Supporting Information

Nickel-Catalyzed Carbodifunctionalization of *N*-Vinylamides Enables Access to γ-Amino Acids

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1. General Information and Materials.

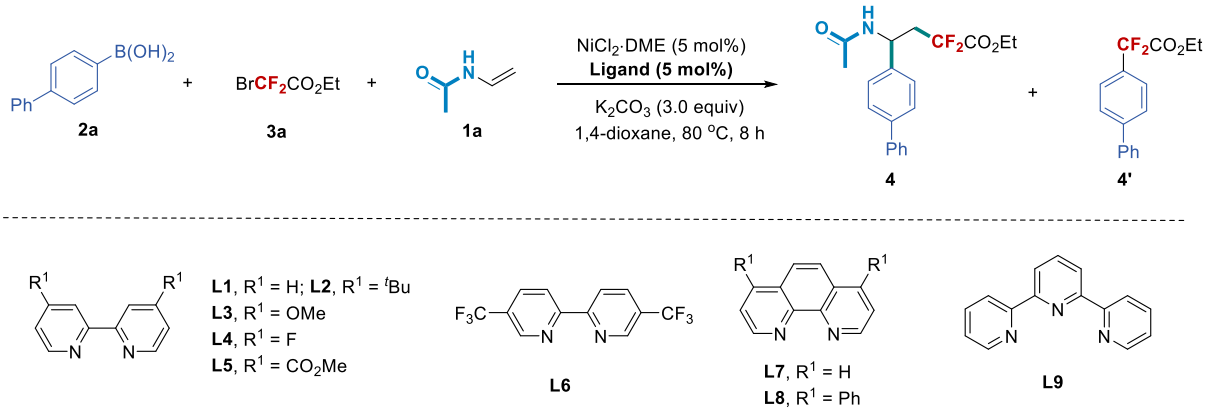
General Information: ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker AM 400 spectrometer and are calibrated using residual undeuterated solvent ($CHCl_3$ at 7.26 ppm ^{1}H NMR; 77.0 ppm ^{13}C NMR; $CFCl_3$ as an external standard and low field is positive). Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. NMR yield was determined by ^{19}F NMR using fluorobenzene as an internal standard before working up the reaction.

Materials: All reagents were used as received from commercial sources, unless otherwise specified, or prepared as described in the literature. $Ni(OTf)_2$ was purchased from Strem Chemicals and used as received. 1,4-Dioxane was purchased from Energy Chemicals and used as received.

2. Optimization of Ni-Catalyzed Difluoroacetylation-Arylation of *N*-Vinylacetamide 1a with Arylboronic Acid 2a and Bromodifluoroacetate 3a (Tables S1-S4).

To a 25 mL of Schlenk tube were added *N*-vinylacetamide **1a** (1.0 equiv), 4-biphenylboronic acid **2a** (2.0 equiv), [Ni]-catalyst (5 mol %), ligand (5 mol %) and base (3.0 equiv) under argon atmosphere, followed by addition of $BrCF_2CO_2Et$ **3a** (1.5 equiv), and solvent (4 mL). The tube was screw-capped and heated to 80 $^{\circ}C$ (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature and fluorobenzene was added. The yield was determined by ^{19}F NMR before working up. The reaction mixture was diluted with ethyl acetate, filtered through a pad of Celite and concentrated. The residue was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1) to afford product **4** as a white solid.

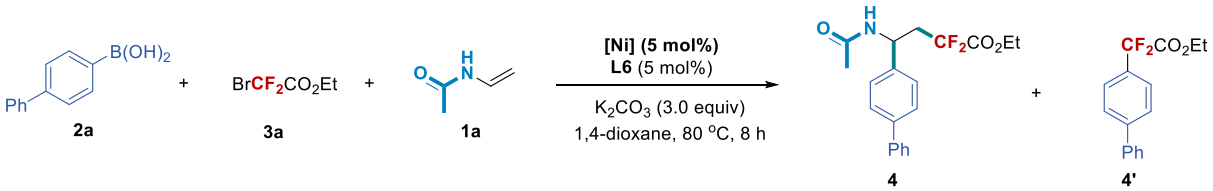
Table S1. Screening of the Ligands.[a]



entry	ligand (**L**)	yields of **4** / **4'** (%)
1	**L1**	44 / 7
2	**L2**	30 / 17
3	**L3**	22 / 3
4	**L4**	32 / 12
5	**L5**	36 / 21
6	**L6**	60 / 21
7	**L7**	24 / 0
8	**L8**	32 / 4
9	**L9**	nd / nd
10	**none**	nd / nd

[a]Reaction conditions (unless otherwise specified): **1a** (0.4 mmol, 1.0 equiv), **2a** (0.8 mmol, 2.0 equiv), **3a** (1.5 equiv), 1,4-dioxane (4 mL). [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard. The yield of **4'** was based on **3a**. nd, not detected.

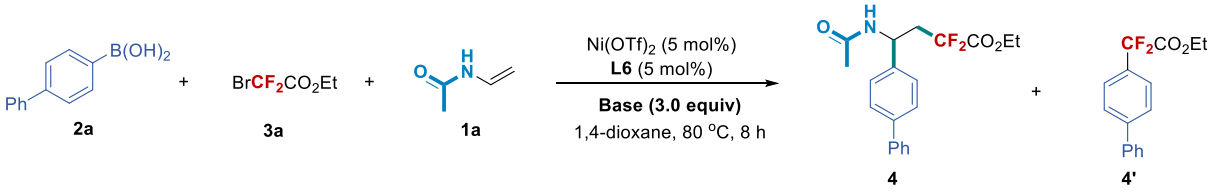
Table S2. Screening of the Nickel Sources.[a]



entry	[Ni]	yields of **4** / **4'** (%)
1	$NiCl_2$·DME	60 / 21
2	$NiBr_2$·DME	76 / 20
3	$NiBr_2$·diglyme	76 / 19
4	$NiBr_2(PPh_3)_2$	36 / 29
5	$NiCl_2$(dppp)	trace / 18
6	$NiCl_2$(dppe)	10 / 30
7	$NiCl_2$	nd / nd
8	$Ni(OT_f)_2$	80 / 20
9	$Ni(COD)_2$	64 / 3
10	None	nd / nd

[a]Reaction conditions (unless otherwise specified): **1a** (0.4 mmol, 1.0 equiv), **2a** (0.8 mmol, 2.0 equiv), **3a** (1.5 equiv), 1,4-dioxane (4 mL). [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard. The yield of **4'** was based on **3a**. nd, not detected.

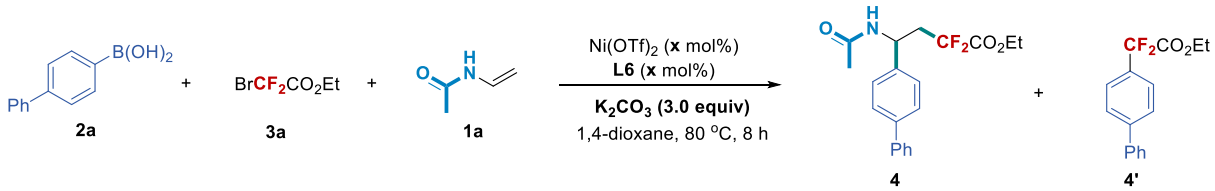
Table S3. Screening of the Bases.[a]



entry	base	yields of **4** / **4'** (%)
1	K_2CO_3	80 / 20
2	$KHCO_3$	76 / 20
3	K_3PO_4	40 / 1
4	KOAc	nd / nd
5	Na_2CO_3	20 / 4
6	$NaHCO_3$	12 / 2
7	Cs_2CO_3	nd / nd
8	none	nd / nd

[a]Reaction conditions (unless otherwise specified): **1a** (0.4 mmol, 1.0 equiv), **2a** (0.8 mmol, 2.0 equiv), **3a** (1.5 equiv), 1,4-dioxane (4 mL). [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard. The yield of **4'** was based on **3a**. nd, not detected.

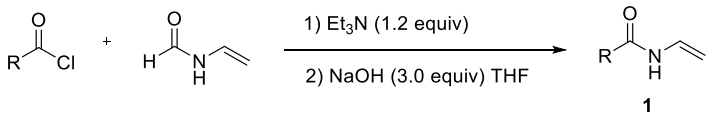
Table S4. Screening of Loading Amount of $Ni(OTf)_2$ and L6.[a]



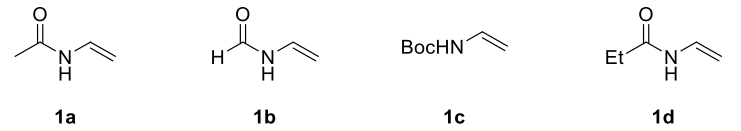
entry	x	yields of **4** / **4'** (%)
1	5	80 / 20
2	3	74 / 16
3	1.5	44 / 2

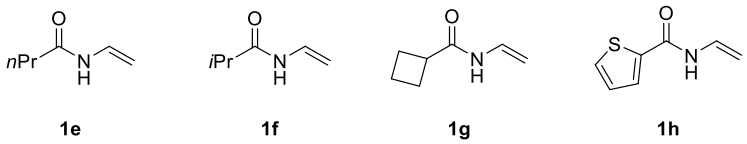
[a]Reaction conditions (unless otherwise specified): **1a** (0.4 mmol, 1.0 equiv), **2a** (0.8 mmol, 2.0 equiv), **3a** (1.5 equiv), 1,4-dioxane (4 mL). [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard. The yield of **4'** was based on **3a**.

3. Preparation of *N*-Vinylamides 1



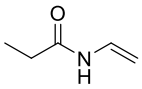
General Procedure: The preparation of **1** is according to the literature.[1] *N*-Vinylformamide (100 mmol, 1.0 equiv), triethylamine (120 mmol, 1.2 equiv), and anhydrous THF (250 mL) were added to a three-necked round-bottomed flask. The reaction mixture was cooled to 0 °C with an ice-water bath. The corresponding acid chloride (115 mmol, 1.15 equiv) was added dropwise over a period of 5 h with stirring. A solution of 5 N NaOH was then slowly added at 0-5 °C over 1 h and the resulting mixture was stirred for 8 h. The reaction mixture was extracted with EtOAc three times. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated, the residue was purified with silica gel chromatography (petroleum) to afford **1**.



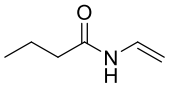


Note: Compounds **1a** and **1b** are commercially available. Compounds **1c**-**1f** and **1h** are known.

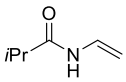
***tert*-Butyl vinylcarbamate (1c).** The reaction was carried out on 50 mmol-scale. Compound **1c** (5.48 g, 77% yield)) as a white solid was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1). This compound is known.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (br, 1H), 6.40 (br, 1H), 4.40 (d, *J* = 16 Hz, 1H), 4.20 (d, *J* = 7.2 Hz, 1H), 1.45 (s, 9H).



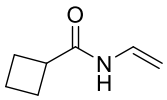
***N*-Vinylpropionamide (1d).** Compound **1d** (3.84 g, 39% yield) as a white solid was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1). This compound is known.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (br, 1H), 7.00 – 6.88 (m, 1H), 4.60 (d, *J* = 16.0 Hz, 1H), 4.35 (d, *J* = 8.8 Hz, 1H), 2.25 (q, *J* = 7.6 Hz, 2H), 1.14 (t, *J* = 7.6 Hz, 3H).



***N*-Vinylbutyramide (1e).** Compound **1e** (1.6 g, 14% yield) as a white solid was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1). This compound is known.[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (br, 1H), 7.04 – 6.90 (m, 1H), 4.59 (d, *J* = 16.0 Hz, 1H), 4.37 (d, *J* = 8.8 Hz, 1H), 2.21 (t, *J* = 7.6 Hz, 2H), 1.68 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H).

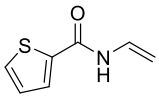


***N*-Vinylisobutyramide (1f).** Compound **1f** (5.8 g, 52% yield) as a white solid was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1). This compound is known.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (br, 1H), 7.04 – 6.93 (m, 1H), 4.60 (d, *J* = 15.6 Hz, 1H), 4.39 (d, *J* = 8.8 Hz, 1H), 2.39 (m, 1H), 1.19 (s, 3H), 1.17 (s, 3H).

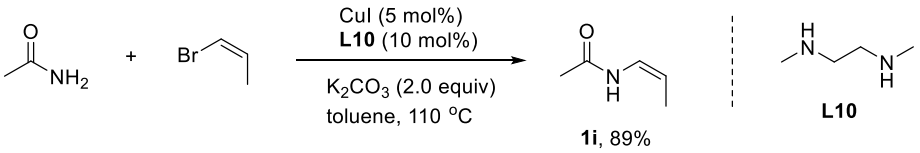


***N*-Vinylcyclobutanecarboxamide (1g).** The reaction was carried out on 83 mmol-scale. Compound **1g** (4.78 g, 47% yield) as a white solid (m.p. 45-46 °C) was purified with silica gel chromatography

(Petroleum ether: Ethyl acetate = 5: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (br, 1H), 7.01 – 6.89 (m, 1H), 4.60 (d, *J* = 16.0 Hz, 1H), 4.35 (d, *J* = 8.8 Hz, 1H), 3.05 (p, *J* = 8.5 Hz, 1H), 2.36 – 2.23 (m, 2H), 2.19 – 2.07 (m, 2H), 2.03 – 1.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.78, 128.65, 95.12, 39.50, 24.97, 18.03. MS (ESI): m/z (%) 126 $(M+H)^+$. HRMS (ESI): Calcd. for $C_7H_{11}ON$: 125.0841 $(M)^+$; Found: 126.0931 $(M+H)^+$.



***N*-Vinylthiophene-2-carboxamide (1h).** Compound **1h** (1.6 g, 11% yield) as a white solid was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1). This compound is known.[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br, 1H), 7.61 (d, *J* = 3.6 Hz, 1H), 7.53 (d, *J* = 5.2 Hz, 1H), 7.19 – 7.06 (m, 2H), 4.77 (d, *J* = 16.0 Hz, 1H), 4.51 (d, *J* = 8.8 Hz, 1H).



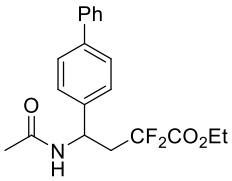
(Z)-*N*-(prop-1-en-1-yl)acetamide (1i). The preparation of **1i** is according to the literature.[6] Acetamide (1.48 g, 25 mmol, 1.0 equiv), CuI (1.25 mmol, 5 mol%), K_2CO_3 (50 mmol, 2.0 equiv), diamine ligand **L10** (2.5 mmol, 0.10 equiv), (*Z*)-1-propenyl bromide (50 mmol, 2.0 equiv), and toluene (35 mL) were added to a 100 mL schlenk tube in glovebox. The reaction was stirred at 110 °C for 24 h. The reaction was cooled to room temperature and filtered through a pad of Celite with EtOAc. The filtrate was concentrated, the residue was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1) to afford **1i** (2.2 g, 89% yield) as a white solid. This compound is known.[6] Data for **1i**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (br, 1H), 7.60 (t, *J* = 9.2 Hz, 1H), 4.78 (m, 1H), 2.08 (s, 3H), 1.61 (d, *J* = 7.2 Hz, 3H).

4. General Procedure for the Ni-Catalyzed Carbodifunctionalization of *N*-Vinylacetamides.

To a 25 mL of Schlenk tube were added *N*-vinylamide **1** (0.4 mmol, 1.0 equiv), arylboronic acid **2** (0.8 mmol, 2.0 equiv), $Ni(OTf)_2$ (5 mol %), **L6** (5 mol %) and K_2CO_3 (3.0 equiv) under Ar. $BrCX_2CO_2Et$ (X = F, H) or 2-bromomalonate (0.6 mmol, 1.5 equiv) and dioxane (4 mL) were then

added. The tube was screw-capped and heated to 80 °C (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with ethyl acetate, filtered through a pad of Celite and concentrated. The residue was purified with silica gel chromatography to afford the product.

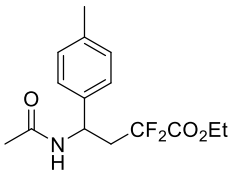
5. Characterization Data of Compounds 4-32.



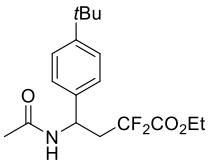
Ethyl 4-([1,1'-biphenyl]-4-yl)-4-acetamido-2,2-difluorobutanoate (4). Compound **4** (114 mg, 79% yield) as a white solid (m.p. 161-164 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 4H), 7.43 (t, *J* = 8.4 Hz, 2H), 7.39 – 7.32 (m, 3H), 6.24 (d, *J* = 7.2 Hz, 1H), 5.40 – 5.32 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.82 – 2.55 (m, 2H), 1.98 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.7 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -103.5 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.7 (t, *J* = 32.0 Hz), 140.9, 140.4, 139.4, 128.8, 127.5, 127.4, 127.0, 126.9, 114.9 (t, *J* = 250.0 Hz), 63.1, 47.9 (t, *J* = 5.0 Hz), 40.2 (t, *J* = 22.0 Hz), 23.2, 13.8. MS (ESI): m/z (%) 362 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{20}H_{22}O_3NF_2$: 362.1562 $(M+H)^+$; Found: 362.1558 $(M+H)^+$.

Gram-Scale Synthesis of Compound 4.

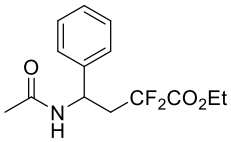
To a 100 mL of Schlenk tube equipped with a magnetic stir bar were added *N*-vinylacetamide **1a** (0.476 g, 5.6 mmol, 1.0 equiv)**,** arylboronic acid **2a** (11.2 mmol, 2.0 equiv), $Ni(OTf)_2$ (0.28 mmol, 5 mol %), 5,5-*di*CF_3-2,2'-bipyridine **L6** (0.28 mmol, 5 mol %), and K_2CO_3 (16.8 mmol, 3.0 equiv) under Ar atmosphere. $BrCF_2CO_2Et$ **3a** (8.4 mmol, 1.5 equiv) and anhydrous 1,4-dioxane (56 mL) were then added. The tube was screw capped and heated to 80 °C (oil bath). After stirring for 24 h, the reaction mixture was cooled to room temperature. The reaction mixture was filtered through a pad of Celite and washed with ethyl acetate (3×30 mL). The filtrate was concentrated. The residue was subjected to column chromatography on silica gel to give product **4** (1.32 g, 65%).



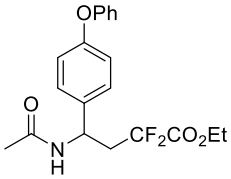
Ethyl 4-acetamido-2,2-difluoro-4-(p-tolyl)butanoate (5). Compound **5** (97 mg, 81% yield) as a white solid (m.p. 78-81 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.60 (d, *J* = 8.0 Hz, 1H), 5.29 – 5.22 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.75 – 2.45 (m, 2H), 2.30 (s, 3H), 1.90 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.8 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -104.0 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 163.6 (t, *J* = 32.0 Hz), 137.6, 137.5, 129.3, 126.4, 114.9 (t, *J* = 250.0 Hz), 62.9, 47.7 (t, *J* = 5.0 Hz), 40.2 (t, *J* = 22.0 Hz), 23.0, 21.5, 13.7. MS (ESI): m/z (%) 300 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{15}H_{20}O_3NF_2$: 300.1406 $(M+H)^+$; Found: 300.1405 $(M+H)^+$.



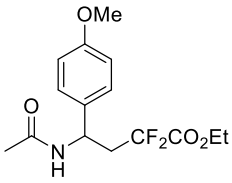
Ethyl 4-acetamido-4-(4-(tert-butyl)phenyl)-2,2-difluorobutanoate (6). Compound **6** (85 mg, 62% yield) as a white solid (m.p. 144-146 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.54 (d, *J* = 8.0 Hz, 1H), 5.32 – 5.22 (m, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 2.76 – 2.48 (m, 2H), 1.91 (s, 3H), 1.28 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.5 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -104.1 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.6 (t, *J* = 31.0 Hz), 150.7, 137.4, 126.2, 125.6, 114.9 (t, *J* = 251.0 Hz), 62.9, 47.7 (t, *J* = 4.0 Hz), 40.2 (t, *J* = 22.0 Hz), 34.4, 31.2, 23.1, 13.7. MS (ESI): m/z (%) 342 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{18}H_{26}O_3NF_2$: 342.1875 $(M+H)^+$; Found: 342.1869 $(M+H)^+$.



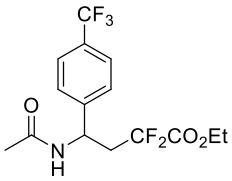
Ethyl 4-acetamido-2,2-difluoro-4-phenylbutanoate (7). Compound **7** (105 mg, 92% yield) as a white solid (m.p. 66-67 °C) was purified with silica gel chromatography (Petroleum ether : Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.22 (s, 5H), 6.60 (d, *J* = 8.0 Hz, 1H), 5.33 – 5.25 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.75 – 2.48 (m, 2H), 1.91 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.8 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -103.9 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 163.6 (t, *J* = 32.0 Hz), 140.5, 128.7, 127.8, 126.4, 114.9 (t, *J* = 251.0 Hz), 63.0, 48.0 (t, *J* = 4.0 Hz), 40.2 (t, *J* = 23.0 Hz), 23.0, 13.7. MS (ESI): m/z (%) 286 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{14}H_{18}O_3NF_2$: 286.1249 $(M+H)^+$; Found: 286.1249 $(M+H)^+$.



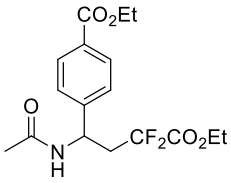
Ethyl 4-acetamido-2,2-difluoro-4-(4-phenoxyphenyl)butanoate (8). Compound **8** (101 mg, 67% yield) as a white solid (m.p. 103-105 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 5.35 – 5.26 (m, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.74 (s, 3H), 2.76 – 2.44 (m, 2H), 1.91 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.1 (dt, *J* = 263.2 Hz, 15.0 Hz, 1F), -104.5 (dt, *J* = 263.2 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 163.5 (t, *J* = 32.0 Hz), 156.69, 156.67, 135.6, 129.6, 127.9, 123.3, 118.7, 118.6, 114.7 (t, *J* = 251.0 Hz), 62.9, 47.2 (t, *J* = 5.0 Hz), 40.2 (t, *J* = 22.0 Hz), 22.8, 13.6. MS (ESI): m/z (%) 378 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{20}H_{22}O_4NF_2$: 378.1511 $(M+H)^+$; Found: 378.1505 $(M+H)^+$.



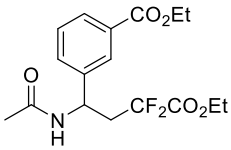
Ethyl 4-acetamido-2,2-difluoro-4-(4-methoxyphenyl)butanoate (9). Compound **9** (106 mg, 84% yield) as a white solid (m.p. 86-88 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.0 Hz, 1H), 5.26 – 5.18 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.74 (s, 3H), 2.74 – 2.45 (m, 2H), 1.89 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.8 (dt, *J* = 263.2 Hz, 15.0 Hz, 1F), -104.3 (dt, *J* = 263.2 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.6 (t, *J* = 33.0 Hz), 159.0, 132.7, 127.7, 114.9 (t, *J* = 251.0 Hz), 114.0, 62.9, 55.1, 47.4 (t, *J* = 5.0 Hz), 40.2 (t, *J* = 22.0 Hz), 23.0, 13.7. MS (ESI): m/z (%) 316 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{15}H_{20}O_4NF_2$: 316.1355 $(M+H)^+$; Found: 316.1350 $(M+H)^+$.



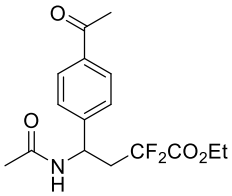
Ethyl 4-acetamido-2,2-difluoro-4-(4-(trifluoromethyl)phenyl)butanoate (10). Compound **10** (115 mg, 81% yield) as a white solid (m.p. 108-109 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 5.38 – 5.29 (m, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.72 – 2.43 (m, 2H), 1.93 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 (s, 3F), -103.2 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -104.0 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 163.5 (t, *J* = 33.0 Hz), 144.9, 130.0 (q, *J* = 32.0 Hz), 126.8, 125.7 (q, *J* = 4.0 Hz), 123.9 (q, *J* = 271.0 Hz), 114.7 (t, *J* = 251.0 Hz), 63.2, 47.8 (t, *J* = 4.0 Hz), 40.0 (t, *J* = 22.0 Hz), 22.9, 13.7. MS (ESI): m/z (%) 354 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{15}H_{17}O_3NF_5$: 354.1123 $(M+H)^+$; Found: 354.1118 $(M+H)^+$.



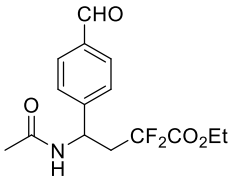
Ethyl 4-(1-acetamido-4-ethoxy-3,3-difluoro-4-oxobutyl)benzoate (11). Compound **11** (123 mg, 86% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.36 – 5.28 (m, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.70 – 2.40 (m, 2H), 1.89 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.4 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -104.3 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 166.1, 163.5 (t, *J* = 32.0 Hz), 145.8, 129.9, 129.8, 126.4, 114.7 (t, *J* = 250.0 Hz), 63.1, 61.0, 47.8 (t, *J* = 4.0 Hz), 39.9 (t, *J* = 23.0 Hz), 22.8, 14.1, 13.7. MS (ESI): m/z (%) 358 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{17}H_{22}O_5NF_2$: 358.1461 $(M+H)^+$; Found: 358.1460 $(M+H)^+$.



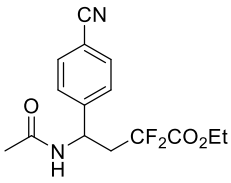
Ethyl 3-(1-acetamido-4-ethoxy-3,3-difluoro-4-oxobutyl)benzoate (12). Compound **12** (121 mg, 85% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 5.38 – 5.29 (m, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.74 – 2.44 (m, 2H), 1.92 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.1 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -104.0 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 166.2, 163.5 (t, *J* = 32.0 Hz), 141.4, 131.2, 130.8, 128.8, 128.7, 127.2, 114.7 (t, *J* = 251.0 Hz), 63.1, 61.0, 47.7 (t, *J* = 4.0 Hz), 40.1 (t, *J* = 22.0 Hz), 22.9, 14.1, 13.6. MS (ESI): m/z (%) 358 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{17}H_{22}O_5NF_2$: 358.1461 $(M+H)^+$; Found: 358.1454 $(M+H)^+$.



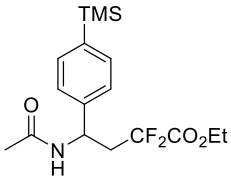
Ethyl 4-acetamido-4-(4-acetylphenyl)-2,2-difluorobutanoate (13). Compound **13** (87 mg, 67% yield) as a white solid (m.p. 138-140 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.38 – 5.29 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.74 – 2.44 (m, 2H), 2.56 (s, 3H), 1.94 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.11 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -103.84 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 169.4, 163.5 (t, *J* = 32.0 Hz), 146.1, 136.5, 128.8, 126.6, 114.7 (t, *J* = 251.0 Hz), 63.2, 47.9 (t, *J* = 4.0 Hz), 39.9 (t, *J* = 23.0 Hz), 26.6, 23.0, 13.8. MS (ESI): m/z (%) 328 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{16}H_{20}O_4NF_2$: 328.1355 $(M+H)^+$; Found: 328.1350 $(M+H)^+$.



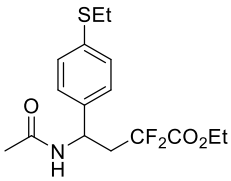
Ethyl 4-acetamido-2,2-difluoro-4-(4-formylphenyl)butanoate (14). Compound **14** (53 mg, 42% yield) as a white solid (m.p. 79-82 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 5.40 – 5.31 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.74 – 2.45 (m, 2H), 1.94 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.1 (dt, *J* = 270.7 Hz, 18.8 Hz, 1F), -103.86 (dt, *J* = 270.7 Hz, 18.8 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 169.6, 163.5 (t, *J* = 32.0 Hz), 147.6, 135.7, 130.1, 127.1, 114.7 (t, *J* = 251.0 Hz), 63.2, 47.9 (t, *J* = 4.0 Hz), 39.9 (t, *J* = 23.0 Hz), 23.0, 13.8. MS (ESI): m/z (%) 314 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{15}H_{18}O_4NF_2$: 314.1198 $(M+H)^+$; Found: 314.1197 $(M+H)^+$.



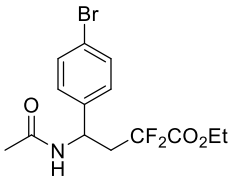
Ethyl 4-acetamido-4-(4-cyanophenyl)-2,2-difluorobutanoate (15). Compound **15** (54 mg, 43% yield) as a white solid (m.p. 108-109 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 5.37 – 5.26 (m, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 2.72 – 2.40 (m, 2H), 1.93 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.4 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -104.11 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 163.4 (t, *J* = 32.0 Hz), 146.3, 132.5, 127.2, 118.4, 114.6 (t, *J* = 251.0 Hz), 111.4, 63.9, 47.8 (t, *J* = 4.0 Hz), 39.7 (t, *J* = 23.0 Hz), 22.9, 13.7. MS (ESI): m/z (%) 311 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{15}H_{17}O_3N_2F_2$: 311.1202 $(M+H)^+$; Found: 311.1197 $(M+H)^+$.



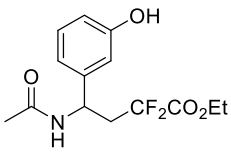
Ethyl 4-acetamido-2,2-difluoro-4-(4-(trimethylsilyl)phenyl)butanoate (16). Compound **16** (84 mg, 59% yield) as a white solid (m.p. 112-114 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.30 (d, *J* = 8.0 Hz, 1H), 5.31 – 5.23 (m, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.74 – 2.48 (m, 2H), 1.92 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.22 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.6 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -103.7 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 163.6 (t, *J* = 32.0 Hz), 141.0, 140.1, 133.7, 125.8, 114.9 (t, *J* = 250.0 Hz), 63.0, 48.0 (t, *J* = 4.0 Hz), 40.1 (t, *J* = 23.0 Hz), 23.0, 13.7. MS (ESI): m/z (%) 358 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{17}H_{26}O_3NF_2Si$: 358.1645 $(M+H)^+$; Found: 358.1646 $(M+H)^+$.



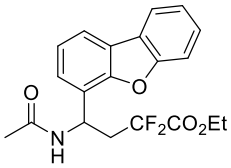
Ethyl 4-acetamido-4-(4-(ethylthio)phenyl)-2,2-difluorobutanoate (17). Compound **17** (117 mg, 85% yield) as a white solid (m.p. 82-85 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 1H), 7.17 (br, 4H), 5.27 – 5.18 (m, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.86 (q, *J* = 7.2 Hz, 2H), 2.70 – 2.39 (m, 2H), 1.86 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.2 (dt, *J* = 263.2 Hz, 15.0 Hz, 1F), -104.6 (dt, *J* = 263.2 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 163.4 (t, *J* = 32.0 Hz), 138.2, 136.1, 128.6, 126.9, 114.7 (t, *J* = 250.0 Hz), 62.8, 47.7 (t, *J* = 4.0 Hz), 40.0 (t, *J* = 23.0 Hz), 27.1, 22.7, 14.0, 13.5. MS (ESI): m/z (%) 346 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{16}H_{22}O_3NF_2S$: 346.1283 $(M+H)^+$; Found: 346.1278 $(M+H)^+$.



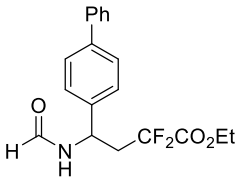
Ethyl 4-acetamido-4-(4-bromophenyl)-2,2-difluorobutanoate (18). Compound **18** (99 mg, 68% yield) as a white solid (m.p. 102-105 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 7.6 Hz, 1H), 5.28 – 5.19 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.70 – 2.41 (m, 2H), 1.91 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.2 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -104.1 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 163.5 (t, *J* = 32.0 Hz), 139.8, 131.8, 128.2, 121.6, 114.7 (t, *J* = 251.0 Hz), 63.1, 47.5 (t, *J* = 4.0 Hz), 40.0 (t, *J* = 23.0 Hz), 22.9, 13.7. MS (ESI): m/z (%) 364 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{14}H_{17}O_3NF_2Br$: 364.0354 $(M+H)^+$; Found: 364.0351 $(M+H)^+$.



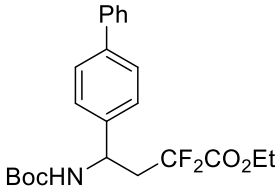
Ethyl 4-acetamido-2,2-difluoro-4-(3-hydroxyphenyl)butanoate (19). Compound **19** (70 mg, 58% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.78 (s, 1H), 6.73 (t, *J* = 8.0 Hz, 2H), 5.28 – 5.18 (m, 1H), 4.20 – 4.12 (m, 2H), 2.71 – 2.43 (m, 2H), 1.98 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.6 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -104.2 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 163.8 (t, *J* = 32.0 Hz), 157.0, 141.7, 130.0, 117.8, 115.3, 114.9 (t, *J* = 250.0 Hz), 113.5, 63.3, 48.0 (t, *J* = 4.0 Hz), 40.0 (t, *J* = 23.0 Hz), 22.7, 13.7. MS (ESI): m/z (%) 302 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{14}H_{18}O_4NF_2$: 302.1198 $(M+H)^+$; Found: 302.1197 $(M+H)^+$.



Ethyl 4-acetamido-4-(dibenzo[b,d]furan-4-yl)-2,2-difluorobutanoate (20). Compound **20** (54 mg, 36% yield) as a white solid (m.p. 116-118 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.86 (m, 2H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.44 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.38 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.31 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 5.52 – 5.44 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.89 – 2.59 (m, 2H), 1.97 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.8 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -103.7 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 163.4 (t, *J* = 32.0 Hz), 156.5, 155.5, 135.5, 127.4, 125.5, 124.5, 123.7, 122.8, 120.6, 118.8, 114.9 (t, *J* = 250.0 Hz), 111.9, 111.7, 63.1, 48.2 (t, *J* = 4.0 Hz), 40.5 (t, *J* = 22.0 Hz), 23.2, 13.7. MS (ESI): m/z (%) 376 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{20}H_{20}O_4NF_2$: 376.1355 $(M+H)^+$; Found: 376.1356 $(M+H)^+$.



Ethyl 4-([1,1'-biphenyl]-4-yl)-2,2-difluoro-4-formamidobutanoate (21). Compound **21** (64 mg, 46% yield) as a white solid (m.p. 134-136 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.61 – 7.53 (m, 4H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.40 – 7.36 (m, 3H), 5.98 (d, *J* = 7.2 Hz, 1H), 5.48 – 5.40 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.83 – 2.64 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.6 (dt, *J* = 268.3 Hz, 14.0 Hz, 1F), -103.5 (dt, *J* = 268.3 Hz, 15.4 Hz, 1F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6 (t, *J* = 32.1 Hz), 160.2, 141.1, 140.3, 138.8, 128.8, 127.6, 127.5, 127.0, 126.8, 114.8 (t, *J* = 250.5 Hz), 63.3, 46.8 (t, *J* = 4.6 Hz), 40.1 (t, *J* = 22.9 Hz), 13.8. MS (ESI): m/z (%) 348 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{19}H_{20}O_3NF_2$: 348.1406 $(M+H)^+$; Found: 348.1404 $(M+H)^+$.

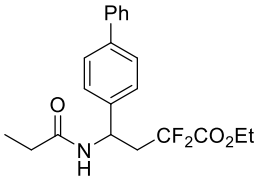


Ethyl 4-([1,1'-biphenyl]-4-yl)-4-((tert-butoxycarbonyl)amino)-2,2-difluorobutanoate (22). Compound **22** (105 mg, 63% yield) as a white solid (m.p. 99-101 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 4: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 4H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.40 – 7.33 (m, 3H), 5.03 (br, 2H), 4.25 – 4.18 (m, 2H), 2.87 – 2.50 (m, 2H), 1.43 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.8 (dt, *J* = 268.3, 11.3 Hz, 1F), -104.0 (dt, *J* = 268.3 13.5 Hz, 1F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7 (t, *J* = 32.0 Hz), 154.7, 140.7, 140.5, 140.0, 128.8, 127.4, 127.4, 127.0, 126.6, 114.9 (t, *J* = 251.0 Hz), 79.9, 63.0, 49.2, 40.8 (t, *J* = 22.1 Hz), 28.3, 13.8. MS (ESI): m/z (%) 442 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{23}H_{27}O_4NF_2Na$: 442.1800 $(M+Na)^+$; Found: 442.1805 $(M+Na)^+$.

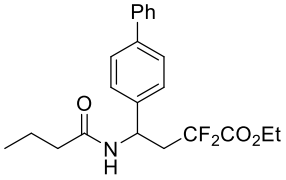
Gram-Scale Synthesis of 22

To a 100 mL of Schlenk tube equipped with a magnetic stir bar were added *tert*-butyl vinylcarbamate **1c** (0.855 g, 6 mmol, 1.0 equiv)**,** arylboronic acid **2a** (12 mmol, 2.0 equiv), $Ni(OTf)_2$ (0.3 mmol, 5

mol %), 5,5-*di*CF_3-2,2'-bipyridine **L6** (0.3 mmol, 5 mol %), K_2CO_3 (18 mmol, 3.0 equiv) under Ar atmosphere. $BrCF_2CO_2Et$ **3a** (9.0 mmol, 1.5 equiv) and anhydrous 1,4-dioxane (60 mL) were then added. The tube was screw capped and heated to 80 °C (oil bath). After stirring for 30 h, the reaction mixture was cooled to room temperature. The reaction mixture was filtered through a pad of Celite and washed with ethyl acetate (3×30 mL). The filtrate was concentrated. The residue was subjected to column chromatography on silica gel to give product **22** (1.15 g, 46%).

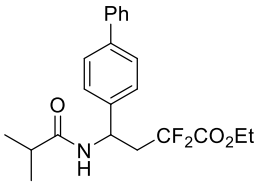


Ethyl 4-([1,1'-biphenyl]-4-yl)-2,2-difluoro-4-propionamidobutanoate (23). Compound **23** (118 mg, 78% yield) as a white solid (m.p. 126-129 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.52 (m, 4H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.40 – 7.32 (m, 3H), 6.07 (d, *J* = 8.0 Hz, 1H), 5.42 – 5.32 (m, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.84 – 2.57 (m, 2H), 2.22 (q, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.6 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.5 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -103.3 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 163.6 (t, *J* = 32.0 Hz), 140.7, 140.4, 139.4, 128.7, 127.4, 127.3, 126.9, 126.8, 117.9 (t, *J* = 251.0 Hz), 63.0, 47.7 (t, *J* = 5.0 Hz), 40.2 (t, *J* = 23.0 Hz), 29.5, 13.7, 9.5. MS (ESI): m/z (%) 376 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{21}H_{24}O_3NF_2$: 376.1719 $(M+H)^+$; Found: 376.1713 $(M+H)^+$.

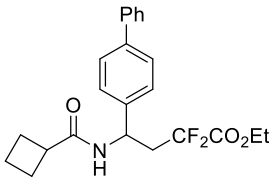


Ethyl 4-([1,1'-biphenyl]-4-yl)-4-butyramido-2,2-difluorobutanoate (24). Compound **24** (110 mg, 70% yield) as a white solid (m.p. 104-106 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 4H), 7.44 (t, *J* = 7.6 Hz, 2 H), 7.39 – 7.32 (m, 3 H), 5.90 (d, *J* = 7.2 Hz, 1H), 5.42 – 5.32 (m, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.84 – 2.56 (m, 2H), 2.17 (t, *J* = 7.2 Hz, 2H), 1.73 – 1.61 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H),

0.94 (t, *J* = 7.6 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.4 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -104.0 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 163.6 (t, *J* = 32.0 Hz), 140.6, 140.4, 139.8, 128.7, 126.53, 126.51, 126.9, 126.8, 114.9 (t, *J* = 251.0 Hz), 63.0, 47.6 (t, *J* = 5.0 Hz), 40.2 (t, *J* = 22.0 Hz), 38.4, 18.9, 13.7, 13.6. MS (ESI): m/z (%) 390 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{22}H_{26}O_3NF_2$: 390.1875 $(M+H)^+$; Found: 390.1870 $(M+H)^+$.

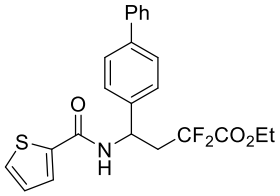


Ethyl 4-([1,1'-biphenyl]-4-yl)-2,2-difluoro-4-isobutyramidobutanoate (25). Compound **25** (138 mg, 88% yield) as a white solid (m.p. 127-128 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 4H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.39 – 7.31 (m, 3H), 6.35 (d, *J* = 7.6 Hz, 1H), 5.42 – 5.33 (m, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.81 – 2.55 (m, 2H), 2.44 – 2.32 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.2 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -103.7 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 163.6 (t, *J* = 32.0 Hz), 140.6, 140.4, 139.8, 128.7, 127.4, 127.3, 126.9, 126.7, 115.0 (t, *J* = 251.0 Hz), 63.1, 47.6 (t, *J* = 5.0 Hz), 40.2 (t, *J* = 23.0 Hz), 35.4, 19.31, 19.29, 13.8. MS (ESI): m/z (%) 390 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{22}H_{26}O_3NF_2$: 390.1875 $(M+H)^+$; Found: 390.1869 $(M+H)^+$.

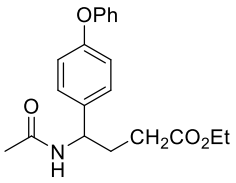


Ethyl 4-([1,1'-biphenyl]-4-yl)-4-(cyclobutanecarboxamido)-2,2-difluorobutanoate (26). Compound **26** (138 mg, 86% yield) as a white solid (m.p. 115-118 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 4H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.39 – 7.31 (m, 3H), 6.21 (d, *J* = 7.6 Hz, 1H), 5.43 – 5.33 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.01 (m, 1 H), 2.82 – 2.55 (m, 2H), 2.35 – 2.19 (m, 2H), 2.18 – 2.05 (m, 2H), 2.01 – 1.79 (m, 2H), 1.30 (td, *J* = 7.2 Hz, 1.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ

-102.4 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -103.6 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 163.7 (t, *J* = 31.0 Hz), 140.7, 140.4, 139.7, 128.7, 127.43, 127.36, 127.0, 126.8, 115.0 (t, *J* = 251.0 Hz), 63.1, 47.6 (t, *J* = 4.0 Hz), 40.2 (t, *J* = 23.0 Hz), 39.7, 25.1, 25.0, 18.1, 13.8. MS (ESI): m/z (%) 402 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{23}H_{26}O_3NF_2$: 402.1875 $(M+H)^+$; Found: 402.1870 $(M+H)^+$.

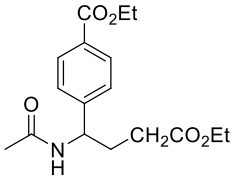


Ethyl 4-([1,1'-biphenyl]-4-yl)-2,2-difluoro-4-(thiophene-2-carboxamido)butanoate (27). Compound **27** (145 mg, 85% yield) as a white solid (m. p. 81- 84 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* =7.6 Hz, 4H), 7.48 – 7.39 (m, 5H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 7.2 Hz, 1H), 5.61 – 5.52 (m, 1H), 4.13 (t, *J* = 7.6 Hz, 2H), 3.01 – 2.84 (m, 1H), 2.79 – 2.63 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.1 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F), -103.9 (dt, *J* = 267.0 Hz, 15.0 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (t, *J* = 32.0 Hz), 161.2, 140.7, 140.4, 139.4, 138.4, 130.4, 128.7, 128.4, 127.6, 127.4, 127.3, 126.92, 126.86, 115.0 (t, *J* = 251.0 Hz), 63.2, 48.2 (t, *J* = 5.0 Hz), 40.1 (t, *J* = 23.0 Hz), 13.6. MS (ESI): m/z (%) 430 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{23}H_{22}O_3NF_2S$: 430.1283 $(M+H)^+$; Found: 430.1277 $(M+H)^+$.

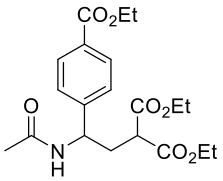


Ethyl 4-acetamido-4-(4-phenoxyphenyl)butanoate (28). Compound **28** (66 mg, 48% yield) as a white solid (m.p. 95-97 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.28 (d, *J* = 8.4 Hz, 1H), 4.99 – 4.91 (m, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.41 – 2.26 (m, 2H), 2.19 – 2.00 (m, 2H), 1.96 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 169.4, 156.9, 156.6, 136.4, 129.7, 127.8,

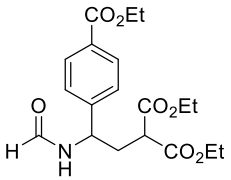
124.3, 118.9, 118.8, 60.6, 52.6, 31.2, 30.8, 23.3, 14.1. MS (ESI): m/z (%) 364 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{21}H_{22}O_4NF_2$: 342.1700 $(M+H)^+$; Found: 342.1697 $(M+H)^+$.



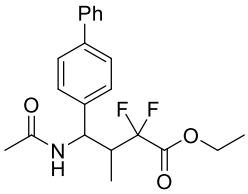
Ethyl 4-(1-acetamido-4-ethoxy-4-oxobutyl)benzoate (29). Compound **29** (69 mg, 53% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.02 – 4.93 (m, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 2.38 – 2.22 (m, 2H), 2.11 – 2.00 (m, 2H), 1.93 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 169.7, 166.2, 146.9, 129.8, 129.5, 126.3, 60.9, 60.6, 52.9, 31.0, 30.6, 23.1, 14.2, 14.1. MS (ESI): m/z (%) 344 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{21}H_{22}O_4NF_2$: 322.1649 $(M+H)^+$; Found: 322.1649 $(M+H)^+$.



Diethyl 2-(2-acetamido-2-(4-(ethoxycarbonyl)phenyl)ethyl)malonate (30). Compound **30** (91 mg, 58% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.09 – 5.00 (m, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.20 – 4.01 (m, 4H), 3.36 (t, *J* = 7.2 Hz, 1H), 2.39 – 2.25 (m, 2H), 1.91 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.6 Hz, 3H), 1.21 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 169.2, 168.8, 166.1, 146.5, 129.9, 129.6, 126.3, 61.68, 61.67, 60.8, 51.5, 49.3, 34.6, 23.0, 14.2, 13.9, 13.8. MS (ESI): m/z (%) 416 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{21}H_{22}O_4NF_2$: 394.1854 $(M+H)^+$; Found: 394.1860 $(M+H)^+$.



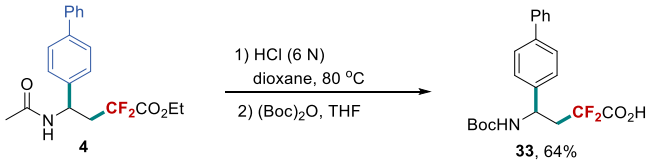
Diethyl 2-(2-(4-(ethoxycarbonyl)phenyl)-2-formamidoethyl)malonate (31). Compound **31** (88 mg, 58% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.25 (d, *J* = 9.2 Hz, 1H), 5.25 – 5.14 (m, 1H), 4.37 (q, *J* = 6.8 Hz, 2H), 4.19 (q, *J* = 6.8 Hz, 4H), 3.39 (t, *J* = 6.8 Hz, 1H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.7, 166.1, 160.8, 145.8, 129.9, 129.8, 126.3, 61.8, 61.7, 60.9, 50.1, 49.2, 34.6, 14.2, 13.9, 13.8. MS (ESI): m/z (%) 402 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{19}H_{26}O_7N$: 380.1704 $(M+H)^+$; Found: 380.1702 $(M+H)^+$.



Ethyl 4-([1,1'-biphenyl]-4-yl)-4-acetamido-2,2-difluoro-3-methylbutanoate (32). Compound **32** (87 mg, 58% yield, dr = 13:1 determined by ^{19}F NMR before column chromatogragphy) as a white solid (m.p. 167-169 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 2: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 4H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.38 – 7.28 (m, 3H), 5.98 (d, *J* = 8.4 Hz, 1H), 5.45 (dd, *J* = 8.8 Hz, 4.4 Hz, 1H), 4.31 – 4.21 (m, 2H), 2.93 – 2.77 (m, 1H), 2.07 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.1 (dd, *J* = 263.6 Hz, 13.9 Hz, 1F), -112.1 (dd, *J* = 263.6 Hz, 15.8 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 163.7 (t, *J* = 32.4 Hz), 140.5, 138.6, 136.2, 128.8, 127.4, 127.3, 127.0, 126.9, 116.7 (t, *J* = 253.1 Hz), 63.1, 51.1 (t, *J* = 2.0 Hz), 42.7 (t, *J* = 20.9 Hz), 23.3, 13.8, 7.5 (t, *J* = 4.1 Hz). MS (ESI): m/z (%) 376 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{21}H_{24}O_3NF_2$: 376.1719 $(M+H)^+$; Found: 398.1536 $(M+Na)^+$.

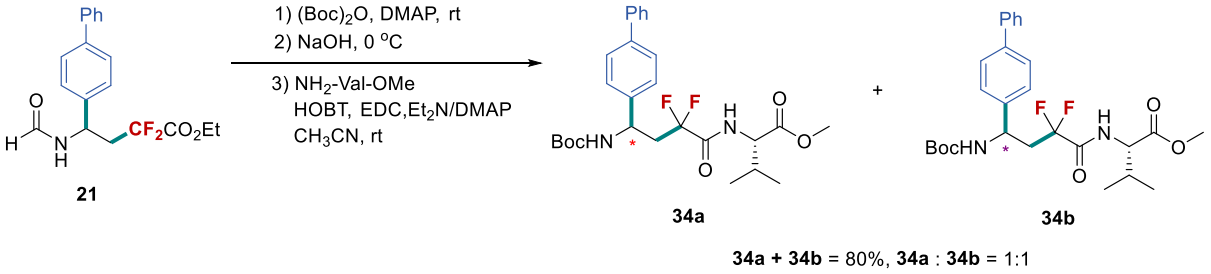
6. Transformations of *N*-Protected α,α-Difluoro-γ-Amino Acid Esters.

Deprotection of compound 4



Procedure: Compound **4** (180 mg, 0.5 mmol) in a 25 mL Schlenk tube was treated with a solution of 6 N HCl/dioxane (4.5 mL, v/v = 2:1). The schlenk tube was screw-capped and the reaction mixture was then heated to 80 °C. After stirring for 60 hours, the reaction mixture was concentrated. The residue was dissolved in a solution of DMAP (0.05 equiv, 0.025 mmol) in THF (10 mL). Then, a solution of Boc_2O (1.2 equiv, 0.6 mmol) in THF (2 mL) was added dropwise for 2 hours. A solution of 1.2 N HCl (1.0 mL) was slowly added to the reaction mixture at 0 °C and to adjust the pH to 1-2. The reaction mixture was extracted with EtOAc (3×20 mL), the organic phase was dried over $MgSO_4$, filtered, concentrated and purified by column chromatography (Dichloromethane: Methanol = 5: 1) to give **33** (125 mg, 64% yield) as a white solid (m. p. 130-132 °C). Data for compound **33**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 4H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.42 – 7.34 (m, 3H), 5.04 (t, *J* = 10.5 Hz, 1H), 3.00 – 2.84 (m, 1H), 2.50 – 2.40 (m, 1H), 1.46 (s, 9H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -99.4 (dd, *J* = 256.7, 11.3 Hz, 1F), -112.8 (dd, *J* = 256.7, 25.4 Hz, 1F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8 (t, *J* = 29.9 Hz), 157.9, 140.8, 140.5, 140.1, 128.8, 127.6, 127.5, 127.1, 126.3, 114.9 (dd, *J* = 258.3, 241.9 Hz), 83.1, 50.3 (dd, *J* = 11.3, 1.5 Hz), 41.8 (t, *J* = 26.3 Hz), 28.1. MS (ESI): m/z (%) 414 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{21}H_{24}O_4NF_2$: 392.1668 $(M+H)^+$; Found: 414.1490 $(M+Na)^+$.

Synthesis of dipeptide 34



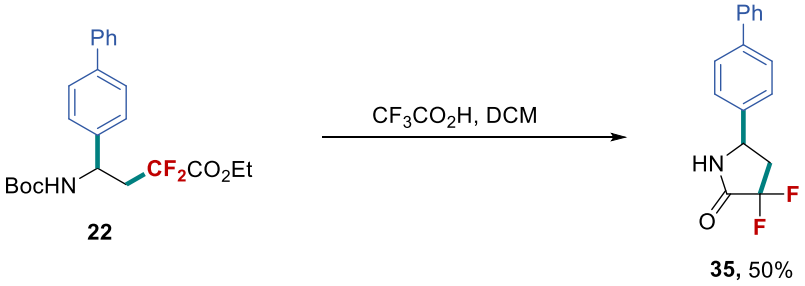
Procedure: Compound **21** (1.0 equiv, 1 mmol) was added to a solution of DMAP (0.05 equiv, 0.05 mmol) in THF (2 mL) at rt. Then, a solution of Boc_2O (1.2 equiv, 1.2 mmol) in THF (5 mL) was

added slowly. After the consumption of compound **21** monitored by TLC, a solution of NaOH (1.2 equiv, 1.2 mmol, 3 mL H_2O) was added at 0 °C. The resulting mixture was stirred at 0 °C for 4 h. The organic solvent was concentrated, the residue was extracted with EtOAc (3×10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was used for the next step without purification. The residue was dissolved in CH_3CN (8 mL). NEt_3 (4 equiv), HOBt (1.5 equiv) and EDC (1.5 equiv) were then added at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc (25 mL), washed with saturated NH_4Cl (7 mL), brine (7 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (Petroleum ether: Ethyl acetate = 5: 1) to give **34a** (207 mg, 41% yield) as a white solid (m.p. 131-133 °C) and **34b** (198 mg, 39% yield) as a white solid (m.p. 131-133 °C).

Data for compound **34a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.52 (m, 4H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.40 – 7.29 (m, 4H), 5.14 (s, 2H), 4.56 (dd, *J* = 8.4 Hz, 4.8 Hz, 1H), 3.72 (s, 3H), 2.81 – 2.49 (m, 2H), 2.33 – 2.19 (m, 1H), 1.41 (s, 9H), 0.97 (d, *J* = 6.4 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.2 (dt, *J* = 263.6, 11.7 Hz, 1F), -104.8 (dt, *J* = 263.6, 14.7 Hz, 1F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 164.0 (t, *J* = 29.1 Hz), 155.1, 140.4, 140.2, 128.7, 127.4, 127.3, 126.9, 126.5, 116.8 (t, *J* = 252.8 Hz), 79.8, 57.5, 52.2, 49.1, 40.2 (t, *J* = 24.4 Hz), 30.8, 28.2, 18.8, 17.7. MS (ESI): m/z (%) 527 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{27}H_{35}O_5N_2F_2$: 505.2509 $(M+H)^+$; Found: 505.2505 $(M+H)^+$.

Data for compound **34b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.52 (m, 4H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.39 – 7.32 (m, 3H), 7.12 (br, 1H), 5.25 (d, *J* = 7.6 Hz, 1H), 5.04 (s, 1H), 4.55 (dd, *J* = 8.4 Hz, 4.8 Hz, 1H), 3.76 (s, 3H), 2.81 – 2.54 (m, 2H), 2.30 – 2.17 (m, 1H), 1.41 (s, 9H), 0.97 (d, *J* = 5.6 Hz, 3H), 0.95 (d, *J* = 5.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.6 (dt, *J* = 263.2, 12.8 Hz, 1F), -104.3 (dt, *J* = 263.2, 13.2 Hz, 1F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 163.7 (t, *J* = 28.5 Hz), 154.8, 140.45, 140.42, 128.7, 127.4, 127.2, 126.9, 126.4, 116.8 (t, *J* = 252.5 Hz), 79.6, 57.3, 52.3, 49.1, 39.8 (t, *J* = 22.1 Hz), 31.3, 28.2, 18.6, 17.7. MS (ESI): m/z (%) 527 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{27}H_{35}O_5N_2F_2$: 505.2509 $(M+H)^+$; Found: 505.2506 $(M+H)^+$.

Synthesis of Lactam 35



Procedure: A solution of TFA/H_2O (2 mL, v/v = 95: 5) was added to the mixture of compound **22** (1.0 equiv, 0.5 mmol) and CH_2Cl_2 (8 mL) at room temperature. The reaction mixture was stirred for 3 h. The reaction mixture was diluted with EtOAc (25 mL), washed with ice-cold saturated $NaHCO_3$ (40 mL), brine (7 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (Dichloromethane: Methanol = 20: 1) to give **35** (137 mg, 50% yield) as a white solid (m.p. 196-198 °C). Data for compound **35**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.44 (s, 1H), 7.73 – 7.64 (m, 4H), 7.51 – 7.41 (m, 4H), 7.37 (t, *J* = 7.2 Hz, 1H), 4.93 – 4.86 (m, 1H), 3.22 – 3.03 (m, 1H), 2.48 – 2.29 (m, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -103.7 (dm, *J* = 264.7 Hz, 1F), - 106.0 (dm, *J* = 264.7, 1F). ^{13}C NMR (125 MHz, CD_3CN) δ 166.1 (t, *J* = 30.5 Hz), 141.9, 141.1, 140.6, 129.95, 128.7, 128.4, 127.9, 127.7, 119.3 (dd, *J* = 248.9 Hz, 248.8 Hz), 52.5 (dd, *J* = 4.8 Hz, 4.6 Hz), 40.6 (dd, *J* = 22.5 Hz, 22.4 Hz). MS (ESI): m/z (%) 274 $(M+H)^+$. HRMS (EI): Calcd. for $C_{16}H_{13}ONF_2$: 273.0965 $(M)^+$; Found: 273.0969 $(M)^+$.

7. References.

(1) S. Tu, C. Zhang, *Org. Proc. Res. Dev.*, 2015, **19**, 2045.

(2) A. F. Kassir, S. S. Ragab, T. A. M. Nguyen, R. Guillot, M. Scherrmann, T. Boddaert, D. J. Aitken, *J. Org. Chem.*, 2016, **81**, 9983.

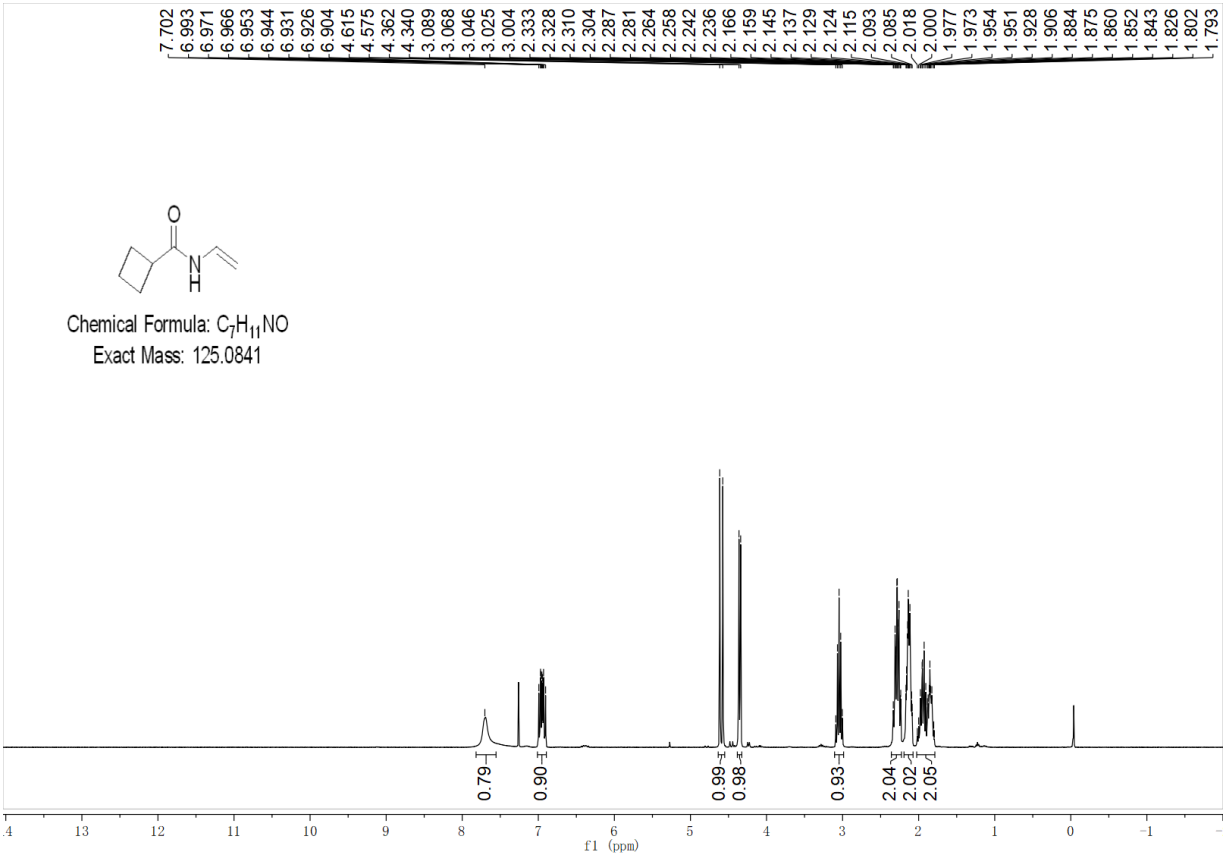
(3) Y. Yi, H. Gholami, M. G. Morrowa, B. Borhan, *Org. Biomol. Chem.*, 2017, **15**, 9570.

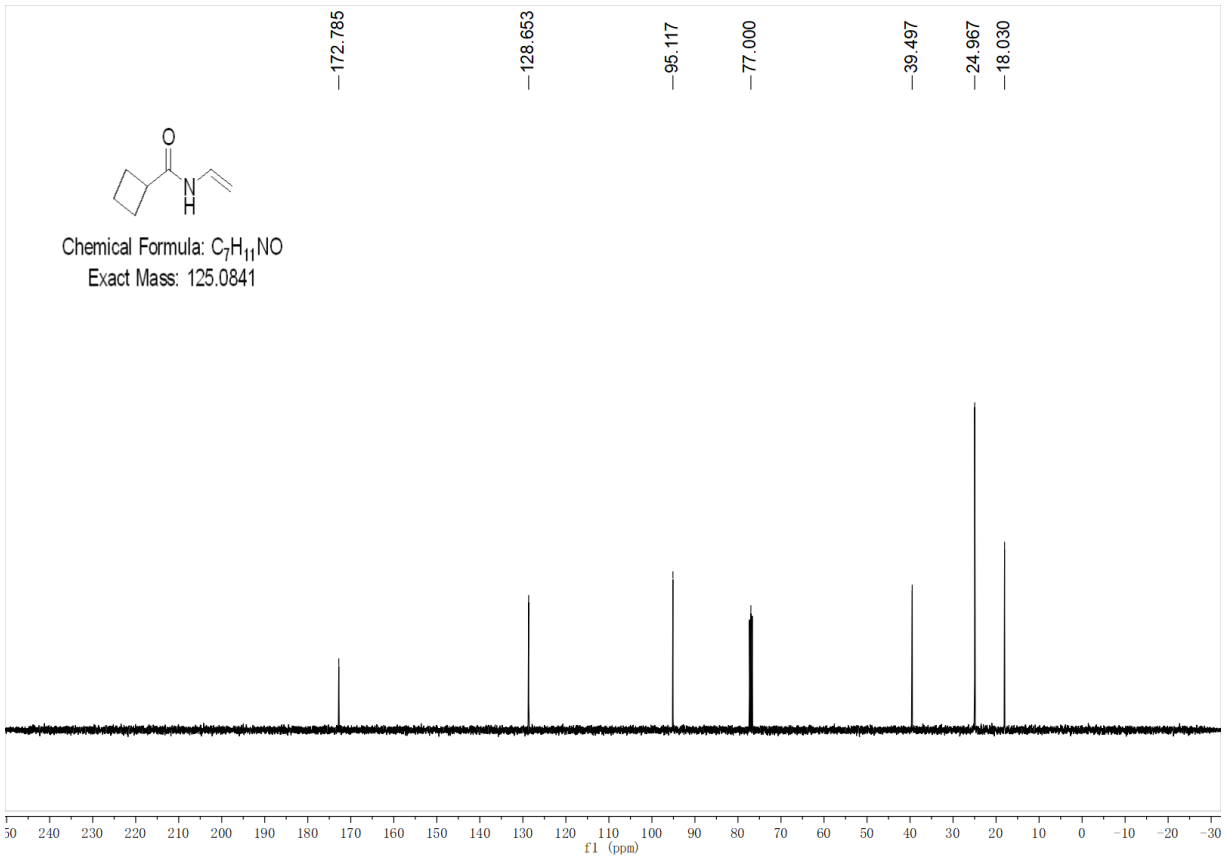
(4) P. Kurtz, H. Disselnkötter, *Justus Liebigs Ann. Chem.*, 1972, **764**, 69.

(5) A. Pavel, P. Alla, B. Sergey, *Tetrahedron Lett.*, 2008, **49**, 5255.

(6) K. M. Geanna and S. Troels, *J. Org. Chem.*, 2012, **77**, 5894.

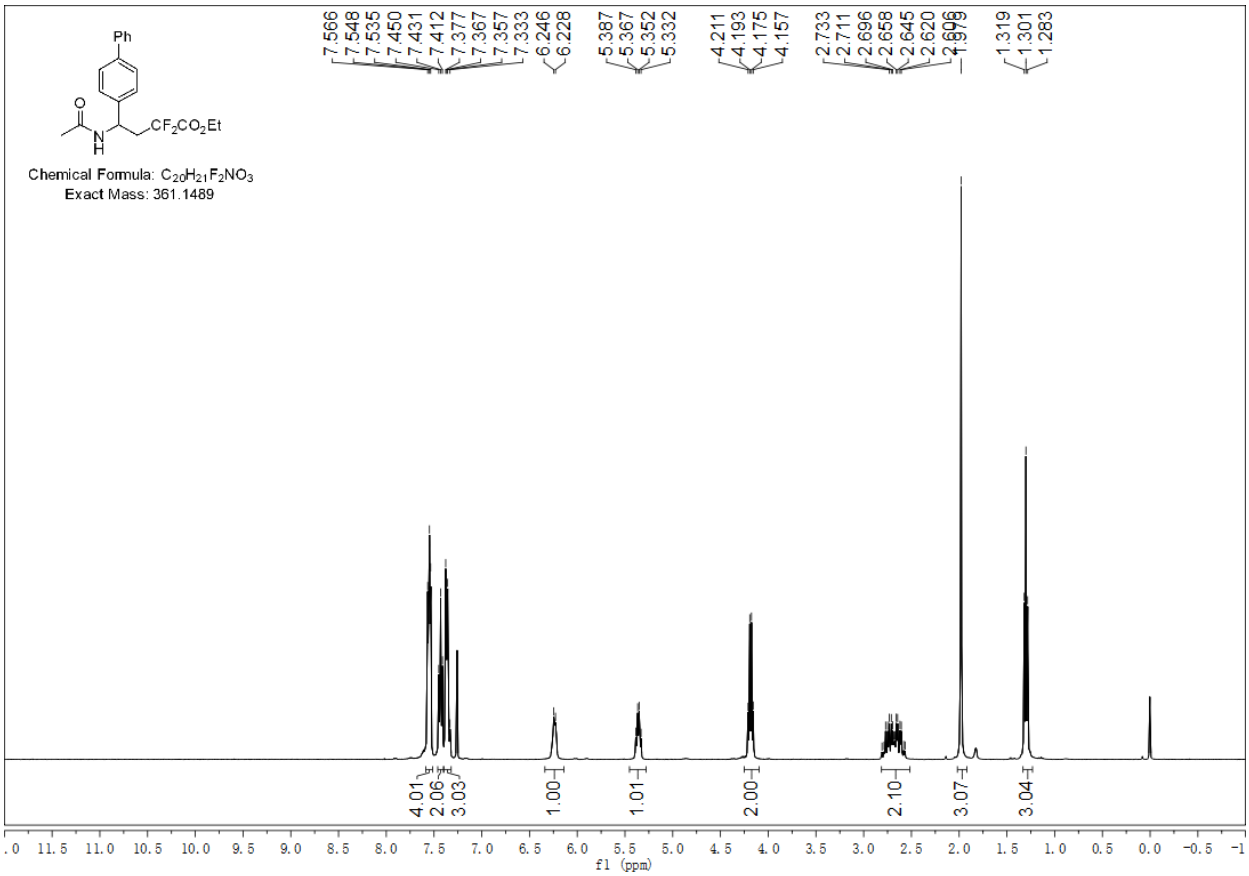
8. Copies of ^{1}H and ^{13}C NMR Spectra of Compound 1g.

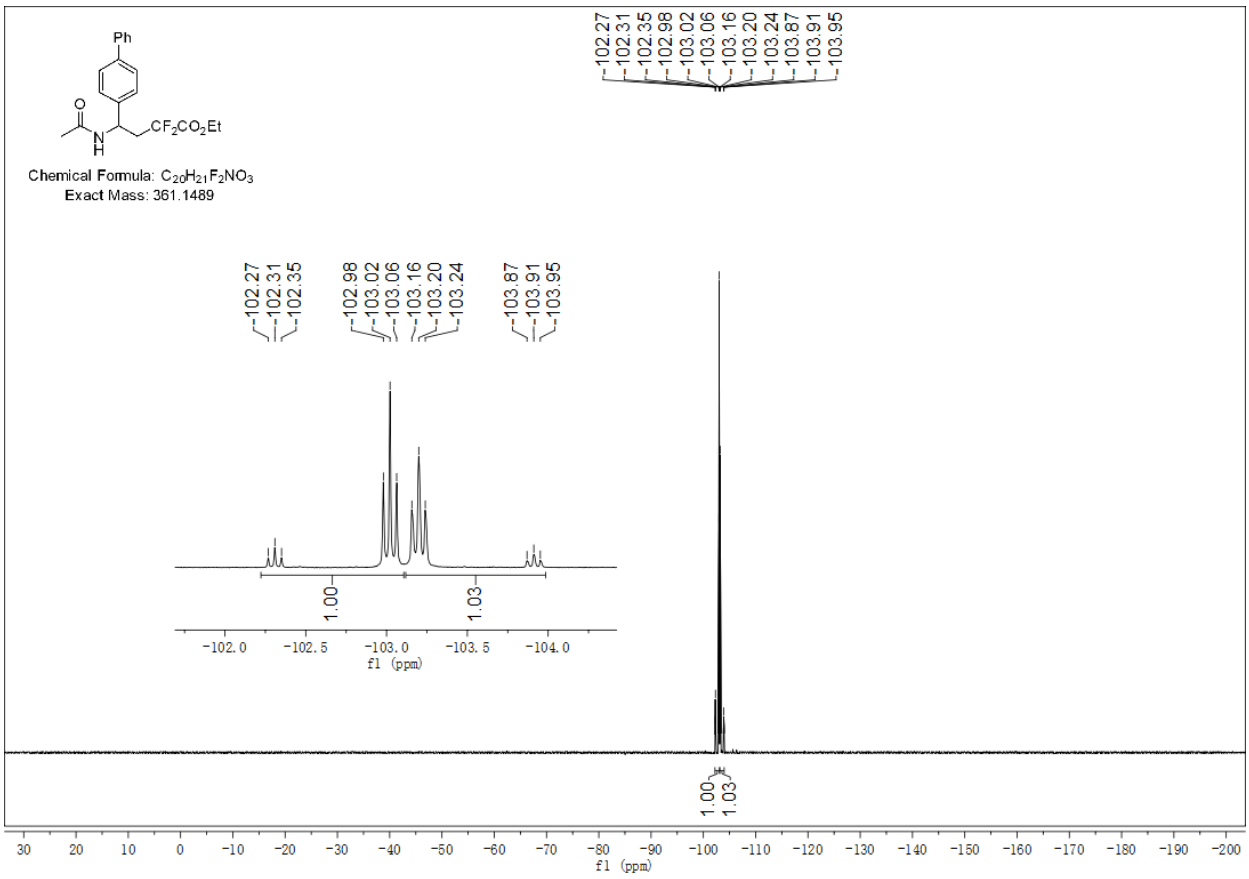


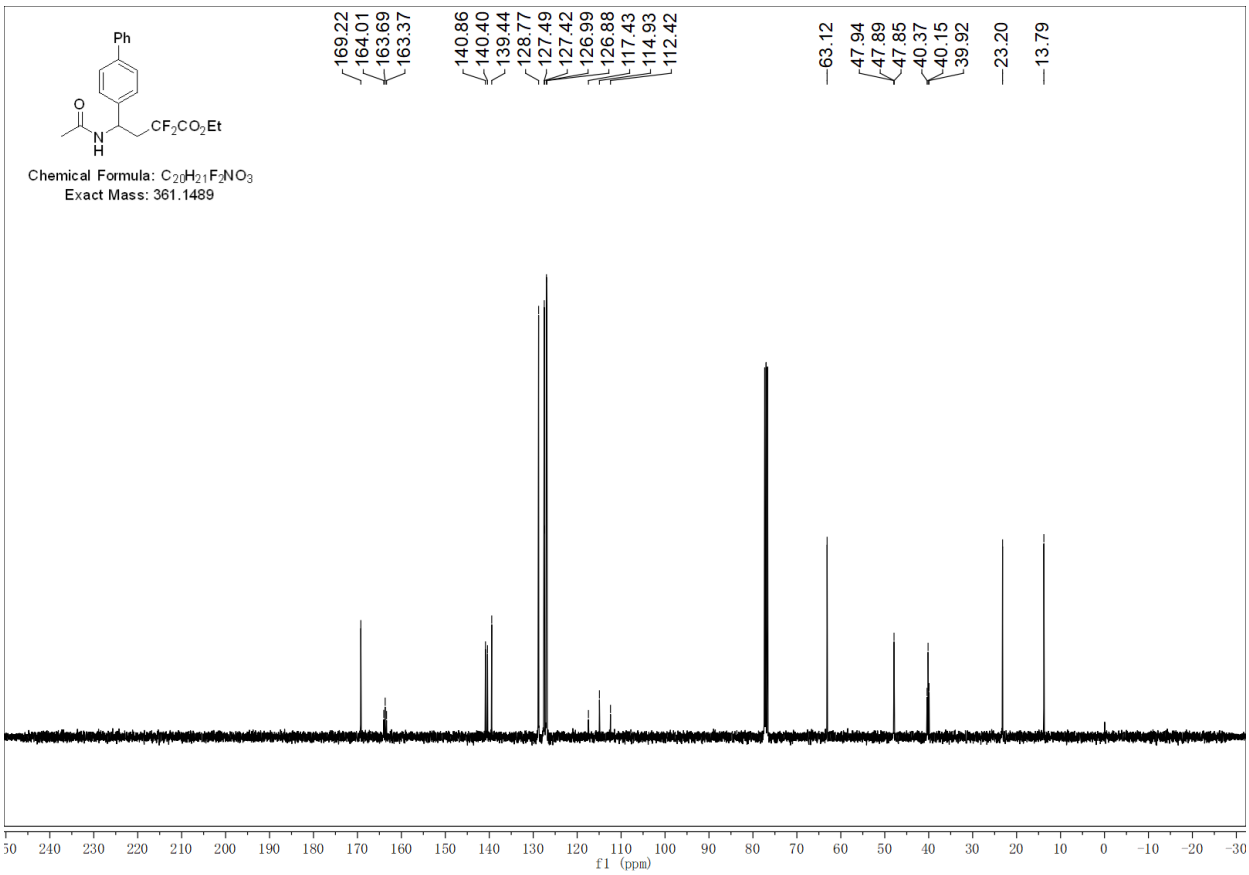


9. Copies of ^{1}HNMR, ^{13}C NMR, and ^{19}F NMR Spectra of Compounds 4-32.

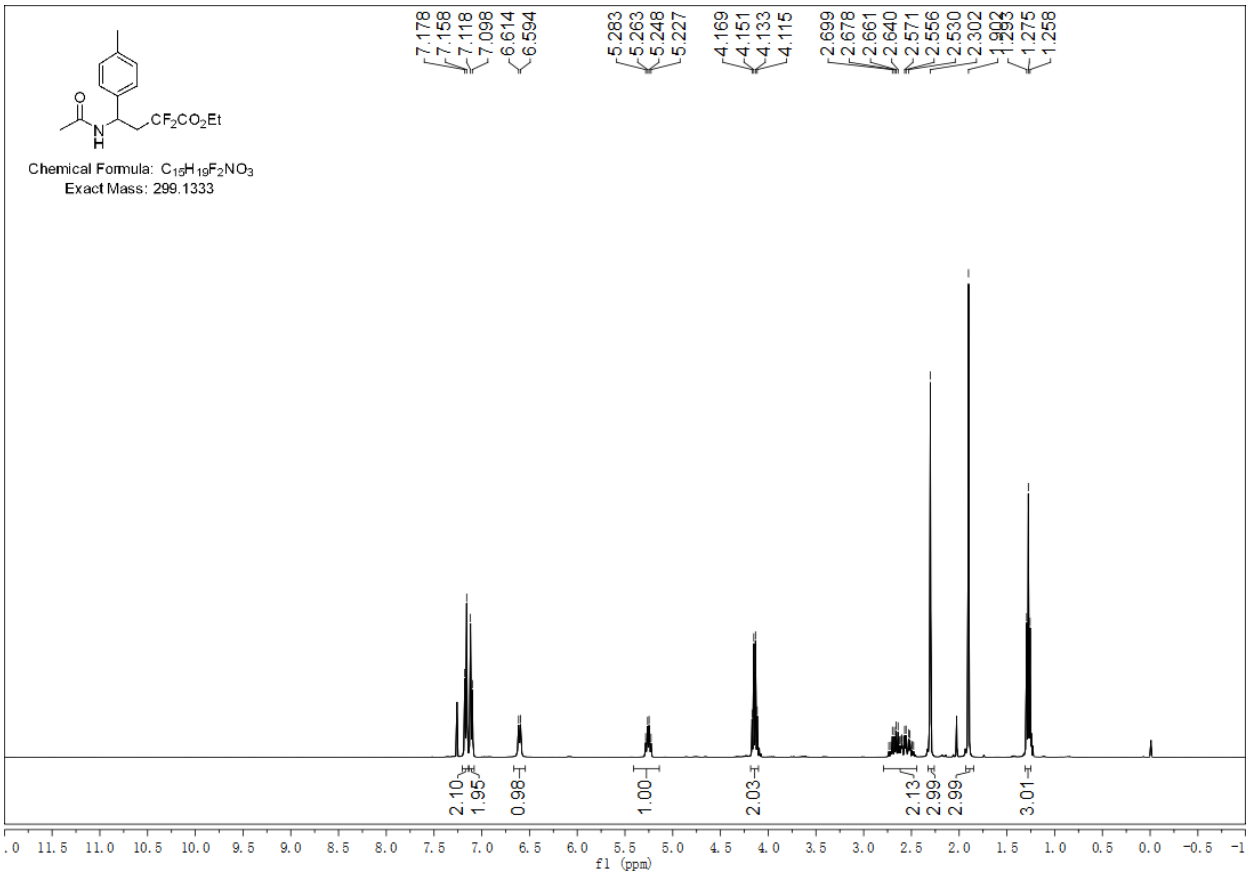
Ethyl 4-([1,1'-biphenyl]-4-yl)-4-acetamido-2,2-difluorobutanoate (4)

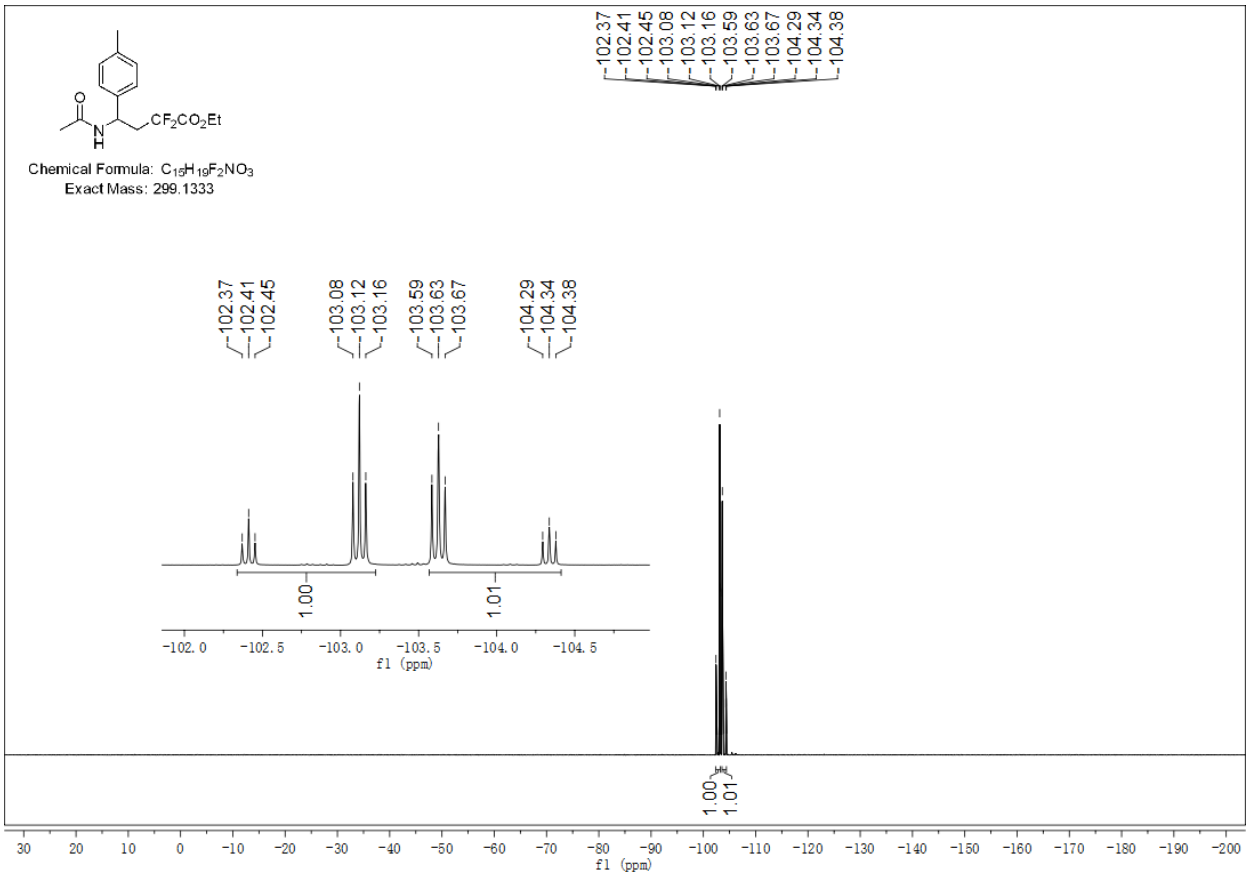






Ethyl 4-acetamido-2,2-difluoro-4-(p-tolyl)butanoate (5)

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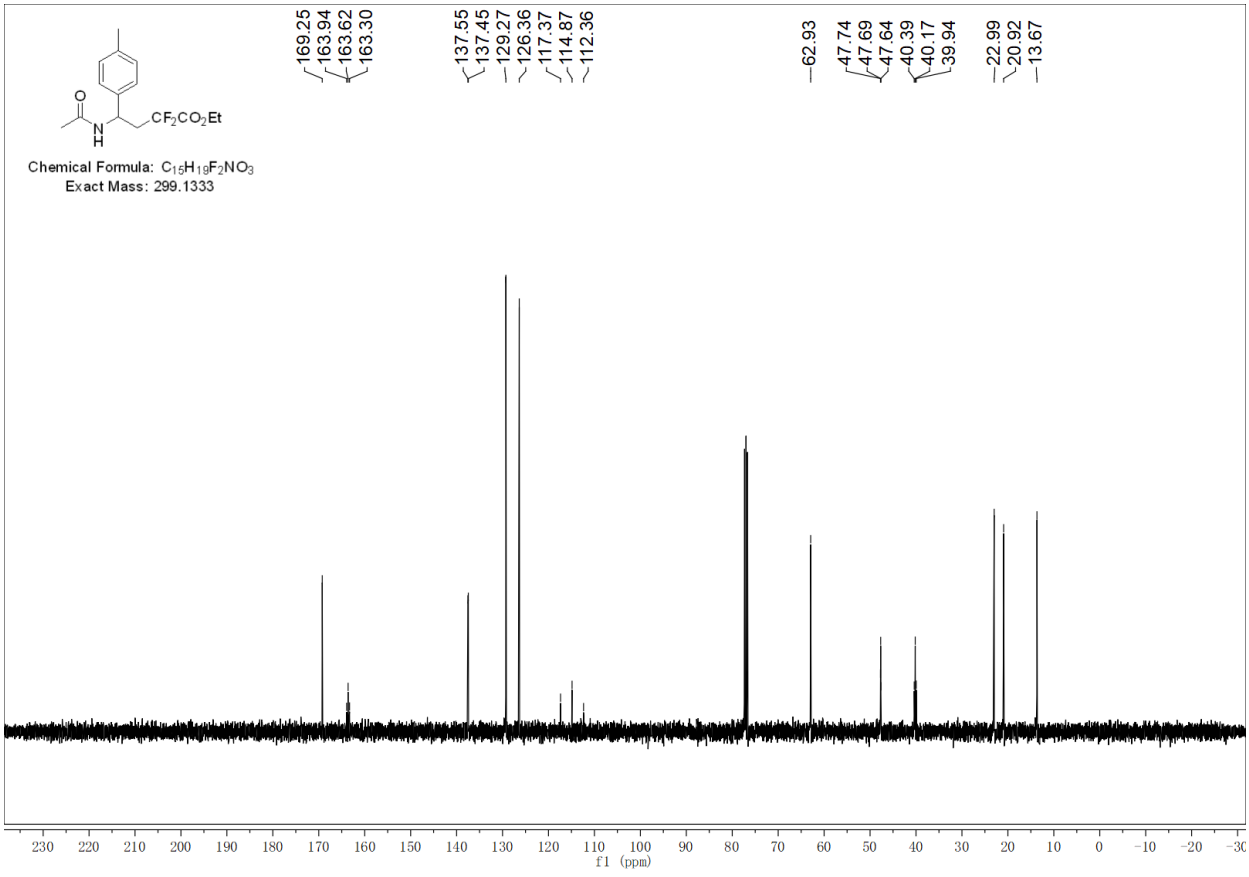
1.00
1.01
f1 (ppm)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114.87
112.36
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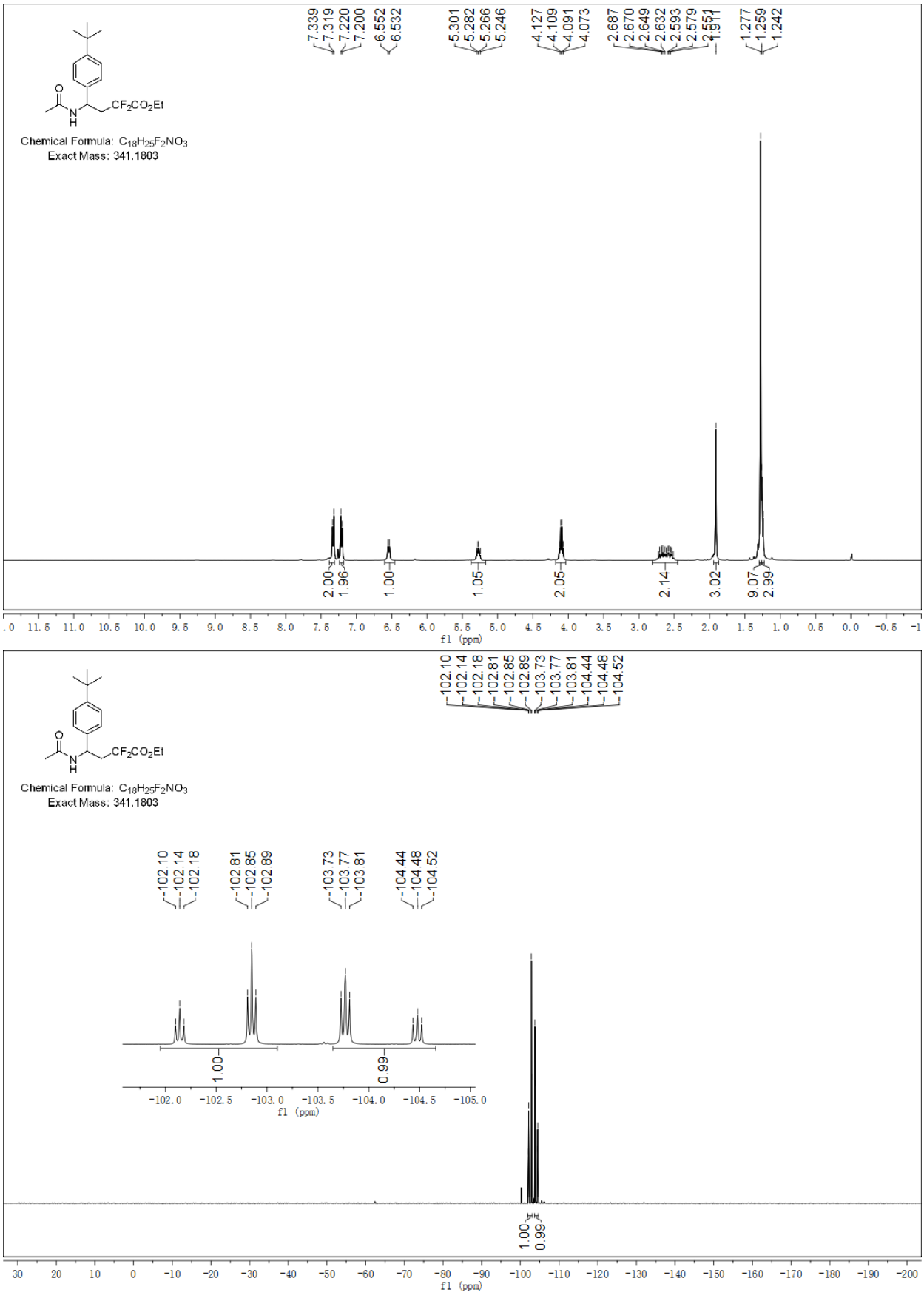
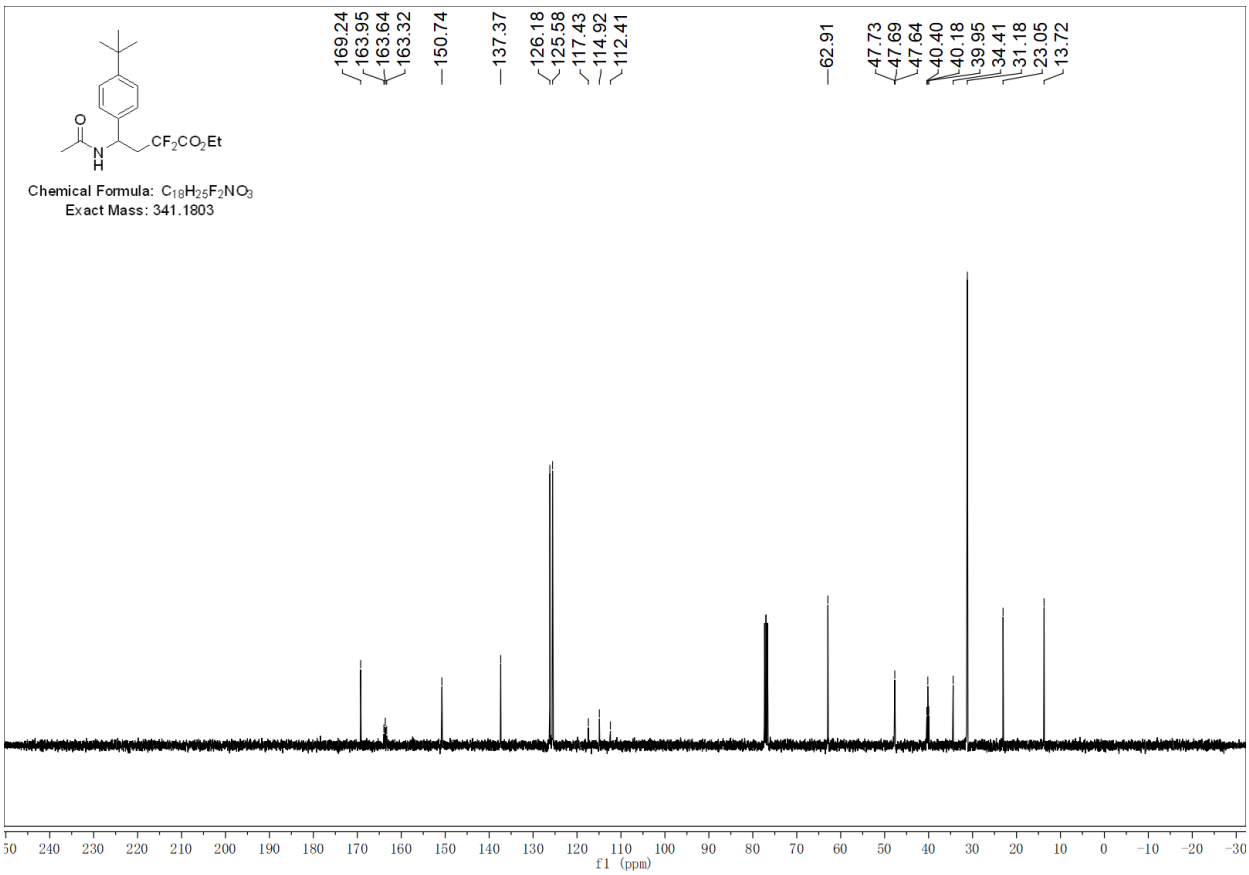
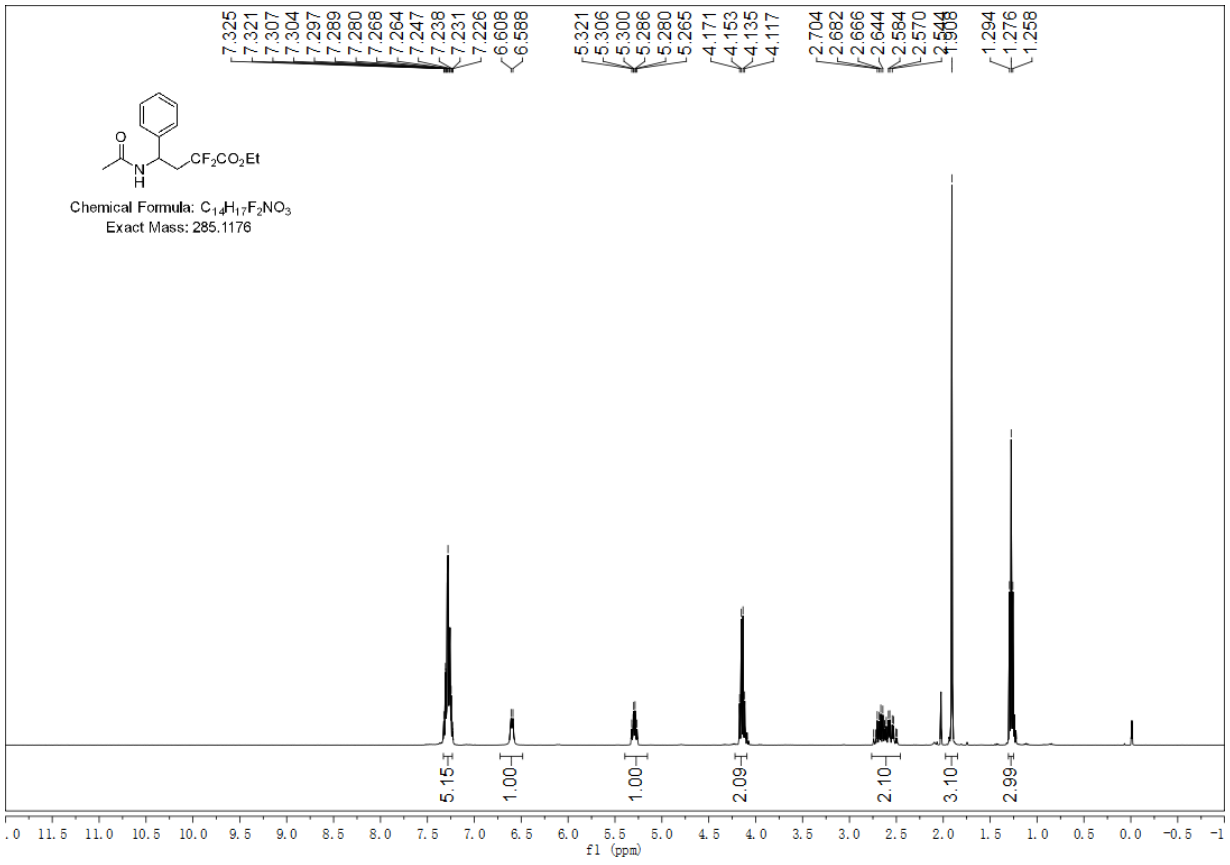
47.74
47.69
47.64
40.39
40.17
39.94
22.99
20.92
13.67
f1 (ppm)

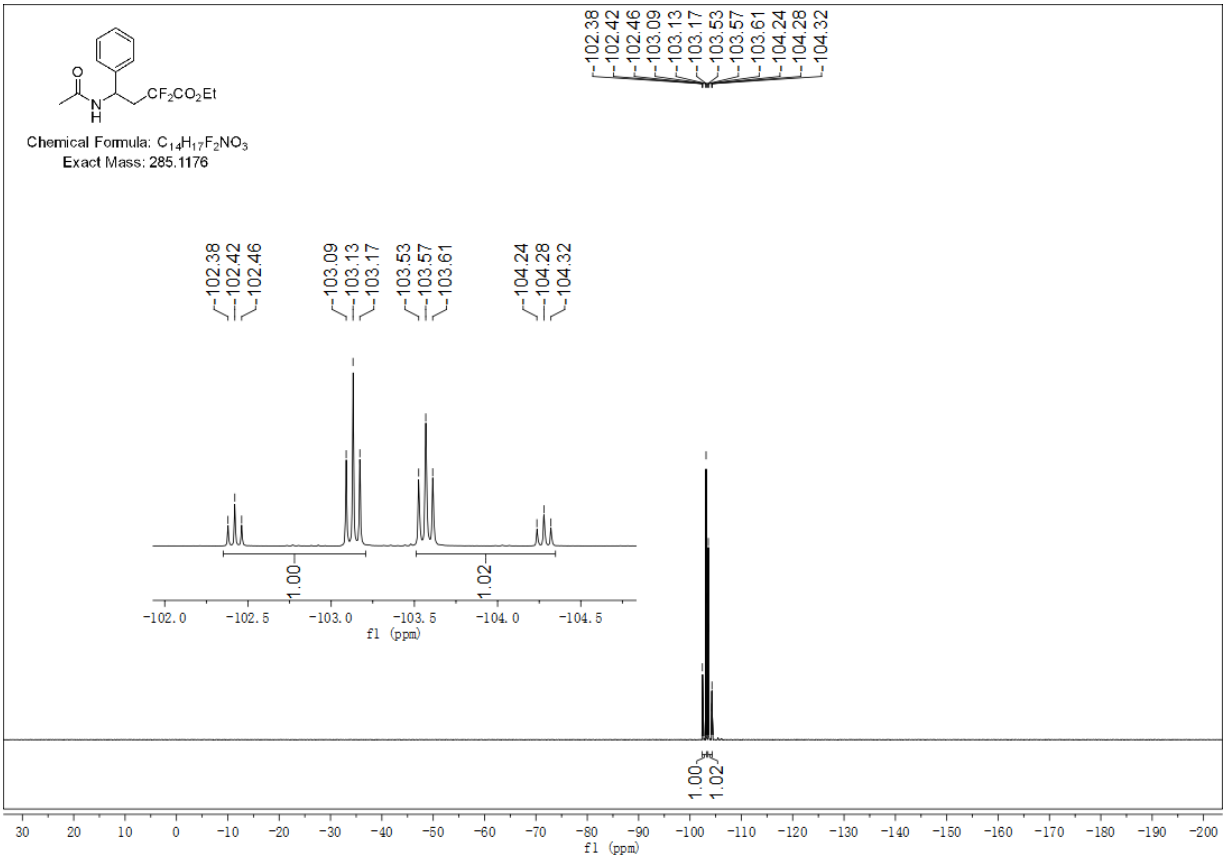
Ethyl 4-acetamido-4-(4-(tert-butyl)phenyl)-2,2-difluorobutanoate (6)





Ethyl 4-acetamido-2,2-difluoro-4-phenylbutanoate (7)

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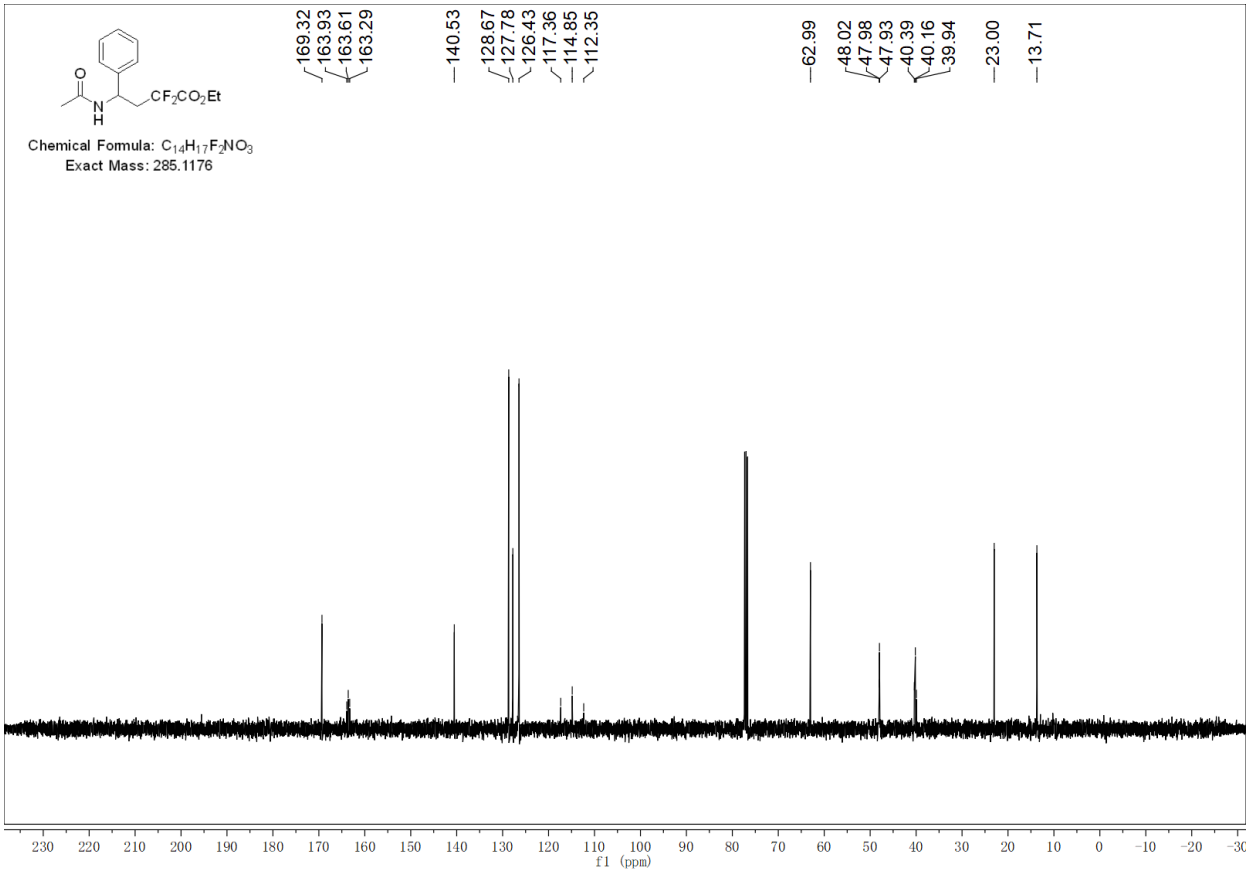
1.02
f1 (ppm)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47.98
47.93
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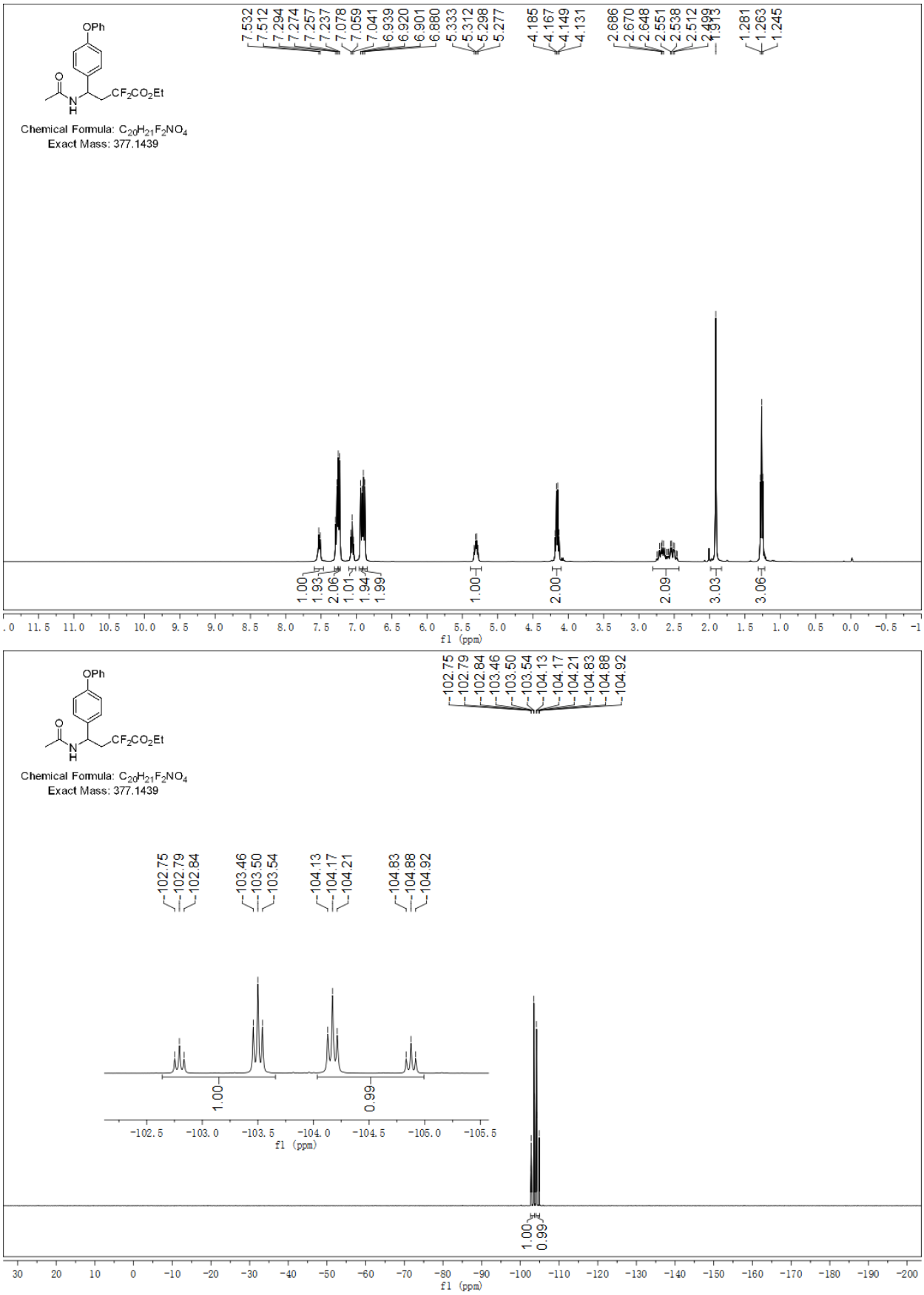
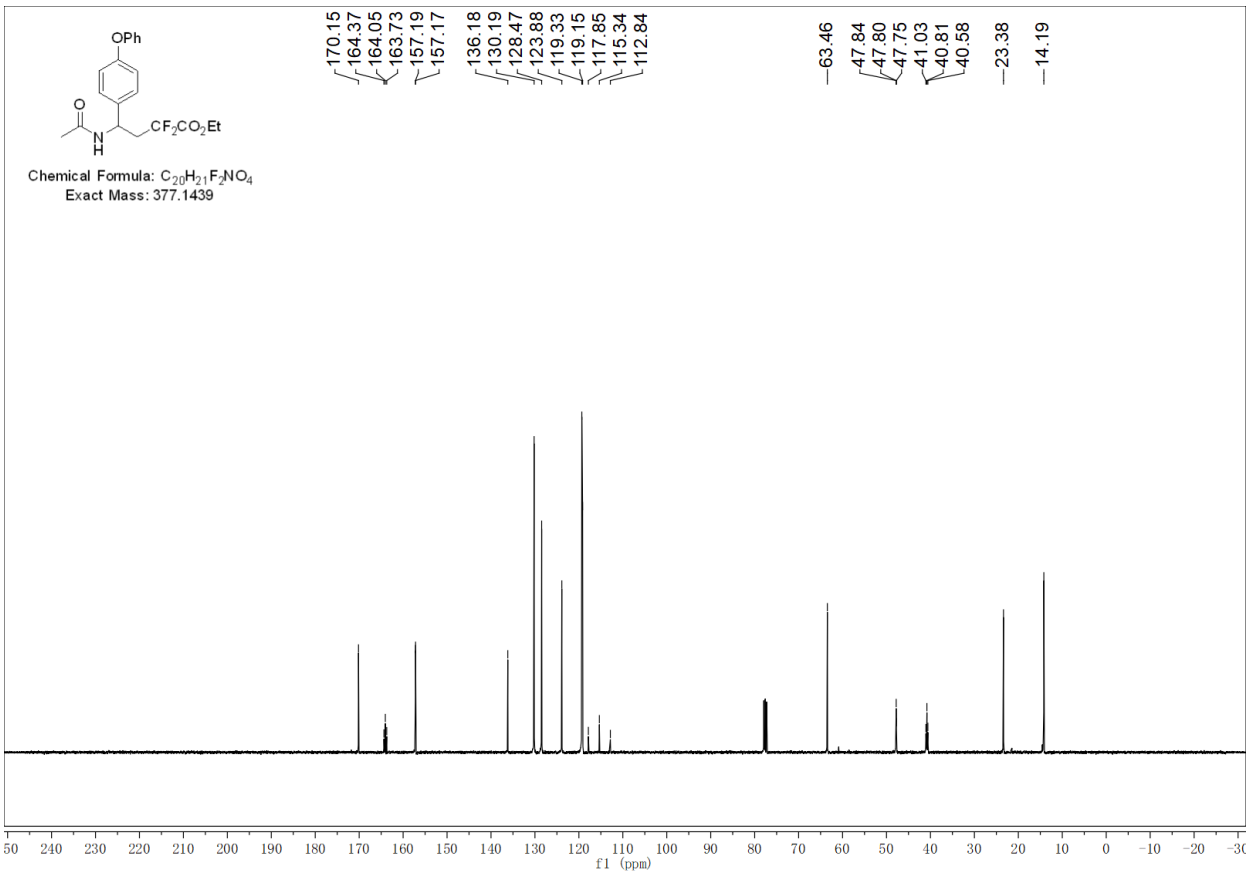
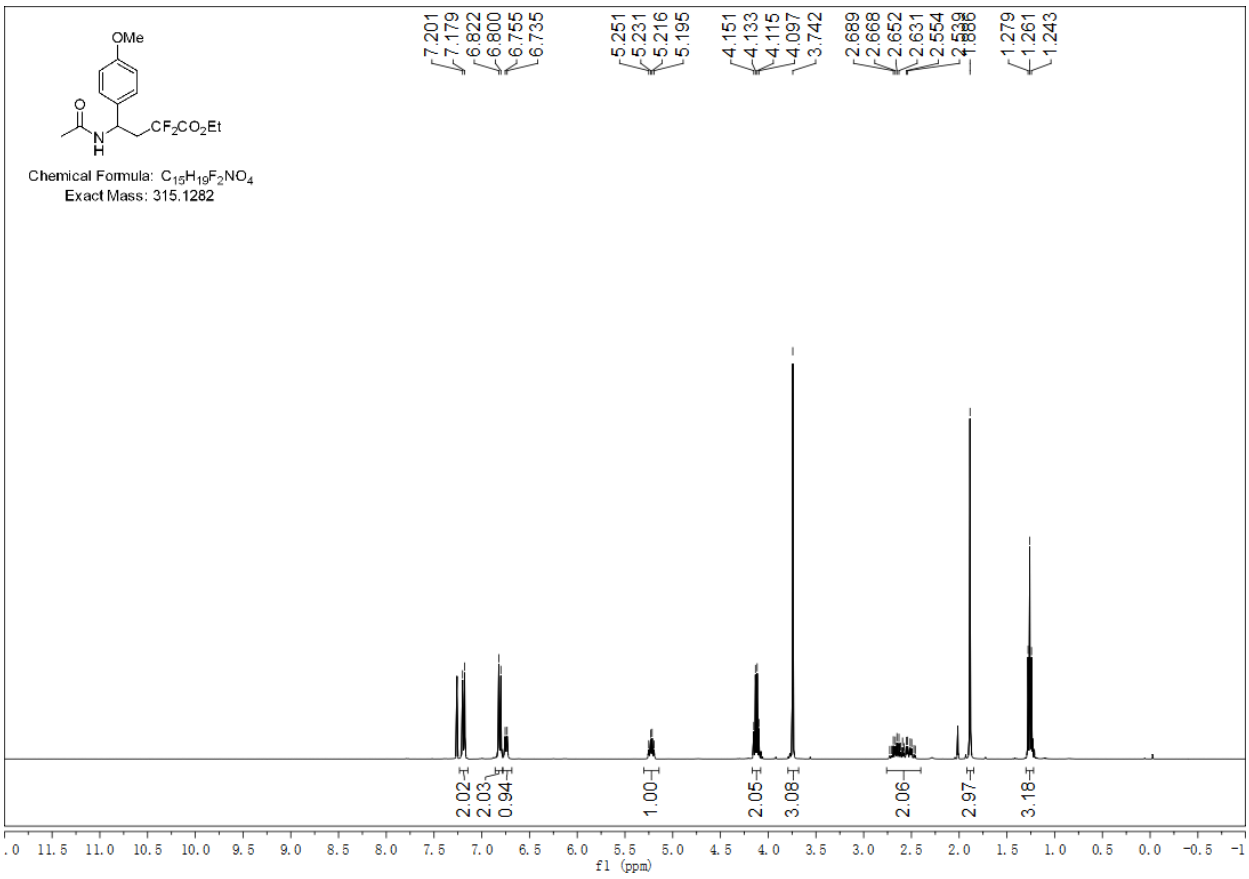
f1 (ppm)

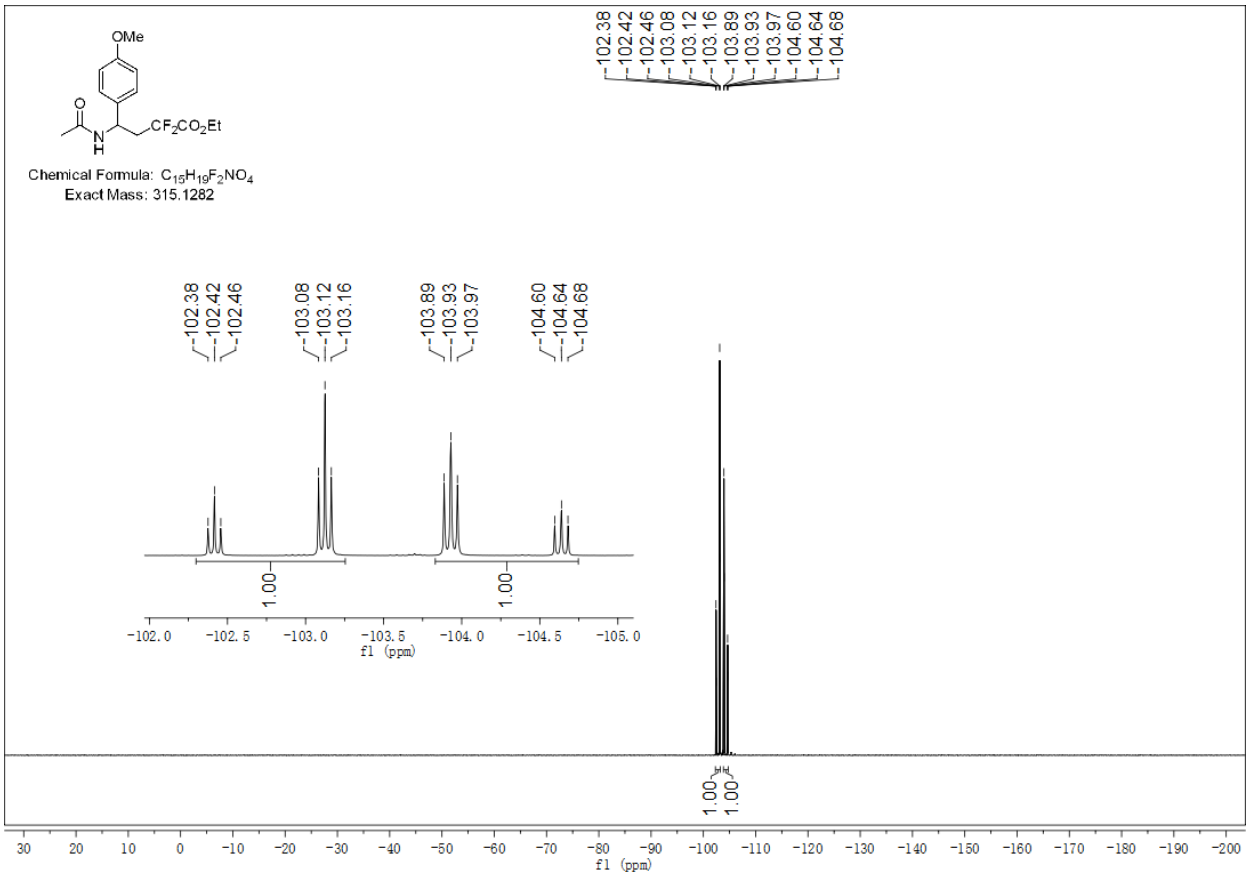
Ethyl 4-acetamido-2,2-difluoro-4-(4-phenoxyphenyl)butanoate (8)





Ethyl 4-acetamido-2,2-difluoro-4-(4-methoxyphenyl)butanoate (9)

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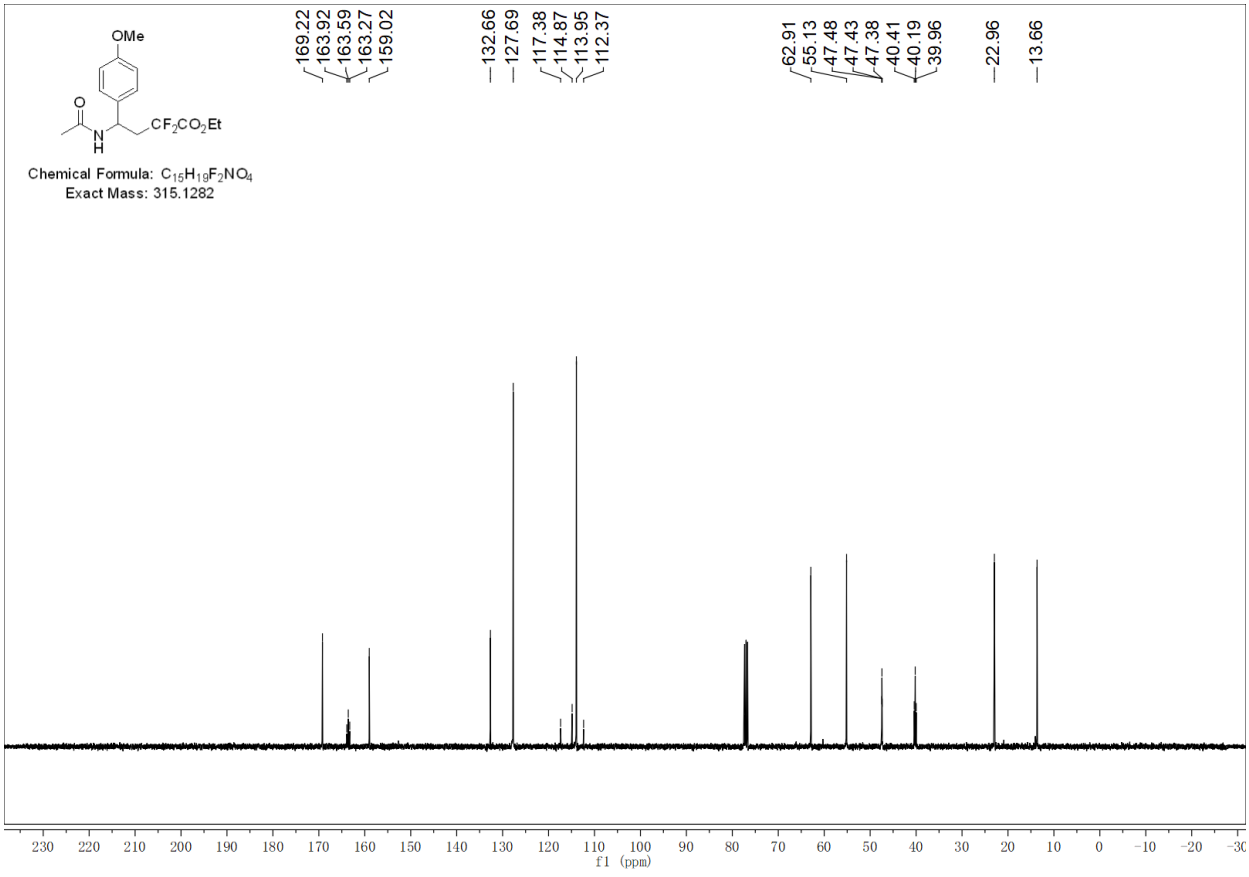
1.00
f1 (ppm)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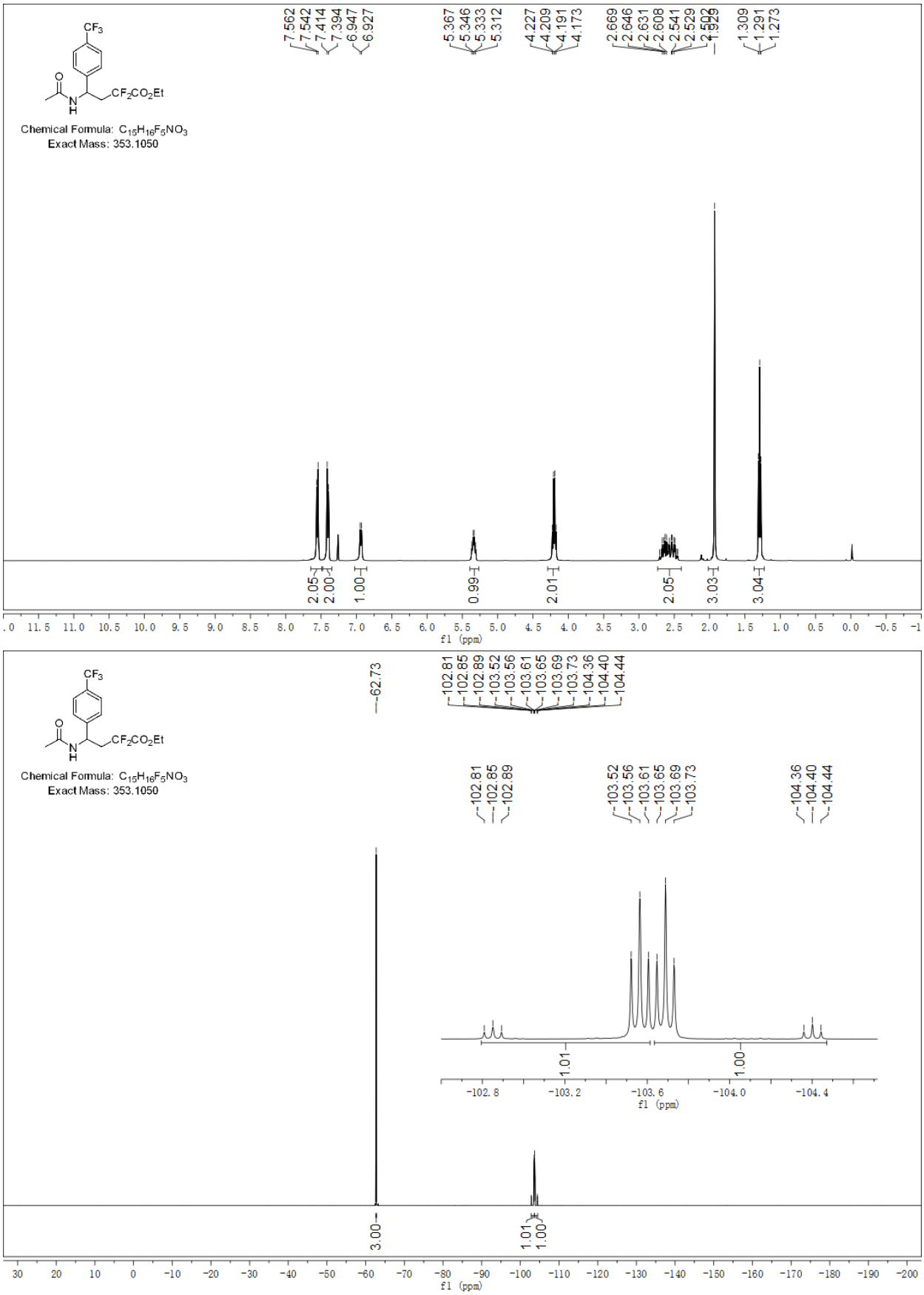
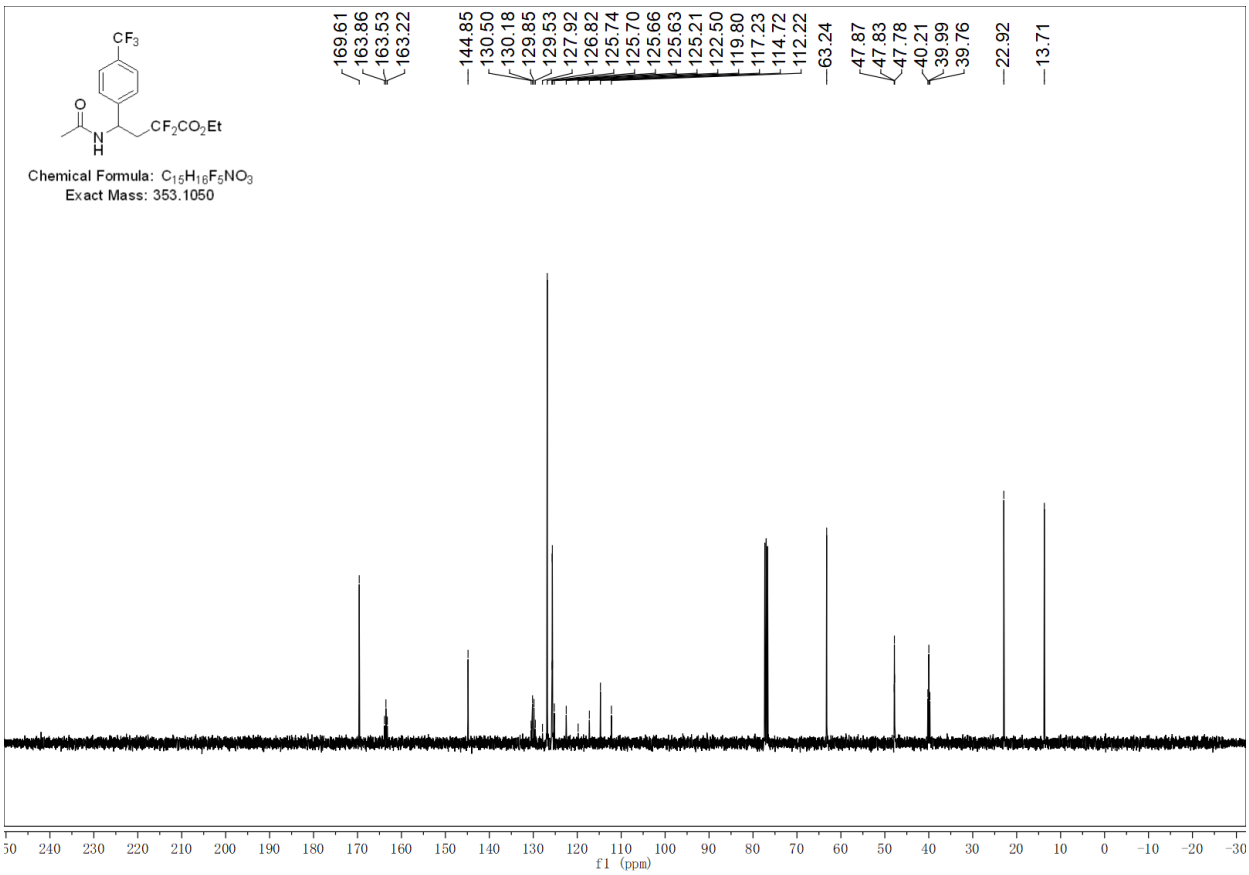
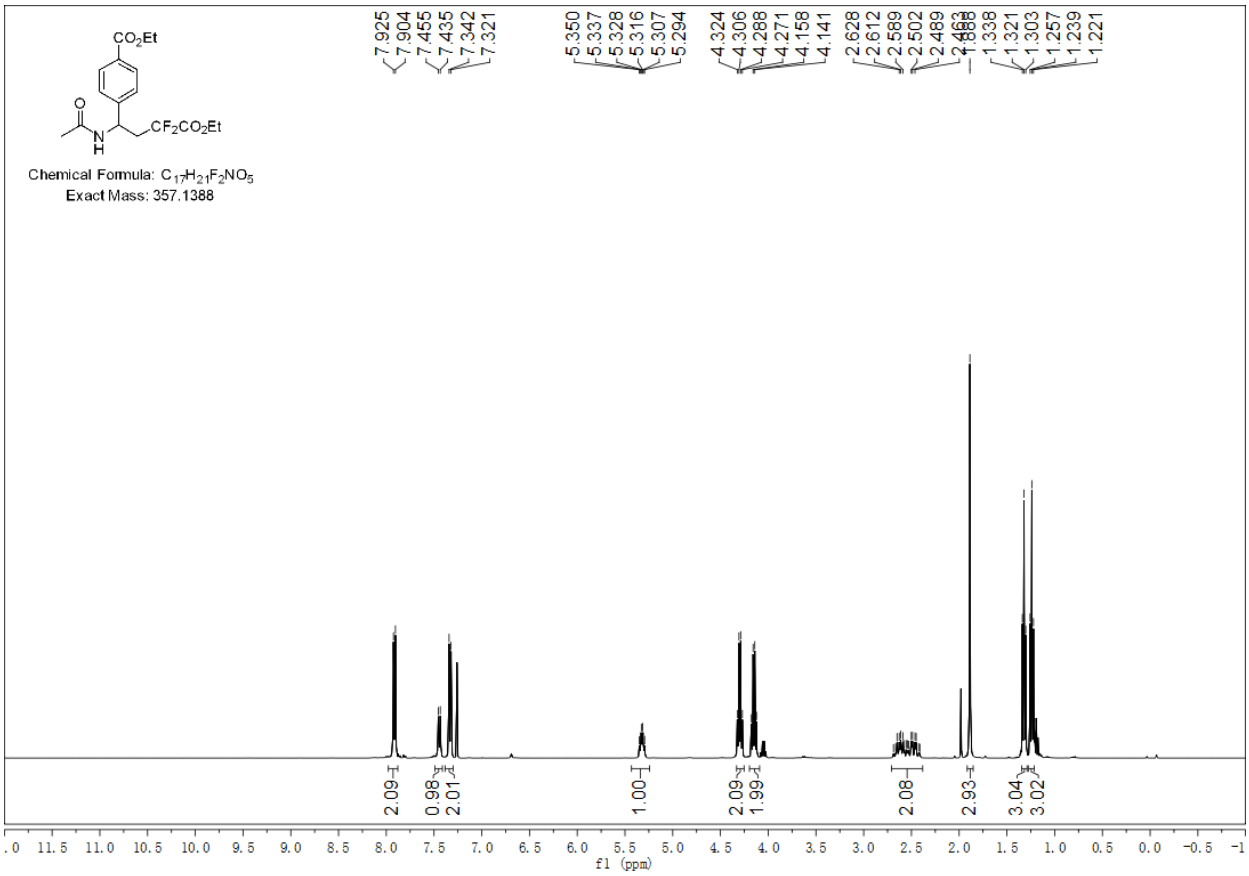
47.43
47.38
40.41
40.19
39.96
22.96
13.66
f1 (ppm)

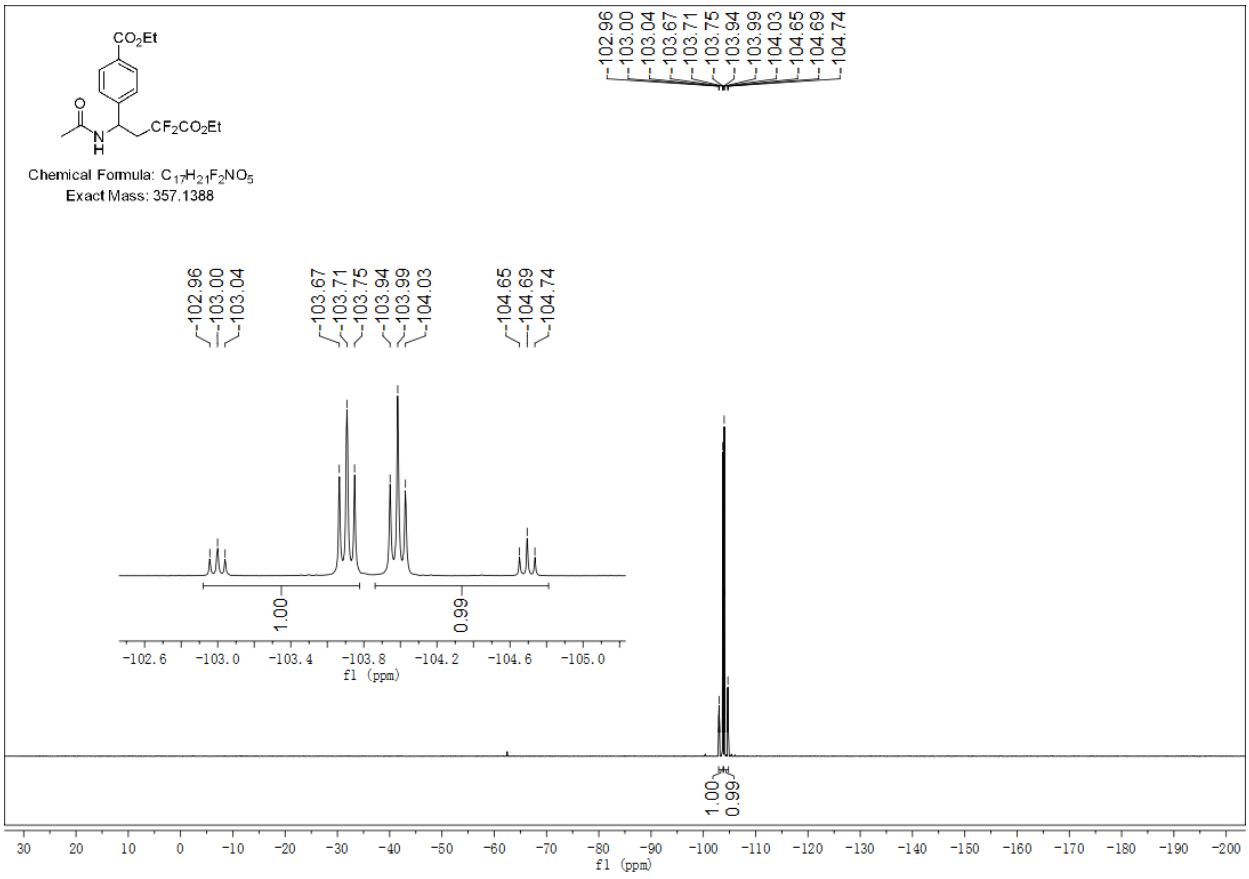
Ethyl 4-acetamido-2,2-difluoro-4-(4-(trifluoromethyl)phenyl)butanoate (10)

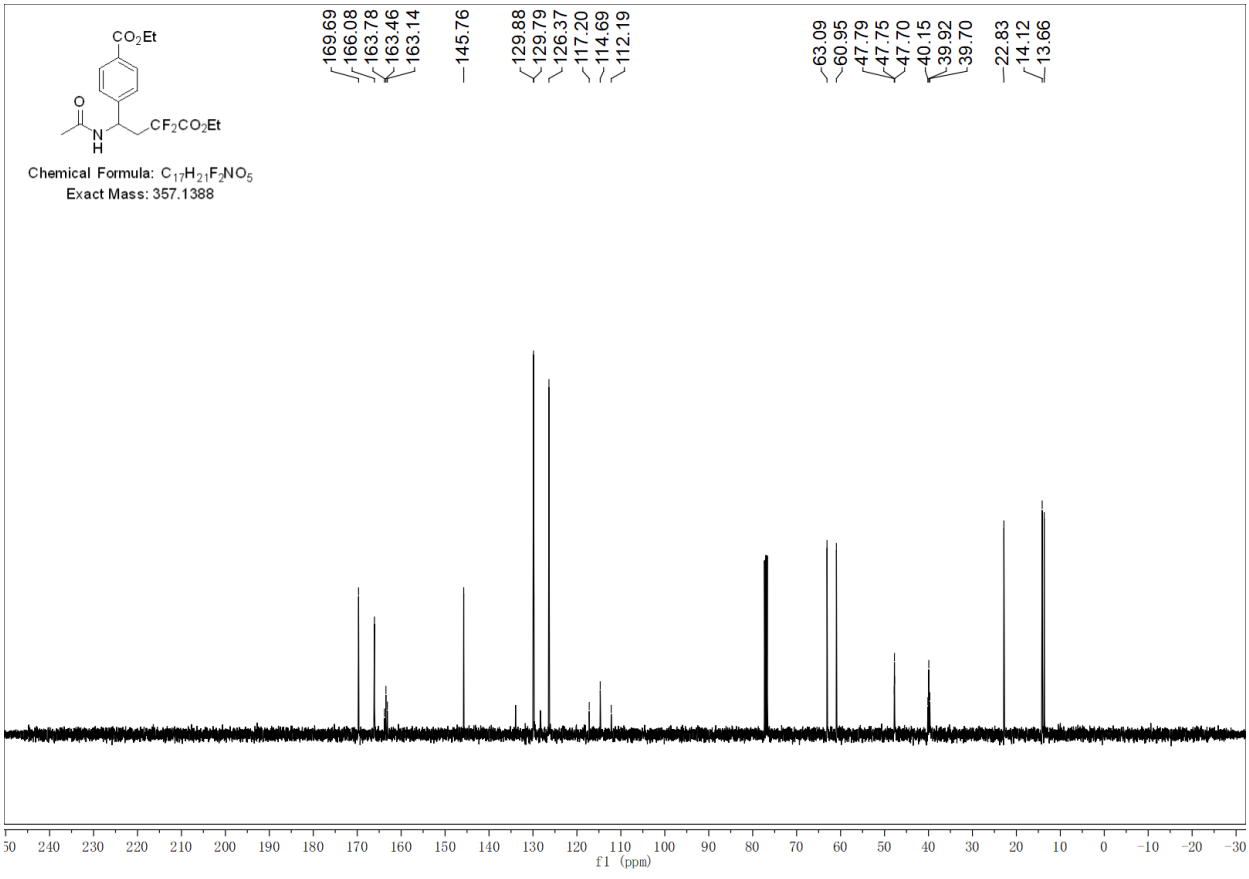




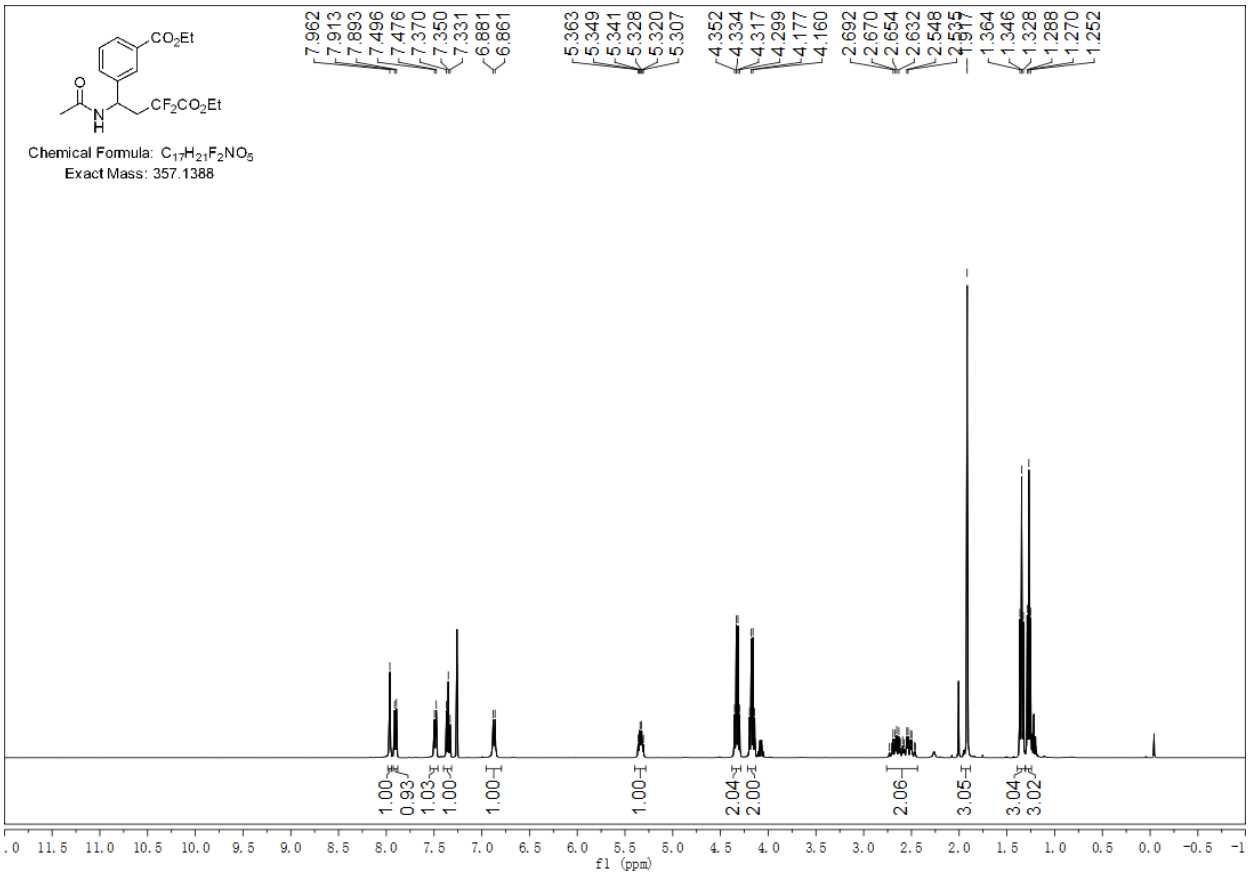
Ethyl 4-(1-acetamido-4-ethoxy-3,3-difluoro-4-oxobutyl)benzoate (11)

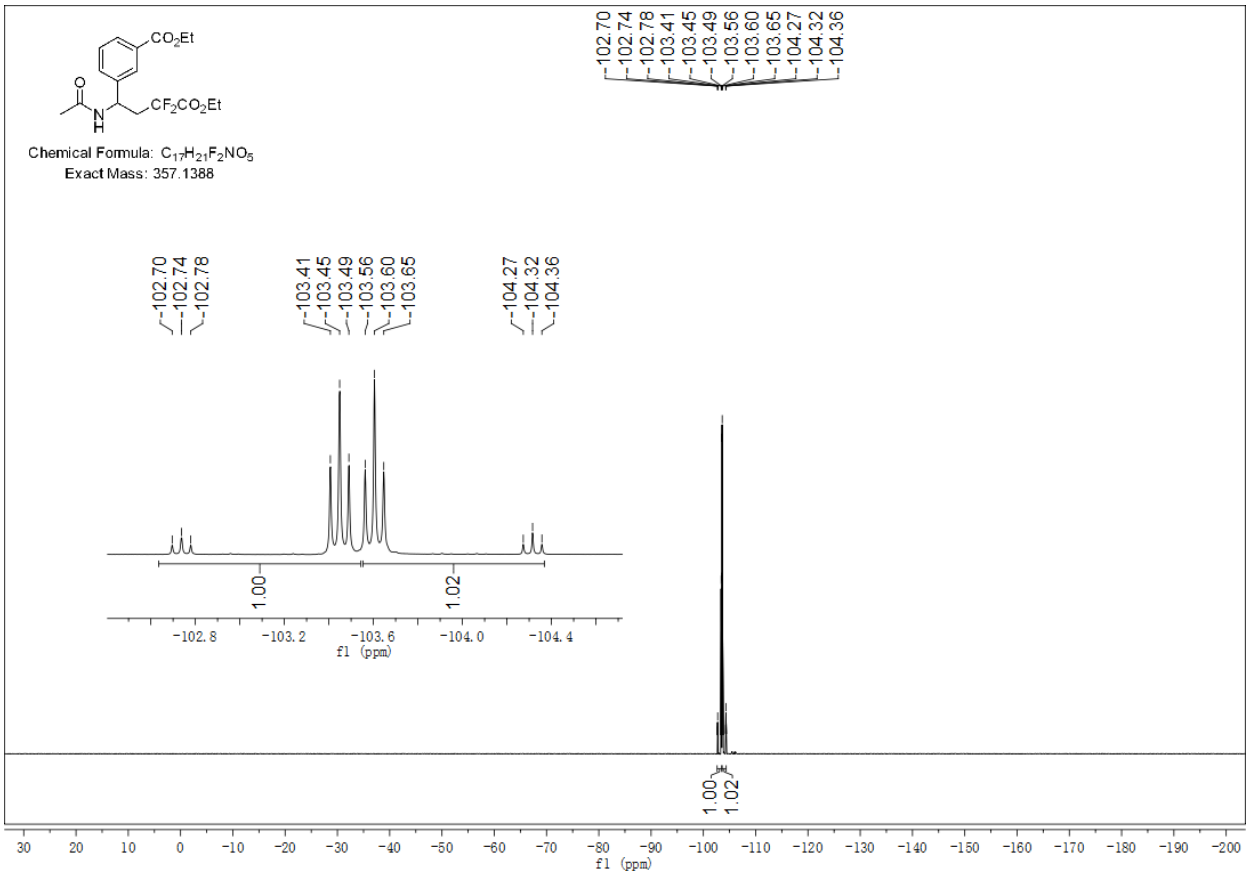


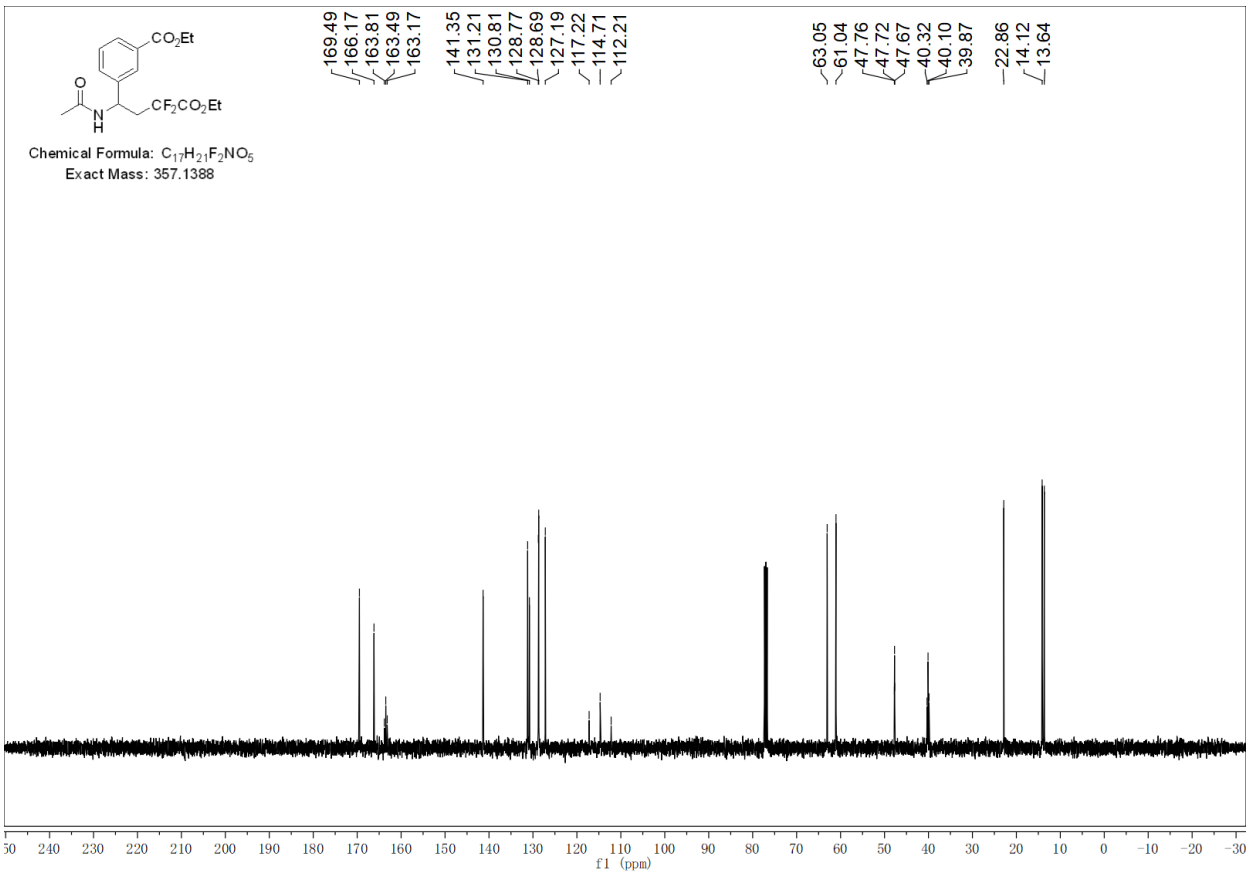

CO2Et
CF2CO2Et
Chemical Formula: C17H21F2NO5
Exact Mass: 357.1388
102.96
103.00
103.04
103.67
103.71
103.75
103.94
103.99
104.03
104.65
104.69
104.74
1.00
0.99
f1 (ppm)


CO2Et
CF2CO2Et
Chemical Formula: C17H21F2NO5
Exact Mass: 357.1388
169.69
166.08
163.78
163.46
163.14
145.76
129.88
129.79
126.37
117.20
114.69
112.19
63.09
60.95
47.79
47.75
47.70
40.15
39.92
39.70
22.83
14.12
13.66
f1 (ppm)

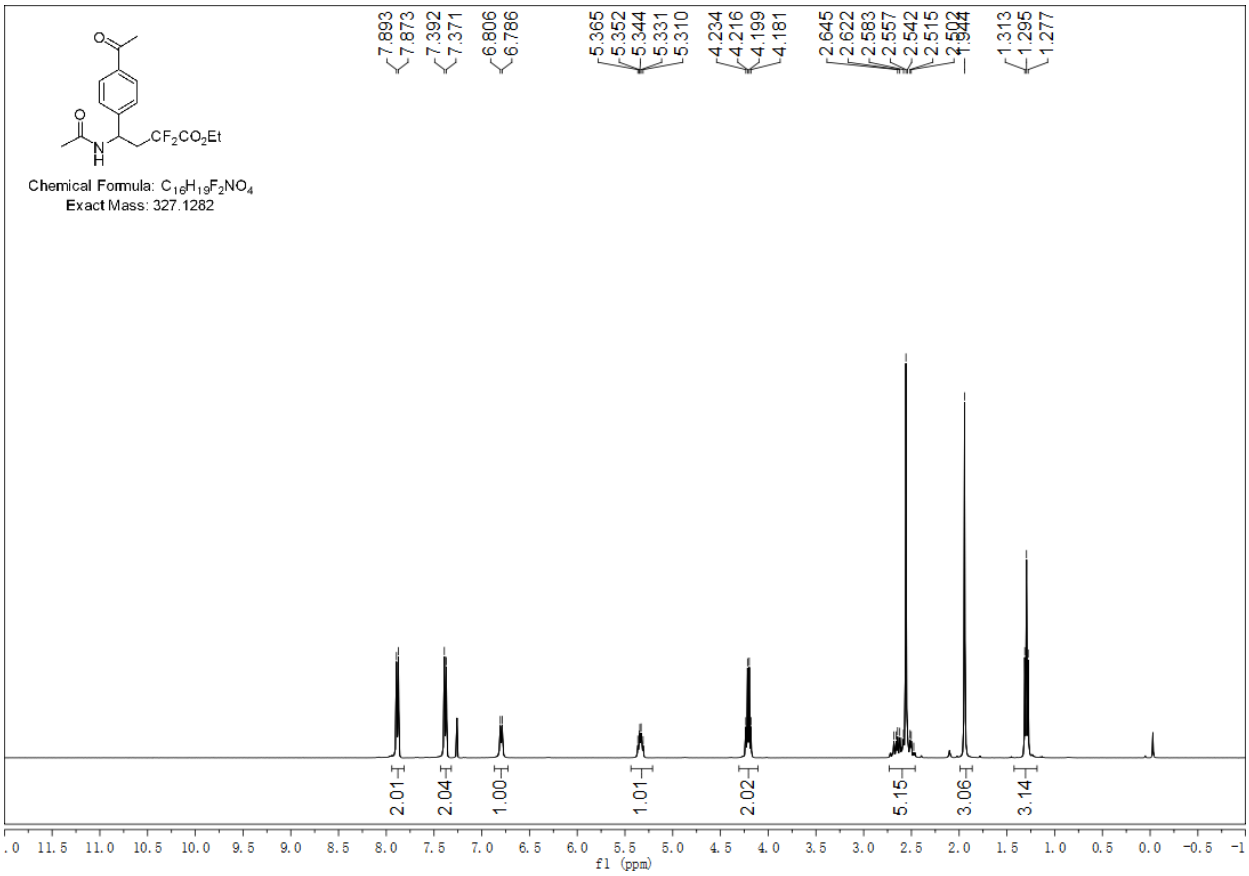
Ethyl 3-(1-acetamido-4-ethoxy-3,3-difluoro-4-oxobutyl)benzoate (12)

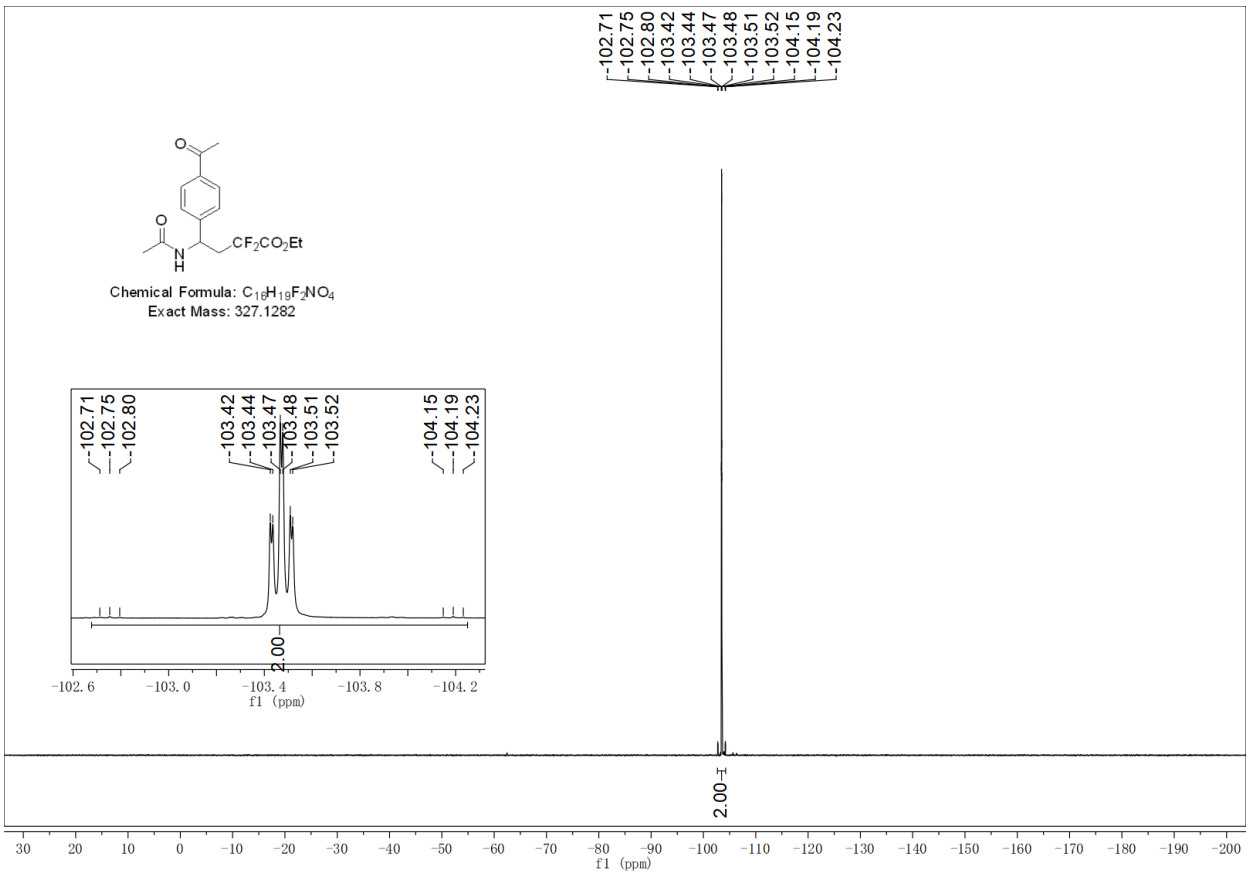


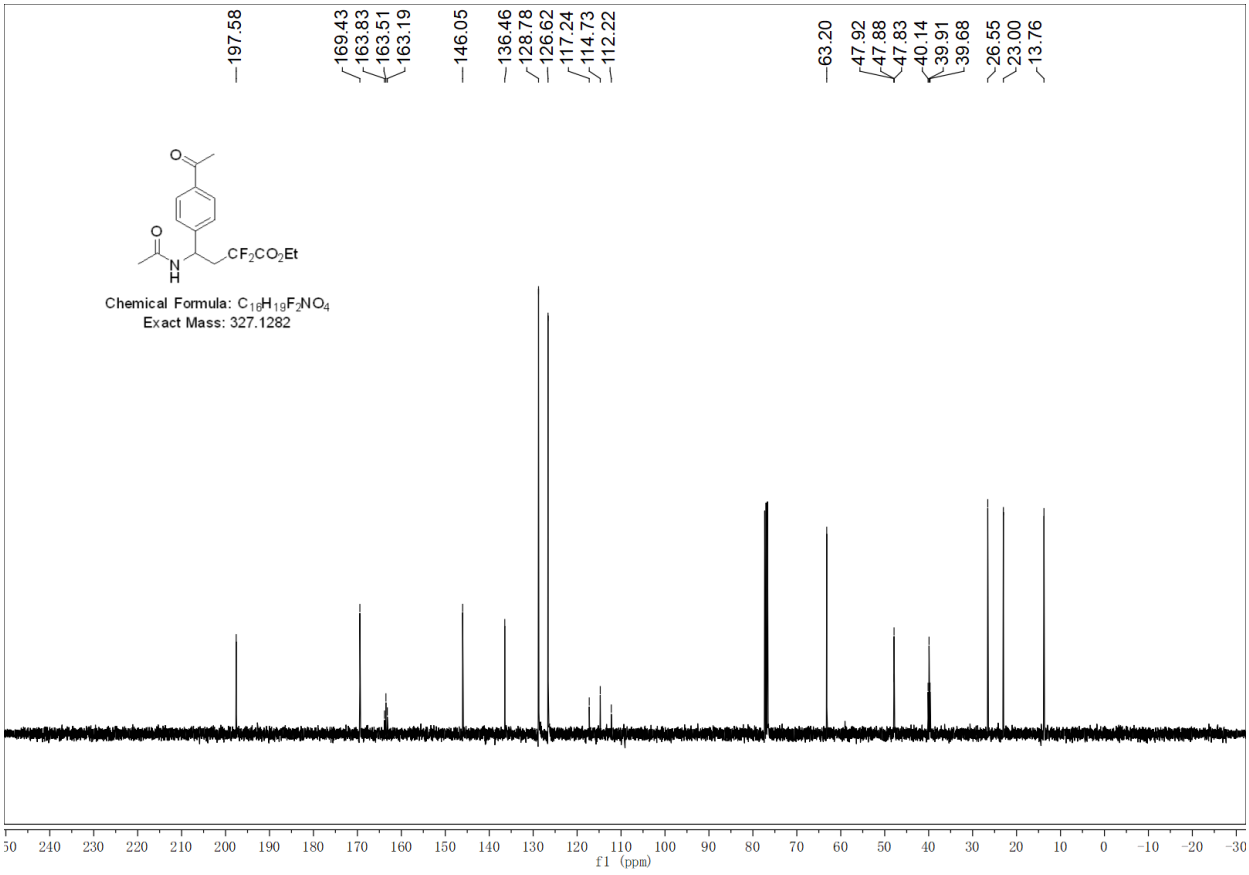




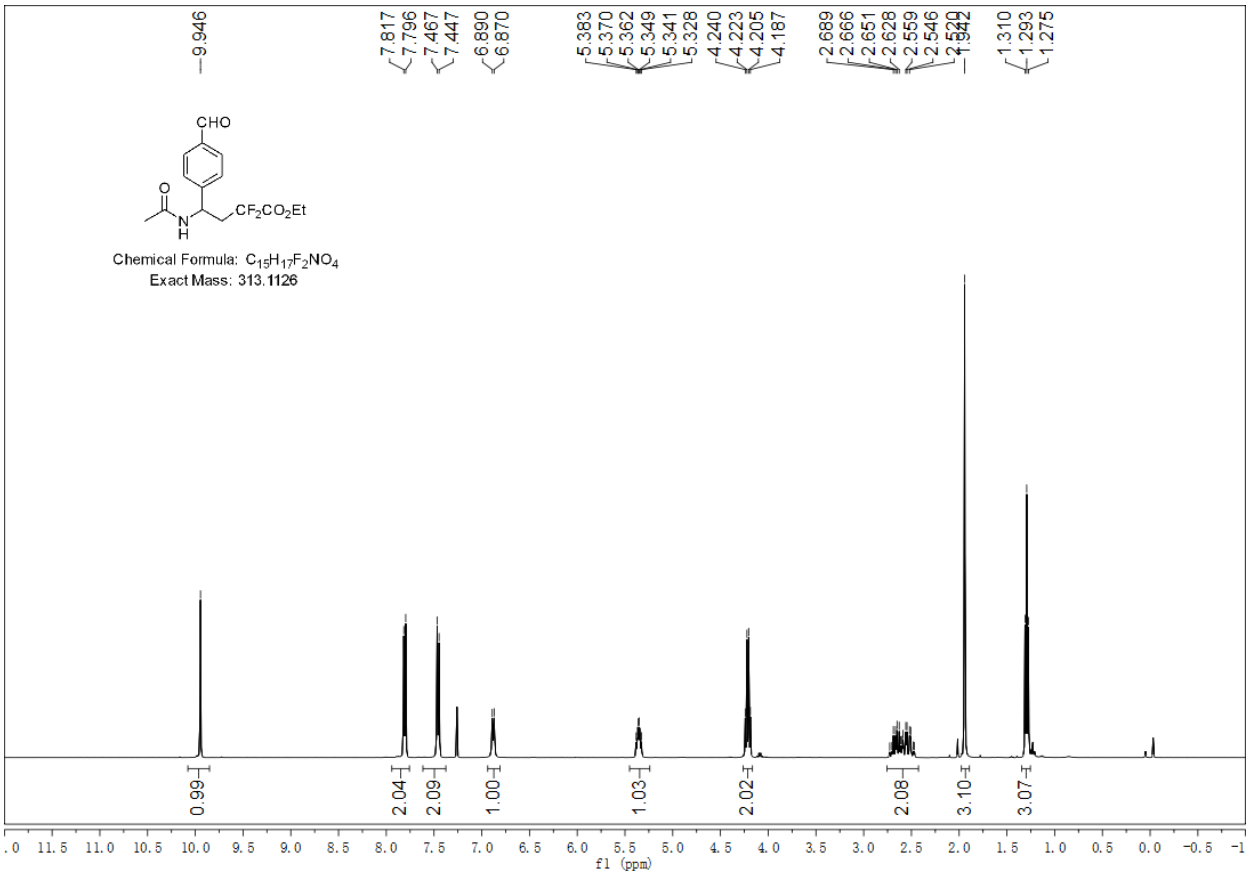
Ethyl 4-acetamido-4-(4-acetylphenyl)-2,2-difluorobutanoate (13)

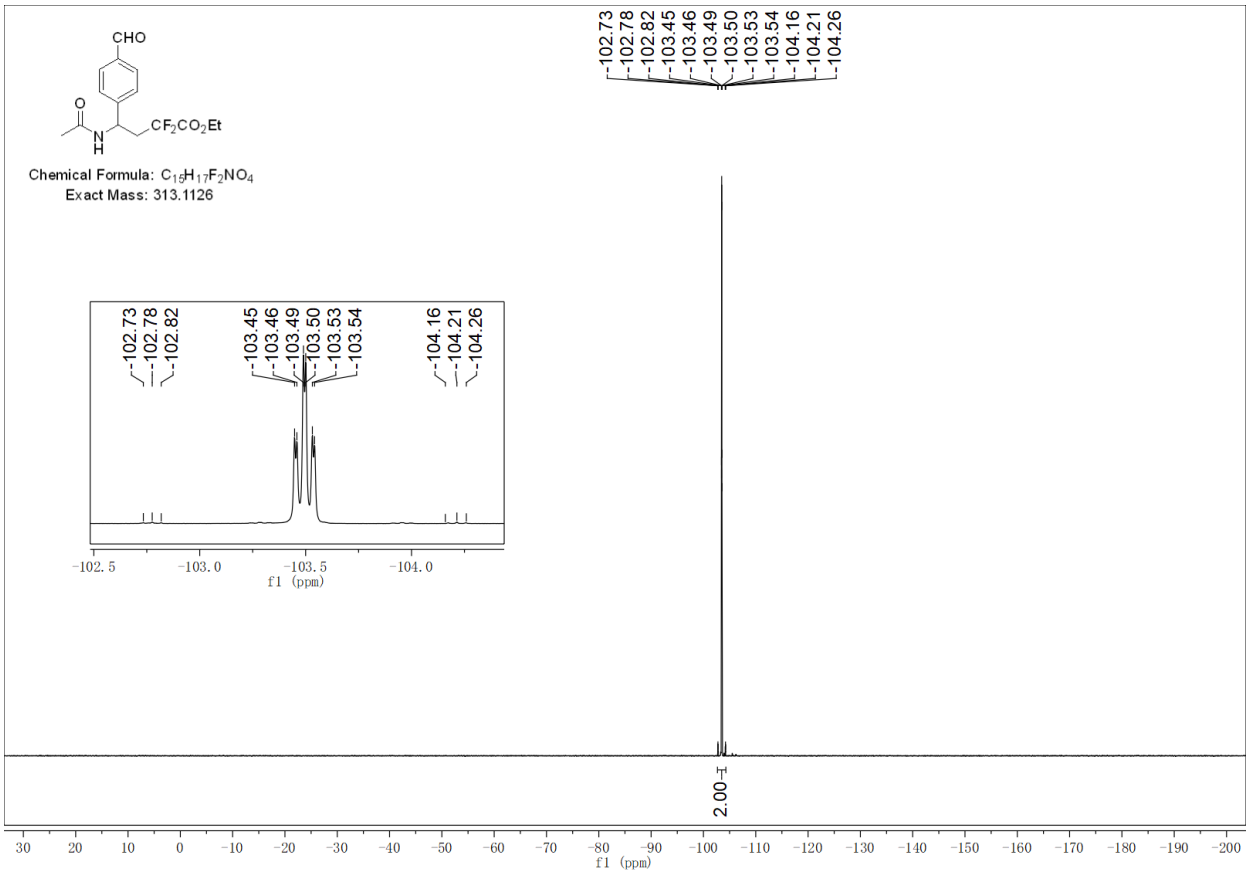


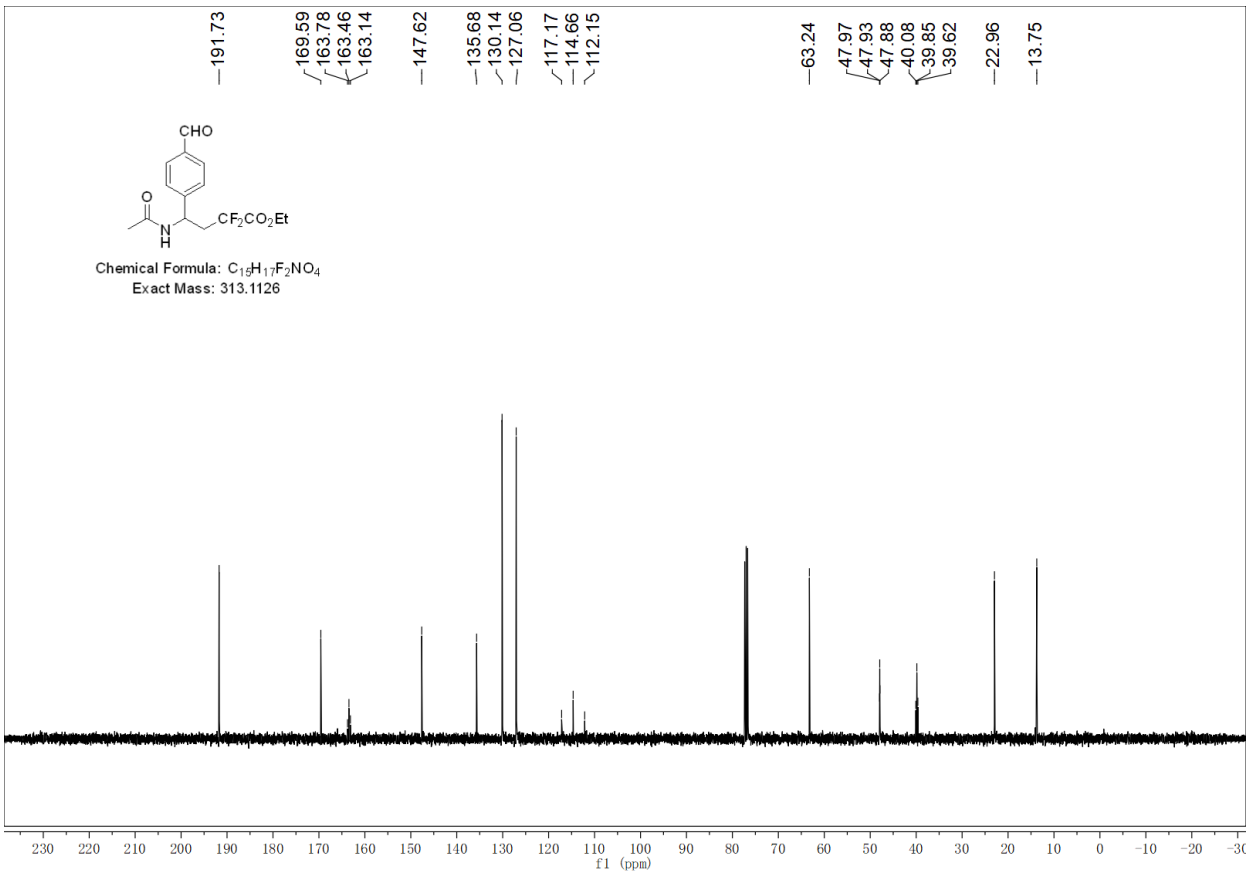

-102.71
-102.75
-102.80
-103.42
-103.44
-103.47
-103.48
-103.51
-103.52
-104.15
-104.19
-104.23
Chemical Formula: C16H19F2NO4
Exact Mass: 327.1282
2.00
2.00
f1 (ppm)
f1 (ppm)


197.58
169.43
163.83
163.51
163.19
146.05
136.46
128.78
126.62
117.24
114.73
112.22
63.20
47.92
47.88
47.83
40.14
39.91
39.68
26.55
23.00
13.76
Chemical Formula: C16H19F2NO4
Exact Mass: 327.1282
f1 (ppm)

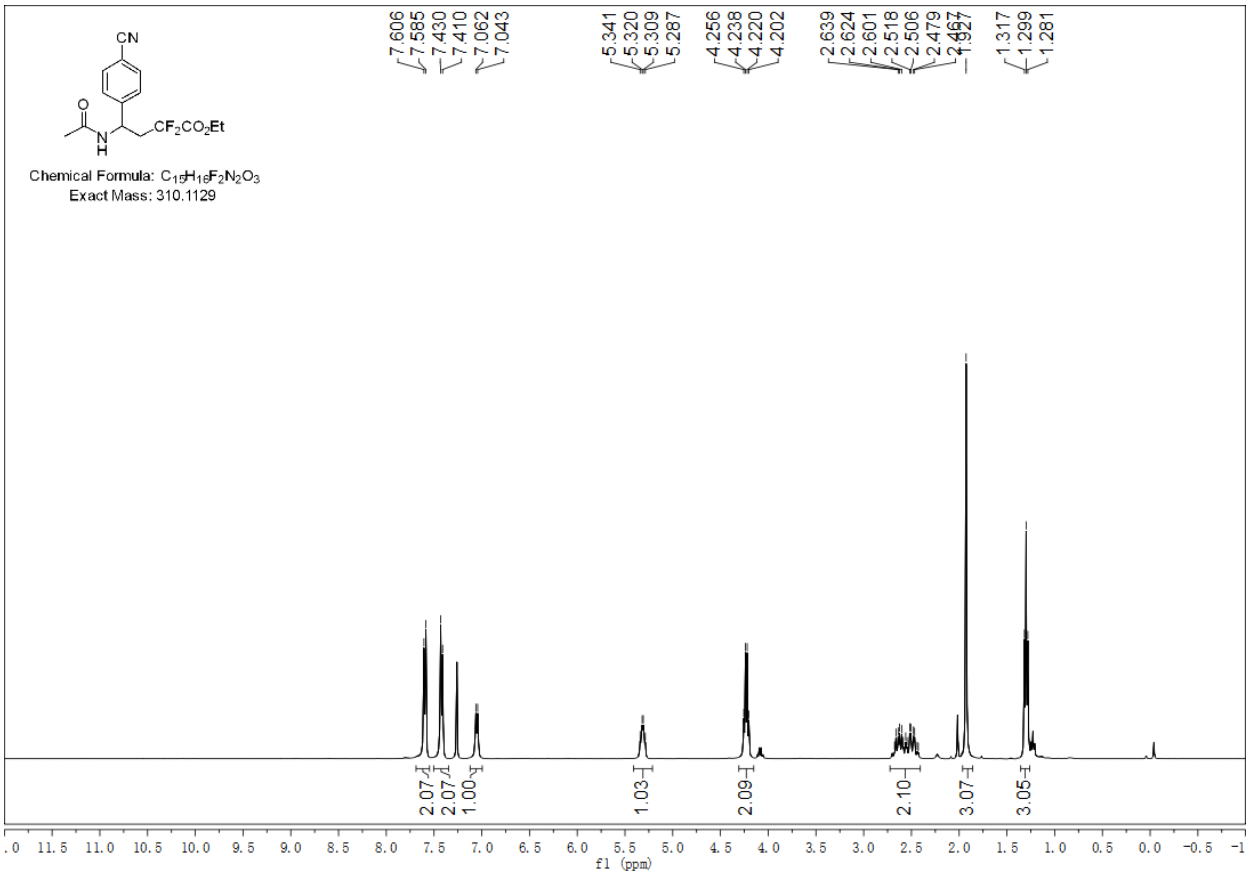
Ethyl 4-acetamido-2,2-difluoro-4-(4-formylphenyl)butanoate (14)

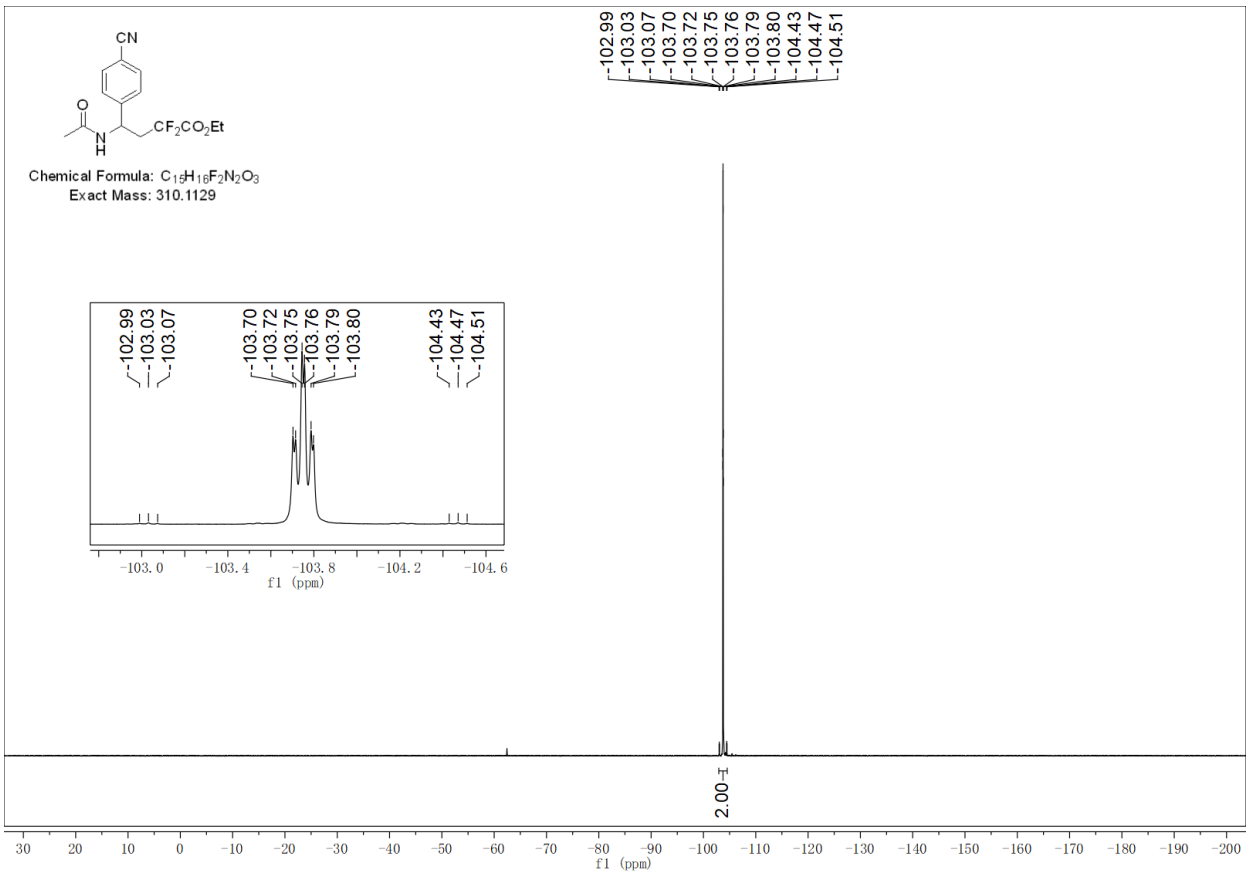


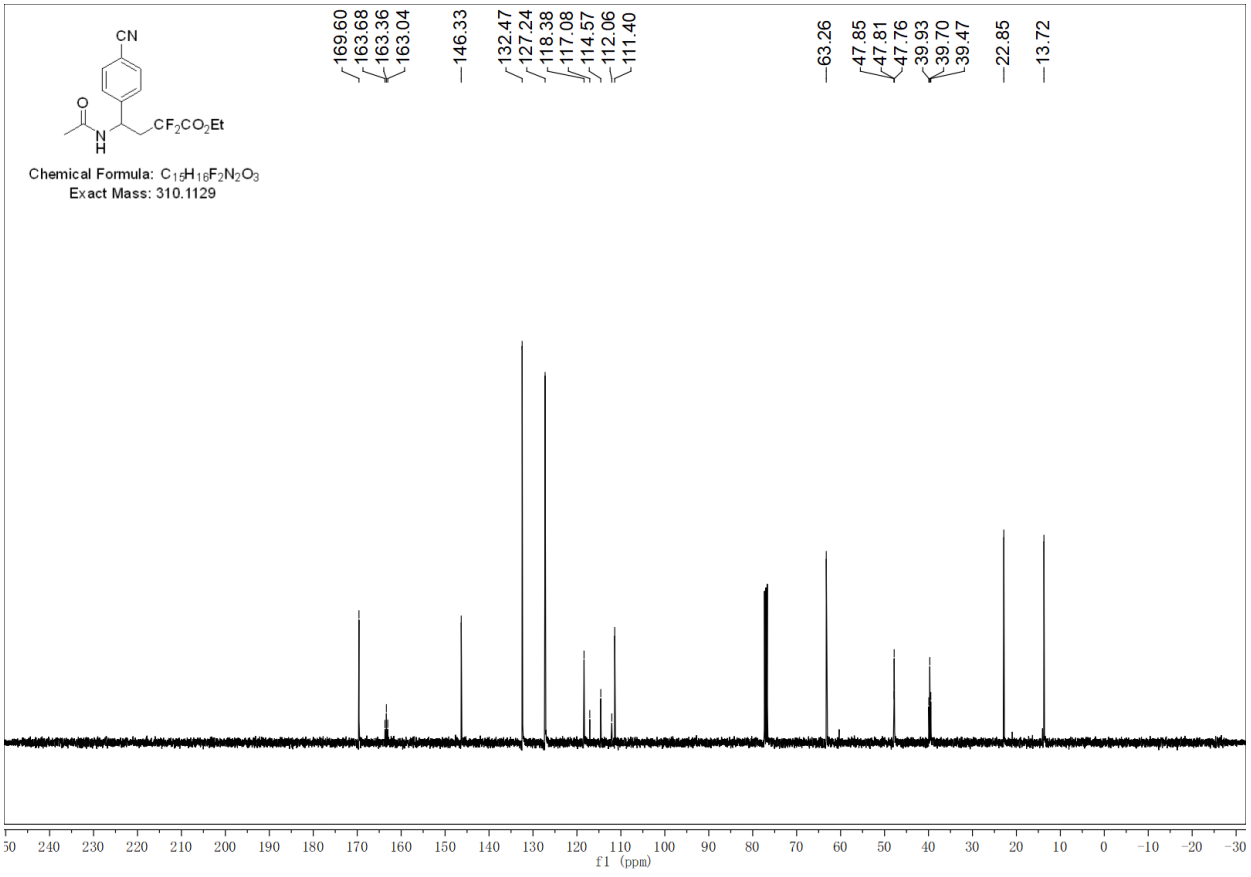




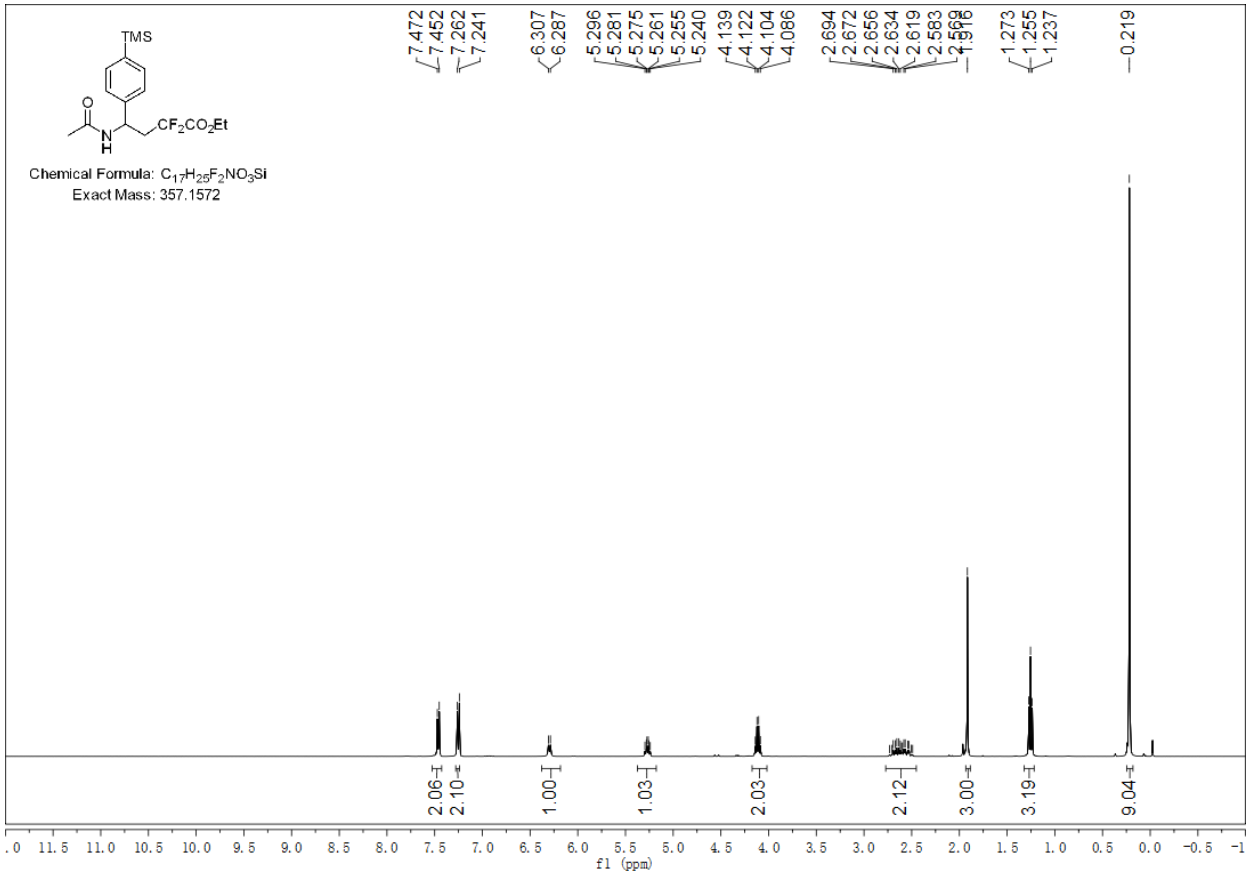
Ethyl 4-acetamido-4-(4-cyanophenyl)-2,2-difluorobutanoate (15)

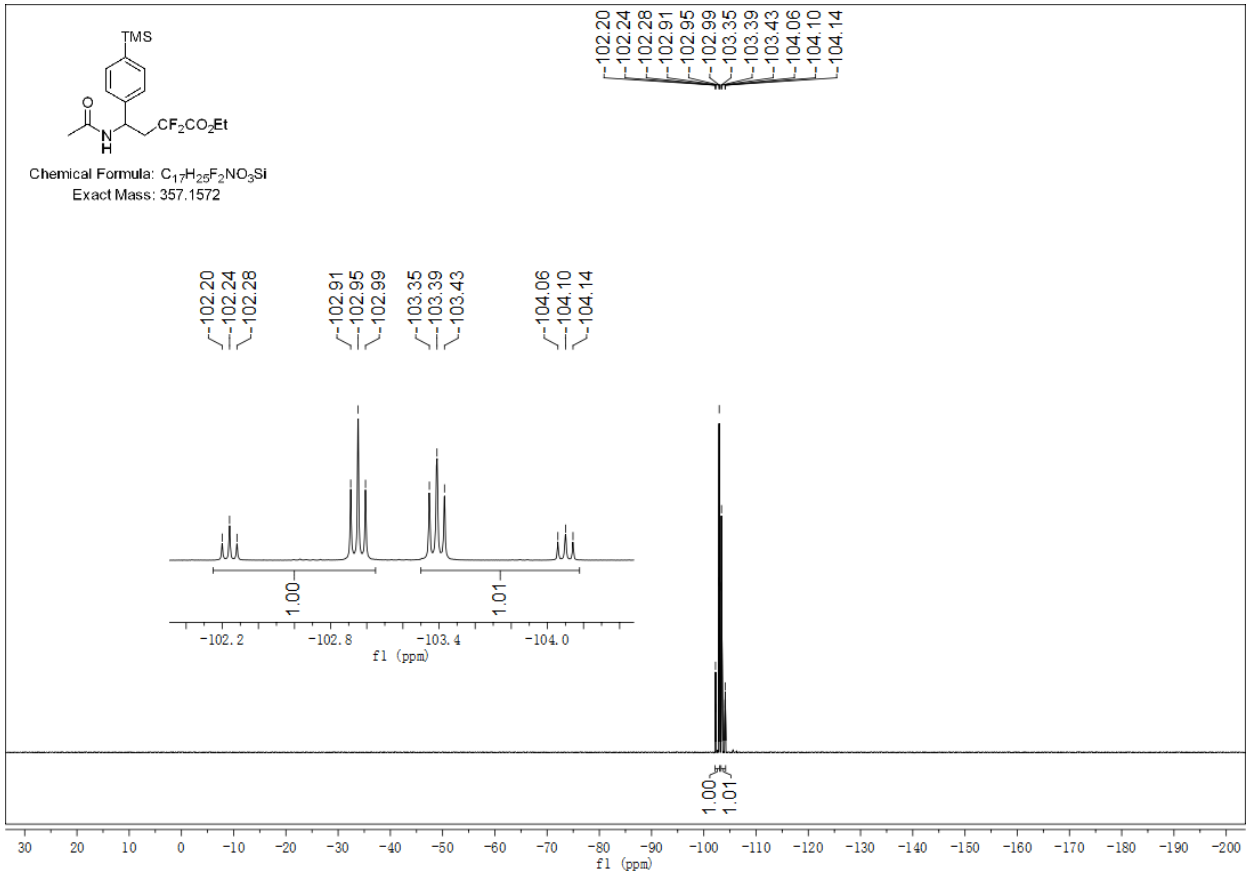


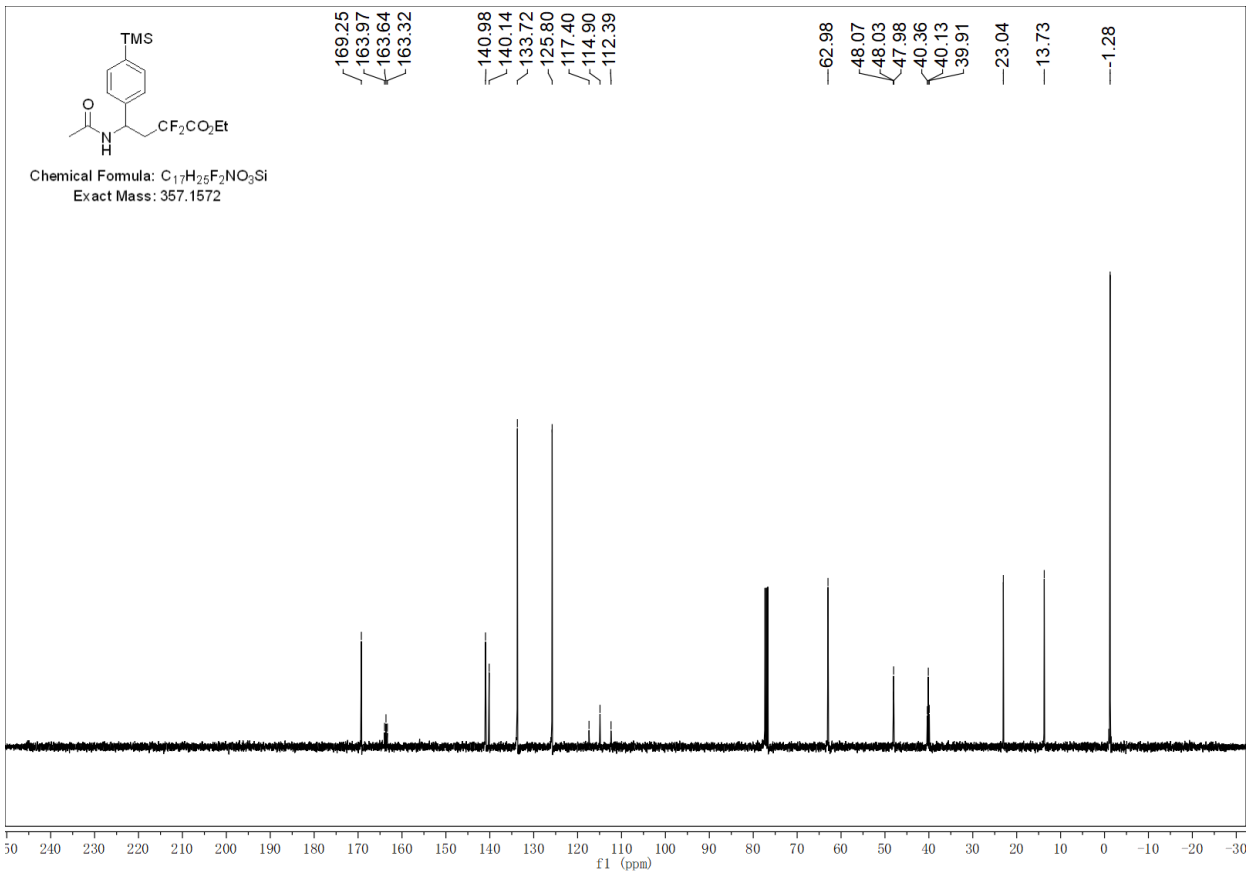

CN
O
N
H
CF2CO2Et
Chemical Formula: C15H16F2N2O3
Exact Mass: 310.1129
-102.99
-103.03
-103.07
-103.70
-103.72
-103.75
-103.76
-103.79
-103.80
-104.43
-104.47
-104.51
2.00
f1 (ppm)


CN
O
N
H
CF2CO2Et
Chemical Formula: C15H16F2N2O3
Exact Mass: 310.1129
169.60
163.68
163.36
163.04
146.33
132.47
127.24
118.38
117.08
114.57
112.06
111.40
63.26
47.85
47.81
47.76
39.93
39.70
39.47
22.85
13.72
f1 (ppm)

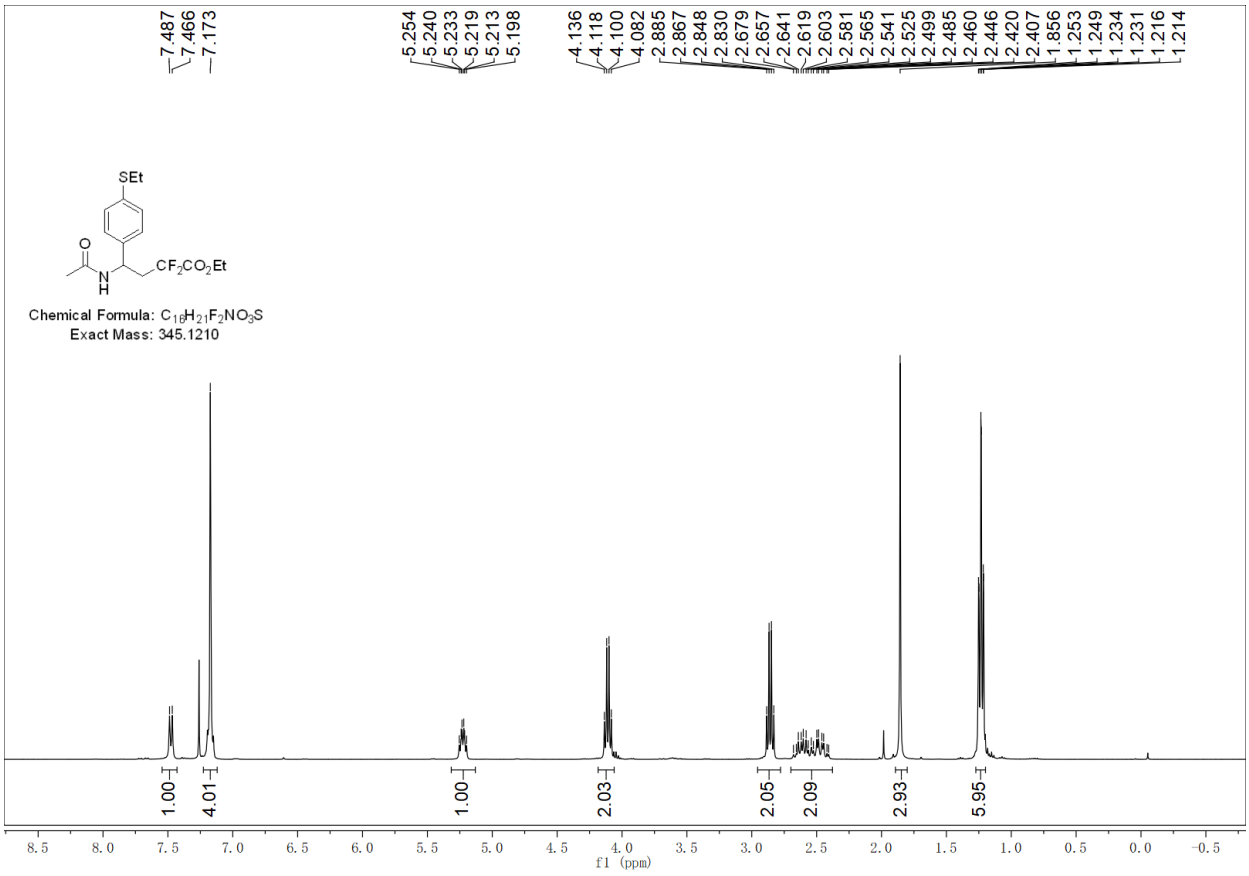
Ethyl 4-acetamido-2,2-difluoro-4-(4-(trimethylsilyl)phenyl)butanoate (16)

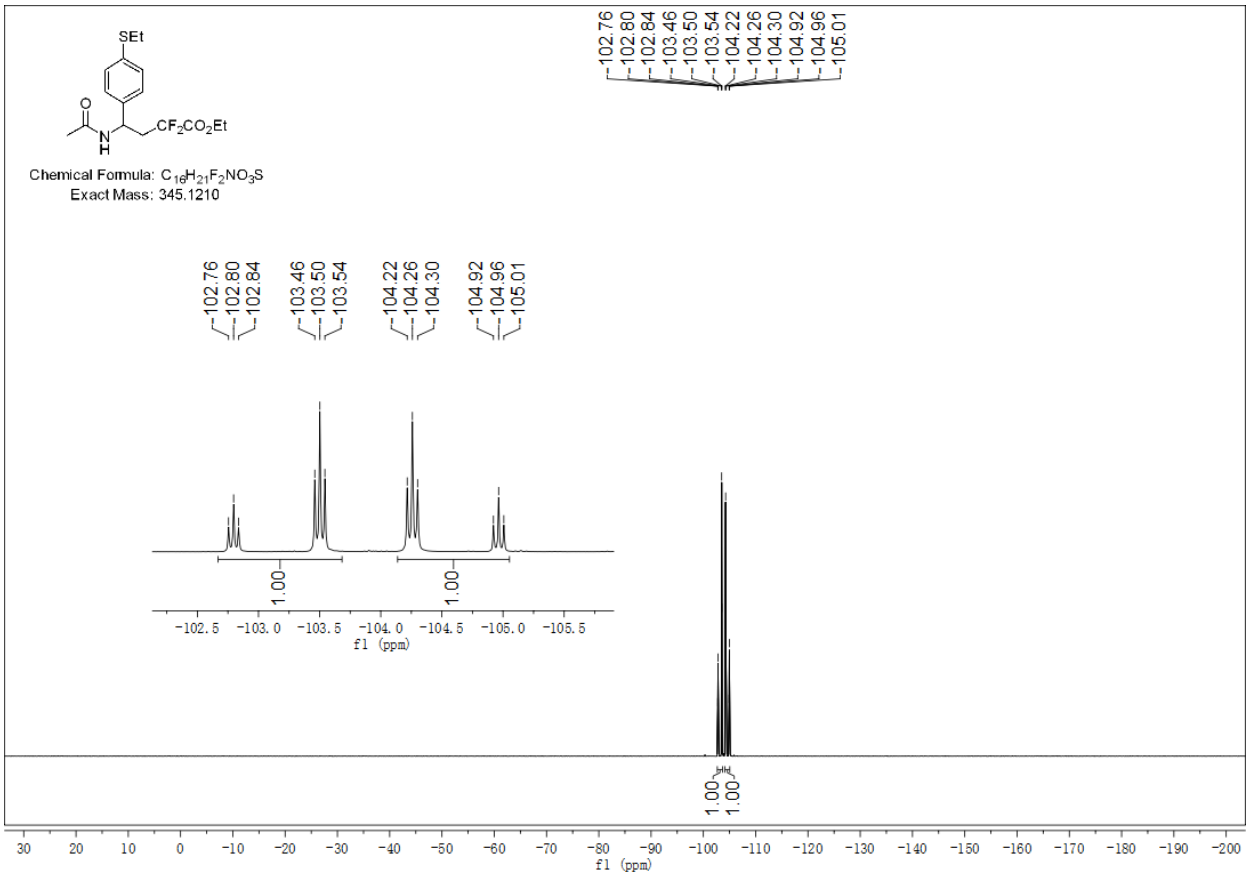


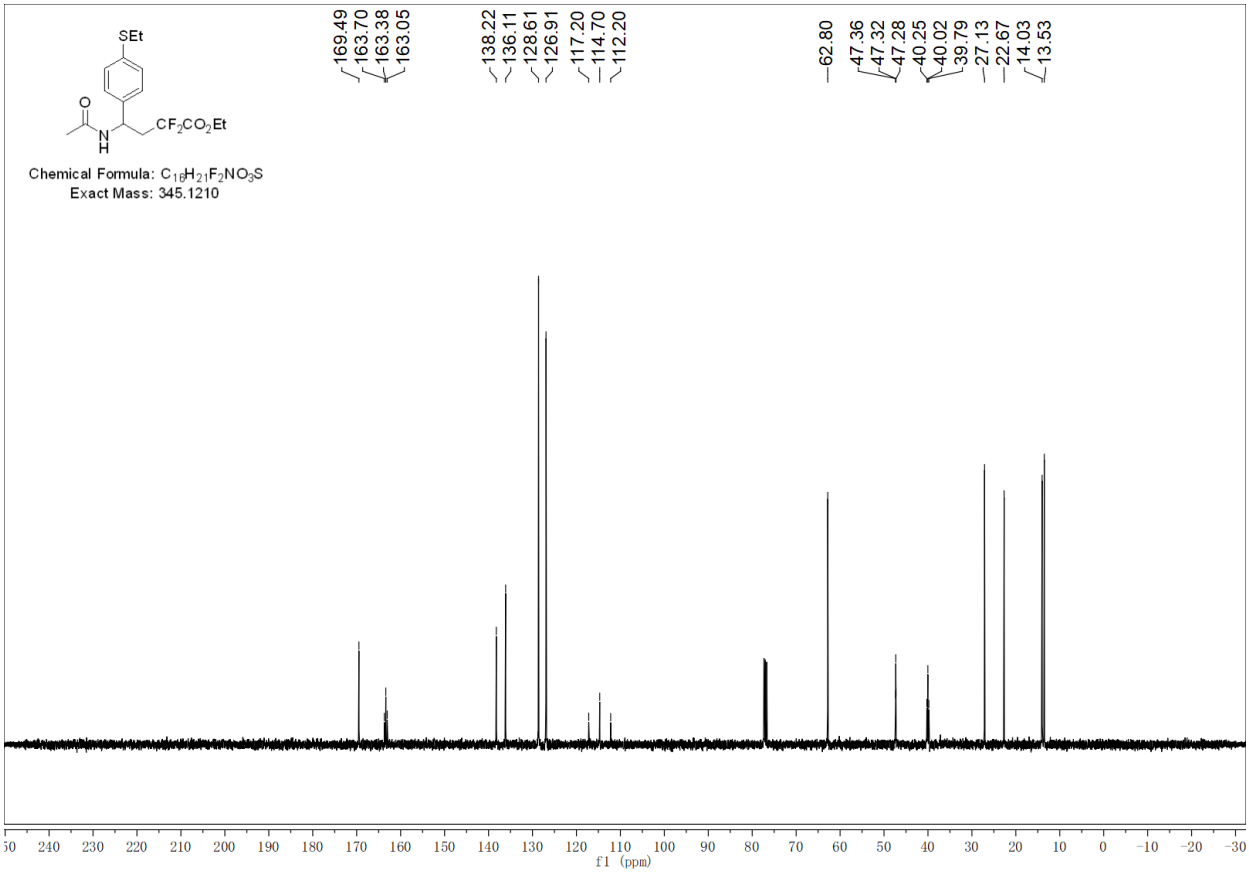




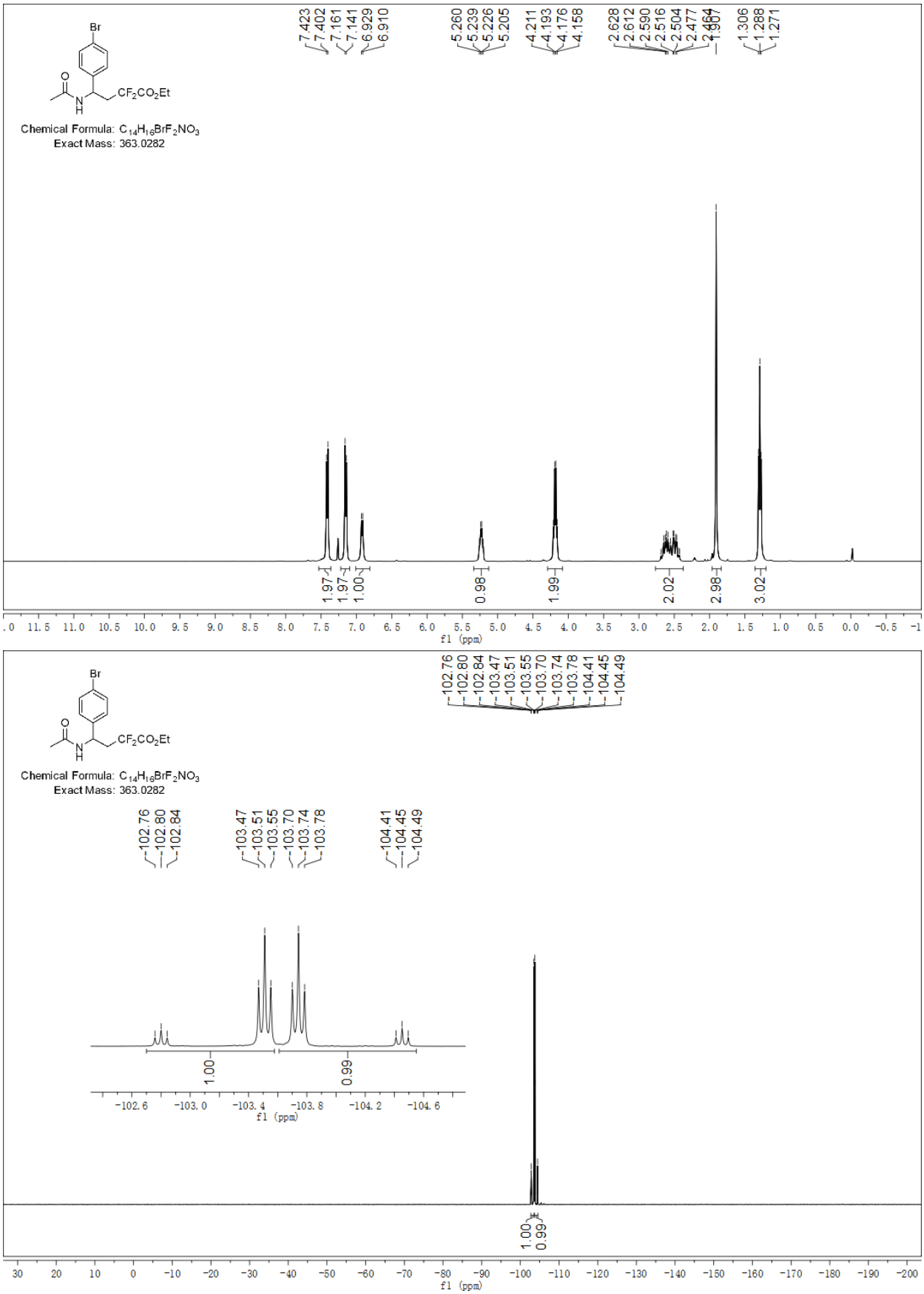
Ethyl 4-acetamido-4-(4-(ethylthio)phenyl)-2,2-difluorobutanoate (17)

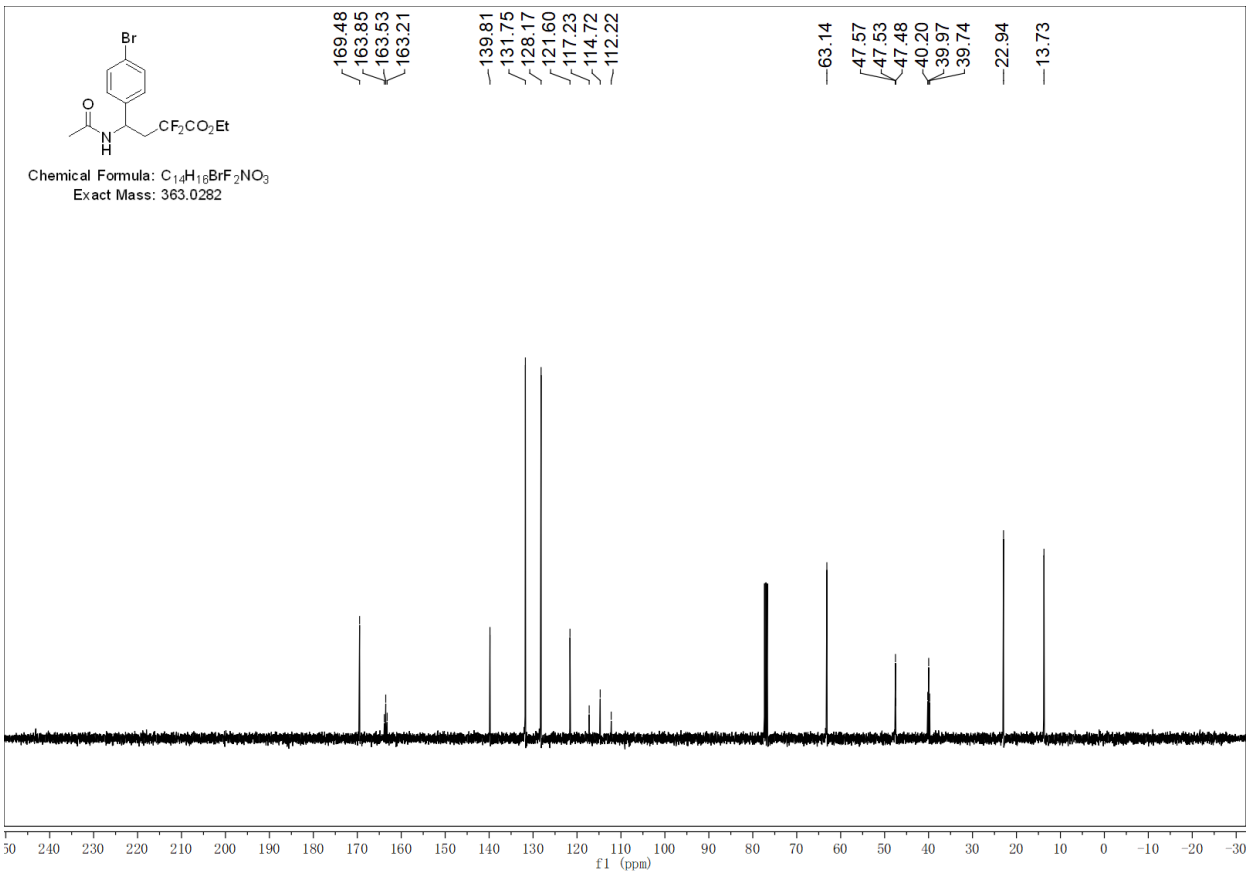



SEt
CF2CO2Et
Chemical Formula: C16H21F2NO3S
Exact Mass: 345.1210
102.76
102.80
102.84
103.46
103.50
103.54
104.22
104.26
104.30
104.92
104.96
105.01
1.00
1.00
1.00
1.00
f1 (ppm)

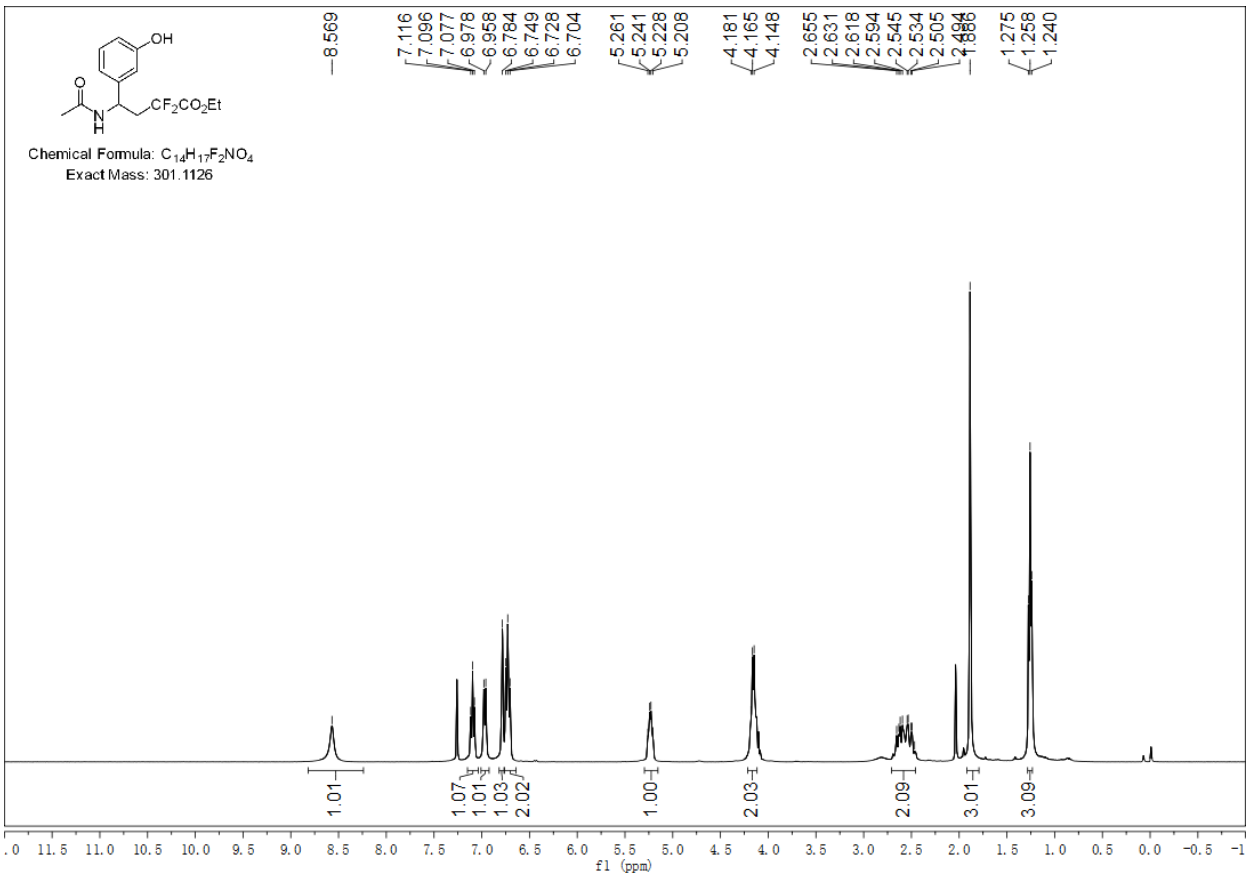

SEt
CF2CO2Et
Chemical Formula: C16H21F2NO3S
Exact Mass: 345.1210
169.49
163.70
163.38
163.05
138.22
136.11
128.61
126.91
117.20
114.70
112.20
62.80
47.36
47.32
47.28
40.25
40.02
39.79
27.13
22.67
14.03
13.53
f1 (ppm)

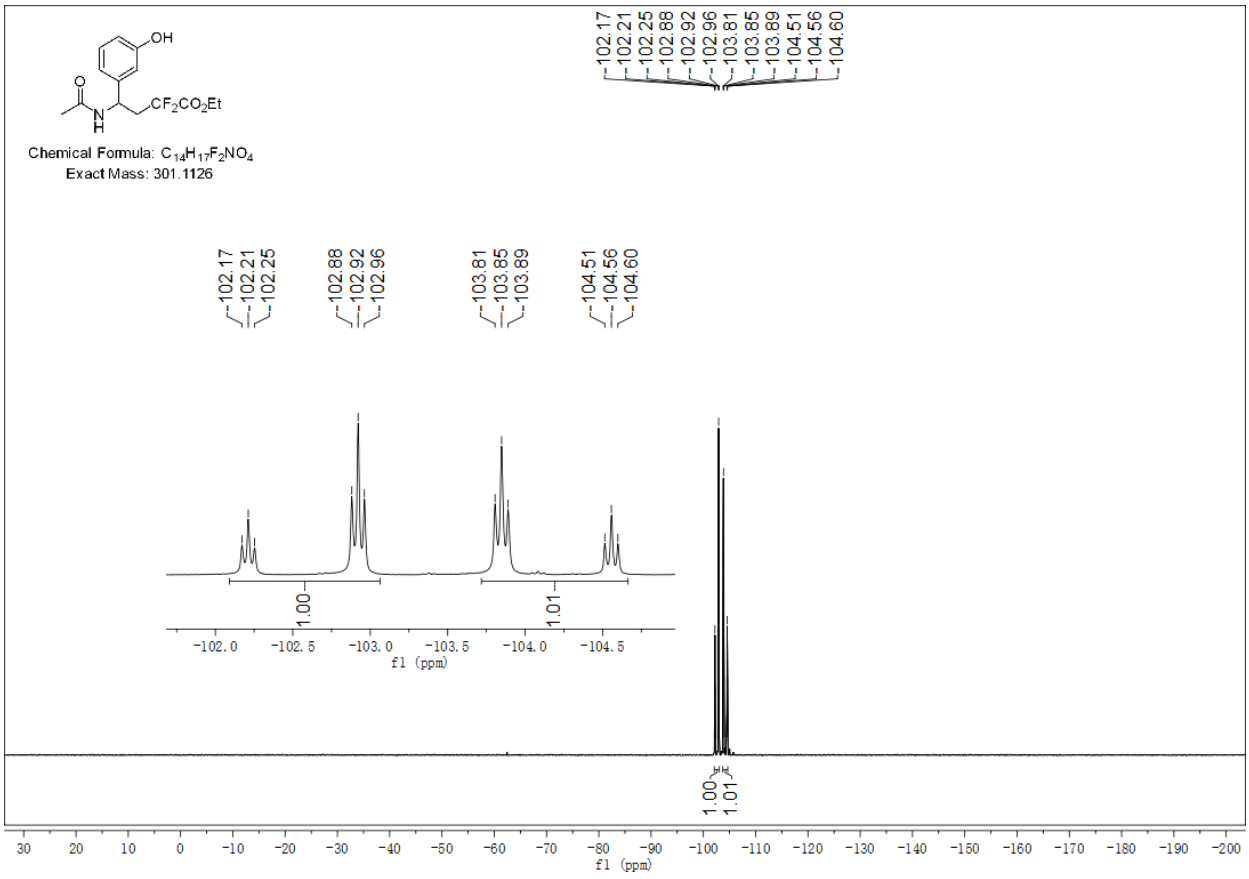
Ethyl 4-acetamido-4-(4-bromophenyl)-2,2-difluorobutanoate (18)

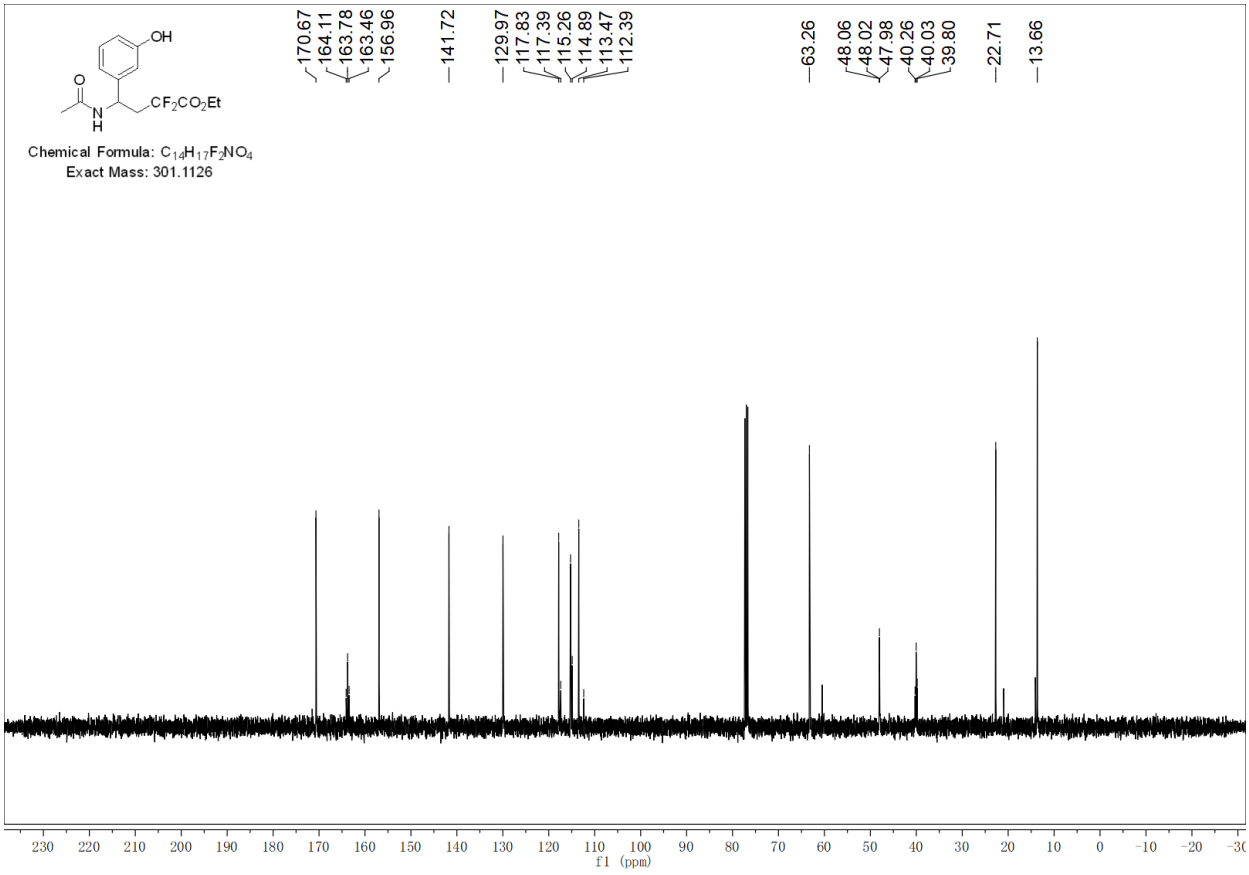




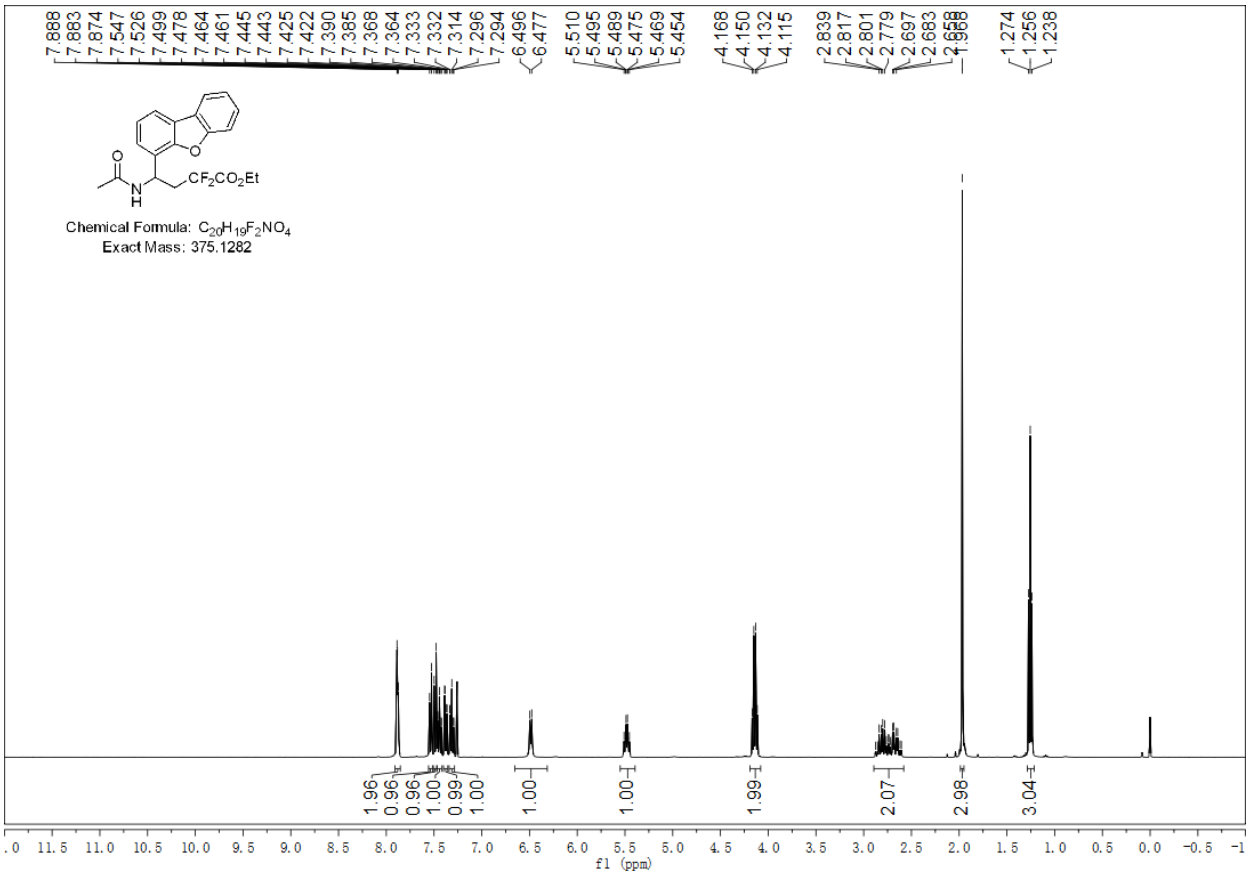
Ethyl 4-acetamido-2,2-difluoro-4-(3-hydroxyphenyl)butanoate (19)

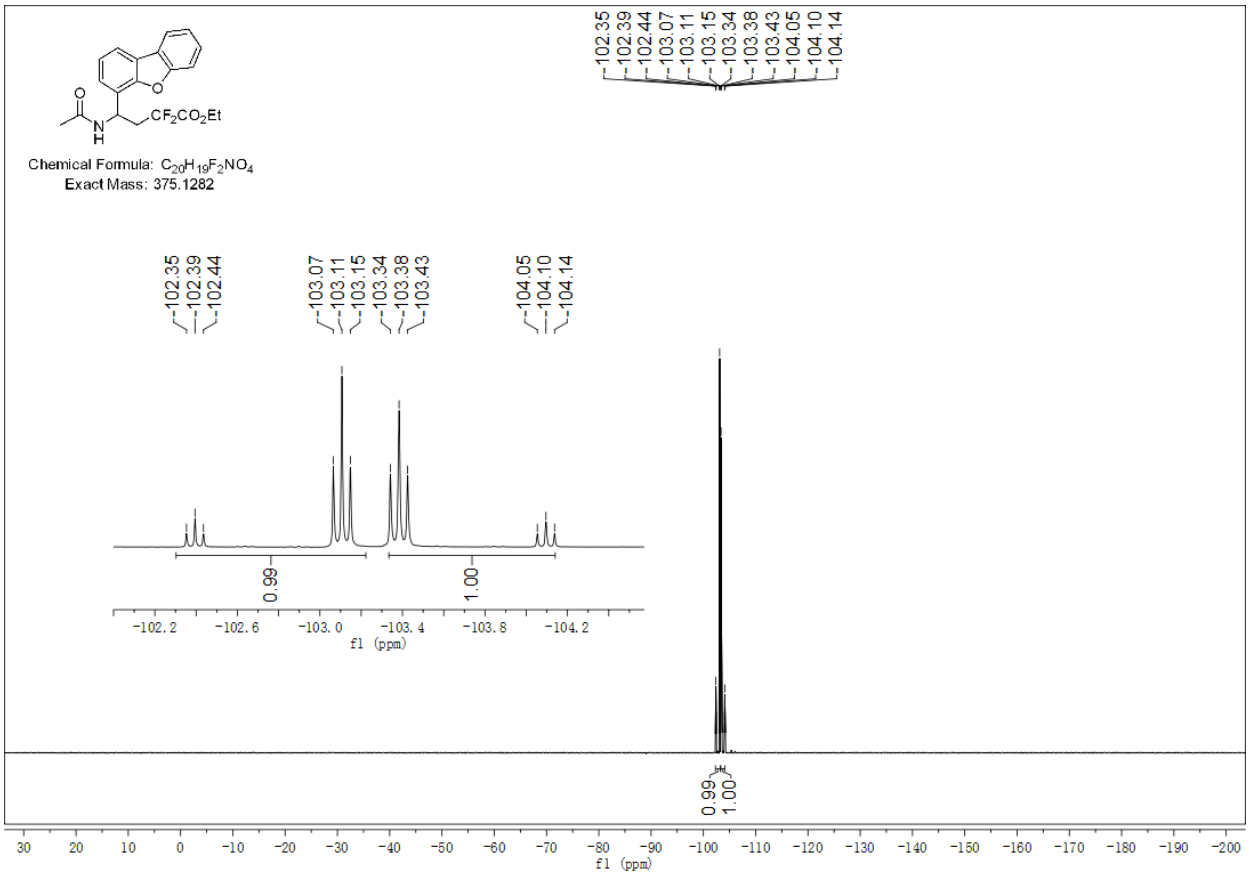


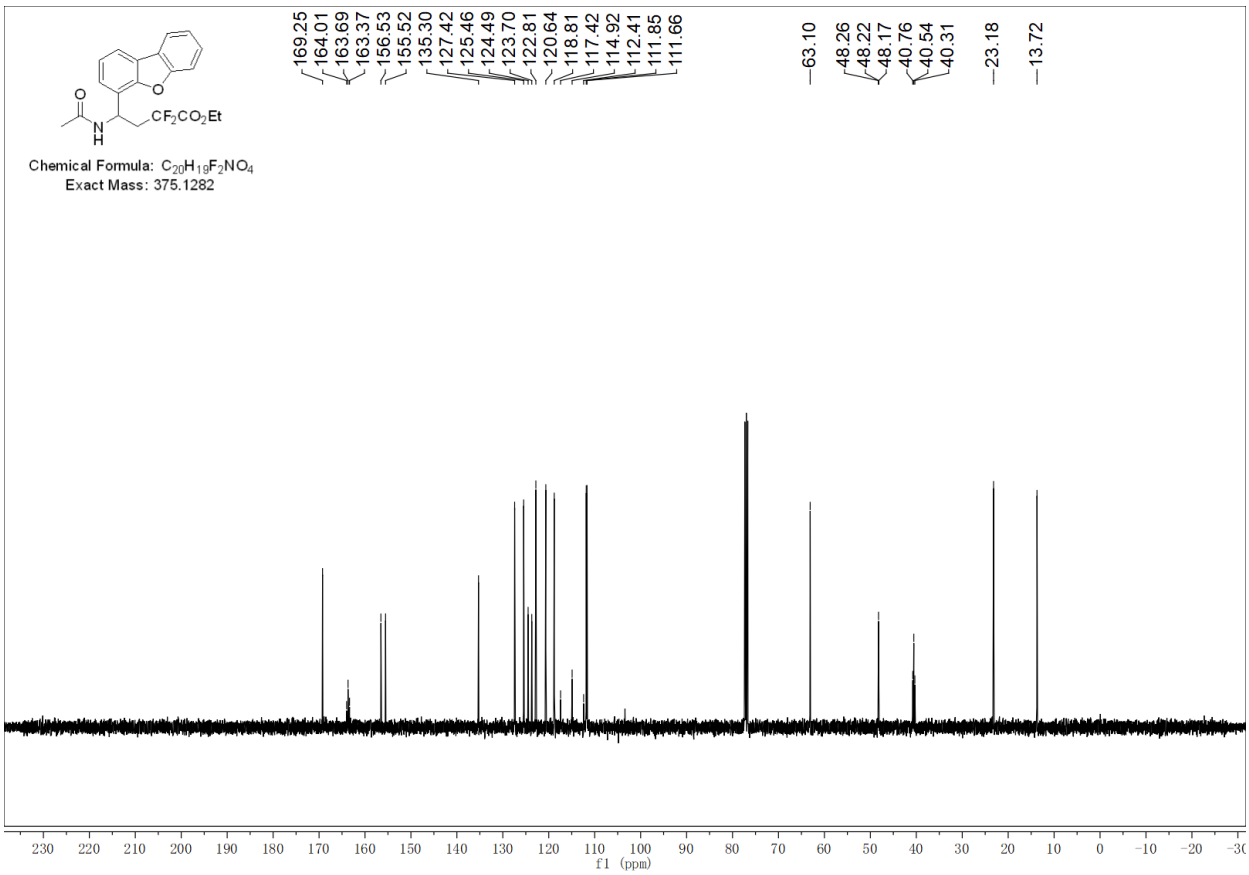

OH
O
N
H
CF2CO2Et
Chemical Formula: C14H17F2NO4
Exact Mass: 301.1126
102.17
102.21
102.25
102.88
102.92
102.96
103.81
103.85
103.89
104.51
104.56
104.60
1.00
1.01
f1 (ppm)


OH
O
N
H
CF2CO2Et
Chemical Formula: C14H17F2NO4
Exact Mass: 301.1126
170.67
164.11
163.78
163.46
156.96
141.72
129.97
117.83
117.39
115.26
114.89
113.47
112.39
63.26
48.06
48.02
47.98
40.26
40.03
39.80
22.71
13.66
f1 (ppm)

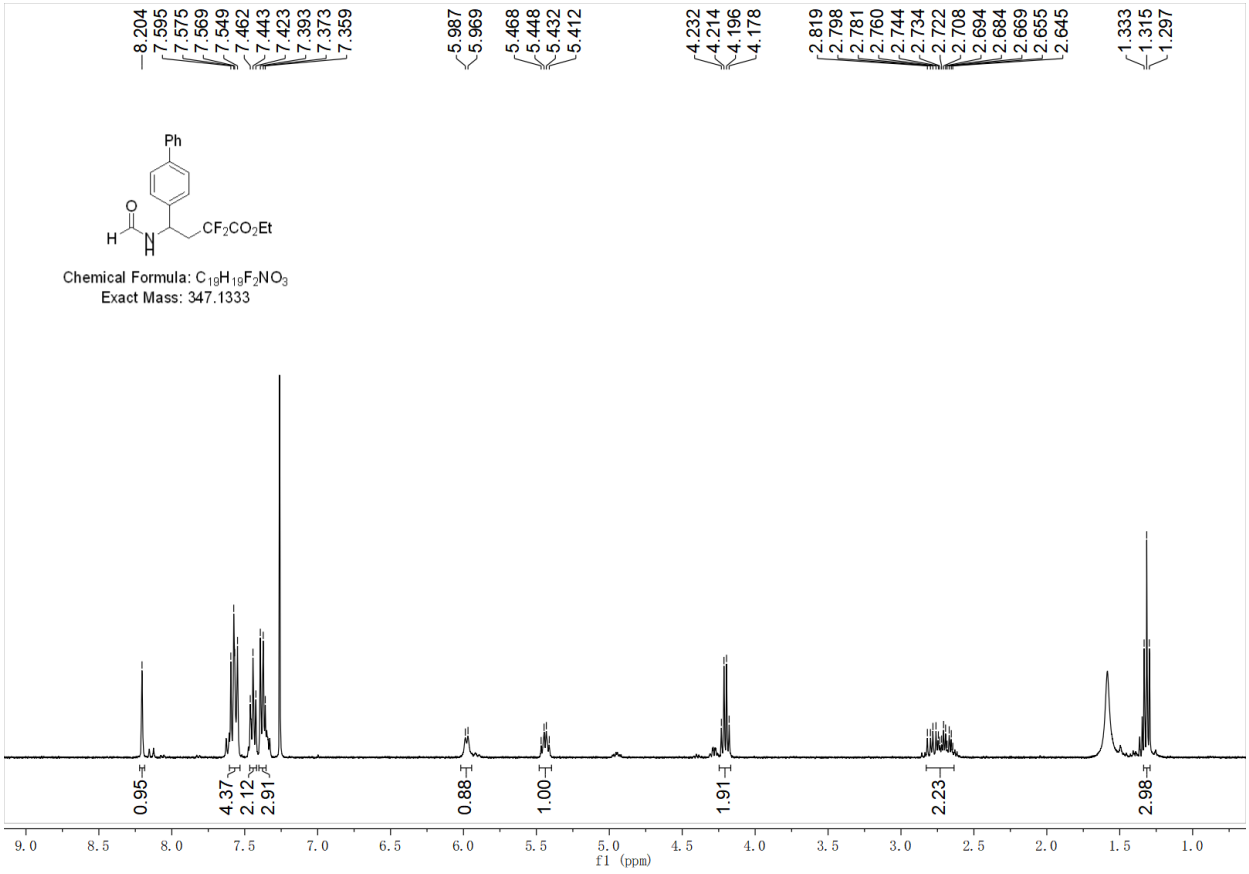
Ethyl 4-acetamido-4-(dibenzo[b,d]furan-4-yl)-2,2-difluorobutanoate (20)

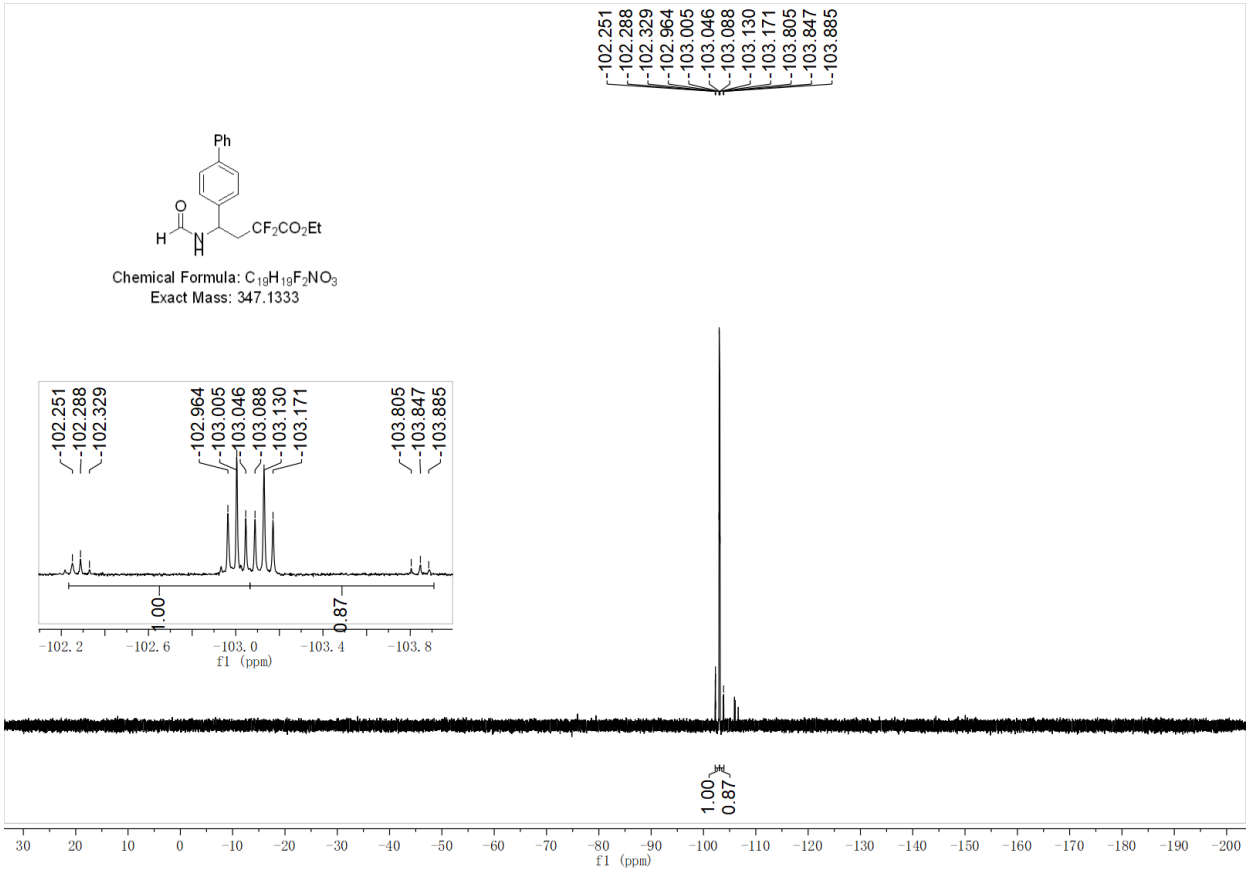


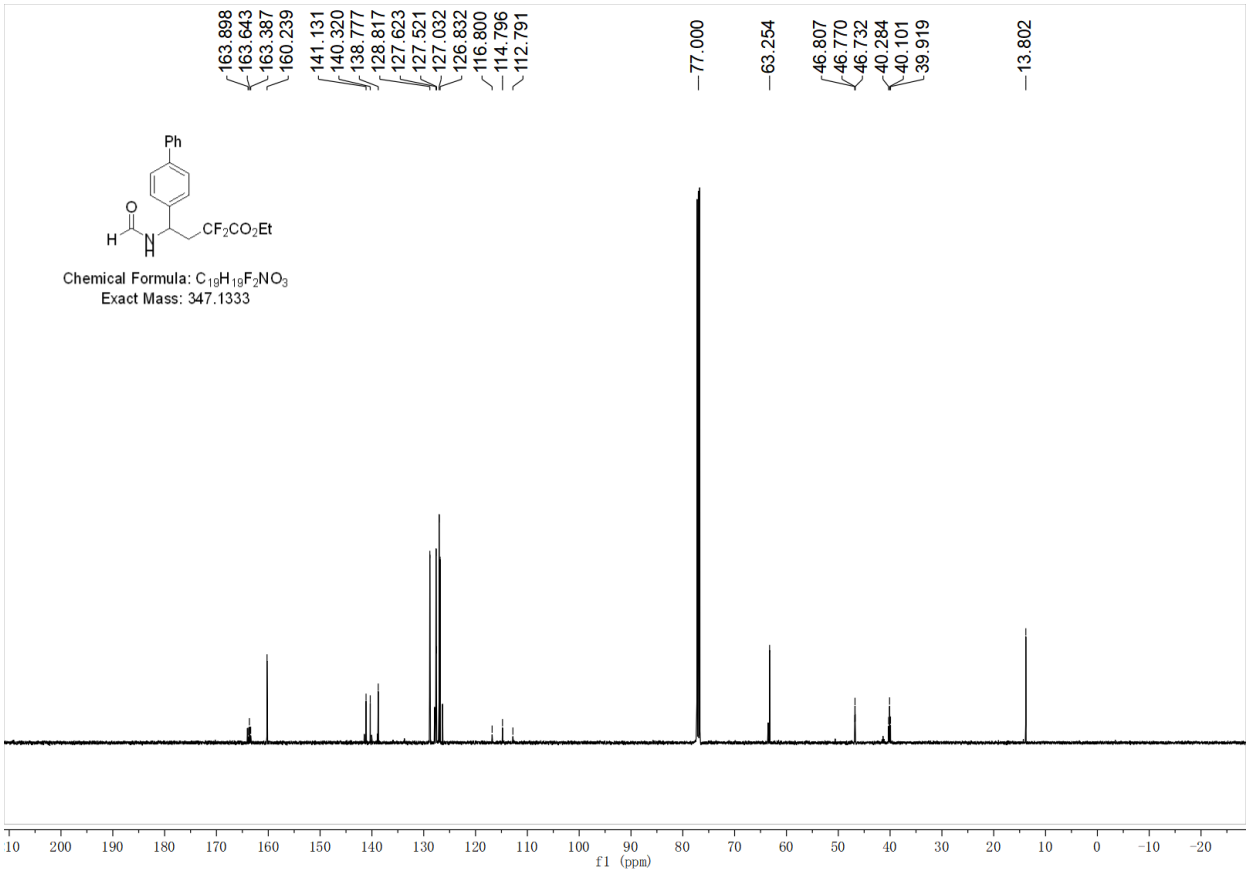




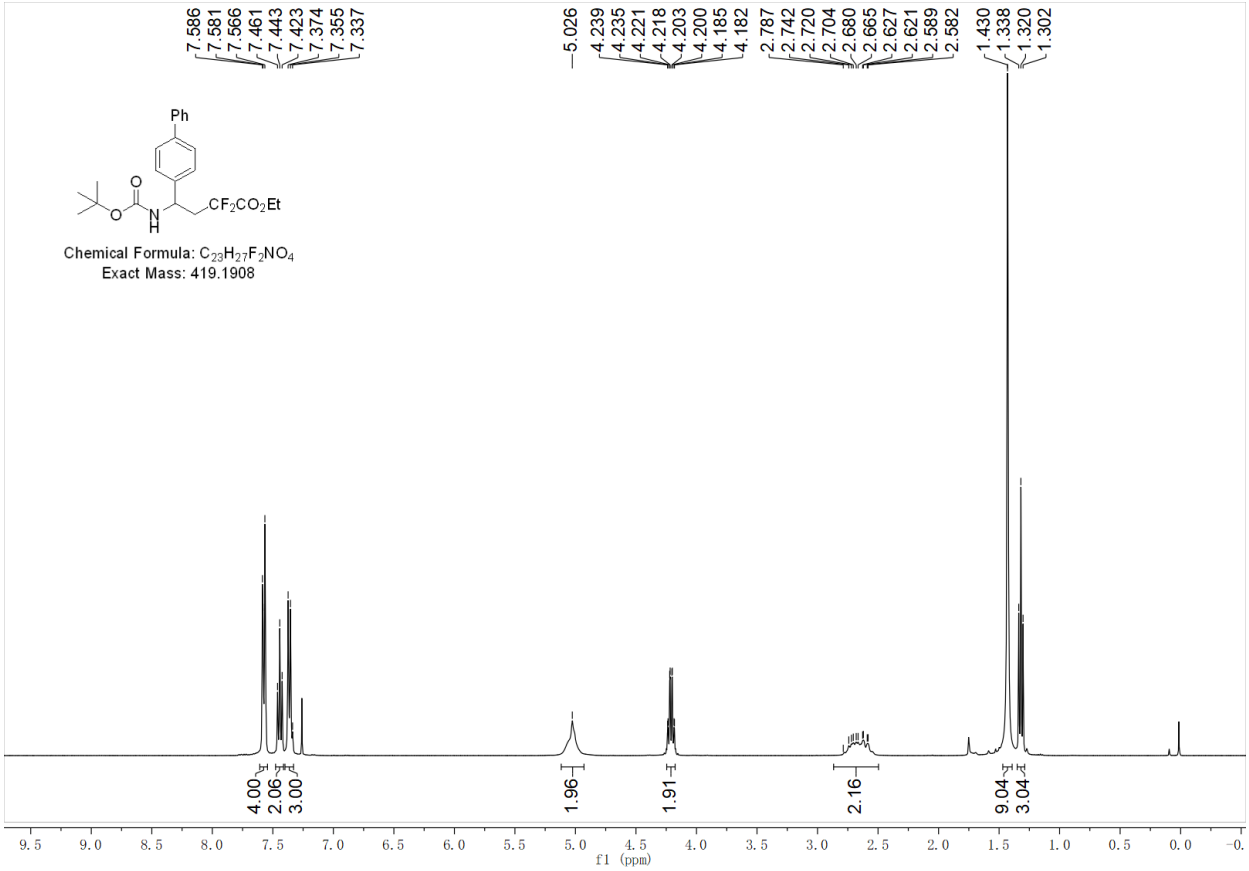
Ethyl 4-([1,1'-biphenyl]-4-yl)-2,2-difluoro-4-formamidobutanoate (21)

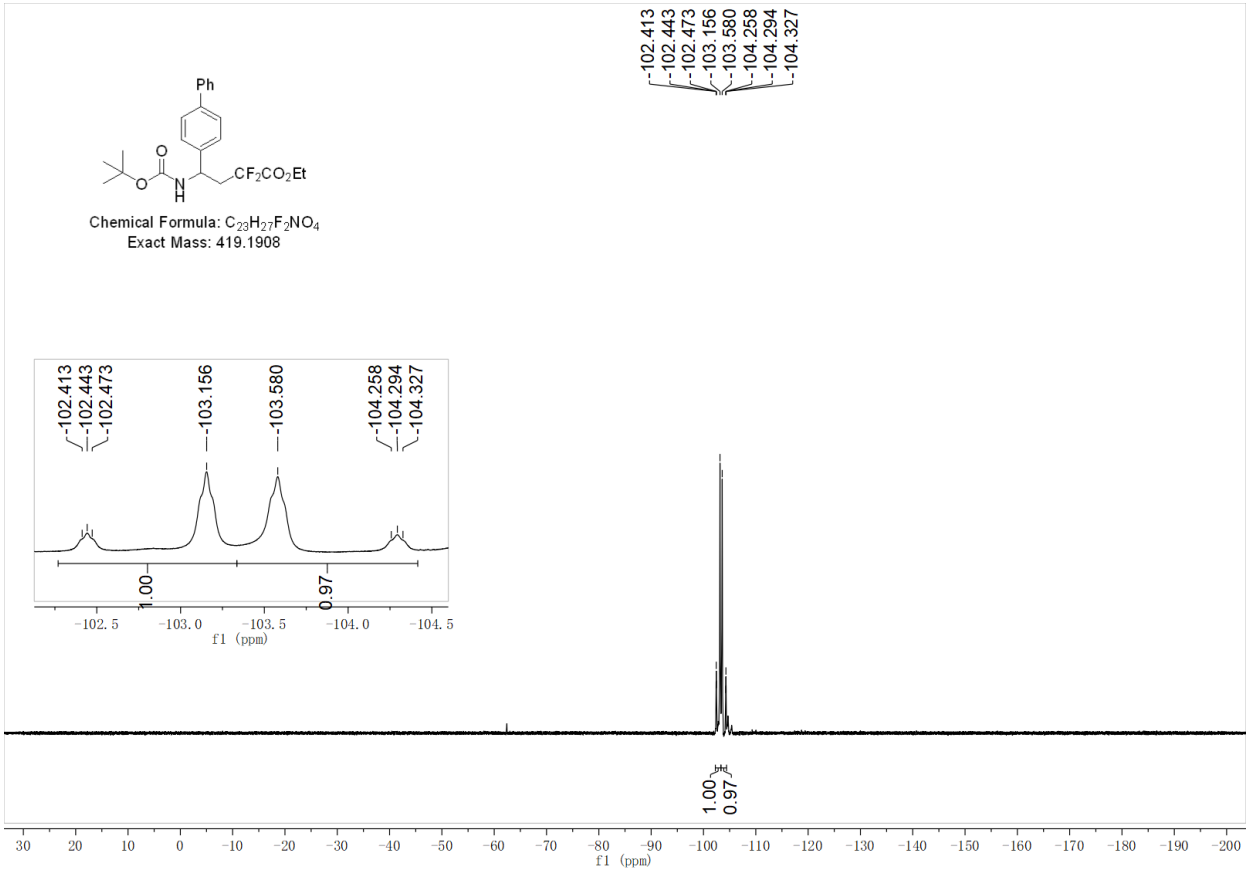


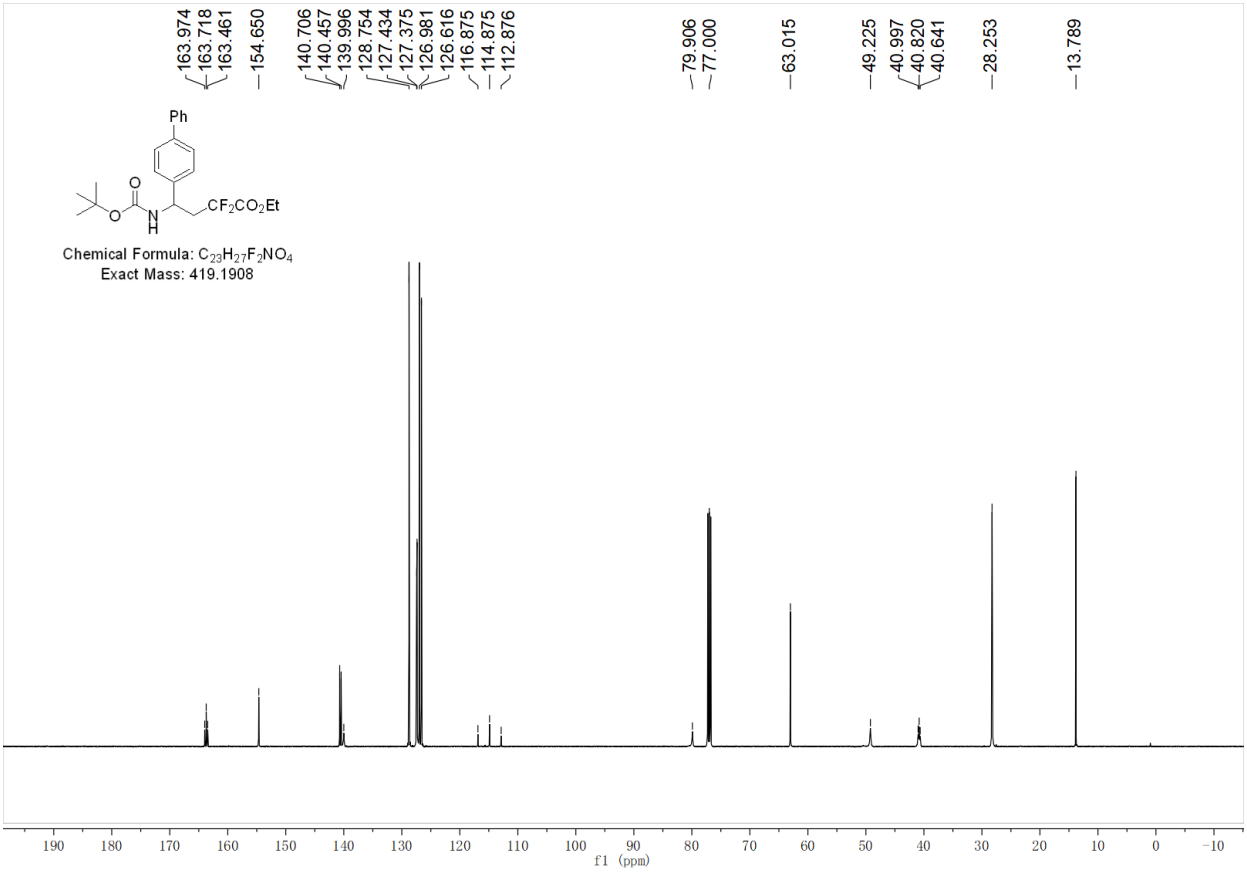

102.251
102.288
102.329
102.964
103.005
103.046
103.088
103.130
103.171
103.805
103.847
103.885
Ph
O
H
N
CF2CO2Et
Chemical Formula: C19H19F2NO3
Exact Mass: 347.1333
1.00
0.87
f1 (ppm)


163.898
163.643
163.387
160.239
141.131
140.320
138.777
128.817
127.623
127.521
127.032
126.832
116.800
114.796
112.791
77.000
63.254
46.807
46.770
46.732
40.284
40.101
39.919
13.802
Ph
O
H
N
CF2CO2Et
Chemical Formula: C19H19F2NO3
Exact Mass: 347.1333
f1 (ppm)

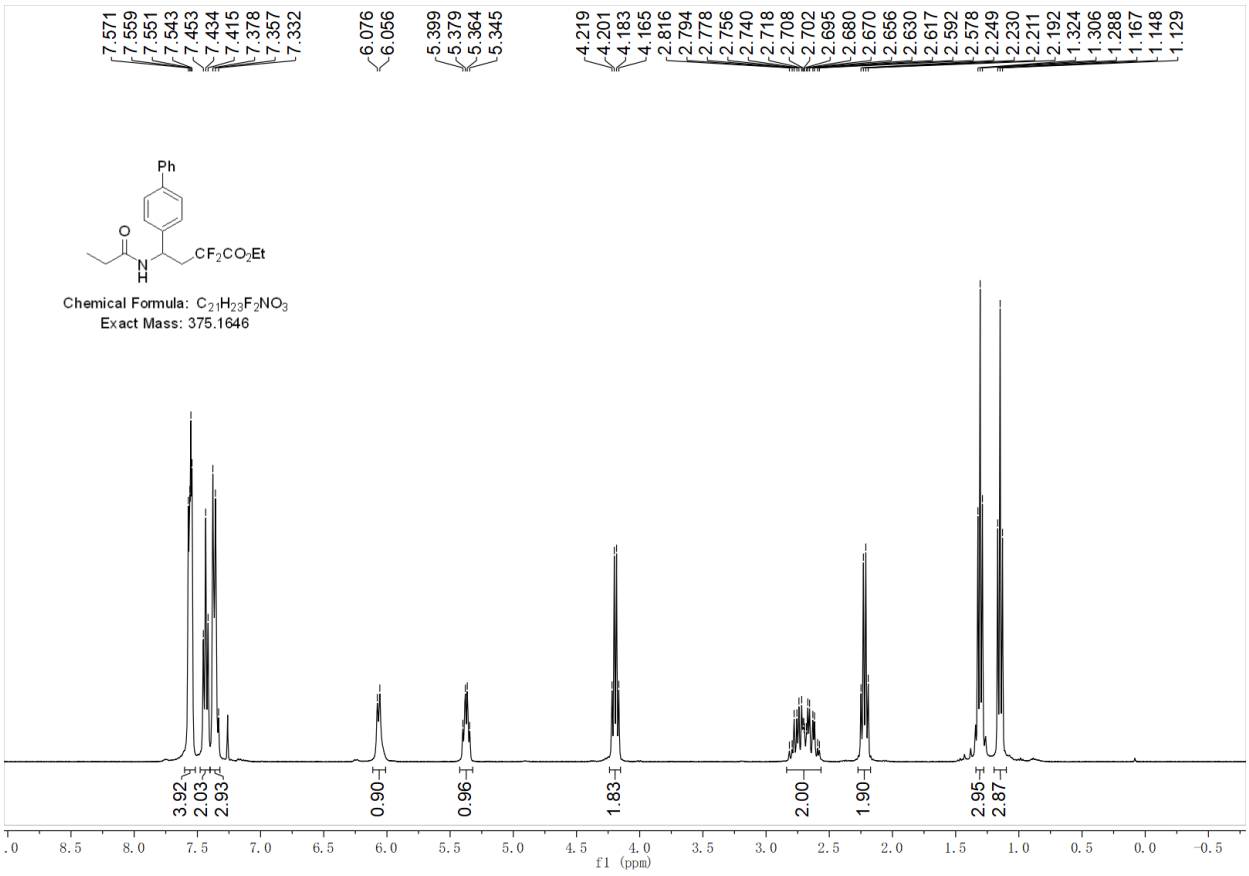
Ethyl 4-([1,1'-biphenyl]-4-yl)-4-((tert-butoxycarbonyl)amino)-2,2-difluorobutanoate (22)

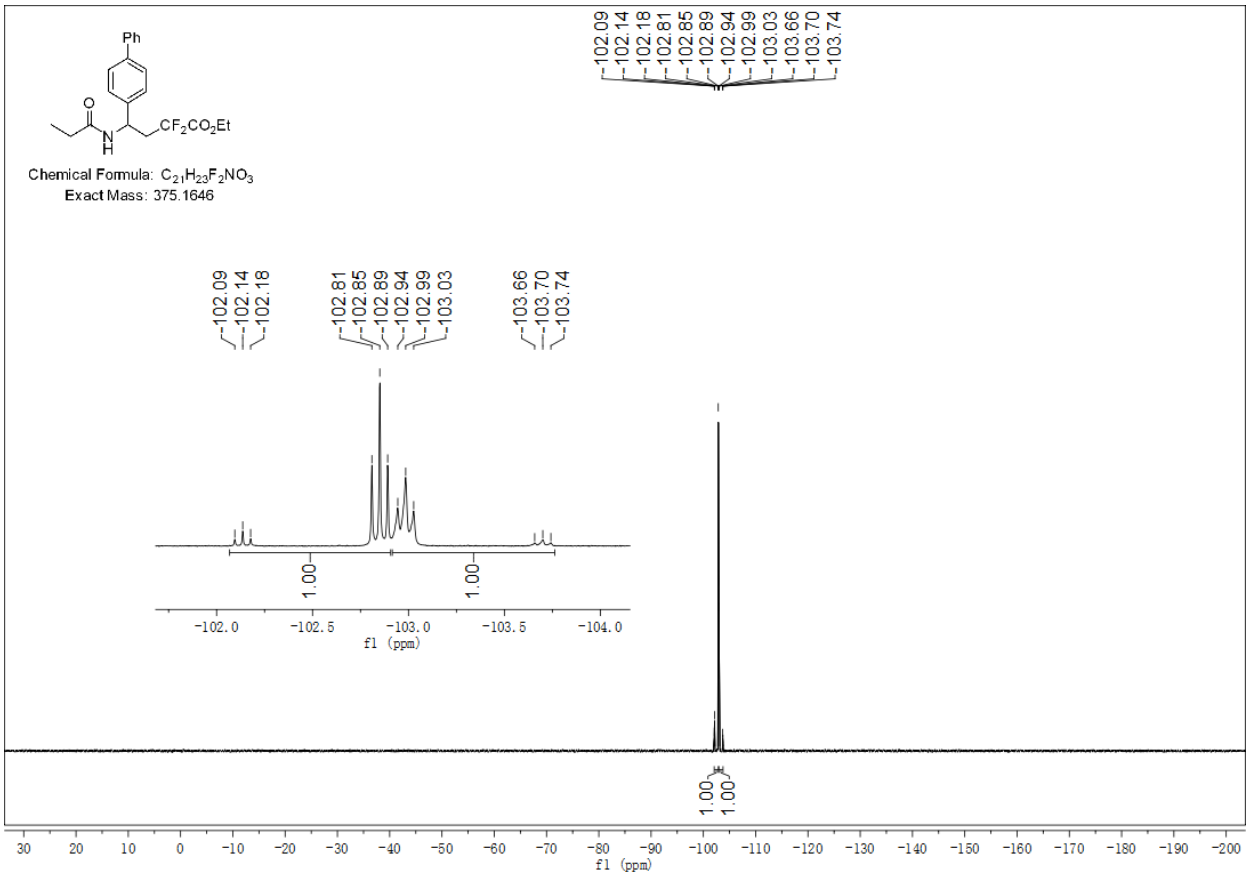


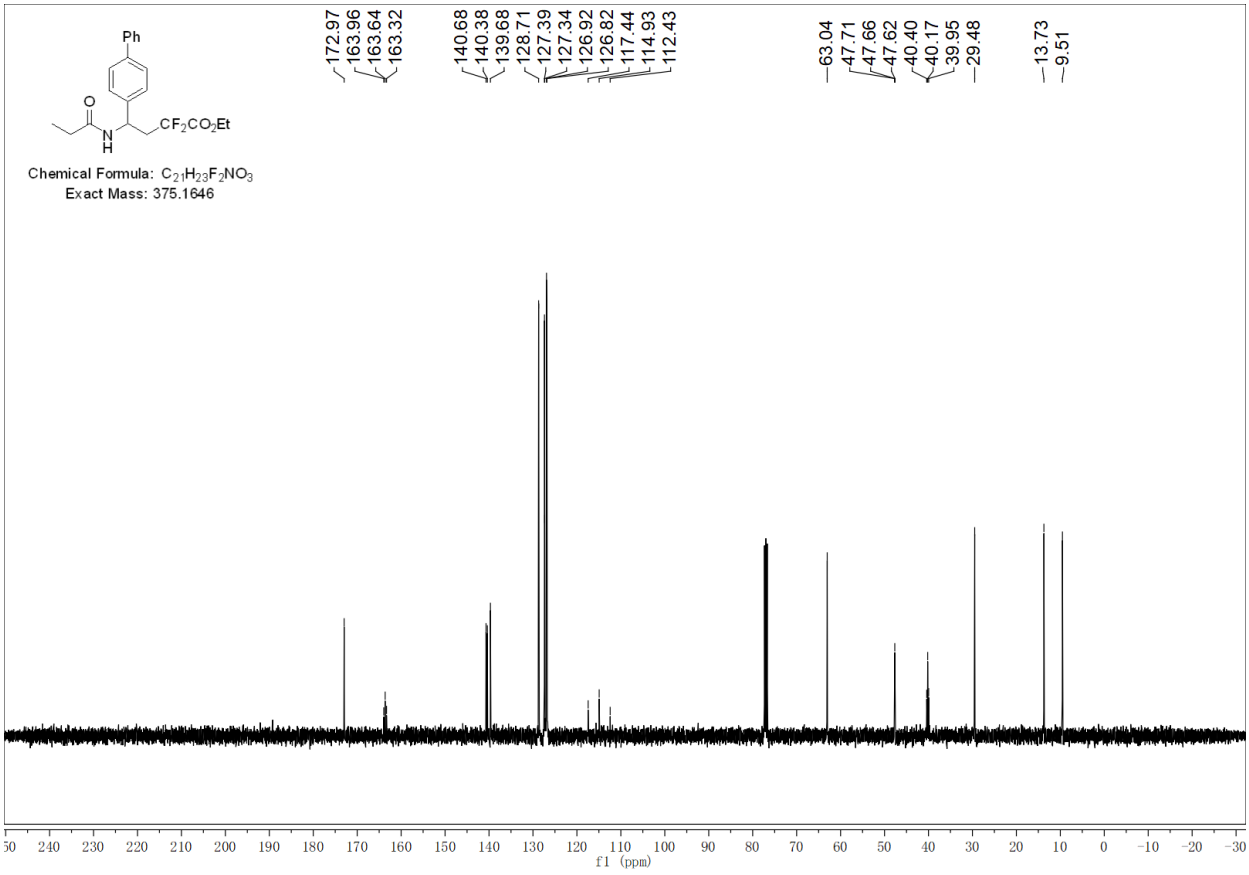




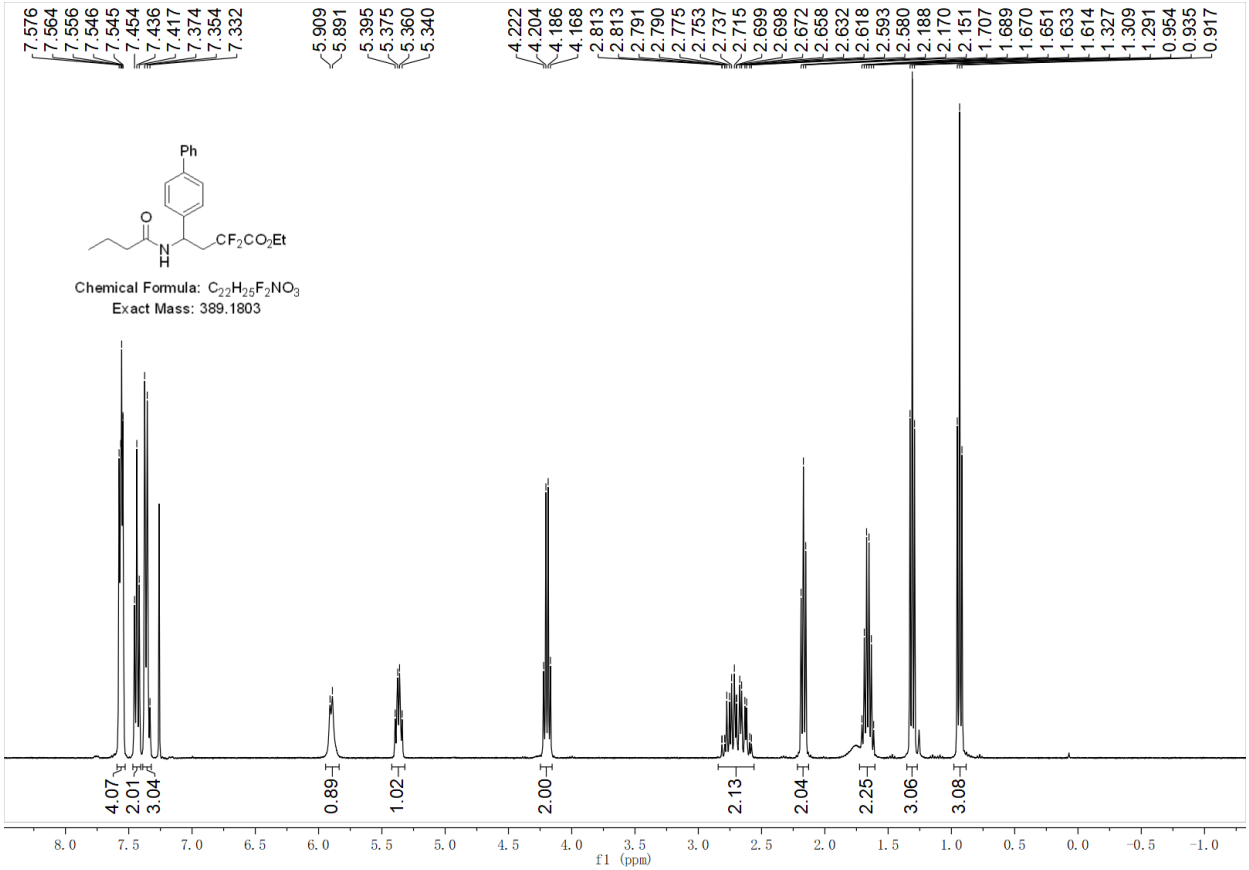
Ethyl 4-([1,1'-biphenyl]-4-yl)-2,2-difluoro-4-propionamidobutanoate (23)

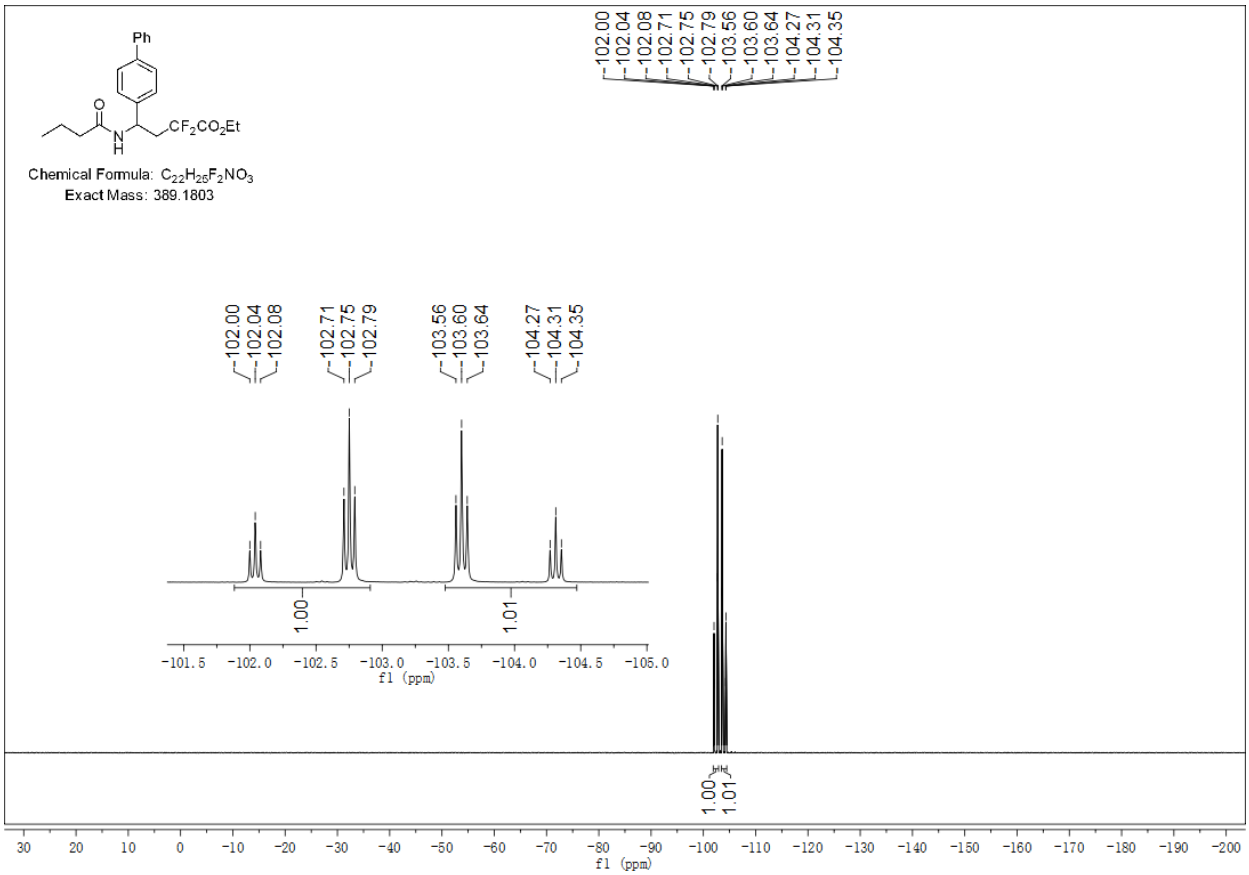


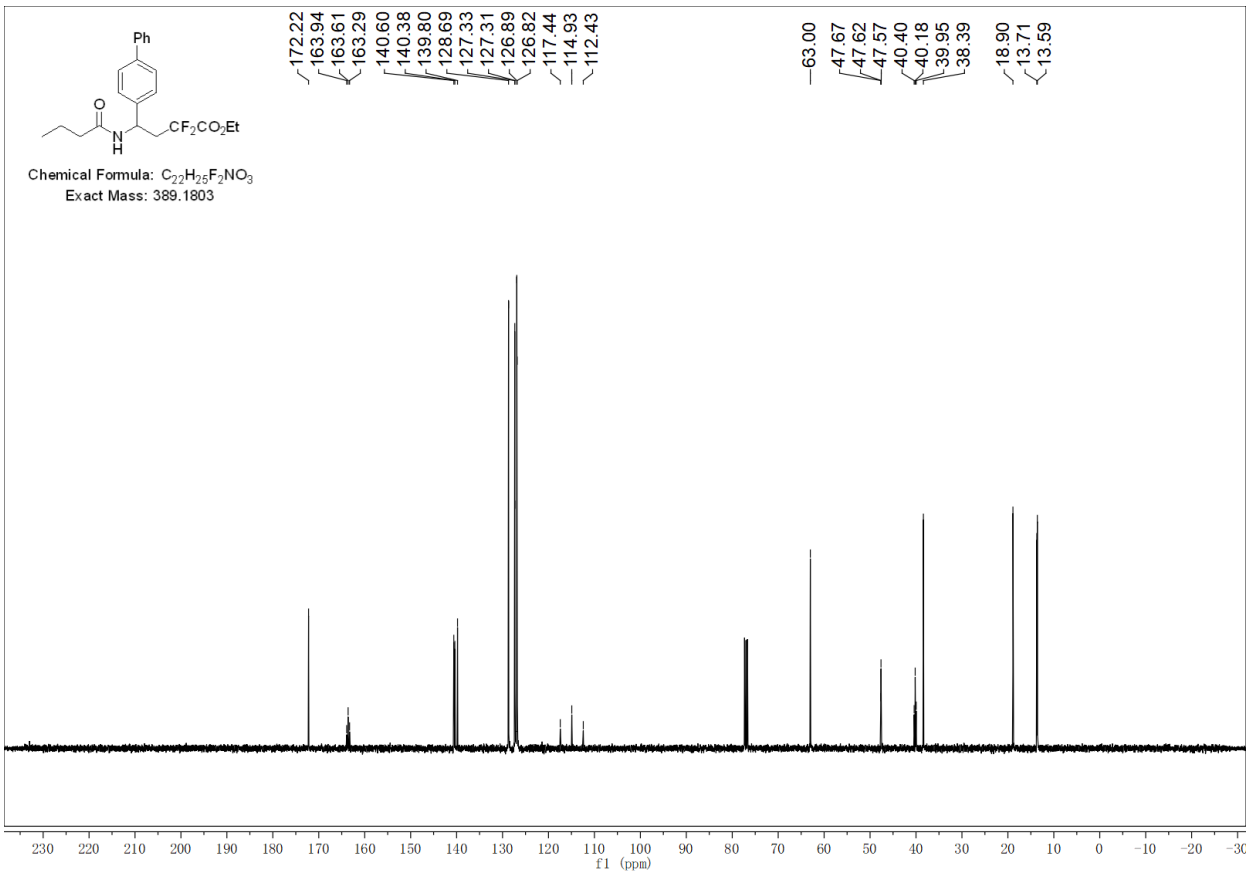

Ph
O
N
H
CF2CO2Et
Chemical Formula: C21H23F2NO3
Exact Mass: 375.1646
102.09
102.14
102.18
102.81
102.85
102.89
102.94
102.99
103.03
103.66
103.70
103.74
1.00
1.00
1.00
1.00
-102.0
-102.5
-103.0
-103.5
-104.0
f1 (ppm)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


Ph
O
N
H
CF2CO2Et
Chemical Formula: C21H23F2NO3
Exact Mass: 375.1646
172.97
163.96
163.64
163.32
140.68
140.38
139.68
128.71
127.39
127.34
126.92
126.82
117.44
114.93
112.43
63.04
47.71
47.66
47.62
40.40
40.17
39.95
29.48
13.73
9.51
50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)

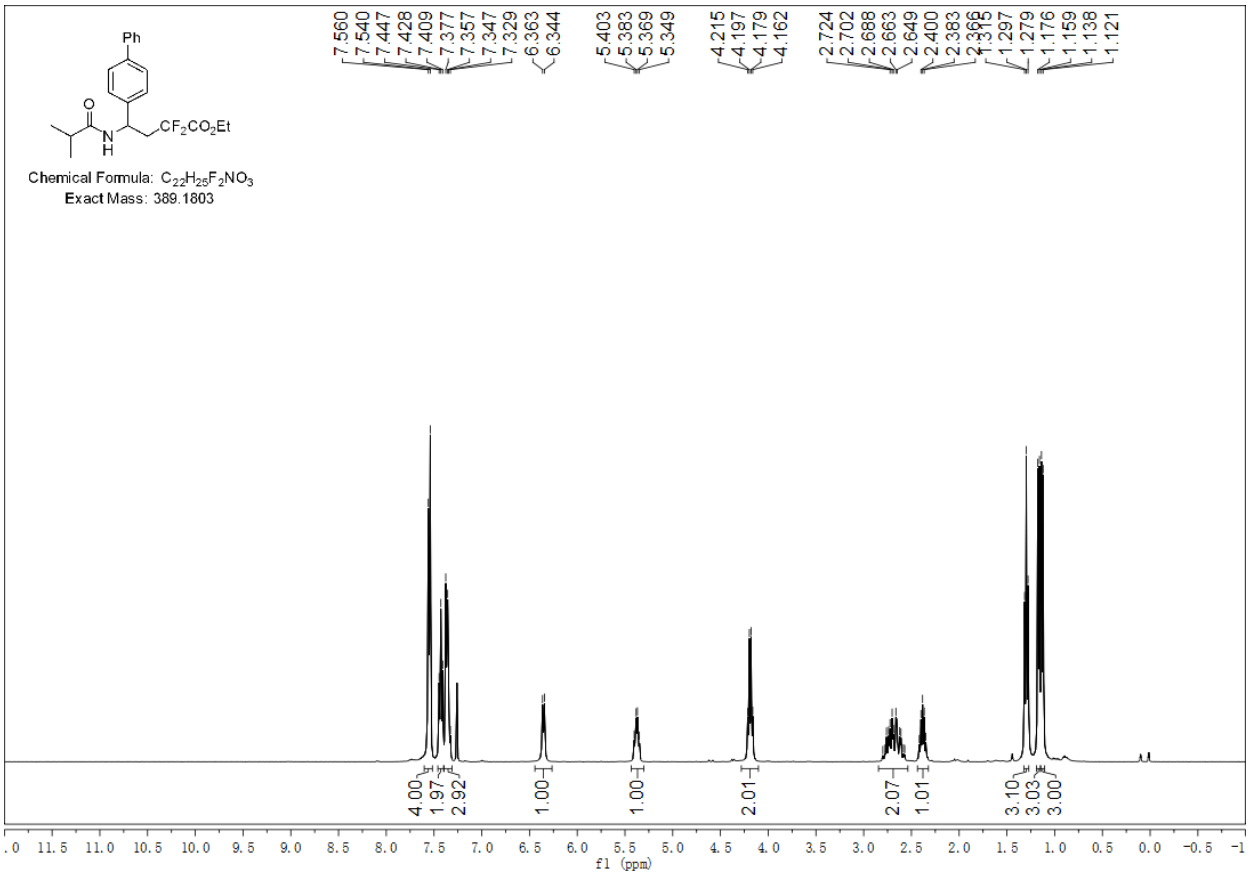
Ethyl 4-([1,1'-biphenyl]-4-yl)-4-butyramido-2,2-difluorobutanoate (24)

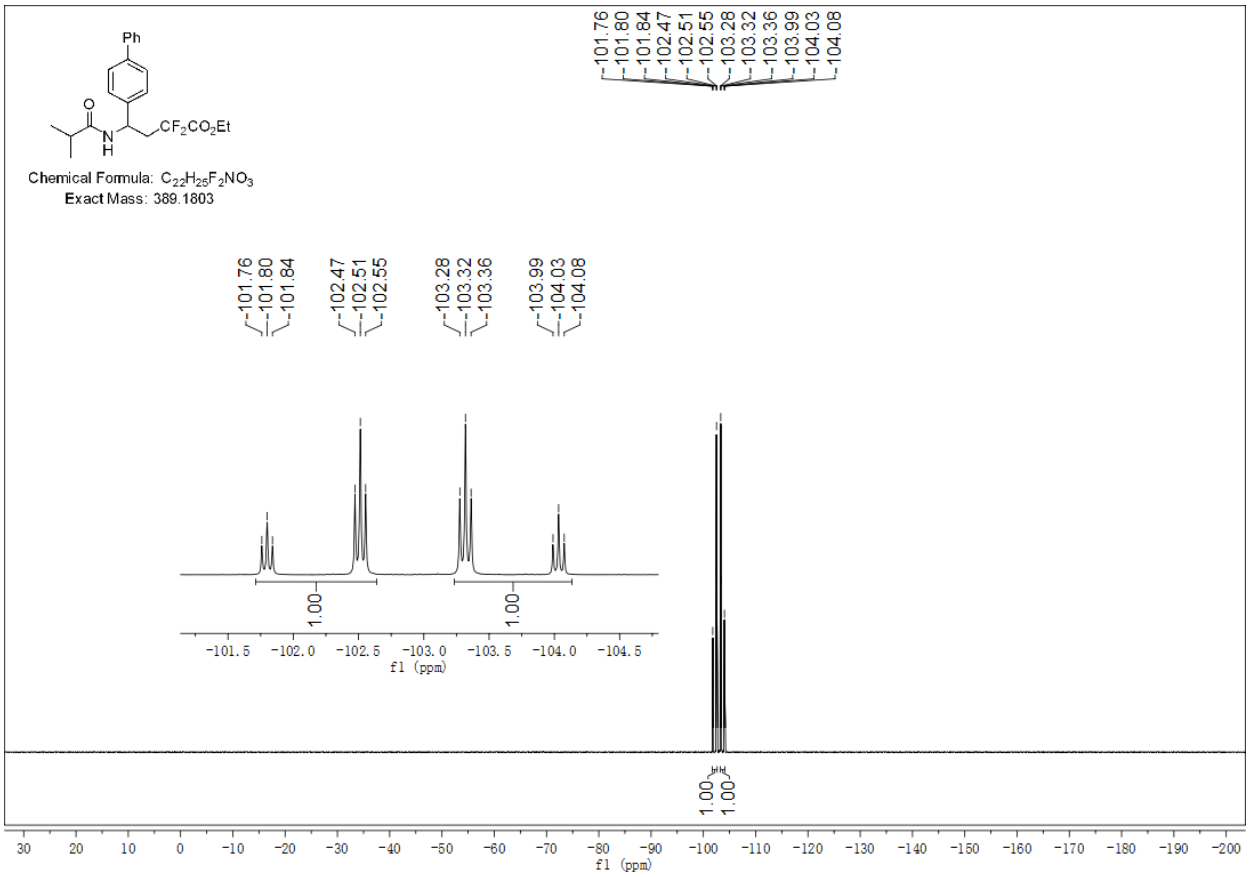


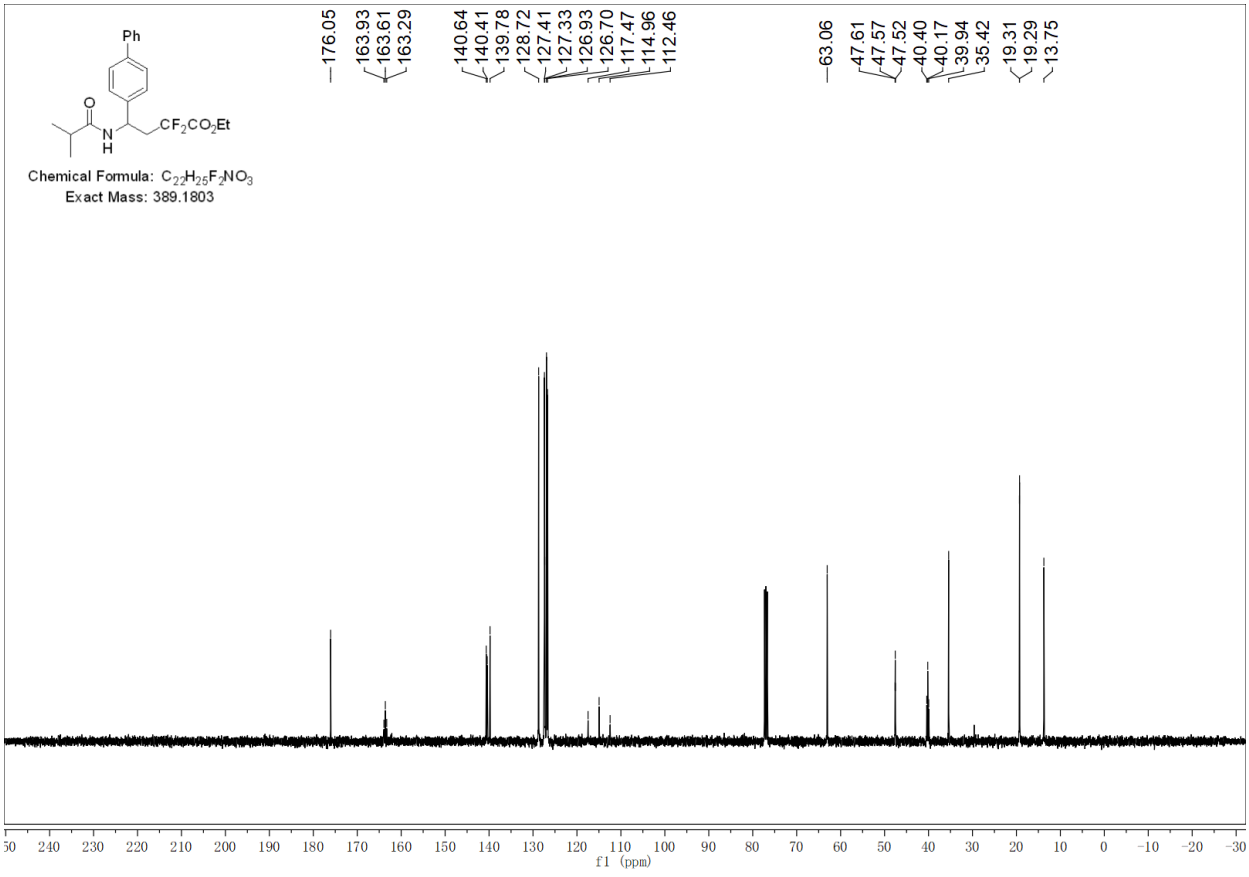




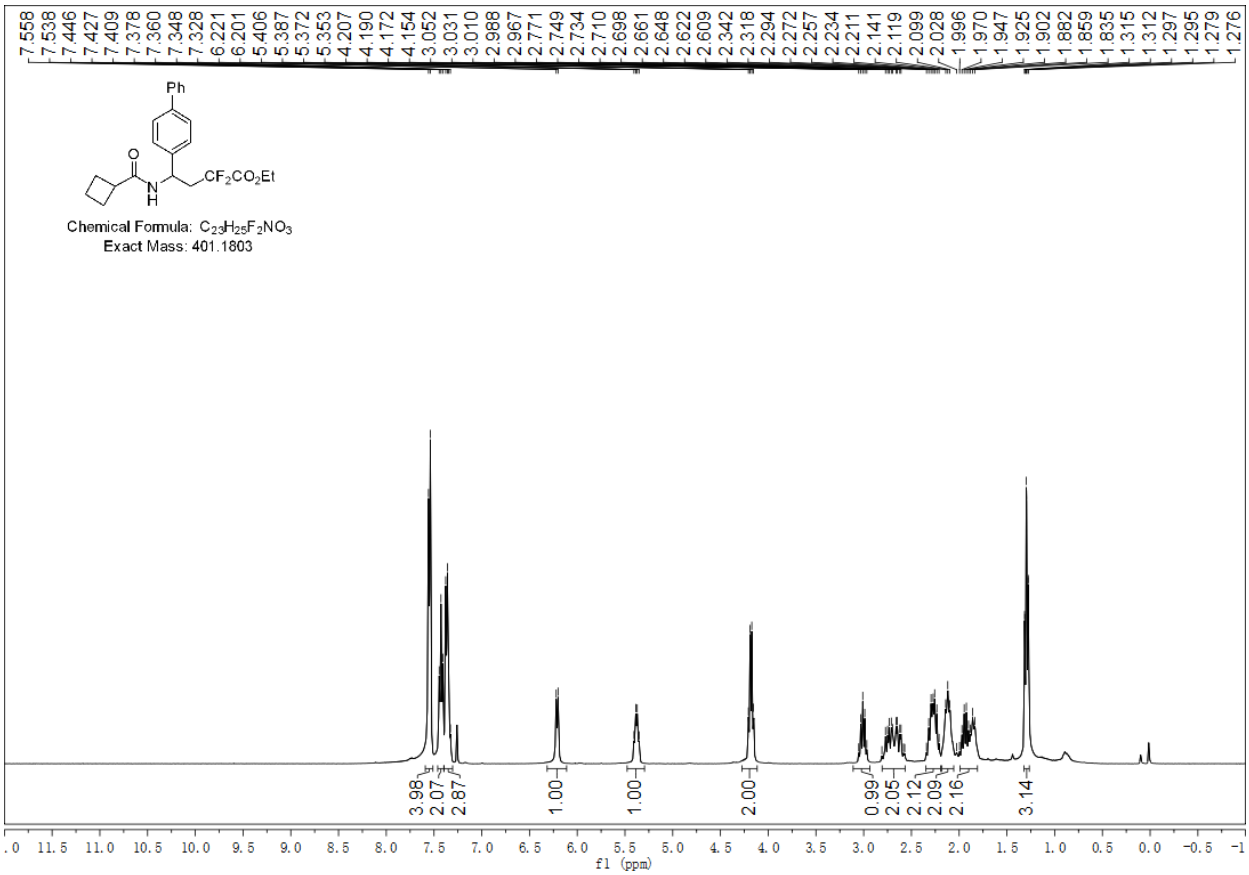
Ethyl 4-([1,1'-biphenyl]-4-yl)-2,2-difluoro-4-isobutyramidobutanoate (25)

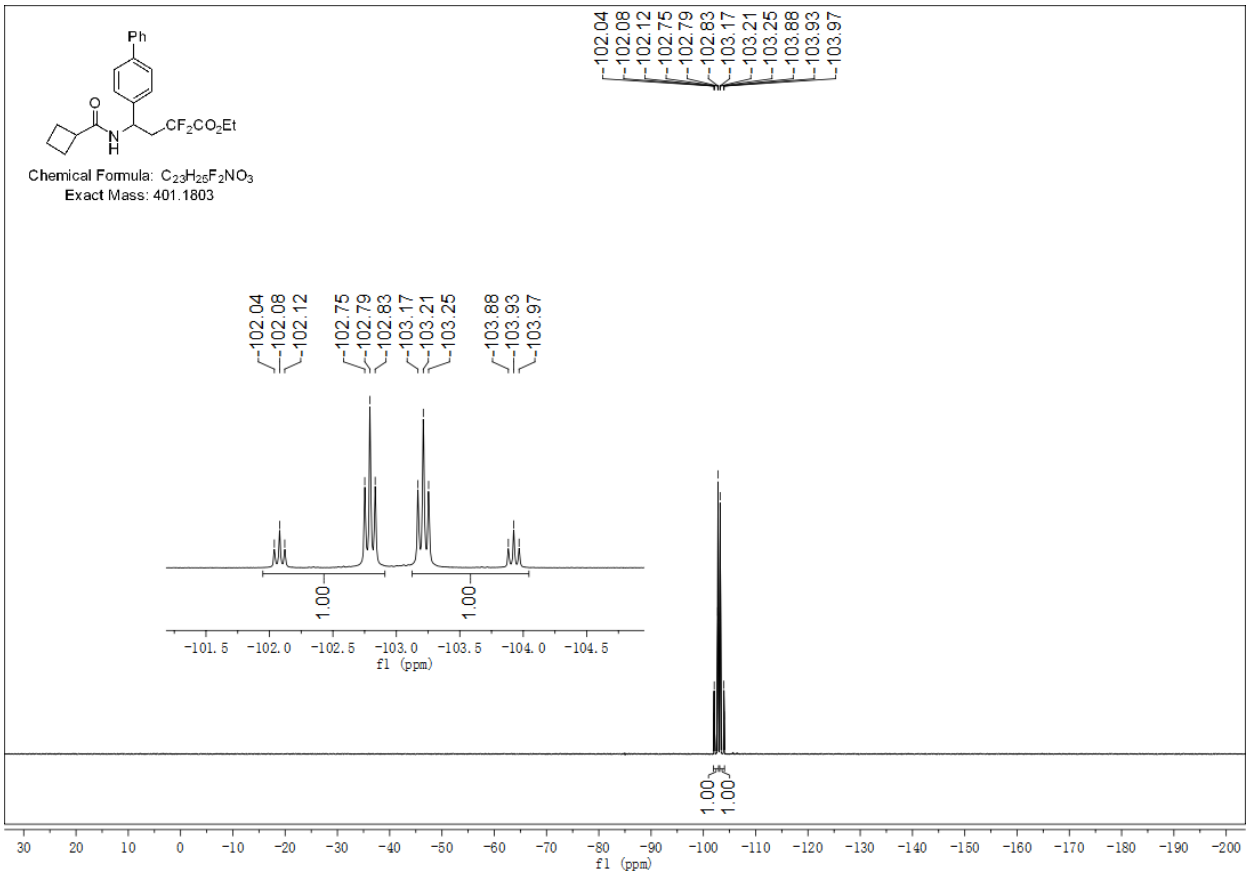


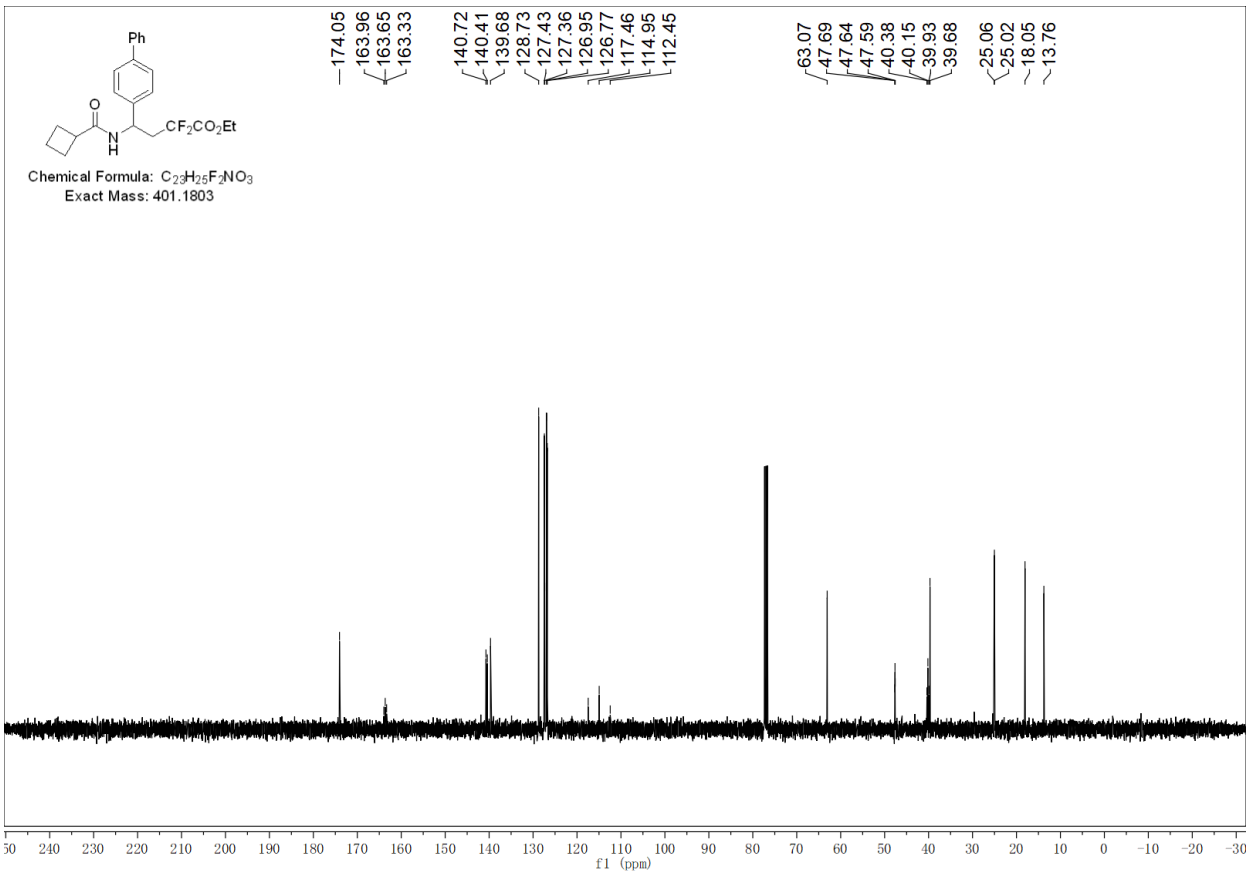

Ph
O
N
H
CF2CO2Et
Chemical Formula: C22H25F2NO3
Exact Mass: 389.1803
101.76
101.80
101.84
102.47
102.51
102.55
103.28
103.32
103.36
103.99
104.03
104.08
1.00
1.00
1.00
1.00
f1 (ppm)


Ph
O
N
H
CF2CO2Et
Chemical Formula: C22H25F2NO3
Exact Mass: 389.1803
176.05
163.93
163.61
163.29
140.64
140.41
139.78
128.72
127.41
127.33
126.93
126.70
117.47
114.96
112.46
63.06
47.61
47.57
47.52
40.40
40.17
39.94
35.42
19.31
19.29
13.75
f1 (ppm)

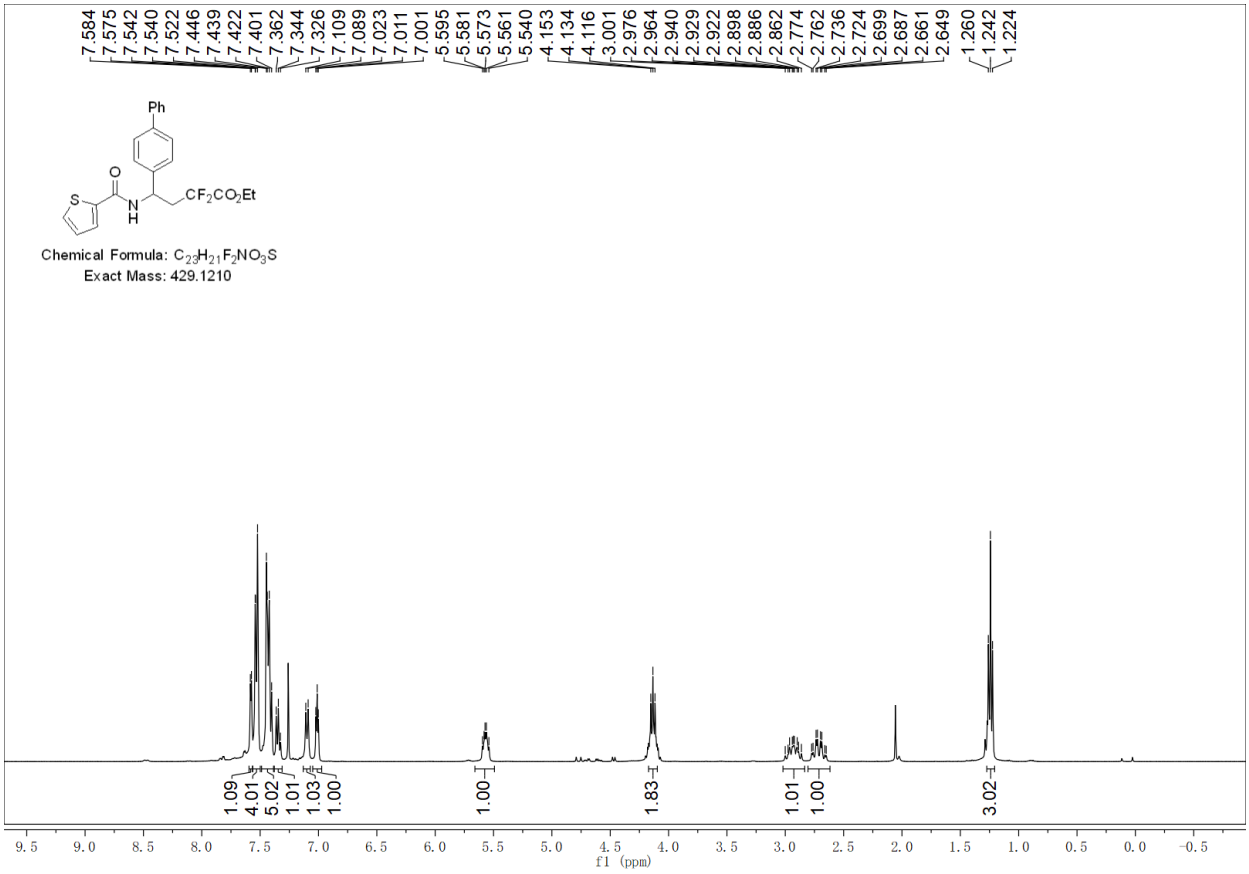
Ethyl 4-([1,1'-biphenyl]-4-yl)-4-(cyclobutanecarboxamido)-2,2-difluorobutanoate (26)

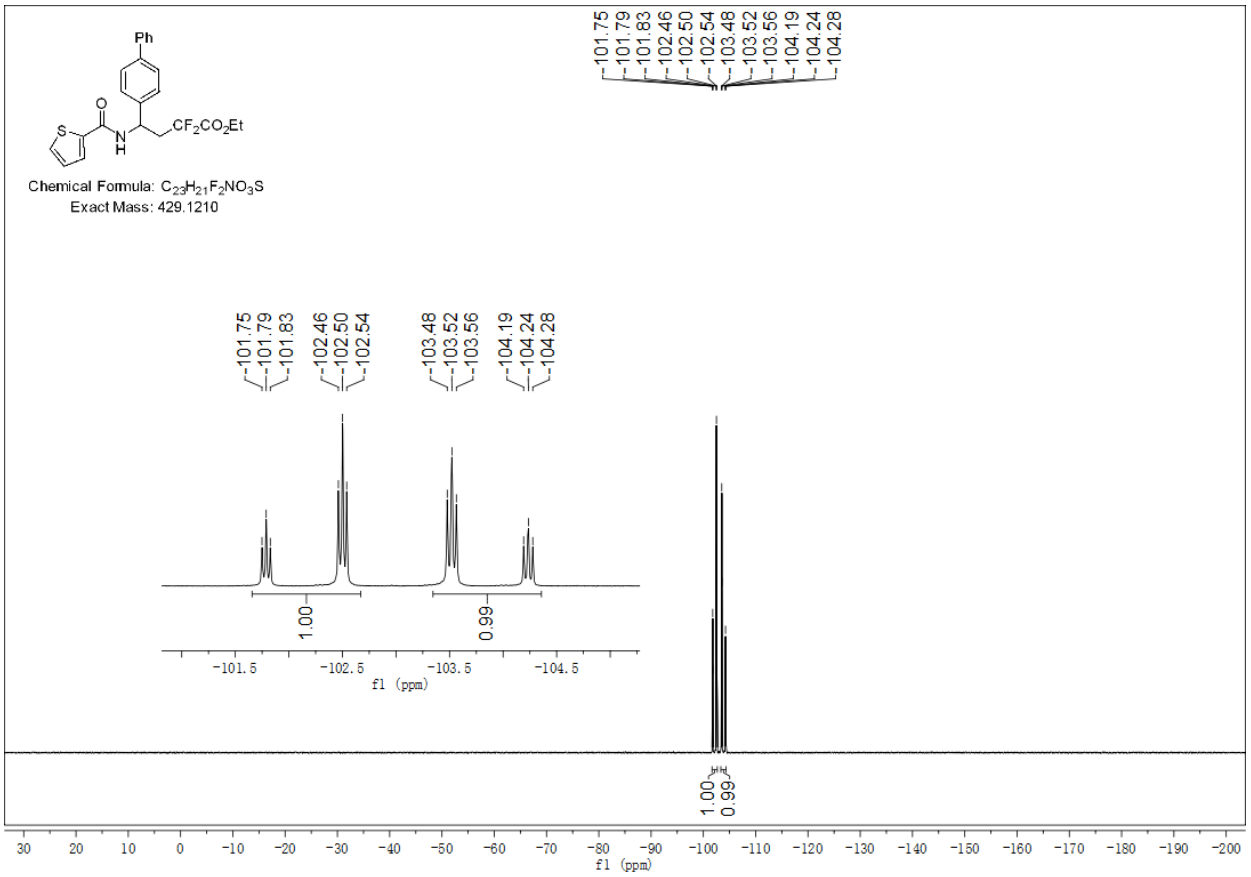


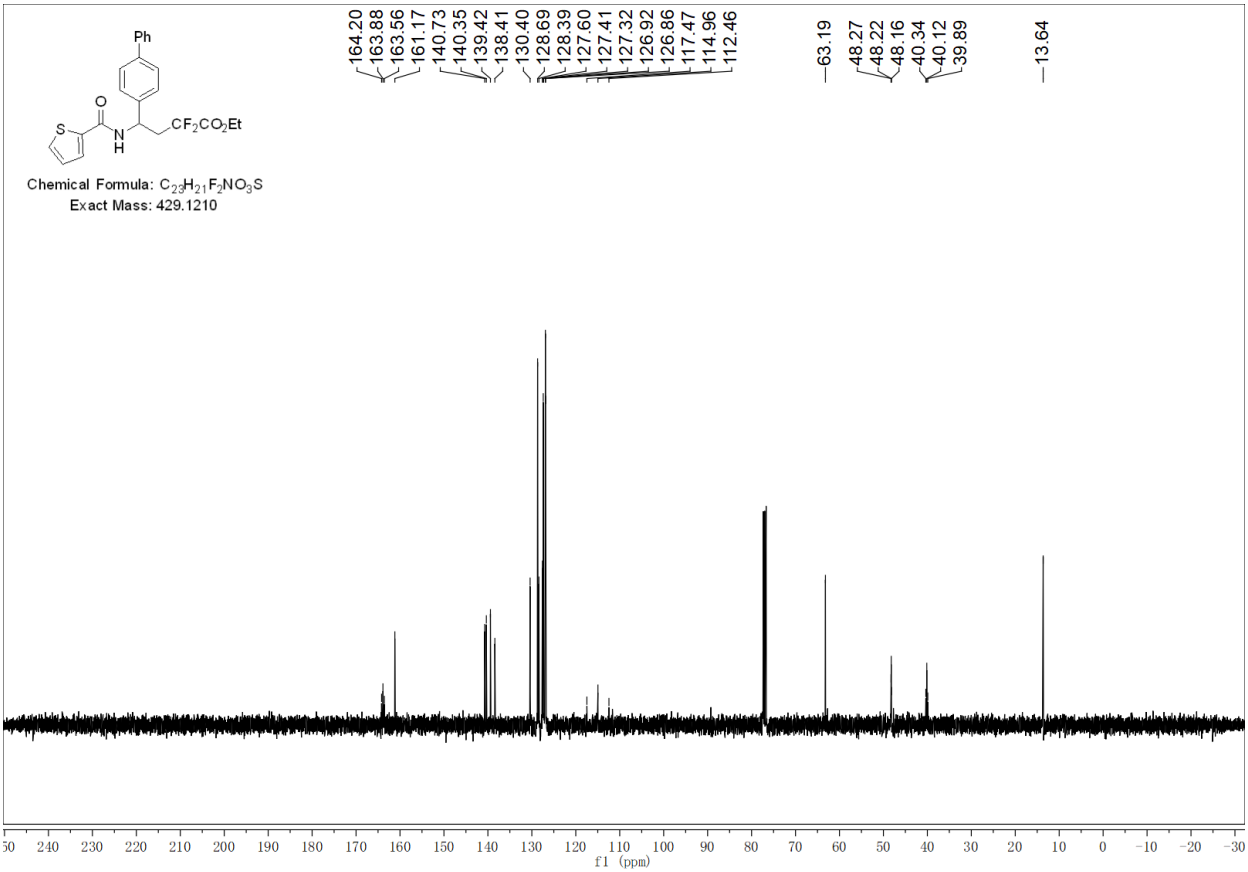




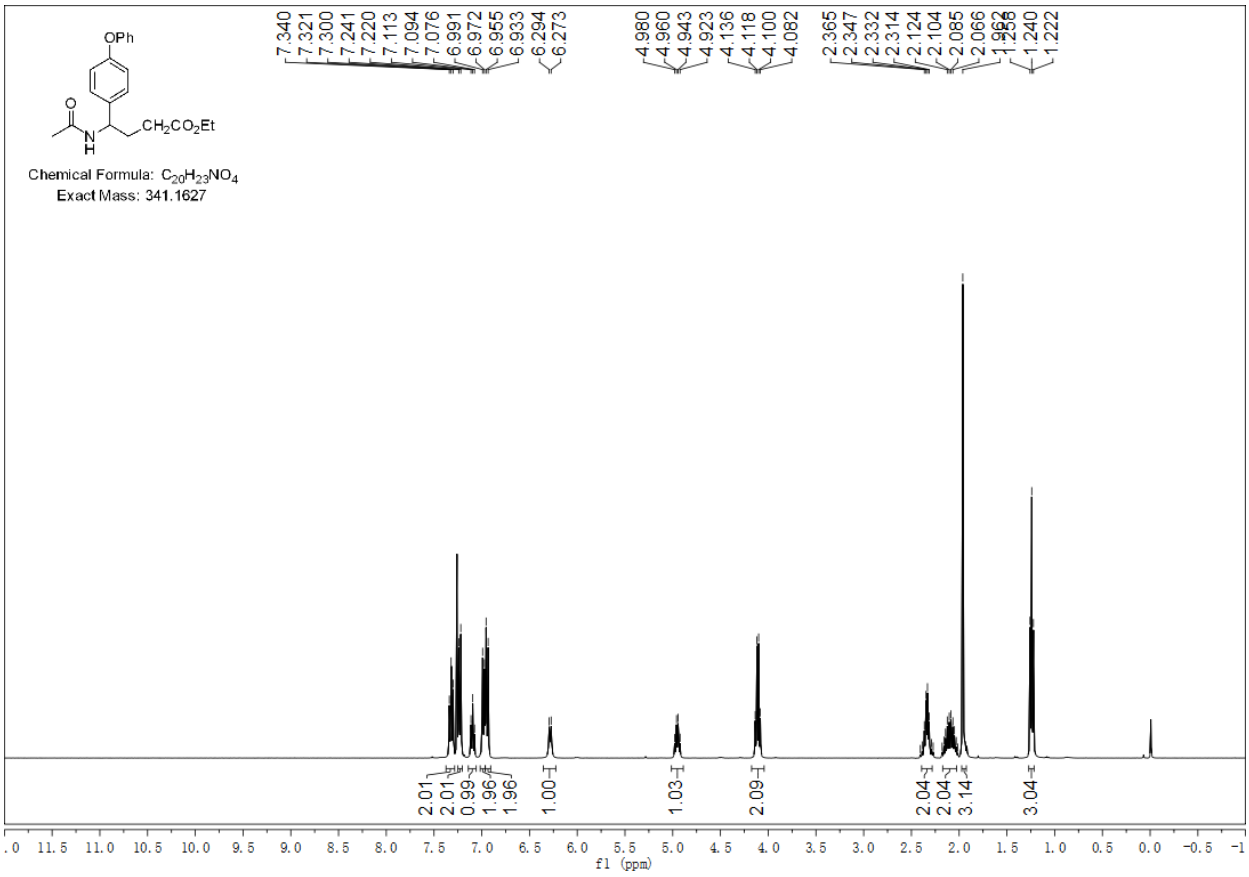
Ethyl 4-([1,1'-biphenyl]-4-yl)-2,2-difluoro-4-(thiophene-2-carboxamido)butanoate (27)

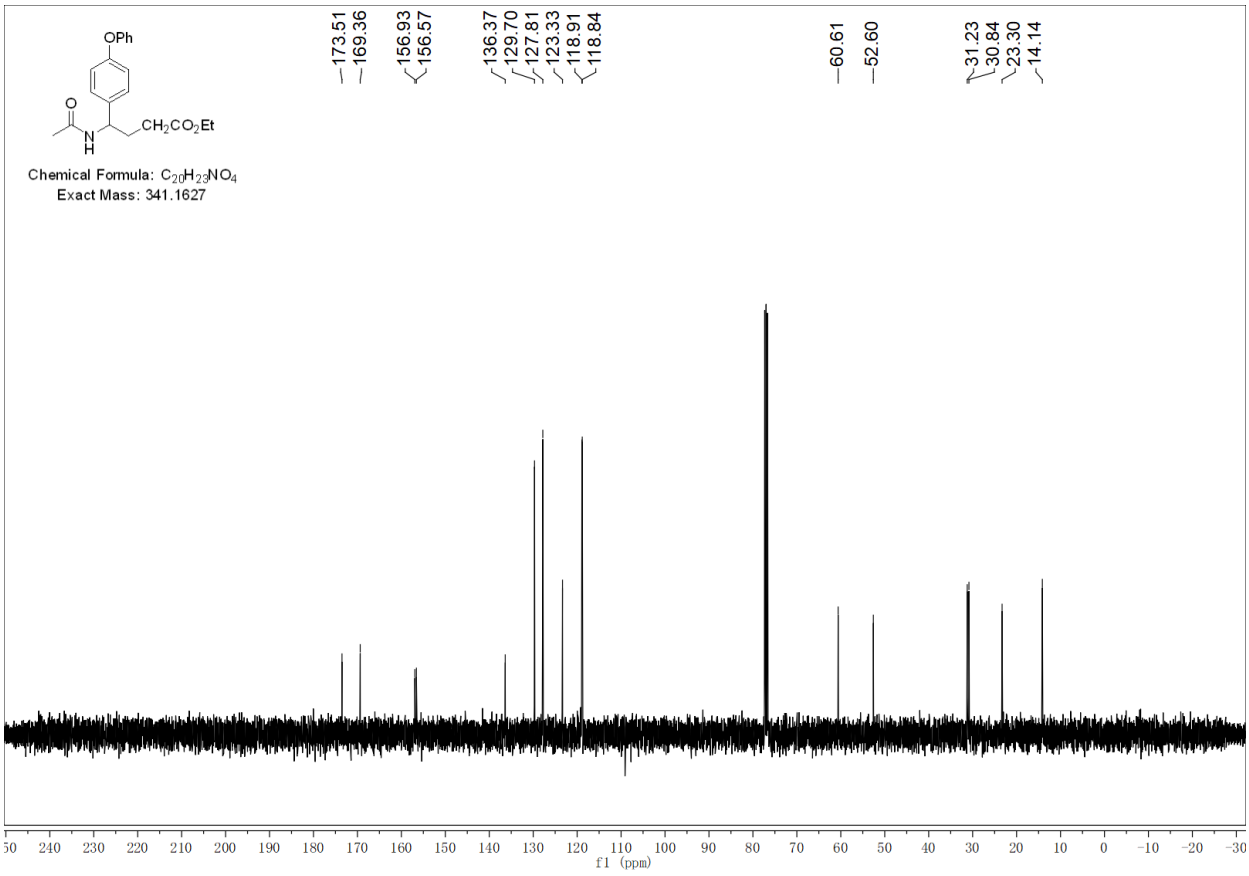



Ph
O
S
N
H
CF2CO2Et
Chemical Formula: C23H21F2NO3S
Exact Mass: 429.1210
101.75
101.79
101.83
102.46
102.50
102.54
103.48
103.52
103.56
104.19
104.24
104.28
1.00
0.99
-101.5
-102.5
-103.5
-104.5
f1 (ppm)
1.00
0.99
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

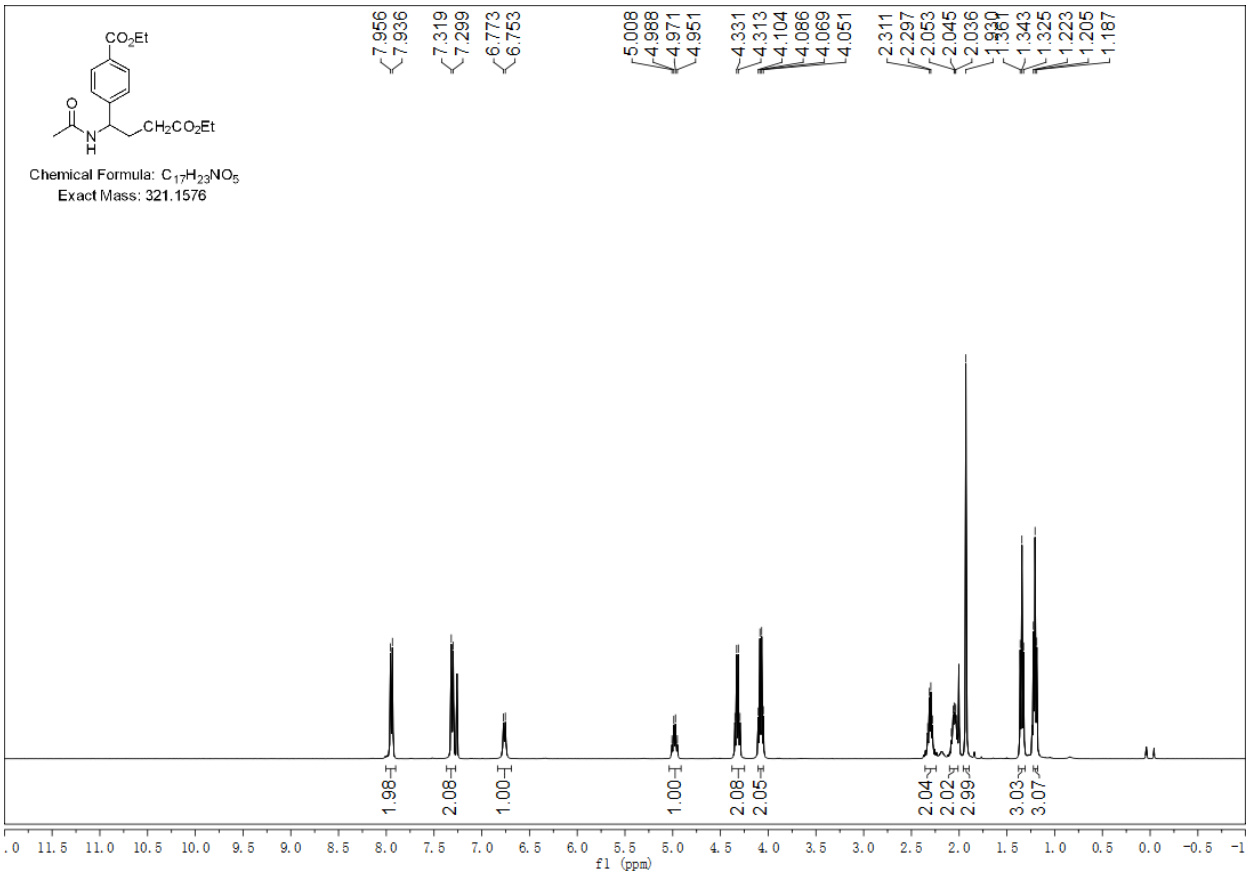

Ph
O
S
N
H
CF2CO2Et
Chemical Formula: C23H21F2NO3S
Exact Mass: 429.1210
164.20
163.88
163.56
161.17
140.73
140.35
139.42
138.41
130.40
128.69
128.39
127.60
127.41
127.32
126.92
126.86
117.47
114.96
112.46
63.19
48.27
48.22
48.16
40.34
40.12
39.89
13.64
50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)

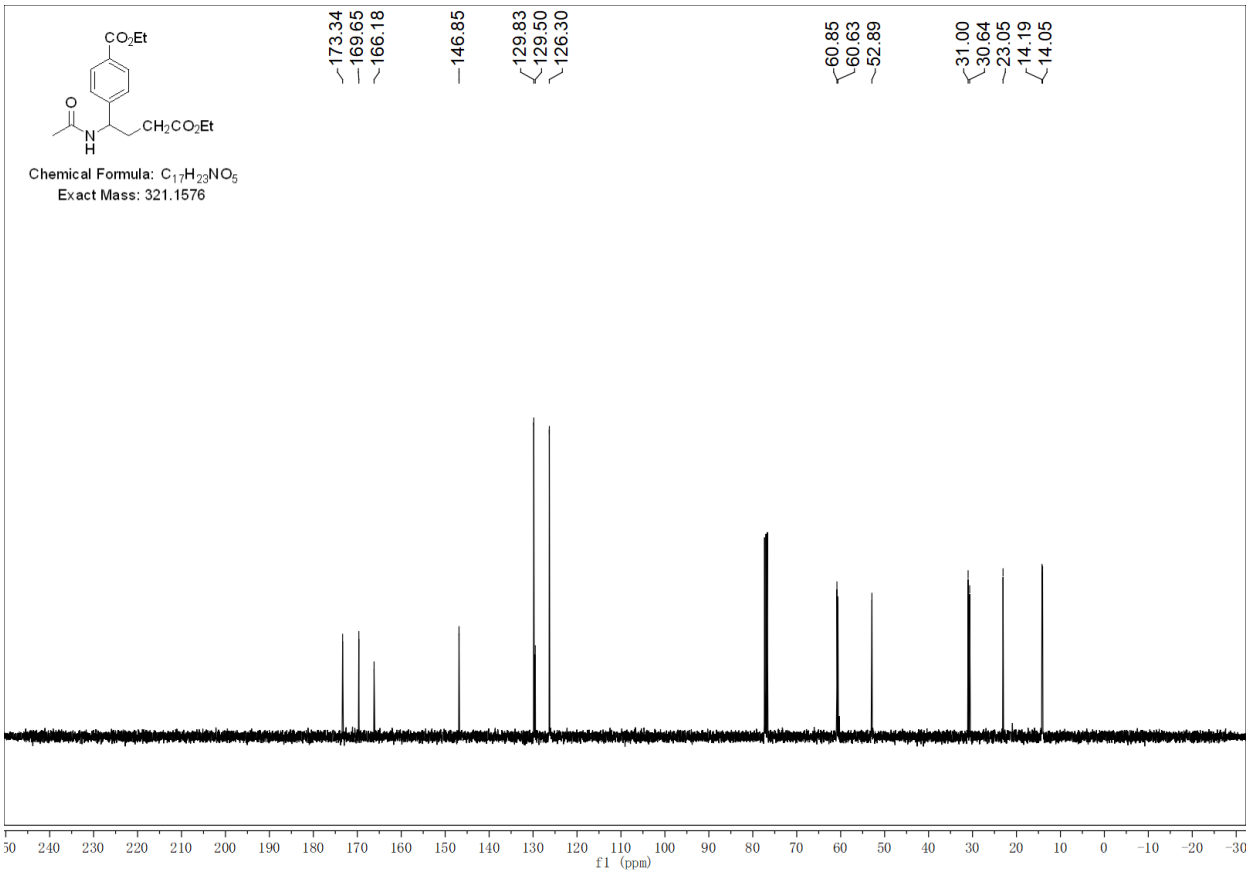
Ethyl 4-acetamido-4-(4-phenoxyphenyl)butanoate (28)



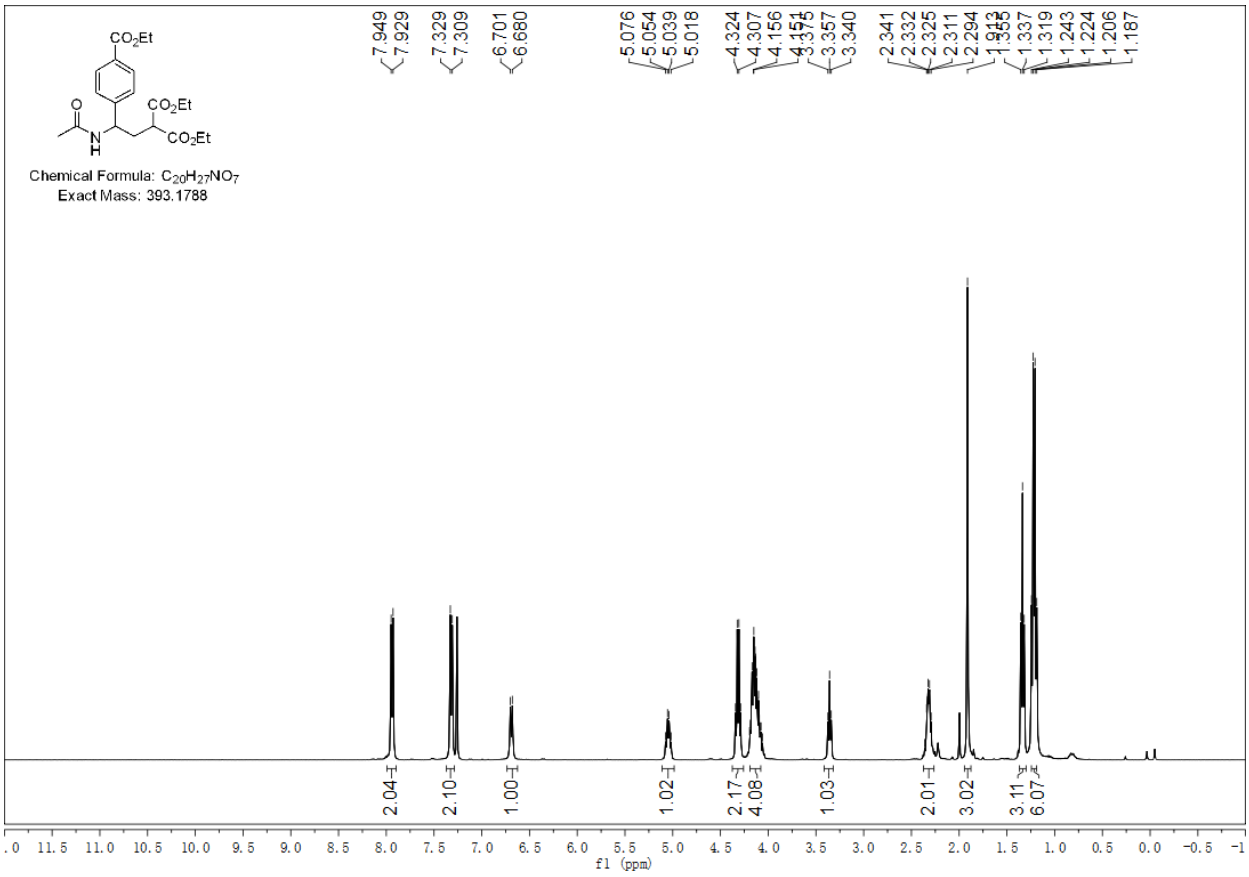


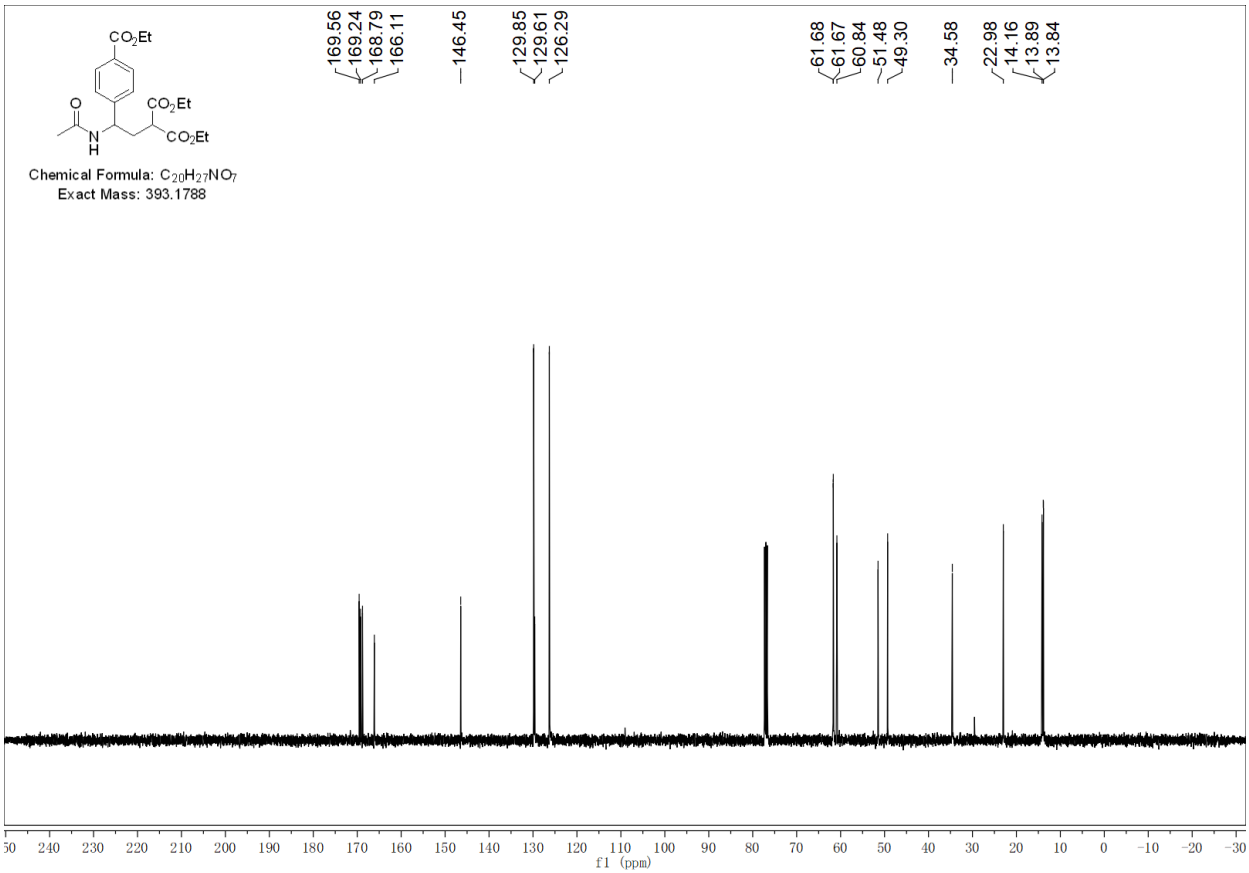
Ethyl 4-(1-acetamido-4-ethoxy-4-oxobutyl)benzoate (29)



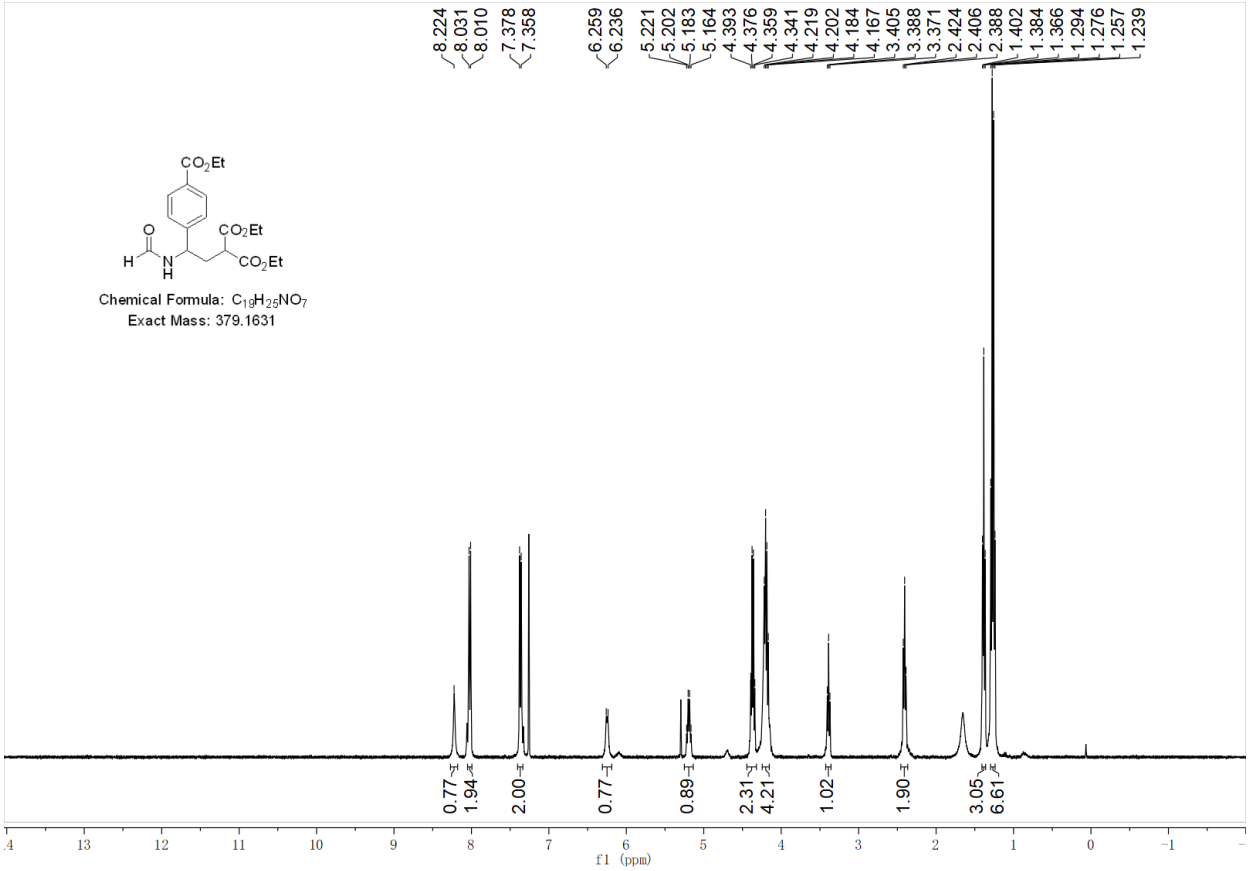


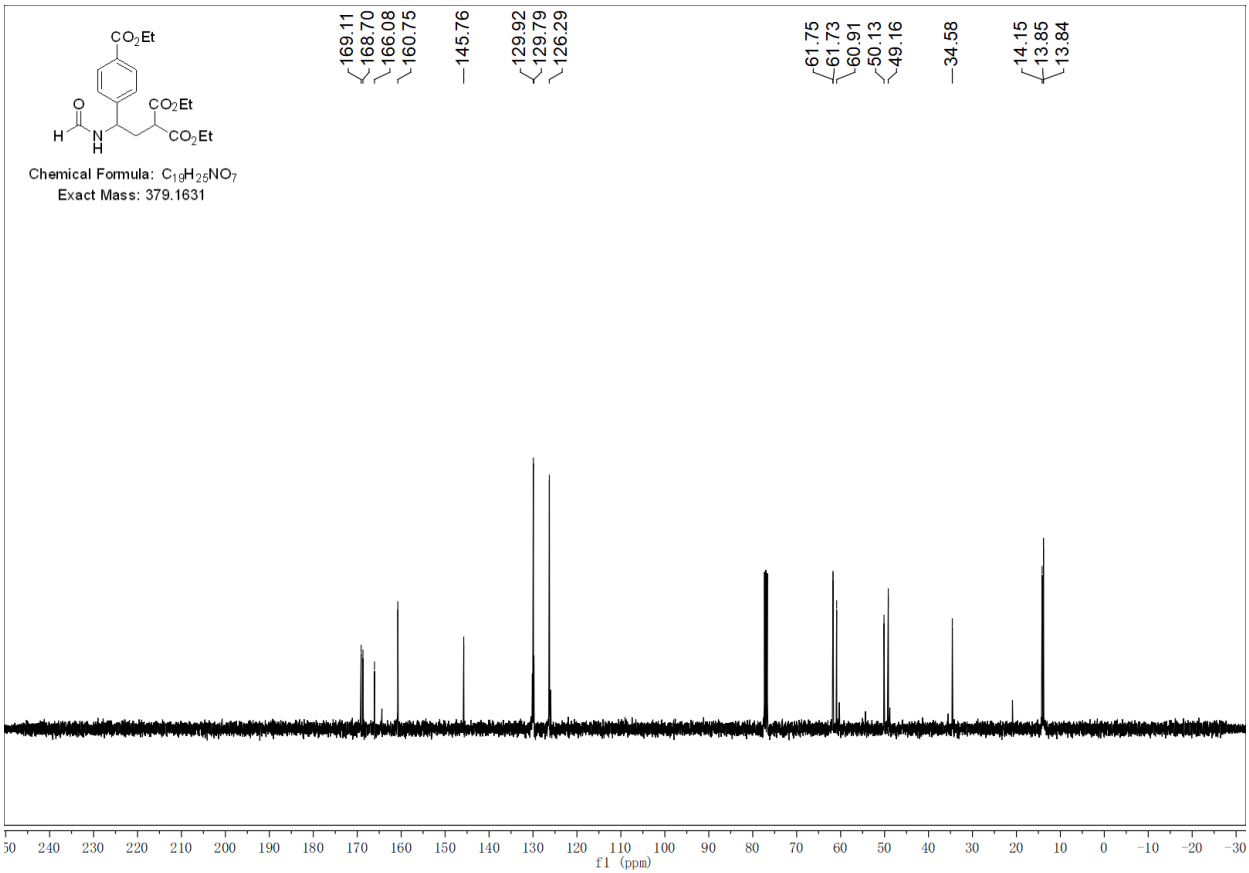
Diethyl 2-(2-acetamido-2-(4-(ethoxycarbonyl)phenyl)ethyl)malonate (30)



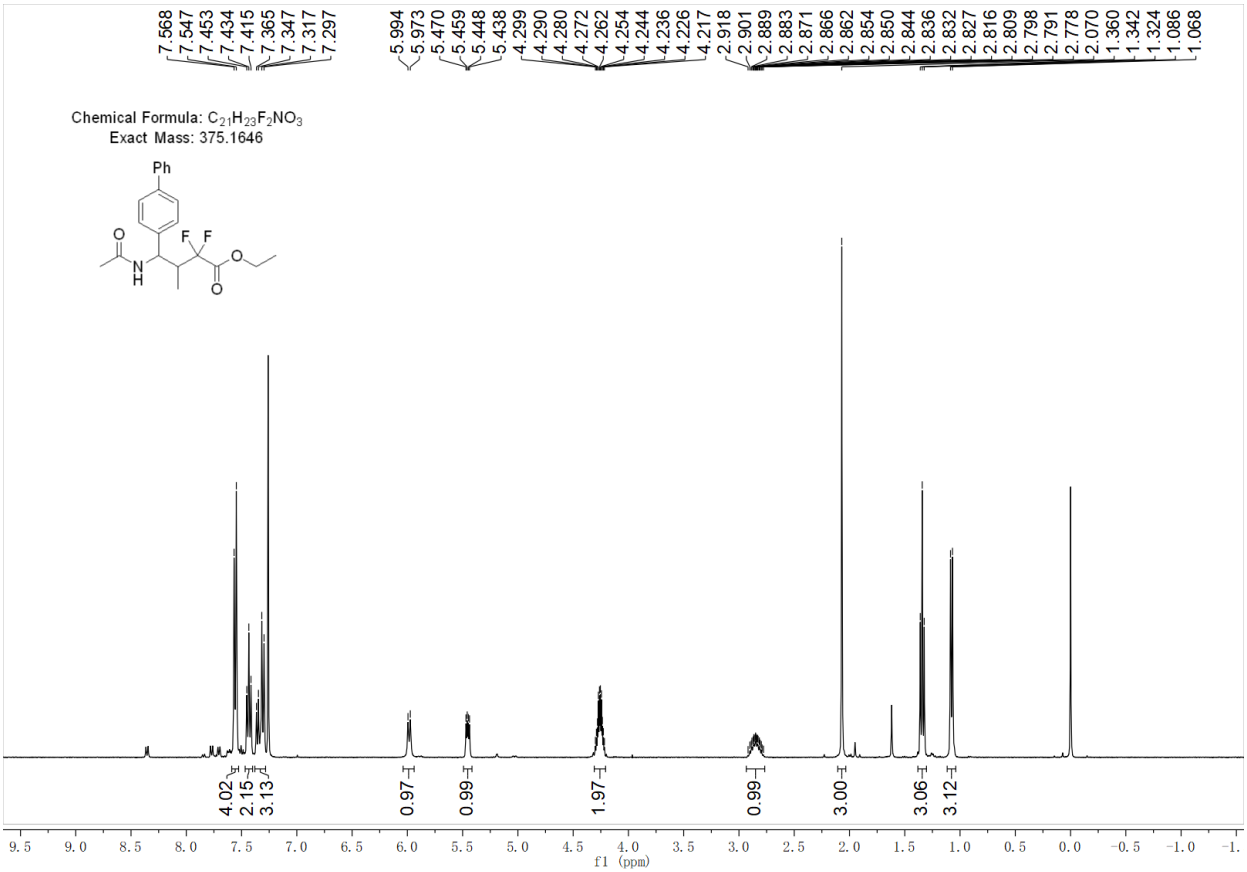


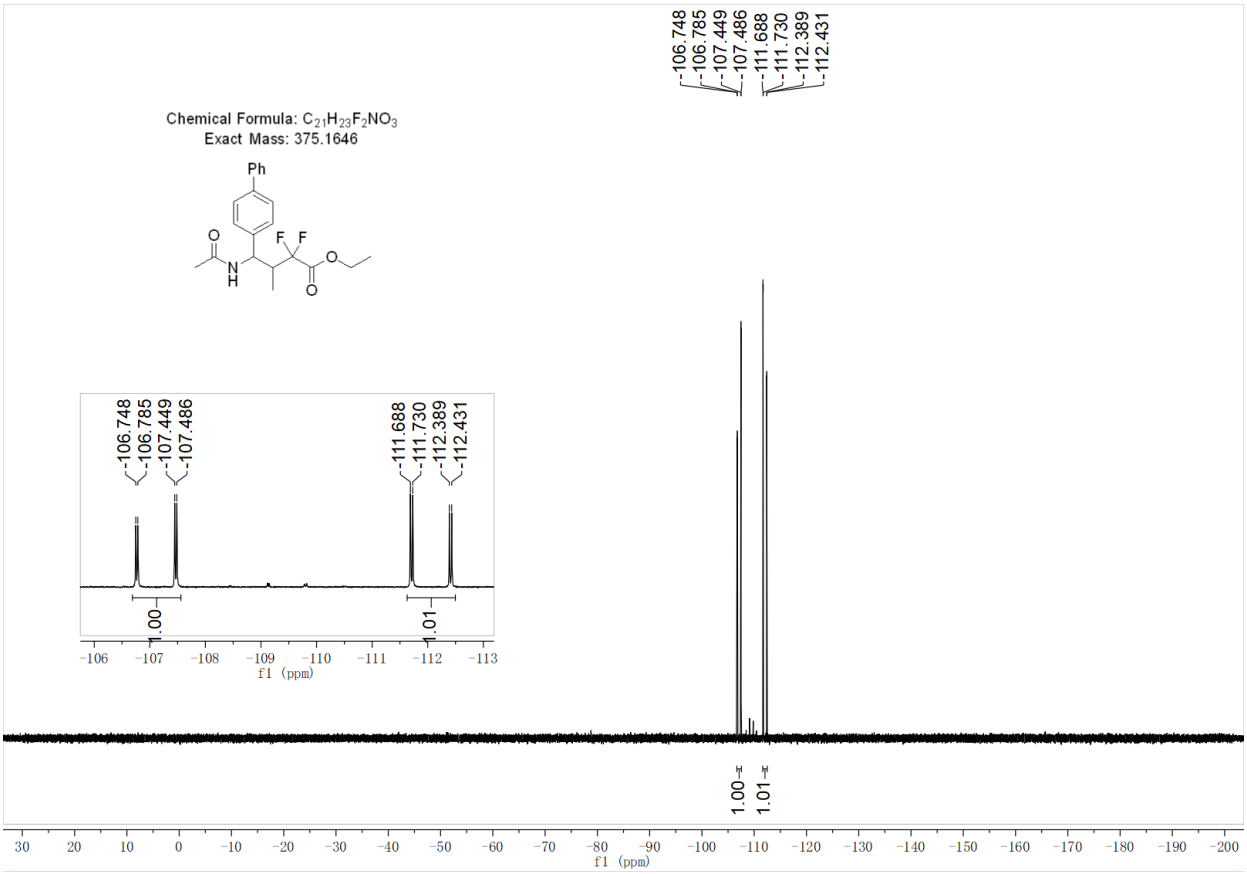
Diethyl 2-(2-(4-(ethoxycarbonyl)phenyl)-2-formamidoethyl)malonate (31)

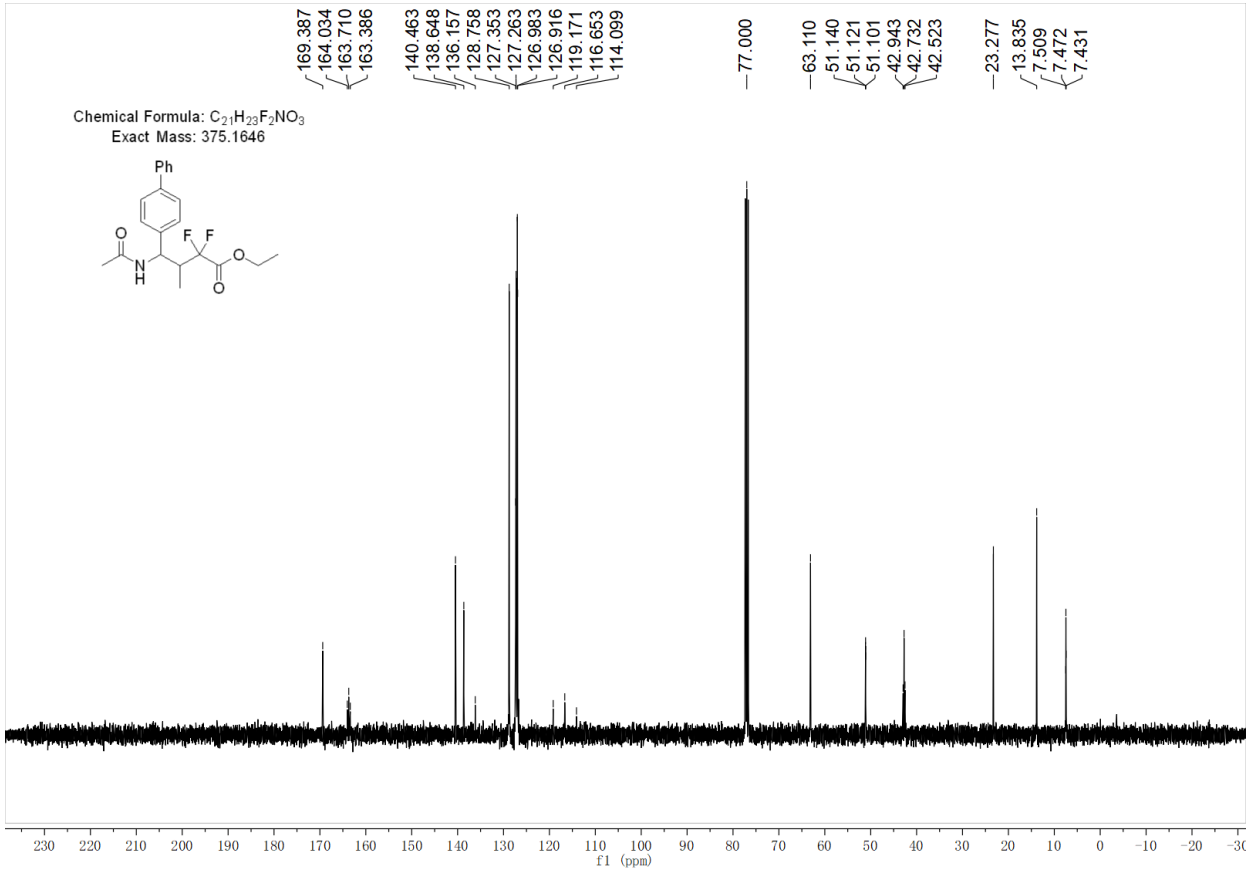




Ethyl 4-([1,1'-biphenyl]-4-yl)-4-acetamido-2,2-difluoro-3-methylbutanoate (32)

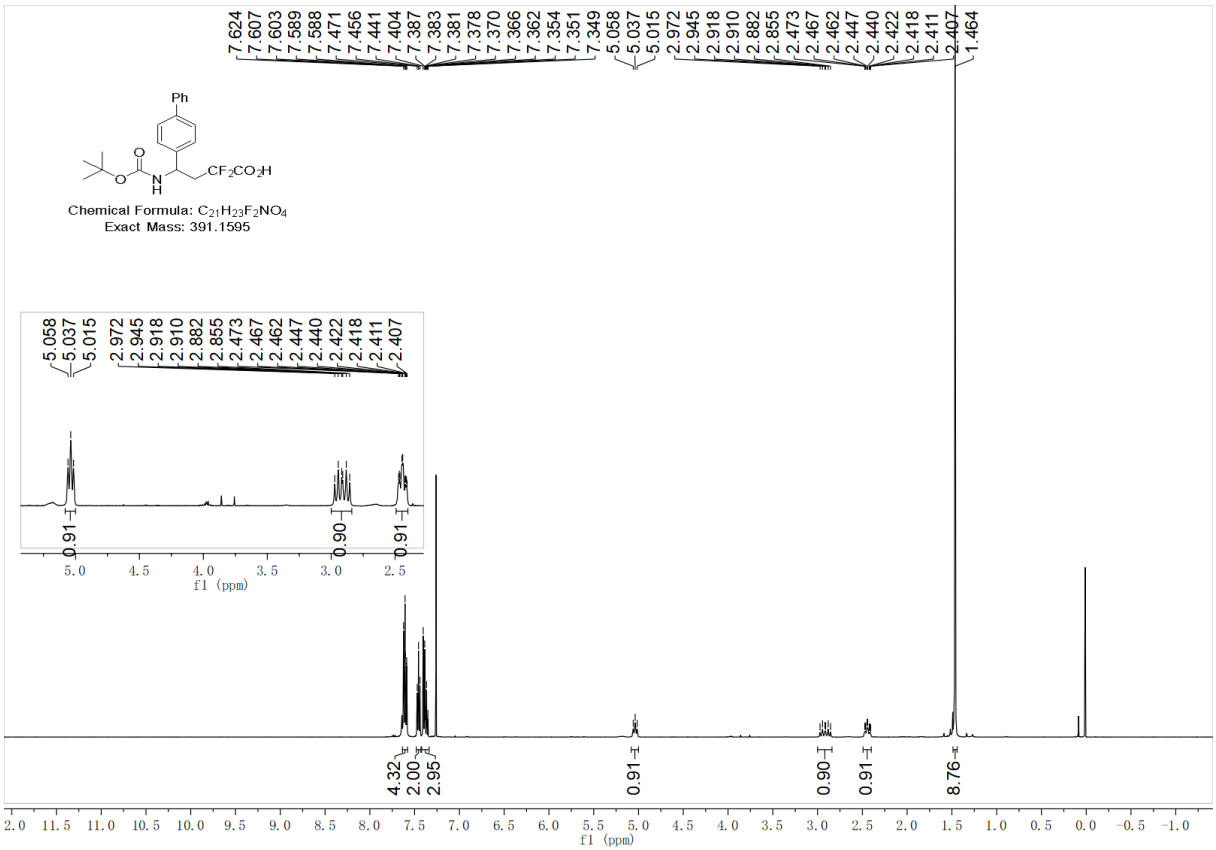


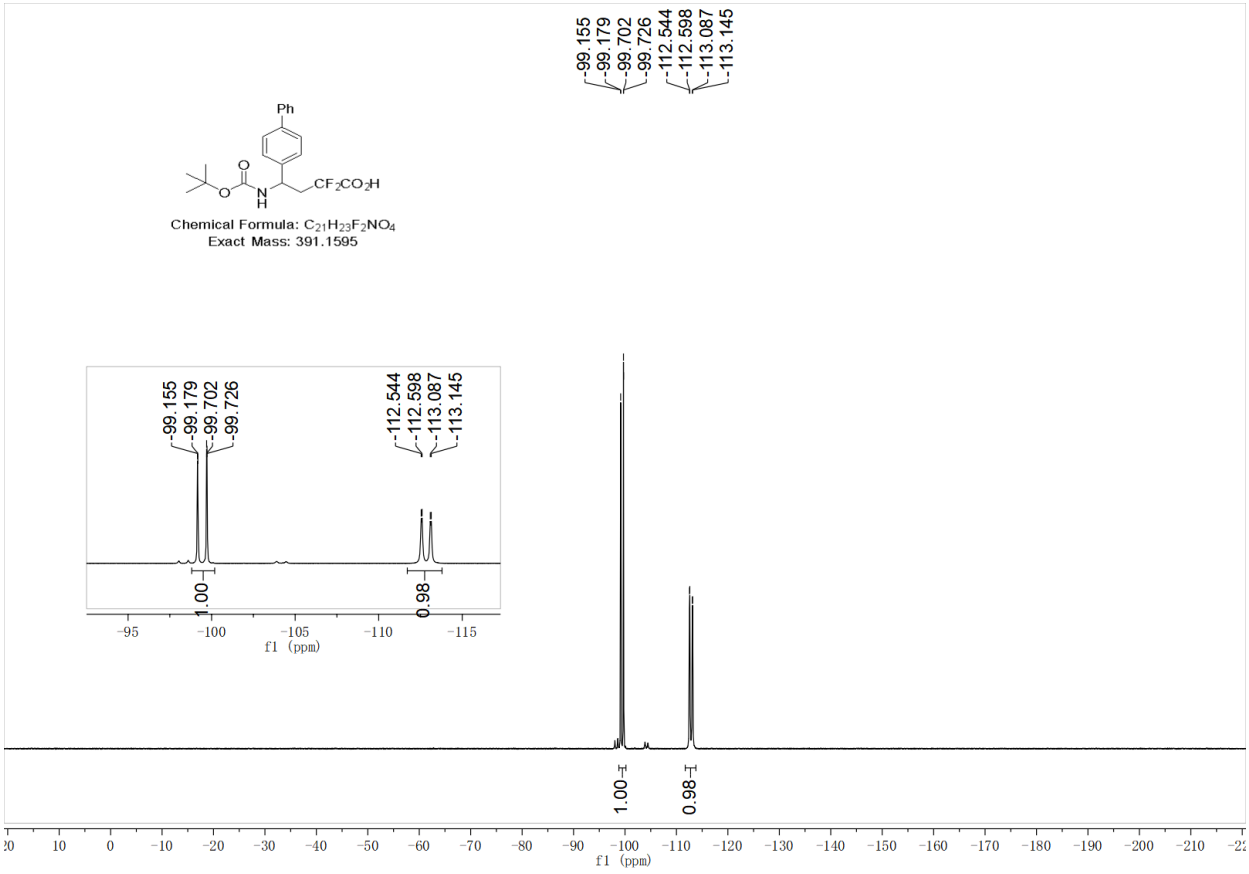


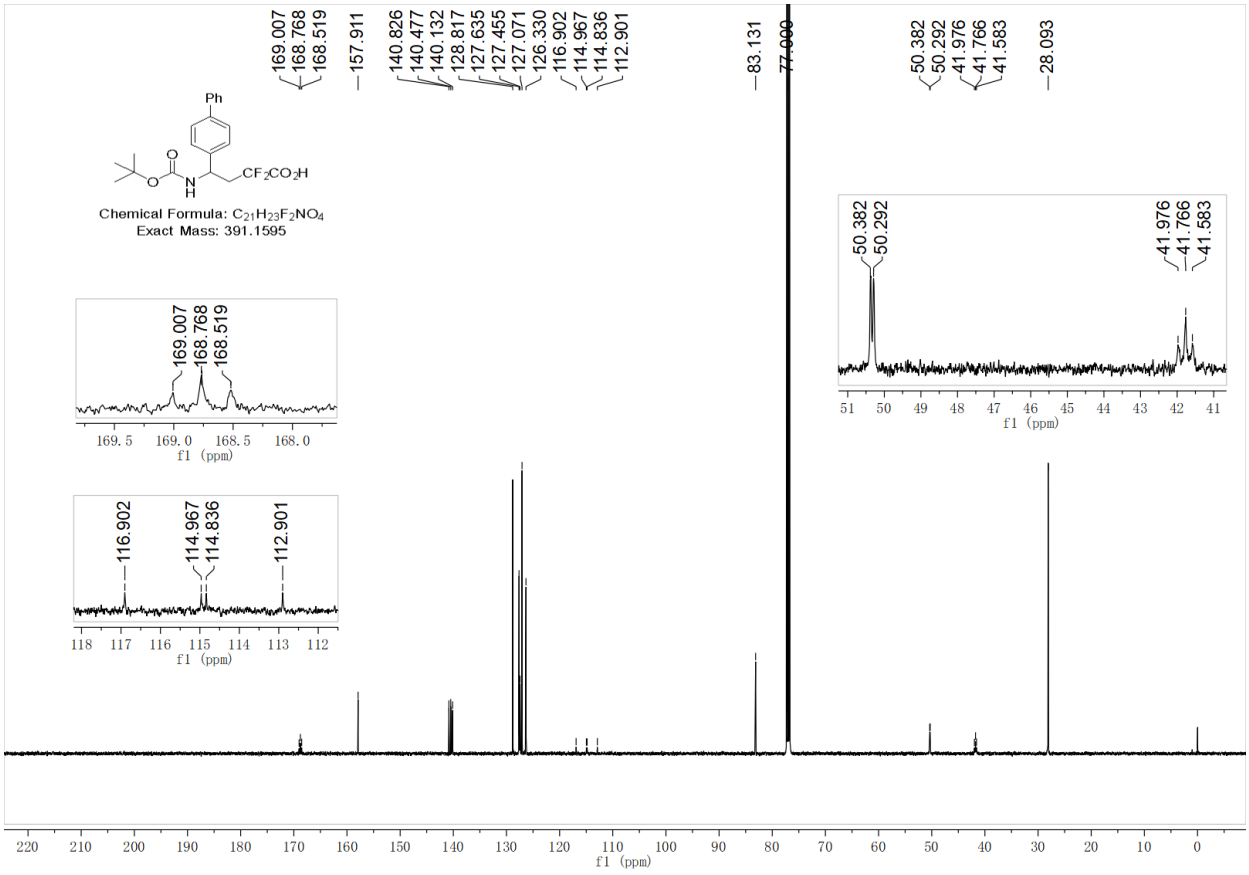


9. Copies of ^{1}HNMR, ^{13}C NMR, and ^{19}F NMR Spectra of Compounds 33-35.

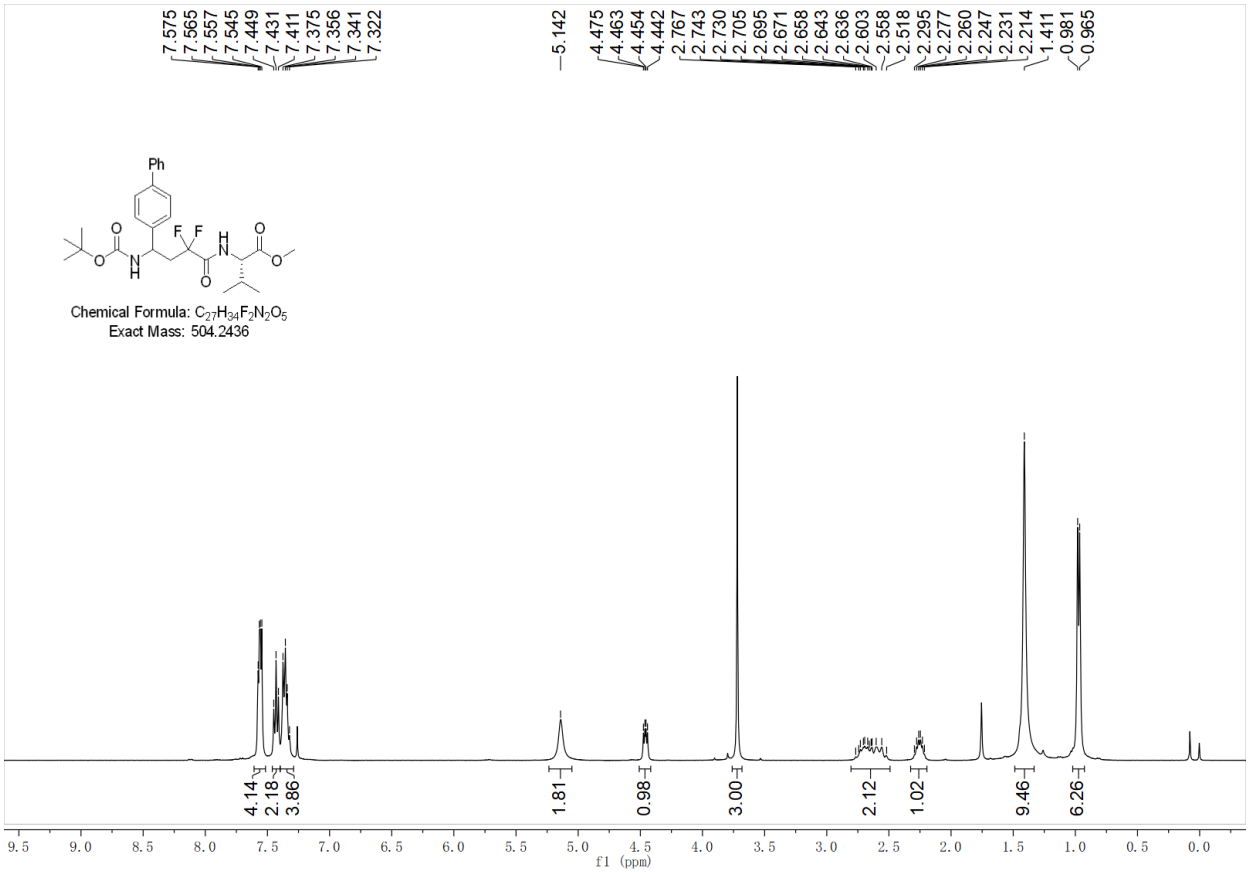
4-([1,1'-biphenyl]-4-yl)-4-((tert-butoxycarbonyl)amino)-2,2-difluorobutanoic acid (33).

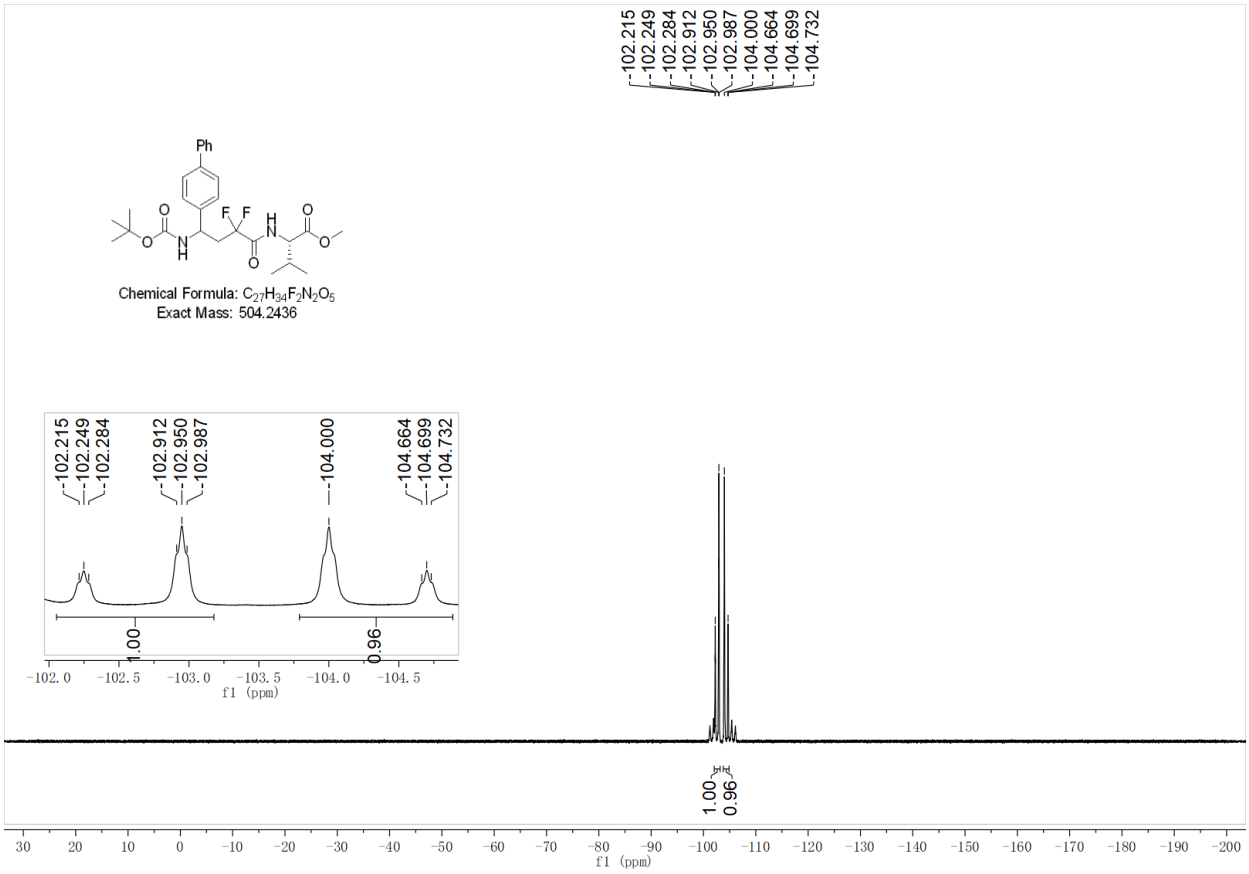


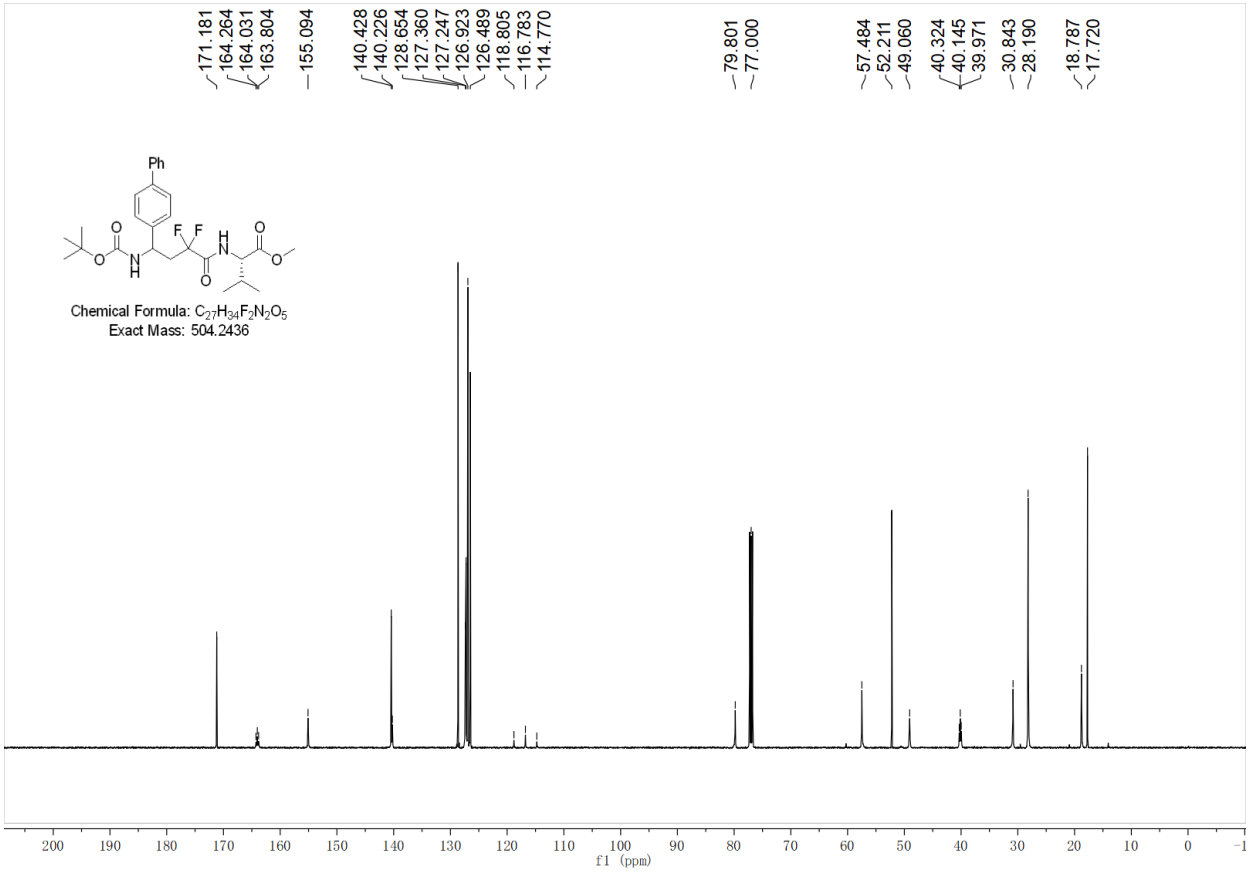

-99.155
-99.179
-99.702
-99.726
-112.544
-112.598
-113.087
-113.145
Ph
CF2CO2H
Chemical Formula: C21H23F2NO4
Exact Mass: 391.1595
1.00
0.98
f1 (ppm)


169.007
168.768
168.519
157.911
140.826
140.477
140.132
128.817
127.635
127.455
127.071
126.330
116.902
114.967
114.836
112.901
83.131
77.000
50.382
50.292
41.976
41.766
41.583
28.093
Ph
CF2CO2H
Chemical Formula: C21H23F2NO4
Exact Mass: 391.1595
f1 (ppm)

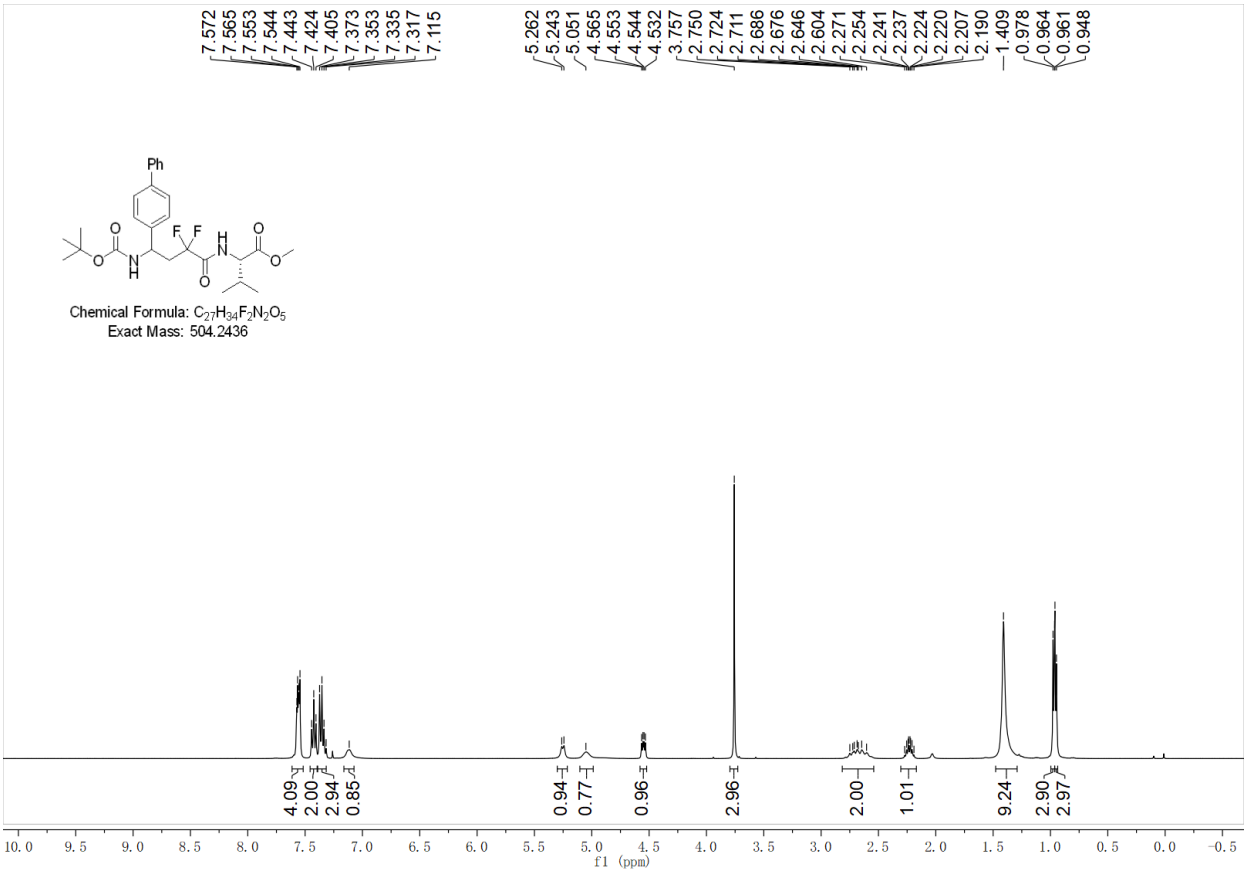
Methyl(4-([1,1'-biphenyl]-4-yl)-4-((tert-butoxycarbonyl)amino)-2,2-difluorobutanoyl)valinate (34a)

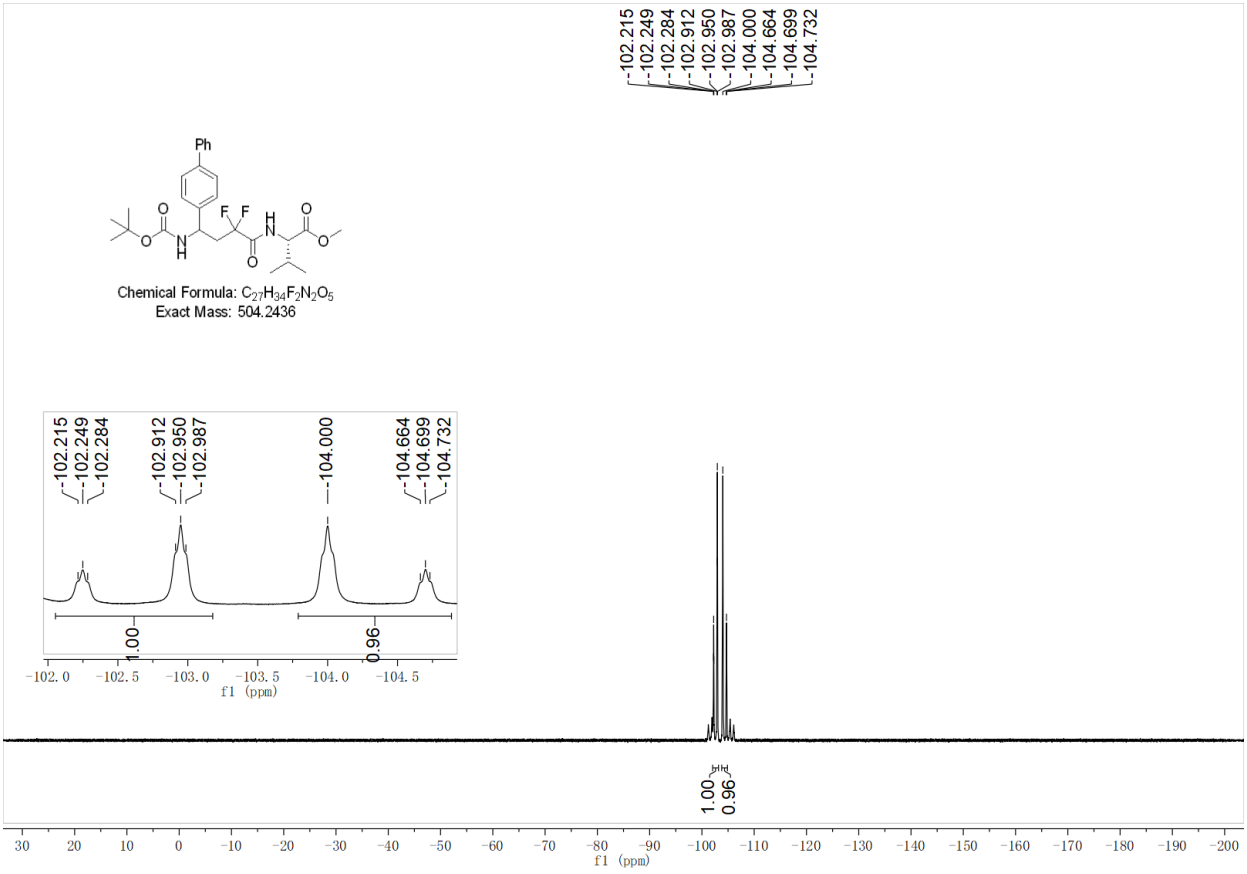


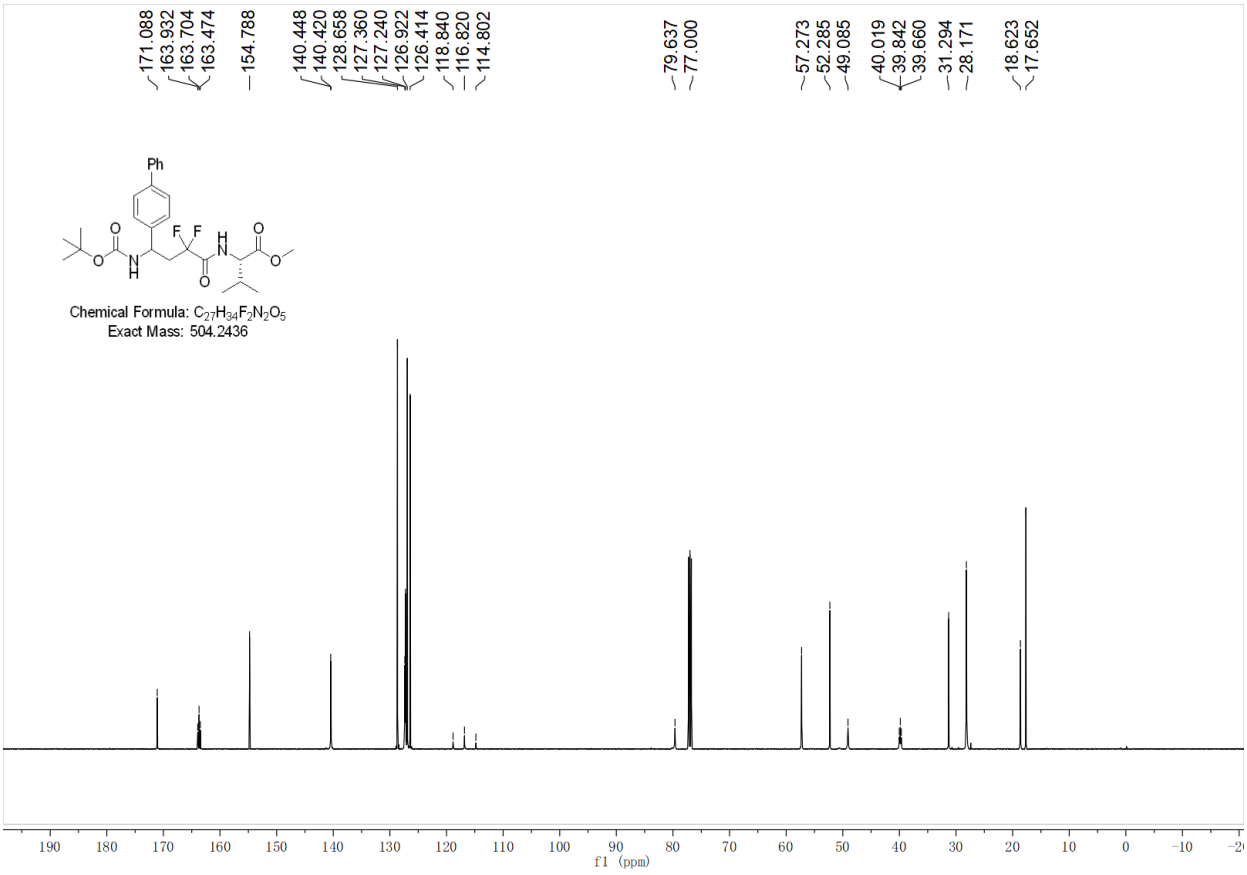




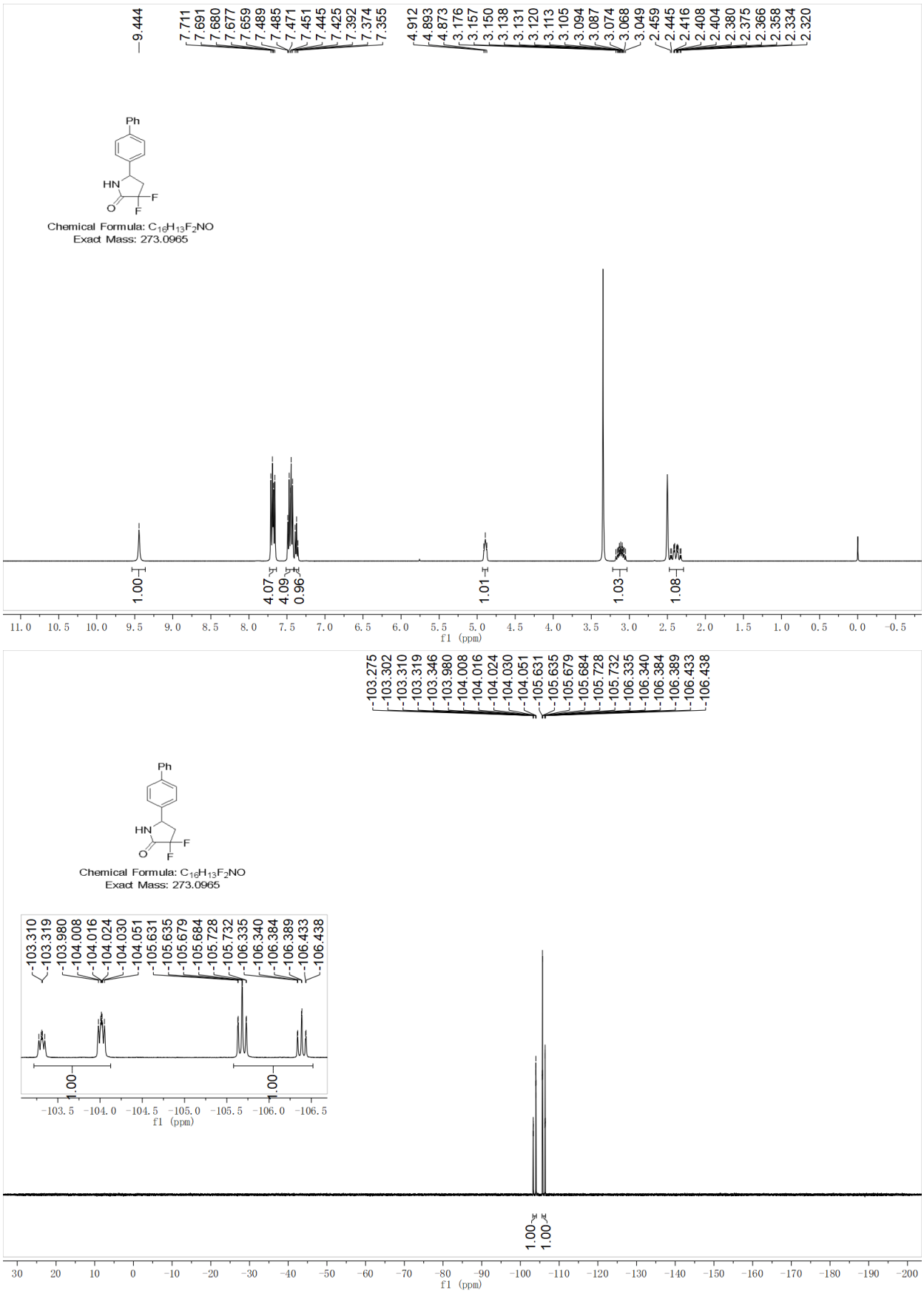
Methyl(4-([1,1'-biphenyl]-4-yl)-4-((tert-butoxycarbonyl)amino)-2,2-difluorobutanoyl)valinate (34b)

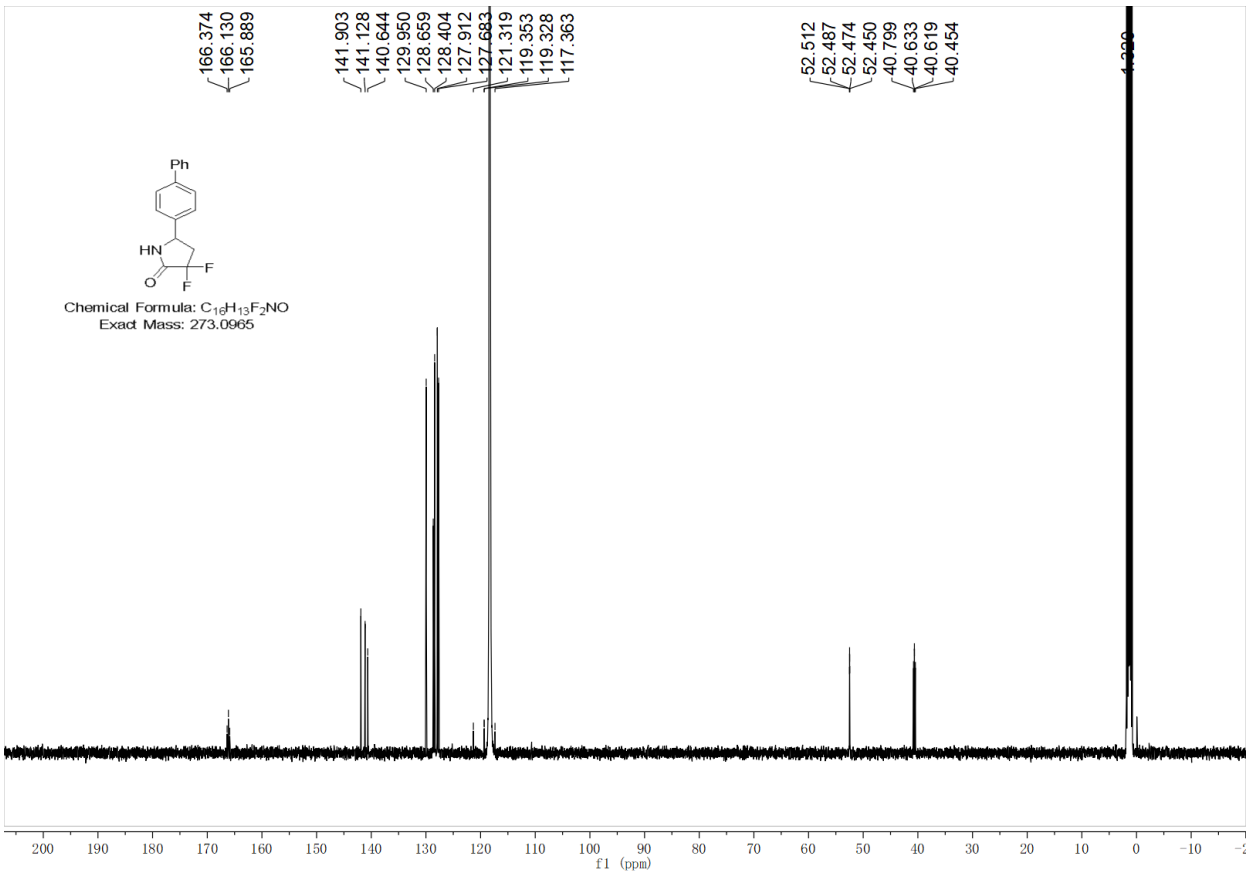



102.215
102.249
102.284
102.912
102.950
102.987
104.000
104.664
104.699
104.732
Ph
Chemical Formula: C27H34F2N2O5
Exact Mass: 504.2436
1.00
0.96
f1 (ppm)


171.088
163.932
163.704
163.474
154.788
140.448
140.420
128.658
127.360
127.240
126.922
126.414
118.840
116.820
114.802
79.637
77.000
57.273
52.285
49.085
40.019
39.842
39.660
31.294
28.171
18.623
17.652
Ph
Chemical Formula: C27H34F2N2O5
Exact Mass: 504.2436
f1 (ppm)

5-([1,1'-biphenyl]-4-yl)-3,3-difluoropyrrolidin-2-one (35)




166.374
166.130
165.889
141.903
141.128
140.644
129.950
128.659
128.404
127.912
127.683
121.319
119.353
119.328
117.363
52.512
52.487
52.474
52.450
40.799
40.633
40.619
40.454
Ph
HN
O
F
F
Chemical Formula: C16H13F2NO
Exact Mass: 273.0965
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)