Supporting Information

Photoredox-Catalyzed Dicarbofunctionalization of Styrenes with Amines and CO_2: A Convenient Entry into γ-Amino Acids

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Contents

1. General Information

All solvents were dried and distilled before use according to the standard methods. Unless otherwise noted, the starting materials were commercially available and used without further purification. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates. Flash chromatography columns were packed with 200-300 mesh silica gel in petroleum ether, ethyl acetate and alcohol.

^{1}H NMR, ^{13}C NMR, ^{19}F NMR data were recorded with 600 MHz, 400 MHz spectrometers with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane and d-solvent peaks, respectively.

2. General Procedure for Reaction Optimization

To a 25 mL Schlenk tube equipped with a magnetic stir bar was added 4CzIPN (2.7 mg, 0.004 mmol) and LiCl (17 mg, 0.4 mmol), the tube was evacuated and filled CO_2 for three times. Then the anhydrous DMSO (1 mL, bubbled with CO_2 for 5 min before usage), methyl 4-vinylbenzoate (16.2 mg, 0.1 mmol) and *N, N*-dimethylaniline (72.7 mg, 0.6 mmol) were added to the tube under a positive CO_2 atmosphere. The reaction tube was sealed and stirred at room temperature under Blue LEDs (5 W) for 48 h. After completion, the reaction was carefully quenched with 2 M HCl and the mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then MeOH: ether (1:1) (0.5 mL) and $TMSCHN_2$ (200 μL, 2 M in hexane) was added to the reaction mixture and stirred at 0 ^{o}C for 30 min. After esterification, the yields were determined by GC technique using *n*-dodecane (20 μL) as an internal standard.

3. General Procedure for Dicarbofunctionalization of Styrenes with CO_2 and Amines

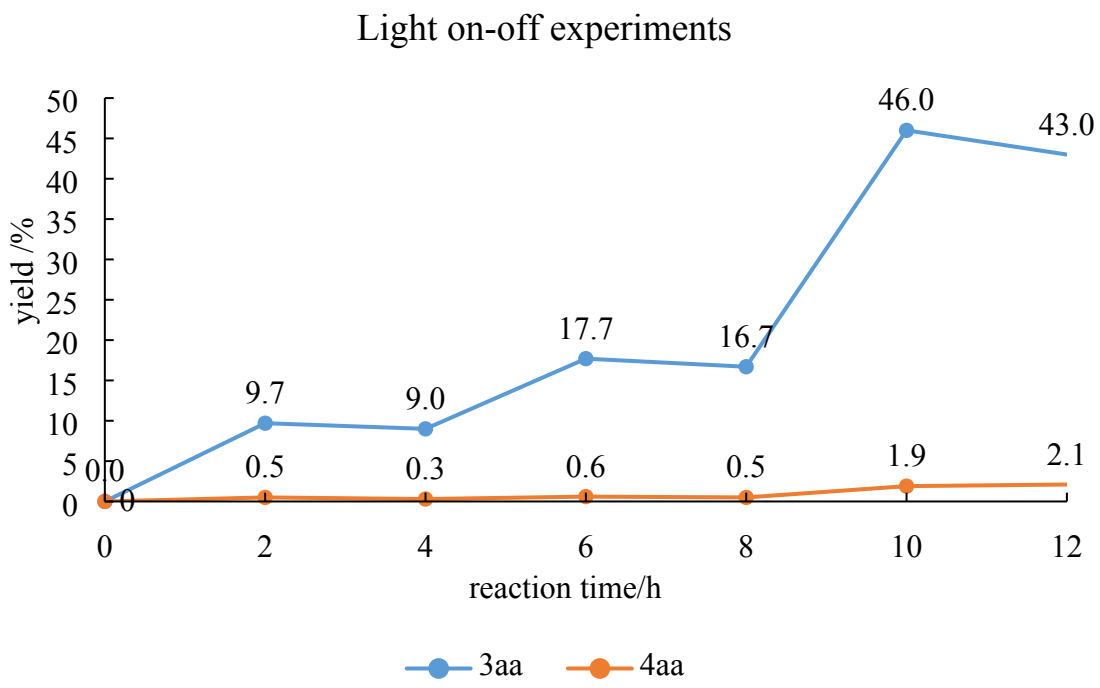
To a 25 mL Schlenk tube equipped with a magnetic stir bar was added 4CzIPN (5.4 mg, 0.008 mmol) and LiCl (34 mg, 0.8 mmol), the tube was evacuated and filled CO_2 for three times. Then the anhydrous DMSO (2 mL, bubbled with CO_2 for 5 min before

usage), styrene (0.2 mmol) and amines (1.2 mmol) were added to the tube under a positive CO_2 atmosphere. The reaction tube was sealed and stirred at room temperature under Blue LEDs (5 W) for 48 h. After completion, the reaction was carefully quenched with 2 M HCl and the mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified by silica gel column chromatography with petroleum ether/ethyl acetate as the eluent to afford the desired γ-amino acid. All of the products were characterized by NMR techniques.

4. Procedure for Mechanistic Studies

Light On-Off Experiments

To six 25 mL-Schlenk tubes equipped with a magnetic stir bar were added 4CzIPN (2.7 mg, 0.004 mmol) and LiCl (17 mg, 0.4 mmol) respectively, the tubes were evacuated and filled CO_2 for three times. Then the anhydrous DMSO (1 mL, bubbled with CO_2 for 5 min before usage), methyl 4-vinylbenzoate (16.2 mg, 0.1 mmol) and *N, N*-dimethylaniline (72.7 mg, 0.6 mmol) were added to the tubes under a positive CO_2 atmosphere. The reaction tubes were sealed and stirred at room temperature under Blue LEDs (5 W). Turn on/off the Blue LEDs every 2 hours and quenched one reaction with 2 M HCl at the same time until all the reactions were quenched. Each reaction mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then MeOH: ether (1:1) (0.5 mL) and $TMSCHN_2$ (200 μL, 2 M in hexane) was added to the reaction mixture and stirred at 0 ^oC for 30 min. After esterification, the yields were determined by GC technique using *n*-dodecane (20 μL) as an internal standard.



Isotope Labelling Experiments with D_2O

To a 25 mL Schlenk tube equipped with a magnetic stir bar was added 4CzIPN (5.4 mg, 0.008 mmol) and LiCl (34 mg, 0.8 mmol), the tube was evacuated and filled N_2 for three times. Then the anhydrous DMSO (1 mL), methyl 4-vinylbenzoate (32.3 mg, 0.2 mmol), *N, N*-dimethylaniline (145.4 mg, 1.2 mmol) and D_2O were added to the tube under a positive N_2 atmosphere. The reaction tube was sealed and stirred at room temperature under Blue LEDs (5 W) for 48 h. After completion, the reaction was carefully quenched with water and the mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified by silica gel column chromatography with petroleum ether/ethyl acetate as the eluent to afford the product. The ratios of deuterated products were determined by ^1H NMR technique.

Determination of quantum yield

To a 25 mL Schlenk tube equipped with a magnetic stir bar was added 4CzIPN (5.4 mg, 0.008 mmol) and LiCl (34 mg, 0.8 mmol), the tube was evacuated and filled CO_2 for three times. Then the anhydrous DMSO (1 mL), methyl 4-vinylbenzoate (32.3 mg, 0.2 mmol) and *N, N*-dimethylaniline (145.4 mg, 1.2 mmol) were added to the tube

under a positive CO_2 atmosphere. The quantum yield was calculated as the ratio of the total molecular number of **2a** that transformed to γ -amino acid to the total number of incident photons on the reactor. The solution was irradiated by a 5 W blue LED (455 ±15 nm) for 4 hours. The average intensity of irradiation was determined to be 3.05 $mW \cdot cm^{-2}$ by Thorlabs PM100D optical power and energy meter. The irradiation area was depending on the height of solution. The number of incident photons (N) is calculated by Equation 1. The quantum yield is calculated from Equation 2.

$$N = \frac{I * S * t * \lambda}{h * c} = \frac{3.05 * 10^{-3} * 2.6 * 4 * 3600 * 455 * 10^{-9}}{6.62 * 10^{-34} * 3 * 10^{8}} = 2.62 * 10^{20}$$

Equation 1

$$\text{Quantum yield} = \frac{M * N_A}{N} = \frac{0.2 * 10^{-3} * 0.09 * 6.02 * 10^{23}}{2.62 * 10^{20}} = 4.14\%$$

Equation 2

Where *I* is light intensity, *S* is irradiation area of solution, *t* is irradiation time, *λ* is wavenumber of incident light, *h* is Planck constant, *c* is light speed, *M* is the molecular number of transformed **2a**, N_A represents Avogadro's constant.

Trapping with Radical Scavengers

To a 25 mL Schlenk tube equipped with a magnetic stir bar was added 4CzIPN (2.7 mg, 0.004 mmol), LiCl (17 mg, 0.4 mmol), and TEMPO (46.9 mg, 0.3 mmol) or BHT (66 mg, 0.3 mmol), the tube was evacuated and filled CO_2 for three times. Then the anhydrous DMSO (1 mL, bubbled with CO_2 for 5 min before usage), methyl 4-vinylbenzoate (16.2 mg, 0.1 mmol) and *N, N*-dimethylaniline (72.7 mg, 0.6 mmol) were added to the tube under a positive CO_2 atmosphere. The reaction tube was sealed and stirred at room temperature under Blue LEDs (5 W) for 48 h. After completion, the reaction was carefully quenched with 2 M HCl and the mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified by silica

gel column chromatography with petroleum ether/ethyl acetate as the eluent. The product was characterized by NMR techniques.

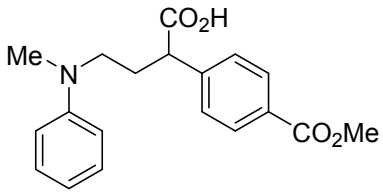
Radical clock reaction

To a 25 mL Schlenk tube equipped with a magnetic stir bar was added 4CzIPN (5.4 mg, 0.008 mmol) and LiCl (34 mg, 0.8 mmol), the tube was evacuated and filled CO_2 for three times. Then the anhydrous DMSO (2 mL, bubbled with CO_2 for 5 min before usage), 1-(1-cyclopropylvinyl)-4-(trifluoromethyl) benzene (42.4 mg, 0.2 mmol) and *N, N*-dimethylaniline (145.4 mg, 1.2 mmol) were added to the tube under a positive CO_2 atmosphere. The reaction tube was sealed and stirred at room temperature under Blue LEDs (5 W) for 48 h. After completion, the reaction was carefully quenched with 2 M HCl and the mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified by silica gel column chromatography with petroleum ether/ethyl acetate as the eluent. The product was characterized by NMR techniques.

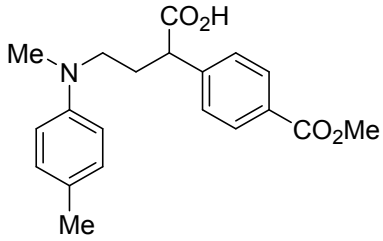
Direct Carboxylation of 4aa

To a 25 mL Schlenk tube equipped with a magnetic stir bar was added 4CzIPN (2.7 mg, 0.004 mmol) and LiCl (17 mg, 0.4 mmol), the tube was evacuated and filled CO_2 for three times. Then the anhydrous DMSO (1 mL, bubbled with CO_2 for 5 min before usage) and methyl 4-(3-(methyl(phenyl) amino) propyl) benzoate **4aa** (32.7 mg, 0.1 mmol) were added to the tube under a positive CO_2 atmosphere. The reaction tube was sealed and stirred at room temperature under Blue LEDs (5 W) for 48 h. After completion, the reaction was carefully quenched with 2 M HCl and the mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified by silica gel column chromatography with petroleum ether/ethyl acetate as the eluent. The product was characterized by NMR techniques.

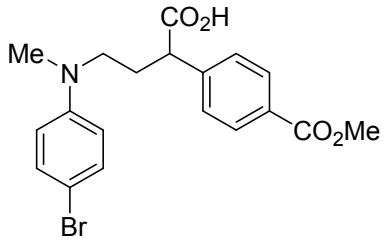
5. Analytical Data of the Products



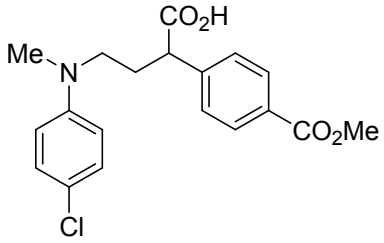
2-(4-(Methoxycarbonyl)phenyl)-4-(methyl(phenyl)amino)butanoic acid (**3aa**): colorless oil, 58.2 mg, 88% yield. ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 2H), 6.71 (t, *J* = 7.2 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 2H), 3.91 (s, 3H), 3.67 (s, 1H), 3.31 (m, 1H), 3.27 – 3.18 (m, 1H), 2.86 (s, 3H), 2.40 (m, 1H), 2.11 – 1.97 (m, 1H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 178.48, 166.89, 149.04, 143.21, 130.21, 129.69, 129.35, 128.30, 117.15, 112.93, 52.32, 50.89, 49.26, 38.72, 29.95. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{19}H_{22}NO_4]^+$: 328.1549, found: 328.1552.



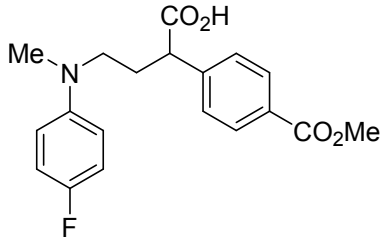
2-(4-(Methoxycarbonyl)phenyl)-4-(methyl(p-tolyl)amino)butanoic acid (**3ba**): colorless oil, 49.8 mg, 73% yield. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.61 (d, *J* = 8.5 Hz, 2H), 3.90 (s, 3H), 3.68 (s, 1H), 3.22 (m, 2H), 2.82 (s, 3H), 2.37 (m, 1H), 2.23 (s, 3H), 2.04 – 1.93 (m, 1H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 178.18, 166.91, 146.90, 143.55, 130.16, 129.90, 129.55, 128.30, 126.98, 113.83, 52.30, 51.48, 49.43, 39.20, 29.83, 20.39. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{20}H_{24}NO_4]^+$: 342.1705, found: 342.1709.



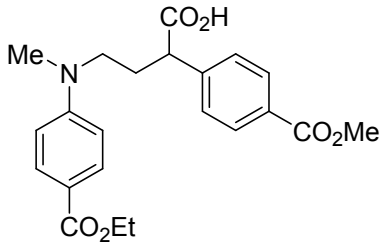
4-((4-Bromophenyl)(methyl)amino)-2-(4-(methoxycarbonyl)phenyl)butanoic acid (**3ca**): colorless oil, 65.6 mg, 81% yield. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 11.21 (s, 1H), 8.00 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.9 Hz, 2H), 6.47 (d, *J* = 9.0 Hz, 2H), 3.91 (s, 3H), 3.63 (t, *J* = 7.5 Hz, 1H), 3.37 – 3.12 (m, 1H), 2.82 (s, 3H), 2.38 (m, 1H), 2.08 – 1.91 (m, 1H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 178.65, 166.84, 147.96, 142.94, 131.92, 130.24, 129.74, 128.21, 114.24, 108.78, 52.35, 50.72, 49.09, 38.64, 29.72. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{19}H_{21}BrNO_4]^+$: 406.0654, found: 406.0660.



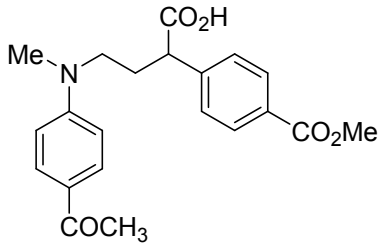
4-((4-Chlorophenyl)(methyl)amino)-2-(4-(methoxycarbonyl)phenyl)butanoic acid (**3da**): colorless oil, 46.3 mg, 64% yield. ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 8.00 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.47 (d, *J* = 8.9 Hz, 2H), 3.91 (s, 3H), 3.63 (t, *J* = 7.4 Hz, 1H), 3.28 (m, 1H), 3.20 (m, 1H), 2.83 (s, 3H), 2.38 (m, 1H), 2.00 (m, 1H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 178.43, 166.86, 147.99, 143.01, 131.94, 130.25, 129.75, 128.22, 114.23, 108.78, 52.36, 50.74, 49.11, 38.64, 29.75. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{19}H_{21}ClNO_4]^+$: 362.1159, found: 362.1156.



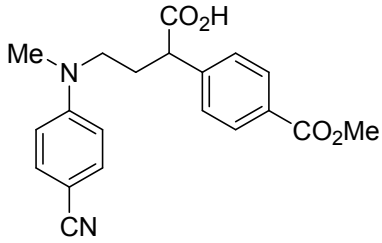
4-((4-Fluorophenyl)(methyl)amino)-2-(4-(methoxycarbonyl)phenyl)butanoic acid (**3ea**): white solid, 51.8 mg, 75% yield. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 7.99 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 6.88 (t, *J* = 8.7 Hz, 2H), 6.59 (dd, *J* = 9.0, 4.3 Hz, 2H), 3.91 (s, 3H), 3.66 (t, *J* = 7.2 Hz, 1H), 3.21 (m, 2H), 2.81 (s, 3H), 2.37 (m, 1H), 2.07 – 1.94 (m, 1H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 178.31, 166.88, 155.97 (d, *J* = 236.3 Hz), 145.78, 143.31, 130.19, 129.63, 128.24, 115.69 (d, *J* = 22.1 Hz), 114.66 (d, *J* = 7.3 Hz), 52.33, 51.74, 49.33, 39.33, 29.78. ^{19}F NMR (565 MHz) δ -127.87. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{19}H_{21}FNO_4]^+$: 346.1455, found: 346.1458.



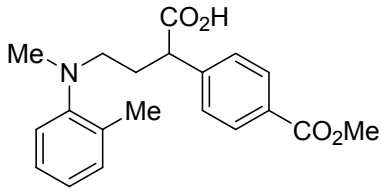
4-((4-(Ethoxycarbonyl)phenyl)(methyl)amino)-2-(4-(methoxycarbonyl)phenyl)butanoic acid (**3fa**): colorless oil, 70.3 mg, 88% yield. ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 8.9 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 6.55 (d, *J* = 8.9 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 3.65 (t, *J* = 7.5 Hz, 1H), 3.41 (m, 1H), 3.30 (m, 1H), 2.94 (s, 3H), 2.42 (m, 1H), 2.10 – 1.99 (m, 1H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 177.61, 167.25, 166.82, 152.06, 142.99, 131.47, 130.24, 129.72, 128.16, 117.53, 110.76, 60.38, 52.30, 50.26, 48.99, 38.44, 29.90, 14.52. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{22}H_{26}NO_6]^+$: 400.1760, found: 400.1761.



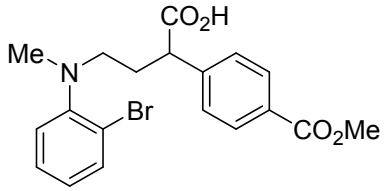
4-((4-Acetylphenyl)(methyl)amino)-2-(4-(methoxycarbonyl)phenyl)butanoic acid (**3ga**): colorless oil, 63.5 mg, 86% yield. ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 6.57 (d, *J* = 8.9 Hz, 2H), 3.91 (s, 3H), 3.66 (t, *J* = 7.5 Hz, 1H), 3.44 (m, 1H), 3.33 (m, 1H), 2.97 (s, 3H), 2.55 – 2.36 (m, 4H), 2.11 – 1.96 (m, 1H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 197.24, 176.93, 166.82, 152.41, 143.11, 130.95, 130.24, 129.70, 128.14, 125.31, 110.68, 52.32, 50.29, 48.99, 38.46, 29.99, 25.91. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{21}H_{24}NO_5]^+$: 370.1654, found: 370.1656.



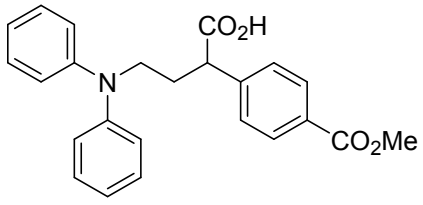
4-((4-Cyanophenyl)(methyl)amino)-2-(4-(methoxycarbonyl)phenyl)butanoic acid (**3ha**): white solid, 56.4 mg, 80% yield. ^{1}H NMR (600 MHz, DMSO-D6) δ 7.93 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 6.70 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H), 3.72 (t, *J* = 7.4 Hz, 1H), 3.43 – 3.34 (m, 2H), 2.91 (s, 3H), 2.28 – 2.18 (m, 1H), 1.92 – 1.81 (m, 1H). ^{13}C NMR (151 MHz, DMSO-D6) δ 173.85, 166.00, 151.33, 144.80, 133.27, 129.49, 128.45, 128.17, 120.47, 111.50, 95.73, 52.10, 49.59, 48.19, 37.81, 29.33. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{20}H_{21}N_2O_4]^+$: 353.1501, found: 353.1503.



2-(4-(Methoxycarbonyl)phenyl)-4-(methyl(*o*-tolyl)amino)butanoic acid (**3ia**): colorless oil, 47.8 mg, 70% yield. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 7.96 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.13 (dd, *J* = 11.0, 7.6 Hz, 2H), 7.05 – 6.93 (m, 2H), 3.90 (s, 3H), 3.79 – 3.68 (m, 1H), 3.03 – 2.76 (m, 2H), 2.62 (d, *J* = 9.8 Hz, 3H), 2.42 – 2.13 (m, 4H), 2.06 – 1.84 (m, 1H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 178.45, 166.88, 151.28, 143.63, 133.45, 131.32, 130.06, 129.42, 128.26, 126.56, 123.61, 120.20, 53.31, 52.23, 49.16, 42.67, 30.84, 18.18. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{20}H_{24}NO_4]^+$: 342.1705, found: 342.1702.

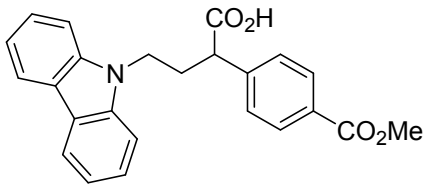


4-((2-Bromophenyl)(methyl)amino)-2-(4-(methoxycarbonyl)phenyl)butanoic acid (**3ja**): colorless oil, 63.4 mg, 78% yield. ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 7.96 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.89 (t, *J* = 7.3 Hz, 1H), 3.89 (s, 3H), 2.98 (m, 1H), 2.87 – 2.78 (m, 1H), 2.67 (s, 3H), 2.34 (m, 1H), 1.96 (m, 1H), 1.31 – 1.17 (m, 1H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 179.10, 166.95, 150.67, 143.49, 133.98, 130.06, 129.41, 128.41, 128.19, 124.83, 122.37, 120.96, 52.80, 52.25, 48.63, 42.39, 30.66. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{19}H_{21}BrNO_4]^+$: 406.0654, found: 406.0655.

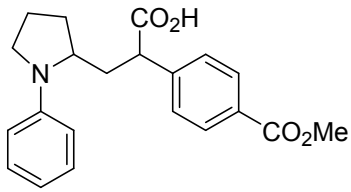


4-(Diphenylamino)-2-(4-(methoxycarbonyl)phenyl)butanoic acid (**3ka**): colorless oil, 70.1 mg, 90% yield. ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.21 (t, *J* = 7.9 Hz, 4H), 6.91 (t, *J* = 7.4 Hz, 6H), 3.89 (d, *J* = 6.4 Hz, 3H), 3.73 – 3.66 (m, 2H), 3.62 (m, 1H), 2.49 (dd, *J* = 14.5, 5.8 Hz, 1H),

2.17 – 2.07 (m, 1H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 178.82, 166.86, 147.77, 142.91, 130.18, 129.65, 129.45, 128.26, 121.65, 121.03, 52.30, 50.01, 49.10, 30.69. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{24}H_{24}NO_4]^+$: 390.1705, found: 390.1702.

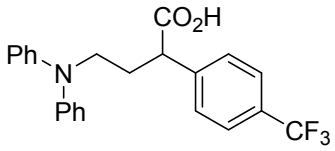


4-(9*H*-Carbazol-9-yl)-2-(4-(methoxycarbonyl)phenyl)butanoic acid (**3la**): white solid, 67.4 mg, 87% yield. ^{1}H NMR (600 MHz, DMSO-D6) δ 12.77 (s, 1H), 8.12 (d, *J* = 7.1 Hz, 2H), 7.92 (d, *J* = 7.3 Hz, 2H), 7.45 (dd, *J* = 25.1, 6.7 Hz, 6H), 7.18 (t, *J* = 6.5 Hz, 2H), 4.34 (m, 2H), 3.85 (s, 3H), 3.42 (s, 1H), 2.50 (s, 1H), 2.12 (s, 1H). ^{13}C NMR (151 MHz, DMSO-D6) δ 173.83, 166.01, 144.61, 139.76, 129.54, 128.54, 128.16, 125.73, 122.22, 120.32, 118.86, 108.93, 52.07, 48.27, 40.60, 31.51. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{24}H_{22}NO_4]^+$: 388.1549, found: 388.1552.

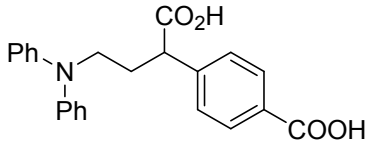


2-(4-(Methoxycarbonyl)phenyl)-3-(1-phenylpyrrolidin-2-yl)propanoic acid (**3ma**): yellow soild and colorless oil, 42.4 mg, 60% yield, dr = 1:1.1. **3ma-1**: ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 11.18 (s, 1H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.22 (dd, *J* = 8.5, 7.1 Hz, 2H), 6.79 – 6.62 (m, 3H), 3.90 (d, *J* = 12.6 Hz, 3H), 3.81 (s, 1H), 3.72 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.37 (t, *J* = 7.4 Hz, 1H), 3.17 – 3.04 (m, 1H), 2.76 – 2.60 (m, 1H), 2.03 – 1.89 (m, 3H), 1.76 (s, 1H), 1.63 – 1.52 (m, 1H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 178.99, 166.88, 147.11, 143.67, 130.18, 129.51, 129.34, 128.02, 116.00, 112.15, 56.90, 52.29, 49.19, 48.40, 36.30, 30.16, 23.34. **3ma-2**: ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 8.06 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.08 (t, *J* = 7.8 Hz, 2H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.26 (d, *J* = 8.2 Hz,

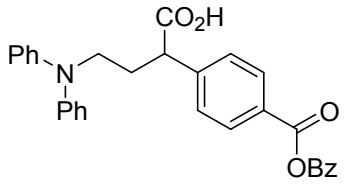
2H), 3.99 – 3.88 (m, 4H), 3.64 (m, 1H), 3.46 (s, 1H), 3.40 (m, 1H), 3.11 (m, 1H), 2.36 – 2.15 (m, 1H), 1.97 (m, 3H), 1.88 (m, 1H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 177.94, 166.88, 146.92, 142.94, 130.20, 129.85, 129.21, 128.64, 115.95, 112.08, 55.81, 49.08, 48.50, 36.04, 30.07, 29.86, 23.53. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{21}H_{24}NO_4]^+$: 354.1705, found: 354.1706.



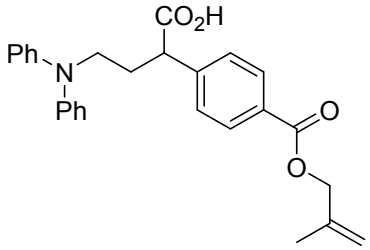
4-(Diphenylamino)-2-(4-(trifluoromethyl)phenyl)butanoic acid (**3kb**): white solid, 70.3 mg, 88% yield. ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.7 Hz, 4H), 6.99 – 6.83 (m, 6H), 3.75 – 3.67 (m, 2H), 3.64 (m, *J* = 9.1, 5.5 Hz, 1H), 2.51 (m, 1H), 2.11 (td, *J* = 13.7, 8.3 Hz, 1H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 179.31, 147.83, 141.72, 130.21 (q, *J* = 32.9 Hz), 129.51, 128.65, 125.89 (d, *J* = 3.0 Hz), 124.11 (q, *J* = 272.0 Hz) 121.79, 121.11, 50.00, 49.02, 30.85. ^{19}F NMR (565 MHz) δ -62.50. HRMS (ESI+): calculated m/z $[M+Na]^+$ for $[C_{23}H_{20}F_3NO_2Na]^+$: 422.1344, found: 422.1343.



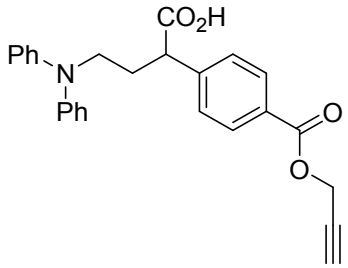
4-(1-Carboxy-3-(diphenylamino)propyl)benzoic acid (**3kc**): yellow solid, 39.8 mg, 53% yield. ^{1}H NMR (600 MHz, DMSO-D6) δ 12.79 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 4H), 6.91 (dd, *J* = 14.3, 7.6 Hz, 6H), 3.83 – 3.66 (m, 2H), 3.58 (m, 1H), 2.41 – 2.26 (m, 1H), 1.91 (m, 1H). ^{13}C NMR (151 MHz, DMSO-D6) δ 174.10, 167.15, 147.38, 144.45, 129.69, 129.64, 129.39, 128.05, 121.25, 120.56, 49.70, 48.20, 30.45. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{23}H_{22}NO_4]^+$: 376.1549, found: 376.1560.



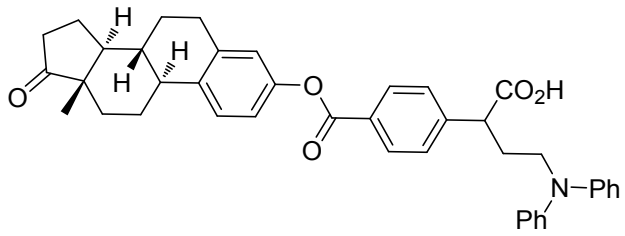
2-(4-((Benzyloxy)carbonyl)phenyl)-4-(diphenylamino)butanoic acid (**3kd**): white solid, 72.9 mg, 76% yield. ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.35 (d, *J* = 7.1 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 4H), 6.94 (d, *J* = 7.3 Hz, 2H), 6.91 (t, *J* = 6.4 Hz, 4H), 5.35 (s, 2H), 3.75 – 3.66 (m, 2H), 3.62 (m, 5.4 Hz, 1H), 2.49 (m, 1H), 2.17 – 2.06 (m, 1H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 178.83, 166.16, 147.76, 143.05, 136.02, 130.31, 129.64, 129.45, 128.69, 128.37, 128.27, 128.24, 121.66, 121.04, 66.87, 49.99, 49.11, 30.68. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{30}H_{26}NO_5]^+$: 480.1811, found: 480.1815.



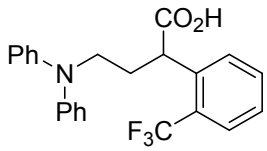
4-(Diphenylamino)-2-(4-(((2-methylallyl)oxy)carbonyl)phenyl)butanoic acid (**3ke**): colorless oil, 62.7 mg, 73% yield. ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 4H), 6.92 (m, 6H), 5.02 (d, *J* = 48.2 Hz, 2H), 4.74 (s, 2H), 3.71 (m, 2H), 3.65 – 3.58 (m, 1H), 2.50 (m, 1H), 2.19 – 2.07 (m, 1H), 1.82 (s, 3H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 178.86, 165.98, 147.78, 142.96, 140.00, 130.27, 129.75, 129.48, 128.31, 121.69, 121.06, 113.14, 68.33, 50.02, 49.09, 30.70, 19.70. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{27}H_{28}NO_4]^+$: 430.2018, found: 430.2020.



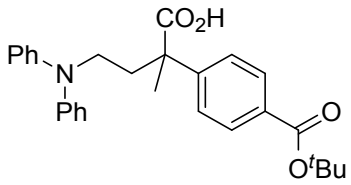
4-(Diphenylamino)-2-(4-((prop-2-yn-1-yloxy)carbonyl)phenyl)butanoic acid (**3kf**): white solid, 65.3 mg, 79% yield. ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 8.01 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.23 (t, *J* = 7.9 Hz, 4H), 6.94 (t, *J* = 7.4 Hz, 2H), 6.91 (d, *J* = 7.7 Hz, 4H), 4.91 (d, *J* = 2.4 Hz, 2H), 3.70 (m, 8.2 Hz, 2H), 3.64 (m, 1H), 2.51 (d, *J* = 2.4 Hz, 2H), 2.13 (m, 1H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 178.34, 165.52, 147.81, 143.38, 130.46, 129.51, 129.01, 128.38, 121.73, 121.09, 77.76, 75.22, 52.67, 50.04, 49.06, 30.76. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{26}H_{24}NO_4]^+$: 414.1705. found: 414.1709.



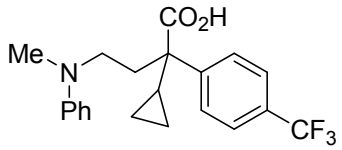
4-(Diphenylamino)-2-(4-((((*8R,9S,13S,14S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-*6H*-cyclopenta*[a]*phenanthren-3-yl)oxy)carbonyl)phenyl)butanoic acid (**3kg**): white solid, 81.6 mg, 65% yield. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 8.13 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.28 – 7.19 (m, 5H), 7.02 – 6.86 (m, 8H), 3.83 – 3.59 (m, 3H), 3.04 – 2.85 (m, 2H), 2.63 – 2.25 (m, 4H), 2.23 – 1.94 (m, 6H), 1.71 – 1.39 (m, 7H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 221.43, 177.97, 165.09, 148.80, 147.75, 143.75, 138.14, 137.53, 130.68, 129.44, 129.09, 128.41, 126.54, 121.71, 121.64, 121.02, 118.89, 50.45, 50.03, 49.11, 48.08, 44.19, 38.05, 35.94, 31.57, 30.72, 29.76, 29.48, 26.41, 25.82, 21.66, 13.89. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{41}H_{42}NO_5]^+$: 628.3063. found: 628.3065.



4-(Diphenylamino)-2-(2-(trifluoromethyl)phenyl)butanoic acid (**3kh**): white solid, 62.3 mg, 78% yield. ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.53 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 4H), 6.98 – 6.85 (m, 6H), 4.09 (t, *J* = 7.3 Hz, 1H), 3.85 – 3.75 (m, 1H), 3.63 – 3.54 (m, 1H), 2.52 – 2.42 (m, 1H), 2.17 – 2.08 (m, 1H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 179.13, 147.70, 136.82, 132.43, 129.43, 128.97, 128.67, 127.79, 126.29 (dd, *J* = 11.1, 5.5 Hz), 124.30 (dd, *J* = 547.5, 273.6 Hz), 121.56, 120.93, 50.33, 44.31, 31.64. ^{19}F NMR (565 MHz) δ -58.22. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{23}H_{21}F_3NO_2]^+$: 400.1524. found: 400.1525.



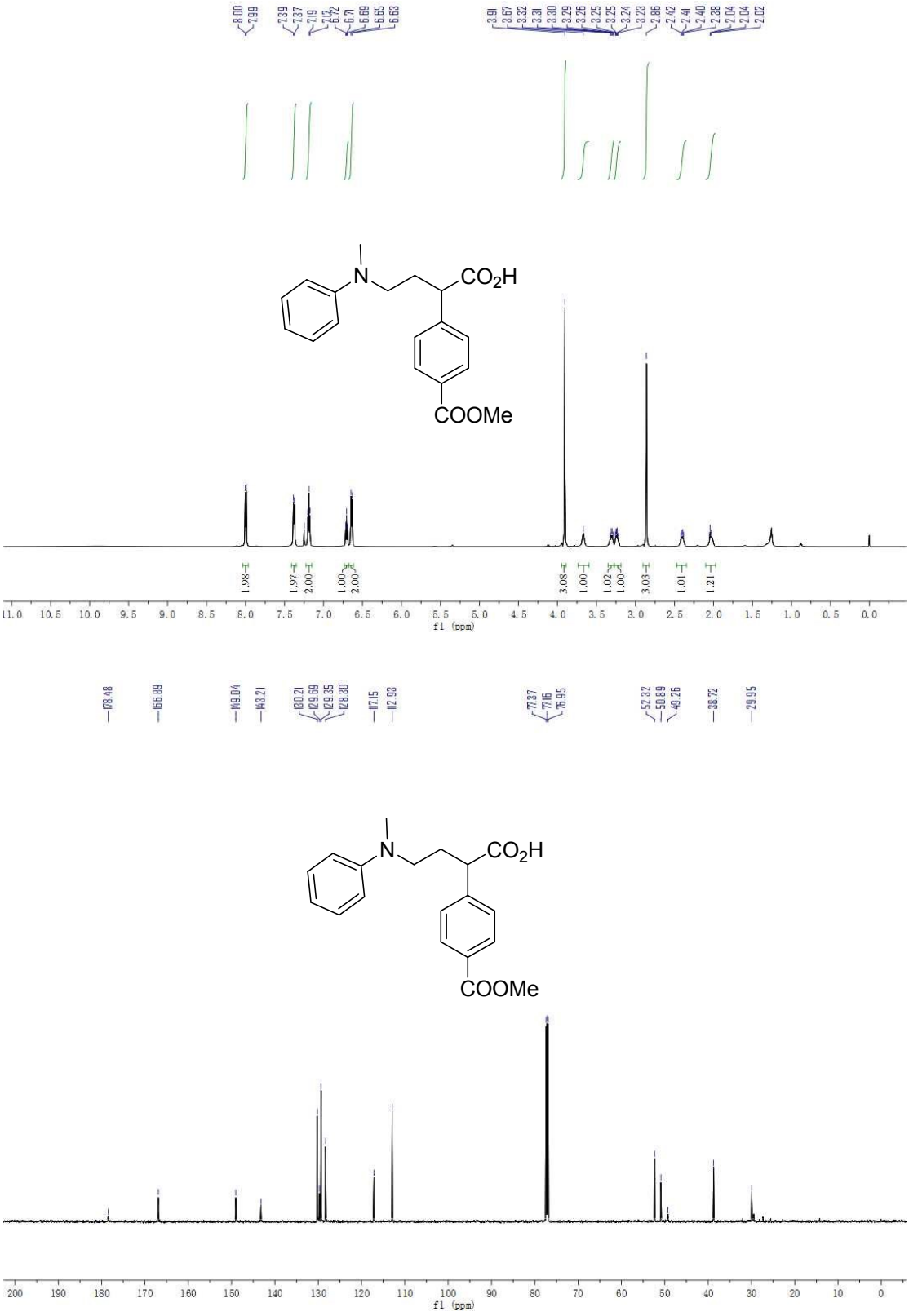
2-(4-(*tert*-Butoxycarbonyl)phenyl)-4-(diphenylamino)-2-methylbutanoic acid (**3ki**): white solid, 53.5 mg, 60% yield. ^{1}H NMR (600 MHz, CHLOROFORM-D) δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.21 (t, *J* = 7.8 Hz, 4H), 6.91 (m, *J* = 11.5, 8.0 Hz, 6H), 3.63 (m, 2H), 2.52 – 2.36 (m, 1H), 2.35 – 2.26 (m, 1H), 1.65 (s, 3H), 1.59 (s, 9H). ^{13}C NMR (151 MHz, CHLOROFORM-D) δ 180.99, 165.54, 147.66, 146.65, 131.10, 129.82, 129.42, 126.16, 121.40, 120.84, 81.28, 49.18, 48.26, 36.17, 28.33, 22.53. HRMS (ESI+): calculated m/z $[M+H]^+$ for $[C_{28}H_{32}NO_4]^+$: 446.2331. found: 446.2330.



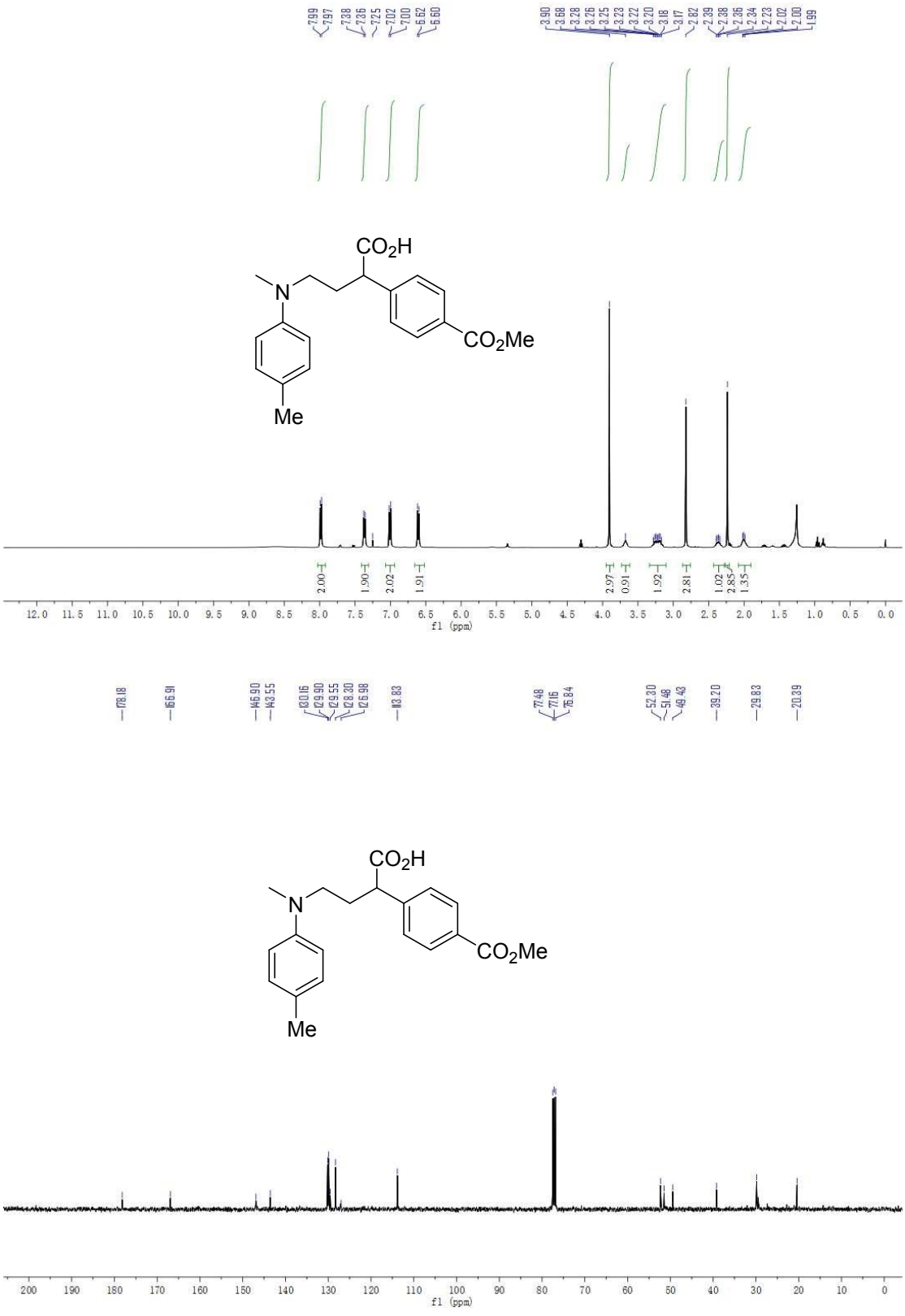
2-Cyclopropyl-4-(methyl(phenyl)amino)-2-(4-(trifluoromethyl)phenyl)butanoic acid (**3aj**): colorless oil, 39.3 mg, 52% yield. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ

7.61 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 2H), 6.72 (t, *J* = 7.2 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 2H), 3.53 – 3.36 (m, 1H), 3.35 – 3.19 (m, 1H), 2.85 (s, 3H), 2.10 (m, 2H), 1.52 – 1.41 (m, 1H), 0.73 (m, 1H), 0.62 (m, 1h), 0.53 – 0.34 (m, 2H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 179.39, 148.66, 145.72, 129.68, 129.43, 128.11, 125.53, 125.26, 117.53, 113.17, 53.82, 49.24, 38.77, 33.09, 18.02, 3.60, 1.67. ^{19}F NMR (565 MHz) δ -62.44. HRMS (ESI+): calculated m/z $[M+Na]^+$ for $[C_{21}H_{22}F_3NO_2Na]^+$: 400.1500. found: 400.1498.

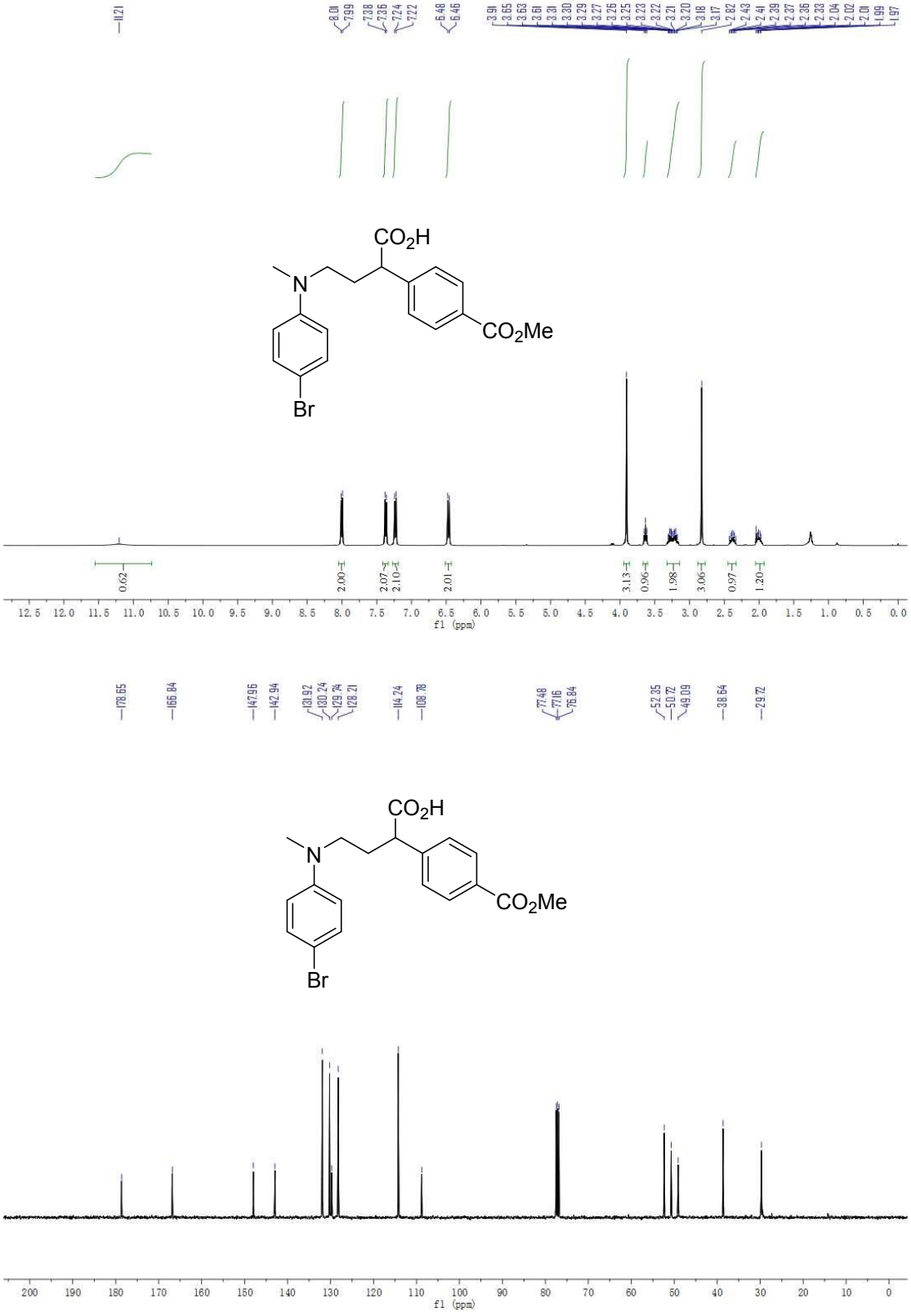
6. ^{1}H and ^{13}C NMR Spectra of Products



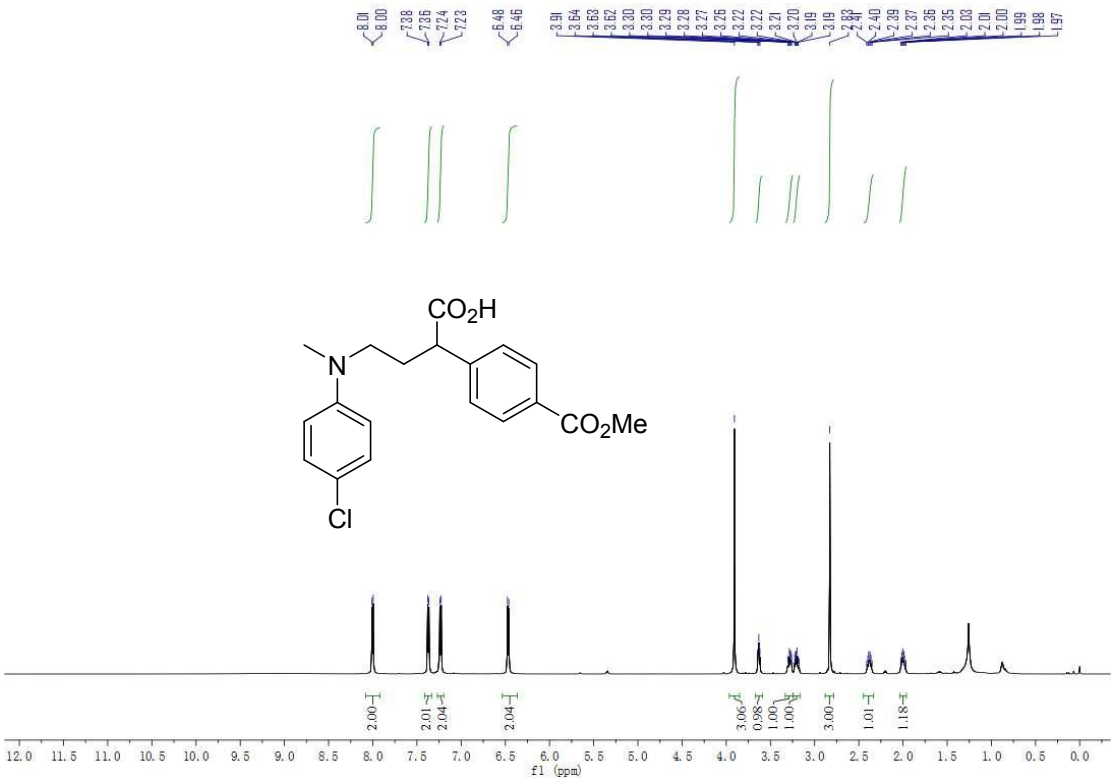
^{1}H and ^{13}C spectra of **3aa**

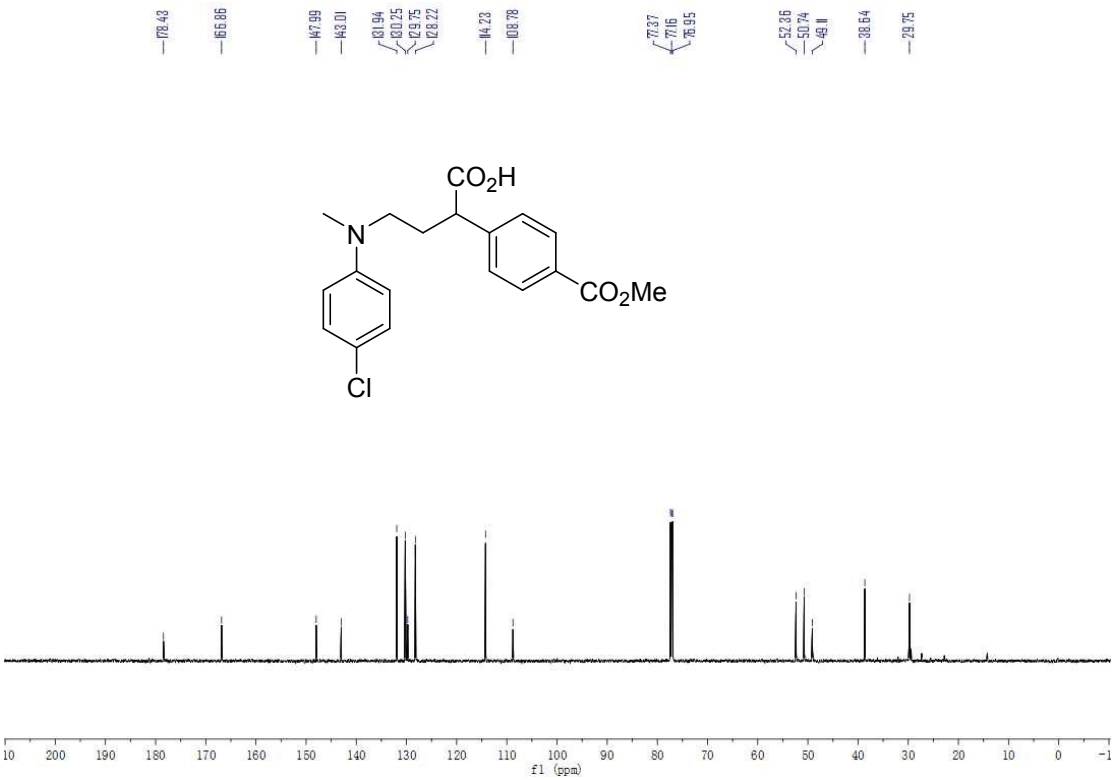


^{1}H and ^{13}C spectra of **3ba**

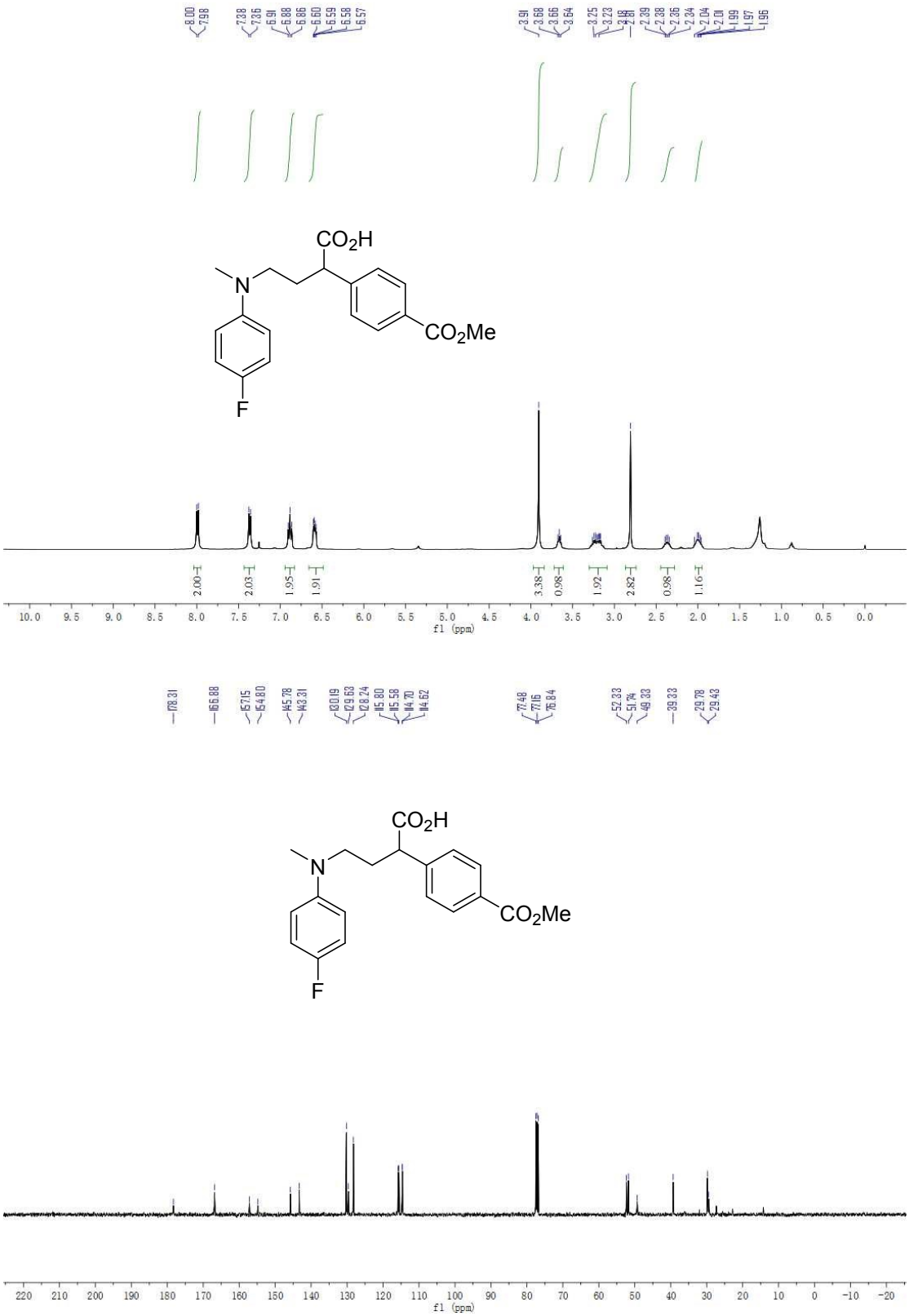


^{1}H and ^{13}C spectra of **3ca**

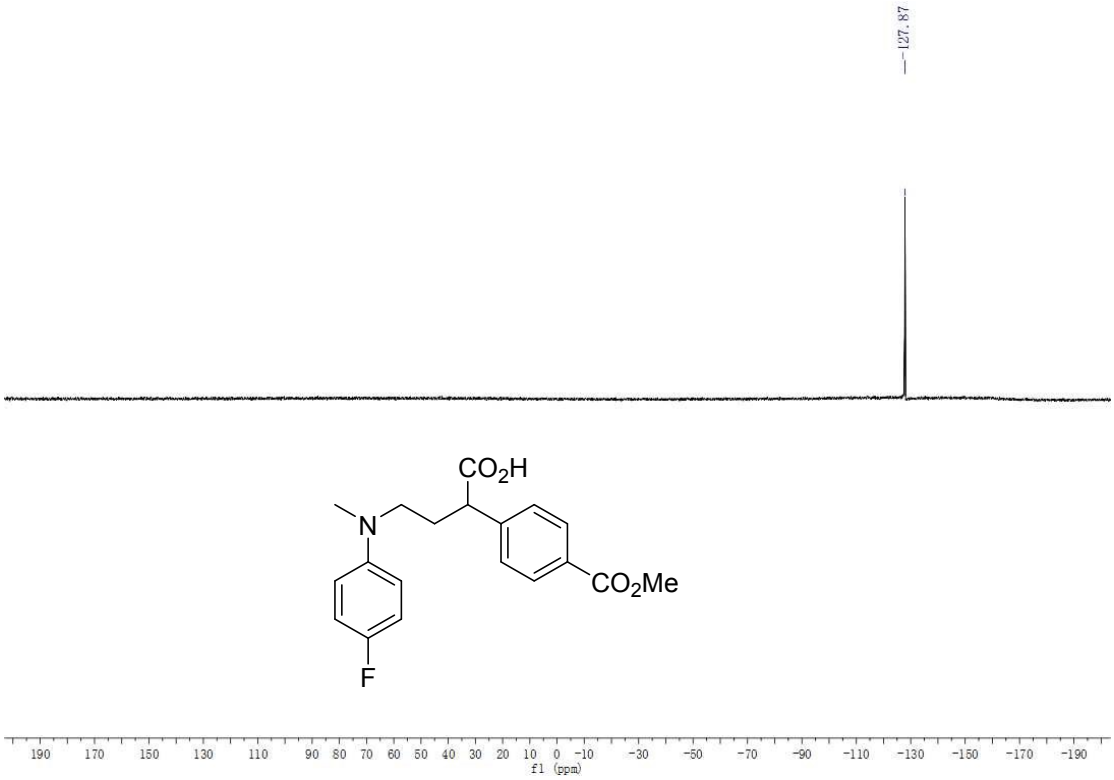




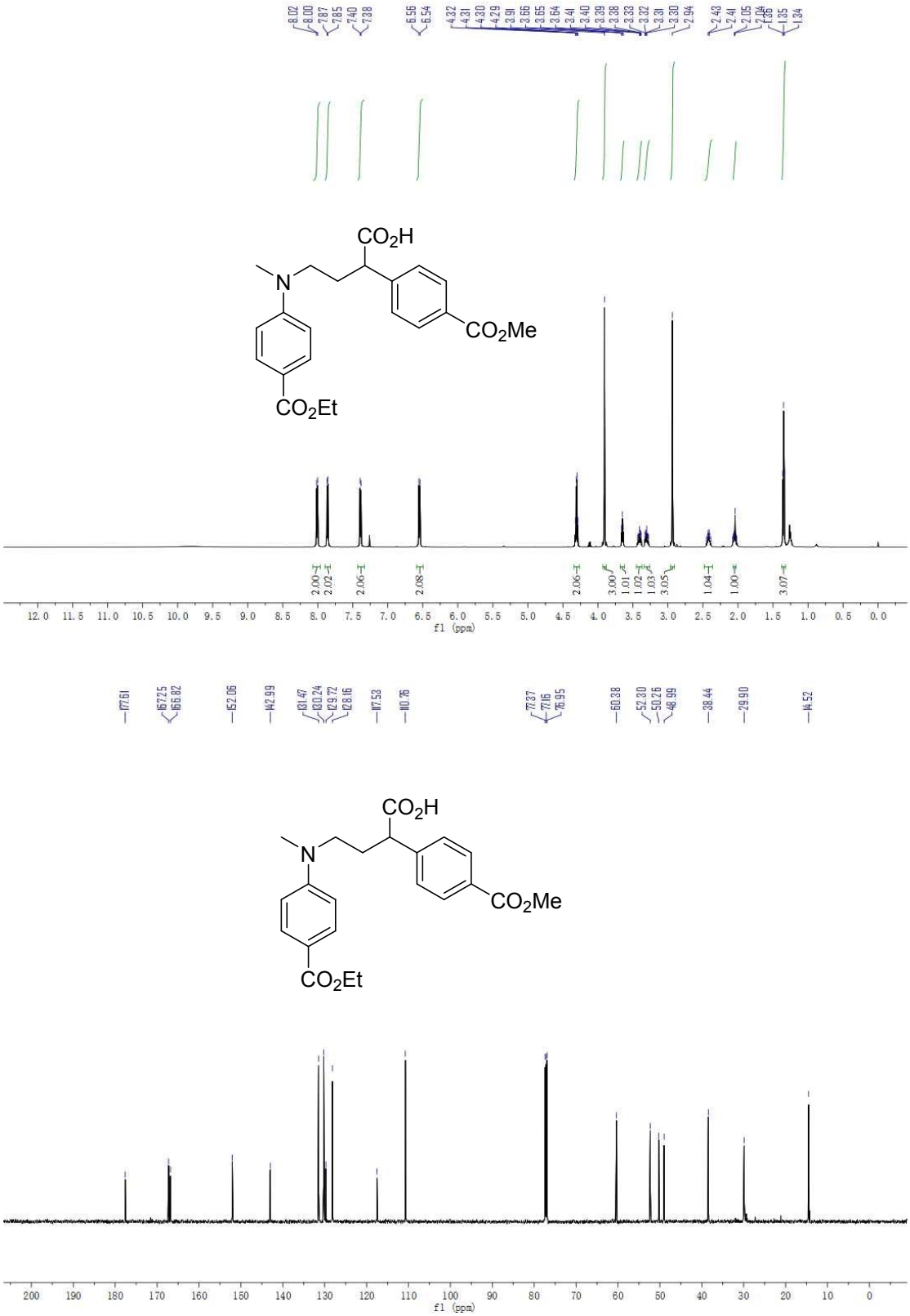
^{1}H and ^{13}C spectra of **3da**



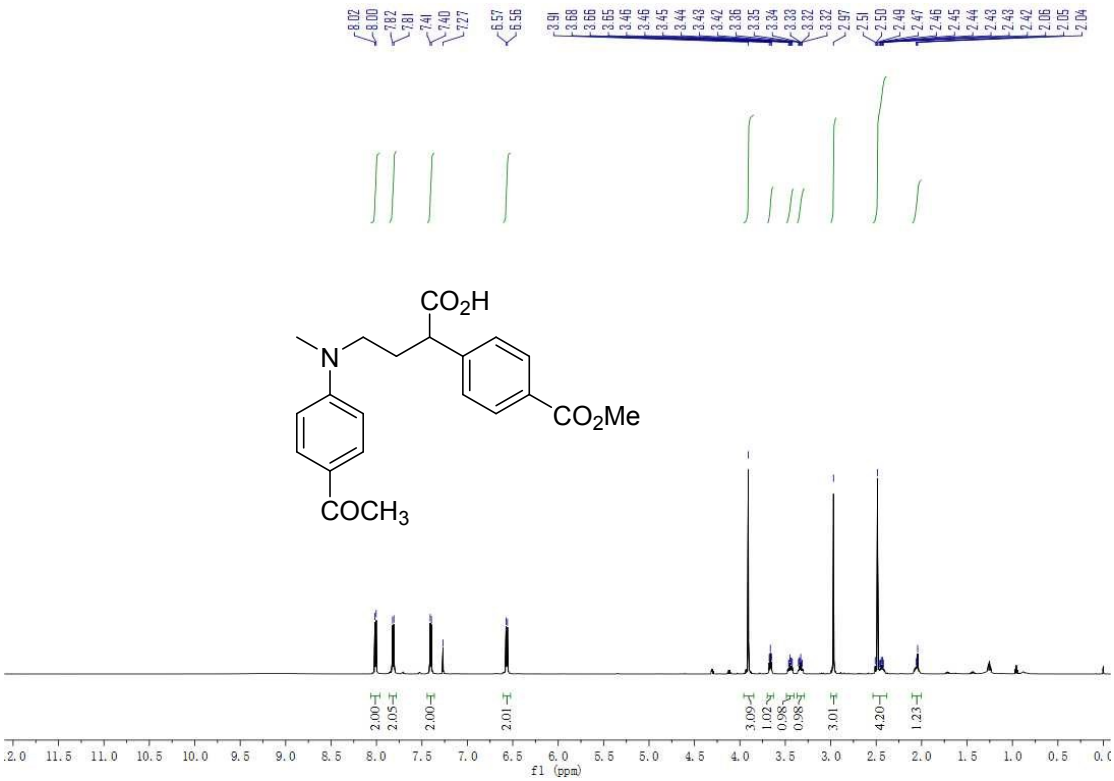
^{1}H and ^{13}C spectra of **3ea**

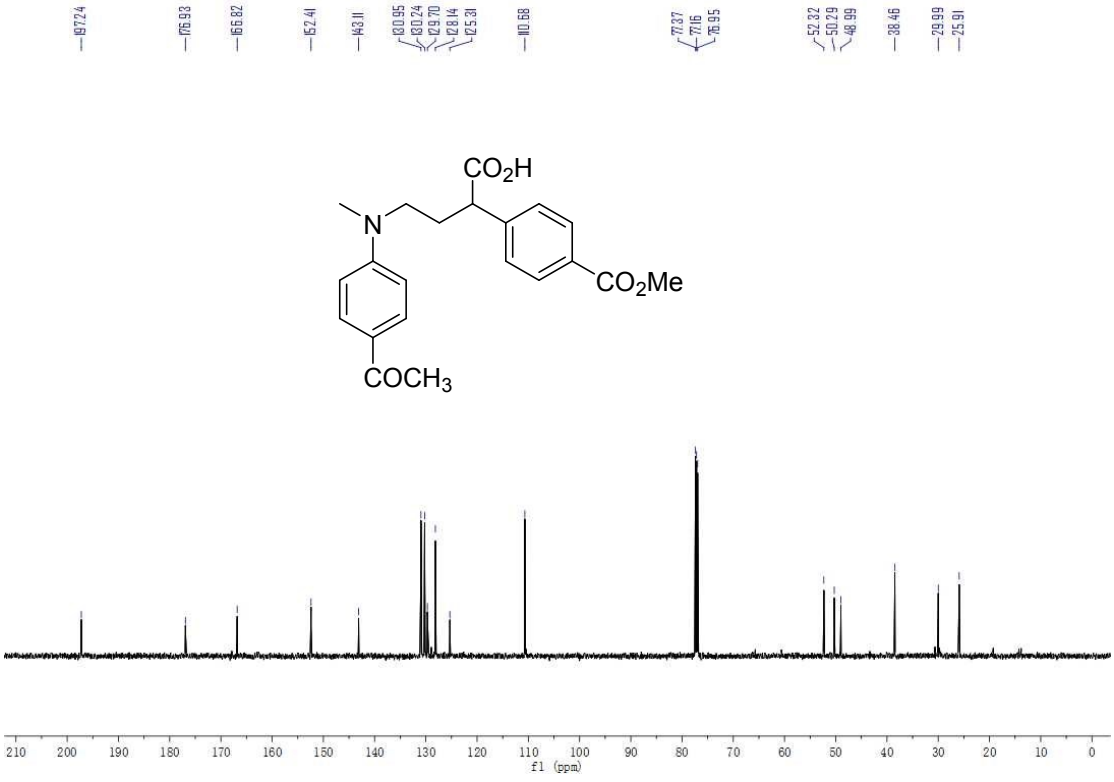


^{19}F spectrum of **3ea**

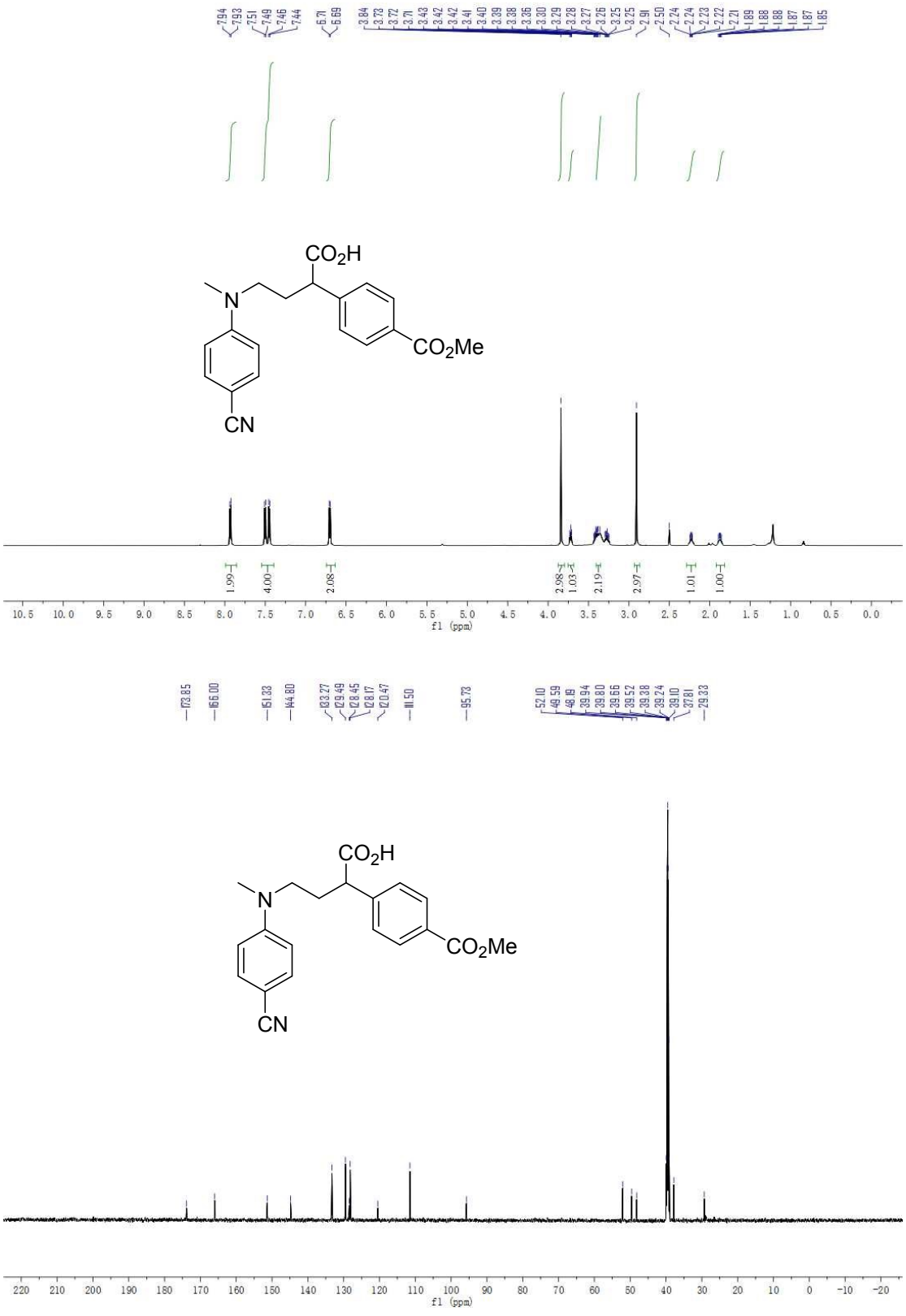


^{1}H and ^{13}C spectra of **3fa**

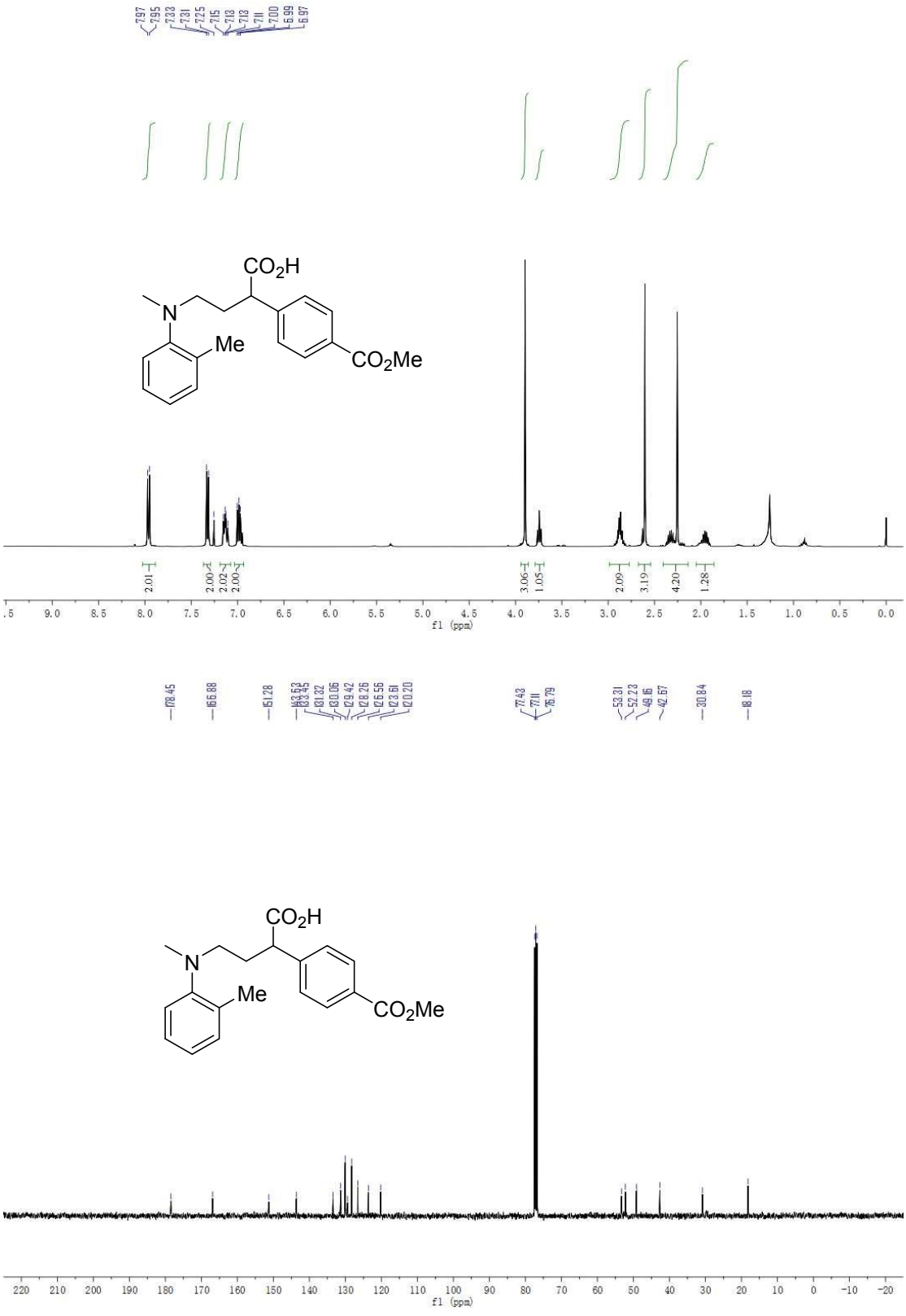




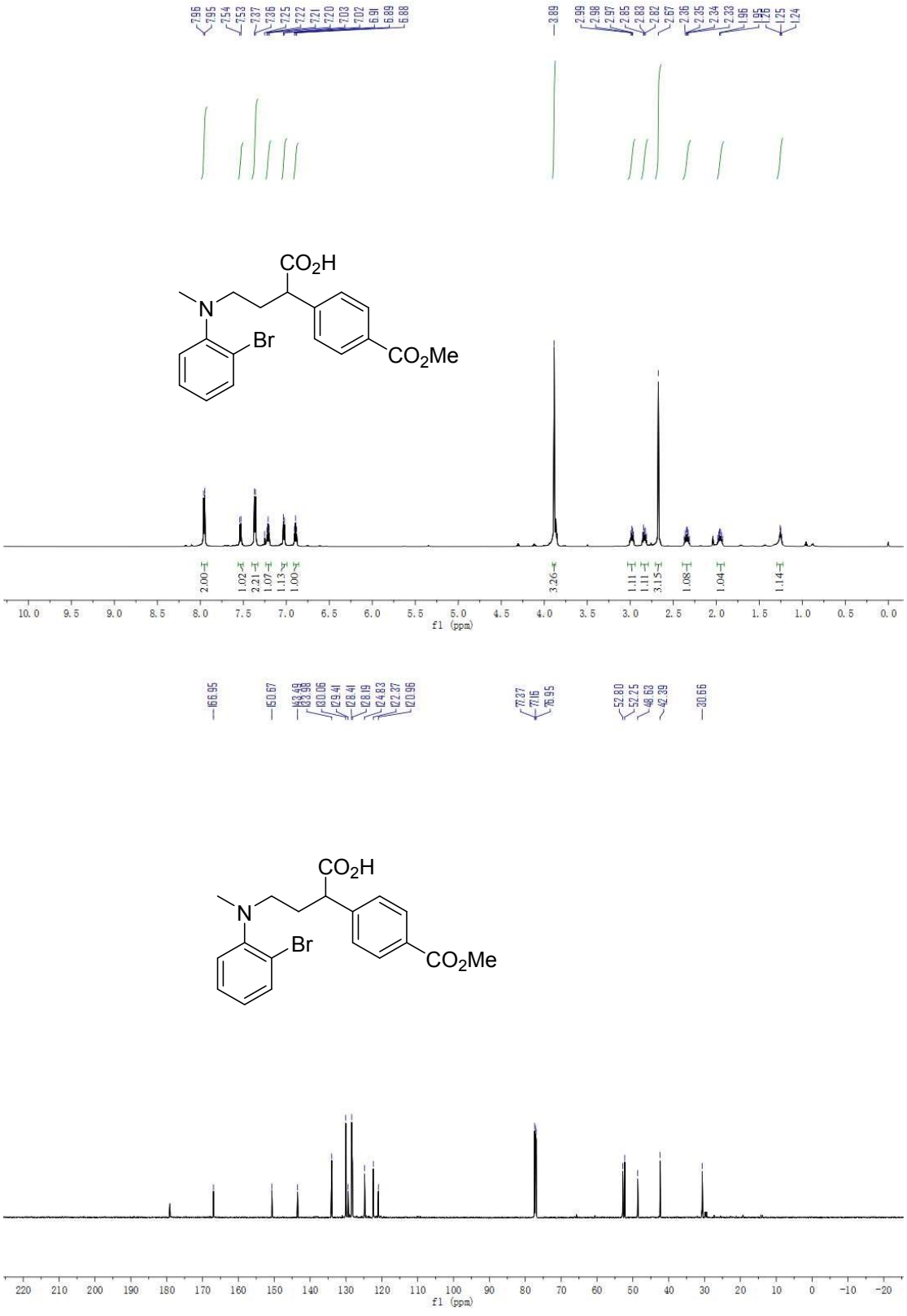
^{1}H and ^{13}C spectra of **3ga**



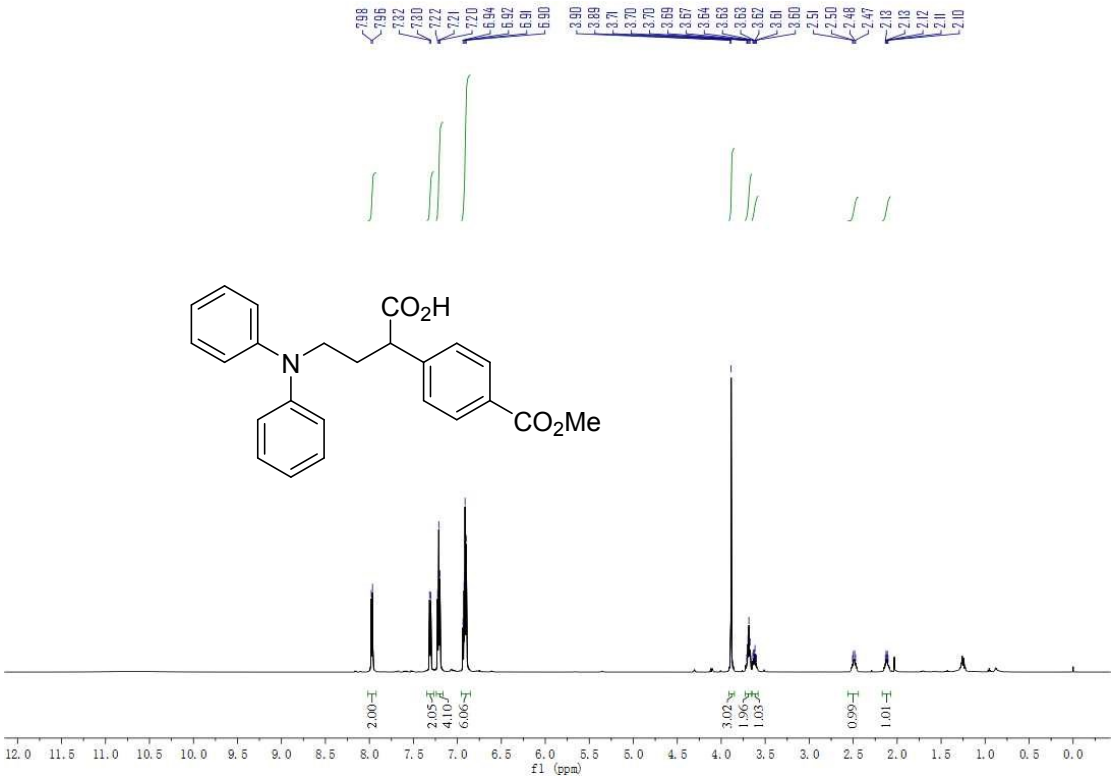
^{1}H and ^{13}C spectra of **3ha**

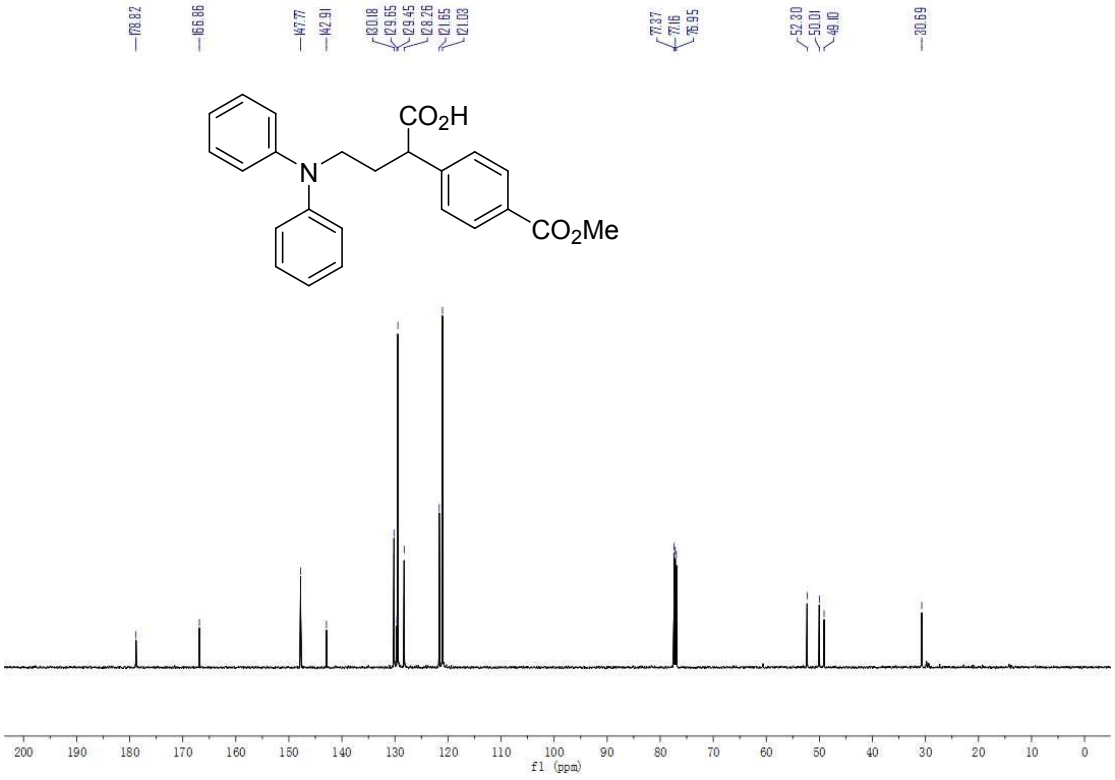


^{1}H and ^{13}C spectra of **3ia**

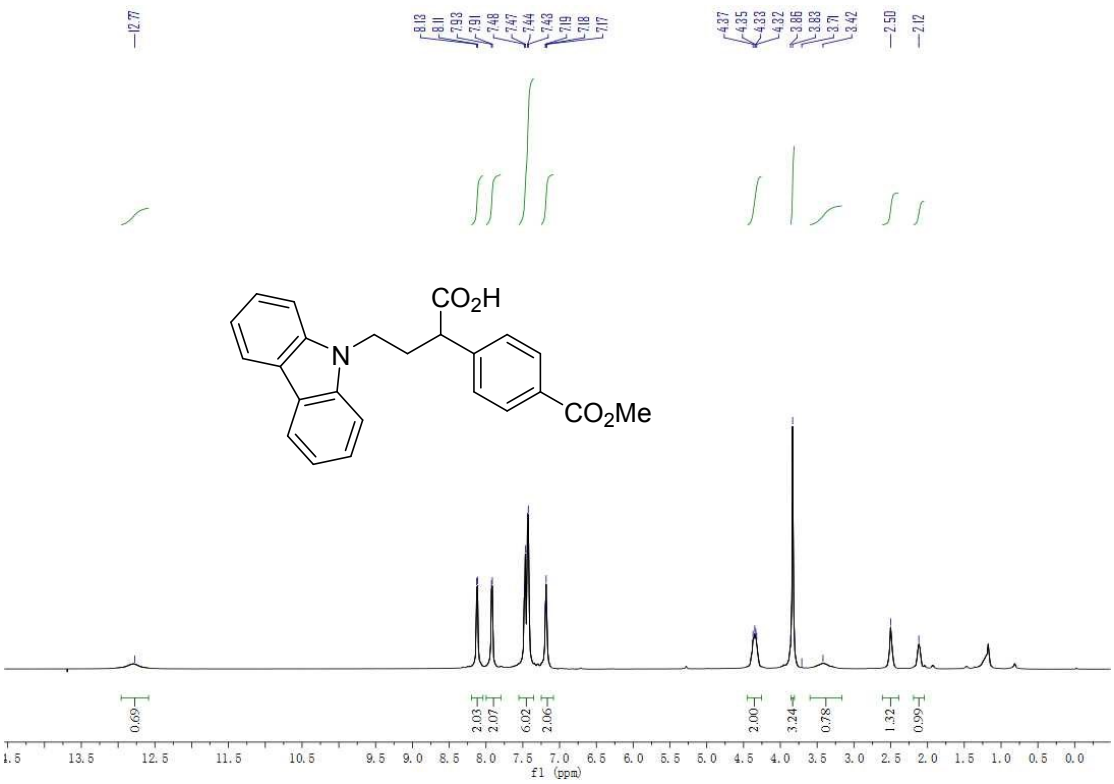


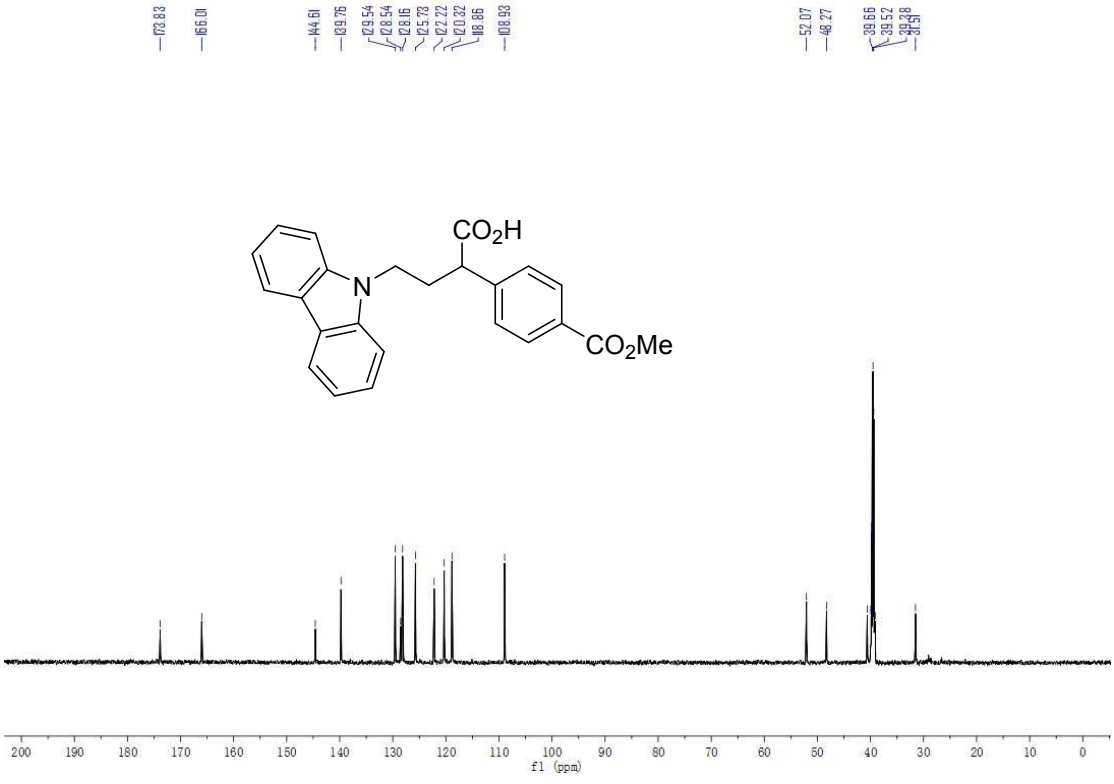
^{1}H and ^{13}C spectra of **3ja**



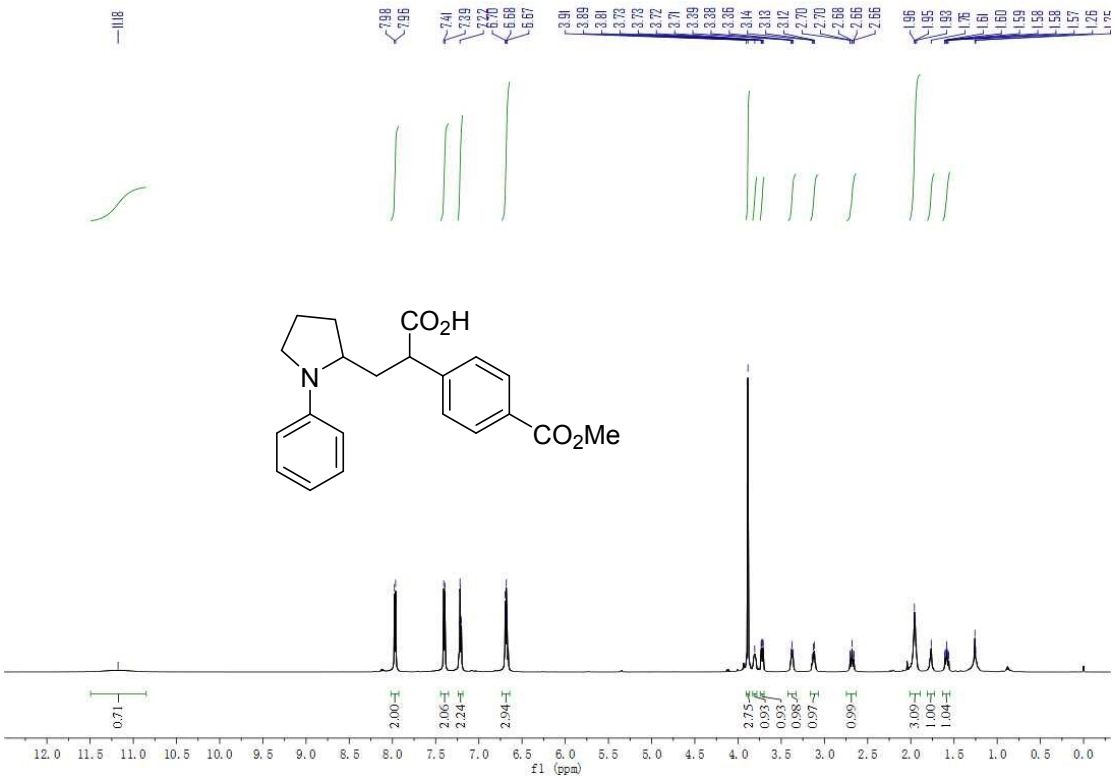


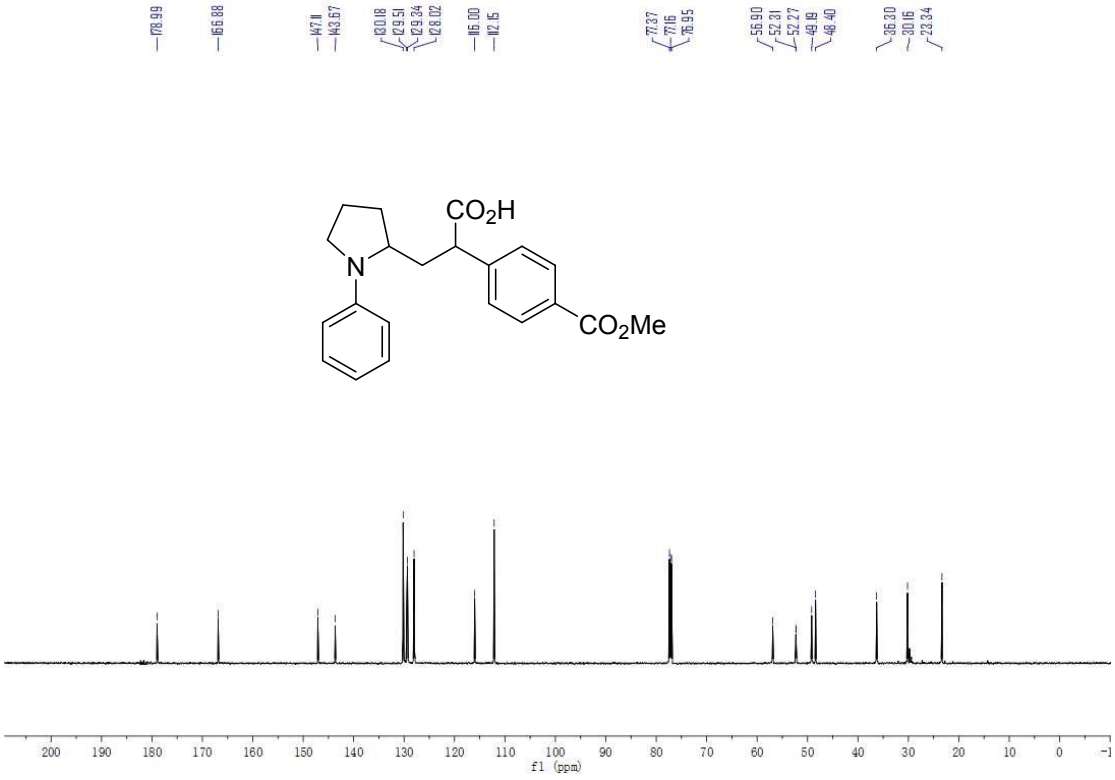
^{1}H and ^{13}C spectra of **3ka**



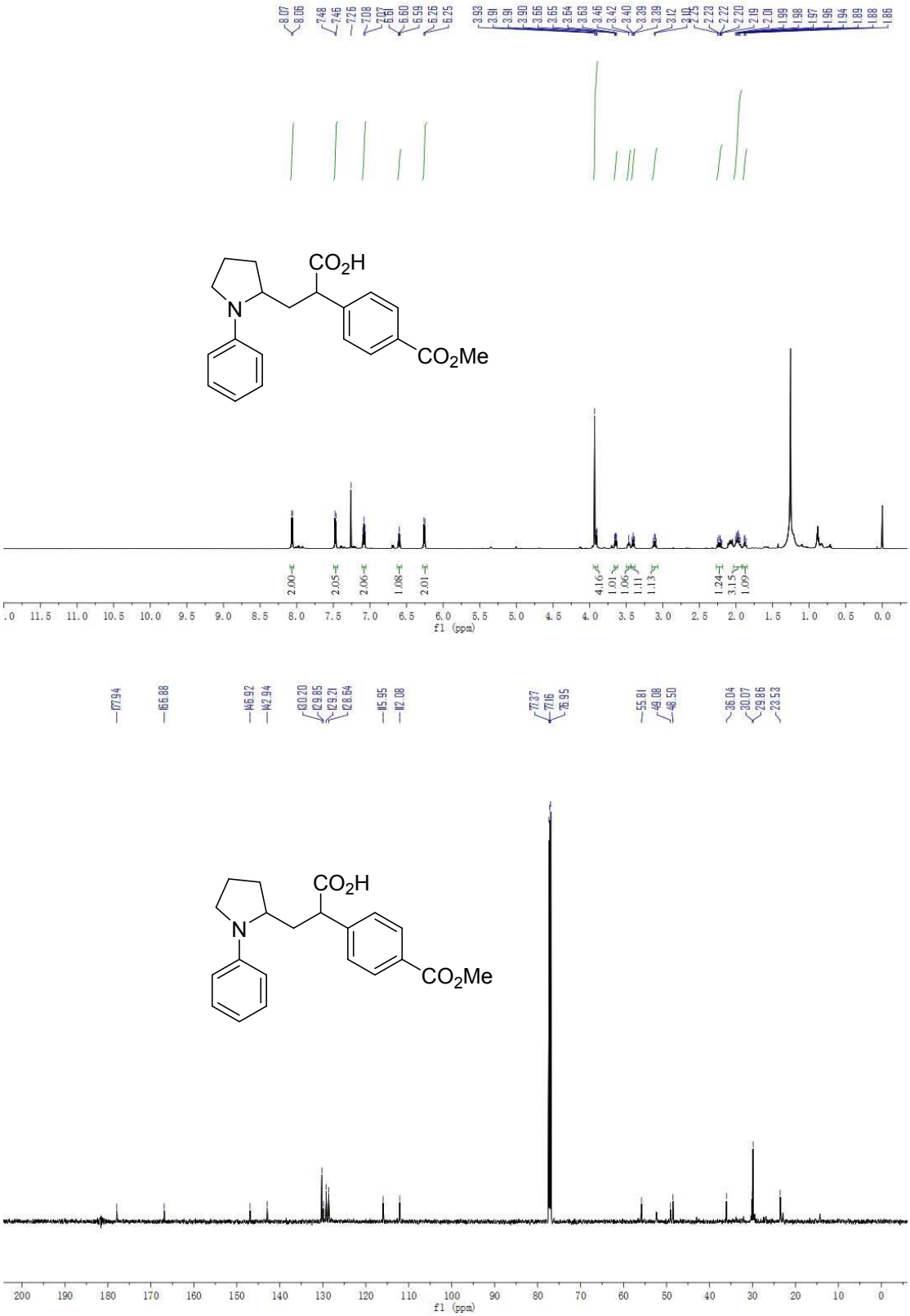


^{1}H and ^{13}C spectra of **3la**

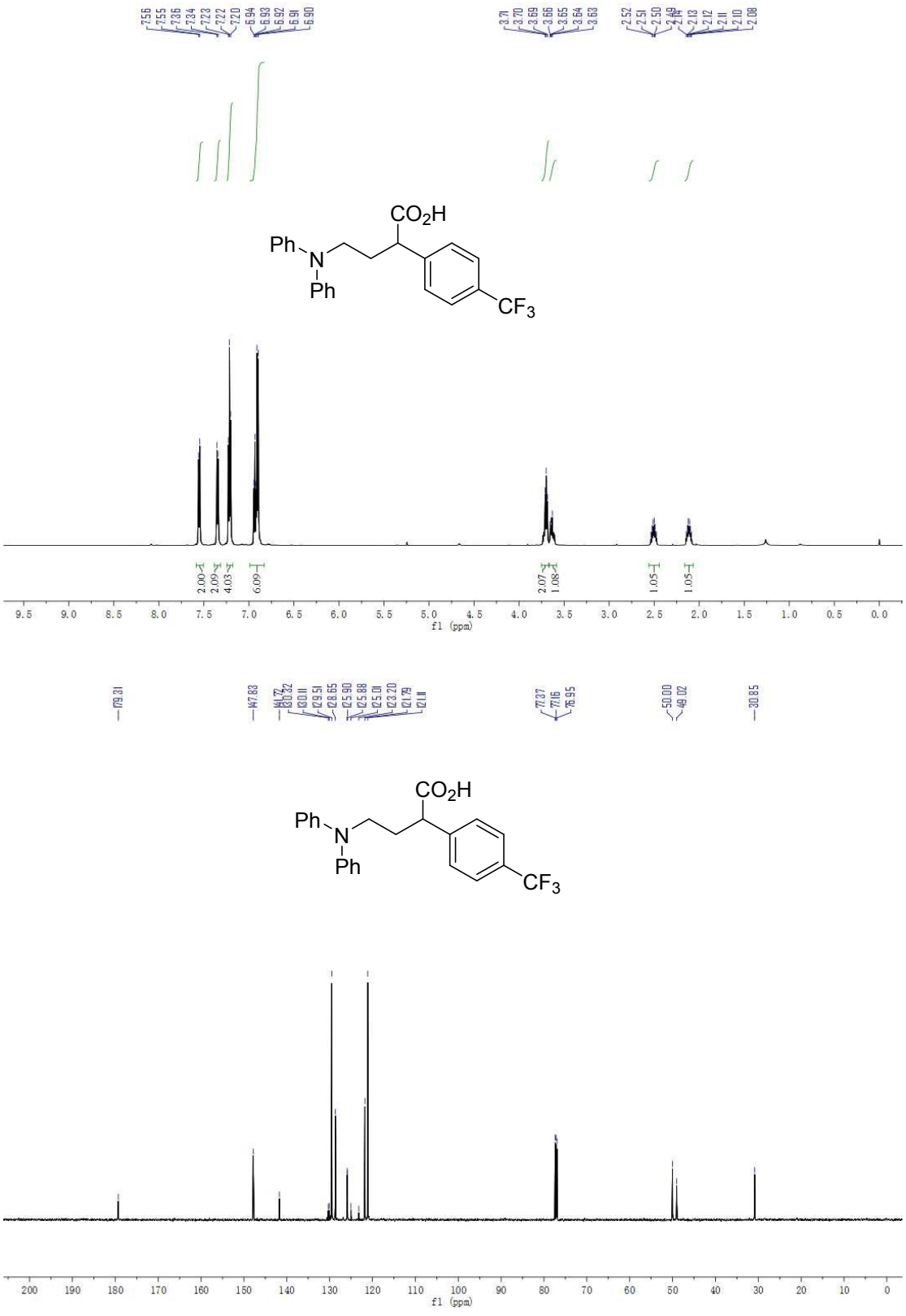




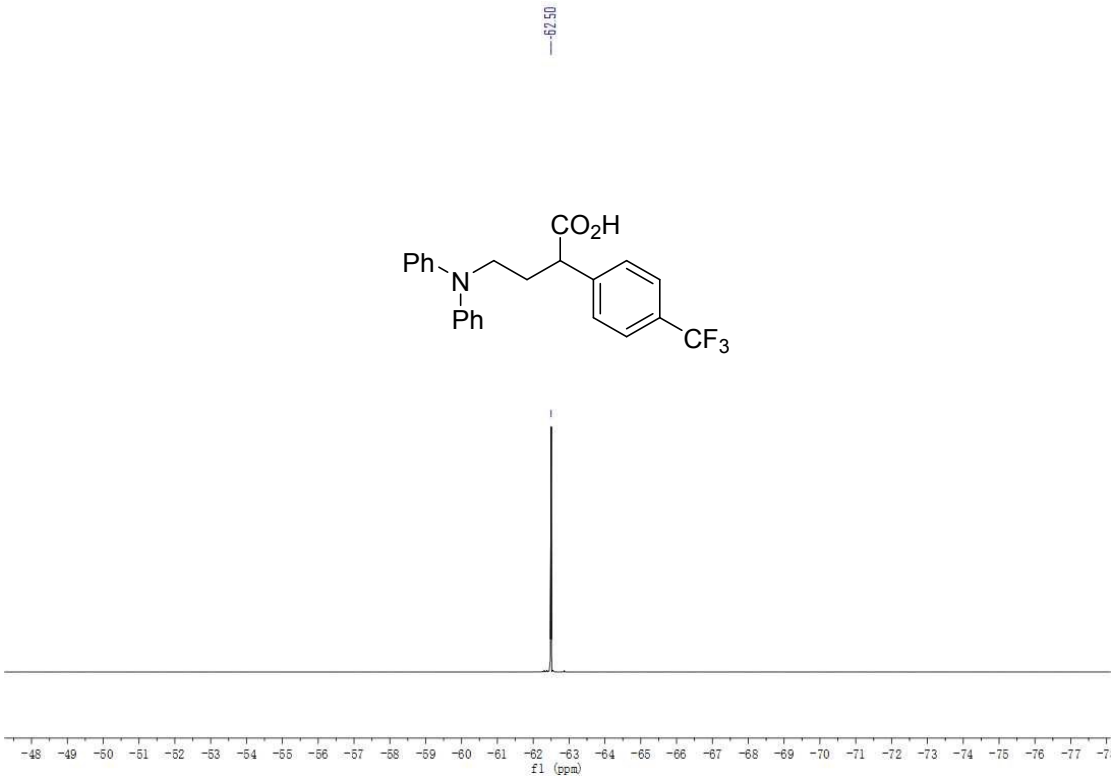
^{1}H and ^{13}C spectra of **3ma-1**



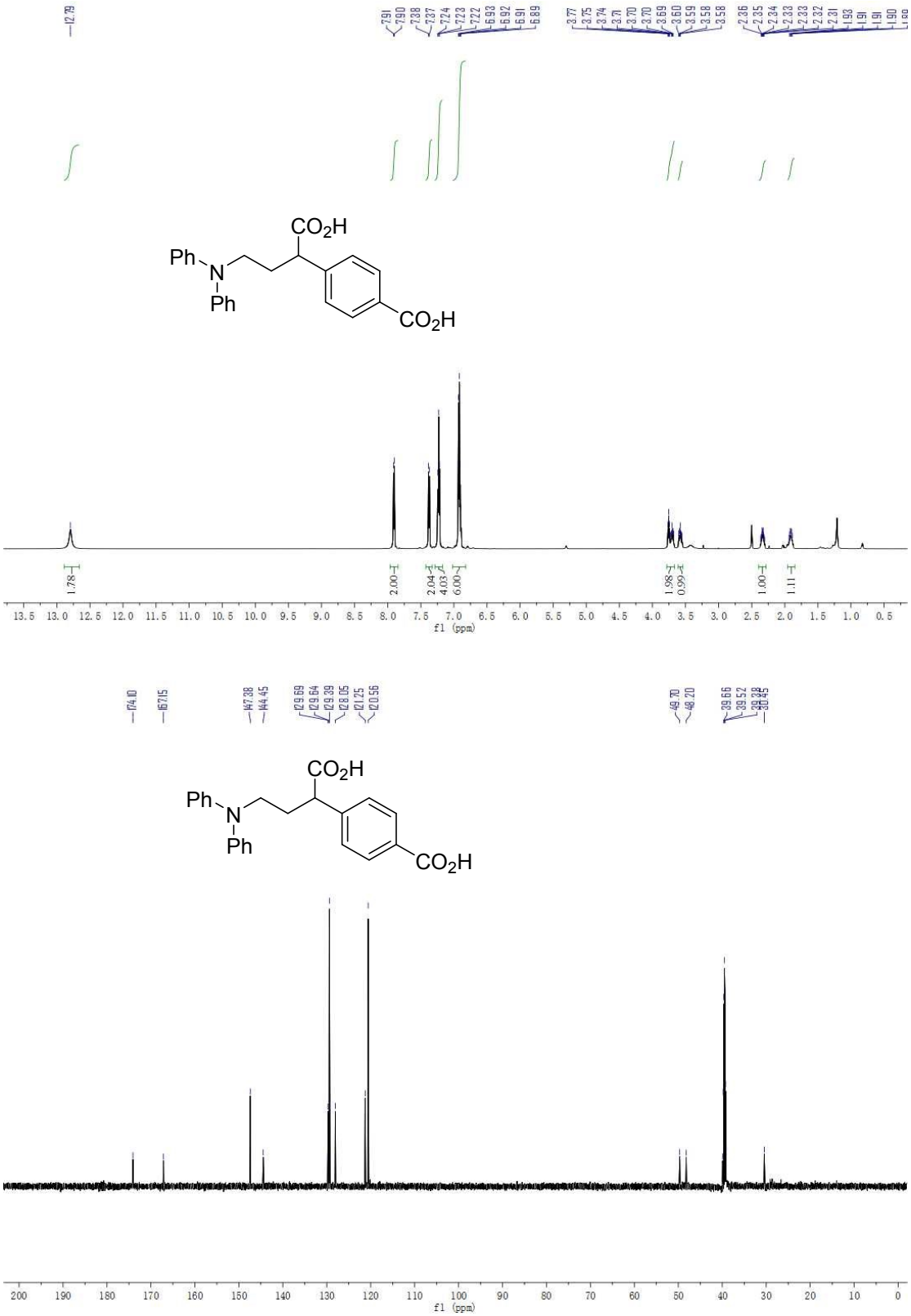
^{1}H and ^{13}C spectra of **3ma-2**



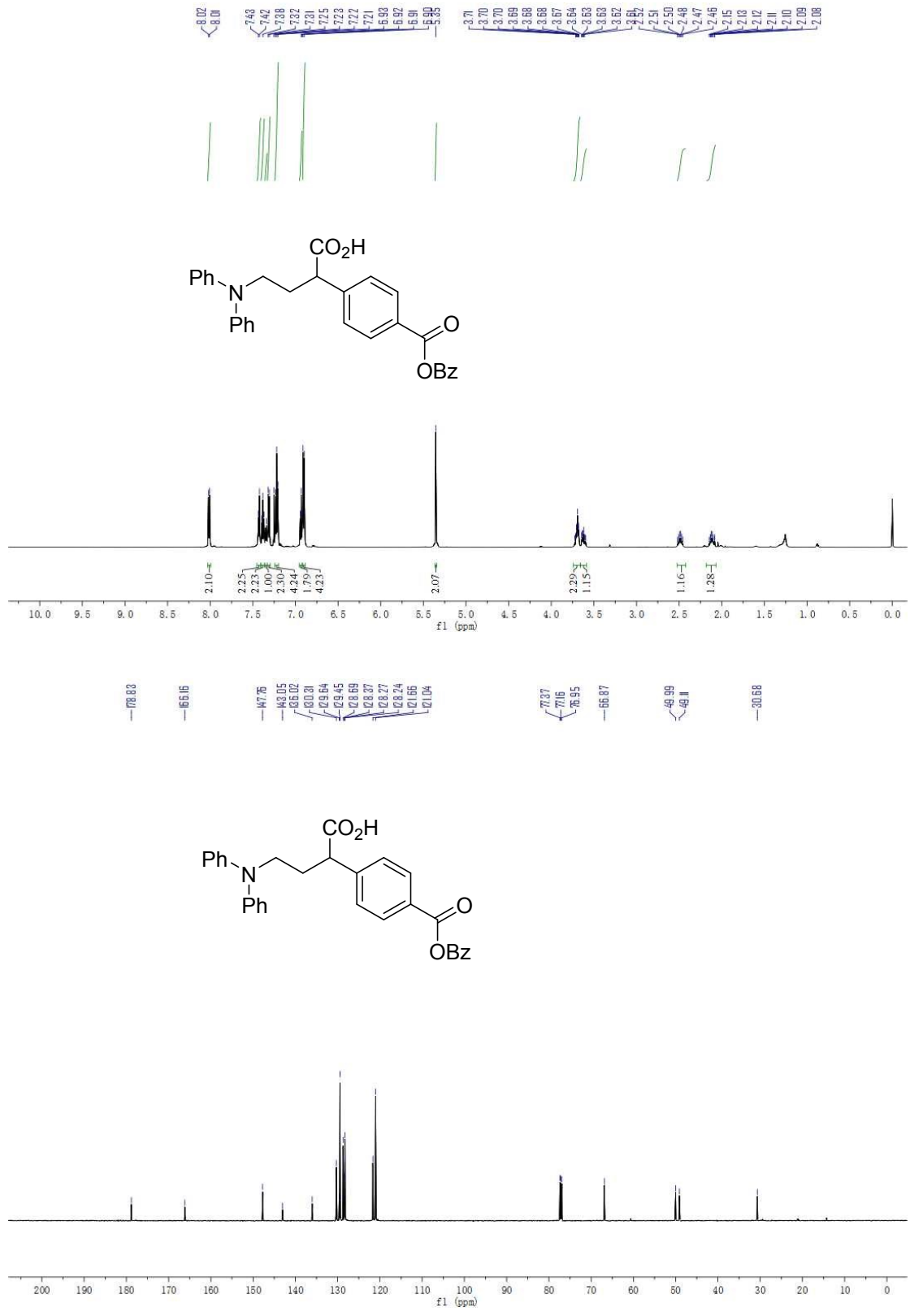
^{1}H and ^{13}C spectra of **3kb**



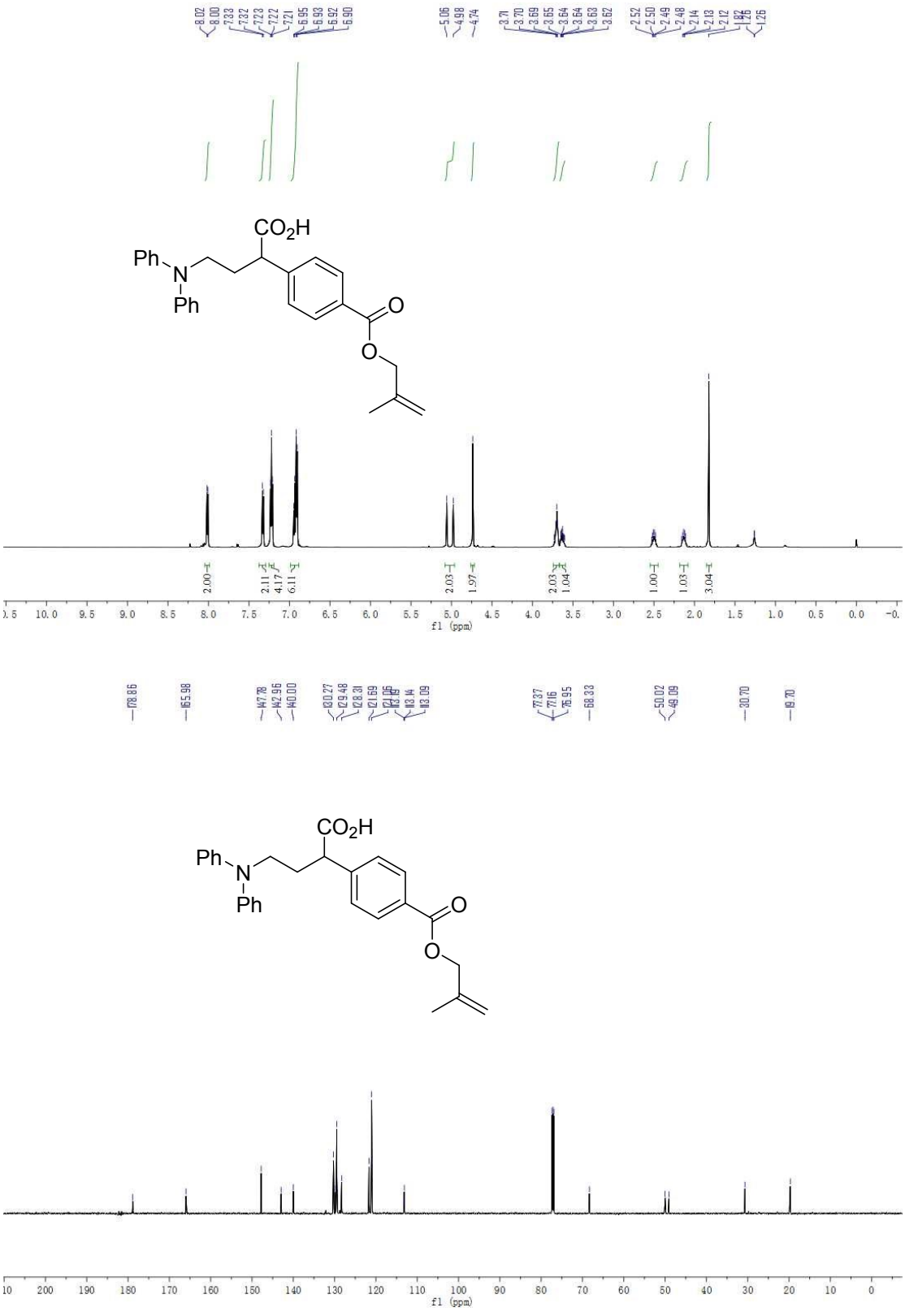
^{19}F spectrum of **3kb**



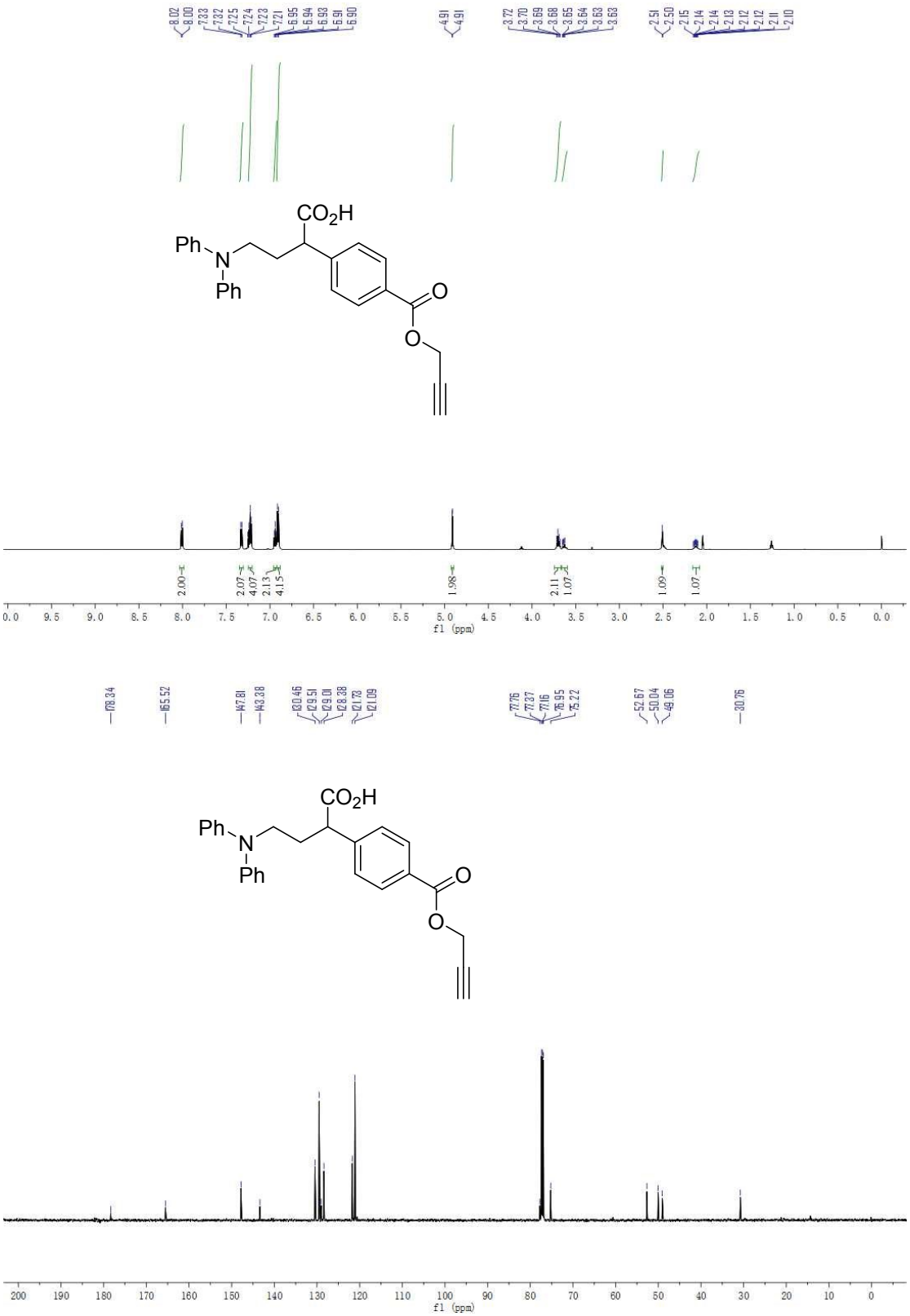
^{1}H and ^{13}C spectra of **3kc**



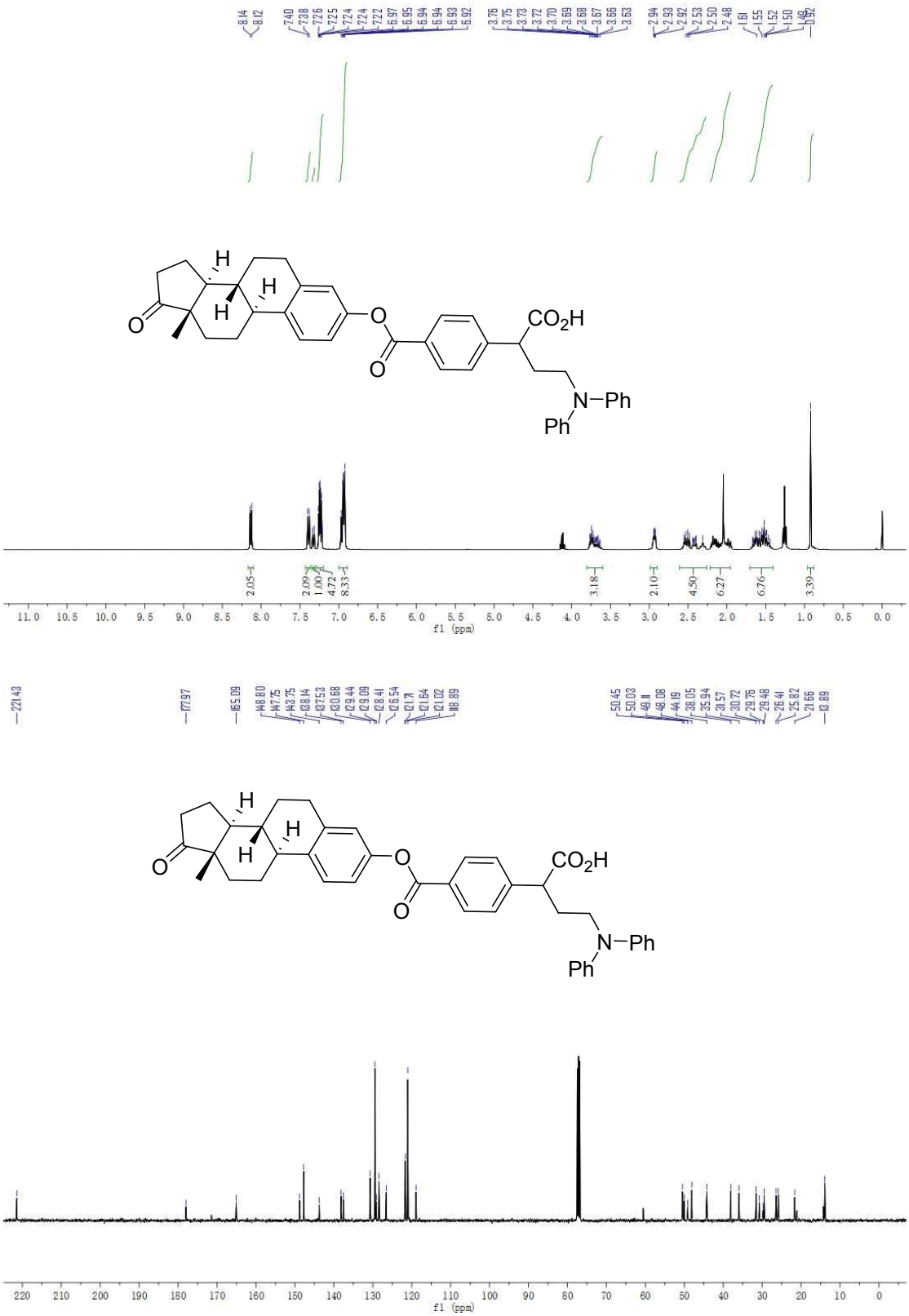
^{1}H and ^{13}C spectra of **3kd**



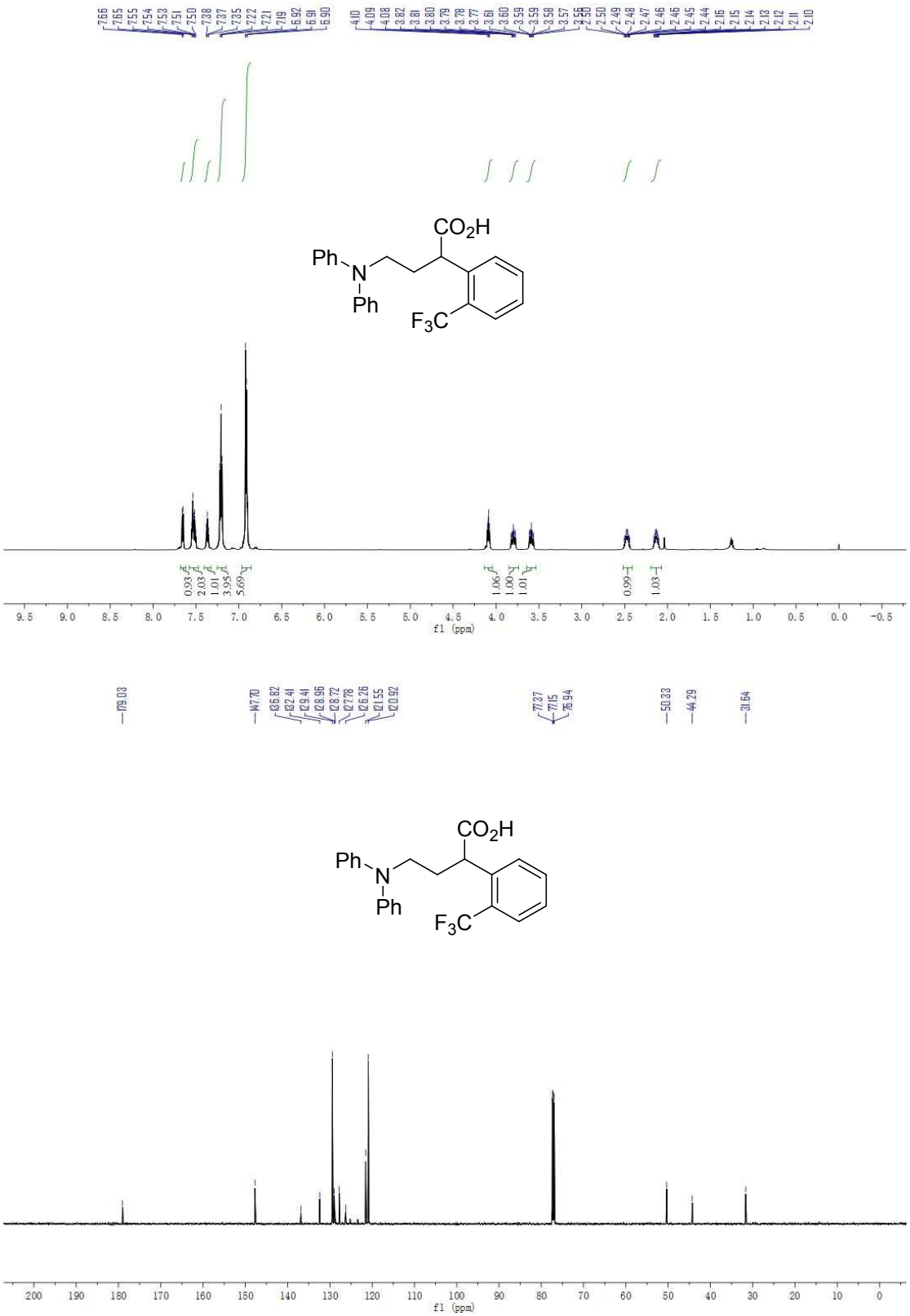
^{1}H and ^{13}C spectra of **3ke**



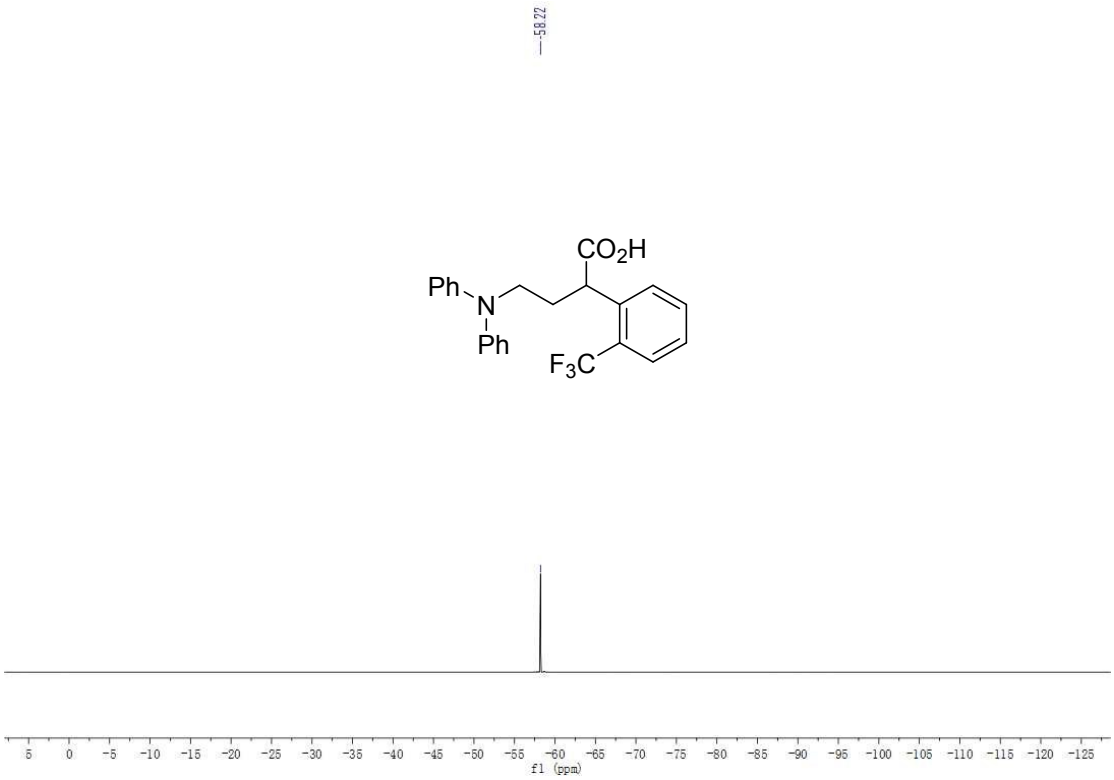
^{1}H and ^{13}C spectra of **3kf**



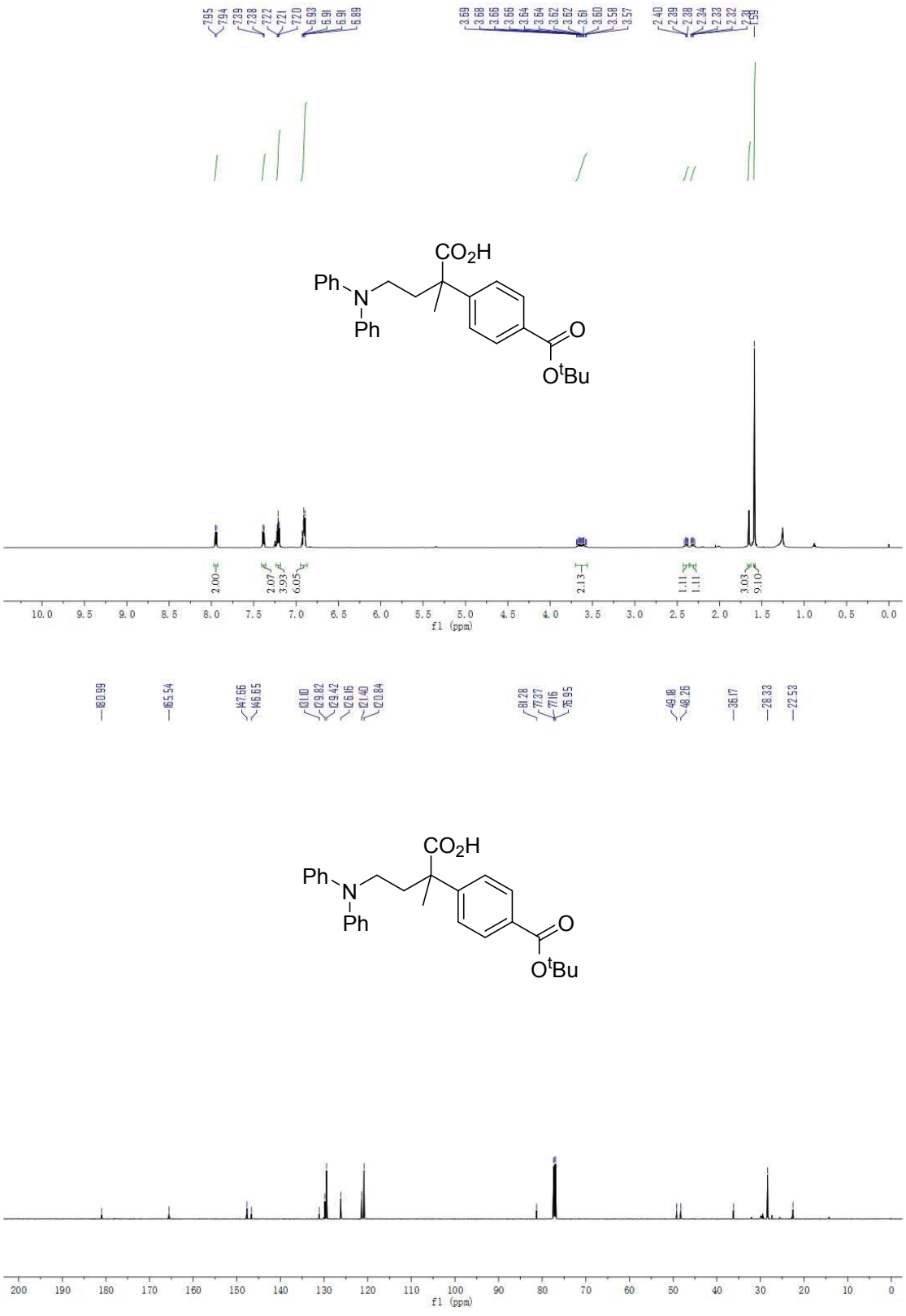
^{1}H and ^{13}C spectra of **3kg**



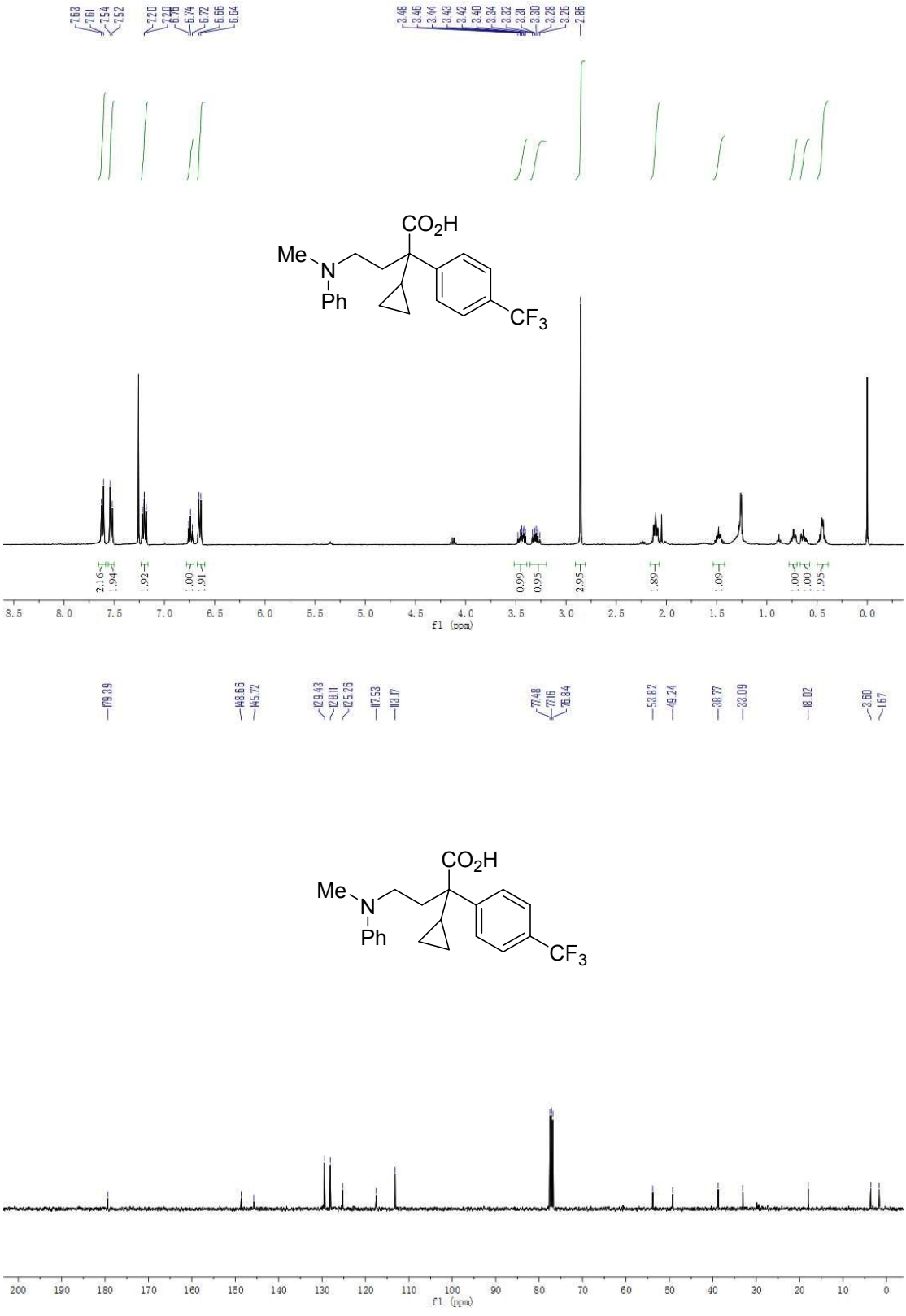
^{1}H and ^{13}C spectra of **3kh**



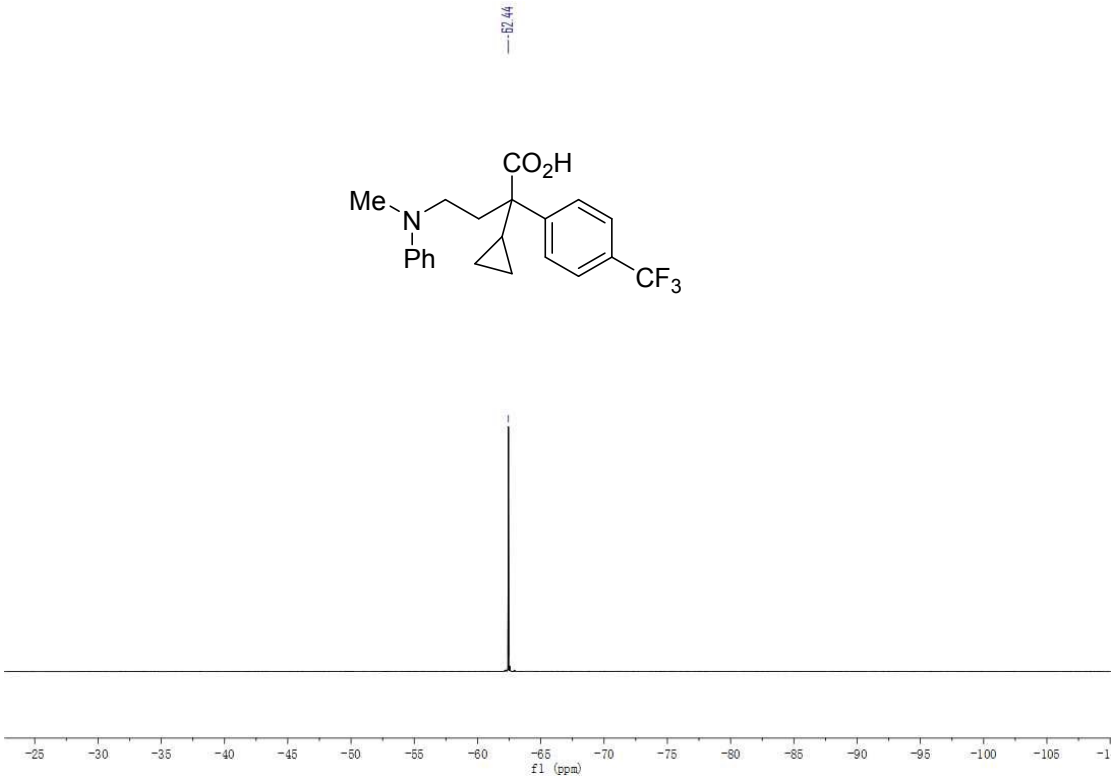
^{19}F spectrum of **3kh**



^{1}H and ^{13}C spectra of **3ki**



^{1}H and ^{13}C spectra of **3aj**



^{19}F spectrum of **3aj**