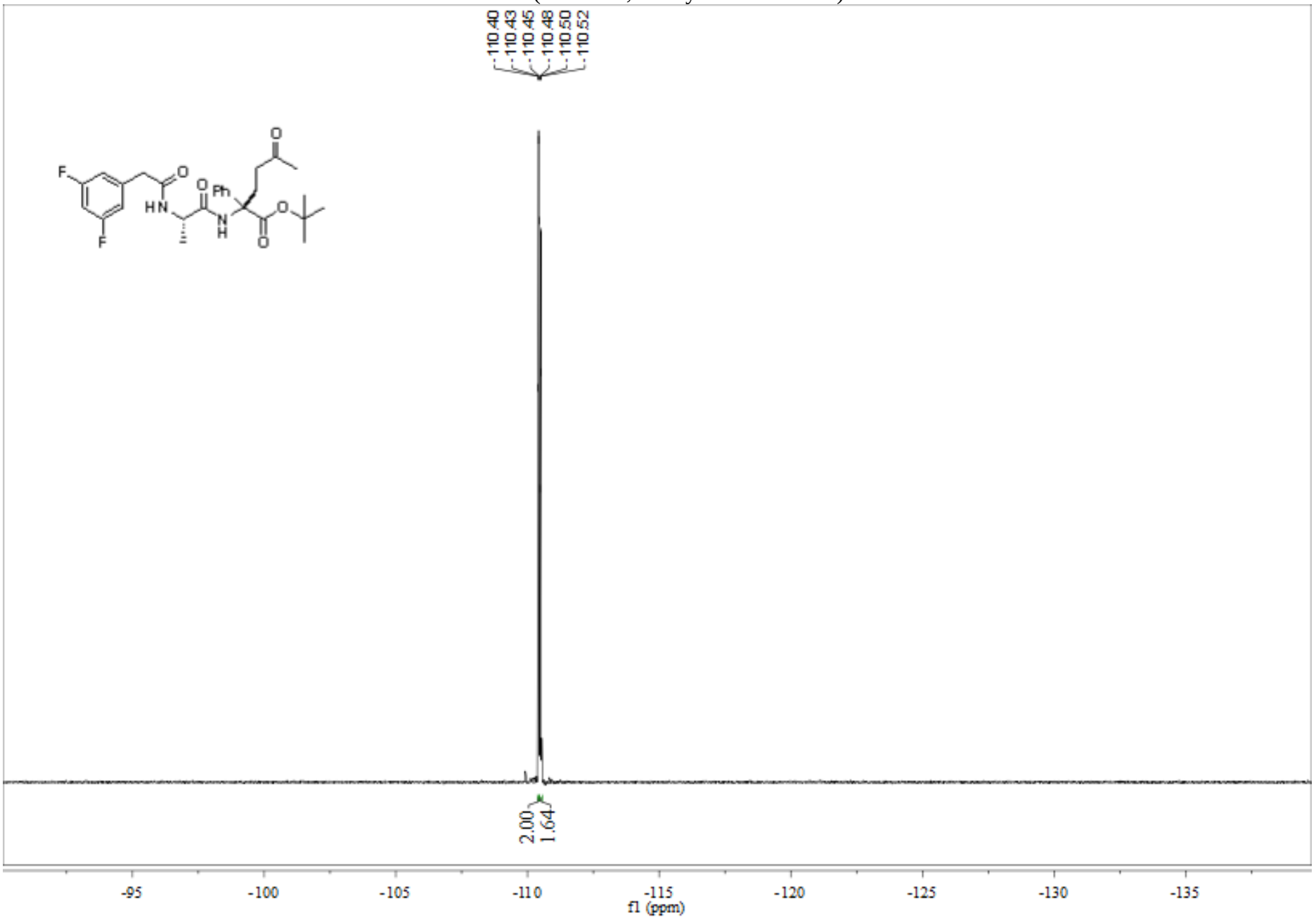
HSQC 2d NMR (400 MHz, Methylene Chloride-*d*) **6b**



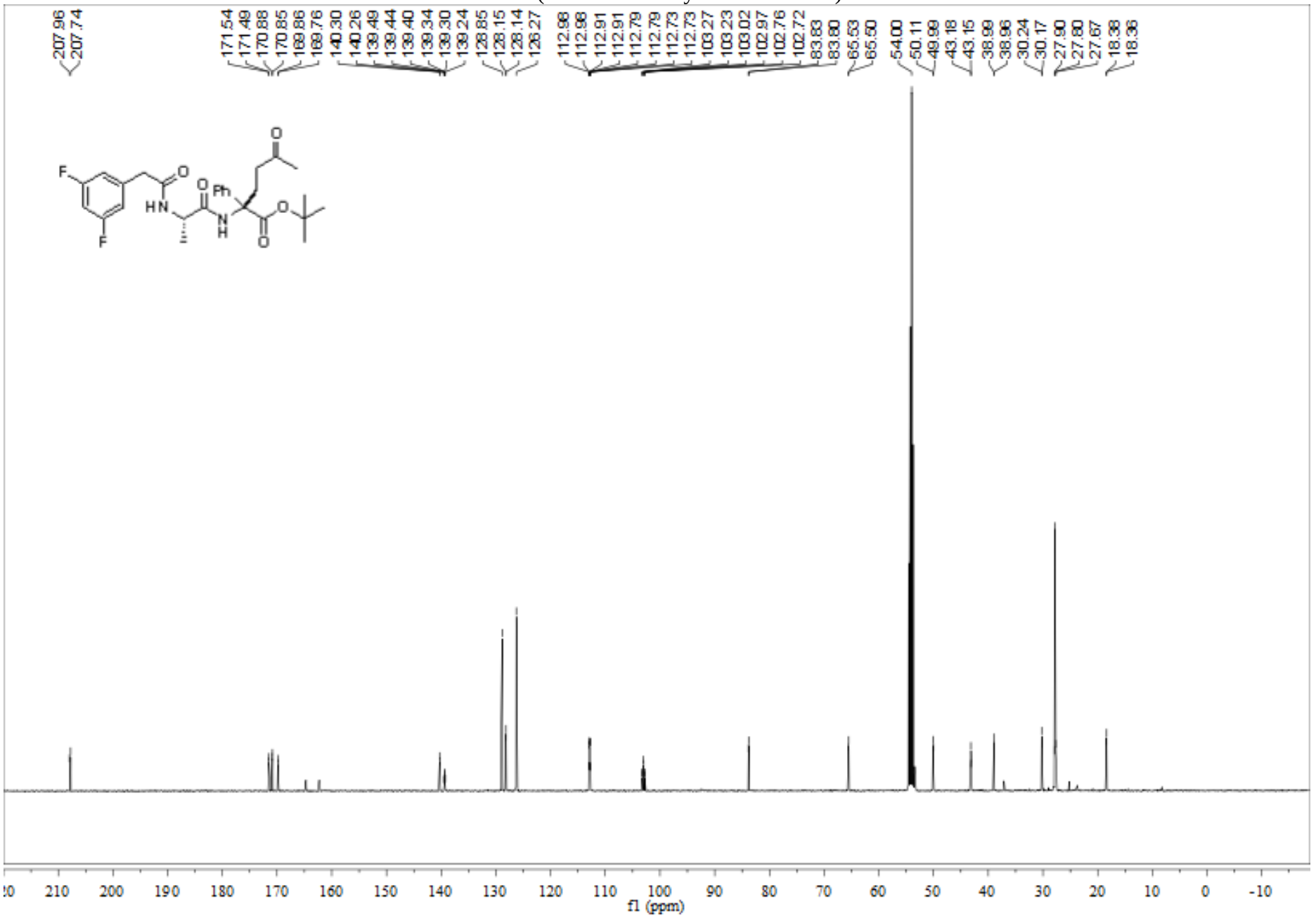
^{1}H NMR (400 MHz, Methylene Chloride-*d*) **6c**



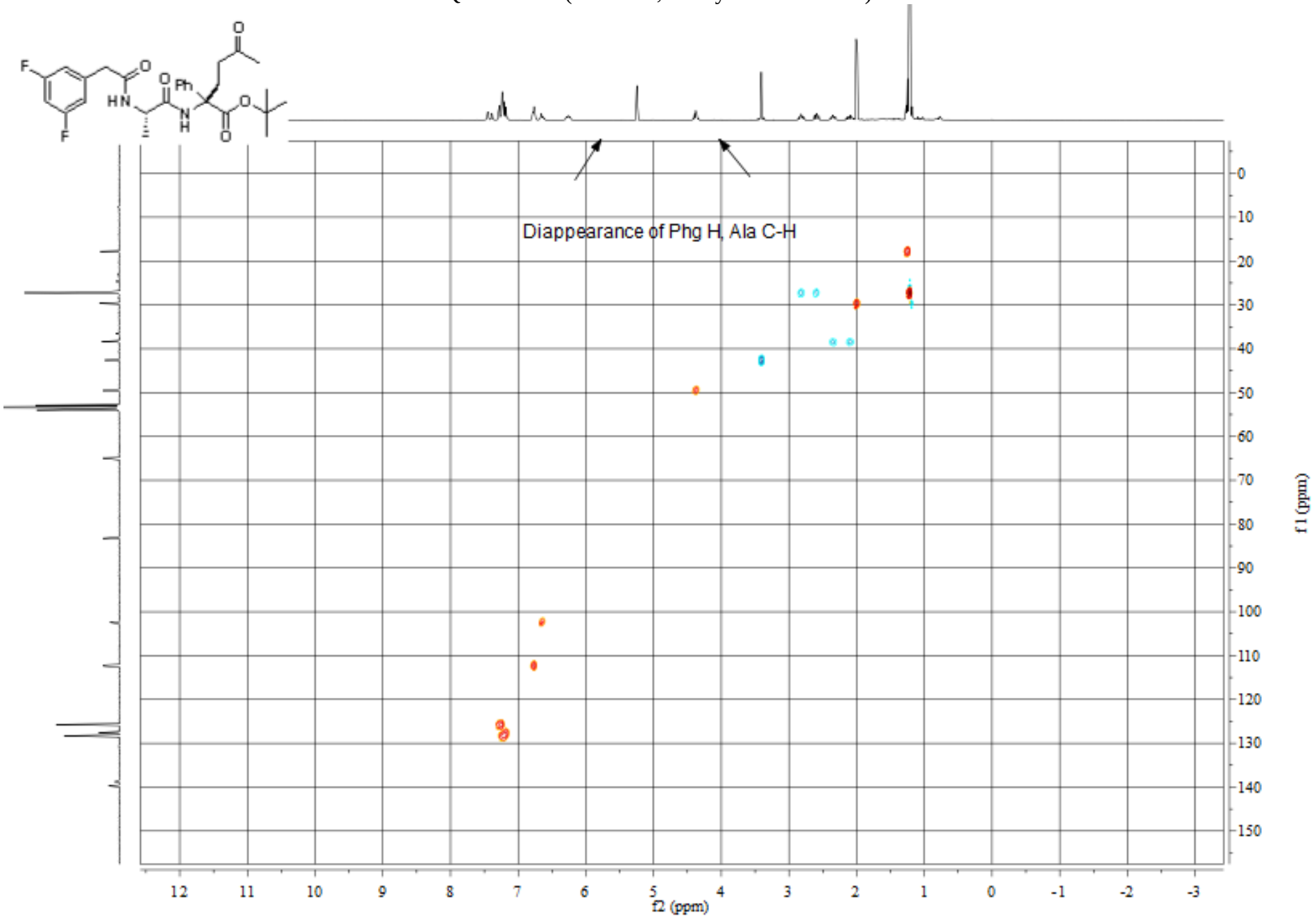
^{19}F NMR (376 MHz, Methylene Chloride-*d*) **6c**



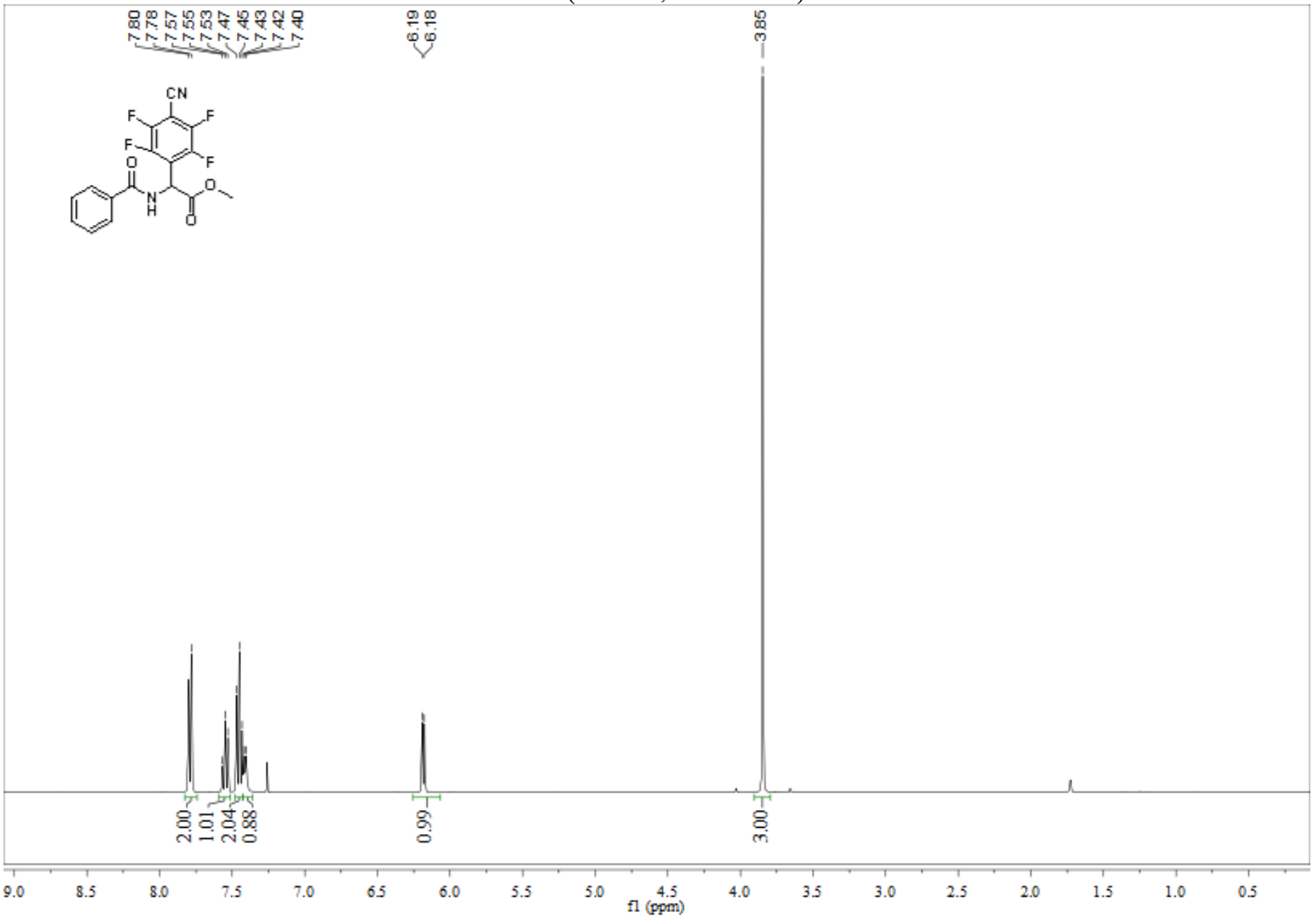
^{13}C NMR (101 MHz Methylene Chloride-*d*) **6c**



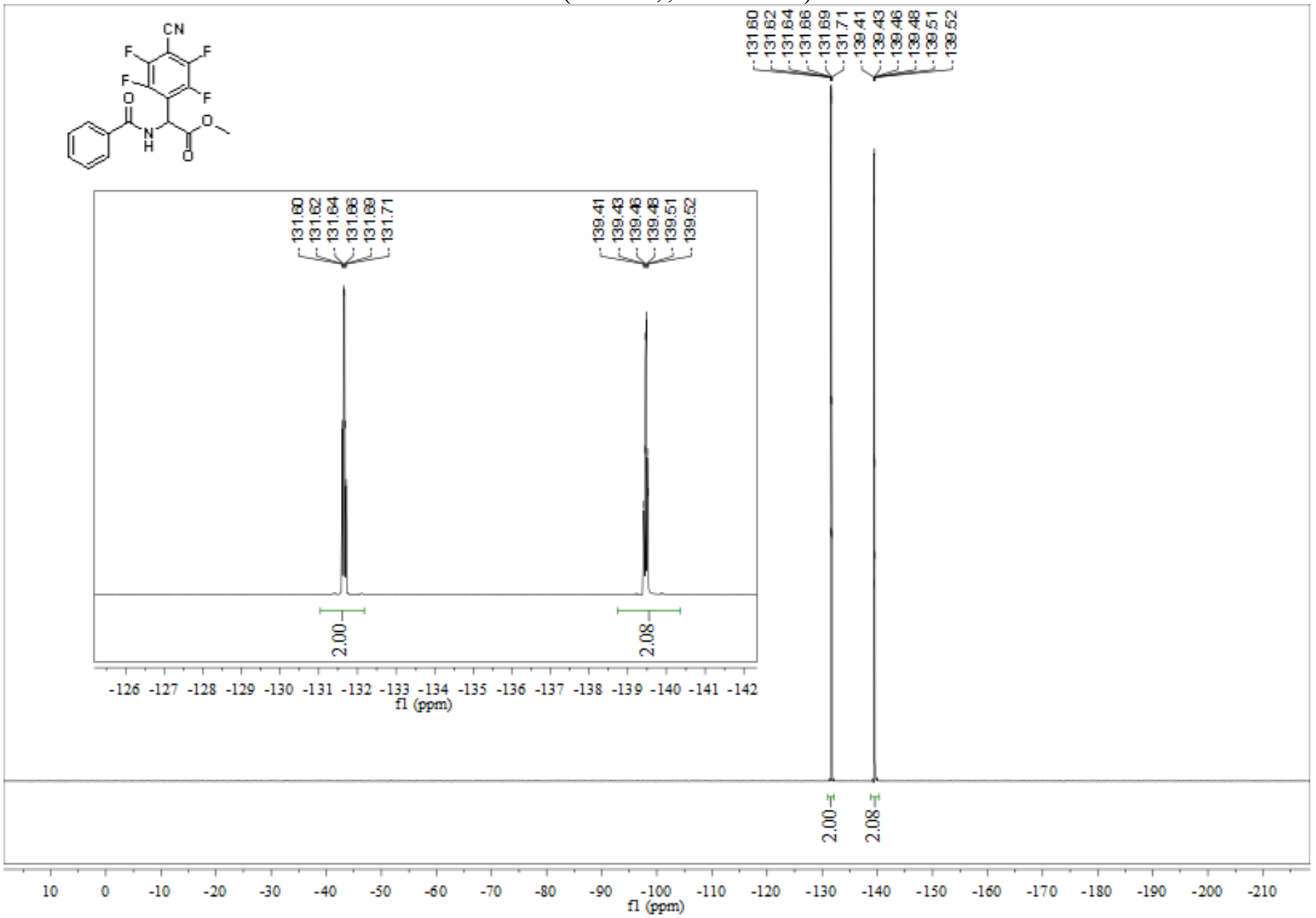
HSQC 2d NMR (400 MHz, Methylene Chloride-*d*) **6c**



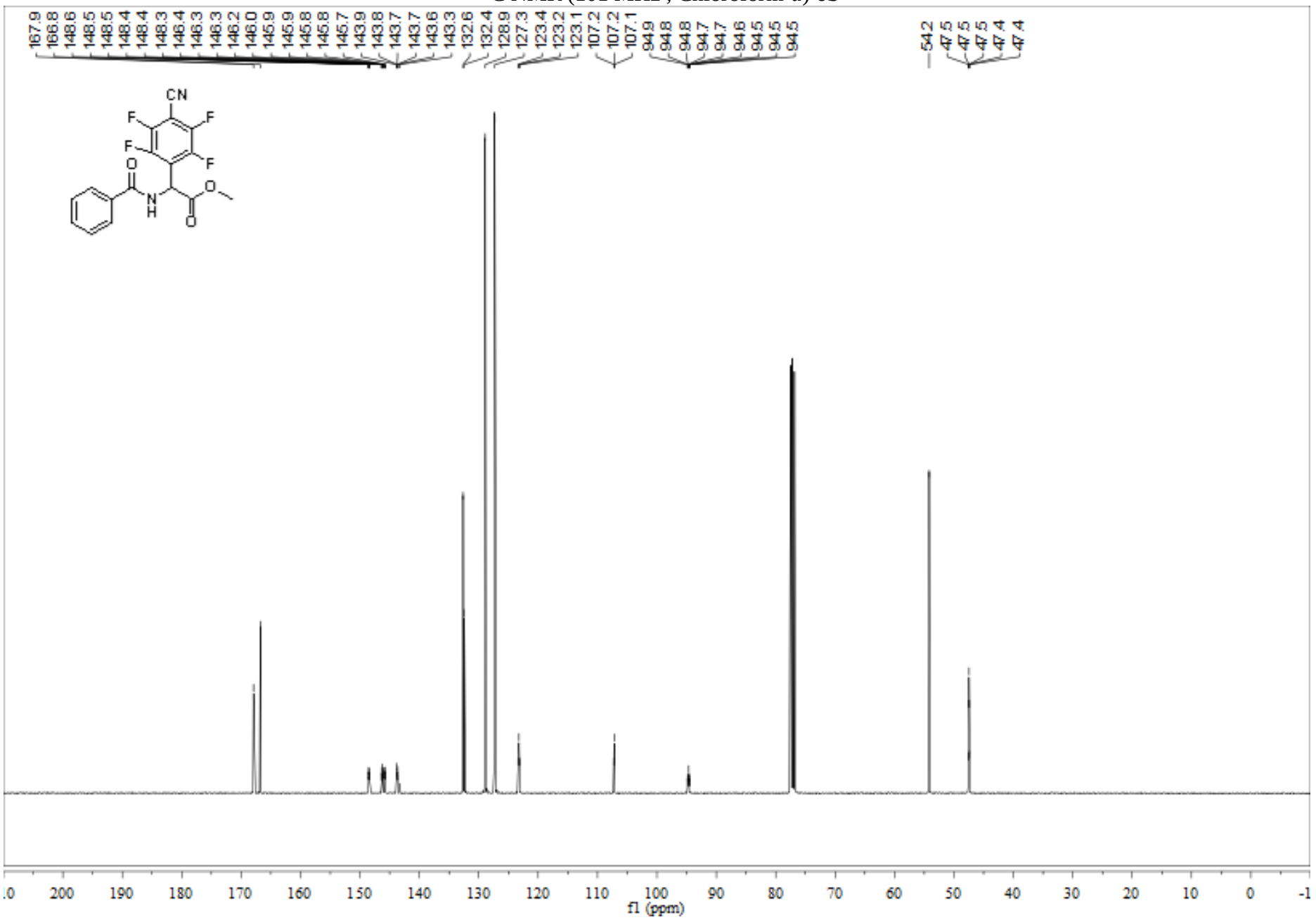
^{1}H NMR (400 MHz, Chloroform-*d*) **6a**



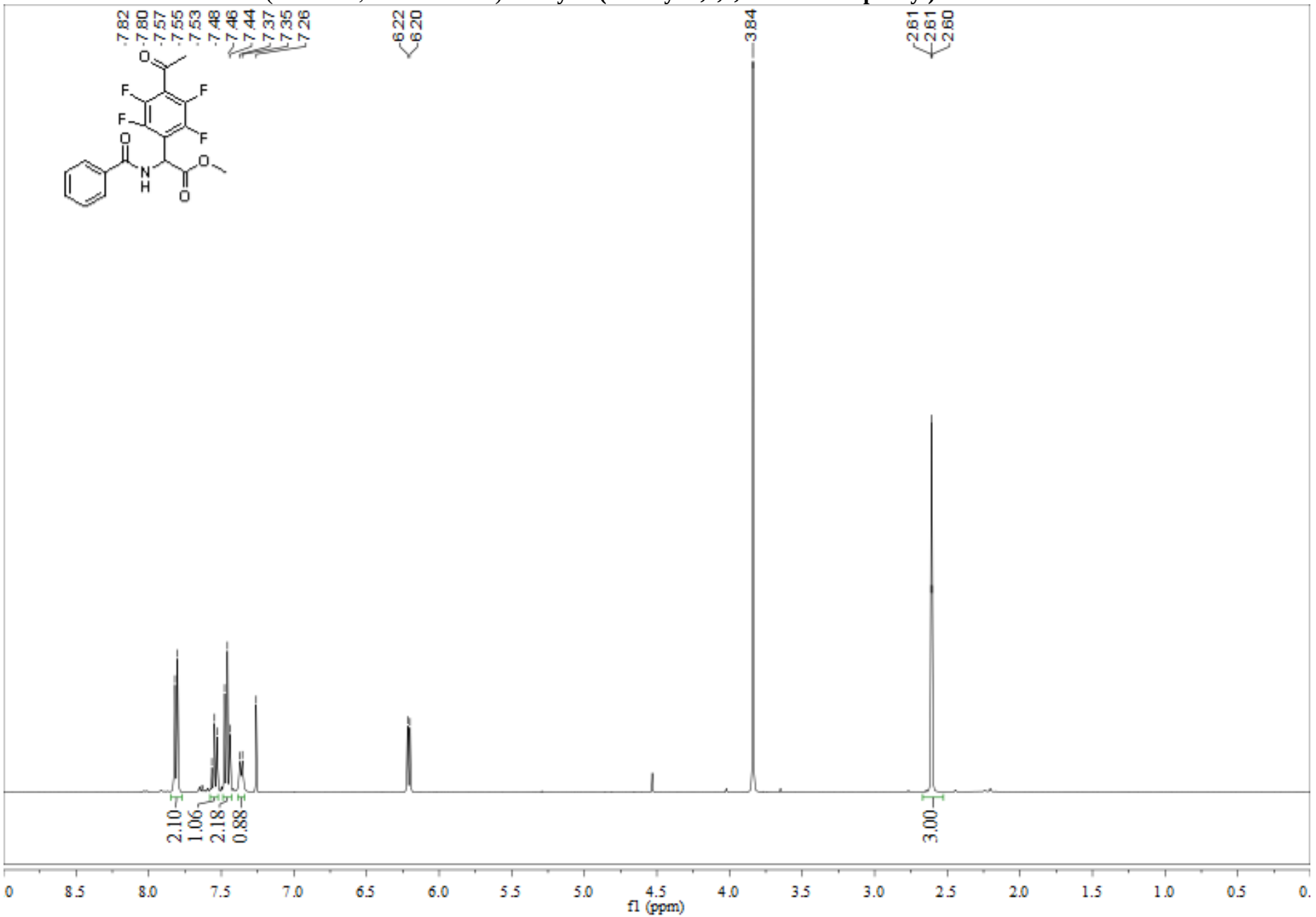
^{19}F NMR (376 MHz, , Chloroform-*d*) **6b**



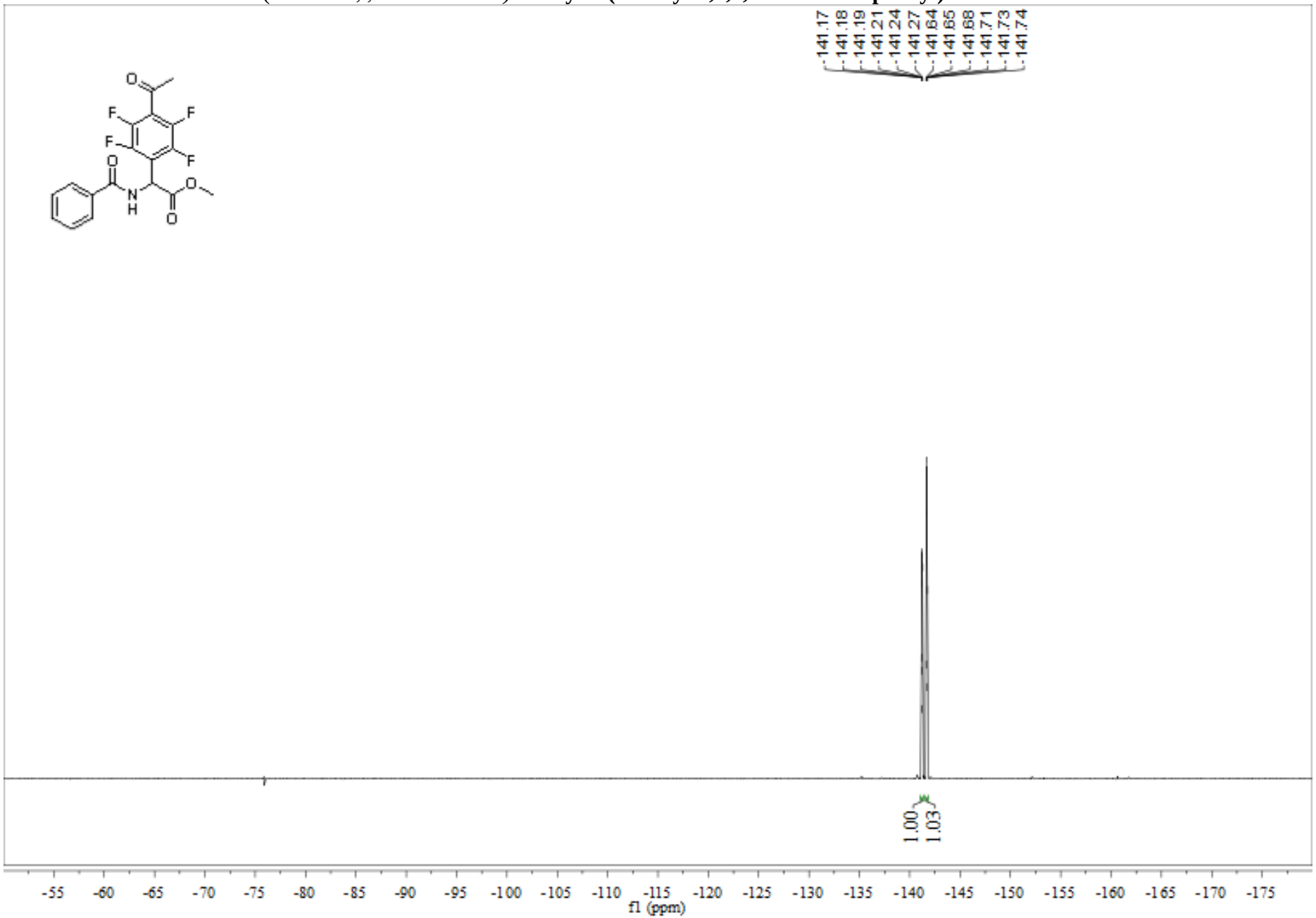
^{13}C NMR (101 MHz , Chloroform-*d*) **6b**



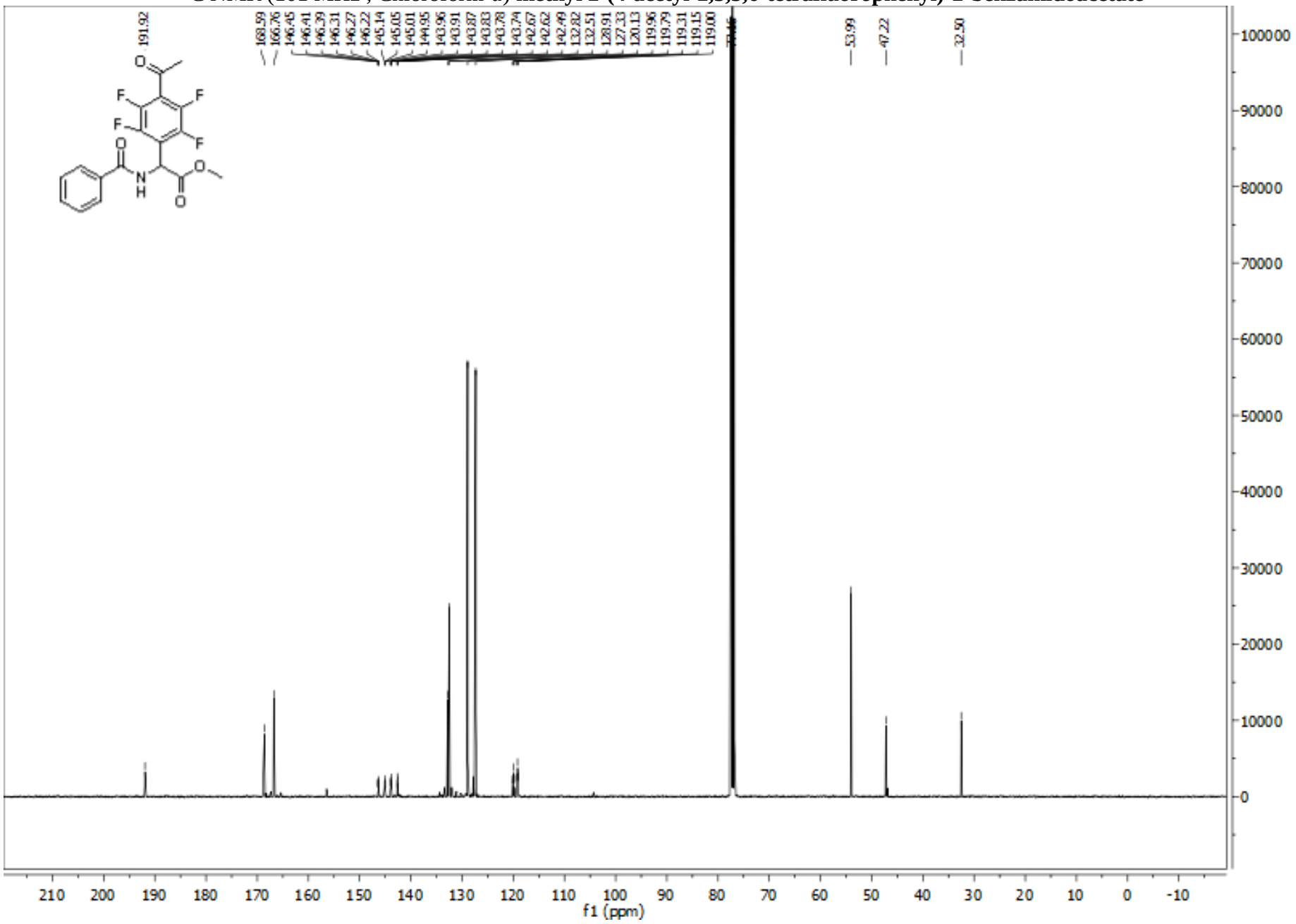
^{1}H NMR (400 MHz, Chloroform-*d*) **methyl 2-(4-acetyl-2,3,5,6-tetrafluorophenyl)-2-benzamidoacetate**



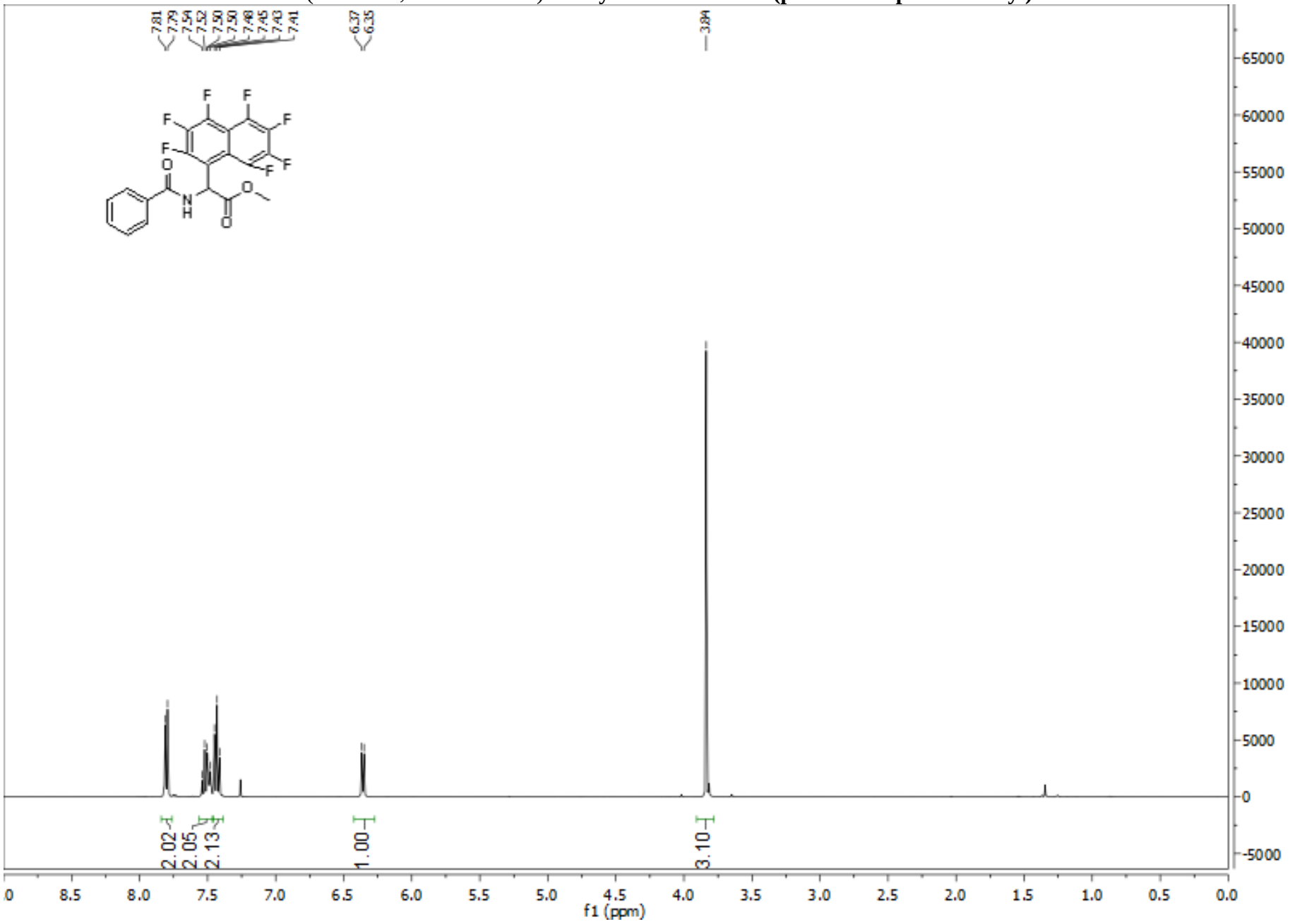
^{19}F NMR (376 MHz, , Chloroform-*d*) **methyl 2-(4-acetyl-2,3,5,6-tetrafluorophenyl)-2-benzamidoacetate**



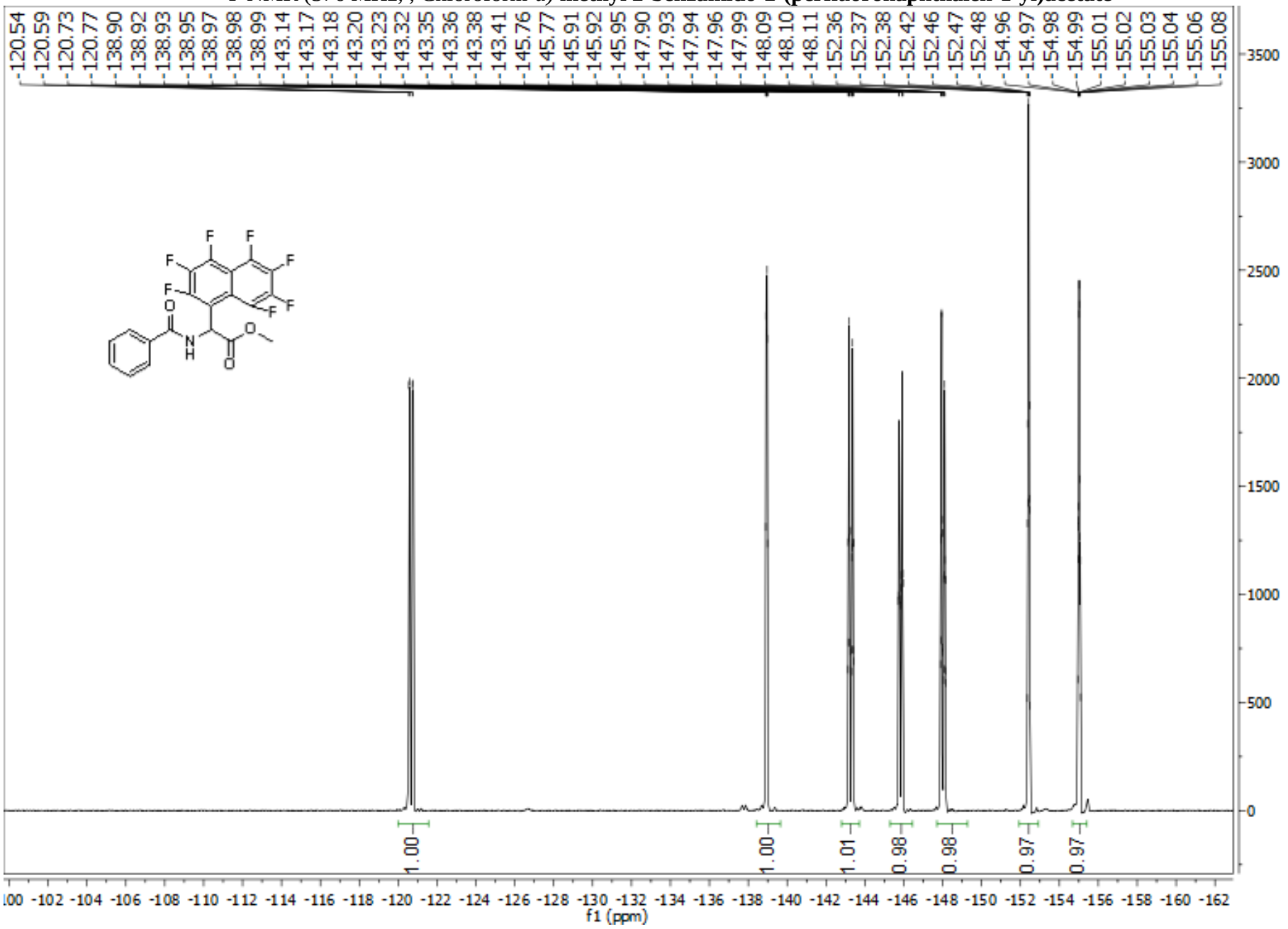
^{13}C NMR (101 MHz , Chloroform-*d*) **methyl 2-(4-acetyl-2,3,5,6-tetrafluorophenyl)-2-benzamidoacetate**



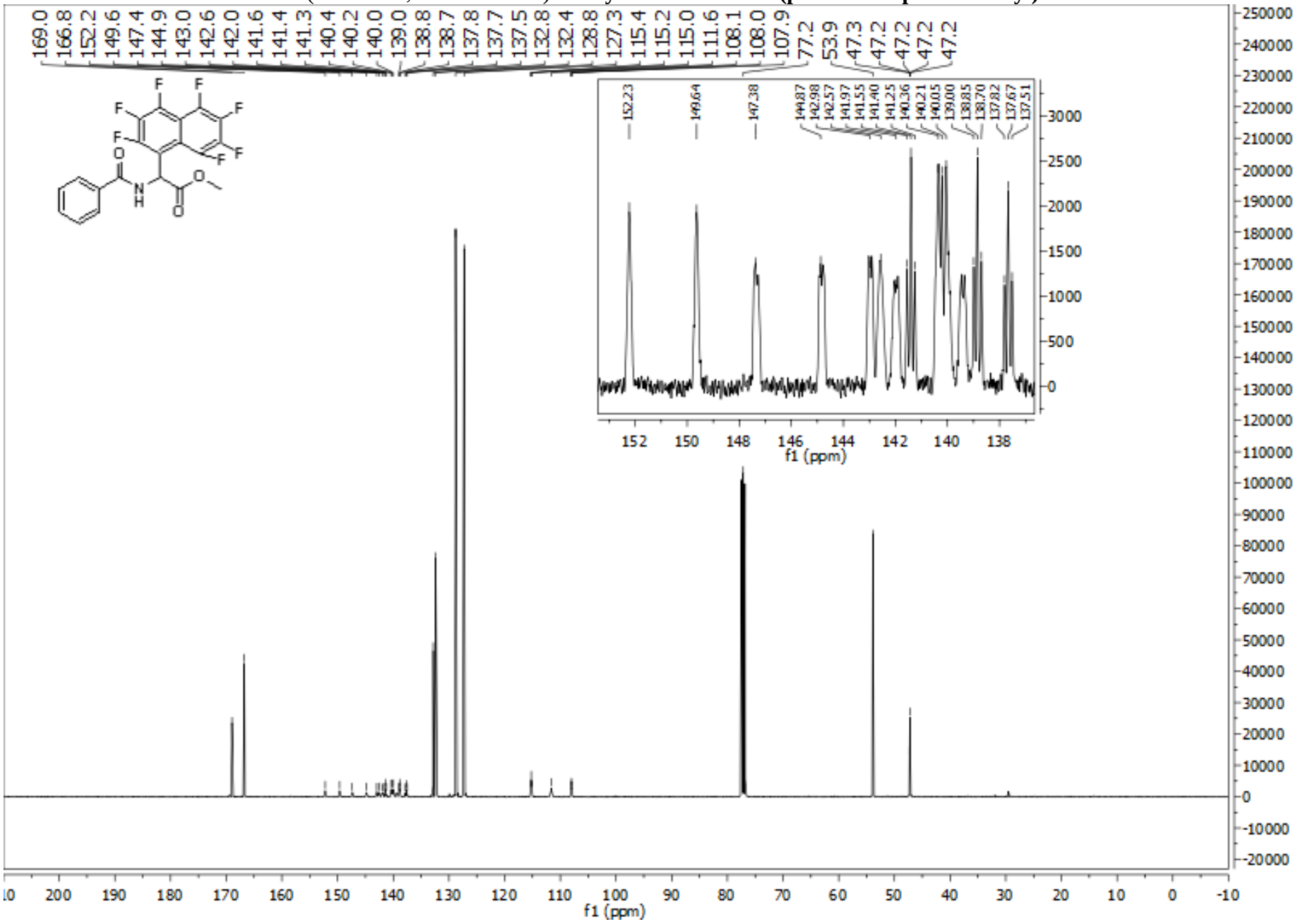
^{1}H NMR (400 MHz, Chloroform-*d*) **methyl 2-benzamido-2-(perfluoronaphthalen-1-yl)acetate**



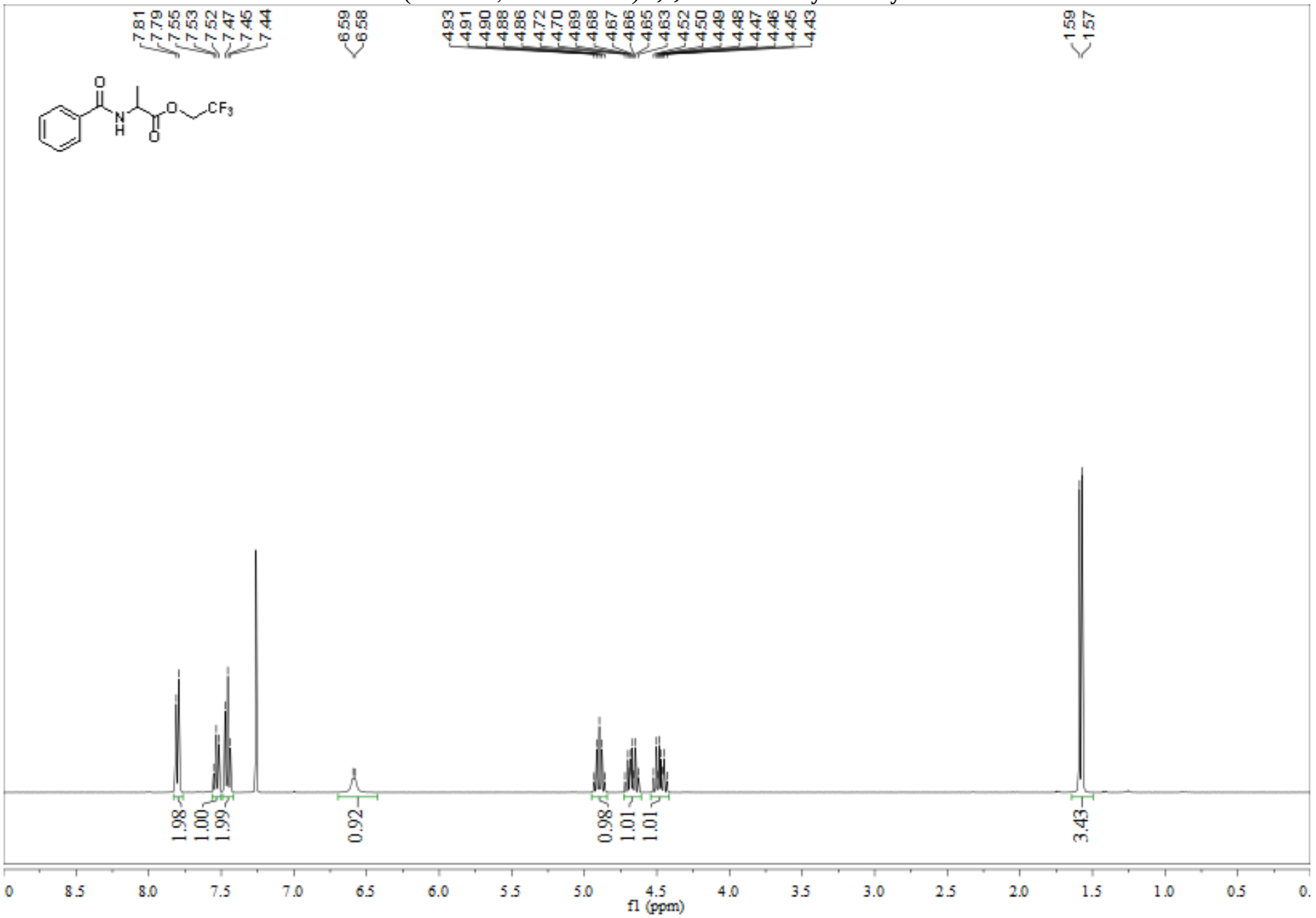
^{19}F NMR (376 MHz, , Chloroform-*d*) **methyl 2-benzamido-2-(perfluoronaphthalen-1-yl)acetate**



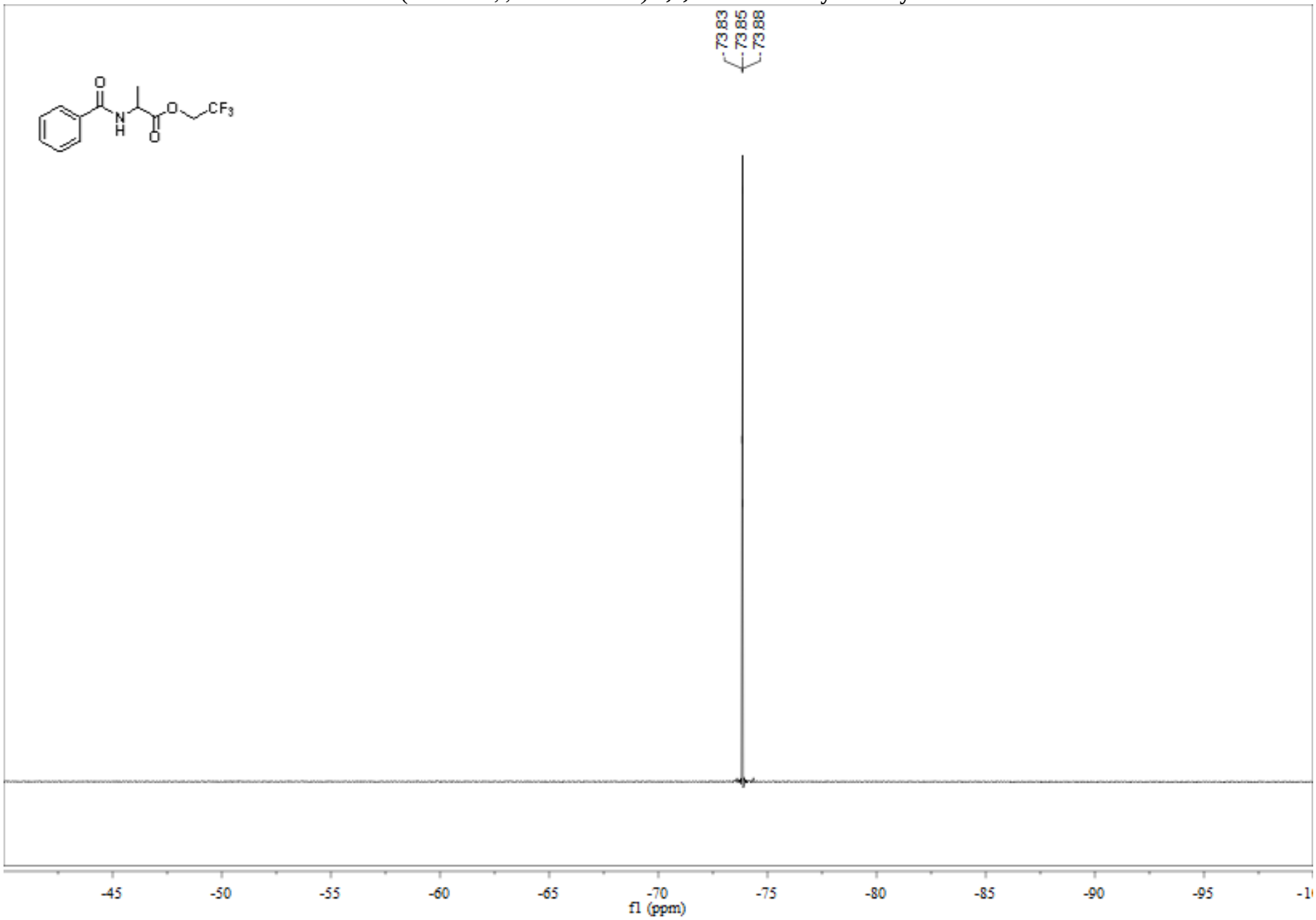
^{13}C NMR (101 MHz , Chloroform-*d*) **methyl 2-benzamido-2-(perfluoronaphthalen-1-yl)acetate**



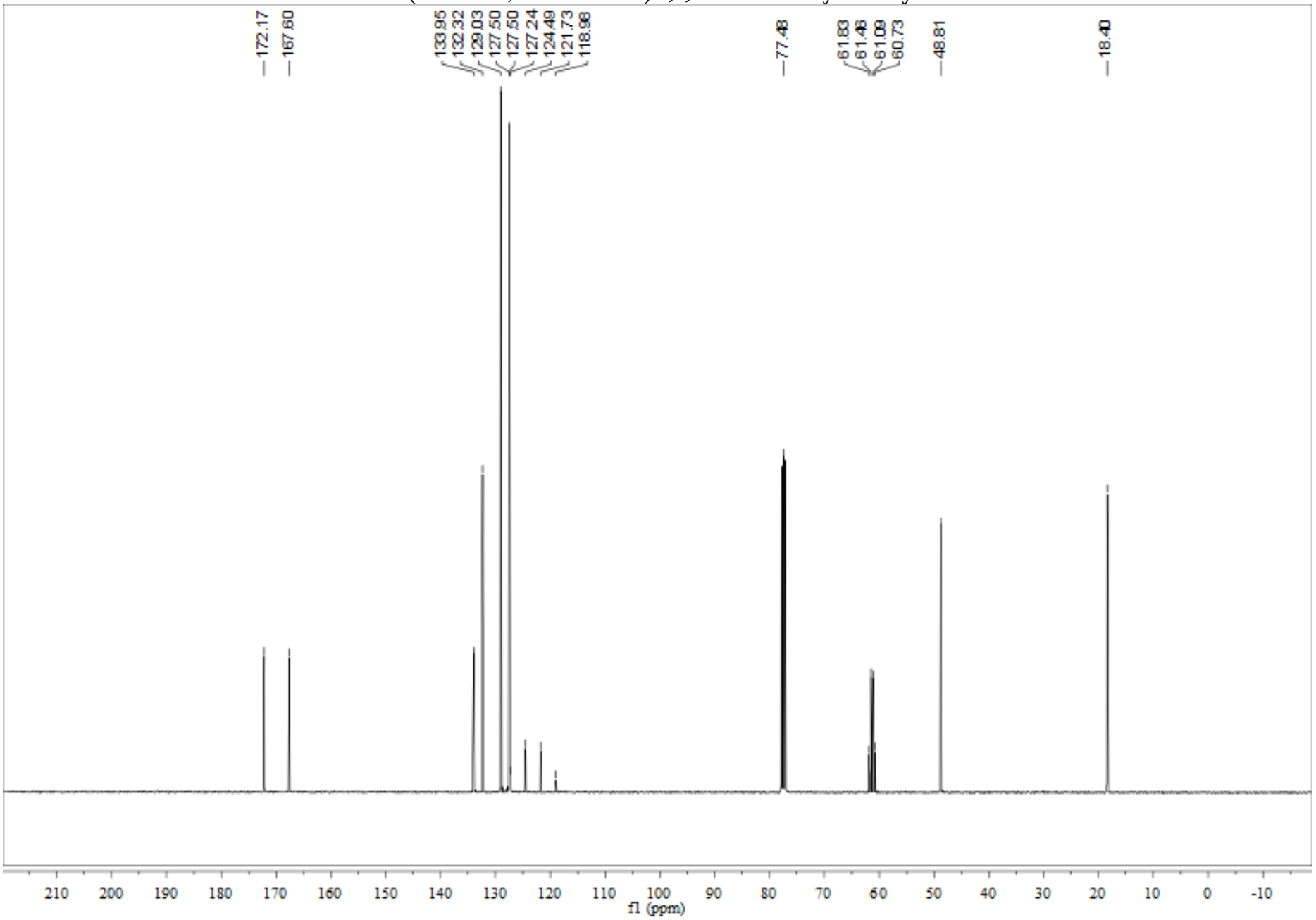
^{1}H NMR (400 MHz, Chloroform-*d)* **2,2,2-trifluoroethyl benzoylalaninate**



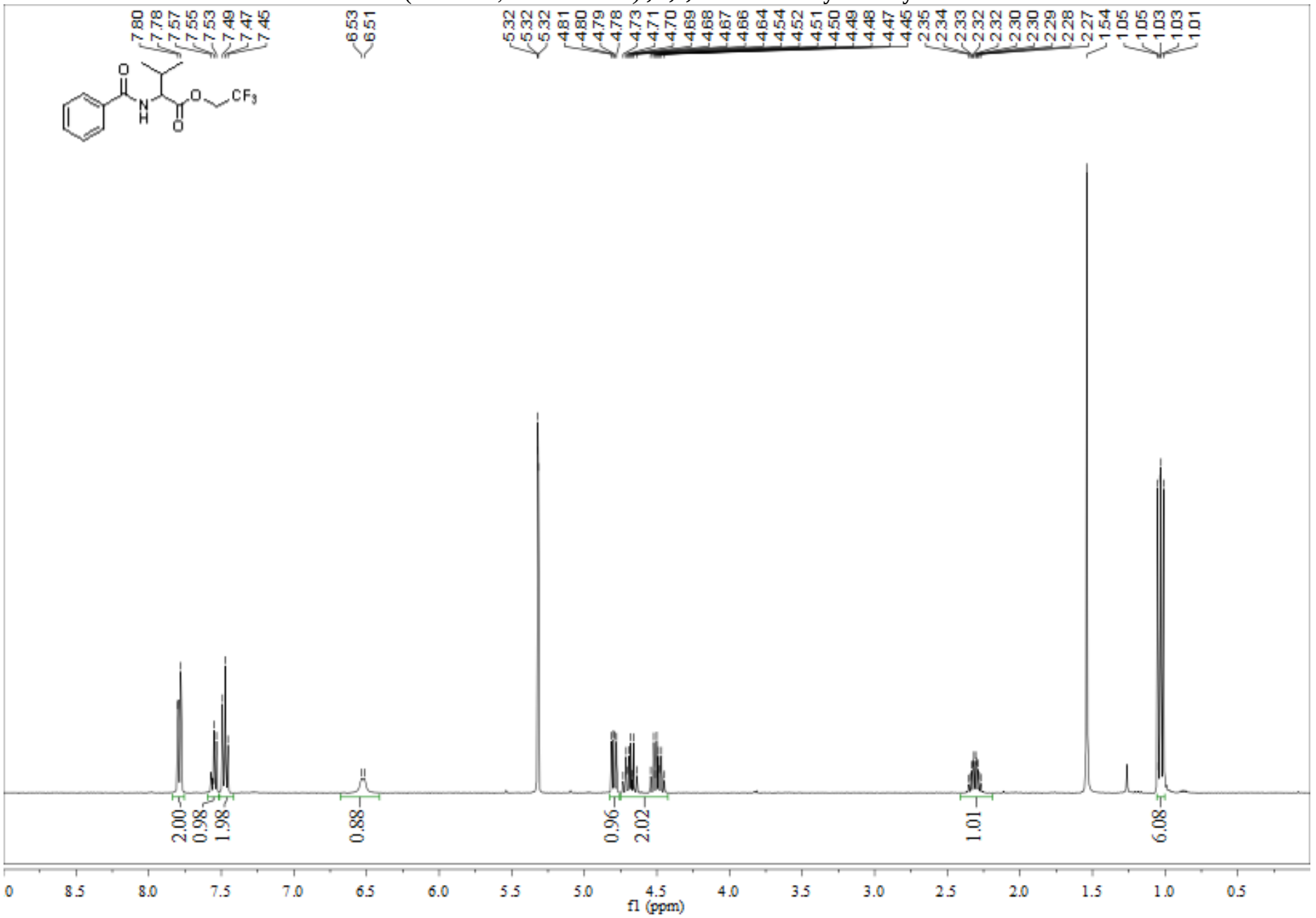
^{19}F NMR (376 MHz, , Chloroform-*d)* **2,2,2-trifluoroethyl benzoylalaninate**



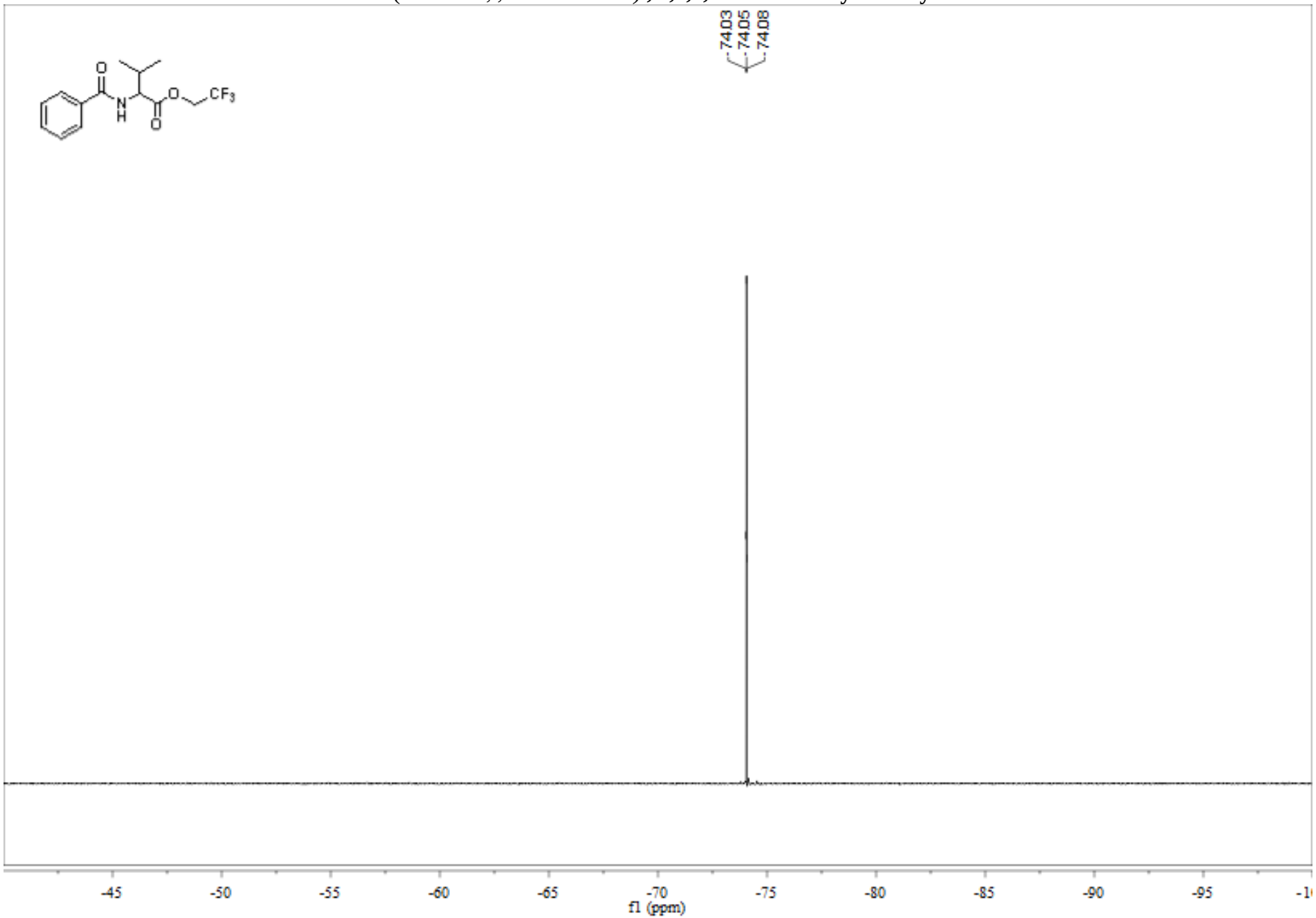
^{13}C NMR (101 MHz , Chloroform-*d*) **2,2,2-trifluoroethyl benzoylalaninate**



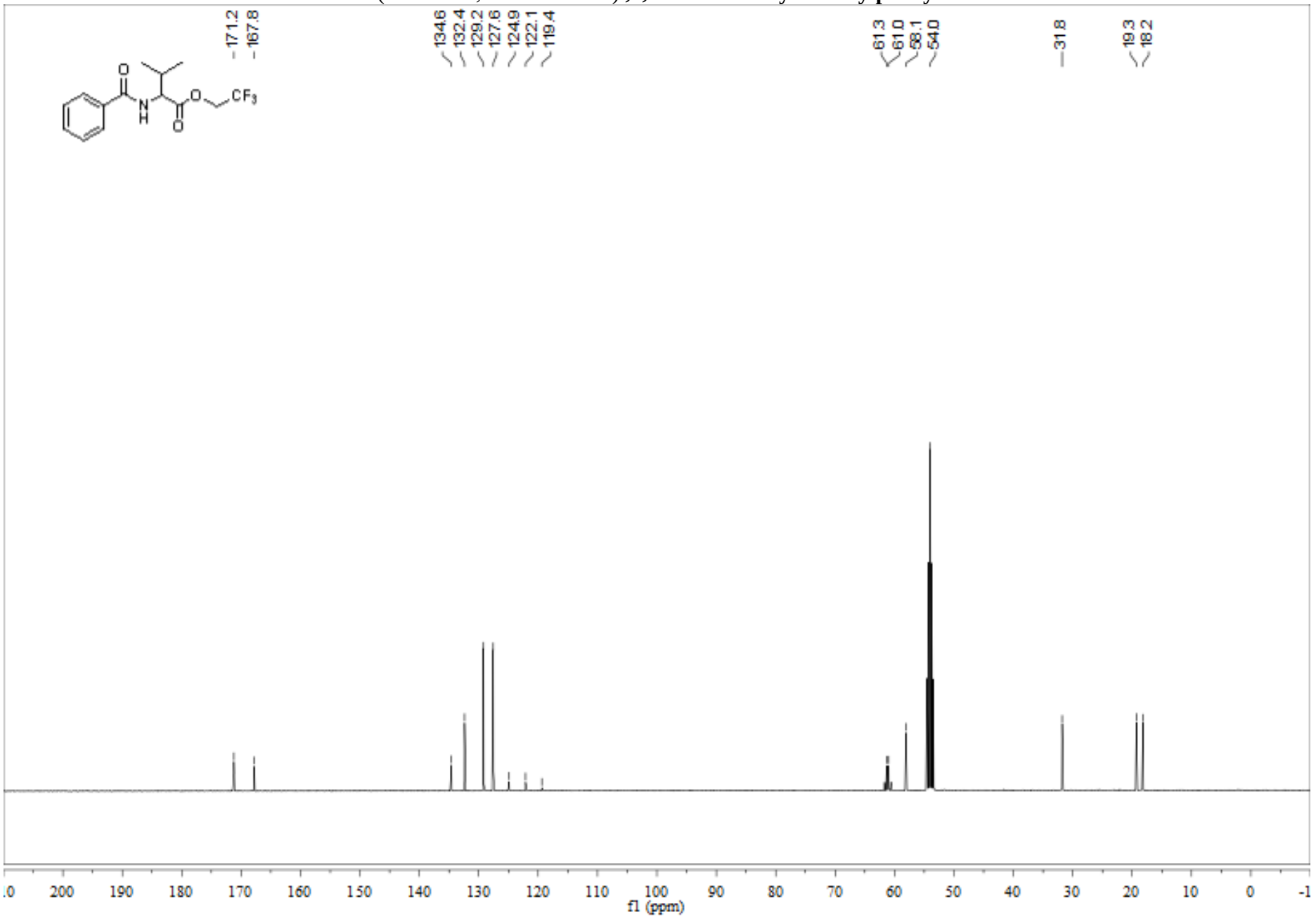
^{1}H NMR (400 MHz, Chloroform-*d*) **, 2,2,2-trifluoroethyl benzoylvalinate**



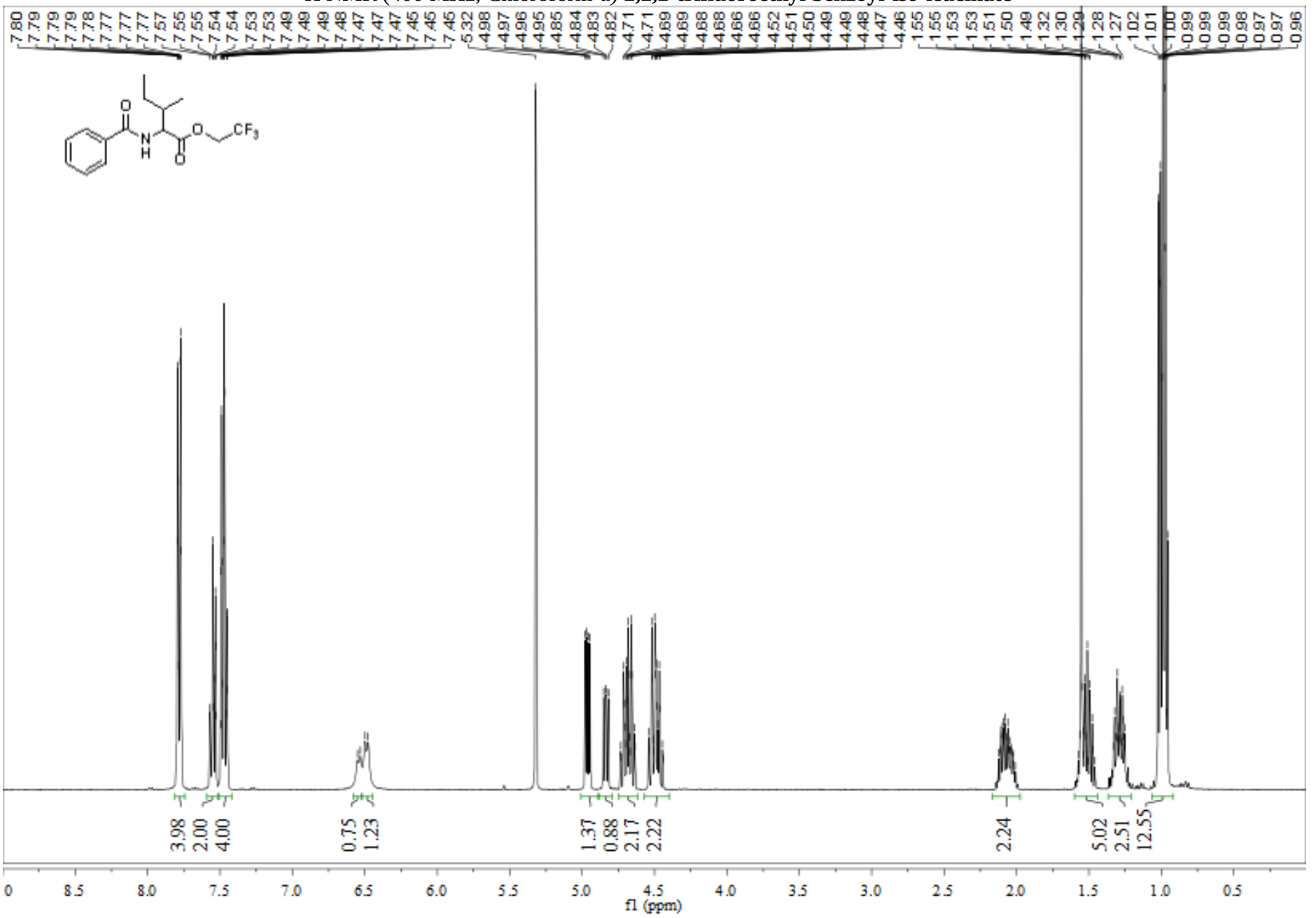
^{19}F NMR (376 MHz, , Chloroform-*d*) **, 2,2,2,2-trifluoroethyl benzoylvalinate**



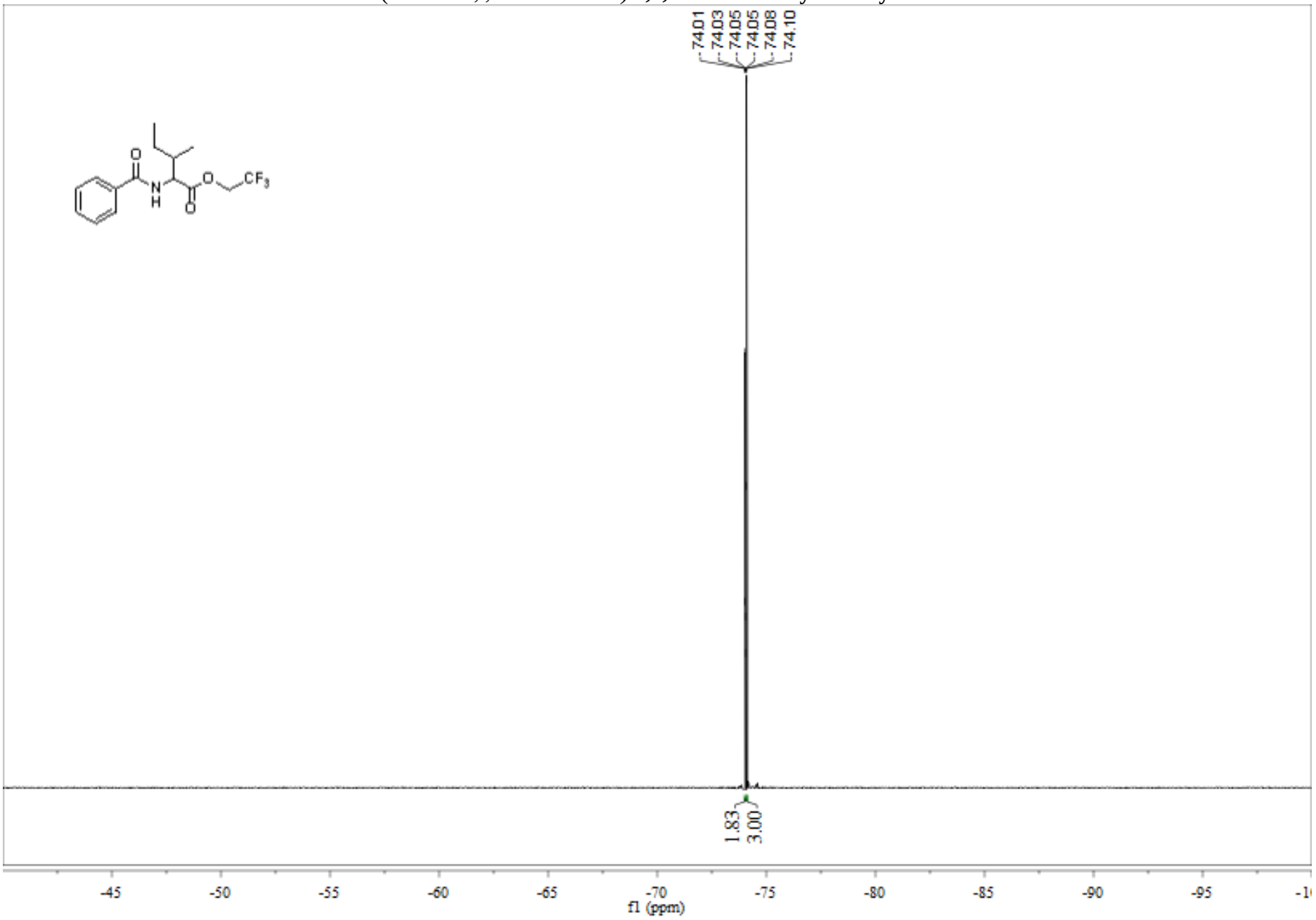
^{13}C NMR (101 MHz , Chloroform-*d*) **,2,2-trifluoroethyl benzoylphenylalaninate**



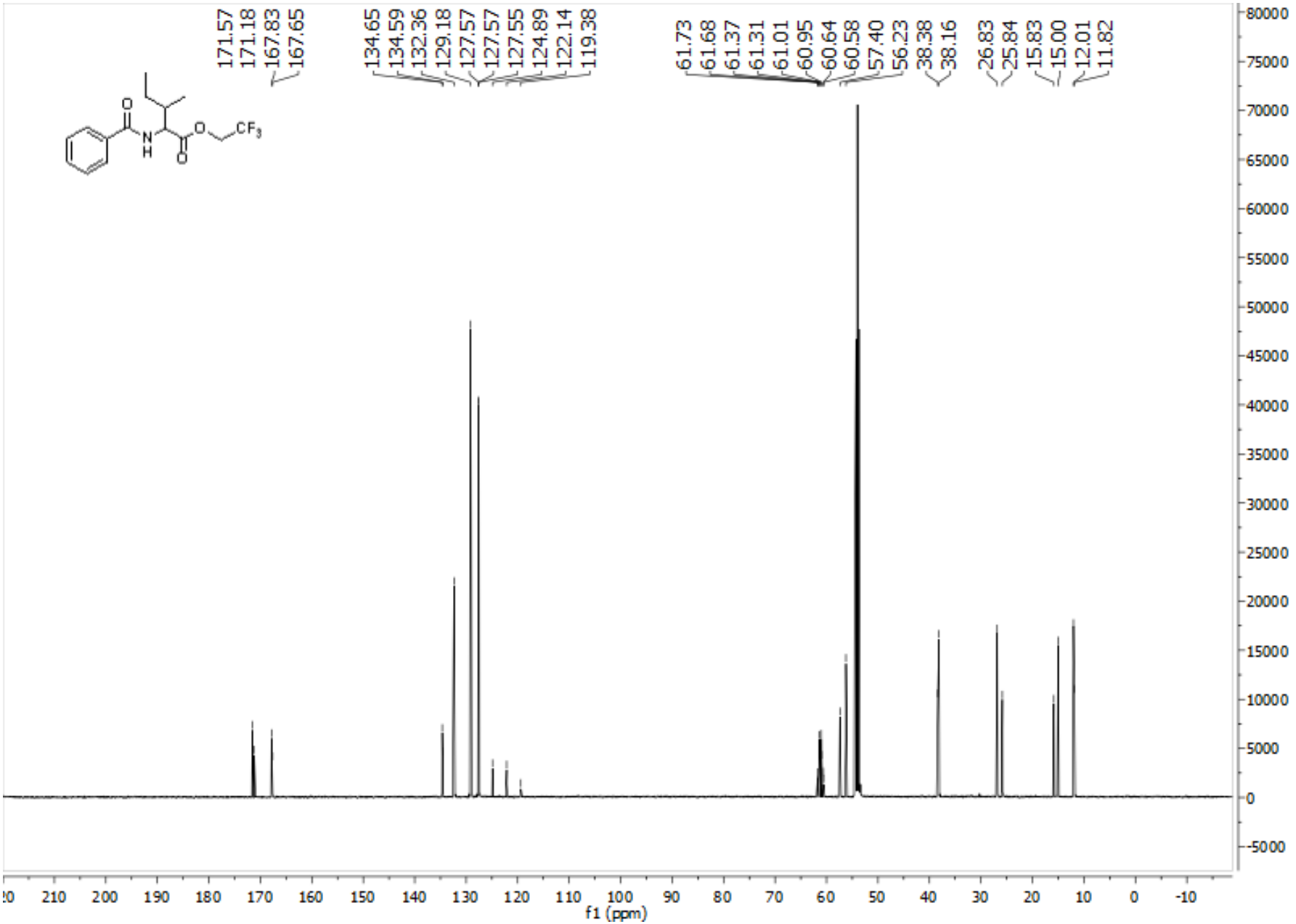
^{1}H NMR (400 MHz, Chloroform-*d*) **2,2,2-trifluoroethyl benzoyl-iso-leucinate**



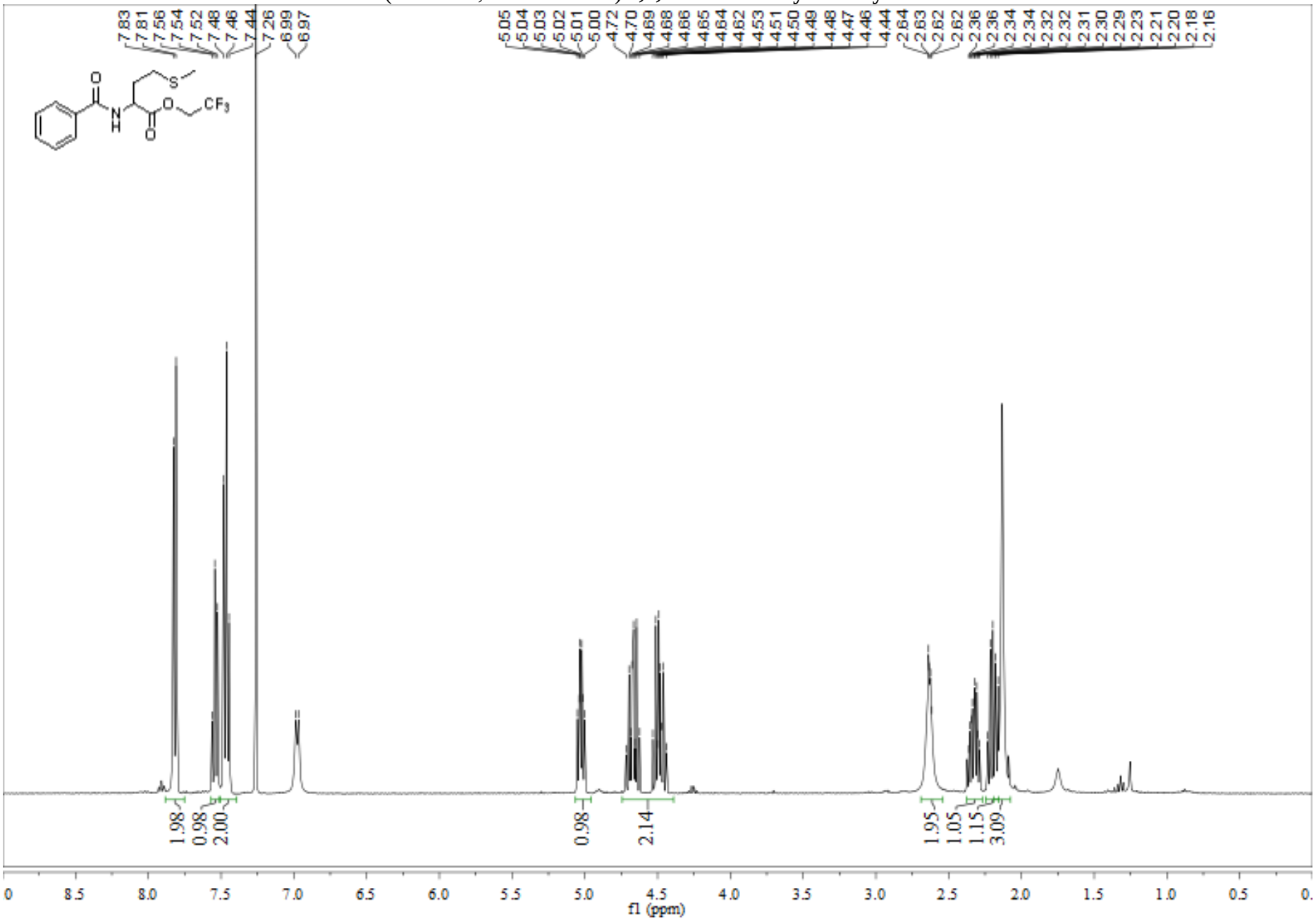
^{19}F NMR (376 MHz, , Chloroform-*d)* **2,2,2-trifluoroethyl benzoyl-iso-leucinate**



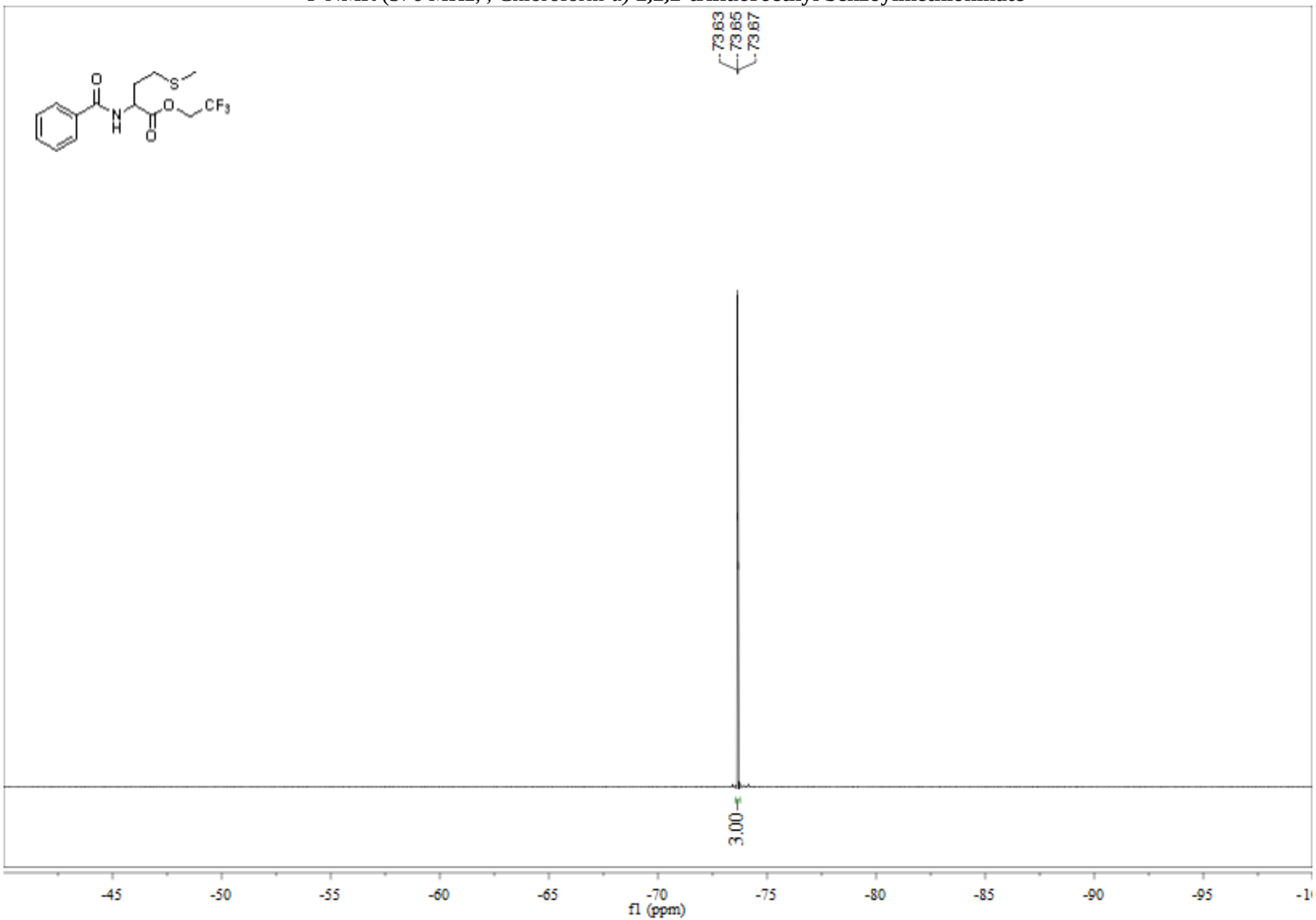
^{13}C NMR (101 MHz , Chloroform-*d*) **2,2,2-trifluoroethyl benzoyl-iso-leucinate**



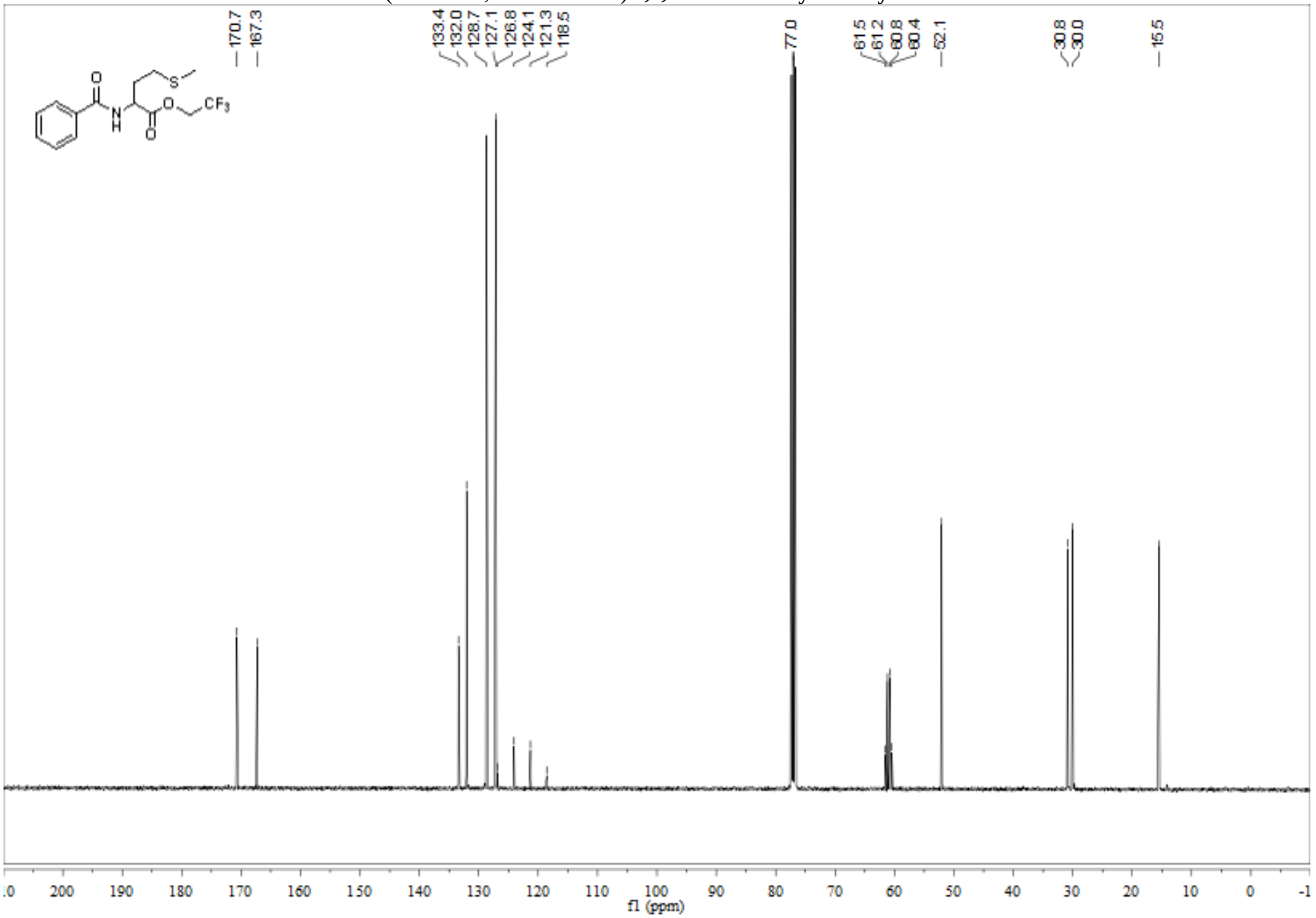
^{1}H NMR (400 MHz, Chloroform-*d*) **2,2,2-trifluoroethyl benzoylmethioninate**



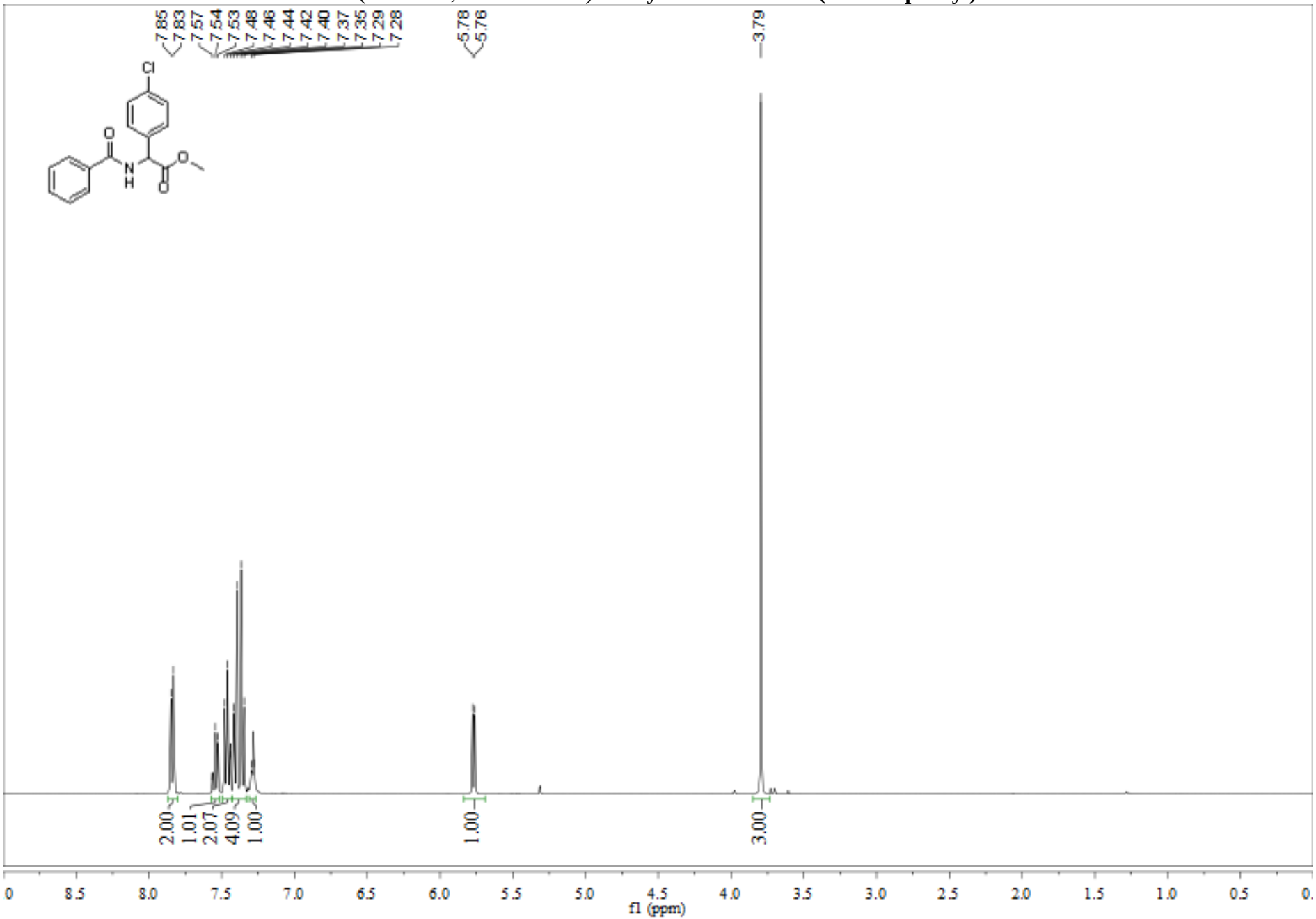
^{19}F NMR (376 MHz, , Chloroform-*d)* **2,2,2-trifluoroethyl benzoylmethioninate**



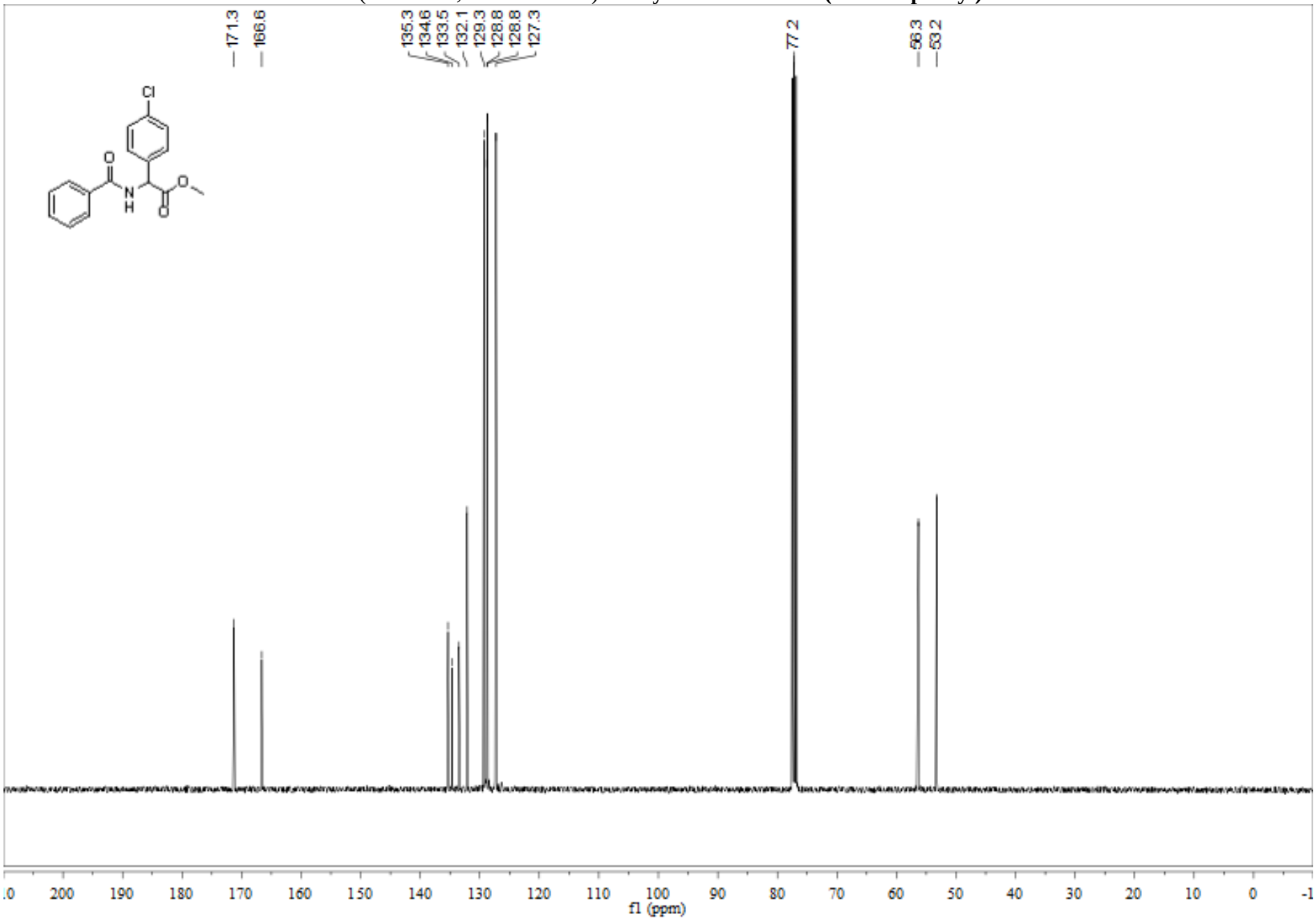
^{13}C NMR (101 MHz , Chloroform-*d*) **2,2,2-trifluoroethyl benzoylmethioninate**



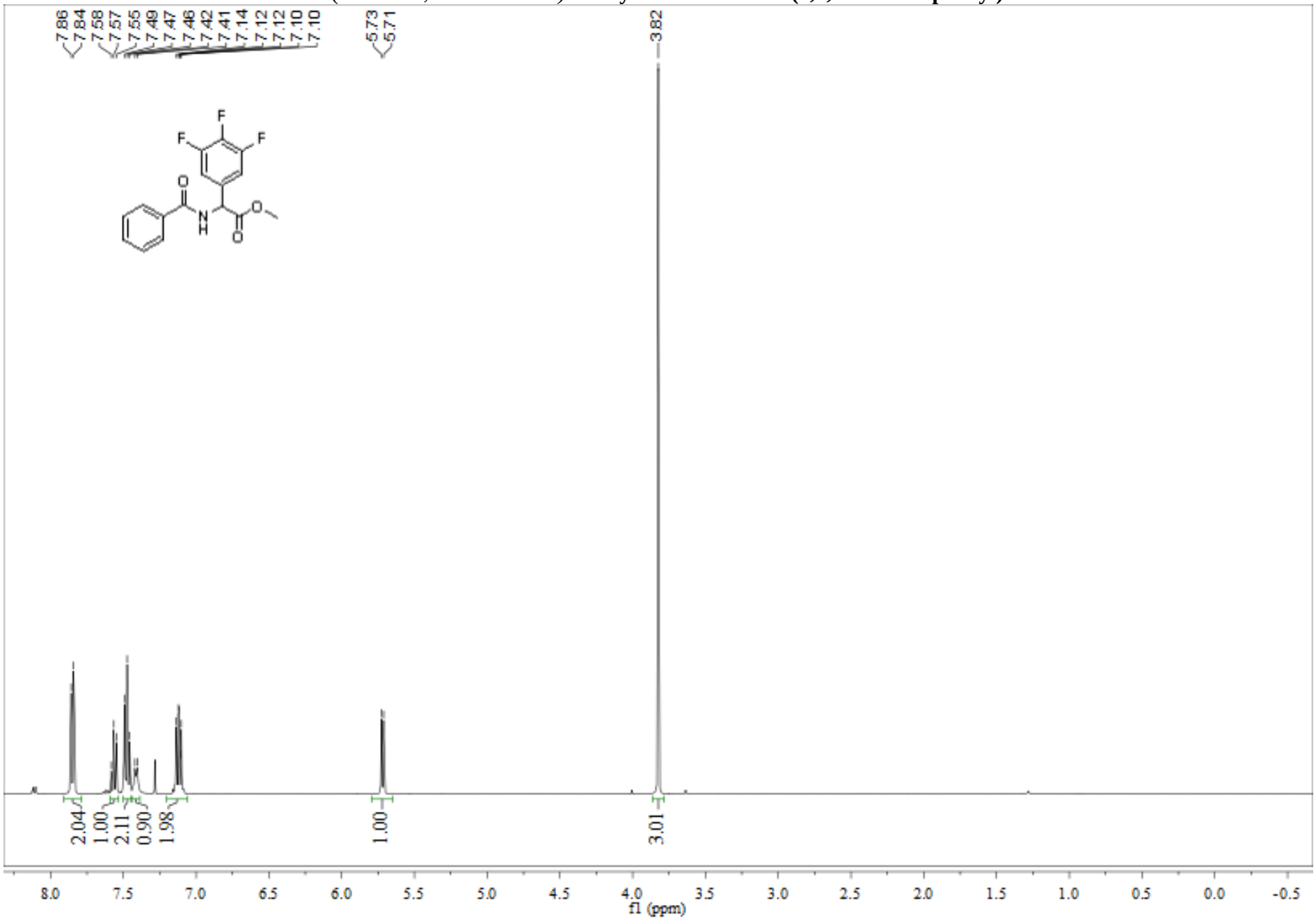
^{1}H NMR (400 MHz, Chloroform-*d*) **methyl 2-benzamido-2-(4-chlorophenyl)acetate**



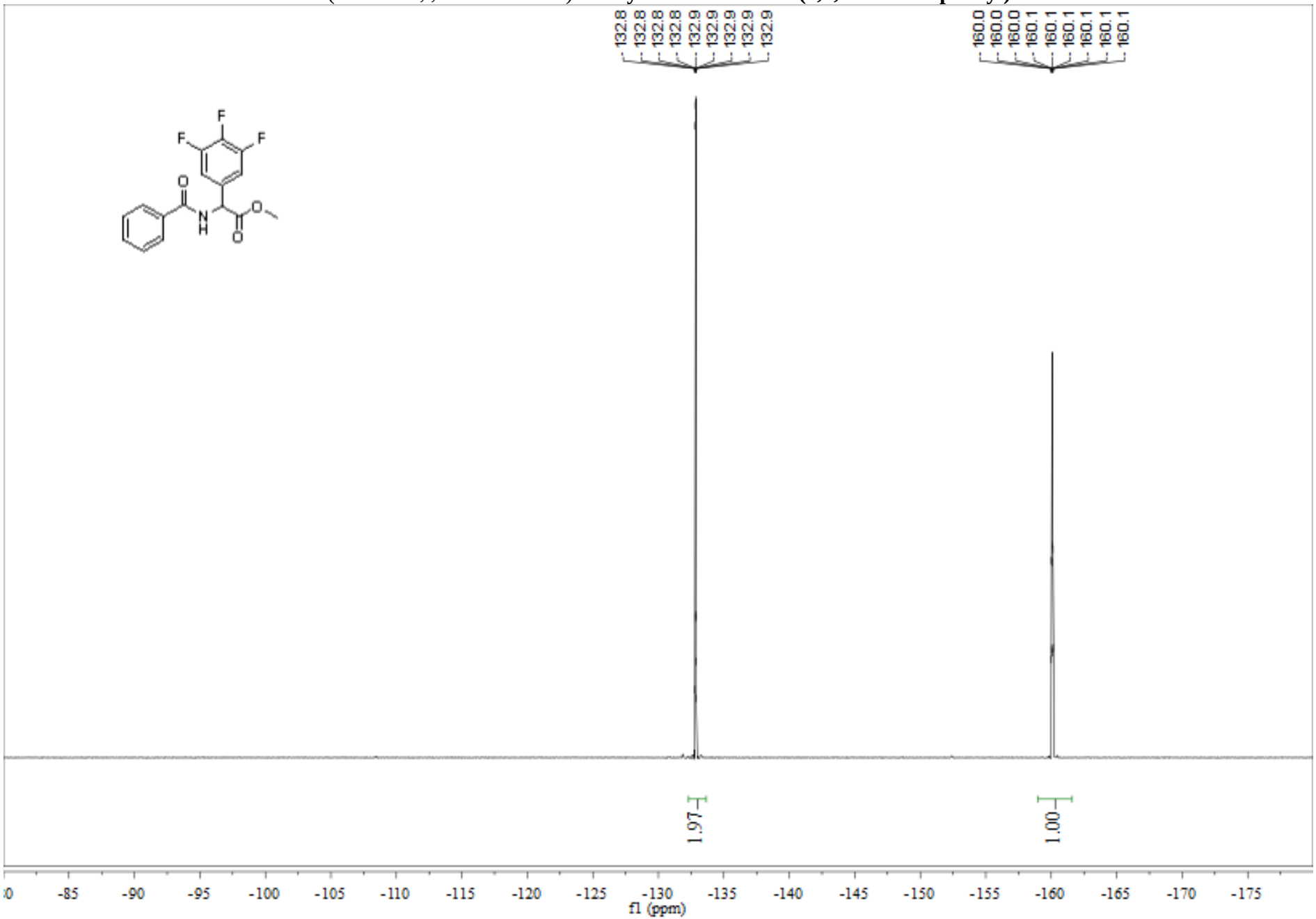
^{13}C NMR (101 MHz , Chloroform-*d*) **methyl 2-benzamido-2-(4-chlorophenyl)acetate**



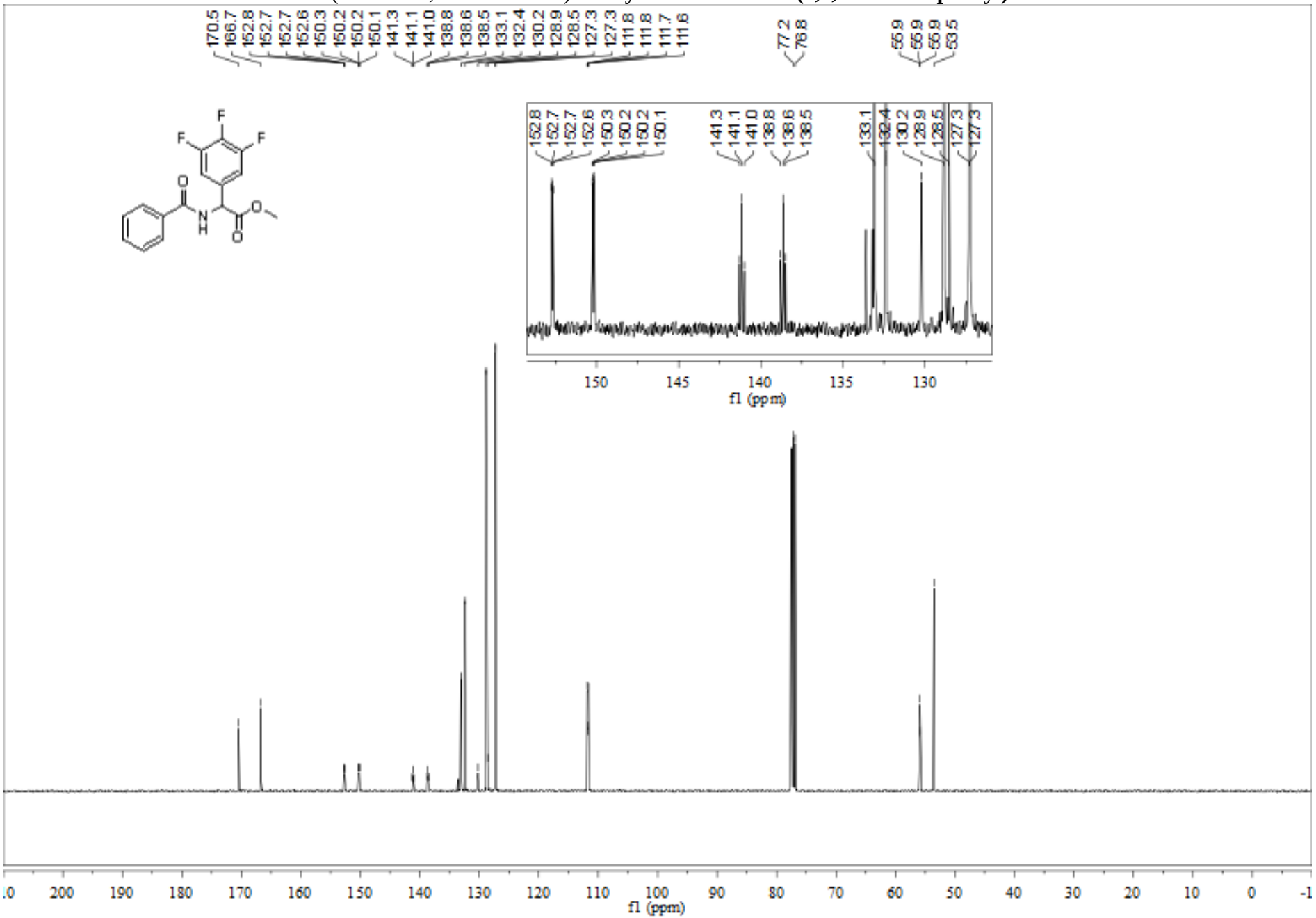
^{1}H NMR (400 MHz, Chloroform-*d*) **methyl 2-benzamido-2-(3,4,5-trifluorophenyl)acetate**



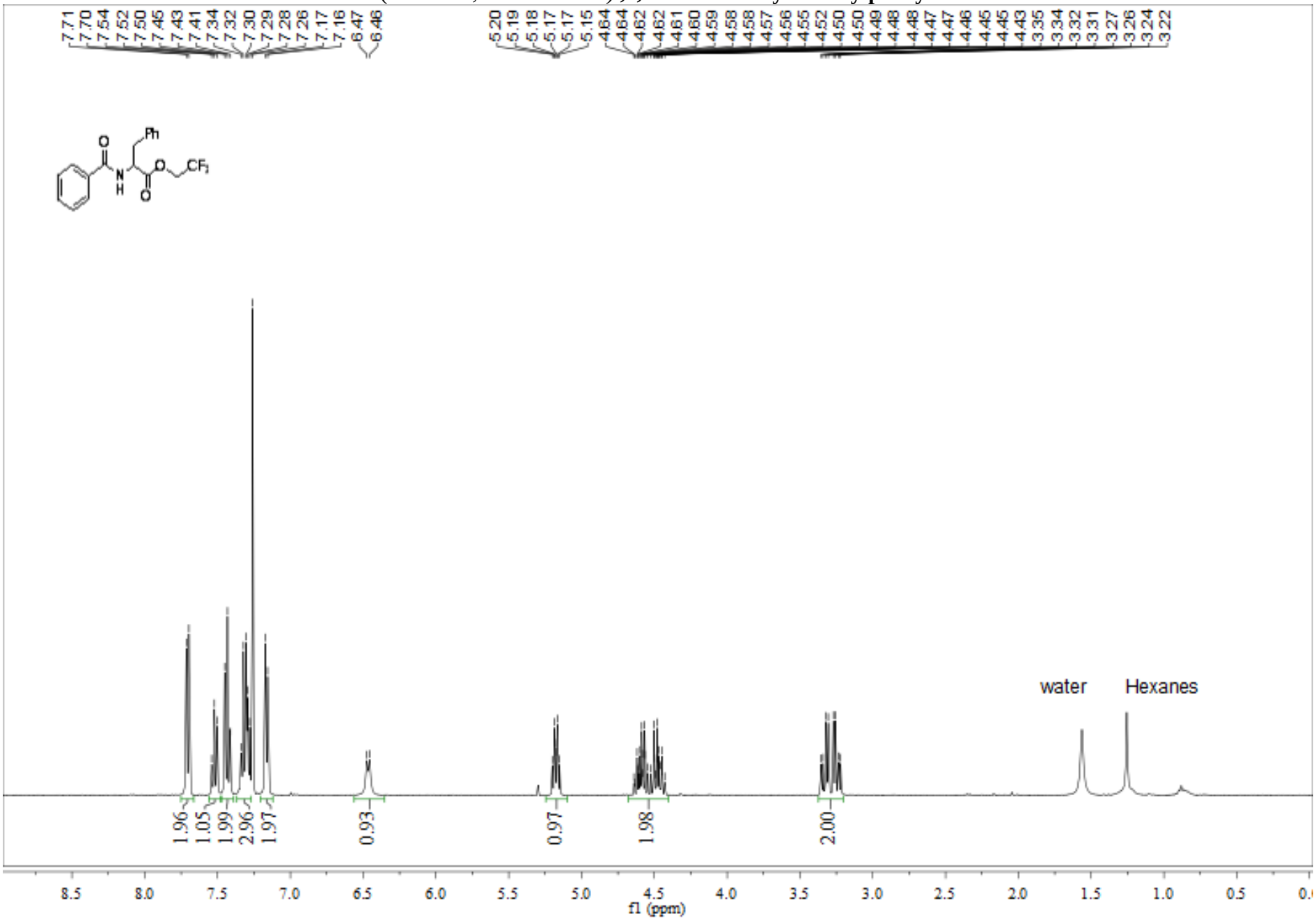
^{19}F NMR (376 MHz, , Chloroform-*d*) **methyl 2-benzamido-2-(3,4,5-trifluorophenyl)acetate**



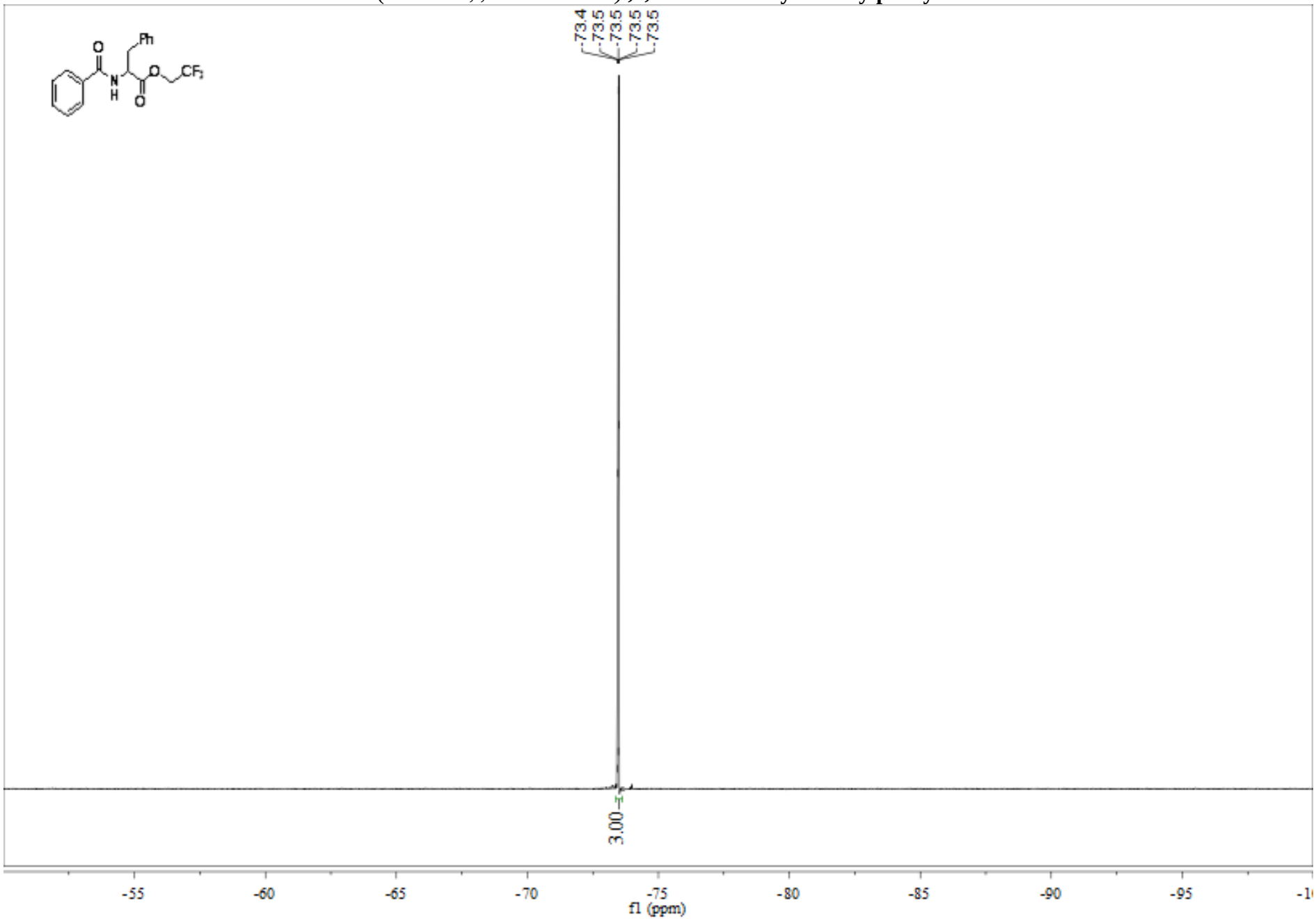
^{13}C NMR (101 MHz , Chloroform-*d*) **methyl 2-benzamido-2-(3,4,5-trifluorophenyl)acetate**



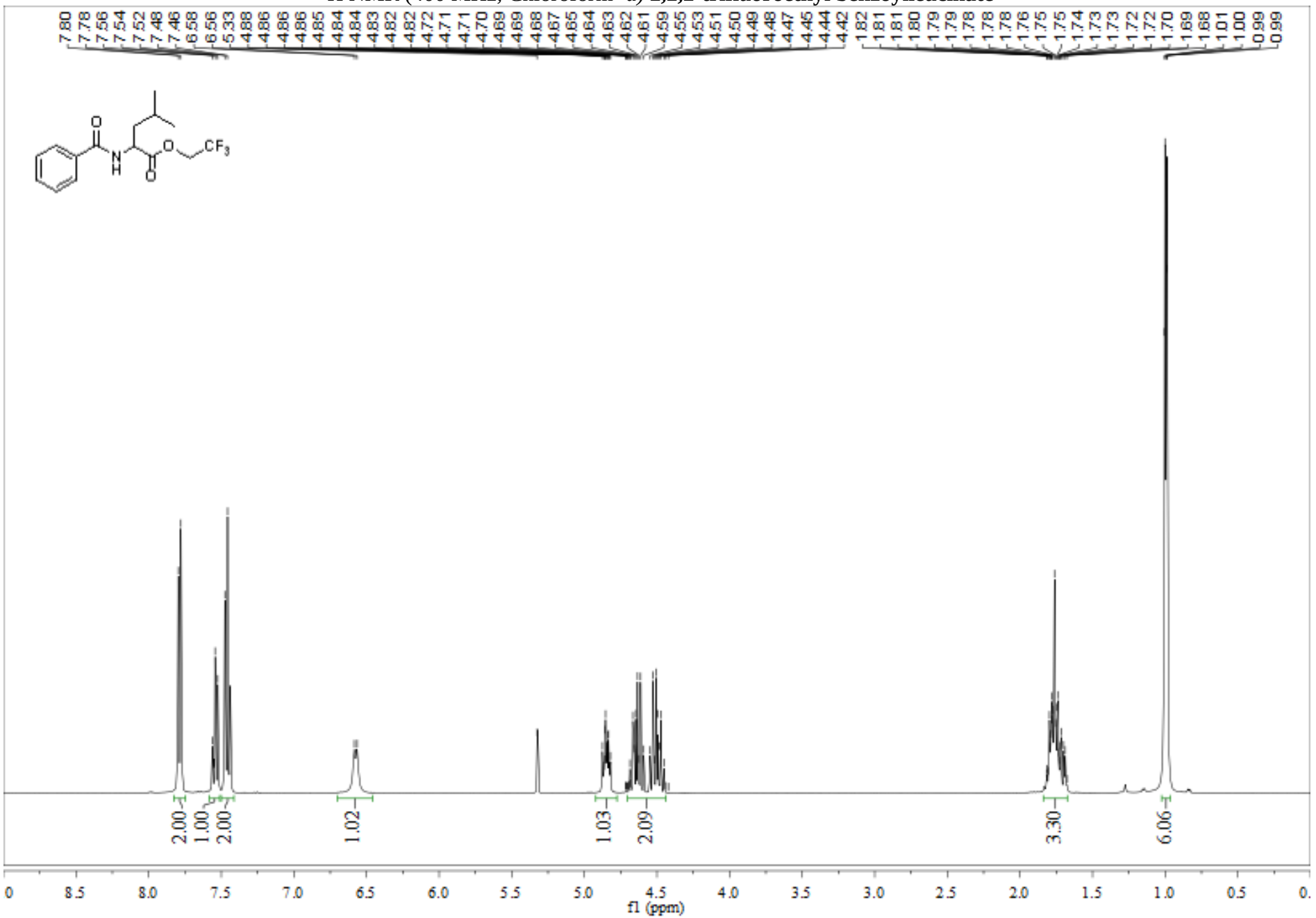
^{1}H NMR (400 MHz, Chloroform-*d*) **,2,2-trifluoroethyl benzoylphenylalaninate**



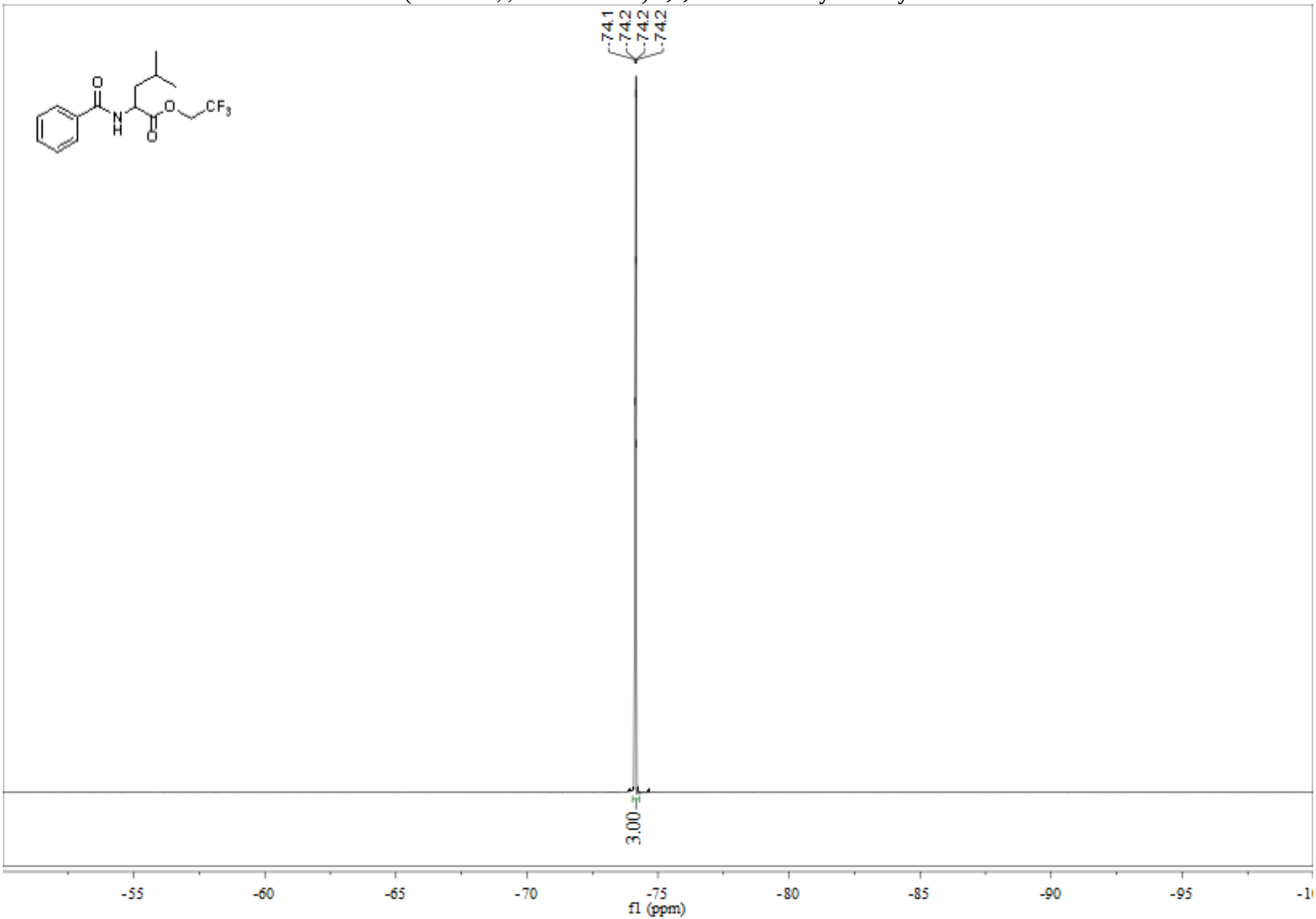
^{19}F NMR (376 MHz, , Chloroform-*d*) **,2,2-trifluoroethyl benzoylphenylalaninate**



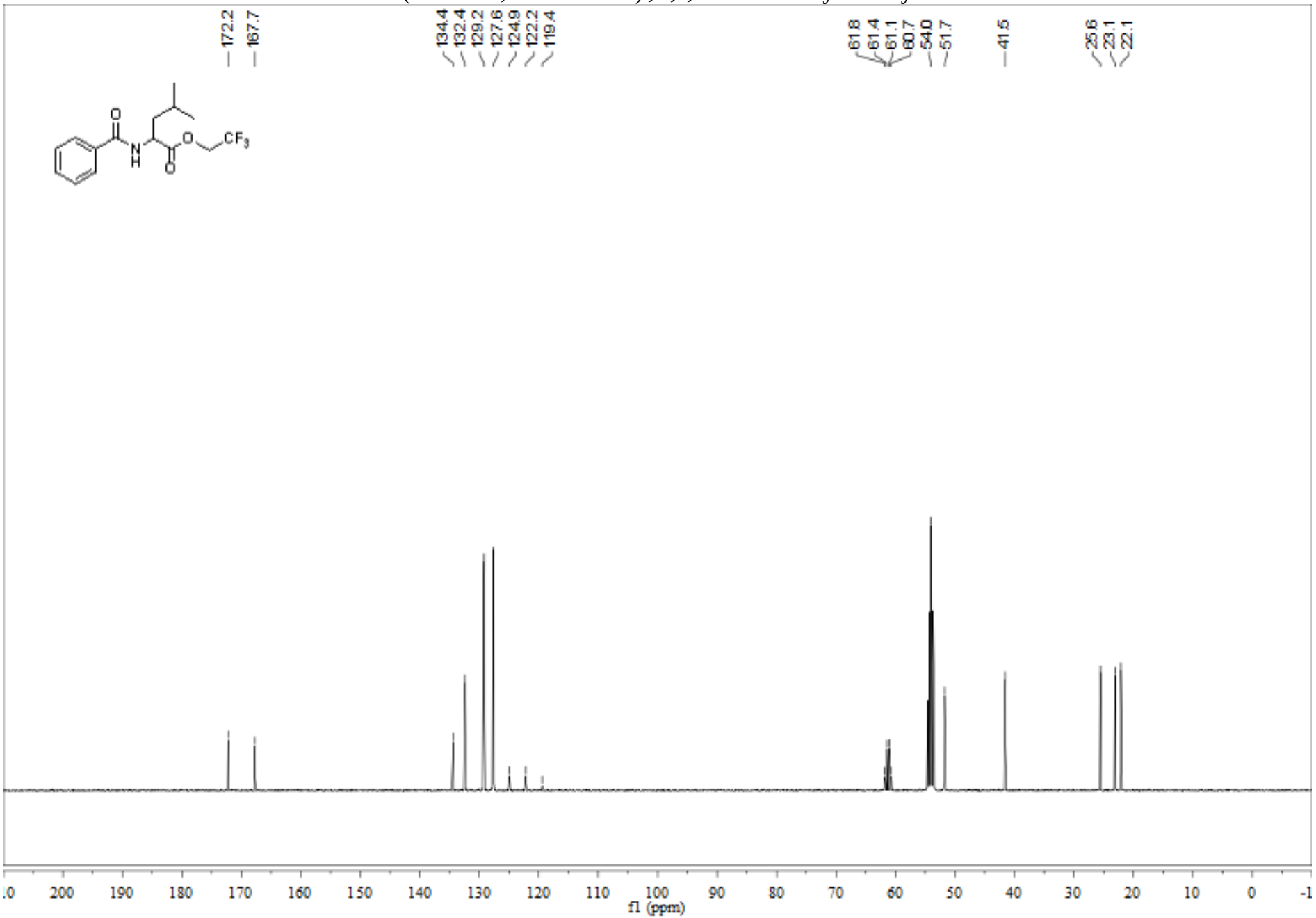
^{1}H NMR (400 MHz, Chloroform- *d)* **2,2,2-trifluoroethyl benzoylleucinate**



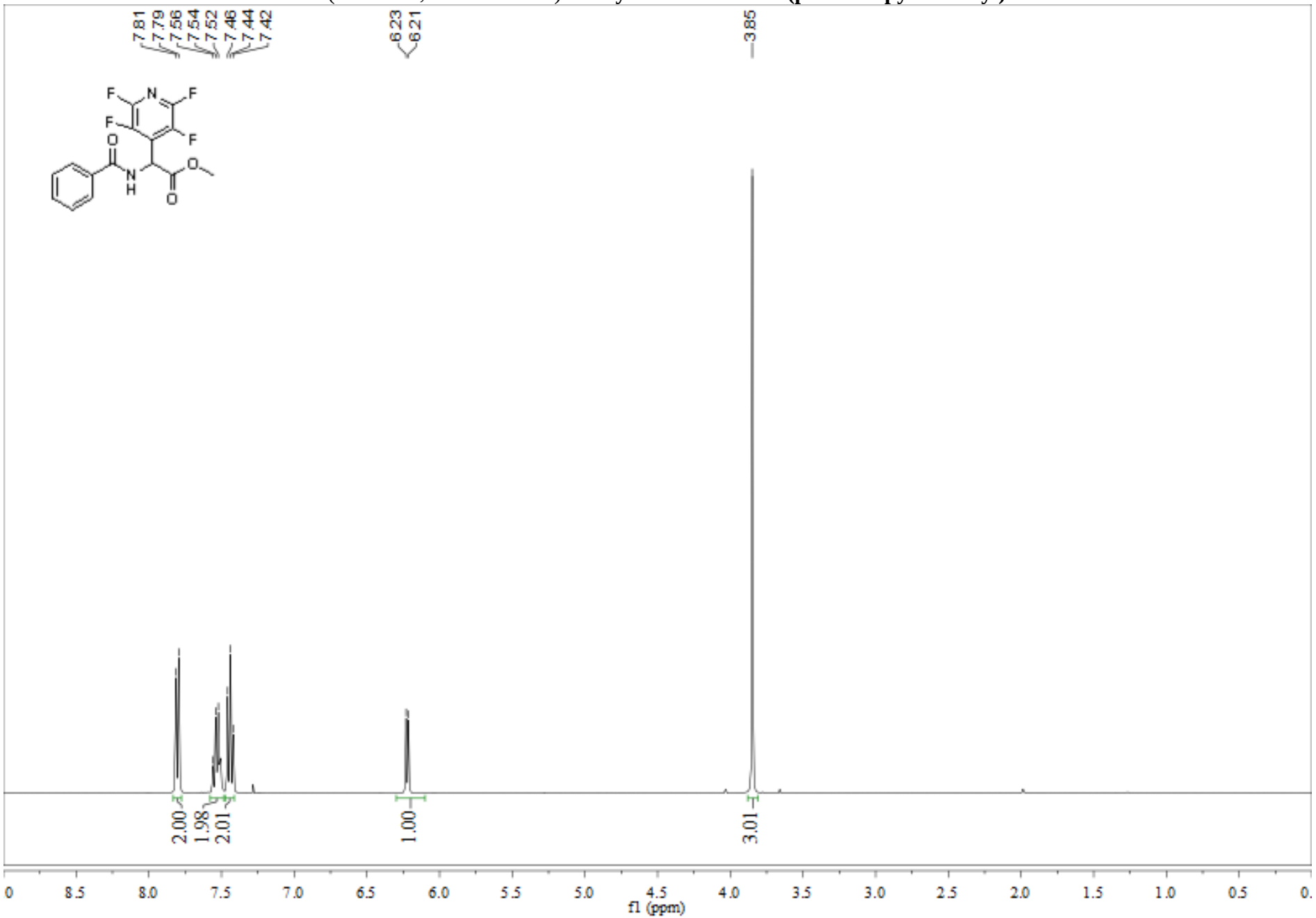
^{19}F NMR (376 MHz, , Chloroform-*d)* **2,2,2-trifluoroethyl benzoylleucinate**



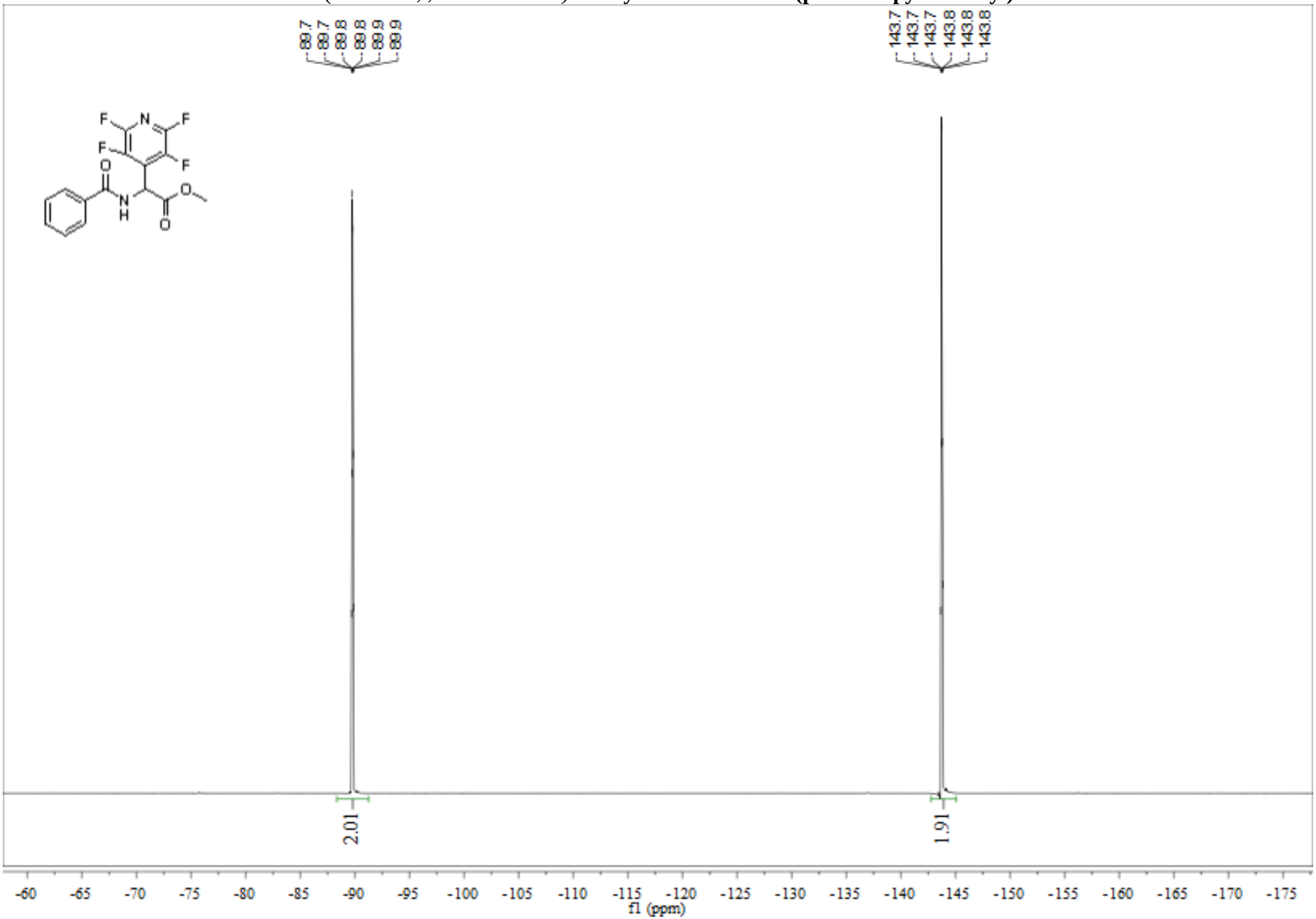
^{13}C NMR (101 MHz , Chloroform-*d*) **, 2,2,2-trifluoroethyl benzoylleucinate**



^{1}H NMR (400 MHz, Chloroform-*d*) **methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate**



^{19}F NMR (376 MHz, , Chloroform-*d)* **methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate**



^{13}C NMR (101 MHz , Chloroform-*d*) **methyl 2-benzamido-2-(perfluoropyridin-4-yl)acetate**