Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Ligand-free copper-catalyzed regio- and stereoselective 1,1-alkylmonofluoroalkylation of terminal alkynes

Yunhe Lv, Weiya Pu and Xiaoxing Wang*

Table of Contents

1. General Information

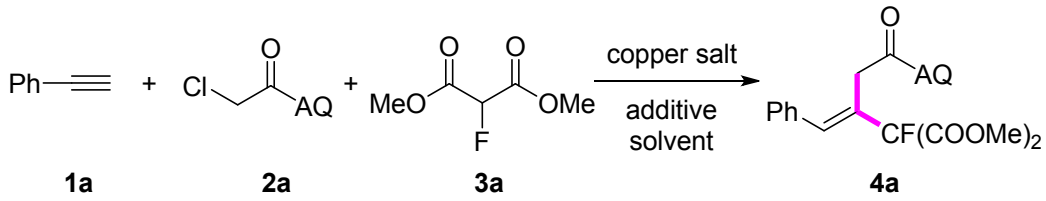
All deuterated solvents were purchased from Cambridge Isotope Laboratories. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at 25 °C on a Brüker Advance 400 spectrometer (^{1}H: 400 MHz, ^{13}C:100 MHz, and ^{19}F:376 MHz). ^{1}H NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at δ 0.00 ppm or to the signal of the residual protonated solvent: $CDCl_3$ at δ 7.26 ppm. ^{13}C NMR chemical shifts were determined relative to the signal of the solvent: $CDCl_3$ at δ 77.00 ppm. Data for ^{1}H, ^{13}C, ^{19}F NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets), coupling constants (Hz) and integration. Melting points were obtained with a micro melting point XT4A Beijing Keyi electrooptic apparatus and are uncorrected. High-resolution mass data were recorded on a Waters LCT PremierxeTM (USA). Single-crystal X-ray crystallography was carried out on a Bruker Smart Apex II diffractometer system.

Materials and Methods:

Unless otherwise stated, starting materials were purchased from Aldrich or Energy-Chemical Limited and used as supplied without further purification. Solvents were used directly without further purification. The following starting materials were prepared according to the procedures described previously in the literature: **1v**,[1] **3c-3e**,[2] **13**,[3] **14**.[3] The alkynes 1,1-alkylmonofluoroalkylation reactions were performed under nitrogen atmosphere in flame dried flasks. All reactions were monitored by thin layer chromatography (TLC) with Taizhou GF254 silica gel coated plates. Flash column chromatography was carried out using 200-300 mesh silica gel at increased pressure.

2. Screening Reaction Conditions

Table 1 Optimization of the reaction conditions[a]



1a **2a** **3a** **4a**

Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	CuI	Cs_2CO_3	dioxane	81
2	CuI	Cs_2CO_3	CH_3CN	76
3	CuI	Cs_2CO_3	acetone	55
4	CuI	Cs_2CO_3	$CHCl_3$	40
5	CuI	Cs_2CO_3	DMF	46
6	**CuI**	**Cs_2CO_3**	**THF**	**94**
7	CuI	none	THF	0
8	none	Cs_2CO_3	THF	0
9	CuI	Na_2CO_3	THF	38
10	CuI	$NaHCO_3$	THF	34
11	CuI	K_2CO_3	THF	32
12	CuI	Et_3N	THF	15
13	CuCl	Cs_2CO_3	THF	89
14	CuBr	Cs_2CO_3	THF	90

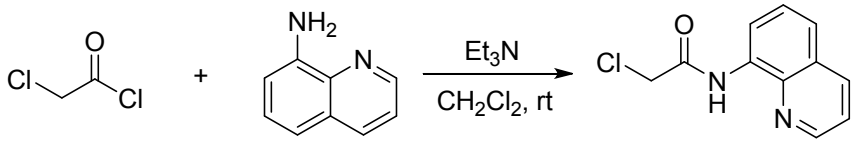
[a] Reactions were carried out with **1a** (0.33 mmol), **2a** (0.3 mmol), **3a** (0.45 mmol), catalyst (10 mol %), and base (0.36 mmol) in 0.9 mL of solvent under a N_2 atmosphere at 80 °C for 1.5 h, unless noted otherwise. [b] Yield of the isolated product.

Dimethyl 2-fluoromalonate derivatives are useful fluorinated building blocks for monofluoroalkylations. Recently, various alkylation, Mannich reaction, Michael addition and heterocycle formation processes using simple and inexpensive nucleophilic monofluoroalkylation reagents for the synthesis of fluorinated derivatives have been reported.[4] Therefore, we first focused on the copper-catalyzed 1,1-alkylmonofluoroalkylation of ethynylbenzene (**1a**), 2-chloro-*N*-(quinolin-8-yl)acetamide (**2a**), and dimethyl 2-fluoromalonate (**3a**) according to our previous work. To our delight, in the presence of CuI, Phen and Cs_2CO_3 and using 0.9 mL of dioxane at 80 °C for 1.5 h under N_2, the desired product **4a** was obtained in 80% yield. Surprisingly, when the reaction was performed under the same conditions but without 1,10-phenanthroline as a

ligand, similar results were obtained (Table 1, entry 1). Encouraged by this first example of a ligand-free copper-catalyzed 1,1-alkylmonofluoroalkylation, a series of solvents were screened, and tetrahydrofuran showed the best activity (Table 1, entries 2-6). Control experiments demonstrated that the base and catalyst were essential (Table 1, entries 7 and 8). However, other bases, such as Na_2CO_3, $NaHCO_3$, K_2CO_3, and Et_3N, were not as effective as Cs_2CO_3 (Table 1, entries 9-12). In addition, when CuCl and CuBr were used as catalysts, **4a** was obtained in good yields (Table 1, entries 13 and 14).

3. Synthesis of Substrates

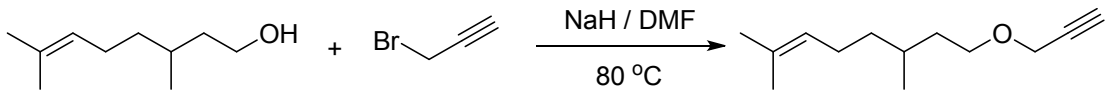
Substrate **2** was prepared through the reaction of quinolin-8-amine and corresponding acyl chlorides in CH_2Cl_2 at room temperature (**2a** as an example).



2a

To a solution of quinolin-8-amine (0.72 g, 5.0 mmol) in CH_2Cl_2 (10 mL) at room temperature was added 2-chloroacetyl chloride (0.48 mL, 6.0 mmol), Et_3N (0.83 mL, 6.0 mmol) in one portion. The reaction mixture was stirred for 20 min. After completion of the reaction (TLC monitoring), the mixture was quenched by water and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered over Celite, evaporated *in vacuo*, and the residue was purified by column chromatography to give the compound **2a** (1.05 g, 95%).

Substrate **8** was prepared through the reaction of citronellol and 3-bromoprop-1-yne in anhydrous DMF at 80 °C.



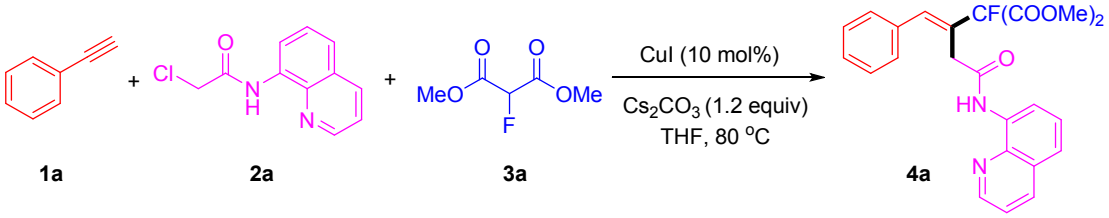
citronellol **8**

To the well stirred anhydrous DMF (5 mL), cooling by ice-water, added citronellol (0.37 mL, 2

mmol), NaH (70%, 0.082 g, 2.4 mmol) and 3-bromoprop-1-yne (0.26 mL, 3 mmol). The reaction mixture was stirred at 80 °C for 4 h (monitored by TLC) before it was slowly poured into water (5 mL). Extracted with CH_2Cl_2 (3×5 mL), then the organic phase was washed with water (3×5 mL), the solvent was removed under reduced pressure, and the residue was purified by column chromatography (eluent: diethyl ether/petroleum ether = 1/50) afforded the product **8** (0.245 g, 63%).

4. General Procedure for 1,1-Alkylmonofluoroalkylation of Terminal Alkynes

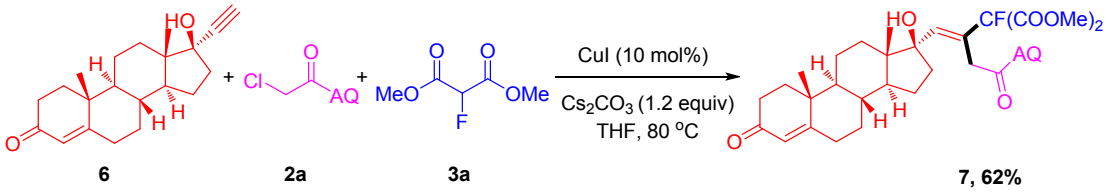
4a as an example



To a solution of the 2-chloro-*N*-(quinolin-8-yl)acetamide **2a** (66.2 mg, 0.3 mmol) in tetrahydrofuran (0.9 mL) was added the ethynylbenzene **1a** (38 μL, 0.33 mmol), dimethyl 2-fluoromalonate **3a** (70.4 mg, 0.45 mmol), CuI (5.7 mg, 0.03 mmol), and Cs_2CO_3 (117.3 mg, 0.36 mmol) under N_2 in screw-cap test tube. The reaction mixture was stirred at 80 °C for 1.5 h. After the reaction finished, the reaction mixture was cooled to room temperature and quenched by water. The mixture was extracted with EtOAc (3.0 mL×3), the combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The residue was purified by column chromatography to give the corresponding products **4a** (123.1 mg, 94%).

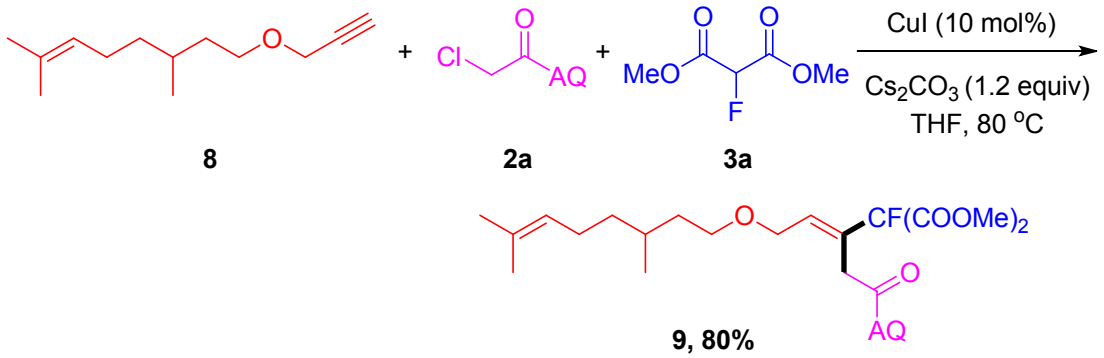
5. Synthetic Applications

5.1 Synthesis of 7



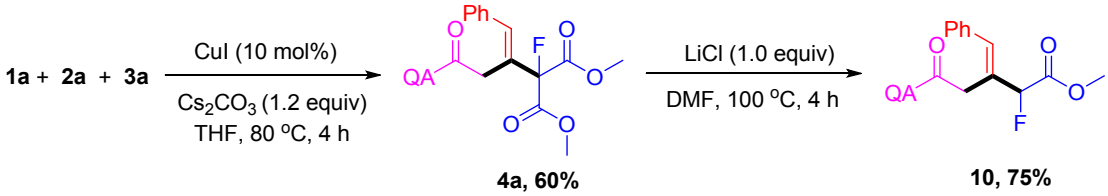
Following the general procedure 4, the reaction with **6** (103.1 mg, 0.33 mmol), **2a** (66.2 mg, 0.3 mmol), **3a** (70.4 mg, 0.45 mmol), CuI (5.7 mg, 0.03 mmol), and Cs_2CO_3 (117.3 mg, 0.36 mmol) under N_2 for 1.5 h at 80 °C afforded **7** as white solid (120.0 mg, 62% yield).

5.2 Synthesis of 9



Following the general procedure 4, the reaction with **8** (64.1 mg, 0.33 mmol), **2a** (66.2 mg, 0.3 mmol), **3a** (70.4 mg, 0.45 mmol), CuI (5.7 mg, 0.03 mmol), and Cs_2CO_3 (117.3 mg, 0.36 mmol) under N_2 for 1.5 h at 80 °C afforded **9** as colorless oil (127.0 mg, 80% yield).

5.3 Synthesis of 4a in Gram Scale and Removing Methyl Ester Group



Synthesis of 4a in gram scale

Following the general procedure 4, the reaction with **1a** (0.63 mL, 5.5 mmol), **2a** (1.10 g, 5 mmol), **3a** (1.17 g, 7.5 mmol.), CuI (95.0 mg, 0.5 mmol), and Cs_2CO_3 (1.95 g, 6.0 mmol) under N_2 for 4 h at 80 °C in THF (15 mL) afforded **4a** as white solid (1.31 g, 60% yield).

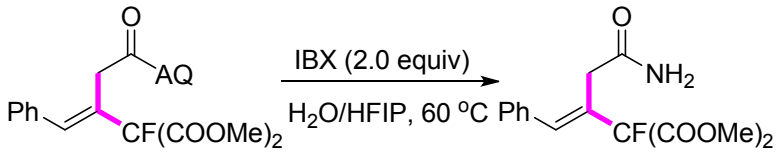
Removing methyl ester group in 4a[5]

Under an atmosphere of N_2, compound **4a** (131 mg, 0.3 mmol) was taken in a seal tube vial in anhydrous DMF (0.6 mL) with LiCl (13 mg, 0.3 mmol). Seal tube was tightly closed with teflon cap and heated at 100 °C for 4 h. After completion of the reaction, the reaction was quenched with the addition of saturated NH_4Cl solution (0.3 mL), and extracted with EtOAc (3 × 3 mL). The

combined extracts were dried over Na_2SO_4. After concentration in vacuum, the residue was purified by column chromatography to give the corresponding products **10** (85.1 mg, 75%).

5.4 Synthesis of 11 and 12

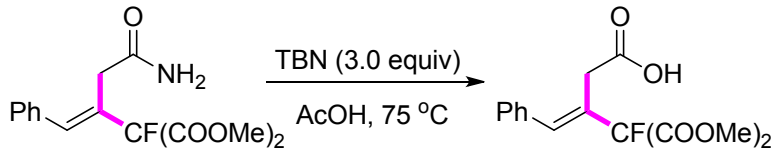
Removing the AQ group in 4a



4a **11, 71%**

Following the general procedure described previously in the literature,[6] to a round-bottom flask (25 mL) were added the compound **4a** (131 mg, 0.3 mmol) and IBX (168 mg, 0.6 mmol). The mixture in 2 mL of mixed solvent (V_{HFIP}/V_{H2O} = 1:1) was stirred at 60 °C in oil bath under air atmosphere for 1.5 h (monitored by TLC). The reaction was quenched by the addition of $NaHCO_3$ (aq 10 mL); the resulting mixture was extracted with dichloromethane (6 mL x 3). The organic solvent was concentrated in vacuo. The residue was purified by column chromatography to give the corresponding products **11** (66.0 mg, 71%).

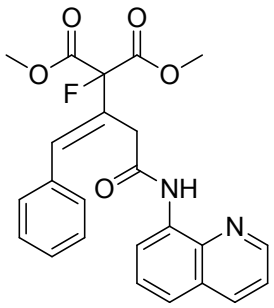
Conversion of primary amide to carboxylic acid



11 **12, 73%**

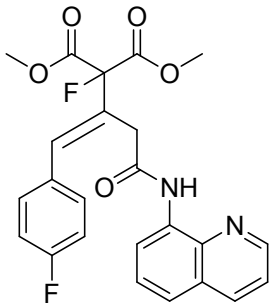
Following the general procedure described previously in the literature,[7] to a stirred solution of the compound **11** (93 mg, 0.3 mmol) in acetic acid (2 mL) was slowly added *tert*-butyl nitrite (107 μL, 0.9 mmol). The reaction mixture was stirred at 75 °C under air atmosphere for 2 h while the progress was monitored by TLC. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography to give the corresponding products **12** (68.0 mg, 73%).

6. Analytical Data of Compounds 4, 5, 7, 9-12



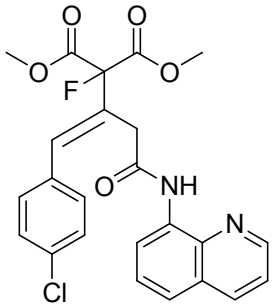
(*E*)-dimethyl 2-fluoro-2-(4-oxo-1-phenyl-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4a

White solid. mp: 124-125 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77 (d, J = 1.6 Hz, 2H), 3.84 (s, 6H), 7.24-7.33 (m, 4H), 7.42-7.45 (m, 3H), 7.48-7.52 (m, 2H), 8.14 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 8.74 (dd, J_1 = 2.4 Hz, J_2 = 6.4 Hz, 1H), 8.78 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H), 9.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.3 (d, J = 4.0 Hz), 53.7, 95.1 (d, J = 201.0 Hz), 116.3, 121.6 (d, J = 6.0 Hz), 127.3, 127.6, 127.8, 127.9, 128.1, 128.5, 128.7, 134.4, 134.6 (d, J = 12.0 Hz), 135.1, 136.2, 138.4, 148.2, 165.7 (d, J = 25.0 Hz), 167.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.9. HRMS (ESI-TOF). Calcd for $C_{24}H_{21}FN_2O_5Na$, $[M+Na]^+$ *m/z* 459.1332, Found 459.1327.



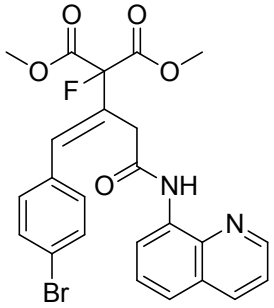
(*E*)-dimethyl 2-fluoro-2-(1-(4-fluorophenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4b

White solid. mp: 111-113 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (d, J = 1.6 Hz, 2H), 3.84 (s, 6H), 7.00 (t, J = 8.4 Hz, 2H), 7.24 (s, 1H), 7.41-7.45 (m, 3H), 7.48-7.53 (m, 2H), 8.14 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 8.73 (dd, J_1 = 2.8 Hz, J_2 = 6.0 Hz, 1H), 8.77 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 9.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.1 (d, J = 4.0 Hz), 53.7, 95.0 (d, J = 201.0 Hz), 115.4, 115.6, 116.3, 121.6 (d, J = 2.0 Hz), 127.2, 127.6, 127.9, 130.5 (d, J = 8.0 Hz), 131.1 (d, J = 3.0 Hz), 133.4 (d, J = 12.0 Hz), 134.2, 136.2, 138.3, 148.2, 162.4 (d, J = 247.0 Hz), 165.6 (d, J = 25.0 Hz), 167.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.3, -113.2. HRMS (ESI-TOF). Calcd for $C_{24}H_{21}F_2N_2O_5$, $[M+H]^+$ *m/z* 455.1419, Found 455.1437.



(*E*)-dimethyl 2-(1-(4-chlorophenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)-2-fluoromalonate 4c

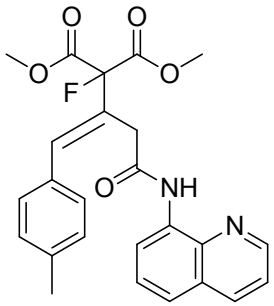
White solid. mp: 94-96 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73 (d, J = 1.6 Hz, 2H), 3.84 (s, 6H), 7.23 (s, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.45 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 7.50-7.55 (m, 2H), 8.16 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 8.72 (dd, J_1 = 3.2 Hz, J_2 = 5.6 Hz, 1H), 8.79 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H), 9.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.2 (d, J = 4.0 Hz), 53.7, 94.9 (d, J = 201.0 Hz), 116.3, 121.7 (d, J = 2.0 Hz), 127.3, 127.9, 128.3, 128.5, 128.7, 130.1, 133.2 (d, J = 11.0 Hz), 133.6, 134.1, 134.3, 136.3, 138.3, 148.2, 165.5 (d, J = 26.0 Hz), 167.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.6. HRMS (ESI-TOF). Calcd for $C_{24}H_{21}ClFN_2O_5$, $[M+H]^+$ *m/z* 471.1123, Found 471.1138.



(*E*)-dimethyl 2-(1-(4-bromophenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)-2-fluoromalonate 4d

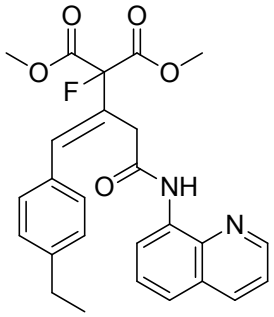
White solid. mp: 114-115 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73 (d, J = 1.2 Hz, 2H), 3.84 (s, 6H), 7.21 (s, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.43-7.47 (m, 3H), 7.51-7.54 (m, 2H), 8.16 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 8.72 (dd, J_1 = 3.2 Hz, J_2 = 5.6 Hz, 1H), 8.79 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H), 9.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.2 (d, J = 4.0 Hz), 53.7, 94.9 (d, J = 202.0 Hz), 116.3, 121.7 (d, J = 2.0 Hz), 122.3, 127.3, 127.9, 128.4, 128.6, 130.3, 131.7, 133.2 (d, J =

12.0 Hz), 134.1, 134.2, 136.3, 138.3, 148.2, 165.5 (d, J = 26.0 Hz), 167.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.6. HRMS (ESI-TOF). Calcd for $C_{24}H_{21}BrFN_2O_5$, $[M+H]^+$ *m/z* 515.0618, 517.0597, Found 515.0611, 517.0565.



(*E*)-dimethyl 2-fluoro-2-(4-oxo-4-(quinolin-8-ylamino)-1-(*p*-tolyl)but-1-en-2-yl)malonate 4e

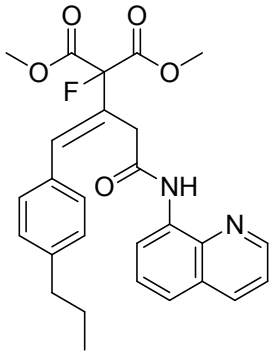
White solid. mp: 68-70 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 3.76 (d, J = 1.6 Hz, 2H), 3.83 (s, 6H), 7.12 (d, J = 8.0 Hz, 2H), 7.25 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.44 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 7.48-7.54 (m, 2H), 8.14 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.74 (dd, J_1 = 2.4 Hz, J_2 = 6.8 Hz, 1H), 8.78 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 9.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 37.4 (d, J = 4.0 Hz), 53.7, 95.2 (d, J = 201.0 Hz), 116.3, 121.6 (d, J = 7.0 Hz), 126.9, 127.1, 127.3, 127.9, 128.7, 129.2, 132.2, 134.4, 134.6 (d, J = 11.0 Hz), 136.2, 138.0, 138.4, 148.2, 165.7 (d, J = 26.0 Hz), 168.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.0. HRMS (ESI-TOF). Calcd for $C_{25}H_{24}FN_2O_5$, $[M+H]^+$ *m/z* 451.1669, Found 451.1691.



(*E*)-dimethyl 2-(1-(4-ethylphenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)-2-fluoromalonate 4f

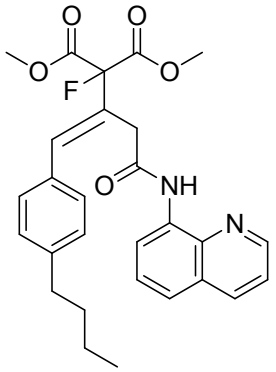
White solid. mp: 78-79 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.6 Hz, 3H), 2.59 (q, J = 7.6 Hz, 2H), 3.77 (d, J = 1.2 Hz, 2H), 3.83 (s, 6H), 7.14 (d, J = 8.0 Hz, 2H), 7.26 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.43 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 7.48-7.53 (m, 2H), 8.14 (dd, J_1 = 1.2 Hz,

J_2 = 8.0 Hz, 1H), 8.75 (dd, J_1 = 2.4 Hz, J_2 = 6.8 Hz, 1H), 8.77 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H), 10.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 28.5, 37.4 (d, J = 4.0 Hz), 53.6, 95.2 (d, J = 200.0 Hz), 116.3, 121.5 (d, J = 7.0 Hz), 126.8, 127.0, 127.3, 127.9, 128.0, 128.7, 132.4, 134.4, 134.6 (d, J = 12.0 Hz), 136.2, 138.4, 144.3, 148.2, 165.7 (d, J = 26.0 Hz), 168.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.0. HRMS (ESI-TOF). Calcd for $C_{26}H_{26}FN_2O_5$, $[M+H]^+$ *m/z* 465.1826, Found 465.1848.



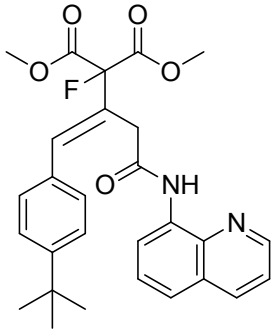
(*E*)-dimethyl 2-fluoro-2-(4-oxo-1-(4-propylphenyl)-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4g

White solid. mp: 91-92 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.2 Hz, 3H), 1.52-1.62 (m, 2H), 2.52 (t, J = 7.6 Hz, 2H), 3.77 (s, 2H), 3.83 (s, 6H), 7.12 (d, J = 8.0 Hz, 2H), 7.25 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.43 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 7.48-7.53 (m, 2H), 8.14 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 8.75 (dd, J_1 = 2.4 Hz, J_2 = 6.8 Hz, 1H), 8.77 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H), 10.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 24.3, 37.4 (d, J = 4.0 Hz), 37.7, 53.6, 95.2 (d, J = 200.0 Hz), 116.3, 121.5 (d, J = 7.0 Hz), 126.8, 127.0, 127.3, 127.9, 128.6, 128.7, 132.4, 134.4, 134.6 (d, J = 12.0 Hz), 136.2, 138.4, 142.8, 148.2, 165.7 (d, J = 26.0 Hz), 168.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.9. HRMS (ESI-TOF). Calcd for $C_{27}H_{28}FN_2O_5$, $[M+H]^+$ *m/z* 479.1982, Found 479.1988.



(*E*)-dimethyl 2-(1-(4-butylphenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)-2-fluoromalonate 4h

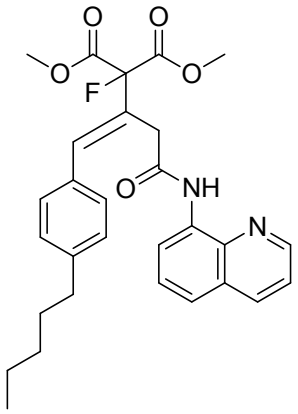
White solid. mp: 104-106 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.2 Hz, 3H), 1.25-1.30 (m, 2H), 1.49-1.55 (m, 2H), 2.55 (t, J = 7.6 Hz, 2H), 3.77 (d, J = 1.2 Hz, 2H), 3.83 (s, 6H), 7.12 (d, J = 8.0 Hz, 2H), 7.25 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.43 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.48-7.53 (m, 2H), 8.14 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.75 (dd, J_1 = 2.4 Hz, J_2 = 6.8 Hz, 1H), 8.77 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 10.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.3, 33.4, 35.3, 37.4 (d, J = 4.0 Hz), 53.6, 95.2 (d, J = 200.0 Hz), 116.3, 121.5 (d, J = 7.0 Hz), 126.8, 127.0, 127.3, 127.9, 128.6, 128.7, 132.4, 134.4, 134.7 (d, J = 12.0 Hz), 136.2, 138.4, 143.1, 148.2, 165.7 (d, J = 26.0 Hz), 168.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.9. HRMS (ESI-TOF). Calcd for $C_{28}H_{30}FN_2O_5$, $[M+H]^+$ *m/z* 493.2139, Found 493.2133.



(*E*)-dimethyl 2-(1-(4-(tert-butyl)phenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)-2-fluoromalonate 4i

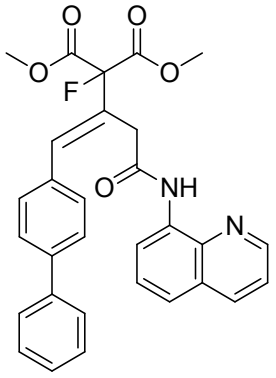
White solid. mp: 93-95 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 9H), 3.77 (d, J = 1.2 Hz, 2H), 3.83 (s, 6H), 7.26 (s, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.44 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 7.48-7.54 (m, 2H), 8.14 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.75 (dd, J_1 = 2.4 Hz,

J_2 = 6.4 Hz, 1H), 8.78 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 10.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.2, 34.6, 37.5 (d, J = 4.0 Hz), 53.6, 95.2 (d, J = 201.0 Hz), 116.3, 121.5 (d, J = 8.0 Hz), 125.4, 126.9, 127.1, 127.3, 127.9, 128.5, 132.2, 134.4, 134.6 (d, J = 11.0 Hz), 136.2, 138.4, 148.2, 151.2, 165.7 (d, J = 26.0 Hz), 168.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.9. HRMS (ESI-TOF). Calcd for $C_{28}H_{30}FN_2O_5$, $[M+H]^+$ *m/z* 493.2139, Found 493.2133.



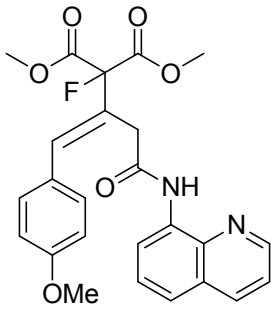
(*E*)-dimethyl 2-fluoro-2-(4-oxo-1-(4-pentylphenyl)-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4j

White solid. mp: 105-106 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.2 Hz, 3H), 1.26-1.32 (m, 4H), 1.51-1.58 (m, 2H), 2.54 (t, J = 7.6 Hz, 2H), 3.77 (s, 2H), 3.83 (s, 6H), 7.12 (d, J = 8.0 Hz, 2H), 7.25 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.43 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.48-7.53 (m, 2H), 8.13 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.74-8.78 (m, 2H), 10.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.4, 30.9, 31.4, 35.6, 37.4 (d, J = 4.0 Hz), 53.6, 95.2 (d, J = 200.0 Hz), 116.3, 121.5 (d, J = 7.0 Hz), 126.8, 127.0, 127.3, 127.9, 128.5, 128.7, 132.4, 134.4, 134.6 (d, J = 12.0 Hz), 136.2, 138.4, 143.1, 148.1, 165.7 (d, J = 26.0 Hz), 168.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.9. HRMS (ESI-TOF). Calcd for $C_{29}H_{32}FN_2O_5$, $[M+H]^+$ *m/z* 507.2295, Found 507.2285.



(*E*)-dimethyl 2-(1-([1,1'-biphenyl]-4-yl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)-2-fluoromalonate 4k

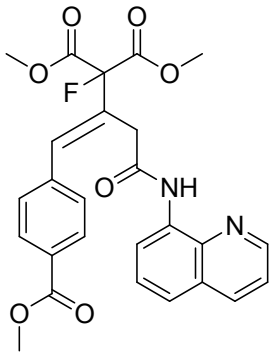
White solid. mp: 170-172 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 2H), 3.85 (s, 6H), 7.29-7.32 (m, 2H), 7.38-7.44 (m, 3H), 7.48-7.56 (m, 8H), 8.13 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 8.75-8.77 (m, 2H), 10.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.4 (d, J = 4.0 Hz), 53.7, 95.1 (d, J = 201.0 Hz), 116.3, 121.6, 126.9, 127.1, 127.3, 127.4, 127.6, 127.8, 127.8, 128.7, 129.2, 134.1, 134.2, 134.3, 136.2, 138.4, 140.3, 140.8, 148.2, 165.7 (d, J = 26.0 Hz), 167.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.1. HRMS (ESI-TOF). Calcd for $C_{30}H_{25}FN_2O_5Na$, $[M+Na]^+$ *m/z* 535.1645, Found 535.1660.



(*E*)-dimethyl 2-fluoro-2-(1-(4-methoxyphenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4l

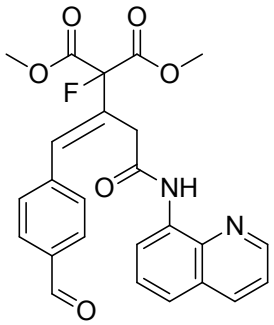
White solid. mp: 121-123 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (s, 3H), 3.76 (s, 2H), 3.83 (s, 6H), 6.84 (d, J = 8.8 Hz, 2H), 7.21 (s, 1H), 7.38-7.53 (m, 5H), 8.13 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 8.74-8.78 (m, 2H), 10.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.4 (d, J = 4.0 Hz), 53.6, 55.2, 95.3 (d, J = 200.0 Hz), 113.9, 116.3, 121.6 (d, J = 4.0 Hz), 125.8, 126.0, 127.3, 127.5, 127.9, 130.2, 134.2 (d, J = 12.0 Hz), 134.4, 136.2, 138.4, 148.2, 159.5, 165.8 (d, J = 26.0 Hz), 168.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.6. HRMS (ESI-TOF). Calcd for $C_{25}H_{24}FN_2O_6$, $[M+H]^+$ *m/z*

467.1618, Found 467.1618.



(*E*)-dimethyl 2-fluoro-2-(1-(4-(methoxycarbonyl)phenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4m

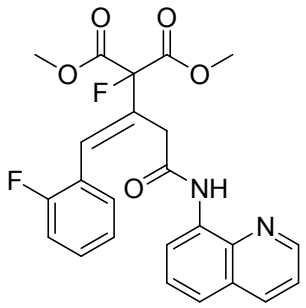
White solid. mp: 121-123 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77 (d, J = 1.2 Hz, 2H), 3.85 (s, 6H), 3.87 (s, 3H), 7.32 (s, 1H), 7.44 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.50-7.52 (m, 4H), 7.98 (d, J = 8.4 Hz, 2H), 8.14 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 8.72 (dd, J_1 = 3.2 Hz, J_2 = 5.6 Hz, 1H), 8.77 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 9.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.1 (d, J = 4.0 Hz), 52.0, 53.7, 94.8 (d, J = 201.0 Hz), 113.9, 116.3, 121.6 (d, J = 3.0 Hz), 127.2, 127.8, 128.6, 129.3, 129.5, 129.7, 133.3 (d, J = 12.0 Hz), 134.1, 136.2, 138.2, 139.8, 148.1, 165.4 (d, J = 26.0 Hz), 166.5, 167.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.8. HRMS (ESI-TOF). Calcd for $C_{26}H_{24}FN_2O_7$, $[M+H]^+$ *m/z* 495.1568, Found 495.1572.



(*E*)-dimethyl 2-fluoro-2-(1-(4-formylphenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4n

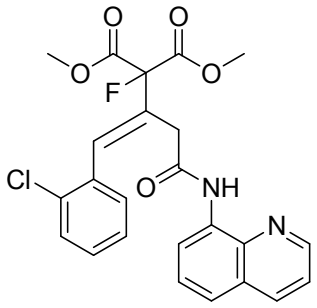
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77 (s, 2H), 3.85 (s, 6H), 7.33 (s, 1H), 7.46 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.51-7.54 (m, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 8.16 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 8.71 (t, J = 4.4 Hz, 1H), 8.78 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz,

1H), 9.92 (s, 1H), 9.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.2, 53.8, 94.8 (d, J = 202.0 Hz), 116.4, 121.7 (d, J = 7.0 Hz), 127.3, 127.9, 129.3, 129.8, 129.9, 130.1, 133.1 (d, J = 12.0 Hz), 134.2, 135.7, 136.3, 138.3, 141.4, 148.2, 165.4 (d, J = 26.0 Hz), 167.4, 191.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.9. HRMS (ESI-TOF). Calcd for $C_{25}H_{22}FN_2O_6$, $[M+H]^+$ *m/z* 465.1462, Found 465.1462.



(*E*)-dimethyl 2-fluoro-2-(1-(2-fluorophenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4o

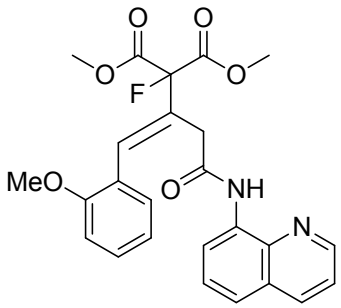
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76 (d, J = 1.6 Hz, 2H), 3.84 (s, 6H), 7.02-7.08 (m, 2H), 7.22-7.29 (m, 2H), 7.42-7.58 (m, 4H), 8.13 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 8.71 (dd, J_1 = 3.2 Hz, J_2 = 5.6 Hz, 1H), 8.78 (dd, J_1 = 1.2 Hz, J_2 = 4.4 Hz, 1H), 9.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.4 (d, J = 4.0 Hz), 53.7, 94.9 (d, J = 202.0 Hz), 115.4 (d, J = 22.0 Hz), 116.3, 121.6 (d, J = 4.0 Hz), 122.9 (d, J = 14.0 Hz), 124.1 (d, J = 3.0 Hz), 127.2, 127.6 (d, J = 3.0 Hz), 127.7 (d, J = 3.0 Hz), 127.8, 129.8 (d, J = 21.0 Hz), 130.0, 130.1 (d, J = 2.0 Hz), 134.3, 136.2, 138.3, 148.1, 160.1 (d, J = 247.0 Hz), 165.5 (d, J = 25.0 Hz), 167.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.7, -113.6. HRMS (ESI-TOF). Calcd for $C_{24}H_{21}F_2N_2O_5$, $[M+H]^+$ *m/z* 455.1419, Found 455.1441.



(*E*)-dimethyl 2-(1-(2-chlorophenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)-2-

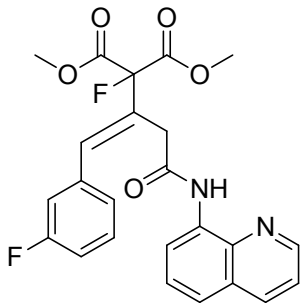
fluoromalonate 4p

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.67 (d, J = 2.0 Hz, 2H), 3.86 (s, 6H), 7.18-7.26 (m, 2H), 7.31 (s, 1H), 7.36-7.39 (m, 1H), 7.44 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.49-7.61 (m, 3H), 8.15 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.71 (dd, J_1 = 3.2 Hz, J_2 = 6.0 Hz, 1H), 8.78 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 9.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.2 (d, J = 4.0 Hz), 53.7, 94.8 (d, J = 202.0 Hz), 116.3, 121.6 (d, J = 3.0 Hz), 126.8, 127.3, 127.9, 129.3, 129.4, 129.4, 129.6, 130.2, 132.2 (d, J = 11.0 Hz), 133.7, 133.8, 134.3, 136.2, 138.3, 148.2, 165.5 (d, J = 26.0 Hz), 167.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -160.2. HRMS (ESI-TOF). Calcd for $C_{24}H_{21}ClFN_2O_5$, $[M+H]^+$ *m/z* 471.1123, Found 471.1109.



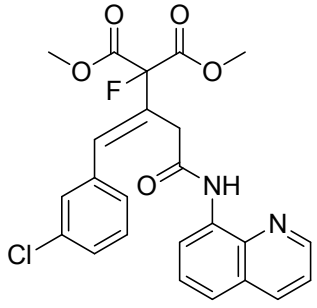
(*E*)-dimethyl 2-fluoro-2-(1-(2-methoxyphenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4q

White solid. mp: 128-130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.70 (s, 3H), 3.72 (d, J = 1.6 Hz, 2H), 3.85 (s, 6H), 6.81 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 7.22-7.24 (m, 1H), 7.31 (s, 1H), 7.43 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.47-7.52 (m, 3H), 8.13 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.71 (dd, J_1 = 2.8 Hz, J_2 = 6.0 Hz, 1H), 8.78 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 9.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.6 (d, J = 4.0 Hz), 53.6, 55.3, 95.2 (d, J = 200.0 Hz), 110.5, 116.3, 120.4, 121.4, 121.5, 124.0, 127.3, 127.5, 127.8, 129.6, 131.1 (d, J = 11.0 Hz), 134.4, 136.1, 138.4, 148.1, 157.2, 165.8 (d, J = 26.0 Hz), 168.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.0. HRMS (ESI-TOF). Calcd for $C_{25}H_{24}FN_2O_6$, $[M+H]^+$ *m/z* 467.1618, Found 467.1624.



(*E*)-dimethyl 2-fluoro-2-(1-(3-fluorophenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4r

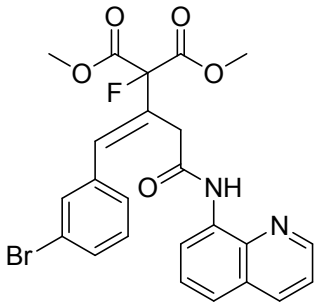
White solid. mp: 131-133 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (d, J = 1.6 Hz, 2H), 3.84 (s, 6H), 6.94-6.98 (m, 1H), 7.16-7.31 (m, 4H), 7.45 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.49-7.54 (m, 2H), 8.15 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 8.73 (dd, J_1 = 3.2 Hz, J_2 = 6.0 Hz, 1H), 8.79 (dd, J_1 = 1.2 Hz, J_2 = 4.4 Hz, 1H), 9.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.1 (d, J = 4.0 Hz), 53.7, 94.9 (d, J = 201.0 Hz), 115.0 (d, J = 21.0 Hz), 115.6 (d, J = 22.0 Hz), 116.3, 121.6, 124.4 (d, J = 3.0 Hz), 127.3, 127.9, 128.9 (d, J = 20.0 Hz), 130.0 (d, J = 9.0 Hz), 133.1 (d, J = 2.0 Hz), 133.3 (d, J = 2.0 Hz), 134.3, 136.2, 137.3 (d, J = 8.0 Hz), 138.3, 148.2, 162.7 (d, J = 245.0 Hz), 165.5 (d, J = 26.0 Hz), 167.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.7, -112.6. HRMS (ESI-TOF). Calcd for $C_{24}H_{21}F_2N_2O_5$, $[M+H]^+$ *m/z* 455.1419, Found 455.1404.



(*E*)-dimethyl 2-(1-(3-chlorophenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)-2-fluoromalonate 4s

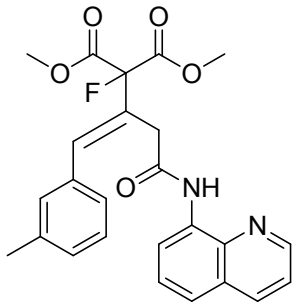
White solid. mp: 103-105 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (d, J = 1.6 Hz, 2H), 3.84 (s, 6H), 7.23-7.24 (m, 3H), 7.35 (d, J = 5.6 Hz, 1H), 7.42-7.53 (m, 4H), 7.45 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.49-7.54 (m, 2H), 8.14 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.72 (dd, J_1 = 3.2 Hz, J_2 = 6.0 Hz, 1H), 8.79 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 9.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.1 (d, J = 4.0 Hz), 53.7, 94.8 (d, J = 202.0 Hz), 116.3, 121.6, 126.6, 127.2, 127.8, 128.1, 128.8,

129.0, 129.2, 129.8, 133.0 (d, J = 12.0 Hz), 134.2, 134.3, 136.2, 136.9, 138.3, 148.2, 165.4 (d, J = 26.0 Hz), 167.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.7. HRMS (ESI-TOF). Calcd for $C_{24}H_{21}ClFN_2O_5$, $[M+H]^+$ *m/z* 471.1123, Found 471.1136.



(*E*)-dimethyl 2-(1-(3-bromophenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)-2-fluoromalonate 4t

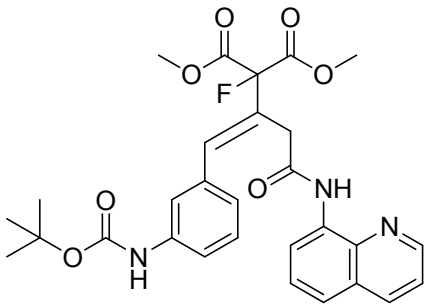
White solid. mp: 102-103 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 2H), 3.84 (s, 6H), 7.17 (t, J = 7.6 Hz, 1H), 7.23 (s, 1H), 7.36-7.53 (m, 5H), 7.57 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 8.72 (dd, J_1 = 3.2 Hz, J_2 = 5.6 Hz, 1H), 8.79 (d, J = 2.8 Hz, 1H), 9.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.1 (d, J = 4.0 Hz), 53.7, 94.8 (d, J = 201.0 Hz), 116.3, 121.6 (d, J = 2.0 Hz), 122.5, 127.0, 127.2, 127.8, 129.1, 129.3, 130.0, 131.0, 131.7, 132.9 (d, J = 11.0 Hz), 134.2, 136.2, 137.2, 138.3, 148.2, 165.4 (d, J = 26.0 Hz), 167.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.7. HRMS (ESI-TOF). Calcd for $C_{24}H_{21}BrFN_2O_5$, $[M+H]^+$ *m/z* 515.0618, 517.0597, Found 515.0616, 517.0593.



(*E*)-dimethyl 2-fluoro-2-(4-oxo-4-(quinolin-8-ylamino)-1-(*m*-tolyl)but-1-en-2-yl)malonate 4u

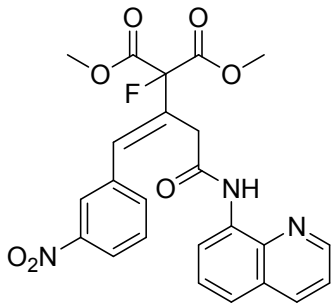
White solid. mp: 67-68 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25 (s, 3H), 3.75 (d, J = 1.6 Hz, 2H), 3.84 (s, 6H), 7.06 (d, J = 7.2 Hz, 1H), 7.18-7.26 (m, 4H), 7.44 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 8.48-8.54 (m, 2H), 8.15 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.74 (dd, J_1 = 2.8 Hz, J_2 = 6.4 Hz, 1H), 8.79 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 9.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 37.3

(d, *J* = 4.0 Hz), 53.7, 95.2 (d, *J* = 201.0 Hz), 116.3, 121.5 (d, *J* = 7.0 Hz), 125.6, 127.3, 127.5, 127.7, 127.9, 128.4, 128.8, 129.5, 134.4, 134.7 (d, *J* = 11.0 Hz), 135.1, 136.2, 138.1, 138.4, 148.1, 165.7 (d, *J* = 26.0 Hz), 167.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.3. HRMS (ESI-TOF). Calcd for $C_{25}H_{24}FN_2O_5$, $[M+H]^+$ *m/z* 451.1669, Found 451.1681.



(*E*)-dimethyl 2-(1-(3-((*tert*-butoxycarbonyl)amino)phenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)-2-fluoromalonate 4v

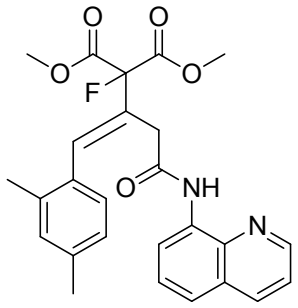
White solid. mp: 117-119 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 1.18 (s, 9H), 3.76 (d, *J* = 1.2 Hz, 2H), 3.84 (s, 6H), 7.17-7.27 (m, 2H), 7.33 (s, 1H), 7.43 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 8.47-8.52 (m, 4H), 8.13 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 8.71 (dd, J_1 = 4.0 Hz, J_2 = 5.2 Hz, 1H), 8.78 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 9.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 27.3, 37.1 (d, *J* = 4.0 Hz), 39.4, 53.6, 95.0 (d, *J* = 201.0 Hz), 116.2, 119.7, 120.3, 121.5 (d, *J* = 5.0 Hz), 124.2, 127.2, 127.8, 128.1, 128.3, 129.1, 134.0 (d, *J* = 11.0 Hz), 134.3, 135.8, 136.1, 138.1, 138.3, 148.2, 165.5 (d, *J* = 26.0 Hz), 167.9, 176.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.4. HRMS (ESI-TOF). Calcd for $C_{29}H_{31}FN_3O_7$, $[M+H]^+$ *m/z* 552.2146, Found 552.2142.



(*E*)-dimethyl 2-fluoro-2-(1-(3-nitrophenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4w

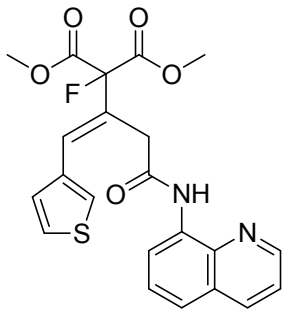
White solid. mp: 131-133 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 3.75 (s, 2H), 3.86 (s, 6H), 7.33 (s,

1H), 7.43-7.50 (m, 4H), 7.82 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.29 (s, 1H), 8.70 (t, J_2 = 4.4 Hz, 1H), 8.78 (d, J = 2.8 Hz, 1H), 9.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.0 (d, J = 4.0 Hz), 53.8, 94.6 (d, J = 203.0 Hz), 116.3, 121.7 (d, J = 12.0 Hz), 122.7, 123.7, 127.2, 127.8, 129.5, 130.4, 130.6, 131.8 (d, J = 12.0 Hz), 134.0, 134.5, 136.2, 136.8, 138.1, 148.1, 148.2, 165.2 (d, J = 26.0 Hz), 167.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -160.0. HRMS (ESI-TOF). Calcd for $C_{24}H_{21}FN_3O_7$, $[M+H]^+$ *m/z* 482.1364, Found 482.1355.



(*E*)-dimethyl 2-(1-(2,4-dimethylphenyl)-4-oxo-4-(quinolin-8-ylamino)but-1-en-2-yl)-2-fluoromalonate 4x

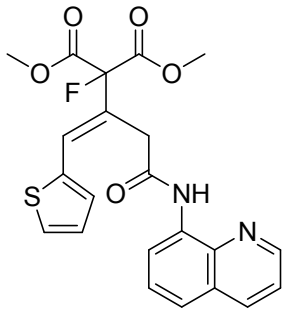
White solid. mp: 70-71 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25 (s, 6H), 3.62 (d, J = 2.0 Hz, 2H), 3.84 (s, 6H), 6.93 (d, J = 7.6 Hz, 1H), 6.97 (s, 1H), 7.23 (s, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.43 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.46-7.52 (m, 2H), 8.13 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.70 (dd, J_1 = 2.4 Hz, J_2 = 6.4 Hz, 1H), 8.77 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 9.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 21.0, 37.1 (d, J = 4.0 Hz), 53.6, 95.2 (d, J = 200.0 Hz), 116.3, 121.5 (d, J = 13.0 Hz), 126.5, 127.3, 127.9, 128.0, 128.2, 128.3, 130.8, 131.5, 134.4 (d, J = 9.0 Hz), 136.2, 136.4, 137.9, 138.3, 148.0, 165.8 (d, J = 26.0 Hz), 167.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.7. HRMS (ESI-TOF). Calcd for $C_{26}H_{26}FN_2O_5$, $[M+H]^+$ *m/z* 465.1826, Found 465.1820.



(*E*)-dimethyl 2-fluoro-2-(4-oxo-4-(quinolin-8-ylamino)-1-(thiophen-3-yl)but-1-en-2-

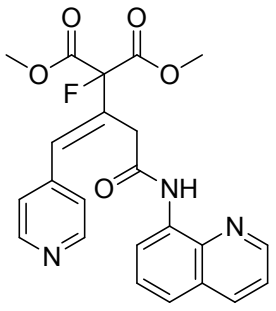
yl)malonate 4y

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 8H), 6.93 (dd, J_1 = 0.8 Hz, J_2 = 8.8 Hz, 1H), 7.21 (s, 1H), 7.26-7.28 (m, 1H), 7.42 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.47-7.53 (m, 3H), 8.12 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.75-8.76 (m, 2H), 10.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.8 (d, J = 4.0 Hz), 53.6, 95.2 (d, J = 201.0 Hz), 116.3, 121.6 (d, J = 5.0 Hz), 125.6, 125.8, 126.0, 126.2, 127.2, 127.8, 128.4, 128.7 (d, J = 12.0 Hz), 134.3, 135.8, 136.1, 138.4, 148.2, 165.6 (d, J = 26.0 Hz), 167.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.3. HRMS (ESI-TOF). Calcd for $C_{22}H_{20}FN_2O_5S$, $[M+H]^+$ *m/z* 443.1077, Found 443.1098.



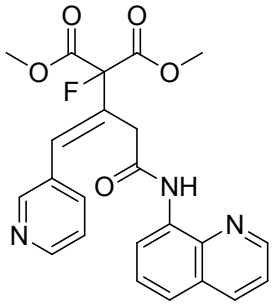
(*E*)-dimethyl 2-fluoro-2-(4-oxo-4-(quinolin-8-ylamino)-1-(thiophen-2-yl)but-1-en-2-yl)malonate 4z

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 6H), 3.97 (s, 2H), 6.99 (dd, J_1 = 3.6 Hz, J_2 = 4.8 Hz, 1H), 7.25 (d, J = 3.2 Hz, 1H), 7.30 (d, J = 5.2 Hz, 1H), 7.39-7.41 (m, 2H), 7.45-7.51 (m, 2H), 8.10 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 8.72-8.75 (m, 2H), 10.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.0 (d, J = 3.0 Hz), 53.7, 95.1 (d, J = 202.0 Hz), 116.3, 121.5, 124.0, 124.2, 126.7, 126.8, 127.2, 127.7, 127.8, 130.4, 134.3, 136.1, 137.4, 138.4, 148.2, 165.5 (d, J = 26.0 Hz), 166.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.3. HRMS (ESI-TOF). Calcd for $C_{22}H_{20}FN_2O_5S$, $[M+H]^+$ *m/z* 443.1077, Found 443.1087.



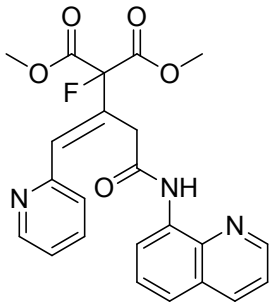
(*E*)-dimethyl 2-fluoro-2-(4-oxo-1-(pyridin-4-yl)-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4aa

White solid. mp: 102-103 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (d, J = 1.6 Hz, 2H), 3.84 (s, 6H), 7.22 (s, 1H), 7.34 (d, J = 6.0 Hz, 2H), 7.46 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 7.51-7.55 (m, 2H), 8.16 (dd, J_1 = 1.6 Hz, J_2 = 7.6 Hz, 1H), 8.56 (dd, J_1 = 1.6 Hz, J_2 = 4.8 Hz, 2H), 8.71 (t, J = 4.4 Hz, 1H), 8.79 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 9.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.1 (d, J = 4.0 Hz), 53.8, 94.6 (d, J = 203.0 Hz), 116.4, 121.8 (d, J = 9.0 Hz), 123.2, 127.3, 127.9, 130.9, 131.1, 131.6 (d, J = 12.0 Hz), 134.1, 136.3, 138.3, 143.1, 148.3, 150.0, 165.3 (d, J = 26.0 Hz), 167.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -160.2. HRMS (ESI-TOF). Calcd for $C_{23}H_{21}FN_3O_5$, $[M+H]^+$ *m/z* 438.1465, Found 438.1449.



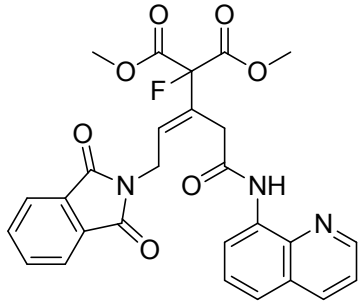
(*E*)-dimethyl 2-fluoro-2-(4-oxo-1-(pyridin-3-yl)-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4ab

White solid. mp: 108-110 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76 (d, J = 1.6 Hz, 2H), 3.84 (s, 6H), 7.24-7.27 (m, 2H), 7.44 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.50-7.51 (m, 2H), 7.83 (d, J = 7.6 Hz, 1H), 8.15 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 8.50 (d, J = 4.0 Hz, 1H), 8.66 (s, 1H), 8.71 (t, J = 4.4 Hz, 1H), 8.78 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 9.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.1 (d, J = 4.0 Hz), 53.8, 94.7 (d, J = 202.0 Hz), 116.3, 121.7 (d, J = 7.0 Hz), 123.3, 127.2, 127.8, 129.9, 130.1, 130.7 (d, J = 12.0 Hz), 131.0, 134.1, 135.8, 136.3, 138.2, 148.2, 149.1, 149.8, 165.3 (d, J = 25.0 Hz), 167.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.8. HRMS (ESI-TOF). Calcd for $C_{23}H_{21}FN_3O_5$, $[M+H]^+$ *m/z* 438.1465, Found 438.1481.



(*E*)-dimethyl 2-fluoro-2-(4-oxo-1-(pyridin-2-yl)-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 4ac

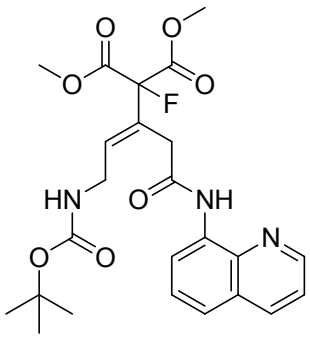
White solid. mp: 165-167 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (s, 6H), 4.26 (s, 2H), 6.99 (s, 1H), 7.23-7.26 (m, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.38 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.43-7.51 (m, 2H), 7.71 (dt, J_1 = 1.6 Hz, J_2 = 7.6 Hz, 1H), 8.10 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.66 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 8.76 (dd, J_1 = 1.2 Hz, J_2 = 7.2 Hz, 1H), 8.88 (d, J = 4.0 Hz, 1H), 11.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.6 (d, J = 3.0 Hz), 53.7, 95.4 (d, J = 200.0 Hz), 116.9, 121.2 (d, J = 5.0 Hz), 122.6, 126.0, 127.3, 128.0, 130.1 (d, J = 11.0 Hz), 132.4, 132.6, 135.6, 136.0, 136.7, 138.9, 147.7, 149.5, 153.8, 165.5 (d, J = 26.0 Hz), 168.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -157.3. HRMS (ESI-TOF). Calcd for $C_{23}H_{20}FN_3O_5Na$, $[M+Na]^+$ *m/z* 460.1285, Found 460.1284.



(*E*)-dimethyl 2-(1-(1,3-dioxoisoindolin-2-yl)-5-oxo-5-(quinolin-8-ylamino)pent-2-en-3-yl)-2-fluoromalonate 4ad

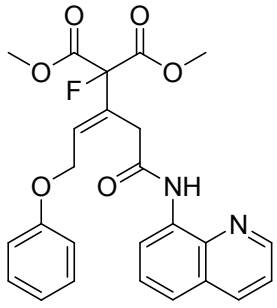
Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 6H), 3.90 (s, 2H), 4.57 (d, J = 7.2 Hz, 2H), 6.34 (t, J = 7.2 Hz, 1H), 7.43 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.48-7.52 (m, 2H), 7.66 (dd, J_1 = 3.2 Hz, J_2 = 5.2 Hz, 2H), 7.76 (dd, J_1 = 3.2 Hz, J_2 = 5.2 Hz, 2H), 8.13 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 8.70 (dd, J_1 = 2.8 Hz, J_2 = 6.0 Hz, 1H), 8.80 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H), 10.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.4, 36.4 (d, J = 3.0 Hz), 53.6, 94.6 (d, J = 201.0 Hz),

116.3, 121.6, 123.2, 127.2, 127.8, 128.8 (d, J = 11.0 Hz), 130.0, 130.2, 132.0, 133.9, 134.2, 136.2, 138.3, 148.3, 165.2 (d, J = 26.0 Hz), 166.9, 167.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.2. HRMS (ESI-TOF). Calcd for $C_{27}H_{23}FN_3O_7$, $[M+H]^+$ *m/z* 520.1520, Found 520.1545.



(*E*)-dimethyl 2-(1-(3,3-dimethylbutanamido)-5-oxo-5-(quinolin-8-ylamino)pent-2-en-3-yl)-2-fluoromalonate 4ae

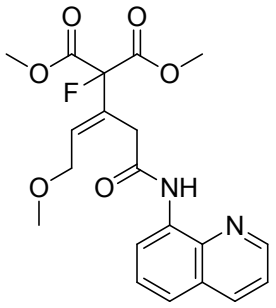
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9H), 3.64 (s, 2H), 3.79 (s, 6H), 4.02 (s, 2H), 5.63 (s, 1H), 6.28 (t, J = 7.2 Hz, 1H), 7.46 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 7.52 (d, J = 4.4 Hz, 2H), 8.16-8.18 (m, 1H), 8.72 (t, J = 4.4 Hz, 1H), 8.87 (d, J = 3.2 Hz, 1H), 9.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 36.1, 38.3, 53.6, 79.4, 94.7 (d, J = 198.0 Hz), 116.7, 121.6, 121.9, 127.2, 127.9, 128.2 (d, J = 18.0 Hz), 132.5 (d, J = 11.0 Hz), 133.9, 136.5, 138.3, 148.5, 155.7, 165.3 (d, J = 26.0 Hz), 166.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.6. HRMS (ESI-TOF). Calcd for $C_{24}H_{29}FN_3O_7$, $[M+H]^+$ *m/z* 490.1990, Found 490.1996.



(*E*)-dimethyl 2-fluoro-2-(5-oxo-1-phenoxy-5-(quinolin-8-ylamino)pent-2-en-3-yl)malonate 4af

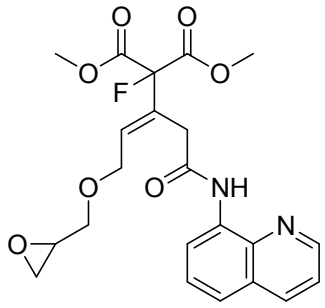
White solid. mp: 118-120 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.67 (s, 2H), 3.81 (s, 6H), 4.85 (dd, J_1 = 1.6 Hz, J_2 = 5.6 Hz, 2H), 6.51 (t, J = 5.6 Hz, 1H), 6.89-6.94 (m, 3H), 7.21-7.26 (m, 2H), 7.45

(dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.50-7.52 (m, 2H), 8.16 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 8.72 (dd, J_1 = 4.0 Hz, J_2 = 5.2 Hz, 1H), 8.80 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H), 10.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.0 (d, J = 3.0 Hz), 53.7, 64.7, 94.7 (d, J = 201.0 Hz), 114.7, 116.4, 121.1, 121.7 (d, J = 12.0 Hz), 127.3, 127.9, 128.0, 128.2, 129.4, 131.8 (d, J = 12.0 Hz), 134.2, 136.3, 138.4, 148.3, 158.2, 165.3 (d, J = 25.0 Hz), 166.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.0. HRMS (ESI-TOF). Calcd for $C_{25}H_{24}FN_2O_6$, $[M+H]^+$ *m/z* 467.1618, Found 467.1612.



(*E*)-dimethyl 2-fluoro-2-(1-methoxy-5-oxo-5-(quinolin-8-ylamino)pent-2-en-3-yl)malonate 4ag

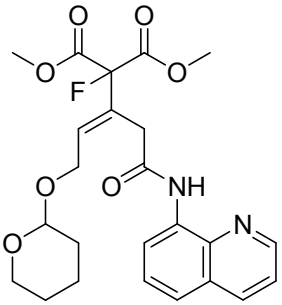
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.36 (s, 3H), 3.62 (s, 2H), 3.81 (s, 6H), 4.25 (dd, J_1 = 2.0 Hz, J_2 = 6.0 Hz, 2H), 6.34 (t, J = 2.0 Hz, 1H), 7.45 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.50-7.52 (m, 2H), 8.15 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 8.72 (dd, J_1 = 3.6 Hz, J_2 = 5.2 Hz, 1H), 8.81 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H), 10.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.9 (d, J = 3.0 Hz), 53.6, 58.5, 69.0, 94.8 (d, J = 200.0 Hz), 116.4, 121.6, 121.7, 127.2, 127.9, 128.0, 132.9 (d, J = 11.0 Hz), 134.3, 136.2, 138.4, 148.2, 165.4 (d, J = 26.0 Hz), 167.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.6. HRMS (ESI-TOF). Calcd for $C_{20}H_{21}FN_2O_6Na$, $[M+Na]^+$ *m/z* 427.1281, Found 427.1272.



(*E*)-dimethyl 2-fluoro-2-(1-(oxiran-2-ylmethoxy)-5-oxo-5-(quinolin-8-ylamino)pent-2-en-3-

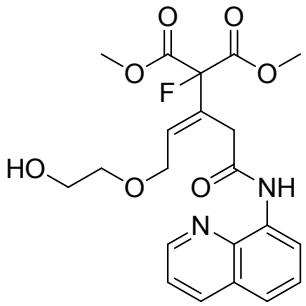
yl)malonate 4ah

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54 (dd, J_1 = 2.4 Hz, J_2 = 5.2 Hz, 1H), 2.71 (t, J = 4.8 Hz, 1H), 3.09-3.11 (m, 1H), 3.38 (dd, J_1 = 6.0 Hz, J_2 = 11.6 Hz, 1H), 3.60 (s, 2H), 3.74 (dd, J_1 = 2.8 Hz, J_2 = 11.6 Hz, 1H), 3.79 (s, 6H), 4.30-4.40 (m, 2H), 6.33 (t, J = 6.0 Hz, 1H), 7.42-7.49 (m, 3H), 8.13 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.69 (t, J = 4.8 Hz, 1H), 8.79 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H), 9.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.8 (d, J = 3.0 Hz), 44.1, 50.5, 53.6, 67.7, 71.2, 94.7 (d, J = 200.0 Hz), 116.3, 121.6 (d, J = 5.0 Hz), 127.2, 127.8, 127.9, 128.1, 132.6 (d, J = 11.0 Hz), 134.2, 136.2, 138.3, 148.2, 165.3 (d, J = 25.0 Hz), 167.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.8. HRMS (ESI-TOF). Calcd for $C_{22}H_{24}FN_2O_7$, $[M+H]^+$ *m/z* 447.1568, Found 447.1561.



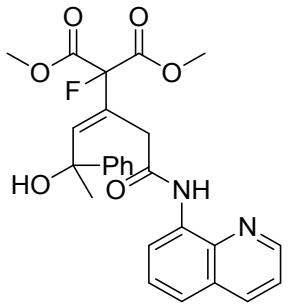
(*E*)-dimethyl 2-fluoro-2-(5-oxo-5-(quinolin-8-ylamino)-1-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-2-en-3-yl)malonate 4ai

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42-1.75 (m, 6H), 3.41-3.44 (m, 1H), 3.57-3.78 (m, 9H), 4.30-4.34 (m, 1H), 4.48-4.53 (m, 1H), 4.62 (t, J = 3.6 Hz, 1H), 6.37 (t, J = 6.0 Hz, 1H), 7.41-7.50 (m, 3H), 8.12 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.69 (dd, J_1 = 3.6 Hz, J_2 = 5.6 Hz, 1H), 8.78 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 9.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 25.2, 30.3, 36.8 (d, J = 3.0 Hz), 53.5, 61.9, 63.5, 94.8 (d, J = 200.0 Hz), 98.0, 116.2, 121.6, 127.2, 127.6, 127.8, 132.7 (d, J = 11.0 Hz), 134.2, 136.2, 138.3, 148.2, 165.4 (d, J = 26.0 Hz), 167.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.8. HRMS (ESI-TOF). Calcd for $C_{24}H_{27}FN_2O_7Na$, $[M+Na]^+$ *m/z* 497.1700, Found 497.1700.



(*E*)-dimethyl 2-fluoro-2-(1-(2-hydroxyethoxy)-5-oxo-5-(quinolin-8-ylamino)pent-2-en-3-yl)malonate 4aj

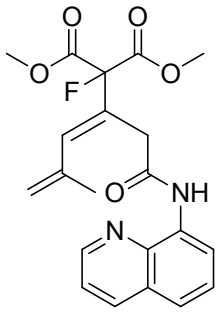
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (s, 1H), 3.53-3.56 (m, 2H), 3.62 (s, 2H), 3.67-3.79 (m, 8H), 4.31 (d, J = 4.4 Hz, 2H), 6.33 (t, J = 6.0 Hz, 1H), 7.43 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 7.48-7.52 (m, 2H), 8.13-8.15 (m, 1H), 8.68-8.79 (m, 2H), 10.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.9 (d, J = 4.0 Hz), 53.6, 61.6, 67.6, 72.1, 94.9 (d, J = 200.0 Hz), 116.5, 121.7 (d, J = 16.0 Hz), 127.2, 127.9, 128.1, 128.3, 132.3 (d, J = 11.0 Hz), 134.2, 136.3, 138.4, 148.3, 165.4 (d, J = 26.0 Hz), 167.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.5. HRMS (ESI-TOF). Calcd for $C_{21}H_{24}FN_2O_7$, $[M+H]^+$ *m/z* 435.1568, Found 435.1584.



(*E*)-dimethyl 2-fluoro-2-(5-hydroxy-1-oxo-5-phenyl-1-(quinolin-8-ylamino)hex-3-en-3-yl)malonate 4ak

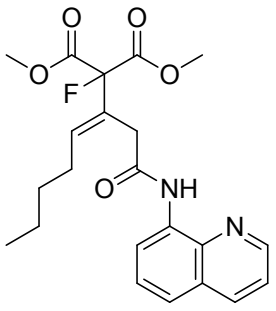
White solid. mp: 96-98 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74 (s, 3H), 3.41 (d, J = 15.2 Hz, 1H), 3.61 (dd, J_1 = 2.0 Hz, J_2 = 15.2 Hz, 1H), 3.77 (d, J = 13.6 Hz, 6H), 5.49 (s, 1H), 6.61 (s, 1H), 7.23 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 7.2 Hz, 2H), 7.45 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.52-7.55 (m, 4H), 8.16 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 8.69 (t, J = 4.4 Hz, 1H), 8.77 (dd, J_1 = 1.2 Hz, J_2 = 4.4 Hz, 1H), 9.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.2, 36.5 (d, J = 4.0 Hz), 53.6, 73.4, 95.4 (d, J = 200.0 Hz), 117.0, 121.7, 122.1, 125.1, 126.7, 126.9 (d, J = 4.0 Hz), 127.3, 127.9, 128.3, 133.9, 136.4, 138.4, 142.5 (d, J = 10.0 Hz), 147.3, 148.4, 165.6 (d, J = 26.0 Hz), 169.4; ^{19}F

NMR (376 MHz, $CDCl_3$): δ = -157.5. HRMS (ESI-TOF). Calcd for $C_{26}H_{25}FN_2O_6Na$, $[M+Na]^+$ *m/z* 503.1594, Found 503.1597.



(*E*)-dimethyl 2-fluoro-2-(5-methyl-1-oxo-1-(quinolin-8-ylamino)hexa-3,5-dien-3-yl)malonate 4al

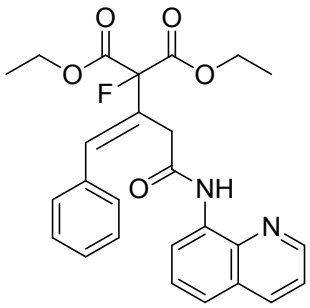
Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.89 (s, 3H), 3.77 (d, J = 1.2 Hz, 2H), 3.80 (s, 6H), 5.11 (s, 1H), 5.17 (s, 1H), 6.63 (s, 1H), 7.44 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 7.48-7.53 (m, 2H), 8.14 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.73 (dd, J_1 = 2.4 Hz, J_2 = 6.4 Hz, 1H), 8.79 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 9.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8, 37.2 (d, J = 4.0 Hz), 53.6, 95.1 (d, J = 201.0 Hz), 116.3, 117.7, 121.5, 121.6, 126.0, 126.2, 127.3, 127.9, 134.4, 136.2 (d, J = 12.0 Hz), 138.4, 139.8, 148.2, 165.7 (d, J = 26.0 Hz), 167.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.1. HRMS (ESI-TOF). Calcd for $C_{21}H_{21}FN_2O_5Na$, $[M+Na]^+$ *m/z* 423.1332, Found 423.1344.



(*E*)-dimethyl 2-fluoro-2-(1-oxo-1-(quinolin-8-ylamino)oct-3-en-3-yl)malonate 4am

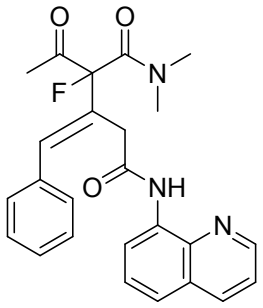
Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, J = 7.2 Hz, 3H), 1.28-1.31 (m, 2H), 1.43-1.51 (m, 2H), 2.27-2.33 (m, 2H), 3.55 (s, 2H), 3.80 (s, 6H), 6.22 (t, J = 7.2 Hz, 1H), 7.43-7.54 (m, 3H), 8.15 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.75 (dd, J_1 = 2.4 Hz, J_2 = 6.4 Hz, 1H), 8.79 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 10.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 22.3, 28.3, 30.8,

36.8 (d, J = 3.0 Hz), 53.5, 95.3 (d, J = 198.0 Hz), 116.3, 121.6, 125.6, 125.8, 127.3, 127.9, 134.4, 136.2, 137.1 (d, J = 11.0 Hz), 138.6, 148.2, 165.8 (d, J = 26.0 Hz), 167.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -157.8. HRMS (ESI-TOF). Calcd for $C_{22}H_{26}FN_2O_5$, $[M+H]^+$ *m/z* 417.1826, Found 417.1831.



(*E*)-diethyl 2-fluoro-2-(4-oxo-1-phenyl-4-(quinolin-8-ylamino)but-1-en-2-yl)malonate 5b

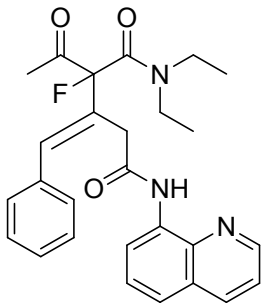
White solid. mp: 121-122 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.2 Hz, 6H), 3.76 (d, J = 1.6 Hz, 2H), 4.25-4.34 (m, 4H), 7.23-7.33 (m, 4H), 7.41-7.53 (m, 5H), 8.13 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 8.74 (dd, J_1 = 2.4 Hz, J_2 = 6.4 Hz, 1H), 8.77 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 10.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 37.4 (d, J = 4.0 Hz), 63.0, 95.1 (d, J = 200.0 Hz), 116.3, 121.5 (d, J = 7.0 Hz), 127.3, 127.8, 128.0, 128.5, 128.7, 134.4, 134.5, 134.6, 135.2, 136.1, 138.4, 148.1, 165.2 (d, J = 26.0 Hz), 167.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -159.0. HRMS (ESI-TOF). Calcd for $C_{26}H_{26}FN_2O_5$, $[M+H]^+$ *m/z* 465.1826, Found 465.1832.



(*E*)-3-benzylidene-4-fluoro-4-(morpholine-4-carbonyl)-5-oxo-*N*-(quinolin-8-yl)hexanamide 5c

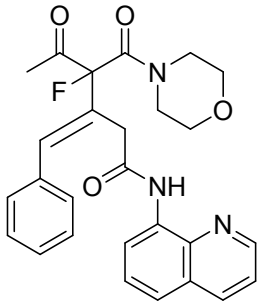
White solid. mp: 178-180 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (d, J = 3.6 Hz, 3H), 2.95 (s, 3H), 3.20 (d, J = 3.2 Hz, 3H), 3.48 (dd, J_1 = 2.0 Hz, J_2 = 16.0 Hz, 1H), 3.74 (d, J = 16.4 Hz, 1H), 6.99 (s, 1H), 7.25-7.35 (m, 3H), 7.42-7.53 (m, 5H), 8.14 (d, J = 8.0 Hz, 1H), 8.73-8.78 (m, 2H),

9.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 36.6, 37.6 (dd, J_1 = 3.0 Hz, J_2 = 7.0 Hz), 102.1 (d, J = 198.0 Hz), 116.2, 121.6 (d, J = 6.0 Hz), 127.2, 127.8, 128.0, 128.2, 128.4, 128.4, 128.6, 134.0 (d, J = 9.0 Hz), 134.4, 135.2, 136.2, 138.2, 148.1, 165.7 (d, J = 21.0 Hz), 168.2, 199.6 (d, J = 30.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -156.2. HRMS (ESI-TOF). Calcd for $C_{25}H_{25}FN_3O_3$, $[M+H]^+$ *m/z* 434.1880, Found 434.1887.



(*E*)-2-acetyl-3-benzylidene-*N*^{1},*N*^{1}-diethyl-2-fluoro-*N*^{5}-(quinolin-8-yl)pentanediamide 5d

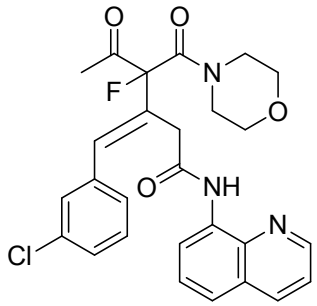
White solid. mp: 128-130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H), 2.40 (d, J = 3.6 Hz, 3H), 3.17-3.25 (m, 2H), 3.41-3.56 (m, 2H), 3.74-3.91 (m, 2H), 6.97 (s, 1H), 7.25-7.35 (m, 3H), 7.42-7.54 (m, 5H), 8.14 (d, J = 8.0 Hz, 1H), 8.71-8.78 (m, 2H), 9.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 13.9 (d, J = 2.0 Hz), 26.1, 37.6 (d, J = 4.0 Hz), 40.9, 42.3 (d, J = 8.0 Hz), 102.3 (d, J = 198.0 Hz), 116.3, 121.6 (d, J = 10.0 Hz), 127.2, 127.9, 128.0, 128.5, 128.6, 128.6, 128.8, 134.1 (d, J = 9.0 Hz), 134.4, 135.3, 136.2, 138.3, 148.1, 165.4 (d, J = 20.0 Hz), 168.2, 199.4 (d, J = 29.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -156.6. HRMS (ESI-TOF). Calcd for $C_{27}H_{28}FN_3O_3Na$, $[M+Na]^+$ *m/z* 484.2012, Found 484.2016.



(*E*)-3-benzylidene-4-fluoro-4-(morpholine-4-carbonyl)-5-oxo-*N*-(quinolin-8-yl)hexanamide 5e

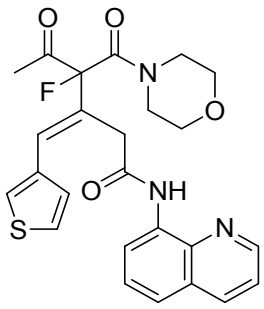
White solid. mp: 153-155 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (d, J = 3.6 Hz, 3H), 3.37 (dd,

J_1 = 2.0 Hz, J_2 = 16.0 Hz, 1H), 3.54-3.92 (m, 9H), 7.00 (d, J = 1.2 Hz, 1H), 7.27-7.37 (m, 3H), 7.43-7.54 (m, 5H), 8.15 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.73 (dd, J_1 = 2.0 Hz, J_2 = 6.0 Hz, 1H), 8.78 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 9.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 37.5 (d, J = 5.0 Hz), 43.0, 46.9 (d, J = 8.0 Hz), 66.5 (d, J = 12.0 Hz), 102.3 (d, J = 196.0 Hz), 116.3, 121.7, 127.2, 127.9, 128.2, 128.4, 128.6, 134.3, 134.7 (d, J = 8.0 Hz), 135.0, 136.3, 138.2, 148.2, 164.6 (d, J = 20.0 Hz), 168.2, 199.3 (d, J = 30.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -157.0. HRMS (ESI-TOF). Calcd for $C_{27}H_{27}FN_3O_4$, $[M+H]^+$ *m/z* 476.1986, Found 476.2000.



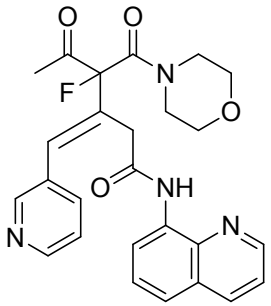
(*E*)-3-(3-chlorobenzylidene)-4-fluoro-4-(morpholine-4-carbonyl)-5-oxo-*N*-(quinolin-8-yl)hexanamide 5f

White solid. mp: 156-157 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (d, J = 3.6 Hz, 3H), 3.36-3.85 (m, 10H), 6.93 (s, 1H), 7.26-7.30 (m, 2H), 7.41-7.56 (m, 5H), 8.16 (d, J = 8.4 Hz, 1H), 8.72 (dd, J_1 = 2.4 Hz, J_2 = 6.0 Hz, 1H), 8.80 (d, J = 4.0 Hz, 1H), 9.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 37.5 (d, J = 4.0 Hz), 43.1, 46.8 (d, J = 9.0 Hz), 66.5 (d, J = 13.0 Hz), 102.0 (d, J = 197.0 Hz), 116.3, 121.7 (d, J = 5.0 Hz), 126.6, 127.2, 127.9, 128.3, 128.7, 129.7, 129.8, 133.0, 133.0, 134.2, 134.5, 136.3, 136.8, 138.2, 148.2, 164.4 (d, J = 21.0 Hz), 167.9, 199.0 (d, J = 30.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -157.1. HRMS (ESI-TOF). Calcd for $C_{27}H_{26}ClFN_3O_4$, $[M+H]^+$ *m/z* 510.1596, Found 510.1599.



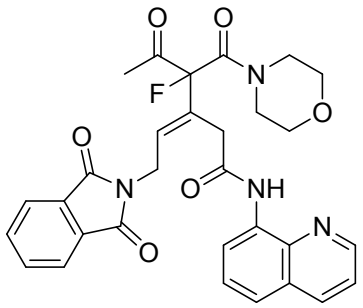
(*E*)-4-fluoro-4-(morpholine-4-carbonyl)-5-oxo-*N*-(quinolin-8-yl)-3-(thiophen-3-ylmethylene)hexanamide 5g

White solid. mp: 182-183 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (d, J = 3.6 Hz, 3H), 3.45-3.84 (m, 10H), 6.92 (s, 1H), 7.21 (d, J = 4.8 Hz, 1H), 7.31 (dd, J_1 = 2.8 Hz, J_2 = 4.8 Hz, 1H), 7.46 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.51-7.56 (m, 2H), 7.61 (d, J = 2.0 Hz, 1H), 8.16 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 8.74 (dd, J_1 = 2.8 Hz, J_2 = 6.0 Hz, 1H), 8.79 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H), 9.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 38.0 (d, J = 4.0 Hz), 43.0, 46.8 (d, J = 9.0 Hz), 66.5 (d, J = 14.0 Hz), 102.3 (d, J = 196.0 Hz), 116.3, 121.7 (d, J = 5.0 Hz), 125.3, 126.0, 127.0 (d, J = 20.0 Hz), 127.2, 127.9, 128.3, 128.7 (d, J = 9.0 Hz), 134.3, 135.8, 136.3, 136.8, 138.2, 148.2, 164.5 (d, J = 20.0 Hz), 168.0, 199.4 (d, J = 30.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -156.0. HRMS (ESI-TOF). Calcd for $C_{25}H_{25}FN_3O_4S$, $[M+H]^+$ *m/z* 482.1550, Found 482.1542.



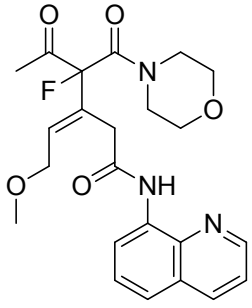
(*E*)-4-fluoro-4-(morpholine-4-carbonyl)-5-oxo-3-(pyridin-3-ylmethylene)-*N*-(quinolin-8-yl)hexanamide 5h

White solid. mp: 117-118 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (d, J = 3.6 Hz, 3H), 3.43-3.86 (m, 10H), 6.96 (s, 1H), 7.27-7.30 (m, 1H), 7.46 (dd, J_1 = 4.0 Hz, J_2 = 8.4 Hz, 1H), 7.52-7.56 (m, 2H), 7.92 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 8.53 (d, J = 3.6 Hz, 1H), 8.70-8.72 (m, 2H), 8.79 (d, J = 2.8 Hz, 1H), 9.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 37.5 (d, J = 4.0 Hz), 43.0, 46.7 (d, J = 9.0 Hz), 66.4 (d, J = 15.0 Hz), 101.9 (d, J = 198.0 Hz), 116.3, 121.7 (d, J = 11.0 Hz), 123.3, 127.2, 127.8, 130.5, 130.6 (d, J = 2.0 Hz), 130.8, 130.9, 134.1, 135.6, 136.3, 138.1, 148.2, 149.2, 149.7, 164.2 (d, J = 20.0 Hz), 167.7, 198.9 (d, J = 30.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -156.9. HRMS (ESI-TOF). Calcd for $C_{26}H_{26}FN_4O_4$, $[M+H]^+$ *m/z* 477.1938, Found 477.1919.



(*E*)-3-(2-(1,3-dioxoisoindolin-2-yl)ethylidene)-4-fluoro-4-(morpholine-4-carbonyl)-5-oxo-*N*-(quinolin-8-yl)hexanamide 5i

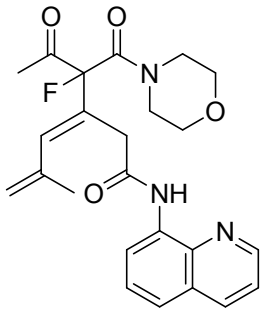
White solid. mp: 97-98 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (d, J = 3.6 Hz, 3H), 3.46-3.66 (m, 9H), 3.85-3.89 (m, 1H), 4.55-4.59 (m, 2H), 6.12 (t, J = 7.2 Hz, 1H), 7.43-7.50 (m, 3H), 7.66-7.69 (m, 2H), 7.75-7.78 (m, 2H), 8.14 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.60 (dd, J_1 = 2.8 Hz, J_2 = 6.4 Hz, 1H), 8.80 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H), 9.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 35.4, 36.3 (d, J = 4.0 Hz), 42.9, 46.5 (d, J = 9.0 Hz), 66.3 (d, J = 20.0 Hz), 101.1 (d, J = 199.0 Hz), 116.2, 121.6, 123.2, 127.1, 127.8, 128.2 (d, J = 10.0 Hz), 130.8, 131.0, 131.9, 133.9, 134.2, 136.1, 138.2, 148.2, 164.0 (d, J = 21.0 Hz), 167.0, 167.6, 199.0 (d, J = 29.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -157.4. HRMS (ESI-TOF). Calcd for $C_{30}H_{28}FN_4O_6$, $[M+H]^+$ *m/z* 559.1993, Found 559.1979.



(*E*)-4-fluoro-3-(2-methoxyethylidene)-4-(morpholine-4-carbonyl)-5-oxo-*N*-(quinolin-8-yl)hexanamide 5j

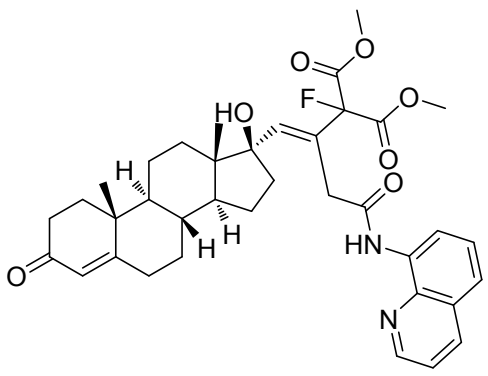
White solid. mp: 120-124 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (d, J = 3.6 Hz, 3H), 3.36-3.40 (m, 4H), 3.53-3.63 (m, 9H), 4.24 (d, J = 4.4 Hz, 2H), 6.10 (t, J = 5.6 Hz, 1H), 7.43-7.53 (m, 3H), 8.14 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.66-8.69 (m, 1H), 8.79 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 9.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8, 36.9 (d, J = 4.0 Hz), 42.9, 46.6 (d, J = 10.0 Hz), 58.5, 66.3 (d, J = 25.0 Hz), 69.0, 101.3 (d, J = 198.0 Hz), 116.3, 121.7 (d, J = 8.0 Hz), 127.2,

127.9, 128.6, 128.8, 132.1 (d, J = 8.0 Hz), 134.3, 136.3, 138.3, 148.2, 164.1 (d, J = 21.0 Hz), 167.2, 199.3 (d, J = 30.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -157.0. HRMS (ESI-TOF). Calcd for $C_{23}H_{27}FN_3O_5$, $[M+H]^+$ *m/z* 444.1935, Found 444.1951.



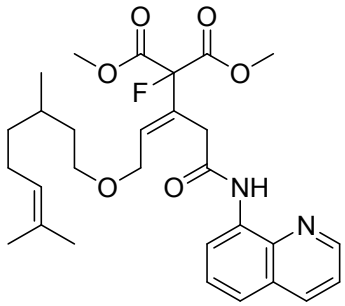
(*E*)-3-(2-fluoro-1-morpholino-1,3-dioxobutan-2-yl)-5-methyl-*N*-(quinolin-8-yl)hexa-3,5-dienamide 5k

White solid. mp: 149-151 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.92 (s, 3H), 2.37 (d, J = 4.0 Hz, 3H), 3.35-3.81 (m, 10H), 5.12 (s, 1H), 5.25 (s, 1H), 6.33 (s, 1H), 7.44-7.54 (m, 3H), 8.15 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.69 (dd, J_1 = 2.8 Hz, J_2 = 6.4 Hz, 1H), 8.79 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 9.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8, 26.1, 37.4 (d, J = 4.0 Hz), 43.0, 46.8 (d, J = 9.0 Hz), 66.5 (d, J = 17.0 Hz), 102.2 (d, J = 196.0 Hz), 116.3, 117.6, 121.6 (d, J = 11.0 Hz), 126.7, 126.9, 127.3, 127.9, 134.4, 136.3, 136.4, 138.2, 139.8, 148.2, 164.6 (d, J = 20.0 Hz), 168.2, 199.4 (d, J = 30.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -157.0. HRMS (ESI-TOF). Calcd for $C_{24}H_{27}FN_3O_4$, $[M+H]^+$ *m/z* 440.1986, Found 440.1992.



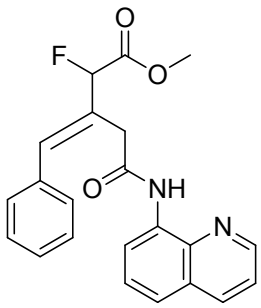
dimethyl 2-fluoro-2-((*E*)-1-((8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-hydroxy-10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)-5-oxo-5-(quinolin-8-ylamino)pent-2-en-3-yl)malonate 7

White solid. mp: 177-178 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84-1.04 (m, 5H), 1.19 (s, 3H), 1.24-1.49 (m, 4H), 1.58-1.73 (m, 5H), 1.85-2.08 (m, 4H), 2.29-2.42 (m, 4H), 3.69-3.98 (s, 8H), 4.87 (s, 1H), 5.72 (s, 1H), 6.24 (s, 1H), 7.46 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 7.50-7.53 (m, 2H), 8.16 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 8.67 (dd, J_1 = 2.8 Hz, J_2 = 6.0 Hz, 1H), 8.81 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 10.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 17.4, 20.7, 23.8, 31.7, 31.9, 32.8, 33.9, 35.7, 36.4, 36.9 (d, J = 4.0 Hz), 38.6, 39.3, 48.3, 50.8, 53.5, 53.8, 84.1, 95.5 (d, J = 200.0 Hz), 117.0, 121.7, 122.1, 123.9, 124.6, 124.8, 127.2, 127.9, 134.0, 136.4, 138.4, 140.2 (d, J = 10.0 Hz), 148.4, 165.8 (dd, J_1 = 6.0 Hz, J_2 = 26.0 Hz), 170.6 (d, J = 100.0 Hz), 199.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -156.6. HRMS (ESI-TOF). Calcd for $C_{37}H_{44}FN_2O_7$, $[M+H]^+$ *m/z* 647.3133, Found 647.3121.



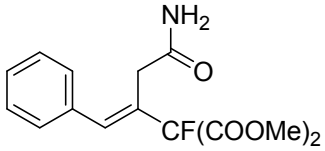
(*E*)-dimethyl 2-(1-((3,7-dimethyloct-6-en-1-yl)oxy)-5-oxo-5-(quinolin-8-ylamino)pent-2-en-3-yl)-2-fluoromalonate 9

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (d, J = 6.4 Hz, 3H), 1.04-1.11 (m, 1H), 1.23-1.34 (m, 2H), 1.43-1.51 (m, 1H), 1.53-1.61 (m, 4H), 1.65 (s, 3H), 1.83-1.95 (m, 2H), 3.42-3.47 (m, 2H), 3.61 (s, 2H), 3.79 (s, 6H), 4.26-4.28 (m, 2H), 5.03 (t, J = 7.2 Hz, 1H), 6.34 (t, J = 6.0 Hz, 1H), 7.41-7.49 (m, 3H), 8.13 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.71 (dd, J_1 = 3.2 Hz, J_2 = 5.6 Hz, 1H), 8.79 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 10.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 19.3, 25.3, 25.6, 29.4, 36.4, 36.9 (d, J = 3.0 Hz), 53.5, 67.4, 69.3, 94.8 (d, J = 200.0 Hz), 116.3, 121.6 (d, J = 3.0 Hz), 124.7, 127.2, 127.3, 127.5, 127.8, 131.0, 133.3 (d, J = 11.0 Hz), 134.3, 136.2, 138.4, 148.2, 165.4 (d, J = 26.0 Hz), 167.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.6. HRMS (ESI-TOF). Calcd for $C_{29}H_{38}FN_2O_6$, $[M+H]^+$ *m/z* 529.2714, Found 529.2730.



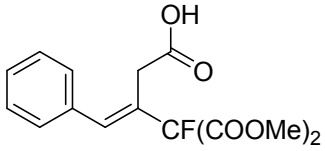
(*E*)-methyl 3-benzylidene-2-fluoro-5-oxo-5-(quinolin-8-ylamino)pentanoate 10

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66 (dd, J_1 = 16.0 Hz, J_2 = 20.0 Hz, 2H), 3.77 (s, 3H), 5.59 (d, J = 47.6 Hz, 1H), 7.15 (s, 1H), 7.29-7.37 (m, 3H), 7.44-7.56 (m, 5H), 8.16 (d, J = 8.0 Hz, 1H), 8.76-8.80 (m, 2H), 10.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.5, 52.7, 91.5 (d, J = 185.0 Hz), 116.5, 121.7 (d, J = 6.0 Hz), 127.3, 127.9, 128.2, 128.6, 128.7, 128.7, 134.3, 135.1, 136.0, 136.1, 136.3, 138.4, 148.2, 167.9, 168.5 (d, J = 27.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -183.3. HRMS (ESI-TOF). Calcd for $C_{22}H_{20}FN_2O_3$, $[M+H]^+$ *m/z* 379.1458, Found 379.1467.



(*E*)-dimethyl 2-(4-amino-4-oxo-1-phenylbut-1-en-2-yl)-2-fluoromalonate 11

Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.40 (s, 2H), 3.89 (s, 6H), 5.75 (d, J = 77.2 Hz, 2H), 7.06 (s, 1H), 7.31-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.5 (d, J = 4.0 Hz), 53.8, 95.4 (d, J = 199.0 Hz), 127.6 (d, J = 20.0 Hz), 128.4, 128.6, 128.8, 134.7 (d, J = 8.0 Hz), 134.8, 165.8 (d, J = 26.0 Hz), 171.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -158.0. HRMS (ESI-TOF). Calcd for $C_{15}H_{17}FNO_5$, $[M+H]^+$ *m/z* 310.1091, Found 310.1095.

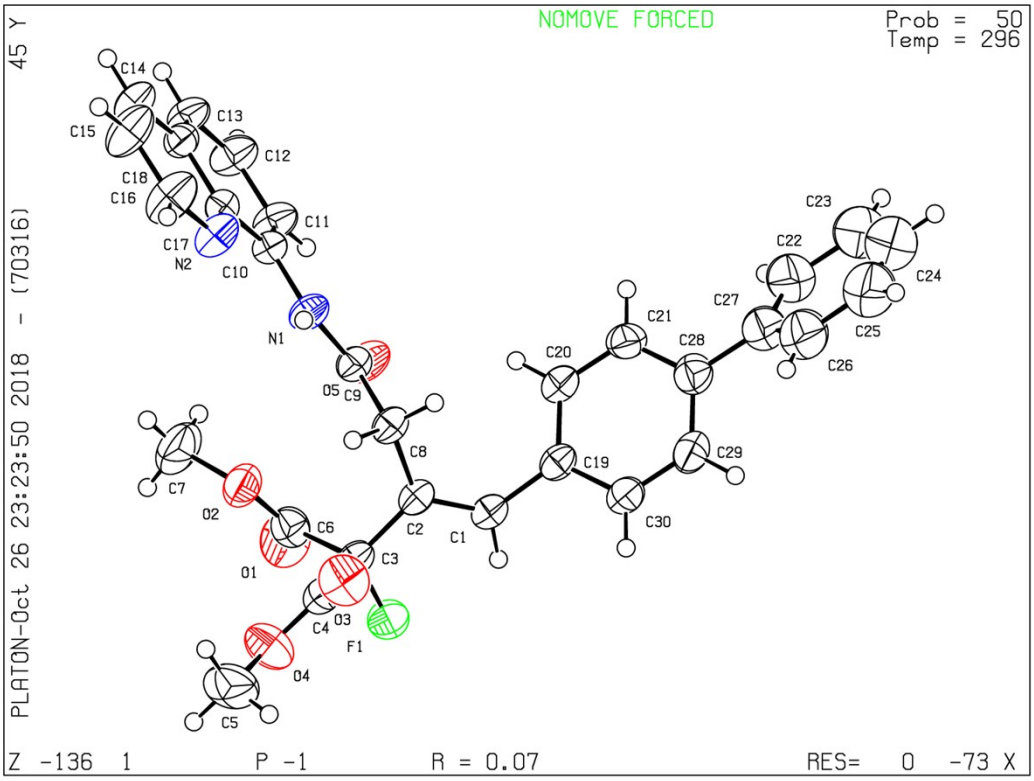


(*E*)-3-benzylidene-4-fluoro-5-methoxy-4-(methoxycarbonyl)-5-oxopentanoic acid 12

Pale yellow oil. ^{1}H NMR (400 MHz, DMSO): δ = 3.44 (s, 2H), 3.81 (s, 6H), 6.94 (s, 1H), 7.33-7.36 (m, 3H), 7.41 (t, J = 7.2 Hz, 2H), 12.59 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ = 34.3 (d, J = 4.0 Hz), 54.2, 95.6 (d, J = 198.0 Hz), 127.8, 128.0, 128.7, 129.0, 132.9 (d, J = 11.0 Hz), 135.2,

165.6 (d, J = 26.0 Hz), 171.9; ^{19}F NMR (376 MHz, DMSO): δ = -158.0. HRMS (ESI-TOF). Calcd for $C_{15}H_{16}FO_6$, $[M+H]^+$ *m/z* 311.0931, Found 311.0928.

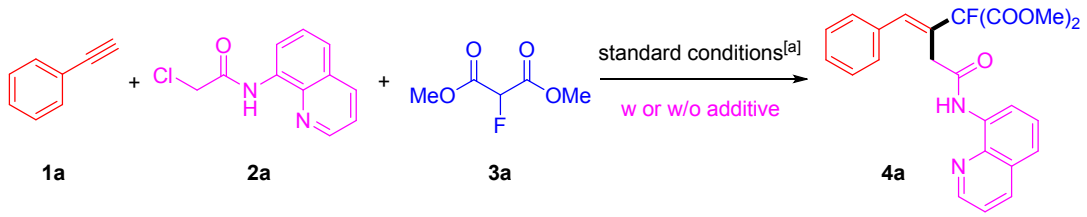
7. Structure Analysis X-Ray Crystallography of 4k



Compound	**4k**
Empirical formula	$C_{30}H_{25}FN_2O_5$
Formula weight	512.52
Crystal system	Triclinic
Space group	P-1
a (Å)	10.0079(5)
b (Å)	11.0103(5)
c (Å)	13.8154(7)
α (°)	68.117(3)
β (°)	74.662(4)
γ (°)	67.141(3)
V (Å3)	1288.87(12)
Z	2
D/g cm-3	1.321
μ/mm-1	0.095
F(000)	536.0
Reflns number	13223
R_{int}	0.0290
R_1	0.0659
GOF	1.087
wR_2 (all data)	0.1960

8. Mechanistic Study

8.1 Radical Inhibition Experiments

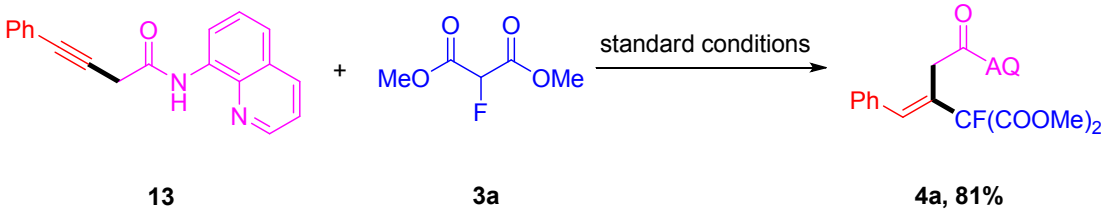


Additive	**4a**, yield (%)[b]
none	94%
BHT (2 equiv)	86%
TEMPO (2 equiv)	80%

[a] Standard conditions: **1a** (0.33 mmol), **2a** (0.3 mmol), **3a** (0.45 mmol), CuI (10 mol %), and Cs_2CO_3 (0.36 mmol) in THF (0.9 mL) under N_2 atmosphere at 80 °C for 1.5 h. [b] Yield of the isolated product.

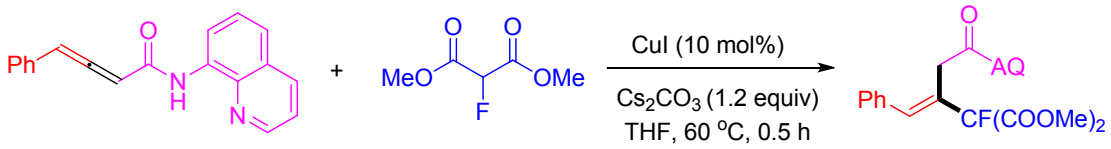
8.2 Control Experiment

To probe the reaction mechanism, compounds **13** and **14** were prepared as possible reaction intermediate, and reacted with another coupling partner under the standard reaction conditions. We conducted the following experiments.



Following the general procedure 4, to a solution of **13** (85.9 mg, 0.3 mmol) in THF (0.9 mL) was added **3a** (70.4 mg, 0.45 mmol), CuI (5.7 mg, 0.03 mmol), and Cs_2CO_3 (117.3 mg, 0.36 mmol) under N_2 in screw-cap test tube. The reaction mixture was stirred at 80 °C for 1.5 h. After the reaction finished, the reaction mixture was cooled to room temperature and quenched by water. The mixture was extracted with EtOAc (3.0 mL×3), the combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The residue was purified by column chromatography to give the corresponding products **4a** (106.0 mg, 81%). This result

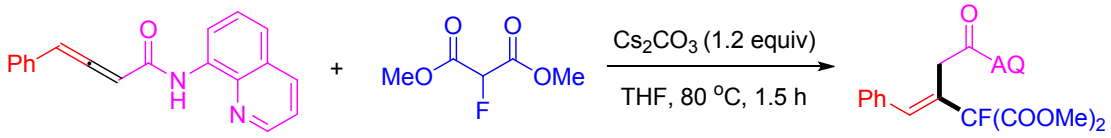
suggested that **13** might be the active intermediate.



14 **3a** **4a, 89%**

Following the general procedure 4, to a solution of **14** (85.9 mg, 0.3 mmol) in THF (0.9 mL) was added **3a** (70.4 mg, 0.45 mmol), CuI (5.7 mg, 0.03 mmol), and Cs_2CO_3 (117.3 mg, 0.36 mmol) under N_2 in screw-cap test tube. The reaction mixture was stirred at 60 °C for 0.5 h. After the reaction finished, the reaction mixture was cooled to room temperature and quenched by water. The mixture was extracted with EtOAc (3.0 mL×3), the combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The residue was purified by column chromatography to give the corresponding products **4a** (117.0 mg, 89%). This result suggested that **14** might be the active intermediate.

To further clarify the reaction mechanism, the reaction of **14** with **3a** in the absence of CuI was conducted.



14 **3a** **4a, 90%**

Following the general procedure 4, to a solution of **14** (85.9 mg, 0.3 mmol) in THF (0.9 mL) was added **3a** (70.4 mg, 0.45 mmol), and Cs_2CO_3 (117.3 mg, 0.36 mmol) under N_2 in screw-cap test tube. The reaction mixture was stirred at 80 °C for 1.5 h. After the reaction finished, the reaction mixture was cooled to room temperature and quenched by water. The mixture was extracted with EtOAc (3.0 mL×3), the combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The residue was purified by column chromatography to give the corresponding products **4a** (117.5 mg, 90%). This result suggested that the presence of CuI has no obvious effect on this step.

9. References

[1] T. Vilaivan, *Tetrahedron Lett*., 2006, **47**, 6739.

[2] J. Bi, Z. Zhang, Q. Liu and G. Zhang, *Green Chem*., 2012, **14**, 1159.

[3] J. Li, D. Ding, L. Liu and J. Sun, *RSC Adv*., 2013, **3**, 21260.

[4] (a) J. Dubois, C. Foures, S. Bory, S. Falcou, M. Gaudry and A. Marquet, *Tetrahedron* 1991, **47**, 1001; (b) K. Kwon, S. M. Kim and D. Y. Kim, *J. Fluorine Chem*., 2009, **130**, 759; (c) E. Lisse and G. Sandford, *J. Fluorine Chem*., 2018, **206**, 117; (d) A. Harsanyi and G. Sandford, *Green Chem*., 2015, **17**, 3000; (e) A. Harsanyi and G. Sandford, *Org. Process Res. Dev*., 2014, **18**, 981.

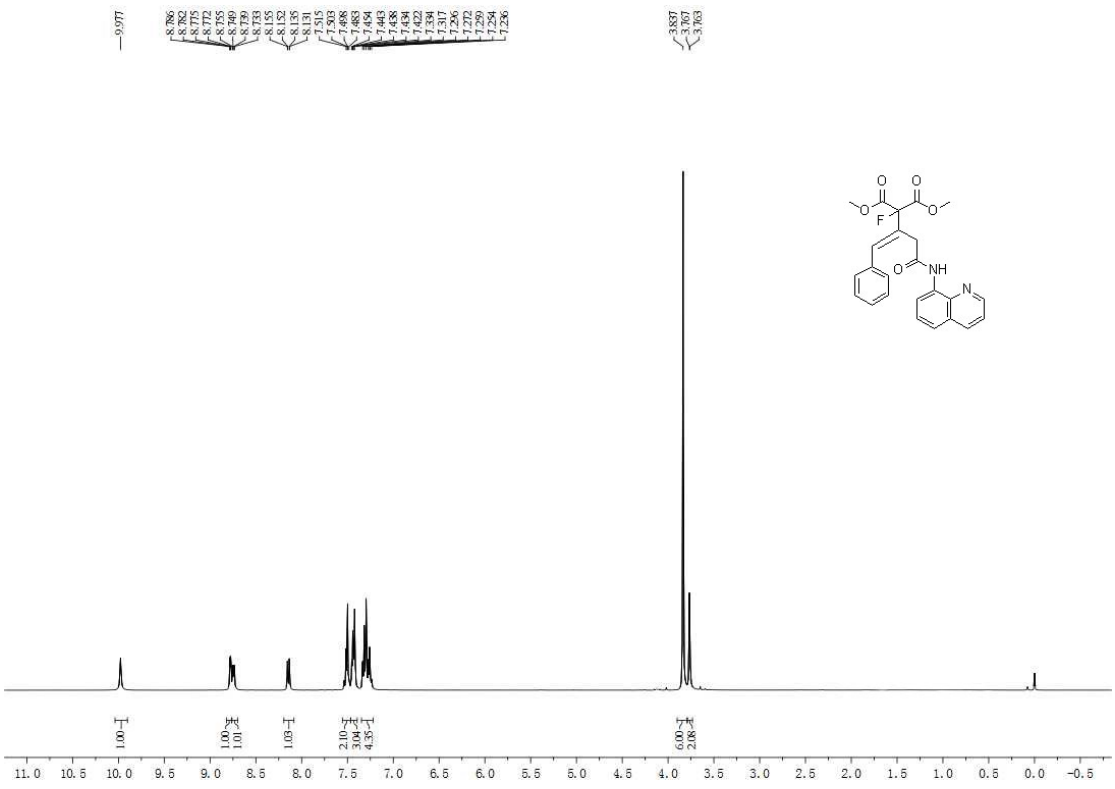
[5] F. Zhu, P.-W. Xu, F. Zhou, C.-H. Wang and J. Zhou, *Org. Lett*., 2015, **17**, 972.

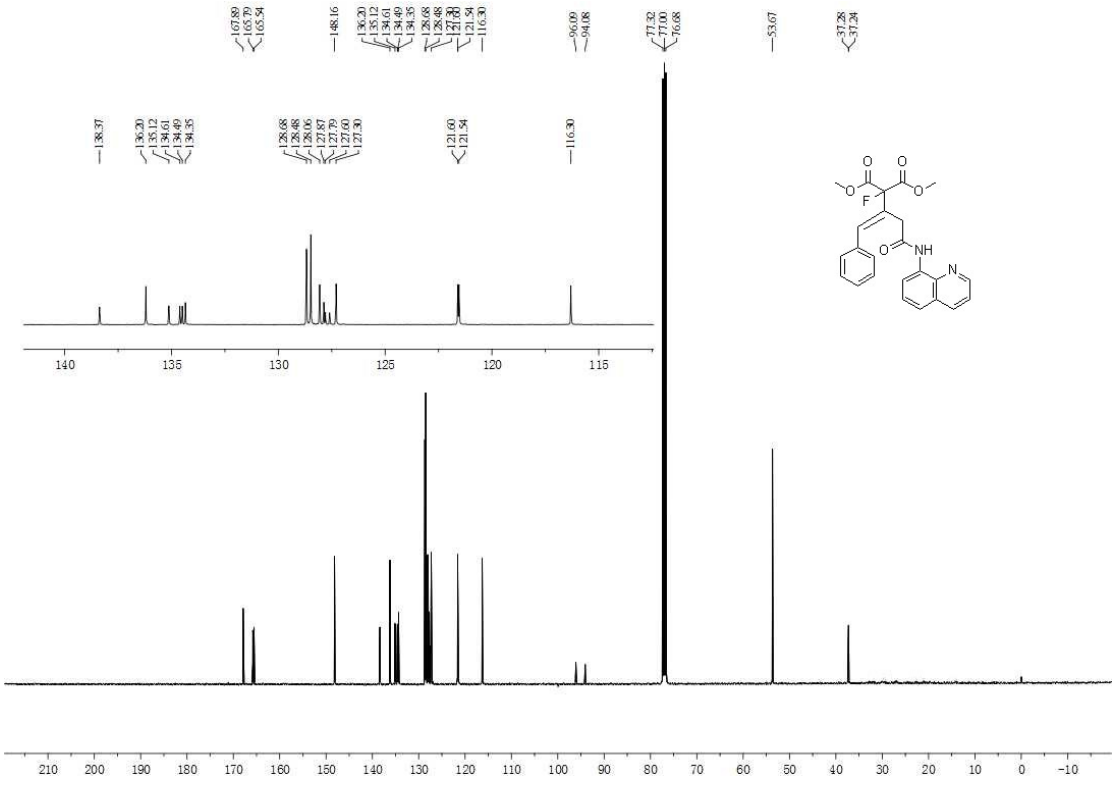
[6] Z. Zhang, X. Li, M. Song, Y. Wan, D. Zheng, G. Zhang and G. Chen, *J. Org. Chem.*, 2019, **84**, 12792.

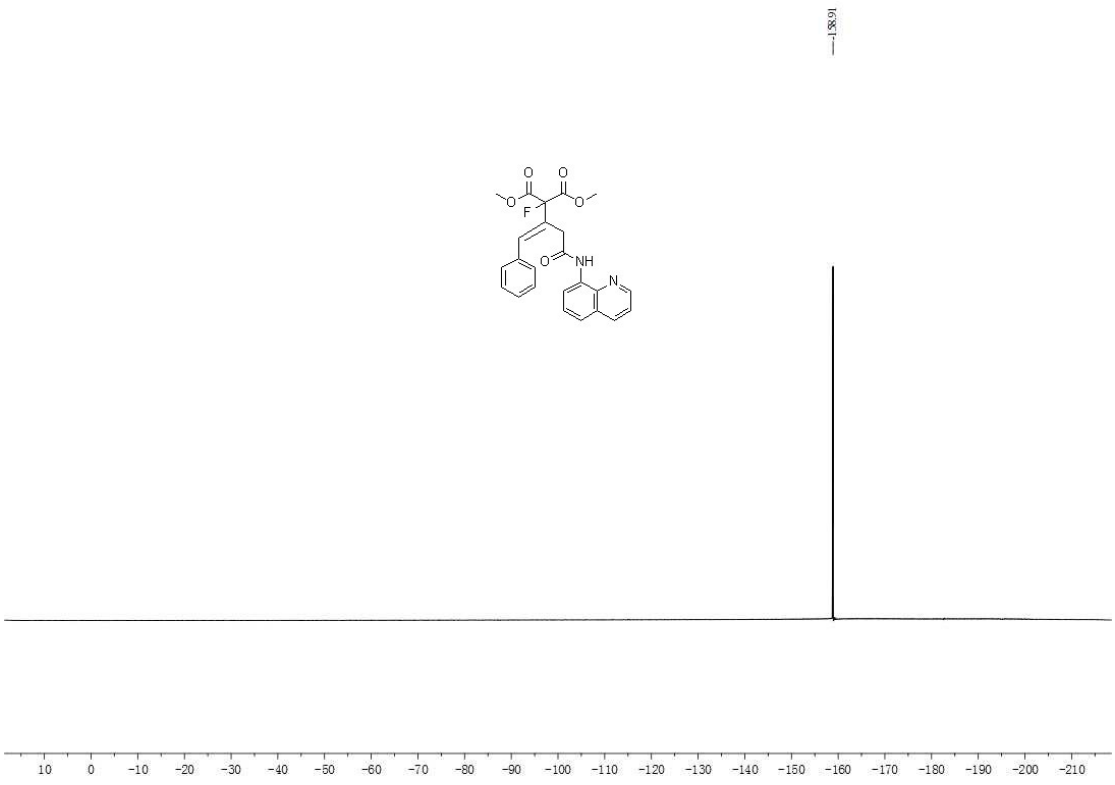
[7] P. Chaudhary, S. Gupta, N. Muniyappan, S. Sabiah and J. Kandasamy, *Green Chem*., 2016, **18**, 2323.

10. ^{1}H, ^{13}C and ^{19}F NMR Spectra of Compounds 4, 5, 7, 9-12

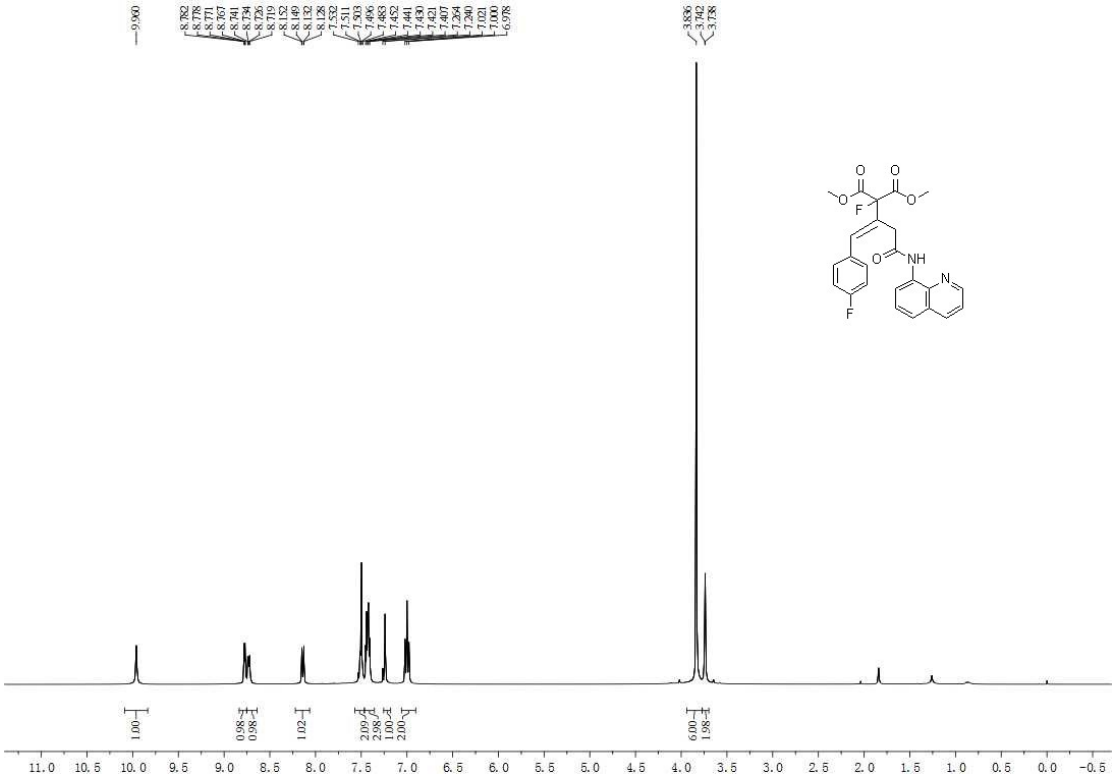
Product 4a

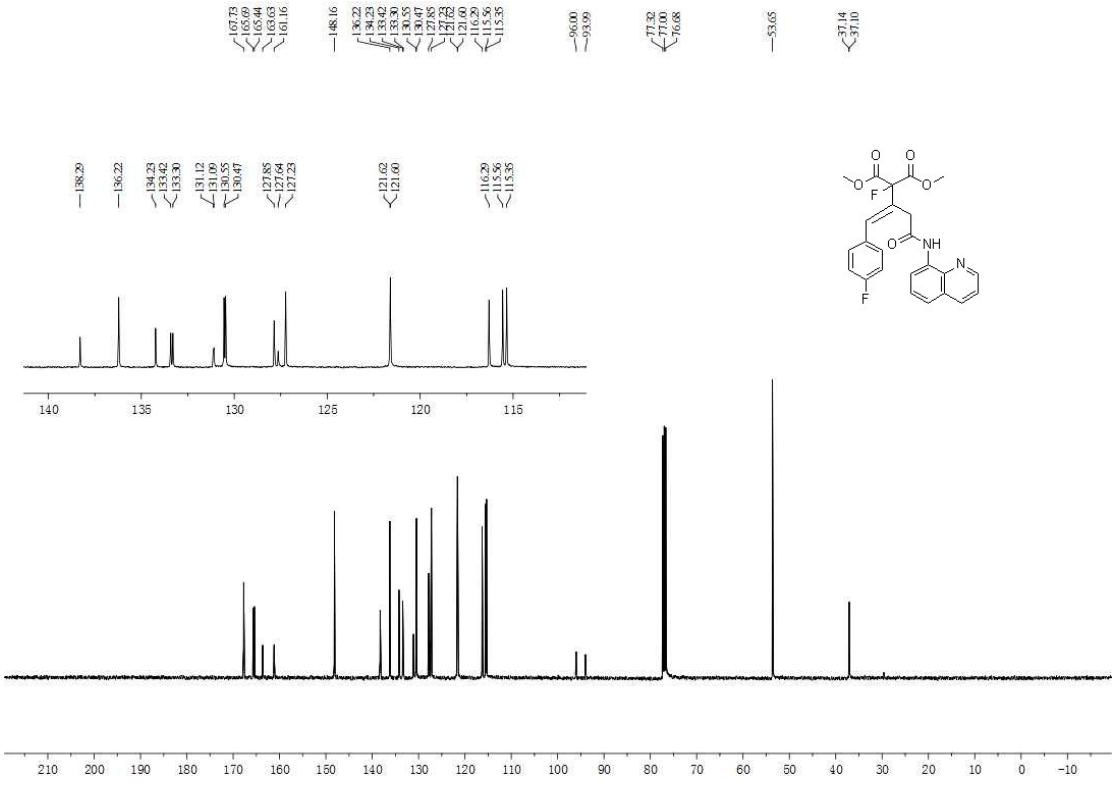


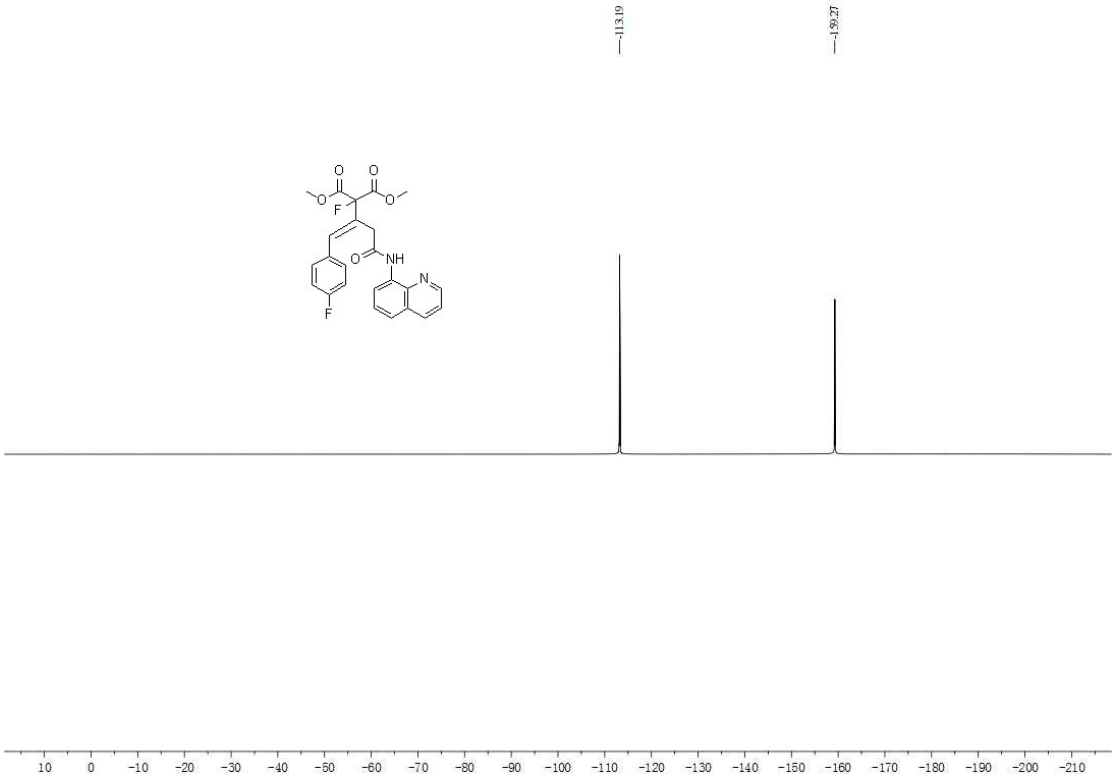



-138.91
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

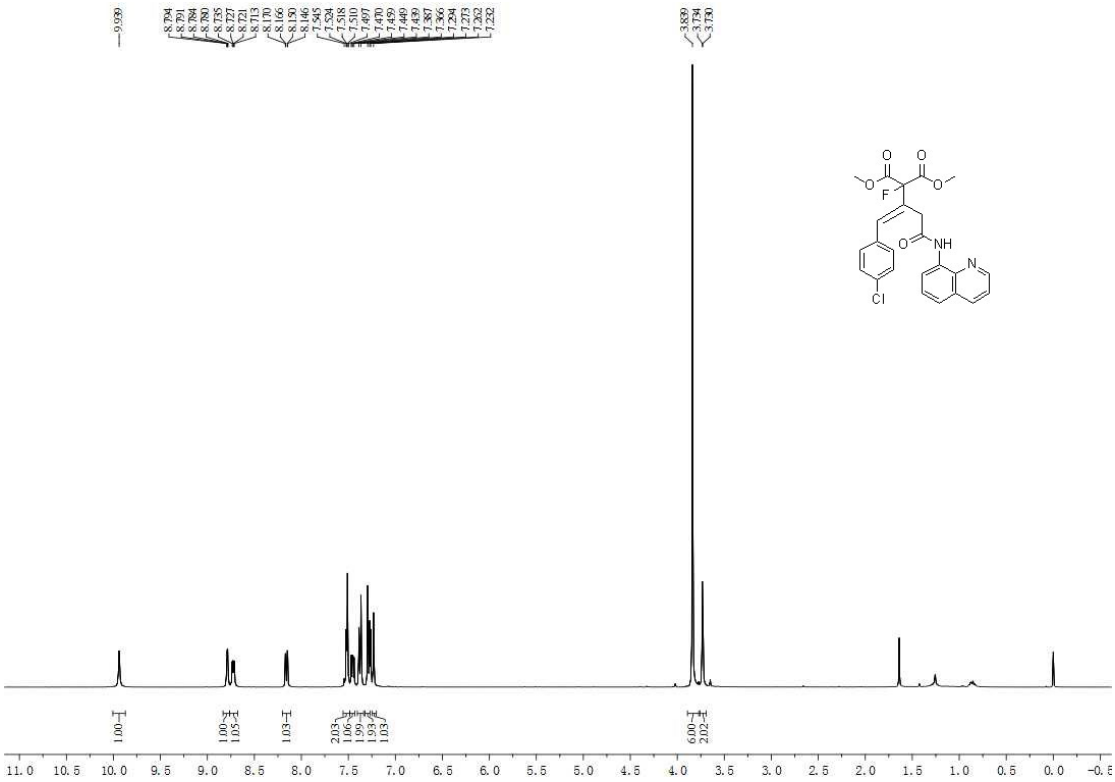
Product 4b

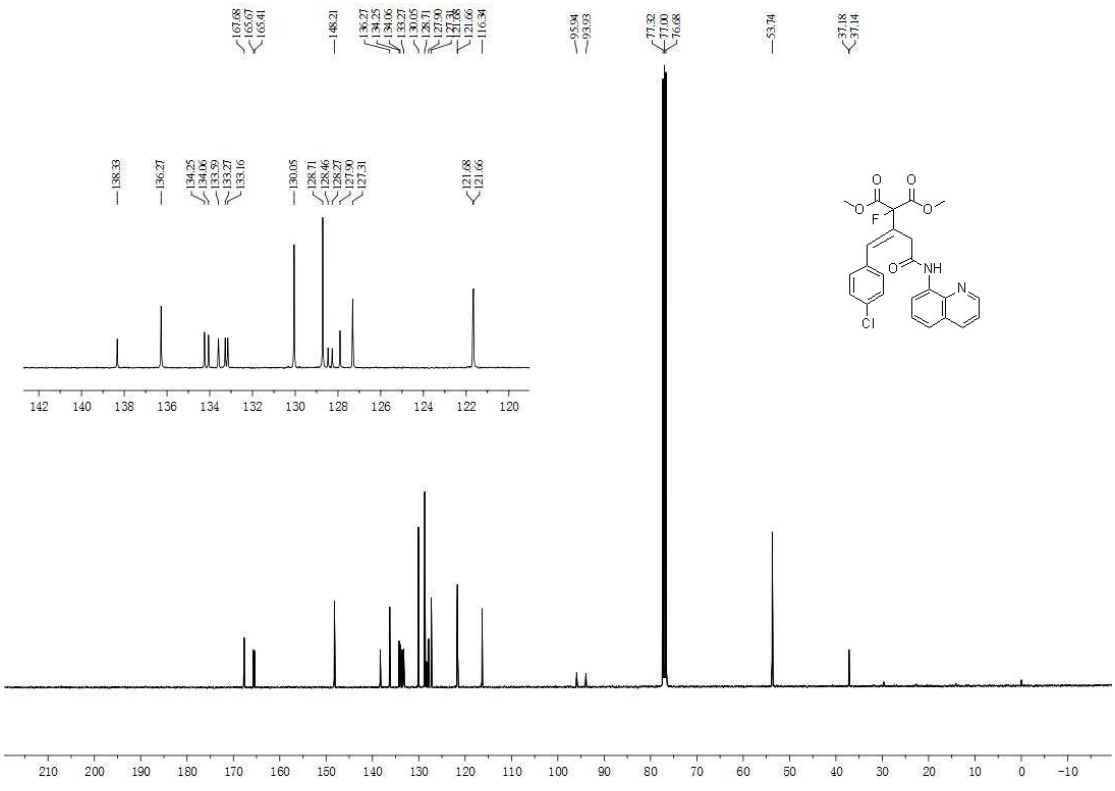

9.900
8.782
8.776
8.771
8.767
8.741
8.734
8.726
8.719
8.152
8.149
8.132
8.128
7.532
7.511
7.503
7.496
7.483
7.452
7.444
7.430
7.421
7.407
7.264
7.240
7.021
7.000
6.978
3.836
3.742
3.738
1.00
0.98
0.98
1.02
2.09
2.98
1.00
2.00
6.00
1.98
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

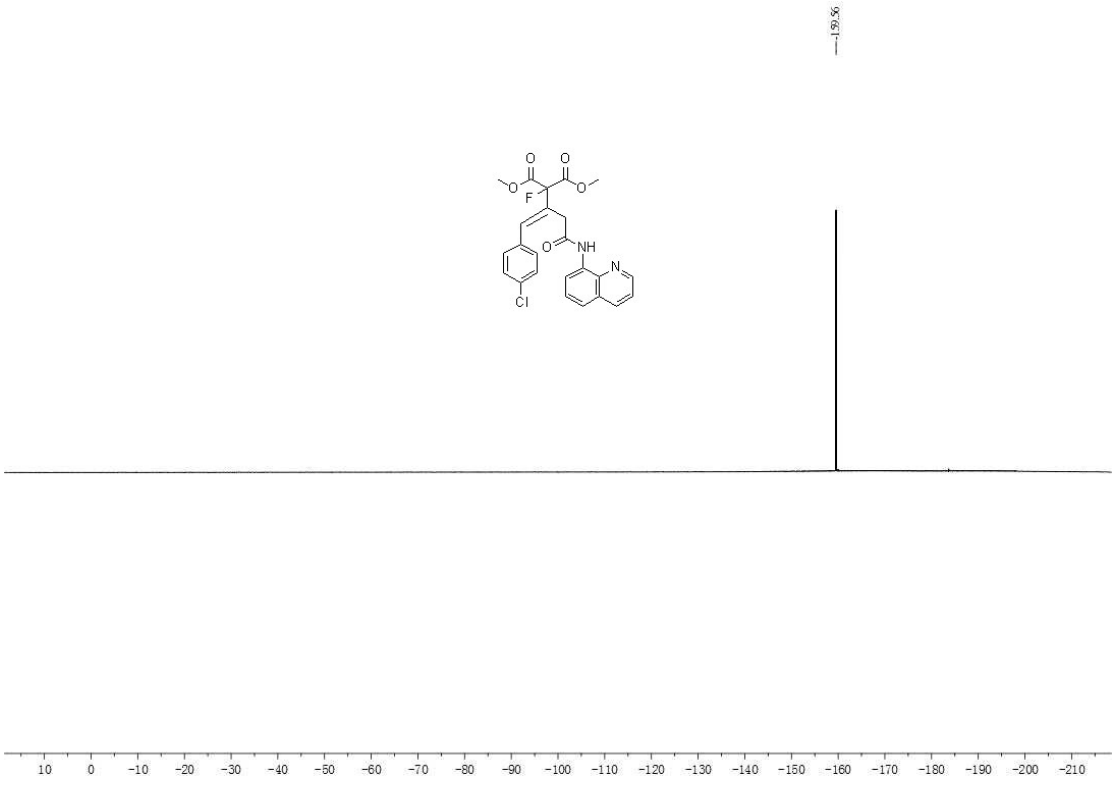

167.73
165.69
165.44
163.63
161.16
148.16
136.22
134.23
133.42
133.30
131.12
131.09
130.55
130.47
127.85
127.64
127.23
121.62
121.60
116.29
115.56
115.35
96.00
93.99
77.32
77.00
76.68
53.65
37.14
37.10
O
O
O
O
F
O
NH
N
F
140
135
130
125
120
115
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


113.19
159.27
O
O
O
O
F
O
NH
N
F
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210

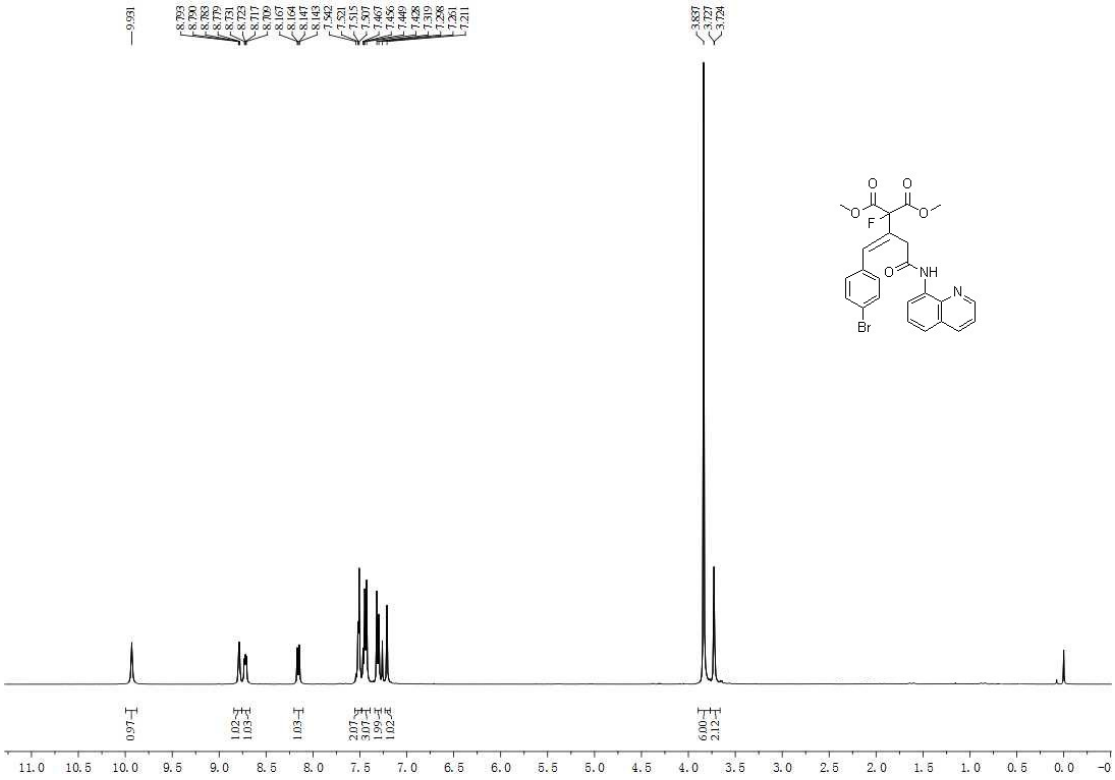
Product 4c

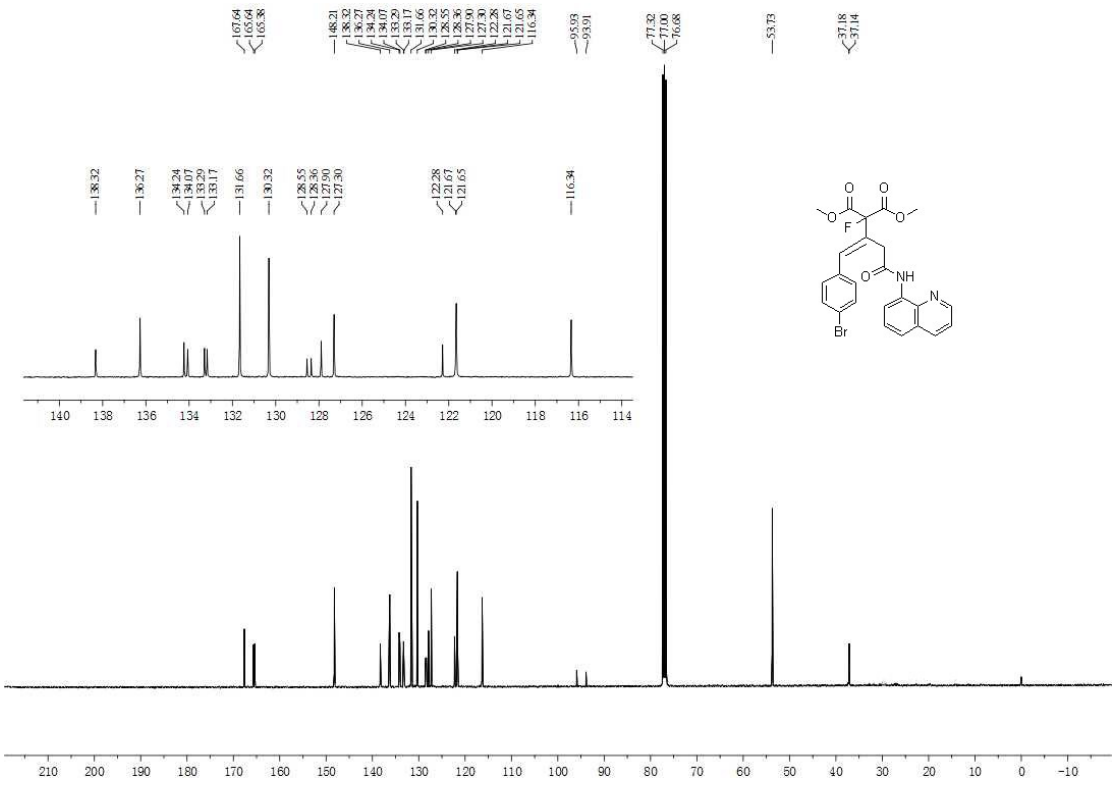


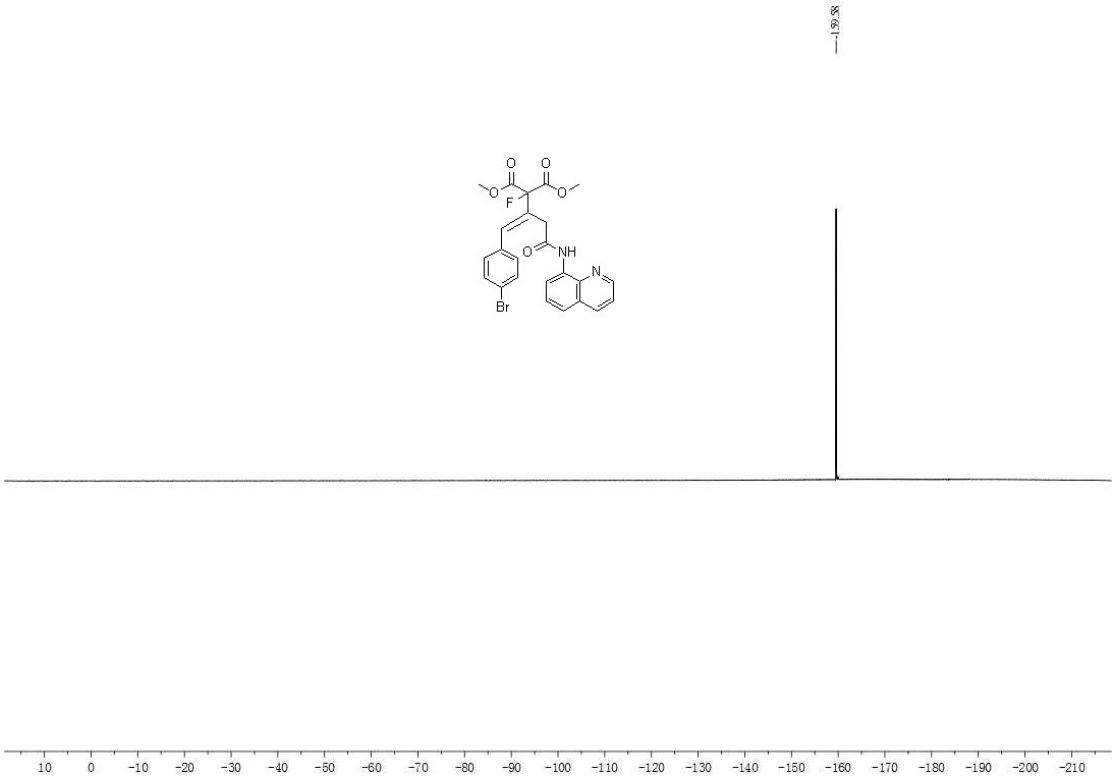



-159.56
O
O
O
O
F
O
NH
N
Cl
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

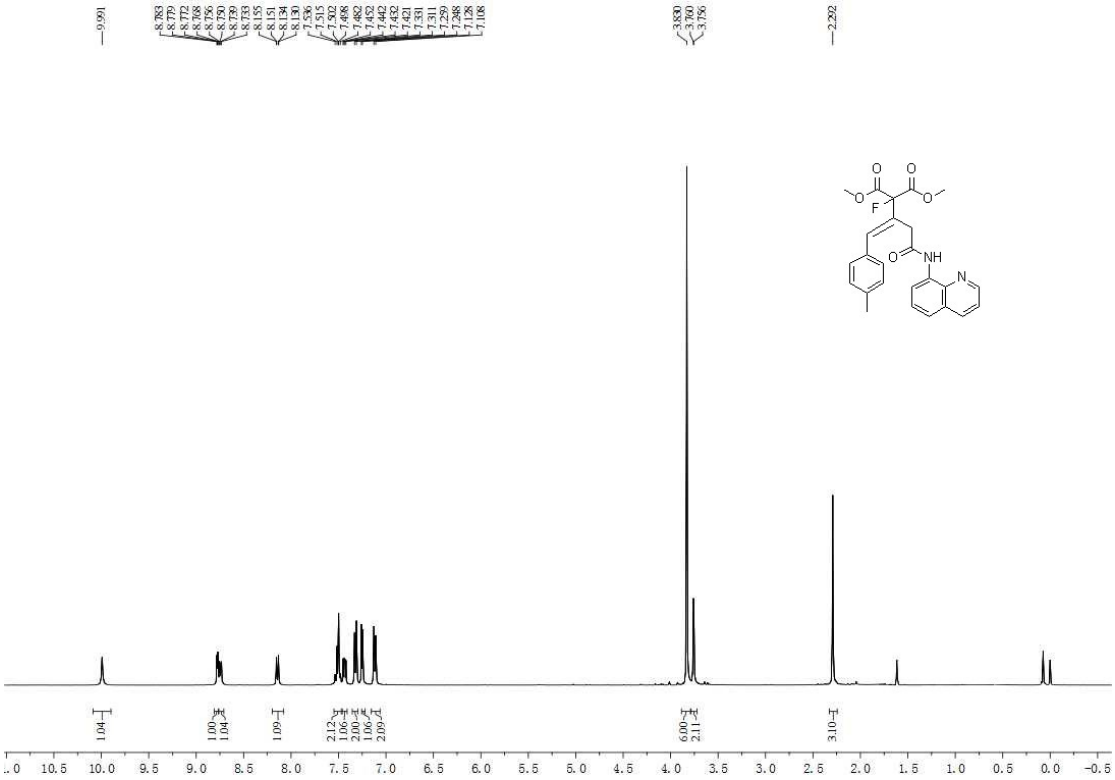
Product 4d

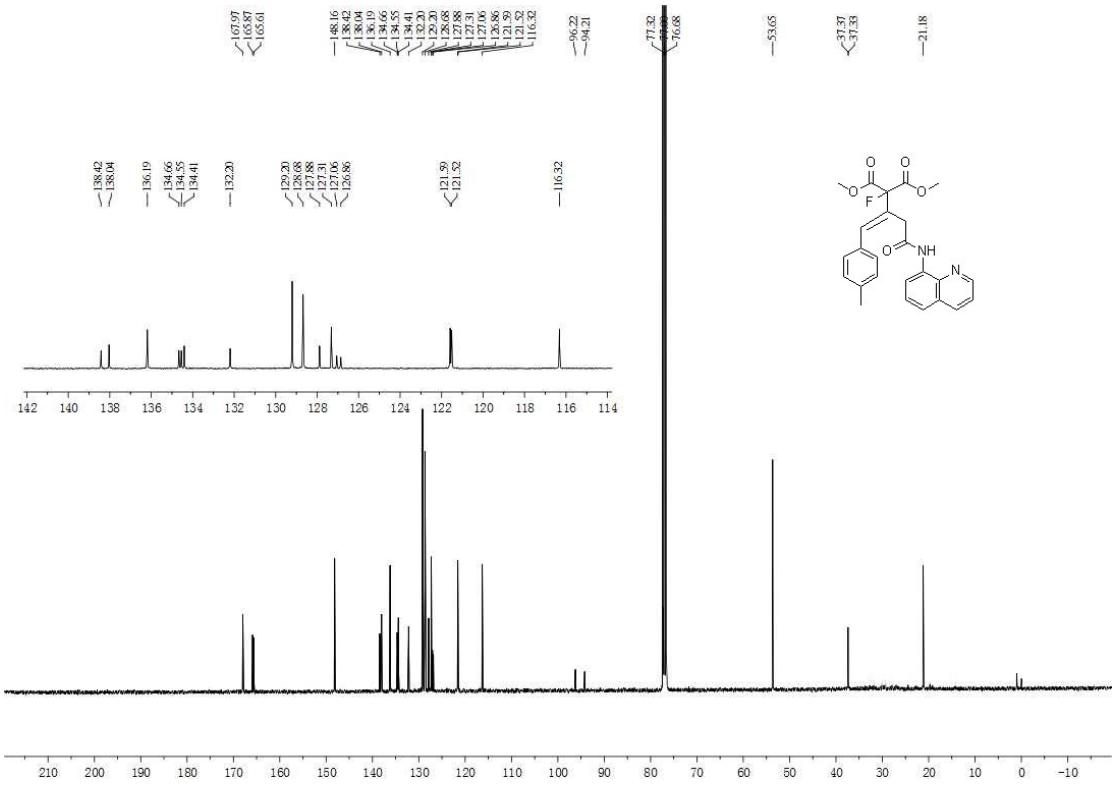

9.931
8.793
8.790
8.783
8.779
8.731
8.723
8.717
8.709
8.167
8.164
8.147
8.143
7.542
7.521
7.515
7.507
7.467
7.456
7.449
7.428
7.319
7.258
7.251
7.211
3.837
3.727
3.724
O
O
O
O
F
O
NH
N
Br
0.97
1.02
1.03
1.03
2.07
3.97
1.99
1.02
6.00
2.12
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0

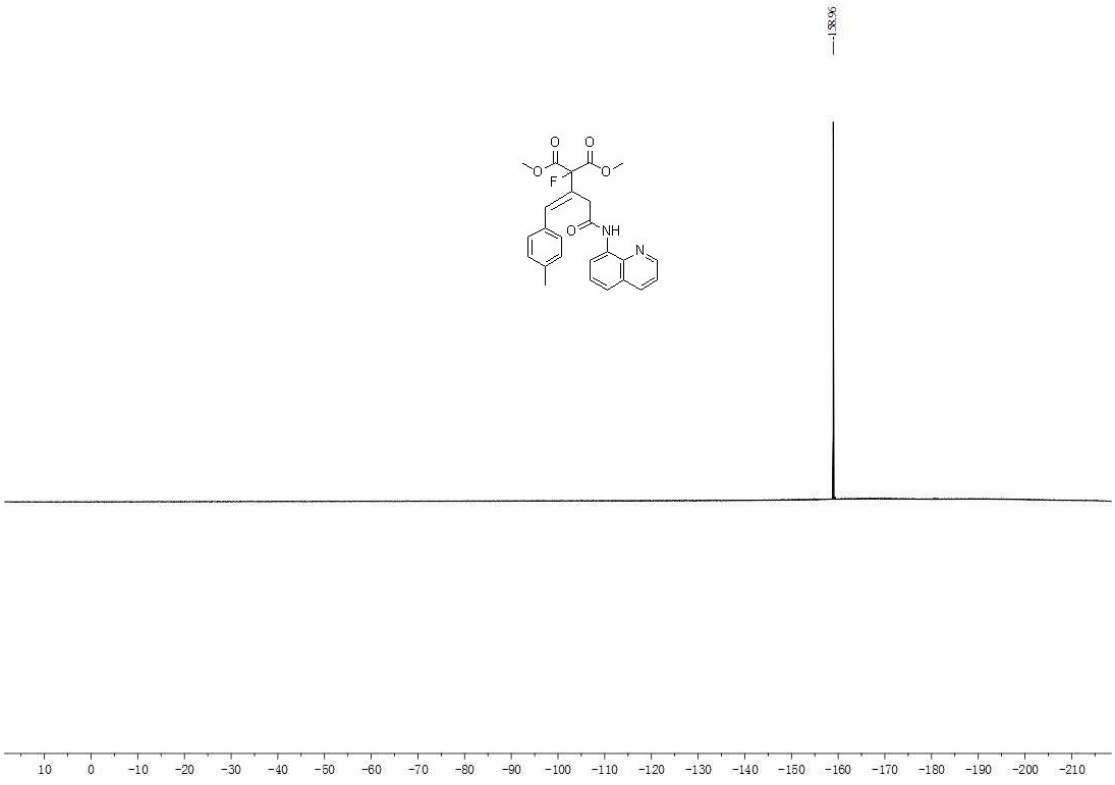

167.64
165.64
165.38
148.21
138.32
136.27
134.24
134.07
133.29
133.17
131.66
130.32
128.55
128.36
127.90
127.30
122.28
121.67
121.65
116.34
95.93
93.91
77.32
77.00
76.68
53.73
37.18
37.14
O
O
O
O
F
O
NH
N
Br


159.58
O
O
O
O
F
O
NH
N
Br

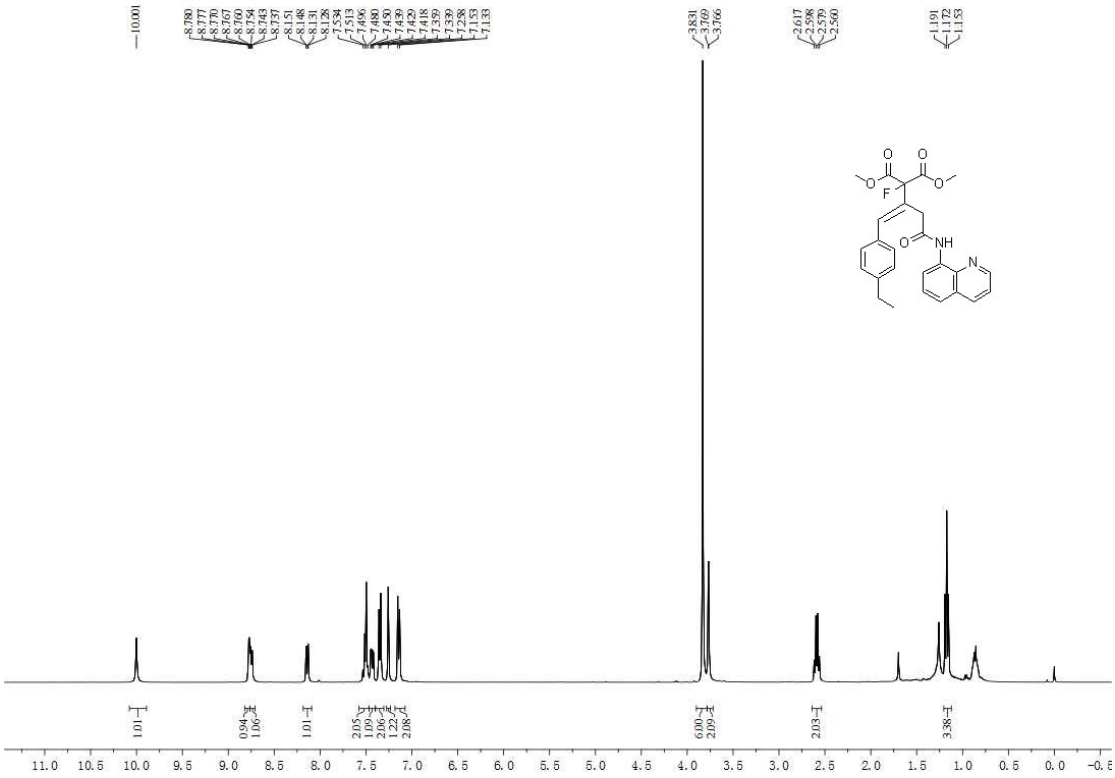
Product 4e

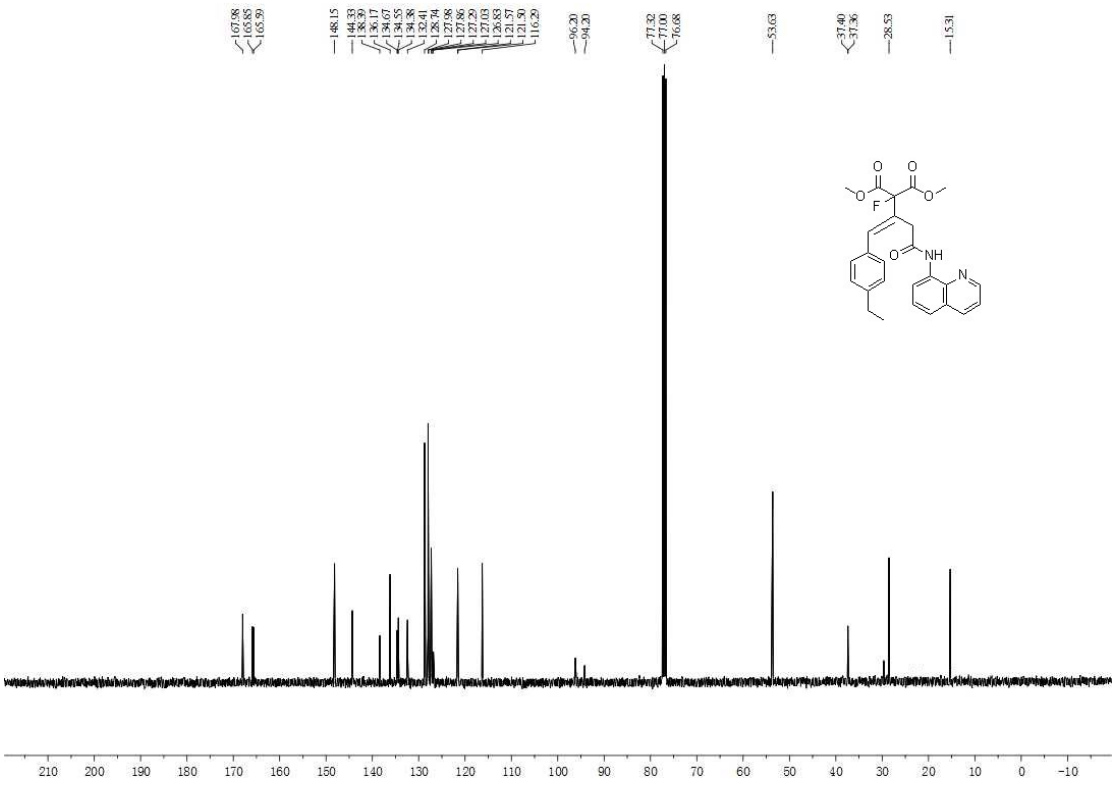


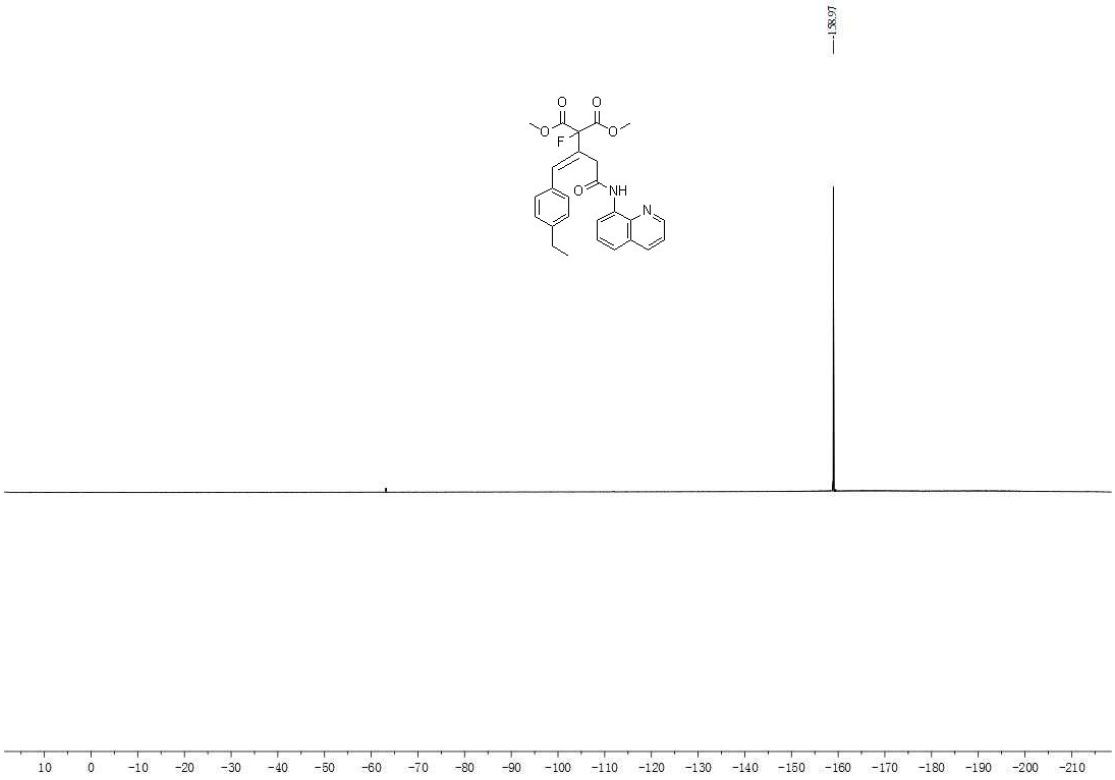



-138.96
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

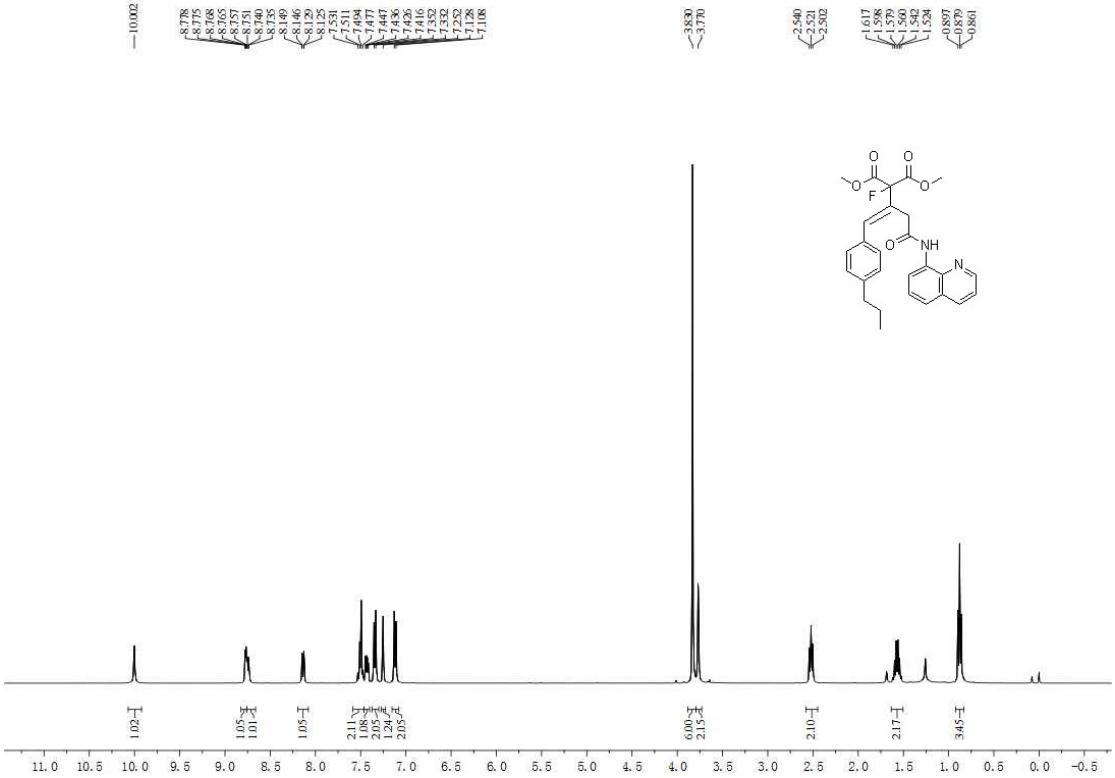
Product 4f

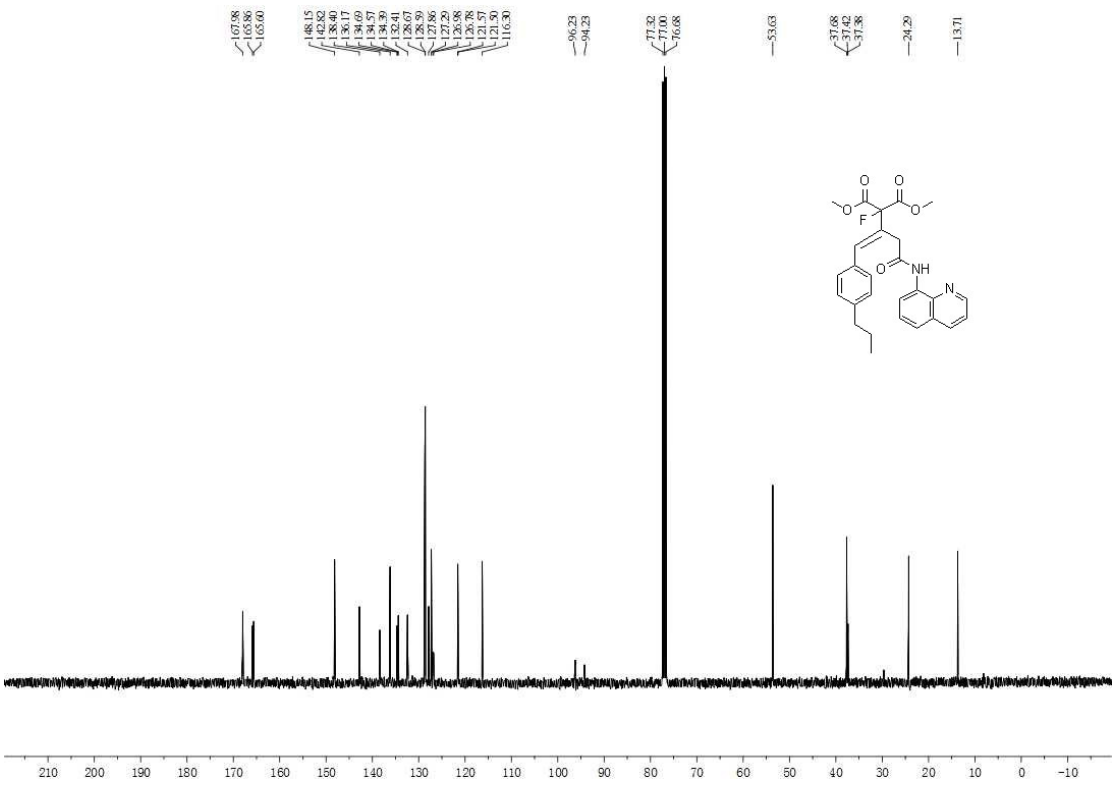

10.000
8.780
8.777
8.770
8.767
8.760
8.754
8.743
8.737
8.151
8.148
8.131
8.128
7.534
7.513
7.496
7.480
7.450
7.439
7.429
7.418
7.339
7.339
7.238
7.153
7.133
3.831
3.769
3.766
2.617
2.598
2.579
2.560
1.191
1.172
1.153
1.01
0.94
1.06
1.01
2.05
1.09
2.06
1.22
2.08
6.00
2.09
2.03
3.38
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

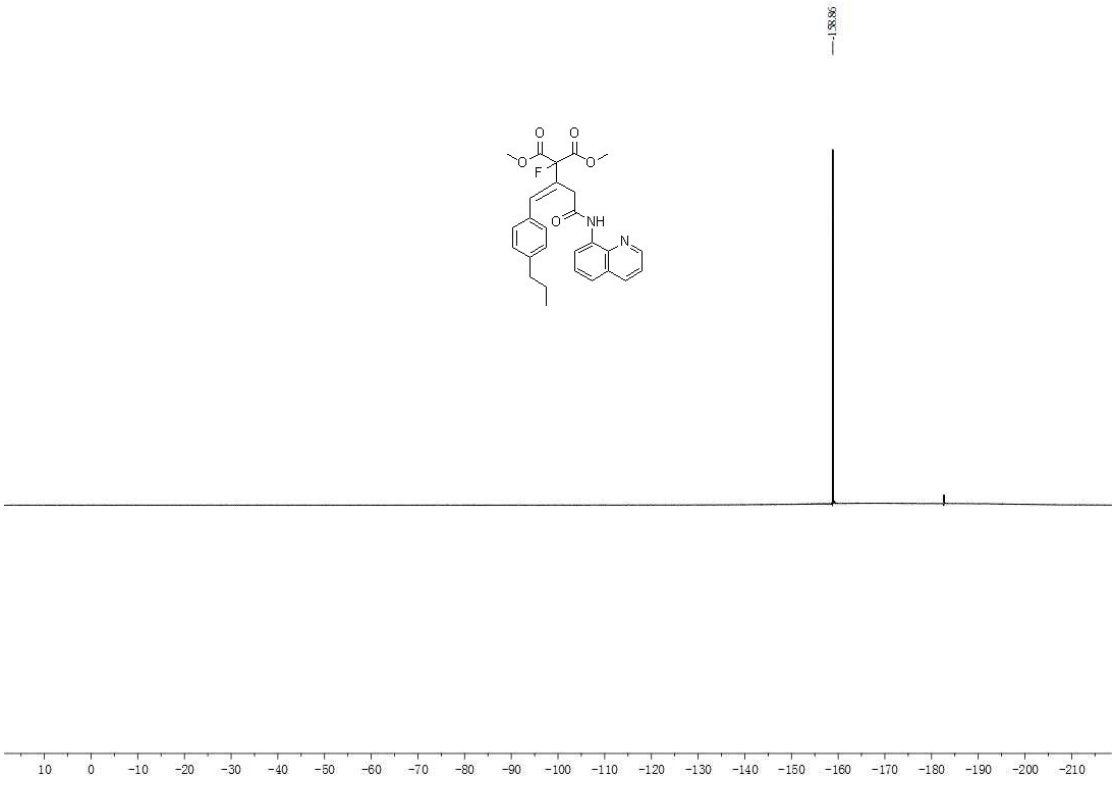

167.98
165.85
165.59
148.15
144.33
138.39
136.17
134.67
134.55
134.38
132.41
129.34
127.98
127.86
127.29
127.03
126.83
121.57
121.30
116.29
96.20
94.20
77.32
77.00
76.68
53.63
37.40
37.36
28.53
15.31
O
O
O
O
F
O
NH
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


-158.97
O
O
O
O
F
O
NH
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

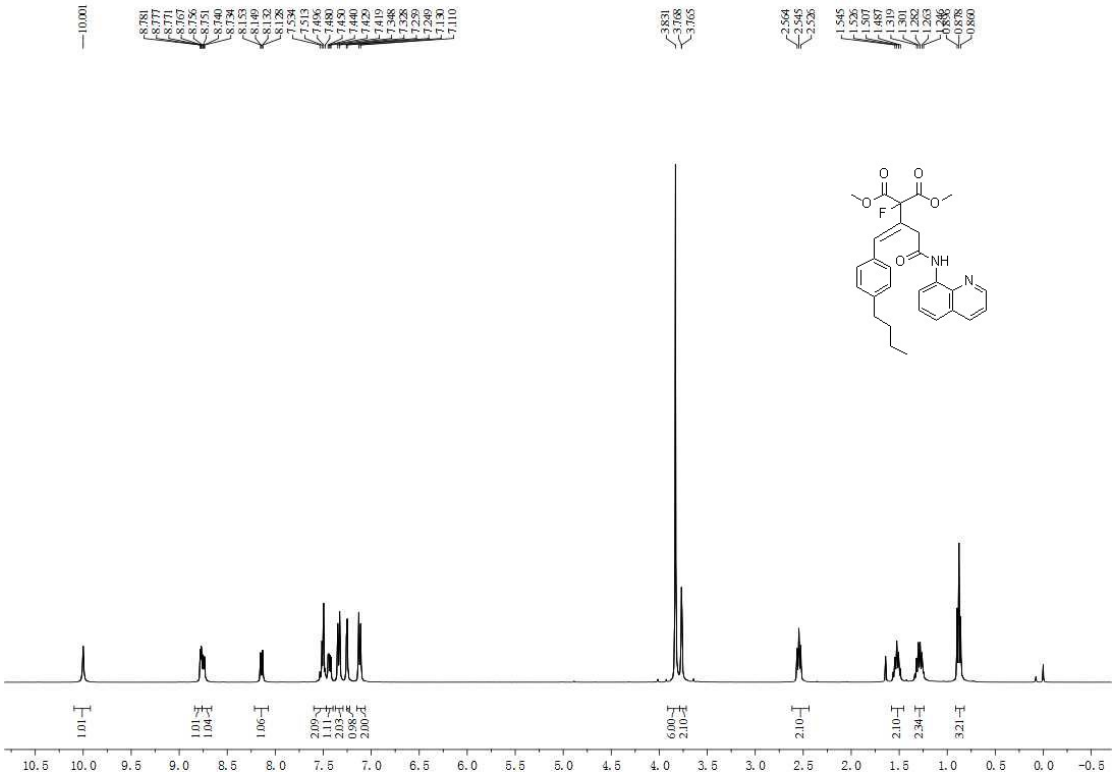
Product 4g

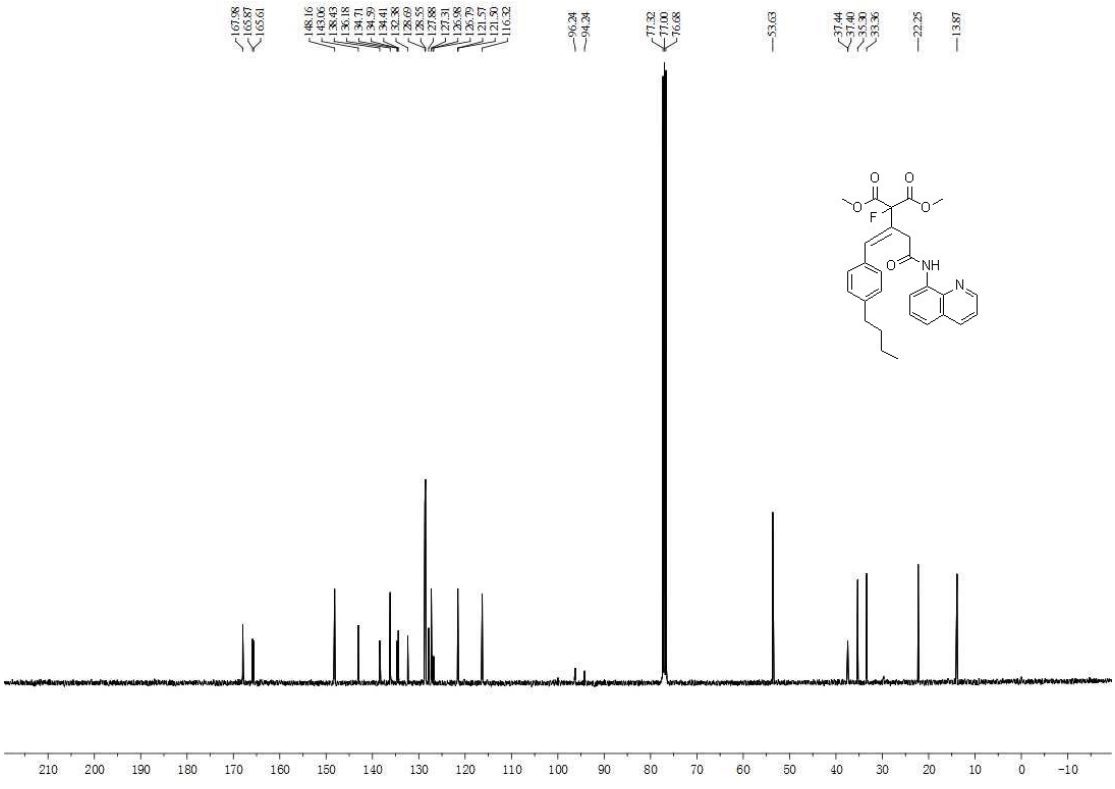


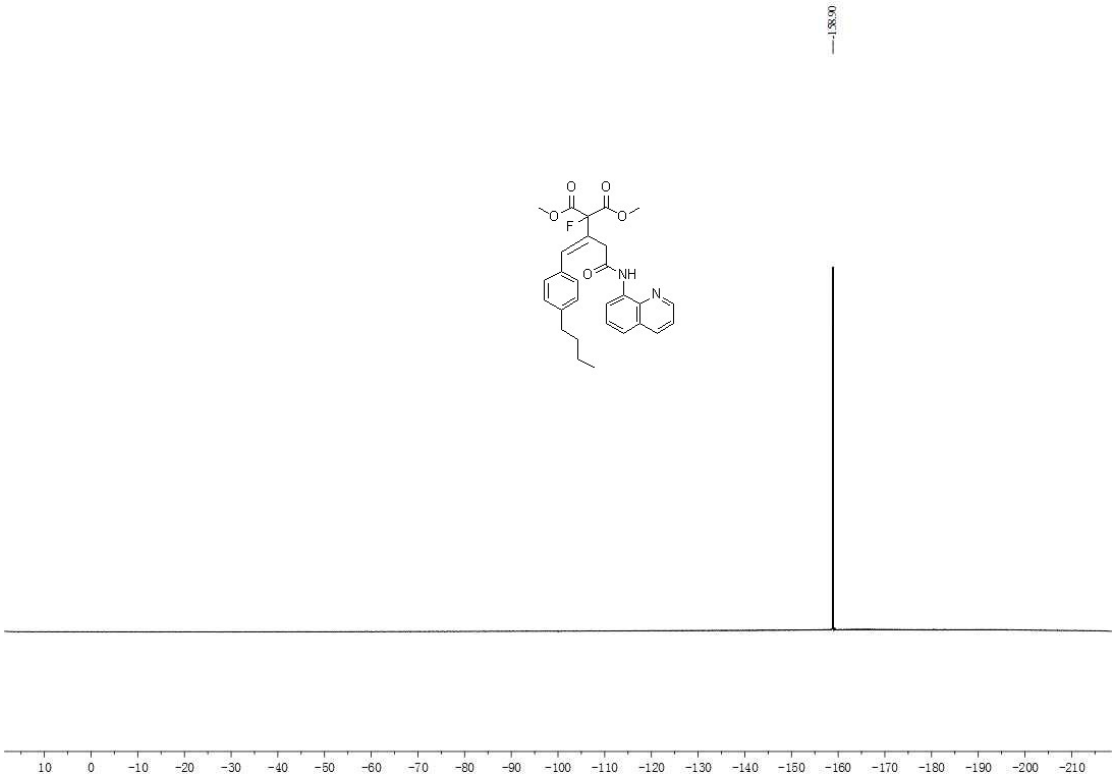



-138.86
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

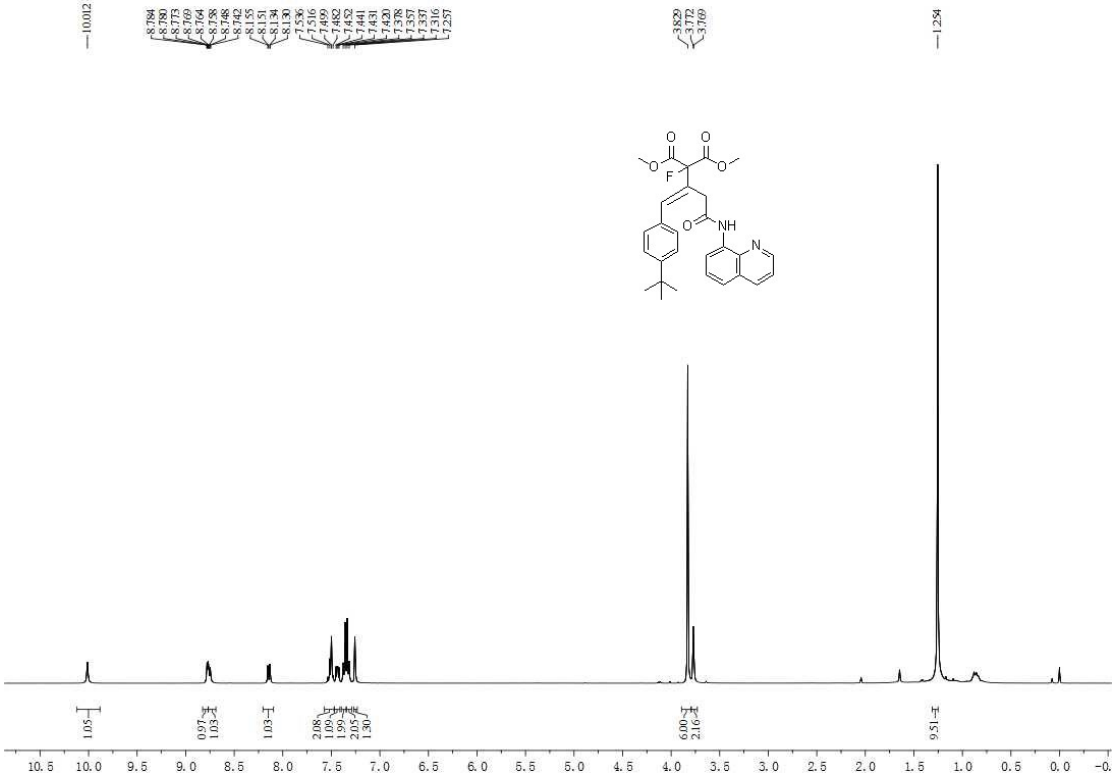
Product 4h

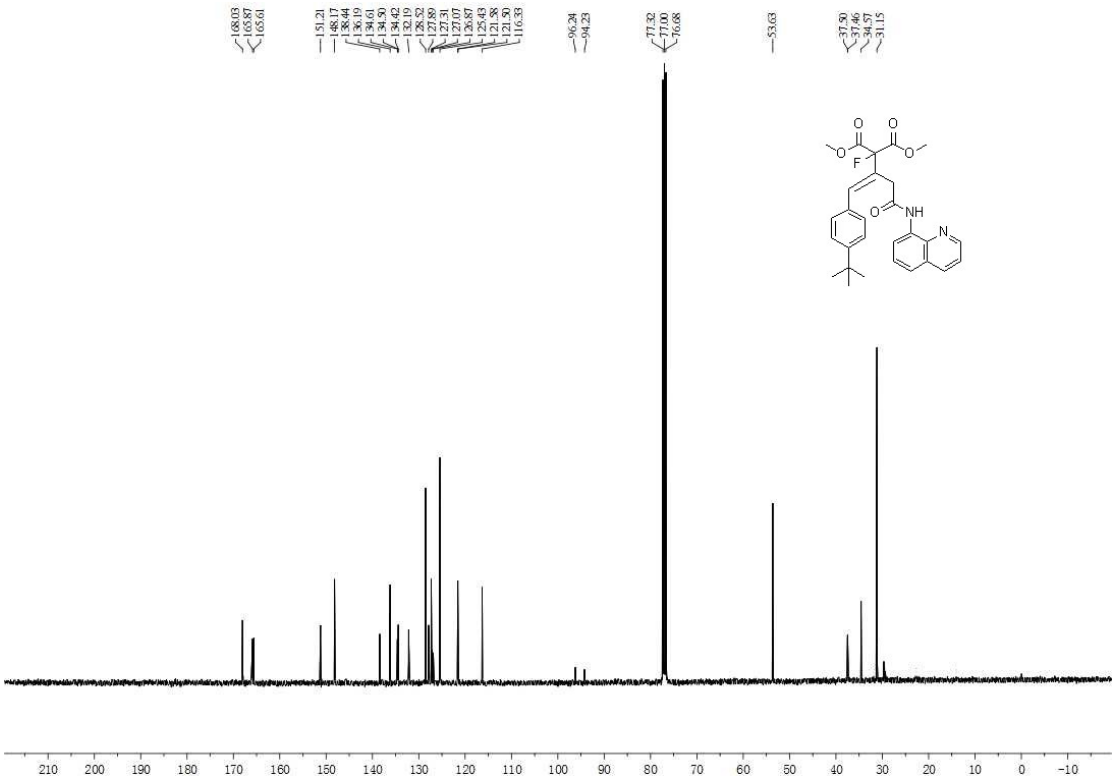

10.001
8.781 8.777 8.771 8.767 8.756 8.751 8.740 8.734 8.153 8.149 8.132 8.128 7.534 7.513 7.496 7.480 7.450 7.440 7.419 7.410 7.348 7.328 7.259 7.249 7.130 7.110
3.831 3.768 3.765
2.564 2.545 2.526
1.545 1.526 1.507 1.487 1.319 1.301 1.282 1.263 0.886 0.878 0.860
1.01 1.01 1.04 1.06 2.09 1.11 2.03 1.98 2.00 6.00 2.10 2.10 2.10 2.34 3.21
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

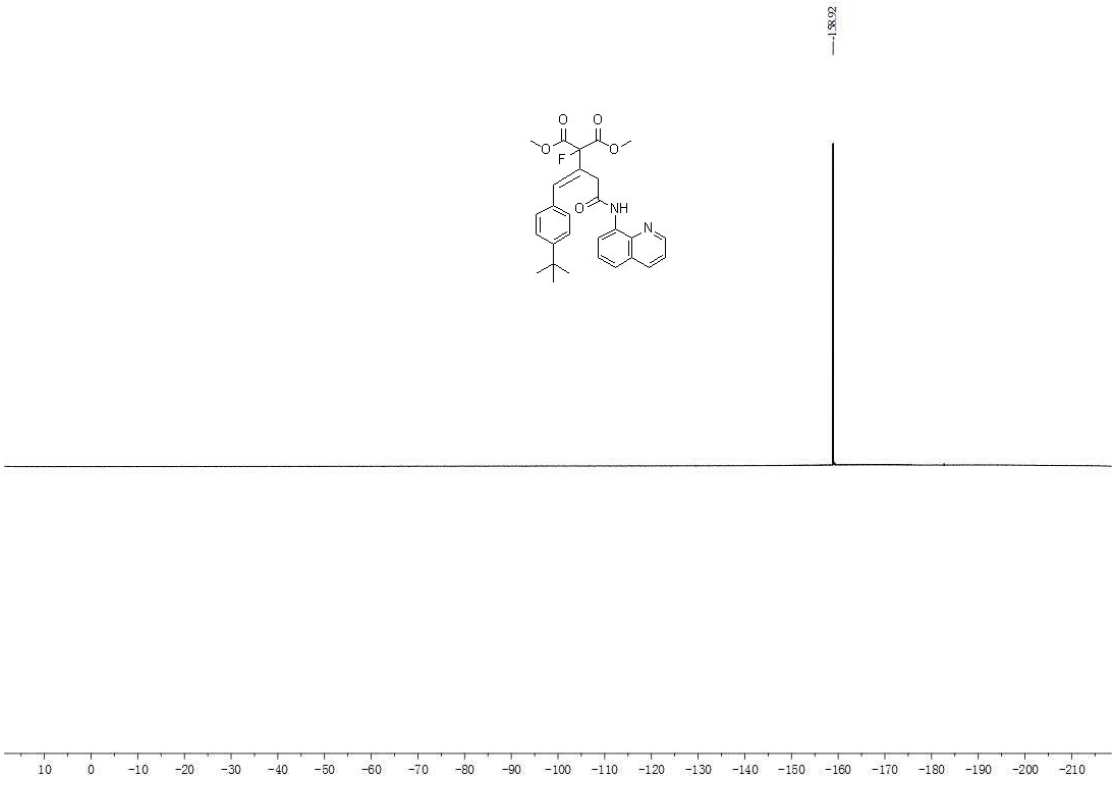

167.98
165.87
165.61
148.16
143.06
138.43
136.18
134.71
134.59
134.41
132.38
128.60
128.55
127.88
127.31
126.98
126.79
121.57
121.30
116.32
96.24
94.24
77.32
77.00
76.68
53.63
37.44
37.40
35.30
33.36
22.25
13.87
O
O
O
O
F
O
NH
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


158.90
O
O
O
O
F
O
NH
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

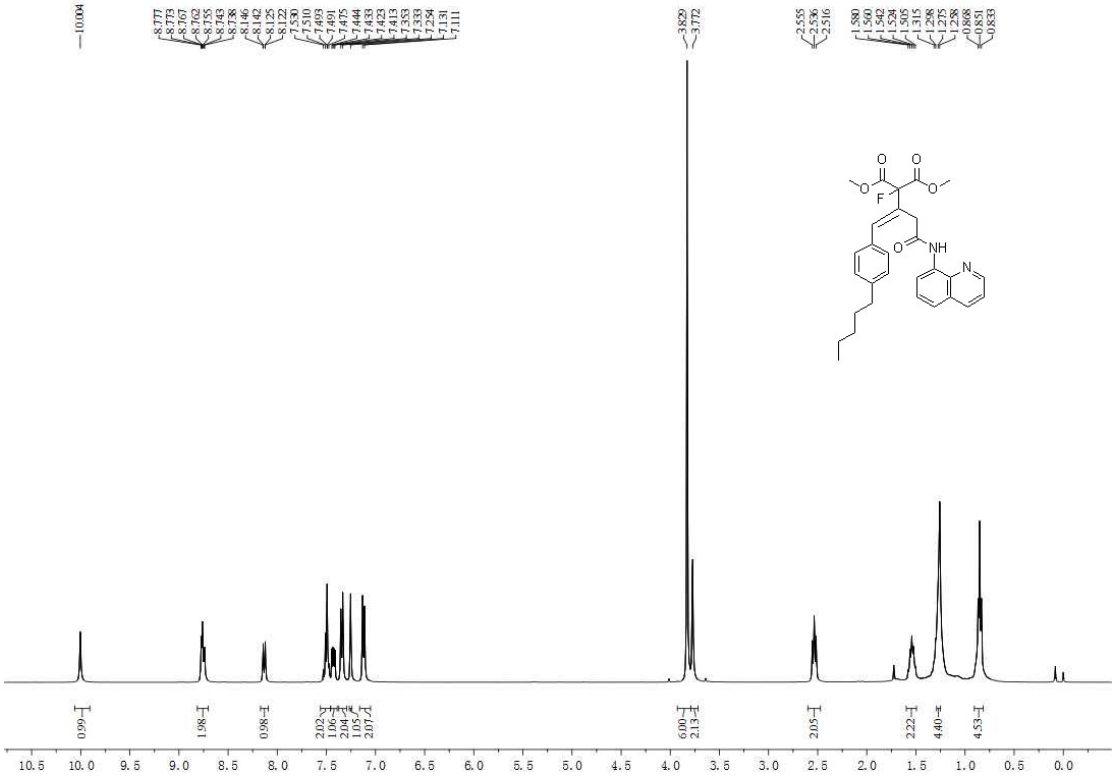
Product 4i

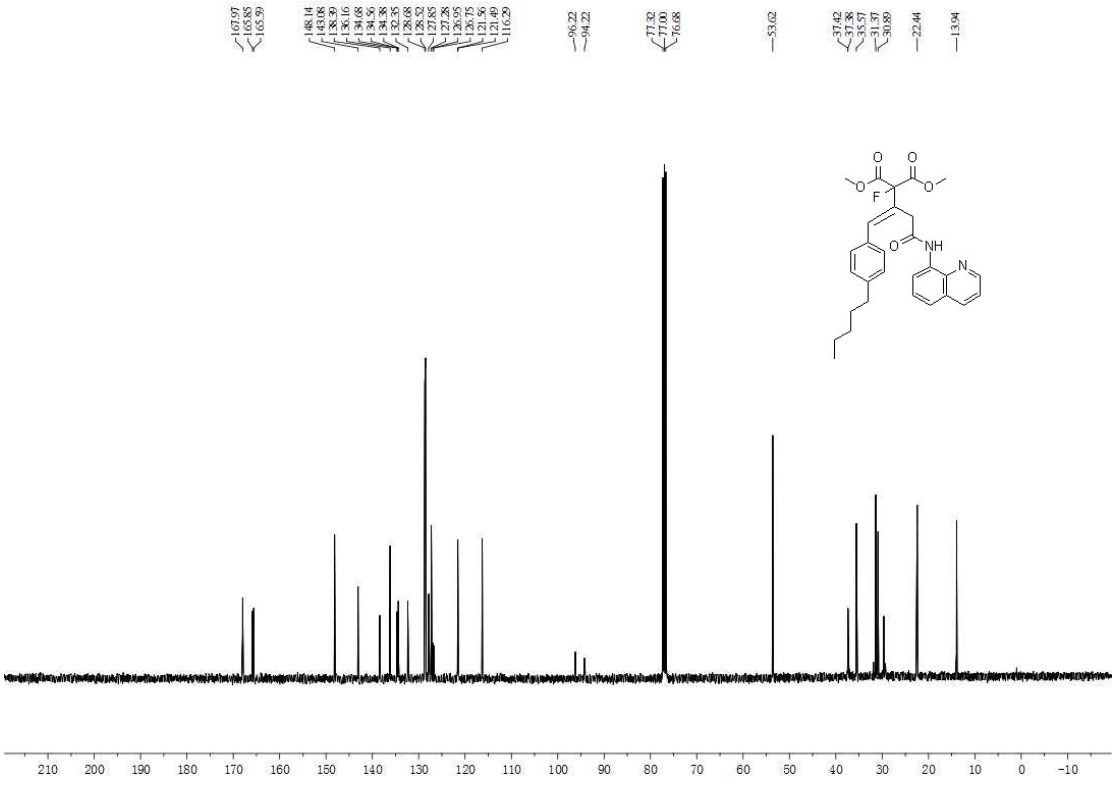


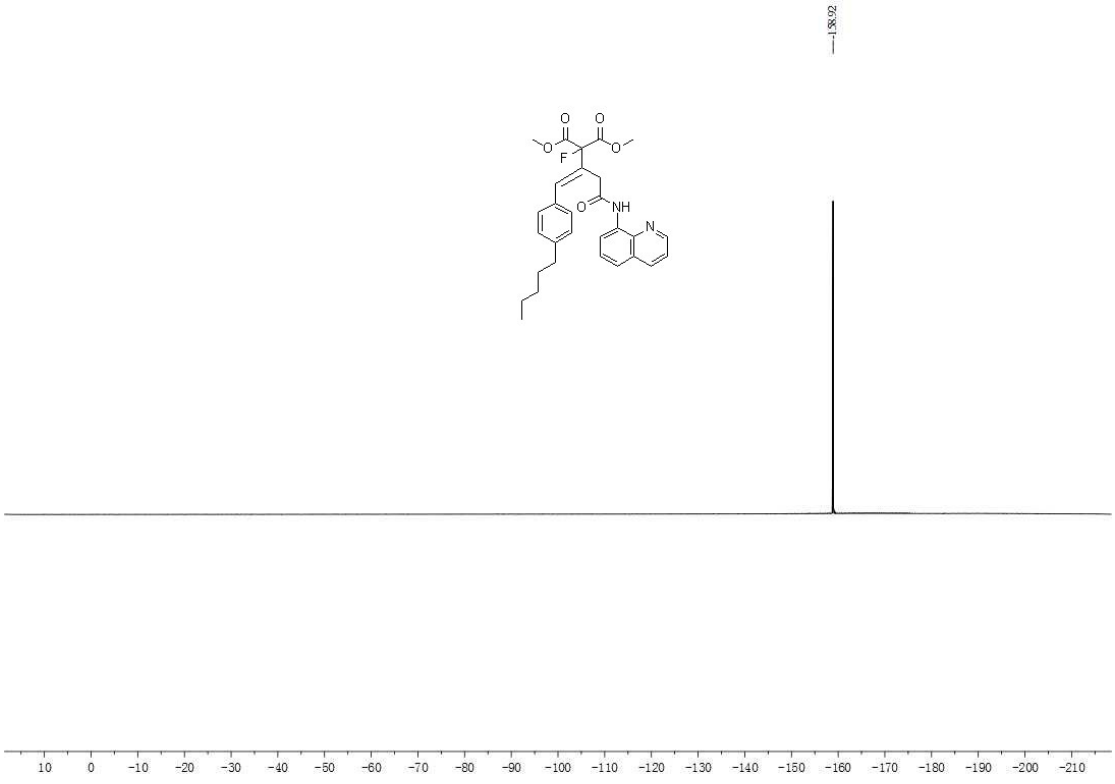



-138.92
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

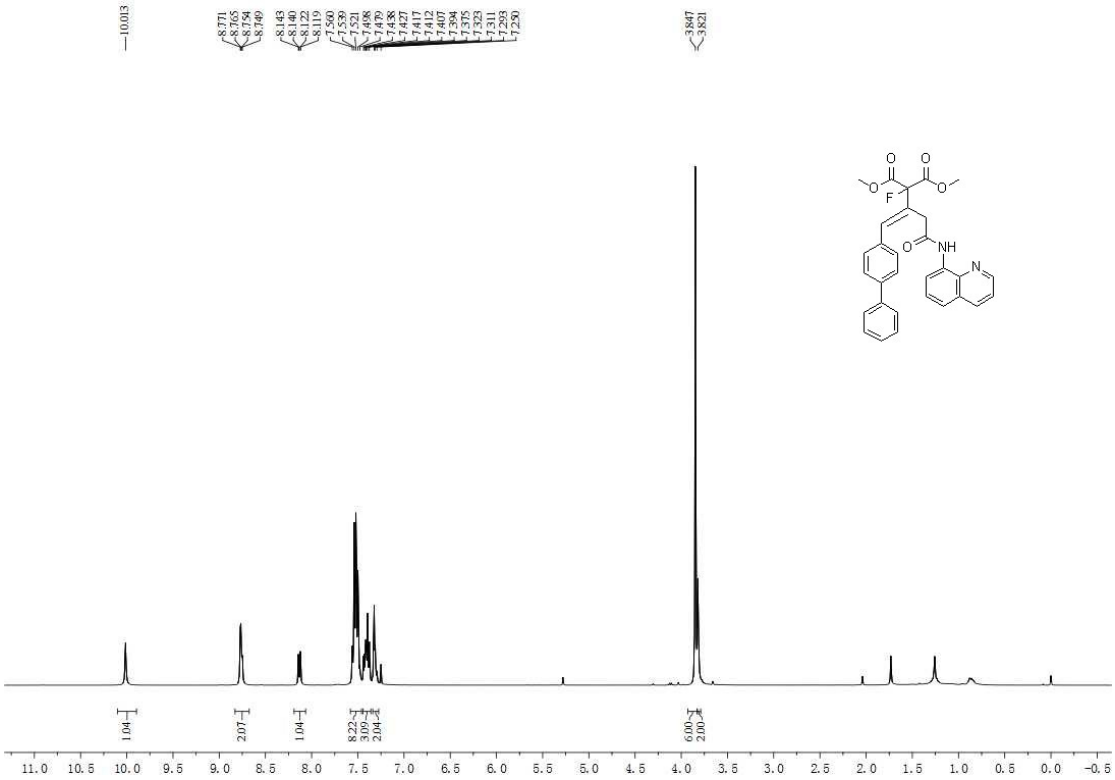
Product 4j

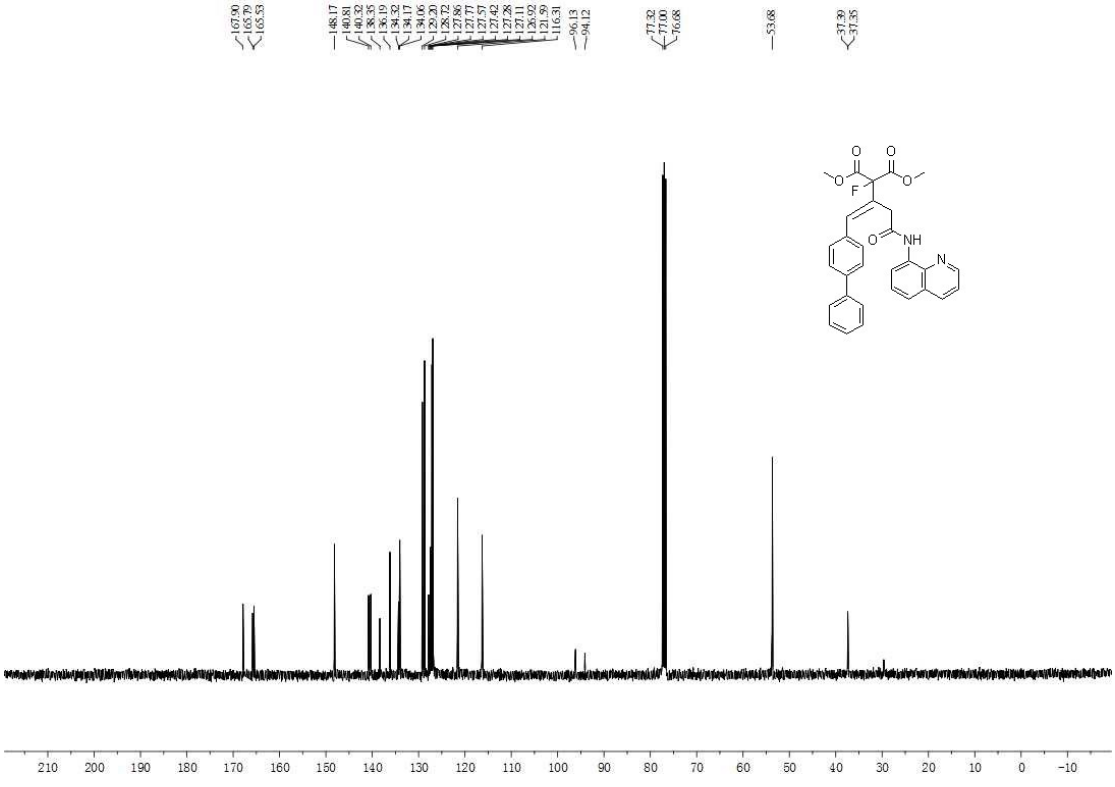

10.004
8.777 8.773 8.767 8.762 8.755 8.743 8.738 8.146 8.142 8.125 7.732 7.530 7.510 7.493 7.491 7.475 7.444 7.433 7.423 7.413 7.353 7.333 7.254 7.131 7.111
3.829 3.772
2.555 2.536 2.516
1.580 1.560 1.542 1.524 1.505 1.315 1.298 1.275 1.258 0.868 0.851 0.833
0.99 1.98 0.98 2.02 1.06 2.04 1.05 2.07 6.00 2.13 2.05 2.22 4.40 4.53
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

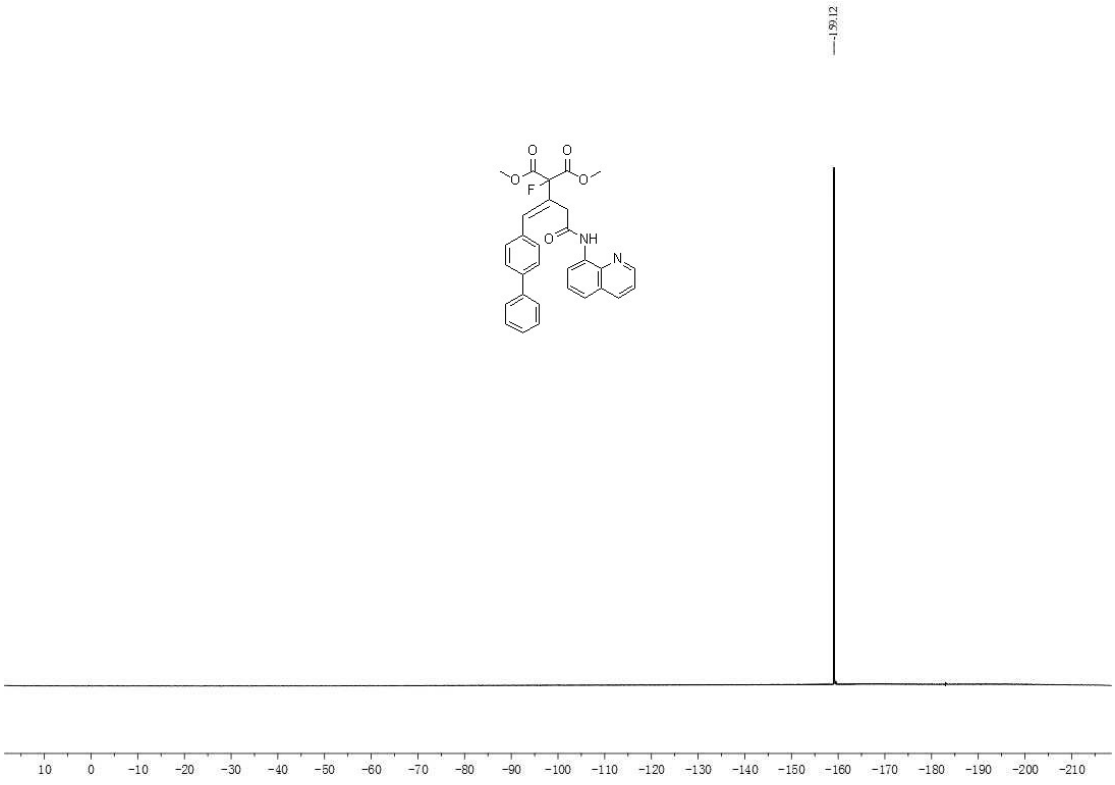

167.97
165.85
165.59
148.14
143.08
138.39
136.16
134.68
134.56
134.38
132.35
128.68
128.52
127.85
127.28
126.95
126.75
121.56
121.49
116.29
96.22
94.22
77.32
77.00
76.68
53.62
37.42
37.38
35.57
31.37
30.89
22.44
13.94
O
O
O
O
F
O
NH
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


158.92
O
O
O
O
F
O
NH
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

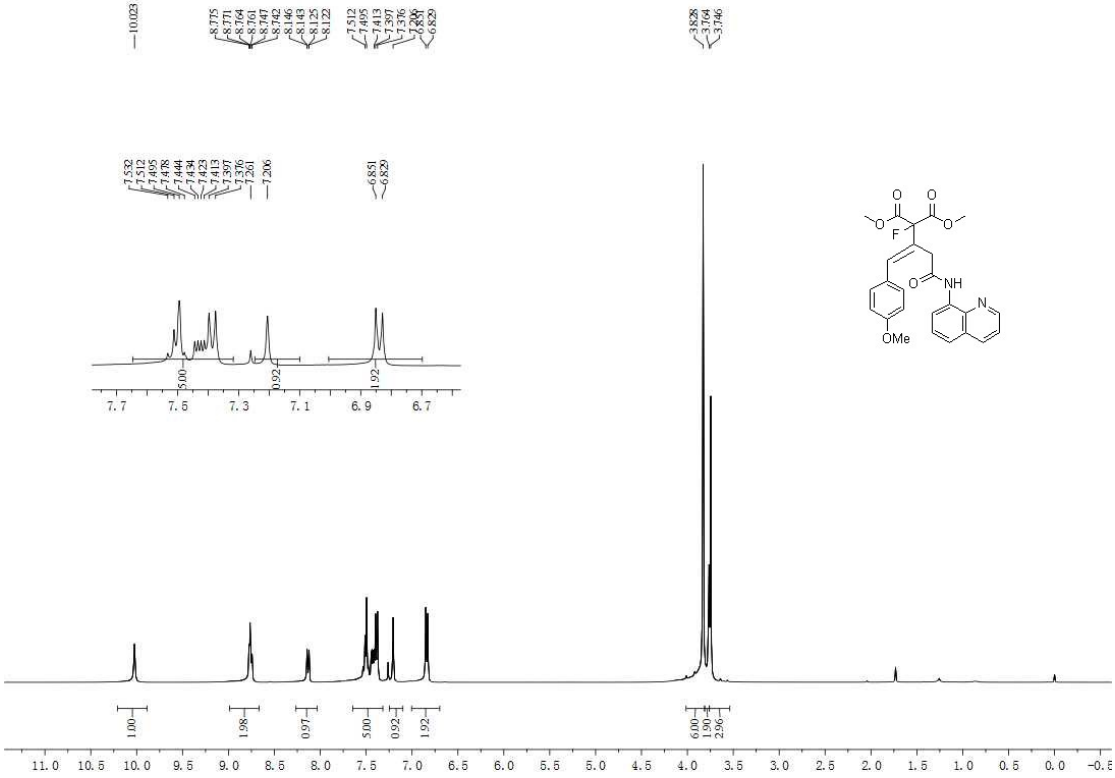
Product 4k

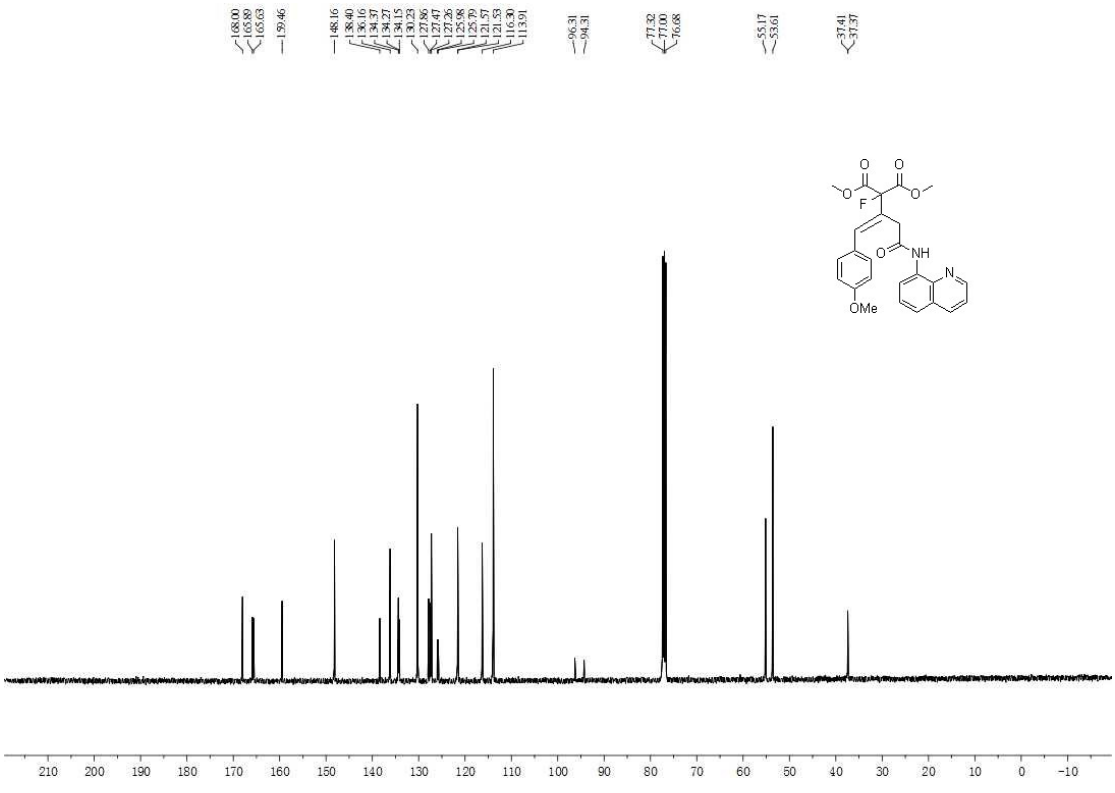

10.013
8.771
8.765
8.754
8.749
8.143
8.140
8.122
8.119
7.560
7.559
7.521
7.498
7.479
7.438
7.427
7.417
7.412
7.407
7.394
7.375
7.329
7.311
7.293
7.250
3.847
3.821
O
O
O
O
F
O
NH
N
1.04
2.07
1.04
8.22
3.09
2.04
6.00
2.00
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

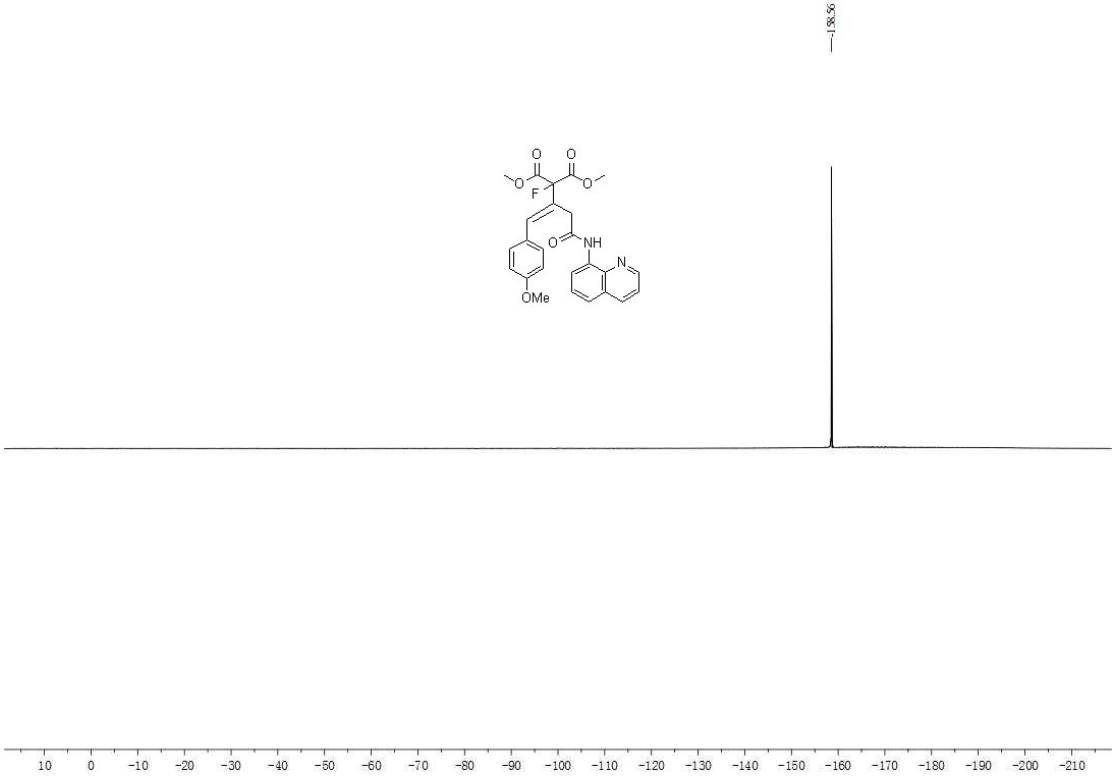

167.90
165.79
165.53
148.17
140.81
140.32
138.35
136.19
134.32
34.17
34.06
129.20
128.72
127.86
127.77
127.57
127.42
127.28
127.11
126.92
121.59
116.31
96.13
94.12
77.32
77.00
76.68
53.68
37.39
37.35
O
O
O
O
F
O
NH
N
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10



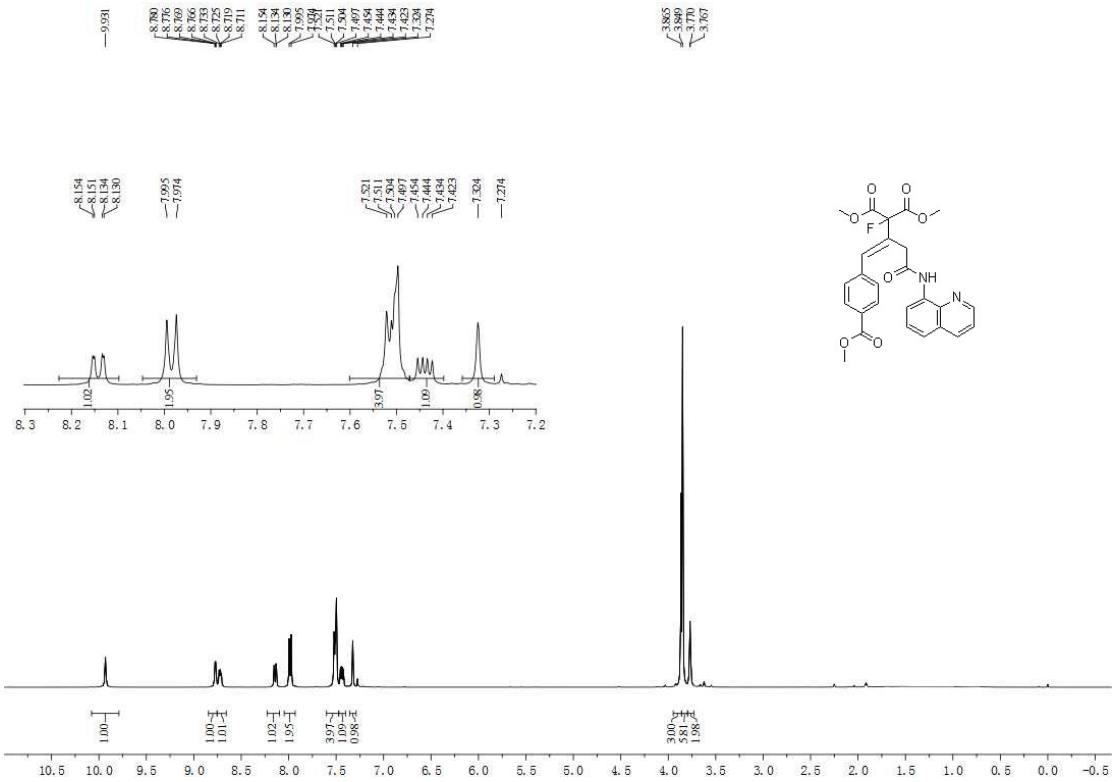
Product 4l

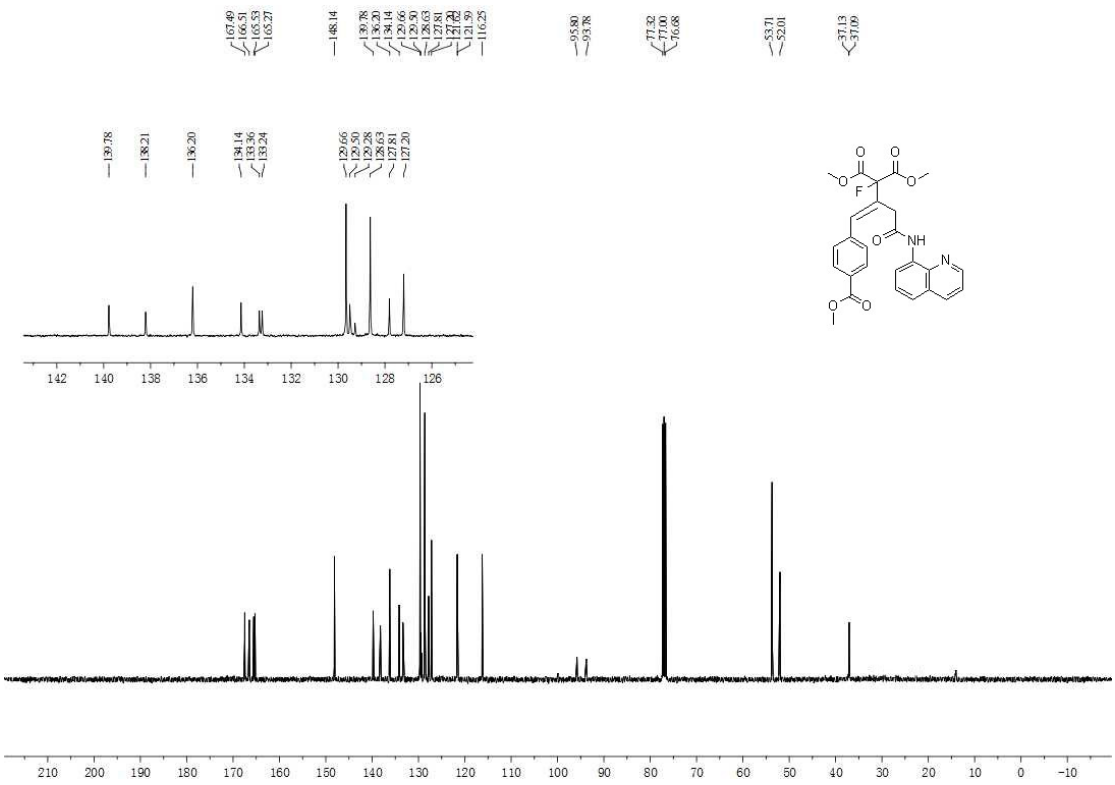


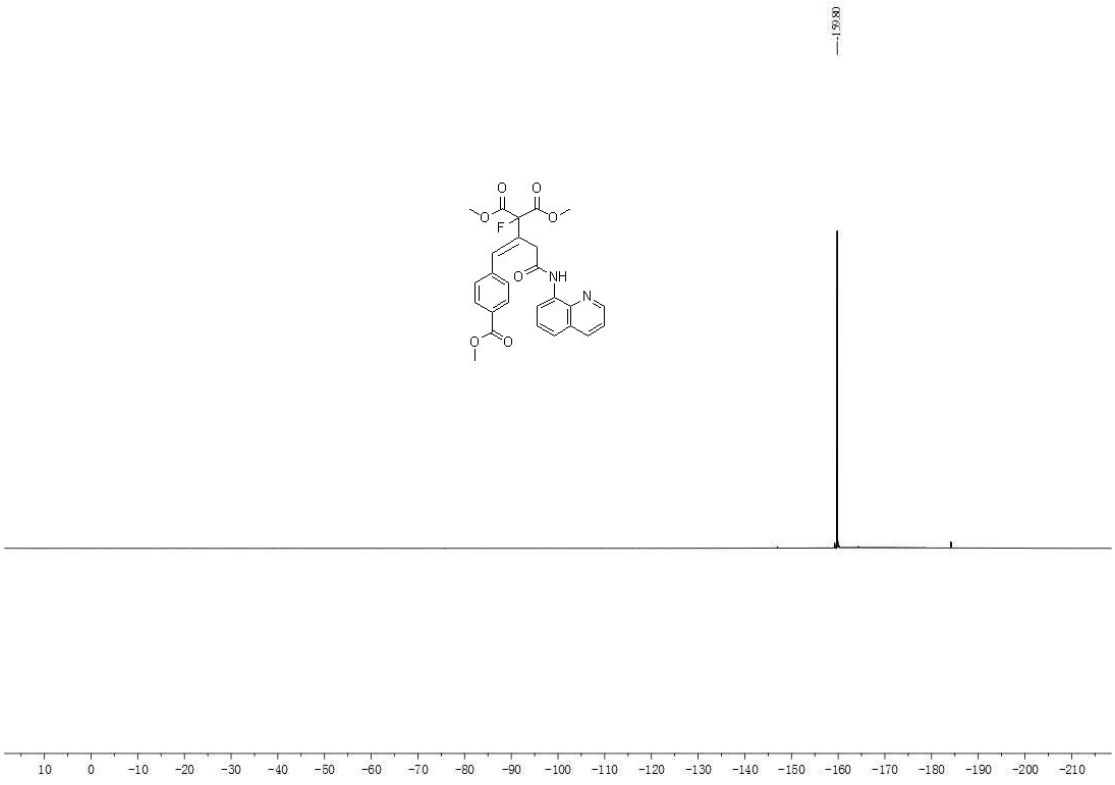

168.00
165.89
165.63
159.46
148.16
138.40
136.16
134.37
134.27
134.15
130.23
127.86
127.47
127.38
125.98
125.79
121.57
121.53
116.30
113.91
96.31
94.31
77.32
77.00
76.68
55.17
53.61
37.41
37.37
OMe
NH
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


-158.56
OMe
NH
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

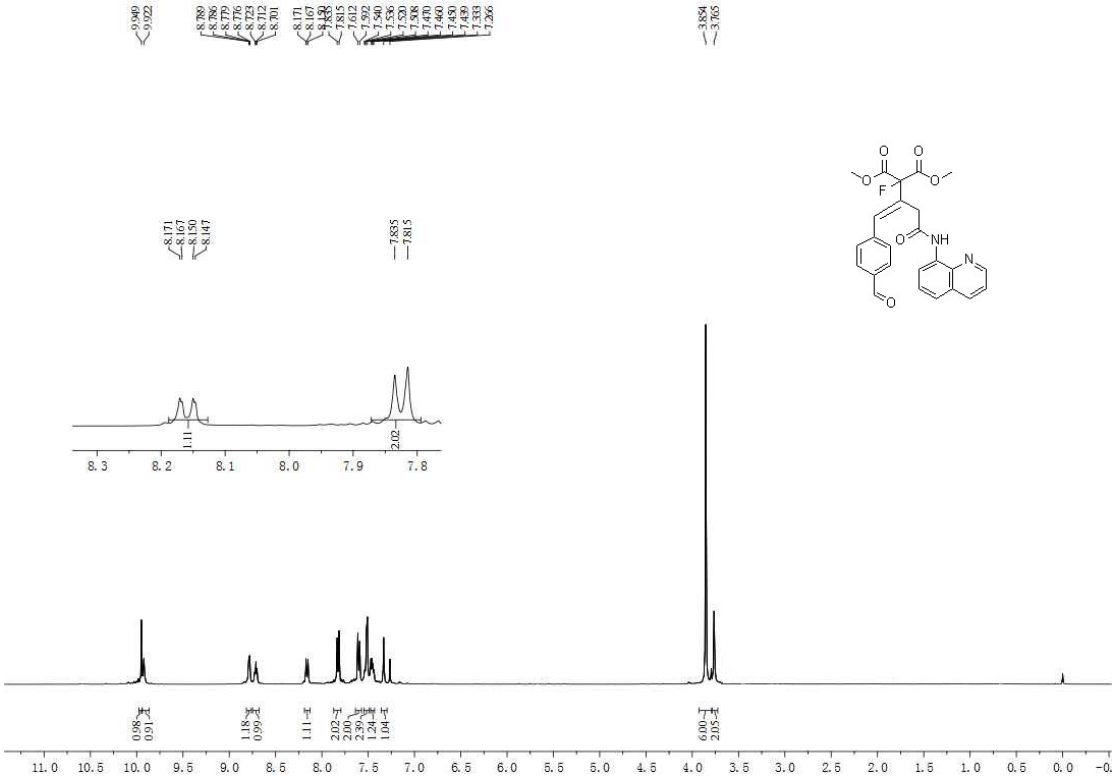
Product 4m

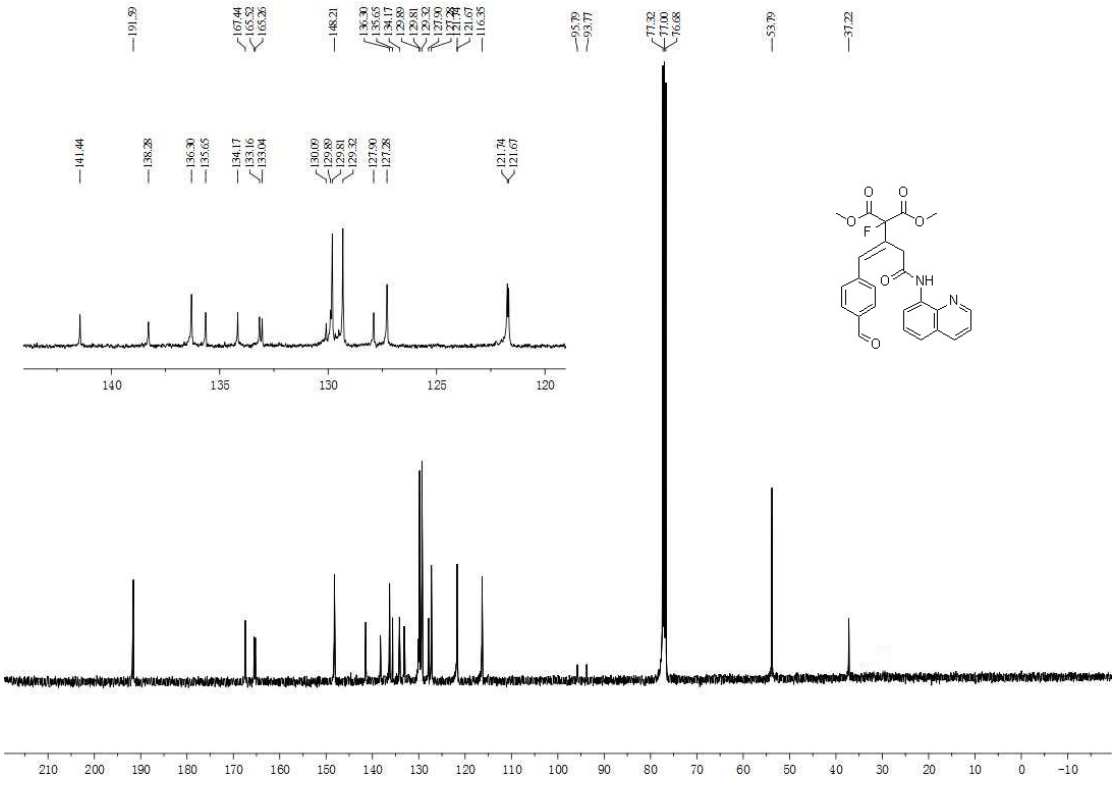


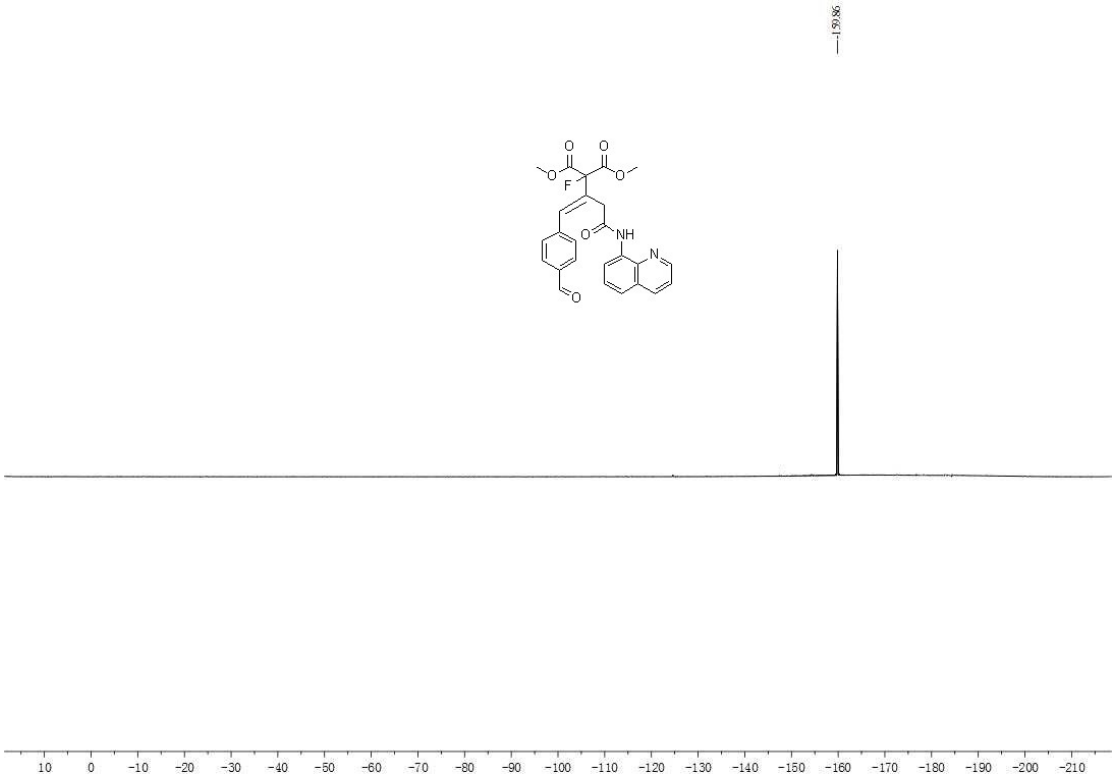



-159.80
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

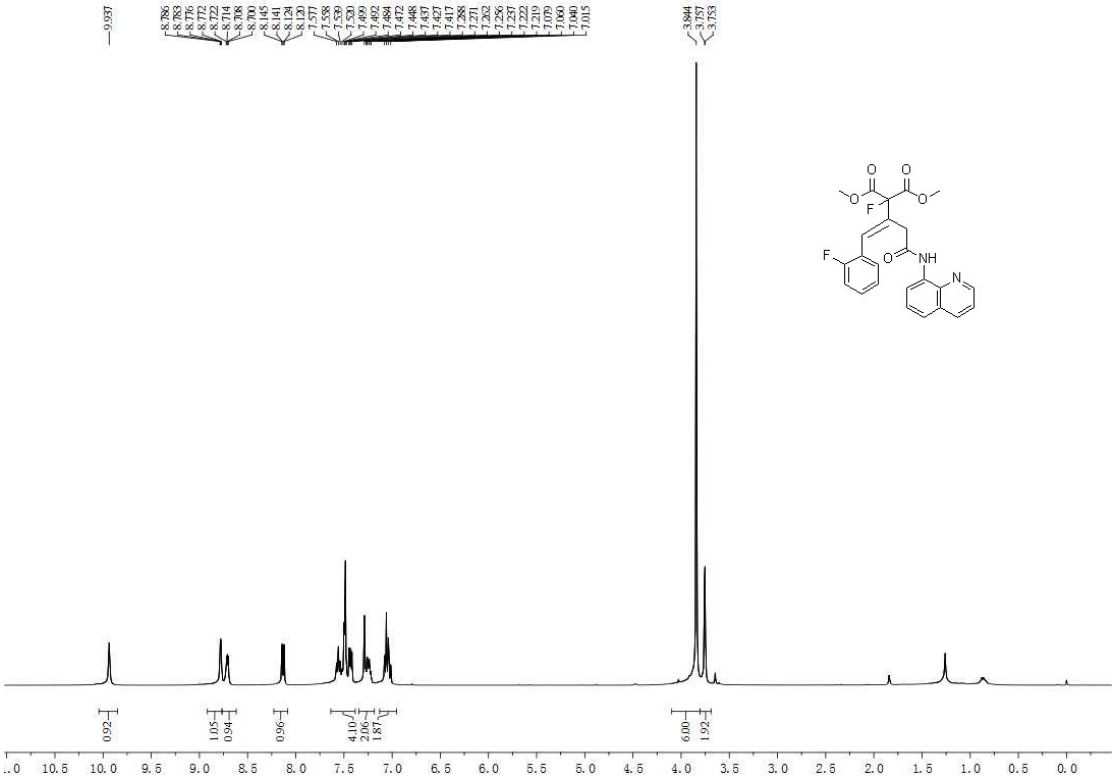
Product 4n

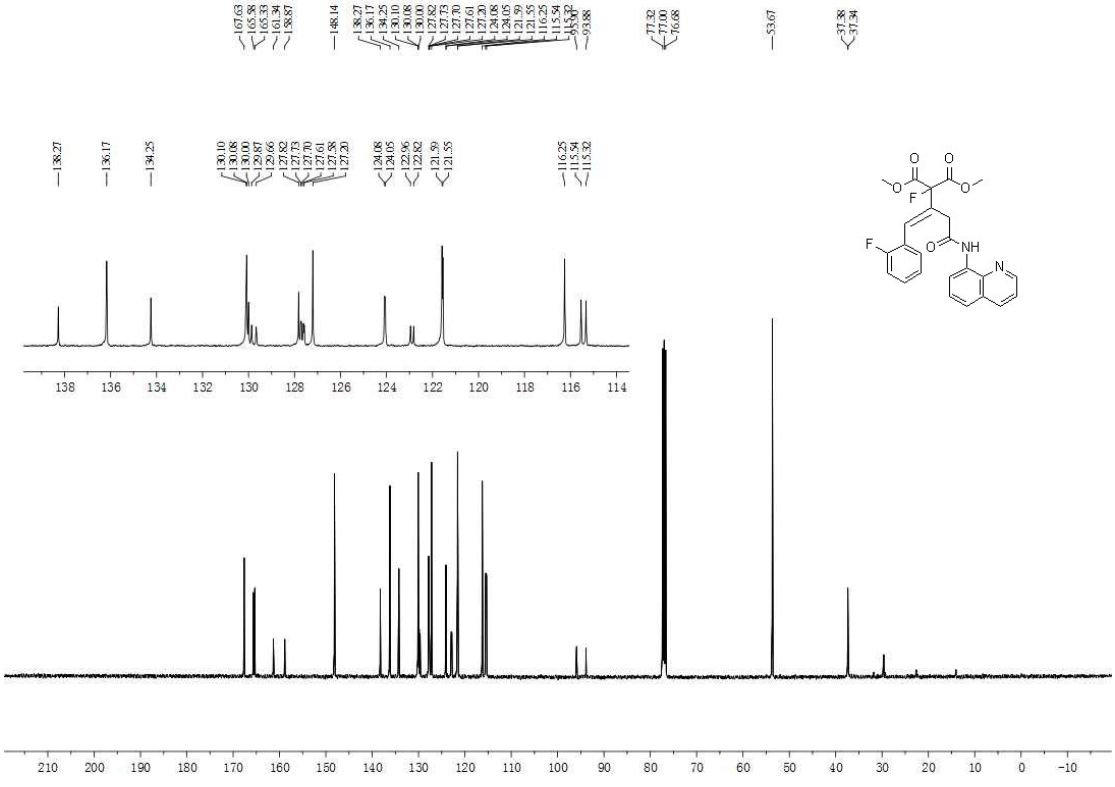

9.949
9.922
8.789
8.786
8.779
8.776
8.723
8.712
8.701
8.171
8.167
8.150
8.147
7.835
7.815
7.612
7.593
7.540
7.536
7.530
7.508
7.470
7.460
7.450
7.439
7.418
7.355
7.266
3.854
3.765
1.11
2.02
8.3 8.2 8.1 8.0 7.9 7.8
0.98
0.91
1.18
0.99
1.11
2.02
2.00
2.39
1.24
1.04
6.00
2.05
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

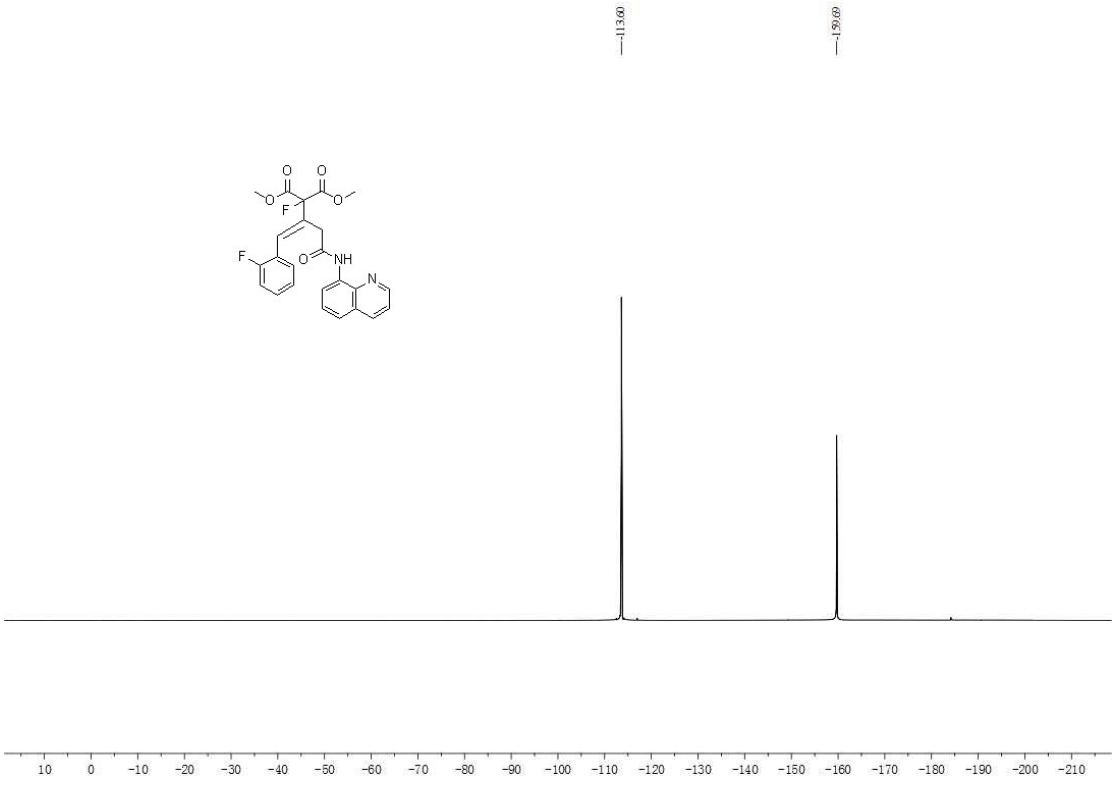

191.59
167.44
165.52
165.26
148.21
136.30
135.65
134.17
129.89
129.81
129.32
127.90
127.78
121.74
121.67
116.35
95.79
93.77
77.32
77.00
76.68
53.79
37.22
141.44
138.28
136.30
135.65
134.17
133.16
133.04
130.09
129.89
129.81
129.32
127.90
127.28
121.74
121.67
140
135
130
125
120
O
O
O
O
F
NH
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


159.86
O
O
O
O
F
NH
N
O
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210

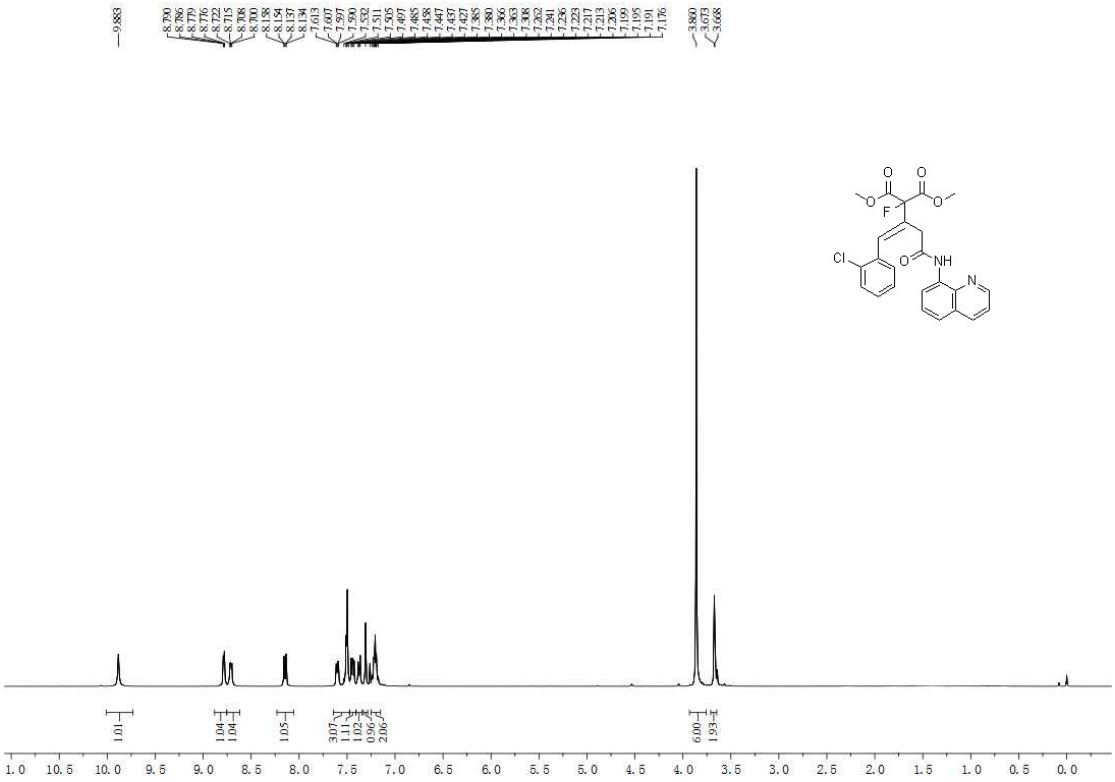
Product 4o

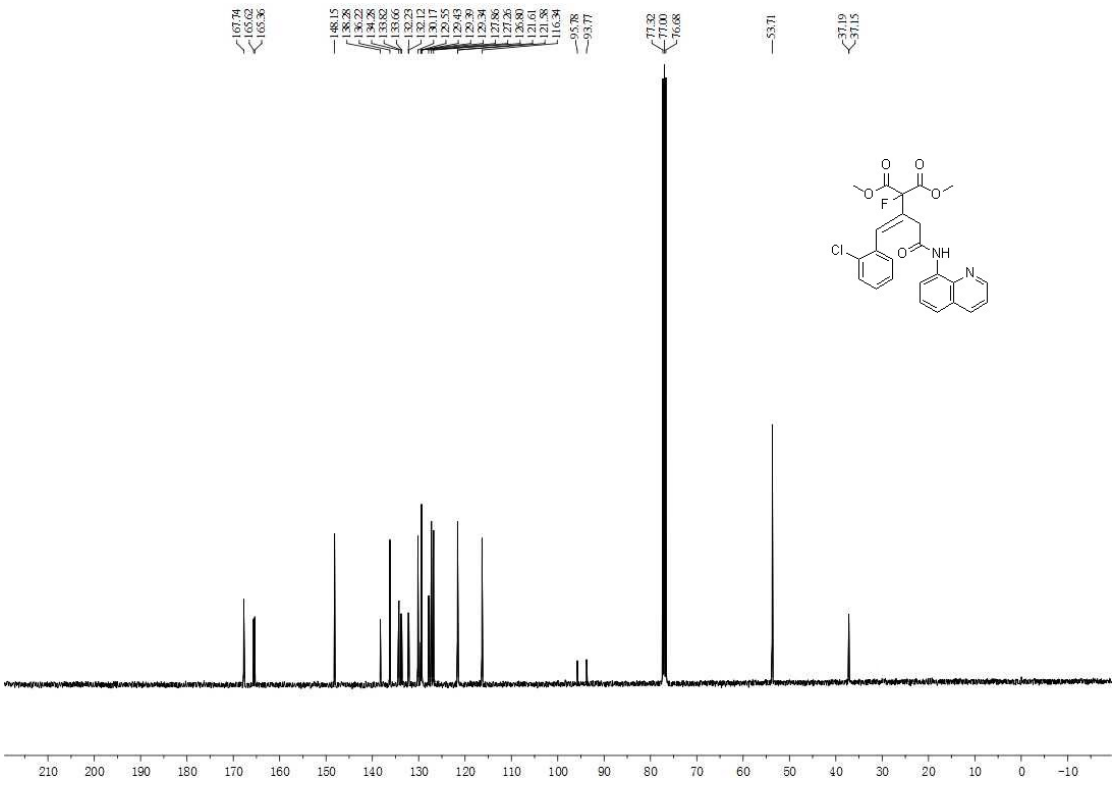


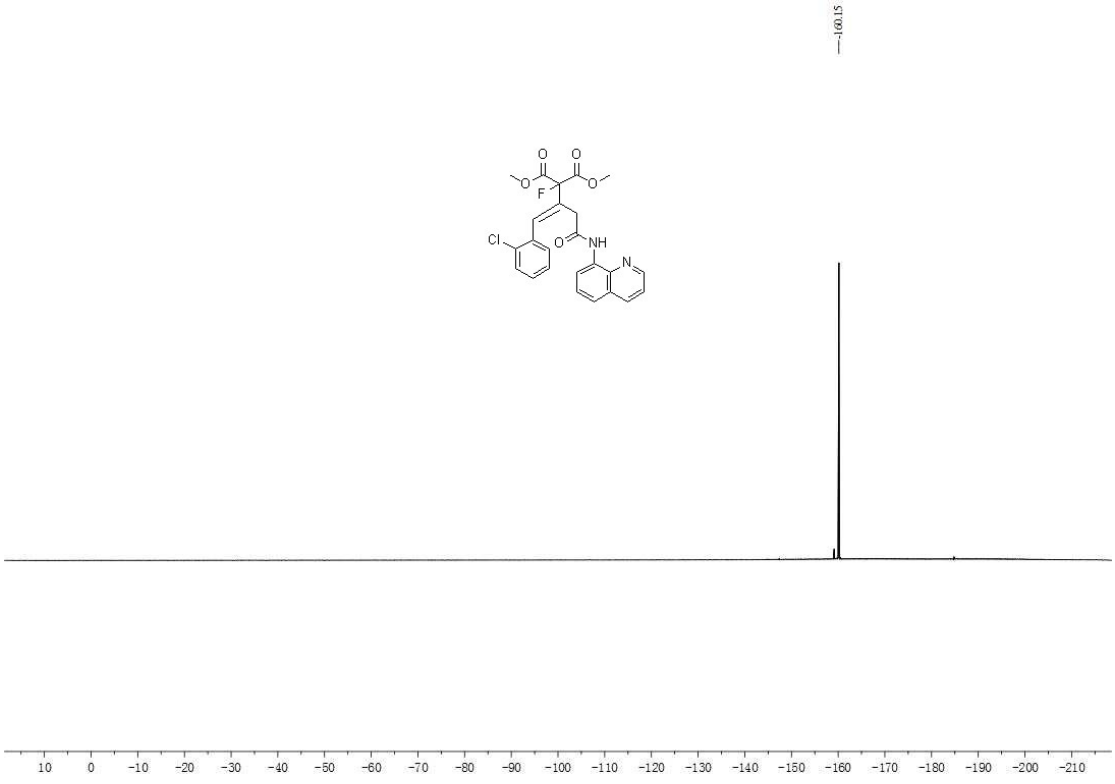



-113.60
-159.69
F
O
O
O
O
F
O
NH
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

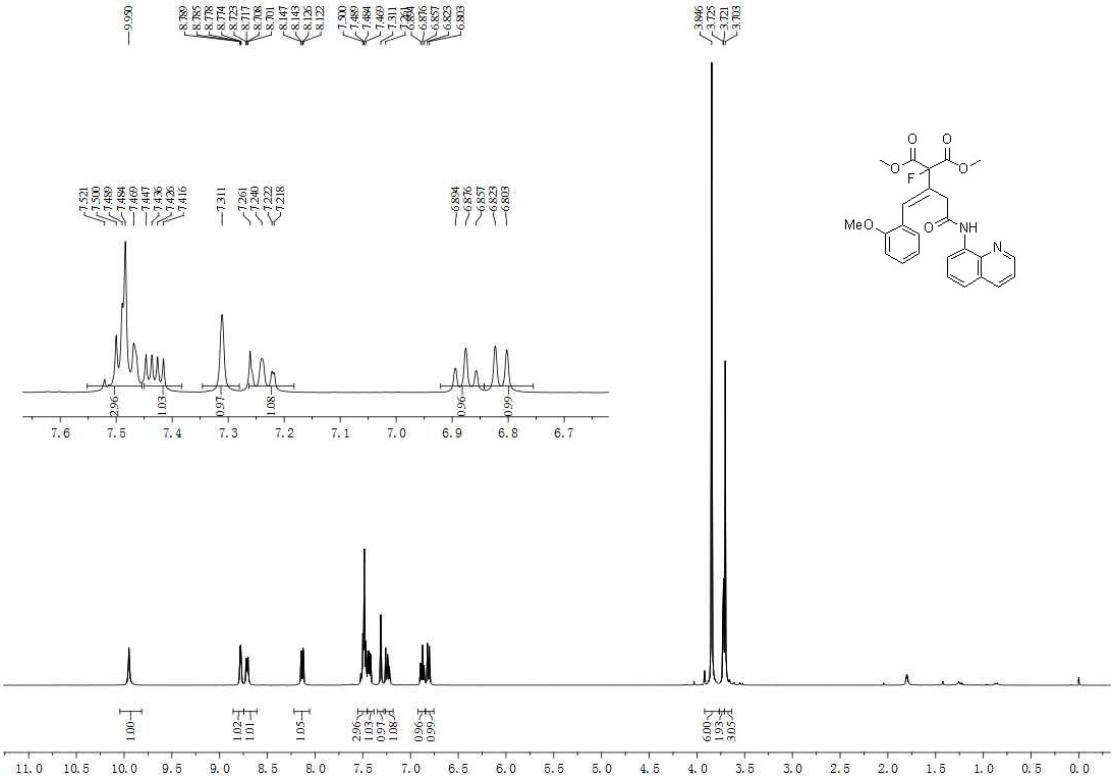
Product 4p

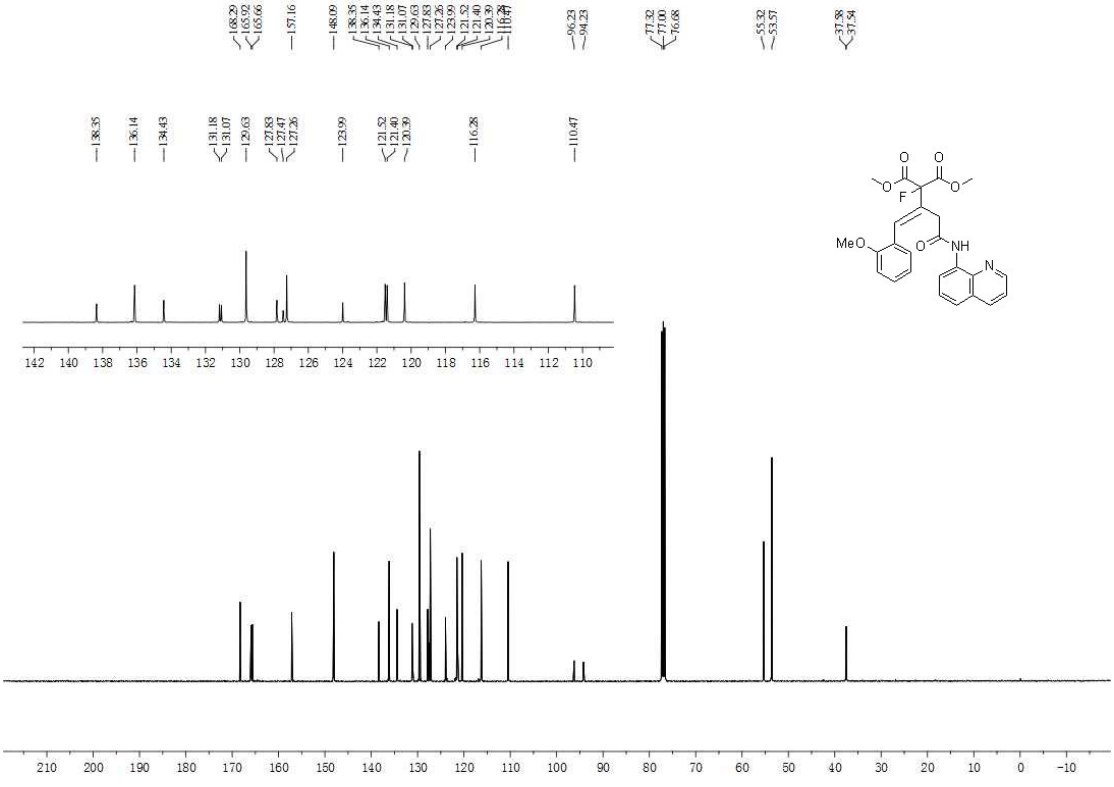

9.883
8.790
8.786
8.779
8.776
8.722
8.715
8.708
8.670
8.158
8.154
8.137
8.134
7.613
7.607
7.597
7.590
7.532
7.511
7.505
7.497
7.485
7.458
7.447
7.437
7.427
7.385
7.380
7.366
7.363
7.308
7.262
7.241
7.236
7.229
7.217
7.213
7.206
7.199
7.195
7.191
7.176
3.880
3.673
3.668
Cl
O
O
O
O
F
O
NH
N
1.01
1.04
1.04
1.05
3.07
1.11
1.02
0.96
2.06
6.00
1.93
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

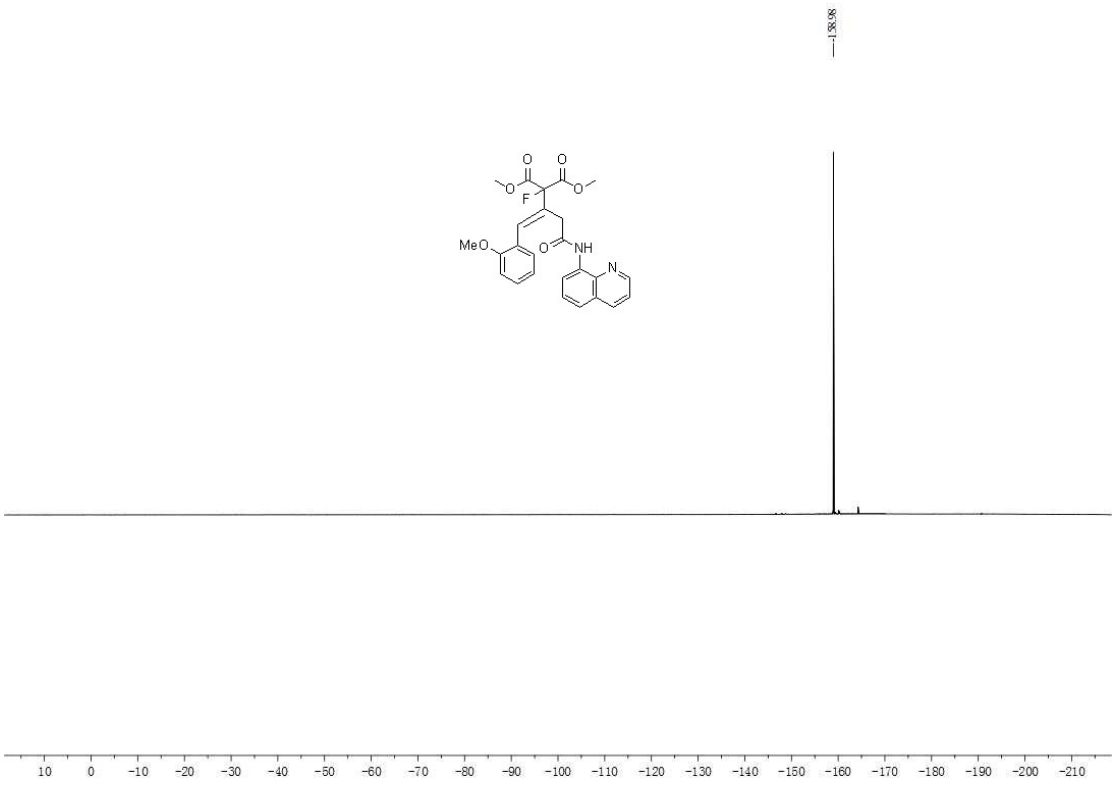

167.74
165.62
165.36
148.15
138.28
136.22
134.28
133.82
133.66
132.23
132.12
130.17
129.55
129.43
129.39
129.34
127.86
127.26
126.90
121.61
121.38
116.34
95.78
93.77
77.32
77.00
76.68
53.71
37.19
37.15
O
O
O
O
F
Cl
O
NH
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


-160.15
O
O
O
O
F
Cl
O
NH
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

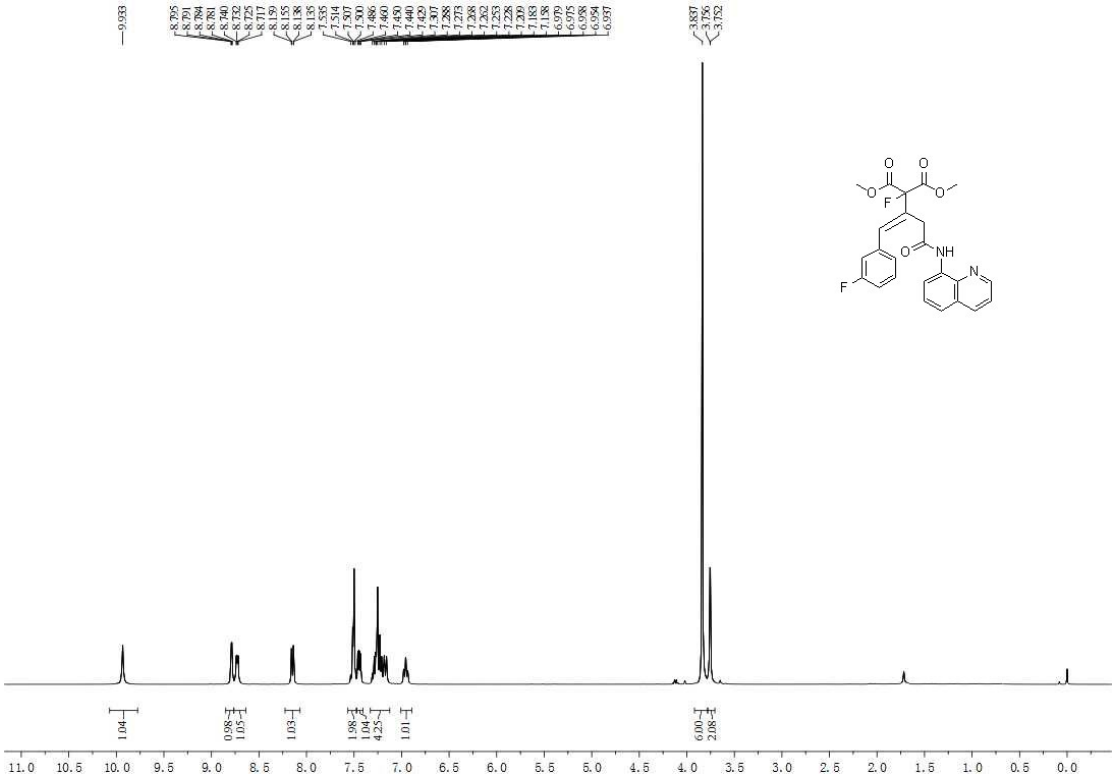
Product 4q

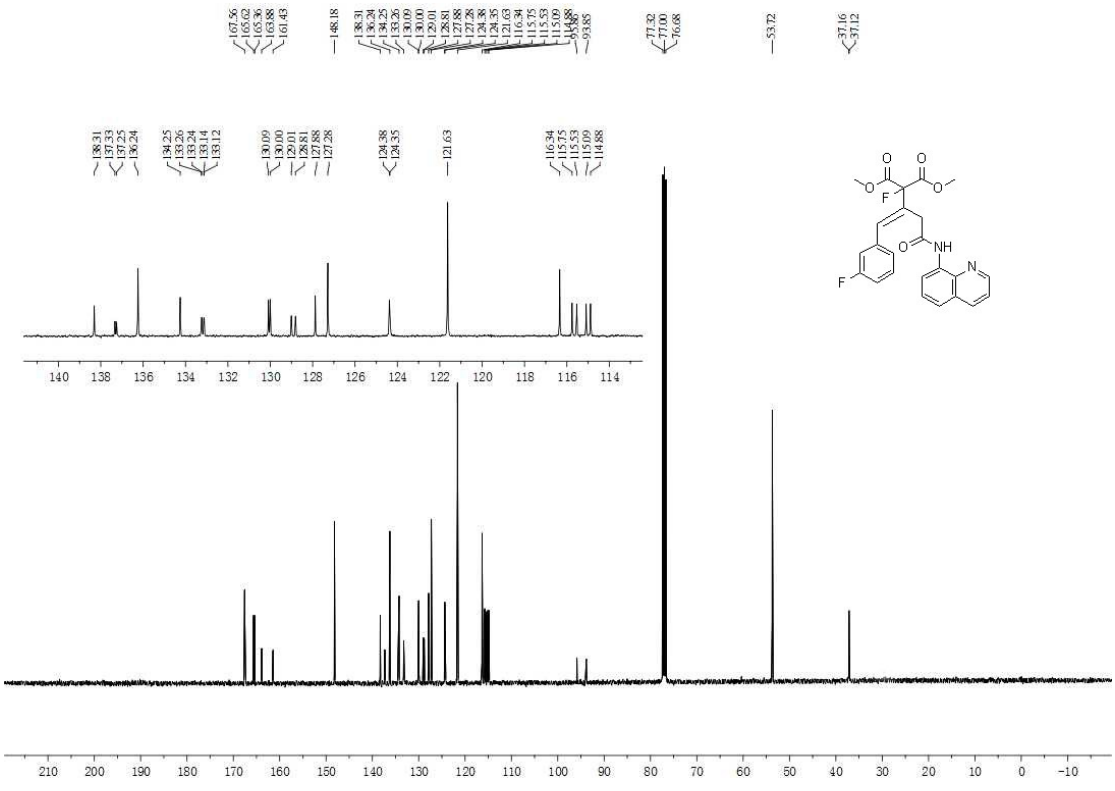


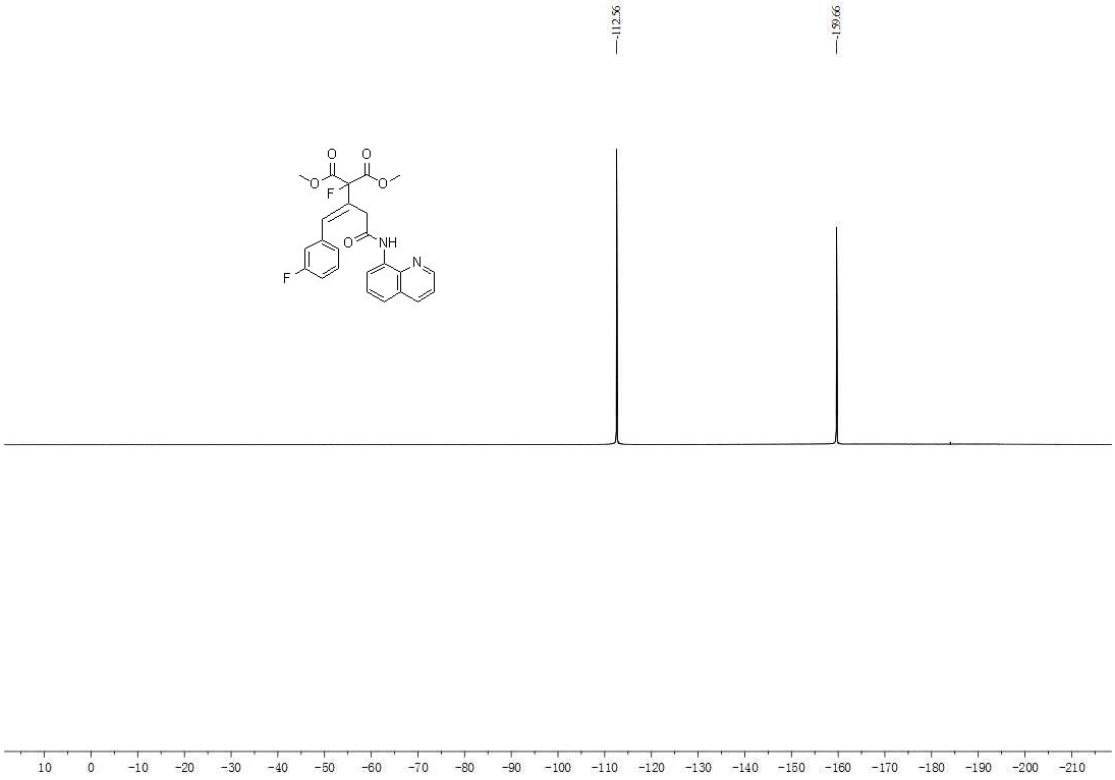



-138.98
MeO
NH
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

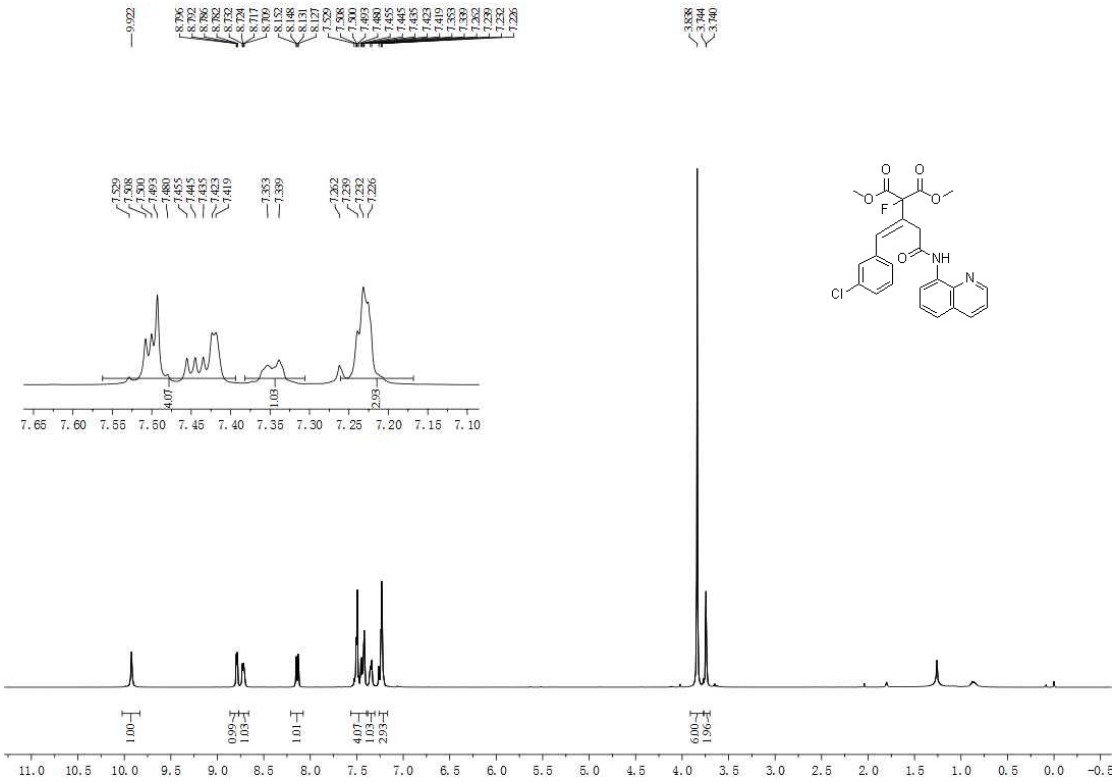
Product 4r

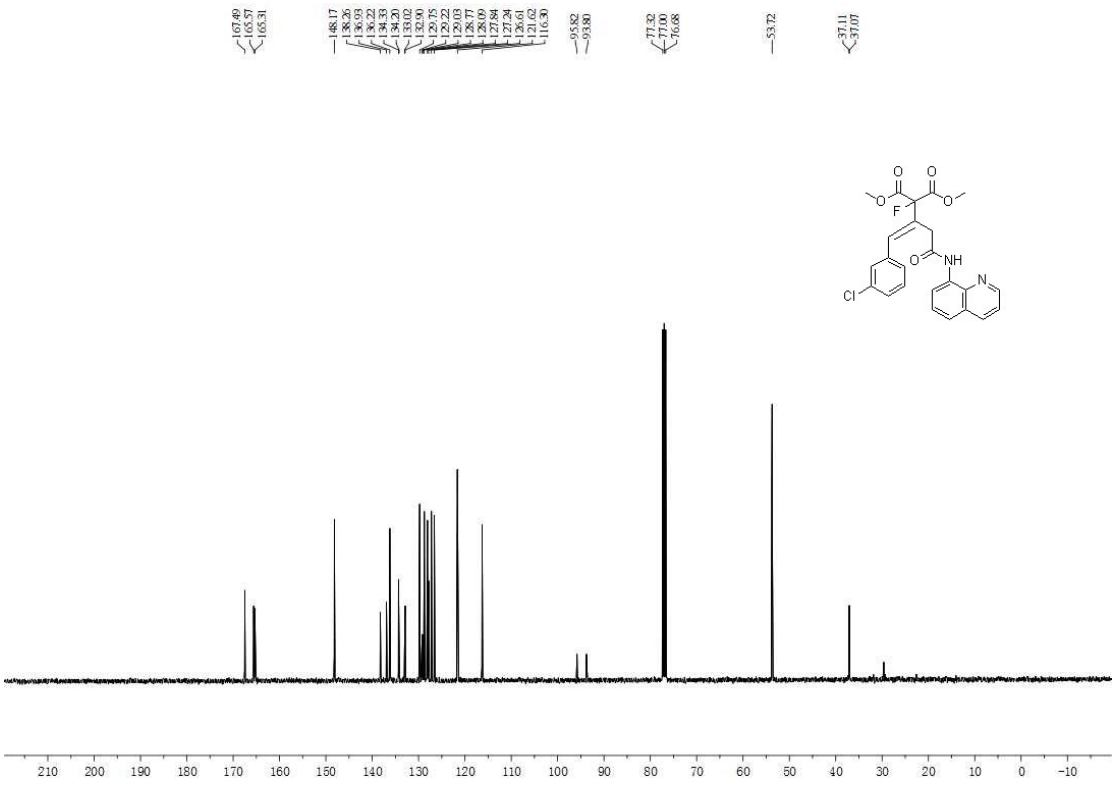

9.933
8.795
8.791
8.784
8.781
8.740
8.732
8.725
8.717
8.159
8.155
8.138
8.135
7.535
7.534
7.507
7.500
7.486
7.460
7.450
7.440
7.429
7.307
7.288
7.273
7.268
7.202
7.253
7.228
7.199
7.189
7.158
6.979
6.975
6.958
6.954
6.937
3.837
3.756
3.752
F
NH
1.04
0.98
1.05
1.03
1.98
1.04
4.25
1.01
6.00
2.08
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

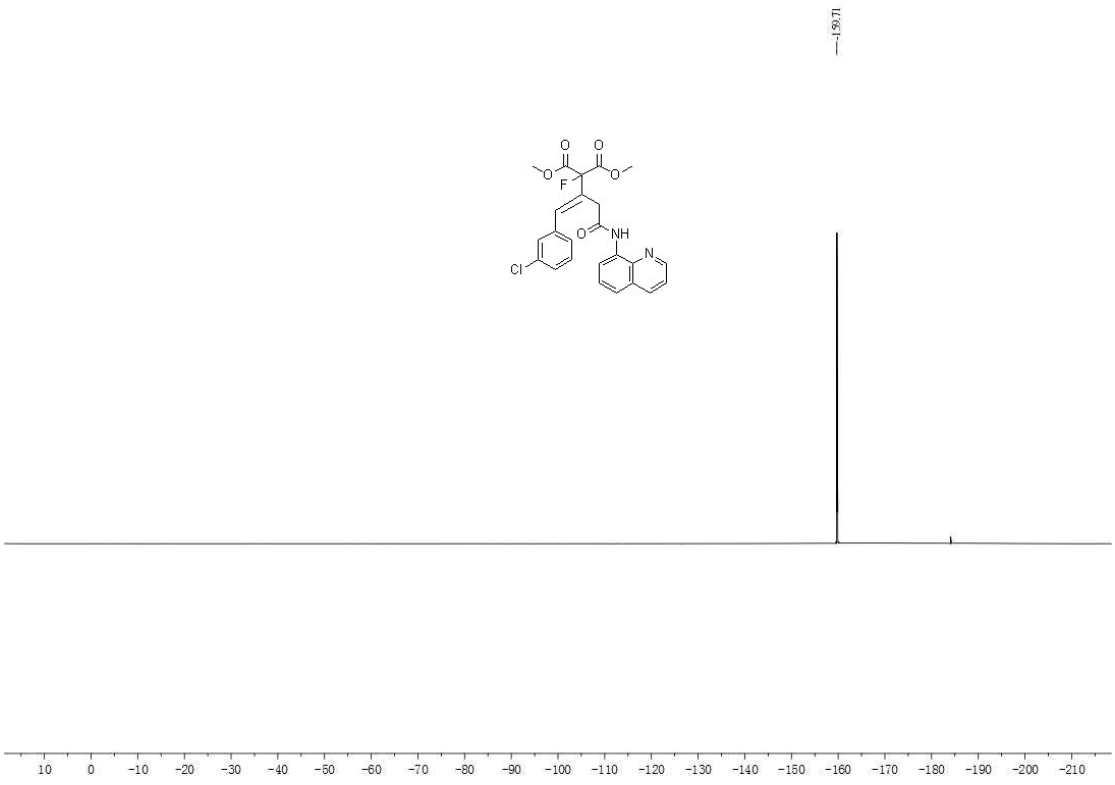




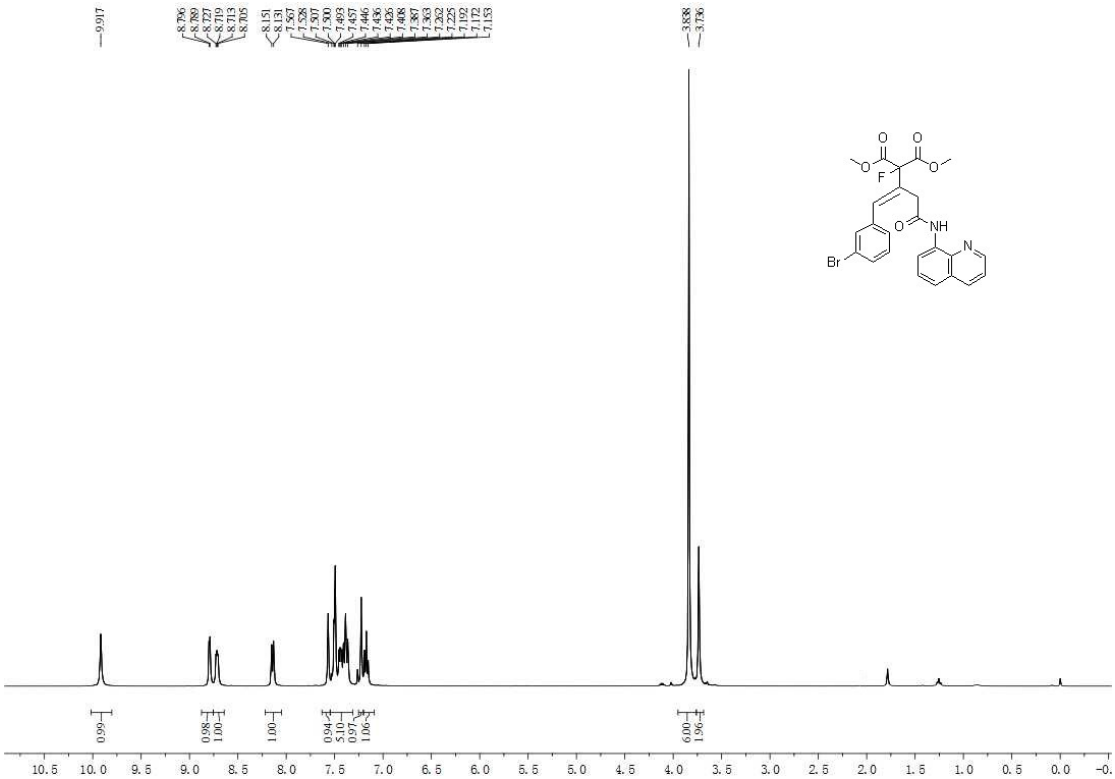
Product 4s

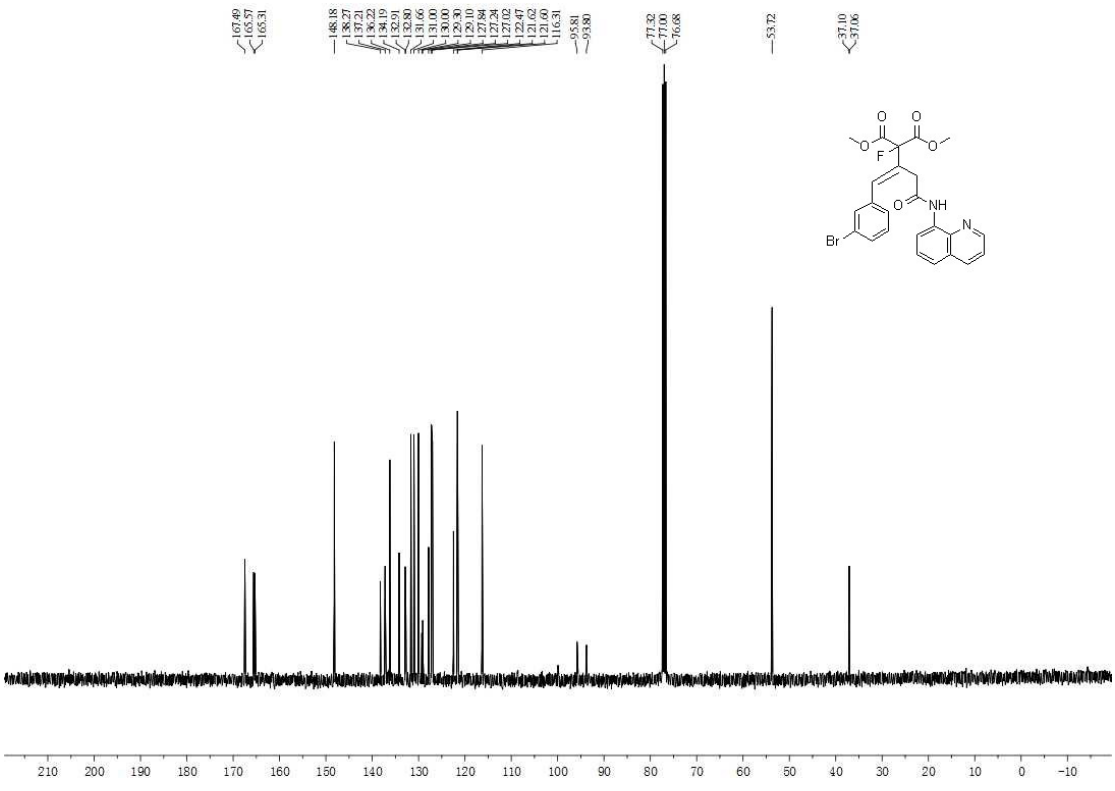


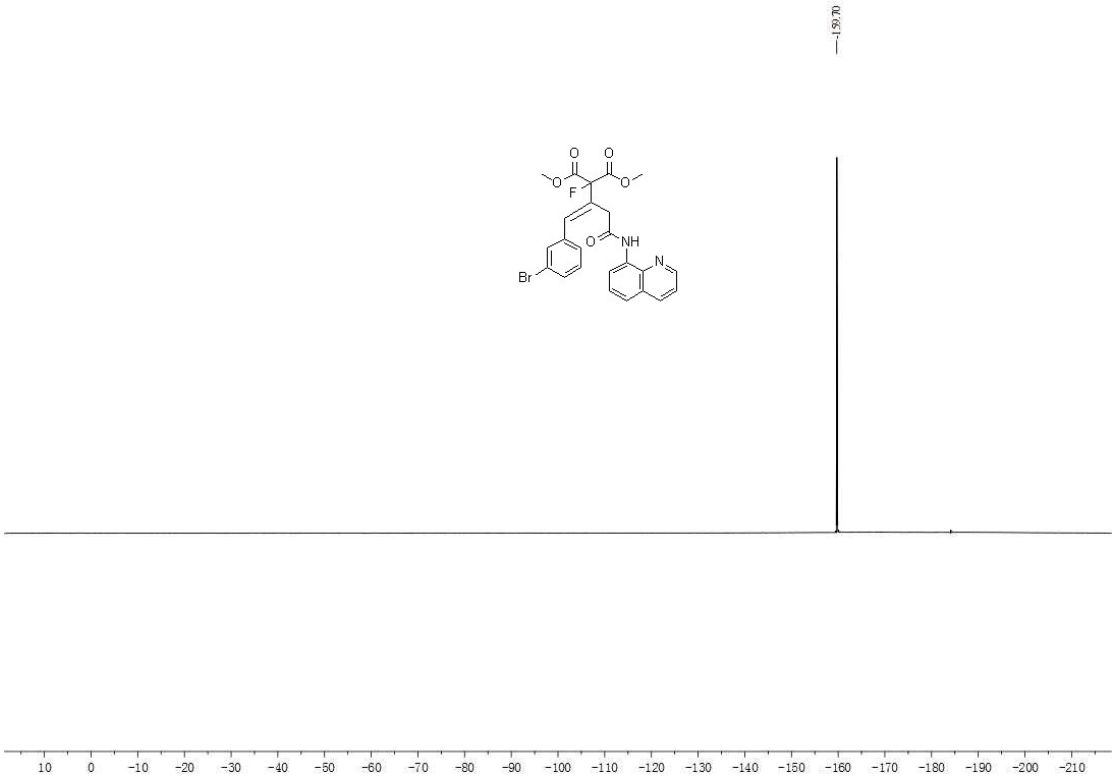



-159.71
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

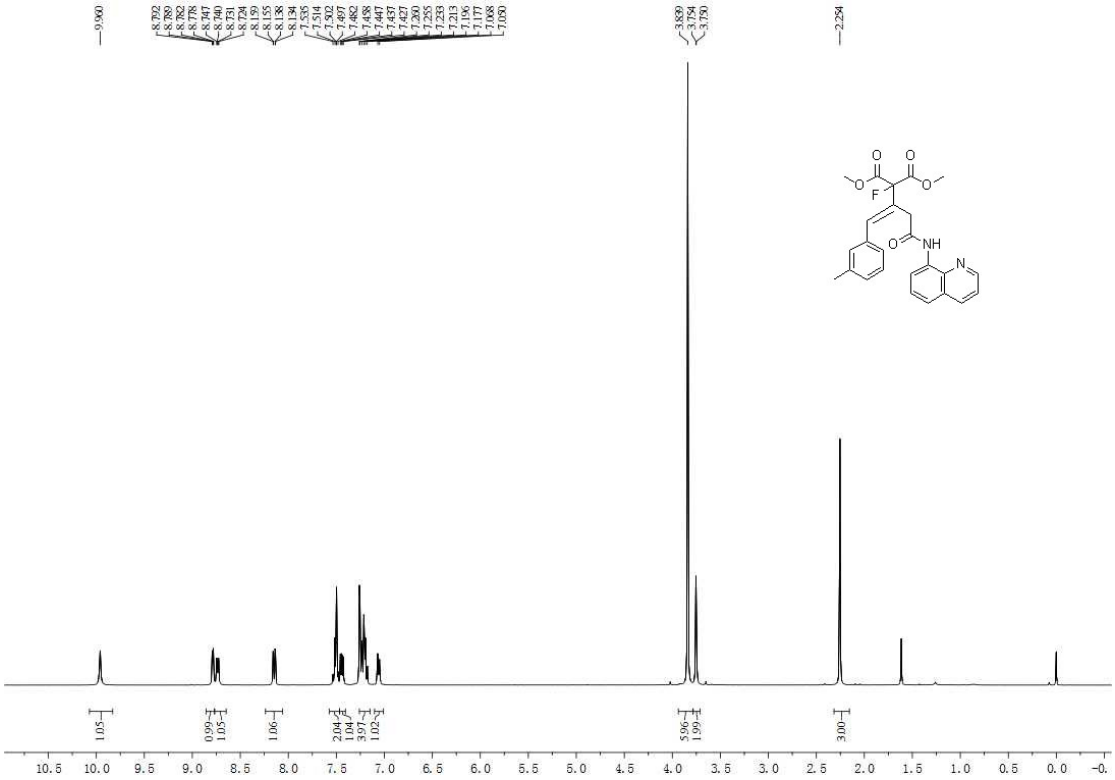
Product 4t

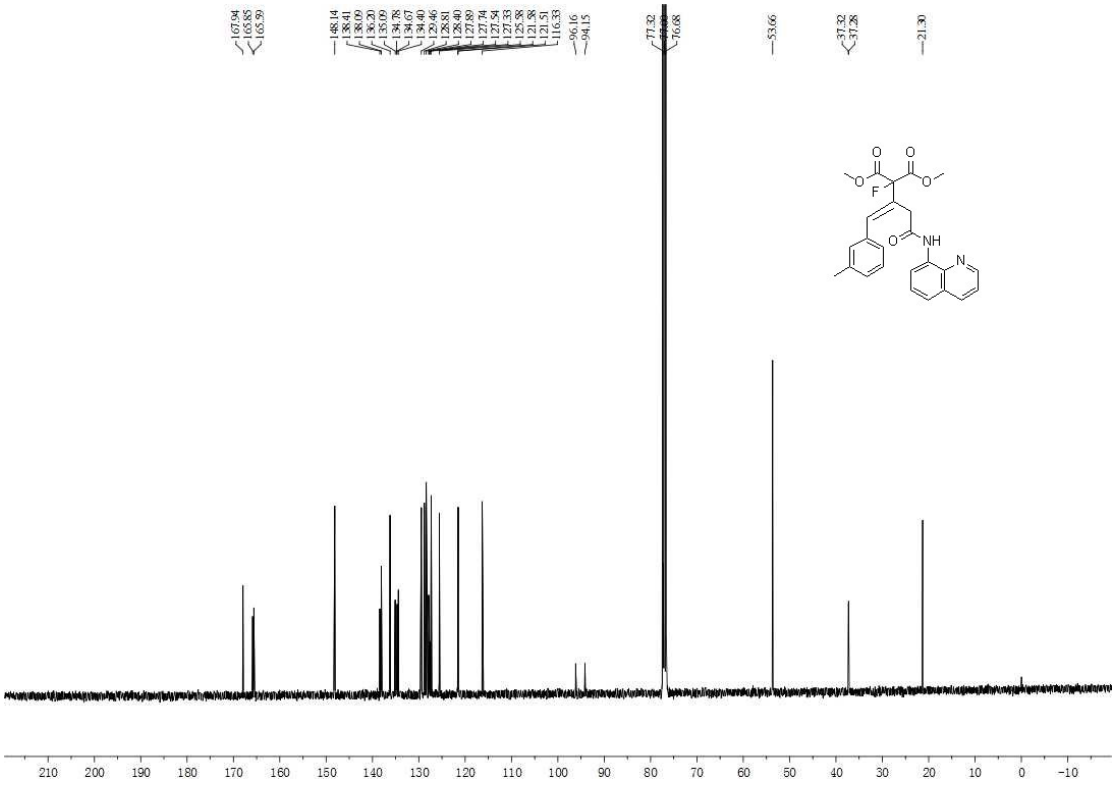

9.917
8.706
8.709
8.727
8.719
8.713
8.705
8.151
8.131
7.567
7.528
7.507
7.500
7.493
7.457
7.446
7.436
7.425
7.408
7.387
7.363
7.252
7.225
7.193
7.172
7.153
3.838
3.736
0.99
0.98
1.00
1.00
0.94
5.10
0.97
1.06
6.00
1.96
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

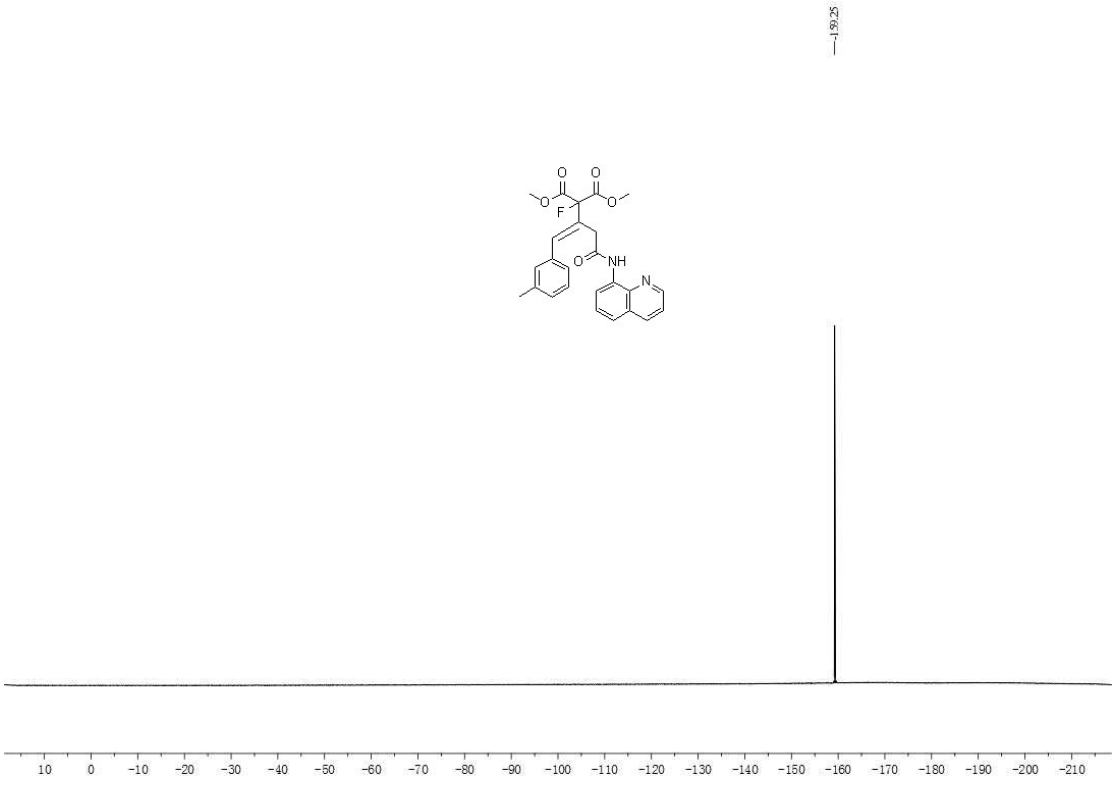

167.49
165.57
165.31
148.18
138.27
137.21
136.22
134.19
132.91
132.50
131.66
131.06
130.00
129.30
129.10
127.84
127.24
127.02
121.67
121.62
121.60
116.31
95.81
93.80
77.32
77.00
76.68
53.72
37.10
37.06
O
O
O
O
F
O
NH
N
Br
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


-159.70
O
O
O
O
F
O
NH
N
Br
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

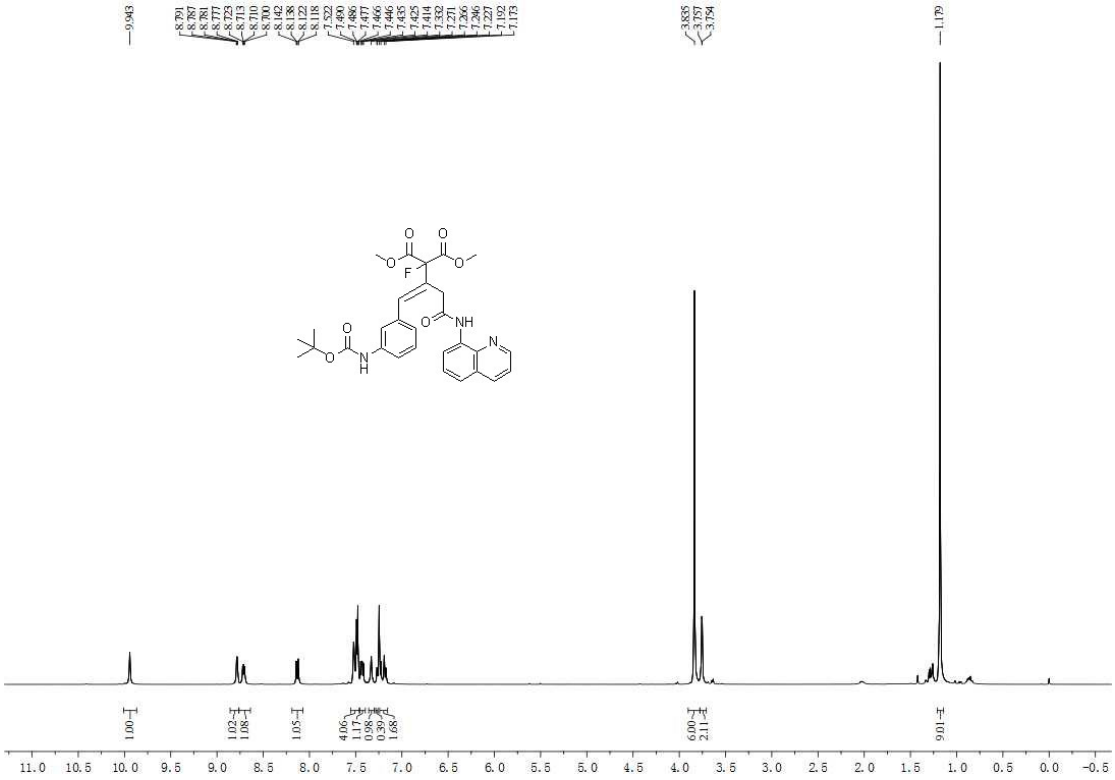
Product 4u

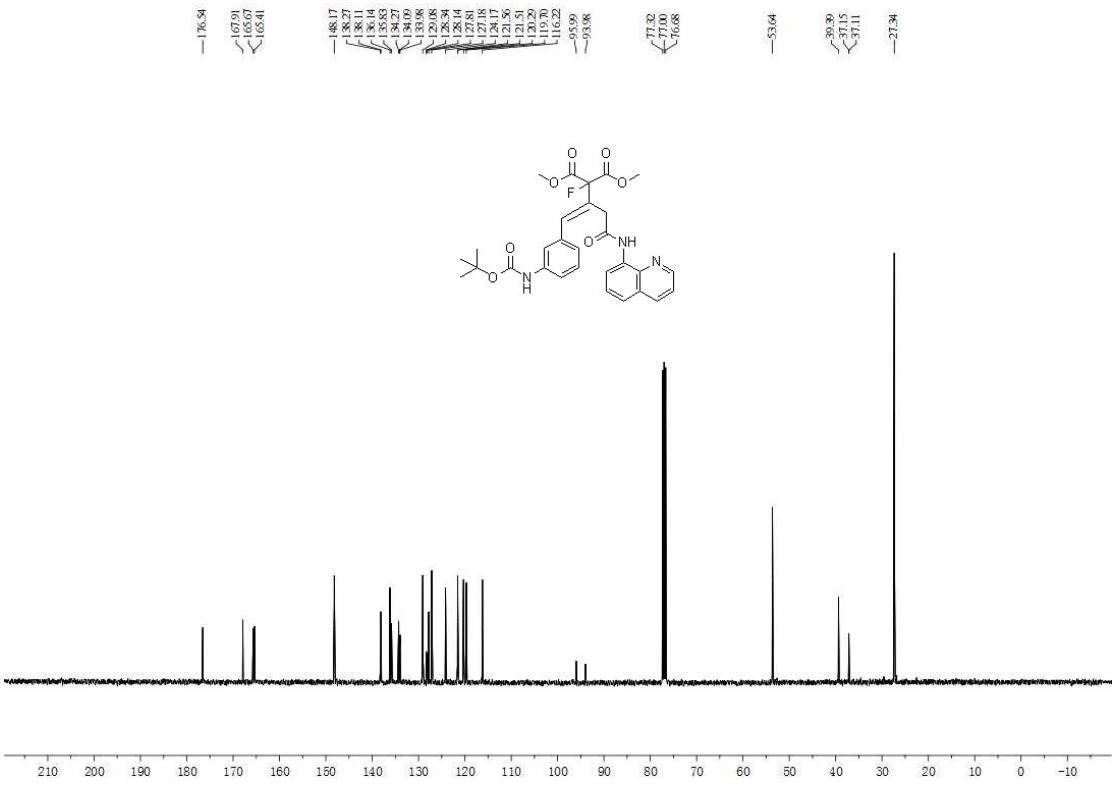

9.960
8.792
8.788
8.782
8.778
8.747
8.740
8.731
8.724
8.159
8.155
8.138
8.134
7.535
7.514
7.502
7.497
7.482
7.478
7.447
7.437
7.427
7.200
7.255
7.233
7.213
7.196
7.177
7.177
7.098
7.090
3.839
3.794
3.790
2.254
1.05
0.99
1.05
1.06
2.04
1.04
3.97
1.02
5.96
1.99
3.00
O
O
O
O
F
NH
N

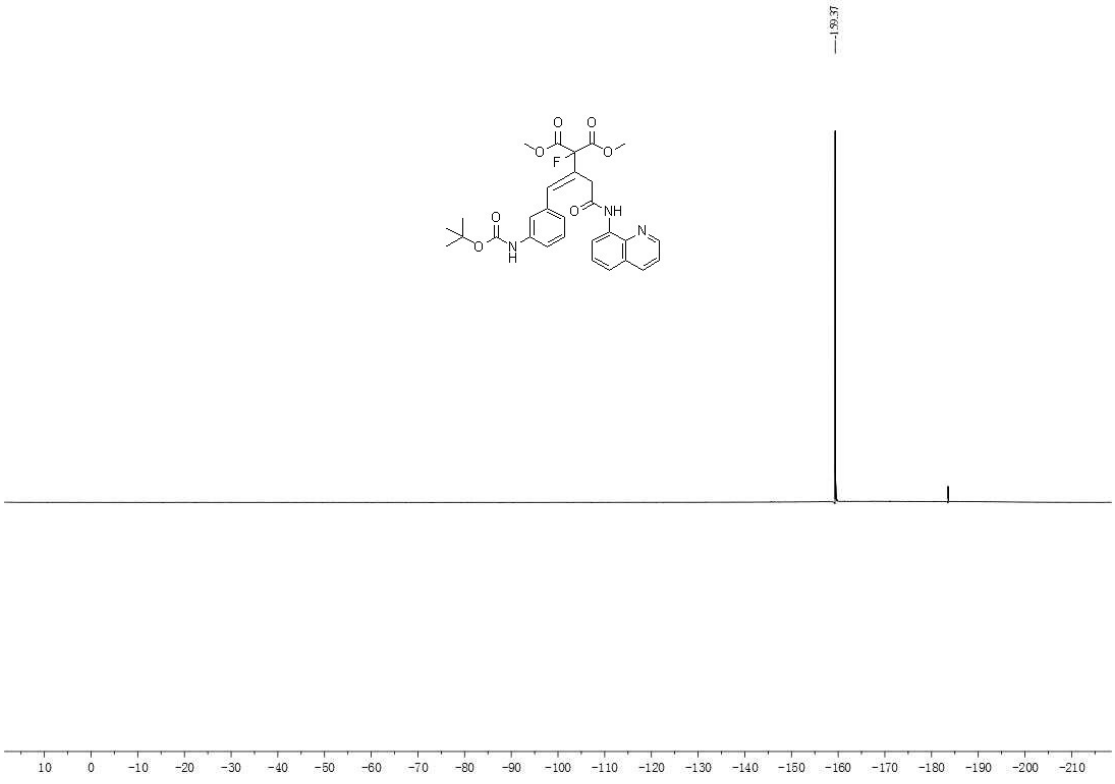

167.94
165.85
165.59
148.14
138.41
138.09
136.20
135.09
134.78
134.67
134.40
129.46
128.81
128.40
127.89
127.74
127.54
127.33
125.58
121.58
121.51
116.33
96.16
94.15
77.32
77.00
76.68
53.66
37.32
37.28
21.30
O
O
O
O
F
NH
N


-159.25
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

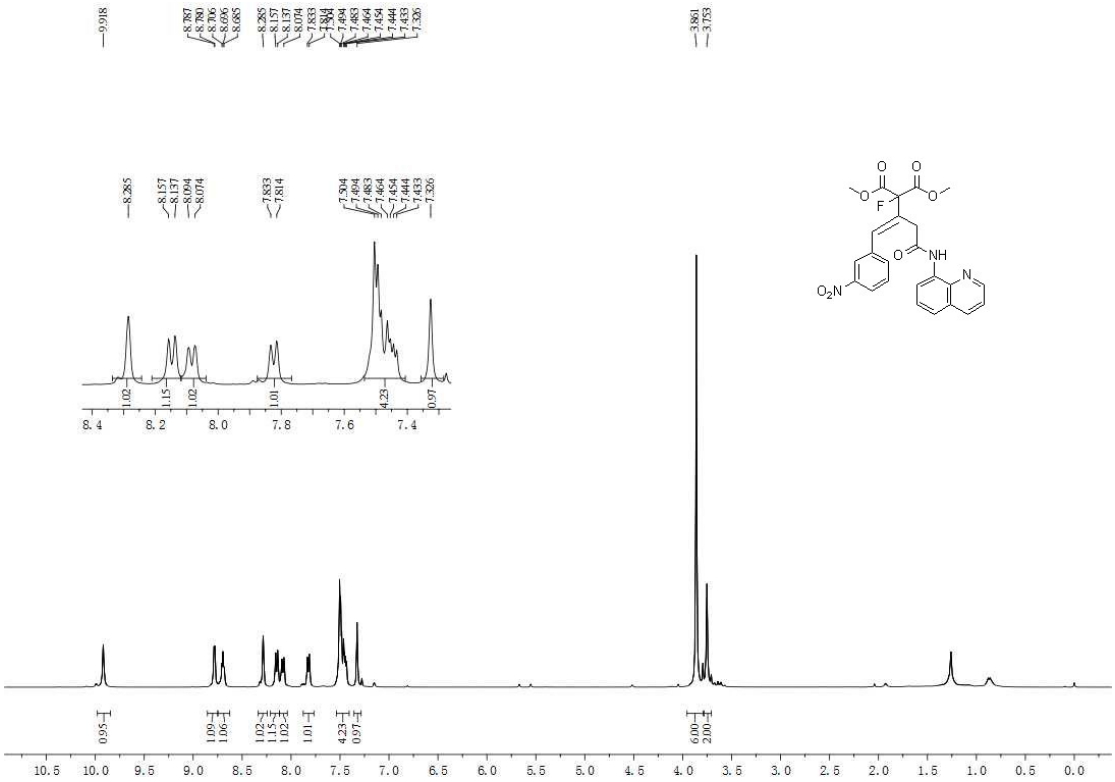
Product 4v

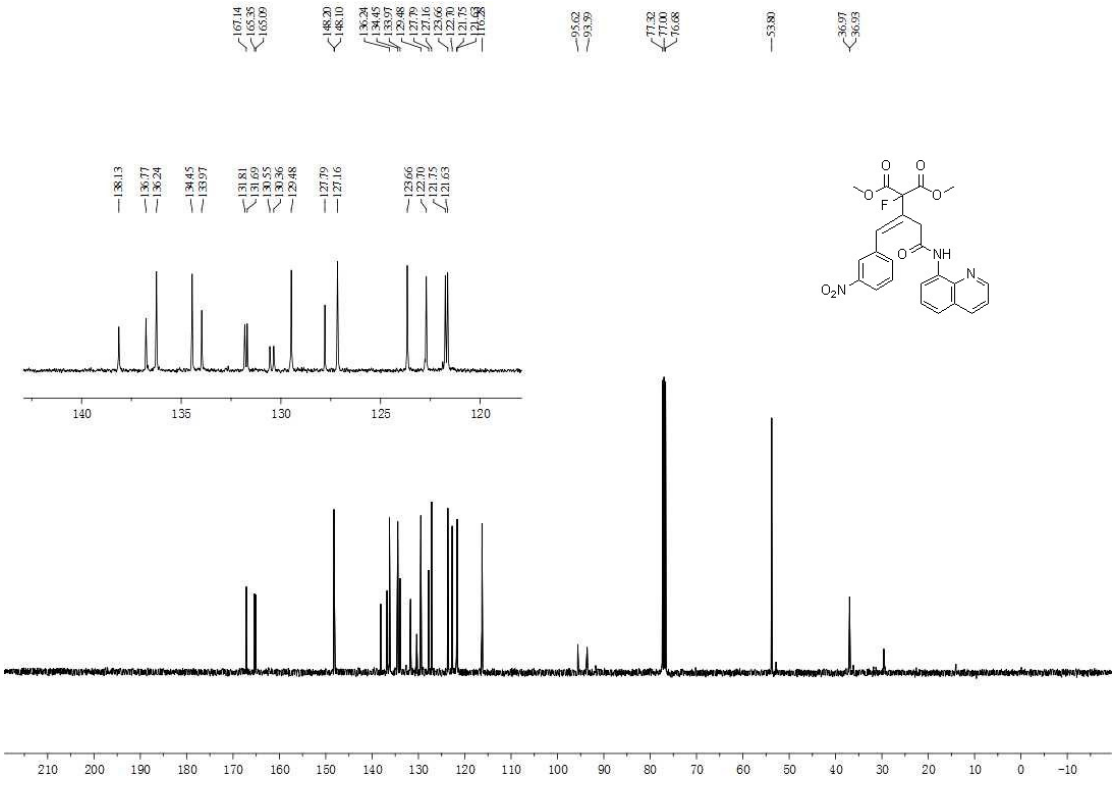

9.943
8.791
8.787
8.781
8.777
8.723
8.713
8.710
8.700
8.142
8.138
8.122
8.118
7.522
7.480
7.466
7.477
7.466
7.446
7.435
7.425
7.414
7.332
7.271
7.266
7.246
7.227
7.192
7.173
3.835
3.757
3.754
1.179
1.00
1.02
1.08
1.05
4.06
1.17
0.98
0.39
1.68
6.00
2.11
9.01
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

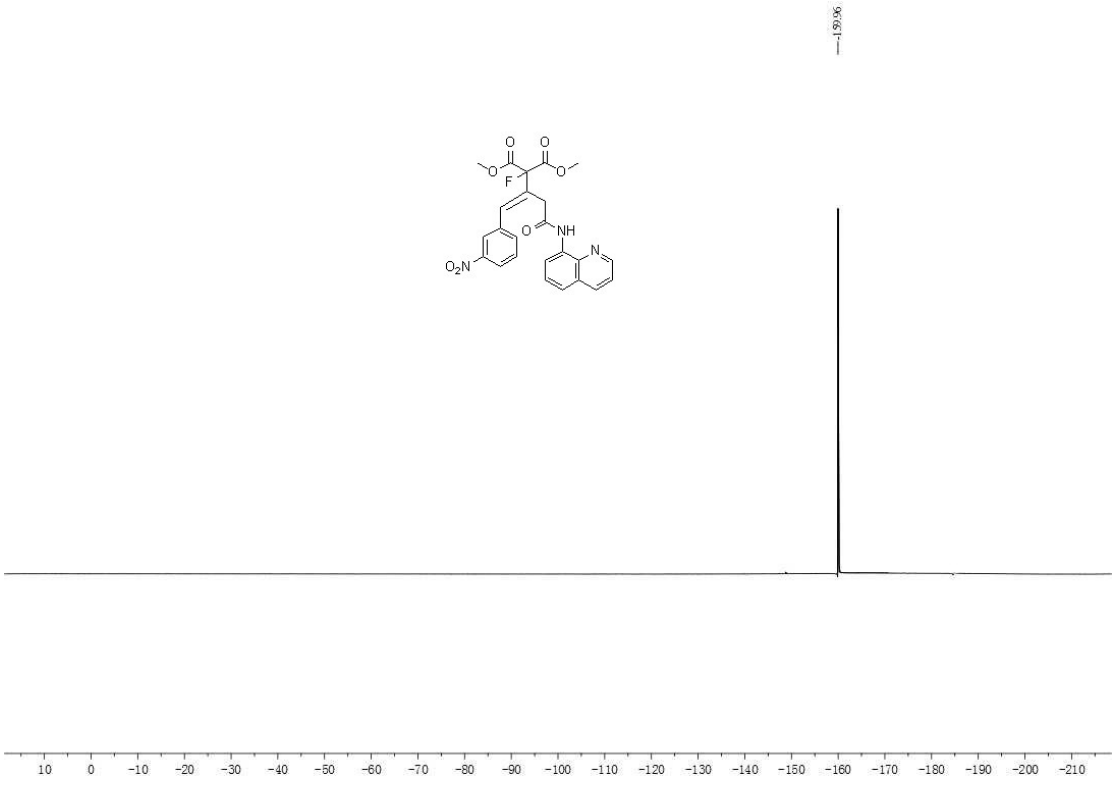

176.54
167.91
165.67
165.41
148.17
138.27
138.11
136.14
135.83
134.27
134.00
133.98
129.08
128.34
128.14
127.81
127.18
124.17
121.56
121.51
120.29
119.70
116.22
95.99
93.98
77.32
77.00
76.68
53.64
39.39
37.15
37.11
27.34
NH
N
F


159.37
NH
N
F

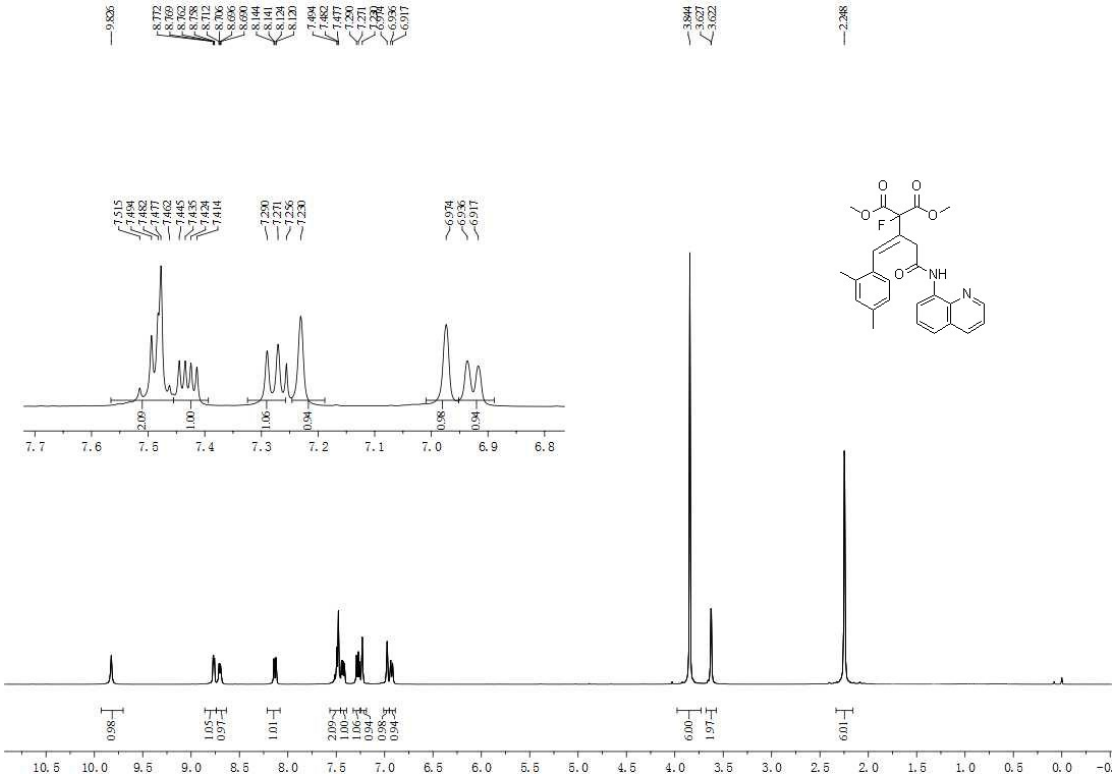
Product 4w

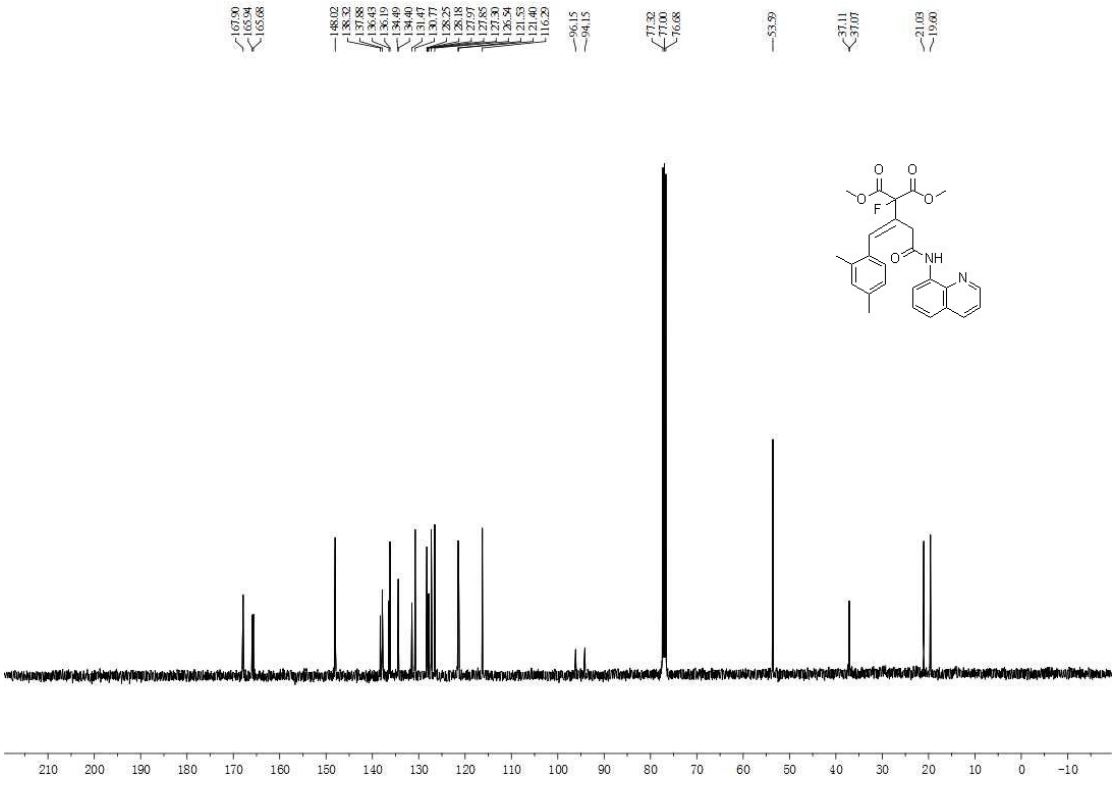


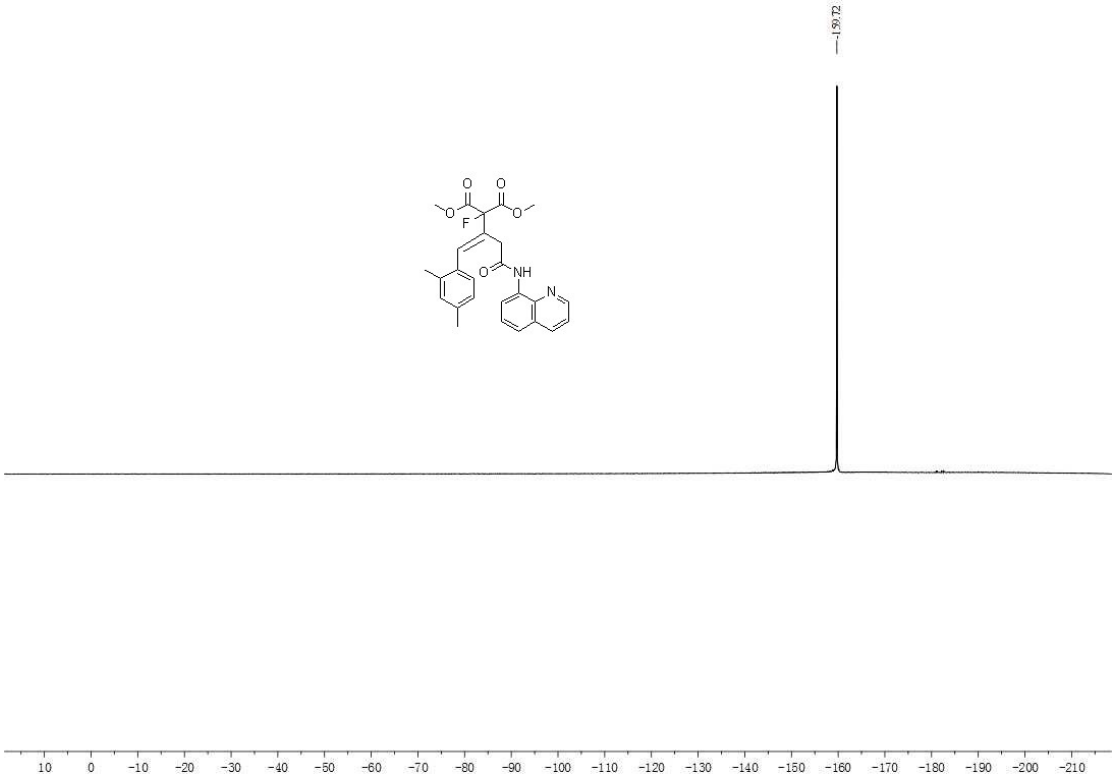




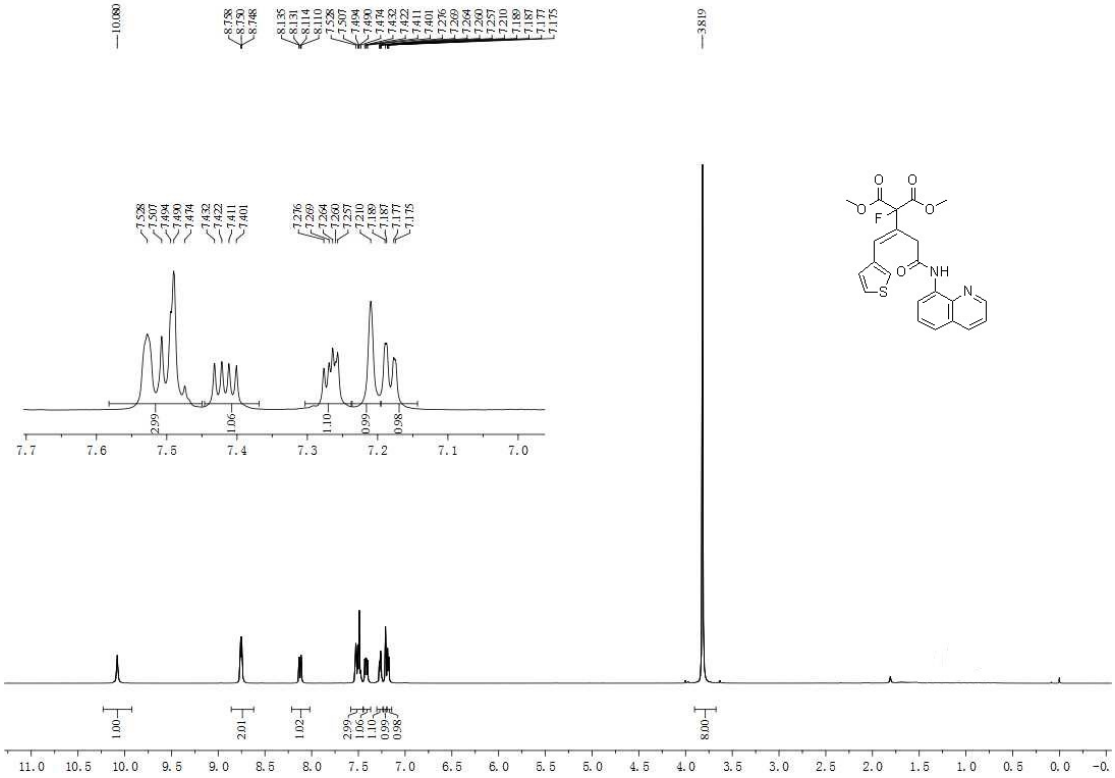
Product 4x

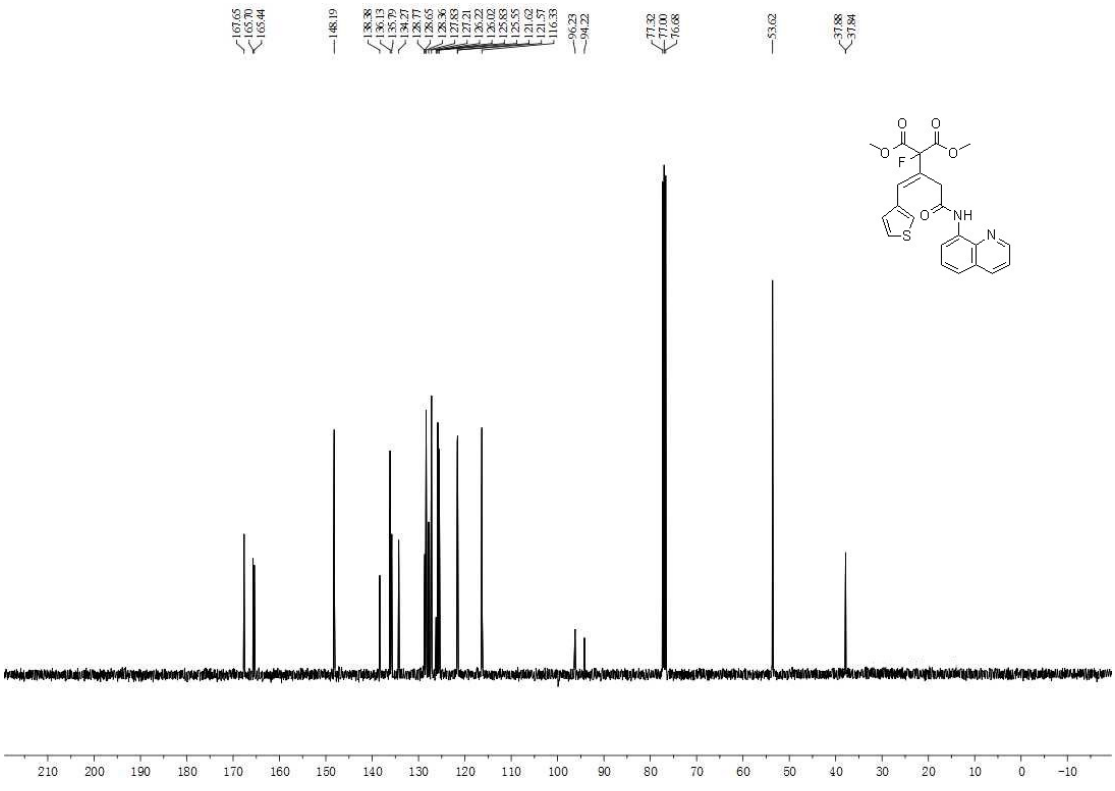


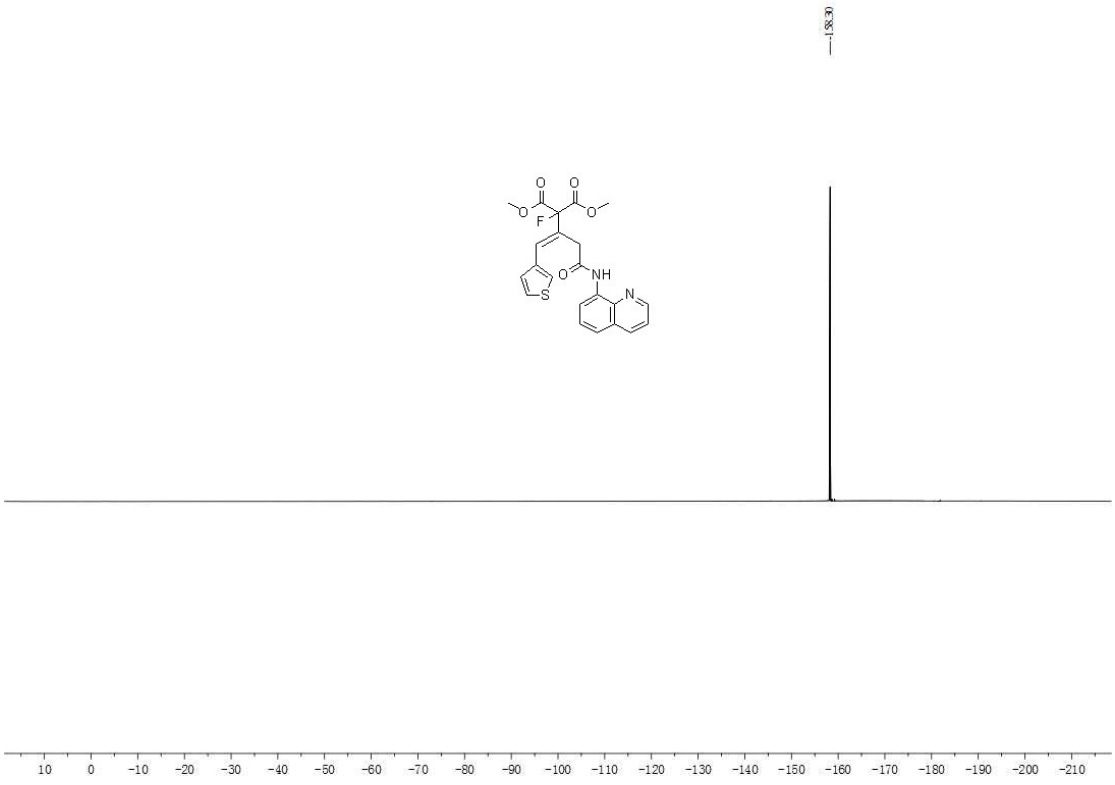

167.90
165.94
165.68
148.02
138.32
137.88
136.43
136.19
134.49
134.40
131.47
130.77
128.25
128.18
127.97
127.85
127.30
126.54
121.53
121.40
116.25
96.15
94.15
77.32
77.00
76.68
53.59
37.11
37.07
21.03
19.60
O
O
O
O
F
NH
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


159.72
O
O
O
O
F
NH
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

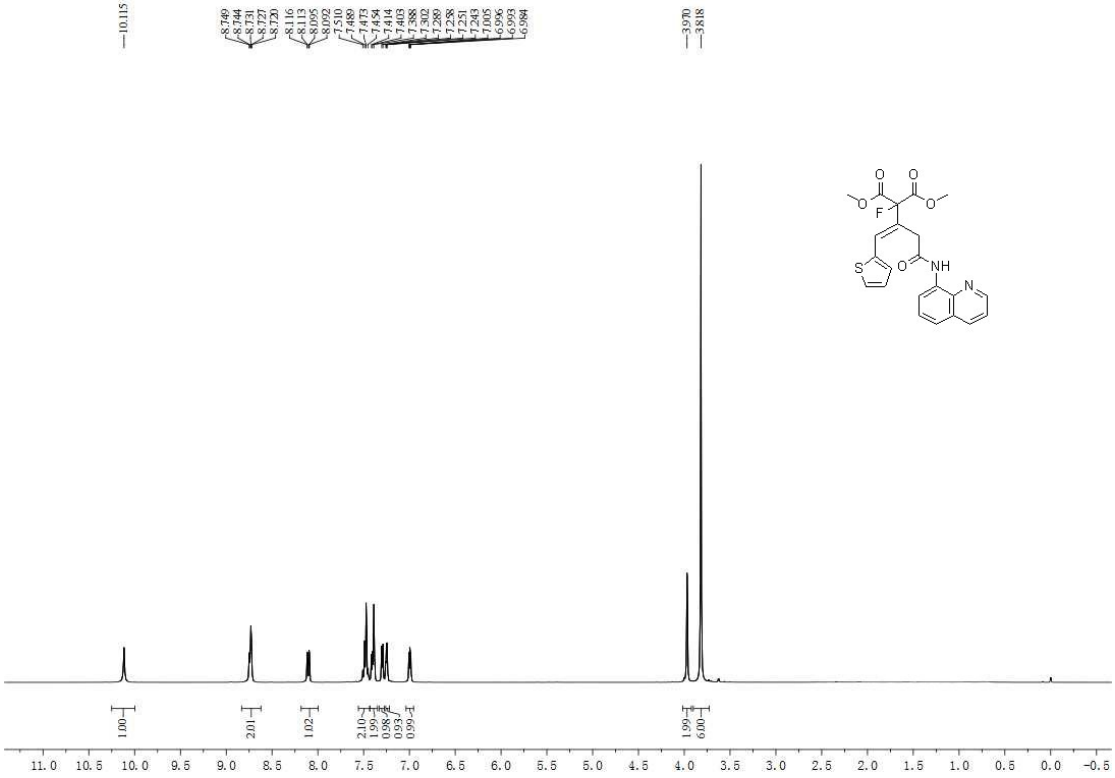
Product 4y

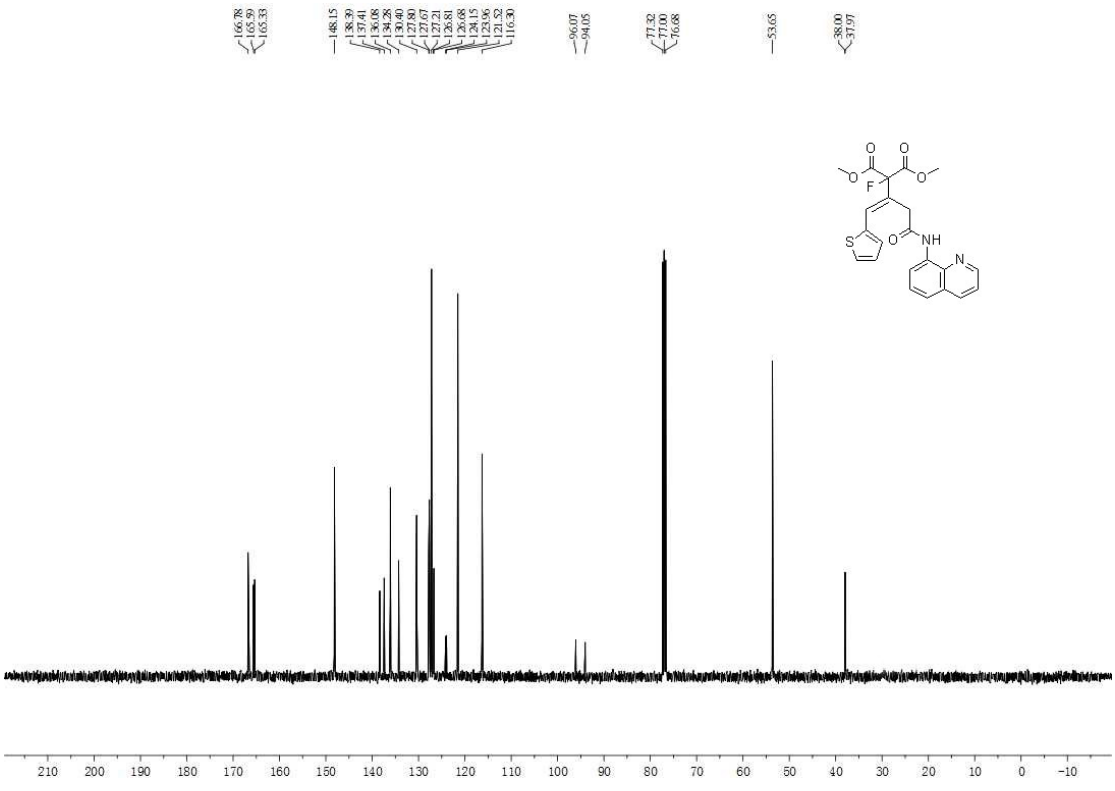


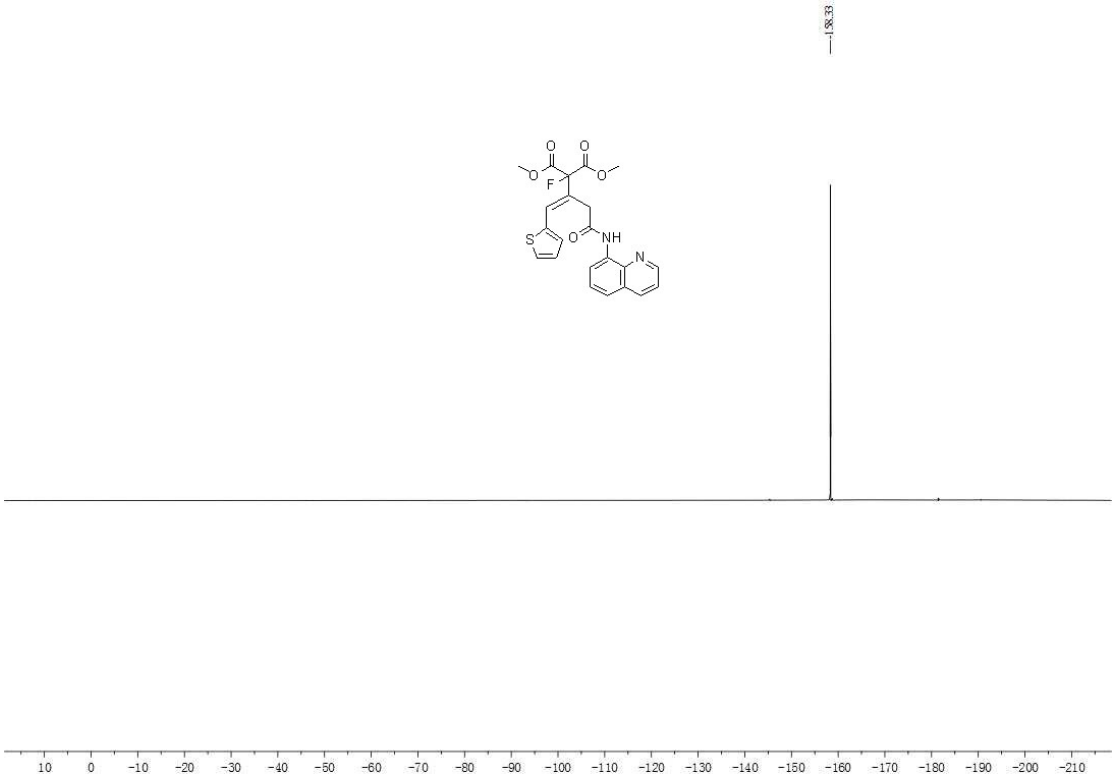



-158.30
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

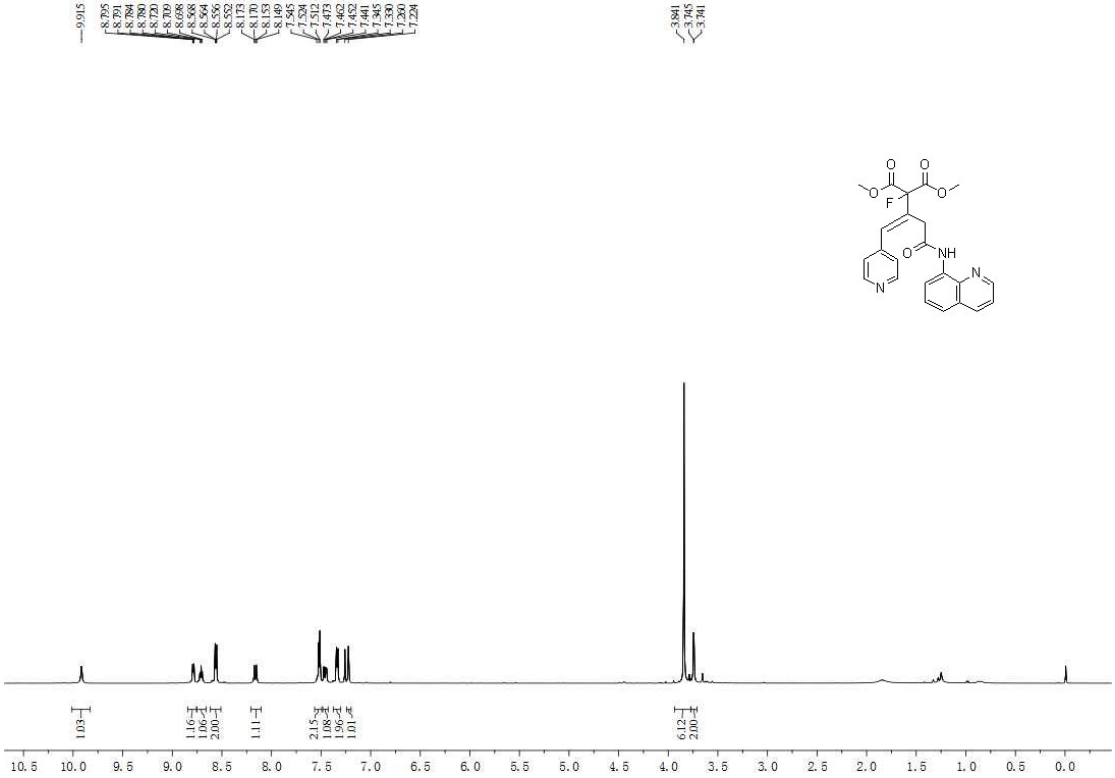
Product 4z

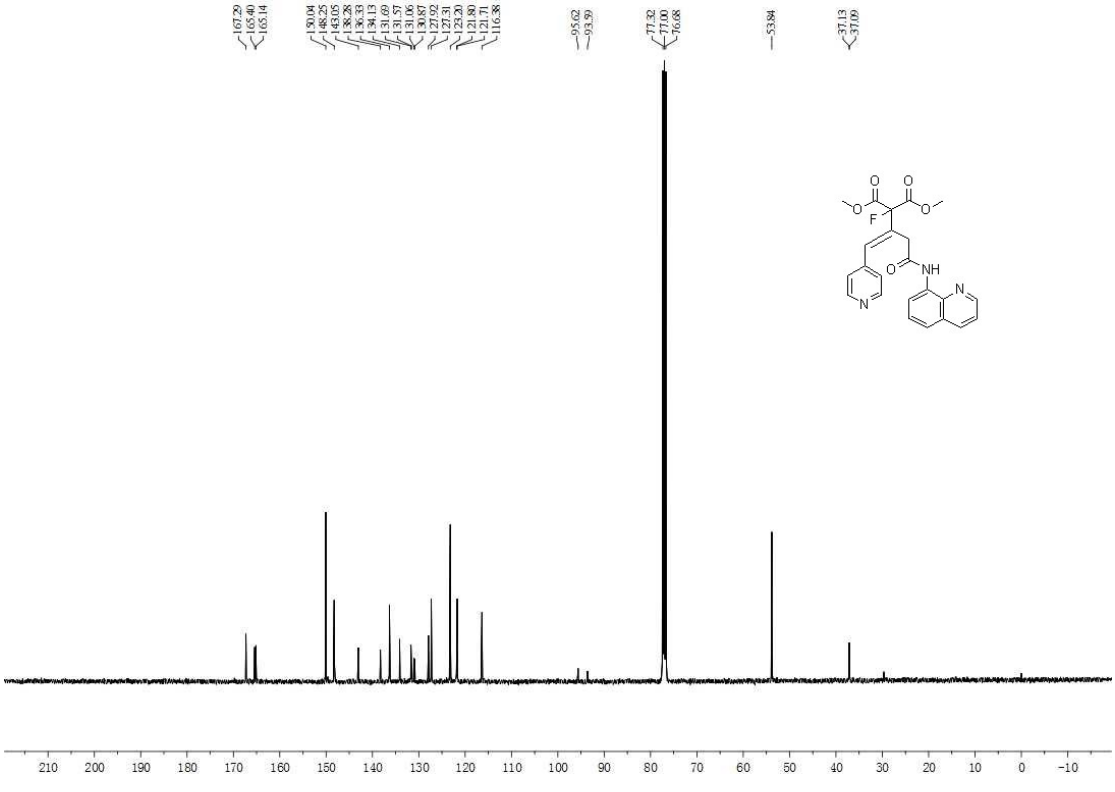

10.115
8.749
8.744
8.731
8.727
8.720
8.116
8.113
8.095
8.092
7.510
7.488
7.473
7.454
7.414
7.403
7.388
7.302
7.289
7.238
7.231
7.243
7.005
6.996
6.993
6.984
3.970
3.818
1.00
2.01
1.02
2.10
1.99
0.98
0.93
0.99
1.99
6.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

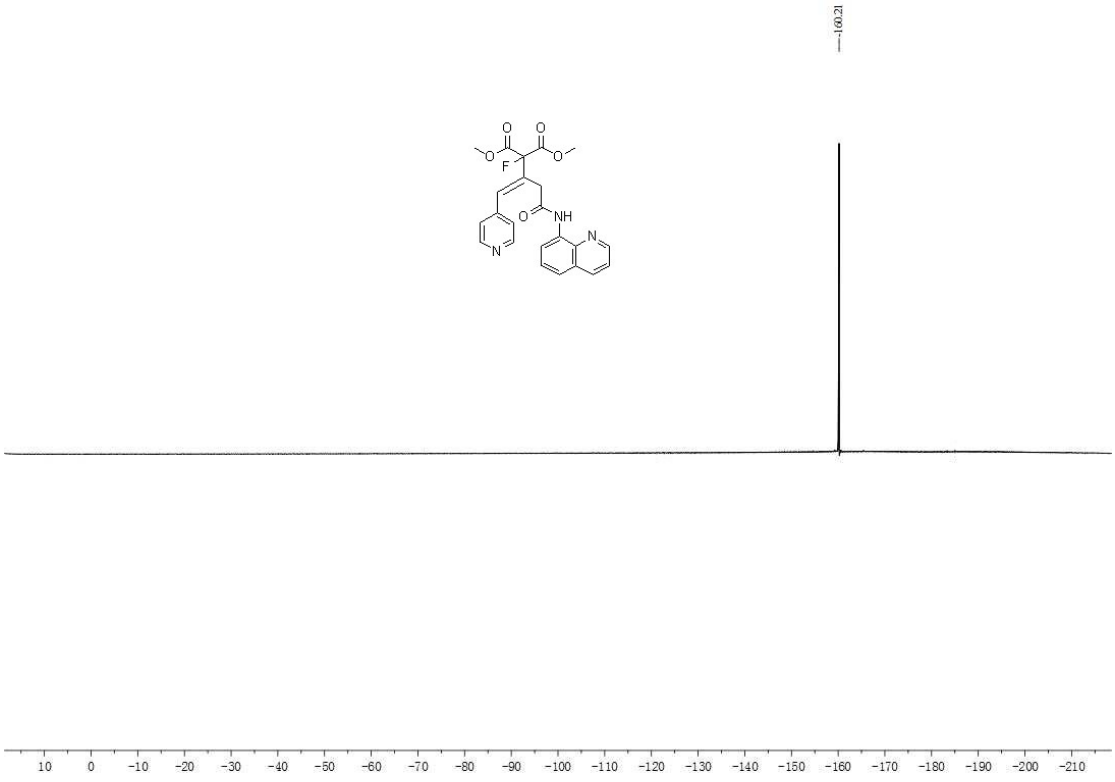

166.78
165.59
165.33
148.15
138.39
137.41
136.08
134.28
130.40
127.80
127.67
127.21
126.81
126.68
124.15
123.96
121.52
116.30
96.07
94.05
77.32
77.00
76.68
53.65
38.00
37.97
O
O
O
O
F
S
O
NH
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


158.33
O
O
O
O
F
S
O
NH
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

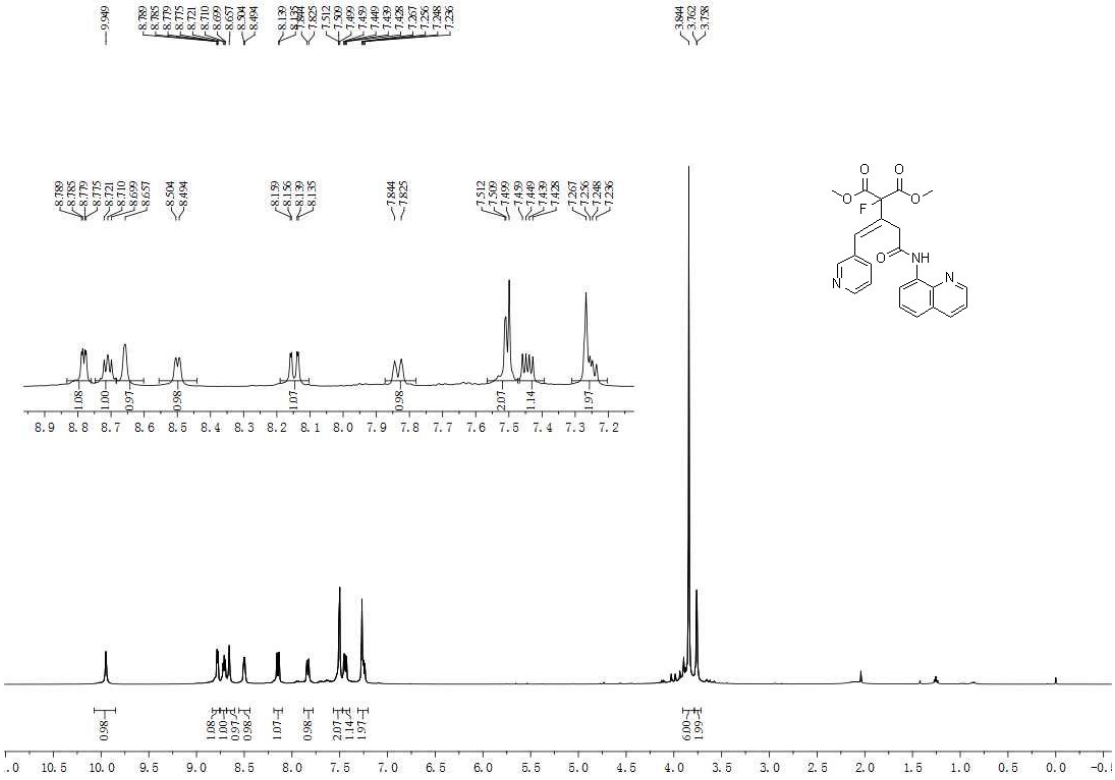
Product 4aa

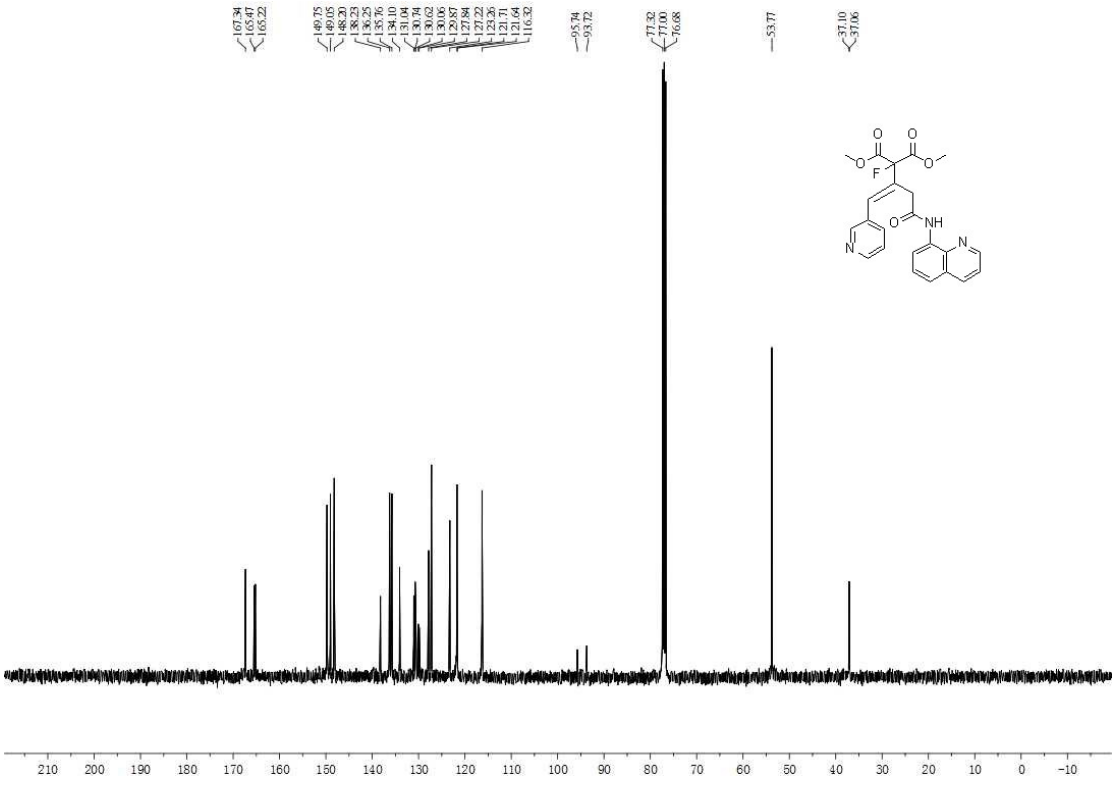


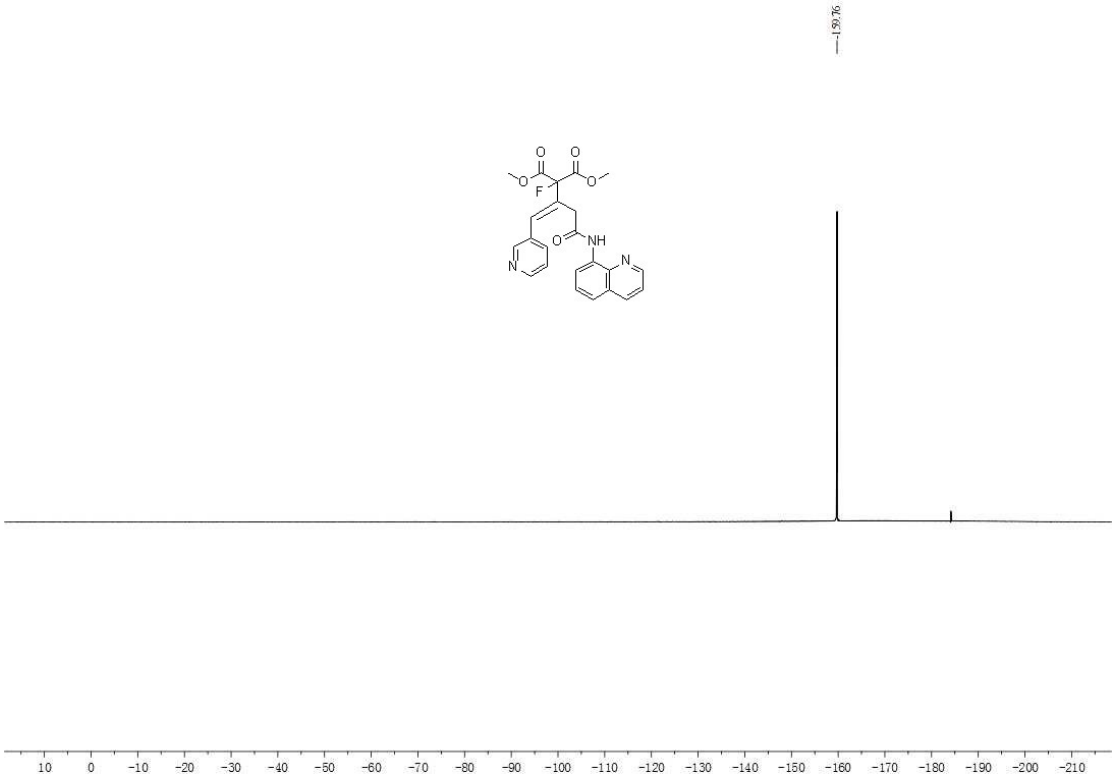



-160.21
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

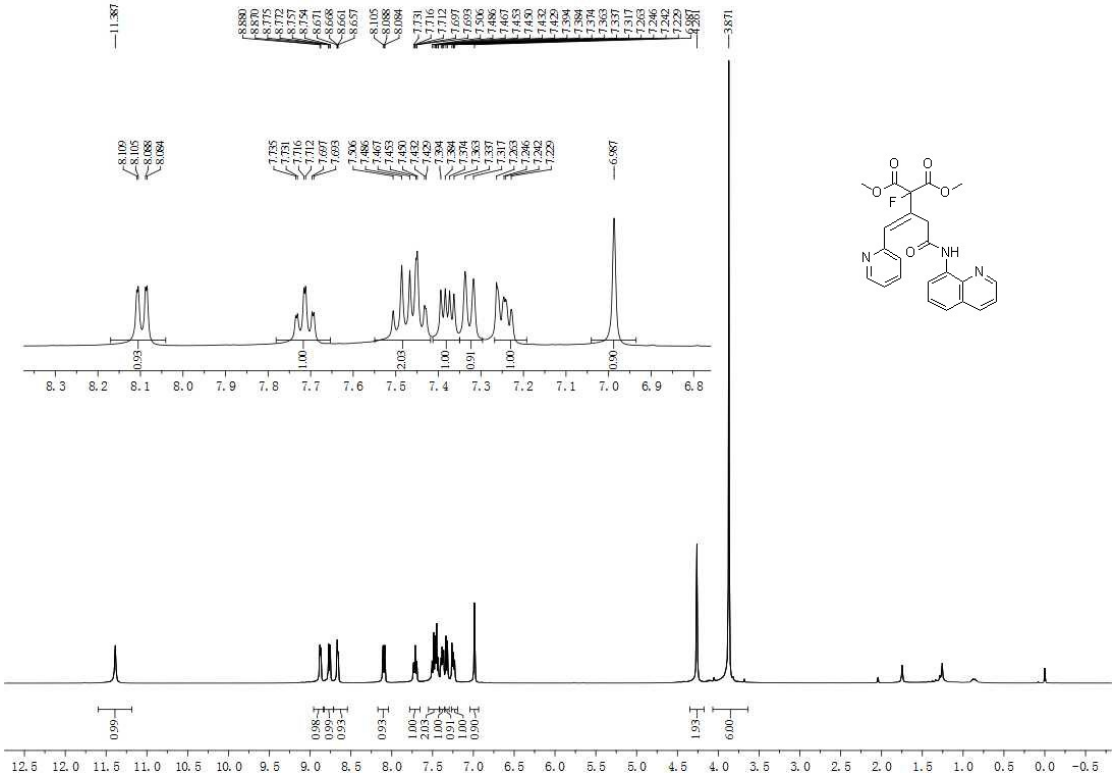
Product 4ab

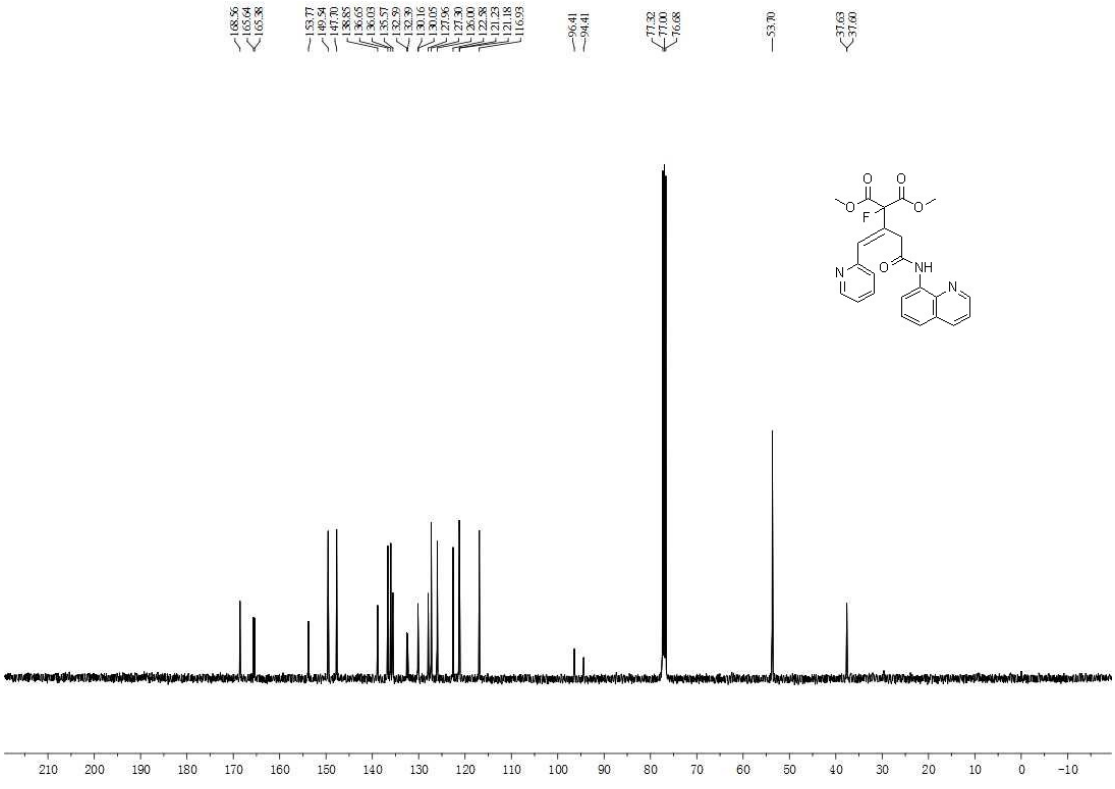

9.949
8.789
8.785
8.779
8.775
8.721
8.710
8.699
8.657
8.504
8.494
8.159
8.156
8.139
8.135
7.844
7.825
7.512
7.509
7.499
7.499
7.449
7.439
7.428
7.267
7.256
7.248
7.236
3.844
3.762
3.758
1.08 1.00 0.97 0.98 1.07 0.98 2.07 1.14 1.97 6.00 1.99
8.9 8.8 8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

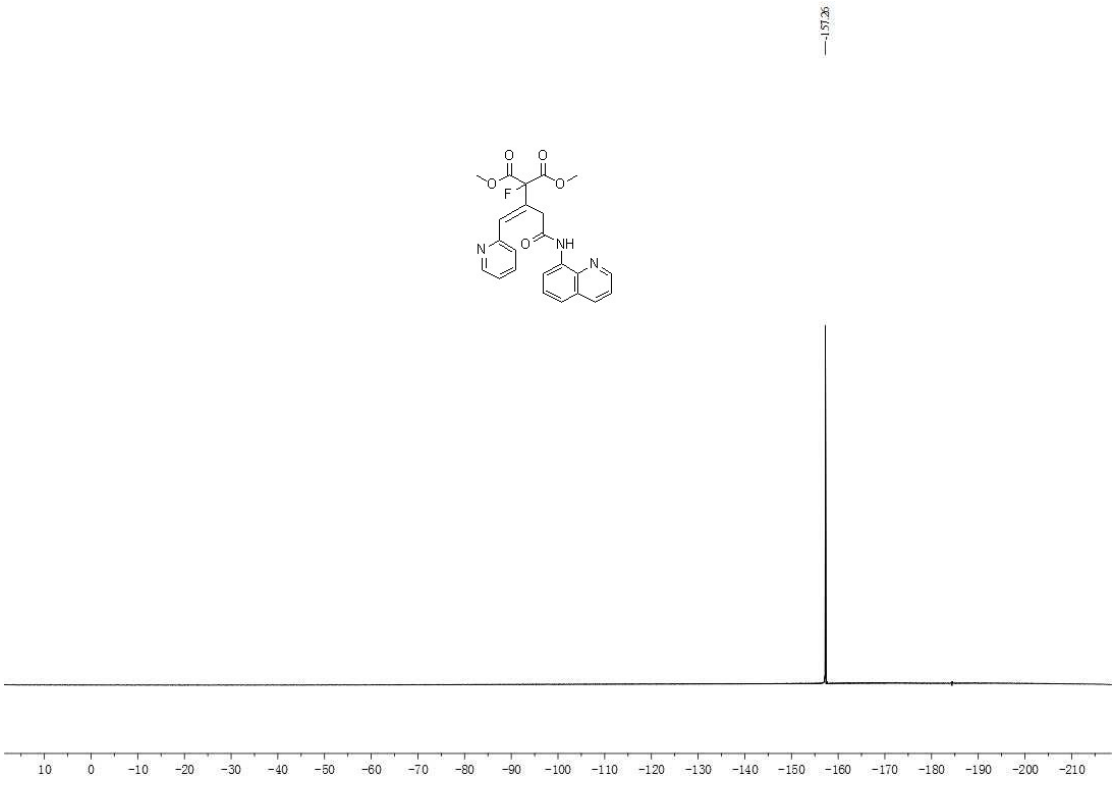

167.34
165.47
165.22
149.75
149.05
148.30
138.23
136.25
135.76
134.10
131.04
130.74
130.02
130.06
129.87
127.84
127.22
123.26
121.71
121.64
116.32
95.74
93.72
77.32
77.00
76.68
53.77
37.10
37.06
F
O
NH
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


-159.76
F
O
NH
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

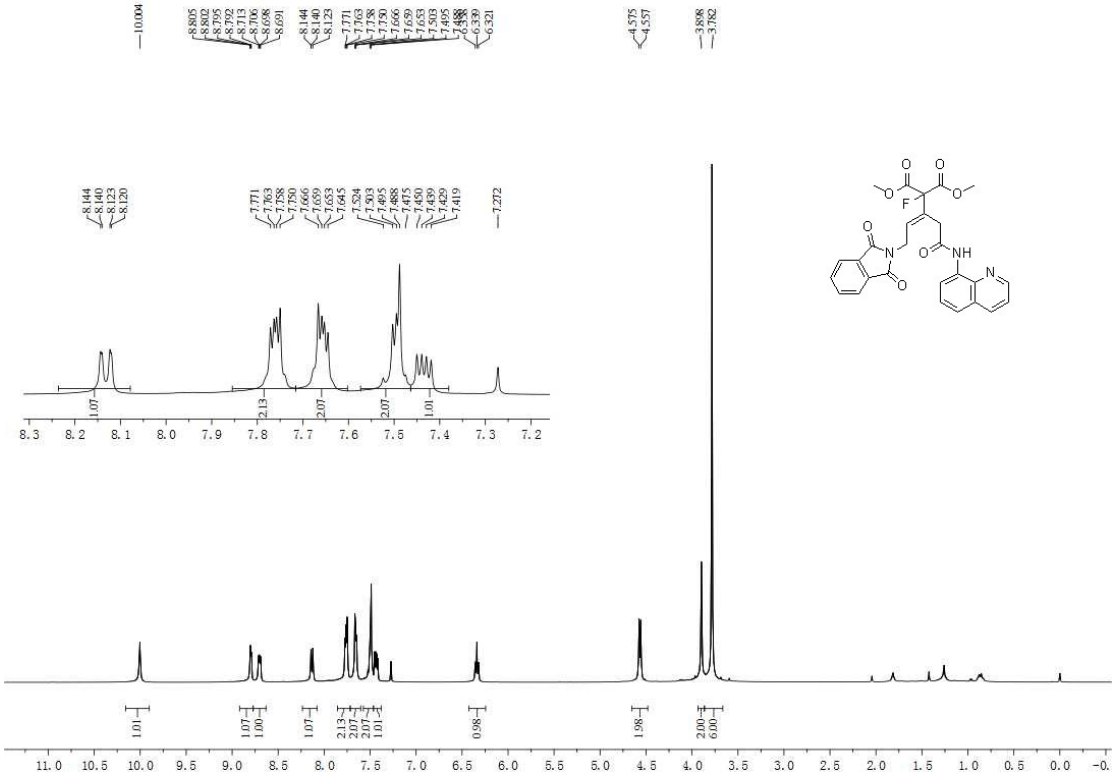
Product 4ac

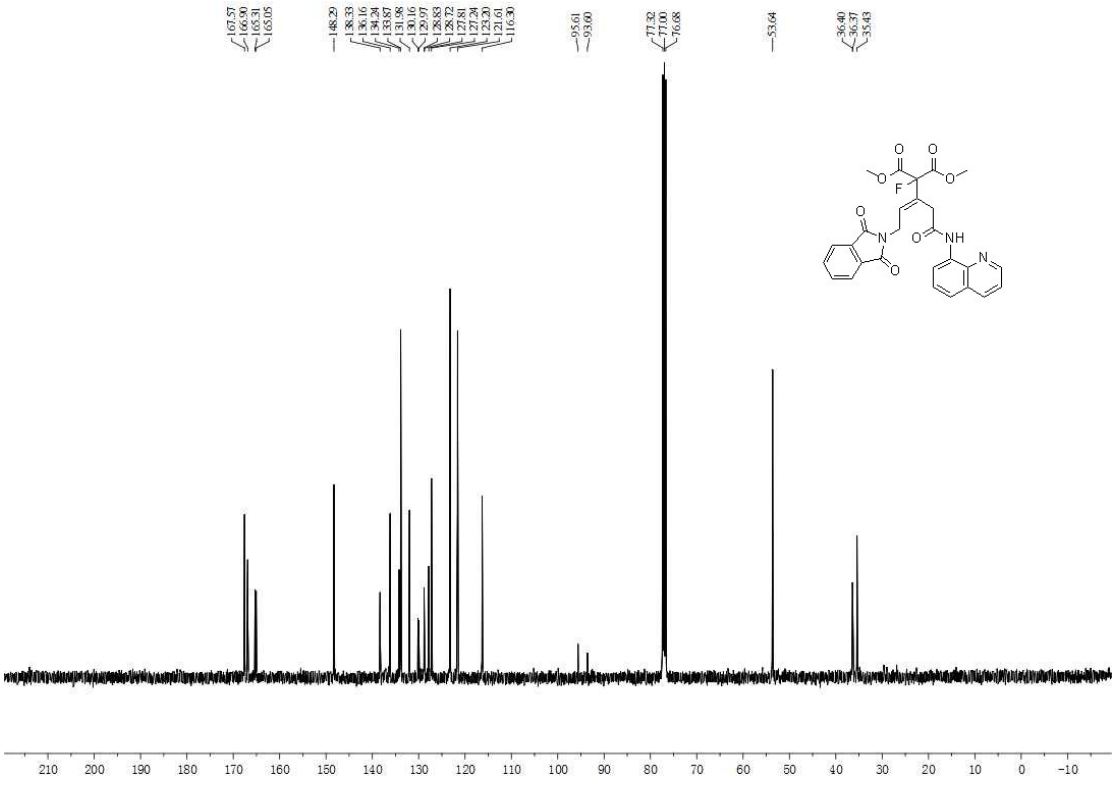


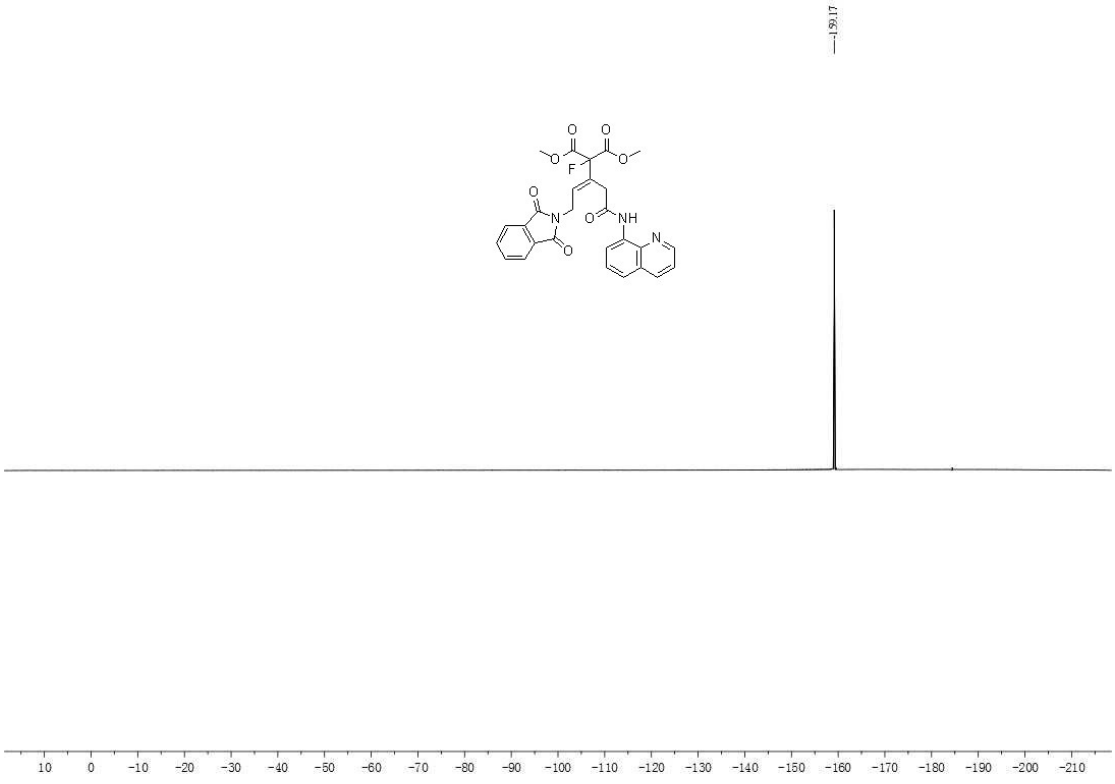




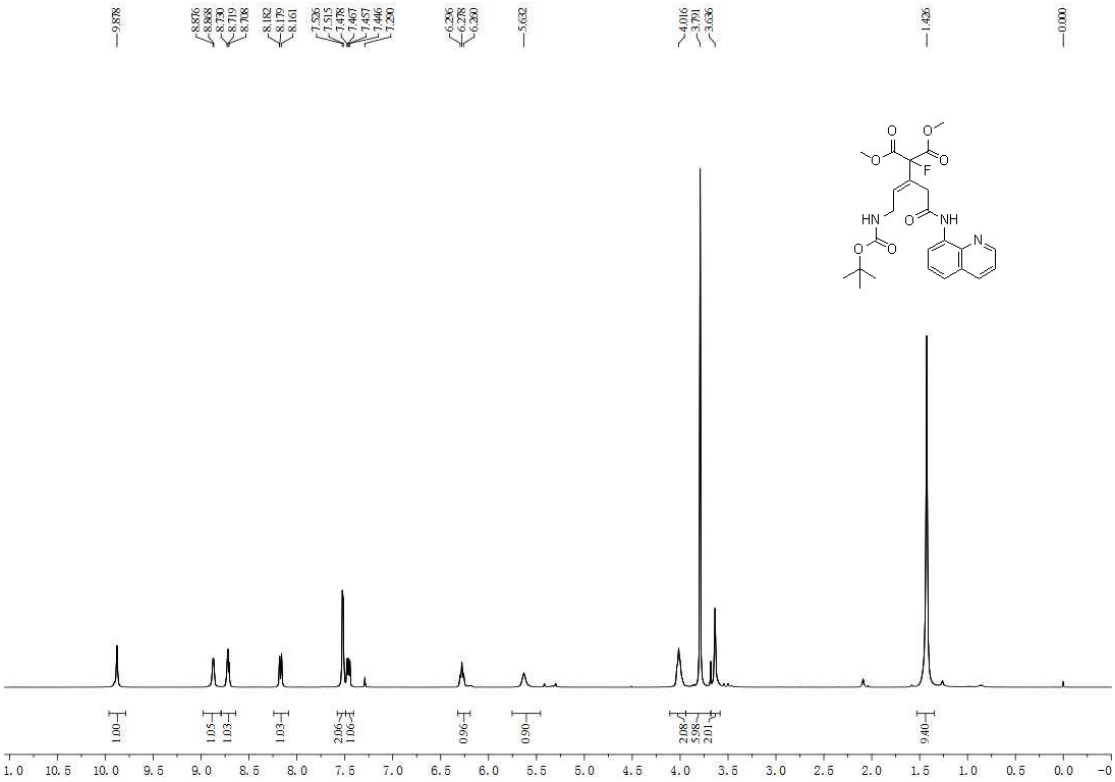
Product 4ad

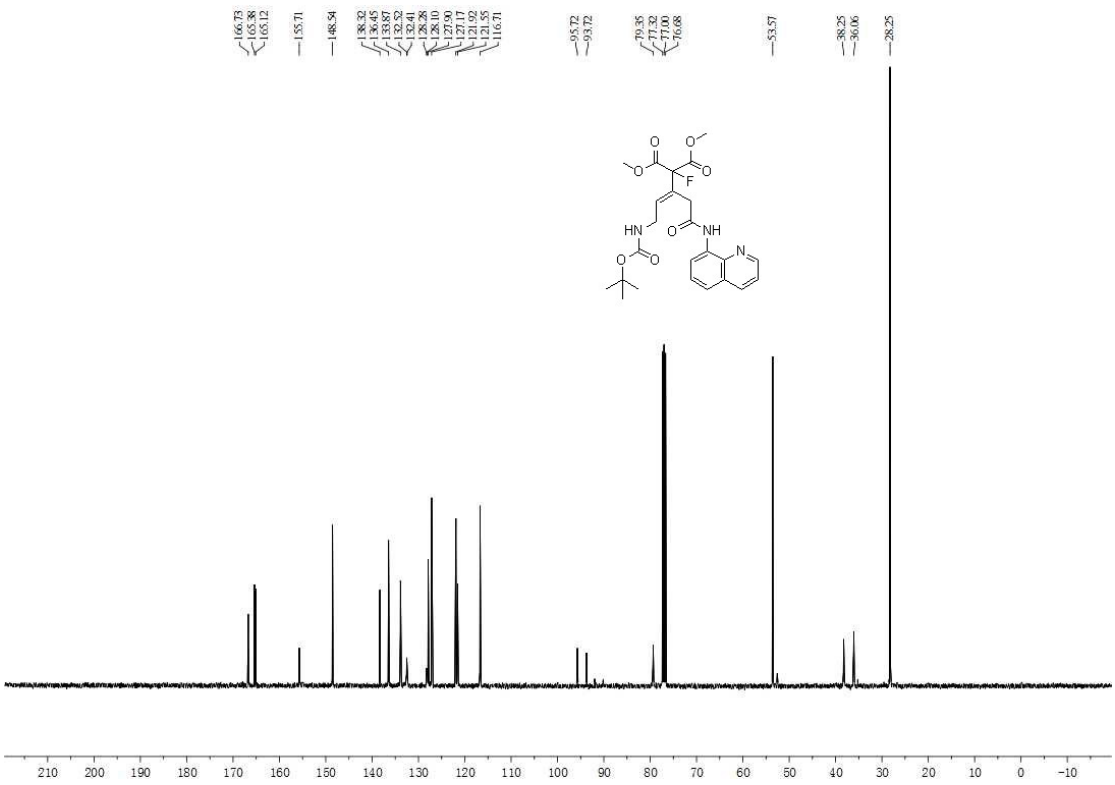


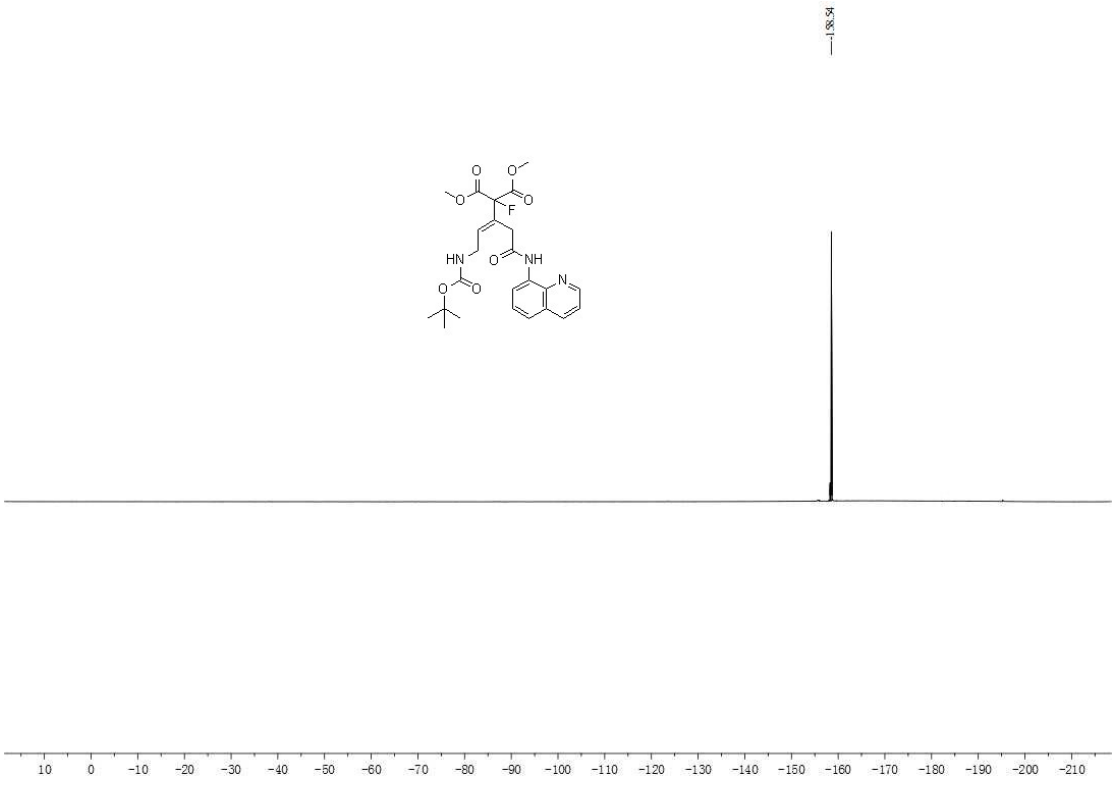

167.57
166.90
165.51
165.05
148.29
138.33
136.16
134.24
133.87
131.98
130.16
129.97
128.83
128.72
127.81
127.24
123.20
121.61
116.30
95.61
93.60
77.32
77.00
76.68
53.64
36.40
36.37
35.43
O
O
O
O
F
O
N
O
NH
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


159.17
O
O
O
O
F
O
N
O
NH
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

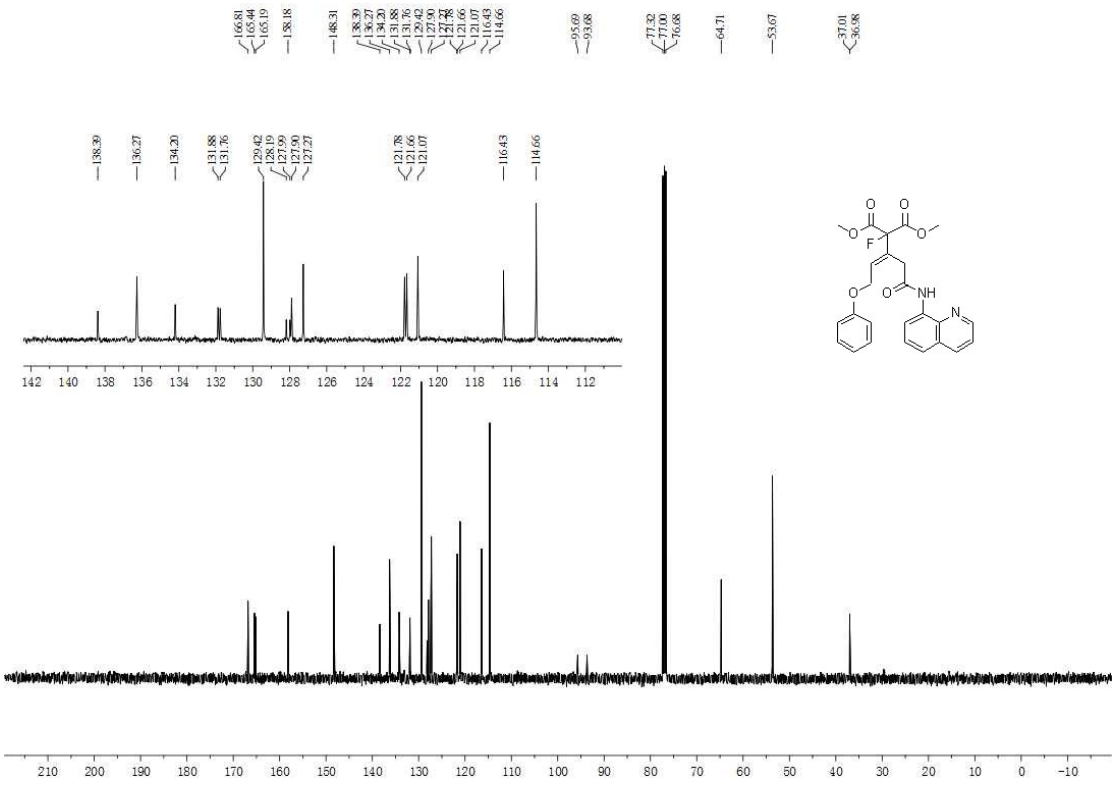
Product 4ae

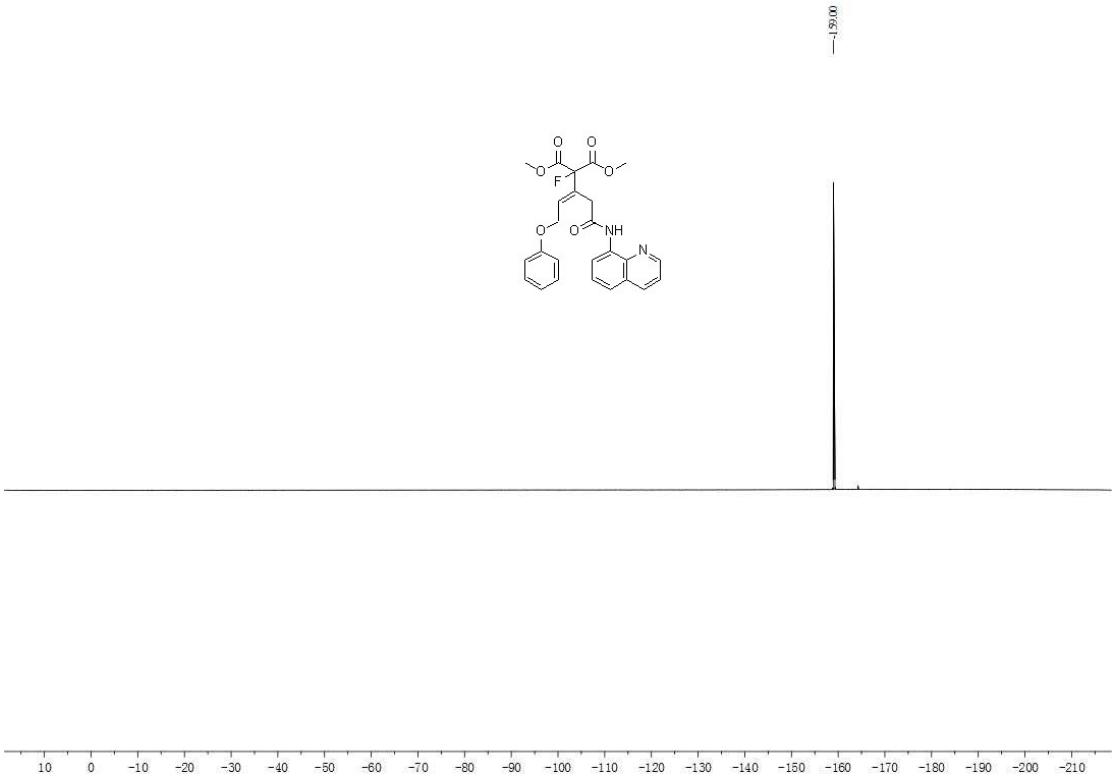

9.878
8.876
8.868
8.730
8.719
8.708
8.182
8.179
8.161
7.526
7.515
7.478
7.467
7.457
7.446
7.290
6.296
6.278
6.260
5.632
4.016
3.791
3.636
1.426
0.000
1.00
1.05
1.03
1.03
2.06
1.06
0.96
0.90
2.08
5.98
2.01
9.40


166.73
165.86
165.12
155.71
148.54
138.32
136.45
133.87
132.52
132.41
128.26
128.10
127.90
127.17
121.92
121.55
116.71
95.72
93.72
79.35
77.32
77.00
76.68
53.57
38.25
36.06
28.25

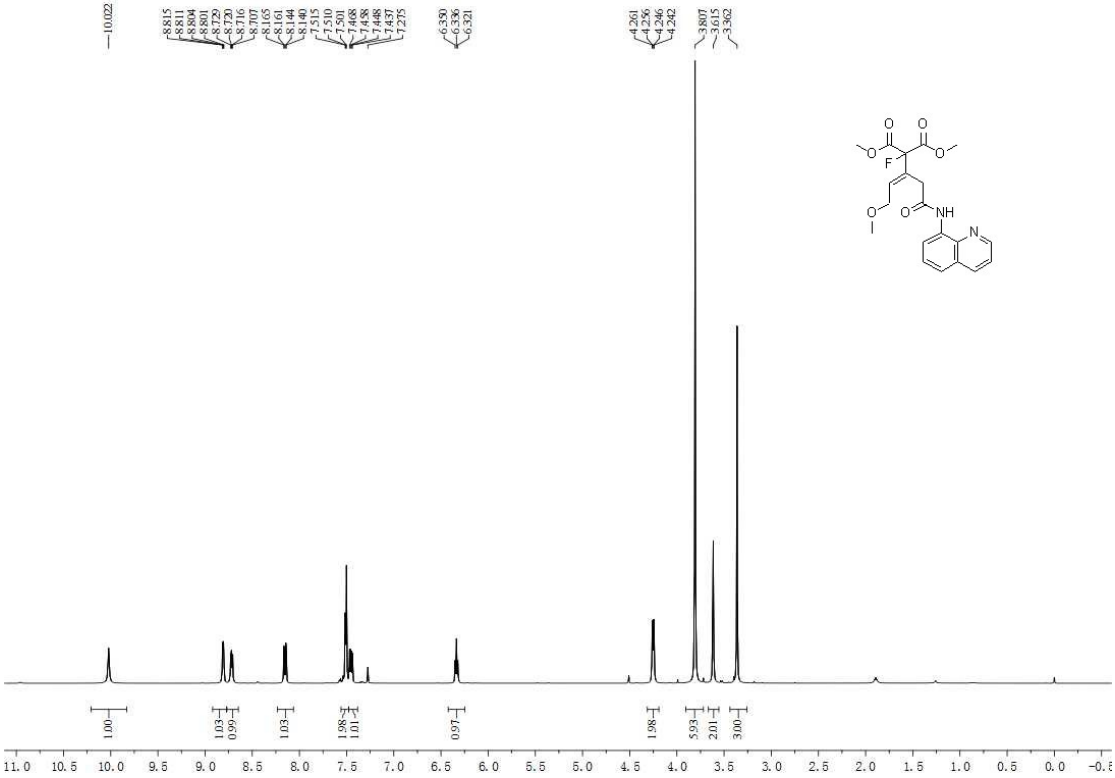


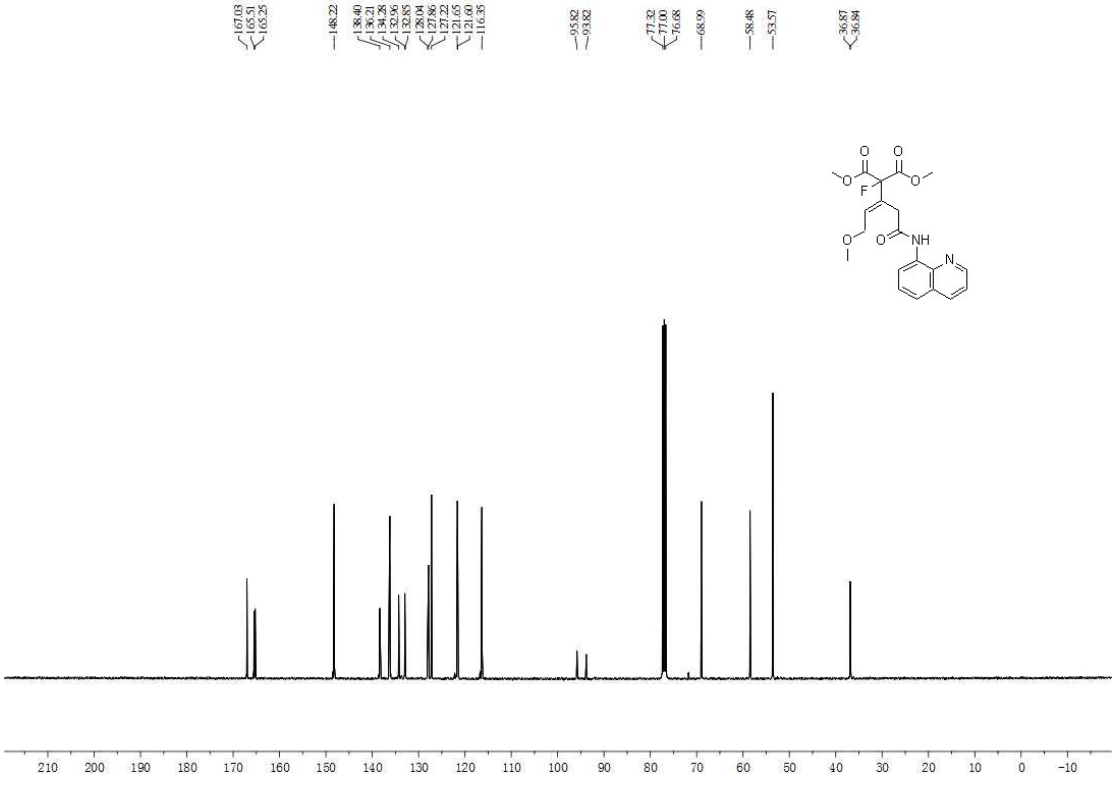
Product 4af

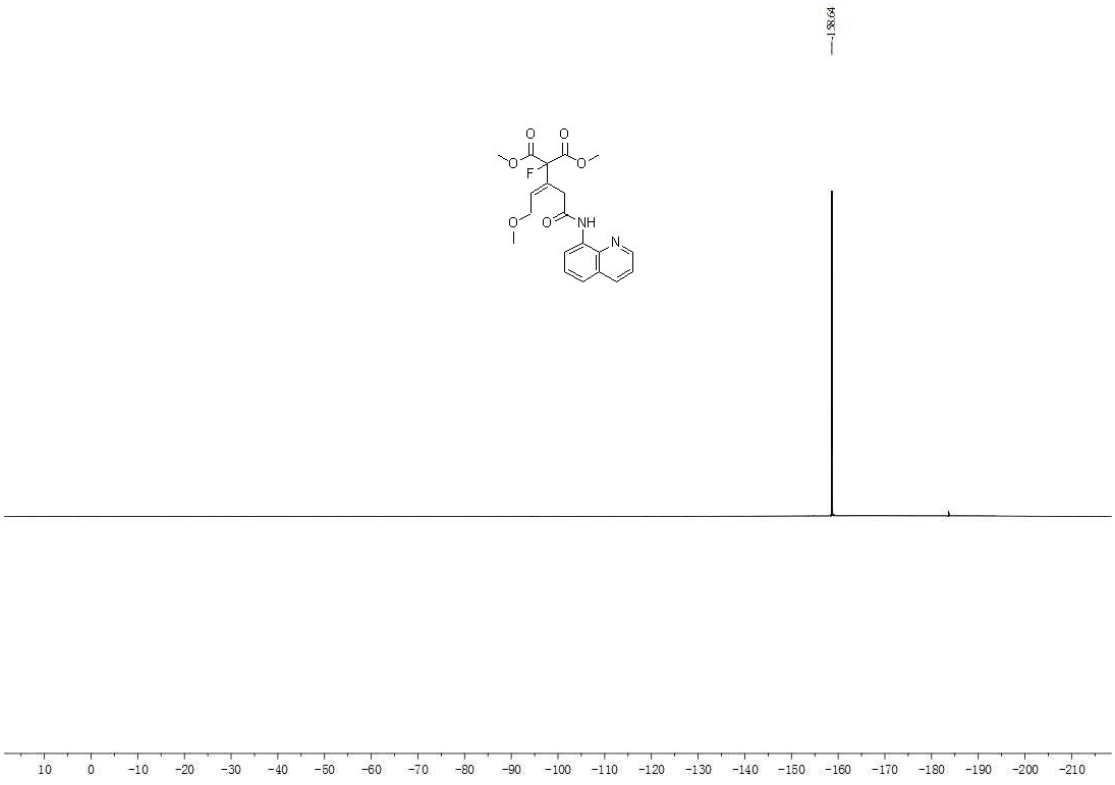

166.81
165.44
165.19
158.18
148.31
138.39
136.27
134.20
131.88
131.76
129.42
128.19
127.99
127.90
127.27
121.78
121.66
121.07
116.43
114.66
95.69
93.68
77.32
77.00
76.68
64.71
53.67
37.01
36.98
O
O
O
O
F
O
NH
N


-159.00
O
O
O
O
F
O
NH
N

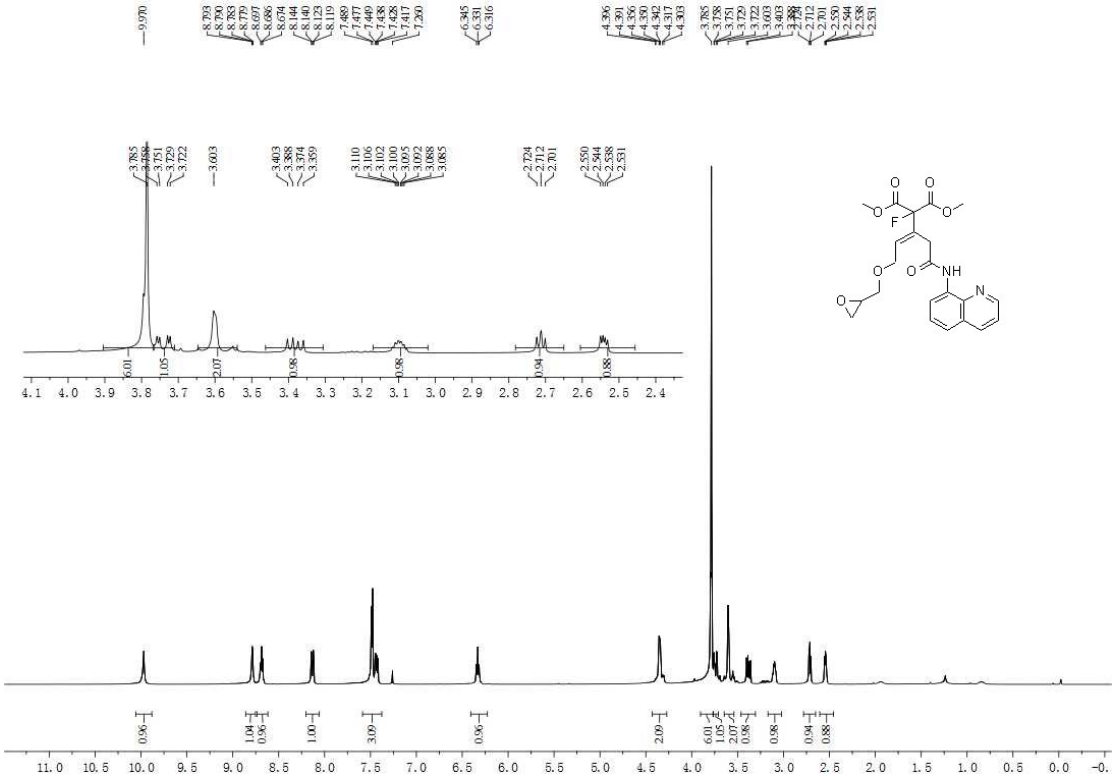
Product 4ag

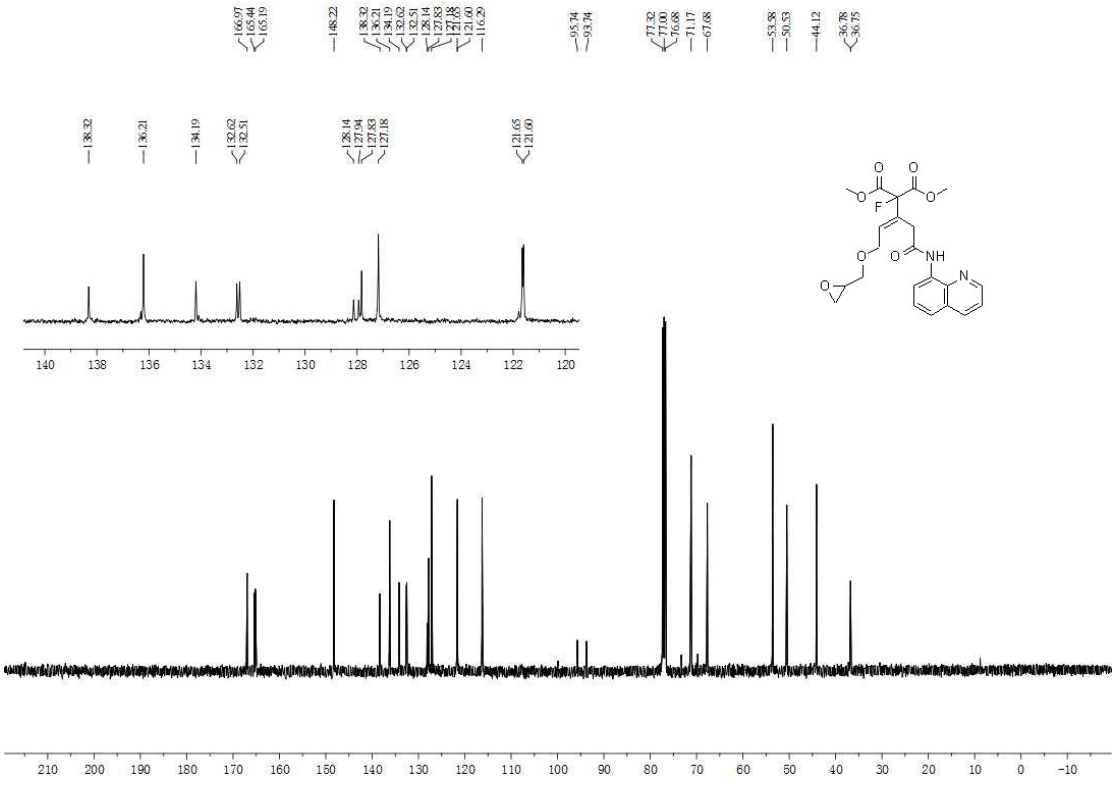


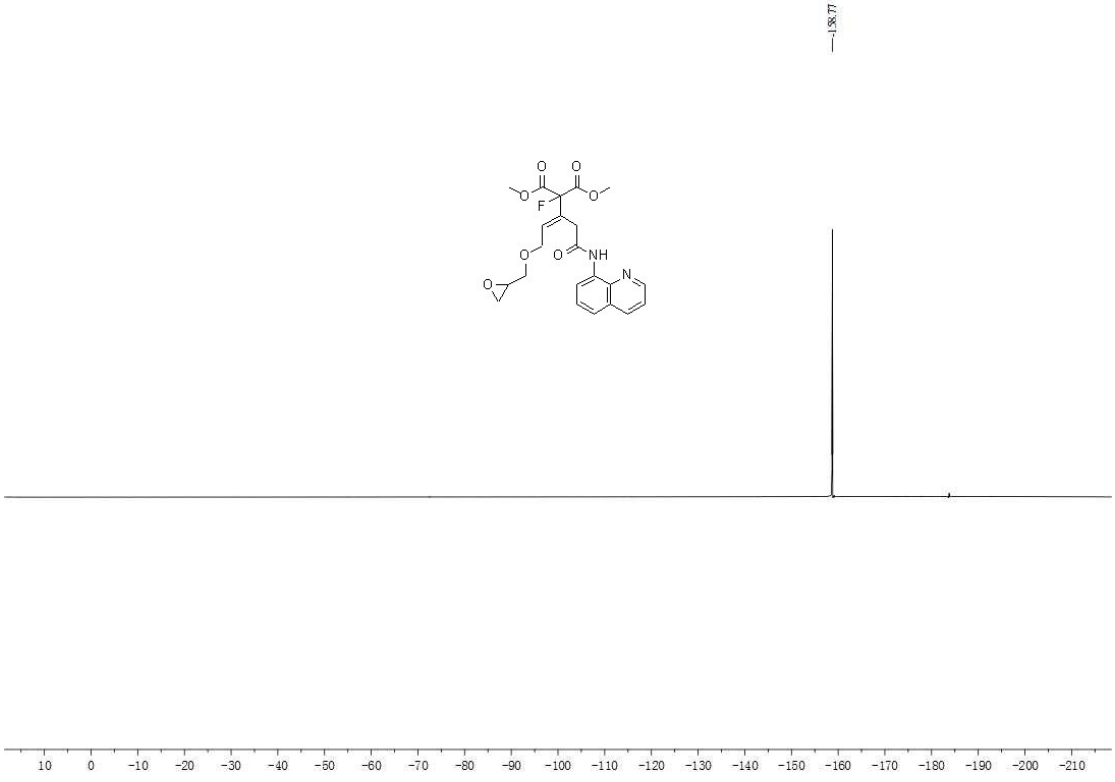




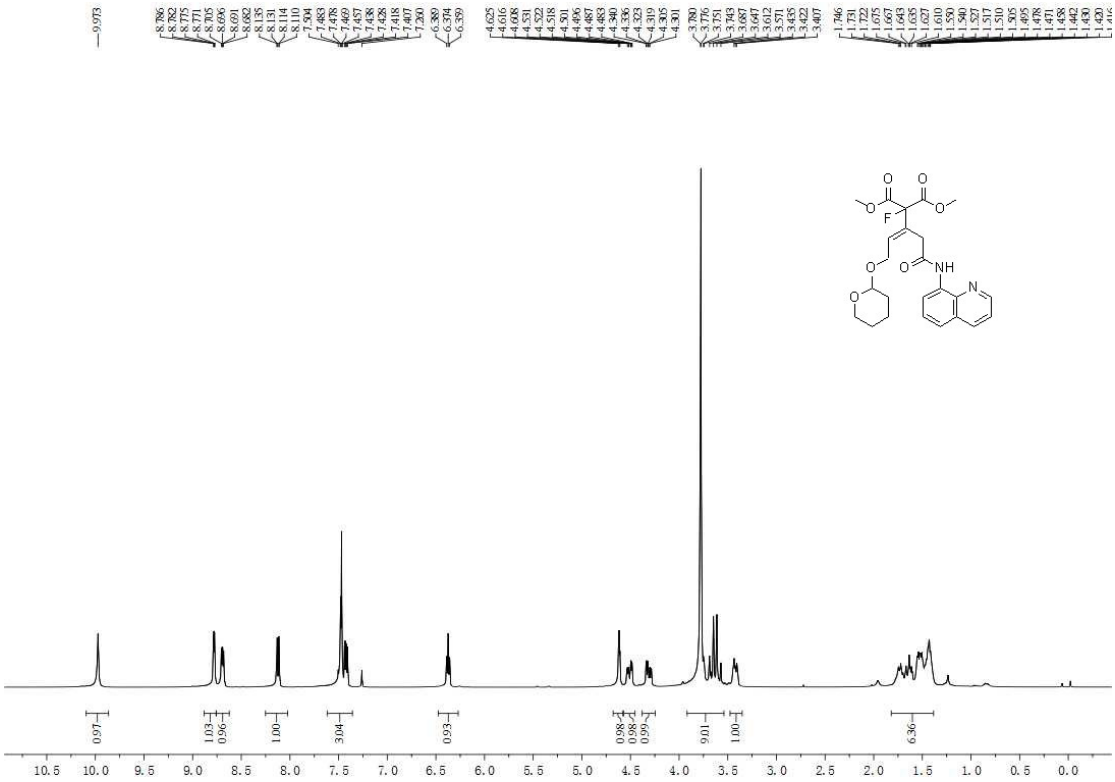
Product 4ah

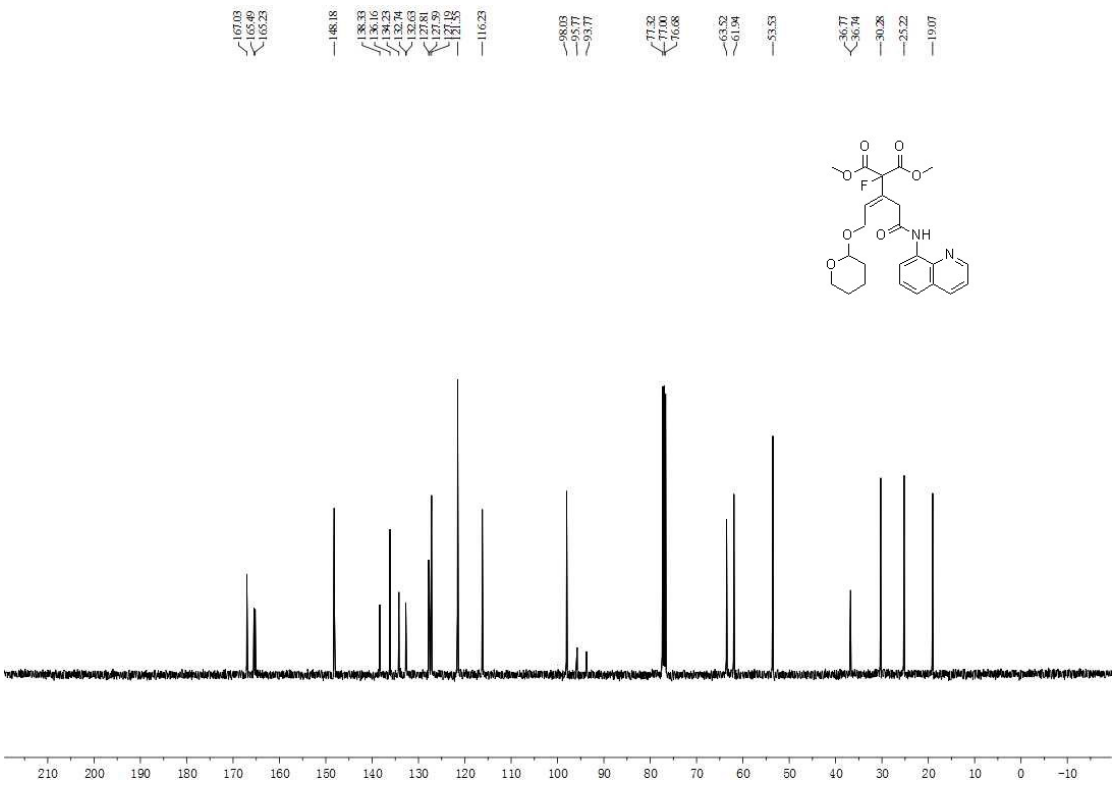


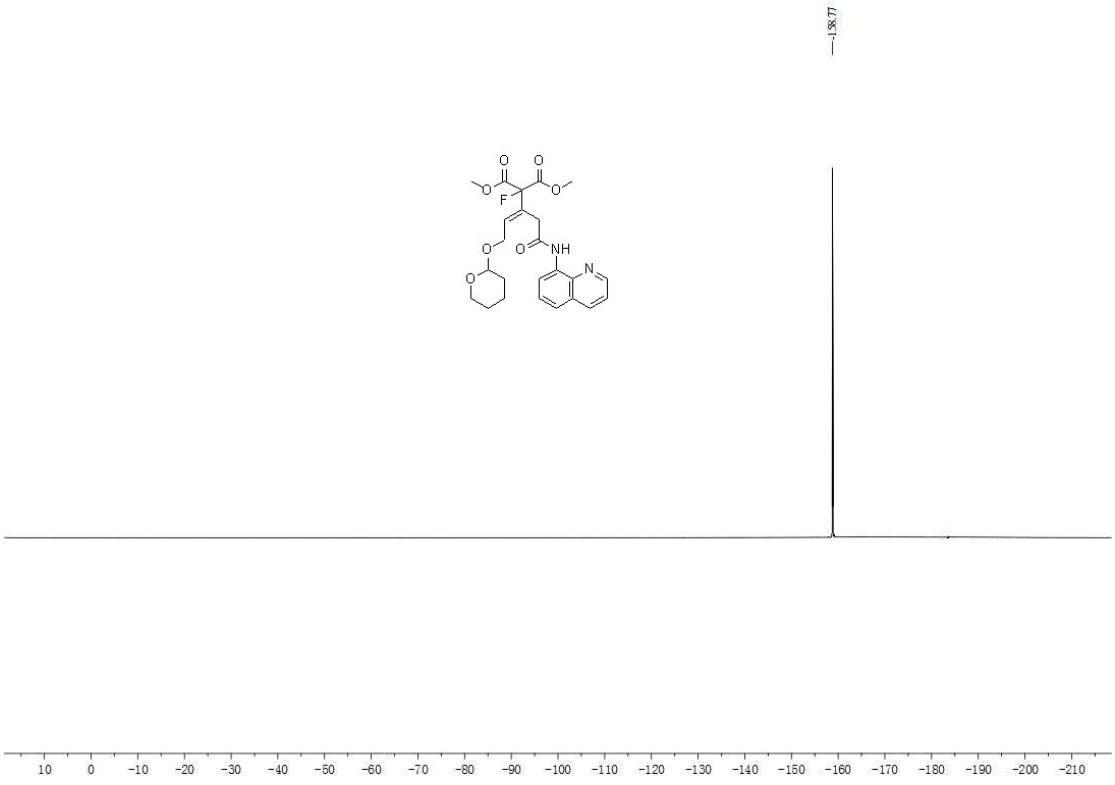

166.97
165.44
165.19
148.22
138.32
136.21
134.19
132.62
132.51
128.14
127.83
127.18
121.65
121.60
116.29
95.74
93.74
77.32
77.00
76.68
71.17
67.68
53.98
50.53
44.12
36.78
36.75
NH
N
O
F


158.77
NH
N
O
F

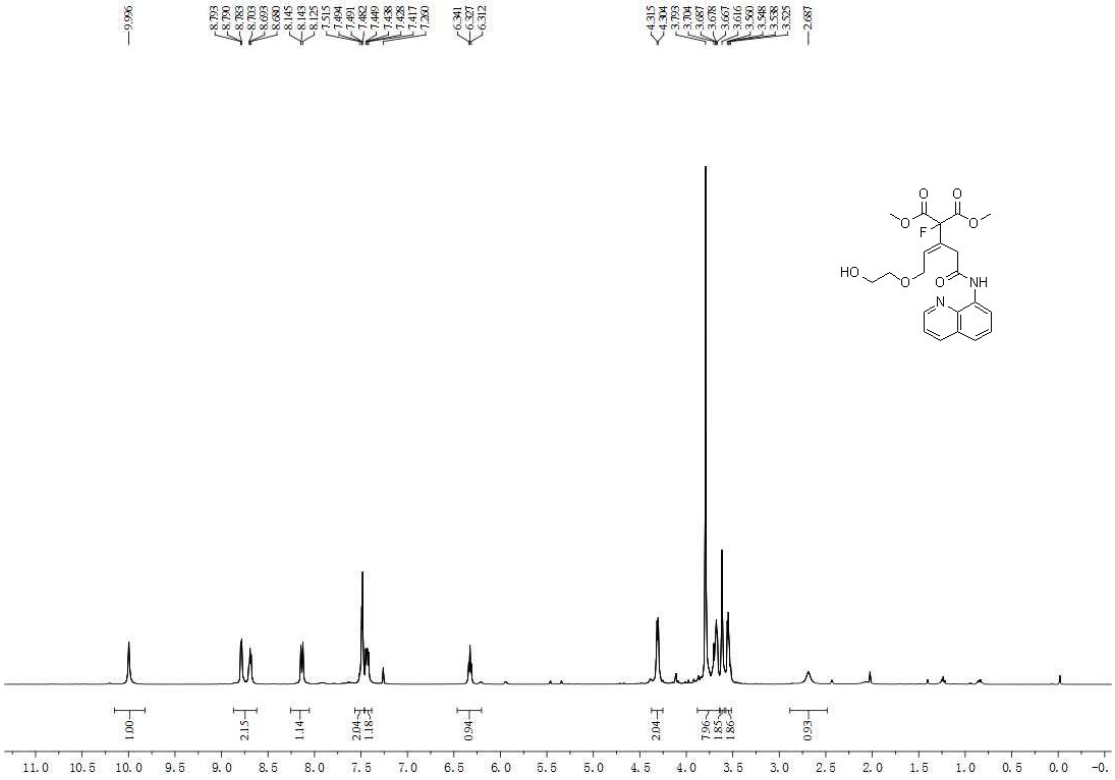
Product 4ai

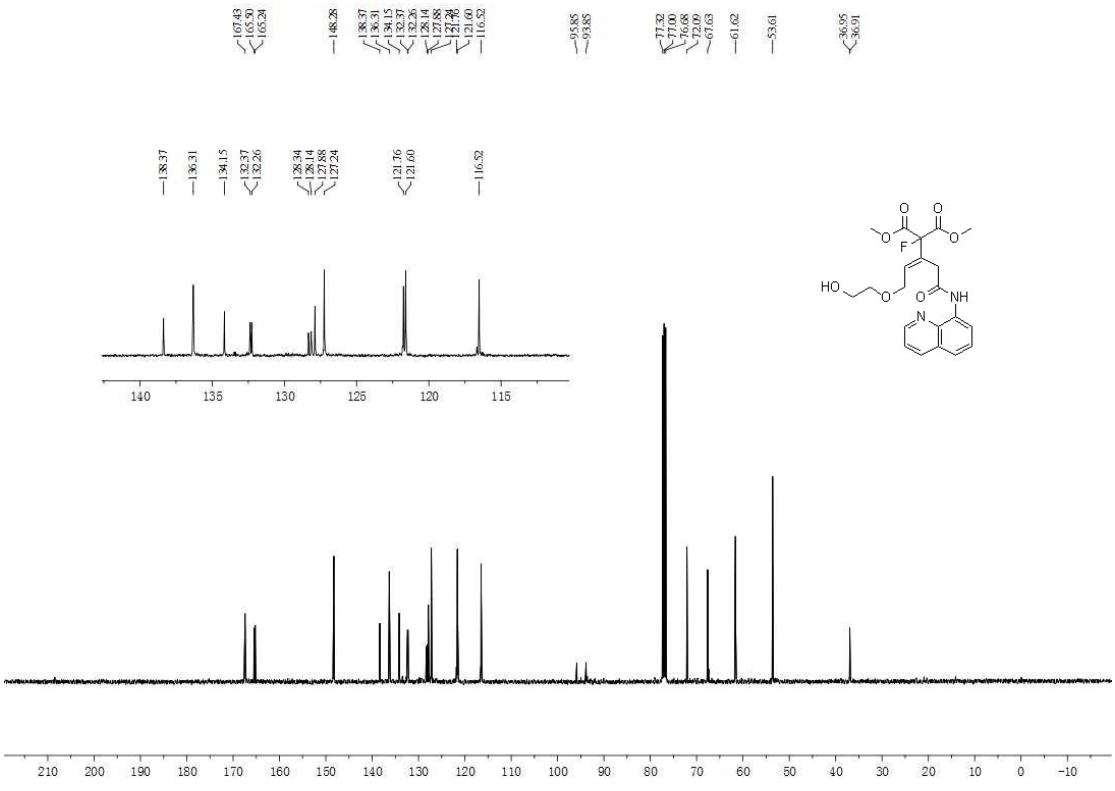


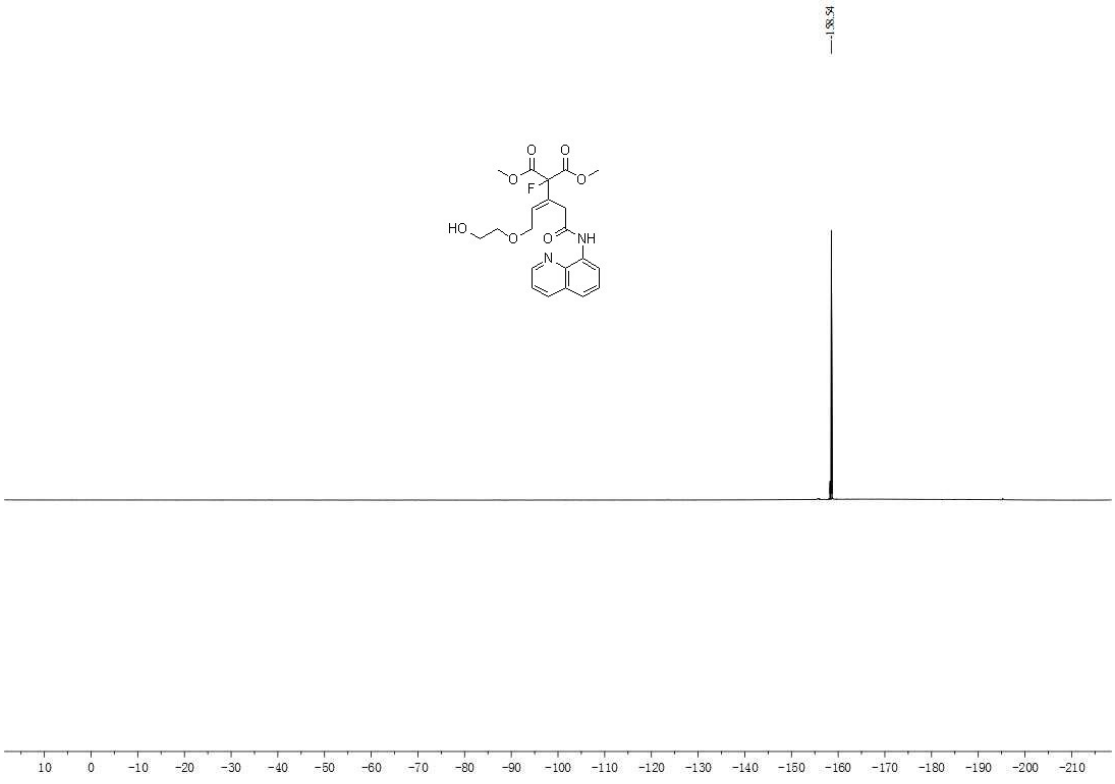



-138.77
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

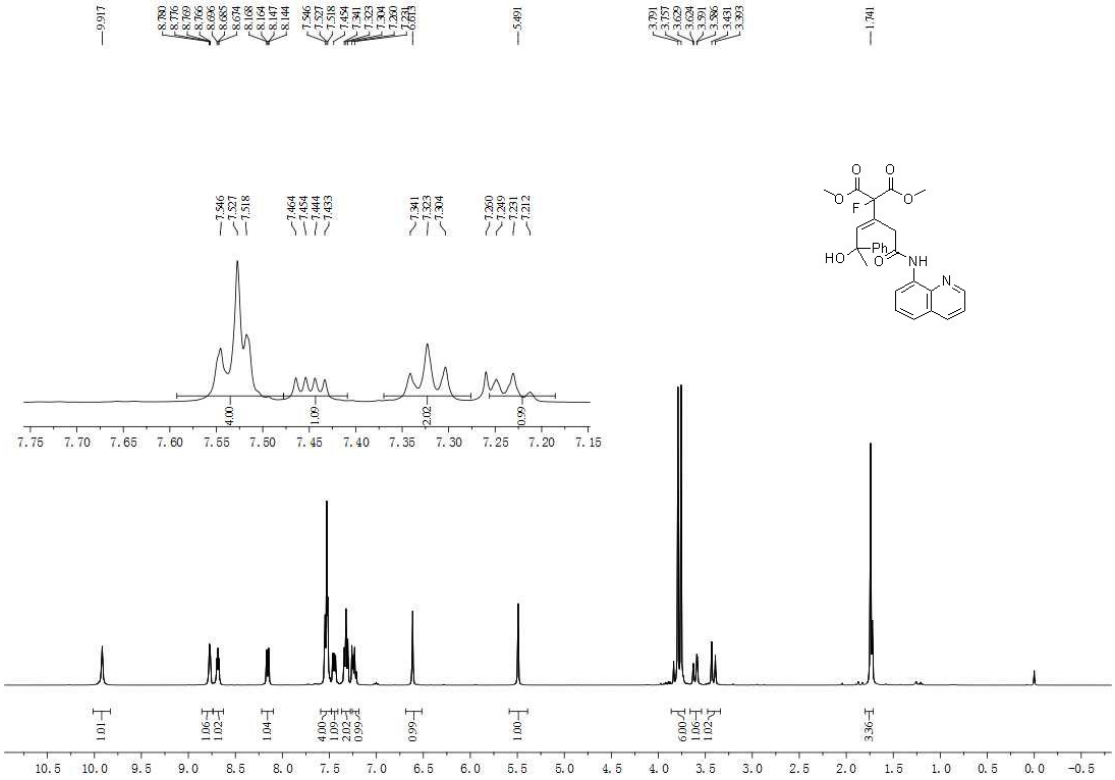
Product 4aj

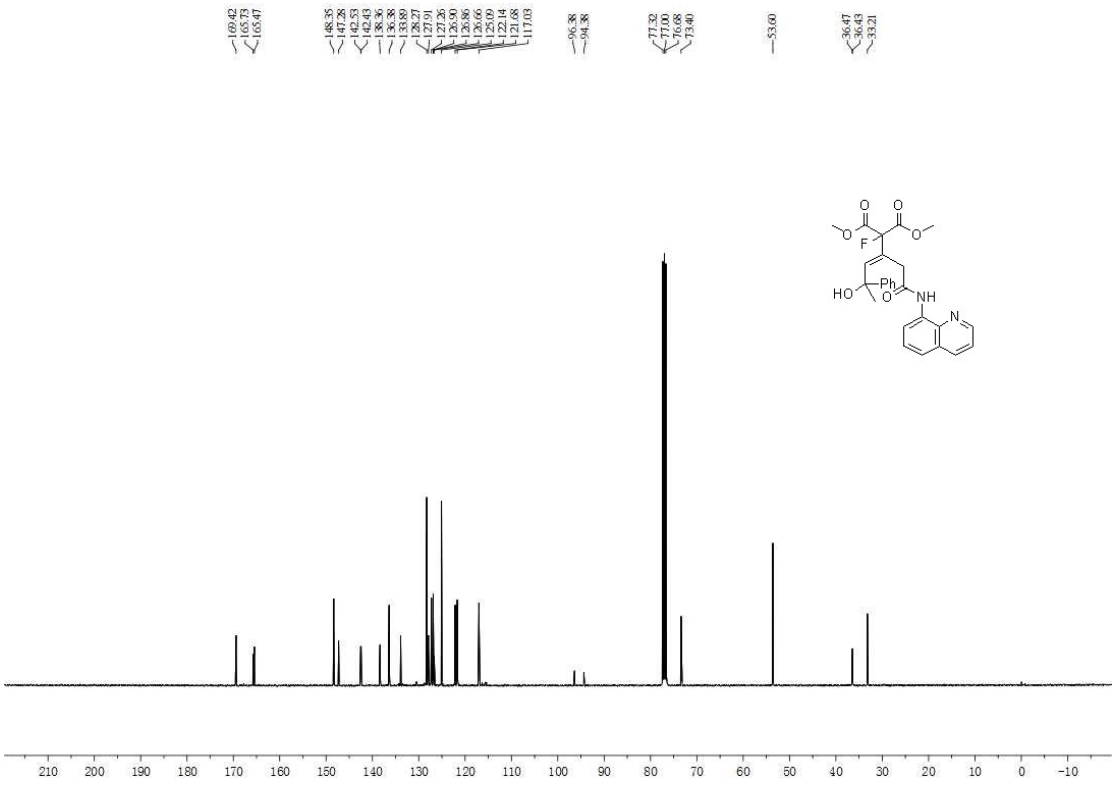

9.996
8.793 8.790 8.788 8.703 8.693 8.680 8.145 8.143 8.125 7.515 7.504 7.491 7.482 7.449 7.438 7.428 7.417 7.200
6.341 6.327 6.312
4.315 4.304 3.793 3.784 3.687 3.678 3.667 3.616 3.600 3.548 3.538 3.525
2.687
1.00 2.15 1.14 2.04 1.18 0.94 2.04 7.96 1.85 1.86 0.93
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

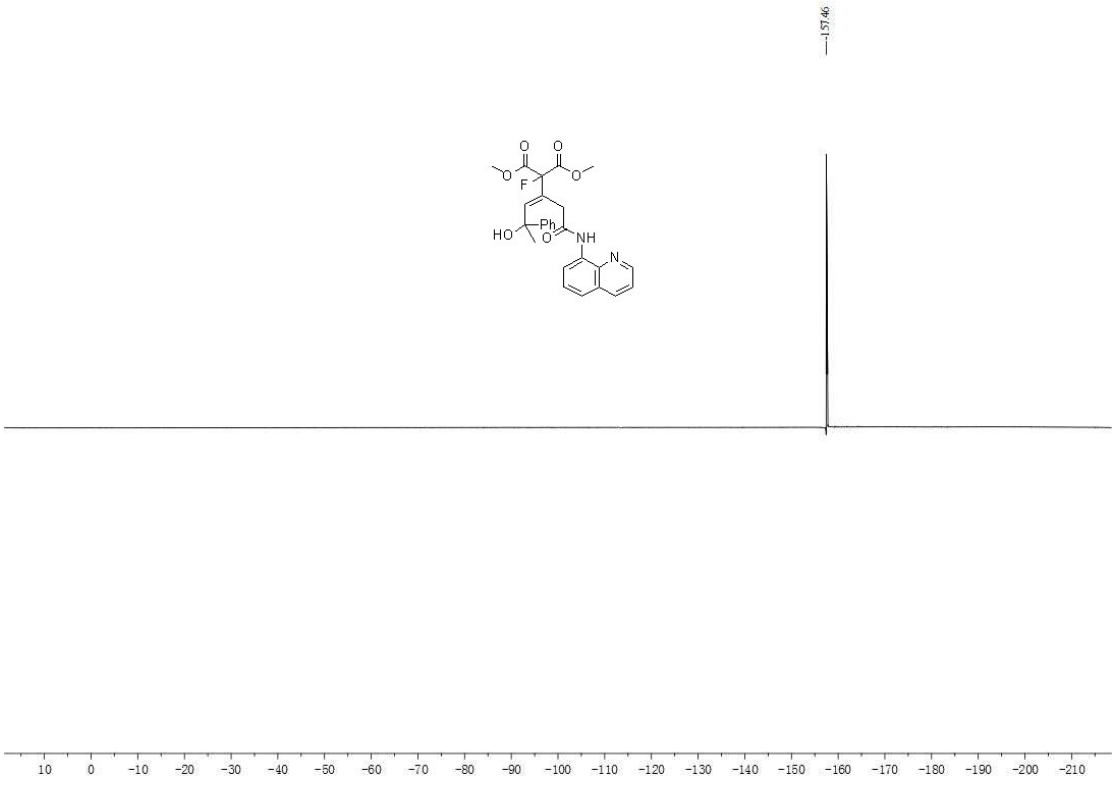

167.43
165.90
165.24
148.28
138.37
136.31
134.15
132.37
132.26
128.14
127.88
127.24
121.76
121.60
116.52
95.85
93.85
77.32
77.00
76.68
72.09
67.63
61.62
53.61
36.95
36.91
HO
O
F
NH
N


-158.54
HO
O
F
NH
N

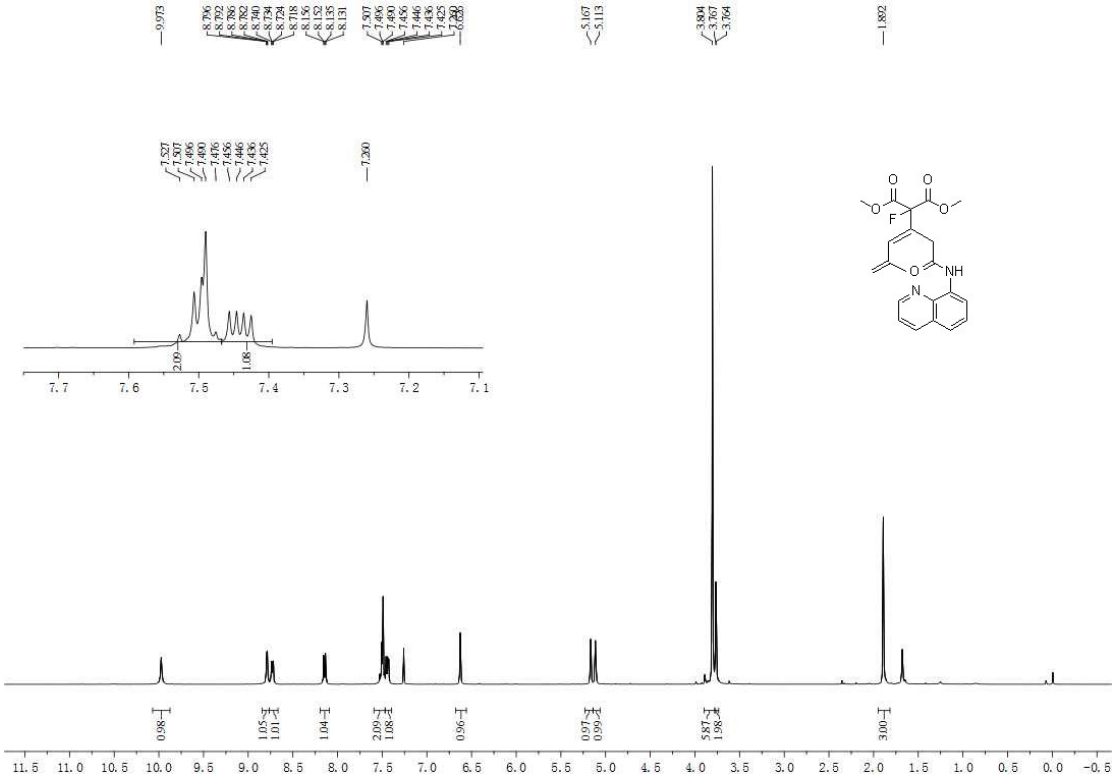
Product 4ak

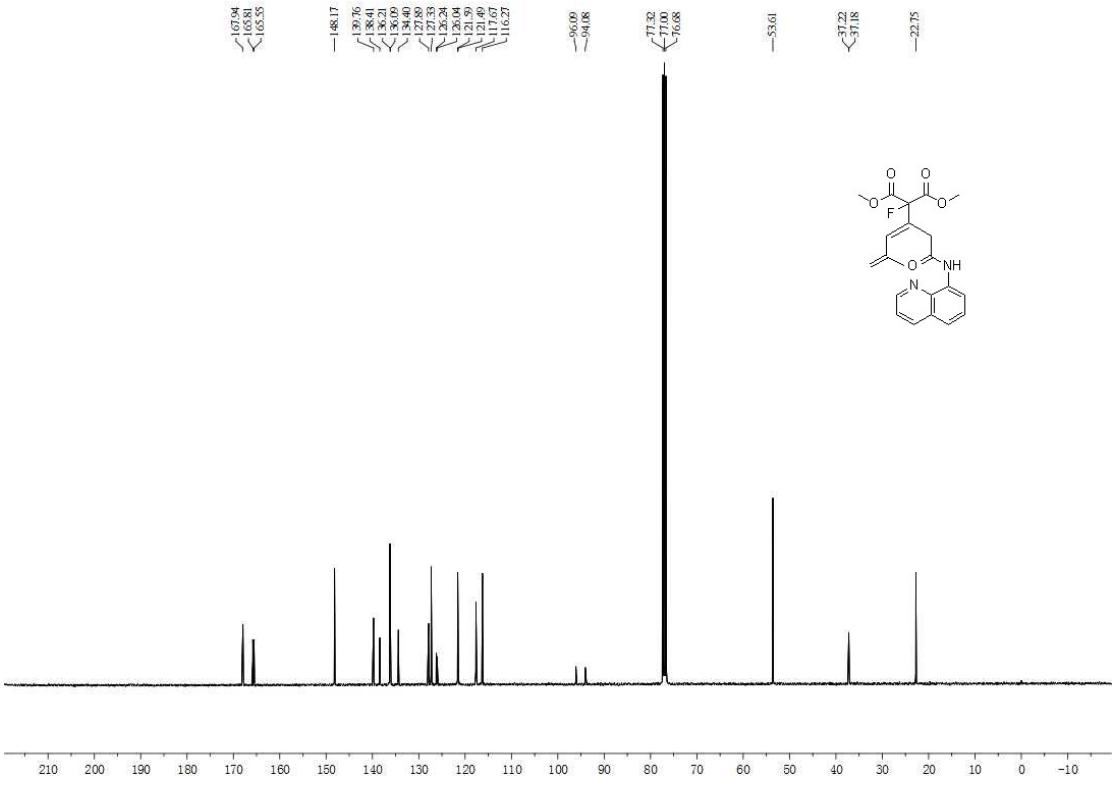


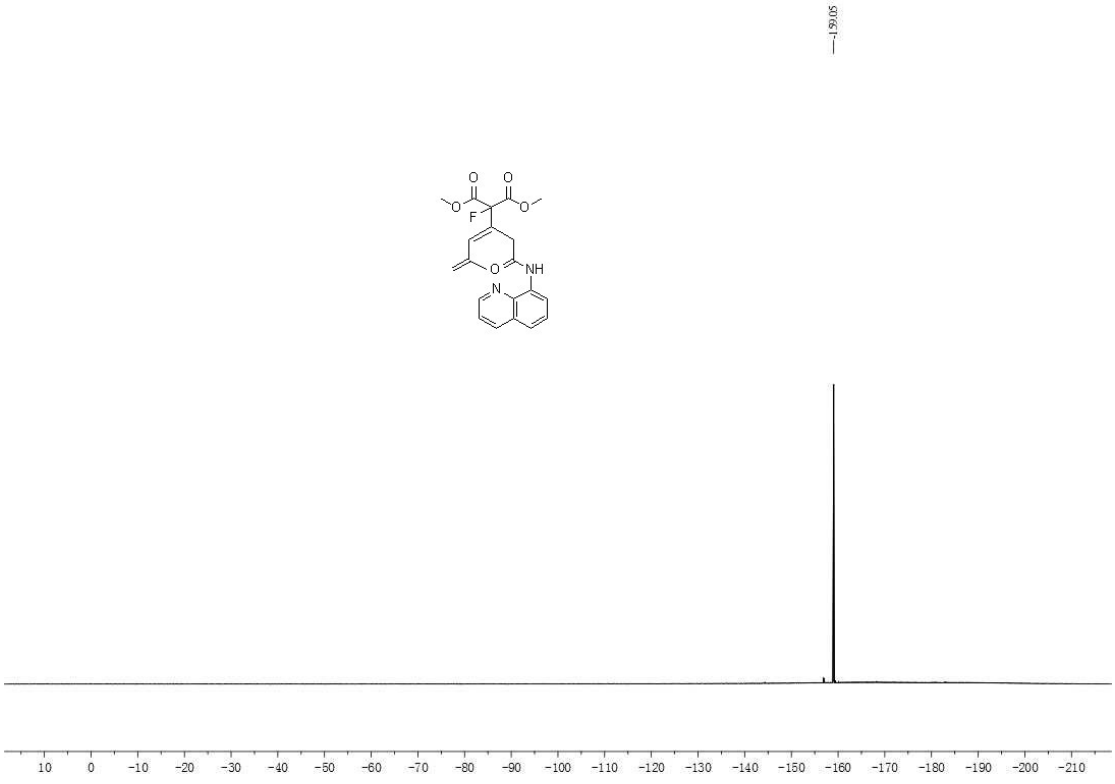



-157.46
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

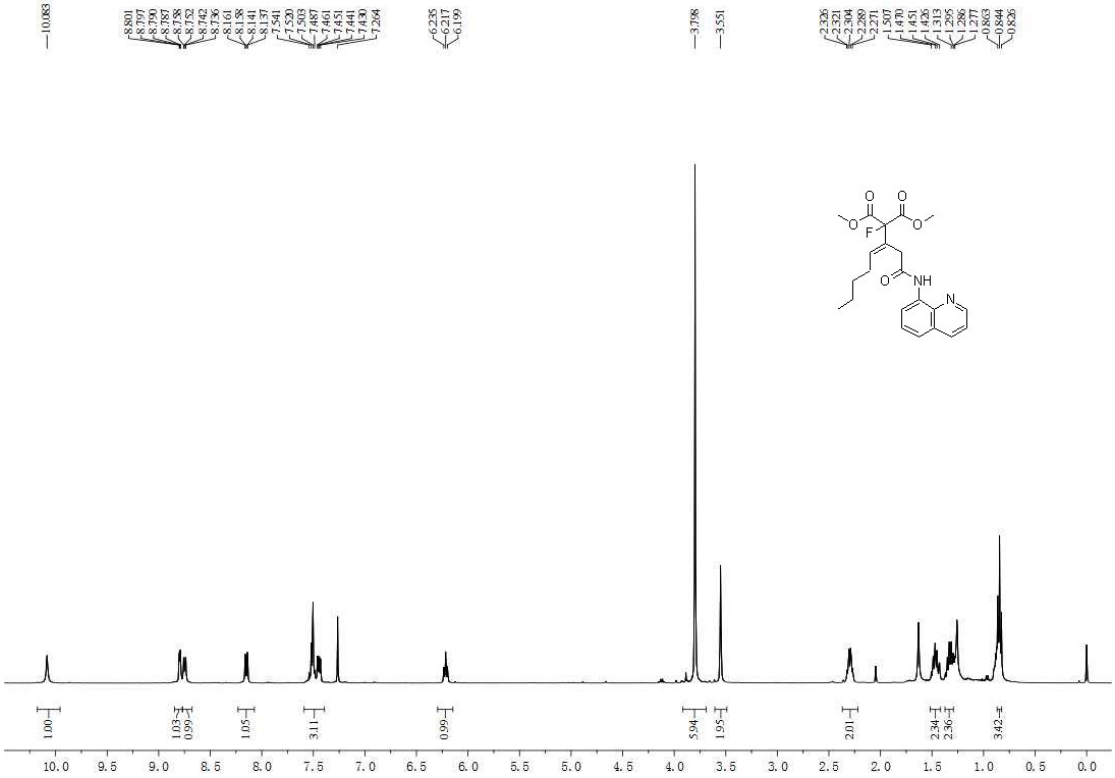
Product 4al

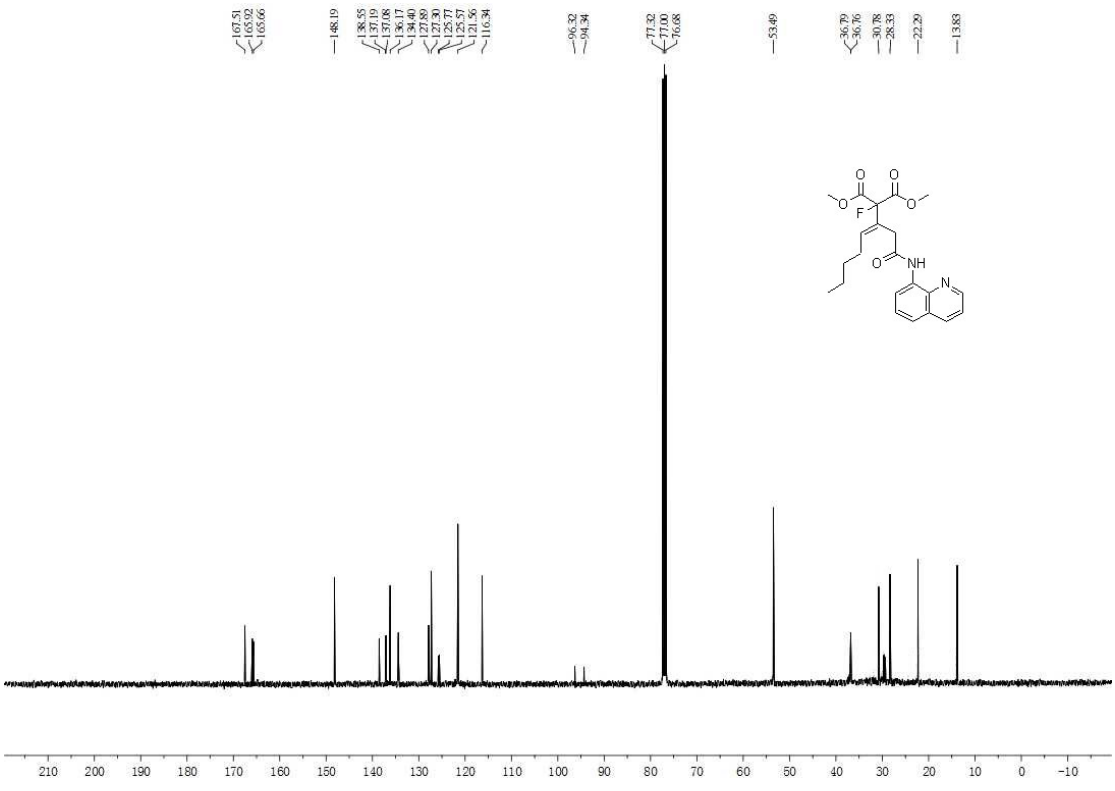

9.973
8.796
8.792
8.786
8.782
8.740
8.734
8.728
8.718
8.156
8.152
8.135
8.131
7.507
7.496
7.490
7.476
7.456
7.446
7.436
7.425
7.420
7.410
7.200
5.167
5.113
3.804
3.767
3.764
1.892
7.527
7.507
7.496
7.490
7.476
7.456
7.446
7.436
7.425
2.09
1.08
7.7 7.6 7.5 7.4 7.3 7.2 7.1
0.98
1.05
1.01
1.04
2.09
1.08
0.96
0.97
0.99
5.87
1.98
3.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

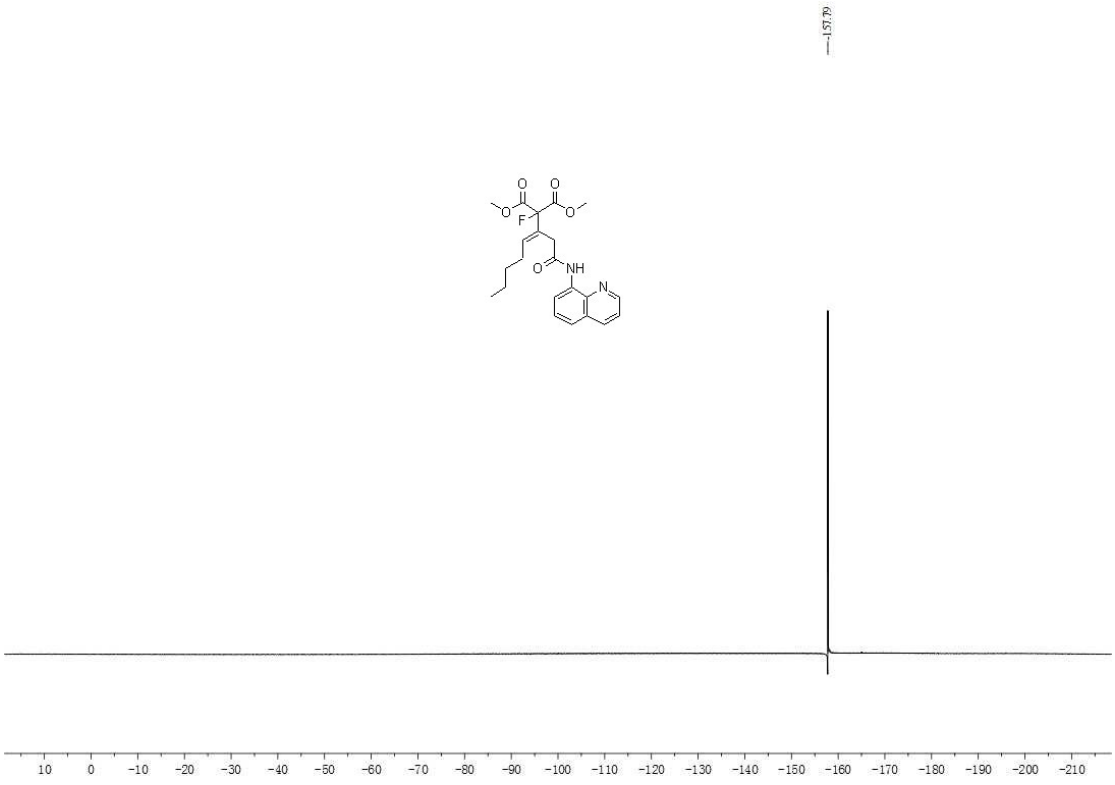

167.94
165.81
165.55
148.17
130.76
128.41
126.21
96.09
94.08
77.32
77.00
76.68
53.61
37.22
37.18
22.75
F
O
NH
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


159.05
F
O
NH
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

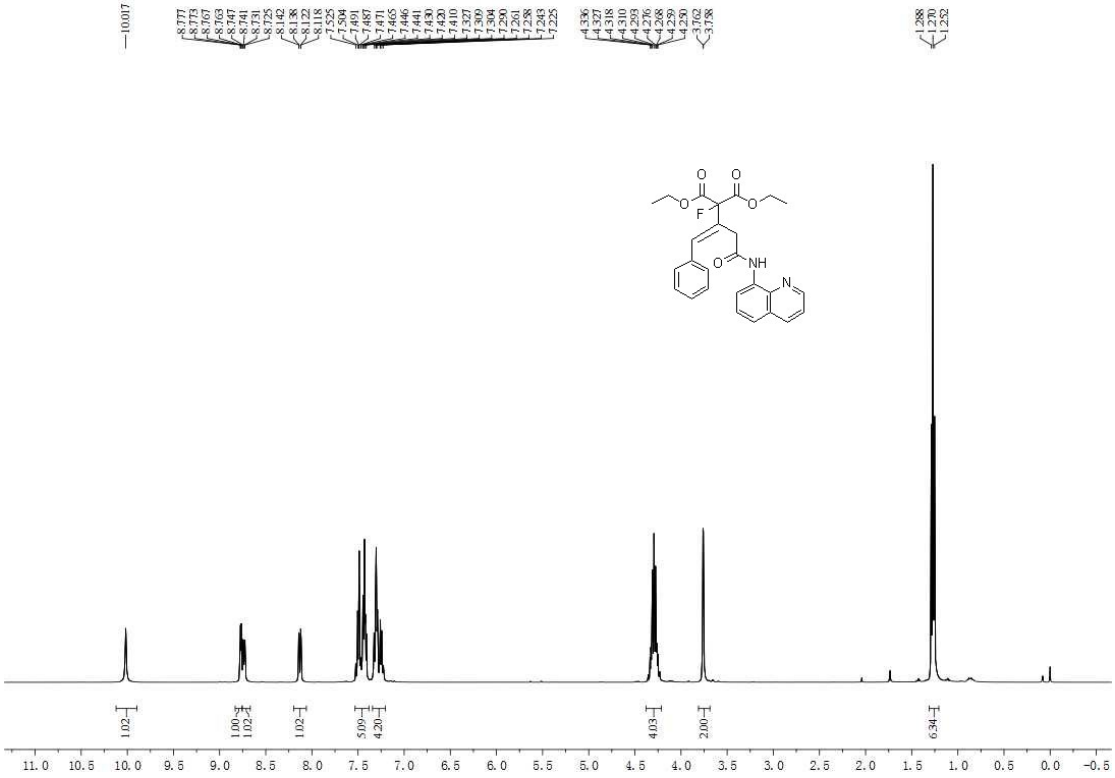
Product 4am

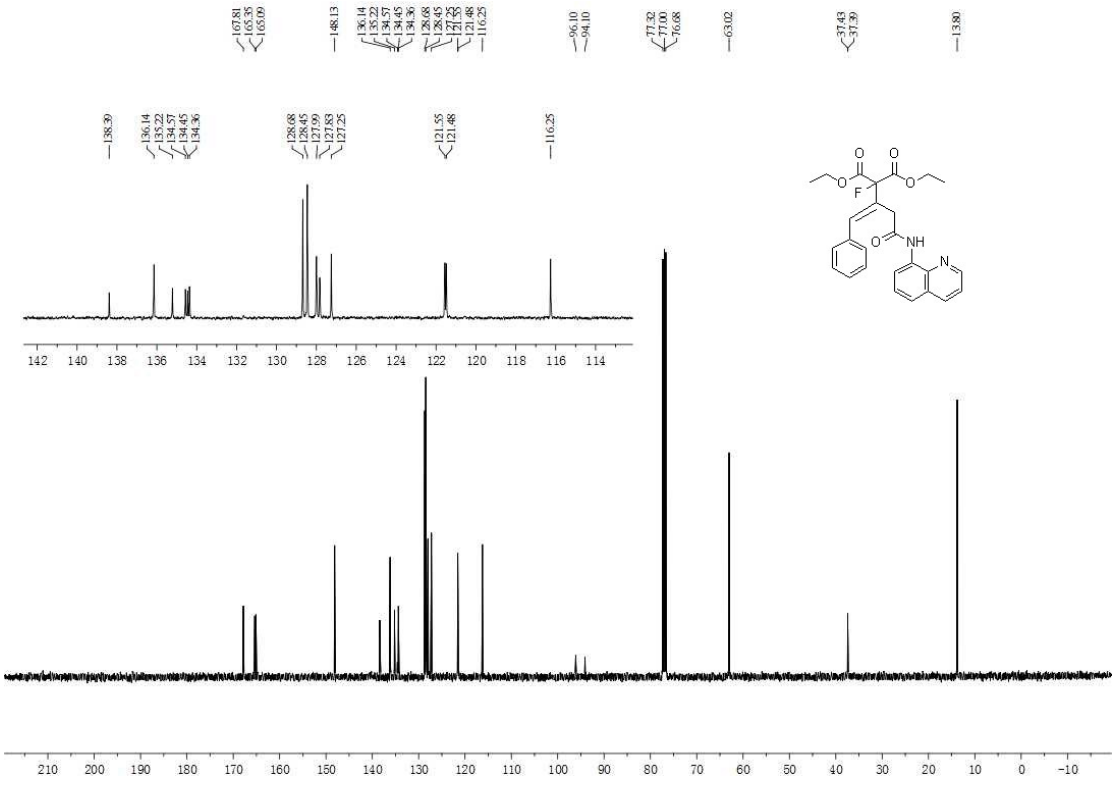


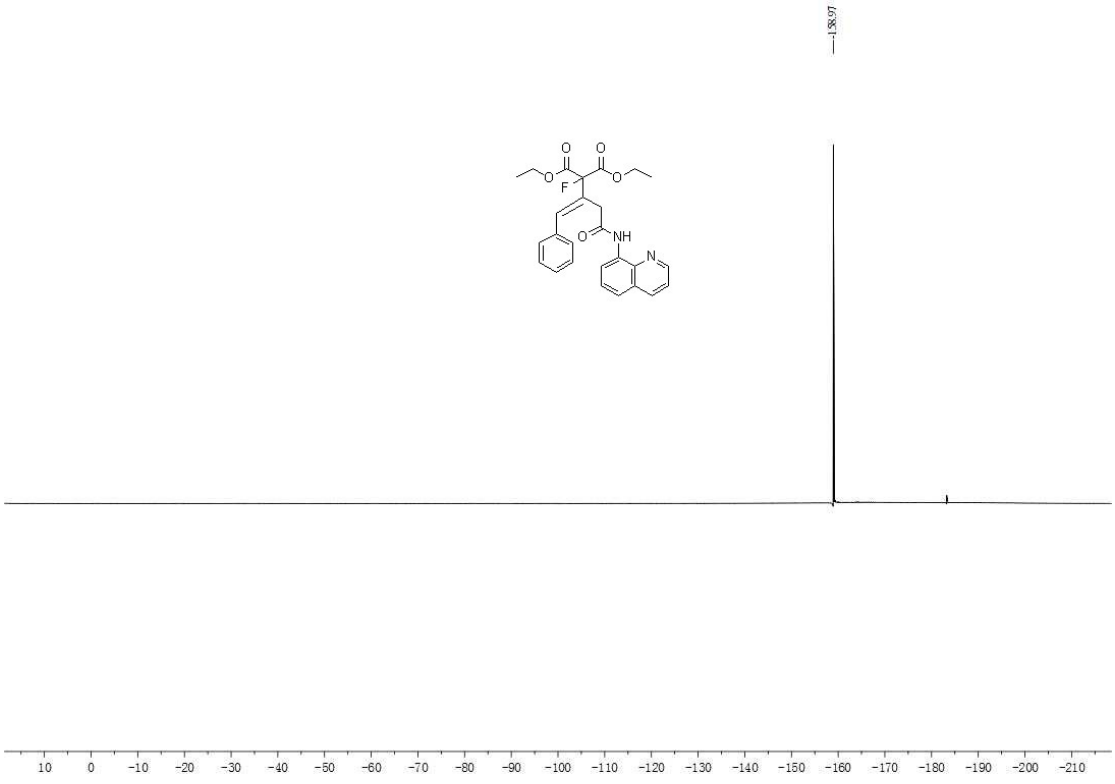



-157.79
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

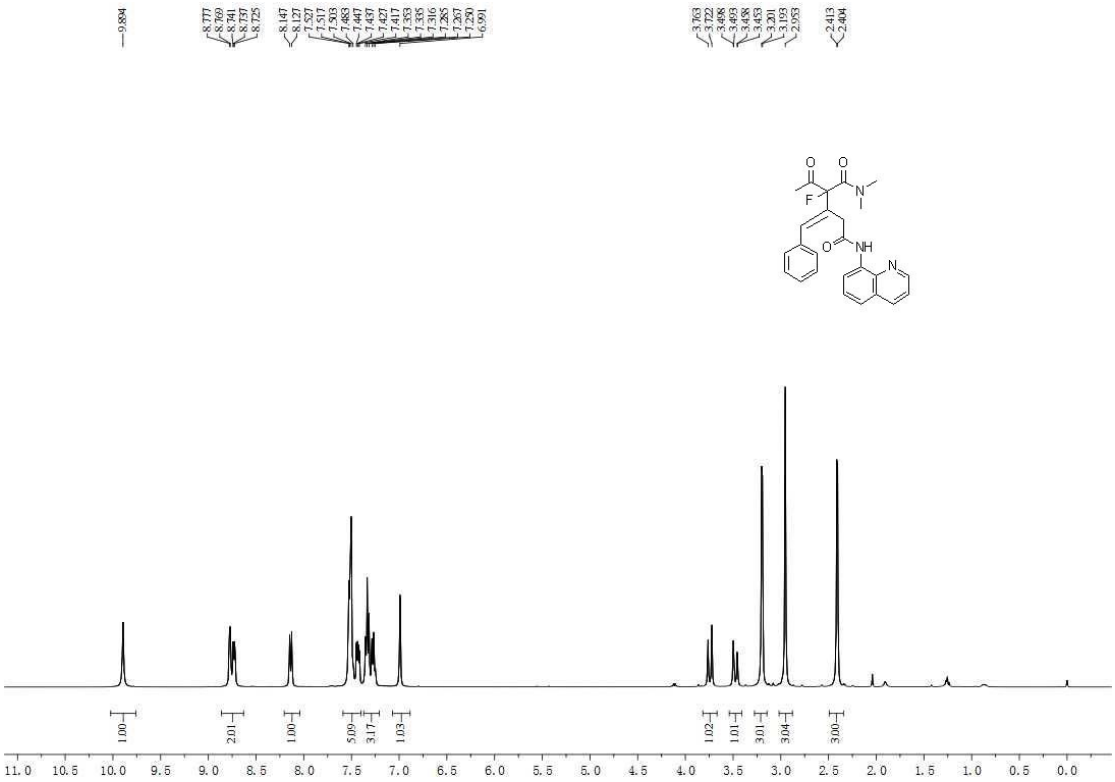
Product 5b

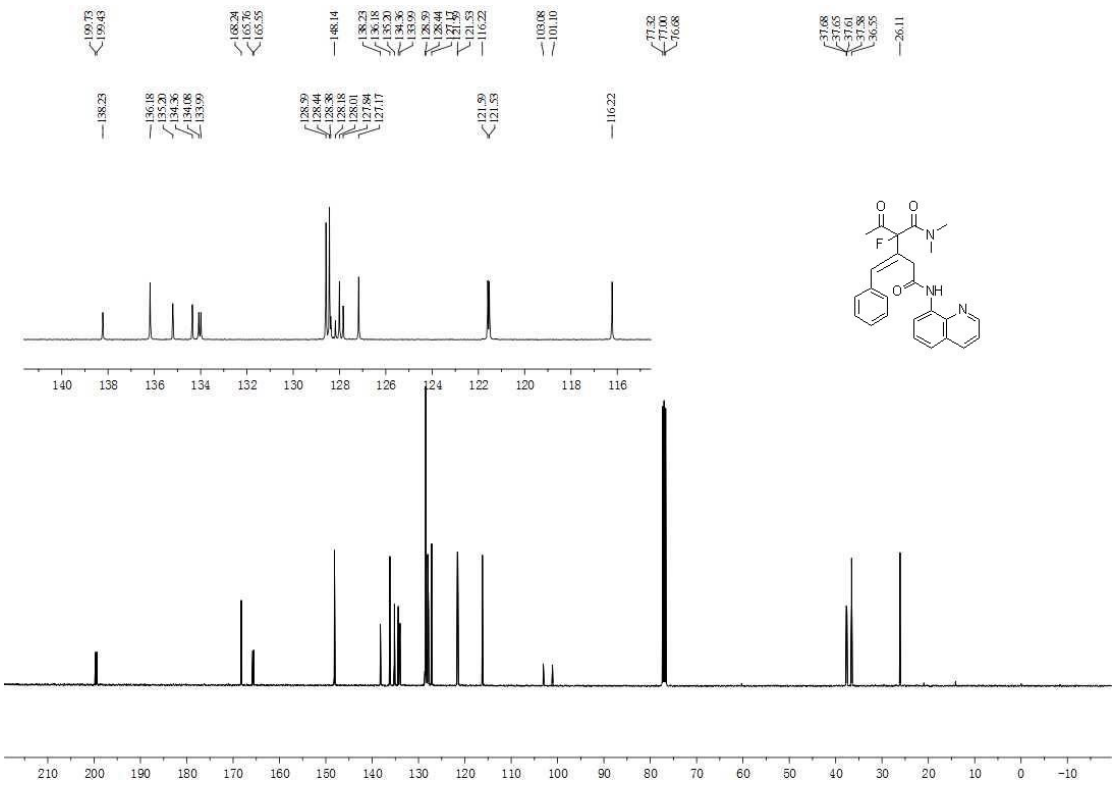

10.017
8.777
8.773
8.767
8.763
8.747
8.741
8.731
8.725
8.142
8.138
8.122
8.118
7.525
7.504
7.491
7.487
7.471
7.465
7.446
7.441
7.430
7.420
7.410
7.327
7.309
7.304
7.290
7.261
7.238
7.243
7.225
4.336
4.327
4.318
4.310
4.293
4.276
4.268
4.259
4.250
3.762
3.758
1.288
1.270
1.252
1.02
1.00
1.02
1.02
5.09
4.20
4.03
2.00
6.34
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

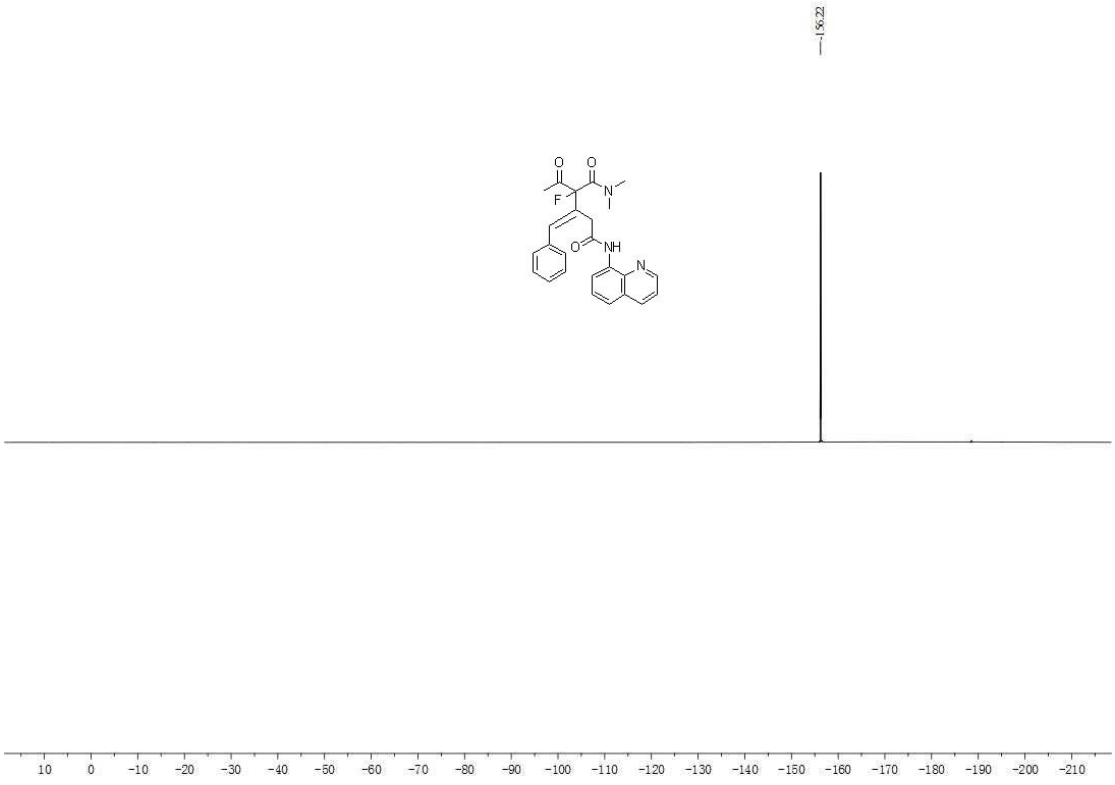

167.81
165.35
165.09
148.13
136.14
135.22
134.57
134.45
134.36
128.68
128.45
127.99
127.83
127.25
121.55
121.48
116.25
96.10
94.10
77.32
77.00
76.68
63.02
37.43
37.39
13.80
O
O
O
O
F
O
NH
N


-158.97
O
O
O
O
F
O
NH
N

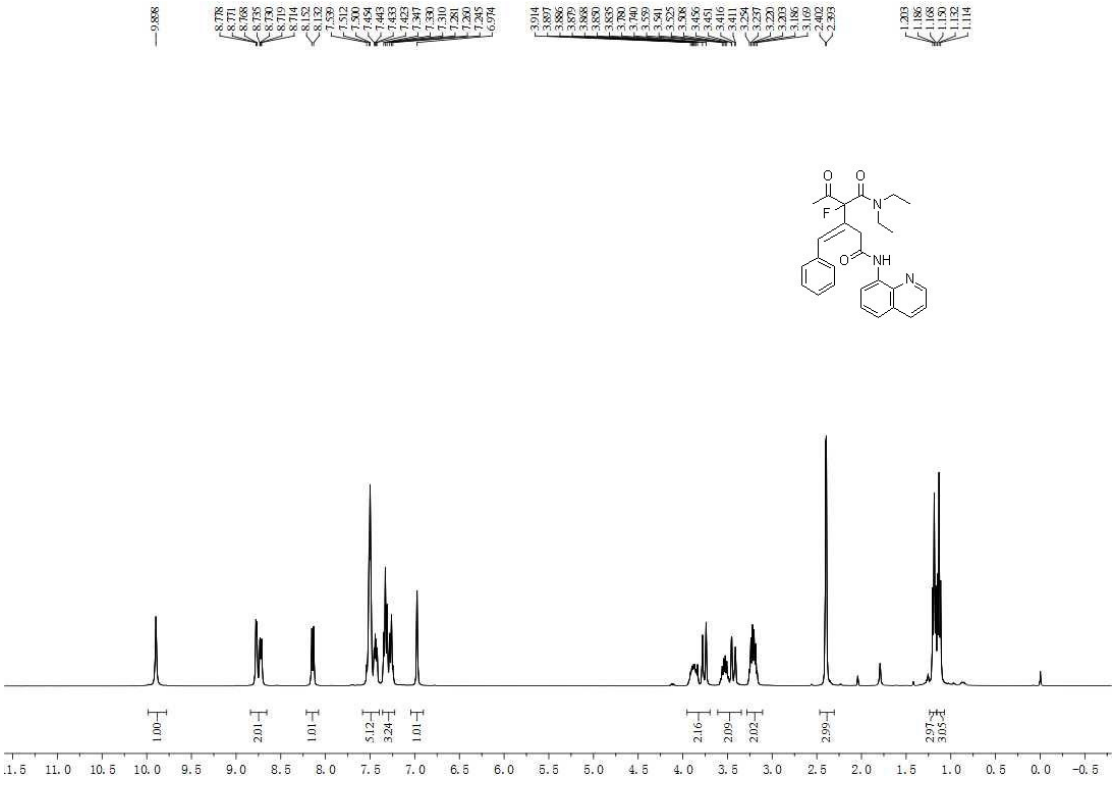
Product 5c

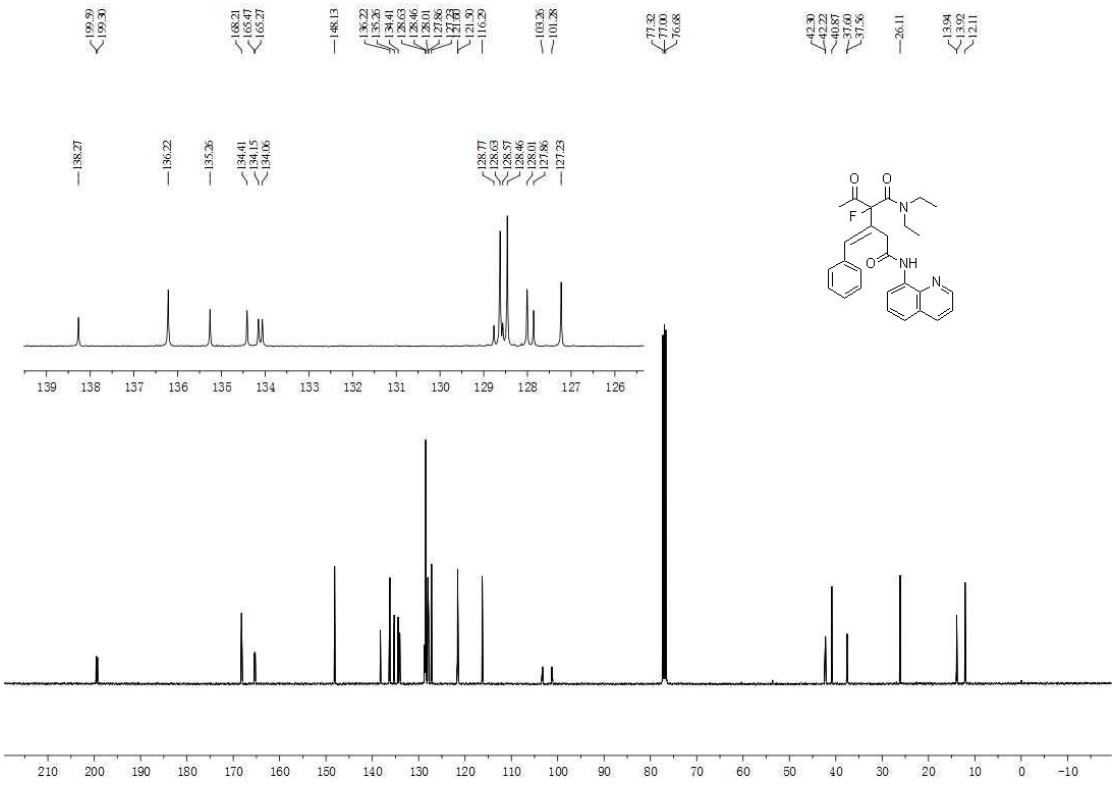


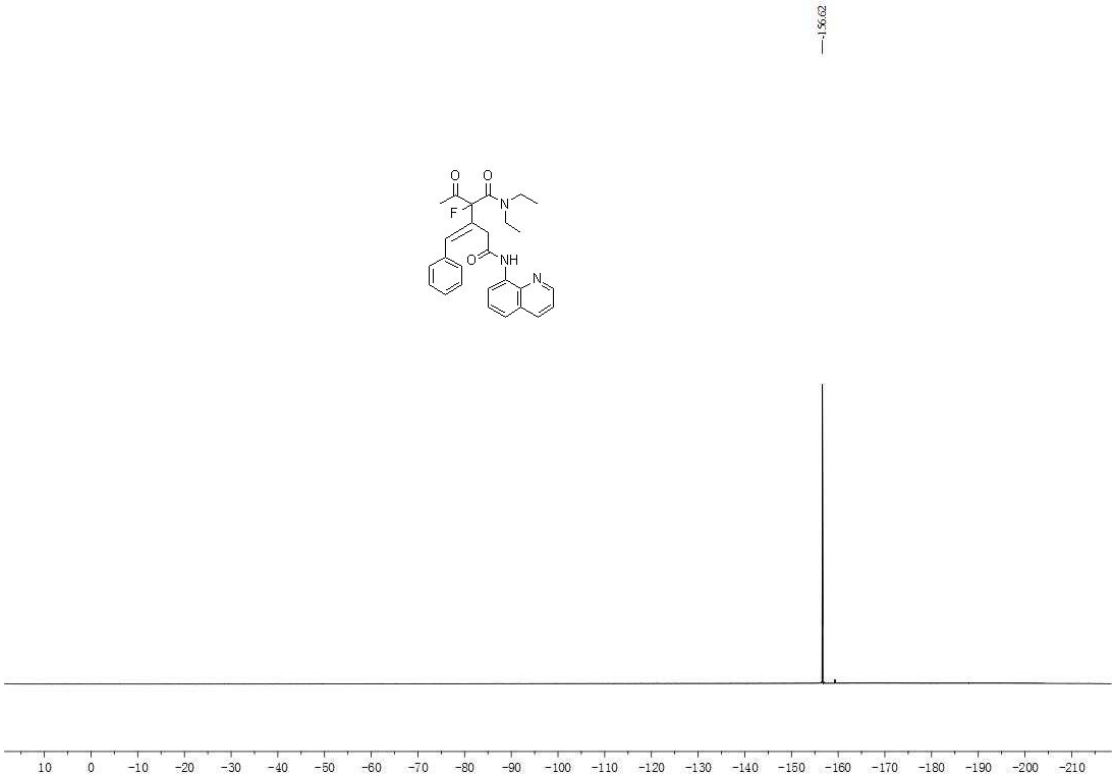



-156.22
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

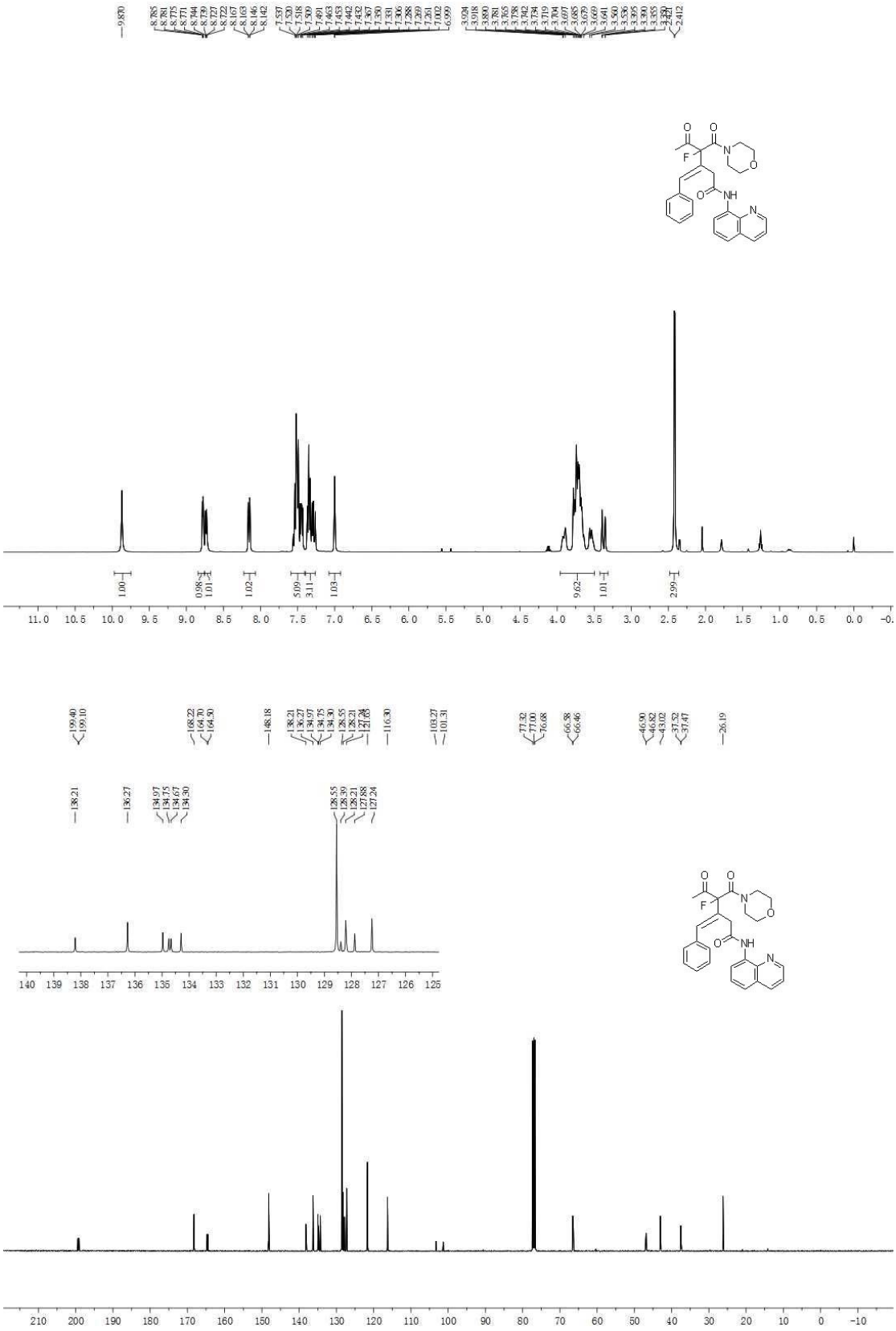
Product 5d

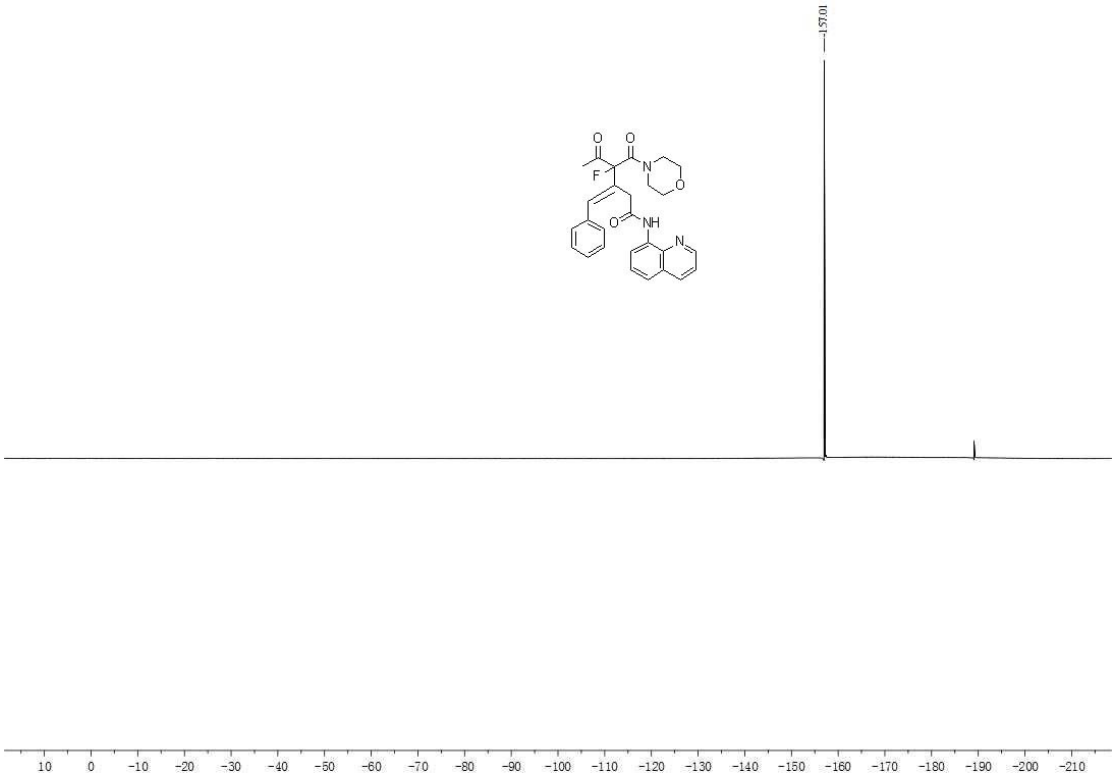

9.808
8.778 8.771 8.768 8.735 8.730 8.719 8.714 8.152 8.132 7.539 7.512 7.500 7.494 7.448 7.443 7.423 7.347 7.330 7.310 7.281 7.200 7.195 6.974
3.914 3.907 3.886 3.879 3.868 3.850 3.835 3.780 3.760 3.699 3.541 3.525 3.508 3.456 3.451 3.416 3.411 3.254 3.237 3.220 3.203 3.186 3.169 2.402 2.393
1.203 1.186 1.168 1.150 1.132 1.114
1.00 2.01 1.01 5.12 3.24 1.01 2.16 2.09 2.02 2.99 2.97 3.05
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


199.59
199.30
168.21
165.47
165.27
148.13
136.22
135.26
134.41
134.15
134.06
128.63
128.46
128.01
127.86
127.63
127.23
121.50
116.29
103.26
101.28
77.32
77.00
76.68
42.30
42.22
40.87
37.60
37.56
26.11
13.94
13.92
12.11
138.27
136.22
135.26
134.41
134.15
134.06
128.77
128.63
128.57
128.46
128.01
127.86
127.23
F
O
N
NH

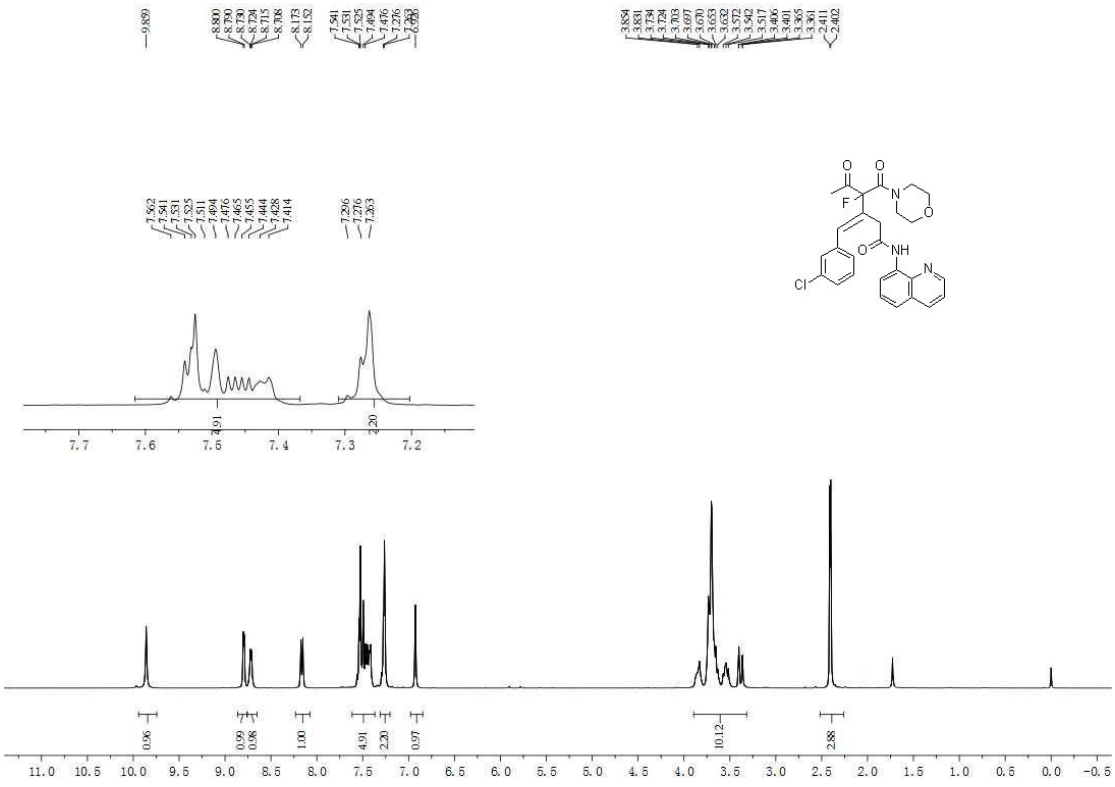

156.62
F
O
N
NH

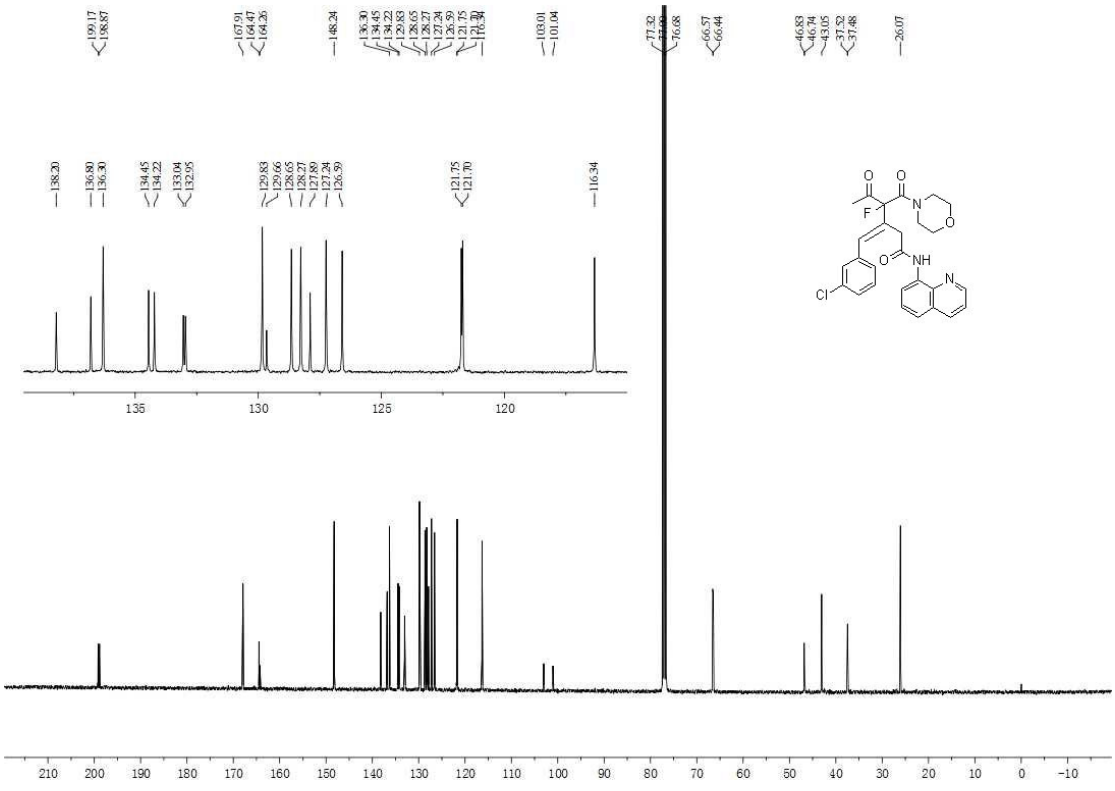
Product 5e

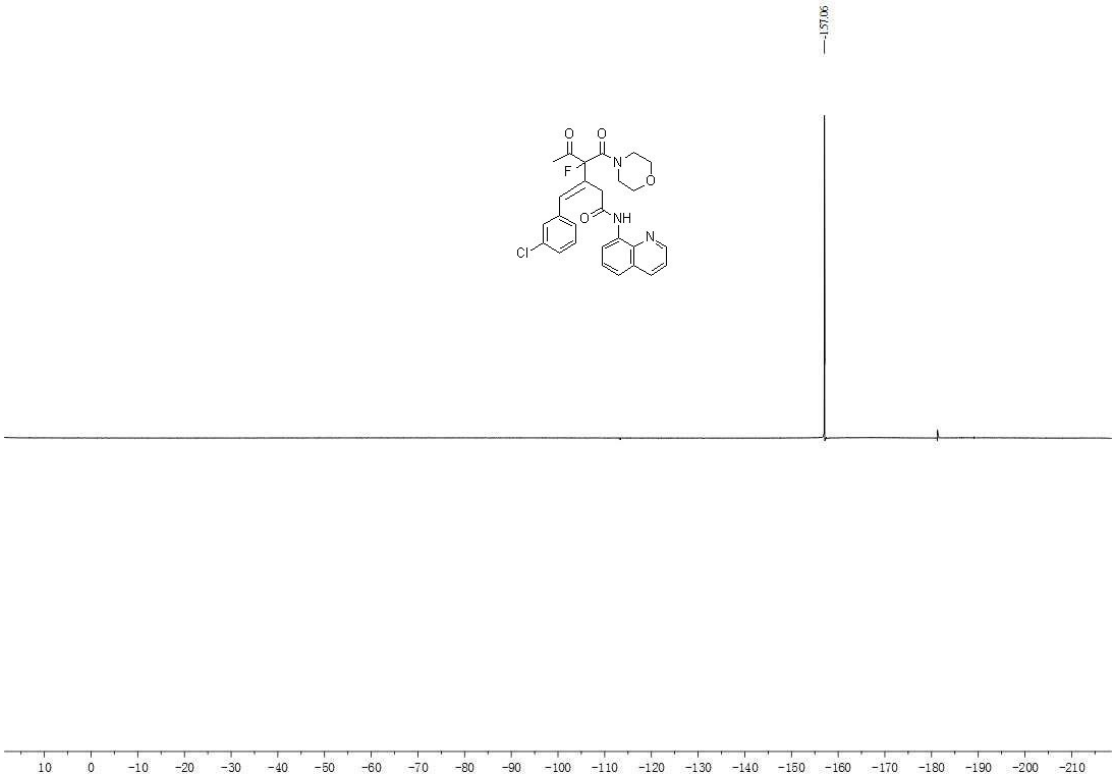



-157.01
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

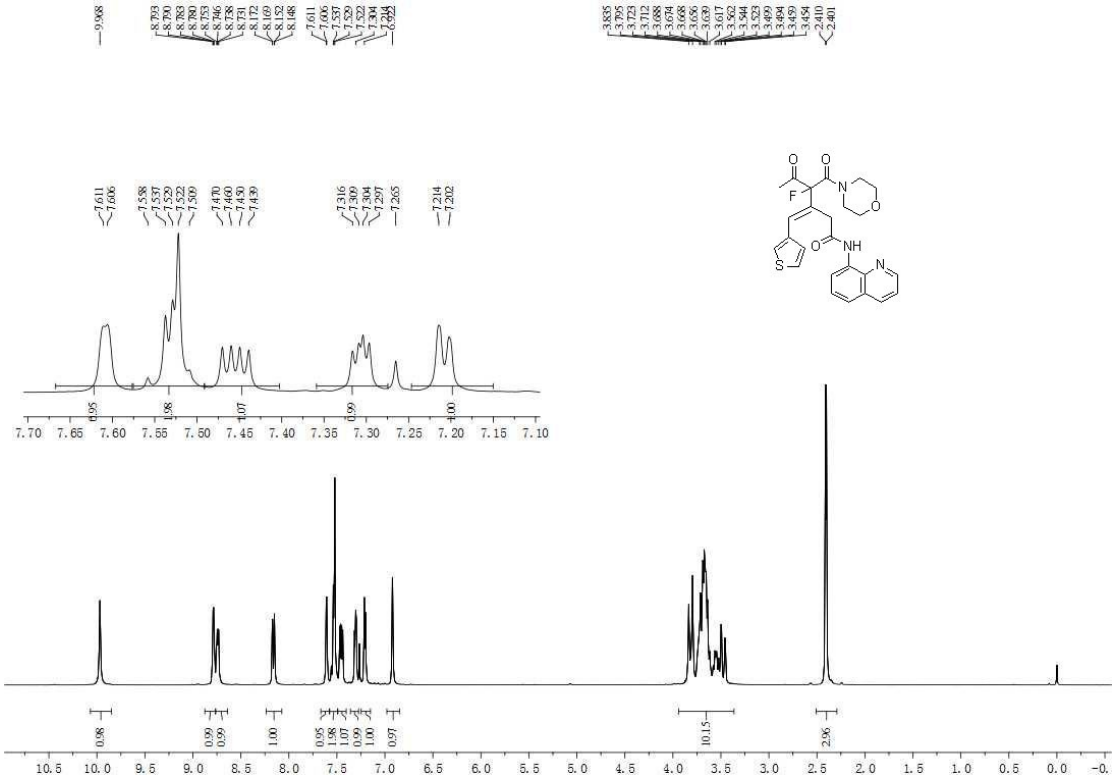
Product 5f

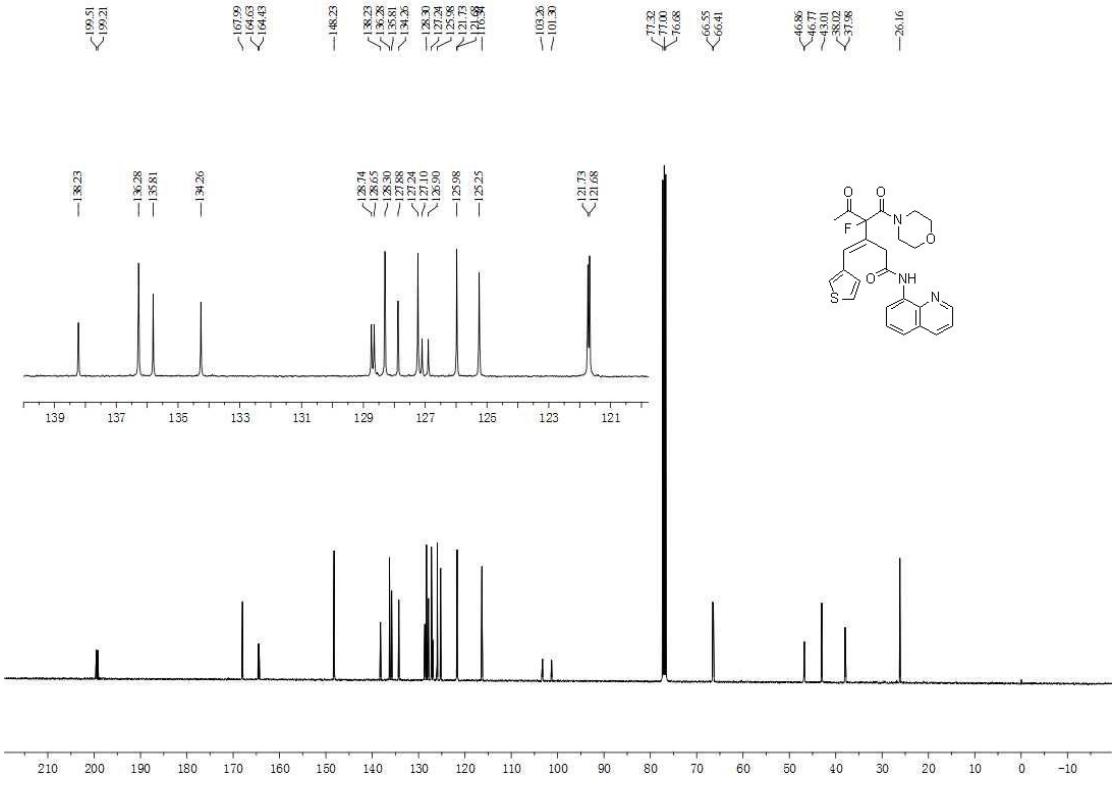

9.859
8.800 8.790 8.730 8.724 8.715 8.708 8.173 8.152
7.541 7.531 7.525 7.494 7.486 7.276 7.263
3.854 3.831 3.794 3.724 3.703 3.697 3.670 3.653 3.632 3.572 3.542 3.517 3.466 3.401 3.365 3.361 2.411 2.402
7.562 7.541 7.531 7.525 7.511 7.494 7.486 7.465 7.455 7.444 7.428 7.414
7.296 7.276 7.263
4.91 2.20
7.7 7.6 7.5 7.4 7.3 7.2
0.96 0.99 0.98 1.00 4.91 2.20 0.97 10.12 2.88
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

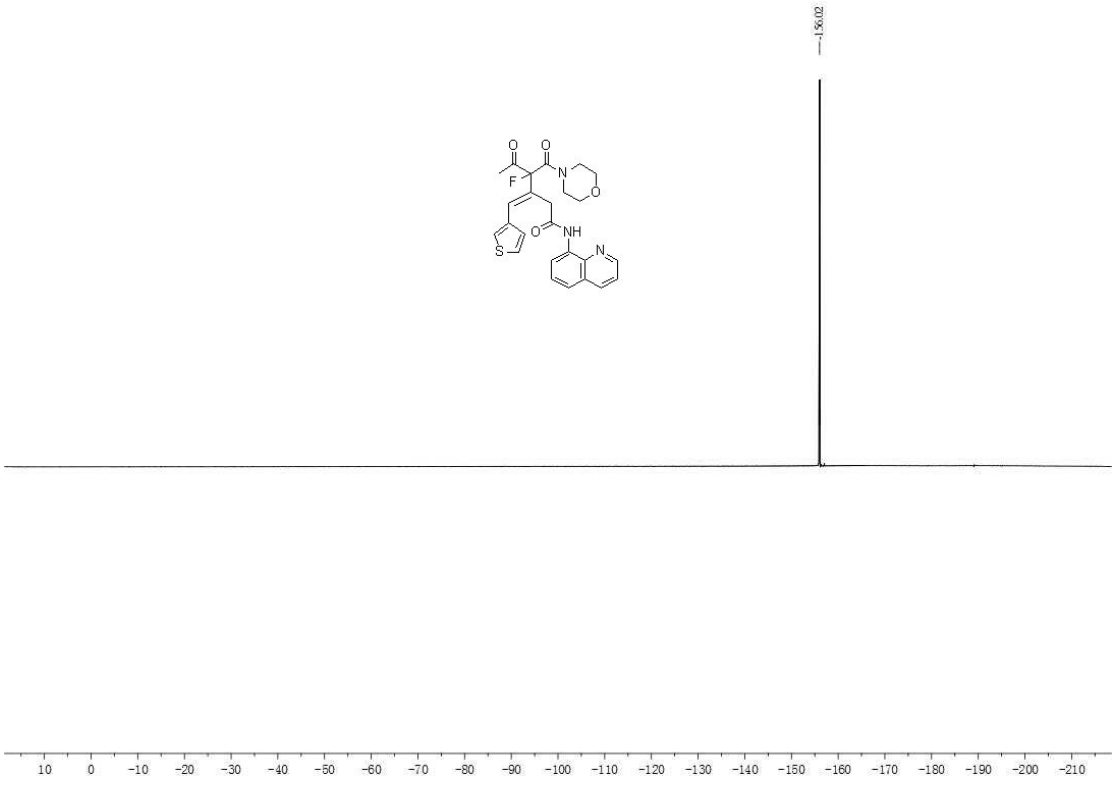

199.17
198.87
167.91
164.47
164.26
148.24
136.30
134.45
134.22
129.83
128.65
128.27
127.24
126.99
121.75
121.70
116.34
103.01
101.04
77.32
76.68
66.57
66.44
46.83
46.74
43.05
37.52
37.48
26.07
138.20
136.80
136.30
134.45
134.22
133.04
132.05
129.83
129.66
128.65
128.27
127.89
127.24
126.59
121.75
121.70
116.34
135
130
125
120
O
O
N
F
O
NH
N
Cl
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


-157.06
O
O
N
F
O
NH
N
Cl
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210

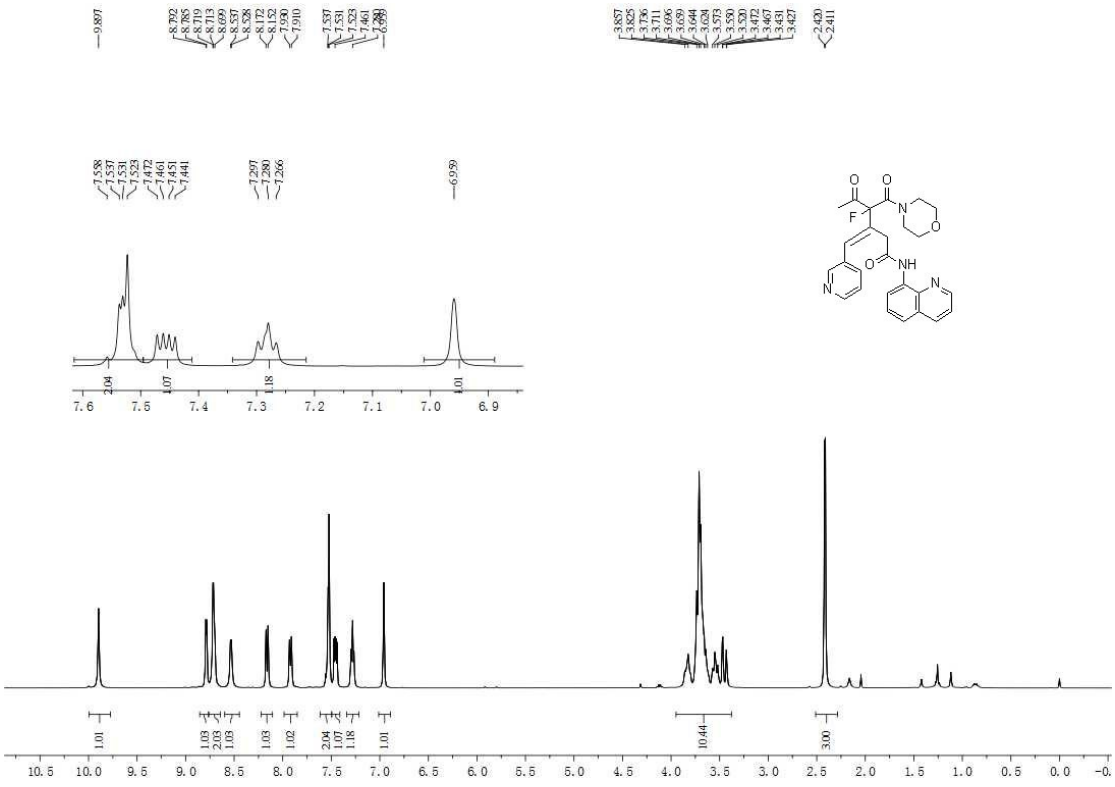
Product 5g

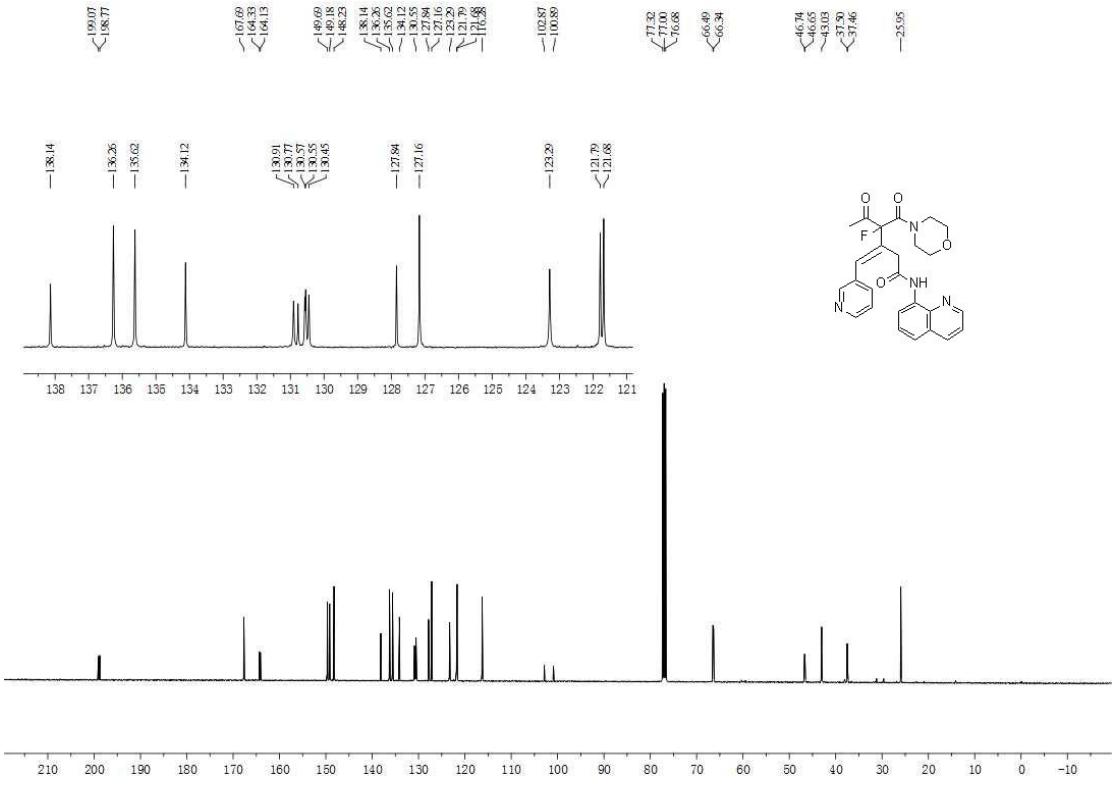


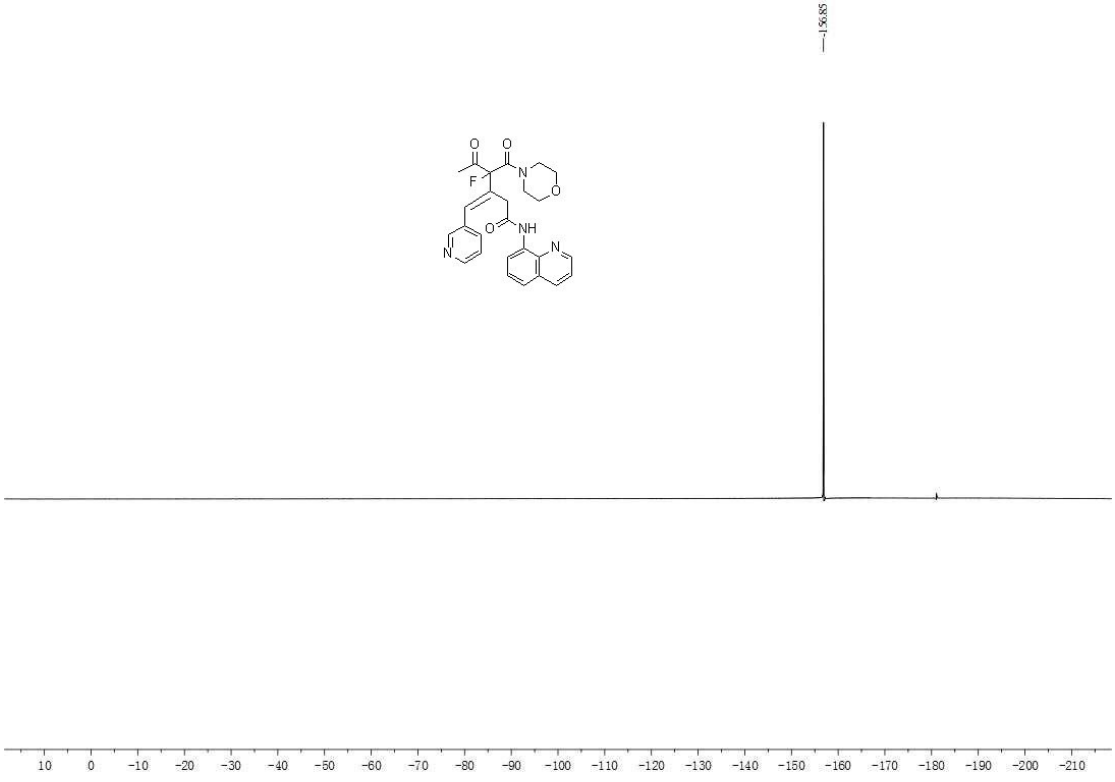



-156.02
F
O
O
N
O
NH
S
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

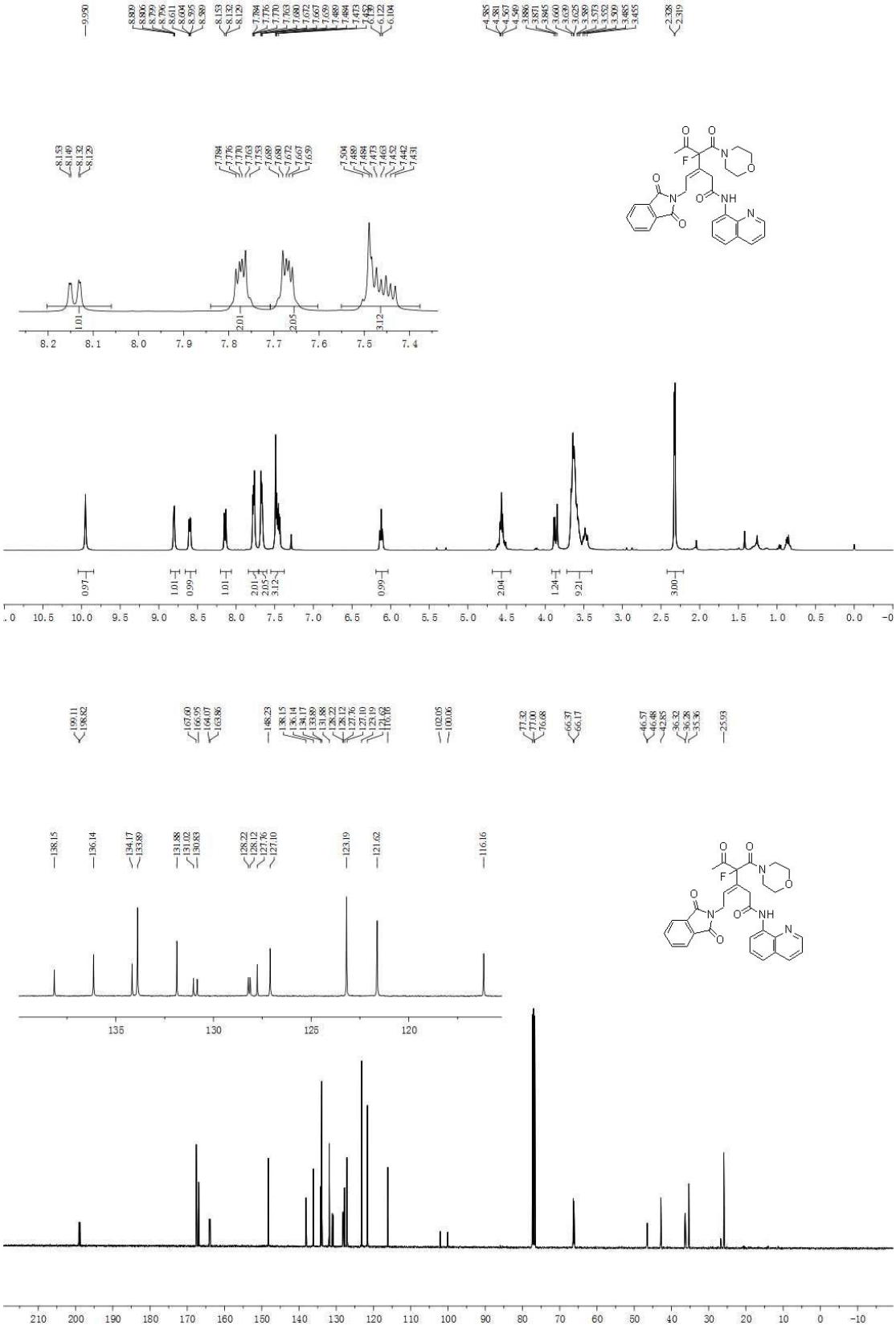
Product 5h

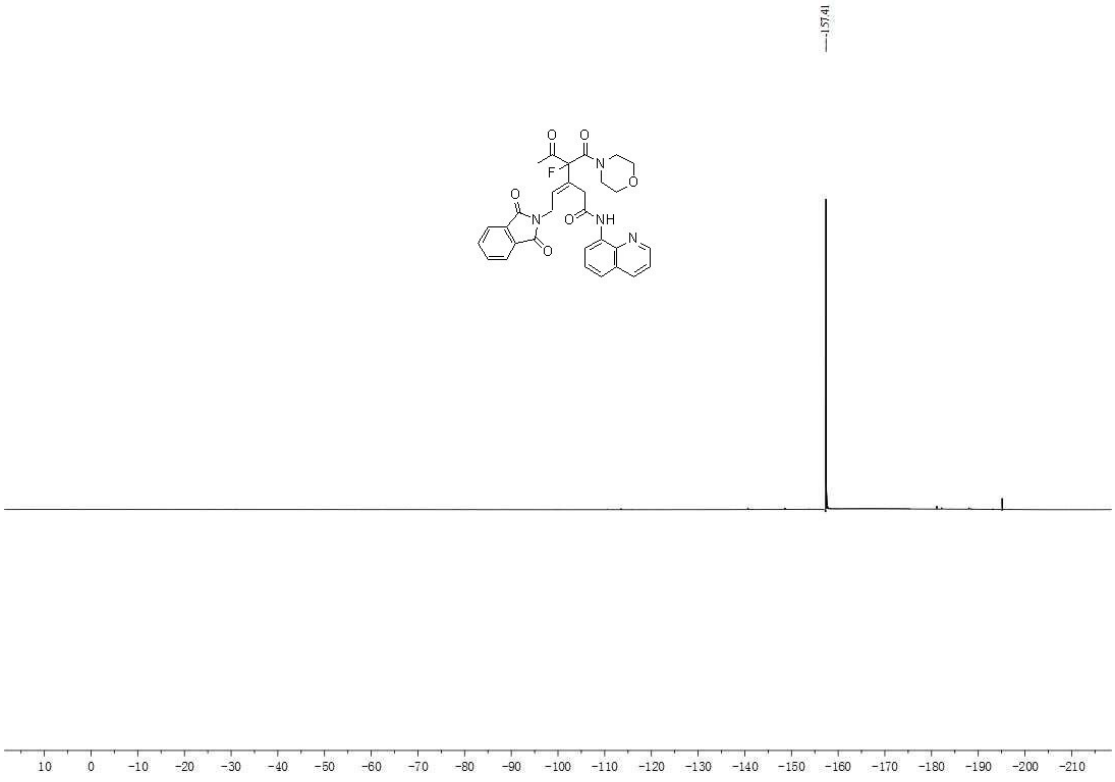

9.897
8.792
8.765
8.719
8.713
8.699
8.537
8.528
8.172
8.152
7.590
7.590
7.537
7.531
7.523
7.461
7.461
6.959
3.887
3.825
3.736
3.711
3.696
3.689
3.644
3.624
3.573
3.550
3.530
3.472
3.467
3.431
3.427
2.420
2.411
7.598
7.537
7.531
7.523
7.472
7.461
7.451
7.441
7.297
7.280
7.266
6.959
2.04
1.07
1.18
1.01
7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9
F
O
O
N
O
NH
N
N
1.01
1.03
2.03
1.03
1.03
1.02
2.04
1.07
1.18
1.01
10.44
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


199.07
198.77
167.69
164.33
164.13
149.69
149.18
148.23
138.14
136.26
135.62
134.12
130.55
127.84
127.16
123.29
121.79
121.68
102.87
100.89
77.32
77.00
76.68
66.49
66.34
46.74
46.65
43.03
37.90
37.46
25.95
138.14
136.26
135.62
134.12
130.91
130.77
130.57
130.35
130.45
127.84
127.16
123.29
121.79
121.68
O
O
F
N
O
O
NH
N
N
138 137 136 135 134 133 132 131 130 129 128 127 126 125 124 123 122 121
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

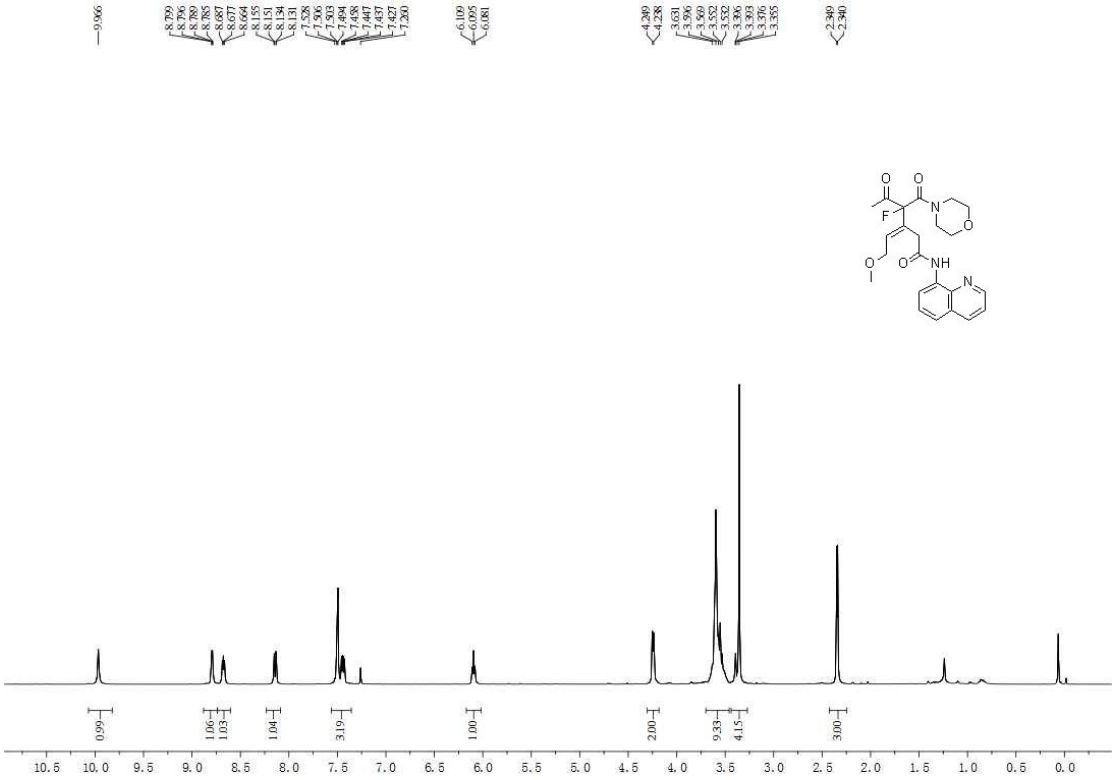

-156.85
O
O
F
N
O
O
NH
N
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

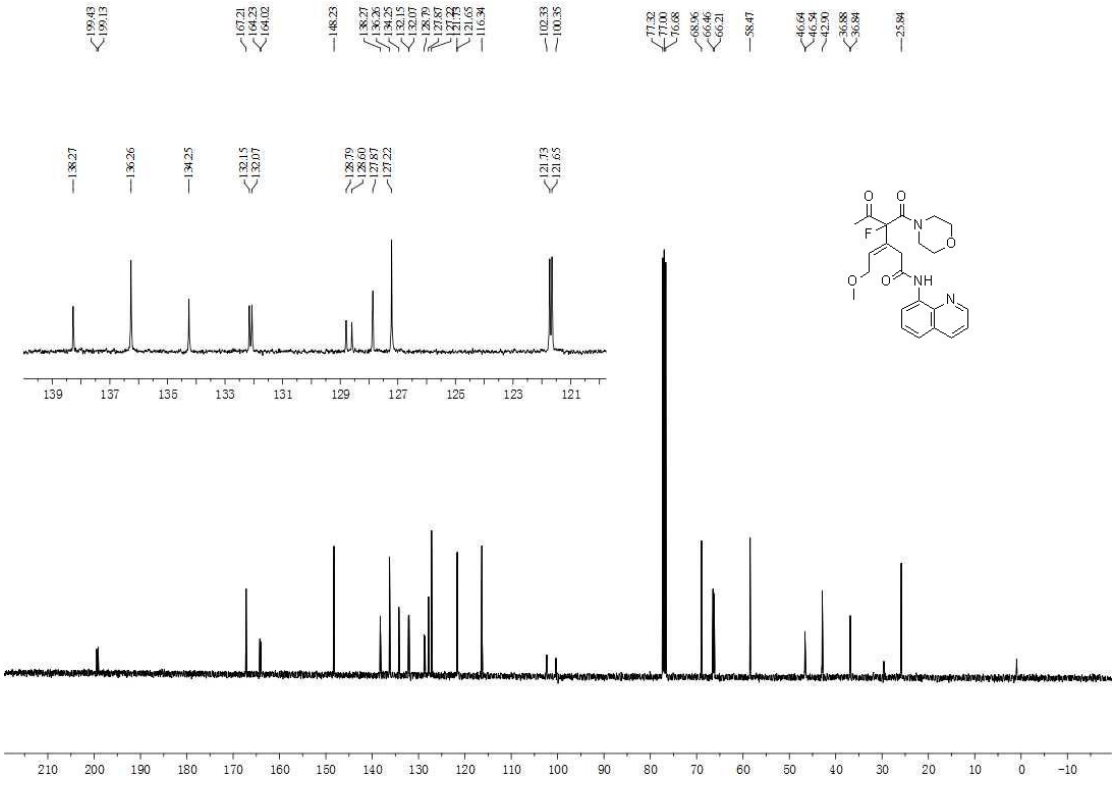
Product 5i

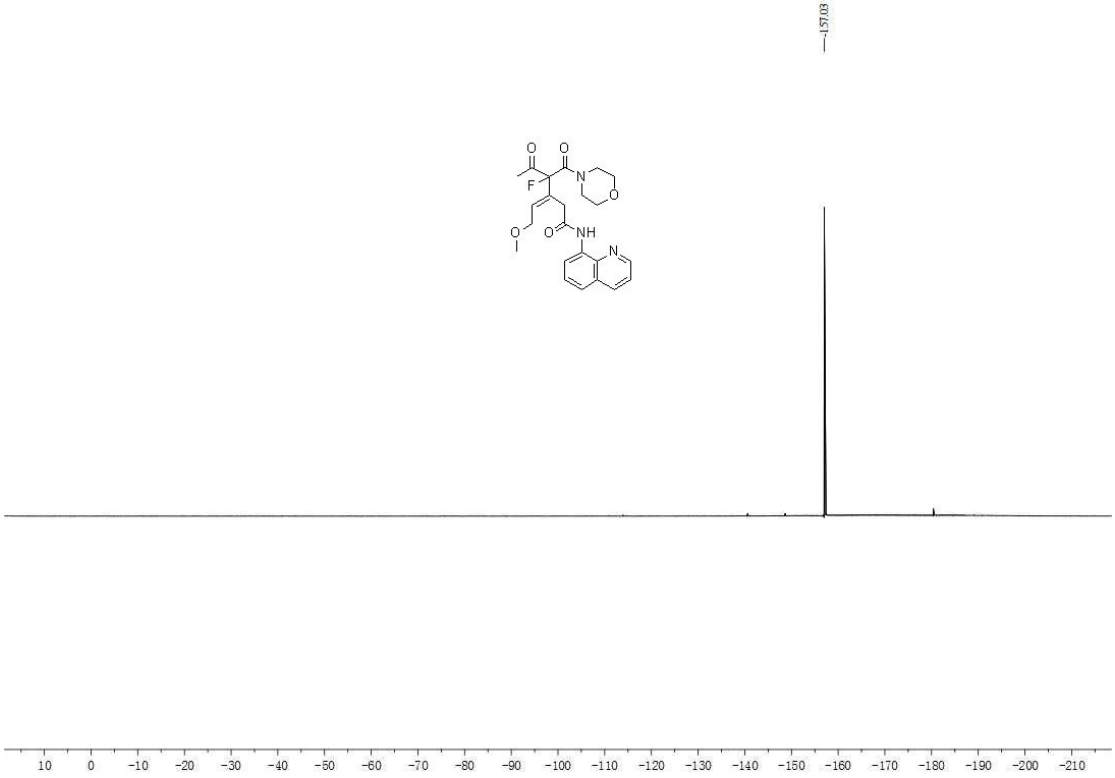



-157.41
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

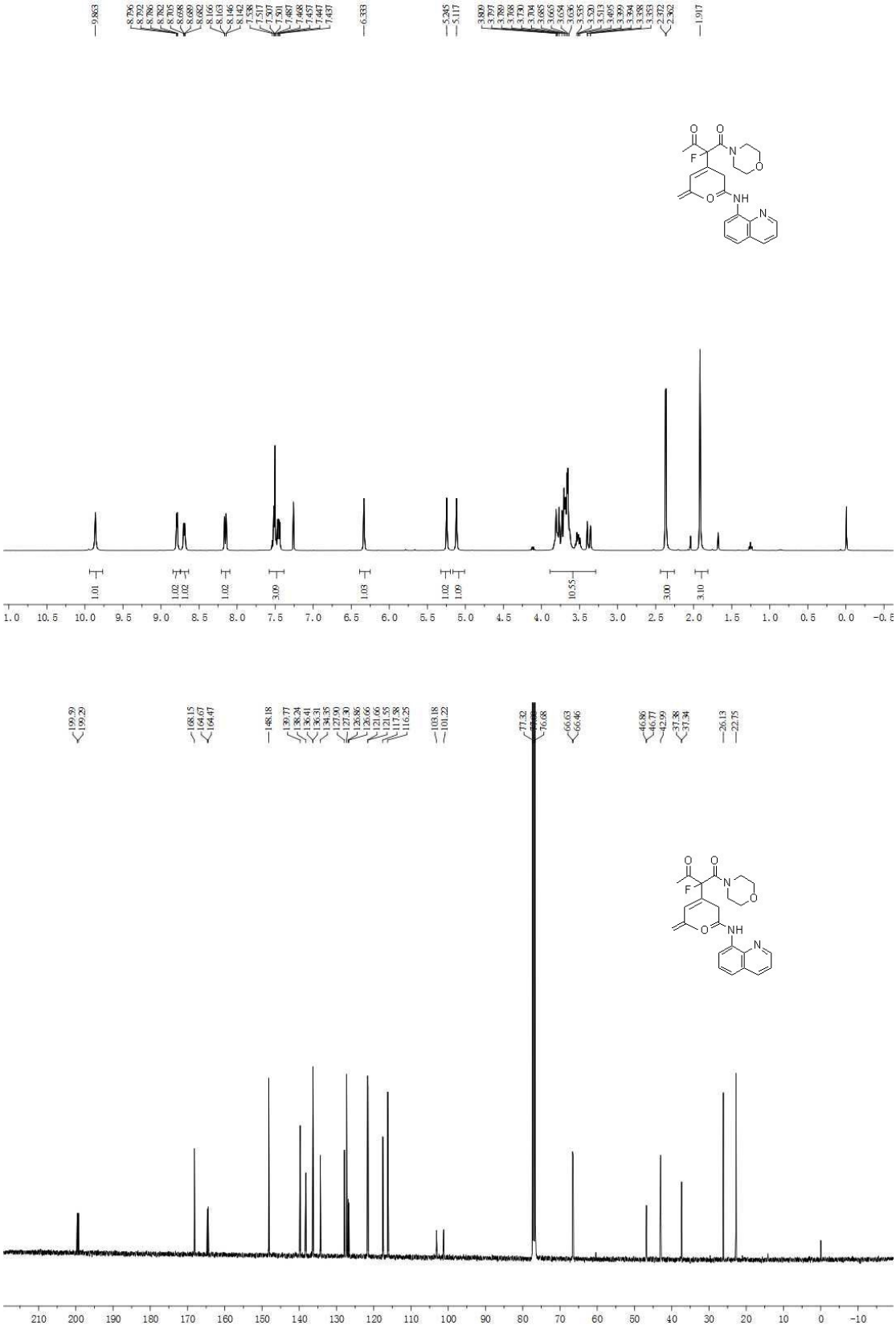
Product 5j

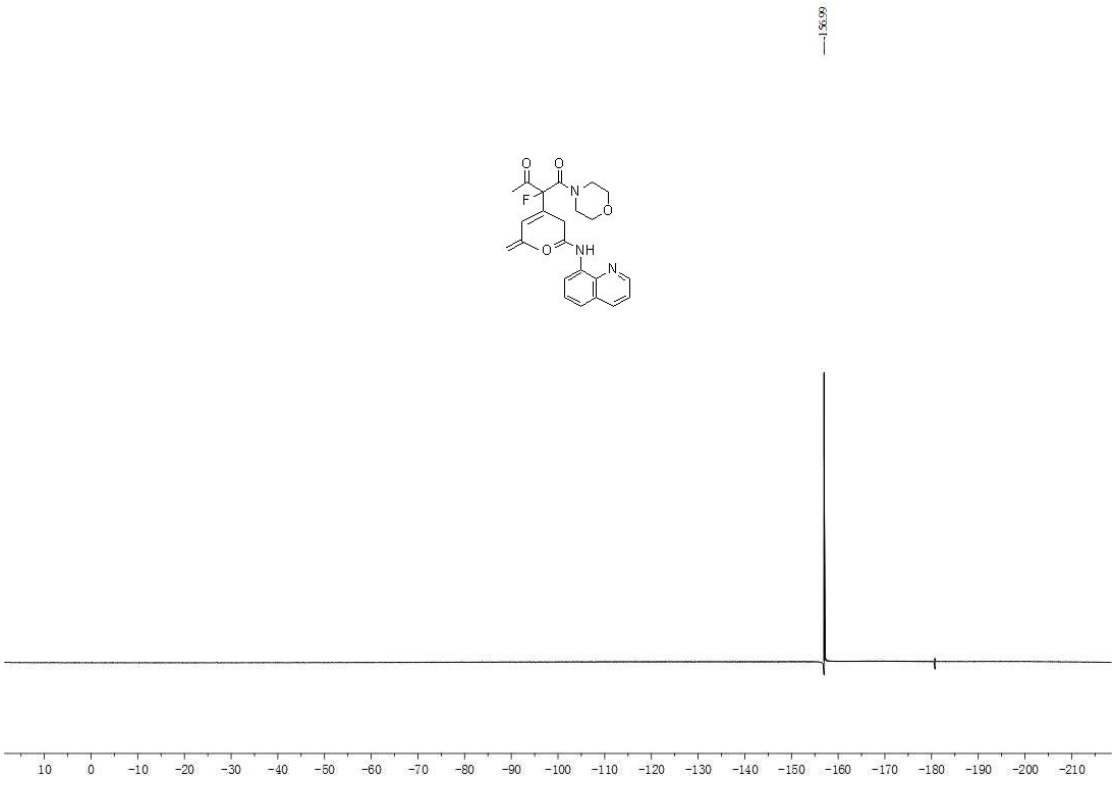

9.966
8.739
8.706
8.789
8.785
8.687
8.677
8.664
8.155
8.151
8.134
8.131
7.526
7.506
7.503
7.494
7.488
7.447
7.437
7.427
7.260
6.109
6.095
6.081
4.249
4.238
3.631
3.596
3.569
3.552
3.532
3.306
3.303
3.376
3.355
2.349
2.340
0.99
1.06
1.03
1.04
3.19
1.00
2.00
9.33
4.15
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


199.43
199.13
167.21
164.25
164.02
148.23
138.27
136.26
134.25
132.15
132.07
128.79
128.60
127.87
127.72
121.73
121.65
116.94
102.33
100.35
77.32
77.00
76.68
68.96
66.46
66.21
58.47
46.64
46.54
42.90
36.88
36.84
25.84
F
O
N
O
O
NH
N

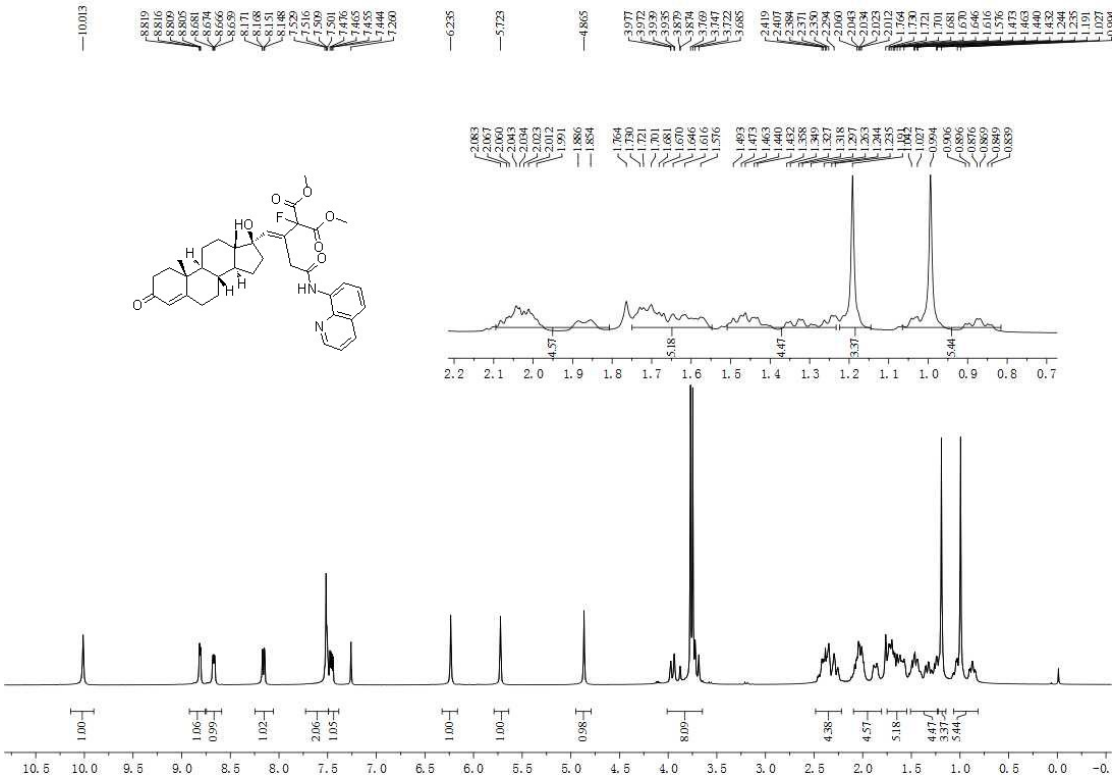

157.03
F
O
N
O
O
NH
N

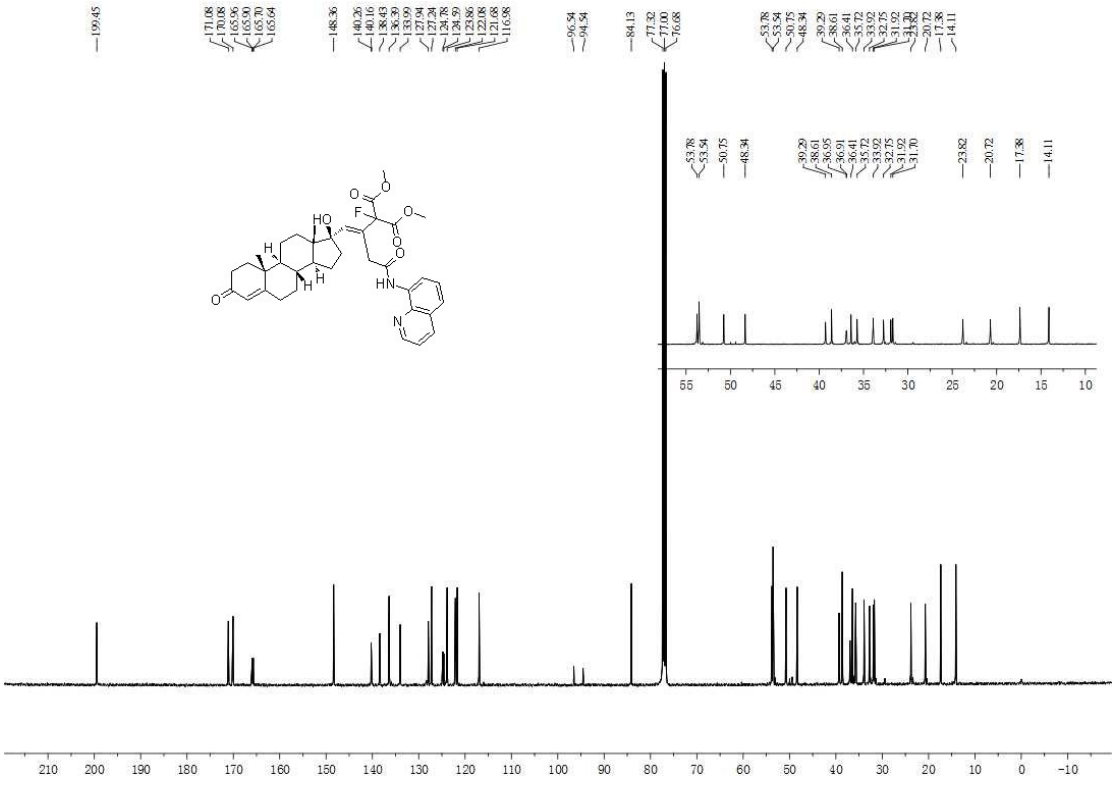
Product 5k

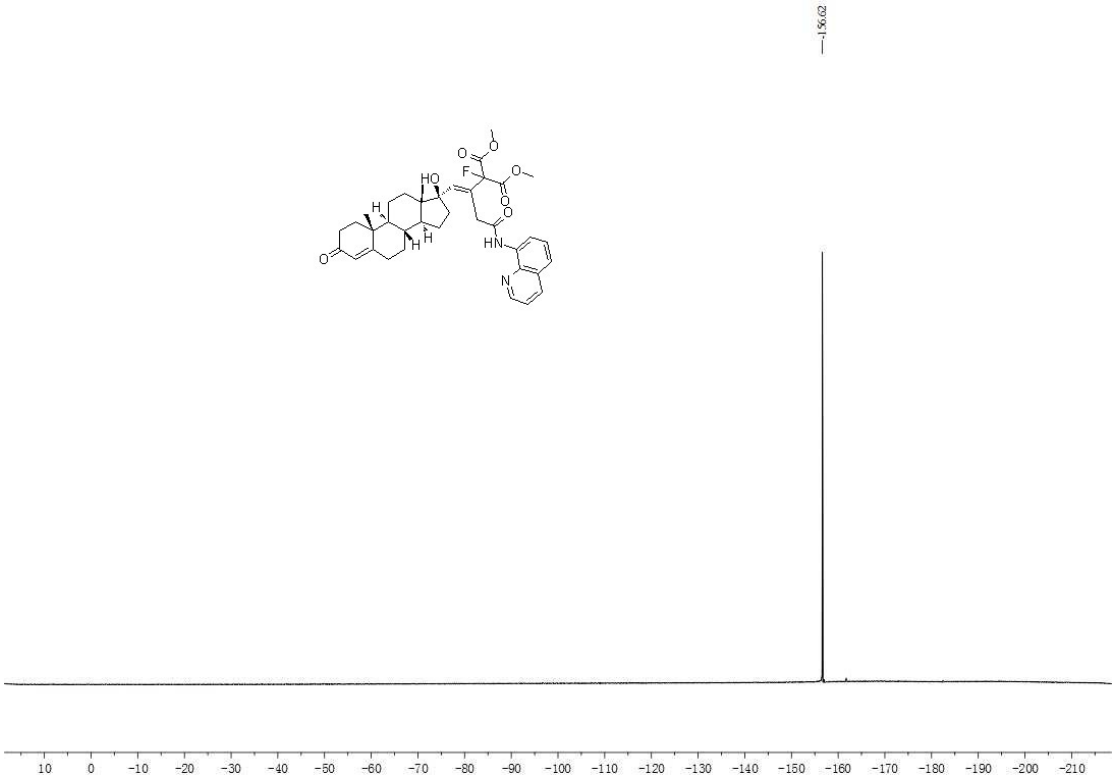

9.863
8.796
8.792
8.786
8.782
8.705
8.698
8.689
8.682
8.166
8.163
8.146
8.142
7.538
7.517
7.501
7.487
7.468
7.457
7.447
7.437
6.333
5.245
5.117
3.809
3.797
3.789
3.708
3.710
3.704
3.695
3.665
3.654
3.636
3.535
3.520
3.513
3.495
3.369
3.359
3.338
3.353
2.372
2.362
1.917
1.01
1.02
1.02
1.02
3.09
1.03
1.02
1.09
10.55
3.00
3.10
199.59
199.29
168.15
164.67
164.47
148.18
139.77
138.24
136.41
136.23
134.35
127.90
127.30
126.86
126.66
121.66
121.55
117.38
116.25
103.18
101.22
77.32
77.00
76.68
66.63
66.46
46.86
46.77
42.99
37.38
37.34
26.13
22.75



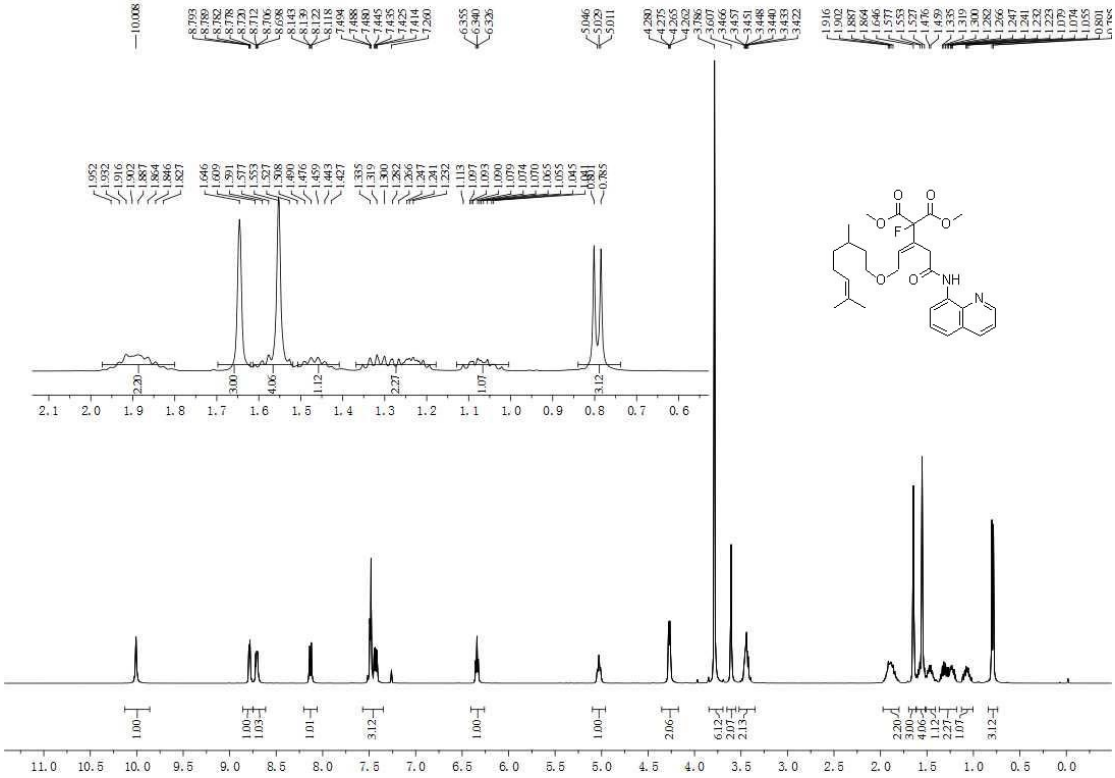
Product 7

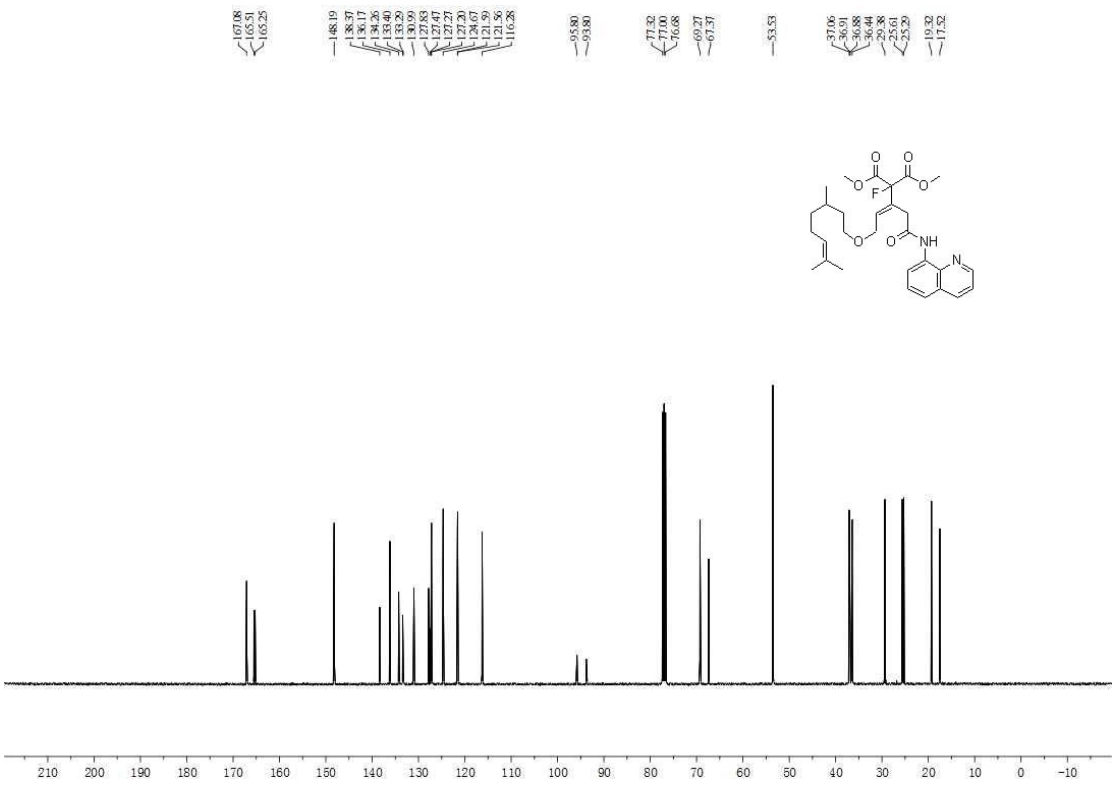


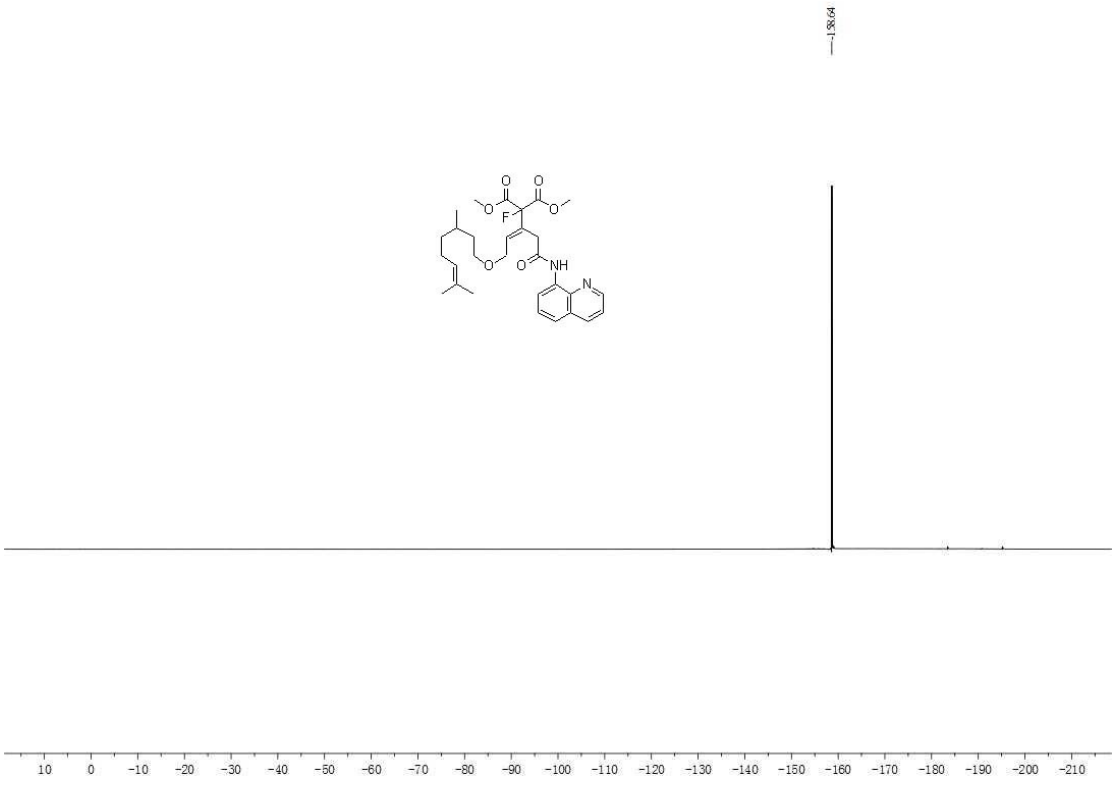




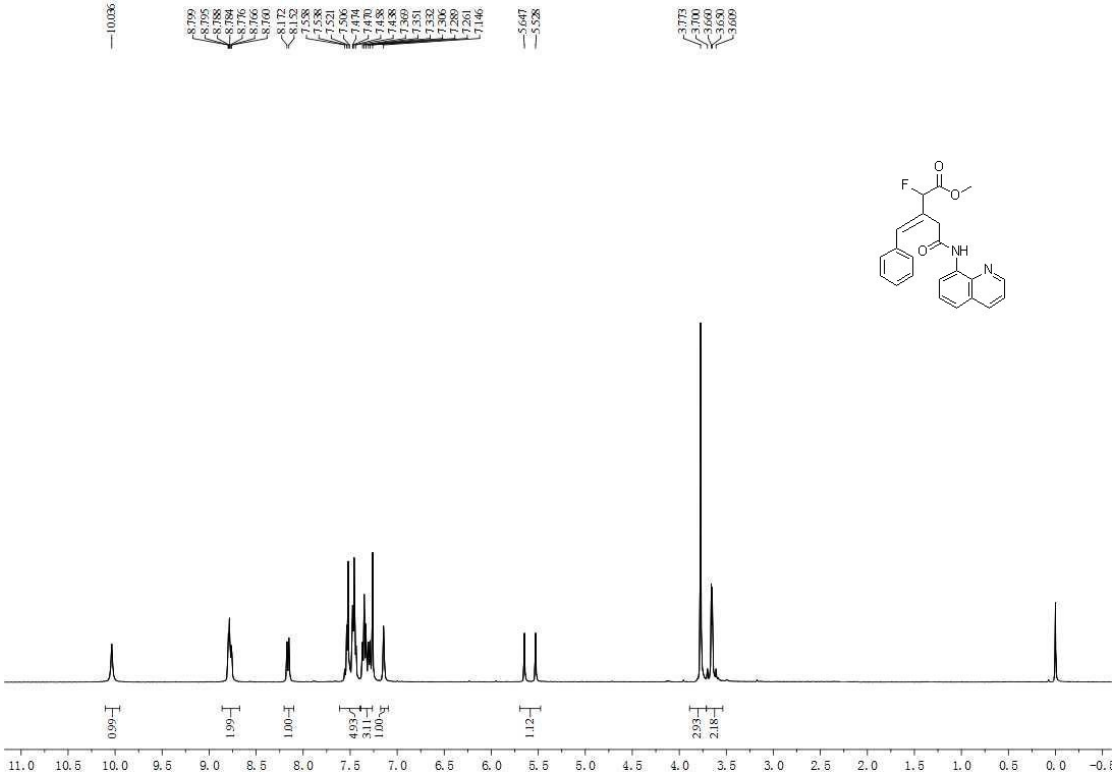
Product 9

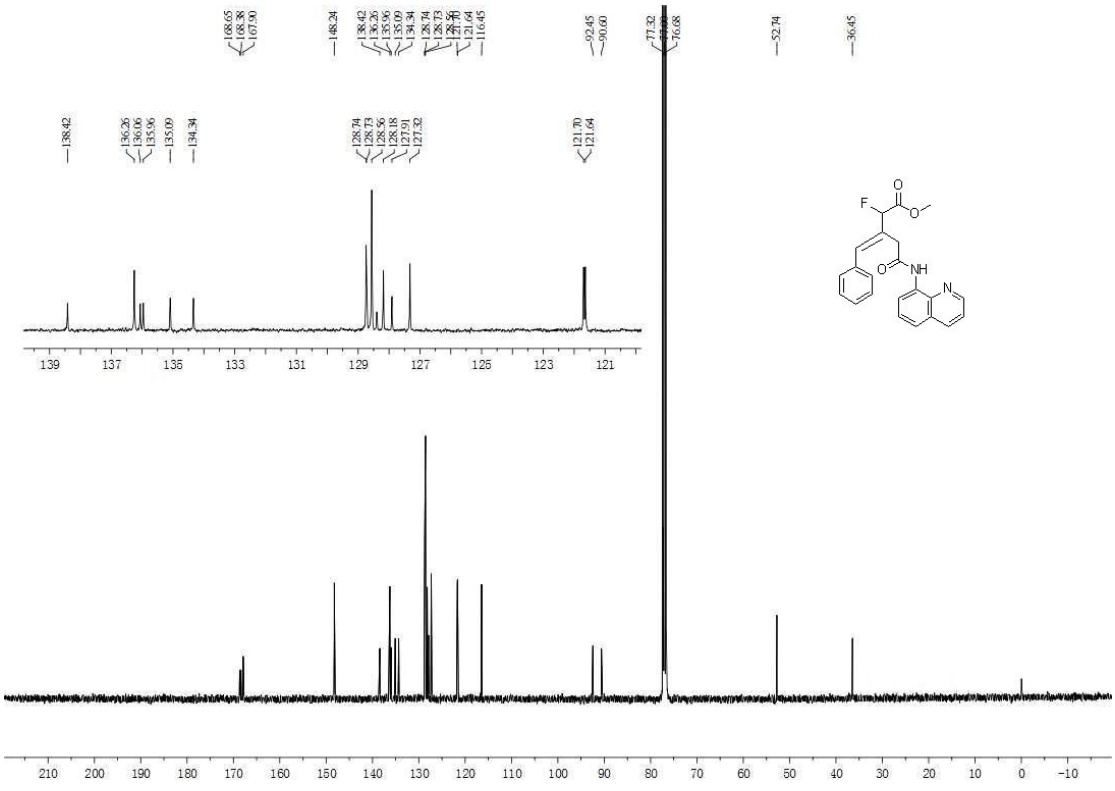


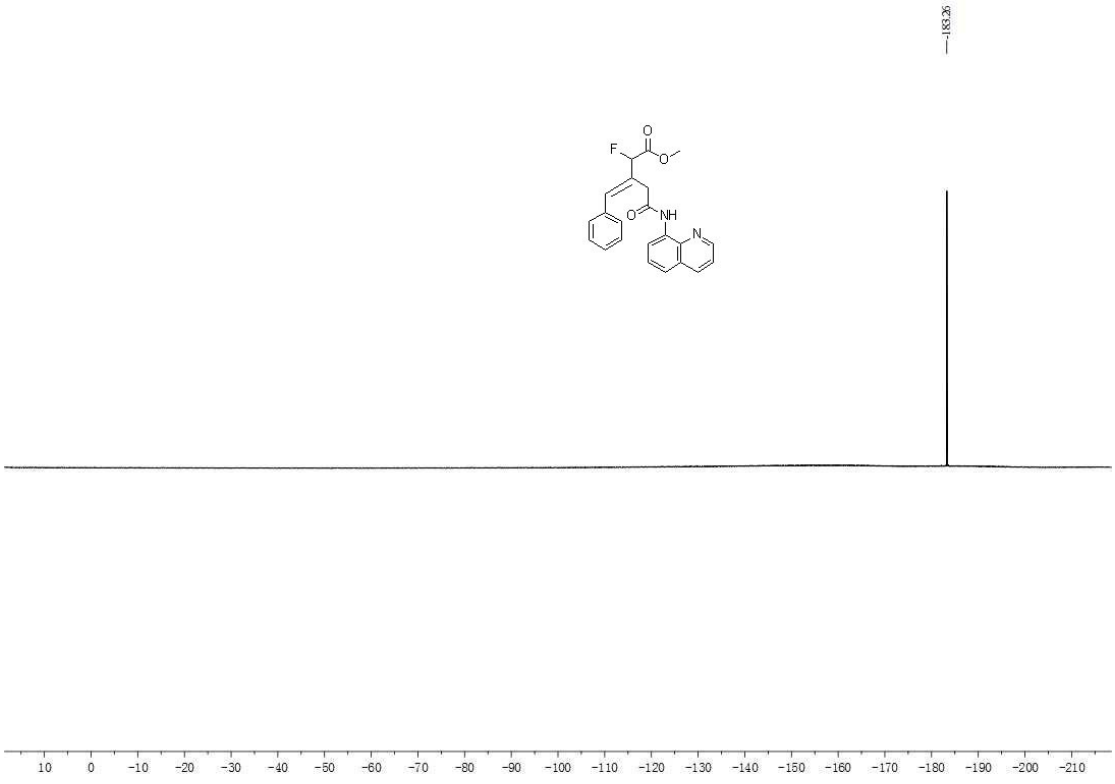



-158.64
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

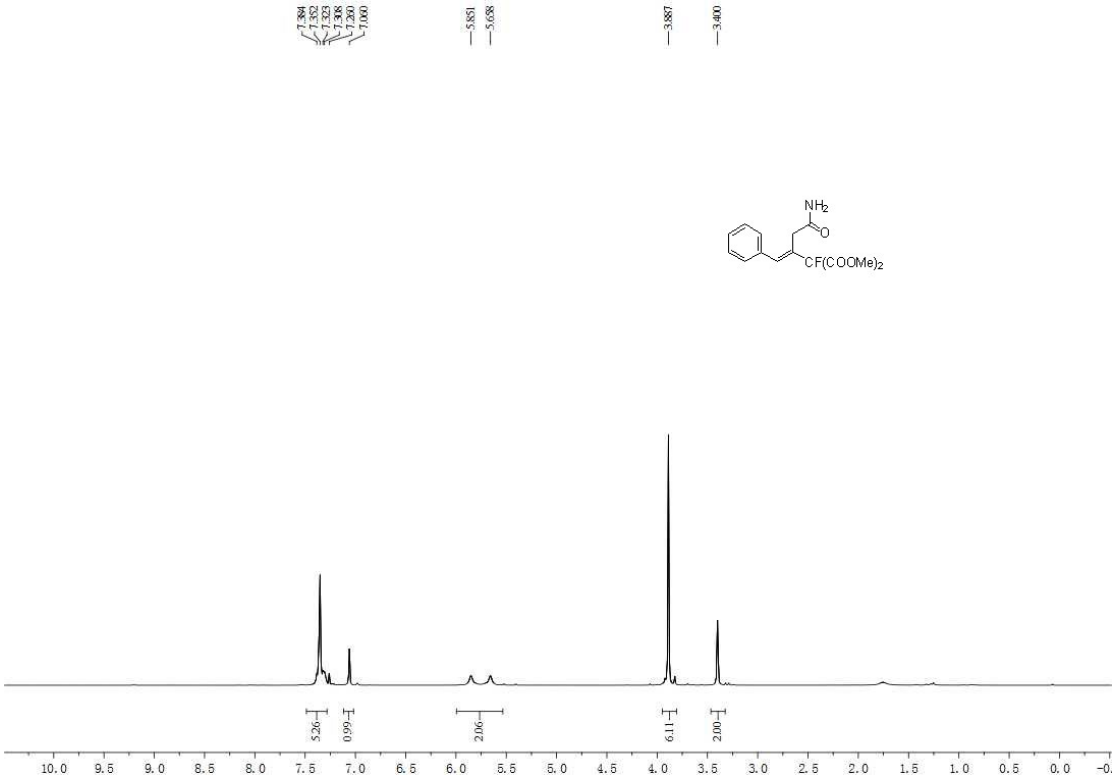
Product 10

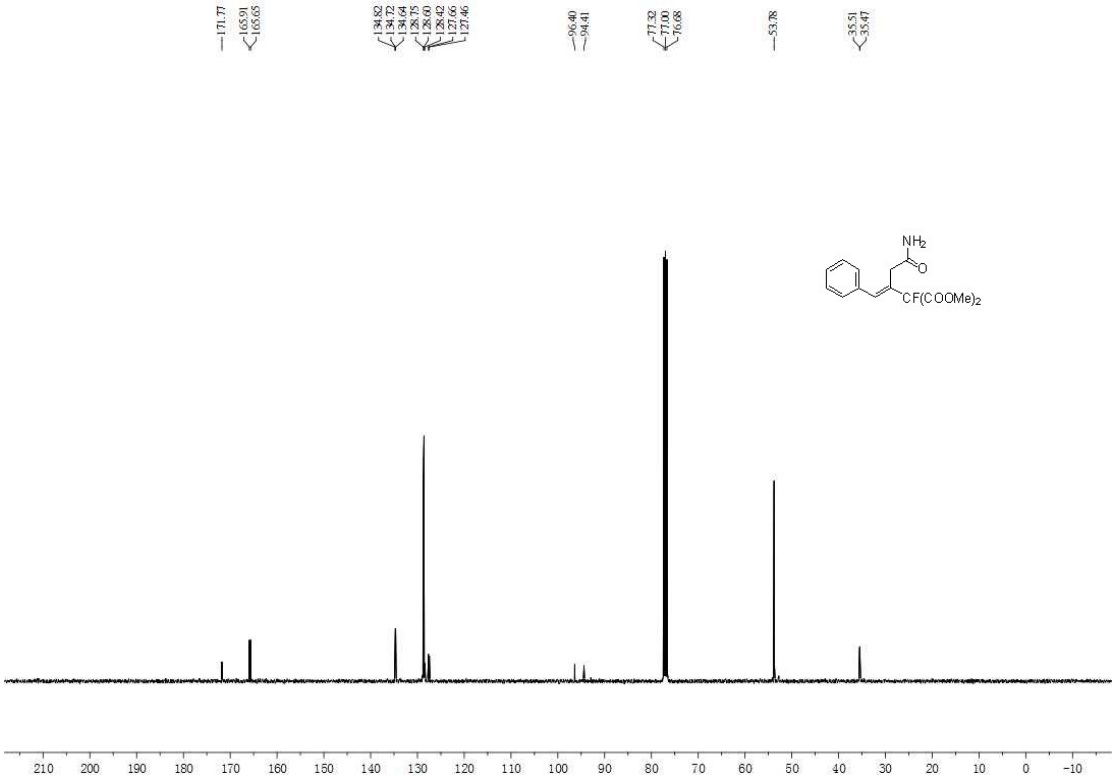

10.036
8.799
8.795
8.788
8.784
8.776
8.766
8.760
8.172
8.152
7.558
7.538
7.521
7.506
7.474
7.470
7.458
7.438
7.369
7.351
7.332
7.306
7.289
7.261
7.146
5.647
5.528
3.773
3.700
3.660
3.650
3.609
0.99
1.99
1.00
4.93
3.11
1.00
1.12
2.93
2.18
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

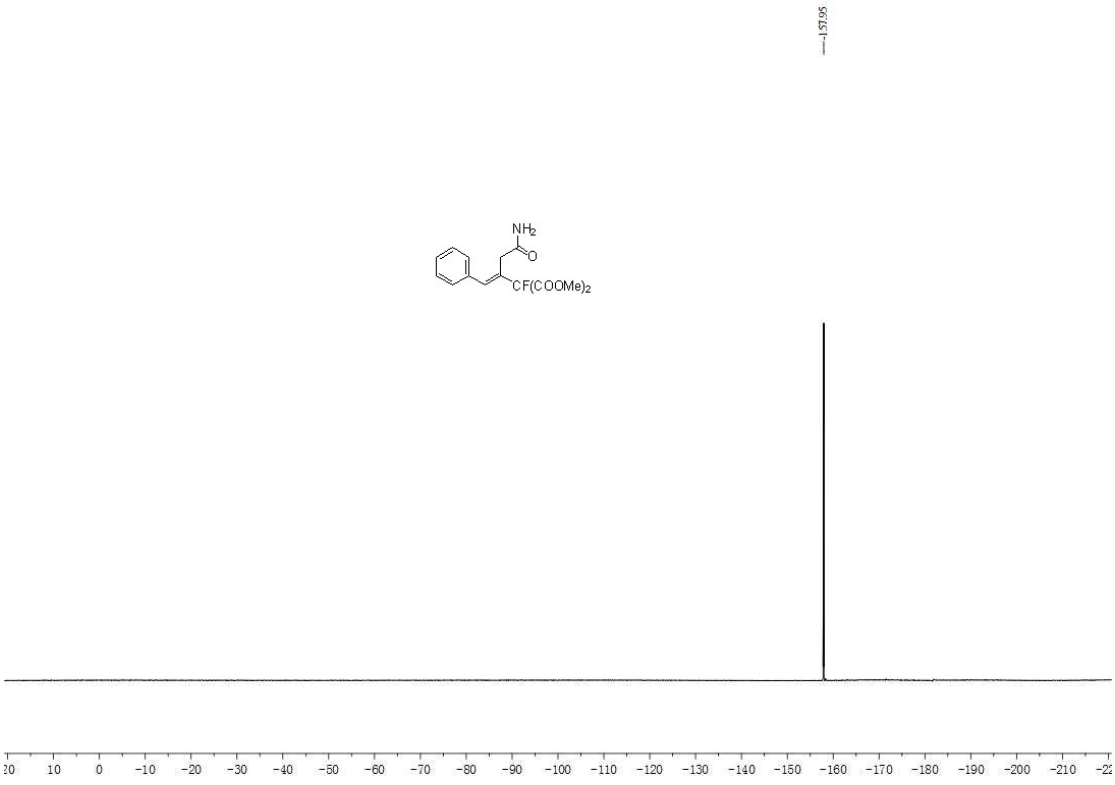

168.65
164.38
167.90
148.24
138.42
136.26
136.06
135.96
135.09
134.34
128.74
128.73
128.56
128.38
127.91
127.32
121.70
121.64
116.45
92.45
90.60
77.32
76.68
52.74
36.45
F
O
O
NH
N


183.26
F
O
O
NH
N

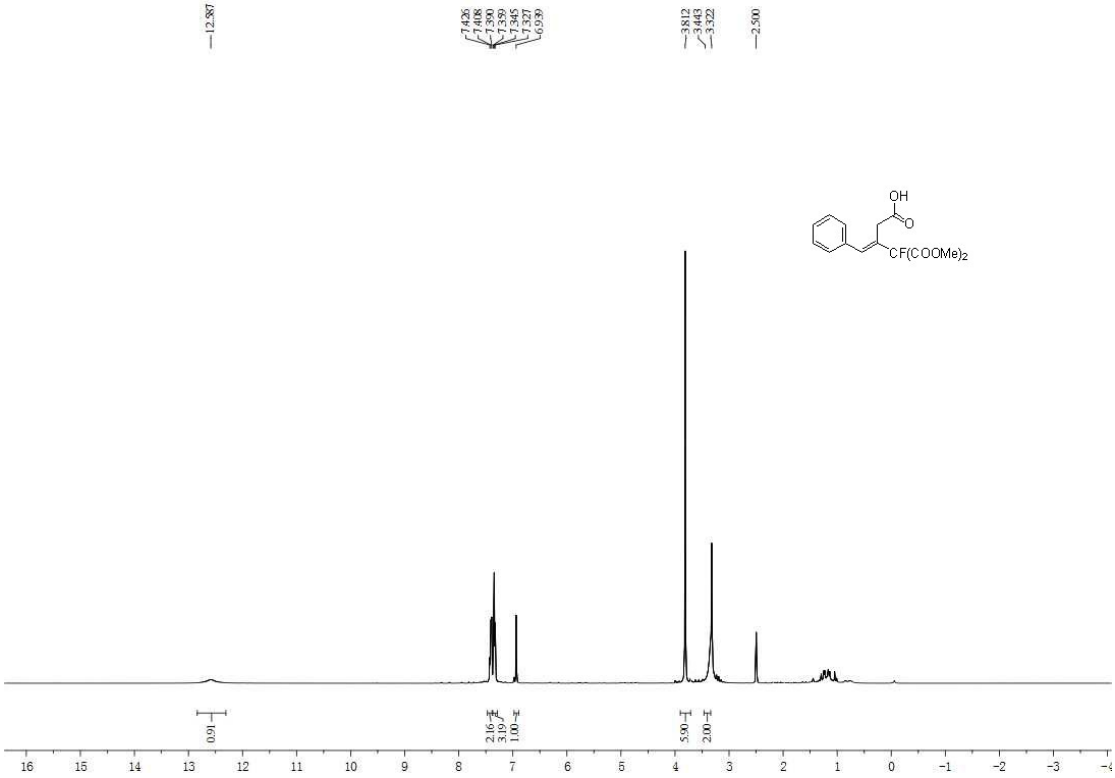
Product 11

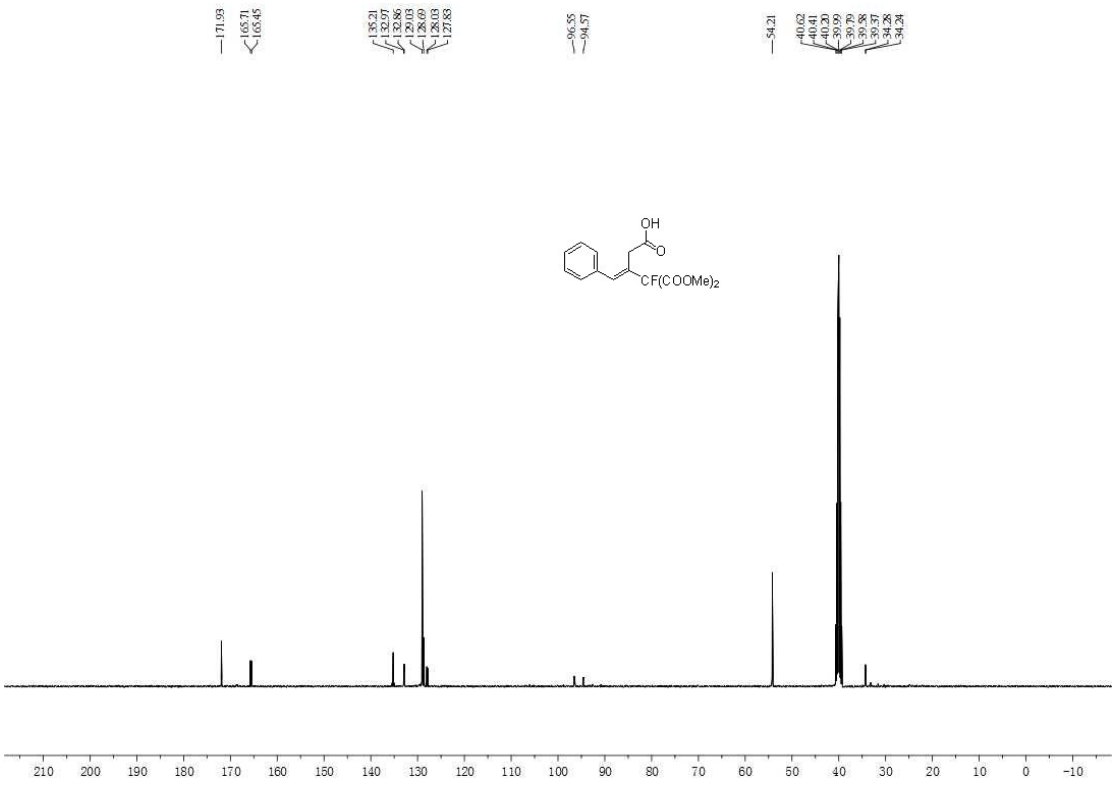

7.384
7.352
7.323
7.308
7.300
7.000
5.851
5.698
3.887
3.400
NH2
O
CF(COOMe)2
5.26
0.99
2.06
6.11
2.00

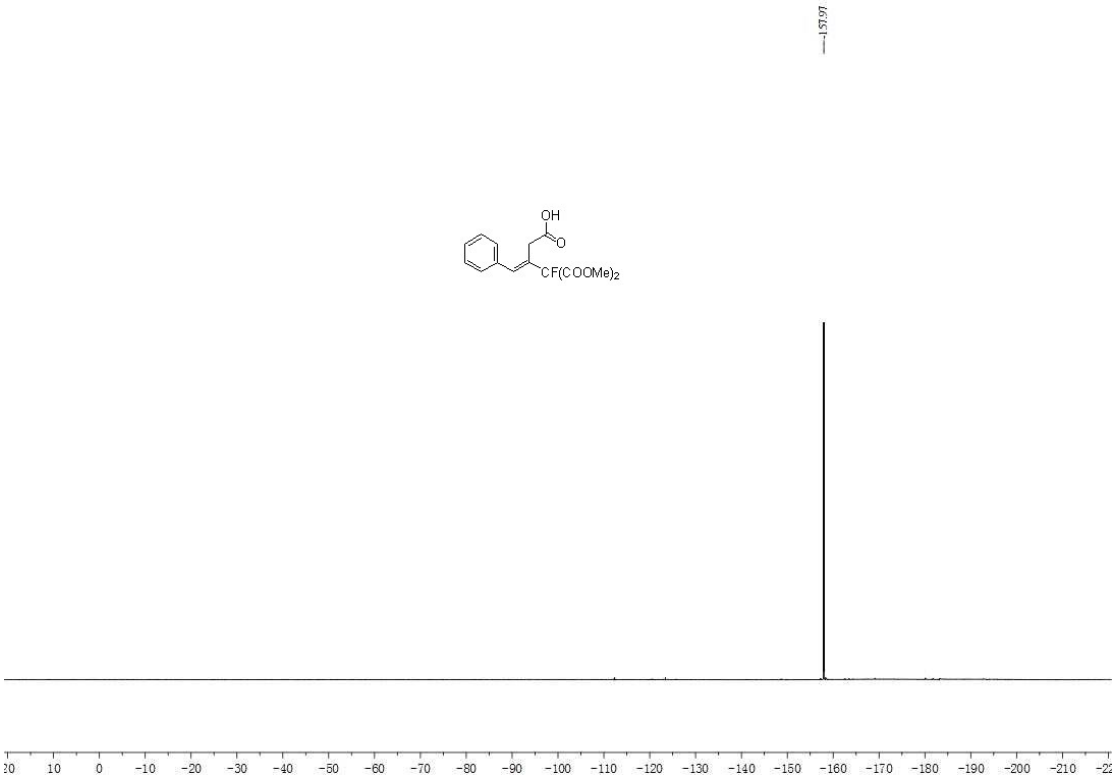

171.77
165.91
165.65
134.82
134.72
134.64
128.75
128.60
128.42
127.66
127.46
96.40
94.41
77.32
77.00
76.68
53.78
35.51
35.47
NH2
O
CF(COOMe)2


-157.95
NH2
O
CF(COOMe)2

Product 12


12.887
7.426
7.408
7.390
7.359
7.345
7.327
6.939
3.812
3.443
3.322
2.500
OH
O
CF(COOMe)2
0.91
2.16
3.19
1.00
5.90
2.00


171.93
165.71
165.45
135.21
132.97
132.86
129.03
128.69
128.05
127.83
96.55
94.57
54.21
40.62
40.41
40.20
39.99
39.79
39.58
39.37
34.26
34.24
OH
O
CF(COOMe)2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


157.97
OH
O
CF(COOMe)2
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210