Supporting information for

# Highly-selective H/D exchange reaction of 1,4-dihydropyridines

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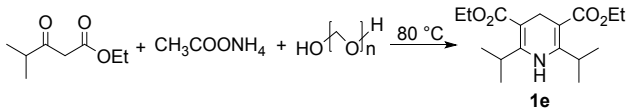
# 1. General information

All reagents were purchased from commercial sources and used without further purification unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC). Visualization was achieved under a UV lamp (254 nm and 365 nm). Column chromatography was performed using 200-300 mesh silica gels. $^{1}H$ and $^{13}C$ NMR spectra were acquired on 400 and 500 MHz Bruker NMR instruments. NMR chemical shifts were reported in ppm and were referenced to TMS (δ = 0.00 ppm, $^{1}H$ NMR) or the residual solvent peak for $CDCl_3$ (δ = 7.26 ppm, $^{1}H$ NMR; δ = 77.16 ppm, $^{13}C$ NMR). Following abbreviations are used for multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J*) are reported in Hertz.

All analytical LC-MS were performed to determine the distribution of hydrogen isotopes of the products on a Shimadzu LC-MS 2020 system equipped with Hedera C18 column (2.1 x 100 mm, 3 μm; heater set on 40 °C) involved a mobile phase of 0.1% formic acid (FA) in water (solvent A) and 0.1% formic acid (FA) in acetonitrile (solvent B) at a flow rate of 0.3 mL/min. All of the samples were tested over the same gradient: from 15 to 55% B in 3 min, then from 55 to 95% B in 7 min, and 95% B for 5 min, 0.1% FA, λ = 254 nm.

# 2. Synthesis of substrates

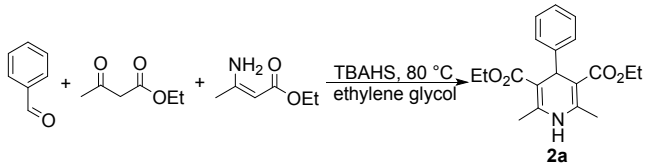
**Note**: **1a**, **2k**, **2l**, **2m**, **2n** and **2o** was obtained in commercial source. **1b**, **1c**, **1d**, **1e** and **1f** were synthesized according to reported literature.[1] **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, **2i**, **2j**, **3a** and **3b** were synthesized according to reported methods.[2-8] The oxidation procedure was performed according to reportedliterature.[9] Typical synthesis procedures were described as following examples.



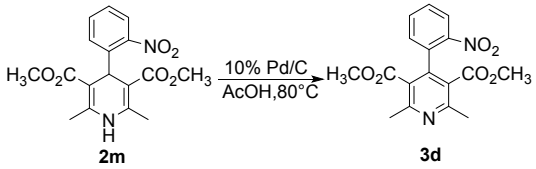

**1e**

Diethyl 2,6-diisopropyl-1,4-dihydropyridine-3,5-dicarboxylate (**1e**): Ethyl 4-methyl-3-oxopentanoate (1.58 g, 10 mmol), paraformaldehyde (0.15 g, 5 mmol) and ammonium acetate (0.58 g, 7.5 mmol) were added to a 25 mL flask, the resulting mixture was heated to 80 °C and stirred for 4 h at this temperature. The mixture was then cooled to room temperature and diluted by ethyl acetate (EA), and washed with brine. The organic layer was dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure after filtration. A silica gel chromatography was performed with PE/EA = 20:1 to afford a pale yellow solid **1e** (0.76g, 49%). $^{1}H$ NMR (500 MHz, $CDCl_3$) δ 5.68 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 4H), 4.02 (p, *J* = 7.0 Hz, 2H), 3.18 (s, 2H), 1.20 (t, *J* = 7.1

Hz, 6H), 1.04 (d, *J* = 7.2 Hz, 12H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.5, 153.4, 97.5, 59.5, 27.5, 25.1, 20.2, 14.4. LRMS (ESI+) *m/z*: 310.3 [M+H$^+$].




Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**2a**): To a solution of ethyl 3-aminocrotonate (0.65 g, 5 mmol), ethyl acetoacetate (0.65 g, 5 mmol) and the corresponding benzaldehyde (0.53 g, 5 mmol) in ethylene glycol (2 mL) was added TBAHS ($Bu_4NHSO_4$, 0.2 g, 0.6 mmol). The mixture was heated to 80 ℃ and stirred for 4 h. After complete consumption of the aldehyde monitored by TLC, the reaction was cooled to room temperature and diluted with EA. The solution was poured into a separatory funnel containing brine and extracted three times with EA. After drying over anhydrous $Na_2SO_4$, it was filtered and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel chromatography using PE/EA=6:1 as eluent to give **2a** as a pale yellow solid (0.86 g, 52%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 2H), 7.22 – 7.17 (m, 2H), 7.14 – 7.09 (m, 1H), 6.07 (s, 1H), 4.99 (s, 1H), 4.15 – 4.02 (m, 4H), 2.29 (s, 6H), 1.21 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 167.9, 147.9, 144.3, 128.0, 127.9, 126.2, 104.0, 59.8, 39.7, 19.5, 14.3. LRMS (ESI+) *m/z*: 330.3 [M+H$^+$].



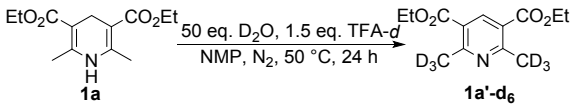

Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate (**3d**): **2m** (1.73 g, 5 mmol ), 10% Pd/C (20% weight of **2m**, 0.35 g) and acetic acid(15mL) were added to a 50 mL flask. The resulting mixture was heated to 80°C and stirred for 4h. After completion of the reaction determined by TLC analysis, Pd/C was filtered off by celite. The filtrate was poured into saturated $NaHCO_3$ and extracted with EA for three times. Then the combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. The solvents were removed under reduced pressure and the crude mixture was purified by silica gel chromatography with PE/EA = 10:1 as eluent to afford pure product **3d** as a pale yellow solid (0.86 g, 50%). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.18 (dq, *J* = 8.4, 1.8 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.58 – 7.53 (m, 1H), 7.21 – 7.16 (m, 1H), 3.48 (s, 6H), 2.63 (s, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.3, 157.1, 147.7, 145.3, 133.0, 132.1, 130.7, 129.7, 124.9, 124.4, 52.3, 23.7. LRMS (ESI+) *m/z*: 345.2 [M+H$^+$].

## 3. General procedure 1 for HIE reactions

To a 10 mL Schlenk tube with a magnetic bar was added 1,4-dihydropyridines (0.2 mmol), $D_2O$ (10 mmol, 181 μL), TFA-*d* (23 μL, 0.3 mmol (or 154 μL, 2 mmol)) and NMP (2 mL). The solution was freezed in liquid nitrogen, then the vessel was evacuated and backfilled with nitrogen following by being warmed to room temperature. The operation was repeated for 3 cycles. The resulting mixture was stirred at 50 °C (or 70 °C) for 24 h (or 48 h), cooled to room temperature, diluted with EA and then washed with saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. The crude product was further purified by silica gel chromatography. Hydrogen isotope distribution of the products was determined by LC-MS. $^1H$ NMR was performed to determine deuterium incorporation.

# 4. Condition optimization.

## 4.1 Condition optimization for deuteration of Hantzsch ester 1a



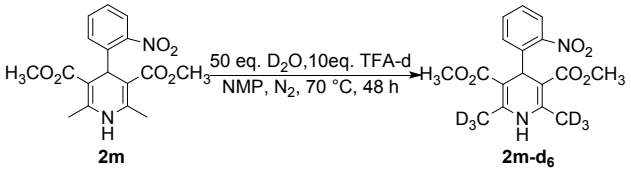

| Entry | Variations | D Incorporation[b] (%) | Yield[c] (%) |
|---|---|---|---|
| 1 | none[a] | 85[d] | 53(71[e]) |
| 2 | no TFA-*d* | 0 | 5 |
| 3 | TFA | 63 | 54 |
| 4 | 3 eq. TFA-*d* | 82 | 53 |
| 5 | RT | 38 | 37 |
| 6 | 70°C | 75 | 68[e] |
| 7 | Air | 45 | 99 |
| 8 | degassed by $N_2$ purging | 65 | 57 |
| 9 | DMF as solvent | 74 | 26 |
| 10 | DMA as solvent | 83 | 31 |
| 11 | MeOH as solvent | 15 | 46 |
| 12 | MeOD as solvent | 75 | 45 |

[a] standard condition: **1a** (0.2 mmol, 50.7 mg), $D_2O$ (10 mmol, 181 μL), TFA-*d* (0.3 mmol, 23 μL), NMP (*N*-Methyl pyrrolidone, 2 mL), $N_2$, 50 °C for 24 h. [b] D incorporation determined by $^1H$ NMR spectroscopy. [c] crude yield determined by $^1H$ NMR spectroscopy. [d] an average of two parallel reactions. [e] isolated yield.

**Note**: The isolated yield was much higher as all materials were exposed to air during purification process. Absolutely no deuteration and little oxidation occurred when TFA-*d* was omitted, showing acid to be critical for both the D incorporation and oxidation process. Only 5% oxidation product was obtained as no acid was added. No other byproduct was detected during the experiments. We also tested the pH value

of the reaction system under standard conditions. The pH value was 2.42 as all reagents were well mixed and after 24 hours reaction it was 2.43. To our best knowledge, the oxidation of **1a** involved unknown hydrogen transfer under heating and acidic conditions. More deeper studies are needed to get approach to the detailed mechanism. D incorporation did not change even the product was immersed in chloroform-*d* for 3 days longer. To confirm the relationship between oxidation and deuteration, we performed the experiment under standard conditions with **1a'** prepared previously[9], whereupon 85% D incorporation showed the deuteration and oxidation processes to be independent of one another.

## 4.2 Condition optimization for deuteration of nifedipine 2m



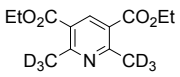

**2m** **2m-$d_6$**

| Entry | Variations | D Incorporation[b] (%) |
|---|---|---|
| 1 | 1.5 eq. TFA-*d*, 50 °C,24 h | 24 |
| 2 | 3 eq. TFA-*d*, 50 °C, 48 h | 25 |
| 3 | 6 eq. TFA-*d* | 74 |
| 4 | none[a] | 80[c] |
| 5 | 12 eq. TFA-*d* | 80 |
| 6 | no TFA-*d*, 24 h | 0 |
| 7 | no $D_2O$ | 15 |
| 8 | 25 eq. $D_2O$ | 47 |
| 9 | 100 eq. $D_2O$ | 76 |
| 10 | 150 eq. $D_2O$ | 80 |
| 11 | 10 eq. TFA | 71 |
| 12 | 10 eq. TfOH | 68 |
| 13 | 10 eq. $BF_3{\cdot}OEt_2$ | 76 |
| 14 | 20 eq. $BF_3{\cdot}OEt_2$ | 72 |
| 15 | 30 eq. $BF_3{\cdot}OEt_2$ | 71 |
| 16 | 24 h | 71 |
| 17 | 150 h | 79 |

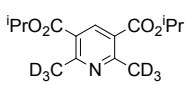
[a] standard condition: **2m** (0.2 mmol, 69.3 mg), $D_2O$ (10 mmol, 181 µL), TFA-*d* (2 mmol, 154 µL), NMP ( *N*-Methyl pyrrolidone, 2 mL), $N_2$, 70 °C for 48 h. [b] D incorporation determined by $^1H$ NMR spectroscopy. [C] an average of two parallel reactions

## 5. Deuteration of 1,4-dihydropyridines and derivatives

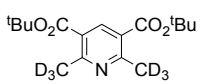
All of the deuteration procedure was done according to general procedure **1** with or without some variations.



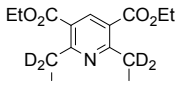
**Diethyl 2,6-bis(methyl-d3)pyridine-3,5-dicarboxylate (1a'-$d_6$)**. **1a** (50.7 mg, 0.2 mmol) and TFA-*d* (23 µL, 0.3 mmol) were used according to general procedure 1 to obtain **1a'-$d_6$** as a white solid (36.5 mg, 0.142 mmol, 71%, 85% D). The same result was obtained as **1a'** (50.3 mg, 0.2 mmol) and TFA-*d* (23 µL, 0.3 mmol) were used according to general procedure 1. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 4.37 (q, *J* = 7.2 Hz, 4H), 2.82 - 2.76 (m, 0.9H), 1.39 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.0, 162.3, 141.0, 123.2, 61.5, 24.9, 24.8, 24.7, 24.5, 24.4, 24.3, 24.2, 24.1, 14.4.



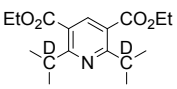
**Diisopropyl 2,6-bis(methyl-d3)pyridine-3,5-dicarboxylate (1b'-$d_6$)**. **1b** (56.3 mg, 0.2 mmol) and TFA-*d* (23 µL, 0.3 mmol) were used according to general procedure 1 to obtain **1b'-$d_6$** as a white solid (40.4 mg, 0.142mmol, 71%, 77% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 5.24 (hept, *J* = 6.3 Hz, 2H), 2.82 - 2.76 (m, 1.4H), 1.37 (d, *J* = 6.3 Hz, 12H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.8, 161.8, 140.9, 123.8, 69.2, 24.9, 24.8, 24.8, 24.7, 24.6, 24.5, 24.4, 24.2, 22.0.



**Di-tert-butyl 2,6-bis(methyl-d3)pyridine-3,5-dicarboxylate (1c'-$d_6$)**. **1c** (61.8 mg, 0.2 mmol) and TFA-*d* (23 µL, 0.3 mmol) were used according to general procedure 1 to obtain **1c'-$d_6$** as a white solid (44.8 mg, 0.144 mmol, 72%, 81% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 2.79 - 2.74 (m, 1.2H), 1.59 (d, *J* = 1.1 Hz, 18H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.6, 161.2, 140.9, 124.8, 82.2, 28.3, 25.0, 24.9, 24.8, 24.7, 24.6, 24.5, 24.4, 24.2.

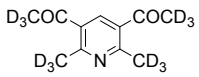


**Diethyl 2,6-bis(ethyl-1,1-d2)pyridine-3,5-dicarboxylate (1d'-$d_4$)**. **1d** (28.1 mg, 0.1 mmol) and TFA-*d* (12 µL, 0.150 mmol) were used according to general procedure 1 to obtain **1d'-$d_4$** as a pale yellow solid (23.2 mg, 0.082 mmol, 82%, 71% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 4H), 3.22-3.13 (m, 1.2H), 1.41 (t, *J* = 7.1 Hz, 6H), 1.29 (d, *J* = 8.5 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.0, 166.2, 141.4, 122.8, 61.6, 30.5, 30.2, 14.4, 14.0, 14.0, 13.9.

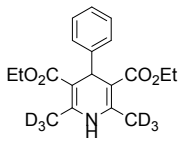


**Diethyl 2,6-bis(propan-2-yl-2-d)pyridine-3,5-dicarboxylate (1e'-$d_2$)**. **1e** (61.9 mg, 0.2 mmol) and TFA-*d* (23 µL, 0.3 mmol) were used according to general procedure 1 to obtain **1e'-$d_2$** as a white solid (46.1 mg, 0.150 mmol, 75%, 19% D). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 4.37 (q, *J* = 7.1

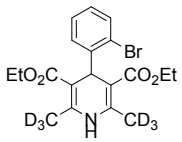
Hz, 4H), 3.86 (hept, *J* = 6.7 Hz, 1.6H), 1.39 (t, *J* = 7.1 Hz, 6H), 1.28 (d, *J* = 6.7 Hz, 12H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 169.4, 166.7, 140.3, 122.2, 61.5, 32.9, 22.3, 22.2, 14.4.



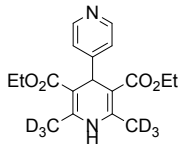

**1,1'-(2,6-bis(methyl-d3)pyridine-3,5-diyl)bis(ethan-1-one-2,2,2-d3) (1f'-$d_{12}$)**. **1f** (38.7 mg, 0.2 mmol) and TFA-*d* (23 µL, 0.3 mmol) were used according to general procedure 1 to obtain **1f'-$d_{12}$** as a pale yellow solid (26.0 mg, 0.128 mmol, 64%, 71% D, 61% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 2.77 – 2.71 (m, 1.7H), 2.62 – 2.57 (m, 2.4H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 199.4, 160.4, 138.0, 130.3, 29.5, 29.4, 29.3, 29.3, 29.2, 29.1, 29.0, 28.8, 24.9, 24.8, 24.7, 24.6, 24.5, 24.4, 24.2.



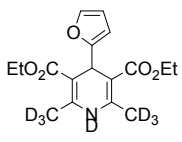

**Diethyl 2,6-bis(methyl-d3)-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (2a-$d_6$)**. **2a** (65.9 mg, 0.2 mmol) and TFA-*d* (46 µL, 0.6 mmol) were used according to general procedure 1 to obtain **2a-$d_6$** as a white solid (65.1 mg, 0.194 mmol, 97%, 77% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.20 (t, *J* = 7.7 Hz, 2H), 7.11 (td, *J* = 7.0, 1.4 Hz, 1H), 5.88 (s, 1H), 4.98 (s, 1H), 4.12 – 4.04 (m, 4H), 2.32 – 2.25 (m, 1.4H), 1.21 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.8, 147.9, 144.1, 128.1, 127.9, 126.2, 104.2, 59.8, 39.7, 19.5, 19.4, 19.4, 19.3, 19.2, 19.1, 19.0, 18.9, 18.7, 14.4.




**Diethyl 4-(2-bromophenyl)-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2b-$d_6$)**. **2b** (81.7 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2b-$d_6$** as a pale yellow solid (81.2 mg, 0.196 mmol, 98%, 77% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.37 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.15 (td, *J* = 7.5, 1.3 Hz, 1H), 6.93 (ddd, *J* = 7.9, 7.2, 1.7 Hz, 1H), 6.07 (s, 1H), 5.35 (s, 1H), 4.09 (qd, *J* = 7.1, 4.7 Hz, 4H), 2.25 – 2.19 (m, 1.4H), 1.19 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.9, 147.6, 143.9, 143.9, 132.8, 131.7, 127.7, 127.5, 122.7, 104.2, 104.1, 59.8, 39.8, 19.5, 19.4, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.8, 18.7, 18.6, 14.5.

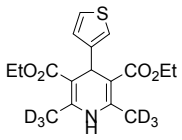



**Diethyl 2,6-bis(methyl-d3)-1,4-dihydro-[4,4'-bipyridine]-3,5-dicarboxylate (2c-$d_6$)**. **2c** (66.1 mg, 0.2 mmol) and $BF_3{\cdot}OEt_2$ (494 µL, 4 mmol) were used according to general procedure 1 to obtain **2c-$d_6$** as a pale yellow solid (63.9 mg, 0.190 mmol, 95%, 70% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.1 Hz, 2H), 7.24 – 7.21 (m, 2H), 6.50 (s, 1H), 5.00 (s, 1H), 4.13 – 4.05 (m, 4H), 2.34 – 2.27 (m, 1.8H), 1.21 (t, *J* = 7.1 Hz,61H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.3, 156.7, 149.1, 145.3, 145.3, 123.6, 102.7, 102.7, 60.1, 39.6, 19.5, 19.4, 19.3, 19.2, 19.1, 19.1, 18.9, 14.4.

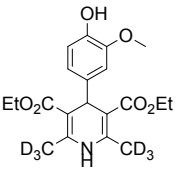



**Diethyl 4-(furan-2-yl)-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate-1-d (2d-$d_7$)**. **2d** (63.9 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2d-$d_7$**

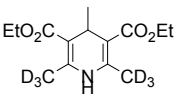
as a white solid (63.5 mg, 0.196 mmol, 98%, 81% D, -ND, 67% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 1.8, 0.9 Hz, 0.3H), 6.23 – 6.16 (m, 1H), 6.03 (s, 1H), 5.92 (d, *J* = 3.2 Hz, 1H), 5.19 (s, 1H), 4.21 – 4.09 (m, 4H), 2.31 – 2.25 (m, 1.1H), 1.25 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.7, 158.8, 158.7, 145.3, 140.9, 110.1, 109.9, 104.5, 100.8, 59.9, 33.5, 19.5, 19.4, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.8, 18.7, 18.5, 14.4.



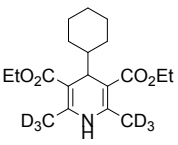
**Diethyl 2,6-bis(methyl-d3)-4-(thiophen-3-yl)-1,4-dihydropyridine-3,5-dicarboxylate (2e-$d_6$)**. **2e** (67.1 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2e-$d_6$** as a pale yellow solid (67.3mg, 0.197 mmol, 99%, 82% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 5.0, 3.1 Hz, 1H), 6.98 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.91 (dd, *J* = 3.3, 1.3 Hz, 1H), 5.96 (s, 1H), 5.13 (s, 1H), 4.19 – 4.07 (m, 4H), 2.30 – 2.24 (m, 1.1H), 1.24 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.8, 148.0, 144.6, 144.6, 127.7, 124.7, 120.4, 103.5, 103.5, 77.4, 77.2, 76.9, 59.9, 34.7, 19.4, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.8, 18.7, 18.6, 14.4.



**Diethyl 4-(4-hydroxy-3-methoxyphenyl)-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2f-$d_6$)**. **2f** (75.1 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2f-$d_6$** as a white solid (75.4 mg, 0.198 mmol, 99%, 80% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 6.84 (d, *J* = 1.6 Hz, 1H), 6.75 – 6.70 (m, 2H), 5.88 (s, 1H), 5.63 – 5.52 (m, 1H), 4.91 (s, 1H), 4.13 – 4.05 (m, 4H), 3.81 (s, 3H), 2.31 – 2.24 (m, 1.2H), 1.23 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.9, 145.9, 144.0, 143.9, 143.8, 140.2, 120.5, 114.0, 111.0, 104.3, 104.3, 59.8, 55.8, 39.2, 19.5, 19.4, 19.4, 19.3, 19.2, 19.1, 19.0, 19.0, 18.9, 18.8, 18.7, 14.4.

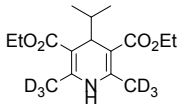


**Diethyl 4-methyl-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2g-$d_6$)**. **2g** (53.5 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2g-$d_6$** as a pale yellow solid (50.8 mg, 0.186 mmol, 93%, 77% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 5.74 (s, 1H), 4.27 – 4.13 (m, 4H), 3.84 (q, *J* = 6.5 Hz, 1H), 2.28 – 2.21 (m, 1.4H), 1.30 (t, *J* = 7.1 Hz, 6H), 0.98 (d, *J* = 6.5 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.0, 144.4, 104.8, 104.8, 59.7, 28.6, 22.4, 19.5, 19.4, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.8, 14.6.

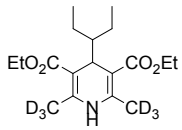


**Diethyl 4-cyclohexyl-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2h-$d_6$)**. **2h** (67.1 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2h-$d_6$** as a pale yellow solid (58.7 mg, 0.172 mmol, 86%, 80% D). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.04 (s, 1H), 4.24 – 4.05 (m, 4H), 3.89 (d, *J* = 5.7 Hz, 1H), 2.28 – 2.20 (m, 1.2H), 1.65 – 1.58 (m, 2H), 1.57 – 1.46 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 6H), 1.17 (dq, *J* = 6.0, 3.0 Hz, 1H), 1.09 – 0.98 (m, 3H), 0.88 (qd, *J* = 13.6, 12.6, 5.1 Hz, 2H). $^{13}$C NMR (101

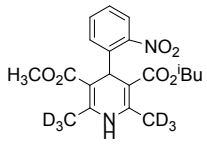
MHz, $CDCl_3$) δ 168.9, 144.7, 101.9, 59.6, 45.9, 38.4, 28.9, 26.8, 26.7, 19.4, 19.2, 19.0, 18.8, 18.6, 14.5.



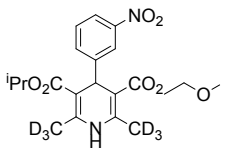
**Diethyl 4-isopropyl-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2i-$d_6$)**. **2i** (59.1 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2i-$d_6$** as a white solid (53.0 mg, 0.176 mmol, 88%, 77% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 5.92 (s, 1H), 4.15 (ddq, *J* = 39.2, 10.8, 7.1 Hz, 4H), 3.89 (d, *J* = 5.5 Hz, 1H), 2.28-2.22 (m, 1.4H), 1.56 (pd, *J* = 6.9, 5.4 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 6H), 0.72 (d, *J* = 6.9 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.9, 144.8, 101.8, 59.7, 38.9, 35.6, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.6, 14.5.



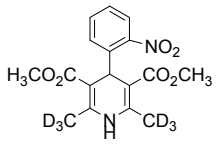
**Diethyl 2,6-bis(methyl-d3)-4-(pentan-3-yl)-1,4-dihydropyridine-3,5-dicarboxylate (2j-$d_6$)**. **2j** (64.7 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2j-$d_6$** as a white solid (55.4 mg, 0.168 mmol, 84%, 77% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 5.70 (s, 1H), 4.21 – 4.09 (m, 5H), 2.27 – 2.21 (m, 1.4H), 1.29 (t, *J* = 7.1 Hz, 6H), 1.14 (ddq, *J* = 20.9, 13.8, 7.1 Hz, 4H), 1.03 (qd, *J* = 6.5, 4.5 Hz, 1H), 0.85 (t, *J* = 7.3 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.9, 144.7, 102.3, 59.7, 50.0, 34.6, 21.3, 19.4, 19.3, 19.2, 19.2, 19.1, 19.0, 18.8, 18.7, 18.6, 14.4, 11.9.



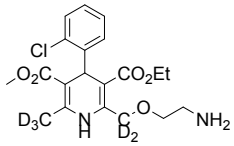
**3-isobutyl 5-methyl 2,6-bis(methyl-d3)-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2k-$d_6$)**. **2k** (77.7 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2k-$d_6$** as a yellow solid (74.9 mg, 0.190mmol, 95%, 79% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.51 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.44 (td, *J* = 7.6, 1.3 Hz, 1H), 7.22 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 6.14 (s, 1H), 5.76 (s, 1H), 3.83 – 3.75 (m, 2H), 3.56 (s, 3H), 2.34 – 2.27 (m, 0.6H), 2.27 – 2.20 (m, 0.6H), 1.87 (dt, *J* = 13.5, 6.7 Hz, 1H), 0.76 (d, *J* = 6.7 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.8, 167.5, 147.9, 145.1, 145.0, 142.5, 132.9, 131.2, 127.1, 124.1, 103.9, 103.5, 70.5, 51.1, 34.7, 27.6, 19.1.



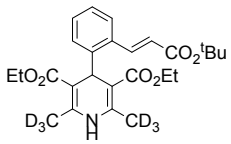
**3-isopropyl 5-(2-methoxyethyl) 2,6-bis(methyl-d3)-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2l-$d_6$)**. **2l** (83.7 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2l-$d_6$** as a pale yellow solid (79.8 mg, 0.188 mmol, 94%, 68% D). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.12 (t, *J* = 2.0 Hz, 1H), 7.98 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 7.65 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 6.04 (s, 1H), 5.08 (s, 1H), 4.93 (p, *J* = 6.2 Hz, 1H), 4.22 – 4.10 (m, 2H), 3.59 – 3.47 (m, 2H), 3.33 (s, 3H), 2.35 – 2.28 (m, 2H), 1.24 (d, *J* = 6.2 Hz, 3H), 1.07 (d, *J* = 6.2 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.2, 166.7, 150.1, 148.2, 145.3, 144.5, 134.8, 128.7, 123.4, 121.4, 104.0, 103.1, 70.6, 67.4, 63.1, 59.0, 40.1, 22.2, 21.9, 19.6, 19.5, 19.4, 19.4, 19.3, 19.2, 19.1, 19.0.



**Dimethyl 2,6-bis(methyl-d3)-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2m-$d_6$)**. **2m** (69.3 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2m-$d_6$** as a yellow solid (67.7 mg, 0.192 mmol, 96%, 79% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.50 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.44 (td, *J* = 7.6, 1.4 Hz, 1H), 7.23 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 6.15 (s, 1H), 5.70 (s, 1H), 3.57 (s, 6H), 2.32 – 2.23 (m, 1.3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.7, 147.9, 145.2, 145.2, 142.3, 132.9, 131.1, 127.1, 124.0, 103.6, 103.6, 51.1, 34.6, 19.4, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.8, 18.7, 18.6.



**3-ethyl 5-methyl 2-((2-aminoethoxy)methyl-d2)-4-(2-chlorophenyl)-6-(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2n-$d_5$)**. Amlodipine besylate (113.4 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2n-$d_5$** as a wite solid (79.9 mg, 0.194 mmol, 97%, 80% D, 77% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.37 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.20 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.11 (td, *J* = 7.5, 1.4 Hz, 1H), 7.01 (td, *J* = 7.5, 1.7 Hz, 1H), 5.38 (s, 1H), 5.07 (s, 2H), 4.81 – 4.67 (m, 0.5H), 4.07 – 3.96 (m, 2H), 3.68 (hept, *J* = 5.2 Hz, 2H), 3.58 (s, 3H), 3.09 (t, *J* = 4.7 Hz, 2H), 2.33 (d, *J* = 11.0 Hz, 0.6H), 1.16 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.3, 167.4, 145.9, 145.2, 145.1, 145.1, 144.8, 132.4, 131.6, 129.3, 127.5, 127.0, 103.8, 102.2, 102.2, 102.1, 70.0, 68.2, 60.0, 50.9, 40.5, 37.3, 18.7, 14.3.

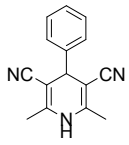


**Diethyl (E)-4-(2-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)phenyl)-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2o-$d_6$)**. **2o** (91.1 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2o-$d_6$** as a white solid (89.5 mg, 0.194 mmol, 97%, 80% D). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 15.8 Hz, 1H), 7.46 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.40 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.23 (td, *J* = 7.6, 1.4 Hz, 1H), 7.10 (td, *J* = 7.6, 1.4 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 5.99 (s, 1H), 5.32 (s, 1H), 4.05 (dq, *J* = 10.8, 7.2 Hz, 2H), 3.93 (dq, *J* = 10.8, 7.1 Hz, 2H), 2.31 – 2.24 (m, 1.2H), 1.53 (s, 9H), 1.13 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.6, 166.8, 148.5, 144.3, 144.3, 143.9, 132.0, 130.6, 130.1, 126.5, 125.5, 120.2, 104.7, 104.6, 80.2, 59.8, 35.8, 28.4, 19.2, 19.1, 19.0, 18.9, 18.8, 18.6, 14.4.

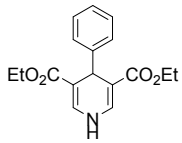
# 6. Controlled experiments

**3c** and **3d** were oxidated according to general procedure **3** and then deuterated according to general procedure 1 using 10 eq. TFA-*d*. Deuteration of **3e**, **3f**, **3g** and **3h** were operated according to general procedure 1 in $CH_2Cl_2$ and 1.5eq TFA-*d* was used for each reaction. When $CH_2Cl_2$ was used as the solvent, the reaction mixture was degassed by $N_2$ gently purging the vial for 3 minutes. After 24 h reaction under 50°C,

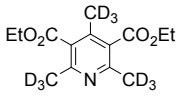
cool to RT. $CDCl_3$ was added to dilute the mixture and $^1H$ NMR was done without further purification to determine D incorporation. **3e** and **3f** were rarely deuterated after reaction. **3g** was deuterated in 17% D content.



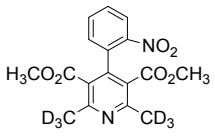
**2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbonitrile (3a-$d_0$)**. **3a** (47.1 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1. No D incorporation was found. **3a** was 98% recovered.



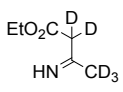
**Diethyl 4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (3b-$d_0$)**. **3b** (60.3 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 . No D incorporation was found. **3b** was 92% recovered. $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.33 (m, 2H), 7.29 – 7.23 (m, 4H), 7.18 – 7.11 (m, 2H), 4.89 (s, 1H), 4.14 – 4.00 (m, 5H), 1.19 (t, J = 7.2 Hz, 6H). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 167.5, 147.1, 134.2, 128.3, 128.0, 126.5, 108.1, 60.1, 37.7, 14.2.



**Diethyl 2,4,6-tris(methyl-d3)pyridine-3,5-dicarboxylate (3c-$d_9$)**. **3c** (53.1 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **3c-$d_9$** as a colorless oil (53.8 mg, 0.196 mmol, 98%, 70% D, 78% D). $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.38 (q, *J* = 7.1 Hz, 4H), 2.50 – 2.44 (m, 1.8H), 2.24 – 2.20 (m, 0.7H), 1.36 (t, *J* = 7.1 Hz, 6H). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 168.4, 155.0, 142.2, 127.7, 61.7, 23.0, 22.9, 22.8, 22.7, 22.6, 22.6, 22.5, 22.4, 22.3, 22.2, 22.2, 17.0, 16.9, 16.8, 16.7, 16.7, 16.6, 16.4, 16.3, 16.3, 16.2, 14.3.



**Dimethyl 2,6-bis(methyl-d3)-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate (3d-$d_6$)**. **3d** (68.9 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **3d-$d_6$** as a white solid (68.0 mg, 0.194 mmol, 97%, 78% D). $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.62 (td, *J* = 7.5, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.9, 7.6, 1.5 Hz, 1H), 7.18 (dd, *J* = 7.5, 1.5 Hz, 1H), 3.48 (s, 6H), 2.64 – 2.59 (m, 1.3H). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 167.3, 157.1, 147.7, 145.3, 133.0, 132.1, 130.7, 129.7, 124.9, 124.4, 52.3, 23.6, 23.5, 23.5, 23.4, 23.3, 23.2, 23.1, 23.1, 23.0, 22.9, 22.8.



**Ethyl 3-iminobutanoate-2,2,4,4,4-d5 (3h'-$d_5$)**. **3h** (12.9 mg, 0.1 mmol), TFA-*d*(23 µL, 0.3 mmol), $D_2O$ (90 µL, 5 mmol) and $CH_2Cl_2$ (1 mL) were added in a 10 mL schlenk tube. $N_2$ purged the headspace of the vial for 3 minutes following by tightly sealed. The raction mixture was heated at 50°C for 24 h. Cool to room temperature and dilute with 1 mL $CDCl_3$ directly for $^1H$ NMR. $^1H$ NMR (500 MHz, Chloroform-d) δ 4.16 (q, *J* = 7.1 Hz, 2H), 3.43 – 3.40 (m, 0.1H), 2.23 (s, 2.3H), 1.24 (t, *J* = 7.1 Hz, 3H).

Research on reversibility of HIE reaction. **2m-$d_6$** (35.2 mg, 0.1 mmol), $H_2O$ (90 µL, 5 mmol), TFA (75 µL, 1 mmol) and NMP were added in a 10 mL schlenk tube. The mixture

was then treated according to general procedure 1 and reacted at 70°C for 48 h. After general work-up and purification, $^1$H NMR was done to show the D incorporation decreased to 12% which meant the HIE reaction was reversible to a great extent. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.50 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.45 (td, *J* = 8.0, 7.6, 1.4 Hz, 1H), 7.29 – 7.21 (m, 2H), 5.78 (s, 1H), 5.72 (s, 1H), 3.59 (s, 6H), 2.34 (s, 5.3H).

# 7. References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6. A. Gutierrez-Bonet, J. C. Tellis, J. K. Matsui, B. A. Vara and G. A. Molander, *ACS Catal.*, 2016, **6**, 8004-8008.
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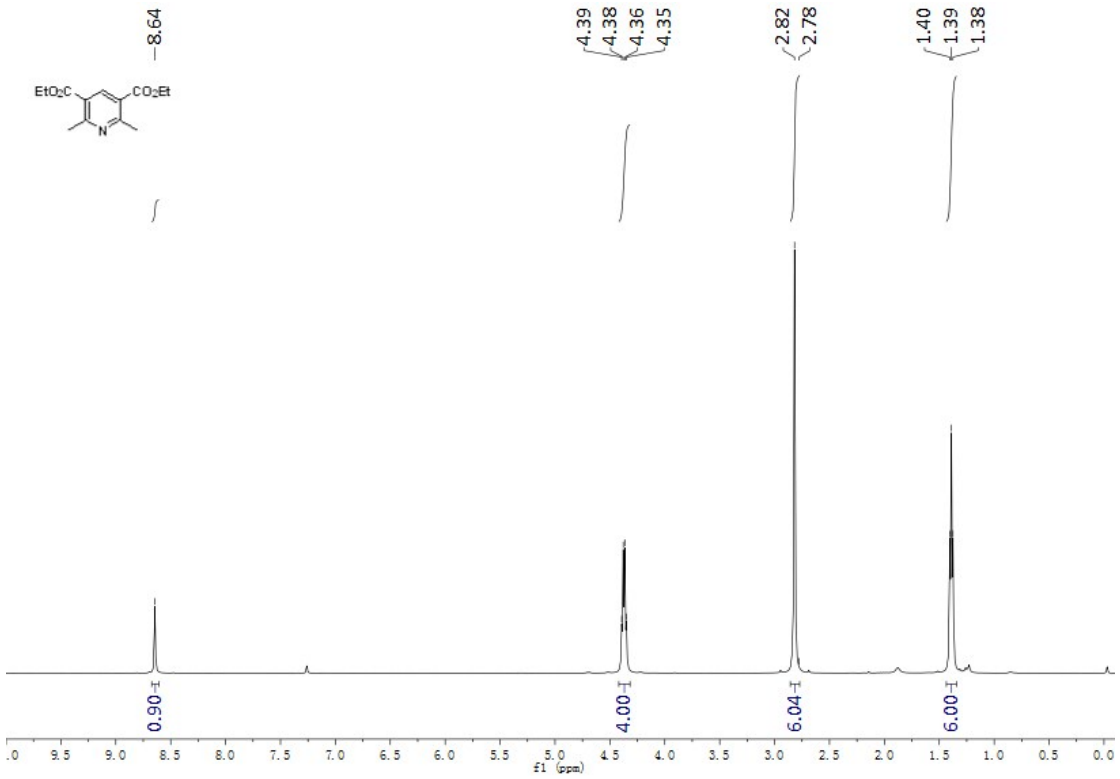
9. N. Nakamichi, Y. Kawashita and M. Hayashi, *Org. Lett.*, 2002, **4**, 3955-3957.

## 8. NMR spectra

**1a'** (oxidative product of **1a**)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4.36
4.35
2.82
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1.39
1.38
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N
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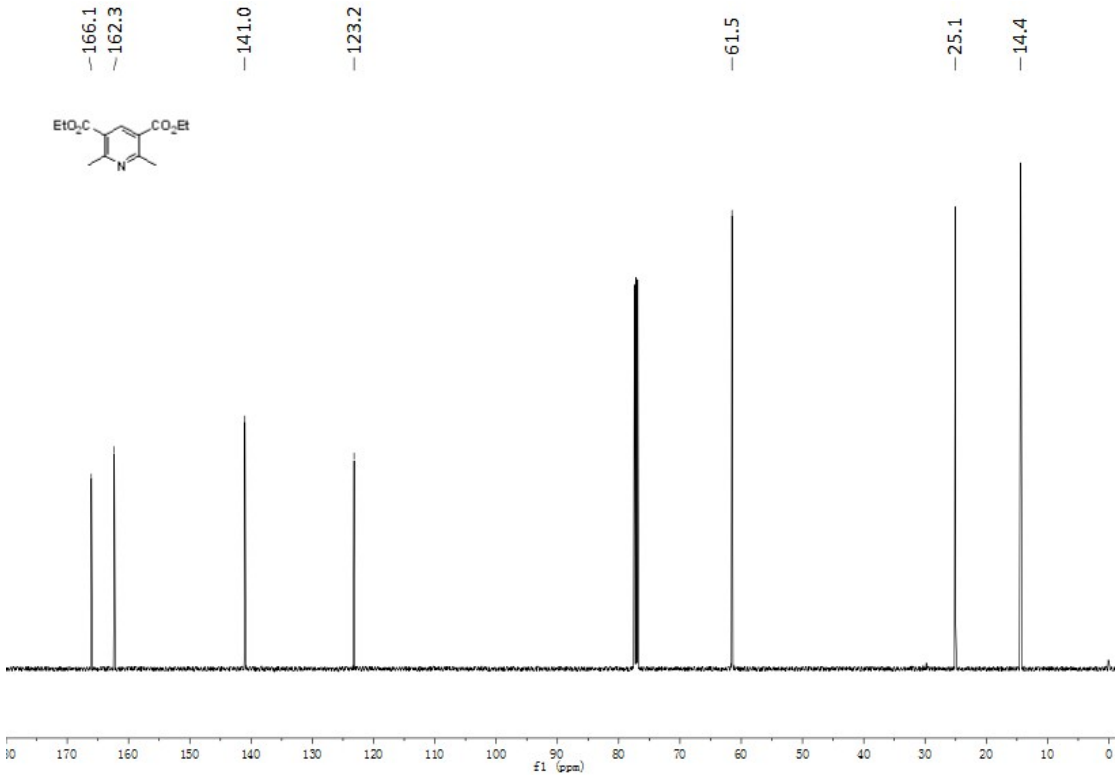
4.00
6.04
6.00
f1 (ppm)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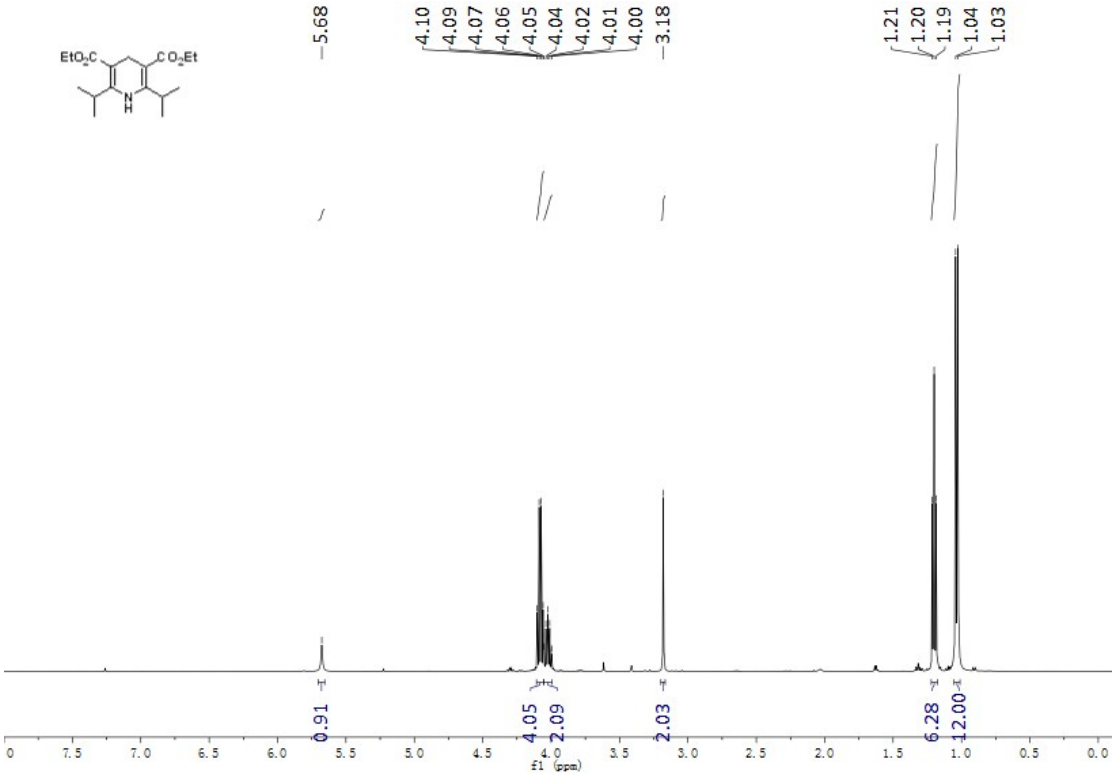
123.2
61.5
25.1
14.4
EtO2C
CO2Et
N
f1 (ppm)

**1e**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4.10
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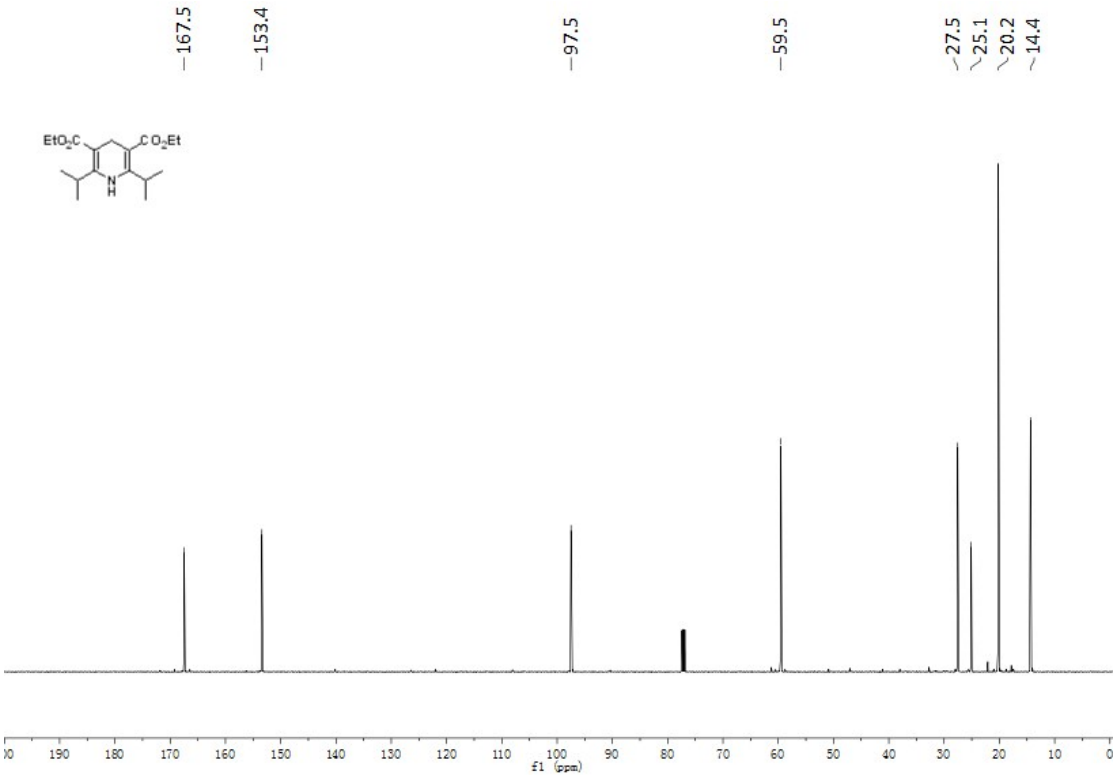
4.07
4.06
4.05
4.04
4.02
4.01
4.00
3.18
1.21
1.20
1.19
1.04
1.03
0.91
4.05
2.09
2.03
6.28
12.00
f1 (ppm)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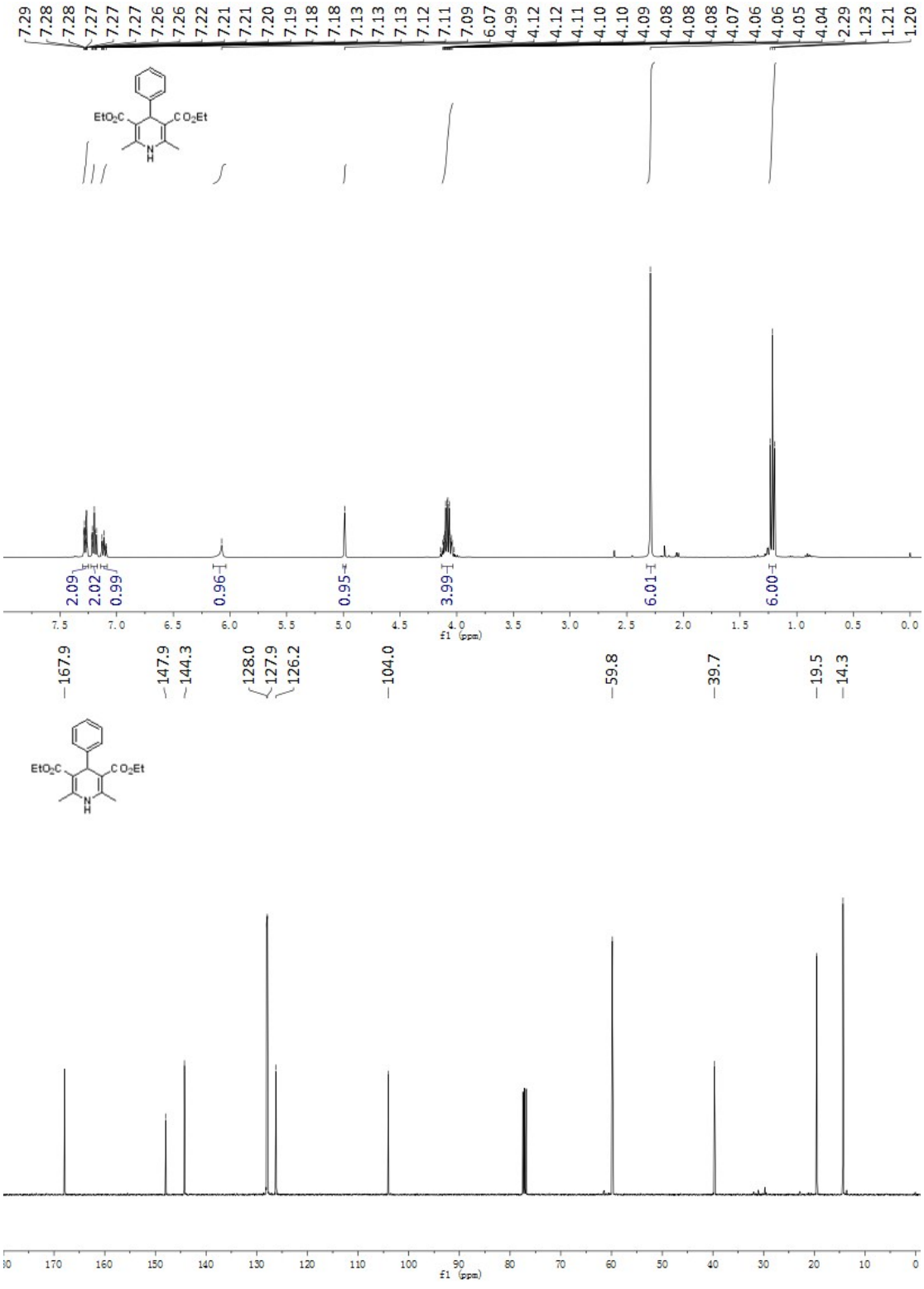
25.1
20.2
14.4
f1 (ppm)

**2a**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7.28
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7.27
7.26
7.26
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7.21
7.21
7.20
7.19
7.18
7.18
7.13
7.13
7.13
7.12
7.11
7.09
6.07
4.99
4.12
4.12
4.11
4.10
4.10
4.09
4.08
4.08
4.08
4.07
4.06
4.06
4.05
4.04
2.29
1.23
1.21
1.20
EtO2C
CO2Et
2.09
2.02
0.99
0.96
0.95
3.99
6.01
6.00
f1 (ppm)
167.9
147.9
144.3
128.0
127.9
126.2
104.0
59.8
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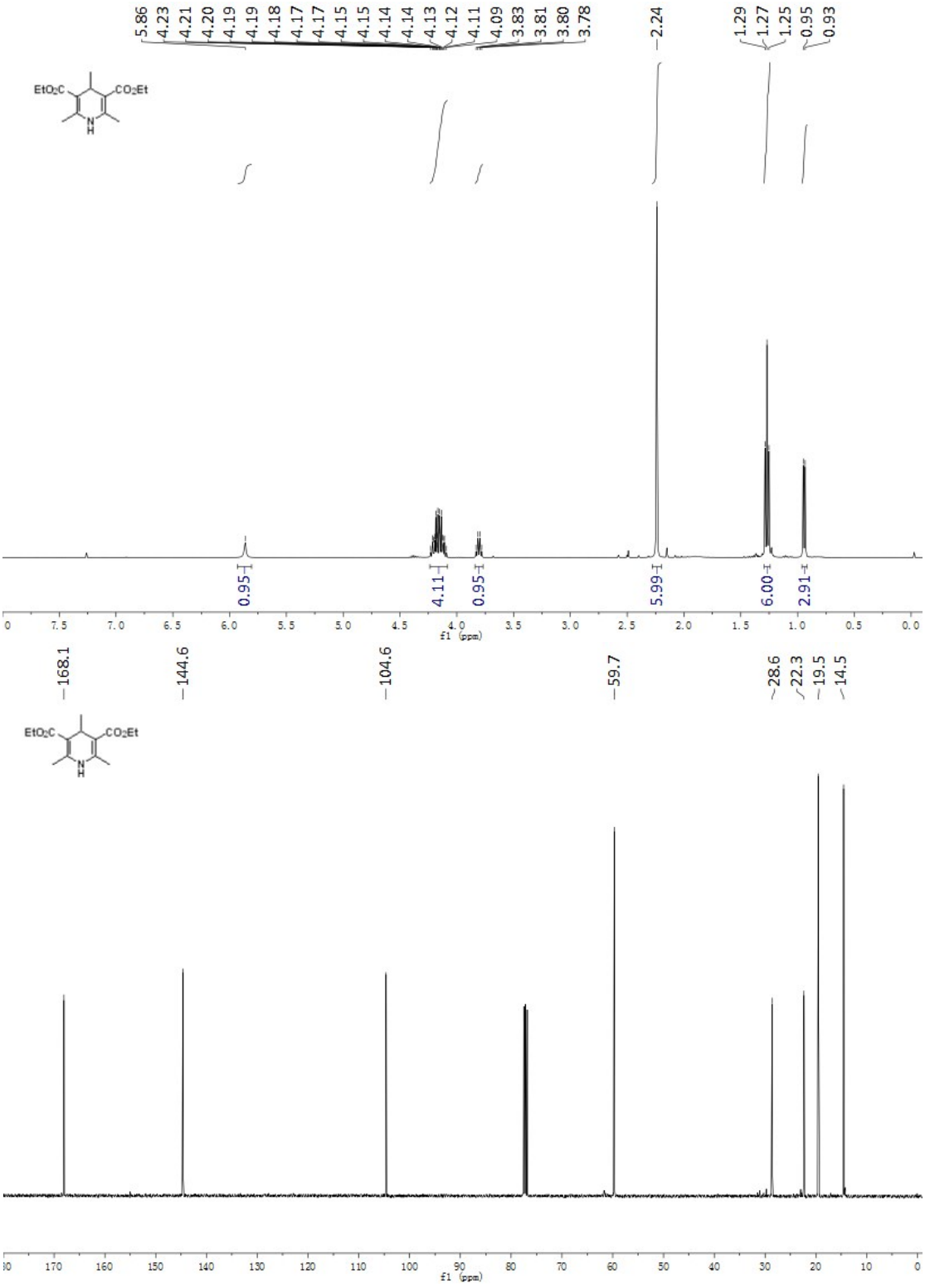
14.3
EtO2C
CO2Et
f1 (ppm)

**2g**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4.17
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4.13
4.12
4.11
4.09
3.83
3.81
3.80
3.78
2.24
1.29
1.27
1.25
0.95
0.93
EtO2C
CO2Et
0.95
4.11
0.95
5.99
6.00
2.91
f1 (ppm)
168.1
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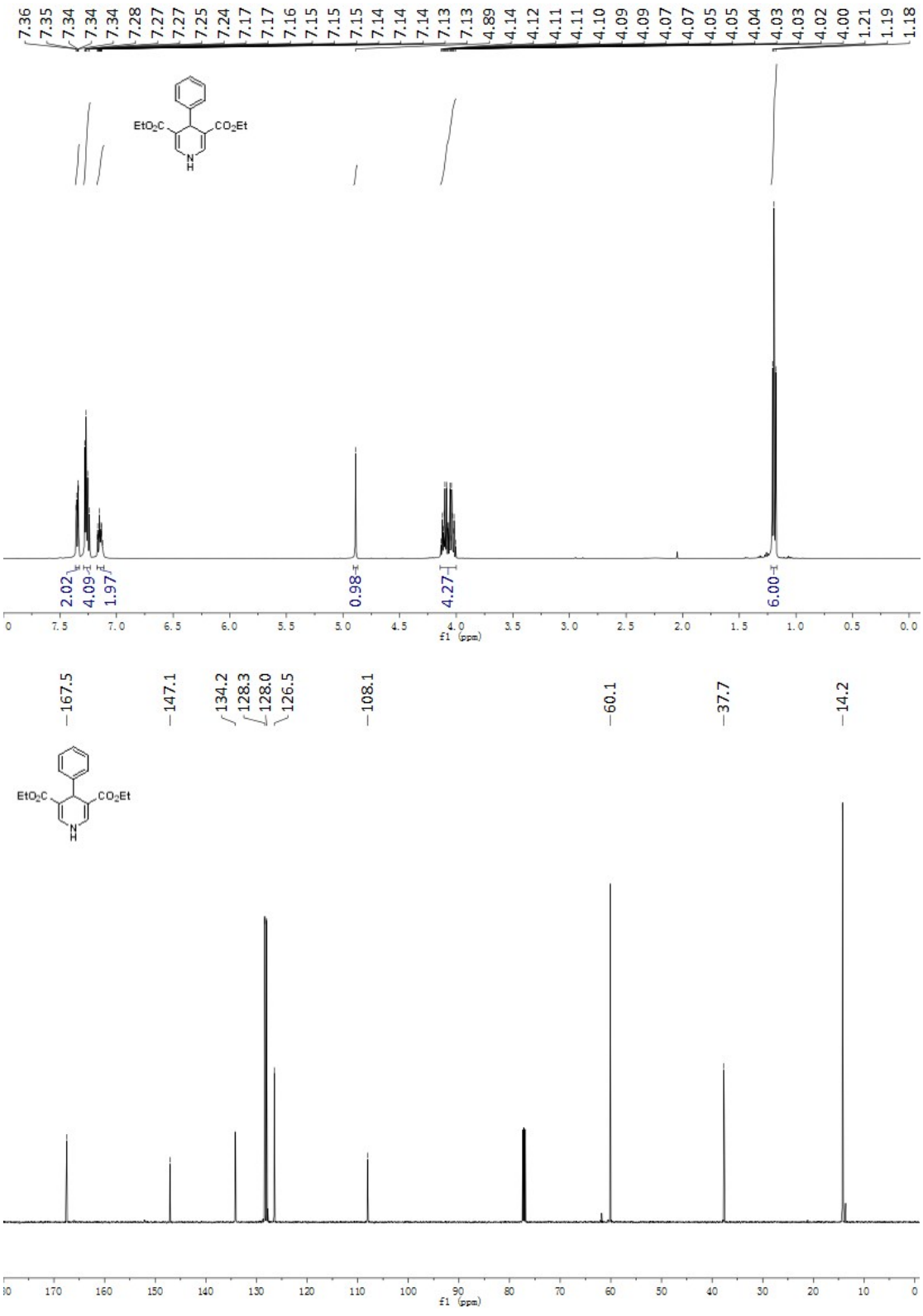
59.7
28.6
22.3
19.5
14.5
EtO2C
CO2Et
f1 (ppm)

**3b**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EtO2C
CO2Et
H
2.02
4.09
1.97
0.98
4.27
6.00
f1 (ppm)
167.5
147.1
134.2
128.3
128.0
126.5
108.1
60.1
37.7
14.2
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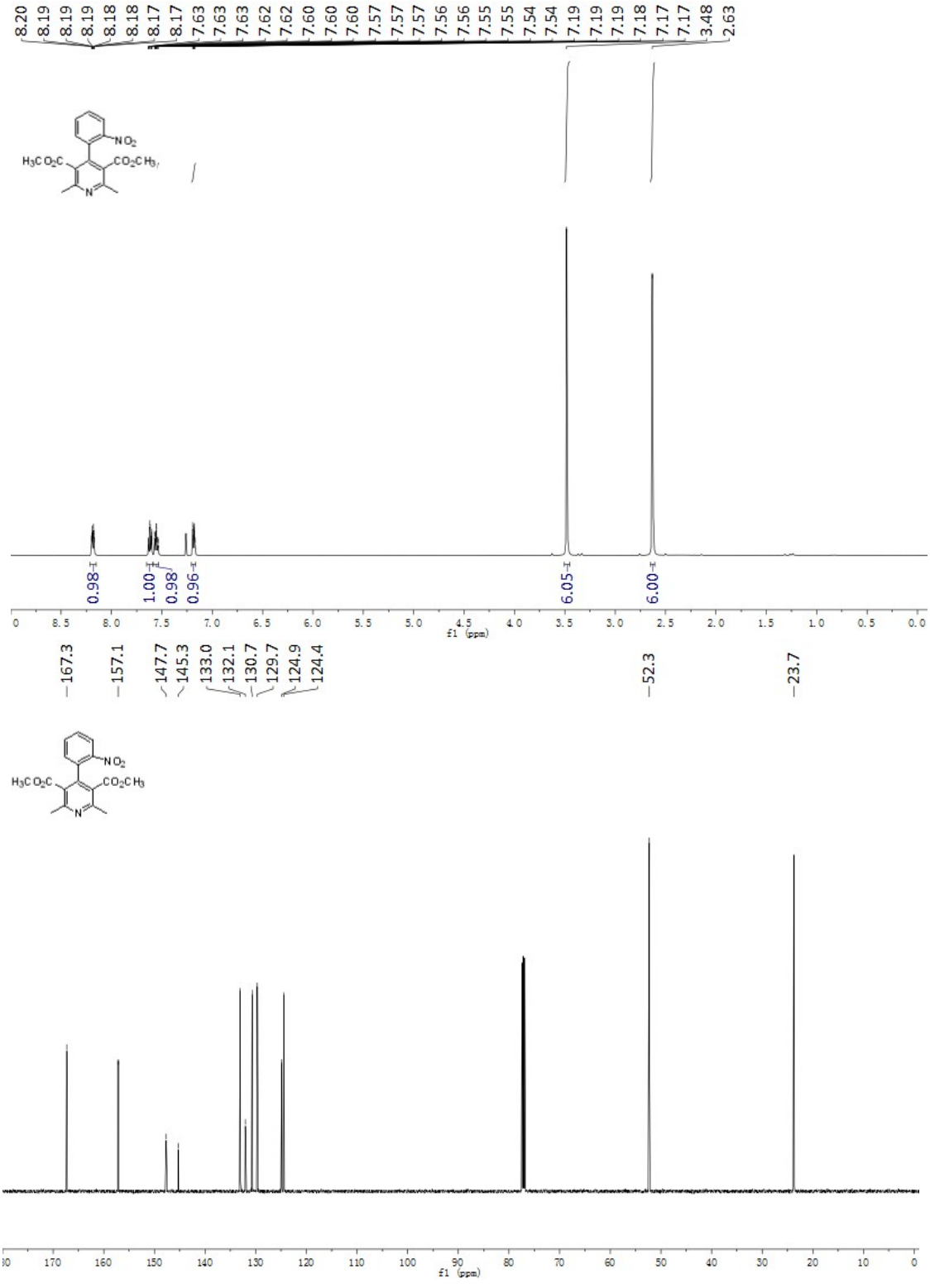
CO2Et
H
f1 (ppm)

**3d**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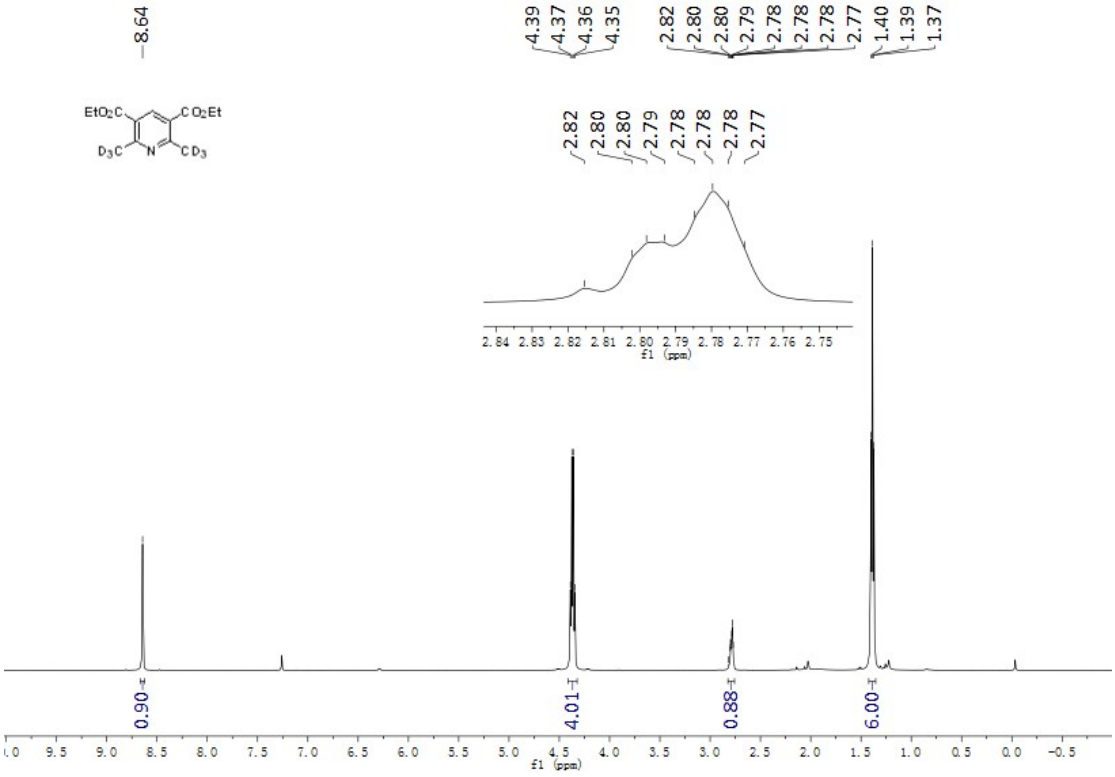
NO2
H3CO2C
CO2CH3
0.98 1.00 0.98 0.96 6.05 6.00
f1 (ppm)
167.3 157.1 147.7 145.3 133.0 132.1 130.7 129.7 124.9 124.4 52.3 23.7
f1 (ppm)

**1a'-$d_6$**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4.35
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2.80
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2.78
2.77
1.40
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1.37
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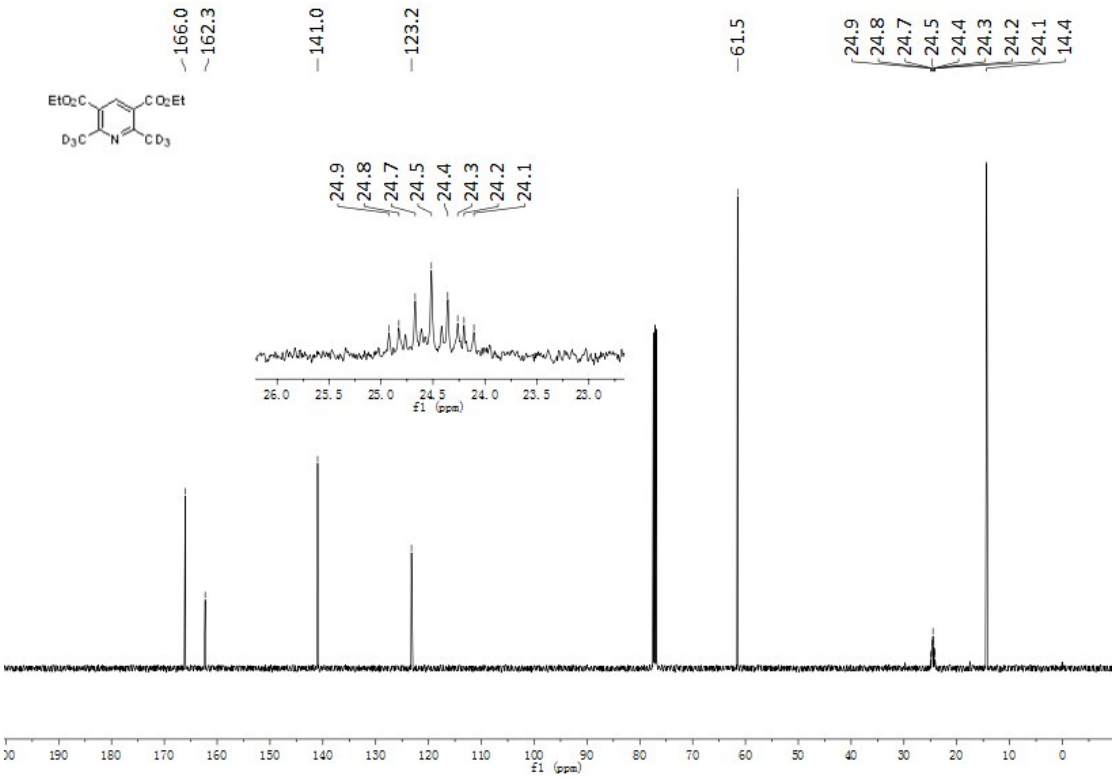
0.88
6.00
f1 (ppm)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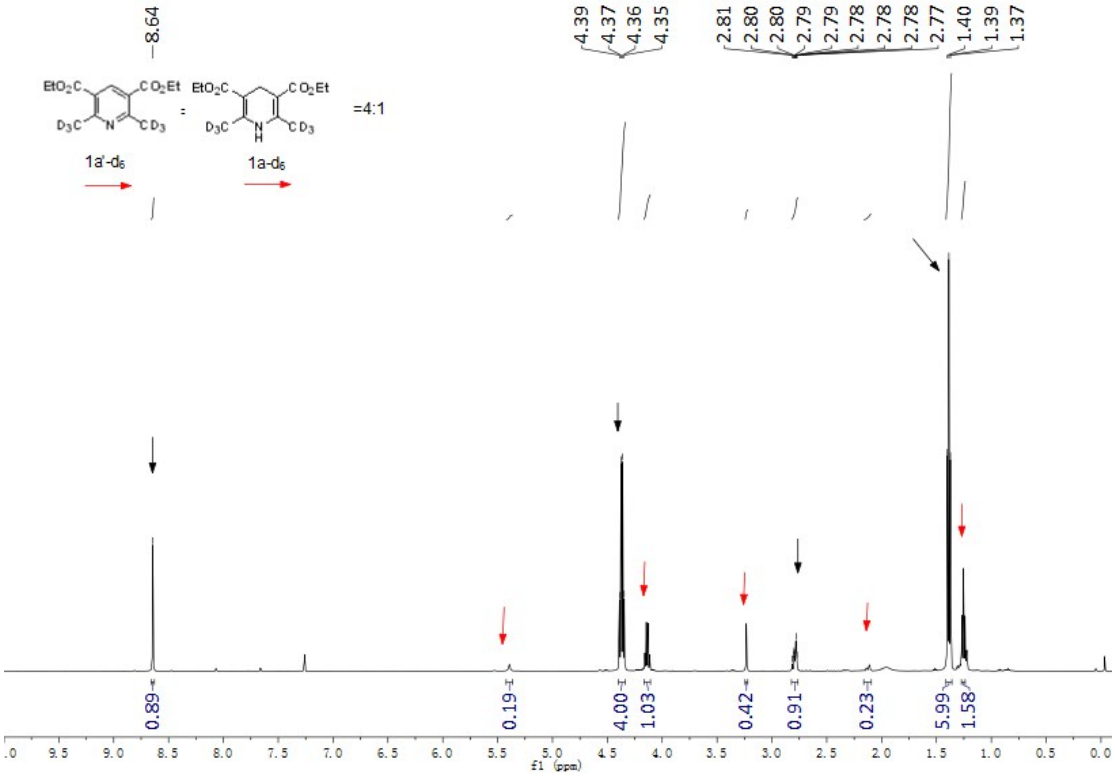
24.7
24.5
24.4
24.3
24.2
24.1
14.4
EtO2C
CO2Et
D3C
N
CD3
f1 (ppm)

**1a'-$d_6$**(reaction for 36h, mixture, **1a'-$d_6$**:**1a-$d_6$**=4:1)



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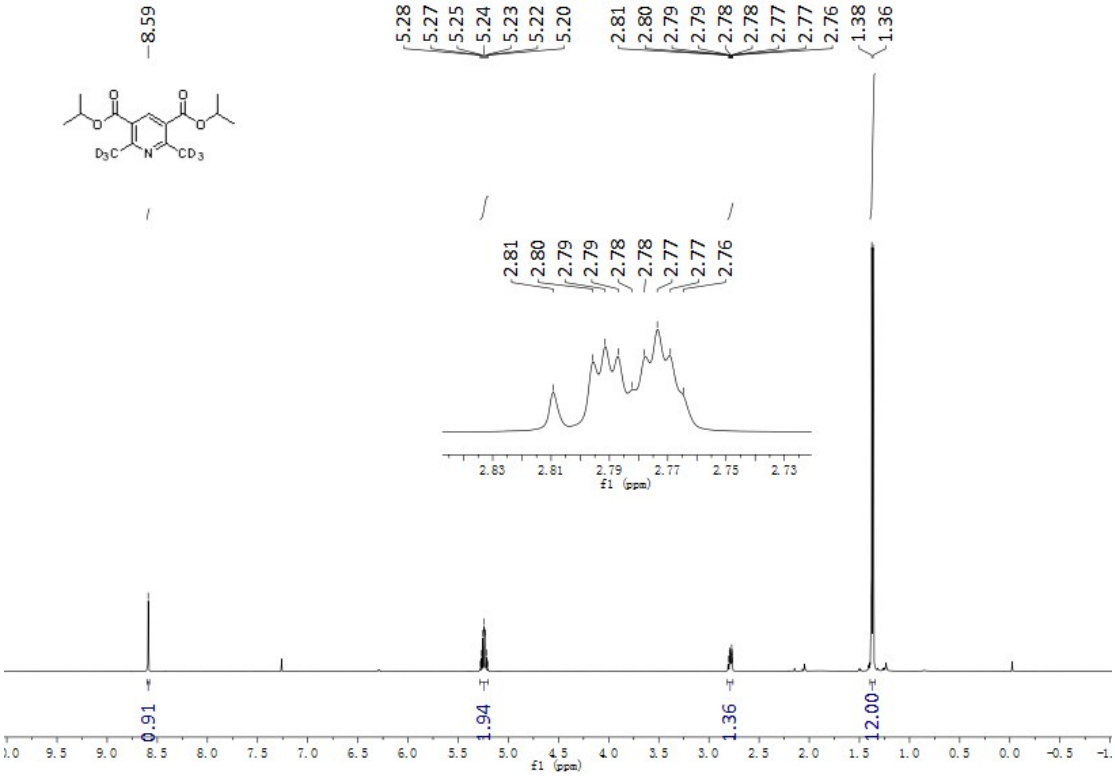
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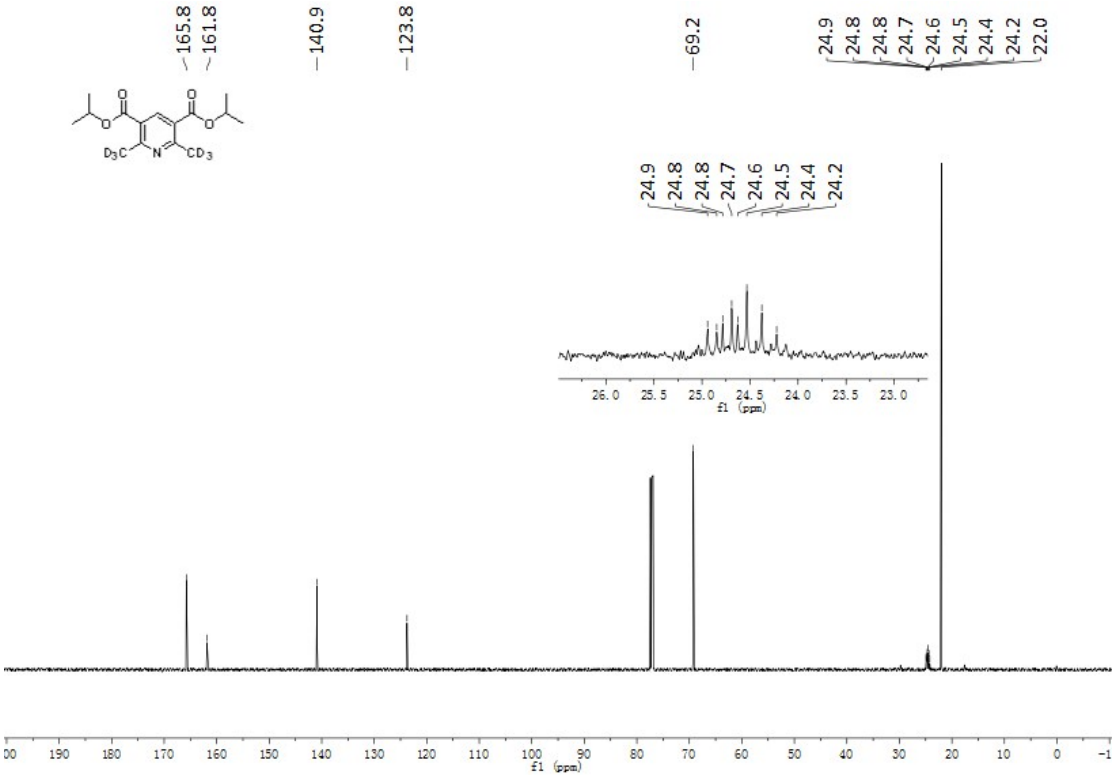
f1 (ppm)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f1 (ppm)

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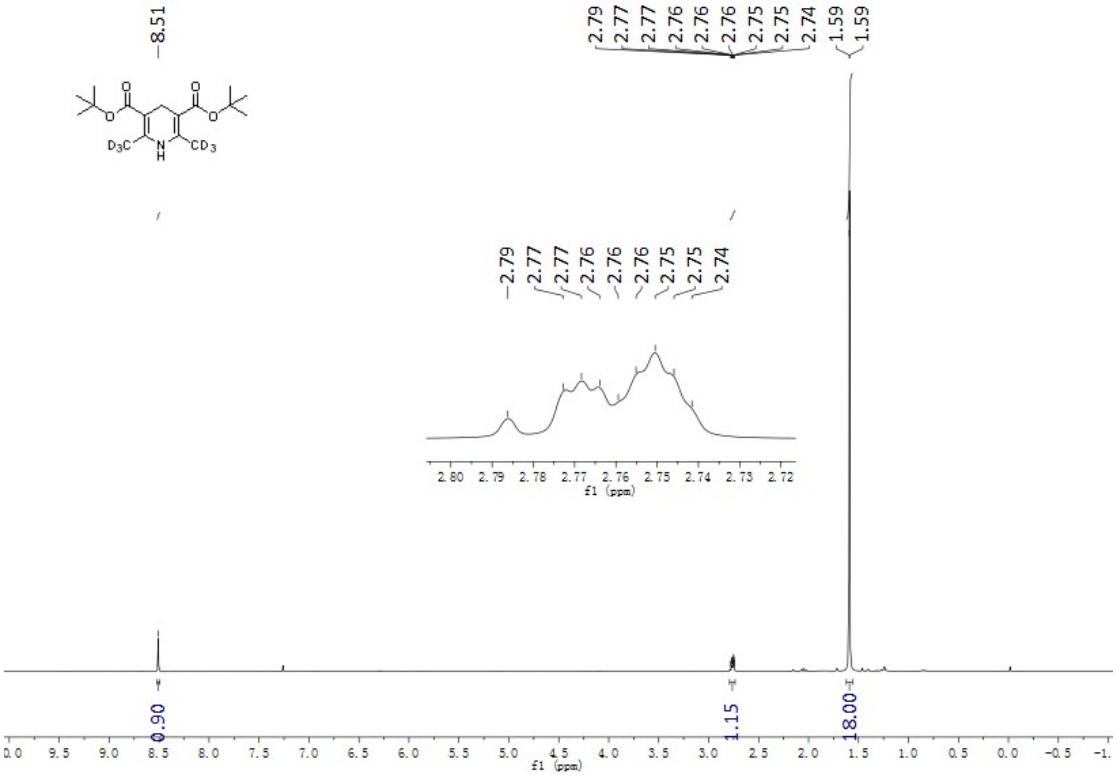
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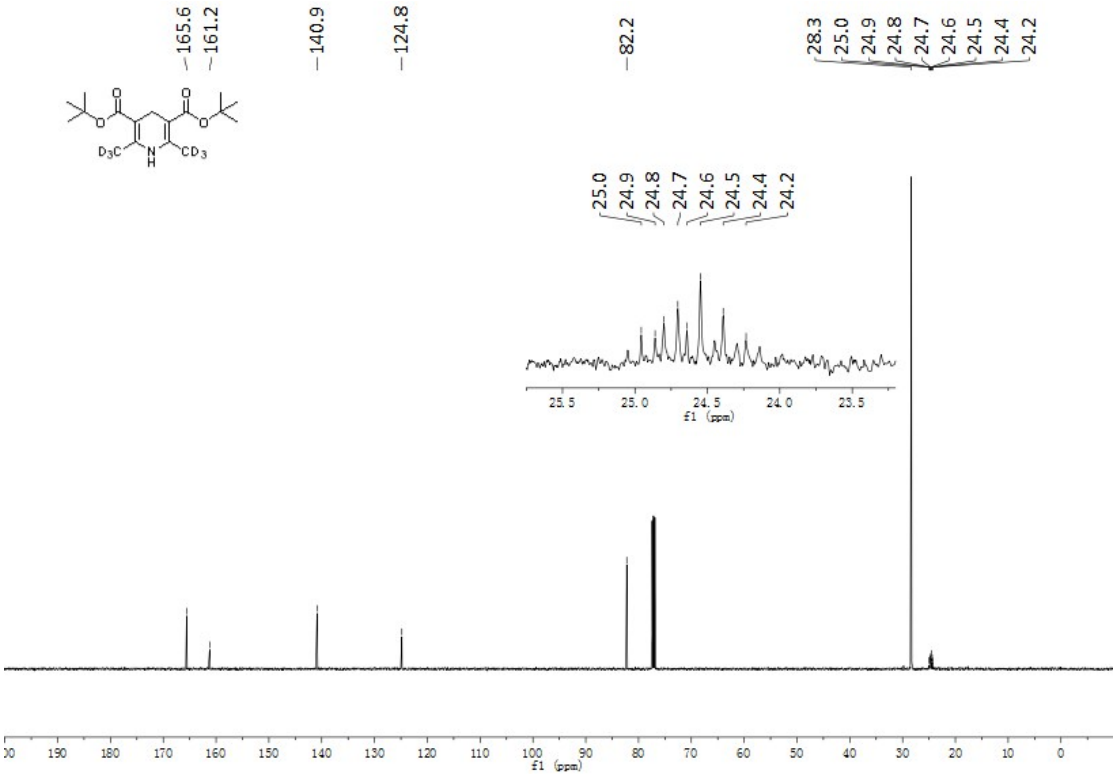
f1 (ppm)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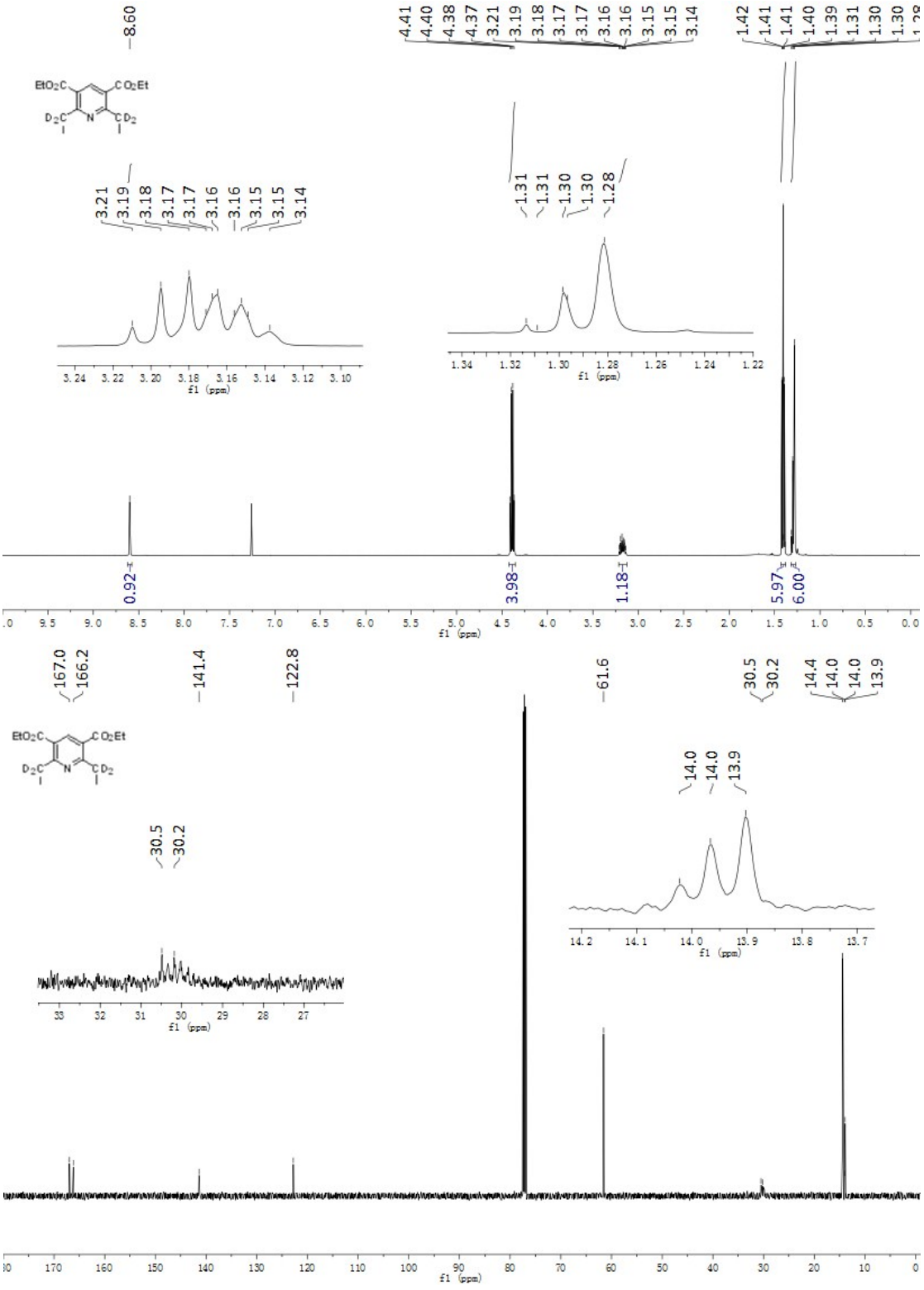
24.2
f1 (ppm)

**1d'-$d_4$**



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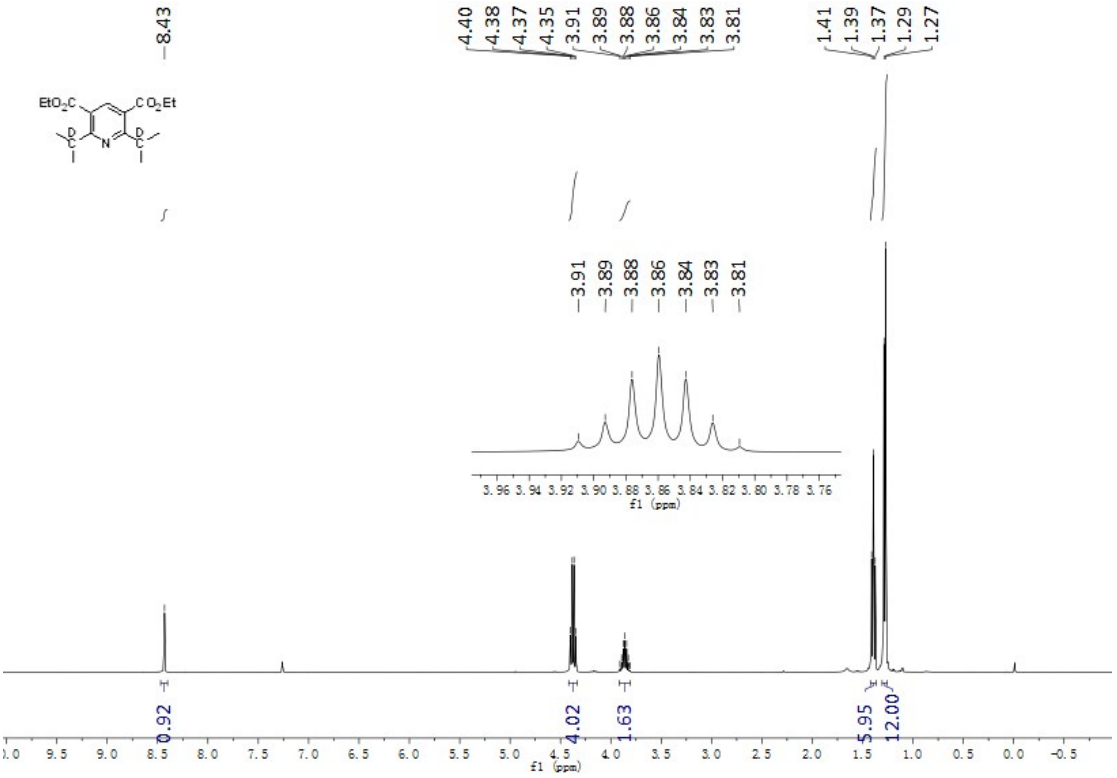
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1.27
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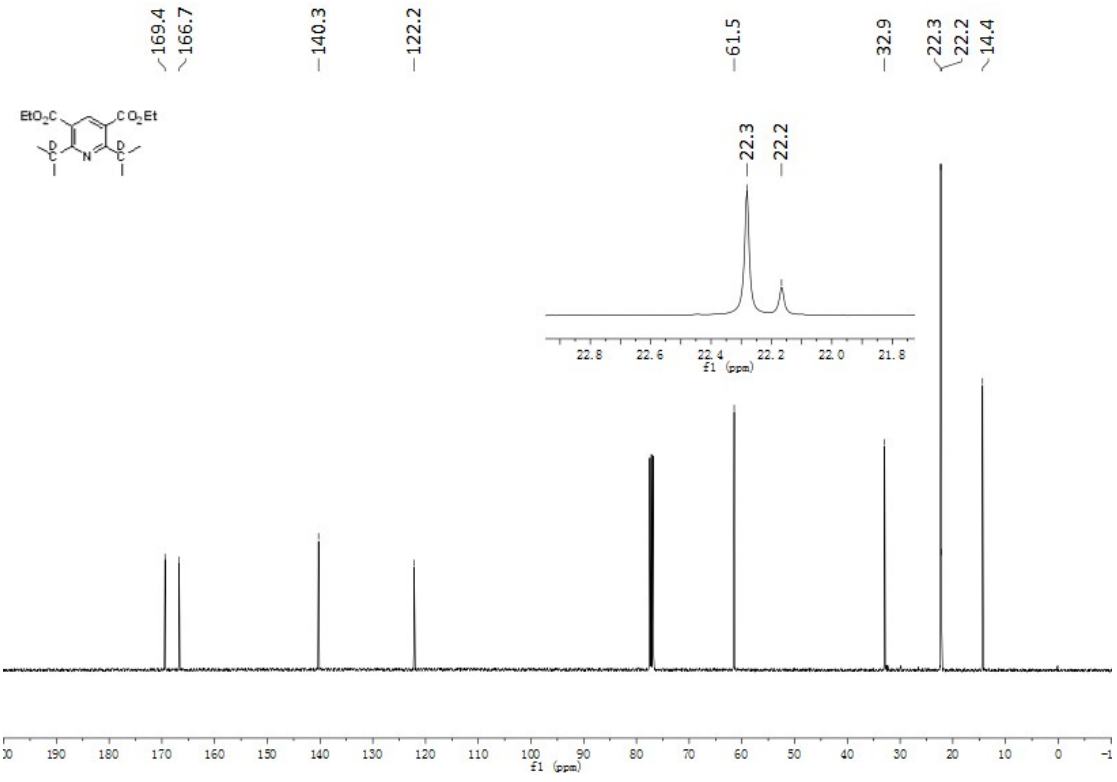
f1 (ppm)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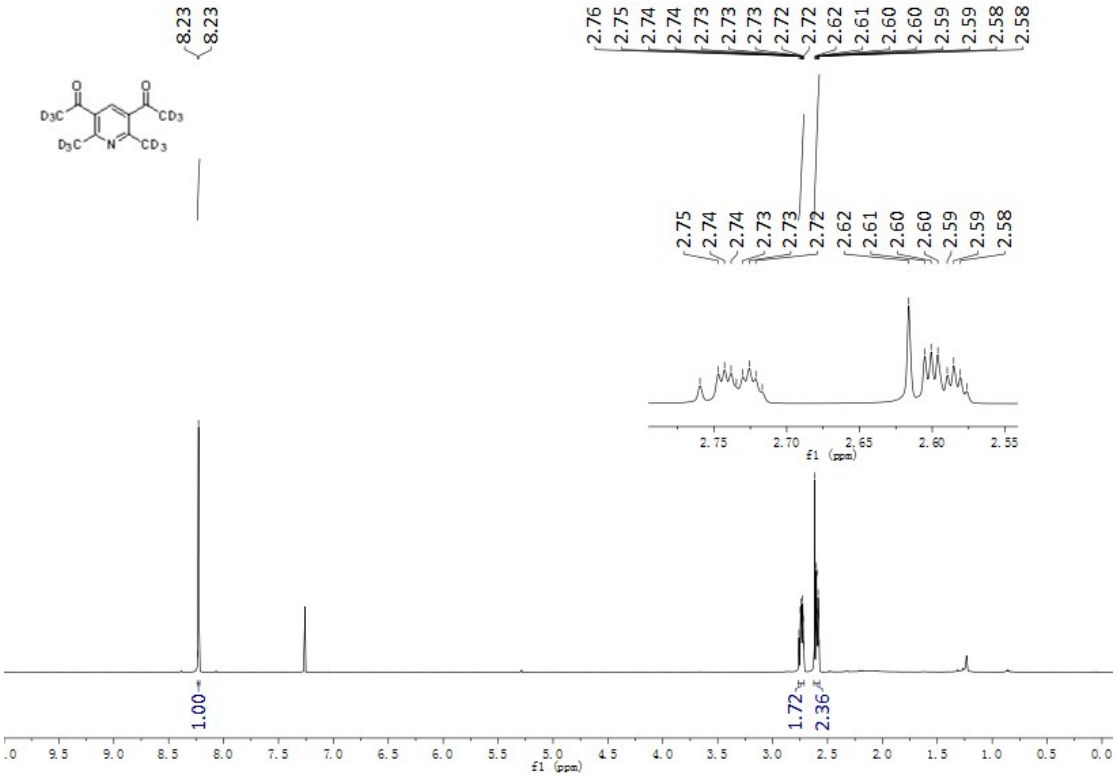
22.2
14.4
f1 (ppm)

**1f'-$d_{12}$**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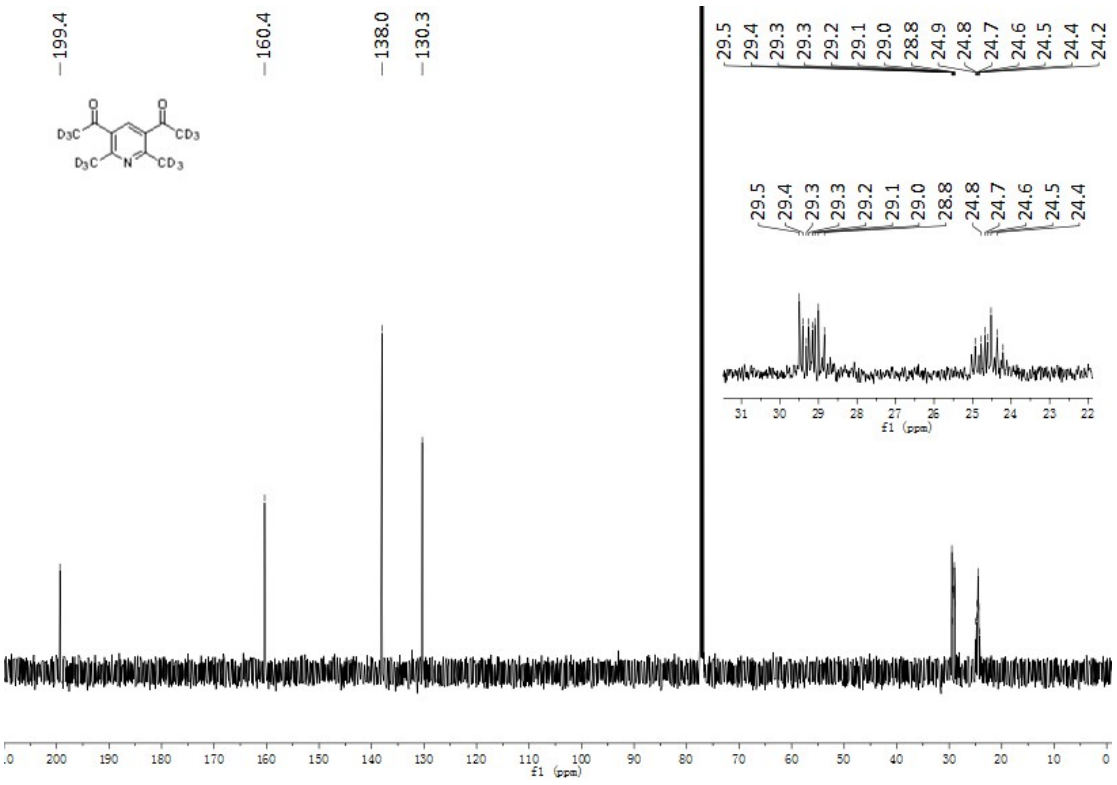
f1 (ppm)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29.5
29.4
29.3
29.3
29.2
29.1
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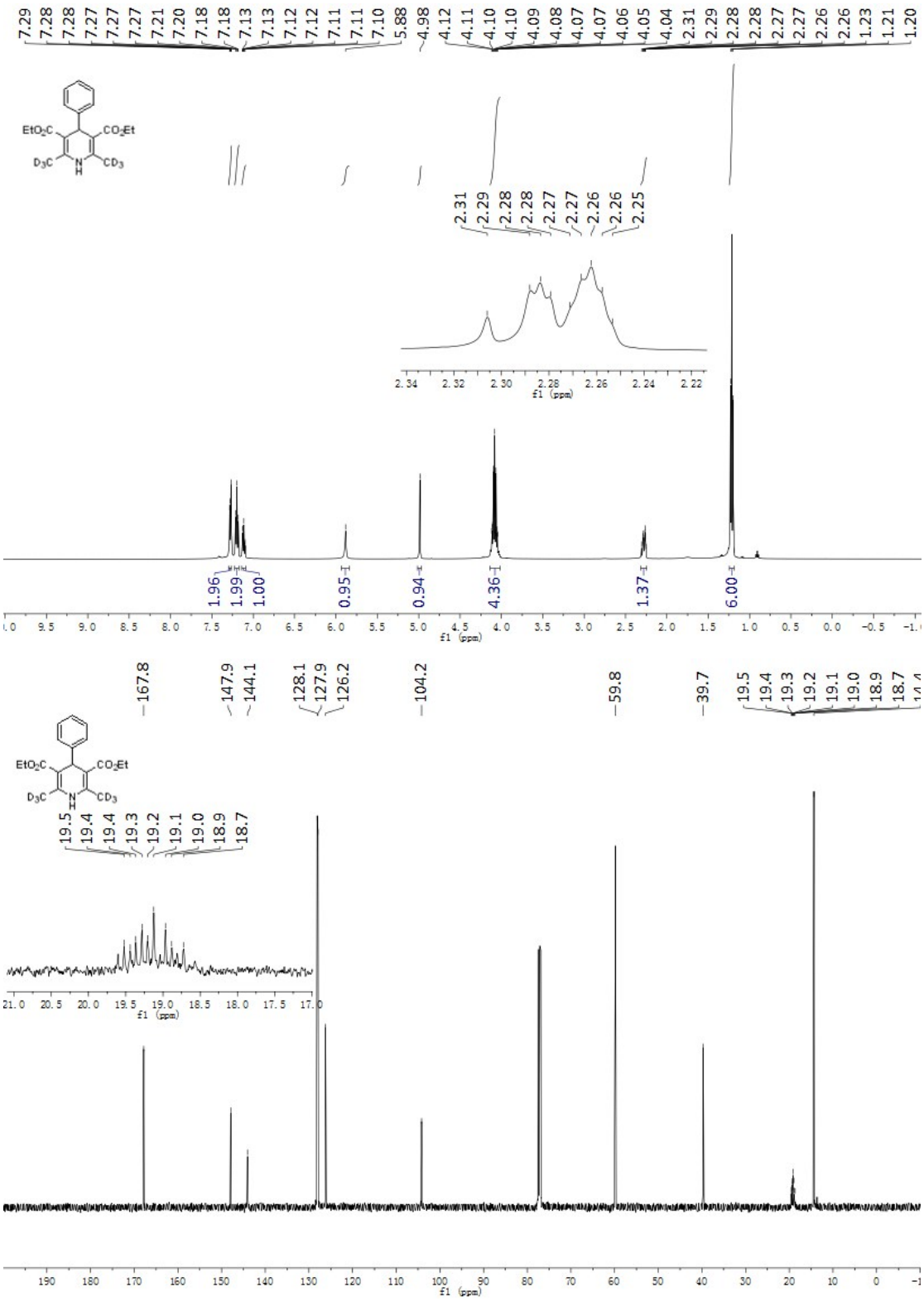
28.8
24.9
24.8
24.7
24.6
24.5
24.4
24.2
f1 (ppm)

**2a-$d_6$**



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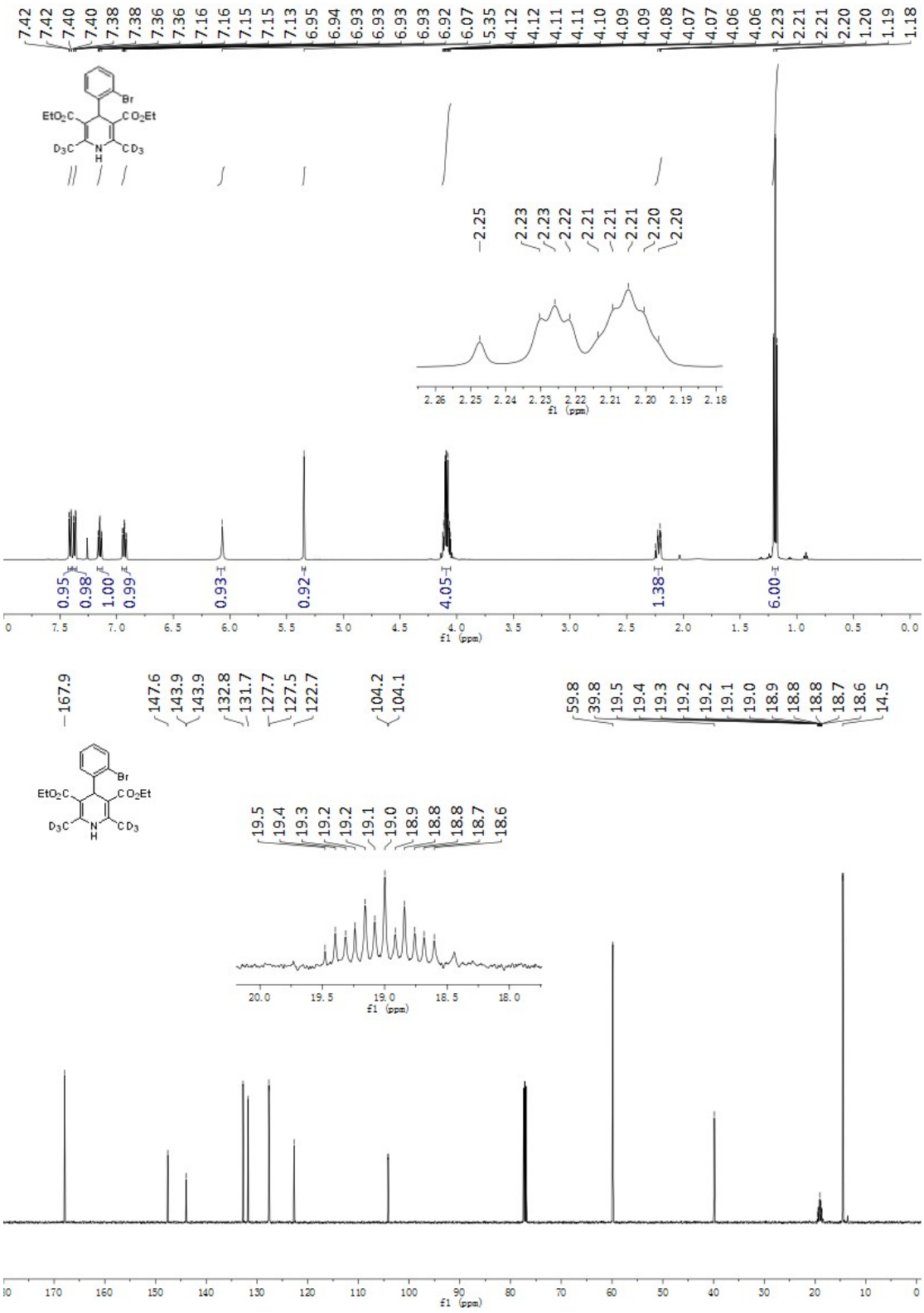

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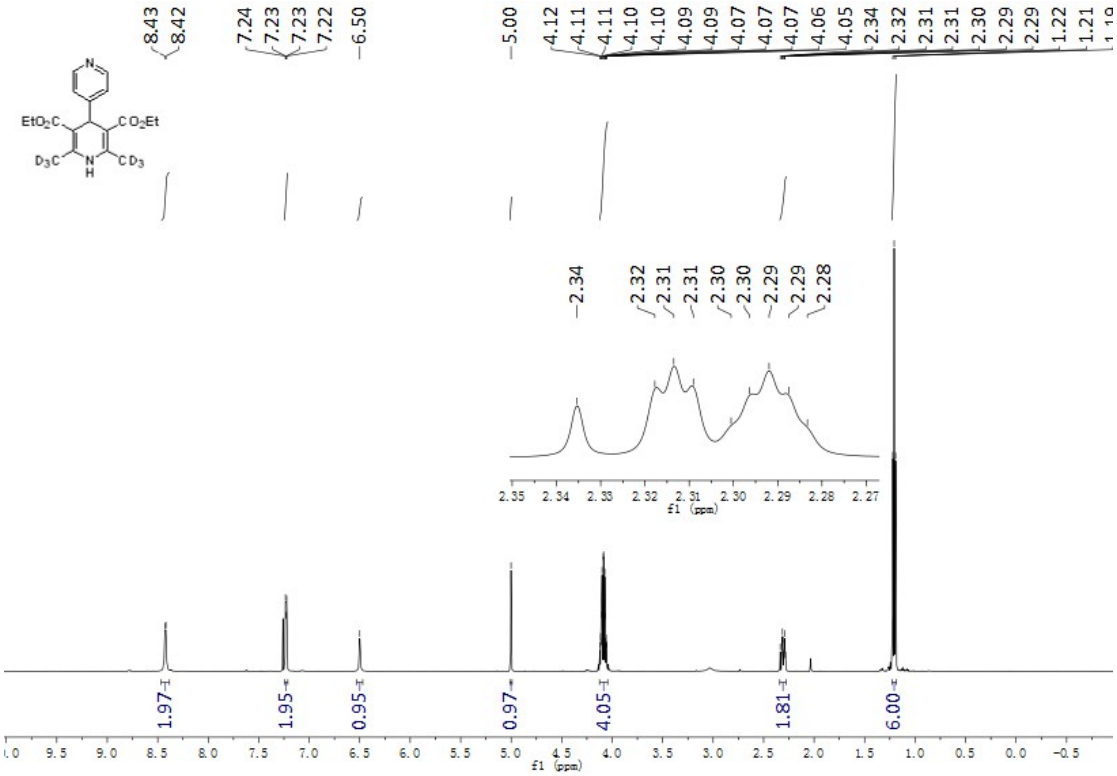
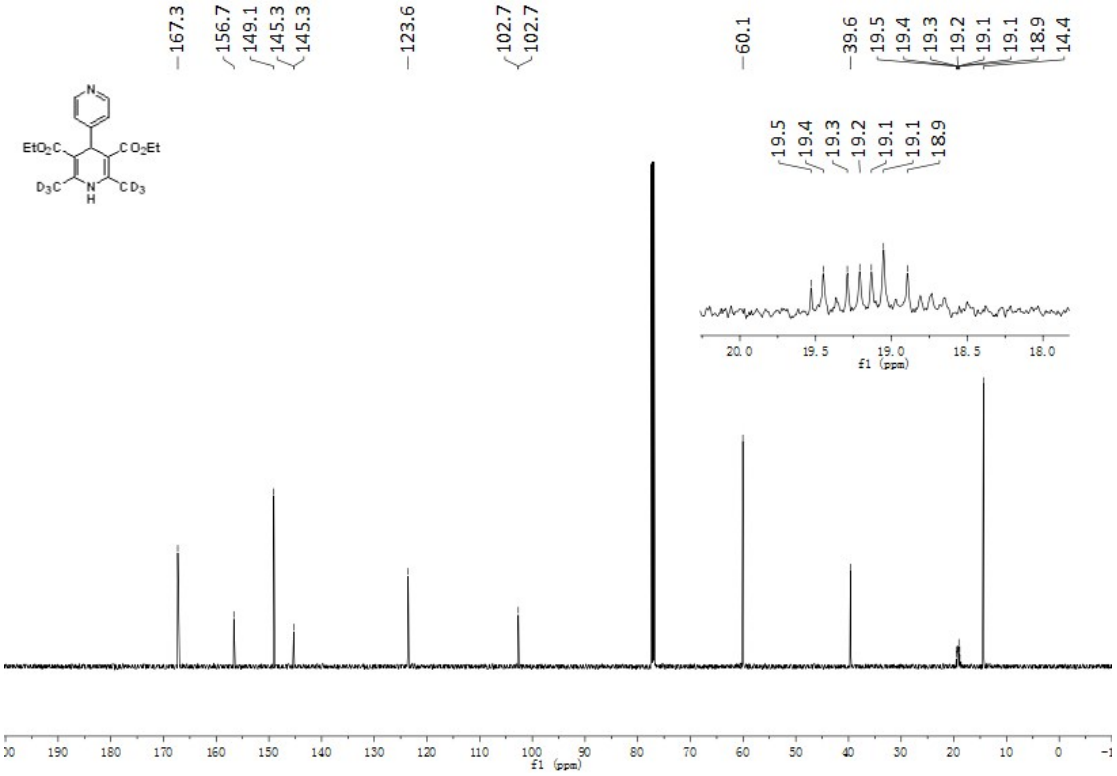
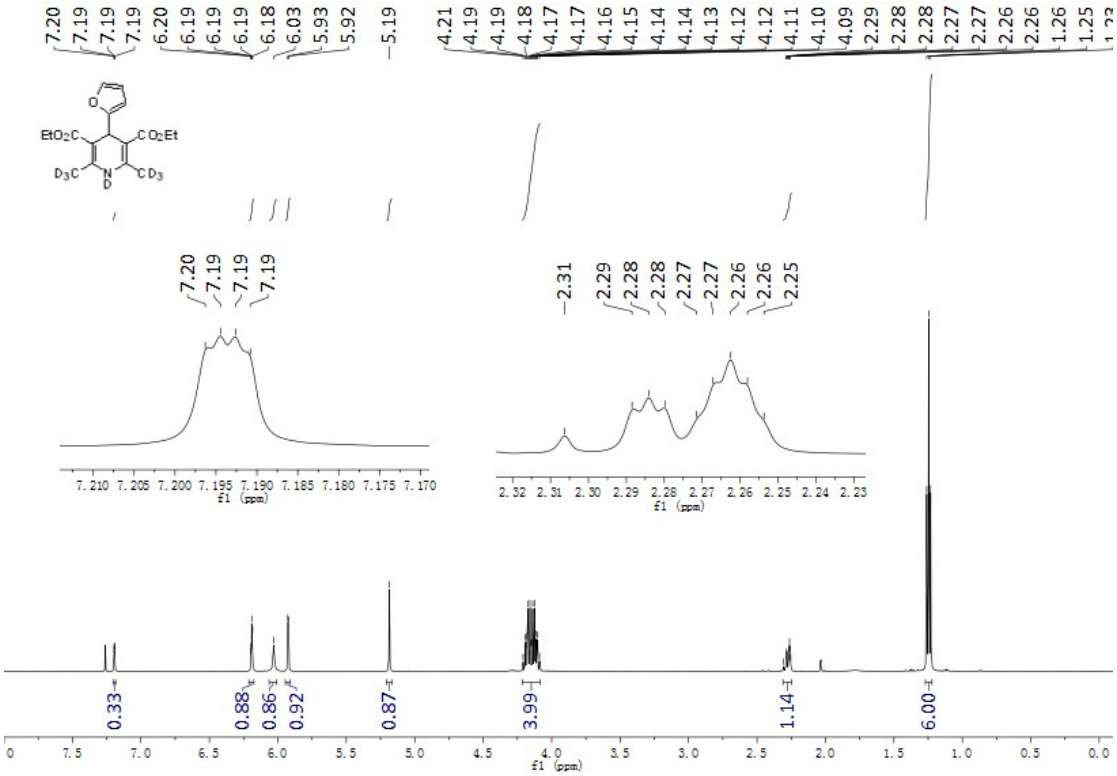
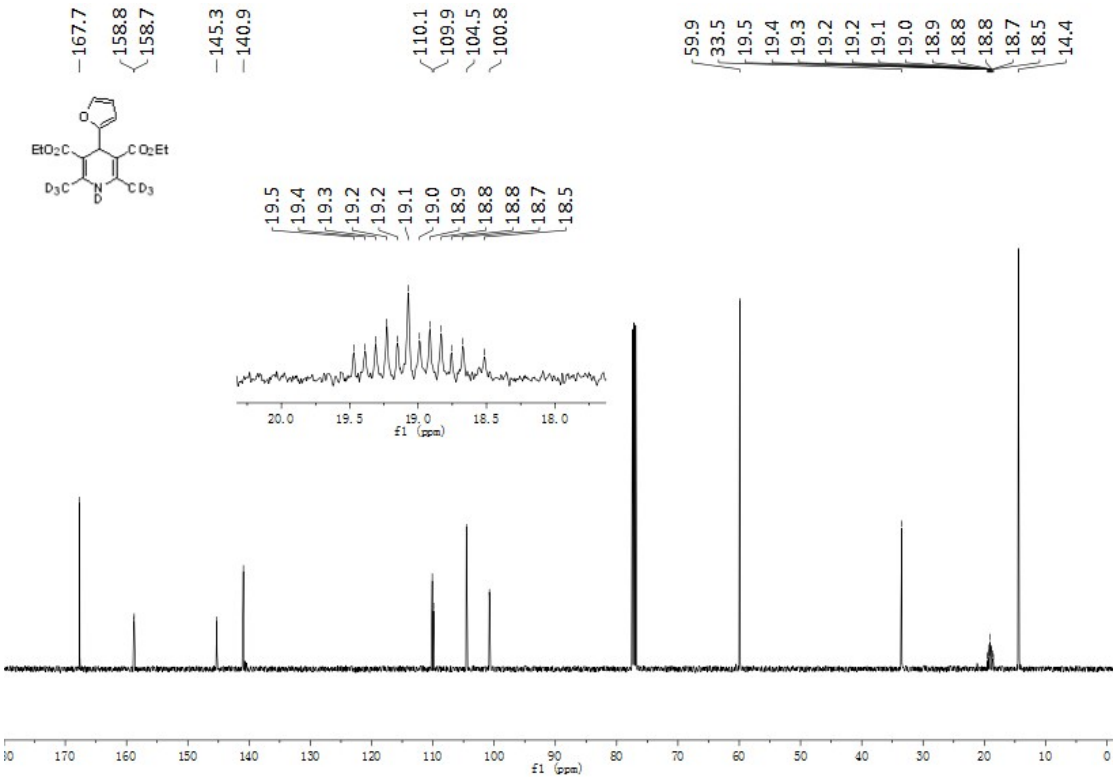




**2d-$d_7$**





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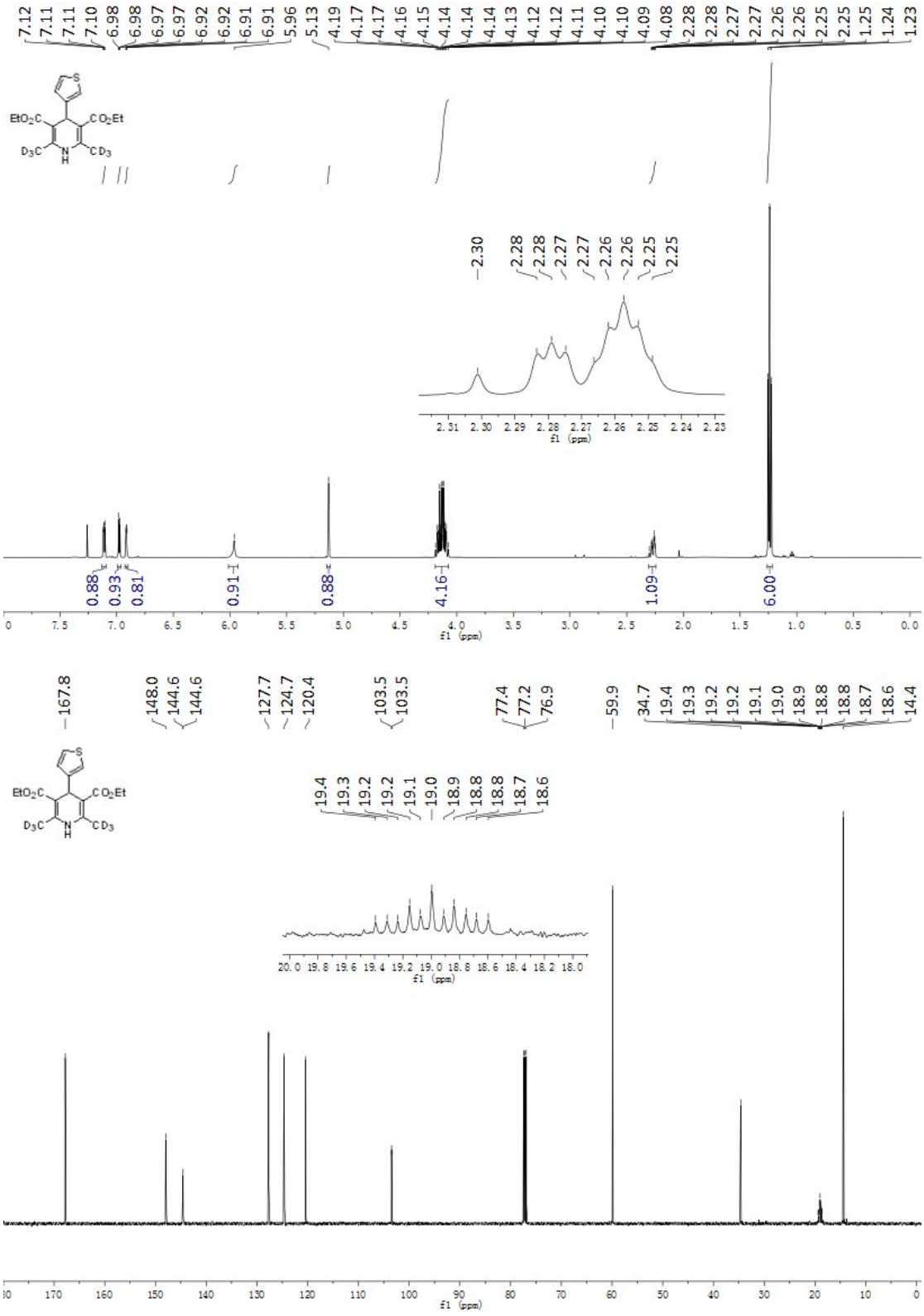
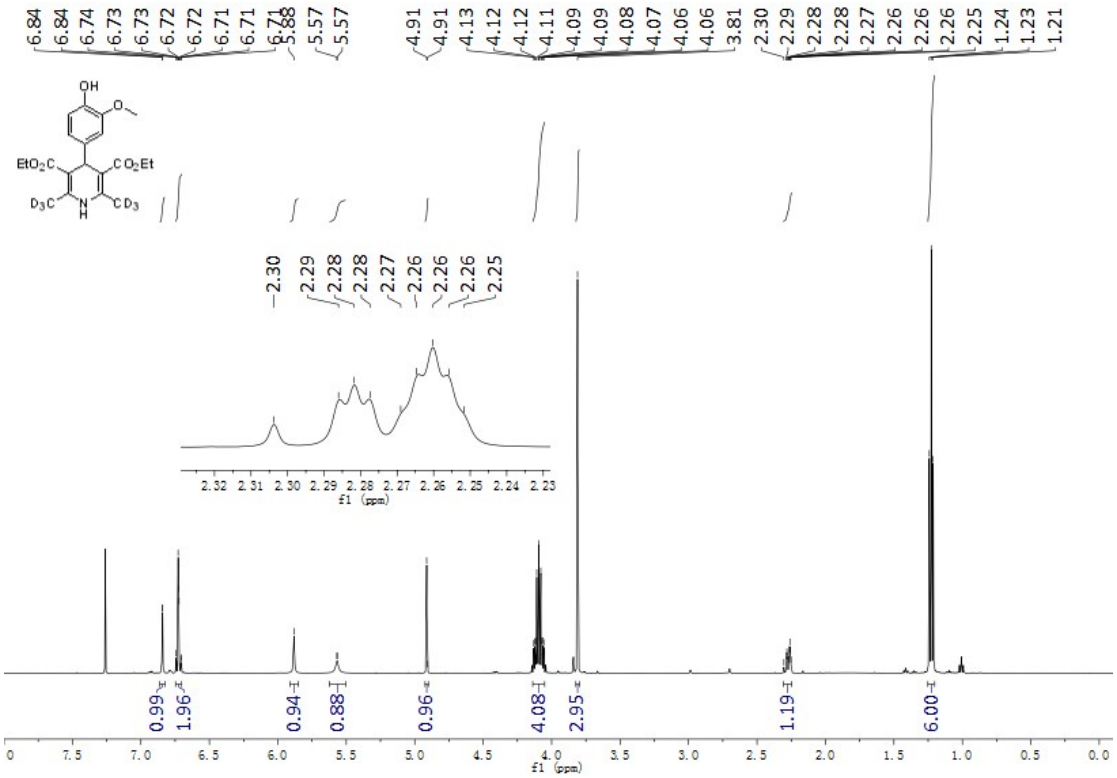
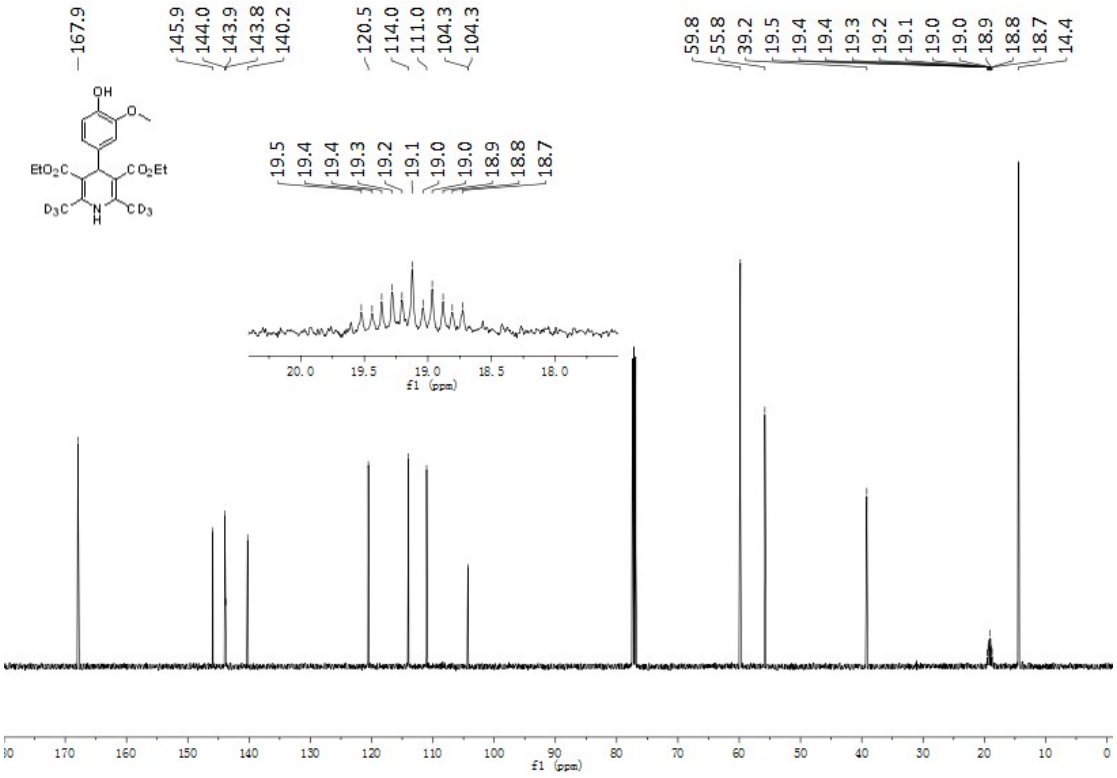
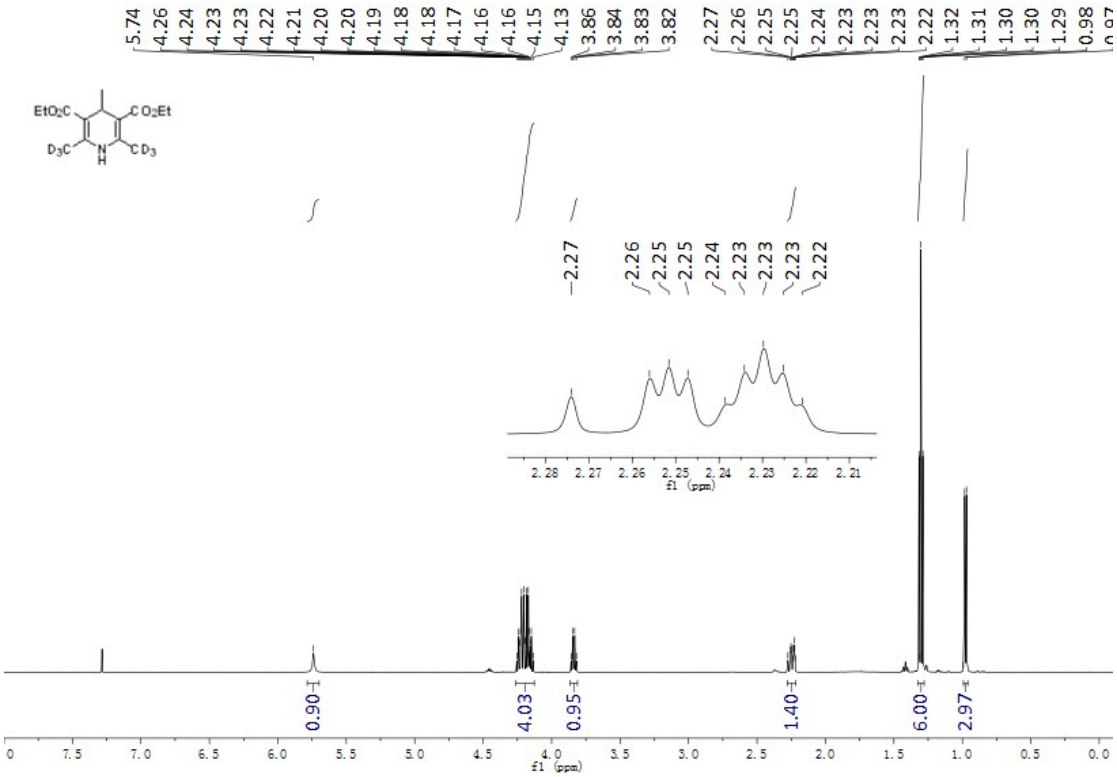


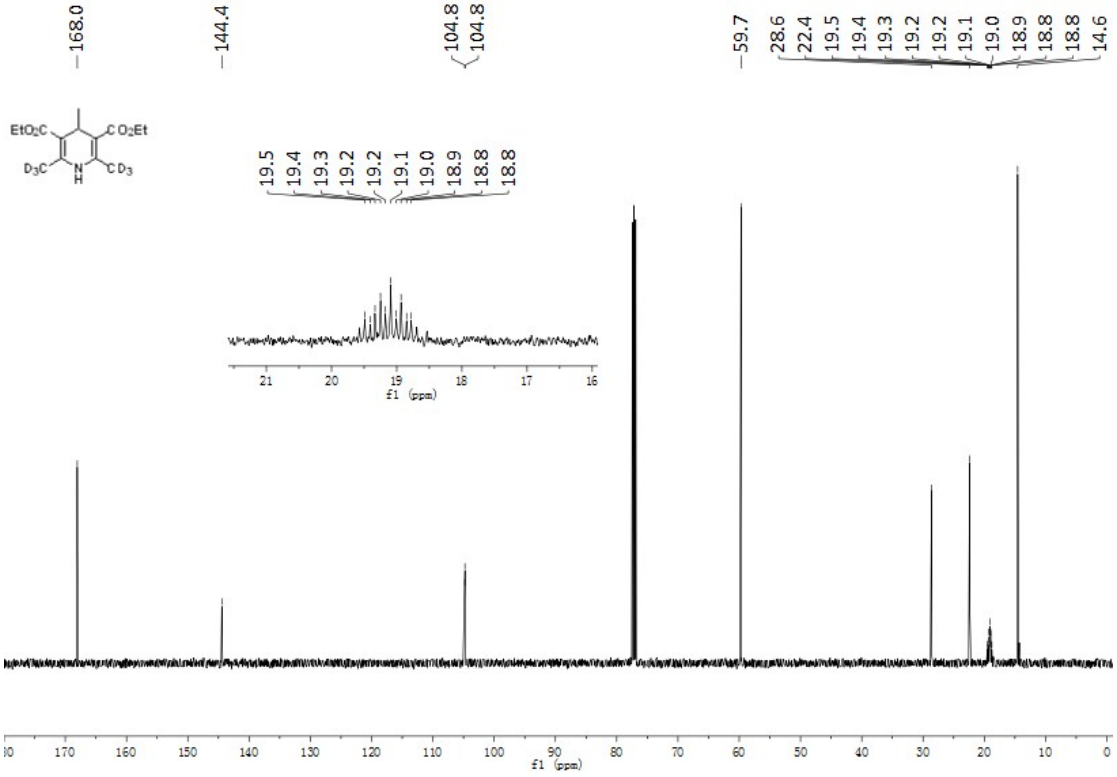
**2f-$d_6$**


6.84 6.84 6.74 6.73 6.73 6.72 6.72 6.71 6.71 5.88 5.57 5.57 4.91 4.91 4.13 4.12 4.12 4.11 4.09 4.09 4.08 4.07 4.06 4.06 3.81 2.30 2.29 2.28 2.28 2.27 2.26 2.26 2.26 2.25 1.24 1.23 1.21
OH
O
EtO2C
CO2Et
D3C
CD3
N
H
2.32 2.31 2.30 2.29 2.28 2.27 2.26 2.25 2.24 2.23
f1 (ppm)
0.99 1.96 0.94 0.88 0.96 4.08 2.95 1.19 6.00
0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

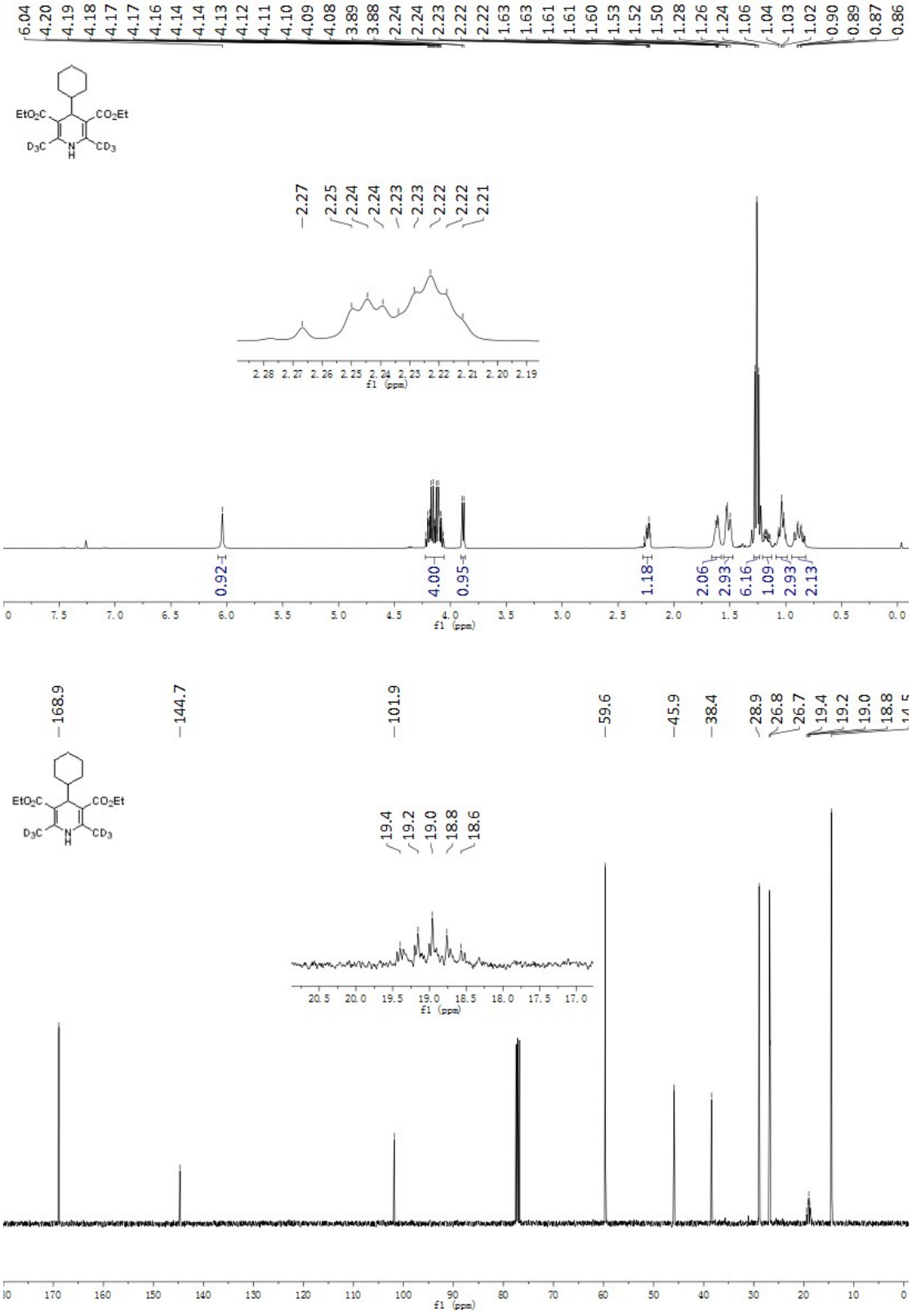

167.9 145.9 144.0 143.9 143.8 140.2 120.5 114.0 111.0 104.3 104.3 59.8 55.8 39.2 19.5 19.4 19.4 19.3 19.2 19.1 19.0 19.0 18.9 18.8 18.7 14.4
OH
O
EtO2C
CO2Et
D3C
CD3
N
H
19.5 19.4 19.4 19.3 19.2 19.1 19.0 19.0 18.9 18.8 18.7
20.0 19.5 19.0 18.5 18.0
f1 (ppm)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

**2g-$d_6$**

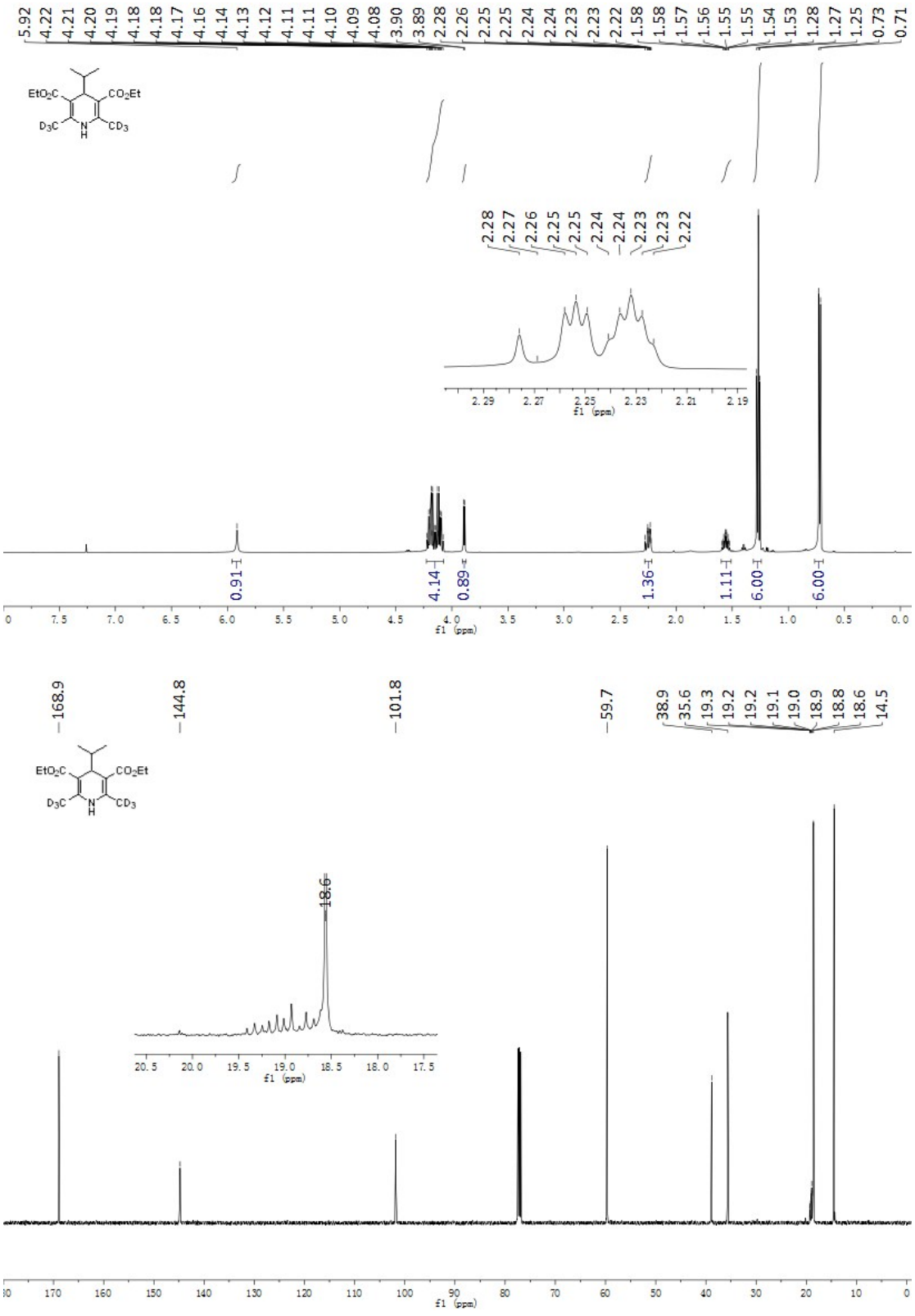

5.74 4.26 4.24 4.23 4.23 4.22 4.21 4.20 4.20 4.19 4.18 4.18 4.17 4.16 4.16 4.15 4.13 3.86 3.84 3.83 3.82 2.27 2.26 2.25 2.25 2.24 2.23 2.23 2.23 2.22 1.32 1.31 1.30 1.30 1.29 0.98
EtO2C
CO2Et
D3C
CD3
N
H
2.27 2.26 2.25 2.25 2.24 2.23 2.23 2.23 2.22
2.28 2.27 2.26 2.25 2.24 2.23 2.22 2.21
f1 (ppm)
0.90 4.03 0.95 1.40 6.00 2.97
0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


168.0 144.4 104.8 104.8 59.7 28.6 22.4 19.5 19.4 19.3 19.2 19.2 19.1 19.0 18.9 18.8 18.8 18.8 14.6
EtO2C
CO2Et
D3C
CD3
N
H
19.5 19.4 19.3 19.2 19.2 19.1 19.0 18.9 18.8 18.8
21 20 19 18 17 16
f1 (ppm)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

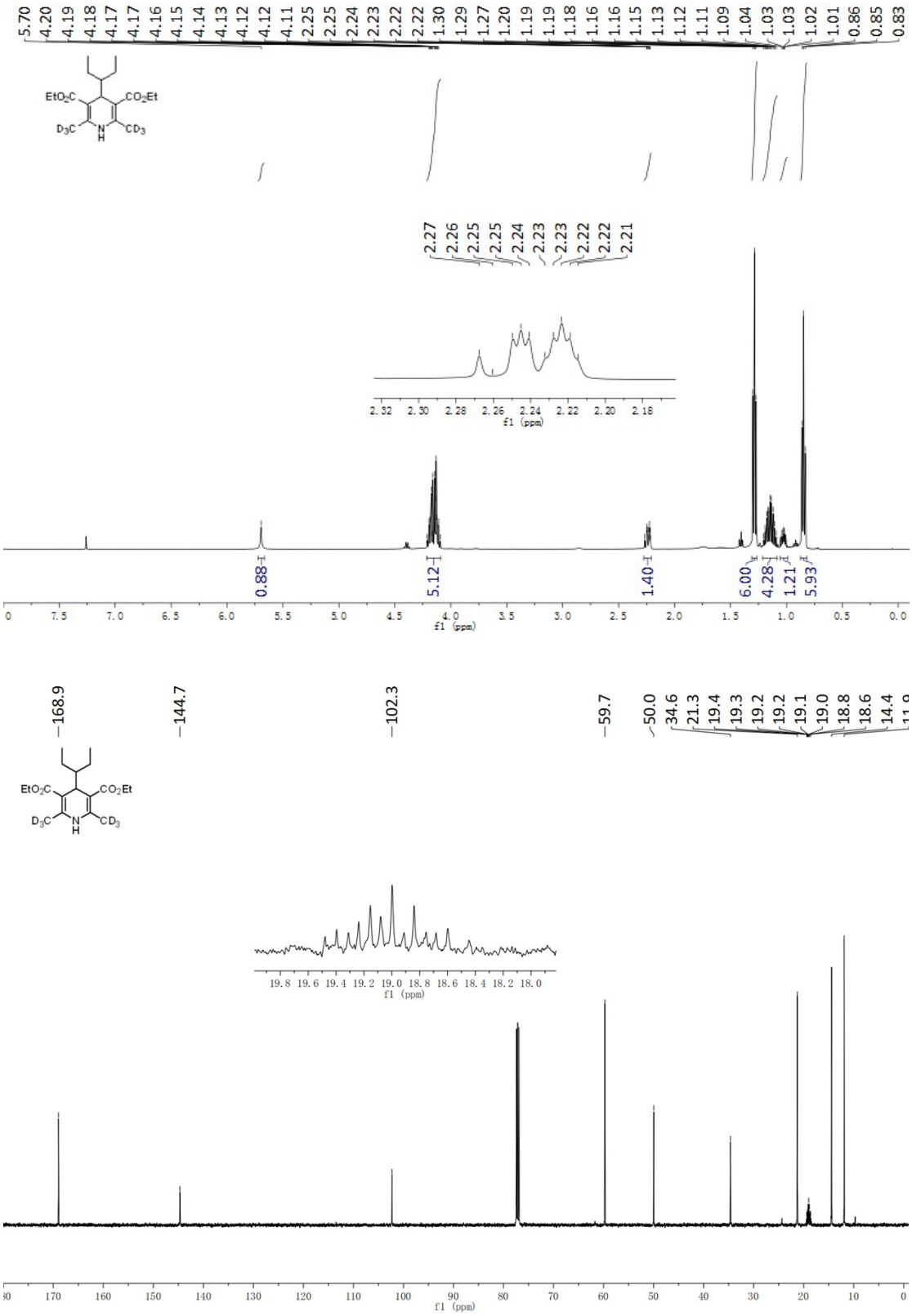
**2h-$d_6$**



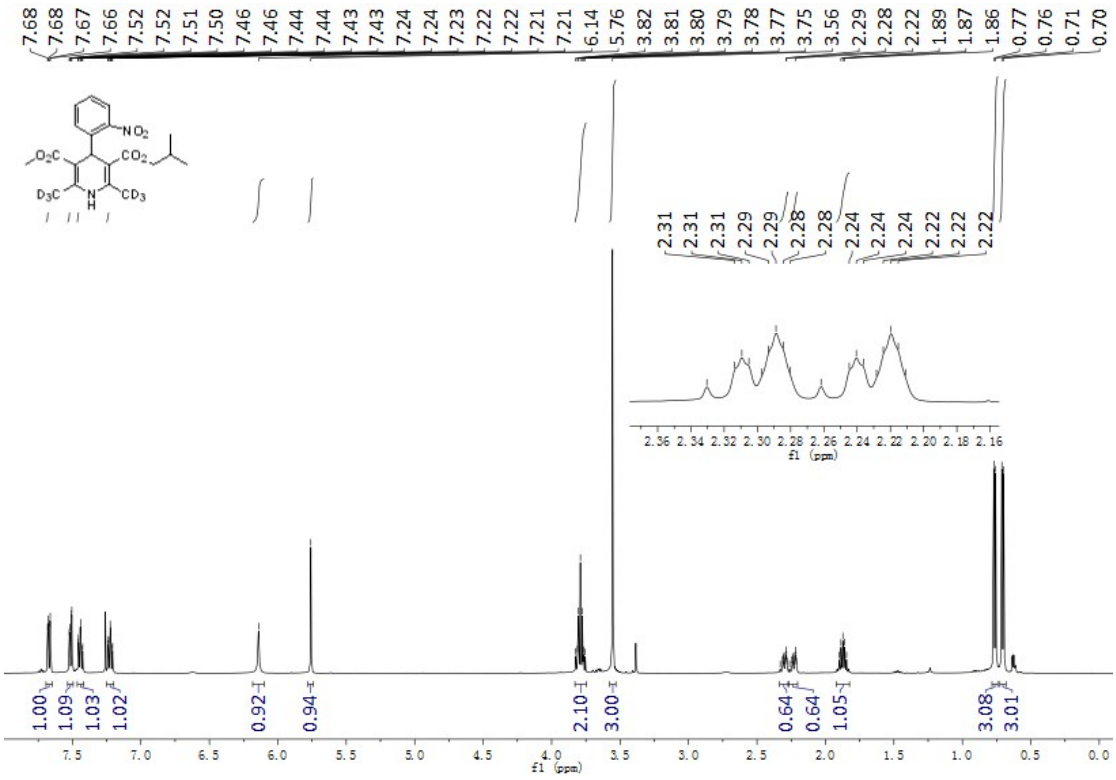
**2i-$d_6$**

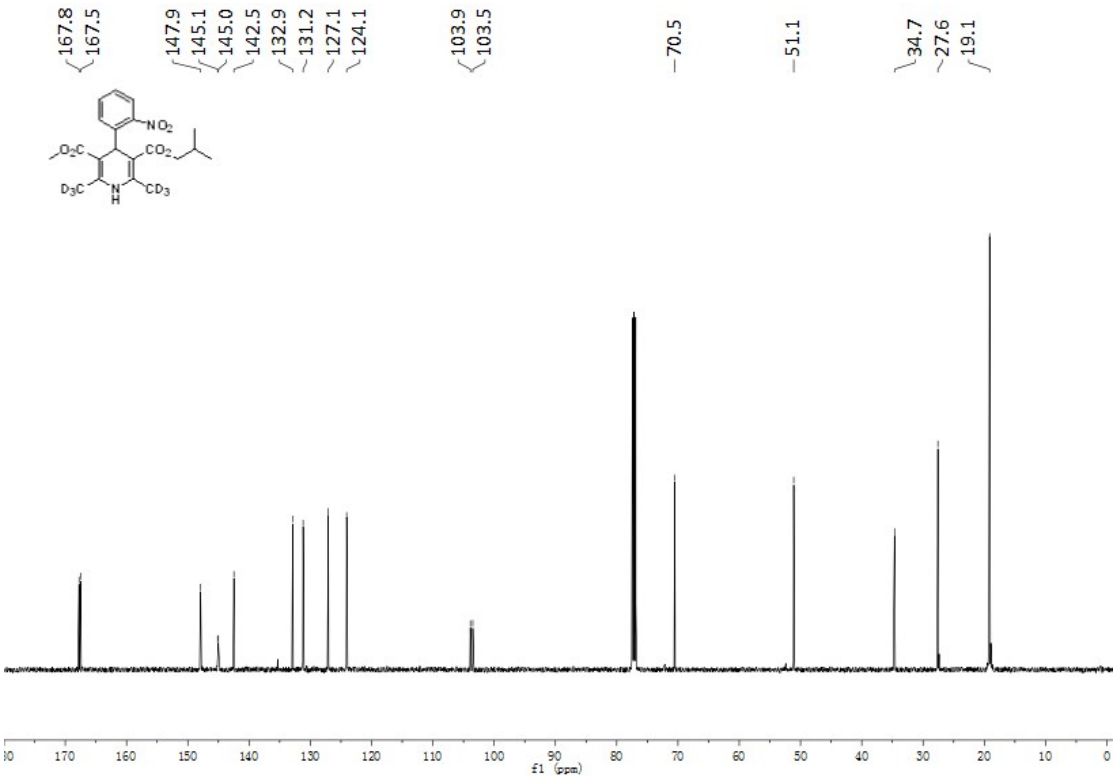


**2j-$d_6$**

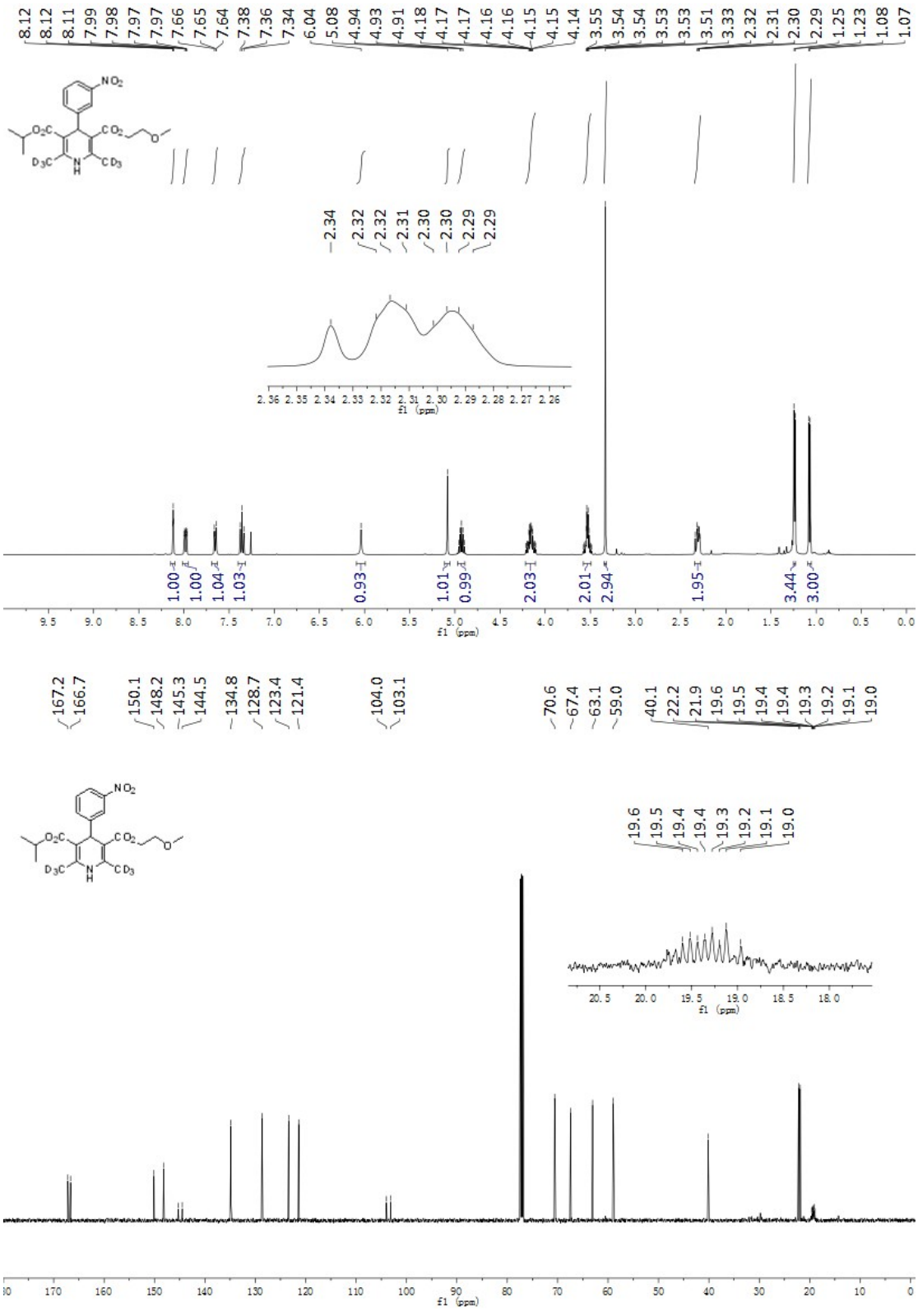


**2k-$d_6$**

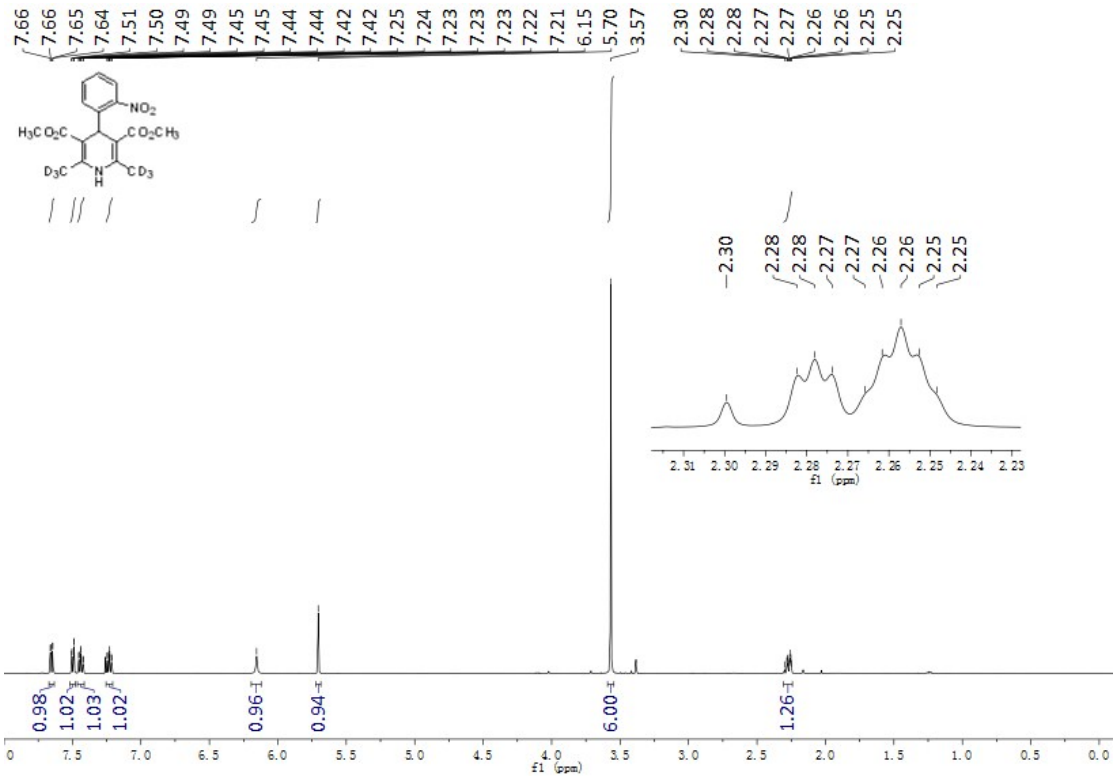

7.68 7.68 7.67 7.66 7.52 7.52 7.51 7.50 7.46 7.46 7.44 7.44 7.43 7.43 7.24 7.24 7.23 7.22 7.22 7.21 7.21 6.14 5.76 3.82 3.81 3.80 3.79 3.78 3.77 3.75 3.56 2.29 2.28 2.22 1.89 1.87 1.86 0.77 0.76 0.71 0.70
2.31 2.31 2.31 2.29 2.29 2.28 2.28 2.24 2.24 2.24 2.22 2.22 2.22
2.36 2.34 2.32 2.30 2.28 2.26 2.24 2.22 2.20 2.18 2.16
f1 (ppm)
1.00 1.09 1.03 1.02 0.92 0.94 2.10 3.00 0.64 0.64 1.05 3.08 3.01
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

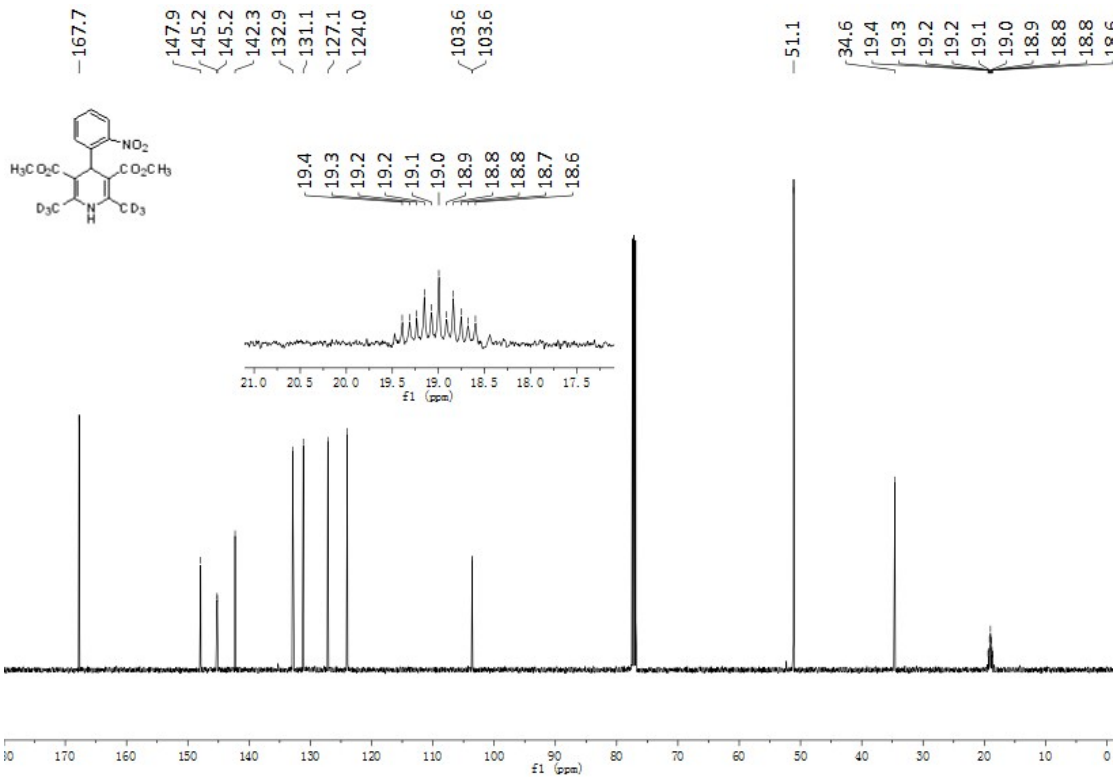

167.8 167.5 147.9 145.1 145.0 142.5 132.9 131.2 127.1 124.1 103.9 103.5 70.5 51.1 34.7 27.6 19.1
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

**2l-$d_6$**

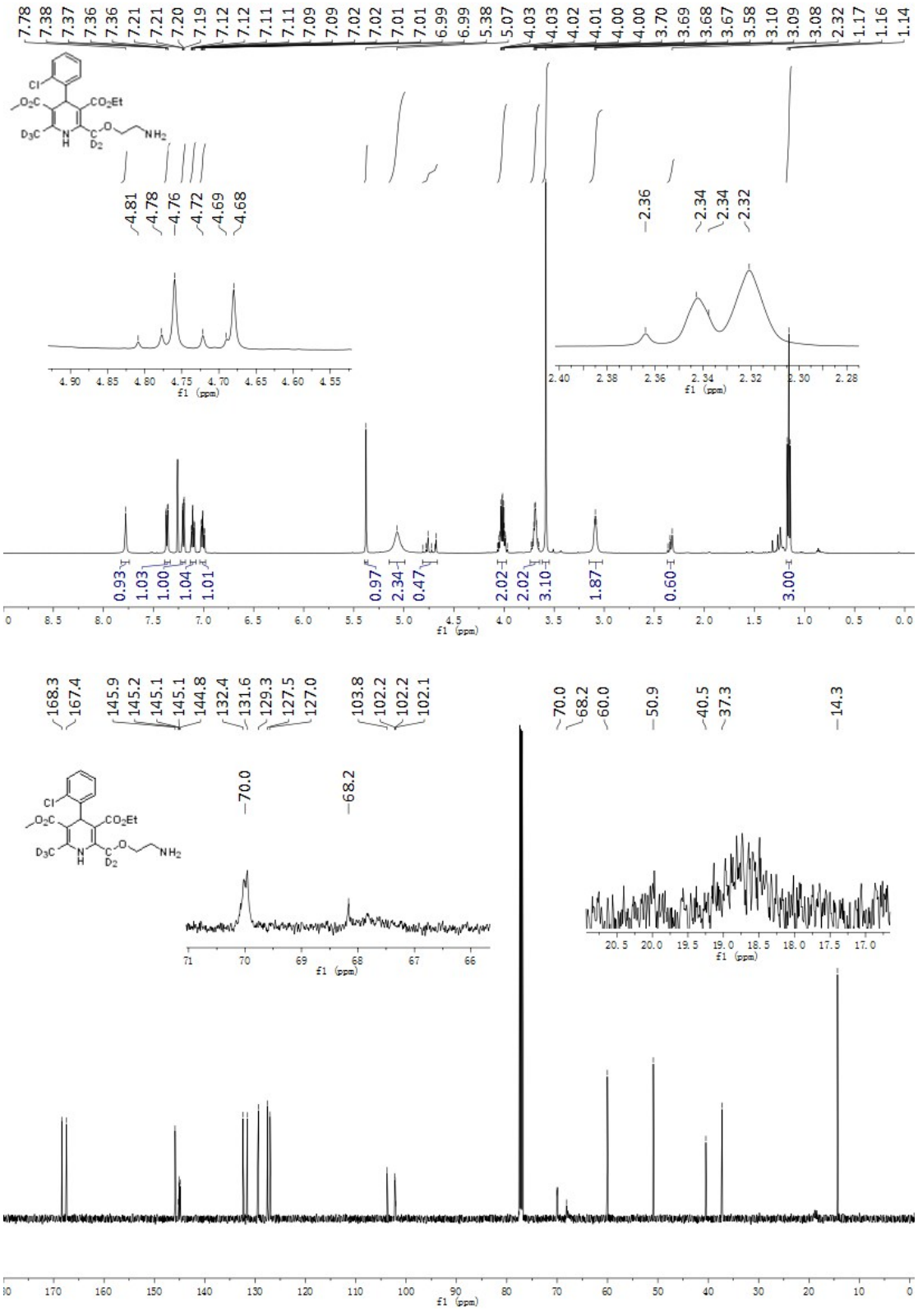


**2m-$d_6$**

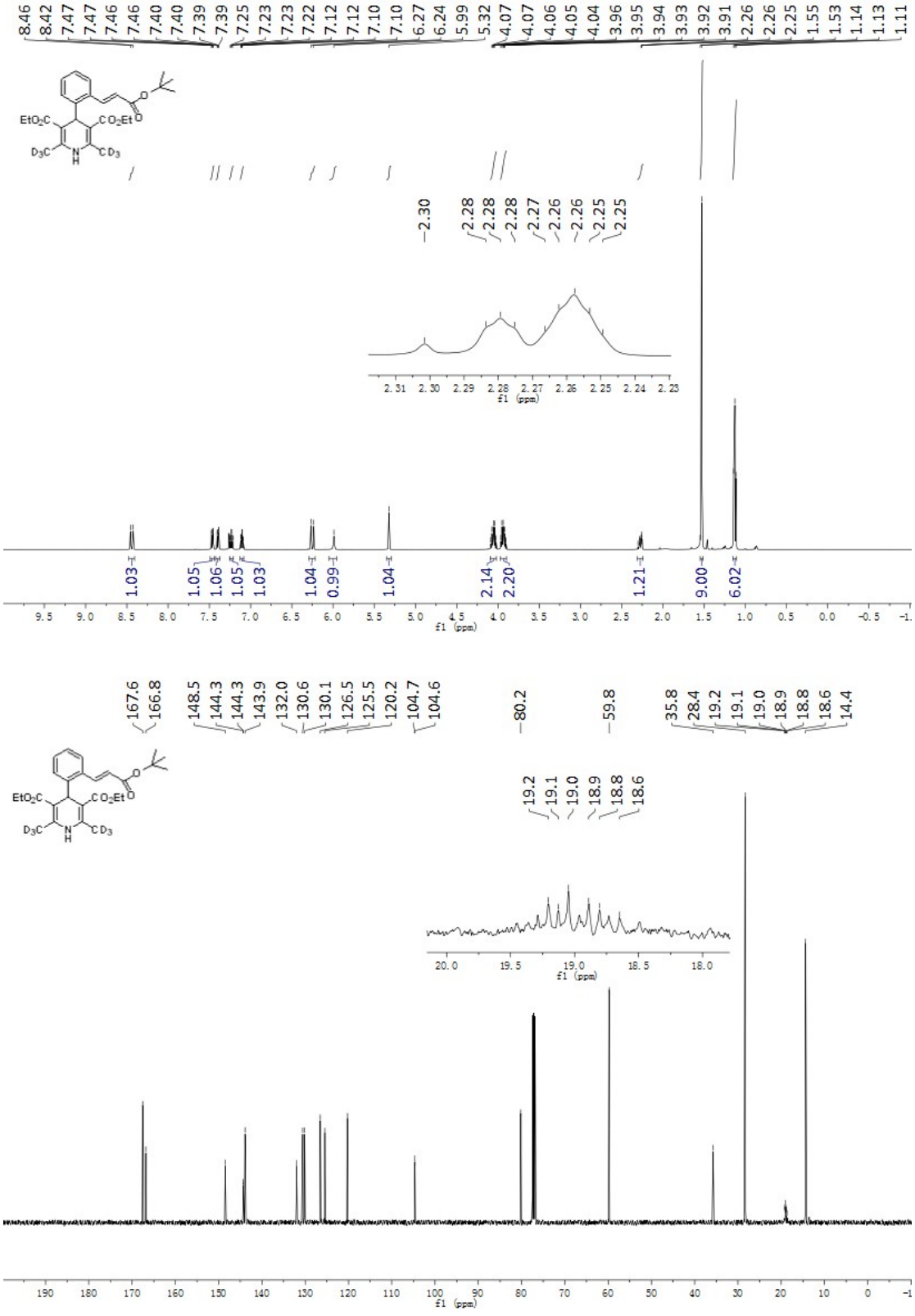




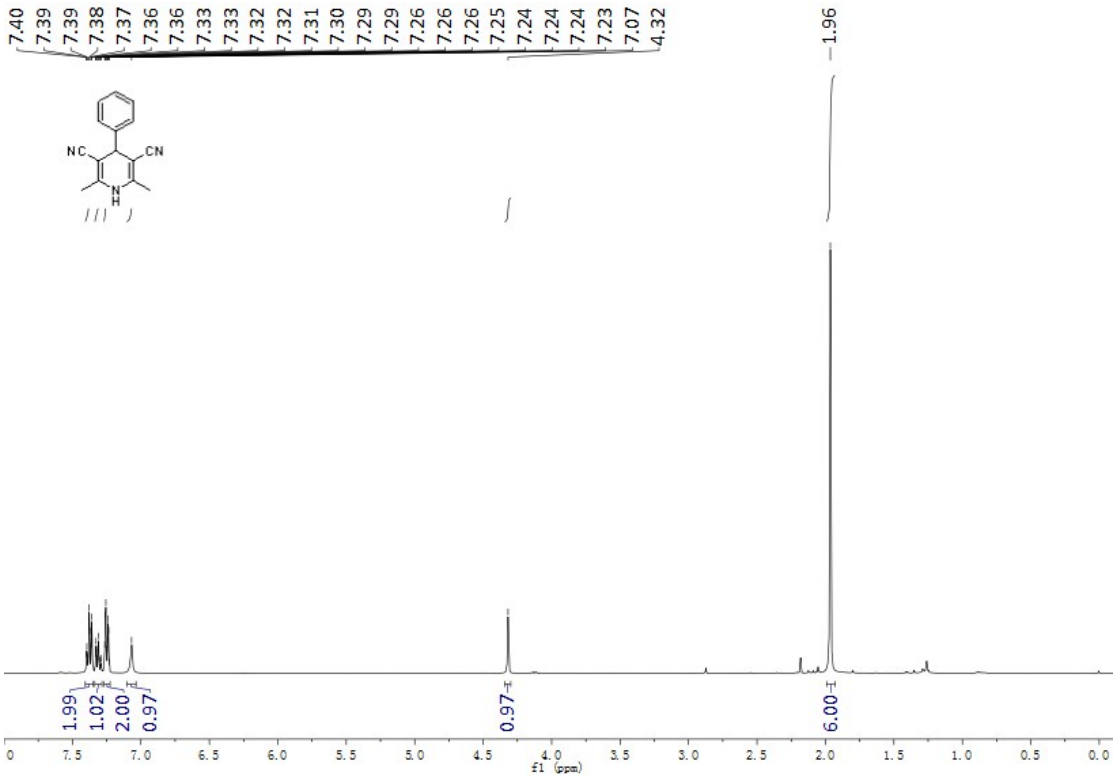
**2n-$d_5$**

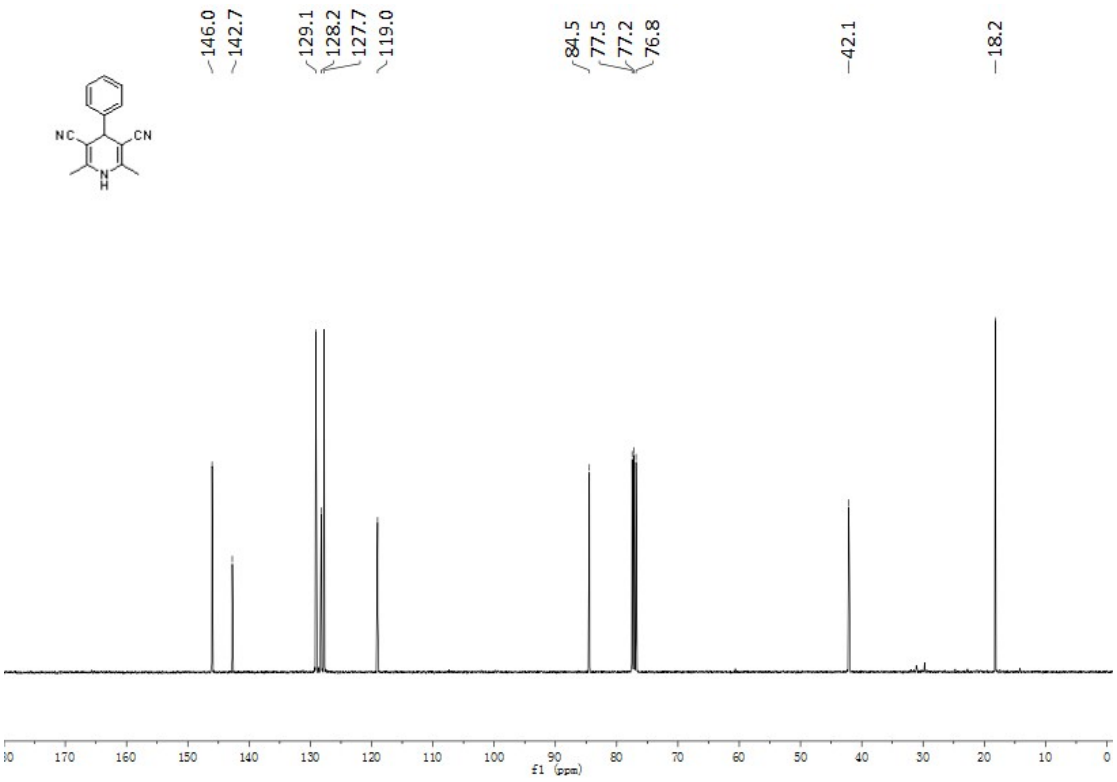


**2o-$d_6$**



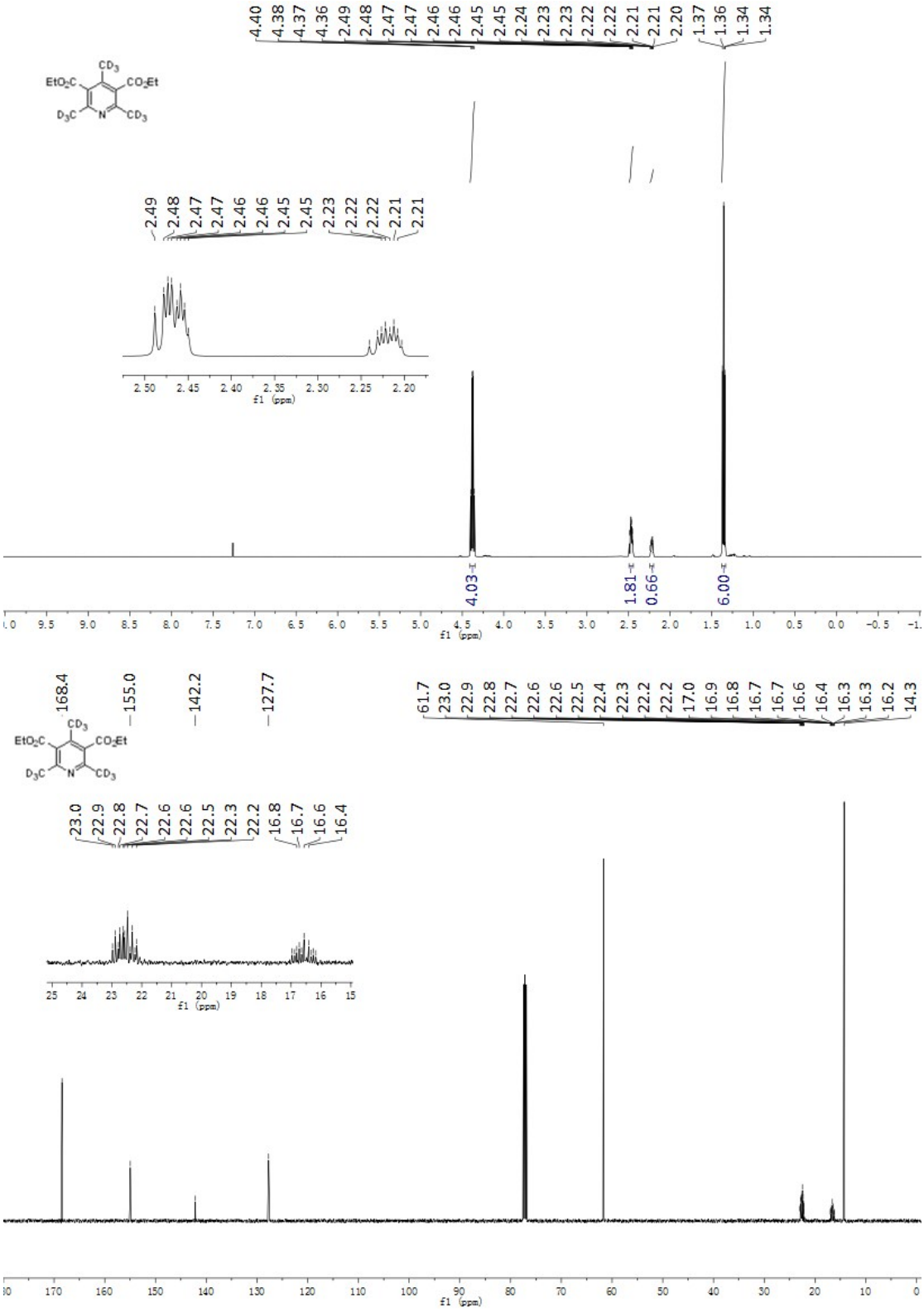
**3a-$d_0$**


7.40
7.39
7.39
7.38
7.37
7.36
7.36
7.33
7.33
7.32
7.32
7.31
7.30
7.29
7.29
7.26
7.26
7.26
7.25
7.24
7.24
7.24
7.23
7.07
4.32
1.96
NC
CN
1.99
1.02
2.00
0.97
0.97
6.00
f1 (ppm)

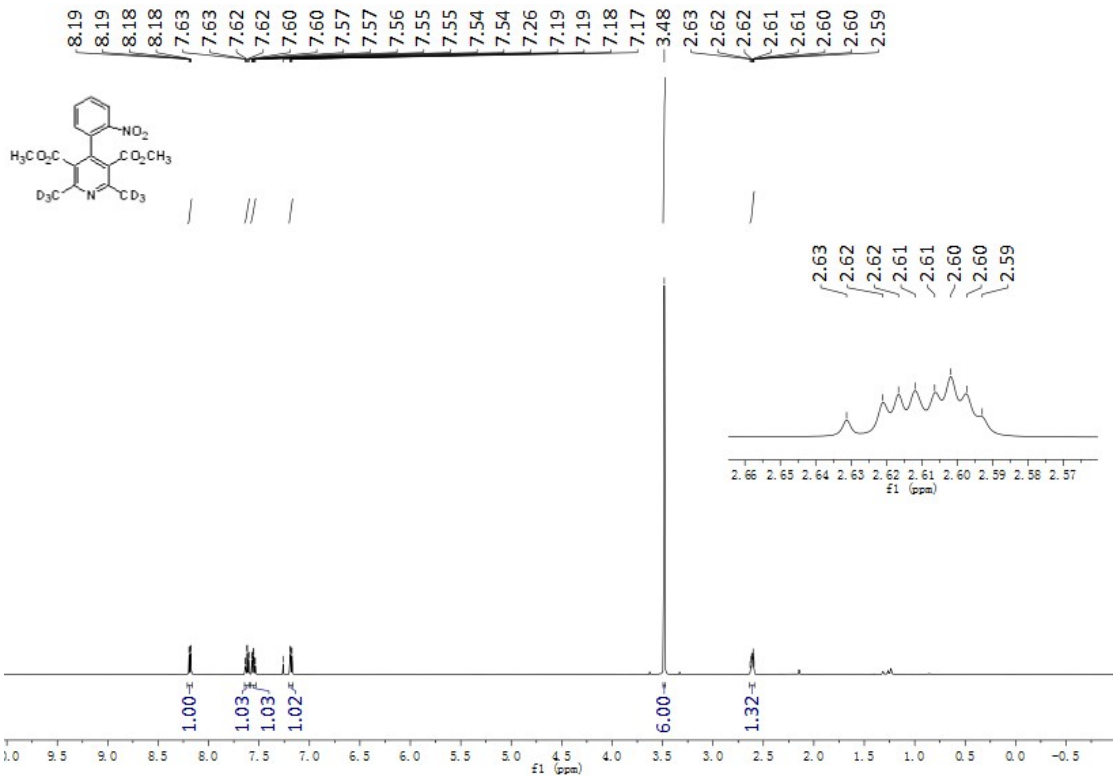

146.0
142.7
129.1
128.2
127.7
119.0
84.5
77.5
77.2
76.8
42.1
18.2
NC
CN
f1 (ppm)

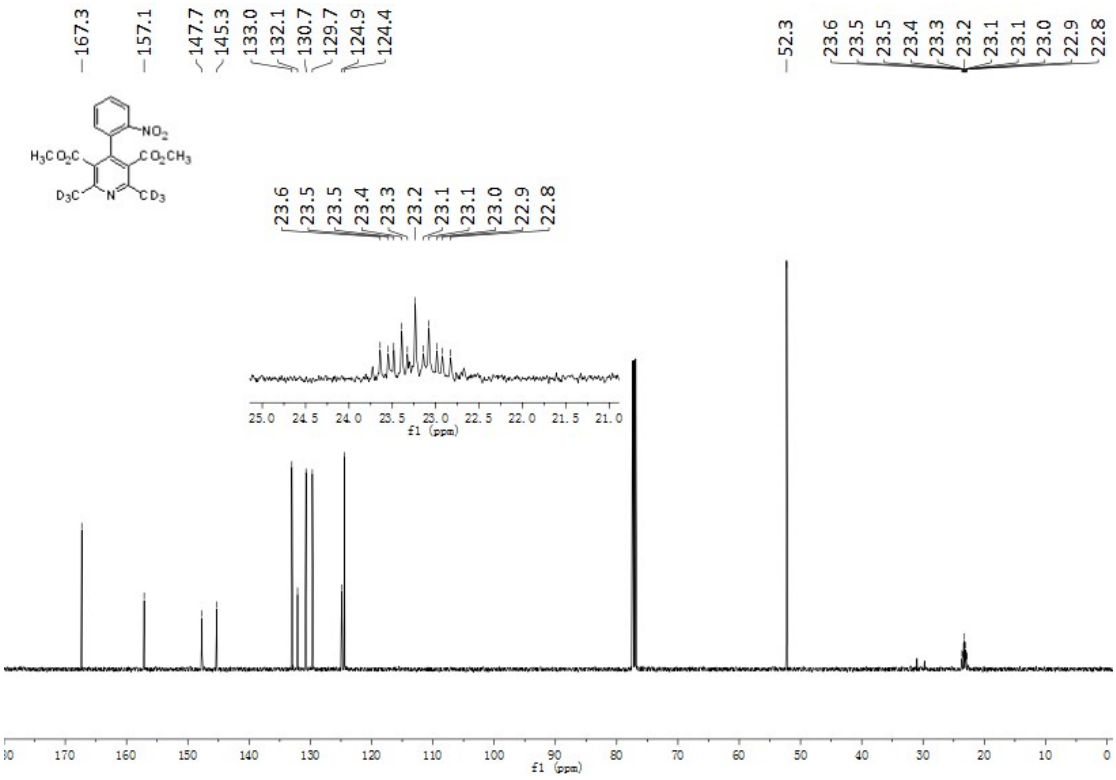
**3b-$d_0$**

**3c-$d_9$**

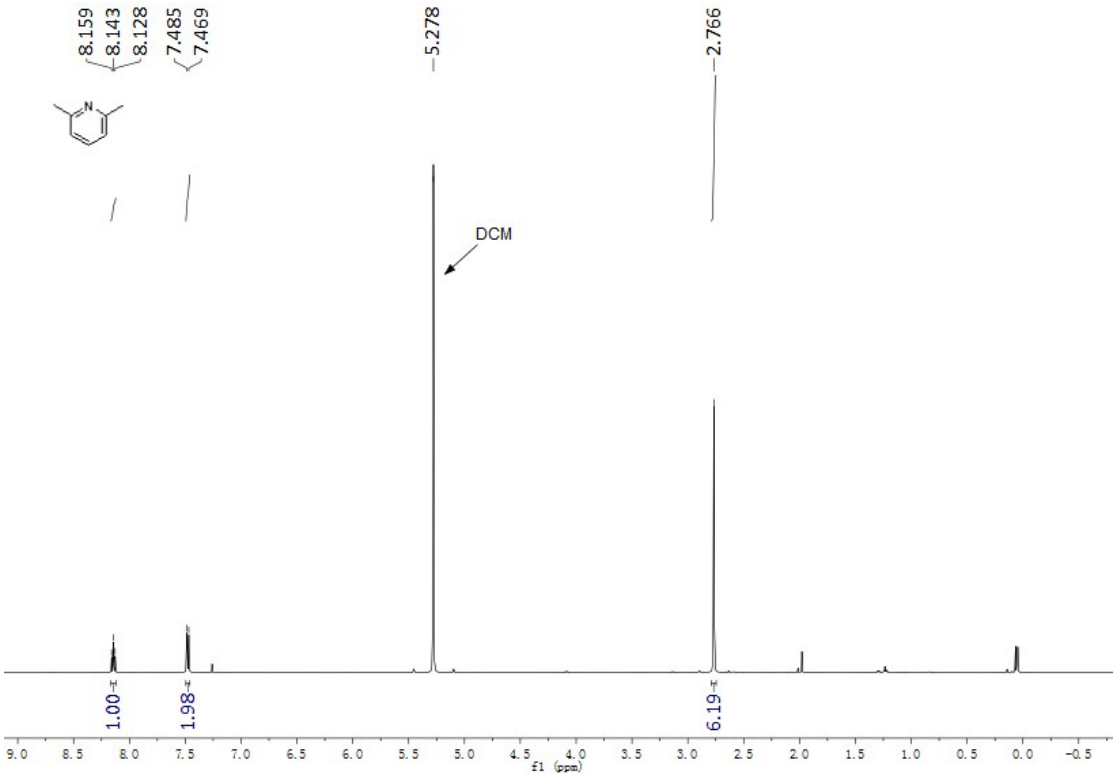

4.40 4.38 4.37 4.36 2.49 2.48 2.47 2.47 2.46 2.46 2.45 2.45 2.24 2.23 2.23 2.22 2.22 2.21 2.21 2.20 1.37 1.36 1.34 1.34
2.49 2.48 2.47 2.47 2.46 2.46 2.45 2.45 2.23 2.22 2.22 2.21 2.21
4.03 1.81 0.66 6.00
f1 (ppm)
168.4 155.0 142.2 127.7
61.7 23.0 22.9 22.8 22.7 22.6 22.6 22.5 22.4 22.3 22.2 22.2 17.0 16.9 16.8 16.7 16.7 16.6 16.4 16.3 16.3 16.2 14.3
23.0 22.9 22.8 22.7 22.6 22.6 22.5 22.3 22.2 16.8 16.7 16.6 16.4
f1 (ppm)

**3d-$d_6$**

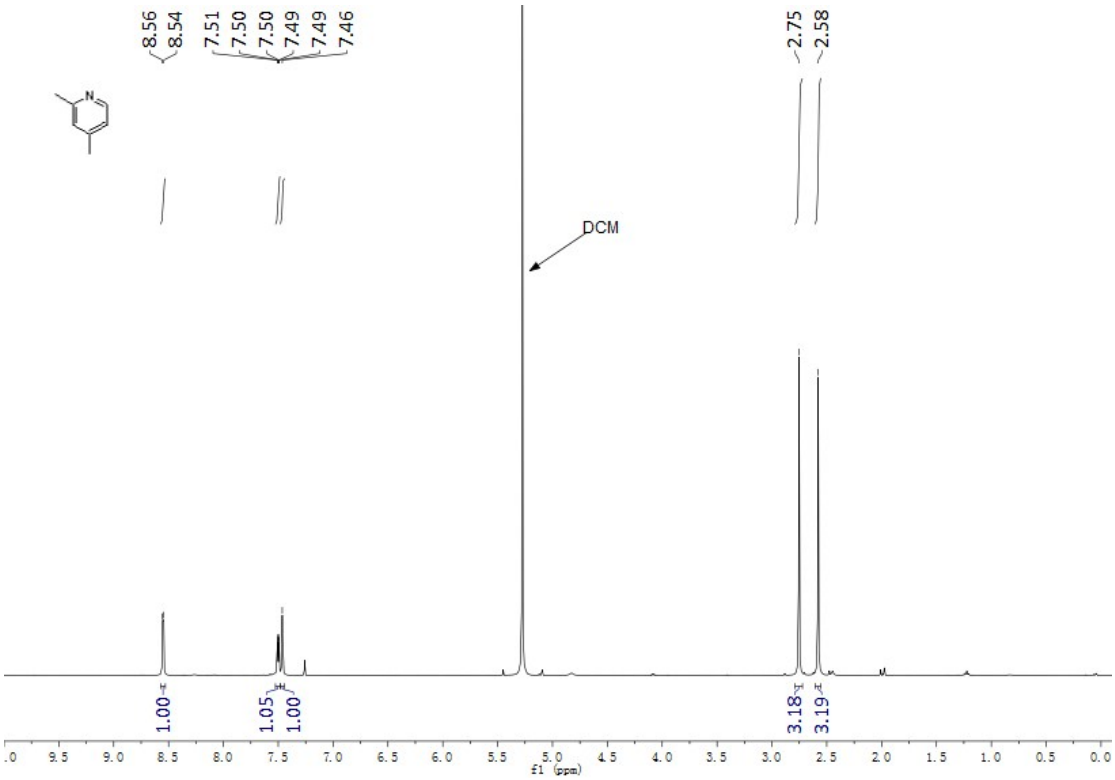

8.19 8.19 8.18 8.18 7.63 7.63 7.62 7.62 7.60 7.60 7.57 7.57 7.56 7.55 7.55 7.54 7.54 7.26 7.19 7.19 7.18 7.17 3.48 2.63 2.62 2.62 2.61 2.61 2.60 2.60 2.59
2.63 2.62 2.62 2.61 2.61 2.60 2.60 2.59
2.66 2.65 2.64 2.63 2.62 2.61 2.60 2.59 2.58 2.57
f1 (ppm)
1.00 1.03 1.03 1.02 6.00 1.32
f1 (ppm)


167.3 157.1 147.7 145.3 133.0 132.1 130.7 129.7 124.9 124.4
52.3 23.6 23.5 23.5 23.4 23.3 23.2 23.1 23.1 23.0 22.9 22.8
23.6 23.5 23.5 23.4 23.3 23.2 23.1 23.1 23.0 22.9 22.8
25.0 24.5 24.0 23.5 23.0 22.5 22.0 21.5 21.0
f1 (ppm)
f1 (ppm)

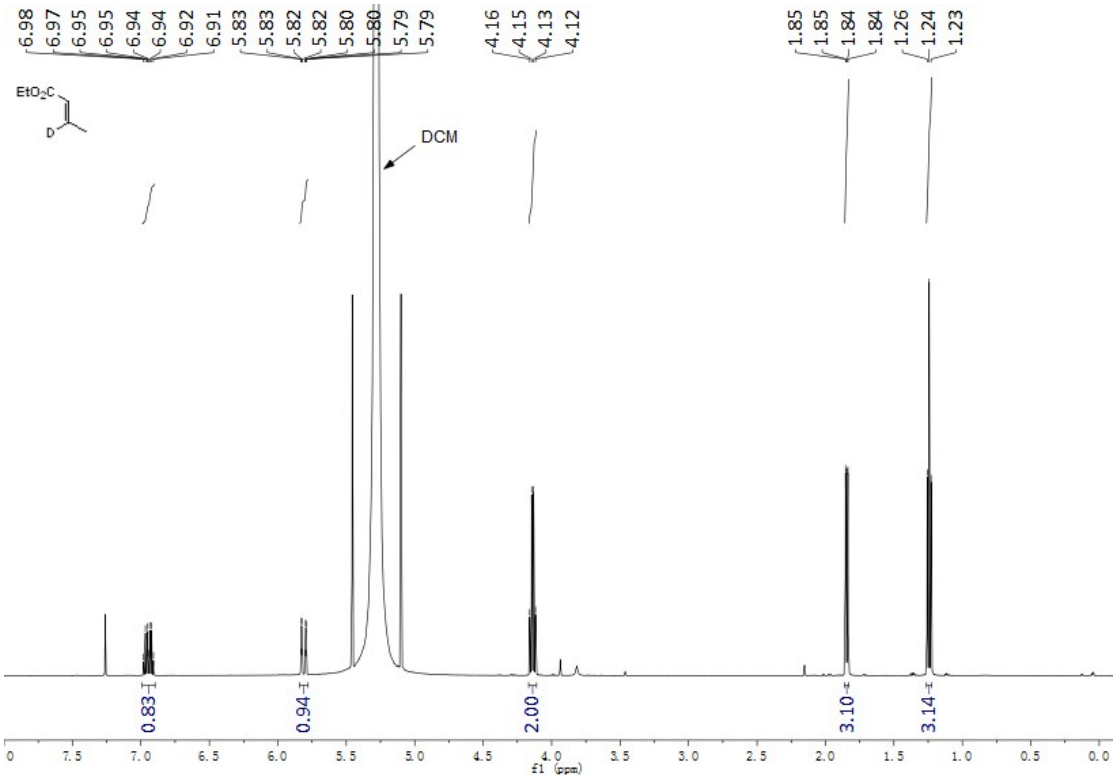
**3e-$d_0$**(crude)



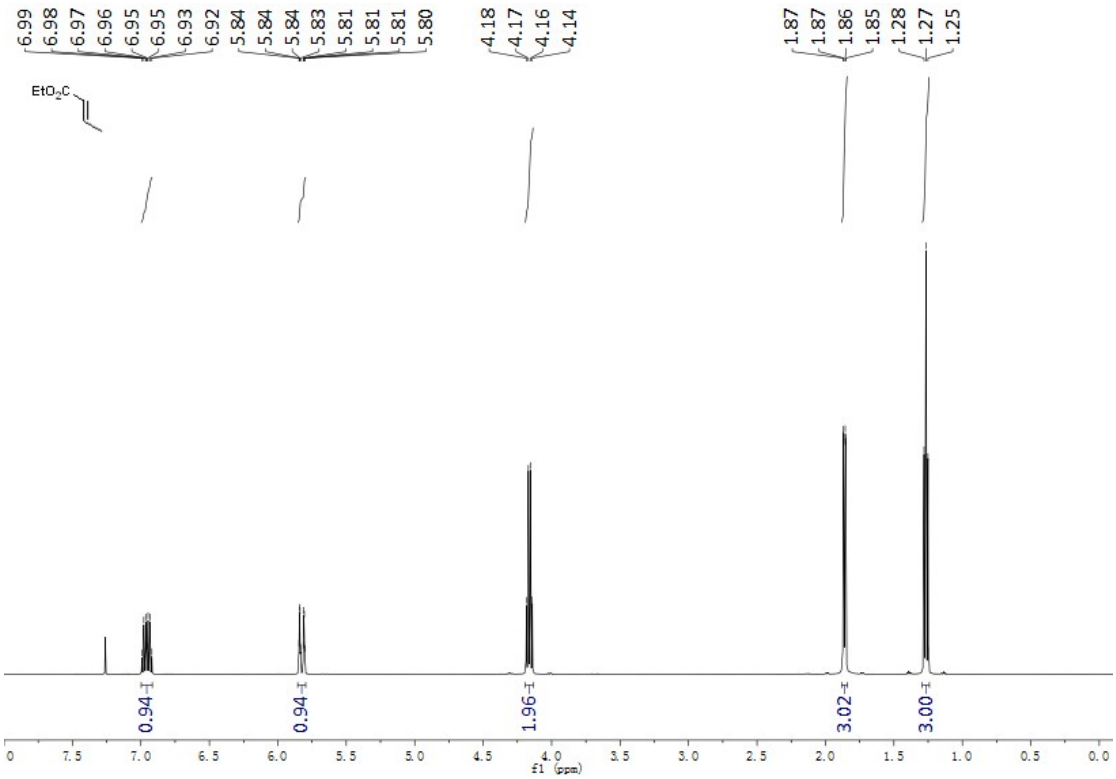

**3f-$d_0$**(crude)



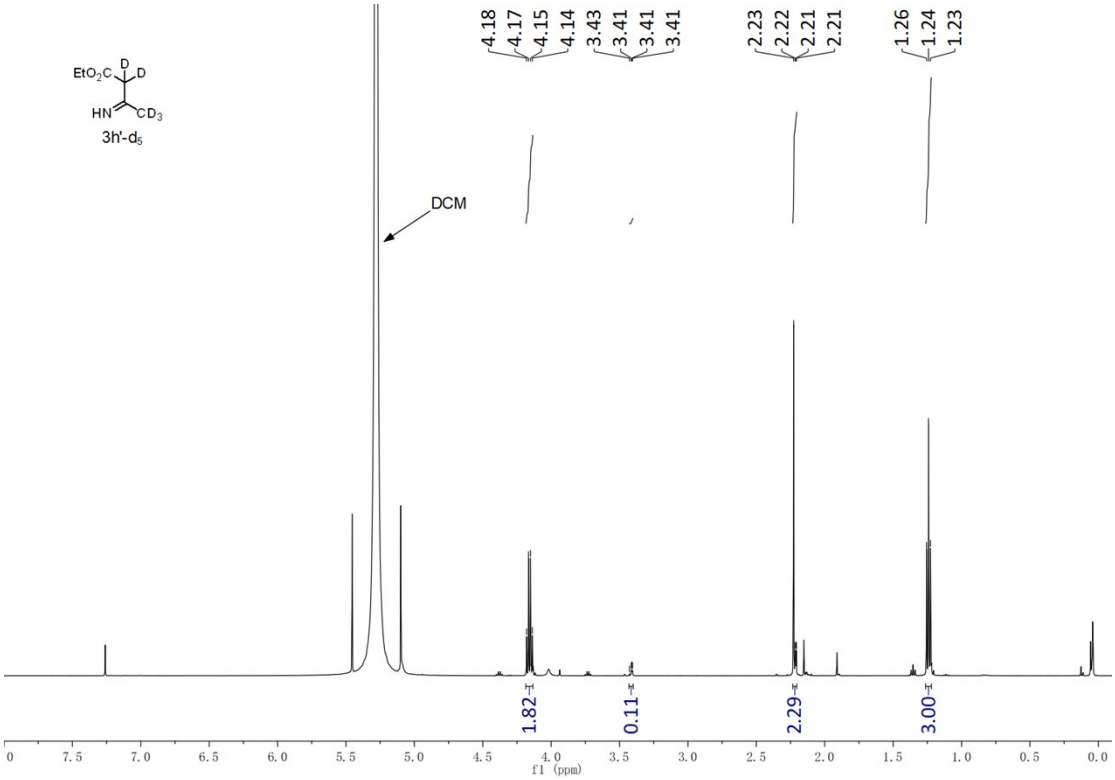
**3g-$d_1$**(crude)



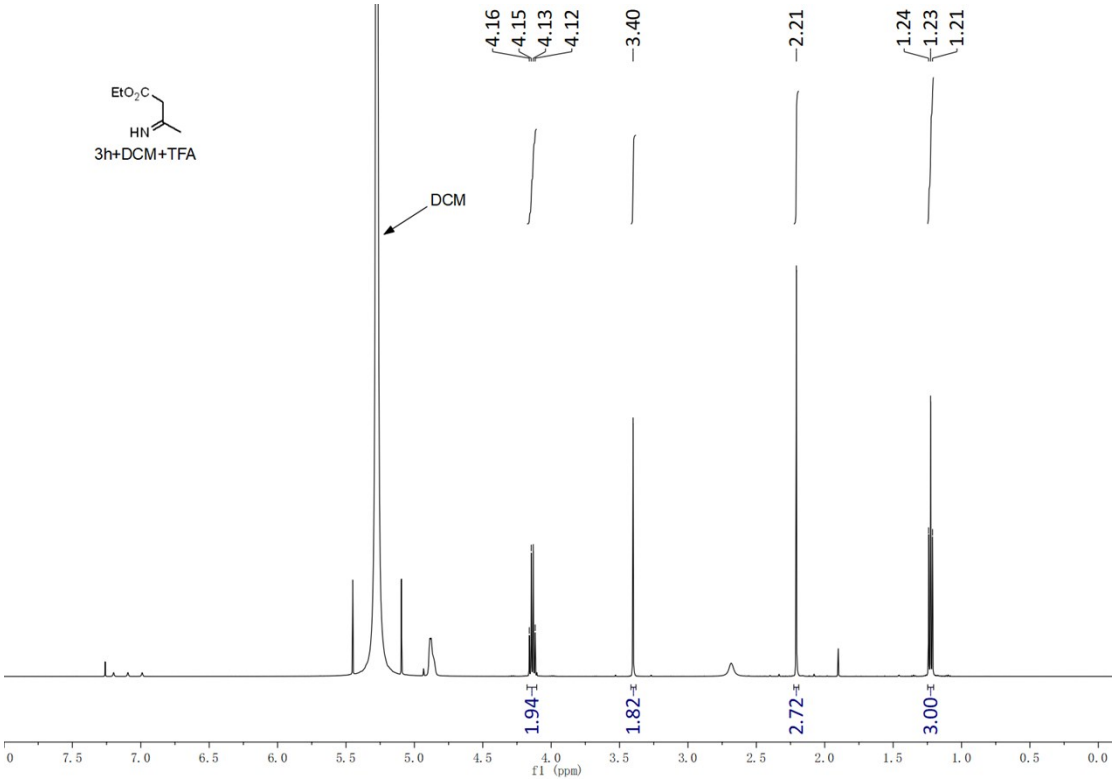

**3g**



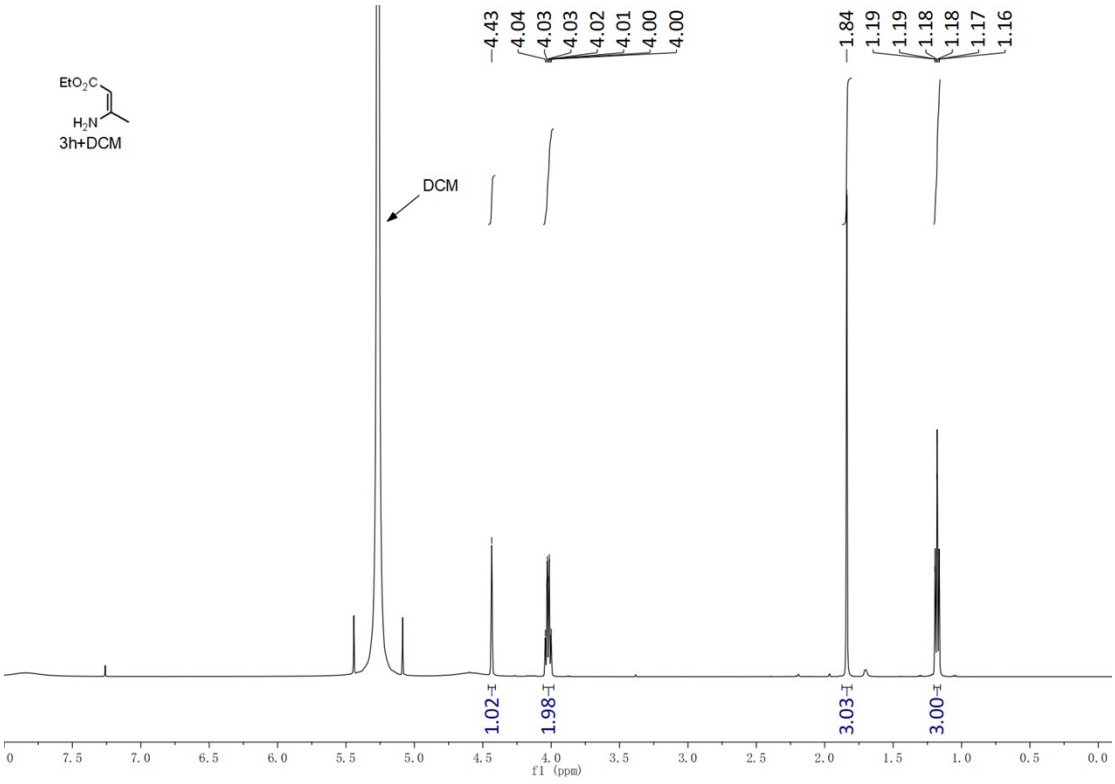
**3h'-$d_5$**(crude)




**3h** + $CH_2Cl_2$**+TFA**

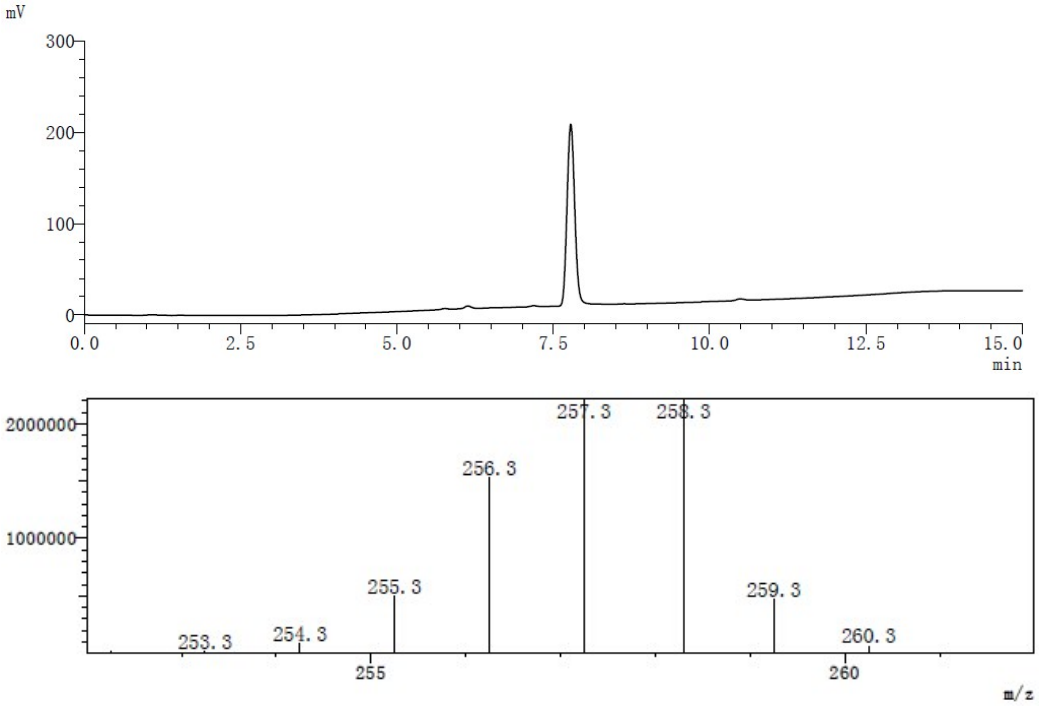


**3h +** $CH_2Cl_2$

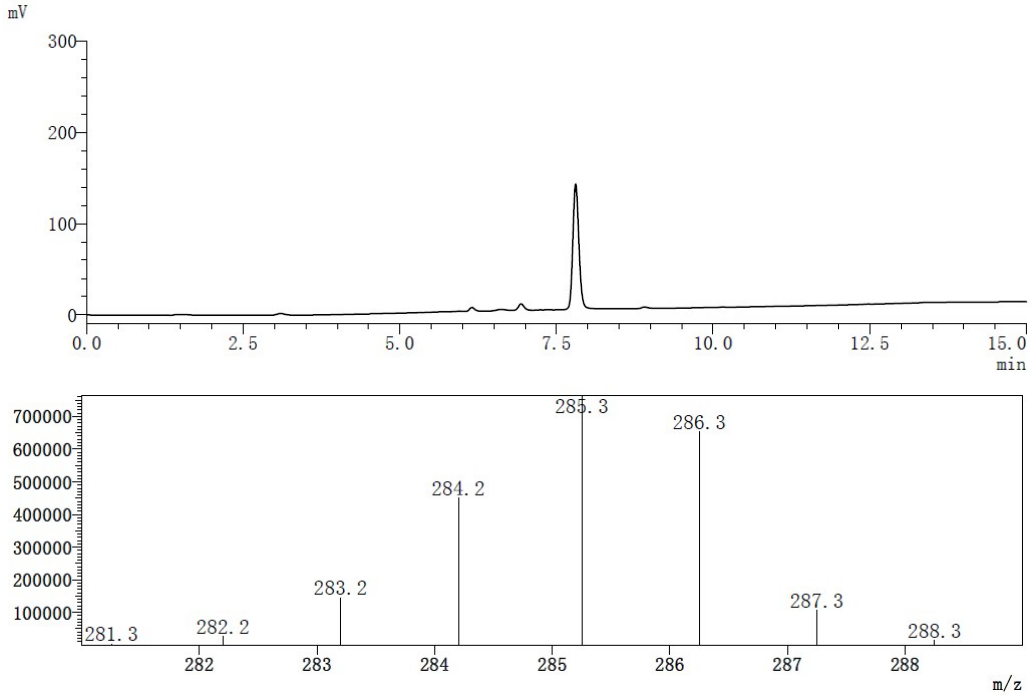

4.43
4.04
4.03
4.03
4.02
4.01
4.00
4.00
1.84
1.19
1.19
1.18
1.18
1.17
1.16
EtO2C
H2N
3h+DCM
DCM
1.02
1.98
3.03
3.00
f1 (ppm)

# 9. LC-MS spectra

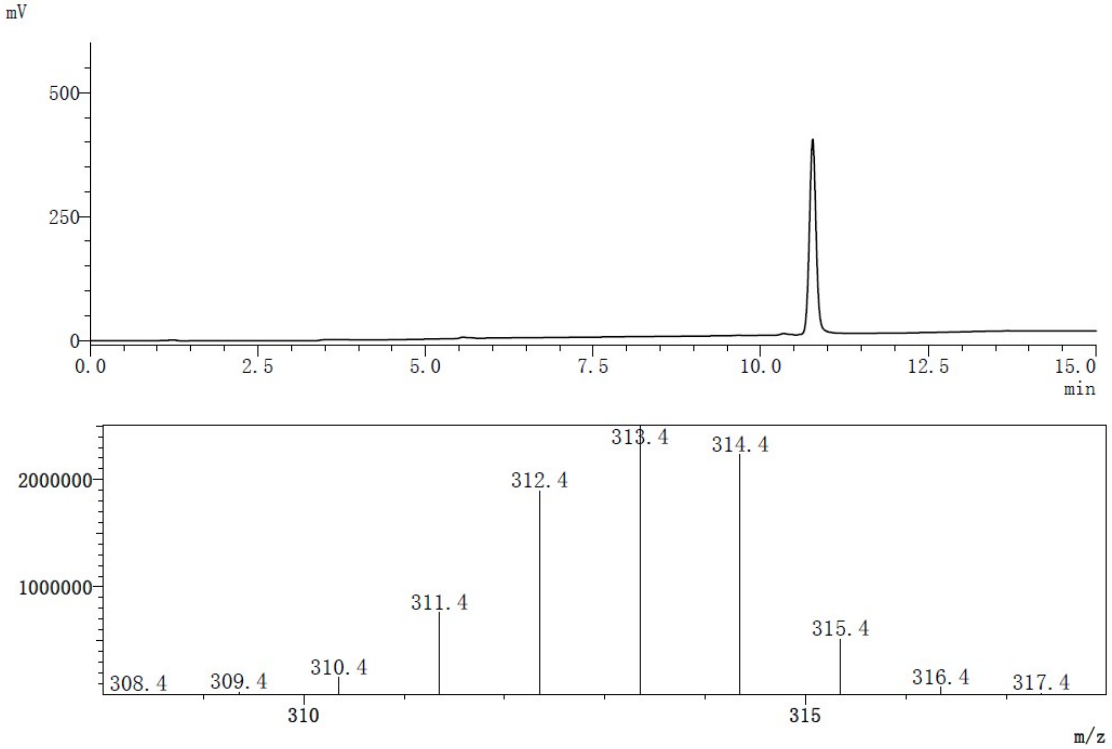
## 1a'-$d_6$



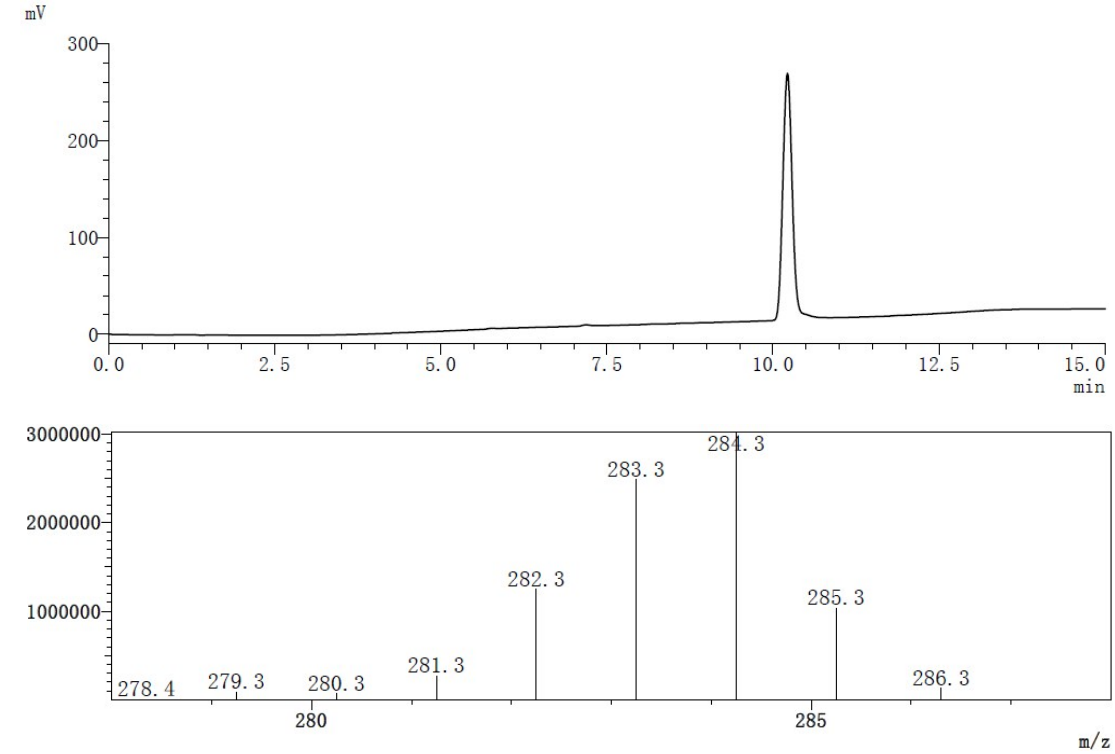

## 1b'-$d_6$



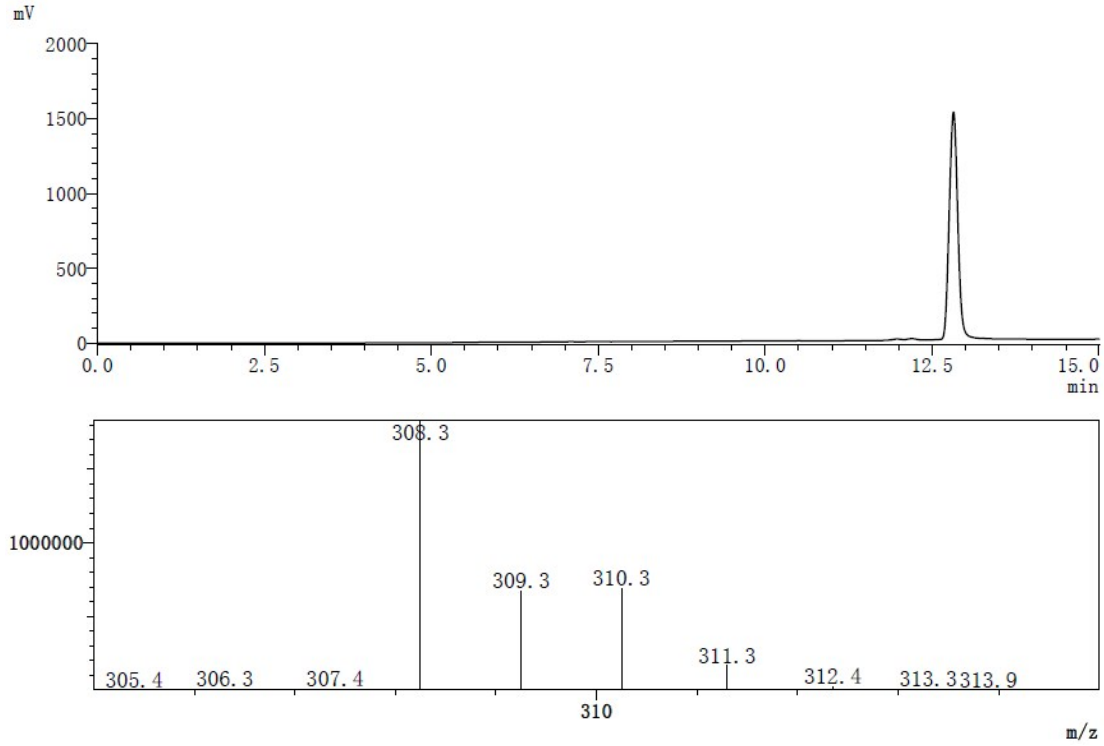
**1c'-$d_6$**


mV
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
2000000
1000000
313.4
314.4
312.4
311.4
315.4
310.4
308.4
309.4
316.4
317.4
310
315
m/z

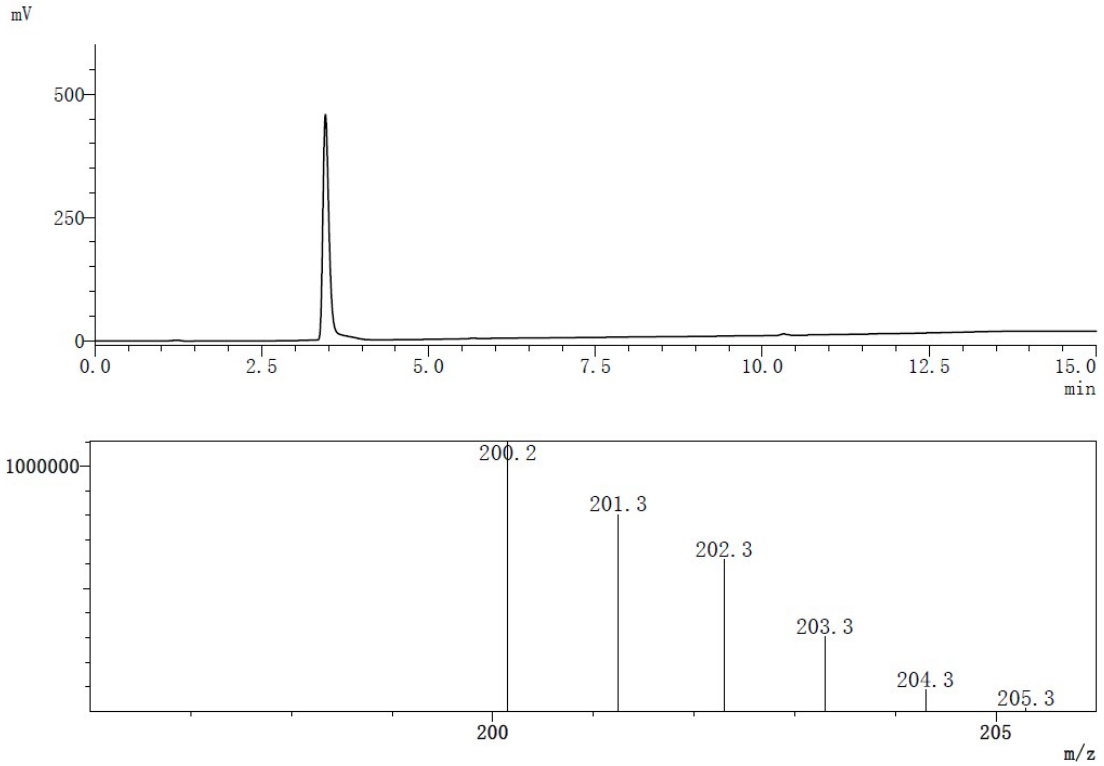
**1d'-$d_4$**


mV
300
200
100
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
3000000
2000000
1000000
284.3
283.3
282.3
285.3
281.3
278.4
279.3
280.3
286.3
280
285
m/z

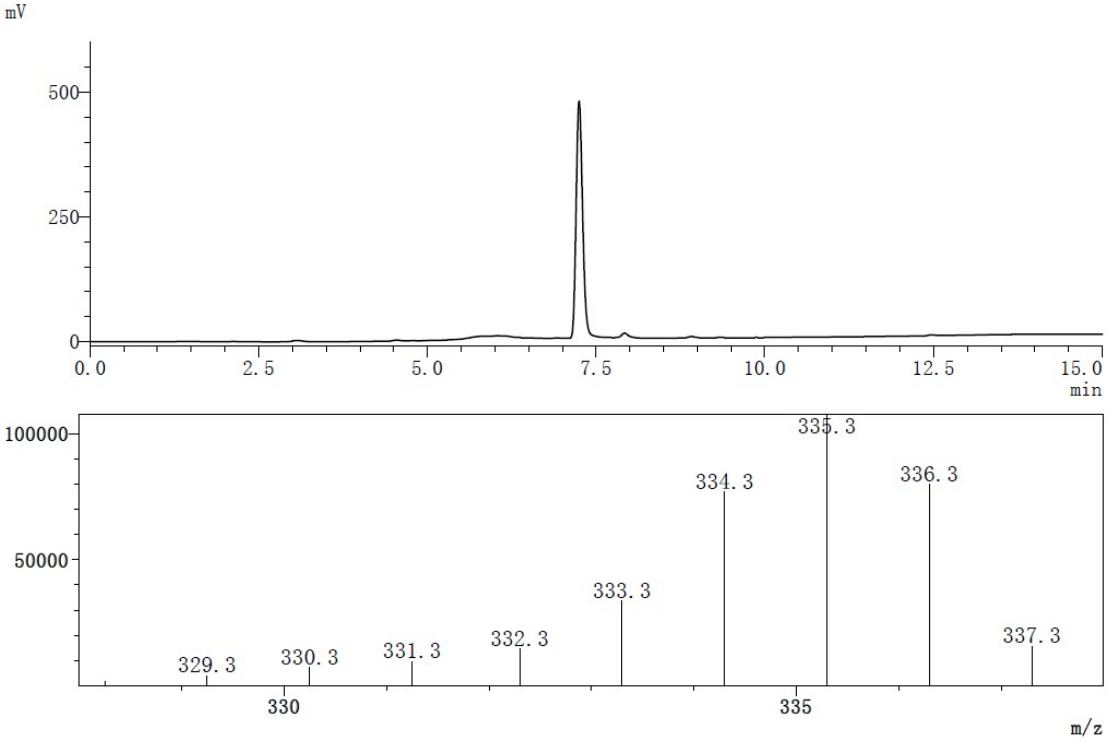
**1e'-$d_2$**


mV
2000
1500
1000
500
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
1000000
308.3
309.3
310.3
311.3
312.4
313.3
313.9
305.4
306.3
307.4
310
m/z

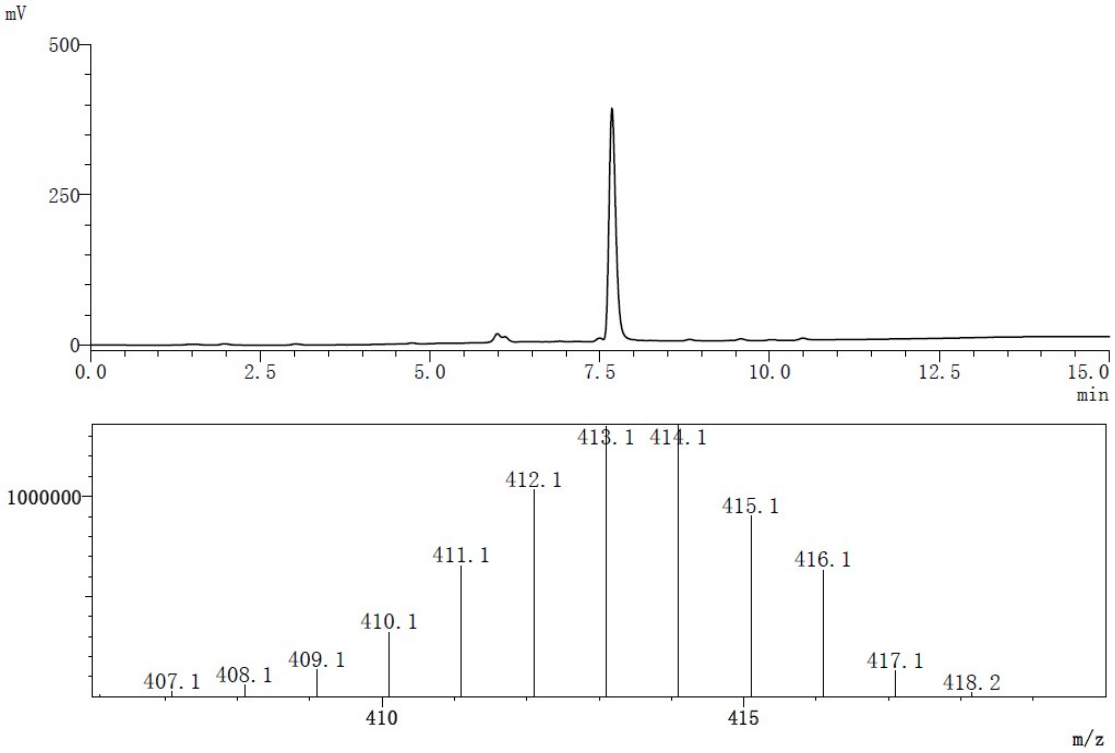
**1f'-$d_{12}$**


mV
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
1000000
200.2
201.3
202.3
203.3
204.3
205.3
200
205
m/z

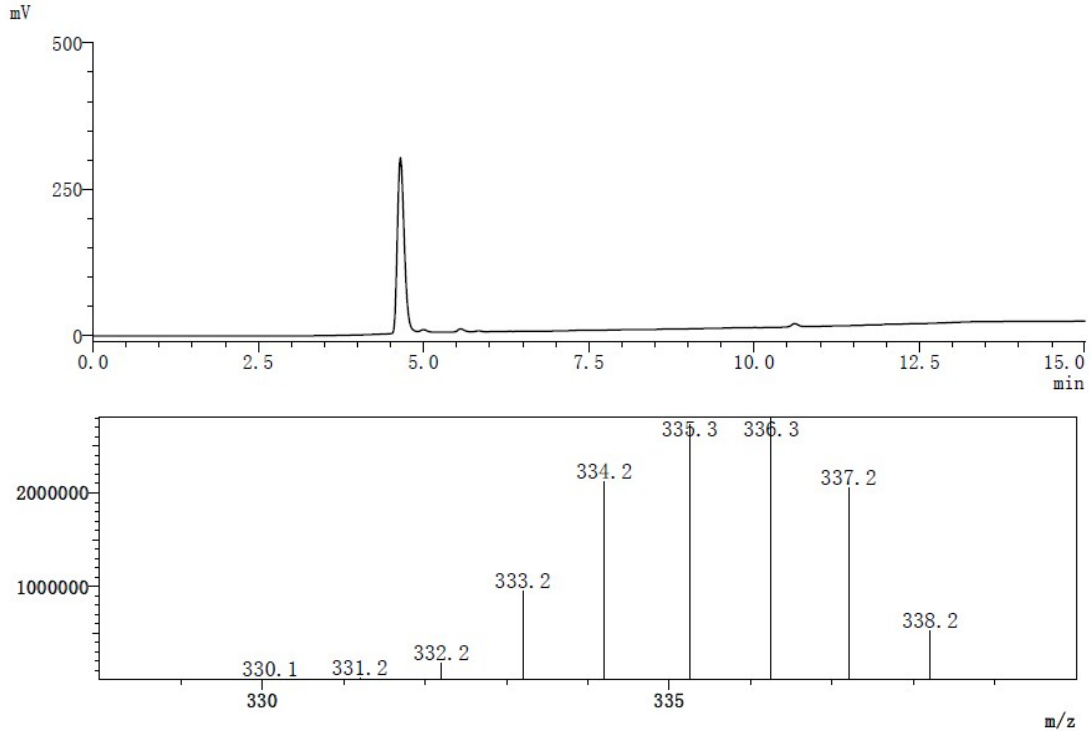
**2a-$d_6$**


mV
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
100000
50000
335.3
334.3
336.3
333.3
337.3
332.3
331.3
330.3
329.3
330
335
m/z

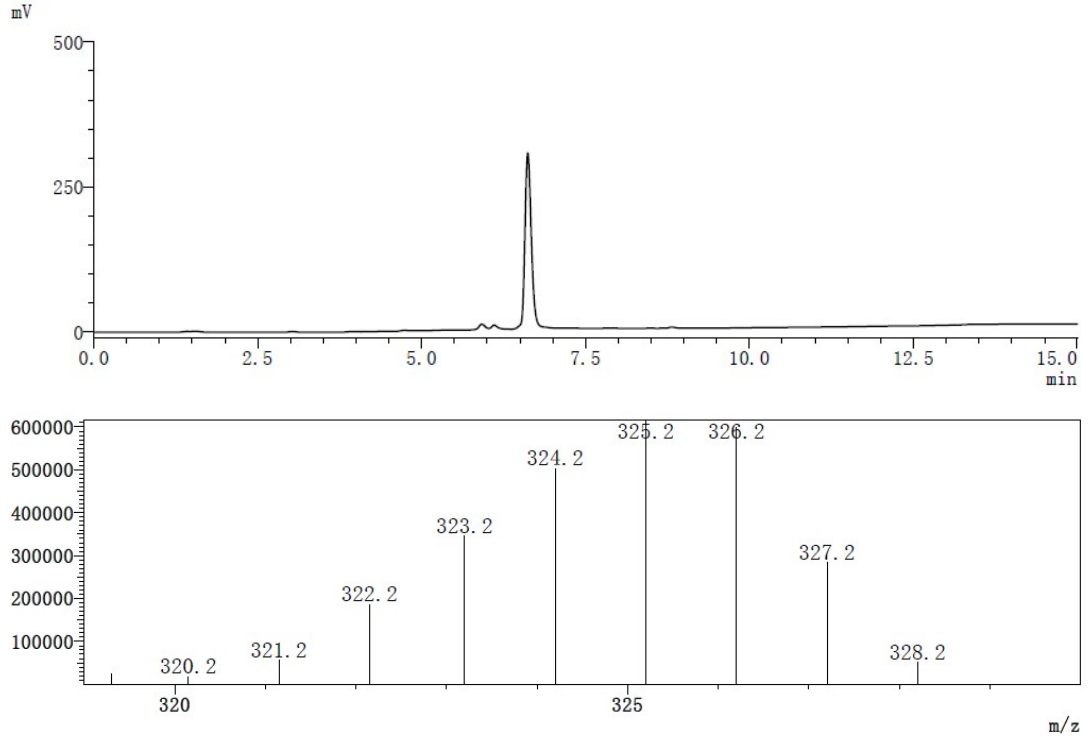
**2b-$d_6$**


mV
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
1000000
413.1
414.1
412.1
415.1
411.1
416.1
410.1
409.1
417.1
407.1
408.1
418.2
410
415
m/z

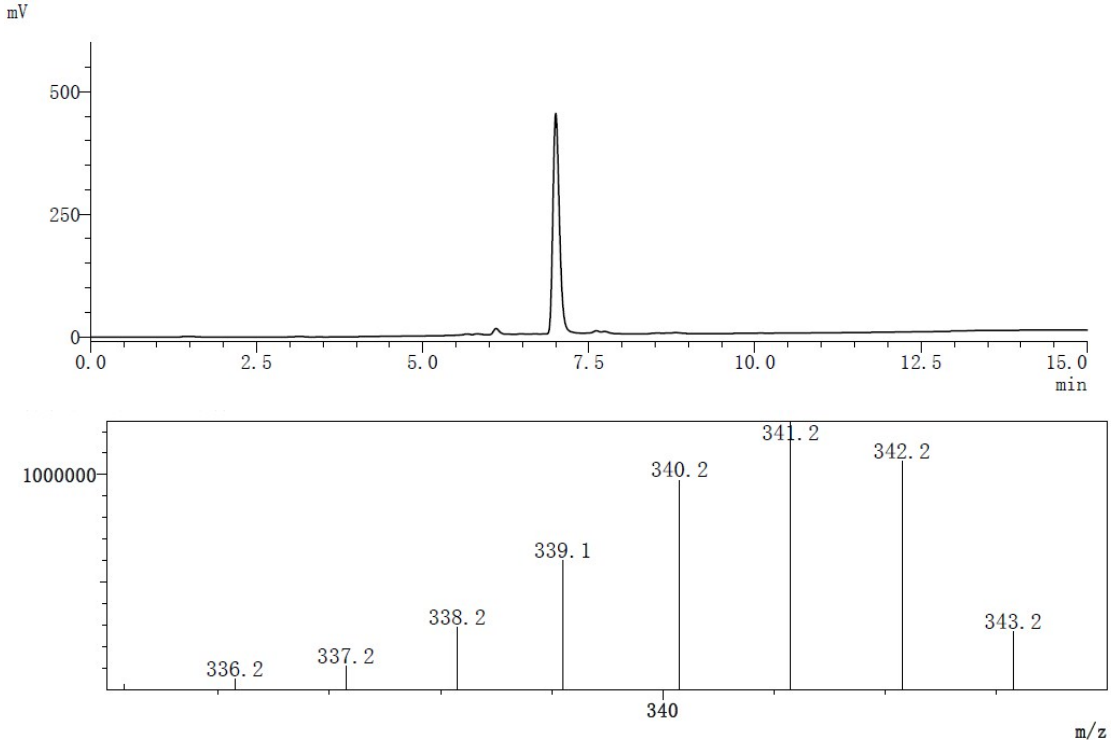
**2c-$d_6$**


mV
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
2000000
1000000
330.1
331.2
332.2
333.2
334.2
335.3
336.3
337.2
338.2
330
335
m/z

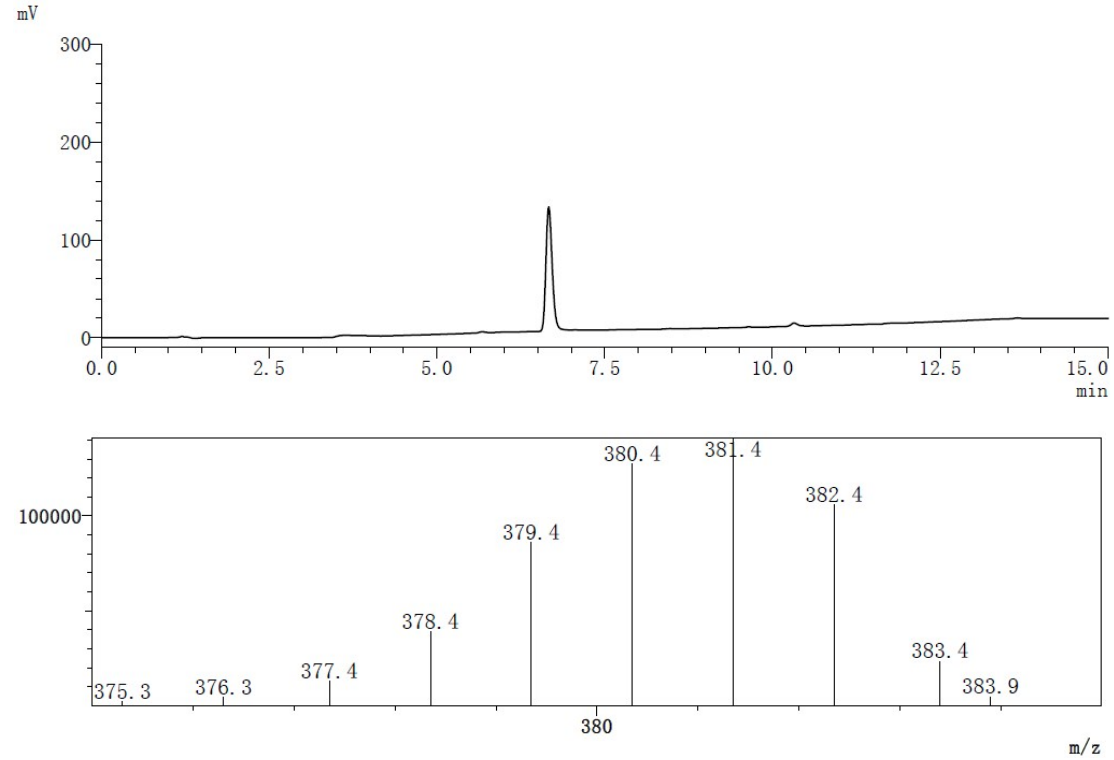
**2d-$d_7$**


mV
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
600000
500000
400000
300000
200000
100000
320.2
321.2
322.2
323.2
324.2
325.2
326.2
327.2
328.2
320
325
m/z

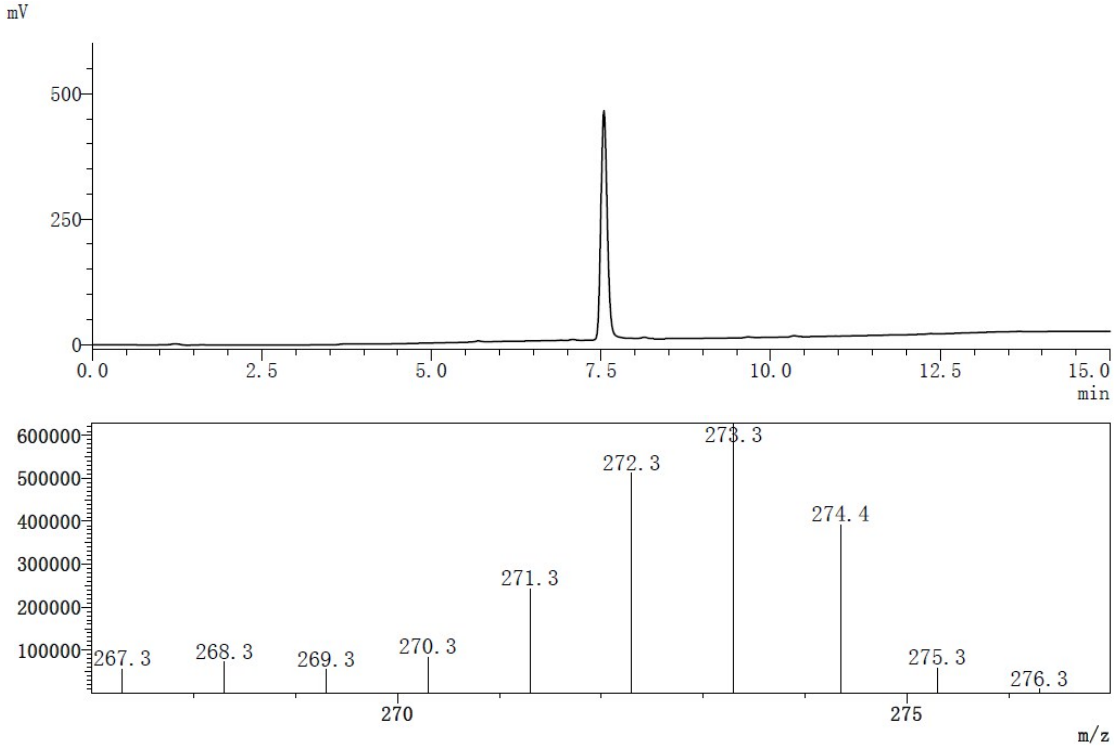
**2e-$d_6$**


mV
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
1000000
341.2
342.2
340.2
339.1
338.2
343.2
336.2
337.2
340
m/z

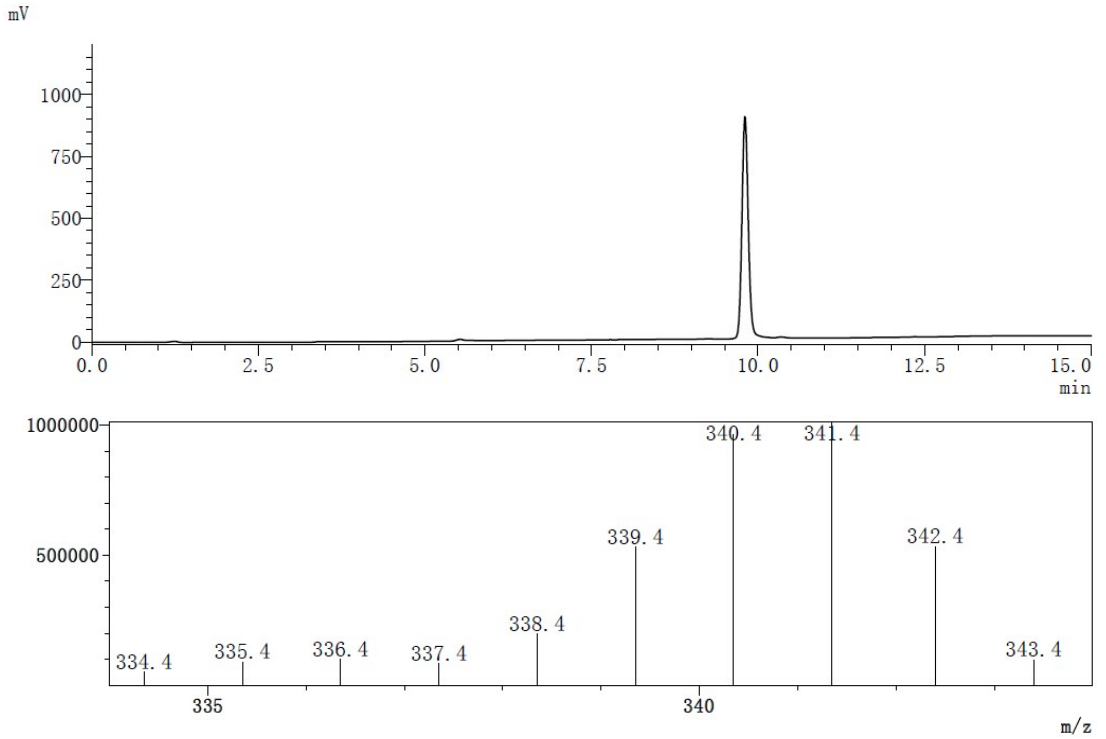
**2f-$d_6$**


mV
300
200
100
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
100000
380.4
381.4
382.4
379.4
378.4
383.4
377.4
375.3
376.3
383.9
380
m/z

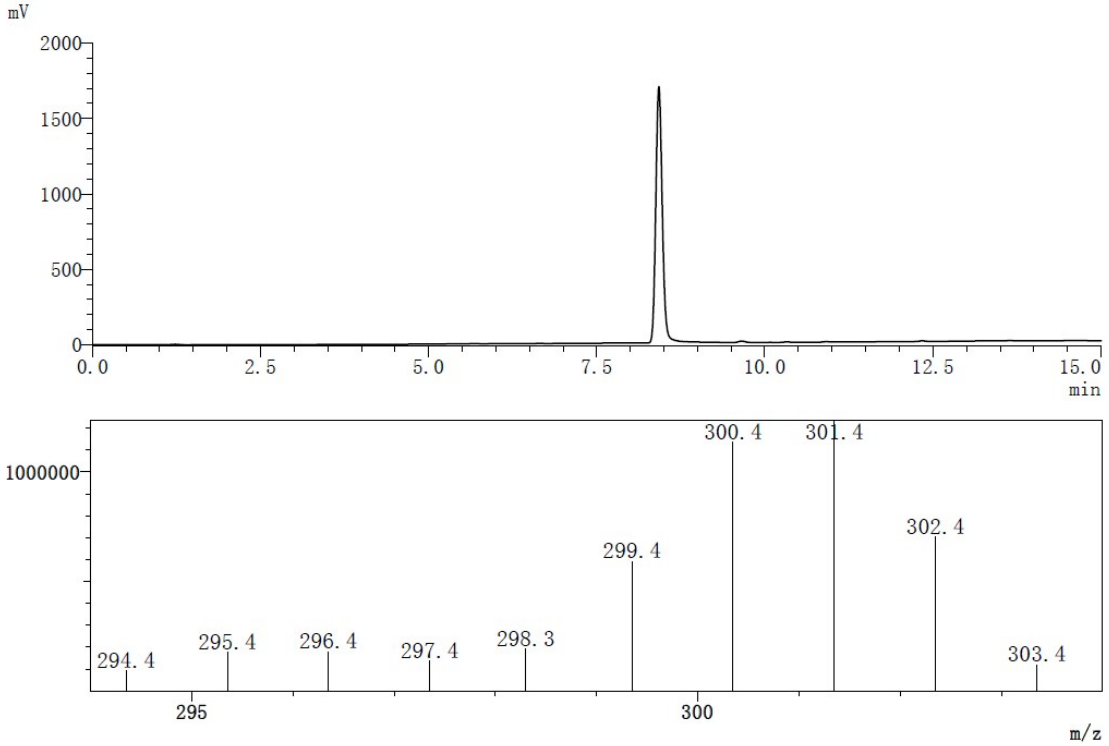
**2g-$d_6$**


mV
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
600000
500000
400000
300000
200000
100000
267.3
268.3
269.3
270.3
271.3
272.3
273.3
274.4
275.3
276.3
270
275
m/z

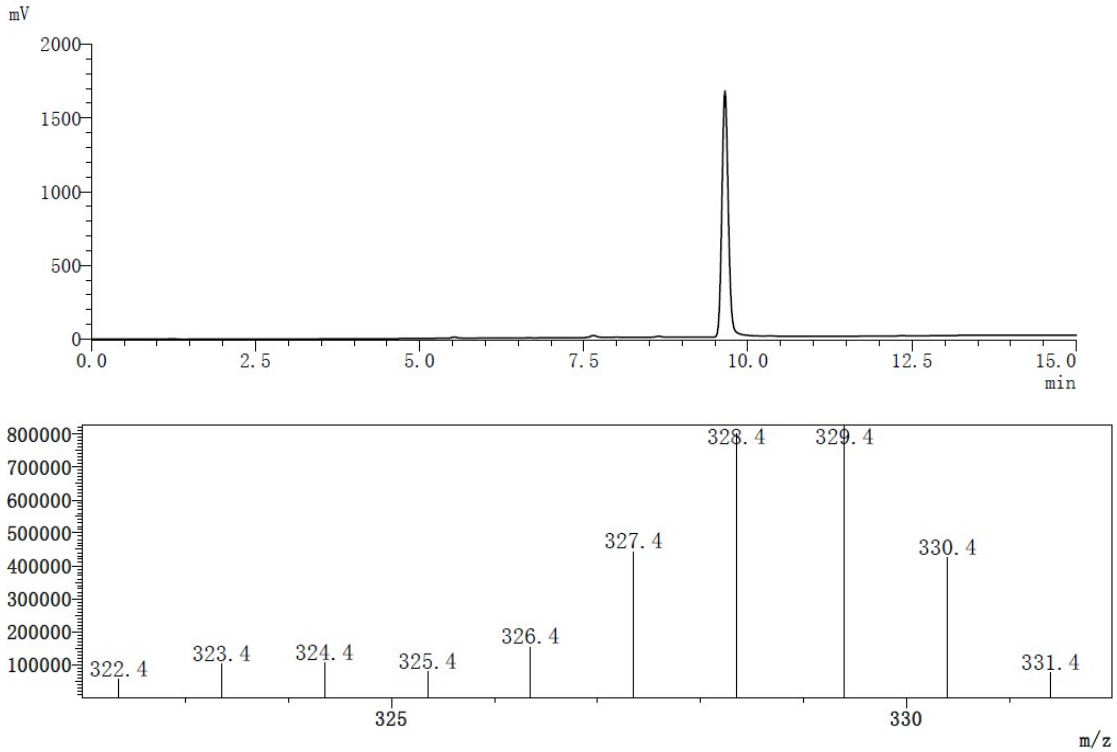
**2h-$d_6$**


mV
1000
750
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
1000000
500000
334.4
335.4
336.4
337.4
338.4
339.4
340.4
341.4
342.4
343.4
335
340
m/z

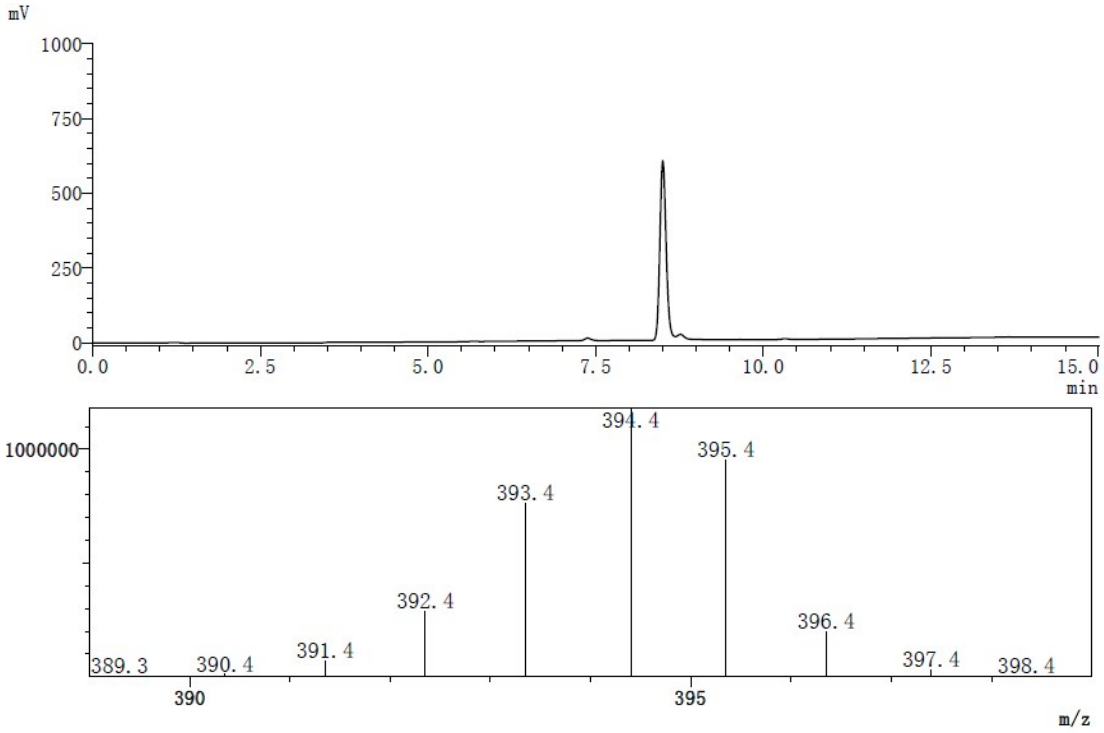
**2i-$d_6$**


mV
2000
1500
1000
500
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
1000000
300.4
301.4
302.4
299.4
294.4
295.4
296.4
297.4
298.3
303.4
295
300
m/z

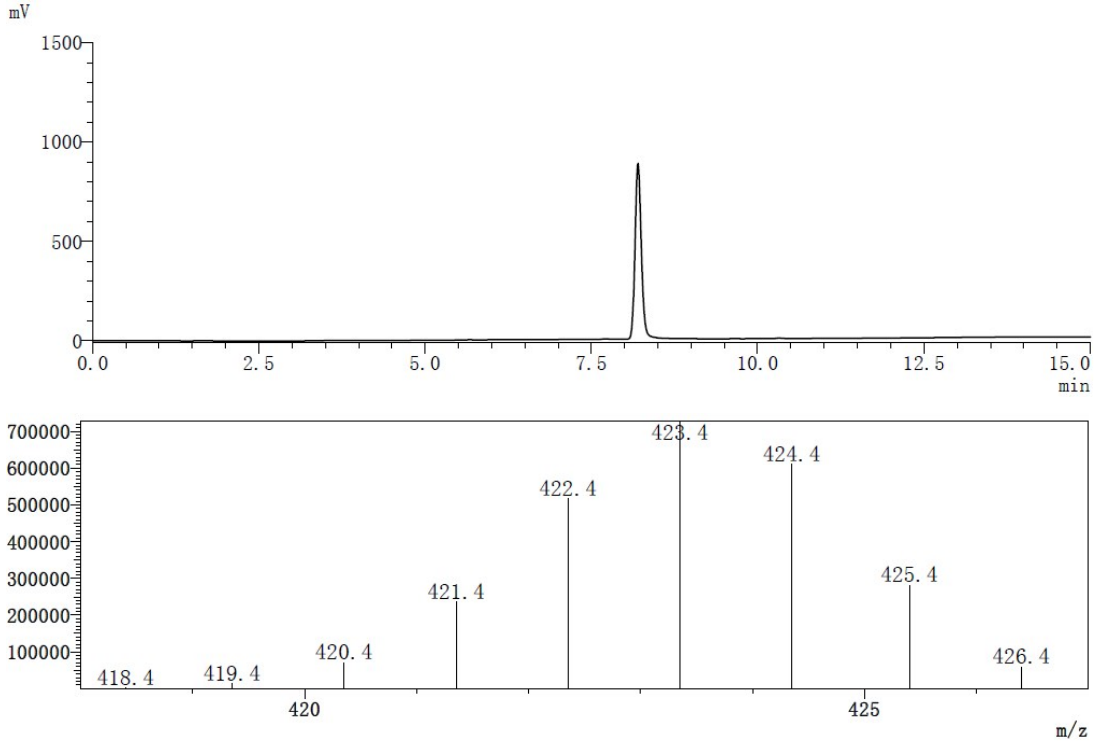
**2j-$d_6$**


mV
2000
1500
1000
500
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
800000
700000
600000
500000
400000
300000
200000
100000
328.4
329.4
327.4
330.4
322.4
323.4
324.4
325.4
326.4
331.4
325
330
m/z

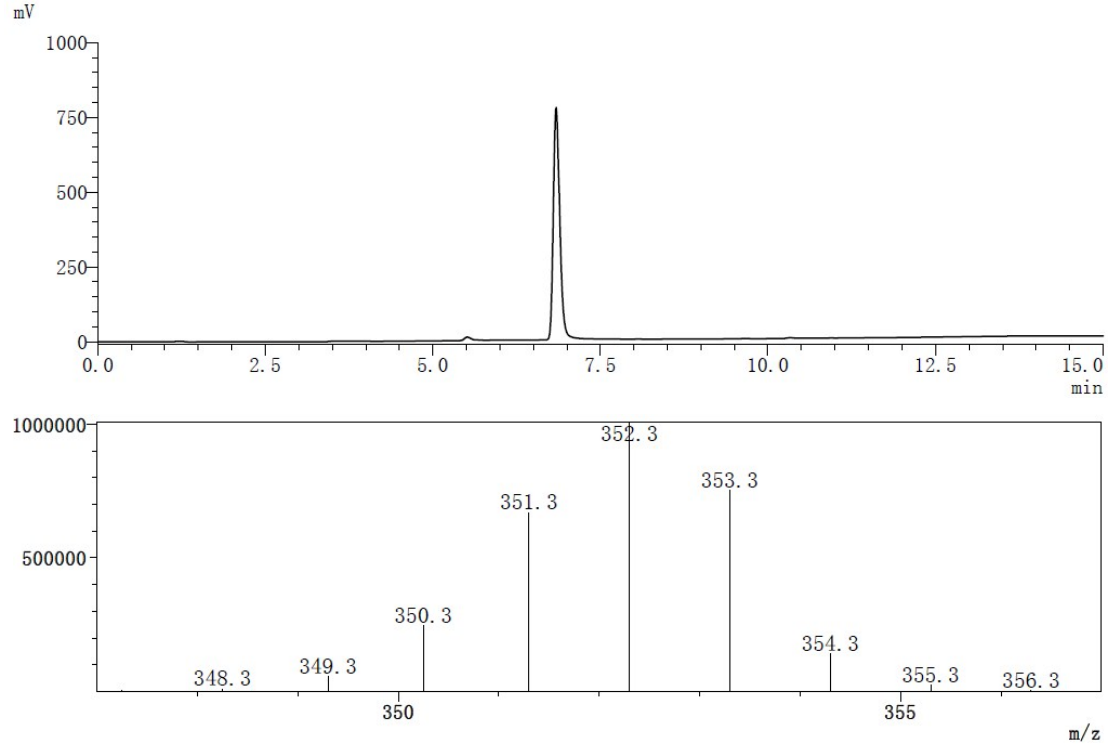
**2k-$d_6$**


mV
1000
750
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
1000000
394.4
395.4
393.4
392.4
396.4
389.3
390.4
391.4
397.4
398.4
390
395
m/z

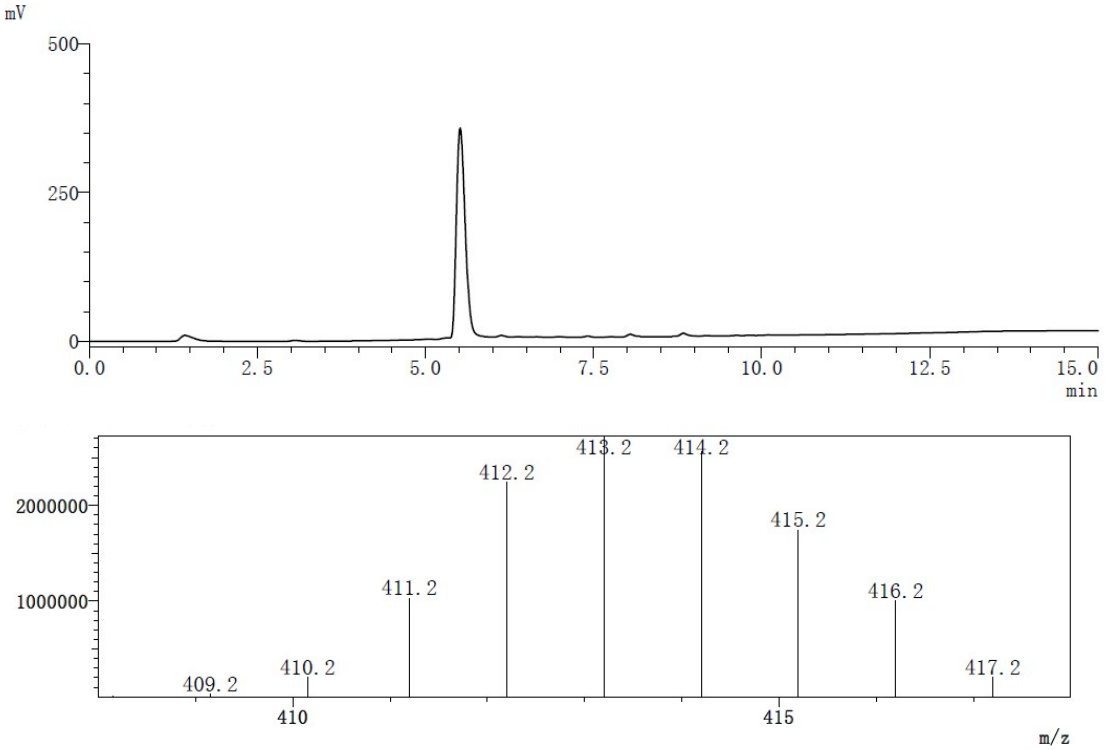
**2l-$d_6$**


mV
1500
1000
500
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
700000
600000
500000
400000
300000
200000
100000
423.4
424.4
422.4
425.4
421.4
420.4
426.4
418.4
419.4
420
425
m/z

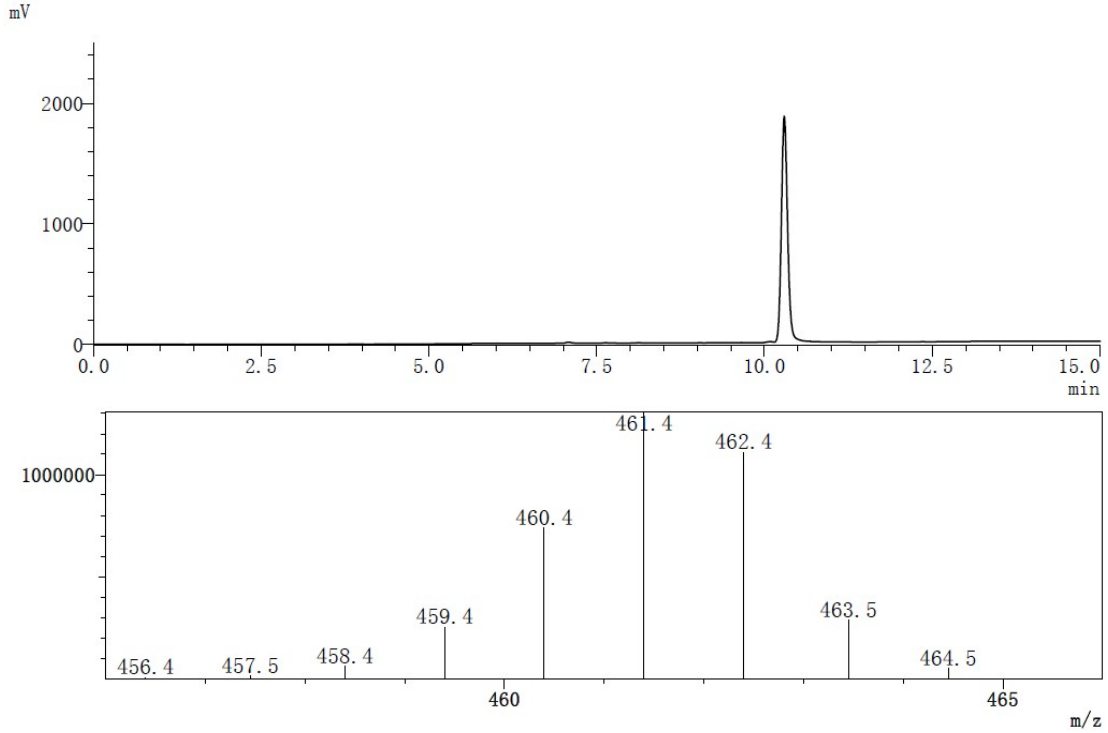
**2m-$d_6$**


mV
1000
750
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
1000000
500000
352.3
353.3
351.3
350.3
354.3
348.3
349.3
355.3
356.3
350
355
m/z

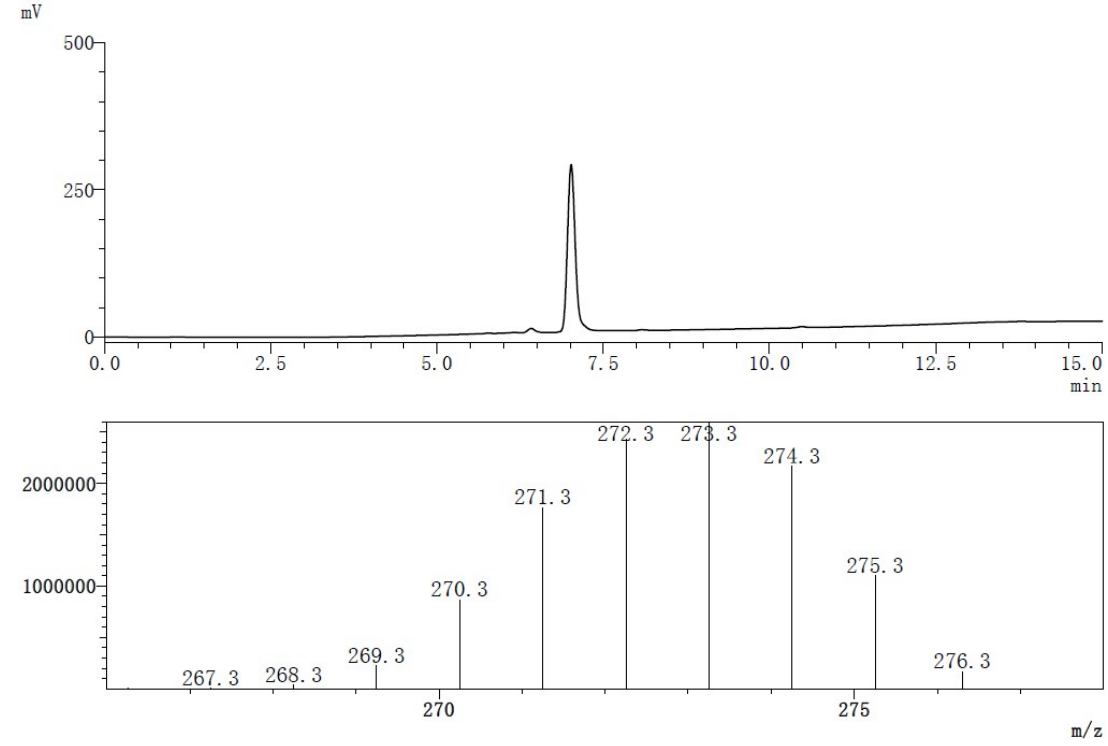
**2n-$d_5$**


mV
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
2000000
1000000
413.2
414.2
412.2
415.2
411.2
416.2
410.2
417.2
409.2
410
415
m/z

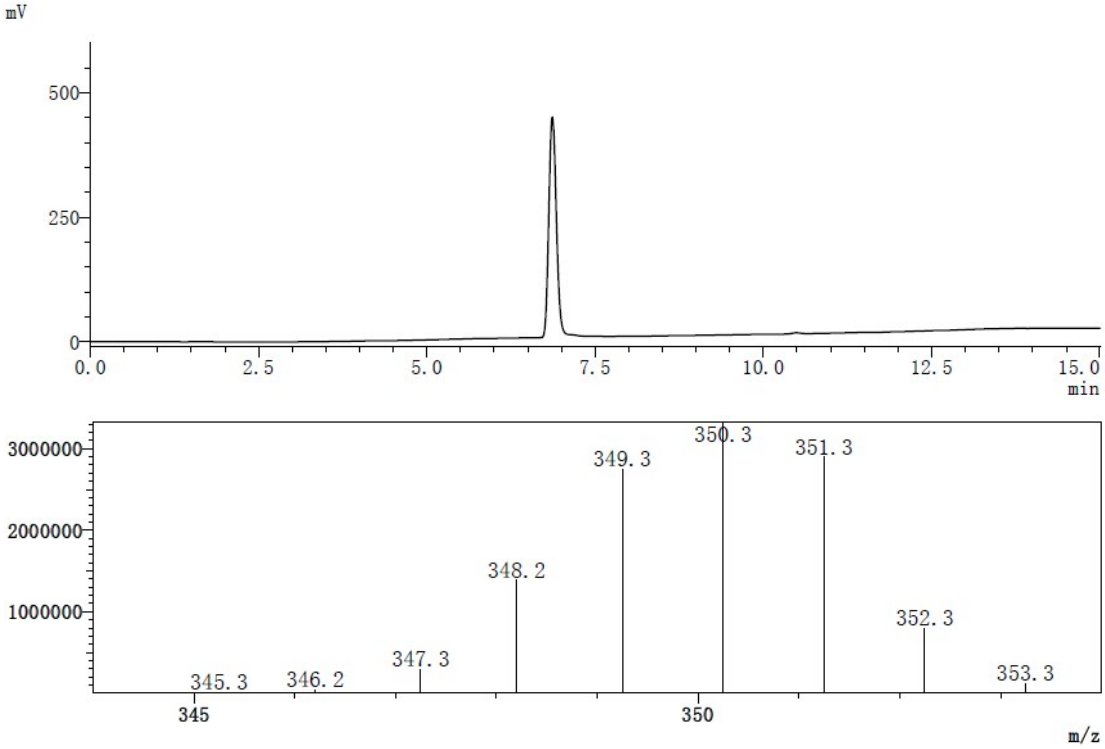
**2o-$d_6$**


mV
2000
1000
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
1000000
461.4
462.4
460.4
459.4
463.5
456.4
457.5
458.4
464.5
460
465
m/z

**3c-$d_9$**


mV
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
2000000
1000000
272.3
273.3
274.3
271.3
275.3
270.3
269.3
276.3
267.3
268.3
270
275
m/z

**3d-$d_6$**


mV
500
250
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
min
3000000
2000000
1000000
345.3
346.2
347.3
348.2
349.3
350.3
351.3
352.3
353.3
345
350
m/z