

Polyfluoroarylation of Oxazolones: Access to Non-Natural Fluorinated Amino Acids

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Electronic Supporting Information (ESI)

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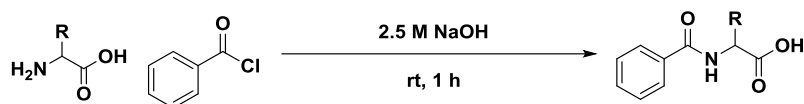
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General Experimental:

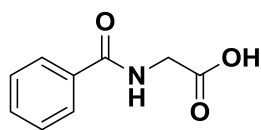
All reagents were obtained from commercial suppliers (Aldrich, VWR, TCI Chemicals, and Oakwood Chemicals) and used without further purification unless otherwise noted. *N*-benzoyl alanine was purchased from Oakwood Chemicals and all other *N*-benzoyl amino acids were synthesized according to literature procedures.¹ Oxazolones were synthesized according to literature procedure.² Reactions were monitored by thin layer chromatography (TLC), (obtained from sorbent technology Silica XHL TLC Plates, w/UV254, glass backed, 250 μ m, 20 x 20 cm) and were visualized with ultraviolet light, potassium permanganate stain, GC-MS (QP 2010S, Shimadzu equipped with auto sampler) and ¹H NMR ¹⁹F NMR.

Isolations were carried out using Teledyne Isco Combiflash Rf 200i flash chromatograph with Sorbent normal phase silica (standard grade) (4 g, 12 g, 24 g, or 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. ¹H, ¹⁹F and ¹³C NMR chemical shifts are reported in ppm relative to the residual protio solvent peak (¹H, ¹³C). IR spectra were recorded on Varian 800 FT-IR. Due to the C-F splitting, carbons that couple with fluorine were reported as multiplets. Melting points were determined on Stuart Digital (SMP10) melting point apparatus. High resolution mass spectrometry (HRMS) analysis was performed on LTQ-OrbitrapXL by Thermo Scientific ltd.

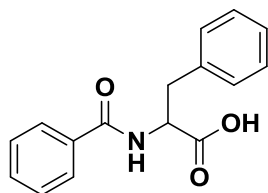
General procedure A for synthesis of *N*-benzoyl amino acids ¹



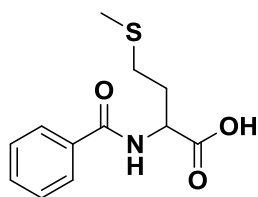
Benzoyl chloride (**1.2 equiv**) was added incrementally in 4 portions over **30** minutes to a solution of the amino acid (**1 equiv**) and 2.5 M NaOH (**3.8 equiv**) in distilled water. After the addition was complete, the ice bath was removed, and the reaction was quenched by the dropwise addition of concentrated aqueous hydrochloric acid until **pH 1** was reached, which resulted in precipitation of the product. The solid product 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 ¹H NMR.



S-1 in 93% yield after isolation (10.86 g, 60.9 mmol) as a white solid. The **general procedure A** was followed using glycine (5.00 g, 66.6 mmol), benzoyl chloride (9.30 mL, 79.2 mmol), 2.5 M NaOH (100 mL, 251 mmol). ¹H-NMR matched that previously reported in the literature.¹

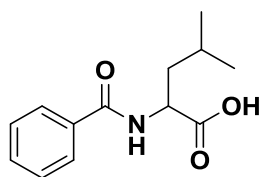


S-2 in 79% yield after isolation (3.20 g, 11.9 mmol) as a white solid. The **general procedure A** was followed using phenyl alanine (2.50 g, 15.1mmol), benzoyl chloride (2.11 mL, 18.1 mmol), 2.5 M NaOH (23.0 mL, 57.4 mmol). ¹H-NMR matched that previously reported in the literature.³



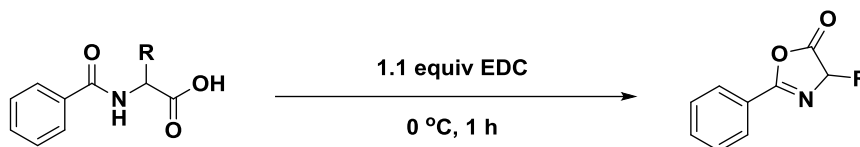
S-3 in 66% yield after isolation (2.80 g, 11.1 mmol) as a white solid. The **general procedure A** was followed using methionine (2.50 g, 16.8 mmol),
ESI-2

benzoyl chloride (2.34 mL, 20.1 mmol), 2.5% NaOH (25.5 mL, 63.8 mmol). ¹H-NMR matched that previously reported in the literature.⁴

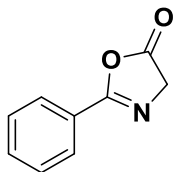


S-4 in 67% yield after isolation (2.41 g, 10.2 mmol) as a white solid. The **general procedure A** was followed using leucine (2.00 g, 15.2 mmol), benzoyl chloride (2.12 mL, 18.3 mmol), 2.5% NaOH (23.1 mL, 57.8 mmol). ¹H-NMR matched that previously reported in the literature.³

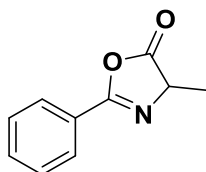
General procedure B: for synthesis of oxazolones



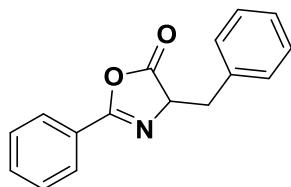
To a flame dried round bottom flask a suspension of *N*-benzoyl amino acid (1 equiv) in dry CH₂Cl₂ (0.07 M), under an argon atmosphere, at 0 °C, was added EDC HCl (1.1 equiv). The materials were stirred at 0 °C for 1 hour. The reaction mixture was diluted with an equal volume of CH₂Cl₂, and washed successively with water, saturated aqueous NaHCO₃, and water (each 1/2 the volume of the organic phase), then dried over MgSO₄ and concentrated under reduced pressure. (Note: the oxazolones are moisture and thermally sensitive reagents. As a precaution the oxazolones were stored under argon at 5 °C until use).



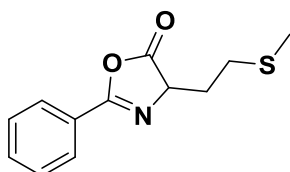
S-5 in 80% yield after isolation (1.80 g, 11.1 mmol) as a pale white solid. The **general procedure B** was followed using *N*-benzoyl glycine (2.50 g, 14.0 mmol), EDC (2.38 g, 15.3 mmol), CH₂Cl₂ (200 mL). ¹H-NMR matched that previously reported in the literature.²



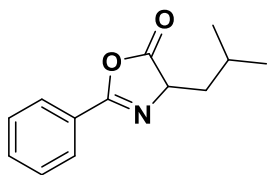
S-6 in >95% yield after isolation (907 mg, 5.18 mmol) as a white solid. The **general procedure B** was followed using *N*-benzoyl alanine (1.00 g, 5.18 mmol), EDC (884 mg, 5.69 mmol), CH₂Cl₂ (74 mL). ¹H-NMR matched that previously reported in the literature.²



S-7 in 87% yield after isolation (806 mg, 3.21 mmol) as a white solid. The **general procedure B** was followed using *N*-benzoyl phenylalanine (990 mg, 3.68 mmol), EDC (628 mg, 4.04 mmol), CH₂Cl₂ (52.5 mL). ¹H-NMR matched that previously reported in the literature.²

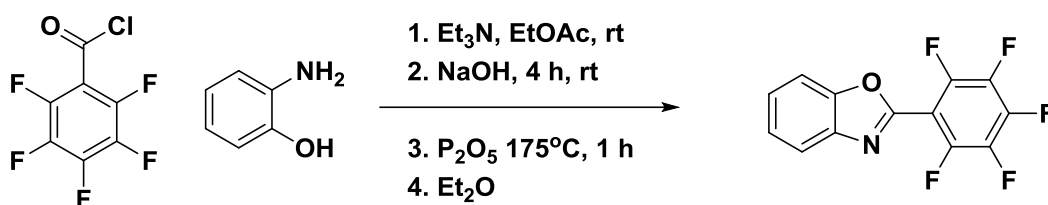


S-8 in 74% yield after isolation (1.1 g, 4.68 mmol) as a pale white solid. The **general procedure B** was followed using *N*-benzoyl methionine (1.6 g, 6.32 mmol), EDC (1.08 g, 6.95 mmol), CH₂Cl₂ (90.2 mL). H-NMR matched that previously reported in the literature.⁴



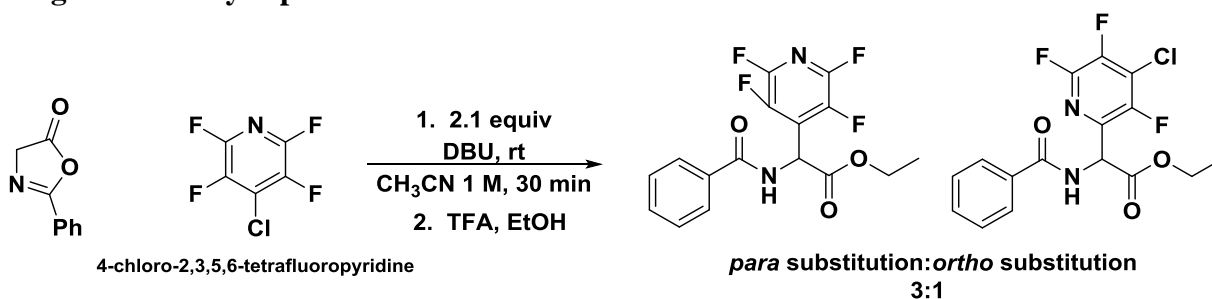
S-9 in 95% yield after isolation (553 mg, 2.45 mmol) as a pale white solid. The **general procedure B** was followed using *N*-benzoyl leucine (610 mg, 2.59 mmol), EDC (443 mg, 2.85 mmol), CH₂Cl₂ (37.0 mL). ¹H-NMR matched that previously reported in the literature.³

Synthesis of 2-(perfluorophenyl)benzo[d]oxazole



2-(perfluorophenyl)benzo[d]oxazole as a white solid in 33% yield. 2-(perfluorophenyl)benzo[d]oxazole was prepared by following the literature procedure.⁵ Triethylamine (1.7 g, 16.9 mmol) was added dropwise to a solution of 2-aminophenol (1.4 g, 12.7 mmol) and pentafluorobenzoyl chloride (3.2 g, 14.1 mmol) in ethyl acetate (50 mL). The mixture was refluxed overnight and then aq NaOH (1M, 30 mL) was added and stirred for 3 hours at room temperature. The resulting mixture was extracted with EtOAc (5 × 20 mL) and washed with H₂O (25 mL) and brine (25 mL). The organic layer was dried over anhydrous MgSO₄ to yield 4 g of intermediate. Next, P₂O₅ (4.0 g, 28 mmol) was added to the intermediate and then heated at 175 °C for 1 hour. After the mixture had cooled to room temperature, ice water (50 mL) was added and mixture was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with aq NaOH (0.25 M, 50 mL), followed by water, brine and dried over anhydrous MgSO₄ and then concentrated *in vacuo* to afford the crude product. The resultant crude residue was purified by automated flash chromatography (hexane:EtOAc 90:10) to give the product (1.2 g, 4.2 mmol), which matches with NMR spectra of product reported in the literature.⁶

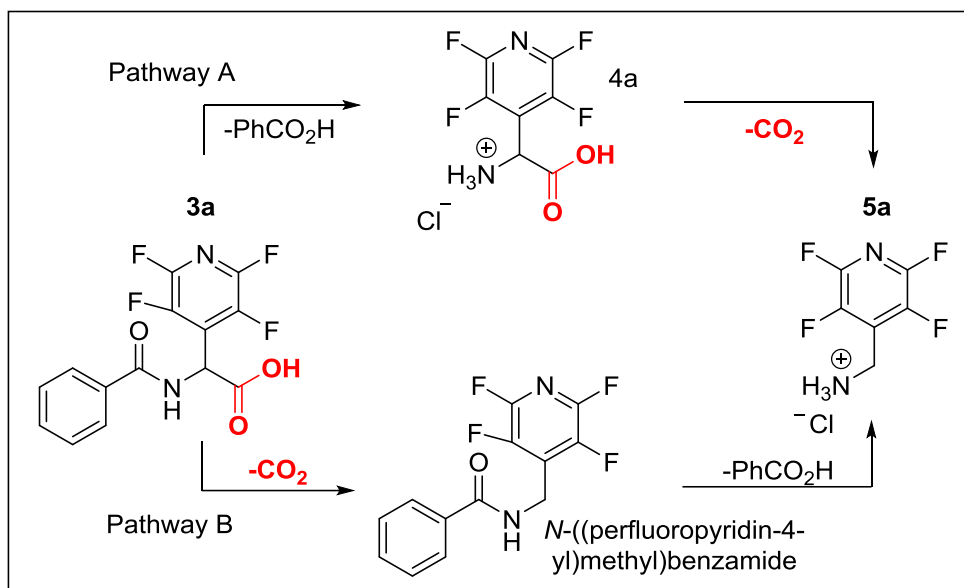
Halogen selectivity experiment:



Under an argon atmosphere, oxazolone (50 mg, 0.310 mmol, 1 equiv), 4-chloro-2,3,5,6-tetrafluoropyridine (69 mg, 0.372 mmol, 1.2 equiv), and CH₃CN (0.310 mL, 1 M) were added to small test tube, which was fitted with a septum. Then a steady stream of 1,8-diazabicyclo(5.4.0)undec-7-ene (95 μ L, 0.651 mmol, 2.1 equiv) was added down the side of the test tube glass. The mixture was allowed to react for 30 min. The reaction was quenched by the addition of a trifluoroacetic acid/ethanol) solution (47.4 μ L, 0.620 mmol, 2 equiv/0.620 mL of ethanol). The solution was concentrated and then diluted with CHCl₃ (5 mL) which was then washed with 1 M HCl brine solution (2.5 mL x 3). The organic layer was dried with MgSO₄, filtered, and concentrated to give the crude product, which was purified by column chromatography. The *para/ortho* product ratio was determined by integrations of peaks in the ¹H and ¹⁹F NMR.

Doping experiment

Scheme 1



During our investigation, we found that under the standard deprotection conditions (refluxing the benzoyl protected amino acid (**3a**) in concentrated HCl) led to the deprotected and decarboxylated ammonium salt (**5a**). While the nature of the final product was apparent, the reaction sequence was not clear. In other words, did debenzoylation precede decarboxylation (Scheme 1, Pathway A) or did it proceed decarboxylation (Scheme 1, Pathway B).

[illegible]

Scheme 3

¹⁹F NMR after workup 60 h+dopant

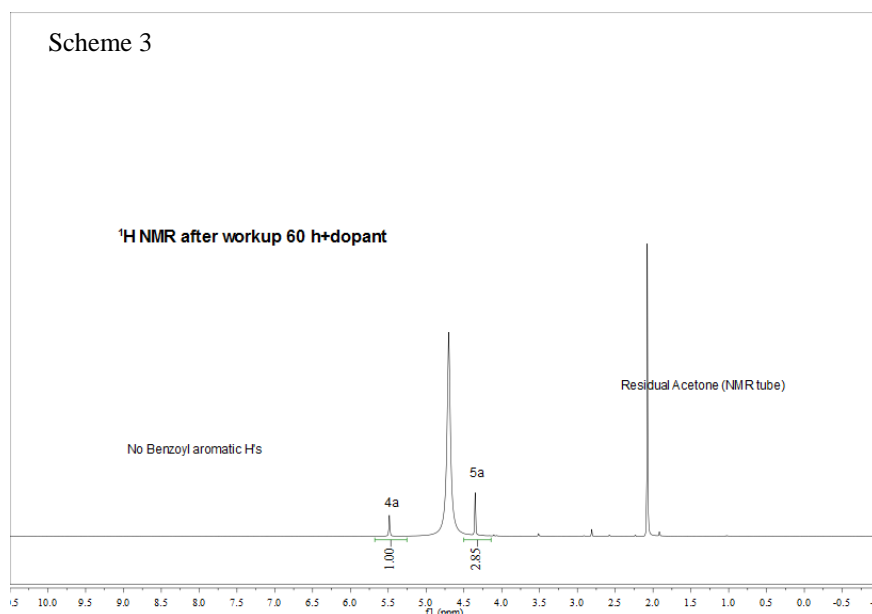
4a 5a

4a 5a

2.06 1.83

2.00 1.82

f1 (ppm)



To probe the reaction, 20 mg of **3a** (0.061 mmol) and 0.50 mL of 12 M HCl was added to a NMR tube and the T_0 ^{19}F NMR was collected (Scheme 2, spectrum 7). The reaction was run at 80 °C and ^{19}F NMR data was collected at 5 h, 12 h, 27 h, 48 h, and 60 h (spectra 2-6, respectively). After the last time point, the NMR tube was doped with previously isolated **5a** (5 mg) and the ^{19}F NMR was taken which confirmed the identity of the second species, and by elimination, the structure of **3a** as well.

The progression of the reaction is displayed in Scheme 2 and after 5 h the conversion of starting material to a new intermediate is apparent and the peak chemical shifts at -88 ppm. With prolonged heat, a second intermediate is formed with a chemical shift of -89.5 ppm. Yet, the doping of the NMR reaction revealed **5a** to be the final product shifting at -89.5 ppm. After a typical workup (see general procedure G) of the incomplete reaction (where starting material is consumed and only partial conversion of the intermediate to the **5a** product), the ^{19}F NMR (Scheme 3) and the ^1H NMR (Scheme 4) revealed that the intermediate *N*-((perfluoropyridin-4-yl)methyl)benzamide was neither of the intermediates observed due to the lack of benzoyl aromatic signals. The first intermediate was found to be **4a** (seen at -88 ppm) matching of what one would expect in the ^1H NMR (s, 1H) ^{19}F NMR δ -89.95 – -90.40 (m), -141.50 – -142.06 (m). With this evidence, we eliminated pathway B (Scheme 1) as the reaction pathway and concluded that the most logical route is pathway A, where the benzoyl protected amino acids undergo deprotection and then thermally decarboxylate giving the benzylic amine. This finding is consistent with TGA experiments which show that for **3b** and **4b**, which differ by the deprotection of the *N*-benzoyl group, that the amide (**3b**) is less prone to thermal decarboxylation than the corresponding ammonium acid (**4b**).

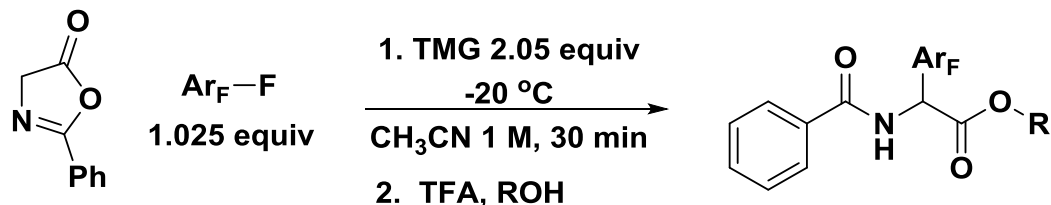
Rationalization of the observed base dependency on fluoroarene substrate

It is puzzling why the same acid (i.e. oxazolone) would require a stronger base as a function of electrophile (see entries 8-10, table 1). One potential explanation for this observation is that the ammonium enolate is the minor product of an equilibrium. Due to the decreased electrophilicity of octafluorotoluene, the rate of attack by the enolate is retarded. The use of a stronger base accelerates the reaction by shifting the equilibrium in favor of the enolate. An alternative possibility is that pentafluoropyridine undergoes an aromatic π -stacking event, more specifically a donor-acceptor interaction,^{7,8} with the phenyl ring of the oxazolone, which could result in an acidification of the C4-H. In contrast, when octafluorotoluene is used, it is less prone to undergo this acidifying, π -stacking event, presumably due to the steric bulk of the trifluoromethyl group,

and thus requires a stronger base to generate the requisite enolate. We are exploring this possibility and will report our findings in time.

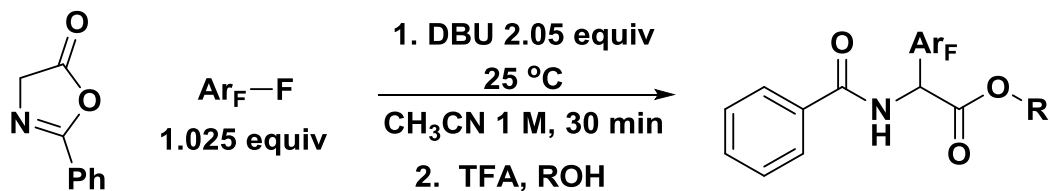
Synthesis of perfluoroaryl-*N*-benzoyl amino acids/esters

General procedure C for synthesis of *N*-benzoyl perfluoroaryl-amino esters **2a,2b,2c,2d,2e,2i**.



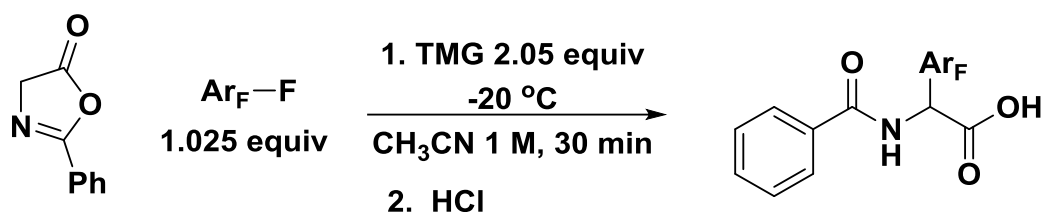
Under an argon atmosphere, oxazolone (**1 equiv**), $\text{Ar}_\text{F}-\text{F}$ (**1.025 equiv**), and CH_3CN (**1 M**) were added to small test tube, which was fitted with a septum and cooled to $-20\text{ }^\circ\text{C}$. Then a steady stream of tetramethylguanidine (**2.05 equiv**) was added down the side of the test tube glass which facilitated the cooling of the TMG solution prior to dissolution. The mixture was allowed to react for 30 min, then the cooling bath was removed, and the reaction was left to warm to room temperature. The reaction was quenched by the addition of a trifluoroacetic acid/alcohol (methanol or ethanol) solution (**2 equiv**/double volume). The solution was concentrated and then diluted with CHCl_3 which was then washed with 1 M HCl brine solution (half the volume of organic layer x 3). The organic layer was dried with MgSO_4 , filtered, and concentrated to give the crude product, which was purified by column chromatography.

General procedure D for synthesis of *N*-benzoyl perfluoroaryl-amino esters **2f, 2g, and 2h**.



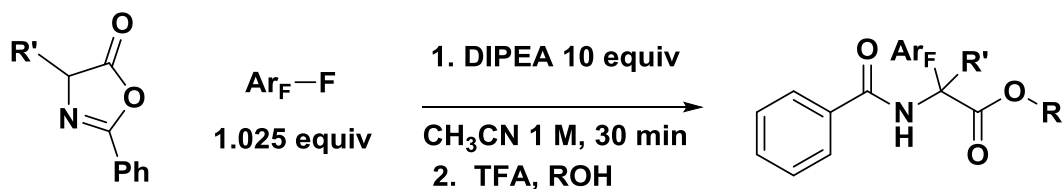
Under an argon atmosphere, oxazolone (**1 equiv**), $\text{Ar}_\text{F}-\text{F}$ (**1.025 equiv**), and CH_3CN (**1 M**) were added to small test tube, which was fitted with a septum. Then a steady stream of 1,8-diazabicyclo(5.4.0)undec-7-ene (**2.05 equiv**) was added down the side of the test tube glass. The mixture was allowed to react for 30 min. The reaction was quenched by the addition of a trifluoroacetic acid/alcohol (methanol or ethanol) solution (**2 equiv**/double volume). The solution was concentrated and then diluted with CHCl_3 which was then washed with 1 M HCl brine solution (half the volume of organic layer x 3). The organic layer was dried with MgSO_4 , filtered, and concentrated to give the crude product, which was purified by column chromatography.

General procedure E for synthesis of *N*-benzoyl perfluoroaryl-amino acids **3a**, **3b**, **3c**, **3d**, and **3e**.



Under an argon atmosphere, oxazolone (**1 equiv**), $\text{Ar}_\text{F}-\text{F}$ (**1.025 equiv**), and CH_3CN (**1 M**) were added to small test tube, which was fitted with a septum and cooled to $-20\text{ }^\circ\text{C}$. Then a steady stream of tetramethylguanidine (**2.05 equiv**) was added down the side of the test tube glass which facilitated the cooling of the TMG solution. The reaction was left to react for 30 min and then the cooling bath was removed, and the reaction was allowed to warm to room temperature and subsequently quenched by the addition of 6 M HCl. The solution was concentrated and extracted with CHCl_3 , and then the organic layer was washed with half volumes of a 1 M HCl-brine solution x 3. The organic layer was dried with MgSO_4 and concentrated giving crude product. Purification of the crude product can be accomplished without chromatography by adding hexanes to a round bottom flask containing the crude product then carefully adding dichloromethane dropwise until the hexanes becomes yellow and a colorless solid is left behind. The solid was filtered and air dried to yield the pure acid.

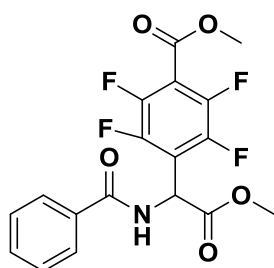
General procedure D for synthesis of *N*-benzoyl perfluoroaryl-amino esters **6a**, **6b**, **6c**, and **6d**.



Under an argon atmosphere, oxazolone (**1 equiv**), $\text{Ar}_\text{F}-\text{F}$ (**1.025 equiv**), CH_3CN (**1 M**) were added to small test tube which was fitted with a septum. Then a steady stream of DIPEA (**10 equiv**) was added to mixture. While stirring vigorously (note: the reaction mixture is biphasic), the reaction was left to react for 30 min. After 30 min. the bottom layer was separated and quenched by the addition of a trifluoroacetic acid/alcohol (methanol or ethanol) solution (**20 equiv/20 equiv**). The solution was concentrated and then diluted with CHCl_3 which was then washed with 1 M HCl-brine solution (half the volume of organic layer x 3). The organic layer was dried with MgSO_4 , filtered, and concentrated to give the crude product, which was purified by column chromatography.

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

Colorless oil, 98.5% yield (122 mg, 0.305 mmol).



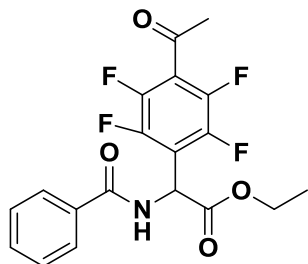
The **general procedure C** was followed using 2-phenyloxazol-5(4H)-one (50.0 mg, 0.310 mmol), 2,3,4,5,6 pentafluorobenzoate (67.4 mg, 0.318 mmol), tetramethylguanidine (73.2 mg, 0.636 mmol), 0.310 mL of MeCN and trifluoroacetic acid (70.7 mg, 0.620 mmol)/methanol (0.620 mL) was

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used to afford **2a**. FT-IR (neat) cm^{-1} 1743, 1754, 1680, 1085. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, J = 7.3 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.36 (d, J = 6.5 Hz, 1H), 6.22 (d, J = 6.7 Hz, 1H), 3.96 (s, 3H), 3.83 (s, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -138.64 – -139.00 (m), -141.86 (q, J = 11.5 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.9, 167.0, 160.3, 146.4 (ddt, J = 37.7, 15.2, 4.8 Hz), 143.9 (ddt, J = 44.6, 15.2, 4.9 Hz), 133.2, 132.8, 129.2, 127.6, 119.9 (t, J = 15.6 Hz), 113.3 (t, J = 16.1 Hz), 54.3, 53.8, 47.5. HRMS (ESI) $\text{C}_{18}\text{H}_{13}\text{F}_4\text{NO}_5$ calcd. $[\text{M}+\text{K}]^+$ 438.0361 observed 438.0337.

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

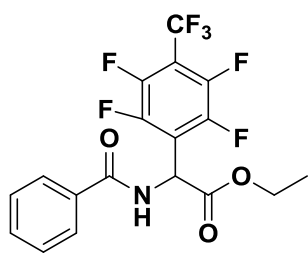
Colorless oil, 80% yield (98.5 mg, 0.248 mmol).



The **general procedure C** was followed using 2-phenyloxazol-5(4H)-one (50 mg, 0.310 mmol), 2',3',4',5',6' pentafluoroacetophenone (66.8 mg, 0.318 mmol), tetramethylguanidine (73.2 mg, 0.636 mmol), trifluoroacetic acid (70.7 mg, 0.620 mmol)/ethanol (0.620 mL) and 0.310 mL of MeCN was used to afford **2b**. FT-IR (neat) cm^{-1} 1730, 1756, 1655, 1105. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, J = 7.1 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.39 (d, J = 6.4 Hz, 1H), 6.17 (d, J = 6.4 Hz, 1H), 4.32 (dq, J = 10.8, 3.7 Hz, 2H), 2.60 (t, J = 1.6 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -141.34 (dd, J = 22.3, 13.2 Hz), -141.72 (ddd, J = 21.9, 13.4 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 192.3, 168.4, 167.0, 146.1 (dd, J = 116.6, 6.9 Hz), 144.4 – 142.5 (m), 133.2, 132.7, 129.2, 127.6, 120.1 (t, J = 16.9 Hz), 119.7 (t, J = 15.6 Hz), 63.7, 47.7, 32.8, 14.4. HRMS (ESI) $\text{C}_{19}\text{H}_{15}\text{F}_4\text{NO}_4$ calcd. $[\text{M}+\text{Na}]^+$ 420.0829 observed 420.0810.

2c ethyl 2-benzamido-2-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetate

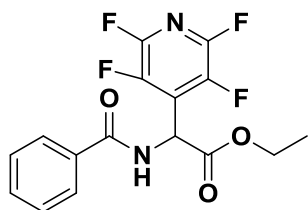
White solid, 81% yield (106 mg, 0.251 mmol).



The **general procedure C** was followed using 2-phenyloxazol-5(4H)-one (50 mg, 0.310 mmol), octafluorotoluene (38 mg, 0.318 mmol), tetramethylguanidine (73.2 mg, 0.636 mmol), trifluoroacetic acid (70.7 mg, 0.620 mmol)/ethanol (0.620 mL) and 0.310 mL of MeCN was used to afford **2c**. FT-IR (neat) cm^{-1} 2496, 1756, 1659, 1095. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.81 (d, J = 7.8 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.49 – 7.35 (m, 3H), 6.18 (d, J = 6.3 Hz, 1H), 4.32 (qd, J = 10.8, 3.7 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -56.48 (t, J = 21.7 Hz), -139.84 (ddt, J = 30.4, 21.7, 11.5 Hz), -140.84 (td, J = 15.6, 5.6 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.7, 166.7, 145.9 (dd, J = 113.0, 15.4 Hz), 143.3 (dd, J = 121.4, 15.4 Hz), 132.6, 132.4, 128.8, 127.2, 121.0 (t, J = 15.4 Hz), 120.6 (d, J = 274.7 Hz), 110.7 – 109.0 (m), 63.5, 47.3, 13.9. HRMS (ESI) $\text{C}_{18}\text{H}_{12}\text{F}_7\text{NO}_3$ calcd. $[\text{M}]^+$ 423.0700 observed 423.0698.

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

Pale white solid, 79% yield (87 mg, 0.245 mmol).

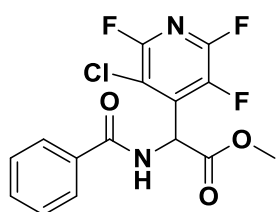


The **general procedure C** was followed using 2-phenyloxazol-5(4H)-one (50 mg, 0.310 mmol), pentafluoropyridine (53.8 mg, 0.318 mmol), tetramethylguanidine (73.2 mg, 0.636 mmol), trifluoroacetic acid (70.7

mg, 0.620 mmol)/ethanol (0.620 mL) and 0.310 mL of MeCN was used to afford **2d**. FT-IR (neat) cm^{-1} 1756, 1669, 1630, 1090. ^1H NMR (400 MHz, Acetonitrile- d_3) δ 7.83 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 6.0 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 6.27 (d, J = 7.2 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, Acetonitrile- d_3) δ -92.87 – -93.35 (m), -144.21 – -144.65 (m). ^{13}C NMR (101 MHz, Acetonitrile- d_3) δ 167.9, 167.7, 145.7 – 142.9 (m), 141.7 (dd, J = 258.7, 35.3 Hz), 133.9, 133.2, 131.3 (t, J = 14.9 Hz), 129.6, 128.4, 63.9, 48.2, 14.1. HRMS (ESI) $\text{C}_{16}\text{H}_{12}\text{F}_4\text{N}_2\text{O}_3$ calcd. $[\text{M}+\text{K}]^+$ 395.0416 observed 395.0405.

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

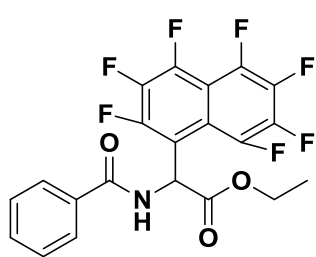
Yellow solid, 85% yield (178 mg, 0.487 mmol).



The **general procedure C** 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 (141 mg, 1.24 mmol)/methanol (1.24 mL) and 0.621 mL of MeCN was used to afford **2e**. FT-IR (neat) cm^{-1} 1731, 1640, 1680, 1085. ^1H NMR (400 MHz, Chloroform- d) δ 7.83 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.48 (m, J = 17.0, 9.2 Hz, 3H), 6.37 (d, J = 5.7 Hz, 1H), 3.88 (s, 3H). ^{19}F NMR (376 MHz, Chloroform- d) δ -72.87 (dd, J = 27.8, 12.3 Hz), -87.48 (dd, J = 21.4, 12.5 Hz), -143.98 – -144.42 (m). ^{13}C NMR (101 MHz, Chloroform- d) δ 168.2, 167.1, 151.6 (dq, J = 244.4, 12.0, 3.0 Hz), 147.6 (ddd, J = 248.6, 17.4, 13.5 Hz), 142.1 (ddd, J = 260.7, 27.2, 6.4 Hz), 139.8 (d, J = 12.3 Hz), 132.9, 132.9, 129.3, 127.7, 113.6 (d, J = 41.9 Hz), 54.5, 50.40. HRMS (ESI) $\text{C}_{15}\text{H}_{10}\text{ClF}_3\text{N}_2\text{O}_3$ calcd. $[\text{M}+\text{Na}]^+$ 381.0224 observed 381.0203.

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

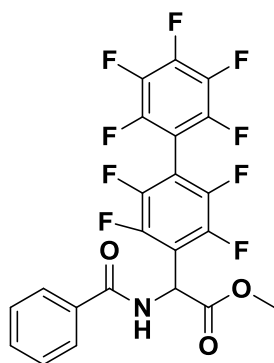
Yellow oil, 82% yield (69.2 mg, 0.254 mmol).



The **general procedure D** was followed using 2-phenyloxazol-5(4H)-one (50 mg, 0.310 mmol), octafluoronapalene (86.5 mg, 0.318 mmol), 1,8-diazabicyclo(5.4.0)undec-7-ene (96.7 mg, 0.636 mmol), trifluoroacetic acid (141 mg, 1.24 mmol)/ethanol (0.620 mL) and 0.310 mL of MeCN was used to afford **2f**. FT-IR (neat) cm^{-1} 2943, 2849, 1760, 1677, 1085. ^1H NMR (400 MHz, Chloroform- d) δ 7.74 (d, J = 7.2 Hz, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.37 (m, J = 7.5 Hz, 3H), 6.25 (d, J = 6.5 Hz, 1H), 4.23 (dq, J = 10.8, 7.1 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform- d) δ -120.69 (dd, J = 68.3, 18.5 Hz), -138.91 (d, J = 16.6 Hz), -143.22 (dt, J = 68.3, 16.8 Hz), -145.79 (dt, J = 61.8, 17.5 Hz), -148.06 (dt, J = 57.6, 18.0 Hz), -152.40 (t, J = 18.5 Hz), -154.99 (t, J = 20.3 Hz). ^{13}C NMR (101 MHz, Chloroform- d) δ 168.8, 167.1, 151.3 (d, J = 266.9 Hz), 148.1 – 145.1 (m), 147.8 – 144.9 (m), 143.1 (d, J = 54.7 Hz), 142.5 – 139.5 (m), 142.0 – 140.2 (m), 138.6 (dd, J = 118.3 Hz), 133.3, 132.7, 129.2, 127.6, 115.8 (t, J = 18.0 Hz), 111.9 (t, J = 13.0 Hz), 108.7 – 108.1 (m), 63.7, 47.7, 14.4. HRMS (ESI) $\text{C}_{21}\text{H}_{12}\text{F}_7\text{NO}_3$ calcd. $[\text{M}+\text{K}]^+$ 498.0337 observed 498.0309.

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

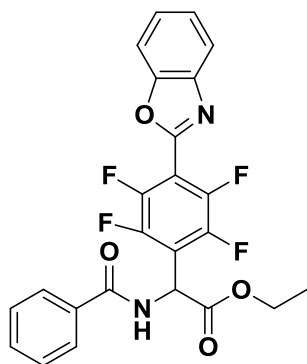
Colorless oil, 82% yield (265 mg, 0.508 mmol).



The **general procedure D** 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 (141 mg, 1.24 mmol)/methanol (1.24 mL) and 0.621 mL of MeCN was used to afford **2g**. FT-IR (neat) cm^{-1} 2950, 1744, 1634, 1085. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.85 (d, J = 7.1 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.38 (d, J = 6.8 Hz, 1H), 6.31 (d, J = 6.8 Hz, 1H), 3.88 (s, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -136.95 (dtt, J = 14.0, 6.0, 2.7 Hz), -137.40 (h, J = 10.4 Hz), -141.84 (q, J = 11.4 Hz), -149.85 (t, J = 21.0 Hz), -160.38 (tt, J = 21.2, 5.4 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.1, 167.1, 147.1 – 145.5 (m), 146.4 – 143.5 (m), 143.3 (dt, J = 14.4, 3.9 Hz), 139.6 (d, J = 8.5 Hz), 137.2 (dd, J = 14.0, 5.8 Hz), 133.2, 132.9, 129.3, 127.7, 119.1 (t, J = 15.6 Hz), 107.1 (t, J = 16.2 Hz), 102.4 (t, J = 16.8 Hz), 54.4, 47.5. HRMS (ESI) $\text{C}_{23}\text{H}_{12}\text{F}_9\text{NO}_3$ calcd. $[\text{M}+\text{H}]^+$ 508.0590 observed 508.0545.

2h ethyl 2-benzamido-2-(4-(benzo[d]oxazol-2-yl)-2,3,5,6-tetrafluorophenyl)acetate

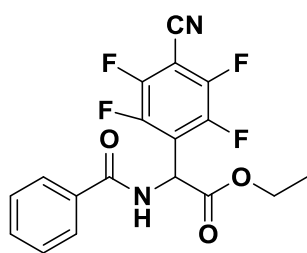
Pale white solid, 82% yield (120 mg, 0.254 mmol).



The **general procedure D** was followed using 2-phenyloxazol-5(4H)-one (50 mg, 0.310 mmol), 2-(perfluorophenyl)benzo[d]oxazole (90.6 mg, 0.318 mmol), 1,8-diazabicyclo(5.4.0)undec-7-ene (96.7 mg, 0.636 mmol), trifluoroacetic acid (70.7 mg, 0.620 mmol)/ethanol (0.620 mL) and 0.310 mL of MeCN was used to afford **2h**. FT-IR (neat) cm^{-1} 2950, 1749, 1634, 1140, 1085, 1052. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.51 – 7.37 (m, 5H), 6.26 (d, J = 6.6 Hz, 1H), 4.33 (dq, J = 7.7, 3.6 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -139.98 – -140.48 (m), -142.52 – -143.05 (m). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.5, 167.1, 153.3, 150.9, 145.8 (ddt, J = 250.1, 14.3, 5.3 Hz), 145.5 (ddt, J = 260.3, 15.6, 4.1 Hz), 141.6, 133.3, 132.8, 129.2, 127.7, 127.0, 125.6, 121.4, 119.9 (t, J = 15.8 Hz), 111.5, 108.9 (t, J = 13.5 Hz), 63.8, 47.8, 14.4. HRMS (ESI) $\text{C}_{24}\text{H}_{16}\text{F}_4\text{N}_2\text{O}_4$ calcd. $[\text{M}+\text{Na}]^+$ 495.0938 observed 495.0911.

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

Yellow oil, 79% yield (93.1 mg, 0.245 mmol).

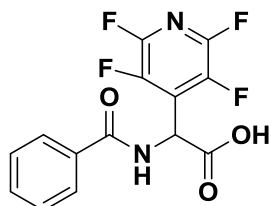


The **general procedure A** was followed using 2-phenyloxazol-5(4H)-one (50 mg, 0.310 mmol), 2,3,4,5,6 pentafluorobenzonitrile (61.4 mg, 0.318 mmol), tetramethylguanidine (73.2 mg, 0.636 mmol), trifluoroacetic acid (72.5 mg, 0.636 mmol)/ethanol (0.620 mL) and 0.310 mL of MeCN was used to afford **2i**. FT-IR (neat) cm^{-1} 2933, 2250, 1714, 1083. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.72 (d, J = 7.4 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.43 – 7.29 (m, 3H), 6.08 (d, J = 5.9 Hz, 1H), 4.24 (qd, J = 10.7, 5.4 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -131.74 (td, J = 16.4, 6.7 Hz), -139.49 (td, J = 16.3, 6.6 Hz).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.3, 166.7, 148.5 – 146.1 (m), 148.6 – 145.7 (m), 145.9 – 143.4 (m), 132.5, 132.4, 128.8, 127.2, 123.4 (t), 107.1, 63.6, 47.5, 13.9. HRMS (ESI) $\text{C}_{18}\text{H}_{12}\text{F}_4\text{N}_2\text{O}_3$ calcd. $[\text{M}+\text{Na}]^+$ 403.0676 observed 403.0654.

3a 2-benzamido-2-(perfluoropyridin-4-yl)acetic acid

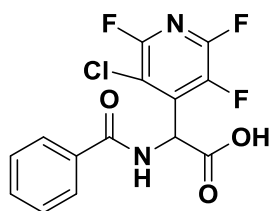
White solid, 85% yield (1.73 g, 5.27 mmol).



The **general procedure E** was followed using 2-phenyloxazol-5(4H)-one (1.00 g, 6.20 mmol), pentafluoropyridine (1.08 g, 6.36 mmol), tetramethylguanidine (1.46 g, 12.71 mmol), and 6.20 mL of MeCN was used to afford **3a**. FT-IR (neat) cm^{-1} 3643, 2250, 1715, 1106. ^1H NMR (400 MHz, Acetonitrile-*d*₃) δ 7.95 – 7.73 (m, 3H), 7.60 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 6.26 (d, J = 6.9 Hz, 1H). ^{19}F NMR (376 MHz, CD_3CN) δ -93.07, -144.38. ^{13}C NMR (101 MHz, Acetonitrile-*d*₃) δ 168.3, 167.7, 151.9 (dd, J = 240.4, 9.7 Hz), 148.1 (dq, J = 244.4, 17.6, 13.9 Hz), 142.8 (ddd, J = 258.2, 27.4, 6.2 Hz), 141.1 (d, J = 12.7 Hz), 133.8, 133.2, 129.6, 128.4, 114.4 (dd, J = 35.3, 6.5 Hz), 50.8. HRMS (ESI) $\text{C}_{14}\text{H}_8\text{F}_4\text{N}_2\text{O}_3$ calcd. $[\text{M}+\text{K}]^+$ 367.0103 observed 367.0083.

3b 2-benzamido-2-(3-chloro-2,5,6-trifluoropyridin-4-yl)acetic acid

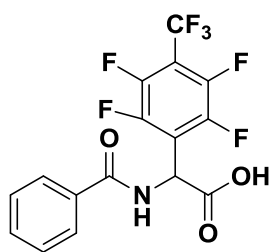
Pale white solid, 86% yield (1.84 g, 5.33 mmol).



The **general procedure E** was followed using 2-phenyloxazol-5(4H)-one (1.00 g, 6.20 mmol), 3-chloro-2,4,5,6 tetrafluoropyridine (1.18 g, 6.36 mmol), tetramethylguanidine (1.46 g, 12.71 mmol), and 6.20 mL of MeCN was used to afford **3b**. FT-IR (neat) cm^{-1} 3604, 1722, 1664, 1085. ^1H NMR (400 MHz, Acetonitrile-*d*₃) δ 7.82 (d, J = 7.4 Hz, 2H), 7.74 (d, J = 5.9 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 6.34 (d, J = 6.6 Hz, 1H). ^{19}F NMR (376 MHz, Acetonitrile-*d*₃) δ -76.02 (dd, J = 27.3, 12.5 Hz), -91.08 (dd, J = 21.1, 13.2 Hz), -144.77 (t, J = 24.3 Hz). ^{13}C NMR (101 MHz, Acetonitrile-*d*₃) δ 168.3, 167.7, 151.9 (dd, J = 240.4, 9.7 Hz), 148.1 (dq, J = 244.4, 17.6, 13.9 Hz), 142.8 (ddd, J = 258.2, 27.4, 6.2 Hz), 141.1 (d, J = 12.7 Hz), 133.8, 133.2, 129.6, 128.4, 114.4 (dd, J = 35.3, 6.5 Hz), 50.8. HRMS (ESI) $\text{C}_{14}\text{H}_8\text{ClF}_3\text{N}_2\text{O}_3$ calcd. $[\text{M}+\text{Na}]^+$ 367.0068 observed 367.0047.

3c 2-benzamido-2-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetic acid

White solid, 82% yield (2.00 g, 5.06 mmol).

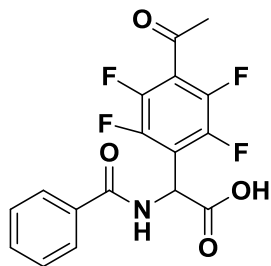


The **general procedure E** was followed using 2-phenyloxazol-5(4H)-one (1.00 g, 6.20 mmol), octafluorotoluene (1.50 g, 6.36 mmol), tetramethylguanidine (1.46 g, 12.71 mmol), and 0.620 mL of MeCN was used to afford **3c**. FT-IR (neat) cm^{-1} 3590, 1743, 1653, 1076. ^1H NMR (400 MHz, Acetonitrile-*d*₃) δ 7.82 (d, J = 7.1 Hz, 2H), 7.74 (d, J = 6.5 Hz, 1H), 7.62 – 7.53 (m, 1H), 7.47 (t, J = 7.6 Hz, 2H), 6.22 (d, J = 7.0 Hz, 1H). ^{19}F NMR (376 MHz, Acetonitrile-*d*₃) δ -57.30 (t, J = 21.8 Hz), -141.58 (td, J = 15.6, 6.2 Hz), -142.47 – -142.84 (m). ^{13}C NMR (101 MHz, Acetonitrile-*d*₃) δ 168.5, 133.5, 167.3, 147.5 – 144.4 (m), 144.7 (dd, J = 256.6, 17.1 Hz), 132.7,

129.1, 127.9, 122.1 (t, $J = 16.2$ Hz), 47.3, 121.5 (d, $J = 273.6$ Hz), 110.5 – 108.3 (m). HRMS (ESI) $C_8H_{11}NO_5$ calcd. $[M+Na]^+$ 418.0285 observed 418.0276.

3d 2-(4-acetyl-2,3,5,6-tetrafluorophenyl)-2-benzamidoacetic acid

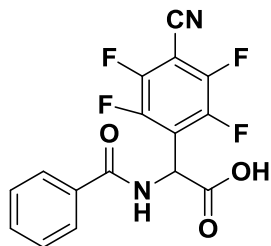
Colorless oil, 87% yield (99.6 mg, 0.270 mmol).



The **general procedure E** was followed using 2-phenyloxazol-5(4H)-one (50 mg, 0.310 mmol), 2',3',4',5',6' pentafluoroacetophenone (66.8 mg, 0.318 mmol), tetramethylguanidine (118.0mg, 0.636 mmol), and 0.310 mL of MeCN was used to afford **3d**. FT-IR (neat) cm^{-1} 3640, 1721, 1630, 1006. 1H NMR (400 MHz, Acetonitrile- d_3) δ 7.84 (d, $J = 7.3$ Hz, 2H), 7.77 (d, $J = 6.5$ Hz, 1H), 7.58 (t, $J = 7.4$ Hz, 1H), 7.49 (t, $J = 7.6$ Hz, 2H), 6.14 (d, $J = 6.7$ Hz, 1H), 2.60 (s, 3H). ^{19}F NMR (376 MHz, Acetonitrile- d_3) δ -143.02 (dd, $J = 21.5, 12.8$ Hz), -143.63 (dd, $J = 21.5, 12.9$ Hz). ^{13}C NMR (101 MHz, Acetonitrile- d_3) δ 193.2, 169.6, 167.6, 147.5 – 144.4 (m), 143.4 (dt, $J = 14.8, 5.4$ Hz), 134.1, 132.9, 129.5, 128.3, 120.7 (t, $J = 16.4$ Hz), 120.3 (t, $J = 17.1$ Hz), 47.9, 32.6. HRMS (ESI) $C_{17}H_{11}F_4NO_4$ calcd. $[M]^+$ 369.0624 observed 369.0601.

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

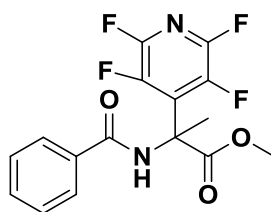
Yellow oil, 78% yield (85.1 mg, 0.241 mmol).



The **general procedure E** was followed using 2-phenyloxazol-5(4H)-one (50 mg, 0.310 mmol), 2,3,4,5,6 pentafluorobenzonitrile (63.4 mg, 0.318 mmol), tetramethylguanidine (118.0 mg, 0.636 mmol), and 0.310 mL of MeCN was used to afford **3e**. FT-IR (neat) cm^{-1} 3590, 2255, 1707, 1674. 1H NMR (400 MHz, Acetonitrile- d_3) δ 7.82 (d, $J = 7.3$ Hz, 2H), 7.75 (d, $J = 6.2$ Hz, 1H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 2H), 6.23 (d, $J = 6.9$ Hz, 1H). ^{19}F NMR (376 MHz, Acetonitrile- d_3) δ -134.83 (td, $J = 15.8, 6.5$ Hz), -140.78 (td, $J = 15.8, 6.5$ Hz). ^{13}C NMR (101 MHz, Acetonitrile- d_3) δ 168.6, 167.7, 148.1 (ddt, $J = 259.1, 16.5, 3.9$ Hz), 147.5 – 144.4 (m), 147.4 – 144.2 (m), 133.8, 133.1, 129.5, 128.4, 124.3 (t, $J = 16.2$ Hz), 108.5, 47.8. HRMS (ESI) $C_{16}H_8F_4N_2O_3$ calcd. $[M+Na]^+$ 403.0676 observed 403.0701.

6a methyl 2-benzamido-2-(perfluoropyridin-4-yl)propanoate

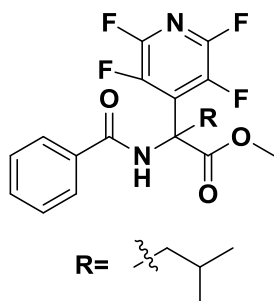
Colorless oil, 80% yield (81.2 mg, 0.228 mmol).



The **general procedure F** was followed using 4-methyl-2-phenyloxazol-5(4H)-one (50.0 mg, 0.285 mmol), pentafluoropyridine (49.5 mg, 0.293 mmol), *N,N*-diisopropylethylamine (368 mg, 2.85 mmol), trifluoroacetic acid (650 mg, 5.7 mmol)/methanol (0.230 mL) and 0.285 mL of MeCN was used to afford **6a**. FT-IR (neat) cm^{-1} 2833, 1740, 1634, 1095. 1H NMR (400 MHz, Chloroform- d) δ 7.81 (s, 1H), 7.77 (d, $J = 7.2$ Hz, 2H), 7.54 (t, $J = 7.4$ Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 2H), 3.89 (s, 3H), 2.22 (t, $J = 3.3$ Hz, 3H). ^{19}F NMR (376 MHz, Chloroform- d) δ -90.86 – -91.11 (m), -140.47 – -140.85 (m). ^{13}C NMR (101 MHz, Chloroform- d) δ 172.4, 166.2, 146.4 (dt, $J = 180.2$ Hz), 141.6 (dd, $J = 261.0$ Hz), 133.5, 132.8, 132.1 (t, $J = 3.3$ Hz), 129.2, 127.5, 59.7, 54.9, 23.7. HRMS (ESI) $C_{16}H_{12}F_4N_2O_3$ calcd. $[M+Na]^+$ 379.0676 observed 379.0698.

6b methyl 2-benzamido-4-methyl-2-(perfluoropyridin-4-yl)pentanoate

Colorless oil, 74% yield (136 mg, 0.340 mmol).

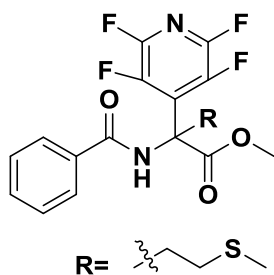


The **general procedure F** was followed using 4-(4-isobutyl-2-phenyloxazol-5(4H)-one) (100 mg, 0.460 mmol), pentafluoropyridine (79.7 mg, 0.472 mmol), *N,N*-diisopropylethylamine (595 mg, 4.6 mmol), trifluoroacetic acid (1040 mg, 9.2 mmol)/methanol (0.372 mL) and 0.460 mL of MeCN was used to afford **6b**. FT-IR (neat) cm^{-1} 2893, 1711, 1637, 1105. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.80 (s, 1H), 7.76 (d, $J = 8.3$ Hz, 2H), 7.54 (t, $J = 7.4$ Hz, 1H), 7.46 (t, $J = 7.8$ Hz, 2H), 3.87 (s, 2H), 3.40 – 2.14 (m, 2H), 1.74 – 1.50 (m, 1H), 0.96 (d, $J = 6.6$ Hz, 2H), 0.93 (d, $J = 6.7$ Hz, 2H).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -90.47 – -91.21 (m), -138.40 – -140.05 (m). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.6, 165.4, 145.4 – 142.3 (m), 140.6 (ddd, $J = 261.1, 27.0, 5.2$ Hz), 132.9, 132.4 (t, $J = 10.4$ Hz), 128.7, 126.8, 62.9, 53.9, 40.9, 24.4, 23.9, 23.7. HRMS (ESI) $\text{C}_{19}\text{H}_{18}\text{F}_4\text{N}_2\text{O}_3$ calcd. $[\text{M}+\text{H}]^+$ 399.1326 observed 399.1299.

6c methyl 2-benzamido-4-(methylthio)-2-(perfluoropyridin-4-yl)butanoate

Colorless oil, in 79% yield (69.7 mg, 0.167 mmol).

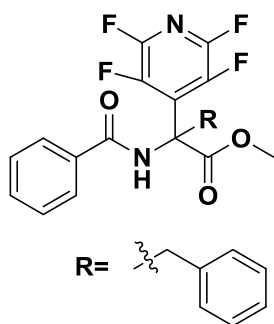


The **general procedure F** was followed using 4-(2-(methylthio)ethyl)-2-phenyloxazol-5(4H)-one (50.0 mg, 0.212 mmol), pentafluoropyridine (36.8 mg, 0.218 mmol), *N,N*-diisopropylethylamine (274 mg, 2.12 mmol), trifluoroacetic acid (483 mg, 4.24 mmol)/methanol (0.171 mL) and 0.212 mL of MeCN was used to afford **6c**. FT-IR (neat) cm^{-1} 2799, 1739, 1655, 1005. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.81 (s, 1H), 7.77 (d, $J = 8.5$ Hz, 2H), 7.56 (t, $J = 7.4$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 2H), 3.89 (s, 3H), 3.65 – 3.52 (m, 1H), 2.67 (dt, $J = 14.2, 5.8$ Hz, 1H), 2.61 – 2.50 (m, 1H), 2.39 – 2.27 (m, 1H), 2.09 (s, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -

90.31 – -90.85 (m), -139.48 (t, $J = 19.6$ Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.5, 166.2, 145.9 – 142.9 (m), 141.4 (dd, $J = 261.5, 35.0$ Hz), 133.3, 132.9, 132.0 (t, $J = 10.4$ Hz), 129.3, 127.5, 63.1, 54.9, 33.4, 28.8, 16.2. HRMS (ESI) $\text{C}_{18}\text{H}_{16}\text{F}_4\text{N}_2\text{O}_3\text{S}$ calcd. $[\text{M}+\text{H}]^+$ 417.0891 observed 417.0862.

6d methyl 7-benzamido-8,9,11-trifluoro-6,7-dihydro-11a-1,5-(metheno)fluoronino[2,3-*c*]pyridine-7-carboxylate

Colorless oil, 71% yield (61.1 mg, 0.141 mmol).

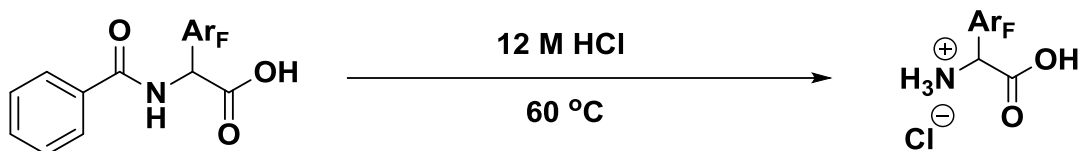


The **general procedure F** was followed using 4-benzyl-2-phenyloxazol-5(4H)-one (50.0 mg, 0.199 mmol), pentafluoropyridine (34.5 mg, 0.204 mmol), *N,N*-diisopropylethylamine (257 mg, 1.99 mmol), trifluoroacetic acid (453 mg, 3.98 mmol)/methanol (0.161 mL) and 0.199 mL of MeCN was used to afford **6d**. FT-IR (neat) cm^{-1} 3080, 1715, 1674, 1040. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, $J = 8.1$ Hz, 2H), 7.48 (dd, $J = 13.9, 6.5$ Hz, 2H), 7.39 (t, $J = 7.6$ Hz, 2H), 7.20 (d, $J = 7.1$ Hz, 3H), 6.94 (d, $J = 7.5$ Hz, 2H), 4.57 (d, $J = 13.5$ Hz, 1H), 3.76 (s, 3H), 3.51 (d, $J = 13.5$ Hz, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -93.05 (ddd, $J = 23.2,$

ESI-15

14.8, 7.7 Hz), -144.30 – -144.54 (m). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.76, 166.49, 144.47 (dt, J = 244.2, 17.1 Hz), 141.44 (dd, J = 260.8, 23.6 Hz), 134.4, 133.6, 132.9, 132.4 (t, J = 10.8 Hz), 130.5, 129.3, 129.0, 128.3, 127.5, 64.4, 54.5, 39.4. HRMS (ESI) $\text{C}_{22}\text{H}_{16}\text{F}_4\text{N}_2\text{O}_3$ calcd. $[\text{M}+\text{H}]^+$ 433.1170 observed 433.1140.

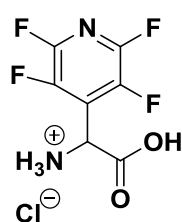
General procedure G for the deprotection of perfluoroaryl-*N*-benzoyl amino acids



The *N*-benzoyl amino acid (1.0 equiv) and 12 M HCl (0.01 M) was added to a round bottom flask and heated to 60 °C. The reaction was monitored by ^{19}F NMR and after consumption of the starting material the mixture was diluted with a half volume of H_2O and washed with equal volumes of toluene x3. The aqueous layer was concentrated *in vacuo* to give the product.

4a carboxy(perfluoropyridin-4-yl)methanaminium chloride

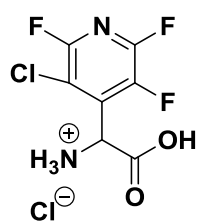
White solid, 99% yield (59 mg, 0.228 mmol).



The **general procedure G** was followed using 2-benzamido-2-(perfluoropyridin-4-yl)acetic acid (75 mg, 0.228 mmol) and 23.4 mL of 12 M HCl to afford **4a**. FT-IR (neat) cm^{-1} 3670, 3300, 1724, 1065. ^1H NMR (400 MHz, Deuterium Oxide) δ 5.52 (s, 1H). ^{19}F NMR (376 MHz, Deuterium Oxide) δ -89.95 – -90.40 (m), -141.50 – -142.06 (m). ^{13}C NMR (101 MHz, Deuterium Oxide) δ 167.55, 143.47 (dt, J = 245.5, 16.5 Hz), 140.43 (dd, J = 260.6, 35.0 Hz), 125.36 (t, J = 16.6 Hz), 46.42. HRMS (ESI) $\text{C}_7\text{H}_5\text{F}_4\text{N}_2\text{O}_2\text{Cl}$ calcd. $[\text{M}]^+$ 259.9976 observed 259.9964.

4b carboxy(3-chloro-2,5,6-trifluoropyridin-4-yl)methanaminium chloride

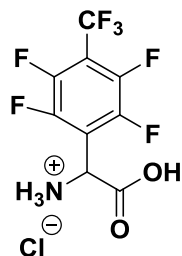
White solid, in 99% yield (119 mg, 0.431 mmol).



The **general procedure G** was followed using 2-benzamido-2-(3-chloro-2,5,6-trifluoropyridin-4-yl)acetic acid (150 mg, 0.435 mmol) and 43.5 mL of 12 M HCl to afford **4b**. FT-IR (neat) cm^{-1} 3683, 3300, 1715, 1034. ^1H NMR (400 MHz, Deuterium Oxide) δ 5.43 (s, 1H). ^{19}F NMR (376 MHz, Deuterium Oxide) δ -72.70 – -141.42 (m), -84.21 – -93.07 (m), -141.39. ^{13}C NMR (101 MHz, Deuterium Oxide) δ 167.2, 151.0 (dd, J = 243.5, 10.3 Hz), 147.0 (dt, J = 246.8, 14.6 Hz), 141.5 (dd, J = 260.3, 31.8 Hz), 134.5 (d, J = 12.7 Hz), 114.1 (dd, J = 35.1, 4.9 Hz), 48.9. HRMS (ESI) $\text{C}_7\text{H}_5\text{F}_3\text{N}_2\text{O}_2\text{Cl}_2$ calcd. $[\text{M}]^+$ 275.9680 observed 275.9672.

4c carboxy(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)methanaminium chloride

White solid, 99% yield (41.1 mg, 0.125 mmol).

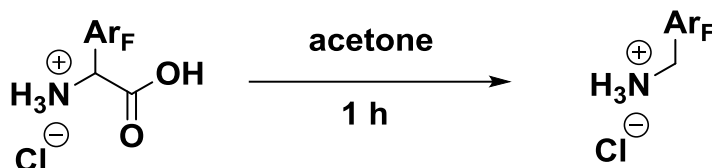


The **general procedure G** was followed using 2-benzamido-2-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetic acid (50 mg, 0.127 mmol) and 12.7

ESI-16

mL of 12 M HCl to afford **4c**. FT-IR (neat) cm^{-1} 3677, 3309, 1725, 1101. ^1H NMR (400 MHz, Acetonitrile- d_3) δ 3.63 (s, 1H). ^{19}F NMR (376 MHz, Acetonitrile- d_3) δ -57.28, -136.68 – -138.28 (m), -140.91. ^{13}C NMR (101 MHz, Acetonitrile- d_3) δ 165.4, 146.8 – 144.9 (m), 144.3 – 142.2 (m), 128.8 – 126.4 (m), 121.7, 115.5 – 114.6 (m), 47.6. HRMS (ESI) $\text{C}_9\text{H}_5\text{F}_7\text{NO}_2\text{Cl}$ calcd. $[\text{M}]^+$ 326.9897 observed 326.9888.

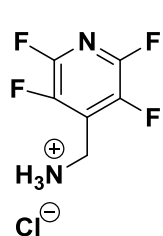
General procedure H for the decarboxylation of perfluoroaryl amino acids



The amino acid (**1.0** equiv) and acetone 1 M was added to a round bottom flask with a magnetic stir bar was left to stir for 1 hour. The reaction was monitored by ^{19}F NMR and after consumption of the starting material; the mixture was concentrated *in vacuo* to give the product.

5a (perfluoropyridin-4-yl)methanaminium chloride

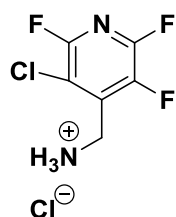
White solid, 99% yield (12.4 mg, 0.0572 mmol)



The **general procedure H** was followed using carboxy(perfluoropyridin-4-yl)methanaminium chloride (15mg, 0.0576 mmol) and 57.6 μL of acetone to afford **5a**. FT-IR (neat) cm^{-1} 3603, 3287, 3044, 1015. ^1H NMR (400 MHz, Deuterium Oxide) δ 4.36 (s, 1H). ^{19}F NMR (376 MHz, Deuterium Oxide) δ -91.12 (dq, J = 28.3, 13.1 Hz), -142.50 – -142.83 (m). ^{13}C NMR (101 MHz, Deuterium Oxide) δ 144.8 – 141.6 (m), 140.7 (dd, J = 259.7, 34.7 Hz), 125.4 (t, J = 15.9 Hz), 31.1. HRMS (ESI) $\text{C}_6\text{H}_5\text{F}_4\text{N}_2\text{Cl}$ calcd. $[\text{M}]^+$ 216.0077 observed 216.0054.

5b (3-chloro-2,5,6-trifluoropyridin-4-yl)methanaminium chloride

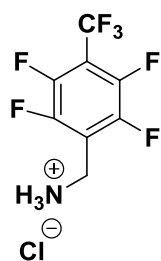
White solid, 99% yield (16.9 mg, 0.0725 mmol).



The **general procedure H** was followed using carboxy(3-chloro-2,5,6-trifluoropyridin-4-yl)methanaminium chloride (25.0 mg, 0.0725 mmol) and 72.5 μL of acetone to afford **5b**. FT-IR (neat) cm^{-1} 3632, 3250, 3033, 1055. ^1H NMR (400 MHz, Deuterium Oxide) δ 4.51 (s, 1H). ^{19}F NMR (376 MHz, Deuterium Oxide) δ -74.14 (dd, J = 27.7, 12.4 Hz), -88.82 (dd, J = 21.4, 12.4 Hz), -140.28 – -147.60 (m). ^{13}C NMR (101 MHz, Deuterium Oxide) δ 151.0 (ddd, J = 242.5, 11.9, 2.9 Hz), 147.1 (ddd, J = 246.8, 17.6, 13.2 Hz), 141.9 (ddd, J = 259.0, 27.0, 6.4 Hz), 135.3 (d, J = 14.2 Hz), 114.1 (dd, J = 34.7, 6.8 Hz), 34.1. HRMS (ESI) $\text{C}_6\text{H}_5\text{ClF}_3\text{N}_2\text{Cl}$ calcd. $[\text{M}]^+$ 231.9782 observed 231.9799.

5c (2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)methanaminium chloride

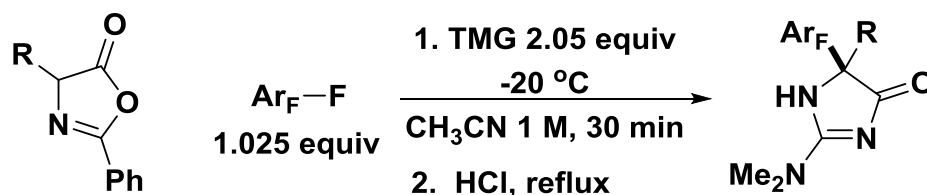
White solid, 99% yield (10.7 mg, 0.027 mmol).



The **general procedure H** was followed using carboxy(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)methanaminium chloride (15 mg, 0.038 mmol) and 38 μ L of acetone to afford **5c**. FT-IR (neat) cm^{-1} 3609, 3277, 3064, 1077. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 4.24 (s, 1H). ^{19}F NMR (376 MHz, Deuterium Oxide) δ -57.69 (t, J = 21.5 Hz), -139.33 (dt, J = 17.2, 9.5 Hz), -139.69 – -140.09 (m). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 145.8 (d, J = 251.7 Hz), 143.6 (dt, J = 259.4, 18.4 Hz), 121.0 (d, J = 276.2 Hz), 118.7 (d, J = 35.9 Hz), 108.9, 30.6. HRMS (ESI) $\text{C}_8\text{H}_5\text{F}_7\text{NCl}$ calcd. $[\text{M}]^+$ 282.9999 observed 283.0023.

Synthesis of 2-aminohydantoins

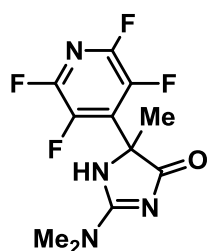
General procedure I for synthesis of 2-aminohydantoins



Under an argon atmosphere, oxazolone (**1 equiv**), $\text{Ar}_\text{F}-\text{F}$ (**1.025 equiv**), CH_3CN (**1 M**) were added to small test tube, which was fitted with a septum and cooled to $-20\text{ }^\circ\text{C}$. Then a steady stream of tetramethylguanidine (**1.025 equiv.**) was added to mixture down the side of the test tube glass which facilitated cooling of the TMG solution. The reaction was left to react for 30 min and then the cooling bath was removed. After, the reaction had warmed to room temperature, then a solution of 12 M aqueous hydrochloric acid (0.1 M) was added and refluxed for 24-48 h. The solution was diluted with a half volume of water and made neutral with NaHCO_3 . The aqueous layer was extracted with $\text{EtOAc} \times 3$ and the organic layer was dried with MgSO_4 and concentrated giving crude product. Purification of the crude product was purified by normal phase column chromatography.

7a 2-(dimethylamino)-5-methyl-5-(perfluoropyridin-4-yl)-1,5-dihydro-4H-imidazol-4-one

White solid, 95% yield (314 mg, 1.08 mmol).

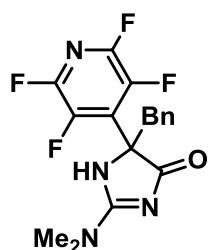


The **general procedure I** was followed using 4-methyl-2-phenyloxazol-5(4H)-one (200 mg, 1.14 mmol), pentafluoropyridine (66.8 mg, 1.17 mmol), tetramethylguanidine (135 mg, 1.17 mmol), 11.4 mL HCl , and 1.14 mL of MeCN was used to afford **7a**. FT-IR (neat) cm^{-1} 3203, 2967, 1730, 1035. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.99 (s, 1H), 3.11 (s, 3H), 2.98 (s, 3H), 1.75 (s, 3H). ^{19}F NMR (376 MHz, CD_3CN) δ -143.03, -143.64. ^{19}F NMR (376 MHz,

DMSO-*d*₆) δ -92.57 – -93.01 (m), -140.20 – -140.83 (m). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 185.8, 169.9, 145.0 – 141.5 (m), 142.6 – 138.8 (m), 133.1 (t, *J* = 10.6 Hz), 64.5, 38.1, 36.2, 23.9. HRMS (ESI) C₁₁H₁₀F₄N₄O calcd. [M+K]⁺ 329.0422 observed 329.0456.

7b 5-benzoyl-2-(dimethylamino)-5-(perfluoropyridin-4-yl)-1,5-dihydro-4H-imidazol-4-one

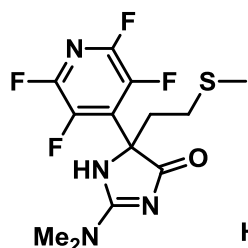
Yellow oil, in 49% yield (37.1 mg, 0.0975 mmol).



The **general procedure** I was followed using 4-benzyl-2-phenyloxazol-5(4H)-one (50 mg, 0.199 mmol), pentafluoropyridine (34.5 mg, 0.204 mmol), tetramethylguanidine (23.5 mg, 0.204 mmol), 1.99 mL HCl, and 0.199 mL of MeCN was used to afford **7b**. FT-IR (neat) cm⁻¹ 3222, 2957, 1710, 1005. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.69 (s, 1H), 7.23 (s, 5H), 3.51 (q, *J* = 13.0 Hz, 2H), 2.86 (s, 3H), 2.72 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -92.27 – -92.81 (m), -138.65 – -138.98 (m). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 183.2, 169.7, 145.23 – 142.16 (m), 142.13 – 138.90 (m), 133.76, 132.87 (t, *J* = 10.9 Hz), 130.5, 127.6, 126.9, 78.6, 69.3, 37.7, 35.9. HRMS (ESI) C₁₇H₁₄F₄N₄O calcd. [M+H]⁺ 367.1177 observed 367.1150.

7c 2-(dimethylamino)-5-(2-(methylthio)ethyl)-5-(perfluoropyridin-4-yl)-1,5-dihydro-4H-imidazol-4-one

Yellow solid, 60% yield (45.6 mg, 0.127 mmol).



The **general procedure** was followed using 4-(2-(methylthio)ethyl)-2-phenyloxazol-5(4H)-one (50 mg, 0.212 mmol), pentafluoropyridine (36.8 mg, 0.218 mmol), tetramethylguanidine (25.1 mg, 0.218 mmol), 2.12 mL HCl, and 0.212 mL of MeCN was used to afford **7c**. FT-IR (neat) cm⁻¹ 2897, 2860, 1734, 1091. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 3.11 (s, 3H), 3.01 (s, 3H), 2.56 (d, *J* = 2.7 Hz, 1H), 2.46 – 2.26 (m, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -92.35 – -92.61 (m), -139.85 – -140.08 (m). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 183.7, 170.3, 145.5 – 142.6 (m), 142.4 – 138.9 (m), 132.5 (t, *J* = 11.0 Hz), 68.8, 38.6, 36.7, 36.2, 27.8, 15.1. HRMS (ESI) C₁₃H₁₄F₄N₄OS calcd. [M+H]⁺ 351.0897 observed 351.0866.

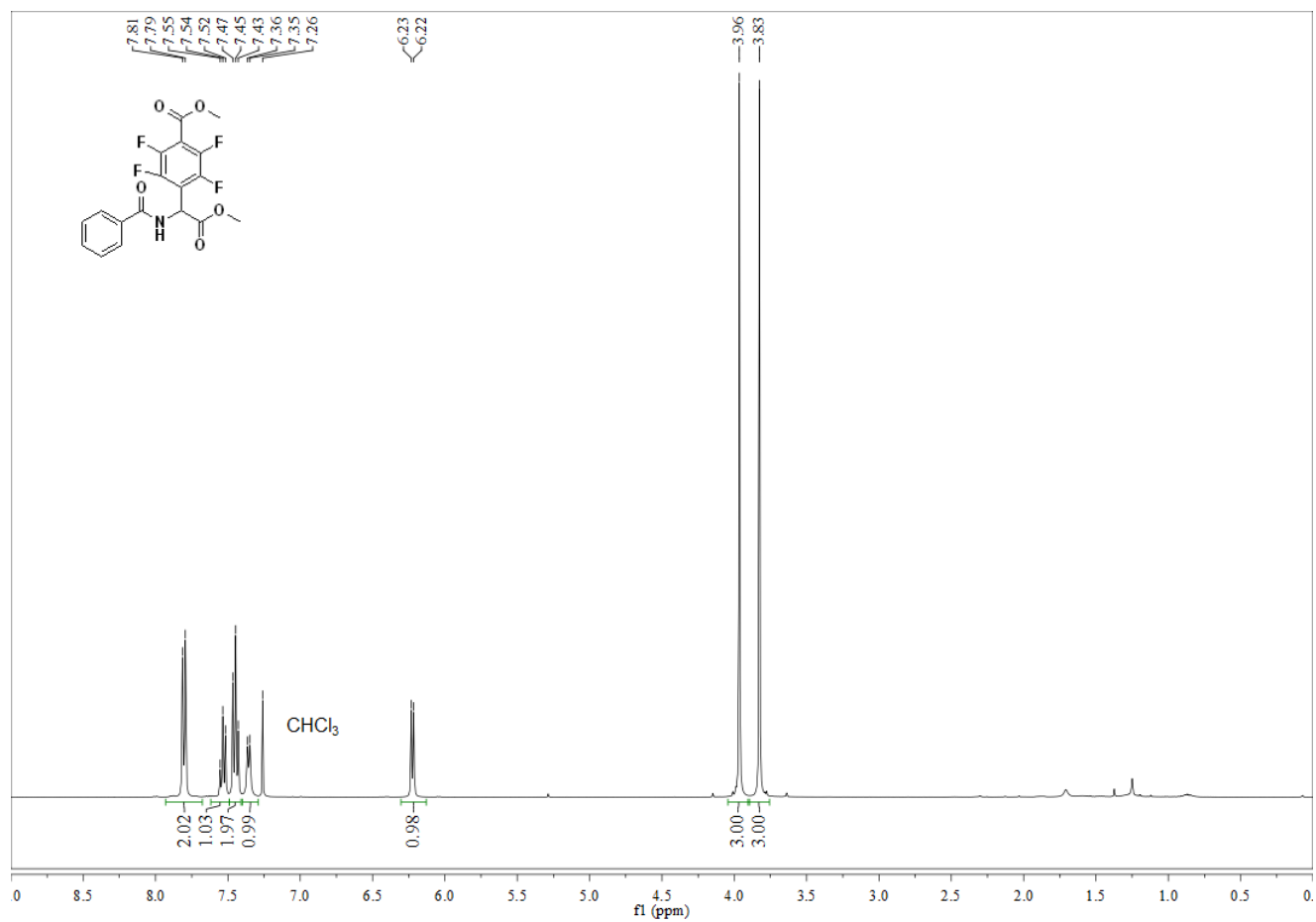
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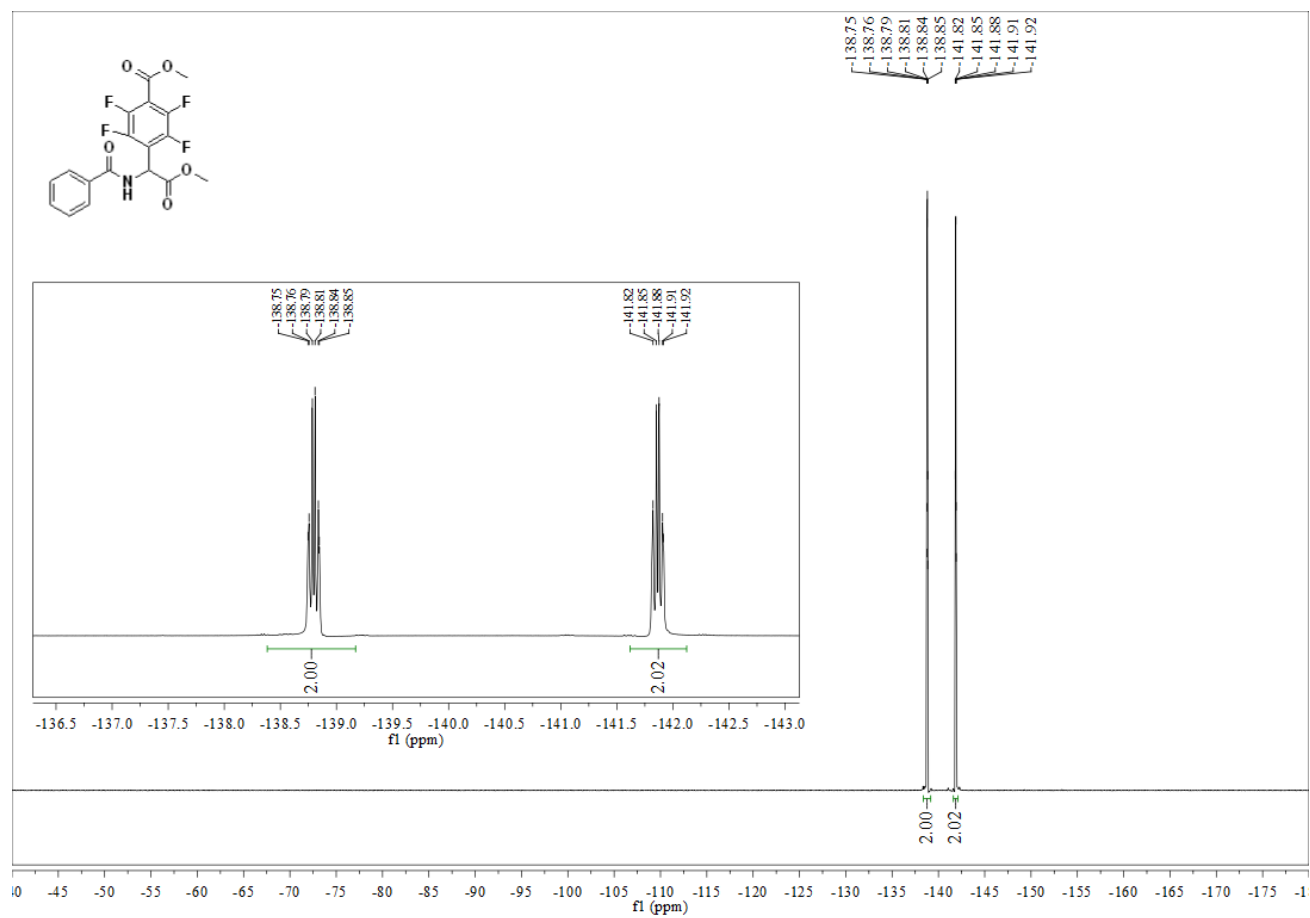
- (8) Gung, B. W.; Amicangelo, J. C. *The Journal of Organic Chemistry* 2006, 71, 9261.

NMR spectra

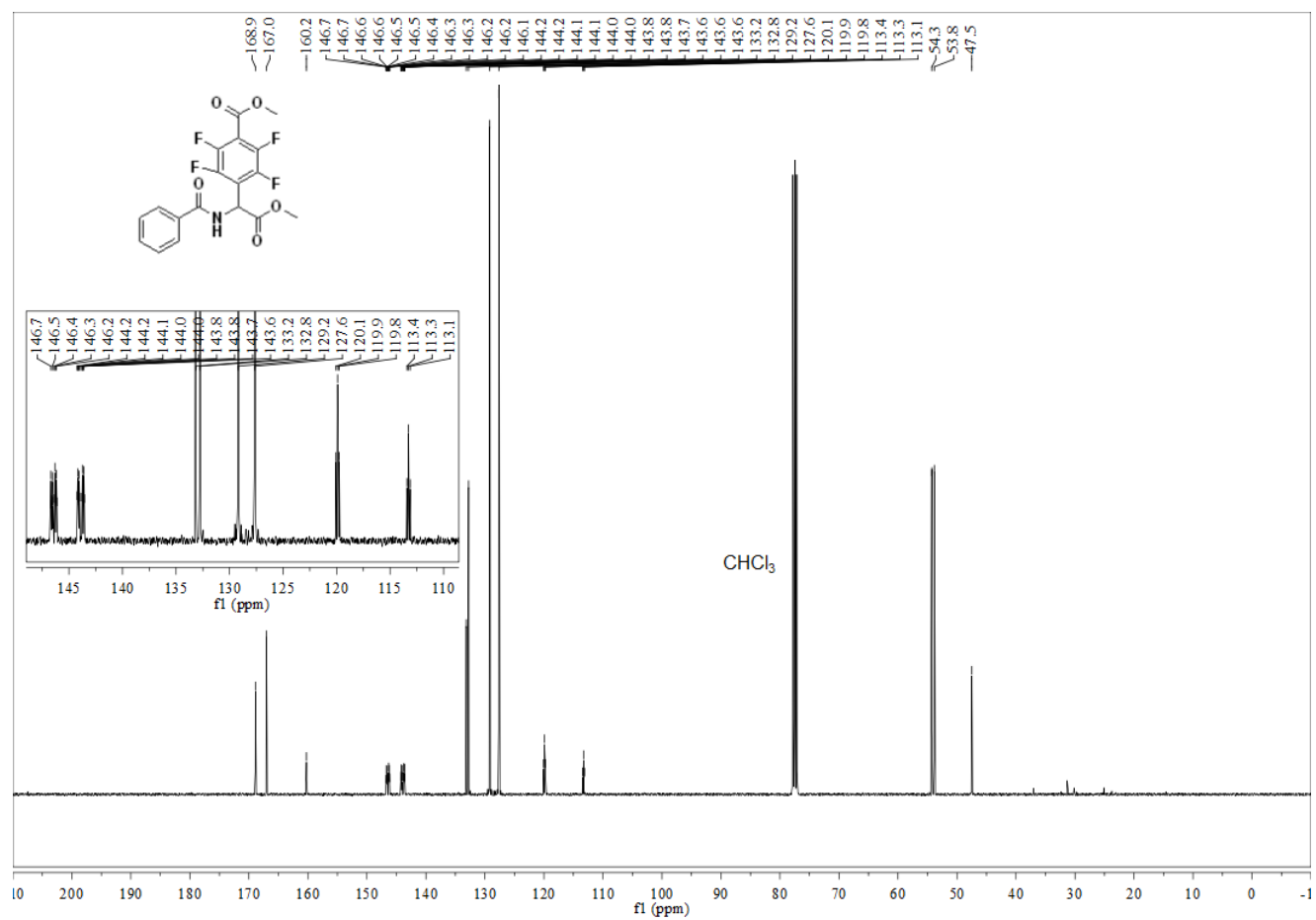
¹H NMR (400 MHz, Chloroform-*d*) **2a**



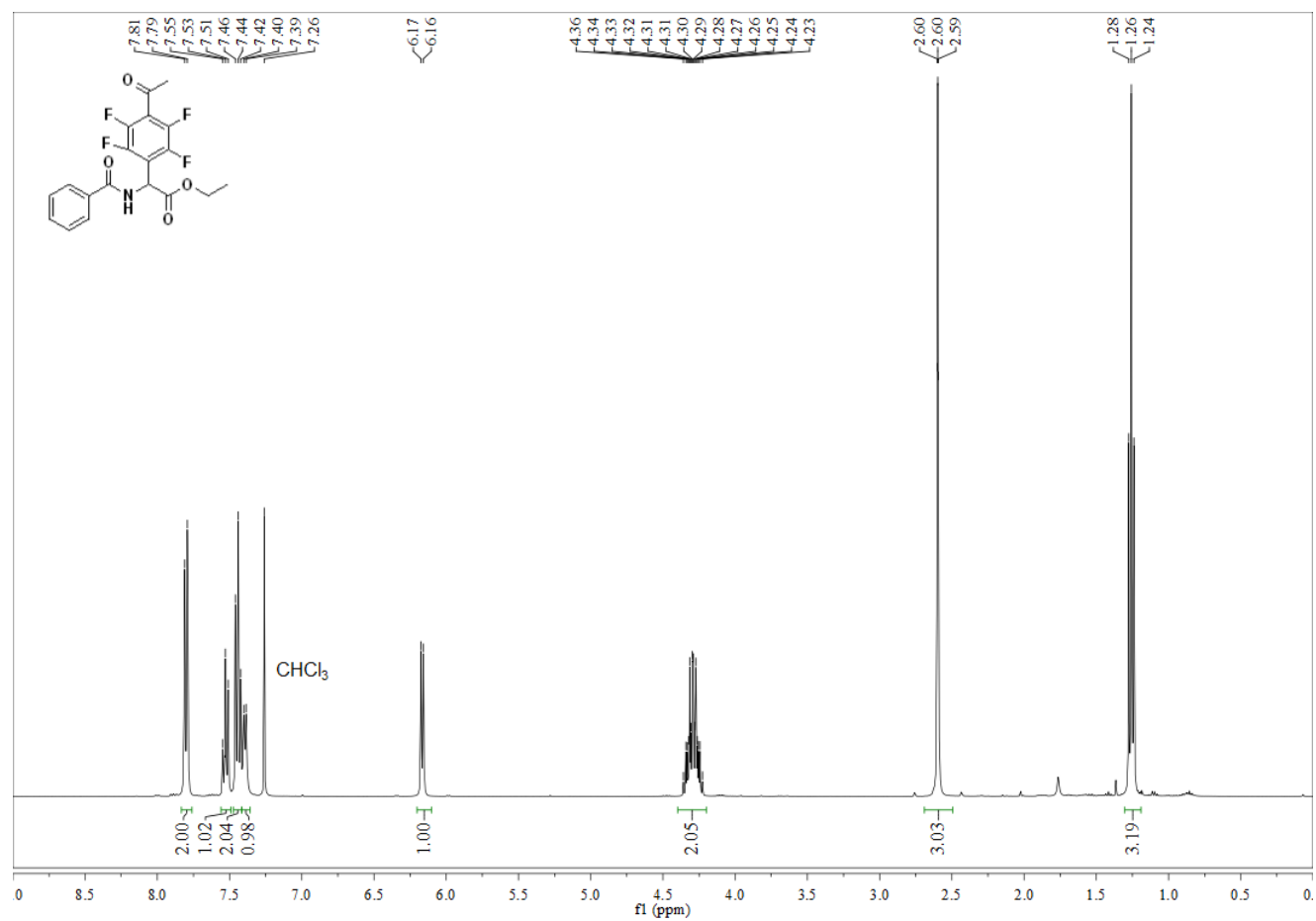
¹⁹F NMR (376 MHz, Chloroform-*d*) **2a**



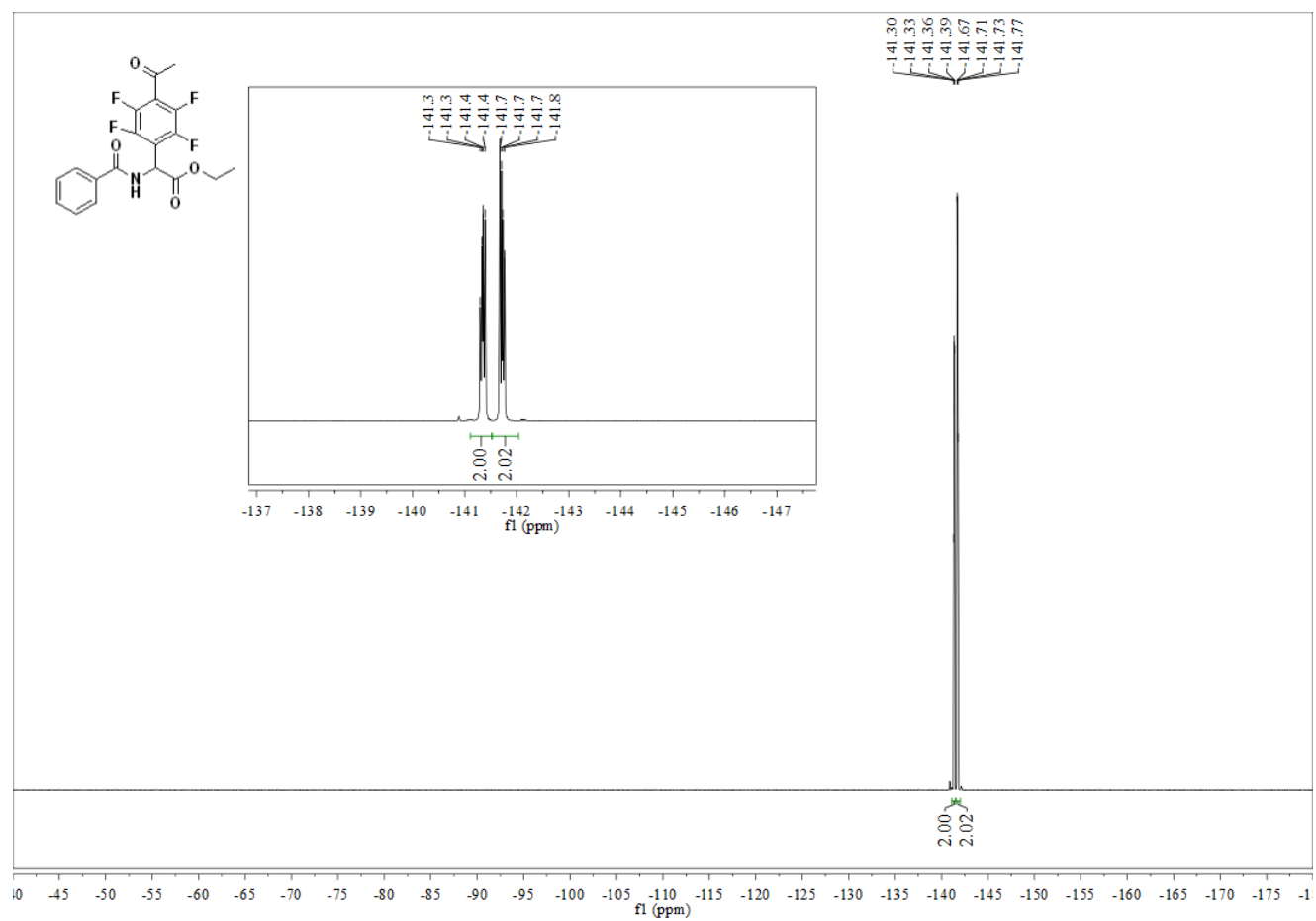
¹³C NMR (101 MHz, Chloroform-*d*) **2a**



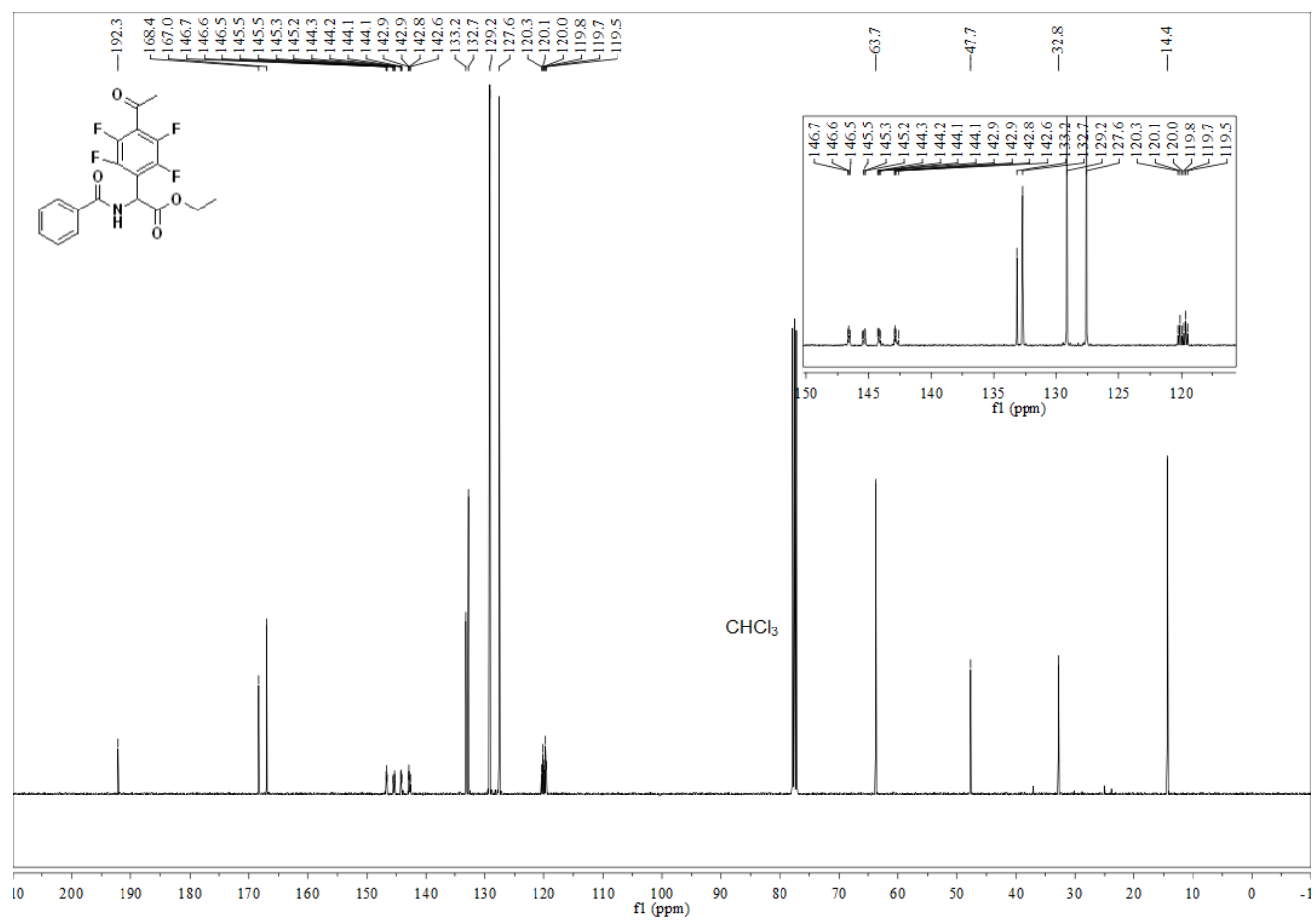
¹H NMR (400 MHz, Chloroform-*d*) **2b**



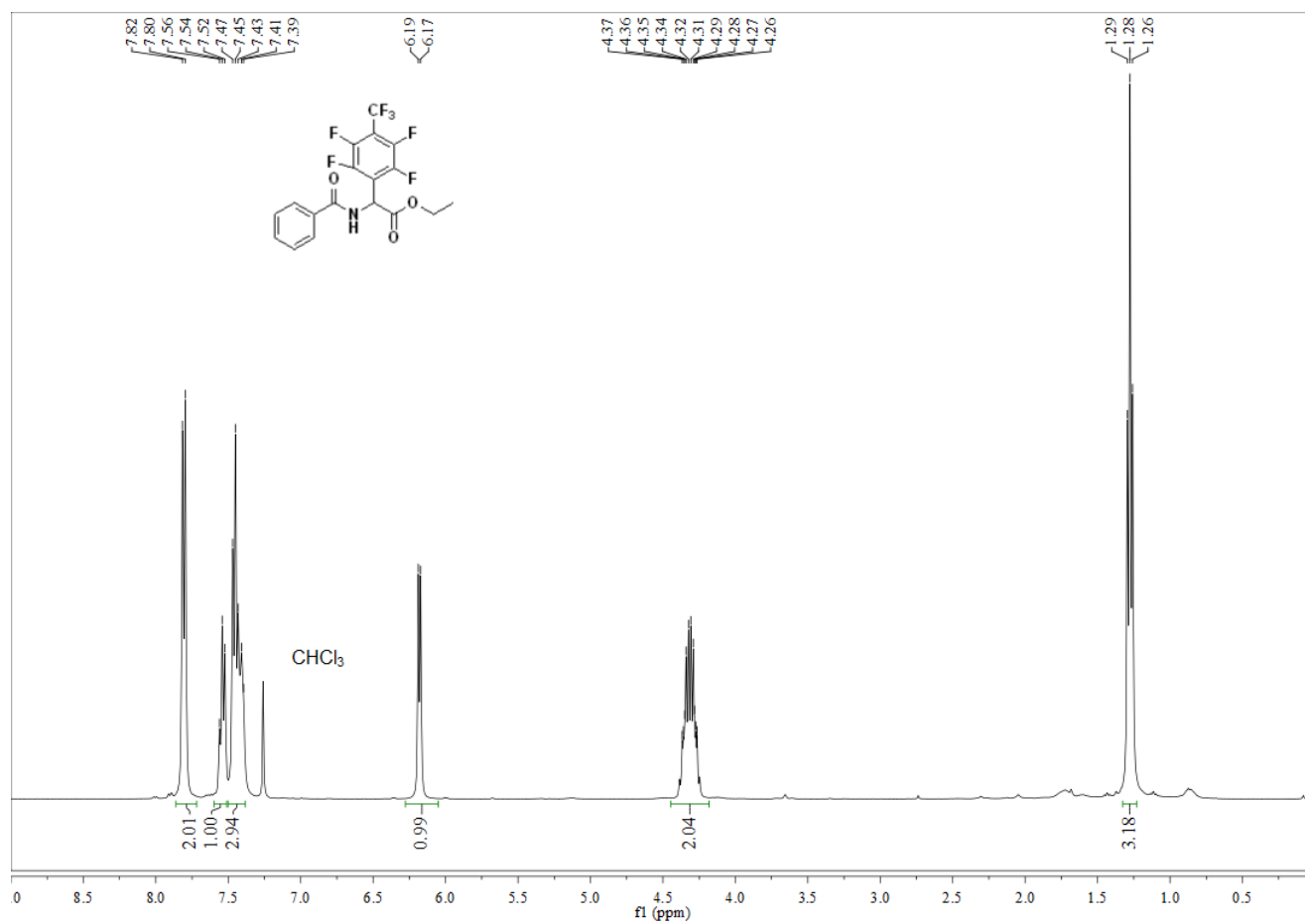
¹⁹F NMR (376 MHz, Chloroform-*d*) **2b**



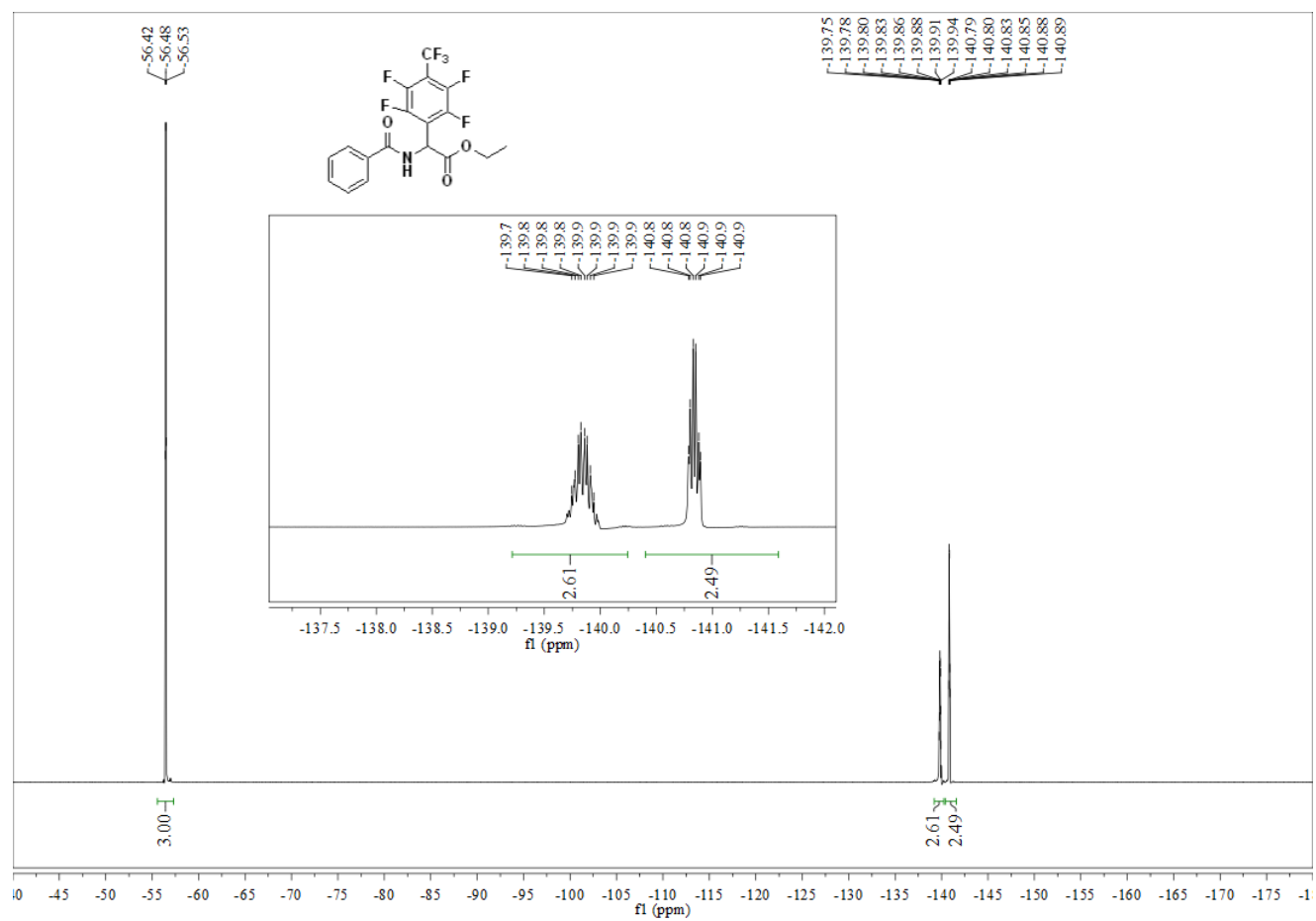
¹³C NMR (101 MHz, Chloroform-*d*) **2b**



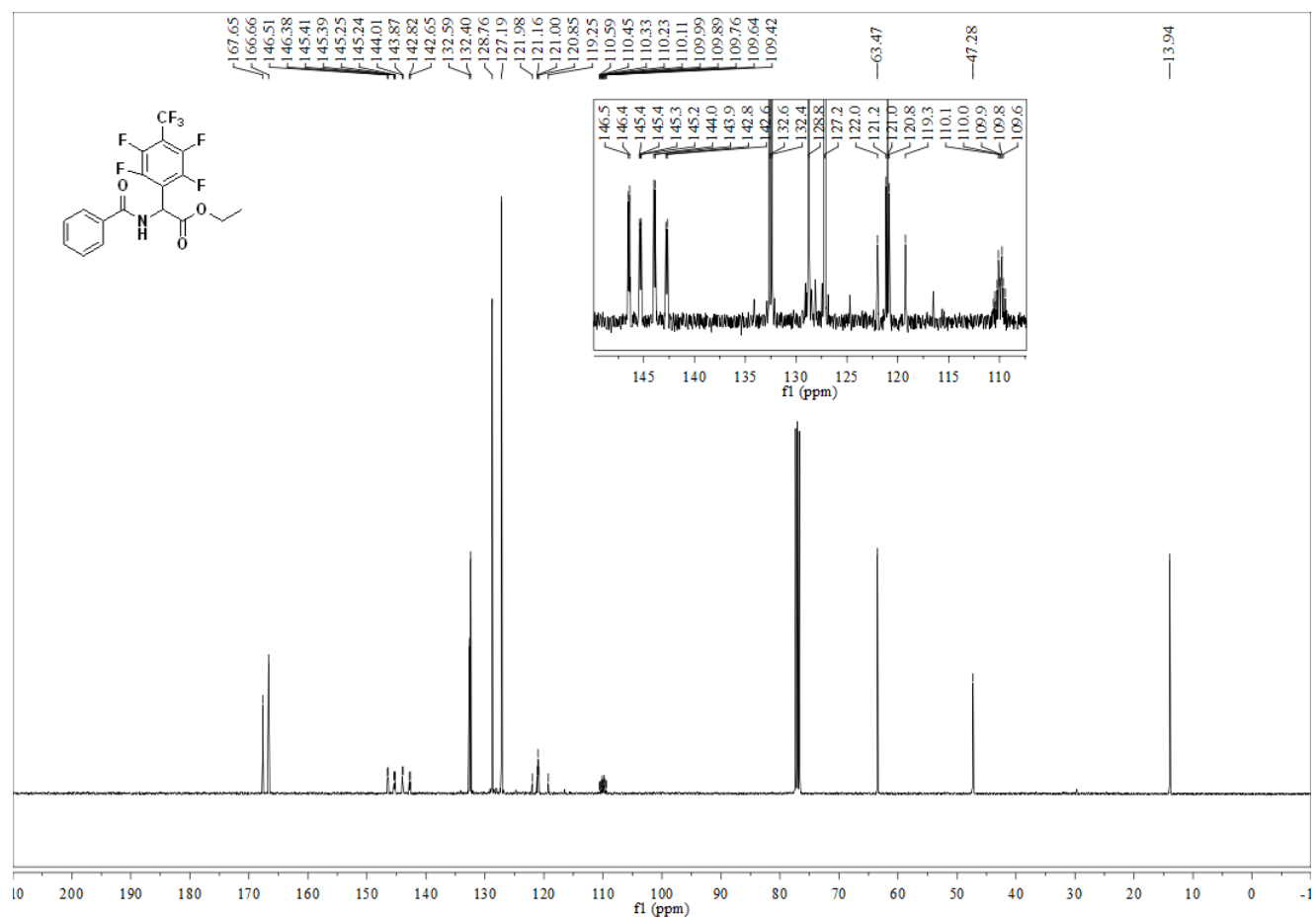
¹H NMR (400 MHz, Chloroform-*d*) **2c**



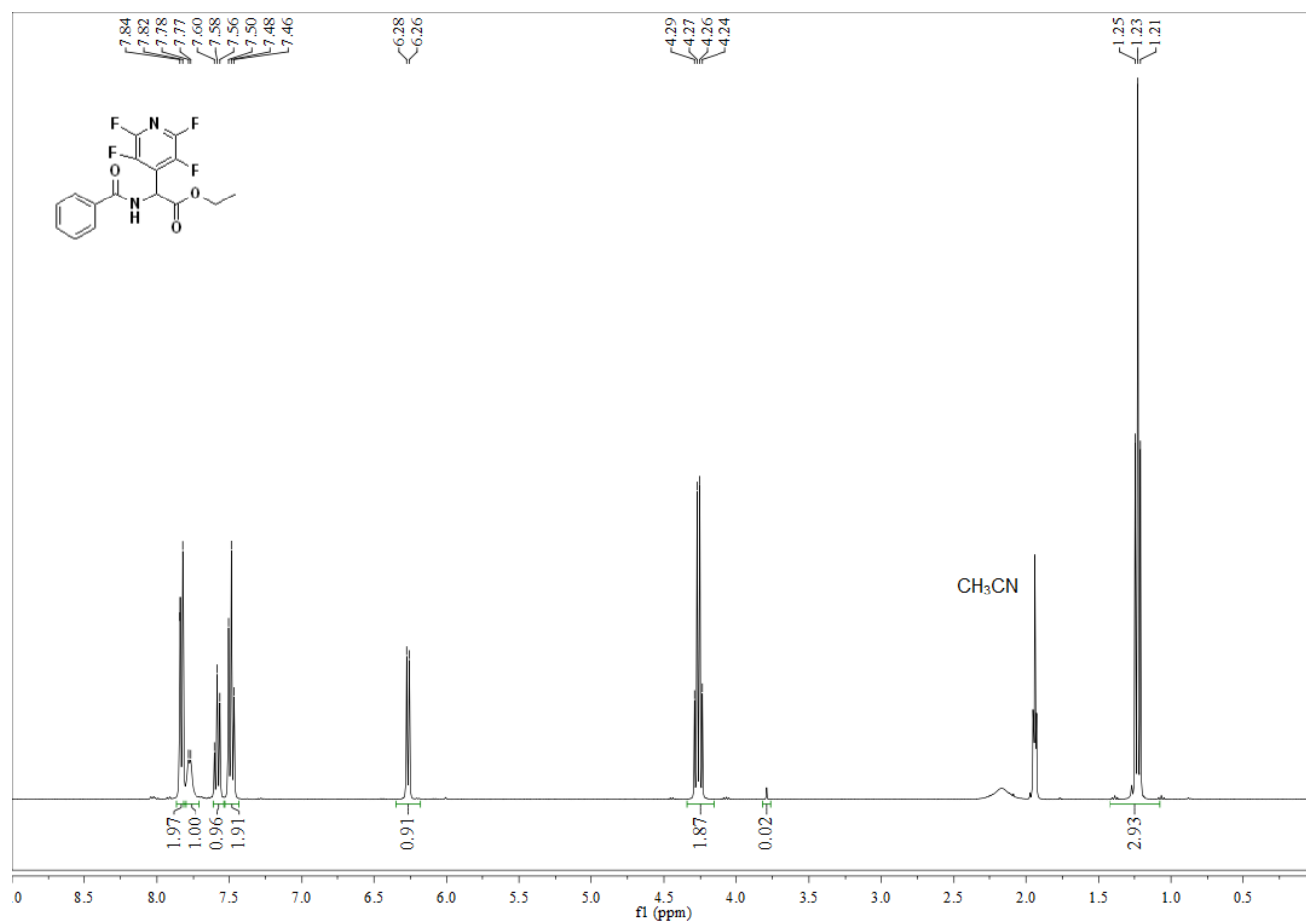
¹⁹F NMR (376 MHz, Chloroform-*d*) **2c**



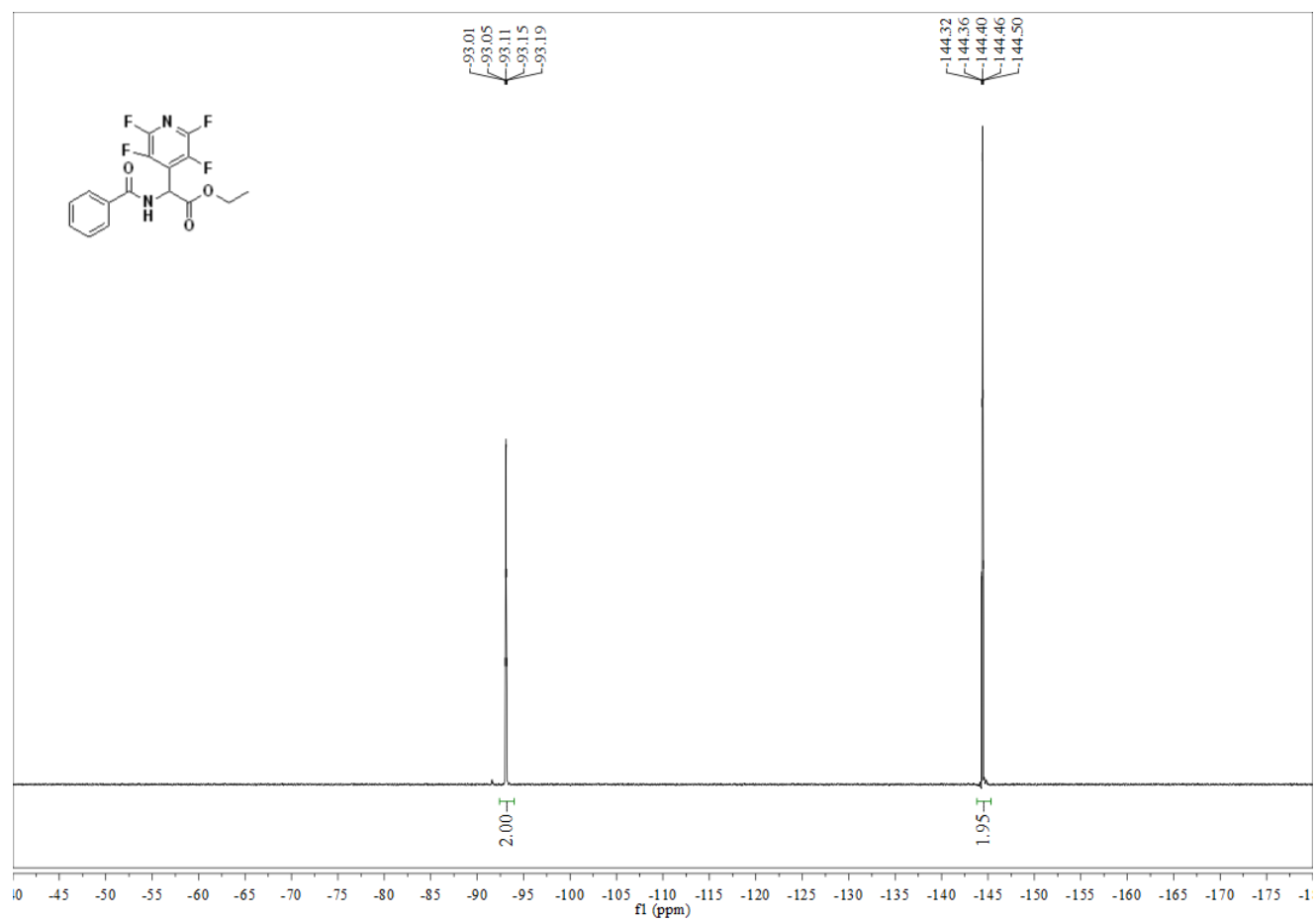
¹³C NMR (101 MHz, Chloroform-*d*) **2c**



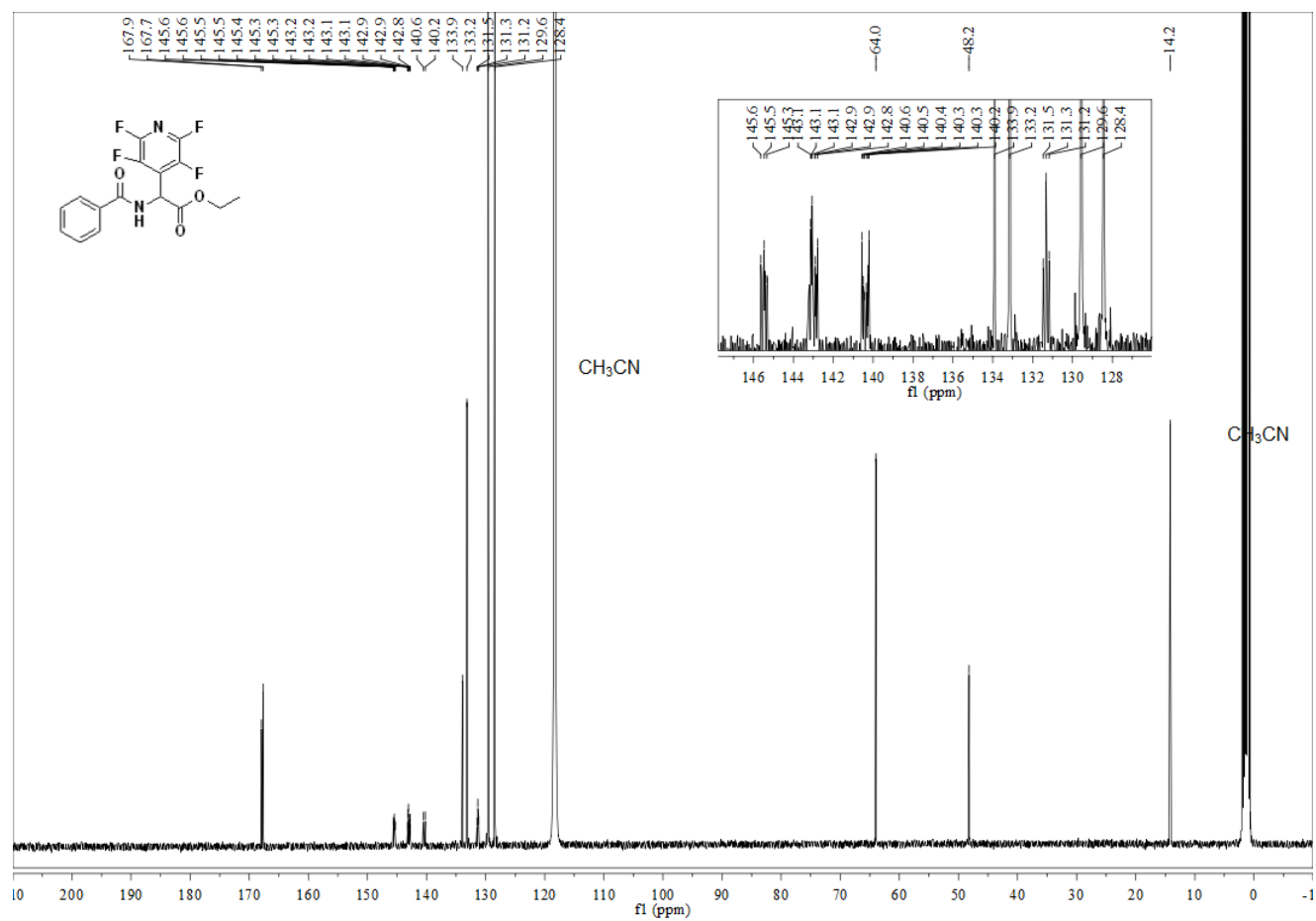
¹H NMR (400 MHz, Acetonitrile-*d*₃) **2d**



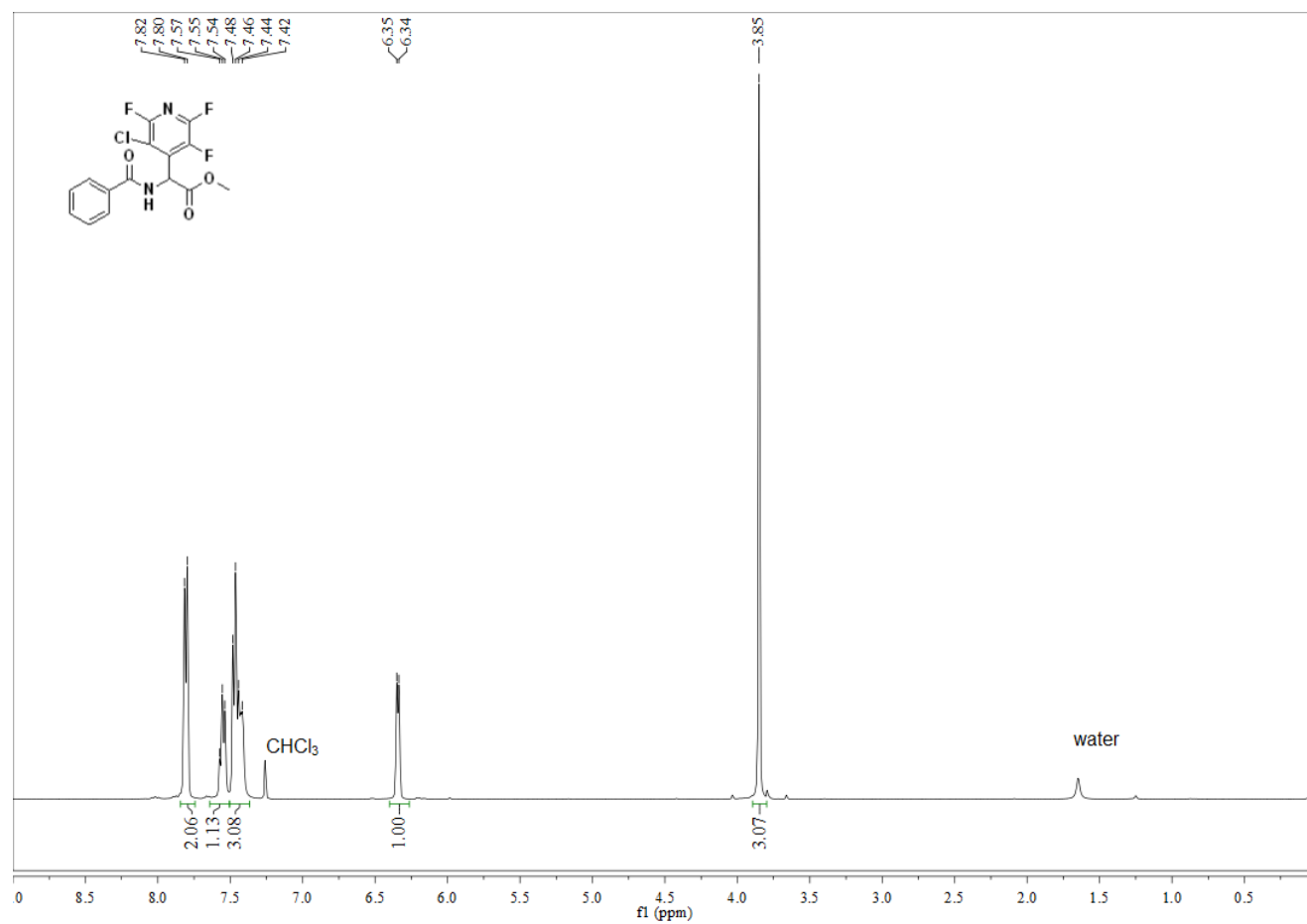
^{19}F NMR (376 MHz, Acetonitrile- d_3) **2d**



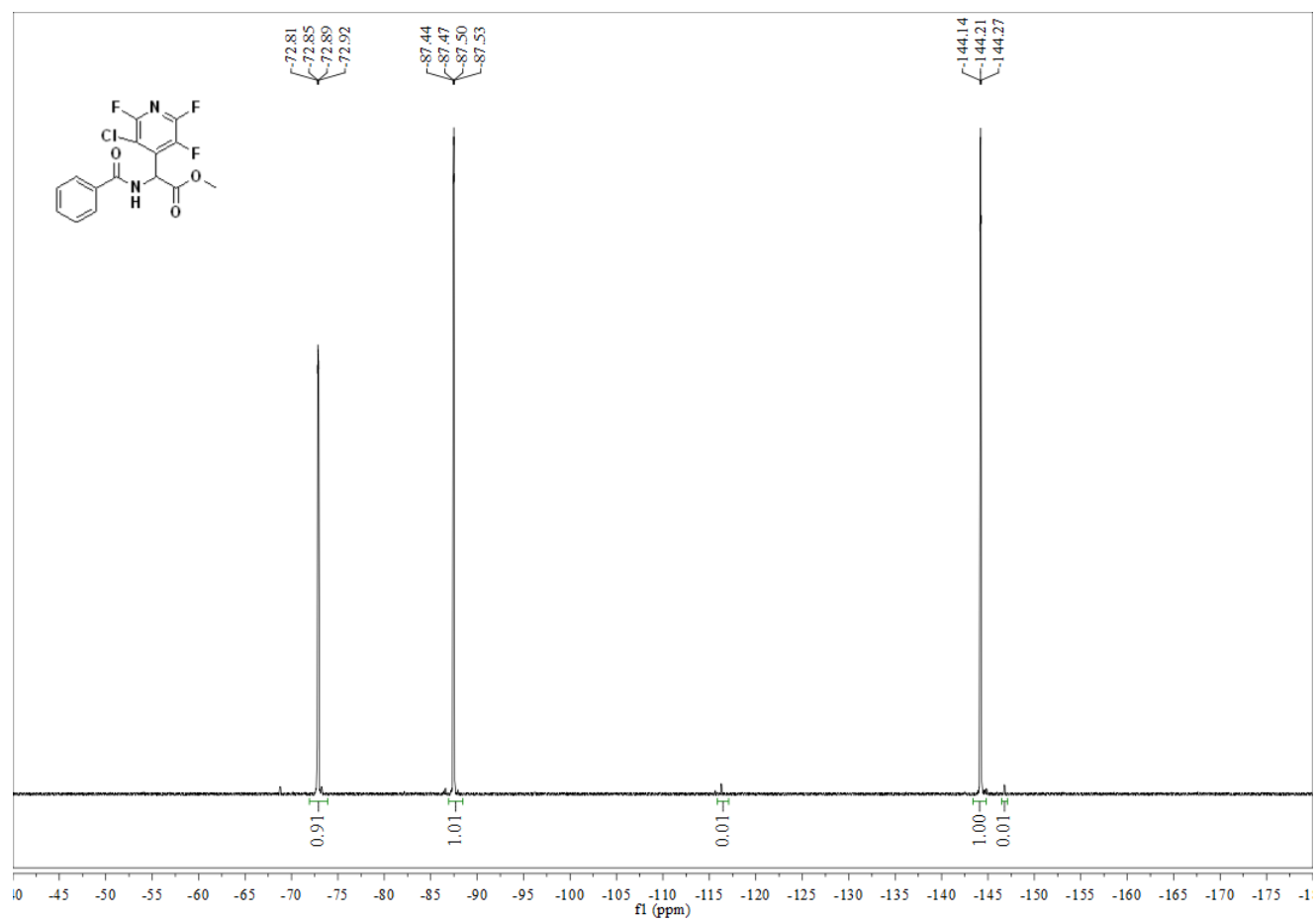
¹³C NMR (101 MHz, Acetonitrile-*d*₃) **2d**



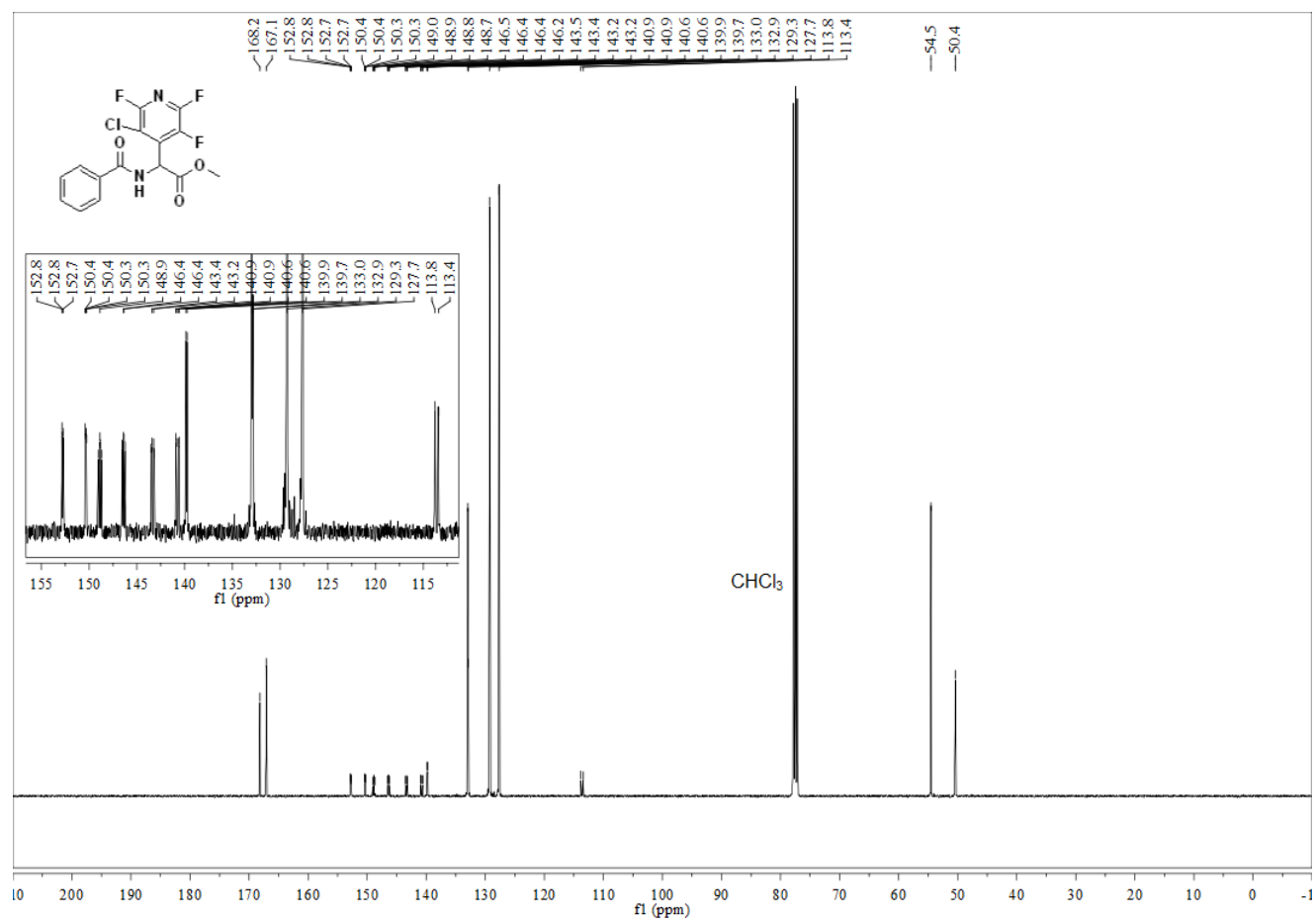
¹H NMR (400 MHz, Chloroform-*d*) **2e**



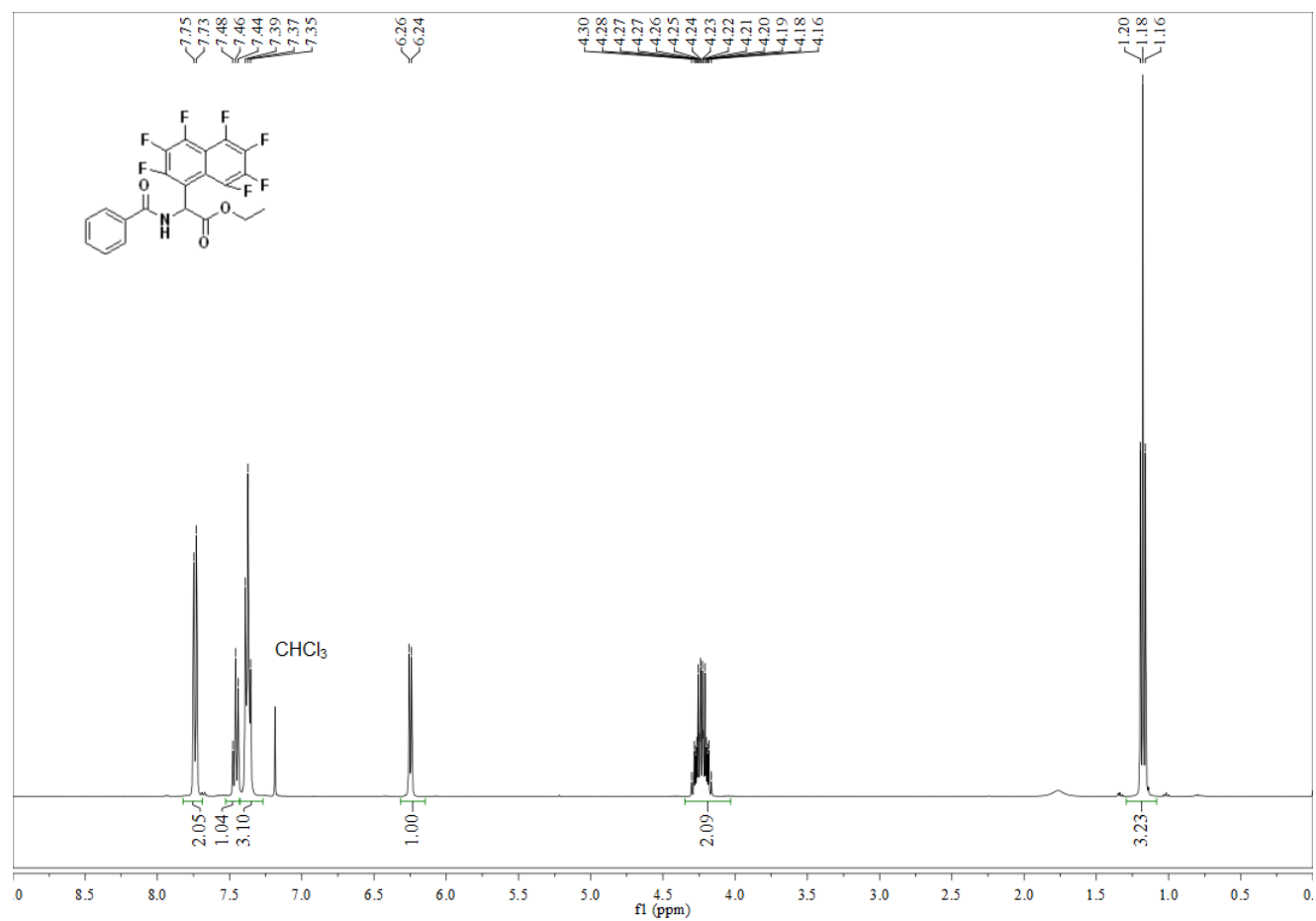
¹⁹F NMR (376 MHz, Chloroform-*d*) **2e**



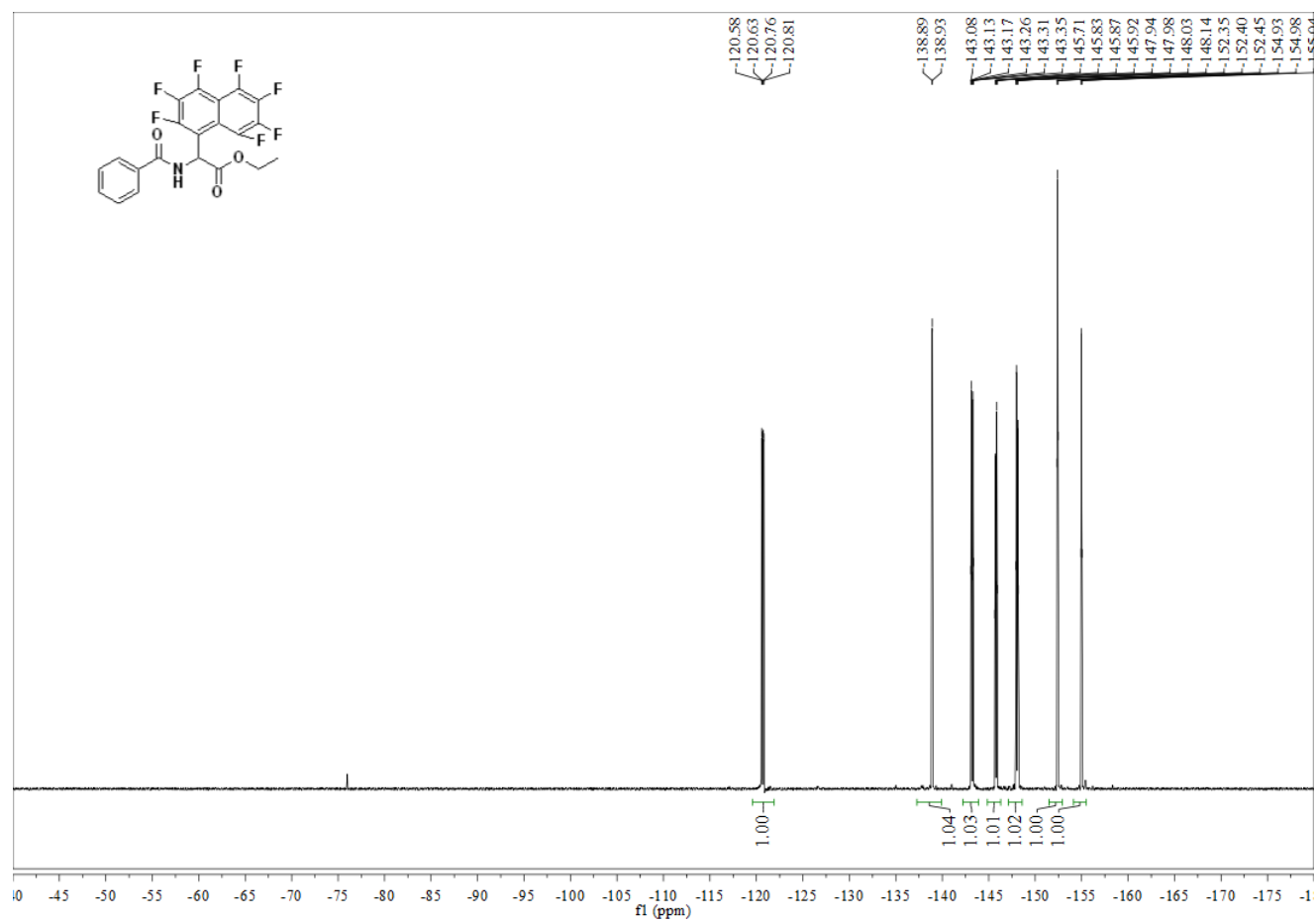
¹³C NMR (101 MHz, Chloroform-*d*) **2e**



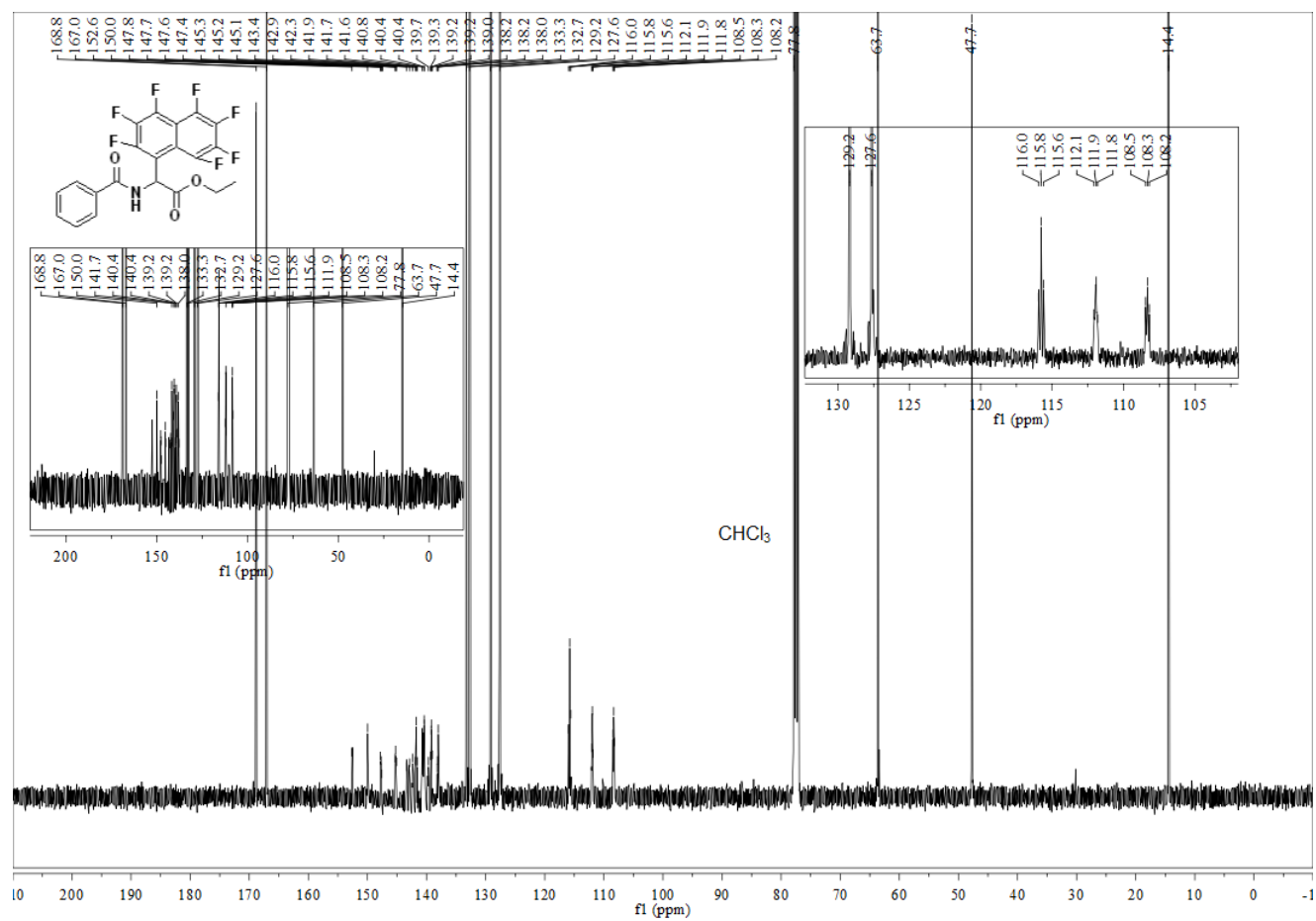
¹H NMR (400 MHz, Chloroform-*d*) **2f**



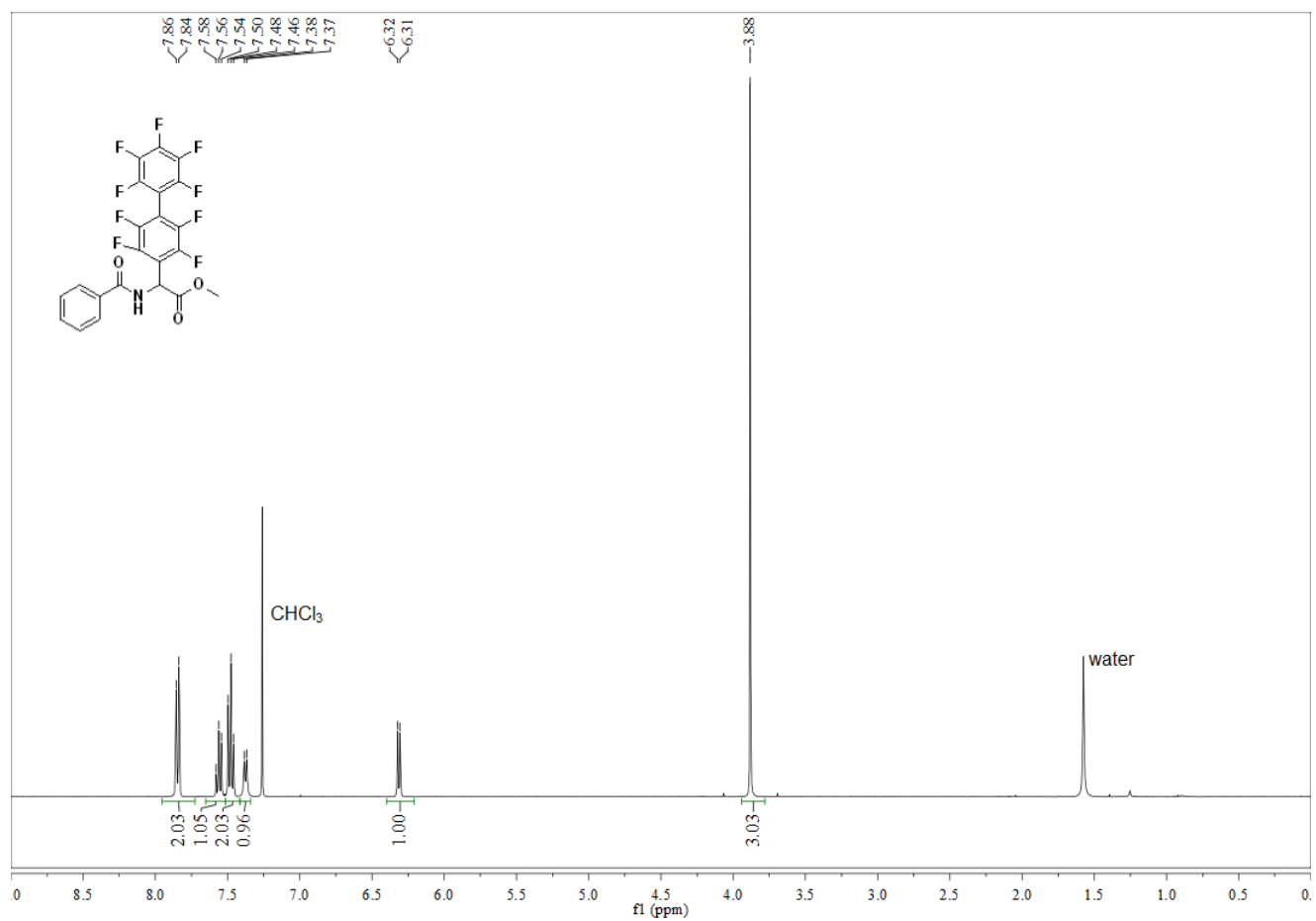
¹⁹F NMR (376 MHz, Chloroform-*d*) **2f**



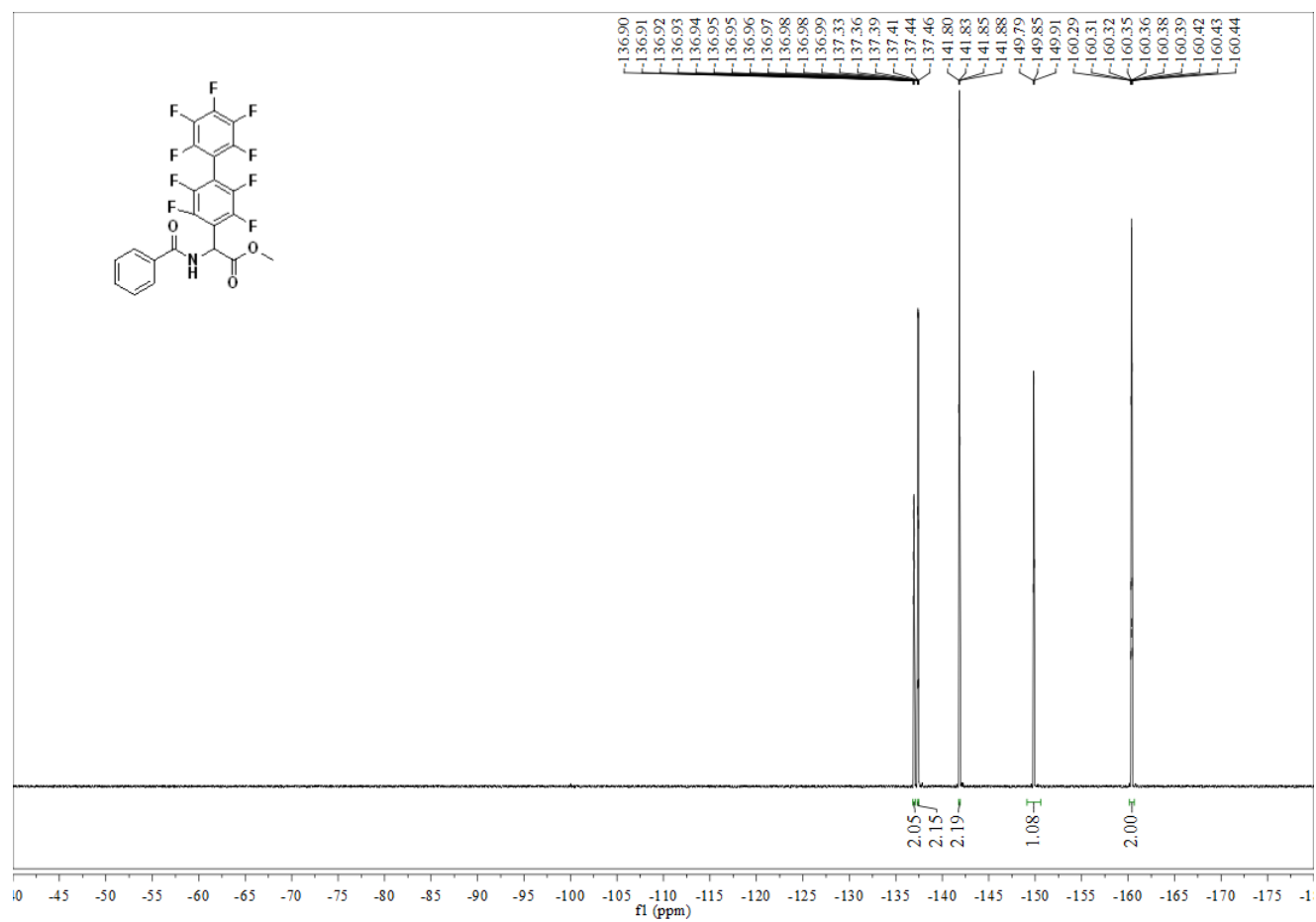
¹³C NMR (101 MHz, Chloroform-*d*) 2f

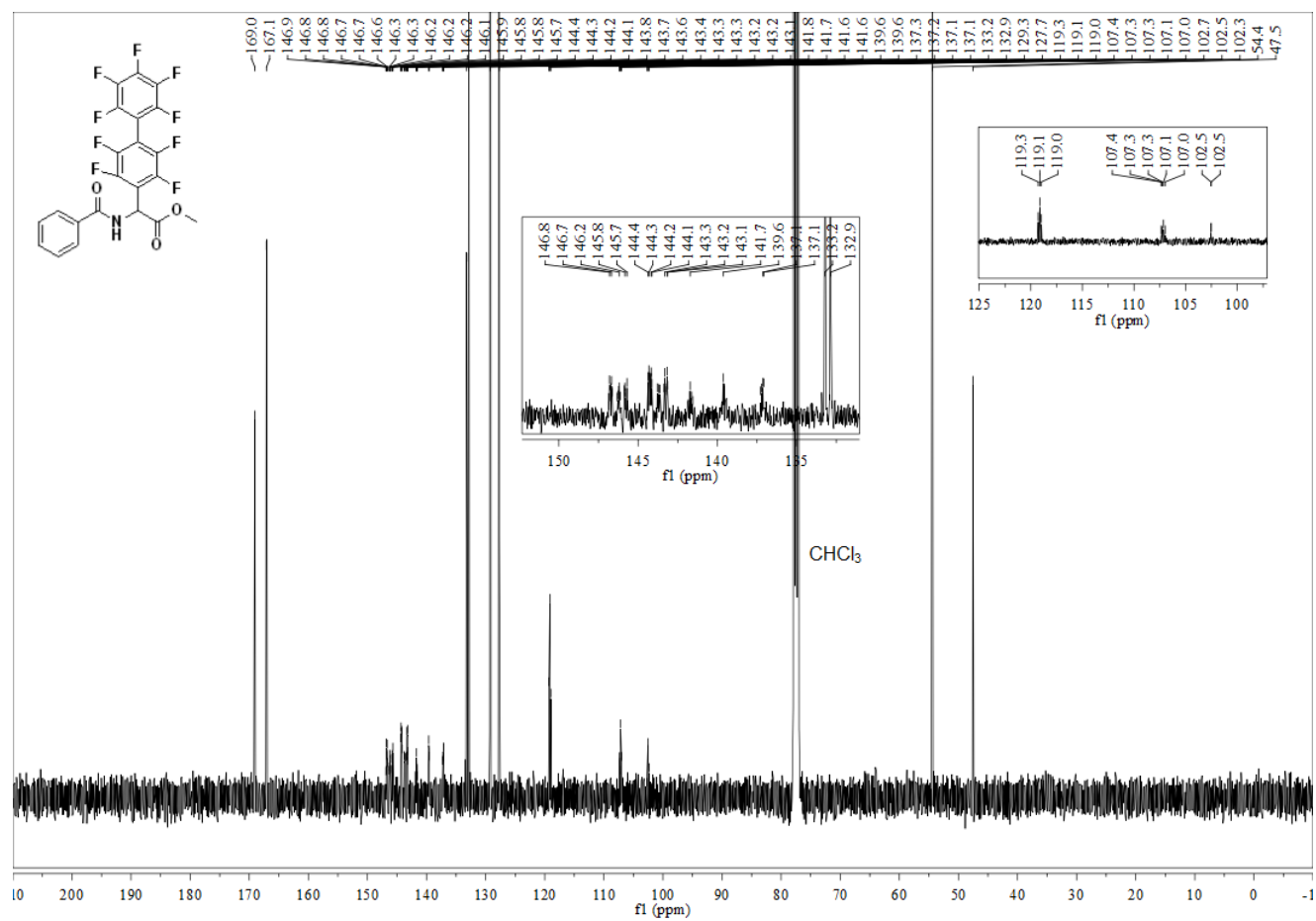


¹H NMR (400 MHz, Chloroform-*d*) **2g**

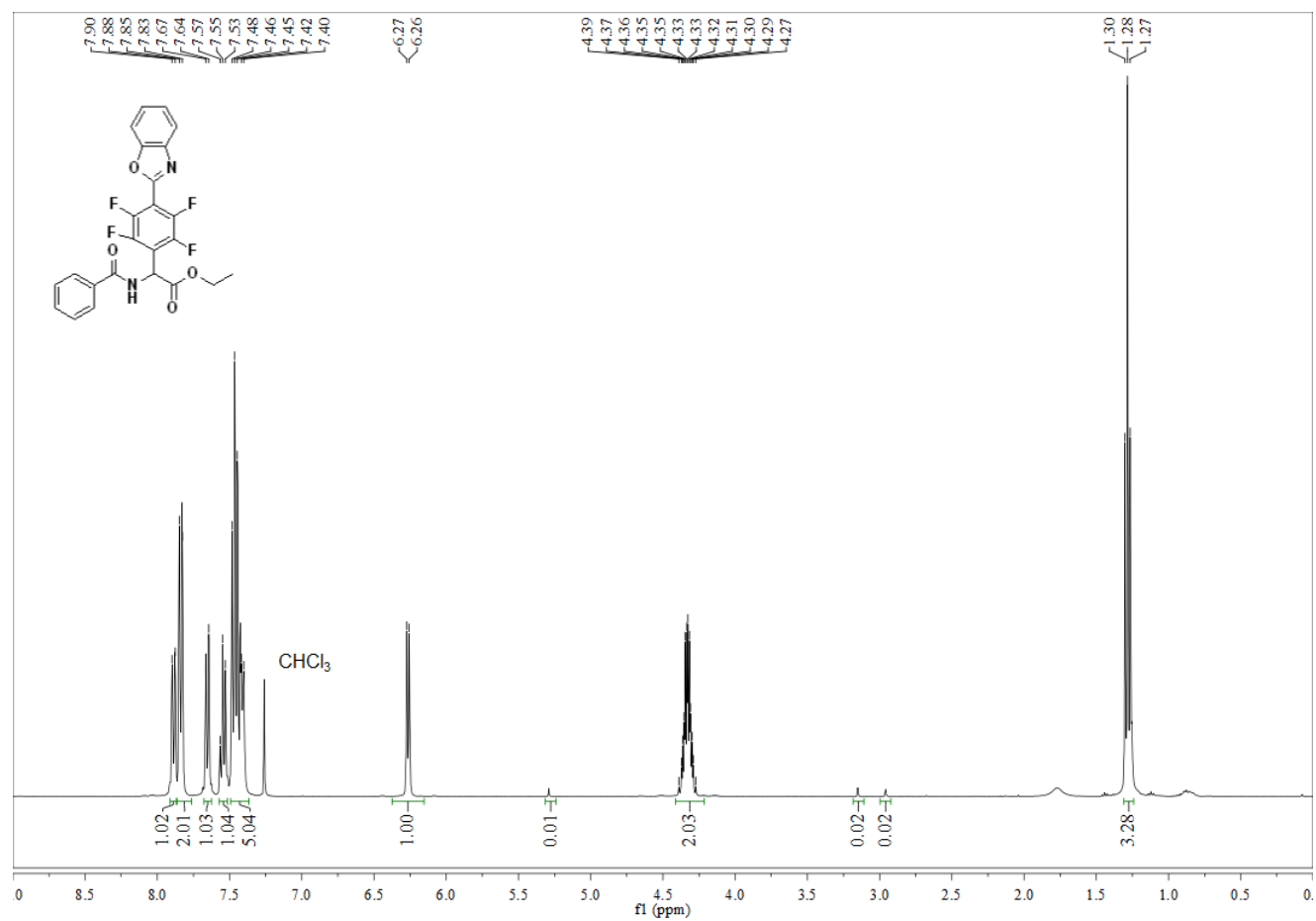


¹⁹F NMR (376 MHz, Chloroform-*d*) **2g**

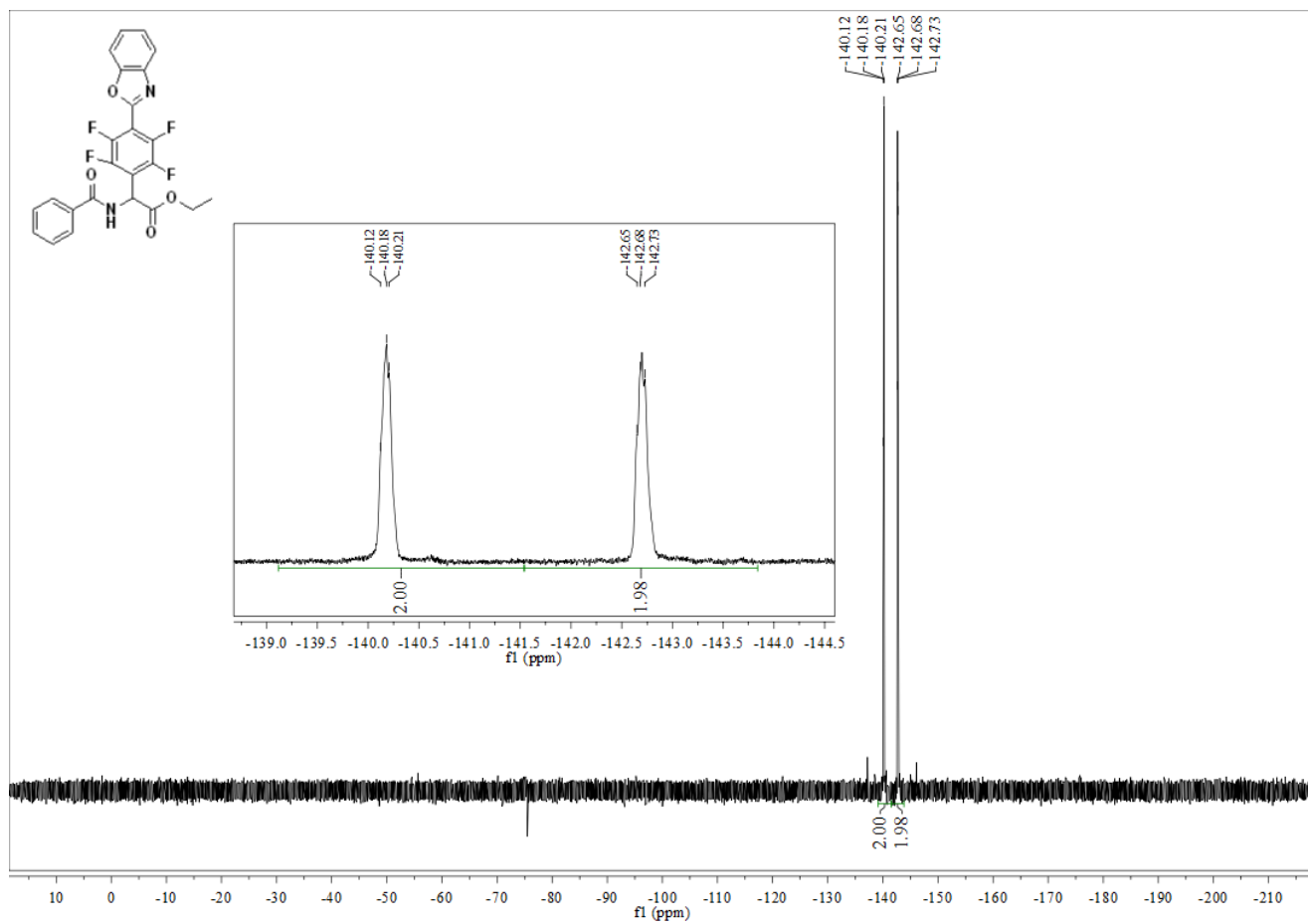


^{13}C NMR (101 MHz, Chloroform-*d* **2g**)

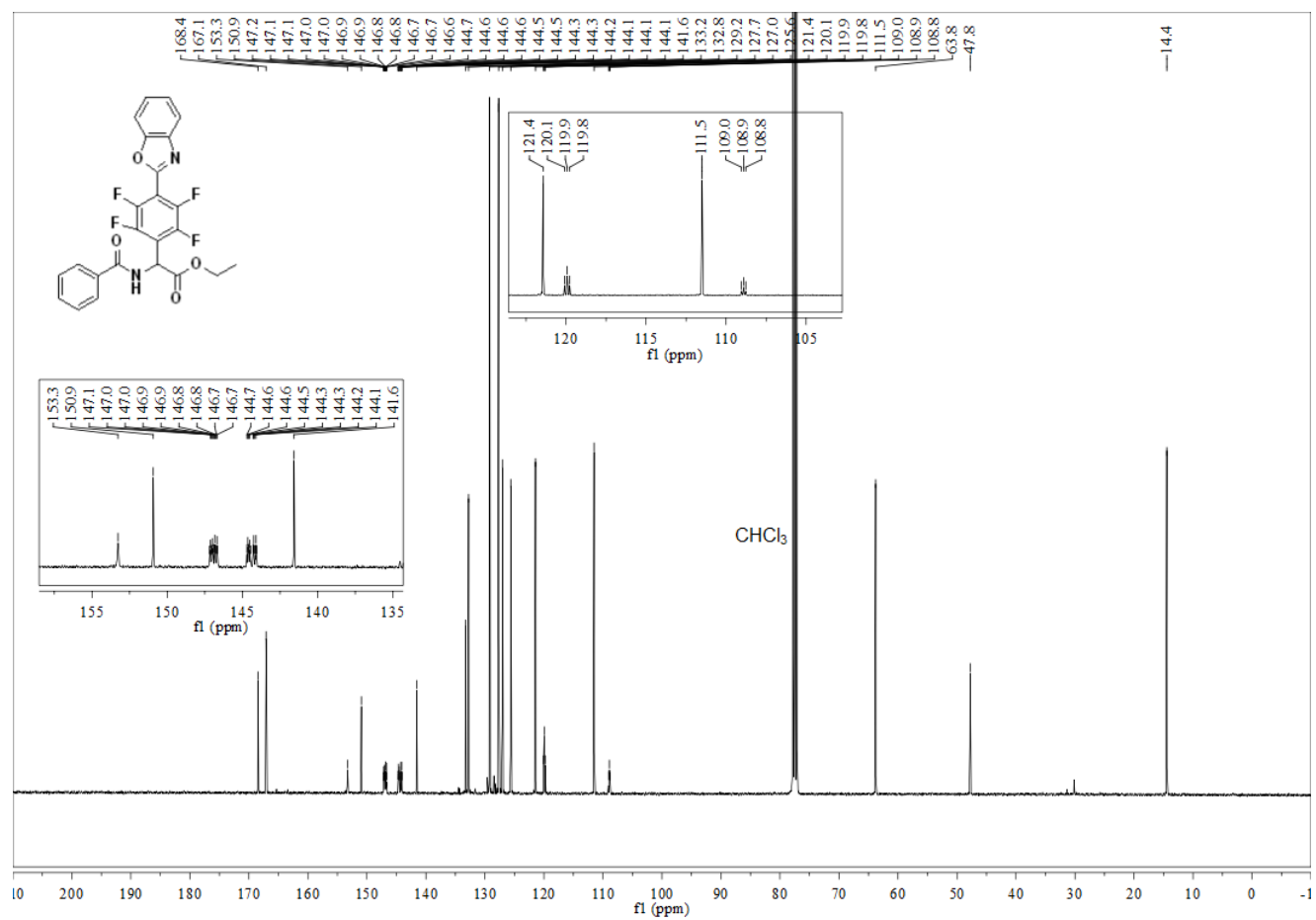
¹H NMR (400 MHz, Chloroform-*d*) **2h**



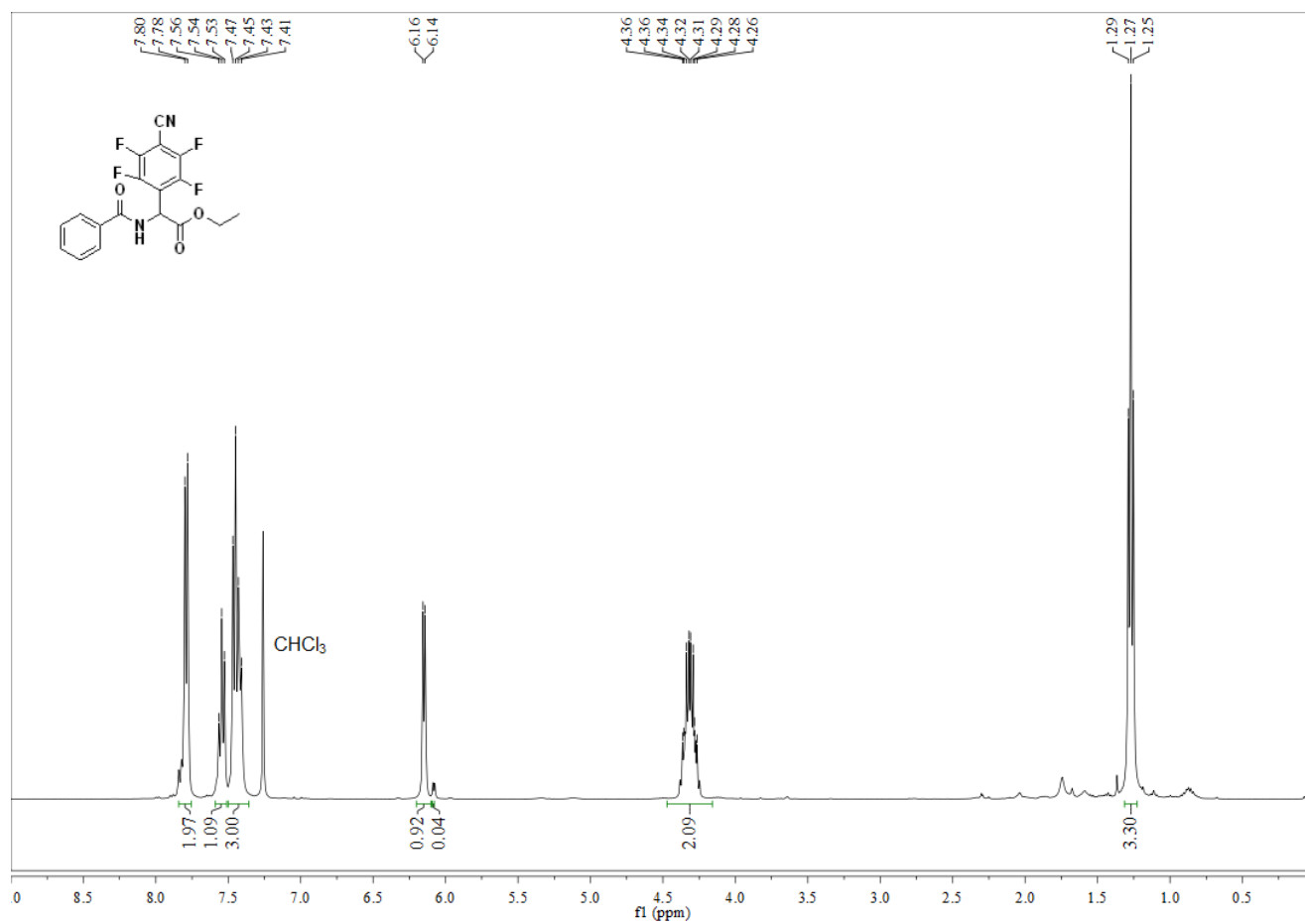
¹⁹F NMR (376 MHz, Chloroform-*d*) **2h**



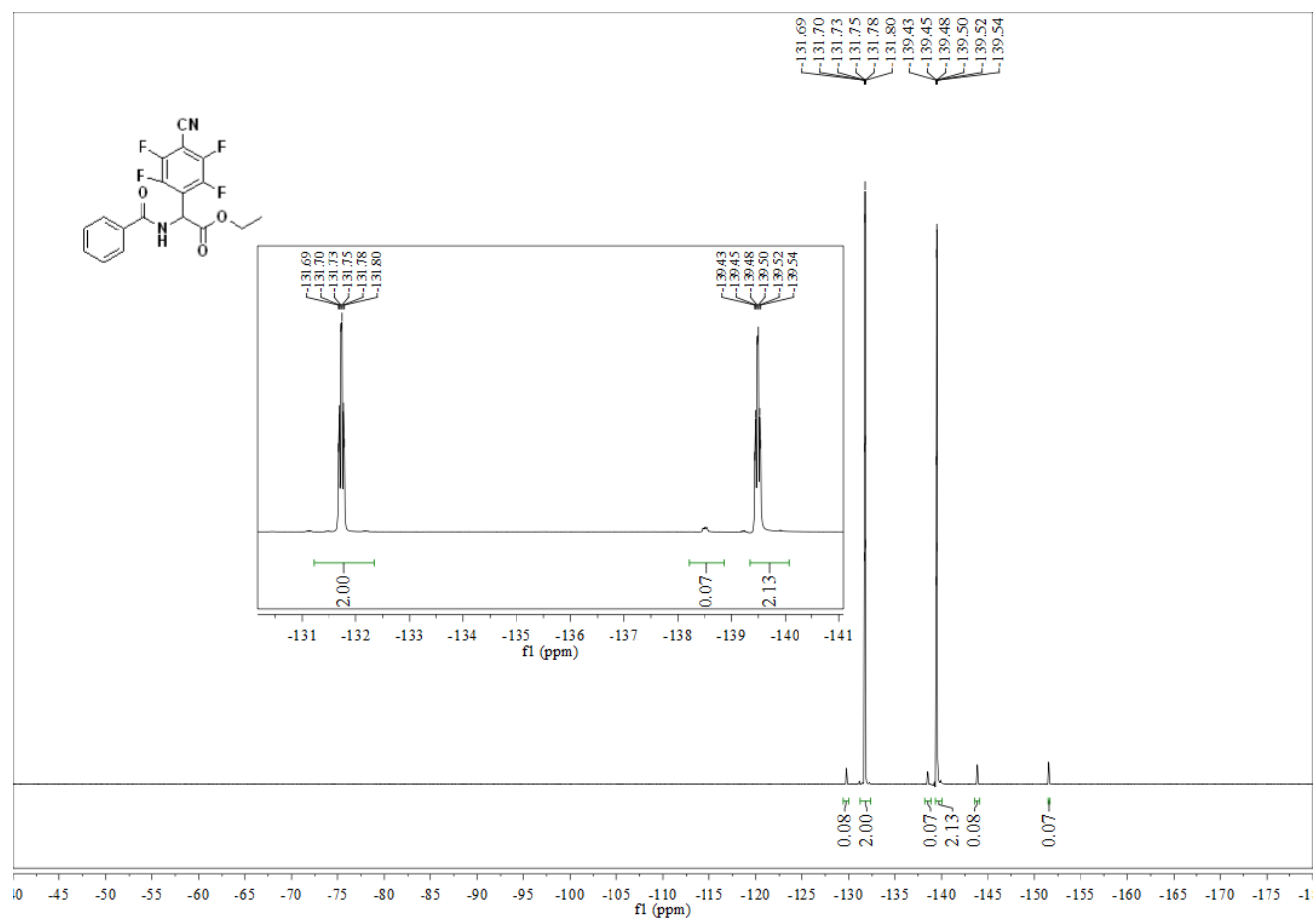
¹³C NMR (101 MHz, Chloroform-*d*) **2h**

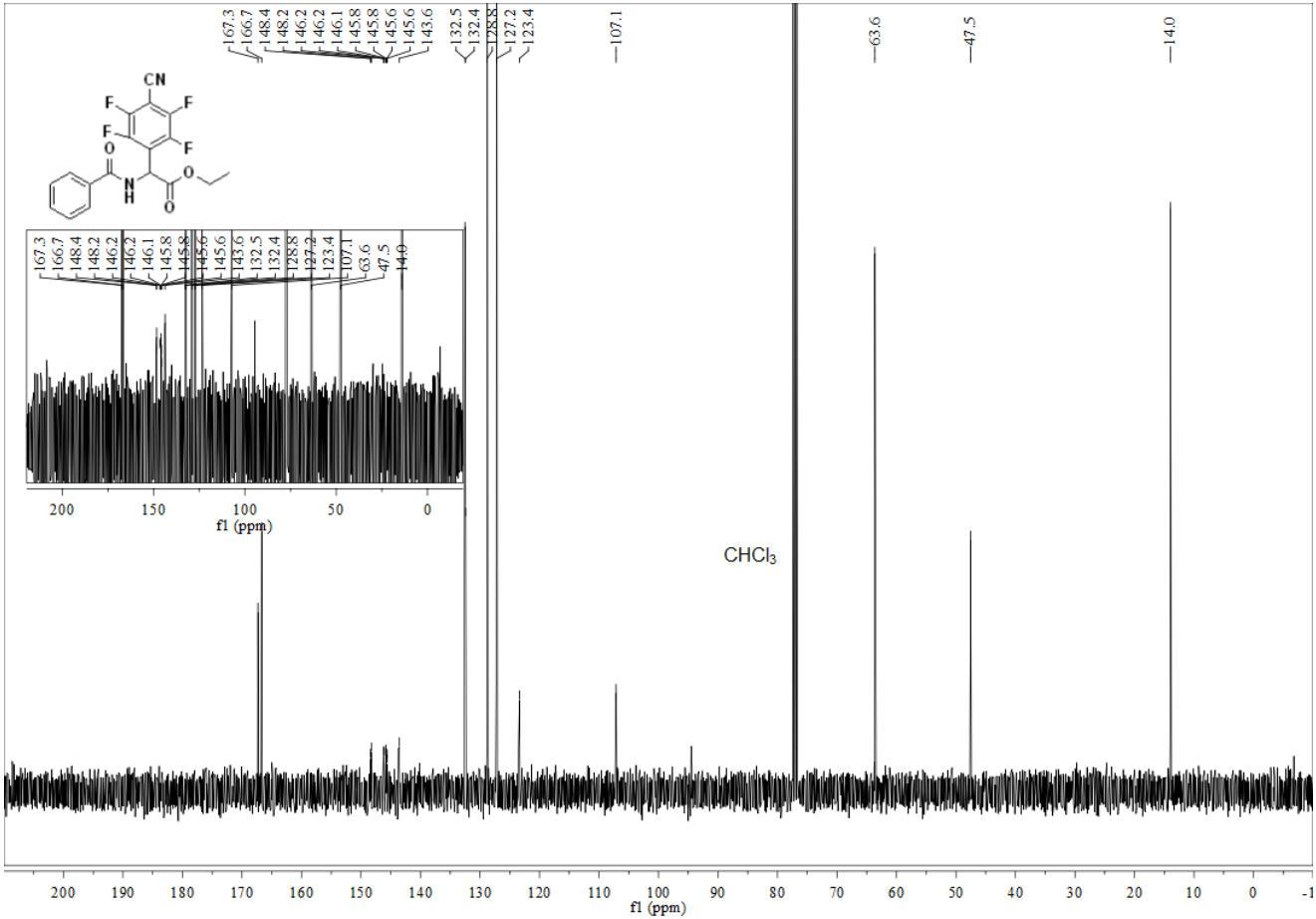


¹H NMR (400 MHz, Chloroform-*d*) **2i**

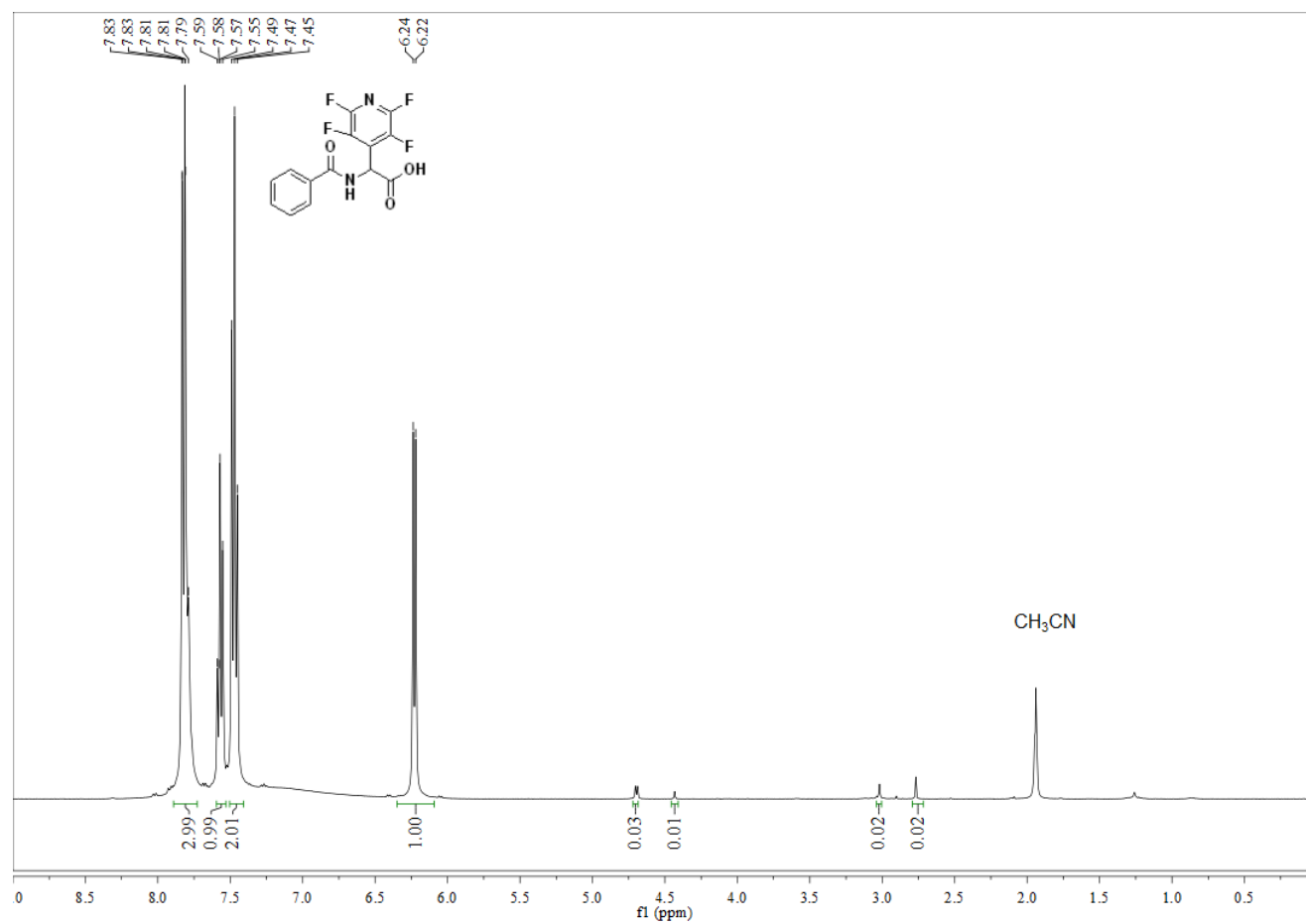


¹⁹F NMR (376 MHz, Chloroform-*d*) **2i**

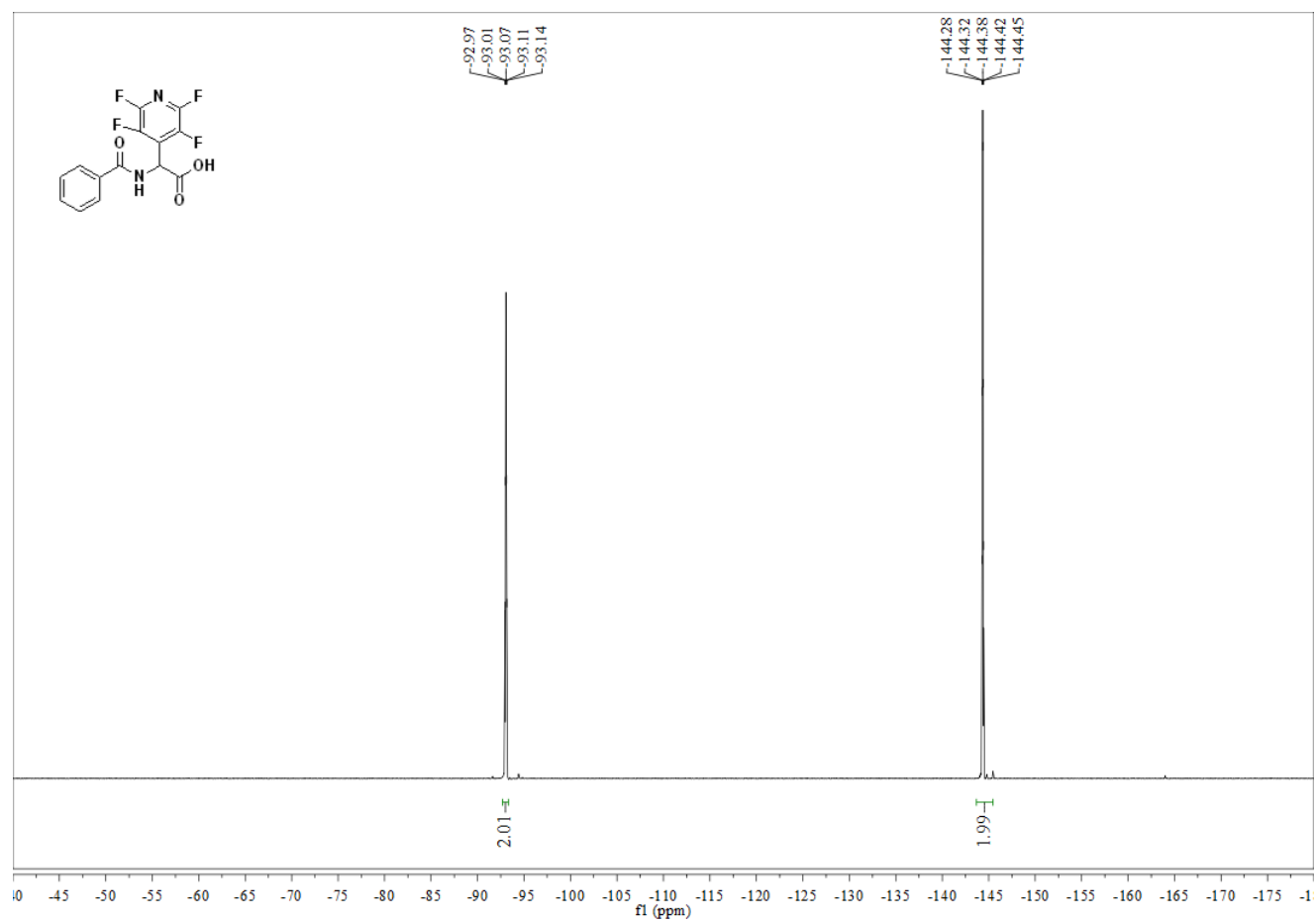


^{13}C NMR (101 MHz, Chloroform-*d*) **2i**

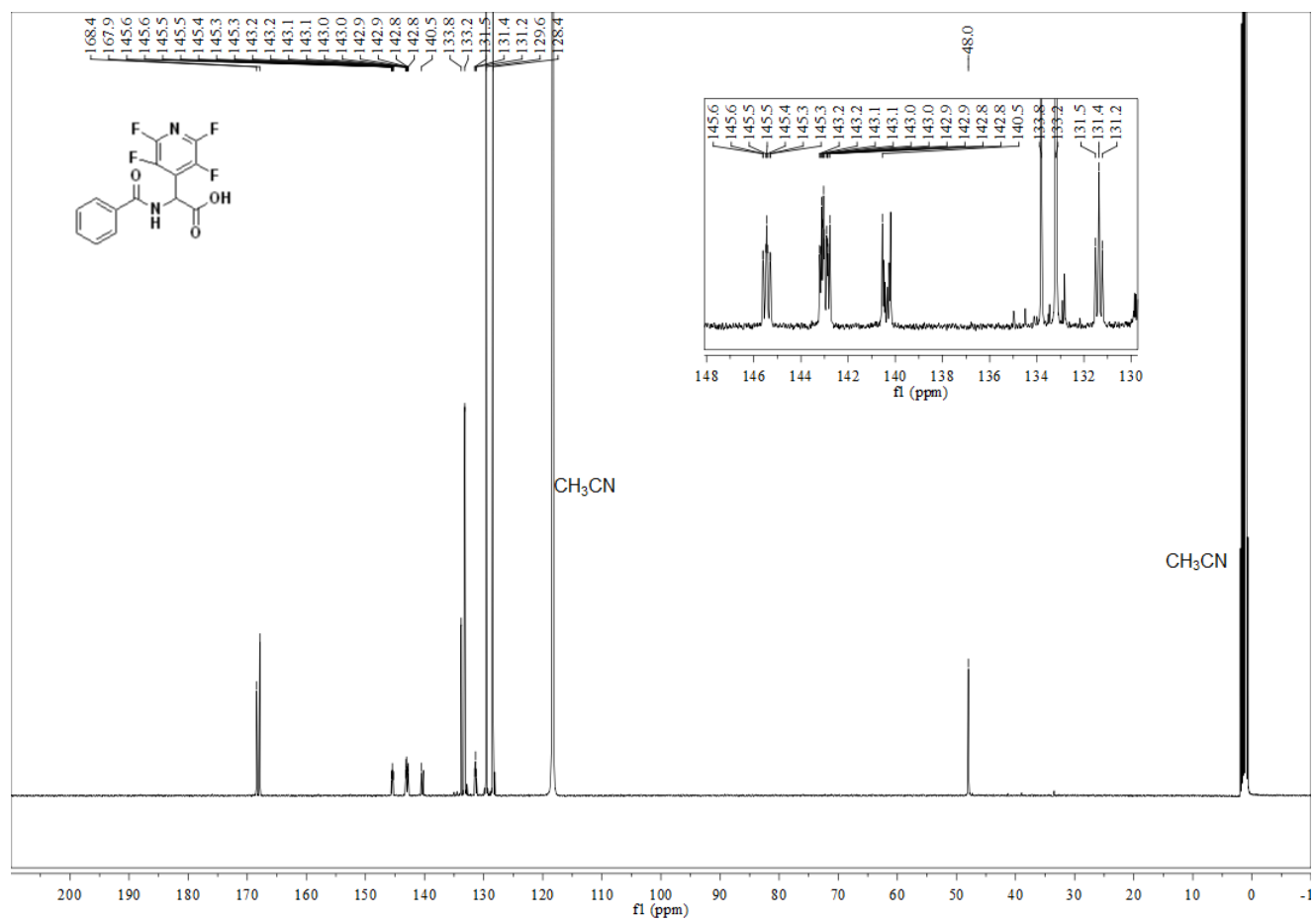
¹H NMR (400 MHz, Acetonitrile-*d*₃) **3a**



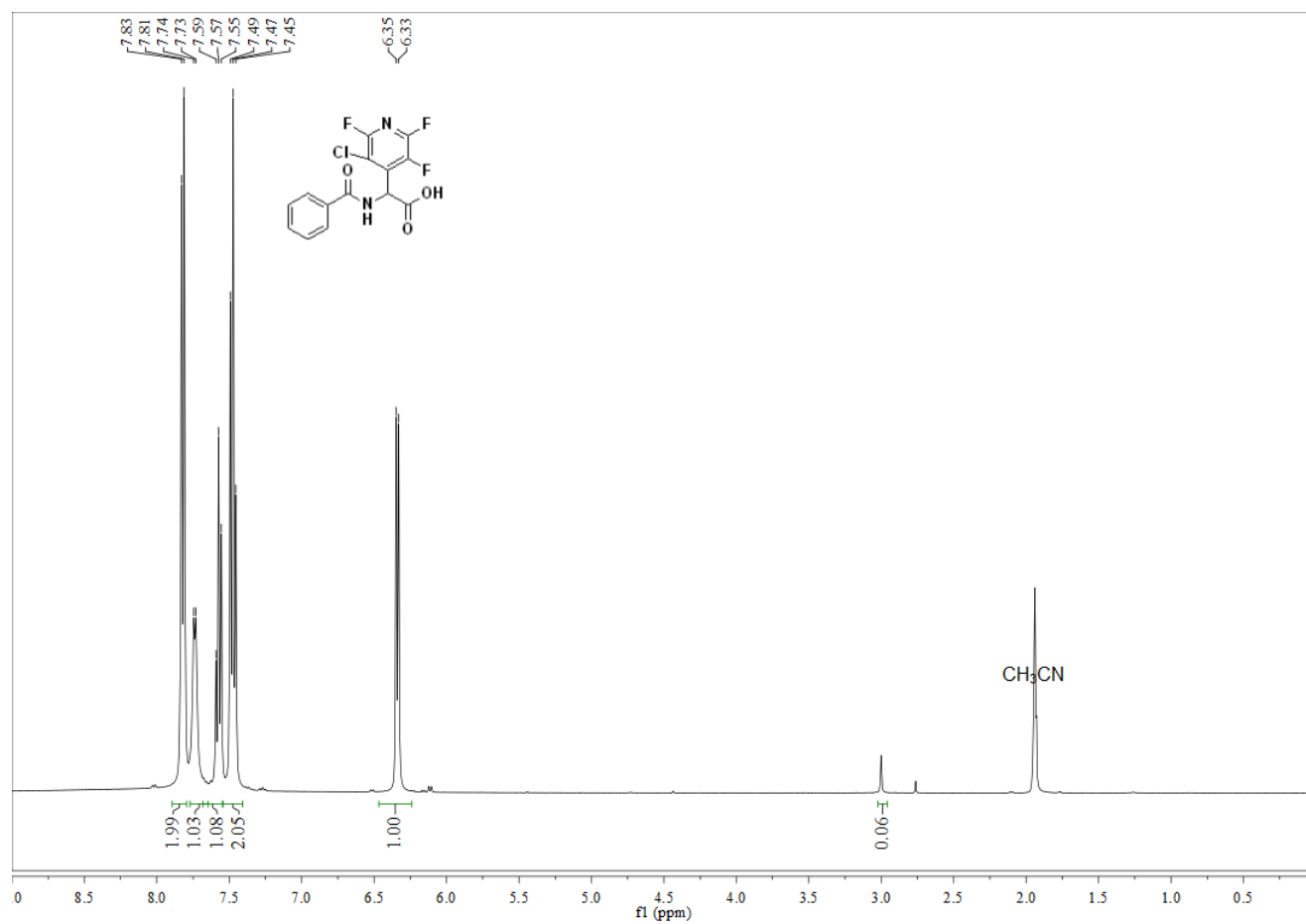
^{19}F NMR (376 MHz, Acetonitrile- d_3) **3a**



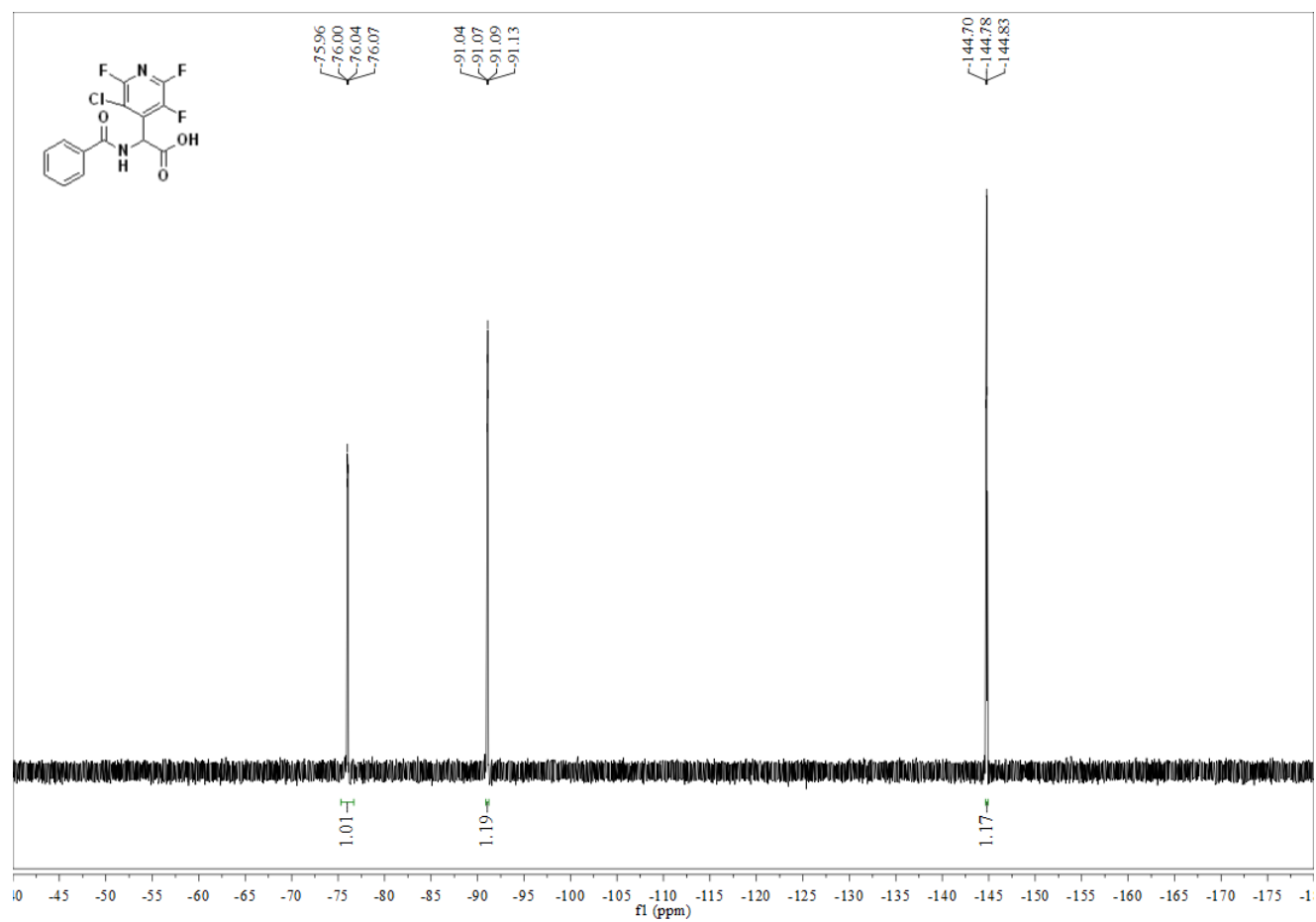
¹³C NMR (101 MHz, Acetonitrile-*d*₃) **3a**



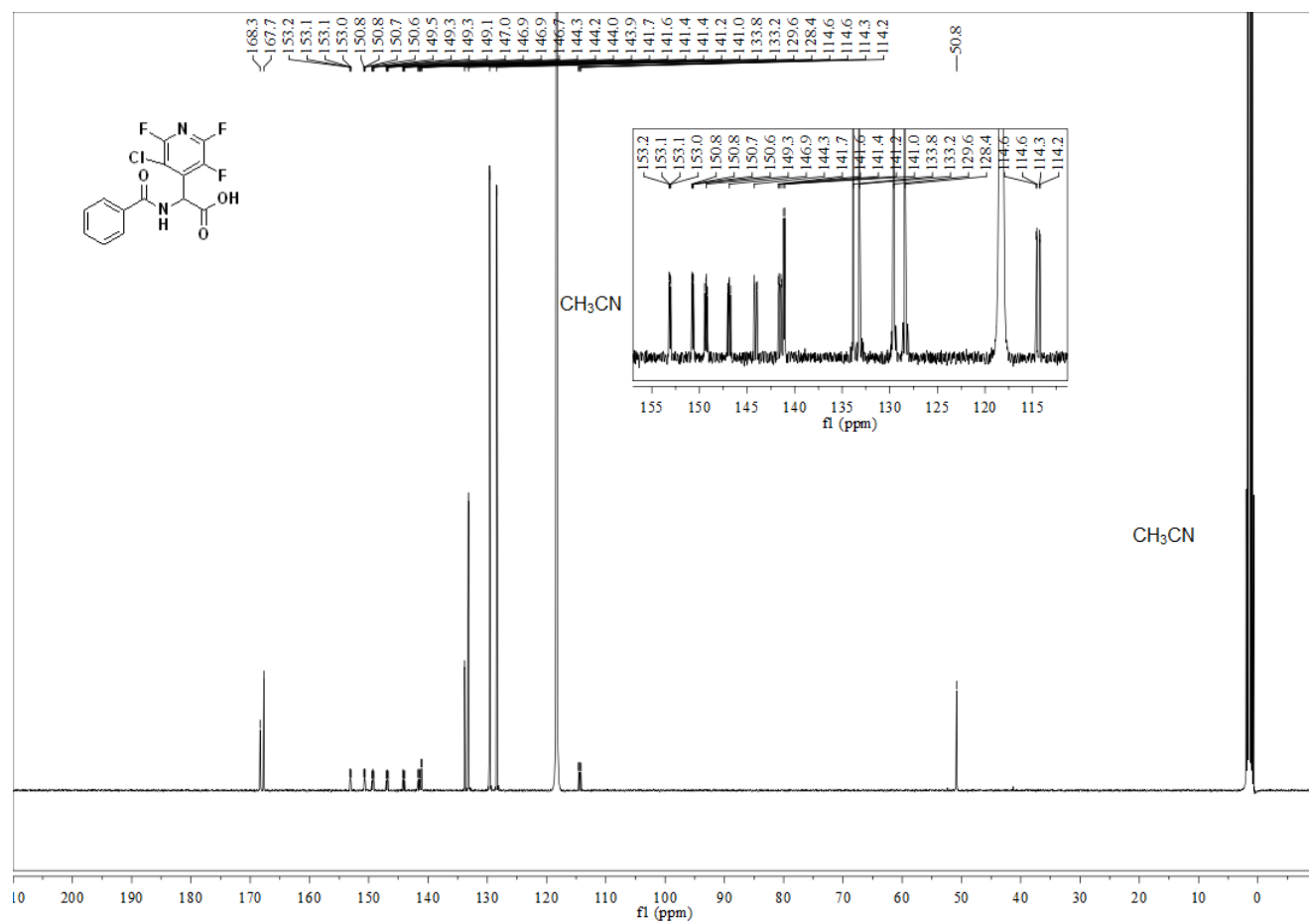
¹H NMR (400 MHz, Acetonitrile-*d*₃) **3b**



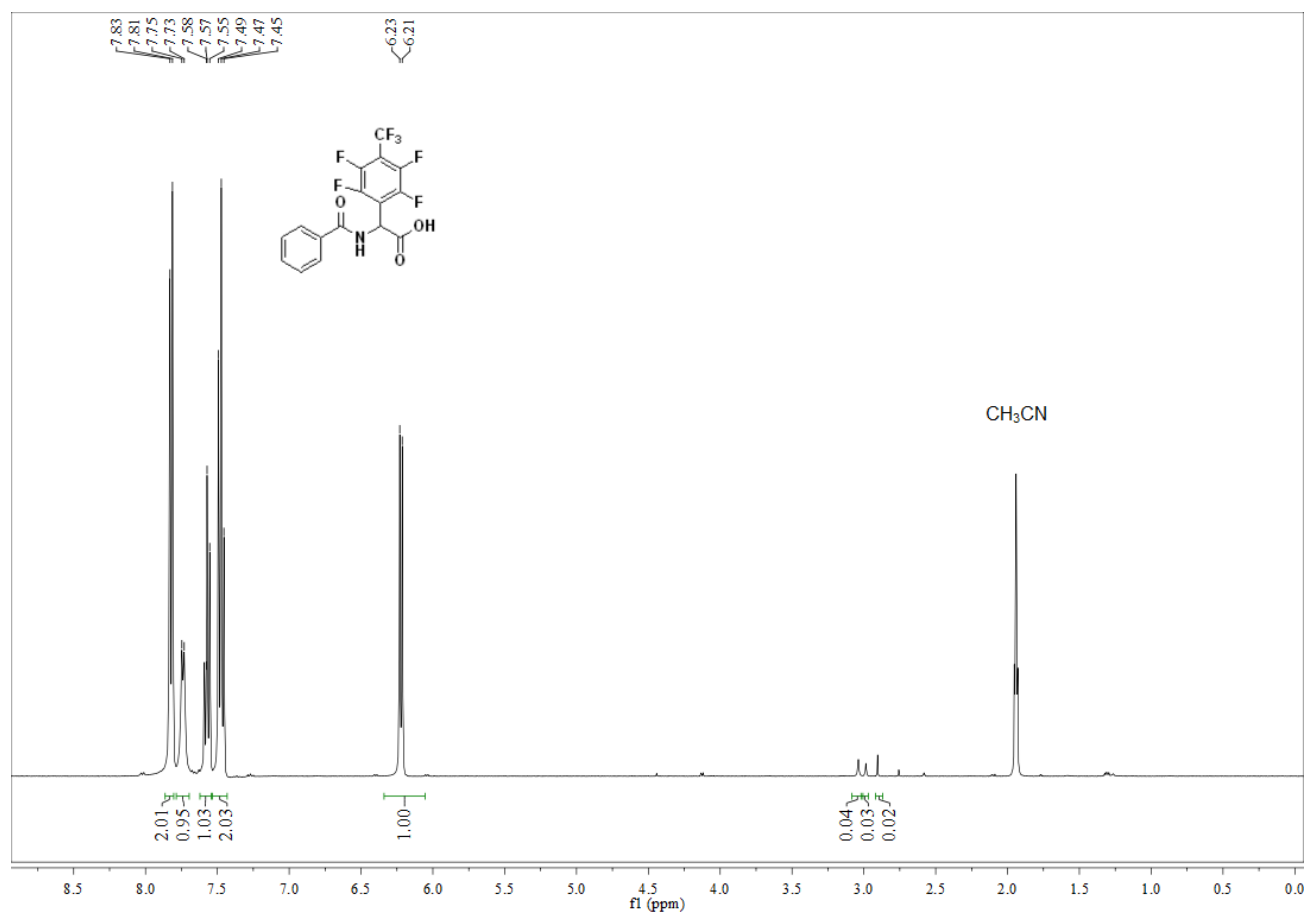
¹⁹F NMR (376 MHz, Acetonitrile-*d*₃) **3b**



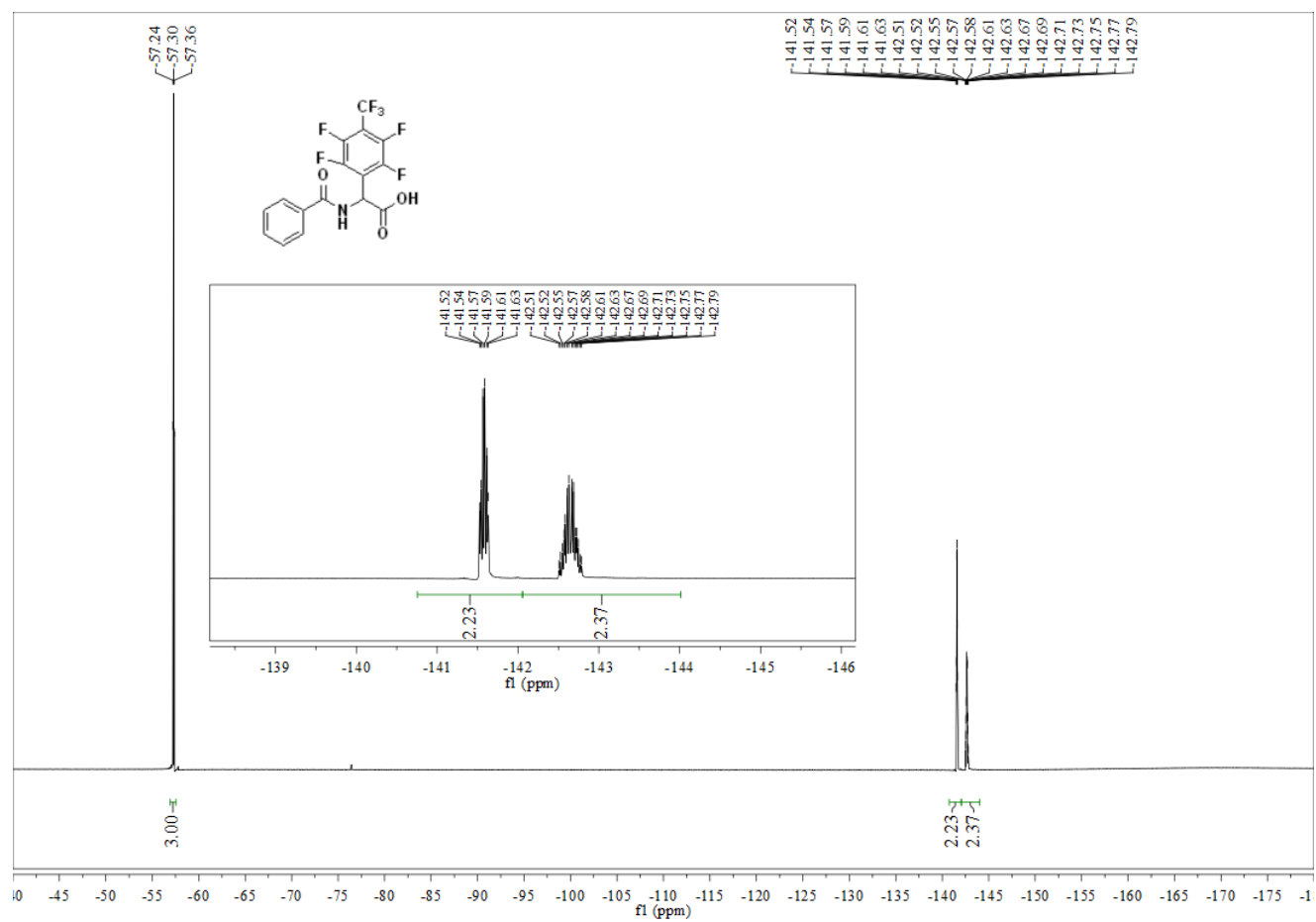
¹³C NMR (101 MHz, Acetonitrile-*d*₃) **3b**



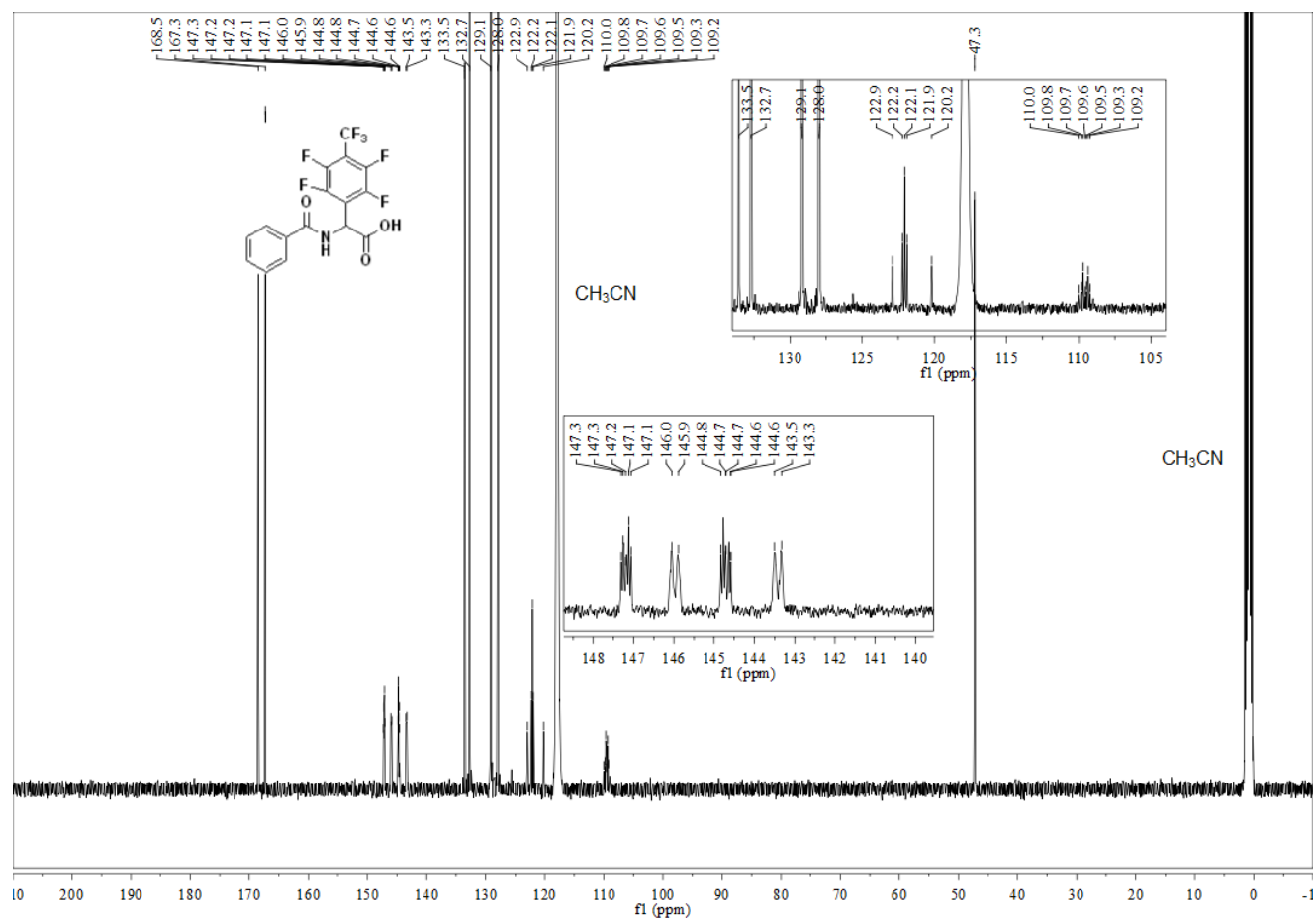
¹H NMR (400 MHz, Acetonitrile-*d*₃) **3c**



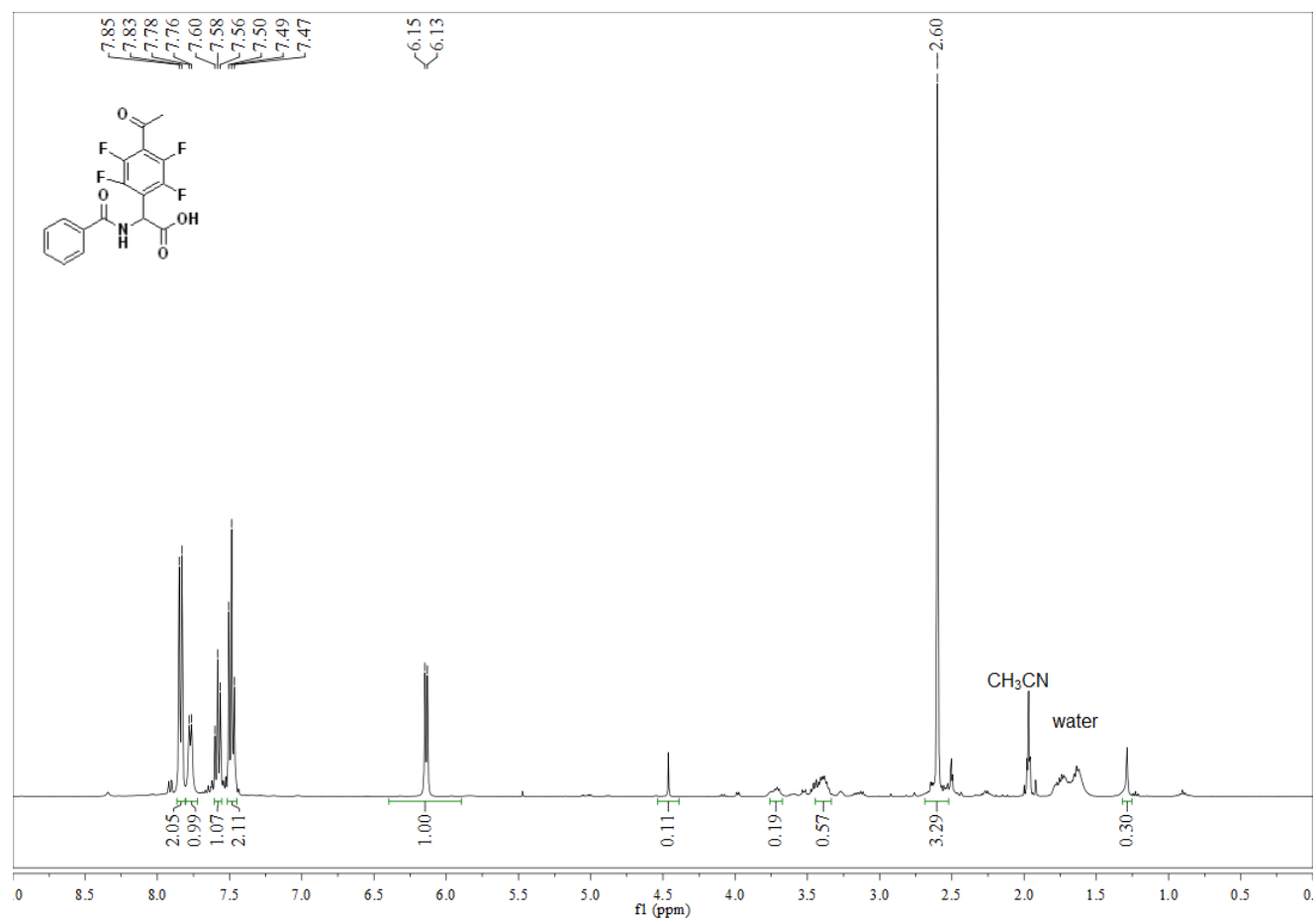
¹⁹F NMR (376 MHz, Acetonitrile-*d*₃) **3c**



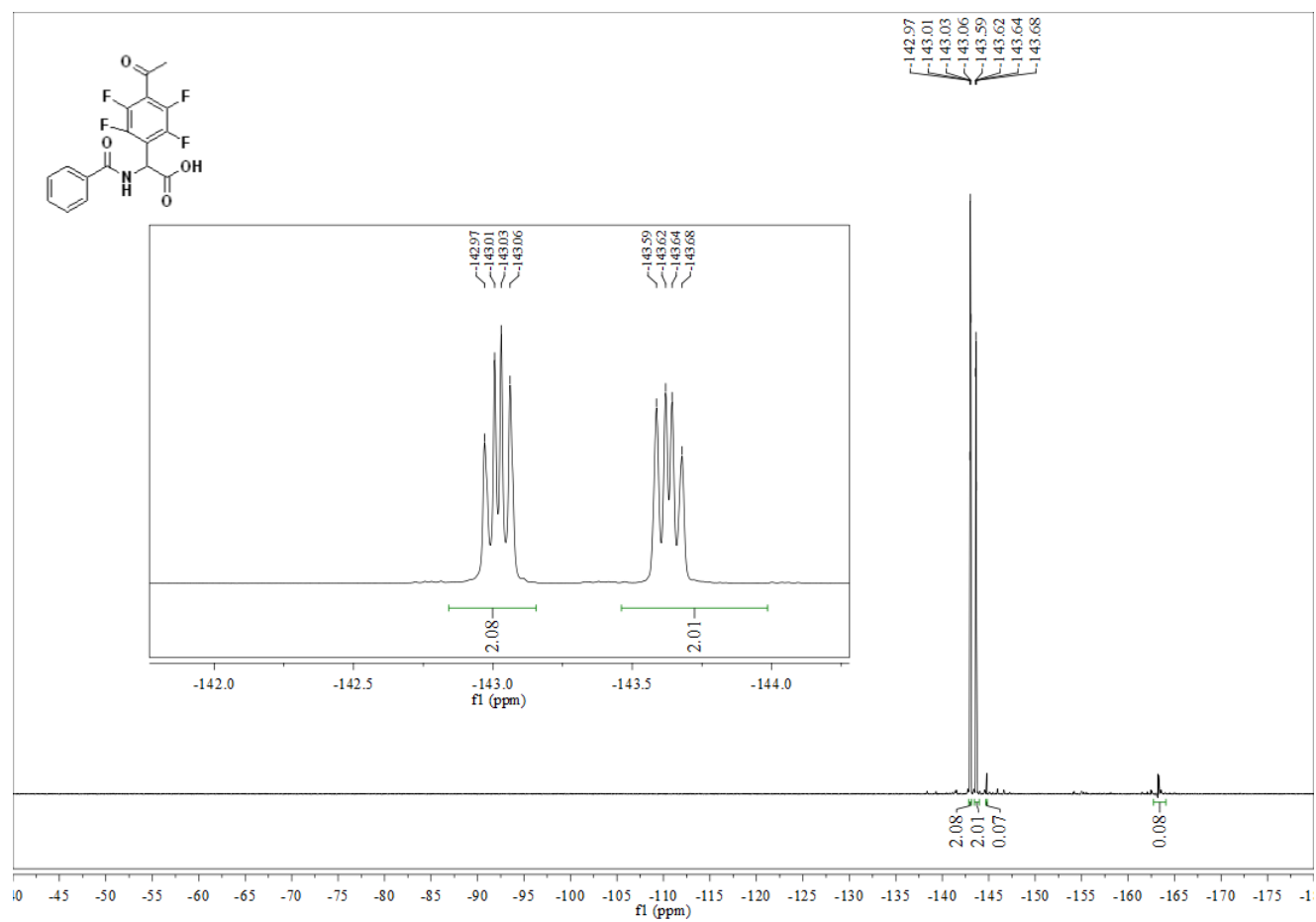
¹³C NMR (101 MHz, Acetonitrile-*d*₃) **3c**



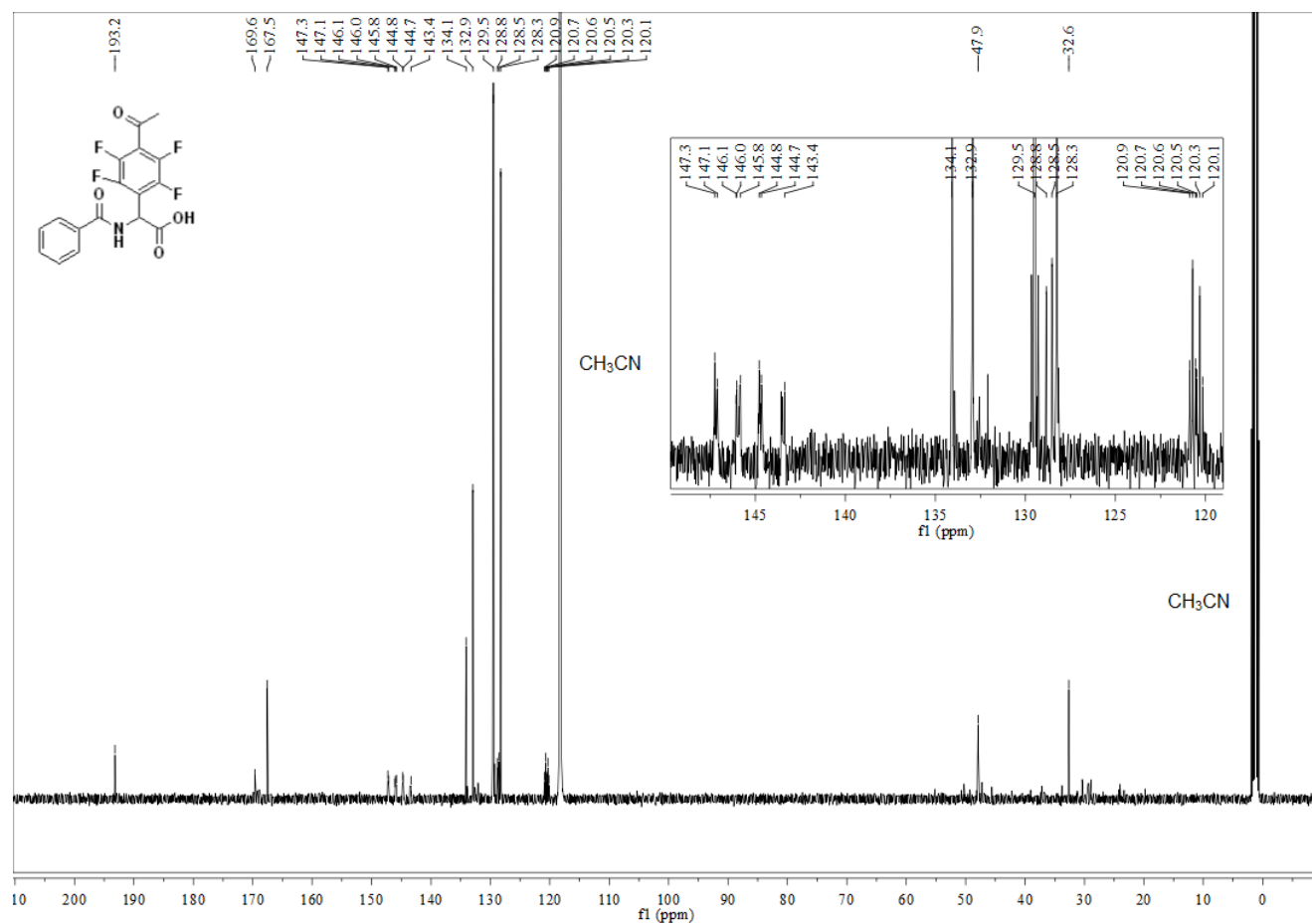
¹H NMR (400 MHz, Acetonitrile-*d*₃) **3d**



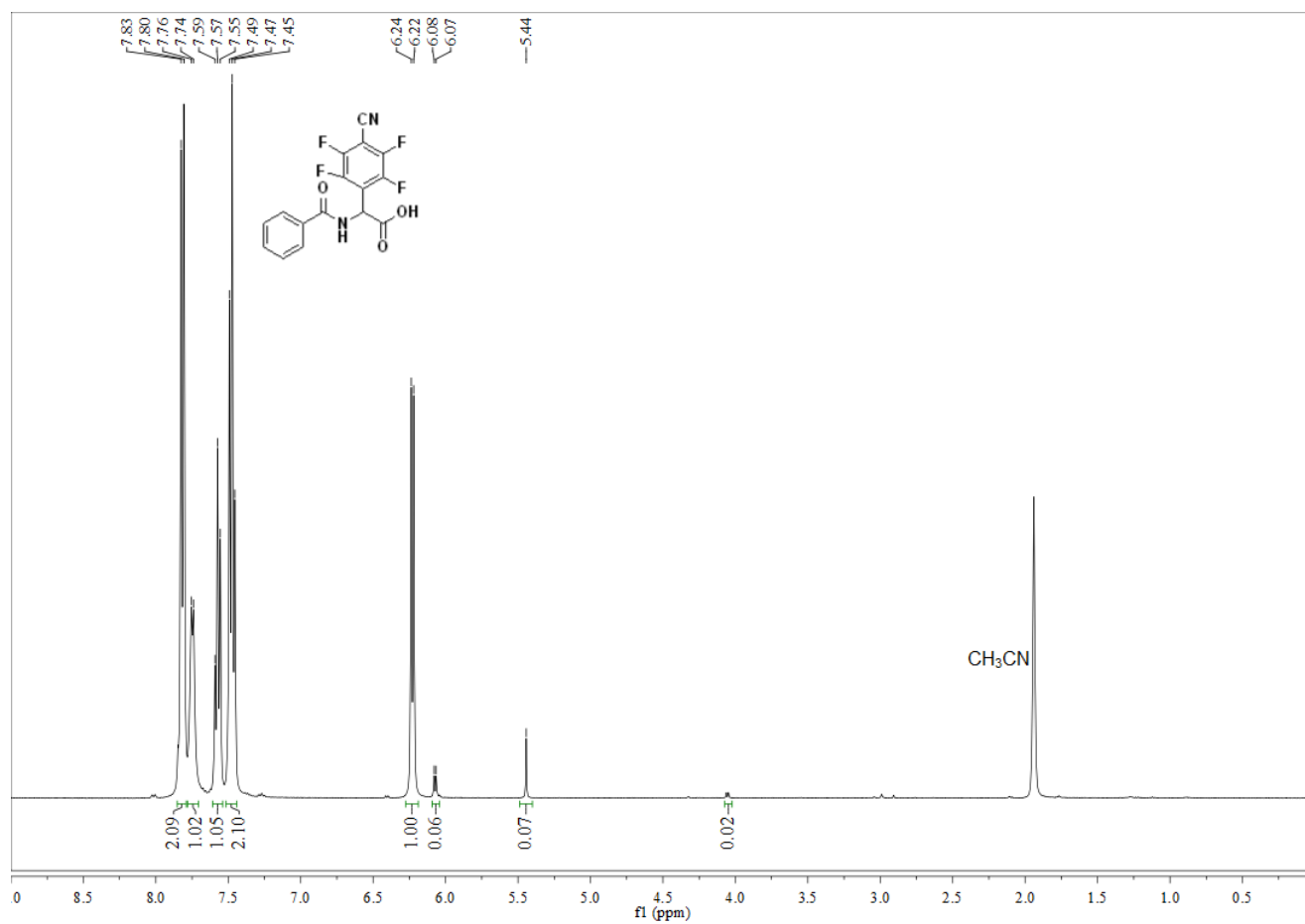
¹⁹F NMR (376 MHz, Acetonitrile-*d*₃) **3d**



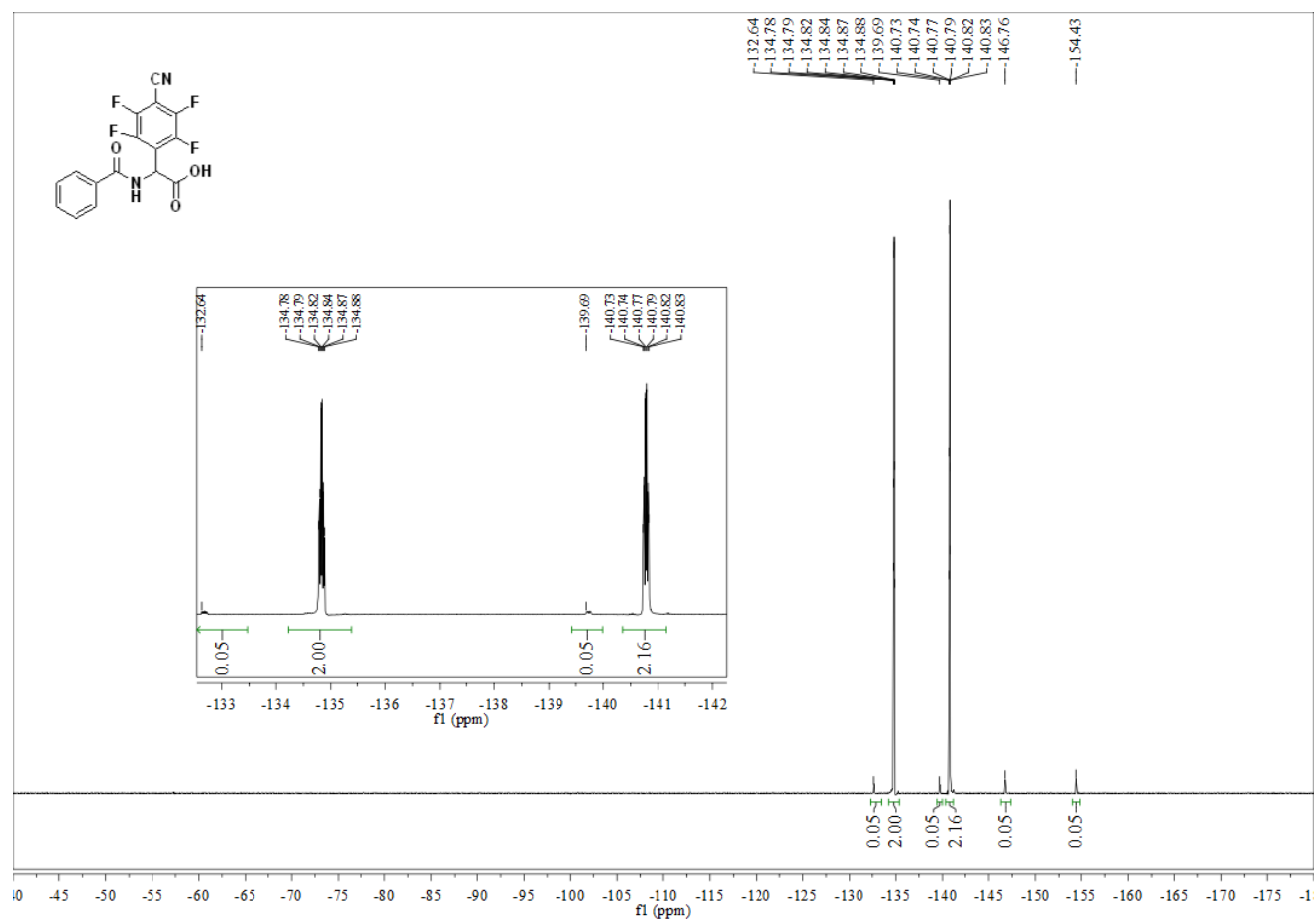
^{13}C NMR (101 MHz, Acetonitrile- d_3) **3d**



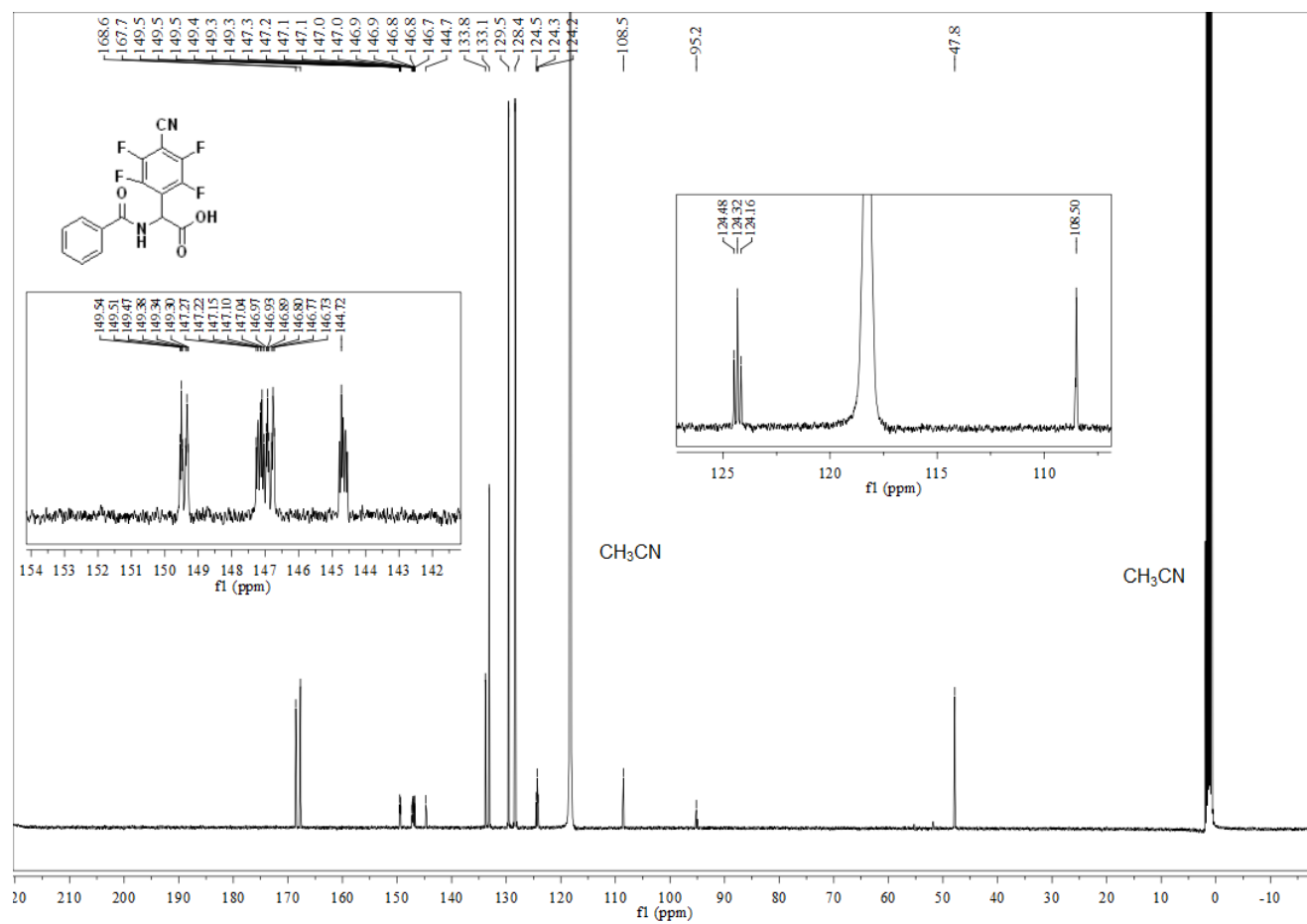
¹H NMR (400 MHz, Acetonitrile-*d*₃) **3e**



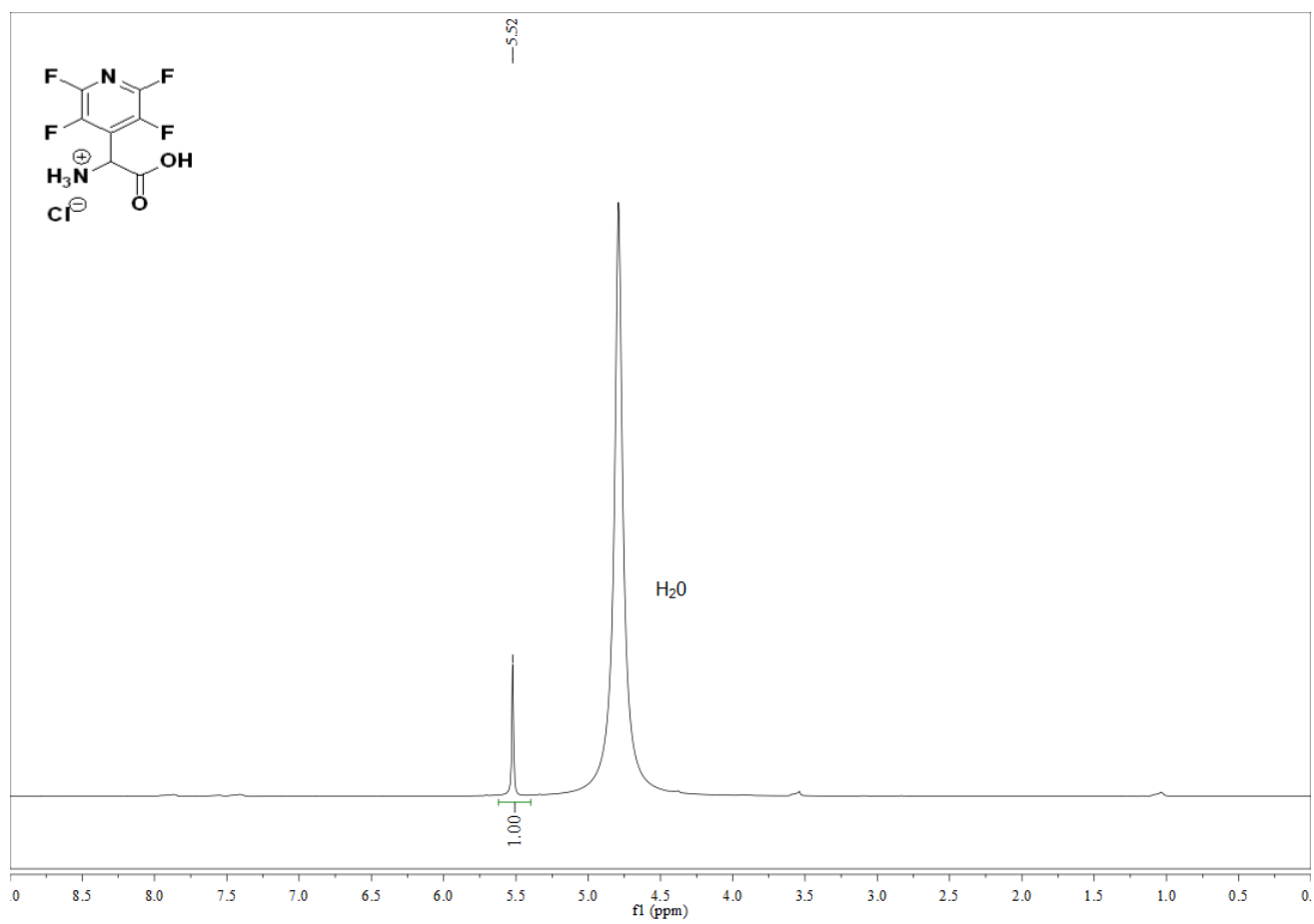
¹⁹F NMR (376 MHz, Acetonitrile-*d*₃) **3e**



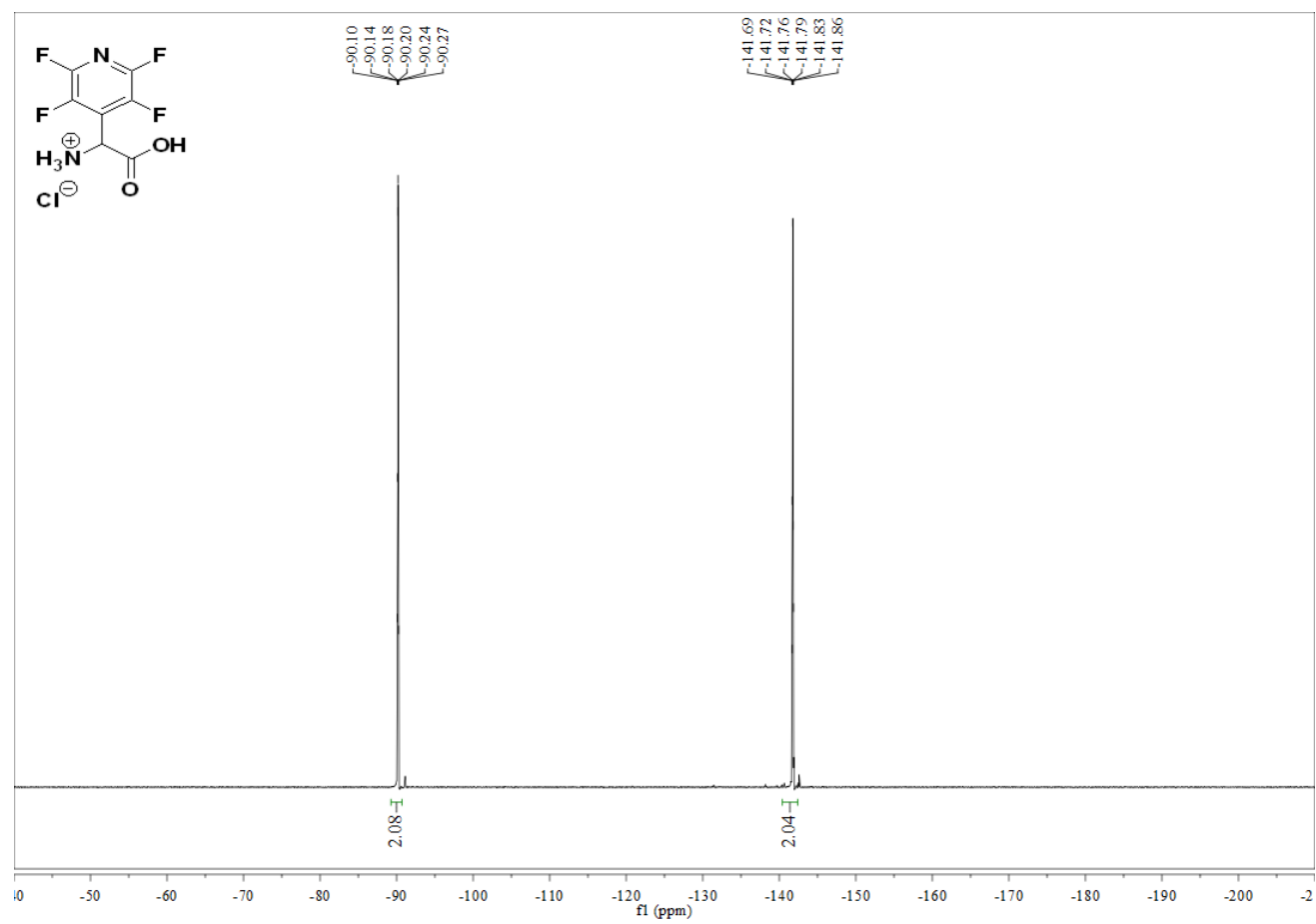
¹³C NMR (101 MHz, Acetonitrile-*d*₃) **3e**



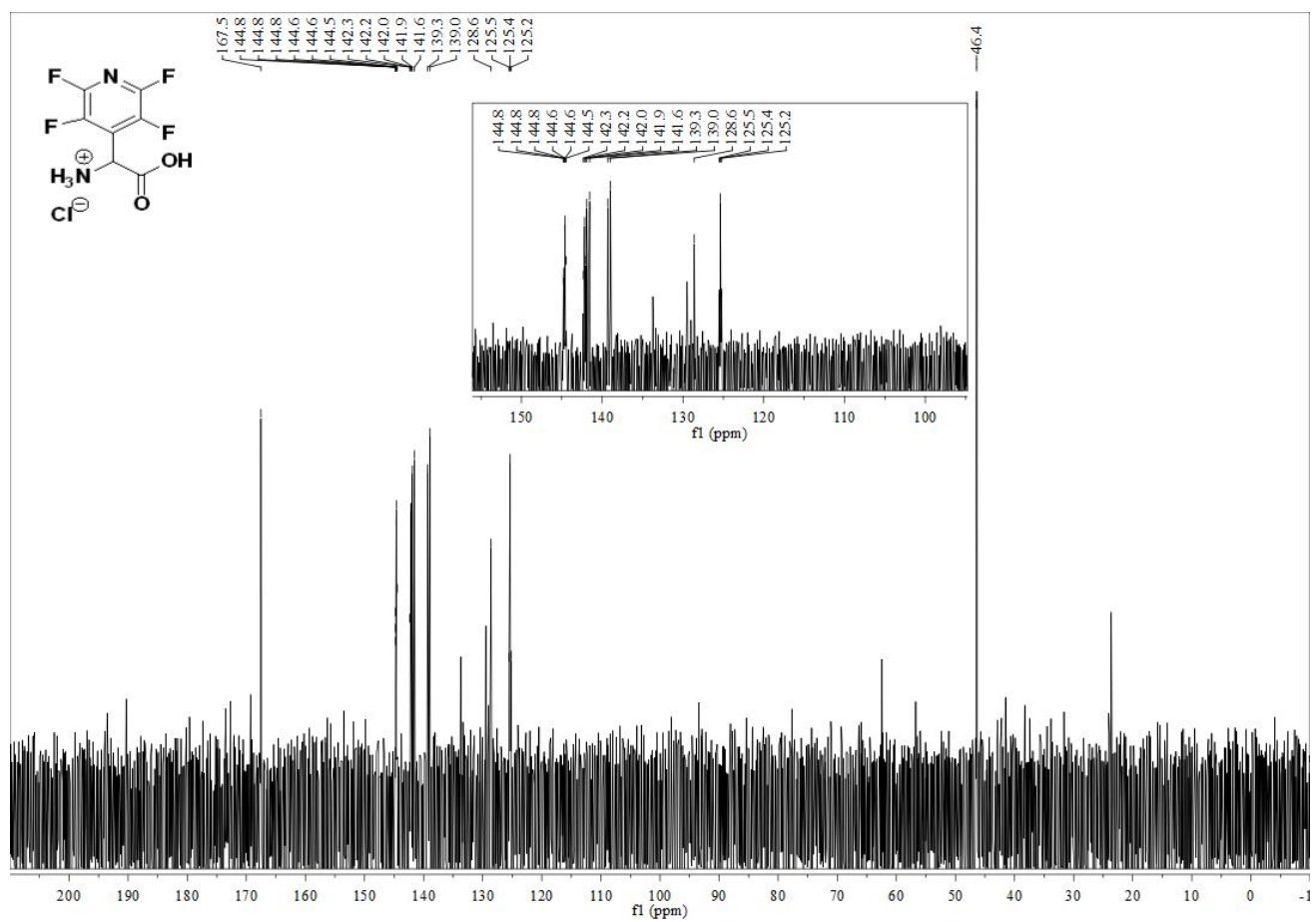
¹H NMR (400 MHz, D₂O) **4a**



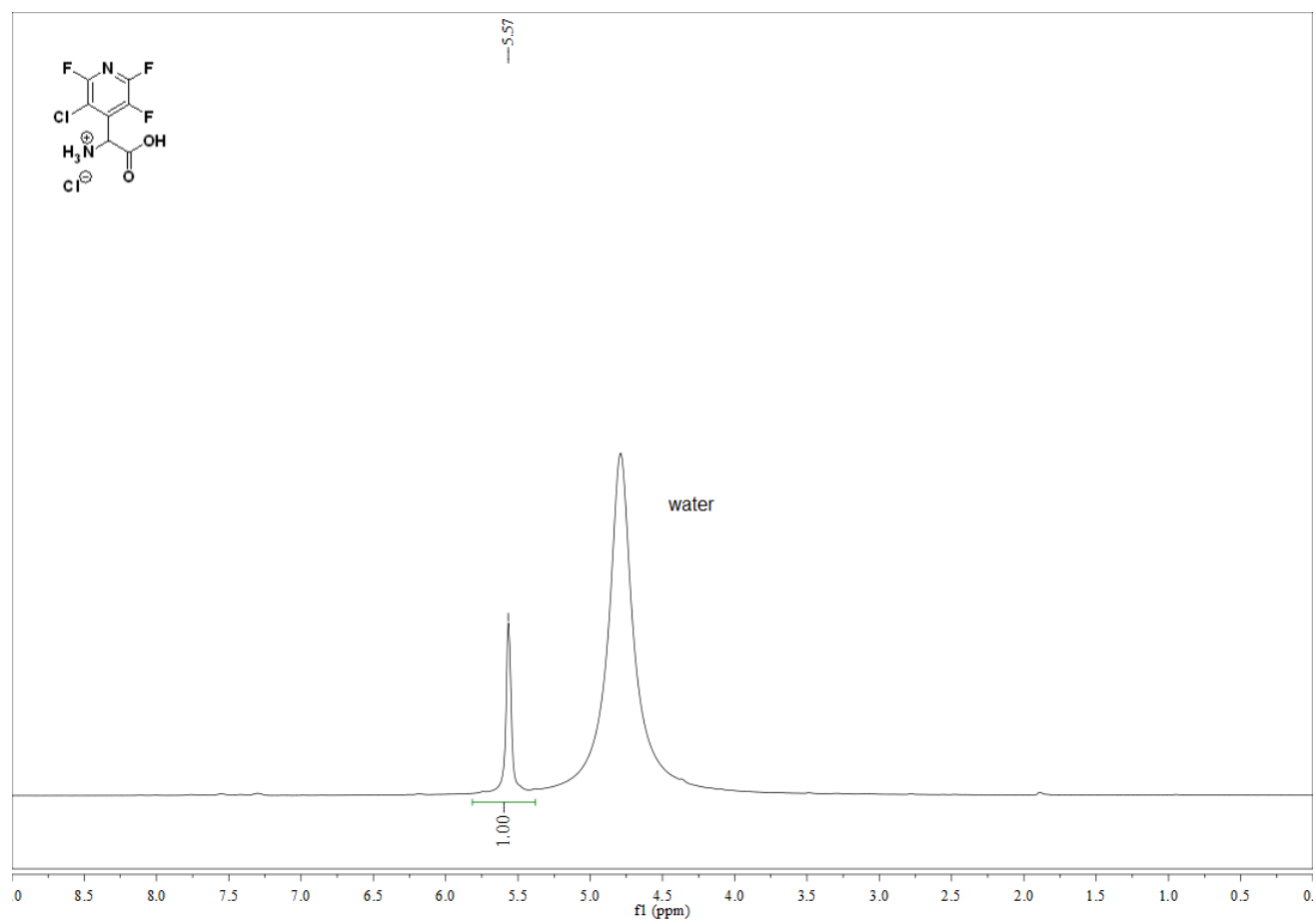
^{19}F NMR (376 MHz, D_2O) **4a**



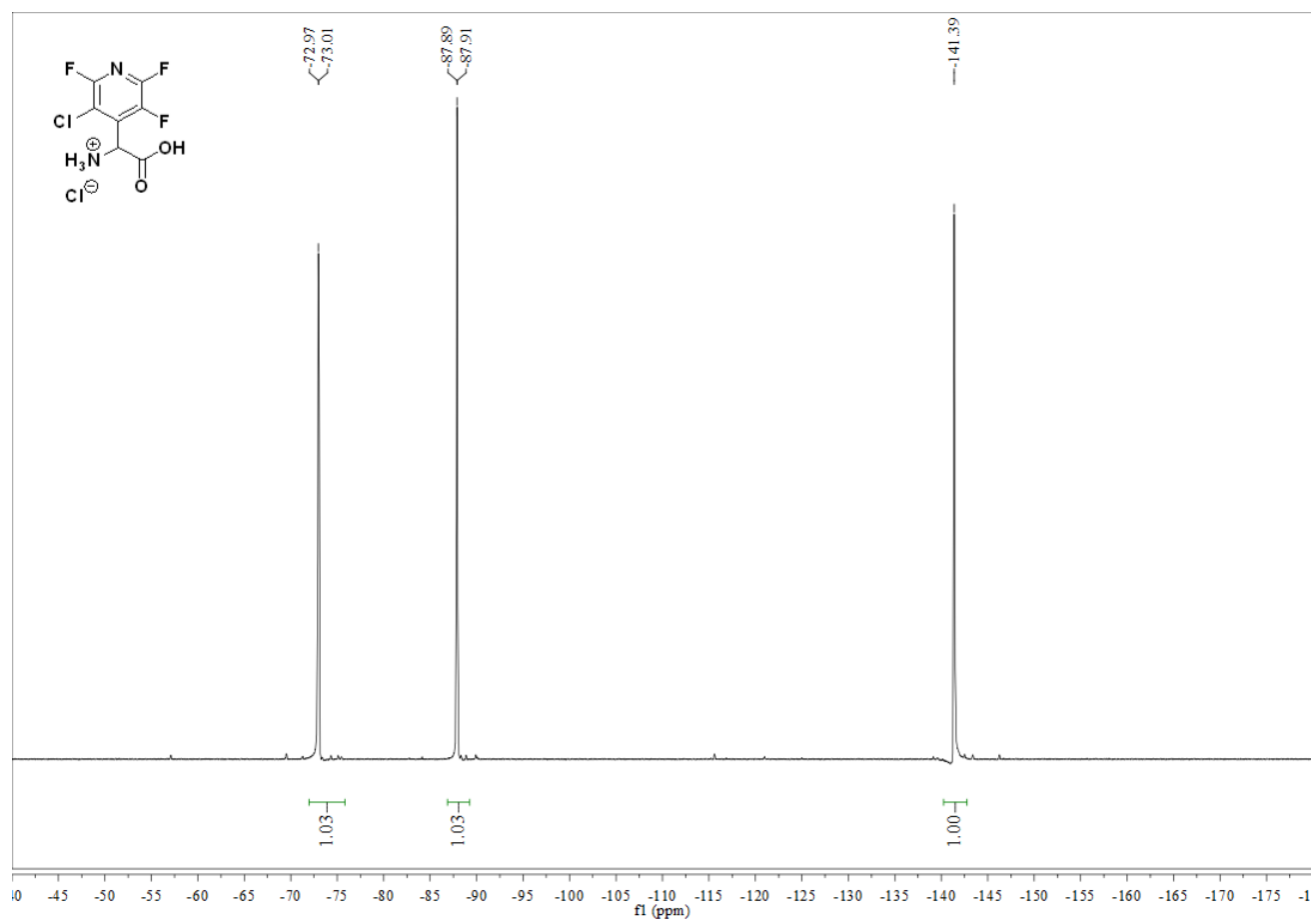
¹³C NMR (101 MHz, D₂O) **4a**



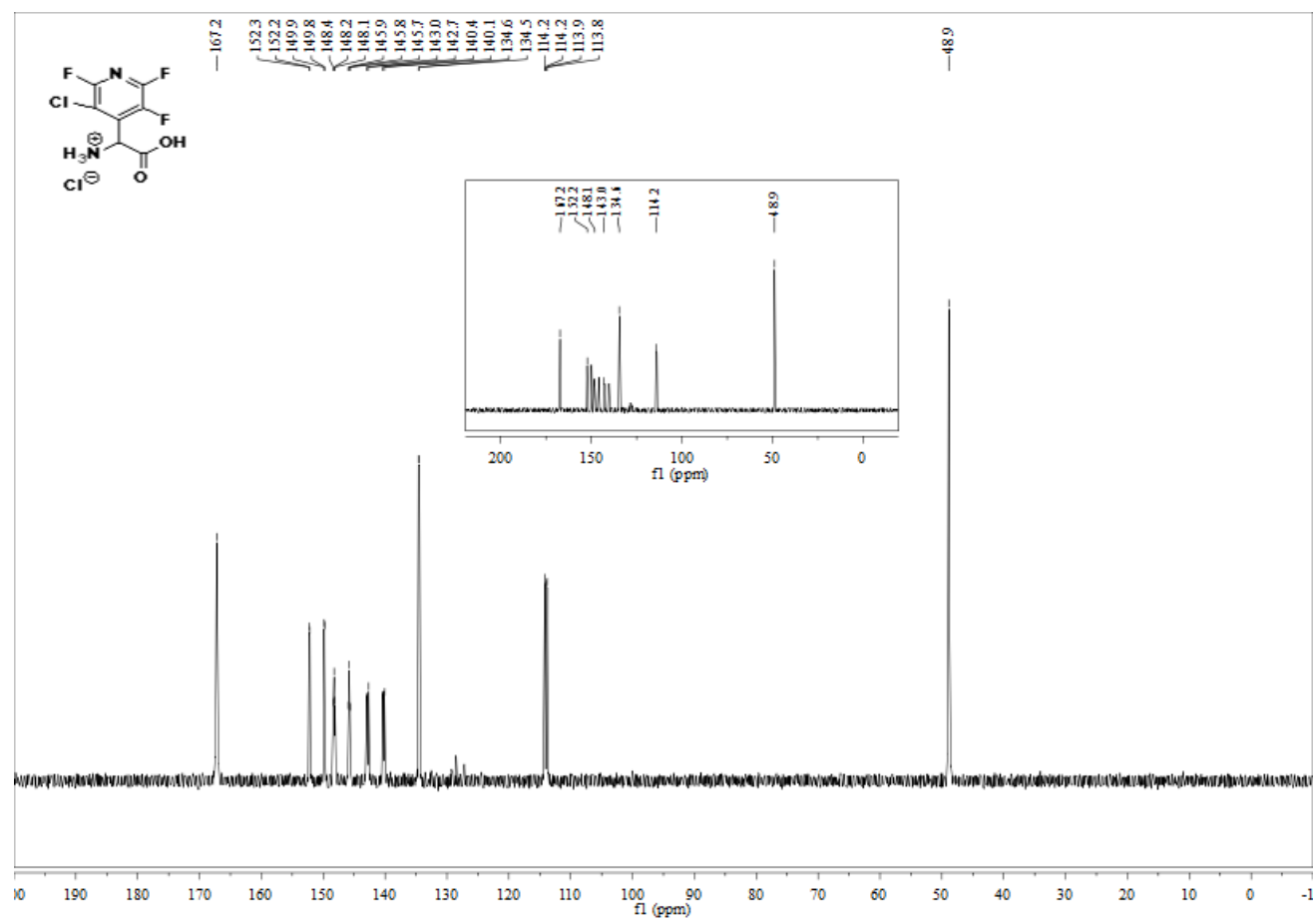
¹H NMR (400 MHz, D₂O) **4b**



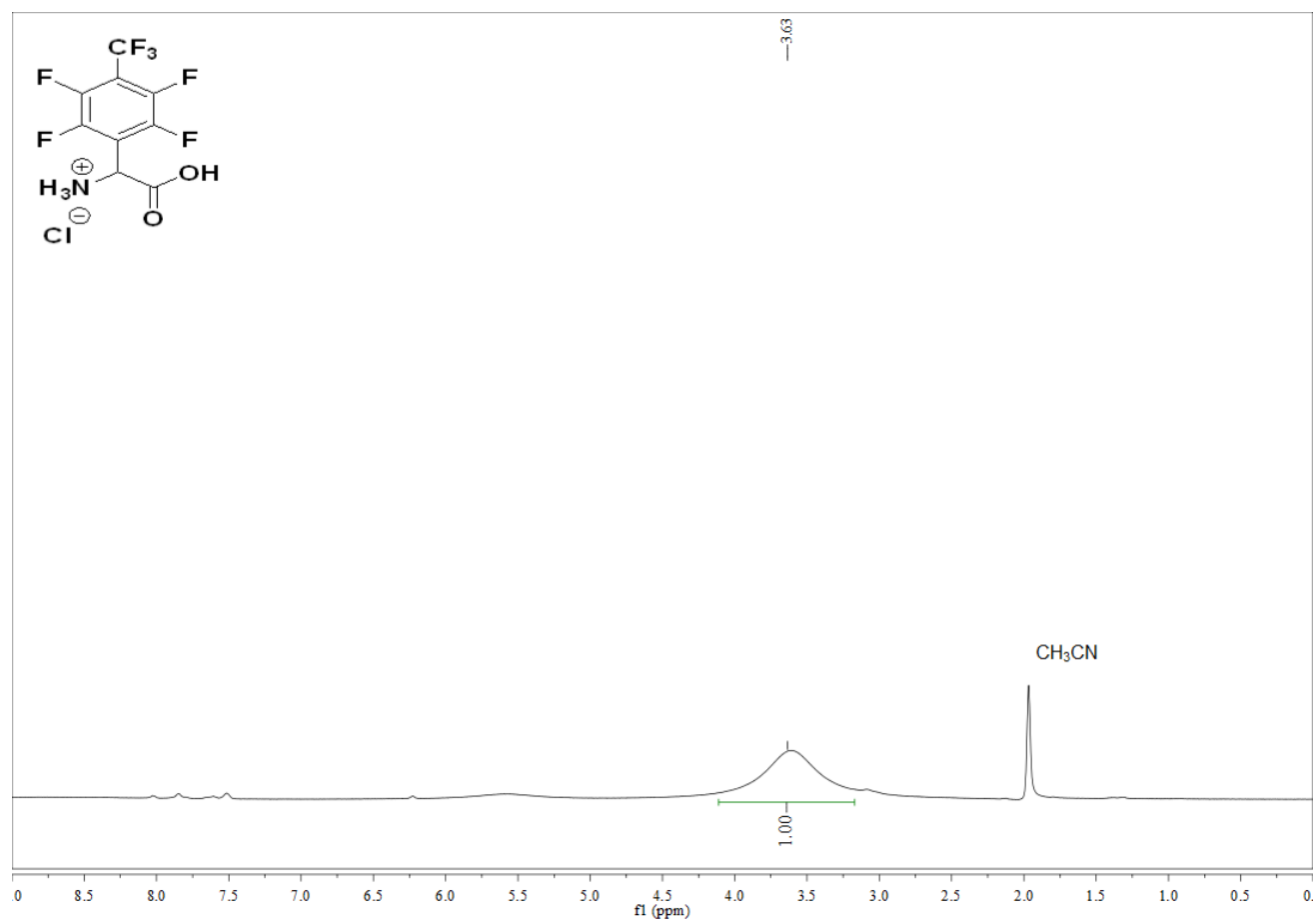
^{19}F NMR (376 MHz, D_2O) **4b**

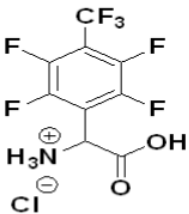


^{13}C NMR (101 MHz, D_2O) **4b**

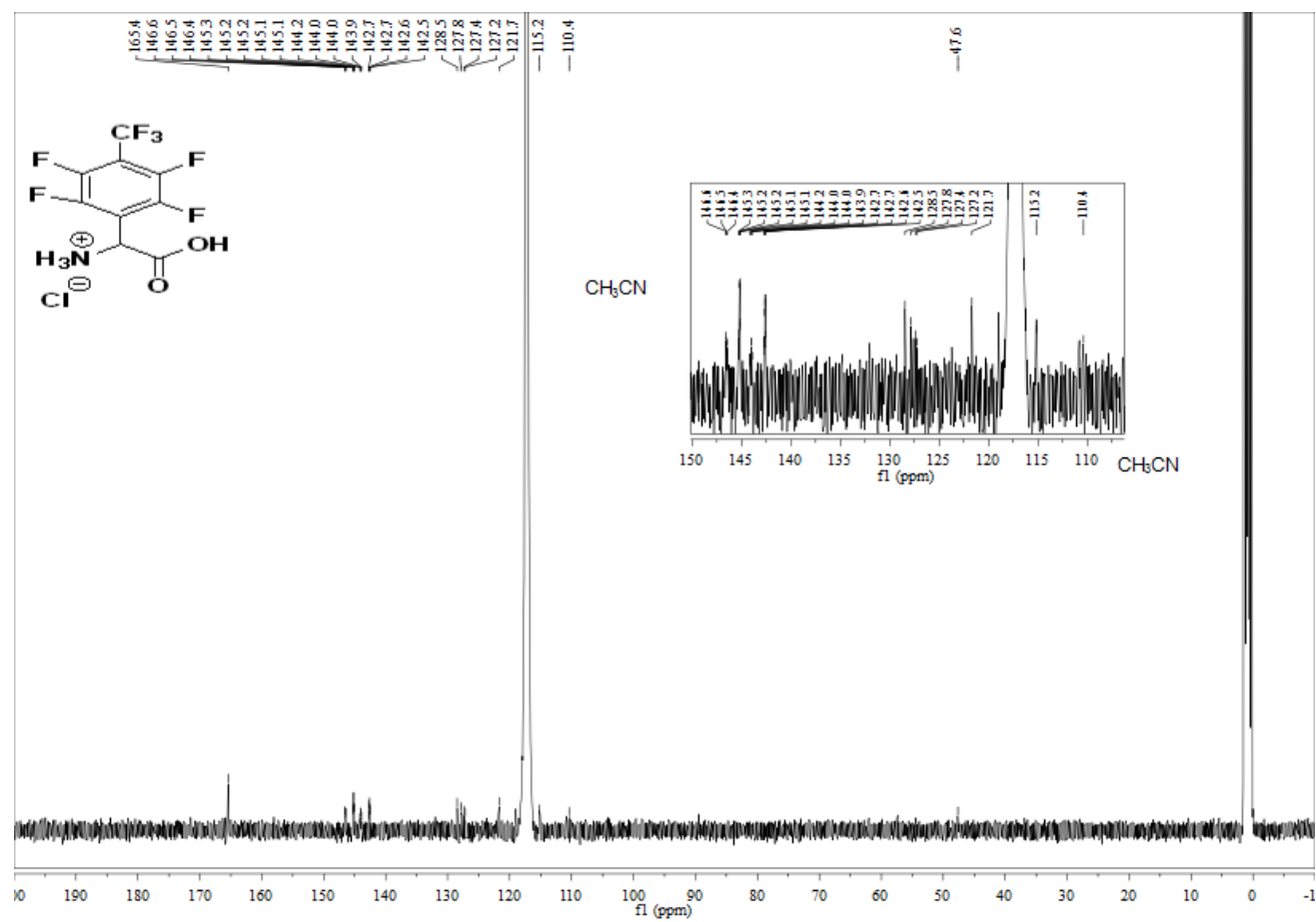


¹H NMR (400 MHz, Acetonitrile-*d*₃) **4c**

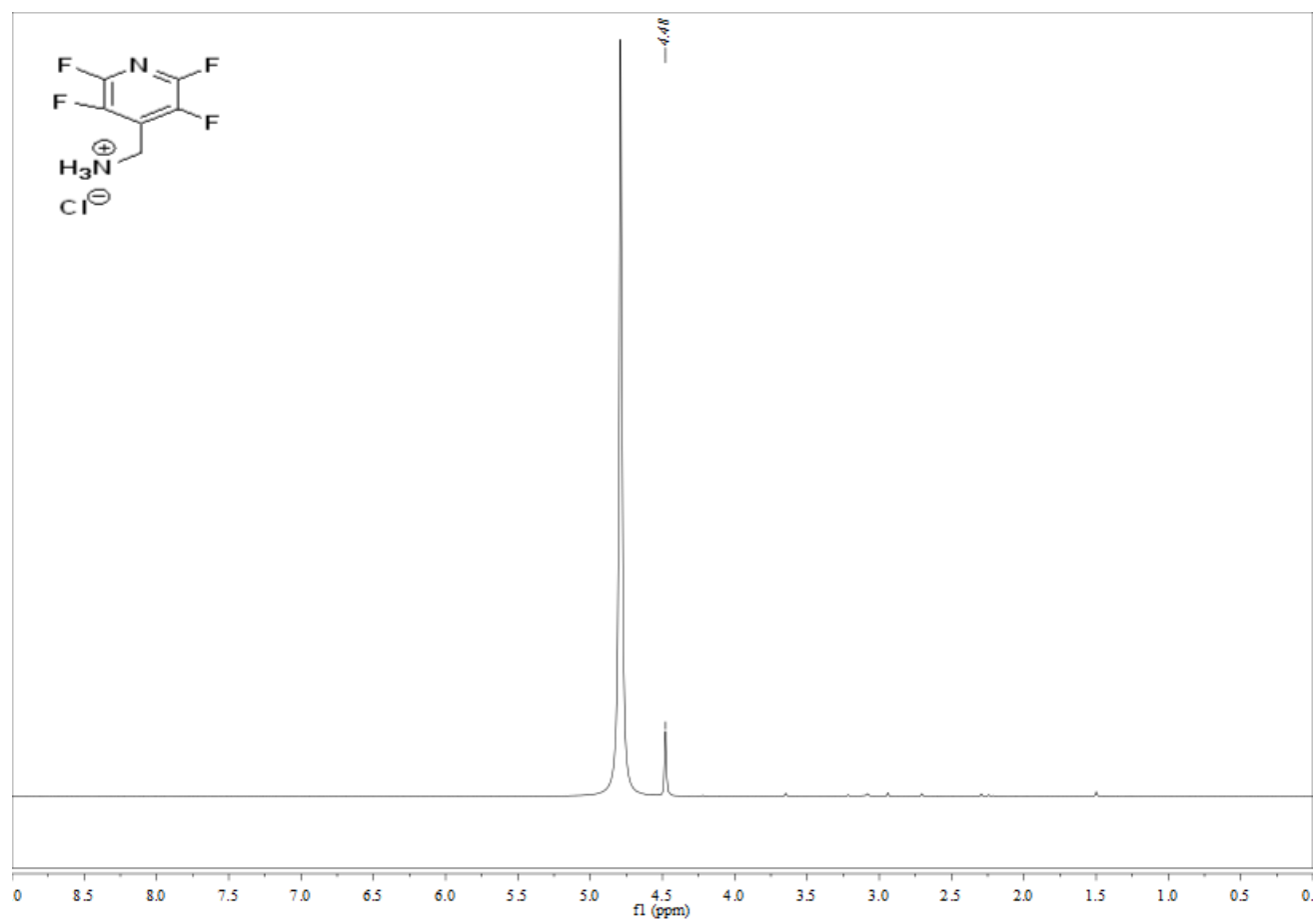


^{19}F NMR (376 MHz, Acetonitrile- d_3) **4c**

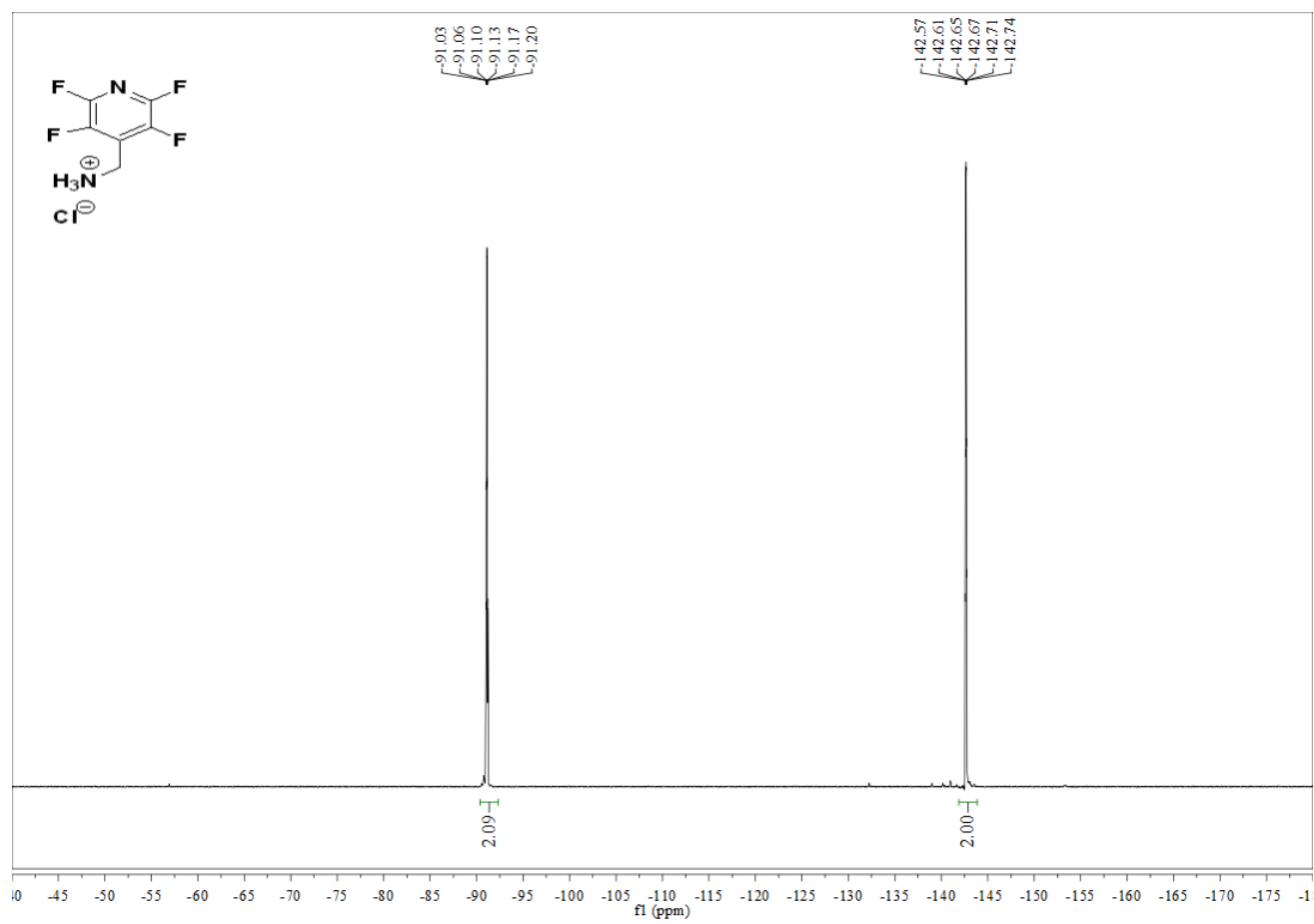
^{13}C NMR (101 MHz, Acetonitrile- d_3) **4c**



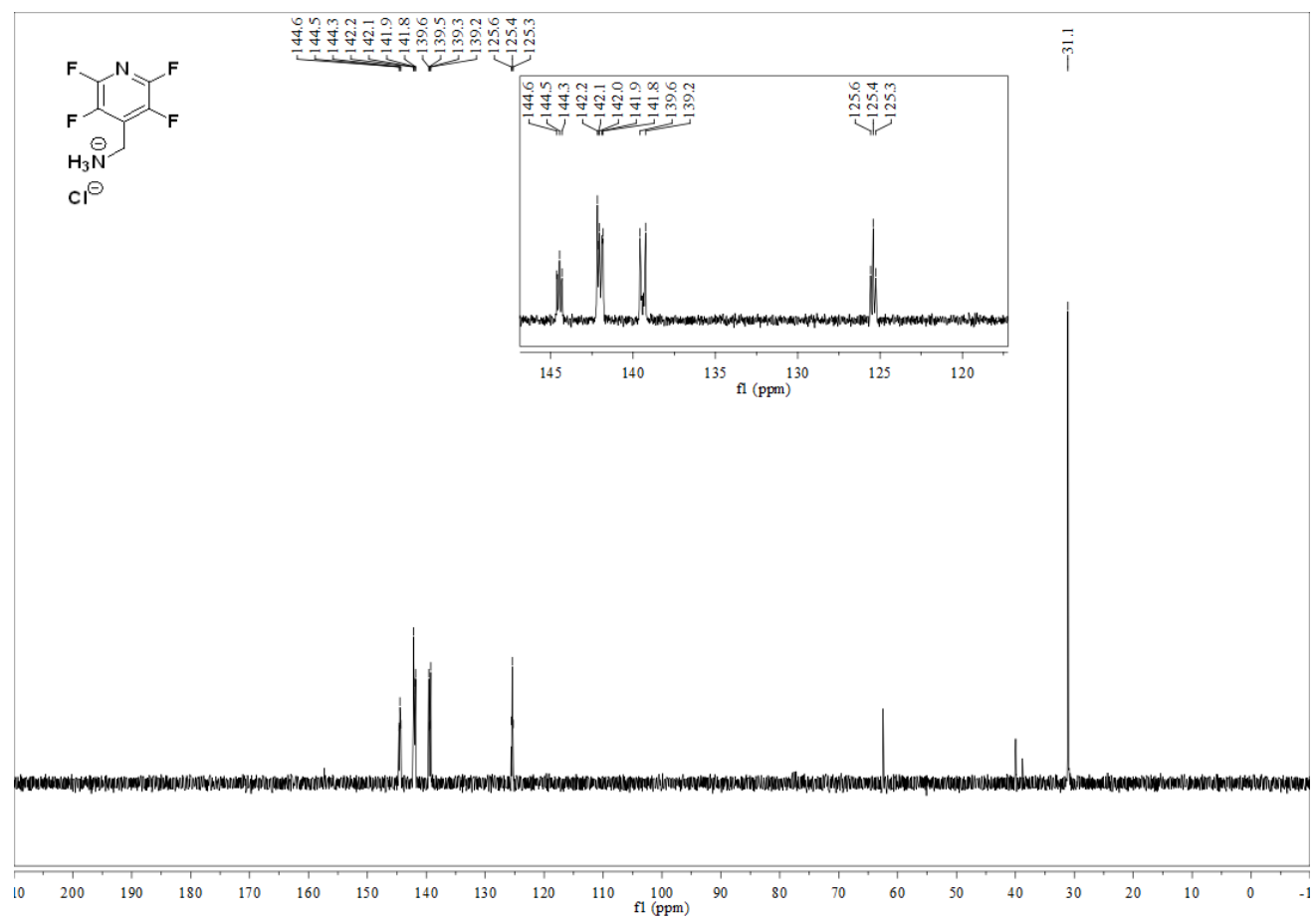
¹H NMR (400 MHz, D₂O) **5a**



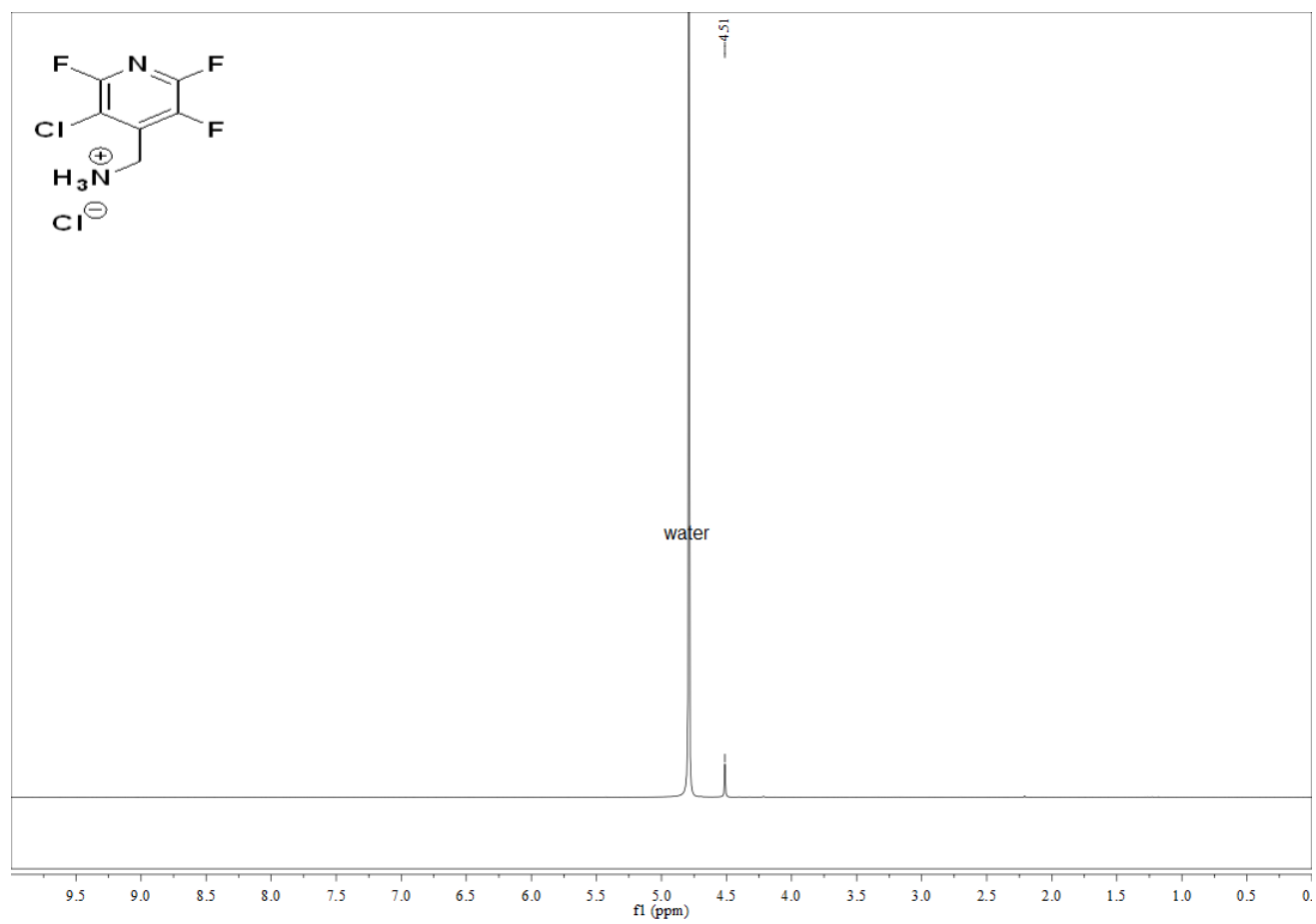
¹⁹F NMR (376 MHz, D₂O) **5a**



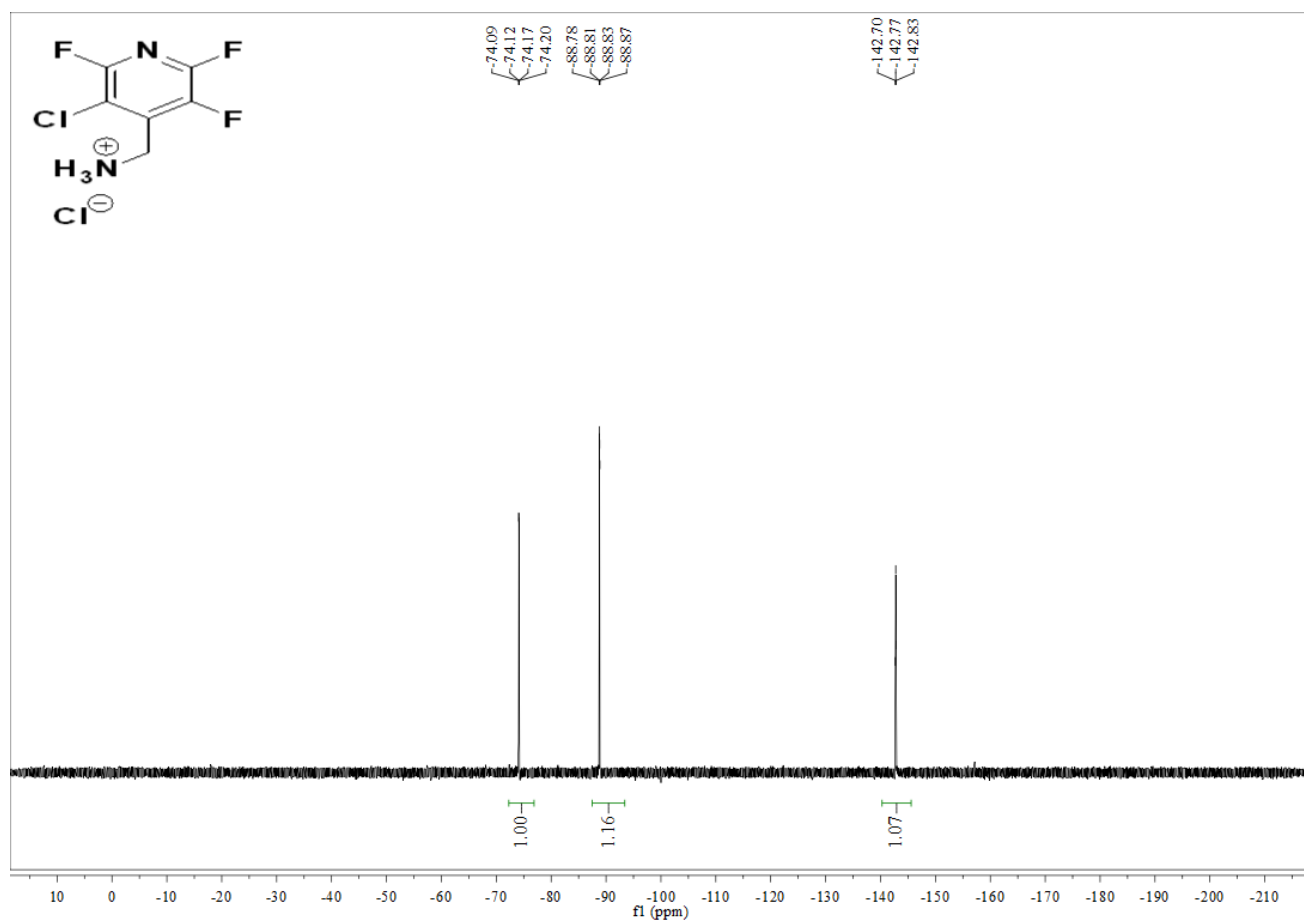
¹³C NMR (101 MHz, D₂O) **5a**



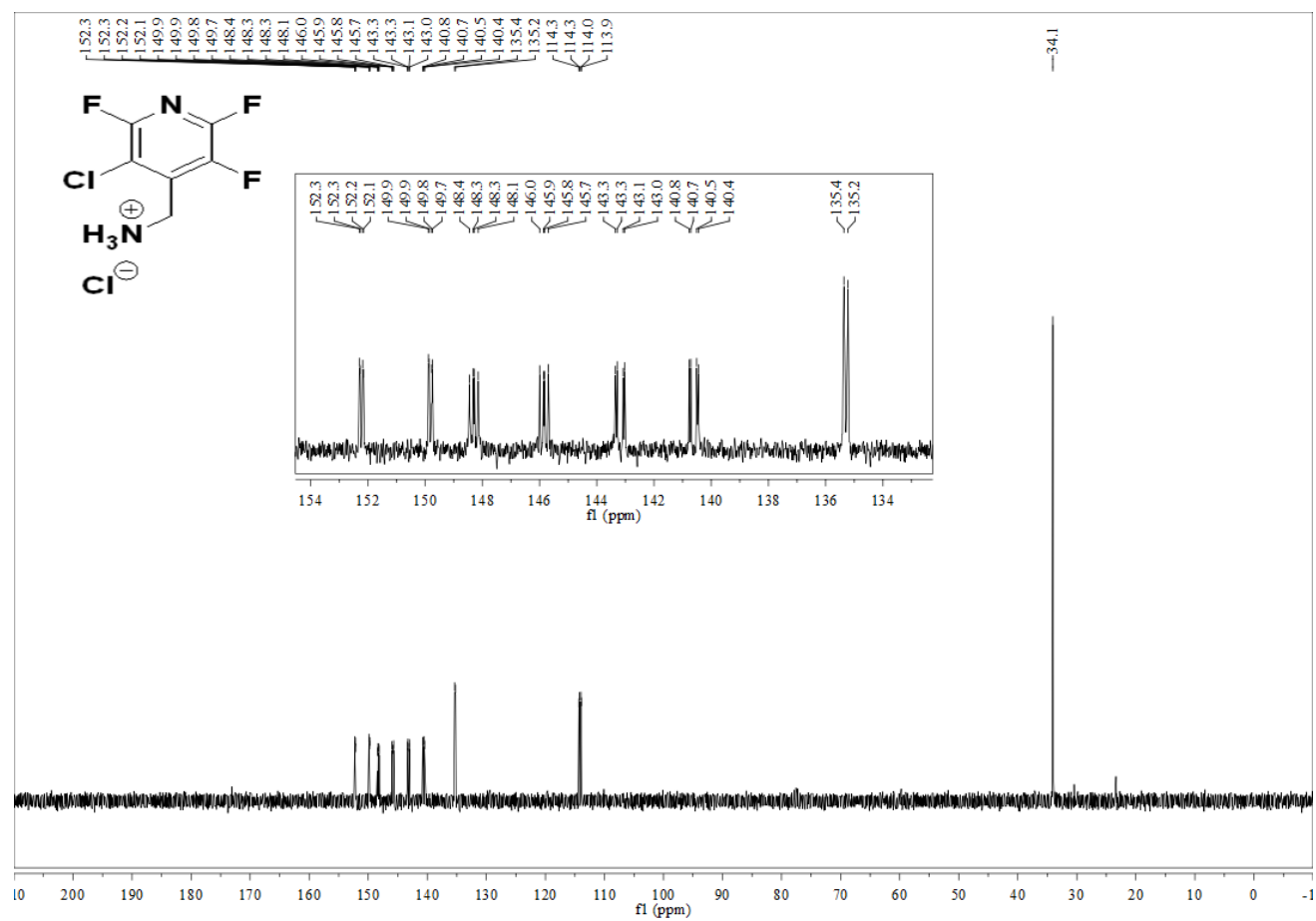
¹H NMR (400 MHz, D₂O) **5b**



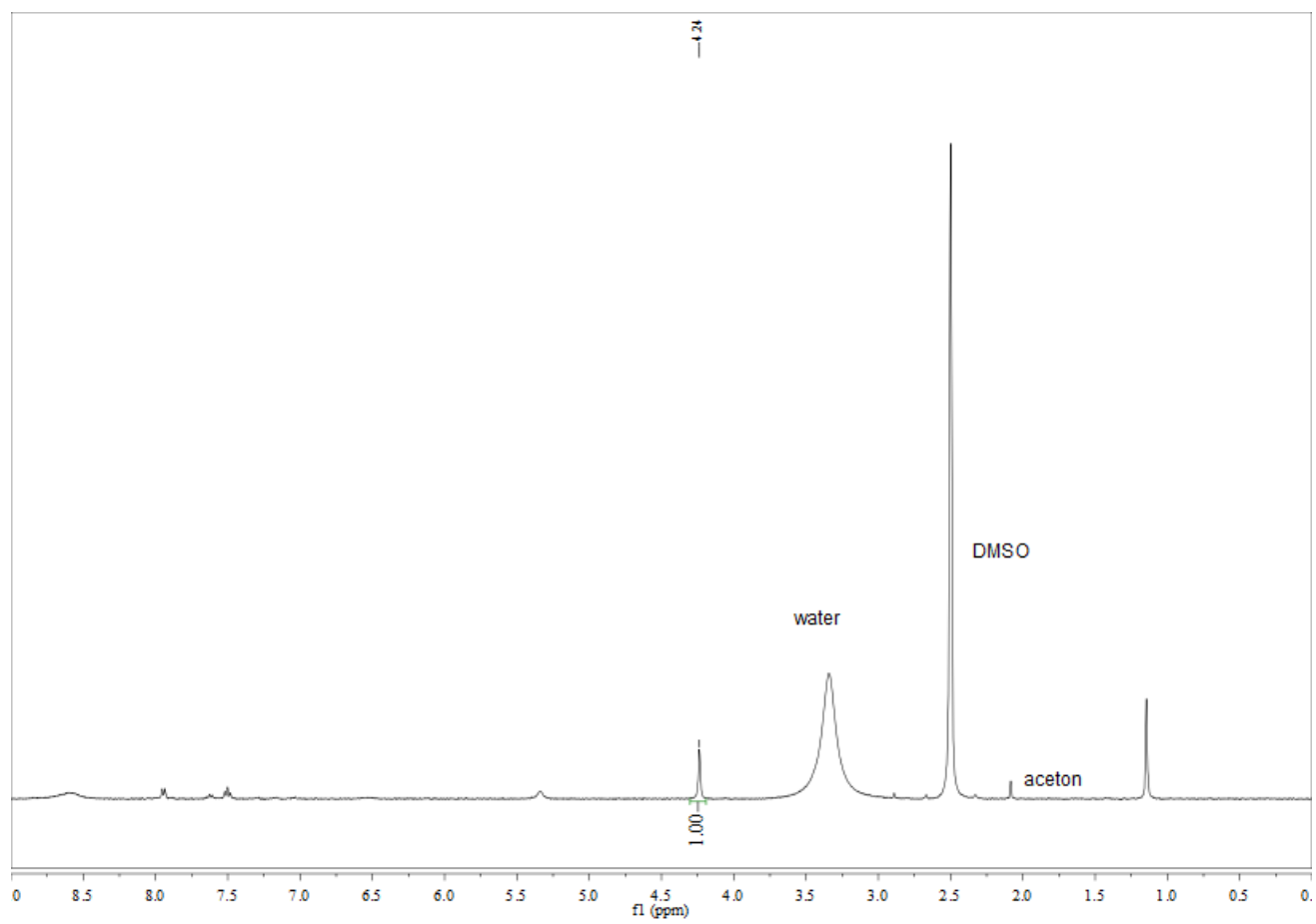
^{19}F NMR (376 MHz, D_2O) **5b**



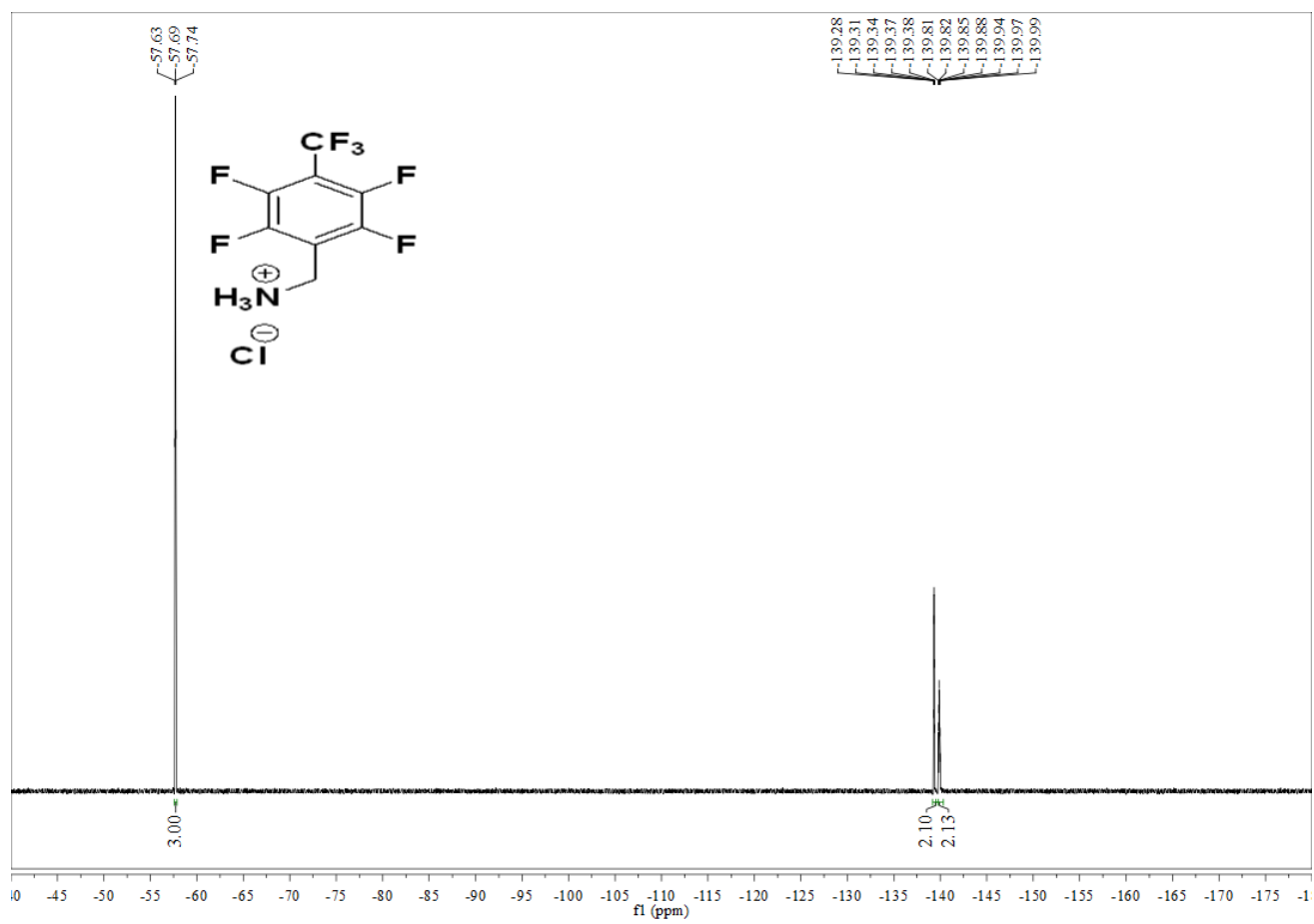
^{13}C NMR (101 MHz, D_2O) **5b**



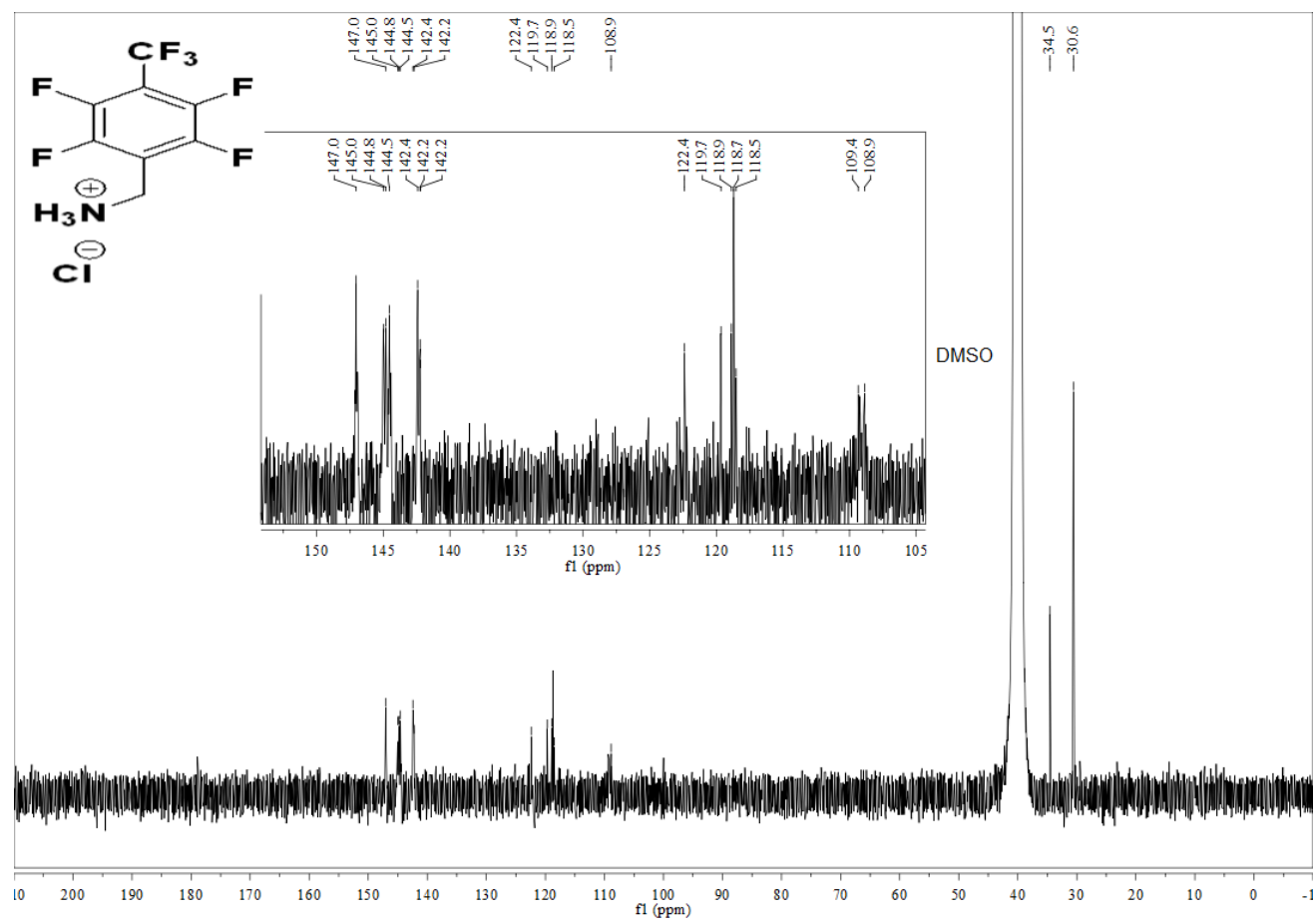
^1H NMR (400 MHz, $\text{DMSO-}d_6$) **5c**



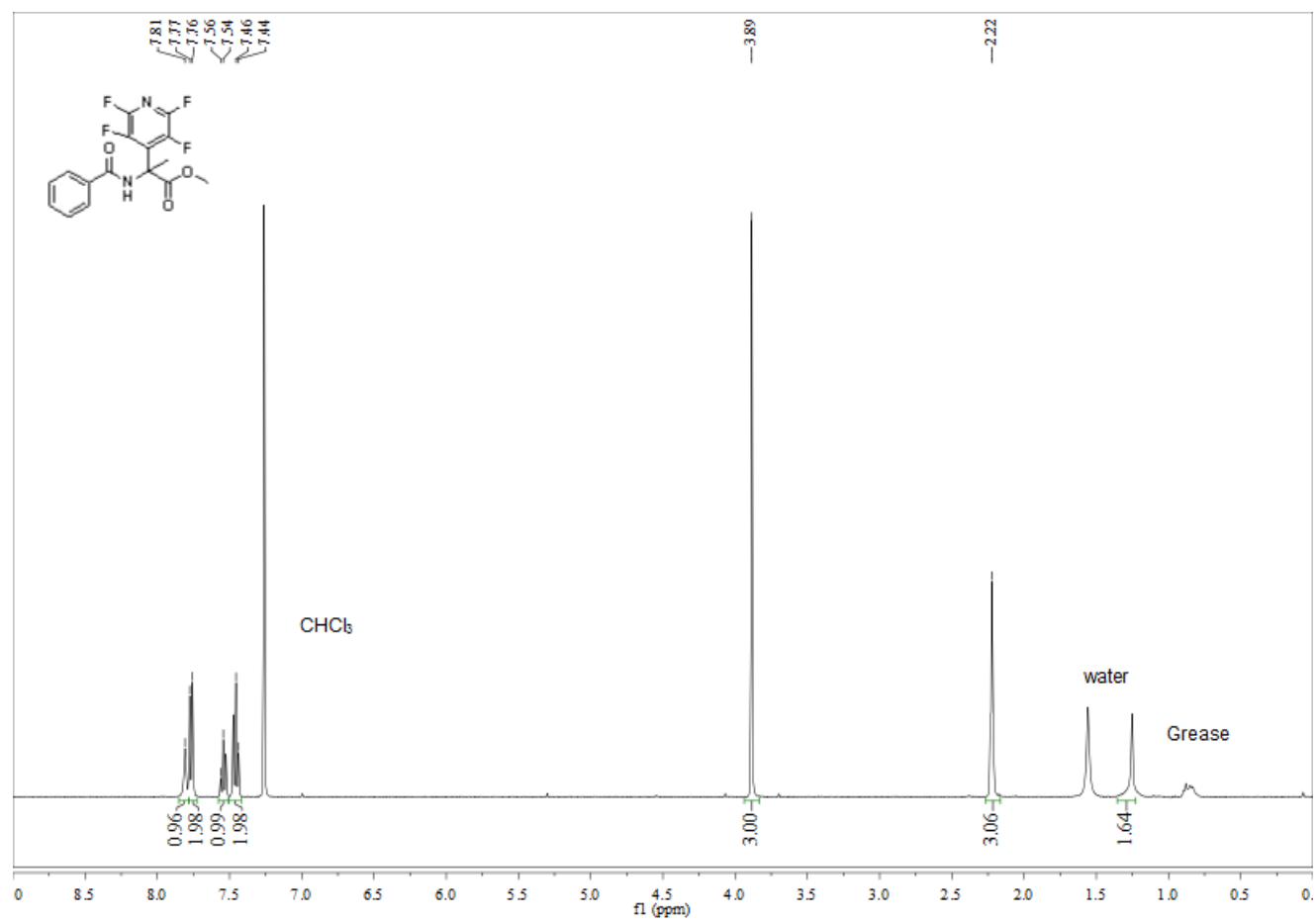
^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) **5c**



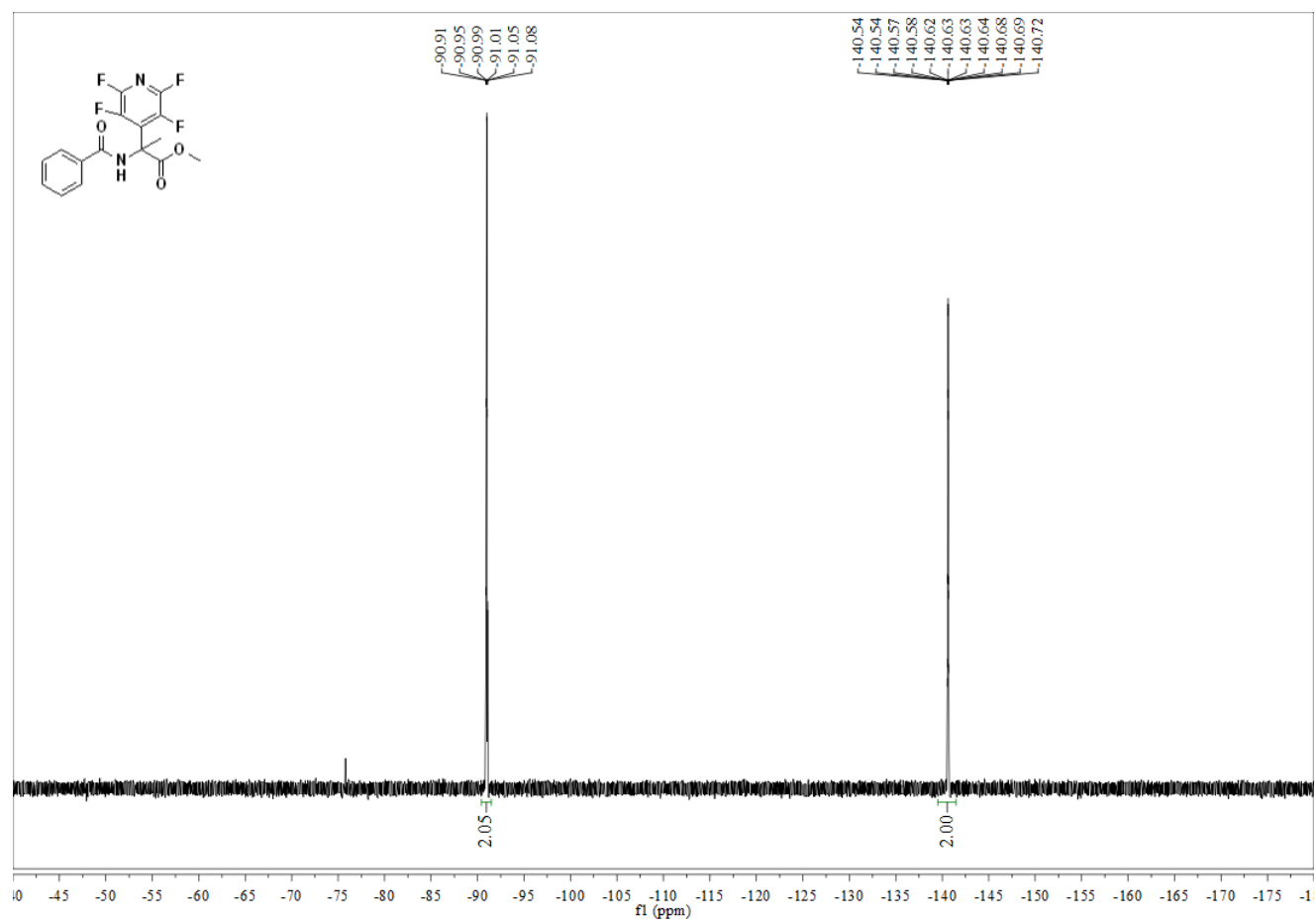
¹³C NMR (101 MHz, DMSO-*d*₆) **5c**



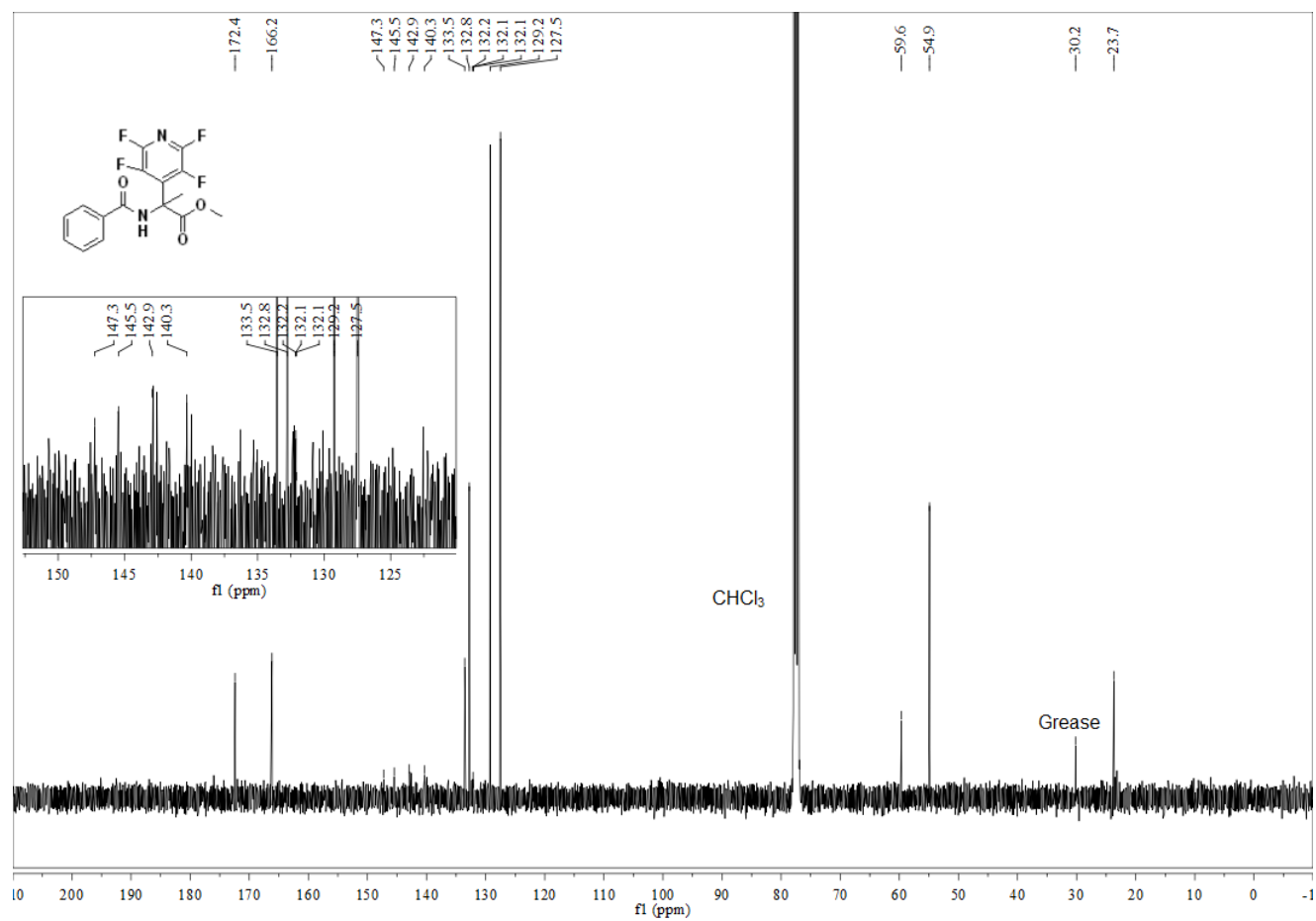
¹H NMR (400 MHz, Chloroform-*d*) **6a**



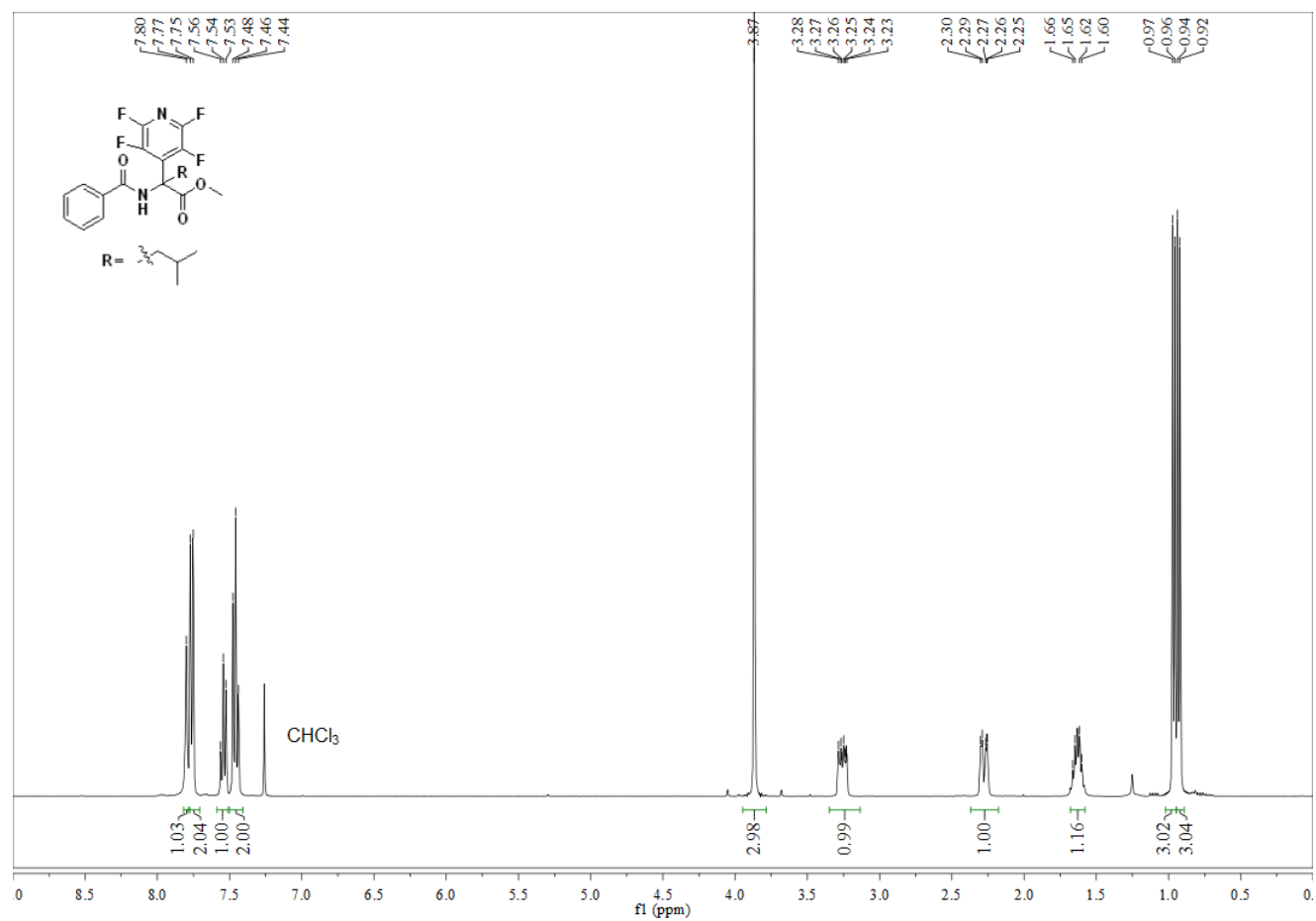
^{19}F NMR (376 MHz, Chloroform-*d*) **6a**



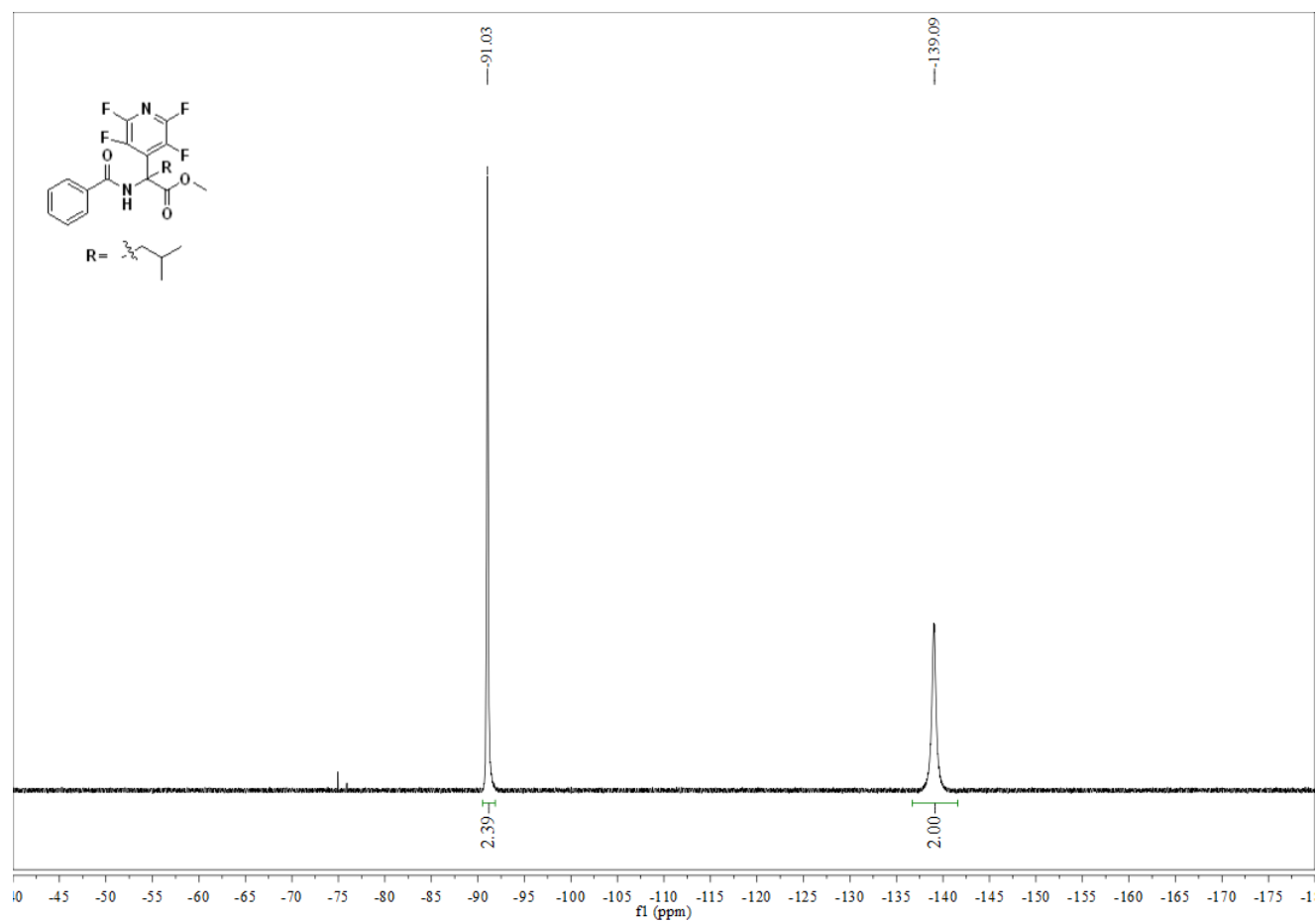
¹³C NMR (101 MHz, Chloroform-*d*) **6a**



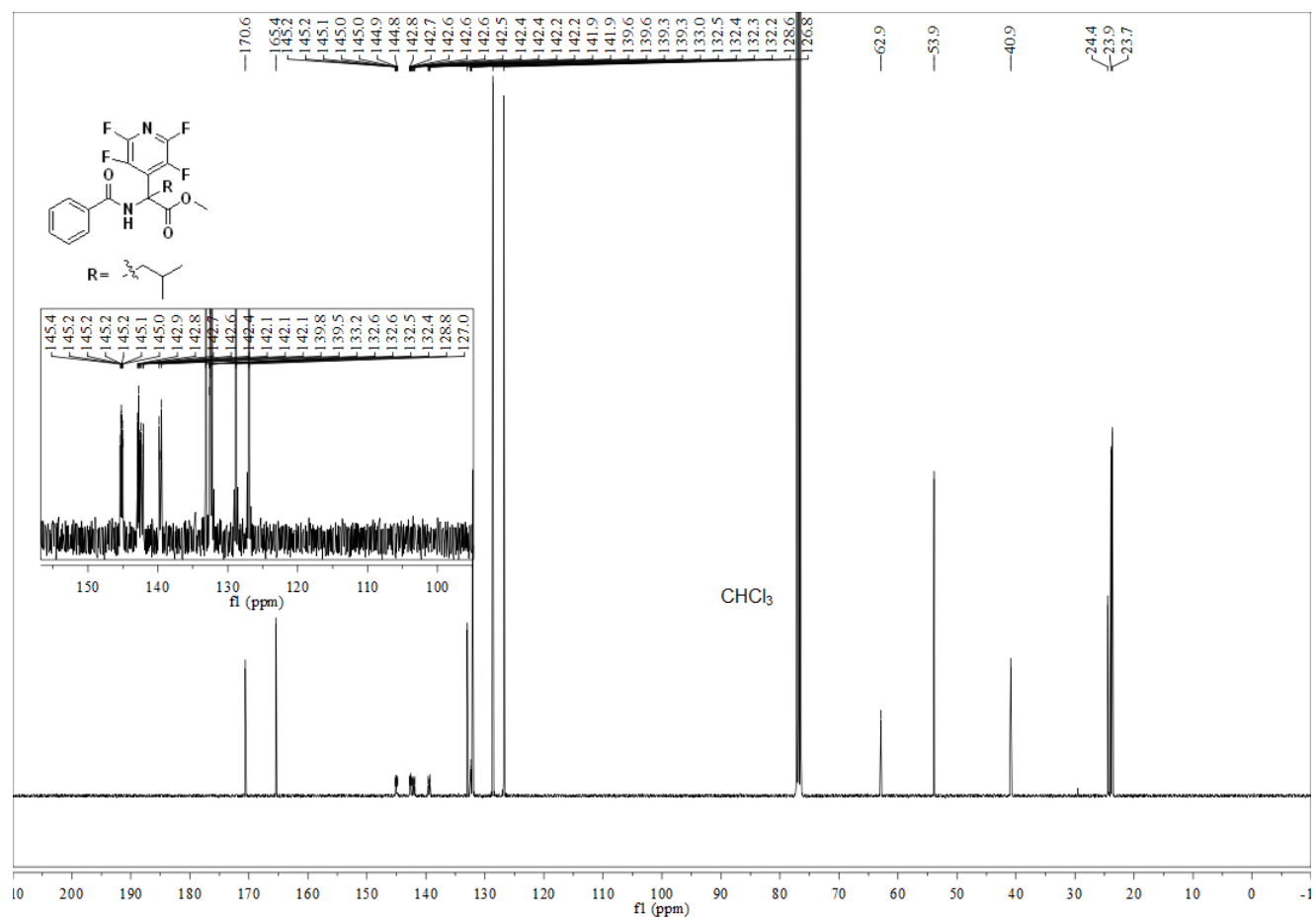
¹H NMR (400 MHz, Chloroform-*d*) **6b**



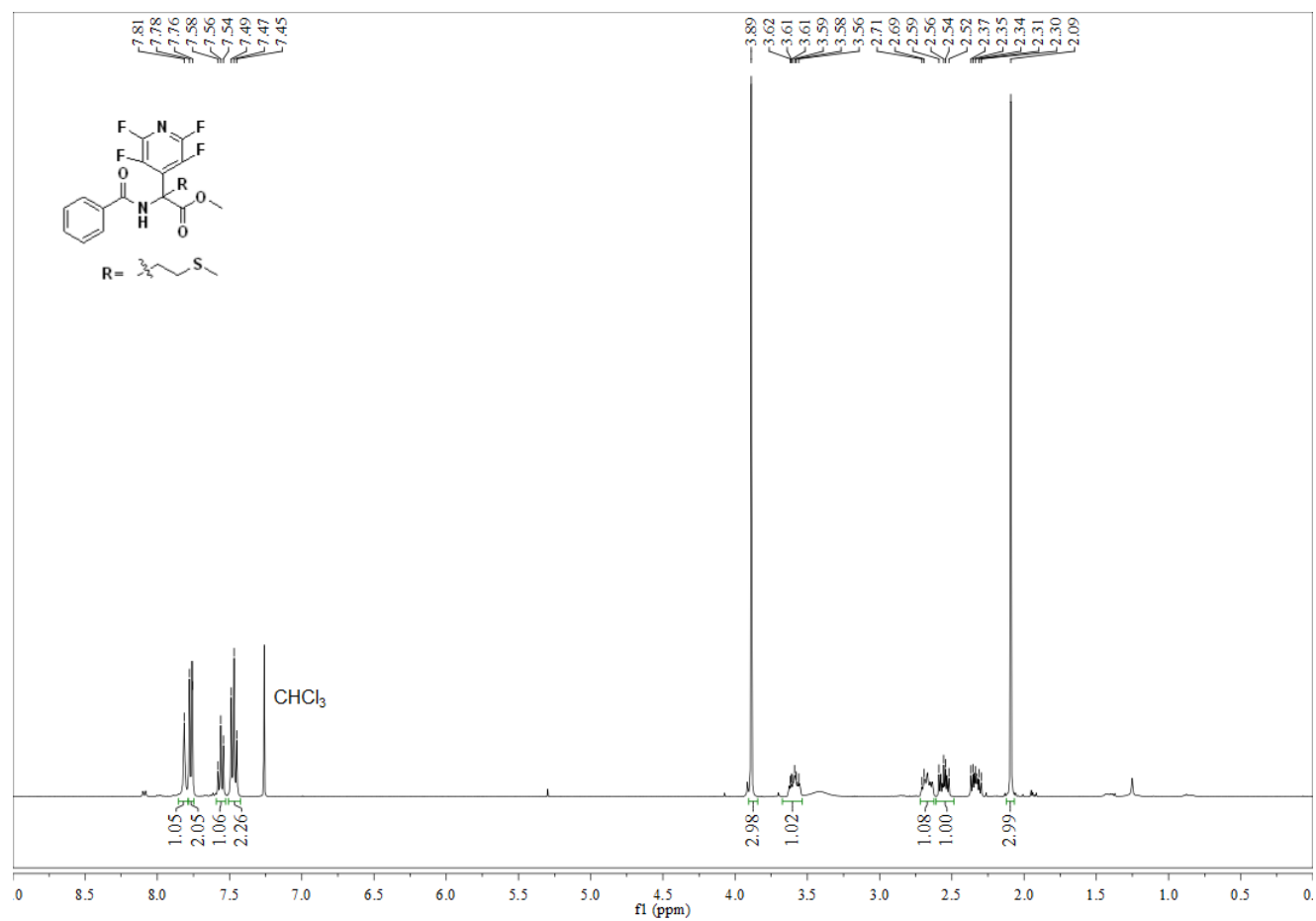
¹⁹F NMR (376 MHz, Chloroform-*d*) **6b**



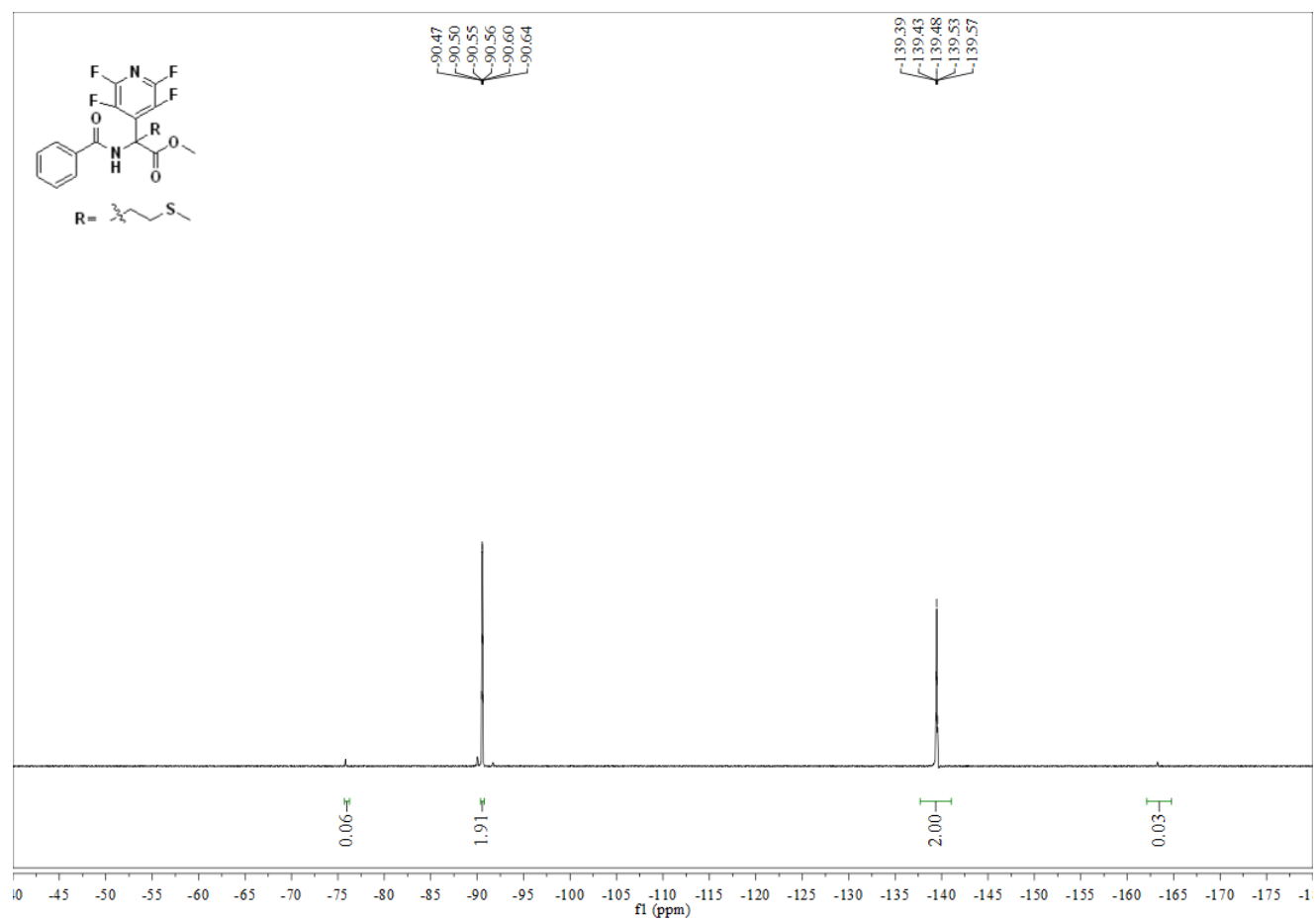
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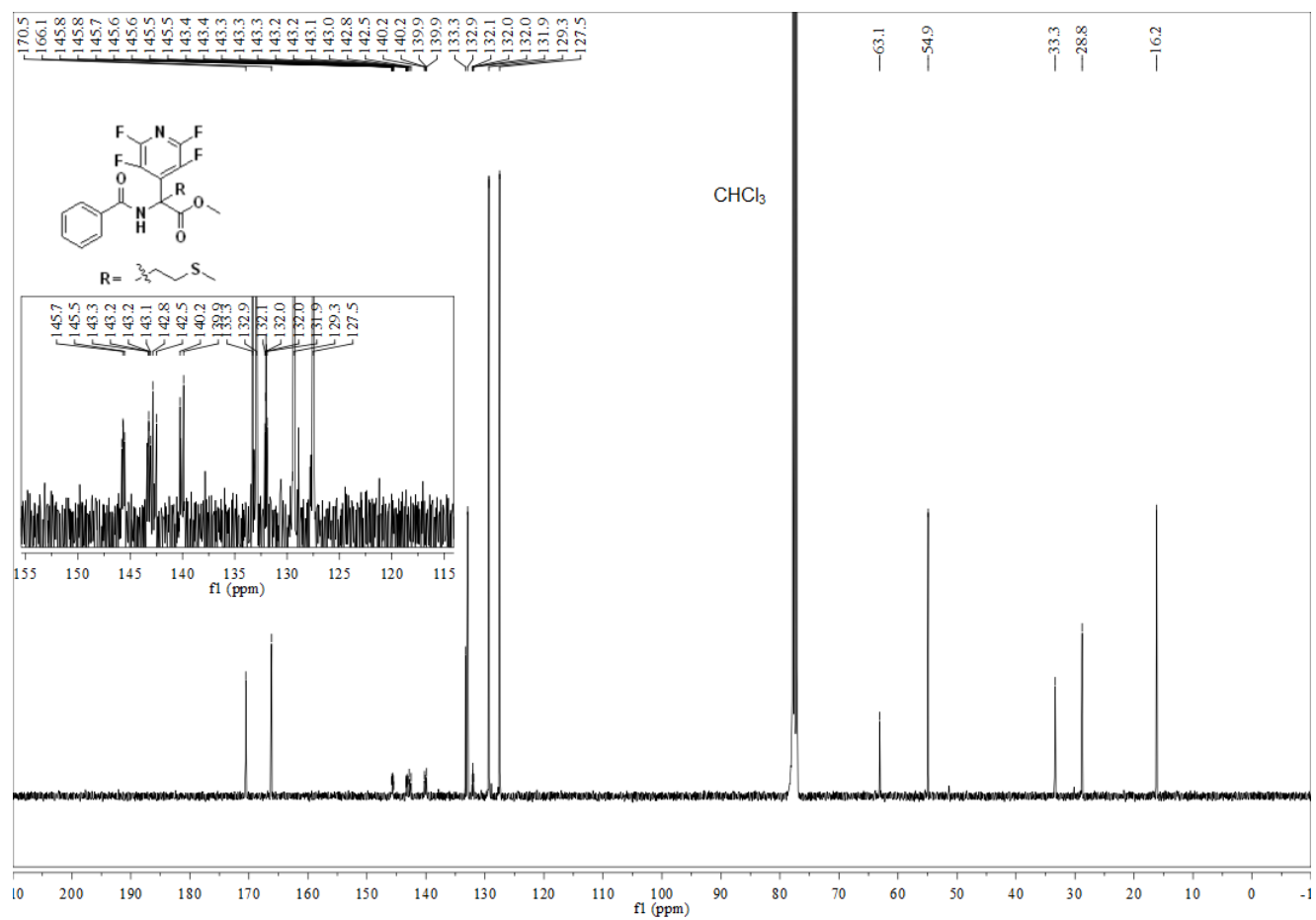
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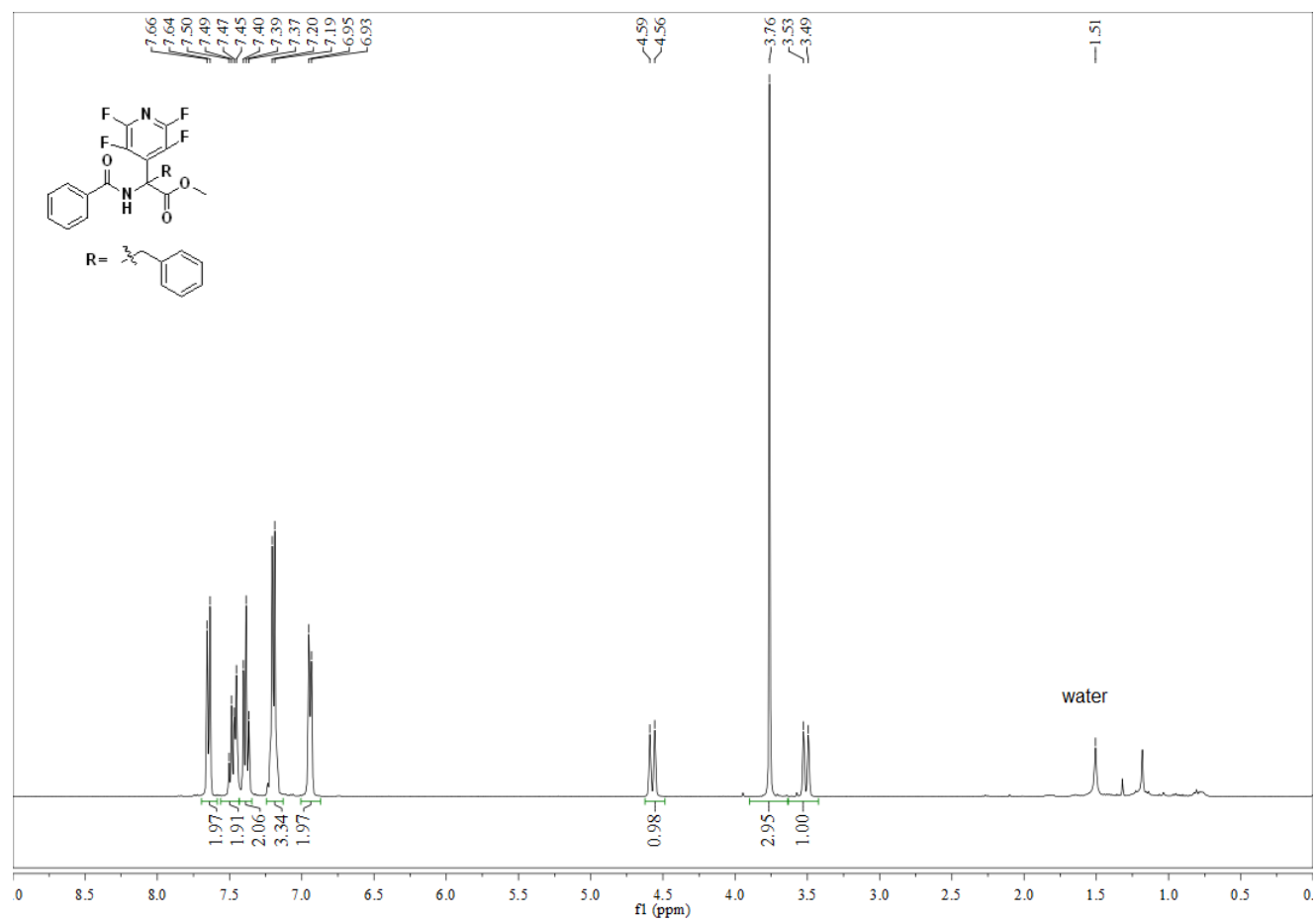
¹⁹F NMR (376 MHz, Chloroform-*d*) **6c**



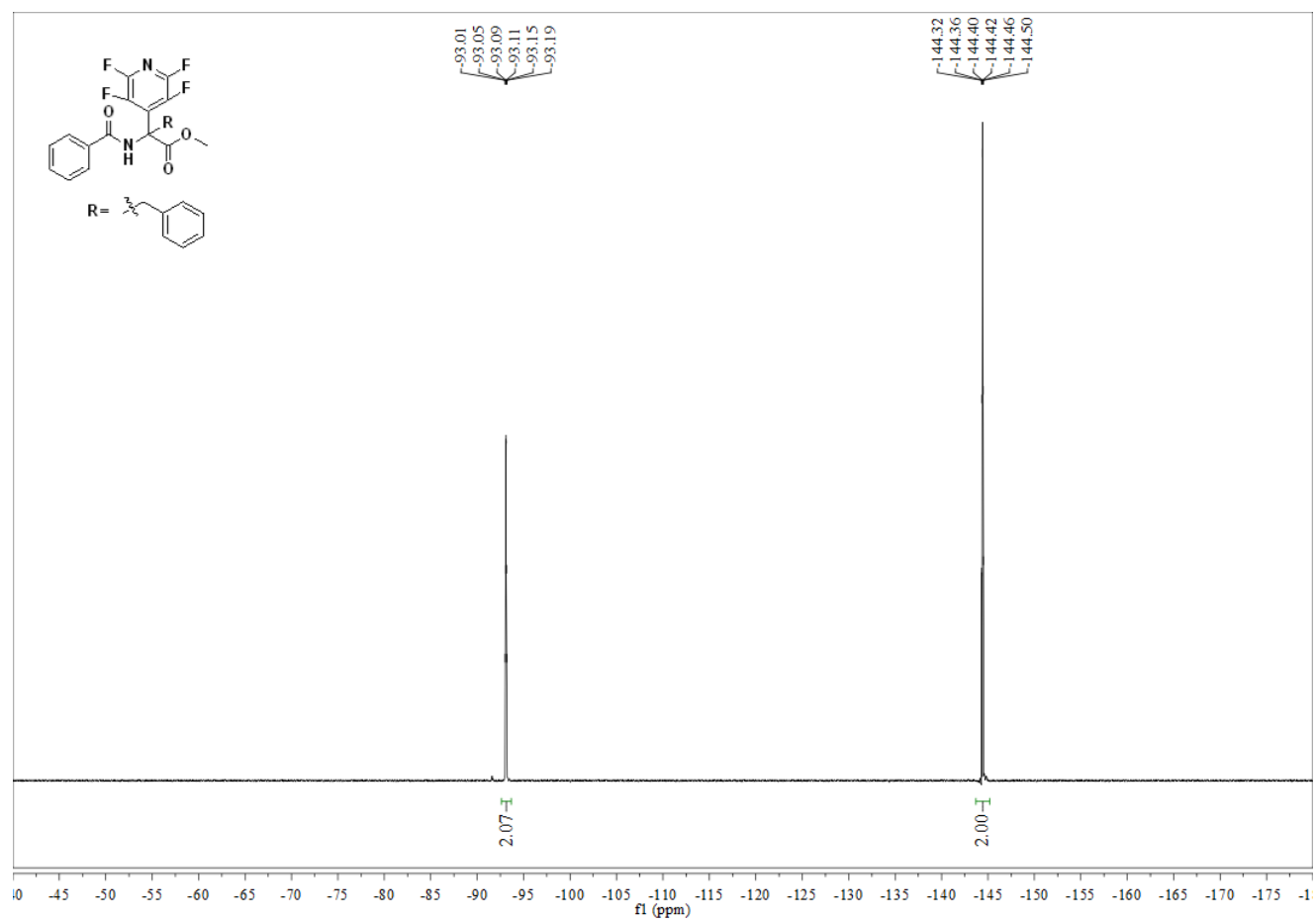
¹³C NMR (101 MHz, Chloroform-*d*) **6c**



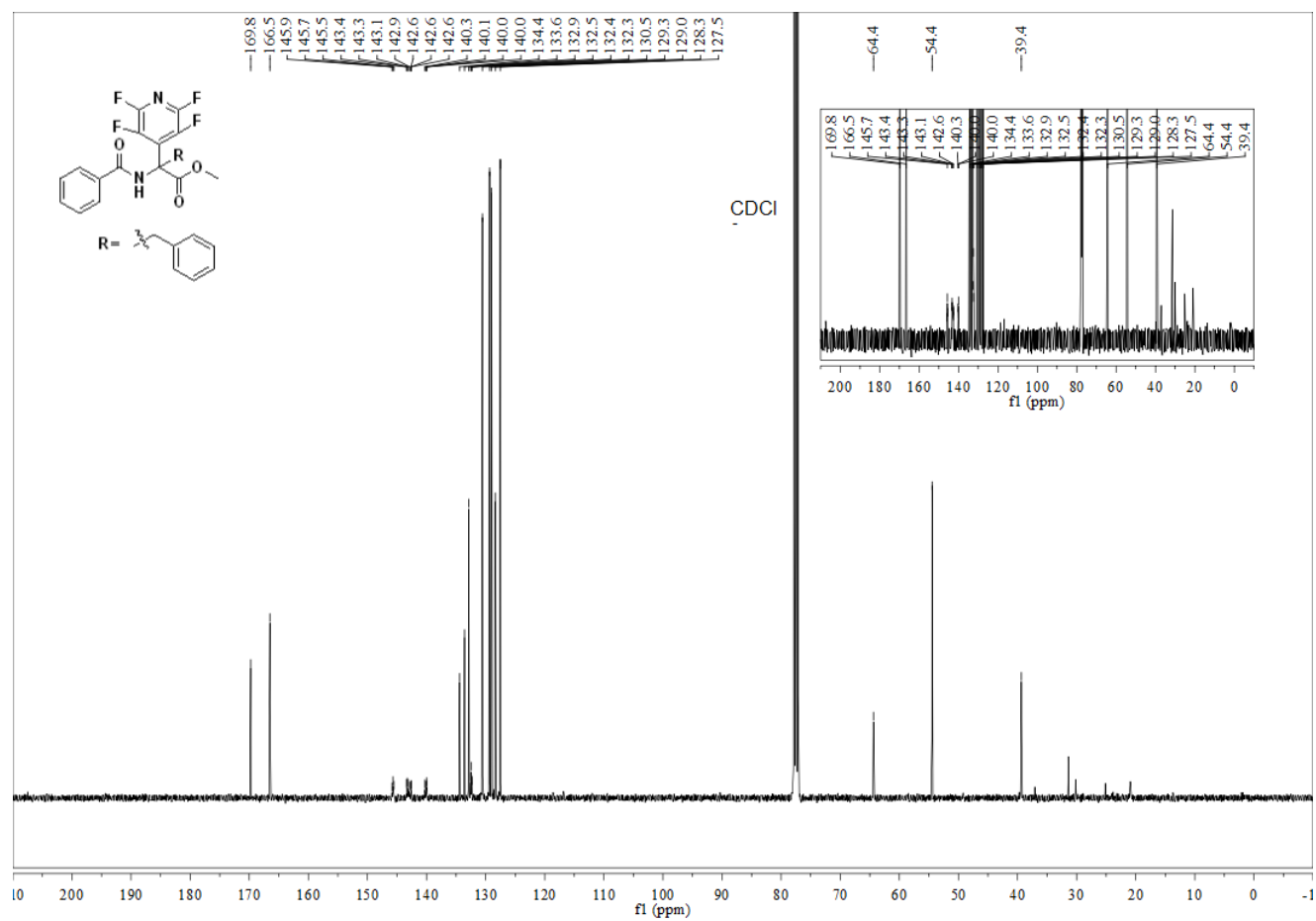
¹H NMR (400 MHz, Chloroform-*d*) **6d**



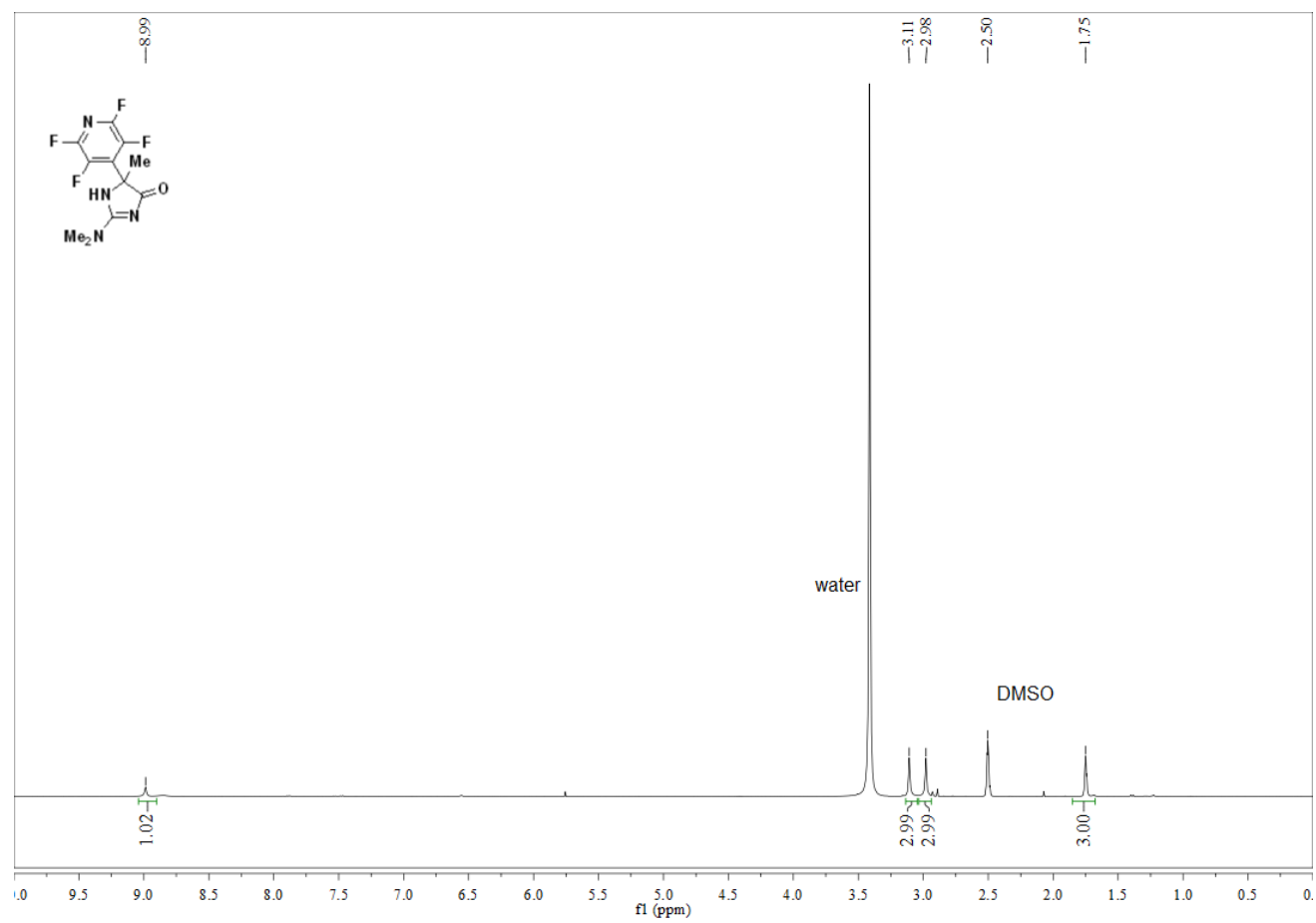
¹⁹F NMR (376 MHz, Chloroform-*d*) **6d**



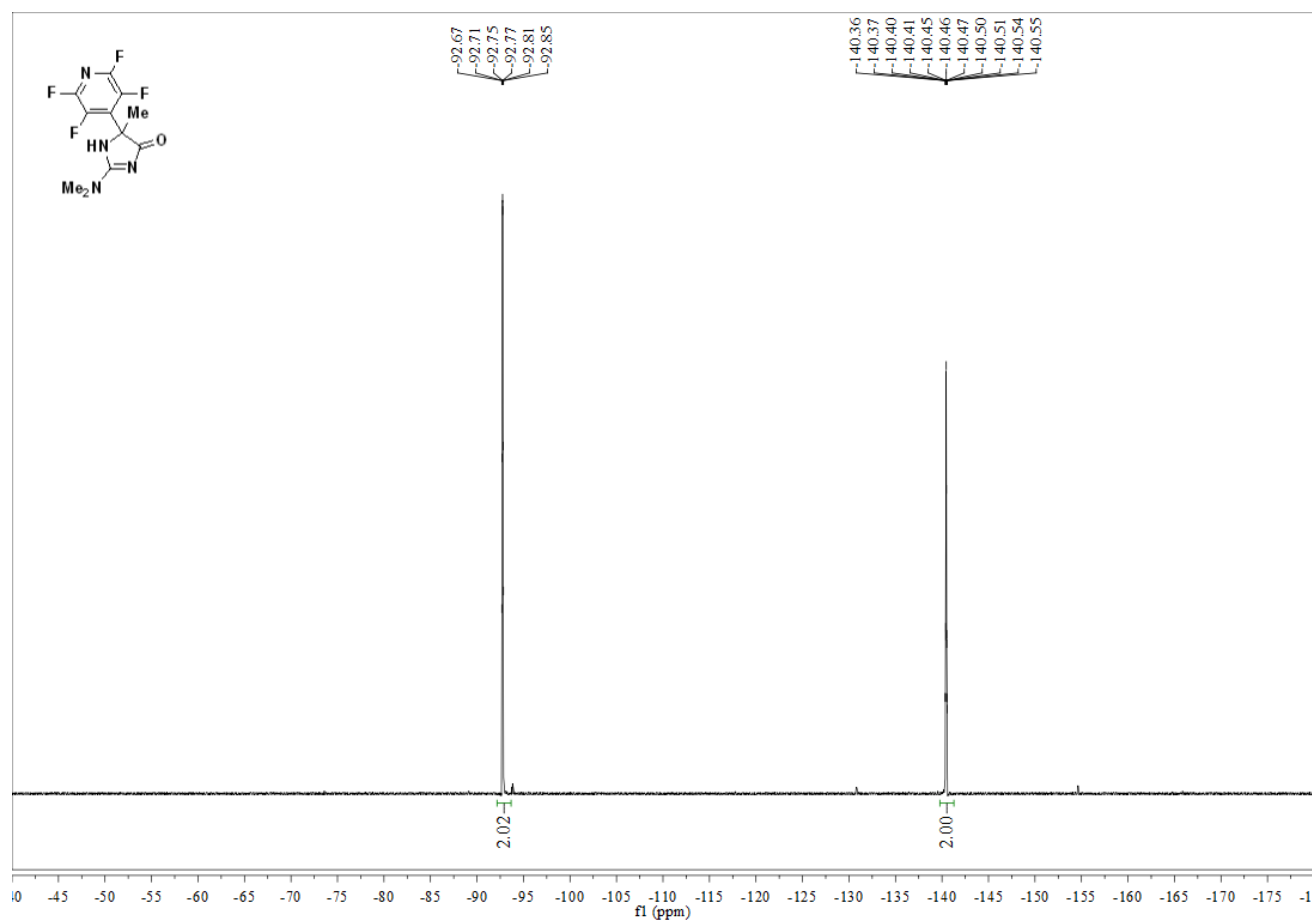
¹³C NMR (101 MHz, Chloroform-*d*) **6d**



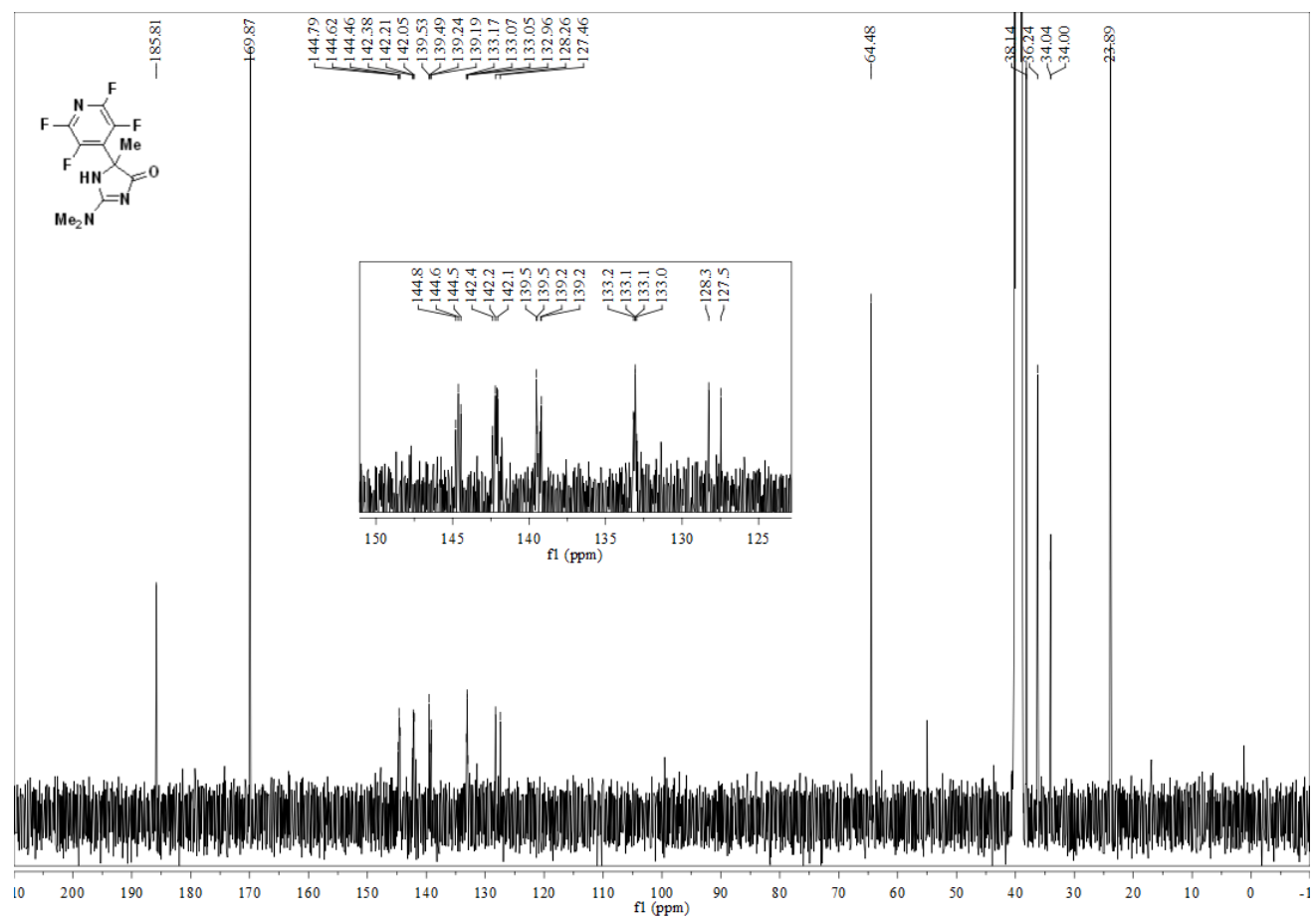
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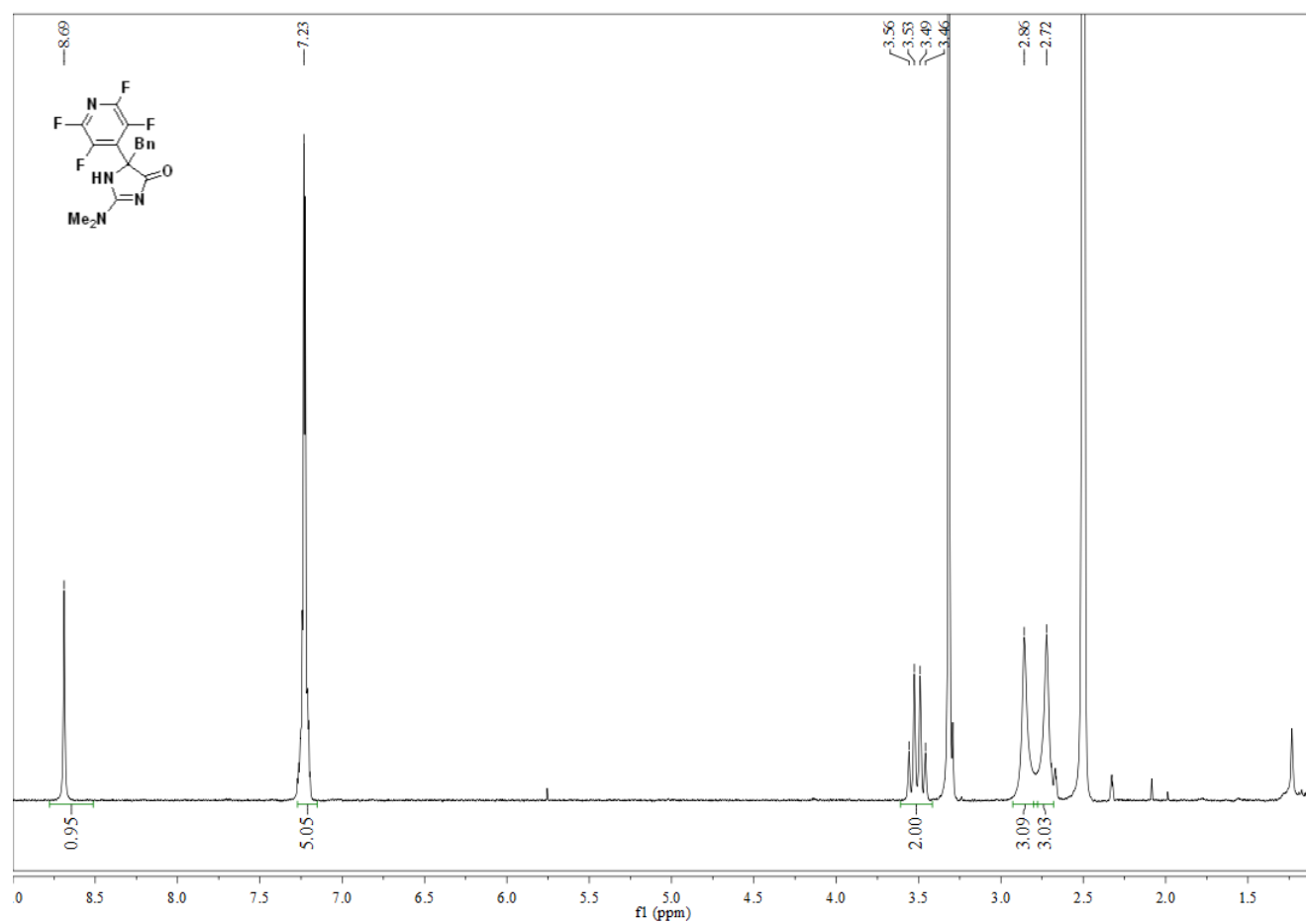
^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) **7a**



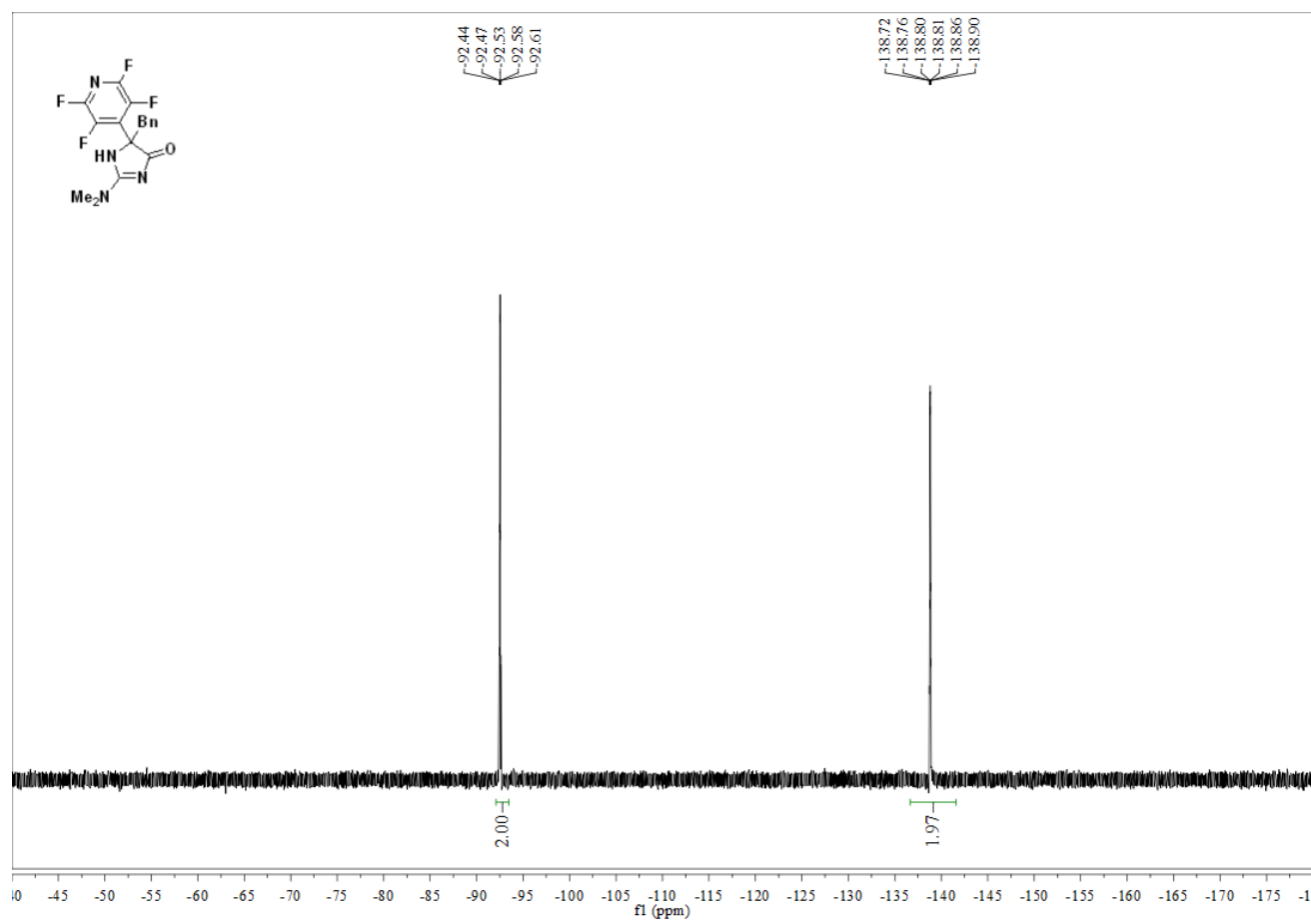
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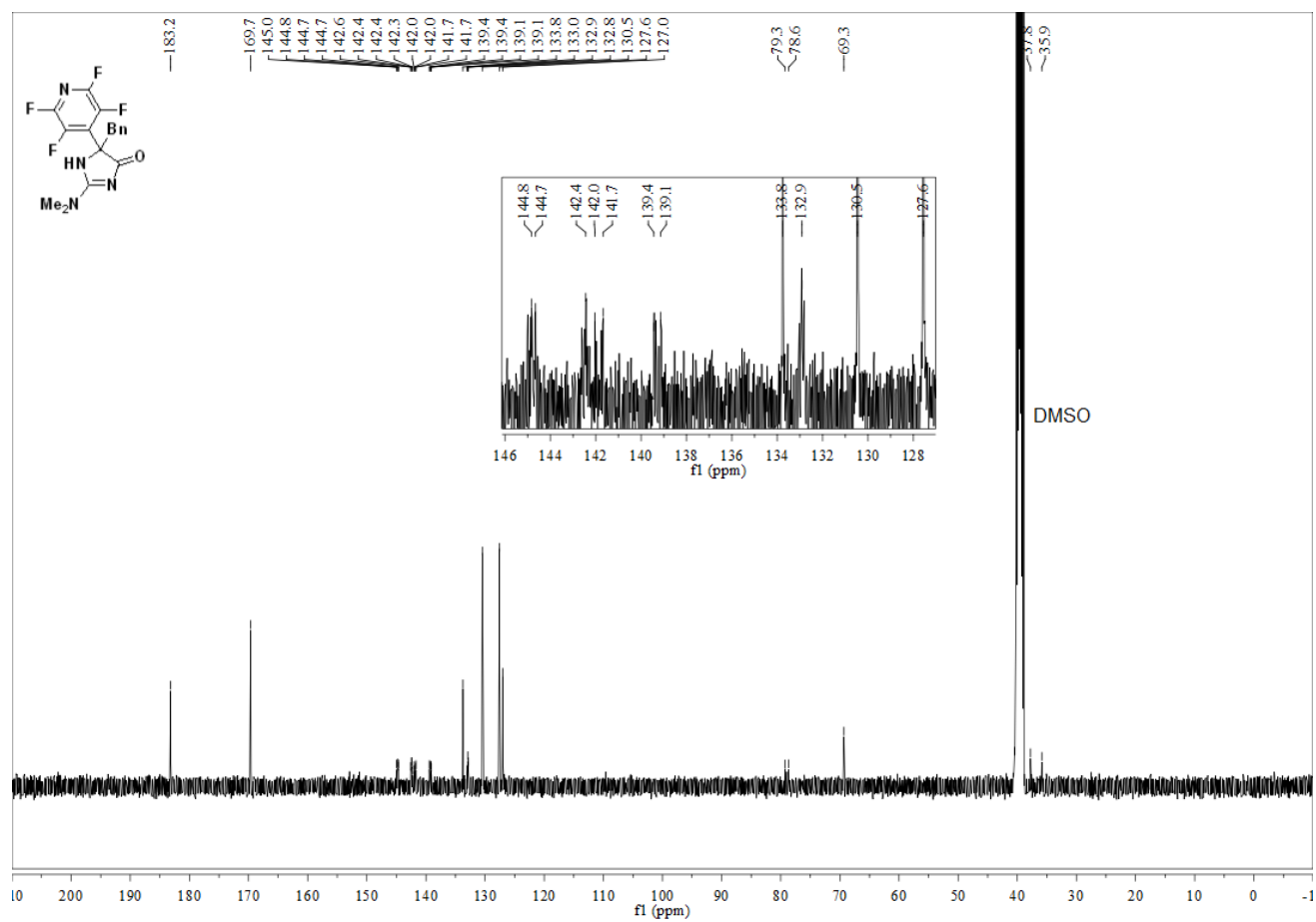
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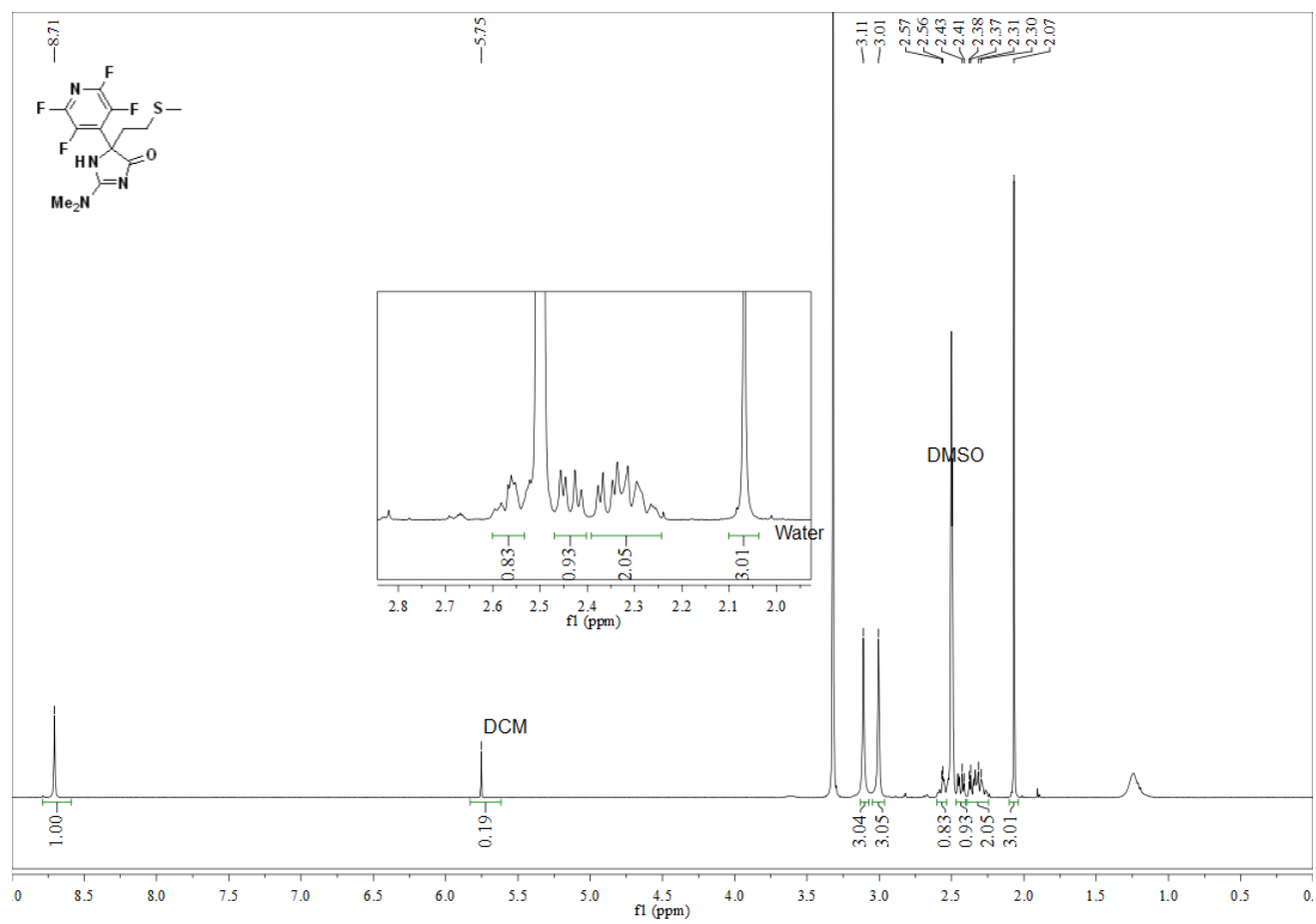
^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) **7b**



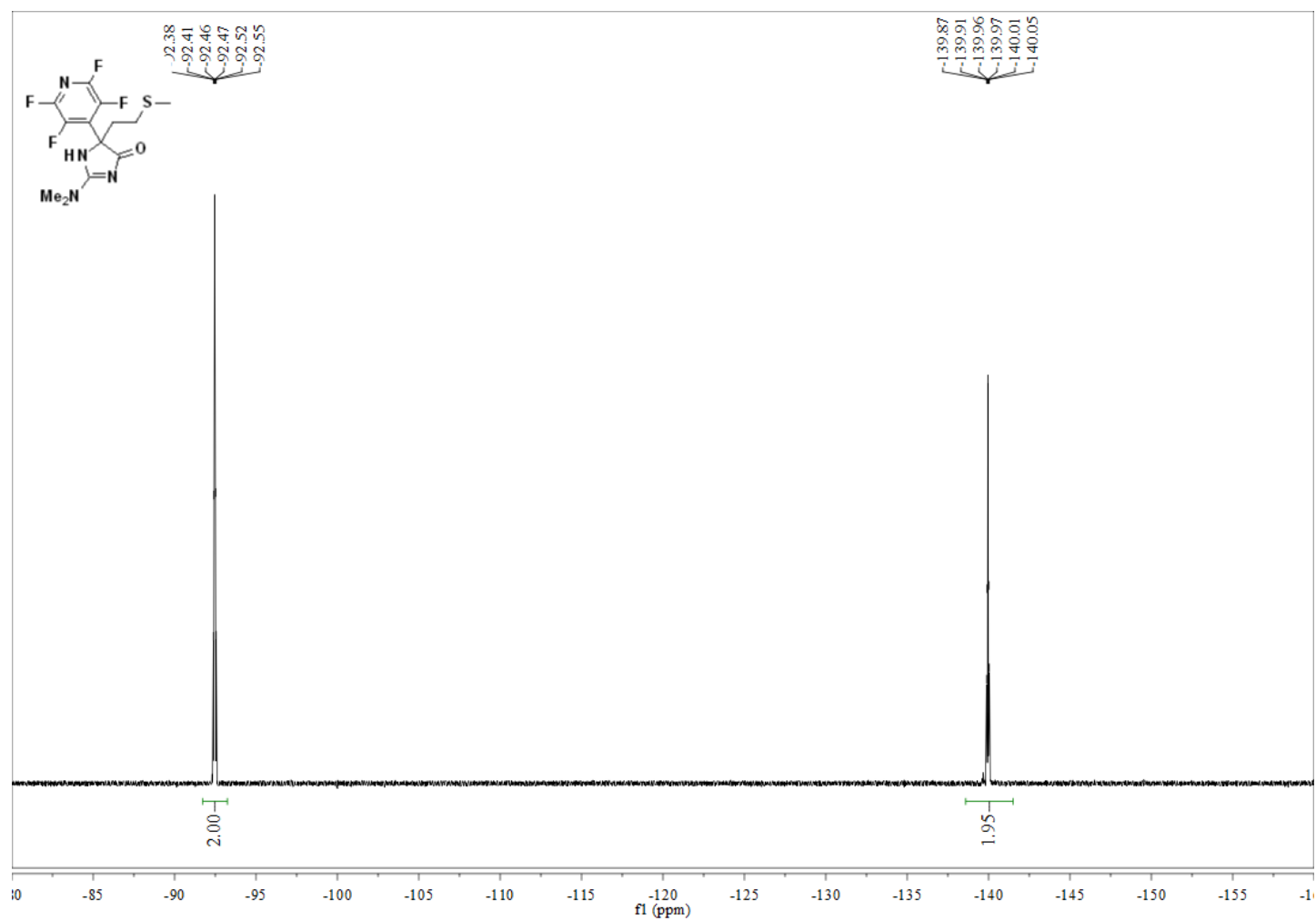
¹³C NMR (101 MHz, DMSO-*d*₆) **7b**



¹H NMR (400 MHz, DMSO-*d*₆) **7c**



^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) **7c**



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

