

Synthesis of Bioactive Fluoropyrrolidines via Copper(I)-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides

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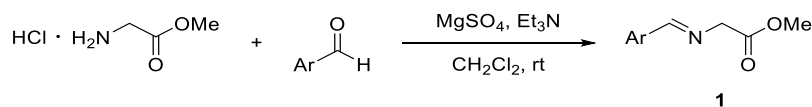
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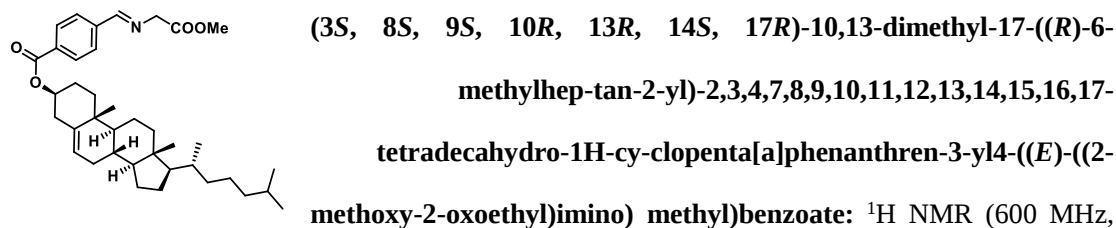
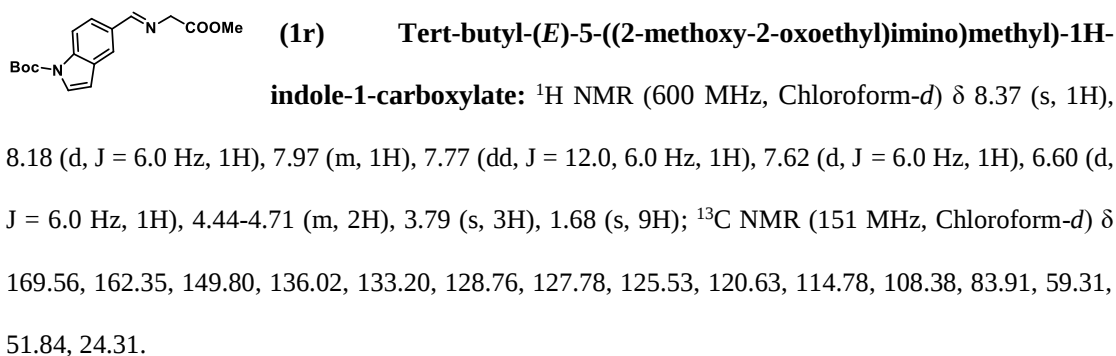
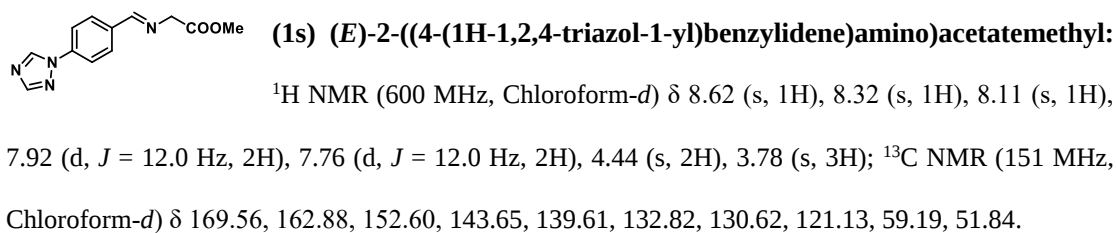
1. General remarks

All preparations and manipulations were carried out using standard Schlenk and Vigor glovebox techniques under an atmosphere of high purity nitrogen. Tetrahydrofuran (THF), dichloromethane (DCM), toluene, 1,4-Dioxane and diethyl ether were freshly distilled from the calcium hydride prior to use. Ethyl acetate (EA) was dried by molecular sieves. All chemical reagents were purchased from Shanghai Titan Scientific Co. Ltd, Bide Pharmatech Ltd, Aladdin Chemical Reagent Co. (China) and Sinopharm Chemical Reagent Company. All fungal phytopathogen materials were obtained from the College of Plant Science & Technology of Huazhong Agricultural University. Commercial fungicides Azoxystrobin and Hymexazol as a positive fungicide control for bioassay were bought from Aladdin Reagent Database Co. (China). All chemicals were of analytical grade or higher. ^1H NMR ^{13}C NMR and ^{19}F NMR spectra were obtained on Bruker Avance II 600MHz NMR spectrometer. Chemical shifts were reported on the form of per million (ppm), and the residual solvent peak was used as an internal reference: ^1H (chloroform δ 7.26), ^{13}C (chloroform δ 77.16). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, m = multiplet, etc.), coupling constants (Hz) and integration. High Resolution Mass Spectra was obtained on a Bruker FTMS. Optical rotation was measured on a Perkin-Elmer 341 MC polarimeter. All reactions were monitored by Thin layer chromatography (TLC) with silica gel-coated plates. Enantiomeric ratios were determined by an Agilent 1220 Infinity autosampler, using chiralpak AS-3 column, chiralpak AD-3 column, chiralcel OD-3 column, chiralpak IB-3 column and chiralpak IA-3 column with hexane and $^i\text{PrOH}$ as solvents. The absolute configuration of 4o was determined unequivocally according to the X-ray diffraction analysis.

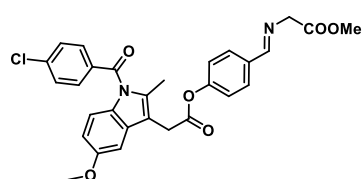
2. General procedure for synthesis of the iminoesters



The synthesis of iminoester substrate were progressed by condensation reaction between aminoesters hydrochlorides and aldehydes¹. A suspension of methyl glycinate hydrochloride (3.0 g, 24.0 mmol), MgSO₄ (4.8 g, 40.0 mmol), and Et₃N (4.2 mL, 30.0 mmol) in dry CH₂Cl₂ (40 mL) was stirred at room temperature for 1 h. Aldehyde (20.0 mmol) was added and the mixture was stirred at room temperature for 24 h. After the reaction was completed, MgSO₄ was removed by filtration and the filtrate was washed with water and brine. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The iminoester was used directly for the next step without additional purification.

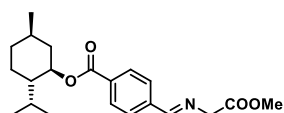


Chloroform-*d*) δ 8.34 (s, 1H), 8.08 (d, J = 6.0 Hz, 2H), 7.84 (d, J = 6.0 Hz, 2H), 5.42 (s, 1H), 4.87 (m, 1H), 4.45 (s, 2H), 3.79 (s, 3H), 2.47 (d, J = 12.0 Hz, 2H), 2.05-1.72 (m, 9H), 1.67-1.13 (m, 10H), 1.40-1.10 (m, 7H), 1.07 (s, 3H), 0.89-0.96 (m, 3H), 0.78-0.86 (m, 6H), 0.69 (s, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.42, 165.57, 164.73, 139.70, 139.27, 133.24, 129.97, 128.44, 123.01, 75.08, 62.13, 56.83, 56.27, 52.38, 50.18, 42.46, 39.87, 39.65, 38.32, 37.16, 36.79, 36.32, 35.94, 32.07, 32.01, 28.37, 28.15, 28.00, 24.43, 23.97, 22.96, 22.70, 21.19, 19.52, 18.86, 12.00.



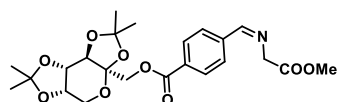
(*E*)-4-(((2-methoxy-2-oxoethyl)imino)methyl)phenyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate:

^1H NMR (600 MHz, Chloroform-*d*) δ 8.45 (s, 1H), 7.76 (d, J = 6.0 Hz, 2H), 7.68 (d, J = 6.0 Hz, 2H), 7.55 (d, J = 6.0 Hz, 2H), 7.25 (m, 2H), 7.10 (d, J = 6.0 Hz, 1H), 7.02 (d, J = 6.0 Hz, 1H), 6.79-6.88 (m, 1H), 4.71 (s, 2H), 3.94 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.68, 169.56, 168.11, 162.97, 156.17, 152.41, 137.62, 136.59, 132.68, 131.80, 131.31, 130.57, 130.06, 129.69, 129.16, 122.13, 112.83, 112.12, 111.13, 102.03, 59.19, 55.68, 51.84, 31.77, 13.23.



(1*R*, 2*R*, 5*R*)-2-isopropyl-5-methylcyclohexyl 4-(((2-methoxy-2-oxoethyl)imino)methyl)benzoate:

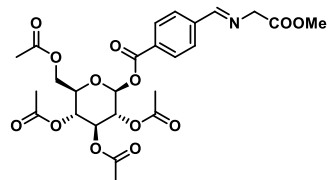
^1H NMR (600 MHz, Chloroform-*d*) δ 8.35 (s, 1H), 8.08 (d, J = 6.0 Hz, 2H), 7.84 (d, J = 6.0 Hz, 2H), 4.92-4.97 (m, 1H), 4.45 (d, J = 6.0 Hz, 2H), 3.79 (s, 3H), 2.16-2.10 (m, 1H), 1.95 (m, 1H), 1.77-1.71 (m, 2H), 1.60-1.50 (m, 3H), 1.19-1.07 (m, 2H), 0.87-0.94 (m, 6H), 0.80 (s, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.43, 165.71, 164.71, 139.28, 133.26, 129.98, 128.48, 75.36, 62.16, 52.39, 47.38, 41.08, 34.44, 31.60, 26.67, 23.79, 22.19, 20.91, 16.67.



((3*aR*, 5*aS*, 8*aS*, 8*bR*)-2,2,7,7-tetramethyltetrahydro-3*aH*-bis-([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran-3*a*-yl)methyl 4-(((2-methoxy-2-oxoethyl)imino)methyl)benzoate:

^1H NMR (600 MHz, Chloroform-*d*) δ 8.35 (s, 1H), 8.12 (d, J = 6.0 Hz, 2H), 7.85 (d, J = 6.0 Hz, 2H), 4.71 (d, J = 12.0 Hz, 1H), 4.64 (dd, J = 12.0, 6.0 Hz, 1H), 4.52-4.44 (m, 2H), 4.33 (d, J = 12.0 Hz, 1H), 4.26 (dd, J = 12.0, 6.0 Hz, 1H), 3.96 (dd, J = 12.0, 6.0 Hz, 1H), 3.82 (m, 1H), 3.79 (s, 3H), 1.54 (s, 3H), 1.46 (s, 3H), 1.35 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (151

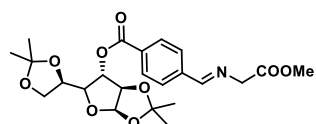
MHz, Chloroform-*d*) δ 170.40, 165.51, 164.59, 139.50, 132.14, 130.15, 128.50, 109.23, 108.98, 101.65, 70.79, 70.57, 70.09, 65.49, 62.05, 61.40, 52.43, 26.60, 25.96, 25.52, 24.05.



(2R, 3R, 4S, 5R, 6S)-2-(acetoxymethyl)-6-((4-((E)-((2-methoxy-2-oxoethyl)imino)methyl)benzoyl)oxy)tetrahydro-2H-pyran-

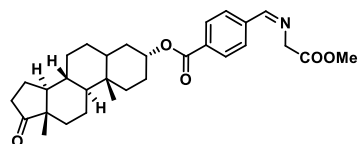
3,4,5-triyl triacetate: ^1H NMR (600 MHz, Chloroform-*d*) δ 8.44 (s, 1H), 8.03 (d, J = 6.0 Hz, 2H), 7.74 (d, J = 6.0 Hz, 2H), 6.18 (m, 1H),

5.25 (m, 1H), 5.18-5.09 (m, 1H), 5.05-4.97 (m, 1H), 4.77-4.65 (m, 2H), 4.44 (dd, J = 12.0, 6.0 Hz, 2H), 4.37-4.23 (m, 1H), 3.79 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.86, 170.23, 170.12, 169.95, 169.56, 166.13, 162.03, 138.70, 131.91, 129.75, 128.60, 92.99, 72.22, 71.19, 70.57, 68.36, 61.63, 60.23, 51.84, 20.80, 20.70, 20.65.



(3aR, 6S, 6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl4-((E)-((2-methoxy-2-oxoethyl)imino)methyl)benzoate: ^1H NMR (600 MHz,

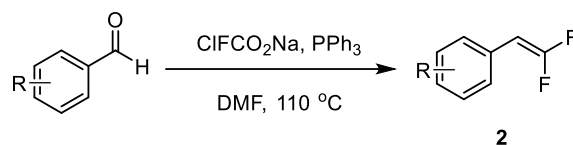
Chloroform-*d*) δ 8.35 (s, 1H), 8.07 (d, J = 6.0 Hz, 2H), 7.86 (d, J = 6.0 Hz, 2H), 5.96 (d, J = 6.0 Hz, 1H), 5.51 (d, J = 6.0 Hz, 1H), 4.65 (m, 1H), 4.46 (s, 2H), 4.39-4.30 (m, 2H), 4.15-4.03 (m, 2H), 3.79 (s, 3H), 1.56 (s, 3H), 1.41 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.34, 164.84, 164.44, 139.97, 131.84, 130.13, 128.65, 112.55, 109.60, 105.29, 83.51, 80.13, 72.68, 67.50, 62.08, 52.41, 26.98, 26.87, 26.35, 25.33.



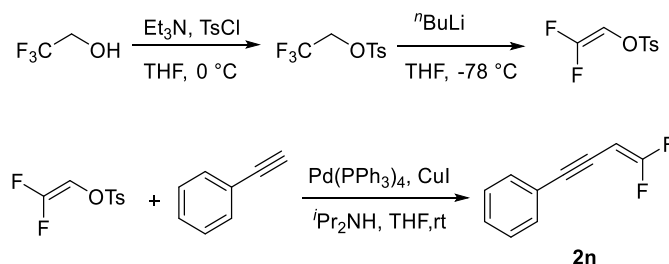
(3R, 8R, 9S, 10S, 13S, 14S)-10,13-dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl4-((Z)-((2-methoxy-2-oxoethyl)imino)methyl)benzoate: ^1H NMR (600 MHz,

Chloroform-*d*) δ 8.35 (s, 1H), 8.09 (d, J = 6.0 Hz, 2H), 7.86 (d, J = 6.0 Hz, 2H), 4.45 (s, 2H), 3.79 (s, 3H), 2.44 (dd, J = 18.0, 6.0 Hz, 2H), 2.04-2.11 (m, 2H), 1.98-1.73 (m, 7H), 1.73-1.45 (m, 7H), 1.42-1.19 (m, 5H), 0.87 (s, 6H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 191.52, 170.12, 165.17, 164.39, 139.15, 133.17, 129.67, 128.27, 70.83, 61.78, 54.30, 52.08, 51.31, 47.66, 40.36, 35.95, 35.71, 34.90, 33.07, 32.79, 31.43, 30.63, 27.96, 26.12, 21.63, 20.01, 13.73, 11.31.

3. General procedure for synthesis of *gem*-difluoroalkenes



Gem-difluoroalkenes were prepared by reacting sodium chlorodifluoroacetate and triphenyl phosphine with the corresponding aldehydes². Aldehyde (20.0 mmol), triphenyl phosphine (6.3 g, 24.0 mmol) and sodium chlorodifluoroacetate (4.6 g, 30.0 mmol) in DMF was stirred at 110 °C under an N₂ atmosphere for 1-10 h. After the aldehyde consumed completely, the mixture was cooled to 0 °C, added water and extracted with Et₂O. The combined organic phase was washed with brine, and then dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography to give the corresponding *gem*-difluoroalkene.



Compound **2n** was synthesized according to literature procedure^{2c}.

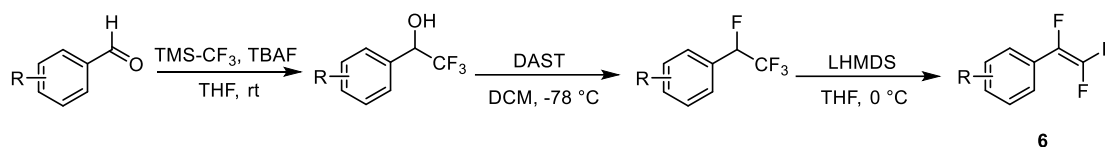
(a) 2,2,2-Trifluoroethanol (2.0 g, 20.0 mmol) and triethylamine (10.0 mL, 72.0 mmol) was dissolved in anhydrous THF (25.0 mL). The solution was cooled to 0 °C and tosylchloride (4.7 g, 25.0 mmol) was added. The reaction was stirred at 0 °C for 1 h, then stirred to room temperature overnight. The organic phase was washed with brine and dried over anhydrous Na₂SO₄. After concentration in vacuo the crude product was purified by flash chromatography to give the desired product.

(b) The step (a) obtained the product (2.5 g, 10 mmol) was dissolved in anhydrous THF (20.0 mL) and cooled to -78 °C. After ⁿBuLi (2.5 M in hexane, 9.2 mL) was added dropwise under nitrogen atmosphere. The reaction was monitored by TLC. The reaction was quenched with H₂O. The mixture was extracted with ethyl acetate and washed with brine. The organic phase was dried over anhydrous Na₂SO₄, filtrated and evaporated. The crude product was purified by flash column

chromatography to give the product.

(c) 2,2-difluoroethenyltosylate (1.18 g, 5.0 mmol), phenylacetylene (765.3 mg, 7.5 mmol), Pd(PPh₃)₄ (425.0 mg, 0.3 mmol), CuI (104.7 mg, 0.55 mmol) in THF-*i*Pr₂NH (1:1, 20 mL) was stirred at room temperature under an N₂ atmosphere for 2 h. After the reaction was completed, the reaction mixture was diluted by ethyl acetate. The organic layer was washed by water and dried over anhydrous Na₂SO₄. After evaporation of the solvent under reduced pressure, product was purified by flash column chromatography using petroleum ether as eluant.

4. General procedure for synthesis of trifluoroalkenes



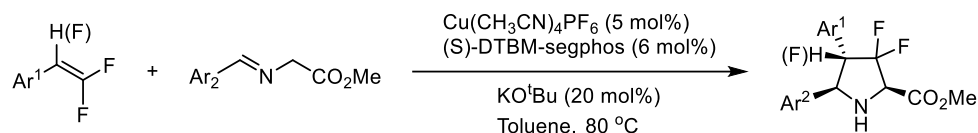
Trifluoroalkenes was prepared according to literature procedures³.

(a) In 100 mL flask, 20 mL anhydrous THF and aldehyde (20 mmol) was added following by adding (trifluoromethyl)trimethylsilane (3.9 mL, 26 mmol) and TBAF (1 M in THF, 0.2 mL, 0.2 mmol) at 0 °C under nitrogen atmosphere. After 10 min, the ice bath was removed, and the solution was stirred at room temperature for 6 h. Then, 1 M HCl solution (30 mL) was added. The reaction mixture was stirred vigorously for 1 h and then extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the desired product.

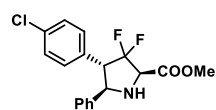
(b) The step (a) obtained the product (20 mmol) was added in dry DCM (20 mL), and DAST (2.6 mL, 20 mmol) was slowly added by syringe at -78 °C under nitrogen atmosphere. The resulting mixture was stirred at -78 °C for 5 h. After the reaction was completed, the reaction mixture was rose to 0 °C and then added to saturate sodium carbonate. The mixture solvent was extracted with DCM. The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the corresponding product.

(c) The step (b) obtained the product (12 mmol) was added in THF (30 mL), and then LHMDS (15 mL, 15 mmol) was slowly added at 0 °C under nitrogen atmosphere. The solution was stirred at room temperature for overnight. After the trifluoromethyl consumed completely, the mixture was cooled to 0 °C, and added water and extracted with ethyl acetate. The combined organic phase was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography to give the desired product.

5. General procedure for the cycloaddition reactions of iminoester to *gem*-difluoroalkenes and trifluoroalkenes

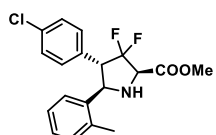


A given amount of catalyst (*S*)-DTBM-segphos (14.2mg, 0.012 mmol) and $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ (3.7mg, 0.01 mmol) were dissolved in 2.0 mL of toluene at room temperature. The mixture was stirred for 30 min. After that, KO^tBu (4.5mg, 0.04mmol), iminoester (0.4mmol, 2.0 equiv), *gem*-difluoroalkenes or trifluoroalkenes (0.2 mmol, 1.0 equiv) was added in the solution and kept at 80°C. After reaction completion (according with the TLC), the reaction mixture was purified by flash chromatography on silica gel to give the pure fluorinated tetrahydropyrrolidine compounds.



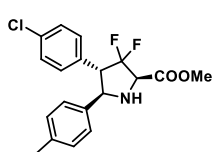
(3a) (2*R*, 4*S*, 5*R*)-4-(4-chlorophenyl)-3,3-difluoro-5-phenylpyrrolidine-2-carboxylatemethyl: Yield (91%); Colorless oil; $[\alpha]^{25}_{\text{D}} = -72.400$ ($c = 1$,

CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.37 (d, $J = 6.0$ Hz, 2H), 7.31-7.19 (m, 5H), 7.16 (d, $J = 6.0$ Hz, 2H), 4.54 (d, $J = 12.0$ Hz, 1H), 4.29 (dd, $J = 18.0, 6.0$ Hz, 1H), 3.87 (s, 3H), 3.50 (m, 1H), 2.68 (s, 1H, NH); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.63 (d, $J = 9.0$ Hz), 138.85, 134.10, 130.98, 130.38, 128.86, 128.85, 128.50, 127.41 (dd, $J = 262.7, 262.7$ Hz), 66.10 (dd, $J = 30.2, 25.7$ Hz), 64.38 (d, $J = 9.0$ Hz), 58.35 (t, $J = 21.1$ Hz), 53.14; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -98.62 (d, $J = 226.0$ Hz), -105.66 (d, $J = 226.0$ Hz). HRMS Calcd. For $[\text{C}_{18}\text{H}_{17}\text{ClF}_2\text{NO}_2]^+$: 352.0910, found: 352.0909. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralcel OD-3 column, *i*propanol/hexane = 20/80, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_{\text{r}} = 20.55$ and 34.47 min.



(3b) (2*R*, 4*S*, 5*R*)-4-(4-chlorophenyl)-3,3-difluoro-5-(*o*-tolyl)pyrrolidine-2-carboxylatemethyl: Yield (66%); Colorless oil; $[\alpha]^{25}_{\text{D}} = -22.400$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.55 (m, 1H), 7.27-7.14 (m,

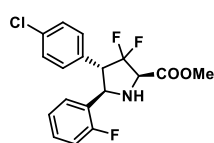
6H), 7.14-7.08 (m, 1H), 4.77 (d, $J = 12.0$ Hz, 1H), 4.28 (dd, $J = 18.0, 6.0$ Hz, 1H), 3.88 (s, 3H), 3.62 (m, 1H), 2.54 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.42 (d, $J = 7.55$ Hz), 137.23, 136.41, 134.11, 131.50, 130.78, 128.85, 128.23, 128.05 (dd, $J = 261.2, 261.2$ Hz), 126.80, 125.77, 66.64 (dd, $J = 30.2, 24.2$ Hz), 60.45 (d, $J = 9.0$ Hz), 57.77 (t, $J = 21.1$ Hz), 53.13, 19.51; ^{19}F NMR (565 MHz, Chloroform- d) δ -98.55 (d, $J = 231.6$ Hz), -105.40 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{19}\text{H}_{19}\text{ClF}_2\text{NO}_2]^+$: 366.1067, found: 366.1070. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralcel OD-3 column, i propanol/hexane = 25/75, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_r = 22.52$ and 23.66 min.



(3c) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(p-tolyl)pyrrolidine-2-

carboxylatemethyl: Yield (95%); Colorless oil; $[\alpha]^{25}_D = -61.400$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.31-7.22 (m, 4H), 7.16 (d, $J =$

12.0 Hz, 2H), 7.10 (d, $J = 6.0$ Hz, 2H), 4.51 (d, $J = 12.0$ Hz, 1H), 4.27 (m, 1H), 3.88 (s, 3H), 3.54-3.43 (m, 1H), 2.68 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.60 (d, $J = 7.55$ Hz), 138.31, 135.79, 134.10, 130.98, 129.59, 128.85, 128.79 (dd, $J = 282.3, 271.8$ Hz), 127.09, 66.29 (t), 64.26 (d, $J = 6.0$ Hz), 58.95 (m), 53.09, 21.23; ^{19}F NMR (565 MHz, Chloroform- d) δ -98.16 (d, $J = 231.6$ Hz), -105.01 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{19}\text{H}_{19}\text{ClF}_2\text{NO}_2]^+$: 366.1067, found: 366.1065. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralcel OD-3 column, i propanol/hexane = 15/85, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_r = 20.14$ and 45.69 min.

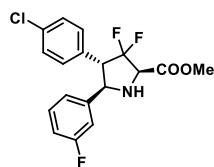


(3d) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(2-fluorophenyl)pyrrolidine-2-

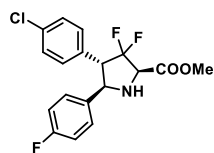
carboxylatemethyl: Yield (88%); Light yellow oil; $[\alpha]^{25}_D = -48.200$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.63 (m, 1H), 7.34-7.21

(m, 3H), 7.19 (d, $J = 6.0$ Hz, 2H), 7.14 (m, 1H), 6.96 (m, 1H), 4.93 (d, $J = 6.0$ Hz, 1H), 4.30 (dd, $J = 12.0, 6.0$ Hz, 1H), 3.88 (s, 3H), 3.62 (m, 1H), 2.76 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.52 (d, $J = 9.0$ Hz), 161.03 (d, $J = 246.1$ Hz), 134.28, 130.89, 130.01 (d, $J = 7.5$ Hz), 129.90, 128.84, 128.54 (d, $J = 4.5$ Hz), 127.06 (dd, $J = 262.7, 259.7$ Hz), 125.78 (d, $J = 12.0$ Hz), 124.91 (d, $J = 4.5$ Hz), 115.80 (d, $J = 22.6$ Hz), 66.06 (dd, $J = 31.7, 25.6$ Hz), 57.43 (t), 57.15 (dd, $J = 7.5, 1.5$ Hz), 53.09; ^{19}F NMR (565 MHz, Chloroform- d) δ -99.38 (d, $J = 231.6$ Hz), -106.18 (d, $J = 231.6$ Hz), -118.48. HRMS Calcd. For $[\text{C}_{18}\text{H}_{16}\text{ClF}_3\text{NO}_2]^+$: 370.0816, found: 370.0818. The product was

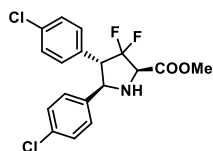
analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 220 nm); t_r = 15.72 and 23.52 min.



(3e) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(3-fluorophenyl)pyrrolidine-2-carboxylate methyl: Yield (60%); Yellow oil; $[\alpha]^{25}_D$ = -66.700 (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.29 (d, J = 6.0 Hz, 2H), 7.23 (m, 1H), 7.17 (d, J = 6.0 Hz, 3H), 7.09 (m, 1H), 6.94 (m, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.30 (dd, J = 18.0, 6.0 Hz, 1H), 3.88 (s, 3H), 3.47 (m, 1H), 2.66 (s, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.68 (d, J = 9.0 Hz), 163.09 (d, J = 247.6 Hz), 142.04 (d, J = 7.5 Hz), 134.40, 131.06, 130.34 (d, J = 7.5 Hz), 130.08, 128.98, 126.95 (dd, J = 261.2, 261.2 Hz), 122.85 (d, J = 3.0 Hz), 115.44 (d, J = 21.1 Hz), 114.18 (d, J = 22.6 Hz), 65.86 (dd, J = 30.2, 24.1 Hz), 63.94 (d, J = 7.5 Hz), 58.34 (t), 53.11; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -99.68 (d, J = 231.6 Hz), -106.75 (d, J = 231.6 Hz), -112.14. HRMS Calcd. For $[\text{C}_{18}\text{H}_{16}\text{ClF}_3\text{NO}_2]^+$: 370.0816, found: 370.0817. The product was analyzed by HPLC to determine the enantiomeric excess: 90% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 220 nm); t_r = 17.34 and 18.20 min.



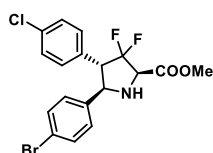
(3f) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(4-fluorophenyl)pyrrolidine-2-carboxylate methyl: Yield (71%); Colorless oil; $[\alpha]^{25}_D$ = -79.200 (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.38-7.30 (m, 2H), 7.28 (d, J = 6.0 Hz, 2H), 7.18 (d, J = 6.0 Hz, 2H), 6.97 (t, J = 6.0 Hz, 2H), 4.54 (d, J = 12.0 Hz, 1H), 4.28 (m, 1H), 3.88 (s, 3H), 3.45 (m, 1H), 2.62 (s, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.75 (d, J = 9.0 Hz), 162.70 (d, J = 247.6 Hz), 135.01 (d, J = 3.0 Hz), 134.30, 131.03, 130.20, 128.93, 128.85 (d, J = 7.2 Hz), 127.07 (dd, J = 264.2, 259.7 Hz), 115.76 (d, J = 21.1 Hz), 65.92 (dd, J = 30.2, 24.1 Hz), 63.81 (d, J = 7.5 Hz), 58.47 (t), 53.07; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -99.51 (d, J = 231.6 Hz), -106.48 (d, J = 231.6 Hz), -113.67. HRMS Calcd. For $[\text{C}_{18}\text{H}_{16}\text{ClF}_3\text{NO}_2]^+$: 370.0816, found: 370.0818. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 220 nm); t_r = 13.31 and 15.38 min.



(3g) (2R, 4S, 5R)-4,5-bis(4-chlorophenyl)-3,3-difluoropyrrolidine-2-carbo-

-xylatemethyl: Yield (81 %); White solid; $[\alpha]^{25}_D = -115.10$ ($c = 1$, CHCl_3);

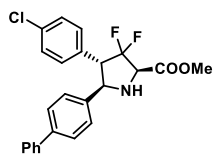
^1H NMR (600 MHz, Chloroform- d) δ 7.34 (m, 4H), 7.25 (d, $J = 6.0$ Hz, 2H), 7.15 (d, $J = 12.0$ Hz, 2H), 4.53 (d, $J = 12.0$ Hz, 1H), 4.33 (m, 1H), 3.87 (s, 3H), 3.44 (m, 1H), 2.62 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.74 (d, $J = 9.0$ Hz), 137.88, 134.36, 134.19, 131.05, 130.05, 129.00, 128.95, 128.54, 126.95 (dd, $J = 262.7, 258.2$ Hz), 65.84 (dd, $J = 30.1, 24.8$ Hz), 63.84 (d, $J = 7.7$ Hz), 58.39 (t), 53.06; ^{19}F NMR (565 MHz, Chloroform- d) δ -99.67 (d, $J = 231.6$ Hz), -106.65 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{F}_2\text{NO}_2]^+$: 386.0521, found: 386.0524. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralcel OD-3 column, i propanol/hexane = 10/90, flow rate = 1.0 mL/min, $\lambda = 220$ nm); $t_r = 18.98$ and 20.24 min.



(3h) (2R, 4S, 5R)-5-(4-bromophenyl)-4-(4-chlorophenyl)-3,3-difluoropyr-

rolidine-2-carboxylatemethyl: Yield (79 %); White solid; $[\alpha]^{25}_D = -95.500$

($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.40 (d, $J = 12.0$ Hz, 2H), 7.29 (d, $J = 6.0$ Hz, 2H), 7.25 (d, $J = 12.0$ Hz, 2H), 7.15 (d, $J = 6.0$ Hz, 2H), 4.52 (d, $J = 12.0$ Hz, 1H), 4.29 (m, 1H), 3.88 (s, 3H), 3.43 (m, 1H), 2.64 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.75 (d, $J = 9.0$ Hz), 138.40, 134.40, 131.98, 131.06, 130.02, 128.97, 128.88, 126.93 (dd, $J = 262.7, 258.2$ Hz), 122.38, 65.84 (dd, $J = 30.2, 25.6$ Hz), 63.91 (d, $J = 7.5$ Hz), 58.36 (t), 53.10; ^{19}F NMR (565 MHz, Chloroform- d) δ -99.70 (d, $J = 231.6$ Hz), -106.72 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{18}\text{H}_{16}\text{BrClF}_2\text{NO}_2]^+$: 430.0016, found: 430.0014. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralcel OD-3 column, i propanol/hexane = 25/75, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_r = 15.87$ and 17.79 min.

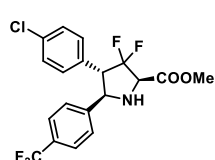


(3i) (2R, 4S, 5R)-5-([1,1'-biphenyl]-4-yl)-4-(4-chlorophenyl)-3,3-difluorop-

yrrolidine-2-carboxylatemethyl: Yield (74 %); White solid; $[\alpha]^{25}_D = -96.600$

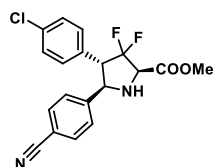
($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.49-7.41 (m, 4H), 7.39-7.30 (m, 4H), 7.28-7.19 (m, 3H), 7.12 (d, $J = 6.0$ Hz, 2H), 4.53 (d, $J = 6.0$ Hz, 1H), 4.23 (dd, $J = 18.0, 6.0$ Hz, 1H), 3.81 (s, 3H), 3.47 (m, 1H), 2.82 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.75 (d, $J = 9.0$ Hz), 141.51, 140.70, 138.06, 134.33, 131.15, 130.60, 129.03, 129.02, 127.72,

127.70, 127.30 (dd, $J = 264.2, 255.1$ Hz), 127.68, 127.27, 66.28 (dd, $J = 30.2, 24.1$ Hz), 64.26 (d, $J = 7.5$ Hz), 58.46 (t), 53.21; ^{19}F NMR (565 MHz, Chloroform- d) δ -98.95 (d, $J = 237.3$ Hz), -105.86 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{24}\text{H}_{21}\text{ClF}_2\text{NO}_2]^+$: 428.1223, found: 428.1226. The product was analyzed by HPLC to determine the enantiomeric excess: 86% ee (Chiralpak AS-3 column, i propanol/hexane = 25/75, flow rate = 0.5 mL/min, $\lambda = 254$ nm); $t_r = 22.52$ and 28.89 min.



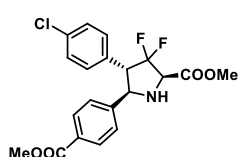
(3j) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate methyl:

Yield (96 %); Colorless oil; $[\alpha]^{25}_D = -61.000$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.56-7.48 (m, 4H), 7.30 (d, $J = 12.0$ Hz, 2H), 7.17 (d, $J = 6.0$ Hz, 2H), 4.64 (d, $J = 12.0$ Hz, 1H), 4.33 (dd, $J = 18.0, 6.0$ Hz, 1H), 3.89 (s, 3H), 3.48 (m, 1H), 2.70 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.79 (d, $J = 9.0$ Hz), 143.61, 134.55, 131.11, 129.82, 129.05, 127.58, 126.75 (dd, $J = 262.7, 258.2$ Hz), 125.78 (q), 65.73 (dd, $J = 30.2, 25.6$ Hz), 63.95 (d, $J = 7.5$ Hz), 58.89 (t), 53.12; ^{19}F NMR (565 MHz, Chloroform- d) δ -62.65, -100.11 (d, $J = 231.6$ Hz), -107.19 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{19}\text{H}_{16}\text{ClF}_5\text{NO}_2]^+$: 420.0784, found: 420.0789. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralcel OD-3 column, i propanol/hexane = 25/75, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_r = 11.33$ and 13.27 min.



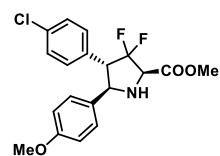
(3k) (2R, 4S, 5R)-4-(4-chlorophenyl)-5-(4-cyanophenyl)-3,3-difluoropyrrolidine-2-carboxylate methyl:

Yield (78 %); Yellow solid; $[\alpha]^{25}_D = -145.40$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.55 (d, $J = 6.0$ Hz, 2H), 7.50 (d, $J = 6.0$ Hz, 2H), 7.30 (d, $J = 6.0$ Hz, 2H), 7.15 (d, $J = 6.0$ Hz, 2H), 4.64 (dd, $J = 12.0, 12.0$ Hz, 1H), 4.34 (m, 1H), 3.87 (s, 3H), 3.56 (m, 1H), 2.67 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.96 (d, $J = 10.5$ Hz), 145.38, 134.59, 132.53, 131.13, 129.31, 129.04, 127.91, 126.75 (dd, $J = 261.2, 256.7$ Hz), 118.71, 112.06, 65.25 (dd, $J = 30.2, 25.6$ Hz), 63.79 (d, $J = 7.5$ Hz), 58.06 (t), 53.12; ^{19}F NMR (565 MHz, Chloroform- d) δ -100.91 (d, $J = 231.6$ Hz), -108.04 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{19}\text{H}_{16}\text{ClF}_2\text{N}_2\text{O}_2]^+$: 377.0863, found: 377.0865. The product was analyzed by HPLC to determine the enantiomeric excess: 85% ee (Chiralcel OD-3 column, i propanol/hexane = 25/75, flow rate 0.5 mL/min, $\lambda = 220$ nm); $t_r = 18.51$ and 27.89 min.



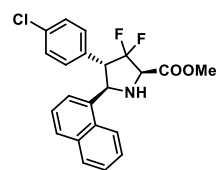
(3l) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(4-(methoxy-carbon-yl)phenyl)pyrrolidine-2-carboxylatemethyl: Yield (81 %); White solid;

$[\alpha]^{25}_D = -84.600$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.94 (d, $J = 6.0$ Hz, 2H), 7.44 (d, $J = 6.0$ Hz, 2H), 7.28 (d, $J = 12.0$ Hz, 2H), 7.15 (d, $J = 12.0$ Hz, 2H), 4.61 (d, $J = 12.0$ Hz, 1H), 4.32 (dd, $J = 18.0, 6.0$ Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.48 (m, 1H), 2.69 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.70 (d, $J = 9.0$ Hz), 166.78, 144.49, 134.42, 131.07, 130.29, 130.09, 129.96, 128.97, 127.20, 126.90 (dd, $J = 259.7, 259.7$ Hz), 65.86 (dd, $J = 31.7, 25.6$ Hz), 64.24 (d, $J = 7.5$ Hz), 58.45 (t), 53.09, 52.26; ^{19}F NMR (565 MHz, Chloroform- d) δ -99.75 (d, $J = 231.6$ Hz), -106.79 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{20}\text{H}_{19}\text{ClF}_2\text{NO}_4]^+$: 410.0965, found: 410.0967. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak IA-3 column, i propanol/hexane = 25/75, flow rate = 0.5 mL/min, $\lambda = 254$ nm); $t_r = 35.11$ and 41.35 min.



(3m) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(4-methoxyphenyl)pyrrolidine-2-carboxylatemethyl: Yield (80%); Yellow oil; $[\alpha]^{25}_D = -$

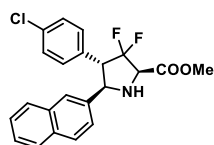
70.500 ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.32-7.25 (m, 4H), 7.16 (d, $J = 12.0$ Hz, 2H), 6.82 (d, $J = 6.0$ Hz, 2H), 4.49 (d, $J = 12.0$ Hz, 1H), 4.27 (dd, $J = 18.0, 6.0$ Hz, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 3.47 (m, 1H), 2.58 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.55 (d, $J = 9.0$ Hz), 159.57, 133.98, 130.88, 130.78, 130.54, 128.74, 128.25, 127.42 (dd, $J = 261.2, 258.2$ Hz), 114.13, 66.10 (dd, $J = 30.2, 24.1$ Hz), 63.87 (d, $J = 7.5$ Hz), 58.23 (t), 55.22, 52.94; ^{19}F NMR (565 MHz, Chloroform- d) δ -98.83 (d, $J = 231.6$ Hz), -105.71 (d, $J = 237.3$ Hz). HRMS Calcd. For $[\text{C}_{19}\text{H}_{19}\text{ClF}_2\text{NO}_3]^+$: 382.1016, found: 382.1019. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralcel OD-3 column, i propanol/hexane = 25/75, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_r = 19.38$ and 30.08 min.



(3n) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(naphthalen-1-yl)pyrrolidine-2-carboxylatemethyl: Yield (83 %); White solid; $[\alpha]^{25}_D = 113.10$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 8.29 (d, $J = 12.0$ Hz, 1H),

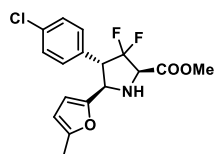
7.82 (d, $J = 6.0$ Hz, 1H), 7.76 (d, $J = 6.0$ Hz, 1H), 7.53 (m, 1H), 7.46-7.49 (m, 2H), 7.36 (m, 1H), 7.24-7.17 (m, 4H), 5.30 (m, 1H), 4.37 (m, 1H), 4.00-3.74 (m, 4H), 2.70 (s, 1H); ^{13}C NMR (151

MHz, Chloroform-*d*) δ 169.11 (d, J = 6.0 Hz), 134.02, 133.92, 133.23, 132.11, 130.74, 130.53, 129.18, 128.91, 128.84, 128.19 (dd, J = 261.2, 261.2 Hz), 126.60, 126.05, 125.38, 123.87, 123.80, 66.66 (dd, J = 30.2, 24.1 Hz), 59.56 (d, J = 7.5 Hz), 56.13 (t), 53.20; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -96.88 (d, J = 231.6 Hz), -104.39 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{22}\text{H}_{19}\text{ClF}_2\text{NO}_2]^+$: 402.1067, found: 402.1069. The product was analyzed by HPLC to determine the enantiomeric excess: 89% ee (Chiralpak AS-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 254 nm); t_r = 21.56 and 26.10 min.



(3o) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(naphthalen-2-yl)pyrrolidine-2-carboxylatemethyl: Yield (97 %); White solid; $[\alpha]^{25}_{\text{D}}$ = -56.700 (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.89-7.68 (m, 4H), 7.56

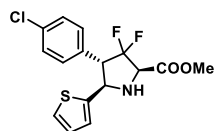
(dd, J = 12.0, 6.0 Hz, 1H), 7.52-7.43 (m, 2H), 7.27 (d, J = 6.0 Hz, 2H), 7.19 (d, J = 6.0 Hz, 2H), 4.71 (d, J = 12.0 Hz, 1H), 4.35 (dd, J = 18.0, 6.0 Hz, 1H), 3.91 (s, 3H), 3.70 (m, 1H), 2.61 (s, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.69 (d, J = 9.0 Hz), 136.41, 134.18, 133.40, 133.25, 131.03, 130.43, 128.87, 128.84, 128.08, 127.78, 127.36 (dd, J = 261.2, 258.2 Hz), 126.53, 126.42, 126.36, 124.68, 66.16 (dd, J = 30.2, 25.6 Hz), 64.69 (d, J = 9.0 Hz), 58.91 (t), 53.08; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -99.02 (d, J = 231.6 Hz), -105.83 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{22}\text{H}_{19}\text{ClF}_2\text{NO}_2]^+$: 402.1067, found: 402.1072. The product was analyzed by HPLC to determine the enantiomeric excess: 87% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 254 nm); t_r = 26.29 and 29.15 min.



(3p) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(5-methylfuran-2-yl)pyrrolidine-2-carboxylatemethyl: Yield (54 %); Yellow oil; $[\alpha]^{25}_{\text{D}}$ = -87.800 (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.30 (d, J = 6.0

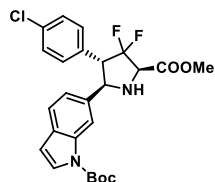
Hz, 2H), 7.17 (d, J = 12.0 Hz, 2H), 6.07 (m, 1H), 5.83 (m, 1H), 4.48 (m, 1H), 4.19 (m, 1H), 3.87 (s, 3H), 3.65 (m, 1H), 2.86 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.78 (d, J = 6.0 Hz), 152.88, 148.95, 134.26, 130.75, 130.74, 130.71, 128.99, 127.97 (dd, J = 261.2, 261.2 Hz), 109.38, 106.53, 66.76 (dd, J = 30.2, 24.1 Hz), 58.52 (d, J = 9.0 Hz), 56.45 (dd, J = 22.6, 21.1 Hz), 53.27, 13.78; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -97.62 (d, J = 231.6 Hz), -104.26 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{17}\text{H}_{16}\text{ClF}_2\text{NO}_3]^+$: 356.0860, found: 356.0862. The product was analyzed

by HPLC to determine the enantiomeric excess: 71% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 220 nm); t_r = 12.20 and 16.82 min.



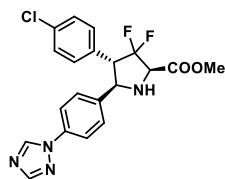
(3q) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(thiophen-2-yl)pyrrolidine-2-carboxylatemethyl: Yield (85 %); Yellow solid; $[\alpha]^{25}_D$ = -37.200 (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.32 (d, J = 12.0 Hz, 2H),

7.23-7.18 (m, 3H), 6.90-6.86 (m, 2H), 4.81 (m, 1H), 4.26 (m, 1H), 3.87 (s, 3H), 3.52 (m, 1H), 2.79 (s, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.03 (d, J = 7.5 Hz), 142.45, 134.41, 130.97, 130.23, 128.99, 127.34 (dd, J = 262.7, 259.7 Hz), 126.97, 125.38, 125.29, 66.35 (dd, J = 30.2, 24.1 Hz), 60.12 (d, J = 9.0 Hz), 59.24 (dd, J = 22.6, 19.6 Hz), 53.15; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -98.38 (d, J = 231.6 Hz), -105.57 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{16}\text{H}_{15}\text{ClF}_2\text{NO}_2\text{S}]^+$: 358.0475, found: 358.0477. The product was analyzed by HPLC to determine the enantiomeric excess: 83% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 220 nm); t_r = 22.65 and 47.24 min.

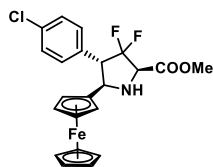


(3r) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(6-tert-butoxycarbonyl-1-indol-1-yl)pyrrolidine-2-carboxylatemethyl: Yield (56 %); Yellow solid; $[\alpha]^{25}_D$ = -68.900 (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 8.05-

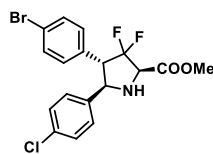
8.02 (m, 1H), 7.56-7.59 (m, 2H), 7.32 (d, J = 6.0 Hz, 1H), 7.25 (d, J = 6.0 Hz, 2H), 7.16 (d, J = 12.0 Hz, 2H), 6.51 (d, J = 6.0 Hz, 1H), 4.61 (dd, J = 12.0, 6.0 Hz, 1H), 4.31 (d, J = 18.0 Hz, 1H), 3.90 (s, 3H), 3.55 (m, 1H), 2.73 (s, 1H), 1.64 (s, 9H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.77 (d, J = 7.5 Hz), 149.69, 134.01, 133.11, 130.98, 130.88, 130.46, 128.81, 127.46 (dd, J = 261.2, 259.7 Hz), 126.66, 123.37, 119.65, 115.50, 107.33, 66.17 (dd, J = 30.2, 25.6 Hz), 64.66 (d, J = 7.5 Hz), 58.69 (t), 53.16, 28.24; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -98.76 (d, J = 231.6 Hz), -105.74 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{25}\text{H}_{26}\text{ClF}_2\text{N}_2\text{O}_4]^+$: 491.1544, found: 491.1547. The product was analyzed by HPLC to determine the enantiomeric excess: 90% ee (Chiralcel OD-3 column, *i*propanol/hexane = 20/80, flow rate = 0.3 mL/min, λ = 254 nm); t_r = 30.91 and 34.32 min.



(3s) (2R, 4S, 5R)-5-(4-(1H-1,2,4-triazol-1-yl)phenyl)-4-(4-chlorophenyl)-3,3-difluoropyrrolidine-2-carboxylatemethyl: Yield (87 %); White solid; $[\alpha]^{25}_D = -95.300$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 8.50 (s, 1H), 8.07 (s, 1H), 7.58 (d, $J = 6.0$ Hz, 2H), 7.52 (d, $J = 12.0$ Hz, 2H), 7.29 (d, $J = 6.0$ Hz, 2H), 7.17 (d, $J = 6.0$ Hz, 2H), 4.64 (m, 1H), 4.33 (d, $J = 18.0$ Hz, 1H), 3.88 (s, 3H), 3.48 (m, 1H), 2.70 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.82 (d, $J = 9.0$ Hz), 152.75, 140.91, 139.77, 136.91, 134.46, 131.56, 131.10, 129.87, 128.99, 128.62, 126.74 (dd, $J = 262.7$, 258.2 Hz), 120.34, 65.73 (dd, $J = 30.2$, 24.1 Hz), 63.88 (d, $J = 7.5$ Hz), 58.89 (t), 53.09; ^{19}F NMR (565 MHz, Chloroform- d) δ -100.03 (d, $J = 237.3$ Hz), -107.07 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{20}\text{H}_{18}\text{ClF}_2\text{N}_4\text{O}_2]^+$: 419.1081, found: 419.1083. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AD-3 column, i propanol/hexane = 35/65, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_r = 45.63$ and 56.33 min.

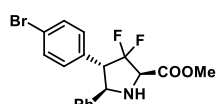


(3t) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(ferrocenyl)pyrrolidine-2-carboxylatemethyl: Yield (68 %); Brown solid; $[\alpha]^{25}_D = -42.400$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.35 (d, $J = 6.0$ Hz, 2H), 7.21 (d, $J = 6.0$ Hz, 2H), 4.23 (s, 5H), 4.17 (d, $J = 12.0$ Hz, 1H), 4.13 (d, $J = 6.0$ Hz, 1H), 4.09 (s, 2H), 3.93 (s, 2H), 3.90 (s, 3H), 3.39 (m, 1H), 3.00 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.01 (d, $J = 4.5$ Hz), 134.15, 131.94 (d, $J = 1.5$ Hz), 130.74, 129.18 (dd, $J = 262.7$, 261.2 Hz), 129.04, 89.09, 68.69, 67.99, 67.89, 67.18 (m), 66.28, 59.87 (dd, $J = 24.1$, 21.1 Hz), 59.22 (d, $J = 7.5$ Hz), 53.21; ^{19}F NMR (565 MHz, Chloroform- d) δ -96.92 (d, $J = 231.6$ Hz), -102.57 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{22}\text{H}_{21}\text{ClF}_2\text{FeNO}_2]^+$: 460.0573, found: 460.0570. The product was analyzed by HPLC to determine the enantiomeric excess: 79% ee (Chiralpak AD-3 column, i propanol/hexane = 25/75, flow rate = 0.5 mL/min, $\lambda = 254$ nm); $t_r = 18.85$ and 24.96 min.

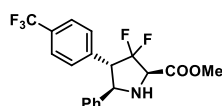


(3u) (2R, 4S, 5R)-4-(4-bromophenyl)-5-(4-chlorophenyl)-3,3-difluoropyrrolidine-2-carboxylatemethyl: Yield (79 %); White solid; $[\alpha]^{25}_D = -99.200$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.44 (d, $J = 6.0$ Hz, 2H), 7.31 (d, $J = 6.0$ Hz, 2H), 7.25 (d, $J = 6.0$ Hz, 2H), 7.09 (d, $J = 12.0$ Hz, 2H), 4.53 (dd, $J = 12.0$, 12.0 Hz, 1H), 4.28 (d, $J = 6.0$ Hz, 1H), 3.88 (s, 3H), 3.42 (m, 1H), 2.61 (s, 1H); ^{13}C NMR (151 MHz,

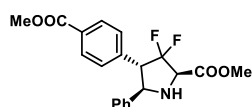
Chloroform-*d*) δ 169.75 (d, J = 9.0 Hz), 137.84, 134.25, 131.93, 131.39, 130.60, 129.04, 128.55, 126.92 (dd, J = 262.7, 259.7 Hz), 122.57, 65.87 (dd, J = 28.6, 25.6 Hz), 63.82 (d, J = 9.0 Hz), 58.48 (t), 53.11; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -99.67 (d, J = 231.6 Hz), -106.68 (d, J = 237.3 Hz). HRMS Calcd. For $[\text{C}_{18}\text{H}_{16}\text{BrClF}_2\text{NO}_2]^+$: 430.0016, found: 430.0014. The product was analyzed by HPLC to determine the enantiomeric excess: 91% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 220 nm); t_r = 13.92 and 15.11 min.



(4a) (2*R*, 4*S*, 5*R*)-4-(4-bromophenyl)-3,3-difluoro-5-phenylpyrrolidine-2-carboxylatemethyl: Yield (85 %); White solid; $[\alpha]^{25}_D$ = -74.200 (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.43 (d, J = 12.0 Hz, 2H), 7.38 (d, J = 6.0 Hz, 2H), 7.32-7.23 (m, 3H), 7.11 (d, J = 12.0 Hz, 2H), 4.55 (d, J = 12.0 Hz, 1H), 4.30 (dd, J = 24.0, 6.0 Hz, 1H), 3.88 (s, 3H), 3.50 (m, 1H), 2.68 (s, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.62 (d, J = 9.0 Hz), 138.83, 131.79, 131.33, 130.91, 128.87, 128.51, 127.36 (dd, J = 261.2, 258.2 Hz), 127.17, 122.32, 66.11 (dd, J = 30.2, 24.1 Hz), 64.33 (d, J = 7.5 Hz), 58.41 (t), 53.15; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -98.83 (d, J = 231.6 Hz), -105.85 (d, J = 237.3 Hz). HRMS Calcd. For $[\text{C}_{18}\text{H}_{17}\text{BrF}_2\text{NO}_2]^+$: 396.0405, found: 396.0404. The product was analyzed by HPLC to determine the enantiomeric excess: 90% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate 0.5 mL/min, λ = 220 nm); t_r = 22.80 and 31.95 min.

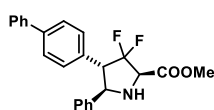


(4b) (2*R*, 4*S*, 5*R*)-3,3-difluoro-5-phenyl-4-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylatemethyl: Yield (94 %); Colorless oil; $[\alpha]^{25}_D$ = -45.200 (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.57 (d, J = 6.0 Hz, 2H), 7.44-7.34 (m, 4H), 7.33-7.25 (m, 3H), 4.62 (d, J = 12.0 Hz, 1H), 4.32 (dd, J = 18.0, 6.0 Hz, 1H), 3.89 (s, 3H), 3.62 (m, 1H), 2.71 (s, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.56 (d, J = 9.0 Hz), 138.76, 136.17, 139.36 (d, J = 33.2 Hz), 130.09, 128.97, 128.64, 127.55 (dd, J = 262.7, 258.2 Hz), 127.21, 125.56 (q), 66.24 (dd, J = 30.2, 25.6 Hz), 64.47 (d, J = 7.5 Hz), 58.75 (t), 53.12; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -62.70, -98.76 (d, J = 231.6 Hz), -105.64 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{19}\text{H}_{17}\text{F}_5\text{NO}_2]^+$: 386.1174, found: 386.1173. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 220 nm); t_r = 20.75 and 27.73 min.



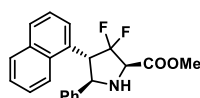
(4c) (2R, 4S, 5R)-3,3-difluoro-4-(4-(methoxycarbonyl)phenyl)-5-phenylpyrrolidine-2-carboxylatemethyl: Yield (96 %); Colorless oil; $[\alpha]^{25}_D =$

-68.500 ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.97 (d, $J = 12.0$ Hz, 2H), 7.37 (d, $J = 6.0$ Hz, 2H), 7.31 (d, $J = 6.0$ Hz, 2H), 7.29-7.22 (m, 3H), 4.62 (dd, $J = 12.0, 6.0$ Hz, 1H), 4.31 (d, $J = 18.0$ Hz, 1H), 3.88 (s, 6H), 3.59 (m, 1H), 2.71 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.50 (d, $J = 9.0$ Hz), 166.82, 138.87, 137.29, 129.98, 129.80, 128.87, 128.51, 127.60 (dd, $J = 262.7, 259.7$ Hz), 127.13, 66.32 (dd, $J = 30.2, 9.0$ Hz), 64.53 (d, $J = 7.5$ Hz), 59.06 (t), 53.07, 52.25; ^{19}F NMR (565 MHz, Chloroform- d) δ -98.68 (d, $J = 231.6$ Hz), -105.22 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{20}\text{H}_{20}\text{F}_2\text{NO}_4]^+$: 376.1355, found: 376.1357. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralcel OD-3 column, i propanol/hexane = 25/75, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_r = 27.59$ and 44.54 min.



(4d) (2R, 4S, 5R)-4-([1,1'-biphenyl]-4-yl)-3,3-difluoro-5-phenylpyrrolidine-2-carboxylatemethyl: Yield (76 %); White solid; $[\alpha]^{25}_D =$

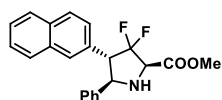
-72.100 ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.61-7.51 (m, 4H), 7.46-7.40 (m, 4H), 7.37-7.25 (m, 6H), 4.66 (d, $J = 6.0$ Hz, 1H), 4.33 (dd, $J = 18.0, 6.0$ Hz, 1H), 3.90 (s, 3H), 3.60 (m, 1H), 2.62 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.67 (d, $J = 7.5$ Hz), 140.92, 140.62, 139.28, 131.05, 130.08, 128.88, 128.85, 128.39, 127.77 (dd, $J = 261.2, 259.7$ Hz), 127.52, 127.30 (d, $J = 4.7$ Hz), 127.16, 66.35 (dd, $J = 30.2, 24.1$ Hz), 64.42 (d, $J = 7.5$ Hz), 58.68 (t), 53.06; ^{19}F NMR (565 MHz, Chloroform- d) δ -98.65 (d, $J = 231.6$ Hz), -105.34 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{24}\text{H}_{24}\text{F}_2\text{NO}_4]^+$: 394.1613, found: 394.1613. The product was analyzed by HPLC to determine the enantiomeric excess: 86% ee (Chiralcel OD-3 column, i propanol/hexane = 25/75, flow rate = 0.5 mL/min, $\lambda = 254$ nm); $t_r = 25.17$ and 38.61 min.



(4e) (2R, 4S, 5R)-3,3-difluoro-4-(naphthalen-1-yl)-5-phenylpyrrolidine-2-carboxylatemethyl: Yield (81 %); White solid; $[\alpha]^{25}_D = 41.900$ ($c = 1$, CHCl_3);

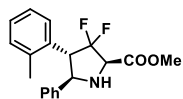
^1H NMR (600 MHz, Chloroform- d) δ 8.07 (d, $J = 6.0$ Hz, 1H), 7.85 (d, $J = 6.0$ Hz, 1H), 7.81 (d, $J = 6.0$ Hz, 1H), 7.61 (d, $J = 6.0$ Hz, 1H), 7.55-7.42 (m, 5H), 7.26-7.15 (m, 3H), 4.93 (d, $J = 10.8$ Hz, 1H), 4.56 (m, 1H), 4.39 (dd, $J = 18.0, 12.0$ Hz, 1H), 3.92 (s, 3H), 2.82 (s, 1H); ^{13}C NMR (151 MHz,

Chloroform-*d*) δ 169.46 (d, J = 6.0 Hz), 139.12, 134.07, 133.06, 128.98, 128.79, 128.68, 128.32, 128.22 (dd, J = 259.7, 259.7 Hz), 126.65, 126.54 125.82, 125.17, 123.23, 66.65 (dd, J = 30.2, 24.1 Hz), 64.15 (d, J = 9.0 Hz), 53.28 (t), 53.06; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -97.89 (d, J = 231.6 Hz), -103.78 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{22}\text{H}_{20}\text{F}_2\text{NO}_2]^+$: 368.1457, found: 368.1457. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 254 nm); t_r = 26.33 and 31.16 min.



(4f) (2R, 4S, 5R)-3,3-difluoro-4-(naphthalen-2-yl)-5-phenylpyrrolidine-2-carboxylate methyl: Yield (72 %); White solid; $[\alpha]^{25}_D$ = -71.600 (c = 1,

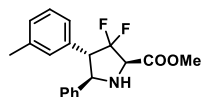
CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.82 (d, J = 12.0 Hz, 2H), 7.78 (m, 1H), 7.70 (s, 1H), 7.52-7.39 (m, 5H), 7.28 (d, J = 6.9 Hz, 2H), 7.24 (d, J = 6.0 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H), 4.37 (dd, J = 18.0, 6.0 Hz, 1H), 3.91 (s, 3H), 3.73 (m, 1H), 2.75 (s, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.62 (d, J = 7.5 Hz), 139.30, 133.32, 133.06, 129.64, 129.28, 128.81, 128.34, 128.26, 128.00, 127.91 (dd, J = 261.2, 261.2 Hz), 127.73, 127.05, 126.31, 126.30, 66.44 (dd, J = 30.2, 24.1 Hz), 64.42 (d, J = 7.5 Hz), 59.29 (t), 53.05; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -98.56 (d, J = 237.3 Hz), -104.89 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{22}\text{H}_{20}\text{F}_2\text{NO}_2]^+$: 368.1457, found: 368.1459. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 254 nm); t_r = 23.21 and 38.57 min.



(4g) (2R, 4S, 5R)-3,3-difluoro-5-phenyl-4-(o-tolyl)pyrrolidine-2-carboxylate methyl: Yield (59 %); Yellow oil; $[\alpha]^{25}_D$ = -44.800 (c = 1, CHCl_3); ^1H NMR

(600 MHz, Chloroform-*d*) δ 7.40 (d, J = 6.0 Hz, 1H), 7.37 (d, J = 6.0 Hz, 2H), 7.31-7.27 (m, 2H), 7.25-7.20 (m, 2H), 7.17 (m, 1H), 7.12 (d, J = 6.0 Hz, 1H), 4.63 (d, J = 6.0 Hz, 1H), 4.32 (dd, J = 18.0, 12.0 Hz, 1H), 4.00-3.82 (m, 4H), 2.73 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.49 (d, J = 7.5 Hz), 139.46, 138.10, 130.70, 130.62, 128.76, 128.26 (dd, J = 261.2, 261.2 Hz), 127.73, 126.99, 126.02, 66.66 (dd, J = 30.2, 25.6 Hz), 65.03 (d, J = 7.5 Hz), 54.70 (t), 52.98, 20.09; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -98.32 (d, J = 231.6 Hz), -103.81 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{19}\text{H}_{20}\text{F}_2\text{NO}_2]^+$: 332.1457, found: 332.1461. The product was analyzed by

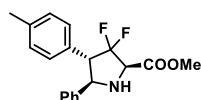
HPLC to determine the enantiomeric excess: 94% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 220 nm); t_r = 22.08 and 36.04 min.



(4h) (2R, 4S, 5R)-3,3-difluoro-5-phenyl-4-(m-tolyl)pyrrolidine-2-carboxyl-

atemethyl: Yield (74 %); Yellow oil; $[\alpha]^{25}_D$ = -40.000 (c = 1, CHCl_3); ^1H NMR

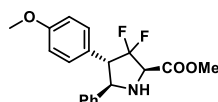
(600 MHz, Chloroform-*d*) δ 7.41 (d, J = 12.0 Hz, 2H), 7.28-7.32 (m, 2H), 7.27-7.24 (m, 1H), 7.21 m, 1H), 7.10 (d, J = 6.0 Hz, 1H), 7.05 (d, J = 12.0 Hz, 2H), 4.62 (d, J = 6.0 Hz, 1H), 4.30 (dd, J = 18.0, 6.0 Hz, 1H), 3.89 (s, 3H), 3.51 (m, 1H), 2.67 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.65 (d, J = 7.5 Hz), 139.28, 138.19, 131.86, 130.48, 128.91, 128.78, 128.43, 128.29, 127.72 (dd, J = 261.2, 258.2 Hz), 127.24, 126.59, 66.28 (dd, J = 30.2, 25.6 Hz), 64.16 (d, J = 9.0 Hz), 58.82 (t), 53.09, 21.56; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -98.67 (d, J = 231.6 Hz), -105.15 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{19}\text{H}_{20}\text{F}_2\text{NO}_2]^+$: 332.1457, found: 332.1455. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 220 nm); t_r = 20.59 and 29.40 min.



(4i) (2R, 4S, 5R)-3,3-difluoro-5-phenyl-4-(p-tolyl)pyrrolidine-2-carboxyla-

temethyl: Yield (57 %); Yellow oil; $[\alpha]^{25}_D$ = -50.000 (c = 1, CHCl_3); ^1H NMR

(600 MHz, Chloroform-*d*) δ 7.40 (d, J = 6.0 Hz, 2H), 7.29-7.22 (m, 2H), 7.24 (m, 1H), 7.16-7.09 (m, 4H), 4.60 (d, J = 12.0 Hz, 1H), 4.29 (dd, J = 18.0, 6.0 Hz, 1H), 3.88 (s, 3H), 3.51 (m, 1H), 2.66 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.70 (d, J = 7.5 Hz), 139.41, 137.81, 129.53, 129.36, 128.96, 128.77, 128.27, 127.72 (dd, J = 259.7, 256.7 Hz), 127.25, 66.33 (dd, J = 25.6, 13.5 Hz), 64.34 (d, J = 7.5 Hz), 58.65 (t), 53.00, 21.22; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -98.81 (d, J = 231.6 Hz), -105.49 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{19}\text{H}_{20}\text{F}_2\text{NO}_2]^+$: 332.1457, found: 332.1457. The product was analyzed by HPLC to determine the enantiomeric excess: 92% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 220 nm); t_r = 22.20 and 31.86 min.

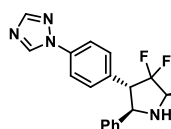


(4j) (2R, 4S, 5R)-3,3-difluoro-4-(4-methoxyphenyl)-5-phenylpyrrolidine-

2-carboxylatemethyl: Yield (75 %); Yellow solid; $[\alpha]^{25}_D$ = -59.900 (c = 1,

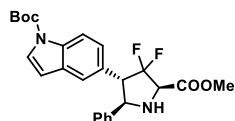
CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.39 (d, J = 12.0 Hz, 2H), 7.31-7.22 (m, 3H), 7.16

(d, $J = 6.0$ Hz, 2H), 6.84 (d, $J = 6.0$ Hz, 2H), 4.55 (d, $J = 6.0$ Hz, 1H), 4.29 (dd, $J = 18.0, 6.0$ Hz, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 3.48 (m, 1H), 2.67 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.75 (d, $J = 6.0$ Hz), 159.41, 139.42, 130.72, 128.76, 128.27, 127.61 (dd, $J = 261.2, 258.2$ Hz), 127.23, 123.89, 114.08, 66.23 (dd, $J = 30.2, 25.6$ Hz), 64.45 (d, $J = 7.5$ Hz), 58.30 (t), 55.28, 53.01; ^{19}F NMR (565 MHz, Chloroform- d) δ -98.92 (d, $J = 231.6$ Hz), -105.91 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{19}\text{H}_{20}\text{F}_2\text{NO}_3]^+$: 348.1406, found: 348.1408. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralcel OD-3 column, i propanol/hexane = 25/75, flow rate 0.5 = mL/min, $\lambda = 220$ nm); $t_r = 26.45$ and 40.50 min.



(4k) (2R, 4S, 5R)-4-(4-(1H-1,2,4-triazol-1-yl)phenyl)-3,3-difluoro-5-phenylpyrrolidine-2-carboxylatemethyl: Yield (91 %); White solid; $[\alpha]^{25}_D = -65.000$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 8.51

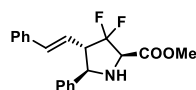
(s, 1H), 8.07 (s, 1H), 7.61 (d, $J = 6.0$ Hz, 2H), 7.44-7.31 (m, 4H), 7.31-7.22 (m, 3H), 4.61 (d, $J = 12.0$ Hz, 1H), 4.33 (dd, $J = 18.0, 6.0$ Hz, 1H), 3.88 (s, 3H), 3.60 (m, 1H), 2.75 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.53 (d, $J = 7.5$ Hz), 152.72, 138.87, 136.69, 132.18, 131.06, 128.83, 128.48, 127.42 (dd, $J = 261.2, 258.2$ Hz), 127.12, 120.07, 66.09 (dd, $J = 30.2, 25.6$ Hz), 64.46 (d, $J = 7.5$ Hz), 58.52 (t), 53.01; ^{19}F NMR (565 MHz, Chloroform- d) δ -98.85 (d, $J = 231.6$ Hz), -105.86 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{20}\text{H}_{19}\text{F}_2\text{N}_4\text{O}_2]^+$: 385.1471, found: 385.1471. The product was analyzed by HPLC to determine the enantiomeric excess: 81% ee (Chiralcel OD-3 column, i propanol/hexane = 40/60, flow rate = 1.0 mL/min, $\lambda = 220$ nm); $t_r = 37.94$ and 62.93 min.



(4l) (2R, 4S, 5R)-3,3-difluoro-4-(5-tert-butoxycarbonyl-L-indole)-5-phenylpyrrolidine-2-carboxylatemethyl: Yield (79 %); Yellow solid; $[\alpha]^{25}_D = -62.000$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 8.09 (s, 1H),

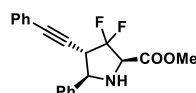
7.59 (s, 1H), 7.46-7.36 (m, 3H), 7.30-7.25 (m, 2H), 7.25-7.16 (m, 2H), 6.53 (m, 1H), 4.69 (dd, $J = 12.0, 6.0$ Hz, 1H), 4.35 (d, $J = 18.0$ Hz, 1H), 3.89 (s, 3H), 3.63 (m, 1H), 2.73 (s, 1H), 1.66 (s, 9H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.70 (d, $J = 7.5$ Hz), 149.73, 139.32, 134.84, 130.80, 128.71, 128.21, 127.64 (dd, $J = 261.2, 258.2$ Hz), 127.18, 126.45, 126.09, 125.69, 122.23, 115.20, 107.27, 66.25 (dd, $J = 30.2, 24.1$ Hz), 64.48 (d, $J = 7.5$ Hz), 59.01 (t), 53.05, 28.20; ^{19}F NMR (565 MHz, Chloroform- d) δ -98.56 (d, $J = 231.6$ Hz), -105.45 (d, $J = 231.6$ Hz). HRMS Calcd. For

$[\text{C}_{25}\text{H}_{27}\text{F}_2\text{N}_2\text{O}_4]^+$: 457.1933, found: 457.1930. The product was analyzed by HPLC to determine the enantiomeric excess: 92% ee (Chiralpak AD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 254 nm); t_r = 30.41 and 50.37 min.



(4m) (2R, 4S, 5R)-3,3-difluoro-5-phenyl-4-((E)-styryl)pyrrolidine-2-carboxylatemethyl: Yield (53 %); Colorless oil; $[\alpha]^{25}_D$ = -67.400 (c = 1, CHCl_3); ^1H

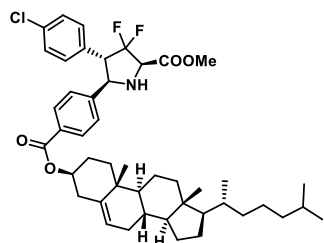
NMR (600 MHz, Chloroform-*d*) δ 7.46 (d, J = 12.0 Hz, 2H), 7.30-7.36 (m, 2H), 7.30-7.27 (m, 3H), 7.25 (d, J = 12.0 Hz, 2H), 7.20 (m, 1H), 6.29 (d, J = 12.0 Hz, 1H), 6.11 (dd, J = 18.0, 6.0 Hz, 1H), 4.24-4.17 (m, 2H), 3.85 (s, 3H), 3.11 (m, 1H), 2.59 (s, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.76 (d, J = 7.5 Hz), 139.45, 136.54, 136.41, 128.80, 128.63, 128.32, 128.24 (dd, J = 262.7, 256.7 Hz), 128.01, 127.42, 126.56, 119.62, 119.60, 65.94 (dd, J = 30.2, 25.6 Hz), 64.69 (d, J = 7.5 Hz), 57.25 (dd, J = 22.1, 19.7 Hz), 52.95; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -101.52 (d, J = 237.3 Hz), -106.13 (d, J = 237.3 Hz). HRMS Calcd. For $[\text{C}_{20}\text{H}_{20}\text{F}_2\text{NO}_2]^+$: 344.1457, found: 344.1456. The product was analyzed by HPLC to determine the enantiomeric excess: 88% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 220 nm); t_r = 20.97 and 31.71 min.



(4n) (2R, 4S, 5R)-3,3-difluoro-5-phenyl-4-(phenylethynyl)pyrrolidine-2-carboxylatemethyl: Yield (51 %); Colorless oil; $[\alpha]^{25}_D$ = -86.700 (c = 1,

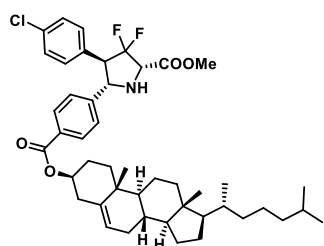
CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.60 (d, J = 6.0 Hz, 2H), 7.48-7.39 (m, 4H), 7.39-7.32 (m, 1H), 7.32-7.27 (m, 3H), 4.38 (m, 1H), 4.24 (m, 1H), 3.88 (s, 3H), 3.42 (m, 1H), 2.65 (s, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.86 (d, J = 7.5 Hz), 138.75, 131.97, 128.90, 128.65, 128.62, 128.35, 127.01, 126.57 (dd, J = 262.7, 262.7 Hz), 122.60, 66.06 (dd, J = 28.6, 25.6 Hz), 65.33 (d, J = 6.0 Hz), 53.05, 48.00 (t); ^{19}F NMR (565 MHz, Chloroform-*d*) δ -98.20 (d, J = 226.0 Hz), -104.69 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{20}\text{H}_{18}\text{F}_2\text{NO}_2]^+$: 342.1300, found: 342.1302. The product was analyzed by HPLC to determine the enantiomeric excess: 84% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 220 nm); t_r = 20.33 and 26.31 min.

(5a) (2R, 4S, 5R)-4-(4-chlorophenyl)-5-(4-((((3S, 8S, 9S, 10R, 13R, 14S, 17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[*a*]phenanthren-3-yl)oxy)carbonyl)phenyl)-3,3-difluoropyrrolidine-2-



carboxylate-methyl: Yield (72 %); White solid; $[\alpha]^{25}_D = -58.700$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.94 (d, $J = 6.0$ Hz, 2H), 7.44 (d, $J = 6.0$ Hz, 2H), 7.28 (d, $J = 6.0$ Hz, 2H), 7.15 (d, $J = 6.0$ Hz, 2H), 5.39 (m, 1H), 4.86–4.76 (m, 1H), 4.61 (dd, $J = 12.0$, 6.0 Hz, 1H), 4.32 (d, $J = 18.0$ Hz, 1H), 3.88 (s, 3H), 3.47 (m, 1H), 2.70 (s, 1H), 2.42 (d, $J = 6.0$ Hz, 2H), 2.04–1.77 (m, 6H), 1.66–1.73 (m, 2H), 1.60–1.43 (m, 7H), 1.39–1.30 (m, 4H), 1.28–1.03 (m, 16H), 0.89–0.94 (m, 3H), 0.67 (s, 3H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.71 (d, $J = 9.0$ Hz), 165.64, 144.17, 139.63, 134.35, 131.06, 130.87, 130.03, 129.85, 128.93, 127.09, 126.84 (dd, $J = 264.2$, 259.7 Hz), 122.95, 74.75, 65.81 (dd, $J = 30.2$, 25.6 Hz), 64.16 (d, $J = 7.5$ Hz), 58.42 (t), 56.73, 56.15, 53.15, 50.04, 42.37, 39.77, 39.60, 38.24, 37.05, 36.70, 36.25, 35.91, 32.00, 31.91, 28.36, 28.13, 27.91, 24.39, 23.92, 22.98, 22.70, 21.11, 19.48, 18.81, 11.96; ^{19}F NMR (565 MHz, Chloroform- d) δ -99.63 (d, $J = 231.6$ Hz), -106.79 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{46}\text{H}_{61}\text{ClF}_2\text{NO}_4]^+$: 764.4252, found: 764.4256.

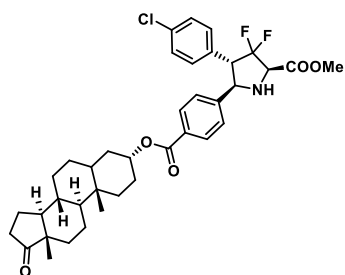
(5a') (2S, 4R, 5S)-4-(4-chlorophenyl)-5-(4-((((3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[*a*]phenanthren-3-yl)oxy)carbonyl)phenyl)-3,3-difluoropyrrolidine-2-



carboxylatemethyl: Yield (54 %); White solid; $[\alpha]^{25}_D = 14.400$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.92 (d, $J = 6.0$ Hz, 1H), 7.41 (d, $J = 6.0$ Hz, 2H), 7.24 (d, $J = 6.0$ Hz, 2H), 7.12 (d, $J = 6.0$ Hz, 2H), 5.40–5.33 (m, 1H), 4.84–4.73 (m, 1H), 4.58 (dd, $J = 12.0$, 6.0 Hz, 1H), 4.29 (d, $J = 18.0$ Hz, 1H), 3.86 (s, 3H), 3.49–3.39 (m, 1H), 2.66 (s, 1H), 2.40 (d, $J = 6.0$ Hz, 2H), 2.01–1.79 (m, 6H), 1.70–1.60 (m, 2H), 1.56–1.41 (m, 7H), 1.36–1.28 (m, 4H), 1.28–1.01 (m, 16H), 0.90–0.89 (m, 3H), 0.66 (s, 3H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.67 (d, $J = 9.0$ Hz), 165.65, 144.21, 139.70, 134.41, 131.06, 130.99, 130.06, 129.99, 128.96, 127.10, 126.94 (dd, $J = 262.7$, 258.2 Hz), 124.42, 74.81, 65.91 (dd, $J = 30.2$, 25.6 Hz), 64.25 (d, $J = 7.5$ Hz), 58.50 (t), 56.82, 56.26, 53.08, 50.16, 42.44, 39.86, 39.65, 38.30, 37.13, 36.76, 36.32, 35.93,

32.05, 32.00, 28.37, 28.14, 27.97, 24.42, 23.96, 22.96, 22.70, 21.17, 19.49, 18.85, 11.99; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -99.65 (d, J = 231.6 Hz), -106.74 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{46}\text{H}_{61}\text{ClF}_2\text{NO}_4]^+$: 764.4252, found: 764.4243.

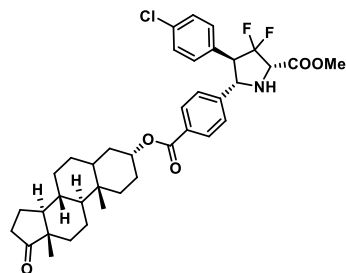
(5b) (2*R*, 4*S*, 5*R*)-4-(4-chlorophenyl)-5-(4-((((3*R*, 8*R*, 9*S*, 10*S*, 13*S*, 14*S*)-10,13-dimethyl-17-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)carbonyl)phenyl)-3,3-difluoro-



pyrrolidine-2-carboxylatemethyl: Yield (72 %); White solid; $[\alpha]^{25}_{\text{D}}$ = -23.200 (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.95 (d, J = 6.0 Hz, 2H), 7.47 (d, J = 6.0 Hz, 2H), 7.26 (d, J = 6.0 Hz, 2H), 7.15 (d, J = 6.0 Hz, 2H), 5.23 (s, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.31 (d, J = 18.0 Hz, 1H), 3.85

(s, 3H), 3.48 (m, 1H), 2.71 (s, 1H), 2.41 (m, 1H), 2.05 (m, 1H), 1.96-1.44 (m, 11H), 1.35-1.19 (m, 9H), 0.84 (d, J = 6.0 Hz, 6H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 191.71, 169.75 (d, J = 9.0 Hz), 165.43, 144.46, 134.28, 131.10, 131.02, 129.95, 128.86, 127.16, 126.78 (dd, J = 262.7, 258.2 Hz), 70.64, 65.68 (dd, J = 30.2, 24.1 Hz), 64.02 (d, J = 7.5 Hz), 58.27 (t), 54.48, 52.98, 51.49, 47.84, 40.50, 36.08, 35.89, 35.05, 33.20, 32.95, 31.59, 30.78, 28.08, 26.27, 21.78, 20.14, 13.87, 11.44; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -100.01 (d, J = 231.6 Hz), -107.13 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{38}\text{H}_{45}\text{ClF}_2\text{NO}_5]^+$: 668.2949, found: 668.2950.

(5b') (2*S*, 4*R*, 5*S*)-4-(4-chlorophenyl)-5-(4-((((3*R*, 8*R*, 9*S*, 10*S*, 13*S*, 14*S*)-10,13-dimethyl-17-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)carbonyl)phenyl)-3,3-difluoro-



pyrrolidine-2-carboxylatemethyl: Yield (61 %); White solid; $[\alpha]^{25}_{\text{D}}$ = 41.600 (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.96 (d, J = 6.0 Hz, 2H), 7.47 (d, J = 6.0 Hz, 2H), 7.28 (d, J = 6.0 Hz, 2H), 7.15 (d, J = 6.0 Hz, 2H), 5.24

(s, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.31 (dd, J = 18.0, 3.0 Hz, 1H), 3.87

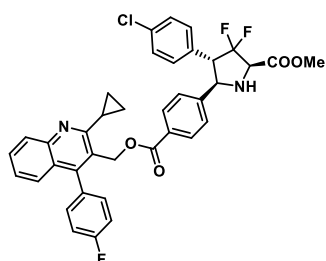
(s, 3H), 3.56 – 3.41 (m, 1H), 2.69 (s, 1H), 2.47 – 2.39 (m, 1H), 2.10 –

2.03 (m, 1H), 1.84 – 1.53 (m, 11H), 1.34 – 1.19 (m, 9H), 0.86 (d, J =

6.0 Hz, 6H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 191.67, 169.72

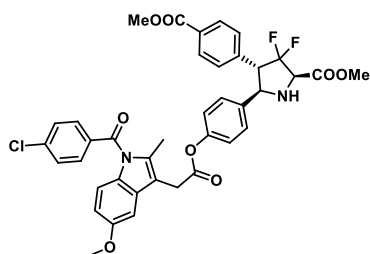
(d), 165.41, 144.35, 134.29, 131.10, 130.97, 129.93, 129.87, 128.85, 127.10, 126.75 (dd, J = 9.0 Hz, J = 261.2, 258.2 Hz), 70.61, 65.66 (dd, J = 30.2, 24.1 Hz), 64.01 (d, J = 7.5 Hz), 58.24 (t), 54.46, 52.98,

51.48, 47.82, 40.48, 36.06, 35.87, 35.03, 33.17, 32.92, 31.55, 30.77, 28.06, 26.25, 21.76, 20.11, 13.84, 11.41; ¹⁹F NMR (565 MHz, Chloroform-*d*) δ -100.01 (d, *J* = 231.6 Hz), -107.17 (d, *J* = 231.6 Hz). HRMS Calcd. For [C₃₈H₄₅ClF₂NO₅]⁺: 668.2949, found: 668.2941.



(5c) (2*R*, 4*S*, 5*R*)-4-(4-chlorophenyl)-5-(4-(((2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)methoxy)carbonyl)phenyl)-3,3-difluoropyrrolidine-2-carboxylatemethyl: Yield (78 %); White solid; [α]_D²⁵ = -63.500 (*c* = 1, CHCl₃); ¹H NMR (600 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 6.0 Hz, 1H), 7.93 (d, *J* = 12.0 Hz, 2H),

7.68-7.63 (m, 1H), 7.45 (d, *J* = 12.0 Hz, 2H), 7.35 (d, *J* = 6.0 Hz, 2H), 7.28 (m, 4H), 7.11-7.19 (m, 4H), 5.40 (s, 2H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.31 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.87 (s, 3H), 3.49 (m, 1H), 2.68 (s, 1H), 2.36 (m, 1H), 1.38-1.33 (m, 2H), 1.08-0.99 (m, 2H); ¹³C NMR (151 MHz, Chloroform-*d*) δ 169.66 (d, *J* = 6.0 Hz), 165.80, 163.59, 162.38, 148.28, 147.82, 144.85, 134.42, 132.01, 131.98, 131.44, 131.38, 131.04, 130.13, 129.93, 129.89, 129.74, 129.12, 128.95, 127.29, 126.81 (dd, *J* = 261.2, 258.2 Hz), 126.59, 126.16, 125.82, 125.05, 115.76, 115.62, 66.75 (dd, *J* = 30.2, 25.6 Hz), 64.04 (d, *J* = 7.5 Hz), 62.16, 58.28 (t), 53.05, 14.90, 9.79; ¹⁹F NMR (565 MHz, Chloroform-*d*) δ -99.84 (d, *J* = 231.6 Hz), -106.91 (d, *J* = 231.6 Hz), -113.19. HRMS Calcd. For [C₃₈H₃₁ClF₃NO₄]⁺: 671.1919, found: 671.1922. The product was analyzed by HPLC to determine the enantiomeric excess: 91% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 254 nm); *t*_r = 19.59 and 27.82 min.

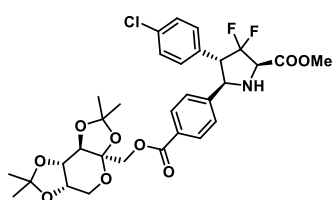


(5d) (2*R*, 4*S*, 5*R*)-5-(4-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetoxy)phenyl)-3,3-difluoro-4-(4-(methoxycarbonyl)phenyl)pyrrolidine-2-carboxylatemethyl: Yield (47 %); Yellow solid; [α]_D²⁵ = -16.200 (*c* = 1, CHCl₃); ¹H NMR (600 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 6.0 Hz, 2H), 7.66

(d, *J* = 6.0 Hz, 2H), 7.46 (d, *J* = 6.0 Hz, 2H), 7.36 (d, *J* = 12.0 Hz, 2H), 7.29 (d, *J* = 6.0 Hz, 2H), 7.01 (m, 1H), 6.97 (d, *J* = 6.0 Hz, 2H), 6.87 (d, *J* = 12.0 Hz, 1H), 6.68 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.30 (dd, *J* = 18.0, 6.0 Hz, 1H), 3.89-3.86 (m, 8H), 3.81 (s, 3H), 3.53 (m, 1H), 2.65 (s, 1H), 2.42 (s, 3H); ¹³C NMR (151 MHz, Chloroform-*d*) δ 169.57 (d, *J* = 9.0 Hz), 169.25,

168.42, 166.78, 156.24, 150.68, 139.50, 136.95, 136.84, 136.35, 133.92, 131.33, 130.95, 130.57, 130.12, 129.87, 129.84, 129.28, 128.24, 127.23 (dd, $J = 262.7, 259.7$ Hz, 1H), 121.79, 115.14, 111.98, 111.91, 101.31, 66.08 (dd, $J = 28.6, 25.6$ Hz, 1H), 63.84 (d, $J = 7.5$ Hz), 59.00 (t), 55.86, 53.09, 52.29, 30.66, 13.52; ^{19}F NMR (565 MHz, Chloroform- d) δ -99.13 (d, $J = 231.6$ Hz), -105.72 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{39}\text{H}_{34}\text{ClF}_2\text{N}_2\text{O}_8]^+$: 731.1966, found: 731.1968. The product was analyzed by HPLC to determine the enantiomeric excess: 87% ee (Chiralpak AD-3 column, i propanol/hexane = 25/75, flow rate = 0.5 mL/min, $\lambda = 254$ nm); $t_r = 40.92$ and 46.68 min.

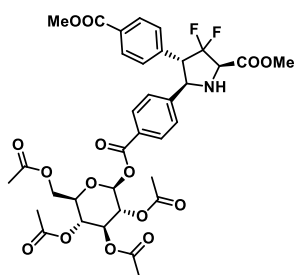
(5e) (2R, 4S, 5R)-4-(4-chlorophenyl)-3,3-difluoro-5-(4-(((3aR, 5aS, 8aS, 8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methoxy)carbonyl)-



phenyl)pyrrolidine-2-carboxylatemethyl: Yield (76 %); White solid; $[\alpha]^{25}_{\text{D}} = -77.100$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.96 (d, $J = 12.0$ Hz, 2H), 7.43 (d, $J = 6.0$ Hz, 2H), 7.27 (d, $J = 6.0$ Hz, 2H), 7.13 (d, $J = 12.0$ Hz, 2H), 4.64-4.56 (m,

3H), 4.41 (m, 1H), 4.34-4.26 (m, 2H), 4.23 (dd, $J = 12.0, 6.0$ Hz, 1H), 3.92 (dd, $J = 18.0, 6.0$ Hz, 1H), 3.87 (s, 3H), 3.77 (d, $J = 6.0$ Hz, 1H), 3.45 (m, 1H), 2.69 (s, 1H), 1.52 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (151 MHz, Chloroform- d) δ 169.71 (d, $J = 9.0$ Hz), 165.64, 144.81, 134.41, 131.07, 130.24, 129.99, 129.90, 128.94, 127.18, 126.90 (dd, $J = 261.2, 256.7$ Hz), 109.24, 108.91, 101.72, 70.86, 70.65, 70.18, 65.78 (dd, $J = 30.2, 25.6$ Hz), 65.59, 64.22 (d, $J = 7.5$ Hz), 61.44, 60.48, 58.47 (t), 53.05, 26.60, 25.93, 25.64, 24.09; ^{19}F NMR (565 MHz, Chloroform- d) δ -99.89 (d, $J = 237.3$ Hz), -106.96 (d, $J = 231.6$ Hz). HRMS Calcd. For $[\text{C}_{31}\text{H}_{35}\text{ClF}_2\text{NO}_9]^+$: 638.1963, found: 638.1966.

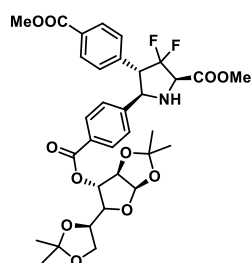
(5f) (2R, 3R, 4S, 5R, 6S)-2-(acetoxymethyl)-6-((4-((2R, 3S, 5R)-4,4-difluoro-5-(methoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)pyrrolidin-2-yl)benzoyl)oxy)tetrahydro-2H-pyran-3,4,5-



triyl triacetate: Yield (69 %); Colorless oil; $[\alpha]^{25}_{\text{D}} = -30.300$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 8.03-7.88 (m, 4H), 7.55-7.44 (m, 2H), 7.35-7.27 (m, 2H), 5.34-5.26 (m, 1H), 5.14-5.19 (m, 2H), 4.71 (dd, $J = 30.0, 12.0$ Hz, 1H), 4.39-4.22 (m, 2H), 4.19-4.04 (m, 2H), 3.88 (s, 6H), 3.59 (m, 1H), 2.72 (s, 1H), 2.06-1.92 (m, 12H);

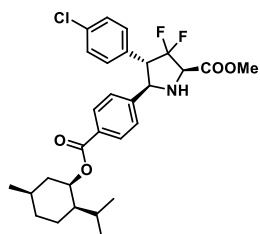
^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.57, 170.12 (d, J = 16.6 Hz), 169.73, 169.43, 169.34, 166.65, 163.98, 145.95, 145.82, 136.57, 130.64, 130.44, 130.41, 129.93, 129.83, 129.00, 127.56, 127.47, 126.90 (dd, J = 256.7, 256.7 Hz), 89.90, 72.80, 70.12, 69.55, 68.15, 65.86 (dd, J = 30.2, 6.0 Hz), 64.07 (d, J = 7.5 Hz), 61.59, 58.89 (t), 52.99, 52.22, 20.68, 20.61, 20.56, 20.46; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -100.06 (d, J = 231.6 Hz), -106.91 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{35}\text{H}_{38}\text{F}_2\text{NO}_{15}]^+$: 750.2204, found: 750.2209.

(5g) (2*R*, 4*S*, 5*R*)-5-(4-(((3*aR*, 6*S*, 6*aR*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)oxy)carbonyl)phenyl)-3,3-difluoro-4-(4-(methoxycarbonyl)phenyl)pyrrolidine-2-carboxylatemethyl: Yield (78 %); White solid;



$[\alpha]^{25}_{\text{D}} = -122.90$ (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.97 (d, J = 6.0 Hz, 2H), 7.91 (d, J = 6.0 Hz, 2H), 7.47 (d, J = 6.0 Hz, 2H), 7.30 (d, J = 6.0 Hz, 2H), 5.89 (d, J = 6.0 Hz, 1H), 5.43 (s, 1H), 4.70 (m, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.38-4.25 (m, 3H), 4.13-4.03 (m, 2H), 3.88

(d, J = 6.0 Hz, 6H), 3.57 (m, 1H), 2.72 (s, 1H), 1.53 (s, 3H), 1.38 (s, 3H), 1.29 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.64 (d, J = 10.5 Hz), 166.67, 164.85, 145.21, 136.53, 130.26, 130.19, 129.89, 129.85, 129.62, 127.36, 126.87 (dd, J = 264.2, 259.7 Hz), 112.45, 109.49, 105.18, 83.42, 79.97, 76.79, 72.62, 67.32, 65.84 (dd, J = 30.2, 25.6 Hz), 64.08 (d, J = 7.5 Hz), 58.87 (t), 53.07, 52.28, 26.94, 26.81, 26.28, 25.30; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -99.83 (d, J = 231.6 Hz), -106.62 (d, J = 231.6 Hz). HRMS Calcd. For $[\text{C}_{32}\text{H}_{38}\text{F}_2\text{NO}_{11}]^+$: 662.2407, found: 662.2403.

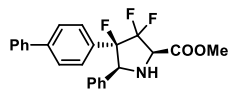


(5h) (2*R*, 4*S*, 5*R*)-4-(4-chlorophenyl)-3,3-difluoro-5-(4-(((1*R*, 2*R*, 5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)carbonyl)phenyl)pyrrolidine-2-

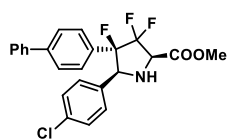
carboxylatemethyl: Yield (79 %); Colorless oil; $[\alpha]^{25}_{\text{D}} = -110.40$ (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.95 (d, J = 12.0 Hz, 2H),

7.46 (d, J = 6.0 Hz, 2H), 7.28 (d, J = 6.0 Hz, 2H), 7.16 (d, J = 12.0 Hz, 2H), 4.89 (m, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.32 (dd, J = 18.0, 6.0 Hz, 1H), 3.88 (s, 3H), 3.50 (m, 1H), 2.70 (s, 1H), 2.07 (m, 1H), 1.90 (m, 1H), 1.68-1.73 (m, 2H), 1.50-1.55 (m, 2H), 1.15-0.97 (m, 2H), 0.96-0.81 (m, 7H), 0.75-0.79 (m, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.72 (d, J = 9.0 Hz), 165.76, 144.17,

134.33, 131.05, 130.90, 130.05, 129.86, 128.93, 127.17, 126.87 (dd, $J = 261.2, 258.2$ Hz), 74.98, 65.78 (dd, $J = 30.2, 25.6$ Hz), 64.06 (d, $J = 7.5$ Hz), 58.29 (t), 53.14, 47.24, 40.96, 34.32, 31.49, 26.45, 23.54, 22.16, 20.89, 16.50; ^{19}F NMR (565 MHz, Chloroform- d) δ -99.66 (d, $J = 237.3$ Hz), -106.83 (d, $J = 237.3$ Hz). HRMS Calcd. For $[\text{C}_{29}\text{H}_{35}\text{ClF}_2\text{NO}_4]^+$: 534.2217, found: 534.2218.

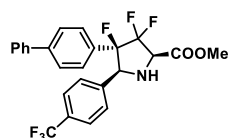


(7a) (2R, 4R, 5S)-4-([1,1'-biphenyl]-4-yl)-3,3,4-trifluoro-5-phenylpyrrolidine-2-carboxylatemethyl: Yield (82 %); White solid; $[\alpha]^{25}_{\text{D}} = -56.300$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.61 (d, $J = 12.0$ Hz, 2H), 7.58 (d, $J = 6.0$ Hz, 2H), 7.51 (d, $J = 6.0$ Hz, 2H), 7.46-7.40 (m, 4H), 7.36 (m, 1H), 7.32-7.28 (m, 3H), 4.86 (dd, $J = 30.0, 12.0$ Hz, 1H), 4.33 (d, $J = 12.0$ Hz, 1H), 3.94 (s, 3H), 3.36 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 168.17 (d, $J = 9.0$ Hz), 142.09, 140.24, 133.62, 129.99 (d, $J = 4.3$ Hz), 128.96, 128.83, 128.82, 128.76, 128.61, 127.82, 127.22, 127.16, 126.97 (dd, $J = 9.0, 3.0$ Hz), 125.06 (ddd, $J = 279.3, 255.19, 25.67$ Hz), 98.73 (ddd, $J = 240.1, 28.7, 19.6$ Hz), 66.18 (dd, $J = 18.7, 3.9$ Hz), 64.86 (dd, $J = 30.4, 22.4$ Hz), 53.38; ^{19}F NMR (565 MHz, Chloroform- d) δ -95.57 (d, $J = 242.9$ Hz), -125.76 (dd, $J = 242.9, 5.6$ Hz), -181.68 (d, $J = 11.3$ Hz). HRMS Calcd. For $[\text{C}_{24}\text{H}_{21}\text{F}_3\text{NO}_2]^+$: 412.1519, found: 412.1520. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralcel OD-3 column, i propanol/hexane = 25/75, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_{\text{r}} = 16.57$ and 22.75 min.



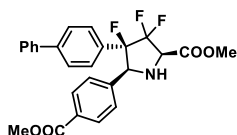
(7b) (2R, 4R, 5S)-4-([1,1'-biphenyl]-4-yl)-5-(4-chlorophenyl)-3,3,4-trifluoropyrrolidine-2-carboxylatemethyl: Yield (66 %); White solid; $[\alpha]^{25}_{\text{D}} = -67.900$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.62 (d, $J = 6.0$ Hz, 2H), 7.58 (d, $J = 6.0$ Hz, 2H), 7.48 (d, $J = 12.0$ Hz, 2H), 7.41-7.47 (m, 2H), 7.38-7.34 (m, 3H), 7.27 (d, $J = 6.0$ Hz, 2H), 4.83 (dd, $J = 30.0, 12.0$ Hz, 1H), 4.33 (d, $J = 24.0$ Hz, 1H), 3.94 (s, 3H), 3.26 (s, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 168.14 (d, $J = 9.0$ Hz), 142.27, 140.13, 134.73, 132.22, 130.16, 130.16, 129.85, 129.65, 128.98, 128.82, 127.89, 127.25, 127.23, 126.88 (dd, $J = 9.0, 3.0$ Hz), 124.79 (ddd, $J = 279.3, 255.1, 27.1$ Hz), 98.73 (ddd, $J = 241.6, 30.2, 19.6$ Hz), 65.67 (dd, $J = 19.6, 4.5$ Hz), 64.70 (dd, $J = 30.2, 22.6$ Hz), 53.41; ^{19}F NMR (565 MHz, Chloroform- d) δ -96.00 (d, $J = 242.9$ Hz), -125.65 (dd, $J = 242.9, 11.3$ Hz), -181.65 (d, $J = 11.3$ Hz). HRMS Calcd. For $[\text{C}_{24}\text{H}_{20}\text{F}_3\text{NO}_2]^+$: 446.1129, found: 446.1134. The product was analyzed by HPLC to

determine the enantiomeric excess: 94% ee (Chiralpak IA-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 220 nm); t_r = 34.13 and 37.96 min.



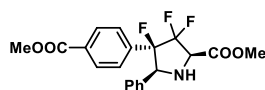
(7c) (2R, 4R, 5S)-4-([1,1'-biphenyl]-4-yl)-3,3,4-trifluoro-5-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylatemethyl: Yield (66 %); White solid; $[\alpha]^{25}_D$ = -70.700 (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*)

δ 7.63 (d, J = 6.0 Hz, 2H), 7.58 (d, J = 6.0 Hz, 2H), 7.54 (d, J = 6.0 Hz, 4H), 7.49 (d, J = 6.0 Hz, 2H), 7.45 (t, J = 6.0 Hz, 2H), 7.37 (m, 1H), 4.92 (dd, J = 30.2, 6.0 Hz, 1H), 4.34 (d, J = 18.0 Hz, 1H), 3.94 (s, 3H), 3.29 (s, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.10 (d, J = 9.0 Hz), 142.43, 140.10, 137.83, 130.93 (q), 129.58 (d, J = 22.6 Hz), 129.21 (d, J = 1.5 Hz), 129.01, 127.96, 127.33, 127.26, 126.88 (dd, J = 9.0, 1.5 Hz), 125.53 (q), 124.70 (ddd, J = 282.3, 253.6, 25.3 Hz), 98.73 (ddd, J = 241.6, 30.2, 19.6 Hz), 65.81 (dd, J = 18.1, 3.0 Hz), 64.68 (dd, J = 30.2, 22.6 Hz), 53.46; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -62.76, -96.16 (d, J = 248.6 Hz), -125.68 (dd, J = 242.9, 5.6 Hz), -181.46 (d, J = 11.3 Hz). HRMS Calcd. For $[\text{C}_{25}\text{H}_{20}\text{F}_6\text{NO}_2]^+$: 480.1393, found: 480.1390. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak IA-3 column, *i*propanol/hexane = 25/75, flow rate 0.5 = mL/min, λ = 254 nm); t_r = 24.10 and 29.39 min.



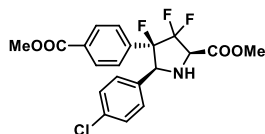
(7d) (2R, 4R, 5S)-4-([1,1'-biphenyl]-4-yl)-3,3,4-trifluoro-5-(4-(methoxy-carbonyl)phenyl)pyrrolidine-2-carboxylatemethyl: Yield

(78 %); White solid; $[\alpha]^{25}_D$ = -49.600 (c = 1, CHCl_3); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.95 (d, J = 6.0 Hz, 2H), 7.60 (d, J = 6.0 Hz, 2H), 7.57 (d, J = 12.0 Hz, 2H), 7.47 (d, J = 12.0 Hz, 4H), 7.44 (t, J = 12.0 Hz, 2H), 7.36 (t, J = 6.0 Hz, 1H), 4.90 (dd, J = 30.0, 12.0 Hz, 1H), 4.34 (d, J = 12.0 Hz, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.32 (s, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.10 (d, J = 9.0 Hz), 166.75, 142.35, 140.17, 138.65, 130.57, 129.78, 128.99, 128.84, 128.83, 127.91, 127.27, 127.26 (ddd, J = 286.9, 258.2, 31.7 Hz), 126.87 (dd, J = 10.5, 3.0 Hz), 98.44 (ddd, J = 241.6, 28.6, 19.6 Hz), 66.12 (dd, J = 19.6, 4.5 Hz), 64.79 (dd, J = 30.2, 21.1 Hz), 53.46, 52.29; ^{19}F NMR (565 MHz, Chloroform-*d*) δ -95.99 (d, J = 242.9 Hz), -125.69 (dd, J = 248.6, 11.3 Hz), -181.56 (d, J = 11.3 Hz). HRMS Calcd. For $[\text{C}_{26}\text{H}_{23}\text{F}_3\text{NO}_4]^+$: 470.1574, found: 470.1576. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak IA-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, λ = 254 nm); t_r = 46.25 and 62.12 min.



(7e) (2R, 4R, 5S)-3,3,4-trifluoro-4-(4-(methoxycarbonyl)phenyl)-5-phenylpyrrolidine-2-carboxylatemethyl: Yield (81 %); White solid;

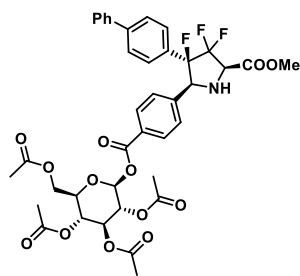
$[\alpha]^{25}_D = -43,400$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, $\text{CHloroform-}d$) δ 8.04 (d, $J = 6.0$ Hz, 2H), 7.49 (d, $J = 6.0$ Hz, 2H), 7.36-7.22 (m, 5H), 4.80 (d, $J = 30.0$ Hz, 1H), 4.32 (d, $J = 24.0$ Hz, 1H), 3.92 (d, $J = 18.0$ Hz, 6H), 3.38 (s, 1H); ^{13}C NMR (151 MHz, $\text{CHloroform-}d$) δ 168.01 (d, $J = 9.0$ Hz), 166.59, 135.98, 135.84, 132.90, 130.96, 129.63, 128.94, 128.64, 128.58, 126.58 (dd, $J = 10.5$, 3.2 Hz), 124.97 (ddd, $J = 279.3$, 256.7, 25.6 Hz), 98.53 (ddd, $J = 241.6$, 30.2, 19.6 Hz), 66.59 (dd, $J = 18.1$, 3.2 Hz), 64.84 (dd, $J = 30.2$, 22.6 Hz), 53.53, 52.47; ^{19}F NMR (565 MHz, $\text{CHloroform-}d$) δ -95.92 (d, $J = 248.6$ Hz), -125.29 (dd, $J = 248.6$, 11.3 Hz), -182.89 (d, $J = 11.3$ Hz). HRMS Calcd. For $[\text{C}_{20}\text{H}_{19}\text{F}_3\text{NO}_4]^+$: 394.1261, found: 394.1265. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralcel OD-3 column, i propanol/hexane = 25/75, flow rate = 0.5 mL/min, $\lambda = 254$ nm); $t_r = 18.38$ and 24.87 min.



(7f) (2R, 4R, 5S)-5-(4-chlorophenyl)-3,3,4-trifluoro-4-(4-(methoxycarbonyl)phenyl)pyrrolidine-2-carboxylatemethyl: Yield (59 %);

Colorless oil; $[\alpha]^{25}_D = -30.900$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, $\text{CHloroform-}d$) δ 8.05 (d, $J = 12.0$ Hz, 2H), 7.48 (d, $J = 12.0$ Hz, 2H), 7.27 (d, $J = 6.0$ Hz, 2H), 7.23 (d, $J = 6.0$ Hz, 2H), 4.79 (dd, $J = 30.0$, 6.0 Hz, 1H), 4.32 (dd, $J = 24.0$, 6.0 Hz, 1H), 3.92 (d, $J = 12.0$ Hz, 6H), 3.24 (s, 1H); ^{13}C NMR (151 MHz, $\text{CHloroform-}d$) δ 167.95 (d, $J = 6.0$ Hz), 166.49, 135.75, 135.60, 134.94, 131.63, 131.22, 129.98, 129.97, 129.74, 128.88, 126.54 (dd, $J = 9.0$, 3.0 Hz), 124.75 (ddd, $J = 279.3$, 256.7, 27.1 Hz), 98.44 (ddd, $J = 241.6$, 28.6, 19.6 Hz), 66.14 (dd, $J = 18.1$, 3.0 Hz), 64.76 (dd, $J = 30.2$, 22.6 Hz), 53.49, 52.45; ^{19}F NMR (565 MHz, $\text{CHloroform-}d$) δ -96.31 (d, $J = 242.9$ Hz), -125.16 (dd, $J = 248.6$, 11.3 Hz), -182.47 (d, $J = 5.6$ Hz). HRMS Calcd. For $[\text{C}_{20}\text{H}_{19}\text{F}_3\text{NO}_4]^+$: 394.1261, found: 394.1265. The product was analyzed by HPLC to determine the enantiomeric excess: 72% ee (Chiralpak IB-3 column, i propanol/hexane = 15/85, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_r = 40.24$ and 42.12 min.

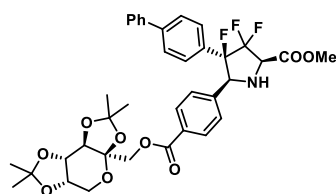
(7g) (2S, 3R, 4S, 5R, 6R)-2-((4-((2S, 3R, 5R)-3-([1,1'-biphenyl]-4-yl)-3,4,4-trifluoro-5-(methoxycarbonyl)pyrrolidin-2-yl)benzoyl)oxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-



3,4,5-triyltriacetate: Yield (65 %); Colorless oil; $[\alpha]^{25}_D = -25.000$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.97-7.87 (m, 2H), 7.64 (d, $J = 6.0$ Hz, 1H), 7.60 (d, $J = 12.0$ Hz, 2H), 7.57 (d, $J = 12.0$ Hz, 2H), 7.51 (d, $J = 6.0$ Hz, 2H), 7.48-7.33 (m, 4H), 5.23-5.11 (m, 2H), 4.90 (m, 1H), 4.39-4.24 (m, 2H), 4.20-4.02 (m, 3H), 3.94 (s, 3H),

3.29 (s, 1H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (151 MHz, Chloroform- d) δ 170.69, 170.23, 169.83, 169.50, 168.06 (d, $J = 7.5$ Hz), 163.97, 142.39, 140.08, 140.02, 130.31, 130.14, 129.12, 128.99, 128.95, 127.94, 127.88, 127.30, 127.24, 127.21, 126.85 (dd, $J = 9.06$, 9.06 Hz), 124.63 (ddd, $J = 274.8$, 255.1, 25.6 Hz), 98.71 (ddd, $J = 243.1$, 30.2, 21.1 Hz), 92.41, 89.84, 72.71, 67.96, 65.86 (dd, $J = 10.5$, 3.0 Hz), 64.61 (dd, $J = 30.2$, 21.1 Hz), 61.48, 60.49, 53.44, 20.76, 20.67, 20.55, 14.30; ^{19}F NMR (565 MHz, Chloroform- d) δ -96.29 (d, $J = 242.9$ Hz), -125.69 (dd, $J = 248.6$, 11.3 Hz), -181.28 (d, $J = 84.7$ Hz). HRMS Calcd. For $[\text{C}_{39}\text{H}_{39}\text{F}_3\text{NO}_{13}]^+$: 786.2368, found: 786.2367.

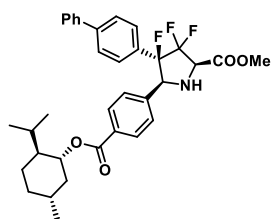
(7h) (2R, 4R, 5S)-4-([1,1'-biphenyl]-4-yl)-3,3,4-trifluoro-5-(4-(((3aR, 5aS, 8aS, 8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methoxy)carbonyl)-



phenyl)pyrrolidine-2-carboxylatemethyl: Yield (64 %); White solid; $[\alpha]^{25}_D = -12.400$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.98 (d, $J = 6.0$ Hz, 2H), 7.60 (d, $J = 6.0$ Hz, 2H), 7.57 (d, $J = 6.0$ Hz, 2H), 7.46 (d, $J = 12.0$ Hz, 4H), 7.43 (d, $J = 12.0$

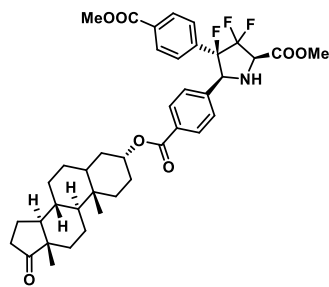
Hz, 2H), 7.36 (t, $J = 6.0$ Hz, 1H), 4.64-4.58 (m, 2H), 4.41 (d, $J = 6.0$ Hz, 1H), 4.36 (d, $J = 6.0$ Hz, 1H), 4.29 (d, $J = 12.0$ Hz, 2H), 4.23 (dd, $J = 6.0$, 6.0 Hz, 1H), 3.94 (s, 3H), 3.92 (d, $J = 6.0$ Hz, 1H), 3.77 (d, $J = 18.0$ Hz, 1H), 3.32 (s, 1H), 1.53 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (151 MHz, Chloroform- d) δ 168.09 (d, $J = 9.0$ Hz), 165.64, 142.35, 140.15, 139.40, 138.85, 135.03, 130.52, 130.31, 129.95, 129.66, 128.99, 128.83, 127.91, 124.63 (ddd, $J = 258.2$, 240.1, 25.6 Hz), 127.27 (d, $J = 2.0$ Hz), 126.86 (dd, $J = 19.6$, 10.5 Hz), 109.28, 108.95, 101.74, 98.71 (ddd, $J = 243.1$, 30.2, 21.1 Hz), 70.89, 70.81, 70.69, 70.21, 66.11, 65.71, 61.47, 53.47, 26.62, 25.96, 25.67, 24.12; ^{19}F NMR (565 MHz, Chloroform- d) δ -96.04 (d, $J = 242.9$ Hz), -125.64 (dd, $J = 248.6$, 11.3 Hz), -181.62 (d, $J = 5.6$ Hz). HRMS Calcd. For $[\text{C}_{37}\text{H}_{39}\text{F}_3\text{NO}_9]^+$: 698.2571, found: 698.2576.

(7i) (2R, 4R, 5S)-4-([1,1'-biphenyl]-4-yl)-3,3,4-trifluoro-5-(4-(((1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl)oxy)carbonyl)phenyl)pyrrolidine-2-carboxylatemethyl: Yield (43 %);



Colorless oil; $[\alpha]^{25}_D = -82.700$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.96 (d, $J = 6.0$ Hz, 2H), 7.61 (d, $J = 6.0$ Hz, 2H), 7.58 (d, $J = 12.0$ Hz, 2H), 7.49 (d, $J = 12.0$ Hz, 4H), 7.44 (t, $J = 6.0$ Hz, 2H), 7.36 (t, $J = 6.0$ Hz, 1H), 4.90 (dd, $J = 24.0, 12.0$ Hz, 1H), 4.34 (d, $J = 24.0$ Hz, 1H), 3.94 (s, 3H), 3.33 (s, 1H), 2.08 (d, $J = 12.2$ Hz, 1H), 1.92 (t, $J = 7.2$ Hz, 1H), 1.71 (d, $J = 11.6$ Hz, 2H), 1.55-1.48 (m, 3H), 1.16-1.01 (m, 2H), 0.94-0.87 (m, 9H); ^{13}C NMR (151 MHz, Chloroform- d) δ 168.08 (d, $J = 9.0$ Hz), 165.73, 142.32, 140.15, 138.46, 131.28, 129.77, 128.99, 128.83, 128.81, 127.90, 127.27, 127.25, 126.90 (dd, $J = 9.0, 3.0$ Hz), 124.82 (ddd, $J = 285.3, 258.2, 27.1$ Hz), 98.73 (ddd, $J = 241.6, 30.2, 19.6$ Hz), 75.09, 65.99 (dd, $J = 18.1, 3.0$ Hz), 64.78 (dd, $J = 30.2, 22.6$ Hz), 53.44, 47.35, 34.41, 31.55, 26.53, 23.67, 22.15, 20.90, 16.56; ^{19}F NMR (565 MHz, Chloroform- d) δ -95.91 (d, $J = 248.6$ Hz), -125.75 (dd, $J = 248.6, 11.3$ Hz), -181.49 (d, $J = 5.6$ Hz). HRMS Calcd. For $[\text{C}_{35}\text{H}_{39}\text{F}_3\text{NO}_4]^+$: 594.2826, found: 594.2827.

(7j) (2R, 4R, 5S)-5-(4-(((3R, 8R, 9S, 10S, 13S, 14S)-10,13-dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)carbonyl)phenyl)-3,3,4-trifluoro-4-(4-(methoxycarbonyl)phenyl)pyrrolidine-2-carboxylatemethyl: Yield (29 %); White

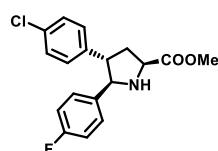


solid; $[\alpha]^{25}_D = -20.100$ ($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 8.05 (d, $J = 6.0$ Hz, 2H), 7.93 (d, $J = 6.0$ Hz, 2H), 7.49 (d, $J = 6.0$ Hz, 2H), 7.42 (d, $J = 6.0$ Hz, 2H), 5.23 (m, 1H), 4.88 (dd, $J = 30.0, 6.0$ Hz, 1H), 4.33 (m, 1H), 3.93 (s, 3H), 3.91 (s, 3H),

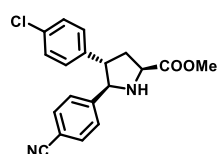
3.33 (s, 1H), 2.44 (dd, $J = 18.0, 6.0$ Hz, 1H), 2.12-2.01 (m, 1H), 1.97-1.90 (m, 1H), 1.86-1.76 (m, 3H), 1.58 (m, 6H), 1.38-1.17 (m, 9H), 1.07-0.93 (m, 1H), 0.86 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (151 MHz, Chloroform- d) δ 167.95 (d, $J = 9.0$ Hz), 166.48, 165.39, 137.97, 135.72, 135.57, 131.64, 131.24, 130.02, 129.75, 129.72, 128.65, 128.65, 126.56 (dd, $J = 10.5, 1.5$ Hz), 124.72 (ddd, $J = 279.3, 256.7, 28.6$ Hz), 98.71 (ddd, $J = 252.1, 27.1, 18.1$ Hz), 70.83, 66.46 (dd, $J = 19.6, 4.5$ Hz), 64.75 (dd, $J = 30.2, 9.0$ Hz), 54.53, 53.50, 52.48, 51.55, 47.94, 40.58, 36.16, 35.99, 35.14, 33.02, 31.65, 30.85, 28.16, 26.35, 21.87, 20.22, 13.95, 11.51; ^{19}F NMR (565 MHz, Chloroform- d) δ -96.38

(d, $J = 242.9$ Hz), -125.18 (dd, $J = 248.6, 11.3$ Hz), -182.06 (d, $J = 5.6$ Hz). HRMS Calcd. For $[C_{40}H_{47}F_3NO_7]^+$: 710.3299, found: 710.3303.

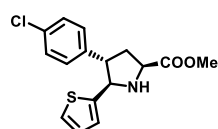
Compound **3f'**, **3k'**, **3q'**, **4b'**, **4k'** was synthesized according to general procedure for the cycloaddition reactions of iminoester to *gem*-difluoroalkenes and trifluoroalkenes.



(3f') (2S, 4S, 5R)-4-(4-chlorophenyl)-5-(4-fluorophenyl)pyrrolidine-2-carboxylatemethyl: Yield (69 %); Yellow solid; $[\alpha]^{25}_D = -63.700$ ($c = 1$, $CHCl_3$); 1H NMR (600 MHz, Chloroform-*d*) δ 7.27-7.24 (m, 2H), 7.19 (d, $J = 6.0$ Hz, 2H), 6.97 (d, $J = 6.0$ Hz, 2H), 6.94 (t, $J = 6.0$ Hz, 2H), 4.12 (dd, $J = 12.0, 6.0$ Hz, 1H), 4.09 (d, $J = 6.0$ Hz, 1H), 3.81 (s, 3H), 3.05 (m, 1H), 2.55-2.51 (m, 1H), 2.50-2.46 (m, 1H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 175.82, 162.36 (d, $J = 244.6$ Hz), 138.54, 136.90 (d, $J = 3.0$ Hz), 132.62, 128.97, 128.80 (d, $J = 7.5$ Hz), 128.75, 115.43 (d, $J = 21.1$ Hz), 70.66, 58.81, 52.52, 52.50, 38.50. HRMS Calcd. For $[C_{18}H_{18}FCINO_2]^+$: 334.1005, found: 334.1005. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralcel OD-3 column, *i*propanol/hexane = 25/75, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_r = 12.51$ and 25.43 min.

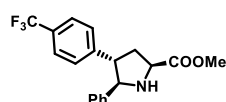


(3k') (2S, 4S, 5R)-4-(4-chlorophenyl)-5-(4-cyanophenyl)pyrrolidine-2-carboxylatemethyl: Yield (77 %); Yellow solid; $[\alpha]^{25}_D = -129.40$ ($c = 1$, $CHCl_3$); 1H NMR (600 MHz, Chloroform-*d*) δ 7.51 (d, $J = 12.0$ Hz, 2H), 7.38 (d, $J = 6.0$ Hz, 2H), 7.20 (d, $J = 12.0$ Hz, 2H), 6.96 (d, $J = 6.0$ Hz, 2H), 4.23-4.12 (m, 2H), 3.80 (s, 3H), 3.04 (m, 1H), 2.66-2.33 (m, 2H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 175.49, 147.41, 137.96, 132.87, 132.27, 128.95, 128.85, 127.84, 118.91, 111.33, 70.63, 58.69, 52.90, 52.45, 38.41. HRMS Calcd. For $[C_{19}H_{18}ClN_2O_2]^+$: 341.1051, found: 341.1053. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralcel OD-3 column, *i*propanol/hexane = 35/65, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_r = 17.05$ and 53.82 min.



(3q') (2S, 4S, 5R)-4-(4-chlorophenyl)-5-(thiophen-2-yl)pyrrolidine-2-carboxylatemethyl: Yield (75 %); Yellow solid; $[\alpha]^{25}_D = -70.900$ ($c = 1$, $CHCl_3$); 1H NMR (600 MHz, Chloroform-*d*) δ 7.23 (d, $J = 6.0$ Hz, 2H), 7.18 (d, $J = 6.0$ Hz,

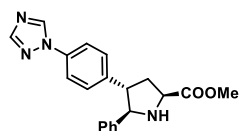
1H), 7.08 (d, $J = 6.0$ Hz, 2H), 6.87 (m, 1H), 6.81 (d, $J = 6.0$ Hz, 1H), 4.42 (d, $J = 12.0$ Hz, 1H), 4.10 (dd, $J = 12.0, 6.0$ Hz, 1H), 3.80 (s, 3H), 3.18 (m, 1H), 2.57 (m, 1H), 2.43 (m, 1H); ^{13}C NMR (151 MHz, Chloroform- d) δ 175.17, 145.04, 138.73, 132.68, 128.99, 128.78, 126.78, 124.86, 124.53, 66.35, 58.92, 52.81, 52.50, 38.75. HRMS Calcd. For $[\text{C}_{16}\text{H}_{17}\text{ClINO}_2\text{S}]^+$: 322.0663, found: 322.0662. The product was analyzed by HPLC to determine the enantiomeric excess: 99% ee (Chiralcel OD-3 column, i propanol/hexane = 15/85, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_r = 17.33$ and 30.56 min.



(4b') (2S, 4S, 5R)-5-phenyl-4-(4-(trifluoromethyl)phenyl)pyrrolidine-2-

carboxylatemethyl: Yield (75 %); Yellow solid; $[\alpha]^{25}_D = -48.500$ ($c = 1$,

CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 7.48 (d, $J = 12.0$ Hz, 2H), 7.33-7.26 (m, 4H), 7.24 (m, 1H), 7.18 (d, $J = 6.0$ Hz, 2H), 4.18 (d, $J = 12.0$ Hz, 1H), 4.16 (dd, $J = 12.0, 6.0$ Hz, 1H), 3.83 (s, 3H), 3.21 (m, 1H), 2.61-2.49 (m, 2H); ^{13}C NMR (151 MHz, Chloroform- d) δ 175.73, 144.65, 140.93, 129.09 (q), 128.70, 128.03, 127.91, 127.25, 126.09 (q), 125.50 (q), 71.32, 59.07, 52.70, 52.55, 38.68. HRMS Calcd. For $[\text{C}_{19}\text{H}_{19}\text{F}_3\text{NO}_2]^+$: 350.1362, found: 350.1362. The product was analyzed by HPLC to determine the enantiomeric excess: 91% ee (Chiralcel OD-3 column, i propanol/hexane = 15/85, flow rate = 0.5 mL/min, $\lambda = 220$ nm); $t_r = 15.42$ and 45.32 min.



(4k') (2S, 4S, 5R)-4-(4-(1H-1,2,4-triazol-1-yl)phenyl)-5-phenylpyrroli-

dine-2-carboxylatemethyl: Yield (63 %); Yellow solid; $[\alpha]^{25}_D = -59.600$

($c = 1$, CHCl_3); ^1H NMR (600 MHz, Chloroform- d) δ 8.48 (s, 1H), 8.06 (s,

1H), 7.52 (d, $J = 12.0$ Hz, 2H), 7.30 (d, $J = 12.0$ Hz, 2H), 7.29-7.21 (m, 3H), 7.19 (d, $J = 12.0$ Hz, 2H), 4.18-4.14 (m, 2H), 3.82 (s, 3H), 3.19 (m, 1H), 2.56-2.50 (m, 2H); ^{13}C NMR (151 MHz, Chloroform- d) δ 175.75, 152.62, 140.93, 140.85, 140.74, 135.71, 129.00, 128.67, 127.87, 127.24, 120.24, 71.46, 58.99, 52.54, 52.50, 38.62. HRMS Calcd. For $[\text{C}_{19}\text{H}_{19}\text{F}_3\text{NO}_2]^+$: 350.1362, found: 350.1362. The product was analyzed by HPLC to determine the enantiomeric excess: 91% ee (Chiralpak IA-3 column, i propanol/hexane = 40/60, flow rate 0.5 = mL/min, $\lambda = 245$ nm); $t_r = 14.58$ and 32.33 min.

6. General procedure for antifungal activity investigation.

Screening test of inhibiting mycelial growth of pathogenic fungi was according to literature procedures⁴.

Each of the test compounds (10 mg) were first dissolved in 1.0 mL acetone to generate a 104 mg·L⁻¹ stock solution, then the stock solution was added to 100 mL of Potato Dextrose Agar medium to prepare a drug-loaded PDA medium plate having a concentration of 100 mg·L⁻¹, and only 1.0 mL acetone was added to the PDA as a blank control, Azoxystrobin and Hymexazol as positive fungicides control. The *Sclerotinia sclerotiorum*, *Pestalotzia theae* and *Monilinia fructicola* pathogens were activated (prepared by a punch with $\Phi=0.50$ cm), and then were cut from the edge of the colony, inoculated into the above PDA plate, and each strain and blank control were repeated twice, sealing with a sealing film to prevent contamination of other bacteria, the poisonous PDA culture dishes were placed in a constant temperature incubator at the temperature condition of 24±1°C. After the blank control group culture was grown to about two-thirds of the culture dish, the colony diameter was measured by the cross method of millimeters (mm) with a cross and a vertical method, and the average value was taken, and the inhibition rate of each compound against the fungus was calculated.

According to the results of primary screening test, 5 compounds with good inhibition rates and *Sclerotinia sclerotiorum* were selected for further screening test for inhibiting mycelial growth of pathogenic fungi in the lower concentration range sequentially. The method used is still the same as the primary screening. The difference is that the selected compounds have five different concentration gradients for the growth inhibition of each strain, that is, 100, 50, 25, 12.5, and 6.25 mg L⁻¹.

7. The results of fungicidal screening test

Primary fungicidal activities: The *in vitro* fungicidal activity results of all compounds against different phytopathogenic fungi at a concentration of 100 mg·L⁻¹ are listed in **Table S1** and **Table S2**. The results of preliminary bioassays were compared with those of Azoxystrobin and Hymexazol.

Table S1. Preliminary inhibitory effect of compounds on four common plant pathogenic fungi (100 mg L⁻¹)

Compound	<i>Sclerotinia sclerotiorum</i>	<i>Pestalotiopsis</i>	<i>Brown-rot fungi</i>	<i>Rhizoctonia solani</i>
Blank control	0.00	0.00	0.00	0.00
Azoxystrobin	92.56	63.26	68.26	41.51
Hymexazol	100.00	75.88	91.91	90.59
3a	82.12	83.67	59.31	59.26
3b	72.56	61.31	58.33	51.23
3c	59.10	70.65	68.46	39.97
3d	75.21	72.59	58.72	64.51
3e	80.88	77.26	64.95	59.88
3g	52.90	74.53	72.35	45.52
3h	56.62	52.95	82.09	43.83
3i	1.20	10.38	0.31	/ ^a
3j	46.71	70.65	65.34	42.28
3l	45.82	48.68	50.93	24.54
3m	59.81	51.01	53.27	38.58
3n	43.34	24.96	58.53	20.37
3o	15.37	40.12	66.90	14.97
3p	38.39	42.65	37.69	37.65
3r	10.59	5.13	0.00	/
3s	65.00	59.72	53.63	66.03
3t	29.89	28.46	59.70	19.44

4a	81.94	81.53	55.61	52.87
4c	55.38	62.09	49.77	49.69
4d	7.05	28.46	14.91	21.30
4e	44.76	62.29	67.48	64.04
4f	30.77	27.29	34.00	4.17
4g	75.92	80.75	70.21	68.52
4h	54.32	78.23	60.28	66.05
4i	66.32	78.55	67.41	72.06
4j	48.48	73.17	58.53	53.09
4l	27.94	25.54	27.57	/
4m	69.37	75.89	42.76	53.09
4n	28.97	64.35	63.88	62.35
4o	42.81	52.95	60.67	41.36
5a	3.38	9.57	36.49	15.88
5b	13.77	7.08	54.63	13.43
5c	0.00	9.50	9.85	/
5d	27.50	8.33	46.24	30.29
5e	23.38	13.58	55.65	37.79
5f	91.18	17.75	70.09	61.91
5g	0.00	13.27	13.61	/
5h	0.00	4.94	38.84	16.91
7a	32.19	24.96	23.29	26.39
7b	18.02	13.49	27.76	/
7c	31.91	33.18	55.14	39.41
7d	73.82	39.35	50.60	46.47
7e	40.51	53.93	66.32	43.21
7f	23.68	57.87	62.20	39.26
7g	21.91	21.91	48.59	30.44
7h	0.00	1.98	0.00	/
7i	0.00	9.57	5.41	30.00

7j	33.09	6.94	58.17	37.65
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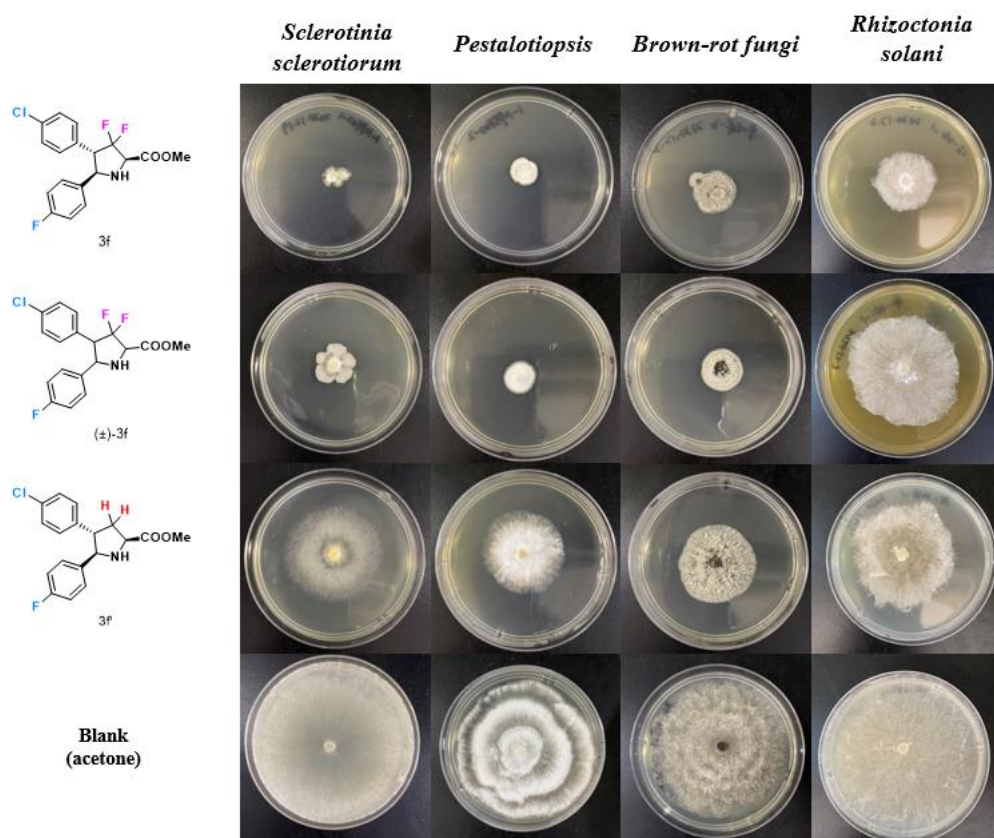
a / denotes that the compound has no inhibitory activity

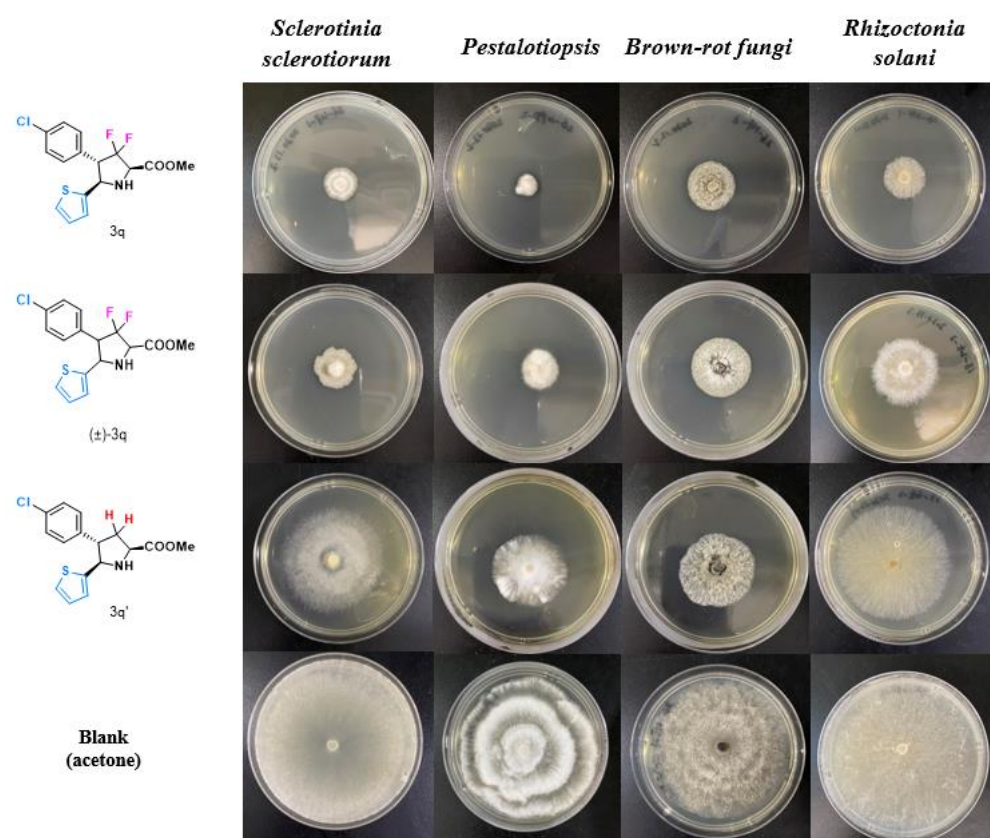
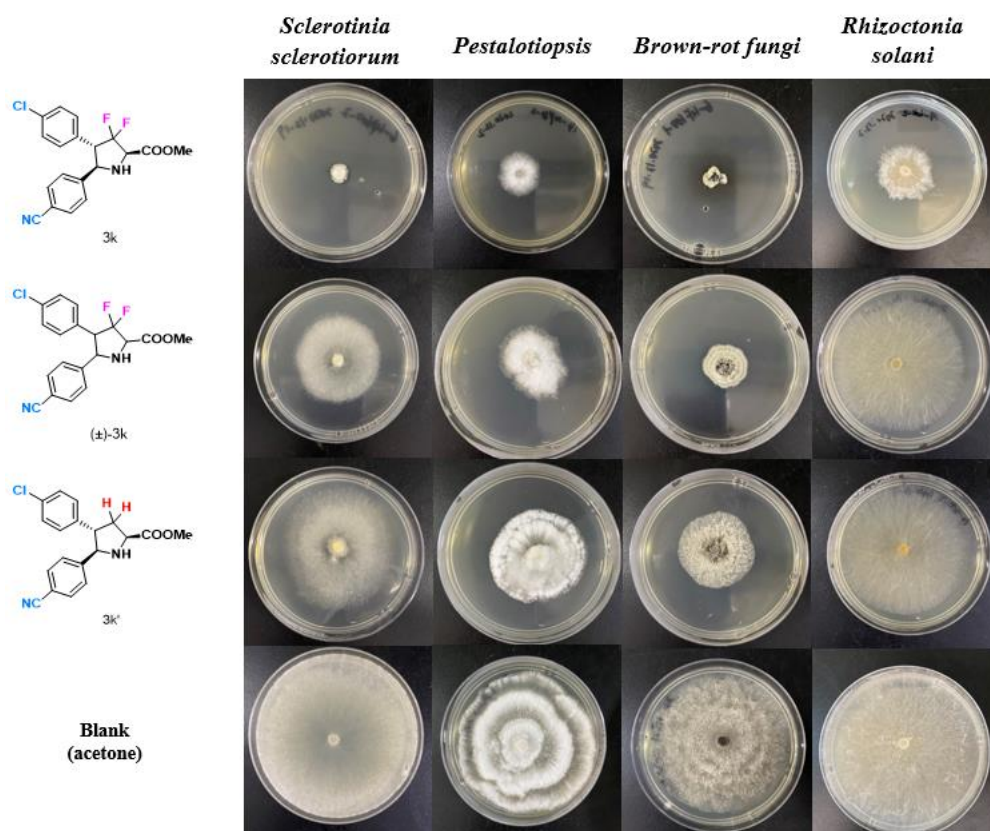
Table S2. Preliminary inhibitory effect of 5 selected compounds and their control group on four common plant pathogenic fungi (100 mg L⁻¹)

Compound	<i>Sclerotinia sclerotiorum</i>	<i>Pestalotiopsis</i>	<i>Brown-rot fungi</i>	<i>Rhizoctonia solani</i>
3f	84.60	80.37	74.49	74.65
3k	90.26	69.09	83.64	73.78
3q	82.83	86.39	68.46	79.32
4b	85.66	85.03	70.62	79.86
4k	92.65	70.59	85.05	78.38
(±)-3f	78.38	85.41	69.32	43.24
(±)-3k	51.18	62.52	70.58	23.53
(±)-3q	77.50	78.67	55.76	67.06
(±)-4b	85.44	70.74	68.91	54.71
(±)-4k	22.21	51.07	44.70	/ ^a
3f'	48.38	49.34	38.44	41.62
3k'	32.06	43.38	38.44	28.24
3q'	38.09	54.83	37.81	55.44
4b'	51.18	46.36	34.06	33.53
4k'	13.24	22.68	14.02	27.65

a / denotes that the compound has no inhibitory activity

Figure S1. Comparison of inhibitory effect of 5 selected compounds and their control group on *Sclerotinia sclerotiorum* plant pathogenic fungi at the concentration of 100 mg L⁻¹.





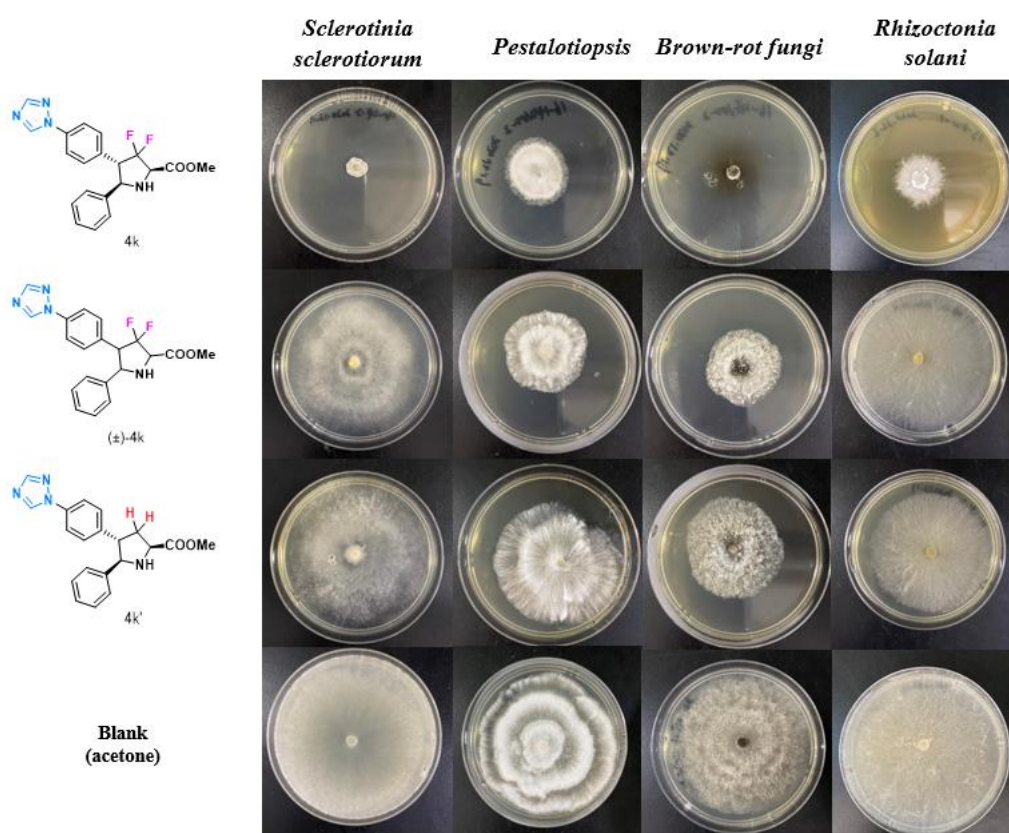
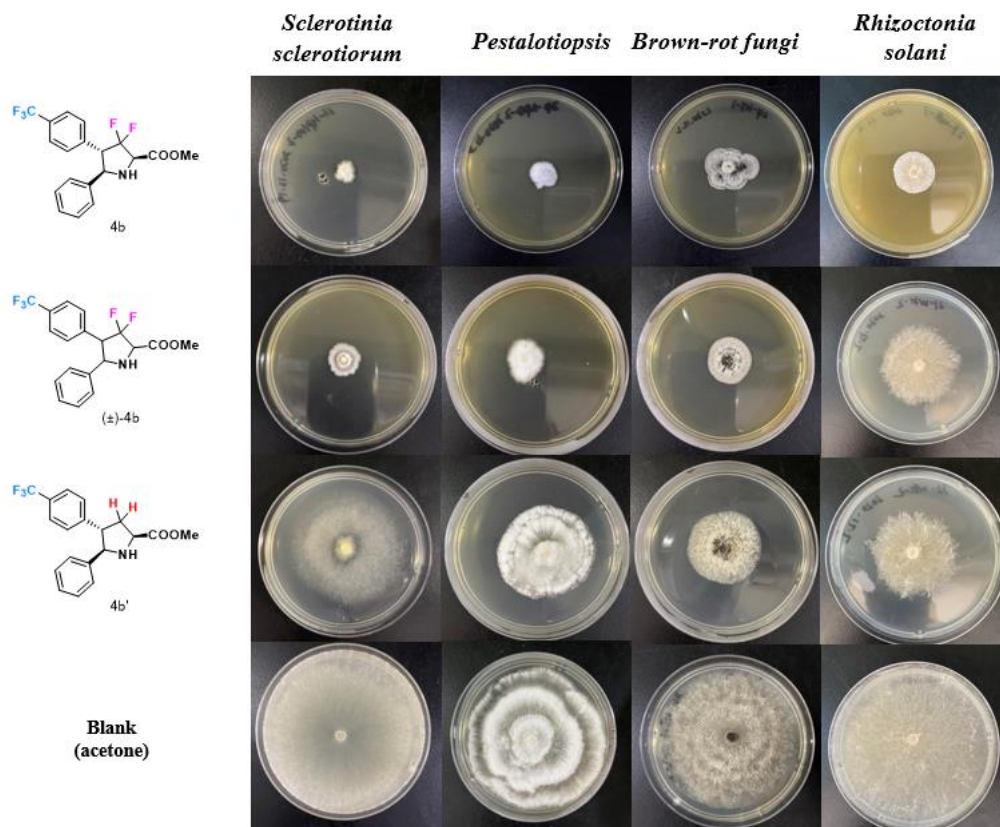
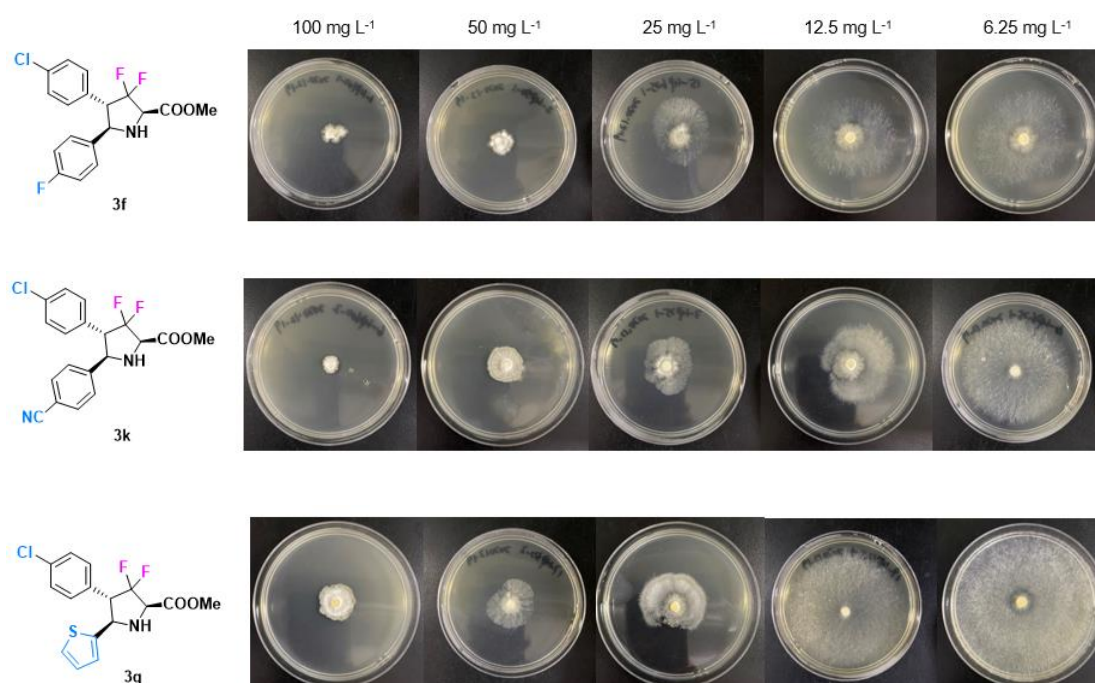
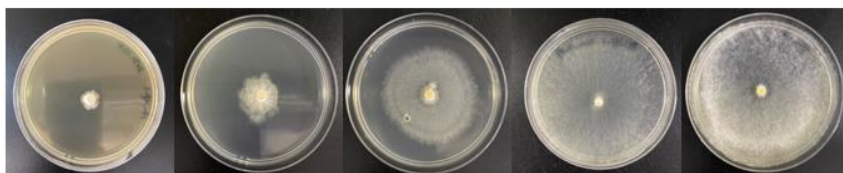
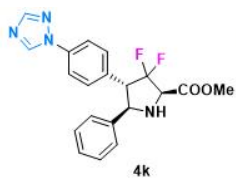
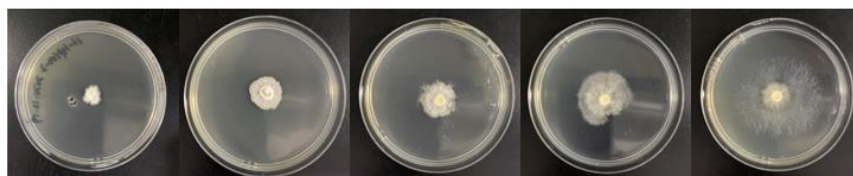
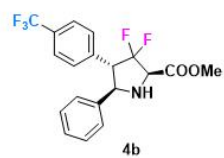


Table S3. Further inhibitory effect of 5 selected **compounds** on *Sclerotinia sclerotiorum* plant pathogenic fungi.

Compound	Antifungal activities <i>in vitro</i> (inhibitory rate/%)				
	Concentration /mg L ⁻¹				
	100	50	25	12.5	6.25
3f	84.60	83.24	64.41	44.56	40.00
3k	90.26	78.82	69.26	50.15	38.53
3q	82.83	71.62	62.35	28.68	0.00
4b	85.66	82.50	81.47	63.97	56.00
4k	92.65	70.62	47.95	13.18	0.00
Hymexazol	100.00	83.61	65.14	59.18	59.33
Azoxystrobin	92.56	95.38	92.55	55.30	45.32

Figure S2. Comparison of inhibitory effect of 5 selected compounds on *Sclerotinia sclerotiorum* plant pathogenic fungi at the concentration of 100, 50, 25, 12.5, and 6.25 mg L⁻¹.





8. The absolute configuration determination of (2*R*, 4*S*, 5*R*)-3u

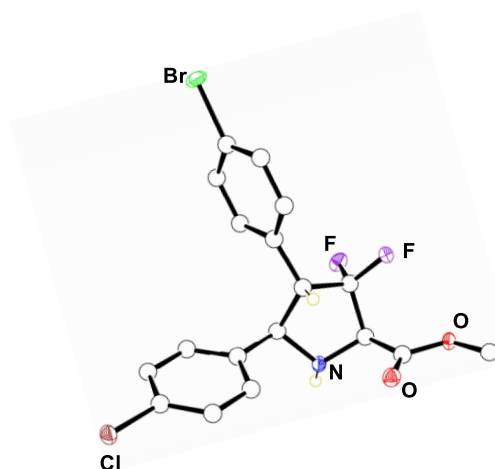


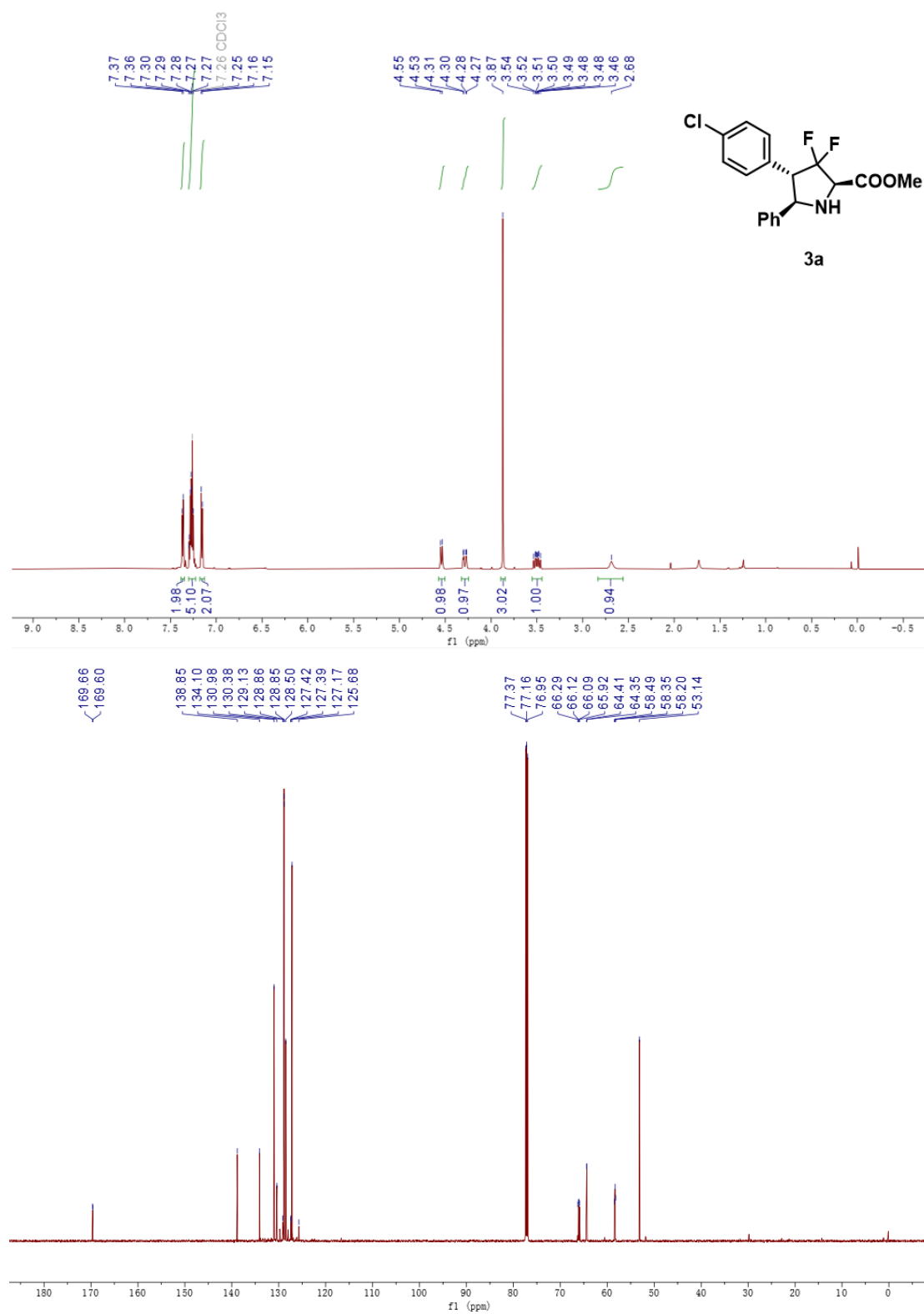
Figure S3. X-ray structure of (2*R*, 4*S*, 5*R*)-3u (hydrogen atoms are omitted for clarity).

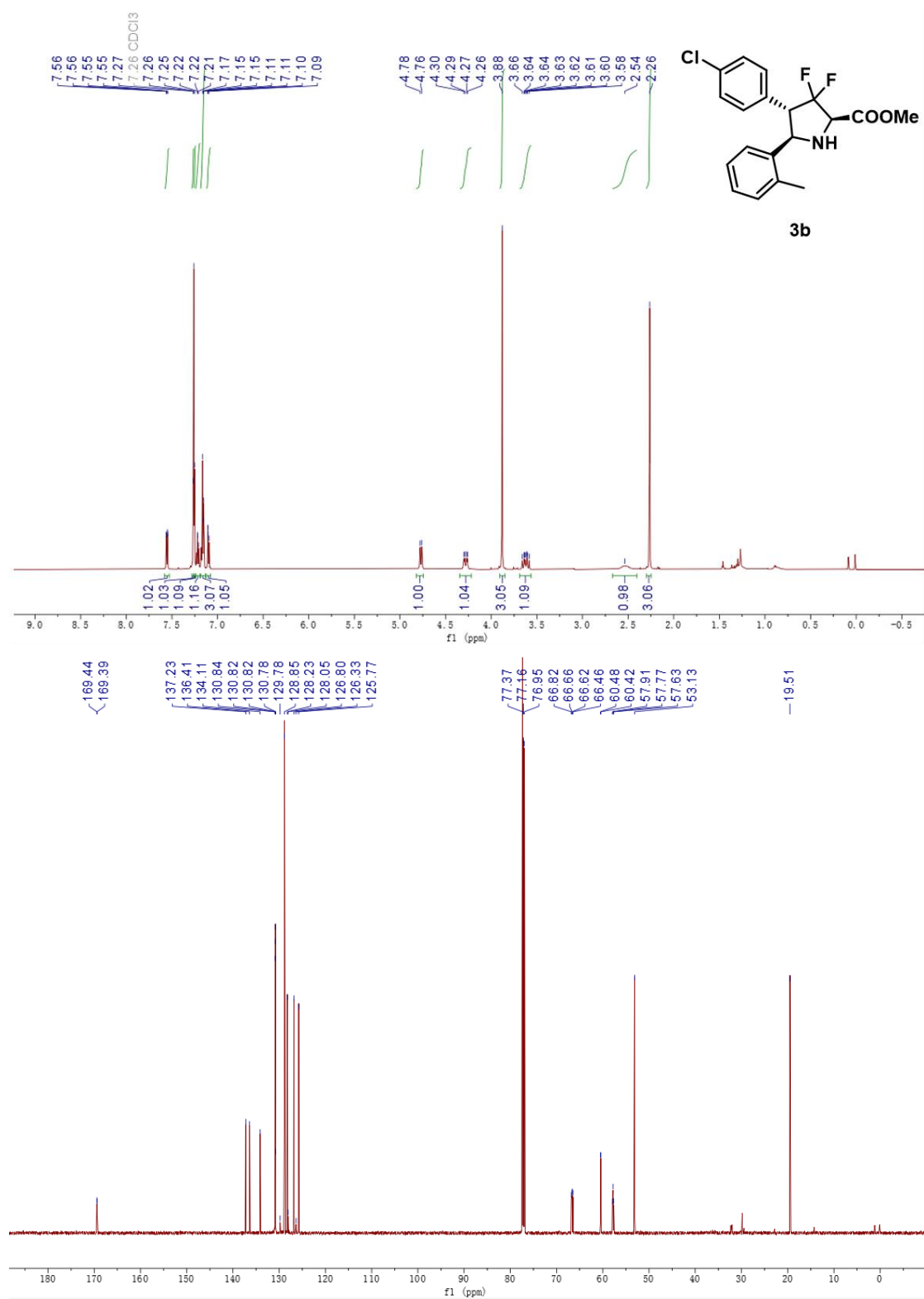
Crystal data for (2*R*, 4*S*, 5*R*)-3u: C₁₈H₁₅BrClF₂NO₂, $M_r = 430.66$, $T = 100$ K, Orthorhombic, space group $P2_1$, $a = 11.04668(8)$, $b = 5.51936(5)$, $c = 14.34857(10)$ Å, $V = 857.627(11)$ Å³, $Z = 2$, Independent reflections = 3235, final $R_1 = 0.0176$ and $wR_2 = 0.0466$, CCDC 2064529 contains the supplementary crystallographic data for this paper.

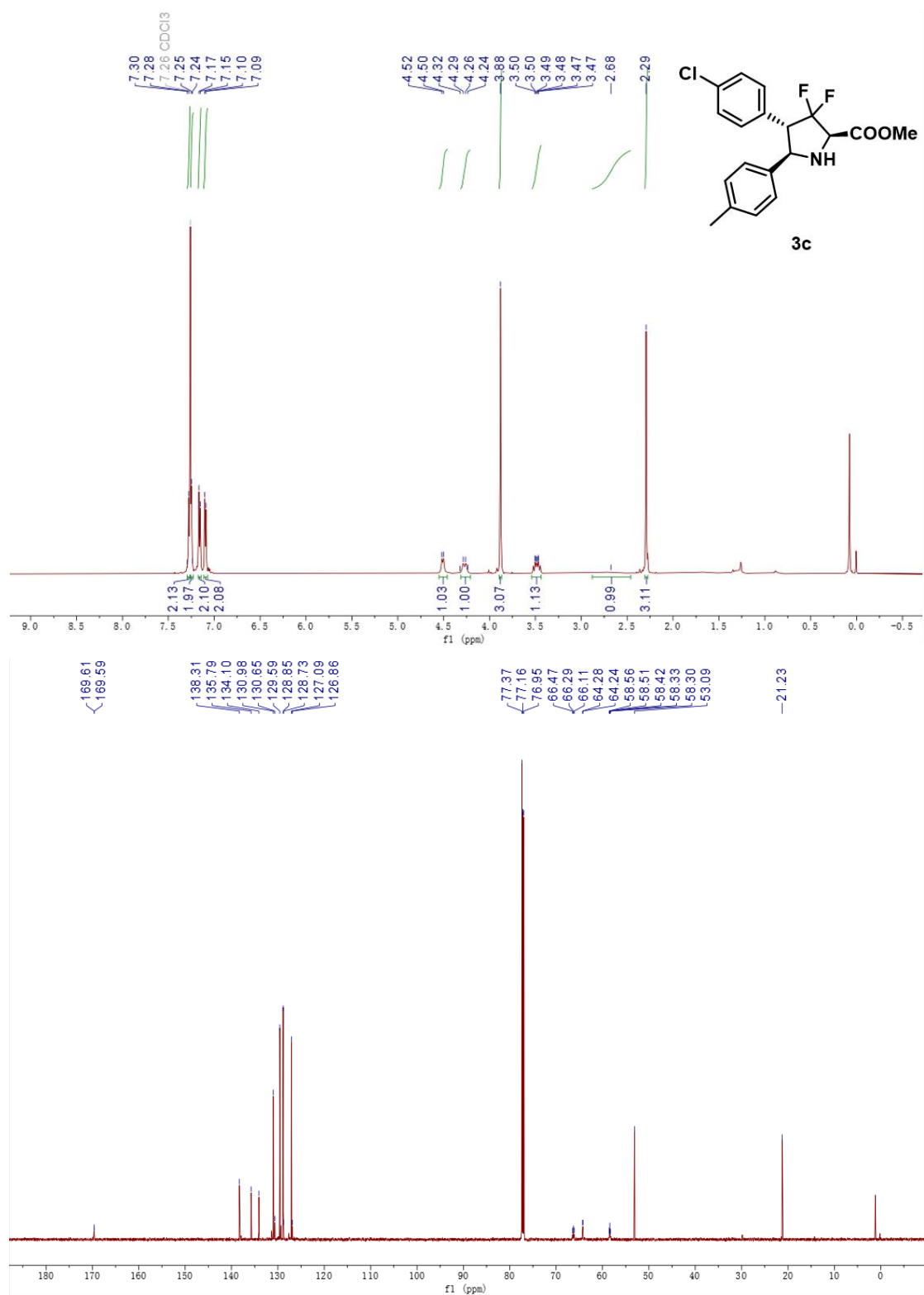
9. References

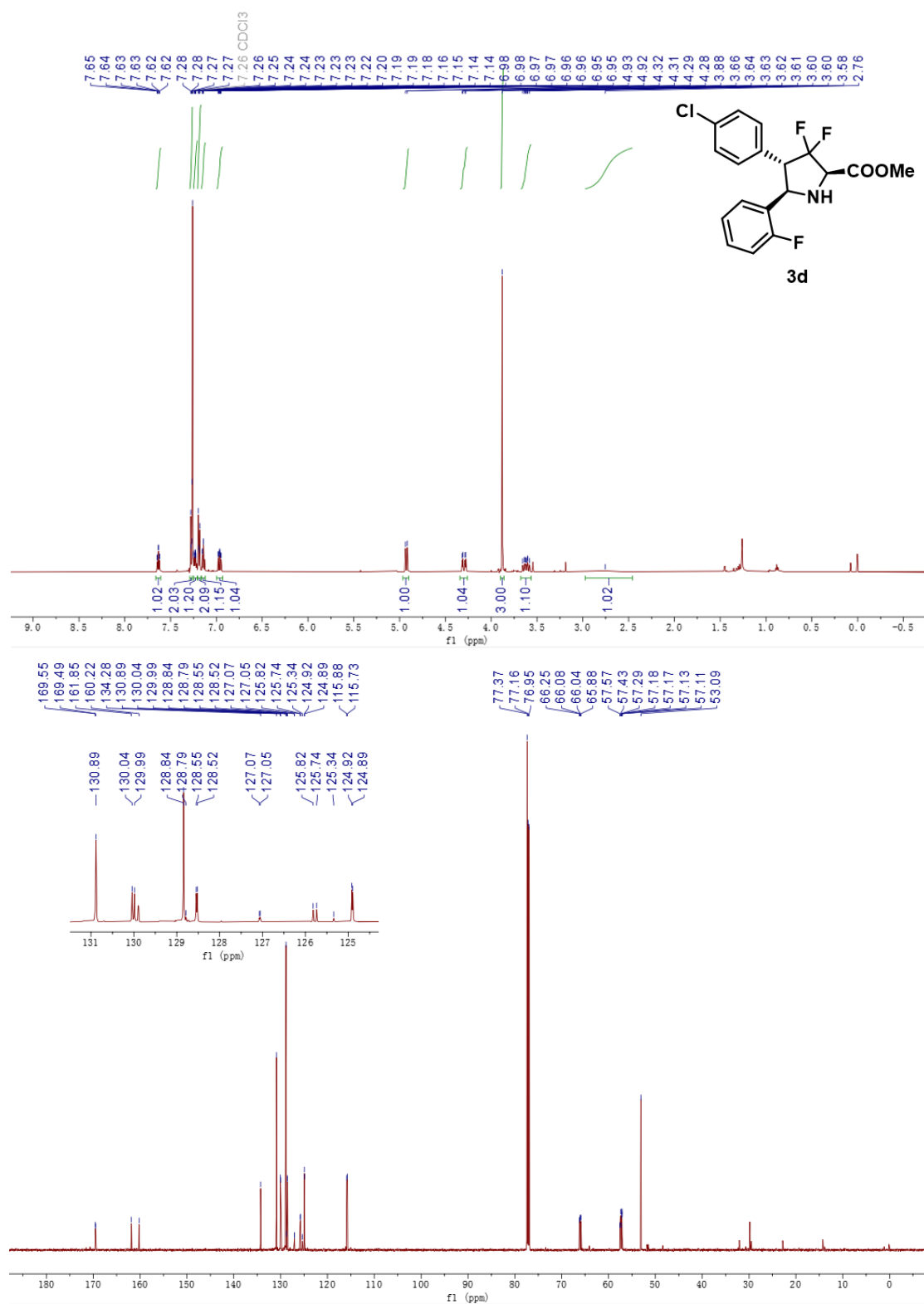
- 1.(a) Pascual-Escudero, A.; de Cózar, A.; Cossío, F. P.; Adrio, J.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2016**, *55*, 15334. (b) Xiong, Y.; Du, Z.; Chen, H.; Yang, Z.; Tan, Q.; Zhang, C.; Zhu, L.; Lan, Y.; Zhang, M. *J. Am. Chem. Soc.* **2019**, *141*, 961. (c) Zhi, M.; Gan, Z.; Ma, R.; Cui, H.; Li, E.-Q.; Duan, Z.; Mathey, F. O. *Org. Lett.* **2019**, *21*, 3210. (d) Caleffi, G. S.; Larrañaga, O.; Ferrándiz-Saperas, M.; Costa, P. R.; Nájera, C.; de Cózar, A.; Cossío, F. P.; Sansano, J. M. *J. Org. Chem.* **2019**, *84*, 10593. (e) Xu, H.; Golz, C.; Strohmman, C.; Antonchick, A. P.; Waldmann, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 7761.
2. (a) Sakaguchi, H.; Uetake, Y.; Ohashi, M.; Niwa, T.; Ogoshi, S.; Hosoya, T. *J. Am. Chem. Soc.* **2017**, *139*, 12855. (b) Zhang, Q.-Q.; Chen, S.-Y.; Lin, E.; Wang, H.; Li, Q. *Org. Lett.* **2019**, *21*, 3123. (c) Lu, C.-J.; Yu, X.; Chen, Y.-T.; Song, Q.-B.; Wang, H. *Org. Chem. Front.* **2020**, *7*, 2313. (d) Yan, S.-S.; Wu, D.-S.; Ye, J.-H.; Gong, L.; Zeng, X.; Ran, C.-K.; Gui, Y.-Y.; Li, J.; Yu, D.-G. *ACS. Catal.* **2019**, *9*, 6987. (e) Qi, S.; Gao, S.; Xie, X.; Yang, J.; Zhang, J. *Org. Lett.* **2020**, *22*, 5229.
3. (a) Kudalkar, G. P.; Tiwari, V. K.; Lee, J. D.; Berkowitz, D. B. *Synlett.* **2020**, *31*, 237.(b) Anilkumar, R.; Burton, D. J. *J. Fluor. Chem.* **2005**, *126*, 1174.
4. Huang, D.; Wang, S.; Song, D.; Cao, X.; Huang, W.; Ke, S. *J. Agric. Food. Chem.* **2020**, *68*, 14438.

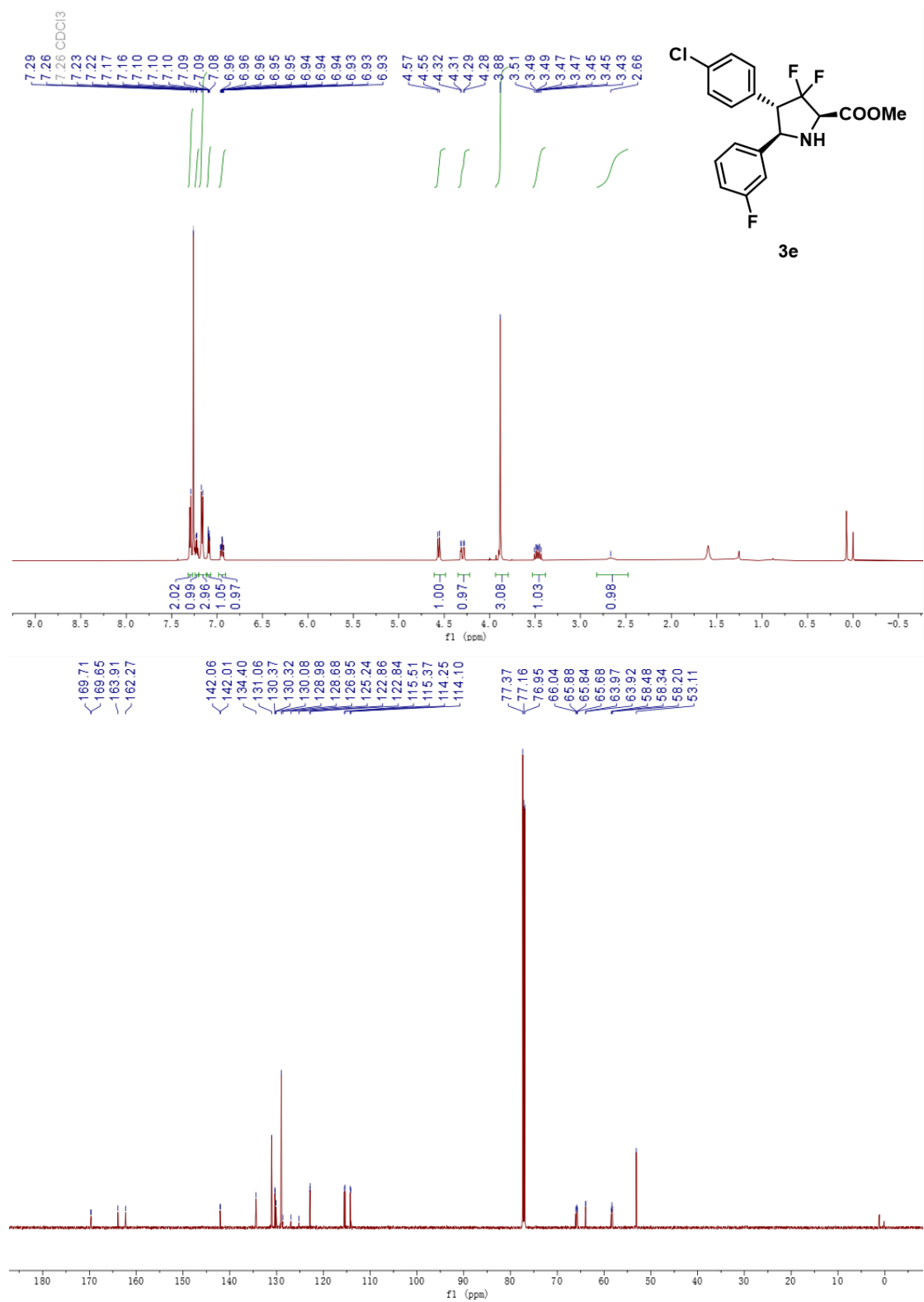
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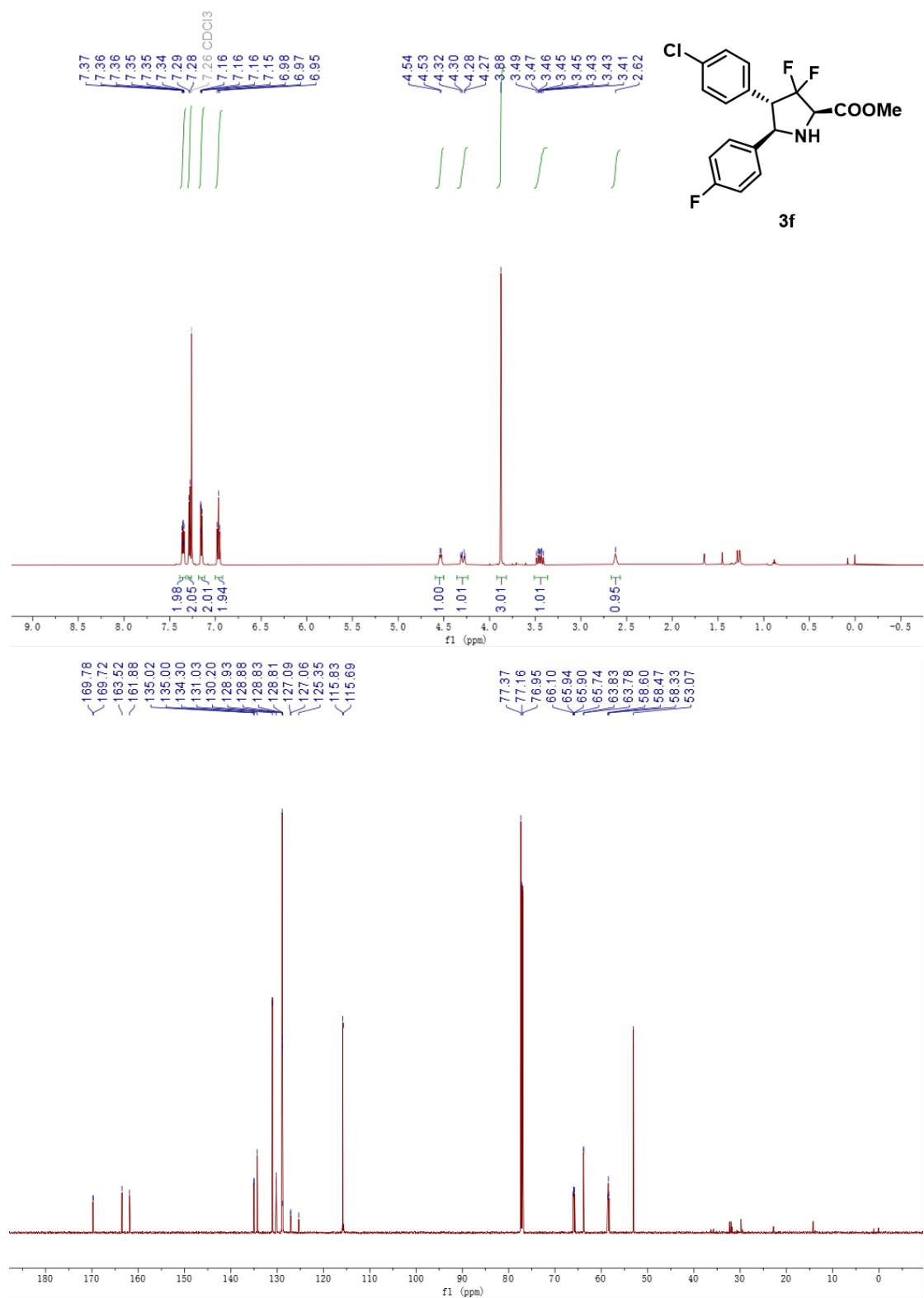


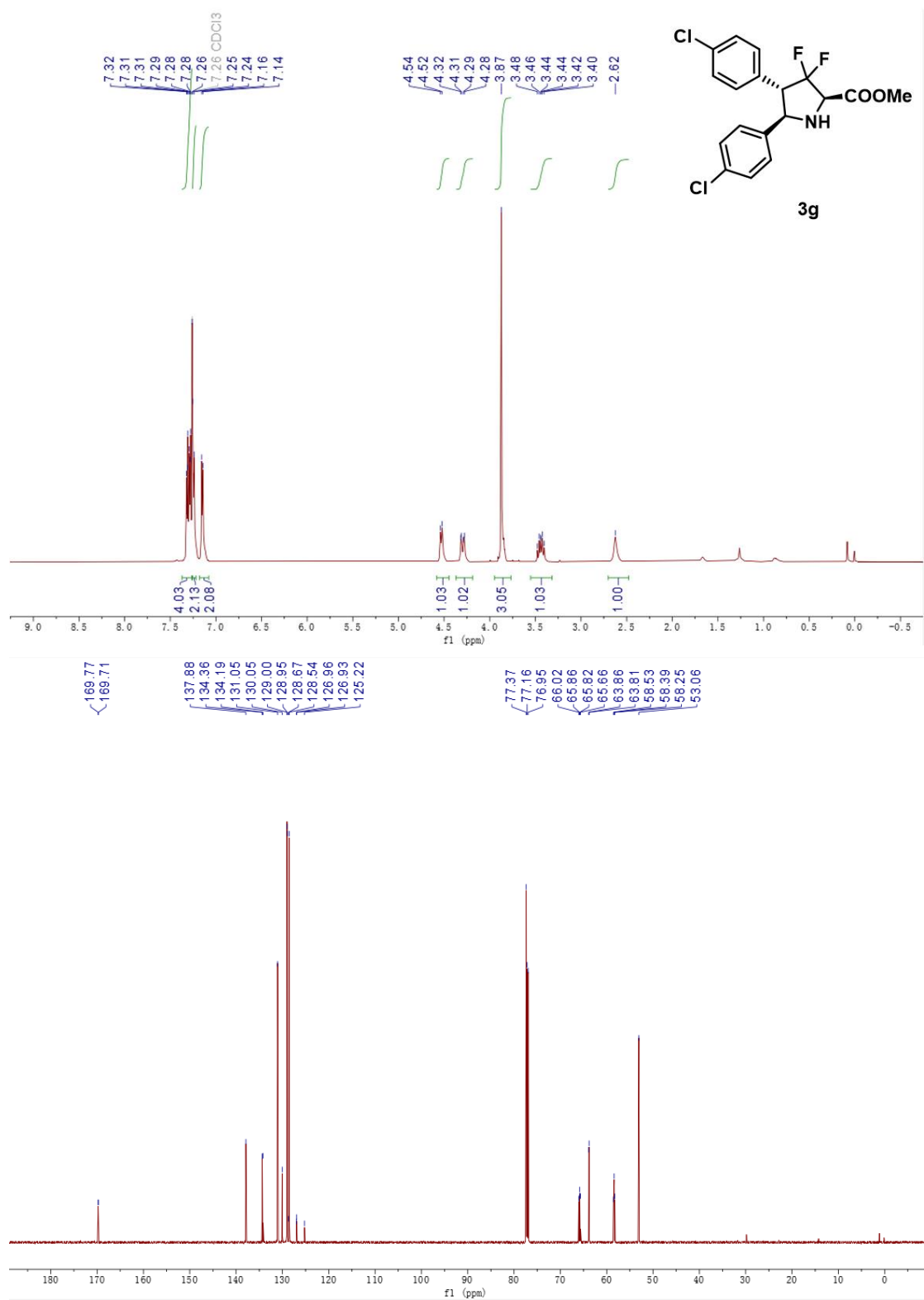


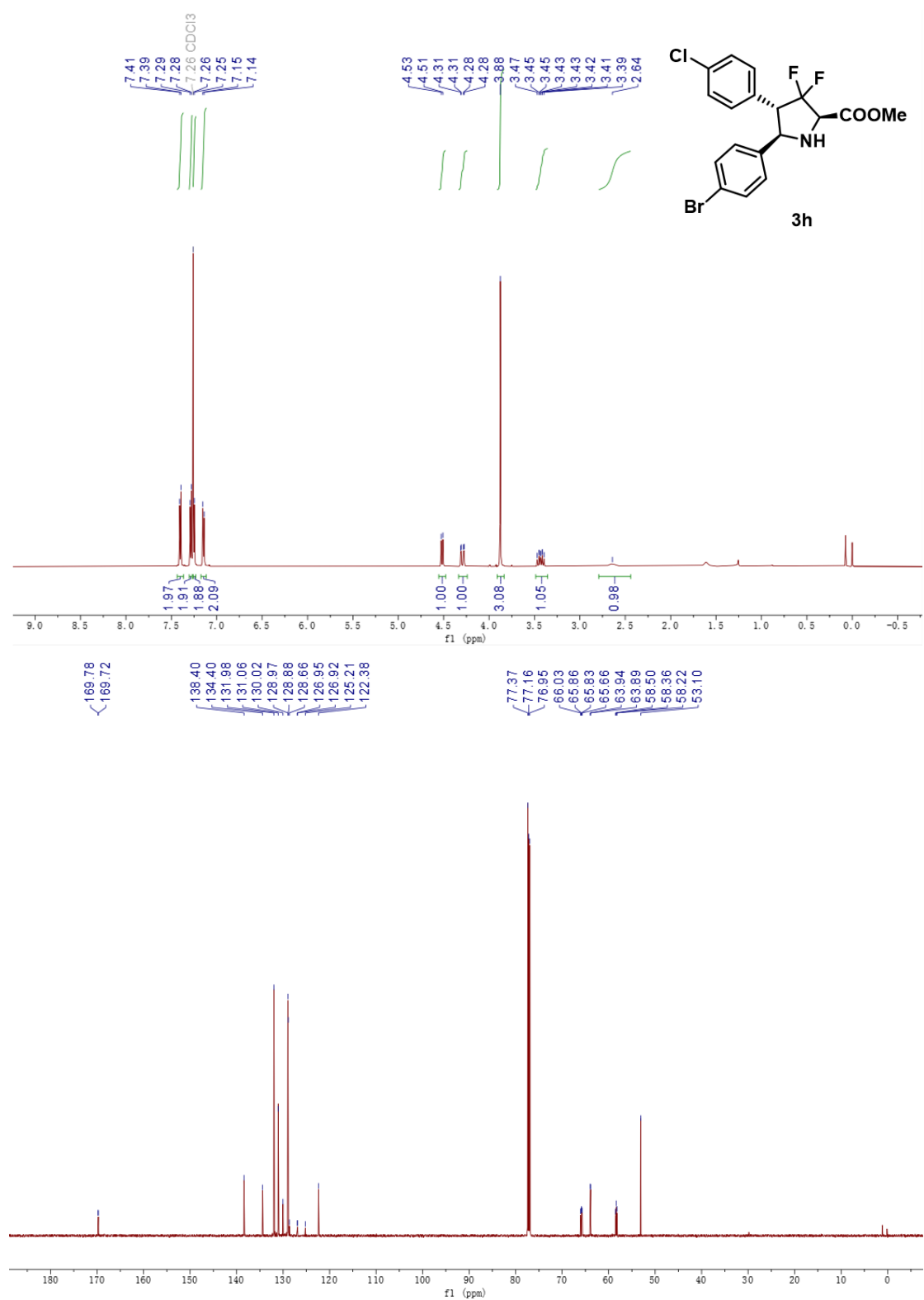


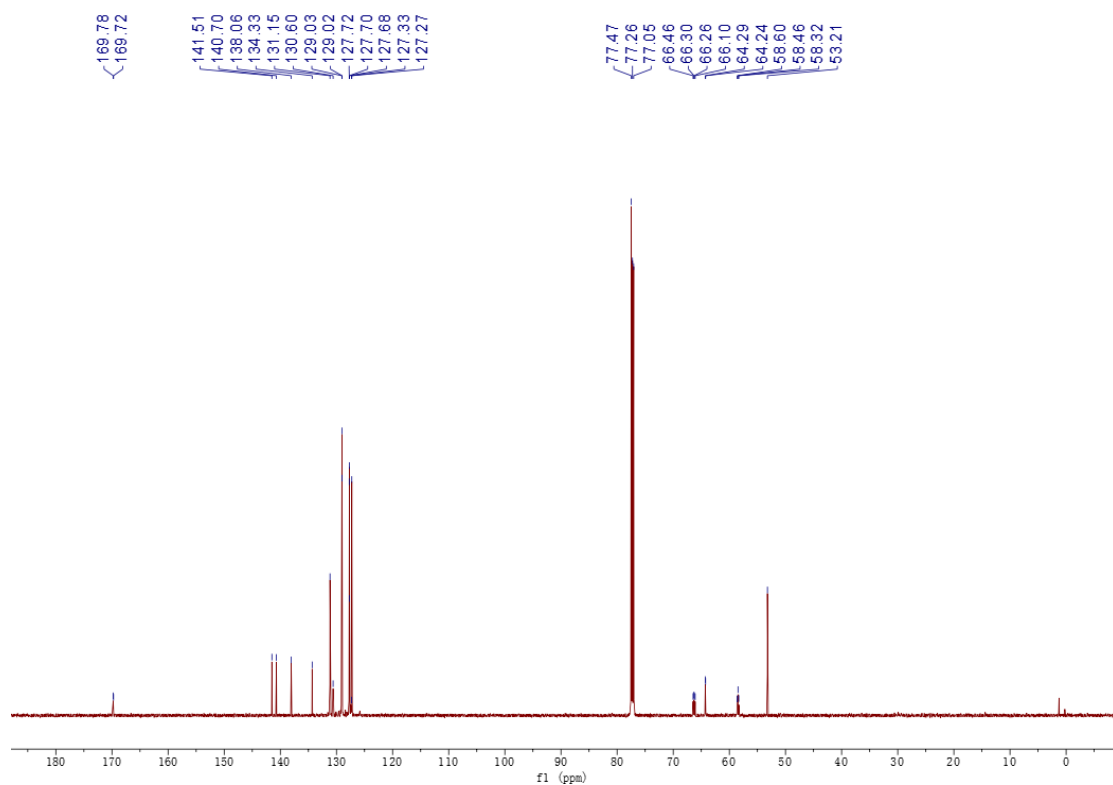
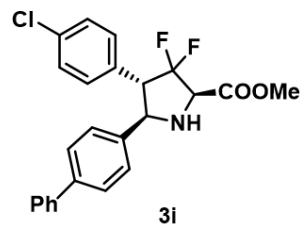
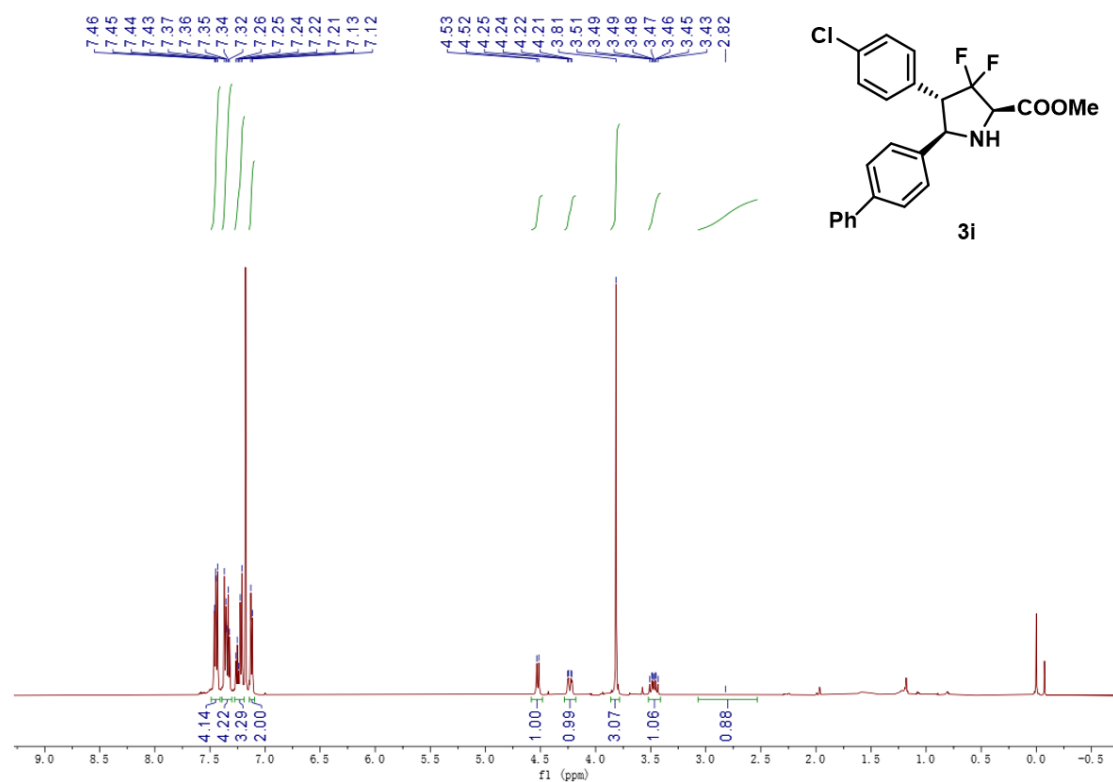


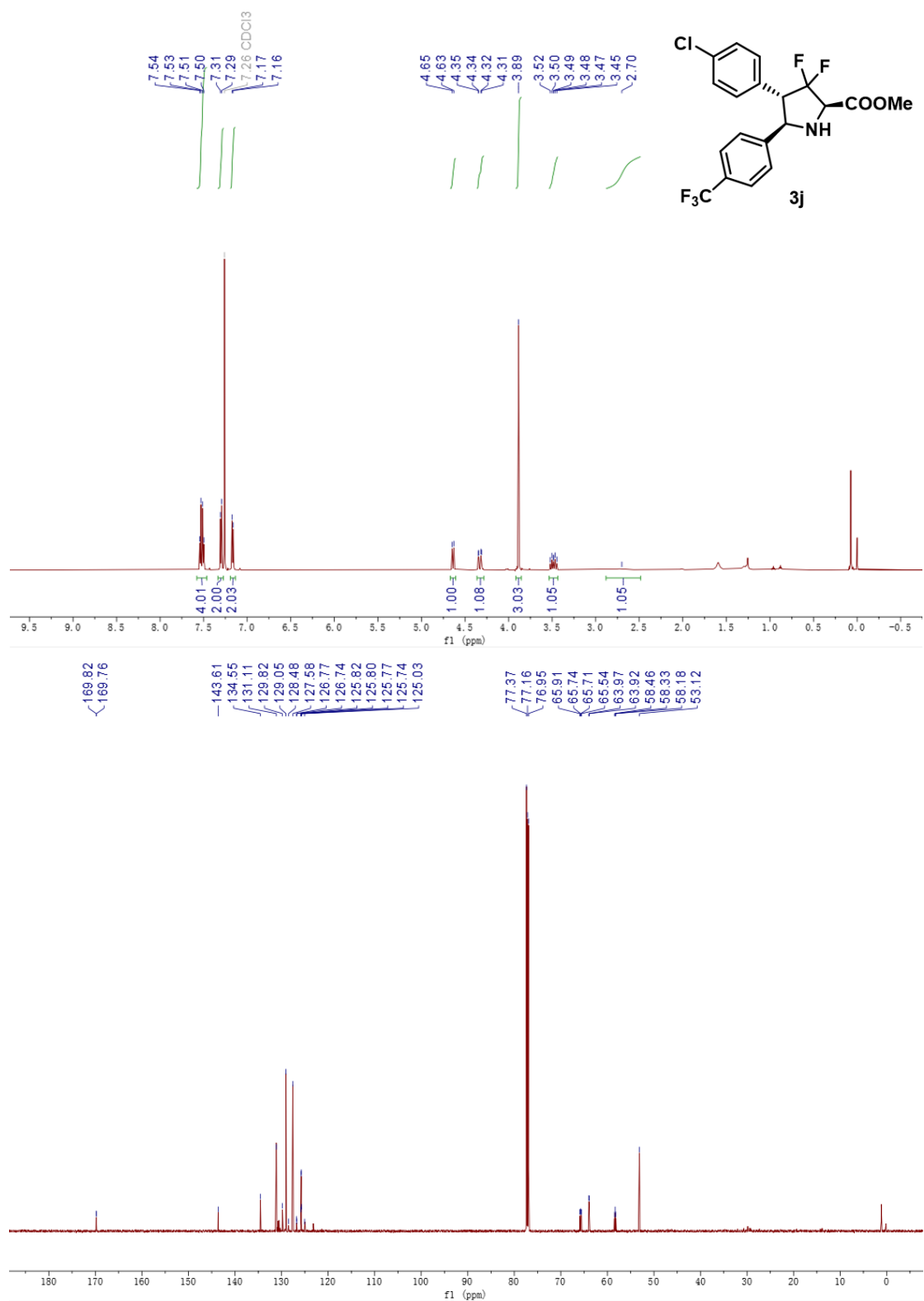


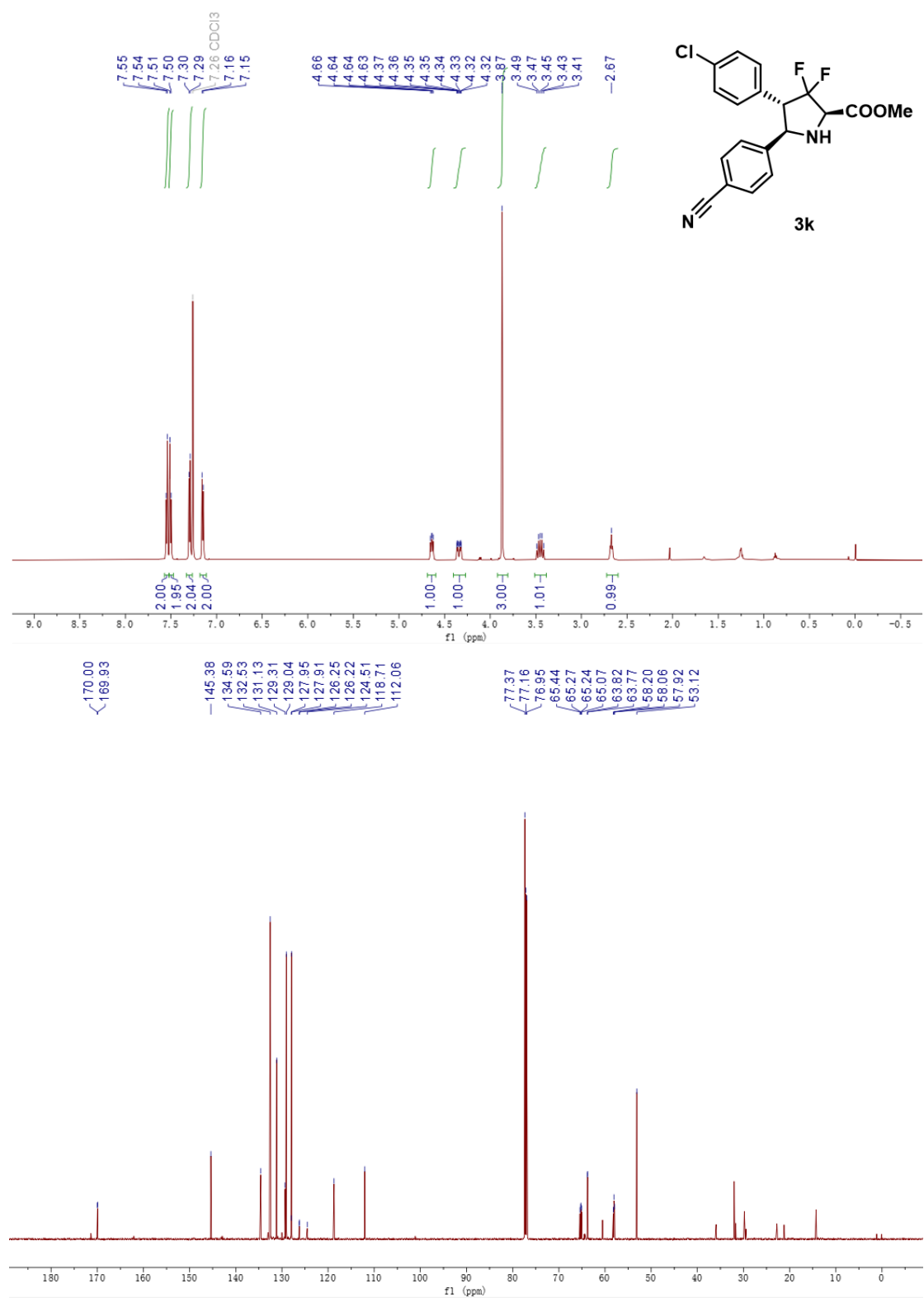


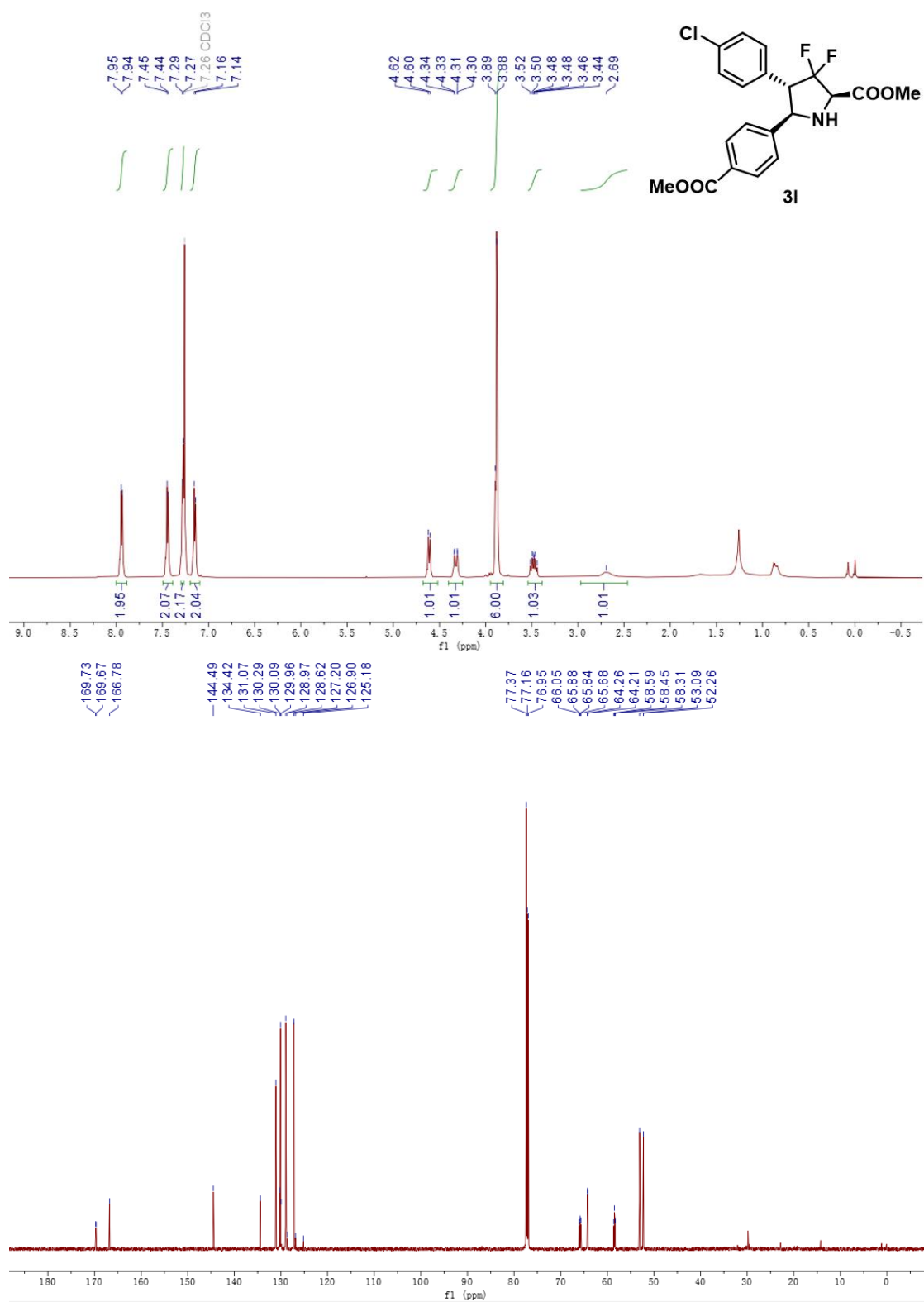


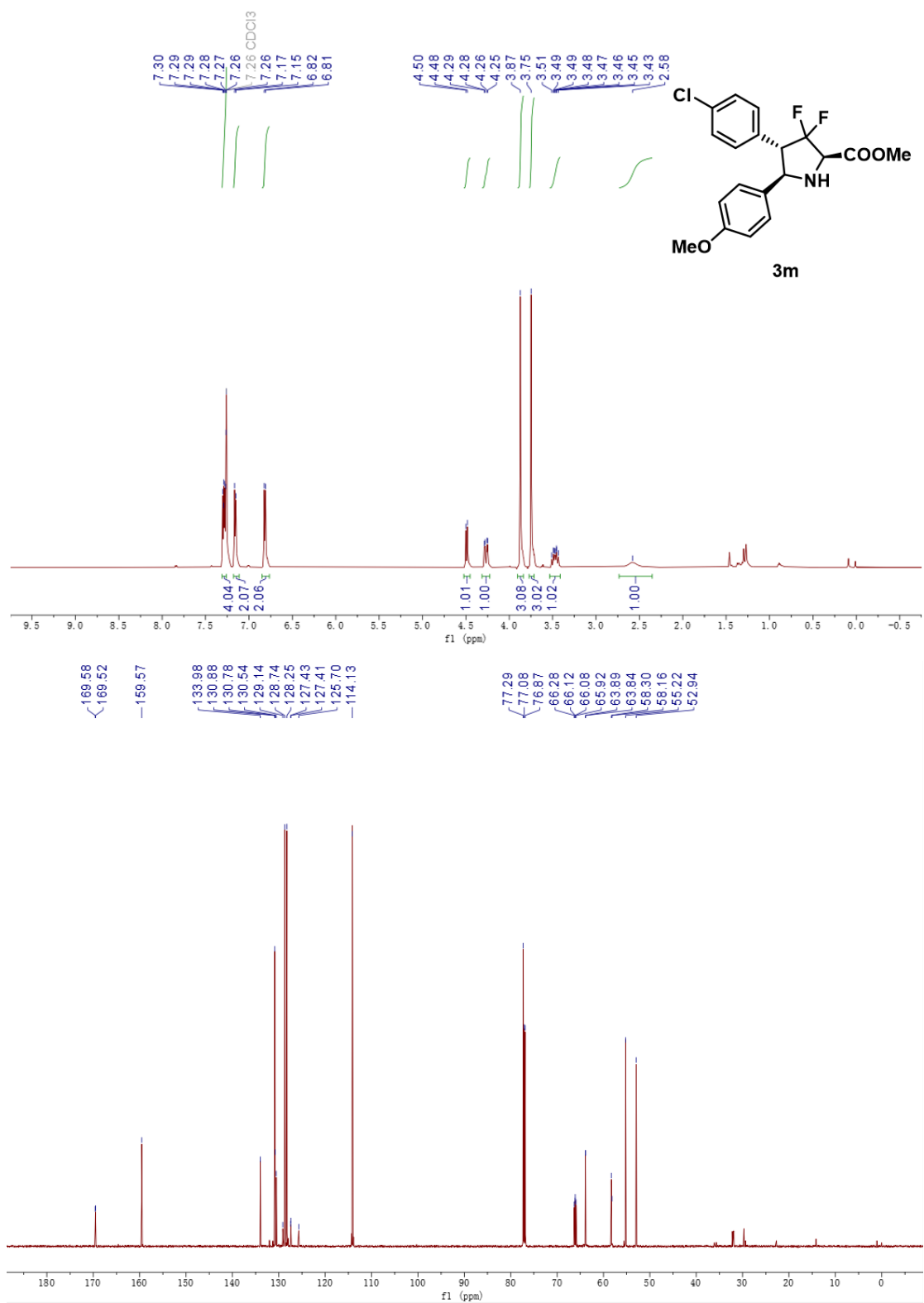


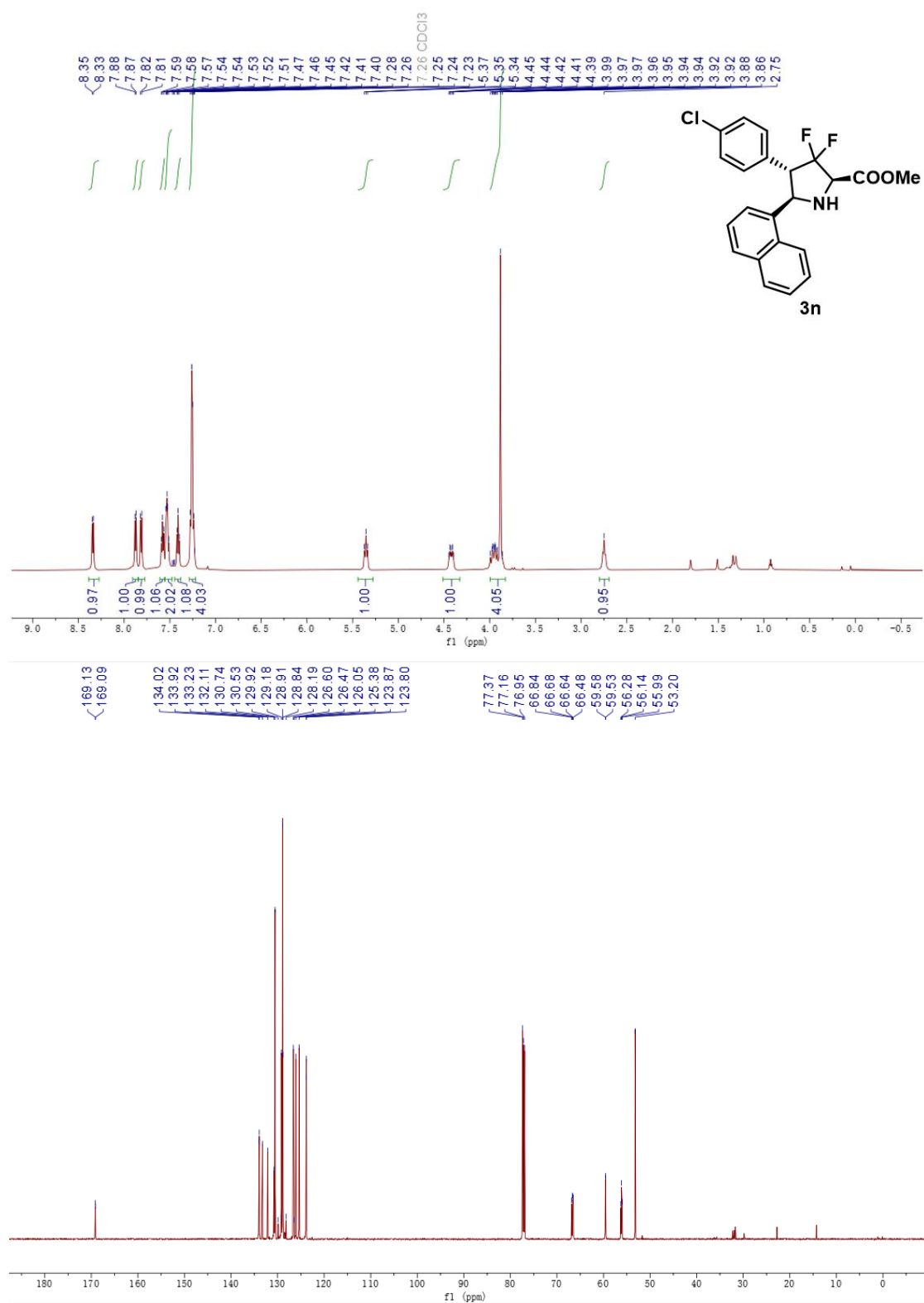


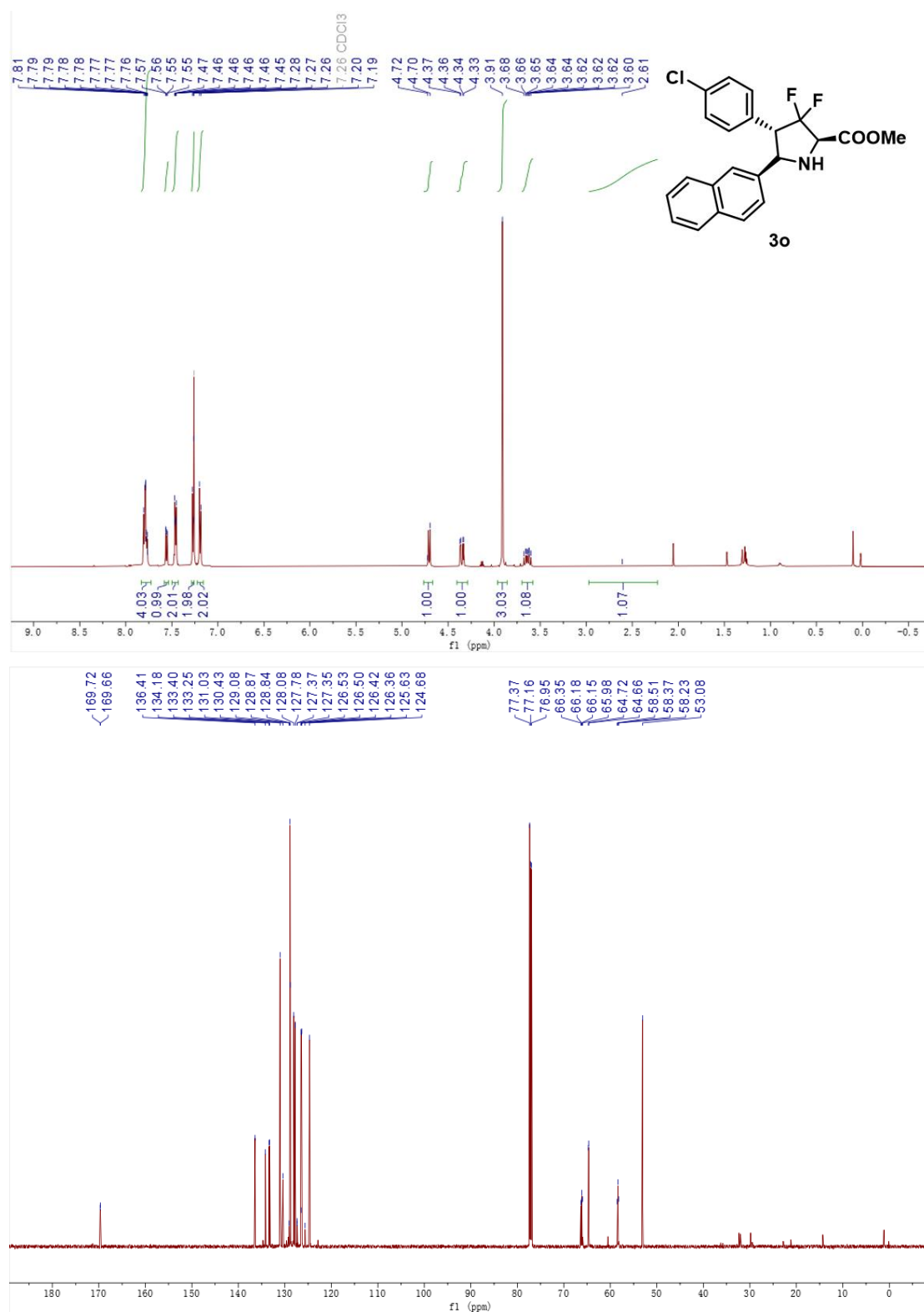


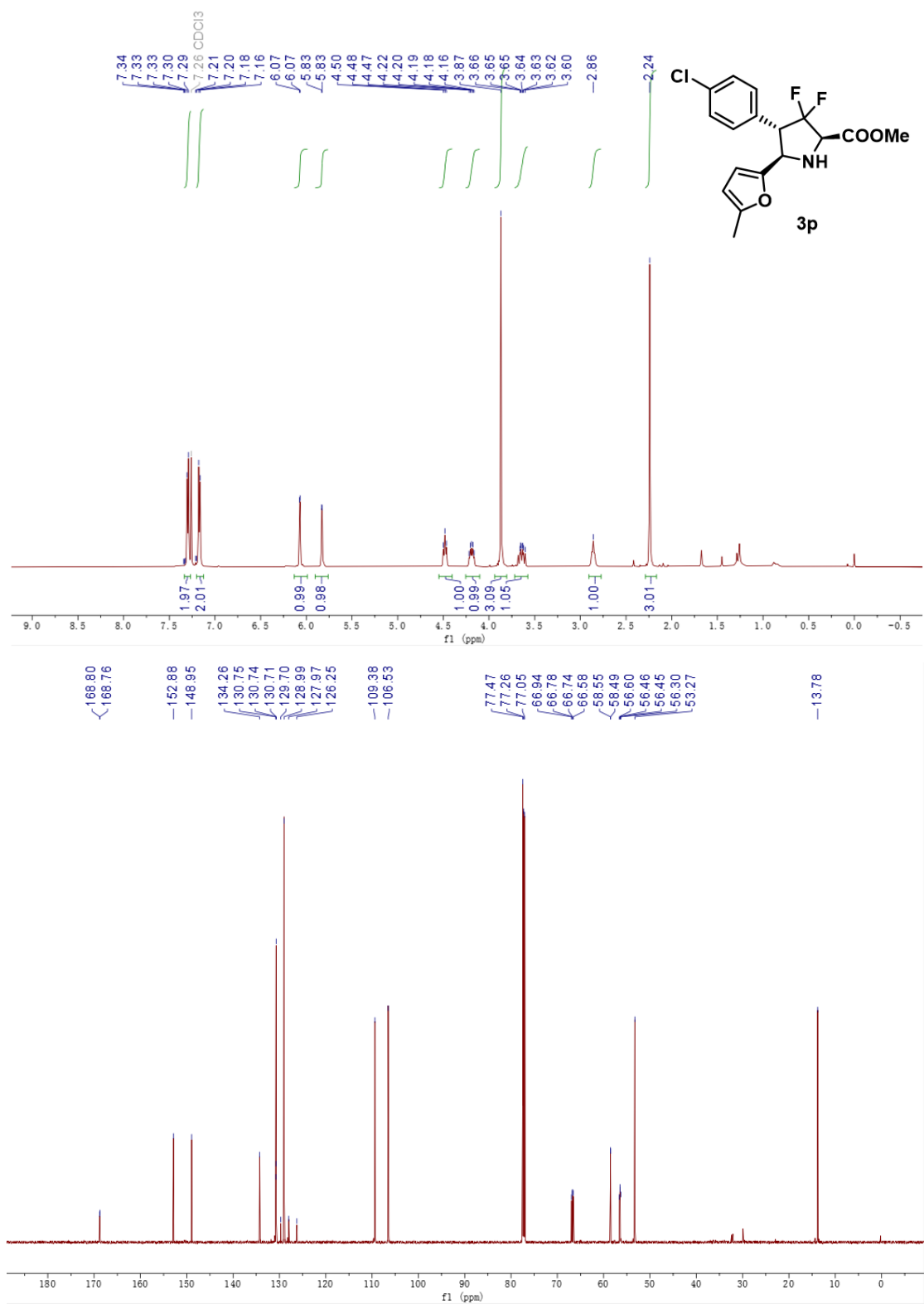


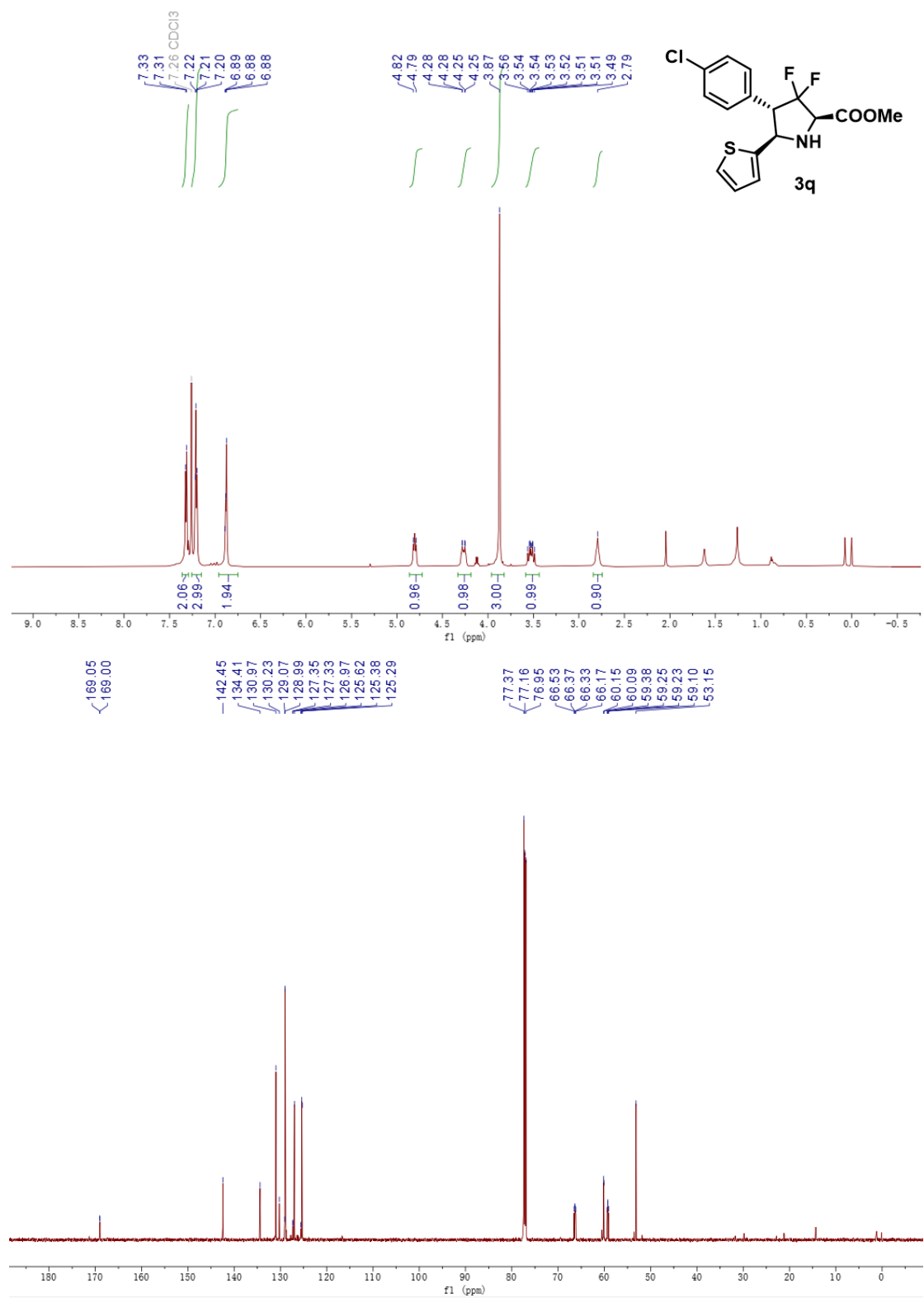


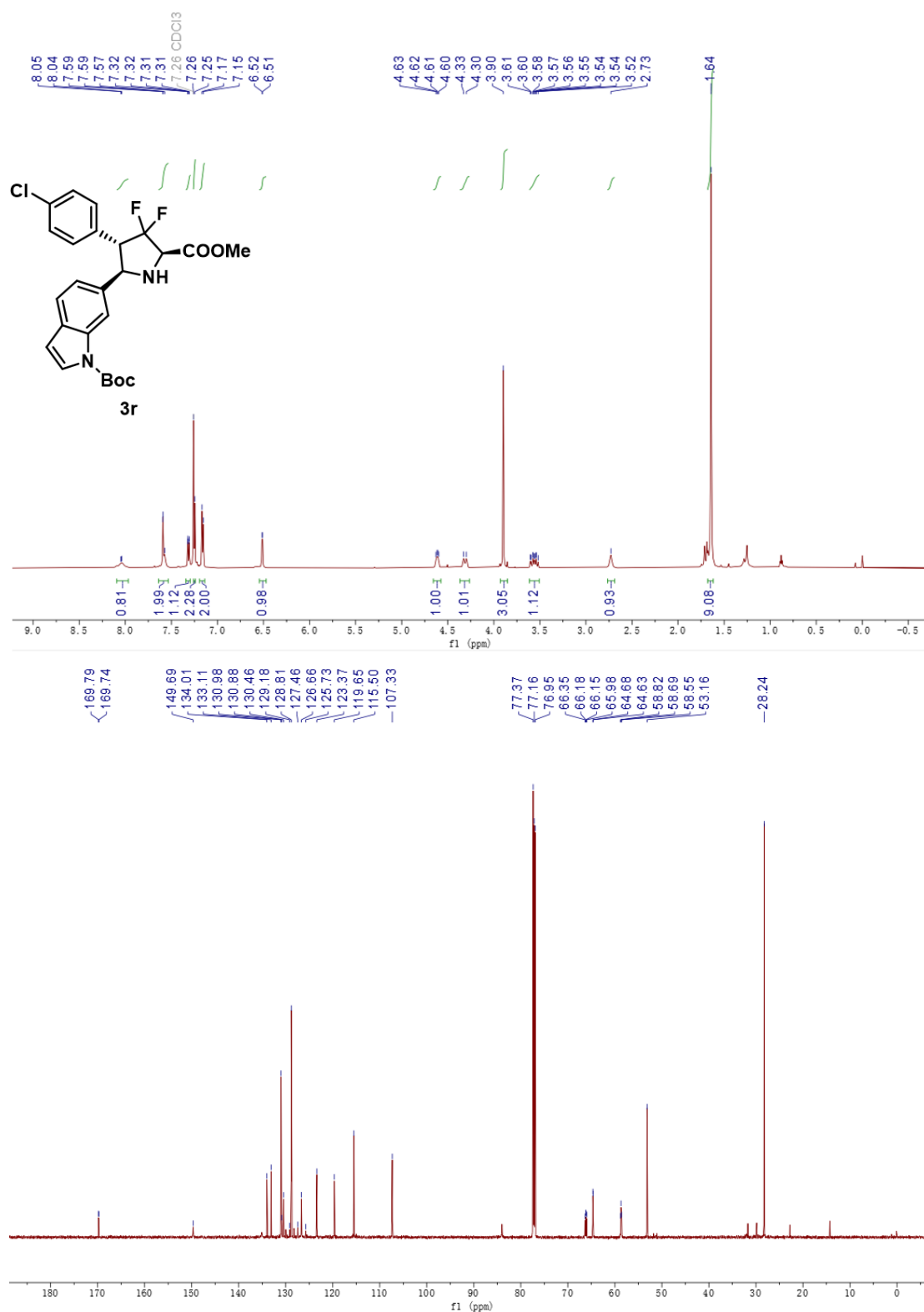


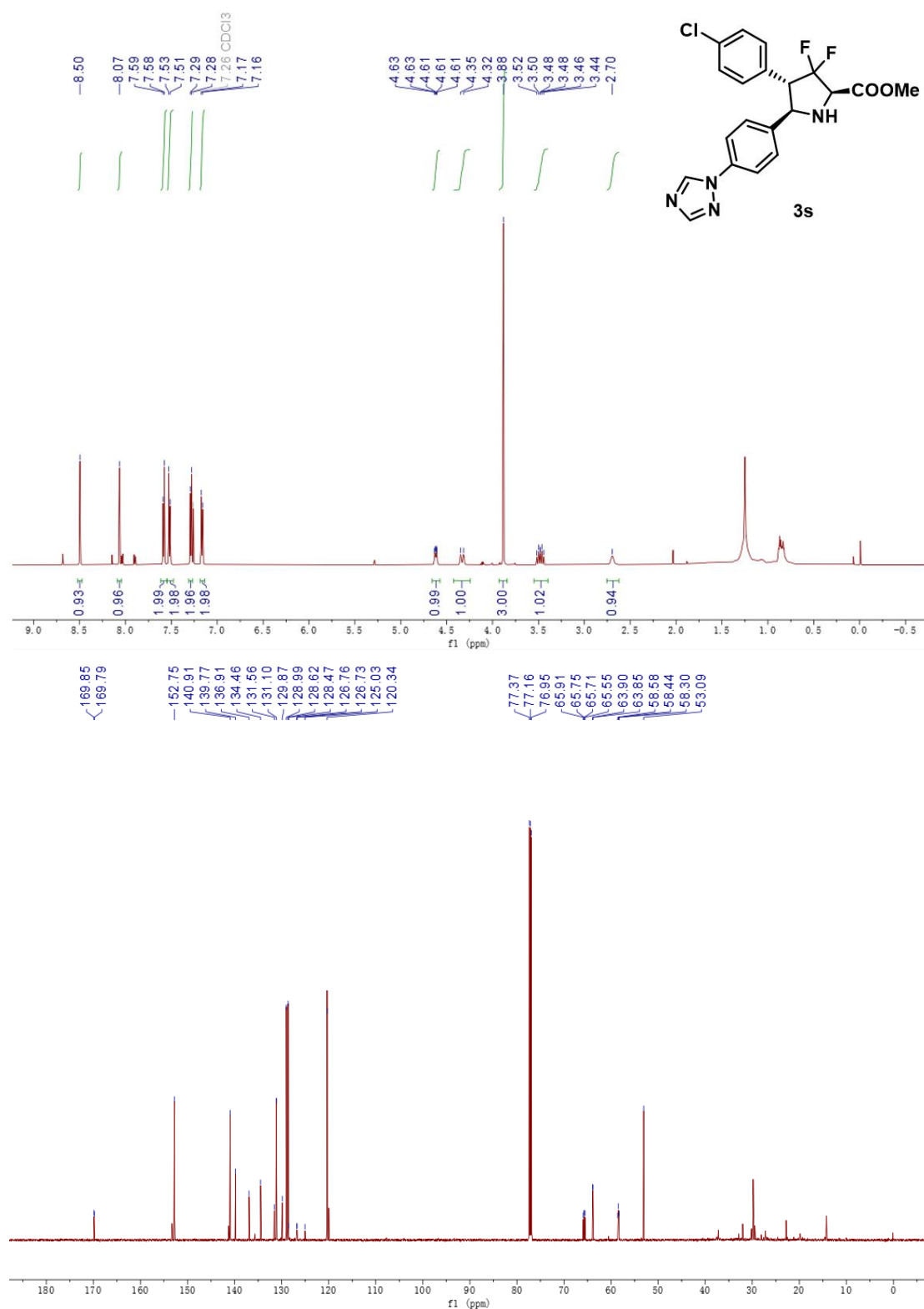


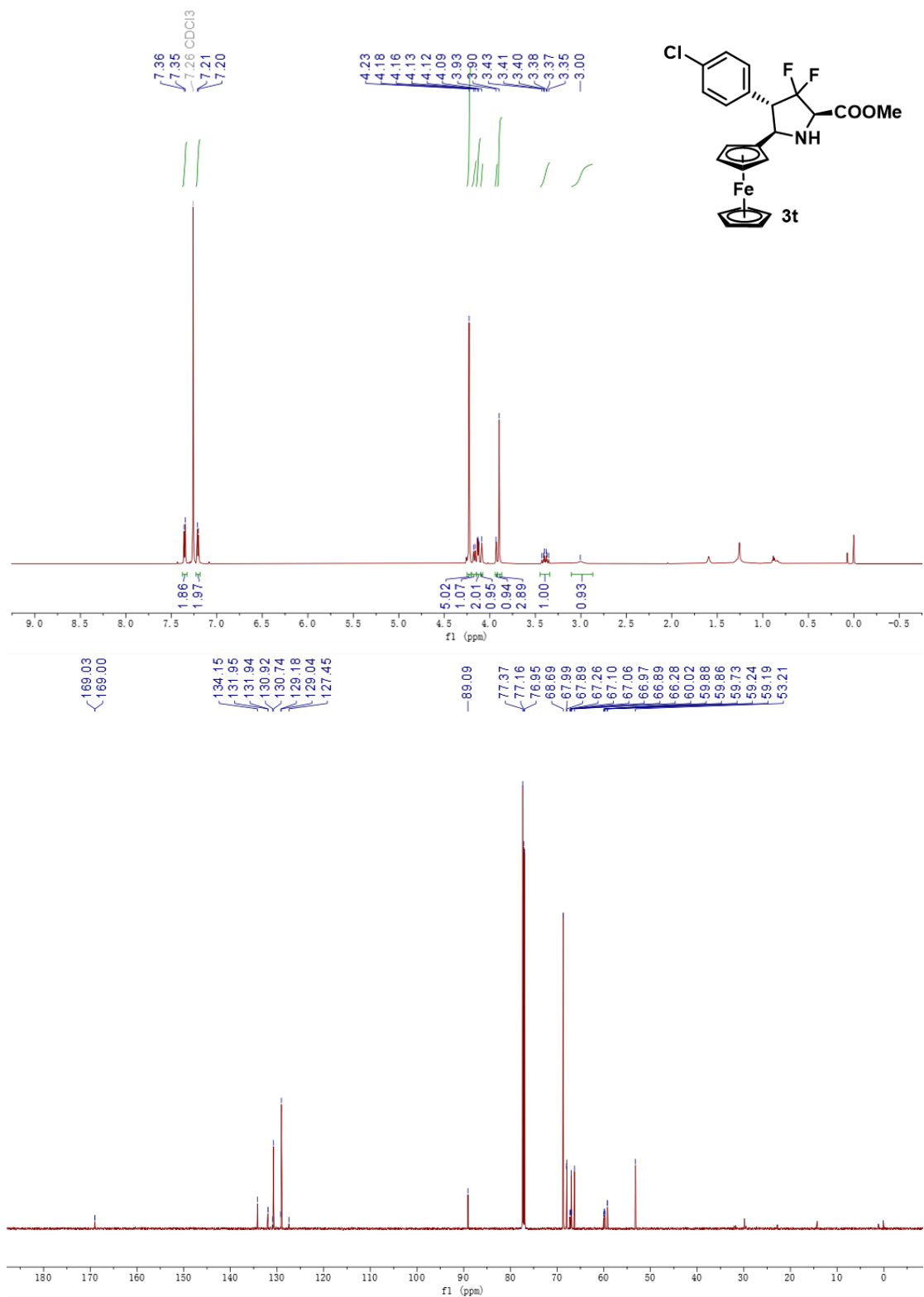


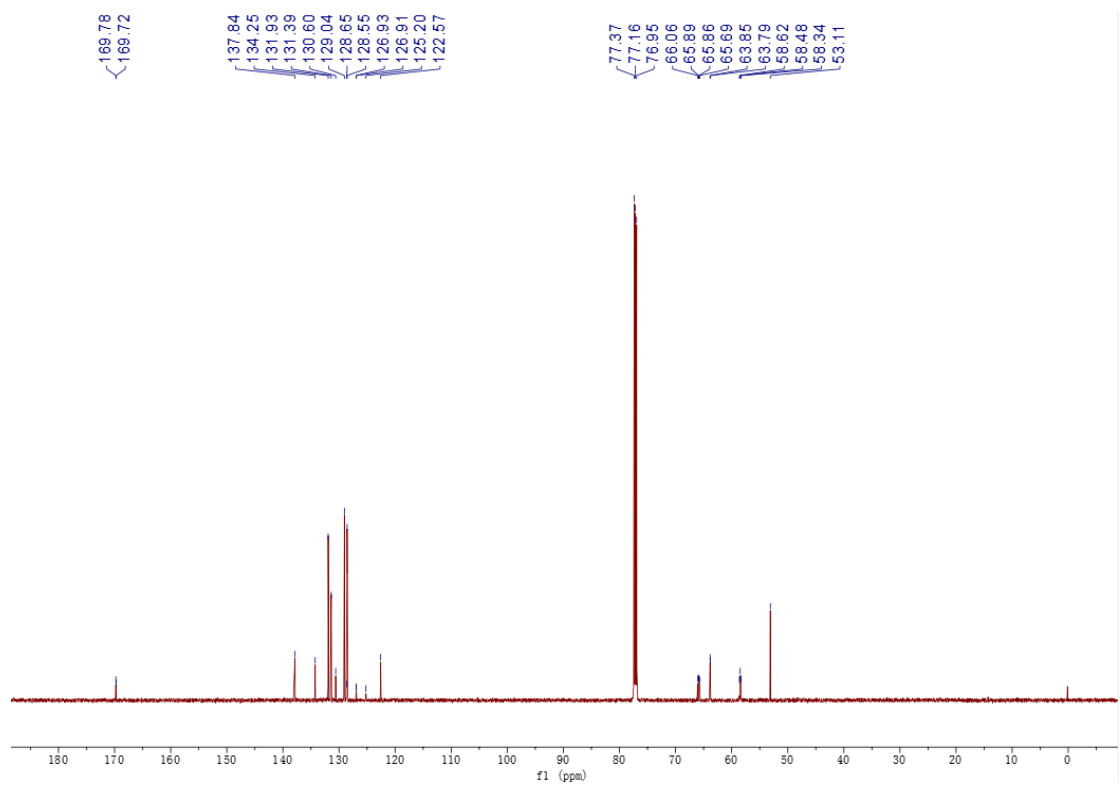
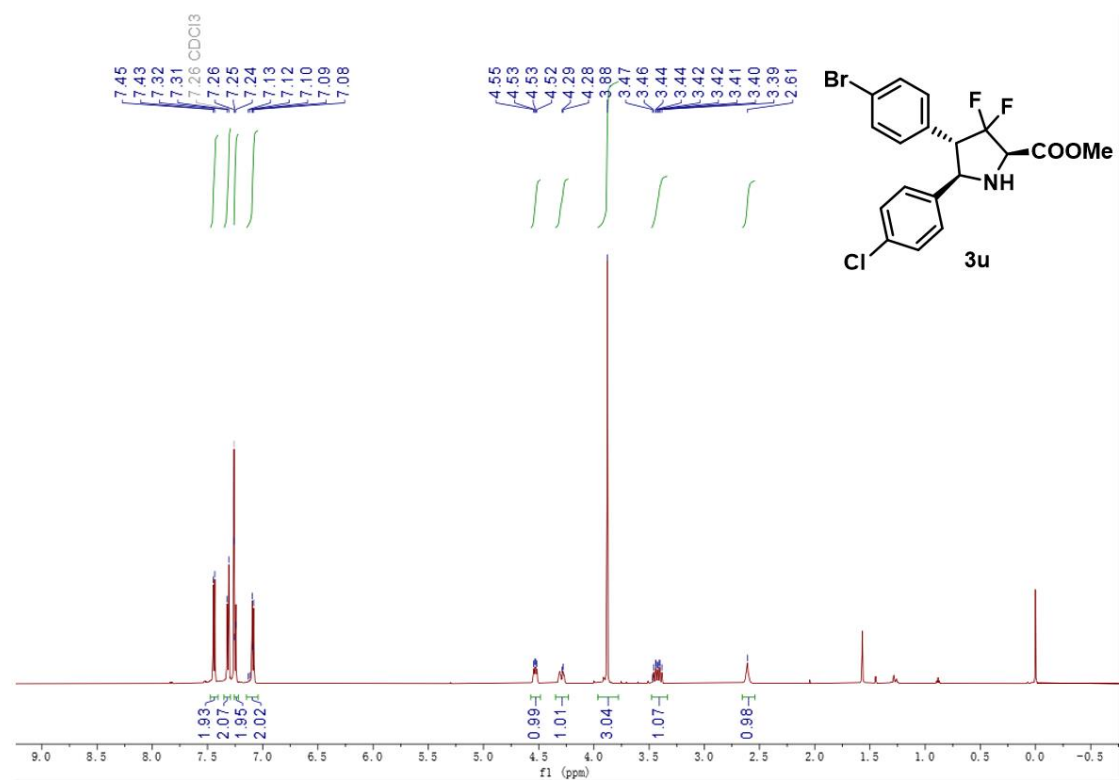


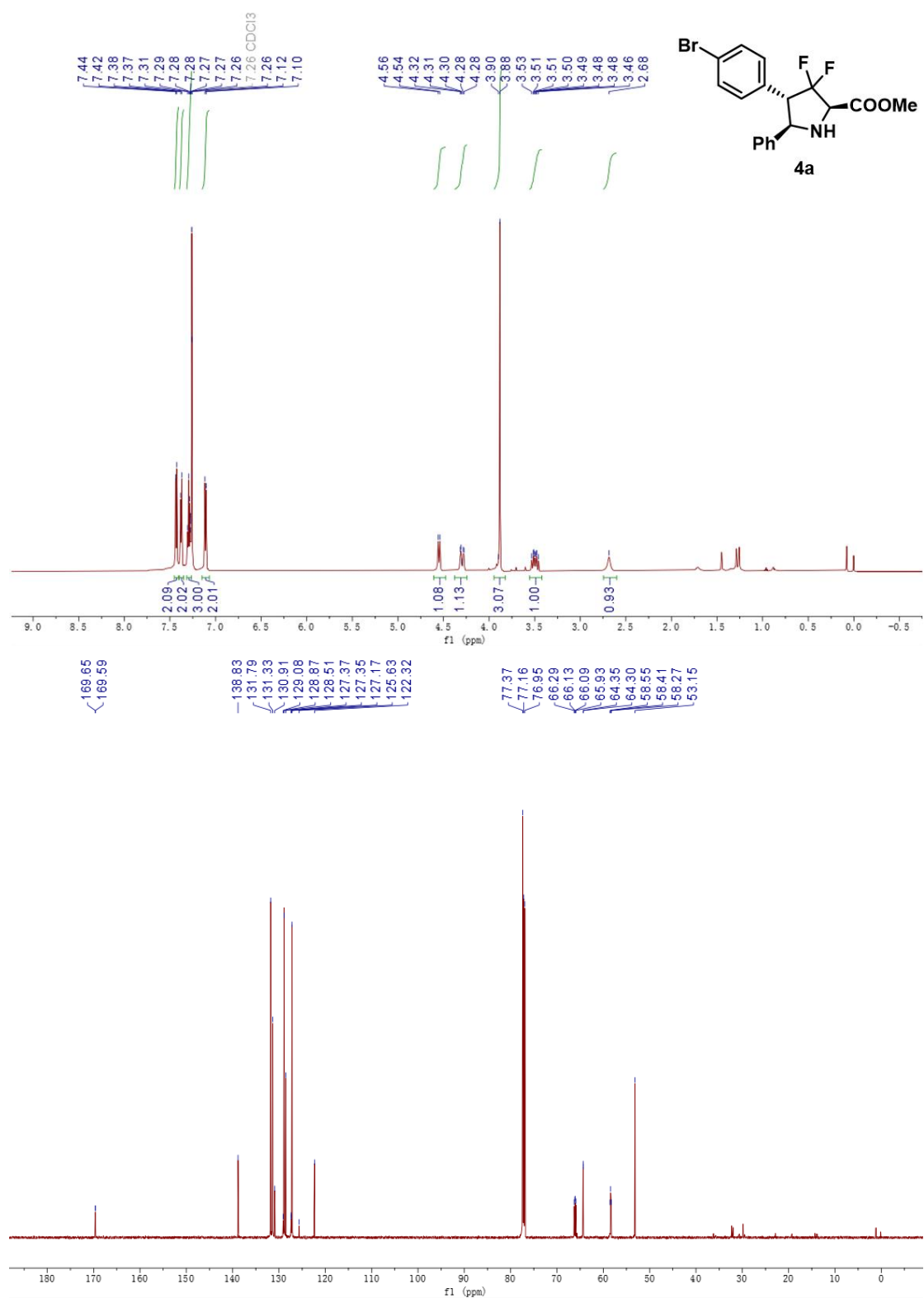


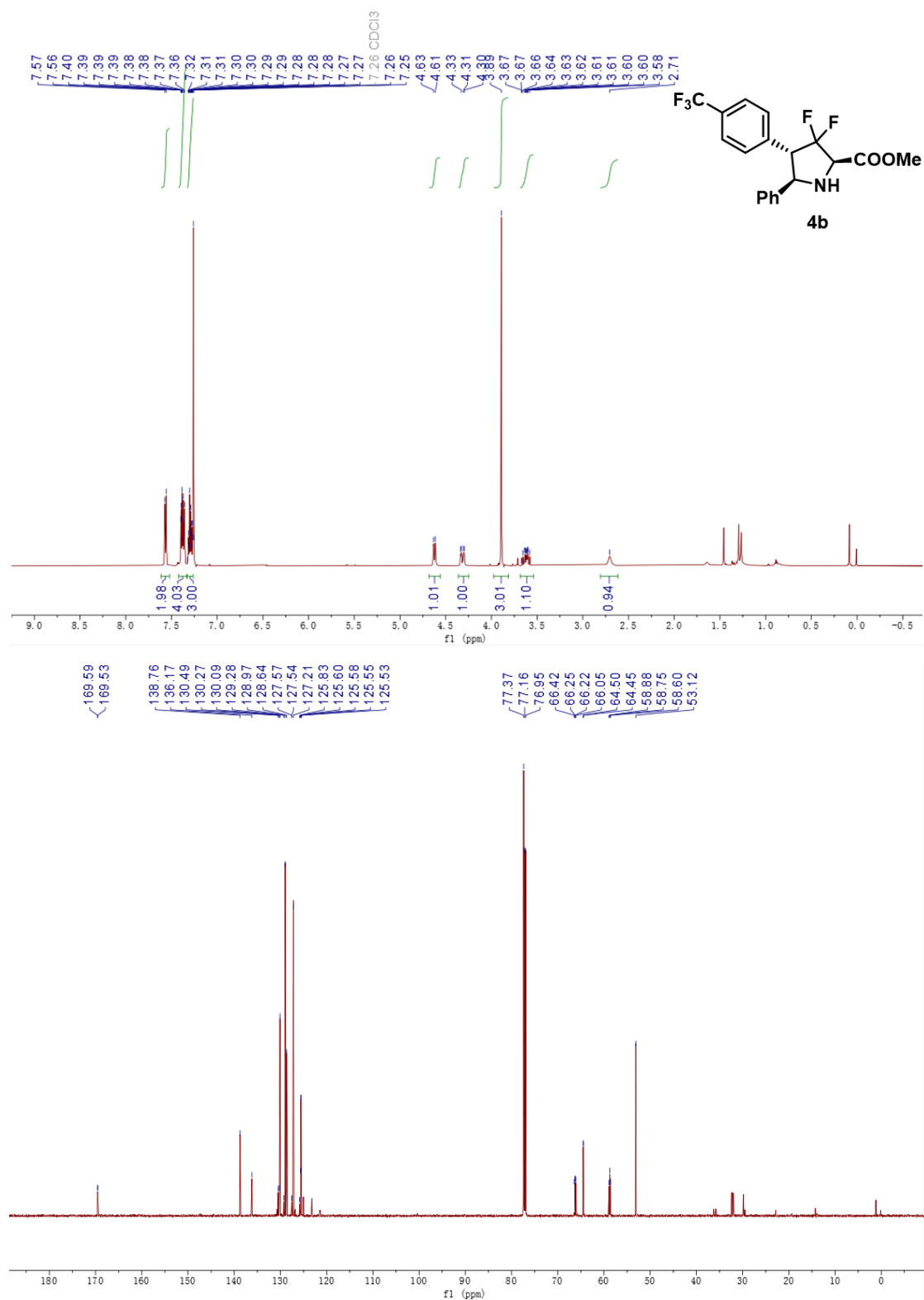


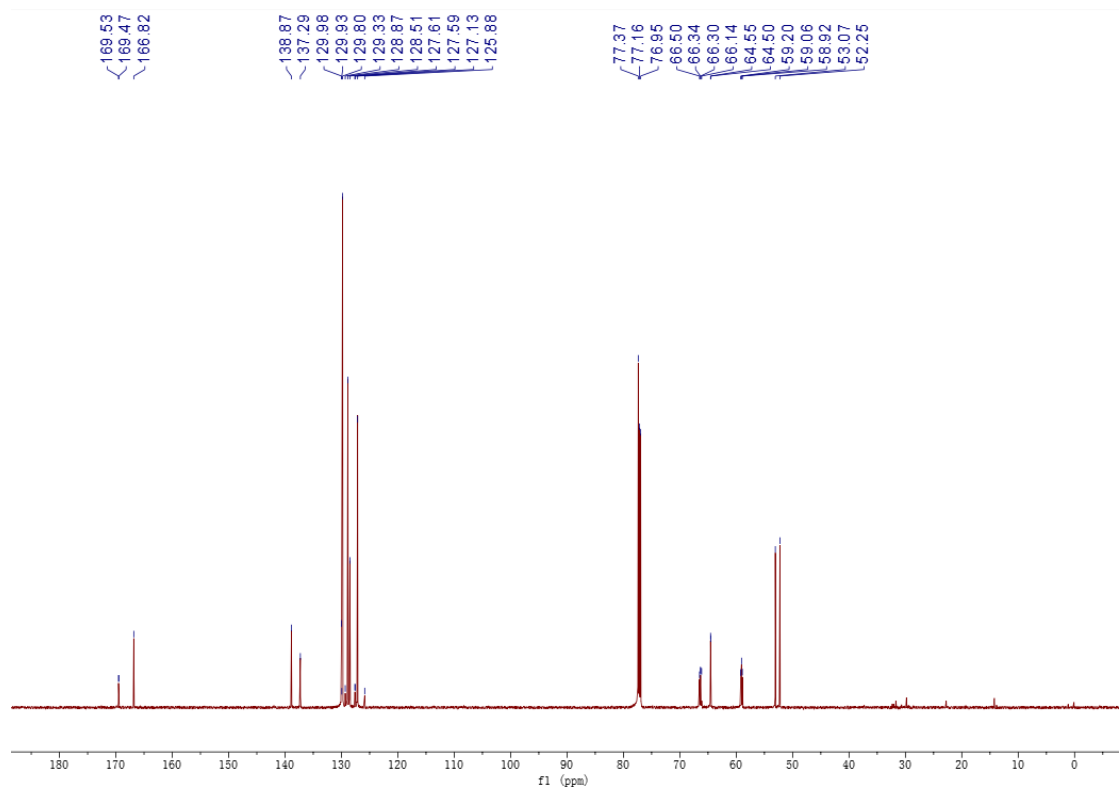
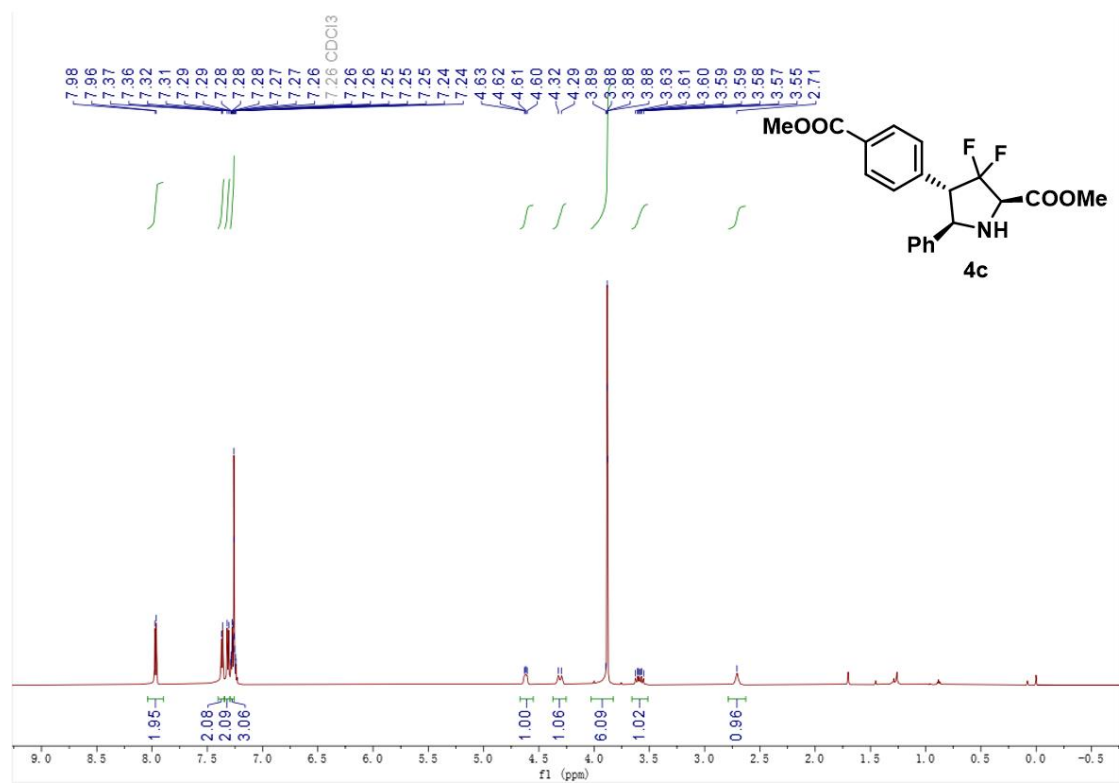


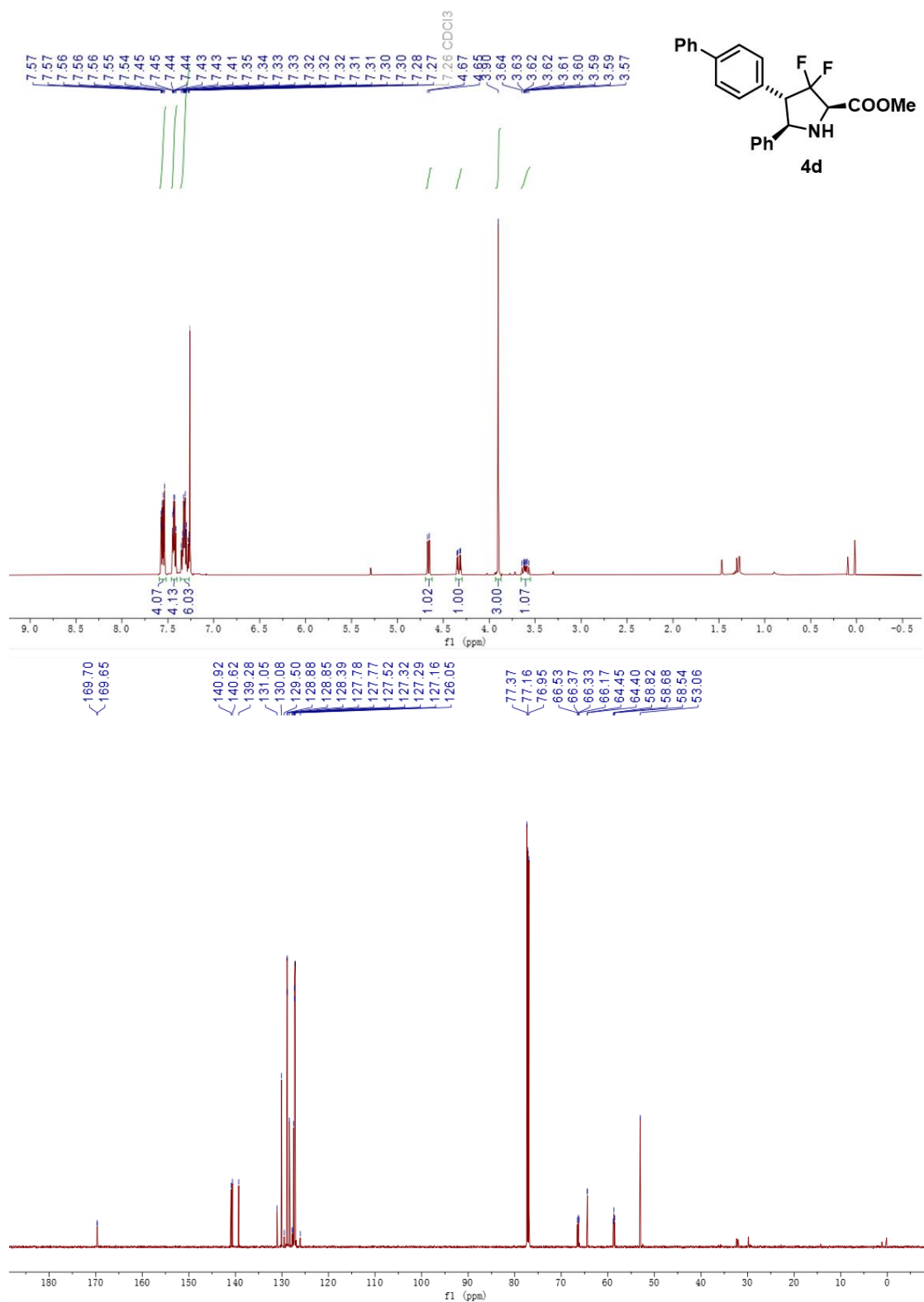


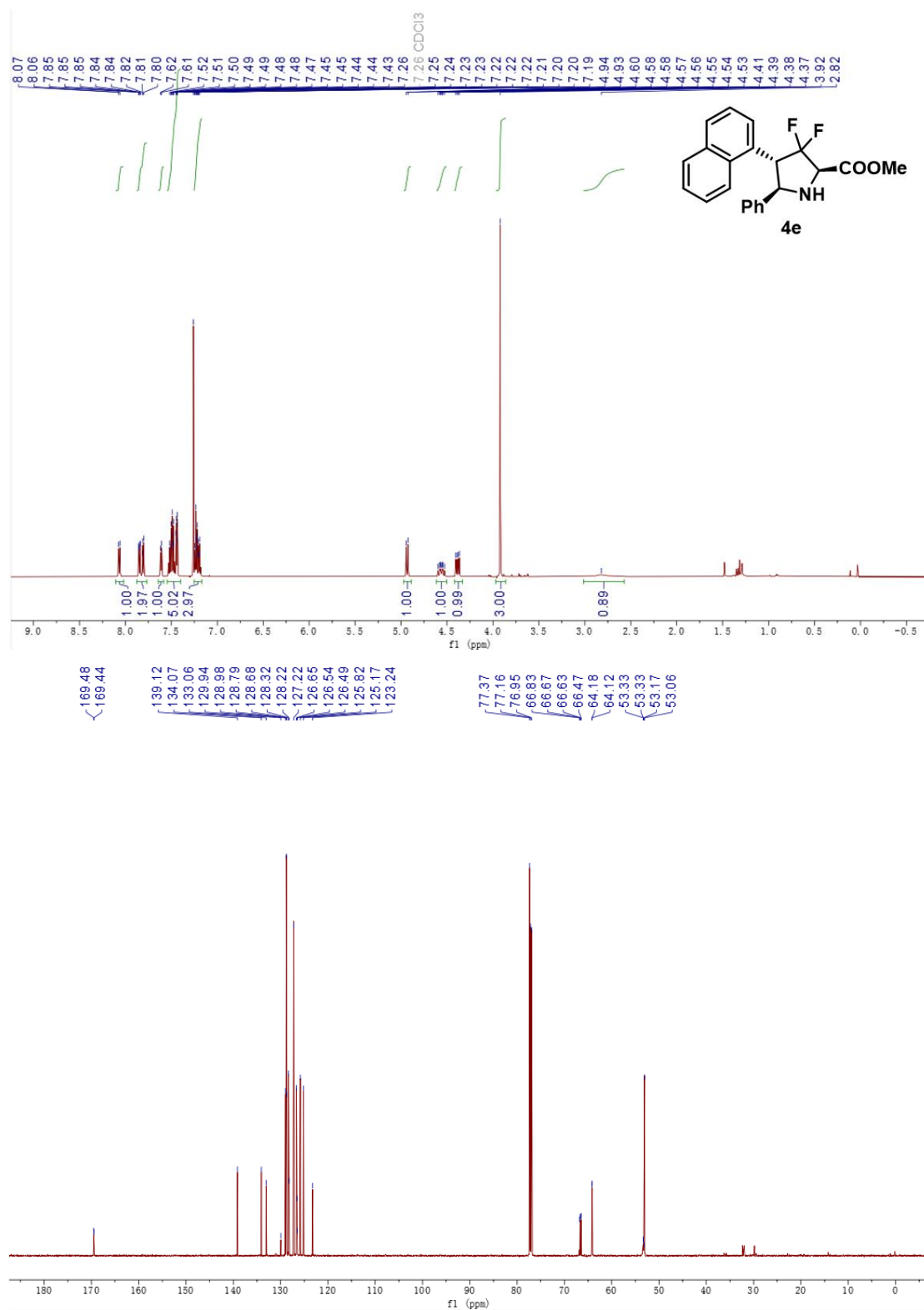


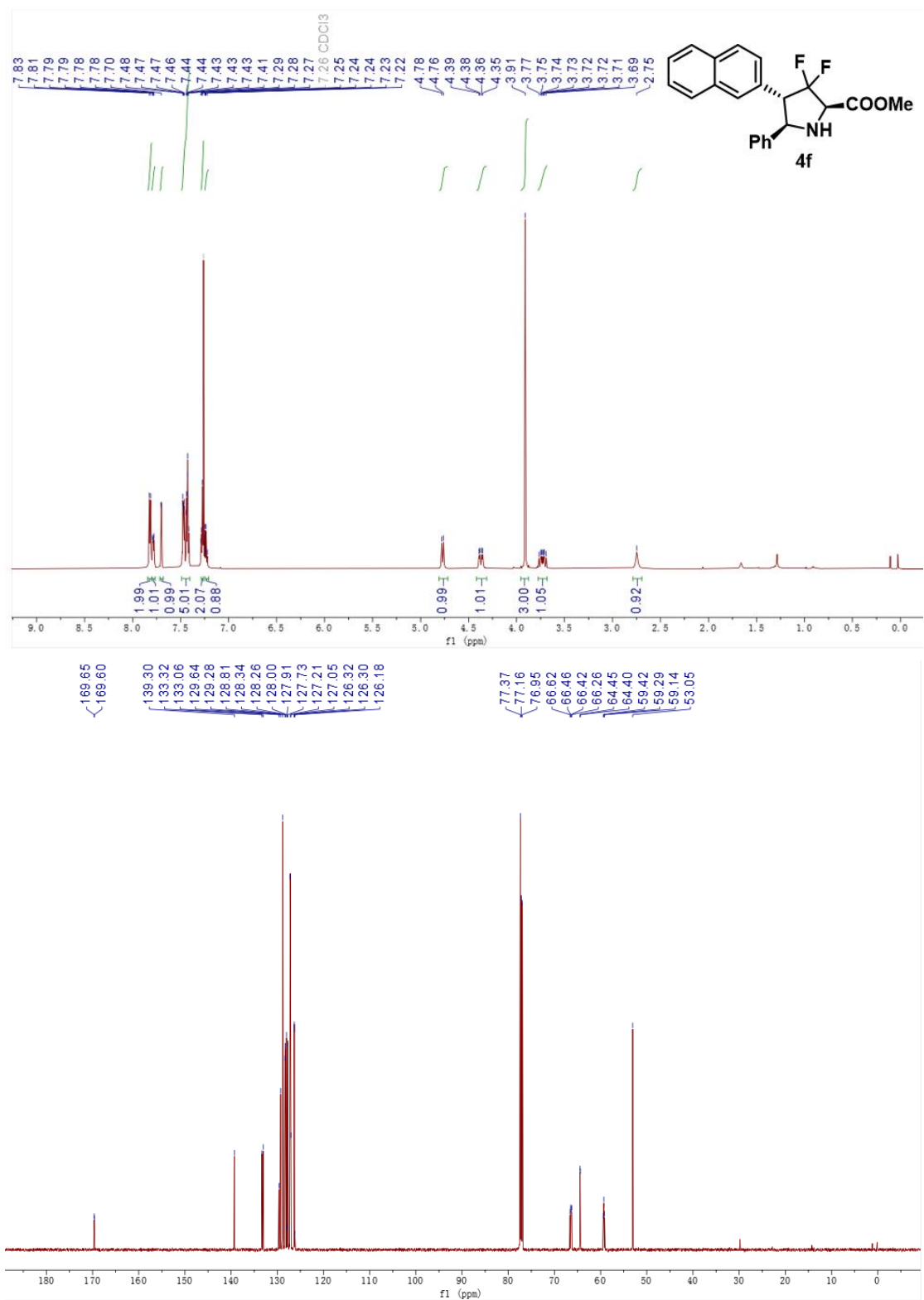


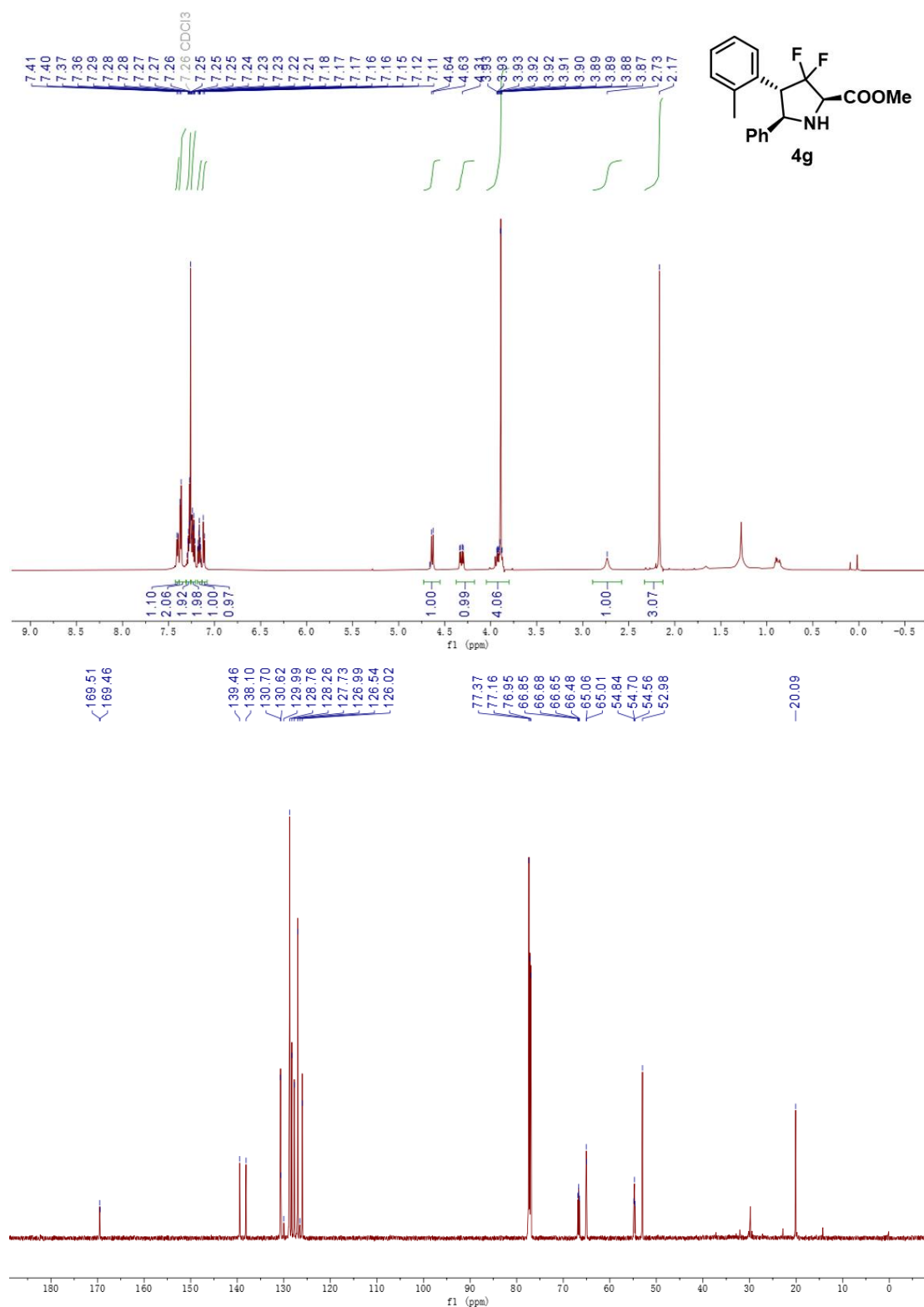


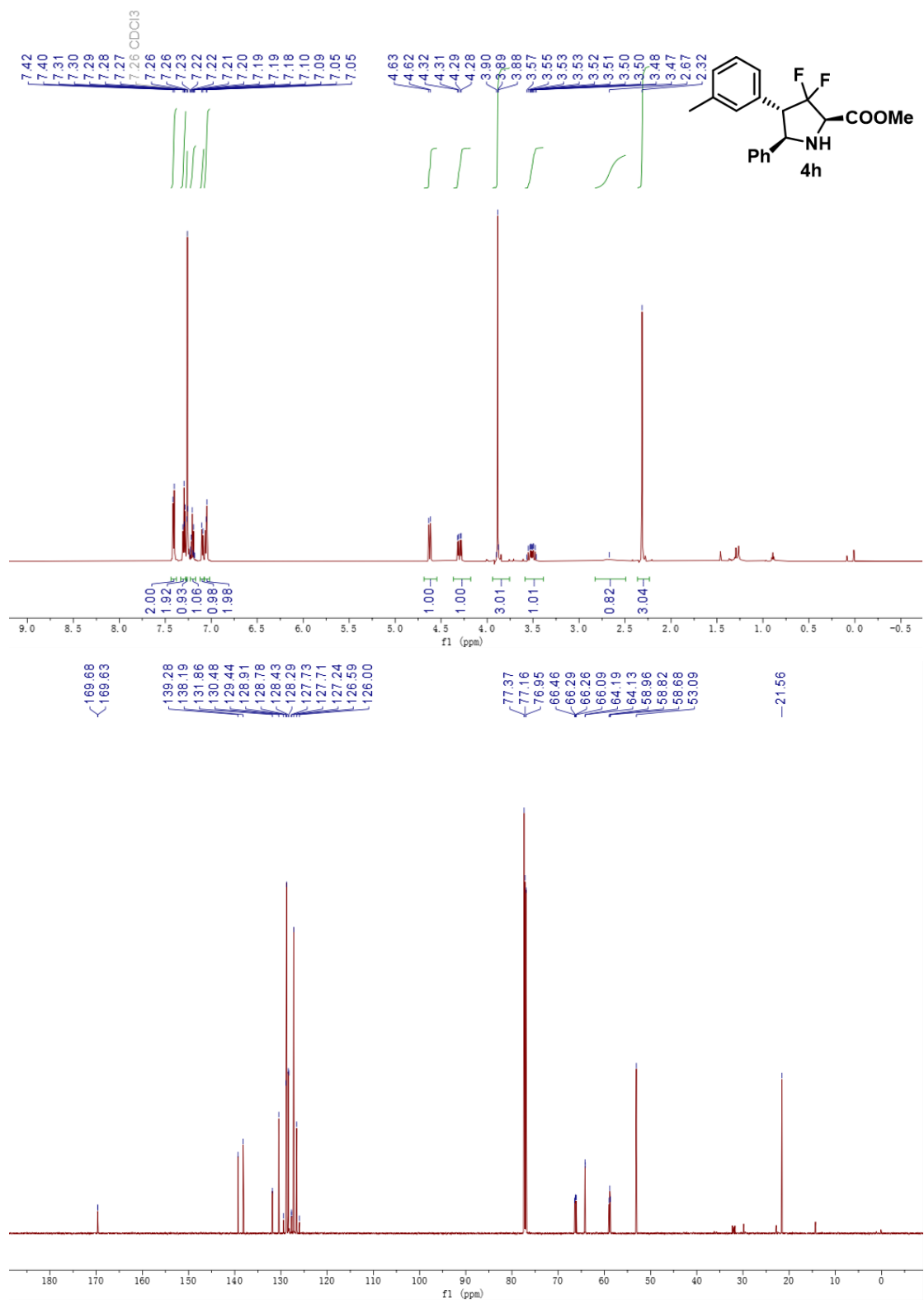


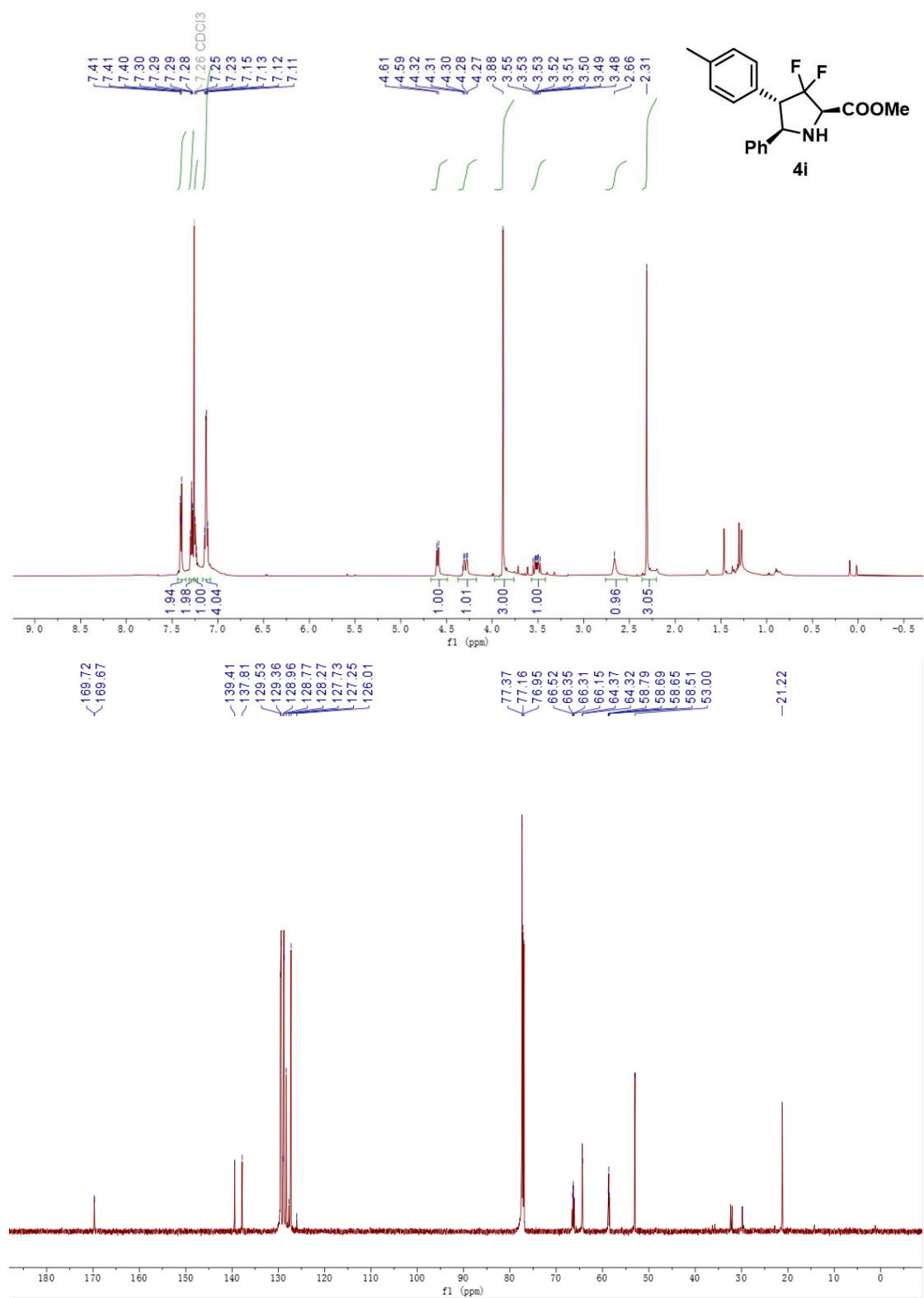


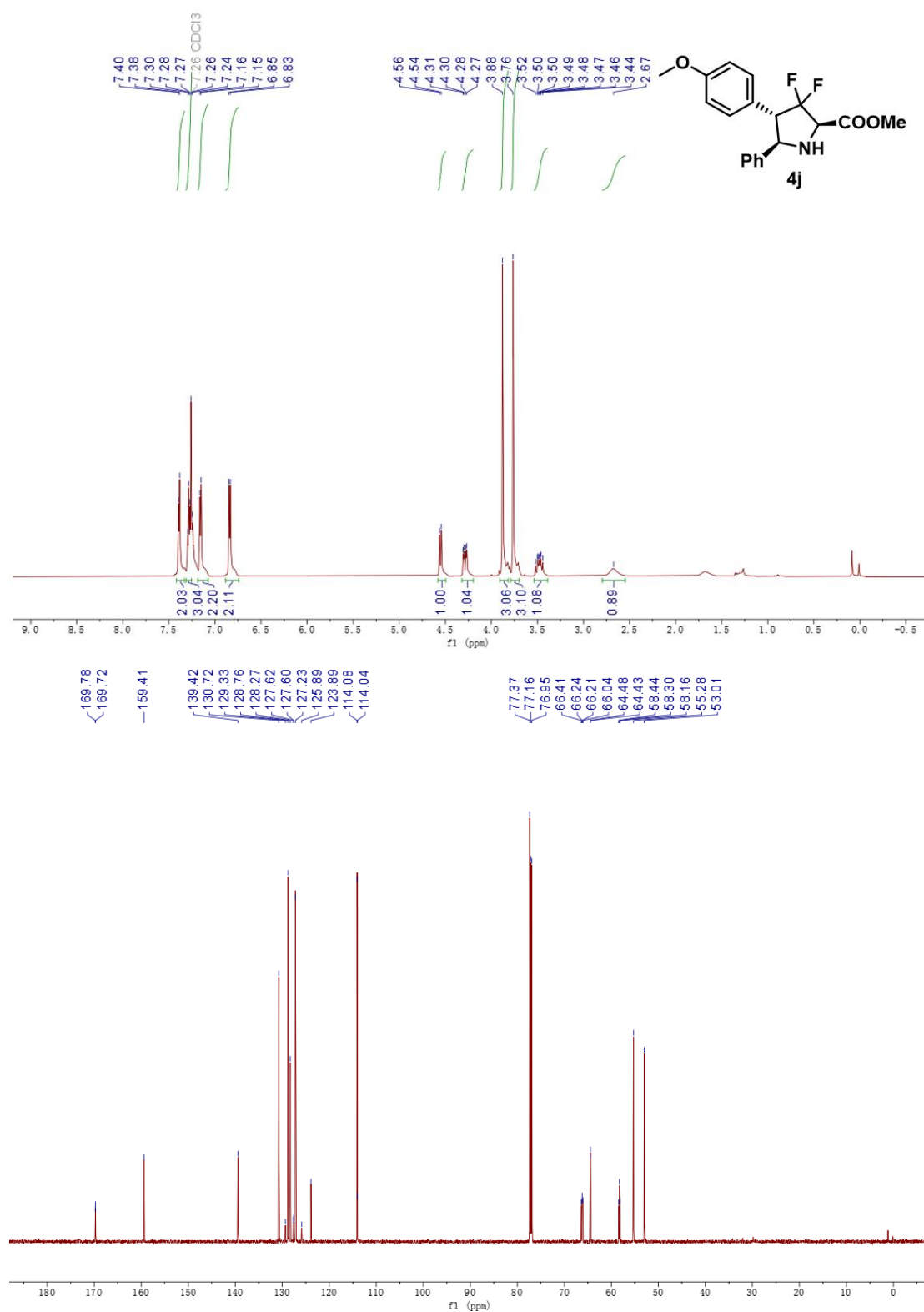


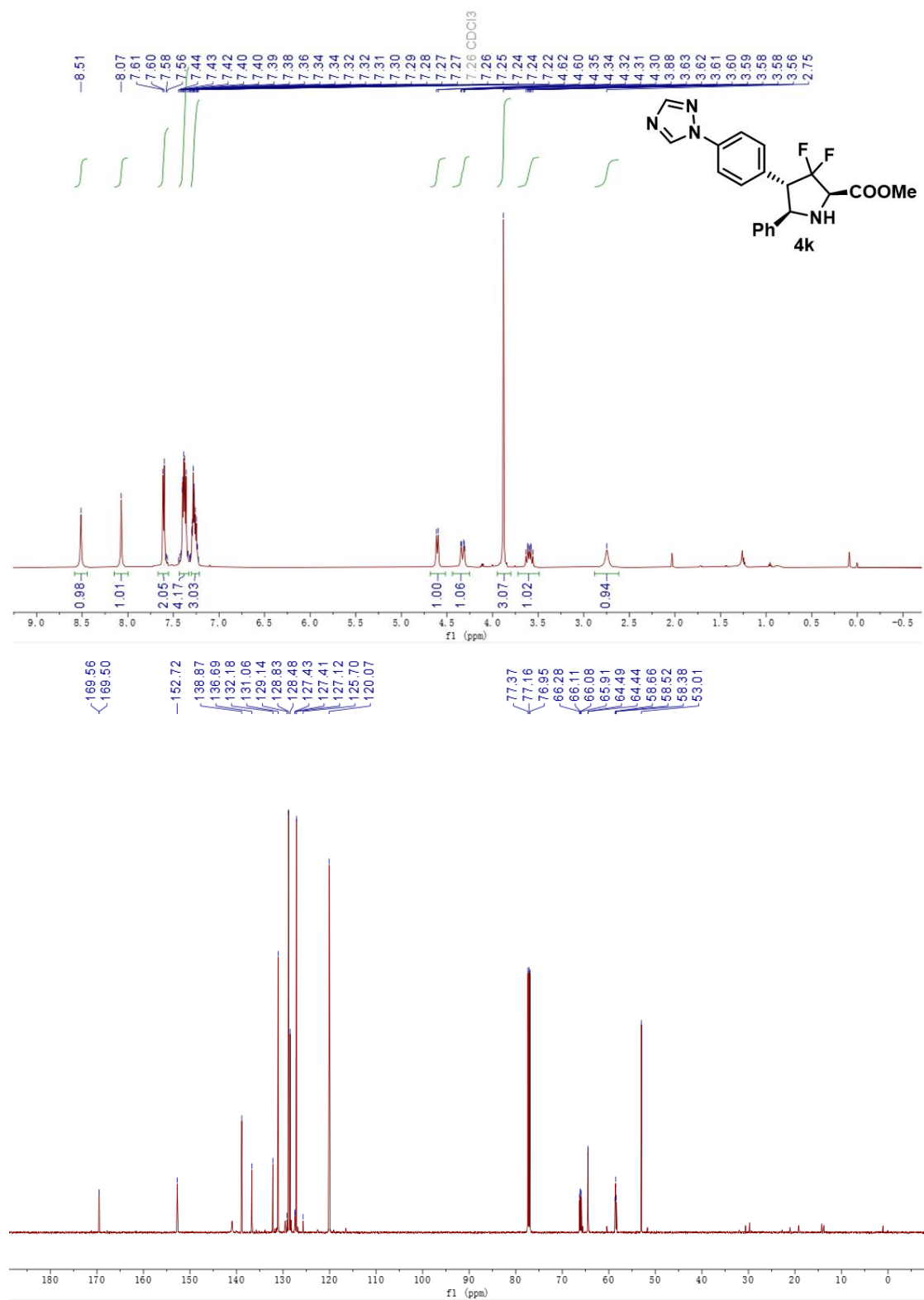


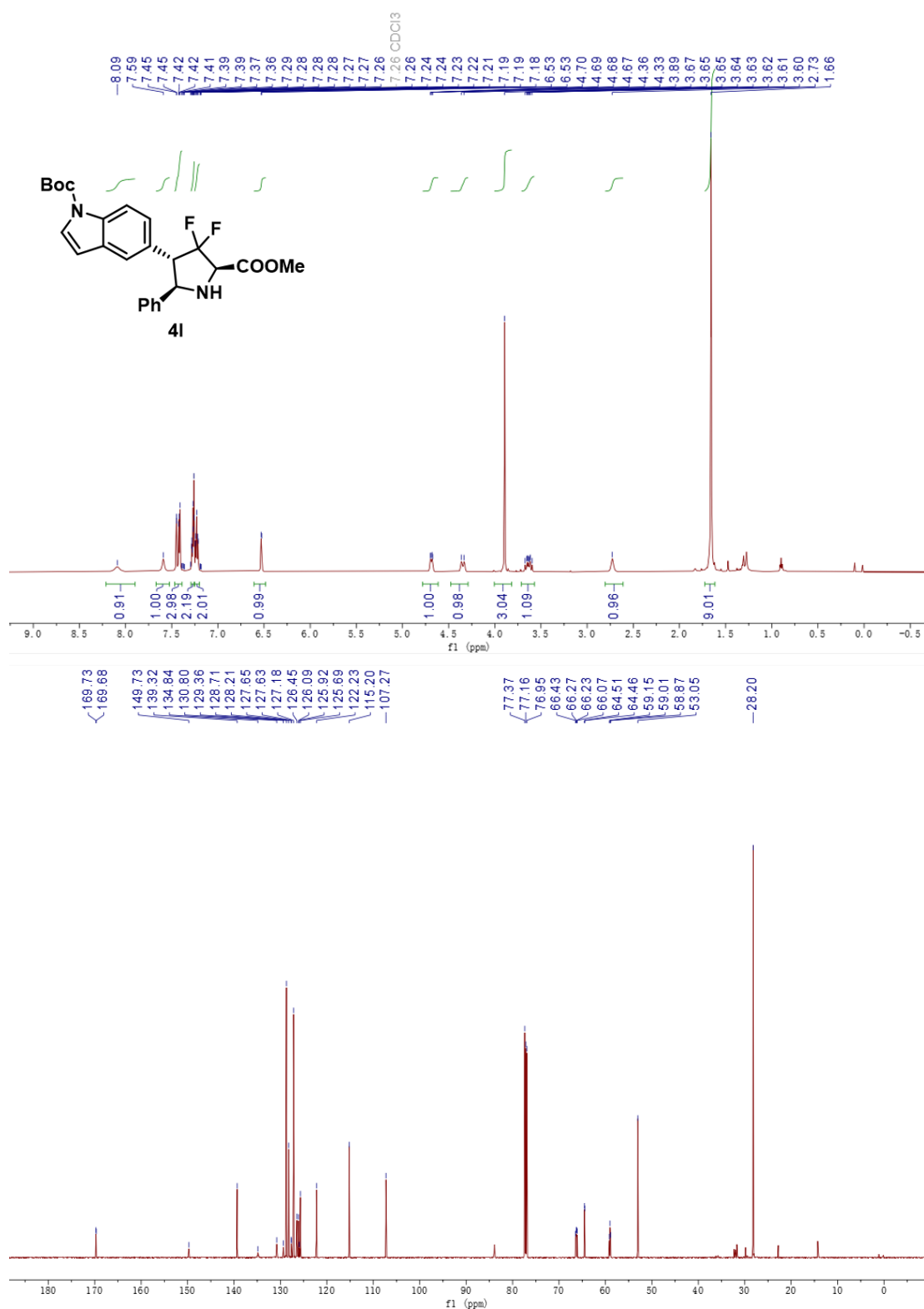


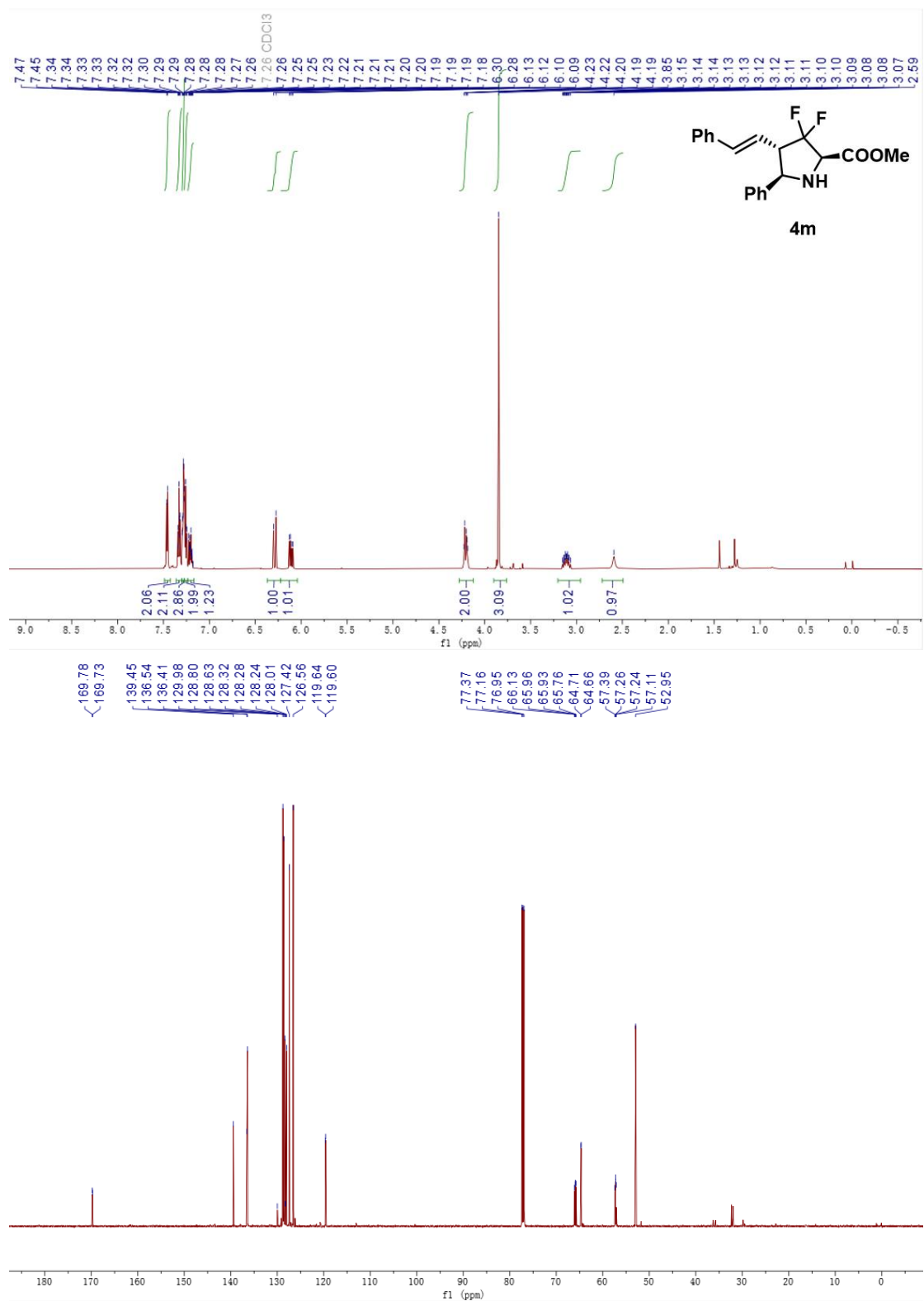


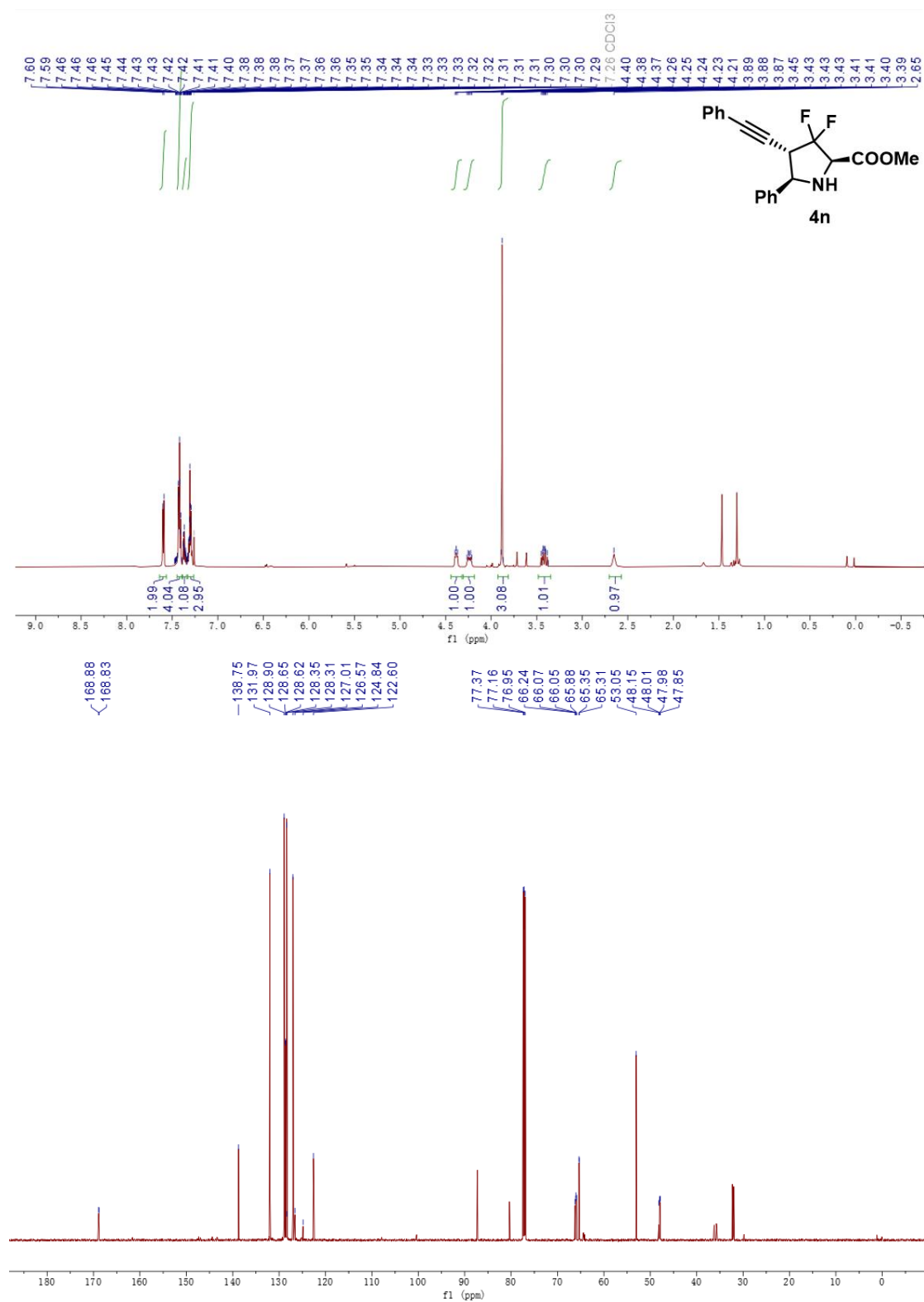


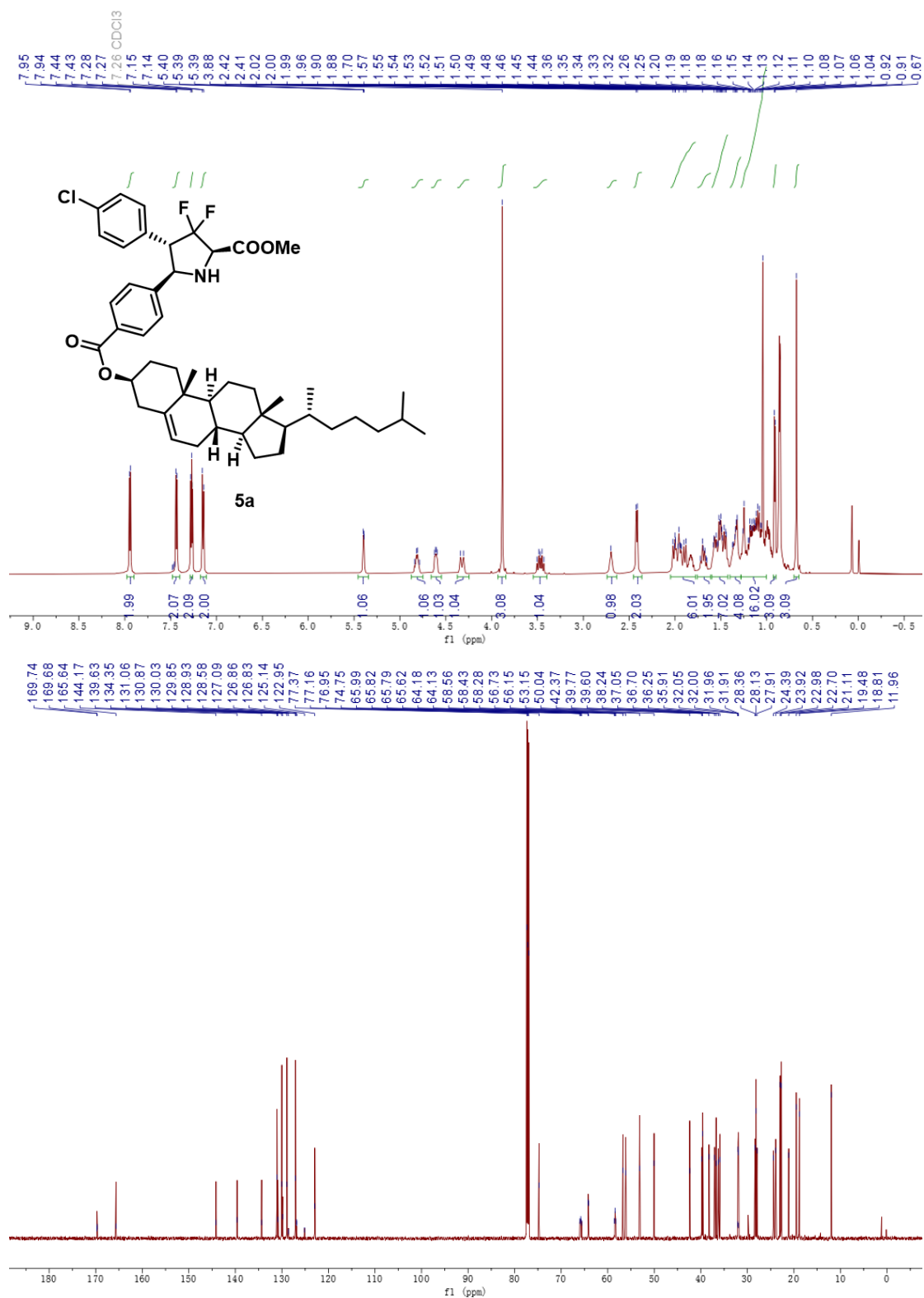


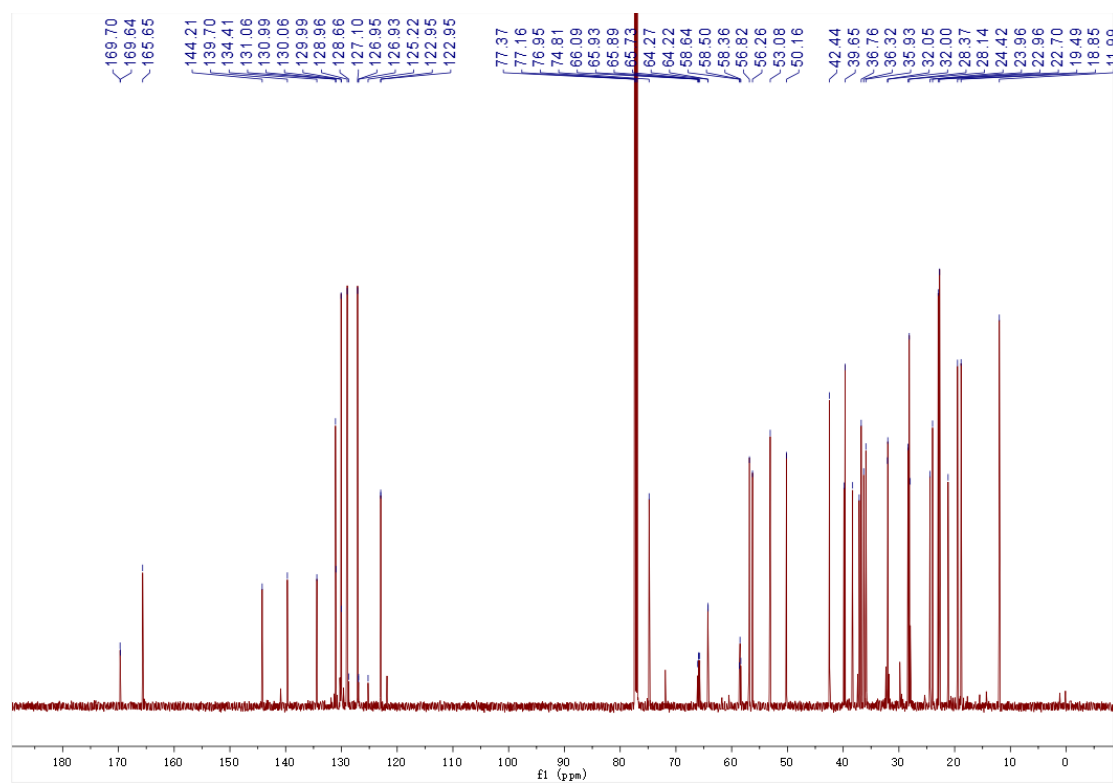
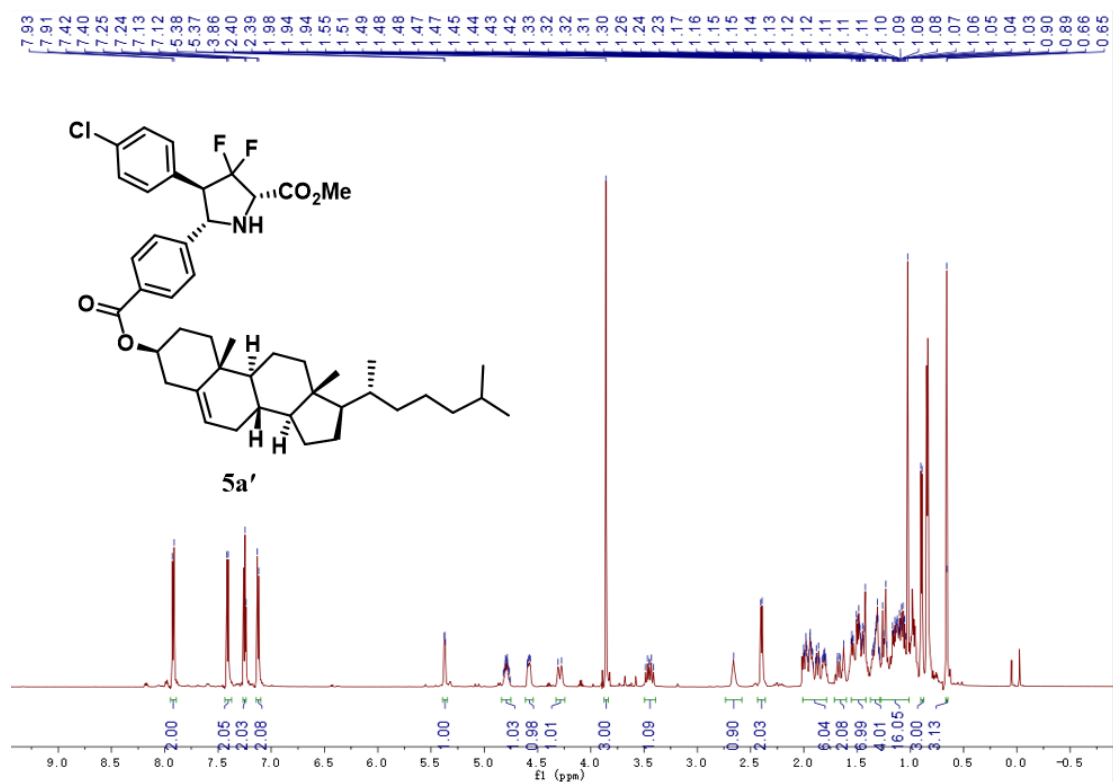


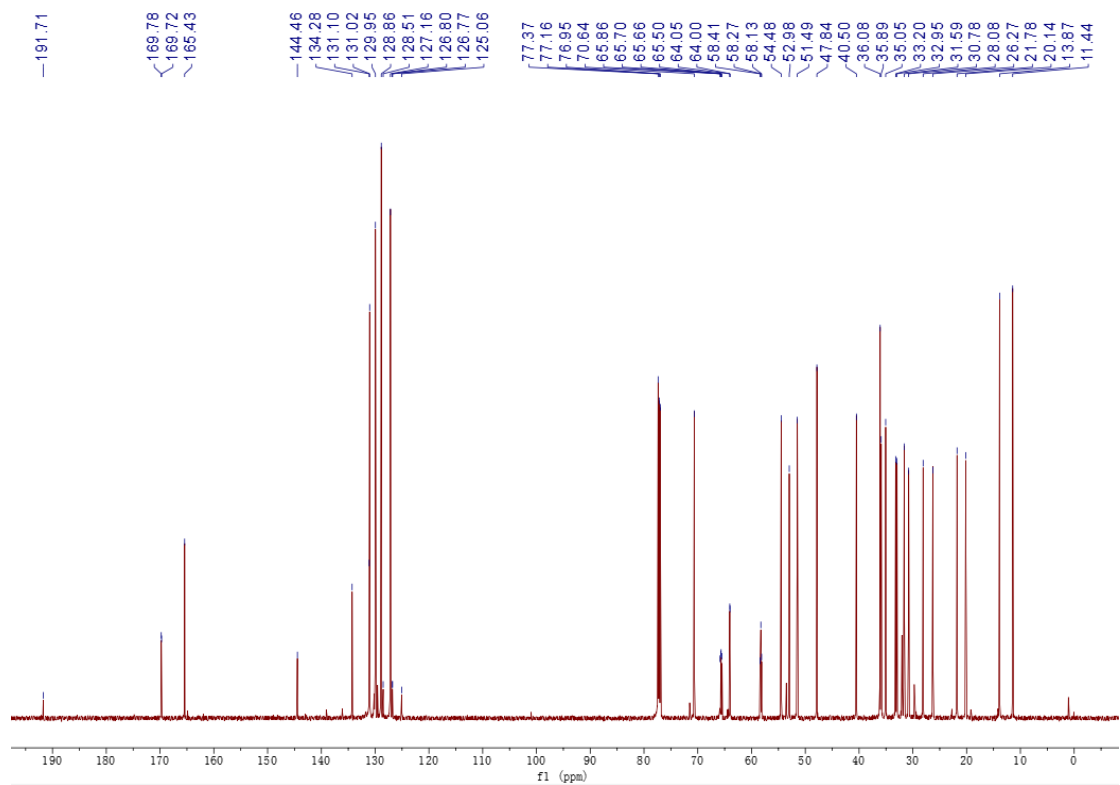
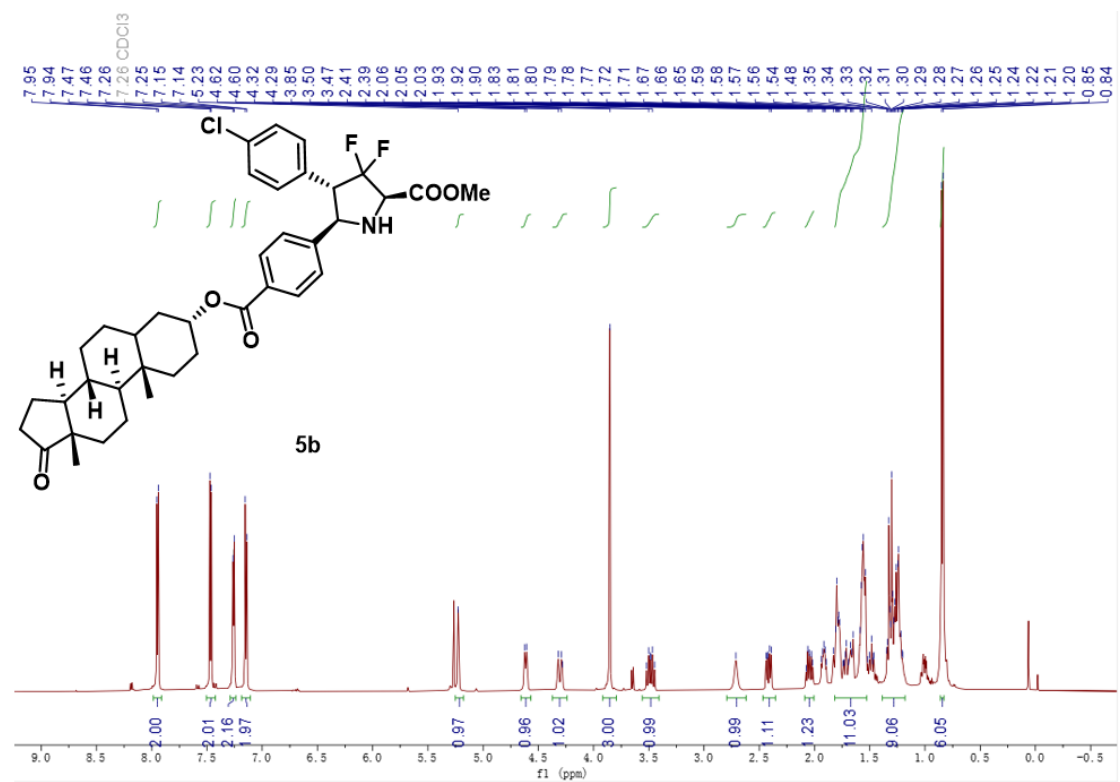


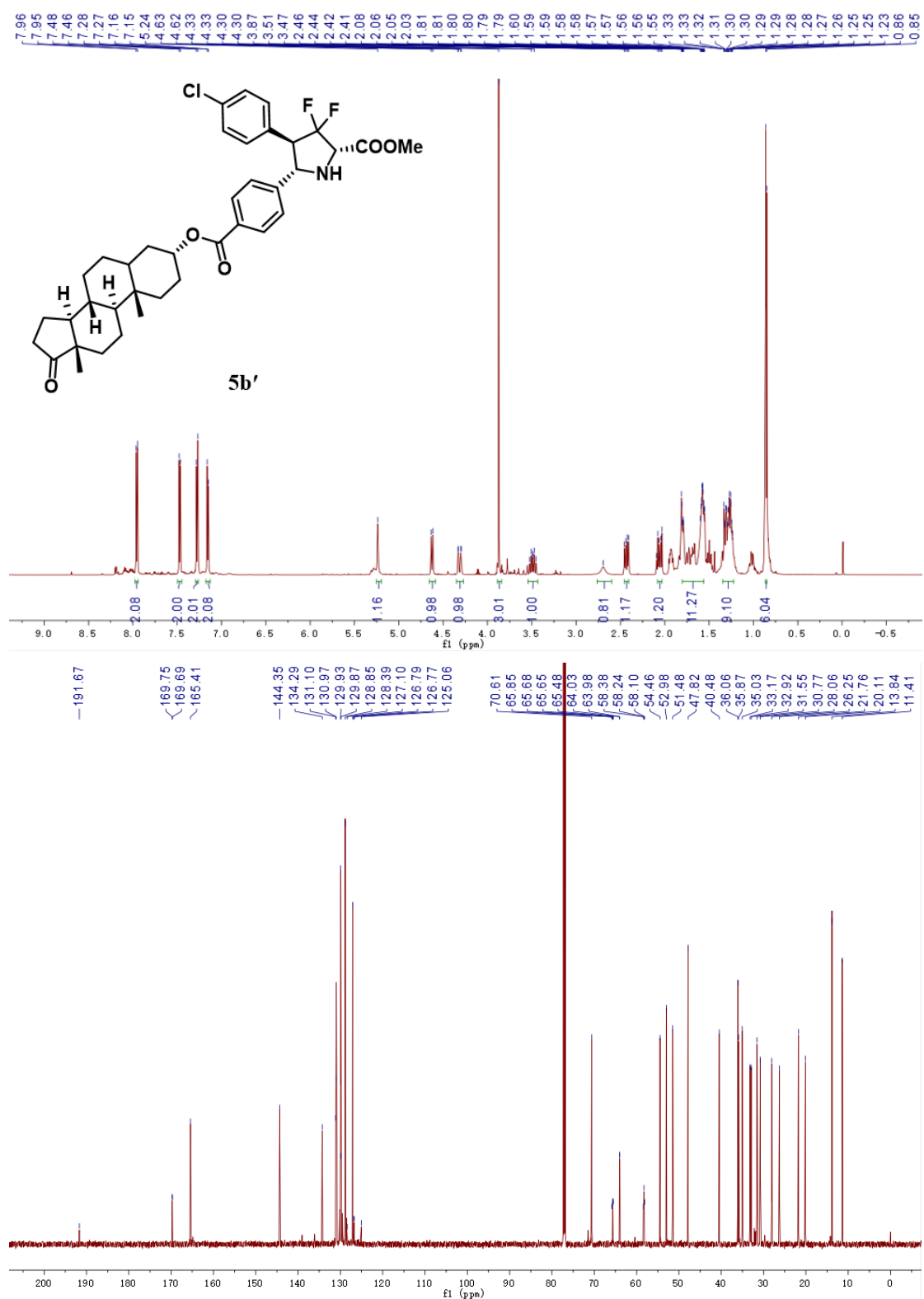


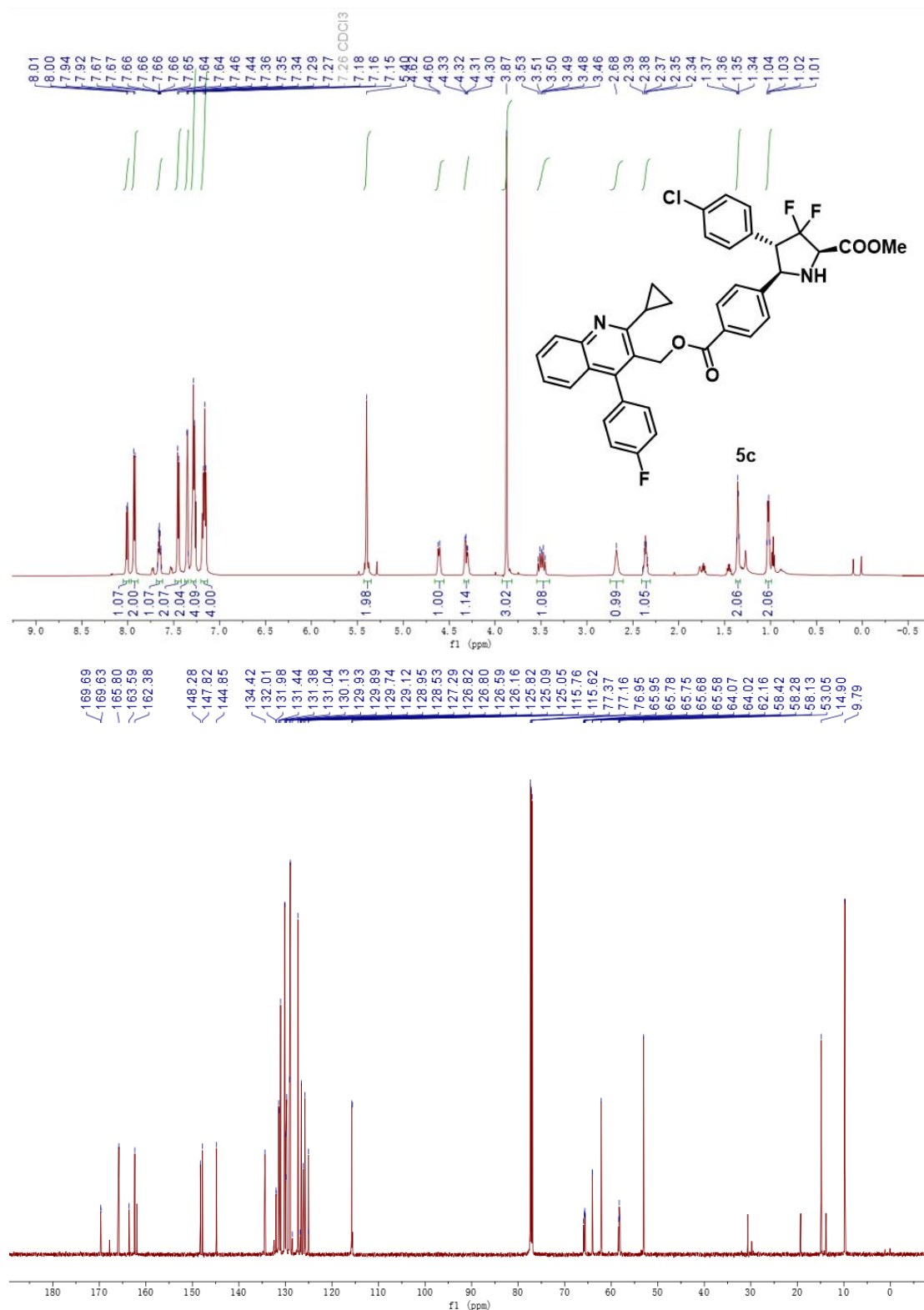


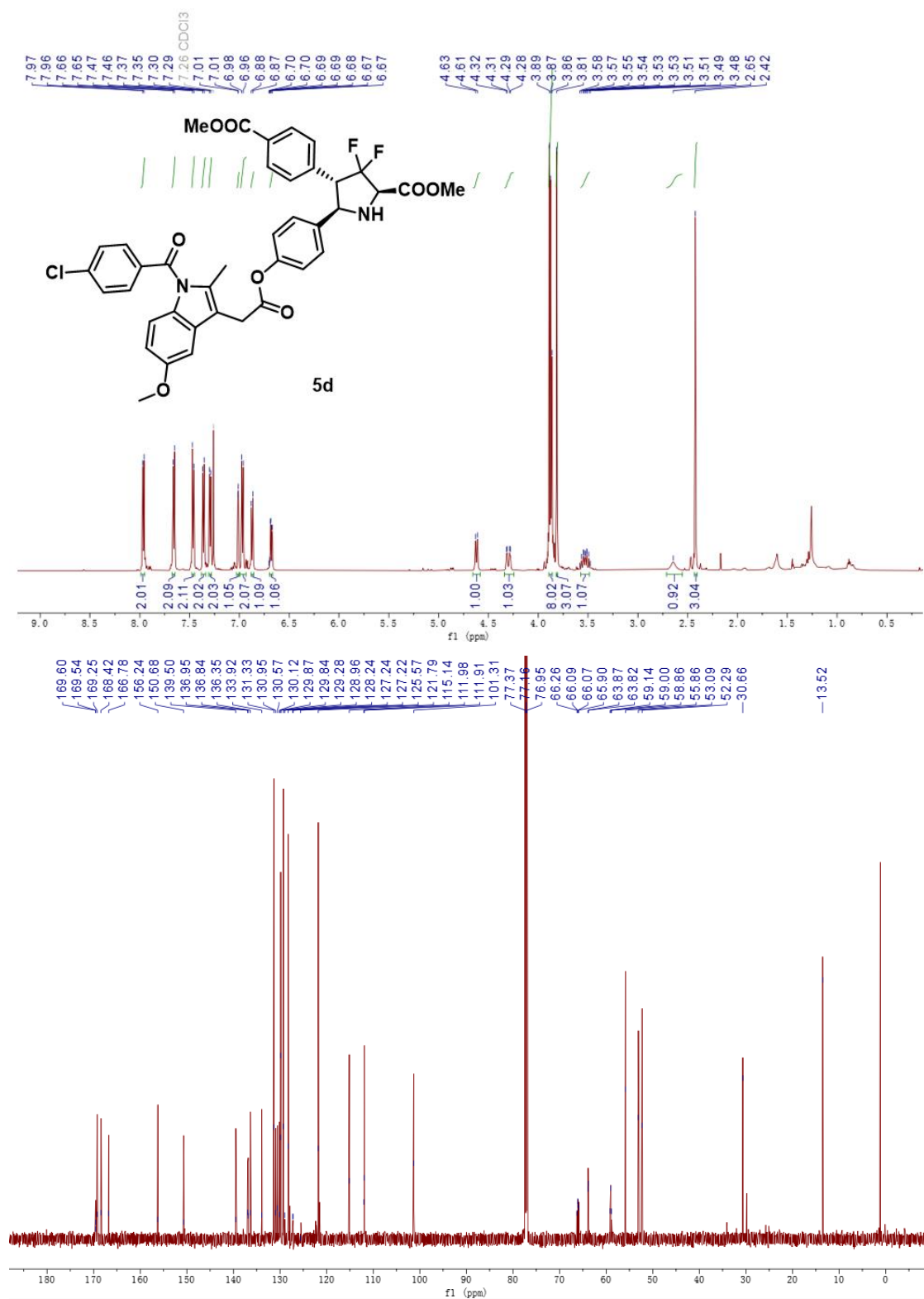


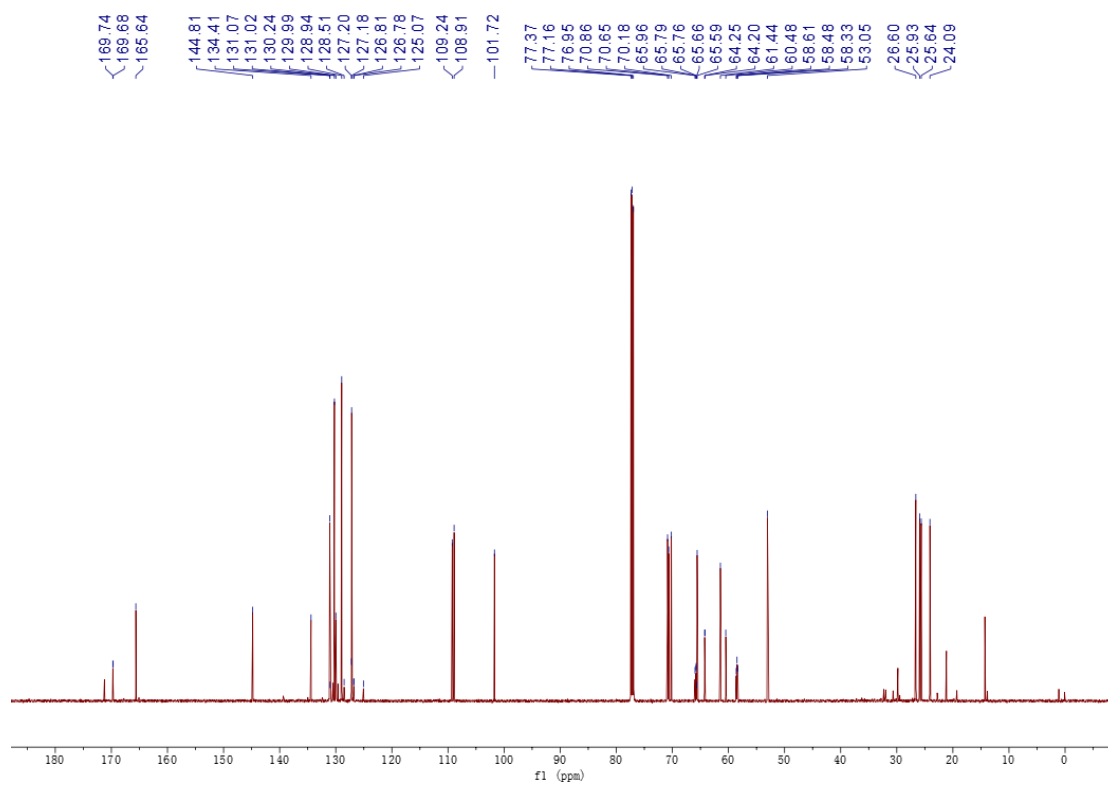
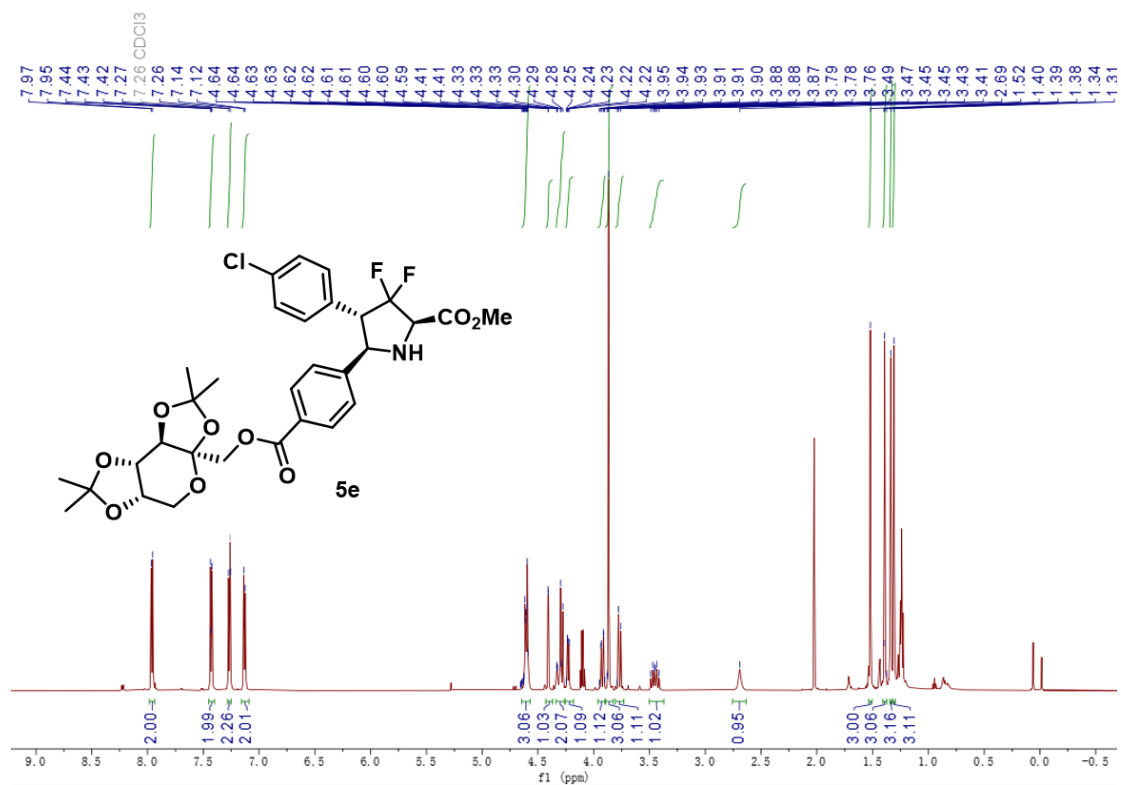


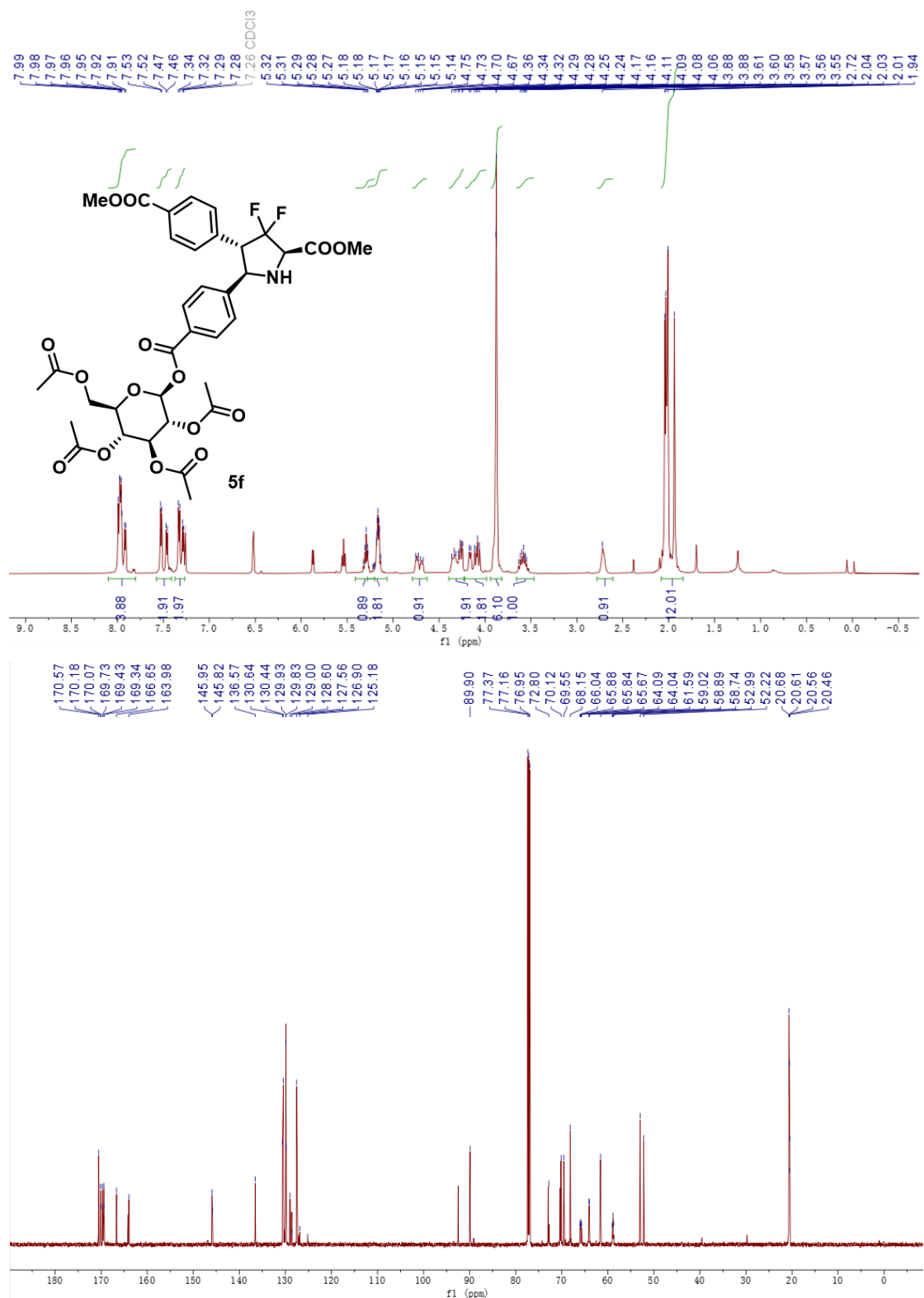


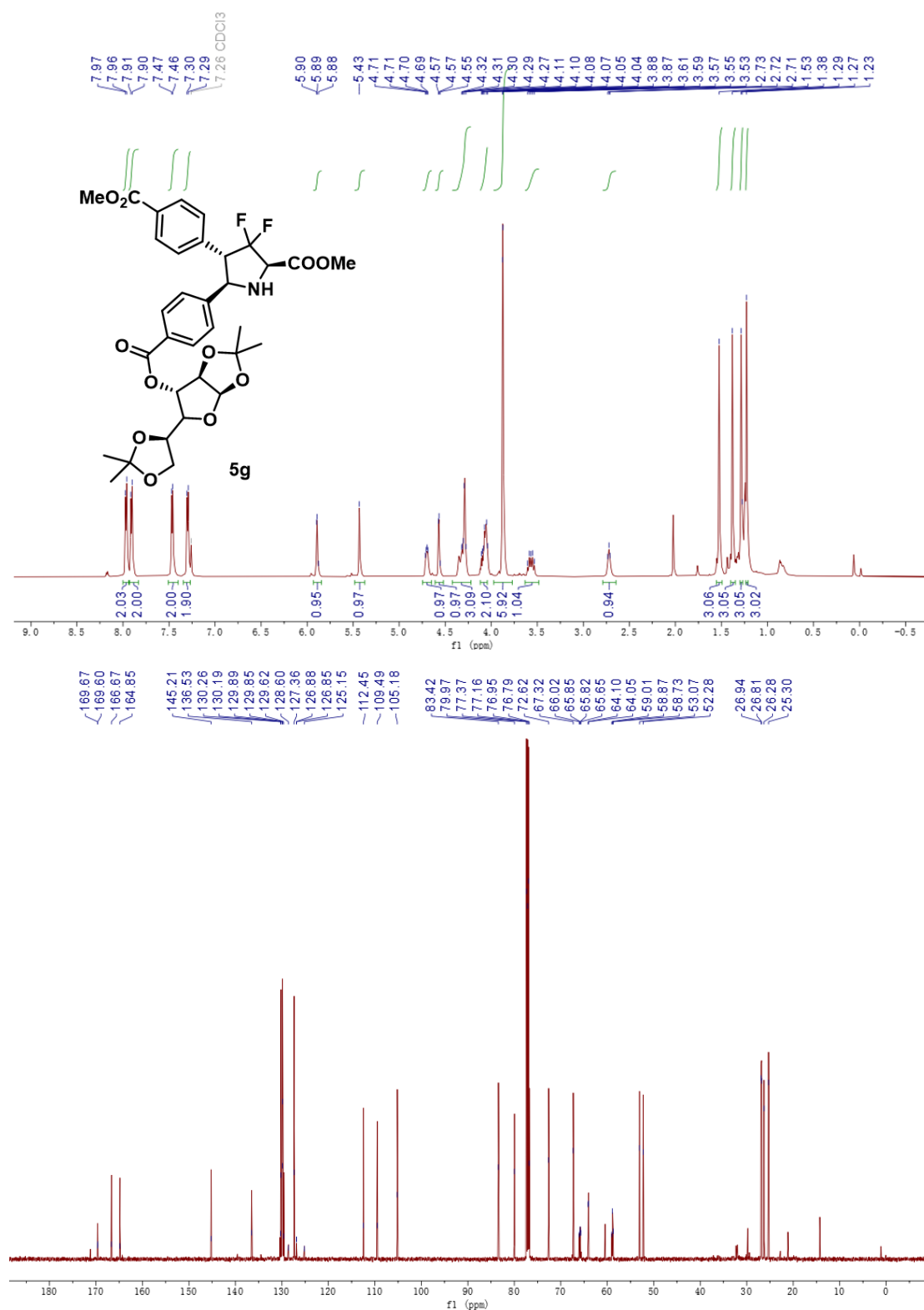


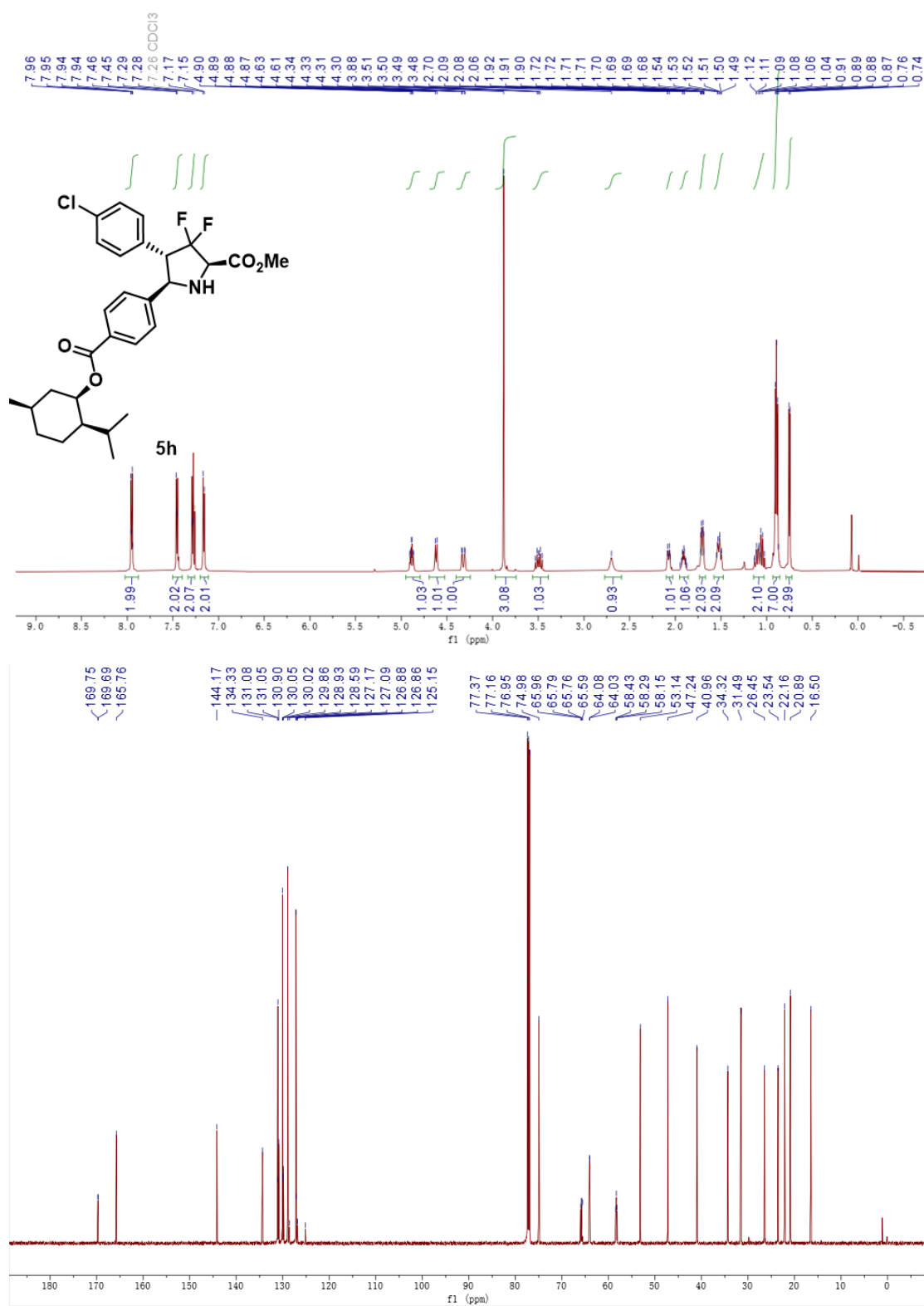


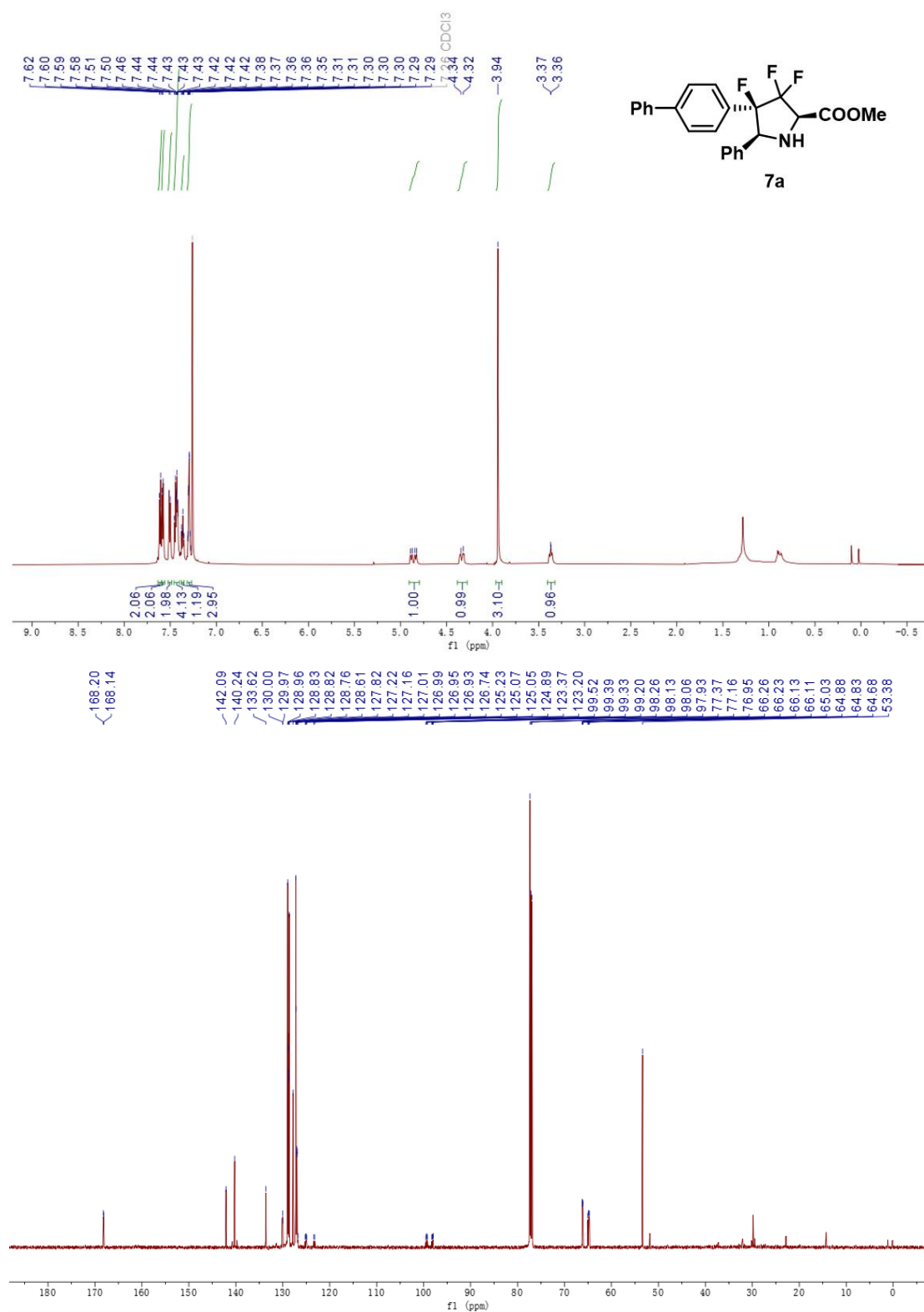


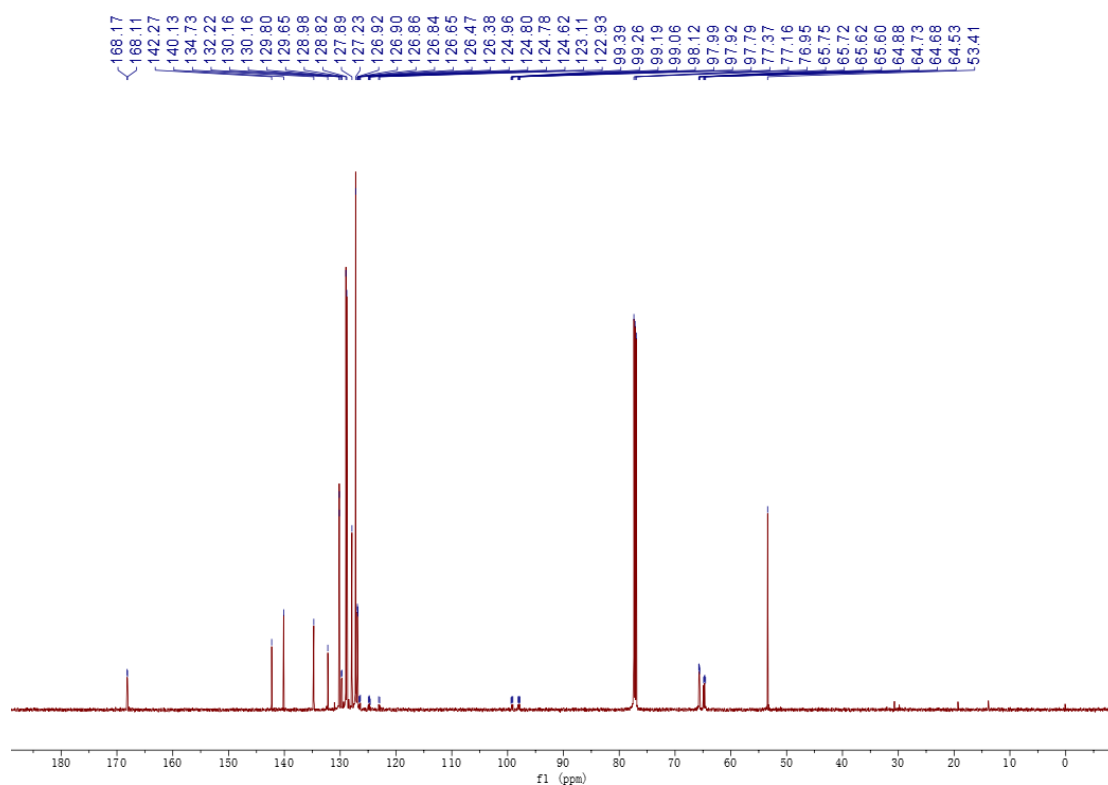
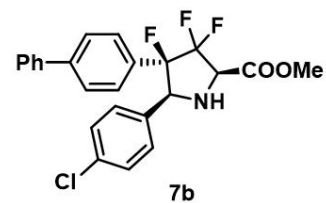
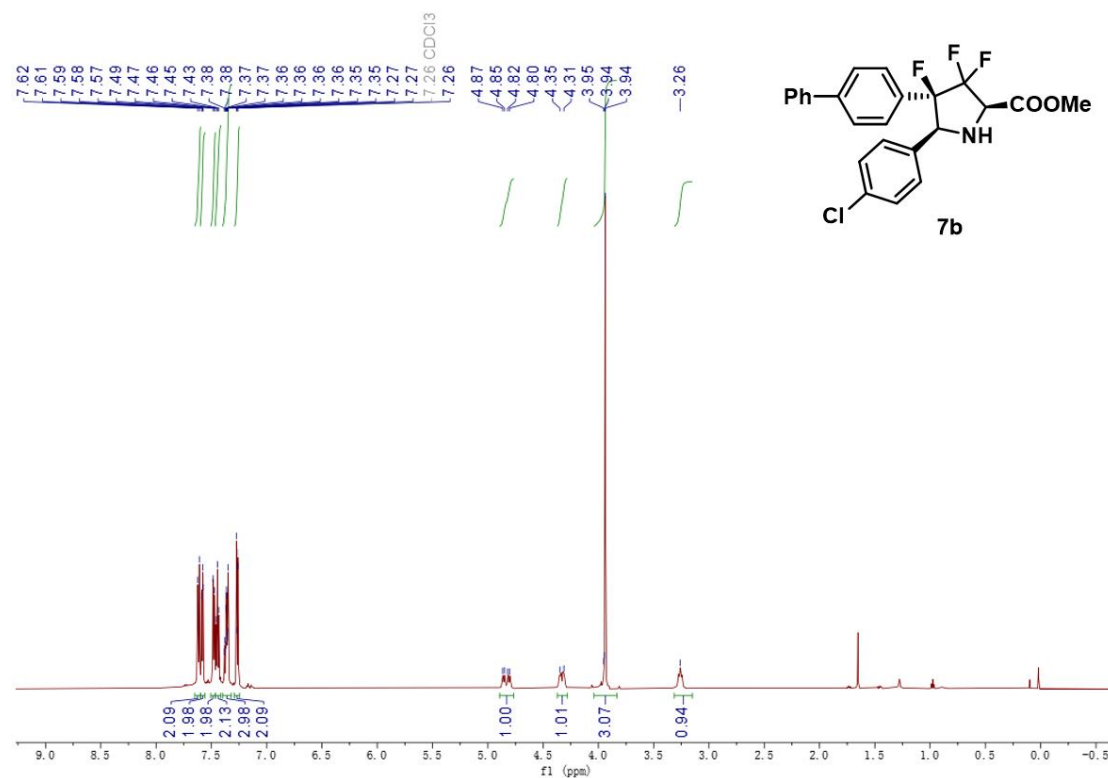


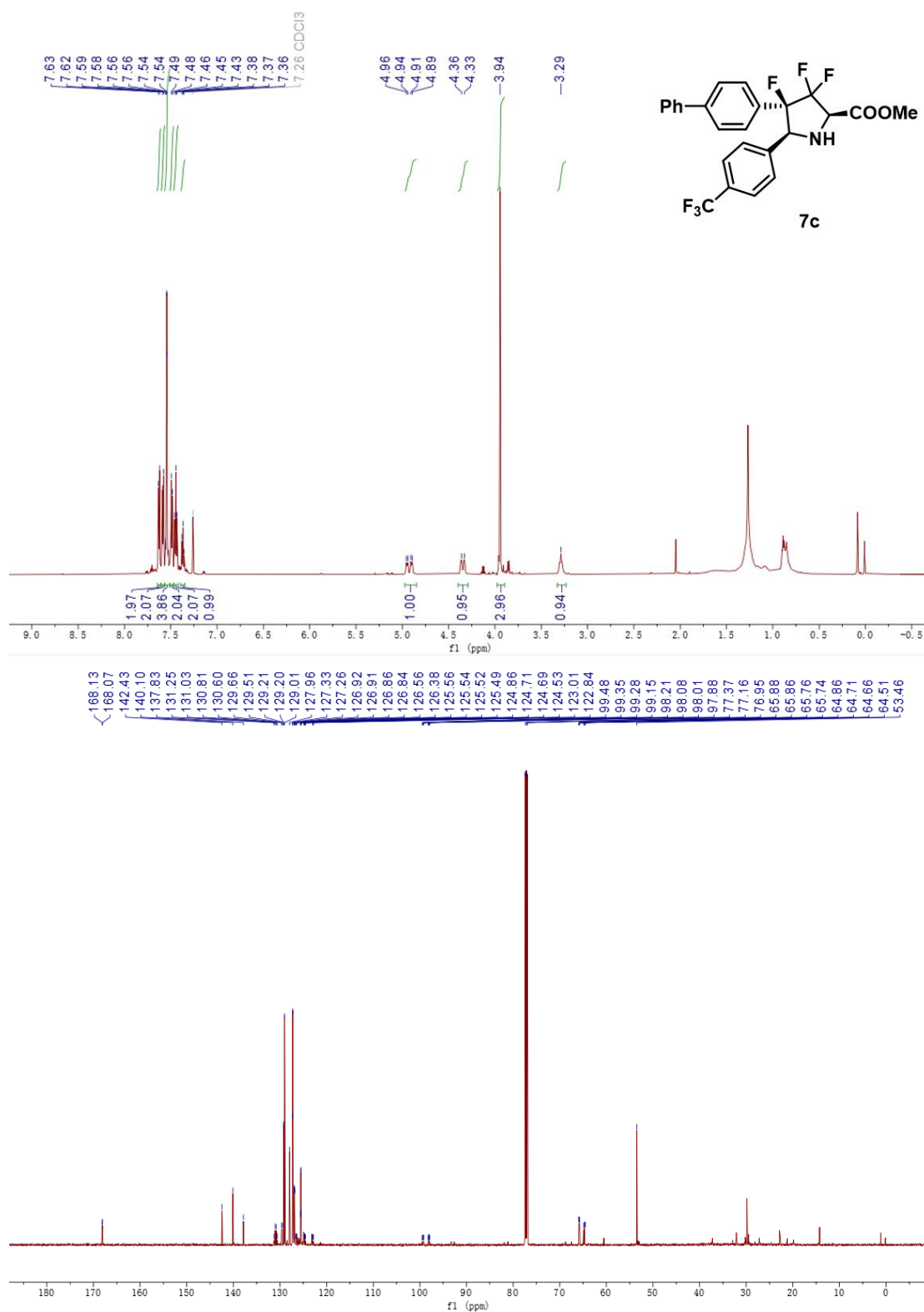


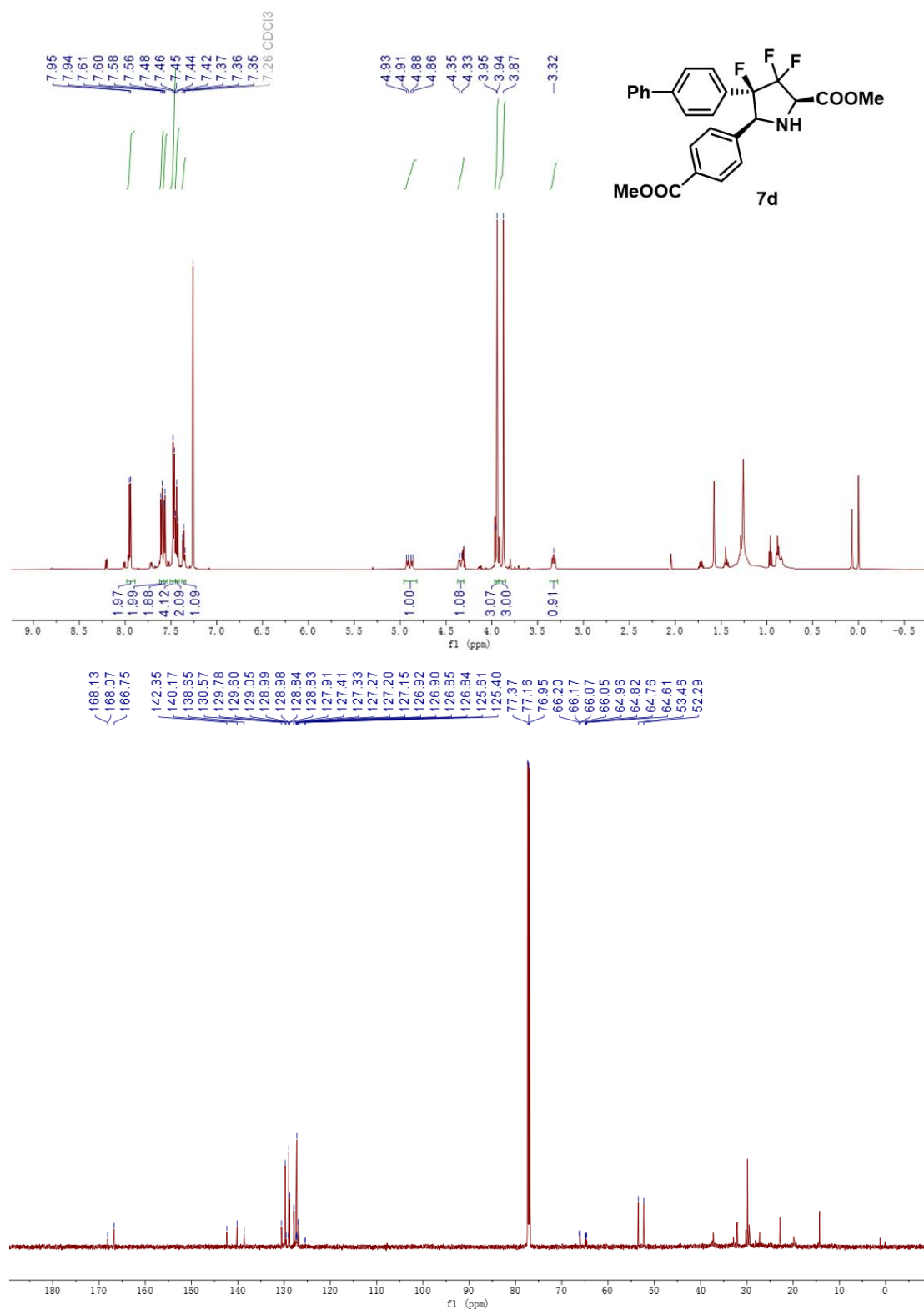


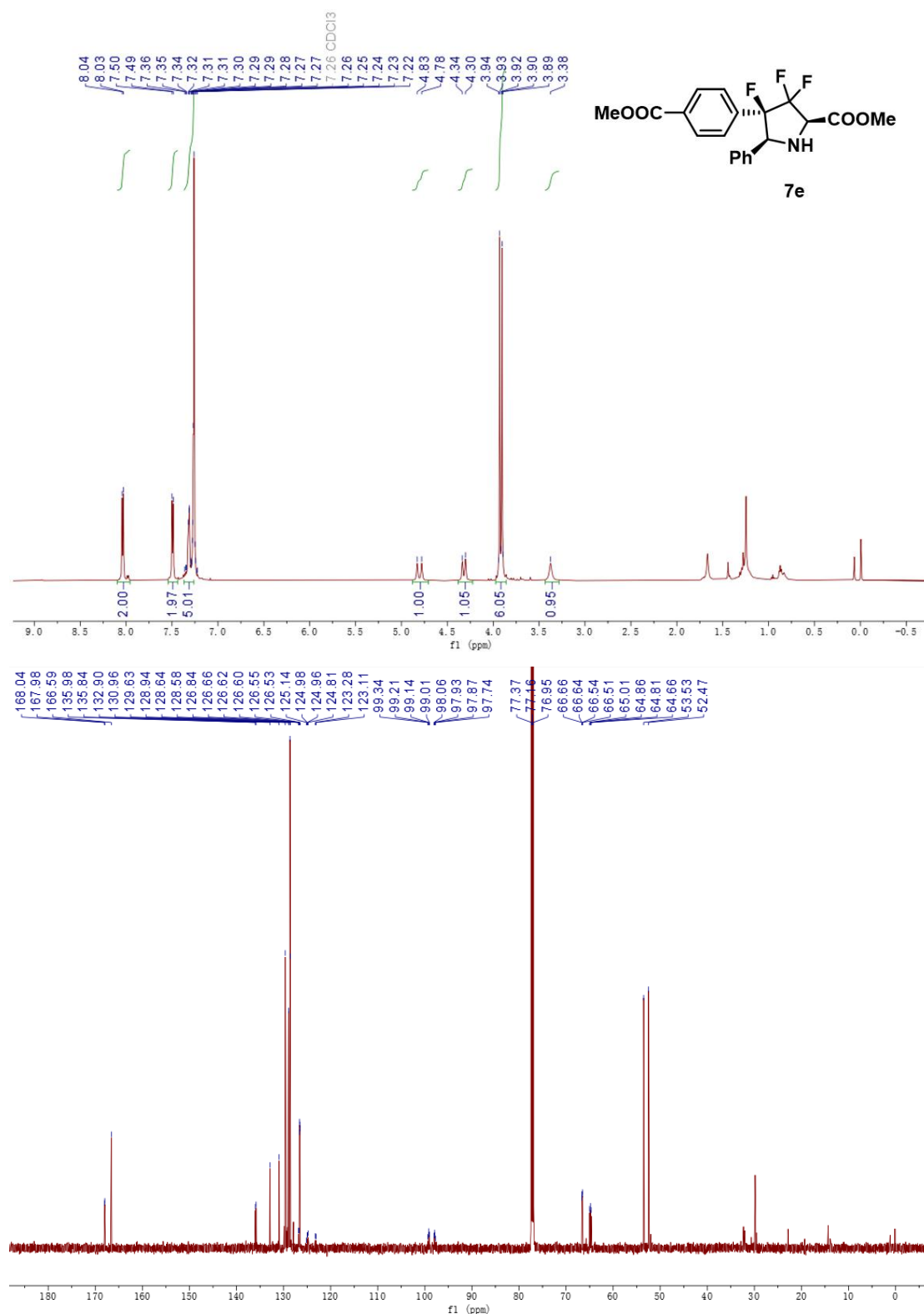


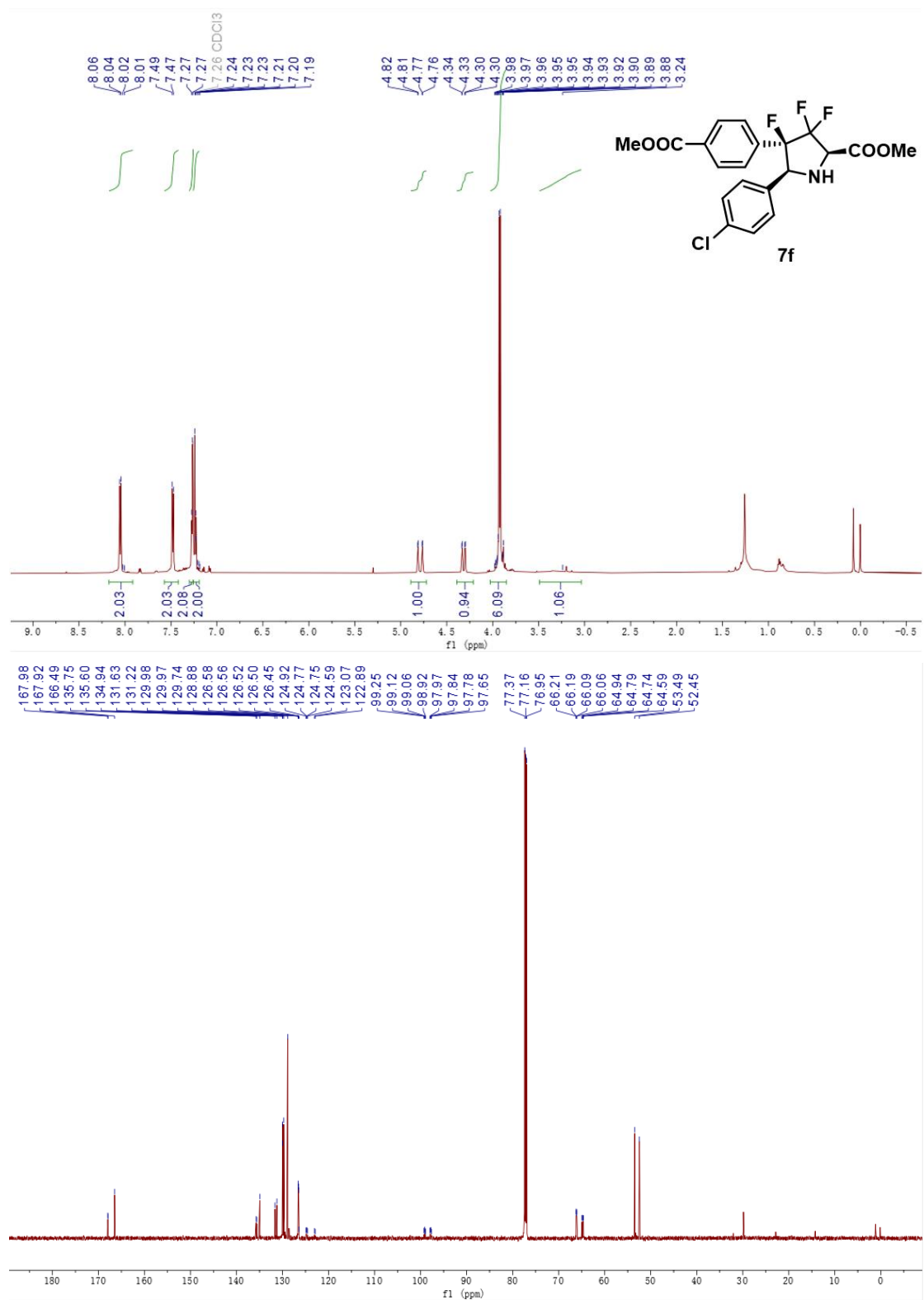


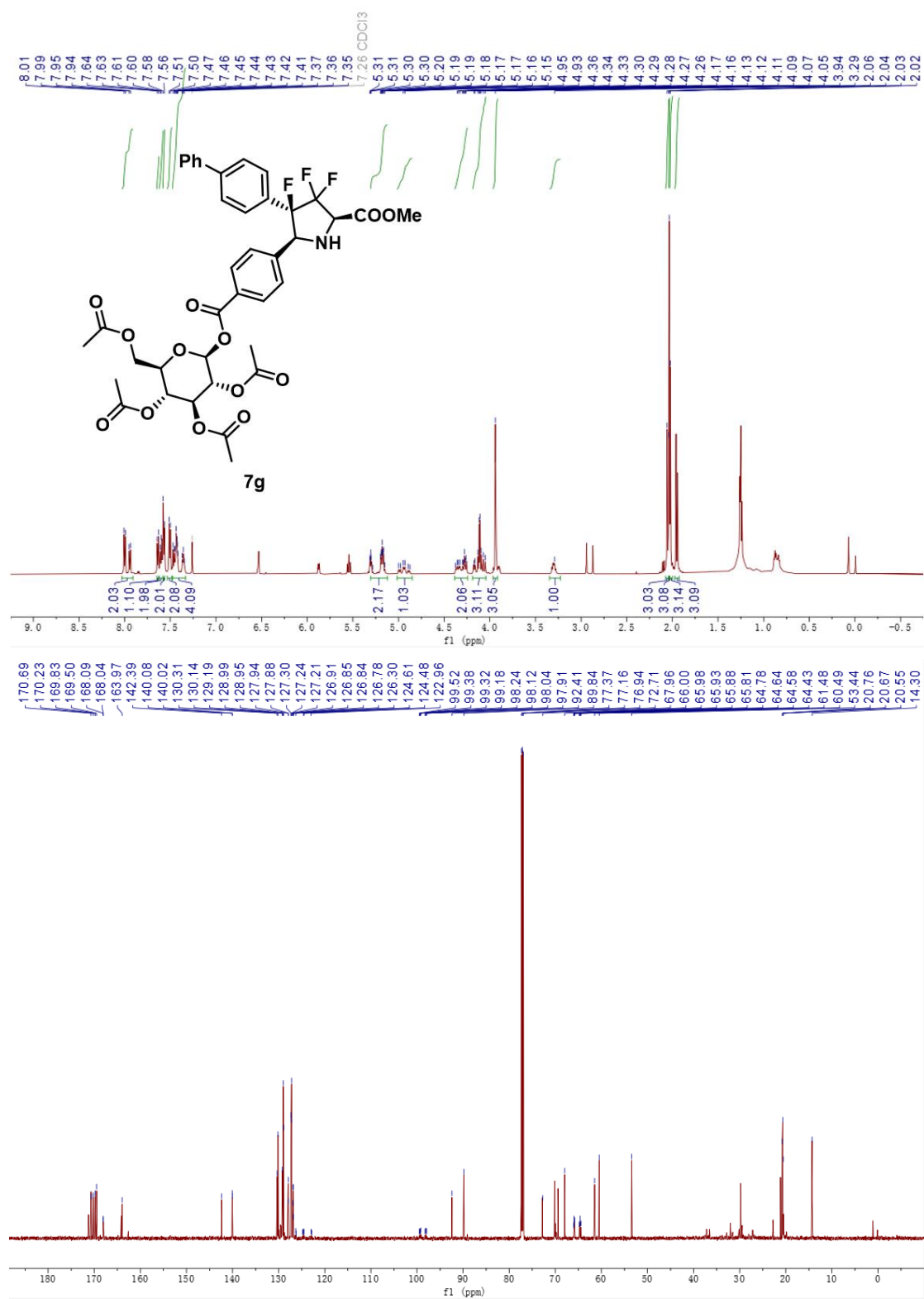


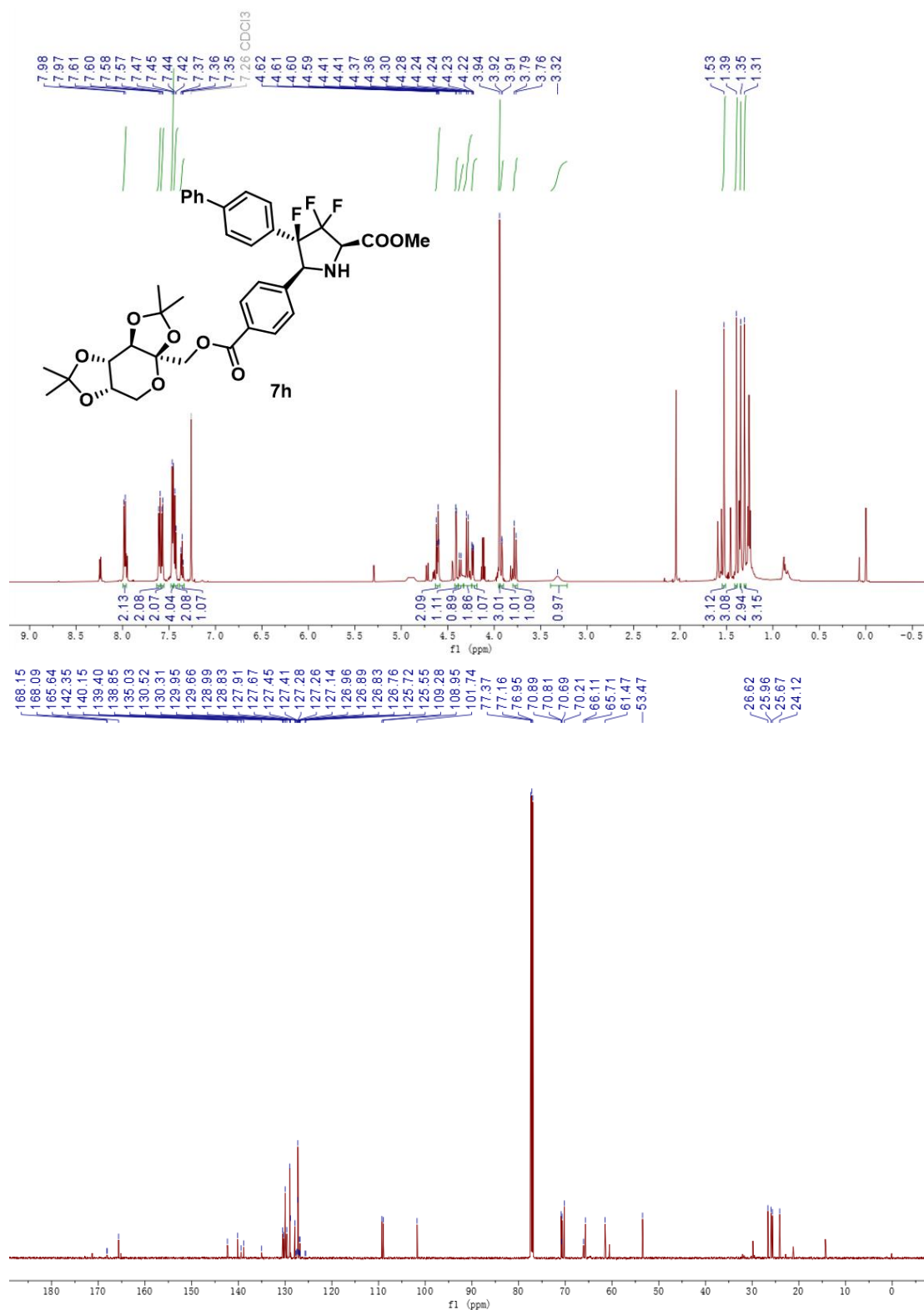


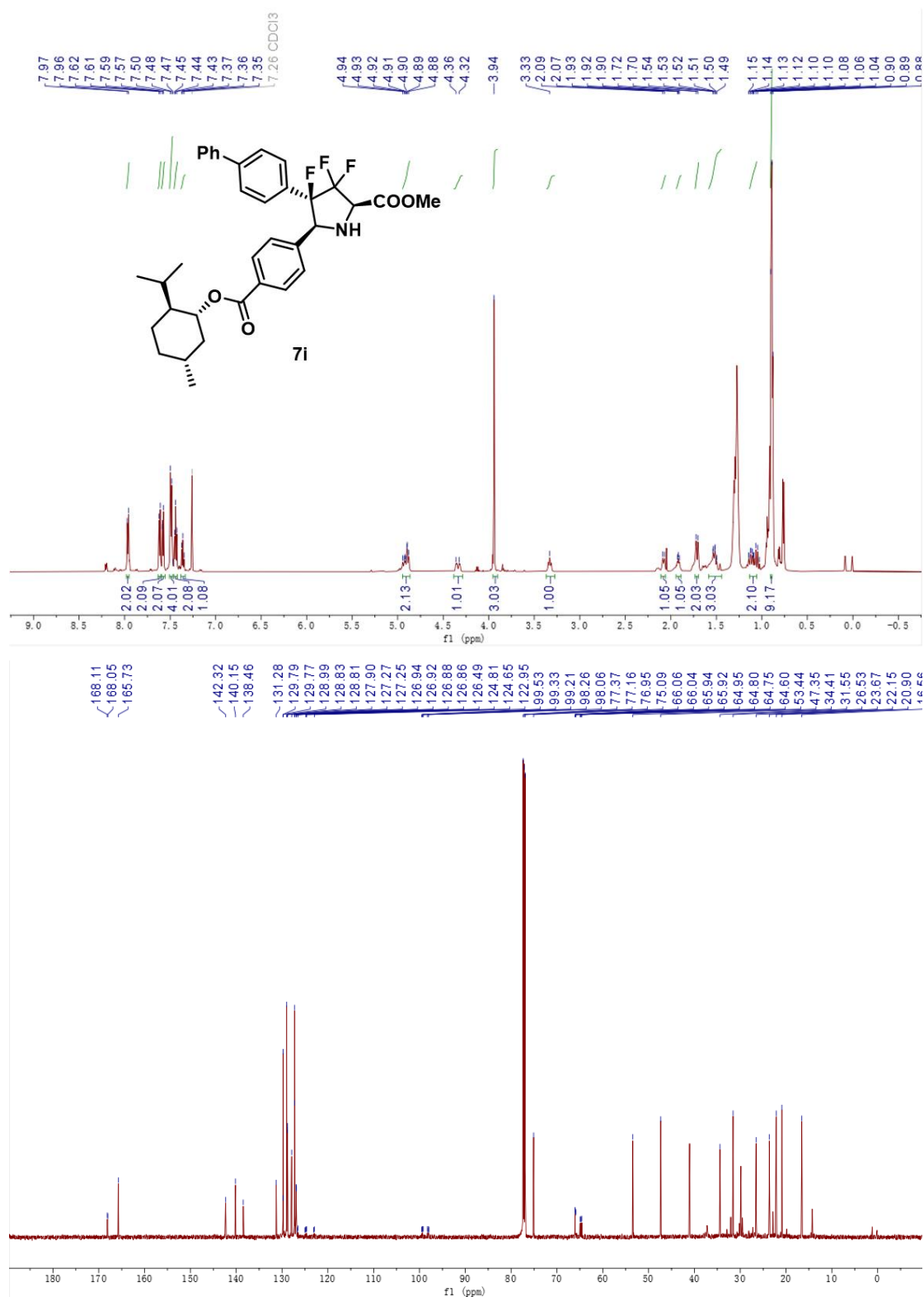


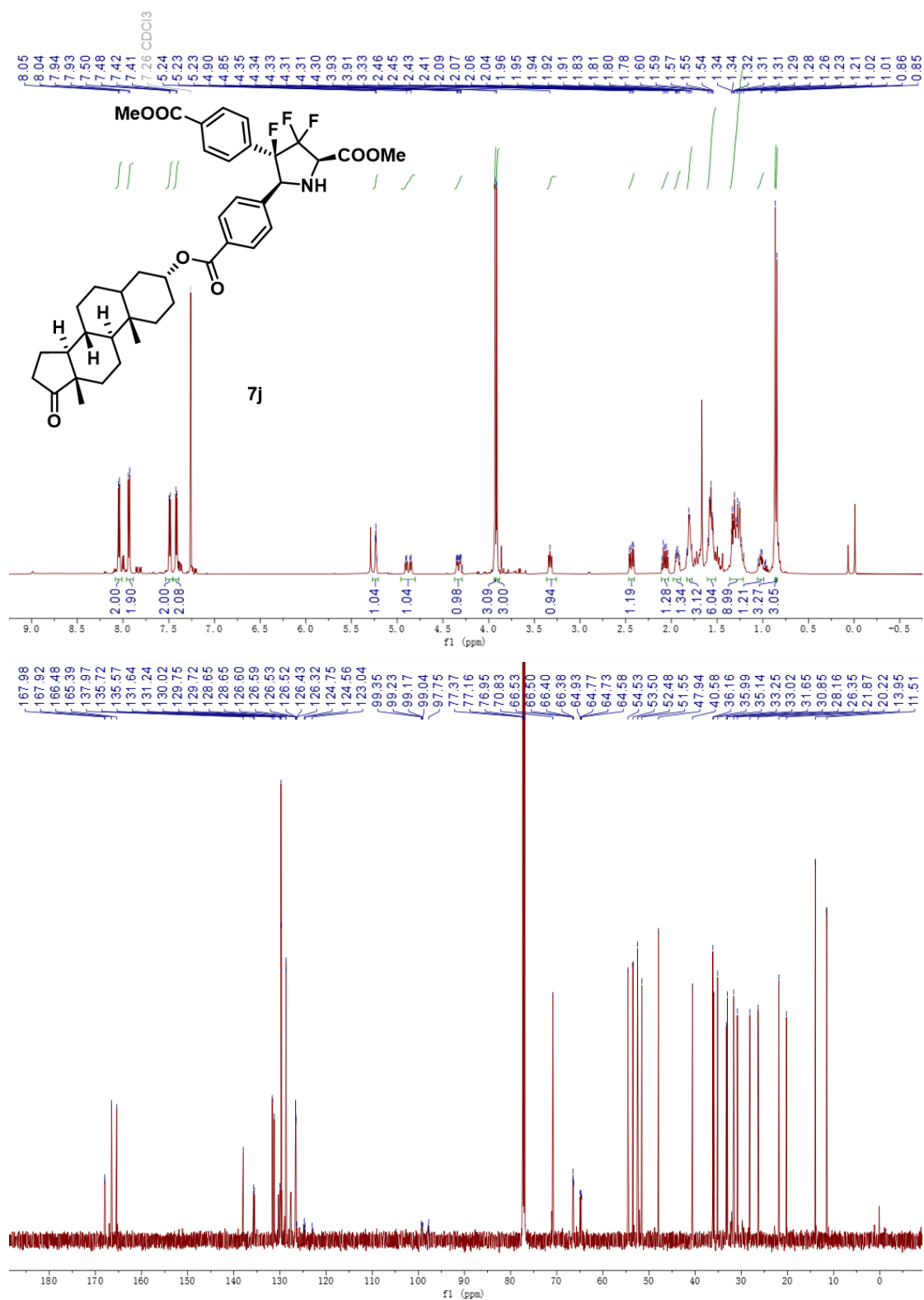


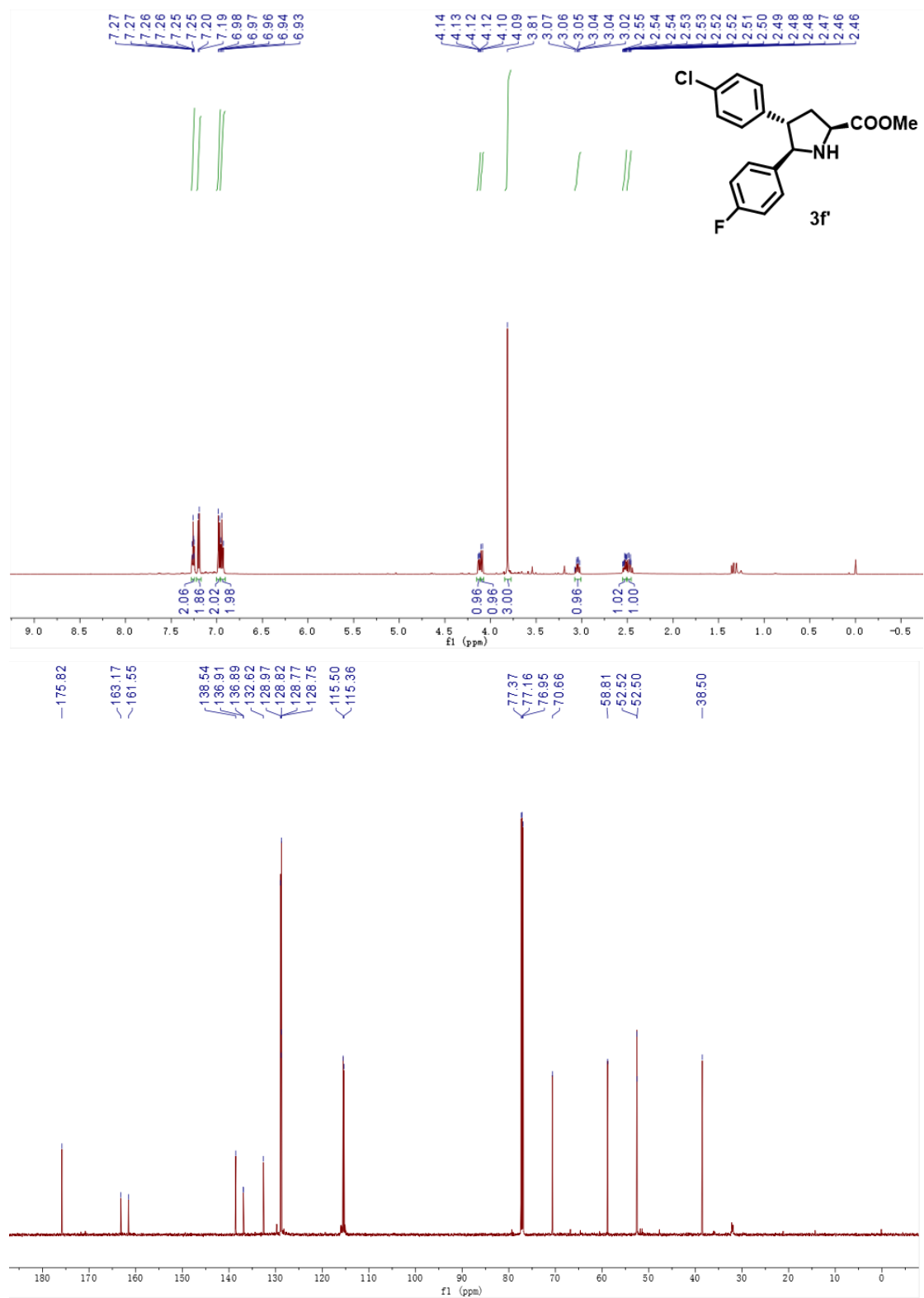


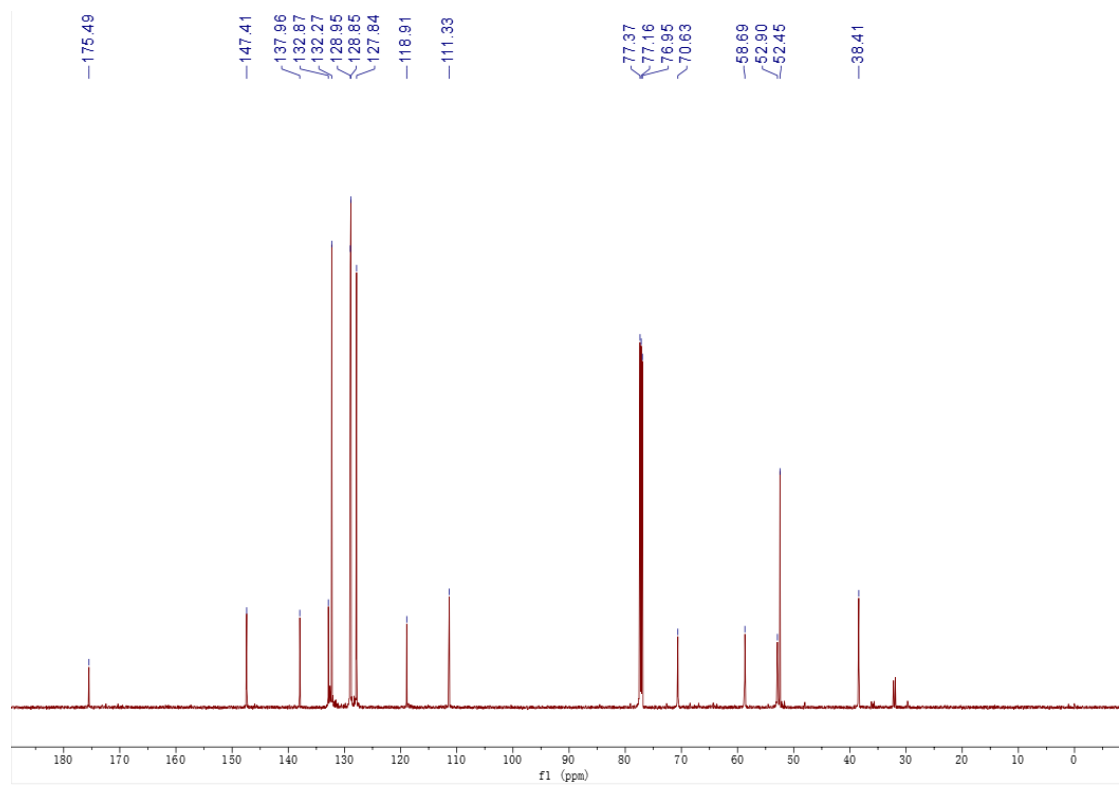
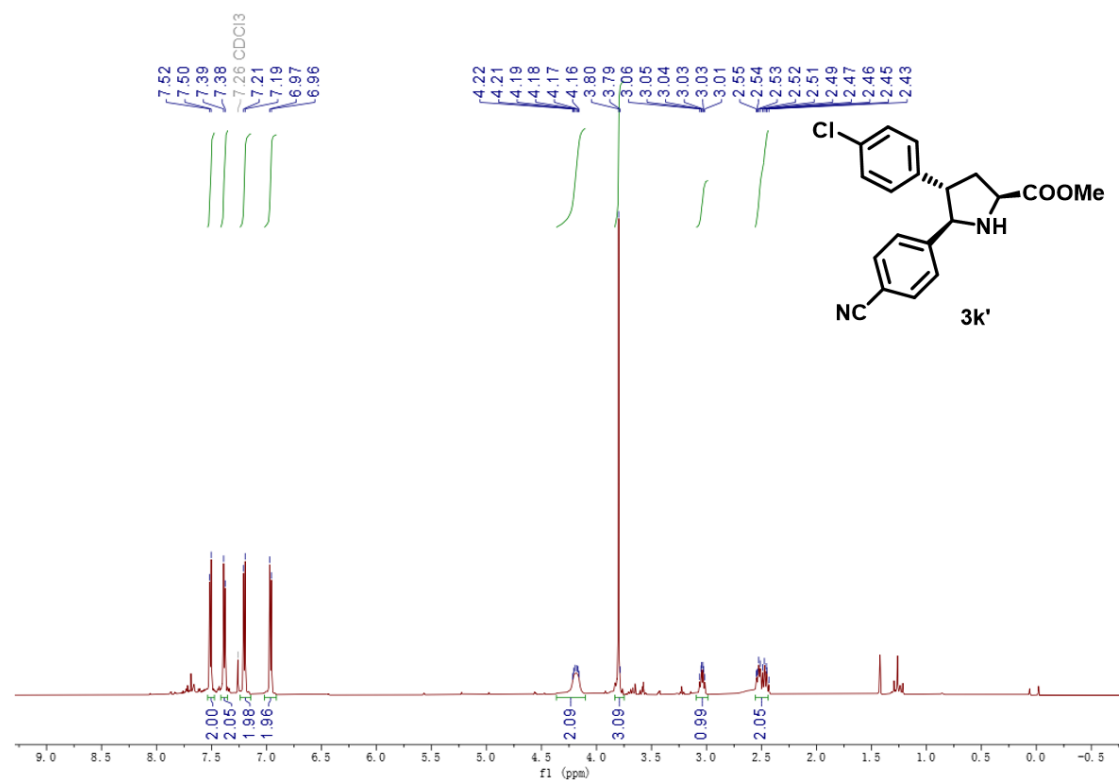


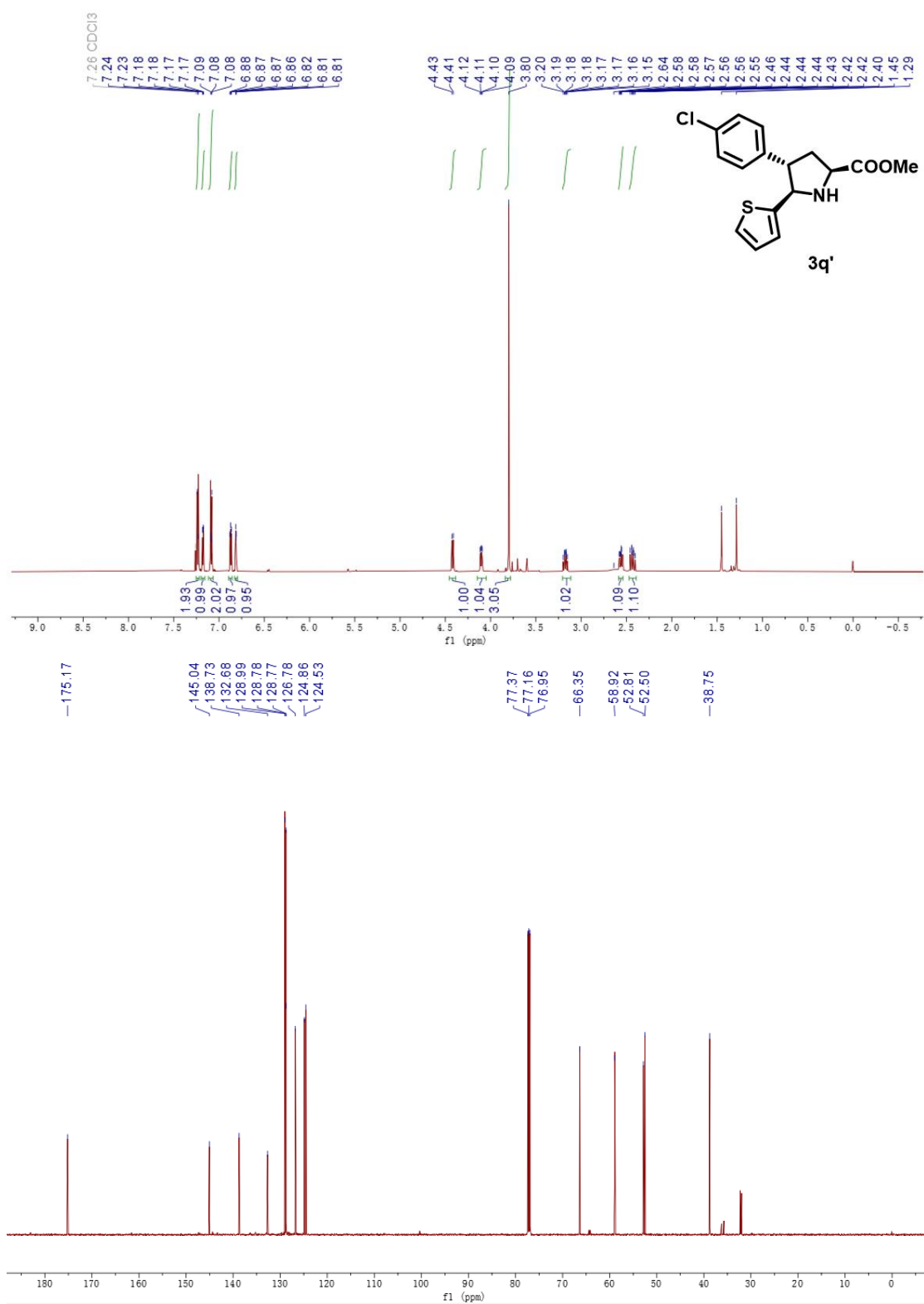


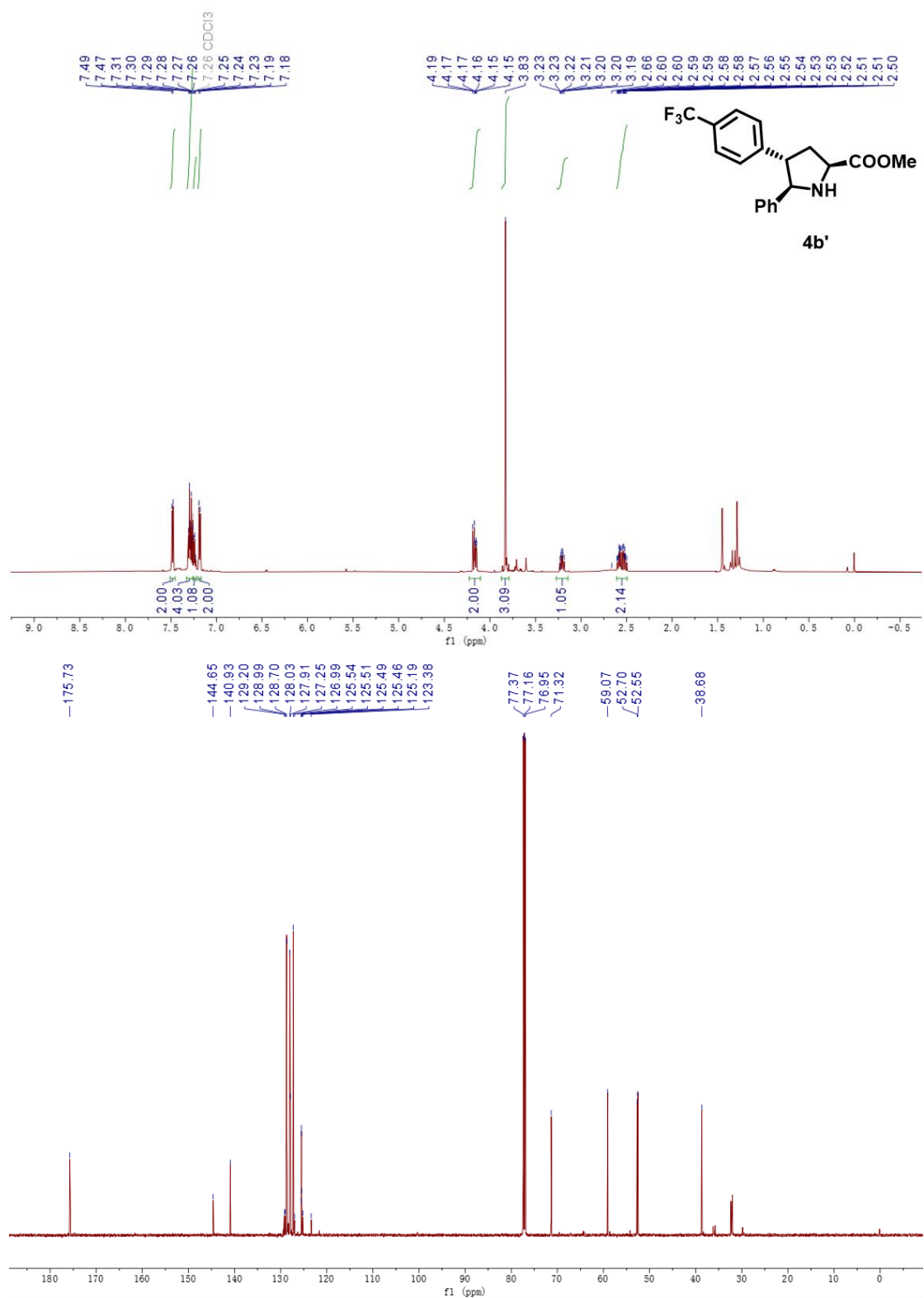


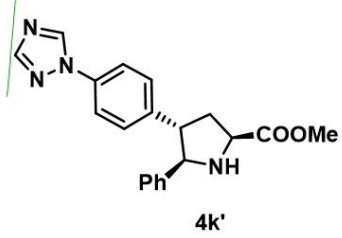




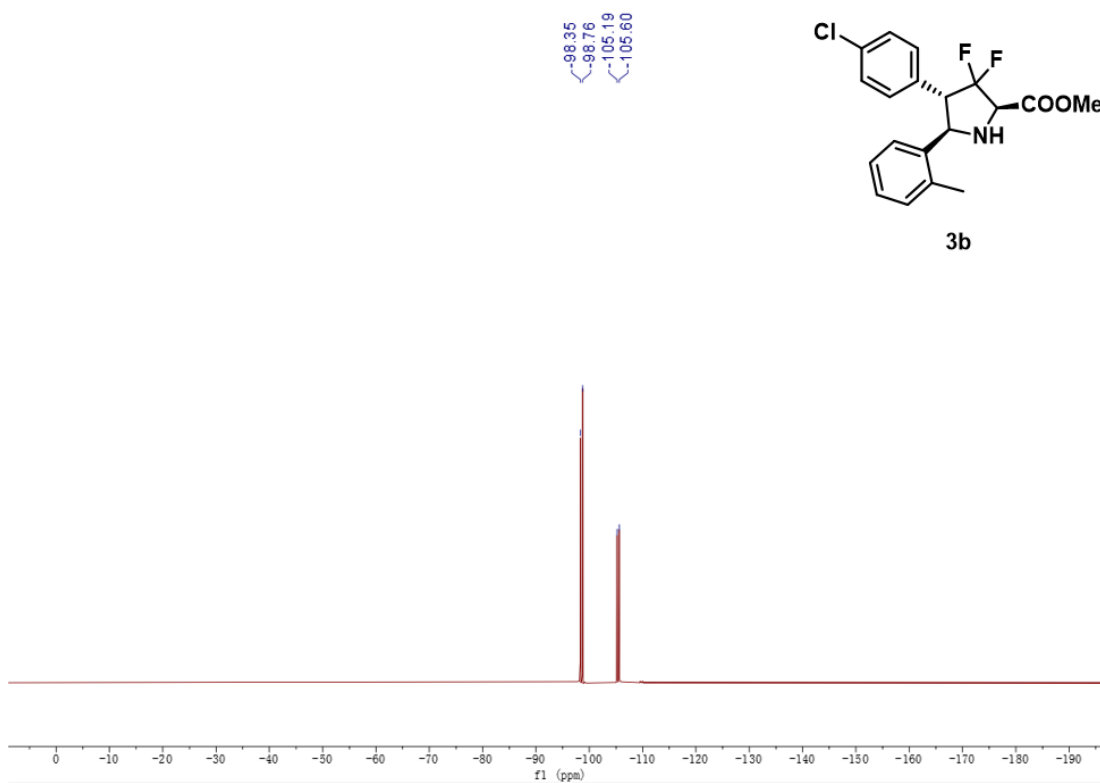


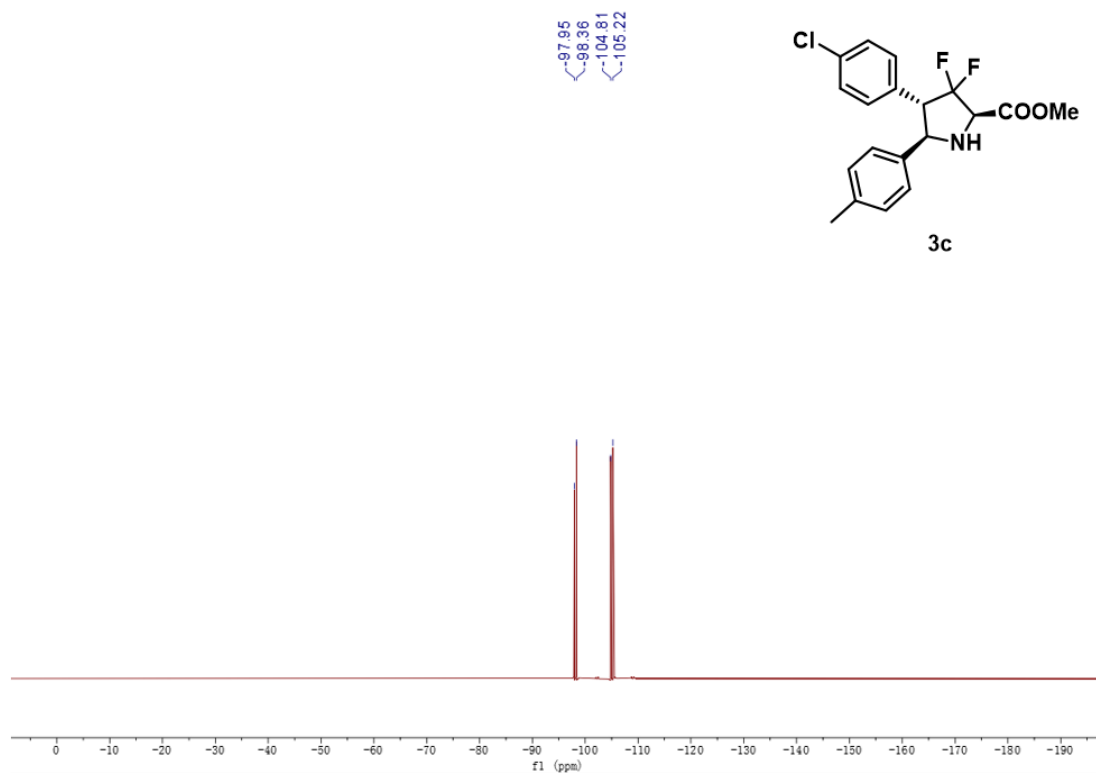


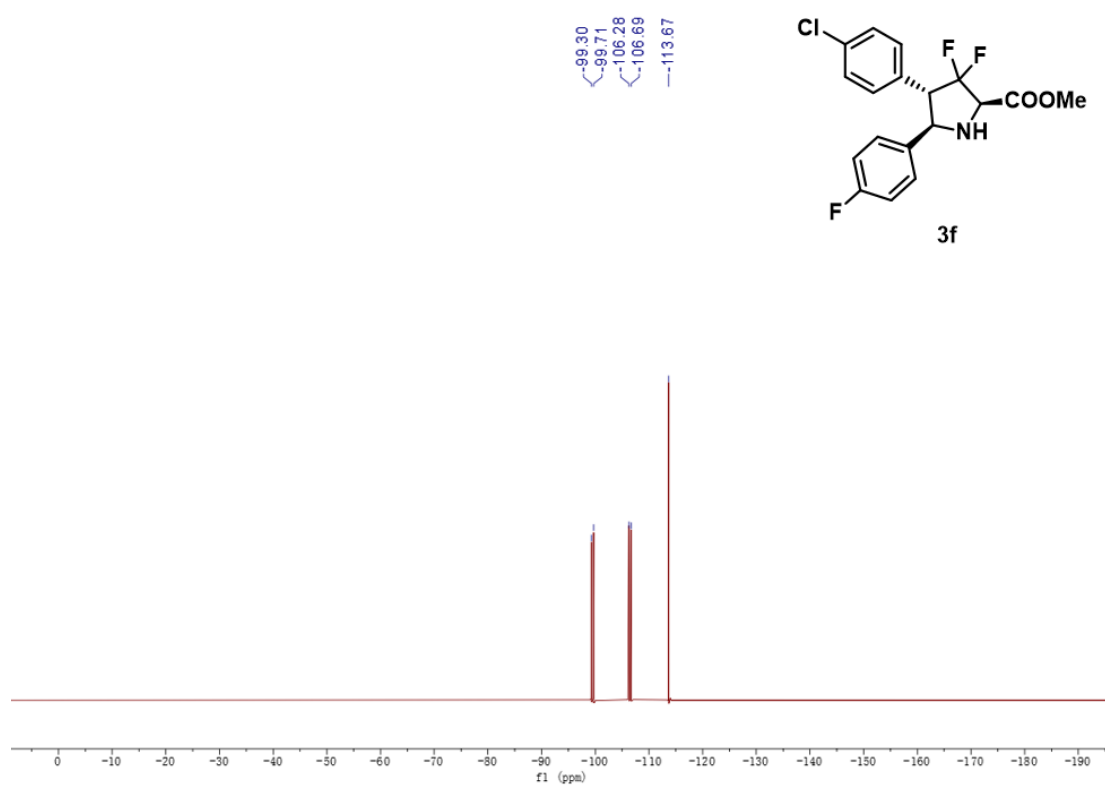
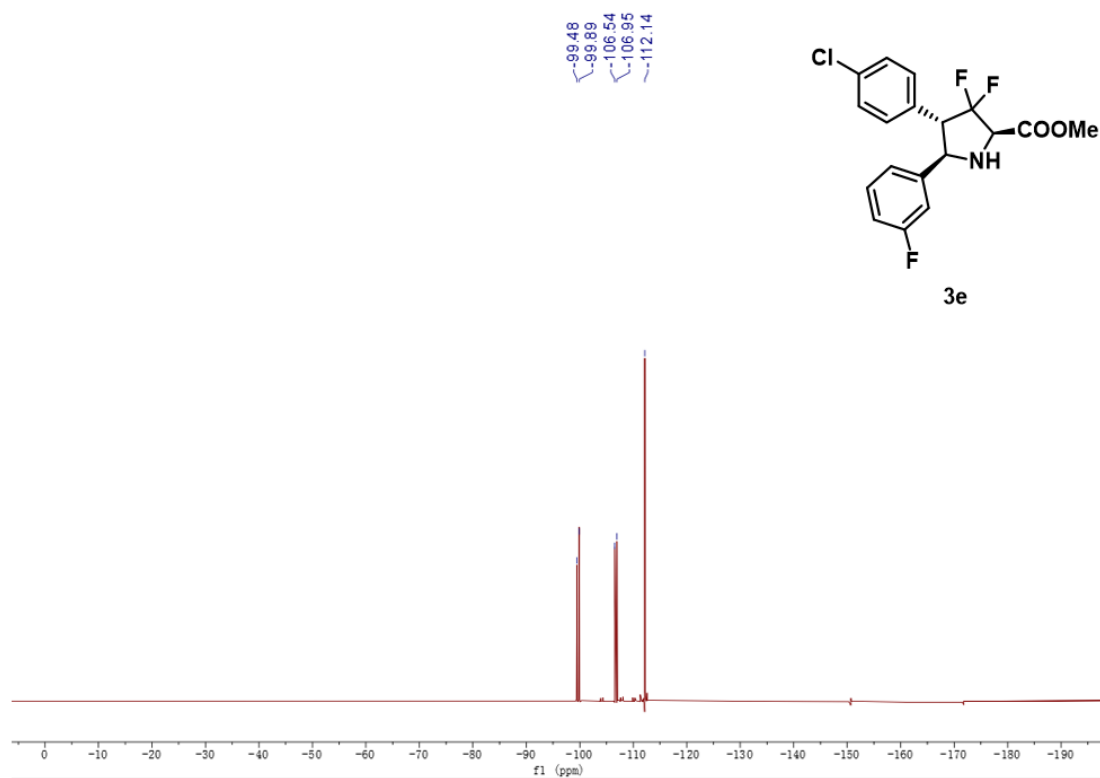


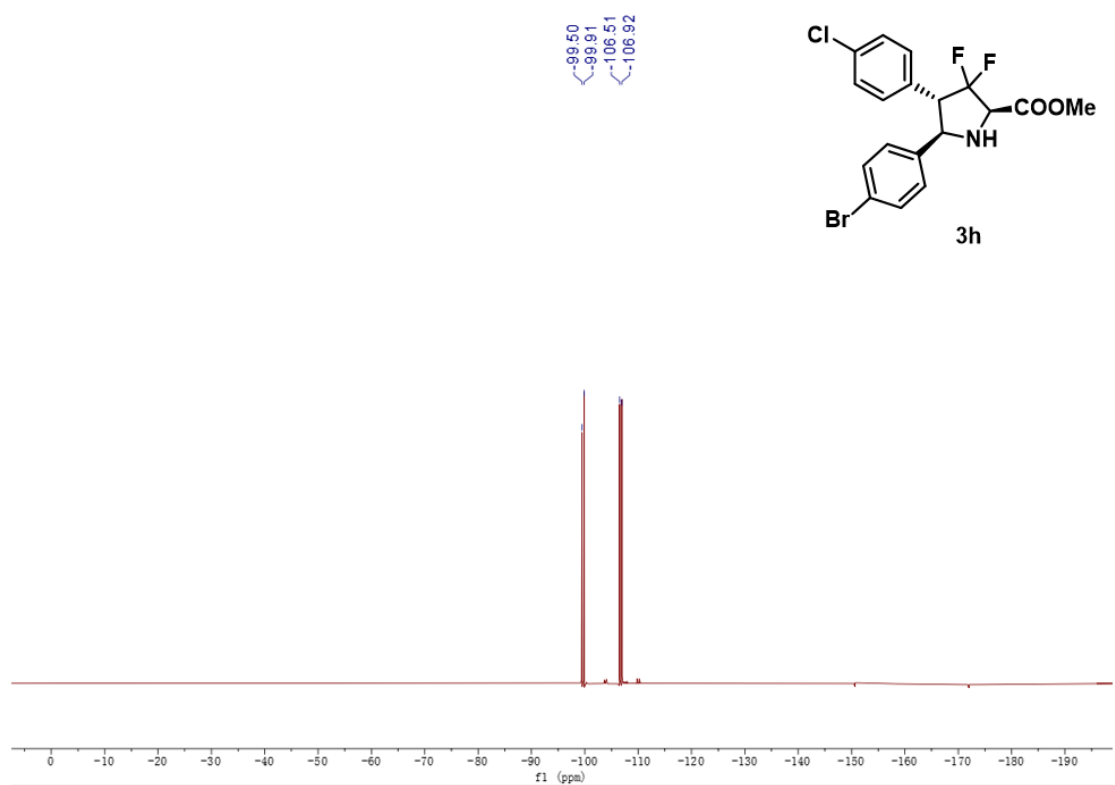
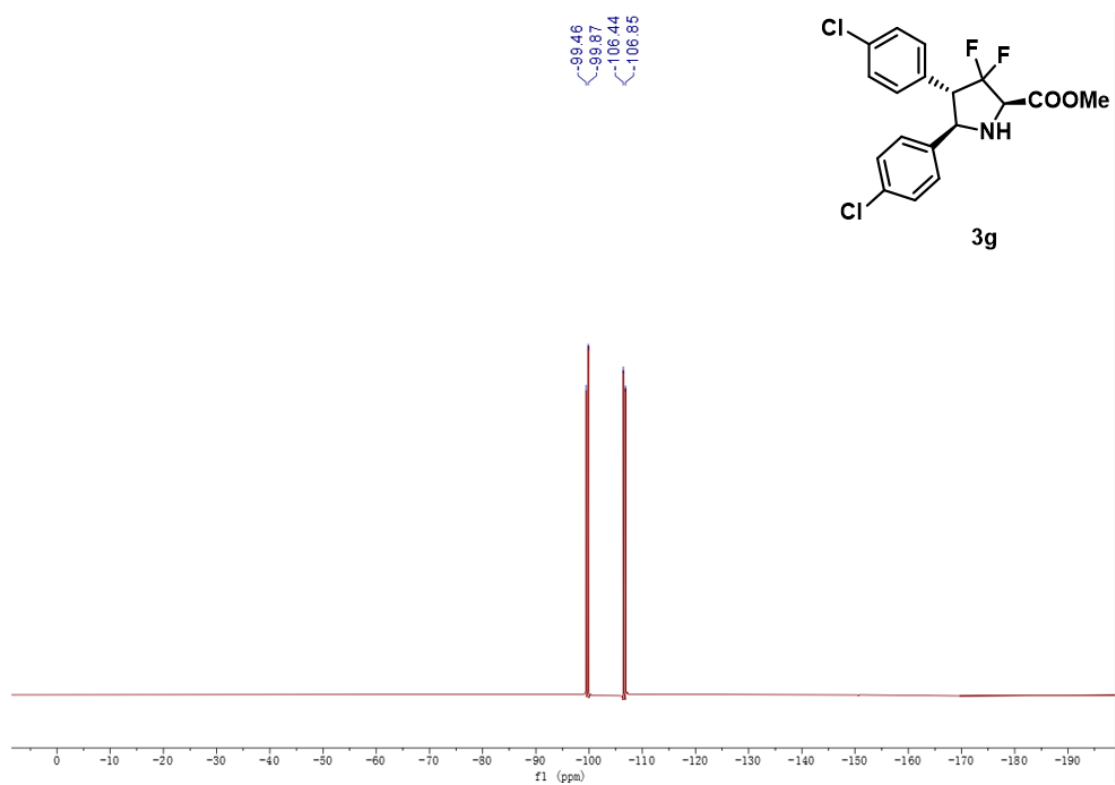


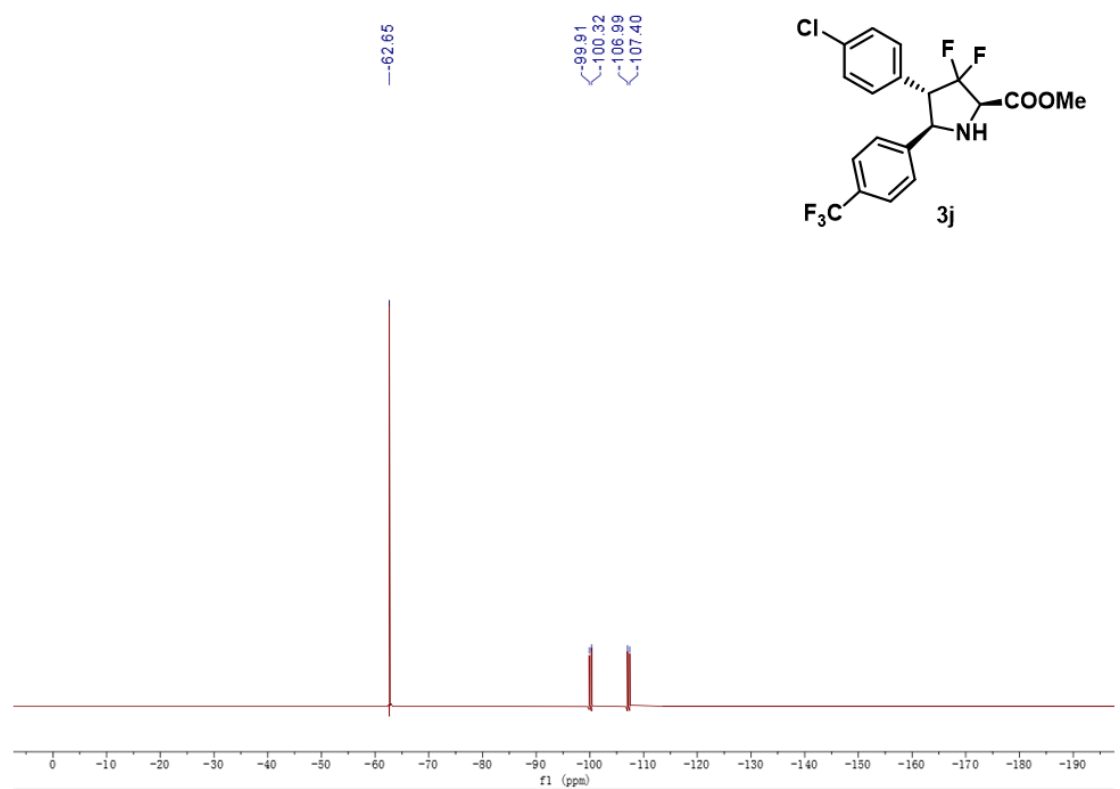
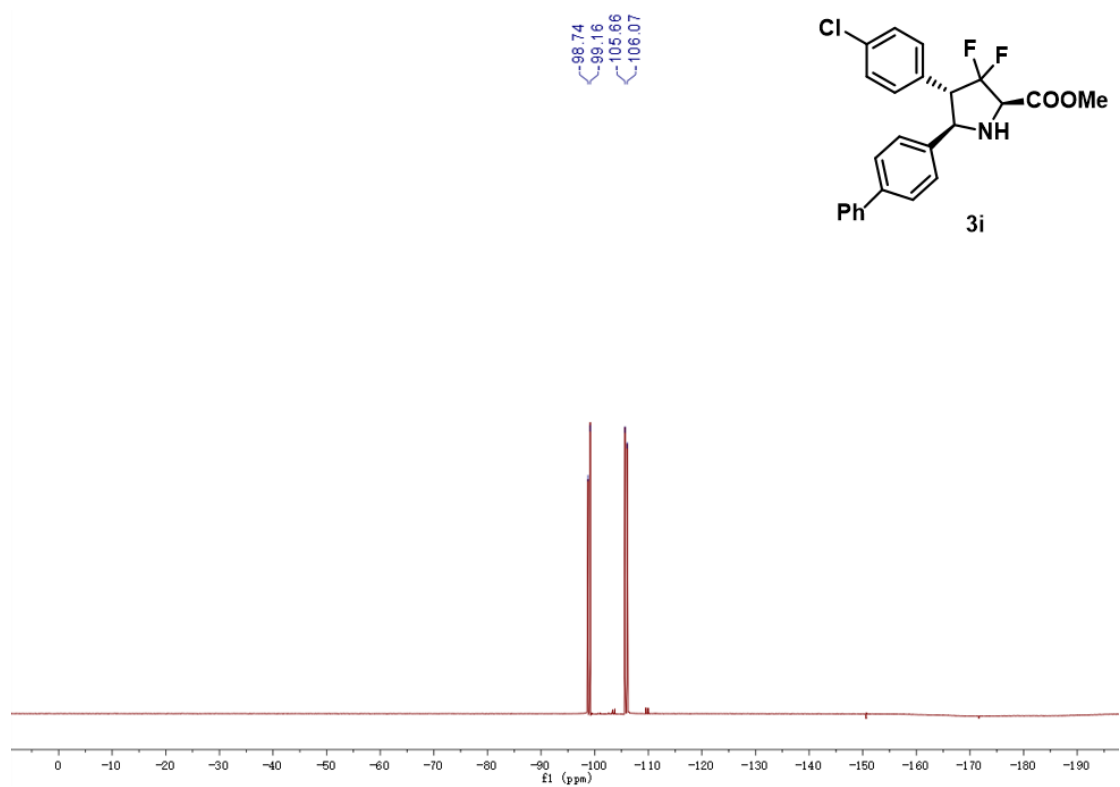
11. ^{19}F NMR spectra

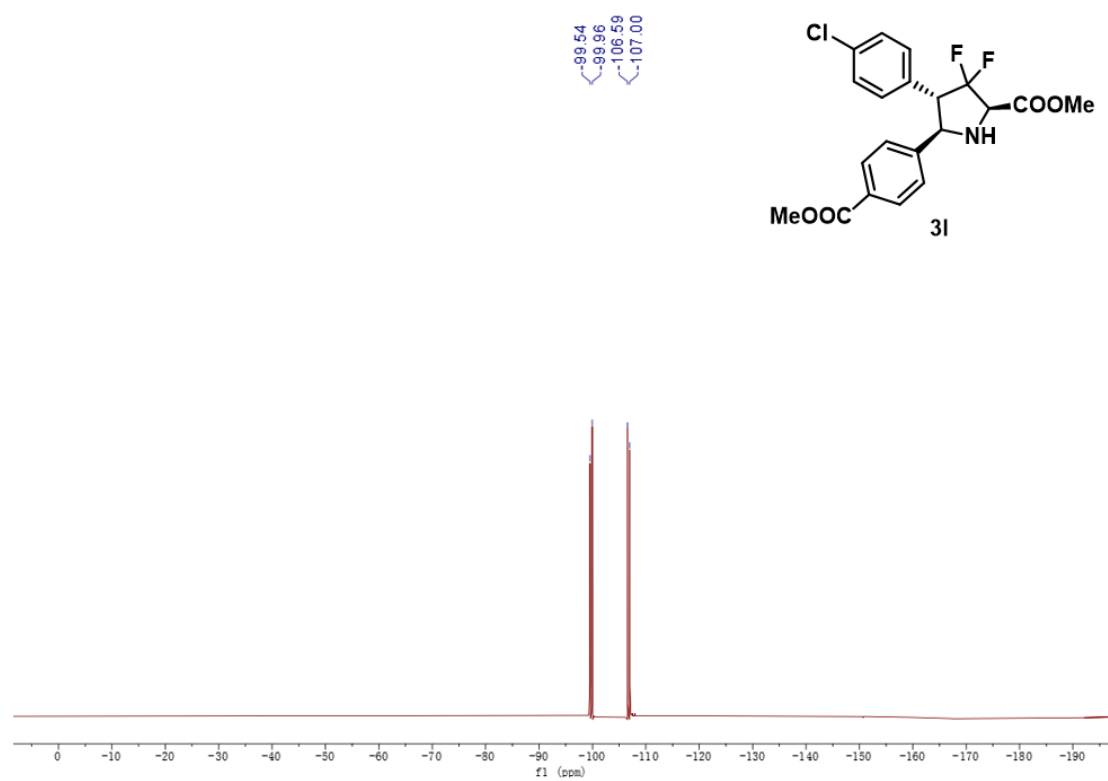
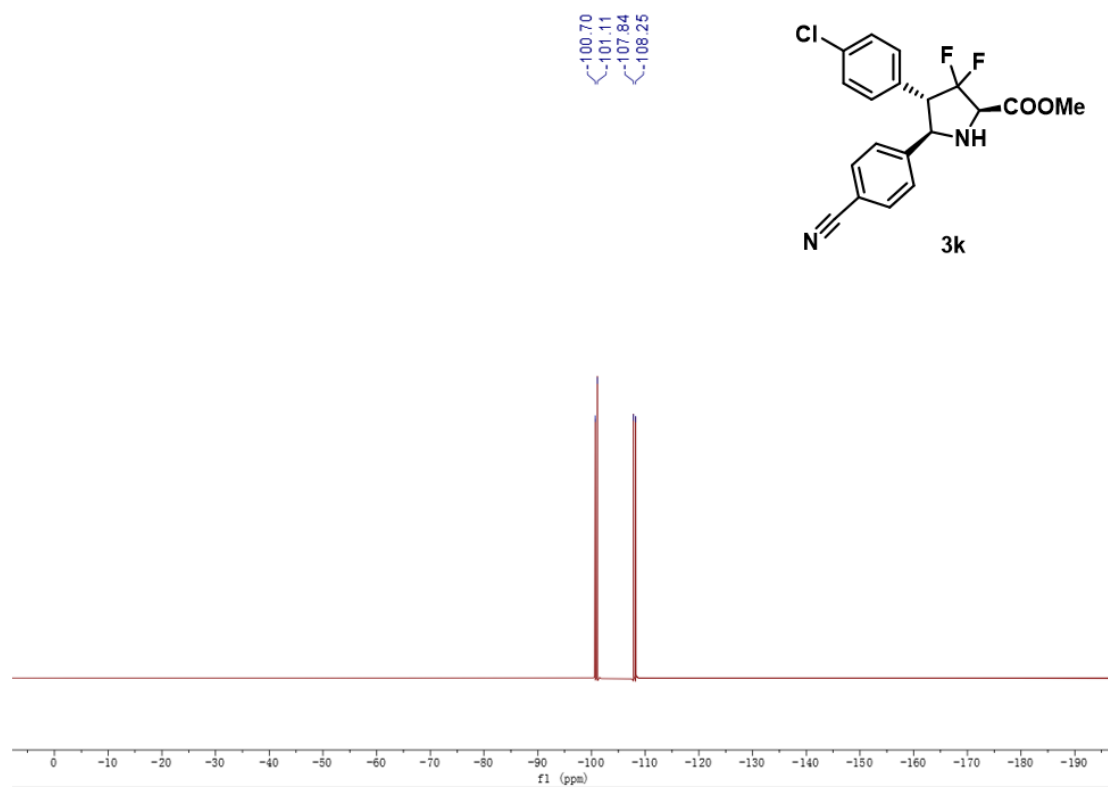


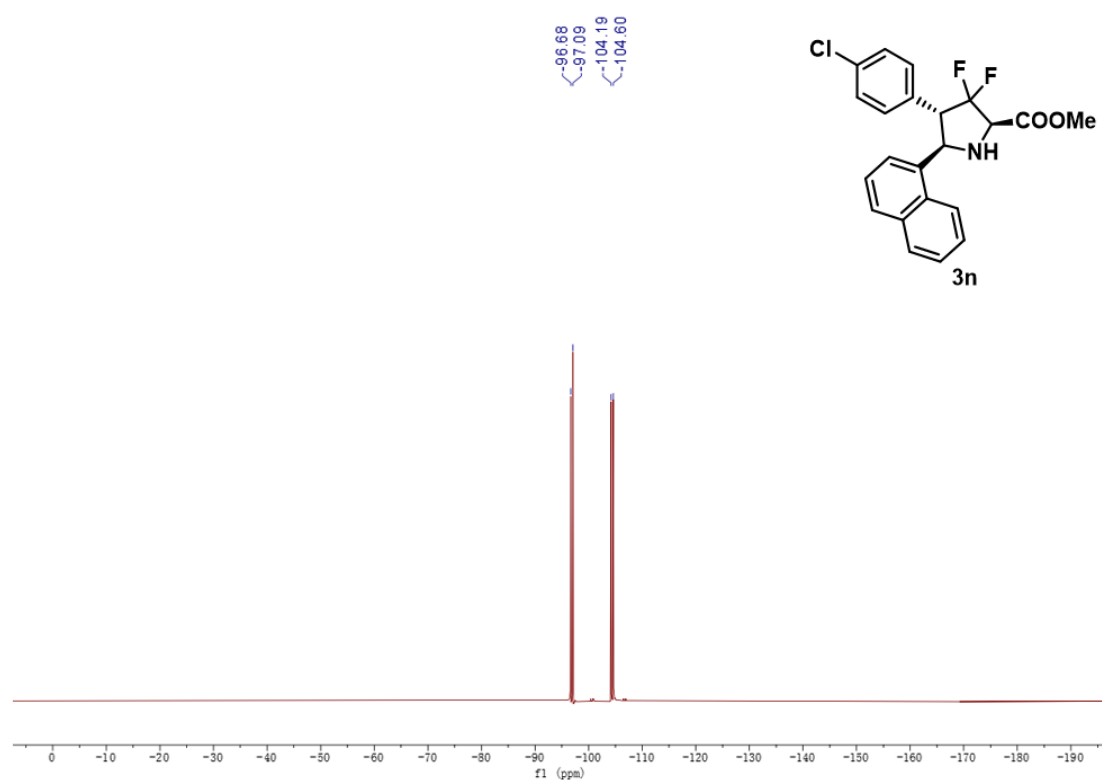
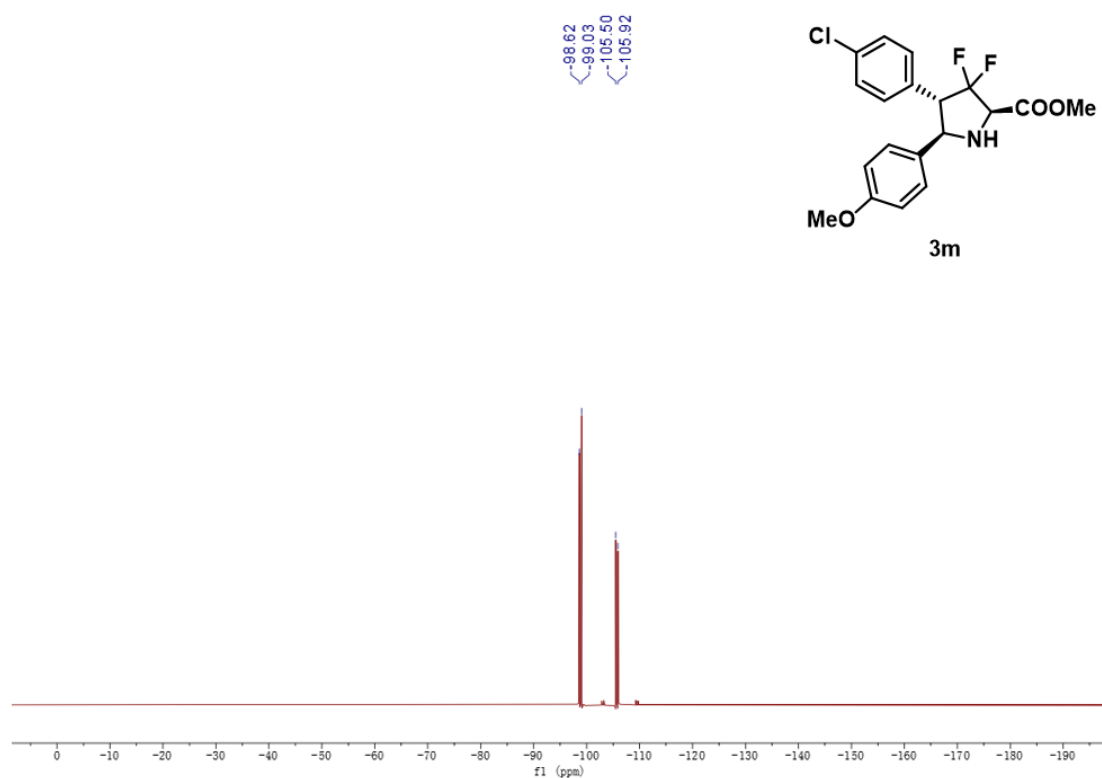


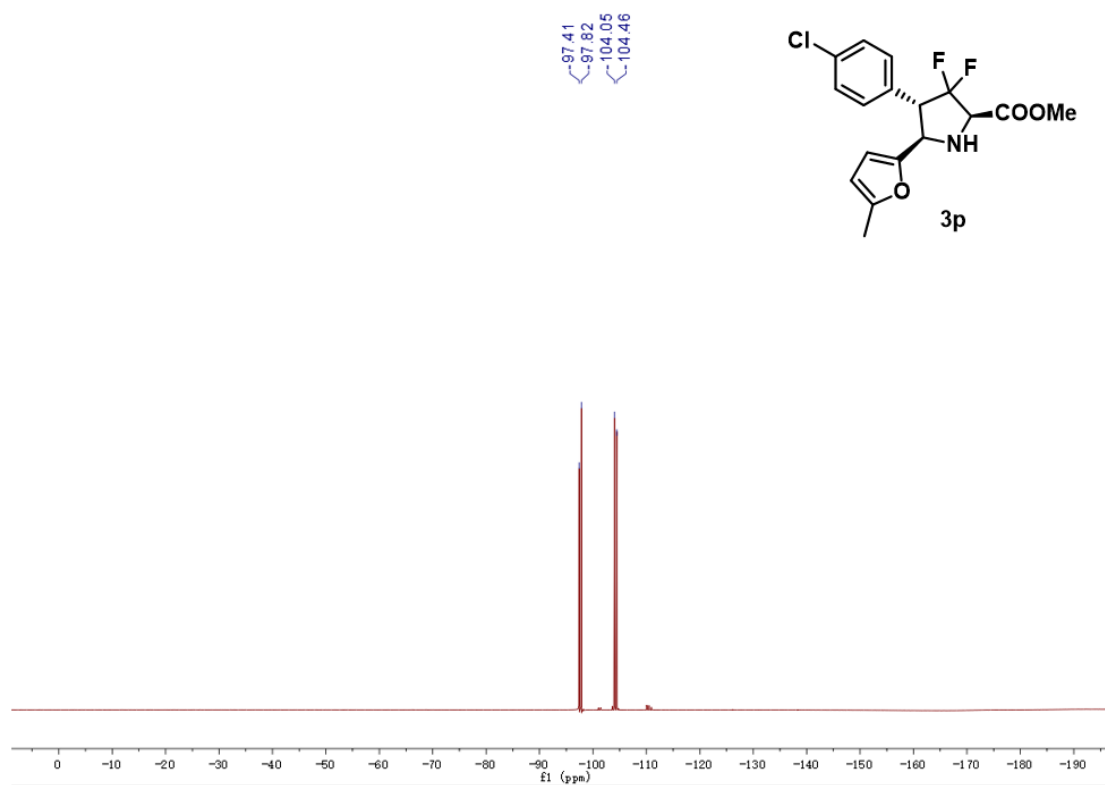


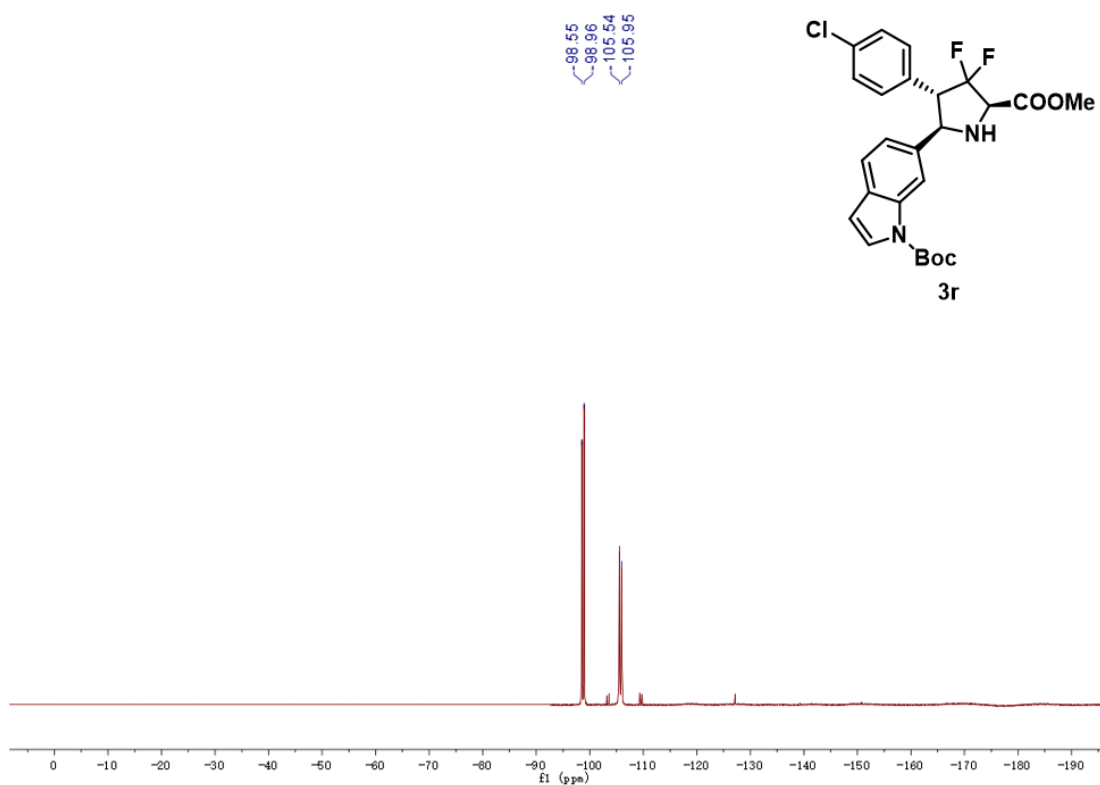


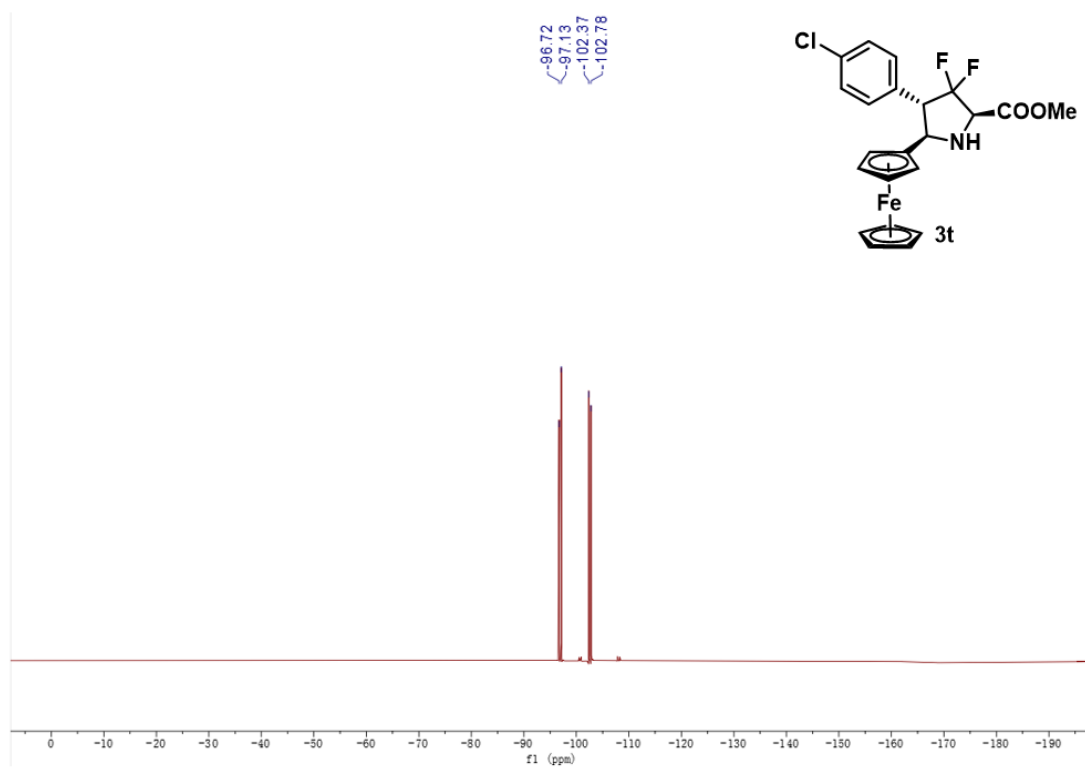


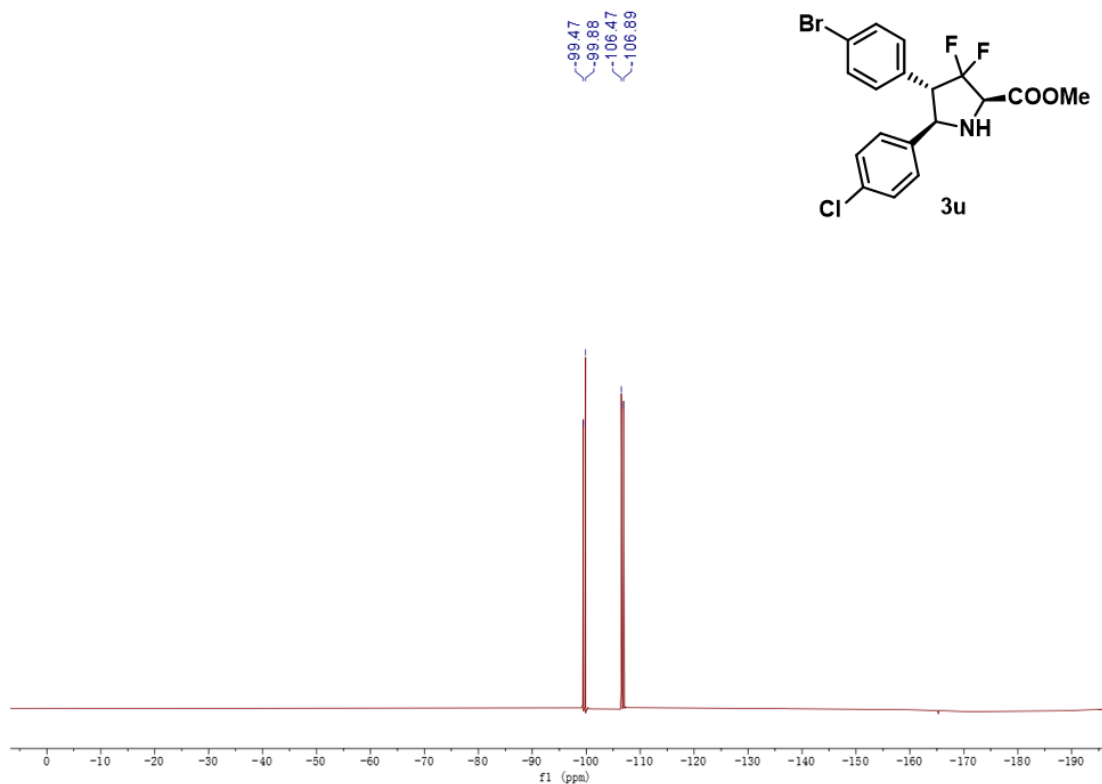


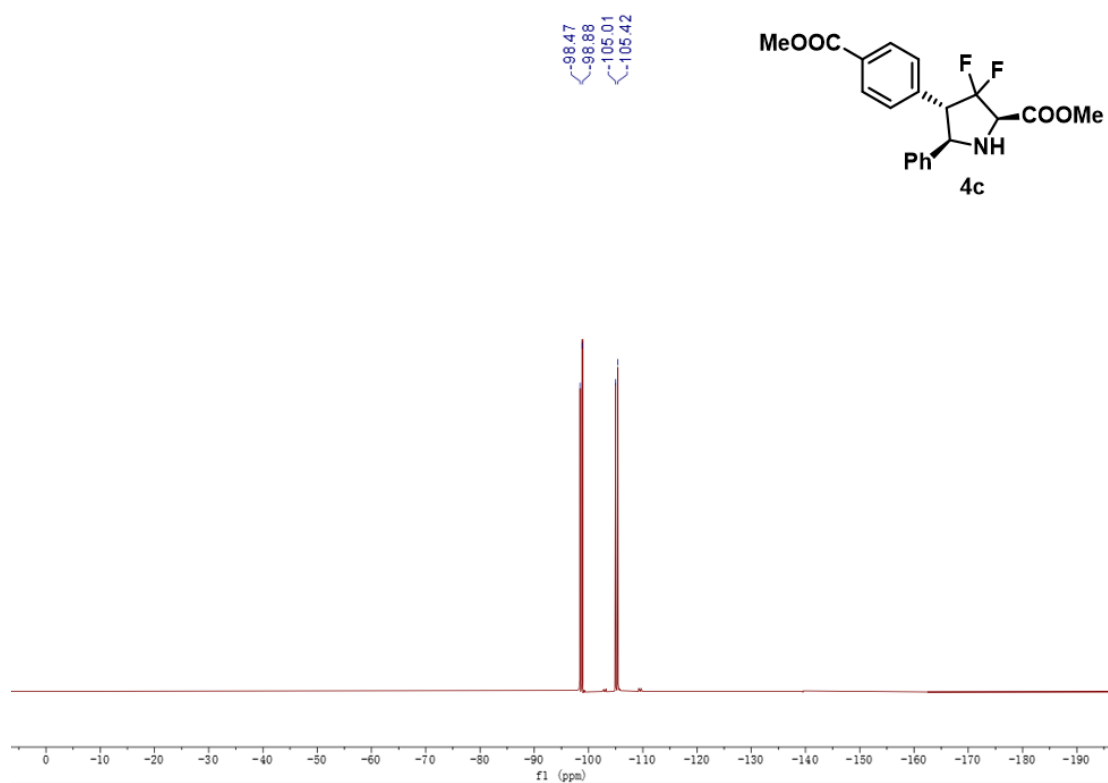


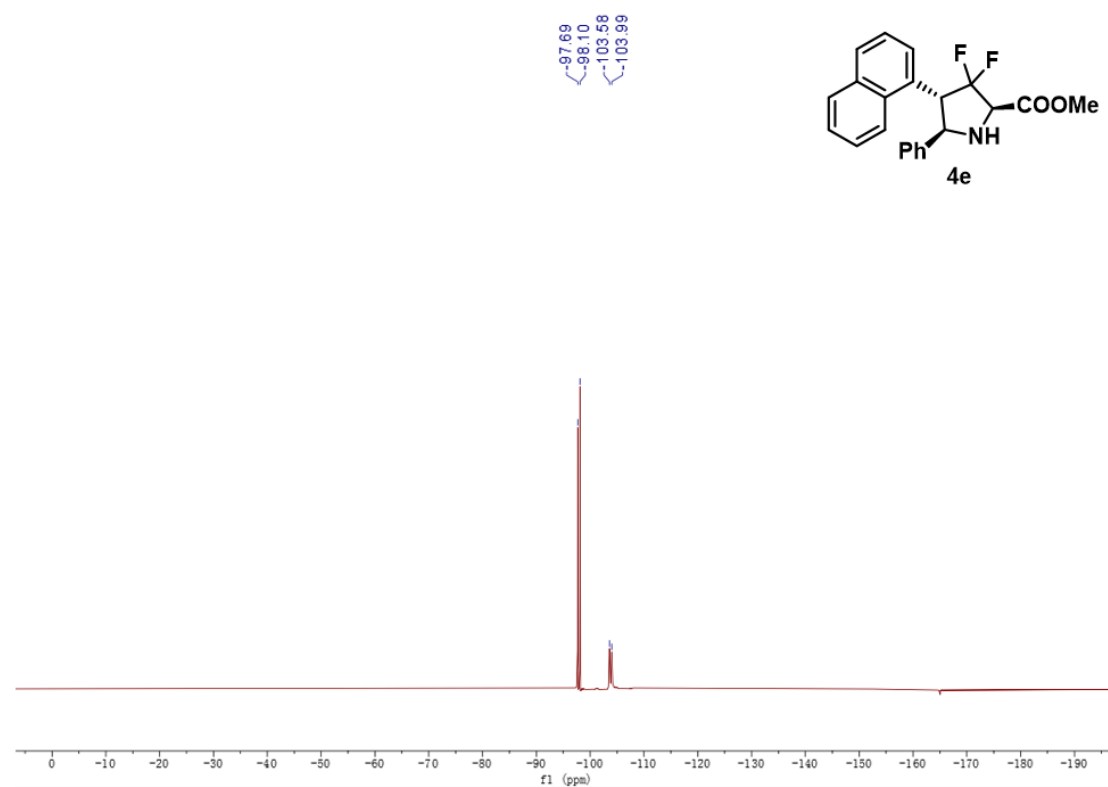
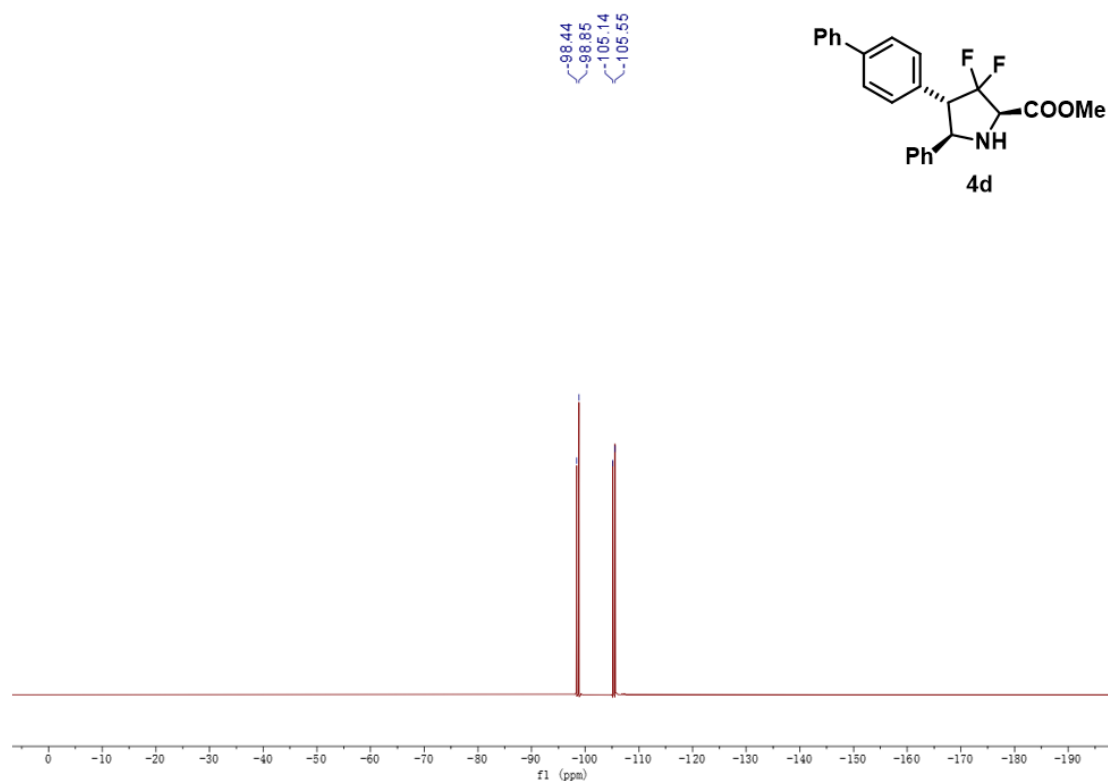


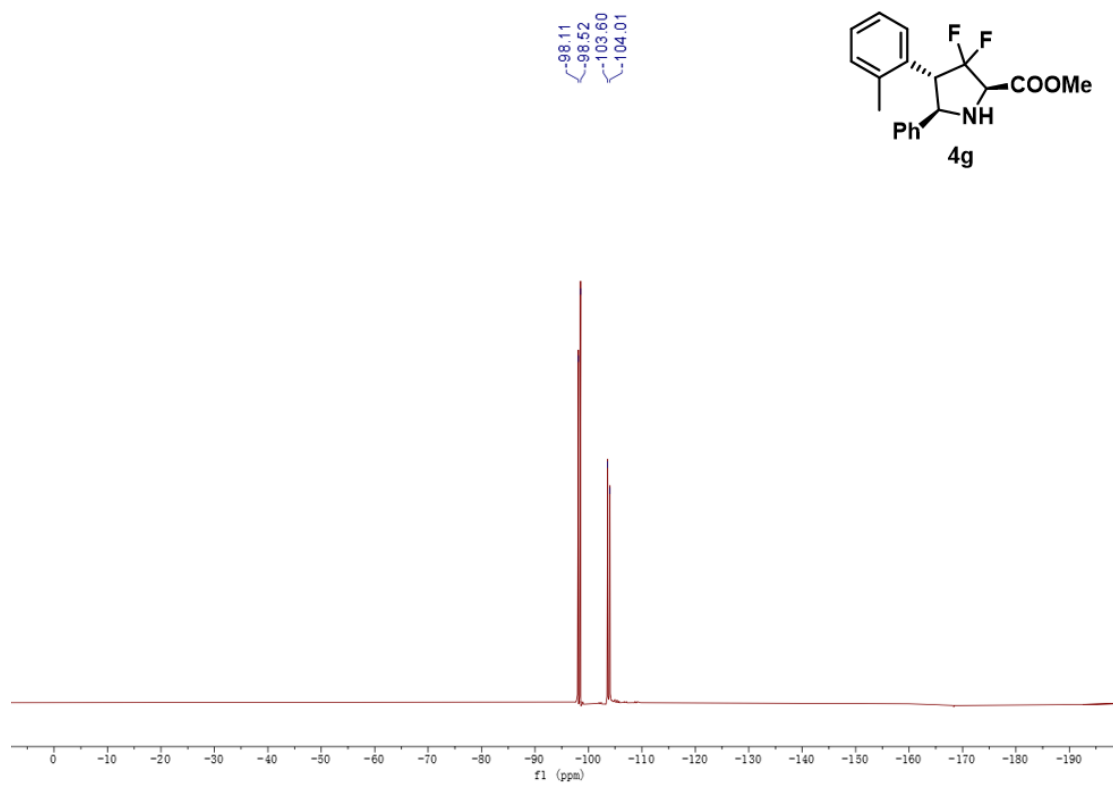
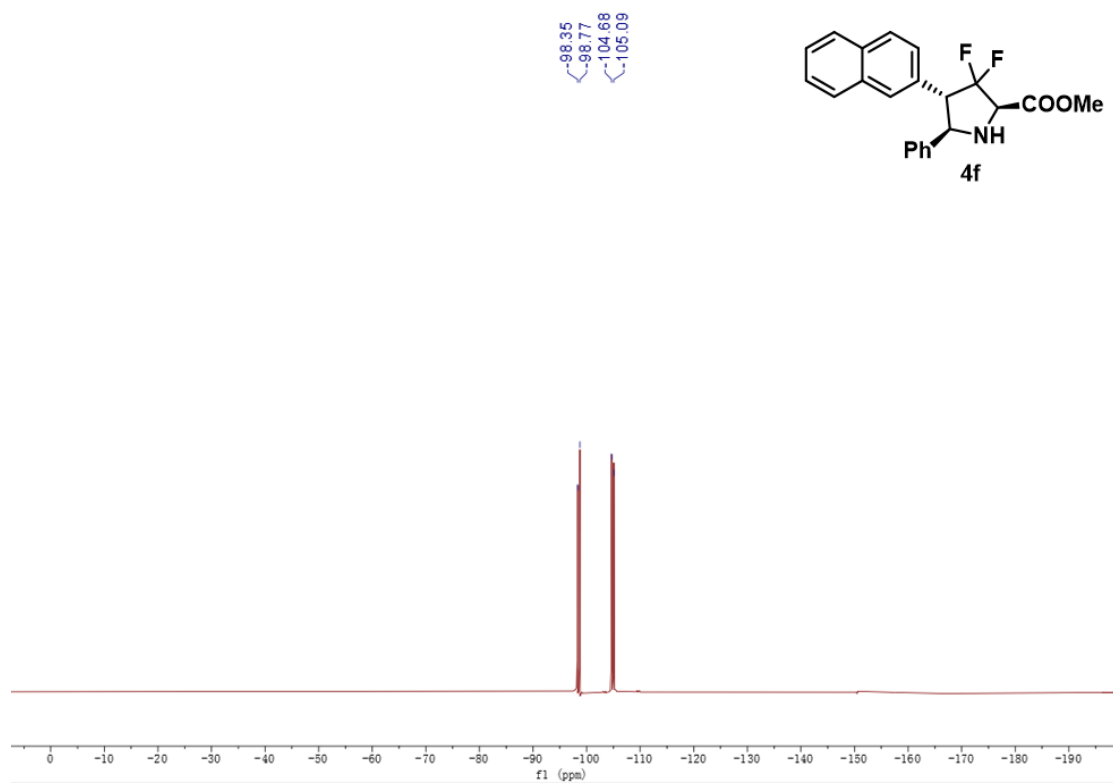


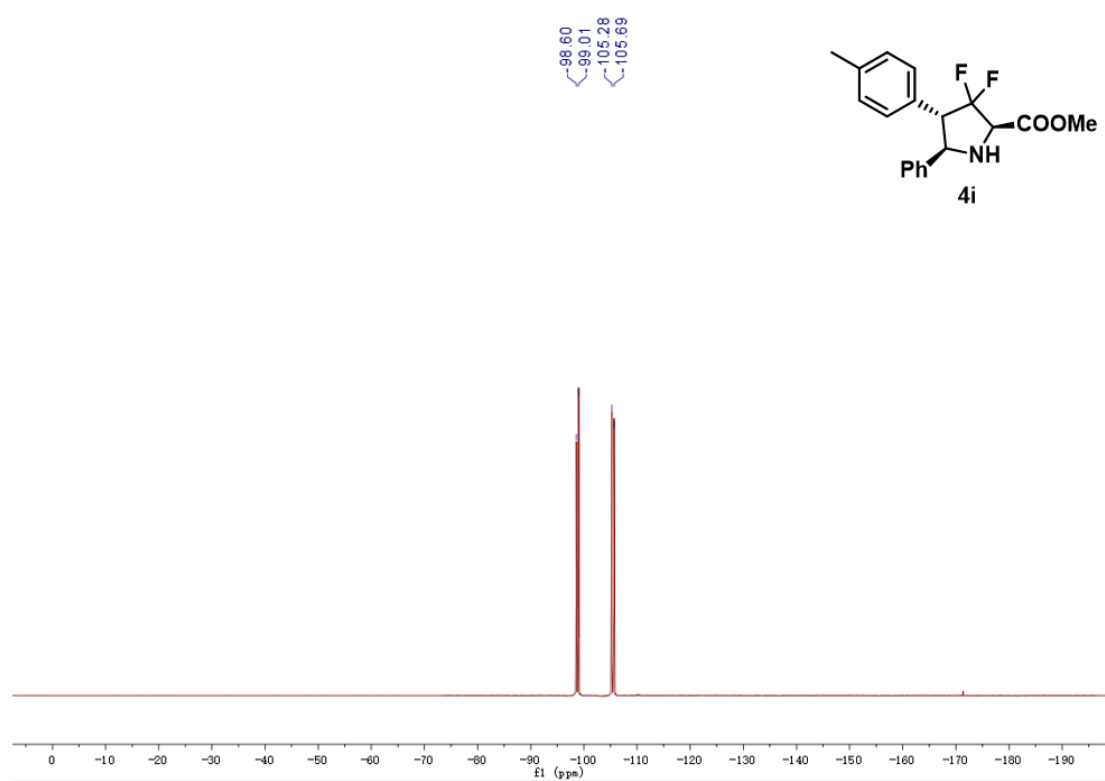
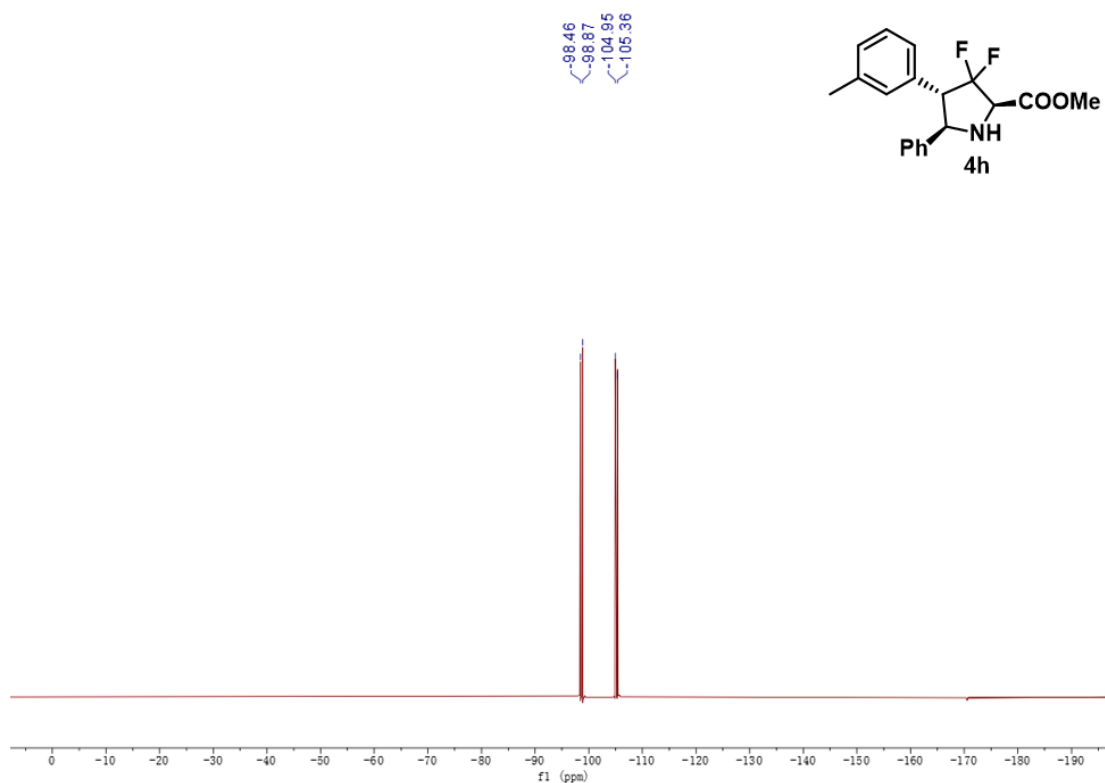


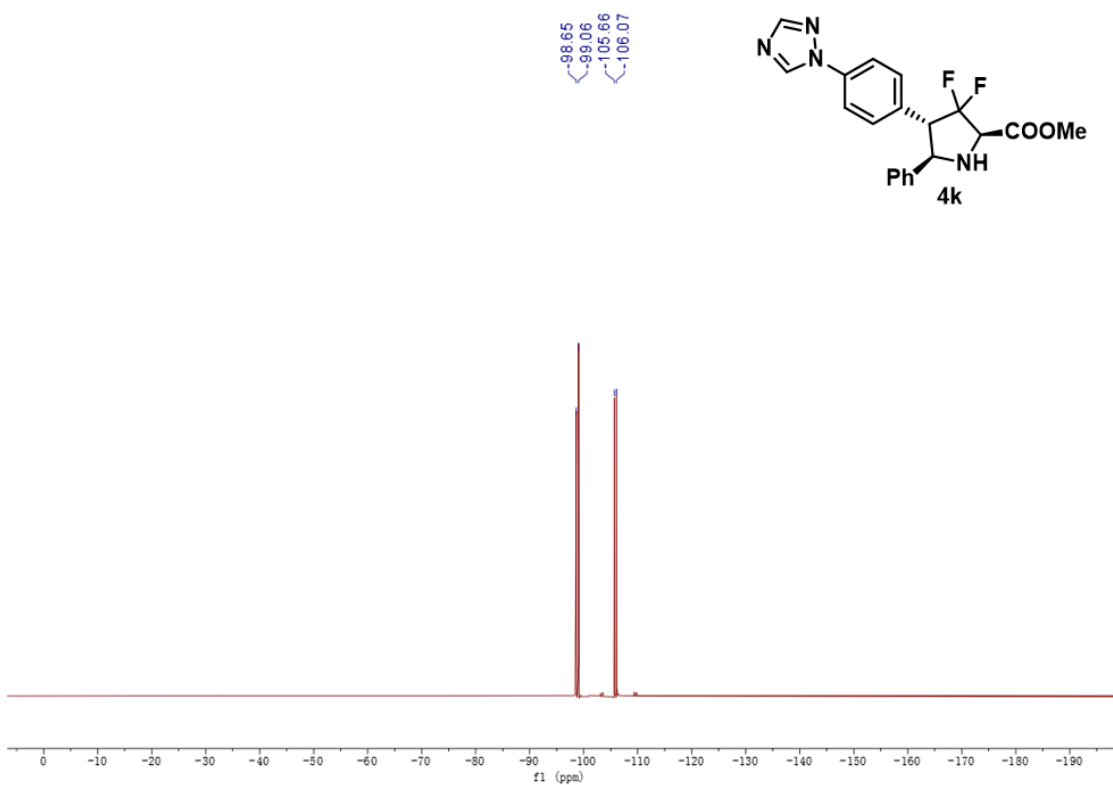
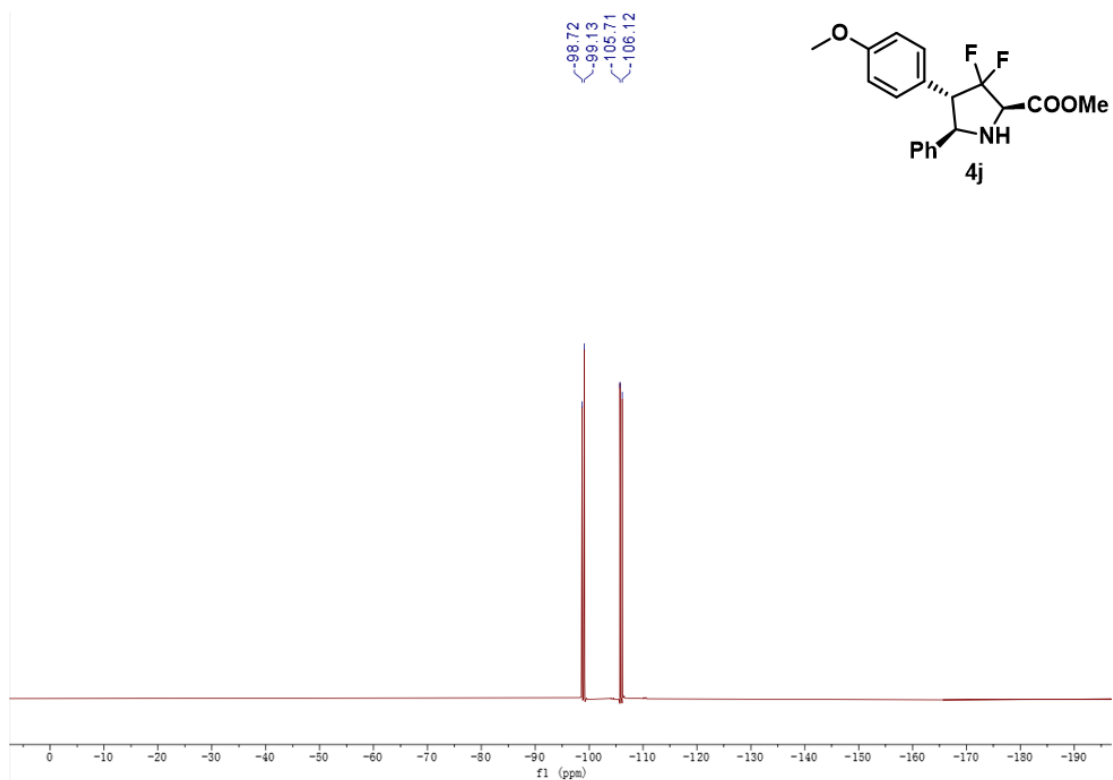


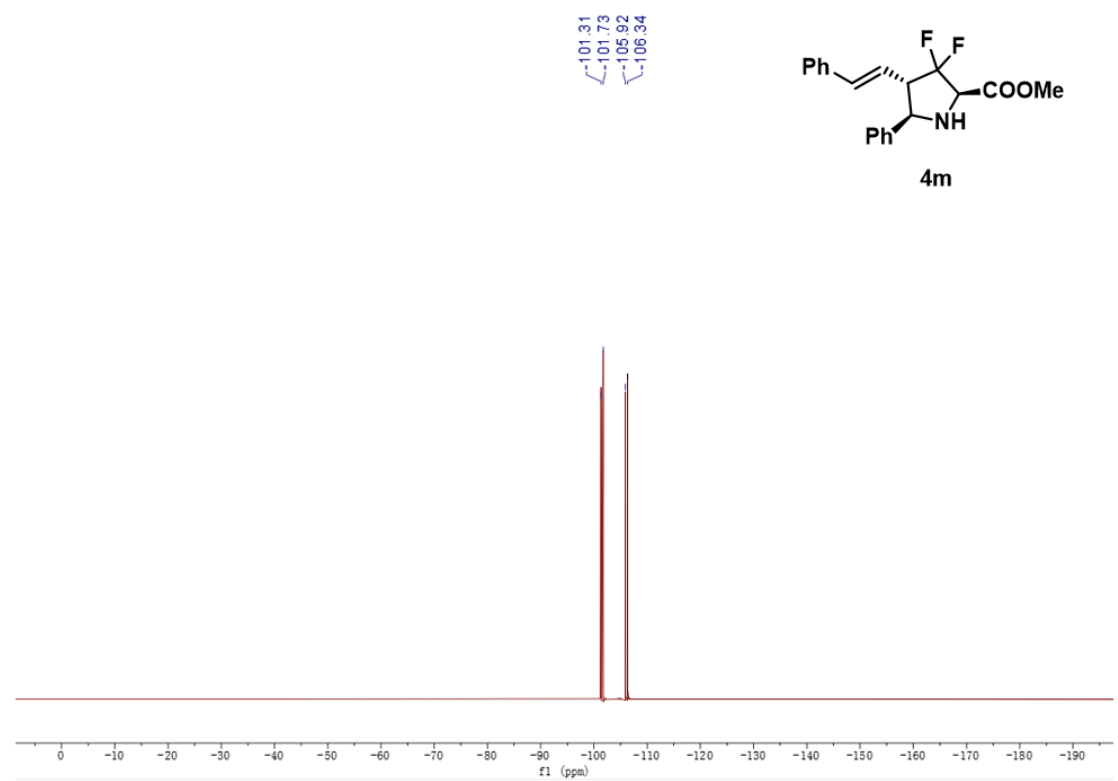
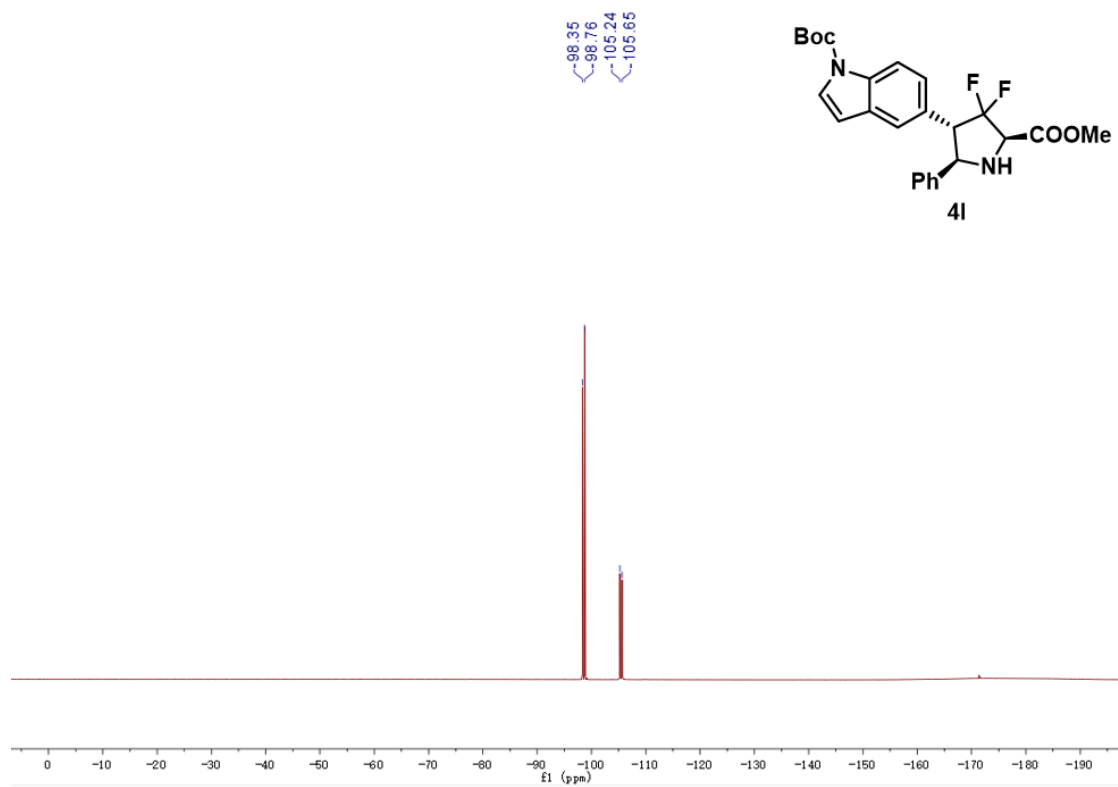


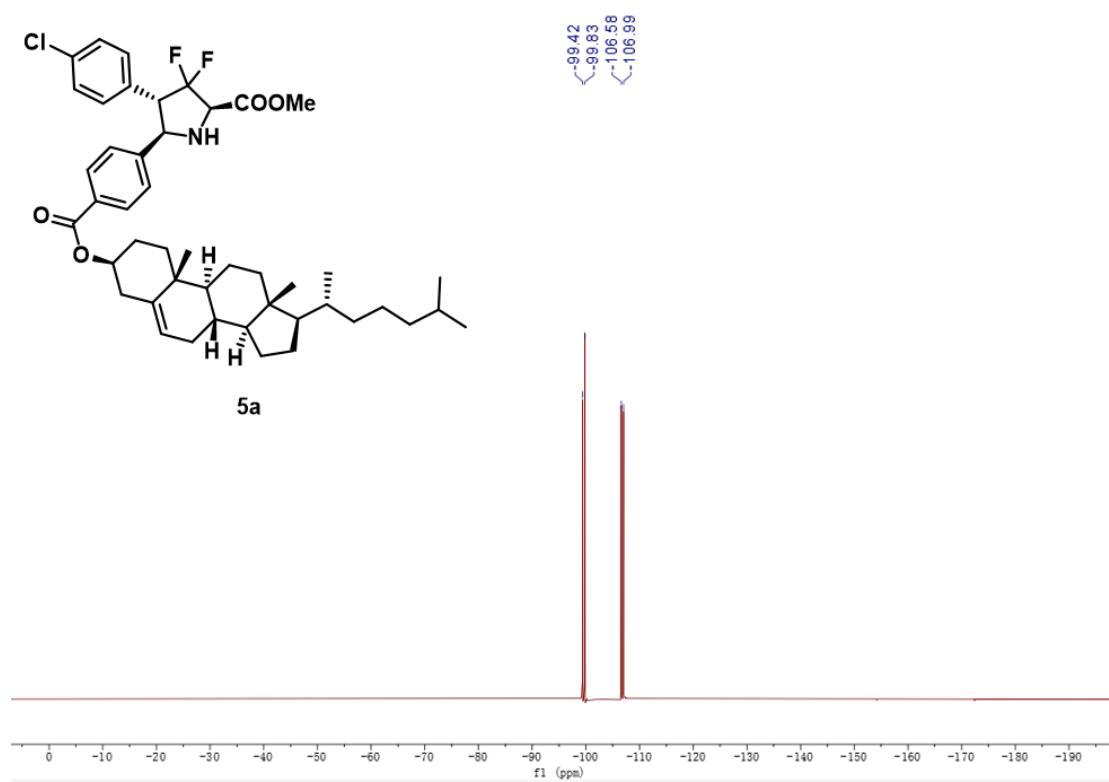
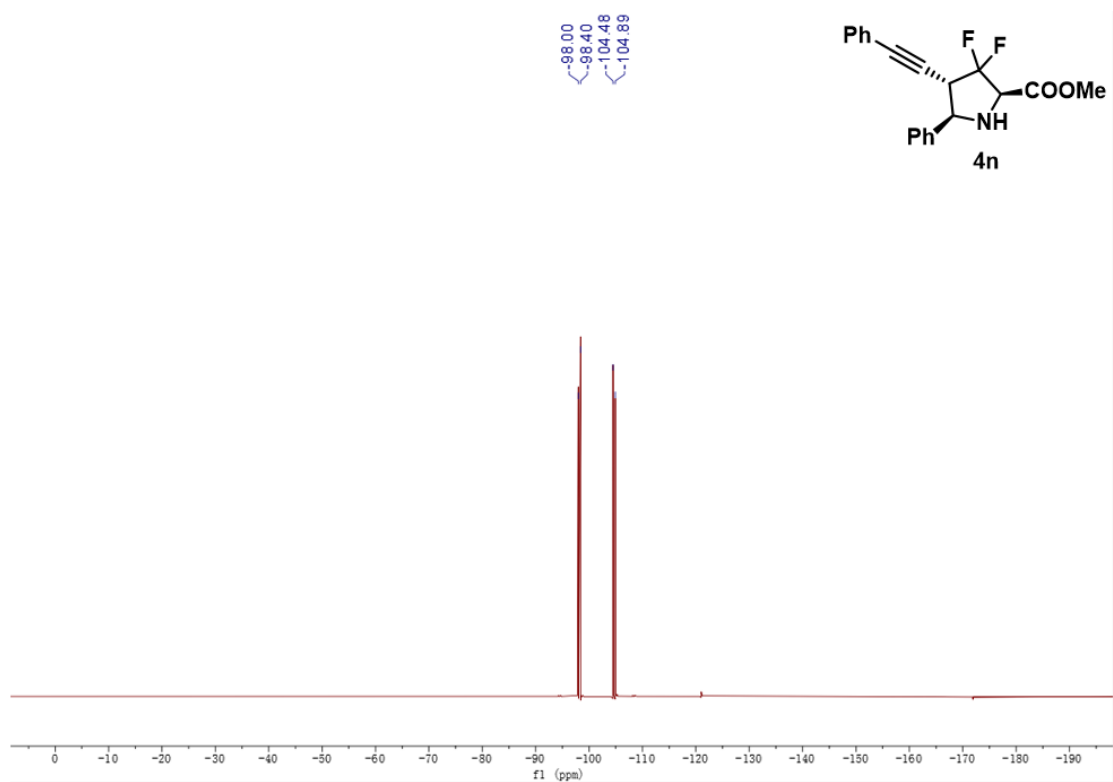


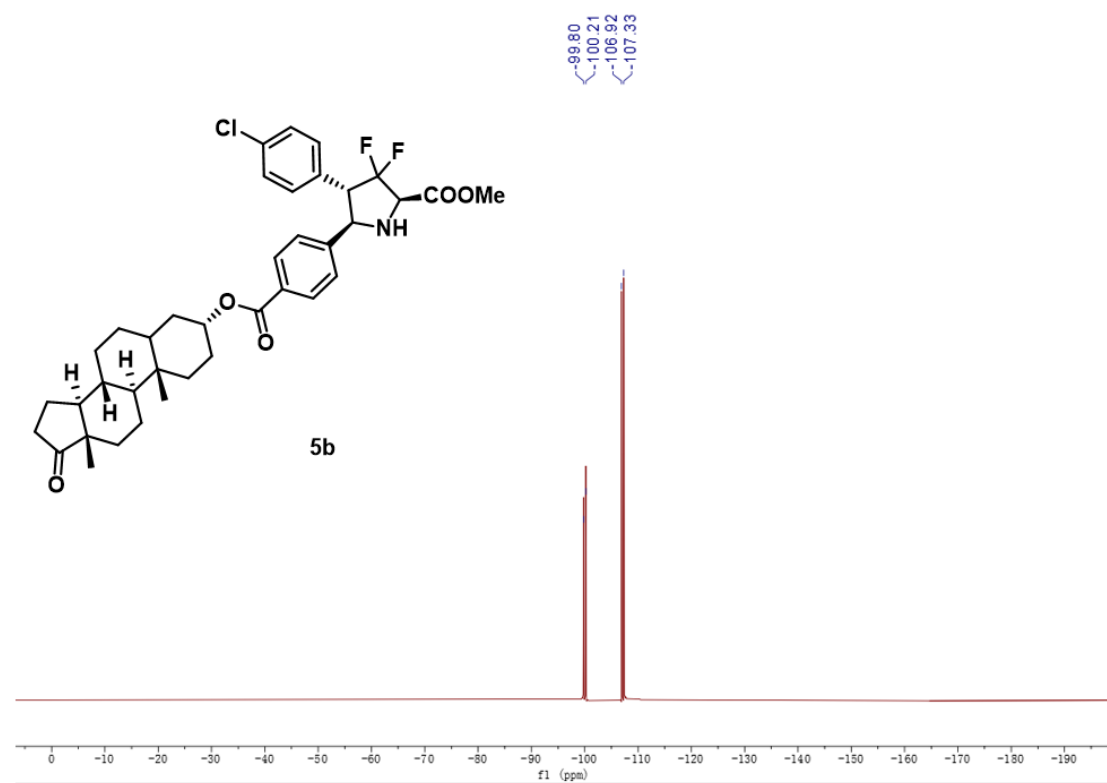
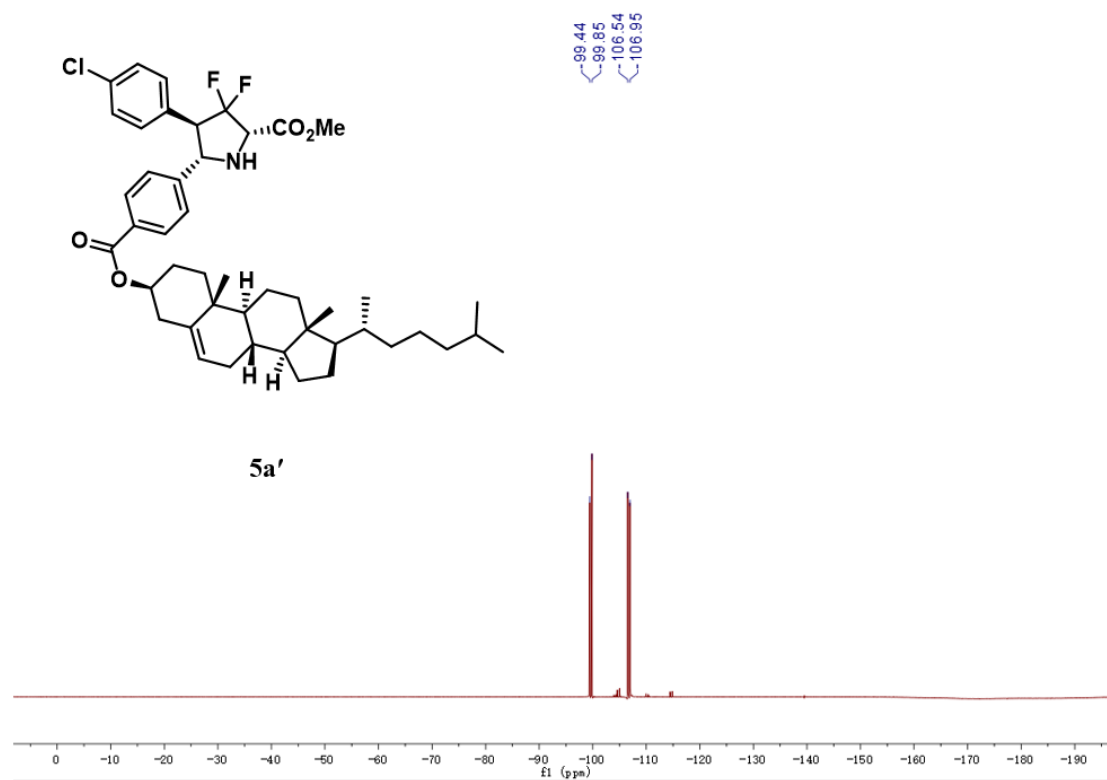


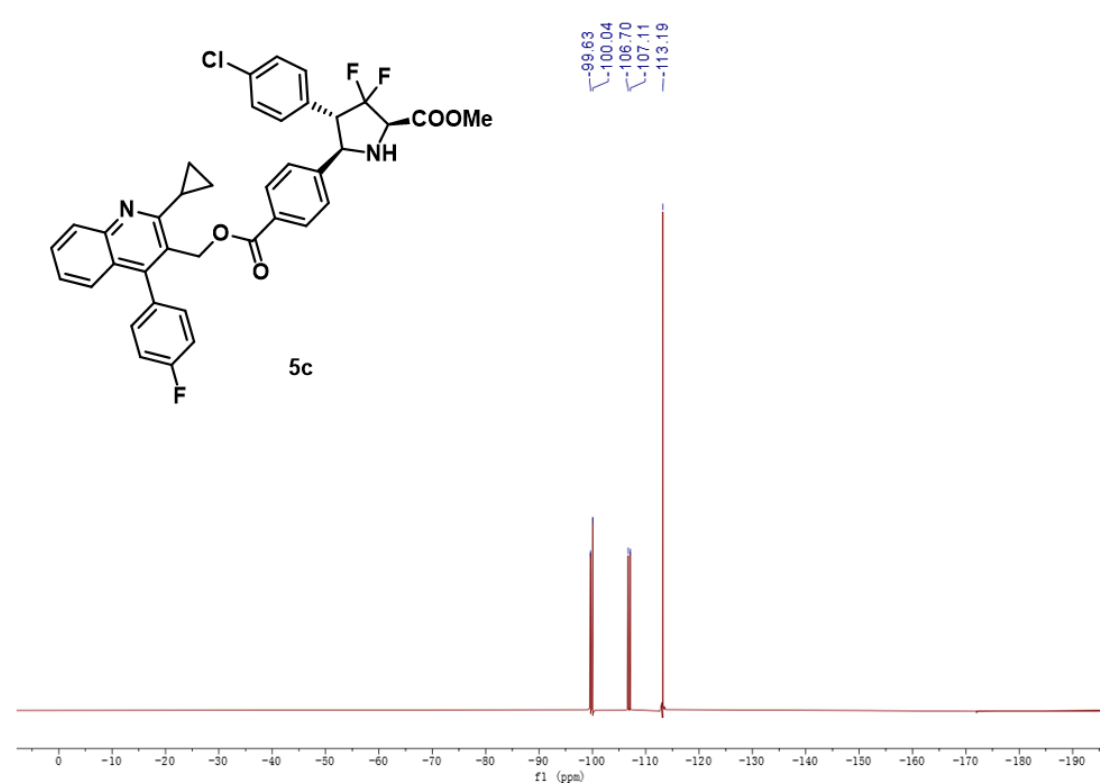
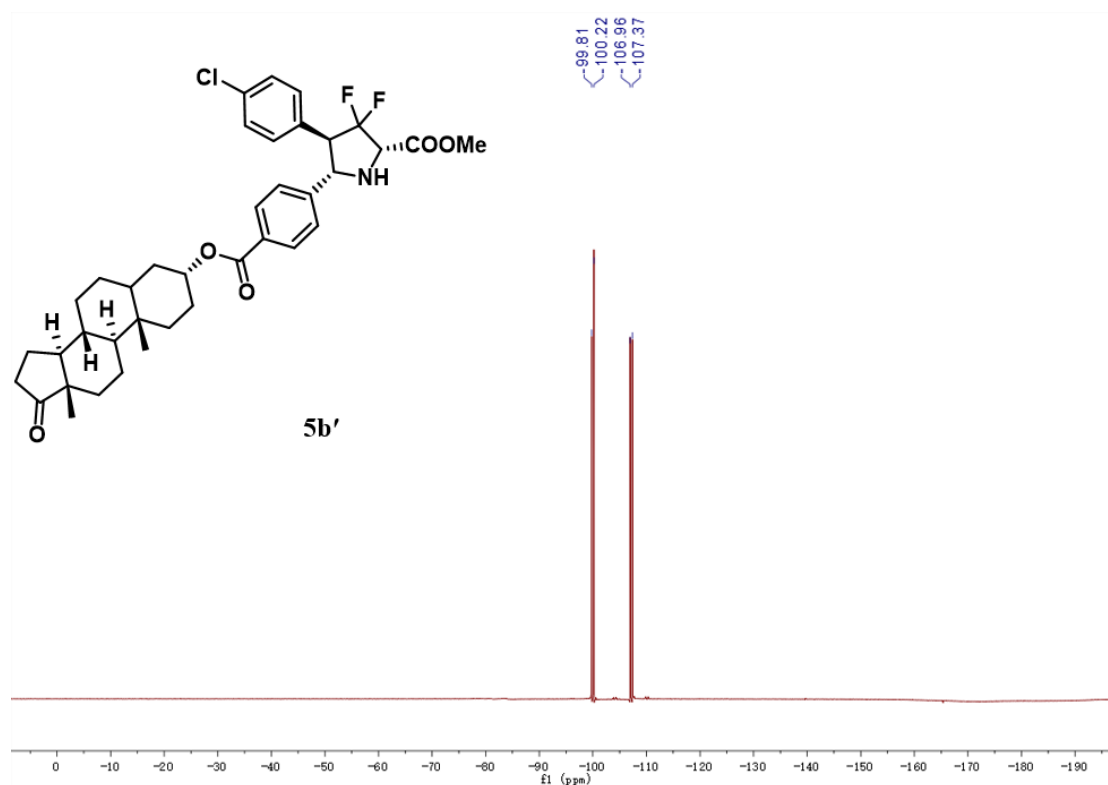


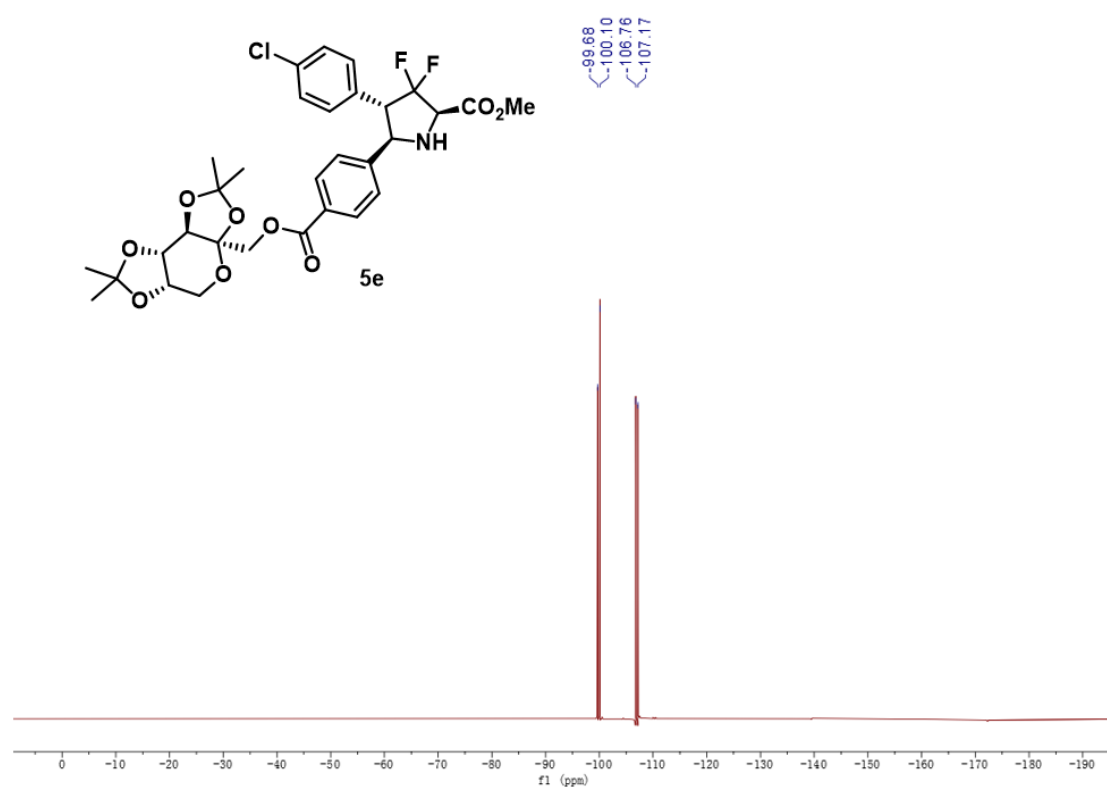
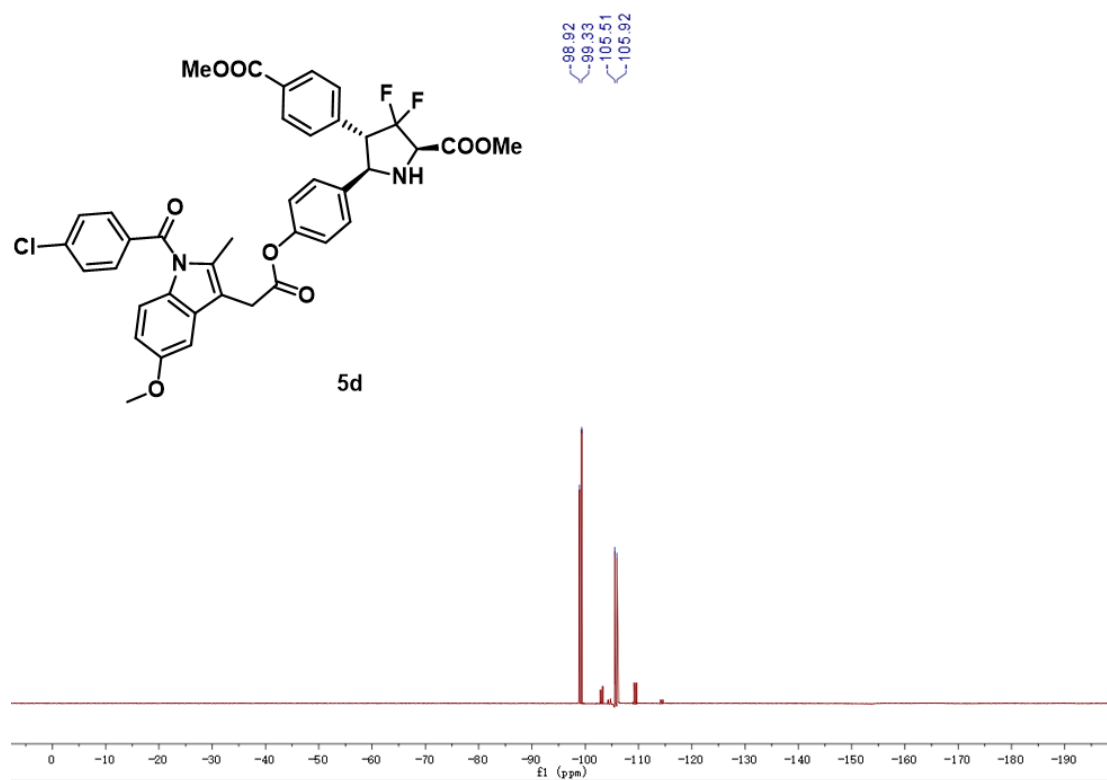


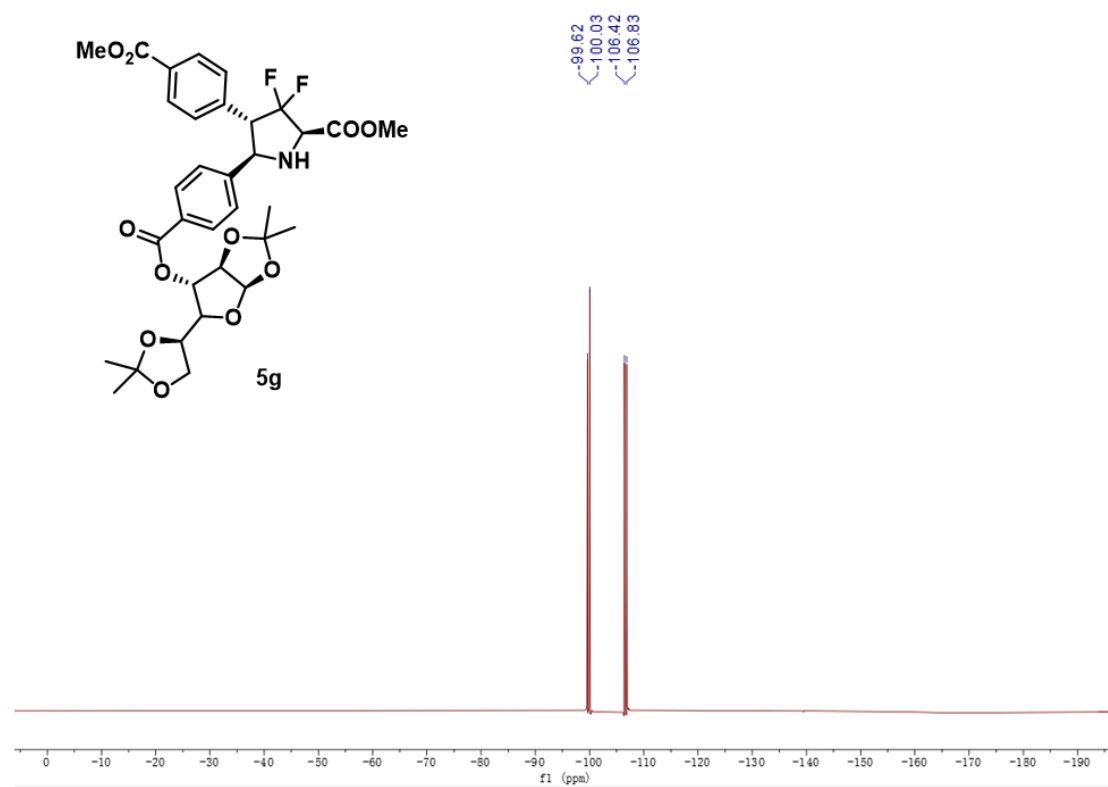
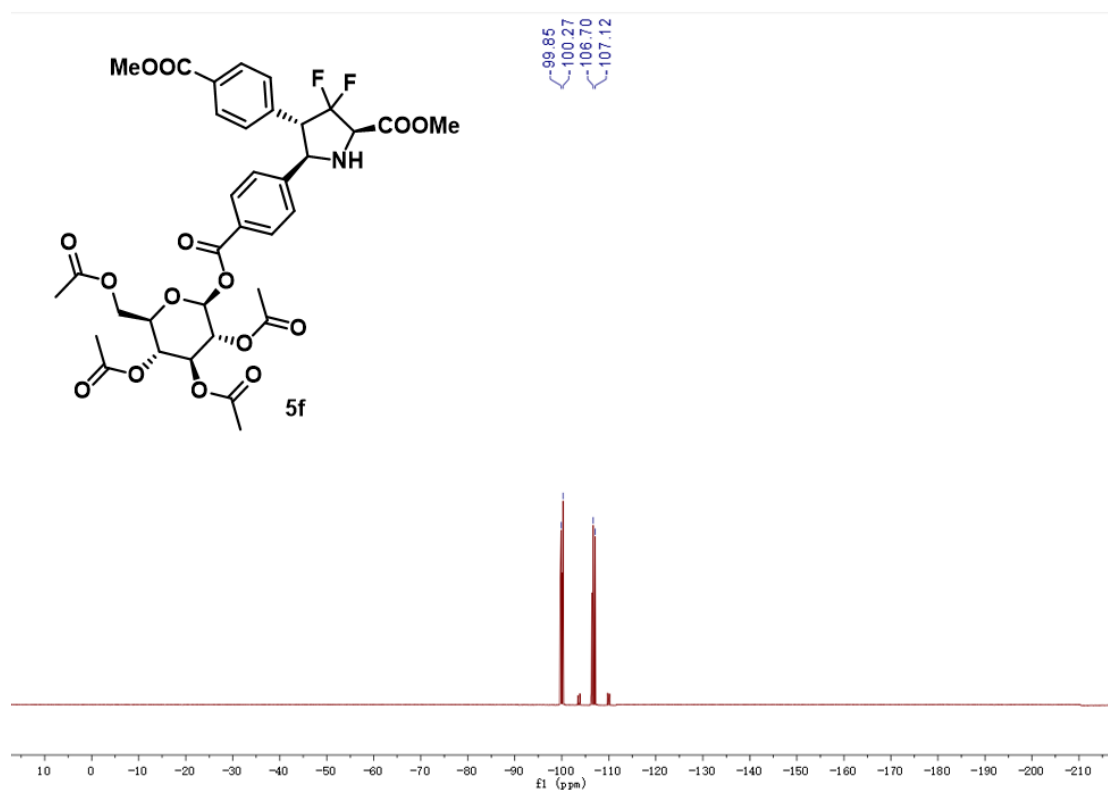


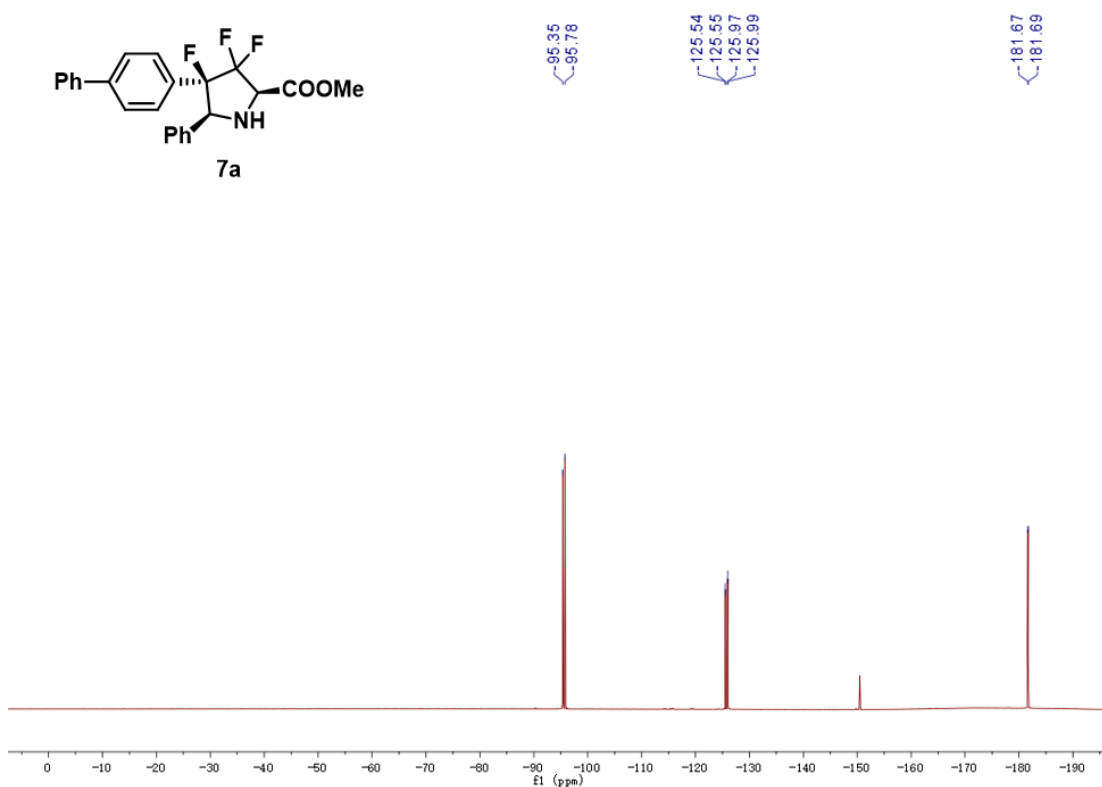
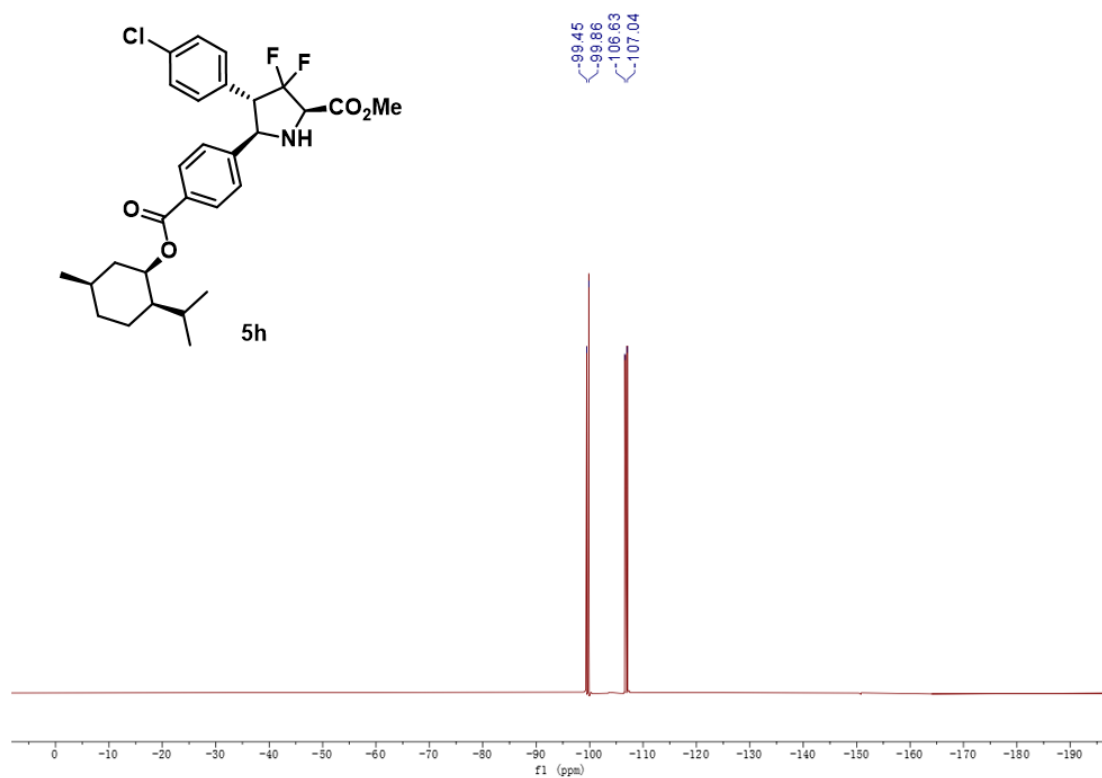


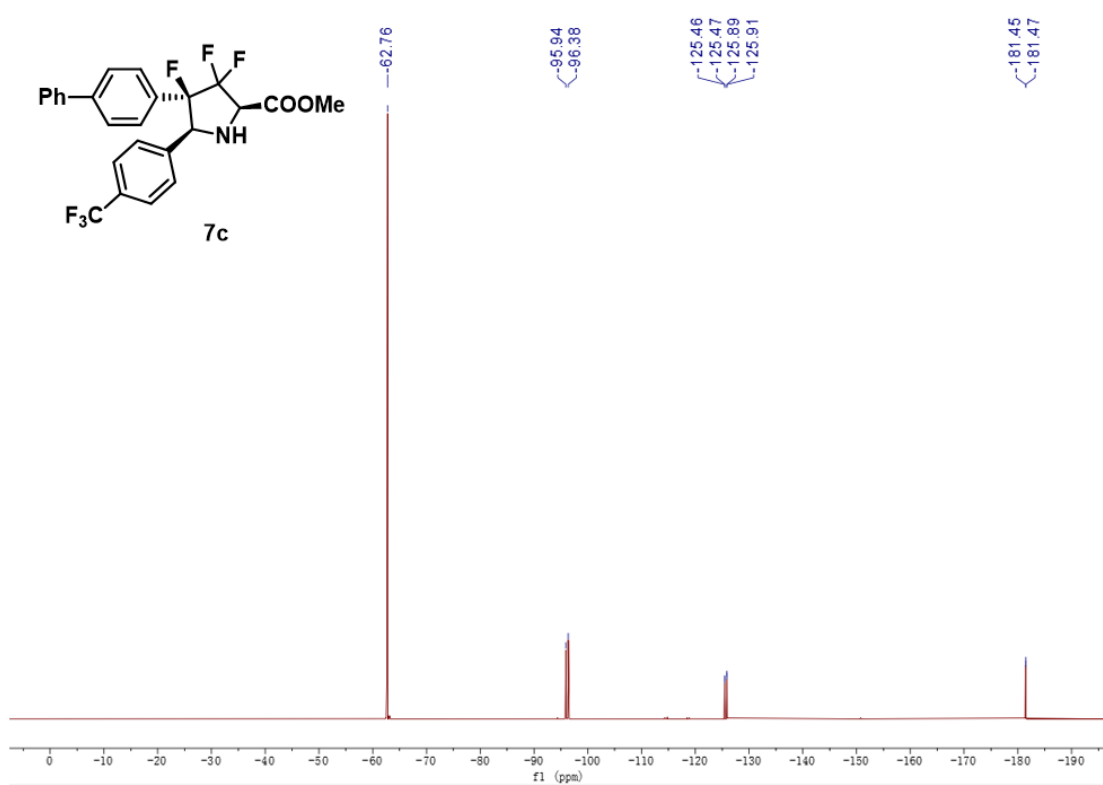
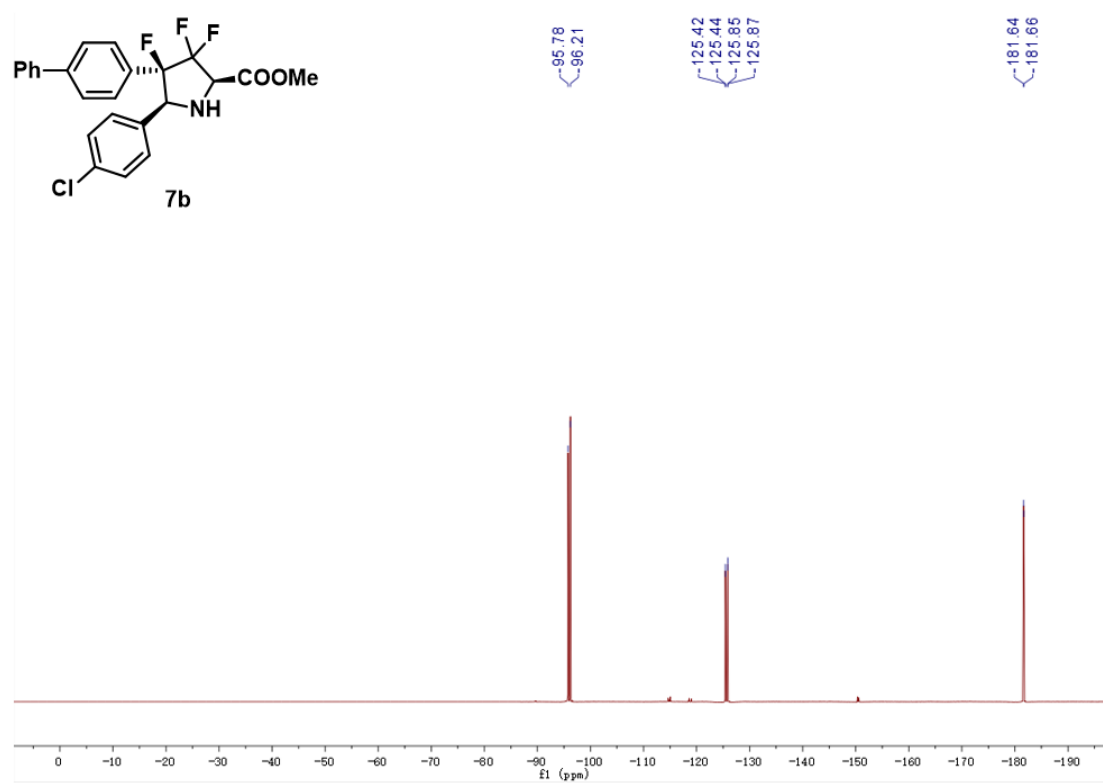


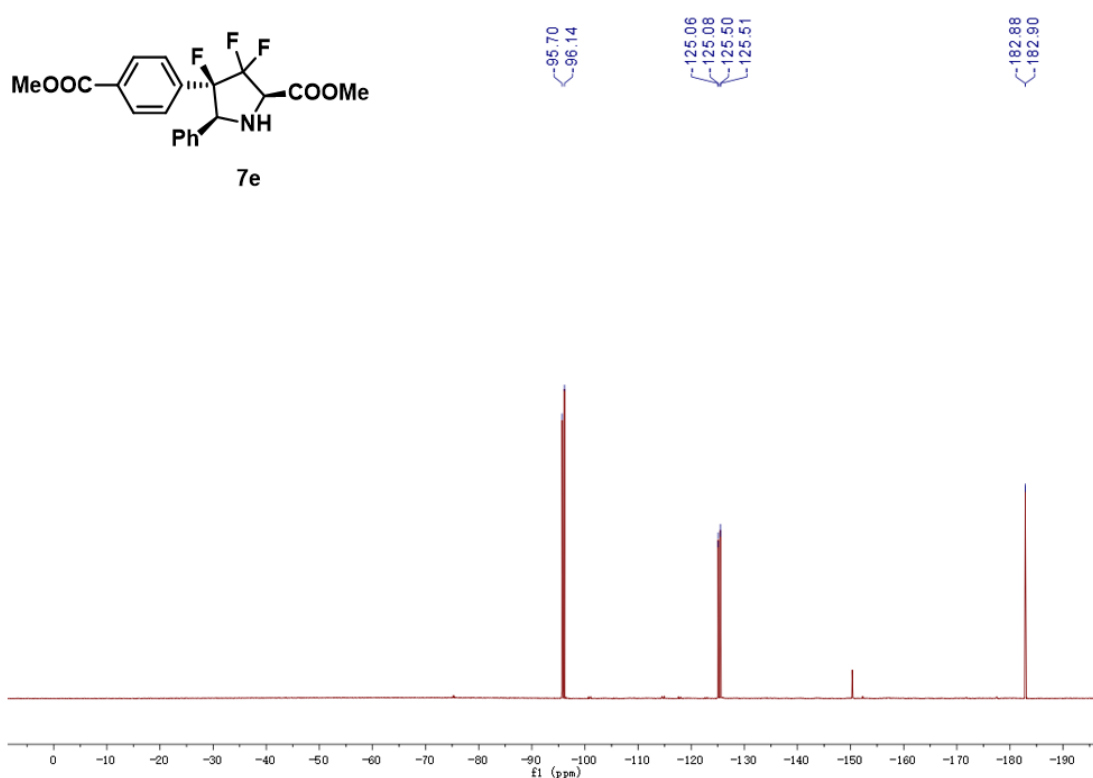
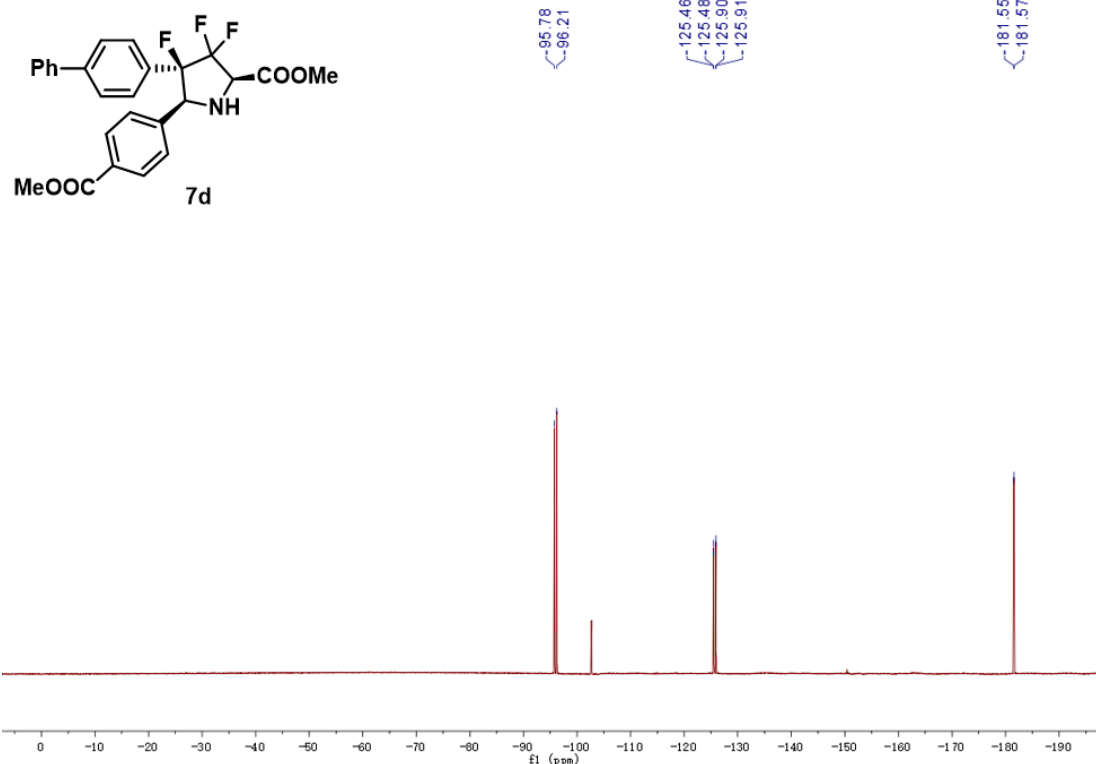


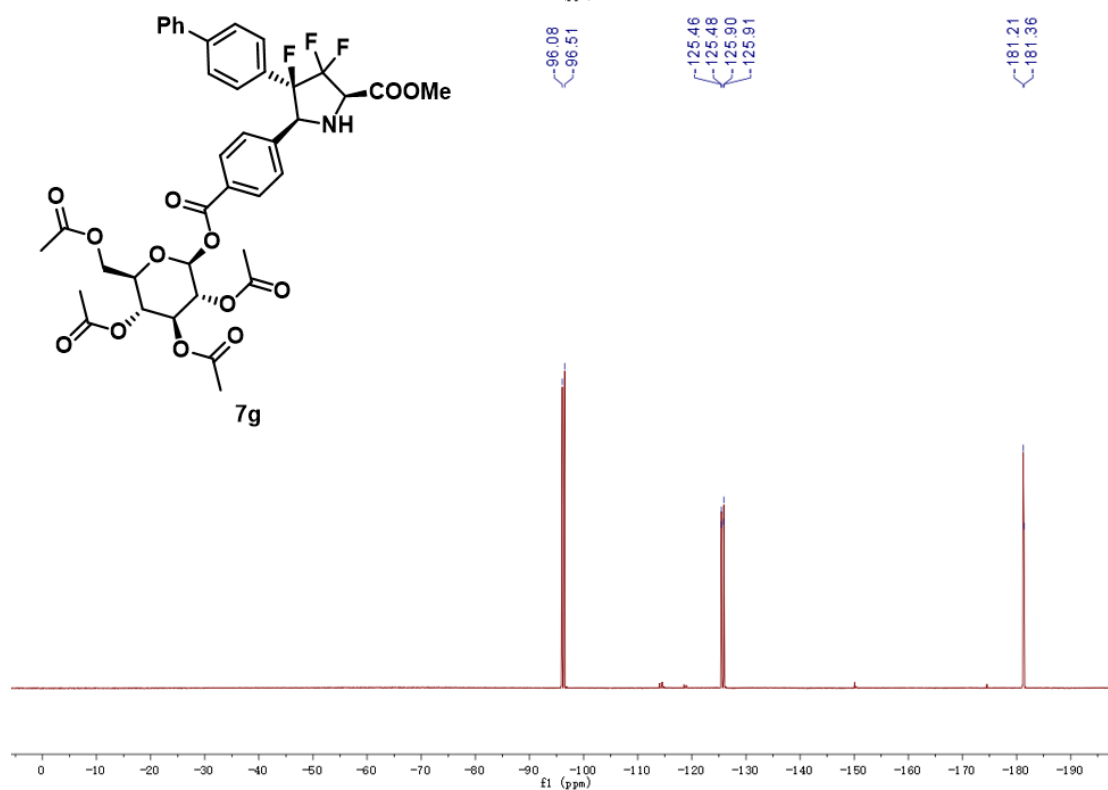
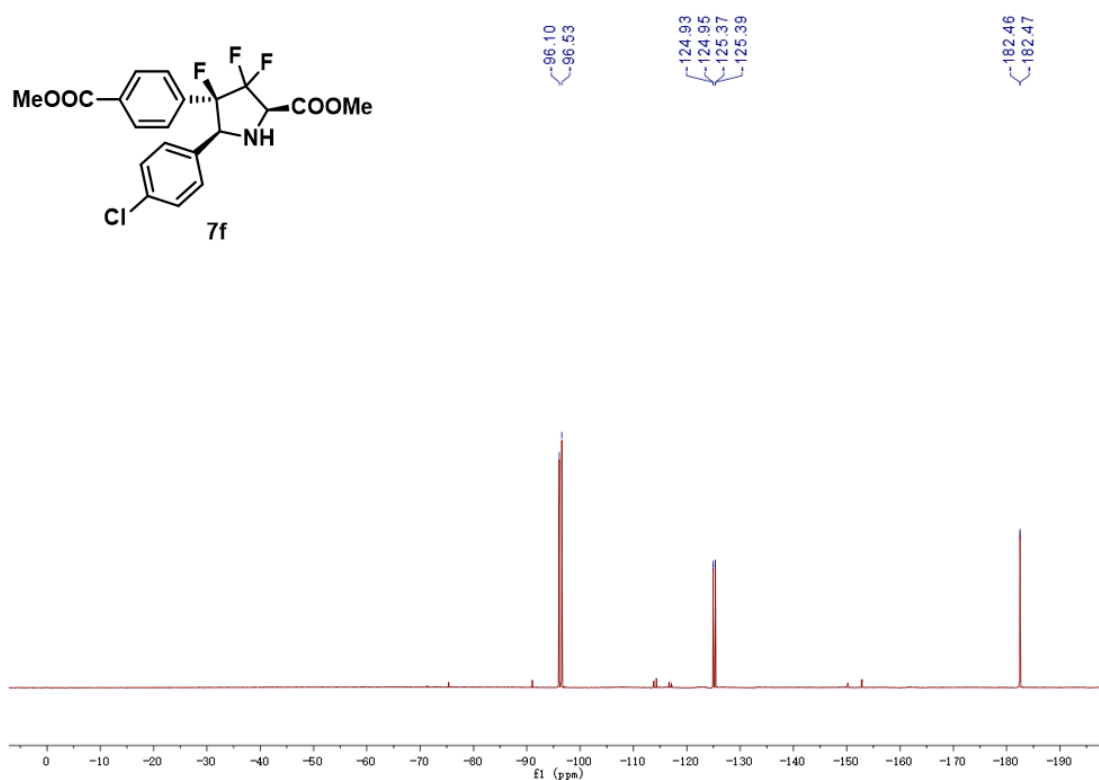


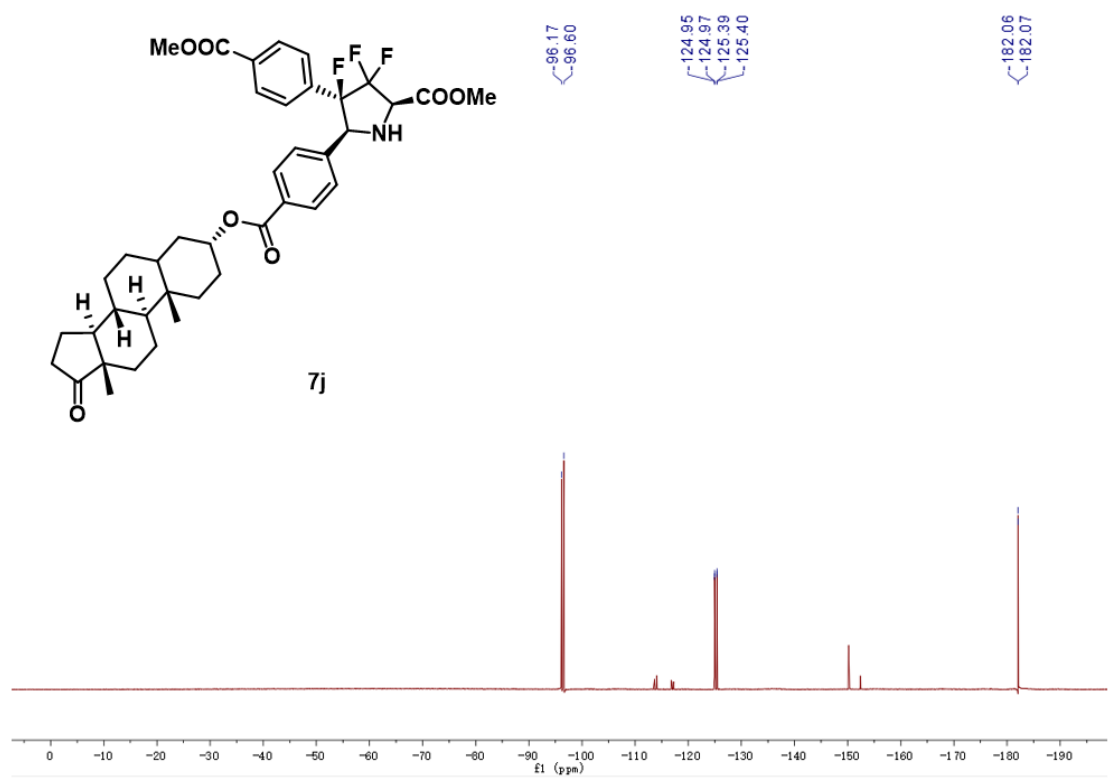




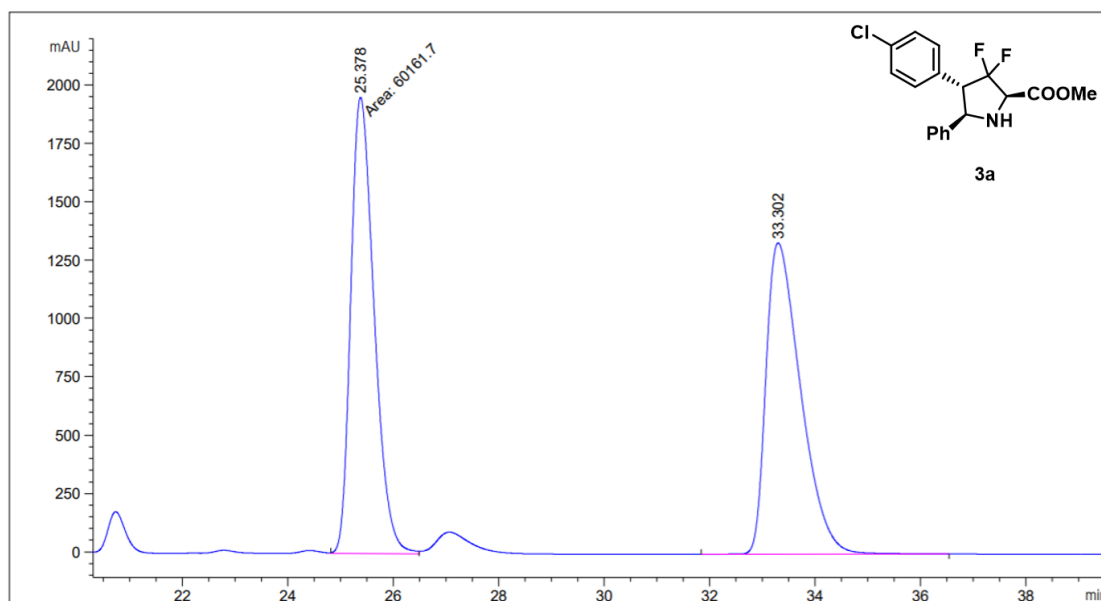




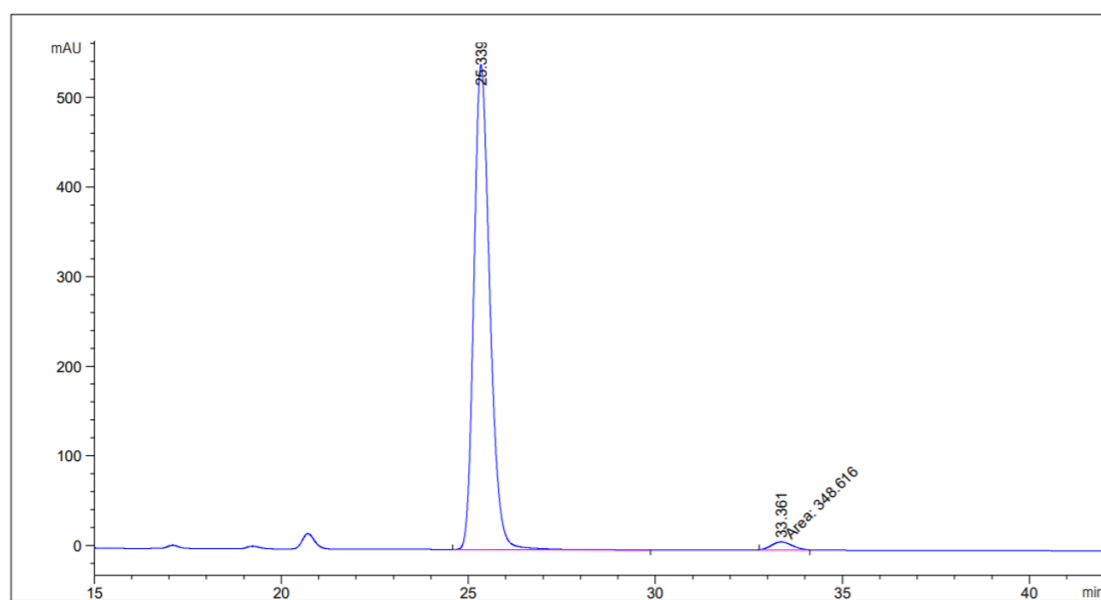




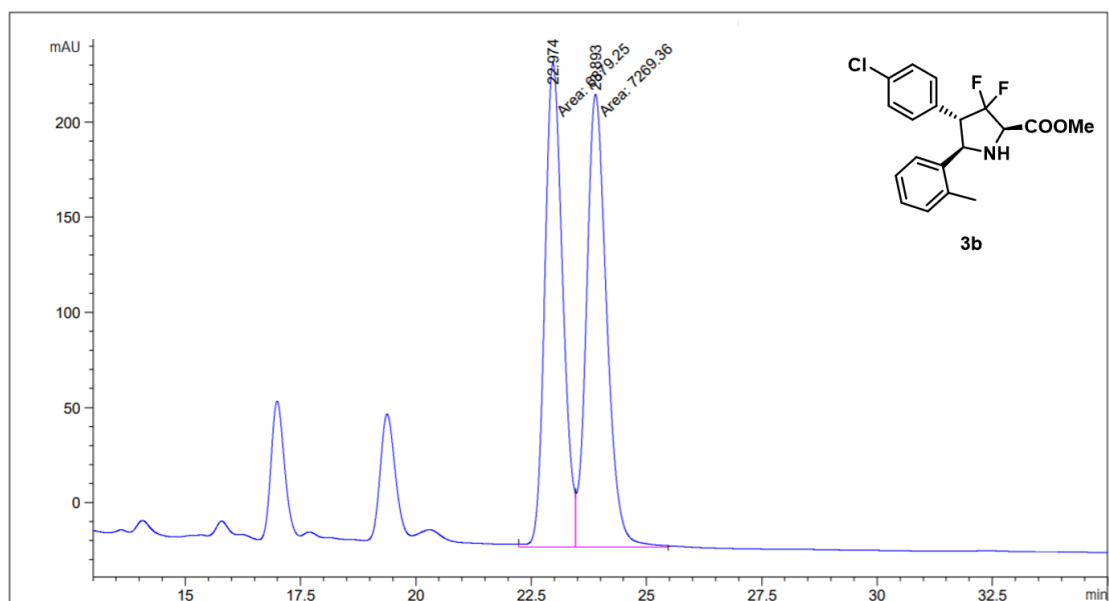
12. HPLC chromatograms



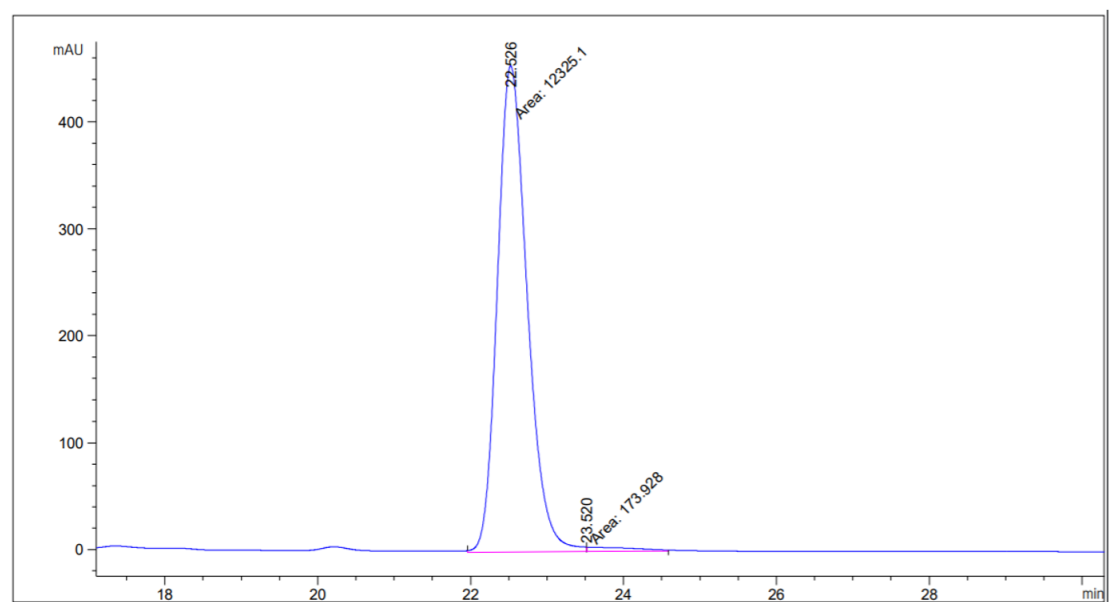
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.378	MF	0.5128	6.01617e4	1955.20239	49.6821
2	33.302	BB	0.6961	6.09315e4	1333.52026	50.3179



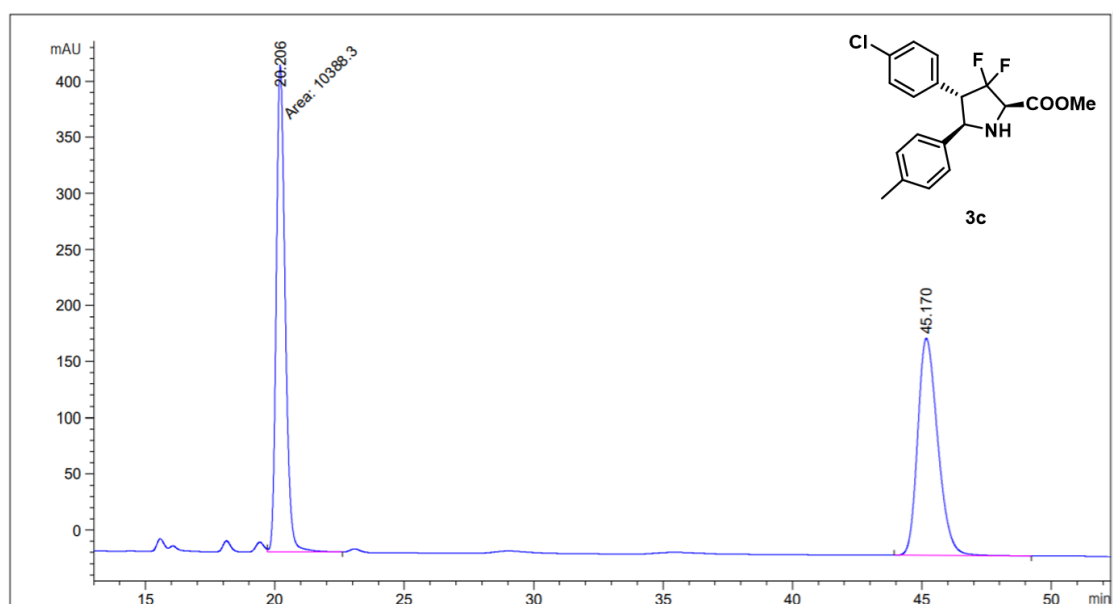
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.339	BB	0.4559	1.60269e4	540.48676	97.8711
2	33.361	MM	0.6433	348.61633	9.03170	2.1289



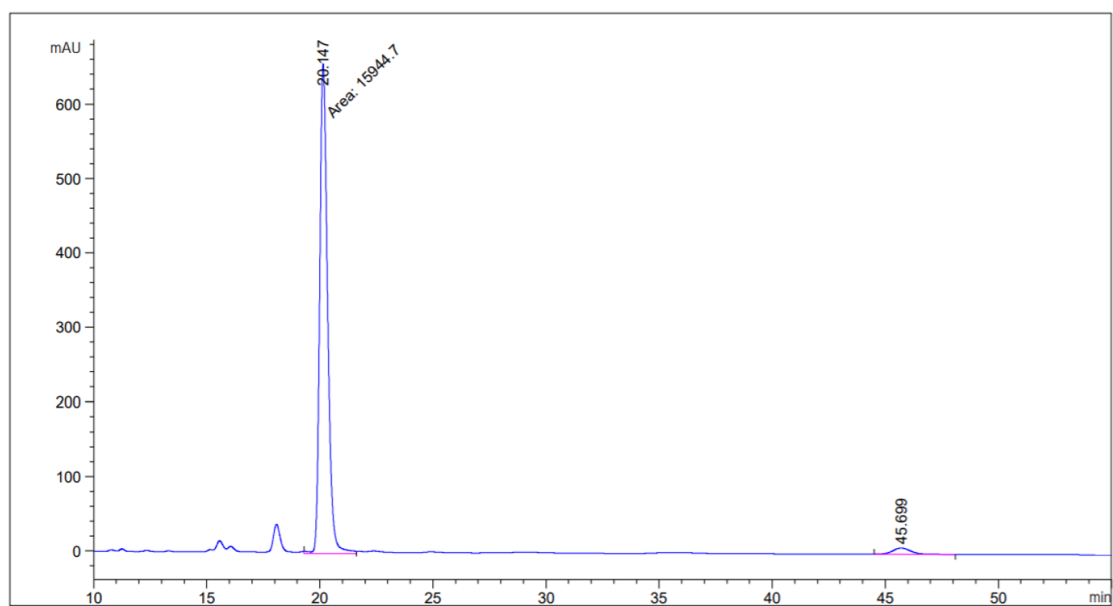
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.974	MF	0.4503	6879.25244	254.64075	48.6214
2	23.893	FM	0.5087	7269.36035	238.18999	51.3786



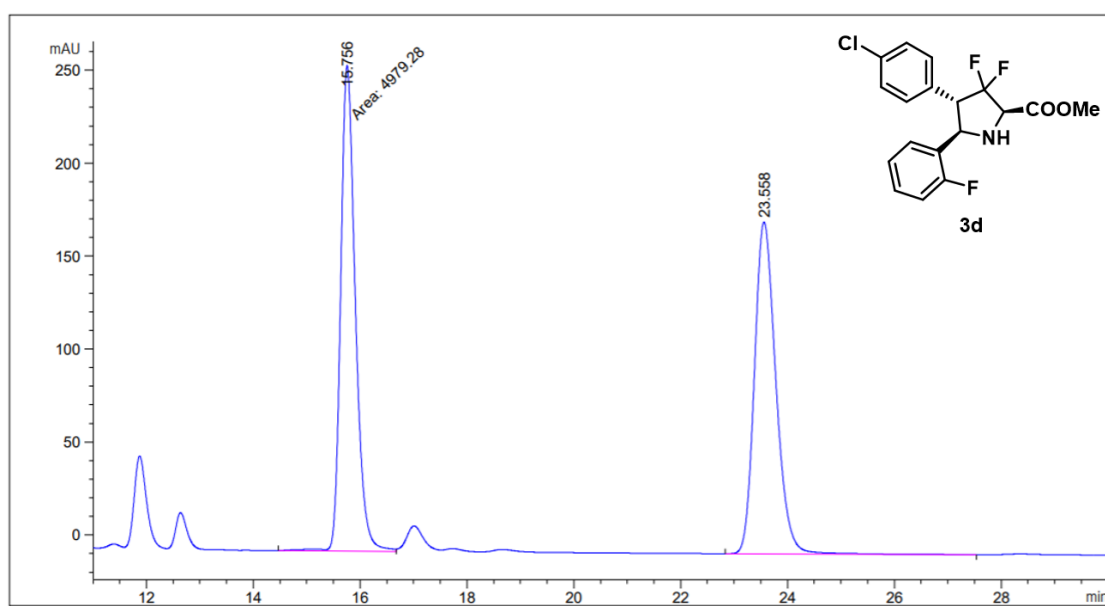
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.526	MF	0.4516	1.23251e4	454.85629	98.6085
2	23.520	FM	0.7027	173.92761	4.12522	1.3915



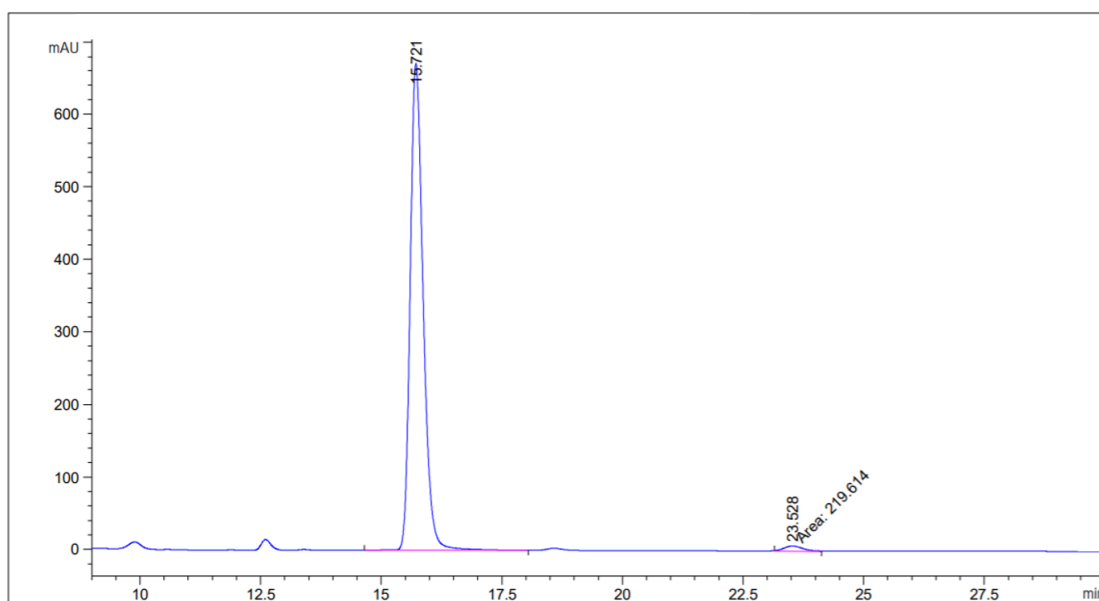
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.206	FM	0.3991	1.03883e4	433.82849	49.9528
2	45.170	BB	0.8326	1.04079e4	193.16638	50.0472



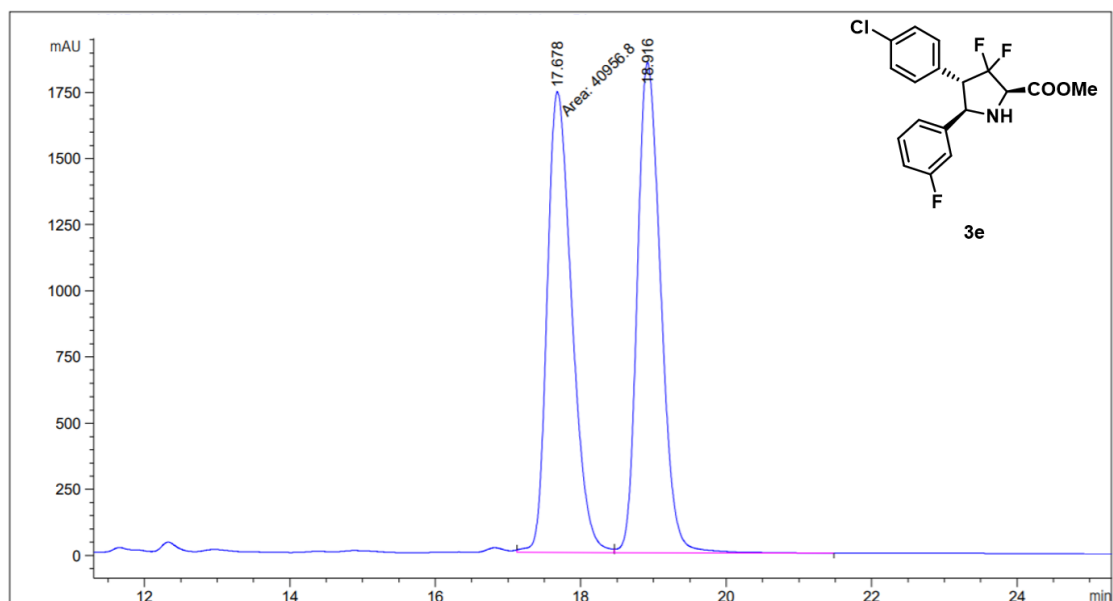
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.147	MM	0.4042	1.59447e4	657.39771	97.2187
2	45.699	BB	0.8278	456.16483	8.35769	2.7813



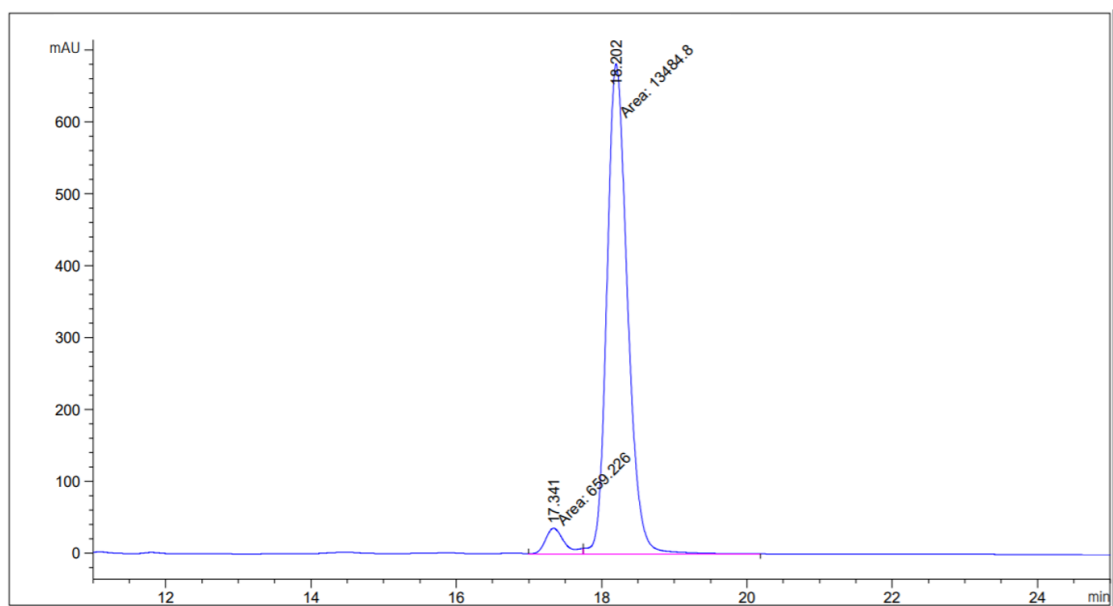
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.756	MF	0.3179	4979.28027	261.07666	50.0522
2	23.558	BB	0.4268	4968.88477	178.49673	49.9478



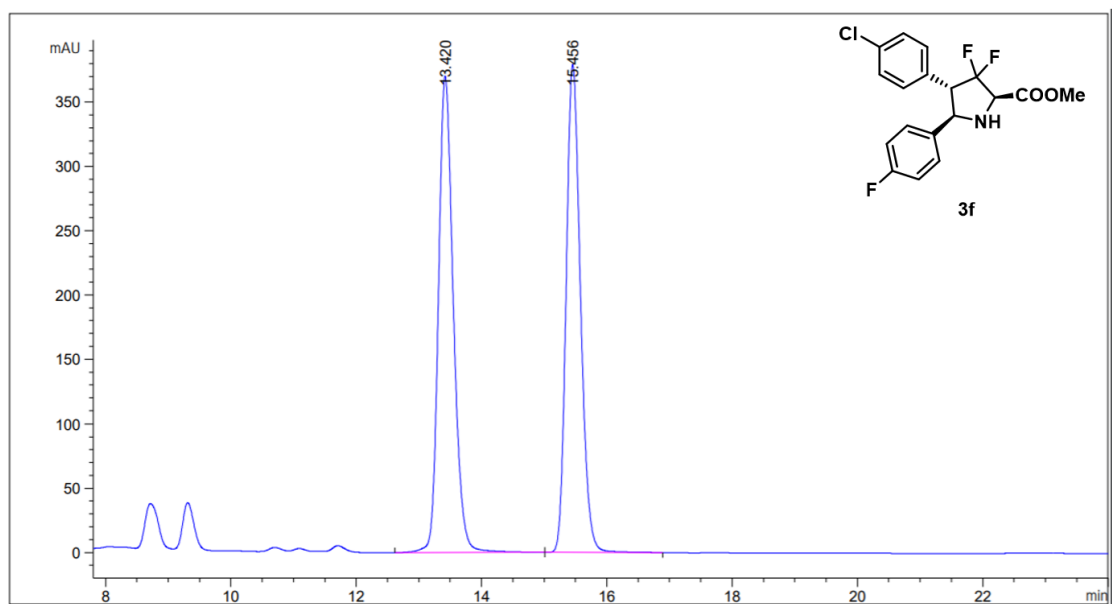
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.721	BB	0.2876	1.25882e4	671.81860	98.5502
2	23.525	BB	0.4151	185.19228	6.92359	1.4498



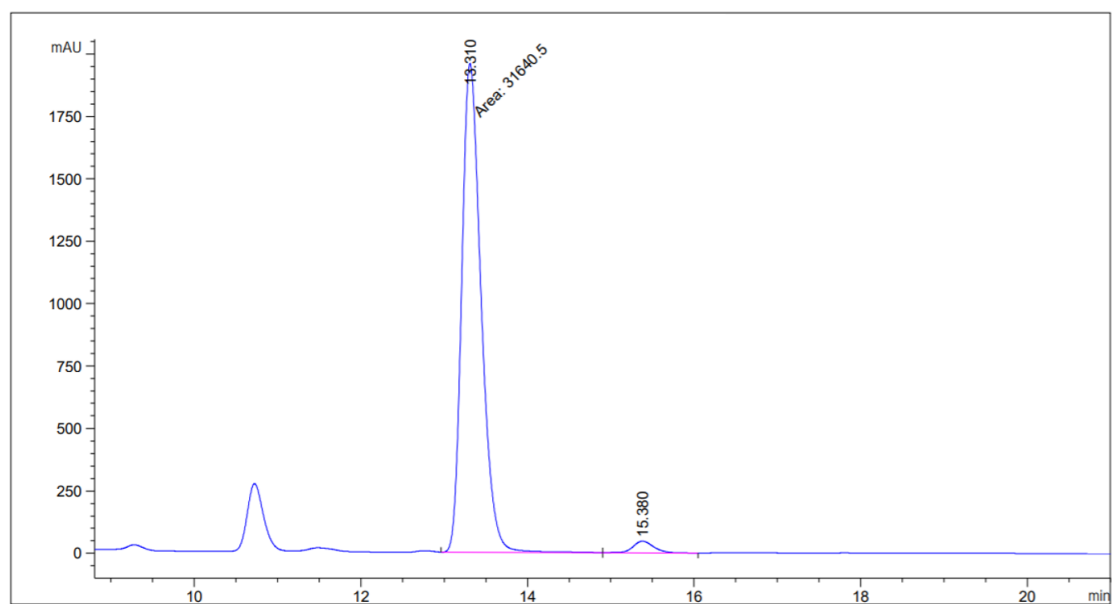
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.678	FM	0.3919	4.09568e4	1741.76294	49.6632
2	18.916	VB	0.3513	4.15123e4	1853.57617	50.3368



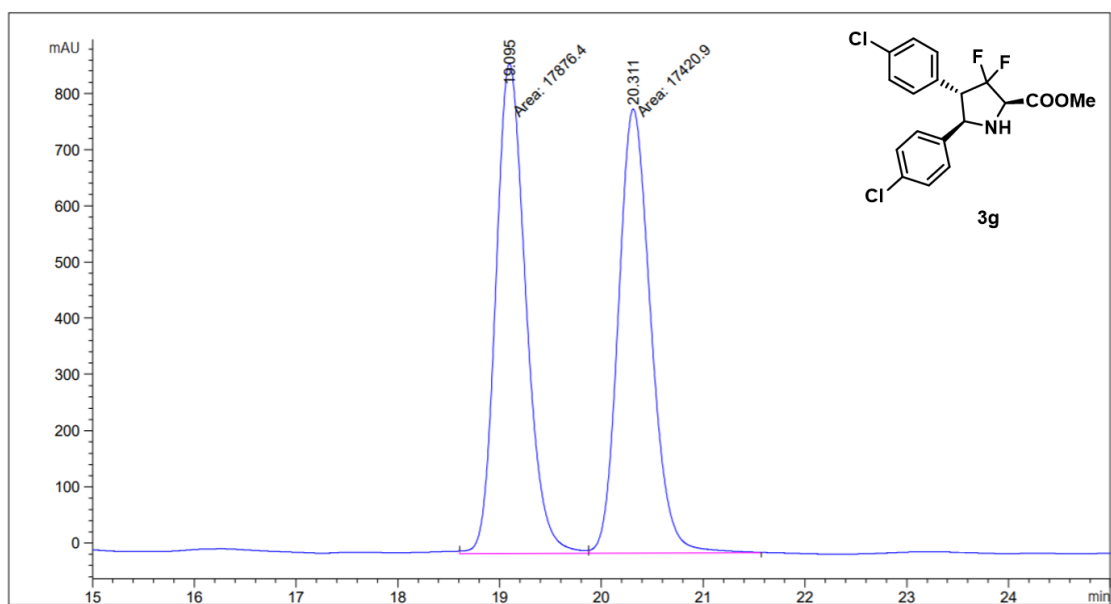
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.341	MF	0.3051	659.22565	36.01219	4.6608
2	18.202	FM	0.3296	1.34848e4	681.89911	95.3392



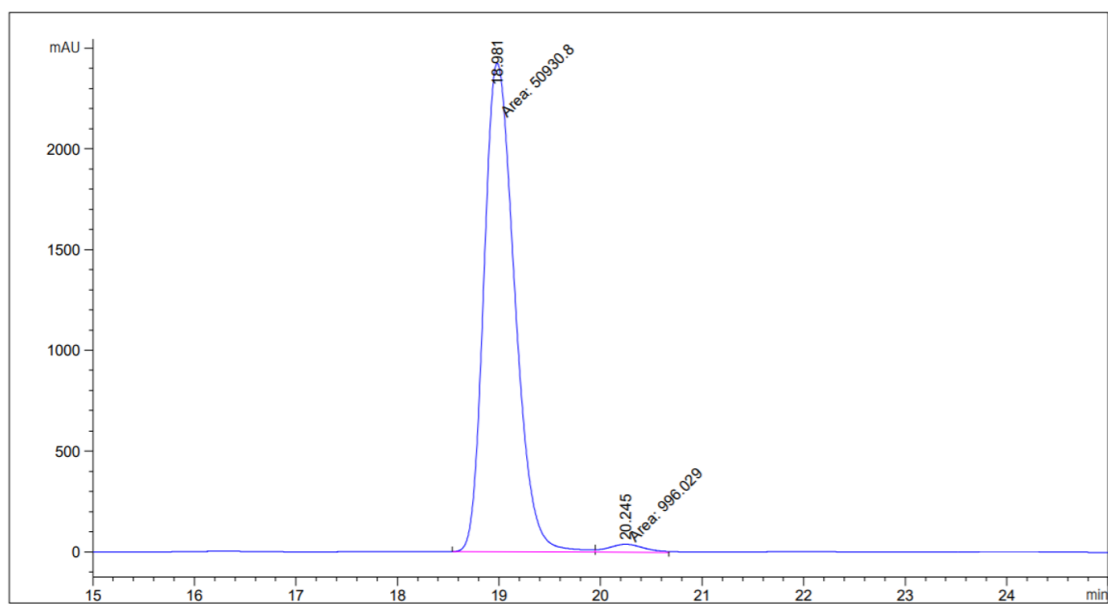
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.420	BB	0.2530	6128.67236	370.49564	50.5504
2	15.456	BB	0.2443	5995.20117	379.45901	49.4496



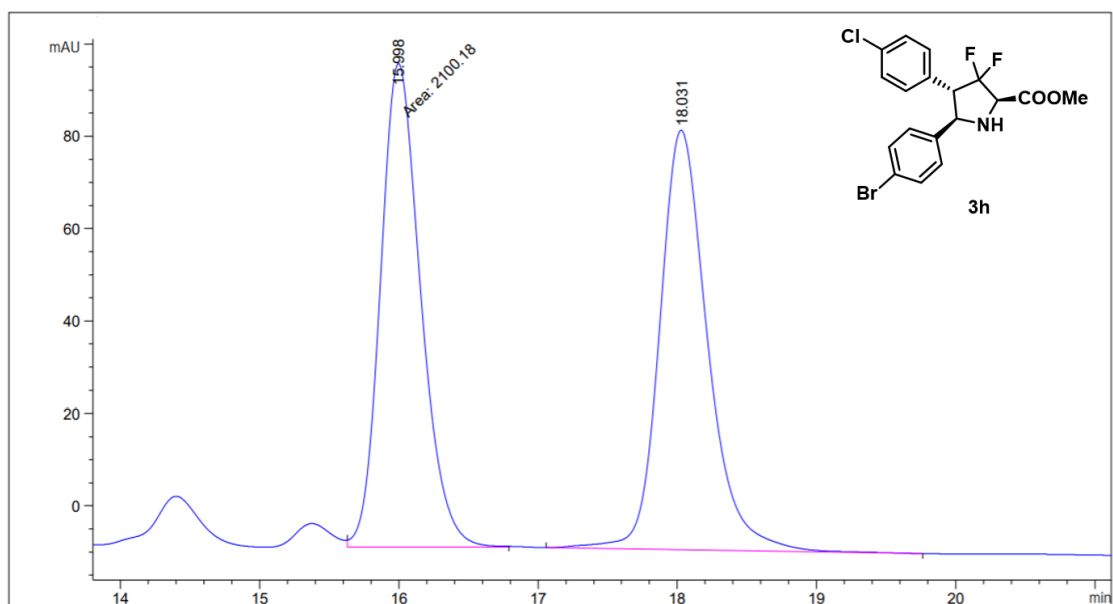
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.310	FM	0.2691	3.16405e4	1959.54822	97.4726
2	15.380	VB	0.2637	820.43378	47.23252	2.5274



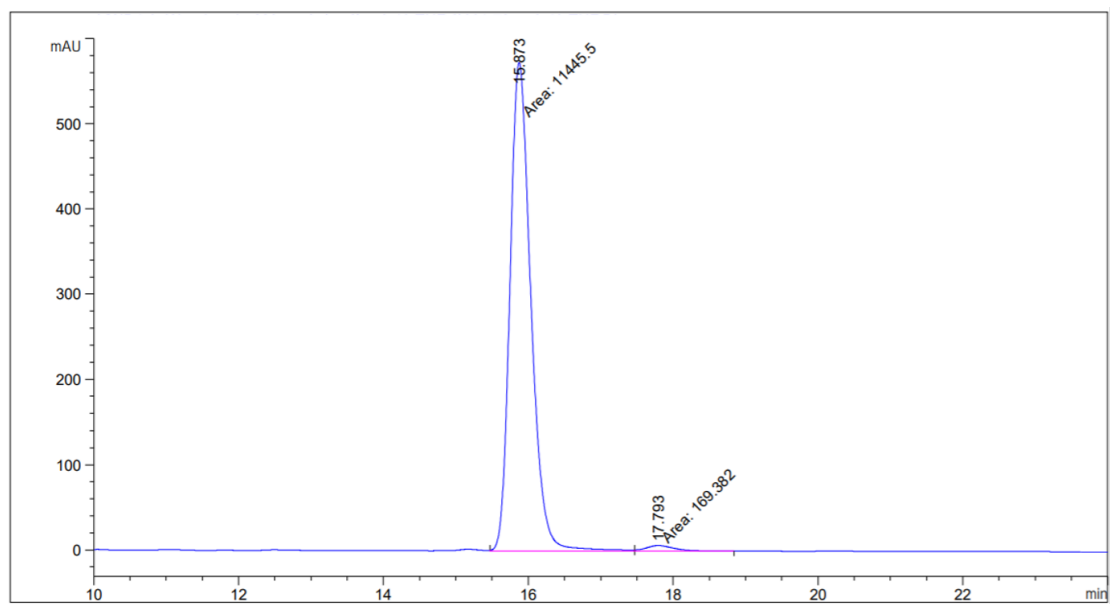
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.095	MF	0.3413	1.78764e4	872.96289	50.6452
2	20.311	FM	0.3674	1.74209e4	790.22546	49.3548



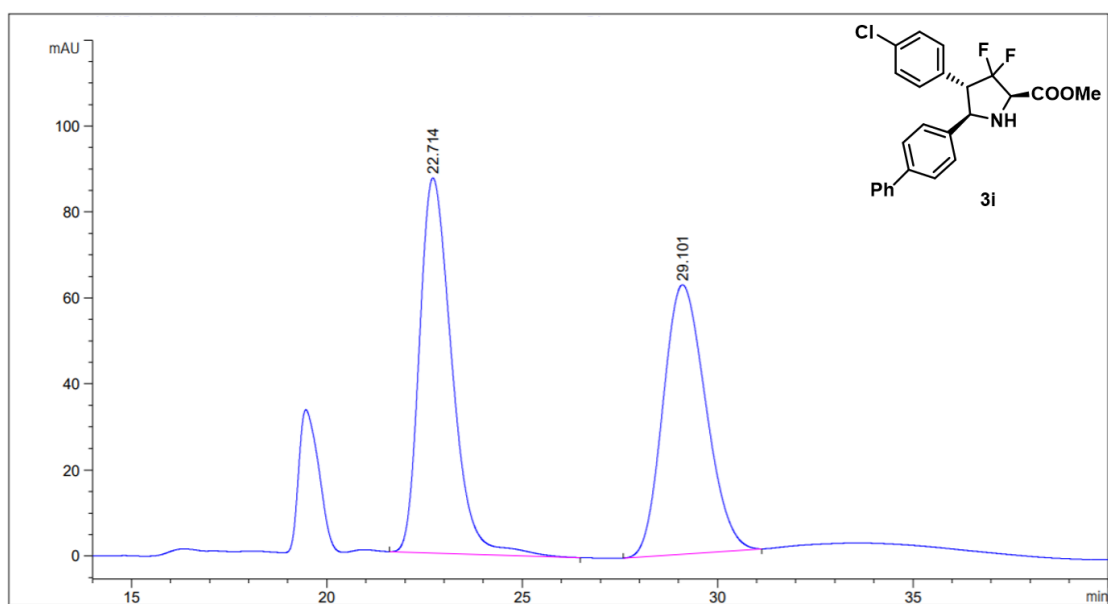
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.981	MF	0.3502	5.09308e4	2424.04614	98.0819
2	20.245	FM	0.4092	996.02905	40.56814	1.9181



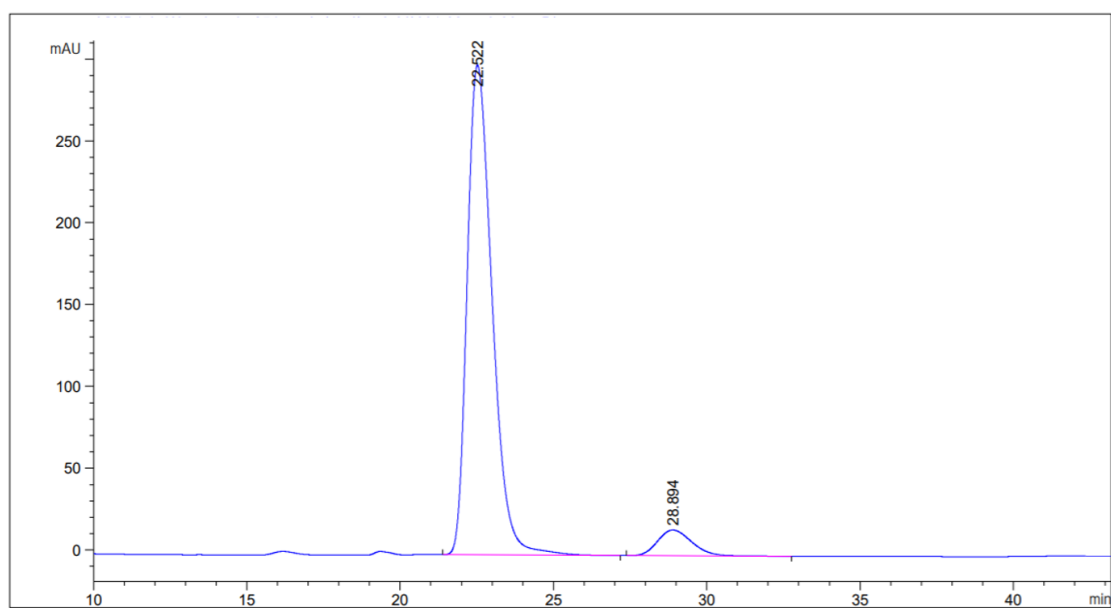
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.998	FM	0.3341	2100.17822	104.76800	49.1284
2	18.031	BB	0.3634	2174.69653	90.82294	50.8716



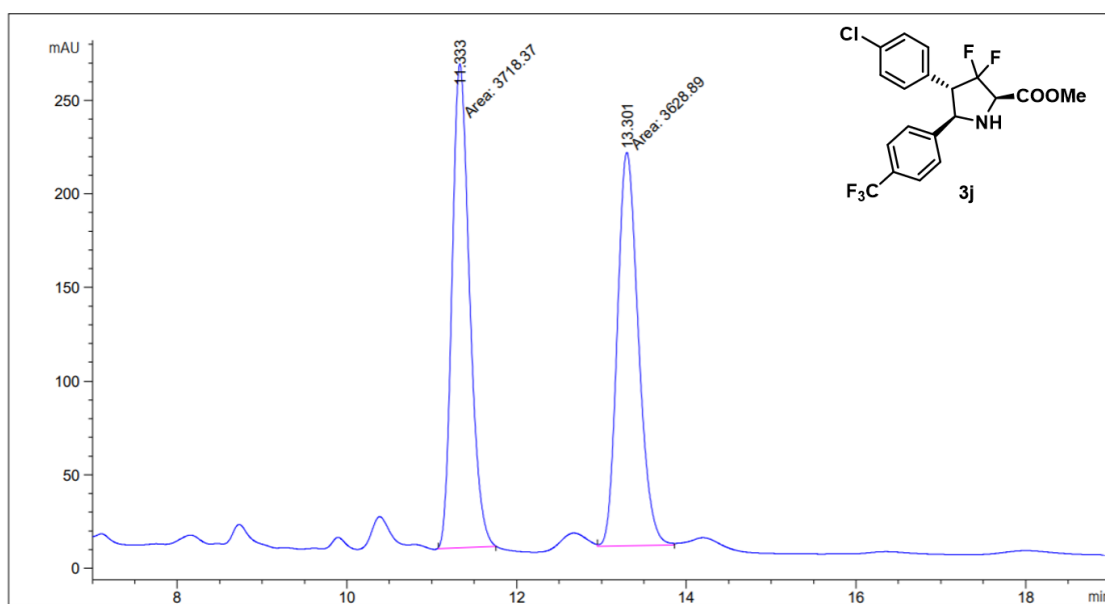
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.873	MF	0.3330	1.14455e4	572.84534	98.5417
2	17.793	FM	0.4383	169.38205	6.44058	1.4583



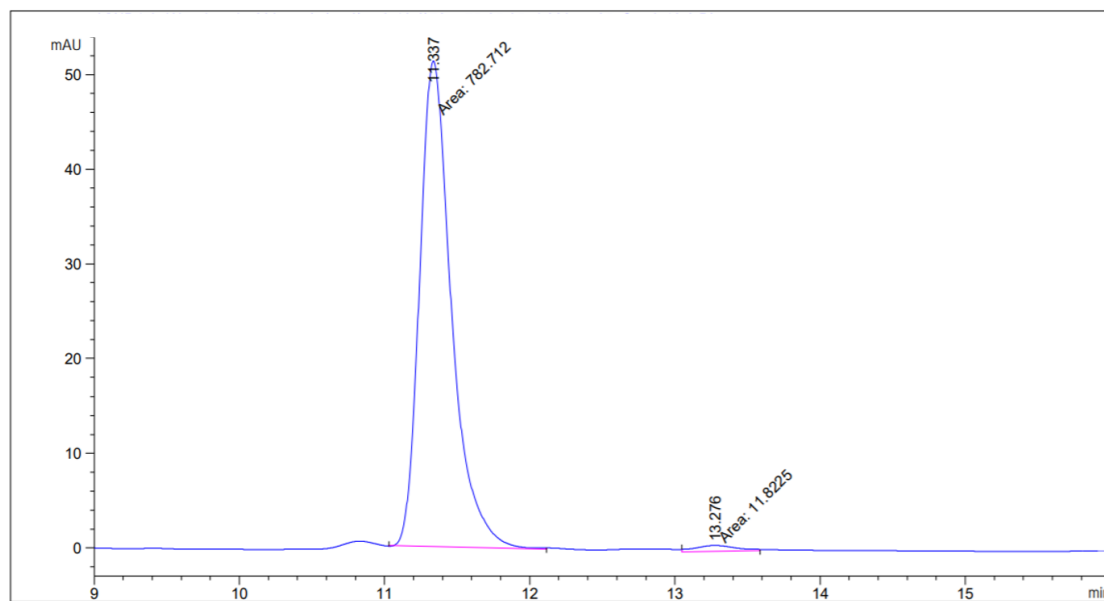
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.714	BB	0.8840	5010.55518	87.24580	51.4024
2	29.101	BB	1.1767	4737.14941	62.61428	48.5976



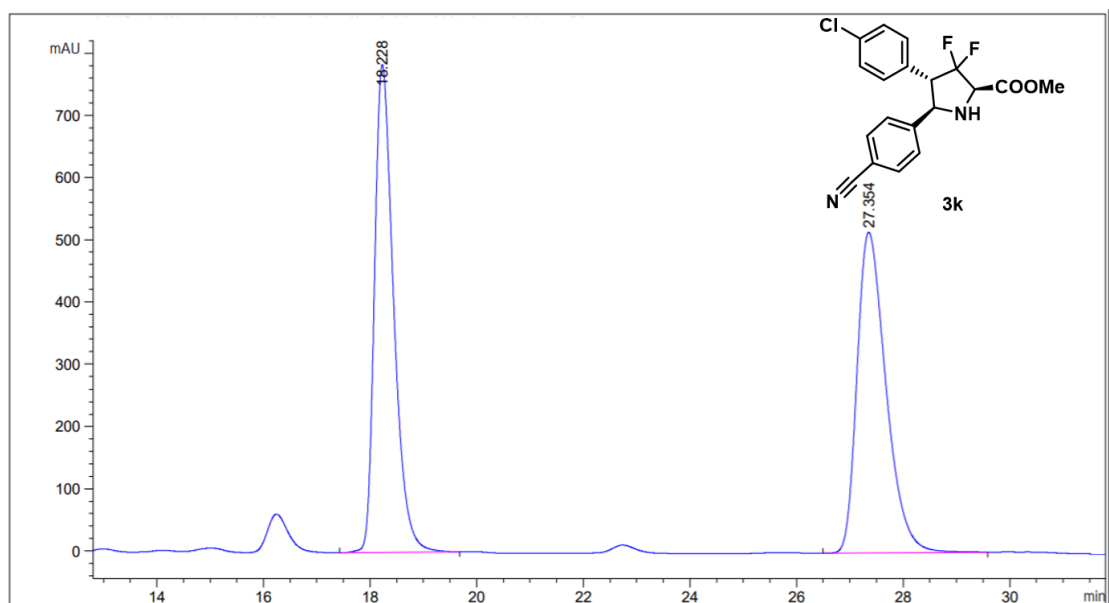
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.522	BB	0.8753	1.68994e4	299.51740	93.2246
2	28.894	BB	1.1757	1228.21338	15.78627	6.7754



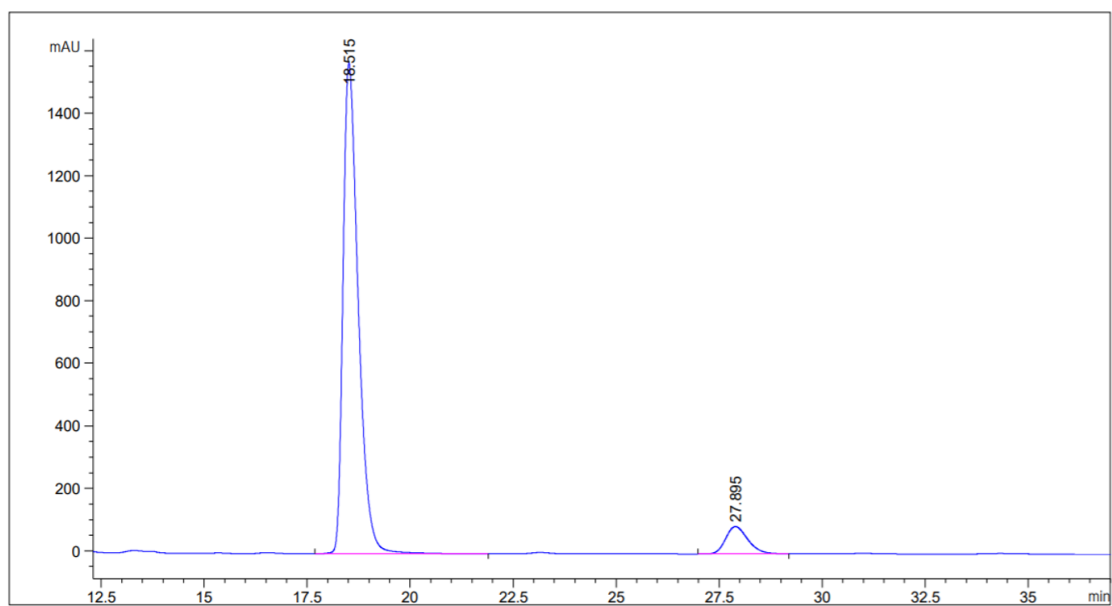
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.333	MM	0.2396	3718.37109	258.66351	50.6090
2	13.301	MM	0.2877	3628.88672	210.24377	49.3910



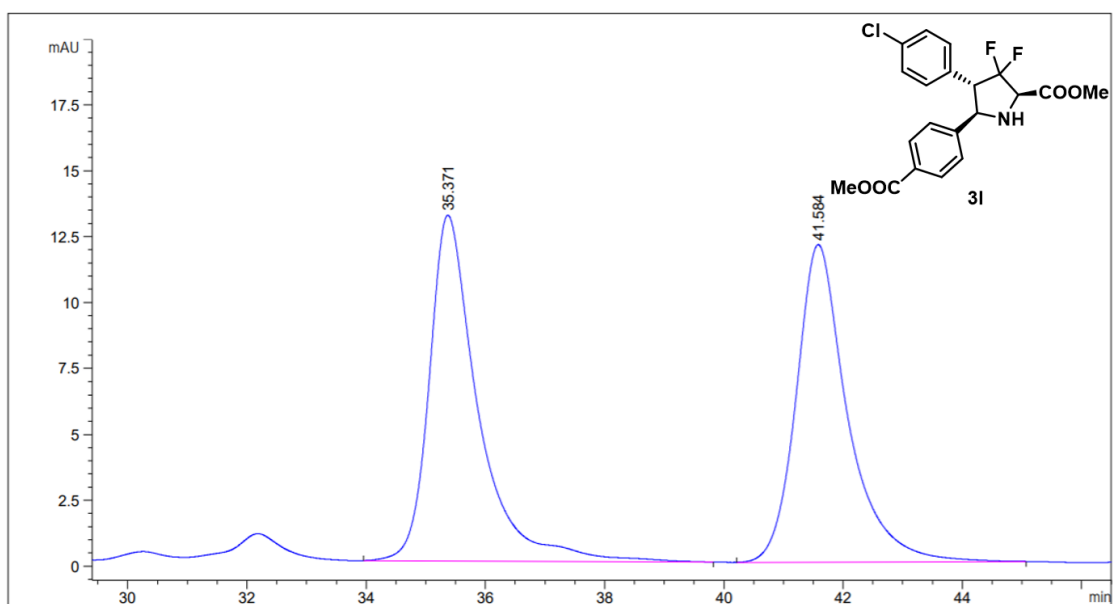
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.337	MM	0.2543	782.71173	51.30677	98.6180
2	13.276	MM	0.3324	10.96906	5.49933e-1	1.3820



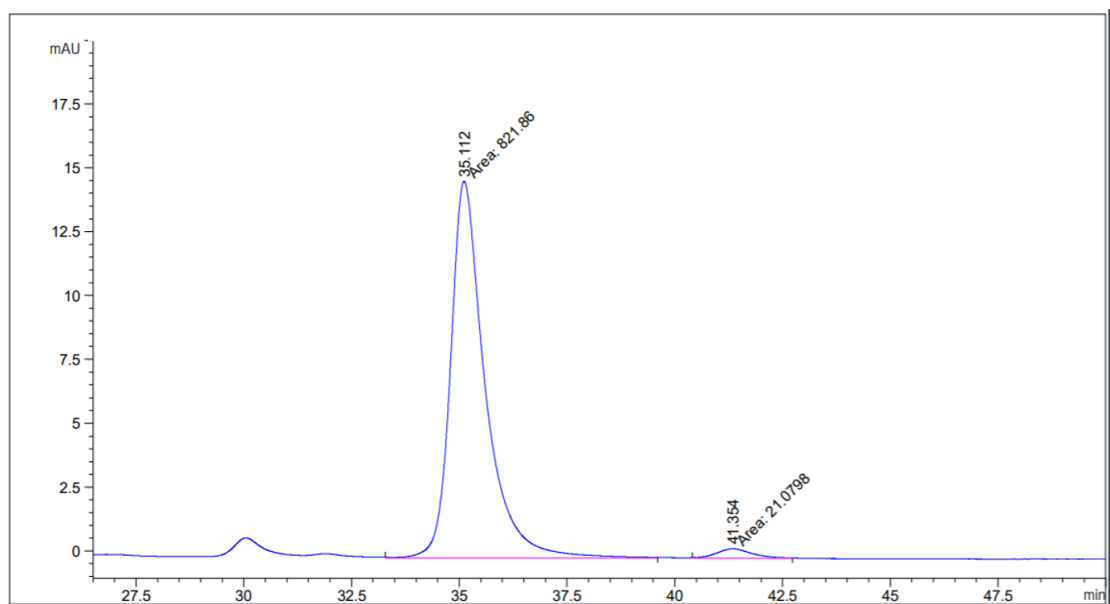
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.228	BB	0.3807	1.95488e4	784.42096	50.1263
2	27.354	BB	0.5802	1.94502e4	515.49249	49.8737



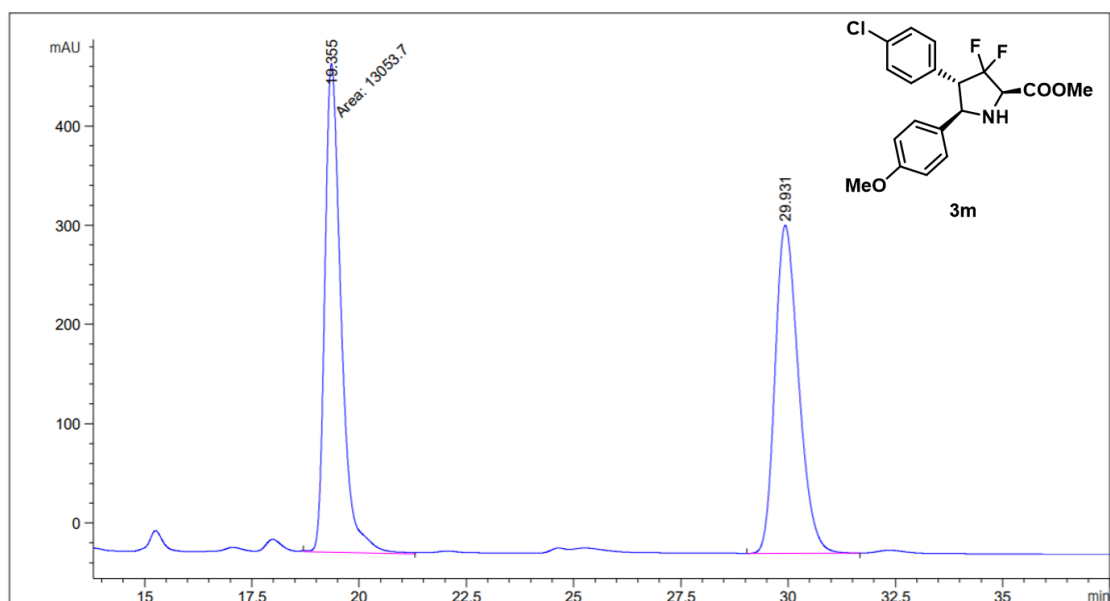
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.515	BB	0.3927	4.03170e4	1569.69702	92.5249
2	27.895	BB	0.5733	3257.23926	87.49548	7.4751



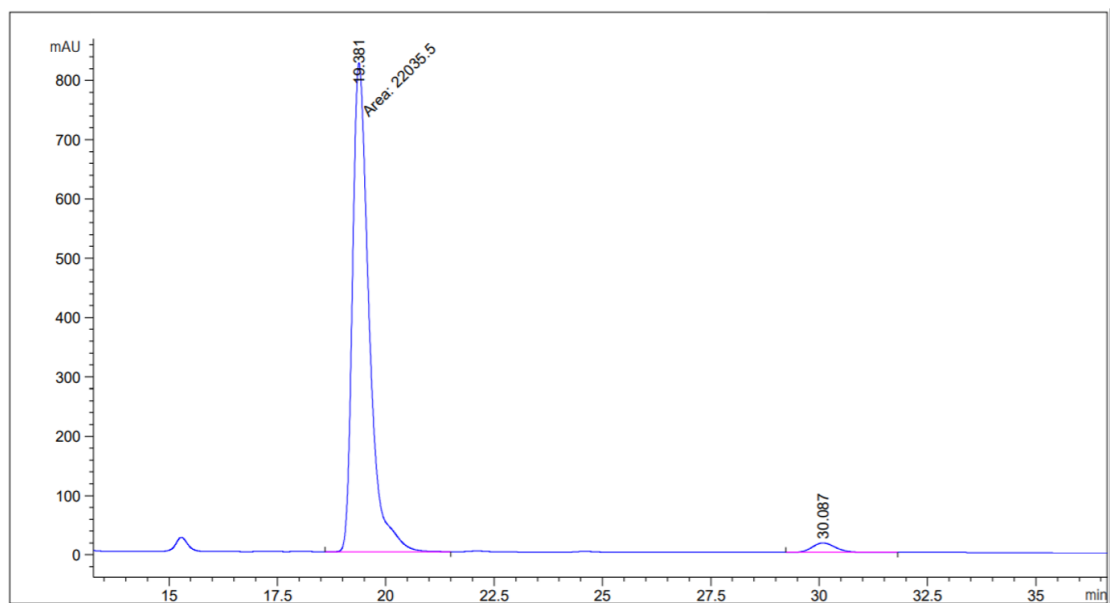
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.371	BB	0.8246	748.29633	13.11530	50.9656
2	41.584	BB	0.8695	719.94226	12.04173	49.0344



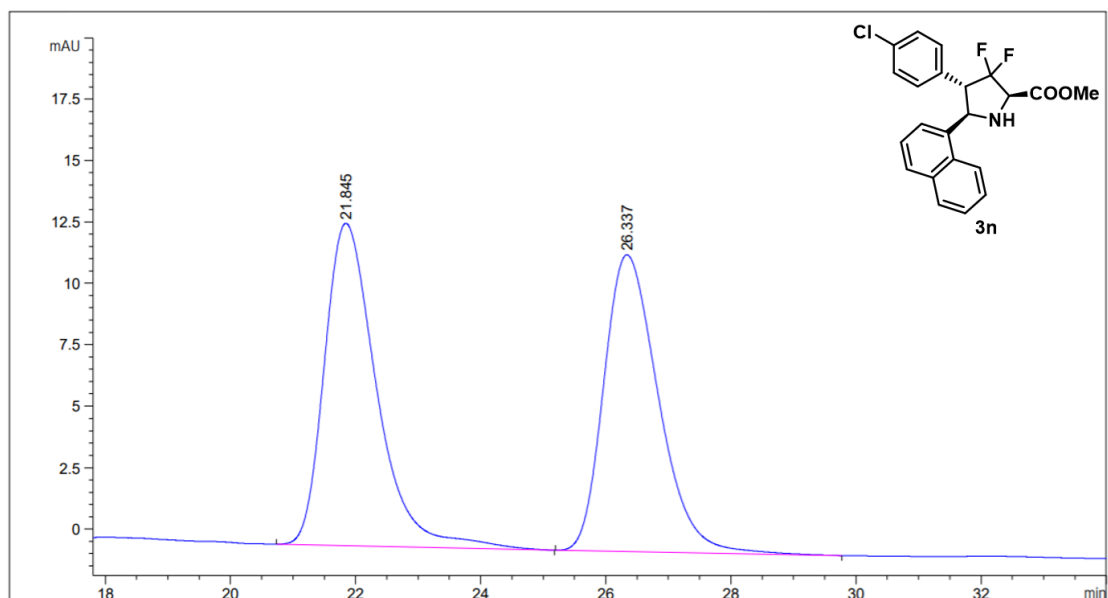
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.112	MM	0.9289	821.86047	14.74672	97.4992
2	41.354	MM	0.9531	21.07984	3.68608e-1	2.5008



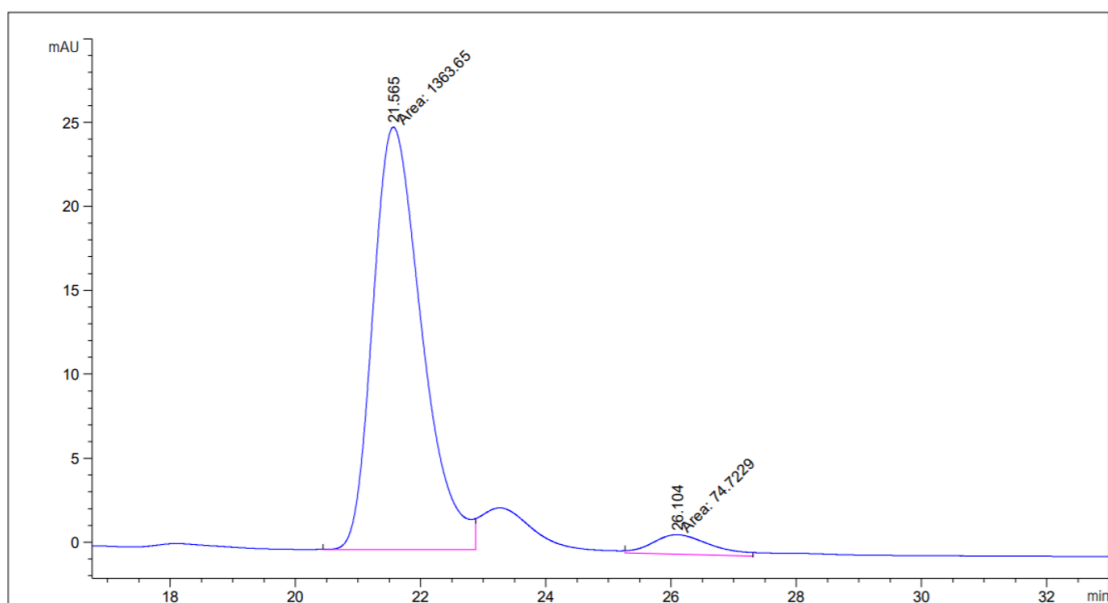
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.355	MM	0.4418	1.30537e4	492.38742	50.8364
2	29.931	BB	0.5898	1.26241e4	330.38055	49.1636



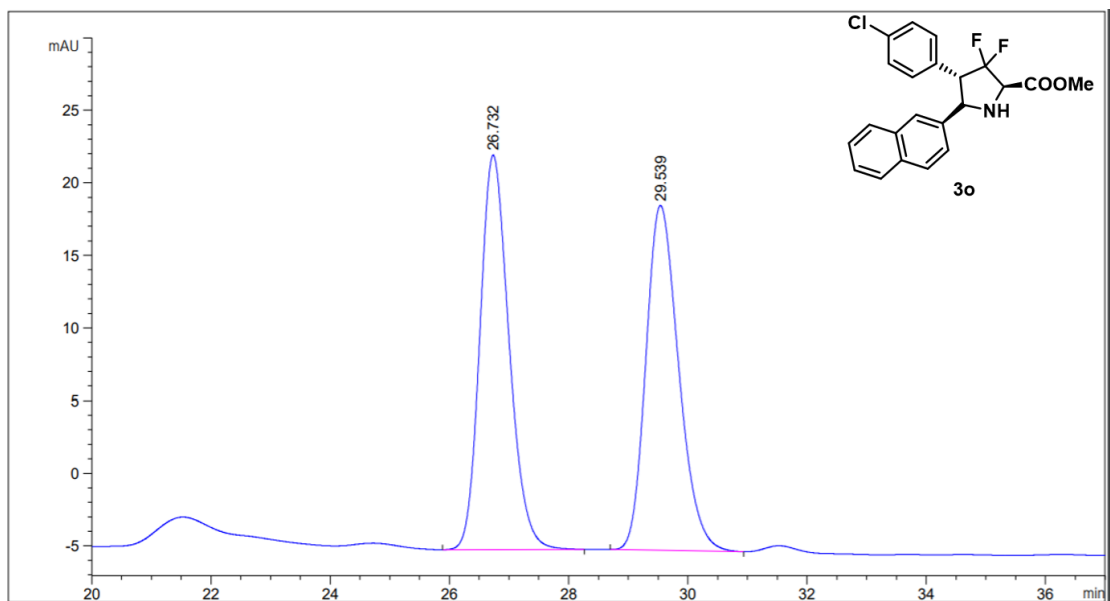
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.381	MM	0.4452	2.20355e4	824.87598	97.3303
2	30.087	BB	0.5767	604.41431	16.07235	2.6697



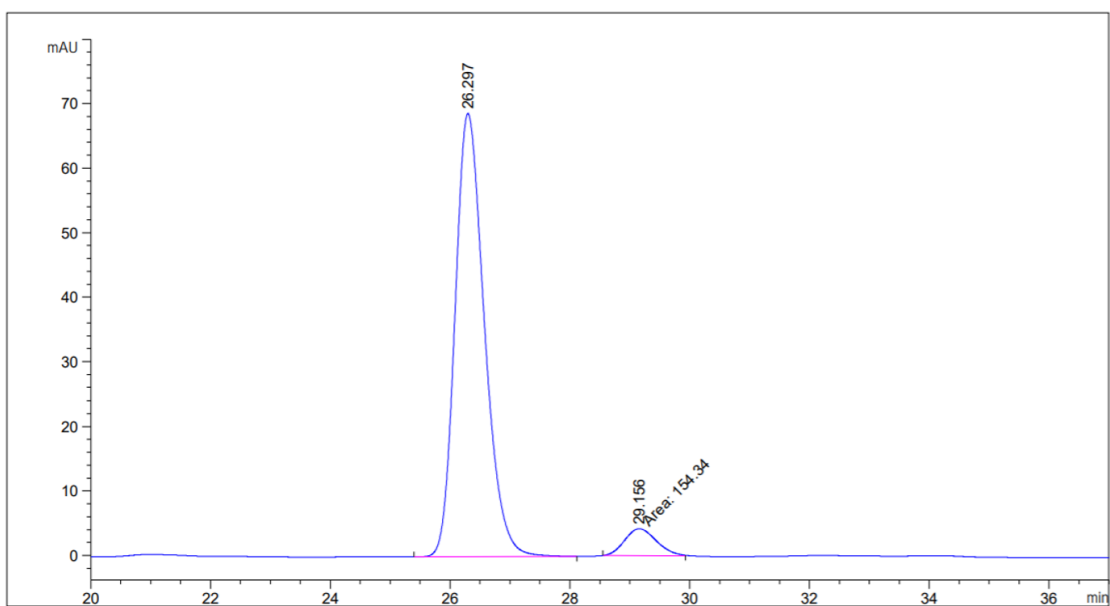
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.845	BB	0.8699	759.98621	13.11804	50.9824
2	26.337	BB	0.9200	730.69586	12.07465	49.0176



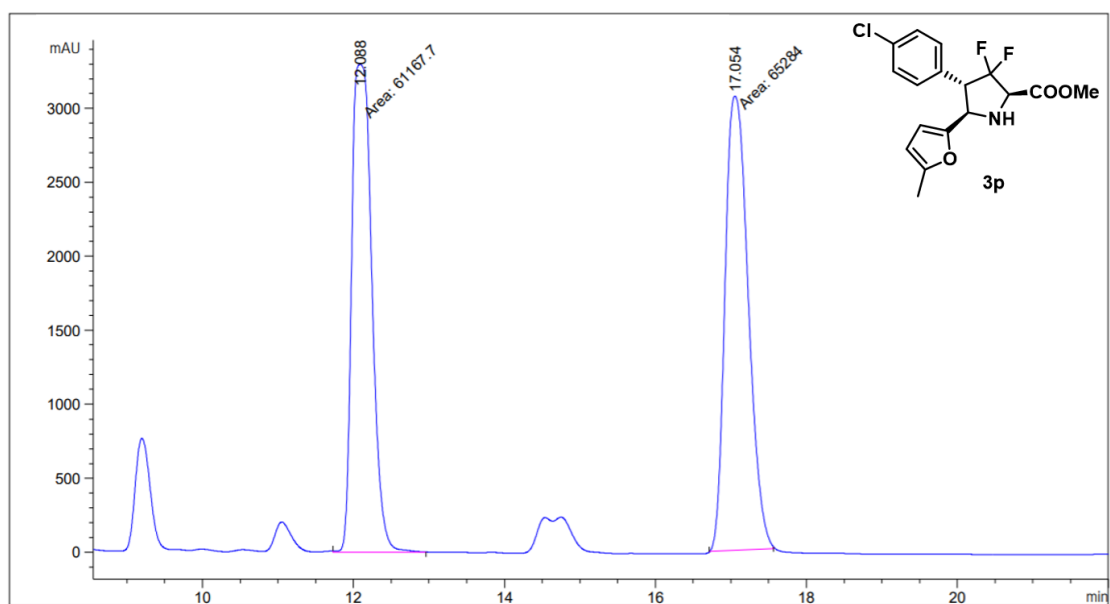
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.565	MF	0.9029	1363.64526	25.17267	94.8050
2	26.104	MM	1.0773	74.72290	1.15600	5.1950



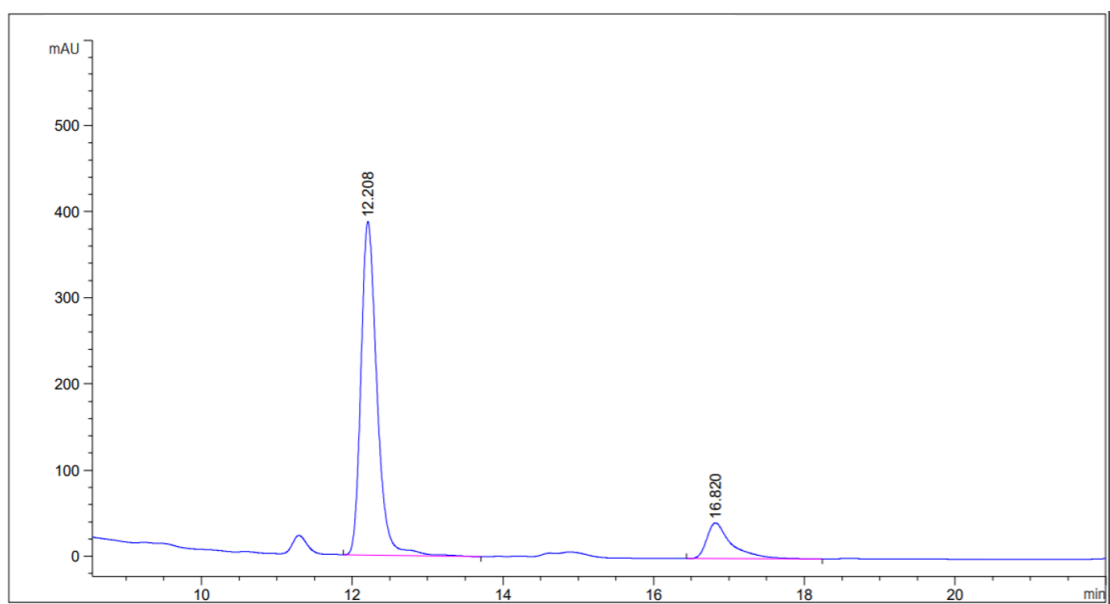
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.732	BB	0.5222	920.13245	27.16635	50.3445
2	29.539	BB	0.5919	907.54071	23.74678	49.6555



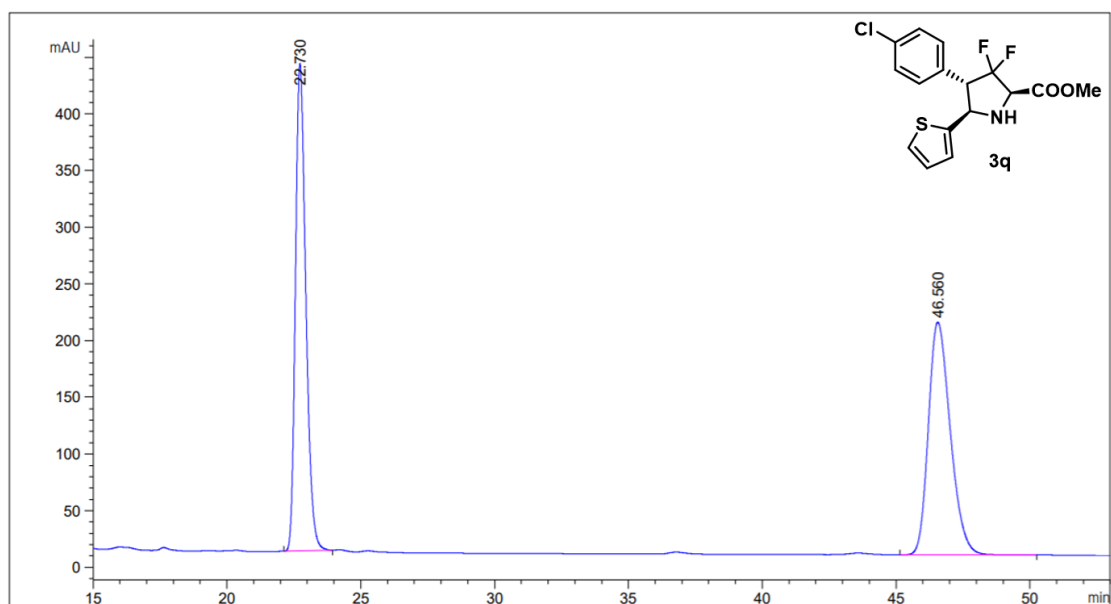
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.297	BB	0.5221	2330.99414	68.65752	93.7900
2	29.156	MM	0.6146	154.34045	4.18536	6.2100



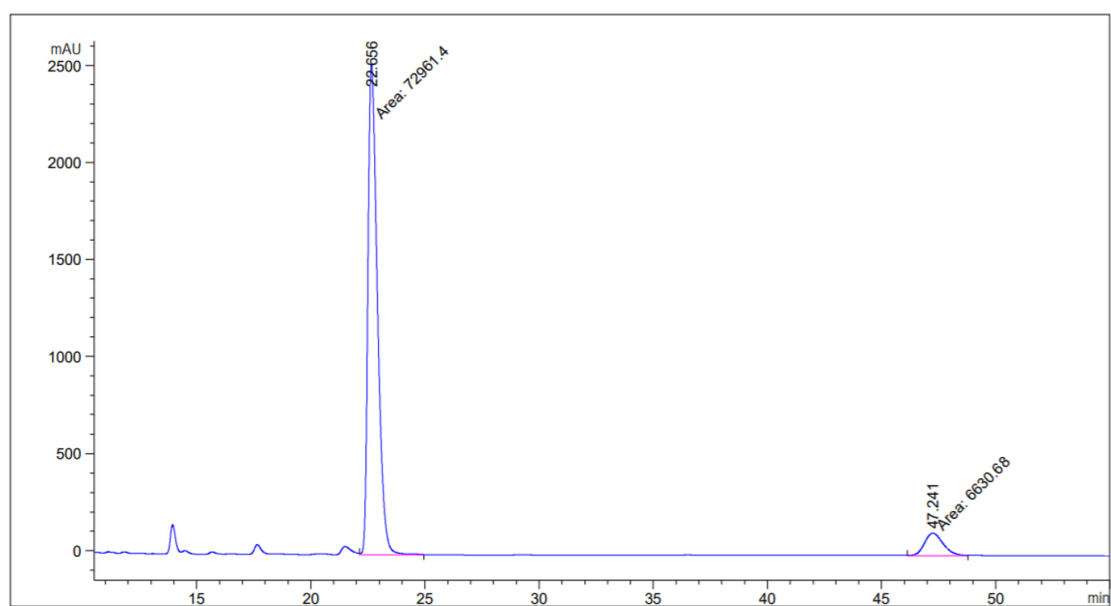
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.088	MM	0.3090	6.11677e4	3299.48706	48.3724
2	17.054	MM	0.3545	6.52840e4	3069.72583	51.6276



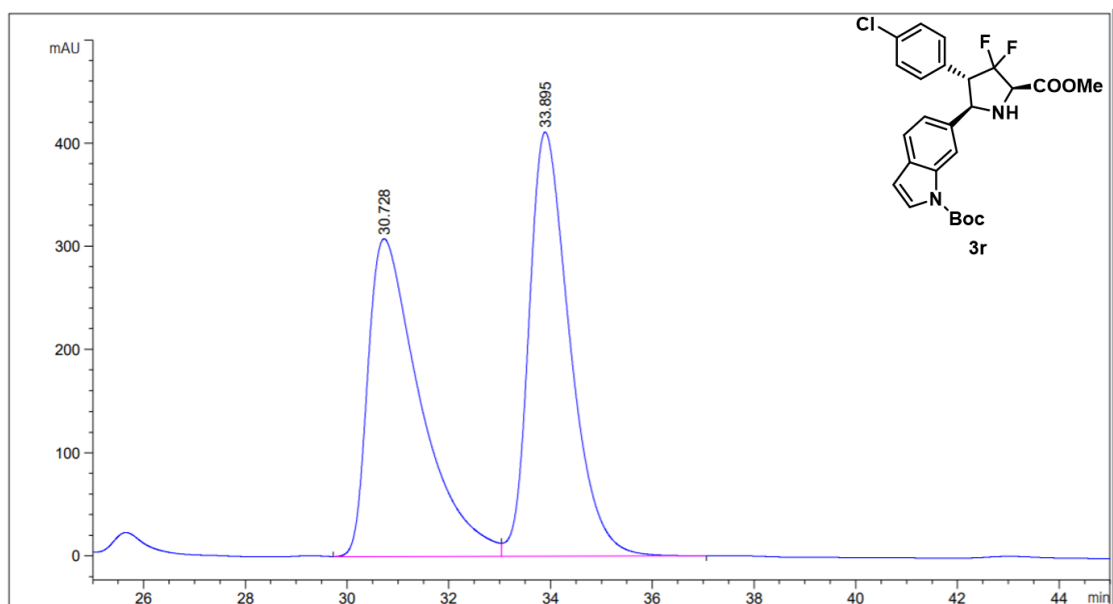
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.208	BV R	0.2249	5734.36426	386.89954	85.7059
2	16.820	BB	0.3295	956.38477	41.71555	14.2941



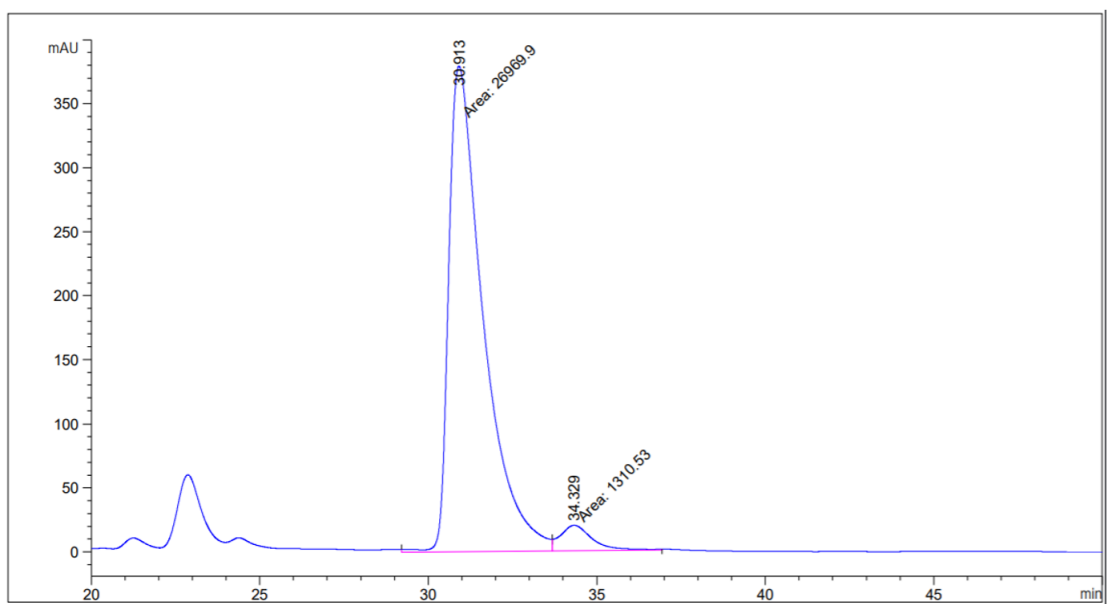
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.730	BB	0.4127	1.15584e4	429.90280	49.7772
2	46.560	BB	0.8761	1.16619e4	205.16594	50.2228



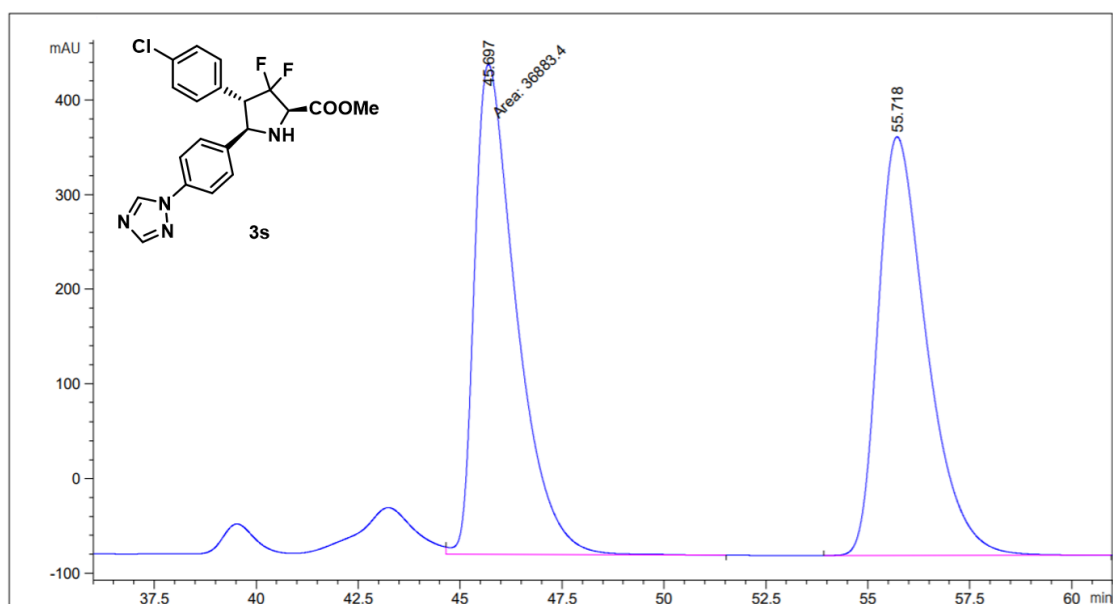
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.656	FM	0.4821	7.29614e4	2522.30249	91.8465
2	47.241	BB	0.8686	6476.99805	115.08098	8.1535



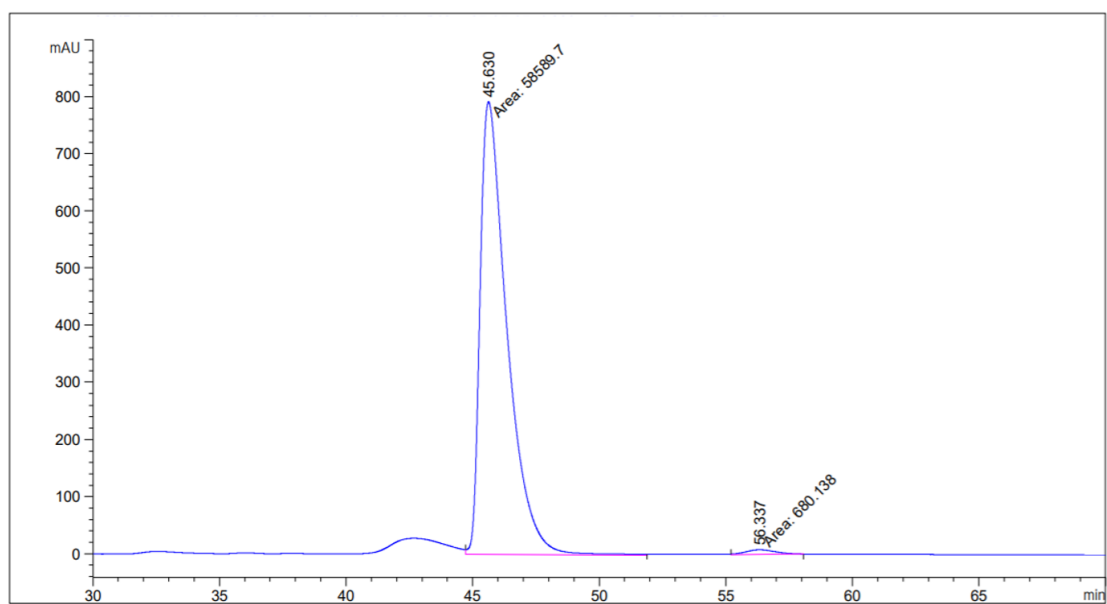
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.728	BV	1.0608	2.19628e4	307.67380	49.0583
2	33.895	VB	0.8426	2.28060e4	410.82809	50.9417



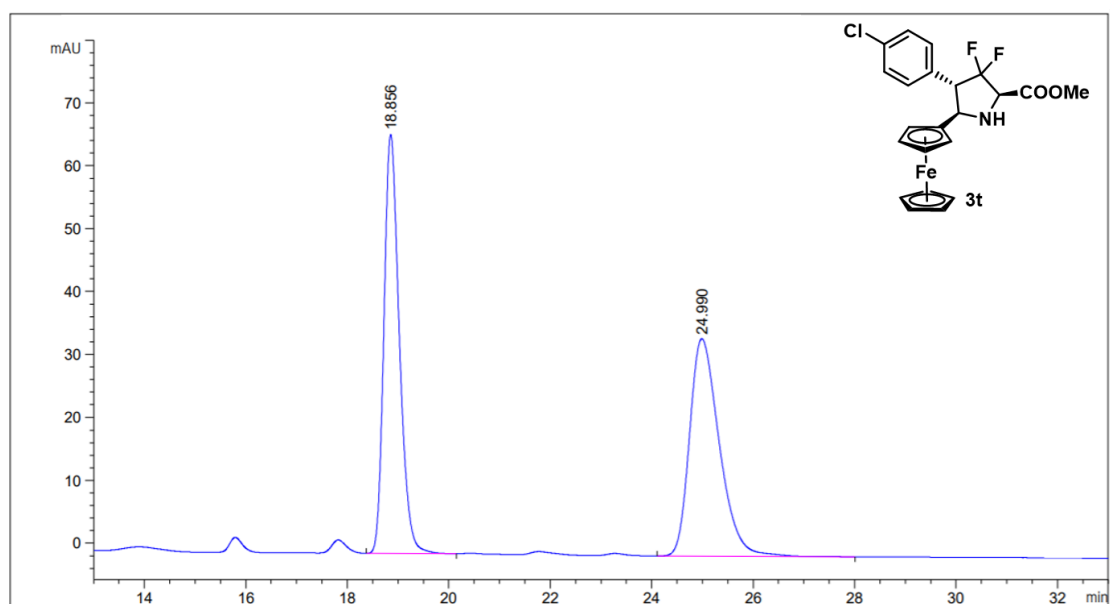
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.913	MF	1.1849	2.69699e4	379.34363	95.3659
2	34.329	FM	1.1004	1310.53442	19.84933	4.6341



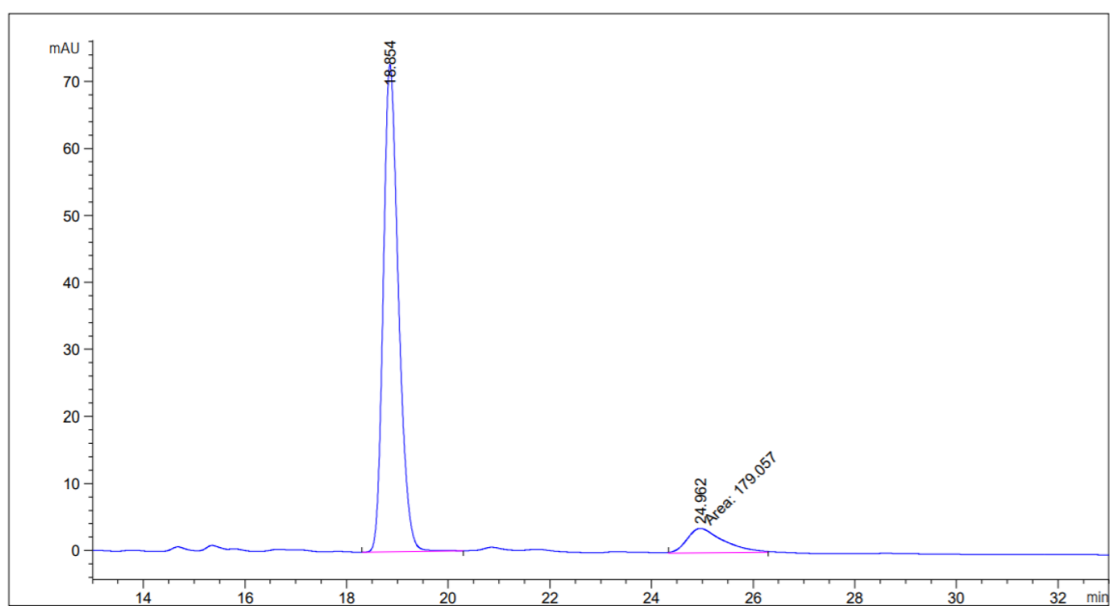
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	45.697	FM	1.1875	3.68834e4	517.65607	50.1656
2	55.718	BB	1.2565	3.66399e4	442.28625	49.8344



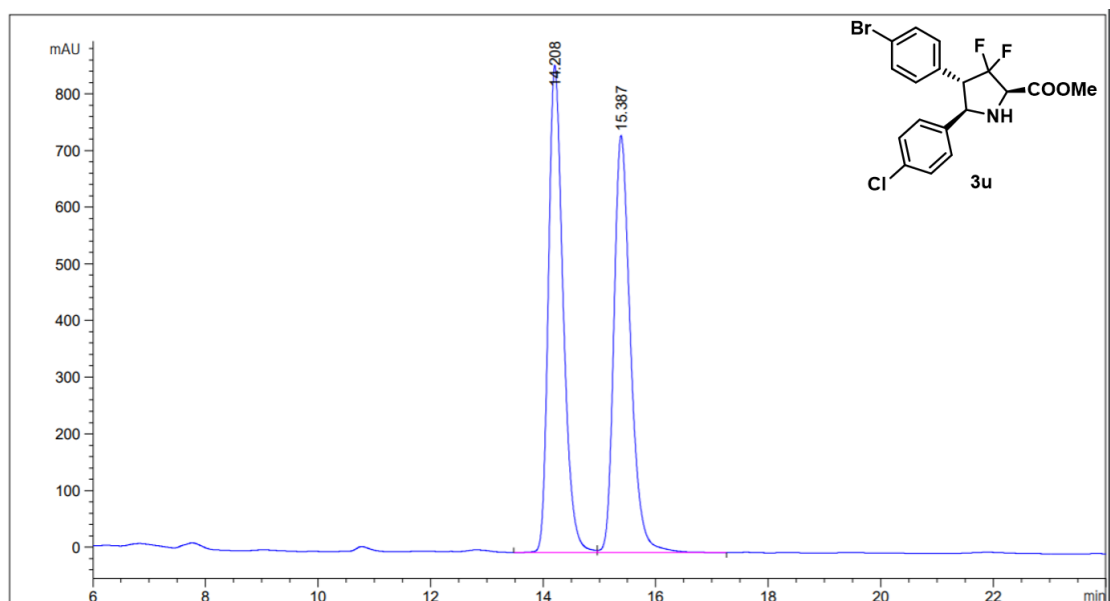
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	45.630	FM	1.2326	5.85897e4	792.21497	98.8376
2	56.337	BB	1.2327	689.05957	8.03332	1.1624



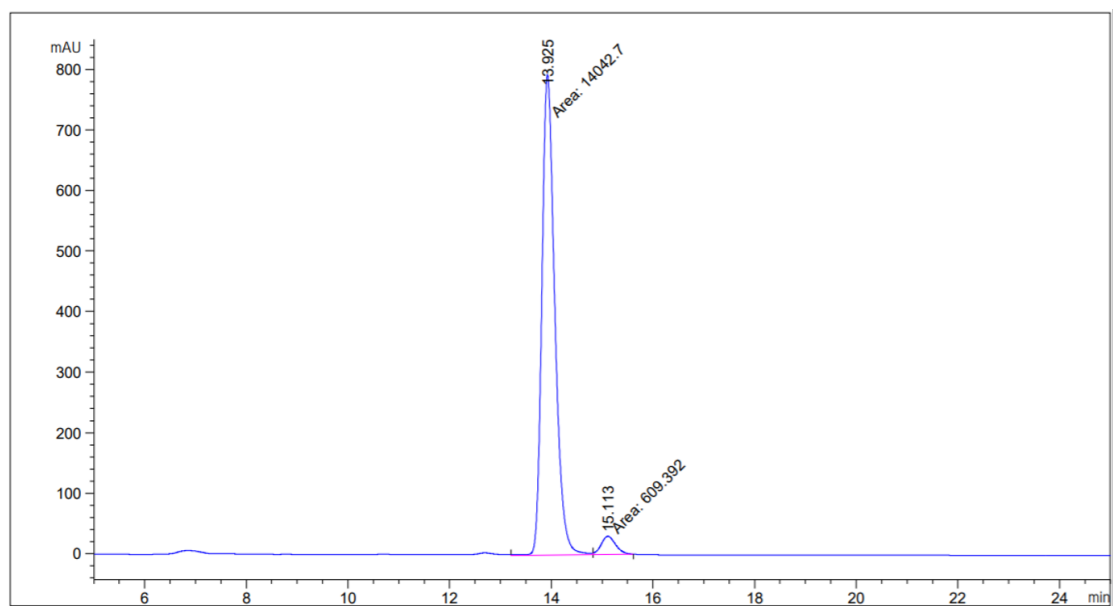
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.856	BB	0.3204	1401.45386	66.63299	49.9044
2	24.990	BB	0.6212	1406.82092	34.53979	50.0956



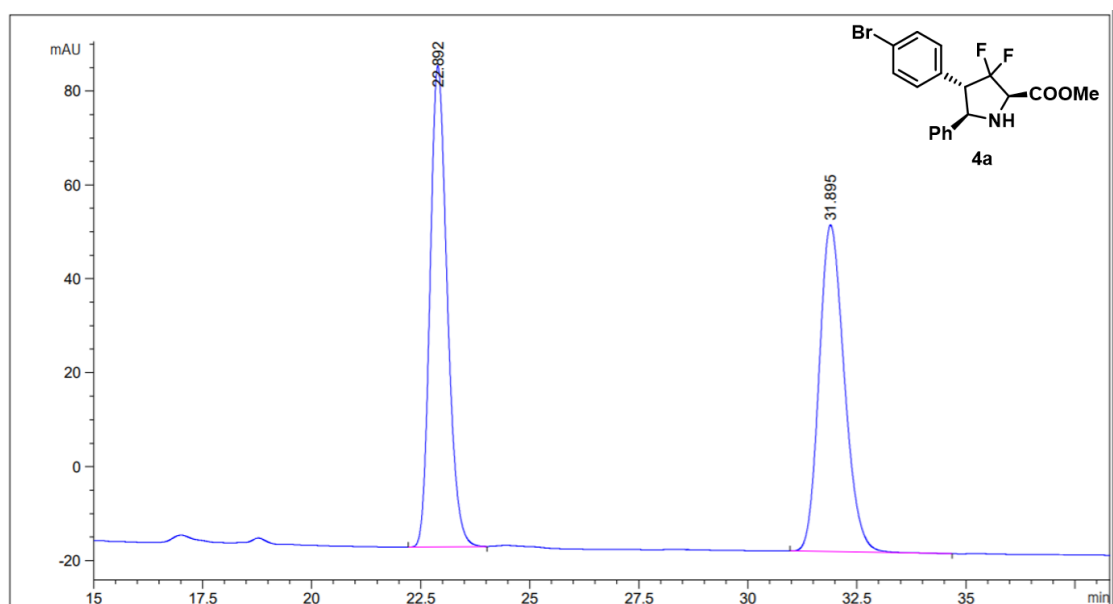
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.854	BB	0.3178	1514.03076	72.75957	88.6900
2	24.962	BB	0.7392	193.07315	3.67365	11.3100



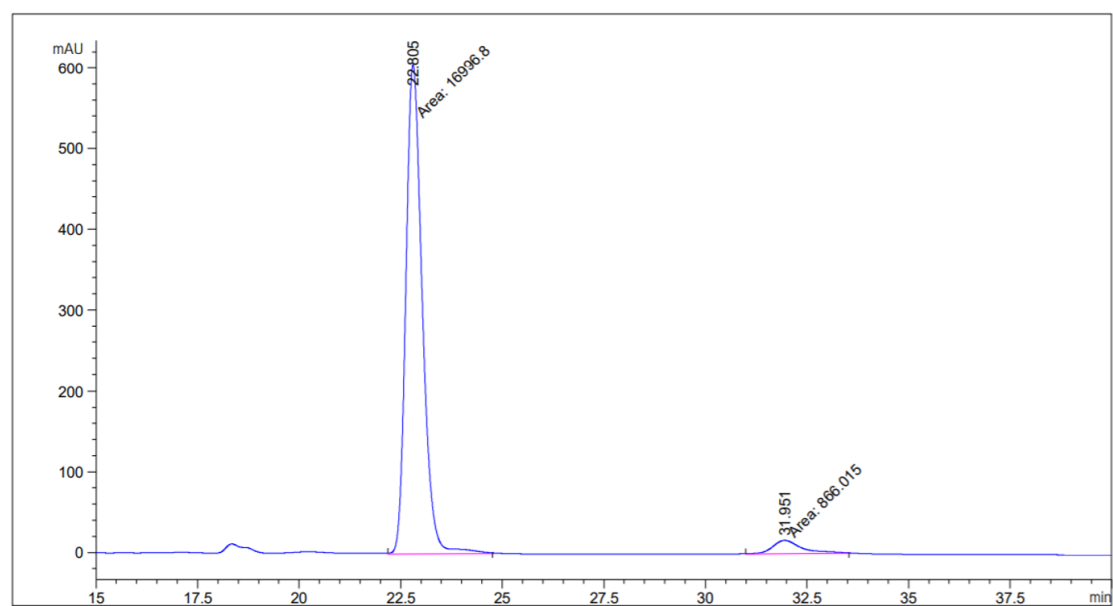
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.208	BV	0.2782	1.56415e4	859.79462	50.8562
2	15.387	VB	0.3136	1.51149e4	735.88098	49.1438



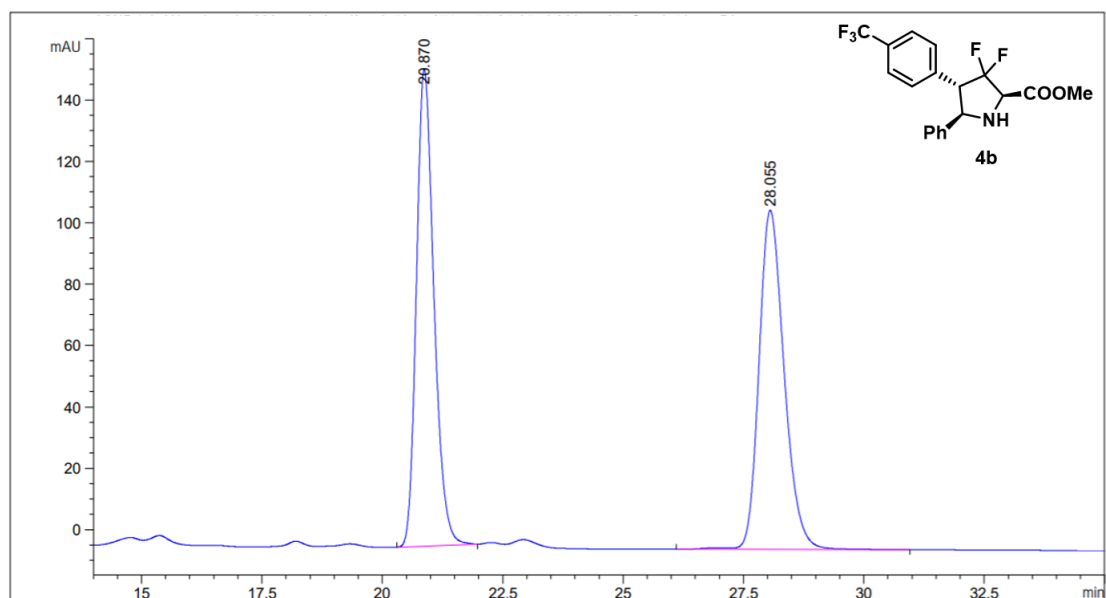
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.925	MF	0.2949	1.40427e4	793.56610	95.8409
2	15.113	FM	0.3333	609.39166	30.47589	4.1591



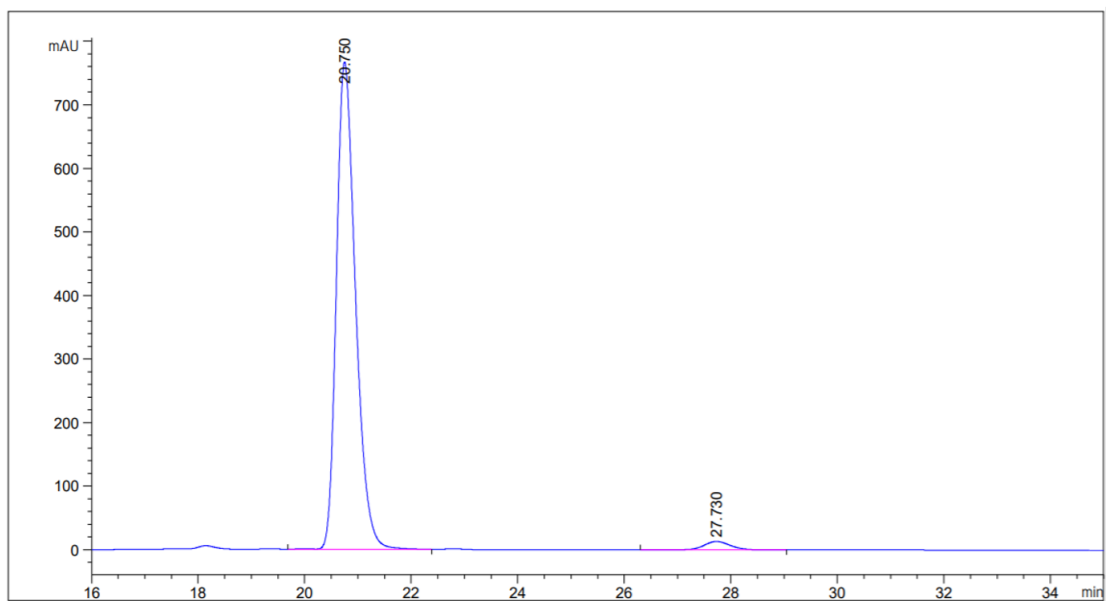
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.892	BB	0.4203	2805.99634	102.51474	50.0976
2	31.895	BB	0.6207	2795.06177	69.56994	49.9024



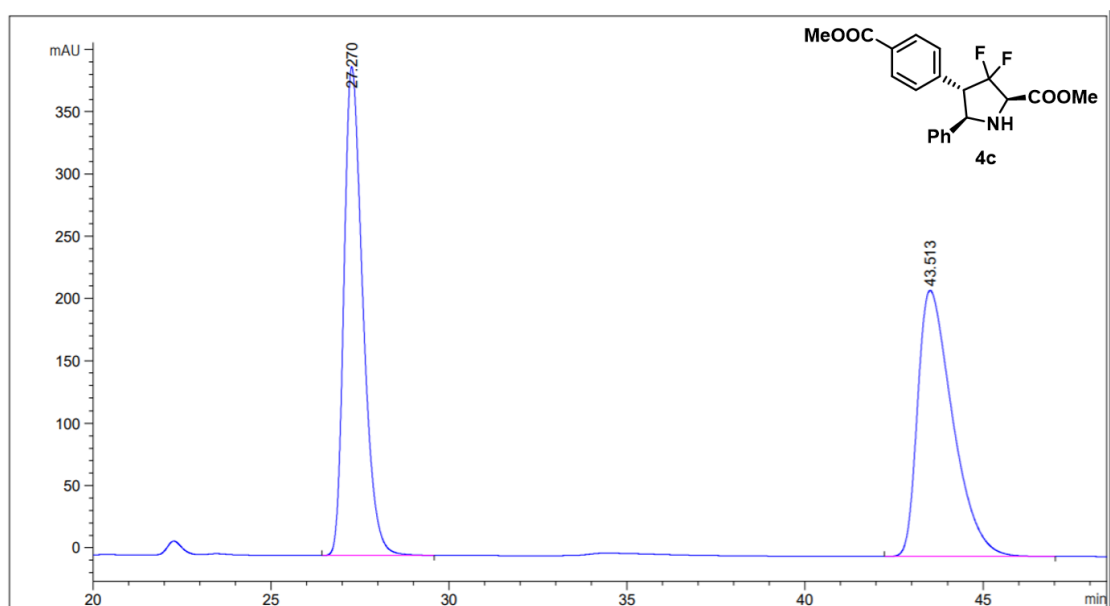
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.805	MM	0.4764	1.73646e4	607.44727	95.2497
2	31.951	MM	0.8593	866.01477	16.79651	4.7503



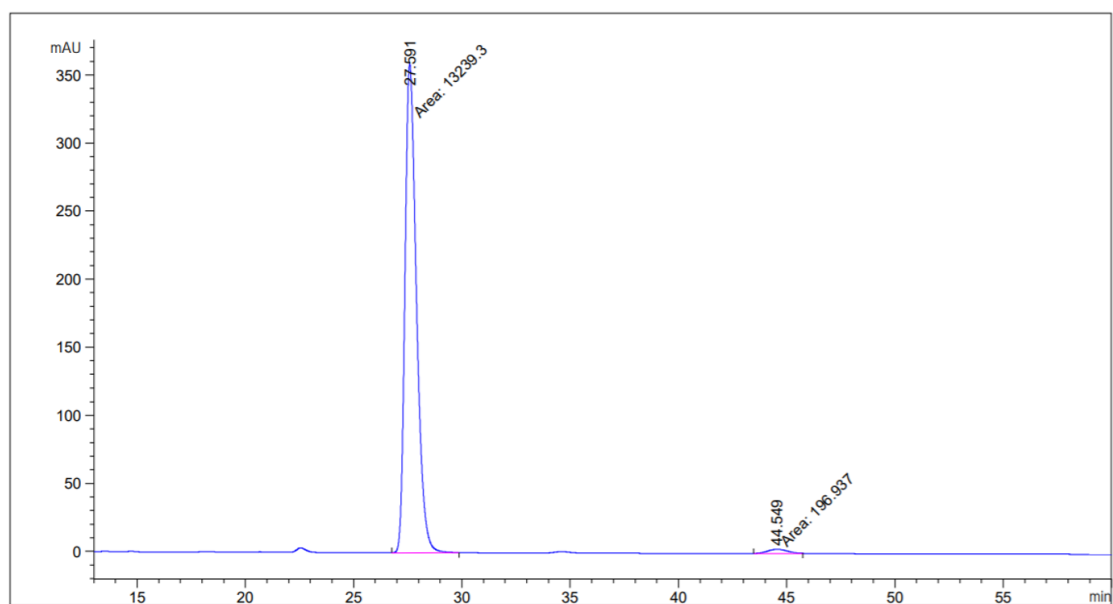
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.870	BB	0.3873	3922.51245	155.49594	49.3643
2	28.055	BB	0.5580	4023.54102	110.45875	50.6357



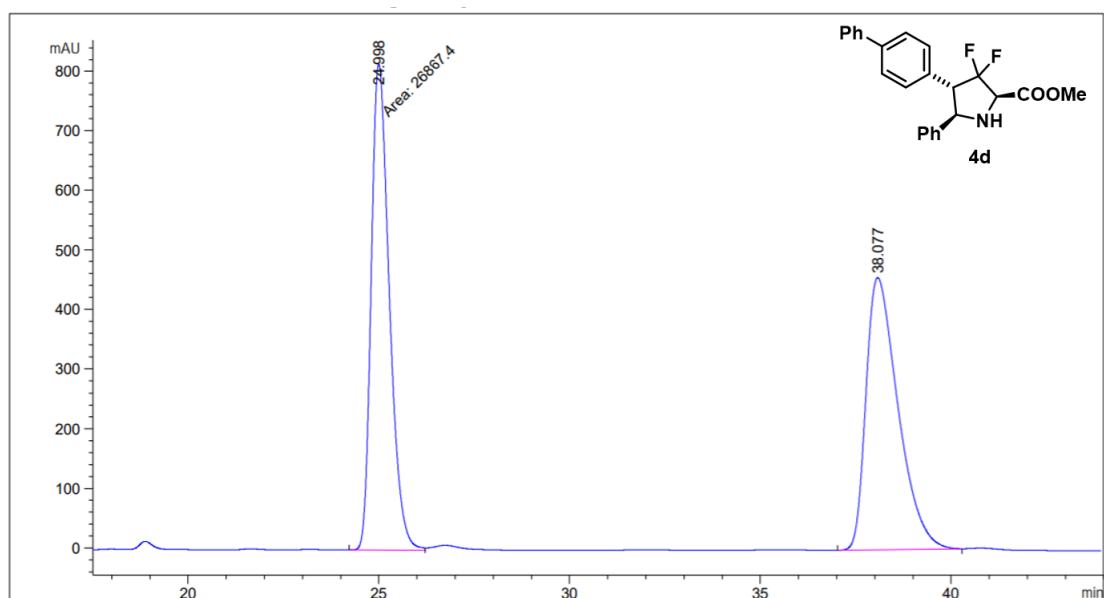
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.750	VB R	0.3812	1.90727e4	766.85950	97.5618
2	27.730	BB	0.5363	476.65494	13.42285	2.4382



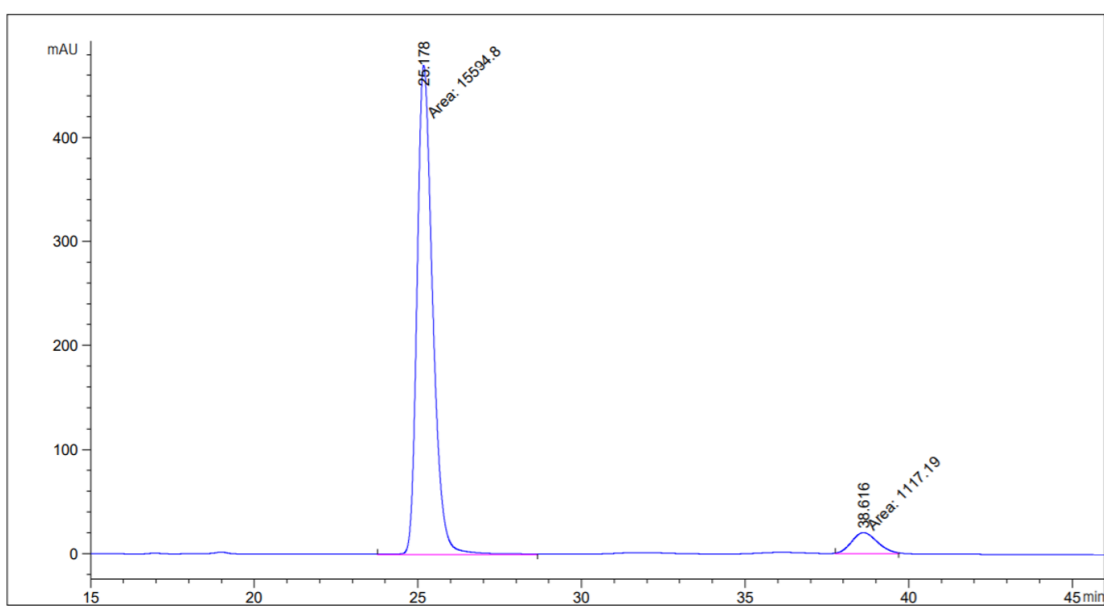
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.270	BB	0.5648	1.44533e4	392.32571	49.8411
2	43.513	BB	1.0347	1.45455e4	213.52693	50.1589



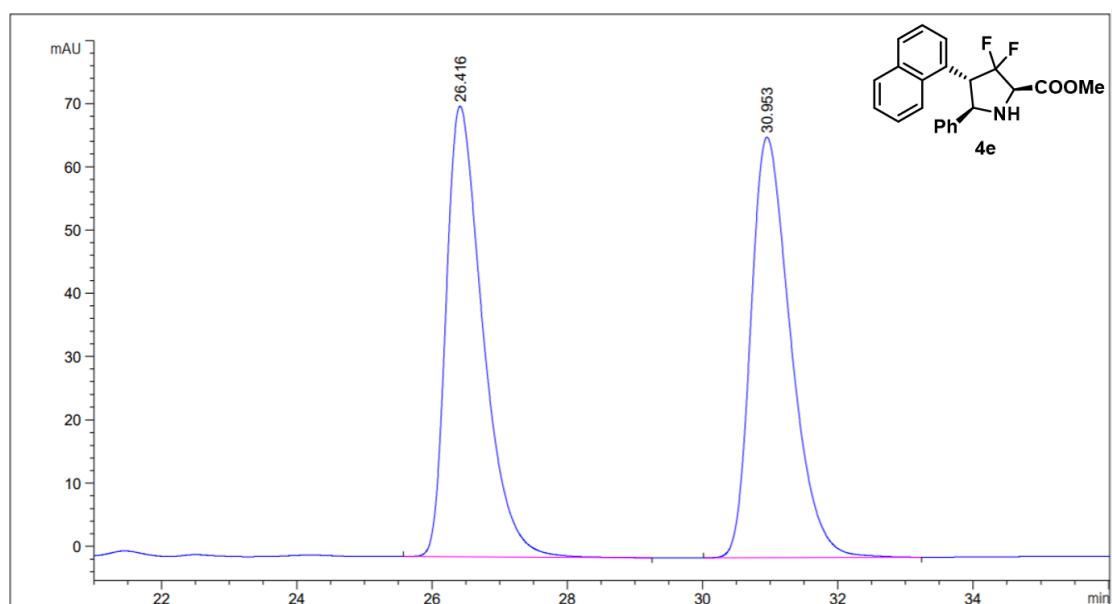
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.591	MM	0.6143	1.32393e4	359.20303	98.5343
2	44.549	MM	1.0558	196.93733	3.10892	1.4657



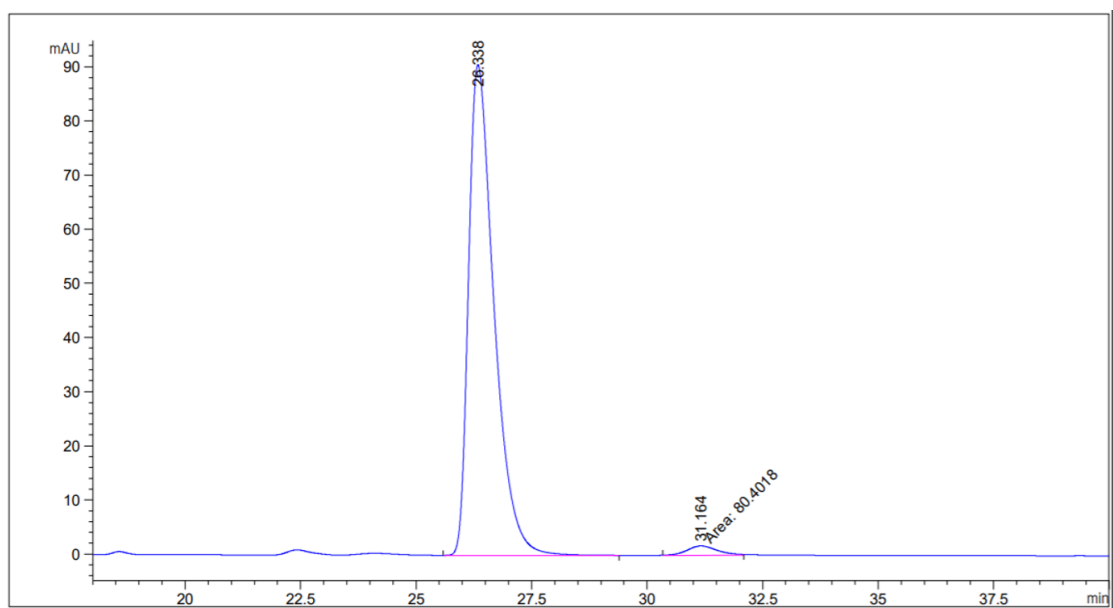
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.998	MF	0.5486	2.68674e4	816.27216	50.2488
2	38.077	BB	0.8893	2.66013e4	456.21490	49.7512



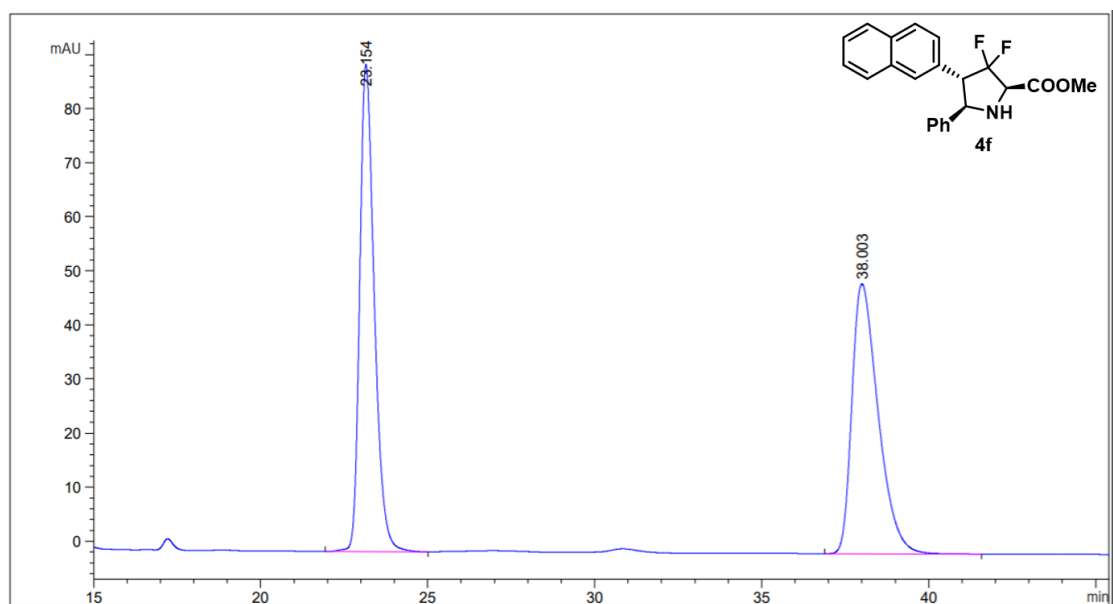
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.178	MM	0.5517	1.55948e4	471.10153	93.1415
2	38.616	BB	0.8624	1148.33301	20.37812	6.8585



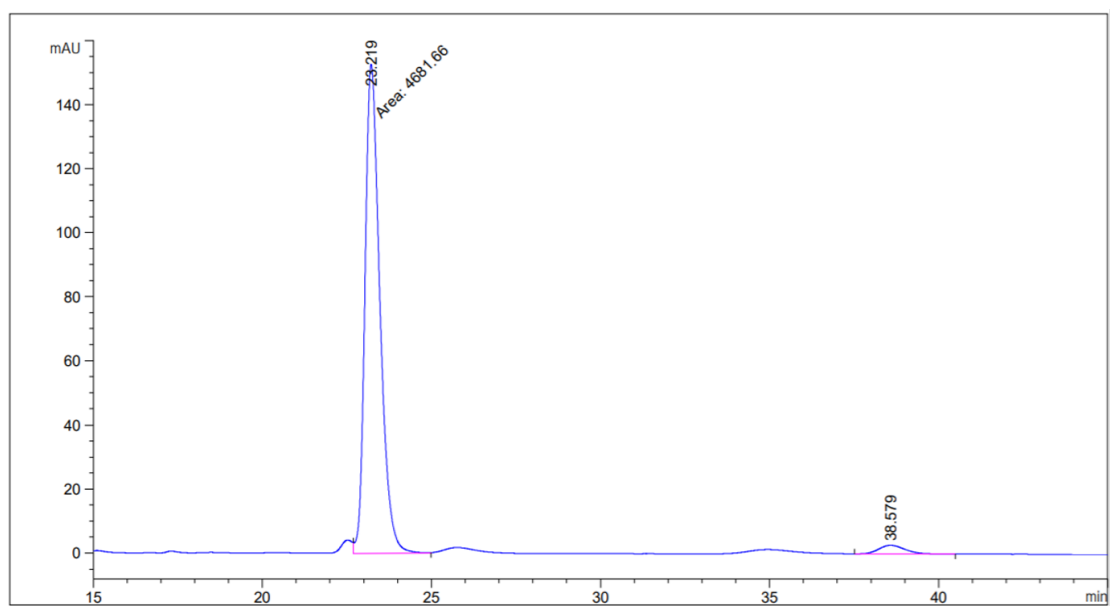
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.416	BB	0.5703	2675.38989	71.21672	49.6464
2	30.953	BB	0.6262	2713.50464	66.48101	50.3536



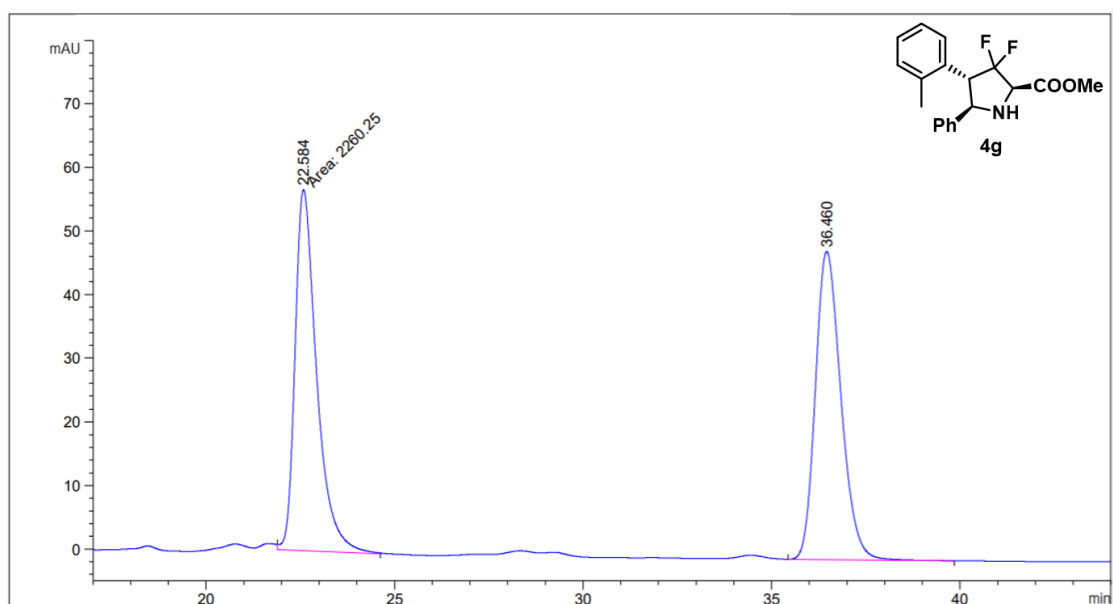
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.338	BB	0.5817	3477.49951	90.61531	97.6792
2	31.164	BB	0.6567	82.62161	1.73460	2.3208



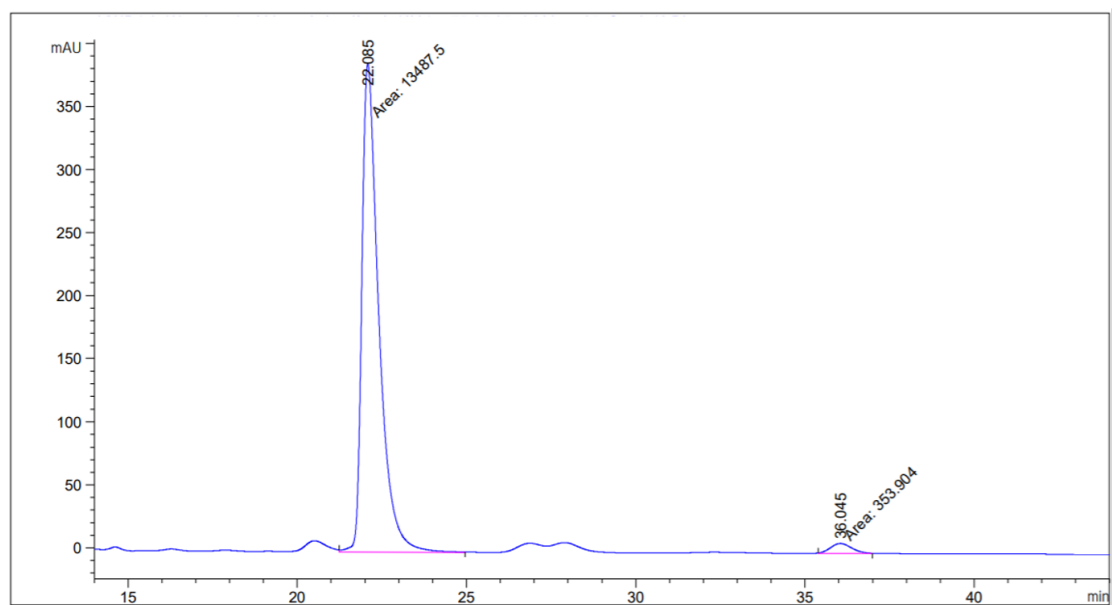
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.154	BB	0.4651	2742.40186	90.09287	50.1673
2	38.003	BB	0.8328	2724.11279	49.90539	49.8327



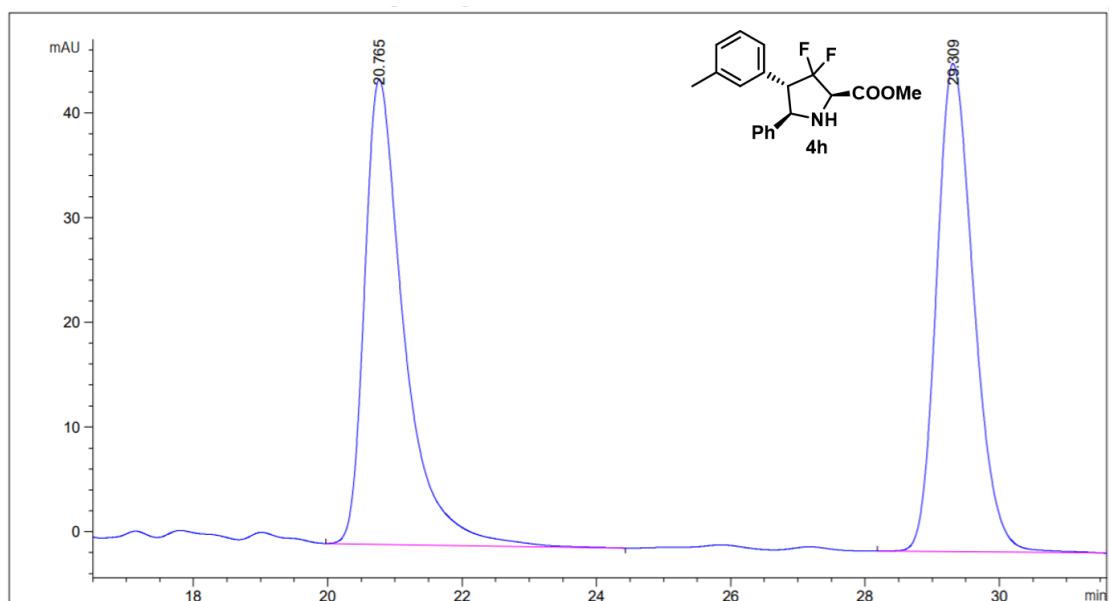
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.219	FM	0.5110	4681.65771	152.68381	96.9604
2	38.579	BB	0.7587	146.76462	2.72347	3.0396



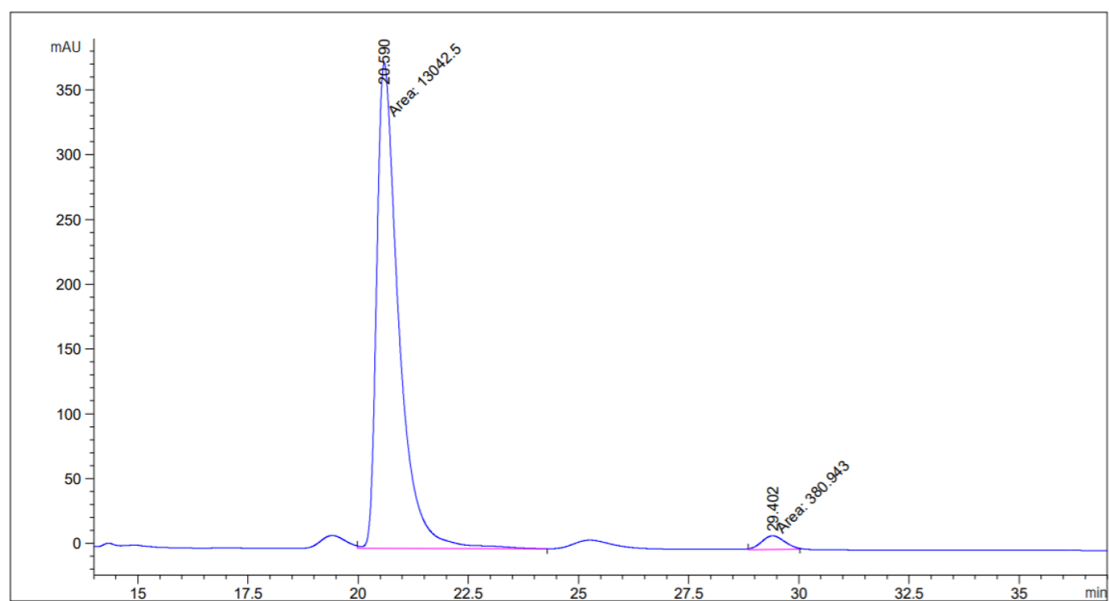
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.584	BB	0.5903	2190.65283	56.13698	48.9624
2	36.460	BB	0.7288	2283.49756	48.45411	51.0376



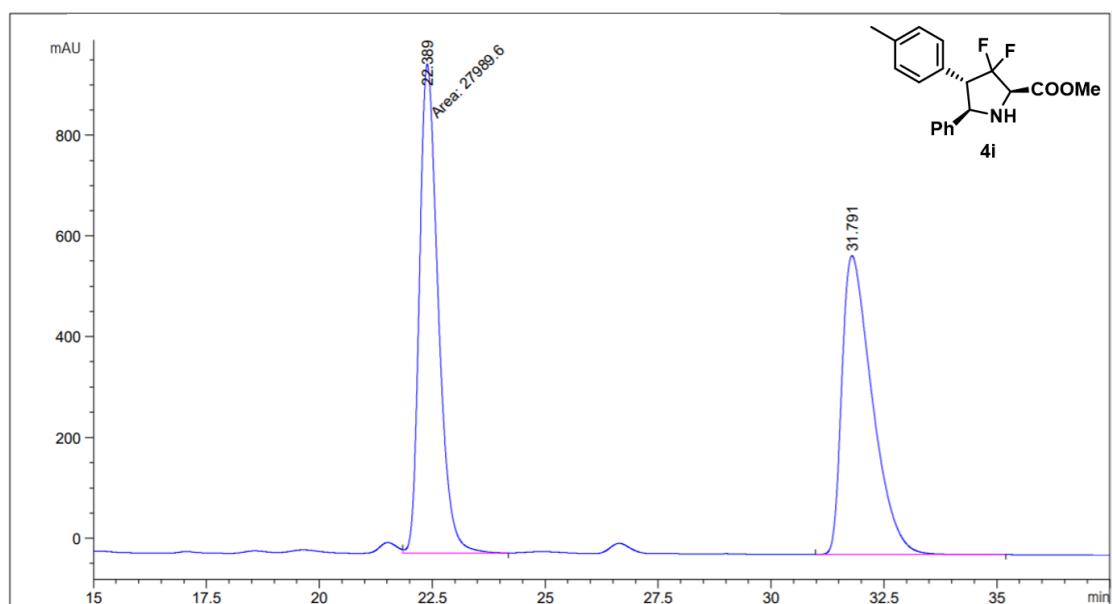
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.085	FM	0.5805	1.34801e4	387.01959	97.3744
2	36.045	BB	0.6917	363.47668	8.02012	2.6256



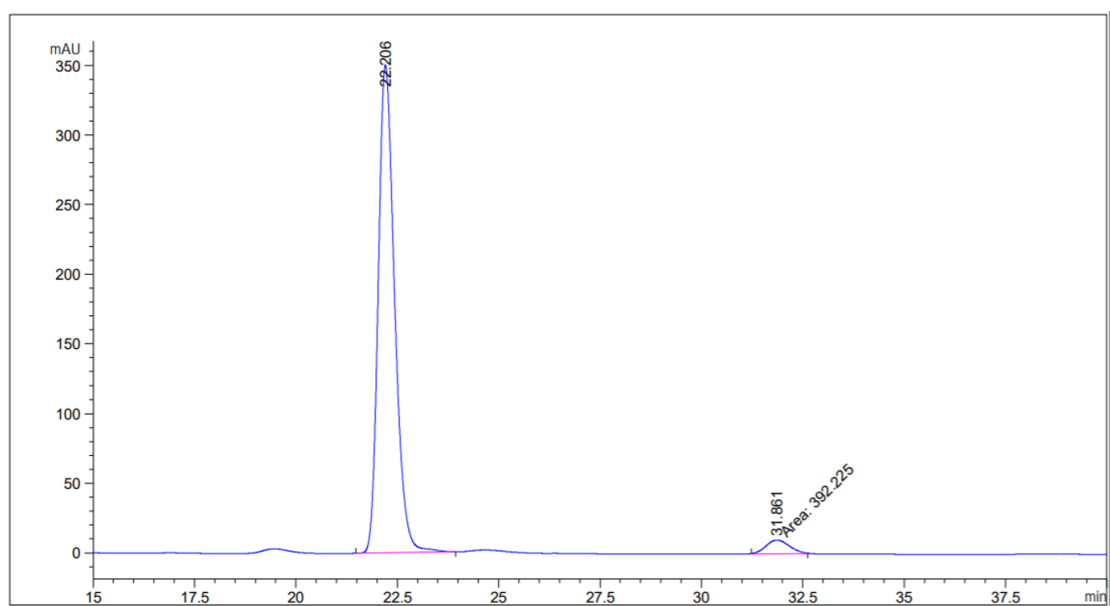
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.765	BB	0.6068	1815.32410	44.41731	50.3778
2	29.309	BBA	0.5913	1788.09460	46.63717	49.6222



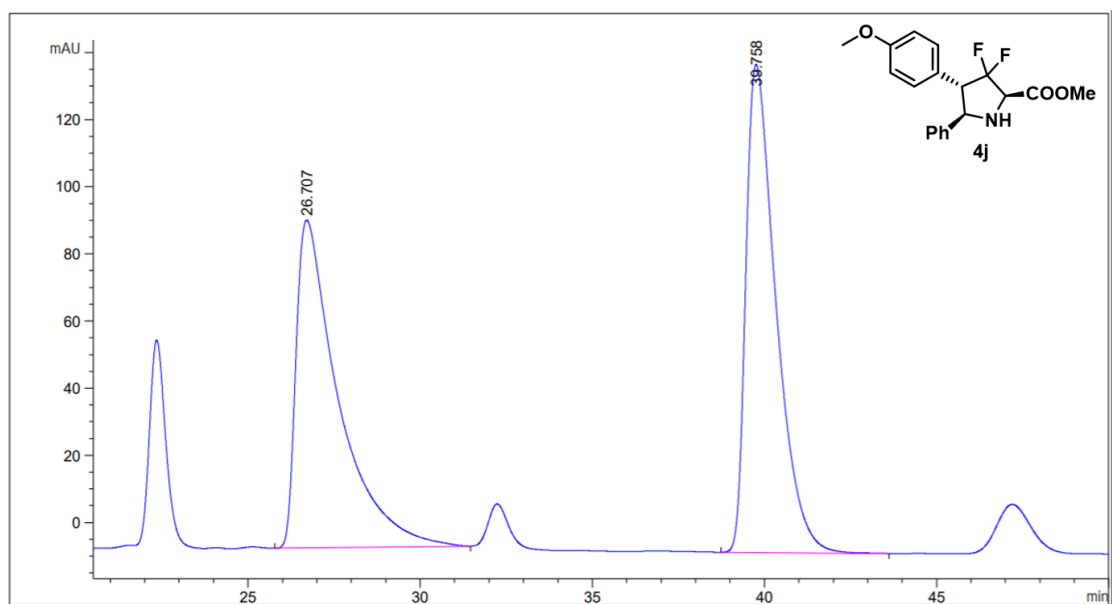
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.590	FM	0.5797	1.30425e4	374.97696	97.0308
2	29.402	BB	0.5809	399.11191	10.63389	2.9692



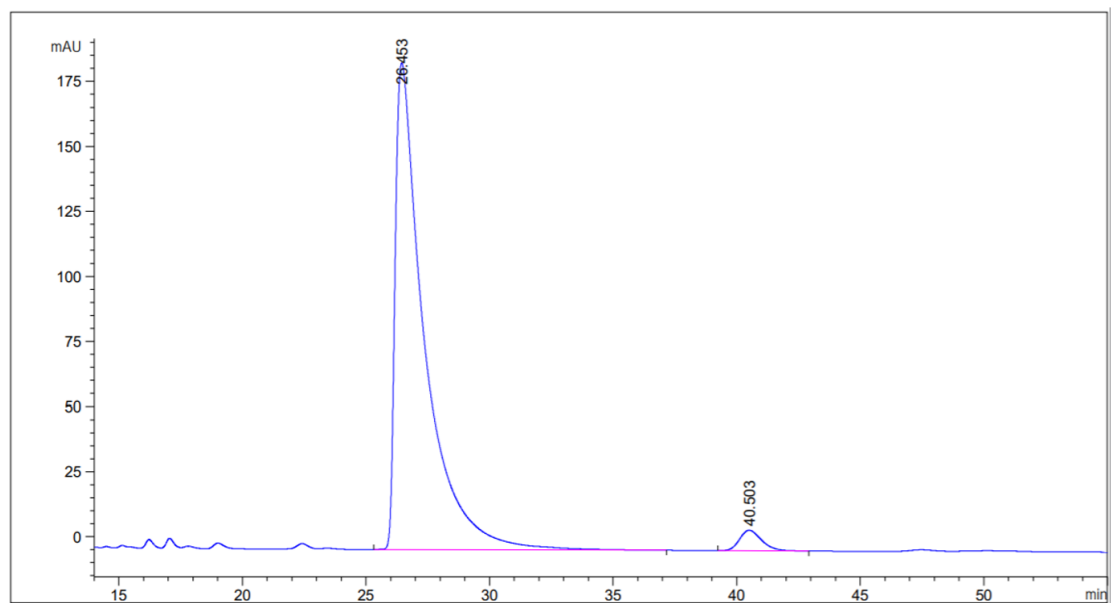
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.389	FM	0.4805	2.79896e4	970.76990	50.3603
2	31.791	BB	0.7048	2.75891e4	592.96344	49.6397



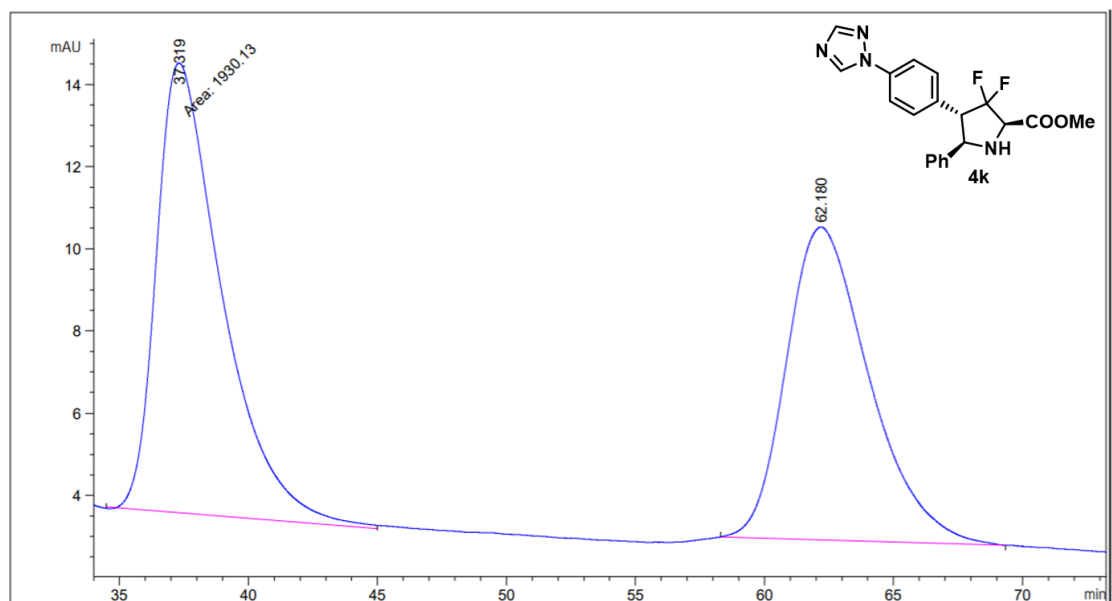
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.206	BB	0.4308	9805.76758	350.05777	96.1539
2	31.861	MM	0.6634	392.22479	9.85325	3.8461



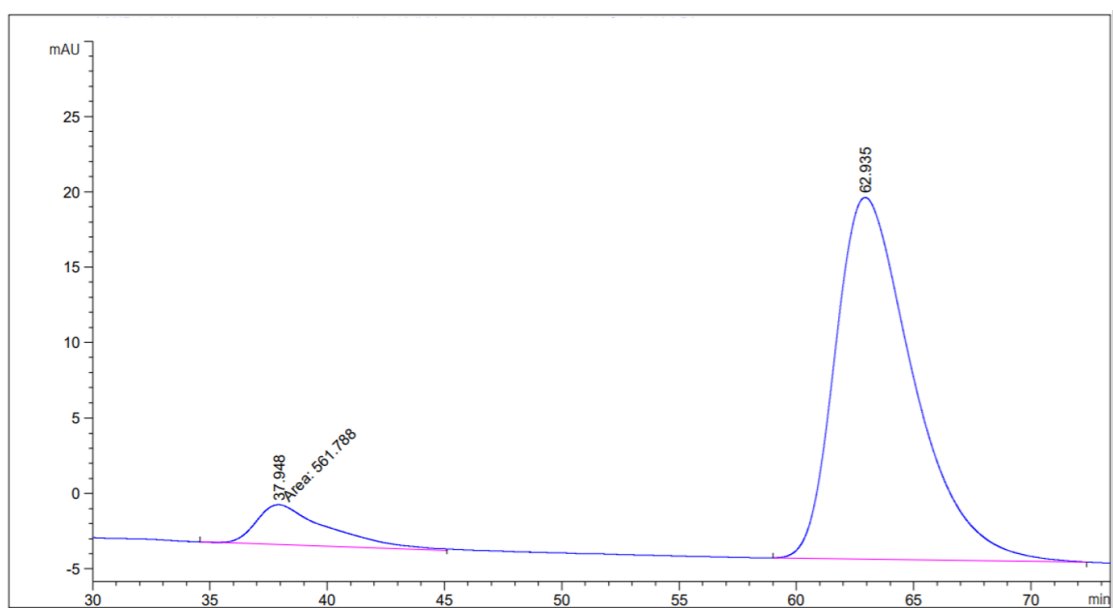
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.707	BB	1.2010	8292.95313	97.63127	48.4523
2	39.758	BB	0.9079	8822.74805	145.39853	51.5477



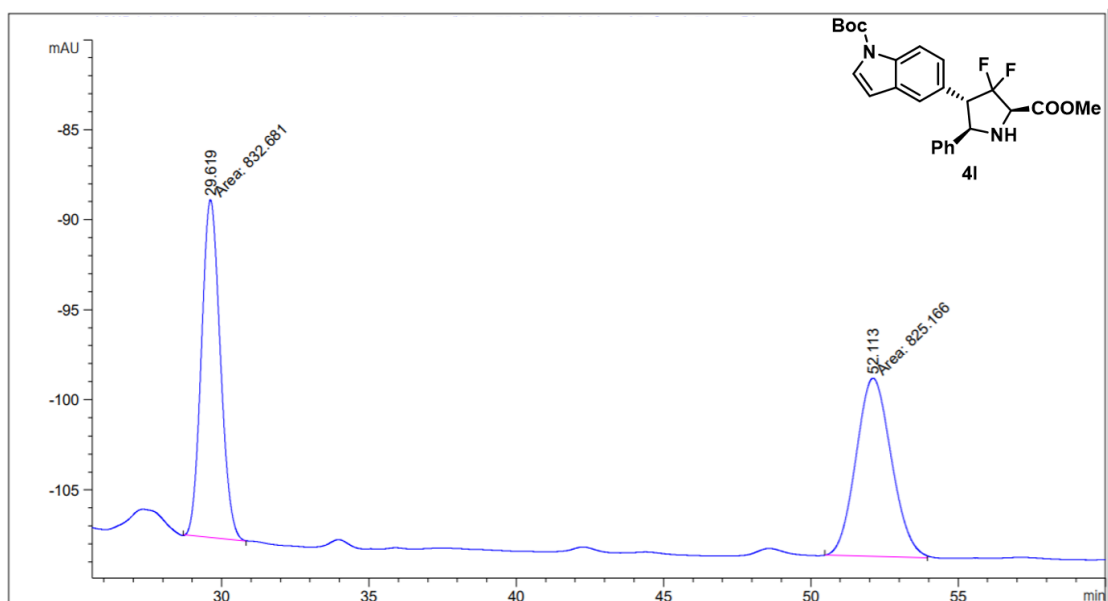
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.453	BB	1.1431	1.53122e4	187.04602	96.9046
2	40.503	BB	0.9277	489.11426	7.89631	3.0954



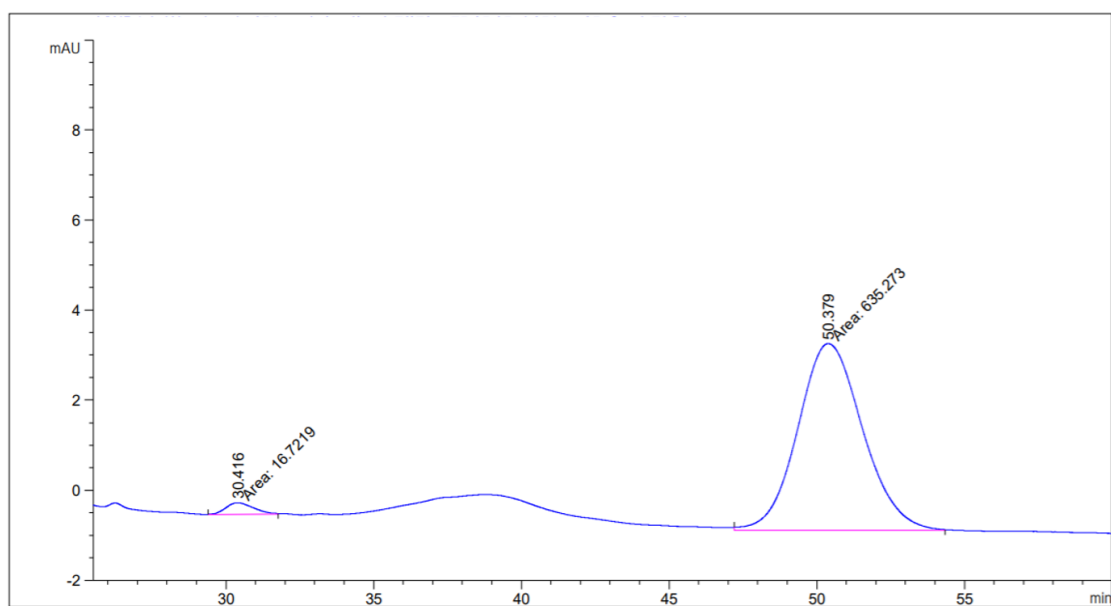
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.319	MM	2.9392	1930.13062	10.94469	53.2165
2	62.180	BB	2.6101	1696.80823	7.60782	46.7835



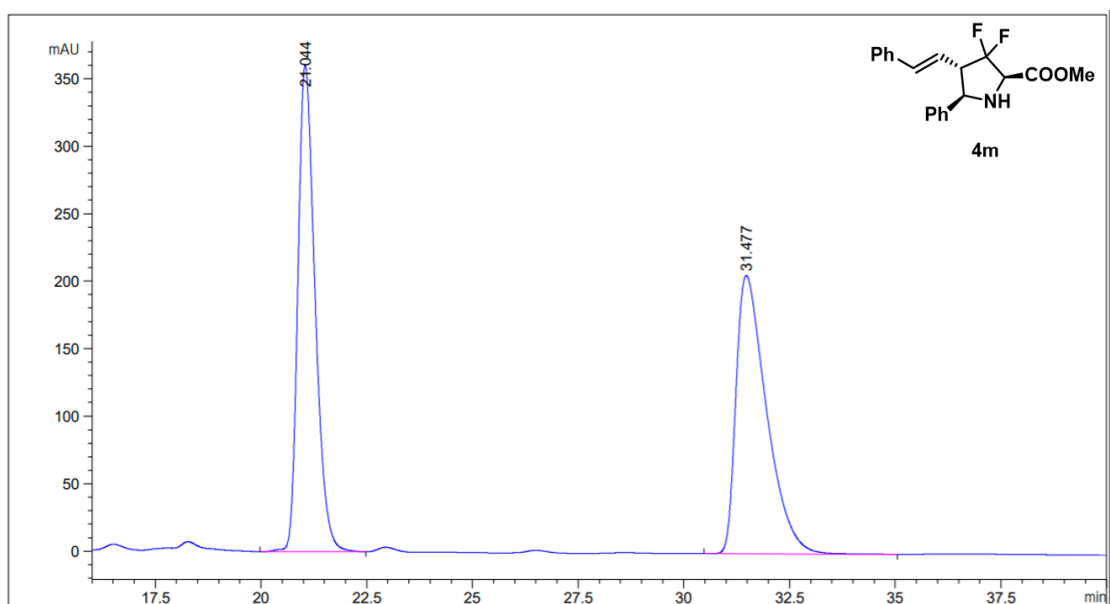
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.948	MM	3.5360	561.78766	2.64796	9.2218
2	62.935	BB	2.7081	5530.17627	23.98359	90.7782



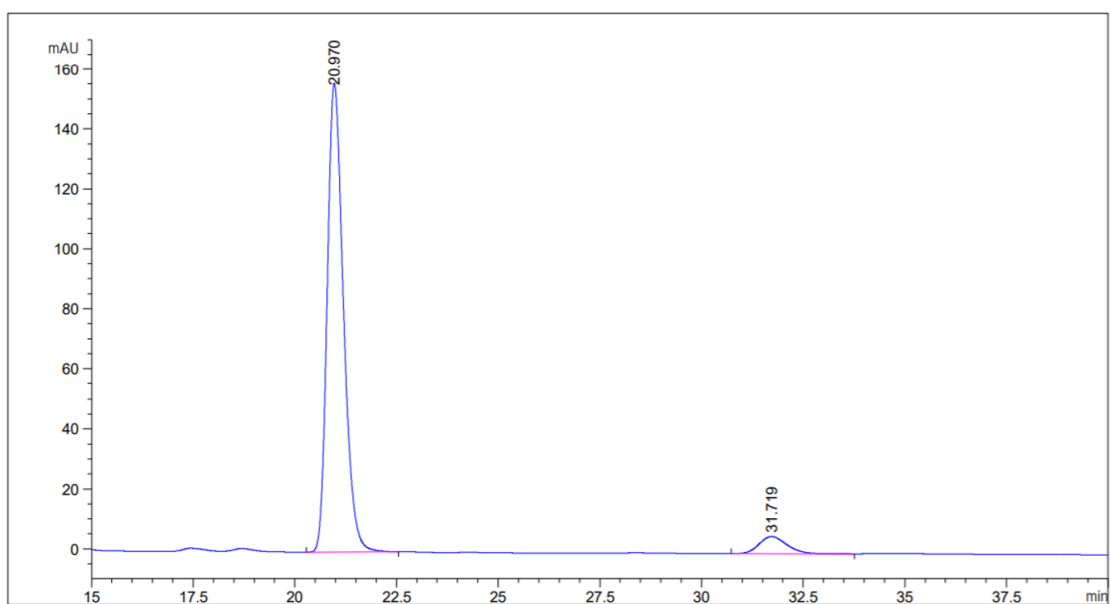
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.619	MM	0.7621	865.61218	18.93126	49.9905
2	52.113	MM	1.4543	865.94037	9.92405	50.0095



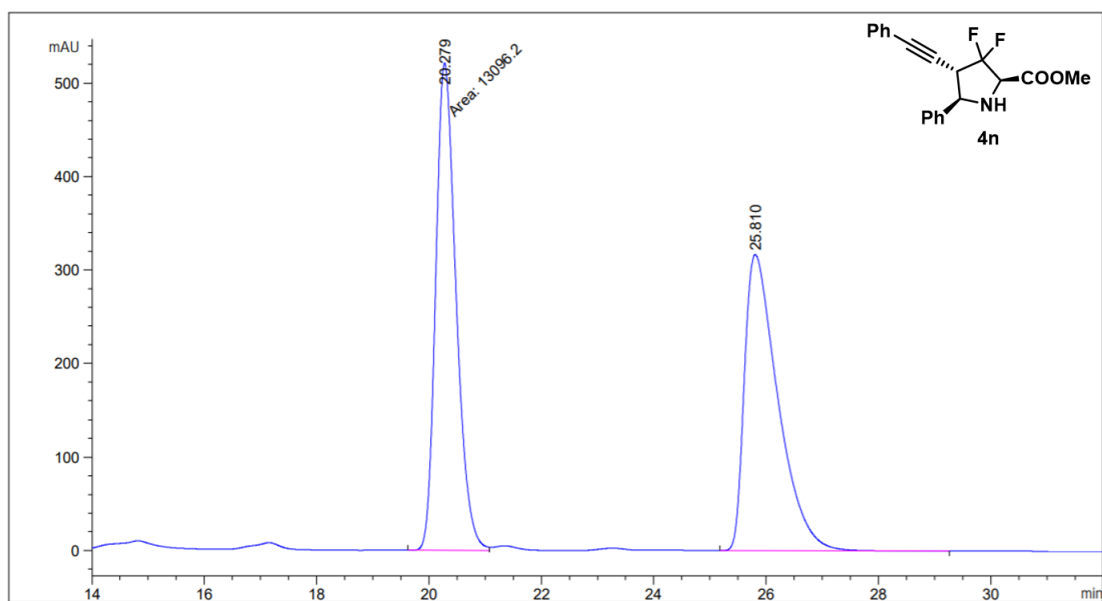
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.416	MM	1.3563	24.03641	2.95374e-1	3.6457
2	50.379	MM	2.5549	635.27313	4.14419	96.3543



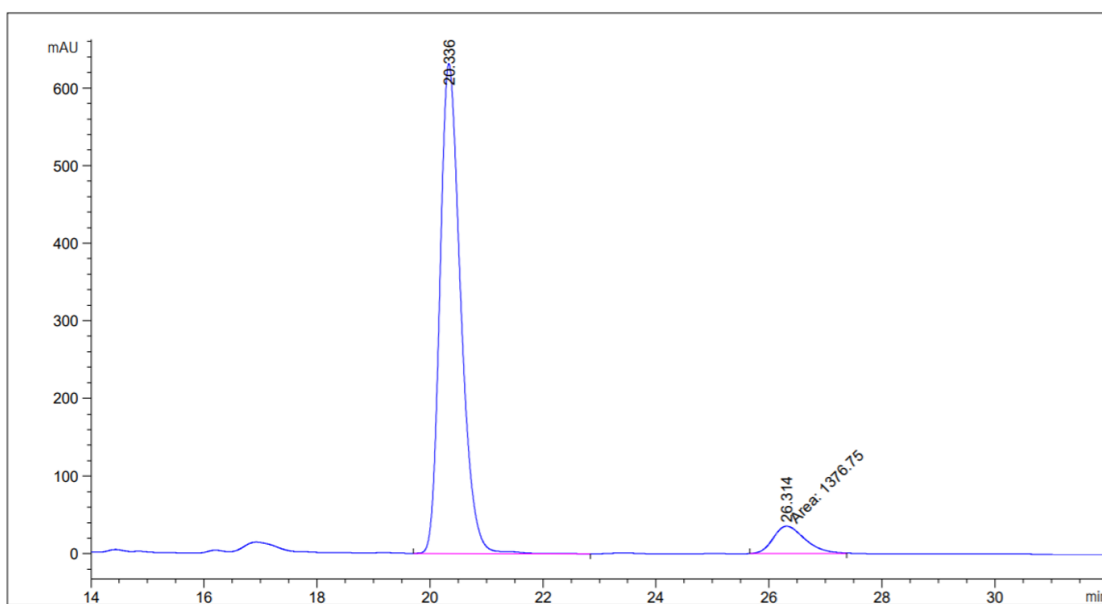
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.044	BB	0.4345	1.01790e4	360.44986	49.5972
2	31.477	BB	0.7573	1.03443e4	206.17702	50.4028



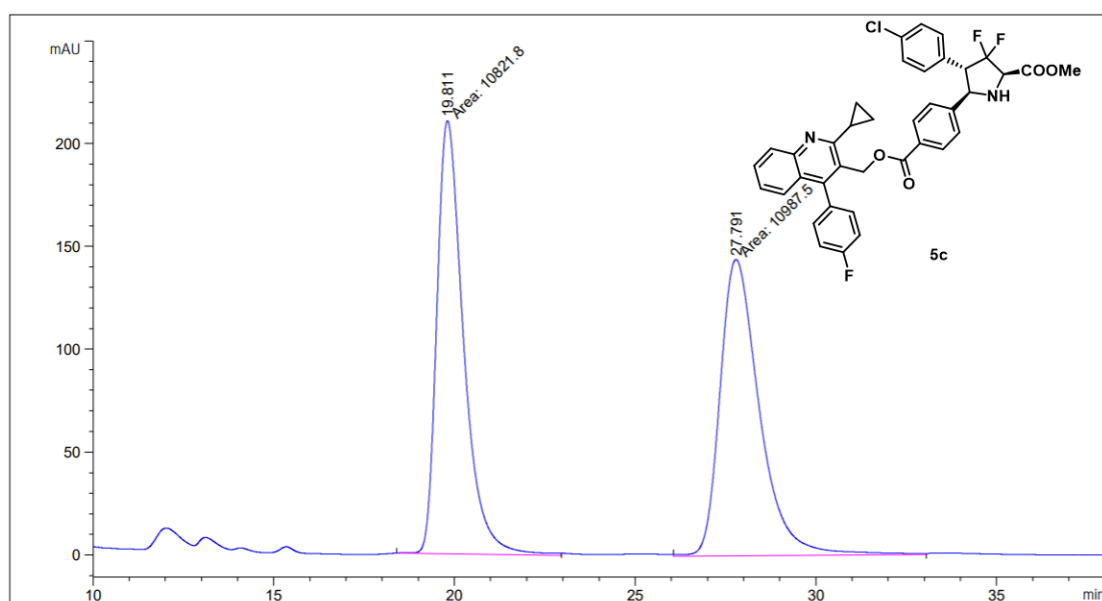
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.970	BB	0.4254	4333.59033	156.31165	94.1326
2	31.719	BB	0.7102	270.11978	5.70748	5.8674



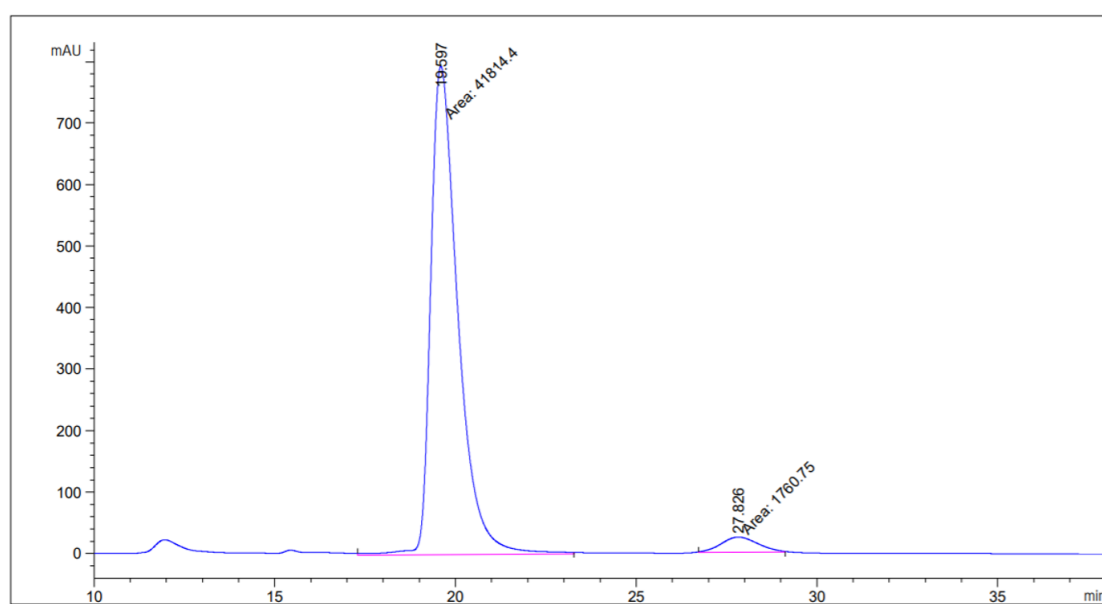
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.279	BV R	0.3873	1.32456e4	521.27240	50.2091
2	25.810	BB	0.6236	1.31352e4	316.86655	49.7909



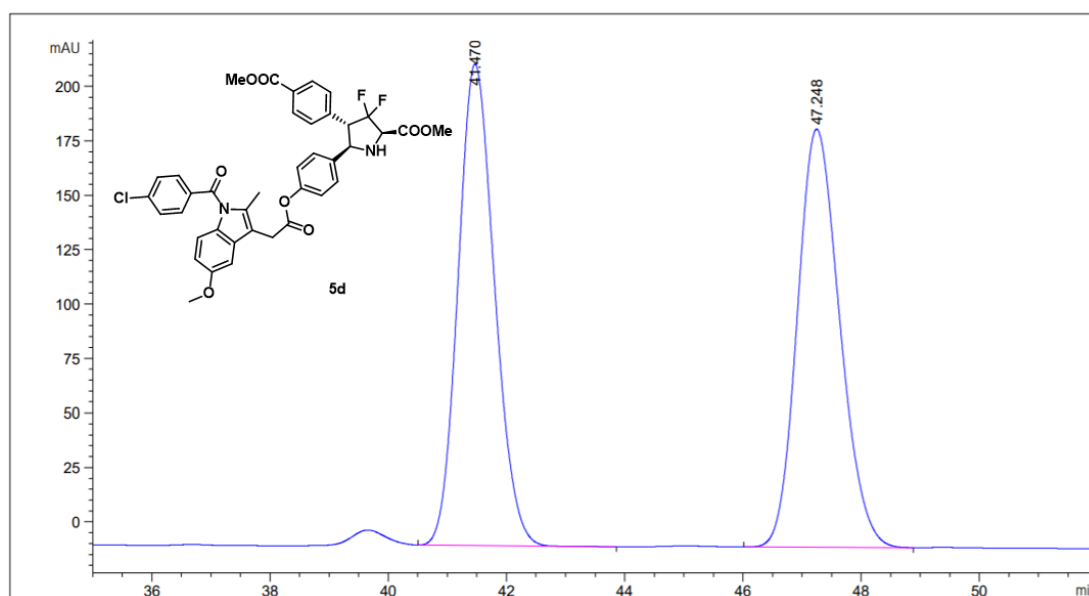
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.336	BB	0.3908	1.60545e4	631.01056	92.1018
2	26.314	MM	0.6520	1376.75073	35.19509	7.8982



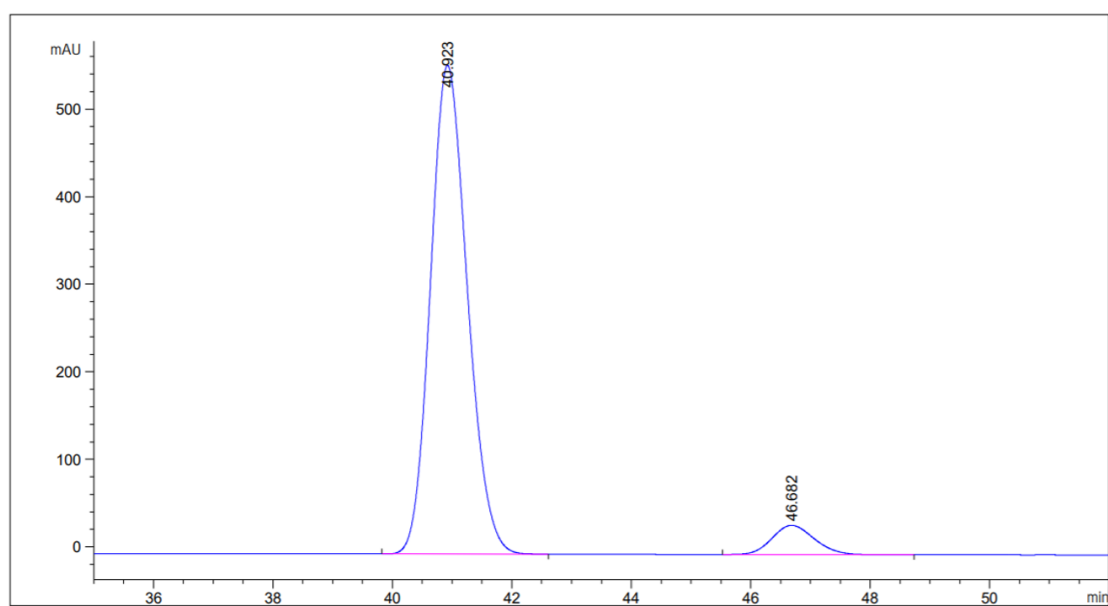
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.811	MM	0.8561	1.08218e4	210.67647	49.6202
2	27.791	MM	1.2701	1.09875e4	144.18129	50.3798



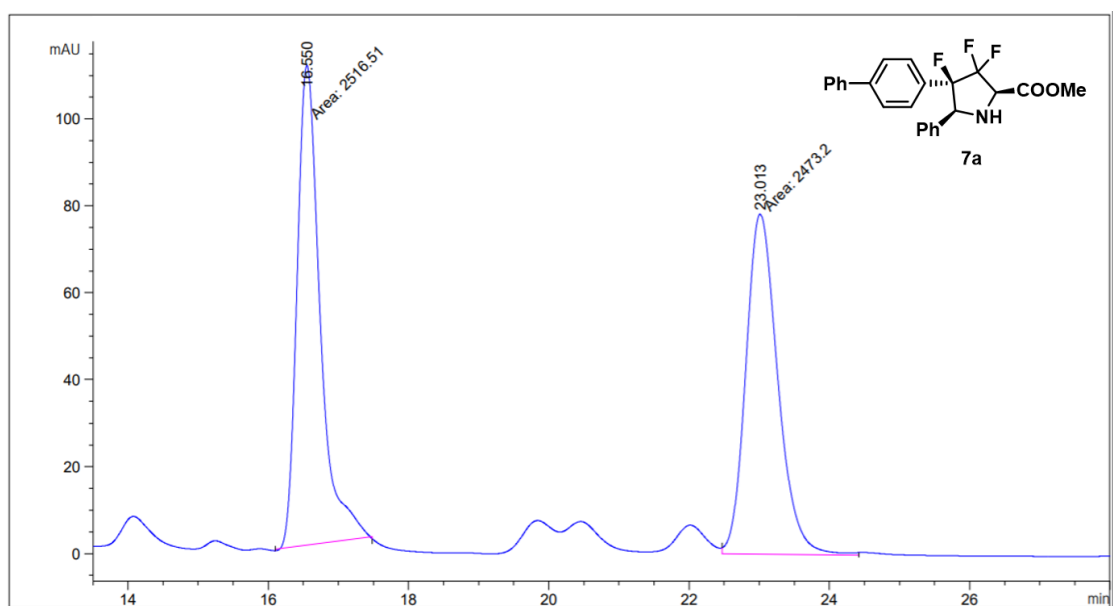
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.597	MM	0.8763	4.18144e4	795.25385	95.9593
2	27.826	MM	1.1848	1760.75427	24.76895	4.0407



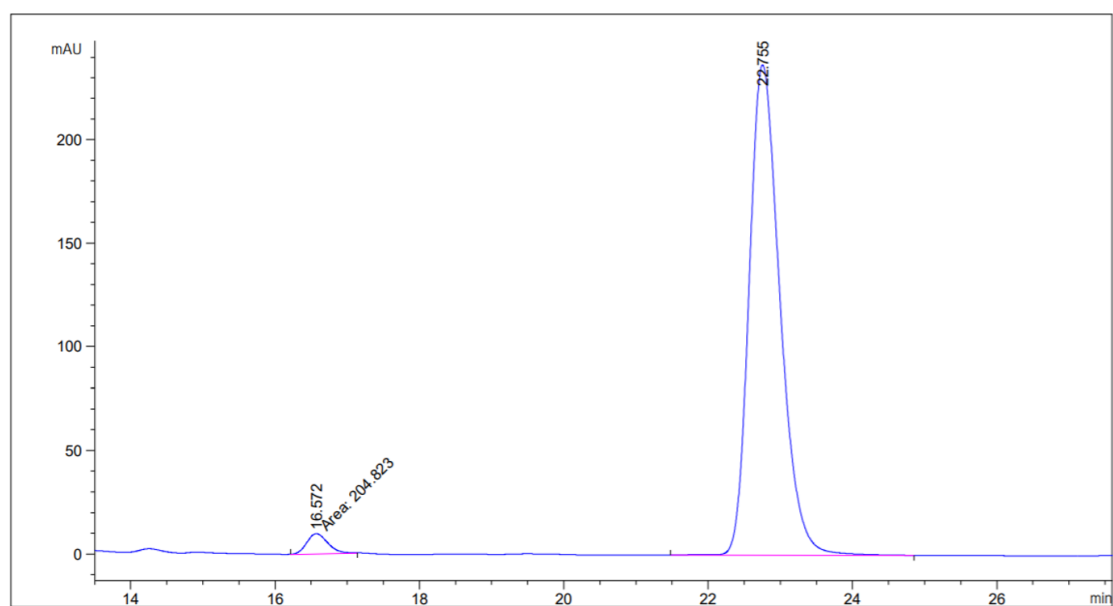
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.470	BB	0.6612	9465.67578	221.21310	49.8014
2	47.248	BB	0.7706	9541.17773	192.04642	50.1986



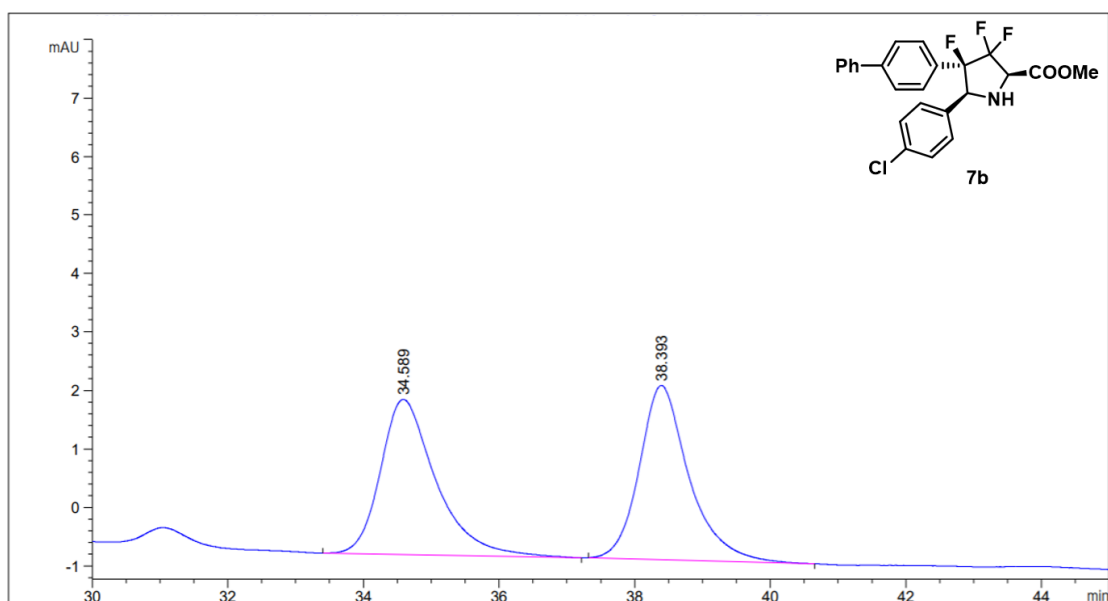
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.923	BB	0.6637	2.39473e4	558.03125	93.6051
2	46.682	BB	0.7597	1636.04041	33.32986	6.3949



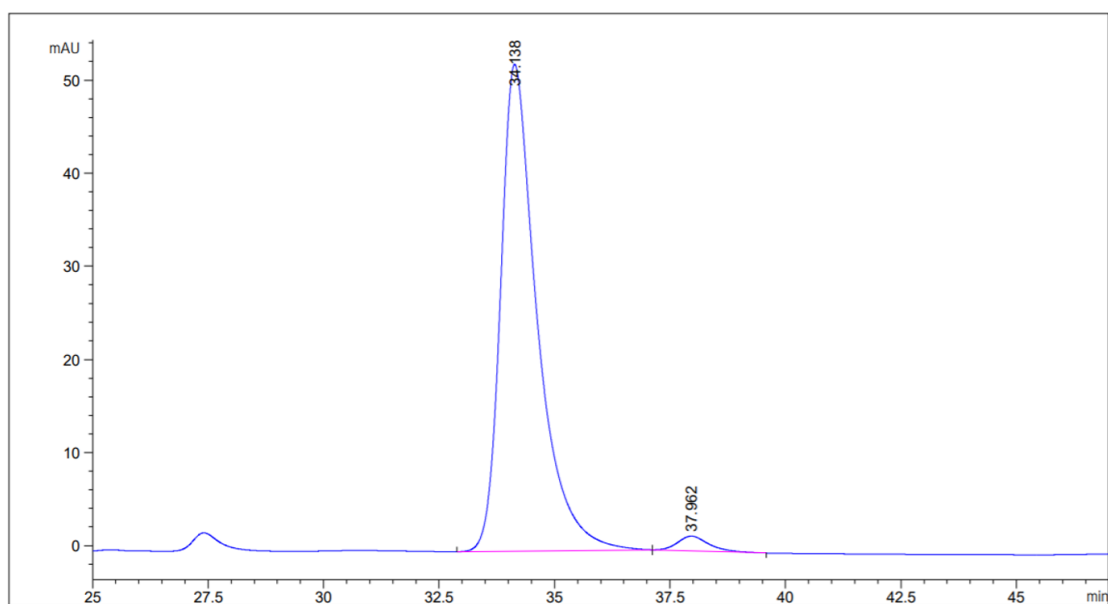
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.550	MM	0.3802	2516.50708	110.32250	50.4339
2	23.013	FM	0.5273	2473.20142	78.17839	49.5661



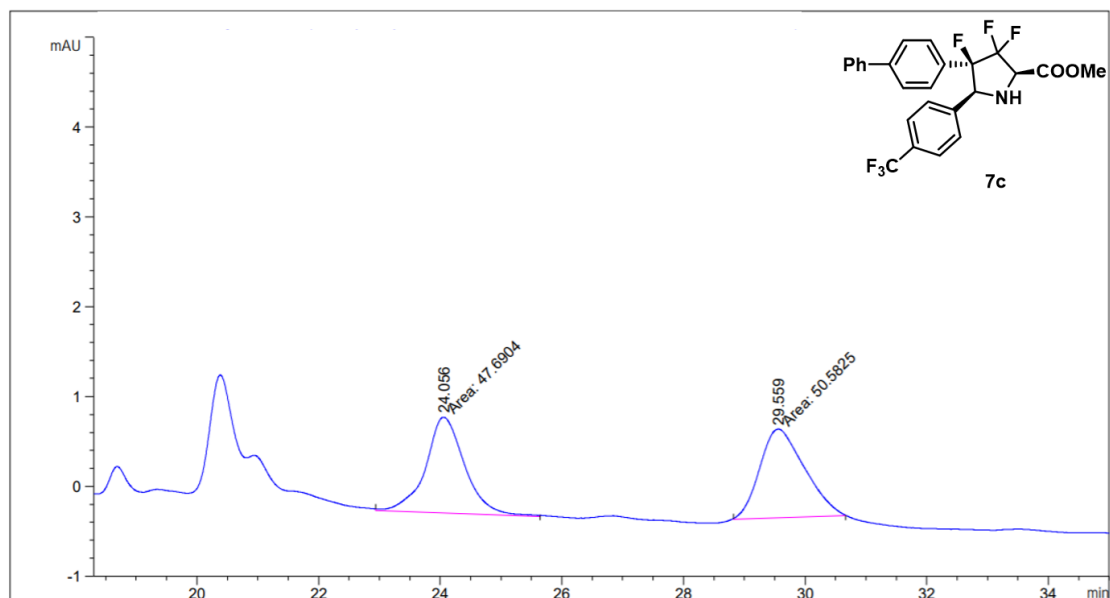
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.572	MM	0.3439	204.82281	9.92533	2.8404
2	22.755	BB	0.4549	7006.11865	236.98688	97.1596



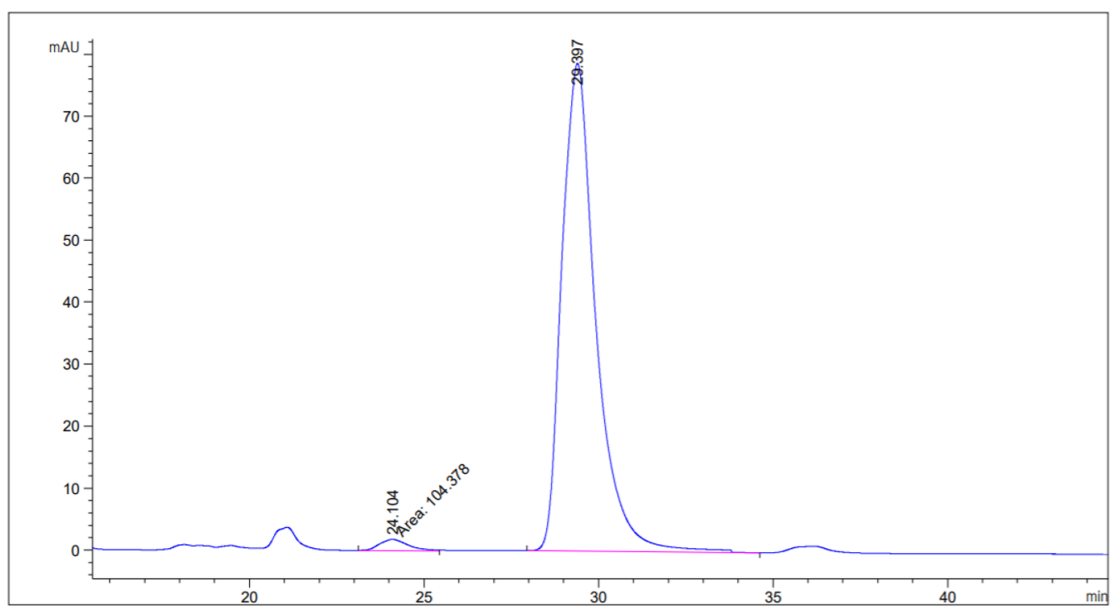
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.589	BB	0.8056	150.99466	2.65464	49.9098
2	38.393	BB	0.7197	151.54056	2.97786	50.0902



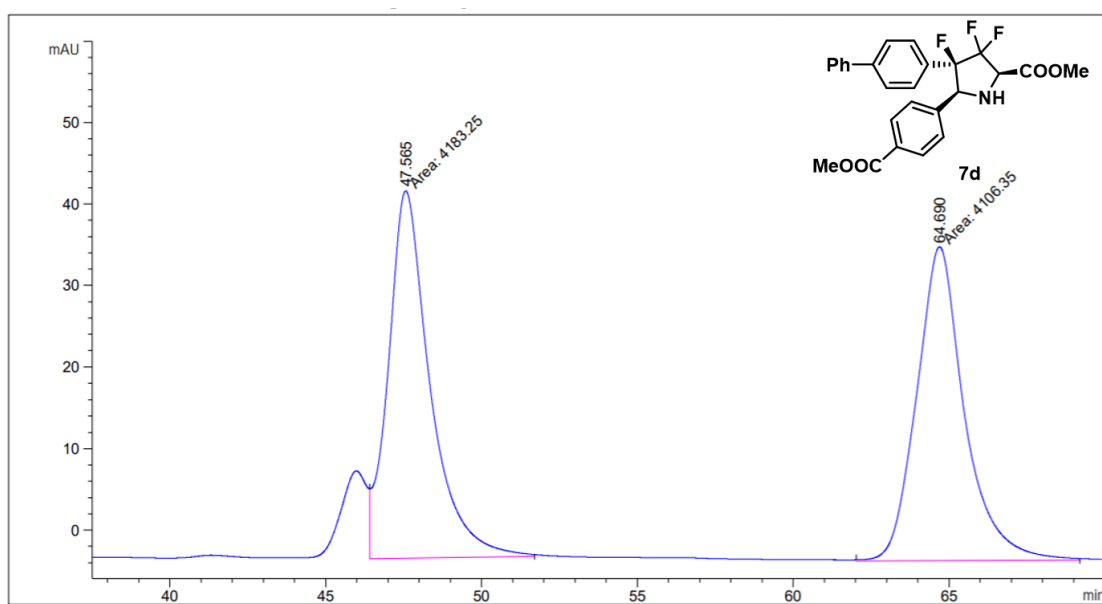
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.138	BB	0.8095	2876.08423	52.30597	97.4991
2	37.962	BB	0.6932	73.77415	1.58442	2.5009



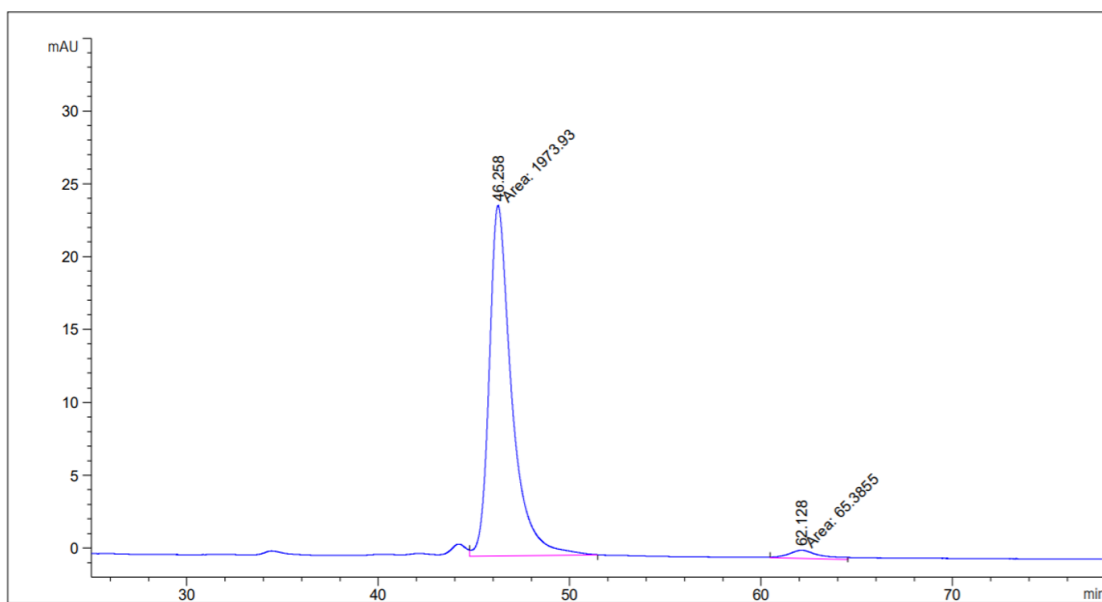
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.614	MM	1.3161	76.71674	9.71481e-1	50.3248
2	29.104	MM	1.5993	75.72632	7.89155e-1	49.6752



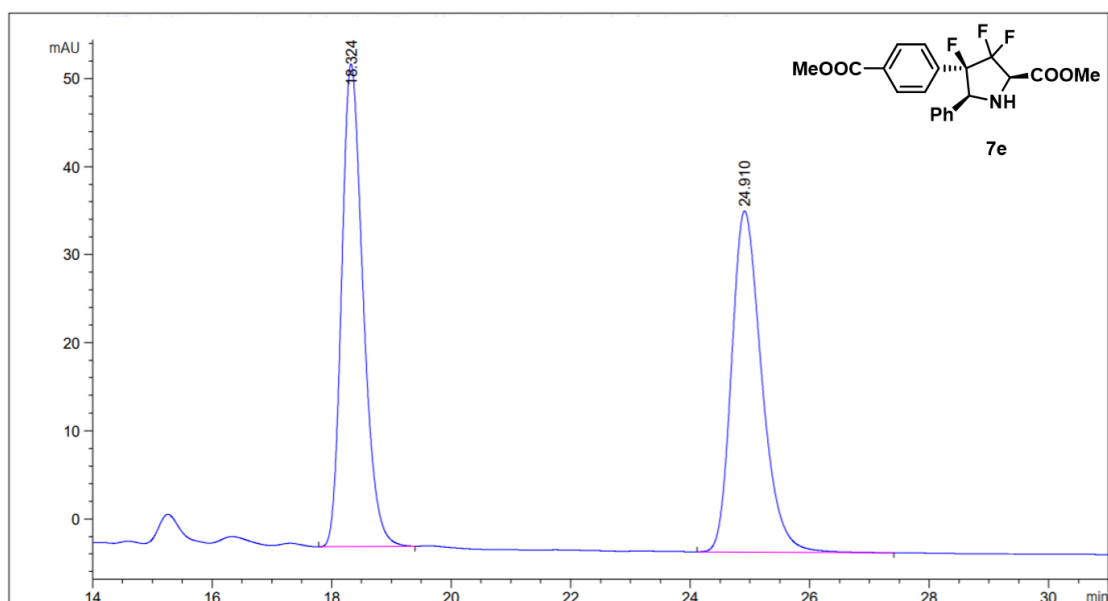
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.102	BB	0.7262	99.67895	1.79674	1.8325
2	29.397	BB	1.0486	5339.96875	78.70550	98.1675



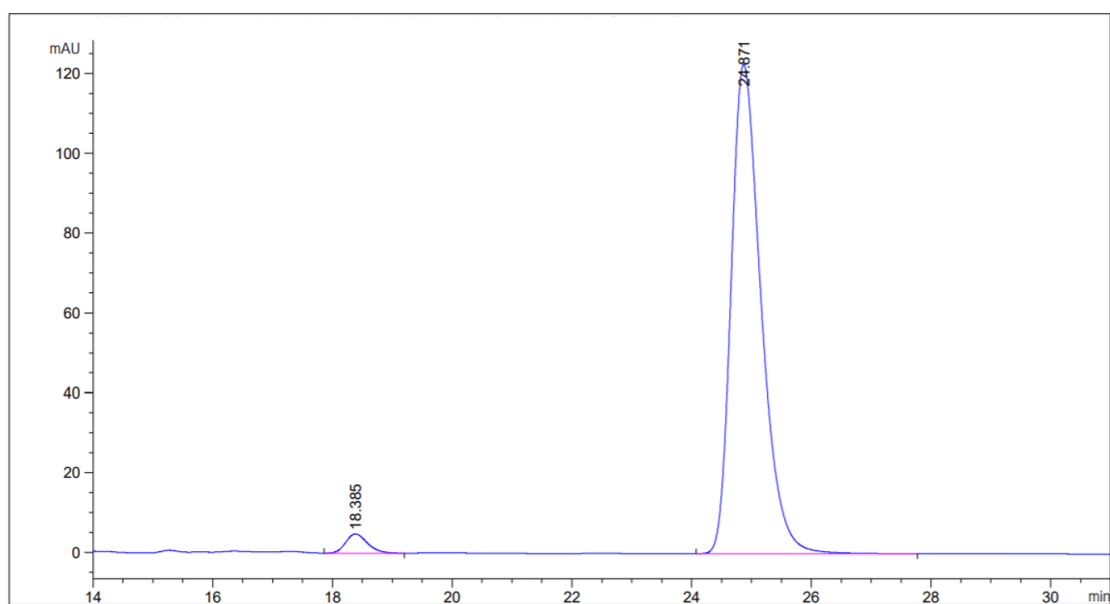
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.565	FM	1.5478	4183.25098	45.04473	50.4638
2	64.690	MM	1.7776	4106.35303	38.50084	49.5362



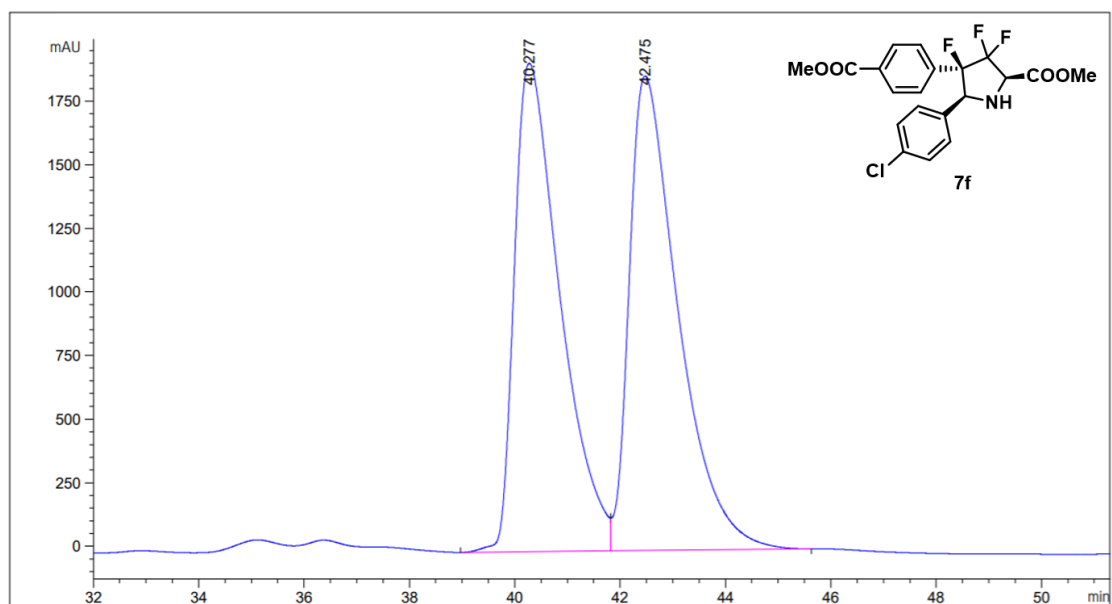
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	46.258	BB	1.1535	1884.54565	23.73032	96.6468
2	62.128	MM	1.9158	65.38551	5.68841e-1	3.3532



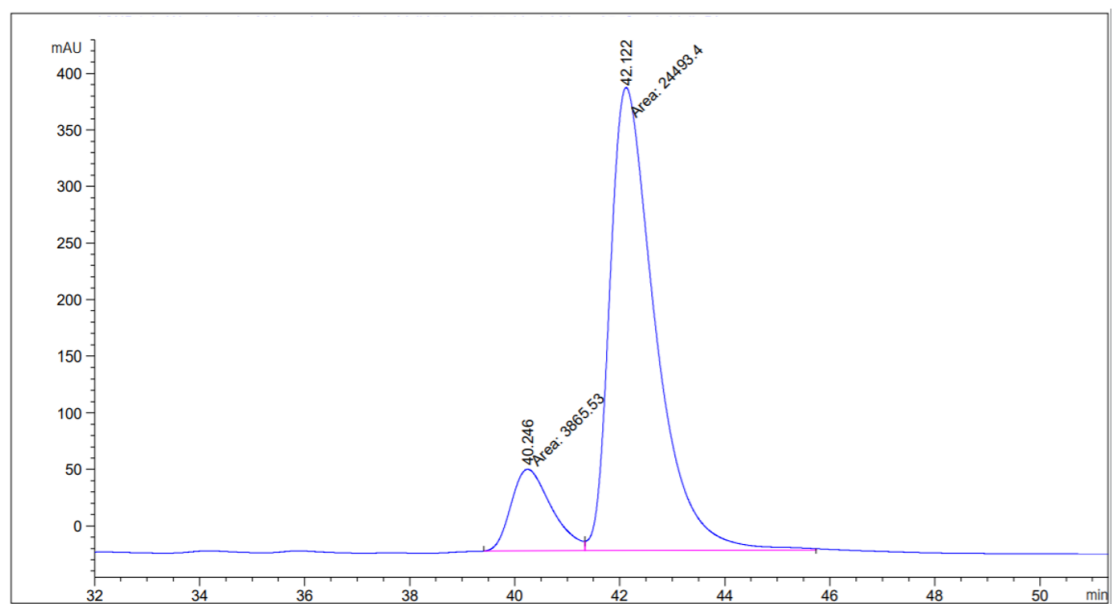
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.324	BB	0.3809	1363.33069	54.85622	50.1371
2	24.910	BB	0.5362	1355.87610	38.75437	49.8629



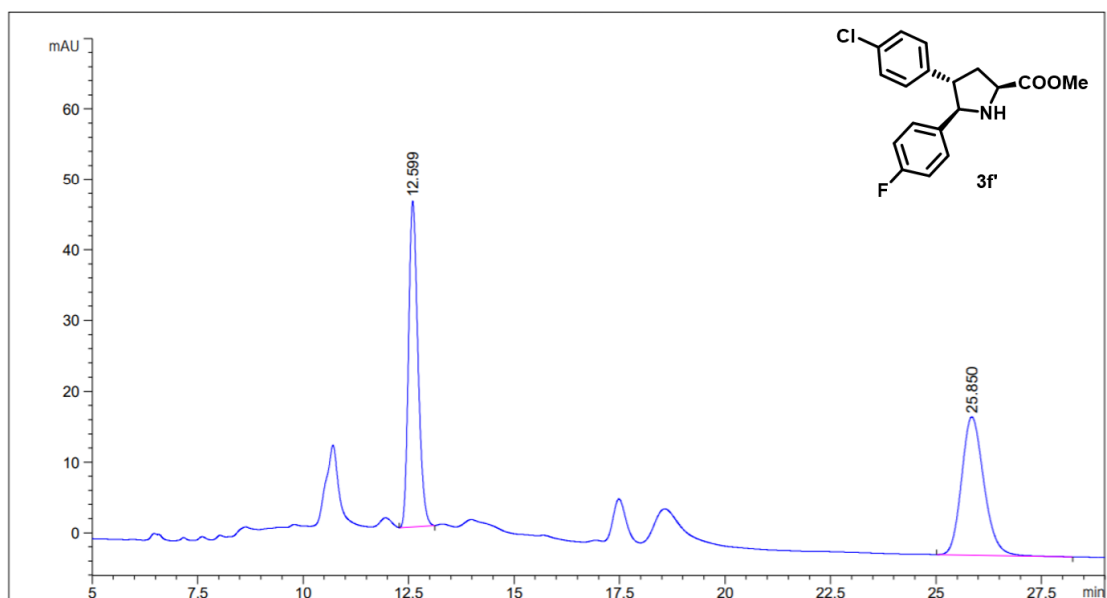
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.385	BB	0.3858	121.21218	4.81273	2.7740
2	24.871	BB	0.5314	4248.38672	122.56305	97.2260



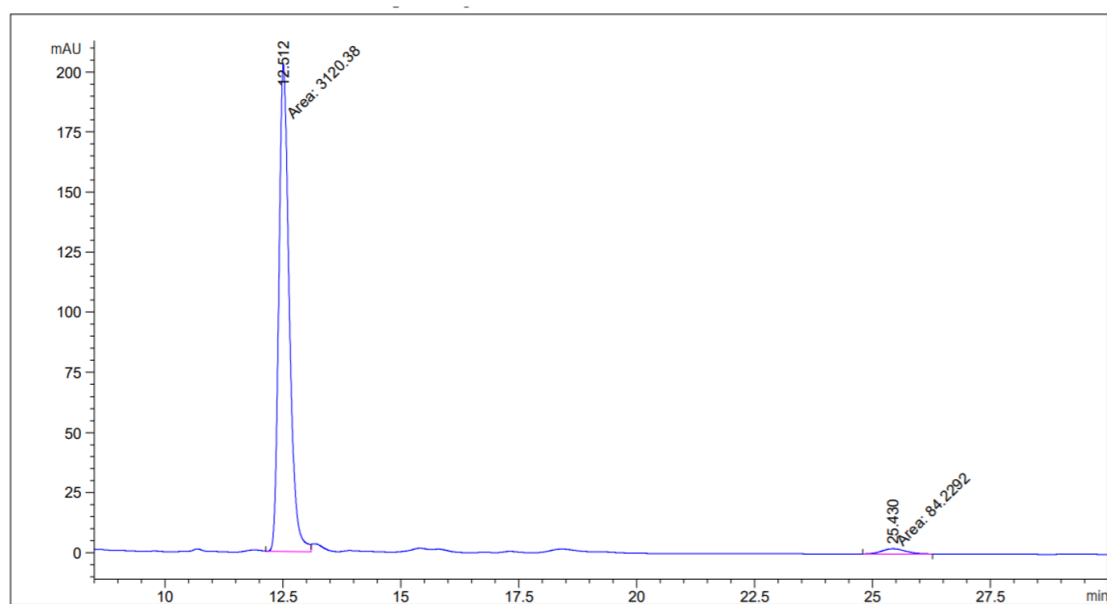
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.277	BV	0.8965	1.15860e5	1921.36694	49.0587
2	42.475	VB	0.9619	1.20306e5	1866.57544	50.9413



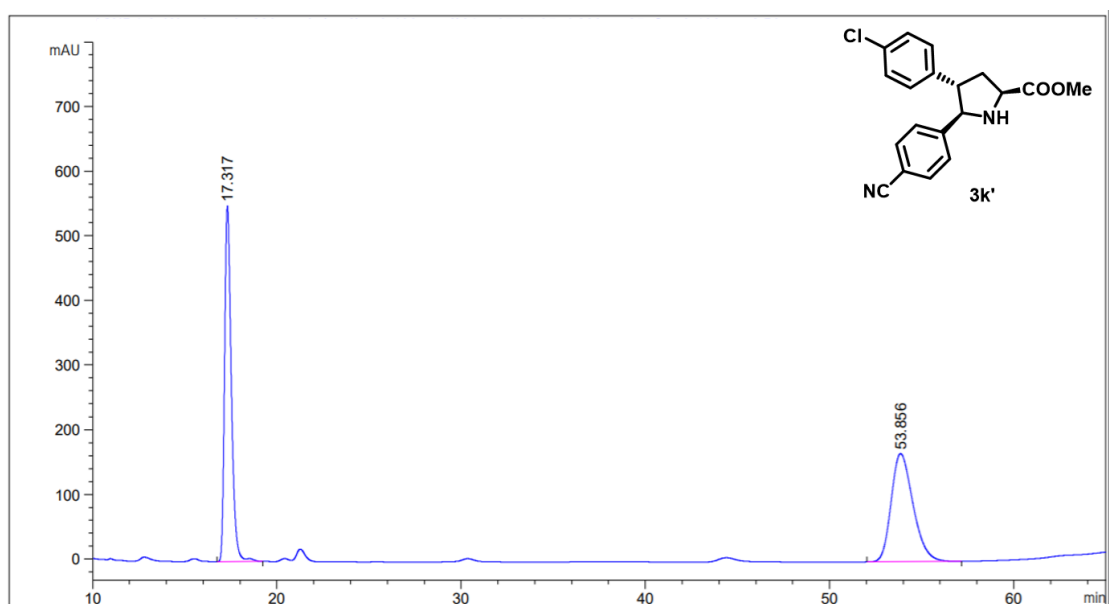
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.246	MF	0.8911	3865.53125	72.30155	13.6307
2	42.122	FM	0.9972	2.44934e4	409.37860	86.3693



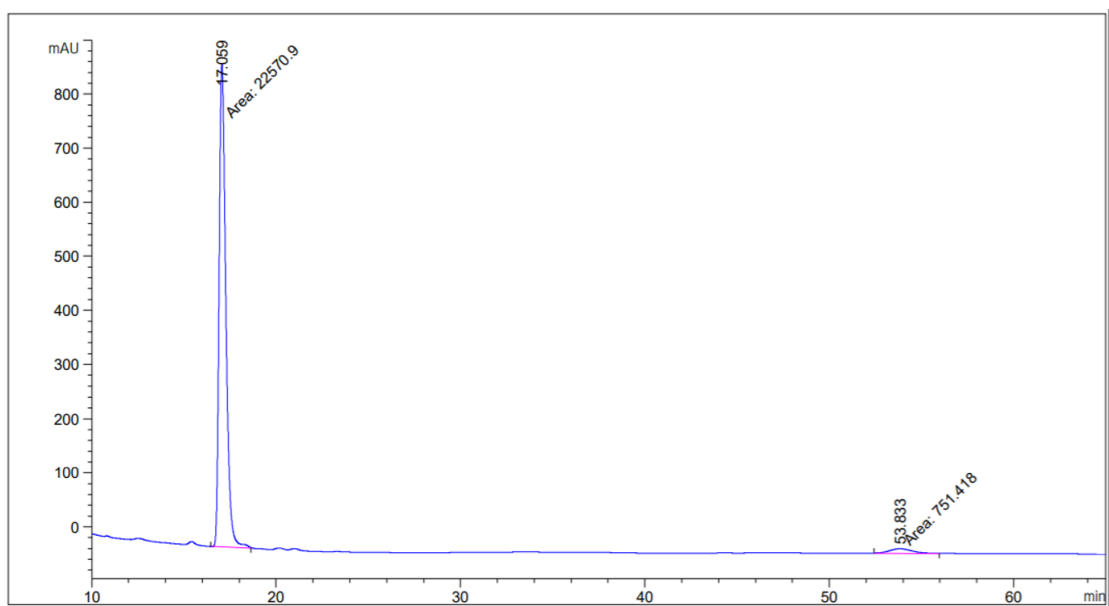
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.599	BB	0.2378	713.64288	46.04202	49.7575
2	25.850	BB	0.5632	720.59802	19.58817	50.2425



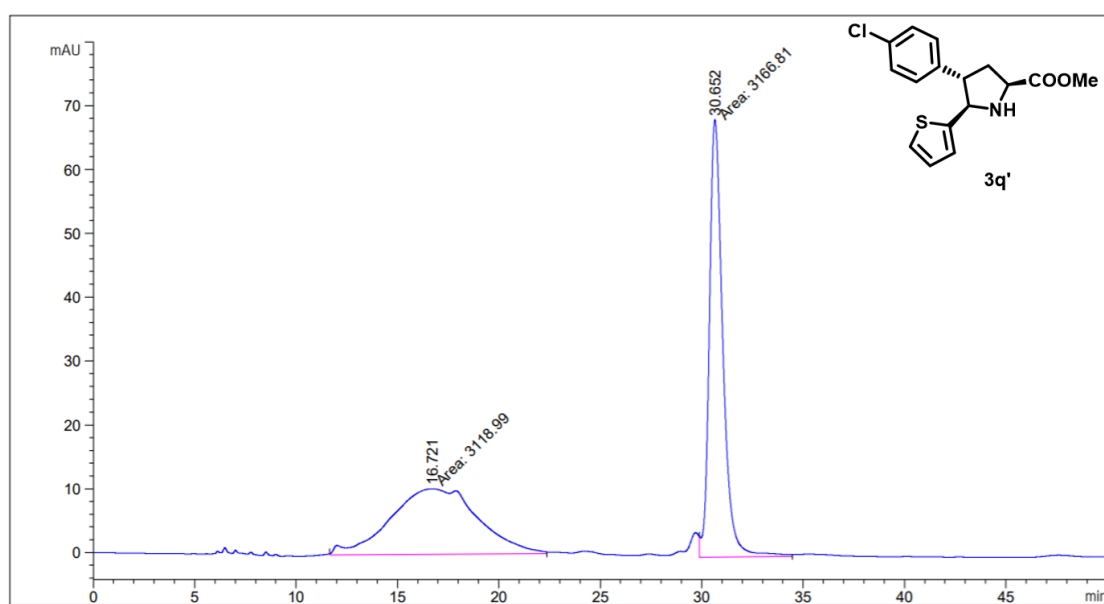
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.512	MF	0.2576	3135.14722	202.86238	97.5931
2	25.430	BB	0.5275	77.32156	2.18709	2.4069



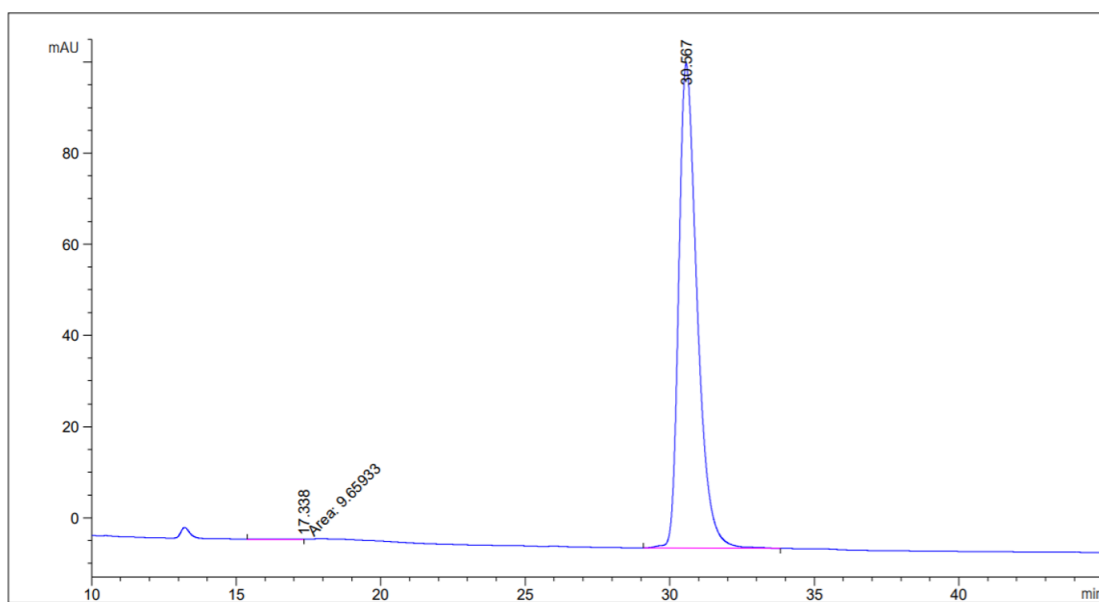
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.317	BV R	0.3846	1.39707e4	550.29541	50.3011
2	53.856	BB	1.2665	1.38035e4	167.49002	49.6989



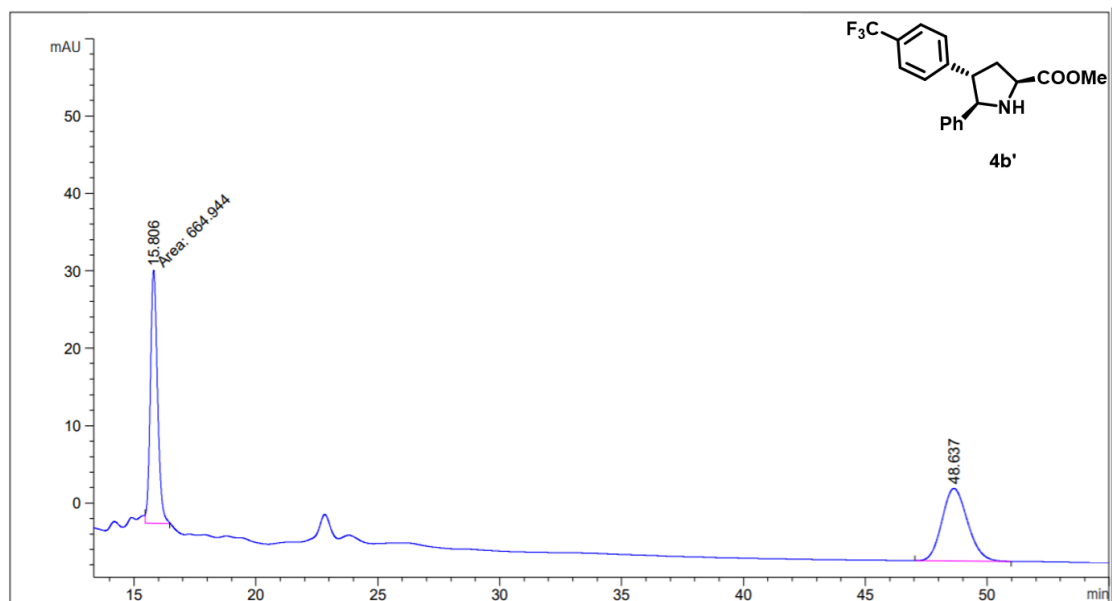
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.059	BB	0.3810	2.21319e4	890.43054	96.6811
2	53.826	BB	1.2755	759.75153	8.55987	3.3189



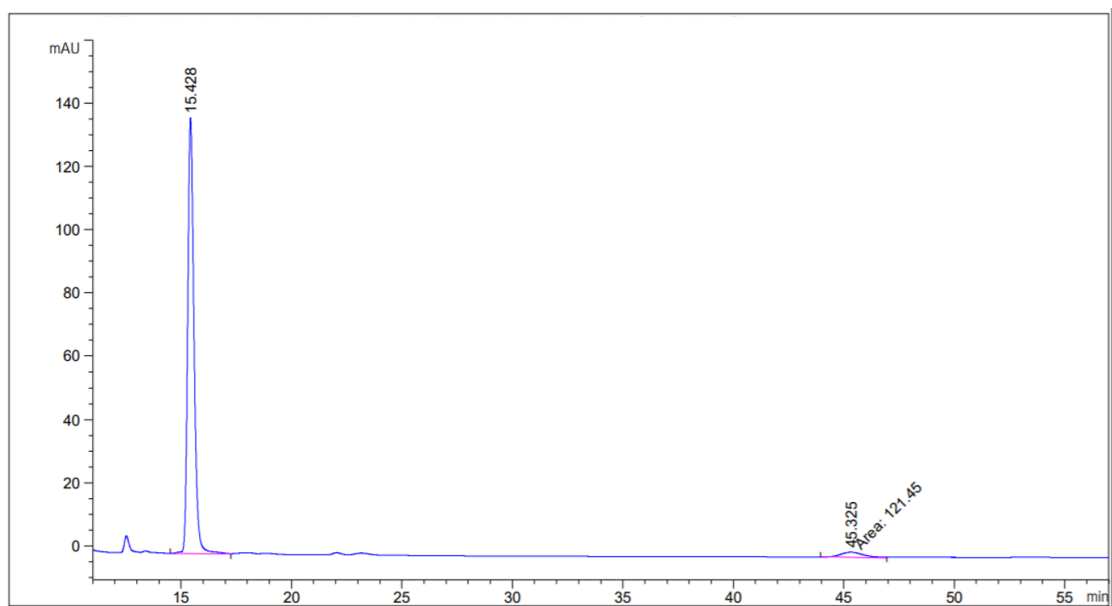
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.721	MM	5.0532	3118.99341	10.28727	49.6196
2	30.652	FM	0.7705	3166.80957	68.49891	50.3804



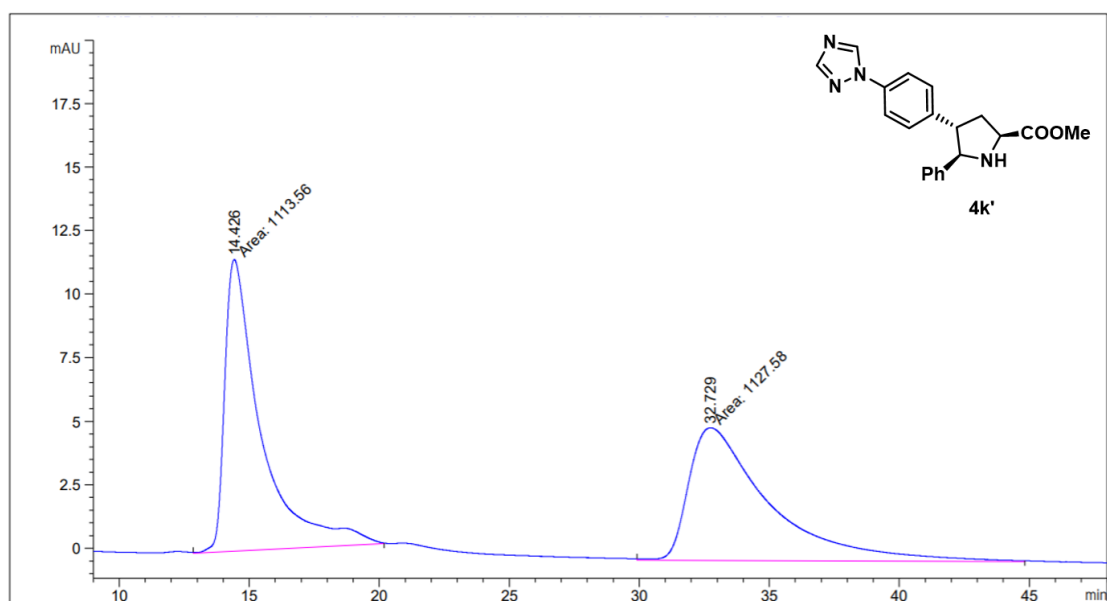
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.338	MM	1.2591	9.65933	1.27859e-1	0.2047
2	30.567	BB	0.6737	4708.22217	106.30862	99.7953



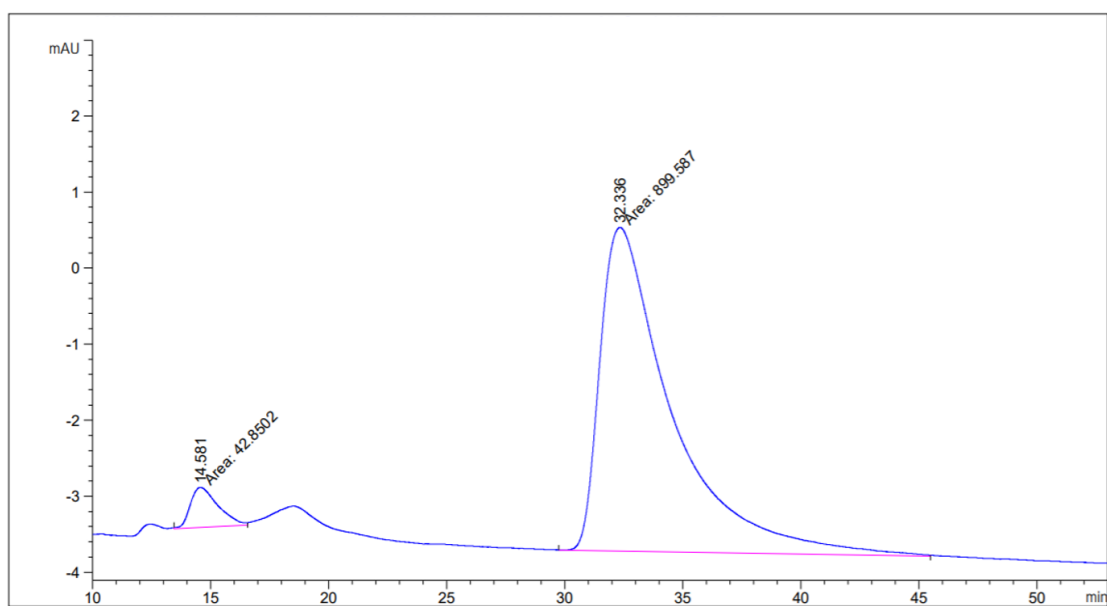
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.346	MM	0.3271	726.11212	37.00180	50.7476
2	44.933	BB	0.9963	704.71863	10.74291	49.2524



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.428	BB	0.3012	2717.17822	137.73526	95.7215
2	45.325	MM	1.2315	121.45018	1.64371	4.2785



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.426	MM	1.6181	1113.56384	11.47019	49.6872
2	32.729	MM	3.5912	1127.58411	5.23312	50.3128



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.581	MM	1.2724	38.91357	5.09731e-1	4.1464
2	32.336	MM	3.5213	899.58698	4.25778	95.8536