Supplementary Information

Rationale for template design of directed remote meta-C–H functionalization of arenes: Geometry, rigidity and steric effect

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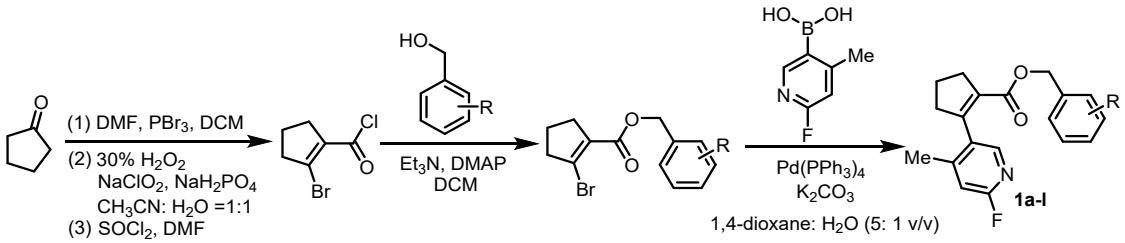
1 General Information

Unless otherwise noted, all solvents and chemicals were commercially available and used directly without further purification. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60 F254. Visualization was carried out with UV light. Preparative TLC was performed on 1.0 mm silica gel (Analtech). Columns for flash chromatography (FC) contained silica gel (32-63μ, Dynamic Adsorbents, Inc.). The melting points were measured with Tektronix X4 microscopic melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker AV 400 instrument (400 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to 7.26 ppm for chloroform-*d*. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, br = broad. Coupling constants, J, were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker AV 400 instrument (100 MHz) and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet peak at 77.0 ppm of chloroform-*d* and the center line of a septet peak at 40.0 ppm of d_6-DMSO. High resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

2 General procedure for preparation of substrates

Route A



Step 1:

(i) To a cooled solution (0 °C) of DMF (3.87 mL, 50 mmol) in CH_2Cl_2 (15 ml) was added PBr_3 (4.7 mL, 50 mmol) dropwise over 10 minutes. The resulting white suspension was warmed to room temperature and stirred for 30 minutes. A solution of cyclopentanone (10 mmol) dissolved in CH_2Cl_2 (15 mL) was added dropwise and the resulting reaction mixture was stirred for 12 hours at room temperature. Then the reaction mixture was poured into ice water (30 mL) and neutralized with $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was dried over anhydrous $MgSO_4$. The solvent was distilled off under reduced pressure to constant weight. The obtained 2-bromocyclopent-1-ene-1-carbaldehyde was used in the next step without further purification.[1]

(ii) To a solution of the above aldehyde (2.33 g, 13.3 mmol) in CH_3CN (13 mL) was added a solution of NaH_2PO_4 (0.42 g, 3.0 mmol) in H_2O (2.0 mL), 30% H_2O_2 (1.40 mL, 13.8 mmol), and $NaClO_2$ (1.68 g, 18.6 mmol) in H_2O (11 mL) in turn. The resultant reaction mixture was stirred at room temperature for 1 hours. Then, the reaction mixture was acidified with 2 M HCl aqueous solution to pH 2~3, followed by extracting with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the obtained acid was subjected to the next-step reaction without further purification.[2]

(iii) To a solution of 2-bromocyclopent-1-enecarboxylic acid (1.0 mmol) in $SOCl_2$ (5 mL) was added DMF (2-3 drops) at room temperature. The reaction mixture was stirred at 80 °C for 8 hours. After removal of the solvent under reduced pressure, acyl chloride thus obtained was subjected to subsequent reaction without further purification.[3]

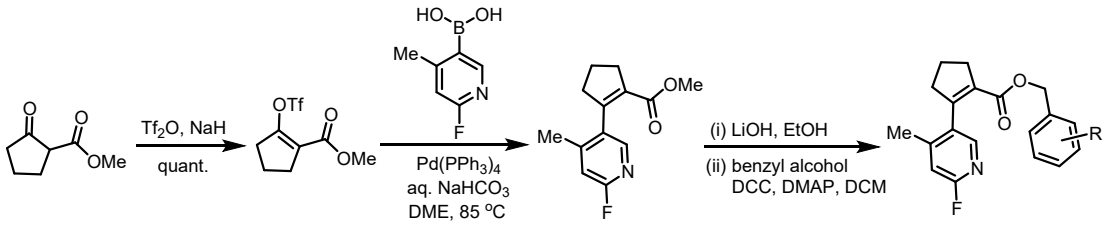
Step 2:

To a cooled solution (0 °C) of benzyl alcohol (1.0 equiv.), Et_3N (2.0 equiv.), DMAP (0.1 equiv.) in DCM was added 2-bromo-1-cyclopentene-1-carbonyl chloride (1.0 equiv.) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for another 1 h. After reaction completion monitored by TLC, the mixture was concentrated in *vacuo* and the resulting residue was purified by column chromatography using an eluent of hexane: ethyl aceate (10:1, V/V).

Step 3:

To a solution of benzylic ester (1.0 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), K_2CO_3 (2.0 equiv.) in dioxane (15 mL)/H_2O (3 mL) was added 2-fluoro-4-methylpyridine-5-boronic acid (1.1 equiv.) at room temperature. The flask was evacuated and backfilled with Ar_2 for three times and then the mixture was heated to 80 °C for 13 h. After being cooled to room temperature, the mixture was diluted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, concentrated in vacuo and purified by column chromatography to give the desired product **1a-n**.[4]

Route B



Step 1:[1]

To a suspension solution of NaH (0.54 g, 13.6 mmol) in THF (30 mL) at 0 °C was added a solution of methyl 2-oxocyclopentanecarboxylate (1.69 mL, 13.6 mmol) in THF (5 mL). The resulting solution was stirred for 10 min. Tf_2O (3.84 g, 13.6 mmol) was then added and the mixture stirred for another 30 min at room temperature. Water (30 mL) was added and the solution extracted with diethyl ether (50 mL x 3). The combined organic layers were dried over anhydrous $MgSO_4$, concentrated in vacuo and purified by column chromatography (petroleum ether (60 °C–90 °C)/ethyl acetate = 20: 1, V/V) to provide the desired product (3.20 g, 86%).[5]

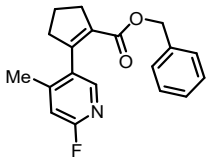
Step 2:

To a solution of the above triflate ester (1.00 g, 3.6 mmol), $Pd(PPh_3)_4$ (0.42 g, 0.36 mmol), 2-fluoro-4-methyl-5-pyridylboronic acid (1.23 g, 4.0 mmol) in DME (15 mL) was added a saturated aqueous solution of $NaHCO_3$ (7.2 mmol, 2 equiv.). The flask was evacuated and backfilled with Ar_2 three times. The mixture was heated to 80 °C for 13 h. After cooled to room temperature, the mixture was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, concentrated in vacuo and purified by column chromatography (petroleum ether (60 °C–90 °C)/ethyl acetate = 15: 1, V/V) to give the desired methyl ester (0.74 g, 88%).

Step 3:

(i) To a solution of the above methyl ester (0.50 g, 2.1 mmol) in EtOH (10 ml) was added an aqueous solution (2 M) of LiOH (0.15 g, 6.3 mmol). The resulted mixture was heated to 60 °C for 12 h. After cooled to room temperature, the mixture was acidified with 3 M HCl solution and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 times). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo to give the acid (0.44 g, 97%).

(ii) To a solution of benzyl alcohol (1.2 equiv), *N,N′*-dicyclohexylcarbodiimide (DCC) (4.0 equiv), 4-dimethylamino pyridine (DMAP) (0.1 equiv) in dichloromethane (DCM) at 0 ºC was added the above acid (1.0 equiv) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After reaction completion, the mixture was concentrated in vacuo and purified by column chromatography to give the target substrates **1a-1n**.

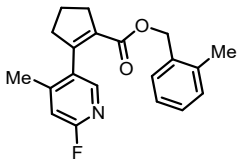


Benzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (1a)

White solid, m.p.: 56–59 ℃, 404 mg, 74%, R_f = 0.35 (petroleum ether/ethyl acetate = 10: 1, V/V). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.37 – 7.3(m, 1H), 7.25 (s, 3H), 7.07 (d, *J* = 9.6 Hz, 2H), 6.83 – 6.76 (m, 1H), 5.02 (s, 2H), 3.84 (s, 3H), 2.91 – 2.73 (m, 4H), 2.00 – 1.97 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 162.9 (d, $J_{C\text{-}F}$ = 237.7 Hz), 150.6, 150.0 (d, $J_{C\text{-}F}$ = 8.2 Hz), 144.3 (d, $J_{C\text{-}F}$ = 15.5 Hz), 135.3, 133.2, 132.2 (d, $J_{C\text{-}F}$ = 4.5 Hz), 128.2, 127.9, 127.8, 109.5 (d, $J_{C\text{-}F}$ = 37.1 Hz), 65.9, 40.9, 33.7, 21.9, 19.0.

HR-MS (ESI) m/z Calcd for $C_{19}H_{18}FNNaO_2^+$ [M+Na$^+$] 334.1214, found 334.1214.



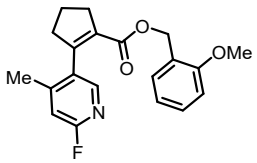
2-Methylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (1b)

White solid, m.p.: 49-52 ℃, 427 mg, 76%, R_f = 0.35 (petroleum ether/ethyl acetate = 10: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.33 (s, 1H), 7.26 – 7.21 (m, 2H), 7.15 – 7.10 (m, 1H), 6.66 (d, J = 1.9 Hz, 1H), 5.12 (s, 2H), 3.00 (d, J = 2.9 Hz, 2H), 2.85 (d, J = 2.7 Hz, 2H), 2.24 (d, J = 2.6 Hz, 6H), 2.21 – 2.14 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 162.8 (d, $J_{C\text{-}F}$ = 237.7 Hz), 150.5, 150.0 (d, $J_{C\text{-}F}$ = 8.2 Hz), 144.2 (d, $J_{C\text{-}F}$ = 15.6 Hz), 136.6, 133.2 (d, $J_{C\text{-}F}$ = 12.0 Hz), 132.1 (d, $J_{C\text{-}F}$ = 4.4 Hz), 130.0, 128.9, 128.2, 125.7, 109.4 (d, $J_{C\text{-}F}$ = 37.0 Hz), 64.2, 41.0, 33.7, 21.9, 19.0 (d, $J_{C\text{-}F}$ = 2.9 Hz), 18.4.

HR-MS (ESI) m/z Calcd for $C_{20}H_{20}FNNaO_2^+$ [M+Na$^+$] 348.1371, found 348.1372.



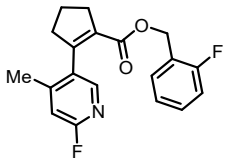
2-Methoxybenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (1c)

Colorless oil, 386 mg, 63%, R_f = 0.35 (petroleum ether/ethyl acetate = 9: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.24 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 7.2 Hz, 1H), 6.81 (dd, J = 20.0, 7.7 Hz, 2H), 6.50 (s, 1H), 5.00 (s, 2H), 3.72 (s, 3H), 2.87 (t, J = 7.6 Hz, 2H), 2.70 (t, J = 7.7 Hz, 2H), 2.10 (s, 3H), 2.06 – 1.99 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 162.6 (d, $J_{C\text{-}F}$ = 237.2 Hz), 157.3, 150.1, 150.1, 144.1 (d, $J_{C\text{-}F}$ = 15.3 Hz), 133.4, 132.2 (d, $J_{C\text{-}F}$ = 4.4 Hz), 129.3, 129.3, 123.5, 119.9, 109.9, 109.0 (d, $J_{C\text{-}F}$ = 37.0 Hz), 61.3, 54.9, 40.9, 33.7, 21.8, 19.0.

HR-MS (ESI) m/z Calcd for $C_{20}H_{20}FNNaO_3^+$ [M+Na$^+$] 364.1320, found 364.1320.



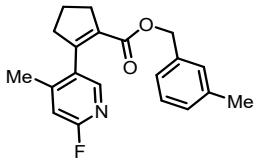
2-Fluorobenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (1d)

White solid, m.p.: 53-56 ℃, 405 mg, 73%, R_f= 0.4 (petroleum ether/ethyl acetate = 9: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.51 (q, J = 6.1, 5.6 Hz, 1H), 7.30 – 7.20 (m, 2H), 6.80 (s, 1H), 5.26 (s, 2H), 3.11 (t, J = 9.0 Hz, 2H), 2.96 (t, J = 9.1 Hz, 2H), 2.38 (s, 3H), 2.32 – 2.24 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 164.1(d, $J_{C\text{-}F}$ = 237.6 Hz), 160.1 (d, $J_{C\text{-}F}$ = 248.5 Hz), 150.9, 150.0 (d, $J_{C\text{-}F}$ = 8.2 Hz), 144.3 (d, $J_{C\text{-}F}$ = 15.5 Hz), 133.1, 132.2 (d, $J_{C\text{-}F}$ = 4.5 Hz), 130.3 (d, $J_{C\text{-}F}$ = 3.8 Hz), 130.2 (d, $J_{C\text{-}F}$ = 8.1 Hz), 123.9 (d, $J_{C\text{-}F}$ = 3.7 Hz), 122.5 (d, $J_{C\text{-}F}$ = 14.6 Hz), 115.2 (d, $J_{C\text{-}F}$ = 21.1 Hz), 109.5 (d, $J_{C\text{-}F}$ = 36.8 Hz), 59.8 (d, $J_{C\text{-}F}$ = 4.2 Hz), 40.9, 33.7, 21.9, 19.0 (d, $J_{C\text{-}F}$ = 2.8 Hz).

HR-MS (ESI) m/z Calcd for $C_{19}H_{17}F_2NNaO_2^+$ [M+Na$^+$] 352.1120, found 352.1121.



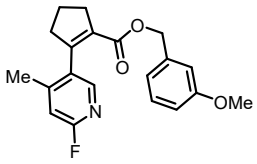
3-Methylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (1e)

Colorless oil, 415 mg, 72%, R_f= 0.35 (petroleum ether/ethyl acetate = 9: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.08 (d, J = 8.1 Hz, 2H), 6.92 (d, J = 8.0 Hz, 2H), 6.59 (d, J = 2.4 Hz, 1H), 4.93 (s, 2H), 2.87 (d, J = 10.2 Hz, 2H), 2.75 – 2.69 (m, 2H), 2.33 (s, 3H), 2.12 (s, 3H), 2.08 – 1.98 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 162.6 (d, $J_{C\text{-}F}$ = 237.4 Hz), 150.2, 149.9 (d, $J_{C\text{-}F}$ = 8.2 Hz), 144.2 (d, $J_{C\text{-}F}$ = 15.6 Hz), 137.6, 135.0, 132.9, 131.9 (d, $J_{C\text{-}F}$ = 4.5 Hz), 128.4, 128.2, 127.8, 124.6, 109.2 (d, $J_{C\text{-}F}$ = 37.0 Hz), 65.6, 40.7, 33.5, 21.6, 20.8, 18.8.

HR-MS (ESI) m/z Calcd for $C_{20}H_{20}FNNaO_2^+$ [M+Na$^+$] 348.1371, found 348.1372.



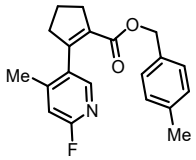
3-Methoxybenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (1f)

Yellow oil, 399 mg, 68%, R_f = 0.32 (petroleum ether/ethyl acetate = 9: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.20 (t, J = 7.9 Hz, 1H), 6.85 – 6.78 (m, 1H), 6.63 (d, J = 6.6 Hz, 2H), 6.61 – 6.56 (m, 1H), 4.95 (s, 2H), 3.79 (s, 3H), 2.88 (t, J = 7.6 Hz, 2H), 2.73 (t, J = 7.6 Hz, 2H), 2.14 (s, 3H), 2.05 – 2.01 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 163.0 (d, $J_{C\text{-}F}$ = 237.8 Hz), 159.5, 150.8, 150.1 (d, $J_{C\text{-}F}$ = 8.3 Hz), 144.4 (d, $J_{C\text{-}F}$ = 15.5 Hz), 136.9, 133.2, 132.2 (d, $J_{C\text{-}F}$ = 4.5 Hz), 129.4, 120.1, 113.6, 113.3, 109.6 (d, $J_{C\text{-}F}$ = 37.0 Hz), 65.9, 55.1, 41.1, 33.9, 22.0, 19.2.

HR-MS (ESI) m/z Calcd for $C_{20}H_{20}FNNaO_3^+$ [M+Na$^+$] 364.1320, found 364.1322



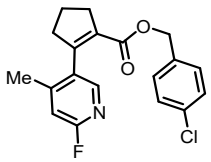
4-Methylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (1g)

Yellow oil, 344 mg, 60%, R_f = 0.36 (petroleum ether/ethyl acetate = 9: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.08 (d, J = 7.9 Hz, 2H), 6.92 (d, J = 7.8 Hz, 2H), 6.60 (s, 1H), 4.24 (s, 2H), 2.86 (t, J = 6.8 Hz, 2H), 2.71 (t, J = 8.6 Hz, 2H), 2.33 (s, 3H), 2.13 (s, 3H), 2.08 – 2.00 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 163.0 (d, $J_{C\text{-}F}$ = 237.6 Hz), 150.6, 150.1 (d, $J_{C\text{-}F}$ = 8.3 Hz), 144.4 (d, $J_{C\text{-}F}$ = 15.4 Hz), 137.8, 133.3, 132.4, 132.3 (d, $J_{C\text{-}F}$ = 4.7 Hz), 129.0, 128.0, 109.6 (d, $J_{C\text{-}F}$ = 37.0 Hz), 66.0, 41.0, 22.0, 21.1, 19.2 (d, $J_{C\text{-}F}$ = 2.9 Hz).

HR-MS (ESI) m/z Calcd for $C_{20}H_{20}FNNaO_2^+$ [M+Na$^+$] 348.1371, found 348.1372.



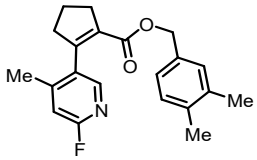
4-Chlorobenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (1h)

Yellow oil, 407 mg, 68%, R_f = 0.35 (petroleum ether/ethyl acetate = 9: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.26 (s, 1H), 7.24 (d, J = 2.1 Hz, 1H), 6.99 – 6.97 (m, 1H), 6.97 – 6.94 (m, 1H), 6.65 (s, 1H), 4.93 (s, 2H), 2.87 (t, J = 7.6 Hz, 2H), 2.73 (t, J = 7.6 Hz, 2H), 2.14 (s, 3H), 2.09 – 2.02 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 163.0 (d, $J_{C\text{-}F}$ = 238.0 Hz), 151.1, 150.0 (d, $J_{C\text{-}F}$ = 8.4 Hz), 144.5 (d, $J_{C\text{-}F}$ = 15.3 Hz), 134.0, 133.9, 133.1, 132.2 (d, $J_{C\text{-}F}$ = 4.7 Hz), 129.3, 128.5, 109.6 (d, $J_{C\text{-}F}$ = 36.9 Hz), 65.2, 41.0, 33.8, 22.0, 19.2 (d, $J_{C\text{-}F}$ = 2.8 Hz).

HR-MS (ESI) m/z Calcd for $C_{19}H_{17}ClFNNaO_2^+$ [M+Na$^+$] 368.0825, found 368.0825.



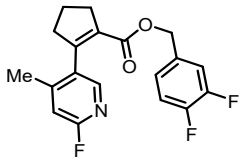
3,4-Dimethylbenzyl 2-(6-fluoropyridin-3-yl)cyclopent-1-ene-1-carboxylate (1i)

Yellow oil, 411 mg, 67%, R_f = 0.35 (petroleum ether/ethyl acetate = 9: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.00 (d, J = 7.5 Hz, 1H), 6.77 (s, 1H), 6.77 (s, 1H), 6.55 (d, J = 1.9 Hz, 1H), 4.88 (s, 2H), 2.85 (t, J = 7.7 Hz, 2H), 2.69 (t, J = 7.7 Hz, 2H), 2.20 (s, 3H), 2.19 (s, 3H), 2.11 (s, 3H), 2.04 – 1.96 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 162.6 (d, $J_{C\text{-}F}$ = 237.2 Hz), 150.1, 149.8 (d, $J_{C\text{-}F}$ = 8.1 Hz), 144.2, 144.0, 136.1 (d, $J_{C\text{-}F}$ = 5.8 Hz), 133.0, 132.5, 132.0 (d, $J_{C\text{-}F}$ = 4.4 Hz), 129.2, 129.0, 125.2, 109.1 (d, $J_{C\text{-}F}$ = 36.8 Hz), 65.6, 40.7, 33.5, 21.6, 19.1, 19.0, 18.9 (d, $J_{C\text{-}F}$ = 2.9 Hz).

HR-MS (ESI) m/z Calcd for $C_{21}H_{22}FNNaO_2^+$ [M+Na$^+$] 362.1527, found 362.1526.



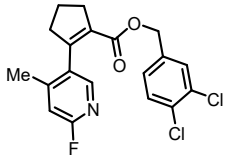
3,4-Difluorobenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (1j)

White solid, m.p.: 53-56 ℃, 354 mg, 51%, R_f = 0.35 (petroleum ether/ethyl acetate = 9: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.02 – 6.94 (m, 1H), 6.77 (dd, J = 13.1, 7.5 Hz, 1H), 6.71 (dd, J = 6.3, 4.2 Hz, 1H), 6.61 (s, 1H), 4.85 (s, 2H), 2.83 – 2.78 (m, 2H), 2.68 (t, J = 7.6 Hz, 2H), 2.11 (s, 3H), 2.03 – 1.95 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 162.8 (d, $J_{C\text{-}F}$ = 236.5Hz), 151.2, 151.1 (d, $J_{C\text{-}F}$ = 246.9 Hz), 150.9 (d, $J_{C\text{-}F}$ = 247.0 Hz), 150.9, 144.2 (d, $J_{C\text{-}F}$ = 15.4 Hz), 132.7, 132.1 (d, $J_{C\text{-}F}$ = 4.4 Hz), 123.8 (d, $J_{C\text{-}F}$ = 6.5, 3.6 Hz), 116.9 (d, $J_{C\text{-}F}$ = 17.4 Hz), 116.6 (d, $J_{C\text{-}F}$ = 17.6 Hz), 109.4 (d, $J_{C\text{-}F}$ = 37.0 Hz), 64.2, 40.8, 33.6, 21.8, 18.9 (d, $J_{C\text{-}F}$ = 2.8 Hz).

HR-MS (ESI) m/z Calcd for $C_{19}H_{18}F_3NNaO_2^+$ [M+Na$^+$] 370.1026 found 370.1027.



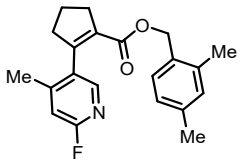
3,4-Dichlorobenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (1k)

Colorless oil, 369 mg, 54%, R_f = 0.36 (petroleum ether/ethyl acetate = 9: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.29 (s, 1H), 7.07 (d, J = 2.1 Hz, 1H), 6.90 – 6.85 (m, 2H), 6.65 (s, 1H), 4.88 (s, 2H), 2.83 (t, J = 7.3 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.14 (s, 3H), 2.06 – 1.98 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 162.9 (d, $J_{C\text{-}F}$ = 237.3 Hz), 151.4, 149.9 (d, $J_{C\text{-}F}$ = 8.2 Hz), 144.5, 144.3, 135.6, 132.7, 132.2, 130.2, 129.4, 126.9, 109.5 (d, $J_{C\text{-}F}$ = 37.0 Hz), 64.3, 40.9, 33.7, 21.8, 19.1 (d, $J_{C\text{-}F}$ = 3.0 Hz).

HR-MS (ESI) m/z Calcd for $C_{19}H_{17}Cl_2FNNaO_2^+$ [M+Na$^+$] 402.0435, found 402.0435.



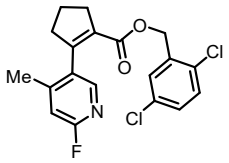
2,4-Dimethylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (1l)

White solid, m.p.: 52-56 ℃, 386 mg, 63%, R_f = 0.36 (petroleum ether/ethyl acetate = 9: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 6.94 (s, 1H), 6.90 (t, J = 6.8 Hz, 2H), 6.53 (s, 1H), 4.95 (s, 2H), 2.85 (d, J = 7.2 Hz, 2H), 2.71 (d, J = 7.4 Hz, 2H), 2.30 (s, 3H), 2.11 (s, 2H), 2.08 (s, 3H), 2.07 – 1.99 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 163.0 (d, $J_{C\text{-}F}$ = 237.7 Hz), 150.6, 150.1 (d, $J_{C\text{-}F}$ = 8.0 Hz), 144.4 (d, $J_{C\text{-}F}$ = 15.3 Hz), 138.3, 136.8, 133.5, 132.3 (d, $J_{C\text{-}F}$ = 4.7 Hz), 131.0, 130.5, 129.4, 126.5, 109.5 (d, $J_{C\text{-}F}$ = 37.0 Hz), 64.5, 41.2, 33.9, 22.1, 21.1, 19.3, 18.5.

HR-MS (ESI) m/z Calcd for $C_{21}H_{22}FNNaO_2^+$ [M+Na$^+$] 362.1527, found 362.1528.



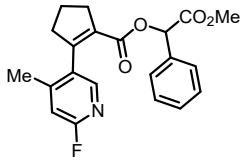
2,5-Dichlorobenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (1m)

White solid, m.p.: 51-56 ℃, 411 mg, 60%, R_f = 0.37 (petroleum ether/ethyl acetate = 9: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.20 – 7.11 (m, 2H), 6.92 (s, 1H), 6.62 (s, 1H), 4.99 (s, 2H), 2.87 (d, J = 7.3 Hz, 2H), 2.72 (t, J = 7.6 Hz, 2H), 2.17 (s, 3H), 2.07 – 1.99 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 162.8 (d, $J_{C\text{-}F}$ = 236.6 Hz), 151.4, 149.8 (d, $J_{C\text{-}F}$ = 8.1 Hz), 144.4 (d, $J_{C\text{-}F}$ = 15.5 Hz), 134.8, 132.6, 132.4, 131.9 (d, $J_{C\text{-}F}$ = 4.4 Hz), 131.2, 130.3, 129.1, 128.8, 109.5 (d, $J_{C\text{-}F}$ = 36.8 Hz), 62.5, 41.0, 33.7, 21.8, 19.1 (d, $J_{C\text{-}F}$ = 2.9 Hz).

HR-MS (ESI) m/z Calcd for $C_{19}H_{17}Cl_2FNNaO_2$+ [M+Na$^+$] 402.0435, found 402.0436.



2-Methoxy-2-oxo-1-phenylethyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (1n)

Yellow oil, 367 mg, 59%, R_f = 0.34 (petroleum ether/ethyl acetate = 9: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.27 – 7.29 (m, 3H), 7.00 – 6.95 (m, 2H), 6.62 (s, 1H), 5.77 (s, 1H), 3.58 (s, 3H), 2.89 (t, J = 7.4 Hz, 2H), 2.74 (d, J = 6.1 Hz, 2H), 2.19 (s, 3H), 2.06 – 1.99 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 163.4, 162.7 (d, $J_{C\text{-}F}$ = 236.1 Hz), 152.0, 150.0 (d, $J_{C\text{-}F}$ = 8.2 Hz), 144.2 (d, $J_{C\text{-}F}$ = 15.5 Hz), 133.0, 132.2, 132.0 (d, $J_{C\text{-}F}$ = 4.5 Hz), 128.7, 128.3, 128.2, 126.9, 109.4 (d, $J_{C\text{-}F}$ = 37.1 Hz), 74.0, 52.0, 41.0, 33.4, 21.6, 18.8 (d, $J_{C\text{-}F}$ = 2.9 Hz).

HR-MS (ESI) m/z Calcd for $C_{21}H_{20}FNNaO_4^+$ [M+Na$^+$] 392.1269, found 392.1269.

3 Screening of template and optimization of reaction conditions

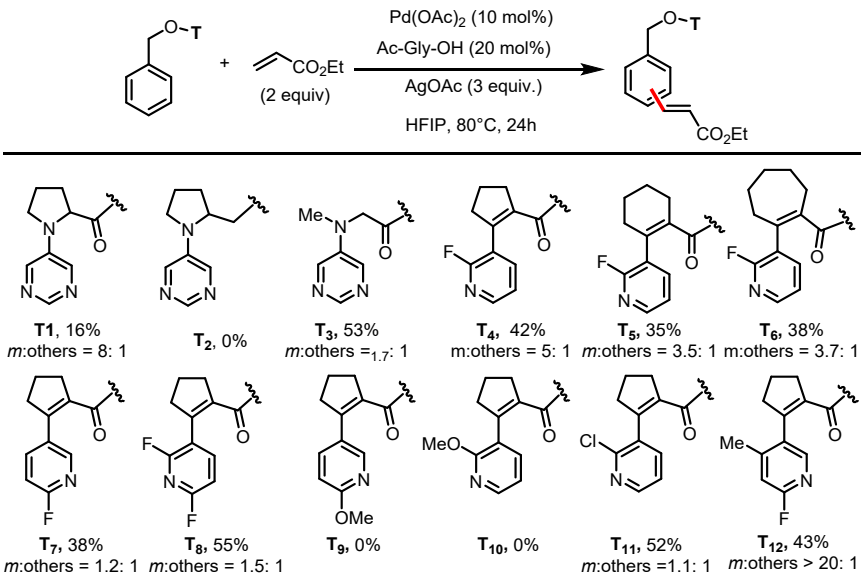
3.1 Screening of template

General procedure:

To a 8-mL sealed tube was charged with substrate (0.2 mmol, 1.0 equiv.), olefin (2.0 equiv.), $Pd(OAc)_2$ (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (3.0 equiv.), and HFIP (2 mL) in turn. The tube was then sealed and submerged into a pre-heated 80 °C heating plate. The reaction mixture was stirred at 80 °C for 24 h. After cooled to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short pad of Celite. Yield and regioselectivity were determined based on the crude ^{1}H NMR spectra with 1,1,2,2-tetrachloroethane as an internal standard.

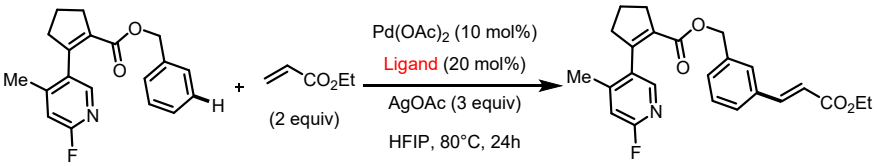
The results for the different directing templates were reported in the ***Table S1.***

Table S1. Screening of template



3.2 Optimization of reaction conditions

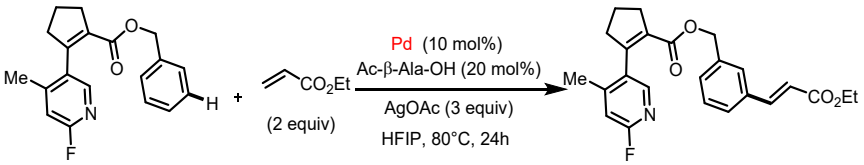
Table S2. Screening of ligand[a,b]



entry	Ligand	Yield(%)	*m*:others
1	Ac-Gly-OH	43	>20: 1
2	Ac-Val-OH	65	>20: 1
3	Ac-β-Ala-OH	80	>20: 1
4	N-Ac-L-phenylalanine	42	>20: 1
5	Ac-Tyr-OH	56	>20: 1
6	N-Acetyl-L-phenylglycine	44	>20: 1
7	N-Acetyl-L-isoleucine	72	13.7: 1
8	Ac-DL-PHG-OH	42	>20: 1
9	N-Acetyl-L-alanine	60	>20: 1
10	2-Acetamido-3,3-dimethylbutanoic Acid	59	>20: 1

[a]Reaction conditions: substrate (0.1 mmol, 1 equiv.), olefin (2.0 equiv.), $Pd(OAc)_2$ (0.01 mmol, 10 mol%), Ligand (0.02 mmol, 20 mol%), AgOAc (0.3 mmol, 3.0 equiv.), HFIP (2 mL), 80 °C, 24 h. [b]Yield and regio-selectivity were determined based on the crude ^1H NMR spectra with 1,1,2,2-tetrachloroethane as an internal standard.

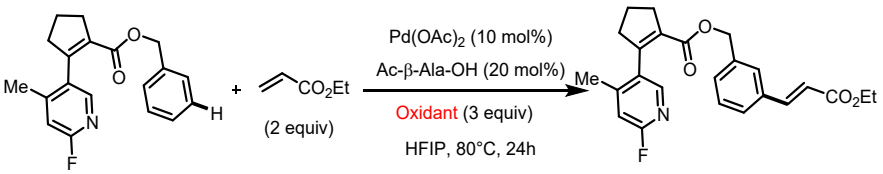
Table S3. Screening of catalyst[a,b]



entry	Pd catalyst	Yield(%)	*m*:others
1	$Pd(OAc)_2$	80	>20: 1
2	$PdCl_2(PhCN)_2$	63	>20: 1
3	$PdCl_2(CH_3CN)_2$	66	>20: 1
4	$Pd(piv)_2$	57	>20: 1
5	$Pd(TFA)_2$	78	>20: 1

[a]Reaction conditions: substrate (0.1 mmol, 1 equiv.), olefin (2.0 equiv.), Pd Catalyst (0.01 mmol, 10 mol%), Ac-β-Ala-OH (0.02 mmol, 20 mol%), AgOAc (0.3 mmol, 3.0 equiv.), HFIP (2 mL), 80 °C, 24 h. [b]Yield and regio-selectivity were determined based on the crude ^1H NMR spectra with 1,1,2,2-tetrachloroethane as an internal standard.

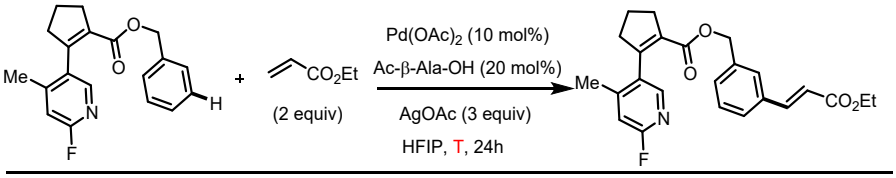
Table S4. Screening of Oxidant[a,b]



entry	oxidant	Yield(%)	*m*:others
1	AgOAc	80	>20: 1
2	OXONE	12	>20: 1
3	AgF	62	16: 1
4	$AgNO_3$	64	17.3: 1
5	Ag_2O	53	18.4: 1
6	Ag_3PO_4	45	>20:1
7	Ag_2CO_3	58	16.4: 1
8	FeO	—	—
9	Silver benzoate	18	>20: 1
10	$Cu(CH_3COO)_2{\cdot}H_2O$	77	16.6: 1
11	Dess-Martin periodinane	—	—

[a]Reaction conditions: substrate (0.1 mmol, 1 equiv.), olefin (2.0 equiv.), $Pd(OAc)_2$ (0.01 mmol, 10 mol%), Ac-β-Ala-OH (0.02 mmol, 20 mol%), Oxidant (0.3 mmol, 3.0 equiv.), HFIP (2 mL), 80 °C, 24 h. [b]Yield and regio-selectivity were determined based on the crude ^{1}H NMR spectra with 1,1,2,2-tetrachloroethane as an internal standard.

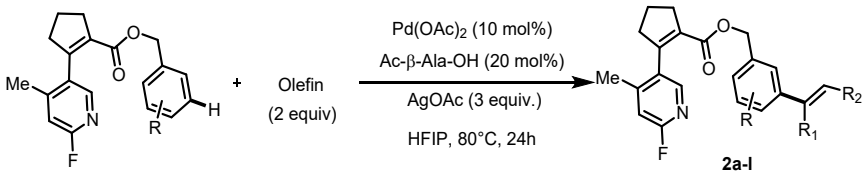
Table S5. Screening of temperature[a,b]



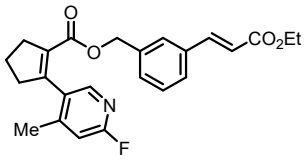
entry	T(°C)	Yield(%)	*m*:others
1	60	75	>20: 1
2	70	78	>20: 1
3	80	80	>20: 1
4	90	84	16.7: 1
5	100	85	14.3: 1

[a]Reaction conditions: substrate (0.1 mmol, 1 equiv.), olefin (2.0 equiv.), $Pd(OAc)_2$ (0.01 mmol, 10 mol%), Ac-β-Ala-OH (0.02 mmol, 20 mol%), AgOAc (0.3 mmol, 3.0 equiv.), HFIP (2 mL),T, 24 h. [b]Yield and regio-selectivity were determined based on the crude ^{1}H NMR spectra with 1,1,2,2-tetrachloroethane as an internal standard.

4 *meta*-C–H olefination of benzyl alcohols



General procedure: An 8-mL sealed tube was charged with substrate (0.1 mmol, 1.0 equiv), olefin (2.0 equiv), $Pd(OAc)_2$ (10 mol%), Ac-β-Ala-OH (20 mol%), AgOAc (3.0 equiv), and HFIP (2 mL). The tube was then sealed and submerged into a pre-heated 80 °C heating plate. The reaction mixture was stirred at 80 °C for 24h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short pad of Celite. The filtrate was concentrated in vacuo, and the resulting residue was purified by preparative TLC using EtOAc/hexanes as the eluent to give the desired product.



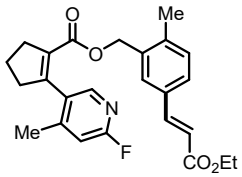
(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)benzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate ($2a_{mono}$)

Colorless oil, 25.0 mg, 61%, R_f = 0.38 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.64 (d, J = 16.0 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.24 (s, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.63 (s, 1H), 6.42 (d, J = 16.0 Hz, 1H), 4.98 (s, 2H), 4.28 (q, J = 7.0 Hz, 2H), 2.87 (d, J = 8.0 Hz, 2H), 2.76 – 2.70 (m, 2H), 2.14 (s, 3H), 2.10 – 2.03 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 164.4, 163.1 (d, $J_{C\text{-}F}$ = 238.3 Hz), 151.2, 150.1 (d, $J_{C\text{-}F}$ = 8.1 Hz), 144.7 (d, $J_{C\text{-}F}$ = 15.5 Hz), 143.9, 136.4, 134.7, 132.2 (d, $J_{C\text{-}F}$ = 4.5 Hz), 129.8, 129.1, 127.7, 127.6, 118.9, 109.7 (d, $J_{C\text{-}F}$ = 37.0 Hz), 65.6, 60.6, 41.1, 33.9, 22.1, 19.3 (d, $J_{C\text{-}F}$ = 2.8 Hz), 14.3.

HR-MS (ESI) m/z Calcd for $C_{24}H_{24}FNNaO_4^+$ [M+Na$^+$] 432.1582, found 432.1583.



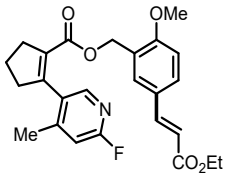
(*E*)-5-(3-Ethoxy-3-oxoprop-1-en-1-yl)-2-methylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (2b)

Colorless oil, 29.6 mg, 70%, R_f = 0.37 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.66 (d, *J* = 16.0 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.26 (s, 1H), 7.17 (d, *J* = 9.0 Hz, 1H), 6.57(s, 1H), 6.41 (d, *J* = 15.9 Hz, 1H), 5.02 (s, 2H), 4.31 (d, *J* = 14.1 Hz, 2H), 2.95 – 2.86 (m, 2H), 2.80 – 2.70 (m, 2H), 2.10 – 2.05 (m, 2H), 1.37 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.76, 165.41 (d, $J_{C\text{-}F}$ = 228.7 Hz), 151.53, 144.61 (d, $J_{C\text{-}F}$ = 15.4 Hz), 143.26, 141.75, 138.47, 135.31 (d, $J_{C\text{-}F}$ = 6.4 Hz), 133.05, 132.40, 130.10, 126.36, 121.55, 118.78, 109.70, 64.19, 60.70, 60.61, 41.07, 33.87, 29.69, 22.07, 19.29, 14.91, 14.31.

HR-MS (ESI) m/z Calcd for $C_{25}H_{26}FNNaO_4^+$ [M+Na$^+$] 446.1739, found 446.1738.



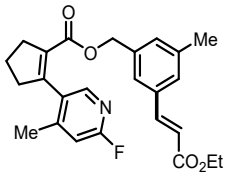
(*E*)-5-(3-Ethoxy-3-oxoprop-1-en-1-yl)-2-methoxybenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (2c)

Colorless oil, 35.2 mg, 80%, R_f = 0.35 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.59 (d, *J* = 16.0 Hz, 1H), 7.44 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.20 (d, *J* = 2.2 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.51 (s, 1H), 6.27 (d, *J* = 16.0 Hz, 1H), 4.98 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 2.91 – 2.83 (m, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 2.12 (s, 3H), 2.08 – 2.01 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 164.6, 162.9 (d, $J_{C\text{-}F}$ = 237.8 Hz), 159.1, 150.7, 150.1 (d, $J_{C\text{-}F}$ = 8.2 Hz), 144.5 (d, $J_{C\text{-}F}$ = 15.5 Hz), 143.9, 133.4, 132.3 (d, $J_{C\text{-}F}$ = 4.4 Hz), 129.8, 129.4, 126.8, 124.5, 116.1, 110.6, 109.4 (d, $J_{C\text{-}F}$ = 36.9 Hz), 61.1, 60.4, 55.5, 41.0, 33.9, 22.1, 19.3 (d, $J_{C\text{-}F}$ = 2.9 Hz), 14.4.

HR-MS (ESI) m/z Calcd for $C_{25}H_{26}FNNaO_5^+$ [M+Na$^+$] 462.1688, found 462.1689.



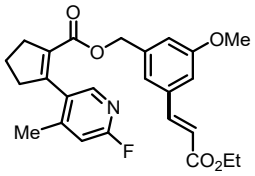
(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)-5-methylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (2d)

Colorless oil, 36.4 mg, 86%, R_f = 0.38 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.61 (d, J = 16.0 Hz, 1H), 7.26 (s, 1H), 7.05 (s, 1H), 6.84 (s, 1H), 6.62 (s, 1H), 6.40 (d, J = 16.0 Hz, 1H), 4.94 (s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 2.93 – 2.86 (m, 2H), 2.77 – 2.71 (m, 2H), 2.34 (s, 3H), 2.14 (s, 3H), 2.08 – 2.03 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 164.5, 163.0 (d, $J_{C\text{-}F}$ = 238.1 Hz), 151.0, 150.1 (d, $J_{C\text{-}F}$ = 8.2 Hz), 144.6 (d, $J_{C\text{-}F}$ = 15.4 Hz), 144.1, 138.9, 136.2, 134.6, 133.2, 132.2 (d, $J_{C\text{-}F}$ = 4.6 Hz), 130.6, 128.4, 124.9, 118.6, 109.6 (d, $J_{C\text{-}F}$ = 36.8 Hz), 65.7, 60.5, 41.1, 33.9, 22.1, 21.1, 19.3 (d, $J_{C\text{-}F}$ = 2.8 Hz), 14.3.

HR-MS (ESI) m/z Calcd for $C_{25}H_{26}FNNaO_4^+$ [M+Na$^+$] 446.1739, found 446.1739.



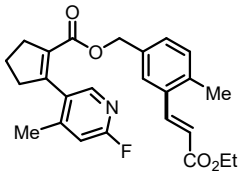
(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)-5-methoxybenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (2e)

Colorless oil, 28.6 mg, 65%, R_f = 0.37 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.60 (d, J = 16.0 Hz, 1H), 6.96 (t, J = 2.0 Hz, 1H), 6.84 (s, 1H), 6.62 (d, J = 15.5 Hz, 2H), 6.40 (d, J = 16.0 Hz, 1H), 4.95 (s, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 2.88 (s, 2H), 2.73 (s, 2H), 2.15 (s, 3H), 2.10 – 2.04 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (d, $J_{C\text{-}F}$ = 245.0 Hz), 156.2, 151.3, 150.1 (d, $J_{C\text{-}F}$ = 8.0 Hz), 144.6 (d, $J_{C\text{-}F}$ = 15.3 Hz), 144.0, 137.7, 136.0, 133.1, 132.1, 120.2, 119.0, 115.8, 112.3, 109.7 (d, $J_{C\text{-}F}$ = 37.0 Hz), 65.5, 60.6, 55.4, 41.1, 33.9, 22.1, 19.3 (d, $J_{C\text{-}F}$ = 2.8 Hz), 14.3.

HR-MS (ESI) m/z Calcd for $C_{25}H_{26}FNNaO_5^+$ [M+Na$^+$] 462.1688, found 462.1689.



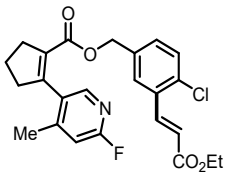
(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)-4-methylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (2f)

Colorless oil, 31.3 mg, 74%, R_f = 0.38 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 15.9 Hz, 1H), 7.79 (s, 1H), 7.29 (d, *J* = 1.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.61 (s, 1H), 6.32 (d, *J* = 15.9 Hz, 1H), 4.94 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.87 (t, *J* = 7.6 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.42 (s, 3H), 2.14 (s, 3H), 2.09 – 2.02 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 164.5, 163.0 (d, $J_{C\text{-}F}$ = 237.9 Hz), 151.0, 150.1 (d, $J_{C\text{-}F}$ = 8.1 Hz), 144.6 (d, $J_{C\text{-}F}$ = 15.3 Hz), 141.8, 137.7, 133.7, 133.5, 133.3, 131.0, 129.7, 126.3, 119.8, 109.6 (d, $J_{C\text{-}F}$ = 36.8 Hz), 65.7, 60.6, 41.1, 33.9, 22.1, 19.5, 19.3 (d, $J_{C\text{-}F}$ = 2.9 Hz), 14.3.

HR-MS (ESI) m/z Calcd for $C_{25}H_{26}FNNaO_4^+$ [M+Na$^+$] 446.1739, found 446.1738.



(*E*)-4-Chloro-3-(3-ethoxy-3-oxoprop-1-en-1-yl)benzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (2g)

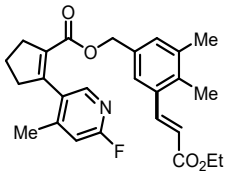
Colorless oil, 22.2 mg, 50%, R_f = 0.36 (petroleum ether/ethyl acetate = 4: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 16.0 Hz, 1H), 7.80 (s, 1H), 7.37 (s, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.66 (s, 1H), 6.39 (d, *J* = 16.0 Hz, 1H), 4.95 (s, 2H), 4.30 (q, *J* =

7.1 Hz, 2H), 2.87 (t, J = 7.6 Hz, 2H), 2.74 (t, J = 6.4 Hz, 2H), 2.16 (s, 3H), 2.10 – 2.03 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 164.3(d, J_{C-F} = 236.9 Hz), 164.3, 151.5, 150.0 (d, J_{C-F} = 8.2 Hz), 144.7 (d, J_{C-F} = 15.4 Hz), 139.8, 134.8, 134.7, 133.0, 132.9, 132.2 (d, J = 4.5 Hz), 130.6, 130.3, 127.3, 121.5, 109.7 (d, J_{C-F} = 36.8 Hz), 65.0, 60.8, 41.1, 33.9, 22.1, 19.3 (d, J_{C-F} = 2.7 Hz), 14.3.

HR-MS (ESI) m/z Calcd for $C_{24}H_{23}ClFNNaO_4^+$ [M+Na$^+$] 466.1192, found 466.1191.



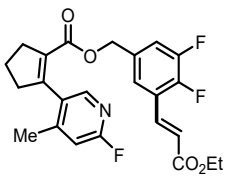
(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)-4,5-dimethylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (2h)

Colorless oil, 30.2 mg, 69%, R_f = 0.39 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 15.8 Hz, 1H), 7.79 (s, 1H), 7.13 (s, 1H), 6.84 (s, 1H), 6.60 (s, 1H), 6.26 (d, J = 15.8 Hz, 1H), 4.90 (s, 2H), 4.28 (q, J = 7.1 Hz, 2H), 2.86 (d, J = 7.7 Hz, 2H), 2.76 – 2.69 (m, 2H), 2.30 (s, 3H), 2.27 (s, 3H), 2.14 (s, 3H), 2.07 – 2.01 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 164.5, 163.0 (d, J_{C-F} = 237.8 Hz), 150.9, 150.1 (d, J_{C-F} = 8.2 Hz), 144.6 (d, J_{C-F} = 15.4 Hz), 142.9, 137.7, 136.2, 133.9, 133.3, 132.9, 132.2 (d, J_{C-F} = 4.4 Hz), 131.3, 124.3, 120.1 (d, J_{C-F} = 2.3 Hz), 109.6 (J_{C-F} = 36.8 Hz), 65.8, 60.5, 41.1, 33.9, 22.1, 20.5, 19.3 (d, J_{C-F} = 2.8 Hz), 15.3, 144.

HR-MS (ESI) m/z Calcd for $C_{26}H_{28}FNNaO_4^+$ [M+Na$^+$] 460.1895, found 460.1896.



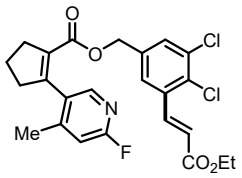
(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)-4,5-difluorobenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (2i)

Colorless oil, 34.7 mg, 78%, R_f = 0.37 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.71 (d, J = 16.2 Hz, 1H), 7.08 – 7.03 (m, 1H), 6.90 – 6.81 (m, 1H), 6.72 (s, 1H), 6.53 (d, J = 16.2 Hz, 1H), 4.93 (s, 2H), 4.29 (q, J = 7.1 Hz, 2H), 2.92 – 2.85 (m, 2H), 2.78 – 2.71 (m, 2H), 2.18 (s, 3H), 2.08 (q, J = 7.6 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 164.4($J_{C\text{-}F}$ = 237.6 Hz), 164.2,151.9($J_{C\text{-}F}$ = 161.5 Hz) 151.8, 150.0 ($J_{C\text{-}F}$ = 8.1 Hz), 149.4($J_{C\text{-}F}$ = 188.6 Hz), 144.9, 144.7, 135.5, 132.8, 132.4, 132.1 ($J_{C\text{-}F}$ = 4.4 Hz), 124.6 ($J_{C\text{-}F}$ = 8.9 Hz), 123.2 ($J_{C\text{-}F}$ = 3.1 Hz), 122.8 ($J_{C\text{-}F}$ = 6.7 Hz), 118.0, 117.8, 109.7 ($J_{C\text{-}F}$ = 36.9 Hz), 64.5, 60.9, 41.1, 33.9, 22.1, 19.3 ($J_{C\text{-}F}$ = 2.8 Hz), 14.3.

HR-MS (ESI) m/z Calcd for $C_{24}H_{22}F_3NNaO_4^+$ [M+Na^+] 468.1394, found 468.1393.



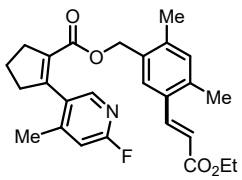
(*E*)-3,4-Dichloro-5-(3-ethoxy-3-oxoprop-1-en-1-yl)benzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (2j)

Colorless oil, 23.0 mg, 48%, R_f = 0.37 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 16.0 Hz, 1H), 7.82 (s, 1H), 7.27 (s, 1H), 7.15 (s, 1H), 6.72 (d, J = 2.0 Hz, 1H), 6.37 (d, J = 16.0 Hz, 1H), 4.93 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H), 2.88 (d, J = 15.2 Hz, 2H), 2.75 (t, J = 7.6 Hz, 2H), 2.18 (s, 3H), 2.11 – 2.04 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 164.4 (d, $J_{C\text{-}F}$ = 237.3 Hz), 164.1, 151.9, 149.9 (d, $J_{C\text{-}F}$ = 8.2 Hz), 144.8 (d, $J_{C\text{-}F}$ = 15.4 Hz), 139.9, 135.5, 135.2, 134.1, 132.8, 132.6, 132.0 (d, $J_{C\text{-}F}$ = 4.6 Hz), 130.6, 125.3, 122.7, 109.7 (d, $J_{C\text{-}F}$ = 37.1 Hz), 64.4, 60.9, 41.1, 33.9, 22.1, 19.3 (d, $J_{C\text{-}F}$ = 2.7 Hz), 14.3.

HR-MS (ESI) m/z Calcd for $C_{24}H_{23}Cl_2FNNaO_4^+$ [M+Na^+] 500.0803, found 500.0805.



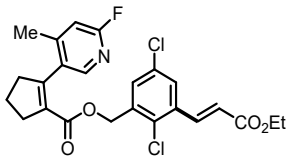
(*E*)-5-(3-Ethoxy-3-oxoprop-1-en-1-yl)-2,4-dimethylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (2k)

Colorless oil, 29.8 mg, 68%, R_f = 0.35 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 15.9 Hz, 1H), 7.76 (s, 1H), 7.30 (s, 1H), 6.97 (s, 1H), 6.52 (s, 1H), 6.30 (d, J = 15.9 Hz, 1H), 4.96 (s, 2H), 4.32 – 4.23 (m, 2H), 2.87 (d, J = 6.4 Hz, 2H), 2.72 (t, J = 7.2 Hz, 2H), 2.39 (s, 3H), 2.12 (s, 2H), 2.08 (s, 2H), 2.07 – 2.01 (m, 2H), 1.38 – 1.32 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 164.5, 163.0 (d, $J_{C\text{-}F}$ = 238.1 Hz), 151.0, 150.1 (d, $J_{C\text{-}F}$ = 8.3 Hz), 144.4 (d, $J_{C\text{-}F}$ $J_{C\text{-}F}$ = 15.4 Hz), 141.7, 139.3, 138.1, 133.3, 132.9, 132.2 (d, $J_{C\text{-}F}$ = 4.4 Hz), 131.7, 131.0, 127.8, 118.7, 109.5 (d, $J_{C\text{-}F}$ = 36.8 Hz), 64.0, 60.5, 41.1, 33.9, 22.1, 19.37, 19.3 (d, $J_{C\text{-}F}$ = 2.8 Hz), 18.5, 14.4.

HR-MS (ESI) m/z Calcd for $C_{26}H_{28}FNNaO_4^+$ [M+Na$^+$] 460.5006, found 460.5004.



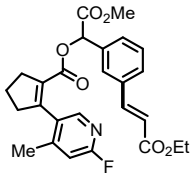
(*E*)-2,5-Dichloro-3-(3-ethoxy-3-oxoprop-1-en-1-yl)benzyl 2-(6-fluoro-4-methylpyridin -3-yl)cyclopent-1-ene-1-carboxylate (2l)

Colorless oil, 26.8 mg, 56%, R_f = 0.39 (petroleum ether/ethyl acetate = 4: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 16.0 Hz, 1H), 7.81 (s, 1H), 7.52 (s, 1H), 6.98 (s, 1H), 6.69 (s, 1H), 6.40 (d, J = 16.0 Hz, 1H), 5.08 (s, 2H), 4.29 (q, J = 7.1 Hz, 2H), 2.92 (t, J = 7.5 Hz, 2H), 2.76 (t, J = 7.6 Hz, 2H), 2.22 (s, 3H), 2.12 – 2.05 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 164.3 (d, $J_{C\text{-}F}$ = 237.1 Hz), 164.0, 151.9, 149.9, 144.7 (d, $J_{C\text{-}F}$ = 15.7 Hz), 139.0, 136.2, 135.0, 132.9, 132.8, 132.1, 131.8, 129.8, 127.0, 122.8, 109.8 (d, $J_{C\text{-}F}$ = 37.1 Hz), 63.0, 60.9, 41.2, 33.9, 22.1, 19.4, 14.2.

HR-MS (ESI) m/z Calcd for $C_{24}H_{23}Cl_2FNNaO_4^+$ [M+Na$^+$] 500.0803, found 501.0804.



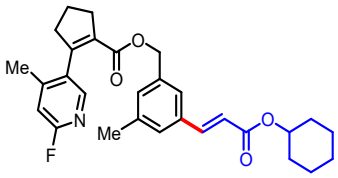
(*E*)-2-Ethoxy-1-(3-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)-2-oxoethyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (2m)

Colorless oil, 29.4 mg, 61%, R_f = 0.38 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.63 (d, J = 16.0 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.68 (s, 1H), 6.42 (d, J = 16.0 Hz, 1H), 5.81 (s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.67 (s, 3H), 2.96 – 2.91 (m, 2H), 2.81 – 2.74 (m, 2H), 2.24 (s, 3H), 2.12 – 2.05 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 166.7, 164.3 (d, $J_{C\text{-}F}$ = 237.0 Hz), 163.7, 152.7, 150.2 (d, $J_{C\text{-}F}$ $J_{C\text{-}F}$ = 7.9 Hz), 144.8, 144.7, 143.5, 135.0, 134.3, 132.3 (d, $J_{C\text{-}F}$ = 27.7 Hz), 132.1, 129.3, 128.9, 127.0, 119.3, 109.7 (d, $J_{C\text{-}F}$ = 36.9 Hz), 73.9, 60.6, 52.7, 41.4, 33.9, 22.1, 19.3 (d, $J_{C\text{-}F}$ = 2.8 Hz), 14.3.

HR-MS (ESI) m/z Calcd for $C_{26}H_{26}FNNaO_6^+$ [M+Na$^+$] 504.1793, found 504.1794.



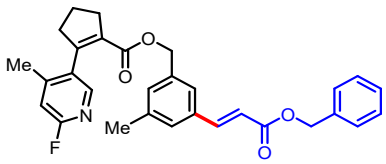
(*E*)-3-(3-(Cyclohexyloxy)-3-oxoprop-1-en-1-yl)-5-methylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (3a)

Colorless oil, 40. 6 mg, 85%, R_f = 0.37 (petroleum ether/ethyl acetate = 4: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.59 (d, J = 16.0 Hz, 1H), 7.05 (s, 1H), 6.83 (s, 1H), 6.62 (s, 1H), 6.40 (d, J = 16.0 Hz, 1H), 4.94 (s, 2H), 4.89 (td, J = 9.0, 4.5 Hz, 1H), 2.88 (t, J = 7.6 Hz, 2H), 2.73 (t, J = 7.6 Hz, 2H), 2.33 (s, 3H), 2.14 (s, 3H), 2.09 – 2.01 (m, 2H), 1.92 (dd, J = 9.4, 4.2 Hz, 2H), 1.83 – 1.73 (m, 2H), 1.61 – 1.34 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 164.5, 163.0 (d, $J_{C\text{-}F}$ = 237.8 Hz), 151.0, 150.1, 144.8, 144.6, 143.8, 138.9, 136.2, 134.7, 133.2, 132.2, 130.6, 128.4, 124.9, 119.2, 109.6 (d, $J_{C\text{-}F}$ = 36.1 Hz), 72.8, 65.7, 41.1, 33.9, 31.7, 29.7, 25.4, 23.8, 22.1, 21.2, 19.3 (d, $J_{C\text{-}F}$ = 2.5 Hz).

HR-MS (ESI) m/z Calcd for $C_{29}H_{32}FNNaO_4^+$ [M+Na$^+$] 500.2208, found 500.2209.



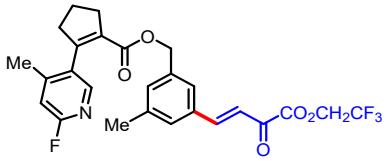
(*E*)-3-(3-(Benzyloxy)-3-oxoprop-1-en-1-yl)-5-methylbenzyl 2-(6-fluoro-4-methylpyridin

-3-yl)cyclopent-1-ene-1-carboxylate (3b)

Colorless oil, 42.7 mg, 88%, R_f = 0.34 (petroleum ether/ethyl acetate = 10: 1, V/V) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.65 (d, J = 16.0 Hz, 1H), 7.49 – 7.29 (m, 5H), 7.05 (s, 1H), 6.84 (s, 1H), 6.60 (s, 1H), 6.45 (d, J = 16.0 Hz, 1H), 5.26 (s, 2H), 4.94 (s, 2H), 2.88 (t, J = 7.6 Hz, 2H), 2.72 (t, J = 7.7 Hz, 2H), 2.33 (s, 3H), 2.13 (s, 3H), 2.09 – 2.01 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 164.5, 163.0 (d, $J_{C\text{-}F}$ = 238.0 Hz), 151.1, 150.0, 144.7, 144.6, 139.0, 136.3, 136.1, 134.5, 133.2, 132.2, 130.8, 128.6, 128.5, 128.3 (d, $J_{C\text{-}F}$ = 1.5 Hz), 125.0, 118.2, 109.6 (d, $J_{C\text{-}F}$ = 36.8 Hz), 66.4, 65.7, 41.1, 33.9, 22.1, 21.2, 19.3.

HR-MS (ESI) m/z Calcd for $C_{30}H_{28}FNNaO_4^+$ [M+Na$^+$] 508.1895, found 508.1895.



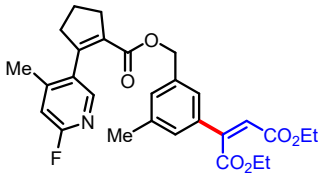
(*E*)-3-Methyl-5-(3-oxo-3-(2,2,2-trifluoroethoxy)prop-1-en-1-yl)benzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (3c)

Colorless oil, 36.8 mg, 77%, R_f = 0.32 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.72 (d, J = 16.0 Hz, 1H), 7.29 (s, 1H), 7.06 (s, 1H), 6.88 (s, 1H), 6.62 (s, 1H), 6.45 (d, J = 16.0 Hz, 1H), 4.94 (s, 2H), 4.60 (q, J = 8.4 Hz, 2H), 2.88 (t, J = 7.7 Hz, 2H), 2.73 (t, J = 7.7 Hz, 2H), 2.35 (s, 3H), 2.15 (s, 3H), 2.07 (q, J = 7.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.5, 164.2 (d, $J_{C\text{-}F}$ = 237.5 Hz), 151.1, 150.1 (d, $J_{C\text{-}F}$ = 7.9 Hz), 146.7, 144.7 (d, $J_{C\text{-}F}$ = 15.2 Hz), 139.1, 136.4, 134.0, 133.2, 131.3, 128.7, 125.2, 116.2, 109.6 (d, $J_{C\text{-}F}$ = 37.1 Hz), 65.6, 60.6, 60.2, 599, 41.1, 33.9, 22.1, 21.1, 19.3 (d, $J_{C\text{-}F}$ = 2.9 Hz).

HR-MS (ESI) m/z Calcd for $C_{25}H_{23}F_4NNaO_4^+$ [M+Na$^+$] 500.1456, found 500.1457.



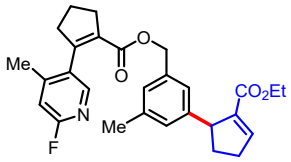
Dimethyl 2-(3-(((2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carbonyl)oxy)methyl)-5-methylphenyl)maleate (3d)

Yellow oil, 38.1 mg, 84%, R_f = 0.35 (petroleum ether/ethyl acetate = 2: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.18 (s, 1H), 7.03 (s, 1H), 6.86 (s, 1H), 6.61 (s, 1H), 6.26 (s, 1H), 4.91 (s, 2H), 3.92 (s, 3H), 3.78 (s, 3H), 2.85 (t, J = 7.7 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.34 (s, 3H), 2.14 (s, 3H), 2.10 – 2.02 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 165.4, 164.4, 163.0 (d, $J_{C\text{-}F}$ = 237.9 Hz), 151.2, 150.1 (d, $J_{C\text{-}F}$ = 8.5 Hz), 148.7, 144.5 (d, $J_{C\text{-}F}$ = 15.5 Hz), 139.3, 136.5, 133.4, 133.1, 131.1, 127.2, 123.6, 117.4, 109.6 (d, $J_{C\text{-}F}$ = 37.1 Hz), 65.6, 52.8, 52.1, 41.1, 33.9, 22.1, 21.2, 19.3 (d, $J_{C\text{-}F}$ = 2.9 Hz).

HR-MS (ESI) m/z Calcd for $C_{26}H_{26}FNNaO_6^+$ [M+Na$^+$] 476.1637, found 476.1638.



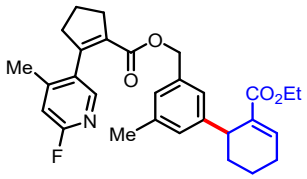
3-(2-(Methoxycarbonyl)cyclopent-2-en-1-yl)-5-methylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (3e)

Colorless oil, 36.0 mg, 80%, R_f = 0.38 (petroleum ether/ethyl acetate = 4: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 6.99 (s, 1H), 6.88 (s, 1H), 6.72 (s, 1H), 6.69 – 6.53 (m, 2H), 4.91 (s, 2H), 4.08 (d, J = 4.8 Hz, 1H), 3.62 (s, 3H), 2.87 (t, J = 7.6 Hz, 2H), 2.72 (t, J = 7.6 Hz, 2H), 2.69 – 2.58 (m, 1H), 2.50 (s, 2H), 2.28 (s, 3H), 2.14 (s, 3H), 2.08 – 2.02 (m, 2H), 1.84 (dq, J = 12.7, 4.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.6, 163.0 (d, $J_{C\text{-}F}$ = 237.6 Hz), 150.6, 150.3 (d, $J_{C\text{-}F}$ = 8.3 Hz), 145.3, 145.1, 144.6 (d, $J_{C\text{-}F}$ = 15.4 Hz), 139.0, 138.2, 135.5, 133.4, 132.3 (d, $J_{C\text{-}F}$ = 4.4 Hz), 127.4, 126.8, 123.9, 109.6 (d, $J_{C\text{-}F}$ = 37.0 Hz), 66.2, 51.3, 49.8, 41.2, 34.1, 33.9, 32.2, 22.1, 21.3, 19.3 (d, $J_{C\text{-}F}$ = 2.7 Hz).

HR-MS (ESI) m/z Calcd for $C_{27}H_{28}FNNaO_4^+$ [M+Na$^+$] 472.1895, found 472.1895.



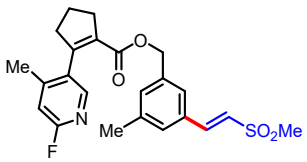
Methyl 3'-(((2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carbonyl)oxy)methyl)-5'-methyl-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (3f)

Yellow oil, 29.2 mg, 63%, R_f = 0.38 (petroleum ether/ethyl acetate = 4: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.25 (t, J = 4.0 Hz, 1H), 6.86 (s, 1H), 6.72 (s, 1H), 6.64 (s, 2H), 3.86 (s, 1H), 3.60 (s, 3H), 2.87 (t, J = 7.6 Hz, 2H), 2.75 – 2.70 (m, 2H), 2.45 – 2.29 (m, 2H), 2.28 (s, 3H), 2.27 – 2.21 (m, 1H), 2.14 (s, 3H), 2.08 – 2.02 (m, 2H), 1.92 – 1.85 (m, 1H), 1.73 – 1.67 (m, 1H), 1.49 (ddd, J = 11.7, 7.2, 2.8 Hz, 2H), 1.26 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 164.5, 163.0 (d, $J_{C\text{-}F}$ = 237.7 Hz), 150.6, 150.3 (d, $J_{C\text{-}F}$ = 8.1 Hz), 145.2, 144.6 (d, $J_{C\text{-}F}$ = 15.4 Hz), 141.7, 137.9, 135.2, 133.4, 132.3, 131.7, 128.3, 126.6, 124.6, 109.6 (d, $J_{C\text{-}F}$ = 36.9 Hz), 66.2, 51.5, 41.2, 39.3, 34.0, 31.3, 25.9, 22.1, 21.3, 19.3, 16.9.

HR-MS (ESI) m/z Calcd for $C_{28}H_{30}FNNaO_4^+$ [M+Na$^+$] 486.2052, found 486.2053.



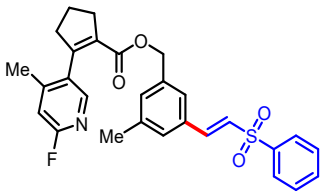
(*E*)-3-Methyl-5-(2-(methylsulfonyl)vinyl)benzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (3g)

Yellow oil, 33.9 mg, 79%, R_f = 0.38 (petroleum ether/ethyl acetate = 2: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.53 (d, J = 15.4 Hz, 1H), 7.23 (s, 1H), 6.98 (s, 1H), 6.92 (d, J = 3.8 Hz, 1H), 6.91 (s, 1H), 6.63(s, 1H), 4.94 (s, 2H), 3.06 (s, 3H), 2.90 – 2.85 (m, 2H), 2.73 (t, J = 7.6 Hz, 2H), 2.34 (s, 3H), 2.15 (s, 3H), 2.10 – 2.04 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 163.0 (d, $J_{C\text{-}F}$ = 238.2 Hz), 151.1, 150.2 (d, $J_{C\text{-}F}$ = 8.2 Hz), 144.7 (d, $J_{C\text{-}F}$ = 15.3 Hz), 143.4, 139.3, 136.6, 133.2, 132.4, 131.6, 129.1, 126.6, 125.1, 109.6 (d, $J_{C\text{-}F}$ = 36.8 Hz), 65.5, 43.3, 41.1, 33.9, 29.7, 22.1, 21.1, 19.3 (d, $J_{C\text{-}F}$ = 2.9 Hz).

HR-MS (ESI) m/z Calcd for $C_{23}H_{24}FNNaO_4S^+$ [M+Na$^+$] 452.1303, found 452.1304.



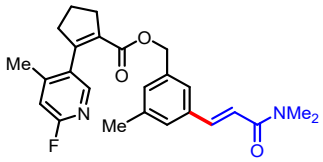
(*E*)-3-Methyl-5-(2-(phenylsulfonyl)vinyl)benzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (3h)

Colorless oil, 28.0 mg, 57%, R_f = 0.36 (petroleum ether/ethyl acetate = 2: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.7 Hz, 2H), 7.79 (s, 1H), 7.65 – 7.52 (m, 4H), 7.22 (s, 1H), 7.01 (s, 1H), 6.85 (d, J = 15.4 Hz, 2H), 6.62 (s, 1H), 4.92 (s, 2H), 2.88 (d, J = 7.9 Hz, 2H), 2.73 (t, J = 7.4 Hz, 2H), 2.32 (s, 3H), 2.14 (s, 3H), 2.10 – 2.02 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 163.0 (d, $J_{C\text{-}F}$ = 237.9 Hz), 151.2, 150.1 (d, $J_{C\text{-}F}$ = 8.1 Hz), 144.7 (d, $J_{C\text{-}F}$ = 15.1 Hz), 142.0, 140.7, 139.2, 136.6, 133.4, 133.1, 132.5, 132.3, 131.5, 129.4, 128.9, 127.7, 127.6, 125.3, 109.6 (d, $J_{C\text{-}F}$ = 36.8 Hz), 65.4, 41.1, 33.9, 22.1, 21.1, 19.3 (d, $J_{C\text{-}F}$ = 2.7 Hz).

HR-MS (ESI) m/z Calcd for $C_{28}H_{26}FNNaO_4S^+$ [M+Na^+] 514.1459, found 514.1458.



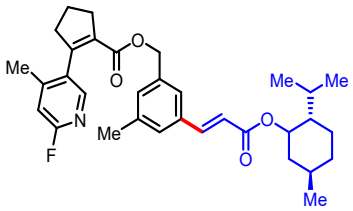
(*E*)-3-(3-(Dimethylamino)-3-oxoprop-1-en-1-yl)-5-methylbenzyl 2-(6-fluoropyridin-3-yl)cyclopent-1-ene-1-carboxylate (3i)

Yellow oil, 27.0 mg, 66%, R_f = 0.38 (petroleum ether/ethyl acetate = 2: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.59 (d, J = 15.4 Hz, 1H), 7.25 (s, 1H), 7.07 (s, 1H), 6.87 (d, J = 15.4 Hz, 1H), 6.82 (s, 1H), 6.62 (s, 1H), 4.94 (s, 2H), 3.20 (s, 3H), 3.08 (s, 3H), 2.87 (t, J = 4.6 Hz, 2H), 2.76 – 2.69 (m, 2H), 2.34 (s, 3H), 2.13 (s, 3H), 2.06 (p, J = 7.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 164.5, 163.0 (d, $J_{C\text{-}F}$ = 238.2 Hz), 150.9, 150.2 (d, $J_{C\text{-}F}$ = 8.7 Hz), 144.6 (d, $J_{C\text{-}F}$ = 15.4 Hz), 141.9, 138.8, 136.1, 135.6, 133.3, 132.3, 130.0, 128.3, 124.6, 117.8, 109.6 (d, $J_{C\text{-}F}$ = 37.1 Hz), 65.8, 41.1, 33.9, 22.1, 21.2, 19.3 (d, $J_{C\text{-}F}$ = 2.9 Hz).

HR-MS (ESI) m/z Calcd for $C_{24}H_{25}FN_2NaO_3^+$ [M+Na^+] 431.1742, found 431.1742.



3-((*E*)-3-(((2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)-3-oxoprop-1-en-1-yl)-5-methylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (3j)

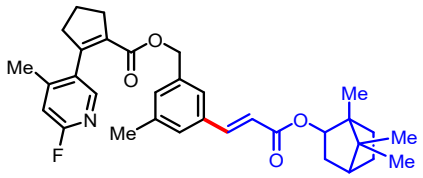
Colorless oil, 42.2 mg, 79%, R_f = 0.38 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.57 (d, J = 15.9 Hz, 1H), 7.24 (s, 1H), 7.03 (s, 1H), 6.80 (s, 1H), 6.60 (s, 1H), 6.37 (d, J = 18.2 Hz, 1H), 4.91 (s, 2H), 4.81 (d, J = 12.5 Hz, 1H), 2.86

(d, J = 5.8 Hz, 2H), 2.70 (t, J = 6.9 Hz, 2H), 2.31 (s, 3H), 2.12 (s, 3H), 2.03 (t, J = 7.1 Hz, 3H), 1.93 (d, J = 14.9 Hz, 1H), 1.68 (d, J = 12.7 Hz, 2H), 1.51 – 1.14 (m, 2H), 1.10 – 1.01 (m, 2H), 0.90 (s, 7H), 0.77 (d, J = 5.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.5, 163.0 (d, $J_{C\text{-}F}$ = 238.0 Hz), 151.0, 150.1 (d, $J_{C\text{-}F}$ = 8.1 Hz), 144.8, 144.6, 143.9, 138.9, 136.2, 134.7, 133.2, 132.2, 130.6, 128.4, 124.9, 119.1, 109.6 (d, $J_{C\text{-}F}$ = 36.9 Hz), 74.3, 65.7, 47.2, 41.1, 41.0, 34.3, 33.9, 31.4, 26.4, 23.56, 22.1 (d, $J_{C\text{-}F}$ = 3.1 Hz), 21.1, 20.8, 19.3 (d, $J_{C\text{-}F}$ = 2.8 Hz), 16.4.

HR-MS (ESI) m/z Calcd for $C_{33}H_{40}FNNaO_4^+$ [M+Na$^+$] 556.2834, found 556.2835.



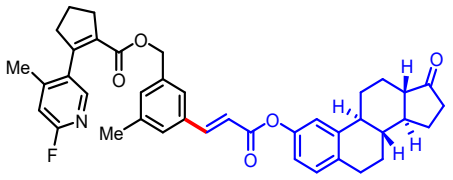
(*E*)-3-Methyl-5-(3-oxo-3-((1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)prop-1-en-1-yl)benzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (3k)

Colorless oil, 43.1 mg, 82%, R_f = 0.36 (petroleum ether/ethyl acetate = 5: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.60 (d, J = 15.9 Hz, 1H), 7.28 (s, 1H), 7.07 (s, 1H), 6.84 (s, 1H), 6.63 (s, 1H), 6.44 (d, J = 15.9 Hz, 1H), 5.03 (d, J = 10.0 Hz, 1H), 4.94 (s, 2H), 2.88 (t, J = 7.6 Hz, 2H), 2.73 (t, J = 7.6 Hz, 2H), 2.43 (t, J = 12.2 Hz, 1H), 2.34 (s, 3H), 2.14 (s, 3H), 2.10 – 2.02 (m, 3H), 1.82 – 1.74 (m, 1H), 1.71 (s, 1H), 1.40 – 1.28 (m, 2H), 1.07 (d, J = 16.9 Hz, 1H), 0.95 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (1010 MHz, $CDCl_3$) δ 167.1, 164.4, 162.9 (d, $J_{C\text{-}F}$ = 237.7 Hz), 150.9, 150.0 (d, $J_{C\text{-}F}$ = 8.1 Hz), 144.6 (d, $J_{C\text{-}F}$ = 15.1 Hz), 143.7, 138.8, 136.1, 134.6, 133.1, 130.5, 128.4, 124.9, 119.0, 109.5 (d, $J_{C\text{-}F}$ = 37.1 Hz), 80.0, 65.6, 48.9, 47.8, 44.9, 41.0, 36.8, 33.8, 28.0, 27.2, 22.0, 21.1, 19.7, 19.2 (d, $J_{C\text{-}F}$ = 2.7 Hz), 18.8, 13.5.

HR-MS (ESI) m/z Calcd for $C_{33}H_{38}FNNaO_4^+$ [M+Na$^+$] 554.2678, found 554.2677.



3-Methyl-5-((*E*)-3-oxo-3-(((8*S*,9*S*,13*S*,14*S*)-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-2-yl)oxy)prop-1-en-1-yl)benzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (3l)

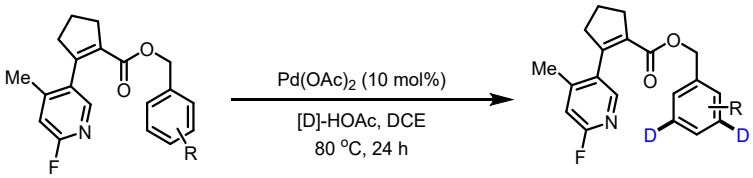
Yellow oil, 46.3 mg, 73%, R_f = 0.35 (petroleum ether/ethyl acetate = 1: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.61 (d, *J* = 15.3 Hz, 1H), 7.22 (s, 1H), 7.03 (s, 1H), 6.83 (t, *J* = 7.9 Hz, 2H), 6.61 (s, 1H), 6.53 (dd, *J* = 16.8, 10.5 Hz, 1H), 6.30 (d, *J* = 16.7 Hz, 1H), 5.71 (d, *J* = 10.5 Hz, 1H), 4.92 (s, 2H), 3.73 (s, 8H), 3.68 (s, 6H), 3.55 (s, 2H), 2.86 (t, *J* = 7.6 Hz, 2H), 2.71 (t, *J* = 8.0 Hz, 2H), 2.32 (s, 3H), 2.12 (s, 3H), 2.08 – 2.00 (m, 2H).

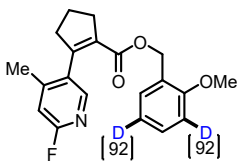
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.49 (d, $J_{C\text{-}F}$ = 8.0 Hz), 164.45, 163.00 (d, $J_{C\text{-}F}$ = 238.0 Hz), 150.94, 150.13 (d, $J_{C\text{-}F}$ = 8.1 Hz), 144.60 (d, $J_{C\text{-}F}$ = 15.0 Hz), 142.69, 138.80, 136.12, 135.34, 133.28, 132.34, 130.28, 128.54, 128.27, 127.04, 124.46, 116.94, 109.60 (d, $J_{C\text{-}F}$ = 36.8 Hz), 66.89, 66.77, 65.74, 46.21, 42.37 (d, $J_{C\text{-}F}$ = 26.4 Hz), 41.10, 33.90, 22.06, 21.14, 19.30 (d, $J_{C\text{-}F}$ = 3.0 Hz).

HR-MS (ESI) m/z Calcd for $C_{40}H_{40}FNNaO_5^+$ [M+Na$^+$] 656.2783, found 656.2782.

5 *meta*-C–H deuteration of benzyl alcohols



An 8-mL sealed tube was charged with substrate (0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol%), Acetic acid-d_1 (0.5 mL) and DCE (0.5 mL). The tube was then sealed and submerged into a pre-heated 80 °C heating plate. The reaction mixture was stirred at 80 °C for 24 h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short pad of Celite. The filtrate was concentrated in vacuo, and the resulting residue was purified by preparative TLC using EtOAc/hexanes as the eluent to give the desired product **4a-h**.



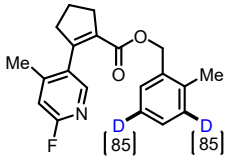
Methoxybenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (4a)

Colorless oil, 30.2 mg, 88%, R_f = 0.35 (petroleum ether/ethyl acetate = 6: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.25 (s, 1H), 6.89 (d, J = 1.7 Hz, 1H), 6.49 (d, J = 1.7 Hz, 1H), 4.99 (s, 2H), 3.73 (s, 3H), 2.86 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 2.09 (s, 3H), 2.06 – 1.99 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 162.9 (d, $J_{C\text{-}F}$ = 237.0 Hz), 157.3, 150.3, 150.2, 144.4 (d, $J_{C\text{-}F}$ = 15.3 Hz), 133.6, 132.4, 129.4 (d, $J_{C\text{-}F}$ = 3.2 Hz), 129.3 (d, $J_{C\text{-}F}$ = 3.3 Hz), 123.7, 119.9, 109.4 (d, $J_{C\text{-}F}$ = 37.5 Hz), 61.6, 55.2, 41.2, 33.9, 22.0, 19.2.

HR-MS (ESI) m/z Calcd for $C_{20}H_{18}D_2FNNaO_3^+$ [M+Na$^+$] 366.3838, found 366.3838.



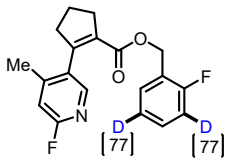
Methylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (4b)

Colorless oil, 28.1 mg, 86%, R_f = 0.39 (petroleum ether/ethyl acetate = 6: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.21 (s, 1H), 7.13 (s, 1H), 7.00 (s, 1H), 6.54 (s, 1H), 5.00 (s, 2H), 2.93 – 2.84 (m, 2H), 2.73 (s, 2H), 2.12 (s, 3H), 2.11 (s, 3H), 2.09 – 2.01 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 163.0 (d, $J_{C\text{-}F}$ = 236.5 Hz), 150.7, 150.1, 144.5, 144.4, 136.8 (d, $J_{C\text{-}F}$ = 8.7 Hz), 133.4, 132.3, 130.2, 129.0, 128.3 (d, $J_{C\text{-}F}$ = 11.1 Hz), 125.9, 109.6 (d, $J_{C\text{-}F}$ = 37.1 Hz), 64.4, 41.2, 33.9 (d, $J_{C\text{-}F}$ = 2.3 Hz), 22.0, 19.3, 18.6 (d, $J_{C\text{-}F}$ = 6.7 Hz).

HR-MS (ESI) m/z Calcd for $C_{20}H_{18}D_2FNNaO_2^+$ [M+Na$^+$]350.3848, found 350.3848.



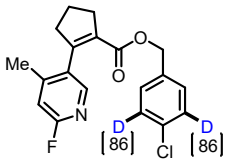
Fluorobenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (4c)

Colorless oil, 26.2 mg, 79%, R_f = 0.44 (petroleum ether/ethyl acetate = 6: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.29 (s, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.57 (s, 1H), 5.03 (s, 2H), 2.88 (t, J = 7.7 Hz, 2H), 2.73 (t, J = 7.7 Hz, 2H), 2.14 (s, 3H), 2.09 – 2.02 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 163.0 (d, $J_{C\text{-}F}$ = 237.8 Hz), 159.6, 151.0, 150.1 (d, $J_{C\text{-}F}$ = 8.2 Hz), 144.5, 144.4, 133.3, 132.3 (d, $J_{C\text{-}F}$ = 4.4 Hz), 130.5 – 130.3 (m), 130.1 (d, $J_{C\text{-}F}$ = 10.9, 8.1 Hz), 124.0, 122.6 (d, $J_{C\text{-}F}$ = 14.6 Hz), 109.5 (d, $J_{C\text{-}F}$ = 36.9 Hz), 60.1 (d, $J_{C\text{-}F}$ = 4.2 Hz), 41.2, 33.9, 22.1, 19.2 (d, $J_{C\text{-}F}$ = 2.8 Hz).

HR-MS (ESI) m/z Calcd for $C_{19}H_{15}D_2F_2NNaO_2^+$ [M+Na$^+$] 354.3482, found 354.3483.



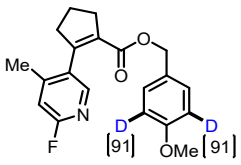
Chlorobenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (4d)

Yellow oil, 28.5 mg, 82%, R_f = 0.41 (petroleum ether/ethyl acetate = 6: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.24, 6.96 (d, J = 7.7 Hz, 2H), 6.65 (d, J = 1.9 Hz, 1H), 4.93 (s, 2H), 2.86 (t, J = 4.2 Hz, 2H), 2.73 (m, 2H), 2.14 (s, 3H), 2.06 – 2.01 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 163.1 (d, $J_{C\text{-}F}$ = 238.0 Hz), 151.2, 150.1 (d, $J_{C\text{-}F}$ = 8.1 Hz), 144.7, 144.5, 134.0, 133.2, 132.3, 129.4, 129.3, 128.6, 109.7 (d, $J_{C\text{-}F}$ = 37.0 Hz), 65.3, 41.1, 33. 9, 29.7, 22.1, 19.3 (d, $J_{C\text{-}F}$ = 2.8 Hz).

HR-MS (ESI) m/z calcd for $C_{19}H_{15}D_2ClFNNaO_2^+$ [M+Na$^+$] 370.7998, found 370.8001.



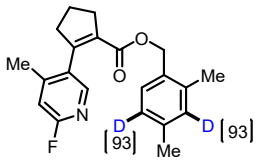
Methoxybenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (4e)

Colorless oil, 29.5 mg, 86%, R_f = 0.54 (petroleum ether/ethyl acetate = 6: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 6.97 (s, 2H), 6.59 (s, 1H), 4.89 (s, 2H), 3.82 (s, 3H), 2.85 (t, J = 7.5 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.11 (s, 3H), 2.07 – 2.00 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 163.0 (d, $J_{C\text{-}F}$ = 237.6 Hz), 159.5, 150.6, 150.2 (d, $J_{C\text{-}F}$ = 8.1 Hz), 144.6, 144.4, 133.5, 132.4, 129.8, 129.7, 127.6, 113.8, 109.6 (d, $J_{C\text{-}F}$ = 36.8 Hz), 65.9, 55.3, 41.1, 33.9, 22.1, 19.3 (d, $J_{C\text{-}F}$ = 2.6 Hz).

HR-MS (ESI) m/z Calcd for $C_{20}H_{18}D_2FNNaO_3^+$ [M+Na$^+$] 366.3838, found 366.3838.



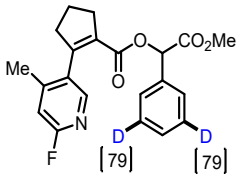
Dimethylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (4f)

Yellow oil, 30.4 mg, 89%, R_f = 0.35 (petroleum ether/ethyl acetate = 6: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 6.89 (s, 1H), 6.53 (s, 1H), 4.85 (s, 2H), 2.86 (t, J = 7.6 Hz, 2H), 2.71 (t, J = 7.5 Hz, 2H), 2.31 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.06 – 2.02 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 163.0 (d, $J_{C\text{-}F}$ = 237.9 Hz), 150.6, 150.1 (d, $J_{C\text{-}F}$ = 8.3 Hz), 144.5, 144.3, 138.2, 136.7, 133.5, 132.3 (d, $J_{C\text{-}F}$ = 4.4 Hz), 131.0, 130.5, 109.6 (d, $J_{C\text{-}F}$ = 37.1 Hz), 64.3, 41.2, 33.9, 22.1, 21.0, 20.9, 19.3 (d, $J_{C\text{-}F}$ = 3.0 Hz).

HR-MS (ESI) m/z Calcd for $C_{21}H_{10}D_2FNNaO_2^+$ [M+Na$^+$] 364.4118, found 364.4116.



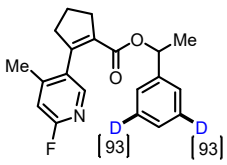
2-Methoxy-2-oxo-1-(phenyl-3,5-d_2)ethyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (4g)

Yellow oil, 27.9 mg, 75%, R_f = 0.33 (petroleum ether/ethyl acetate = 6: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.28 (d, J = 7.7 Hz, 1H), 6.99 (dd, J = 5.1, 2.4 Hz, 2H), 6.64 (s, 1H), 5.78 (s, 1H), 3.65 (s, 3H), 2.91 (d, J = 9.1 Hz, 2H), 2.80 – 2.71 (m, 2H), 2.21 (s, 3H), 2.10 – 2.03 (m, 2H), 2.05 (s, 3H), 2.03 (t, J = 7.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 163.1 (d, $J_{C\text{-}F}$ = 237.8 Hz),163.8, 152.4, 150.3 (d, $J_{C\text{-}F}$ = 8.0 Hz), 144.7, 144.5, 133.3, 132.6, 132.3, 129.1 (d, $J_{C\text{-}F}$ = 11.1 Hz), 128.6, 127.3, 127.2, 109.8 (d, $J_{C\text{-}F}$ = 37.0 Hz), 74.4, 52.6, 41.5, 33.9, 22.0, 19.3 (d, $J_{C\text{-}F}$ = 2.7 Hz).

HR-MS (ESI) m/z Calcd for $C_{21}H_{18}D_2FNNaO_4^+$ [M+Na$^+$] 394.3938, found 394.3937.



1-(Phenyl-3,5-d_2)ethyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (4h)

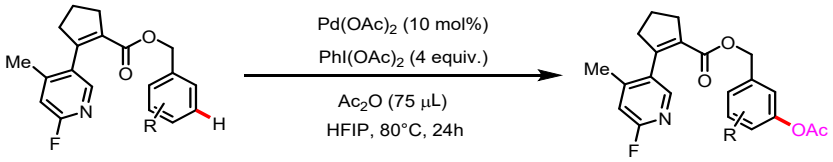
Colorless oil, 29.1 mg, 89%, R_f = 0.36 (petroleum ether/ethyl acetate = 6: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.7 (s, 1H), 7.25 (s, 2H), 7.03 – 6.95 (m, 2H), 6.67 (s, 1H), 5.75 (t, *J* = 6.5 Hz, 1H), 2.85 (d, *J* = 7.7 Hz, 2H), 2.72 (t, *J* = 7.7 Hz, 2H), 2.15 (s, 3H), 2.03 (q, *J* = 7.6 Hz, 2H), 1.30 (d, *J* = 6.5 Hz, 3H).

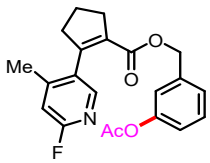
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 164.4 (d, $J_{C\text{-}F}$ = 237.2 Hz), 150.1, 144.7 (d, $J_{C\text{-}F}$ = 15.2 Hz), 141.2, 133.8, 128.4, 127.9, 127.7, 126.0, 125.9, 109.7 (d, $J_{C\text{-}F}$ = 37.0 Hz), 72.4, 34.0, 29.7, 22.0, 21.9, 19.3 (d, $J_{C\text{-}F}$ = 2.8 Hz).

HR-MS (ESI) m/z Calcd for $C_{20}H_{18}D_2FNNaO_2^+$ [M+Na$^+$]350.3848, found 350.3846.

6 *meta*-C–H acetoxylation of benzyl alcohols



An 8-mL sealed tube was charged with substrate (0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.001 mmol, 10 mol%), $PhI(OAc)_2$ (0.4 mmol, 4 equiv), Ac_2O (75 μl), and HFIP (20 mL). The tube was then sealed and submerged into a pre-heated 80 °C heating plate. The reaction mixture was stirred at 80 °C for 24h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short pad of Celite. The filtrate was concentrated in vacuo, and the resulting residue was purified by preparative TLC using EtOAc/hexanes as the eluent to give the desired product.



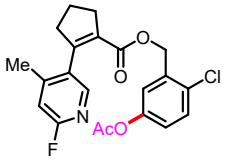
3-Acetoxybenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (5a)

Yellow oil, 20.3 mg, 55%, R_f = 0.55 (petroleum ether/ethyl acetate = 3: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.01 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.68 (s, 1H), 6.65 (s, 1H), 4.97 (s, 2H), 2.99 – 2.80 (m, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.32 (s, 3H), 2.12 (s, 3H), 2.04 (q, *J* = 7.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 164.4, 163.1 (d, $J_{C\text{-}F}$ = 238.2 Hz), 151.0, 150. 7, 150.3 (d, $J_{C\text{-}F}$ = 8.1 Hz), 144.6 (d, $J_{C\text{-}F}$ = 14.9 Hz), 137.1, 133.2, 132.3, 129.4, 125.3, 121.4, 121.0, 109.8 (d, $J_{C\text{-}F}$ = 36.7 Hz), 65.5, 41.3, 34.0, 22.1, 21.1, 19.3 (d, $J_{C\text{-}F}$ = 2.6 Hz).

HR-MS (ESI) m/z Calcd for $C_{21}H_{20}FNNaO_4^+$ [M+Na$^+$] 392.1269, found392.1268.



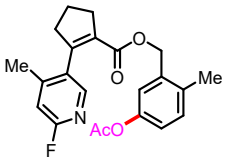
5-Acetoxy-2-chlorobenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (5b)

Yellow oil, 19.35 mg, 48%, R_f = 0.59 (petroleum ether/ethyl acetate = 3: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.32 (d, J = 8.6 Hz, 1H), 6.99 (dd, J = 8.7, 2.8 Hz, 1H), 6.64 (dd, J = 4.9, 2.2 Hz, 2H), 5.06 (s, 2H), 2.90 (d, J = 7.7 Hz, 2H), 2.74 (d, J = 7.8 Hz, 2H), 2.34 (s, 3H), 2.17 (s, 3H), 2.11 – 2.03 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 164.3 (d, $J_{C\text{-}F}$ = 236.5Hz), 164.2,151.3, 150.2 (d, $J_{C\text{-}F}$ = 8.2 Hz), 149.2, 144.6 (d, $J_{C\text{-}F}$ = 15.5 Hz), 134.5, 133.0, 130.2, 130.2, 127.2 (d, $J_{C\text{-}F}$ = 7.3 Hz), 122.6, 122.5, 109.7 (d, $J_{C\text{-}F}$ = 36.8 Hz), 63.1, 41.4, 34.0, 22.1, 21.1, 19.3 (d, $J_{C\text{-}F}$ = 2.7 Hz).

HR-MS (ESI) m/z Calcd for $C_{21}H_{19}ClFNNaO_4^+$ [M+Na$^+$] 426.0879, found 426.0879.



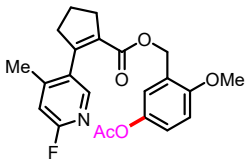
5-Acetoxy-2-methylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (5c)

Yellow oil, 23.37 mg, 61%, R_f = 0.62 (petroleum ether/ethyl acetate = 3: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.11 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 10.7 Hz, 1H), 6.67 (s, 1H), 6.59 (s, 1H), 4.97 (s, 2H), 2.90 – 2.86 (m, 2H), 2.76 – 2.71 (m, 2H), 2.32 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 2.08 – 2.03 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 164.4, 163.1 (d, $J_{C\text{-}F}$ = 237.7 Hz), 150.9, 150.3 (d, $J_{C\text{-}F}$ = 8.0 Hz), 148.7, 144.4 (d, $J_{C\text{-}F}$ = 15.4 Hz), 134.8, 134.1, 133.2, 131.1, 121.7, 121.4, 109.7 (d, $J_{C\text{-}F}$ = 36.8 Hz), 77.2, 63.8, 41.3, 34.0, 22.0, 21.1, 19.2 (d, $J_{C\text{-}F}$ = 2.8 Hz), 18.1.

HR-MS (ESI) m/z Calcd for $C_{22}H_{22}FNNaO_4^+$ [M+Na^+] 406.1426, found 406.1426.



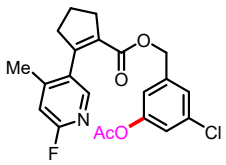
5-Acetoxy-2-methoxybenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (5d)

Yellow oil, 18.30 mg, 46%, R_f = 0.57 (petroleum ether/ethyl acetate = 4: 1, V/V).

1H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 6.96 (dd, J = 8.8, 4.8 Hz, 1H), 6.77 (d, J = 8.9 Hz, 1H), 6.58 (s, 1H), 6.55 (s, 1H), 4.99 (s, 2H), 3.74 (s, 3H), 2.89 (d, J = 8.5 Hz, 2H), 2.72 (t, J = 8.8 Hz, 2H), 2.31 (s, 3H), 2.12 (s, 3H), 2.09 – 2.01 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 164.6, 163.0(d, $J_{C\text{-}F}$ = 237.8 Hz), 154.8, 150.4, 150.3 (d, $J_{C\text{-}F}$ = 8.3 Hz), 144.4 (d, $J_{C\text{-}F}$ = 15.0 Hz), 143.7, 133.5, 124.8, 122.1 (d, $J_{C\text{-}F}$ = 26 Hz), 110.7, 109.6 (d, $J_{C\text{-}F}$ = 36.9 Hz), 61.1, 55.6, 41.3, 34.0, 22.1, 21.1, 19.2 (d, $J_{C\text{-}F}$ = 2.8 Hz).

HR-MS (ESI) m/z Calcd for $C_{22}H_{22}FNNaO_5^+$ [M+Na^+] 422.1375, found422.1376.



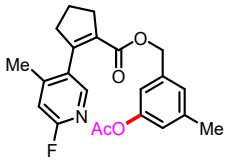
3-Acetoxy-5-chlorobenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (5e)

Yellow oil, 20.59 mg, 51%, R_f = 0.45 (petroleum ether/ethyl acetate = 4: 1, V/V).

1H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.05 (s, 1H), 6.89 (s, 1H), 6.71 (s, 1H), 6.59 (s, 1H), 4.93 (s, 2H), 2.88 (t, J = 7.4 Hz, 2H), 2.77 – 2.67 (m, 2H), 2.32 (s, 3H), 2.16 (s, 3H), 2.10 – 2.02 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 163.3 (d, $J_{C\text{-}F}$ = 238.2 Hz), 164.2 151.4, 151.1, 150.2 (d, $J_{C\text{-}F}$ = 8.0 Hz), 144.7 (d, $J_{C\text{-}F}$ = 15.4 Hz), 138.4, 134.7, 133.0, 125.2, 121.9, 119.3, 109.8 (d, $J_{C\text{-}F}$ = 37.0 Hz), 64.7, 41.3, 34.0, 22.1, 21.0, 19.3 (d, $J_{C\text{-}F}$ = 2.7 Hz).

HR-MS (ESI) m/z Calcd for $C_{21}H_{19}ClFNNaO_4^+$ [M+Na$^+$] 426.0879, found426.0878.



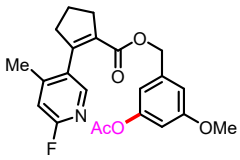
3-Acetoxy-5-methylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (5f)

Yellow oil, 25.28 mg, 66%, R_f = 0.57 (petroleum ether/ethyl acetate = 3: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 6.83 (s, 1H), 6.71 (s, 1H), 6.65 (s, 1H), 6.49 (s, 1H), 4.93 (s, 2H), 2.92 – 2.85 (m, 2H), 2.72 (d, J = 7.6 Hz, 2H), 2.32 (d, J = 1.7 Hz, 6H), 2.13 (s, 3H), 2.09 – 2.02 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 164.5, 163.1 (d, $J_{C\text{-}F}$ = 237.9 Hz), 150.8, 150.6, 150.3 (d, $J_{C\text{-}F}$ = 8.5 Hz), 144.6 (d, $J_{C\text{-}F}$ = 15.8 Hz), 139.8, 136.8, 133.3, 132.3, 126.2, 122.0, 118.1, 109.7 (d, $J_{C\text{-}F}$ = 36.8 Hz), 65.6, 41.3, 34.0, 22.1, 21.2, 21.1, 19.3 (d, $J_{C\text{-}F}$ = 2.6 Hz).

HR-MS (ESI) m/z Calcd for $C_{22}H_{22}FNNaO_4^+$ [M+Na$^+$] 406.1426, found 406.1425.



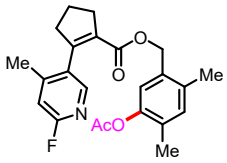
3-Acetoxy-5-methoxybenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (5g)

Yellow oil, 15.56 mg, 39%, R_f = 0.6 (petroleum ether/ethyl acetate = 3: 1, V/V).

1H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 6.66 (s, 1H), 6.55 (d, J = 2.1 Hz, 1H), 6.46 (s, 1H), 6.29 (s, 1H), 4.92 (s, 2H), 3.77 (d, J = 1.3 Hz, 3H), 2.87 (d, J = 7.9 Hz, 3H), 2.73 (t, J = 7.4 Hz, 3H), 2.31 (d, J = 1.4 Hz, 3H), 2.14 (s, 3H), 2.09 – 2.01 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 164.4, 164.3 (d, $J_{C\text{-}F}$ = 236.5 Hz), 160.4, 151.6, 151.0, 150.3 (d, $J_{C\text{-}F}$ = 8.3 Hz), 144.6, 144.5 (d, $J_{C\text{-}F}$ = 15.3 Hz). 144.5, 137.8, 133.2, 113.2, 111.4, 109.8 (d, $J_{C\text{-}F}$ = 36.9 Hz), 107.2, 65.5, 55.5, 41.3, 34.0, 22.1, 21.1, 19.3 (d, $J_{C\text{-}F}$ = 2.6 Hz).

HR-MS (ESI) m/z Calcd for $C_{22}H_{22}FNNaO_5^+$ [M+Na$^+$] 422.1375, found422.1376.



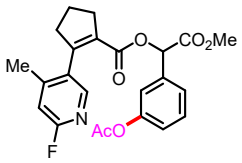
5-Acetoxy-2,4-dimethylbenzyl 2-(6-fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylate (5h)

Yellow oil, 17.01 mg, 43%, R_f = 0.65 (petroleum ether/ethyl acetate = 2: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 6.98 (s, 1H), 6.61 (s, 1H), 6.58 (s, 1H), 4.93 (s, 2H), 2.87 (tt, J = 7.7, 2.5 Hz, 2H), 2.72 (tt, J = 7.8, 2.6 Hz, 2H), 2.34 (s, 3H), 2.13 (s, 3H), 2.10 (d, J = 10.7 Hz, 3H), 2.05 (d, J = 2.1 Hz, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 164.5, 163.1 (d, $J_{C\text{-}F}$ = 237.9 Hz), 150.8, 150.3 (d, $J_{C\text{-}F}$ = 8.2 Hz), 147.2, 144.3 (d, $J_{C\text{-}F}$ = 15.7 Hz), 134.4, 133.3, 132.9, 132.3, 132.2, 130.1, 122.3, 109.7 (d, $J_{C\text{-}F}$ = 36.8 Hz), 63.8, 41.3, 33.9, 22.0, 20.8, 19.2 (d, $J_{C\text{-}F}$ = 2.5 Hz), 18.0, 15. 8.

HR-MS (ESI) m/z Calcd for $C_{23}H_{24}FNNaO_4^+$ [M+Na$^+$] 420.1582, found 420.1583.



1-(3-Acetoxyphenyl)-2-methoxy-2-oxoethyl 2-(6-fluoro-4-methylpyridin-3-yl) cyclopent-1-ene-1-carboxylate (5i)

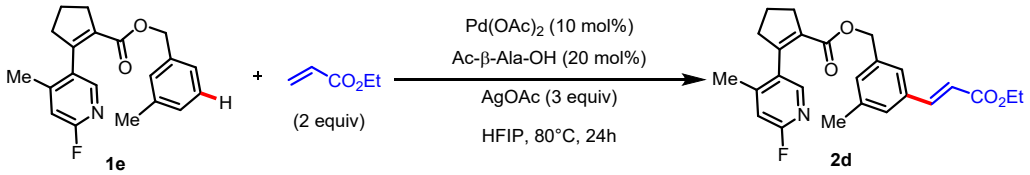
Yellow oil, 29.22 mg, 45%, R_f = 0.6 (petroleum ether/ethyl acetate = 2: 1, V/V).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 11.5 Hz, 1H), 6.91 (d, J = 9.2 Hz, 1H), 6.70 (s, 1H), 6.63 (t, J = 2.0 Hz, 1H), 5.81 (s, 1H), 3.66 (s, 3H), 2.93 (t, J = 7.6 Hz, 2H), 2.81 – 2.71 (m, 2H), 2.34 (s, 3H), 2.22 (s, 3H), 2.11 – 2.05 (m, 2H).

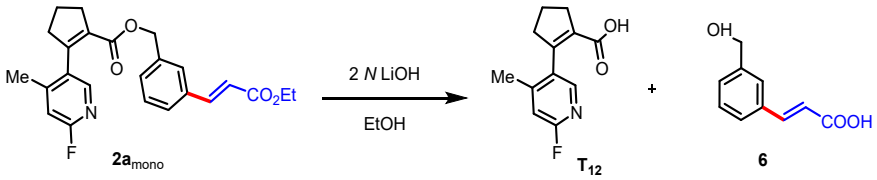
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 168.6, 164.4 (d, $J_{C\text{-}F}$ = 237.3 Hz), 163.7, 152. 4, 150.8, 150.3 (d, $J_{C\text{-}F}$ = 8.4 Hz), 144.7 (d, $J_{C\text{-}F}$ = 15.7 Hz), 134.9, 132.4, 132.3, 129.5, 124.8, 122.5, 120.2, 109.8 (d, $J_{C\text{-}F}$ = 36.9 Hz), 73.8, 52.7, 41.6, 33.9, 22.0, 21.1, 19.3 (d, $J_{C\text{-}F}$ = 2.8 Hz).

HR-MS (ESI) m/z Calcd for $C_{23}H_{22}FNNaO_6^+$ [M+Na$^+$] 450.1324, found 450.1324.

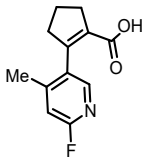
7 Scale-up reaction and removal of template



Compound **1d** (3 mmol, 1 equiv), olefin (6 mmol, 2.0 equiv), $Pd(OAc)_2$ (0.3 mmol, 10 mol%), Ac-β-Ala-OH (0.6 mmol, 20 mol%), AgOAc (9 mmol, 3.0 equiv), and HFIP (20 mL) were charged into the 50 ml round-bottomed flasks in turn. The tube was then sealed and submerged into a pre-heated 80 °C heating plate. The reaction mixture was stirred at 80 °C for 24 h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short pad of Celite. The filtrate was concentrated in vacuo, and the resulting residue was purified by preparative TLC using EtOAc/hexanes as the eluent to give **2d** (1.08 g, 85%).



A solution of 2 *N* LiOH (1.42mmol, 3 equiv), substrate (0.47mmol, 1 equiv) in EtOH (15 ml) was placed in a 50 mL round bottom flask. The mixture was heated to 60 °C for 12 h. After being allowed to cool to room temperature, the mixture was acidified with 3 M HCl solution and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 times). The combined organic layer was dried over Na_2SO_4, concentrated in vacuo and purified by preparative TLC to give $\mathbf{T_{12}}$ and **6**.



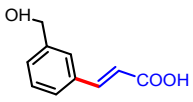
2-(6-Fluoro-4-methylpyridin-3-yl)cyclopent-1-ene-1-carboxylic acid ($\mathbf{T_{12}}$)

Yellow solid, 101.82 mg, 98%, R_f = 0.6 (petroleum ether/ethyl acetate = 1: 1, V/V).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.05 (s, 1H), 2.73 – 2.68 (m, 4H), 2.22 (s, 3H), 1.96 (q, J = 7.6 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d6) δ 166.4, 163.9 (d, J_{C-F} = 234.2 Hz), 151.2 (d, J_{C-F} = 8.5 Hz), 145.1 (d, J_{C-F} = 15.8 Hz), 134.5, 133.3 (d, J_{C-F} = 4.3 Hz), 109.7 (d, J_{C-F} = 37.5 Hz), 34.0, 22.1, 19.4 (d, J_{C-F} = 2.9 Hz).

HR-MS (ESI) m/z Calcd for $C_{12}H_{12}FNNaO_2^+$ [M+Na$^+$] 244.0745, found 244.0746.



(*E*)-3-(3-(hydroxymethyl)-5-methylphenyl)acrylic acid (6)

Yellow solid, m.p.: 114-115 °C, 82.0 mg, 98%, R_f = 0.65 (petroleum ether/ethyl acetate = 1: 1, V/V).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.38 (br, 1H), 7.62 – 7.50 (m, 3H), 7.42 – 7.33 (m, 2H), 6.49 (d, J = 16.0 Hz, 1H), 5.24 (br, 1H), 4.54 (s, 2H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 168.3, 144.7, 143.9, 134.7, 129.4, 129.1, 127.3, 126.7, 119.7, 63.3.

HR-MS (ESI) m/z Calcd for $C_{10}H_{10}NaO_3^+$ [M+Na$^+$] 201.0523, found 201.0524.

8 References

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2 F. Karaki, K. Ohgane, H. Fukuda, M. Nakamura, K. Dodo and Y. Hashimoto, *Bioorganic & Medicinal Chemistry*, 2014, **22**, 3587–3609.

3 Y. Shi, L. Chen, Q. Gao, J. Li, Y. Guo and B. Fan, *Org. Lett.*, 2023, **25**, 6495–6500.

4 J.-G. Gu, C.-X. Wang, G.-Q. Hu, K. Shen and H.-H. Zhang, *Org. Lett.*, 2023, **25**, 3055–3059.

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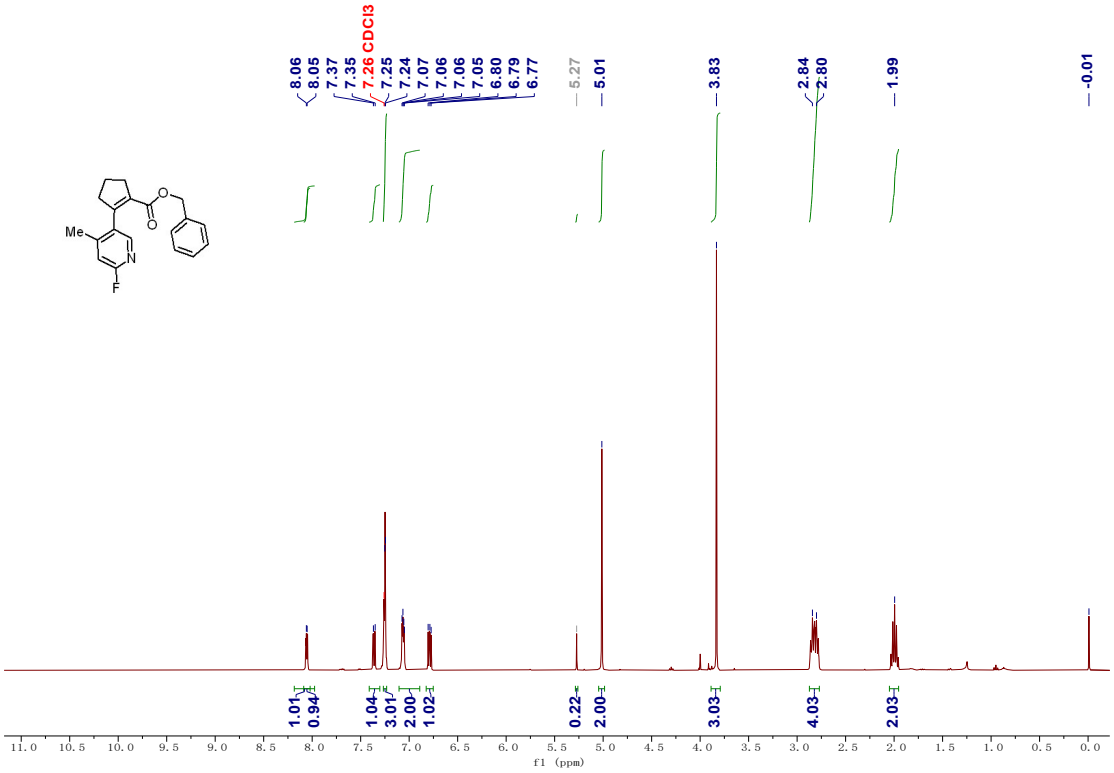
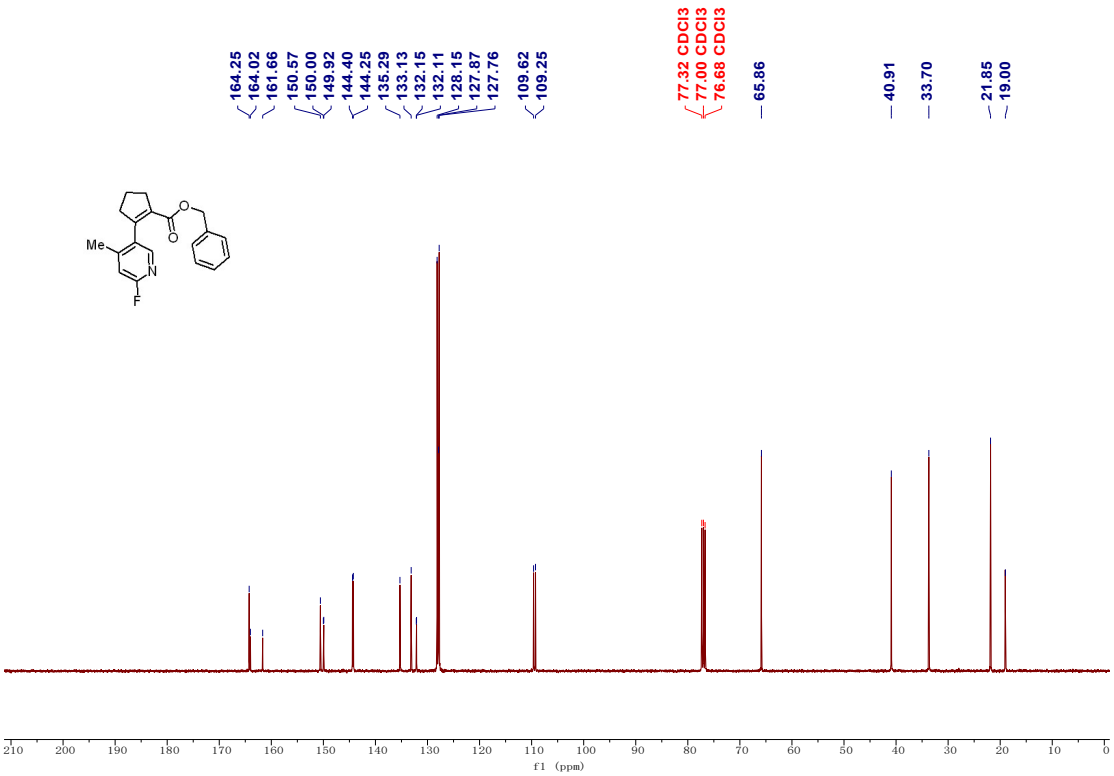
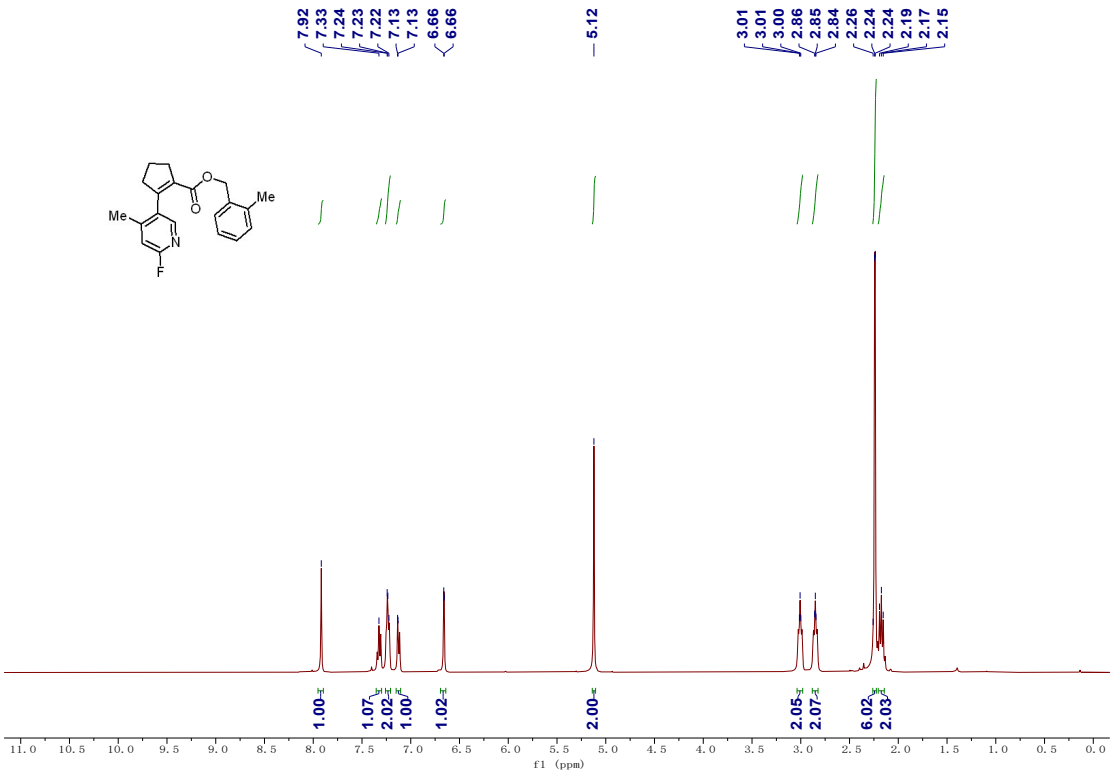
NMR Spectra for All New Compounds



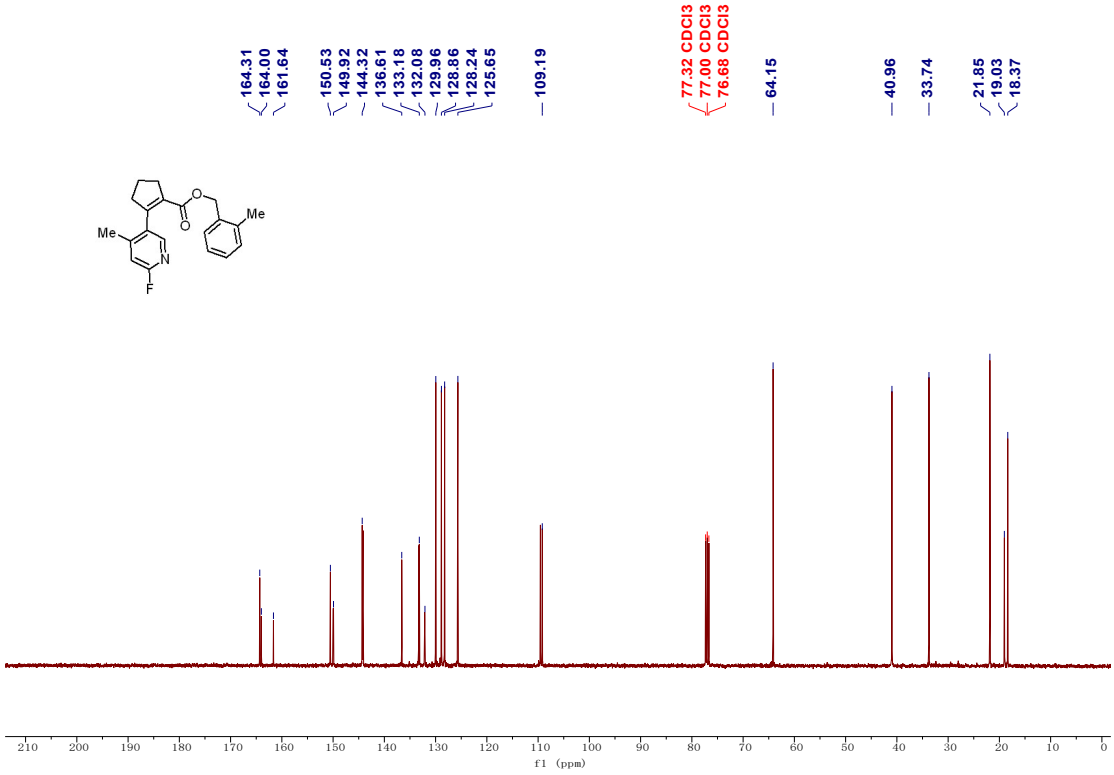
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **1a**



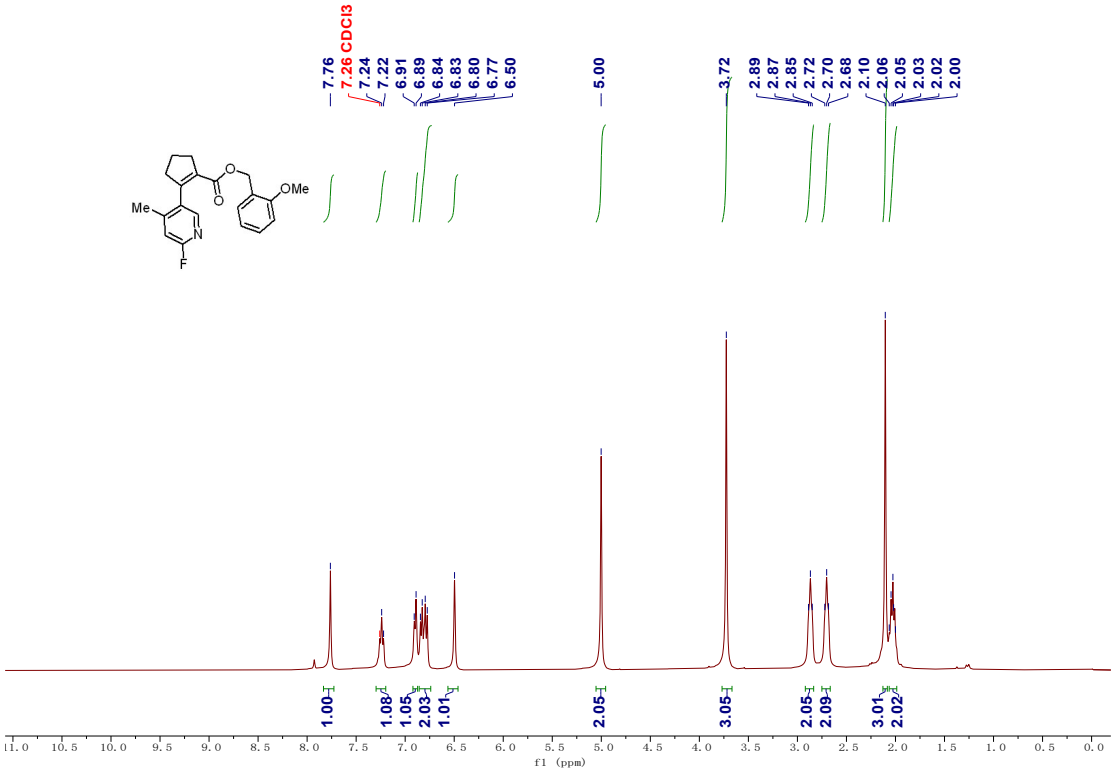
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **1a**



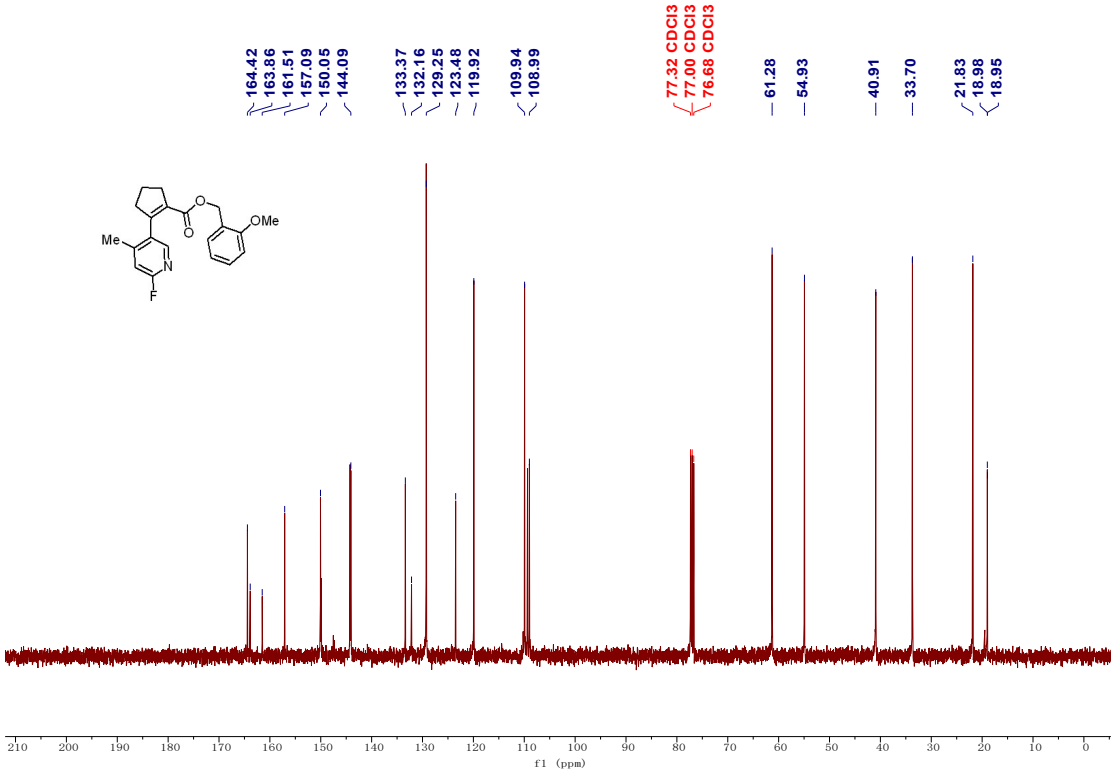
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **1b**



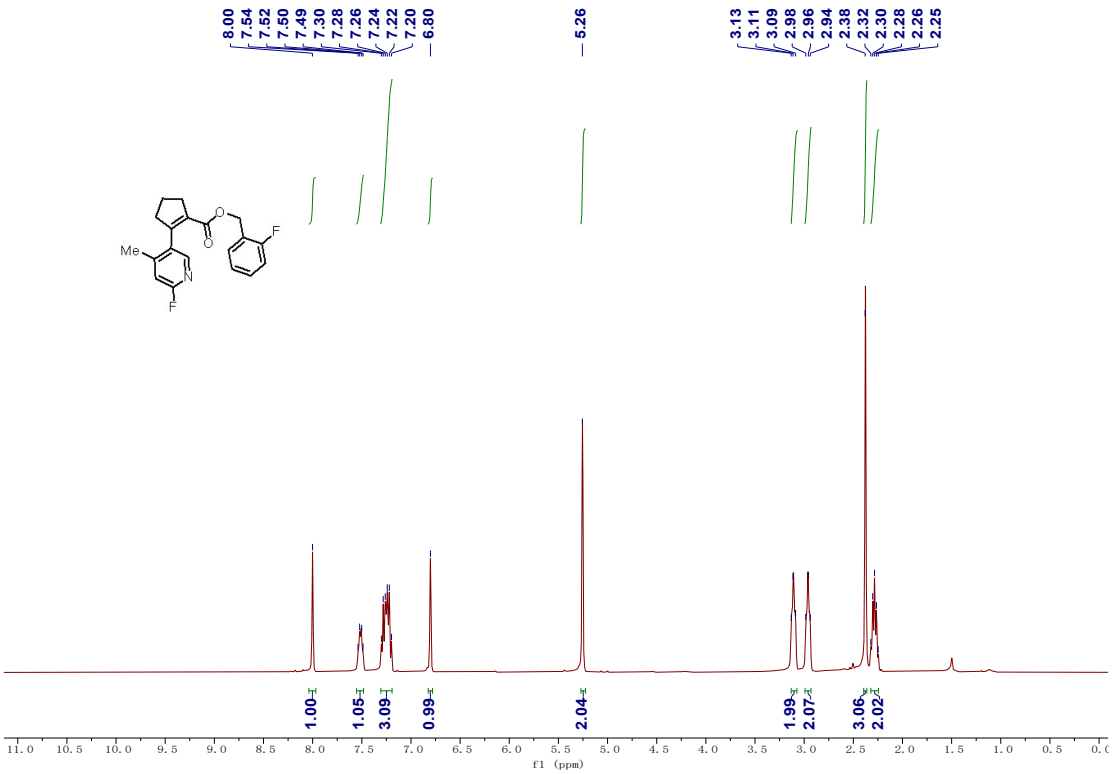
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **1b**



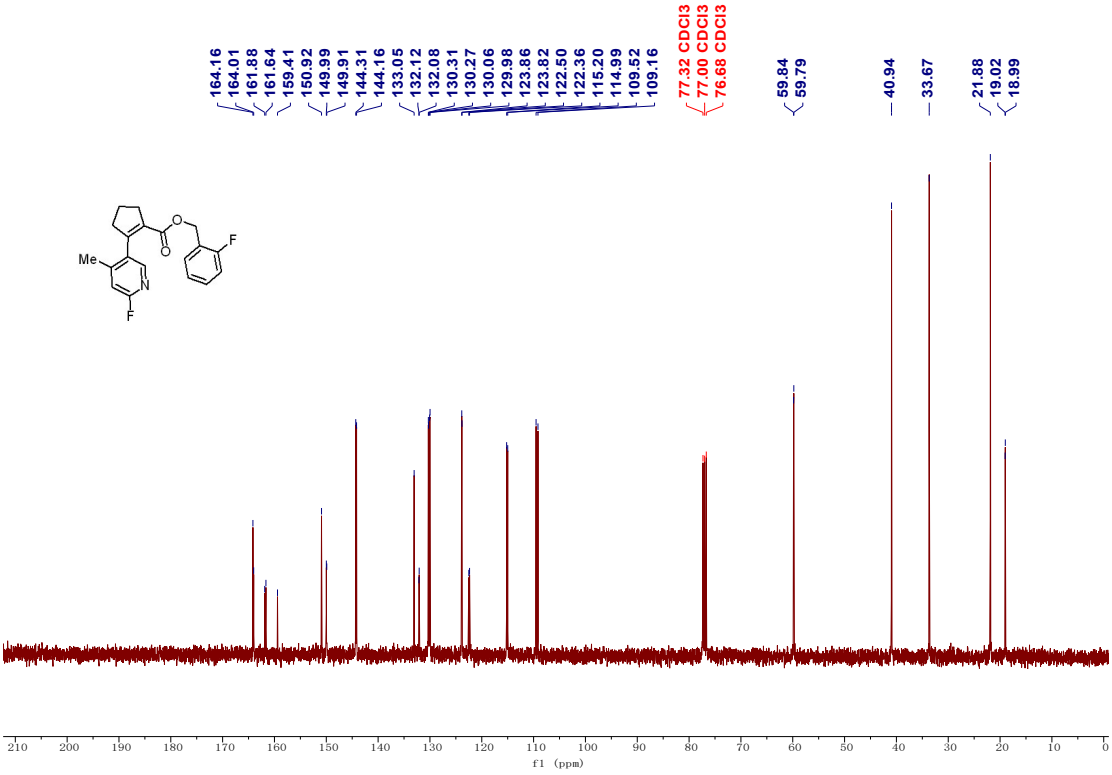
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **1c**



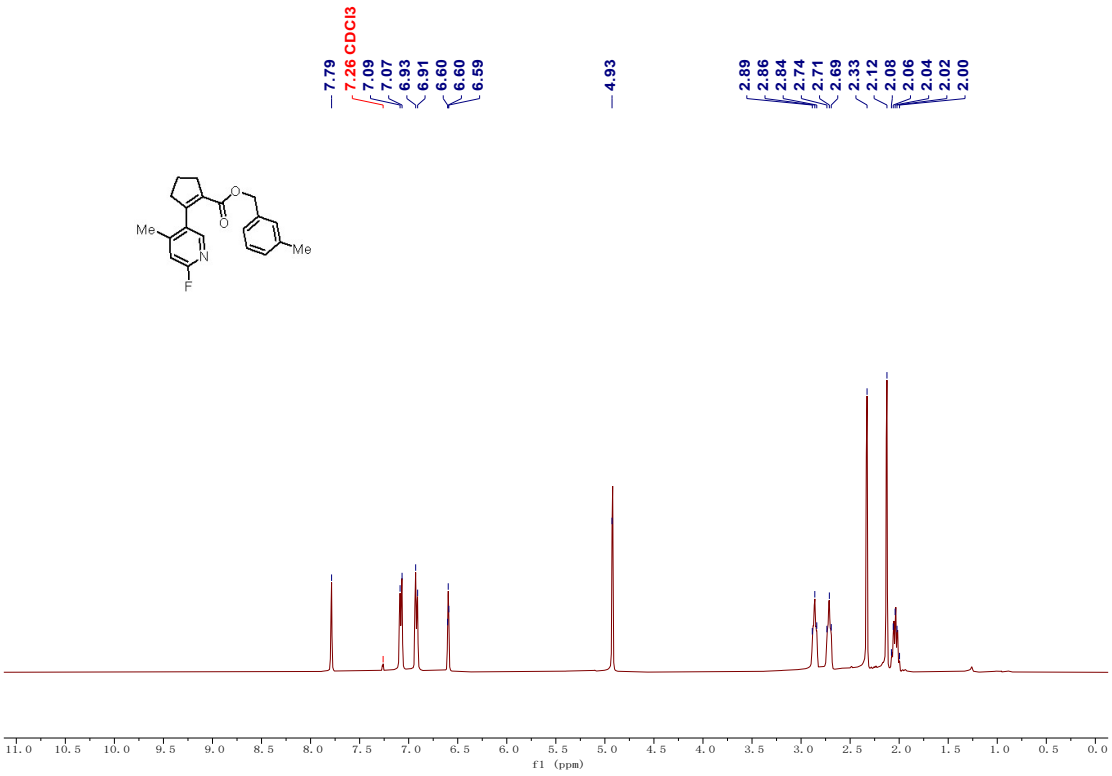
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **1c**



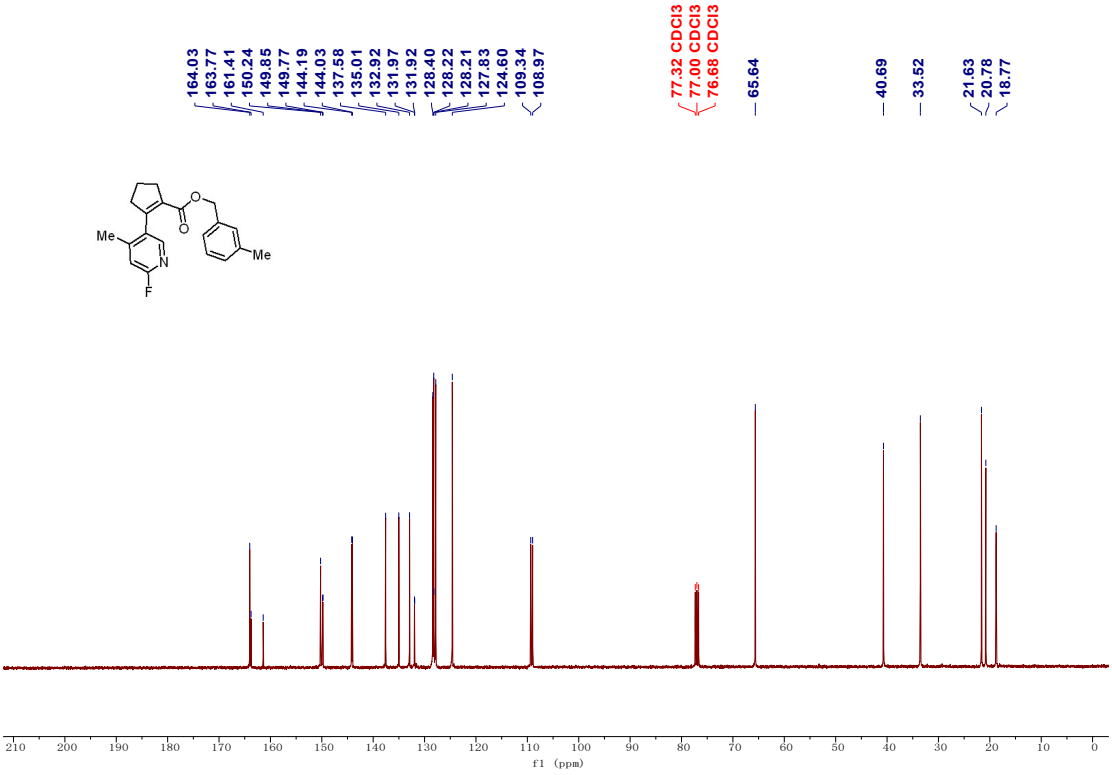
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **1d**



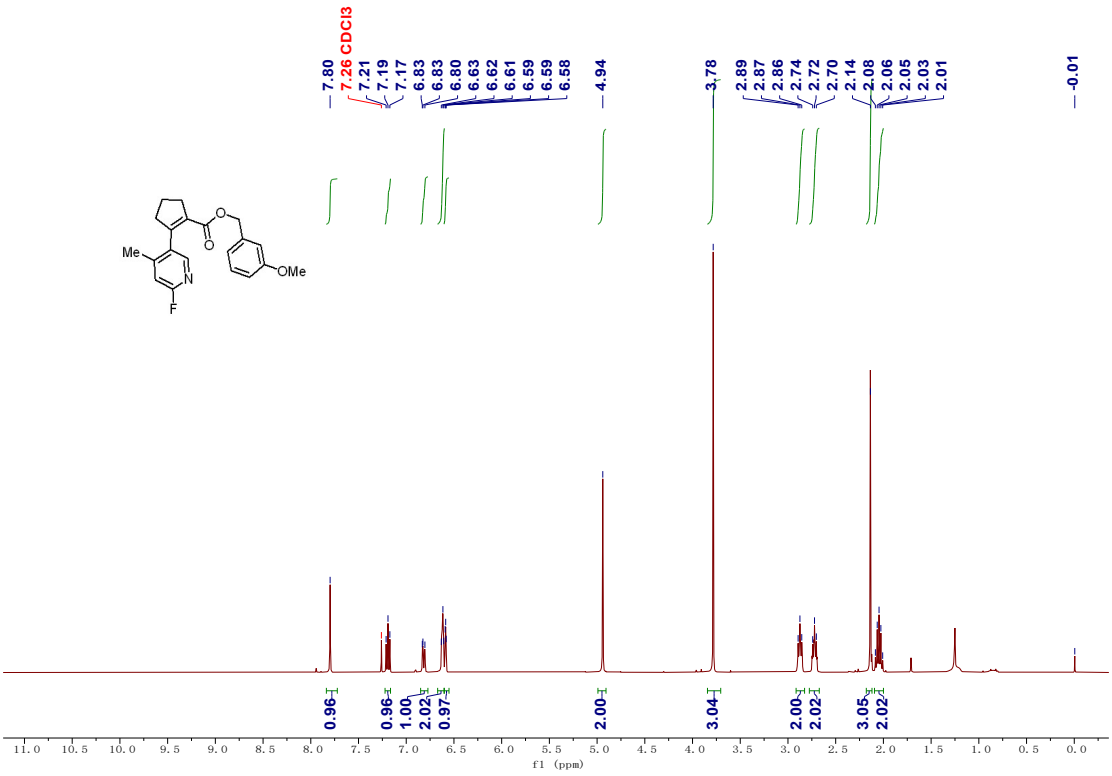
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **1d**



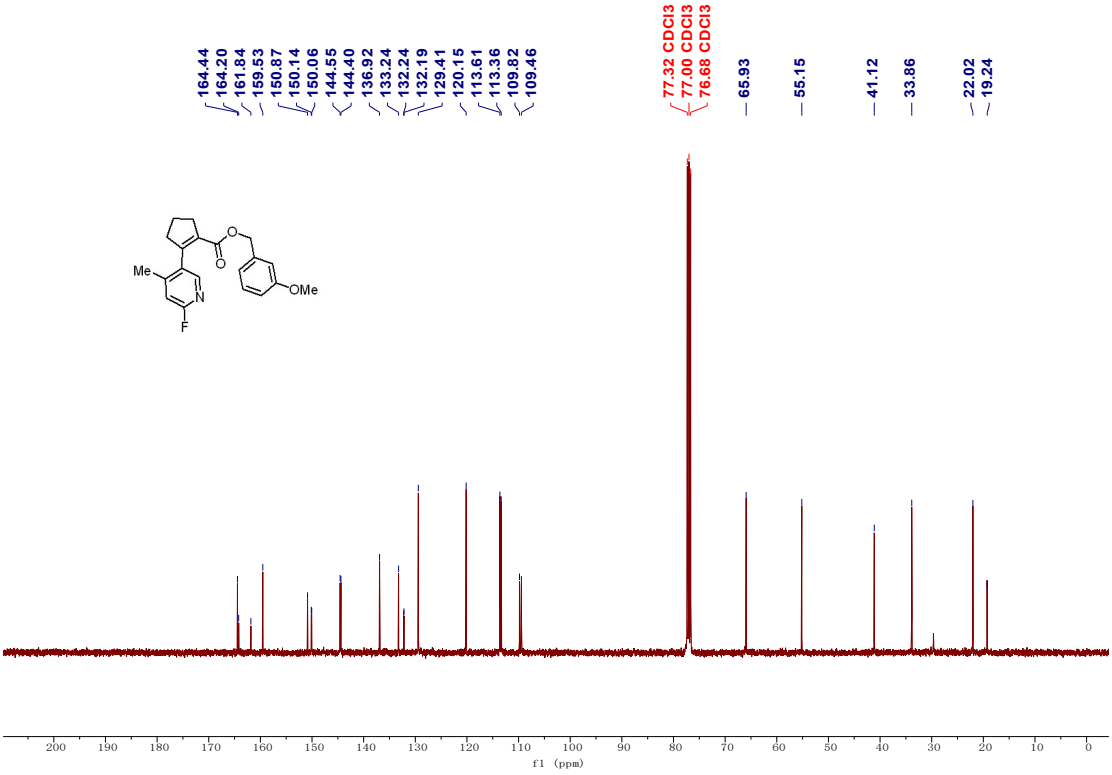
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **1e**



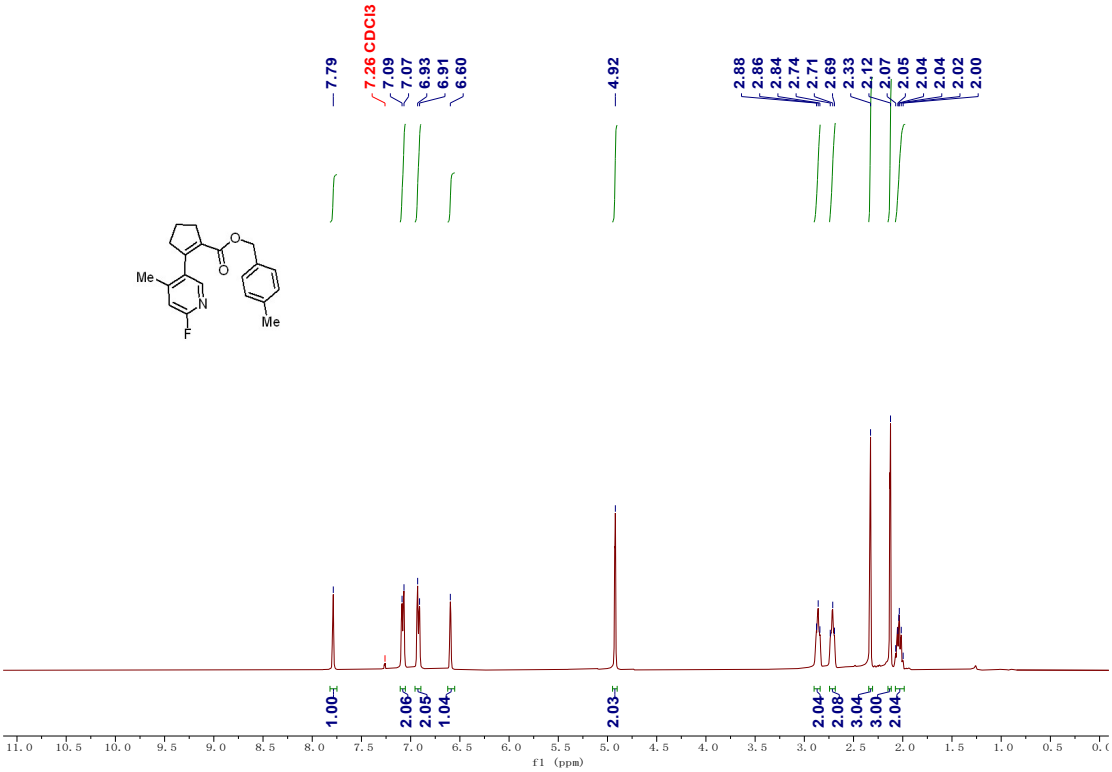
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **1e**



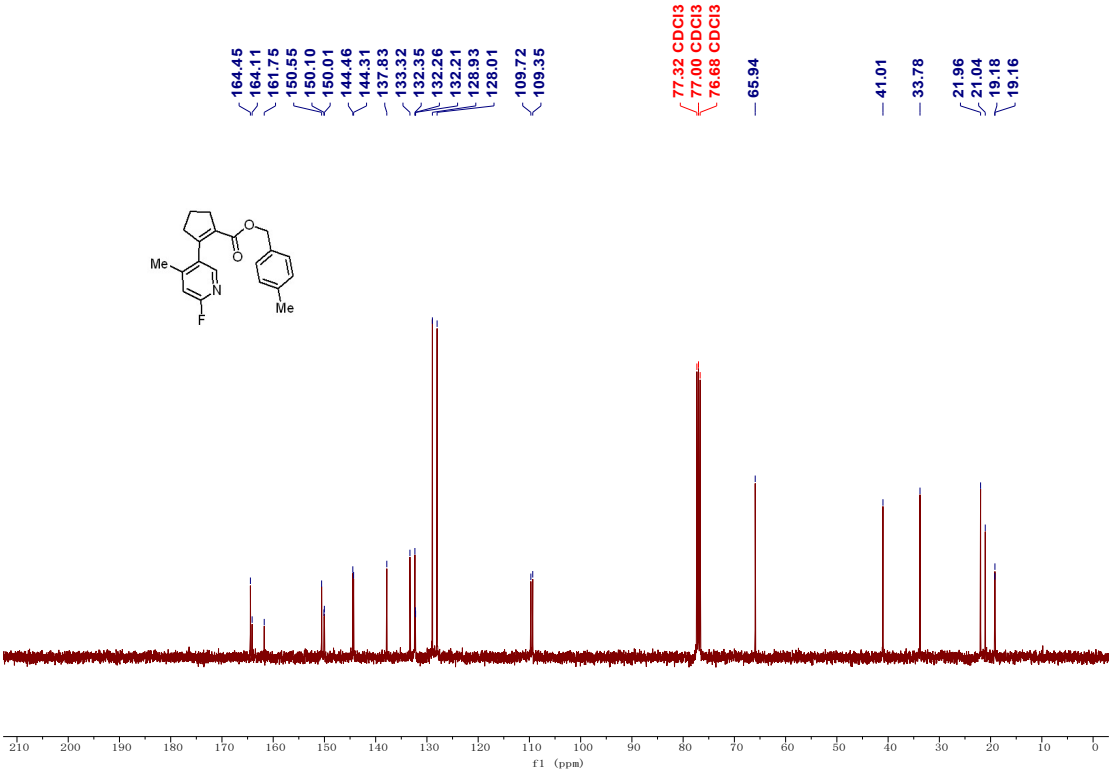
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **1f**



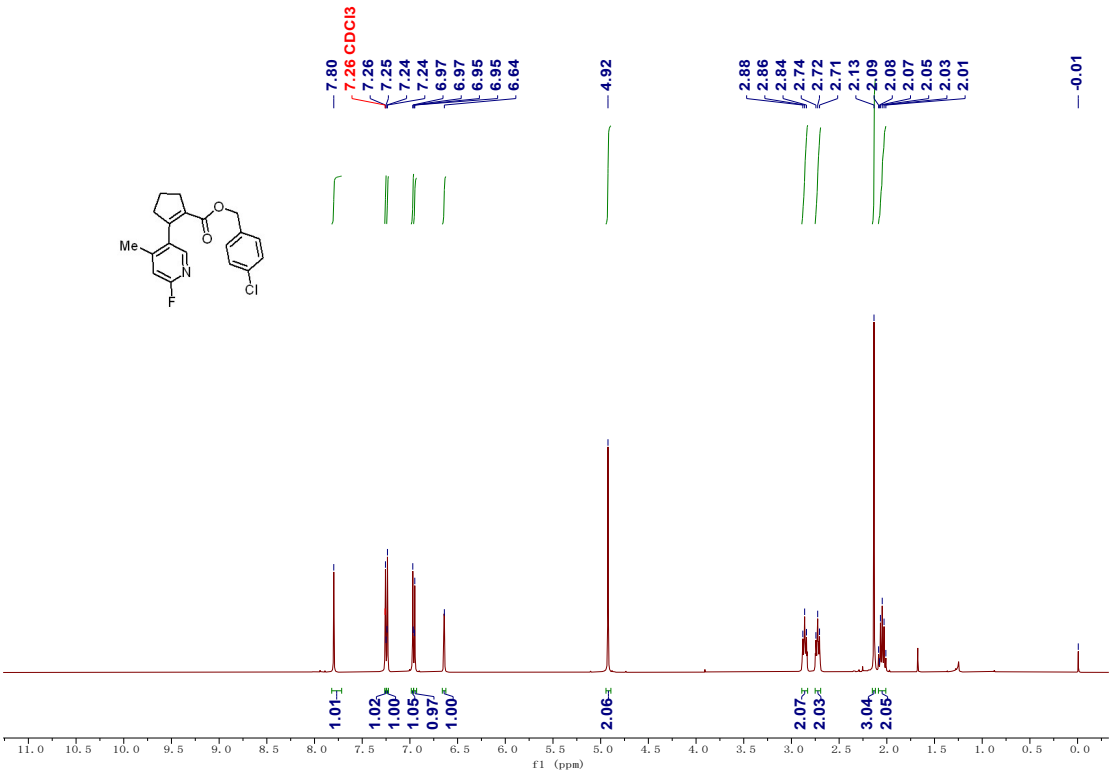
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **1f**



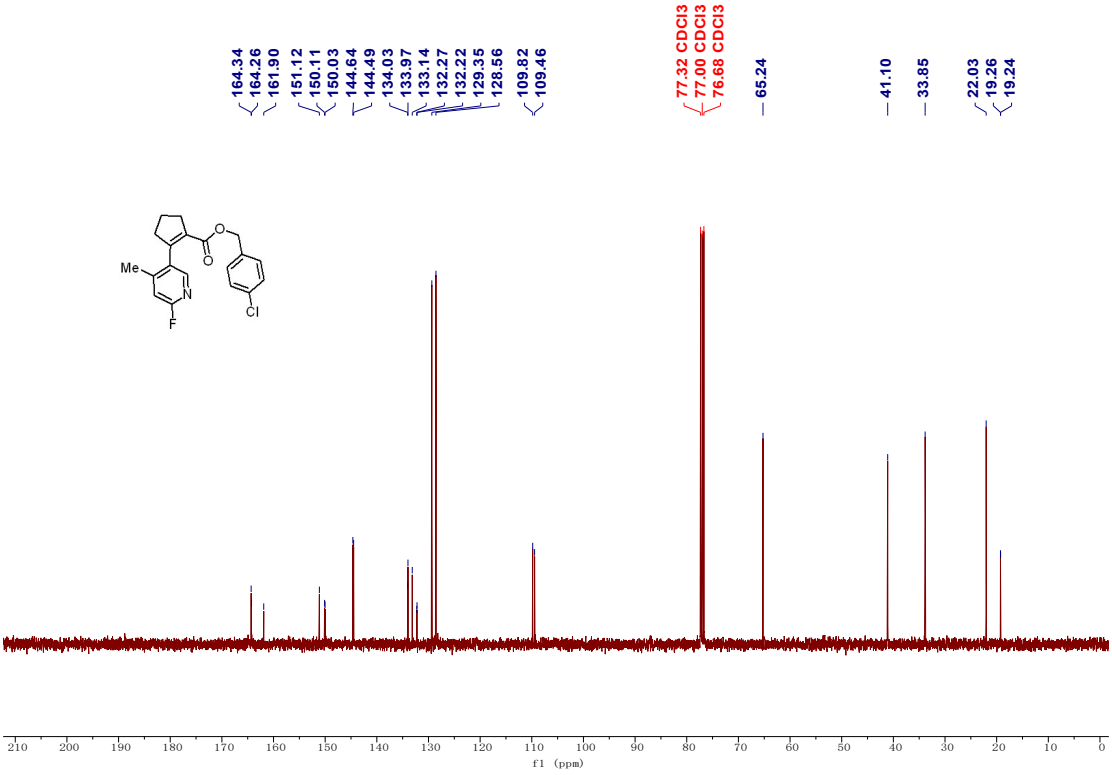
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **1g**



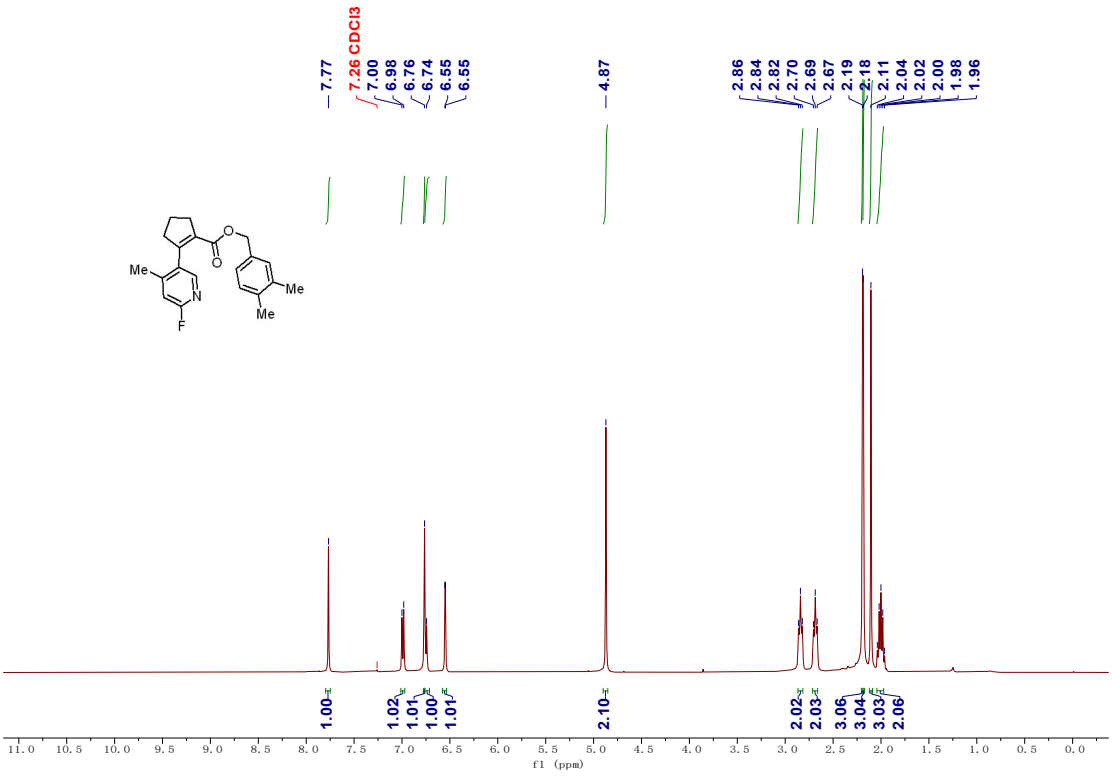
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **1g**



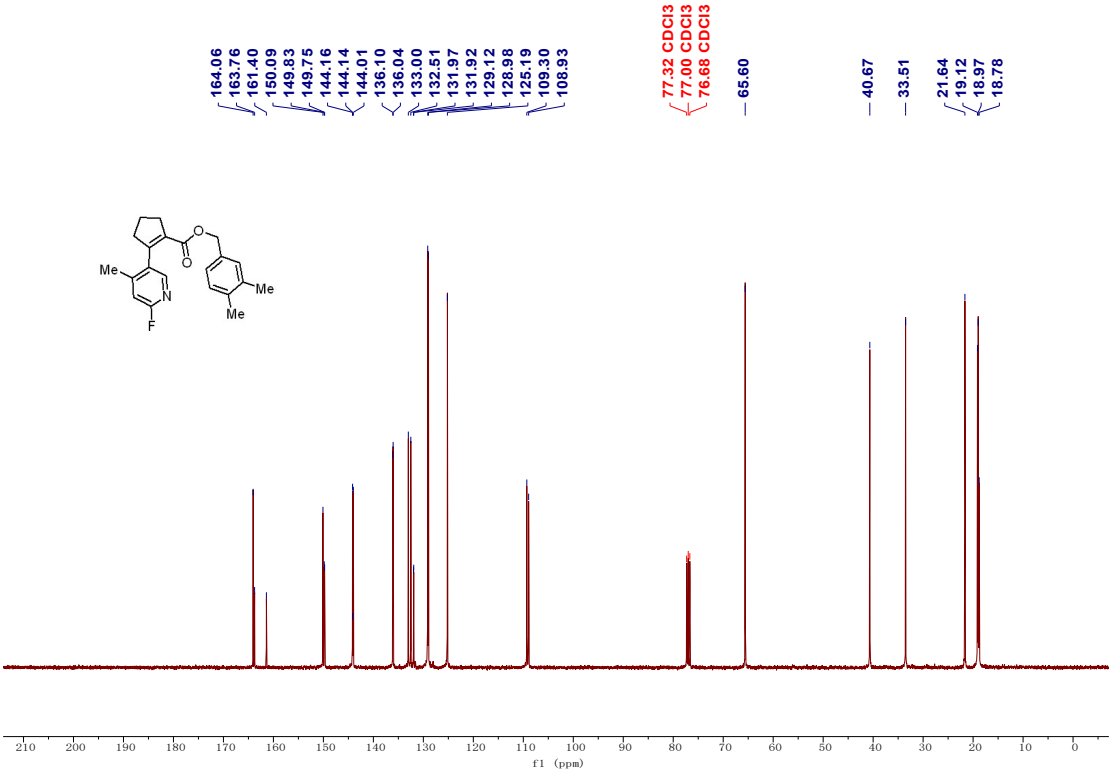
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **1h**



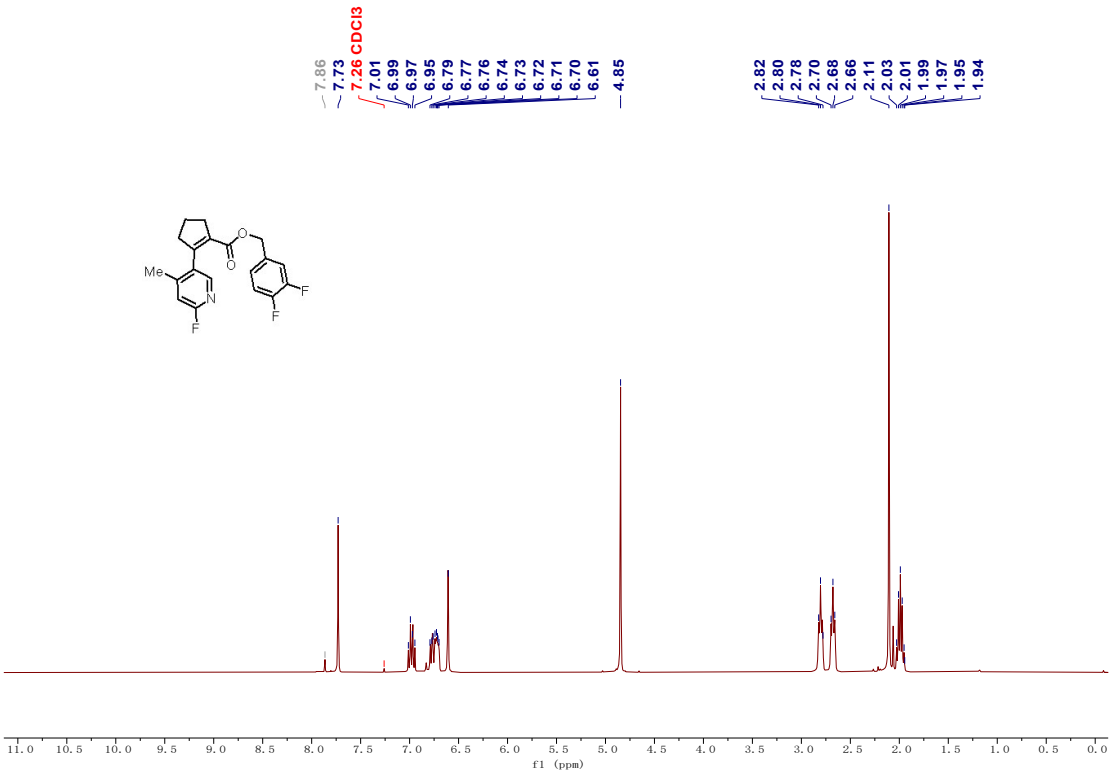
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **1h**



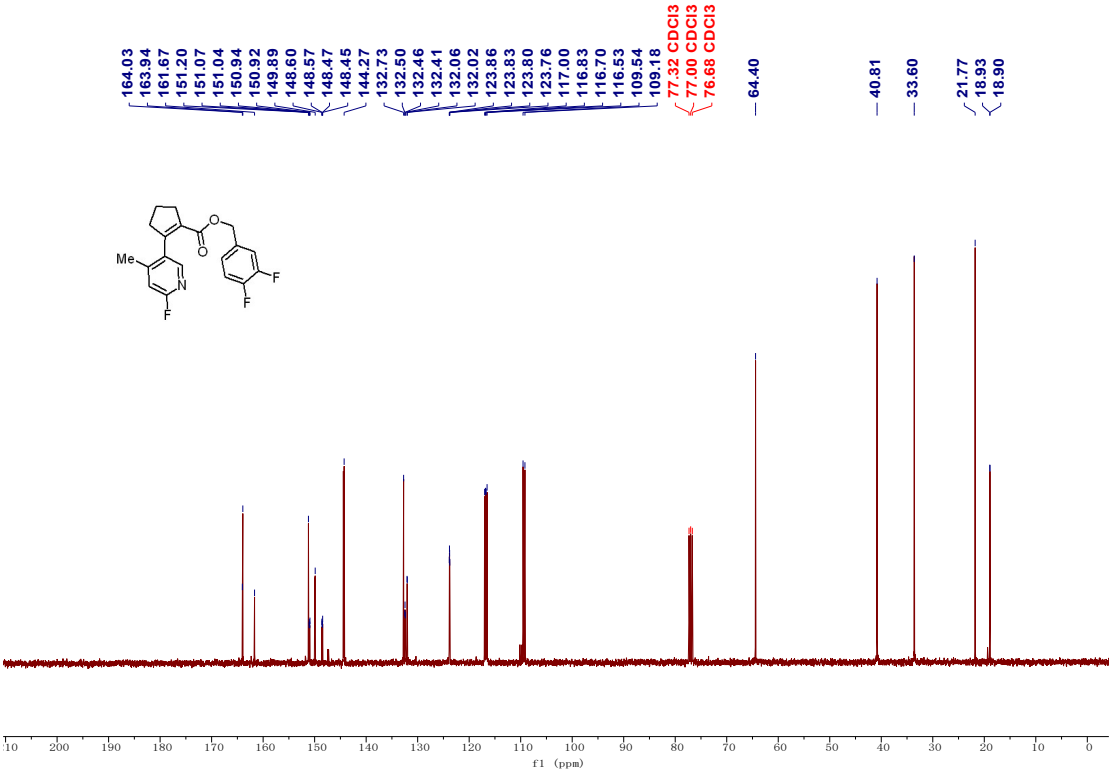
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **1i**



^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **1i**



^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **1j**



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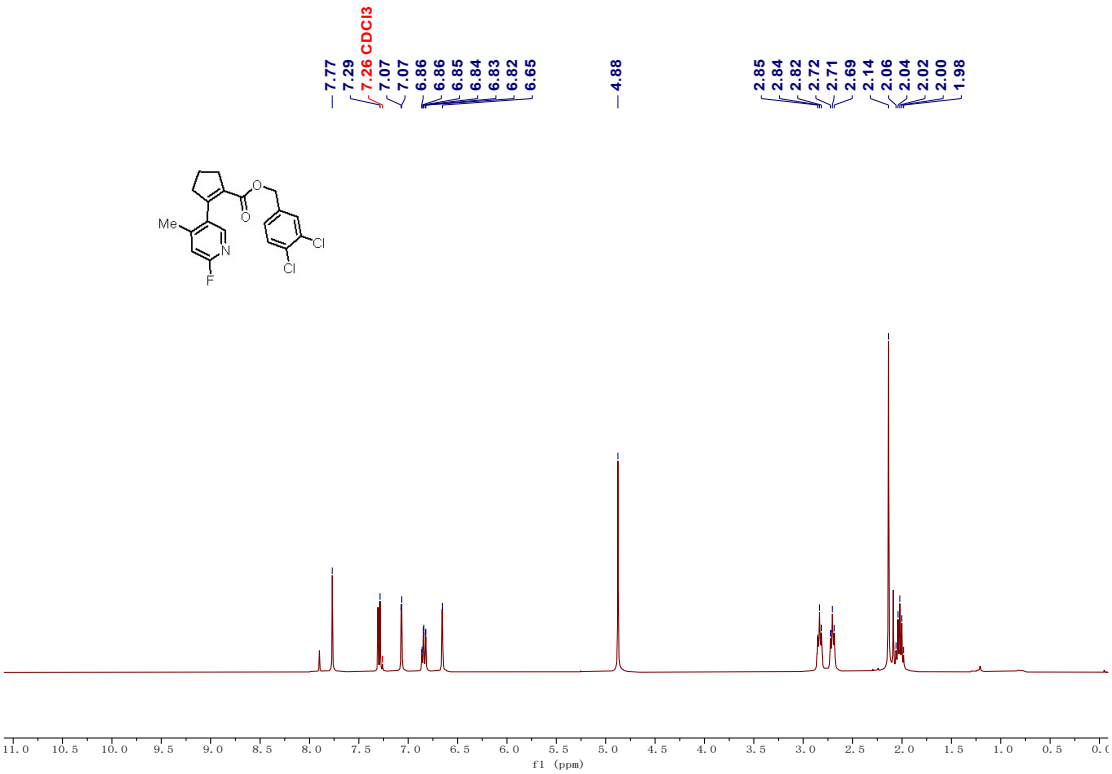

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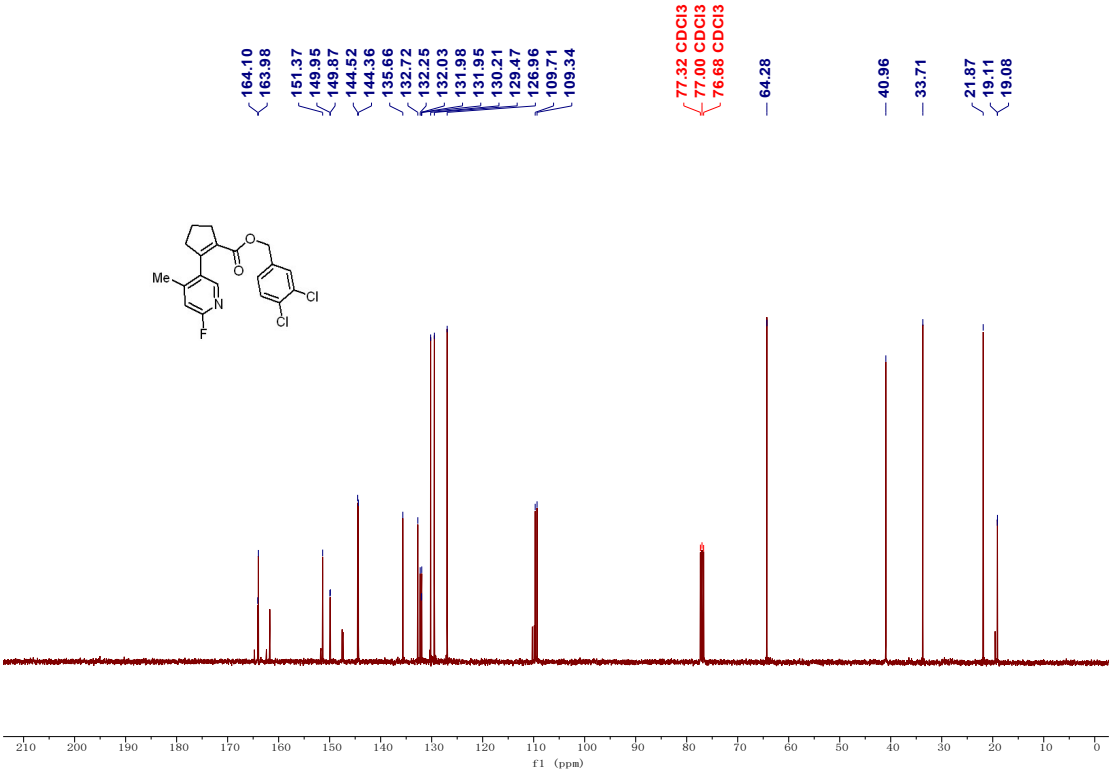

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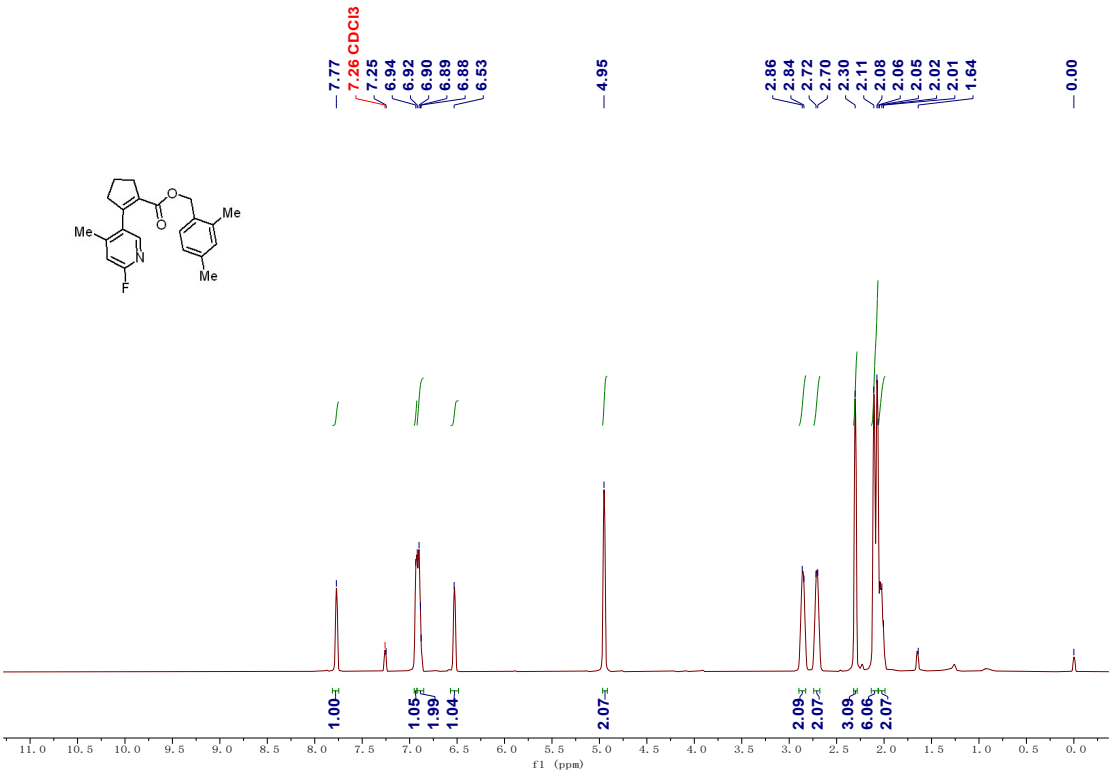
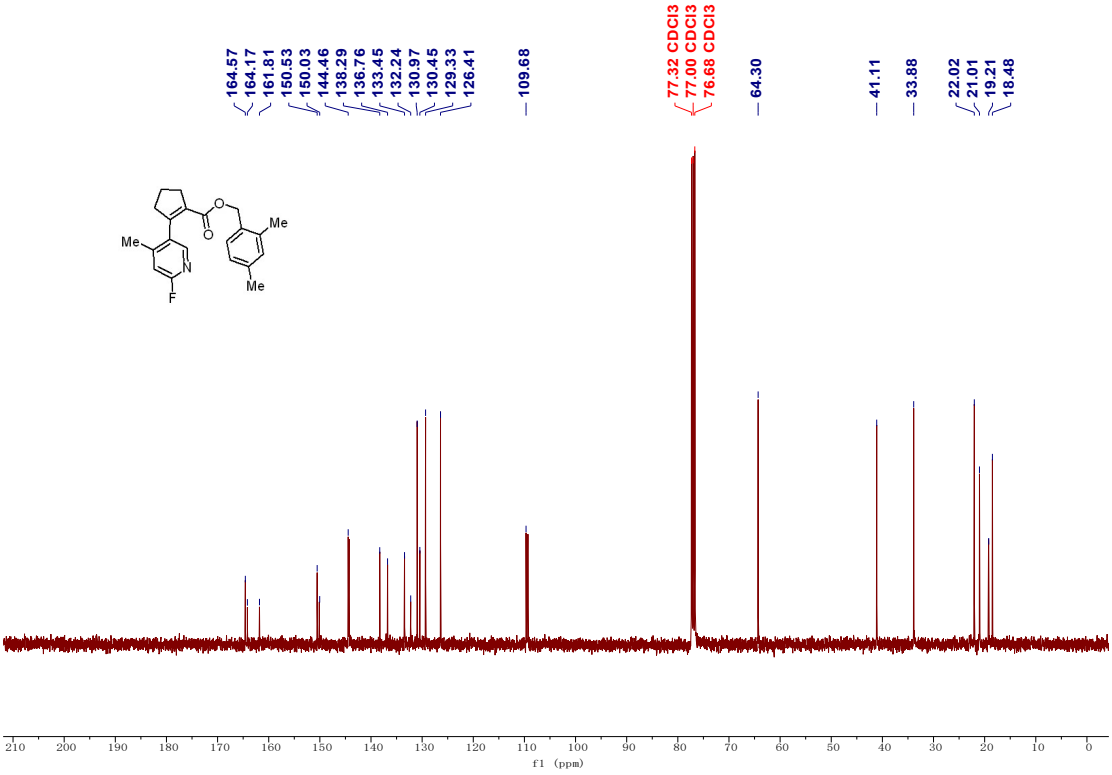


^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **1l**



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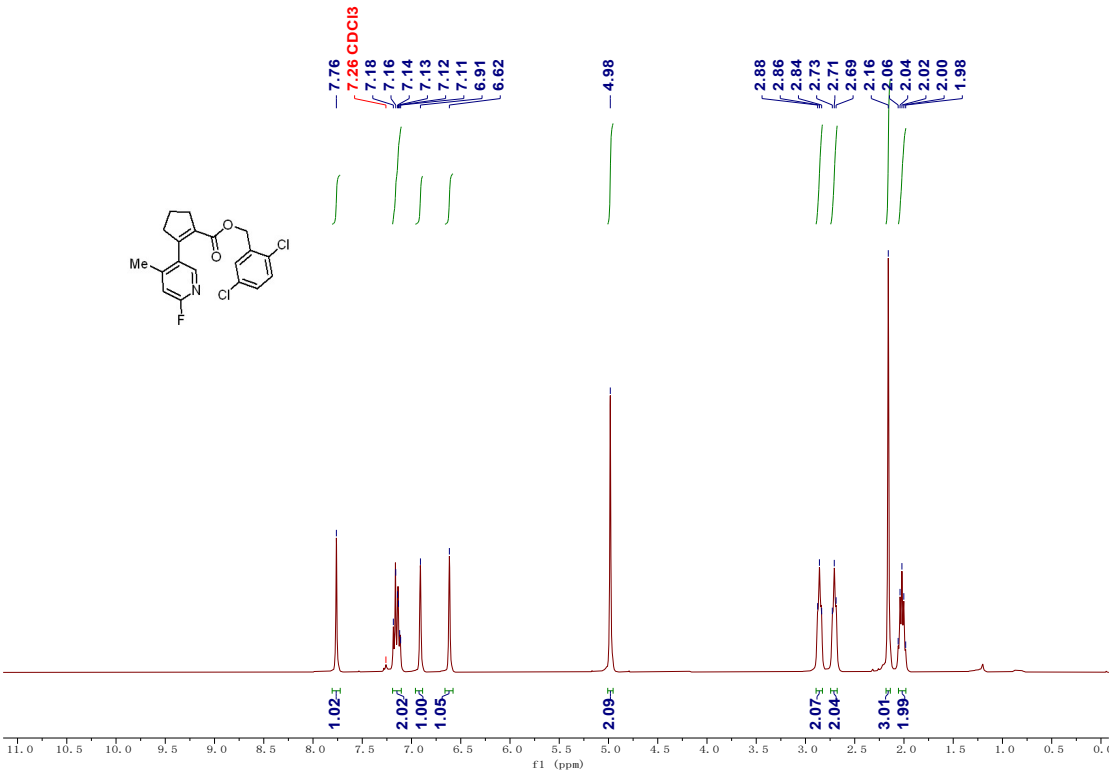
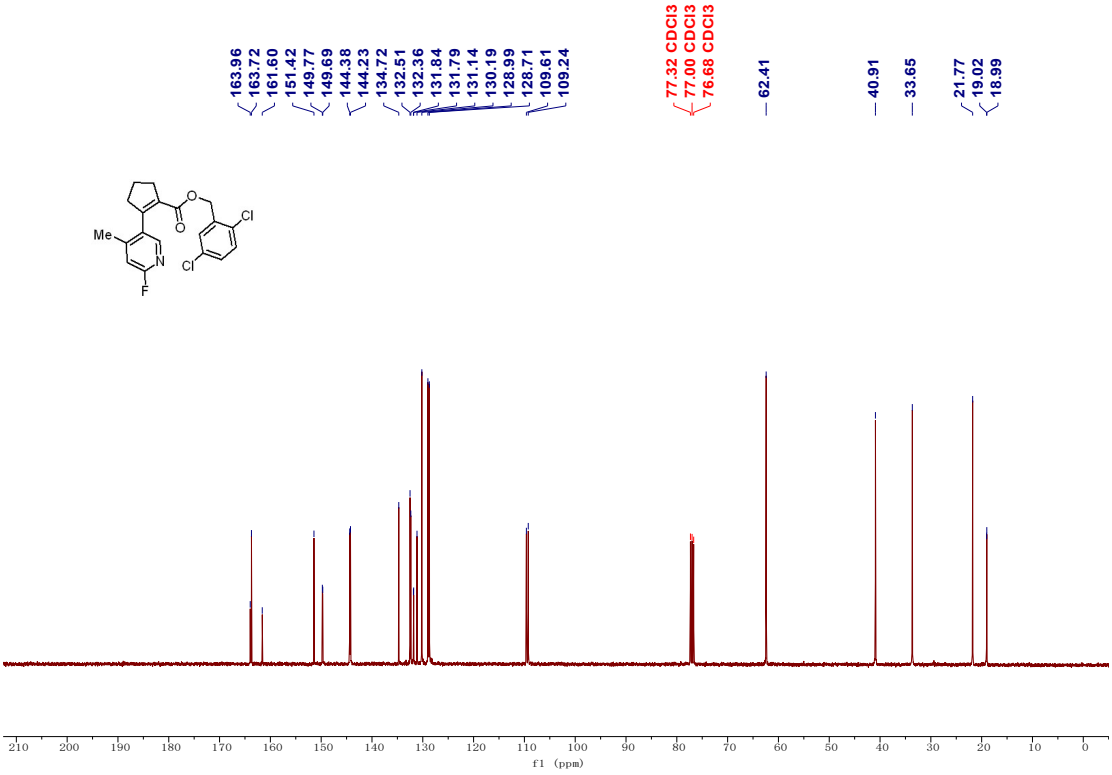
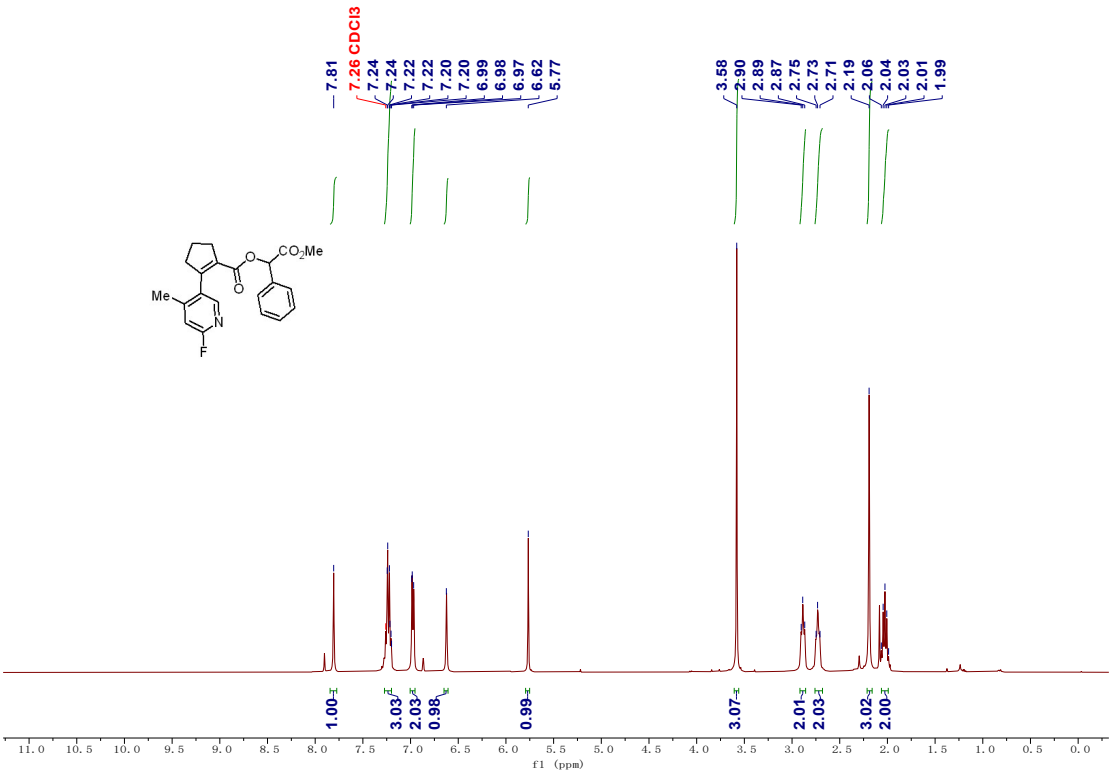


^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **1m**



^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **1m**



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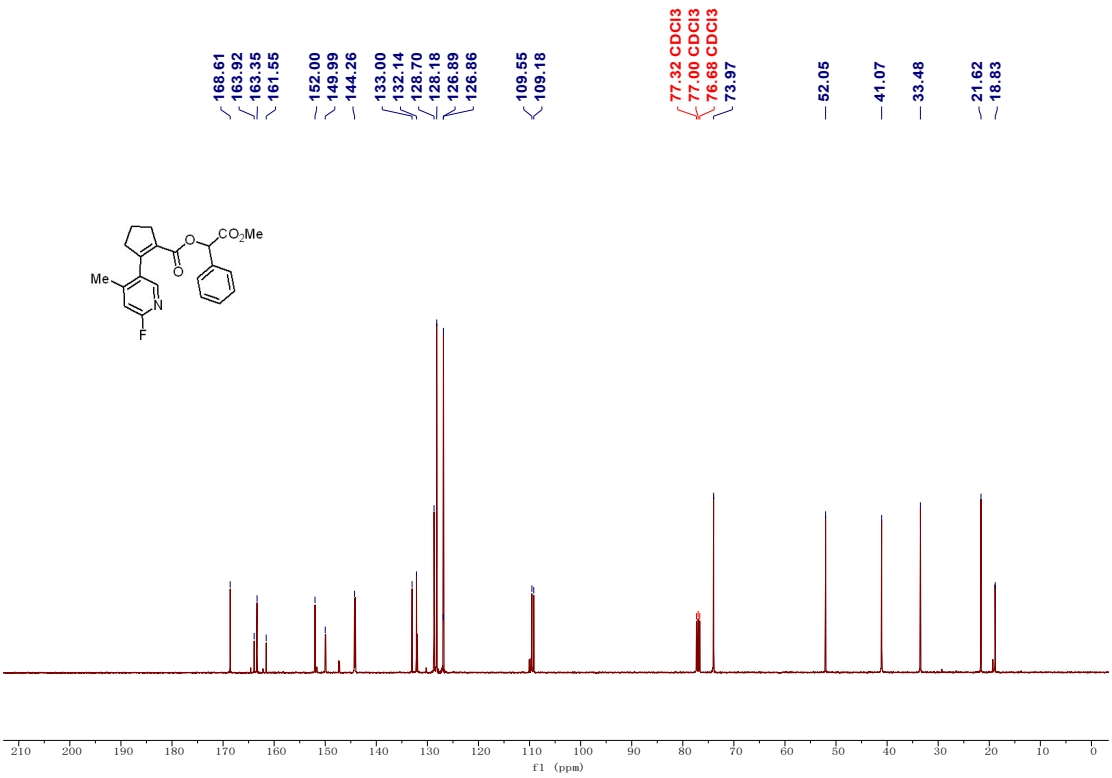

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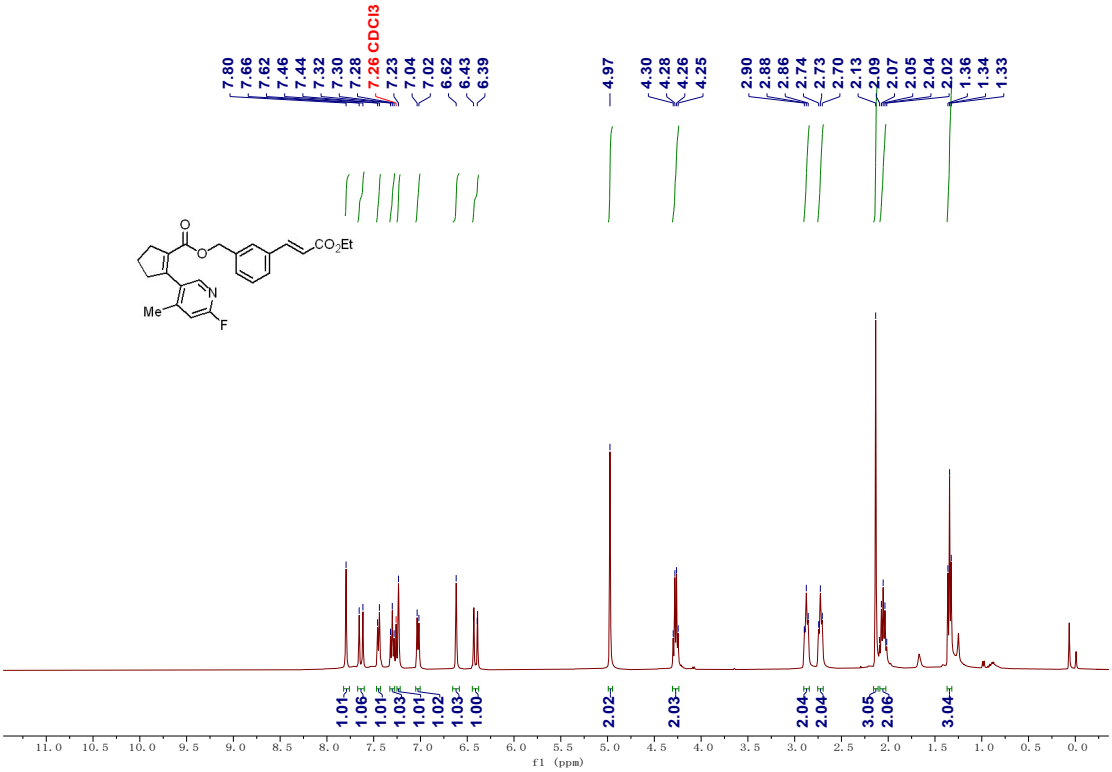
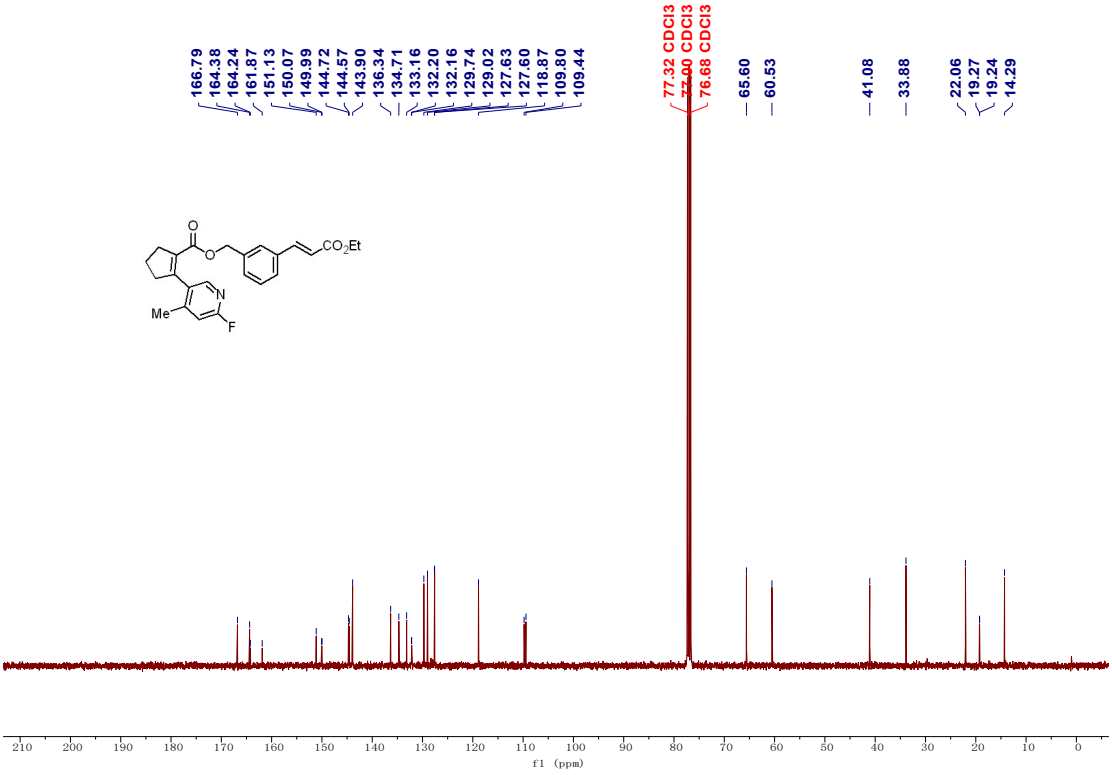
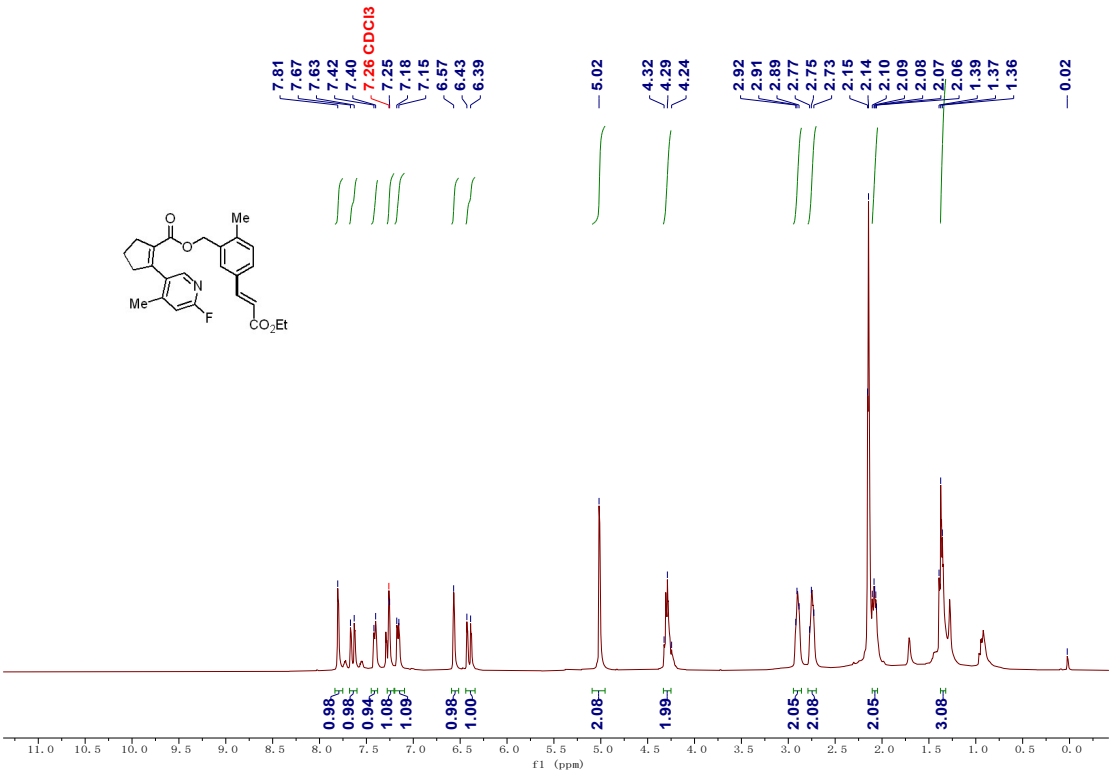


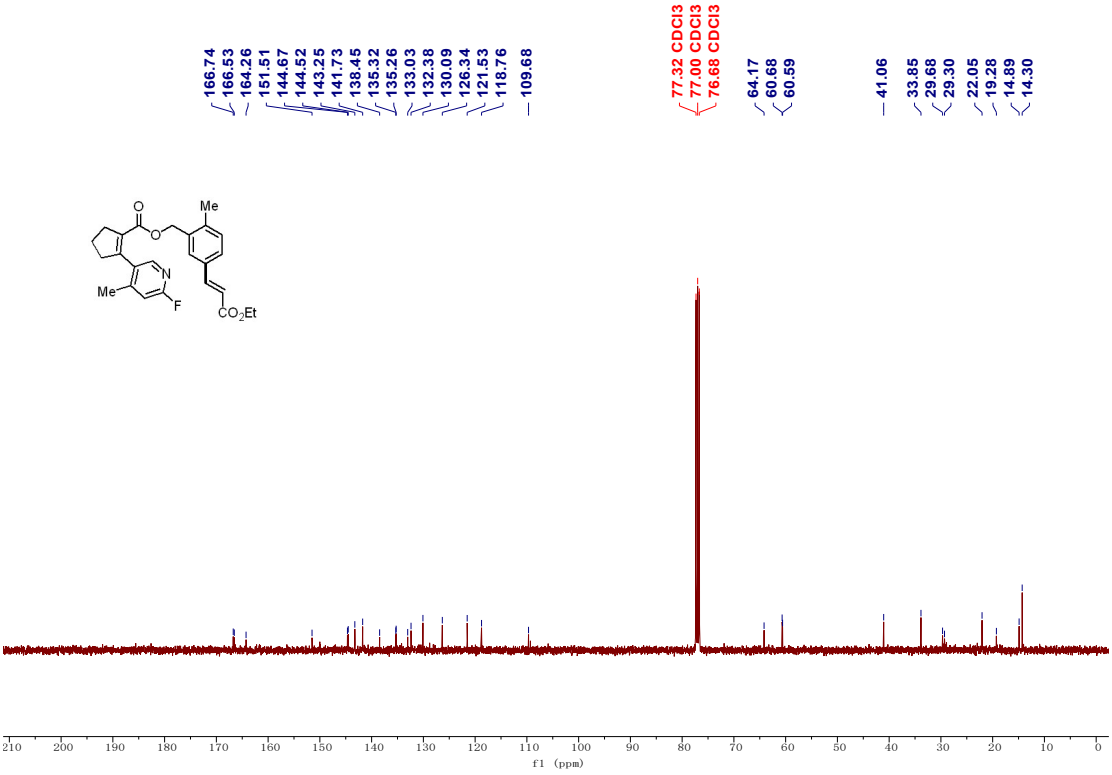
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **2a**



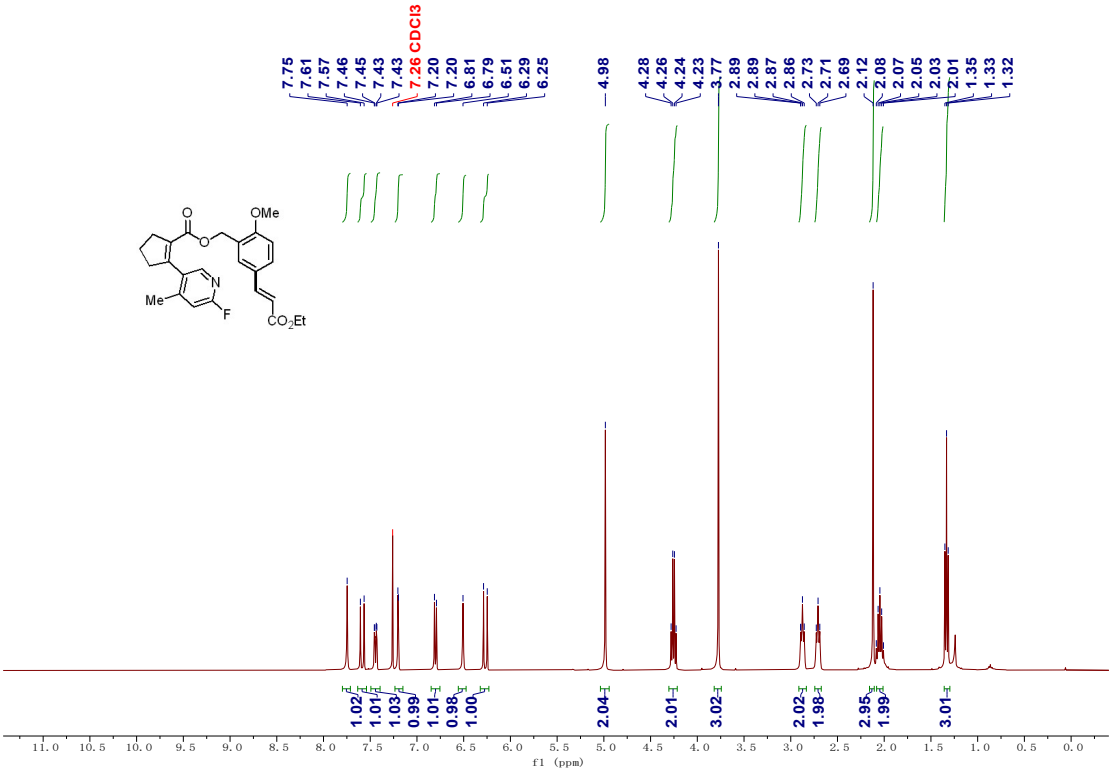
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **2a**



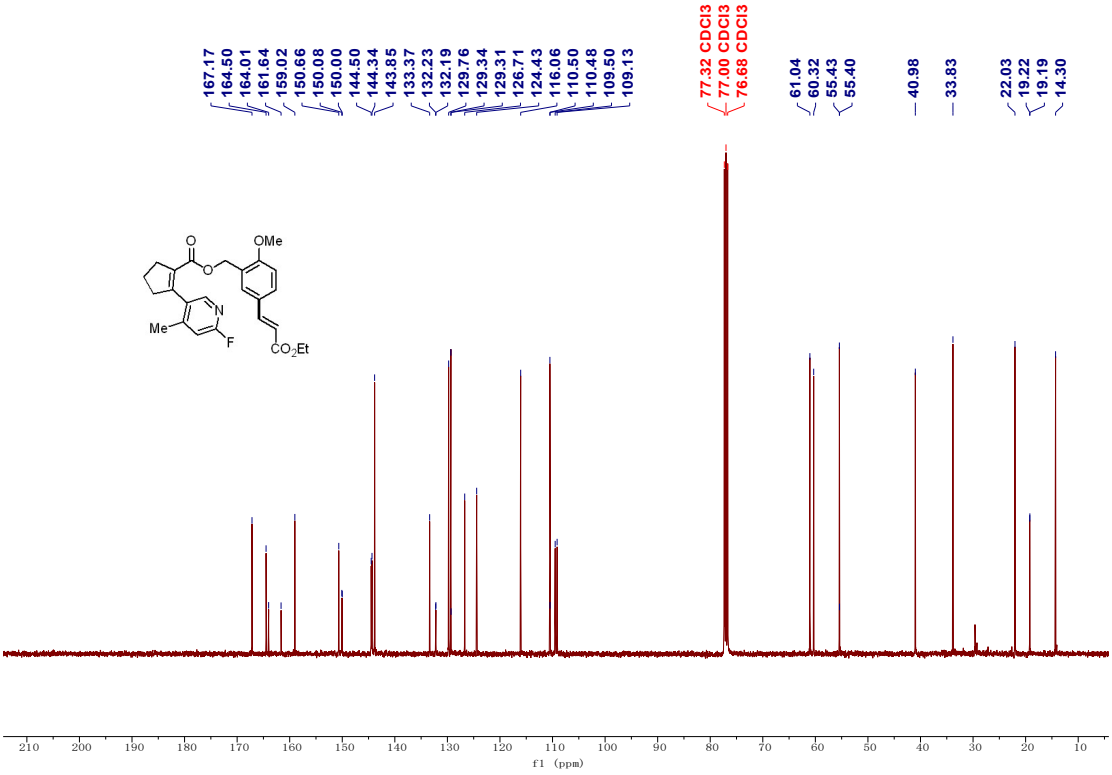
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **2b**



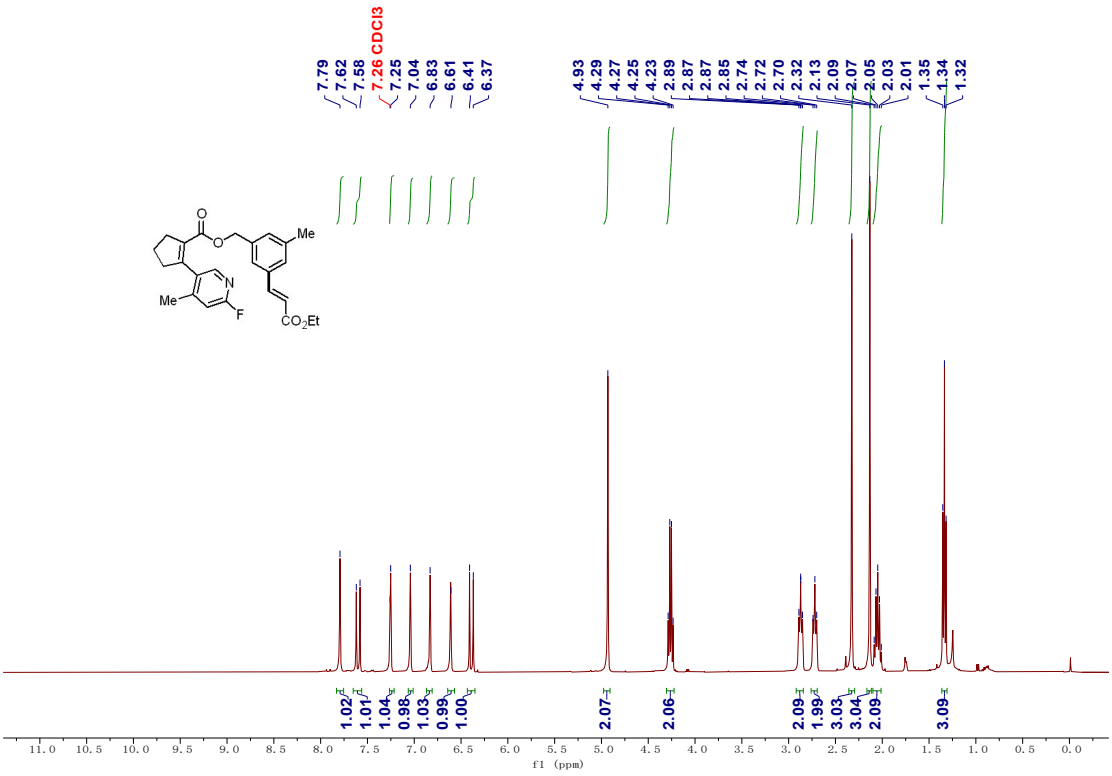
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **2b**



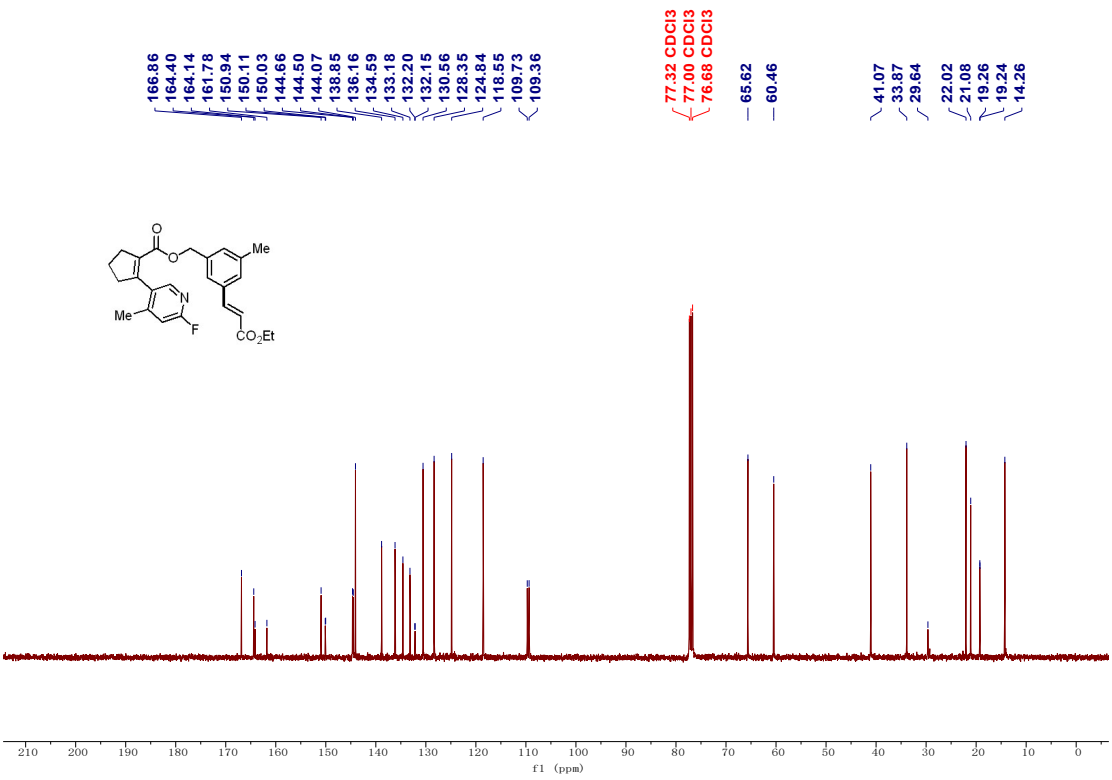
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **2c**



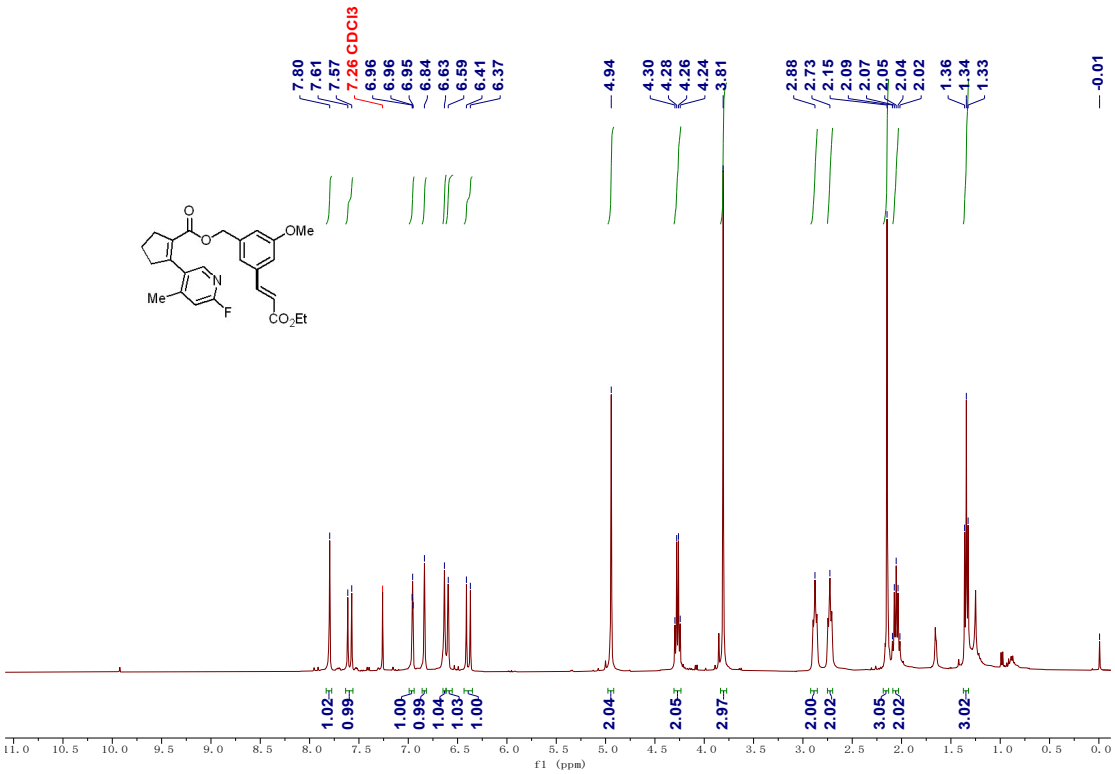
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **2c**



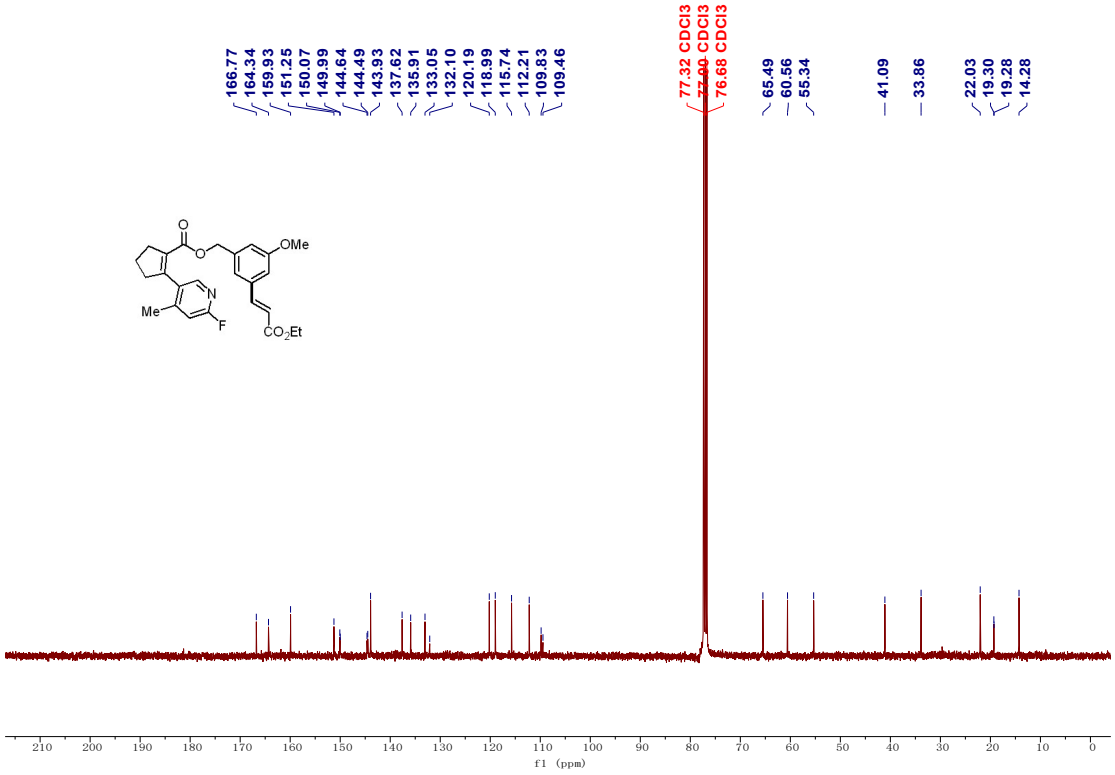
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **2d**



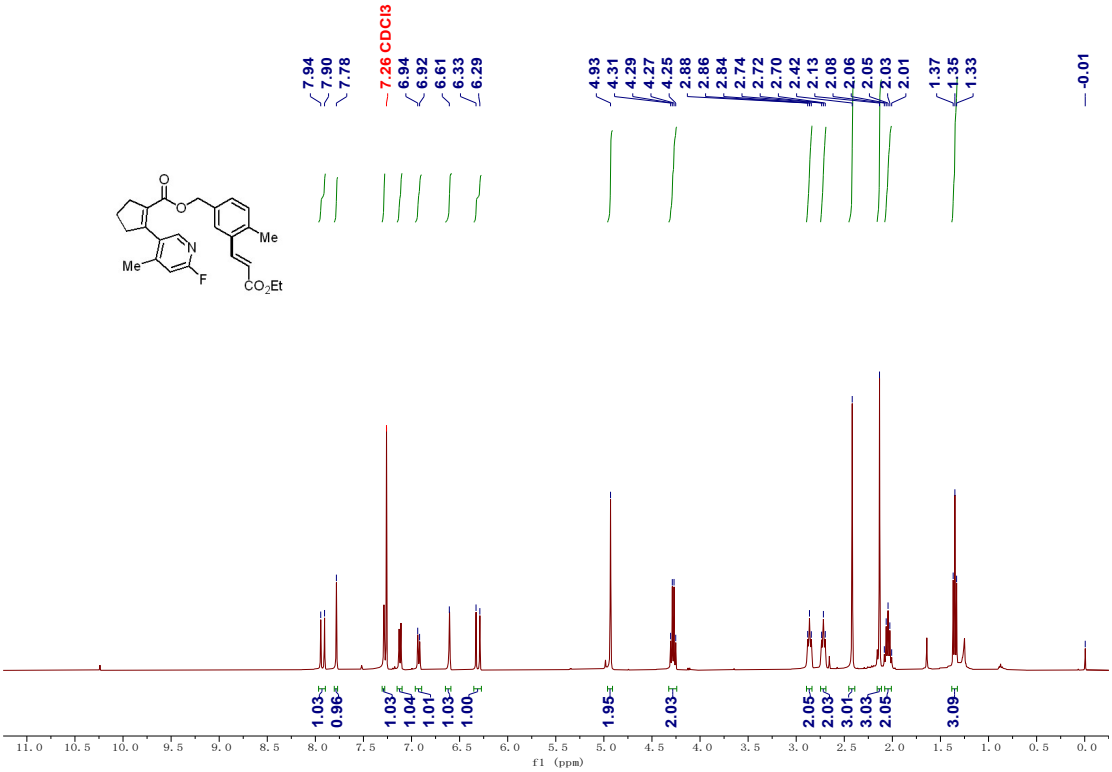
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **2d**



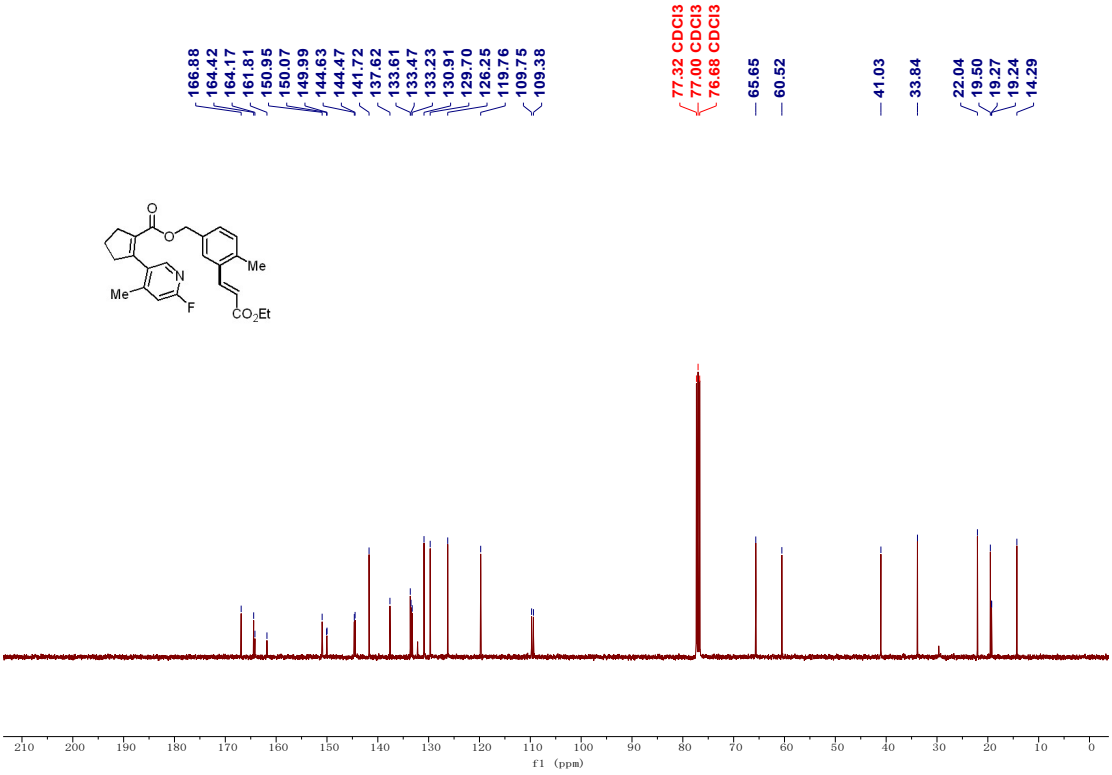
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **2e**



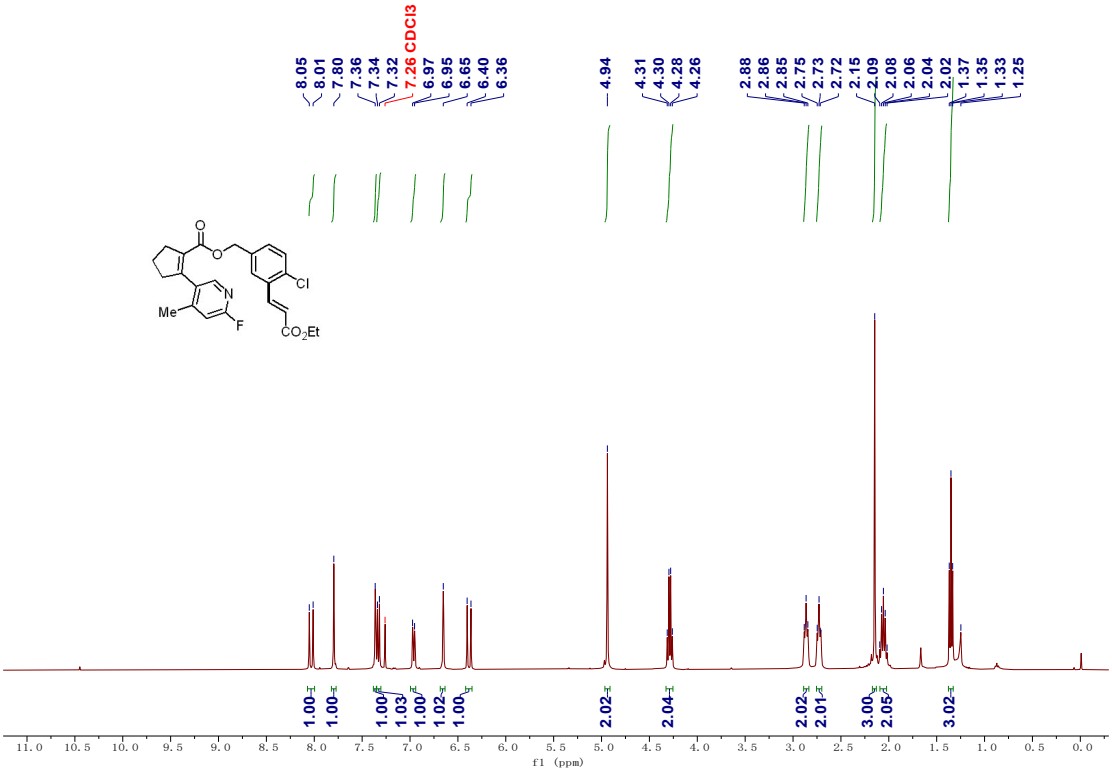
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **2e**



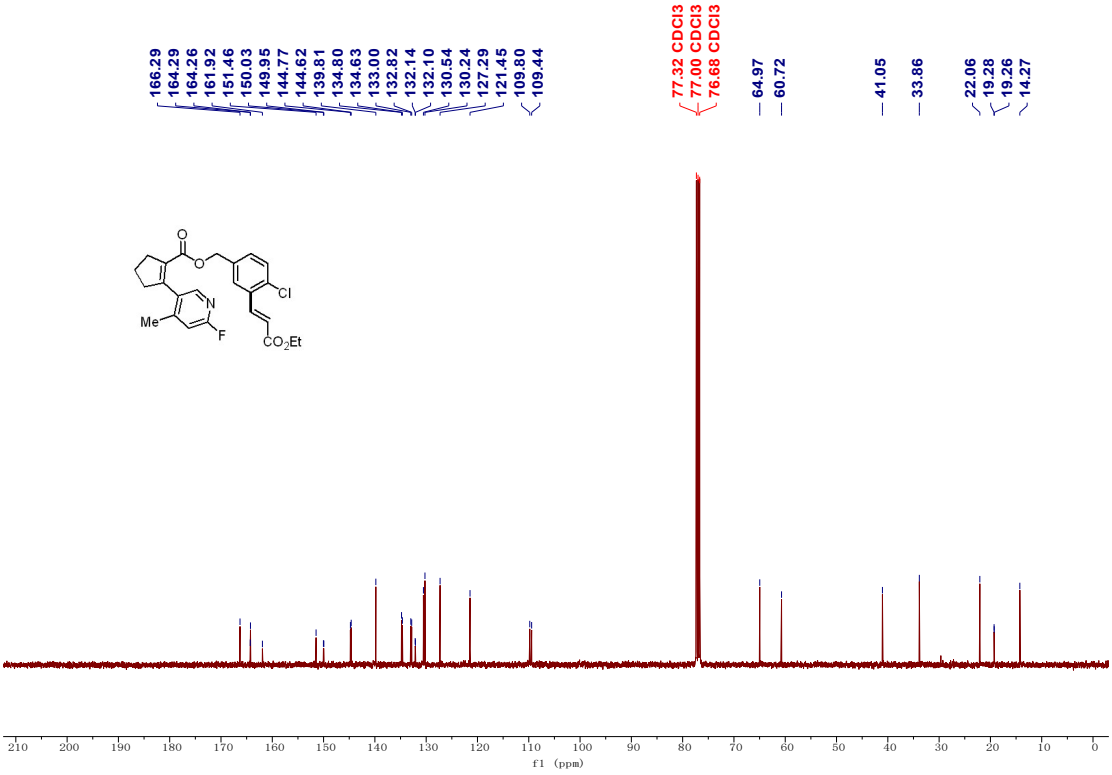
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **2f**



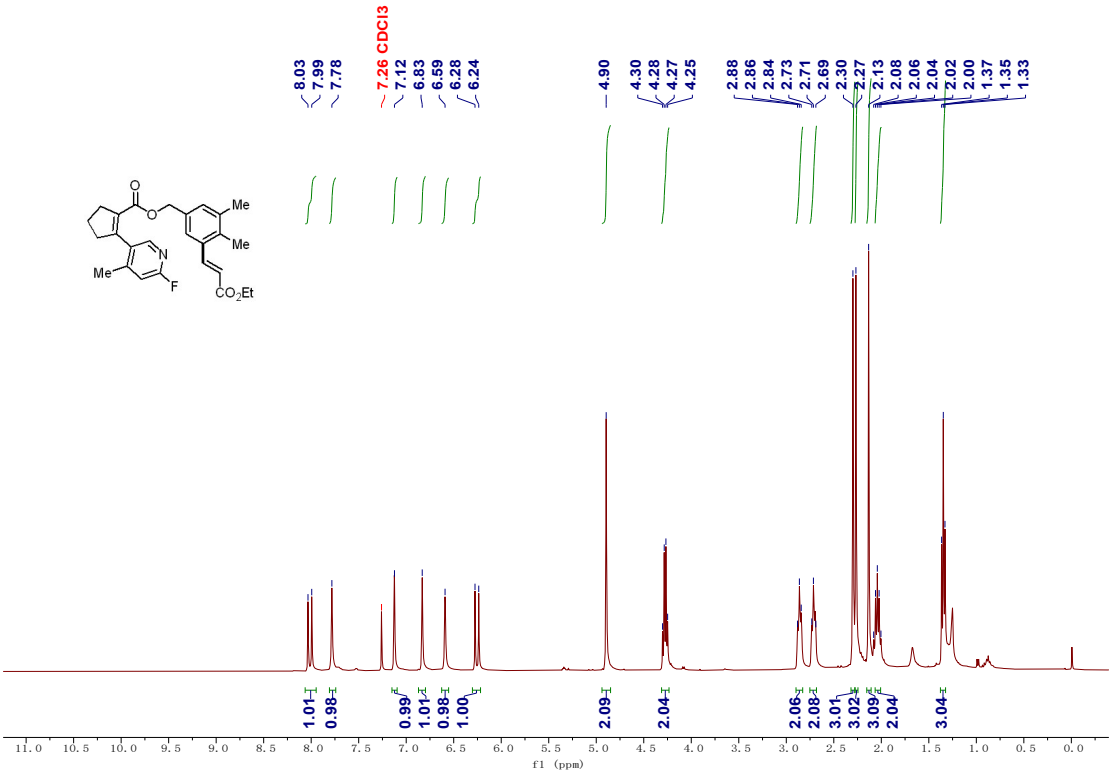
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **2f**



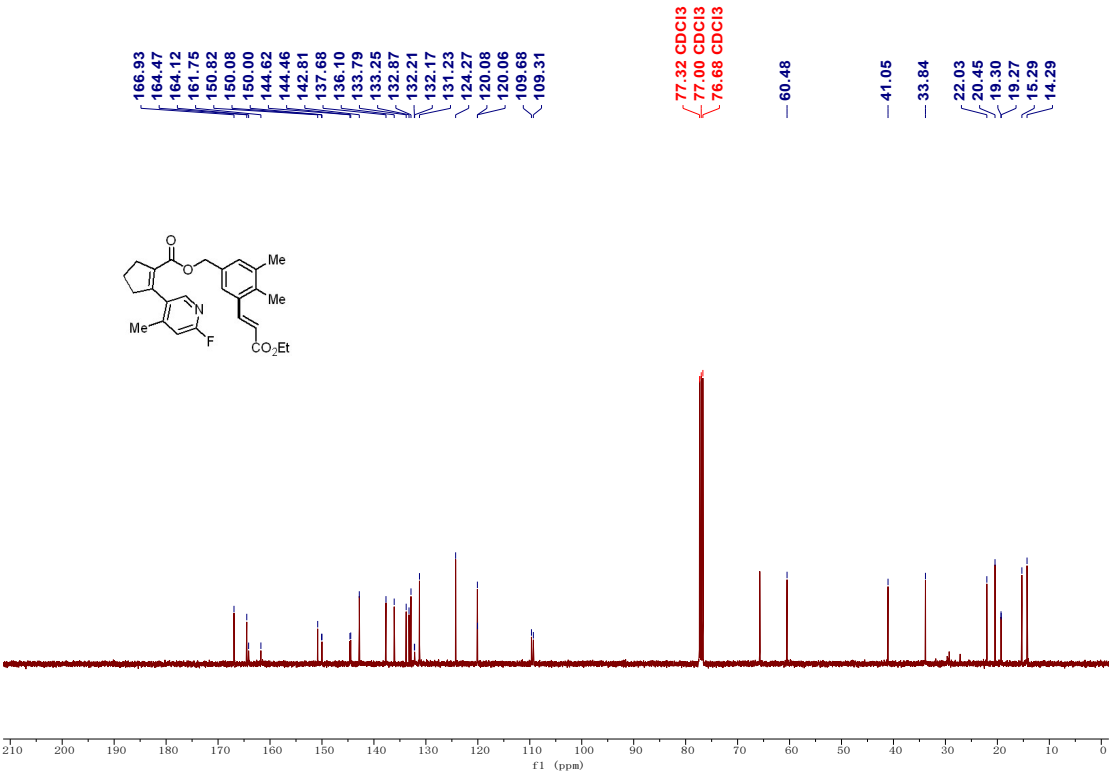
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **2g**



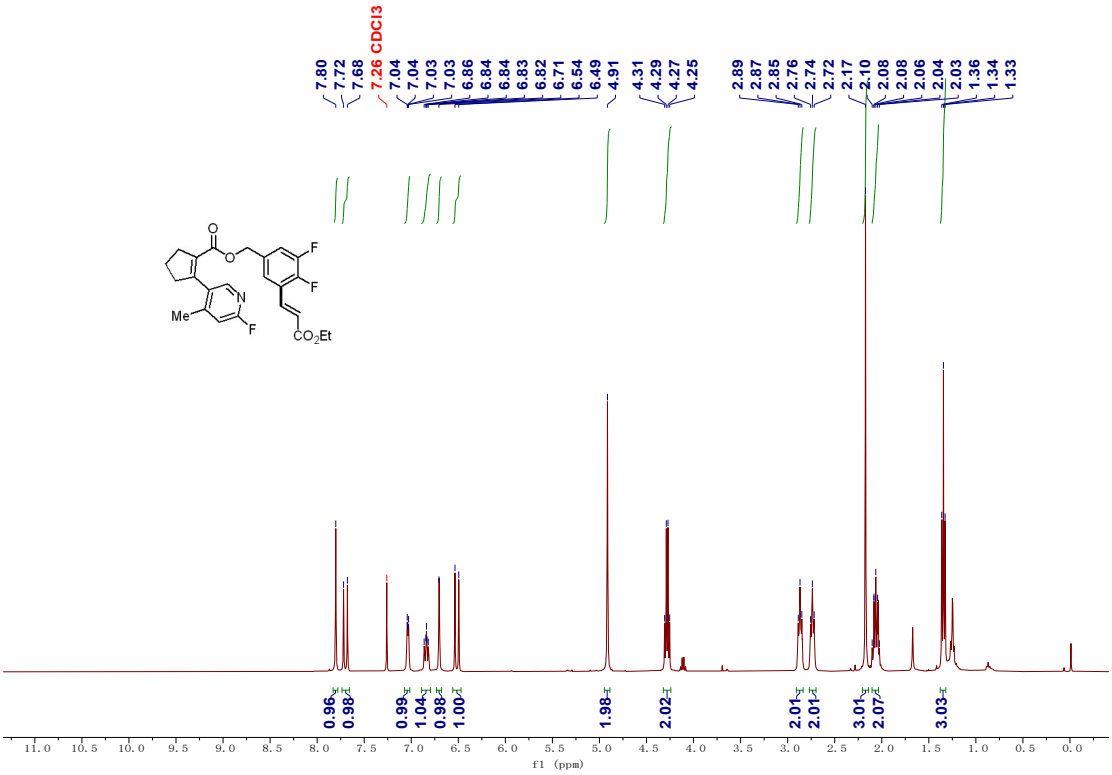
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **2g**



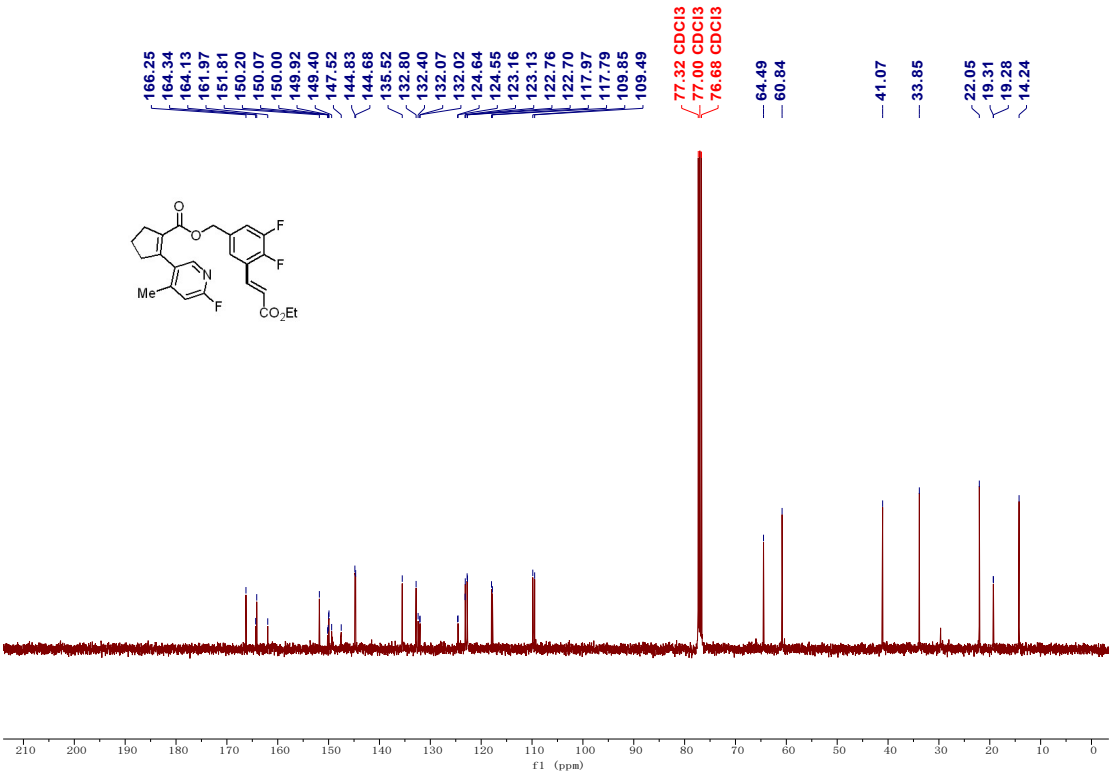
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **2h**



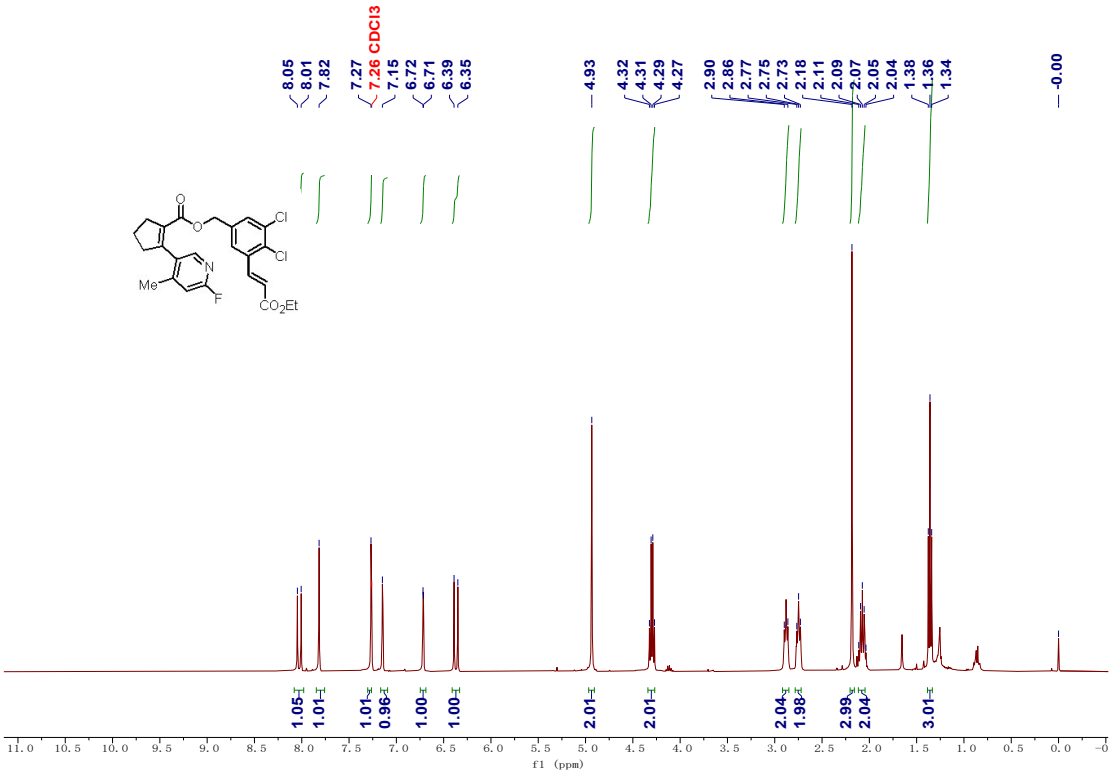
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **2h**



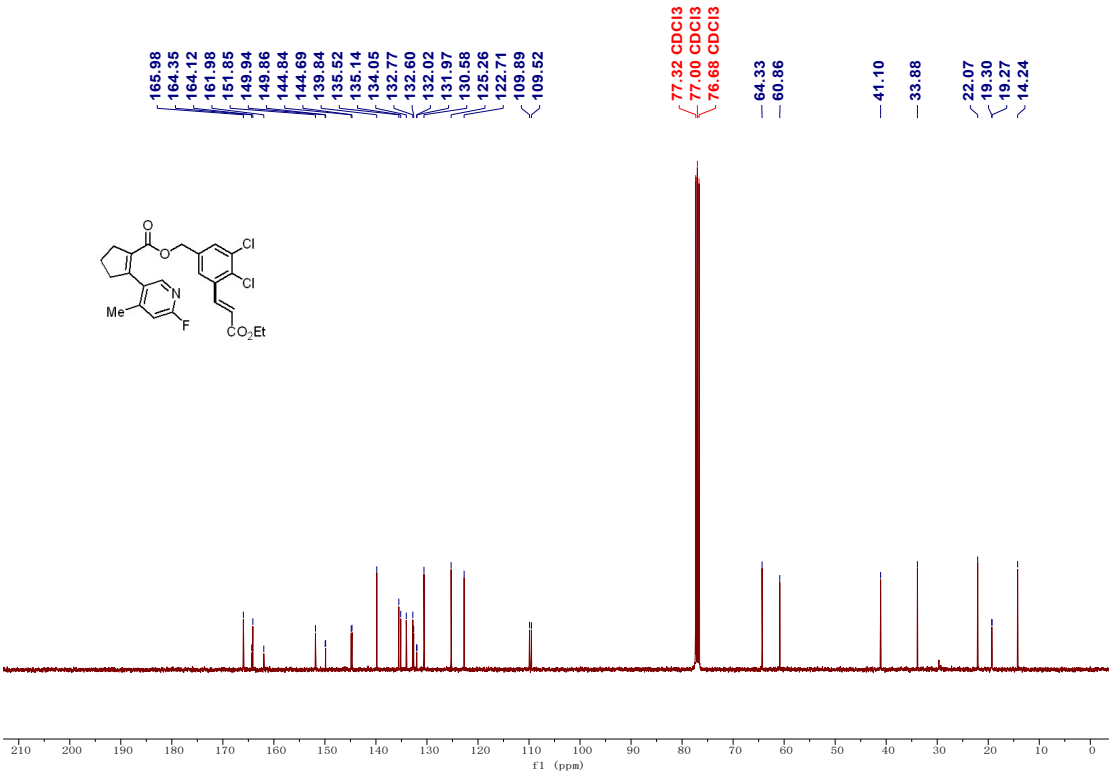
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **2i**



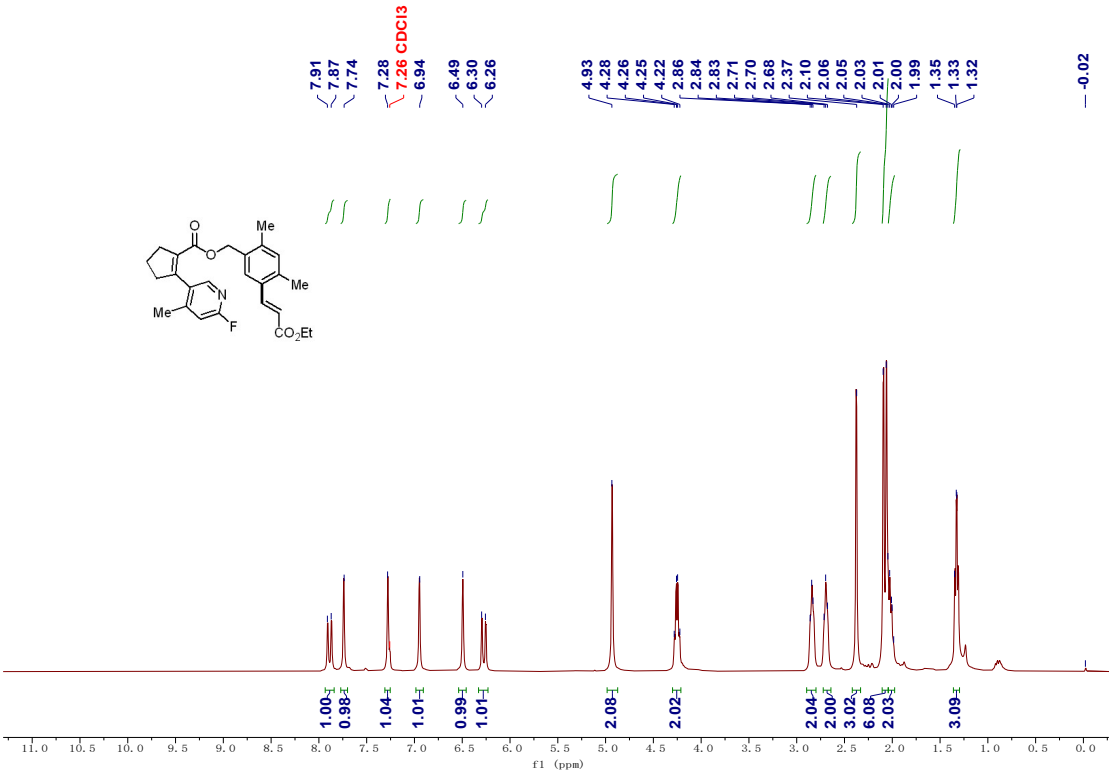
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **2i**



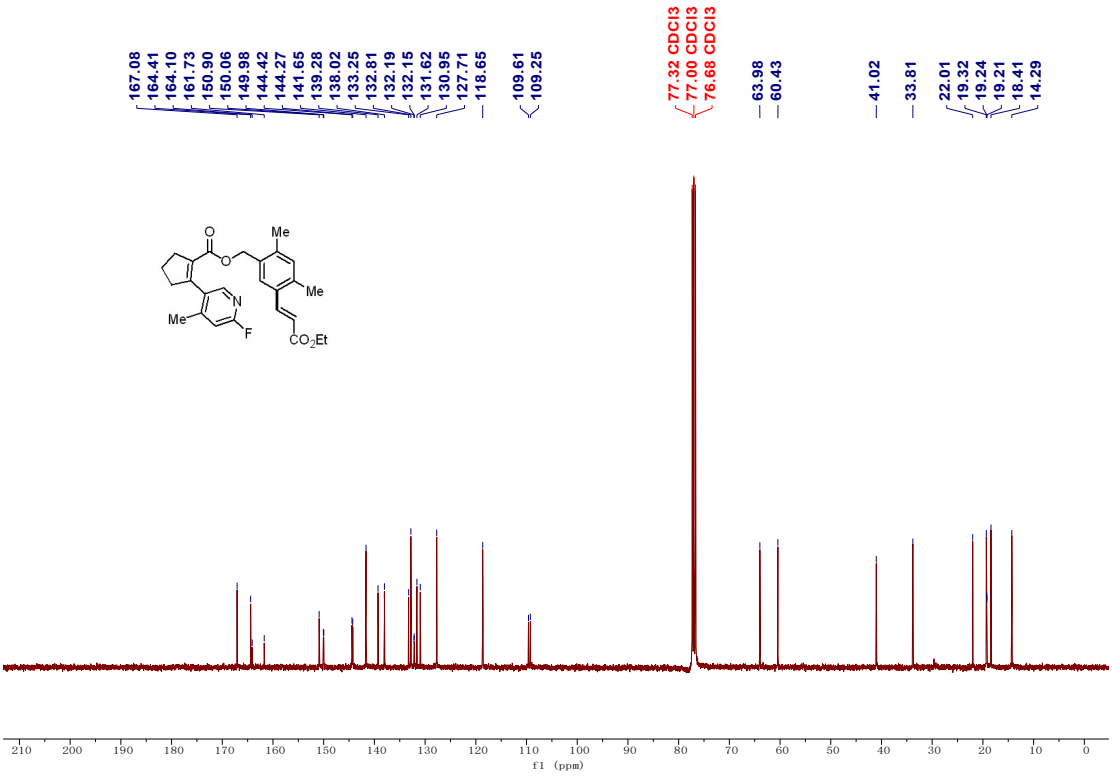
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **2j**



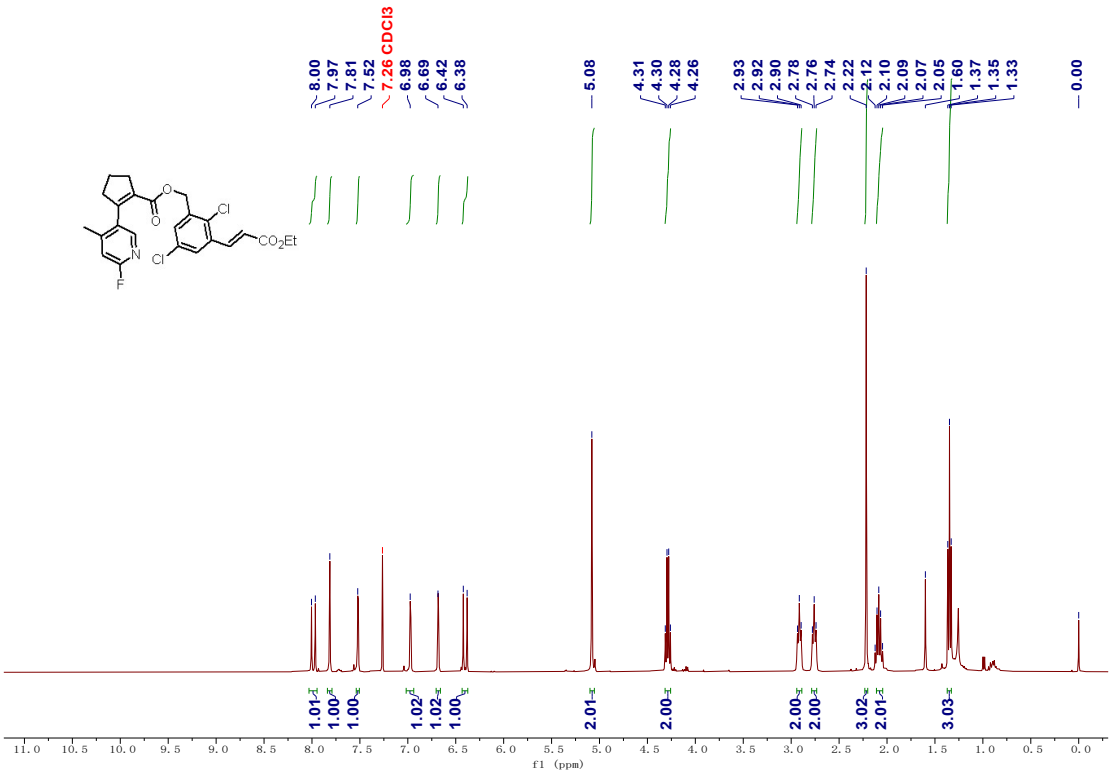
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **2j**



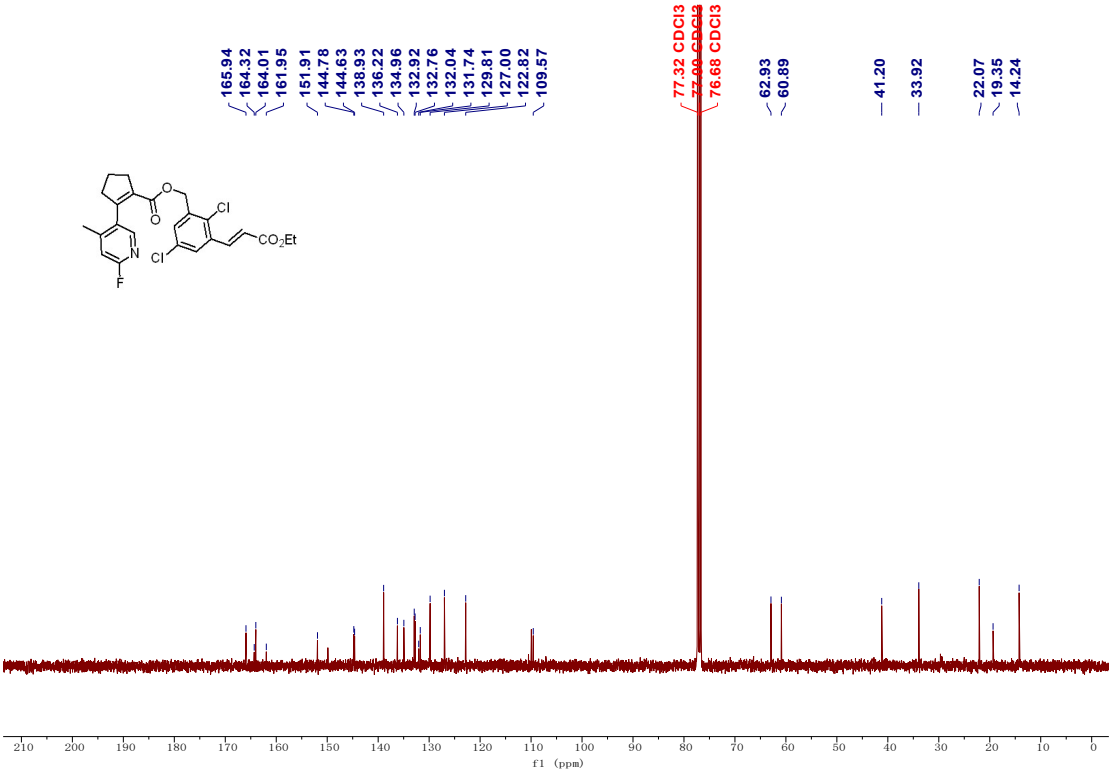
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **2k**



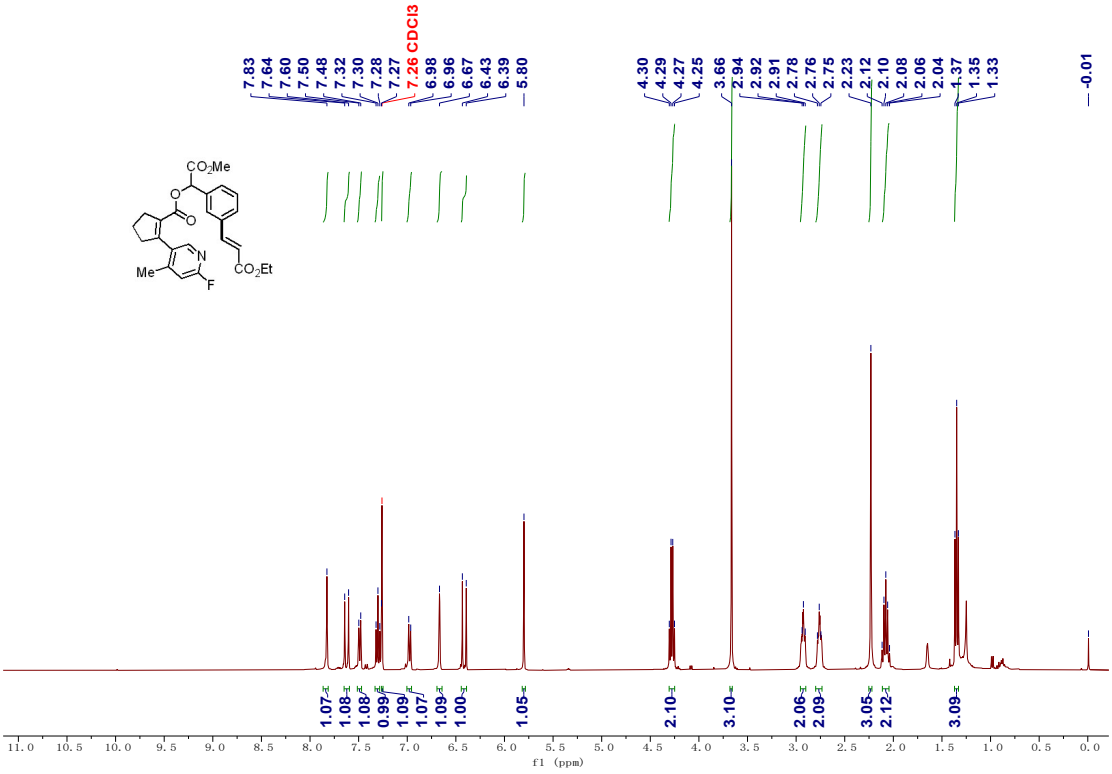
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **2k**



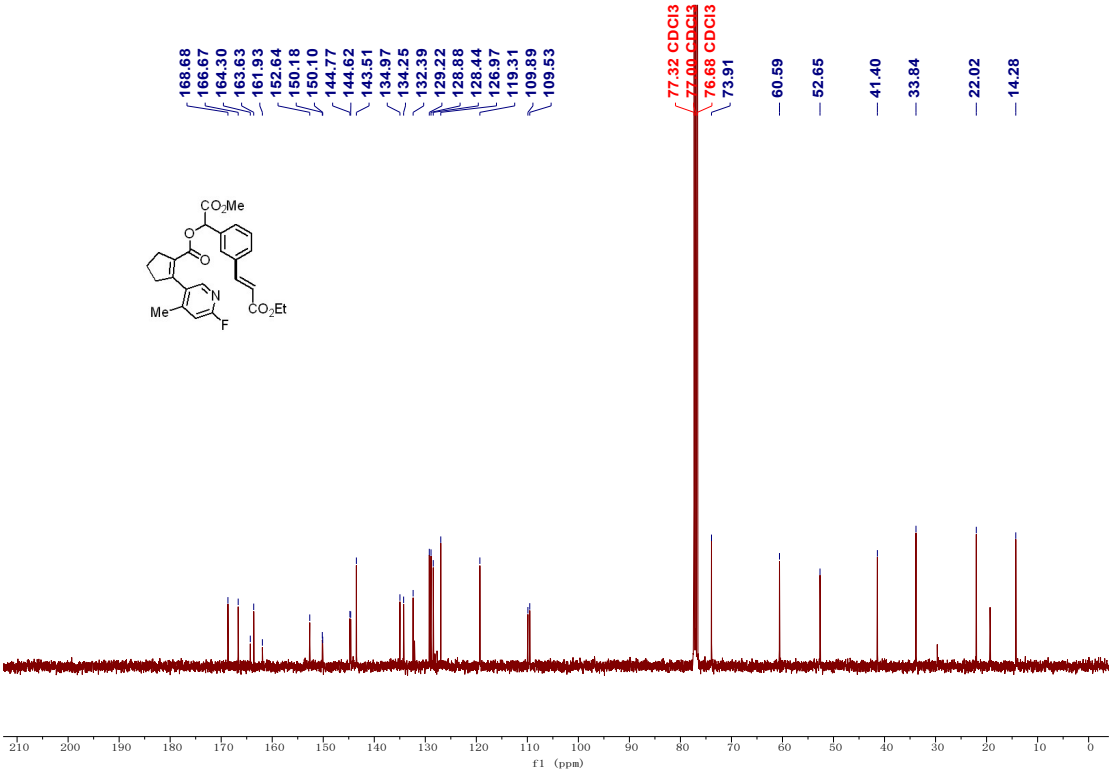
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **2l**



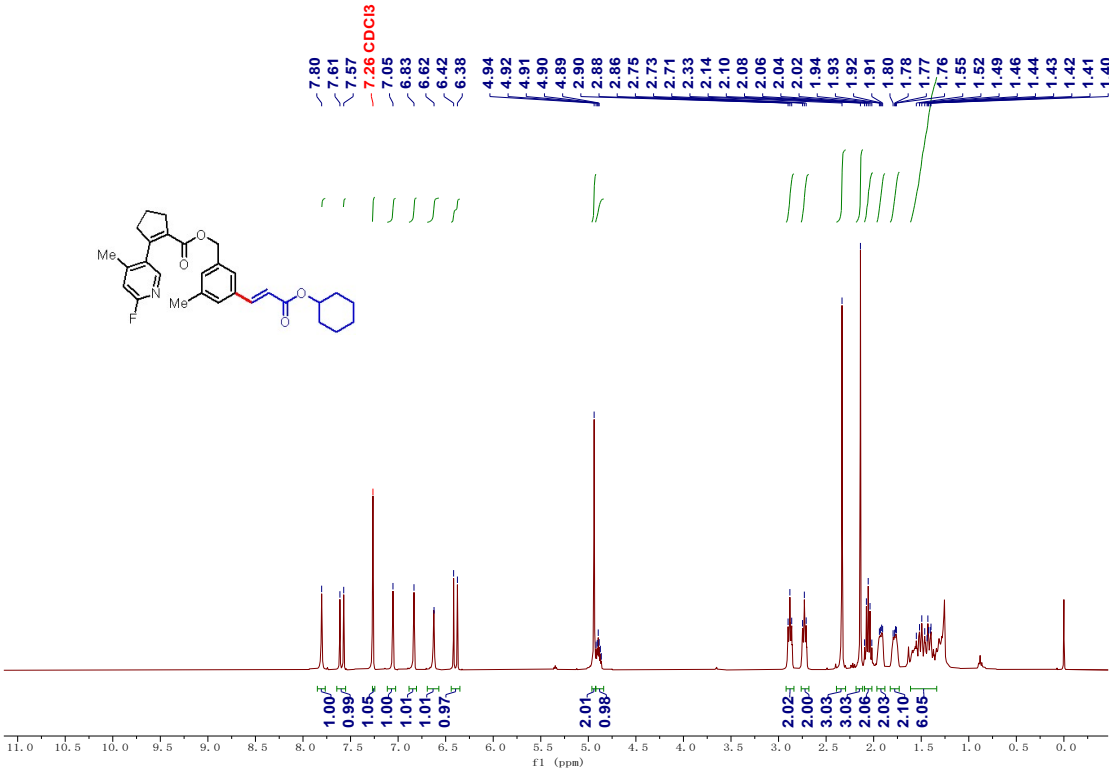
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **2l**



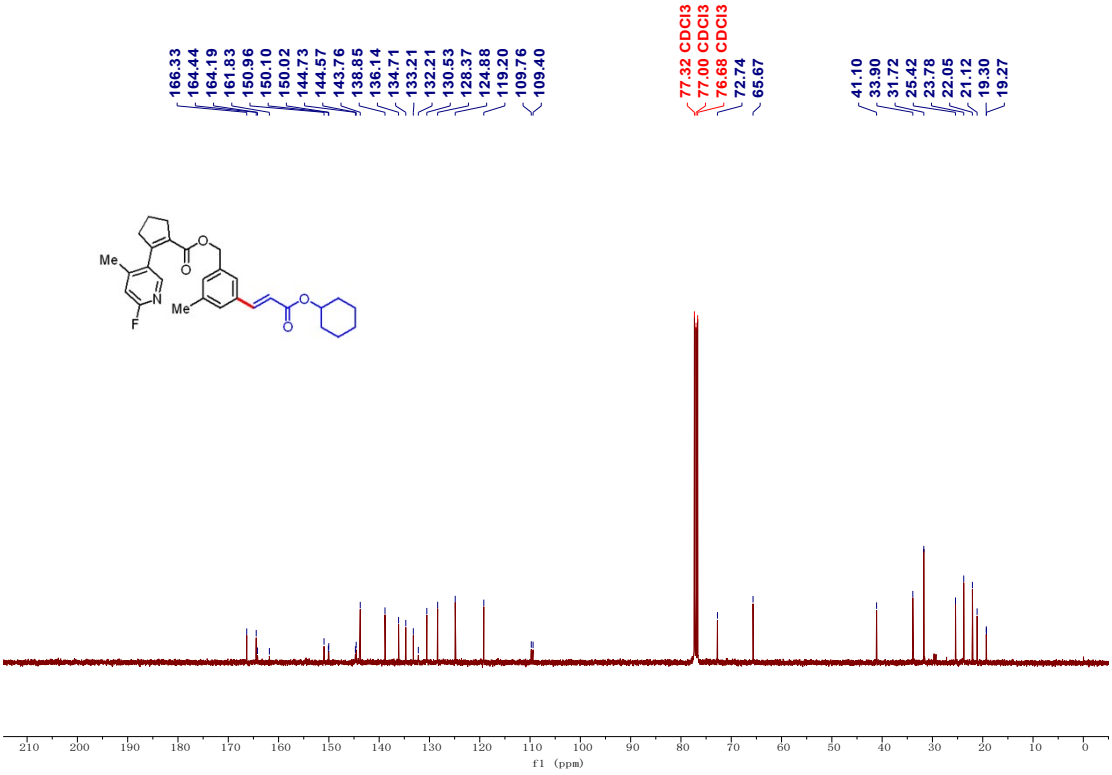
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **2m**



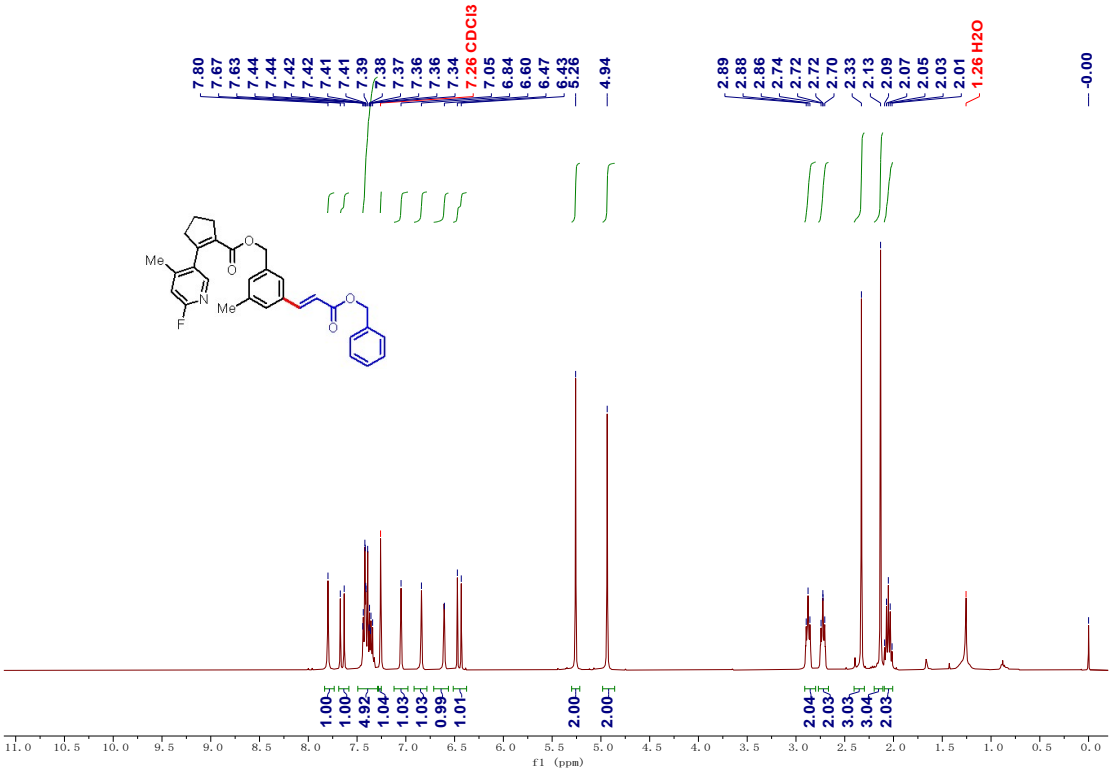
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **2m**



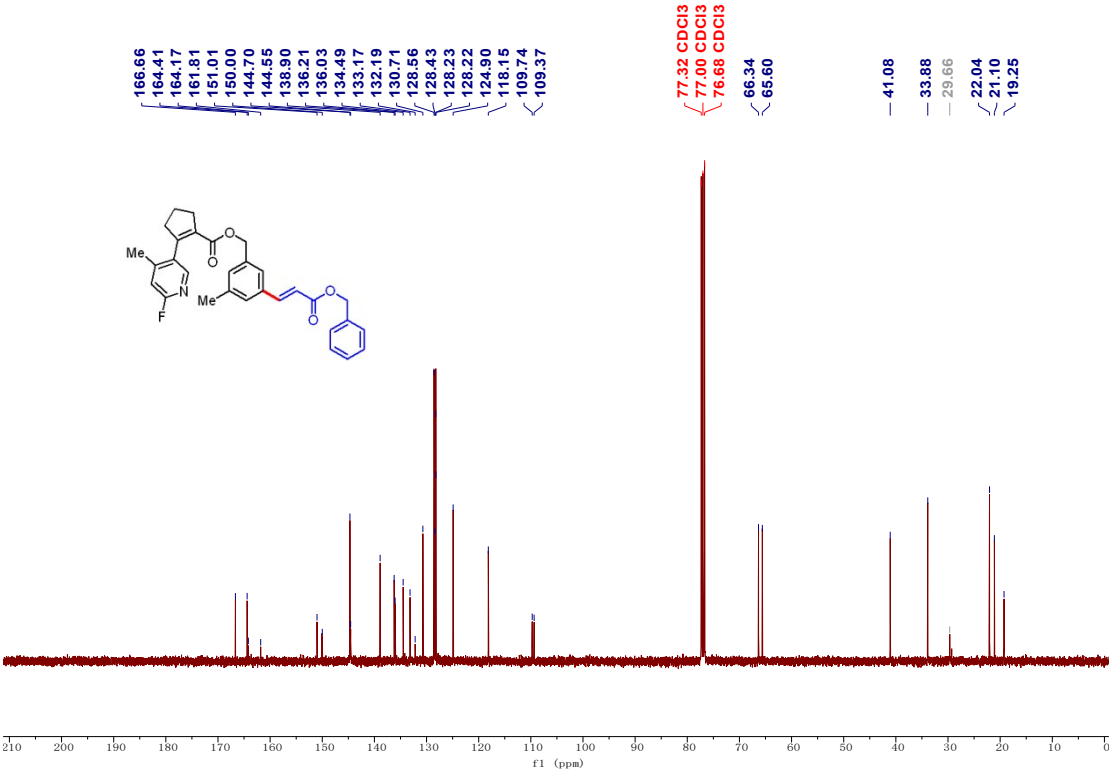
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **3a**



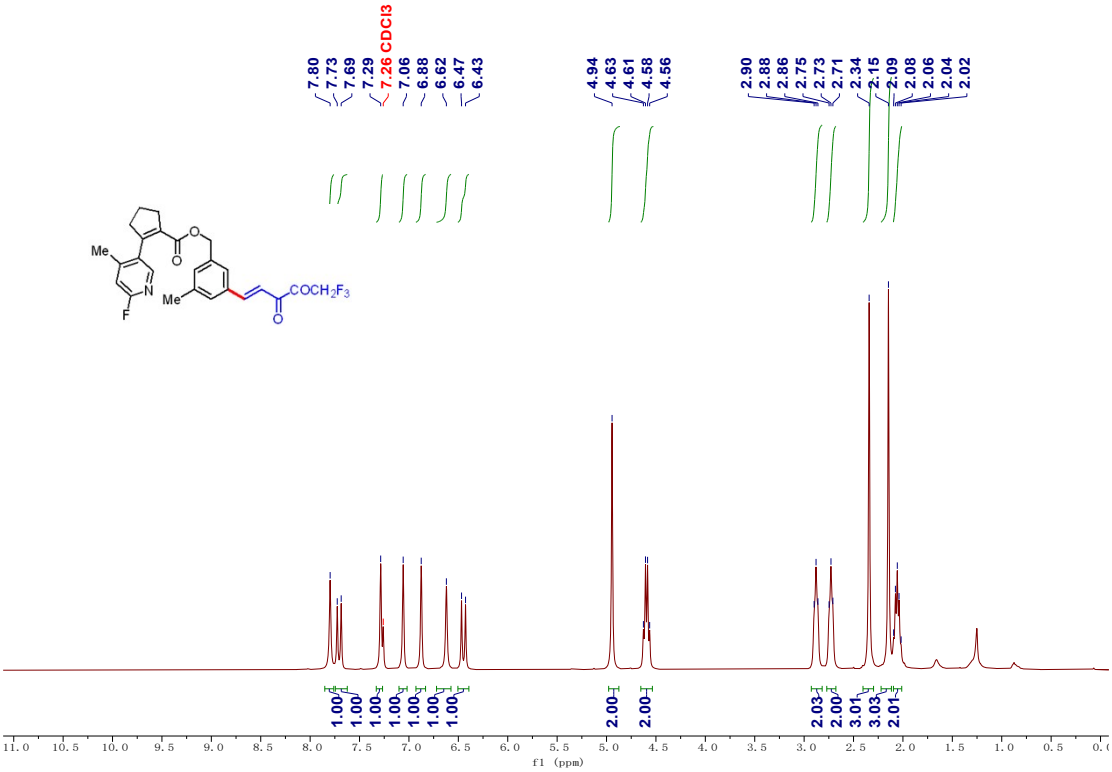
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **3a**



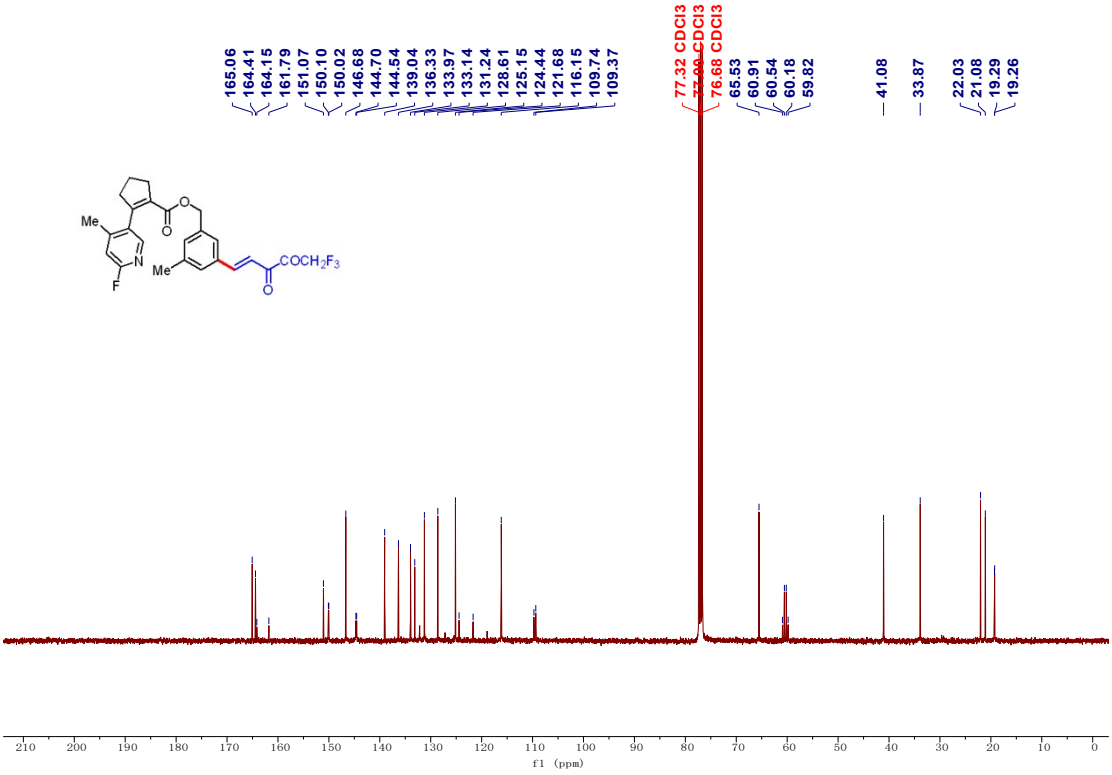
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **3b**



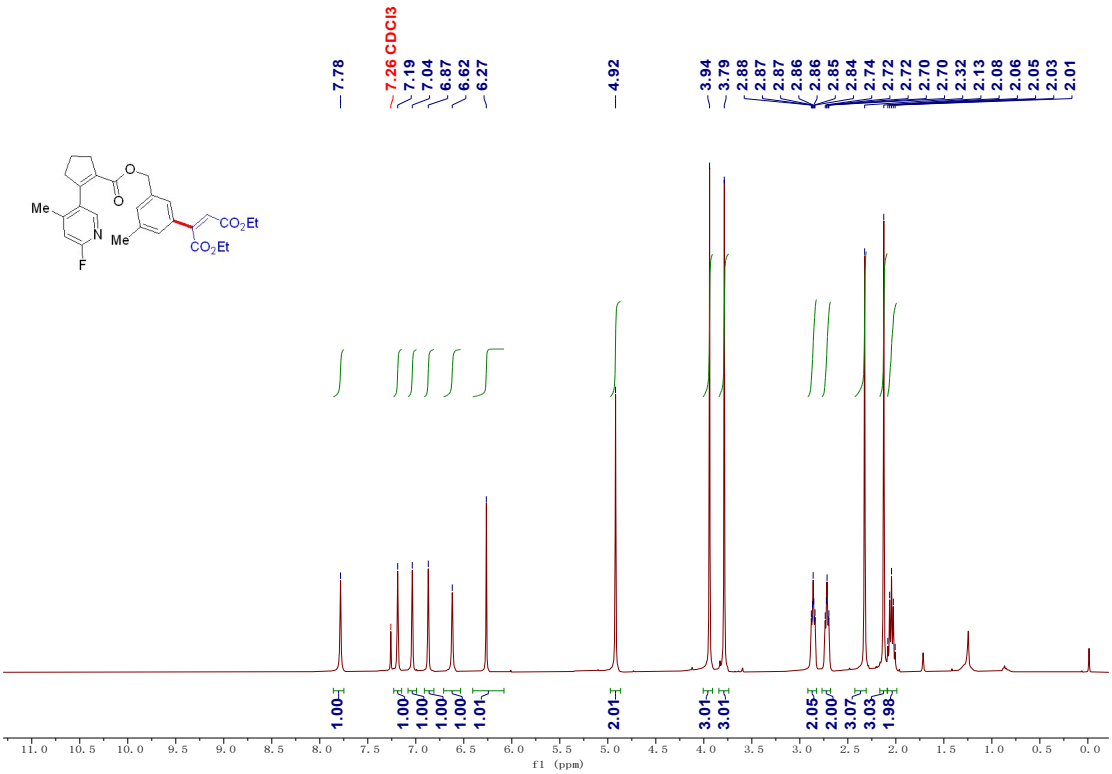
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **3b**



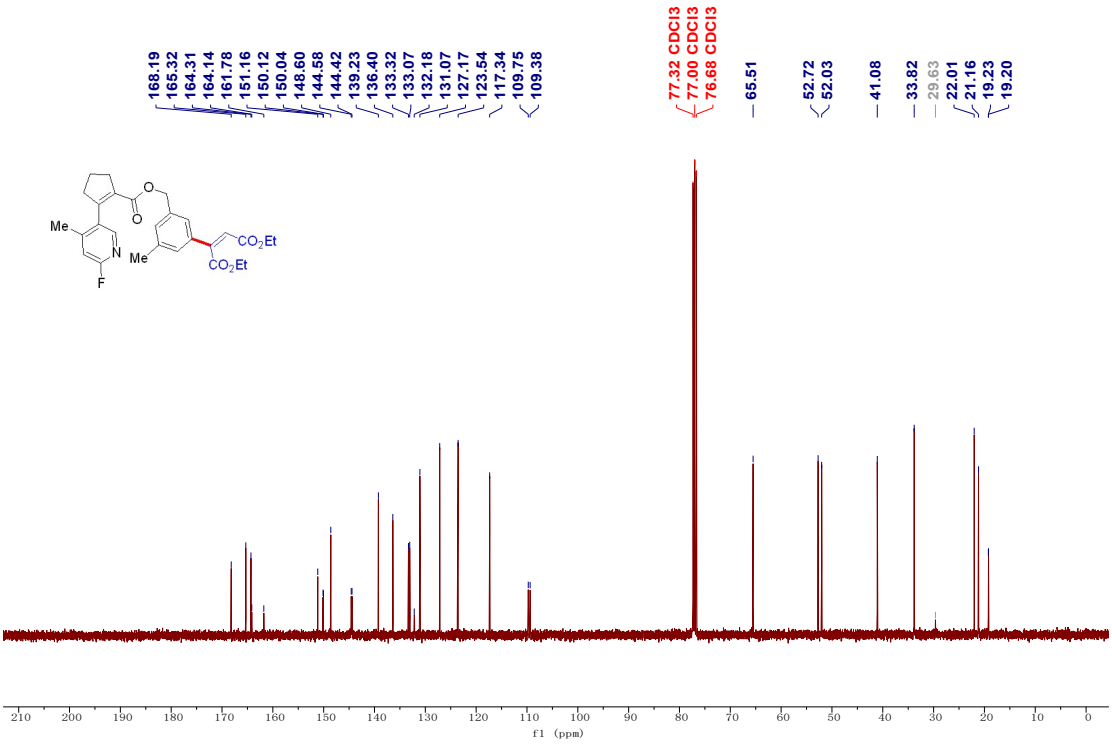
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **3c**



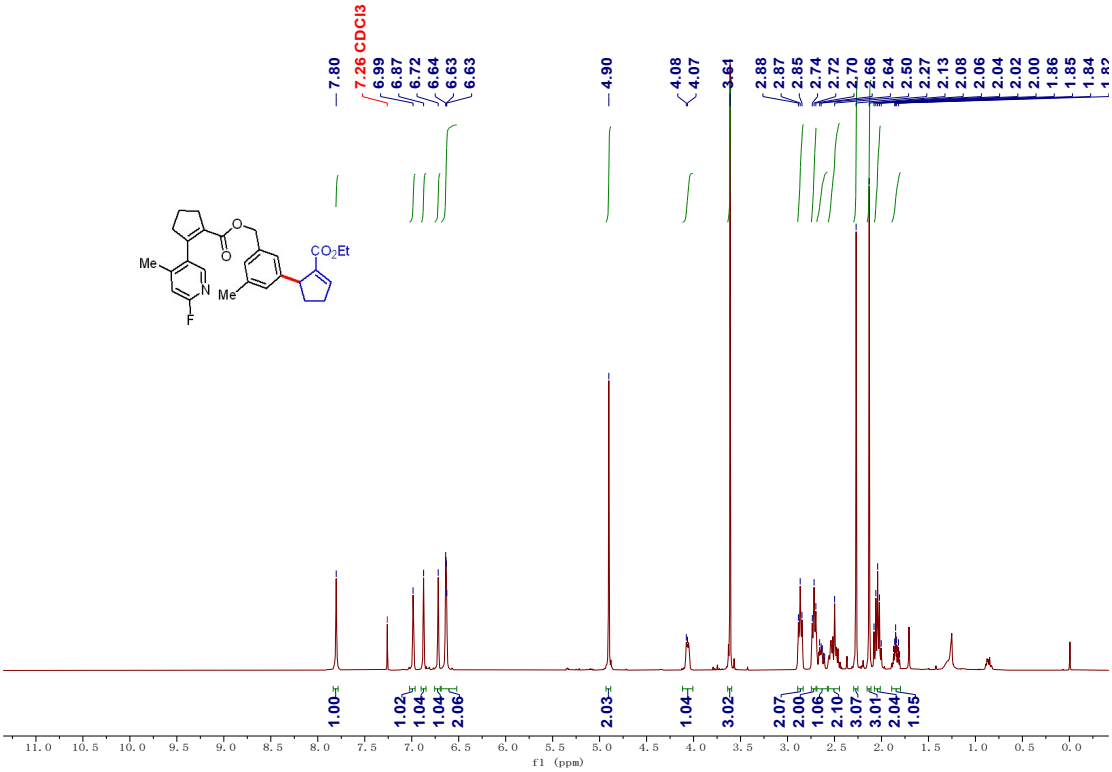
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **3c**



^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **3d**



^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **3d**



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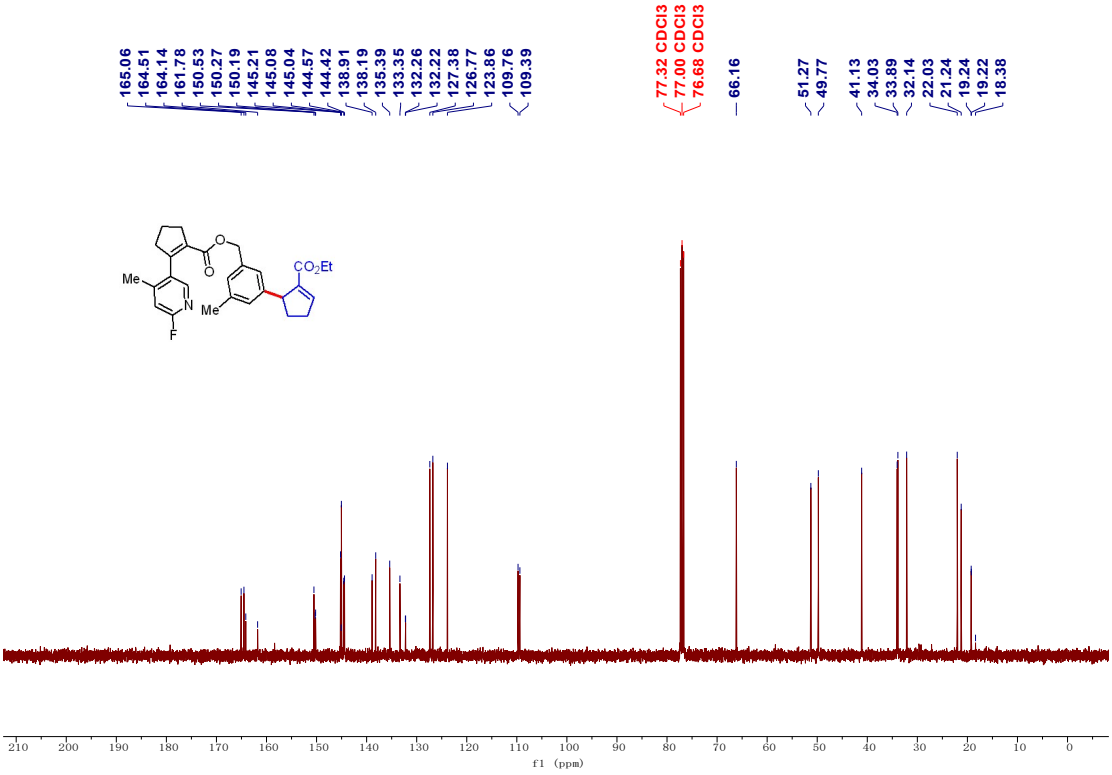
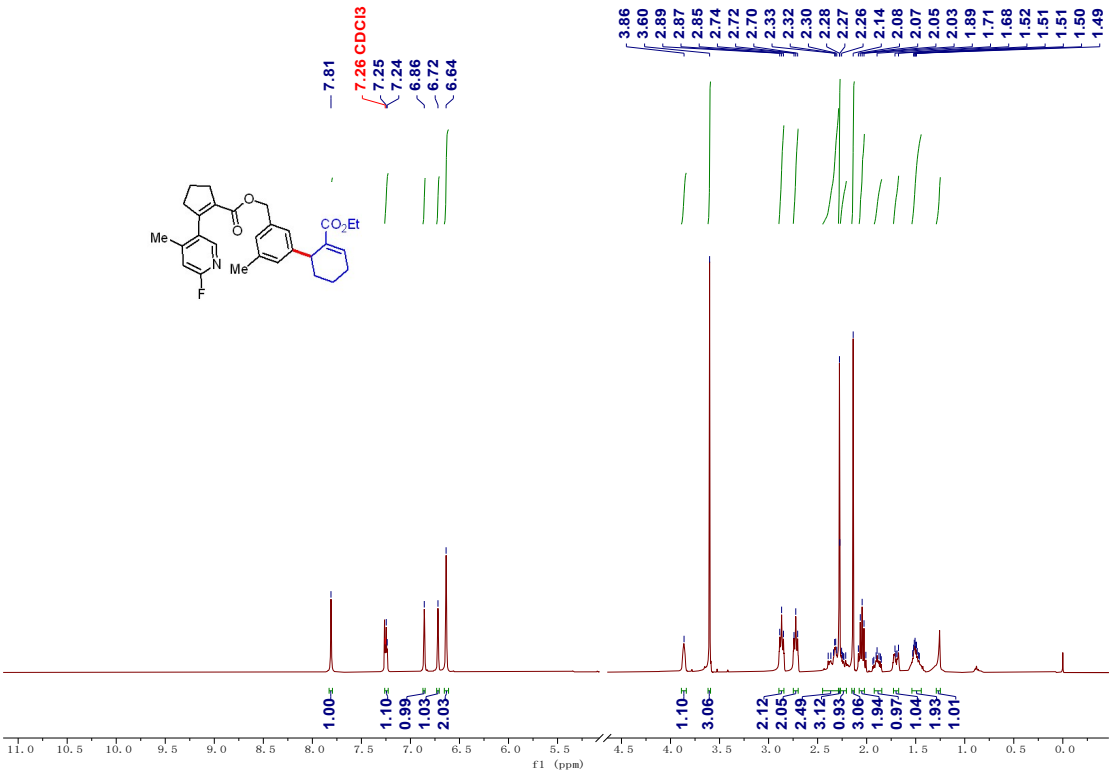
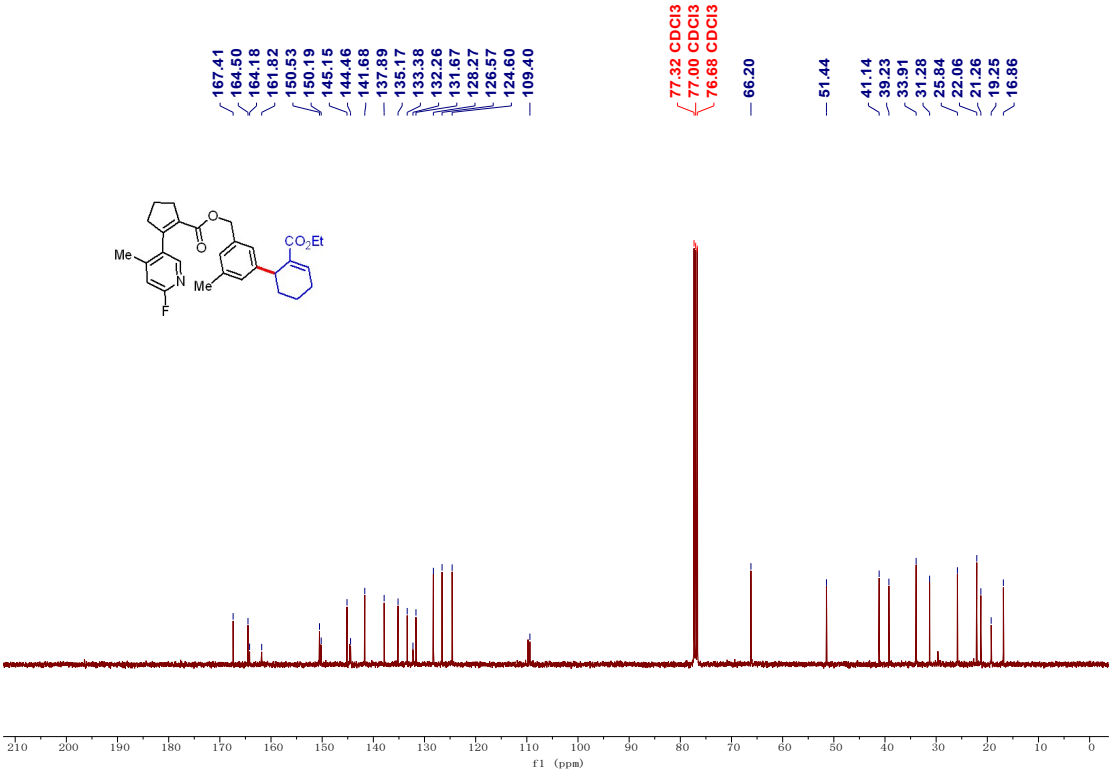


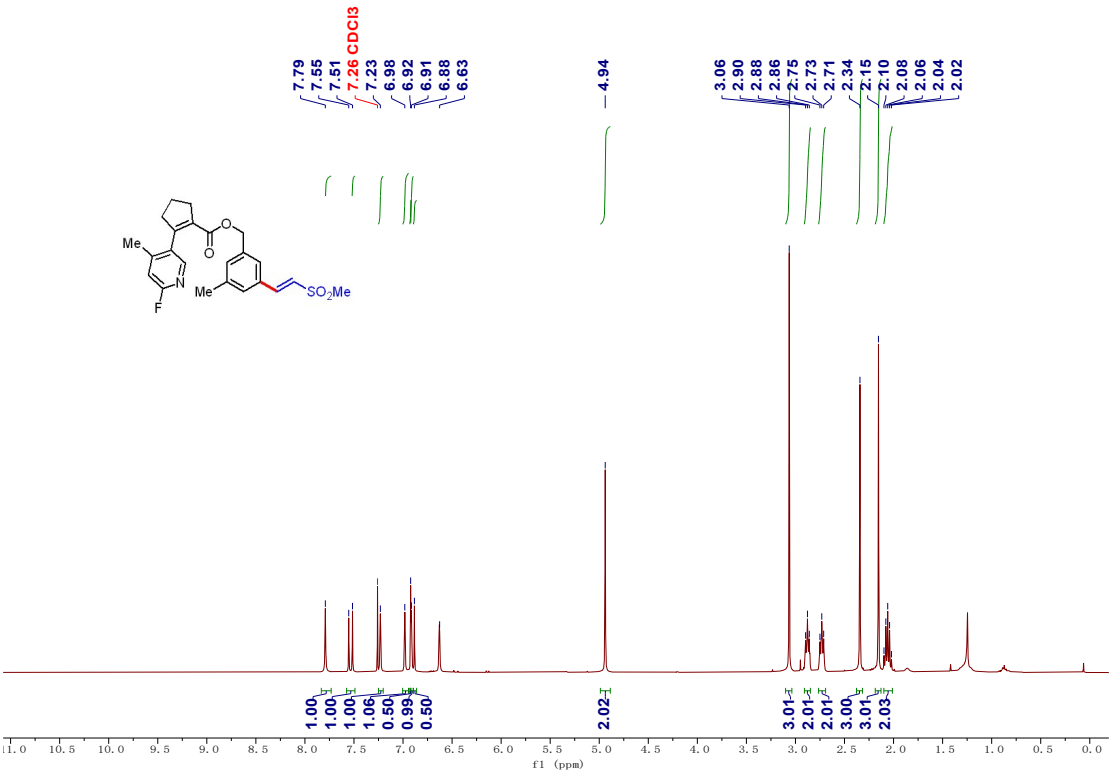
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **3e**



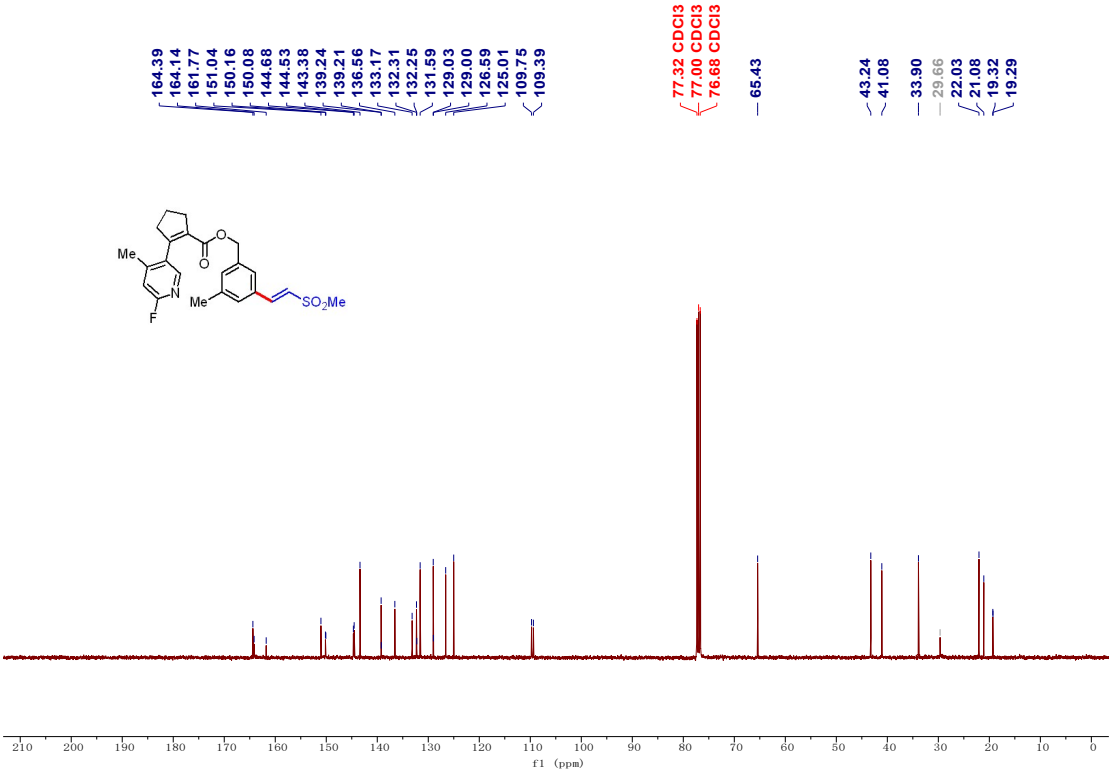
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **3f**



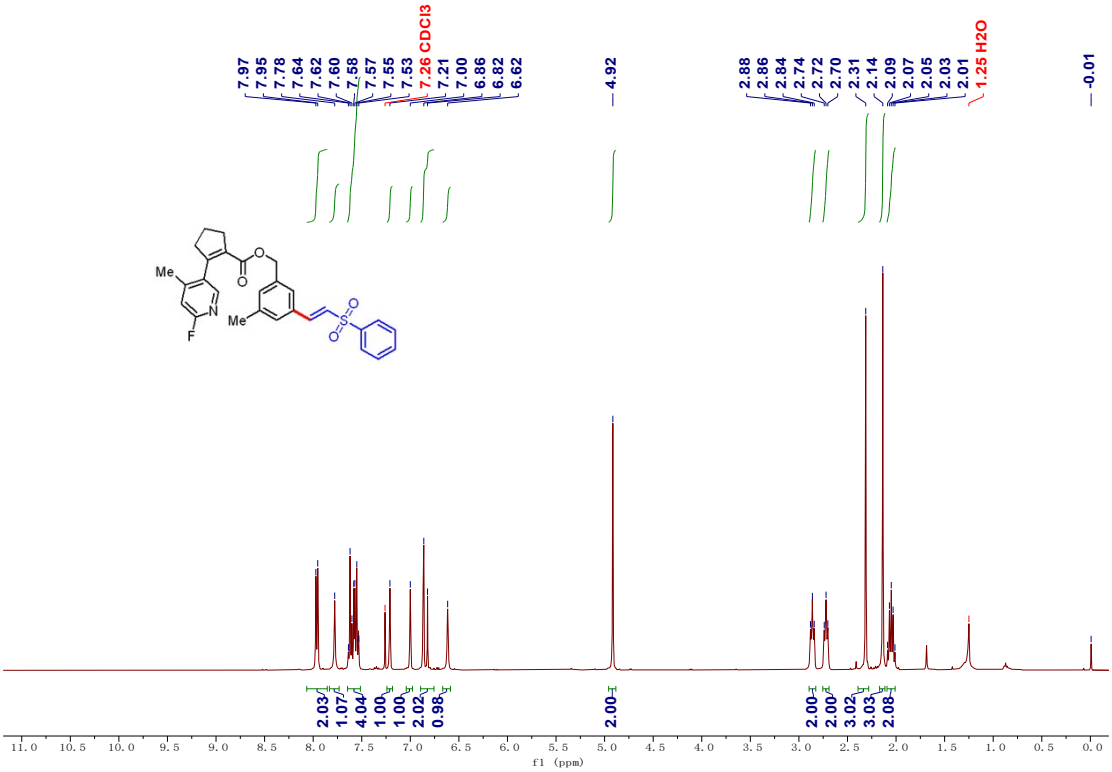
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **3f**



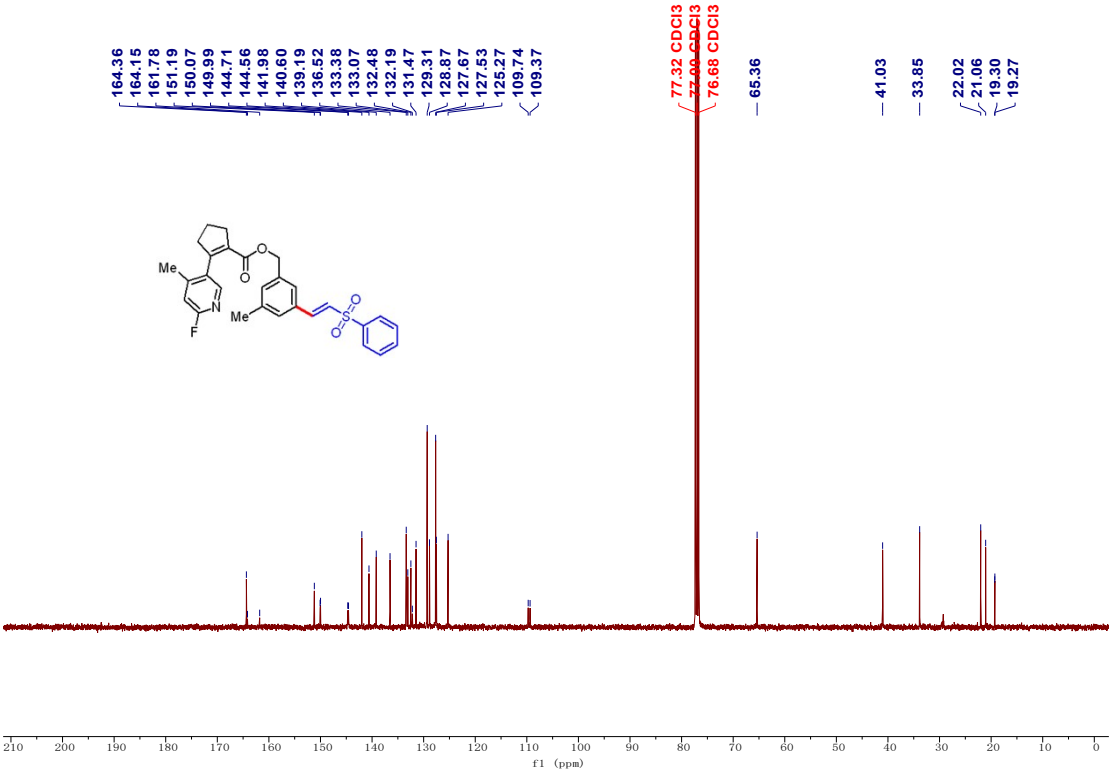
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **3g**



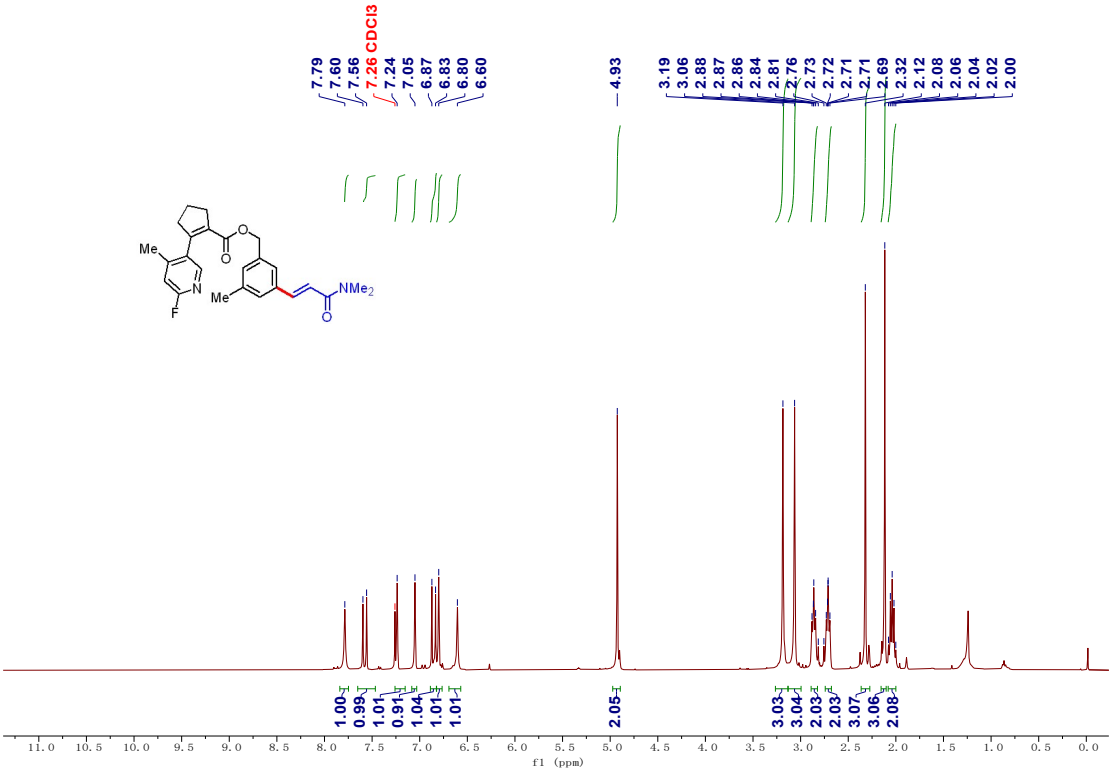
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **3g**



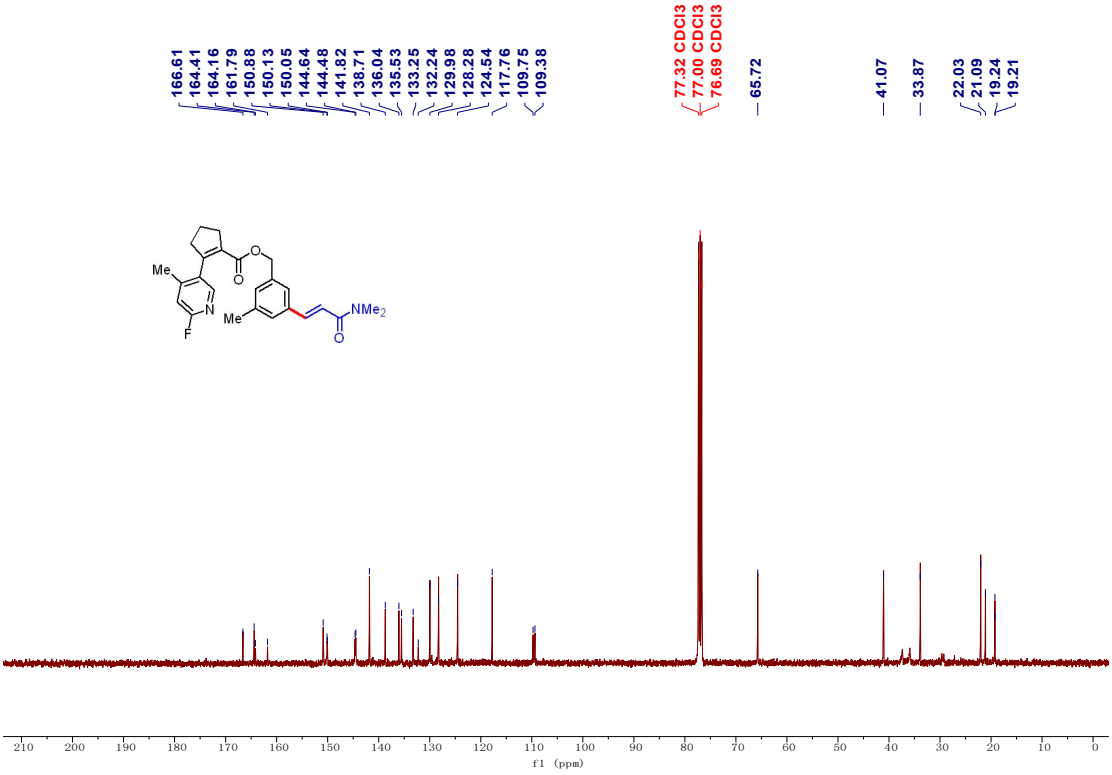
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **3h**



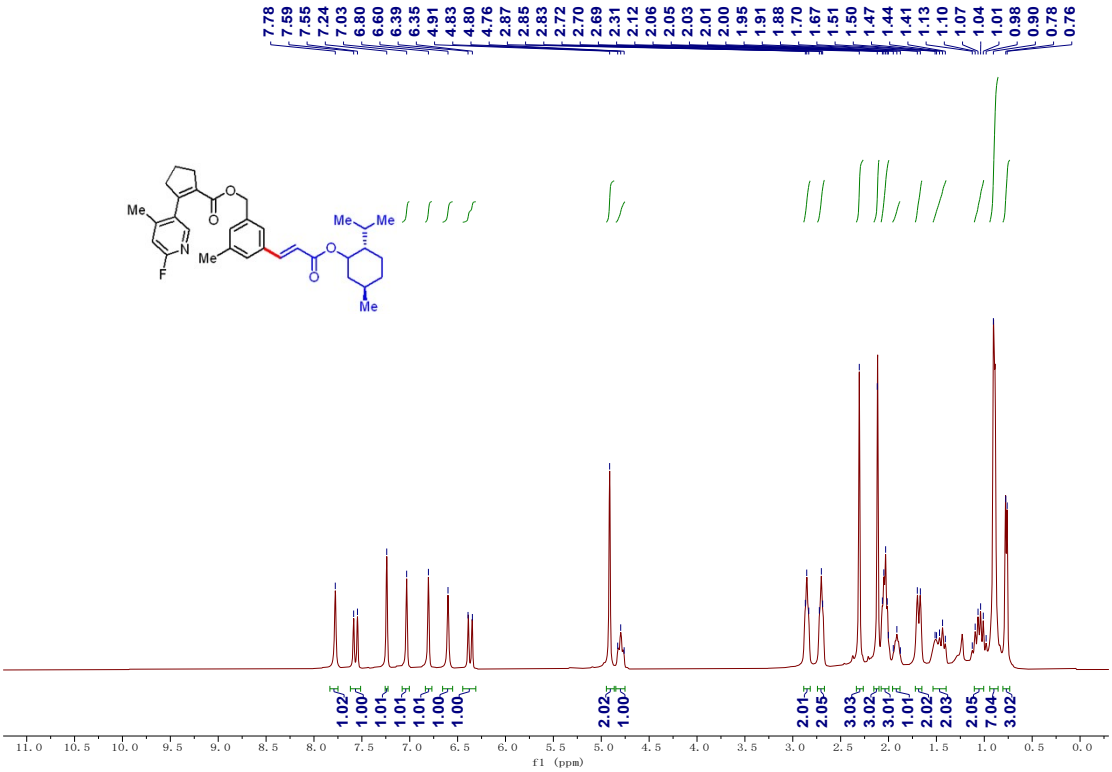
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **3h**



^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **3i**



^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **3i**



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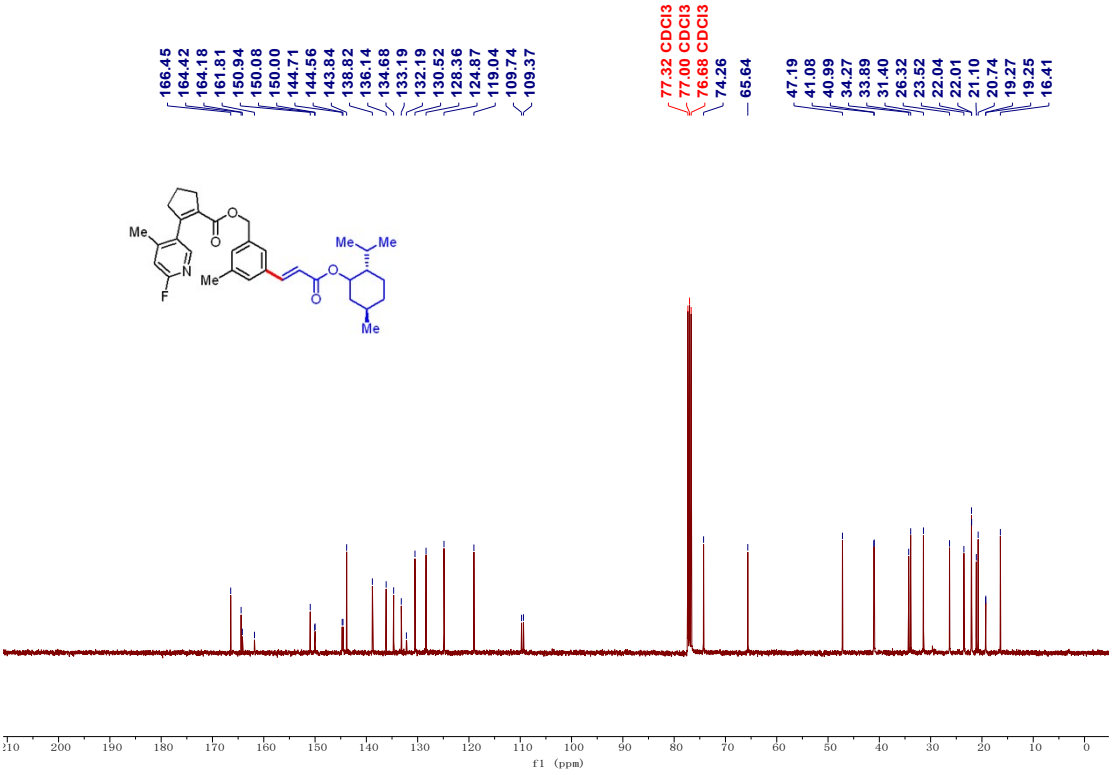
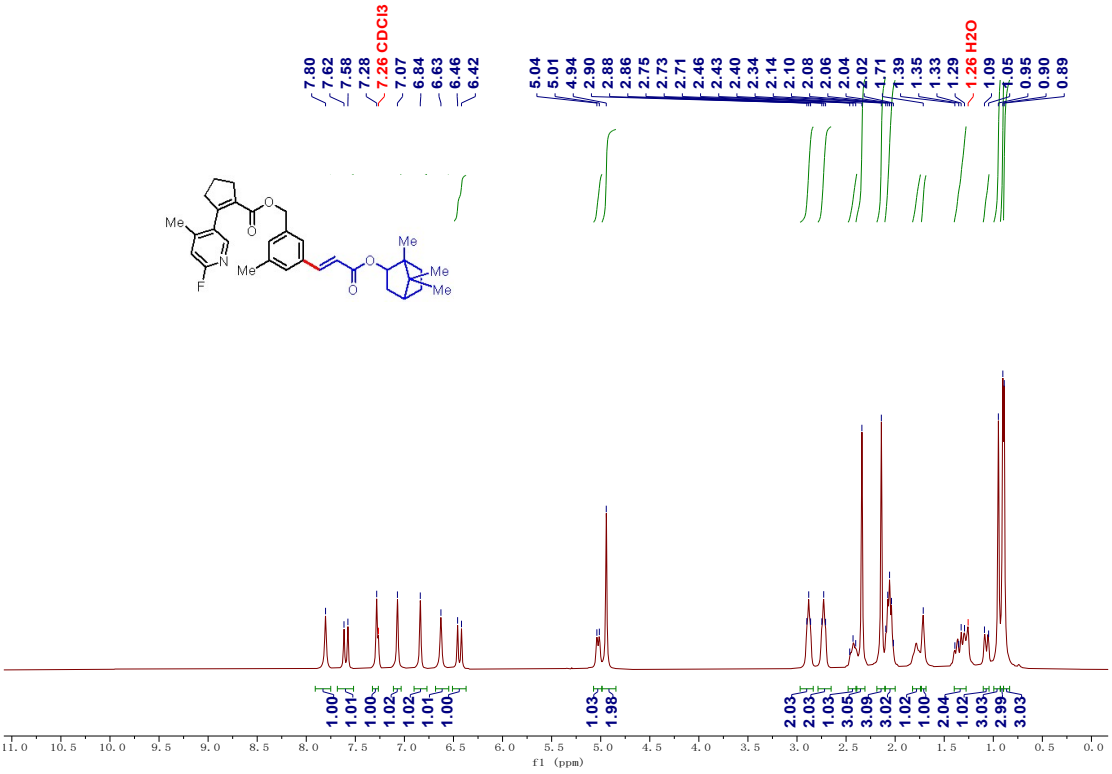
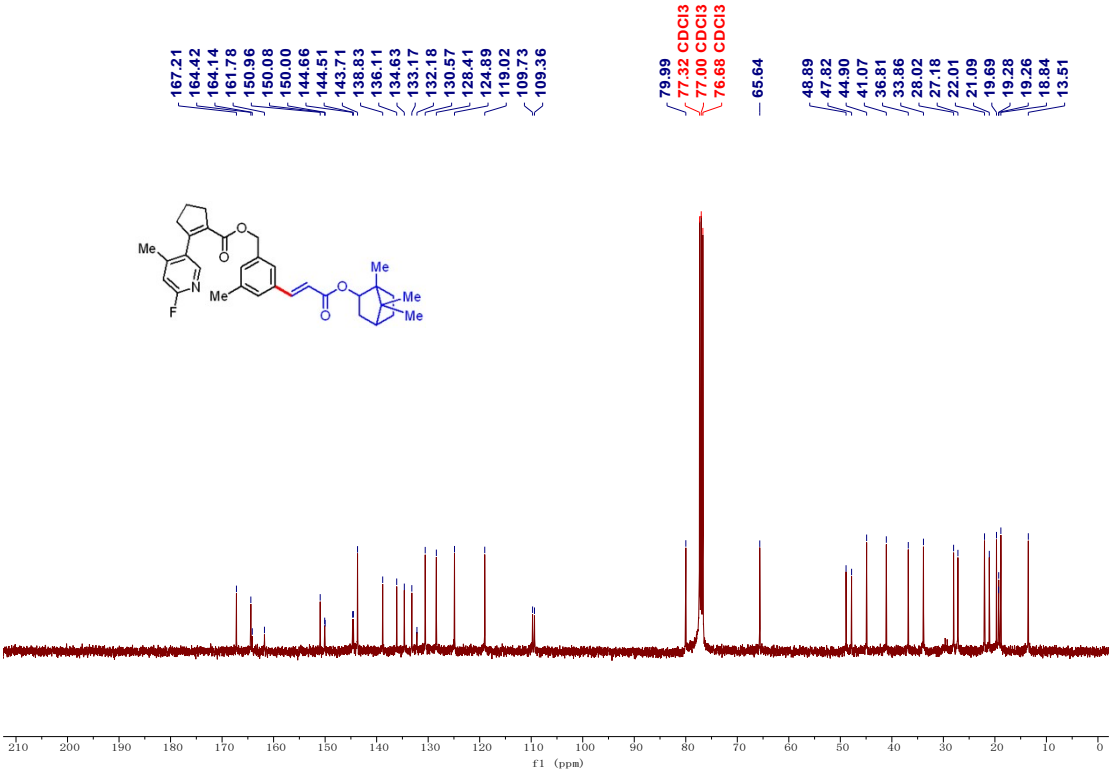


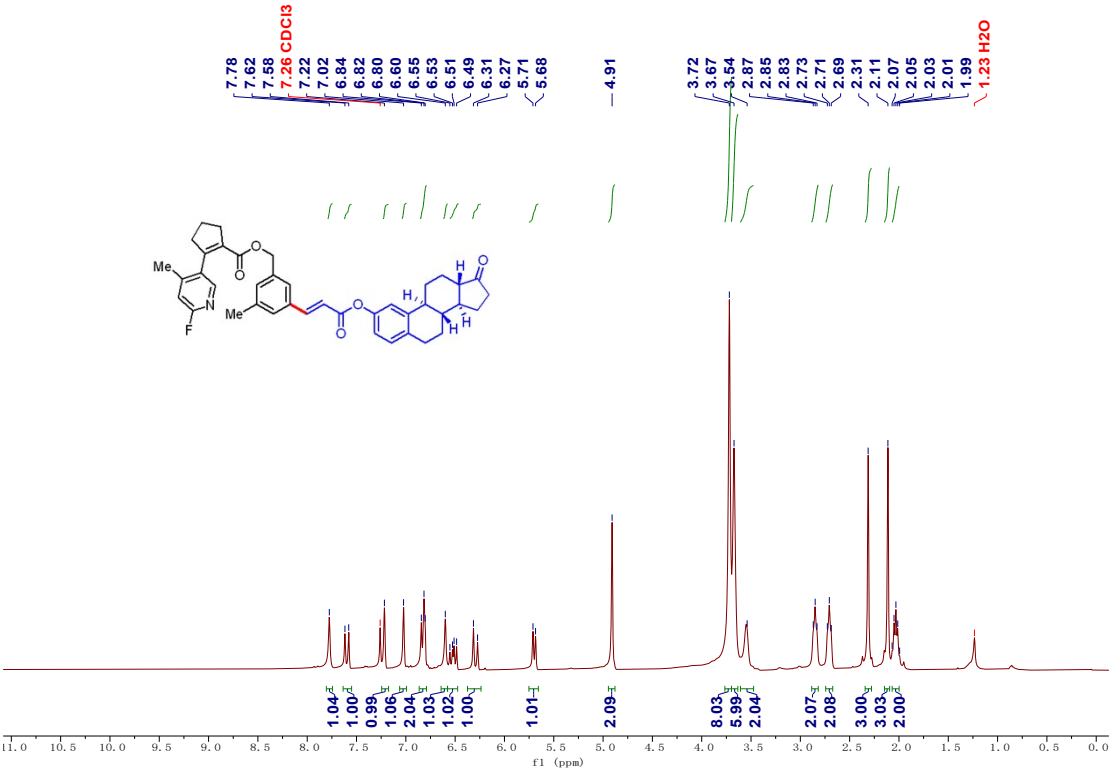
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **3j**



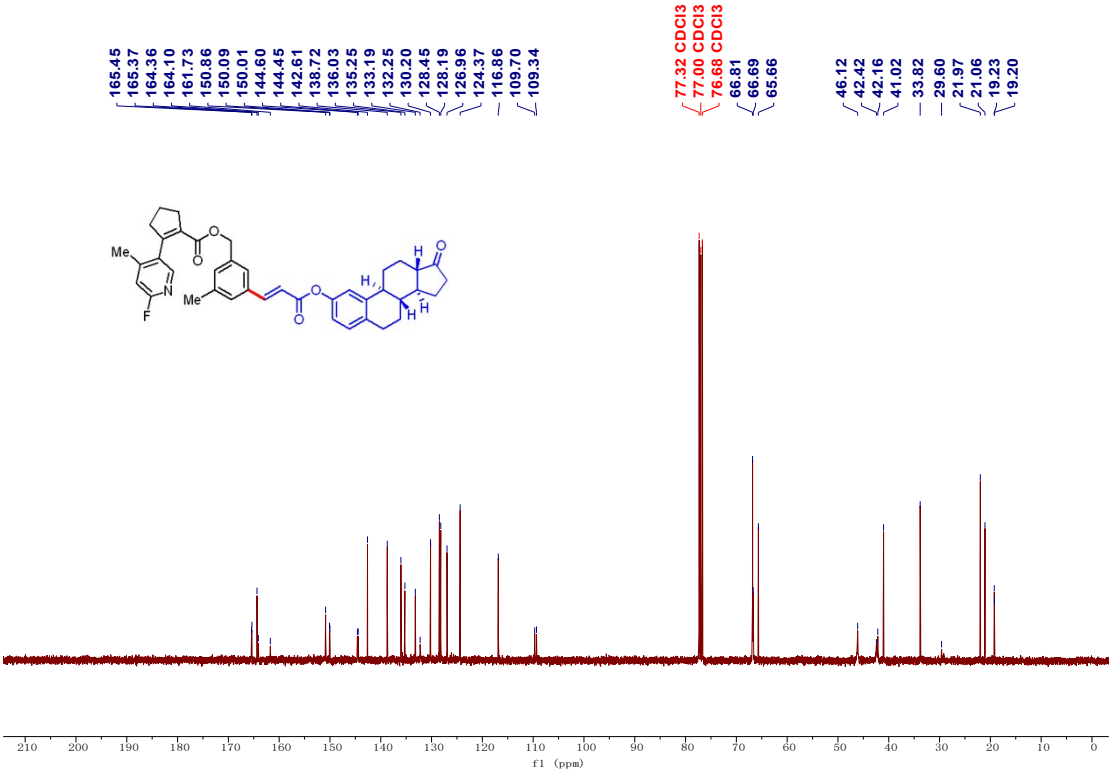
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **3k**



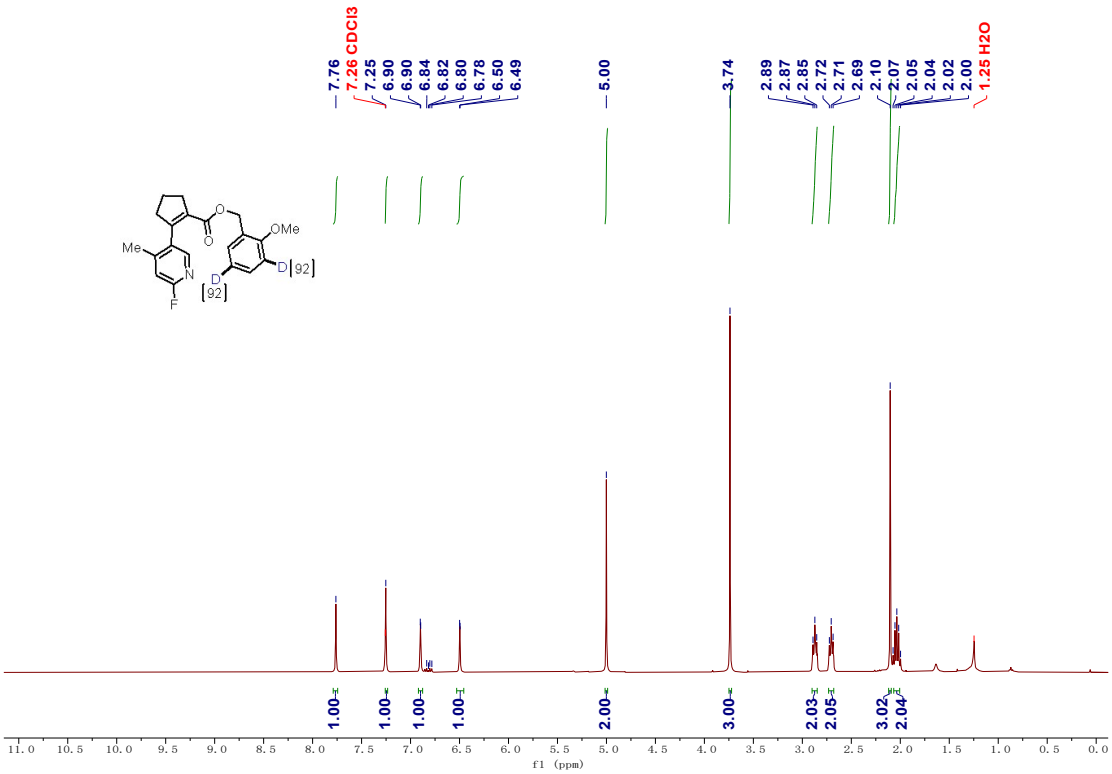
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **3k**



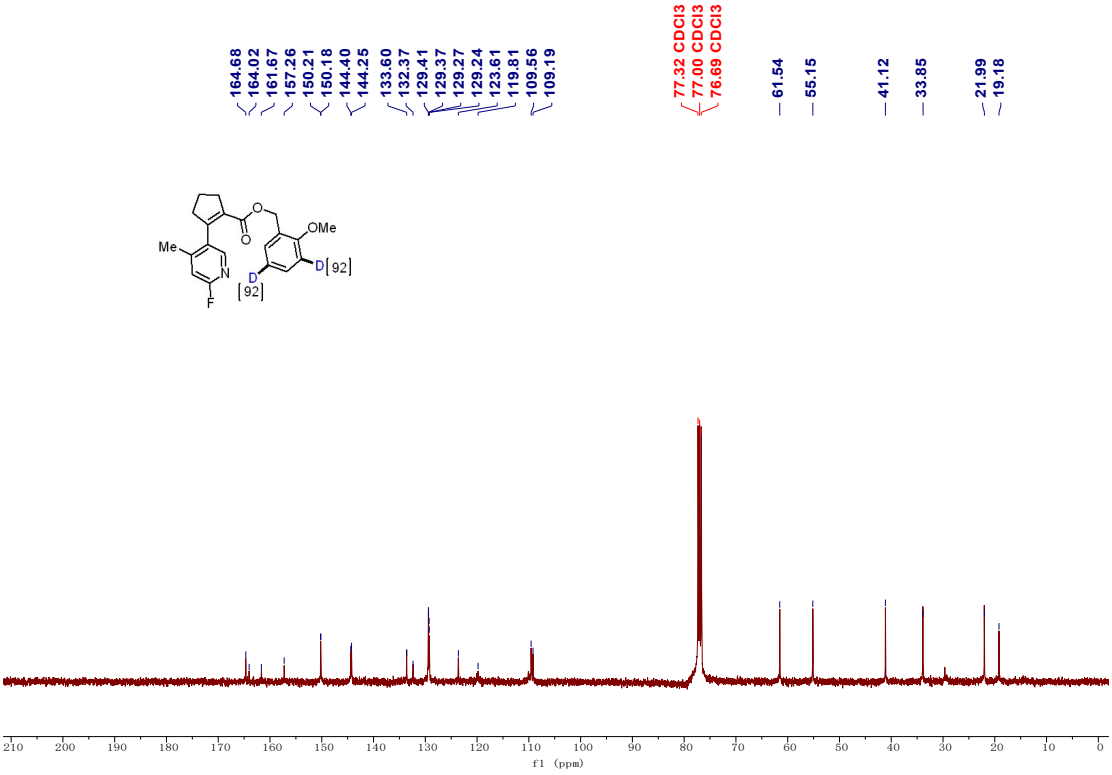
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **3l**



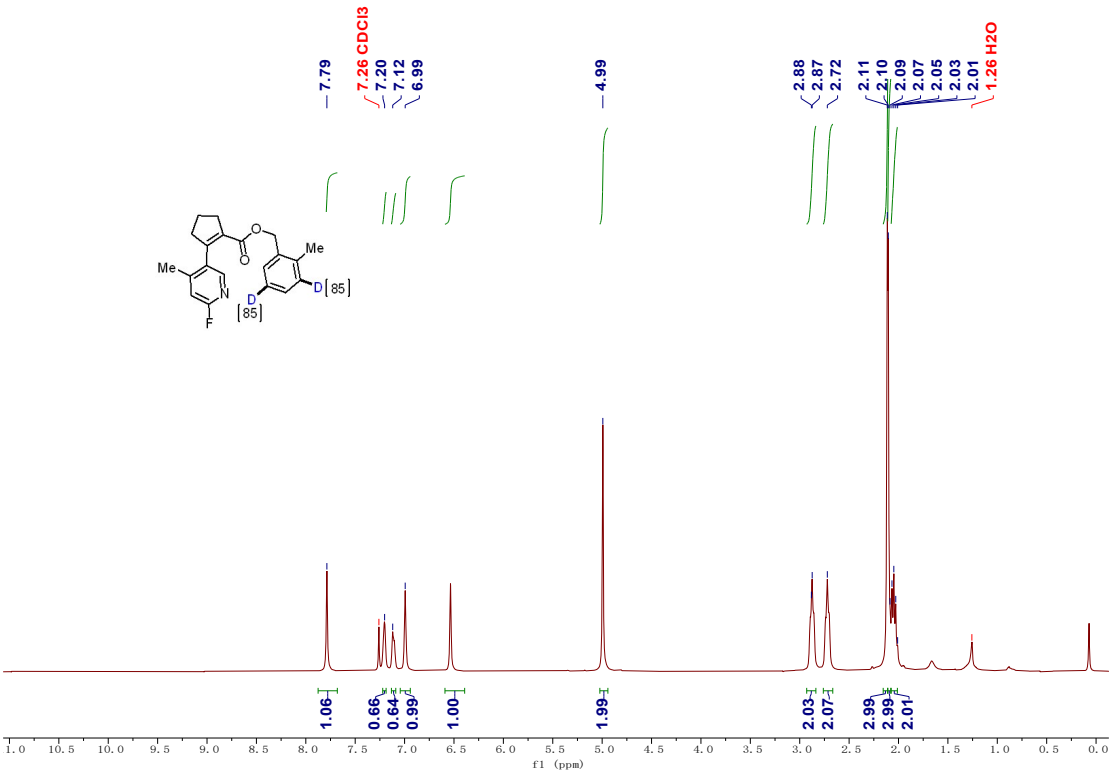
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **3l**



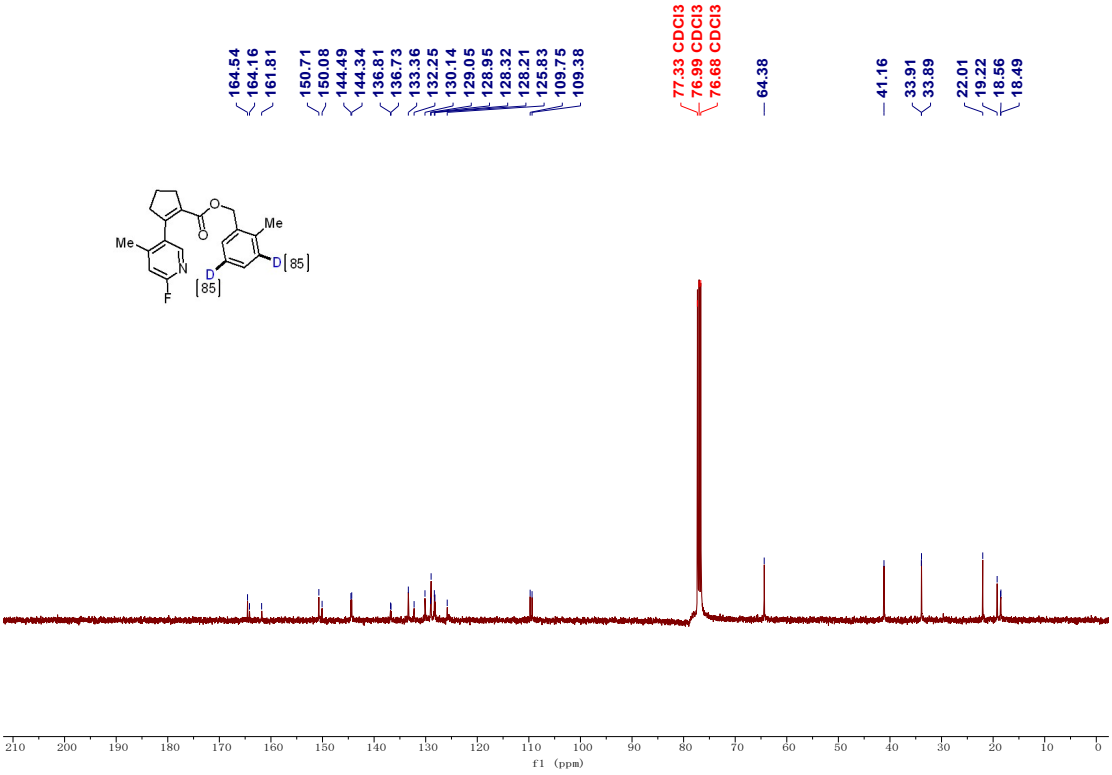
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **4a**



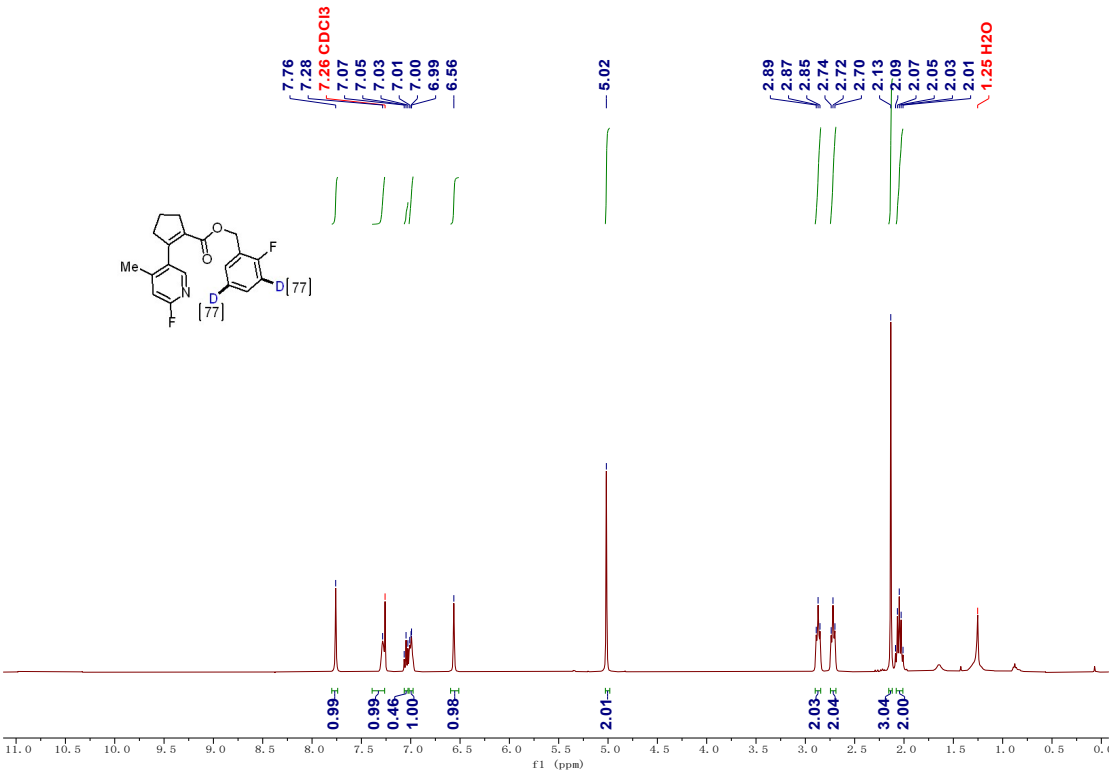
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **4a**



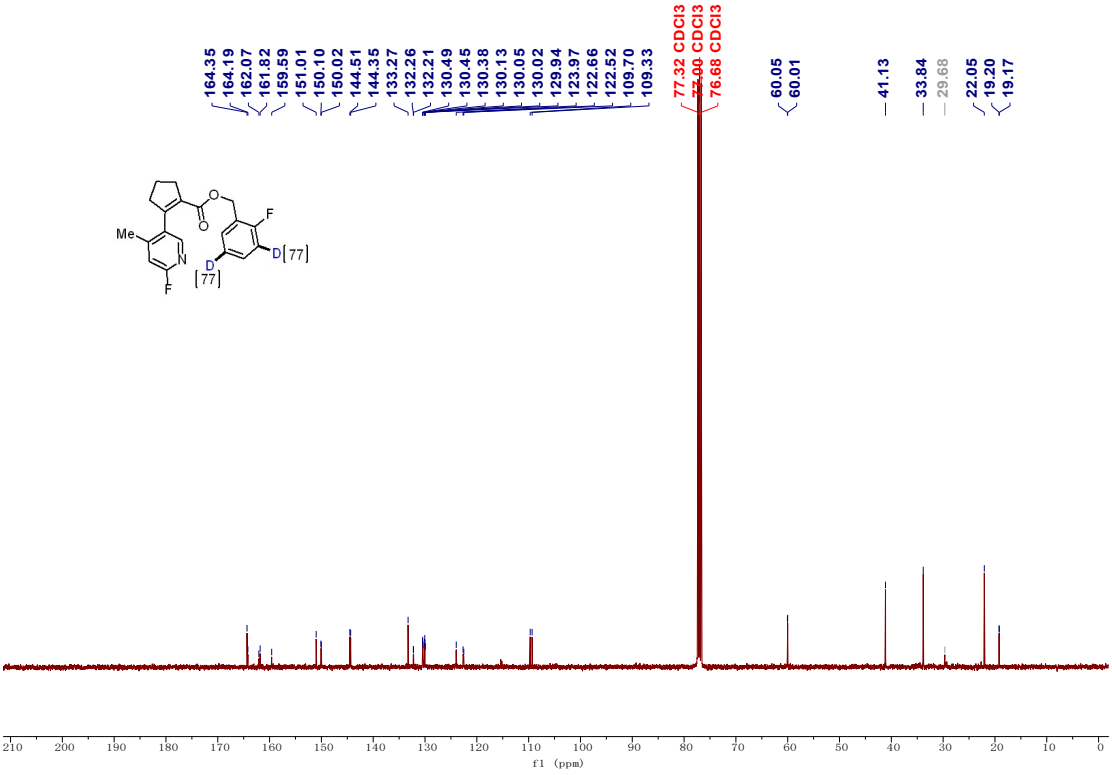
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **4b**



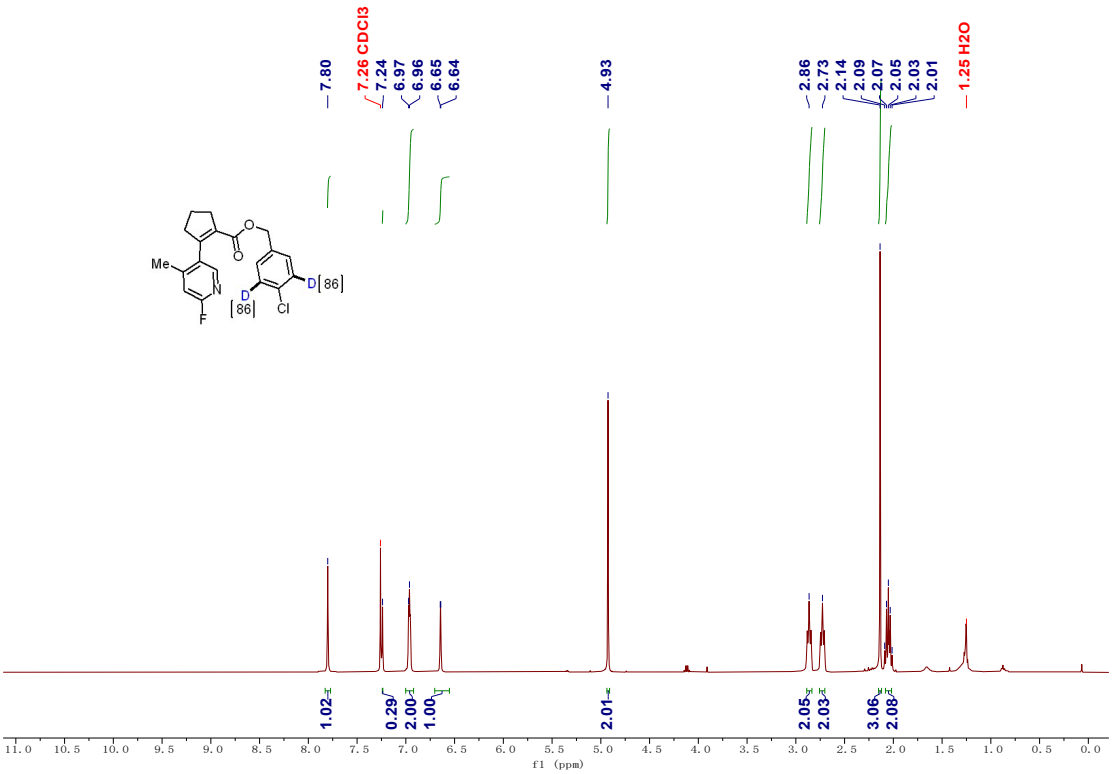
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **4b**



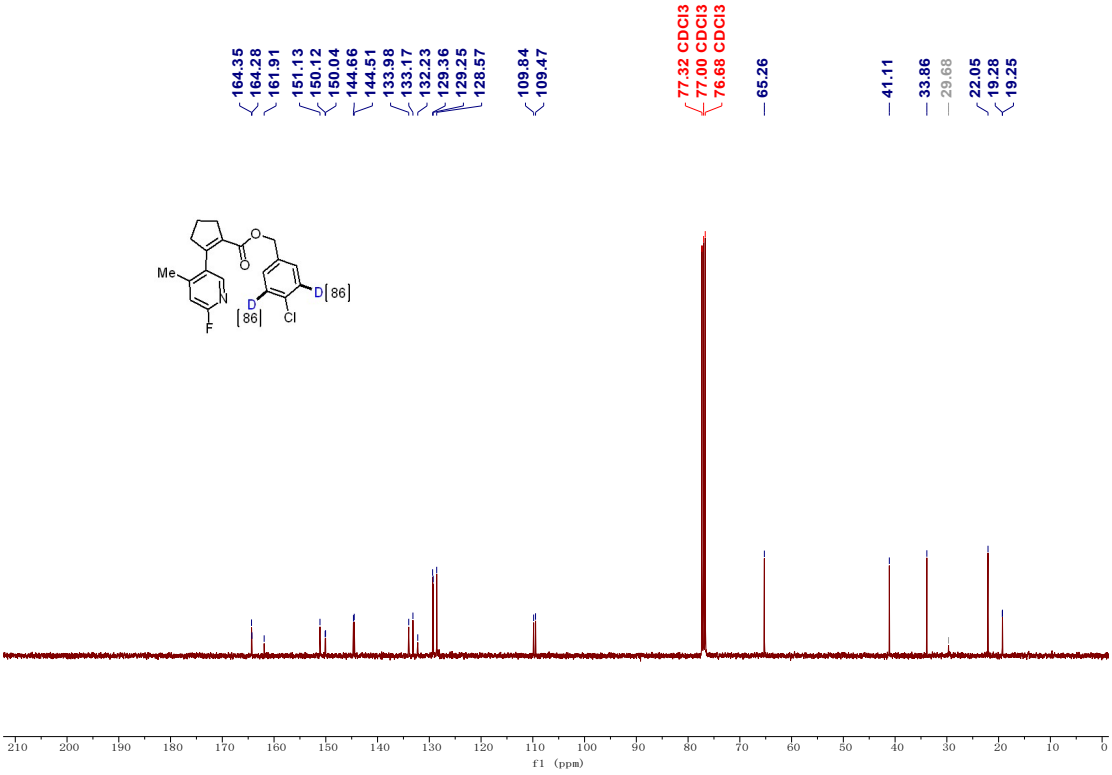
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **4c**



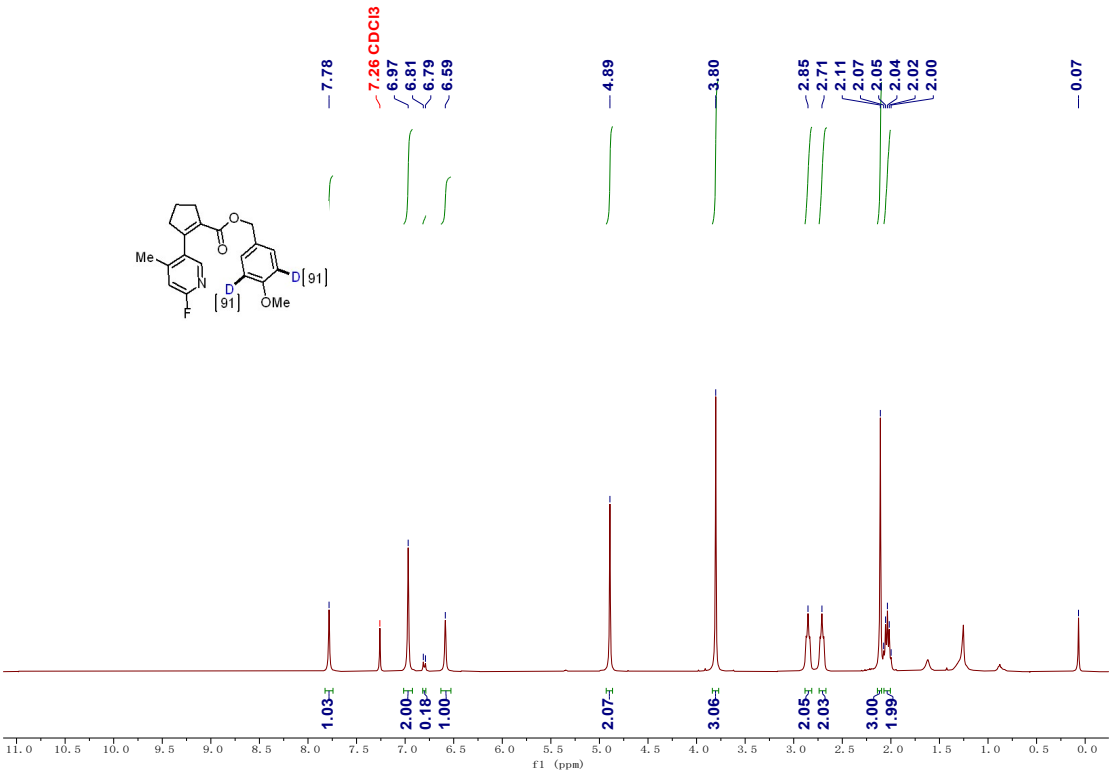
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **4c**



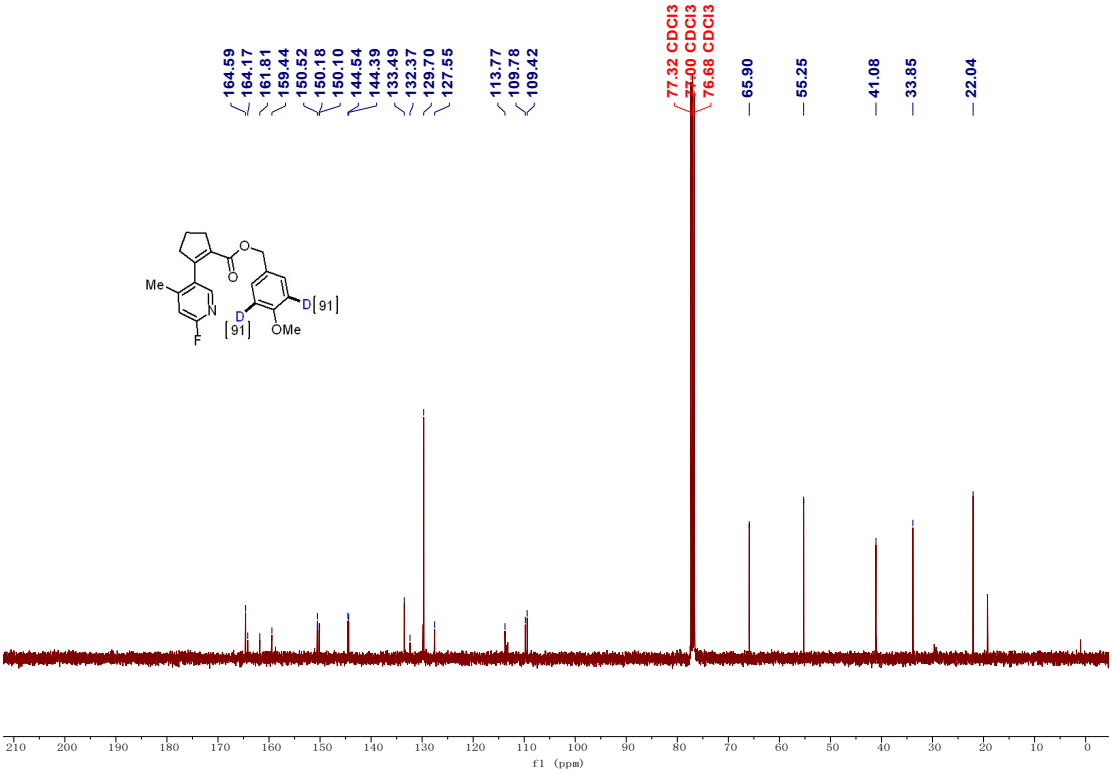
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **4d**



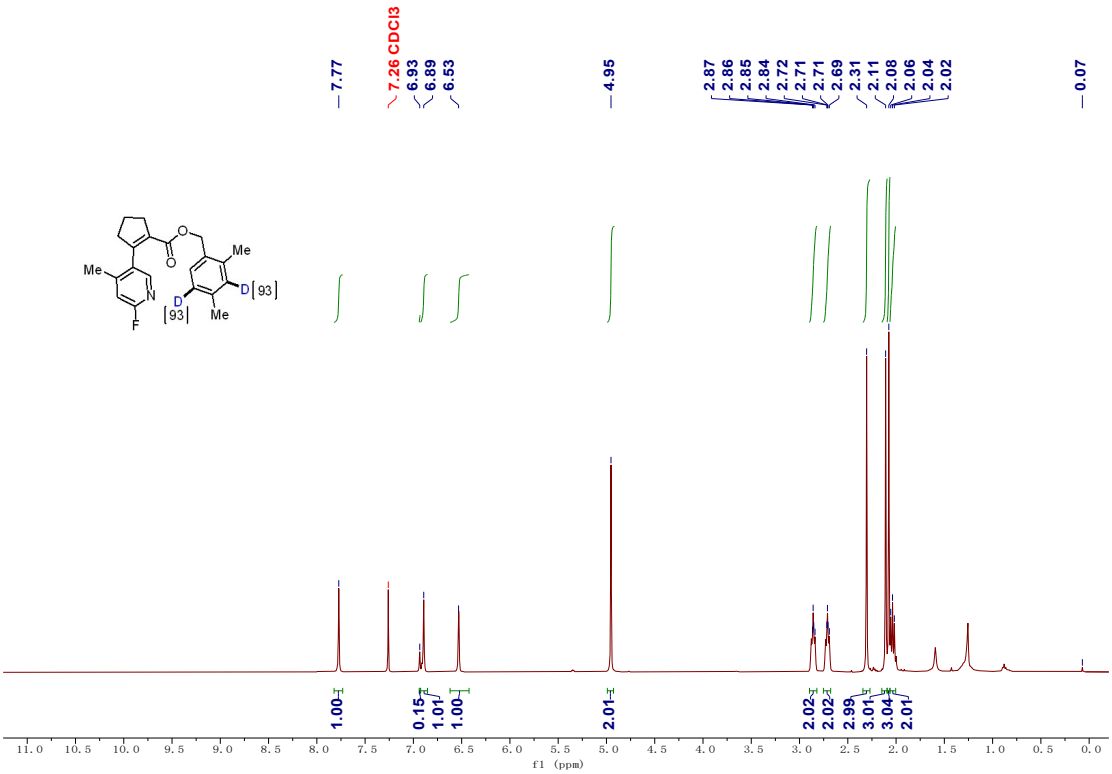
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **4d**



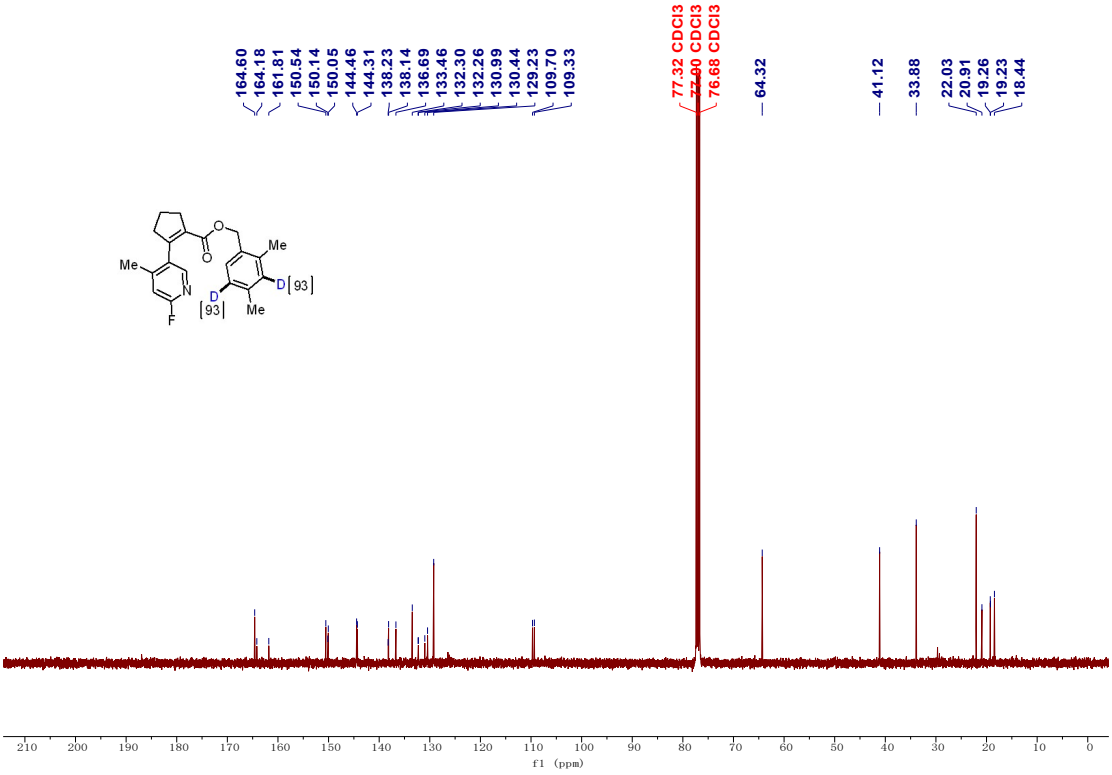
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **4e**



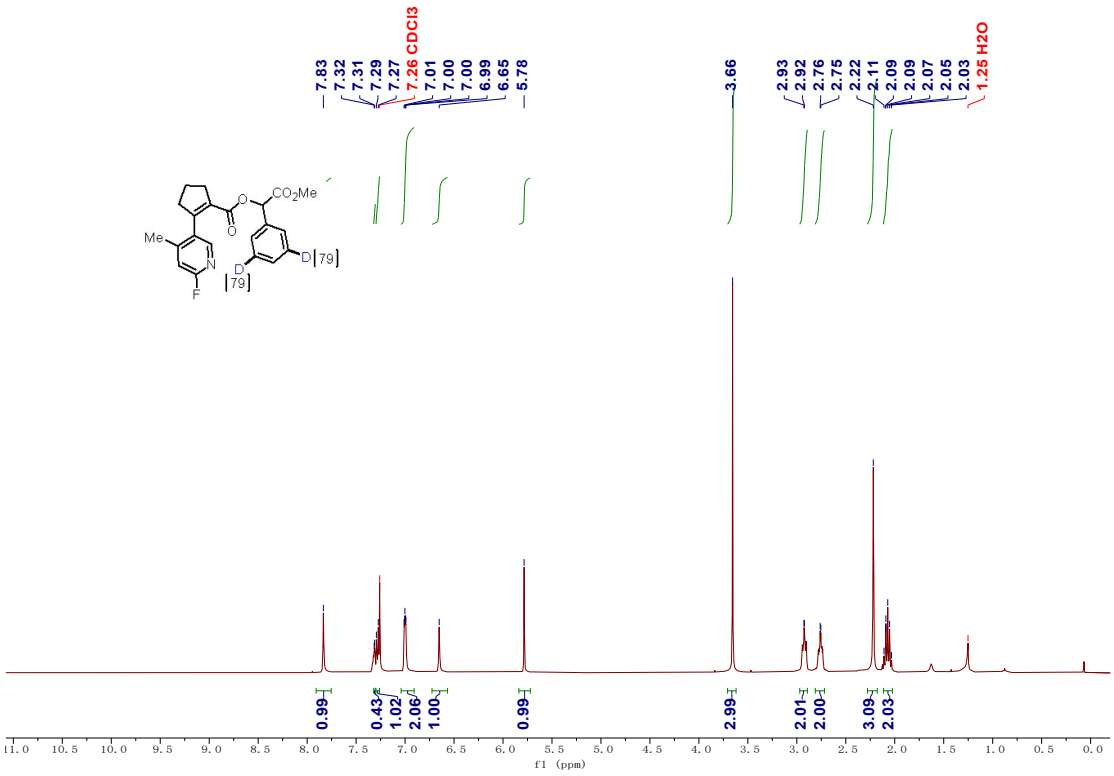
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **4e**



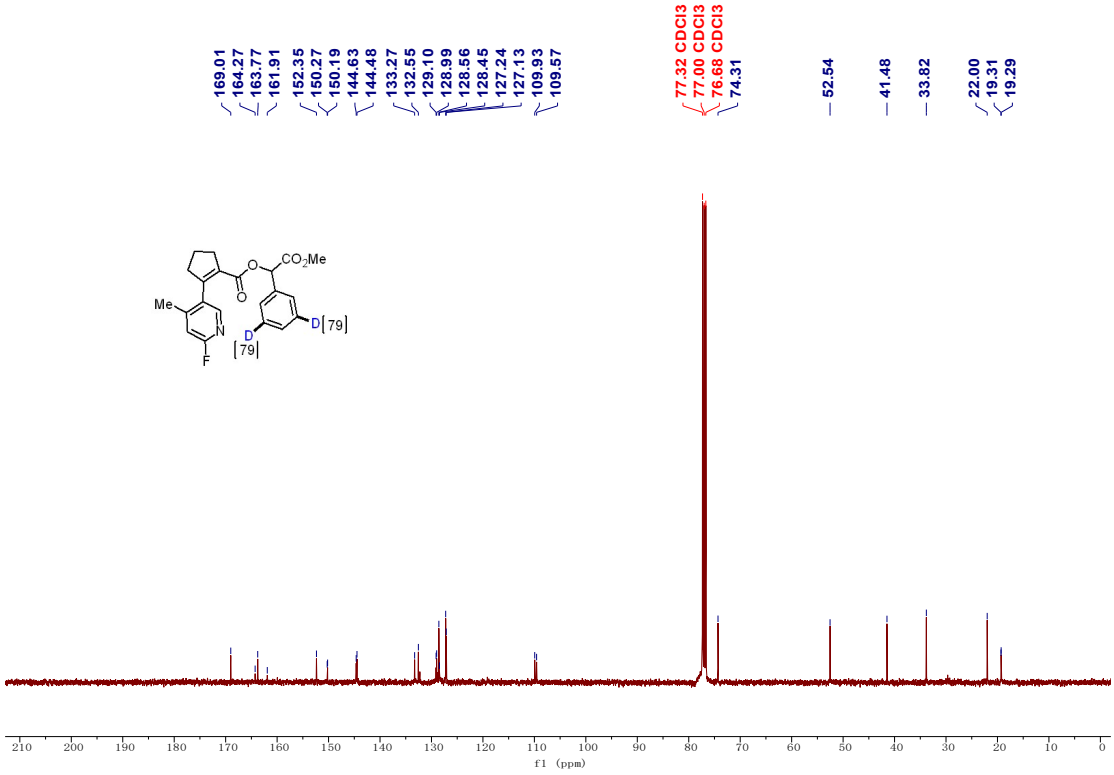
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **4f**



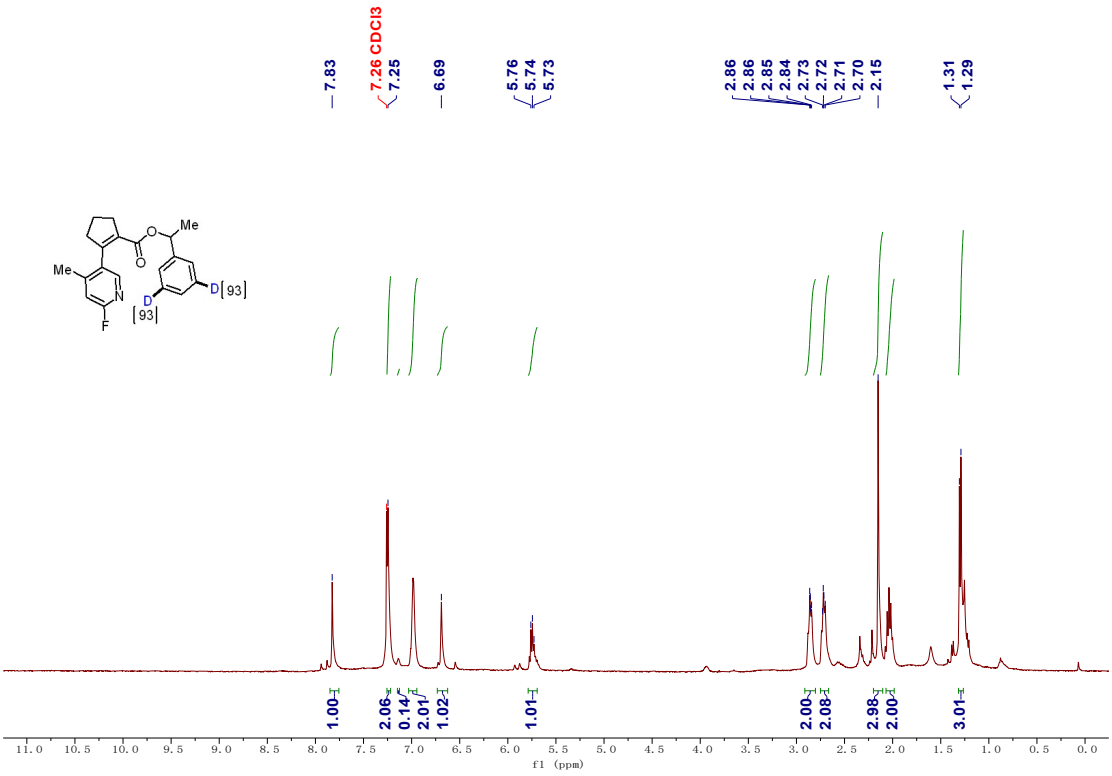
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **4f**



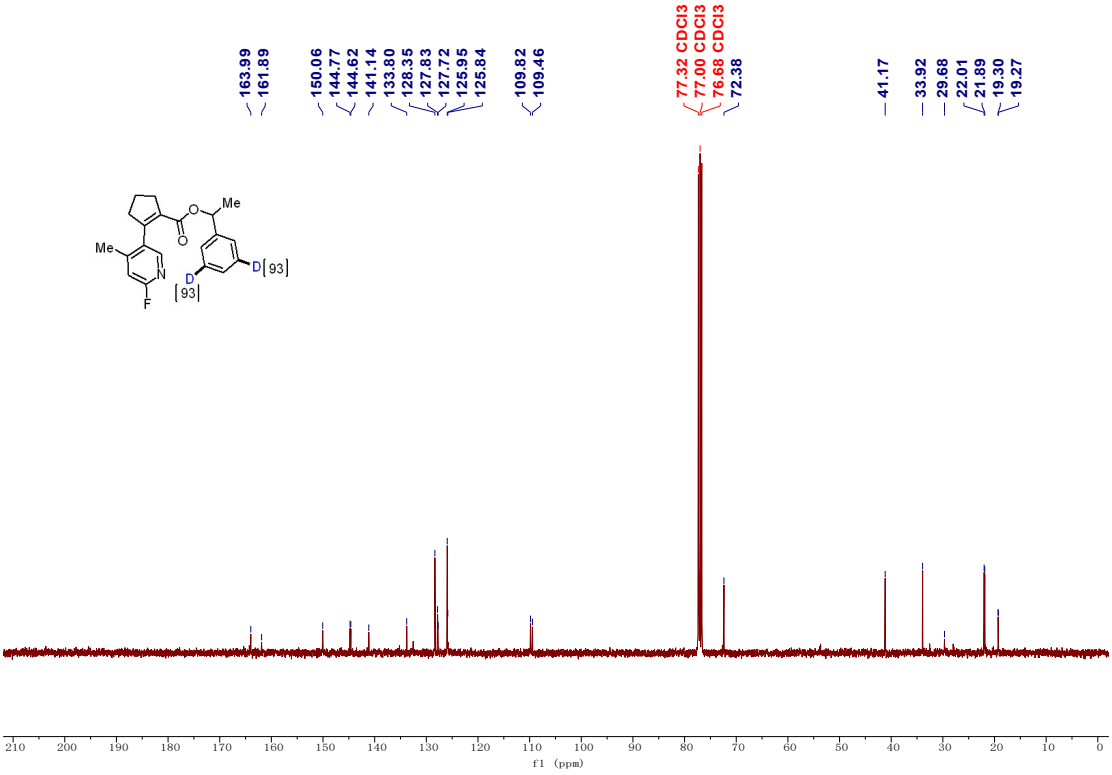
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **4g**



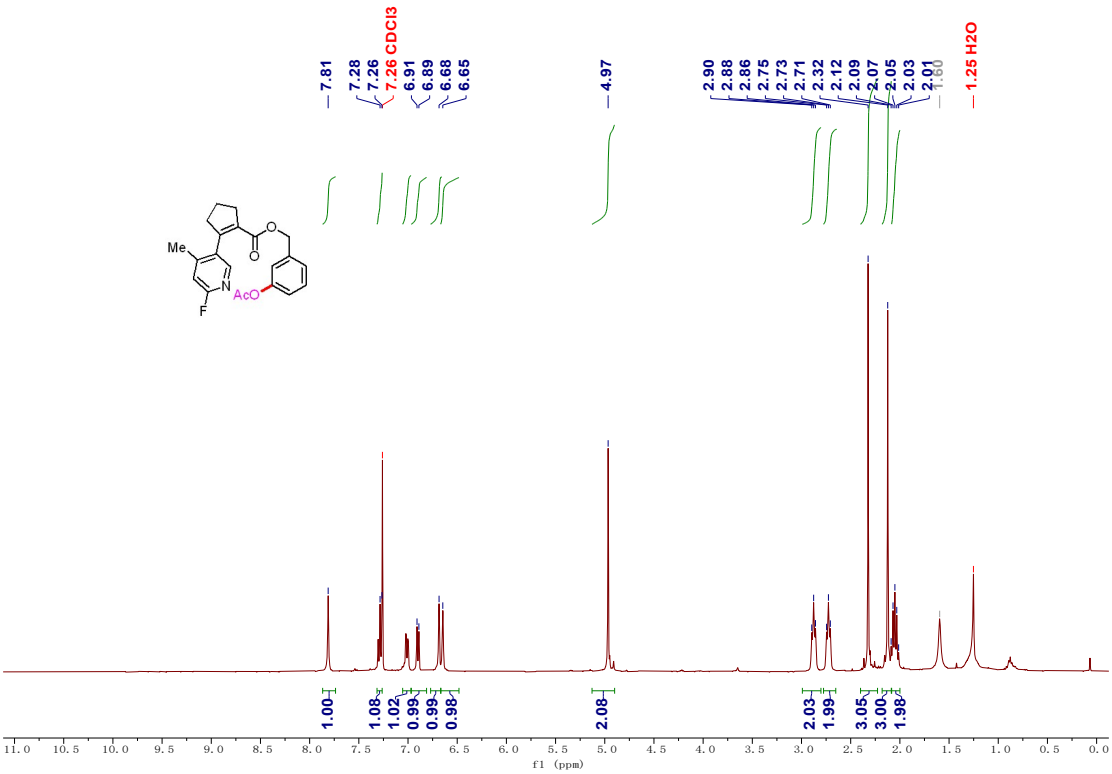
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **4g**



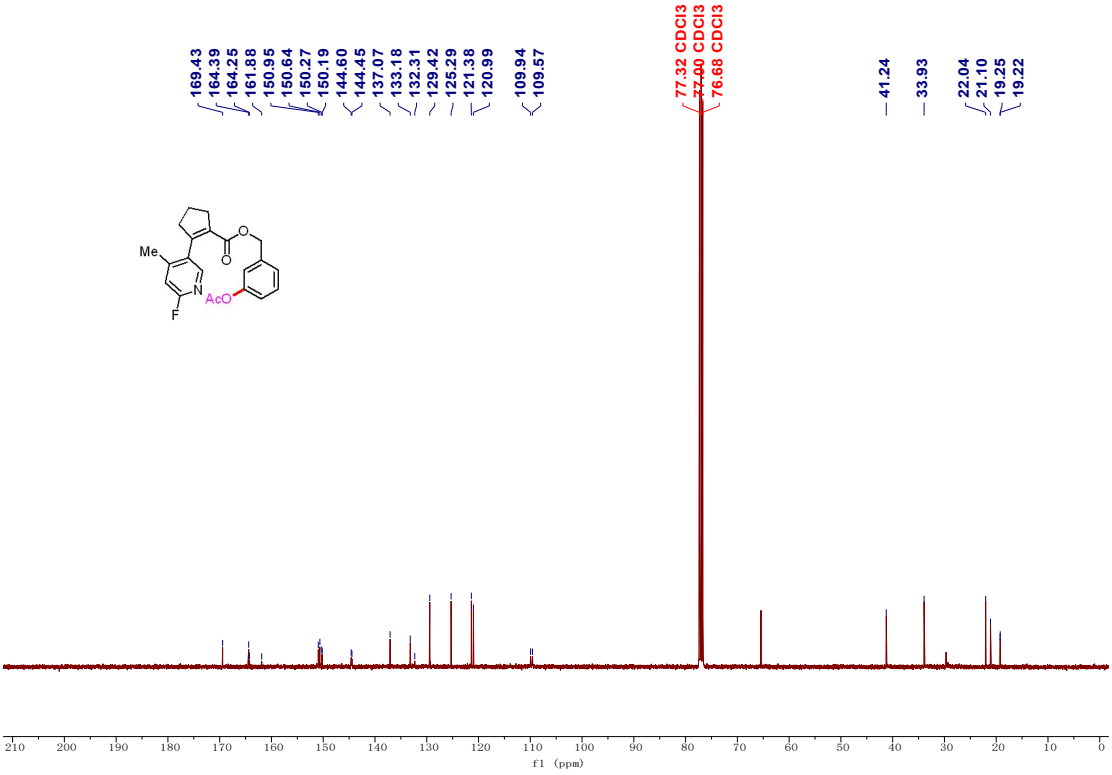
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **4h**



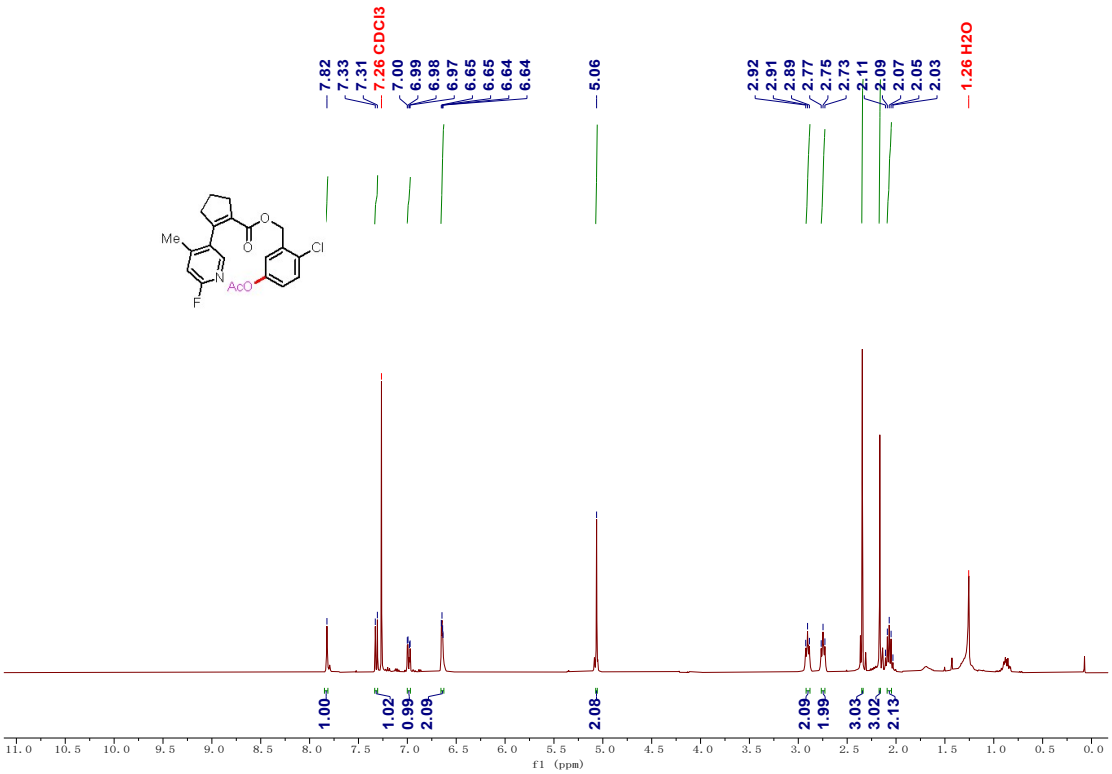
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **4h**



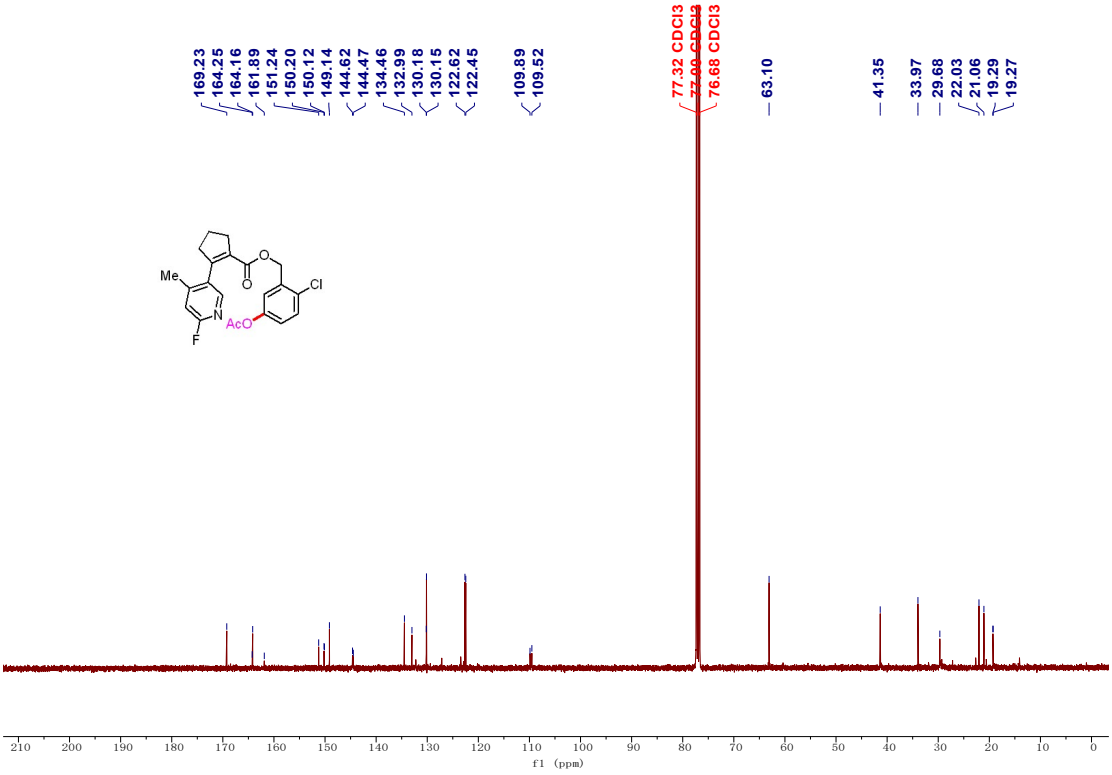
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **5a**



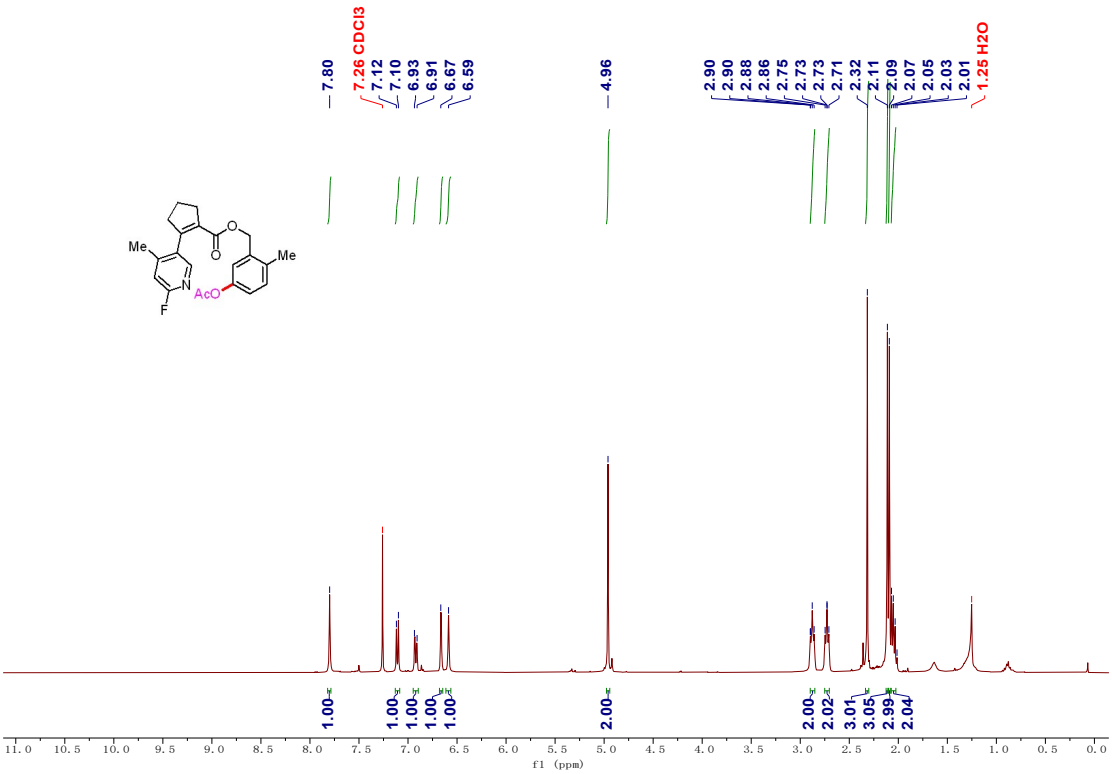
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **5a**



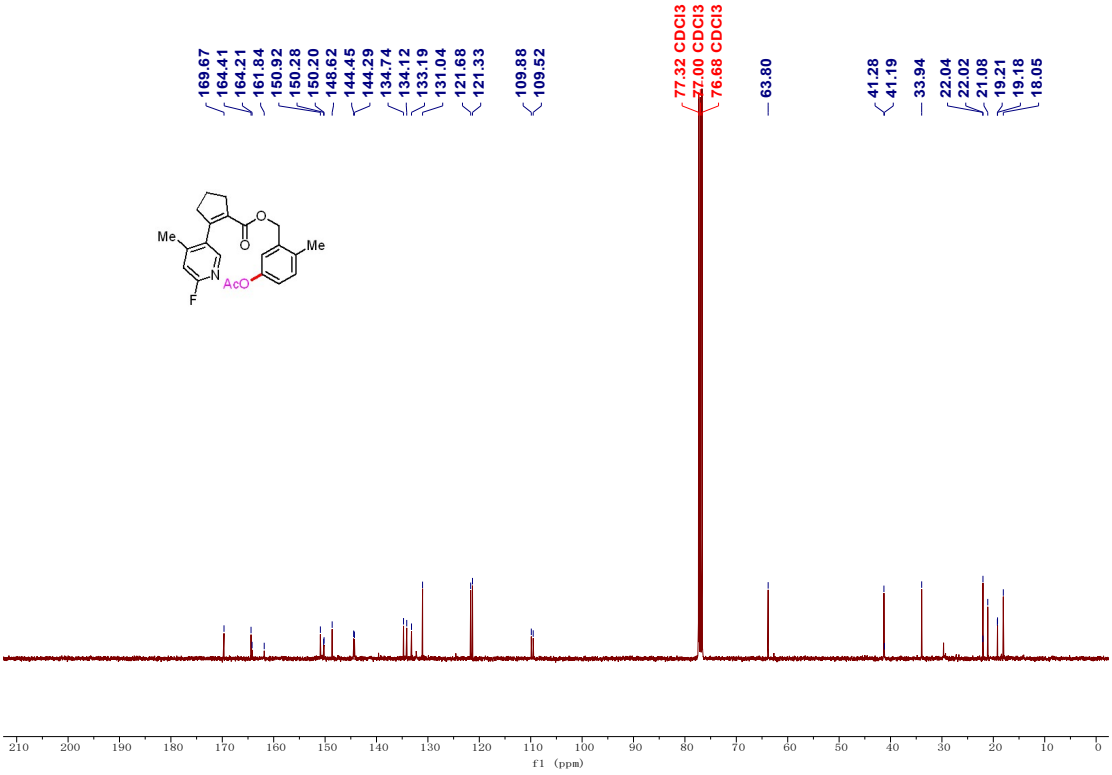
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **5b**



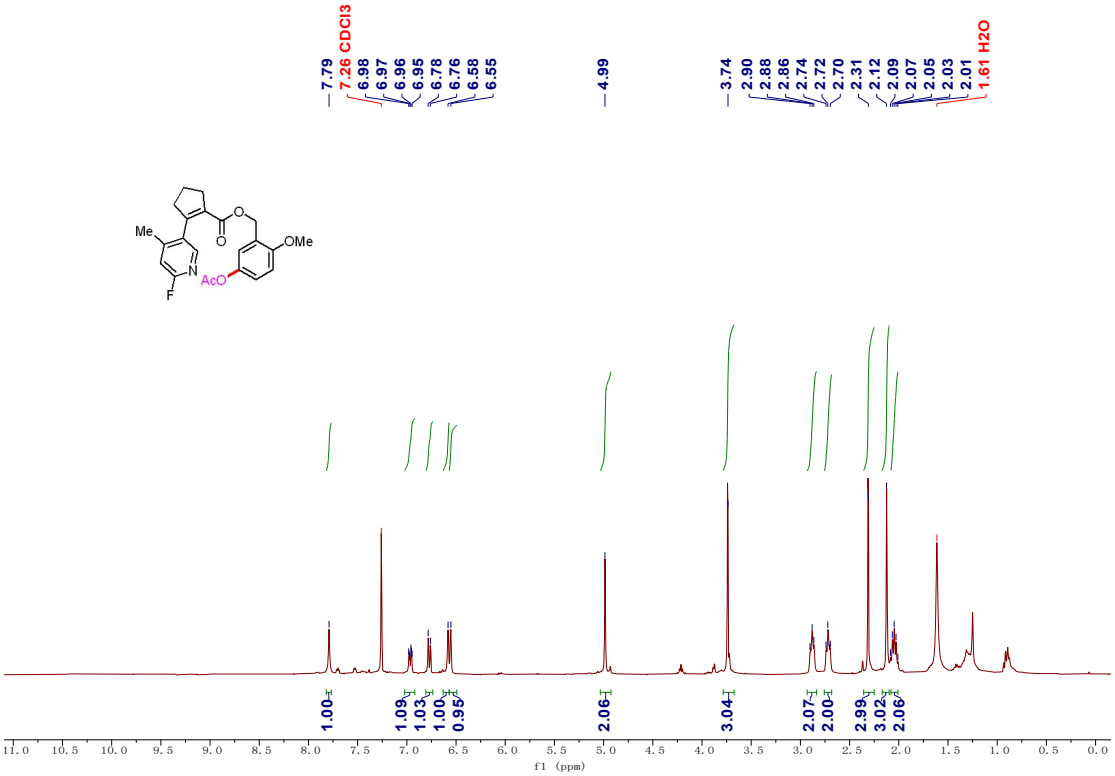
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **5b**



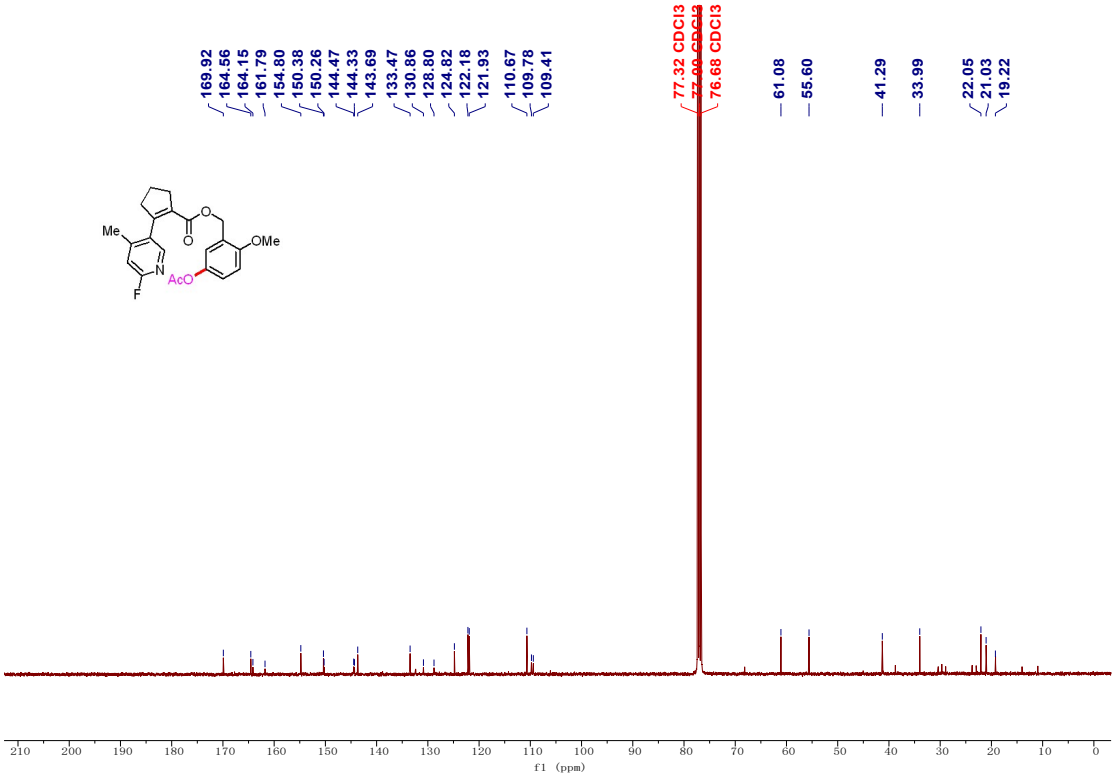
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **5c**



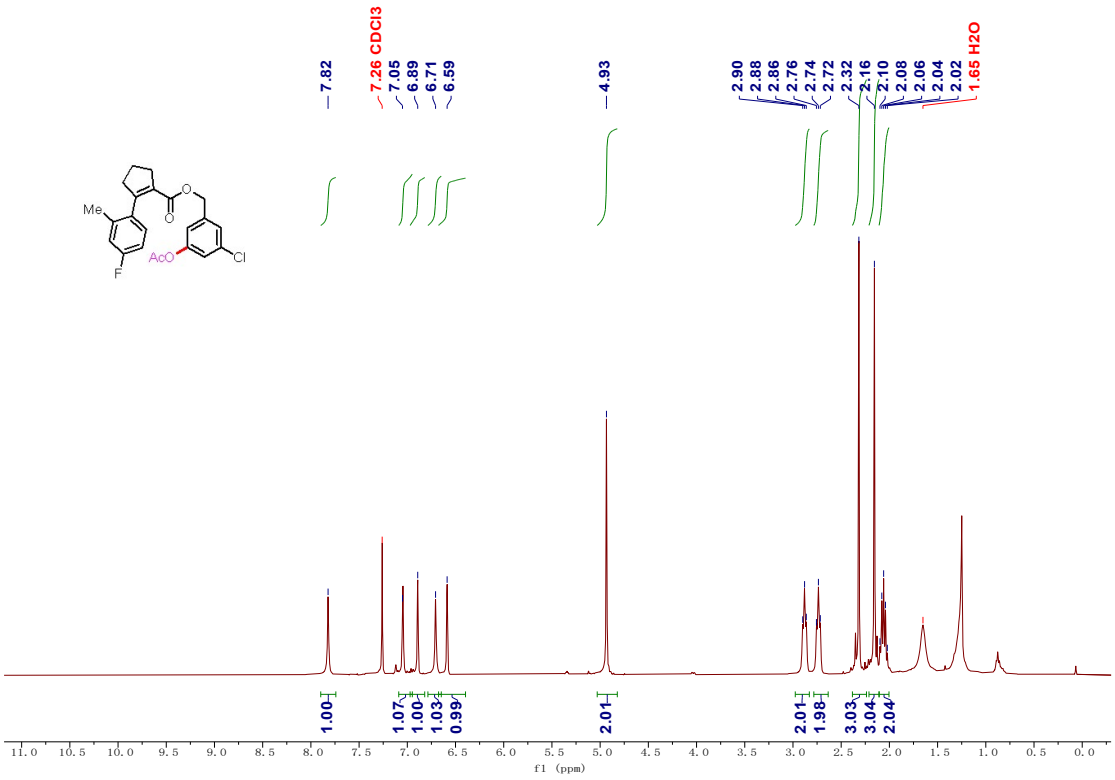
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **5c**



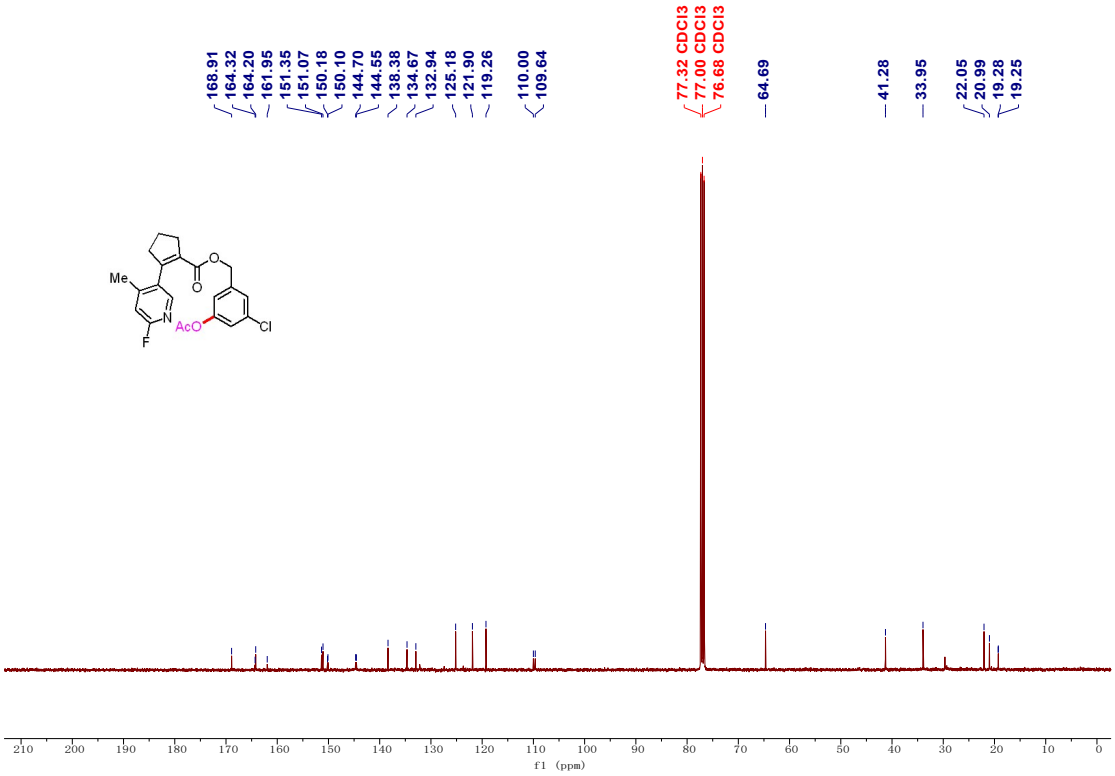
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **5d**



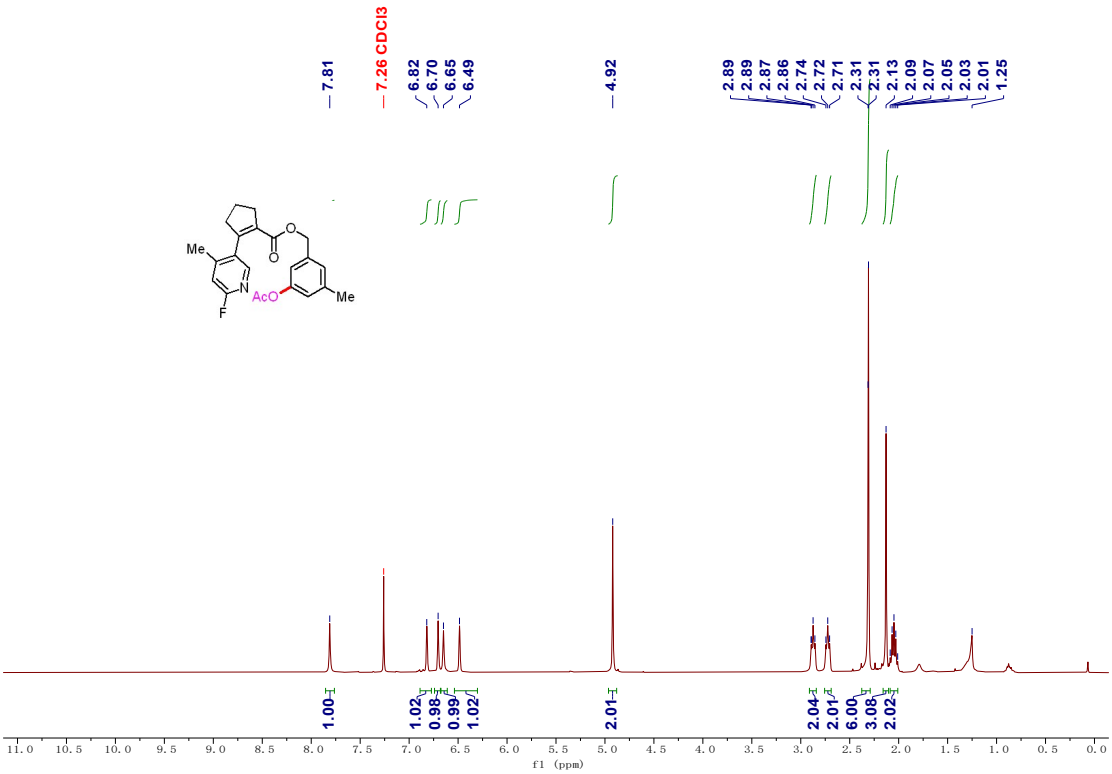
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **5d**



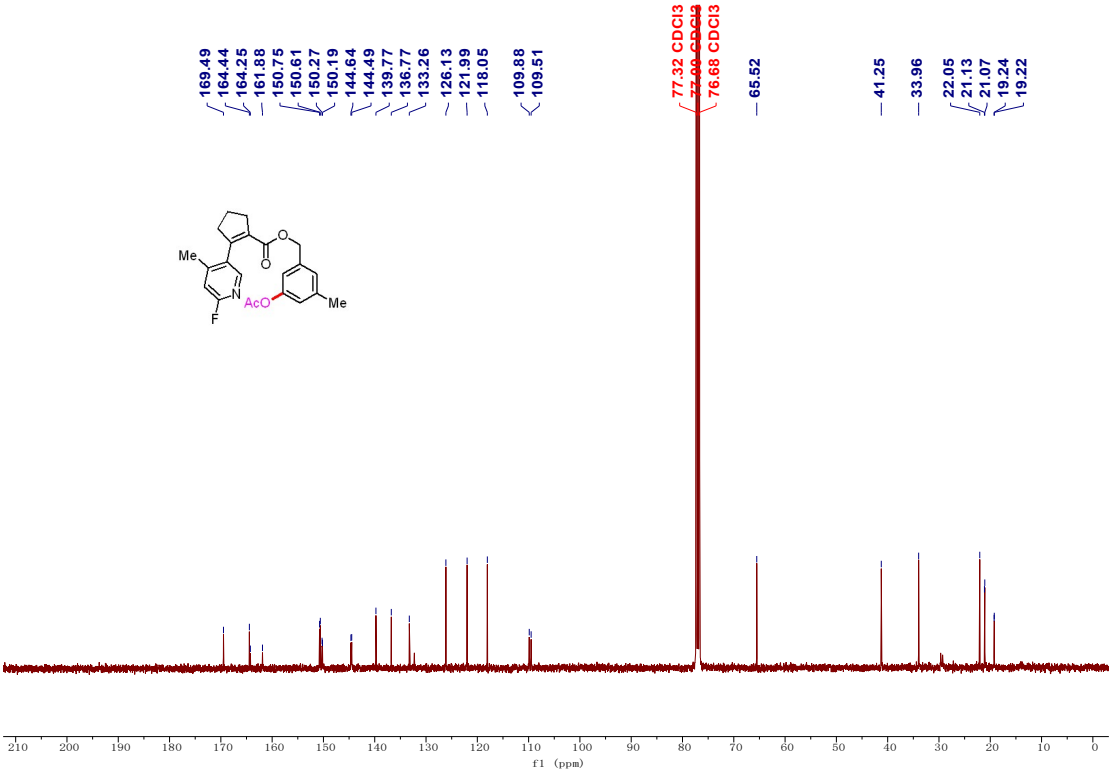
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **5e**



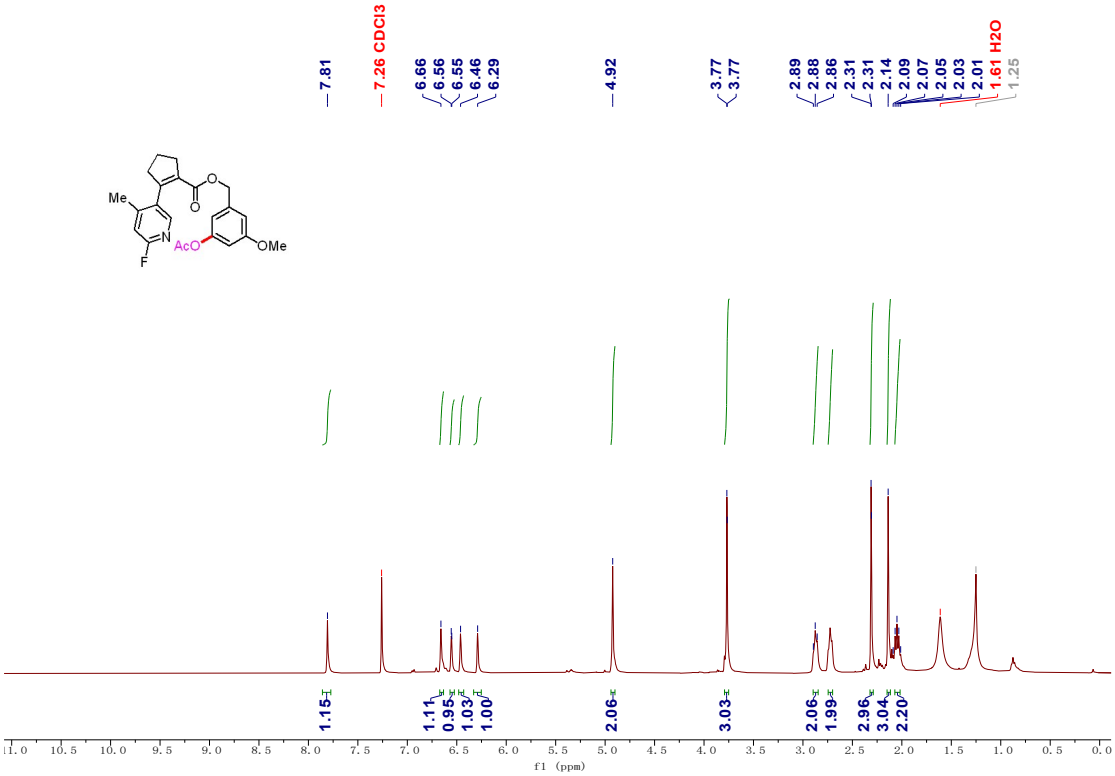
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **5e**



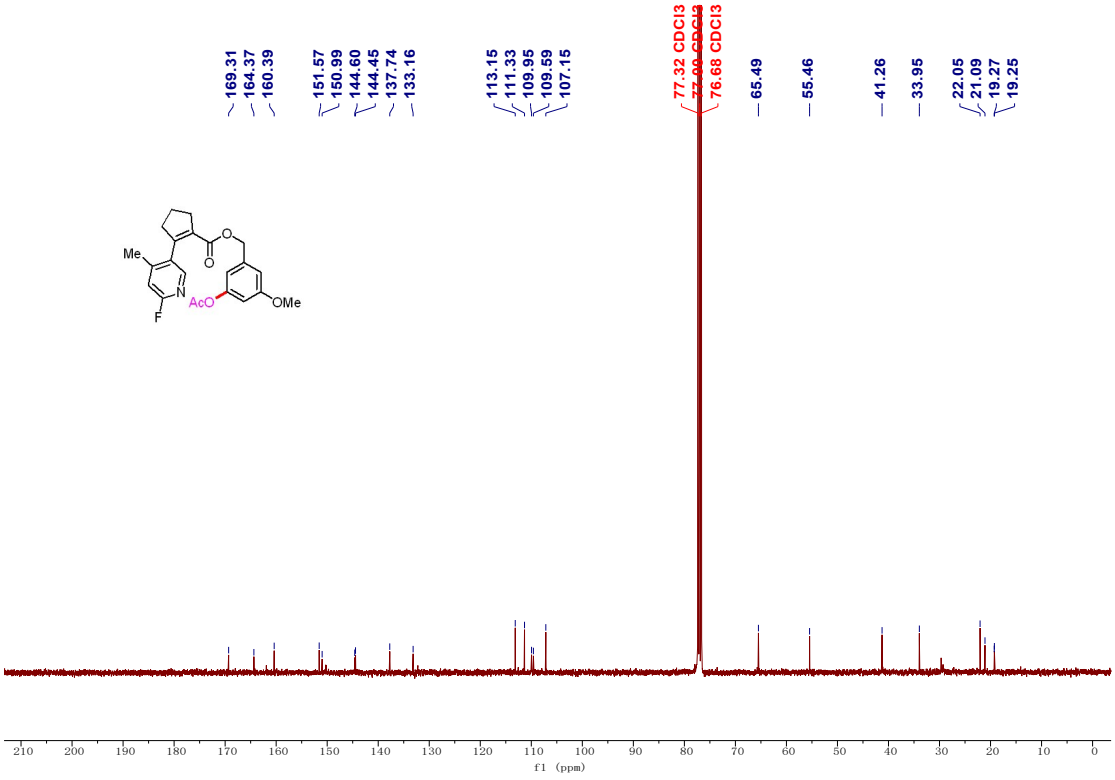
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **5f**



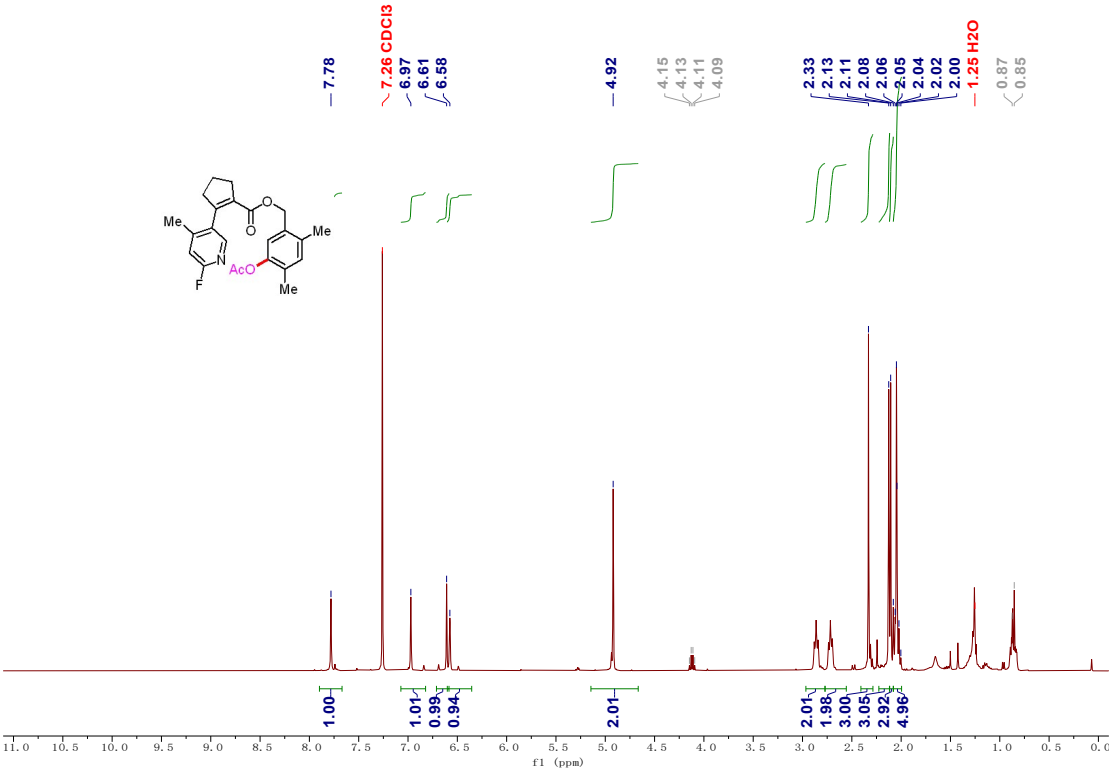
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **5f**



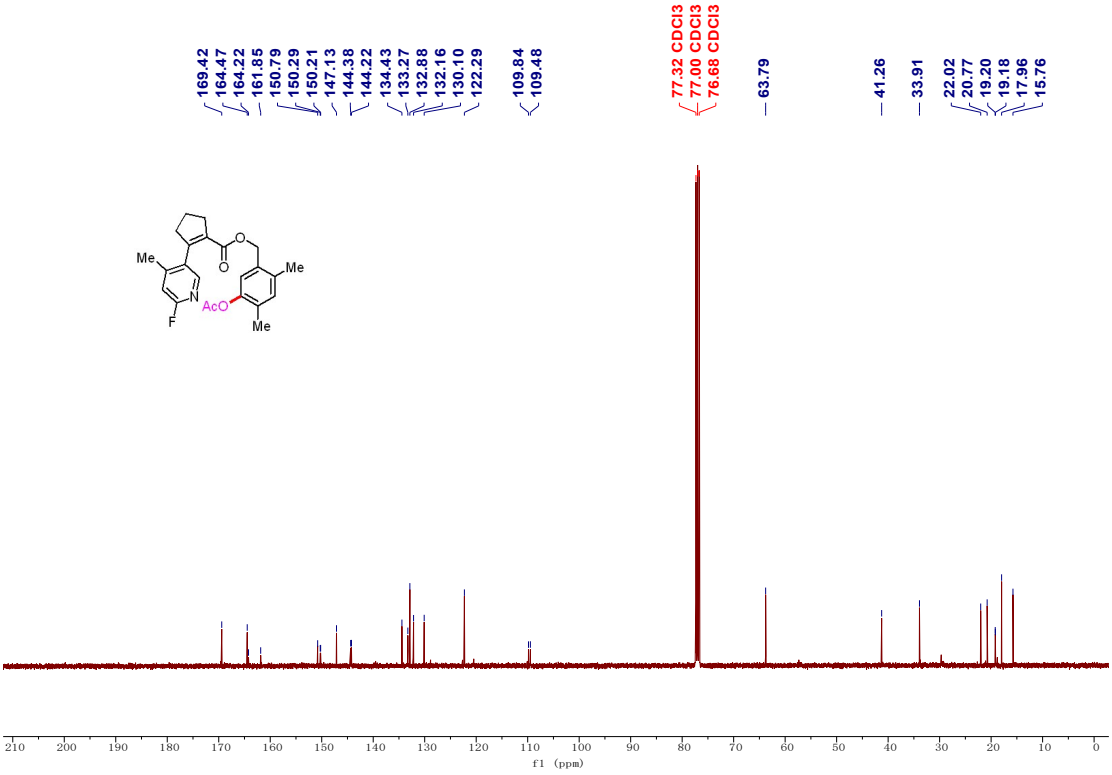
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **5g**



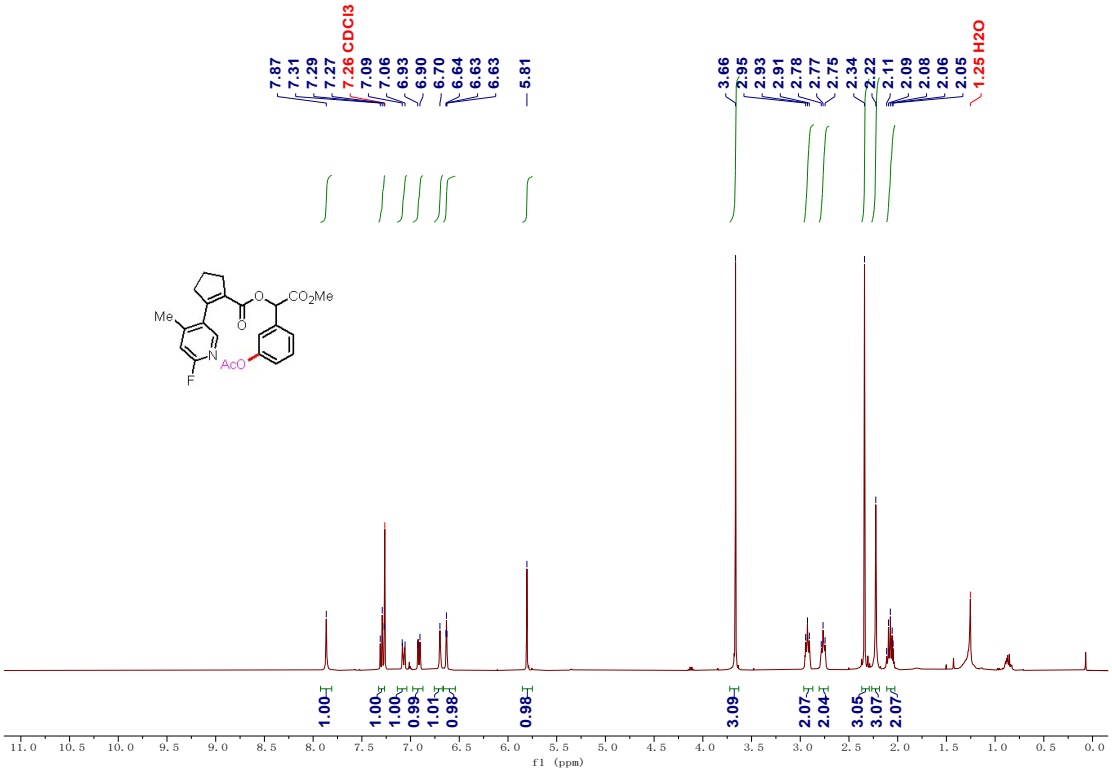
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **5g**



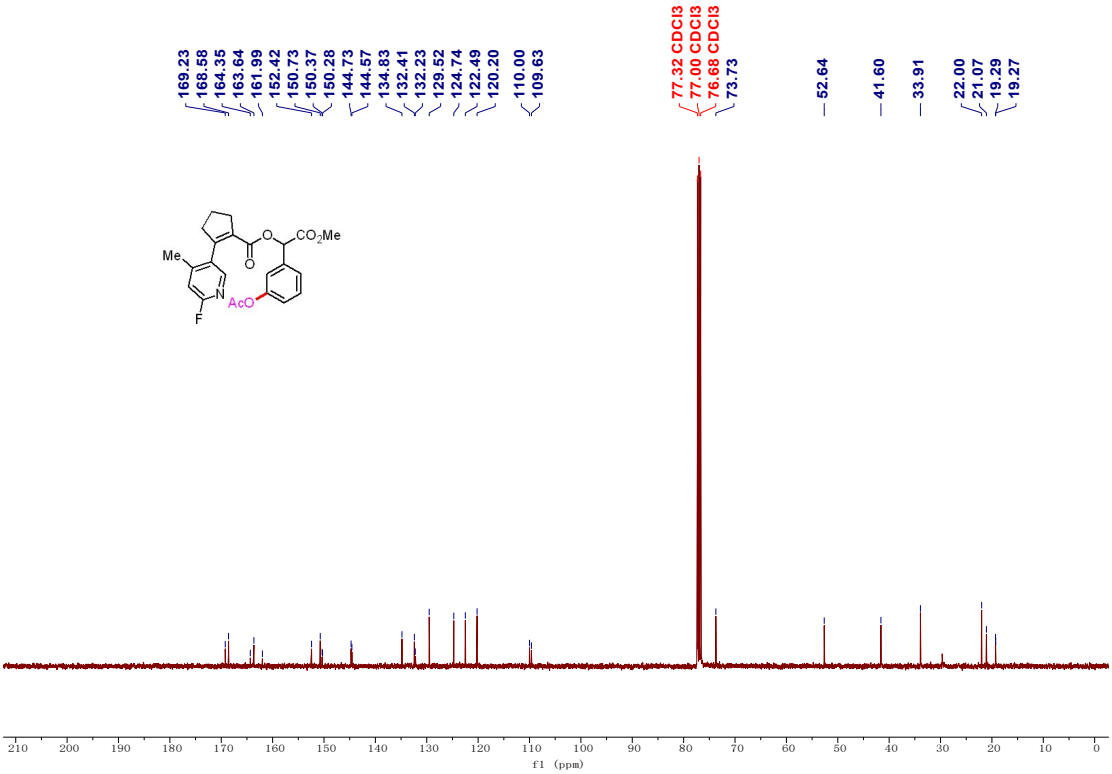
^{1}H NMR (400 MHz, $CDCl_3$) Spectra of Compound **5h**



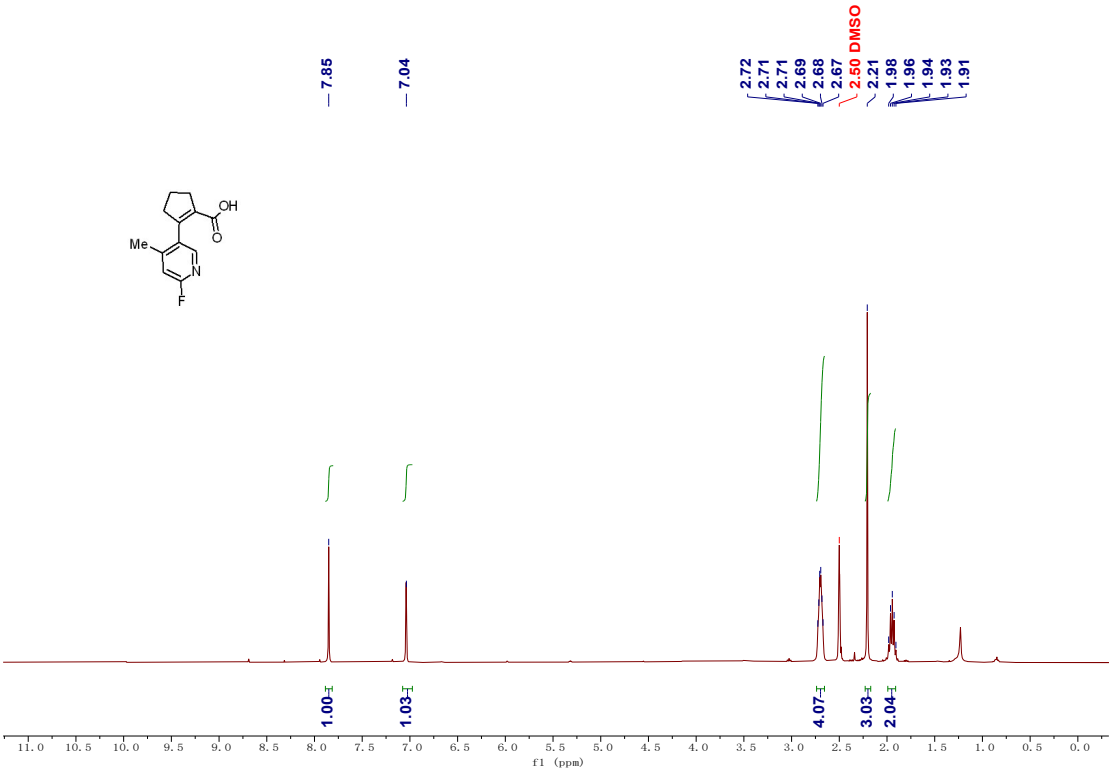
^{13}C NMR (100 MHz, $CDCl_3$) Spectra of Compound **5h**



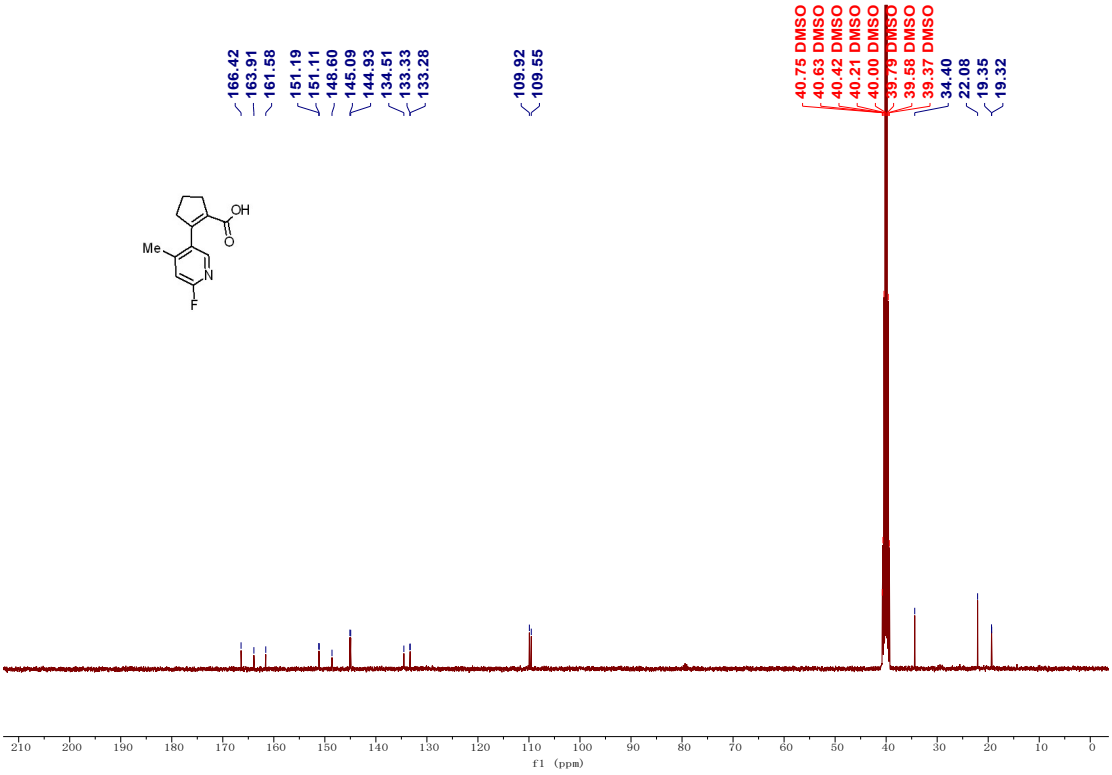
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Compound **5i**



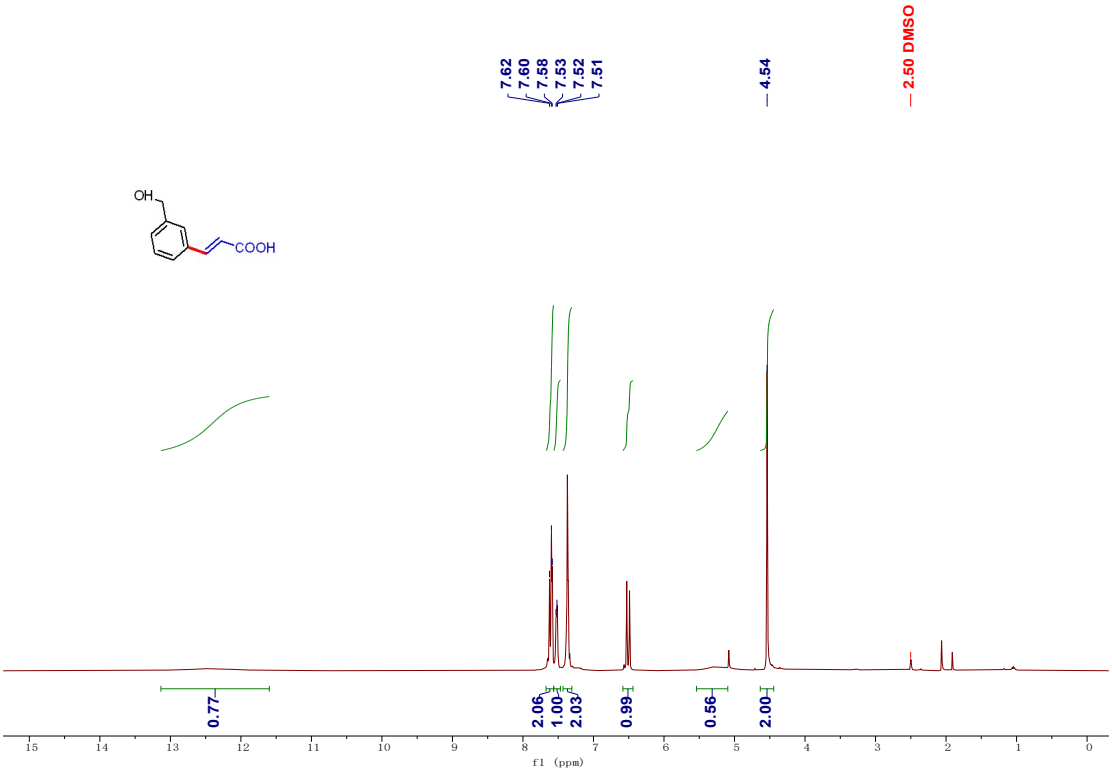
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of Compound **5i**



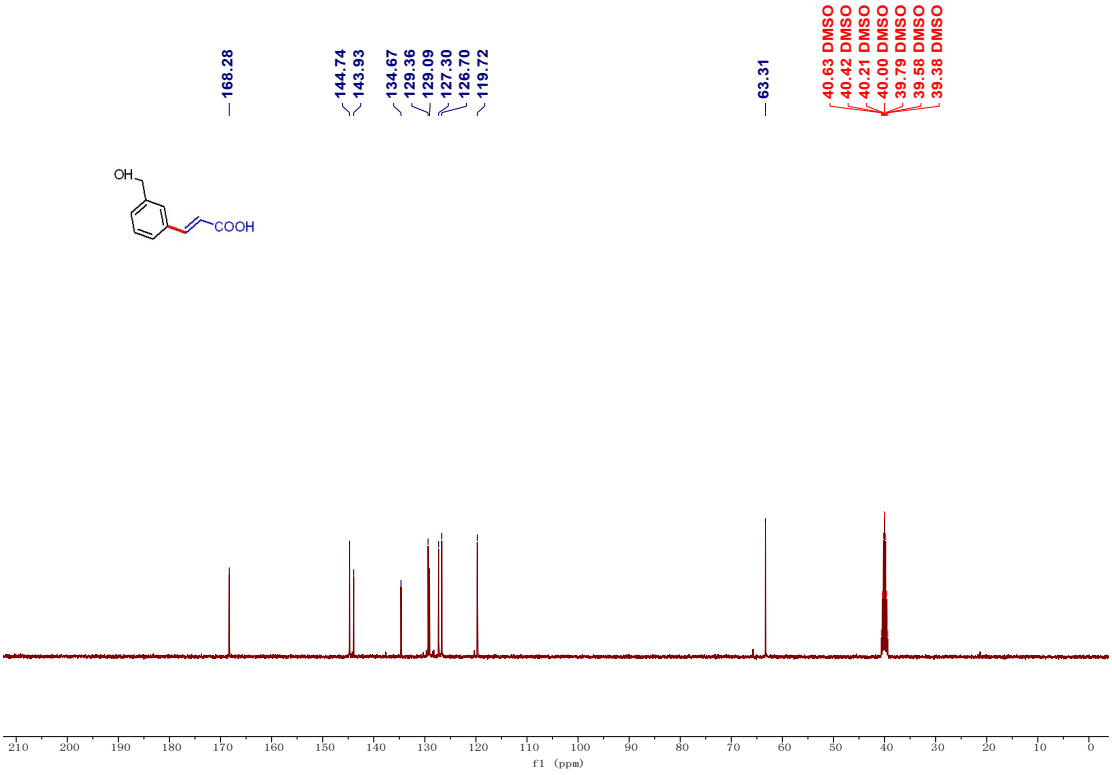
^{1}H NMR (400 MHz, DMSO-d_6) Spectrum of Compound **T_{12}**



^{13}C NMR (100 MHz, DMSO-d_6) Spectra of Compound **T_{12}**



^{1}H NMR (400 MHz, DMSO-d_6) Spectra of Compound **6**



^{13}C NMR (100 MHz, DMSO-d_6) Spectra of Compound **6**