

Supporting Information

Catalyst- and additive-free [3+3] cyclization–aromatization of β,γ -dioxobutanoate with amines for synthesis of *p*-aminophenols

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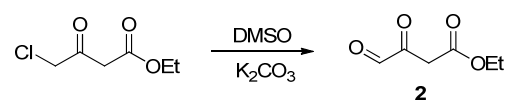
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1 General Procedures

All reactions were carried out under air atmosphere. Chemicals were purchased from commercial sources without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates (0.4-0.5 mm) using UV light as visualizing agent and an Phosphomolybdic acid, Iodine powder, and heat as developing agents. Flash chromatography was performed with silica gel (100-200 mesh) under pressure. NMR spectra were recorded on a Bruker AV-500 spectrometer in CDCl_3 . The chemical shift (δ) of each signal is reported in parts per million (ppm) and all coupling constants (J) are reported in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, m = multiplet. Melting points were measured on Kofler hot stage and are uncorrected. High-resolution Mass spectral (HRMS) data were measured on an Agilent 6210 ESI/TOF MS.

2 Experimental Procedure for Synthesis of Ethyl β,γ -Dioxobutanoate (**2**)



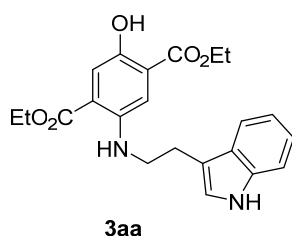
To a solution of ethyl 4-chloroacetoacetate (16.5 g, 0.1 mol) in DMSO (50.0 mL) was added K_2CO_3 (13.8 g, 0.1 mol). The reaction mixture was stirred at room temperature for 4 hours. To the reaction was added water (50.0 mL) and the mixture was extracted with EtOAc (3 $\times$ 100 mL). The combined organic phases were washed with water, brine and dried over Na_2SO_4 . The solvent was filtered and the filtrate was concentrated in vacuo to give the crude product **2** (14.1 g, 0.098 mol, 98%), which was used directly in the cyclization–aromatization

reactions. White solid; **mp.** 126-128 °C; **R_f** = 0.80 (Petroleum ether/EtOAc = 2:1); **¹H NMR** (500 MHz, CDCl₃) δ 12.18 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.15 (s, 2H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm; **¹³C NMR** (125 MHz, CDCl₃) δ 171.3, 168.5, 93.3, 60.8, 28.6, 14.2 ppm; **HRMS** (ESI) *m/z* [M + H]⁺ found 145.0501, calcd for C₆H₉O₄ 145.0501.

3 Experimental Procedure and Spectroscopic Data of *p*-Aminophenols

To a solution of ethyl β,γ-dioxobutanoate **2** (144 mg, 1.0 mmol) in MeCN (5.0 mL) was added amine (1.0 mmol). The reaction was stirred for 1 hour at 70 °C. The reaction mixture was concentrated under reduced pressure, the solvent was collected, and the residue was purified by flash column chromatography eluting with petroleum ether/EtOAc to give the *p*-aminophenol product. The unreacted amine was also obtained.

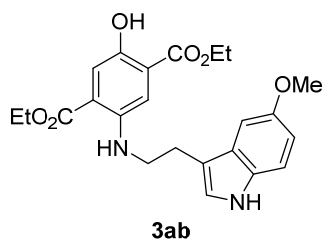
Diethyl 2-((2-(1H-indol-3-yl)ethyl)amino)-5-hydroxyterephthalate (3aa) Yellow solid (158.4



mg, 80%); **mp.** 128-129 °C; **R_f** = 0.55 (Petroleum ether/EtOAc = 2:1); **¹H NMR** (500 MHz, CDCl₃) δ 9.87 (s, 1H), 8.04 (s, 1H), 7.69 – 7.65 (m, 1H), 7.59 (s, 1H), 7.41 – 7.36 (m, 1H), 7.24 – 7.17 (m, 3H), 7.17 – 7.11 (m, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.30 (q, *J* = 7.1

Hz, 2H), 3.50 (td, *J* = 7.2, 4.5 Hz, 2H), 3.16 (t, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H) ppm; **¹³C NMR** (125 MHz, CDCl₃) δ 169.6, 167.5, 150.2, 143.8, 136.4, 127.4, 122.3, 122.2, 119.6, 119.4, 118.8, 117.8, 117.2, 113.5, 111.5, 111.3, 61.8, 60.9, 44.2, 25.3, 14.3, 14.3 ppm; **HRMS** (ESI) *m/z* [M + H]⁺ found 397.1754, calcd for C₂₂H₂₄ClN₂O₅ 397.1763.

Diethyl 2-hydroxy-5-((2-(5-methoxy-1H-indol-3-yl)ethyl)amino)terephthalate (3ab) Yellow



solid (170.4 mg, 80%); **mp.** 135-137 °C; **R_f** = 0.55 (Petroleum

ether/EtOAc = 2:1); **¹H NMR** (500 MHz, CDCl₃) δ 9.84 (s, 1H),

7.93 (s, 1H), 7.57 (s, 1H), 7.25 (d, *J* = 3.5 Hz, 1H), 7.15 (s, 2H),

7.08 (dd, *J* = 15.0, 2.4 Hz, 2H), 6.86 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.41

(q, *J* = 7.1 Hz, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 3.47 (p, *J* = 3.7 Hz, 2H), 3.11 (t, *J* = 7.1

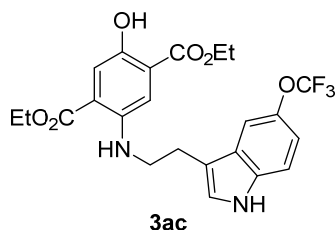
Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H) ppm; **¹³C NMR** (125 MHz, CDCl₃) δ

169.6, 167.5, 154.1, 150.2, 143.8, 131.5, 127.8, 123.0, 119.6, 117.8, 117.2, 113.3, 112.2,

111.9, 111.5, 100.8, 61.8, 60.9, 56.0, 44.1, 25.3, 14.3, 14.3 ppm; **HRMS** (ESI) *m/z* [M + H]⁺

found 427.1872, calcd for C₂₃H₂₇N₂O₆ 427.1869.

Diethyl 2-hydroxy-5-((2-(5-(trifluoromethoxy)-1H-indol-3-yl)ethyl)amino)terephthalate



(3ac) Yellow solid (172.8 mg, 72%); **mp.** 148-151 °C; **R_f** = 0.55

(Petroleum ether/EtOAc = 2:1); **¹H NMR** (500 MHz, CDCl₃) δ

9.85 (s, 1H), 8.01 (s, 1H), 7.58 (s, 1H), 7.53 (dd, *J* = 8.7, 5.3 Hz,

1H), 7.16 (s, 2H), 7.10 (d, *J* = 2.3 Hz, 1H), 7.05 (dd, *J* = 9.6, 2.3

Hz, 1H), 6.89 (ddd, *J* = 9.6, 8.6, 2.3 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H),

3.48 (q, *J* = 6.1 Hz, 2H), 3.12 (t, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H)

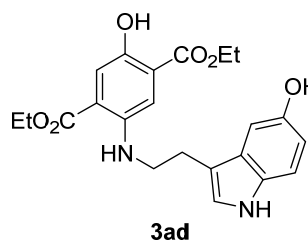
ppm; **¹³C NMR** (125 MHz, CDCl₃) δ 169.5, 167.5, 150.2, 143.7, 124.0, 122.4, 122.4, 119.7,

119.5, 119.4, 117.8, 117.3, 113.7, 111.4, 108.3, 108.1, 97.6 (d, *J* = 26.25 Hz, 1C), 61.8, 60.9,

44.0, 25.2, 14.3, 14.2 ppm; **HRMS** (ESI) *m/z* [M + H]⁺ found 481.1585, calcd for C₂₃H₂₄N₂O₆F₃

481.1586.

Diethyl 2-hydroxy-5-((2-(5-hydroxy-1H-indol-3-yl)ethyl)amino)terephthalate (3ad) Yellow



solid (160.7 mg, 78%); **mp.** 126-128 °C; **R_f** = 0.55 (Petroleum

ether/EtOAc = 2:1); **¹H NMR** (500 MHz, CDCl₃) δ 9.82 (s, 1H),

7.94 – 7.88 (m, 1H), 7.58 (s, 1H), 7.22 (d, *J* = 8.6 Hz, 1H), 7.17 (s,

1H), 7.14 (s, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H),

6.78 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.72 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.45

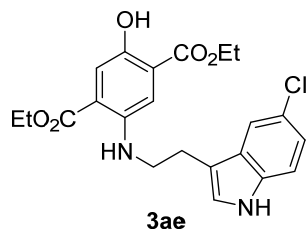
(t, *J* = 7.3 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H) ppm;

¹³C NMR (125 MHz, CDCl₃) δ 169.5, 167.6, 150.2, 149.5, 143.7, 131.7, 128.1, 123.5, 119.6,

117.9, 117.2, 112.9, 111.93, 111.92, 111.7, 103.4, 61.9, 61.0, 44.1, 25.2, 14.3, 14.2 ppm;

HRMS (ESI) *m/z* [M + H]⁺ found 413.1712, calcd for C₂₂H₂₅N₂O₆ 413.1713.

Diethyl 2-((2-(5-chloro-1H-indol-3-yl)ethyl)amino)-5-hydroxyterephthalate (3ae) Yellow



solid (169.8 mg, 79%); **mp.** 132-133 °C; **R_f** = 0.55 (Petroleum

ether/EtOAc = 2:1); **¹H NMR** (500 MHz, CDCl₃) δ 9.86 (s, 1H), 8.06

(s, 1H), 7.61 – 7.56 (m, 2H), 7.28 (d, *J* = 8.6 Hz, 1H), 7.20 – 7.12

(m, 4H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.47 (q, *J*

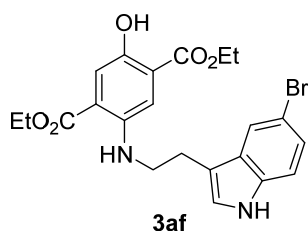
= 6.6 Hz, 2H), 3.10 (t, *J* = 7.0 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H) ppm; **¹³C**

NMR (125 MHz, CDCl₃) δ 169.6, 167.5, 150.3, 143.7, 134.7, 128.6, 125.2, 123.7, 122.5, 119.7,

118.4, 117.8, 117.3, 113.4, 112.2, 111.4, 61.9, 60.9, 44.0, 25.1, 14.3, 14.3 ppm; **HRMS** (ESI)

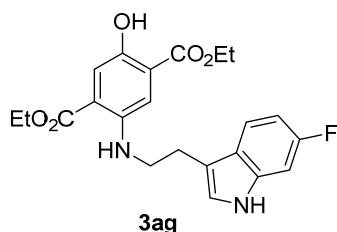
m/z [M + H]⁺ found 431.1367, calcd for C₂₂H₂₄ClN₂O₅ 431.1374.

Diethyl2-((2-(5-bromo-1H-indol-3-yl)ethyl)amino)-5-hydroxyterephthalate (3af) Yellow



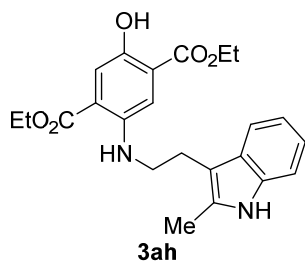
solid (191.9 mg, 81%); **mp.** 153-155 °C; **R_f** = 0.55 (Petroleum ether/EtOAc = 2:1); **¹H NMR** (500 MHz, CDCl₃) δ 9.86 (s, 1H), 8.06 (s, 1H), 7.74 (d, *J* = 1.9 Hz, 1H), 7.58 (s, 1H), 7.28 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.19 – 7.12 (m, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.47 (q, *J* = 6.0 Hz, 2H), 3.10 (t, *J* = 7.0 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H) ppm; **¹³C NMR** (125 MHz, CDCl₃) δ 169.6, 167.5, 150.3, 143.6, 135.0, 129.2, 125.0, 123.5, 121.5, 119.7, 117.8, 117.3, 113.4, 112.8, 112.7, 111.4, 61.9, 60.9, 44.0, 25.1, 14.3, 14.3 ppm; **HRMS** (ESI) *m/z* [M + H]⁺ found 475.0877, calcd for C₂₂H₂₄N₂O₅Br 475.0869.

Diethyl 2-((2-(6-fluoro-1H-indol-3-yl)ethyl)amino)-5-hydroxyterephthalate (3ag) Yellow



solid (175.9 mg, 85%); **mp.** 153-155 °C; **R_f** = 0.55 (Petroleum ether/EtOAc = 2:1); **mp.** 133-138°C; **¹H NMR** (500 MHz, CDCl₃) δ 9.87 (s, 1H), 8.14 (s, 1H), 7.58 (s, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.22 – 7.17 (m, 2H), 7.16 (s, 1H), 7.11 – 7.05 (m, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.48 (q, *J* = 6.6 Hz, 2H), 3.12 (t, *J* = 7.0 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H) ppm; **¹³C NMR** (125 MHz, CDCl₃) δ 169.6, 167.6, 150.3, 143.6, 142.9, 142.9, 134.6, 127.7, 124.2, 119.7, 117.8, 117.3, 116.1, 114.1, 111.8, 111.4, 111.4, 61.9, 60.9, 43.9, 25.1, 14.3, 14.2 ppm; **HRMS** (ESI) *m/z* [M + H]⁺ found 415.1671, calcd for C₂₂H₂₄N₂O₅F 415.1669.

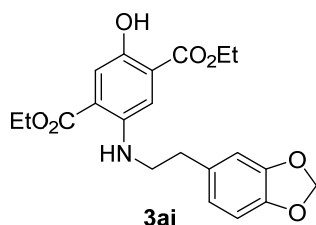
Diethyl 2-hydroxy-5-((2-(2-methyl-1H-indol-3-yl)ethyl)amino)terephthalate (3ah) Yellow



solid (137.4 mg, 67%); **mp.** 166-168 °C; **R_f** = 0.55 (Petroleum ether/EtOAc = 2:1); **¹H NMR** (500 MHz, CDCl₃) δ 9.88 (s, 1H), 7.82 (s, 1H), 7.59 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.18 (s, 2H), 7.11 (dtd, *J* = 19.9, 7.1, 1.2 Hz, 2H), 4.42 (q, *J* =

7.1 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.42 (td, *J* = 7.4, 4.7 Hz, 2H), 3.07 (t, *J* = 7.5 Hz, 2H), 2.41 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H) ppm; **¹³C NMR** (125 MHz, CDCl₃) δ 169.6, 167.5, 150.1, 143.8, 135.4, 132.0, 128.6, 121.2, 119.6, 119.3, 117.9, 117.8, 117.2, 111.4, 110.4, 108.9, 61.9, 60.9, 44.0, 24.3, 14.3, 14.3, 11.7 ppm; **HRMS** (ESI) *m/z* [M + H]⁺ found 411.1914, calcd for C₂₃H₂₇N₂O₅ 411.1920.

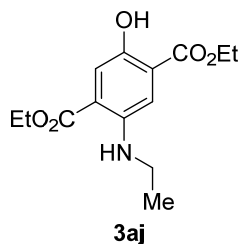
Diethyl 2-((2-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-5-hydroxyterephthalate (3ai) Yellow



solid (172.5 mg, 86%); **mp.** 166-168 °C; **R_f** = 0.70 (Petroleum ether/EtOAc = 6:1); **¹H NMR** (500 MHz, CDCl₃) δ 9.85 (s, 1H), 7.58 (s, 1H), 7.13 (s, 2H), 6.79 – 6.75 (m, 2H), 6.72 (dd, *J* = 7.8, 1.7 Hz, 1H), 5.93 (s, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.31 (q, *J* = 7.1

Hz, 2H), 3.37 (td, *J* = 7.2, 4.4 Hz, 2H), 2.89 (t, *J* = 7.3 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H) ppm; **¹³C NMR** (125 MHz, CDCl₃) δ 169.5, 167.5, 150.3, 147.8, 143.5, 133.1, 121.7, 119.7, 117.8, 117.4, 111.4, 109.1, 108.4, 100.9, 61.8, 61.0, 45.5, 35.4, 14.3, 14.3 ppm; **HRMS** (ESI) *m/z* [M + H]⁺ found 402.1551, calcd for C₂₁H₂₄NO₇ 402.1553.

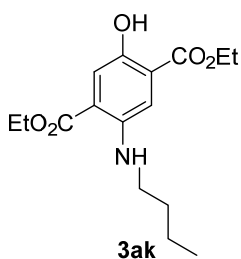
Diethyl 2-(ethylamino)-5-hydroxyterephthalate (3aj) Yellow solid (116.6 mg, 83%); **mp.**



102-104 °C; R_f = 0.70 (Petroleum ether/EtOAc = 6:1); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.82 (s, 1H), 7.57 (s, 1H), 7.11 (s, 1H), 6.94 (s, 1H), 4.42 (q, J = 7.1 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.19 (q, J = 7.4 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H), 1.38 ppm (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H)

ppm; $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 169.6, 167.6, 150.1, 143.9, 119.5, 117.8, 117.0, 111.3, 61.8, 60.9, 38.1, 14.6, 14.3 ppm; **HRMS** (ESI) m/z $[\text{M} + \text{H}]^+$ found 282.1348, calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_5$ 282.1341.

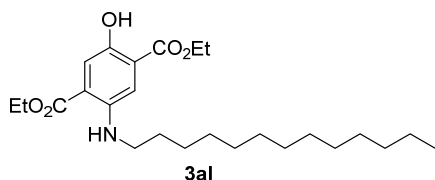
Diethyl 2-(butylamino)-5-hydroxyterephthalate (3ak) Yellow solid (125.1 mg, 81%); **mp.**



103-105 °C; R_f = 0.70 (Petroleum ether/EtOAc = 6:1); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.81 (s, 1H), 7.58 (s, 1H), 7.11 (s, 1H), 7.03 (s, 1H), 4.43 (q, J = 7.1 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.16 (dt, J = 10.4, 5.1 Hz, 2H), 1.72 – 1.64 (m, 2H), 1.49 (p, J = 7.4 Hz, 2H), 1.43 (t, J = 7.1

Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H) ppm; $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 169.6, 167.7, 150.0, 144.1, 119.5, 117.9, 116.9, 111.3, 61.8, 60.9, 43.2, 31.3, 20.4, 14.3, 14.0 ppm; **HRMS** (ESI) m/z $[\text{M} + \text{H}]^+$ found 310.1656, calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_5$ 310.1654.

Diethyl 2-(dodecylamino)-5-hydroxyterephthalate (3al) Yellow solid (158.8 mg, 73%); **mp.**

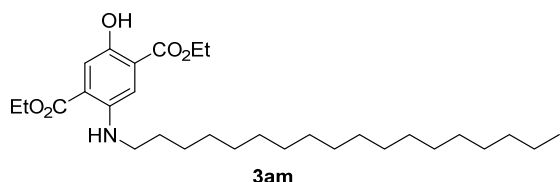


59-60 °C; R_f = 0.90 (Petroleum ether/EtOAc = 10:1); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.81 (s, 1H), 7.58 (s, 1H), 7.11 (s, 1H), 7.03 (s, 1H), 4.43 (q, J = 7.1 Hz, 2H), 4.32

(q, J = 7.1 Hz, 2H), 3.14 (t, J = 7.1 Hz, 2H), 1.68 (p, J = 7.2 Hz, 2H), 1.43 (t, J = 7.1 Hz, 5H), 1.38 (t, J = 7.1 Hz, 3H), 1.27 (d, J = 10.0 Hz, 18H), 0.88 (t, J = 6.8 Hz, 3H) ppm; $^{13}\text{C NMR}$ (125 MHz,

CDCl₃) δ 169.6, 167.6, 150.0, 144.1, 119.5, 117.9, 116.9, 111.3, 61.8, 60.9, 43.6, 32.0, 29.8, 29.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 27.3, 22.7, 14.3, 14.2 ppm; **HRMS** (ESI) m/z [M + Na]⁺ found 458.2884, calcd for C₂₅H₄₁NO₅Na 458.2882.

Diethyl 2-hydroxy-5-(octadecylamino)terephthalate (3am) Yellow solid (194.7 mg, 75%); **mp.**



59-60 °C; **R_f** = 0.85 (Petroleum ether/EtOAc

= 10:1); ¹H NMR (500 MHz, CDCl₃) δ 9.81 (s, 1H), 7.58 (s, 1H), 7.11 (s, 1H), 7.03 (s, 1H),

4.43 (q, J = 7.1 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.13 (d, J = 7.4 Hz, 2H), 1.68 (p, J = 7.1 Hz, 2H),

1.43 (t, J = 7.1 Hz, 4H), 1.38 (t, J = 7.1 Hz, 4H), 1.26 (s, 28H), 0.88 (t, J = 6.8 Hz, 3H) ppm; ¹³C

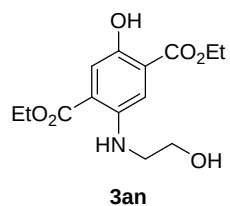
NMR (125 MHz, CDCl₃) δ 169.6, 167.7, 150.0, 144.1, 119.5, 117.9, 116.9, 111.3, 61.8, 60.9,

43.6, 32.0, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 27.3, 22.7, 14.3, 14.2 ppm; **HRMS** (ESI) m/z

[M + H]⁺ found 520.3994, calcd for C₃₁H₅₄NO₅ 520.4002.

Diethyl 2-hydroxy-5-((2-hydroxyethyl)amino)terephthalate (3an) Yellow solid (109.9 mg,

74%); **mp.** 99-101 °C; **R_f** = 0.65 (Petroleum ether/EtOAc = 2:1); ¹H NMR



(500 MHz, CDCl₃) δ 9.89 (s, 1H), 7.60 (s, 1H), 7.18 (s, 1H), 4.43 (q, J =

7.1 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 3.89 (t, J = 5.4 Hz, 2H), 3.39 (t, J =

5.4 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H), 1.39 (t, J = 7.2 Hz, 3H) ppm; ¹³C

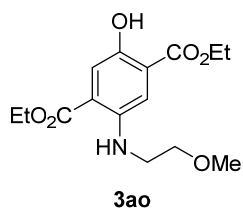
NMR (125 MHz, CDCl₃) δ 169.5, 167.5, 150.5, 143.7, 119.8, 117.7, 117.7, 111.4, 76.8, 71.1,

61.8, 61.0, 59.0, 43.4, 14.3 ppm; **HRMS** (ESI) m/z [M + H]⁺ found 298.1289, calcd for

C₁₄H₂₀NO₆ 298.1291.

Diethyl 2-hydroxy-5-((2-methoxyethyl)amino)terephthalate (3ao) Yellow solid (121.3 mg,

78%); **mp.** 79-81 °C; **R_f** = 0.55 (Petroleum ether/EtOAc = 6:1); **¹H NMR**



(500 MHz, CDCl₃) δ 9.86 (s, 1H), 7.59 (s, 1H), 7.24 (s, 1H), 7.15 (s, 1H),

4.43 (q, *J* = 7.1 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.67 (t, *J* = 5.5 Hz, 2H),

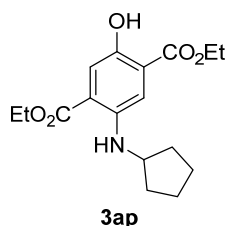
3.43 (s, 3H), 3.40 – 3.33 (m, 2H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.38 (t, *J* = 7.1

Hz, 3H) ppm; **¹³C NMR** (125 MHz, CDCl₃) δ 169.5, 167.6, 150.7, 143.7, 119.8, 118.0, 117.7,

111.7, 61.9, 61.4, 61.1, 45.8, 29.8, 14.3, 14.3 ppm; **HRMS** (ESI) *m/z* [M + H]⁺ found 312.1445,

calcd for C₁₅H₂₂NO₆ 312.1447.

Diethyl 2-(cyclopentylamino)-5-hydroxyterephthalate (3ap) Yellow solid (128.4 mg, 80%);



mp. 118-121 °C; **R_f** = 0.60 (Petroleum ether/EtOAc = 30:1); **¹H NMR**

(500 MHz, CDCl₃) δ 9.85 (s, 1H), 7.57 (s, 1H), 7.23 (s, 1H), 7.12 (s, 1H),

4.42 (q, *J* = 7.3 Hz, 2H), 4.31 (q, *J* = 7.3 Hz, 2H), 4.12 (q, *J* = 7.3 Hz, 1H),

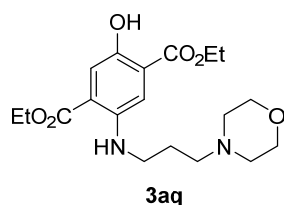
3.75 (t, *J* = 5.6 Hz, 2H), 3.70 (s, 4H), 3.36 (s, 2H), 1.42 (t, *J* = 7.2 Hz, 3H),

1.37 (t, *J* = 7.2 Hz, 3H) ppm; **¹³C NMR** (125 MHz, CDCl₃) δ 169.5, 167.4, 150.4, 143.7, 119.7,

117.7, 111.4, 70.7, 70.7, 69.7, 61.8, 60.9, 53.5, 43.3, 14.27, 14.25 ppm; **HRMS** (ESI) *m/z* [M +

H]⁺ found 322.1649, calcd for C₁₇H₂₄NO₅ 322.1654.

Diethyl 2-hydroxy-5-((3-morpholinopropyl)amino)terephthalate (3aq) Yellow solid (153.7



mg, 84%); **mp.** 80-83 °C; **R_f** = 0.15 (Petroleum ether/EtOAc = 1:1);

¹H NMR (500 MHz, CDCl₃) δ 9.82 (s, 1H), 7.57 (s, 1H), 7.12 (s, 2H),

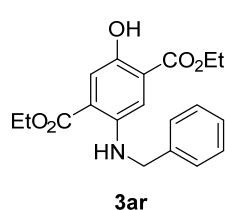
4.43 (q, *J* = 7.1 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.73 (t, *J* = 4.6 Hz,

4H), 3.23 (t, *J* = 6.8 Hz, 2H), 2.47 (q, *J* = 6.6, 6.0 Hz, 6H), 1.86 (p, *J* =

6.9 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H) ppm; **¹³C NMR** (125 MHz, CDCl₃) δ

169.5, 167.6, 150.1, 143.9, 119.6, 117.8, 117.2, 111.3, 67.0, 61.8, 60.9, 56.8, 53.9, 41.8, 26.1, 14.29, 14.26 ppm; **HRMS** (ESI) m/z $[M + H]^+$ found 367.1866, calcd for $C_{18}H_{27}N_2O_6$ 367.1869.

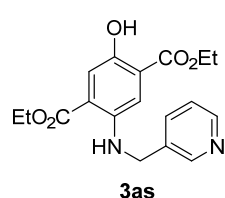
Diethyl 2-(benzylamino)-5-hydroxyterephthalate (3ar) Yellow solid (128.6 mg, 75%); **mp.**



93-95 °C; R_f = 0.80 (Petroleum ether/EtOAc = 2:1); 1H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.60 (s, 1H), 7.54 (s, 1H), 7.38 (d, J = 7.2 Hz, 2H), 7.34 (dd, J = 8.5, 6.7 Hz, 2H), 7.26 (s, 1H), 7.13 (s, 1H), 4.40 (d, J = 4.9 Hz,

2H), 4.35 (dq, J = 16.8, 7.1 Hz, 4H), 1.38 (td, J = 7.1, 4.6 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 167.6, 150.5, 143.5, 139.1, 128.7, 127.4, 127.3, 119.6, 117.7, 117.5, 112.0, 61.7, 61.0, 47.9, 14.3, 14.1 ppm; **HRMS** (ESI) m/z $[M + H]^+$ found 344.1494, calcd for $C_{19}H_{22}NO_5$ 344.1498.

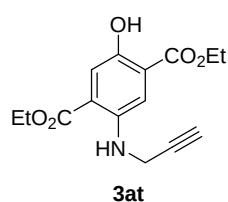
Diethyl 2-hydroxy-5-((pyridin-3-ylmethyl)amino)terephthalate (3as) Yellow solid (120.4 mg,



70%); **mp.** 118-121 °C; R_f = 0.55 (Petroleum ether/EtOAc = 6:1); 1H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.65 (d, J = 2.3 Hz, 1H), 8.53 (dd, J = 4.8, 1.6 Hz, 1H), 7.70 (dt, J = 7.9, 2.0 Hz, 1H), 7.61 (s, 1H), 7.58 (t, J =

5.7 Hz, 1H), 7.27 (d, J = 5.0 Hz, 1H), 7.08 (s, 1H), 4.43 (d, J = 5.5 Hz, 2H), 4.35 (dq, J = 15.4, 7.1 Hz, 4H), 1.38 (q, J = 7.4 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 167.6, 150.9, 149.2, 148.8, 143.0, 135.0, 134.6, 123.7, 119.9, 117.9, 117.7, 111.8, 61.8, 61.2, 45.3, 14.2, 14.1 ppm; **HRMS** (ESI) m/z $[M + H]^+$ found 345.1442, calcd for $C_{18}H_{21}N_2O_5$ 345.1450.

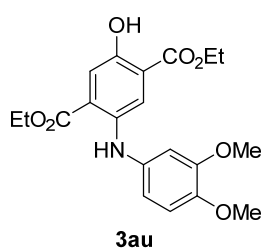
Diethyl 2-hydroxy-5-(prop-2-yn-1-ylamino)terephthalate (3at) Yellow solid (120.7 mg, 83%);



mp. 116-117 °C; R_f = 0.35 (Petroleum ether/EtOAc = 10:1); 1H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.61 (s, 1H), 7.30 (s, 1H), 7.25 (s, 1H),

4.44 (q, $J = 7.1$ Hz, 2H), 4.33 (q, $J = 7.1$ Hz, 2H), 4.01 (dd, $J = 5.8, 2.5$ Hz, 2H), 2.22 (s, 1H), 1.44 (t, $J = 7.1$ Hz, 3H), 1.38 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 169.5, 167.4, 151.3, 142.3, 119.9, 118.5, 117.6, 112.0, 80.5, 71.2, 61.9, 61.2, 33.1, 14.2 ppm; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ found 292.1183, calcd for $\text{C}_{15}\text{H}_{18}\text{NO}_5$ 292.1185.

Diethyl 2-((3,4-dimethoxyphenyl)amino)-5-hydroxyterephthalate (3au) Yellow solid (126.4

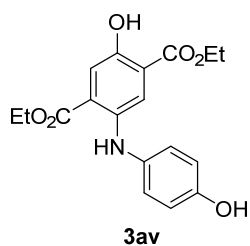


mg, 65%); mp. 99-101 °C; $R_f = 0.50$ (Petroleum ether/EtOAc = 6:1);

^1H NMR (500 MHz, CDCl_3) δ 9.81 (s, 1H), 7.57 (s, 1H), 7.40 (s, 1H), 7.20 (t, $J = 4.1$ Hz, 2H), 6.48 (d, $J = 2.4$ Hz, 1H), 6.43 (dd, $J = 8.3, 2.4$ Hz, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 4.32 – 4.28 (m, 2H), 3.85 (s, 3H),

3.79 (s, 3H), 1.41 (t, $J = 7.1$ Hz, 3H), 1.37 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 169.6, 167.5, 160.2, 158.5, 150.2, 143.8, 129.5, 119.5, 119.4, 117.7, 117.5, 112.0, 104.1, 98.7, 61.7, 60.9, 55.5, 55.4, 42.2, 14.3, 14.2 ppm; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ found 390.1541, calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_7$ 390.1553.

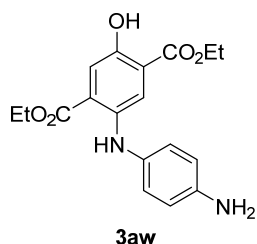
Diethyl 2-hydroxy-5-((4-hydroxyphenyl)amino)terephthalate (3av) Yellow solid (105.2 mg,



61%); mp. 169-171 °C; $R_f = 0.80$ (Petroleum ether/EtOAc = 1:1); ^1H NMR (500 MHz, CDCl_3) δ 9.96 (s, 1H), 8.69 (s, 1H), 7.59 (d, $J = 17.6$ Hz, 2H), 7.08 (d, $J = 8.6$ Hz, 2H), 6.83 (d, $J = 8.7$ Hz, 2H), 4.66 (s, 1H), 4.36 (qd, $J = 7.2, 3.2$ Hz, 4H), 1.41 (t, $J = 7.1$ Hz, 3H), 1.34 (t, $J = 7.1$ Hz, 3H)

ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 169.4, 167.5, 151.1, 142.7, 141.7, 132.8, 124.6, 119.3, 118.2, 117.7, 116.3, 114.6, 61.8, 61.2, 14.3, 14.2 ppm; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ found 346.1283, calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_6$ 346.1291.

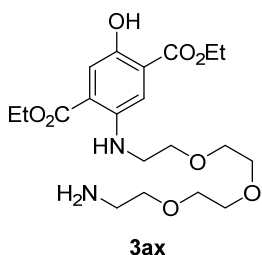
Diethyl 2-((4-aminophenyl)amino)-5-hydroxyterephthalate (3aw) Yellow solid (94.6 mg,



55%); **mp.** 129-131 °C; **R_f** = 0.55 (Petroleum ether/EtOAc = 1:1); **¹H NMR** (500 MHz, CDCl₃) δ 9.93 (s, 1H), 8.64 (s, 1H), 7.59 (s, 1H), 7.53 (s, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.6 Hz, 2H), 4.35 (qd, *J* = 7.1, 3.4 Hz, 4H), 3.62 (s, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H)

ppm; **¹³C NMR** (125 MHz, CDCl₃) δ 169.4, 167.6, 151.0, 142.8, 141.7, 132.7, 124.6, 119.2, 118.1, 117.7, 116.2, 114.5, 61.8, 61.2, 14.3, 14.2 ppm; **HRMS** (ESI) *m/z* [M + H]⁺ found 345.1456, calcd for C₁₈H₂₁N₂O₅ 345.1450.

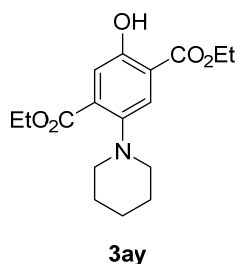
Diethyl 2-((2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)amino)-5-hydroxyterephthalate



(3ax) Yellow oil (137.2 mg, 61%); **R_f** = 0.35 (Petroleum ether/EtOAc = 1:2); **¹H NMR** (500 MHz, CDCl₃) δ 9.84 (s, 1H), 7.56 (s, 1H), 7.22 (s, 1H), 7.12 (s, 1H), 5.05 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.74 (t, *J* = 5.6 Hz, 2H), 3.68 (s, 2H), 3.67 – 3.64 (m, 4H), 3.63 –

3.57 (m, 4H), 3.52 (t, *J* = 5.2 Hz, 2H), 3.36 (t, *J* = 5.7 Hz, 2H), 3.29 (d, *J* = 5.5 Hz, 2H), 1.41 (d, *J* = 7.5 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H) ppm; **¹³C NMR** (125 MHz, CDCl₃) δ 169.5, 167.4, 150.4, 143.7, 119.7, 117.7, 117.7, 111.4, 70.7, 70.7, 70.6, 70.3, 69.7, 61.8, 60.9, 43.3, 40.4, 29.7, 28.5, 14.3 ppm; **HRMS** (ESI) *m/z* [M + Na]⁺ found 451.2055, calcd for C₂₀H₃₂N₂O₈Na 451.2056.

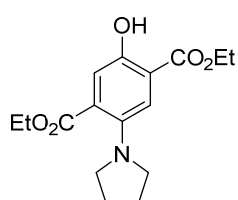
Diethyl 2-hydroxy-5-(piperidin-1-yl)terephthalate (3ay) Yellow oil (136.4 mg, 85%); **R_f** = 0.65



(Petroleum ether/EtOAc = 2:1); **¹H NMR** (500 MHz, CDCl₃) δ 9.75 (s, 1H), 7.57 (s, 1H), 7.15 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.36 (s, 1H), 2.01 (dd, *J* = 13.2, 4.5 Hz, 2H), 1.76 (dt, *J* = 13.1, 4.4 Hz, 2H), 1.67 – 1.59 (m, 1H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.31

(tdd, $J = 16.4, 9.8, 4.8$ Hz, 4H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 169.5, 167.7, 149.6, 143.1, 119.6, 117.9, 116.9, 112.2, 61.8, 60.9, 51.0, 32.9, 26.0, 24.6, 14.3, 14.2 ppm; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ found 322.1653, calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_5$ 322.1654.

Diethyl 2-hydroxy-5-(pyrrolidin-1-yl)terephthalate (3az) Yellow solid (133.5 mg, 87%); mp.



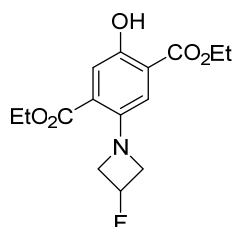
3az

88-90 °C; $R_f = 0.70$ (Petroleum ether/EtOAc = 2:1); ^1H NMR (500 MHz, CDCl_3) δ 10.05 (s, 1H), 7.25 (s, 1H), 7.18 (s, 1H), 4.42 (q, $J = 7.1$ Hz, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 3.24 – 3.14 (m, 4H), 1.99 – 1.90 (m, 4H), 1.42 (t, $J = 7.1$ Hz, 3H), 1.38 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ

169.7, 168.1, 152.3, 141.0, 126.2, 119.0, 114.9, 114.4, 61.7, 61.4, 51.2, 25.8, 14.3 ppm;

HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ found for 308.1489 calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_5$ 308.1498.

Diethyl 2-(3-fluoroazetidin-1-yl)-5-hydroxyterephthalate (3ba) Yellow solid (127.5 mg, 82%);



3ba

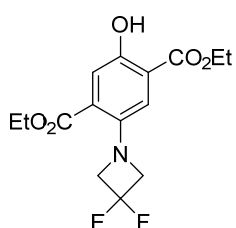
mp. 99-101 °C; $R_f = 0.35$ (Petroleum ether/EtOAc = 6:1); ^1H NMR (500 MHz, CDCl_3) δ 10.13 (s, 1H), 7.31 (s, 1H), 7.01 (s, 1H), 5.36 (dtt, $J = 57.7, 5.9, 3.9$ Hz, 1H), 4.43 (q, $J = 7.1$ Hz, 2H), 4.35 (q, $J = 7.1$ Hz, 2H), 4.26 – 4.13 (m, 2H), 3.95 – 3.82 (m, 2H), 1.43 (t, $J = 7.1$ Hz, 3H), 1.38 (t, $J = 7.1$

Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 169.3, 166.3, 153.5, 143.1, 124.3, 119.8, 115.6,

114.7, 82.4 (d, $J = 201.25$ Hz, 1C), 61.9, 61.5, 61.1, 60.9, 14.3 ppm; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$

found 312.1249, calcd for $\text{C}_{15}\text{H}_{19}\text{FNO}_5$ 312.1247.

Diethyl 2-(3,3-difluoroazetidin-1-yl)-5-hydroxyterephthalate (3ca) Yellow solid (141.4 mg,

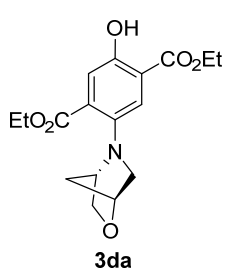


3ca

86%); mp. 93-95 °C; $R_f = 0.35$ (Petroleum ether/EtOAc = 6:1); ^1H NMR (500 MHz, CDCl_3) δ 10.18 (s, 1H), 7.37 (s, 1H), 7.02 (s, 1H), 4.44 (q, $J = 7.1$ Hz, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 4.20 (t, $J = 12.0$ Hz, 4H), 1.43 (t, $J =$

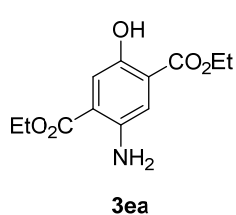
7.1 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 169.1, 165.9, 154.0, 141.7 (d, J = 2.5 Hz, 1C), 124.6, 120.2, 115.7, 115.7, 115.0, 64.6 (t, J = 25 Hz, 2C), 62.1, 61.6, 14.3 ppm; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ found 330.1154, calcd for $\text{C}_{15}\text{H}_{18}\text{F}_2\text{NO}_5$ 330.1153.

Diethyl 2-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-5-hydroxyterephthalate (3da) Yellow oil



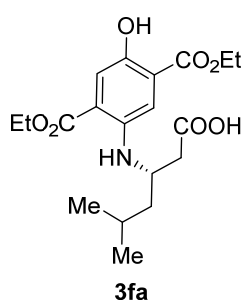
(147.4 mg, 88%); R_f = 0.55 (Petroleum ether/EtOAc = 1:1); ^1H NMR (500 MHz, CDCl_3) δ 10.11 (s, 1H), 7.19 (d, J = 11.5 Hz, 2H), 4.54 (s, 1H), 4.42 (qd, J = 7.2, 3.0 Hz, 2H), 4.34 (p, J = 6.9 Hz, 2H), 4.29 (s, 1H), 4.02 (d, J = 7.7 Hz, 1H), 3.84 (d, J = 7.7 Hz, 1H), 3.56 (d, J = 9.5 Hz, 1H), 2.80 (d, J = 9.5 Hz, 1H), 2.05 (dd, J = 9.7, 2.3 Hz, 1H), 1.92 (d, J = 9.8 Hz, 1H), 1.41 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 169.4, 167.6, 153.2, 139.3, 127.6, 119.8, 115.9, 114.8, 76.6, 70.8, 61.9, 61.5, 60.5, 60.0, 36.7, 14.27, 14.25 ppm; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ found 336.1442, calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_6$ 336.1447.

Diethyl 2-amino-5-hydroxyterephthalate (3ea) Yellow solid; mp. 102-105 °C; R_f = 0.80



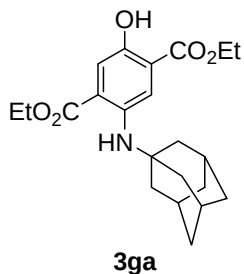
(Petroleum ether/EtOAc = 2:1); ^1H NMR (500 MHz, CDCl_3) δ 9.85 (s, 1H), 7.53 (s, 1H), 7.22 (s, 1H), 5.28 (s, 2H), 4.41 (q, J = 7.1 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 169.2, 167.2, 151.4, 142.5, 118.9, 118.2, 117.7, 117.2, 61.9, 61.1, 14.3, 14.2 ppm; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ found 254.1035, calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_5$ 254.1028.

(S)-3-((2,5-bis(ethoxycarbonyl)-4-hydroxyphenyl)amino)-5-methylhexanoic acid (3fa) Yellow

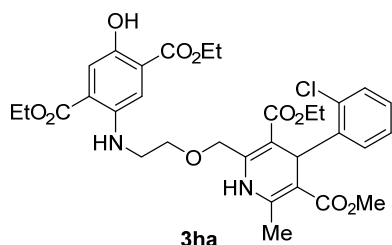


solid (125.7 mg, 66%); **mp.** 84-85 °C; **R_f** = 0.55 (Petroleum ether/EtOAc = 2:1); **¹H NMR** (500 MHz, CDCl₃) δ 9.85 (s, 1H), 7.57 (s, 1H), 7.15 (s, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.22 (dd, *J* = 12.9, 4.9 Hz, 1H), 3.11 (dd, *J* = 12.9, 7.2 Hz, 1H), 2.43 (dt, *J* = 15.8, 7.9 Hz, 1H), 2.39 – 2.32 (m, 1H), 1.72 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 6.9 Hz, 1H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H) ppm; **¹³C NMR** (125 MHz, CDCl₃) δ 178.2, 169.5, 167.6, 150.3, 143.7, 119.7, 117.8, 117.3, 111.3, 61.8, 61.0, 47.2, 41.9, 37.6, 32.4, 25.4, 22.9, 22.8, 14.2 ppm; **HRMS** (ESI) *m/z* [M + H]⁺ found 382.1868, calcd for C₁₉H₂₈NO₇ 382.1866.

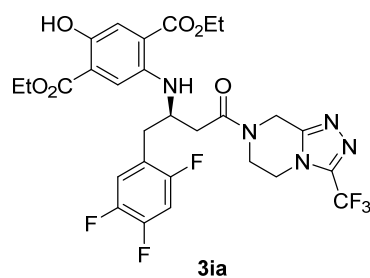
Diethyl 2-(((3s,5s,7s)-adamantan-1-yl)amino)-5-hydroxyterephthalate (3ga) Yellow solid



(152.8 mg, 79%); **mp.** 145-147 °C; **R_f** = 0.70 (Petroleum ether/EtOAc = 2:1); **¹H NMR** (500 MHz, CDCl₃) δ 9.75 (s, 1H), 7.55 (d, *J* = 4.0 Hz, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.23 – 2.17 (m, 1H), 1.85 – 1.80 (m, 2H), 1.65 (d, *J* = 11.9 Hz, 2H), 1.56 (s, 2H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.39 – 1.36 (m, 3H), 1.20 – 1.16 (m, 2H), 0.87 (s, 6H) ppm; **¹³C NMR** (125 MHz, CDCl₃) δ 169.4, 167.8, 150.4, 142.2, 119.8, 119.5, 117.5, 116.9, 61.7, 61.0, 53.8, 50.9, 49.2, 42.9, 41.3, 32.7, 30.4, 30.3, 14.3, 14.1 ppm; **HRMS** (ESI) *m/z* [M + H]⁺ found 388.2134, calcd for C₂₂H₃₀NO₅ 388.2124.

3-ethyl**5-methyl****2-((2-((2,5-bis(ethoxycarbonyl)-4-hydroxyphenyl)amino)ethoxy)methyl)-4-(2-chlorophenyl)****-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (3ha)** Yellow solid (241.5 mg, 75%); mp.145-147 °C; R_f = 0.6 (Petroleum ether/EtOAc = 2:1); ^1H **NMR** (500 MHz, CDCl_3) δ 9.90 (s, 1H), 7.62 (s, 1H), 7.51(s, 1H), 7.38 (dd, J = 7.8, 1.7 Hz, 1H), 7.21 (dd, J = 12.0,8.2 Hz, 3H), 7.11 (t, J = 7.5 Hz, 1H), 7.03 (t, J = 7.6 Hz,1H), 5.40 (s, 1H), 4.80 (q, J = 16.0 Hz, 2H), 4.44 (q, J = 7.1 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 4.04(tdd, J = 10.6, 7.3, 3.7 Hz, 2H), 3.85 (t, J = 5.1 Hz, 2H), 3.60 (s, 3H), 3.45 (t, J = 5.2 Hz, 2H), 2.30(s, 3H), 1.43 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H) ppm; ^{13}C **NMR**(125 MHz, CDCl_3) δ 169.4, 168.1, 167.8, 167.2, 150.9, 145.9, 145.3, 144.3, 143.7, 132.4, 131.5,

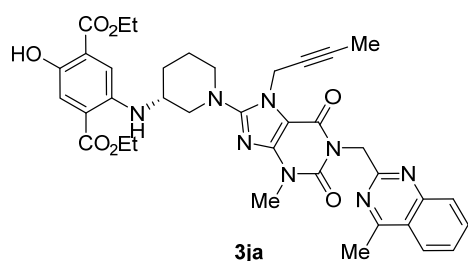
129.3, 127.4, 126.9, 119.9, 117.9, 117.8, 111.7, 103.9, 101.5, 69.8, 68.0, 61.9, 61.2, 59.9,

50.8, 43.1, 37.2, 19.2, 14.3, 14.3, 14.2 ppm; **HRMS** (ESI) m/z $[\text{M} + \text{H}]^+$ found 645.2215, calcdfor $\text{C}_{32}\text{H}_{38}\text{ClN}_2\text{O}_{10}$ 645.1942.**Diethyl****(R)-2-hydroxy-5-((4-oxo-4-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8****H)-yl)-1-(2,4,5-****trifluorophenyl)butan-2-yl)amino)terephthalate (3ia)** Yellow solid (221.8 mg, 69%); mp.75-76 °C; R_f = 0.60 (Petroleum ether/EtOAc = 1:5); ^1H **NMR** (500 MHz, CDCl_3) δ 9.87 (d, J = 12.9 Hz, 1H), 7.54 (d, J = 18.3 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 7.23 (s, 1H), 7.04(q, J = 9.1 Hz, 1H), 6.84 (q, J = 8.7 Hz, 1H), 4.95 (s, 2H),

4.43 (qt, $J = 7.3, 3.6$ Hz, 2H), 4.29 (s, 1H), 4.28 – 4.20 (m, 2H), 4.20 – 4.07 (m, 2H), 4.01 (q, $J = 16.5, 12.4$ Hz, 2H), 3.01 (dd, $J = 14.0, 6.3$ Hz, 1H), 2.89 (dd, $J = 14.0, 6.8$ Hz, 1H), 2.68 (tt, $J = 16.5, 8.8$ Hz, 2H), 1.45 (t, $J = 7.1$ Hz, 3H), 1.36 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 169.9, 169.2, 167.5, 157.2 (1C, d, $J = 10$ Hz), 155.26 (1C, d, $J = 8.8$ Hz), 151.0, 150.0 (1C, t, $J = 12.5$ Hz), 149.5, 148.0 (1C, t, $J = 13.8$ Hz), 145.8 (1C, d, $J = 12.5$ Hz), 143.6 (1C, t, $J = 38.8$ Hz), 141.9, 121.1 (1C, d, $J = 18.8$ Hz), 120.1, 119.5, 119.4, 119.3, 117.9, 112.0, 105.5 (1C, q, $J = 28.8, 20.0$ Hz), 62.0, 61.3, 50.8, 43.2, 43.0, 38.3, 37.2, 33.4, 31.6, 22.7, 14.2, 14.1 ppm; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ found 644.1930, calcd for $\text{C}_{28}\text{H}_{28}\text{F}_2\text{N}_7\text{O}_9$ 644.1917.

Diethyl

(R)-2-((1-(7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)piperidin-3-yl)amino)-5-hydroxyterephthalate (3ja) Yellow solid



(272.6 mg, 77%); mp. 93-95 °C; $R_f = 0.80$

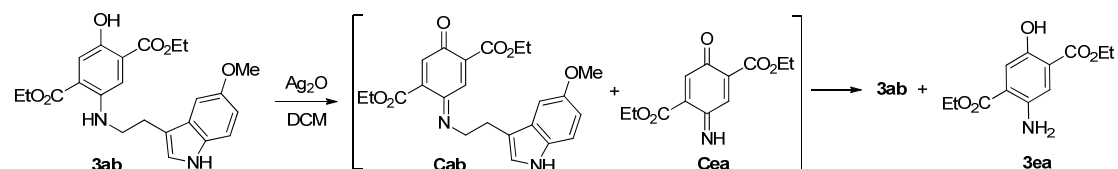
(DCM/MeOH = 10:1); ^1H NMR (500 MHz, CDCl_3) δ

9.84 (s, 1H), 8.01 (d, $J = 8.3$ Hz, 1H), 7.87 (d, $J = 8.5$ Hz, 1H), 7.75 (t, $J = 7.6$ Hz, 1H), 7.61 (s, 1H), 7.56 –

7.49 (m, 2H), 5.56 (d, $J = 3.6$ Hz, 2H), 4.95 (qd, $J = 17.4, 2.5$ Hz, 2H), 4.43 (qd, $J = 7.1, 5.2$ Hz, 2H), 4.31 (q, $J = 7.1$ Hz, 2H), 3.85 (s, 1H), 3.81 – 3.71 (m, 1H), 3.56 (s, 3H), 3.49 – 3.42 (m, 1H), 3.38 (dd, $J = 10.8, 7.2$ Hz, 1H), 3.15 (dd, $J = 12.4, 7.0$ Hz, 1H), 2.88 (s, 3H), 2.07 – 1.95 (m, 2H), 1.86 – 1.71 (m, 2H), 1.42 (d, $J = 7.1$ Hz, 3H), 1.39 – 1.36 (m, 3H), 0.88 (t, $J = 6.6$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 169.4, 168.5, 167.6, 161.2, 156.0, 154.5, 151.9, 150.4, 150.1, 147.8, 142.3, 133.2, 129.0, 126.7, 124.9, 123.2, 120.0, 118.0, 117.7, 112.0, 104.8, 81.3, 73.3, 62.0, 61.1, 55.5, 50.9, 48.1, 46.4, 35.5, 29.8, 29.5, 22.9, 21.8, 14.3, 14.2, 3.6 ppm; HRMS (ESI)

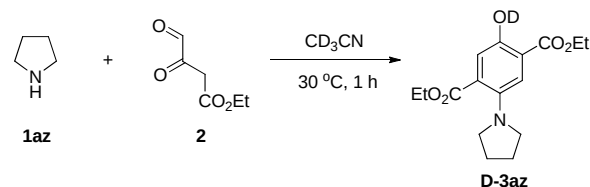
m/z $[M + H]^+$ found 709.3102, calcd for $C_{37}H_{41}N_8O_7$ 709.3098.

4 Experimental Procedure for Oxidation of compound **3ab**



To a solution of compound **3ab** (85.2 mg, 0.2 mmol) in 10 mL of dry DCM was added Ag_2O (115 mg, 0.5 mmol) and $MgSO_4$ (60 mg, 0.5 mmol). The reaction mixture was stirred at 25 °C for 2 h. TLC then showed complete consumption of the compound **3ab**. The mixture was filtered and the filtrate was taken in 30 mL of EtOAc. The solvent was washed with water, brine, dried, and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether/EtOAc to give the *p*-Aminophenols **3ab** and **3ea**.

5 Experimental Procedure for Synthesis of D-3az in CD_3CN

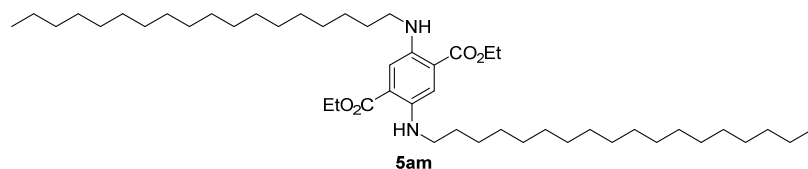


To a solution of ethyl β,γ -dioxobutanoate **2** (43.2 mg, 0.3 mmol) in 1.0 mL of CD_3CN was added tetrahydropyrrole (14.2 mg, 0.2 mmol). The reaction was stirred for 1 hour at 30 °C. In situ 1H NMR data indicated that the compound **D-3az** was formed.

6 Experimental Procedures for synthesis of *p*-Phenylenediamines

To a solution of ethyl β,γ -dioxobutanoate **2** (144 mg, 1.0 mmol) in MeCN (5.0 mL) was added amine (3.0 mmol). The reaction was stirred for 1 hour at 70 °C. The reaction mixture was concentrated under reduced pressure, the solvent was collected, and the residue was purified by flash column chromatography eluting with petroleum ether/EtOAc to give the *p*-phenylenediamine product. The unreacted amine was also obtained.

Diethyl 2,5-bis(octadecylamino)terephthalate (5am) Yellow solid (151.2 mg, 40%); mp.

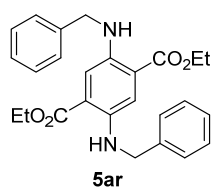


145-146 °C; R_f = 0.7

(Petroleum ether/EtOAc = 10:1);

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.29 (s, 2H), 4.35 (q, J = 7.1 Hz, 4H), 3.14 (t, J = 7.0 Hz, 4H), 1.67 (t, J = 7.4 Hz, 4H), 1.40 (t, J = 7.2 Hz, 6H), 1.26 (s, 58H), 0.88 (t, J = 6.8 Hz, 6H) ppm; $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 168.1, 141.4, 116.8, 114.1, 60.7, 43.8, 32.0, 29.8, 29.7, 29.7, 29.7, 29.5, 29.4, 29.4, 27.3, 22.7, 14.4, 14.2 ppm; **HRMS** (ESI) m/z $[\text{M} + \text{Na}]^+$ found 779.6634, calcd for $\text{C}_{48}\text{H}_{88}\text{N}_2\text{O}_4\text{Na}$ 779.6642.

Diethyl 2,5-bis(benzylamino)terephthalate (5ar) Yellow solid (99.4 mg, 46%); mp. 145-146

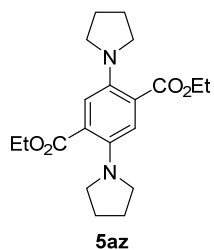


°C; R_f = 0.55 (Petroleum ether/EtOAc = 6:1); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ

7.38 (d, J = 7.5 Hz, 4H), 7.35 – 7.29 (m, 6H), 7.25 (d, J = 7.2 Hz, 4H), 4.39 (s, 4H), 4.28 (q, J = 7.1 Hz, 4H), 1.33 (t, J = 7.1 Hz, 6H) ppm; $^{13}\text{C NMR}$

(125 MHz, CDCl_3) δ 168.0, 141.1, 139.6, 128.6, 127.5, 127.1, 117.0, 114.6, 60.7, 48.0, 29.8, 22.7, 14.2, 14.2 ppm; **HRMS** (ESI) m/z $[\text{M} + \text{H}]^+$ found 433.2135, calcd for $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_4$ 433.2127.

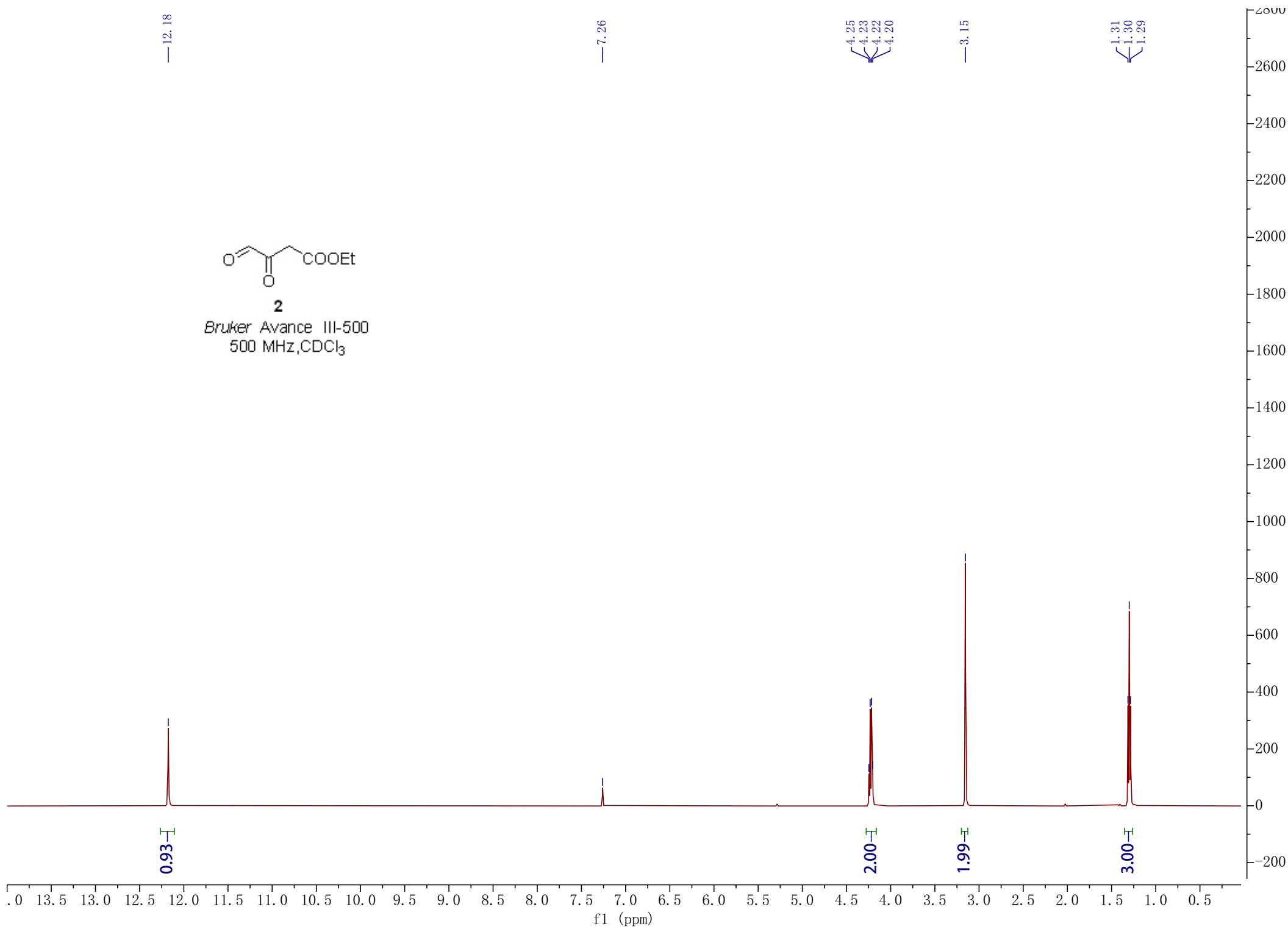
Diethyl 2,5-di(pyrrolidin-1-yl)terephthalate (5az) Yellow solid (88.2 mg, 49%); **mp.**

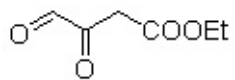


133-136°C; R_f = 0.55 (Petroleum ether/EtOAc = 2:1); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.06 (s, 2H), 4.36 (q, J = 7.1 Hz, 4H), 3.23 – 3.13 (m, 8H), 1.96 – 1.86 (m, 8H), 1.38 (t, J = 7.1 Hz, 6H) ppm; $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 169.0, 140.0, 122.5, 116.7, 61.1, 51.2, 25.7, 14.4 ppm; **HRMS** (ESI) m/z

$[\text{M} + \text{H}]^+$ found 361.2127, calcd for $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_5$ 361.1975.

7 ^1H and ^{13}C NMR Spectra of *p*-Aminophenols and *p*-Phenylenediamines





2

Bruker Avance III-500
125 MHz, CDCl₃

171.32
168.47

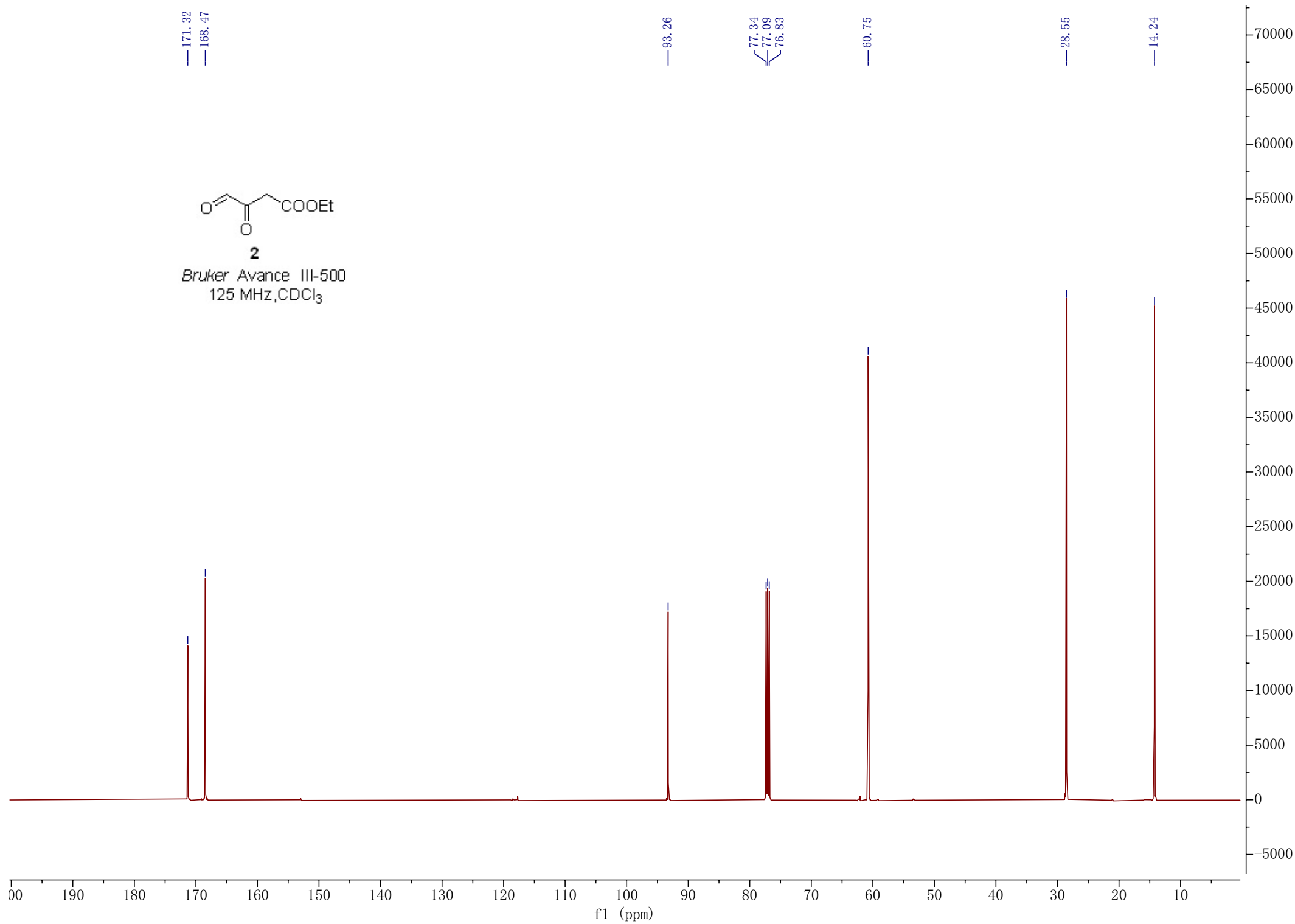
93.26

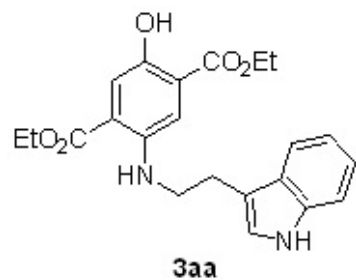
77.34
77.09
76.83

60.75

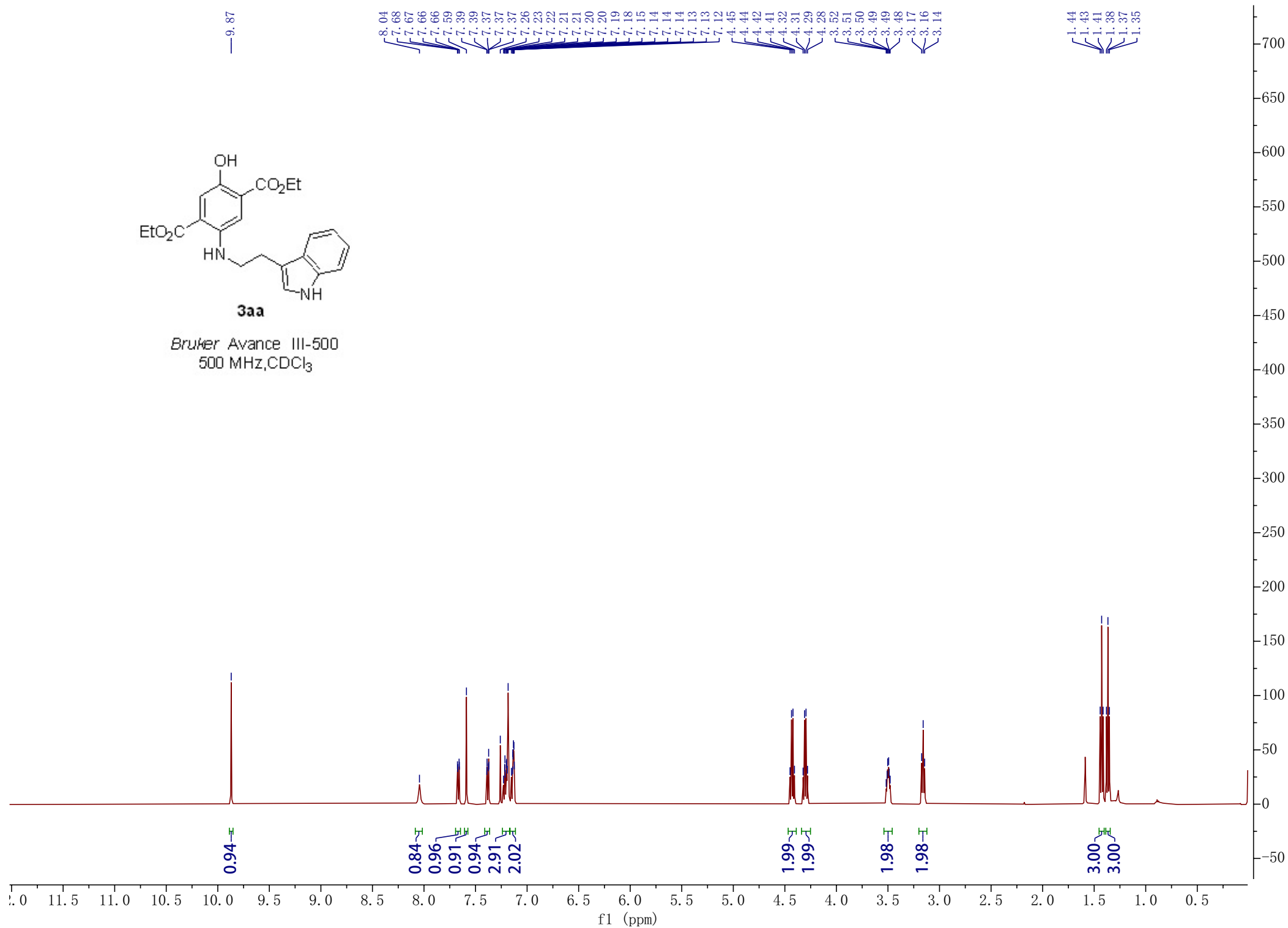
28.55

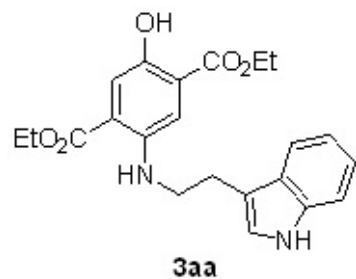
14.24



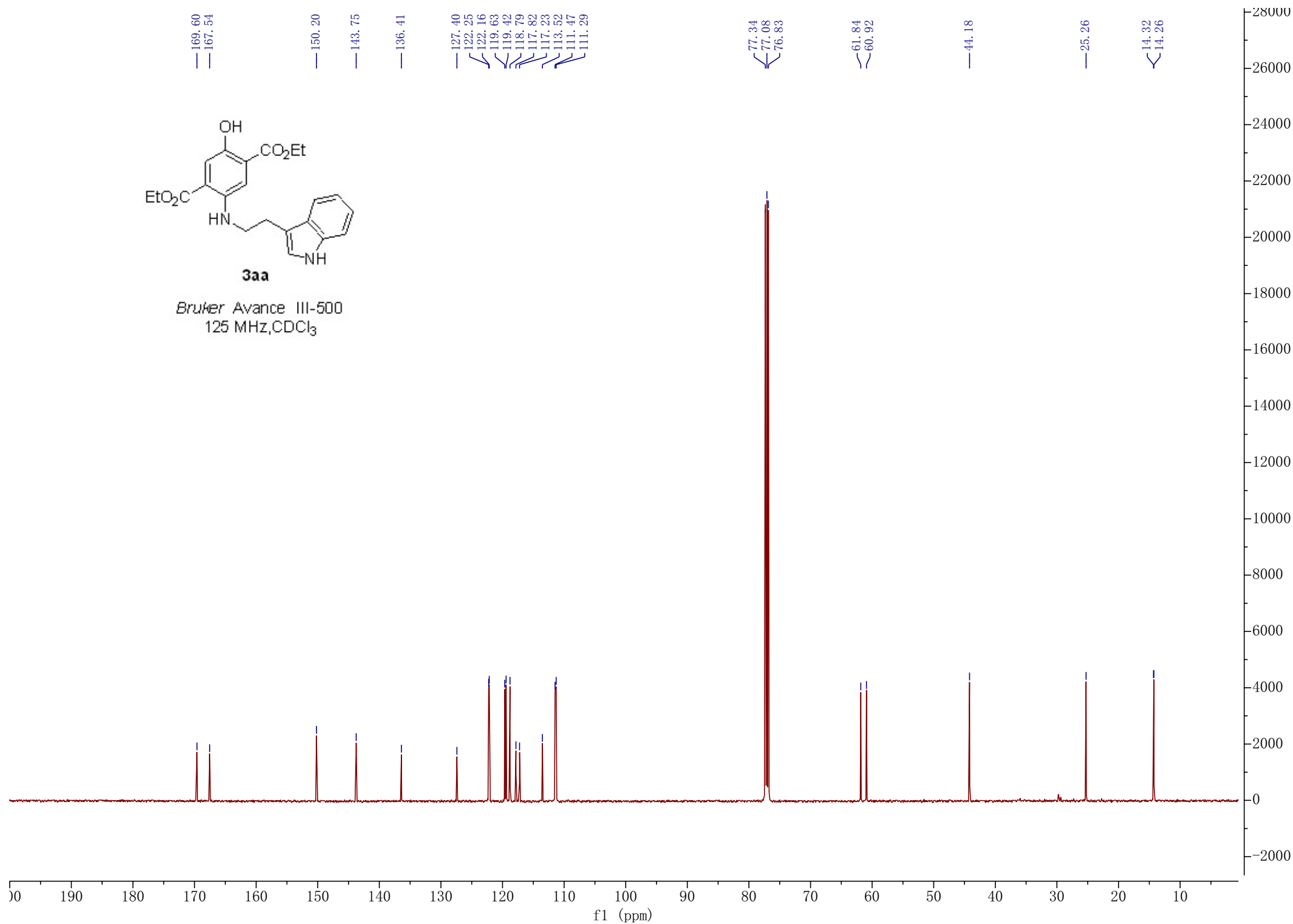


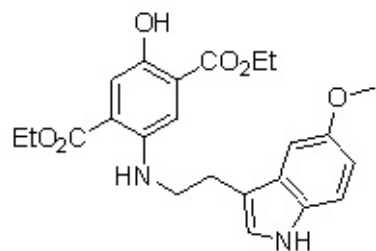
Bruker Avance III-500
500 MHz, CDCl₃





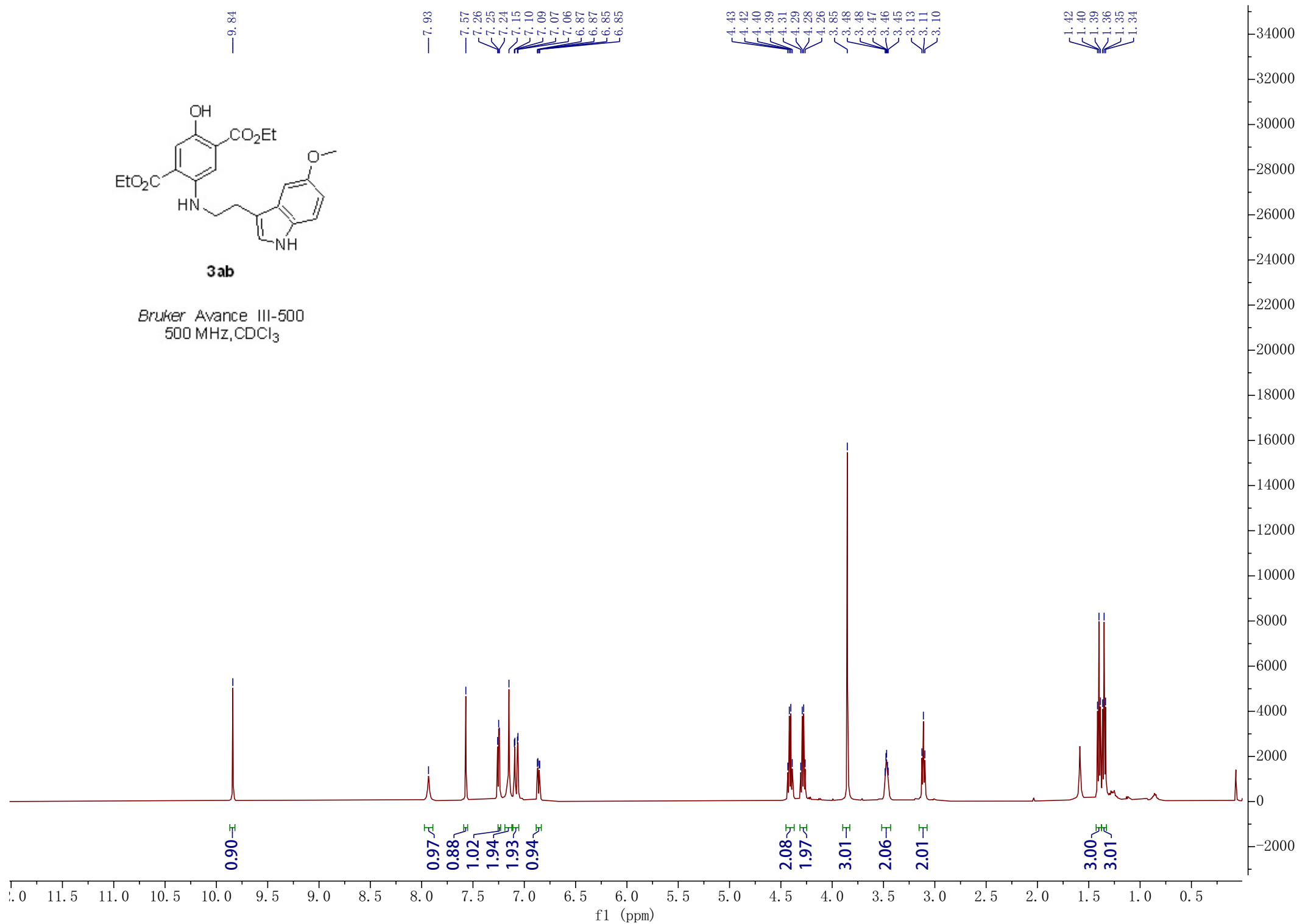
Brüker Avance III-500
125 MHz, CDCl₃

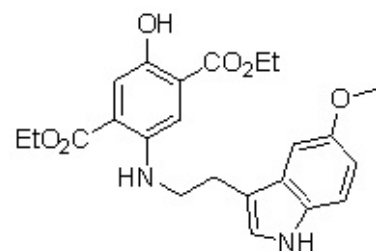




3ab

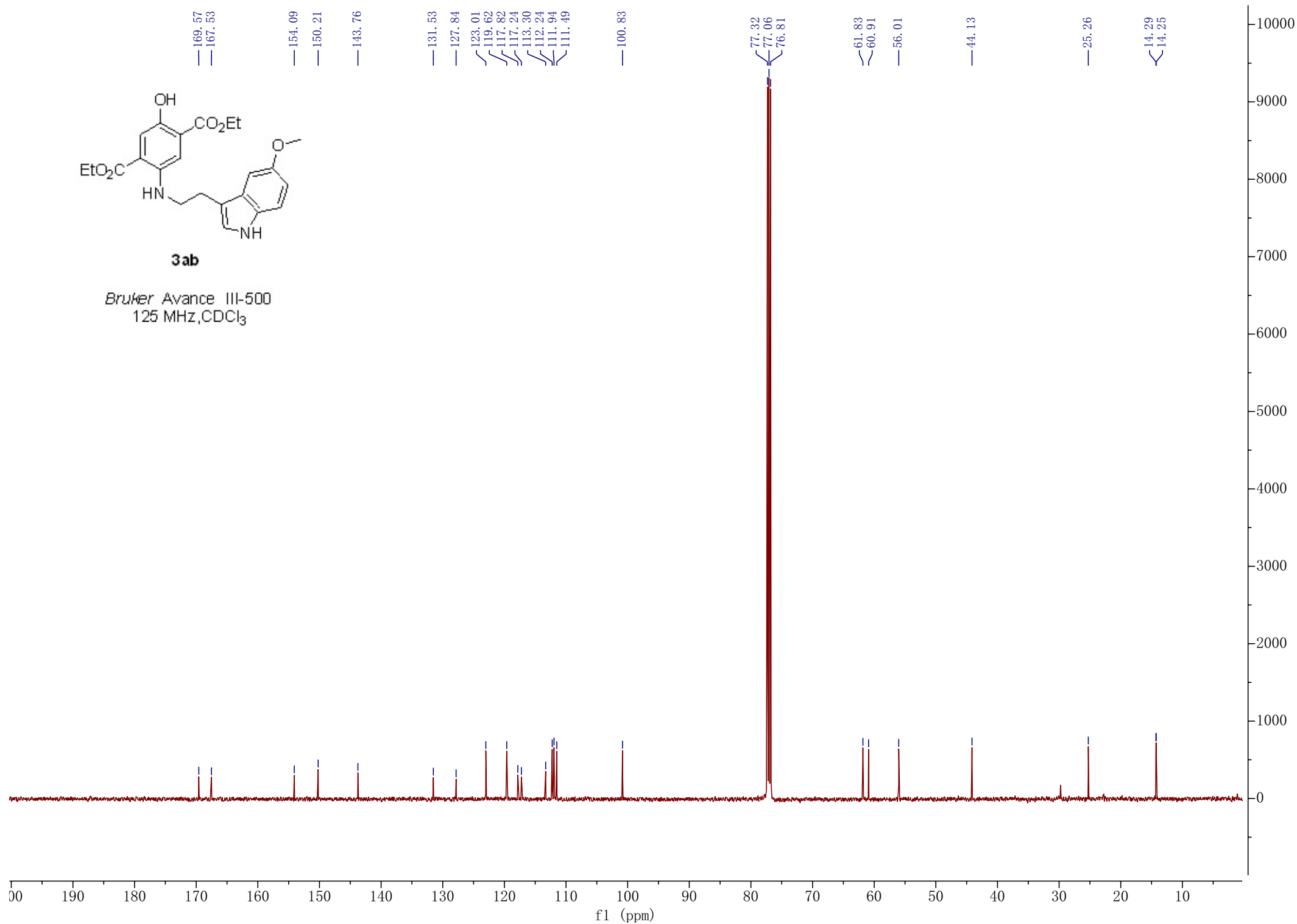
Bruker Avance III-500
500 MHz, CDCl₃

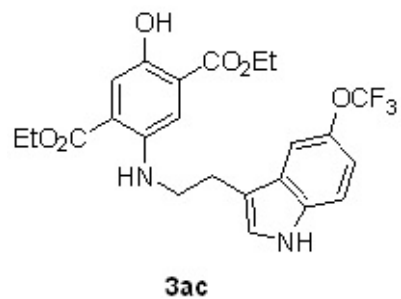




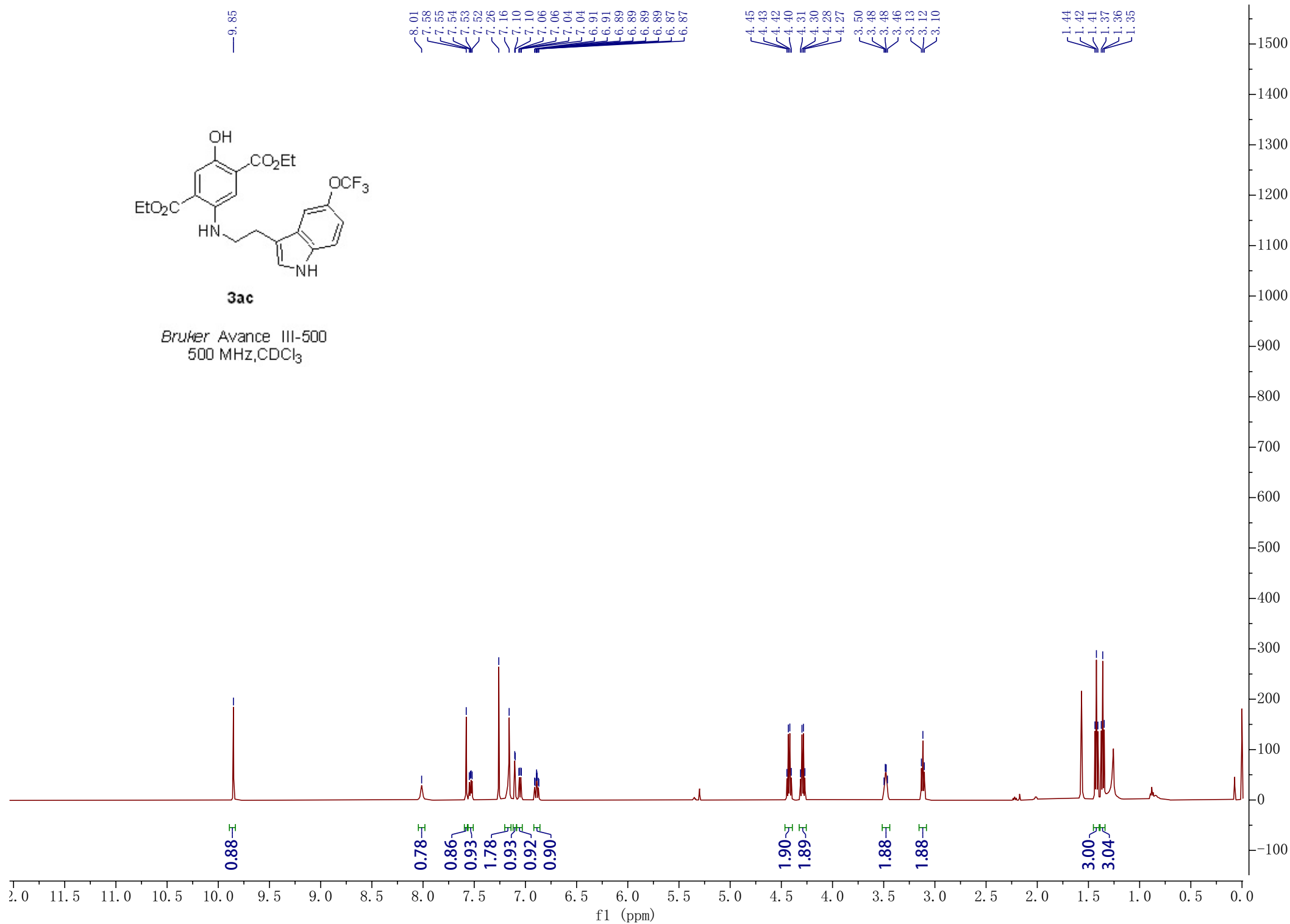
3ab

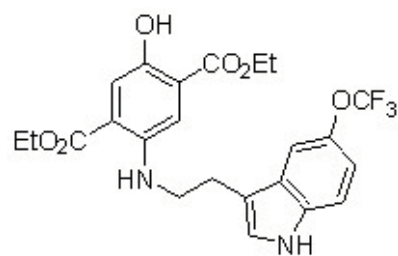
Bruker Avance III-500
125 MHz, CDCl₃





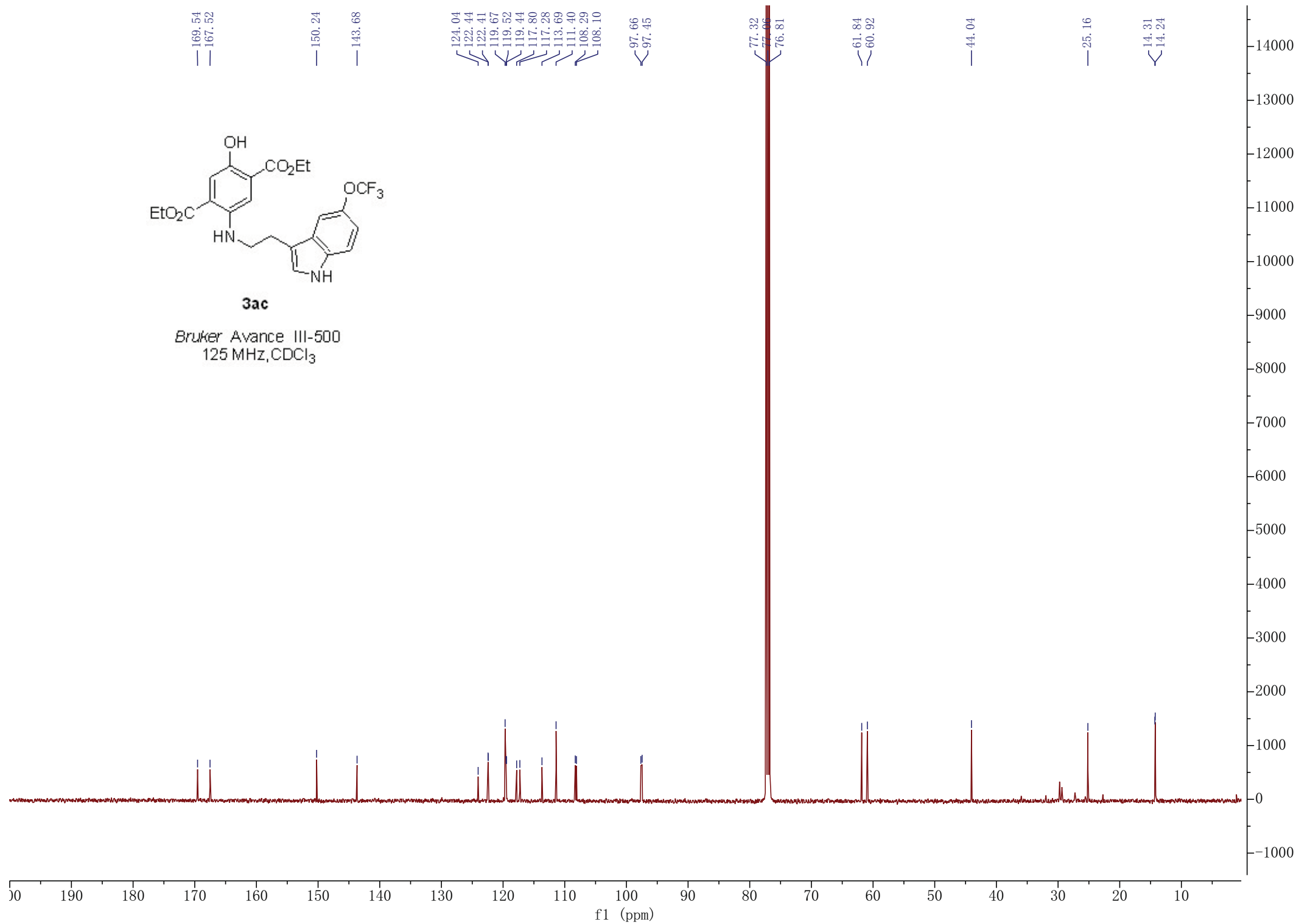
Bruker Avance III-500
500 MHz, CDCl₃

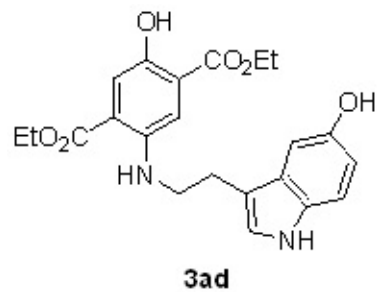




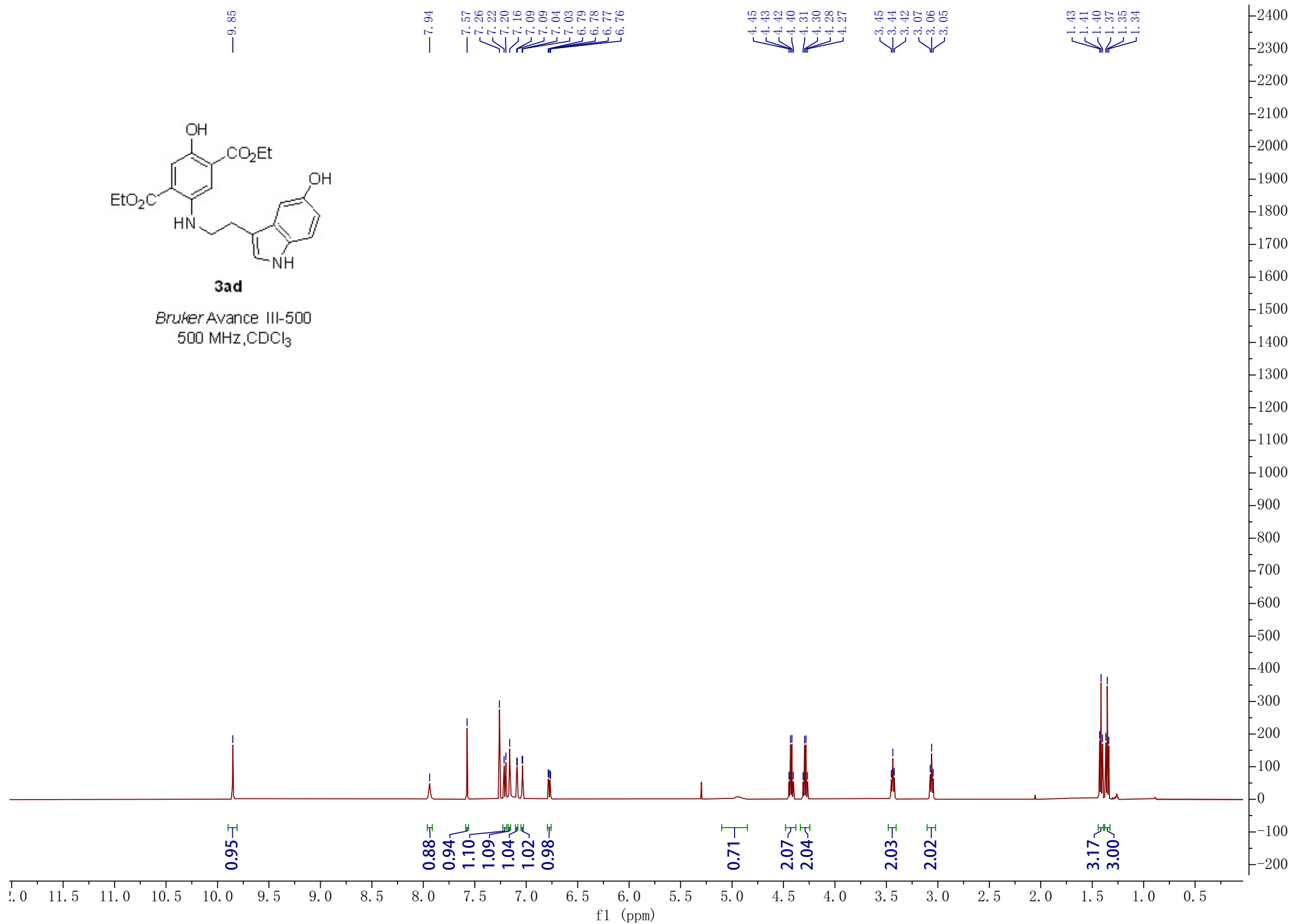
3ac

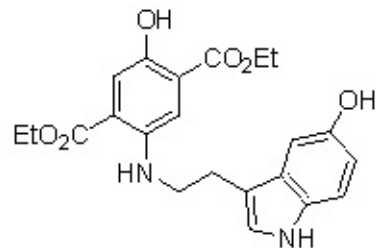
Bruker Avance III-500
125 MHz, CDCl₃





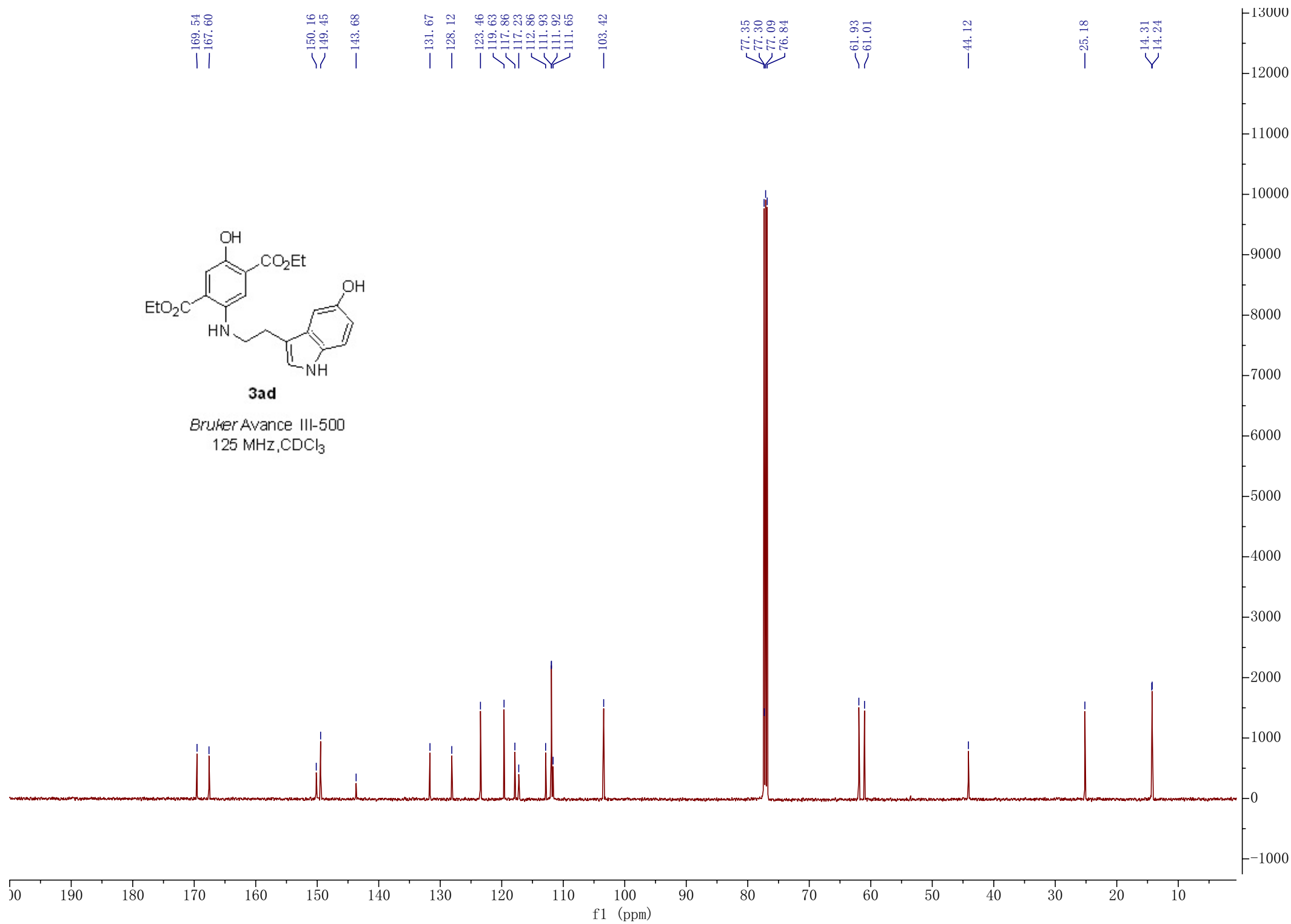
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500 MHz, CDCl₃

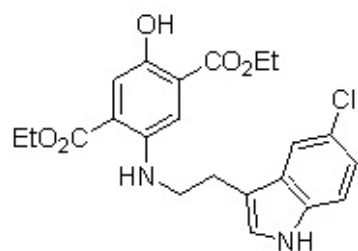




3ad

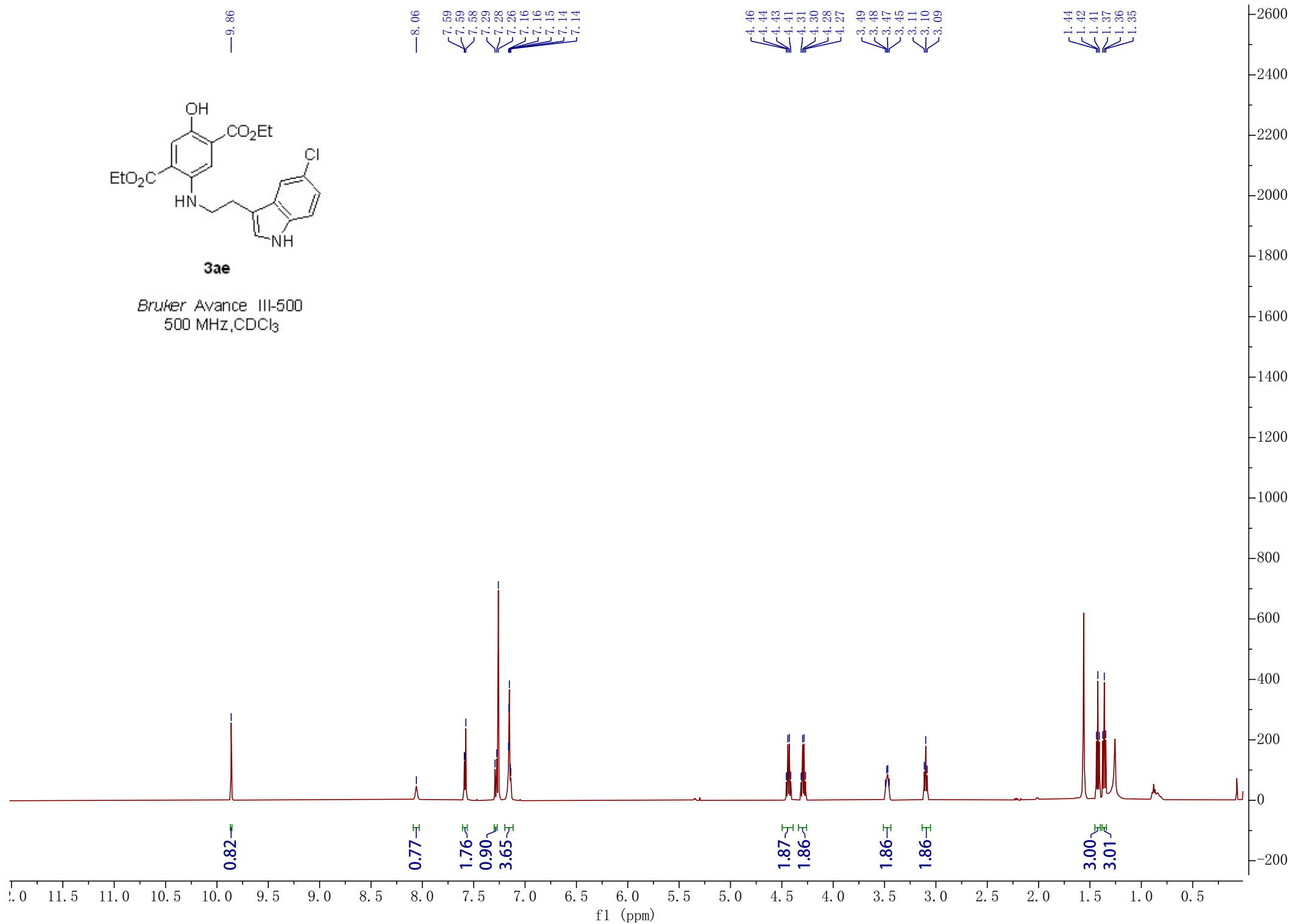
Bruker Avance III-500
125 MHz, CDCl₃

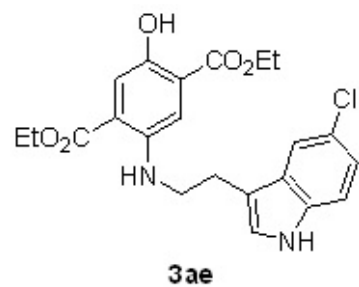




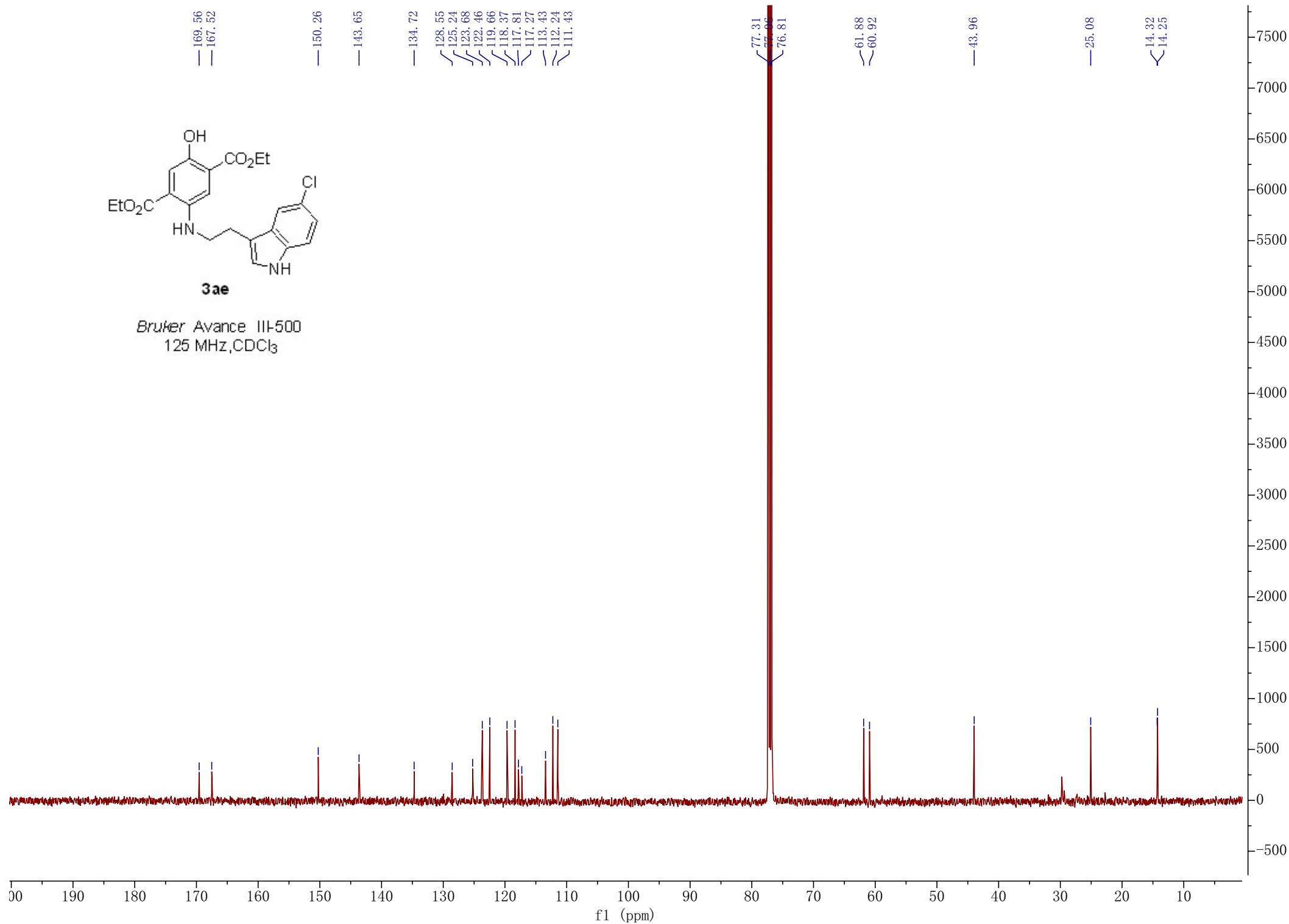
3ae

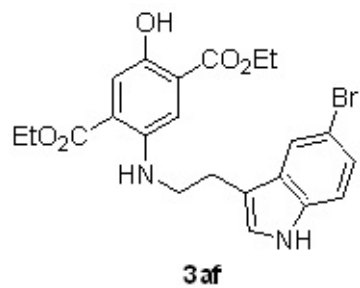
Bruker Avance III-500
500 MHz, CDCl₃



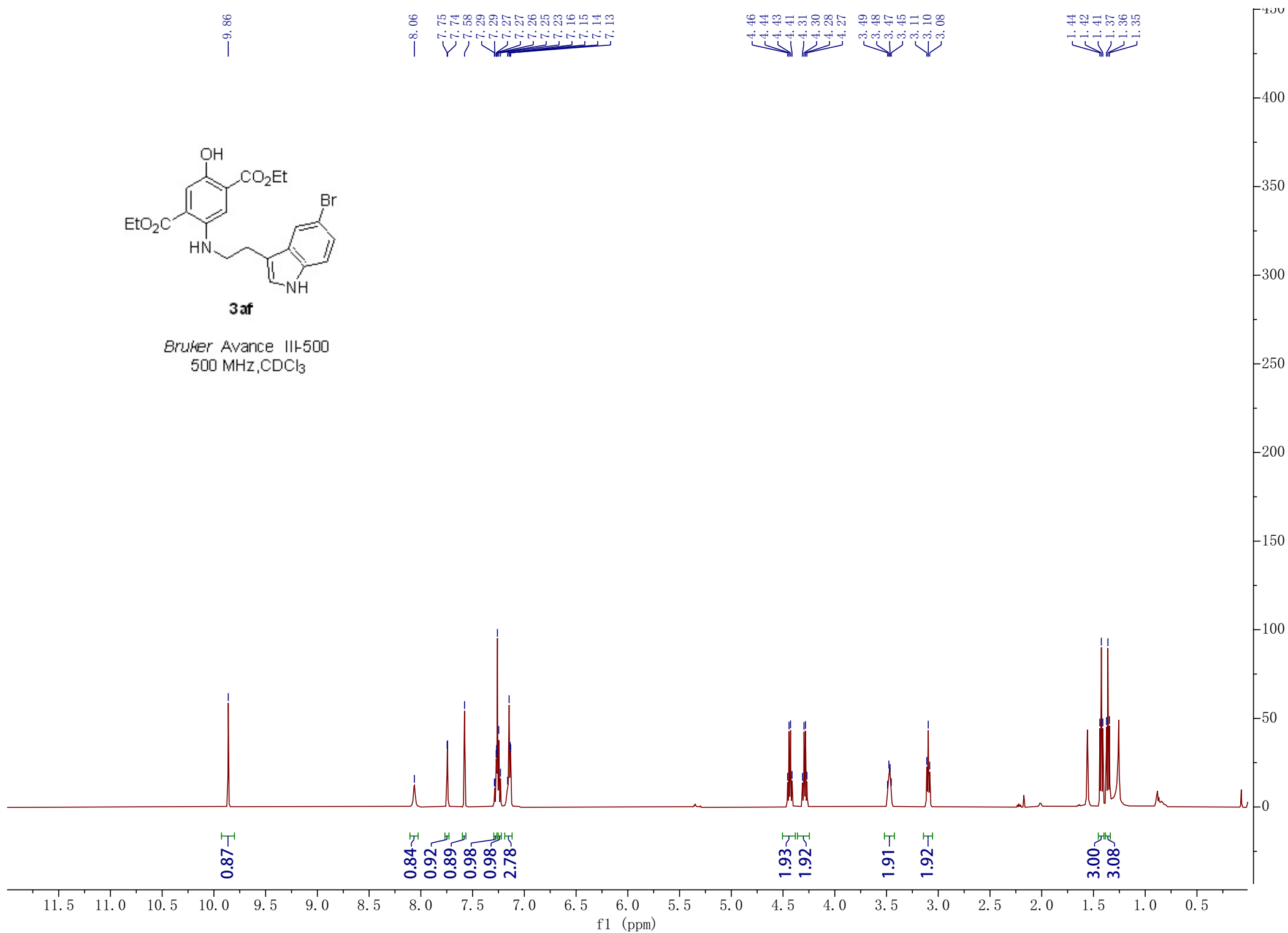


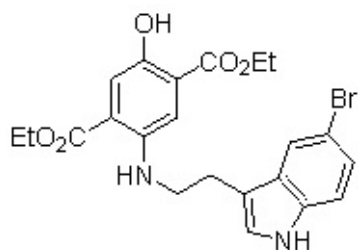
Bruker Avance III-500
125 MHz, CDCl₃





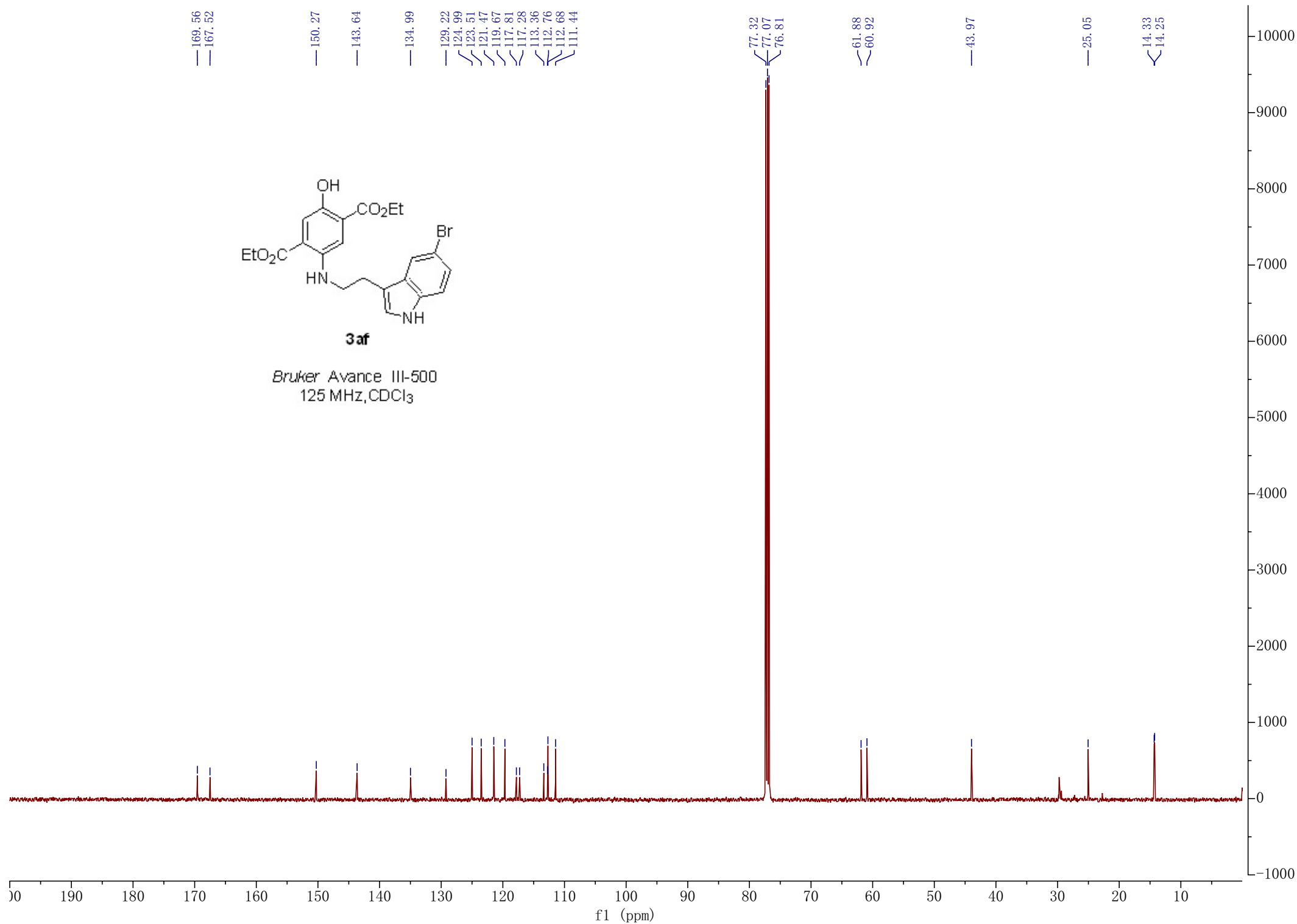
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500 MHz, CDCl₃

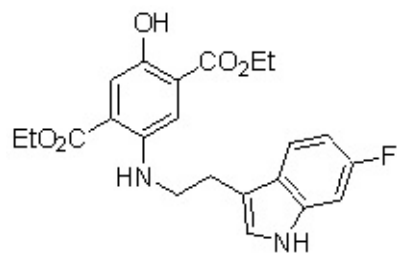




3af

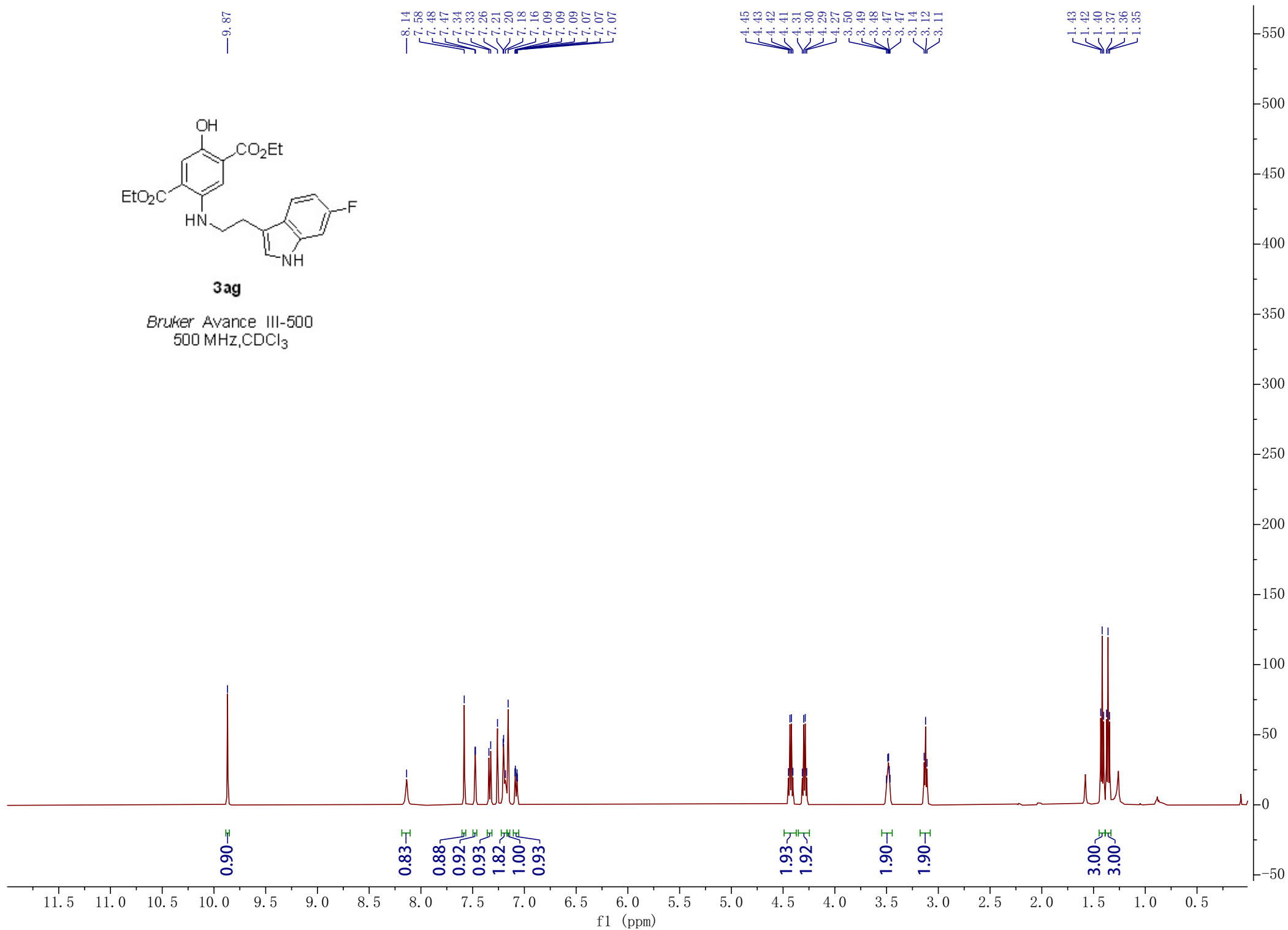
Bruker Avance III-500
125 MHz, CDCl₃

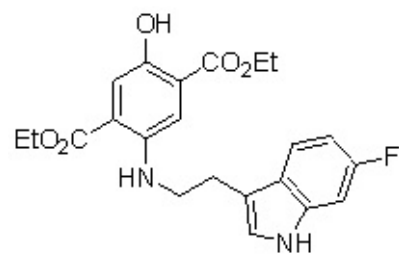




3ag

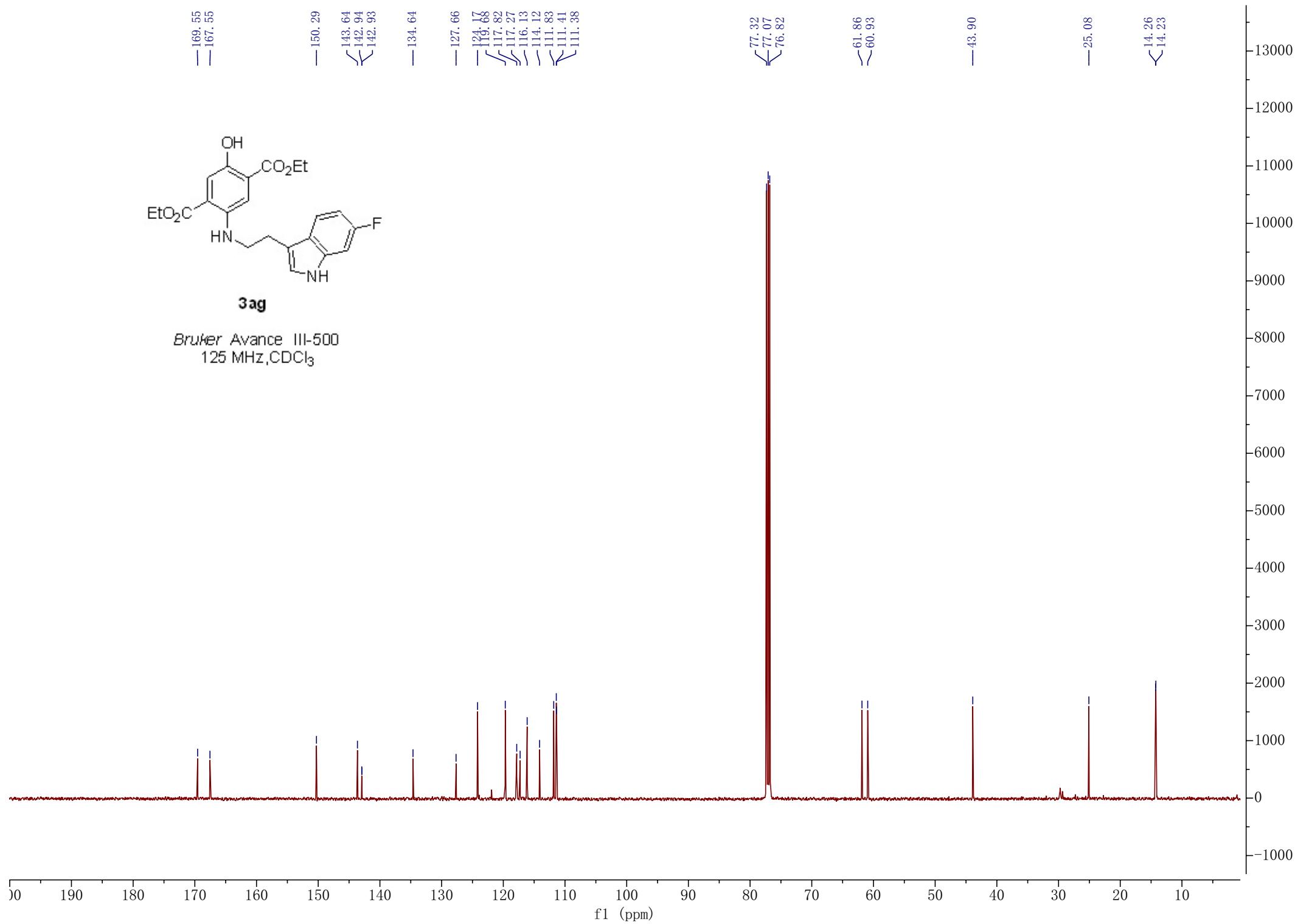
Bruker Avance III-500
500 MHz, CDCl₃

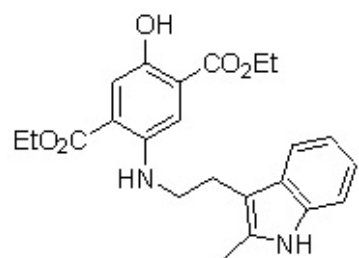




3ag

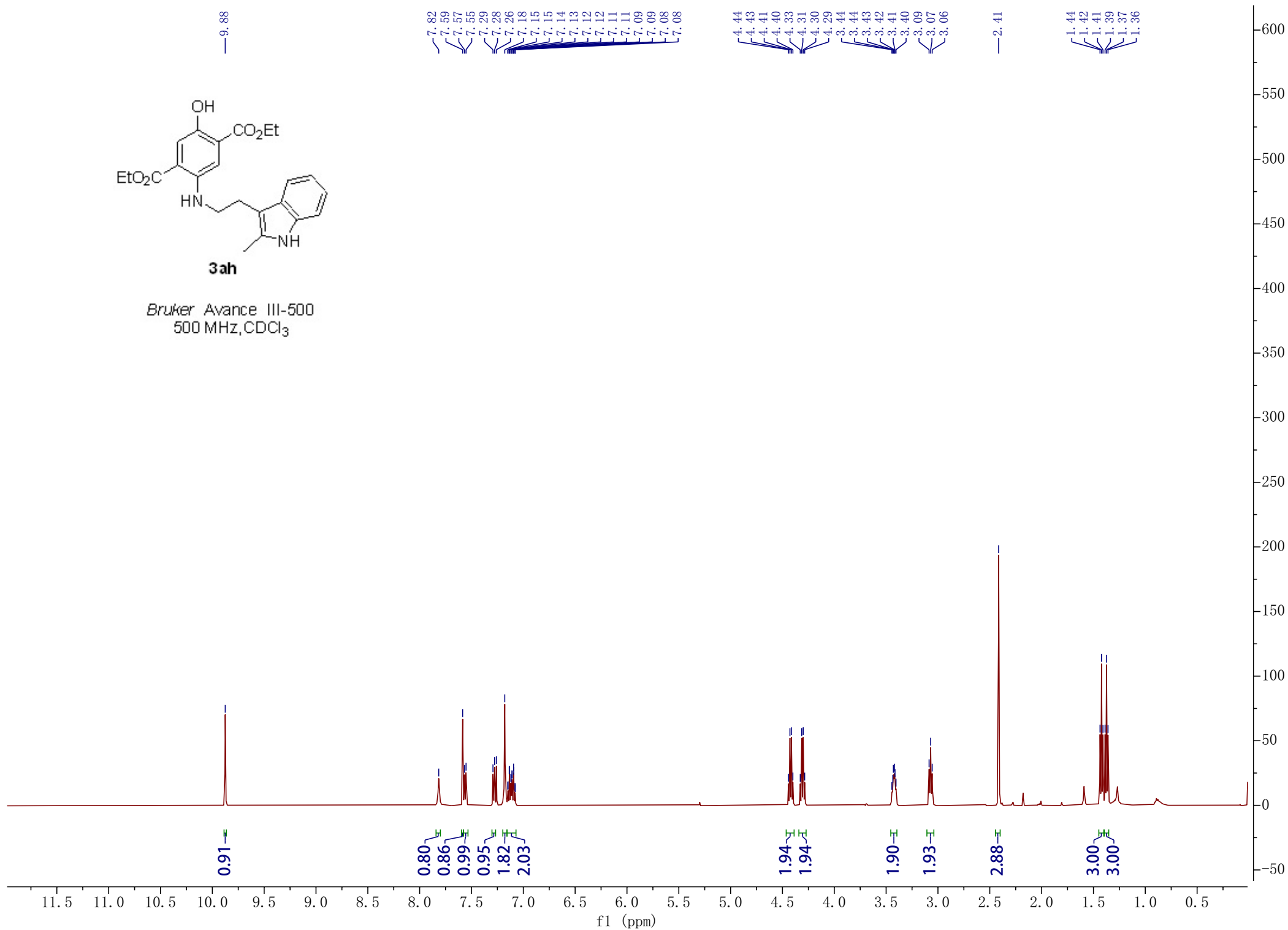
Bruker Avance III-500
125 MHz, CDCl₃

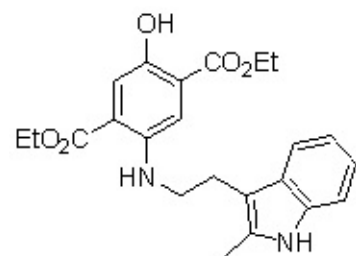




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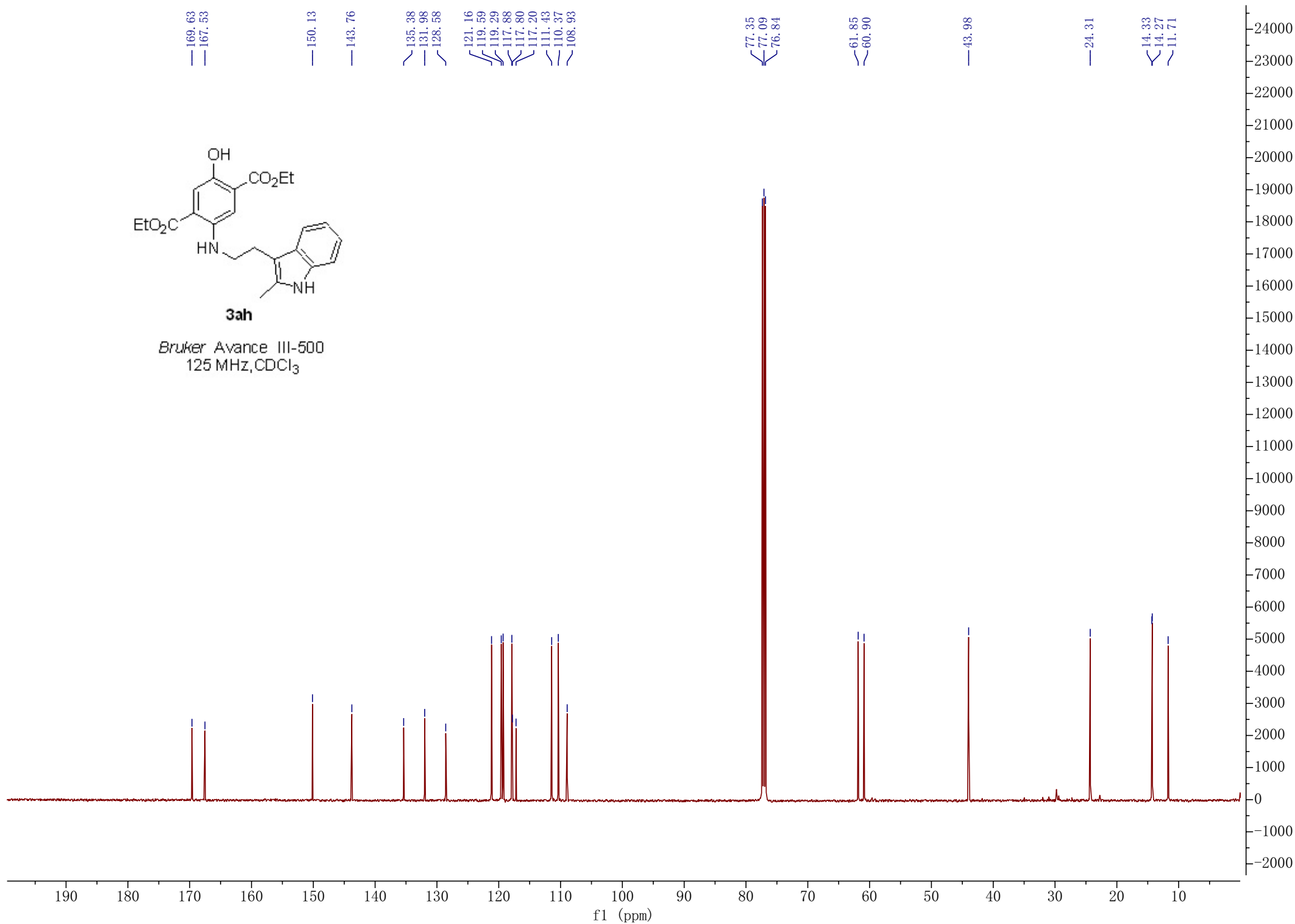
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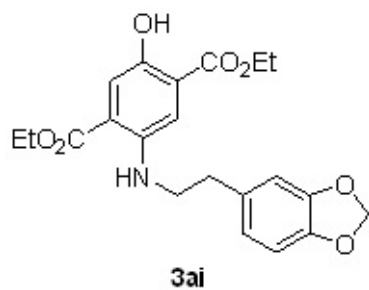




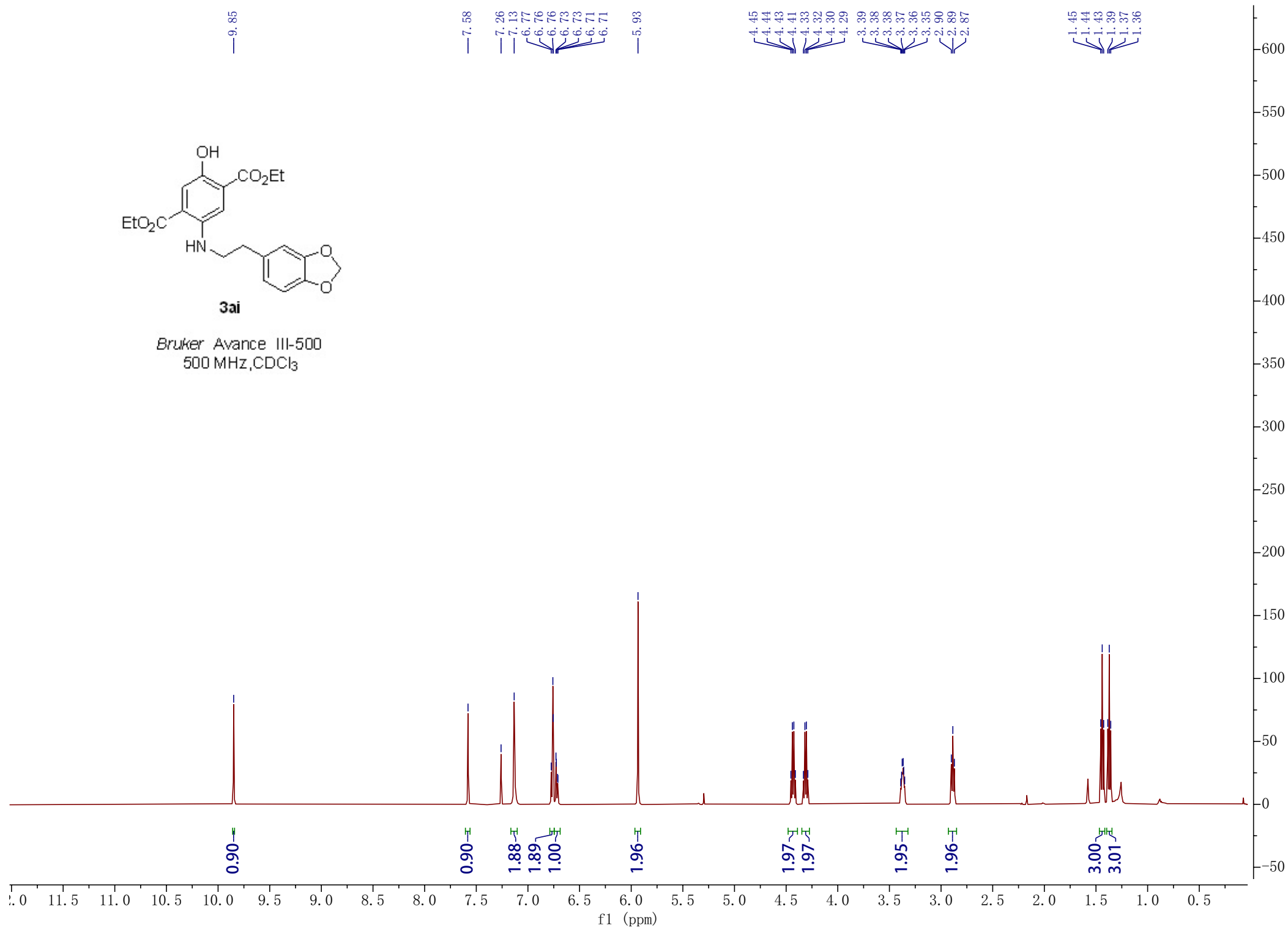
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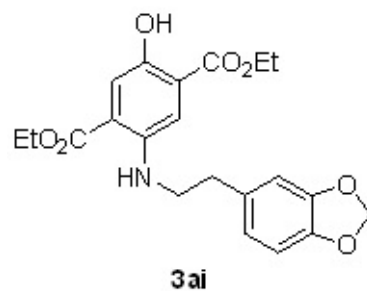
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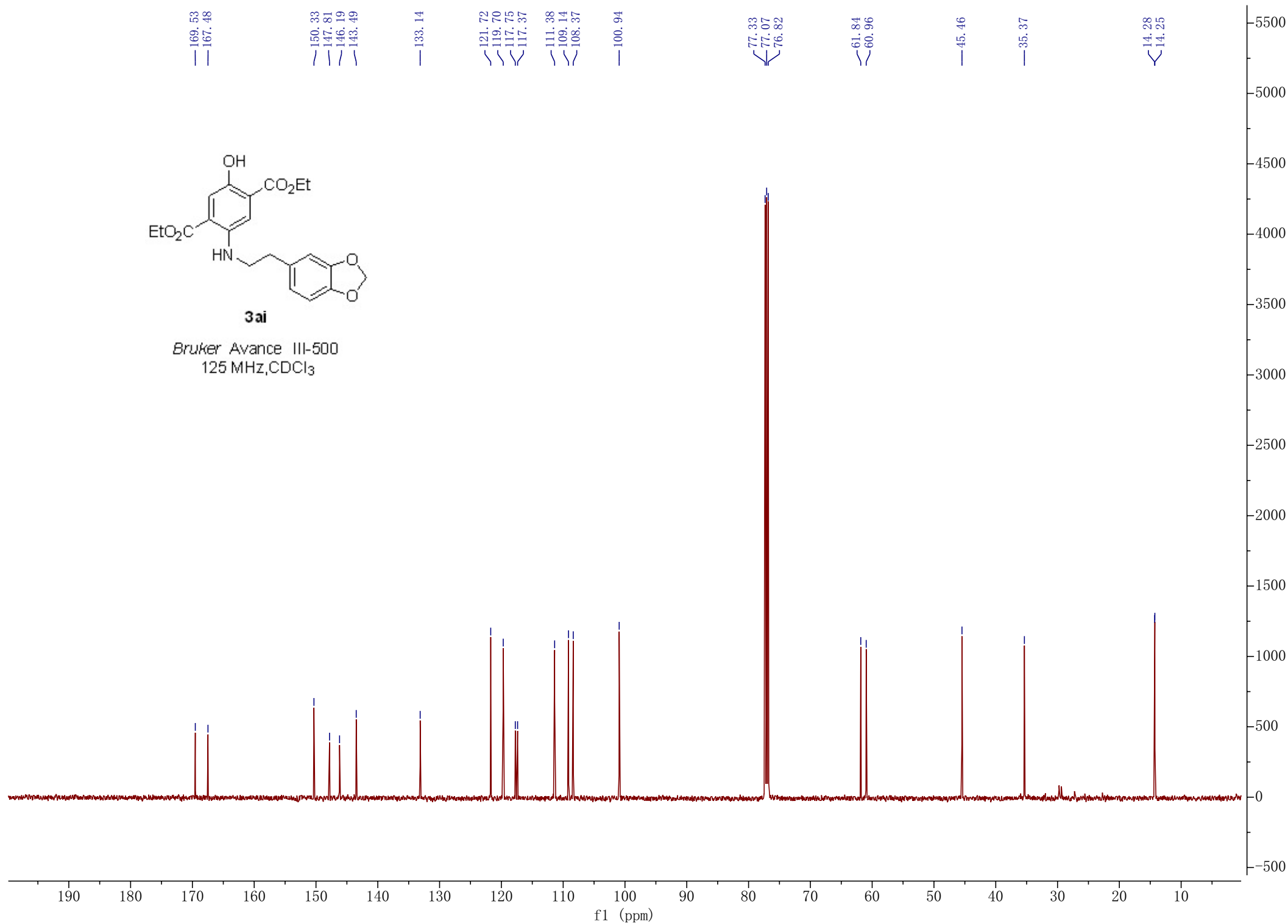


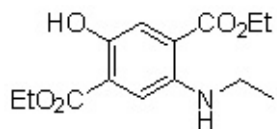
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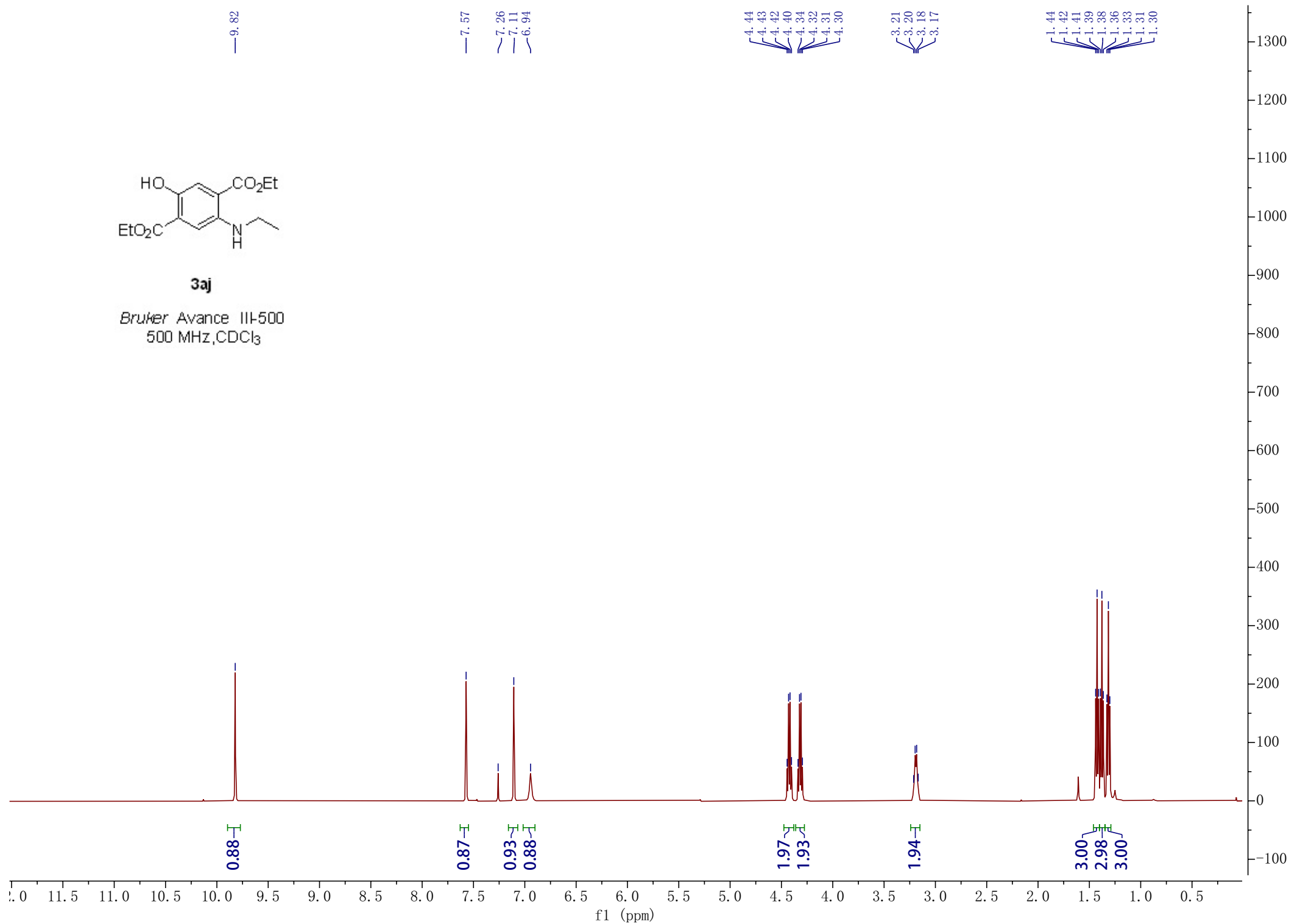
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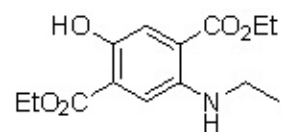




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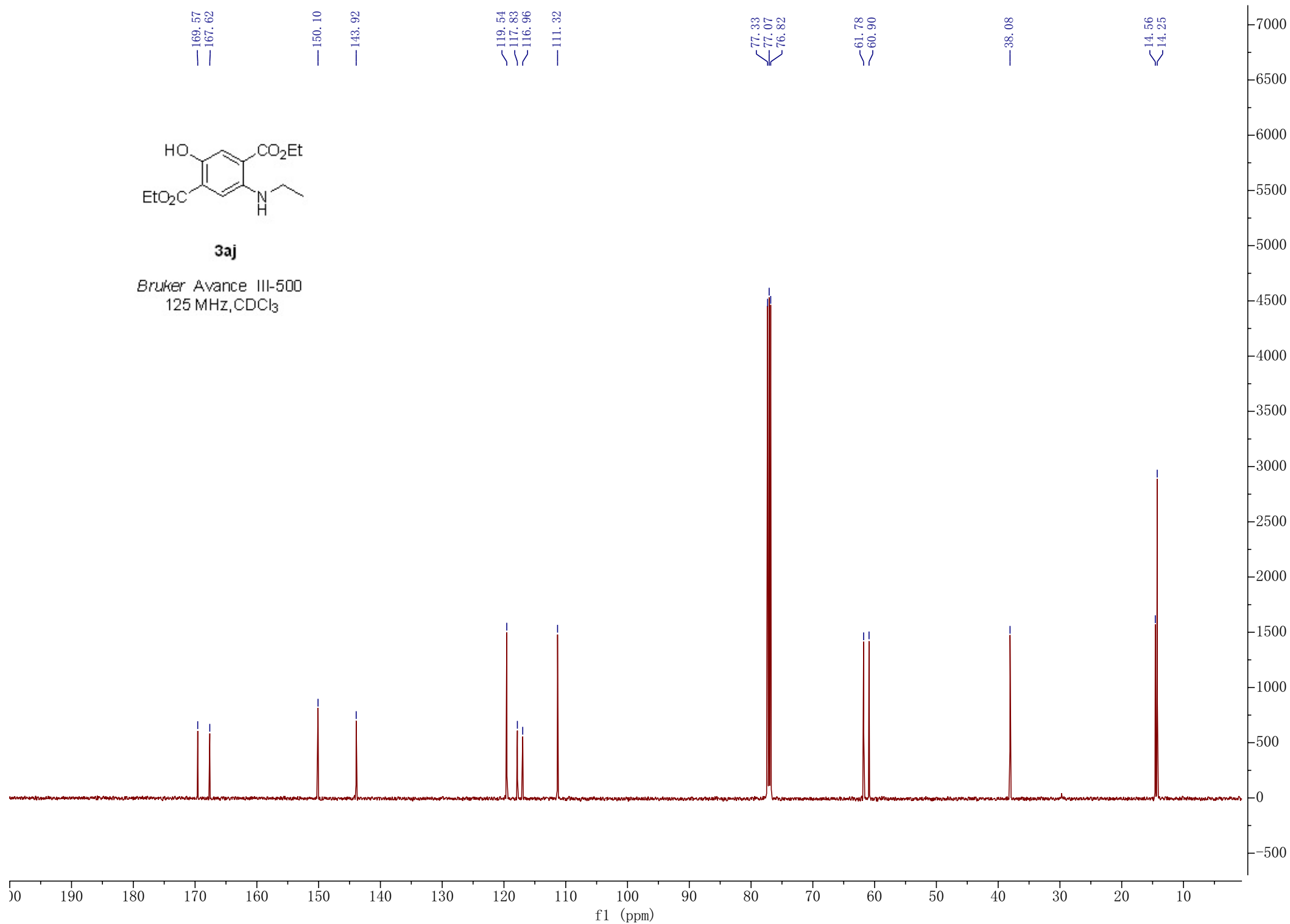
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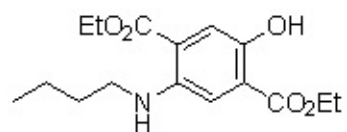




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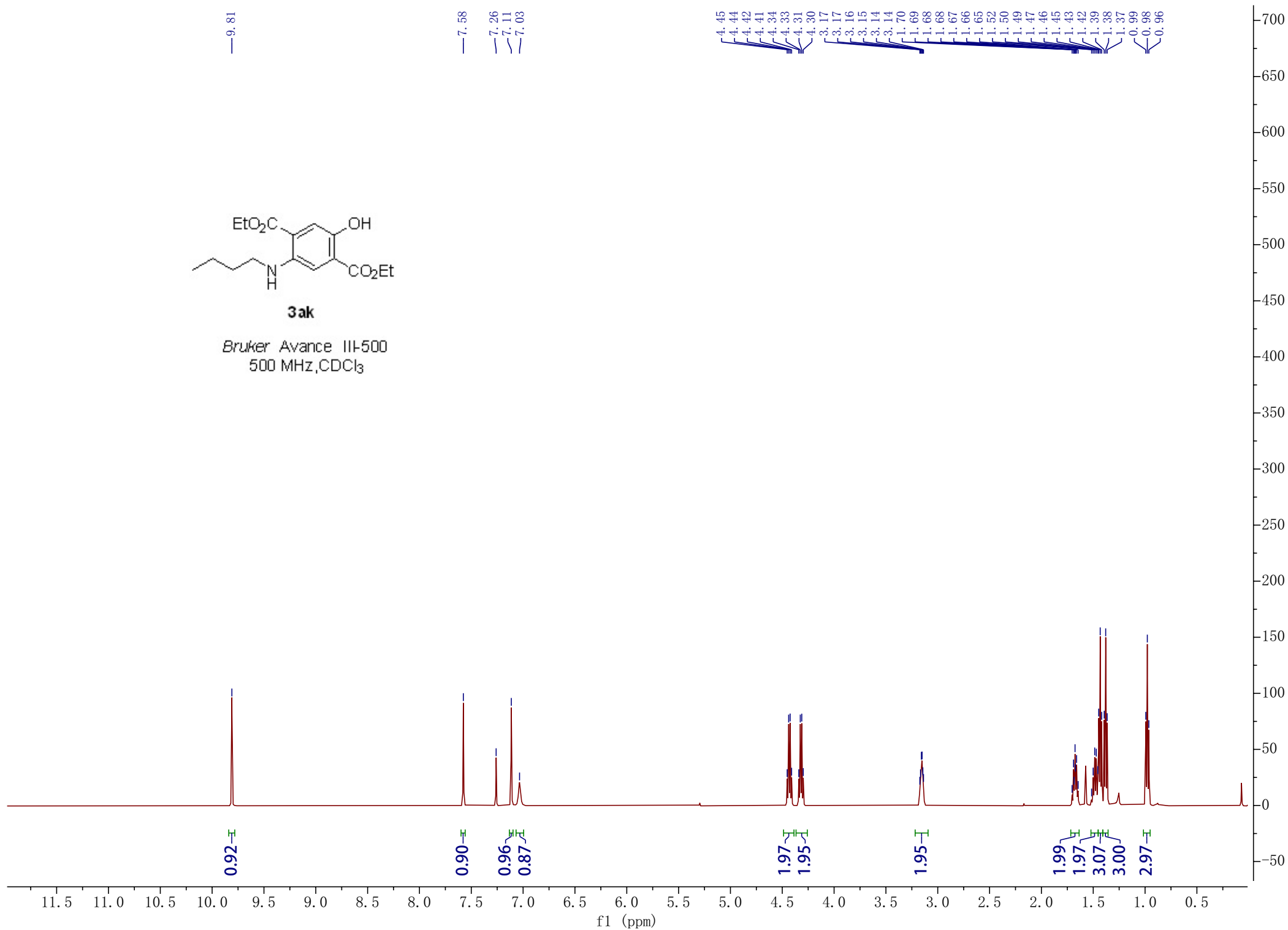
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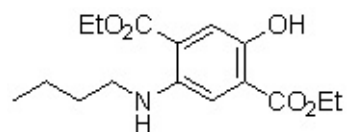




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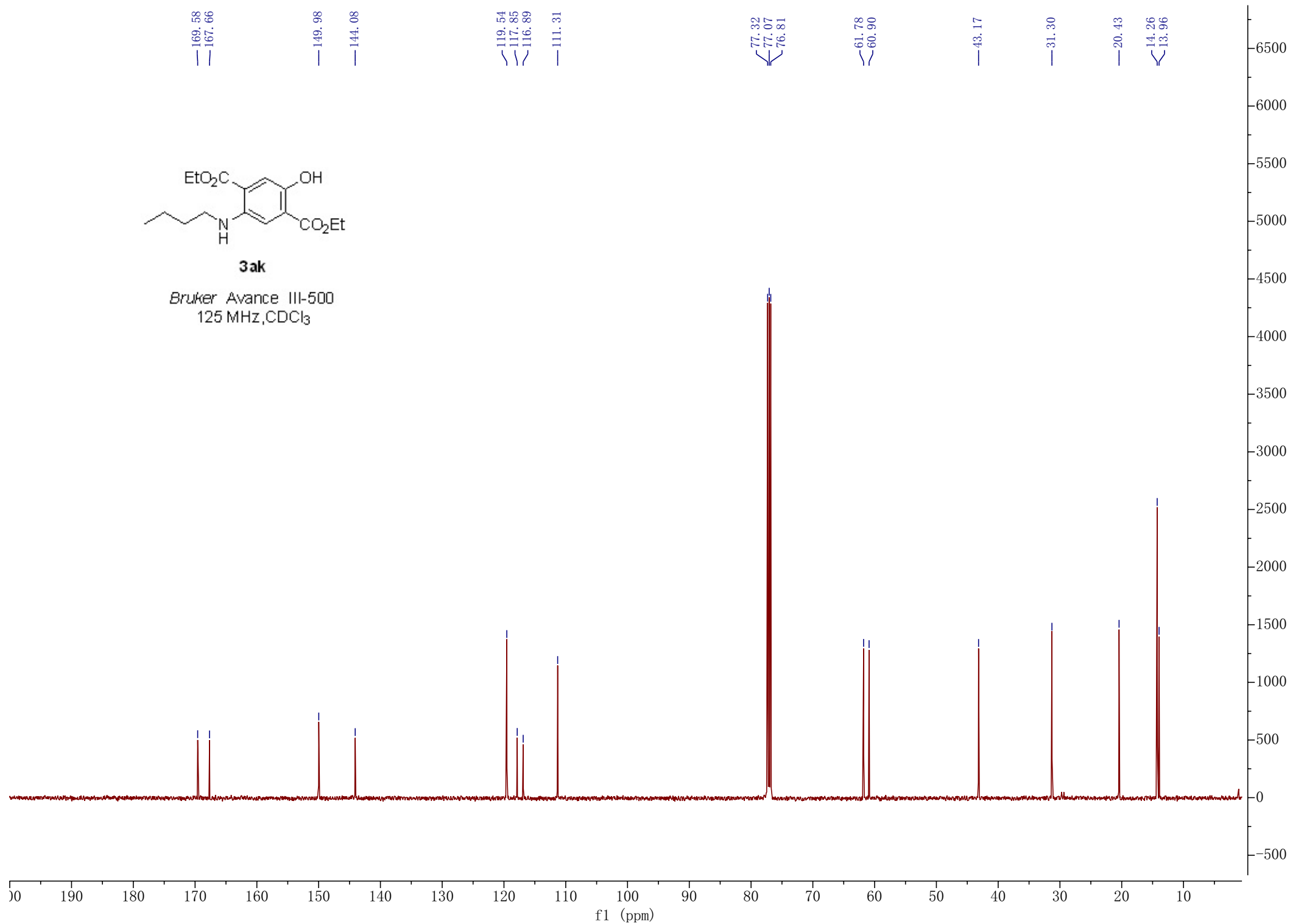
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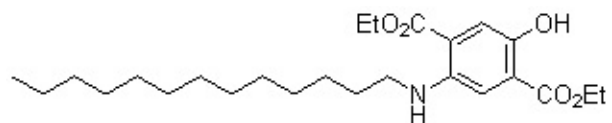




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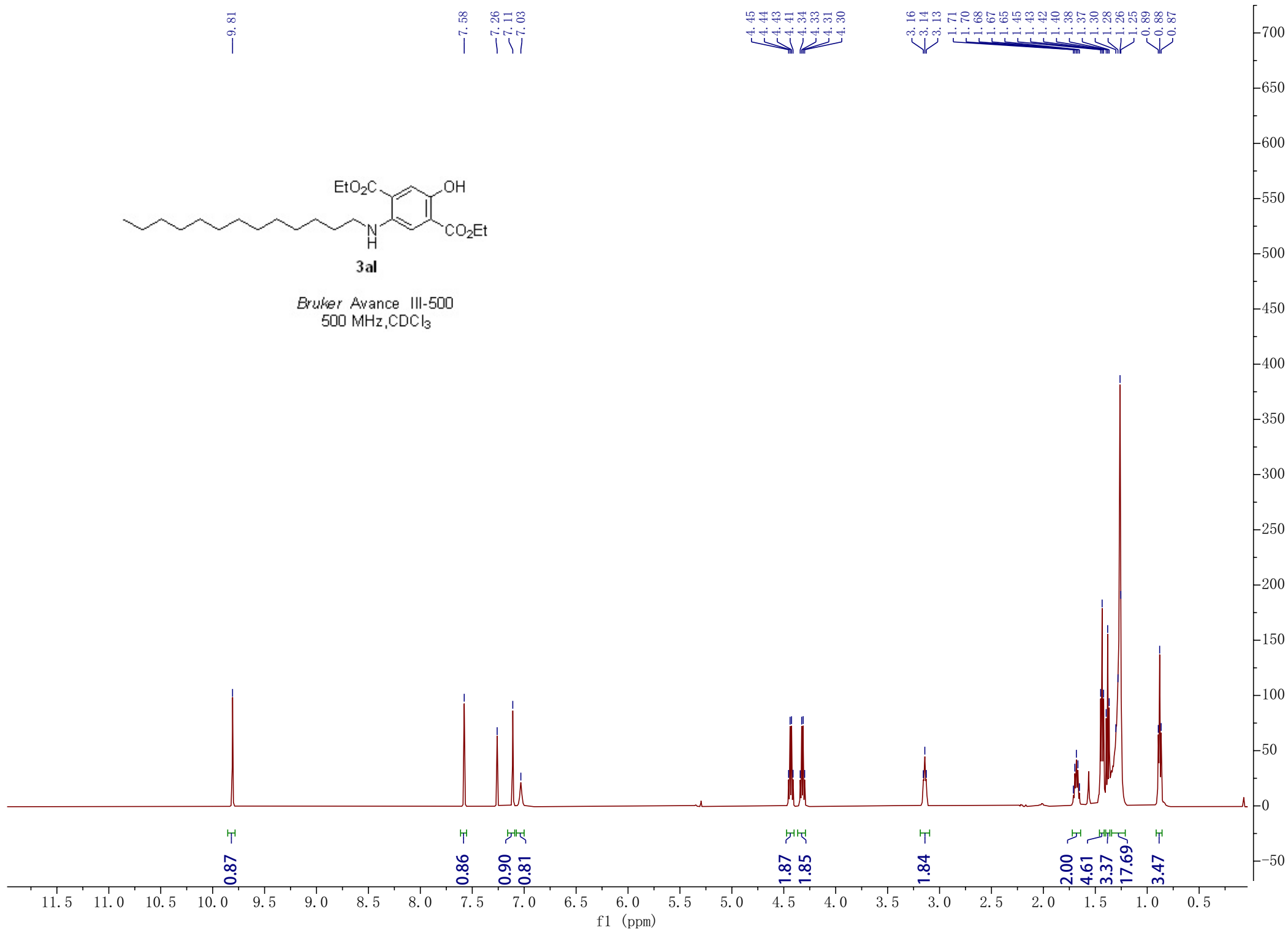
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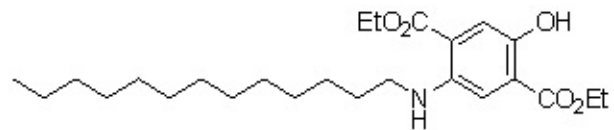




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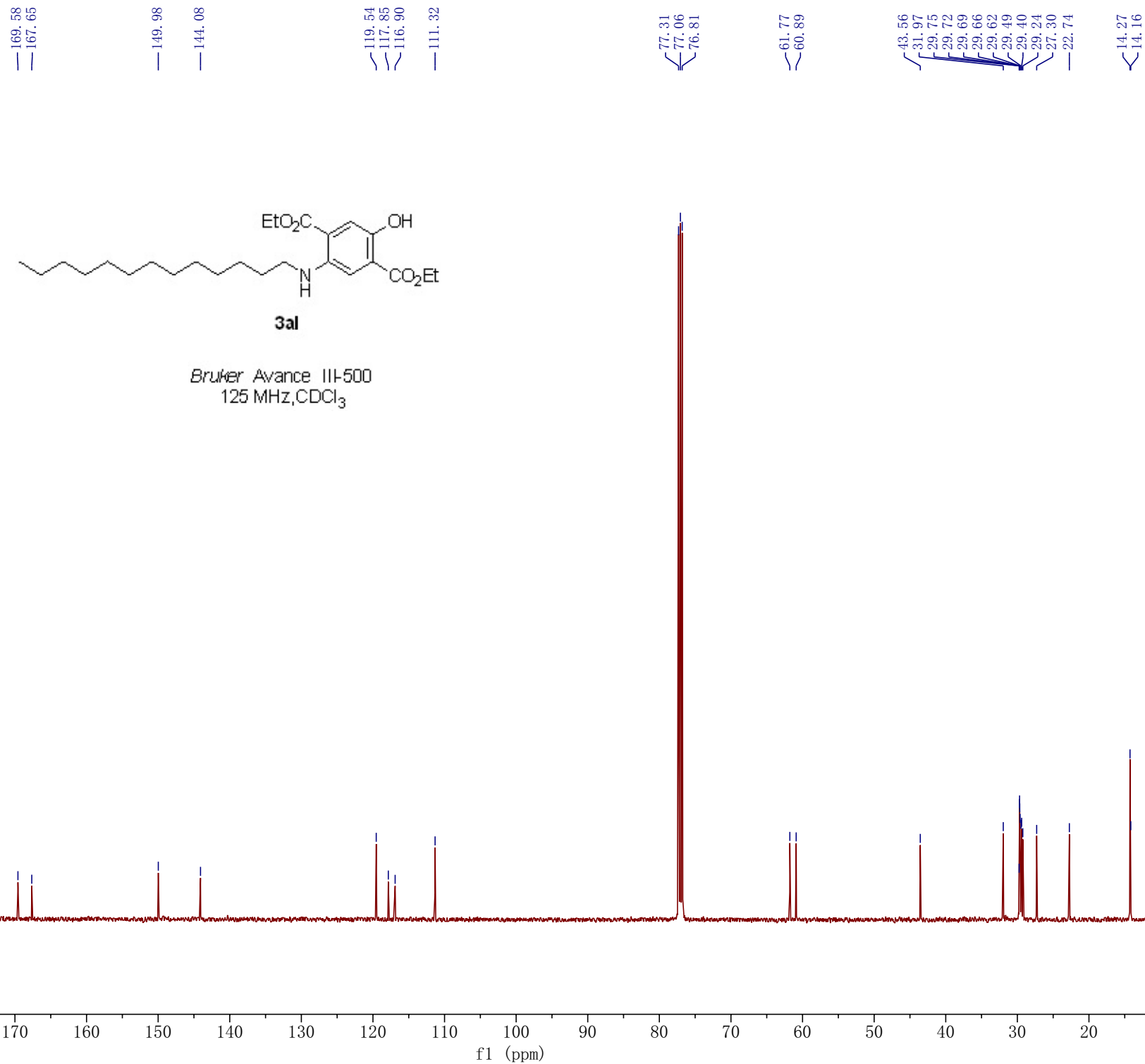
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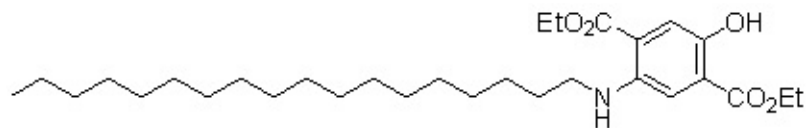




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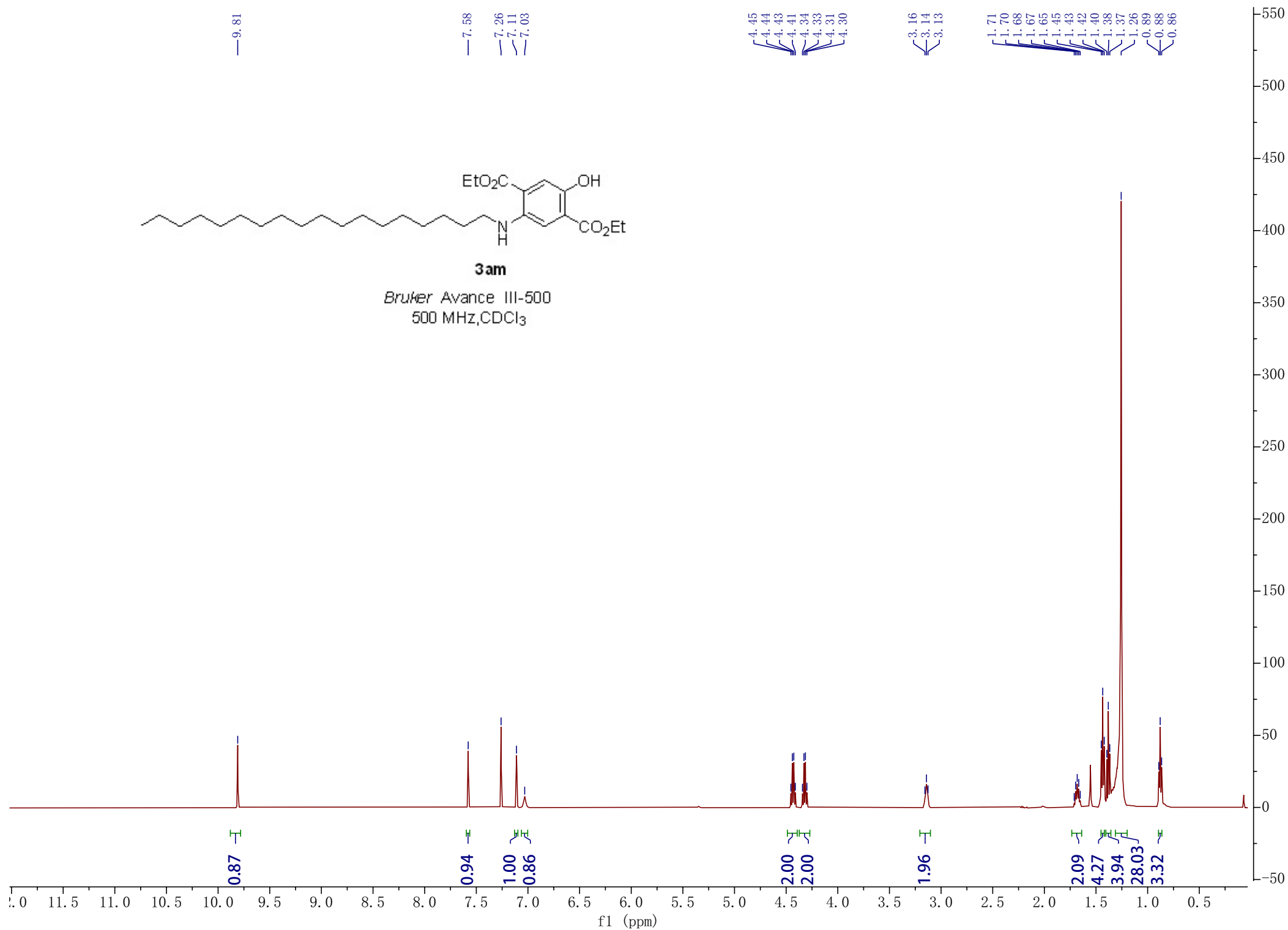
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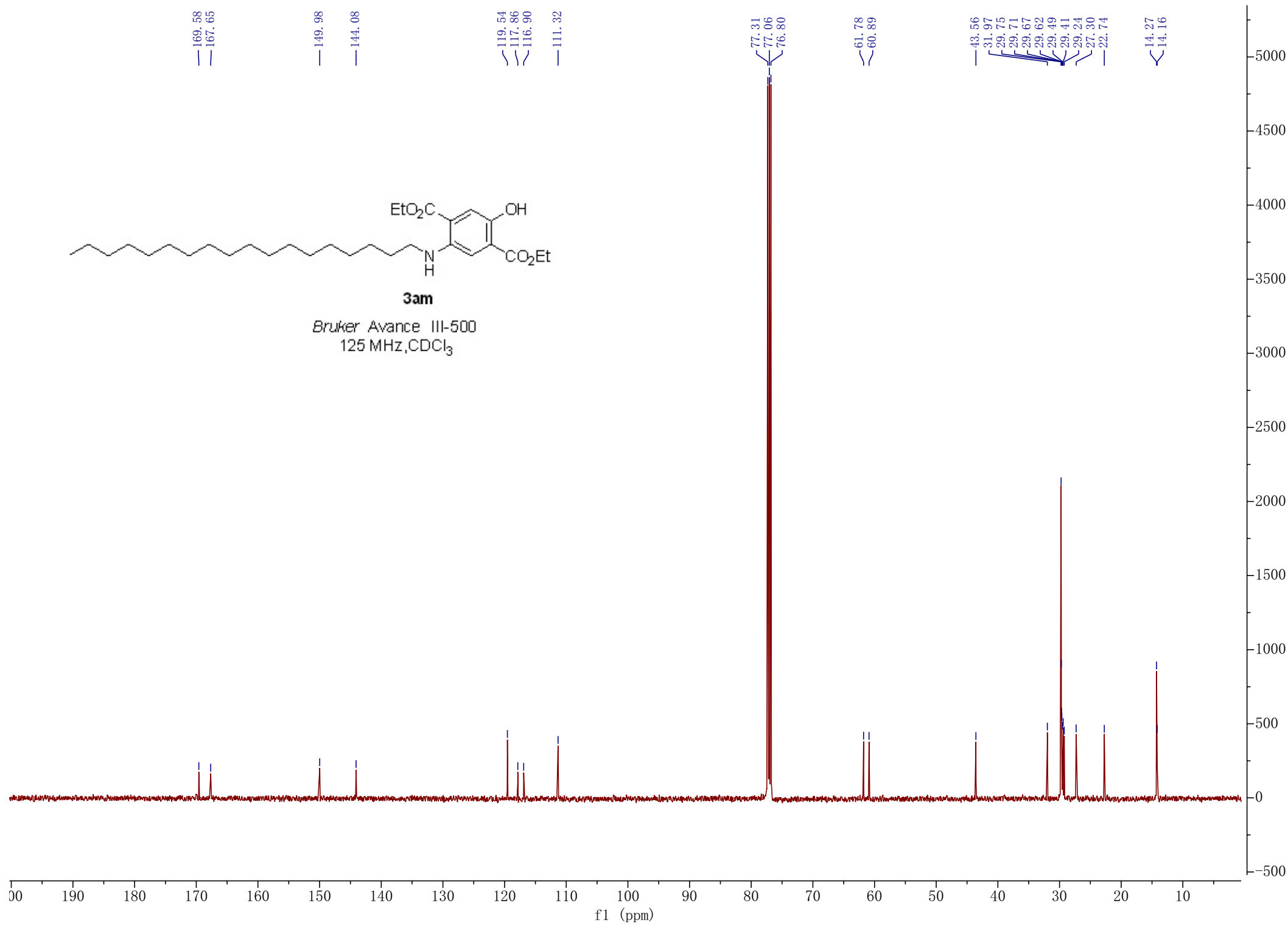


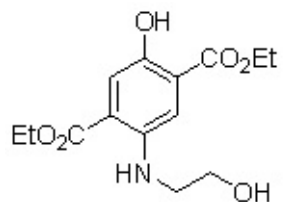


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Bruker Avance III-500
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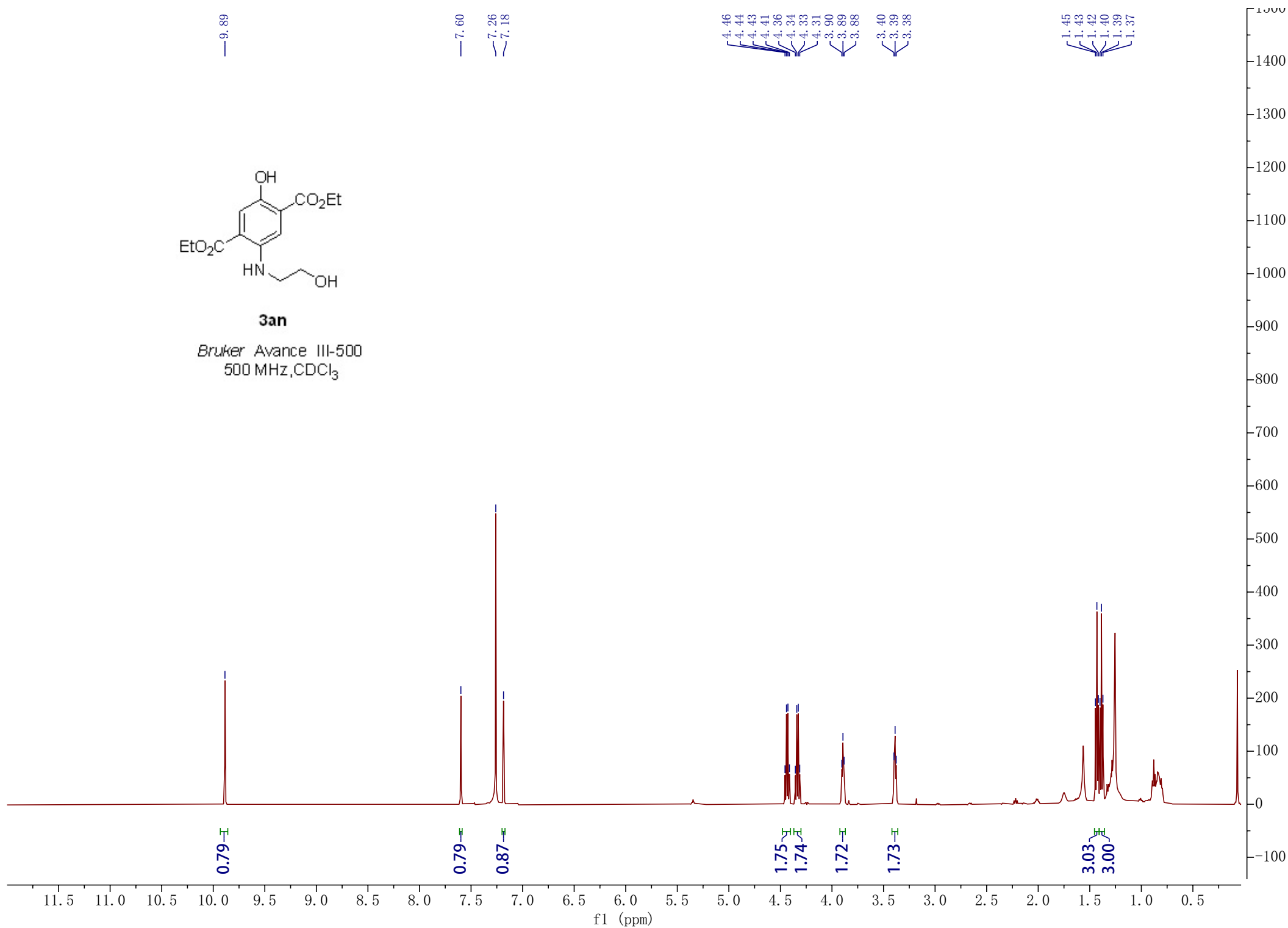


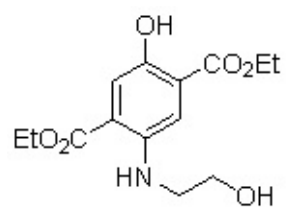




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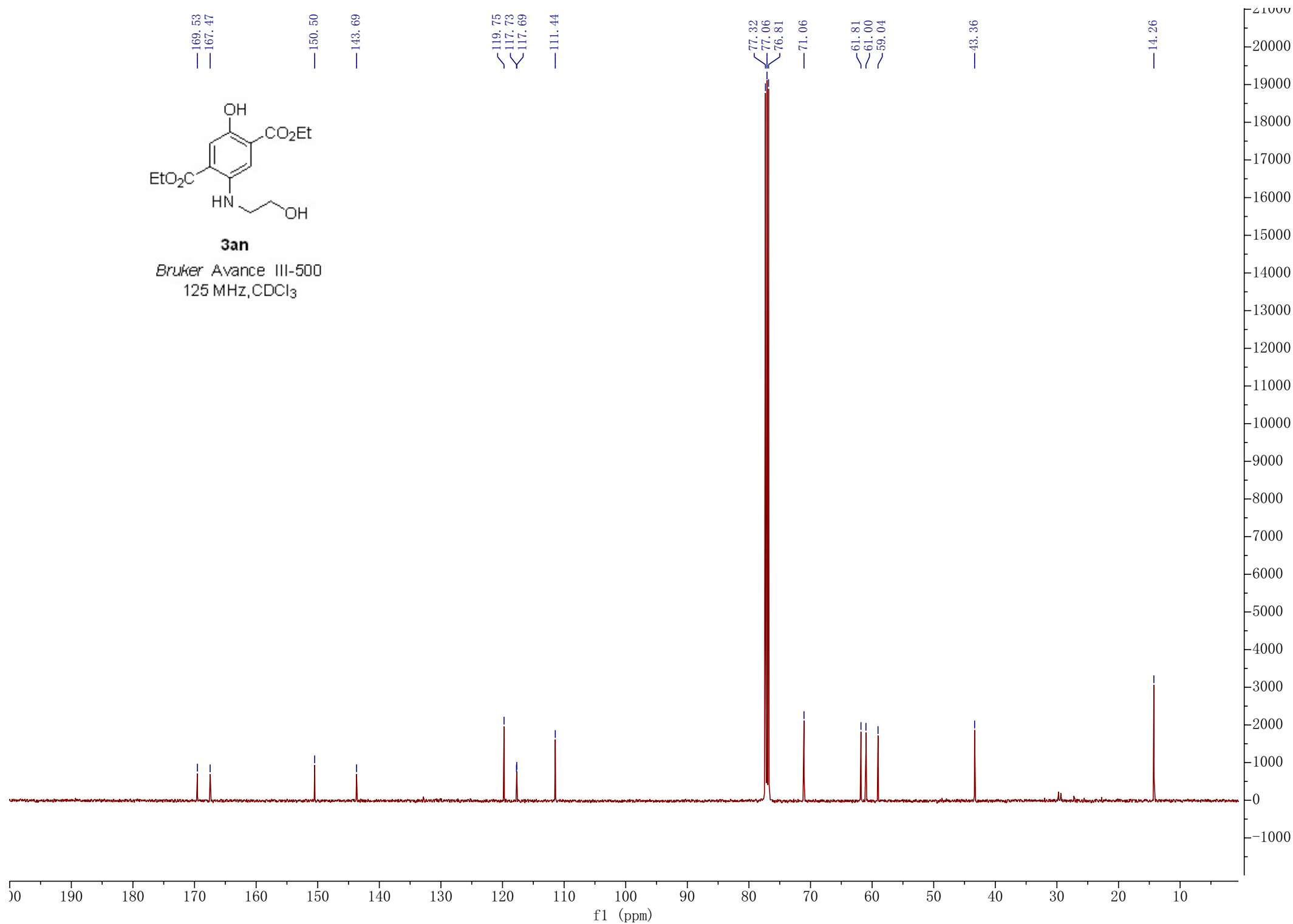
Bruker Avance III-500
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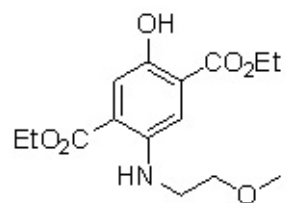




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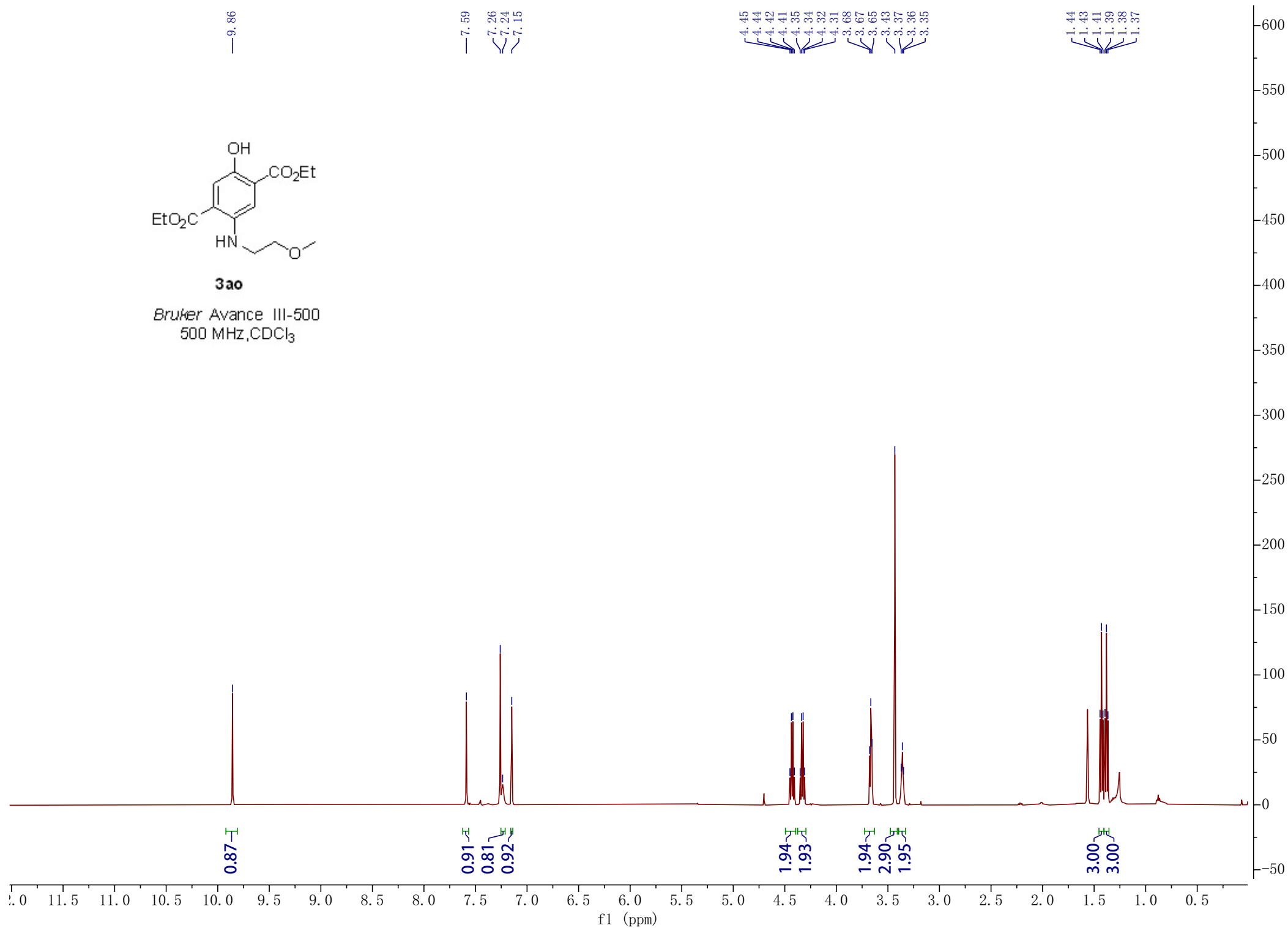
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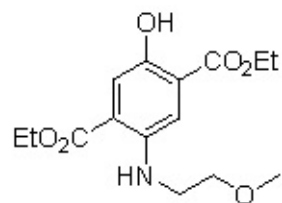




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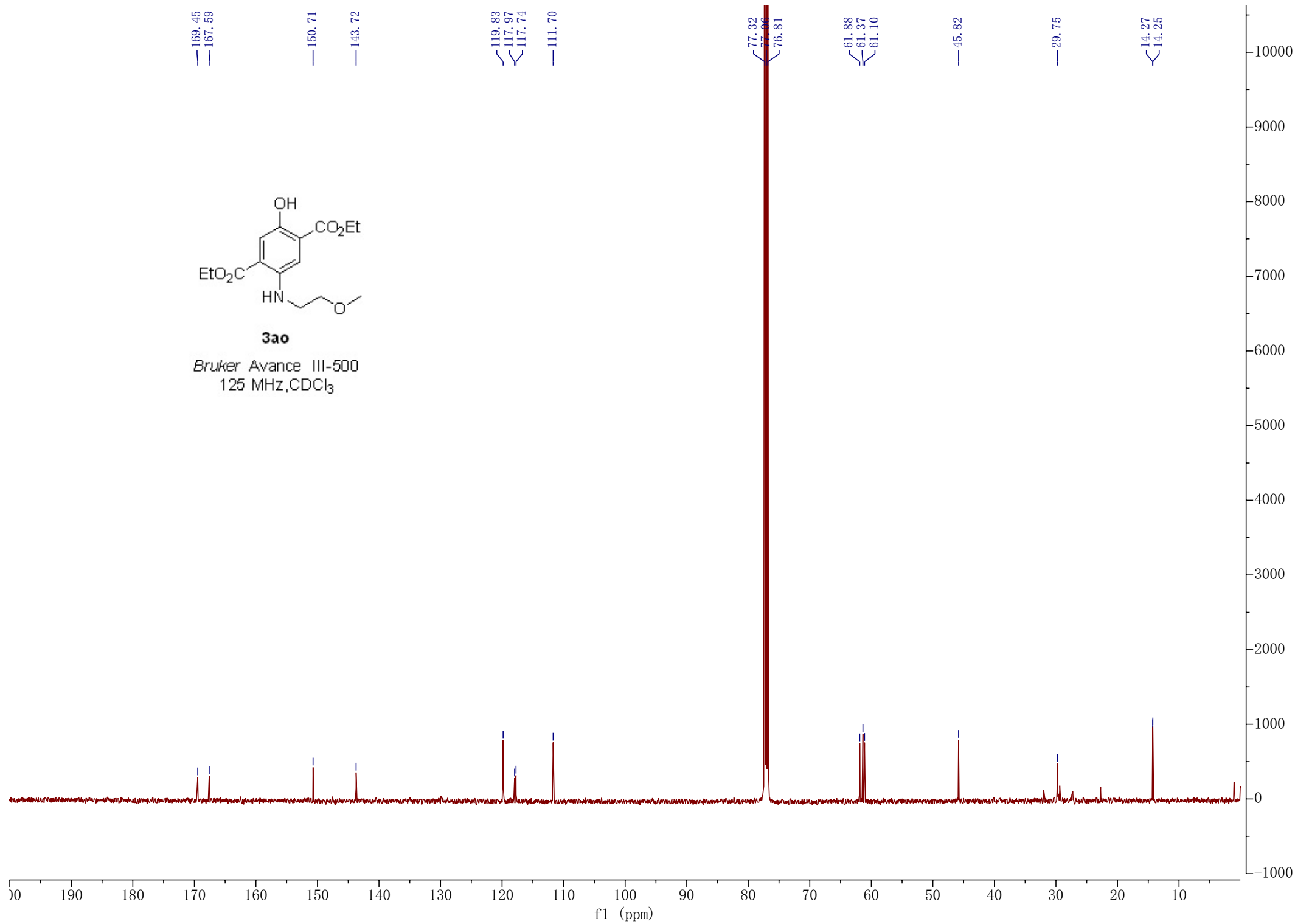
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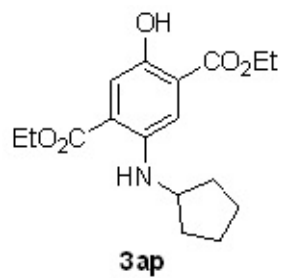




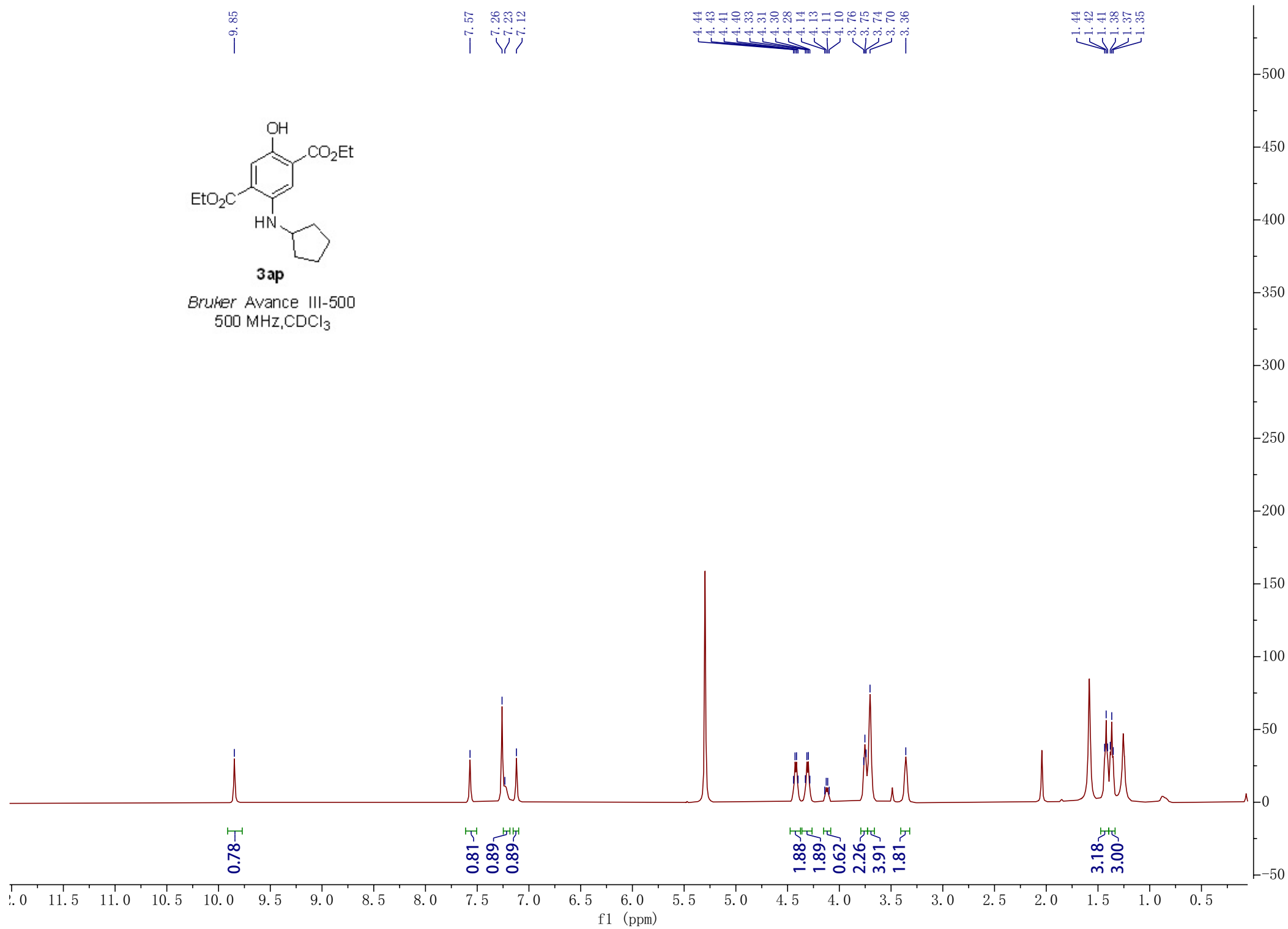
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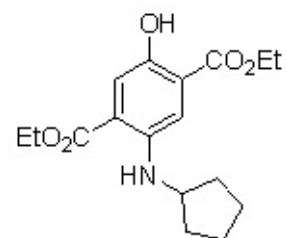
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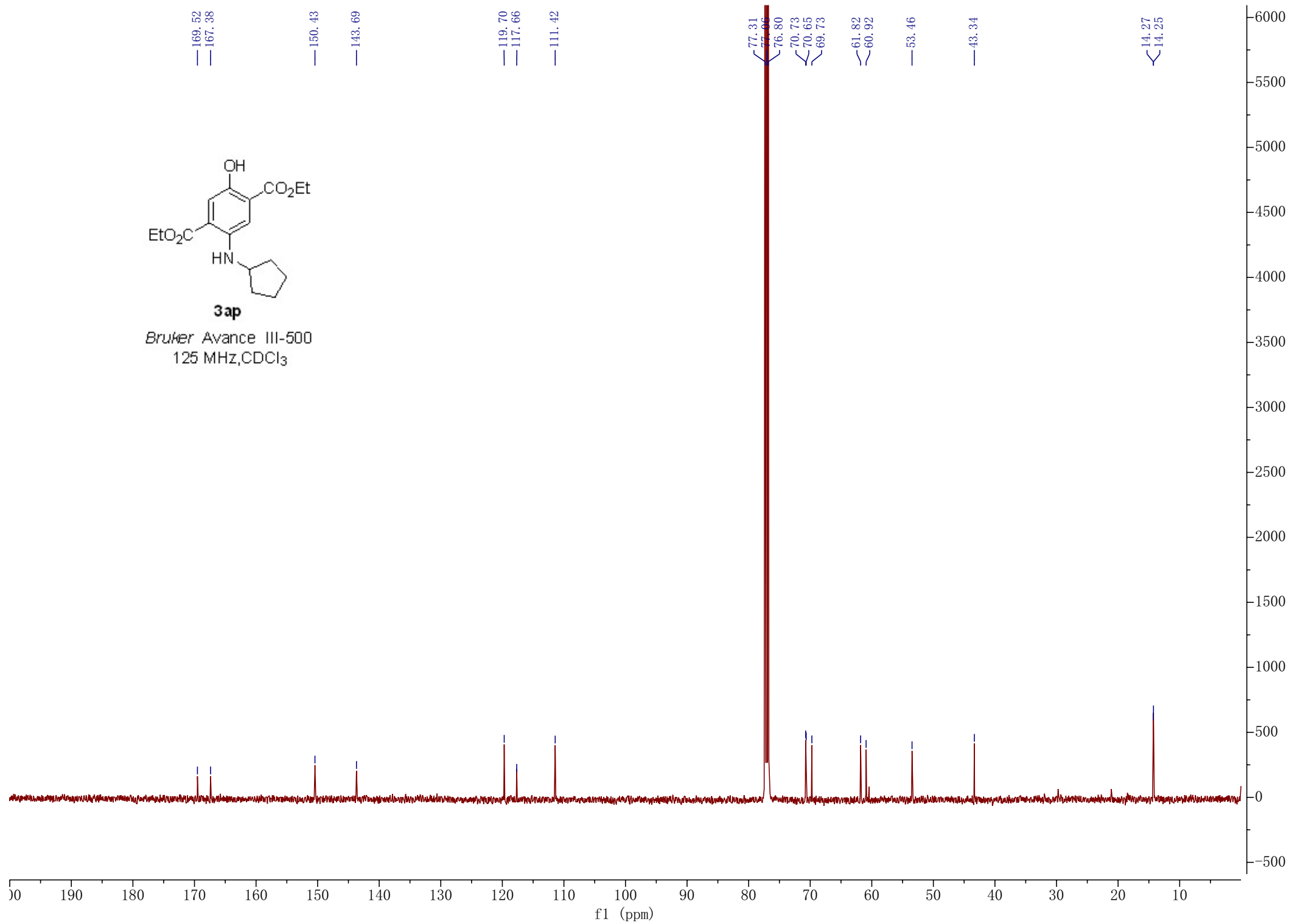
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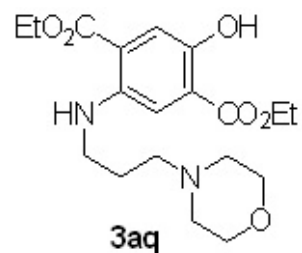




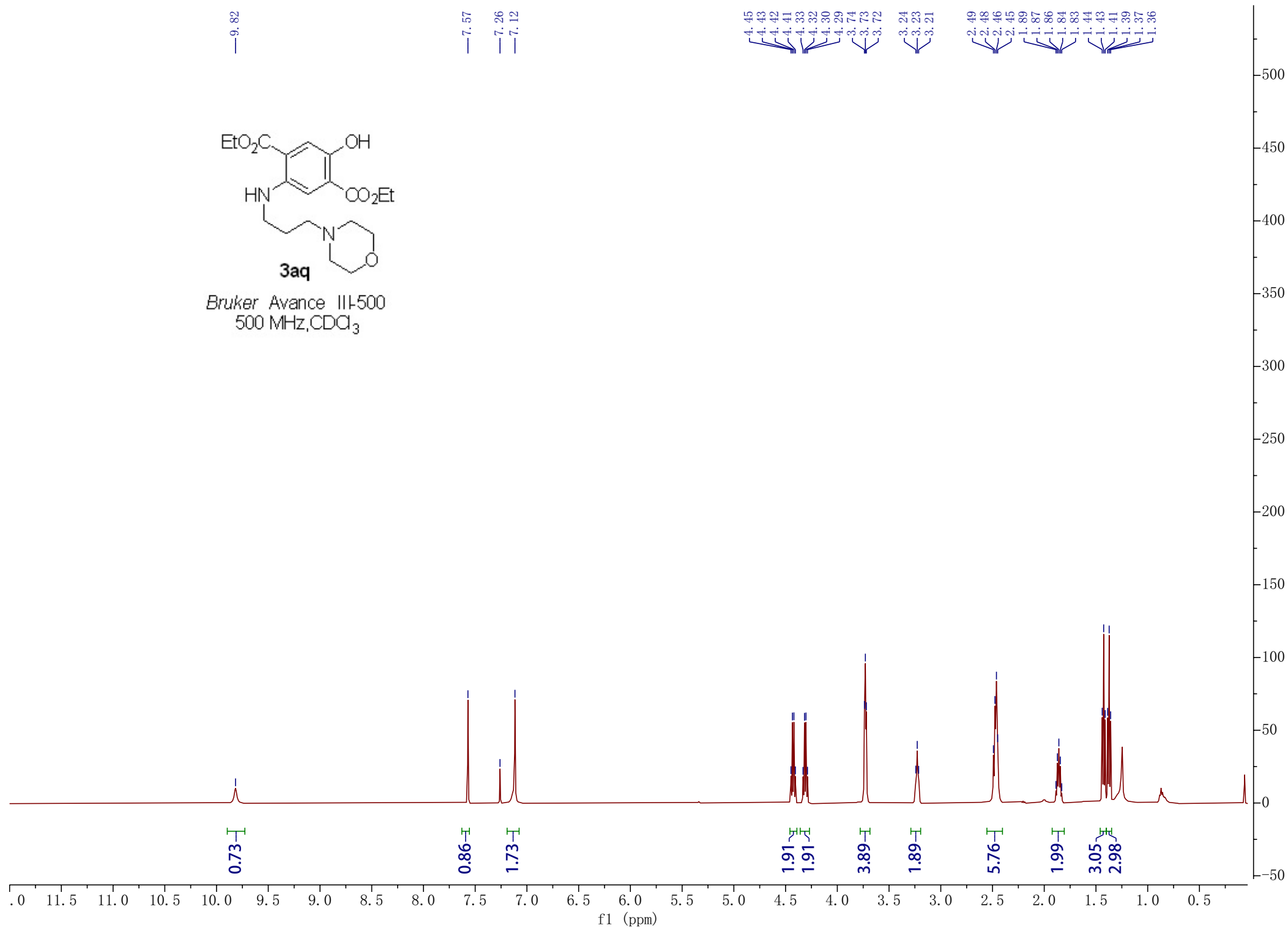
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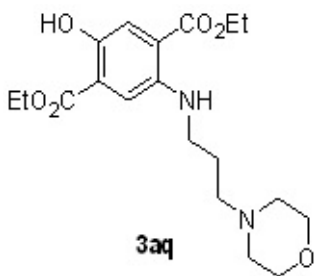
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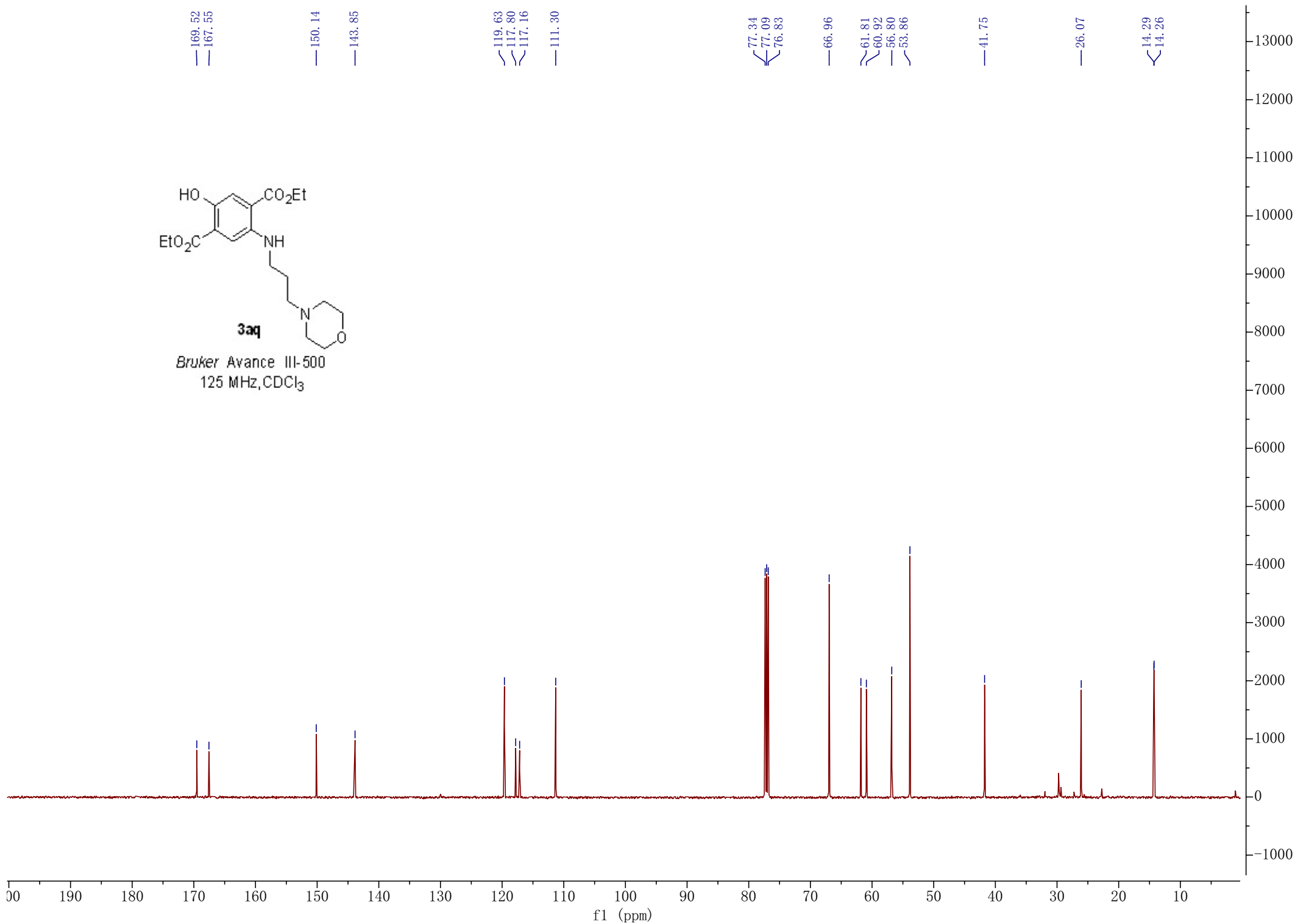
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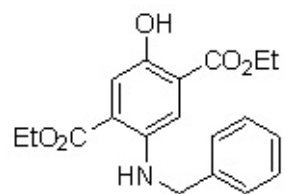




Bruker Avance III-500
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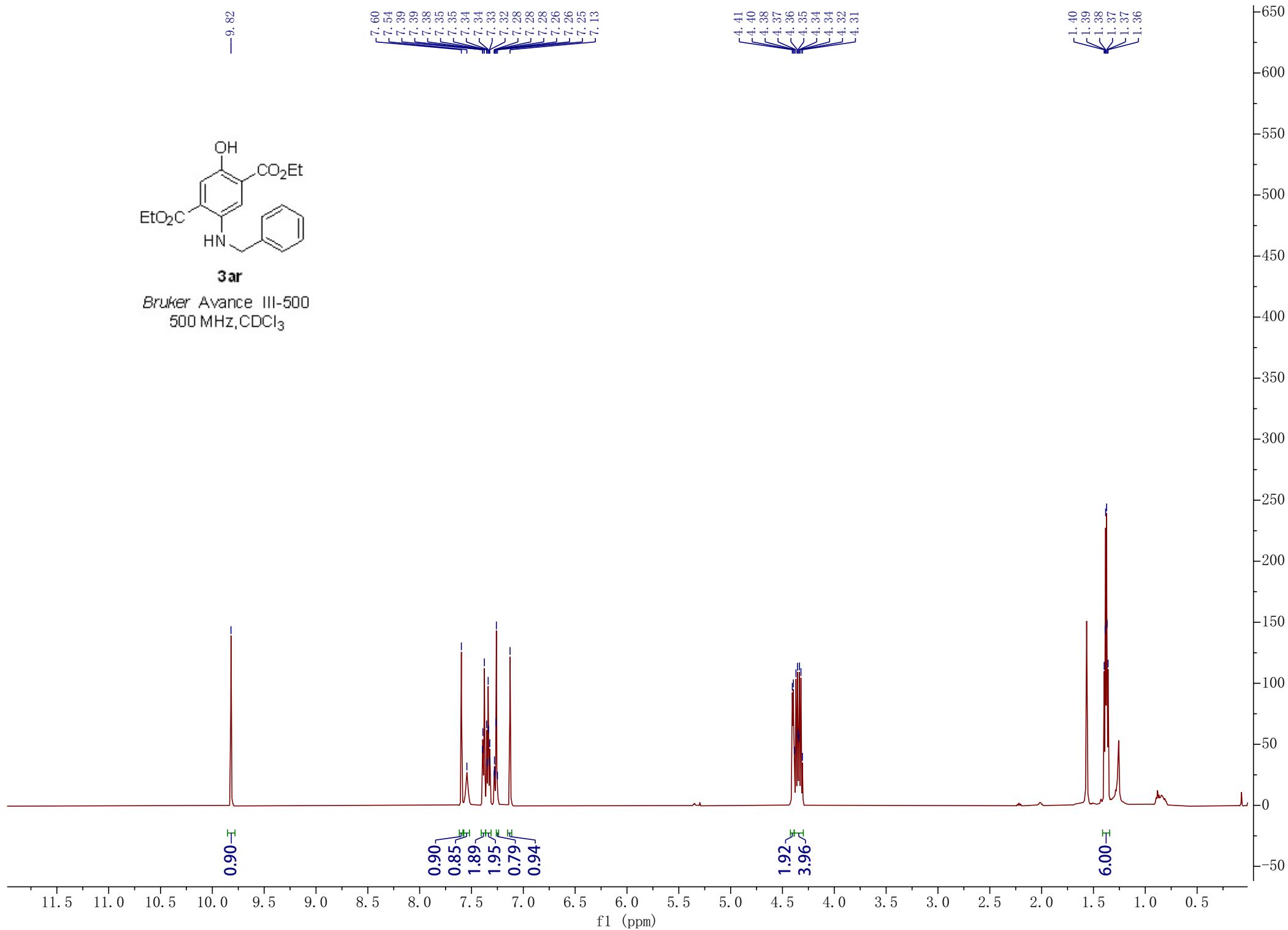
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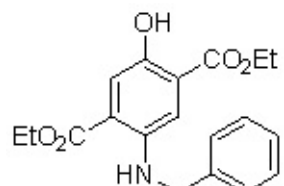




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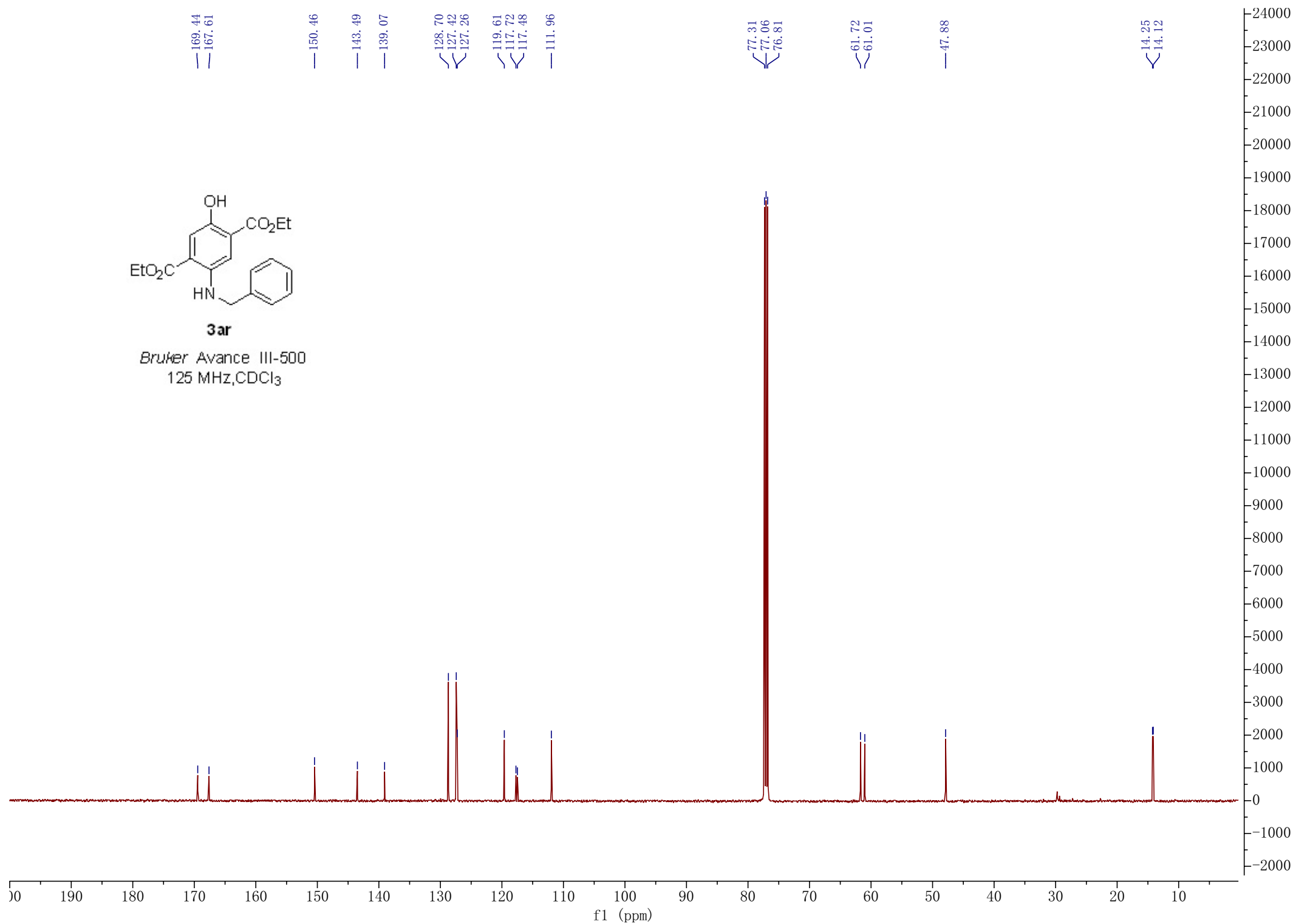
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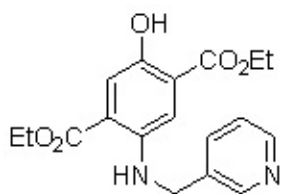




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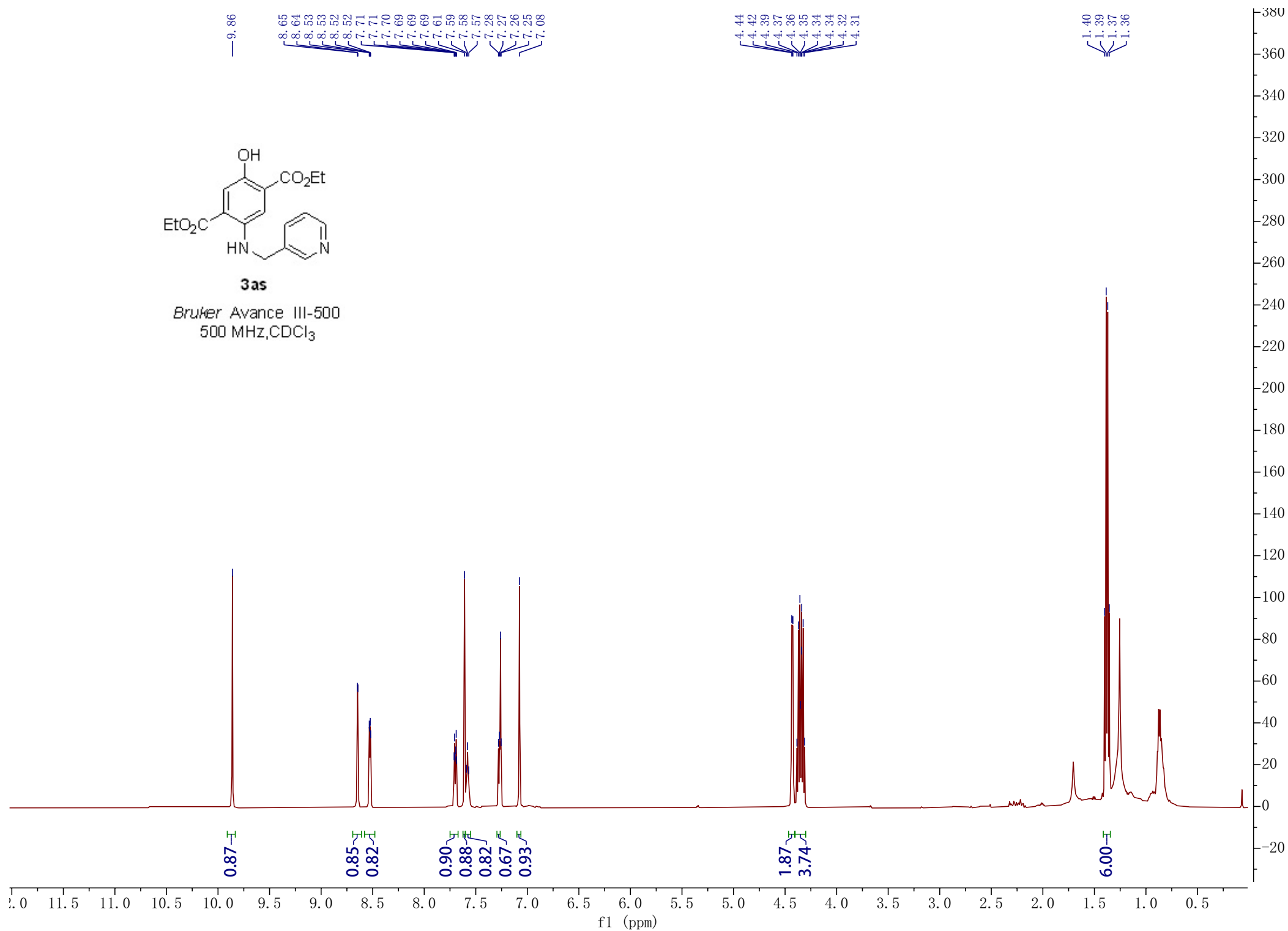
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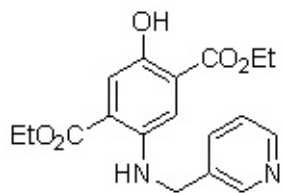




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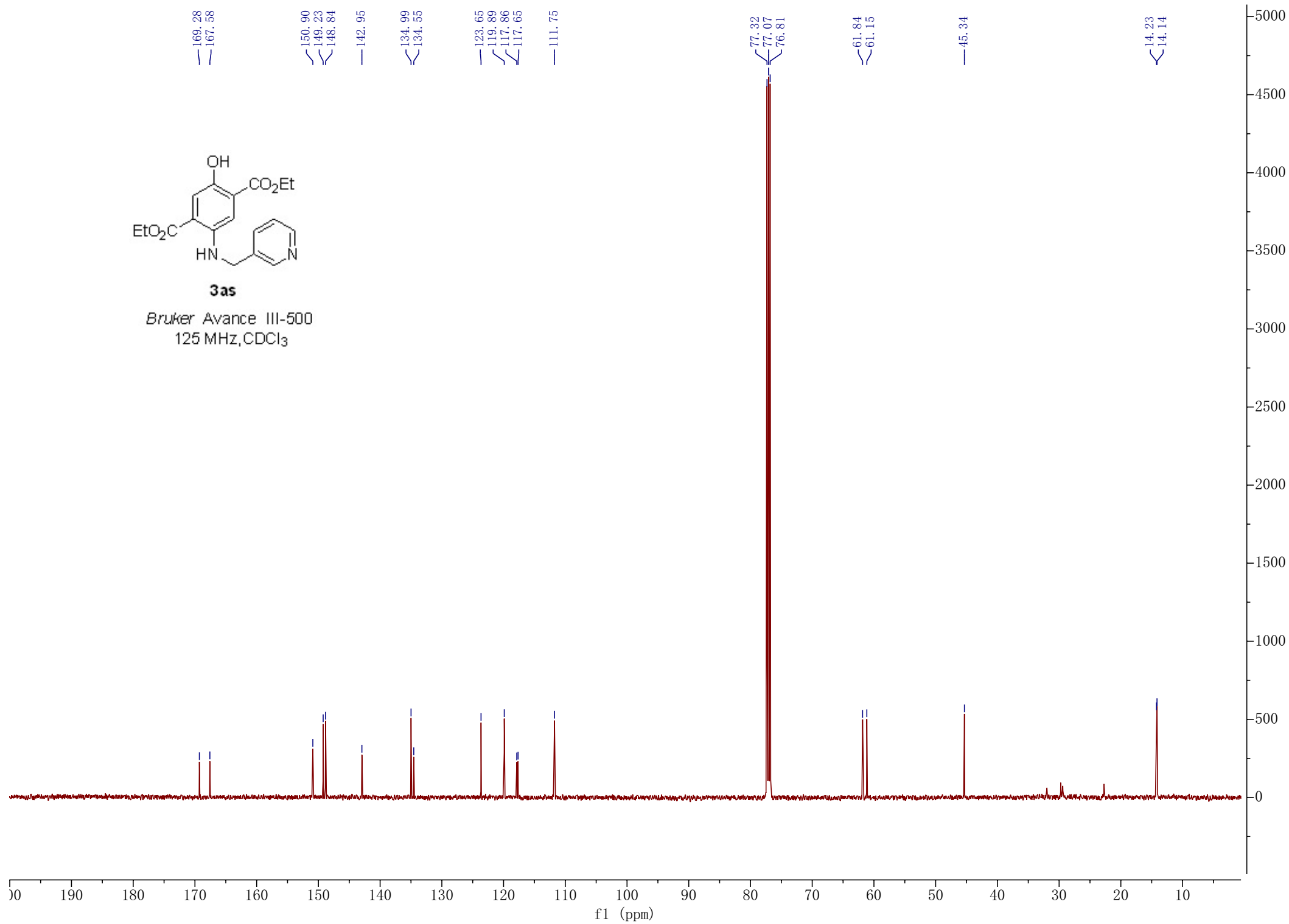
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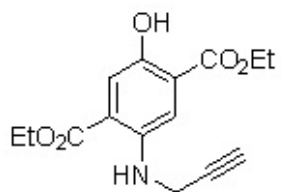




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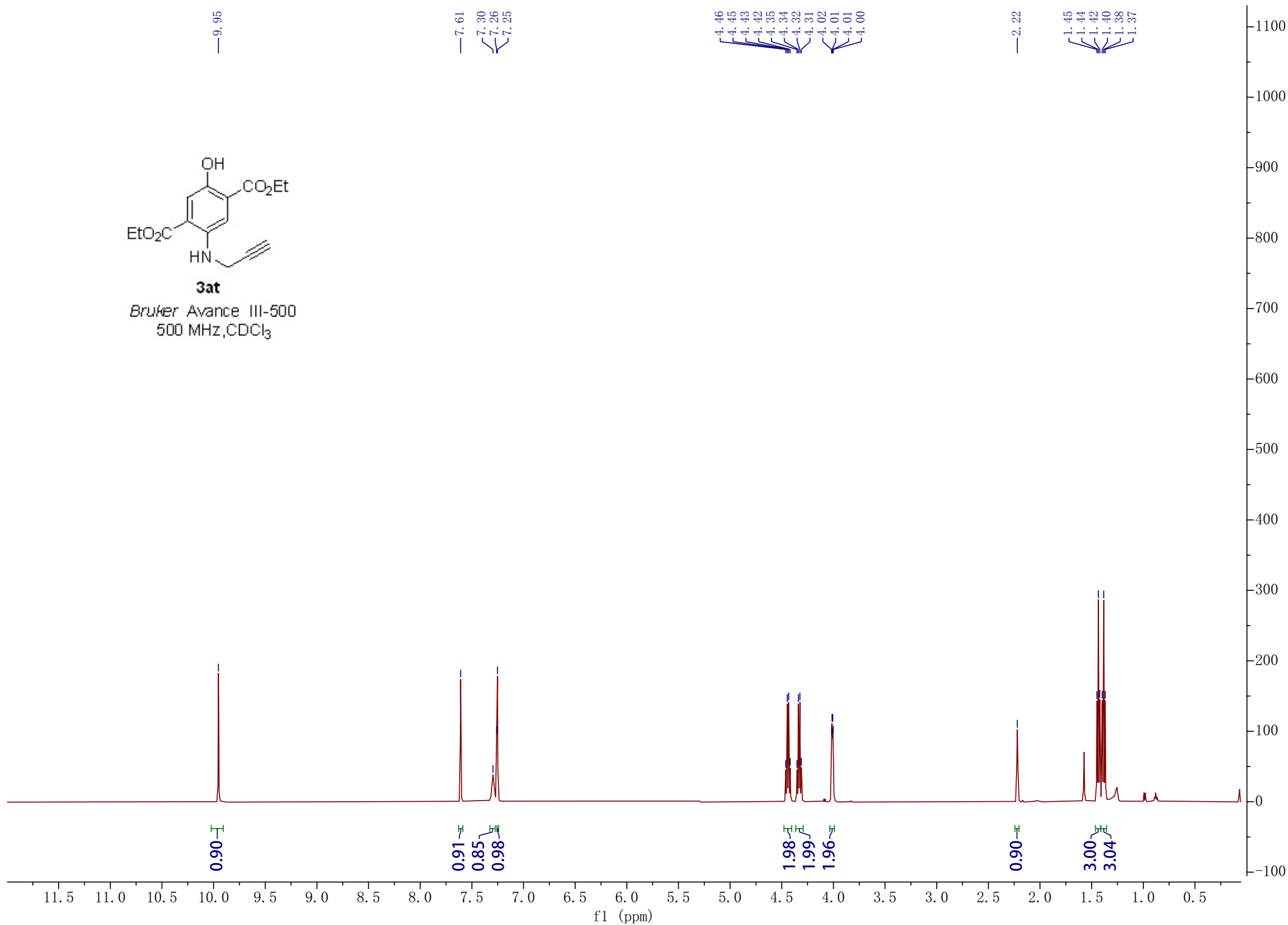
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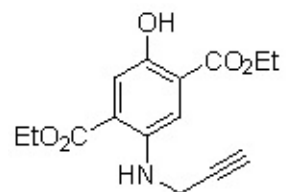




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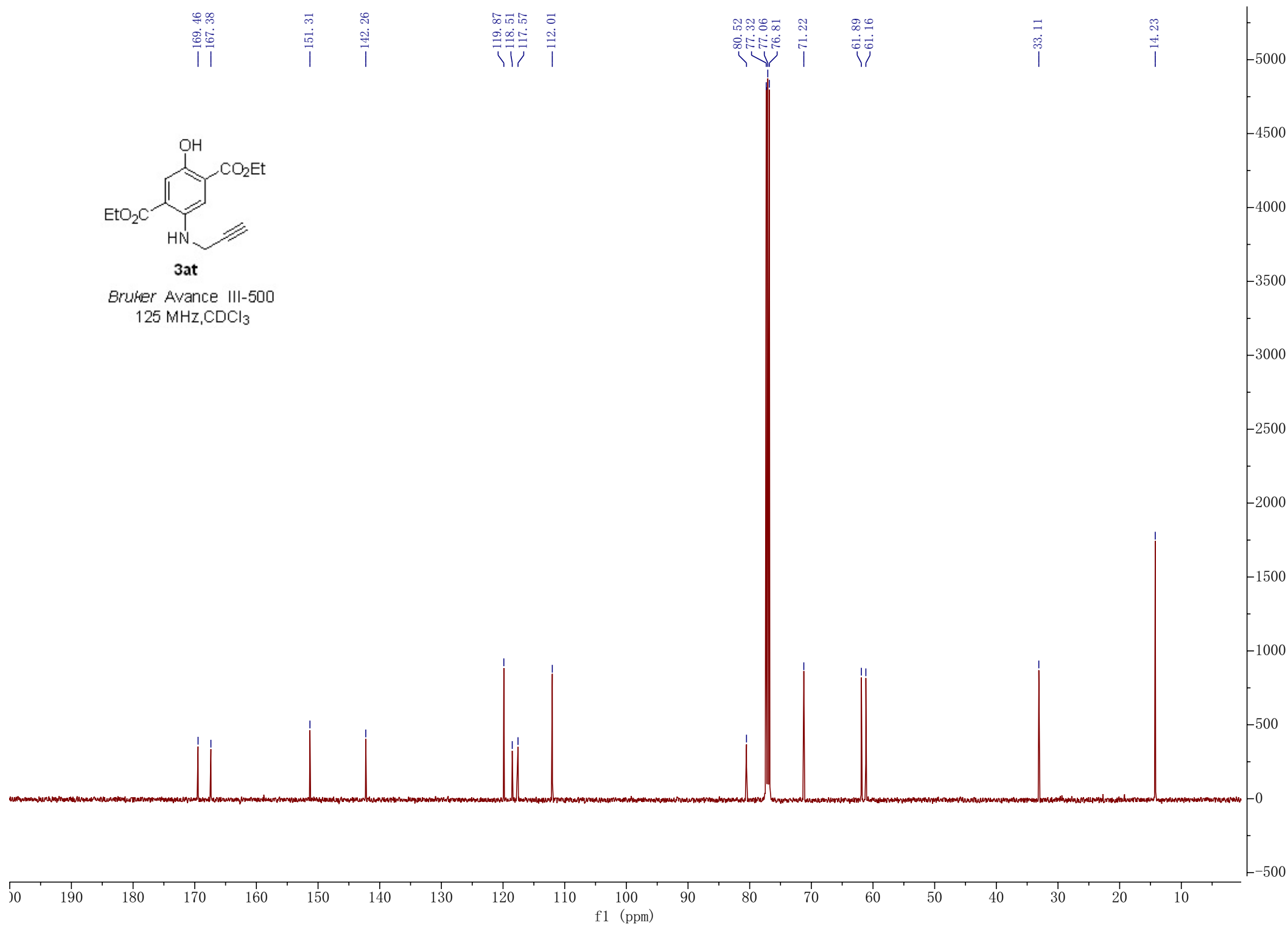
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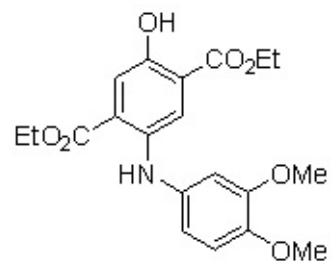




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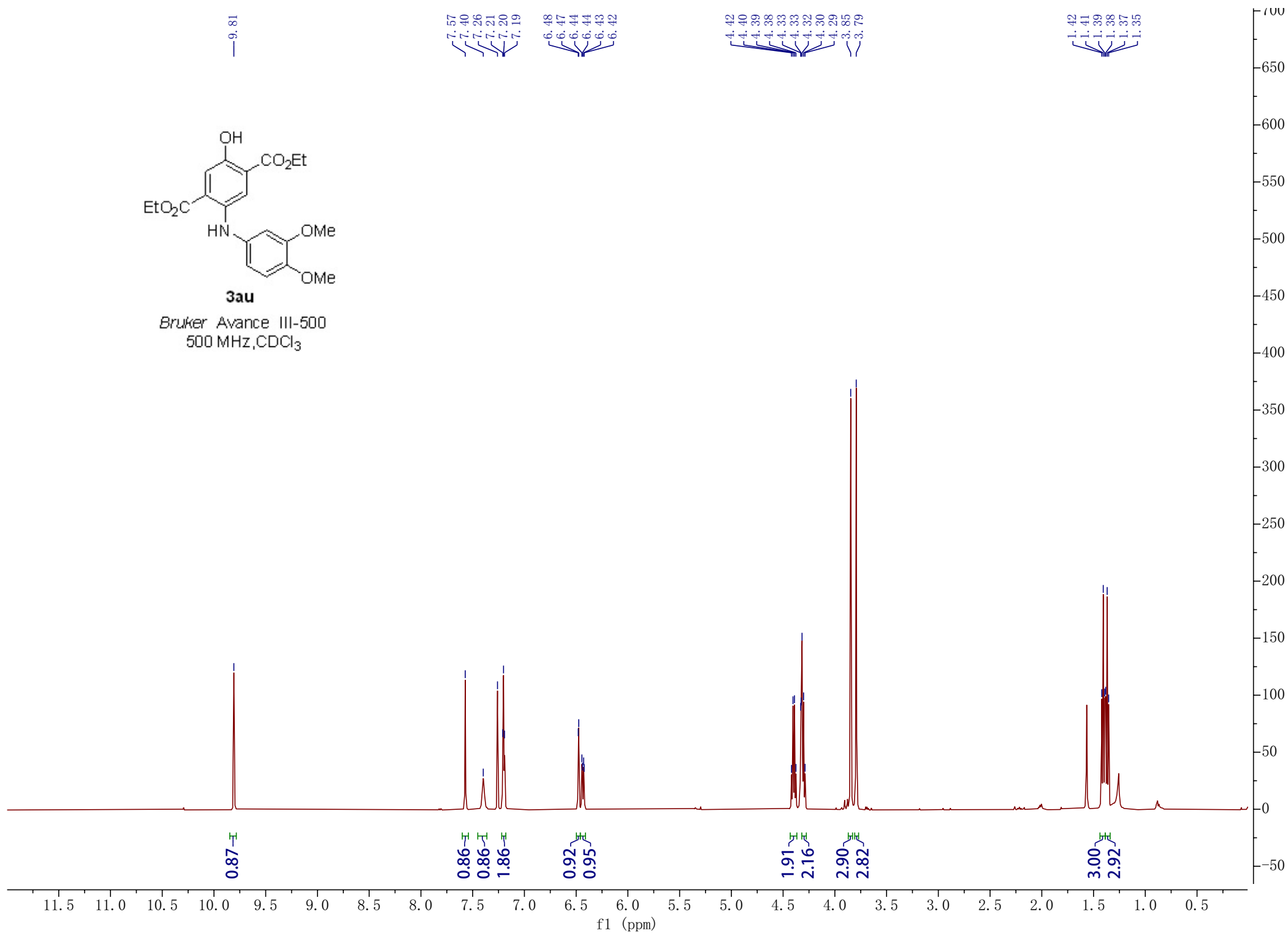
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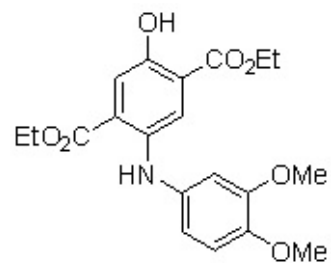




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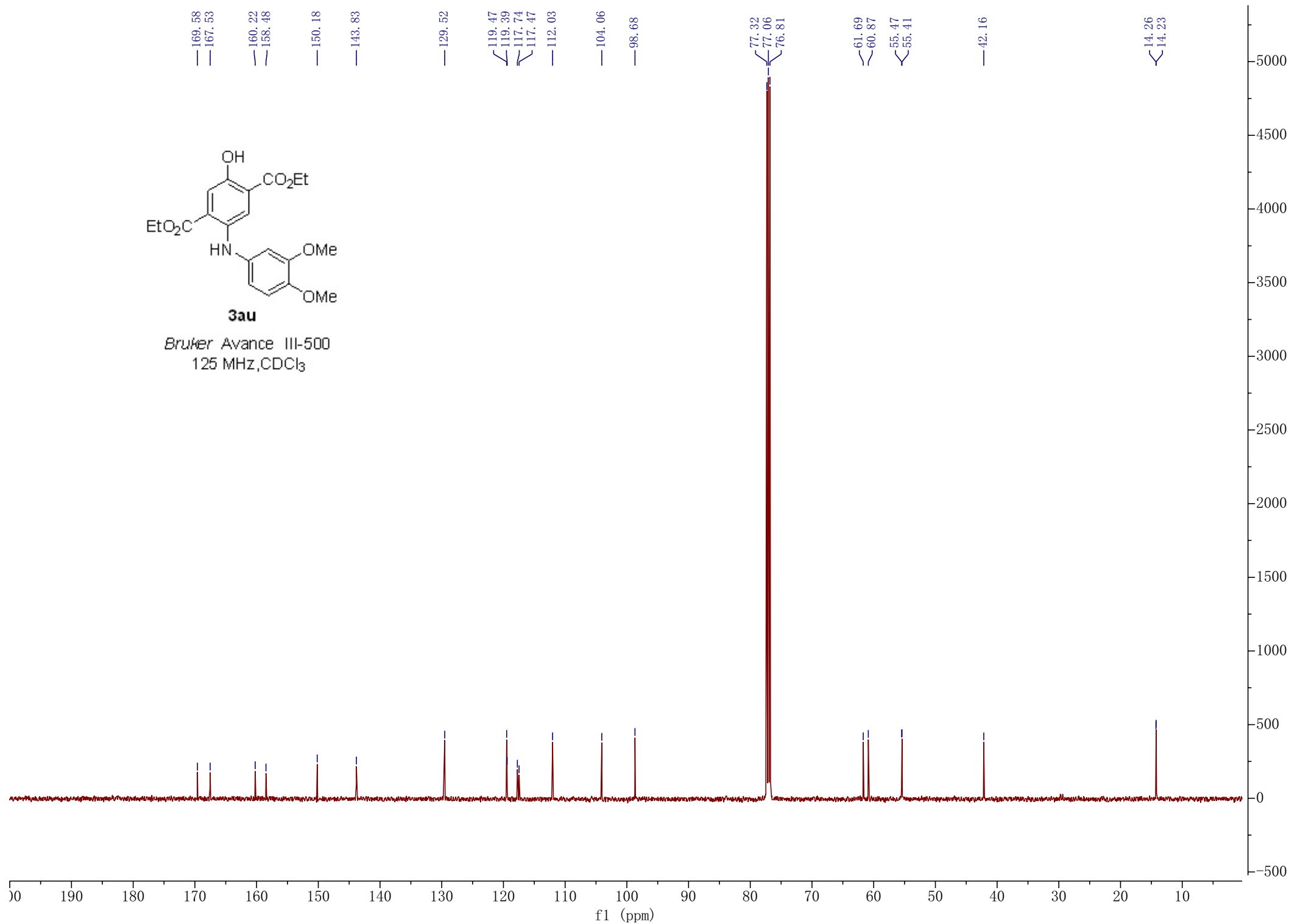
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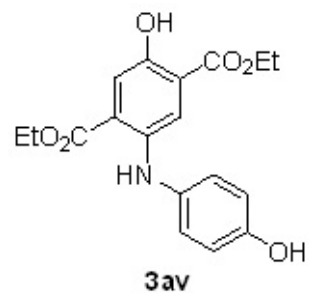




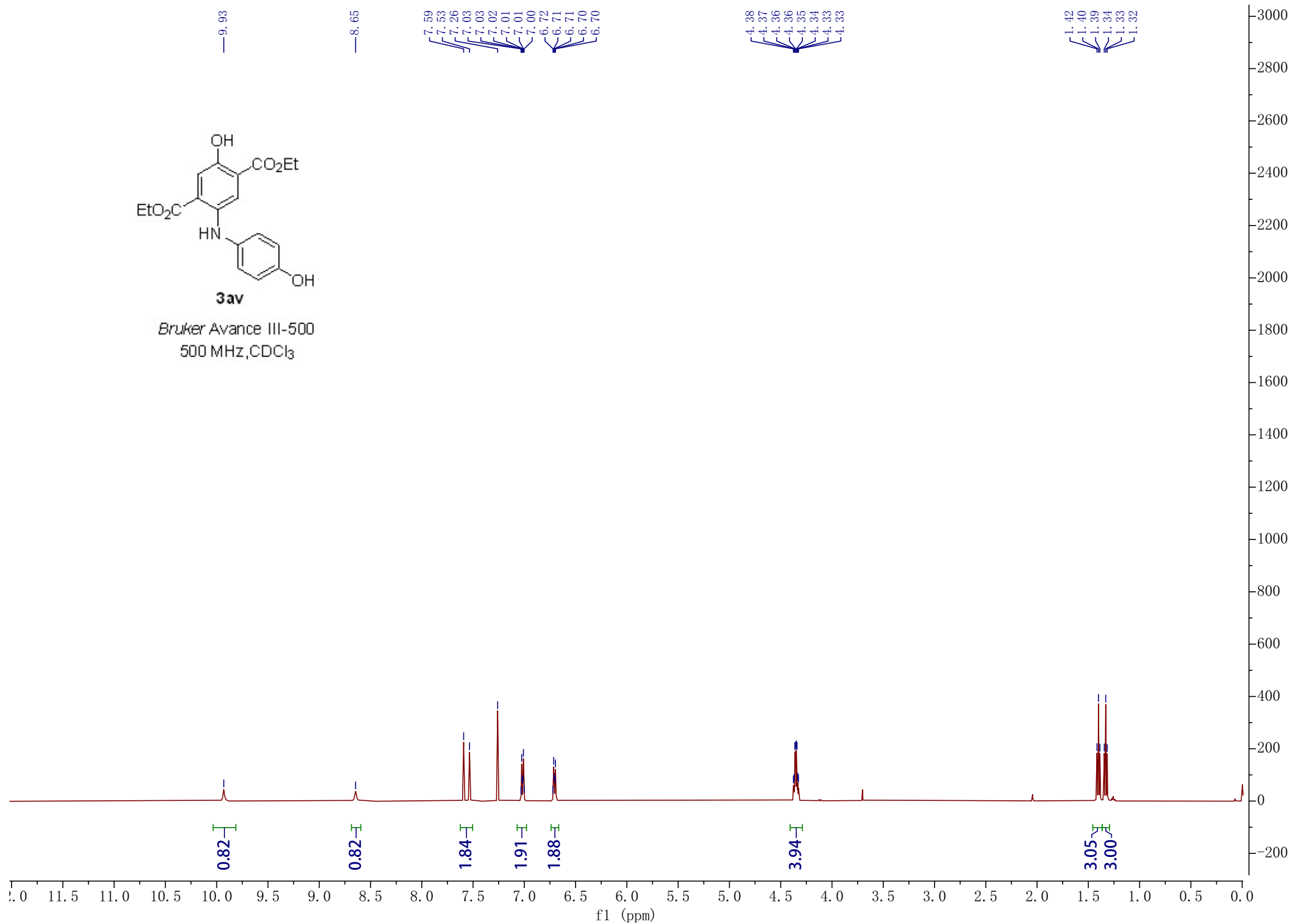
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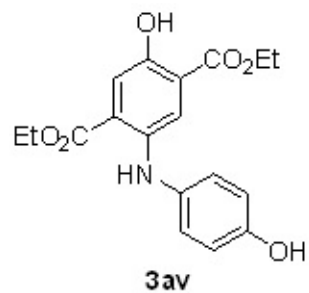
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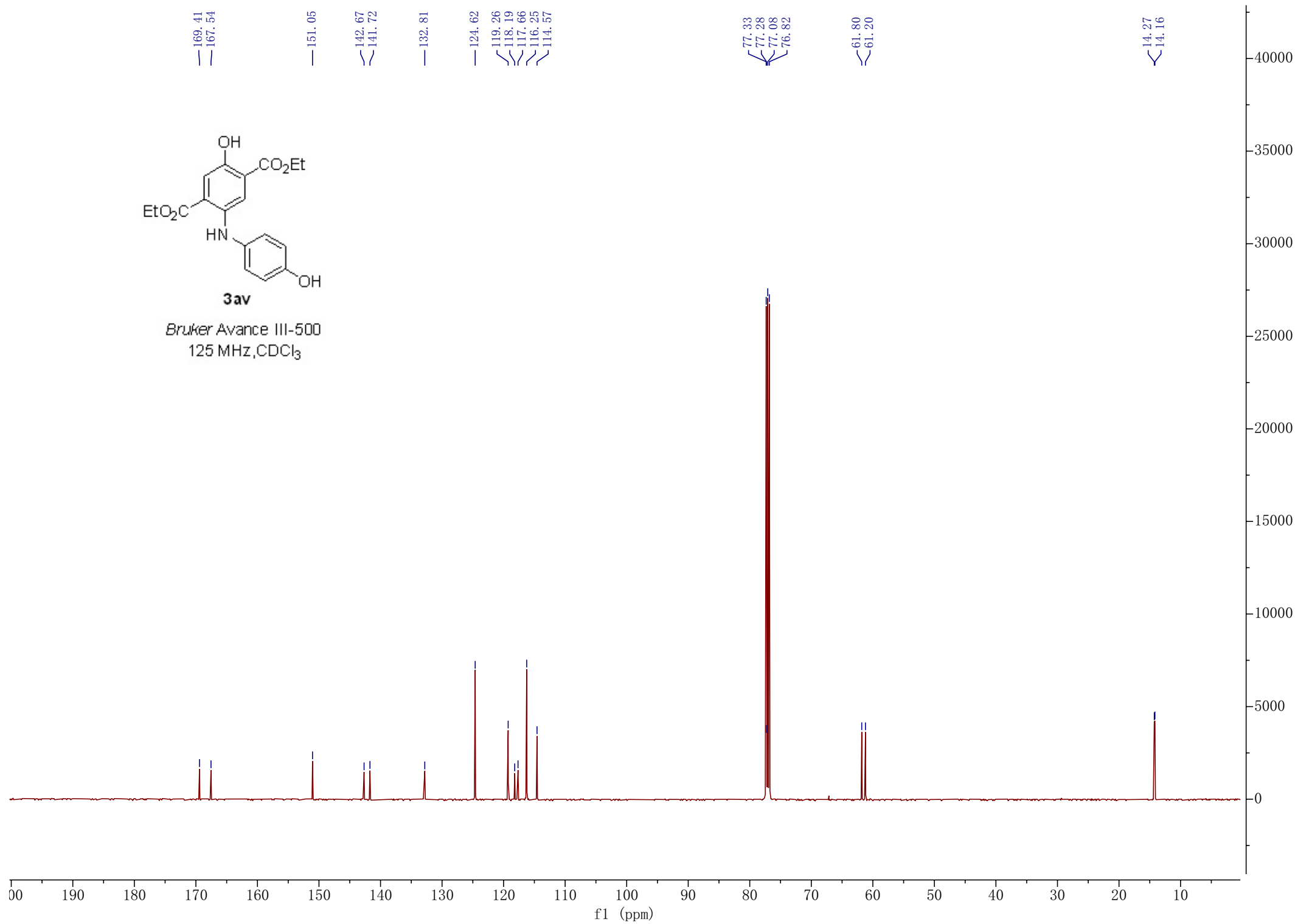


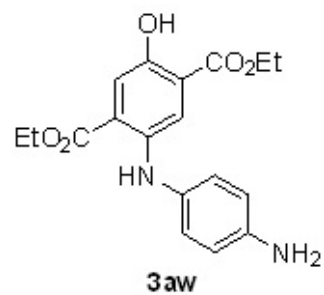
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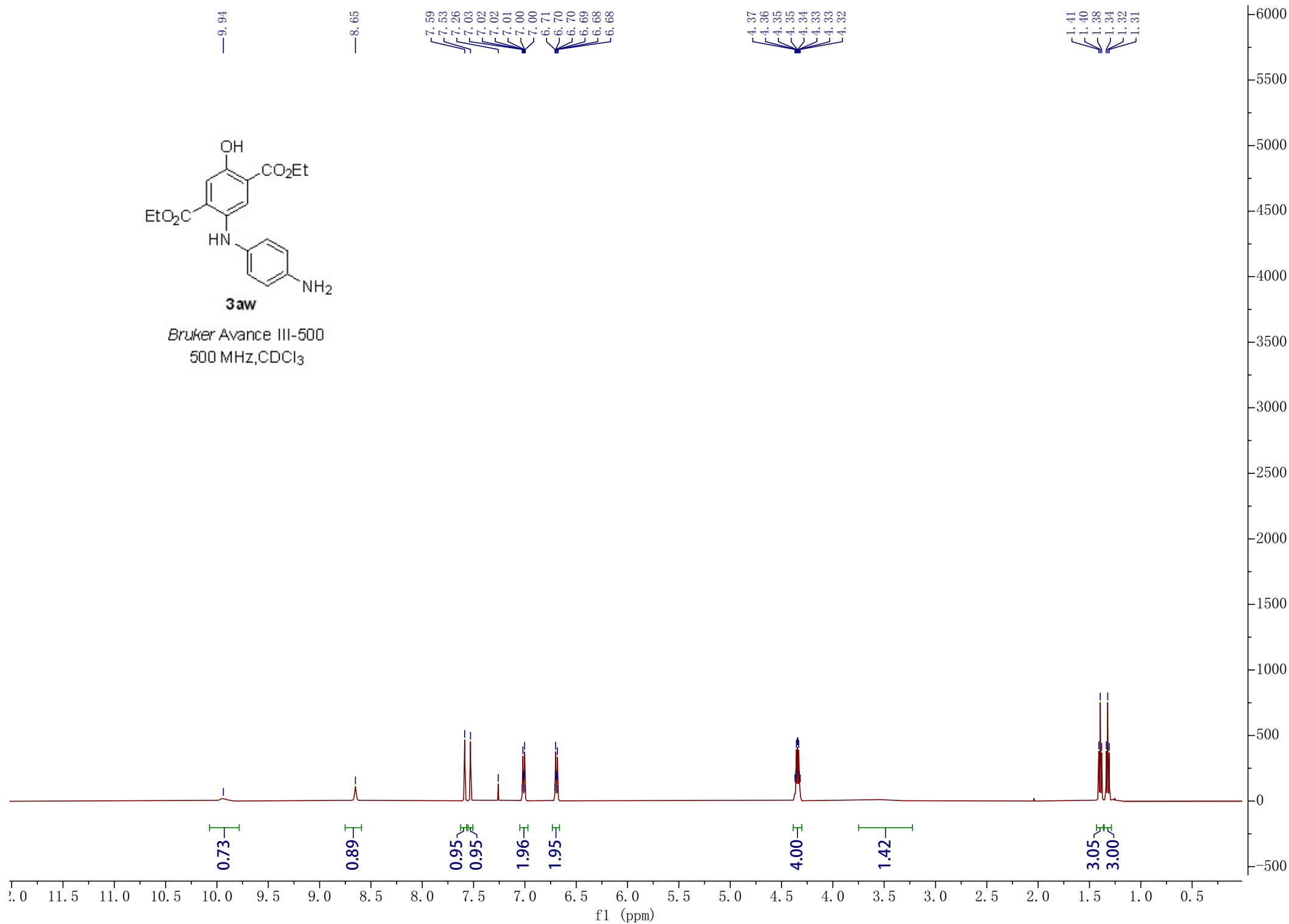


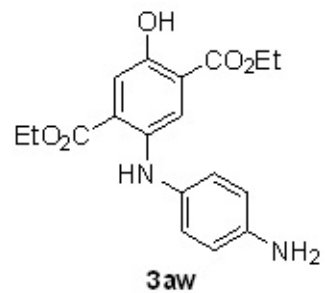
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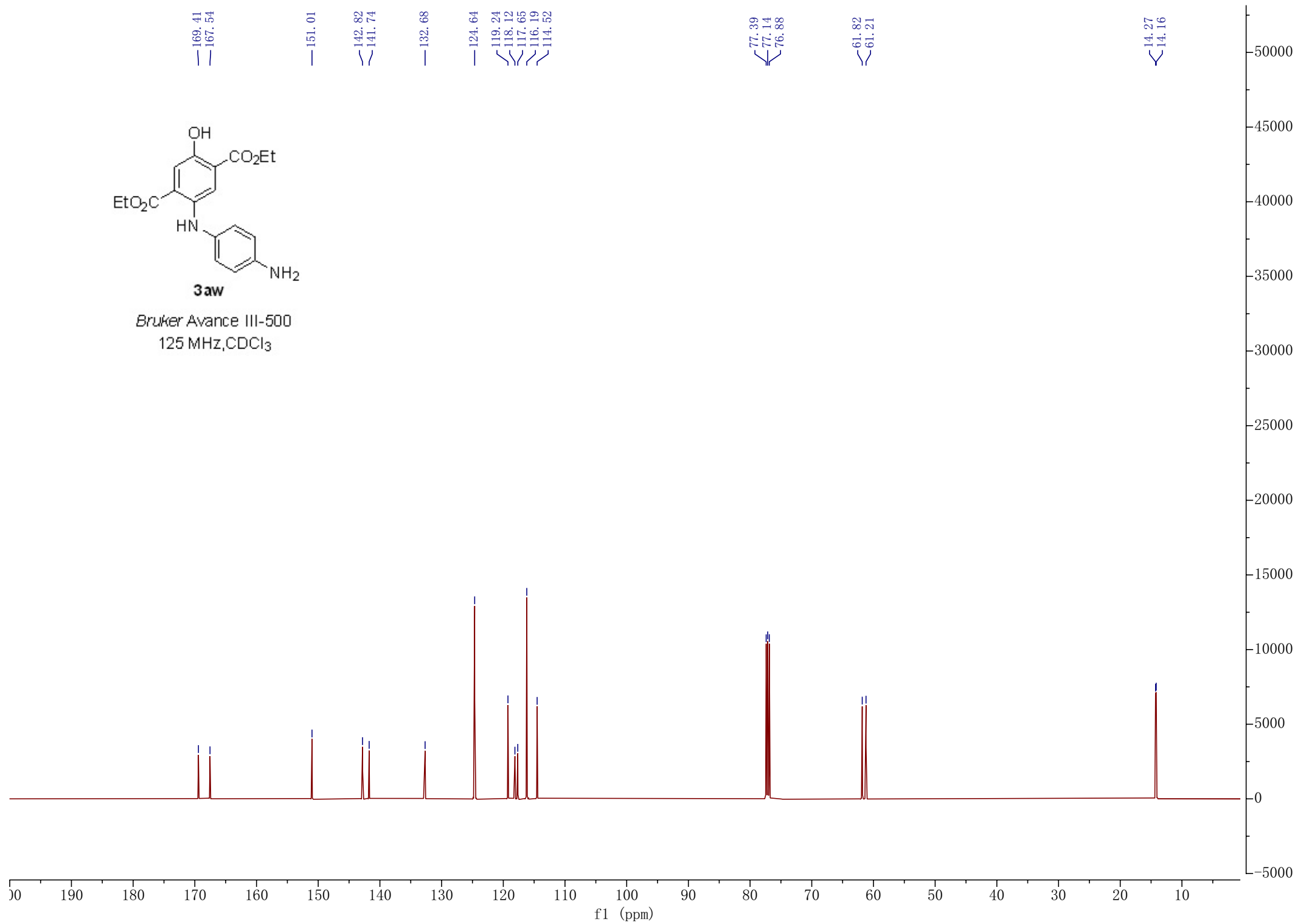


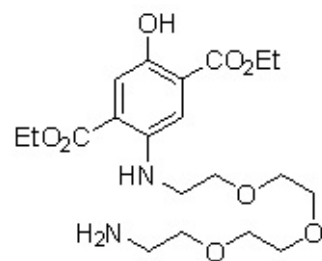
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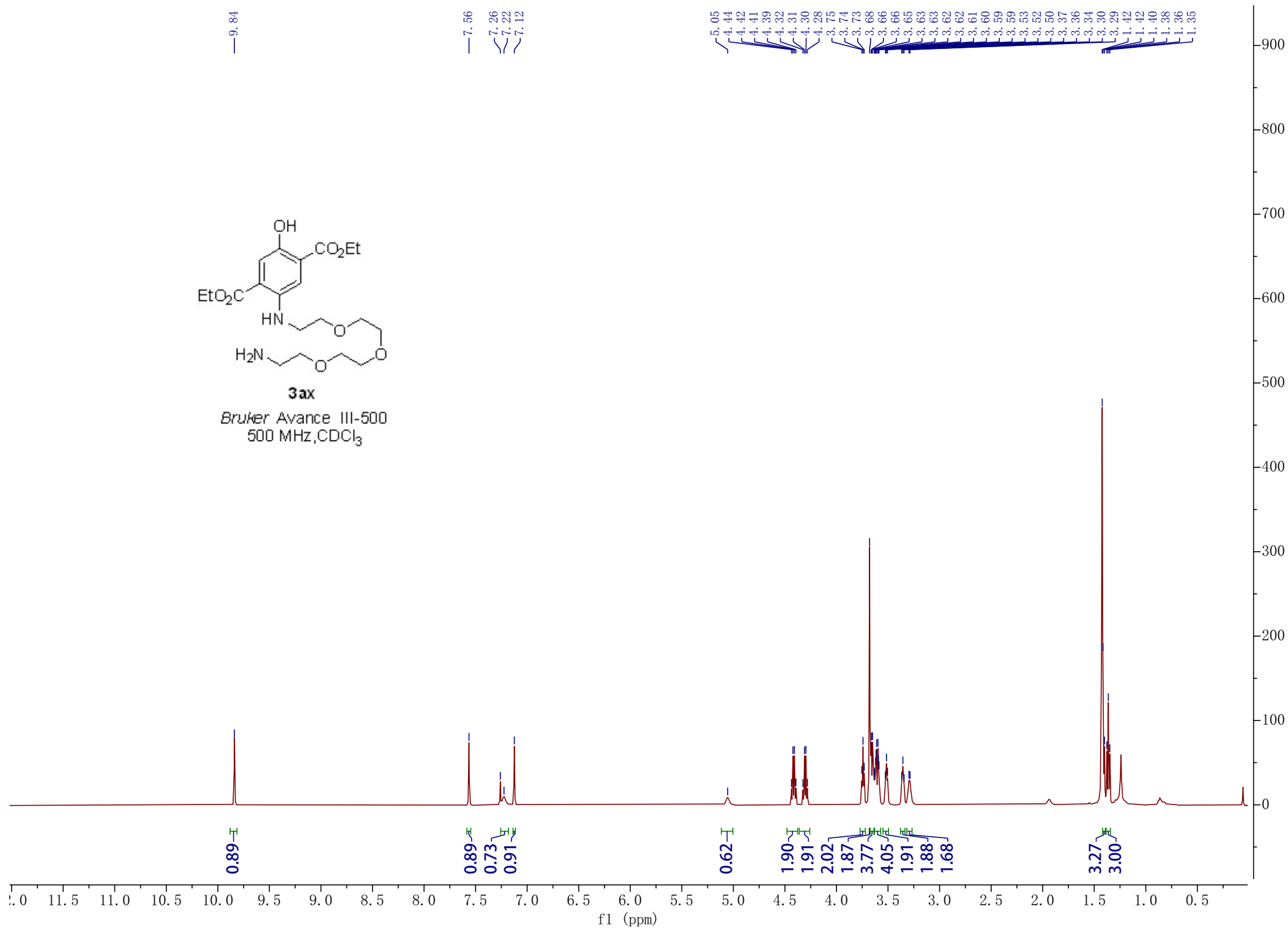
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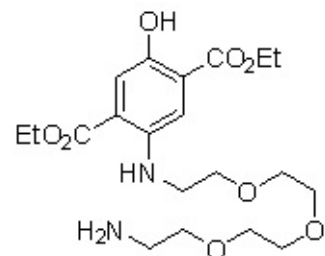




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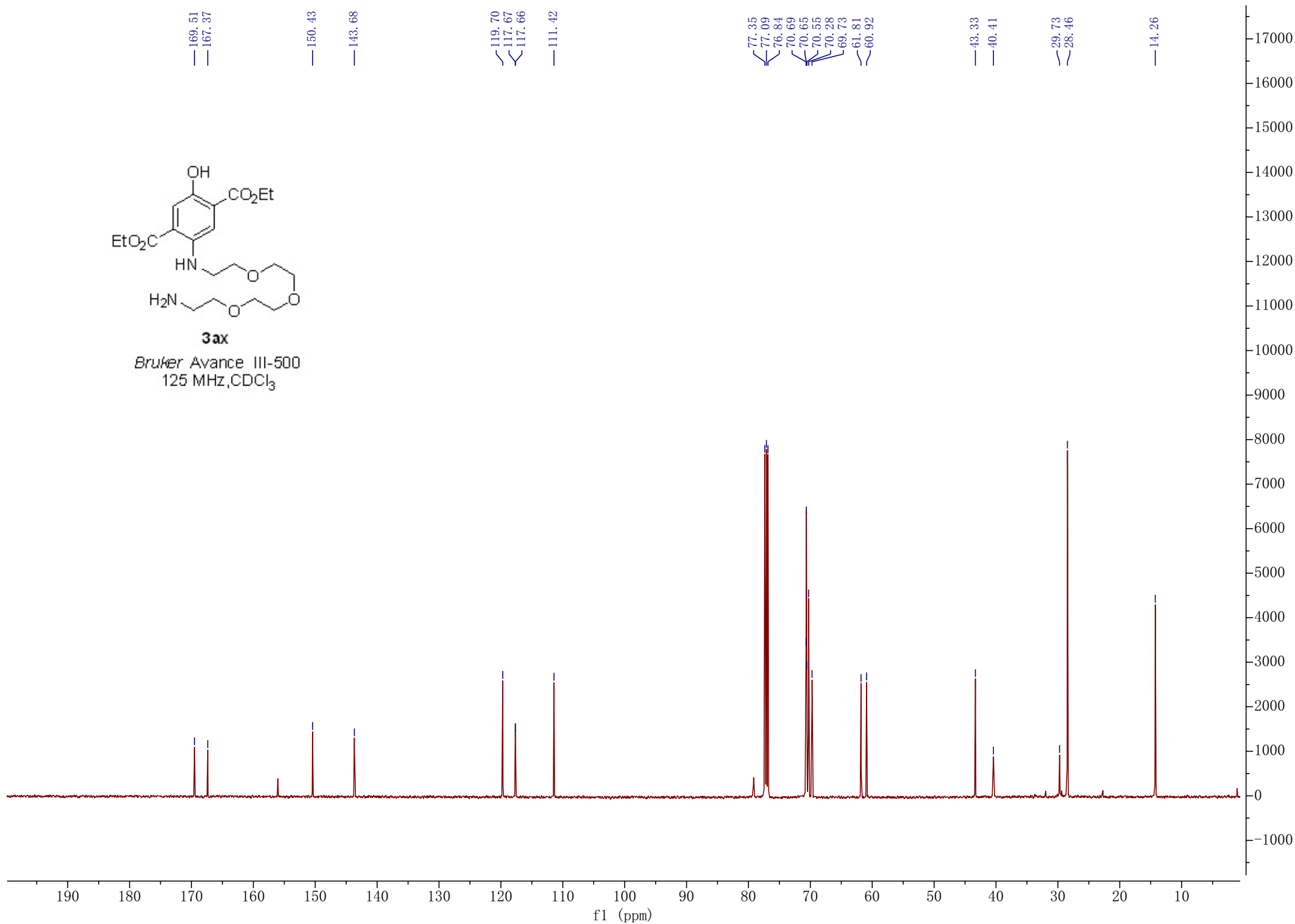
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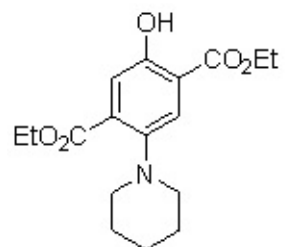




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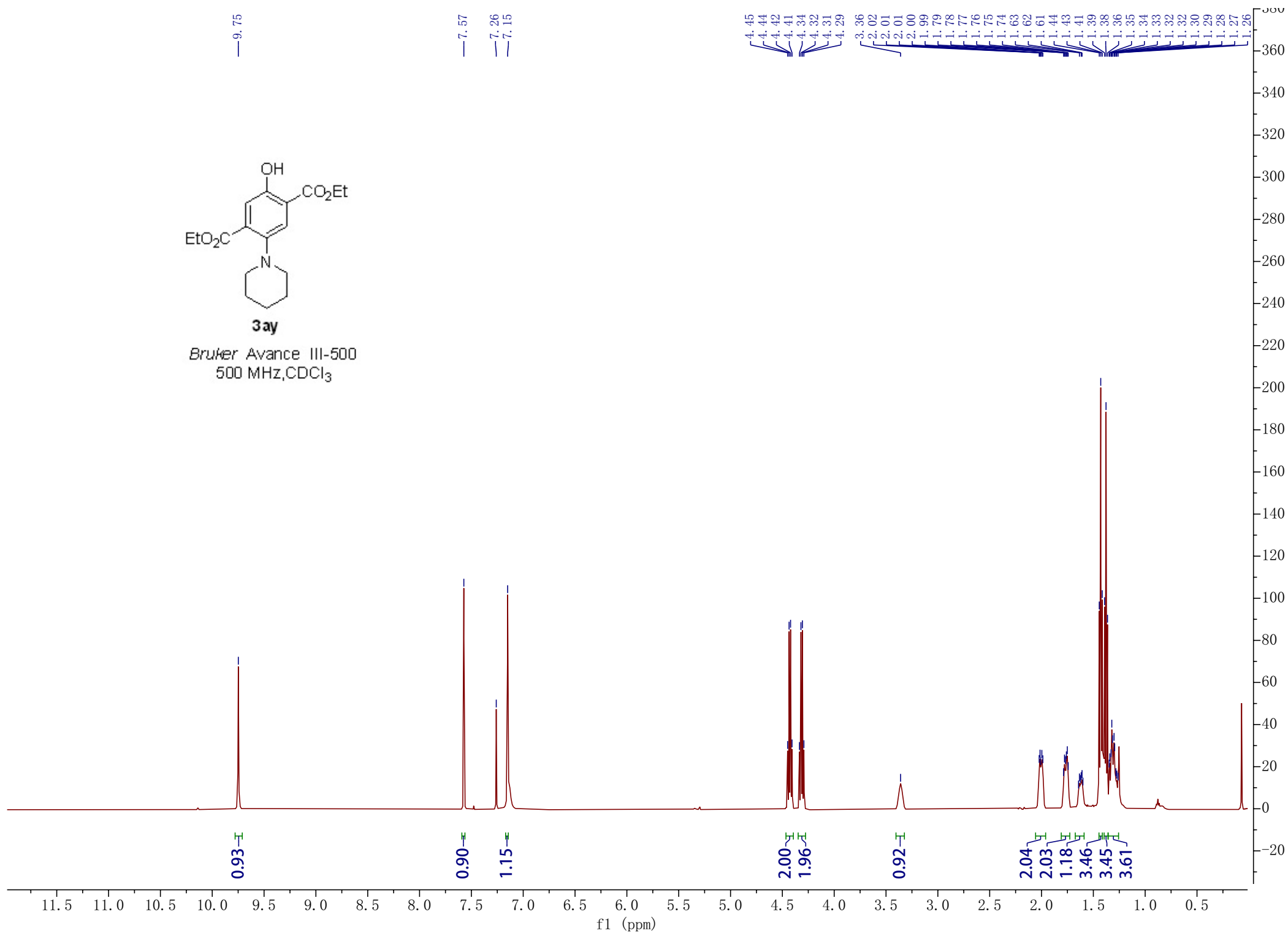
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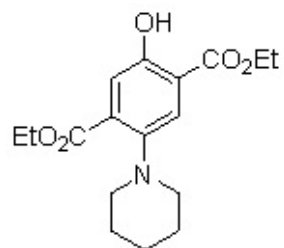




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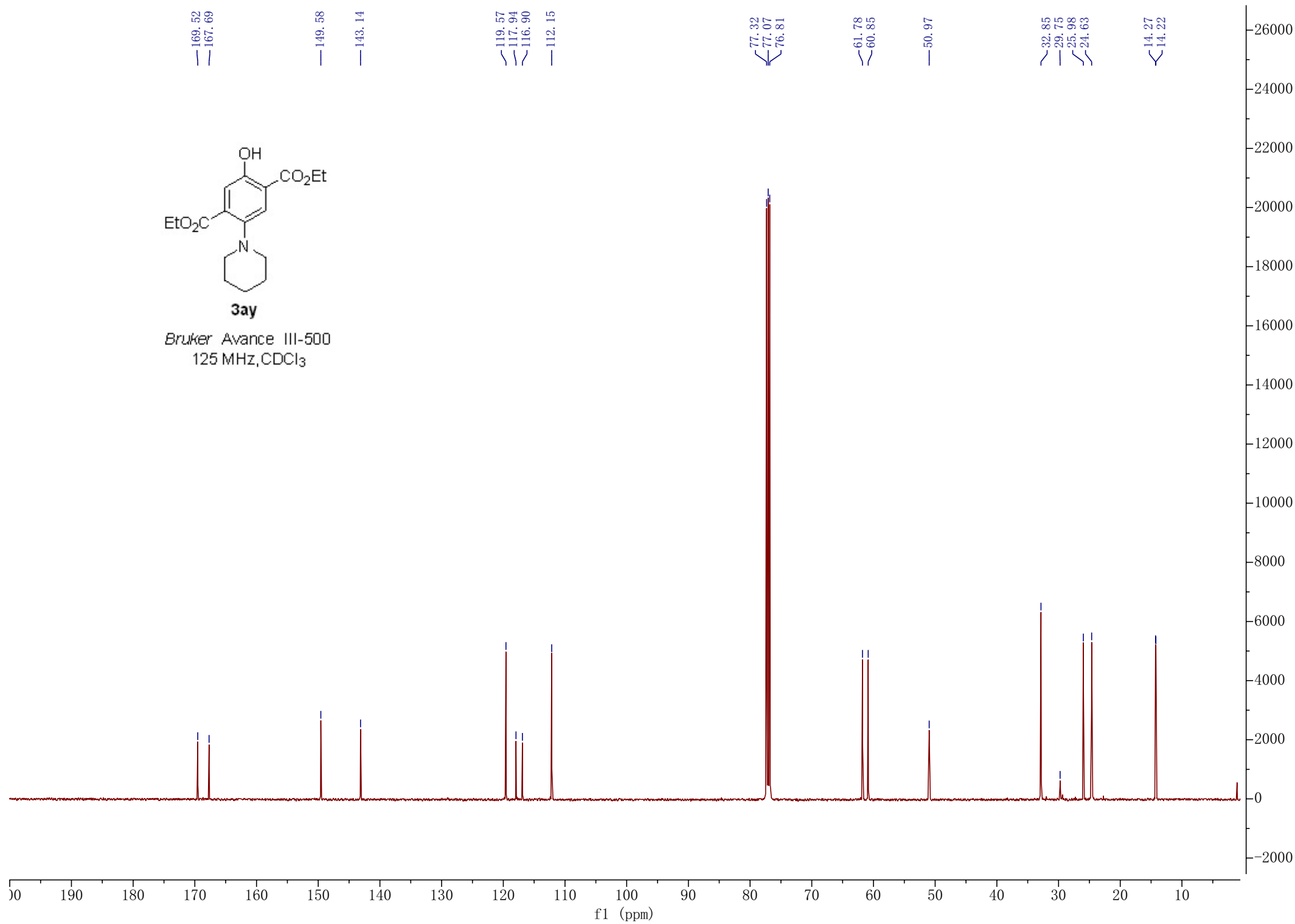
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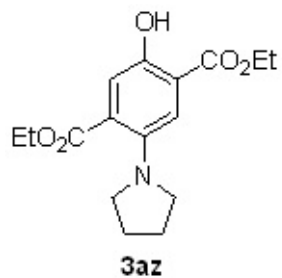




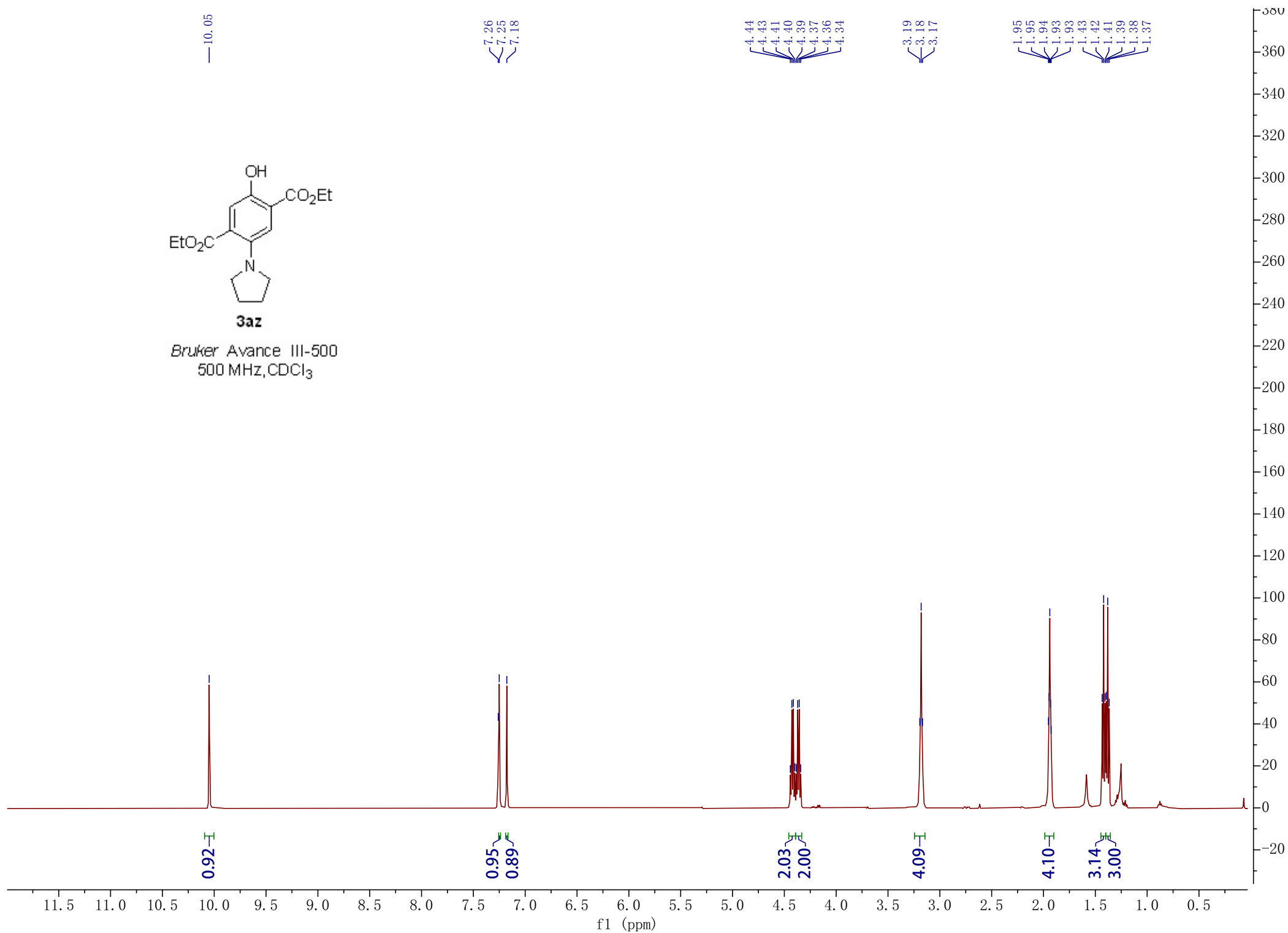
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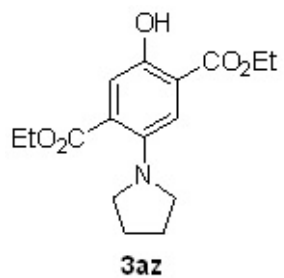
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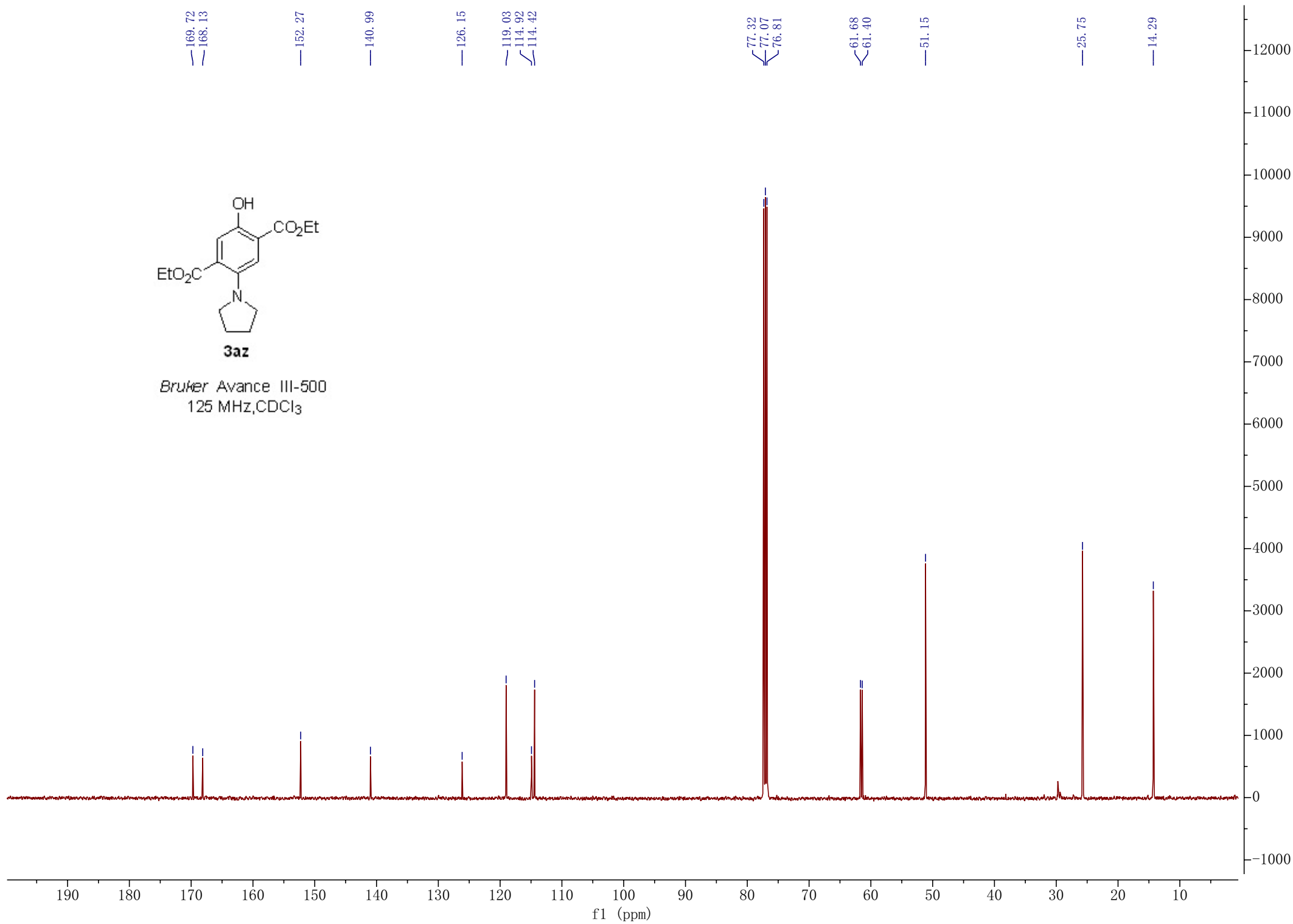


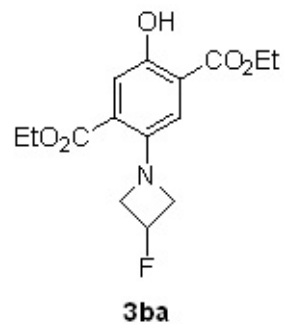
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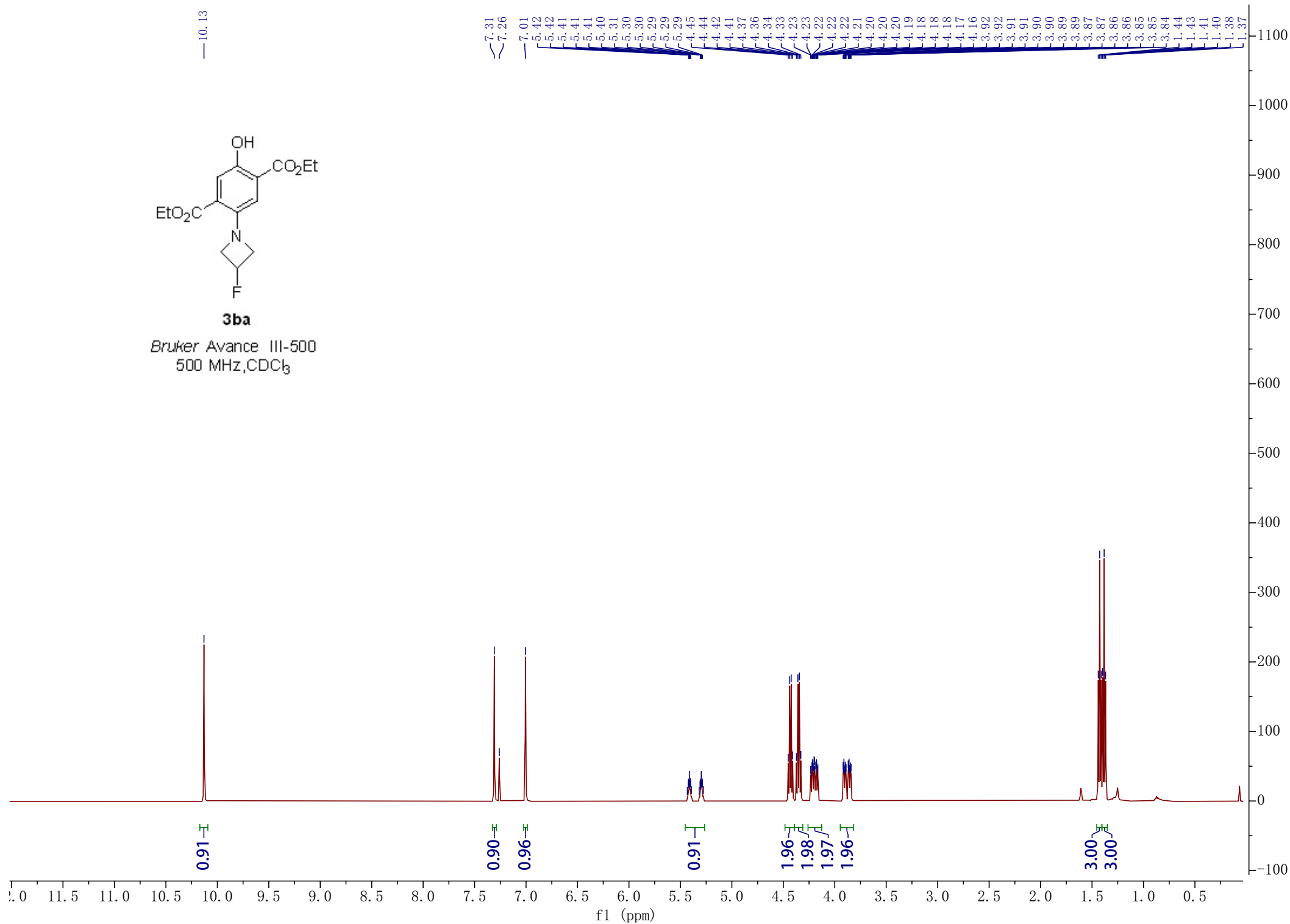


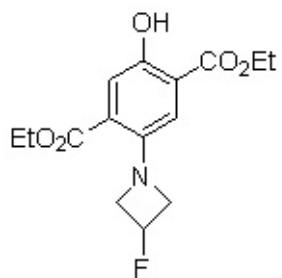
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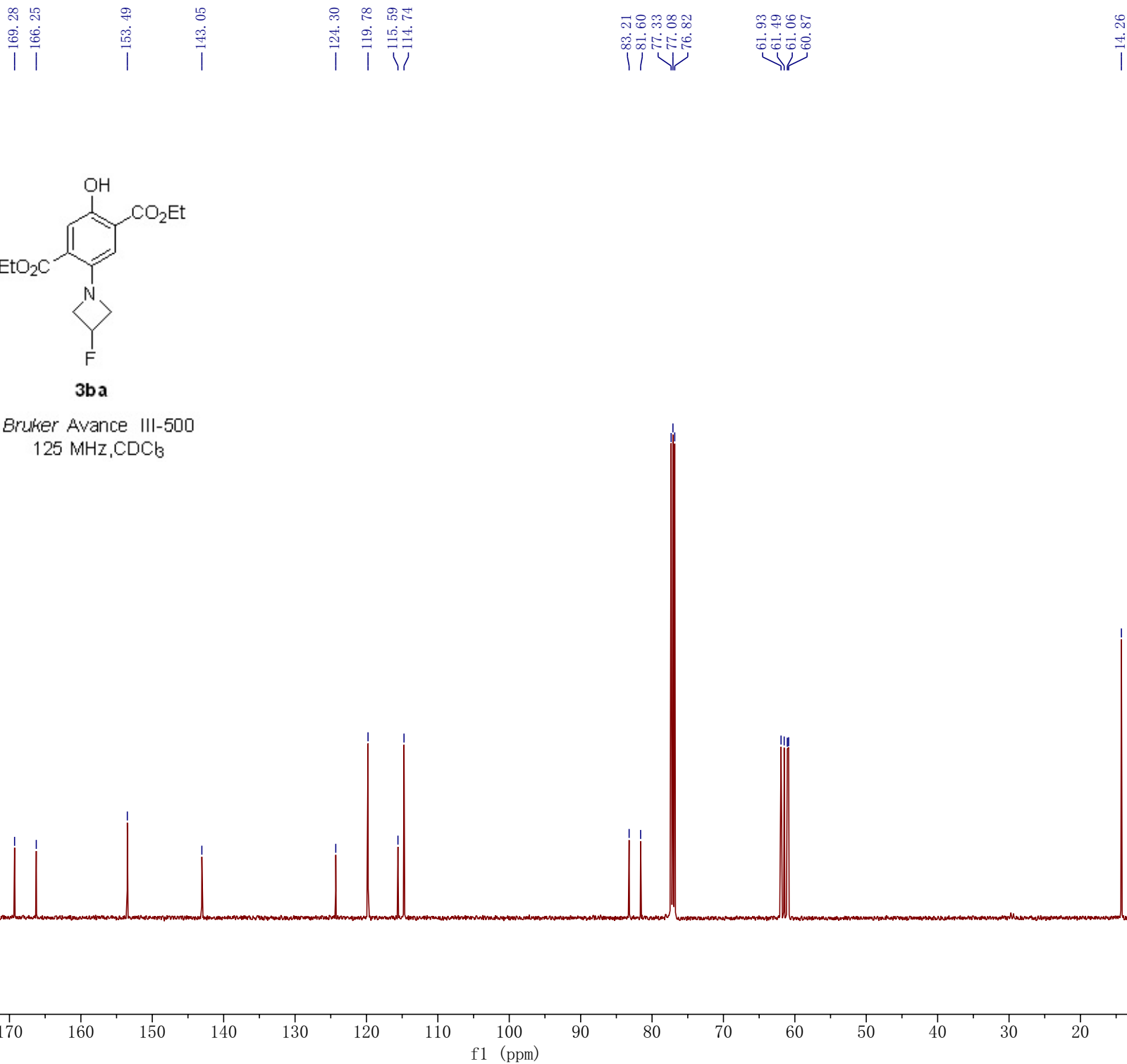
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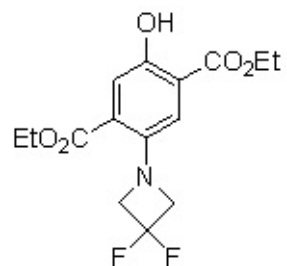




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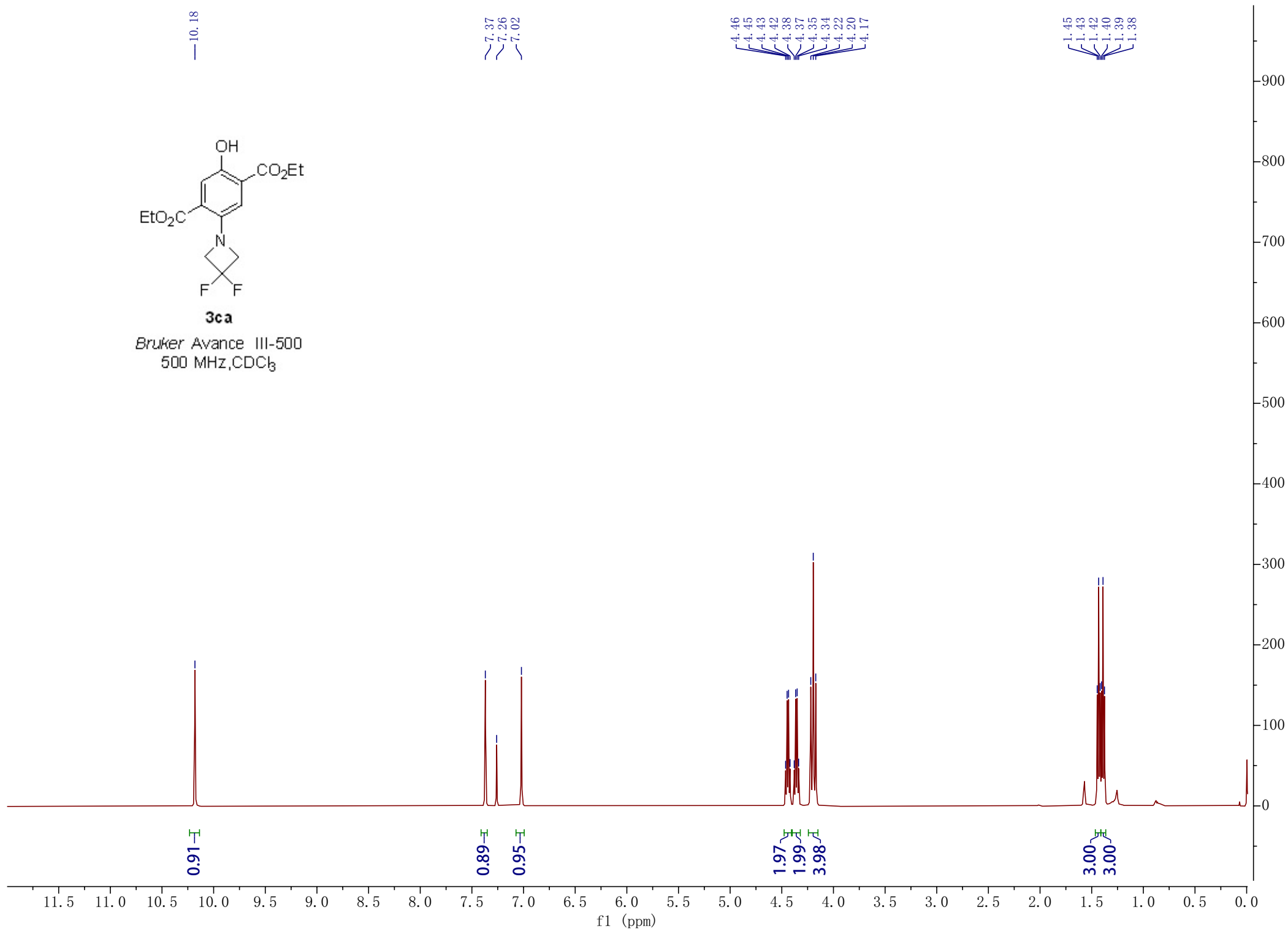
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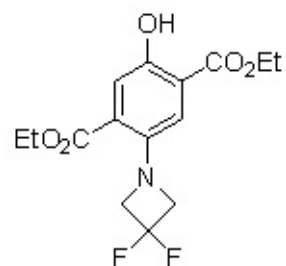




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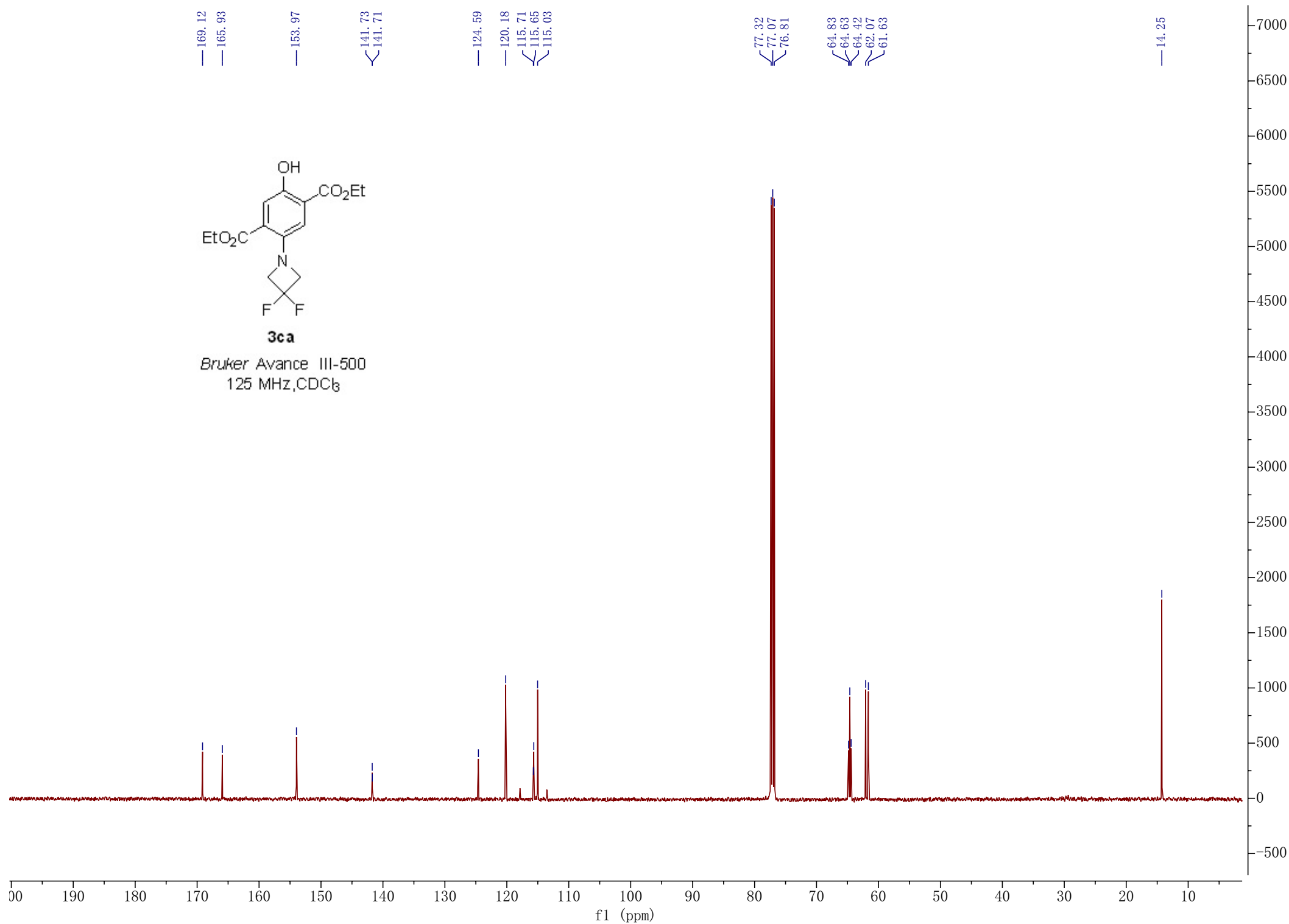
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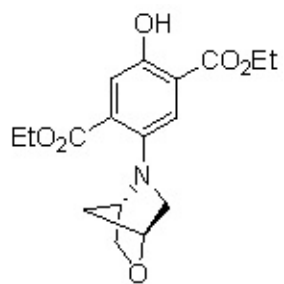




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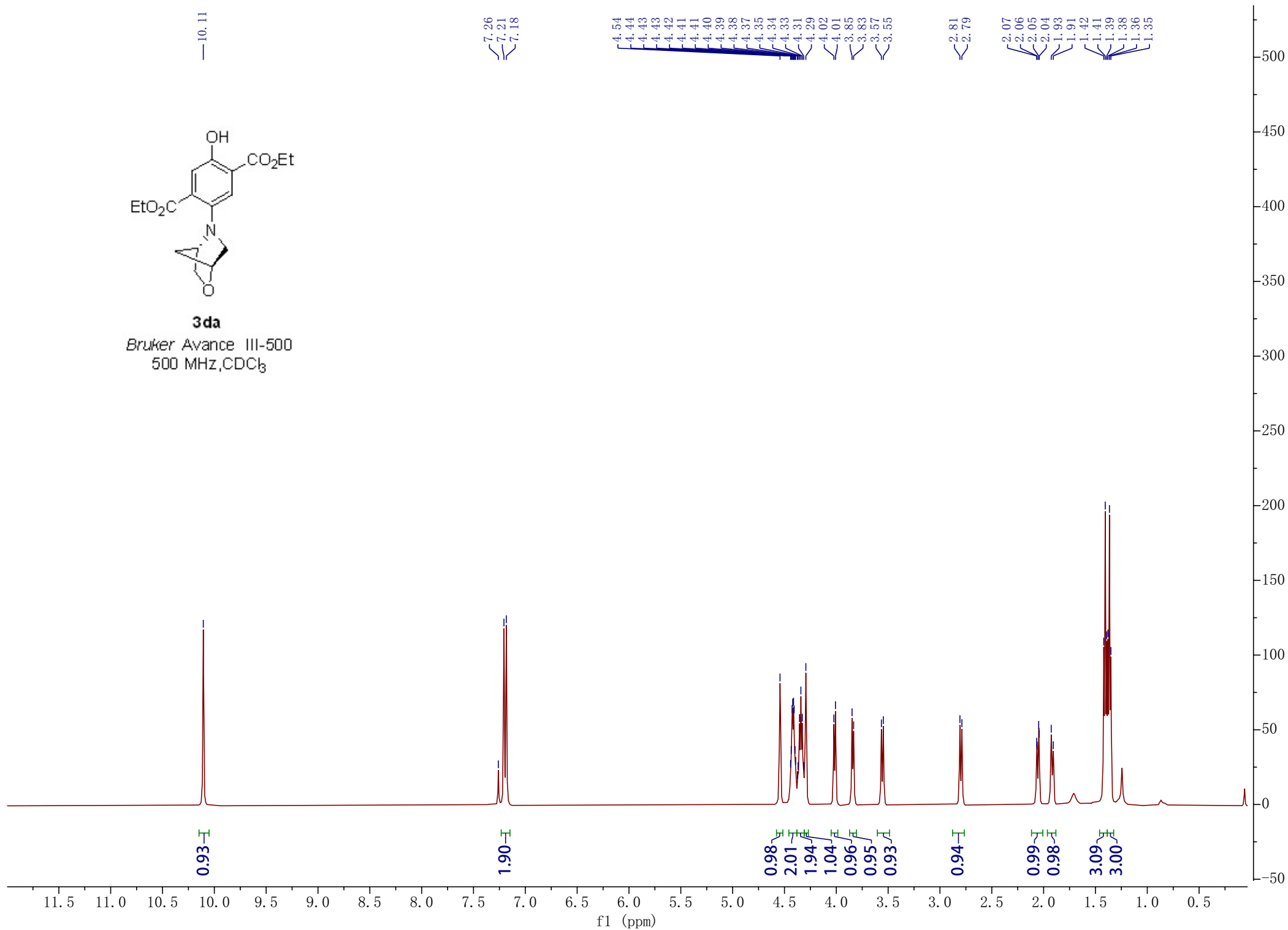
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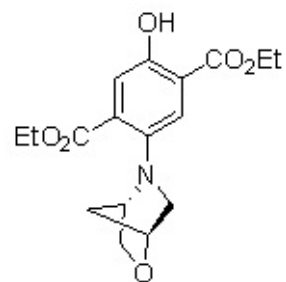




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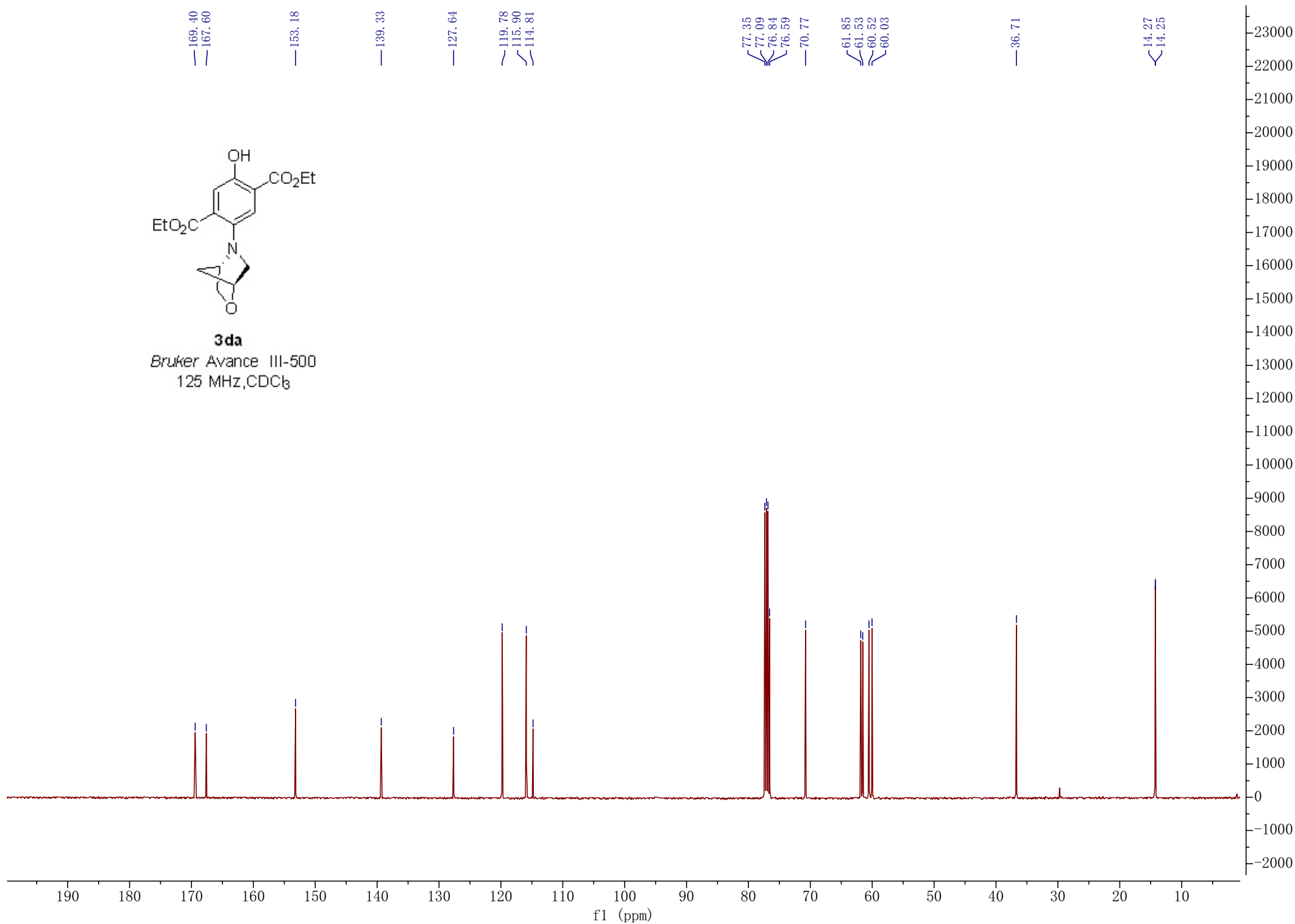
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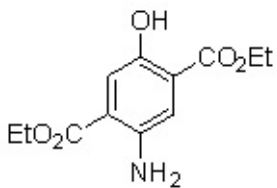




3da

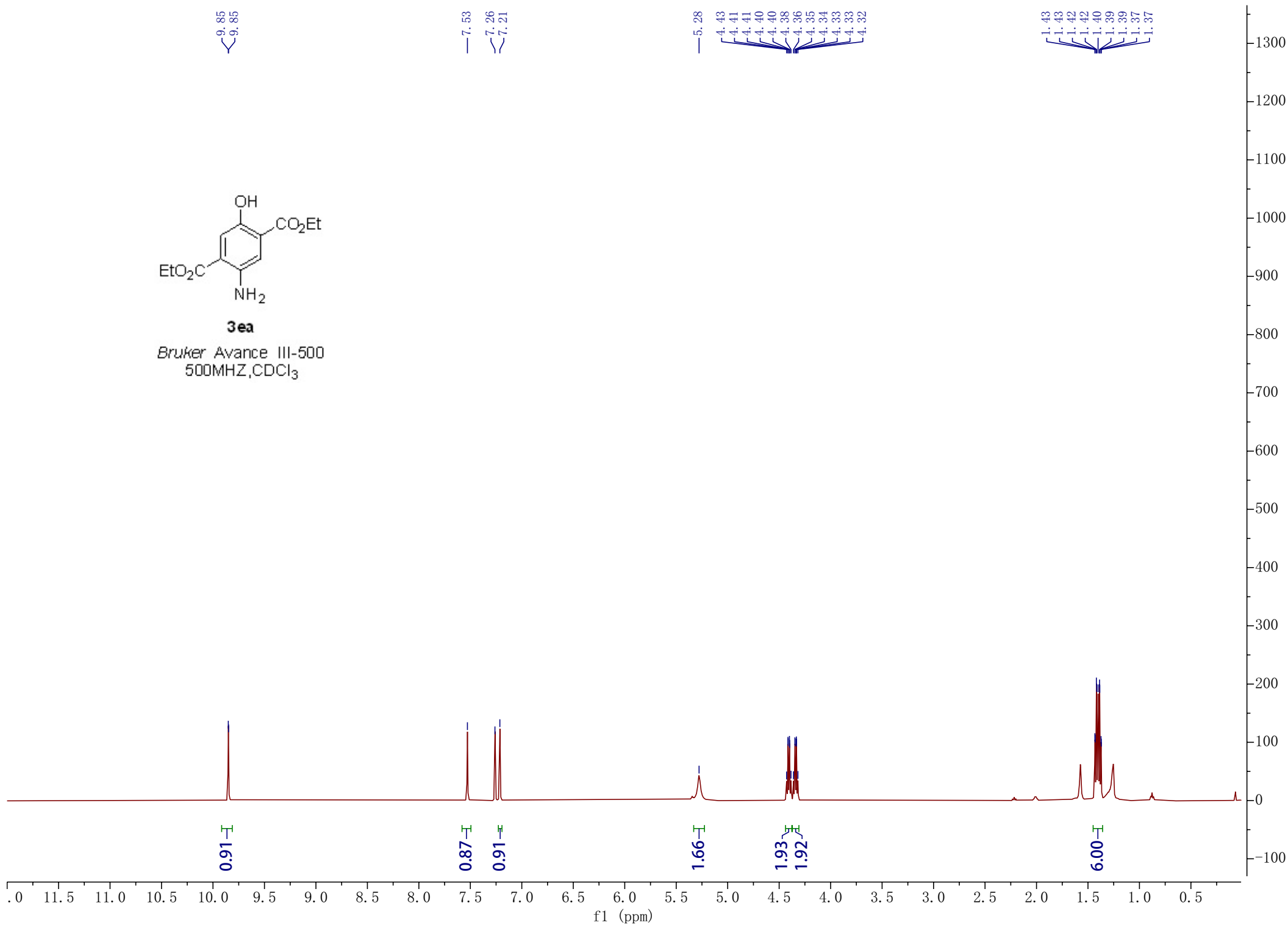
Bruker Avance III-500
125 MHz, CDCl₃

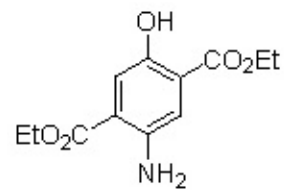




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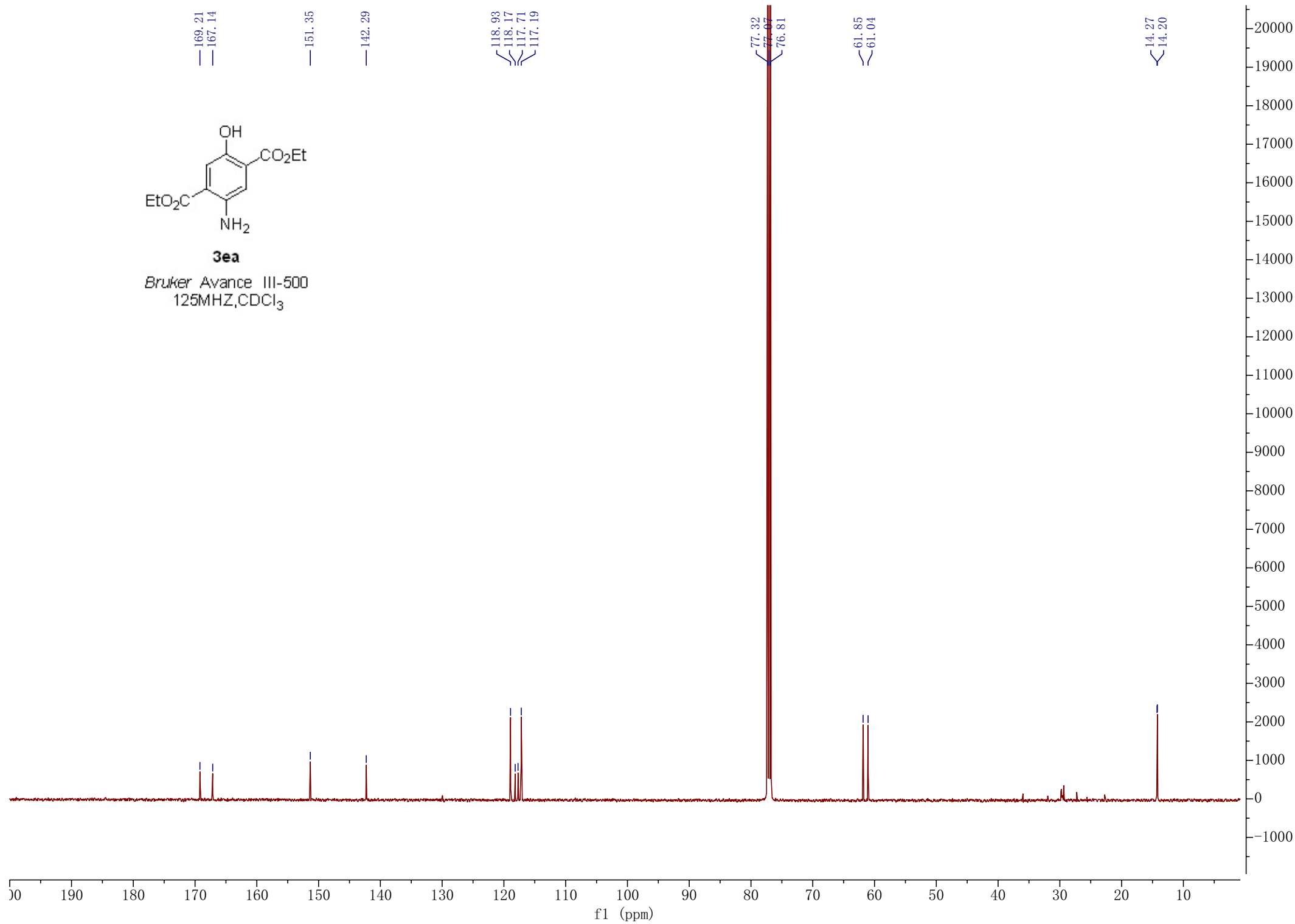
Bruker Avance III-500
500MHZ,CDCl₃

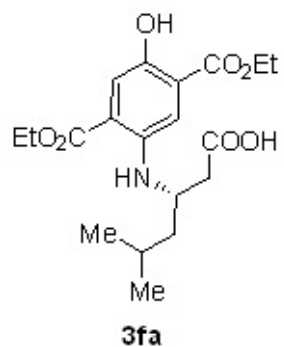




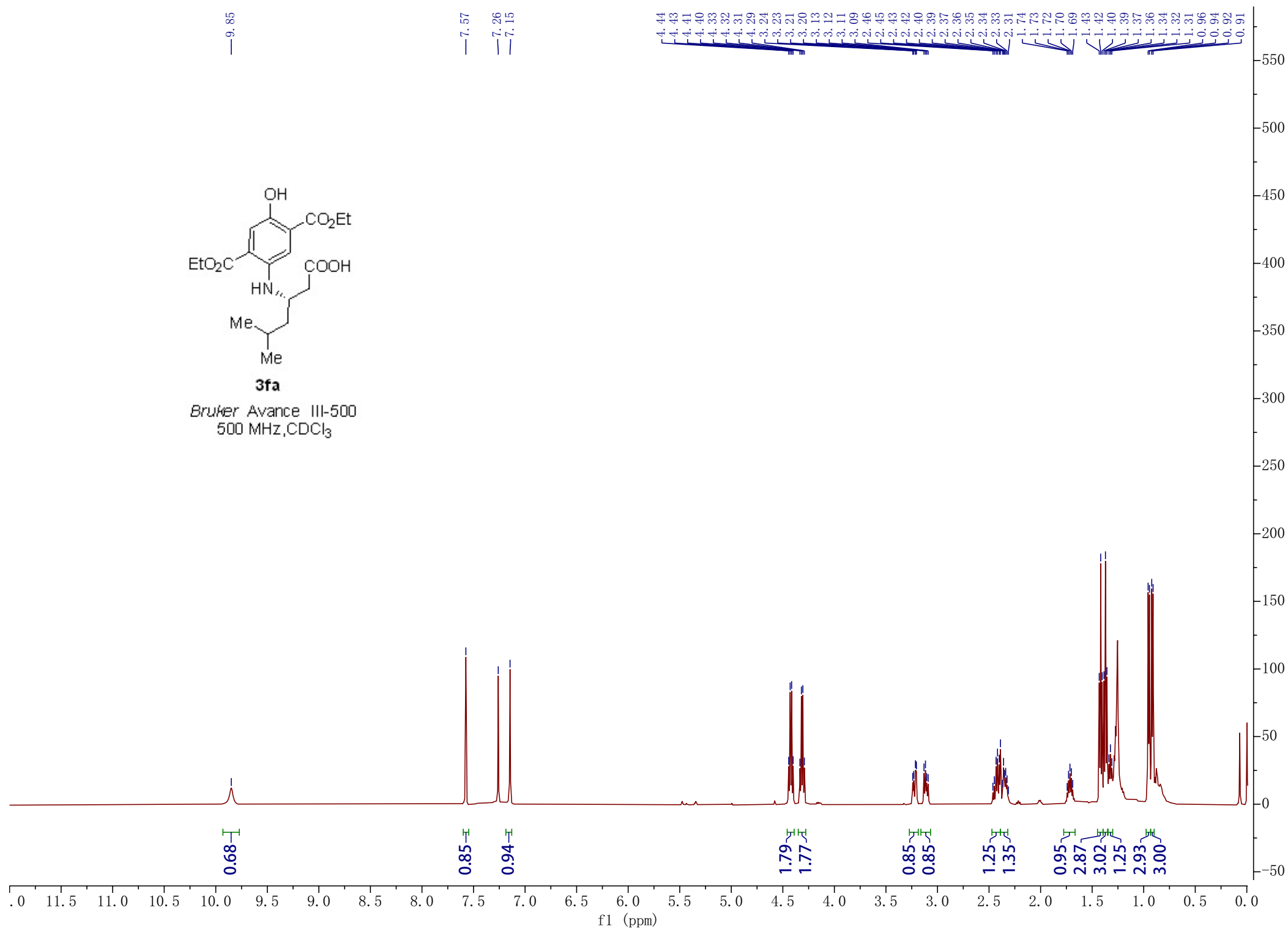
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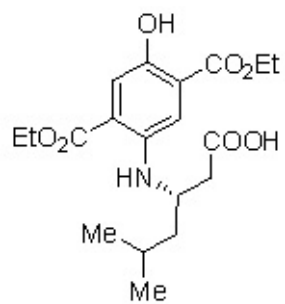
Bruker Avance III-500
125MHZ,CDCl₃





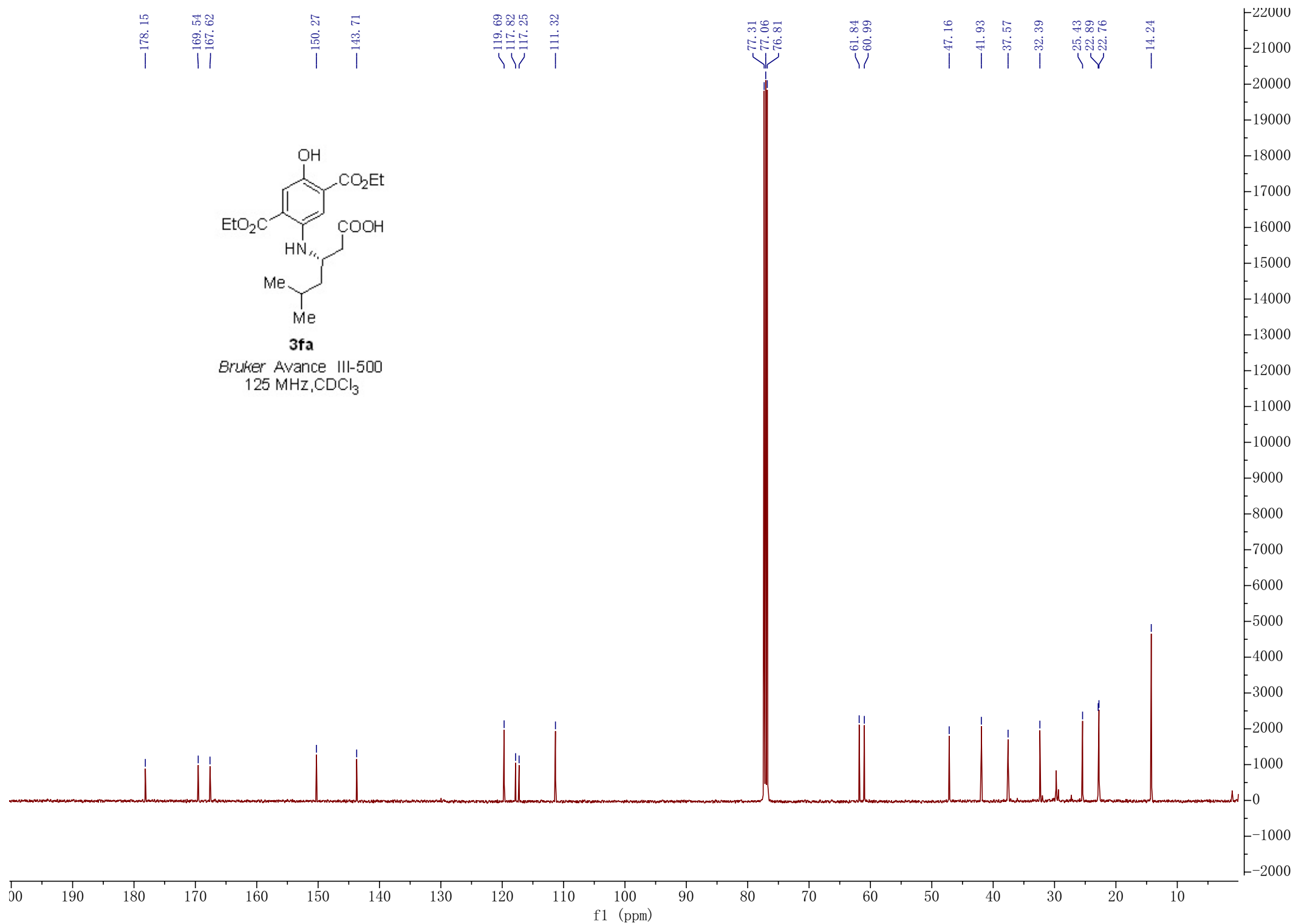
Bruker Avance III-500
500 MHz, CDCl₃

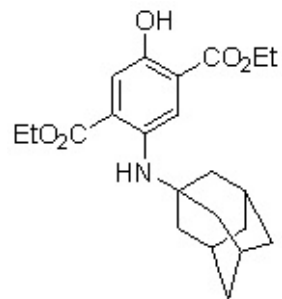




3fa

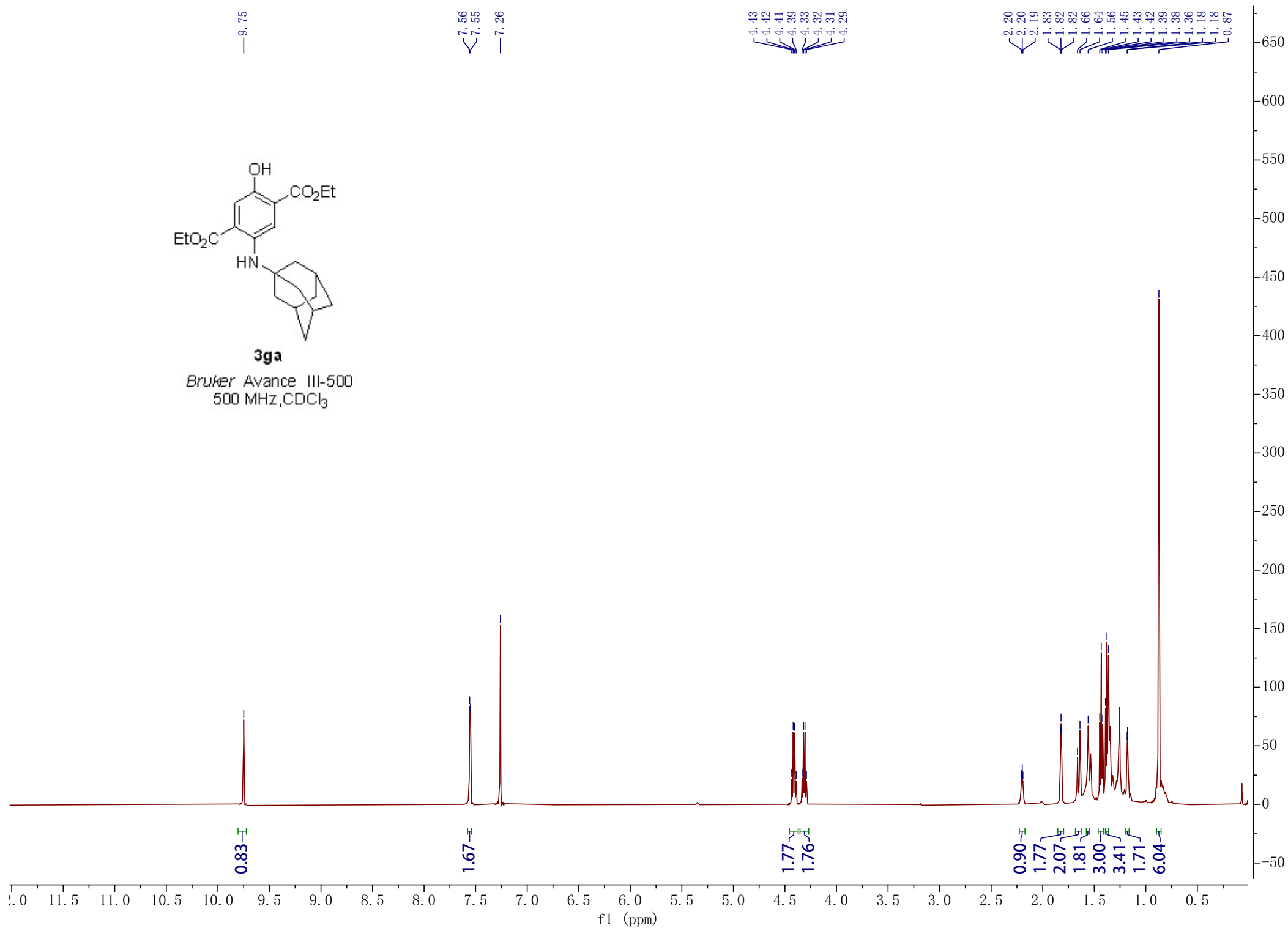
Bruker Avance III-500
125 MHz, CDCl₃

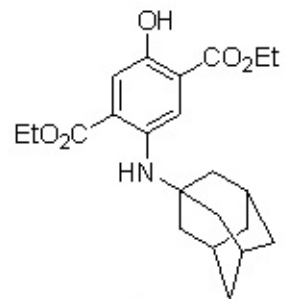




3ga

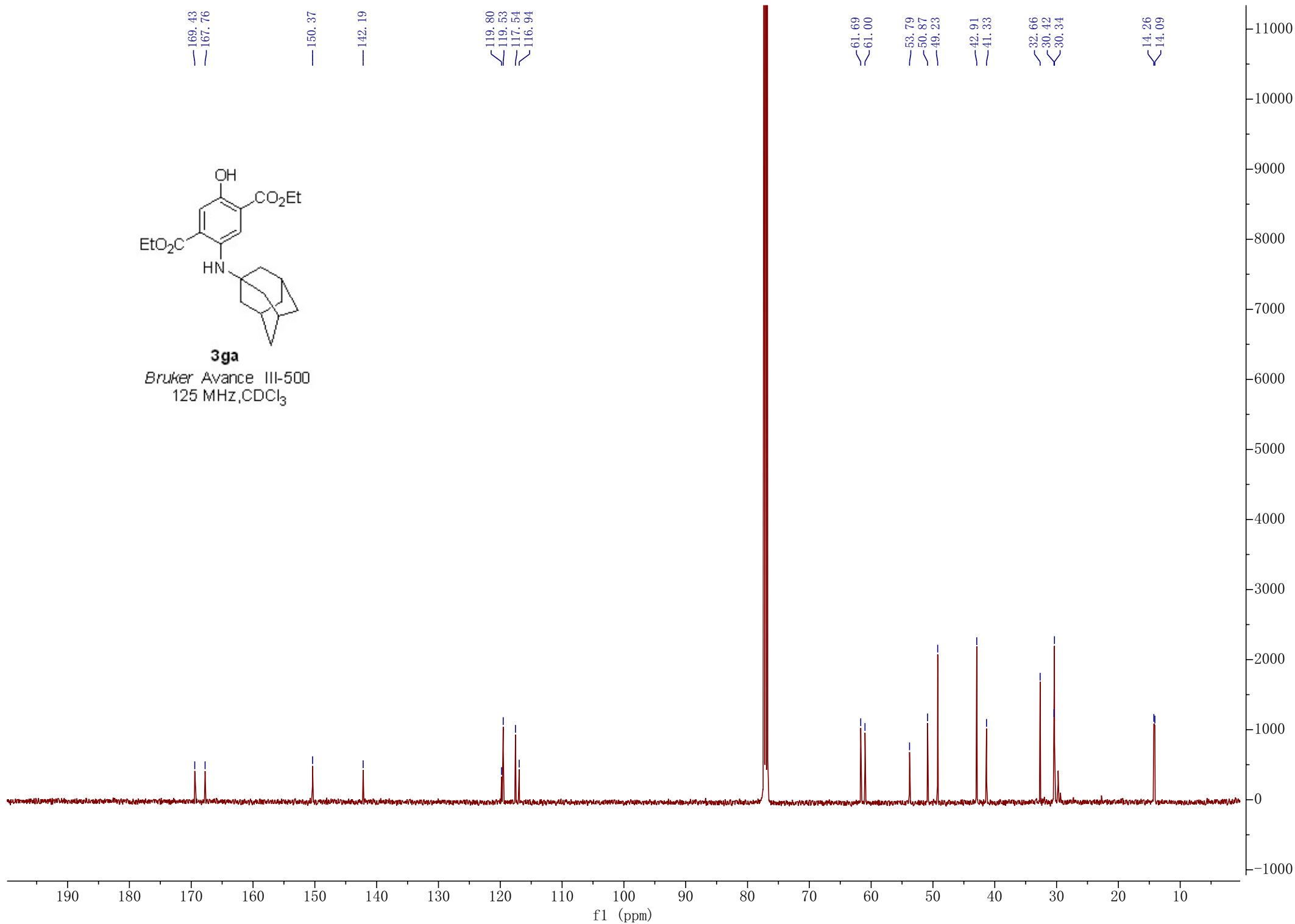
Bruker Avance III-500
500 MHz, CDCl₃

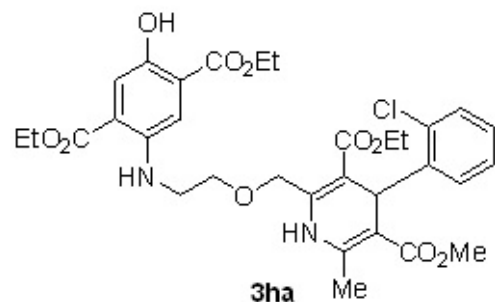




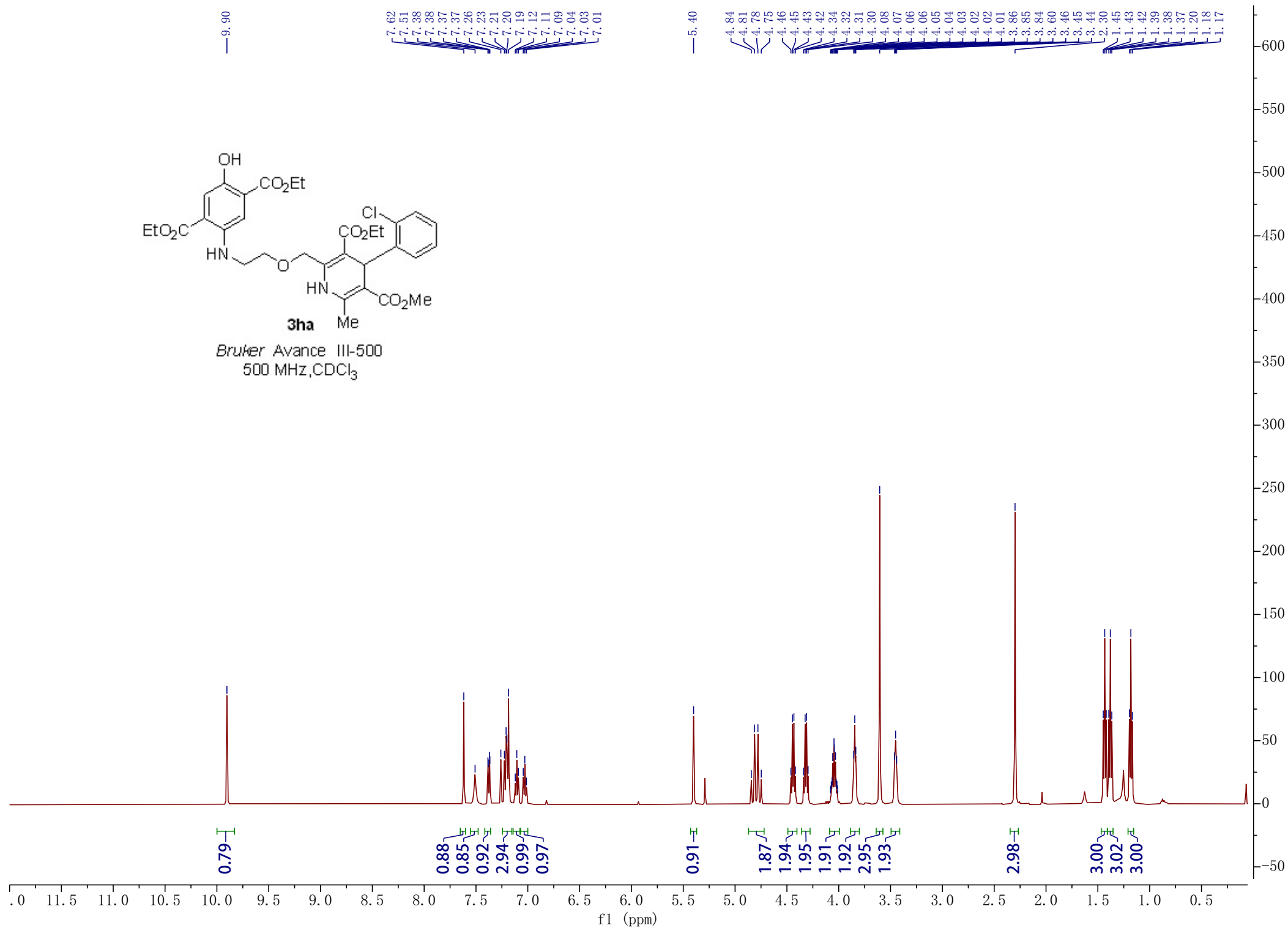
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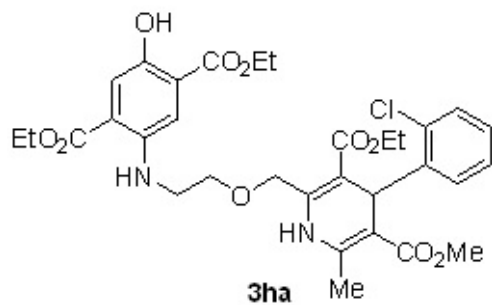
Bruker Avance III-500
125 MHz, CDCl₃





Bruker Avance III-500
500 MHz, CDCl₃





Bruker Avance III-500
125 MHz, CDCl₃

169.37
168.08
167.75
167.24

150.88
145.85
145.25
144.34
143.67

132.37
131.54
129.25
127.38
126.89

119.92
117.86
117.84
111.70

103.89
101.54

77.34
77.08
76.83

69.84
67.98

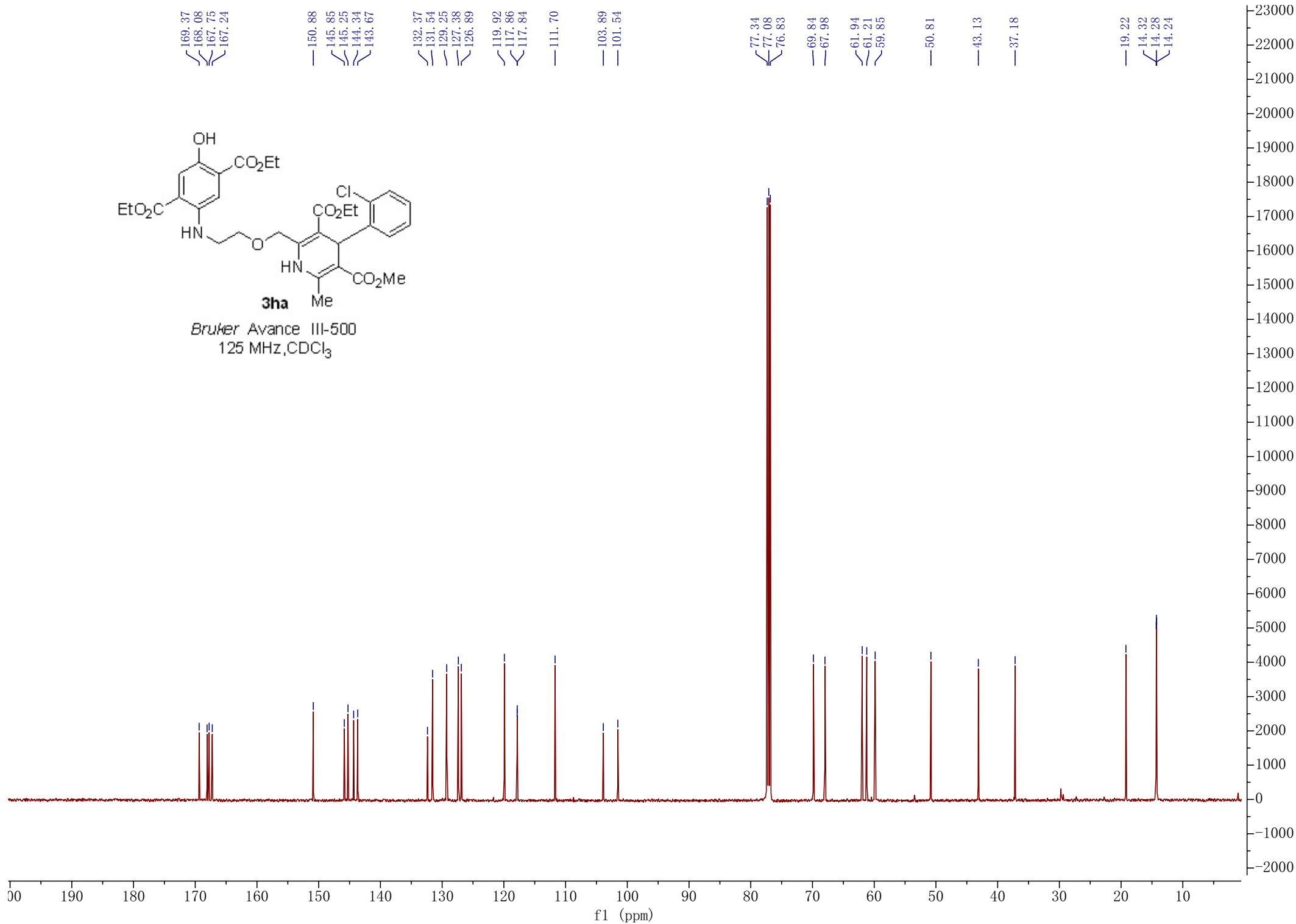
61.94
61.21
59.85

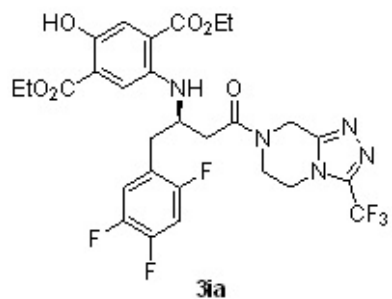
50.81

43.13

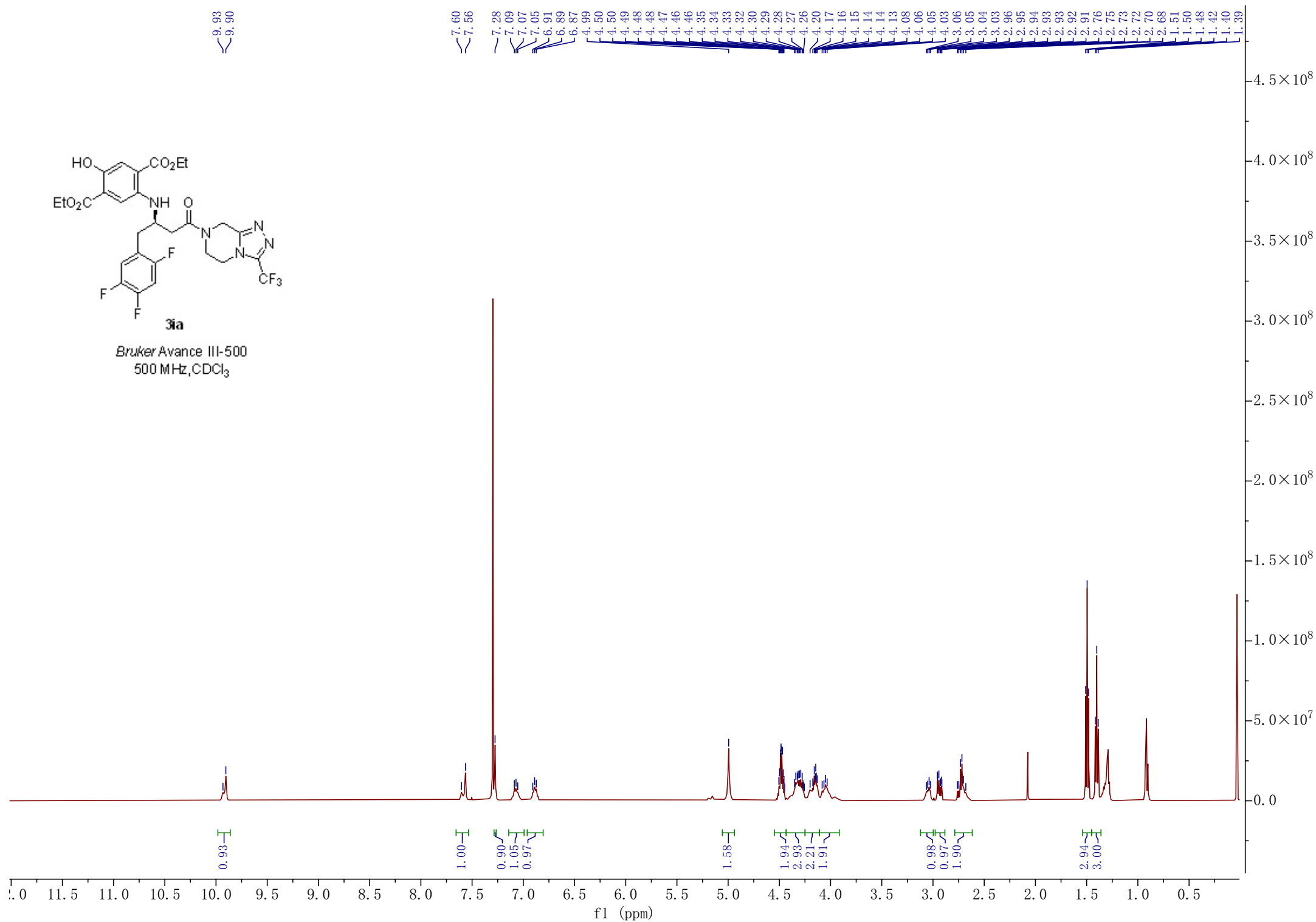
37.18

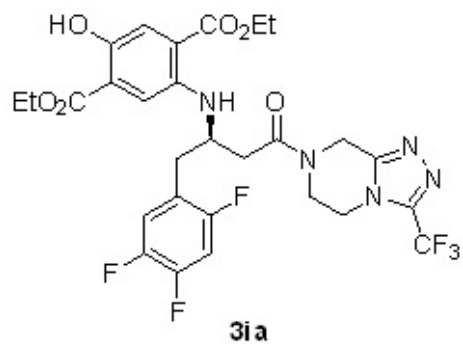
19.22
14.32
14.28
14.24



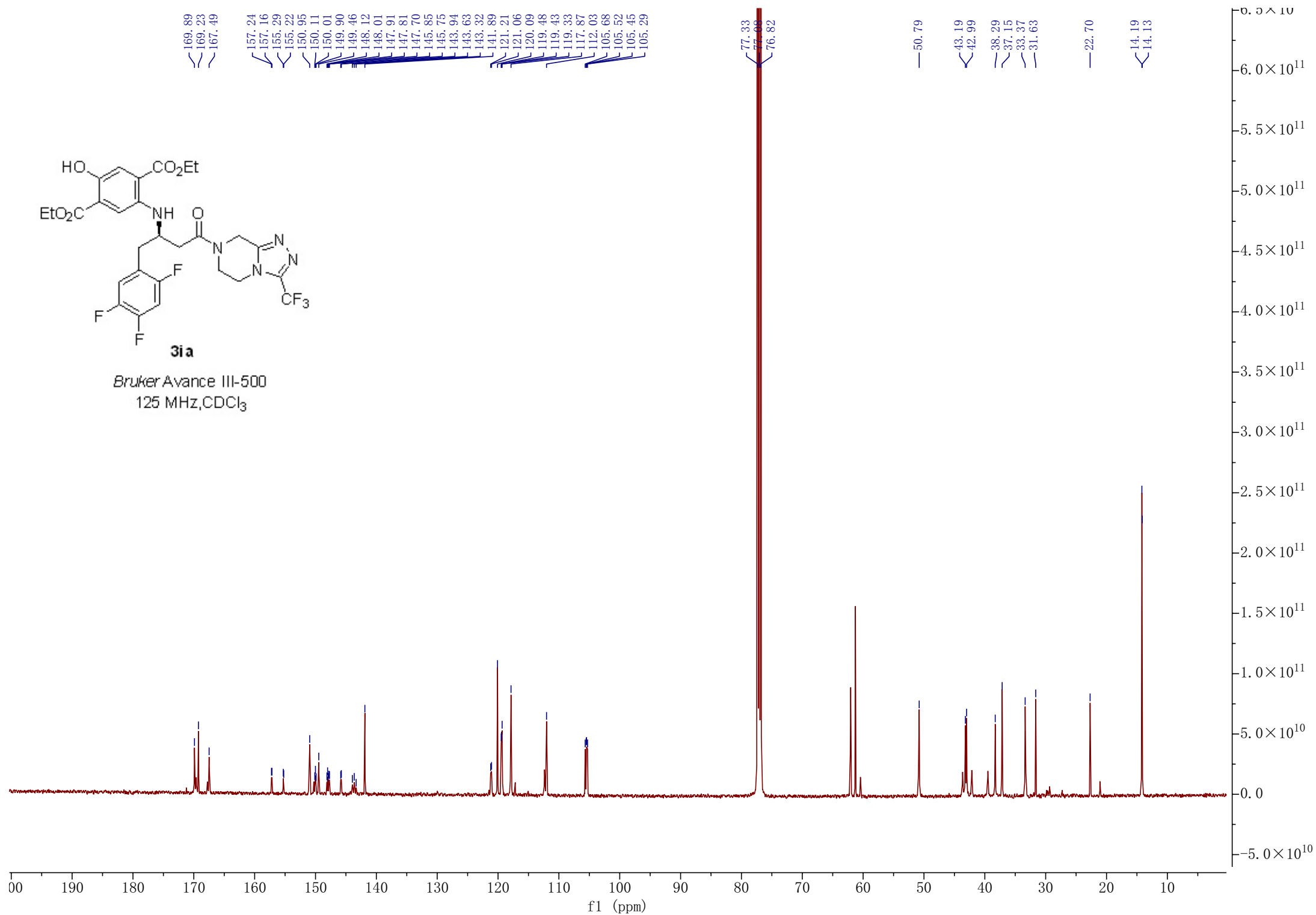


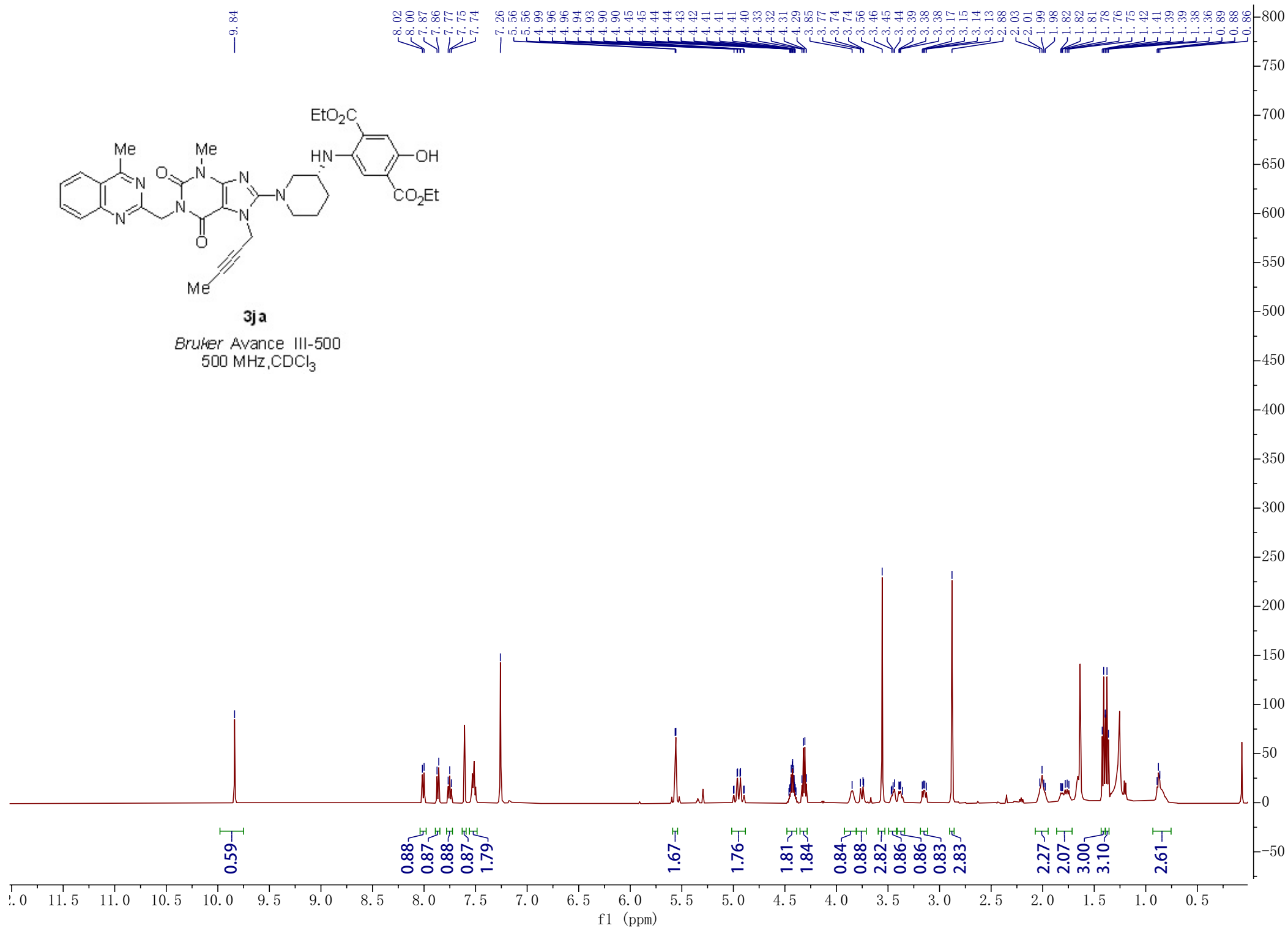
Bruker Avance III-500
500 MHz, CDCl₃

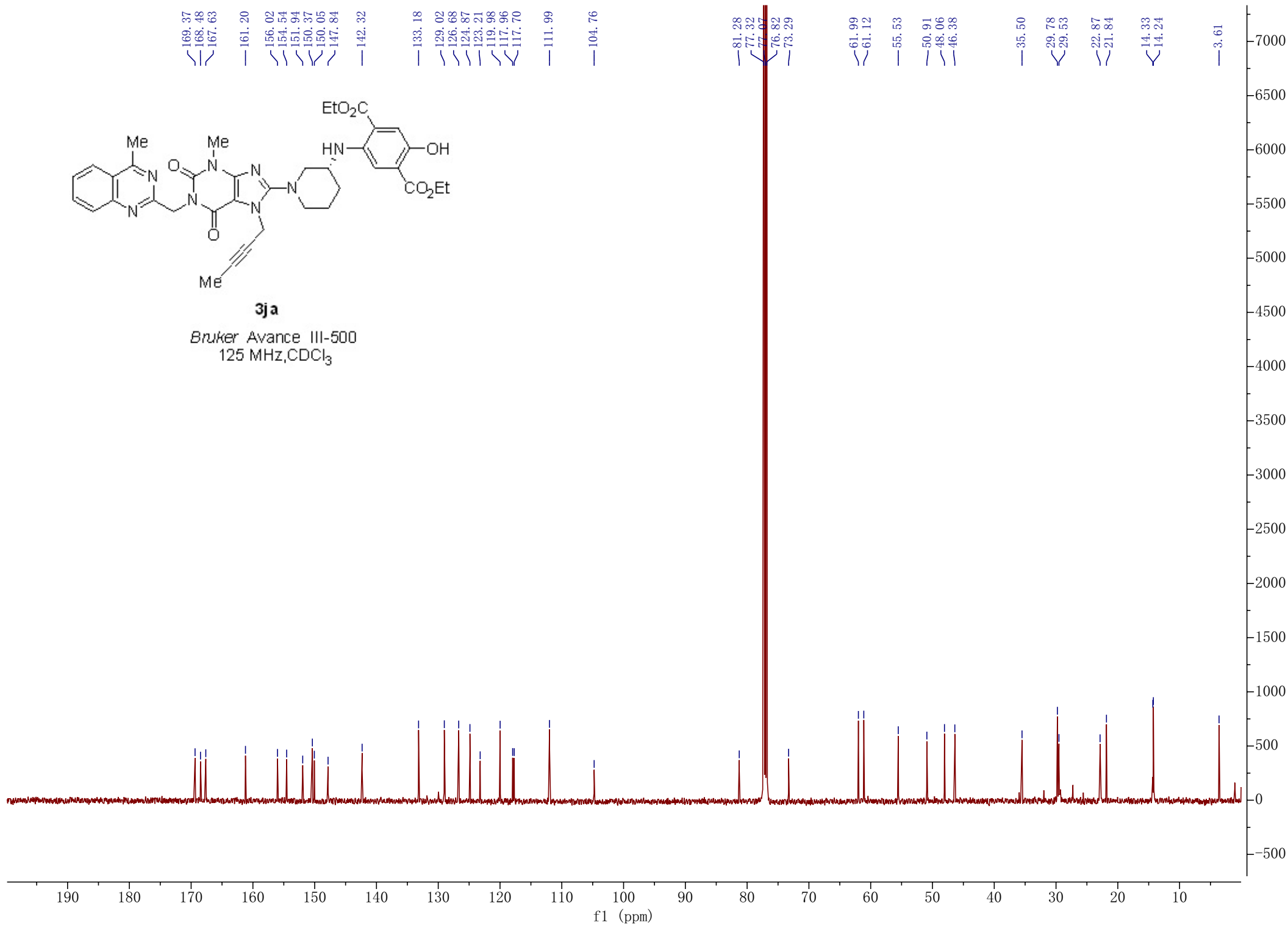


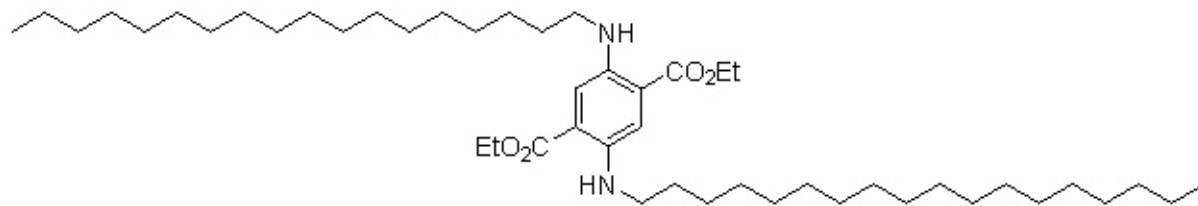


Bruker Avance III-500
125 MHz, CDCl₃



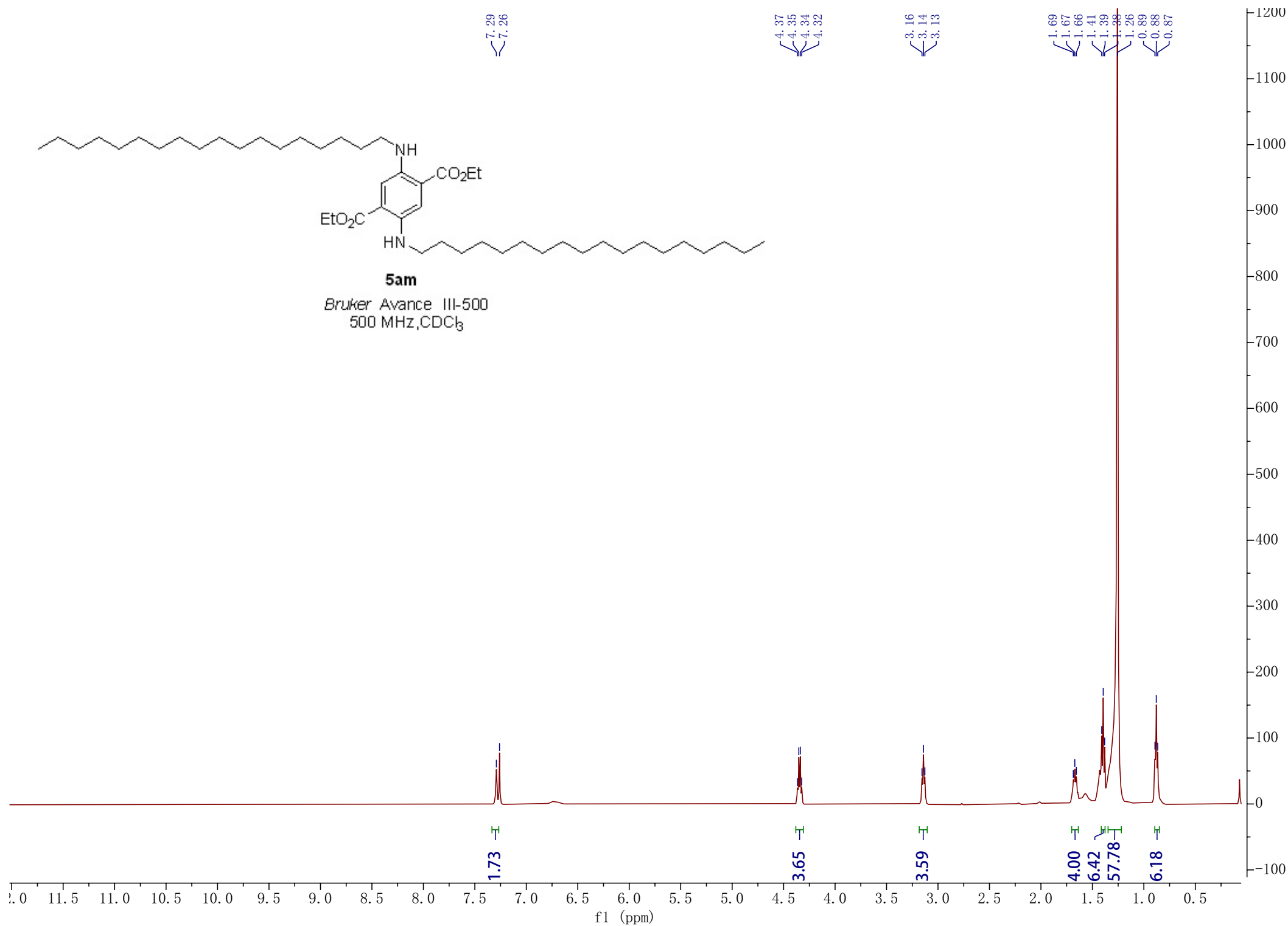


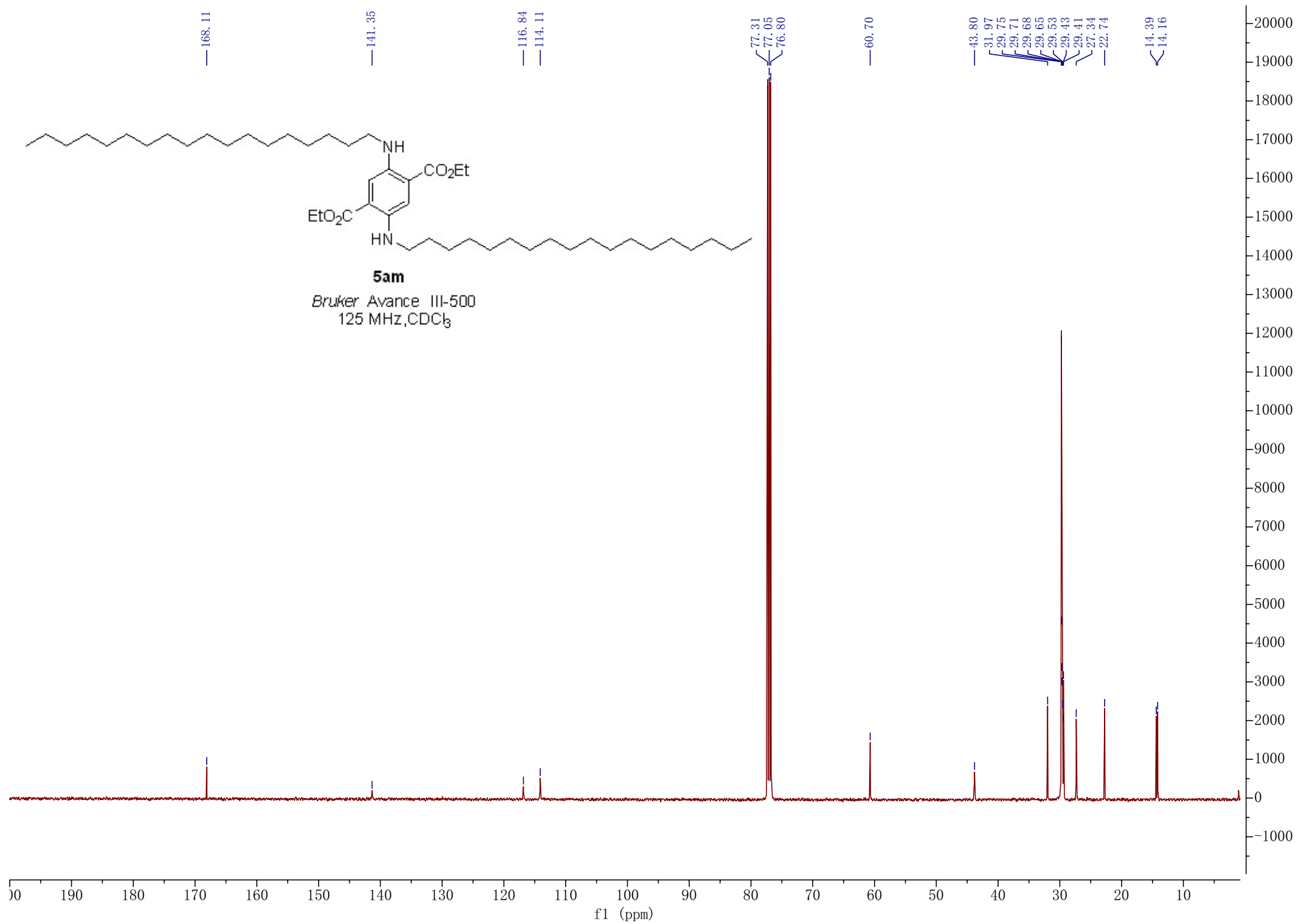


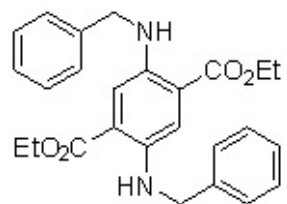


5am

Bruker Avance III-500
500 MHz, CDCl_3

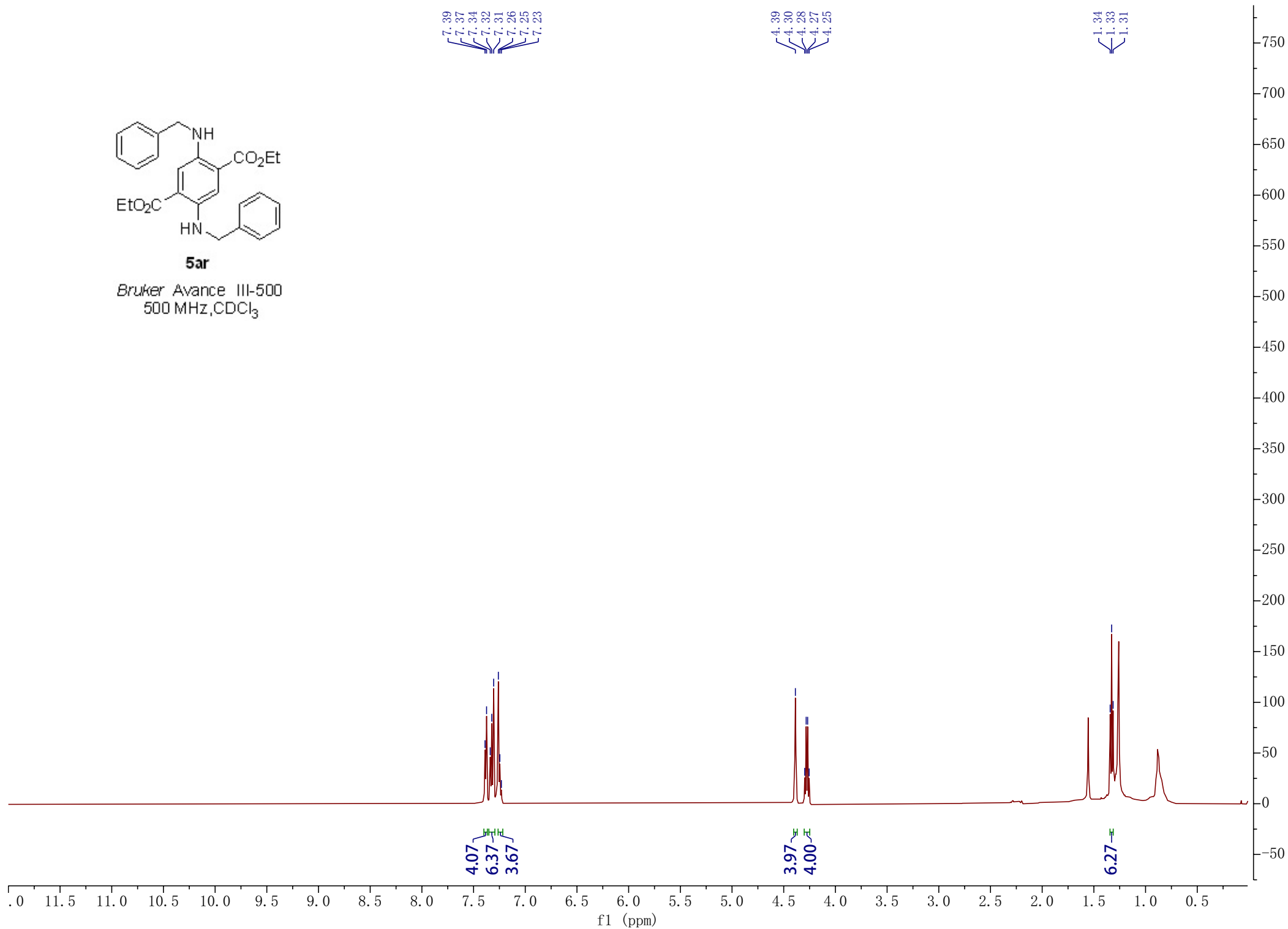


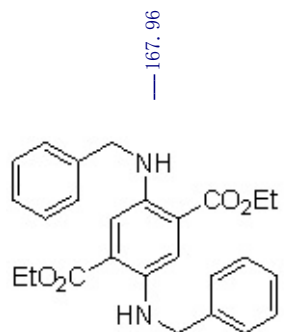




5ar

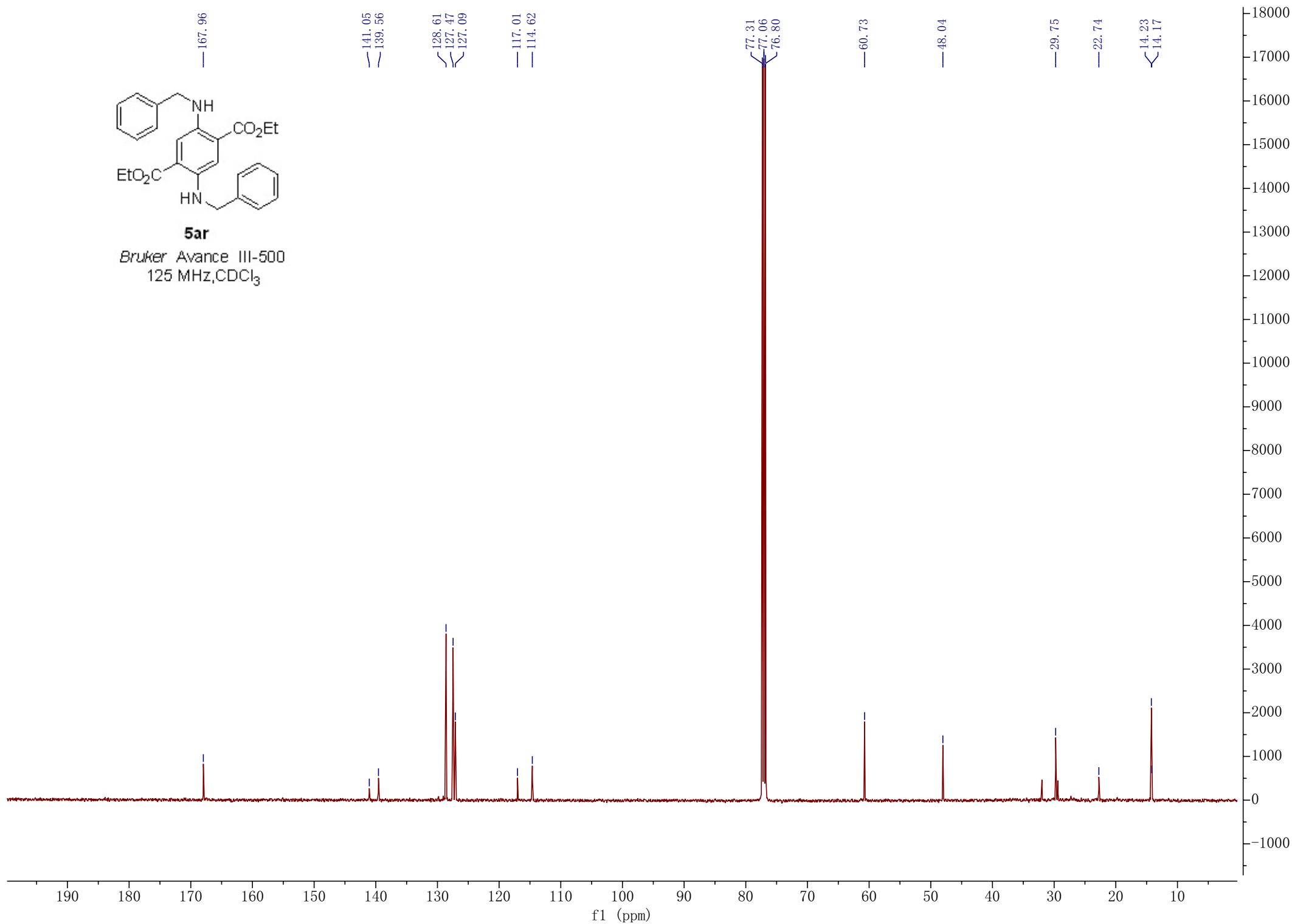
Bruker Avance III-500
500 MHz, CDCl₃

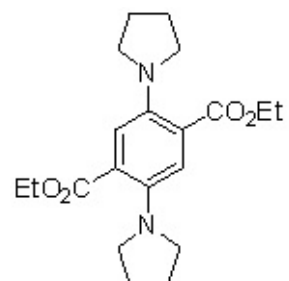




5ar

Bruker Avance III-500
125 MHz, CDCl₃

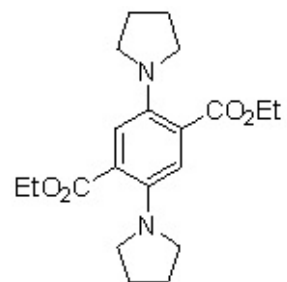




5az

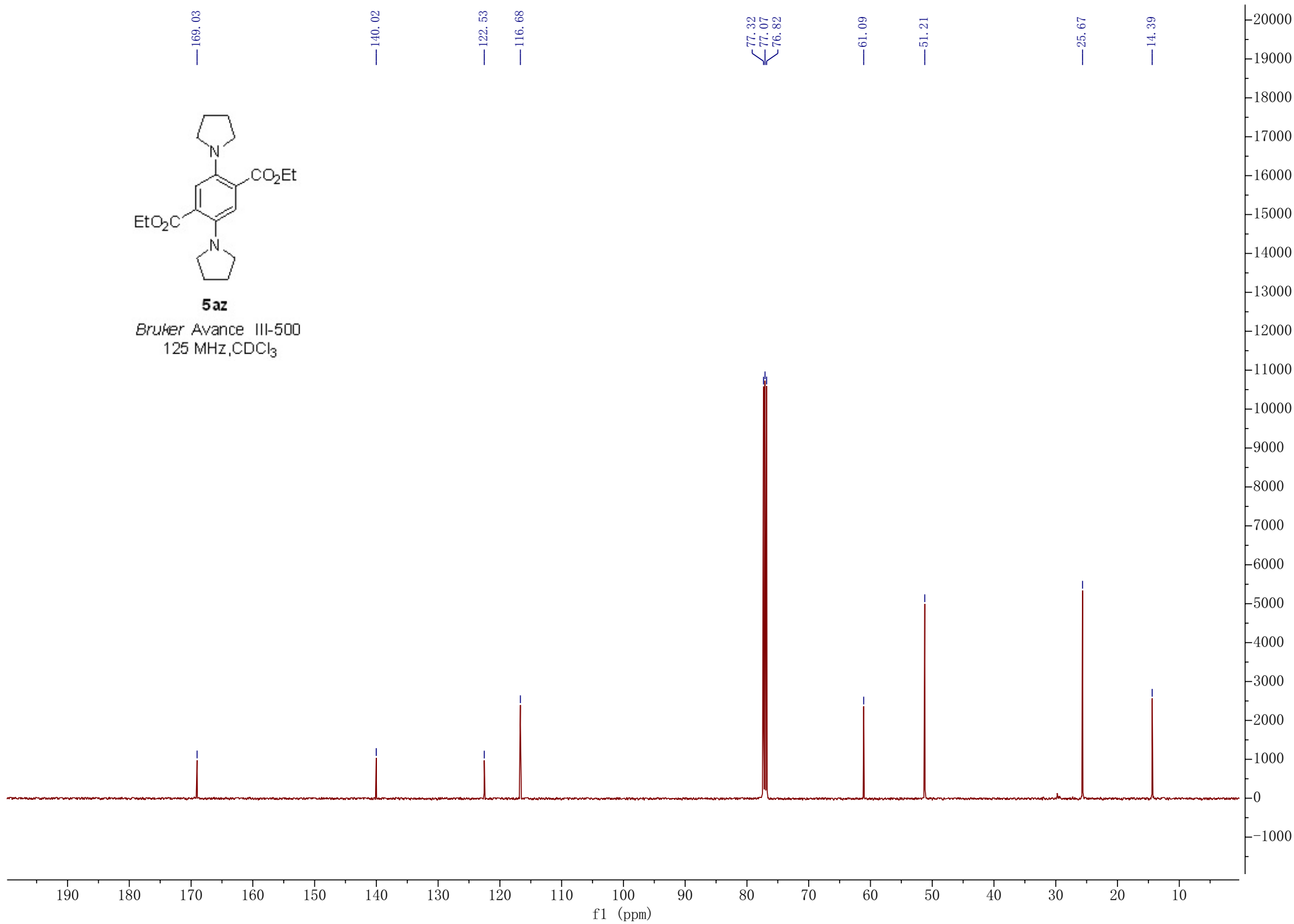
Bruker Avance III-500
500 MHz, CDCl₃



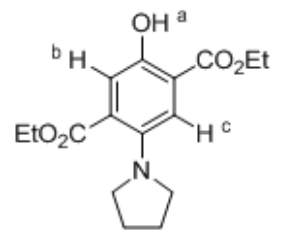


5az

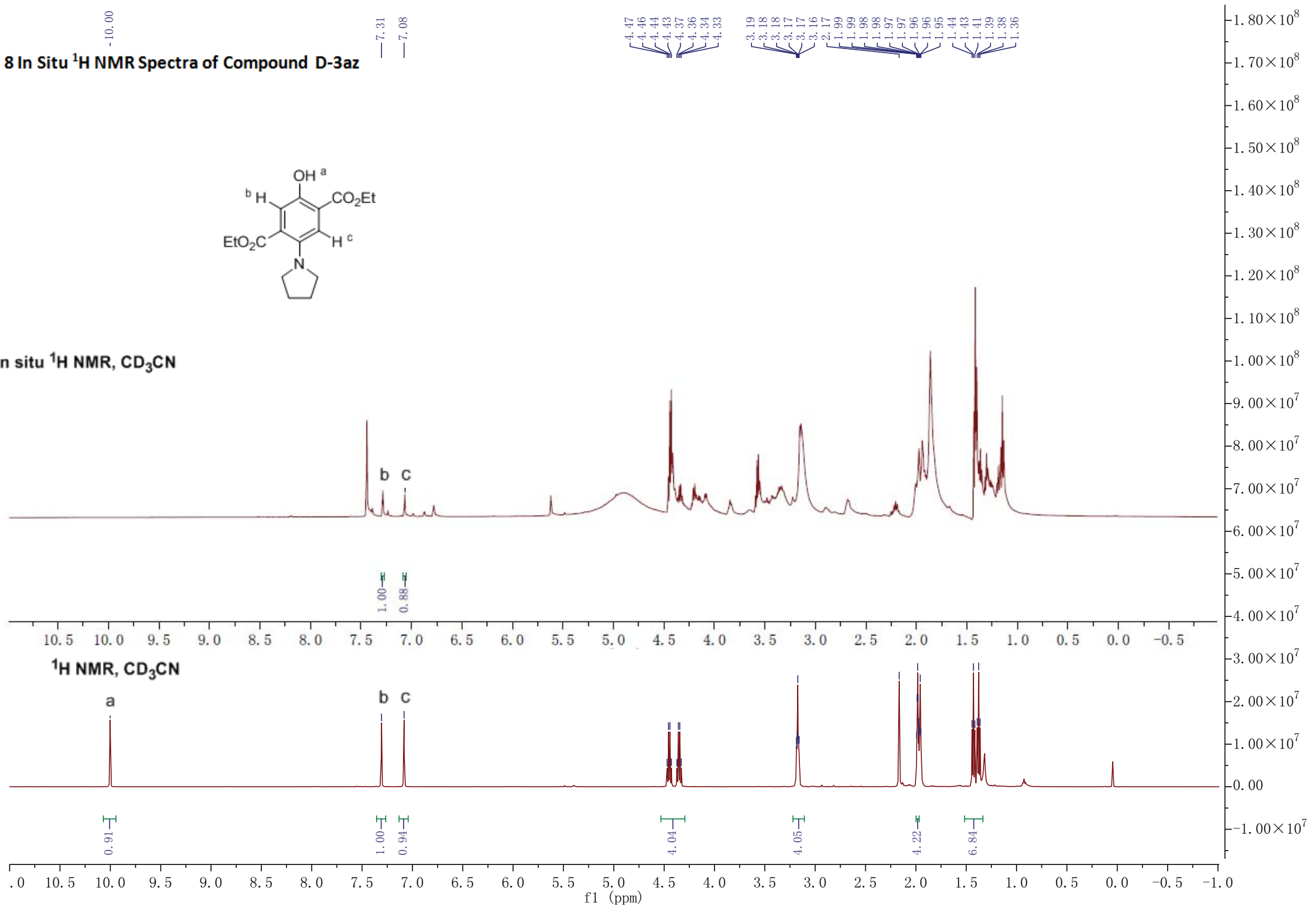
Bruker Avance III-500
125 MHz, CDCl₃



8 In Situ ¹H NMR Spectra of Compound D-3az



In situ ¹H NMR, CD₃CN



¹H NMR, CD₃CN

