

Derivatives of amodiaquine as potent human cholinesterases inhibitors: implication for treatment of Alzheimer's disease

Ana Matošević¹, Dejan M. Opsenica^{2,3,*}, Marija Bartolić¹, Nikola Maraković¹, Andriana Stoilković², Katarina Komatović⁴, Antonio Zandona¹, Suzana Žunec¹, Anita Bosak^{1,*}

¹ *Institute for Medical Research and Occupational Health, 10000 Zagreb, Croatia*

² *Institute of Chemistry Technology and Metallurgy, University of Belgrade, 11000 Beograd, Serbia*

³ *Centre of Excellence in Environmental Chemistry and Engineering, 11000 Belgrade, Serbia*

⁴ *Faculty of Chemistry, University of Belgrade, 11158 Belgrade, Serbia*

* Corresponding author:

Dr Dejan Opsenica, University of Belgrade Institute of Chemistry, Technology and Metallurgy, Studentski trg 12-16, 11000 Beograd, Serbia; e-mail: dopsen@chem.bg.ac.rs

Dr Anita Bosak, Institute for Medical Research and Occupational Health, POBox 291, Ksaverska cesta 2, 10000 Zagreb, Croatia; e-mail: abosak@imi.hr

Table of contents

1. Synthesis	S3
1.1. General information	S3
1.2. Synthetic procedures and spectral data	S4
1.2.1. Synthesis of starting noncommercial 4-chloroquinolines	S4
Scheme S1	S4
Scheme S2	S4
	S1

1.2.2. Synthesis of AMQ and amodiaquine derivatives 1 – 14	S10
Scheme S3	S10
1.2.3. ¹ H and ¹³ C NMR spectra	S20
1.2.4. HRMS spectra of the tested compounds	S90
2. List of interactions between tested compounds and cholinesterases	S106
2.1. List of interactions between derivatives 1 – 14 and AChE	S106
2.2. List of interactions between derivatives 1 – 14 and BChE	S110
3. Metal chelation study	
3.1. UV/Vis spectra of compounds, metals and compounds-biometal mixtures	S114
3.2. Differential UV/VIS spectra of the compounds-biometal mixtures	S122
4. <i>In silico</i> calculations	S125
Table S1. Calculated physiochemical properties	S125
Table S2. <i>In silico</i> estimated % of compounds that will be absorbed through the human intestine	S126
References	S126

1. Synthesis

1.1. General information

Melting points were recorded on an electrothermal melting point apparatus (1428 6/4 457), England. IR spectra were recorded on a Perkin-Elmer spectrophotometer FT-IR 1725X (Perkin-Elmer, Waltham, MA 02451, USA). Positions of absorbance bands are expressed in cm^{-1} , and intensity is labelled as w (weak), m (medium) or s (strong). ^1H and ^{13}C NMR spectra were recorded on a Varian spectrometer (Agilent Technology, Santa Clara, CA 95051, USA) (at 400 and 100 MHz for the ^1H and ^{13}C NMR spectra, respectively) and on a Bruker Ultrashield Advance III spectrometer (Bruker Scientific Instruments, Billerica, MA 01821, USA) (at 500 and 125 MHz for the ^1H and ^{13}C NMR spectra, respectively) employing indicated solvents using TMS as the internal standard. Chemical shifts are expressed in ppm (δ) values and coupling constants (J) in Hz. Mass spectra were recorded on a 4800 Plus MALDI TOF/TOF Analyzer (Applied Biosystems, US instrument, Mundelein, USA) in positive ion mode (fixed laser intensity 4280) using a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ gradient with 0.2% HCOOH as the carrying solvent solution. Samples were dissolved in MeOH (HPLC grade purity) mixed with CHCA (α -Cyano-4-hydroxycinnamic acid) MALDI matrix (5 mg/mL in 50% acetonitrile (v/v)). Internal calibrants: Azithromycin and Azithromycin fragments (m/z 156-749).

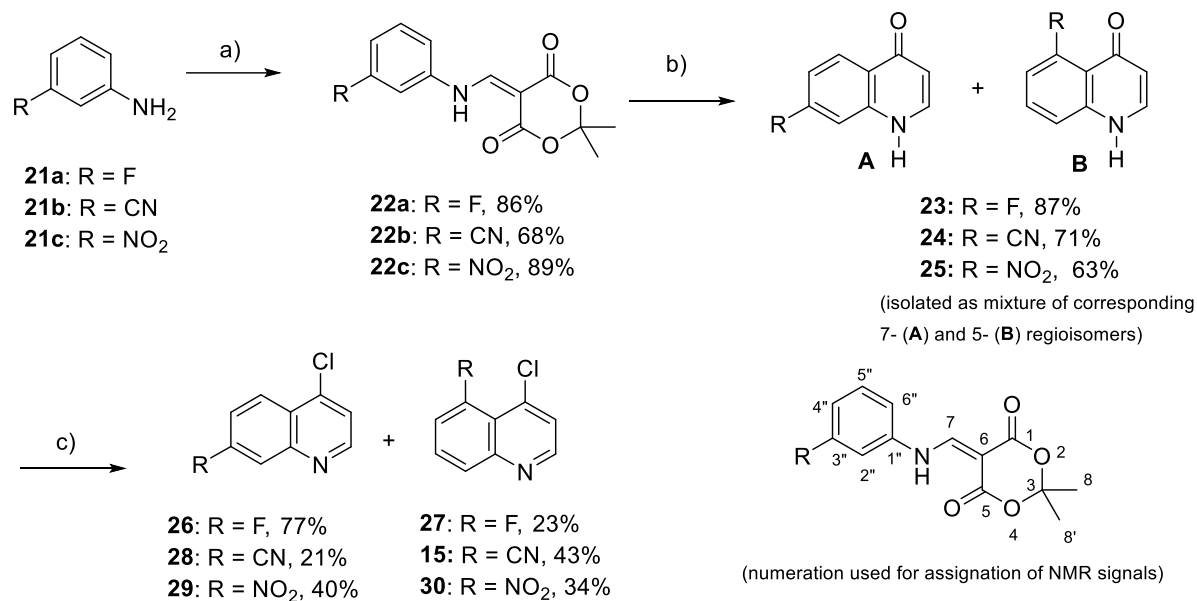
HPLC purity: Purity of compounds was analyzed using an Agilent 1260 HPLC system equipped with Quat Pump (G1311B), InJector (G1329B) 1260 ALS, TCC 1260 (G1316A) and Detector 1260 DAD VL+ (G1315C), using 1.0 mL/min flow rate. Compounds (0.5 mg/mL) were dissolved in MeOH. The analysis was performed at the UV max of the compounds to maximize selectivity in two diverse systems:

Method A: Column Zorbax Eclipse (XDB-C18, 4.6×150 nm, $5.0 \mu\text{m}$, S.N. USKBM01053) was used as the stationary phase. Eluent was made from the following solvents: 0.2% formic acid in water (A) and acetonitrile (B). Compounds were eluted using gradient protocol: 0 – 1 min 95% A, 1 – 6 min 95% A \rightarrow 5% A, 6 – 11 min 5% A, 11 – 14 min 5% A \rightarrow 95% A, 14 – 15 min 95% A.

Method B: Column Zorbax Eclipse (XDB-C18, 4.6×150 nm, $5.0 \mu\text{m}$, S.N. USKBM01053) was used as the stationary phase. Eluent was made from the following solvents: 0.2% formic acid in water (A) and methanol (B). Compounds were eluted using gradient protocol: 0 – 1 min 95% A, 1 – 6 min 95% A \rightarrow 5% A, 6 – 11 min 5% A, 11 – 14 min 5% A \rightarrow 95% A, 14 – 15 min 95% A.

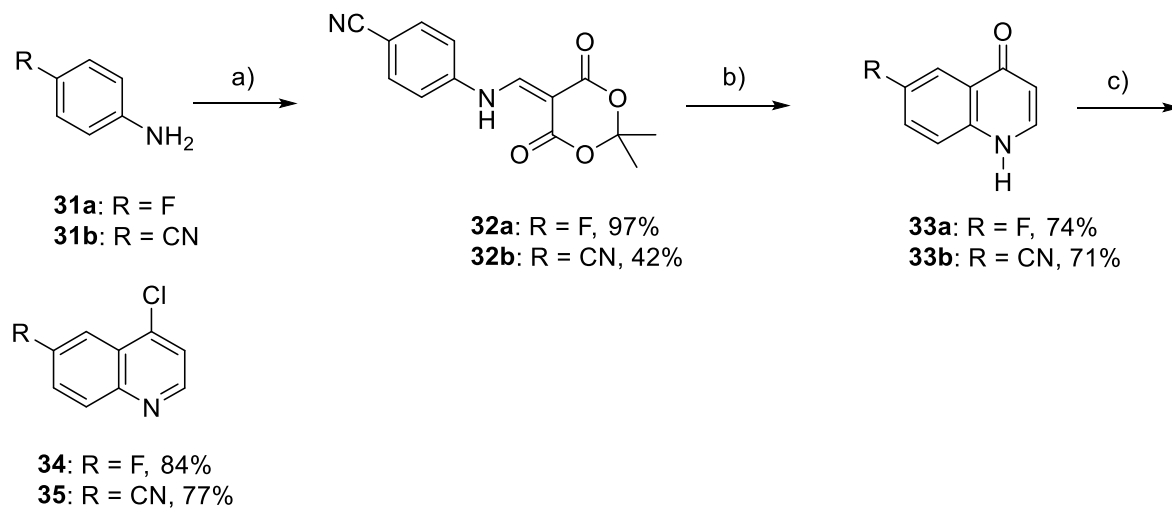
1.2. Synthetic procedures and spectral data

1.2.1. Synthesis of starting noncommercial 4-chloroquinolines



a) Meldrum's acid, orthoformate, EtOH dry, 80 °C (reflux), 2.5h; b) Ph₂O, 250 °C, 30 min.;
 c) POCl₃, 145 °C, 45 min.;

Scheme S1. Synthesis of noncommercial 4-chloroquinolines **30**, **31**, **32**, **15**, **33** and **34**. Percentages denote the yield.



a) Meldrum's acid, orthoformate, EtOH dry, 80 °C (reflux), 2.5h; b) Ph₂O, 250 °C, 30 min.;
 c) POCl₃, 145 °C, 45 min.;

Scheme S2. Synthesis of noncommercial 4-chloroquinolines **34** and **35**.

Starting non-commercial 4-chloro quinolines **26**, **27**, **28**, **15**, **29** and **30** (Scheme S1) and **34** and **35** (Scheme S2), including corresponding intermediates, were synthesized according to the procedure described in the literature [1]. Obtained NMR spectra are in accordance with previously published data. [1]

Schemes S1 and S2: Briefly, the Meldrum's acid and triethyl-orthoformate were added into the intensively stirred solution of corresponding aniline (**21a-c** or **31a-b**; 1.5 mmol) in absolute ethanol (1.5 mL), and the reaction mixture was stirred at reflux for 2.5 hours. The enamine (**22a-c** or **32a-b**) separated as precipitate was filtered, rinsed with cold absolute EtOH, dried under reduced pressure and used without additional purification. In the next reaction, the corresponding enamine (1.13 mmol) was added slowly in small portions into the boiling Ph₂O (6 mL), and after 0.5 hours, the reaction mixture was cooled to room temperature, and the corresponding substituted 4-quinolones **23-25** or **33** separated as the precipitate were filtered, rinsed with hexane and dried under reduced pressure and used in the next reaction without additional purification. The products **23-25** were isolated as the mixtures of corresponding 7- and 5-substituted 4-quinolone regioisomers, and as such used in the next reaction without separation of isomers. In the next step, 4-substituted quinolones (**23-25** or **33**; 3.34 mmol) were dissolved in phosphoryl chloride (6.4 mL) and stirred at 145°C for 45 min, after which they were cooled down at room temperature. Phosphoryl chloride was removed under reduced pressure. Obtained solids were dissolved in water, and 0.1 M NaOH was added until the solution become basic (pH = 11). Emulsion was extracted with dichloromethane, and combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. Solvent was removed under reduced pressure, and corresponding crude substituted 4-chloro quinoline derivatives were purified by column chromatography on silica gel using hexane/ethyl acetate gradient. Regioisomers **26** and **27**, **28** and **15**, and **29** and **30**, obtained from corresponding mixtures of corresponding 7- and 5-substituted 4-quinolone regioisomers **23-25**, were separated during purification and identified from their NMR spectra. Substituted 4-chloro quinolines **34** and **35** were obtained as the only products.

As a proof of identity of compounds and corresponding intermediates, ¹H and ¹³C are given. The assignment of NMR signals was performed in accordance with numeration given in Scheme S1.

5-(((3-fluorophenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (22a)

Compound **22a** was synthesized using 3-fluoroaniline **21a** (175.0 mg, 1.48 mmol, 1 eq), Meldrum's acid (311.0 mg, 2.16 mmol, 1.5 eq) and triethyl-orthoformate. Yield: 337.9 mg (86%). ¹H NMR (500 MHz, DMSO-*d*₆, δ): 10.98 (d, *J* = 14.4 Hz, 1H, NH), 8.34 (d, *J* = 14.5 Hz, 1H, H-7), 7.28 (dt, *J*₁ = 10.8, *J*₂ = 2.2 Hz, 1H, H-6''), 7.25 – 7.17 (m, 1H, H-5''), 7.13 (dd, *J*₁ = 8.1, *J*₂ = 1.7 Hz, 1H, H-2''), 6.84 (td, *J*₁ = 8.4, *J*₂ = 2.3 Hz, 1H, H-4''), 1.42 (s, 6H, H-8 and H-8'). ¹³C NMR (125 MHz, DMSO-*d*₆, δ): 164.55, 163.49, 163.26 (d, *J* = 194.0), 154.14, 141.0 (d, *J* = 10.9, C-1), 140.96, 132.07 (d, *J* = 9.1, C-5), 115.75, 113.56 (d, *J* = 21, C-4), 107.19 (d, *J* = 26.3, C-2), 105.05, 87.97, 27.14.

3-(((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)amino)benzonitrile (22b)

Compound **22b** was synthesized using 3-cyanoaniline **21b** (175.0 mg, 1.58 mmol, 1 eq), Meldrum's acid (341.6 mg, 2.37 mmol, 1.5 eq) and triethyl-orthoformate (0.36 mL, 2.37 mmol, 1.5 eq). Yield: 234.4 mg (68%). ¹H NMR (500 MHz, DMSO-*d*₆, δ): 11.27 (d, *J* = 14.3 Hz, 1H, NH), 8.61 (d, *J* = 14.4 Hz, 1H, H-7), 8.15 – 8.10 (m, 1H, H-2''), 7.91 – 7.85 (m, 1H, H-4''), 7.70 – 7.85 (m, 1H, H-6''), 7.62 – 7.55 (m, 1H, H-5''), 1.65 (s, 6H, H-8 and H-8'). ¹³C NMR (125 MHz, DMSO-*d*₆, δ): 163.69, 162.58, 153.79, 139.61, 130.69, 129.52, 124.23, 122.76, 118.17, 112.29, 104.27, 87.78, 26.52.

2,2-dimethyl-5-(((3-nitrophenyl)amino)methylene)-1,3-dioxane-4,6-dione (22c)

Compound **22c** was synthesized using 3-nitroaniline **21c** (175.0 mg, 1.27 mmol, 1 eq), Meldrum's acid (250.0 mg, 1.74 mmol, 1.5 eq) and triethyl-orthoformate (0.28 mL, 1.65 mmol, 1.5 eq). Yield: 328.2 mg (89%). ¹H NMR (500 MHz, DMSO-*d*₆, δ): 11.25 (s, 1H, NH), 8.52 (s, 1H, H-7), 8.36 (s, 1H, H-2''), 7.99 – 7.92 (m, *J* = 8.0 Hz, 1H, H-4''), 7.92 – 7.85 (m, *J* = 8.1 Hz, 1H, H-6''), 7.57 (t, *J* = 8.2 Hz, 1H, H-5''), 1.55 (s, 6H, H-8 and H-8'). ¹³C NMR (125 MHz, DMSO-*d*₆, δ): 163.64, 162.85, 154.09, 148.51, 140.19, 130.94, 125.70, 120.57, 114.68, 104.44, 88.05, 26.63.

Mixture of 7-fluoro-and 5-fluoro-4-quinolone (23)

The mixture **23** was synthesized using enamine **22a** (300.0 mg, 1.13 mmol) and 6.0 mL Ph₂O. The obtained product was a mixture of corresponding 7-fluoro and 5-fluoro regioisomers in the ratio 2:1. Yield: 160.5 mg (87%). Although corresponding isomers were isolated as mixture, in the ¹H NMR spectrum, signals of isomers are well-defined, which enables assignation and determination of isomer ratio. However, that was not possible for ¹³C NMR, and corresponding signals were given collectively.

7-fluoro isomer: ^1H NMR (400 MHz, CD_3OD , δ): 8.29– 8.20 (m, 1H, H-2), 7.96 – 7.88 (m, 1H, H-8), 7.26 – 7.19 (m, 1H, H-5), 7.19 – 7.11 (m, 1H, H-6), 6.29 – 6.24 (m, 1H, H-3).

5-fluoro isomer: ^1H NMR (400 MHz, CD_3OD , δ): 7.88 – 7.82 (m, 1H, H-2), 7.63 – 7.54 (m, 1H, H-6), 7.33 – 7.28 (m, 1H, H-8), 7.02 – 6.94 (m, 1H, H-5), 6.24 – 6.19 (m, 1H, H-3).

Mixture: ^{13}C NMR (100 MHz, CD_3OD , δ): 180.17, 167.58, 165.08, 141.91, 140.85, 133.95, 133.84, 129.60, 129.49, 123.69, 115.35, 115.30, 114.38, 114.14, 111.70, 110.95, 110.73, 110.08, 104.54, 104.29.

Mixture of 7-cyano- and 5-cyano-4-quinolone (24)

The mixture **24** was synthesized using enamine **22b** (320.0 mg, 1.15 mmol) and 6.4 mL Ph_2O . The obtained product was a mixture of corresponding 7-cyano and 5-cyano regioisomers. Yield: 139.9 mg (71%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ): 7.23 – 7.16 (m, 1H), 7.06 – 6.92 (m, 2H), 6.86 – 6.69 (m, 4H), 6.67 – 6.58 (m, $J = 8.3$ Hz, 1H), 5.20 – 5.10 (m, 2H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$, δ): 176.24, 175.18, 140.99, 140.76, 140.12, 139.66, 132.11, 131.60, 127.89, 126.70, 125.08, 124.99, 123.74, 119.03, 118.28, 113.92, 110.18, 109.99, 108.78.

Mixture of 7-nitro-and 5-nitro-4-quinolone (25)

The mixture **25** was synthesized using enamine **22c** (100.0 mg, 0.34 mmol) and 2.0 mL Ph_2O . The obtained product was a mixture of corresponding 7-nitro and 5-nitro regioisomers. Yield: 45.3 mg (70%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ): 8.28 (s, 1H), 8.14 (d, $J = 8.9$ Hz, 1H), 7.95 (d, $J = 7.5$ Hz, 1H), 7.87 (dd, $J = 15.1, 8.2$ Hz, 2H), 7.61 (s, 1H), 7.39 – 7.31 (m, 1H), 7.24 (t, $J = 7.8$ Hz, 1H), 6.98 (t, $J = 7.5$ Hz, 1H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.05 (d, $J = 7.5$ Hz, 1H), 5.96 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$, δ): 149.13, 148.22, 141.51, 141.01, 140.16, 139.82, 131.88, 130.19, 128.95, 127.51, 123.59, 121.38, 118.73, 117.44, 116.87, 115.85, 114.72, 110.39, 110.26.

4-chloro-7-fluoro- and 4-chloro-5-fluoroquinolines (26 and 27)

Compounds **26** and **27** were synthesized using **23** (545.1 mg, 3.34 mmol) and 6.4 mL phosphoryl chloride. Yield: **26** 440.6 mg (77%) and **27** 131.6 mg (23%).

26: ^1H NMR (400 MHz, CDCl_3 , δ): 8.75 (d, $J = 4.7$, 1H, H-2), 8.22 (dd, $J_1 = 9.3, J_2 = 5.9$, 1H, H-5), 7.73 (dd, $J_1 = 9.8, J_2 = 2.5$, 1H, H-8), 7.49–7.33 (m, 2H, H-3 and H-6). ^{13}C NMR (100 MHz, CDCl_3) δ 163.46 (d, $J = 252.0$, C-7), 151.04 (C-2), 150.17 (d, $J = 12.7$), 142.69 (d, $J = 1.4$), 126.55 (d, $J = 9.9$, C-5), 123.56 (d, $J = 1.2$), 120.62 (d, $J = 2.5$, C-3), 118.08 (d, $J = 25.3$, C-6), 113.46 (d, $J = 20.6$, C-8).

27: ¹H NMR (400 MHz, CDCl₃, δ): 8.73 (d, *J* = 4.7, 1H, H-2), 7.92 (d, *J* = 8.5, 1H, H-8), 7.65 (td, *J*₁ = 8.2, *J*₂ = 5.2, 1H, H-7), 7.46 (d, *J* = 4.7, 1H, H-3), 7.31-7.19 (m, 1H, H-6). ¹³C NMR (100 MHz, CDCl₃, δ): 157.52 (d, *J* = 260.9, C-5), 150.71, 150.33 (d, *J* = 2.0, C-2), 139.40, 129.72 (d, *J* = 9.5, C-7), 126.19 (d, *J* = 4.6, C-8), 123.39 (d, *J* = 1.6, C-3), 112.76 (d, *J* = 21.9, C-)

4-chloroquinoline-7-carbonitrile and 4-chloroquinoline-5-carbonitrile (28 and 29)

Compounds **28** and **29** were synthesized using **24** (348.5 mg, 2.05 mmol) and 4.6 mL phosphorylchloride. Yield: **28** 81.1 mg (21%) and **29** 166.1 mg (43%).

28: ¹H NMR (400 MHz, CDCl₃, δ): 8.90 (d, *J* = 4.6 Hz, 1H, H-2), 8.50 (s, 1H, H-8), 8.35 (d, *J* = 8.7 Hz, 1H, H-5), 7.80 (dd, *J* = 8.7, 1.0 Hz, 1H, H-6), 7.64 (d, *J* = 4.7 Hz, 1H, H-3). ¹³C NMR (100 MHz, CDCl₃, δ): 151.92, 148.18, 142.98, 135.83, 128.79, 128.43, 128.41, 126.06, 123.70, 118.07, 114.29.

29: ¹H NMR (400 MHz, CDCl₃, δ): 8.86 (d, *J* = 4.6 Hz, 1H, H-2), 8.38 (dd, *J* = 8.5, 1.3 Hz, 1H, H-8), 8.12 (dd, *J* = 7.3, 1.3 Hz, 1H, H-6), 7.82 (dd, *J*₁ = 8.5, *J*₂ = 7.3 Hz, 1H, H-5), 7.62 (d, *J* = 4.6 Hz, 1H, H-3). ¹³C NMR (100 MHz, CDCl₃, δ): 151.21, 149.47, 141.47, 138.01, 136.11, 129.37, 125.62, 124.79, 118.57, 108.42.

4-chloro-7-nitroquinoline and 4-chloro-5-nitroquinoline (29 and 30)

Compounds **29** and **30** were synthesized using **25** (802.1 mg, 4.21 mmol) and 10.7 mL phosphoryl chloride. Yield: **29** 341.9 mg (40%) and **30** 290.6 mg (34%).

29: ¹H NMR (400 MHz, CDCl₃, δ): 9.02 (s, 1H, H-8), 8.95 (d, *J* = 4.6 Hz, 1H, H-2), 8.42 – 8.41 (m, 2H, H-5 and H-6), 7.68 (d, *J* = 4.6 Hz, 1H, H-3). ¹³C NMR (100 MHz, CDCl₃, δ): 152.39, 148.87, 148.42, 143.02, 129.85, 126.45, 126.21, 124.00, 121.12.

30: ¹H NMR (400 MHz, CDCl₃, δ): 8.88 (d, *J* = 4.7 Hz, 1H, H-2), 8.33 (dd, *J* = 7.6, 2.1 Hz, 1H, H-8), 7.83 – 7.76 (m, 2H, H-6 and H-7), 7.63 (d, *J* = 4.7 Hz, 1H, H-3). ¹³C NMR (100 MHz, CDCl₃, δ): 151.26, 149.75, 146.87, 139.19, 134.21, 128.83, 125.14, 123.45, 118.24.

The assignation of NMR signals was performed in accordance with numeration given in Scheme S1.

5-(((4-fluorophenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (32a)

Compound **32a** was synthesized using 4-fluoroaniline **21** (175.0 mg, 1.48 mmol, 1 eq), Meldrum's acid (311.0 mg, 2.16 mmol, 1.5 eq) and triethyl-orthoformate (0.36 mL, 2.37, 1.5 eq). Yield: 381.1 mg (97%). ¹H NMR (500 MHz, DMSO-*d*₆, δ): 11.00 (d, *J* = 14.6 Hz, 1H, NH), 8.25 (d, *J* = 14.6 Hz, 1H, H-7), 7.38 – 7.30 (m, 2H, H-3'' and H-5'), 7.06 – 6.98 (m, 2H,

H-2'' and H-6''), 1.42 (s, 6H, H-8 and H-8'). ¹³C NMR (125 MHz, DMSO-*d*₆, δ): 164.59, 163.65, 160.92 (d, *J* = 243.6 Hz), 154.44, 135.88, 122.03 (d, 8.4 Hz), 116.98 (d, *J* = 22.9 Hz), 104.92, 87.23, 27.11.

4-(((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)amino)benzonitrile (32b)

Compound **32b** was synthesized using the 4-cyanoaniline **22** (175 mg, 1.48 mmol, 1 eq), Meldrum's acid (311.0 mg, 2.16 mmol, 1.5 eq) and triethyl-orthoformate (0.36 mL, 2.37, 1.5 eq). Yield: 165.0 mg (42%). ¹H NMR (500 MHz, DMSO-*d*₆, δ): 8.50 (s, 1H, H-7), 7.78 – 7.64 (m, 2H, H-3'' and H-5'), 7.64 – 7.07 (m, 2H, H-2'' and H-6'), 1.54 (s, 6H, H-8 and H-8'). ¹³C NMR (125 MHz, DMSO-*d*₆, δ): 153.24, 142.60, 133.91, 119.76, 118.69, 108.12, 104.60, 88.57, 26.66.

6-fluoro-4-quinolone (33a)

Compound **33a** was synthesized using Ph₂O (6.0 mL) and enamine **32a** (300.0 mg, 1.13 mmol). Yield: 179.0 mg (97%). ¹H NMR (400 MHz, CD₃OD, δ): 7.95 (d, *J* = 7.3 Hz, 1H, H-2), 7.84 (dd, *J* = 9.3, 2.9 Hz, 1H, H-5), 7.61 (dd, *J* = 9.1, 4.5 Hz, 1H, H-8), 7.50 (td, *J* = 8.6, 2.9 Hz, 1H, H-7), 6.29 (d, *J* = 7.2 Hz, 1H, H-3). ¹³C NMR (100 MHz, CD₃OD, δ): 179.90, 160.77 (d, *J* = 244.3 Hz), 142.54, 141.48, 138.20, 127.94 (d, *J* = 7.2 Hz), 122.54 (d, *J* = 26.0 Hz), 122.16 (d, *J* = 8.2 Hz), 110.13 (d, *J* = 22.9 Hz), 109.14.

6-cyano-4-quinolone (33b)

Compound **33b** was synthesized using Ph₂O (6.4 mL) and enamine **32b** (320.0 mg, 1.15 mmol). Yield: 82.6 mg (41%). ¹H NMR (400 MHz, DMSO-*d*₆, δ): 11.97 (s, NH), 8.21 (d, *J* = 2.0 Hz, 1H, H-5), 7.84 – 7.67 (m, 2H, H-2 and H-7), 7.46 (d, *J* = 8.7 Hz, 1H, H-8), 5.96 (d, *J* = 7.5 Hz, 1H, H-3). ¹³C NMR (100 MHz, DMSO-*d*₆, δ): 176.22, 142.52, 141.81, 140.85, 133.75, 131.08, 125.36, 120.18, 118.91, 110.54, 105.64.

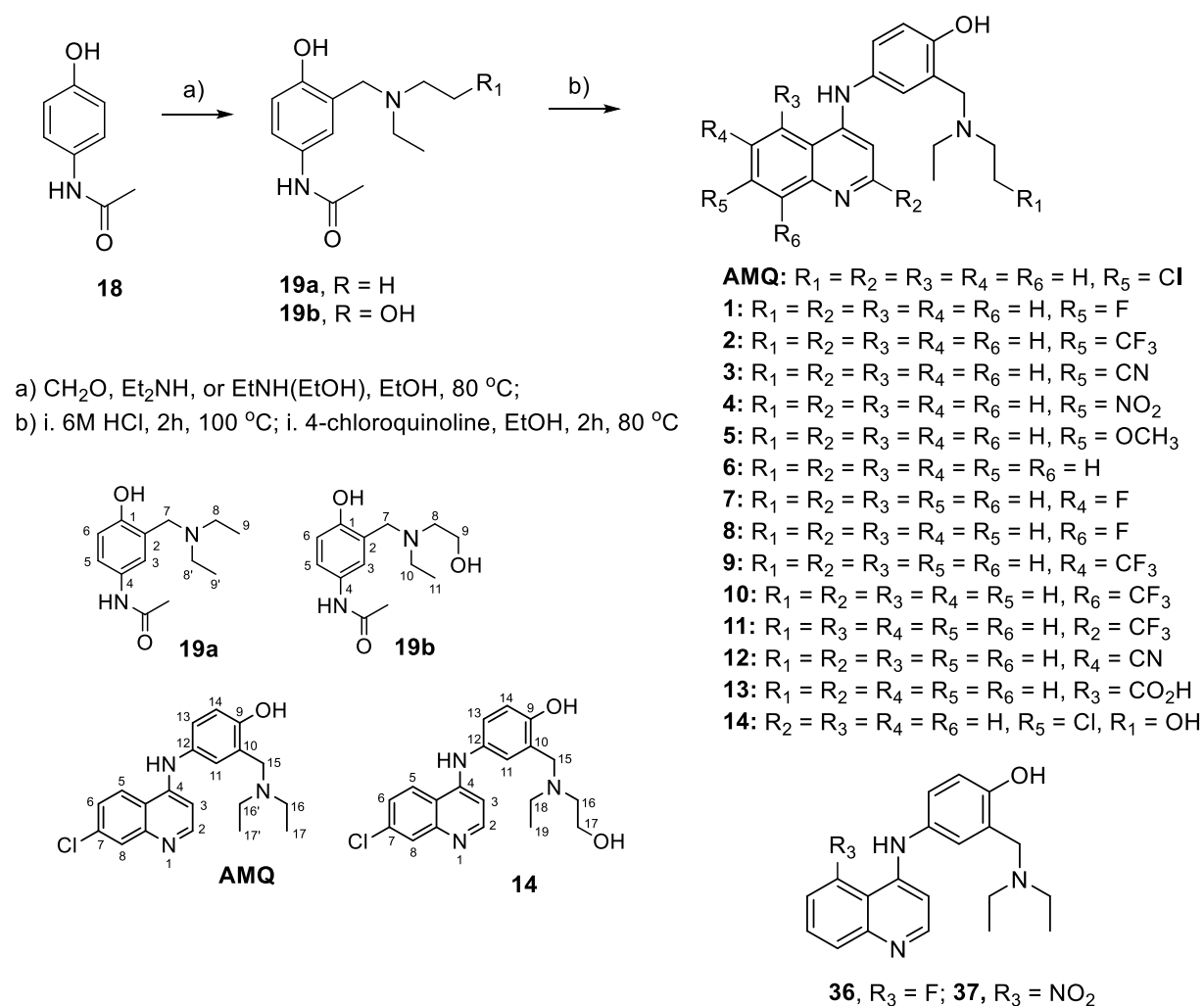
4-chloro-6-fluoroquinoline (34)

Compound **34** was synthesized using **33a** (440.9 mg, 2.70 mmol) and Ph₂O (5.3 mL). Yield: 361.9 mg (84%). ¹H NMR (400 MHz, CDCl₃, δ): 8.75 (d, *J* = 4.7 Hz, 1H, H-2), 8.12 (dd, *J* = 9.2, 5.3 Hz, 1H, H-8), 7.84 (dd, *J* = 9.4, 2.8 Hz, 1H, H-5), 7.58 – 7.48 (m, 2H, H-3 and H-7). ¹³C NMR (100 MHz, CDCl₃, δ): 161.15 (d, *J* = 249.9, C-6), 159.92, 149.09 (d, *J* = 2.8, C-2), 146.18, 141.81 (d, *J* = 5.7), 132.54 (d, *J* = 9.2, C-8), 127.47 (d, *J* = 10.3), 121.76 (C-3), 120.70 (d, *J* = 25.8, C-7), 107.87 (d, *J* = 24.4, C-5).

4-chloroquinoline-6-carbonitrile (35)

Compound **35** was synthesized using **33b** (120.8 mg, 0.71 mmol) and Ph₂O (1.6 mL). Yield: 103.1 mg (77%). ¹H NMR (400 MHz, CDCl₃, δ): 8.92 (d, *J* = 4.7 Hz, 1H, H-2), 8.65 (d, *J* = 1.5 Hz, 1H, H-5), 8.22 (d, *J* = 8.7 Hz, 1H, H-8), 7.92 (dd, *J* = 8.7, 1.7 Hz, 1H, H-7), 7.62 (d, *J* = 4.7 Hz, 1H, H-3). ¹³C NMR (100 MHz, CDCl₃, δ): 152.91, 150.11, 143.26, 131.65, 131.20, 130.80, 126.37, 122.92, 118.31, 111.70.

1.2.2. Synthesis of AMQ and amodiaquine derivatives 1 – 14



Scheme S3. Synthesis of amodiaquine derivatives 1 – 14.

General procedure for synthesis of compounds 19a and 19b: A mixture of compound **1''**, formaldehyde and corresponding amine in EtOH was heated to reflux. After 48 hours, EtOH

was removed under reduced pressure. The residue was dissolved in dichloromethane and washed with 0.1 M HCl (2 x 120 mL). Solid NaOH (0.96 g) was added to the aqueous layer and extracted with dichloromethane (6 x 30 mL). Combined organic extracts were dried under Na₂SO₄ anhydrous. Solvent was removed under reduced pressure and product was isolated by dry-flash column chromatography on silica gel. Our attempt to synthesize amodiaquine derivatives **36** and **37** (Scheme S3), using 5-fluoro-4chloroquinoline (**27**) or 5-nitro-4-chloroquinoline (**30**), failed. During the procedure, a complex mixture was obtained from which, to the best of our knowledge, the isolation of desired compounds was not possible.

The assignation of NMR signals was performed in accordance with numeration given in Scheme S3.

4-amino-2-((diethylamino)methyl)phenol (19a)

Compound **19a** was synthesized using compound **18** (4.53 g, 30 mmol), formaldehyde (4.5 mL, 60 mmol, 2 eq) and diethylamine (6.18 mL, 60 mmol, 2 eq) in EtOH (90 mL). Yield: 2.84 g (40%). Yellow powder, Mp = 124 °C. IR (ATR): 3278 m, 3208 w, 3160 w, 3108 m, 2972 m, 2929 w, 2853 m, 1652 s, 1623 m, 1564 s, 1492 s, 1469 m, 1333 w, 1260 s, 1195 w, 1113 w, 1013 w, 898 w, 832 m, 768 m, 654 w. ¹H NMR (400 MHz, CDCl₃, δ): 7.64 (s, 1H, H-O), 7.30 (s, 1H, H-3), 7.05 (d, *J* = 8.5 Hz, 1H, H-5), 6.70 (d, *J* = 8.6 Hz, 1H, H-6), 3.69 (s, 2H, H-7), 2.58 (q, *J* = 7.1 Hz, 4H, H-8 and H-8'), 2.09 (s, 3H, CH₃CO), 1.07 (t, *J* = 7.1 Hz, 6H, H-9 and H-9'). ¹³C NMR (100 MHz, CDCl₃, δ): 168.35, 155.07, 129.48, 122.16, 121.14, 120.79, 116.00, 77.35, 77.03, 76.71, 56.80, 46.27, 24.19, 11.13.

N-(3-((ethyl(2-hydroxyethyl)amino)methyl)-4-hydroxyphenyl)acetamide (19b)

Compound **19b** was synthesized using compound **18** (1.51 g, 10 mmol), formaldehyde (1.5 mL, 20 mmol, 2 eq) and 2-(ethylamino)ethan-1-ol (1.96 mL, 20 mmol, 2 eq) in EtOH (30 mL). Yield: 376.6 mg (15%). Dark yellow wax-like solid, softens at 84–100 °C. IR (ATR): 3278 m, 3208 w, 3160 w, 3108 m, 2972 m, 2929 w, 2853 m, 1652 s, 1623 m, 1564 s, 1492 s, 1469 m, 1333 w, 1260 s, 1195 w, 1113 w, 1013 w, 898 w, 832 m, 768 m, 654 w. ¹H NMR (400 MHz, CD₃OD, δ): 7.22 (d, *J* = 2.6 Hz, 1H, H-3), 7.17 (dd, *J* = 8.6, 2.6 Hz, 1H, H-5), 6.65 (d, *J* = 8.6 Hz, 1H, H-6), 3.76 (s, 2H, H-7), 3.67 (t, *J* = 5.9 Hz, 2H, H-9), 2.73 – 2.54 (m, 4H, H-8 and H-10), 2.05 (s, 3H, CH₃CO), 1.07 (t, *J* = 7.2 Hz, 3H, H-11). ¹³C NMR (100 MHz, CD₃OD, δ):

171.33, 155.77, 131.41, 124.04, 122.79, 122.27, 116.73, 60.13, 58.08, 55.89, 49.65, 49.44, 49.22, 49.00, 48.80, 48.58, 48.44, 48.37, 23.52, 11.31.

General procedure for synthesis of AMQ and compounds 1 – 14: Compound **19a** or **19b** was heated to reflux for 2 hours in 6M HCl (0.50 mL, 3 mmol), solvent was evaporated to dryness under reduced pressure. The remaining oil was dissolved in absolute EtOH and corresponding 4-chloroquinoline was added. The reaction mixture was heated to reflux for 2 hours, solvent was removed under reduced pressure, water and 30% ammonia were added and solid was extracted with dichloromethane. Combined organic extracts were washed with brine and dried under Na₂SO₄ anhydrous. Solvent was removed under reduced pressure and product was isolated by dry-flash column chromatography on silica-gel.

4-((7-chloroquinolin-4-yl)amino)-2-((diethylamino)methyl)phenol (AMQ)

AMQ was obtained using **19a** (112.6 mg, 0.476 mmol), 4,7-dichloroquinoline (94.3 mg, 0.476 mmol) and absolute EtOH (2 mL). Yield: 109.5 mg (71.8 %). Yellow powder, Mp = 192-194 °C. IR (ATR): 3243 m, 3102 m, 3057 m, 3026 m, 2978 s, 2936 m, 2850 m, 1613 m, 1568 s, 1542 s, 1494 s, 1420 m, 1391 m, 1215 m, 1167 m, 1106 m, 1000 w, 955 w, 880 m, 855 m, 818 m, 765 m, 676 w, 610 w. ¹H NMR (400 MHz, CDCl₃, δ): 8.48 (d, *J* = 5.4 Hz, 1H, H-2), 8.00 (s, 1H, H-8), 7.83 (d, *J* = 9.0 Hz, 1H, H-5), 7.40 (dd, *J* = 9.0, 2.2 Hz, 1H, H-6), 7.08 (dd, *J* = 8.5, 2.6 Hz, 1H, H-13), 6.93 (d, *J* = 2.6 Hz, 1H, H-11), 6.86 (d, *J* = 8.5 Hz, 1H, H-14), 6.62 (d, *J* = 5.4 Hz, 1H, H-3), 3.78 (s, 2H, H-15), 2.65 (q, *J* = 7.2 Hz, 4H, H-16 and H-16'), 1.13 (t, *J* = 7.2 Hz, 6H, H-17 and H-17'). ¹³C NMR (100 MHz, CDCl₃, δ): 165.04, 164.51, 156.87, 152.06, 149.48, 135.31, 129.91, 128.92, 125.87, 125.65, 125.40, 123.46, 121.20, 117.52, 117.29, 101.45, 77.48, 77.16, 77.16, 76.84, 56.95, 46.56, 11.37. (+)ESI-HRMS (*m/z*): calc. for [C₂₀H₂₂ClN₃O + H]⁺ 356.1530, found 356.1528. HPLC purity: Method A: RT 7.486, area 100.00%; method B: RT 8.414, area 99.36%.

2-((diethylamino)methyl)-4-((7-fluoroquinolin-4-yl)amino)phenol (1)

Compound **1** was obtained using **19a** (116.7 mg, 0.494 mmol), 4-chloro-7-fluoroquinoline (**26**, 89.7 mg, 0.494 mmol) and absolute EtOH (2 mL). Yield: 89.3 mg (53%). Pale yellow powder, Mp = 182-188 °C. IR (ATR): 3189 m, 3064 m, 2977 m, 2939 m, 1630 m, 1577 s, 1544 s, 1493 s, 1426 m, 1374 m, 1262 s, 1227 m, 1159 m, 1110 w, 965 m, 870 m, 816 m, 782 w, 764 m, 648 w. ¹H NMR (400 MHz, CDCl₃, δ): 8.46 (d, *J* = 5.4 Hz, 1H, H-2), 7.91 (dd, *J* = 9.2, 5.8 Hz, 1H,

H-5), 7.61 (dd, $J = 10.3, 2.5$ Hz, 1H, H-8), 7.24 – 7.19 (m, 1H, H-6), 7.07 (dd, $J = 8.5, 2.4$ Hz, 1H, H-13), 6.91 (d, $J = 2.1$ Hz, 1H, H-11), 6.85 (d, $J = 8.5$ Hz, 1H, H-14), 6.71 (bs, 1H, H-O), 6.59 (d, $J = 5.4$ Hz, 1H, H-3), 3.76 (s, 2H, H-15), 2.64 (q, $J = 7.2$ Hz, 4H, H-16 and H-16'), 1.12 (t, $J = 7.2$ Hz, 6H, H-17 and H-17'). ^{13}C NMR (100 MHz, CDCl_3 , δ): 163.10 (d, $J = 249.0$ Hz), 156.74, 152.15, 150.42 (d, $J = 12.3$ Hz), 149.59, 130.11, 125.52 (d, $J = 24.7$ Hz), 123.41, 121.95 (d, $J = 10.1$ Hz), 117.23, 116.09, 115.01 (d, $J = 25.1$ Hz), 113.62 (d, $J = 19.8$ Hz), 100.92, 56.94, 46.54, 11.35. (+)ESI-HRMS (m/z): calc. for $[\text{C}_{20}\text{H}_{22}\text{FN}_3\text{O} + \text{H}]^+$ 340.1825, found 340.1831. HPLC purity: Method A: RT 7.357, area 100.00%; method B: RT 8.288, area 99.18%.

2-((diethylamino)methyl)-4-((7-(trifluoromethyl)quinolin-4-yl)amino)phenol (2)

Compound **2** was obtained using **19a** (120.4 mg, 0.509 mmol), 4-chloro-7-(trifluoromethyl)quinoline (117.9 mg, 0.509 mmol) and absolute EtOH (2 mL). Yield: 123.4 mg (62.3%). Pale yellow powder, Mp = 192-194 °C. IR (ATR): 3188 m, 3064 m, 2980 m, 2945 m, 1583 s, 1569 s, 1489 s, 1379 s, 1328 s, 1292 m, 1257 s, 1196 m, 1119 s, 1076 w, 996 w, 916 w, 830 m, 820 m, 798 w, 7390 w, 683 w. ^1H NMR (400 MHz, CDCl_3 , δ): 8.54 (d, $J = 5.2$ Hz, 1H, H-2), 8.28 (s, 1H, H-8), 8.00 (d, $J = 8.8$ Hz, 1H, H-5), 7.62 (d, $J = 8.7$ Hz, 1H, H-6), 7.08 (dd, $J = 8.5, 2.3$ Hz, 1H, H-13), 6.92 (d, $J = 2.0$ Hz, 1H, H-11), 6.85 (d, $J = 8.5$ Hz, 1H, H-14), 6.72 – 6.65 (m, 2H, H-3 and H-O), 3.77 (s, 2H, H-15), 2.64 (q, $J = 7.2$ Hz, 4H, H-16 and H-16'), 1.12 (t, $J = 7.2$ Hz, 6H, H-17 and H-17'). ^{13}C NMR (100 MHz, CDCl_3 , δ): 165.01, 157.00, 152.34, 149.35, 148.25, 131.68, 131.35, 131.04, 130.71, 129.80, 128.00, 127.95, 127.91, 127.87, 125.75, 125.48, 123.54, 122.75, 121.02, 120.78, 120.66, 120.62, 120.59, 120.56, 117.36, 102.47, 77.48, 77.16, 76.84, 56.95, 46.57, 11.36. (+)ESI-HRMS (m/z): calc. for $[\text{C}_{21}\text{H}_{22}\text{F}_3\text{N}_3\text{O} + \text{H}]^+$ 390.1793, found 390.1786. HPLC purity: Method A: RT 7.629, area 99.43%; method B: RT 8.583, area 98.65%.

4-(((diethylamino)methyl)-4-hydroxyphenyl)amino)quinoline-7-carbonitrile (3)

Compound **3** was obtained using **19a** (114.4 mg, 0.484 mmol), 4-chloroquinoline-7-carbonitrile (**28**, 91.3 mg, 0.484 mmol) and absolute EtOH (2 mL). Yield: 144.9 mg (86.4%). Yellow powder, Mp = 168-170 °C. IR (ATR): 3130 m, 3087 m, 2977 m, 2931 m, 2227 m, 1582 s, 1566 s, 1531 m, 1494 s, 1454 w, 1379 s, 1328 w, 1261 m, 1251 m, 1225 m, 1166 m, 1105 m, 980 w, 915 w, 889 w, 822 w, 759 w, 656 w. ^1H NMR (400 MHz, CDCl_3 , δ): 8.55 (d, $J = 5.3$ Hz, 1H, H-2), 8.33 (s, 1H, H-8), 8.01 (d, $J = 8.7$ Hz, 1H, H-5), 7.59 (d, $J = 8.4$ Hz, 1H, H-6), 7.08 (dd, $J = 8.5, 2.3$ Hz, 1H, H-13), 6.93 (d, $J = 2.1$ Hz, 1H, H-11), 6.86 (d, $J = 8.5$ Hz,

1H, H-14), 6.79 (s, 1H, H-O), 6.72 (d, $J = 5.3$ Hz, 1H, H-3), 3.78 (s, 2H, H-15), 2.65 (q, $J = 7.1$ Hz, 4H, H-16 and H-16'), 1.13 (t, $J = 7.2$ Hz, 6H, H-17 and H-17'). ^{13}C NMR (100 MHz, CDCl_3 , δ): 157.12, 152.69, 149.44, 148.01, 135.81, 129.49, 125.76, 125.64, 125.49, 123.55, 121.53, 121.42, 118.67, 117.40, 112.85, 102.96, 77.48, 77.16, 76.84, 56.88, 46.54, 29.81, 11.33. (+)ESI-HRMS (m/z): calc. for $[\text{C}_{21}\text{H}_{22}\text{N}_4\text{O} + \text{H}]^+$ 347.1872, found 347.1871. HPLC purity: Method A: RT 7.311, area 98.57%; method B: RT 8.232, area 99.17%.

2-((diethylamino)methyl)-4-((7-nitroquinolin-4-yl)amino)phenol (4)

Compound **4** was obtained using **19a** (112.4 mg, 0.476 mmol), 4-chloro-7-nitroquinoline (**29**, 99.3 mg, 0.476 mmol) and absolute EtOH (2 mL). Yield: 148.0 mg (84.8 %). Yellow powder, $\text{Mp} = 188\text{--}192^\circ\text{C}$. IR (ATR): 3183 w, 3096 w, 2976 m, 2940 m, 1582 s, 1535 s, 1488 s, 1422 m, 1373 s, 1350 m, 1262 s, 1196 w, 1161 w, 1107 w, 1078 w, 997 w, 908 w, 836 w, 823 m, 764 m, 741 m, 656 w. ^1H NMR (400 MHz, CDCl_3 , δ): 8.84 (d, $J = 1.9$ Hz, 1H, H-8), 8.59 (d, $J = 5.3$ Hz, 1H, H-2), 8.19 (dd, $J = 9.2, 2.0$ Hz, 1H, H-6), 8.06 (d, $J = 9.2$ Hz, 1H, H-5), 7.09 (dd, $J = 8.4, 2.1$ Hz, 1H, H-13), 6.95 (d, $J = 1.6$ Hz, 1H, H-11), 6.89 – 6.81 (m, 2H, H-14 and H-O), 6.74 (d, $J = 5.3$ Hz, 1H, H-3), 3.78 (s, 2H, H-15), 2.65 (q, $J = 7.1$ Hz, 4H, H-16 and H-16'), 1.13 (t, $J = 7.1$ Hz, 6H, H-17 and H-17'). ^{13}C NMR (100 MHz, CDCl_3 , δ): 157.19, 153.21, 149.57, 148.33, 148.09, 129.43, 126.12, 125.82, 125.55, 123.61, 122.54, 121.76, 118.17, 117.41, 103.23, 77.16, 56.90, 46.55, 11.34. (+)ESI-HRMS (m/z): calc. for $[\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_3 + \text{H}]^+$ 367.1770, found 367.1784. HPLC purity: Method A: RT 7.383, area 98.78%; method B: RT 8.428, area 99.66%.

2-((diethylamino)methyl)-4-((7-methoxyquinolin-4-yl)amino)phenol (5)

Compound **5** was obtained using **19a** (100 mg, 0.423 mmol) and 4-chloro-7-methoxyquinoline (81.9 mg, 0.423 mmol) and absolute EtOH (2 mL). Yield: 98.2 mg (66 %). Brownish powder, $\text{Mp} = 178\text{--}184^\circ\text{C}$. IR (ATR): 2972m, 2934m, 2831m, 1621m, 1577s, 1549m, 1496s, 1476s, 1436s, 1383m, 1361m, 1327w, 1308m, 1292m, 1257s, 1229s, 1198m, 1173m, 1111w, 1068w, 1025m, 1001w, 953w, 871w, 851m, 811m, 769m, 660w, 558w, 452w, cm^{-1} . ^1H NMR (400 MHz, CDCl_3 , δ): 8.41 (d, 1H, $J = 5.3$, H-2), 7.80 (d, 1H, $J = 9.2$, H-5), 7.35 (bs, 1H, H-8), 7.15 – 7.04 (m, 2H, H-6 and H-13), 6.92 (d, 1H, $J = 1.9$, H-11), 6.85 (d, 1H, $J = 8.5$, H-14), 6.63 (bs, 1H, H-O), 6.55 (d, 1H, $J = 5.4$, H-3), 3.91 (s, 3H, $\text{CH}_3\text{-O}$), 3.77 (s, 2H, H-15), 2.65 (q, 4H, $J = 7.2$, H-16 and H-16'), 1.13 (t, 6H, $J = 7.2$, H-17 and H-17'). ^{13}C NMR (100 MHz, CDCl_3 , δ): 160.61, 156.48, 151.20, 150.74, 149.43, 130.47, 125.45, 125.24, 123.31, 120.97, 117.66, 117.13, 113.67, 108.15, 100.14, 56.95, 55.57, 46.52, 11.36. (+)ESI-HRMS (m/z): calc. for

[C₂₁H₂₅N₃O₂+ H]⁺ 352.2025, found 352.2011. HPLC purity: Method A: RT 7.513, area 100.00%; method B: RT 8.830, area 97.93%.

2-((diethylamino)methyl)-4-(quinolin-4-ylamino)phenol (6)

Compound **6** was obtained using **19a** (123.6 mg, 0.523 mmol) and 4-chloroquinoline (86.3 mg, 0.527 mmol) and absolute EtOH (2 mL). Yield: 49.3 mg (29 %). Brownish powder, Mp = 152-156 °C. IR (ATR): 3181m, 3057m, 2978m, 2924m, 2846m, 1619w, 1578s, 1540m, 1490s, 1442m, 1389s, 1333m, 1294m, 1254s, 1218m, 1191m, 1166m, 1106w, 1049w, 1026w, 994w, 962w, 943w, 911w, 892m, 877w, 816m, 767s, 652m, 631w, 556m, 499w, 479w, 445w, 430w, cm⁻¹. ¹H NMR (400 MHz, CDCl₃, δ): 8.43 (*d*, 1H, *J* = 5.2, H-2), 8.01 (*d*, 1H, *J* = 8.5, H-5), 7.92 (*d*, 1H, *J* = 8.3, H-8), 7.65 (*t*, 1H, *J* = 7.6, H-6), 7.46 (*t*, 1H, *J* = 7.5, H-7), 7.09 (*d*, 1H, *J* = 8.5, H-13), 6.93 (*s*, 1H, H-11), 6.85 (*d*, 1H, *J* = 8.5, H-14), 6.76 (*bs*, 1H, H-O), 6.65 (*d*, 1H, *J* = 5.3, H-3), 3.77 (*s*, 2H, H-17), 2.65 (*q*, 4H, *J* = 7.1, H-18 and H-18'), 1.13 (*t*, 6H, *J* = 7.1, H-19 and H-19'). ¹³C NMR (100 MHz, CDCl₃, δ): 156.61, 150.78, 149.48, 148.74, 130.42, 129.91, 129.42, 125.54, 125.30, 125.14, 123.39, 119.65, 119.12, 117.20, 101.12, 56.98, 46.58, 11.36. (+)ESI-HRMS (*m/z*): calc. for [C₂₀H₂₃N₃O+ H]⁺ 322.1919, found 322.1923. HPLC purity: Method A: RT 7.296, area 100.00%; method B: RT 8.309, area 99.29%.

2-((diethylamino)methyl)-4-((6-fluoroquinolin-4-yl)amino)phenol (7)

Compound **7** was obtained using **19a** (121.8 mg, 0.515 mmol), 4-chloro-6-fluoroquinoline (**34**, 93.5 mg, 0.515 mmol) and absolute EtOH (2 mL). Yield: 130.3 mg (74.5 %). Yellow powder, Mp = 162-164 °C. IR (ATR): 3238 m, 3040 m, 2969 m, 2935 m, 2874 m, 2829m, 1626 w, 1603 w, 1574 m, 1544 m, 1515 m, 1496 s, 1449 m, 1378 m, 1328 w, 1291 w, 1260 m, 1244 m, 1195 m, 1168 w, 1096 w, 1052 w, 996 w, 921 m, 876 m, 839 w, 829 m, 766 w, 668 w. ¹H NMR (400 MHz, CDCl₃, δ): 8.45 (*d*, *J* = 5.3 Hz, 1H, H-2), 7.98 (*dd*, *J* = 9.3, 5.6 Hz, 1H, H-8), 7.56 (*d*, *J* = 9.8 Hz, 1H, H-5), 7.40 (*td*, *J* = 9.3, 2.4 Hz, 1H, H-7), 7.06 (*dd*, *J* = 8.5, 2.6 Hz, 1H, H-15), 6.90 (*d*, *J* = 1.1 Hz, 1H, H-11), 6.84 (*d*, *J* = 8.5 Hz, 1H, H-14), 6.71 – 6.61 (*m*, 2H, H-3 and H-O), 3.75 (*s*, 2H, H-15), 2.63 (*q*, *J* = 7.1 Hz, 4H, H-16 and H-16'), 1.12 (*t*, *J* = 7.1 Hz, 6H, H-17 and H-17'). ¹³C NMR (100 MHz, CDCl₃, δ): 159.89 (*d*, *J* = 246.0 Hz), 156.55, 150.31 (*d*, *J* = 2.2 Hz), 149.09 (*d*, *J* = 4.9 Hz), 146.04, 132.45 (*d*, *J* = 8.9 Hz), 130.31, 125.33 (*d*, *J* = 23.1 Hz), 123.37, 119.68 (*d*, *J* = 8.5 Hz), 119.13 (*d*, *J* = 25.0 Hz), 117.18, 103.99 (*d*, *J* = 23.0 Hz), 101.53, 56.91, 46.50, 11.32. (+)ESI-HRMS (*m/z*): calc. for [C₂₀H₂₂FN₃O + H]⁺ 340.1825, found 340.1823. HPLC purity: Method A: RT 7.332, area 99.55%; method B: RT 8.233, area 99.57%.

2-((diethylamino)methyl)-4-((8-fluoroquinolin-4-yl)amino)phenol (8)

Compound **8** was obtained using **19a** (117.4 mg, 0.497 mmol), 4-chloro-8-fluoroquinoline (90.3 mg, 0.497 mmol) and absolute EtOH (2 mL). Yield: 119.4 mg (70.1%). Brownish powder, Mp = 166-168 °C. IR (ATR): 3195 m, 3104 w, 3080 w, 2980 m, 2938 m, 2836 m, 1596 w, 1579 m, 1539 s, 1493 s, 1422 m, 1258 s, 1223 w, 1193 w, 1060 w, 964 m, 919 m, 810 m, 753 m, 741 w, 609 w. ¹H NMR (400 MHz, CDCl₃, δ): 8.51 (d, *J* = 5.2 Hz, 1H, H-2), 7.67 (d, *J* = 8.1 Hz, 1H, H-7), 7.42 – 7.29 (m, 2H, H-5 and H-6), 7.07 (d, *J* = 8.5 Hz, 1H, H-13), 6.92 (s, 1H, H-11), 6.85 (d, *J* = 8.5 Hz, 1H, H-14), 6.92 (bs, 1H, H-O), 6.85 (d, *J* = 8.5 Hz, 1H, H-3), 3.76 (s, 2H, H-15), 2.64 (q, *J* = 7.1 Hz, 4H, H-16 and H-16'), 1.12 (t, *J* = 7.1 Hz, 6H, H-17 and H-17'). ¹³C NMR (100 MHz, CDCl₃, δ): 163.68, 158.57 (d, *J* = 254.8 Hz), 156.64, 150.94, 149.04 (d, *J* = 3.4 Hz), 139.35 (d, *J* = 11.9 Hz), 129.80, 125.41 (d, *J* = 24.9 Hz), 124.32 (d, *J* = 8.4 Hz), 123.26, 120.72 (d, *J* = 3.0 Hz), 117.08, 115.13 (d, *J* = 4.6 Hz), 113.35 (d, *J* = 19.3 Hz), 101.6, 56.76, 46.37, 11.18. (+)ESI-HRMS (*m/z*): calc. for [C₂₀H₂₂FN₃O + H]⁺ 340.1825, found 340.1828. HPLC purity: Method A: RT 7.279, area 100.00%; method B: RT 8.234, area 99.27%.

2-((diethylamino)methyl)-4-((6-(trifluoromethyl)quinolin-4-yl)amino)phenol (9)

Compound **9** was obtained using **19a** (112.4 mg, 0.476 mmol), 4-chloro-6-(trifluoromethyl)quinoline (110.2 mg, 0.476 mmol) and absolute EtOH (2 mL). Yield: 135.6 mg (73.1 %). Yellow powder, Mp = 192-196 °C. IR (ATR): 3231 m, 3049 m, 2973 m, 2935 m, 2879 w, 2833 w, 1636 w, 1576 s, 1541 s, 1494 s, 1452 s, 1379 s, 1317 s, 1252 s, 1195 w, 1114 s, 1071 m, 996 w, 942 w, 892 w, 835 m, 794 w, 628 w. ¹H NMR (400 MHz, CDCl₃, δ): 8.58 (d, *J* = 5.4 Hz, 1H, H-2), 8.23 (s, 1H, H-5), 8.12 (d, *J* = 8.9 Hz, 1H, H-8), 7.82 (dd, *J* = 8.8, 1.9 Hz, 1H, H-7), 7.11 (dd, *J* = 8.5, 2.6 Hz, 1H, H-13), 6.94 (d, *J* = 2.6 Hz, 1H, H-11), 6.87 (d, *J* = 8.5 Hz, 1H, H-14), 6.76 (bs, 1H, H-O), 6.70 (d, *J* = 5.4 Hz, 1H, H-3), 3.79 (s, 2H, H-15), 2.66 (q, *J* = 7.2 Hz, 4H, H-16 and H-16'), 1.14 (t, *J* = 7.2 Hz, 6H, H-17 and H-17'). ¹³C NMR (100 MHz, CDCl₃, δ): 165.14, 157.13, 152.98, 150.24, 131.20, 131.14, 131.12, 131.08, 129.59, 126.89, 126.60, 125.82, 125.54, 125.30, 125.24, 125.21, 125.16, 123.56, 118.21, 118.13, 118.09, 118.04, 118.00, 117.39, 102.14, 77.48, 77.16, 76.84, 56.94, 46.57, 11.36. (+)ESI-HRMS (*m/z*): calc. for [C₂₁H₂₂F₃N₃O + H]⁺ 390.1793, found 390.1798. HPLC purity: Method A: RT 7.646, area 99.54%; method B: RT 8.629, area 98.46%.

2-((diethylamino)methyl)-4-((8-(trifluoromethyl)quinolin-4-yl)amino)phenol (10)

Compound **10** was obtained using **19a** (112.7 mg, 0.477 mmol), 4-chloro-8-(trifluoromethyl)quinoline (110.5 mg, 0.477 mmol) and absolute EtOH (2 mL). Yield: 30.7 mg (70.4%). Yellow powder, Mp = 162-166 °C. IR (ATR): 3235 m, 2972 m, 2934 m, 2823 m, 1584 s, 1540 s, 1423 w, 1386 m, 1313 s, 1253 s, 1150 m, 1128 s, 1058 m, 987 w, 895 w, 816 w, 774 m, 715 w, 603 w. ¹H NMR (400 MHz, CDCl₃, δ): 8.61 (dd, *J* = 5.4, 1.5 Hz, 1H, H-2), 8.10 (d, *J* = 8.5 Hz, 1H, H-7), 8.01 (d, *J* = 7.3 Hz, 1H, H-6), 7.47 (t, *J* = 8.0 Hz, 1H, H-5), 7.07 (dd, *J* = 8.5, 2.6 Hz, 1H, H-13), 6.91 (d, *J* = 2.6 Hz, 1H, H-11), 6.85 (d, *J* = 8.5 Hz, 1H, H-14), 6.69 (t, *J* = 6.7 Hz, 1H, H-3), 6.65 (s, 1H, H-O), 3.77 (s, 2H, H-15), 2.64 (q, *J* = 7.1 Hz, 4H, H-16 and H-16'), 1.13 (t, *J* = 7.1 Hz, 6H, H-17 and H-17'). ¹³C NMR (100 MHz, CDCl₃, δ): 156.87, 156.83, 151.76, 149.50, 145.80, 129.90, 129.88, 127.98, 127.93, 127.87, 127.81, 125.78, 125.64, 125.39, 124.24, 124.19, 123.47, 123.36, 119.78, 117.29, 101.94, 77.48, 77.16, 76.84, 56.91, 46.53, 11.33. (+)ESI-HRMS (*m/z*): calc. for [C₂₁H₂₂F₃N₃O + H]⁺ 390.1793, found 390.1797. HPLC purity: Method A: RT 7.503, area 100.00%; method B: RT 8.418, area 98.96%.

2-((diethylamino)methyl)-4-((2-(trifluoromethyl)quinolin-4-yl)amino)phenol (11)

Compound **11** was obtained using **19a** (115.1 mg, 0.487 mmol), 4-chloro-2-(trifluoromethyl)quinoline (112.8 mg, 0.487 mmol) and absolute EtOH (2 mL). Yield: 79.3 mg (41.8%). Yellow powder, Mp = 112-114 °C. IR (ATR): 3331 w, 2975 m, 2936 m, 2877 m, 2851 m, 1589 s, 1574 s, 1499 s, 1460 m, 1404 m, 1367 w, 1340 w, 1276 s, 1259 s, 1183 s, 1141 s, 1074 w, 998 w, 948 w, 844 w, 765 w, 554 w. ¹H NMR (400 MHz, CDCl₃, δ): 8.13 (d, *J* = 8.5 Hz, 1H, H-5), 7.91 (d, *J* = 8.4 Hz, 1H, H-8), 7.75 (t, *J* = 7.7 Hz, 1H, H-6), 7.58 (t, *J* = 7.6 Hz, 1H, H-7), 7.11 (dd, *J* = 8.5, 2.6 Hz, 1H, H-15), 6.95 (d, *J* = 2.6 Hz, 1H, H-11), 6.93 – 6.88 (m, 2H, H-14 and H-O), 6.75 (d, *J* = 4.6 Hz, 1H, H-3), 3.80 (s, 2H, H-15), 2.67 (q, *J* = 7.2 Hz, 4H, H-16 and H-16'), 1.14 (t, *J* = 7.2 Hz, 6H, H-17, H-17'). ¹³C NMR (100 MHz, CDCl₃, δ): 157.32, 151.03, 149.11, 148.78, 148.19, 130.98, 130.45, 129.30, 126.84, 125.92, 125.66, 123.71, 119.34, 119.01, 117.54, 96.65, 96.62, 96.60, 96.57, 77.48, 77.16, 76.84, 56.85, 46.55, 11.29. (+)ESI-HRMS (*m/z*): calc. for [C₂₁H₂₂F₃N₃O + H]⁺ 390.1793, found 390.1797. HPLC purity: Method A: RT 8.338, area 98.85%; method B: RT 9.922, area 98.47%.

4-((3-((diethylamino)methyl)-4-hydroxyphenyl)amino)quinoline-6-carbonitrile (12)

Compound **12** was obtained using **19a** (118.4 mg, 0.501 mmol), 4-chloroquinoline-6-carbonitrile (**35**, 94.5 mg, 0.501 mmol) and absolute EtOH (2 mL). Yield: 72.1 mg (41.5%). Yellow powder, Mp = 184-186 °C. IR (ATR): 3233 m, 3040 m, 2975 m, 2933m, 2874 m, 2226 m, 1604 m, 1568 s, 1542 m, 1496 s, 1450 m, 1496 s, 1450 m, 1378 m, 1365 m, 1321 m, 1263 m, 1249 s, 1219 m, 1168 w, 1119 w, 1054 w, 878 m, 837 m, 796 w, 767 w, 671 w. ¹H NMR (400 MHz, CDCl₃, δ): 8.56 (d, *J* = 5.3 Hz, 1H, H-2), 8.41 (s, 1H, H-5), 8.04 (d, *J* = 8.7 Hz, 1H, H-8), 7.78 (d, *J* = 8.8 Hz, 1H, H-7), 7.10 (dd, *J* = 8.5, 2.2 Hz, 1H, H-13), 6.98 – 6.83 (m, 3H, H-11, H-14 and H-O), 6.71 (d, *J* = 5.4 Hz, 1H, H-3), 3.79 (s, 2H, H-15), 2.66 (q, *J* = 7.1 Hz, 4H, H-16 and H-16'), 1.14 (t, *J* = 7.2 Hz, 6H, H-17 and H-17'). ¹³C NMR (100 MHz, CDCl₃, δ): 157.18, 153.75, 150.42, 149.82, 131.43, 130.03, 129.39, 127.08, 125.74, 125.45, 123.58, 119.35, 118.90, 117.40, 107.94, 102.44, 77.48, 77.16, 76.84, 56.95, 46.57, 11.36. (+)ESI-HRMS (m/z): calc. for [C₂₁H₂₂N₄O + H]⁺ 347.1872, found 347.1862. HPLC purity: Method A: RT 7.308, area 100.00%; method B: RT 8.178, area 97.39%.

4-((3-((diethylamino)methyl)-4-hydroxyphenyl)amino)quinoline-5-carboxylic acid (13)

Compound **13** was obtained according to general procedure using **19a** (112.4 mg, 0.476 mmol), 4-chloroquinoline-5-carbonitrile (**15**, 89.8 mg, 0.476 mmol) and absolute EtOH (2 mL). Yield: 109.4 (62.9 %). Brown solid, Mp = 112-114°C. IR (ATR): 2972 w, 2945 w, 2826 w, 1728 s, 1638 m, 1620 m, 1603 w, 1498 s, 1415 w, 1389 w, 1314w, 1268 m, 1072 w, 1021 m, 912 w, 835 w, 773 w, 742 w, 607 w. ¹H NMR (400 MHz, CDCl₃, δ): 8.85 (d, *J* = 4.8 Hz, 1H, H-2), 8.24 (d, *J* = 8.4 Hz, 1H, H-8), 8.11 (d, *J* = 7.0 Hz, 1H, H-6), 7.95 – 7.86 (m, 1H, H-7), 7.29 – 7.21 (m, 1H, H-13), 7.12 (d, *J* = 2.1 Hz, 1H, H-11), 6.94 (d, *J* = 8.5 Hz, 1H, H-14), 6.85 (d, *J* = 4.8 Hz, 1H, H-3), 3.84 (s, 2H, H-15), 2.67 (q, *J* = 7.1 Hz, 4H, H-16 and H-16'), 1.14 (t, *J* = 7.2 Hz, 6H, H-17 and H-17'). ¹³C NMR (100 MHz, CDCl₃, δ): 167.08, 166.89, 158.49, 154.28, 147.33, 143.77, 132.85, 131.95, 126.15, 126.10, 126.08, 125.40, 125.06, 123.22, 121.85, 117.14, 101.69, 77.48, 77.16, 76.84, 56.94, 46.54, 11.34. (+)ESI-HRMS (m/z): calc. for [C₂₁H₂₃N₃O₃ + H]⁺ 366.1818, found 366.1815. HPLC purity: Method A: RT 7.581, area 98.76%; method B: RT 9.156, area 99.33%.

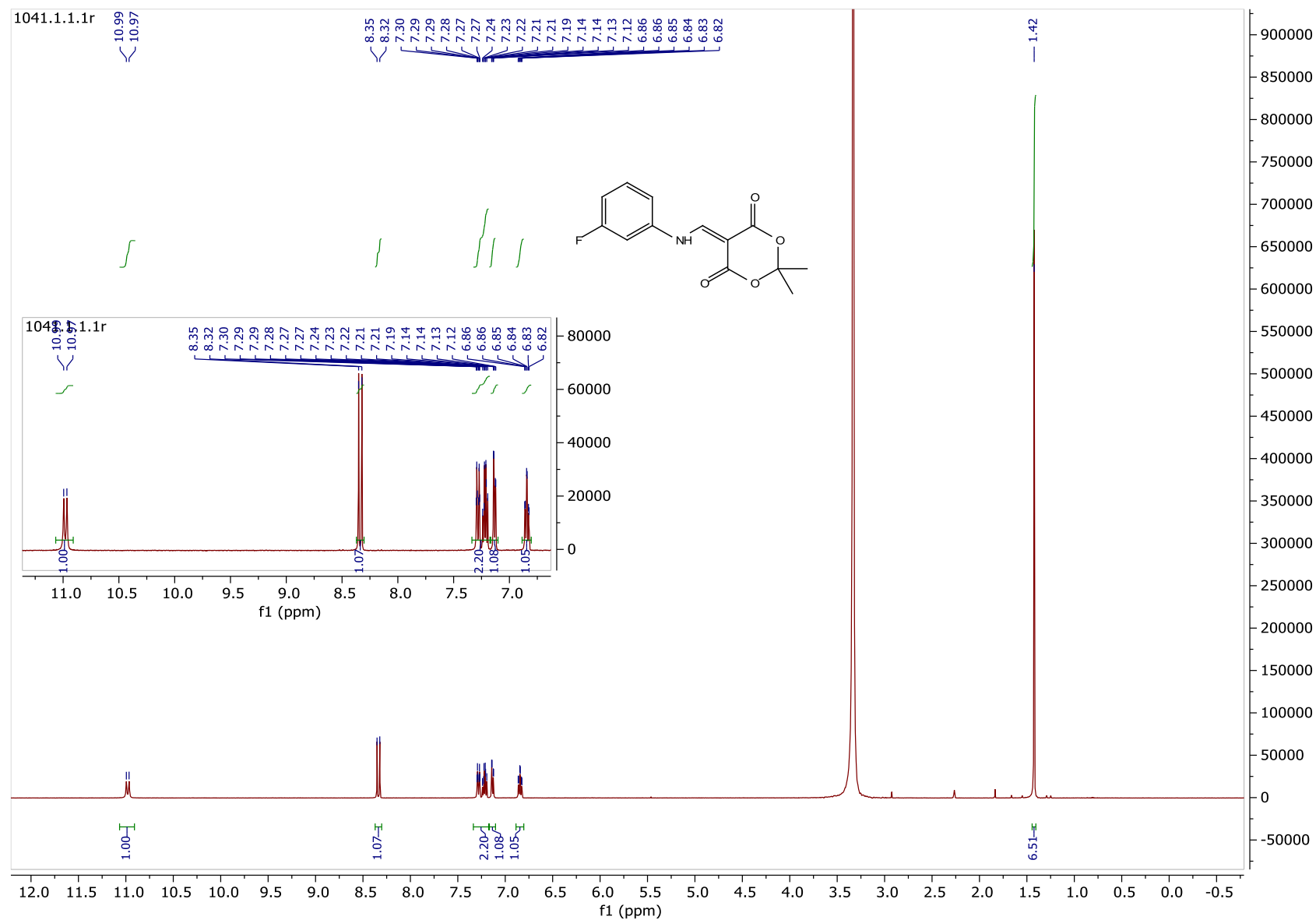
4-((7-chloroquinolin-4-yl)amino)-2-((ethyl(2-hydroxyethyl)amino)methyl)phenol (14)

Compound **14** was obtained using **19b** (100 mg, 0.396 mmol) and 4,7-dichloroquinoline (78.5 mg, 0.396 mmol) and absolute EtOH (2 mL). Yield: 96.4 mg (65 %). Pale-yellow powder, Mp = 214-218 °C. IR (ATR): 3274m, 3064m, 2974m, 2896m, 2809m, 1608m, 1572s, 1535m, 1494s, 1472m, 1446m, 1415m, 1373s, 1329m, 1304w, 1259s, 1215w, 1198w, 1182w, 1162w,

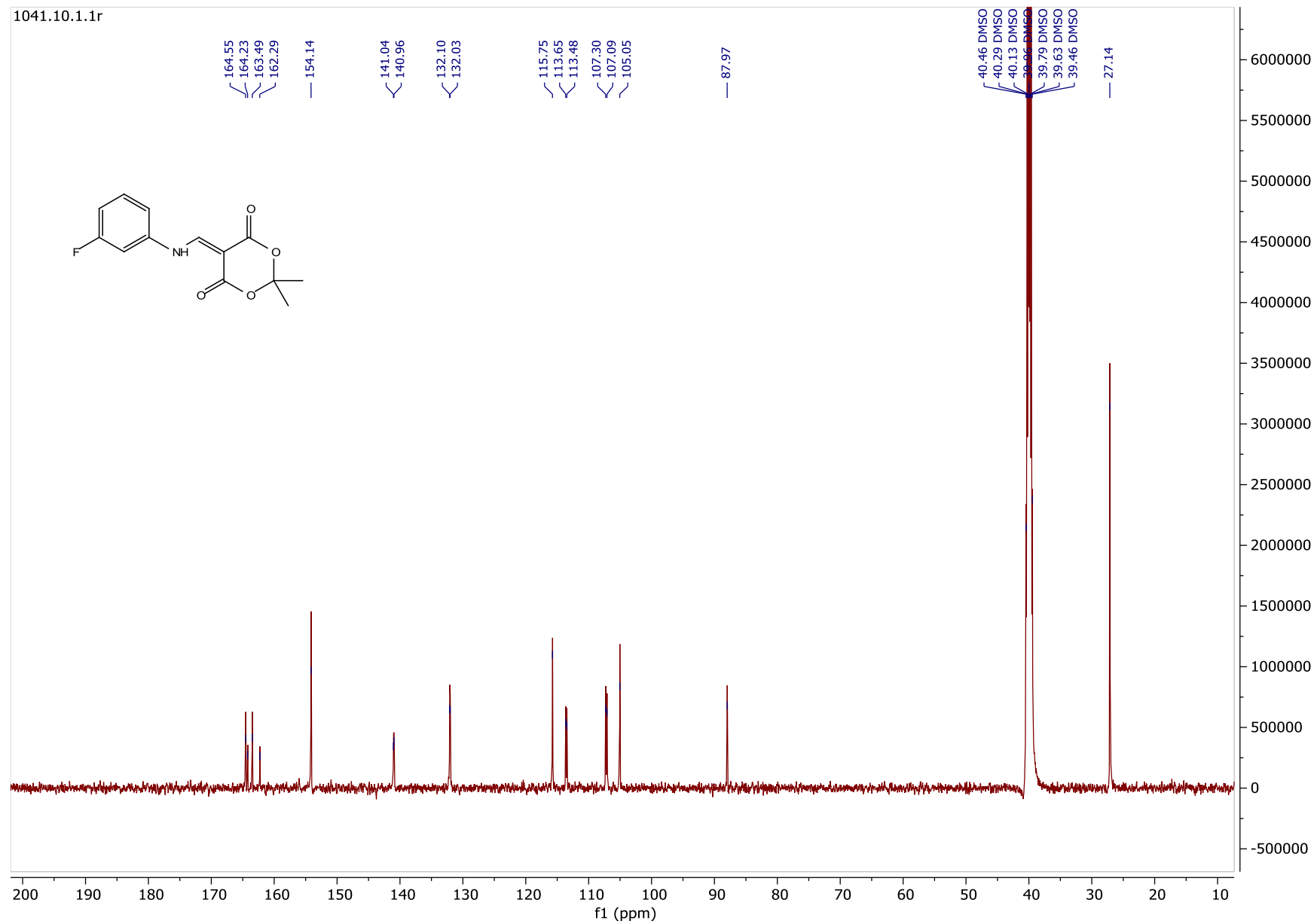
1139w, 1108w, 1078m, 1061w, 1046m, 1001w, 911m, 869m, 857m, 817w, 802m, 783m, 762m, 666w, 647w, 629w, 607w, 587w, 571w, 539m, 498w, 451w, 427w, cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO-}d_6$, δ): 8.89 (*s*, 1H, H-O), 8.40 (*d*, 1H, $J = 9.0$, H-5), 8.35 (*d*, 1H, $J = 4.3$, H-2), 7.84 (*s*, 1H, H-8), 7.50 (*d*, 1H, $J = 9.0$, H-6), 7.08 – 7.06 (*m*, 2H, H-11 and H-13), 6.78 (*d*, 1H, $J = 9.1$, H-14), 6.56 (*d*, 1H, $J = 5.3$, H-3), 3.76 (*s*, 2H, H-15), 3.57 – 3.53 (*m*, 2H, H-19), 2.63 – 2.52 (*m*, 4H, H-16 and H-18), 1.01 (*t*, 3H, $J = 7.0$, H-19). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$, δ): 155.02, 151.91, 149.61, 149.47, 133.81, 130.41, 127.57, 125.57, 124.76, 124.63, 124.29, 117.76, 116.19, 100.54, 58.44, 55.53, 54.69, 46.90, 10.89. (+)ESI-HRMS (m/z): calc. for $[\text{C}_{20}\text{H}_{22}\text{ClN}_3\text{O}_2 + \text{H}]^+$ 372.1479, found 372.1486. HPLC purity: Method A: RT 7.434, area 97.43%; method B: RT 8.650, area 97.65%.

1.2.3. ^1H and ^{13}C NMR spectra

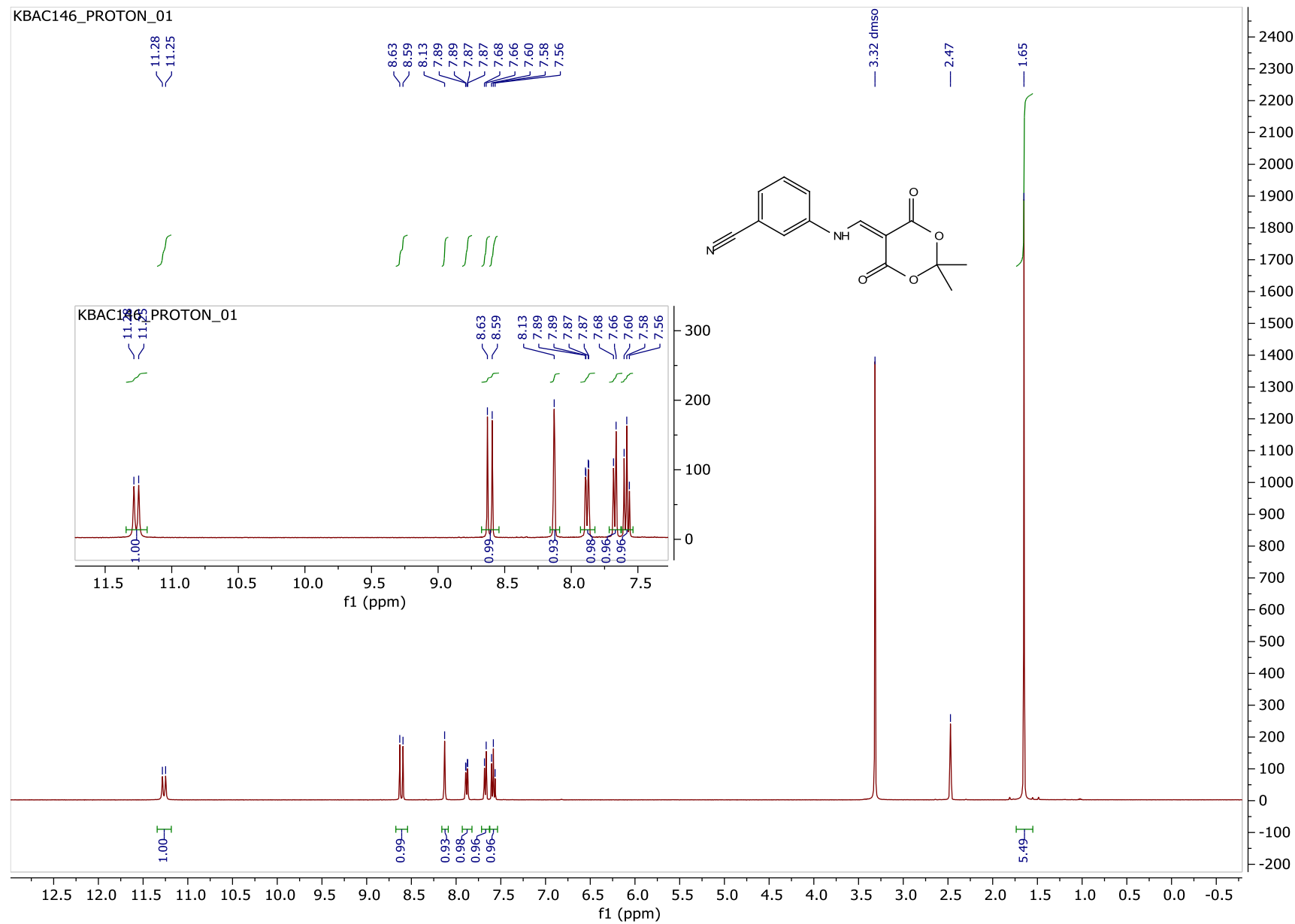
^1H NMR spectrum of 5-(((3-fluorophenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (22a)



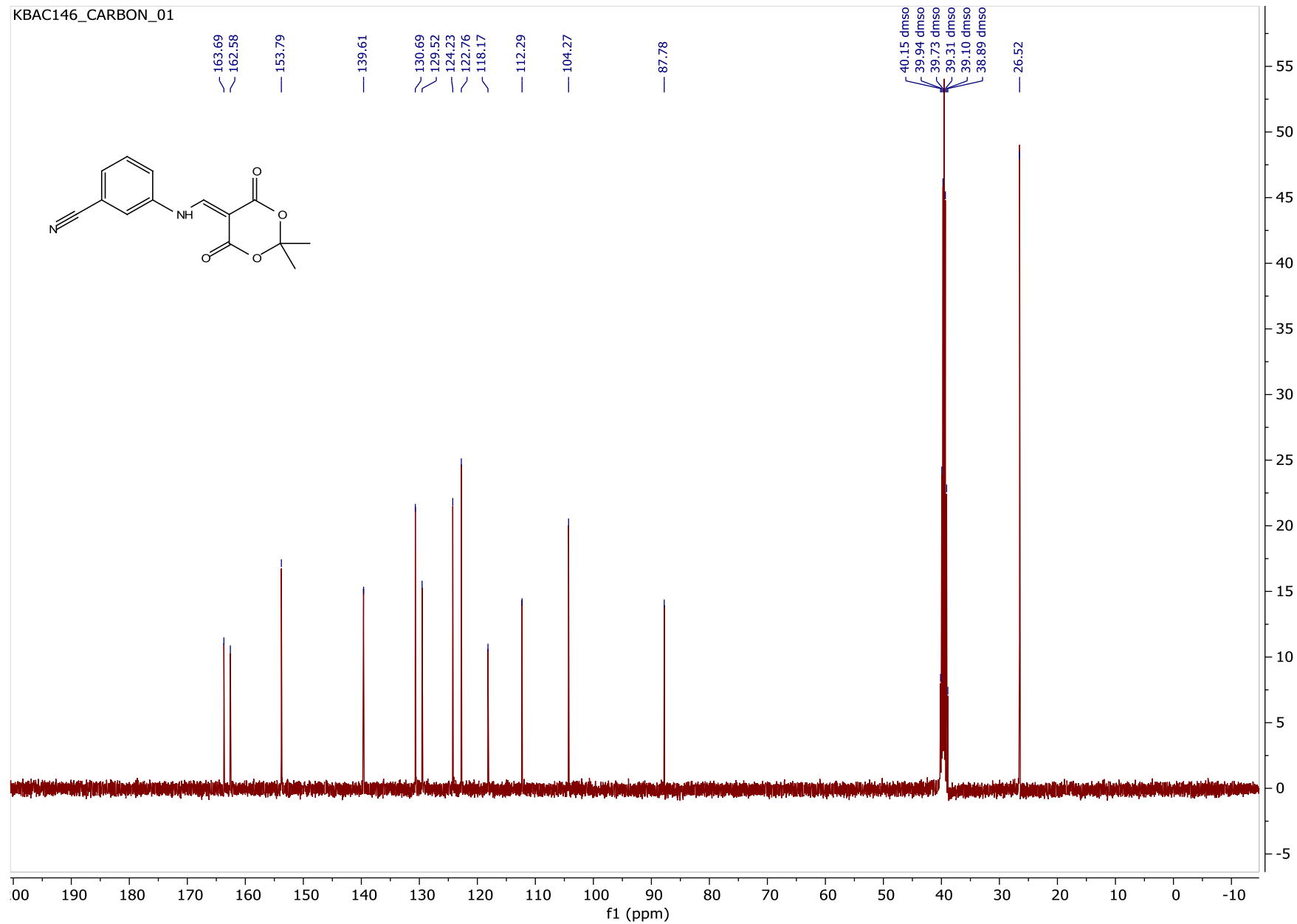
^{13}C NMR spectrum of 5-(((3-fluorophenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (22a)



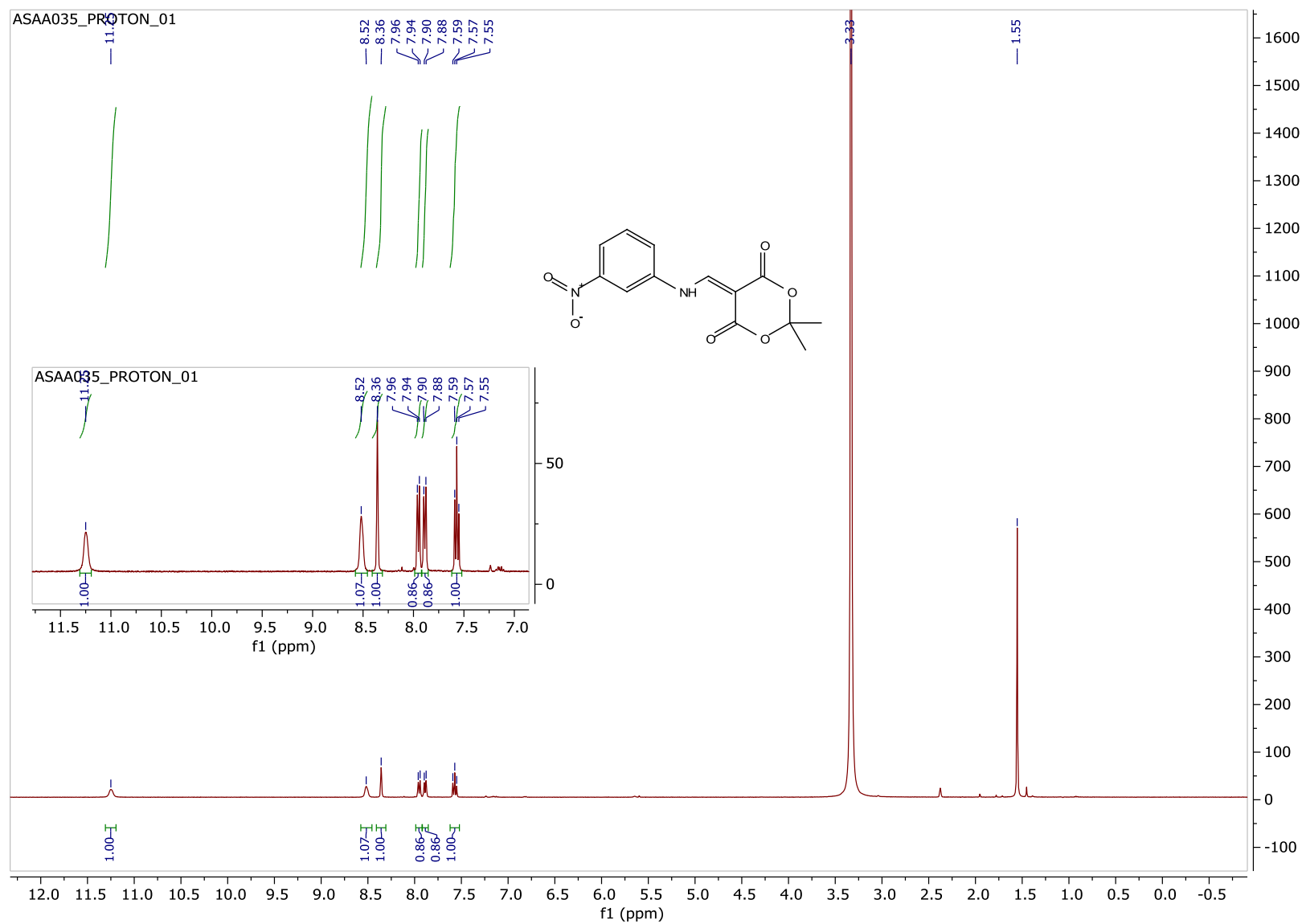
¹H NMR spectrum of 3-(((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)amino)benzonitrile (22b)



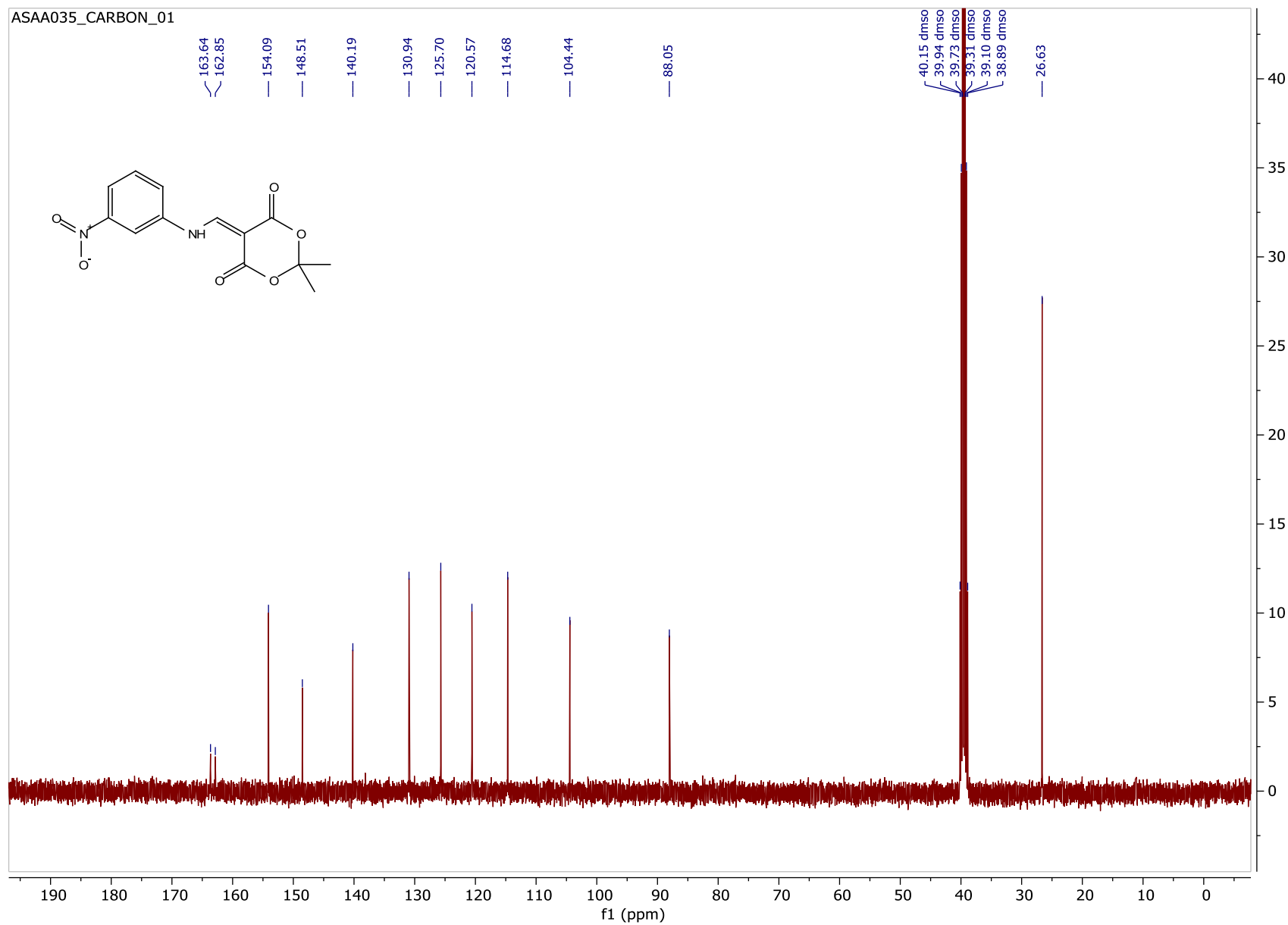
^{13}C NMR spectrum of 3-(((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)amino)benzonitrile (22b)



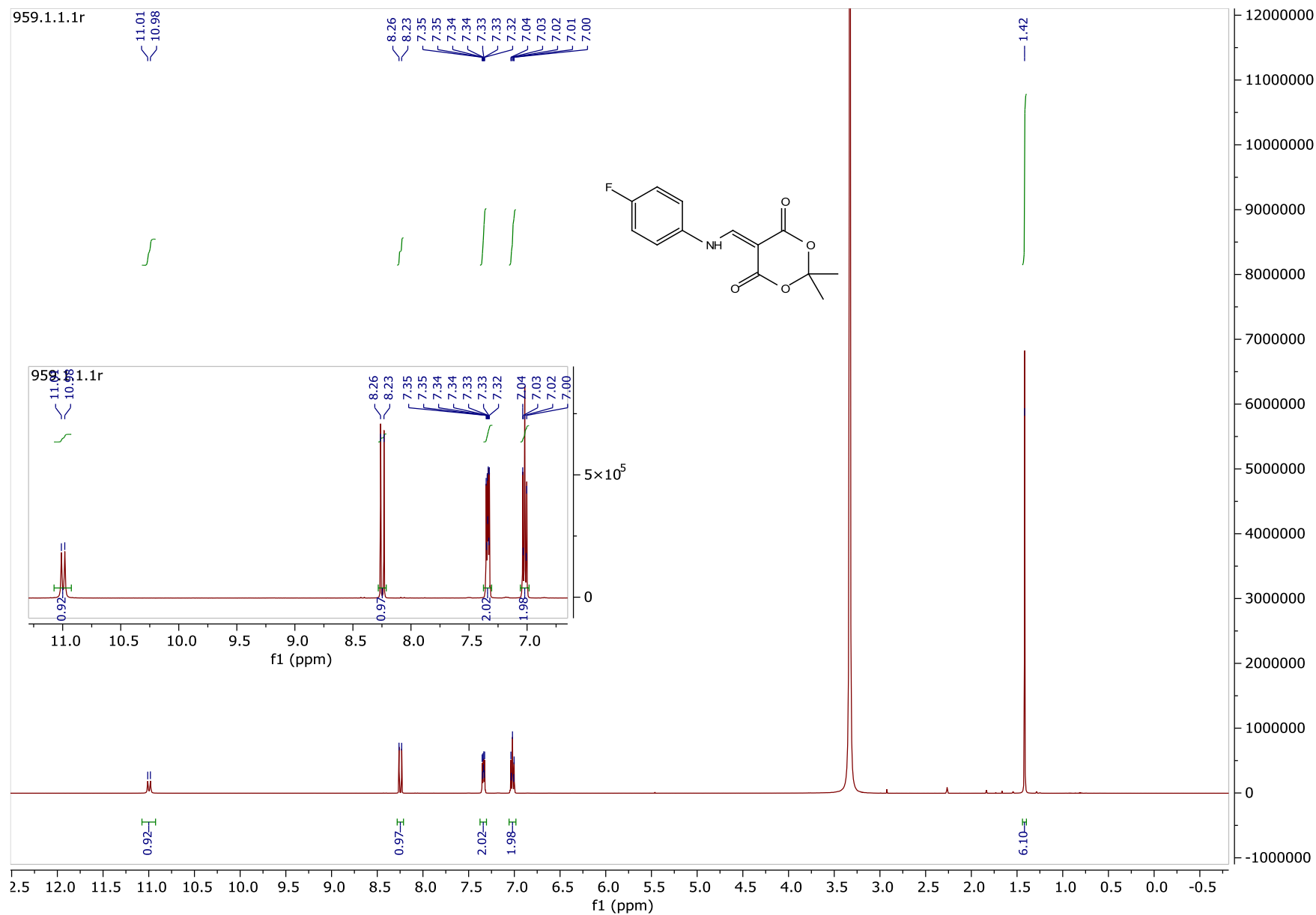
^1H NMR spectrum of 2,2-dimethyl-5-(((3-nitrophenyl)amino)methylene)-1,3-dioxane-4,6-dione (22c)



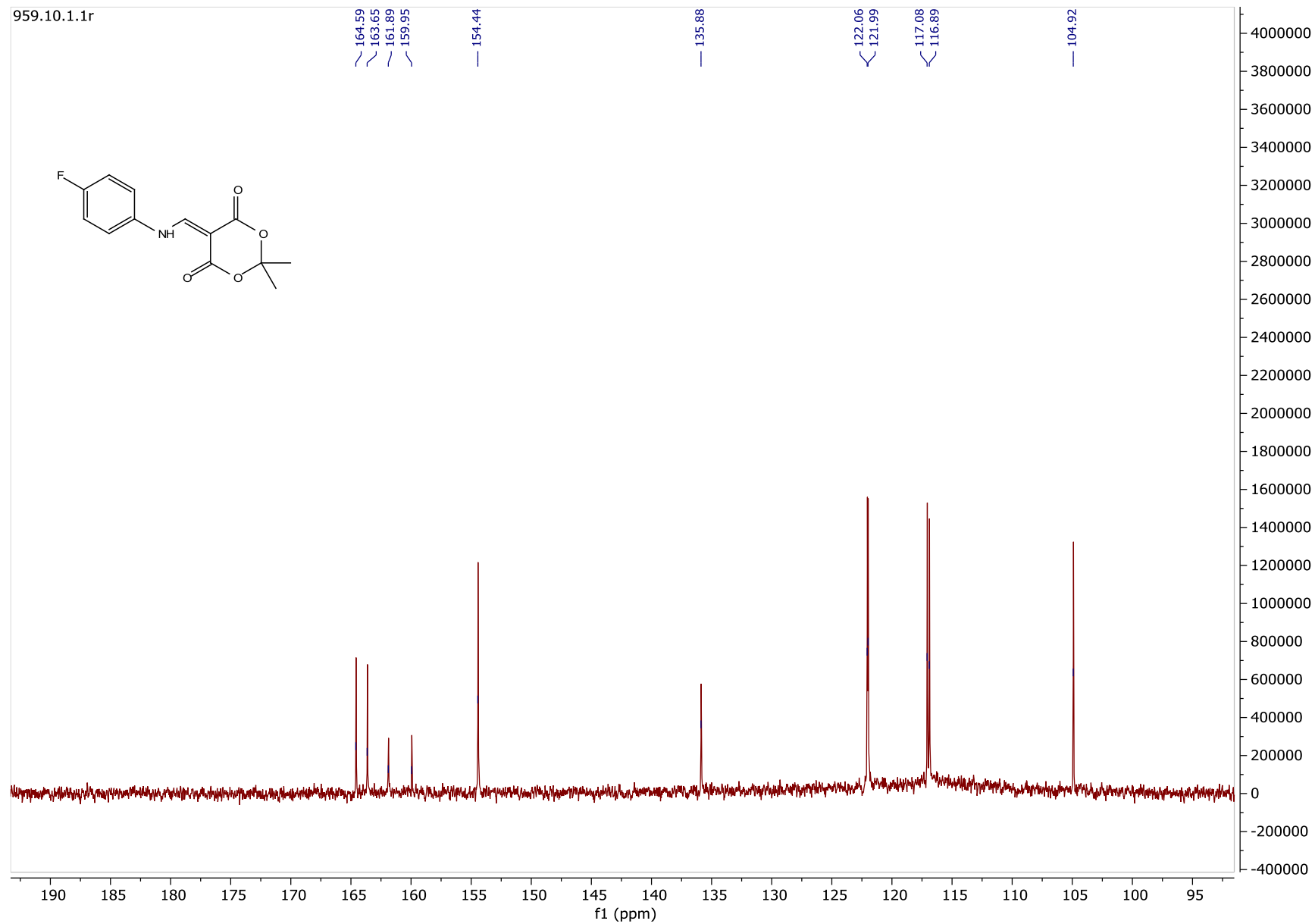
^{13}C NMR spectrum of 2,2-dimethyl-5-(((3-nitrophenyl)amino)methylene)-1,3-dioxane-4,6-dione (22c)



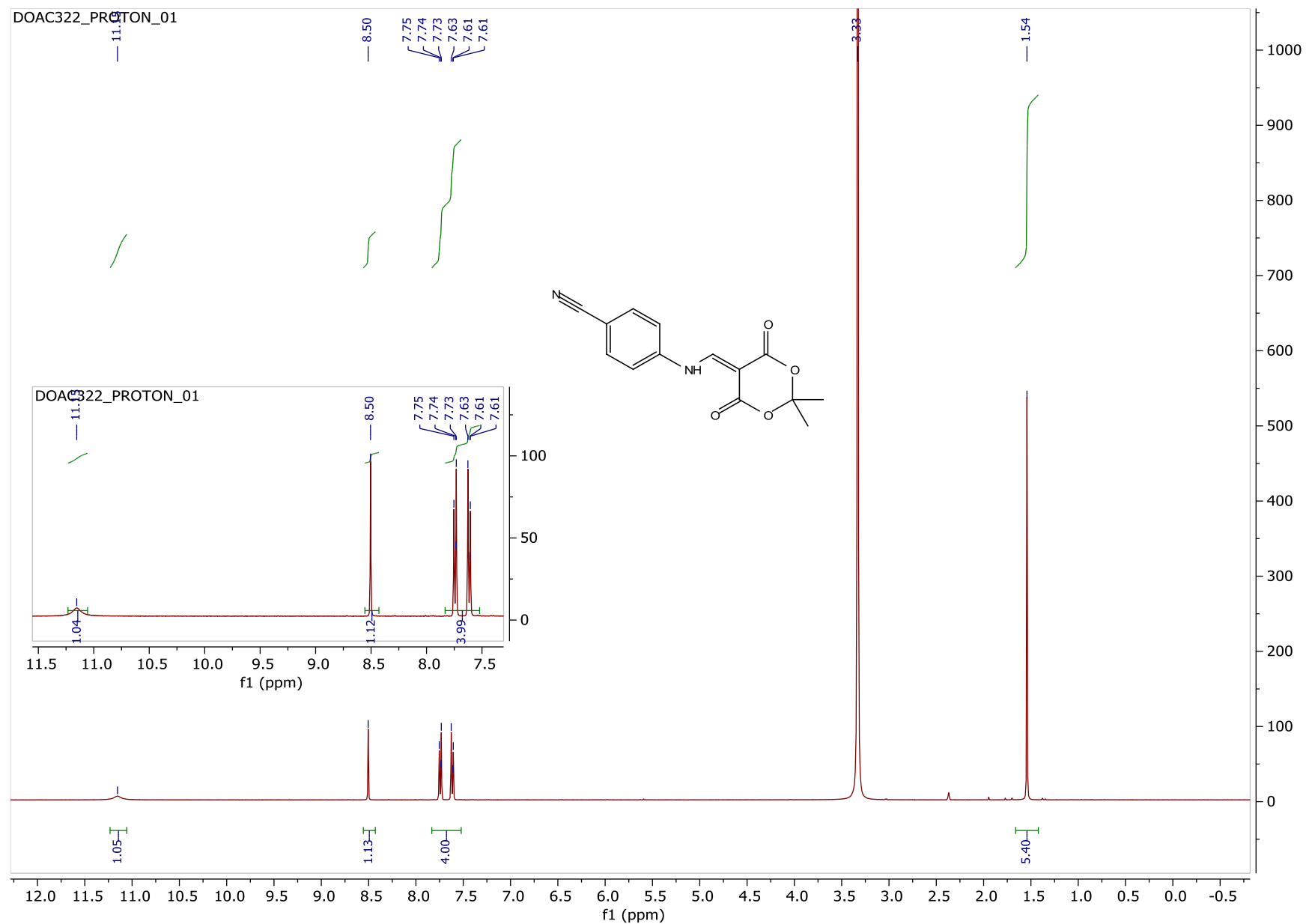
¹H NMR spectrum of 5-(((4-fluorophenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (32a)



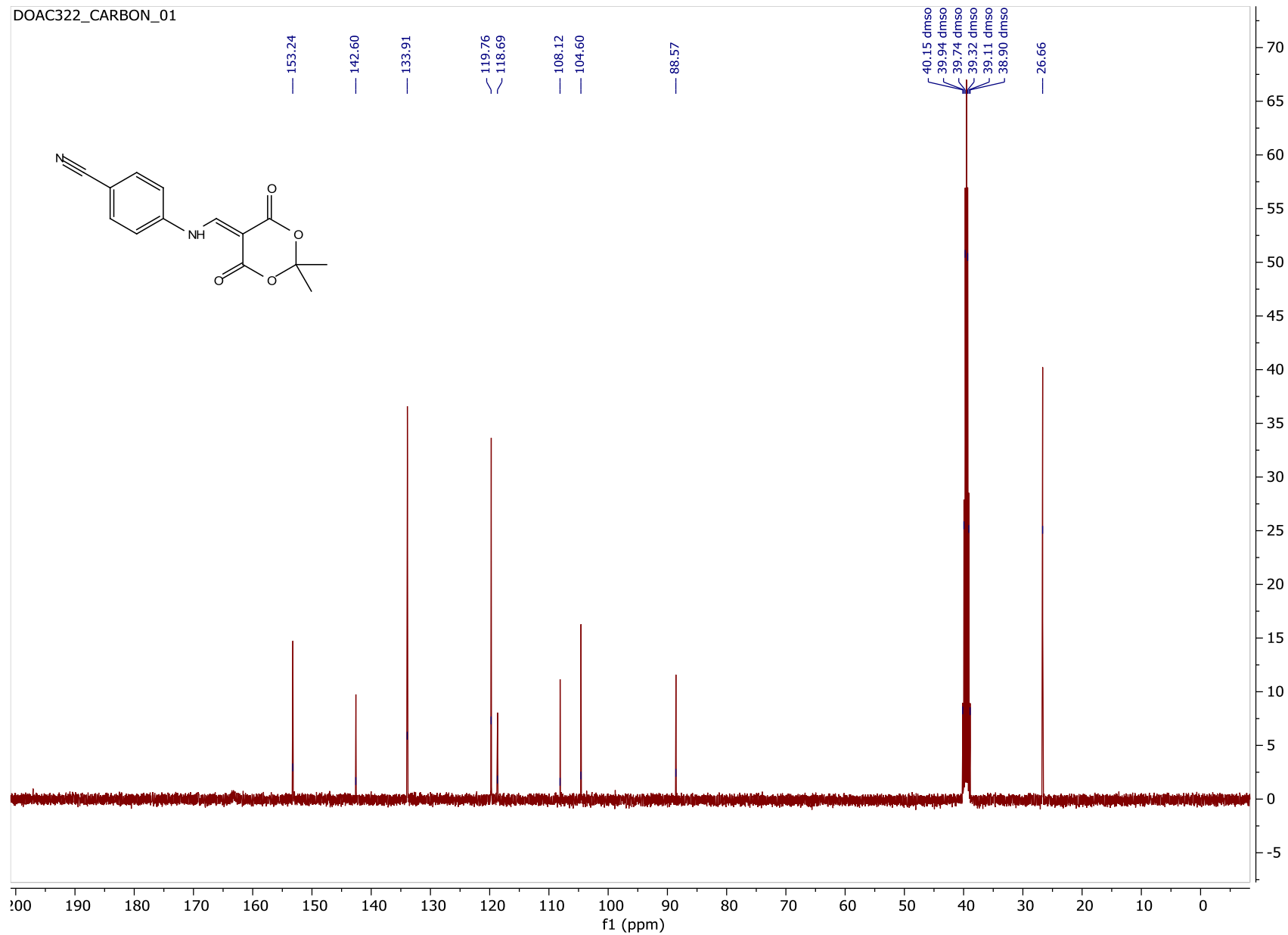
^{13}C NMR spectrum of 5-(((4-fluorophenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (32a)



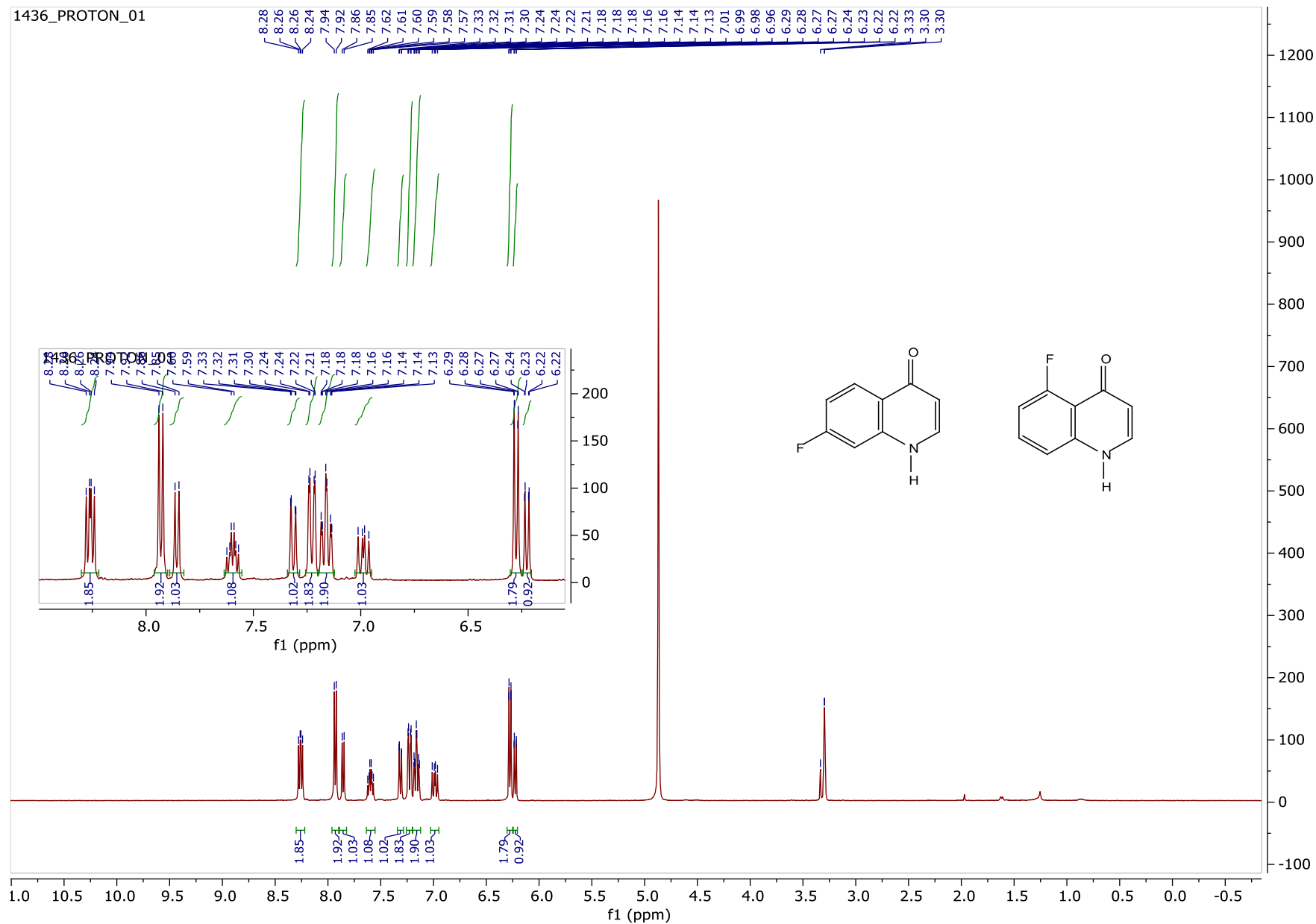
¹H NMR spectrum of 4-(((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)amino)benzonitrile (32b)



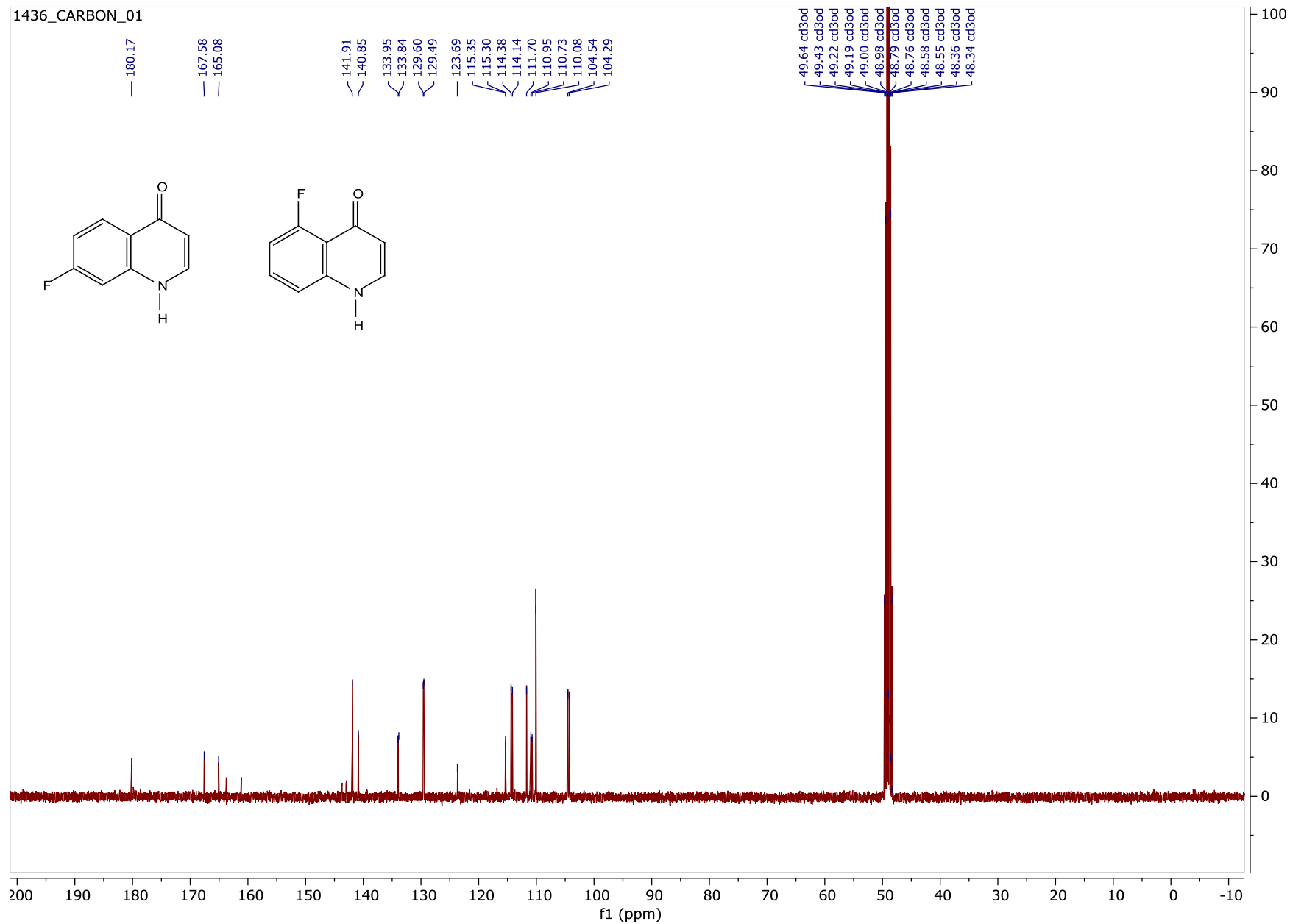
^{13}C NMR spectrum of 4-(((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)amino)benzonitrile (32b)



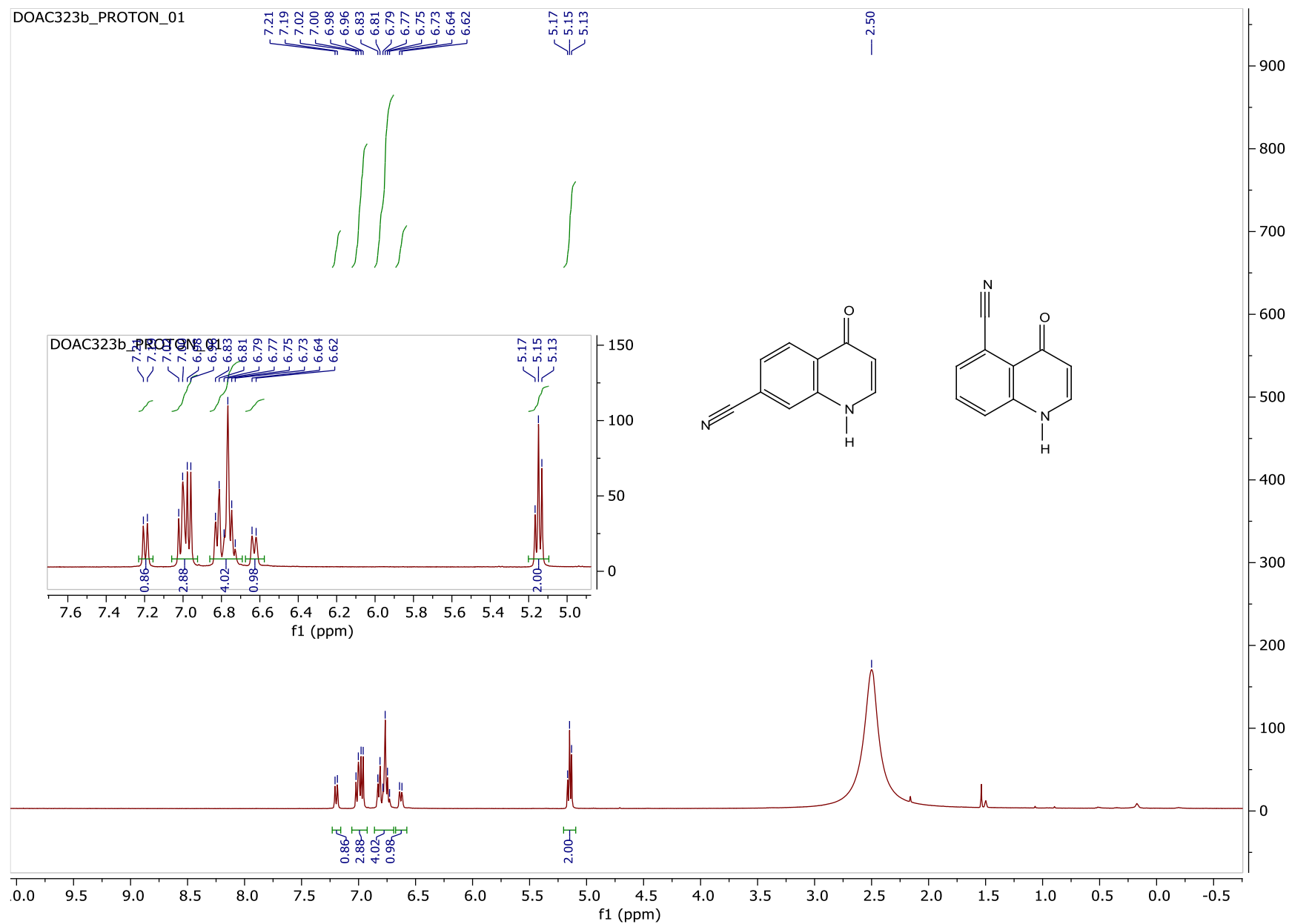
¹H NMR spectrum of mixture of 7-fluoro- and 5-fluoro-4-quinolone (23)



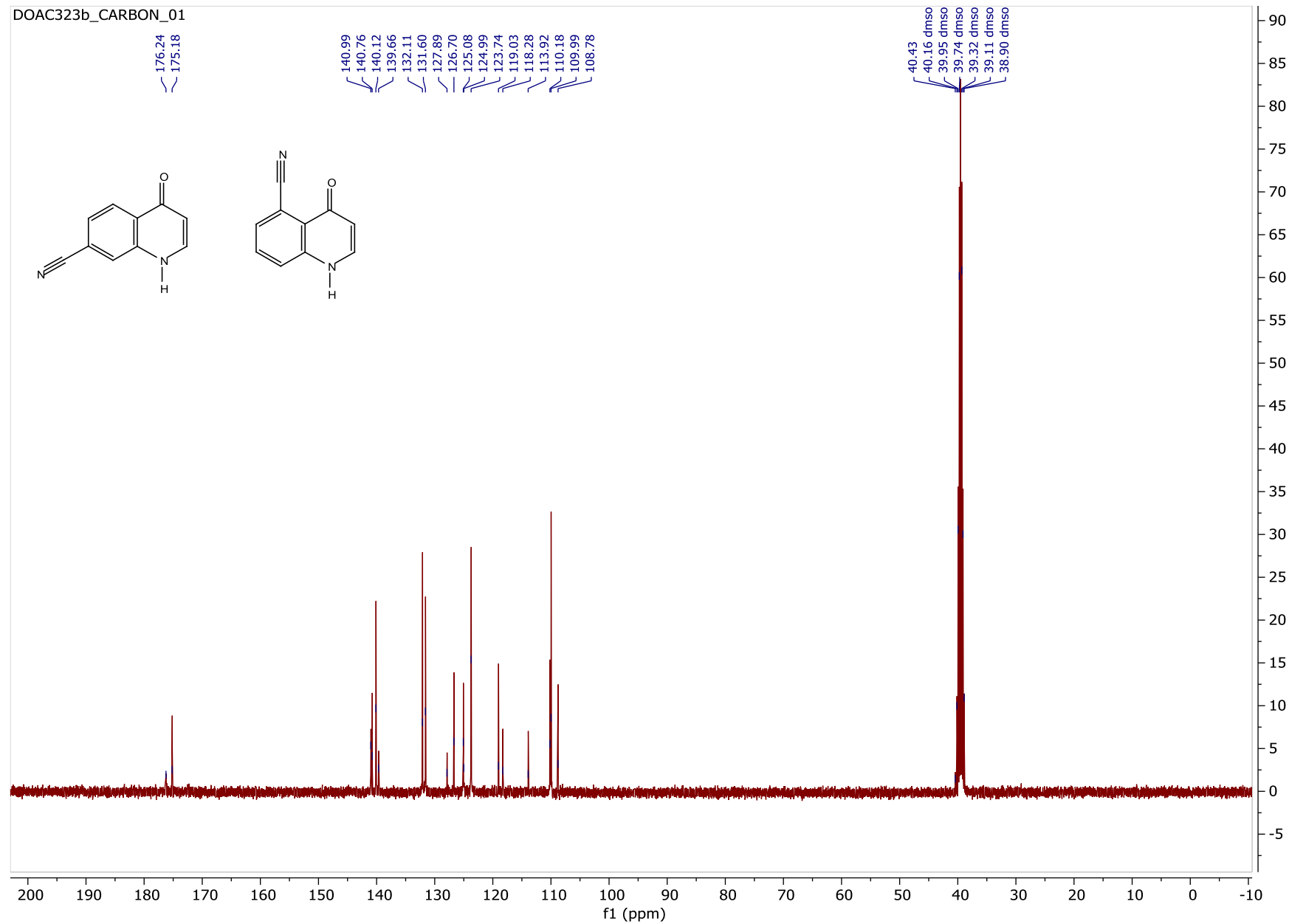
^{13}C NMR spectrum of mixture of 7-fluoro- and 5-fluoro-4-quinolone (23)



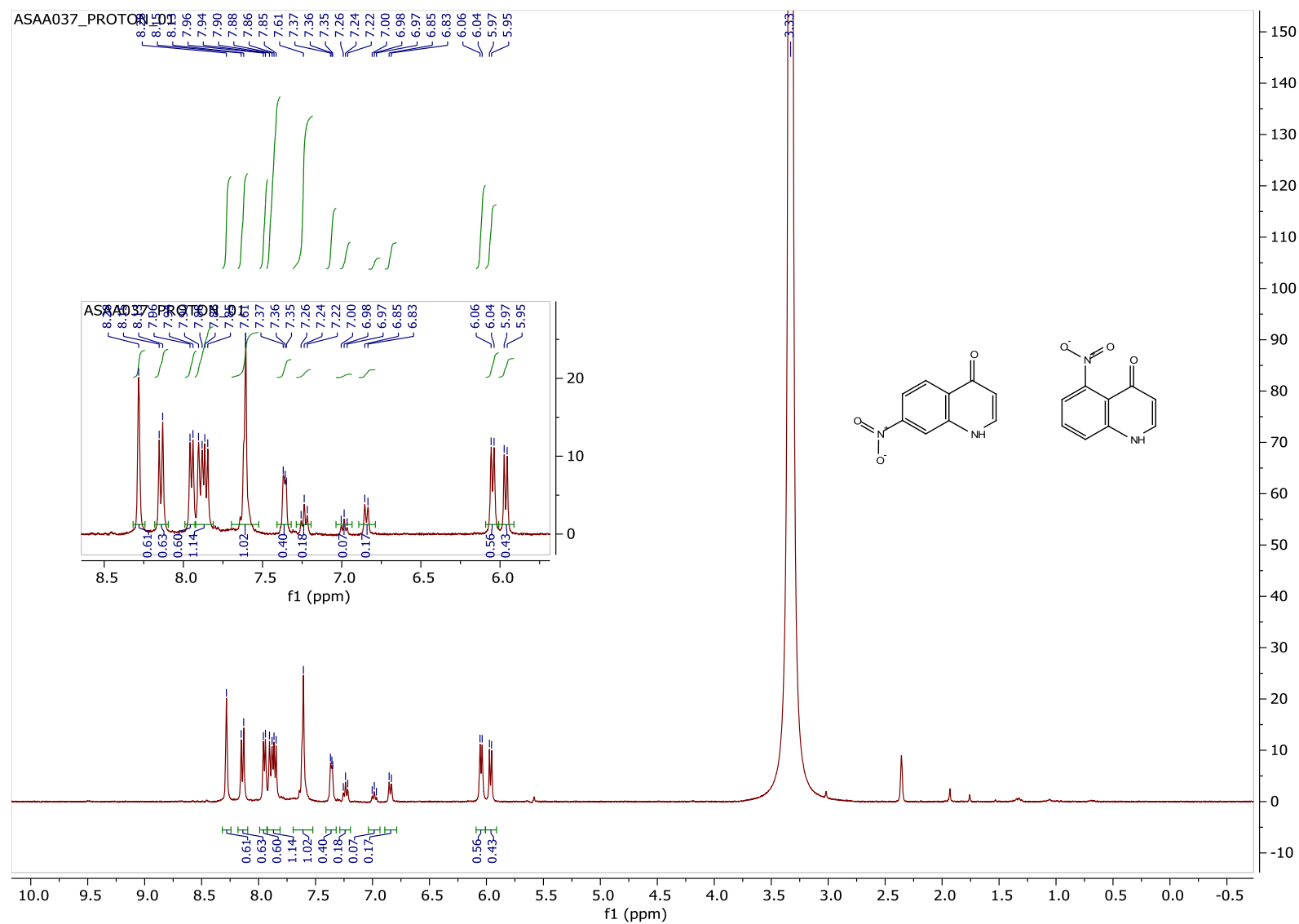
¹H NMR spectrum of mixture of 7-ciano-and 5-ciano-4-quinolone (24)



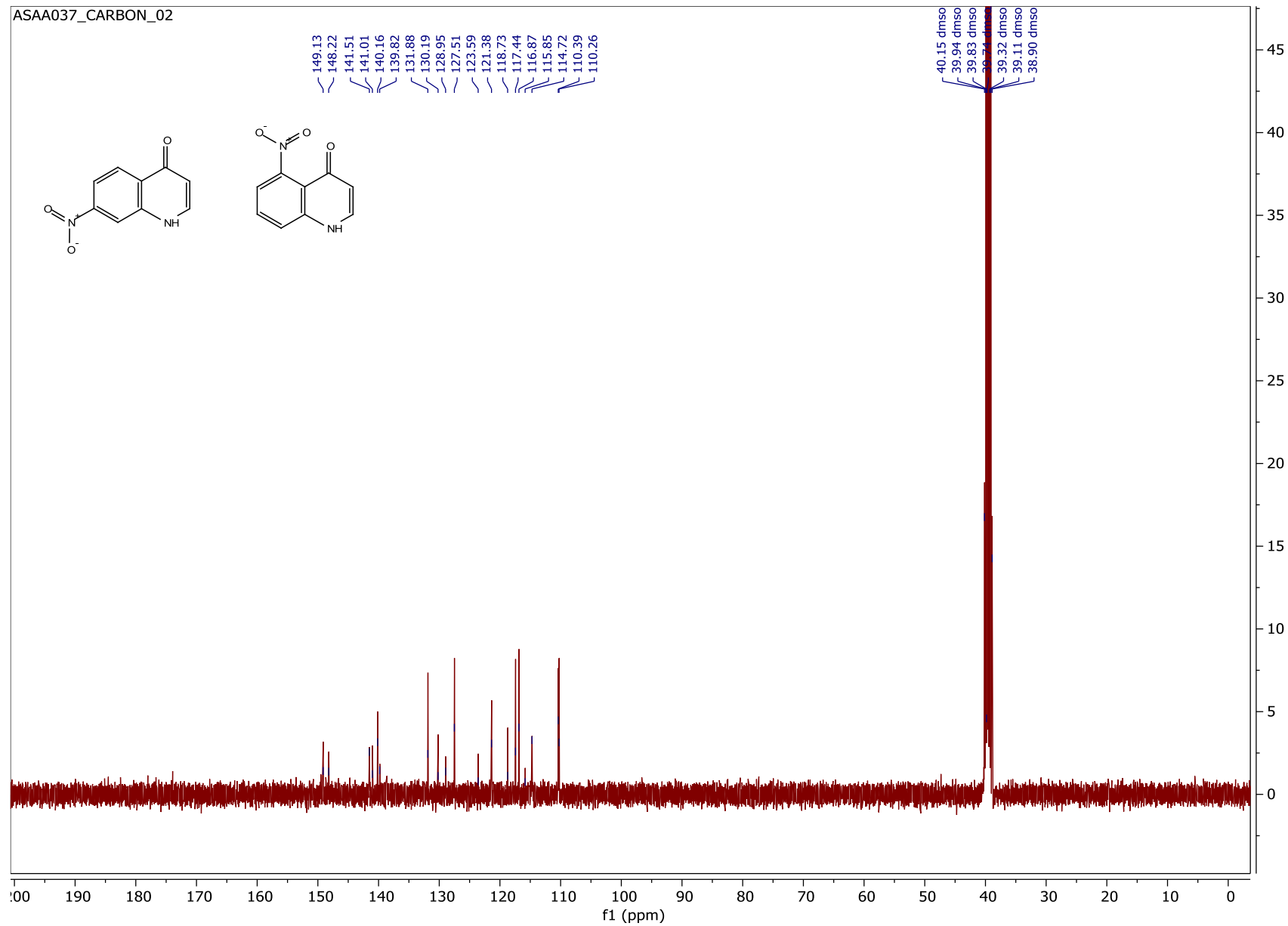
^{13}C NMR spectrum of mixture of 7-ciano-and 5-ciano-4-quinolone (24)



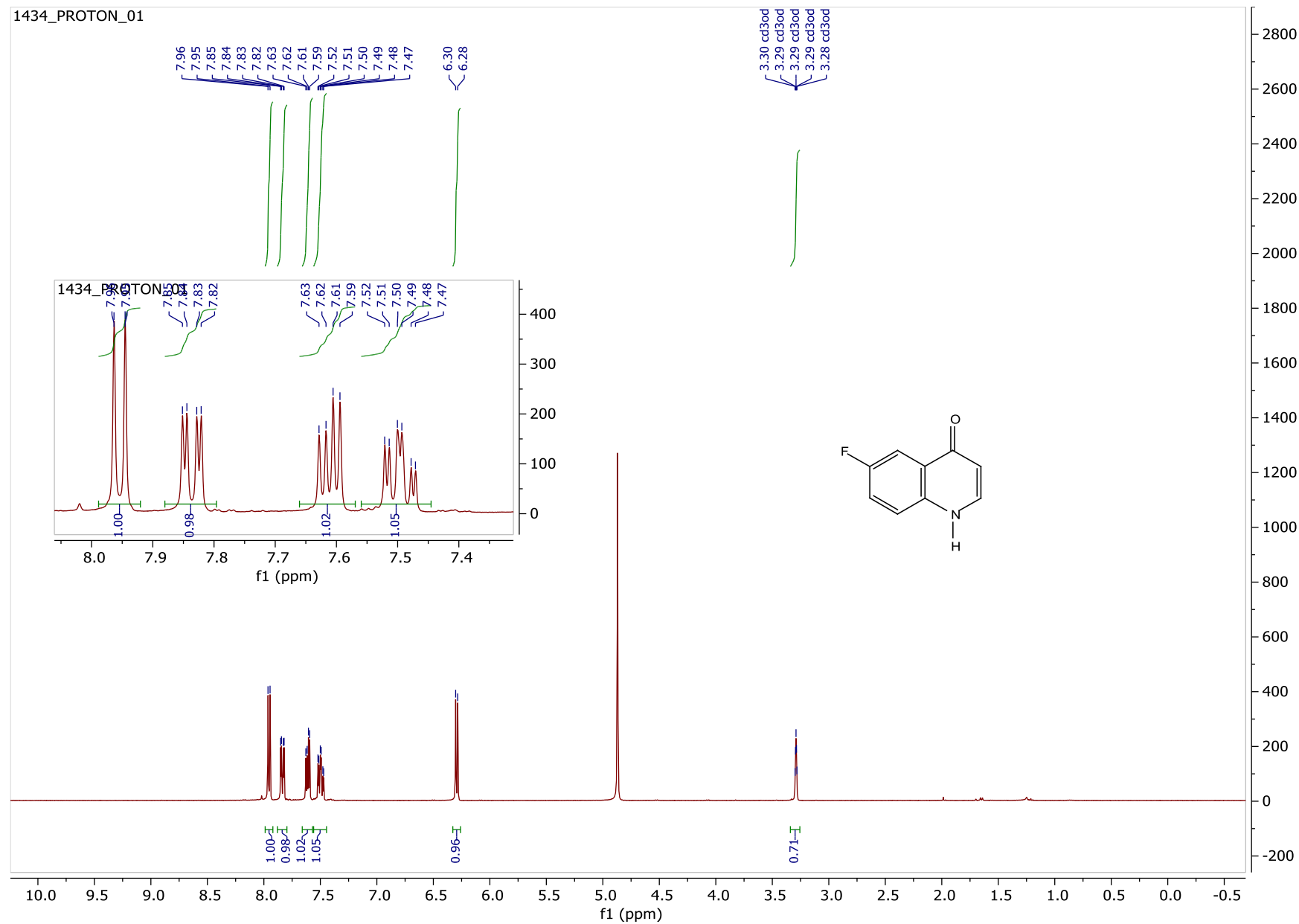
¹H NMR spectrum of mixture of 7-nitro-and 5-nitro-4-quinolone (25)



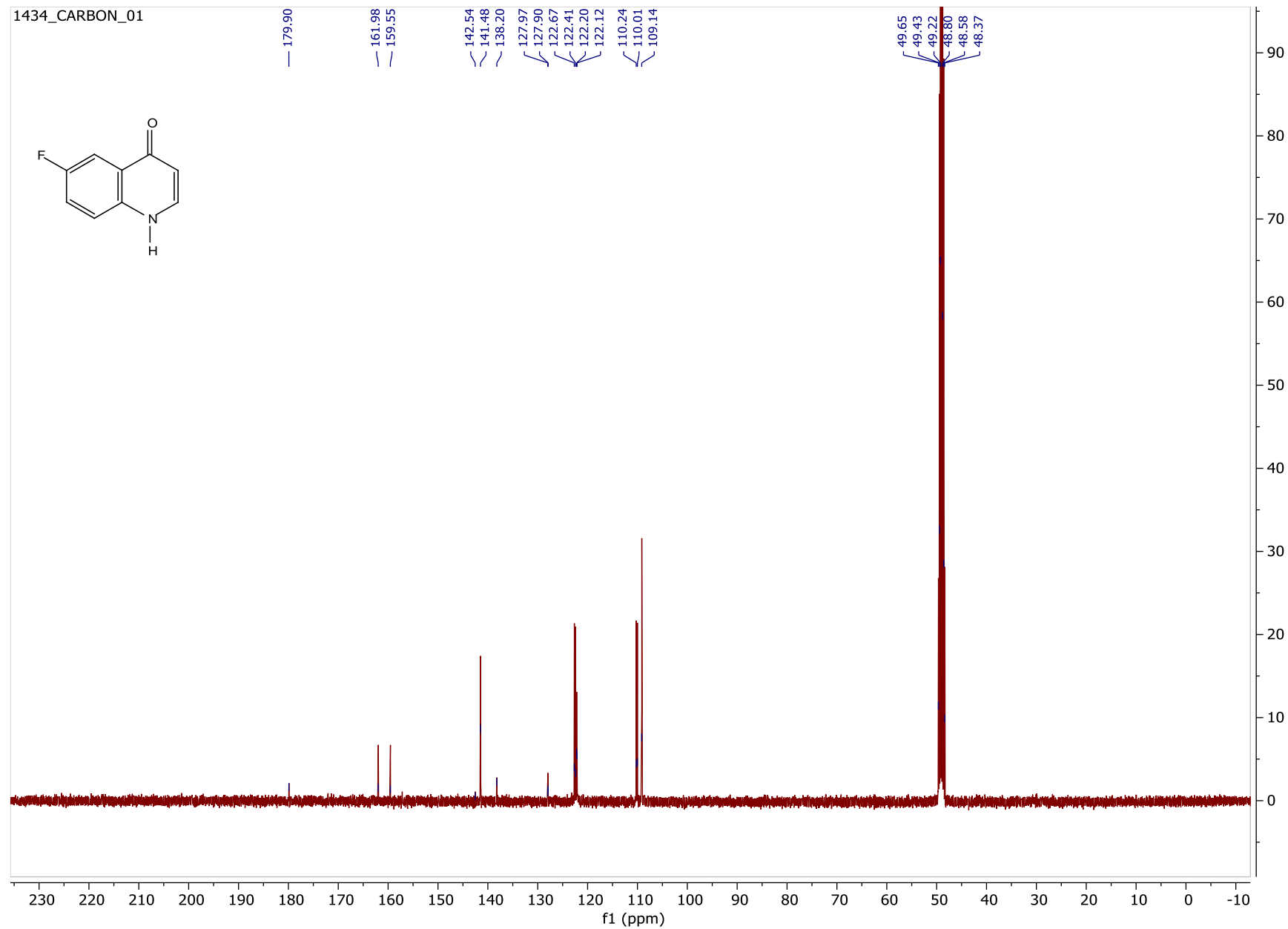
^{13}C NMR spectrum of mixture of 7-nitro-and 5-nitro-4-quinolone (AS12)



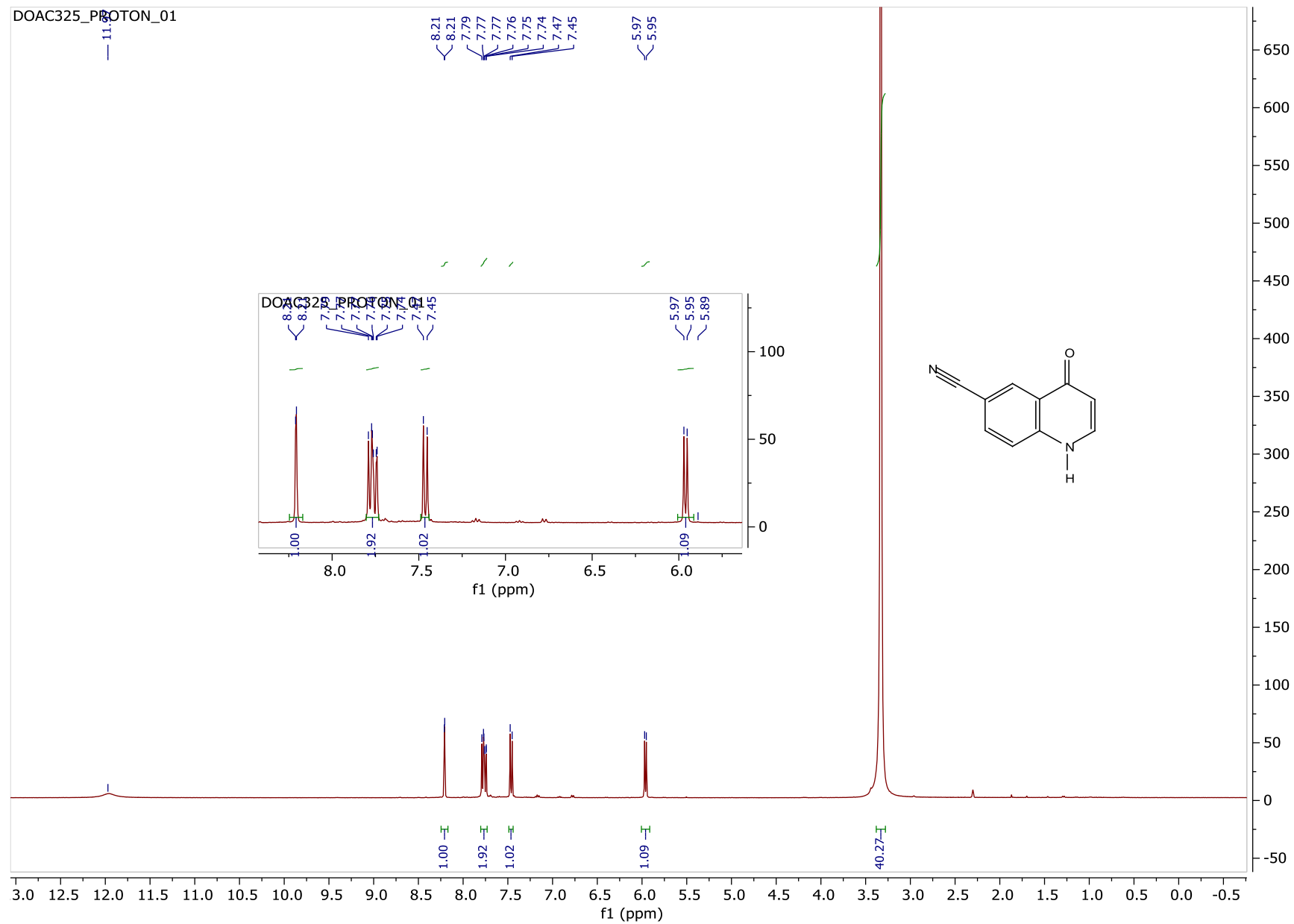
¹H NMR spectrum of 6-fluoro-4-quinolone (33a)



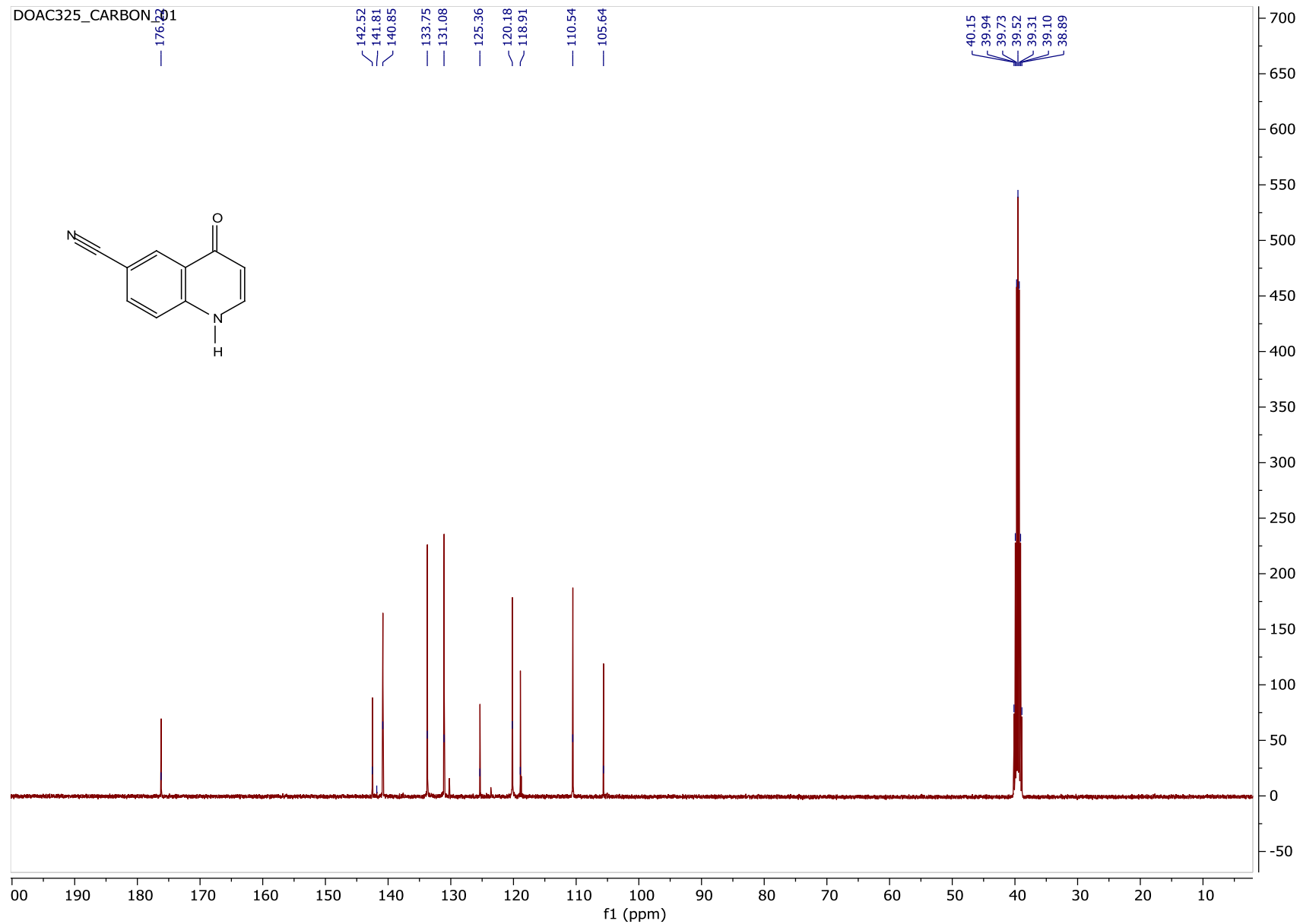
^{13}C NMR spectrum of 6-fluoro-4-quinolone (33a)



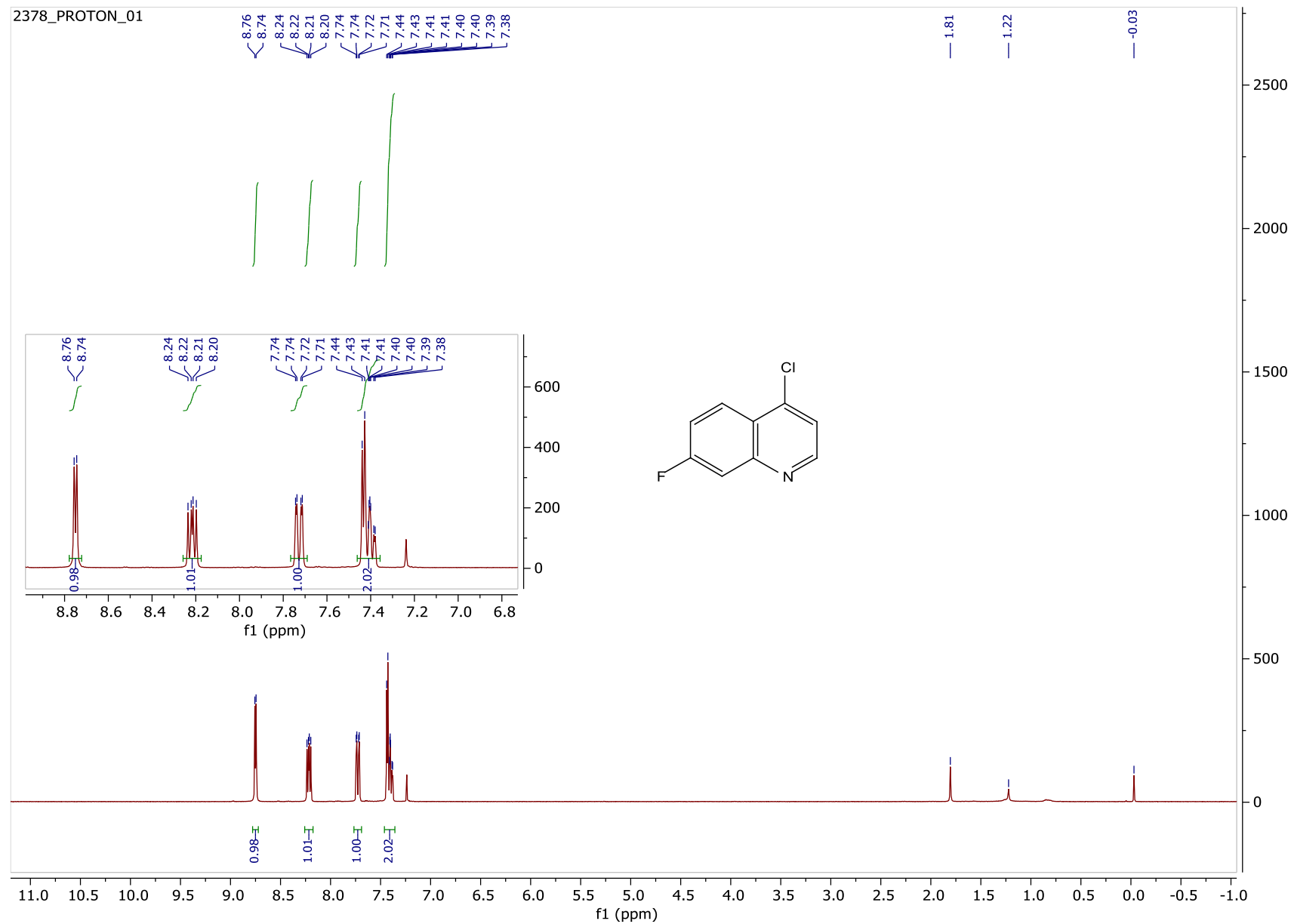
¹H NMR spectrum of 6-ciano-4-quinolone (33b)



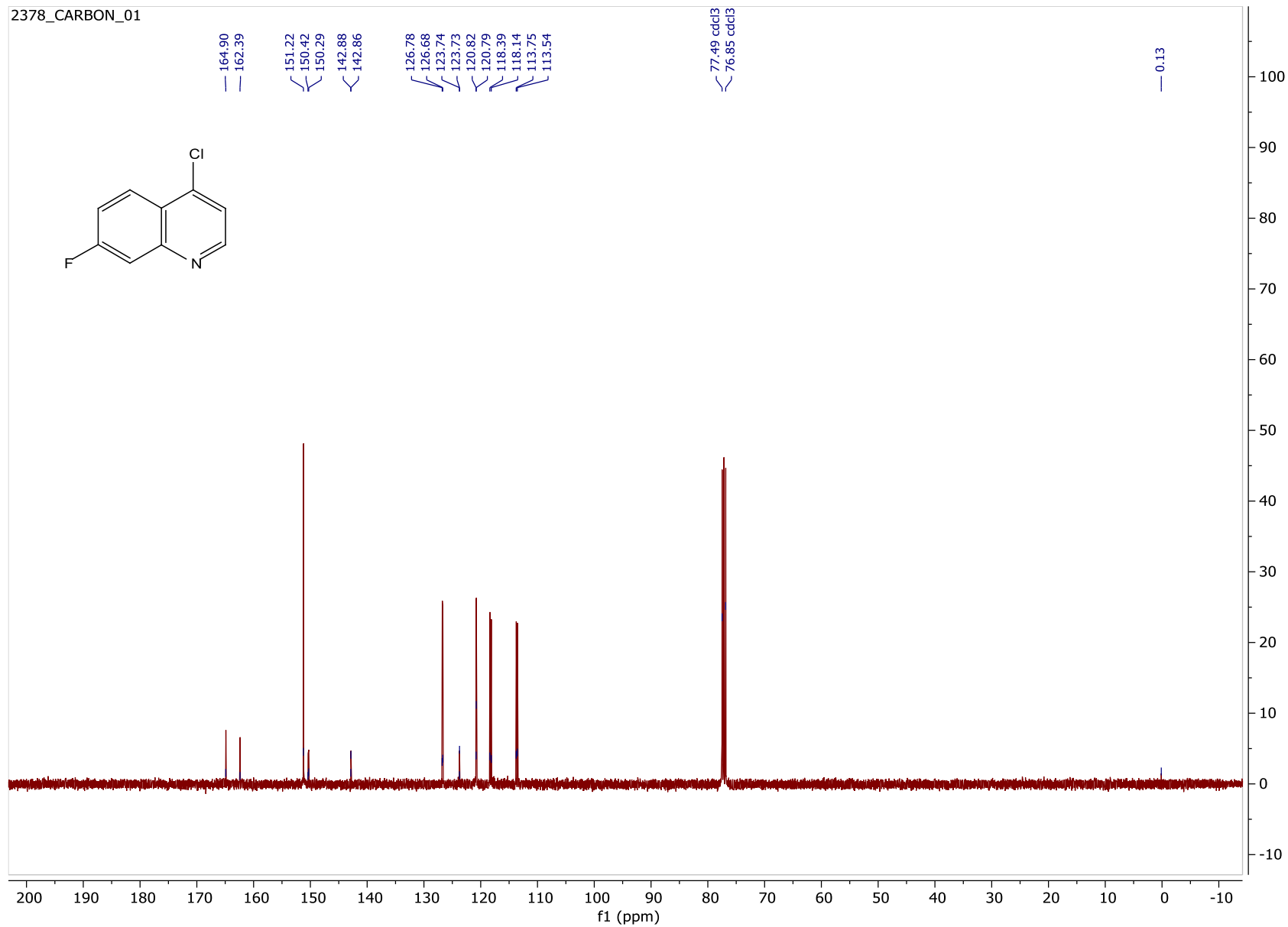
^{13}C NMR spectrum of 6-ciano-4-quinolone (33b)



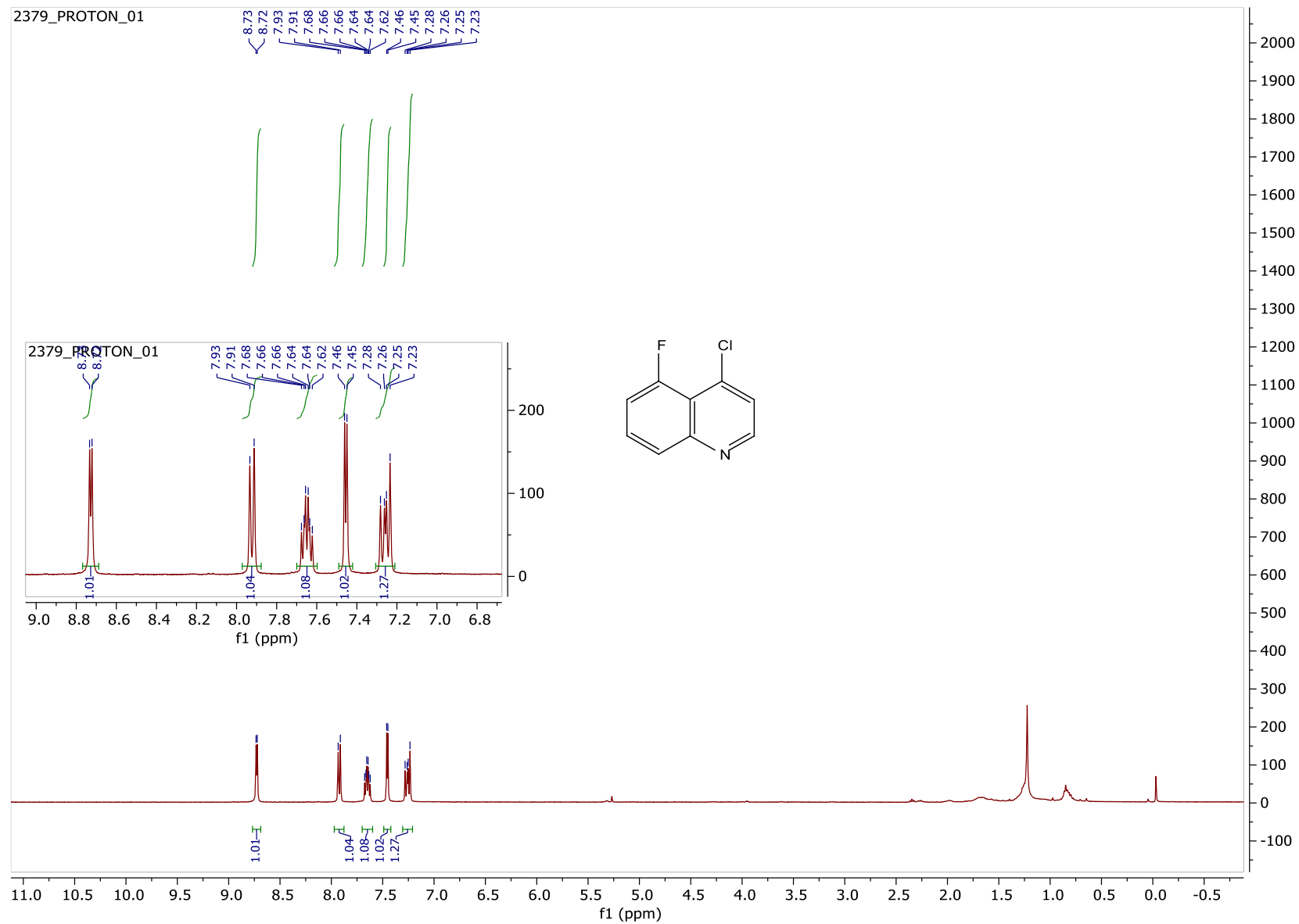
¹H NMR spectrum of 7-fluoro-4-chloroquinolines (26)



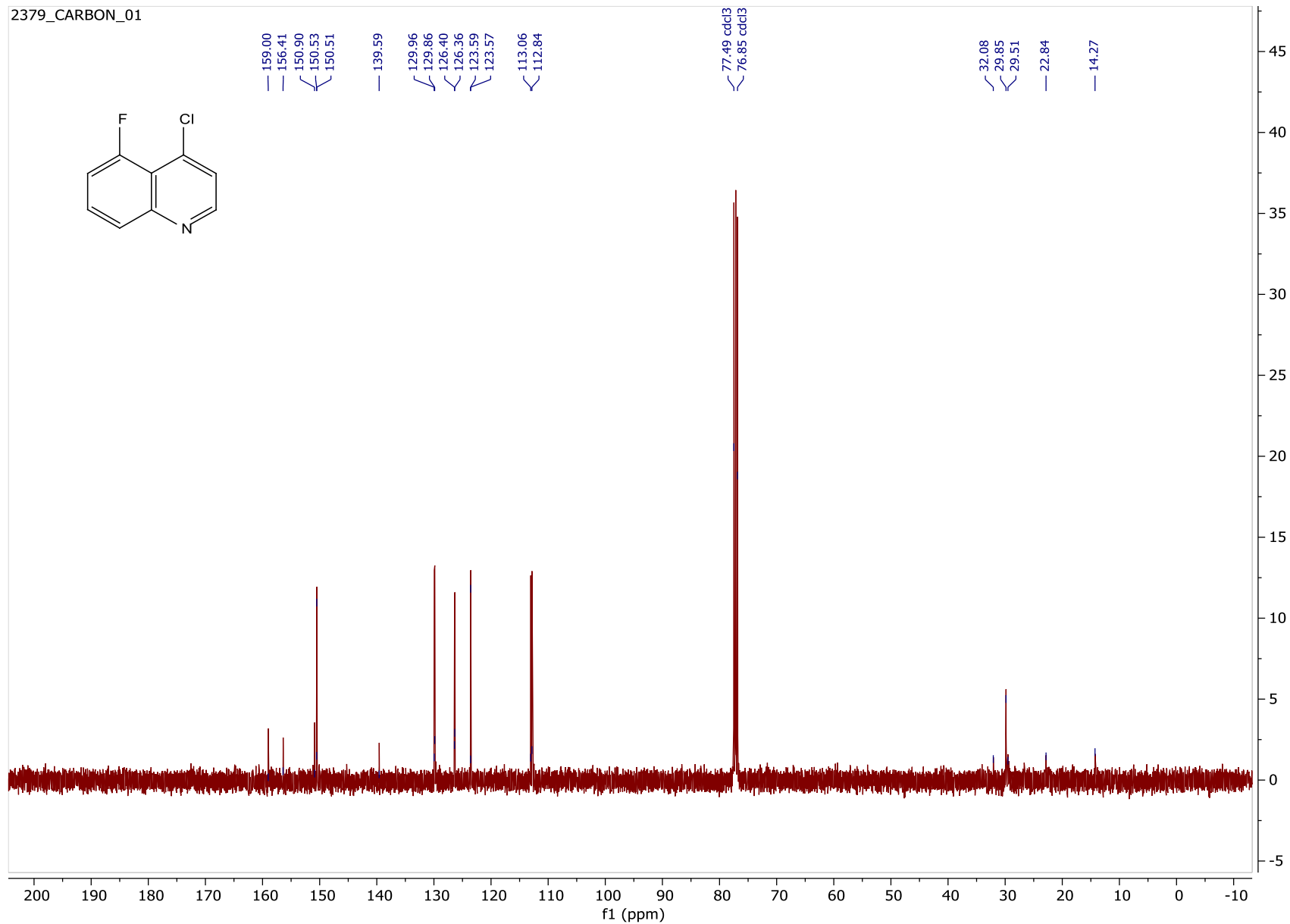
^{13}C NMR spectrum of 7-fluoro-4-chloroquinolines (26)



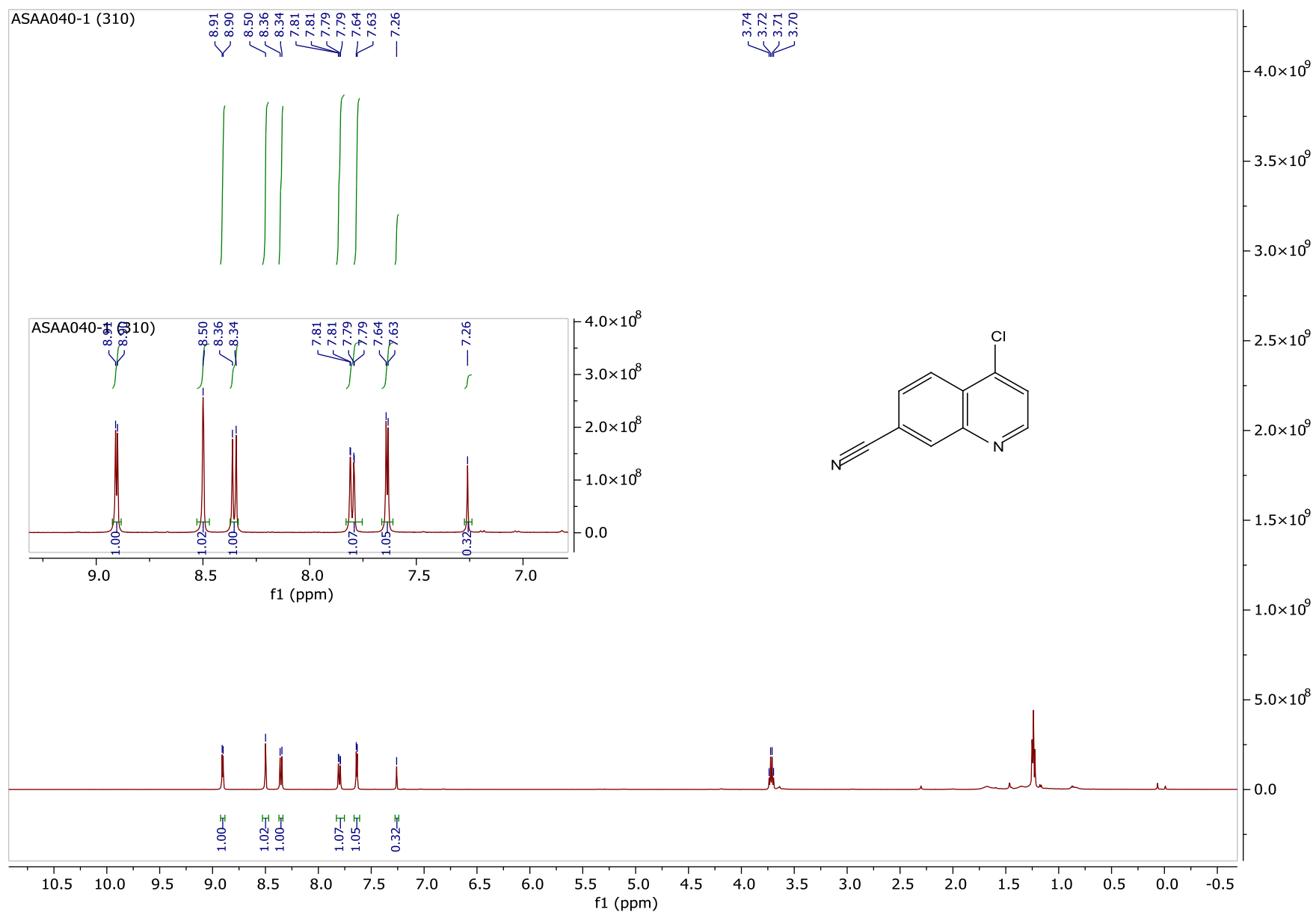
¹H NMR spectrum of 5-fluoro-4-chloroquinolines (27)



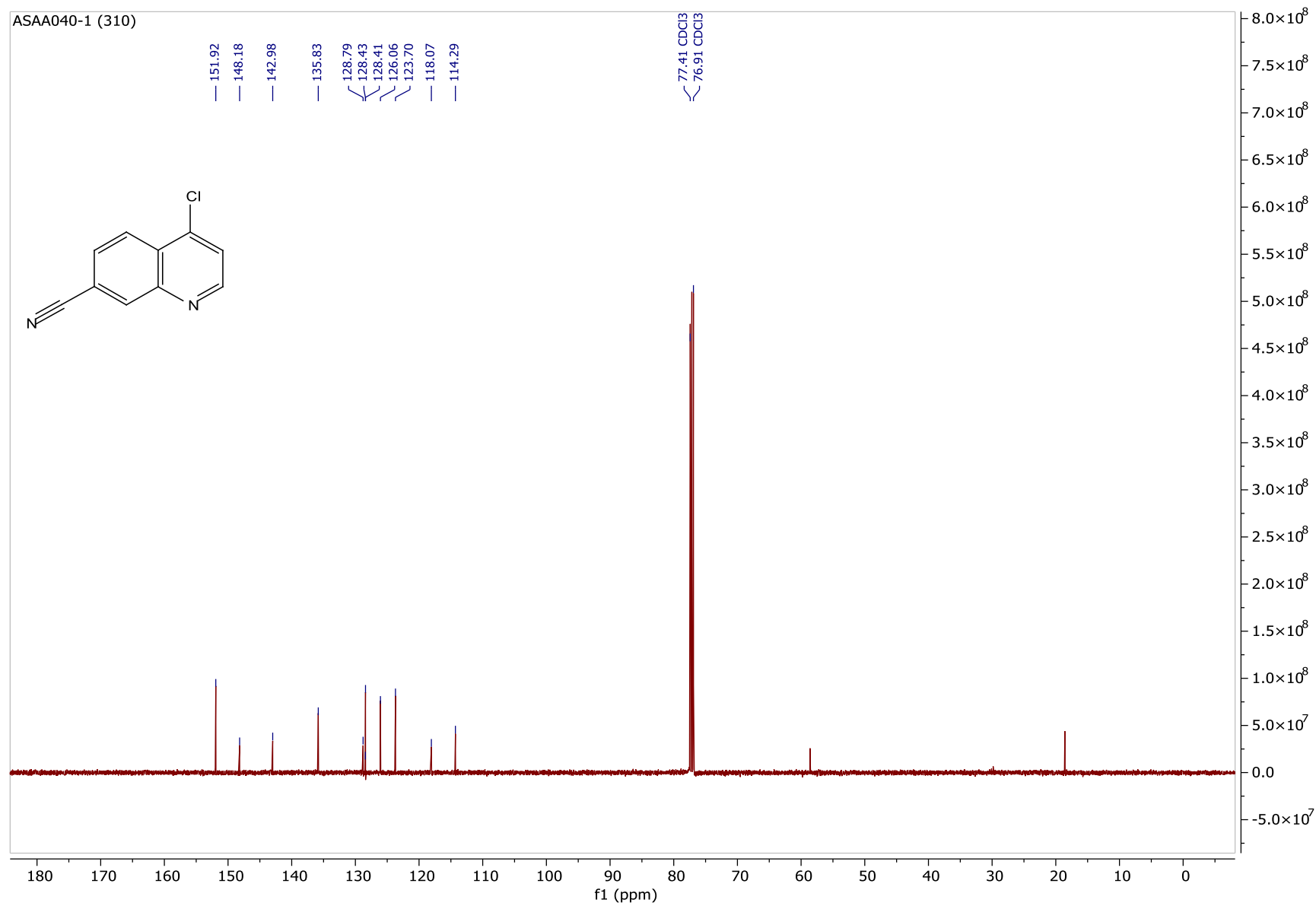
^{13}C NMR spectrum of 5-fluoro-4-chloroquinolines (27)



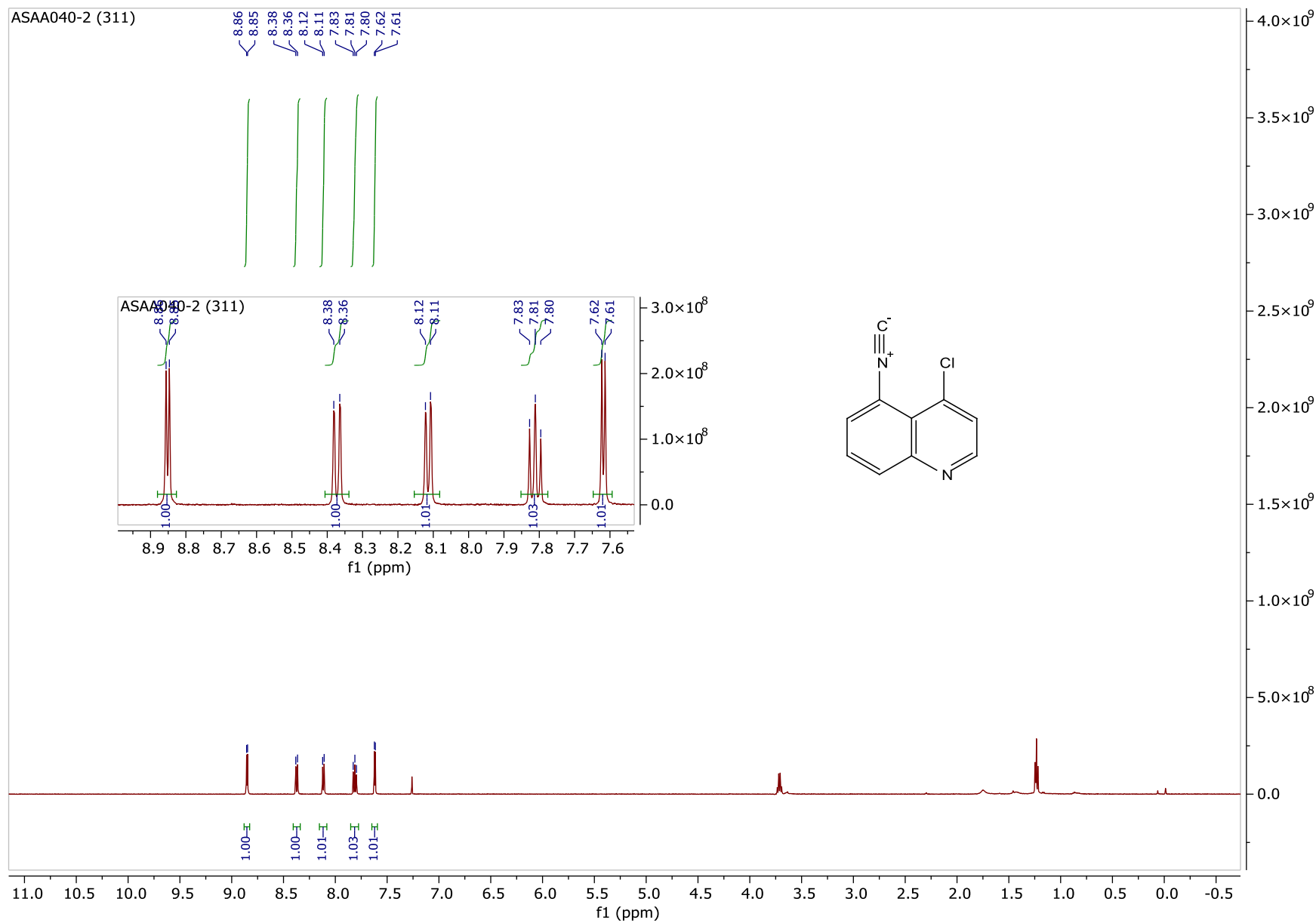
^1H NMR spectrum of 7-ciano-4-chloroquinolines (28)



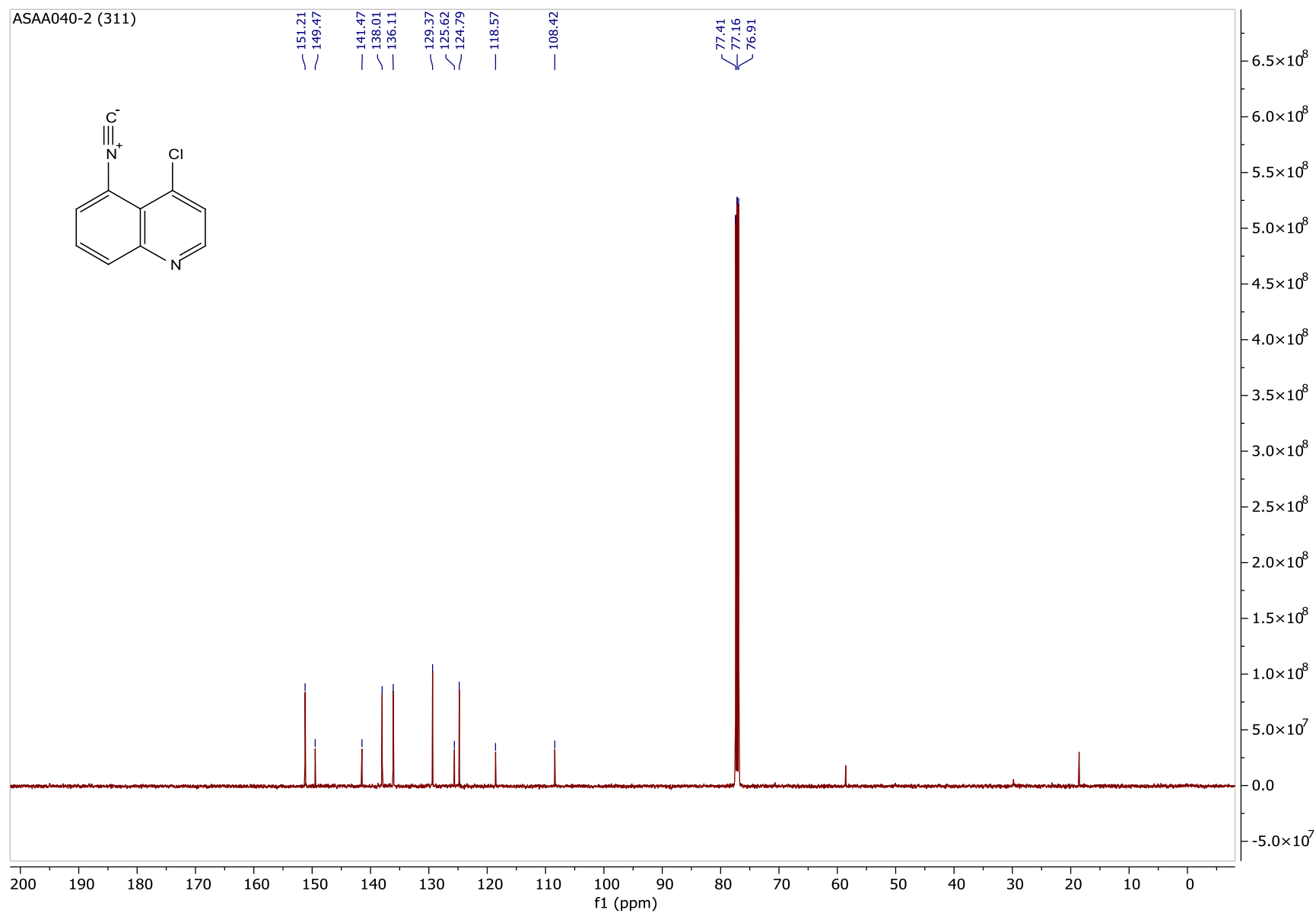
¹³C NMR spectrum of 7-ciano-4-chloroquinolines (28)



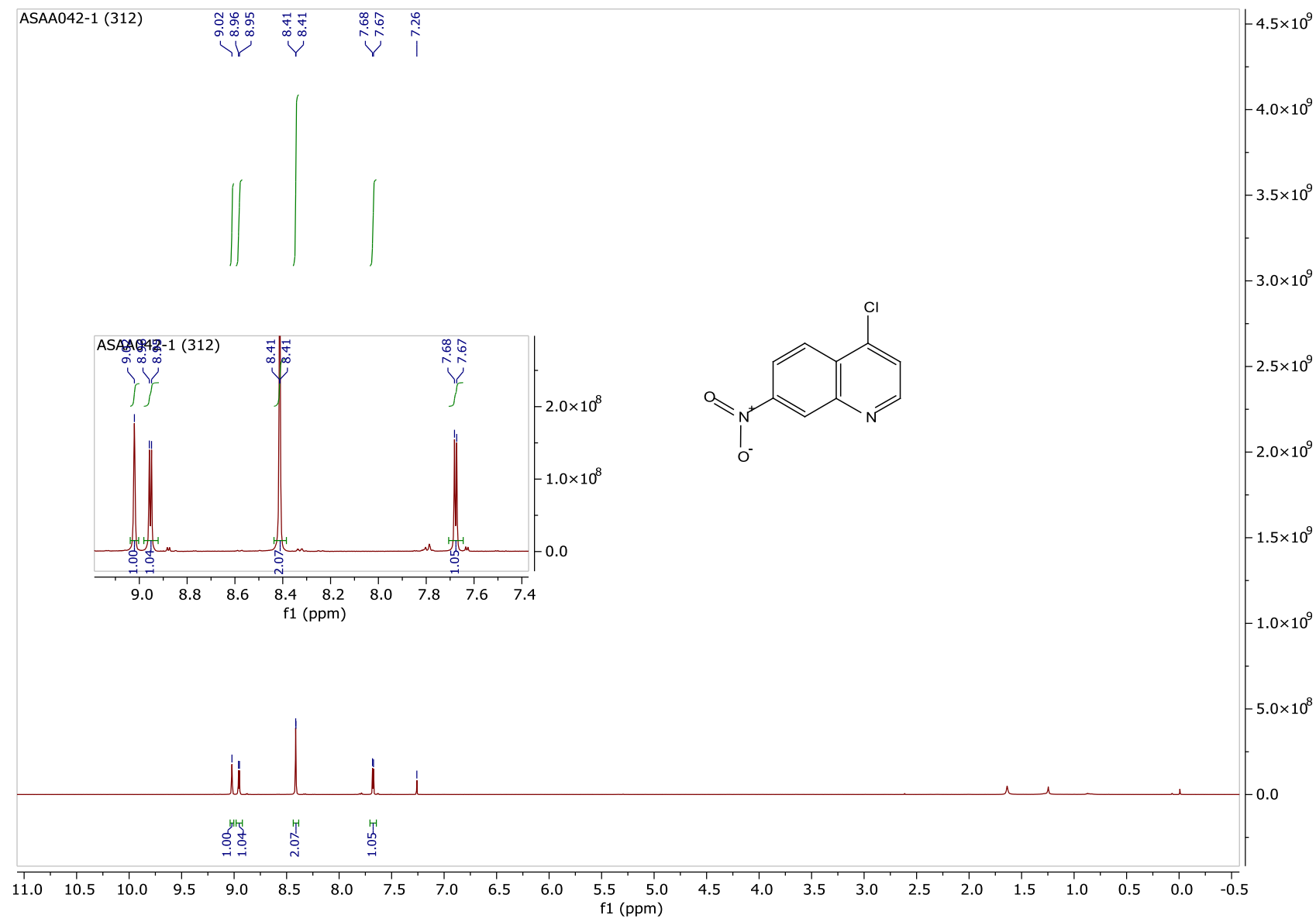
¹H NMR spectrum of 5-ciano-4-chloroquinolines (15)



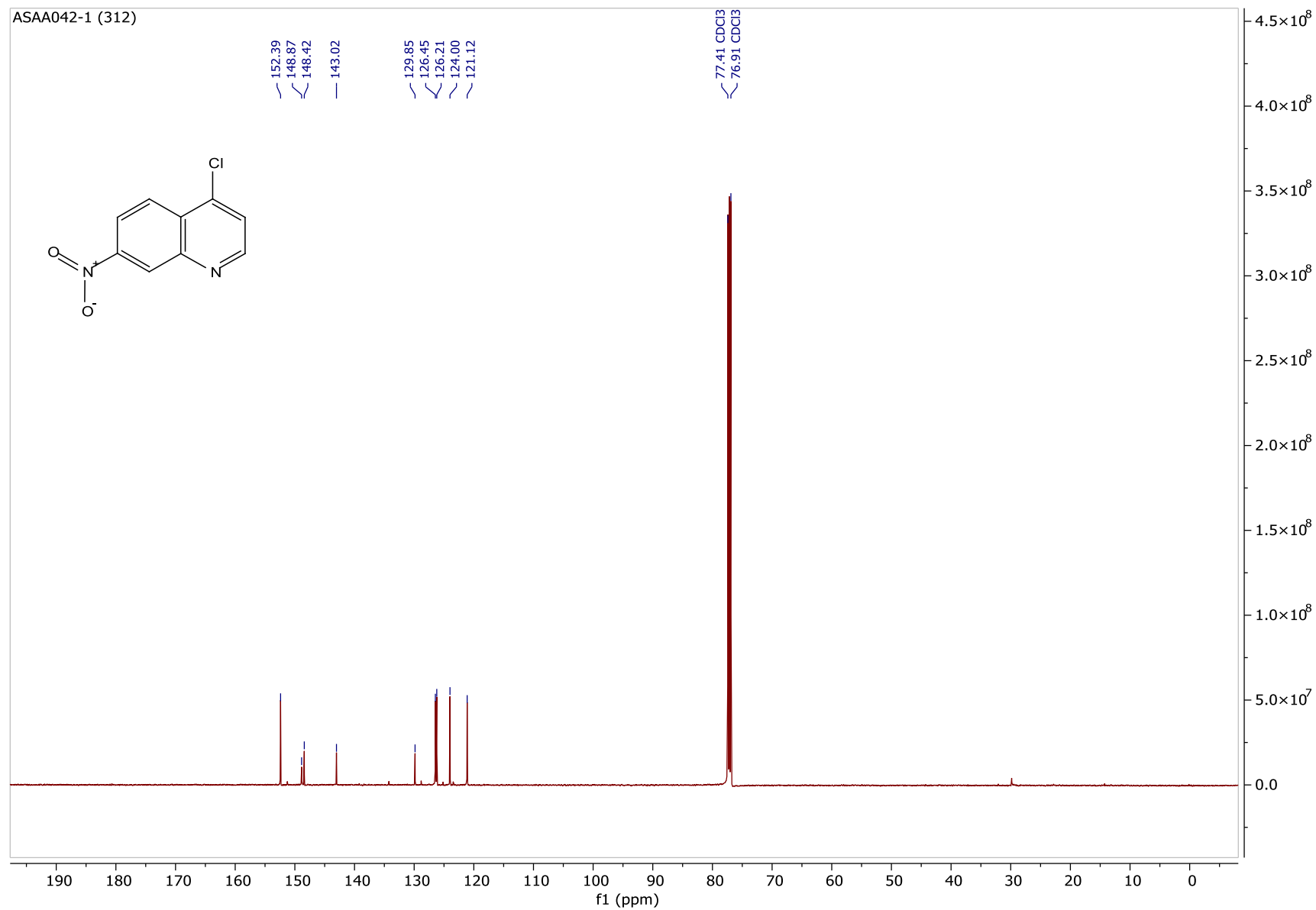
^{13}C NMR spectrum of 5-ciano-4-chloroquinolines (15)



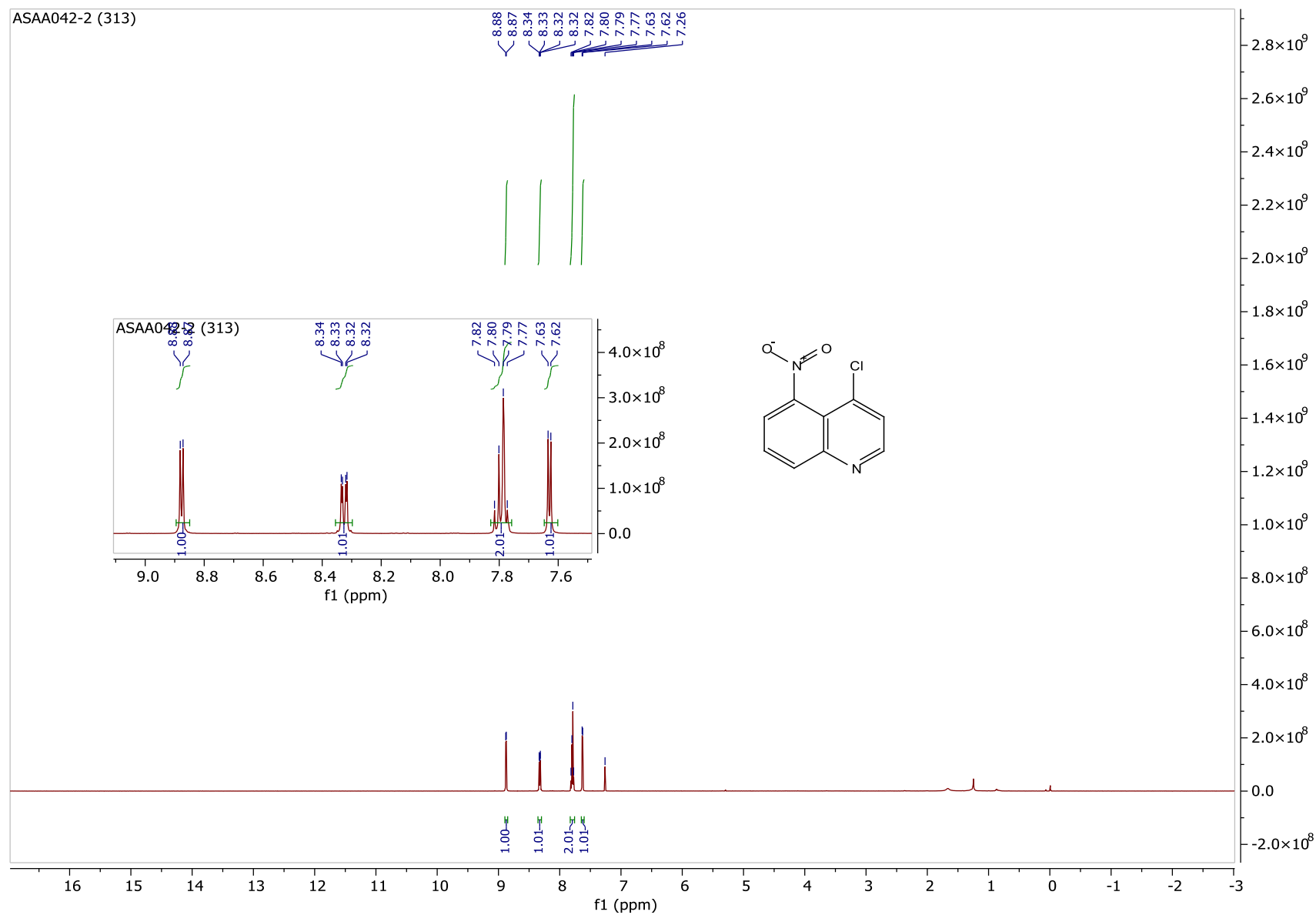
^1H NMR spectrum of 7-nitro-4-chloroquinoline (29)



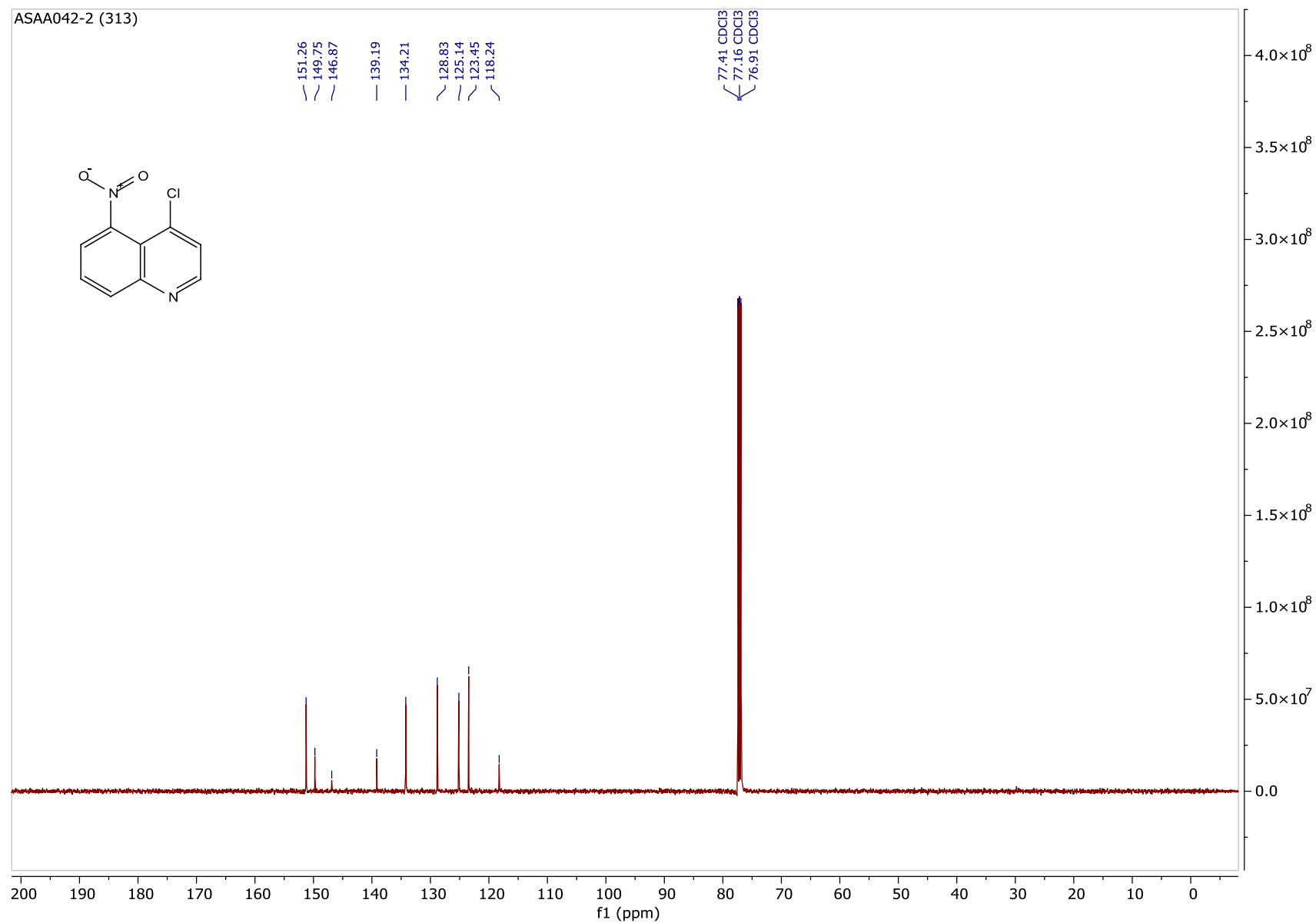
^{13}C NMR spectrum of 7-nitro-4-chloroquinoline (29)



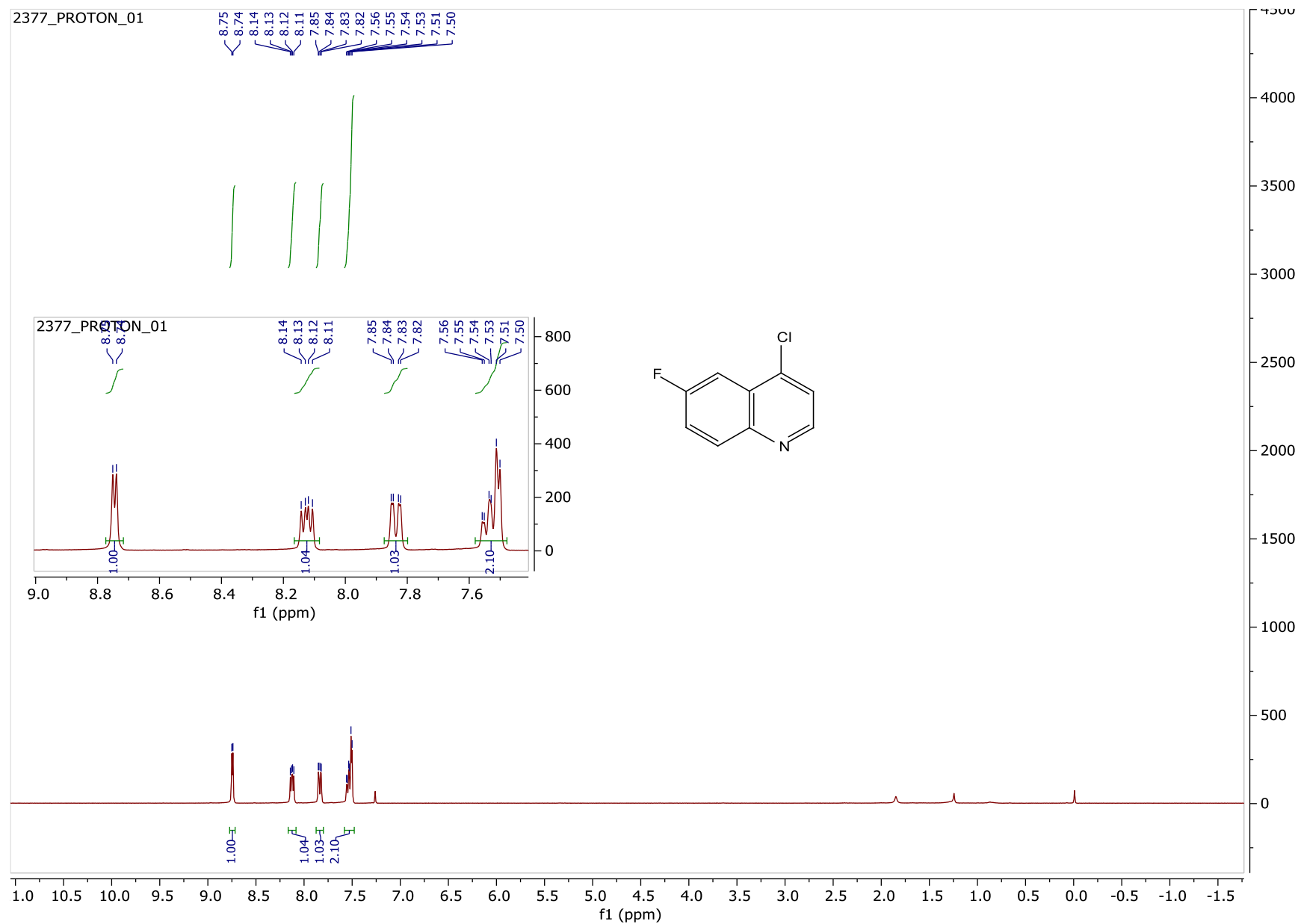
^1H NMR spectrum of 5-nitro-4-chloroquinoline (30)



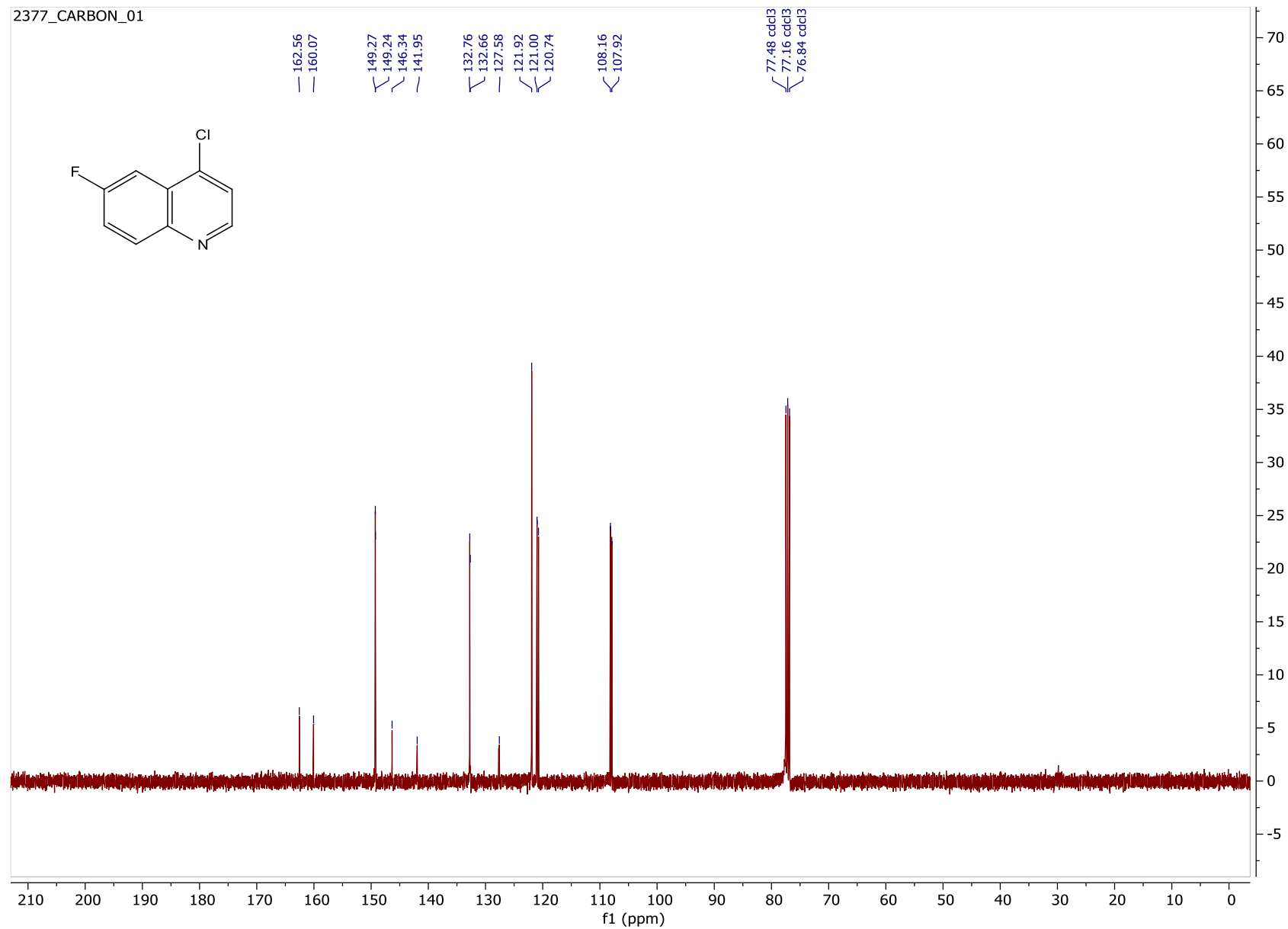
^{13}C NMR spectrum of 5-nitro-4-chloroquinoline (30)



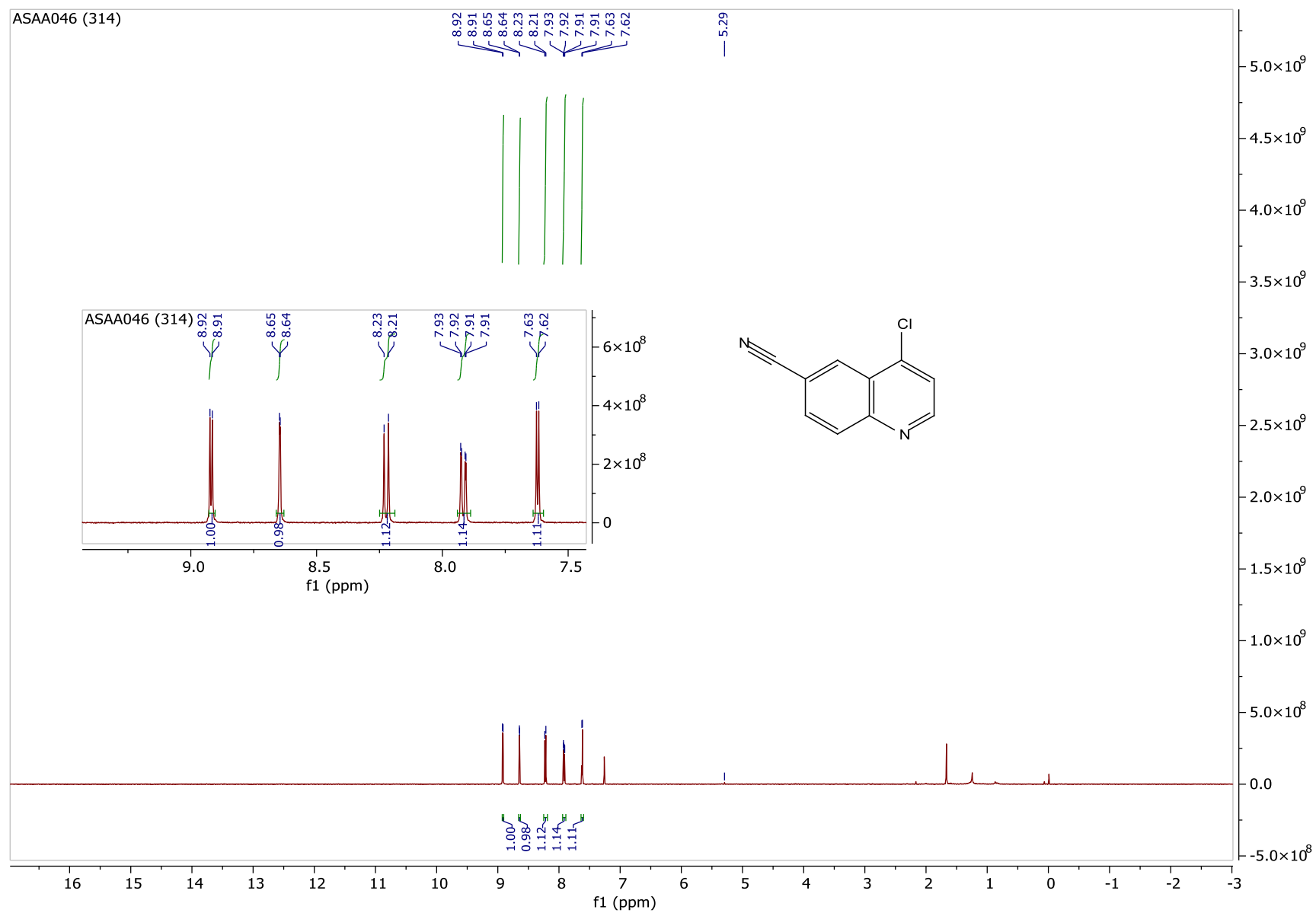
¹H NMR spectrum of 6-fluoro-4-chloroquinoline (34)



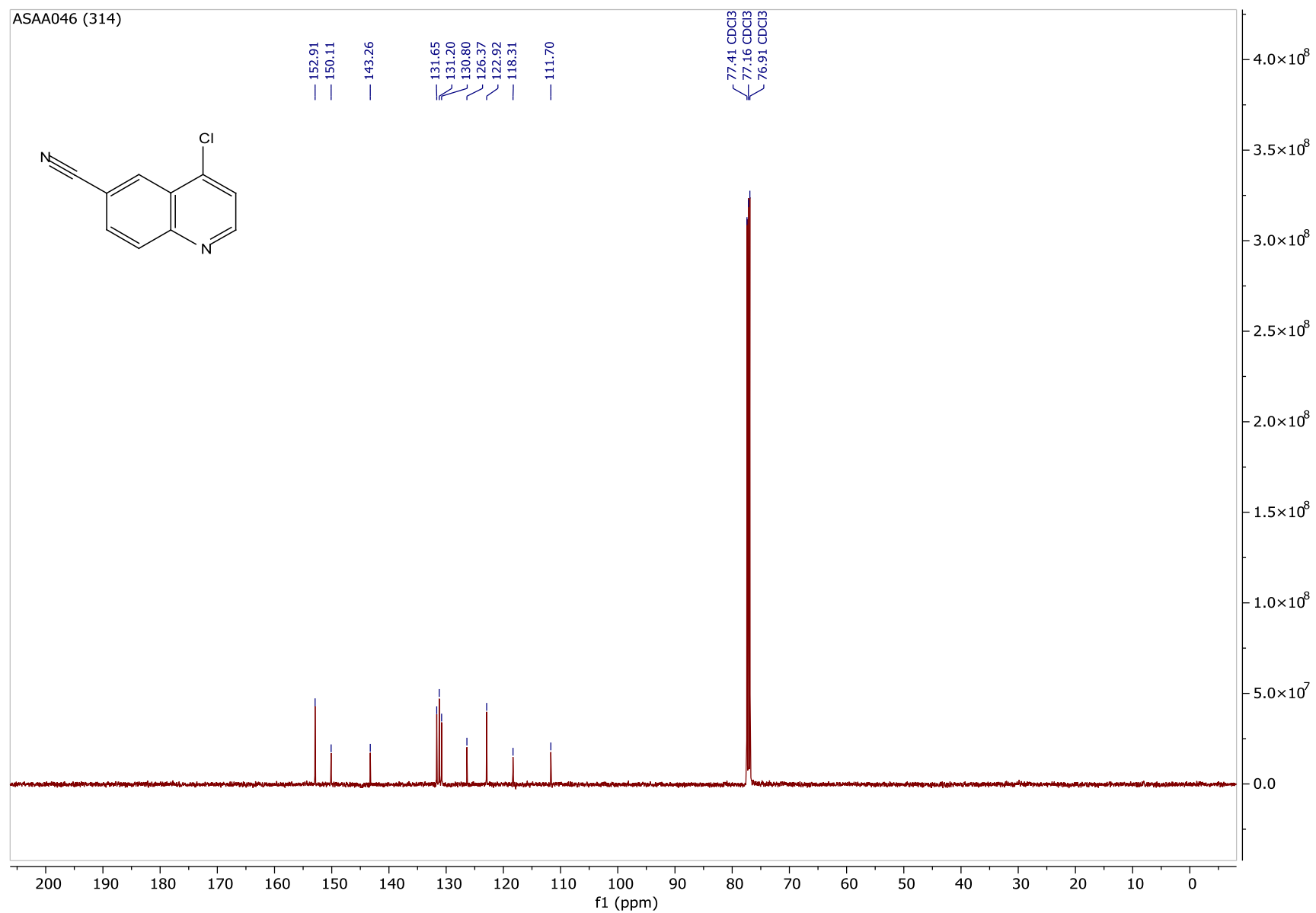
^{13}C NMR spectrum of 6-fluoro-4-chloroquinoline (34)



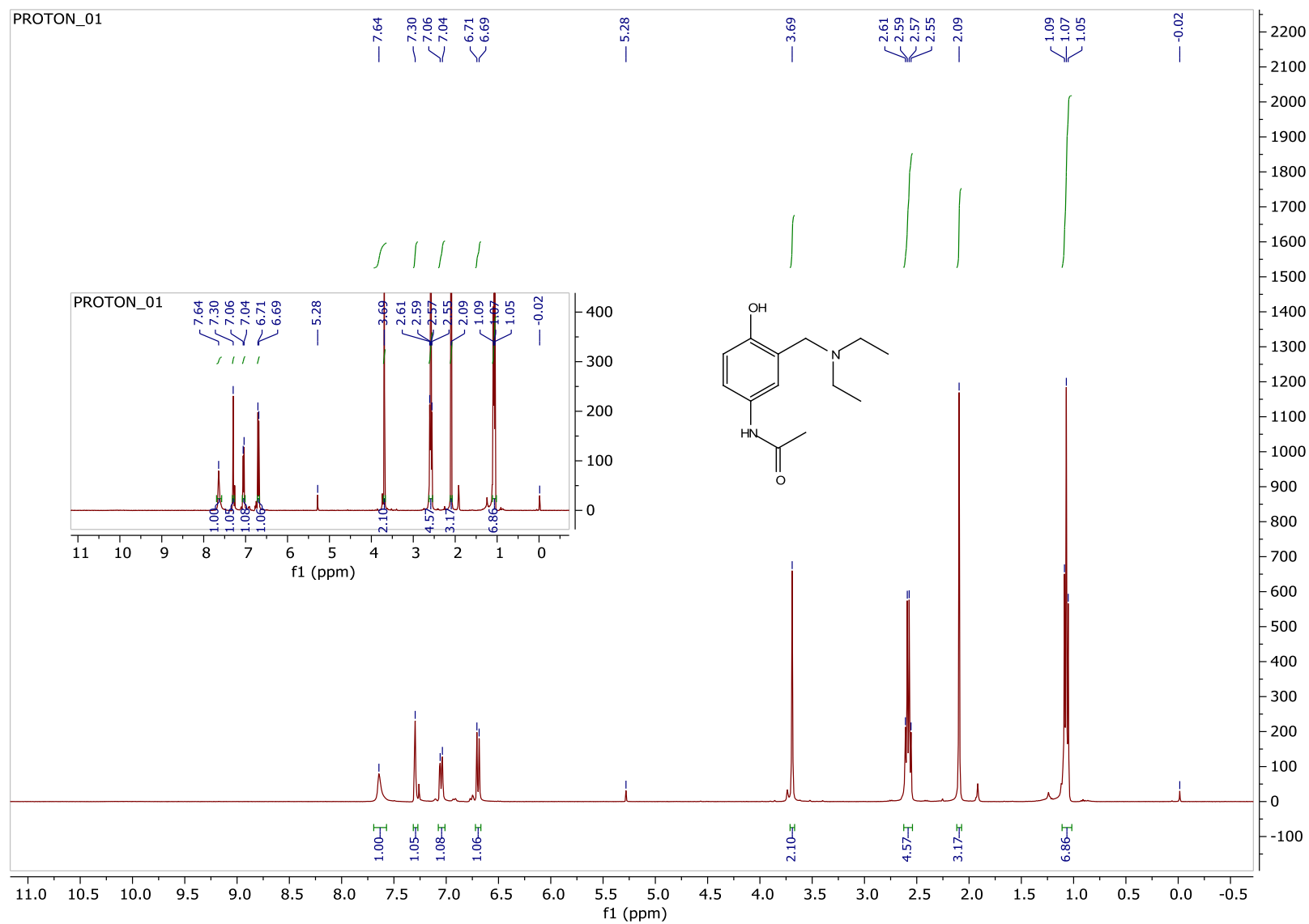
^1H NMR spectrum of 6-ciano-4-chloroquinoline (35)



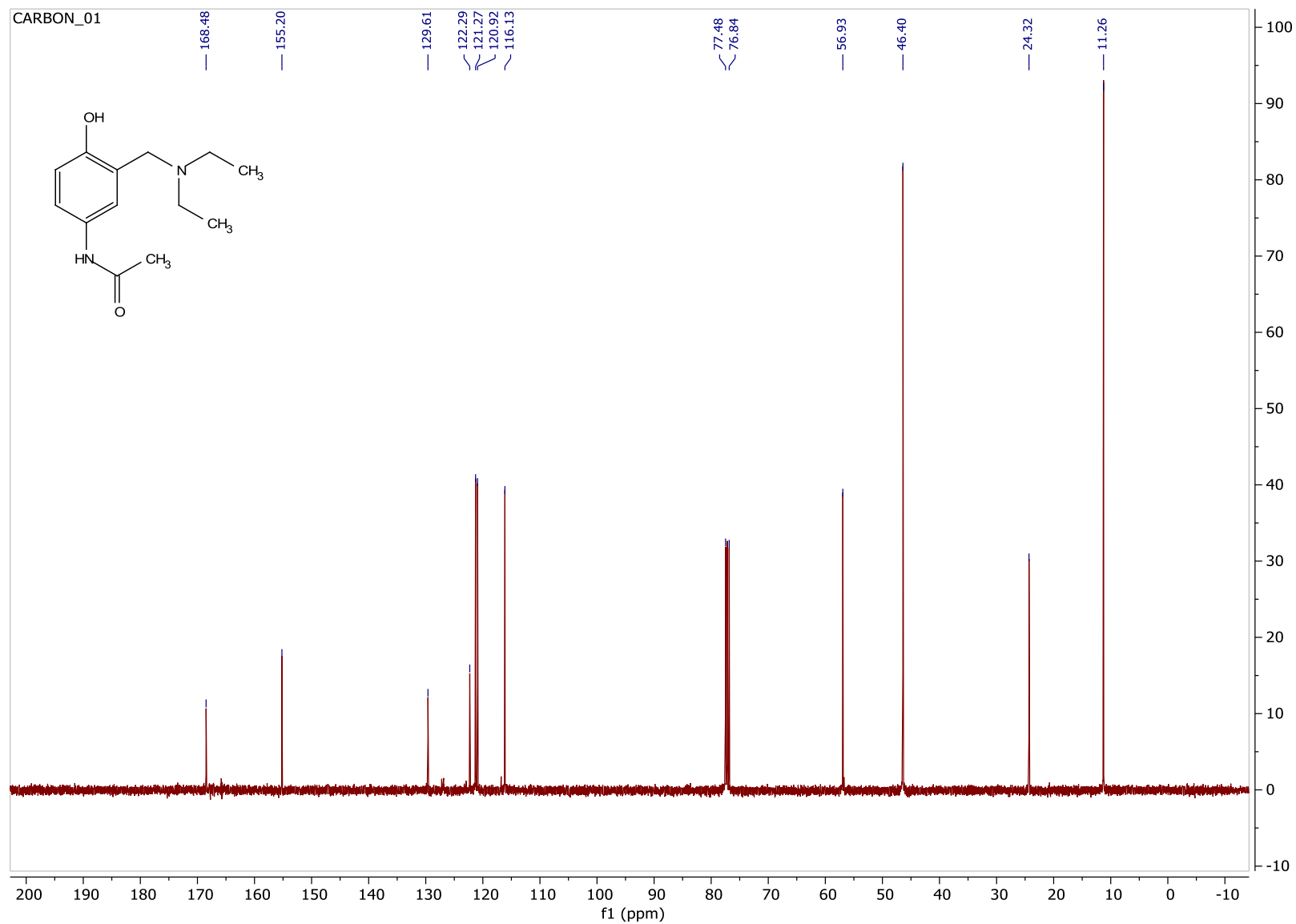
¹³C NMR spectrum of 6-ciano-4-chloroquinoline (35)



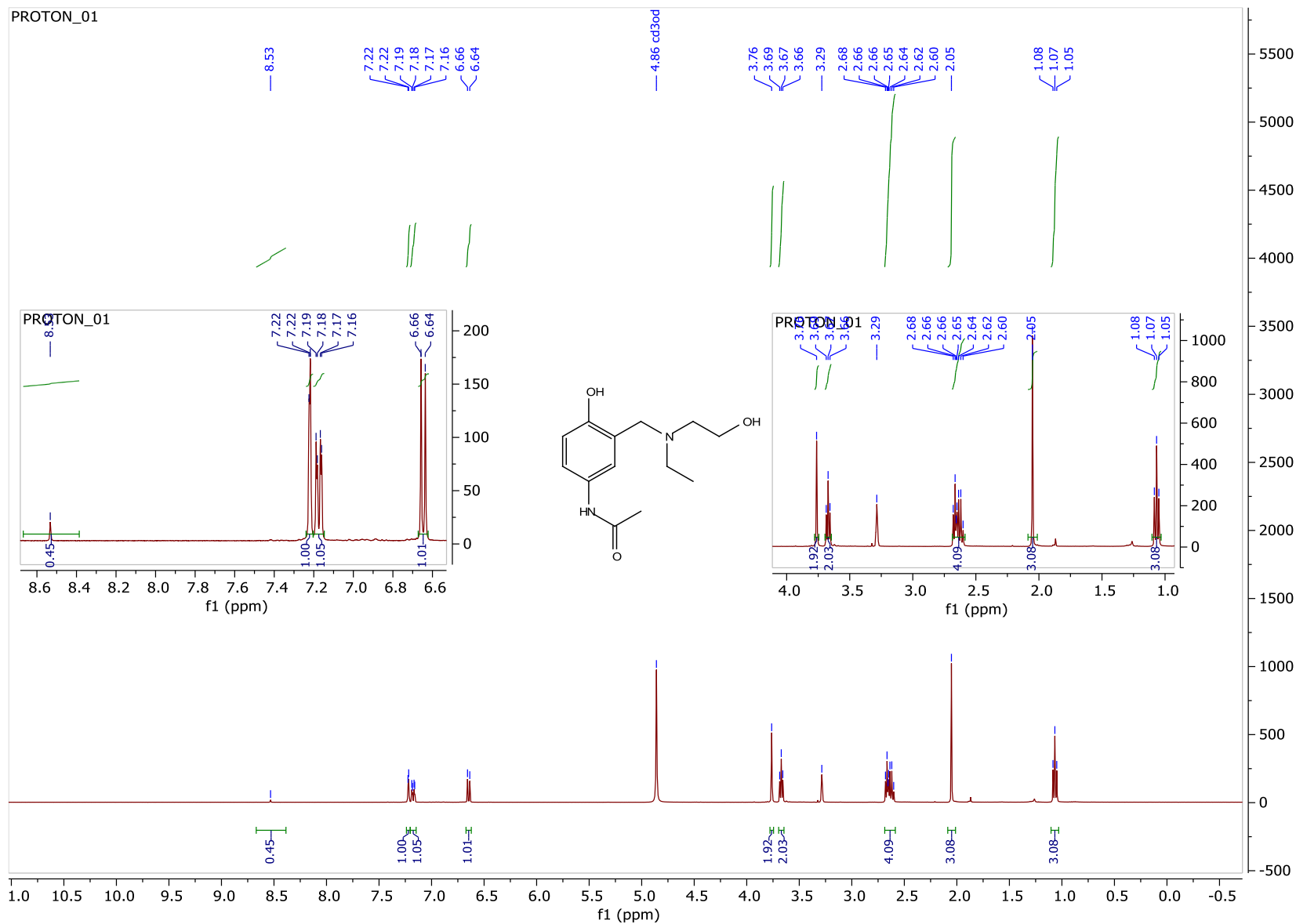
^1H NMR spectrum of 4-amino-2-((diethylamino)methyl)phenol (19a)



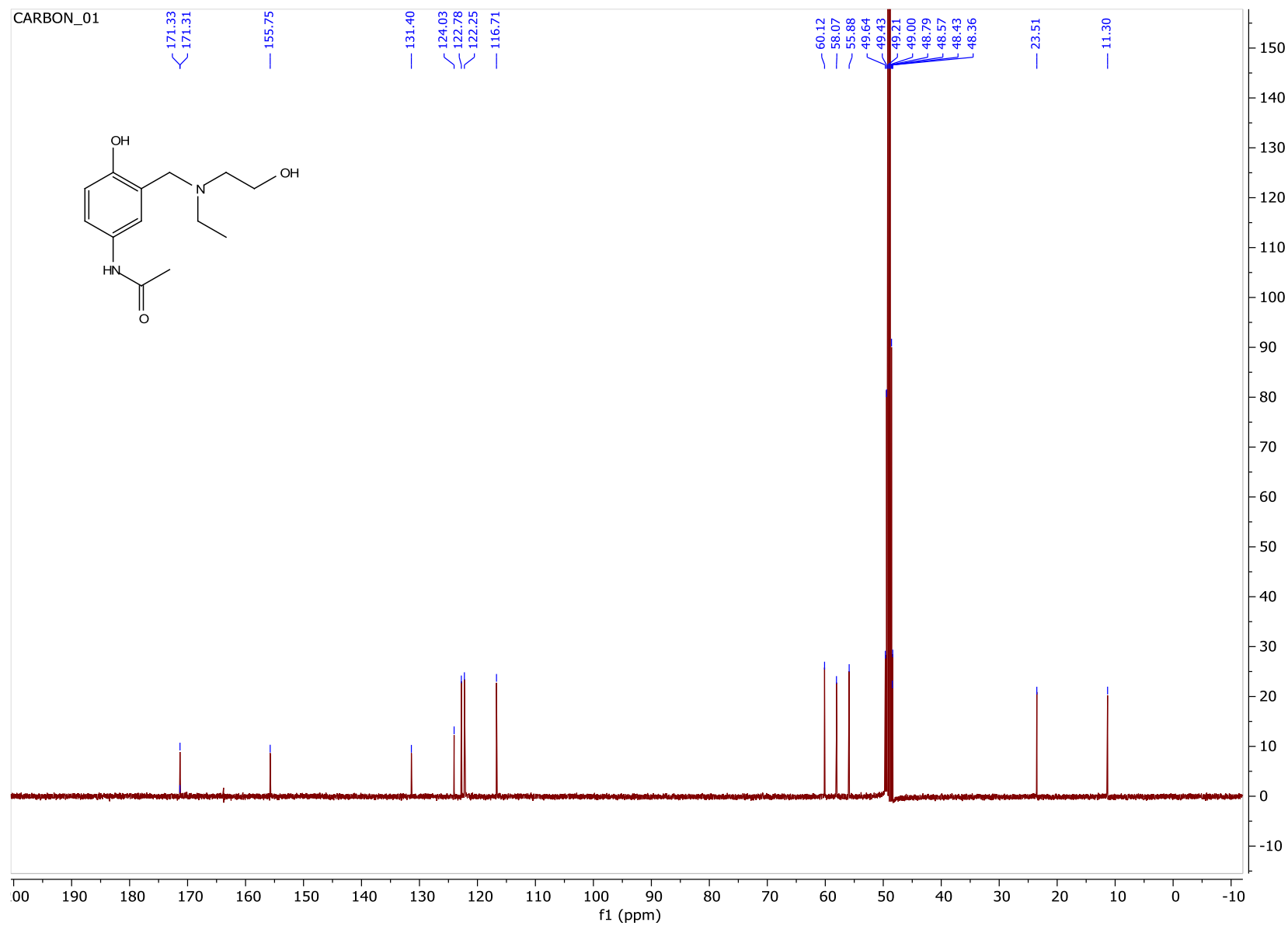
^{13}C NMR spectrum of 4-amino-2-((diethylamino)methyl)phenol (19a)



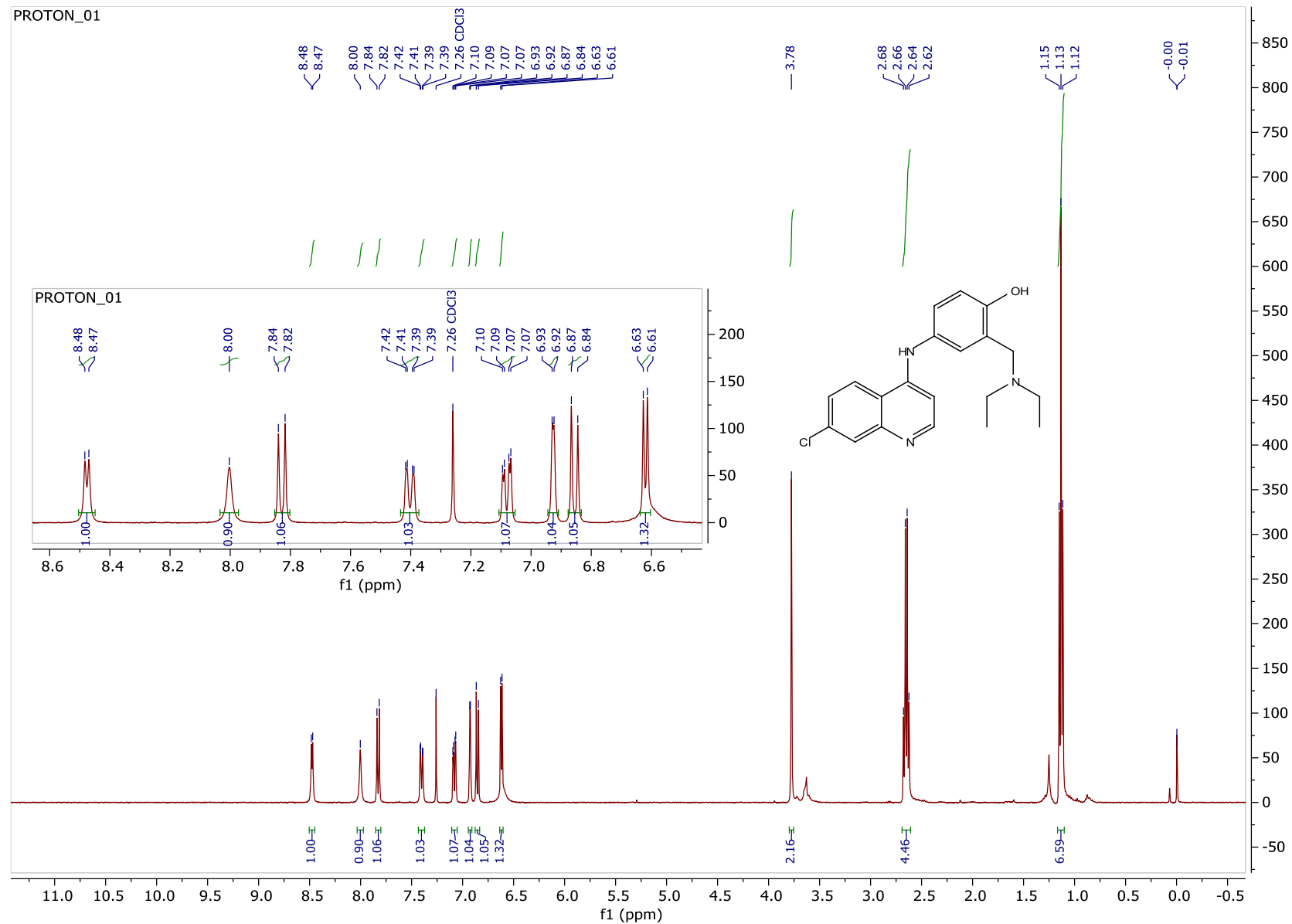
¹H NMR spectrum of N-(3-((ethyl(2-hydroxyethyl)amino)methyl)-4-hydroxyphenyl)acetamide (19b)



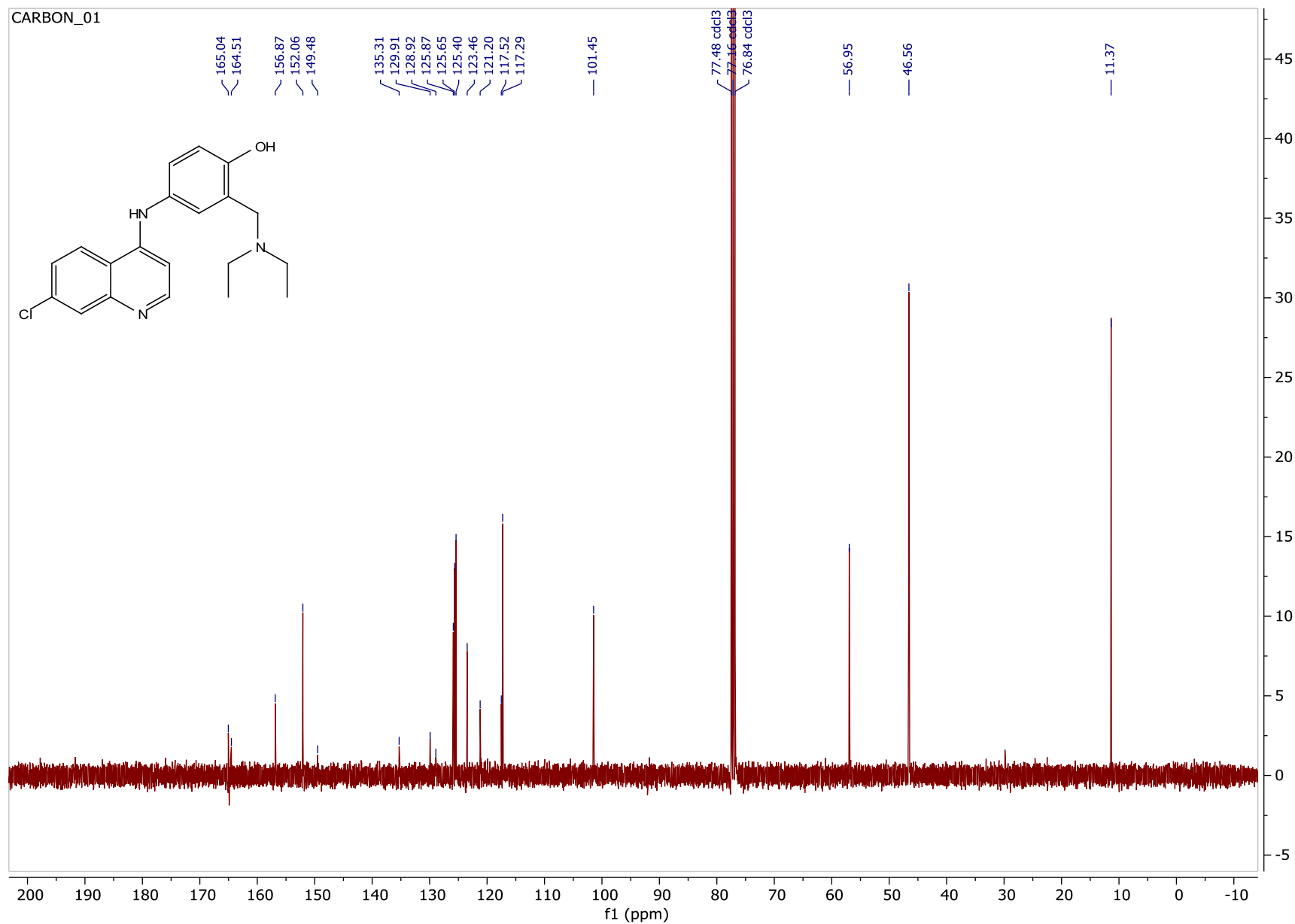
^{13}C NMR spectrum of N-(3-((ethyl(2-hydroxyethyl)amino)methyl)-4-hydroxyphenyl)acetamide (19b)



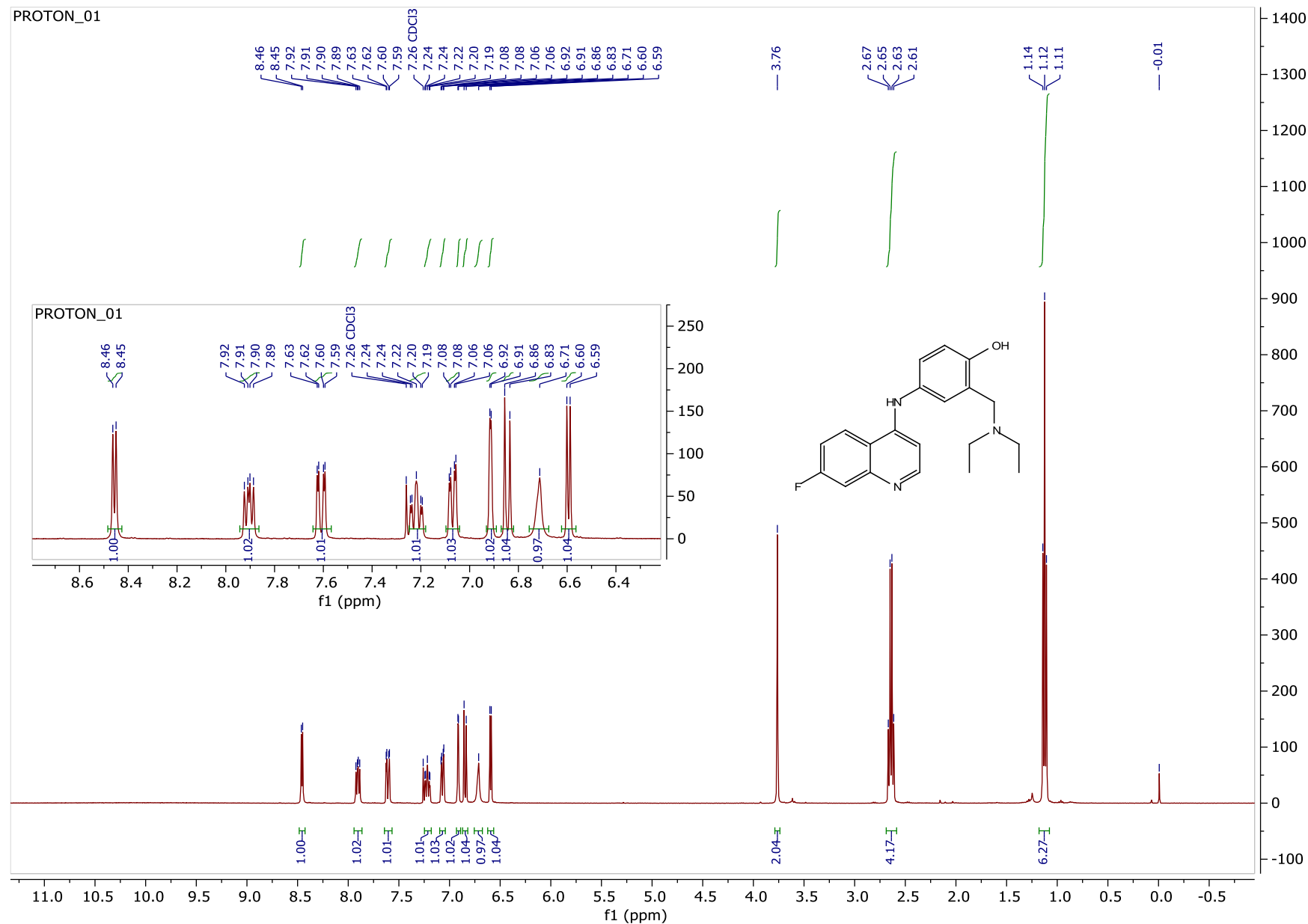
^1H NMR spectrum of 4-((7-chloroquinolin-4-yl)amino)-2-((diethylamino)methyl)phenol (AMQ)



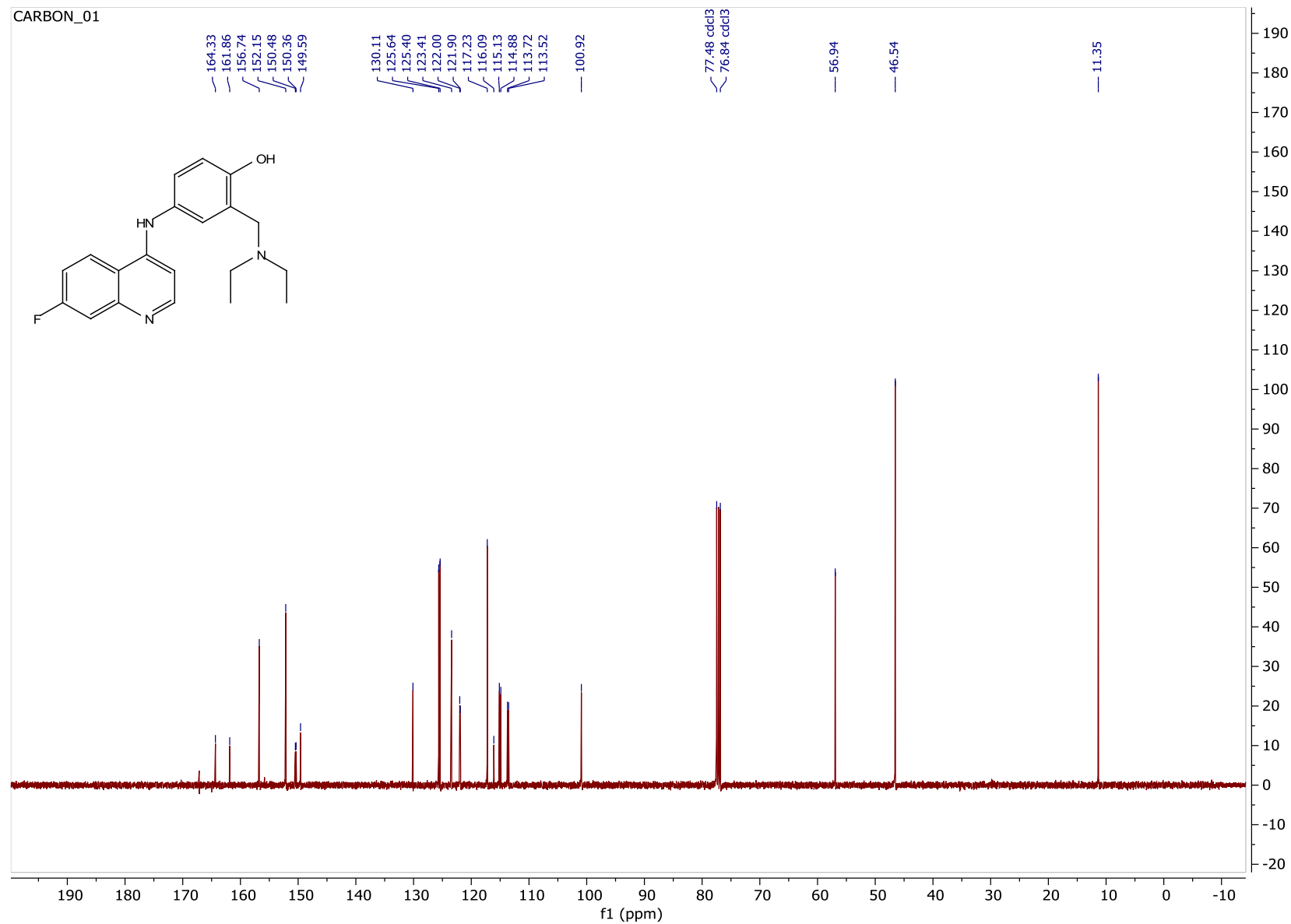
¹³C NMR spectrum of 4-((7-chloroquinolin-4-yl)amino)-2-((diethylamino)methyl)phenol (AMQ)



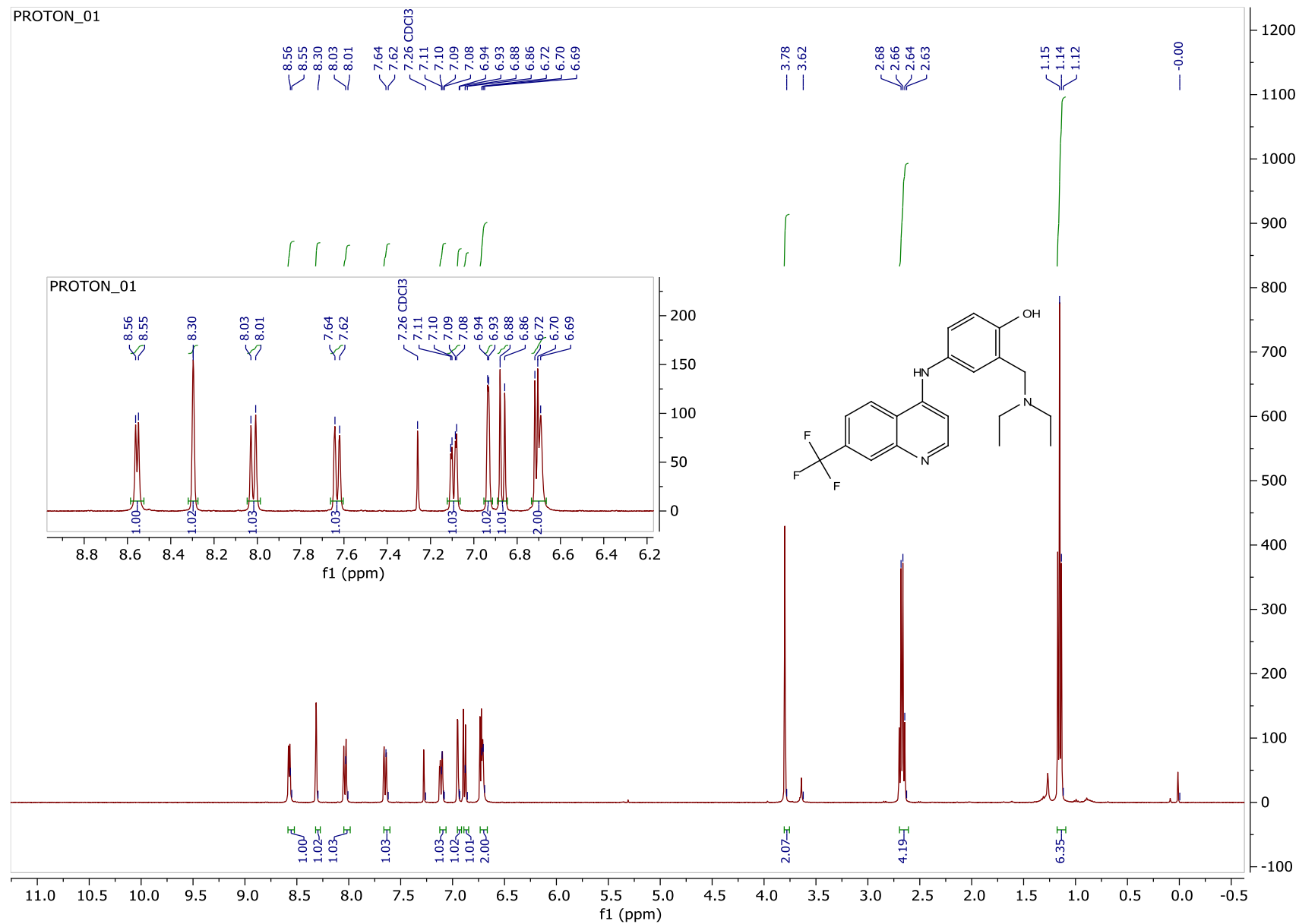
¹H NMR spectrum of 2-((diethylamino)methyl)-4-((7-fluoroquinolin-4-yl)amino)phenol (1)



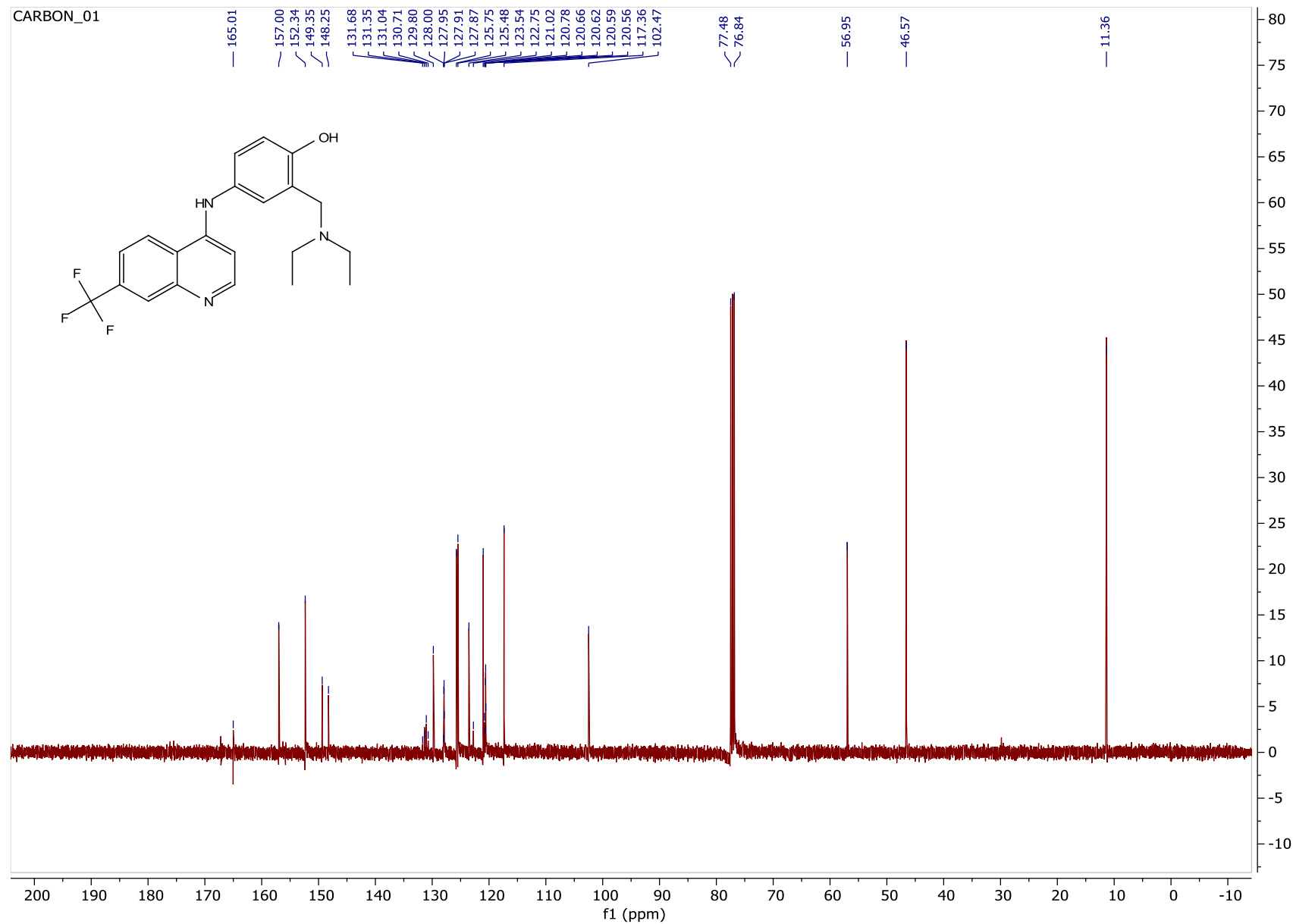
^{13}C NMR spectrum of 2-((diethylamino)methyl)-4-((7-fluoroquinolin-4-yl)amino)phenol (1)



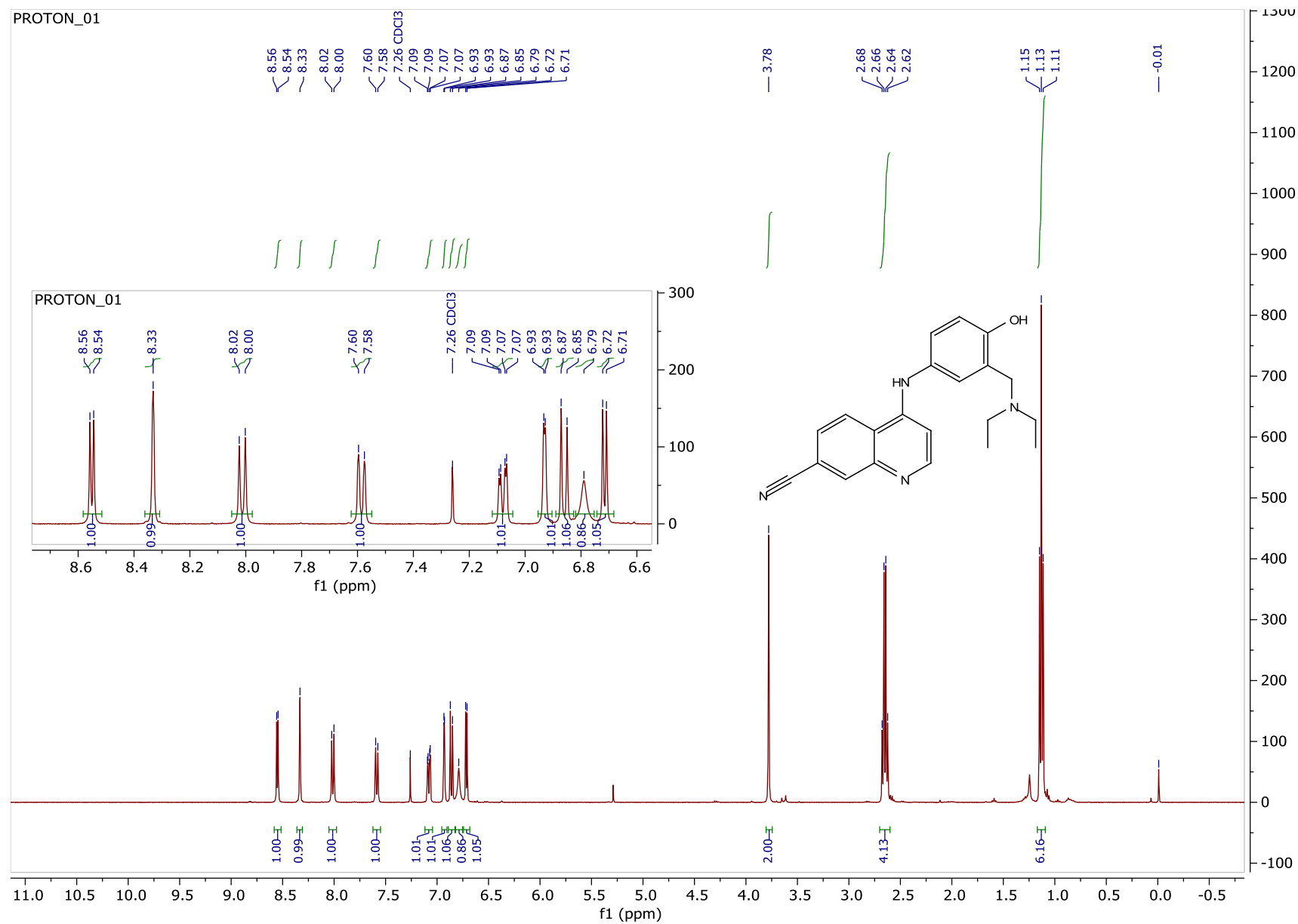
¹H NMR spectrum of 2-((diethylamino)methyl)-4-((7-(trifluoromethyl)quinolin-4-yl)amino)phenol (2)



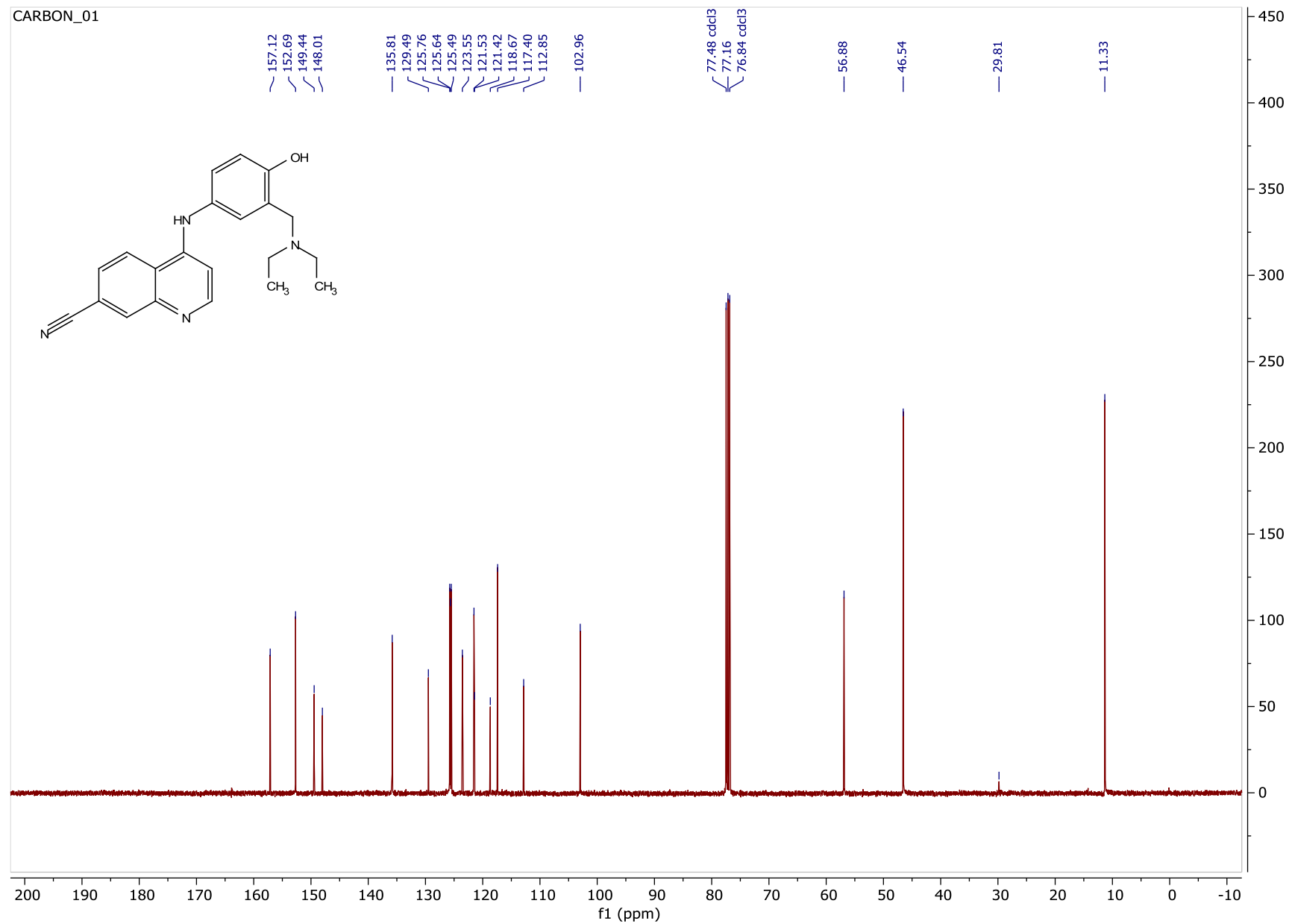
^{13}C NMR spectrum of 2-((diethylamino)methyl)-4-((7-(trifluoromethyl)quinolin-4-yl)amino)phenol (2)



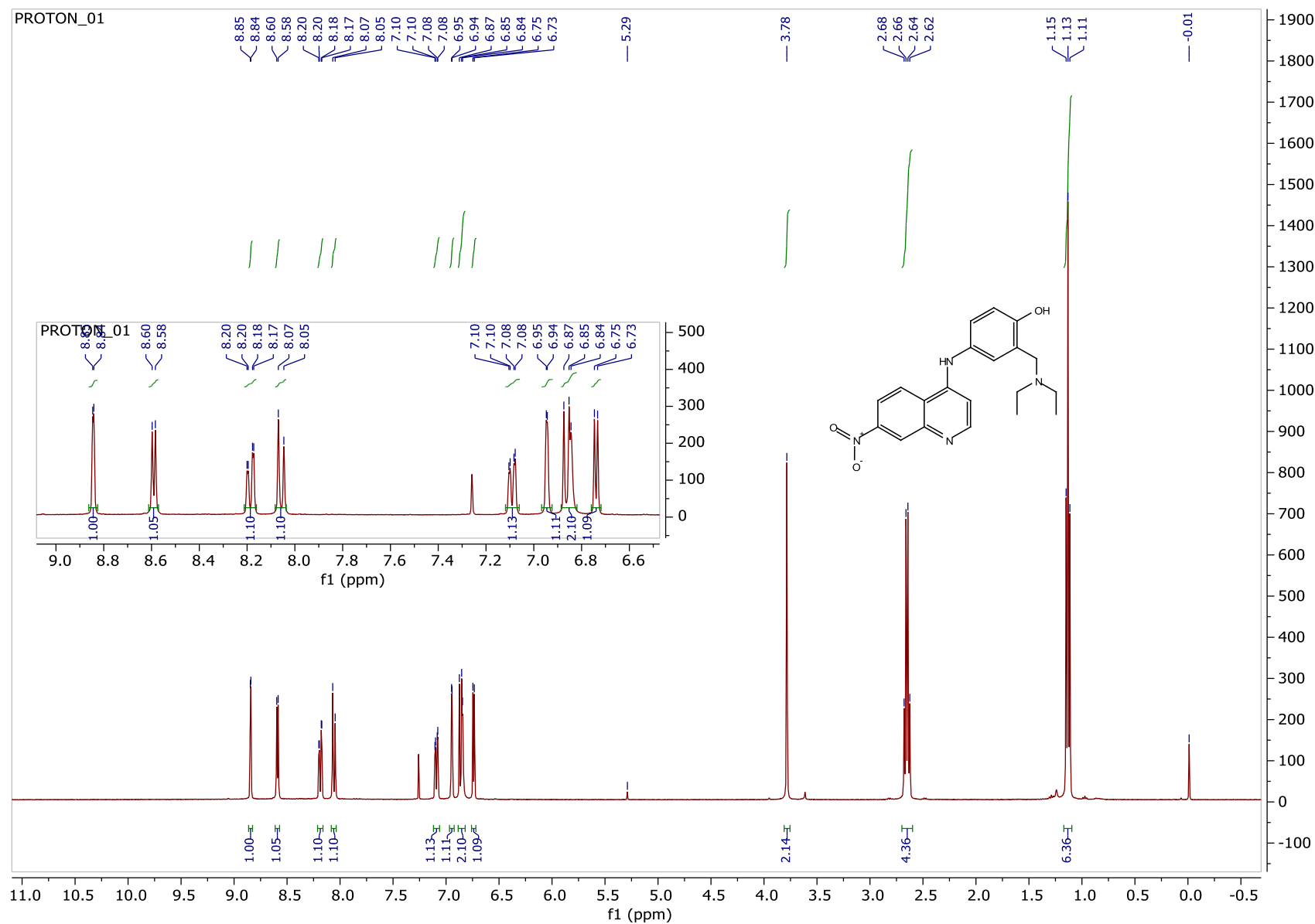
¹H NMR spectrum of 4-((3-((diethylamino)methyl)-4-hydroxyphenyl)amino)quinoline-7-carbonitrile (3)



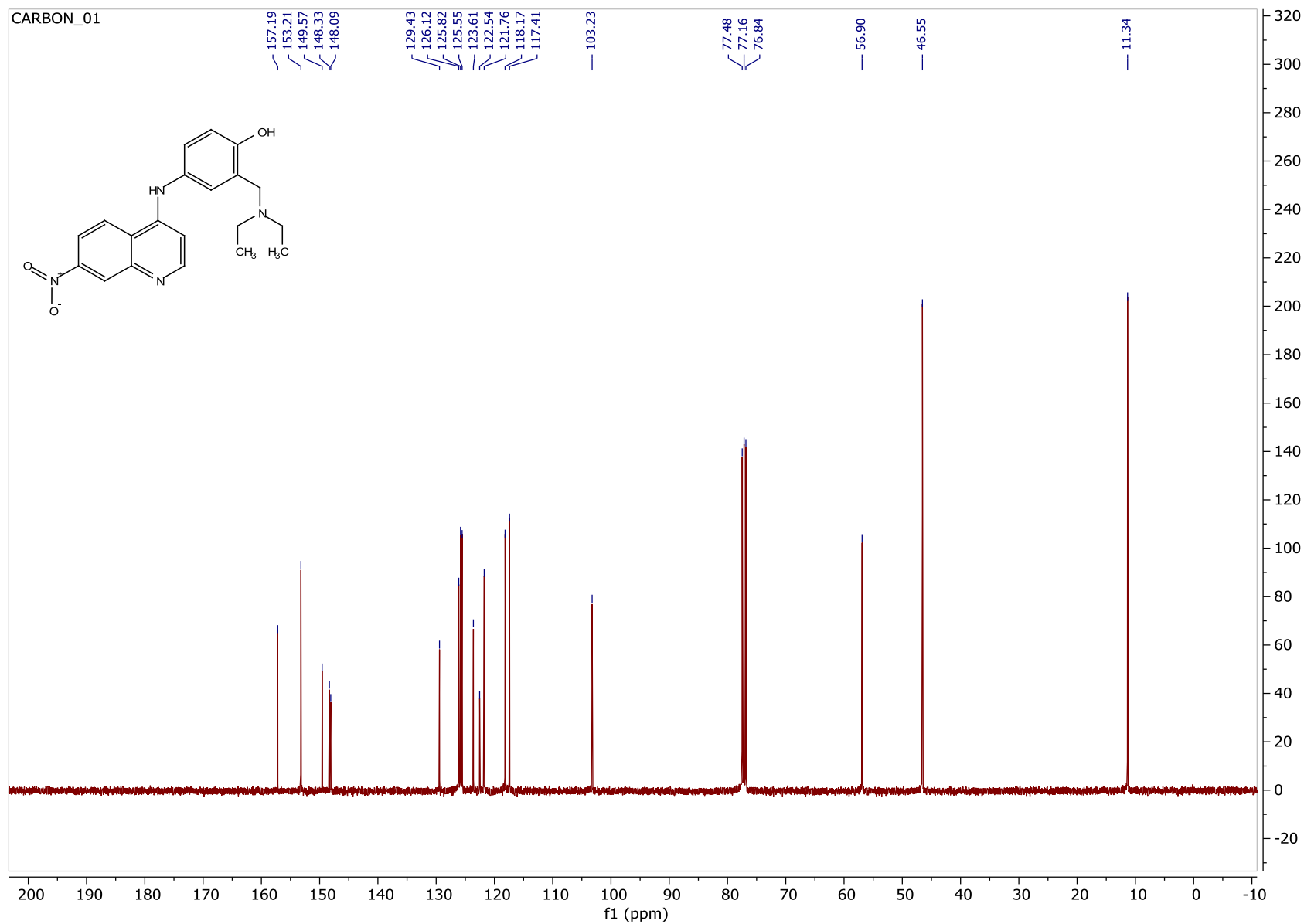
^{13}C NMR spectrum of 4-((3-((diethylamino)methyl)-4-hydroxyphenyl)amino)quinoline-7-carbonitrile (3)



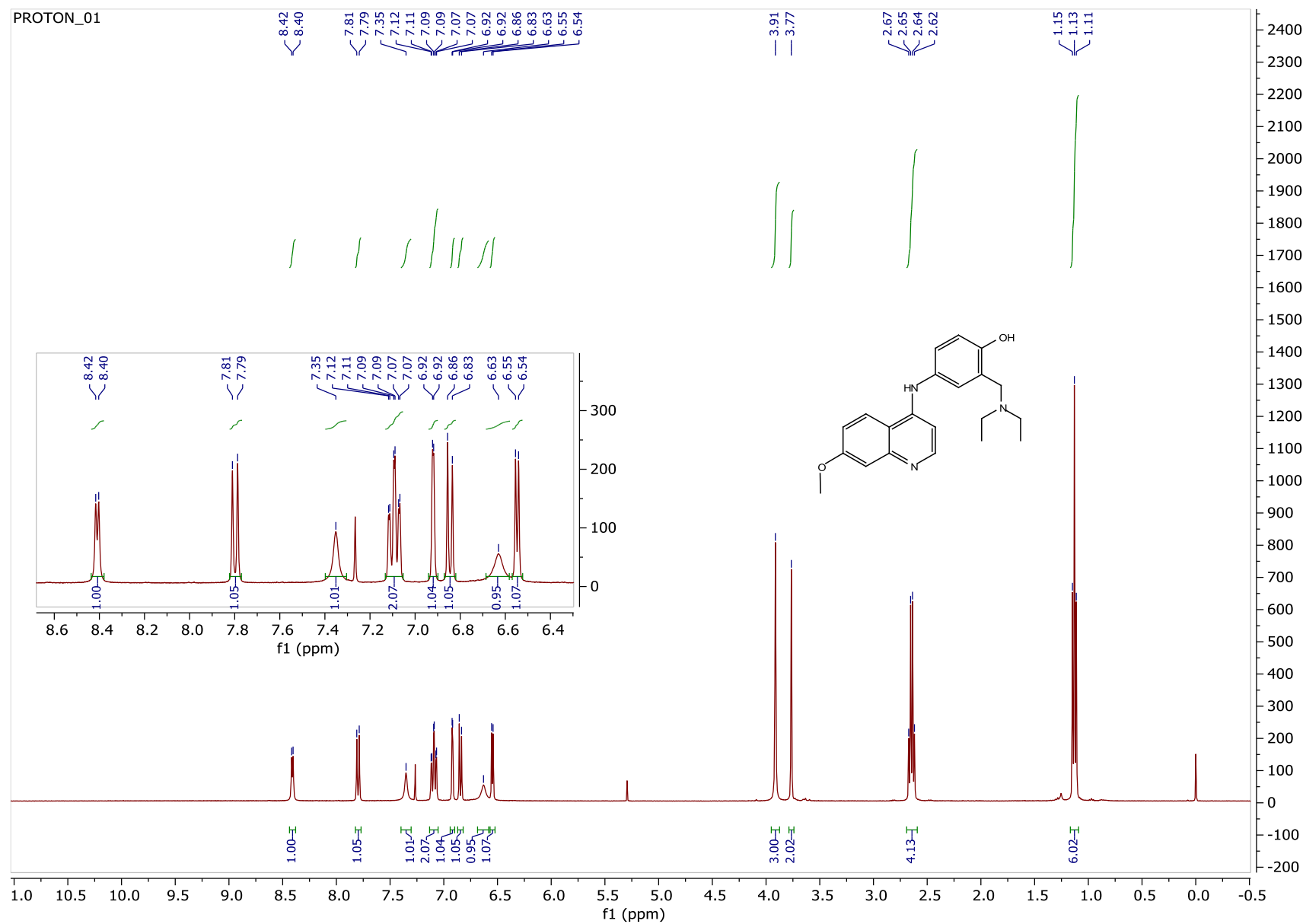
¹H NMR spectrum of 2-((diethylamino)methyl)-4-((7-nitroquinolin-4-yl)amino)phenol (4)



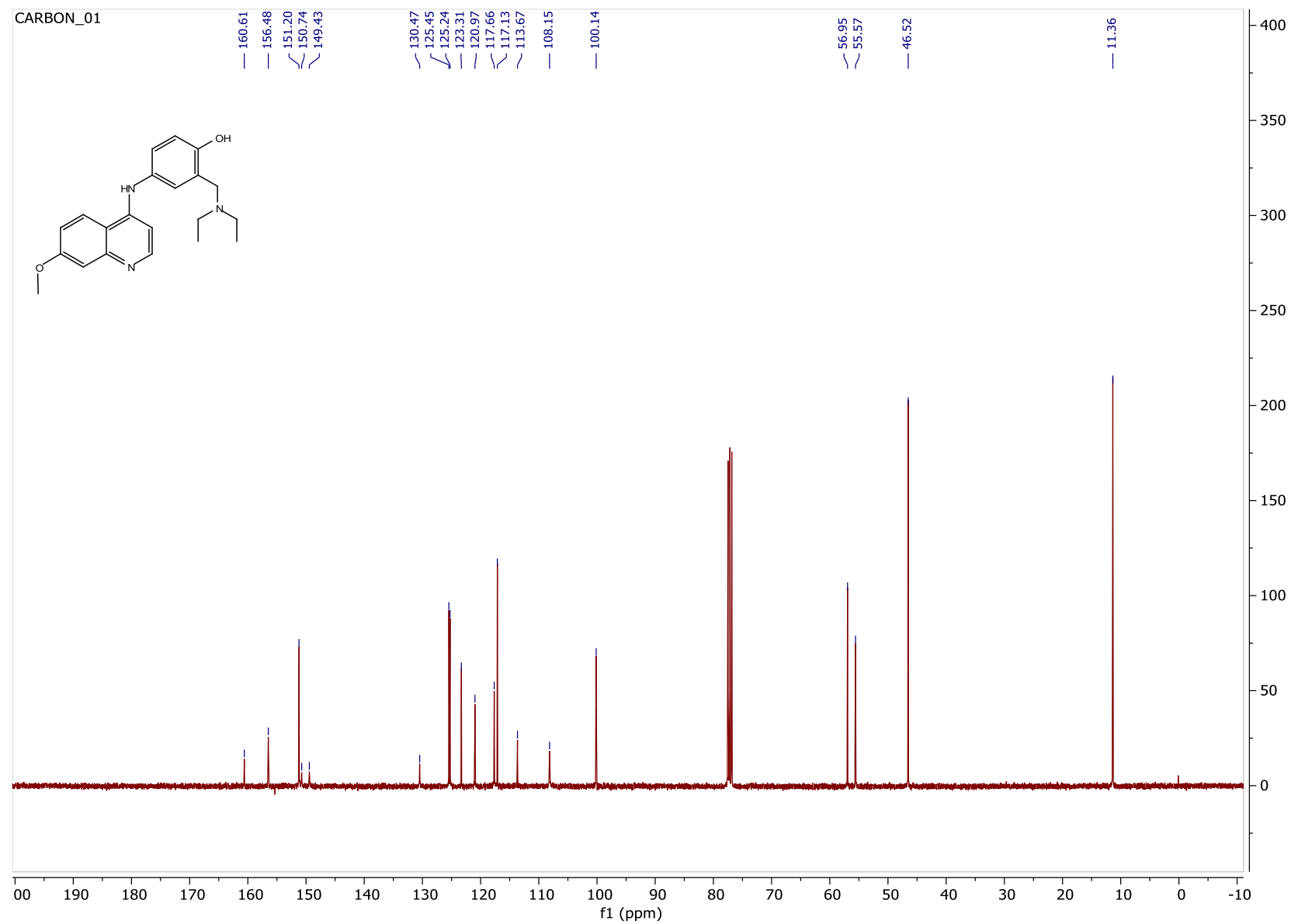
¹³C NMR spectrum of 2-((diethylamino)methyl)-4-((7-nitroquinolin-4-yl)amino)phenol (4)



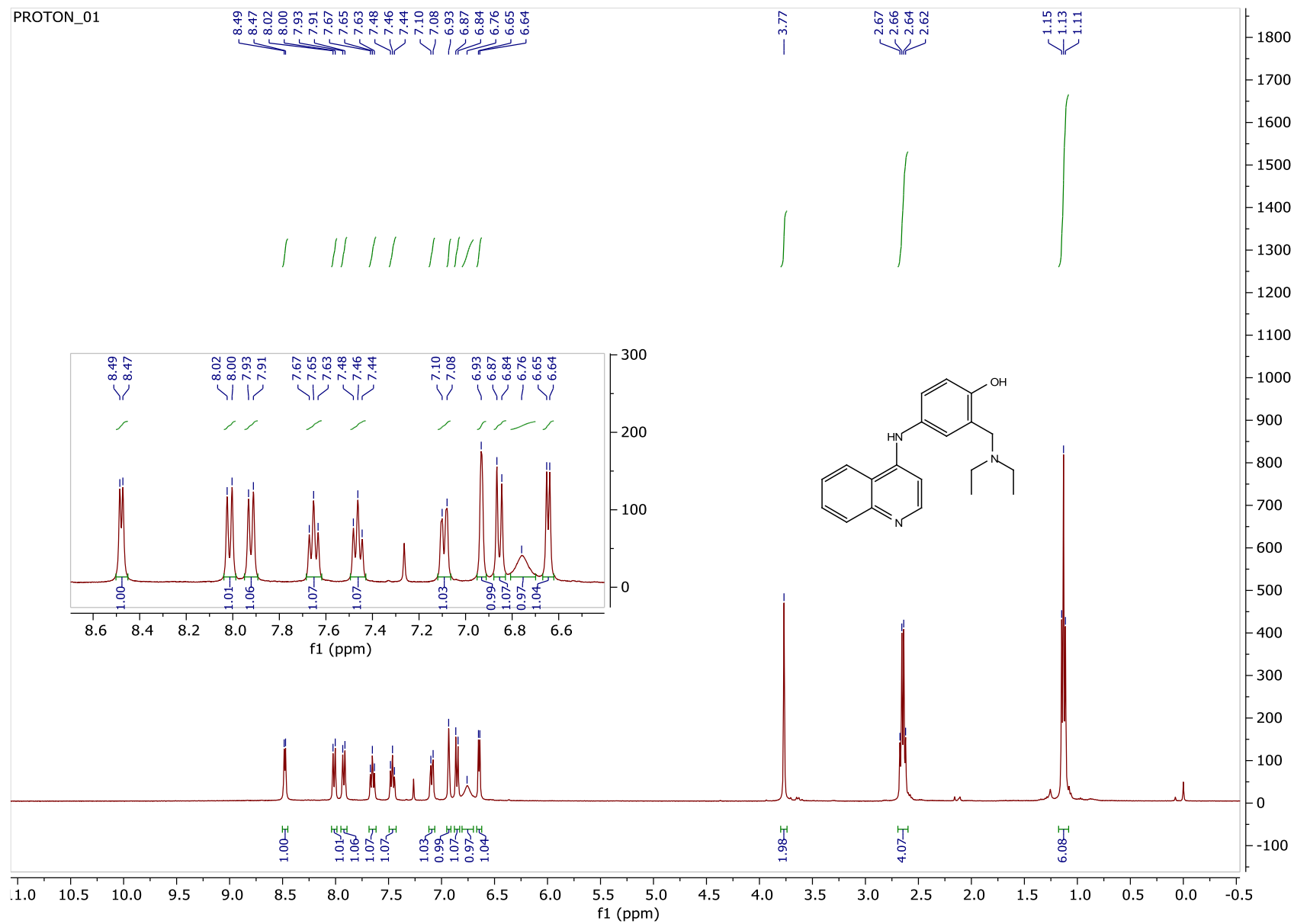
¹H NMR spectrum of 2-((diethylamino)methyl)-4-((7-methoxyquinolin-4-yl)amino)phenol (5)



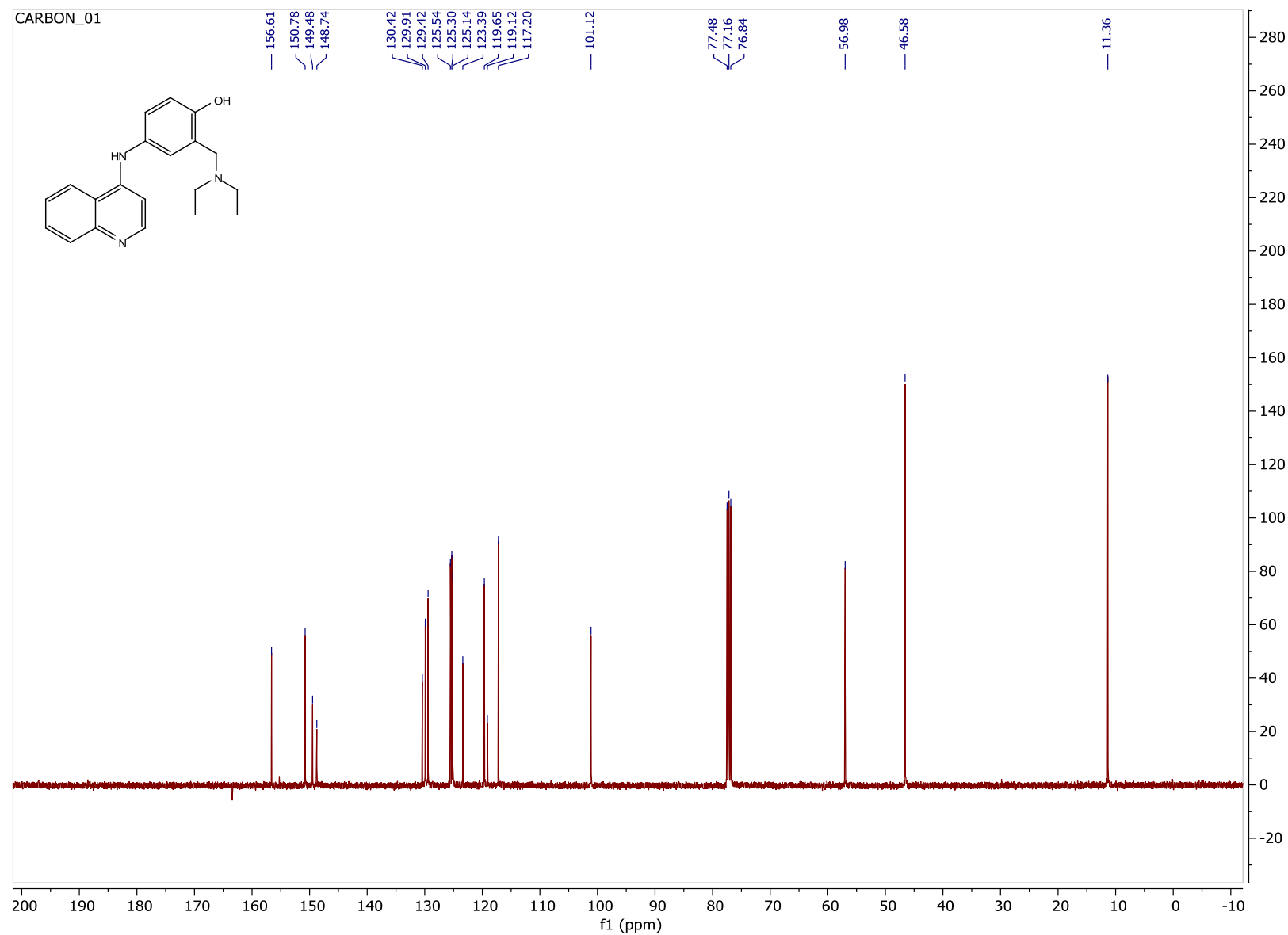
^{13}C NMR spectrum of 2-((diethylamino)methyl)-4-((7-methoxyquinolin-4-yl)amino)phenol (5)



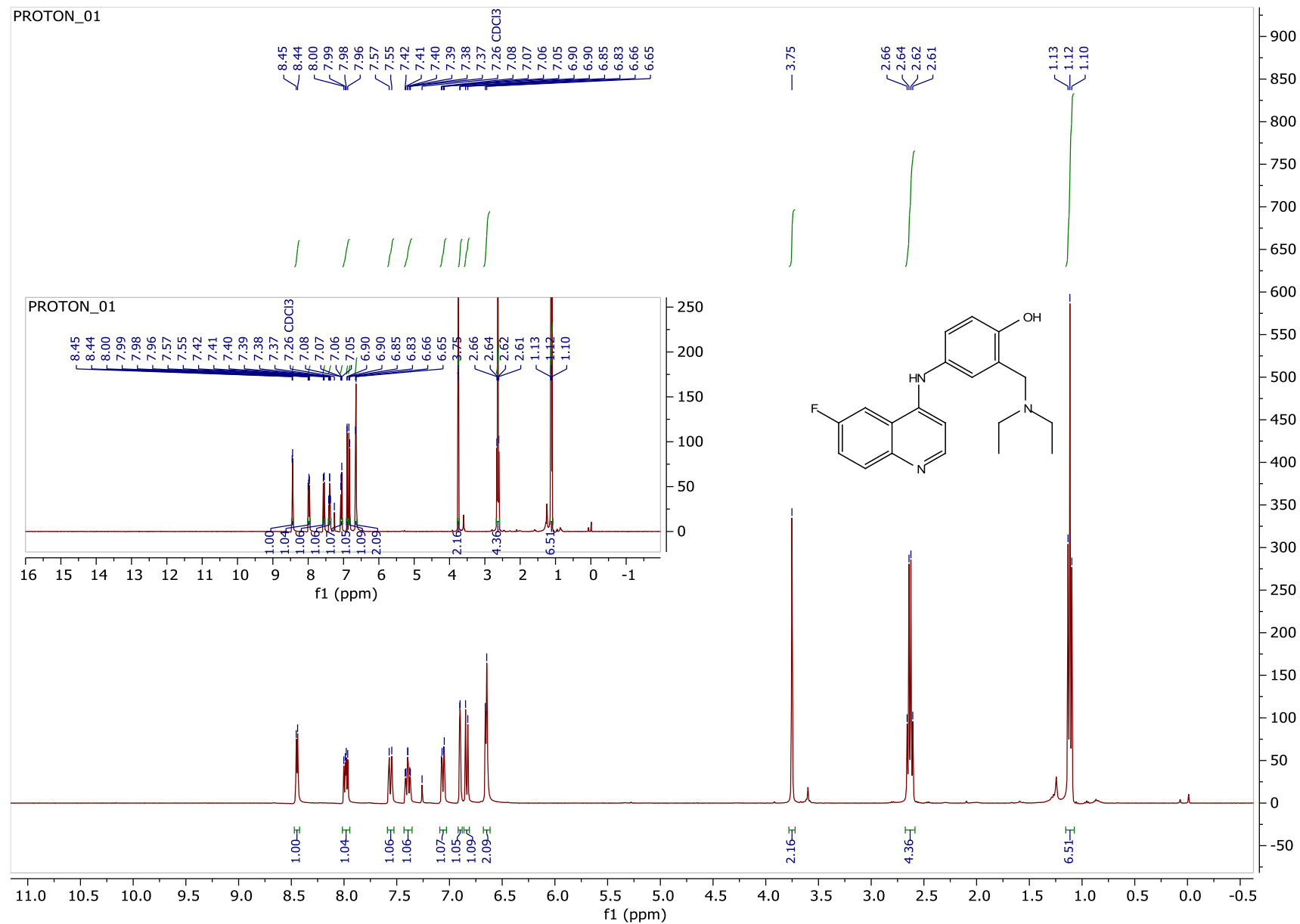
¹H NMR spectrum of 2-((diethylamino)methyl)-4-(quinolin-4-ylamino)phenol (6)



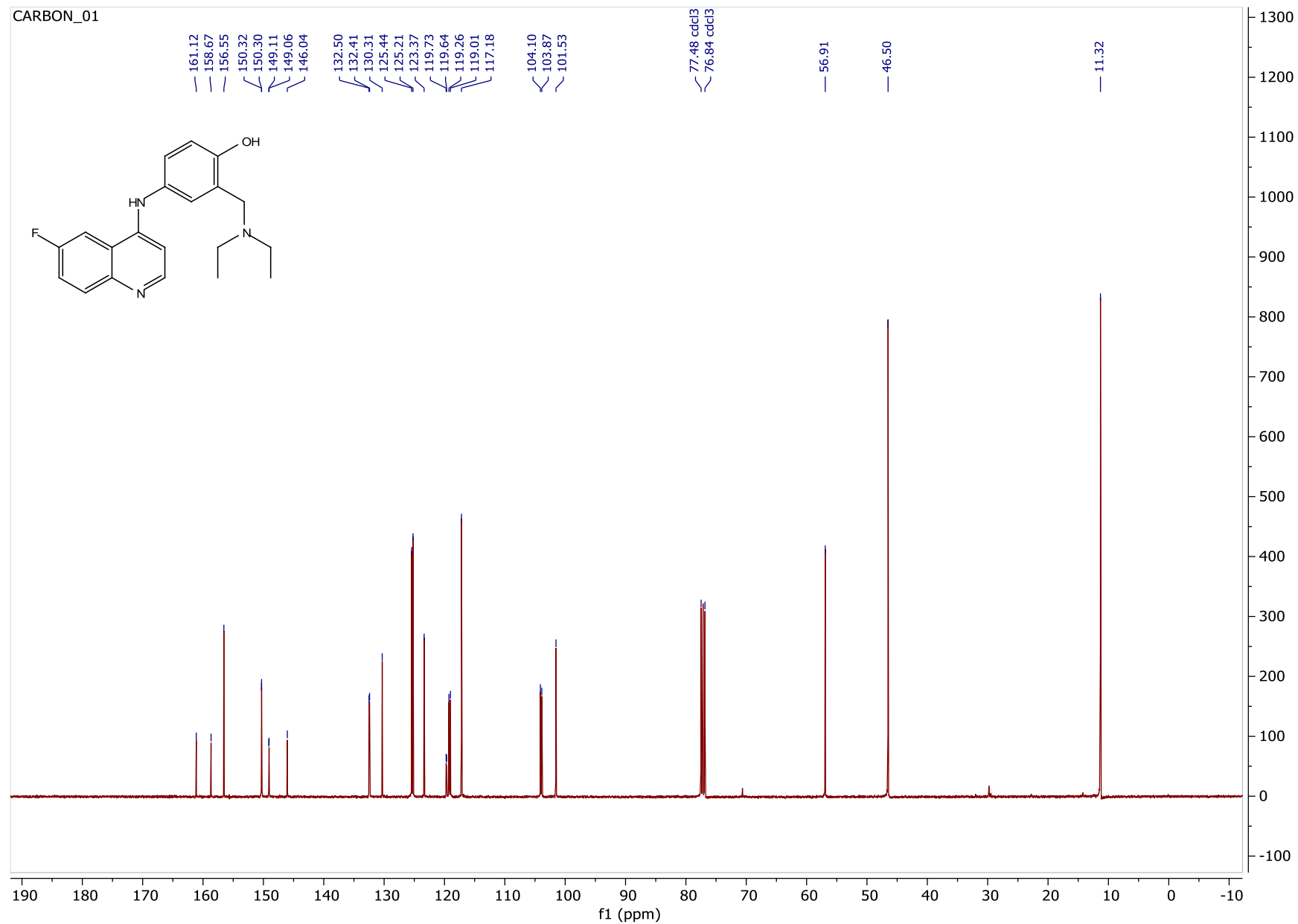
^{13}C NMR spectrum of 2-((diethylamino)methyl)-4-(quinolin-4-ylamino)phenol (6)



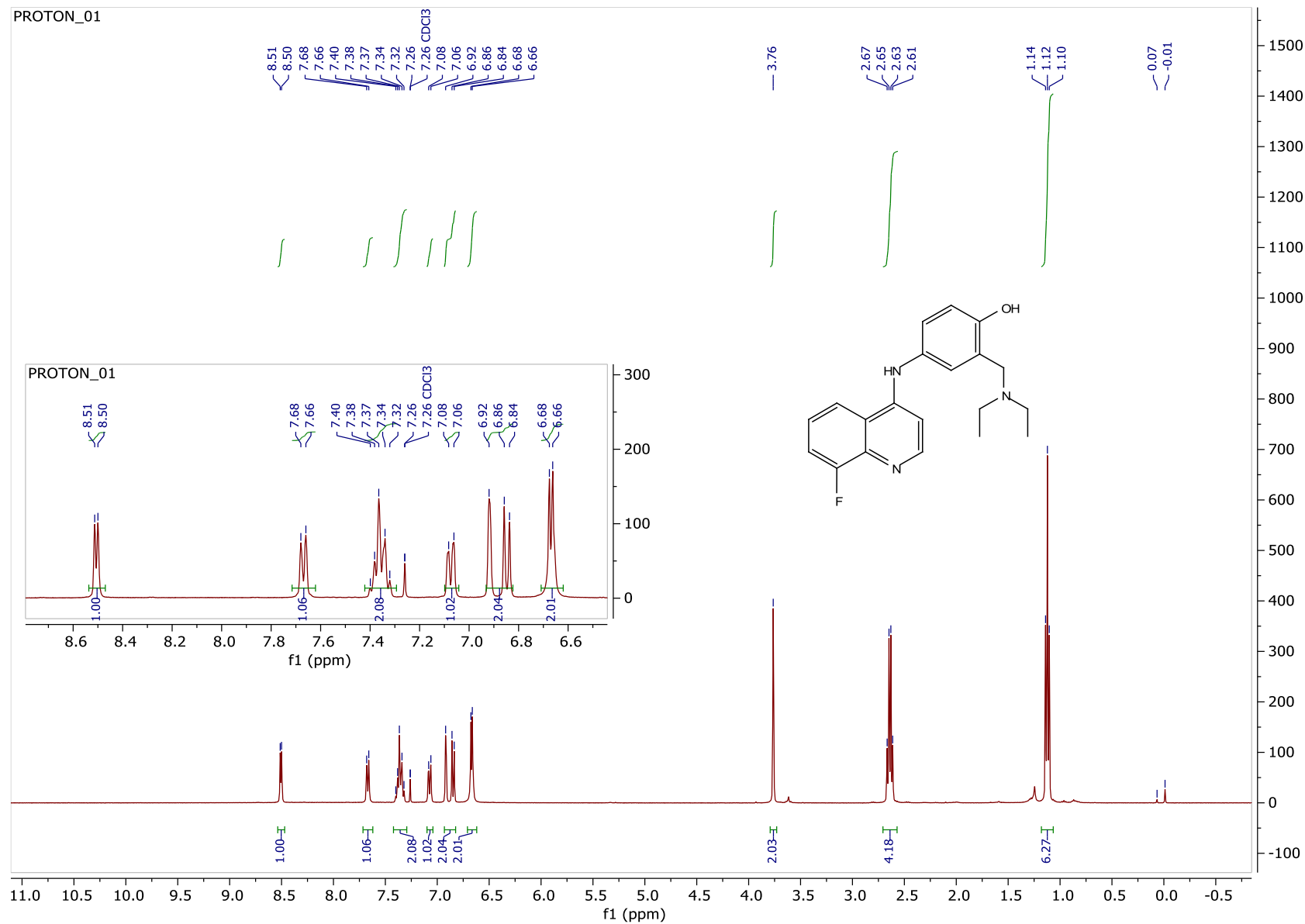
¹H NMR spectrum of 2-((diethylamino)methyl)-4-((6-fluoroquinolin-4-yl)amino)phenol (7)



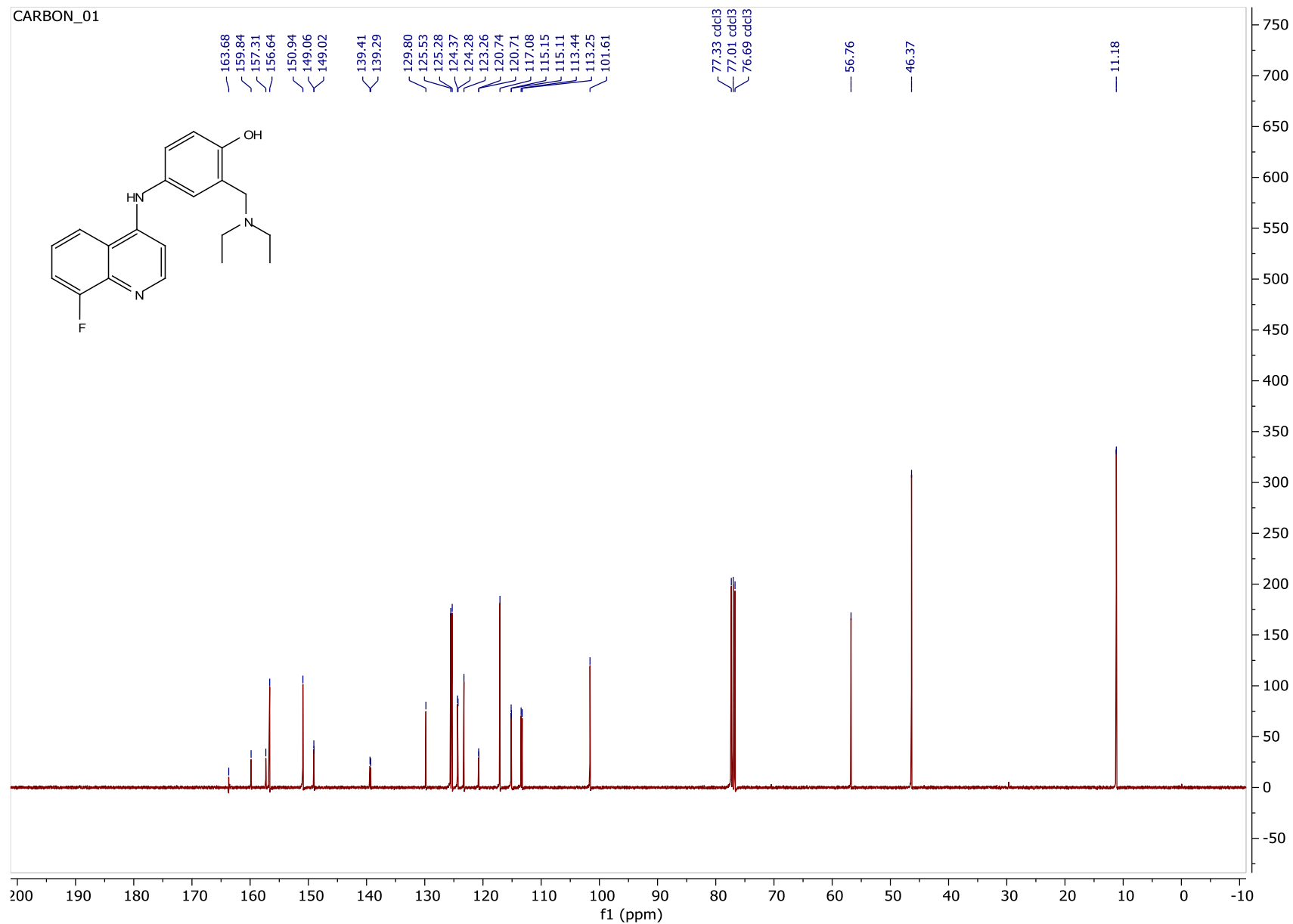
¹³C NMR spectrum of 2-((diethylamino)methyl)-4-((6-fluoroquinolin-4-yl)amino)phenol (7)



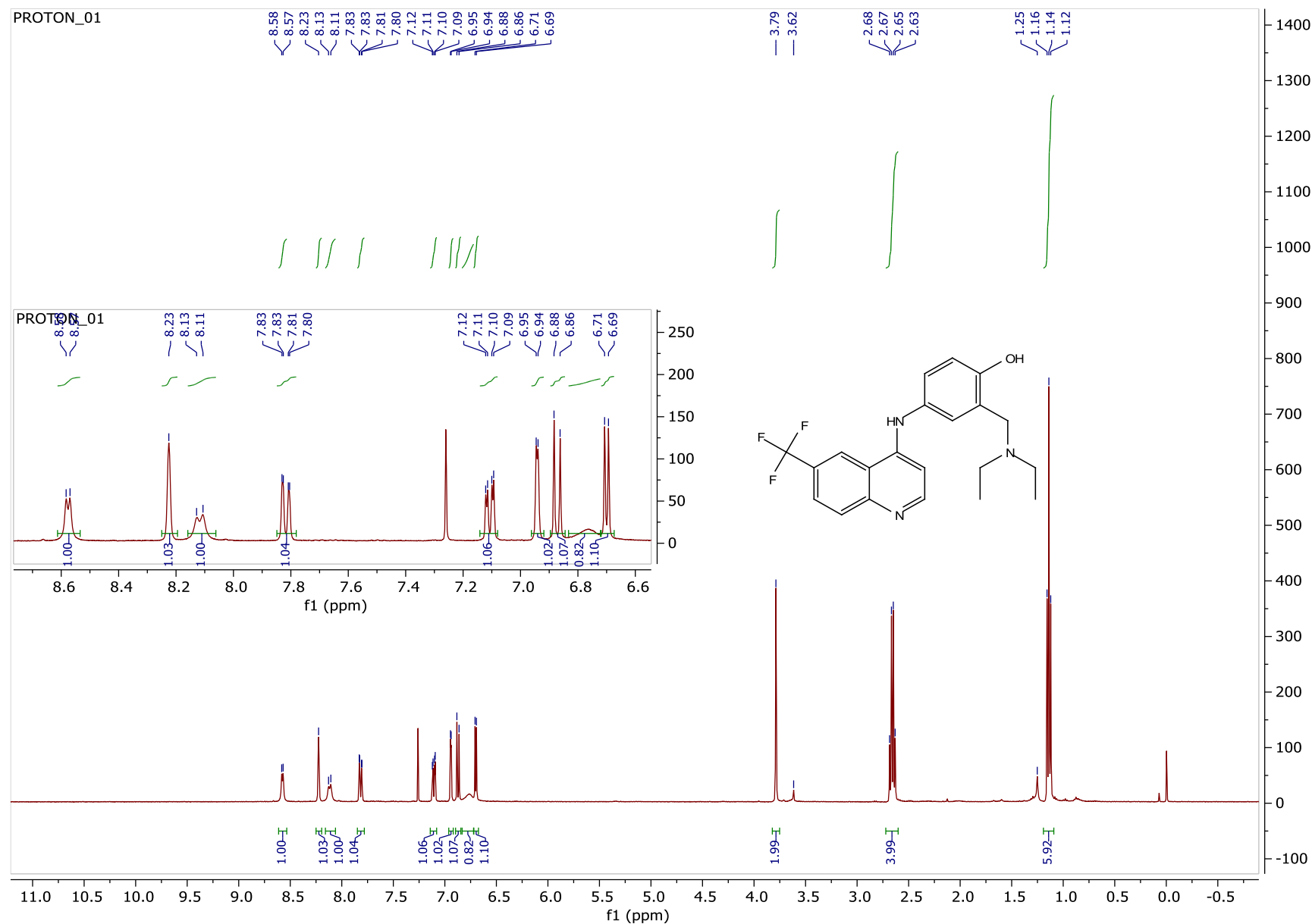
¹H NMR spectrum of 2-((diethylamino)methyl)-4-((8-fluoroquinolin-4-yl)amino)phenol (8)



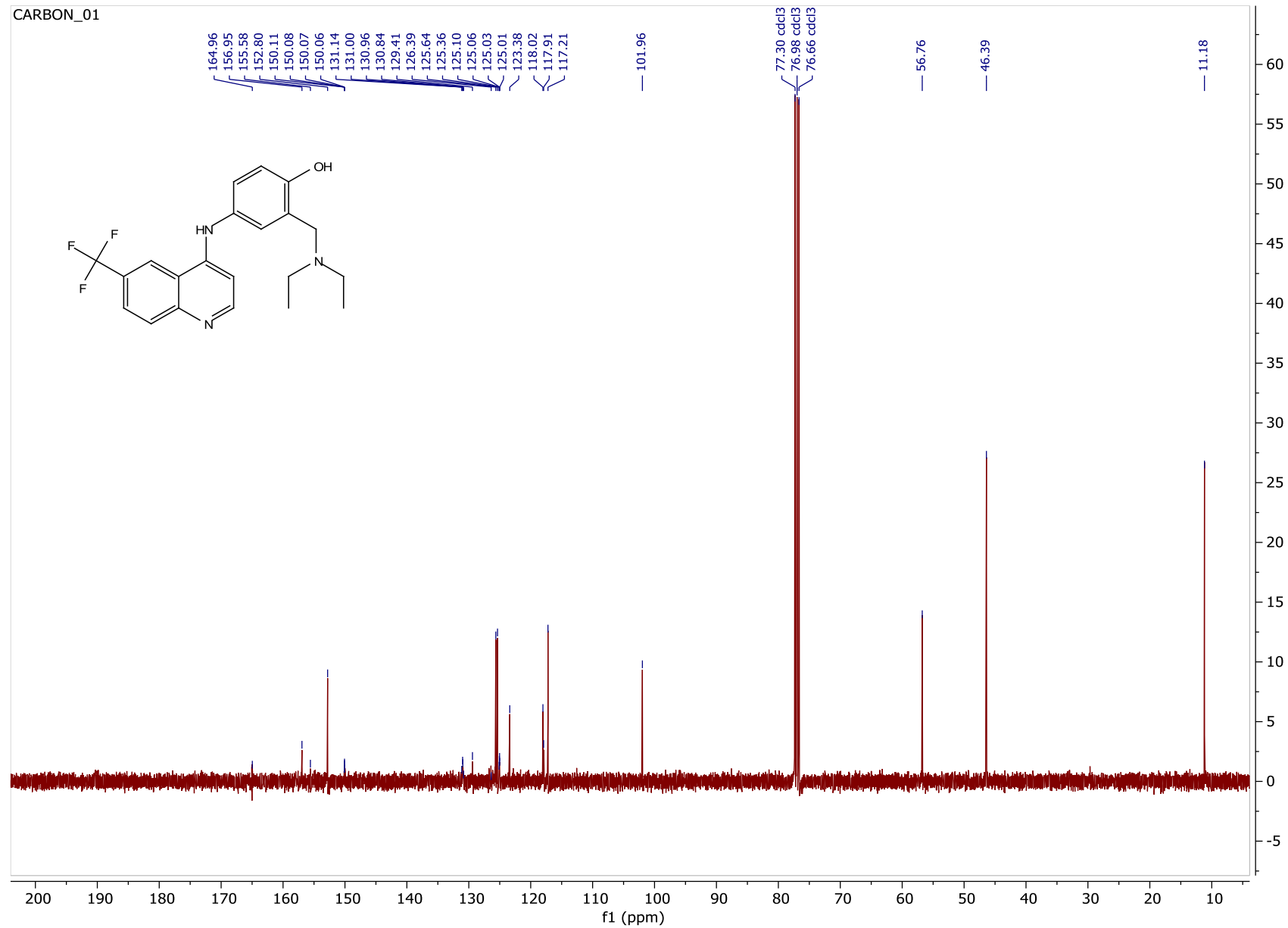
^{13}C NMR spectrum of 2-((diethylamino)methyl)-4-((8-fluoroquinolin-4-yl)amino)phenol (8)



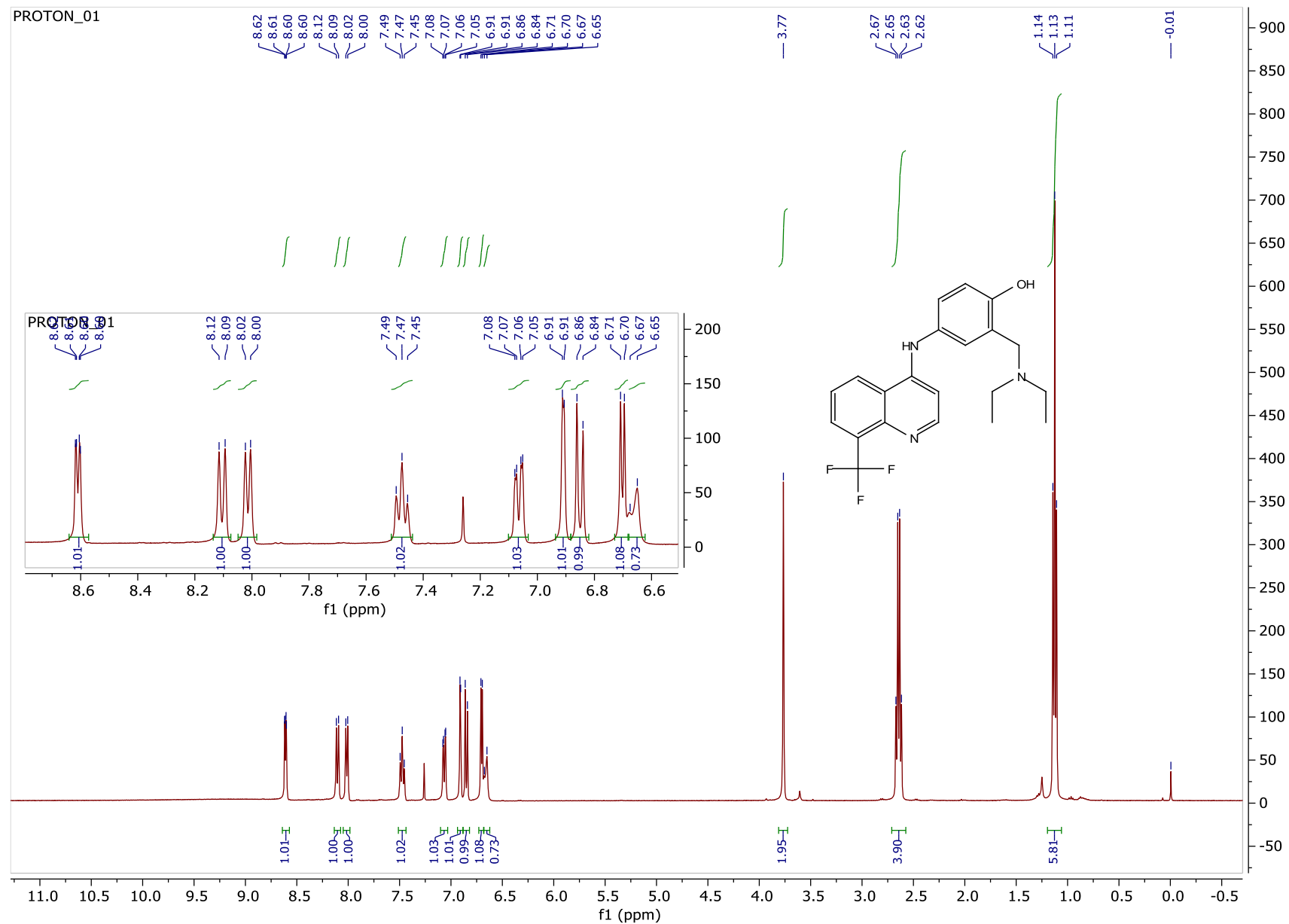
¹H NMR spectrum of 2-((diethylamino)methyl)-4-((6-(trifluoromethyl)quinolin-4-yl)amino)phenol (9)



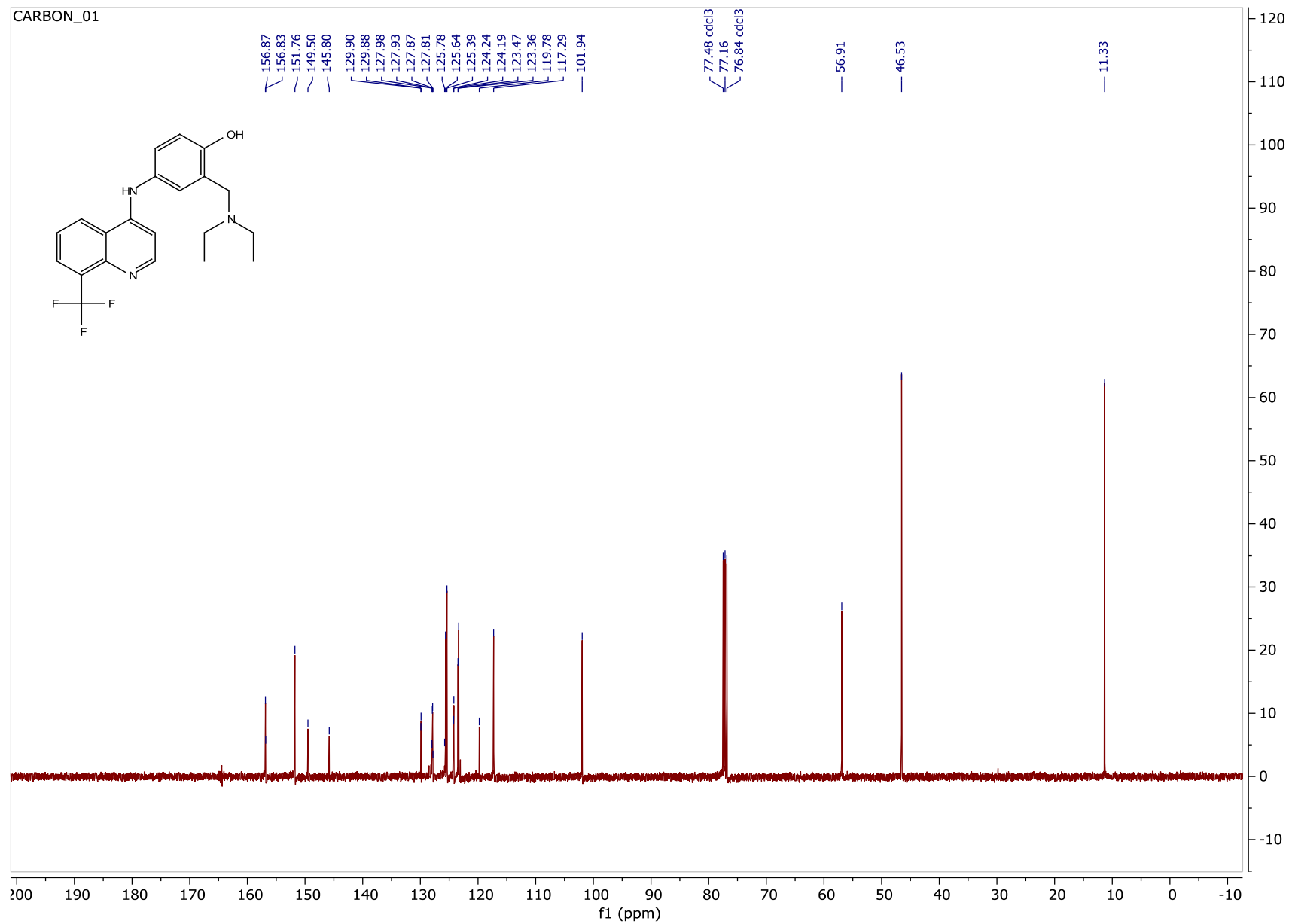
^{13}C NMR spectrum of 2-((diethylamino)methyl)-4-((6-(trifluoromethyl)quinolin-4-yl)amino)phenol (9)



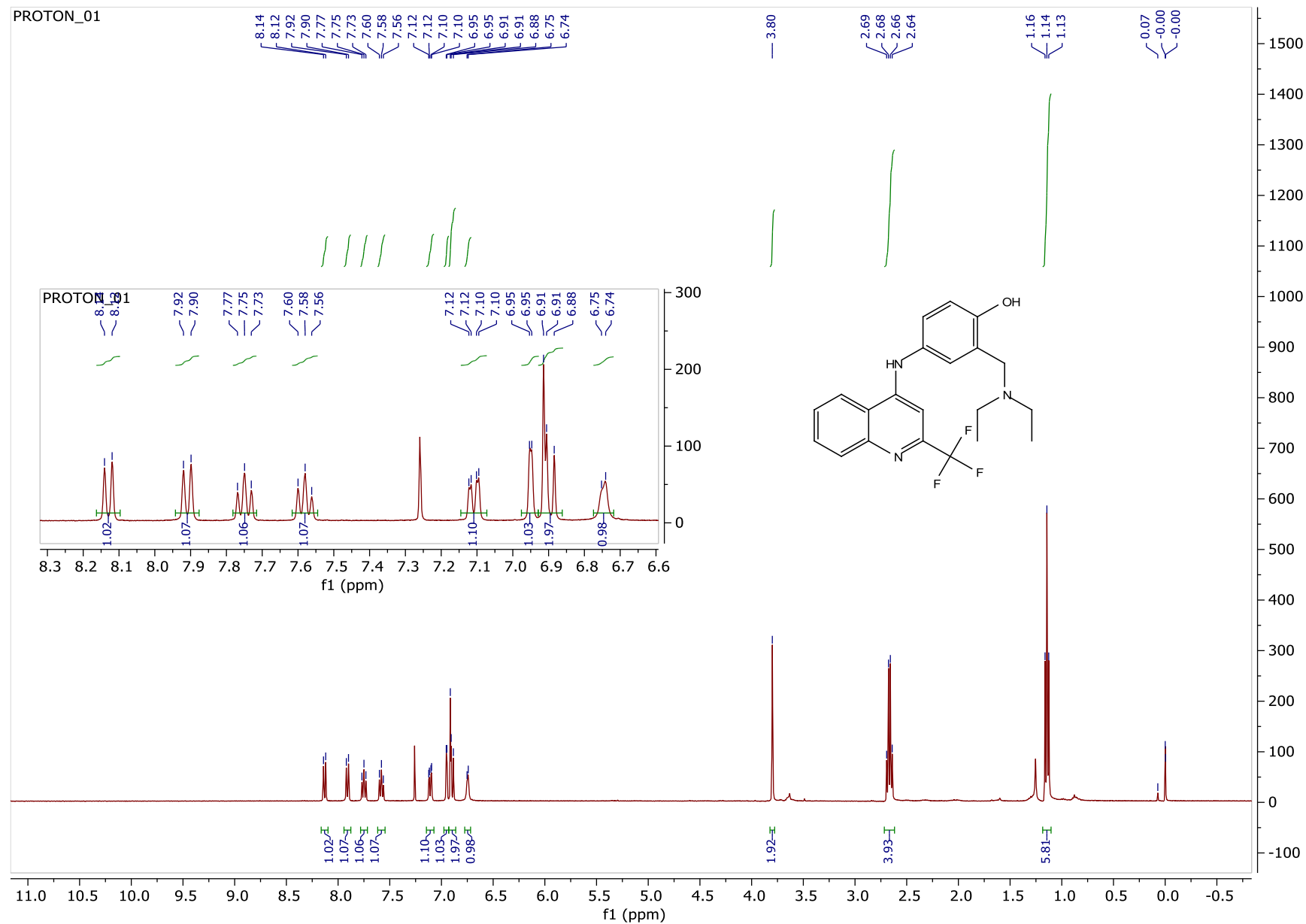
¹H NMR spectrum of 2-((diethylamino)methyl)-4-((8-(trifluoromethyl)quinolin-4-yl)amino)phenol (10)



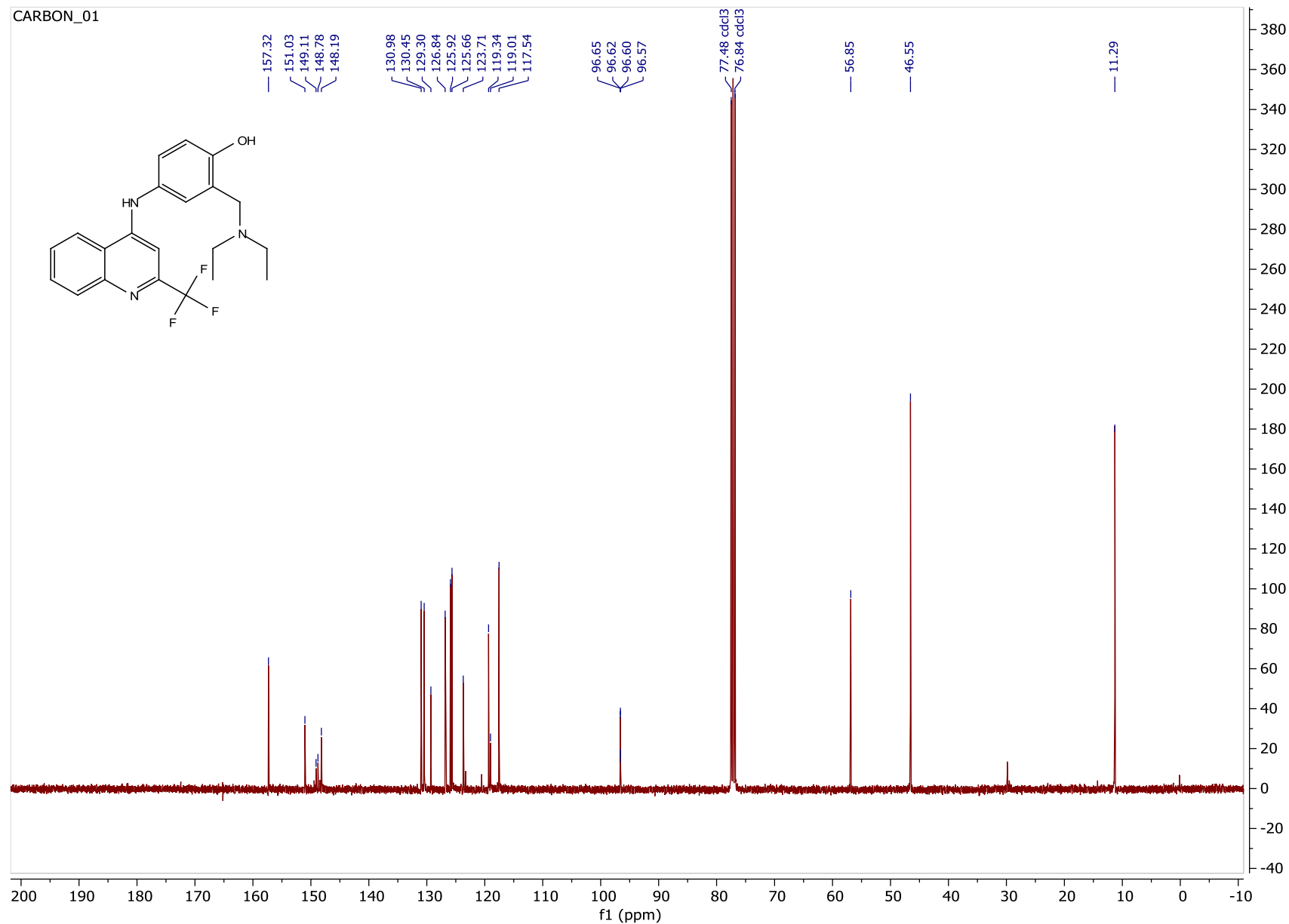
^{13}C NMR spectrum of 2-((diethylamino)methyl)-4-((8-(trifluoromethyl)quinolin-4-yl)amino)phenol (10)



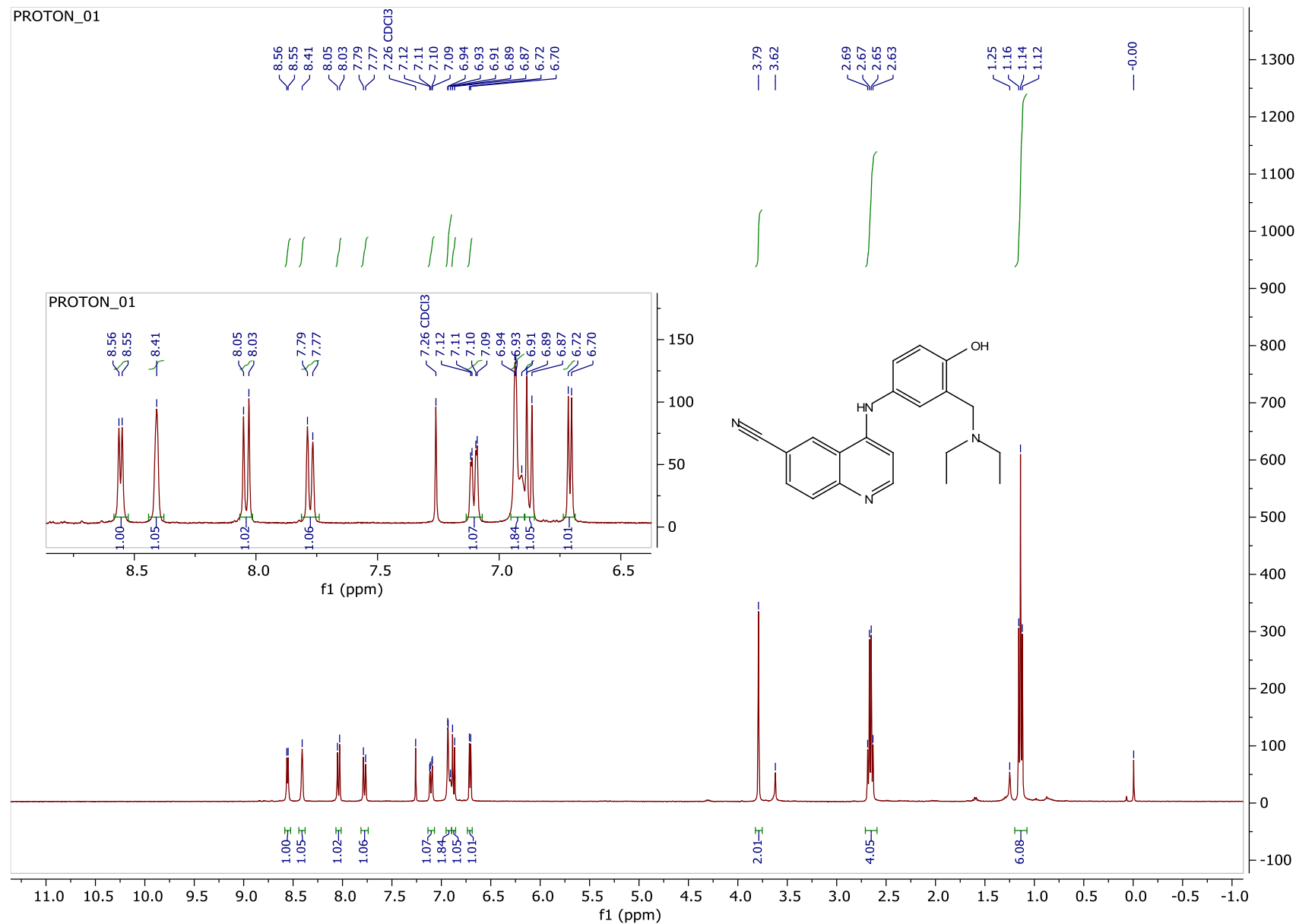
¹H NMR spectrum of 2-((diethylamino)methyl)-4-((2-(trifluoromethyl)quinolin-4-yl)amino)phenol (11)



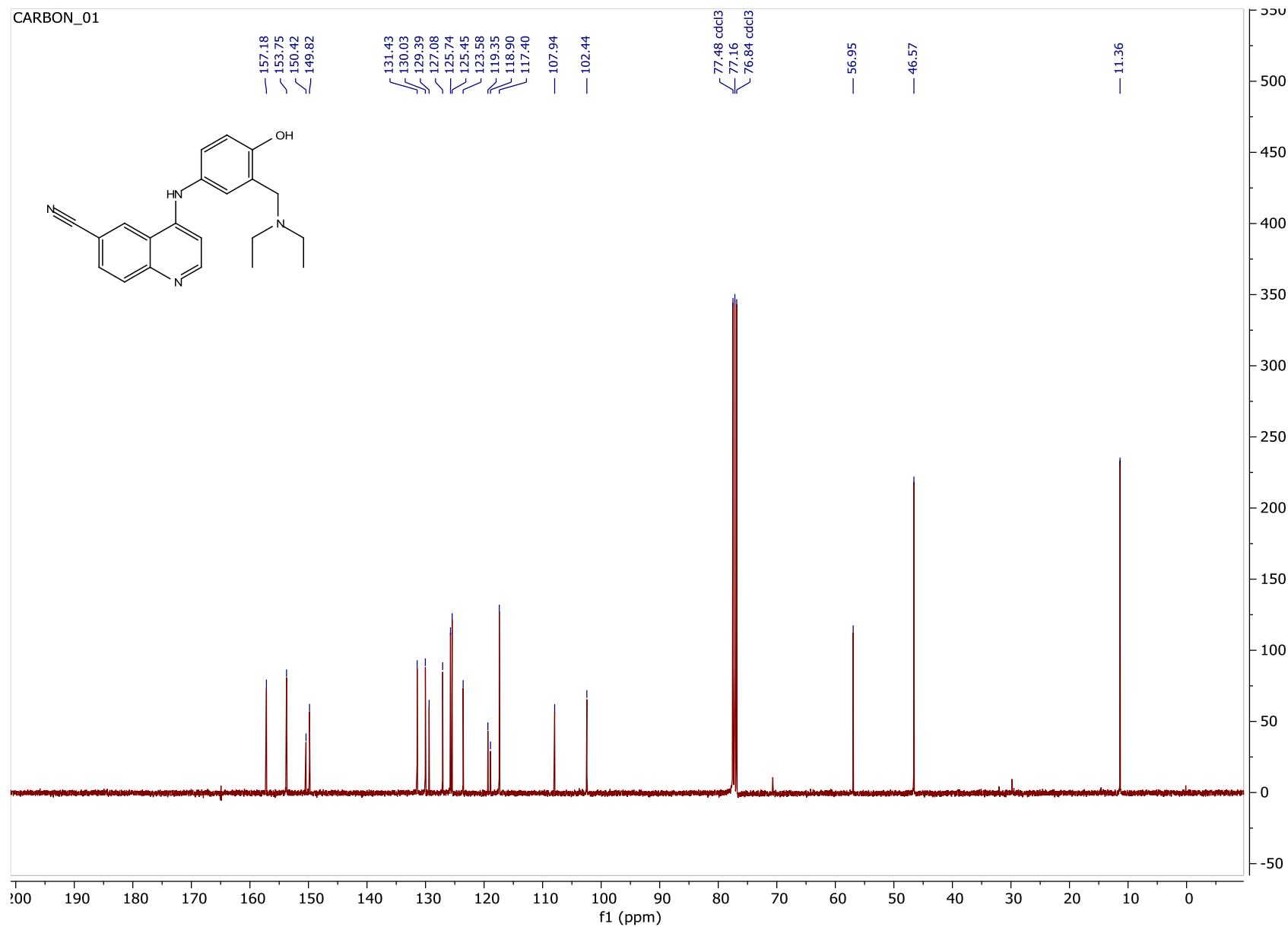
¹³C NMR spectrum of 2-((diethylamino)methyl)-4-((2-(trifluoromethyl)quinolin-4-yl)amino)phenol (11)



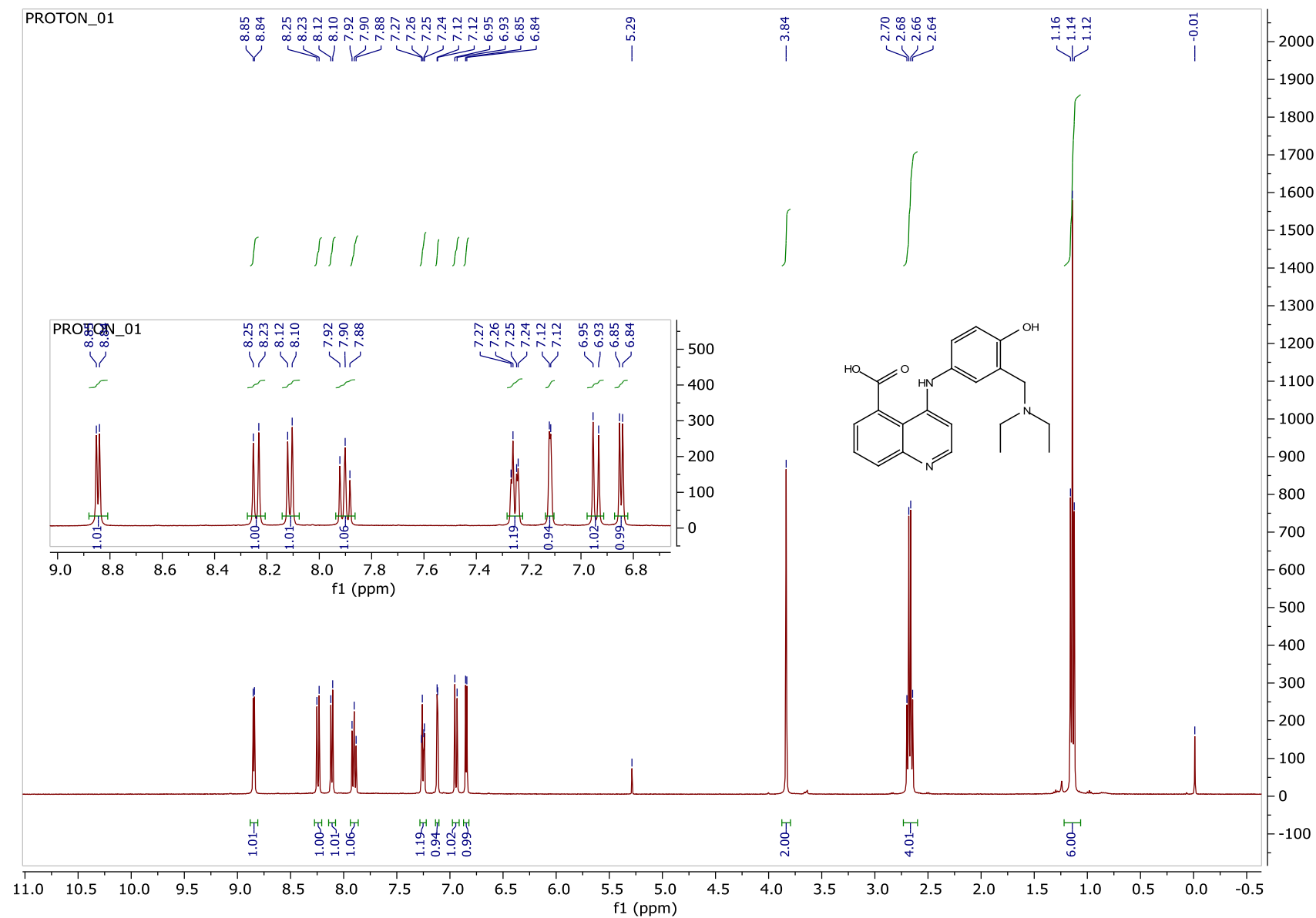
¹H NMR spectrum of 4-((3-((diethylamino)methyl)-4-hydroxyphenyl)amino)quinoline-6-carbonitrile (12)



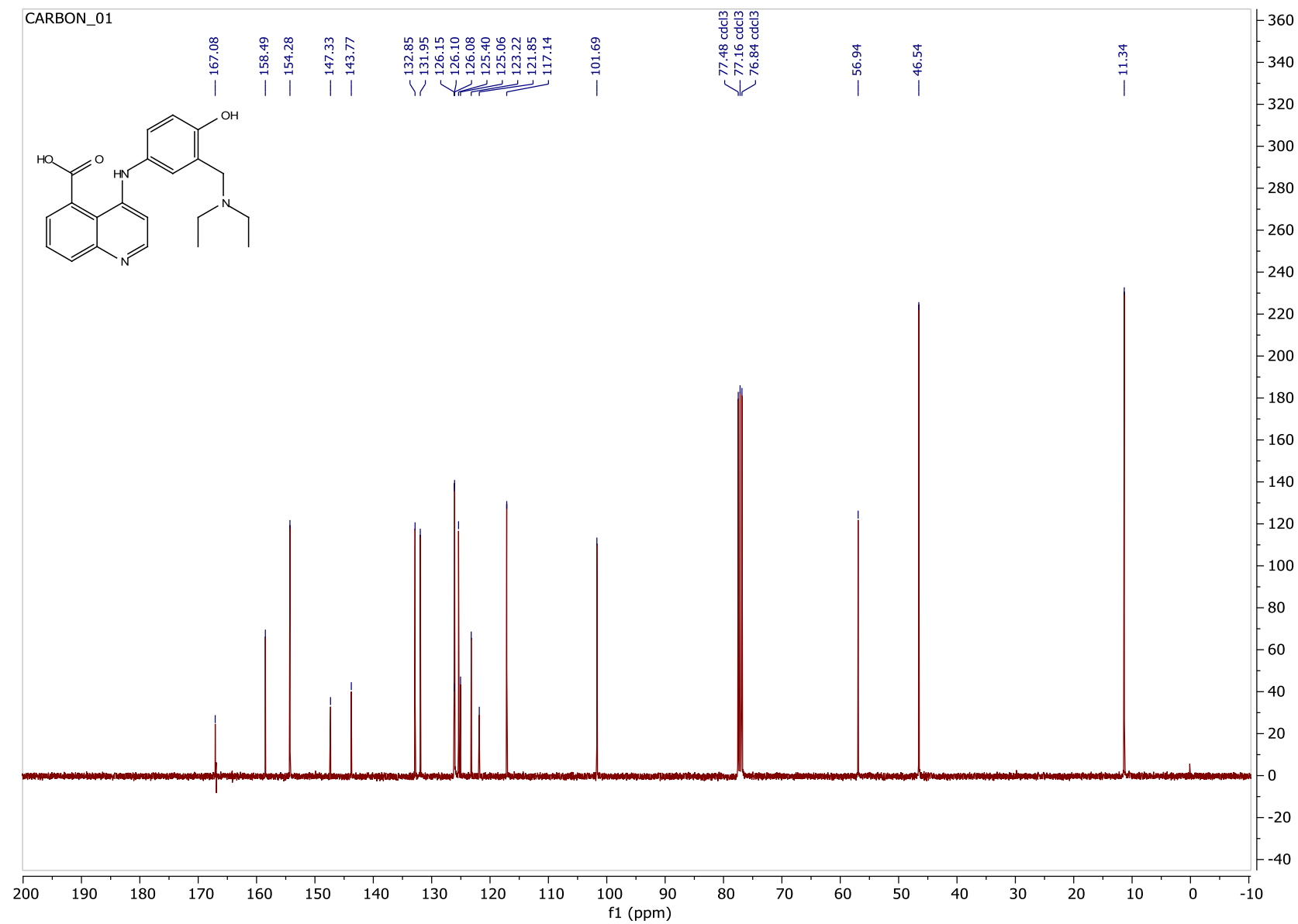
^{13}C NMR spectrum of 4-((3-((diethylamino)methyl)-4-hydroxyphenyl)amino)quinoline-6-carbonitrile (12)



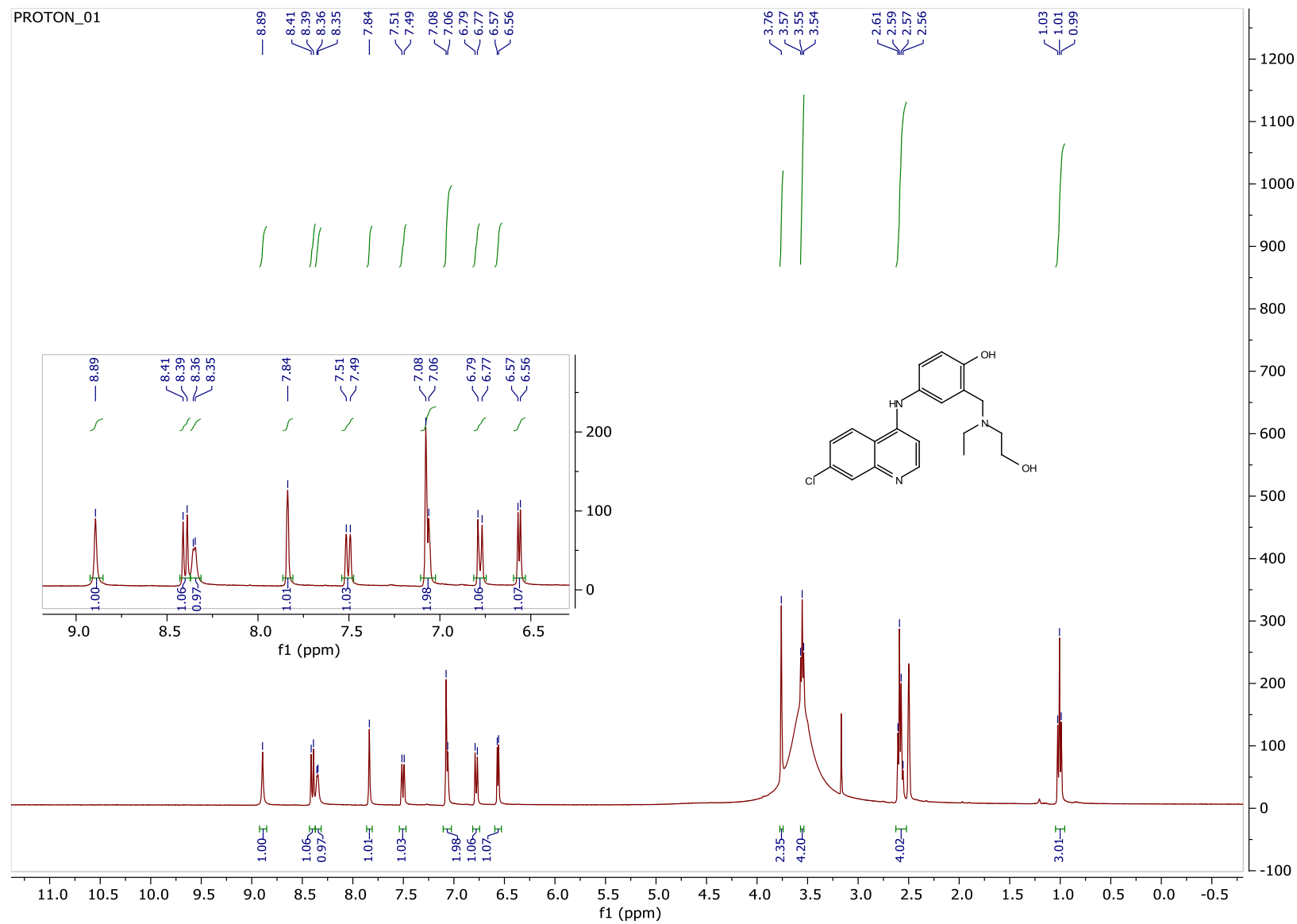
¹H NMR spectrum of 4-((3-((diethylamino)methyl)-4-hydroxyphenyl)amino)quinoline-5-carboxylic acid (13)



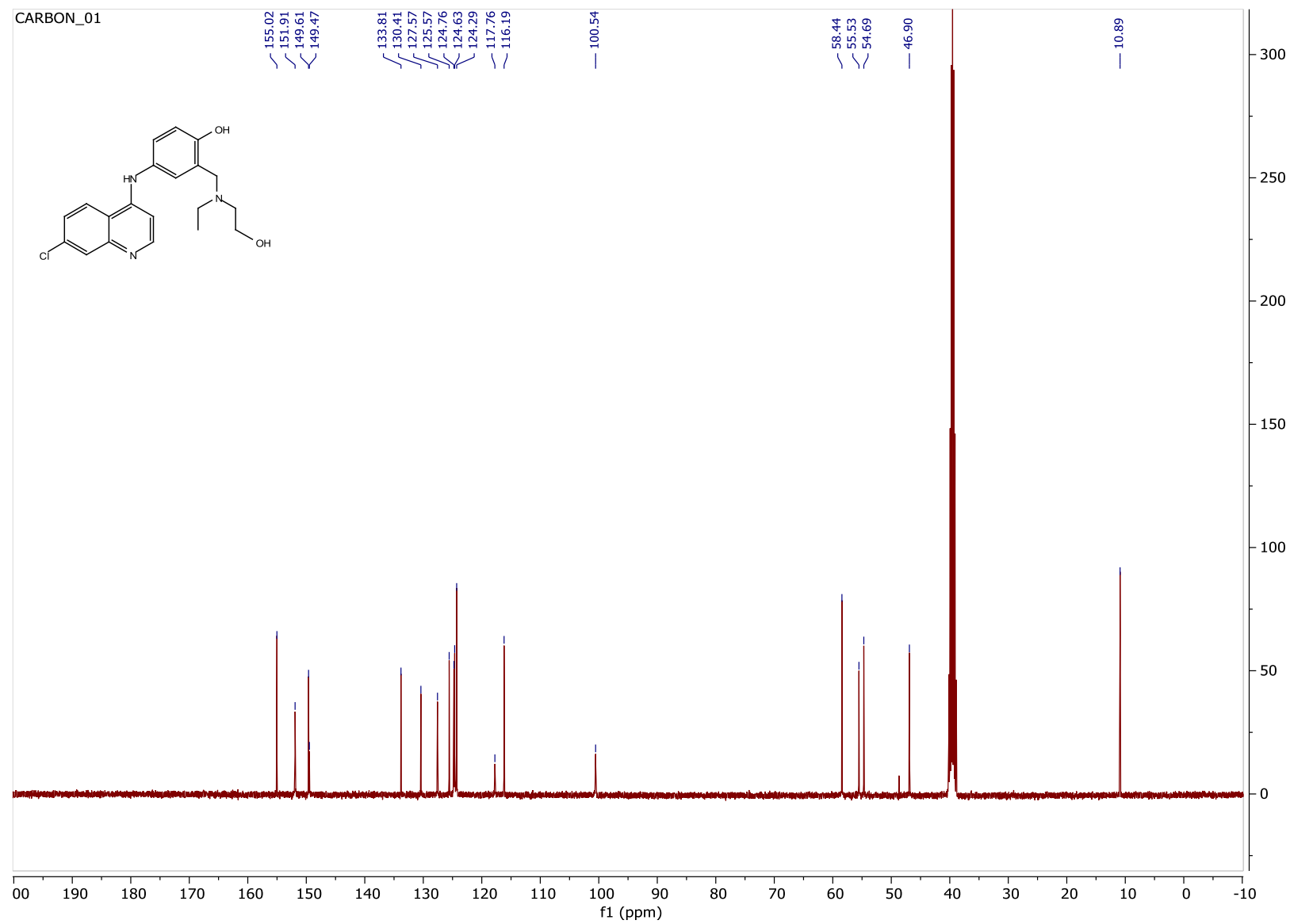
^{13}C NMR spectrum of 4-((3-((diethylamino)methyl)-4-hydroxyphenyl)amino)quinoline-5-carboxylic acid (13)



¹H NMR spectrum of 4-((7-chloroquinolin-4-yl)amino)-2-((ethyl(2-hydroxyethyl)amino)methyl)phenol (14)



^{13}C NMR spectrum of 4-((7-chloroquinolin-4-yl)amino)-2-((ethyl(2-hydroxyethyl)amino)methyl)phenol (14)

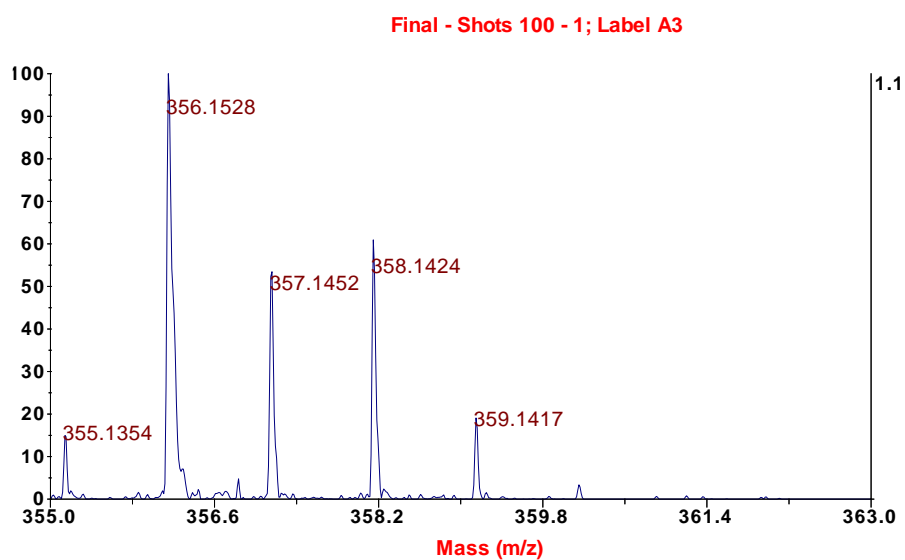
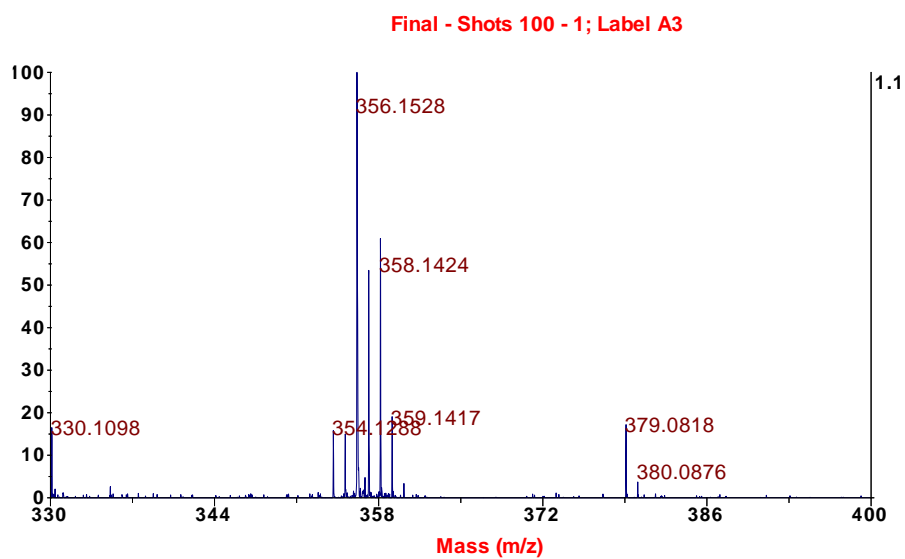


1.2.4. HRMS spectra of the tested compounds

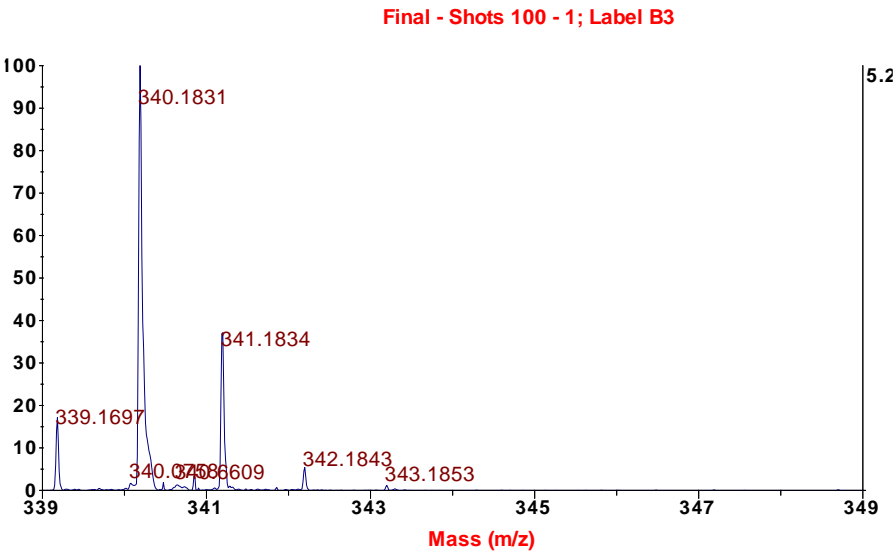
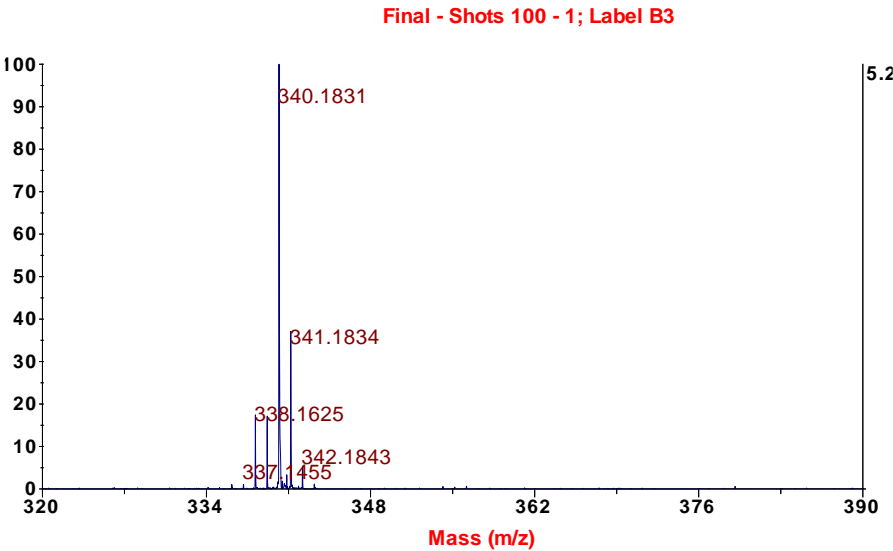
Mass spectra were recorded on a 4800 Plus MALDI TOF/TOF Analyzer (Applied Biosystems, US instrument, Mundelein, USA) in positive ion mode (fixed laser intensity 4280) using CH₃CN/H₂O gradient with 0.2% HCOOH as the carrying solvent solution. Samples were dissolved in MeOH (HPLC grade purity) mixed with CHCA (α -Cyano-4-hydroxycinnamic acid) MALDI matrix (5 mg/mL in 50% acetonitrile (v/v)). Internal calibrants: Azithromycin and Azithromycin fragments (m/z 156-749).

HRMS data for tested compounds AMQ and 1 -14.

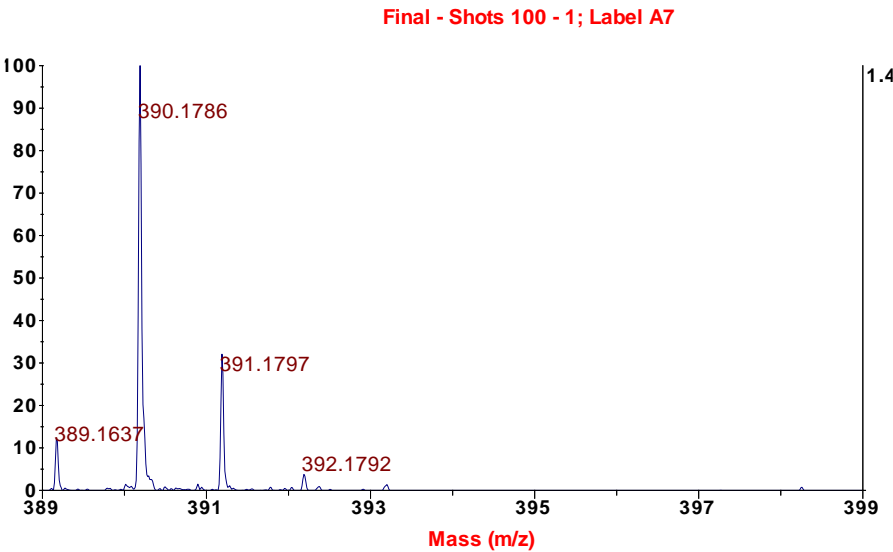
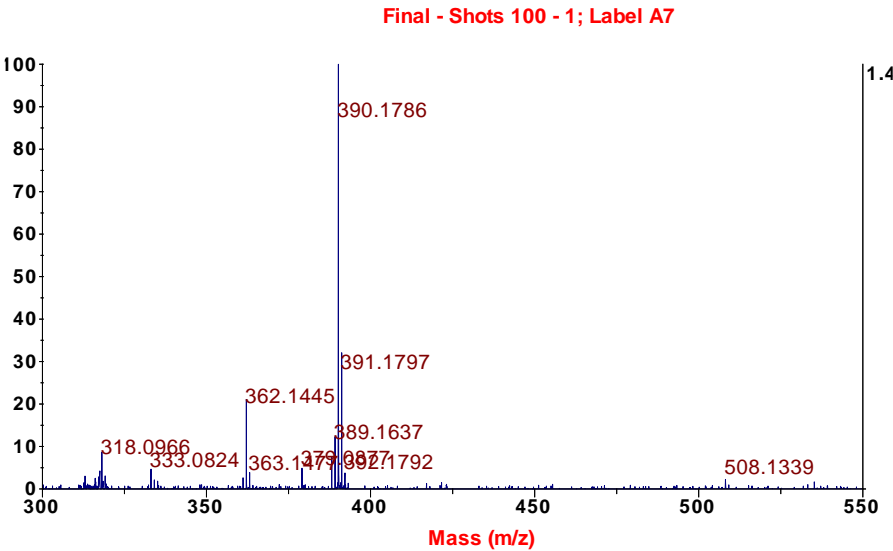
Specimen	Compound	Molecular formula	Ion	Calculated mass	Found mass	Error (ppm)
DO316	AMQ	C ₂₀ H ₂₂ ClN ₃ O	[M+H] ⁺	356.1530	356.1528	0.6
DO324	1	C ₂₀ H ₂₂ FN ₃ O	[M+H] ⁺	340.1825	340.1831	1.8
DO317	2	C ₂₁ H ₂₂ F ₃ N ₃ O	[M+H] ⁺	390.1793	390.1786	1.8
DO335	3	C ₂₁ H ₂₂ N ₄ O	[M+H] ⁺	347.1872	347.1871	0.3
AS36	4	C ₂₀ H ₂₂ N ₄ O ₃	[M+H] ⁺	367.1770	367.1784	3.8
KBK33	5	C ₂₁ H ₂₅ N ₃ O ₂	[M+H] ⁺	352.2025	352.2011	4.0
DB03	6	C ₂₀ H ₂₃ N ₃ O	[M+H] ⁺	322.1919	322.1923	1.2
DO323	7	C ₂₀ H ₂₂ FN ₃ O	[M+H] ⁺	340.1825	340.1823	0.6
DO334	8	C ₂₀ H ₂₂ FN ₃ O	[M+H] ⁺	340.1825	340.1828	0.9
DO320	9	C ₂₁ H ₂₂ F ₃ N ₃ O	[M+H] ⁺	390.1793	390.1798	1.3
DO321	10	C ₂₁ H ₂₂ F ₃ N ₃ O	[M+H] ⁺	390.1793	390.1797	1.0
DO322	11	C ₂₁ H ₂₂ F ₃ N ₃ O	[M+H] ⁺	390.1793	390.1797	1.0
DO325	12	C ₂₁ H ₂₂ N ₄ O	[M+H] ⁺	347.1872	347.1862	2.9
AS37	13	C ₂₁ H ₂₃ N ₃ O ₃	[M+H] ⁺	366.1818	366.1815	0.8
KBK32	14	C ₂₀ H ₂₂ ClN ₃ O ₂	[M+H] ⁺	372.1479	372.1486	1.9



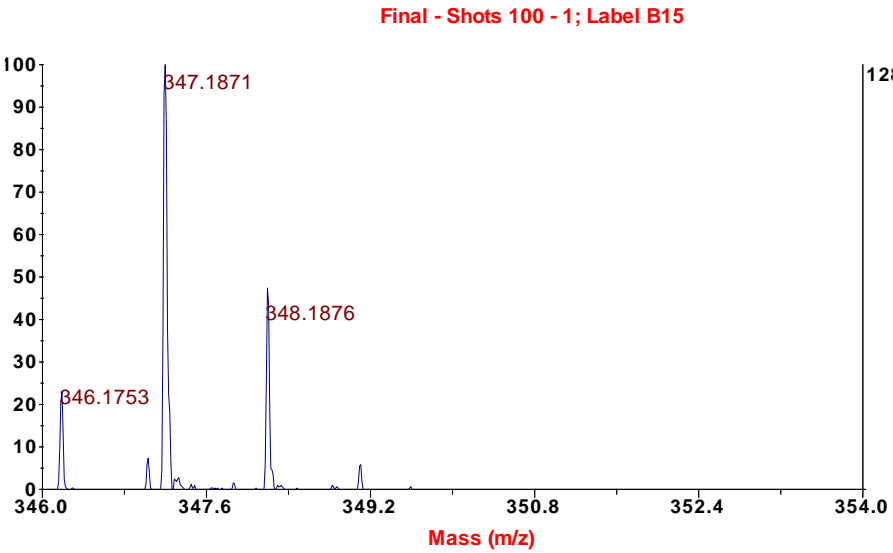
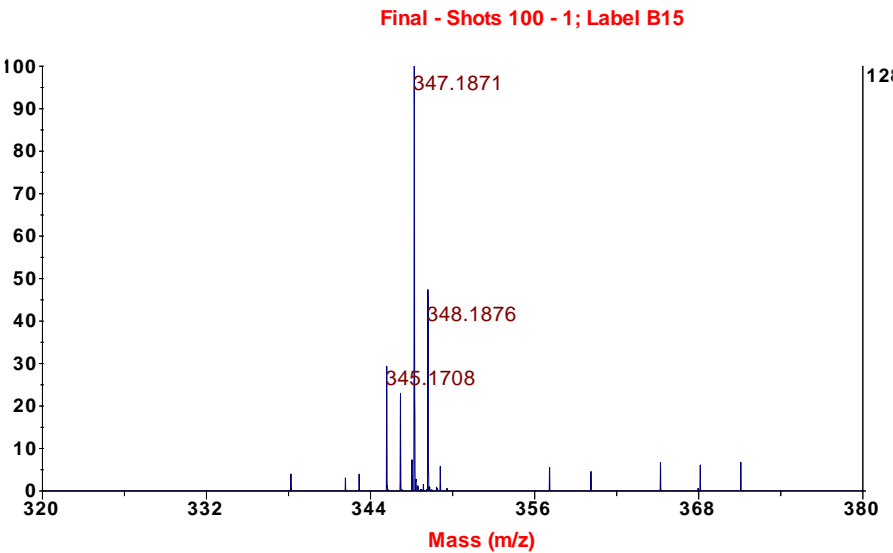
Compound 1



Compound 2

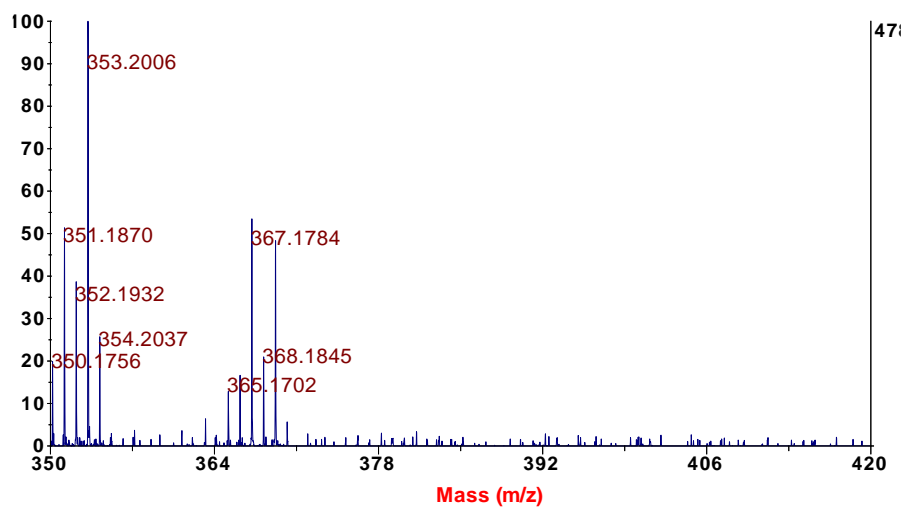


Compound 3

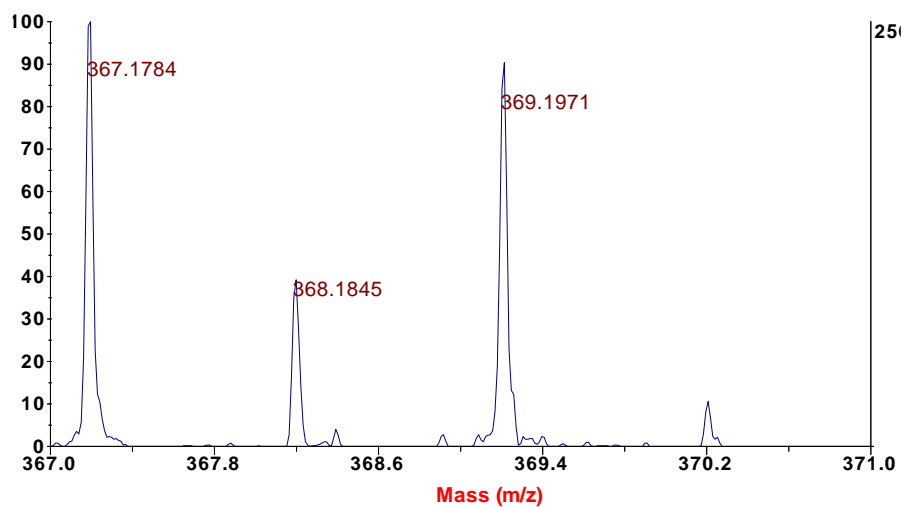


Compound 4

Final - Shots 100 - 1; Label B23

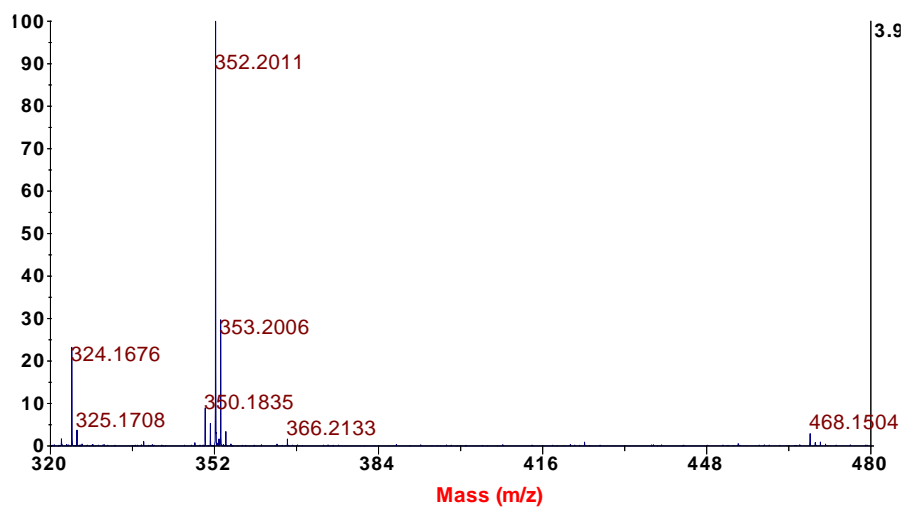


Final - Shots 100 - 1; Label B23

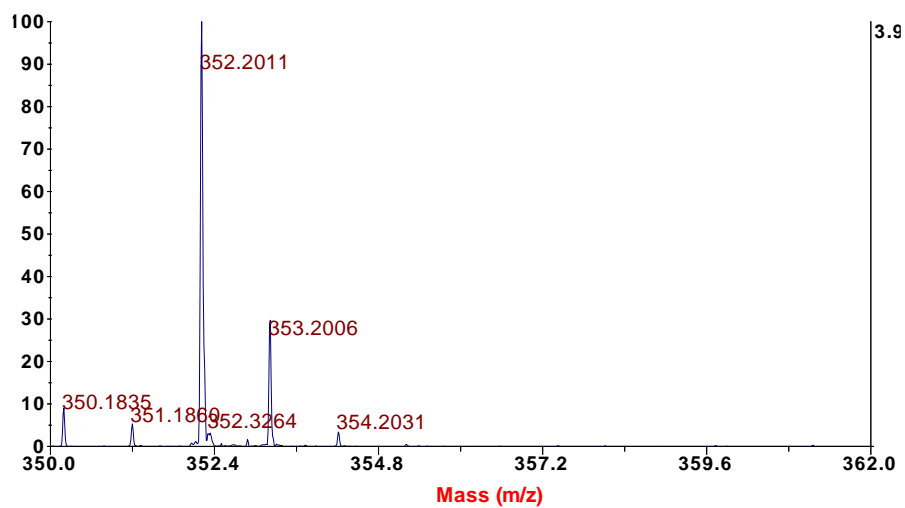


Compound 5

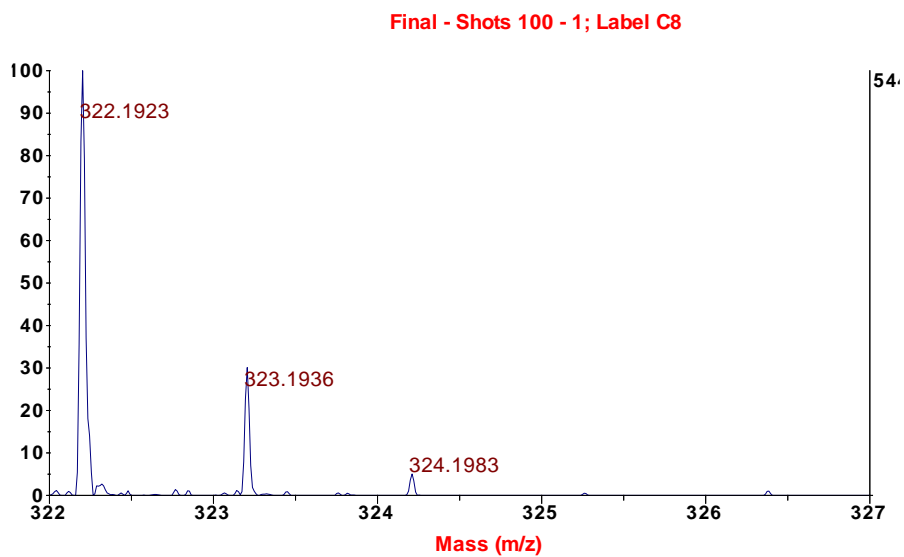
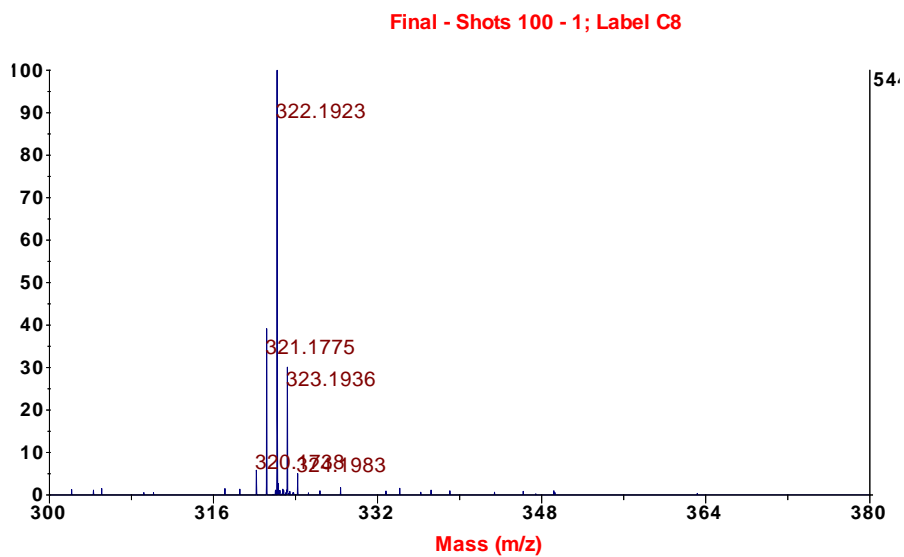
Final - Shots 100 - 1; Label C3



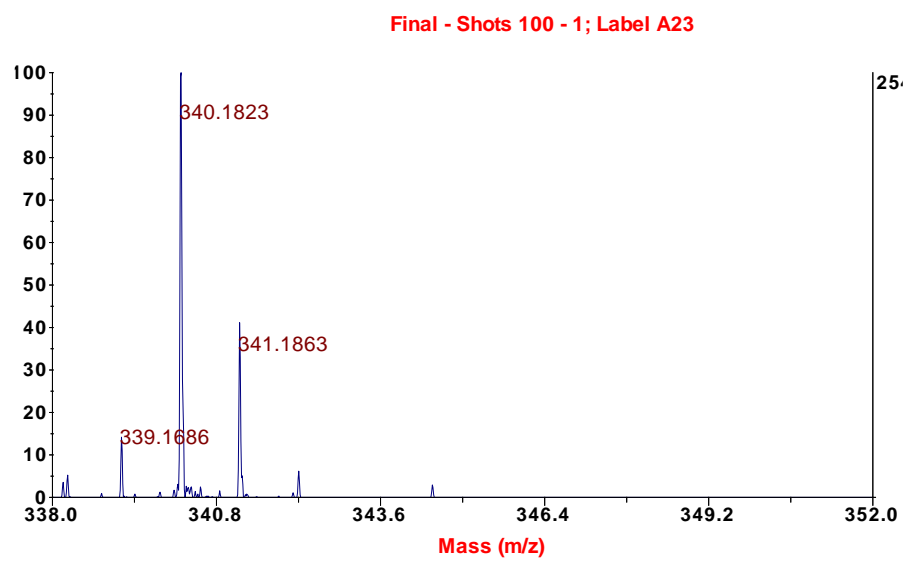
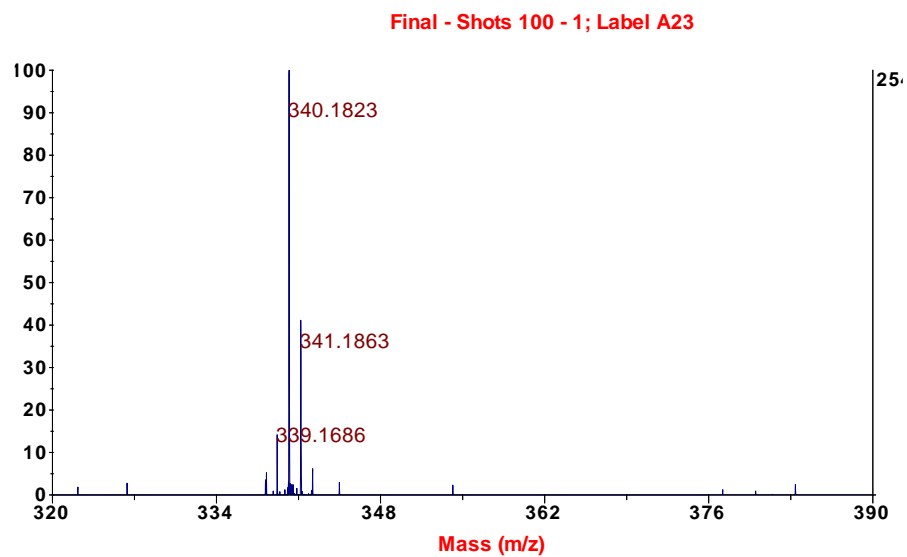
Final - Shots 100 - 1; Label C3



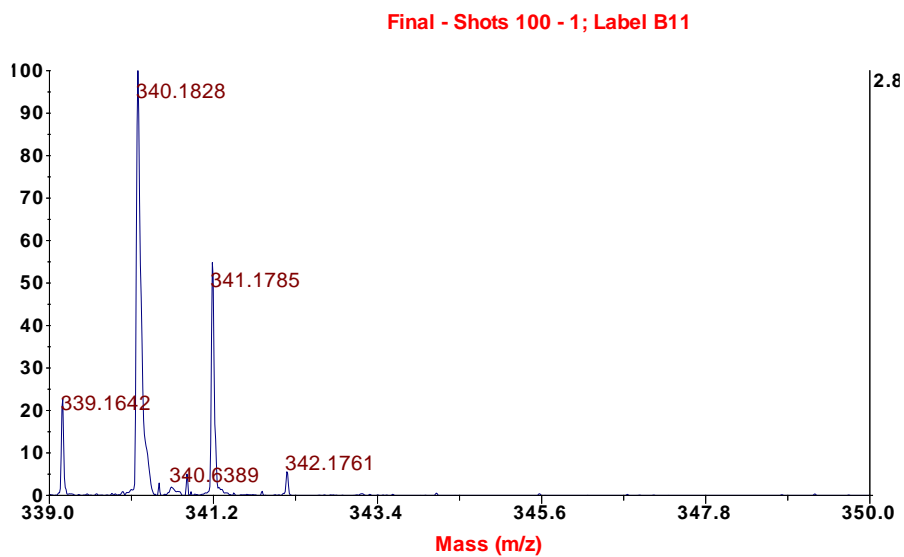
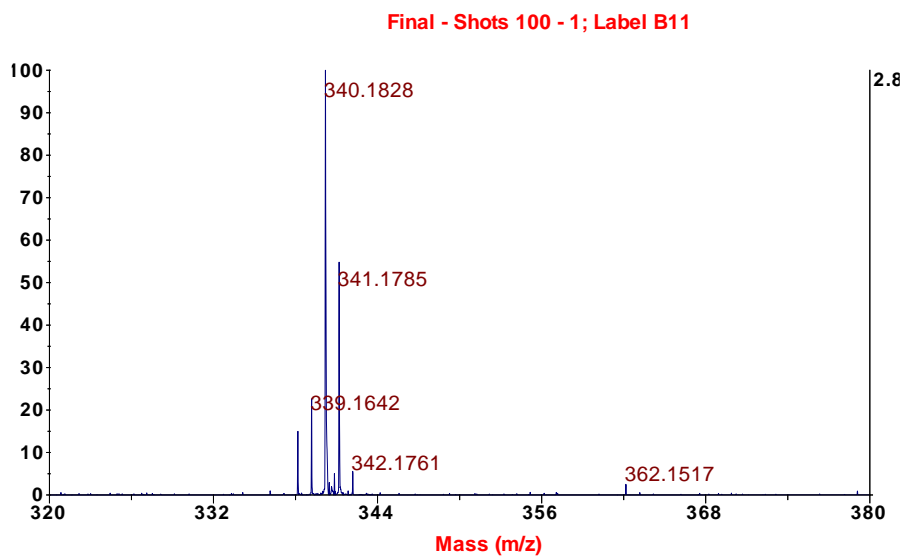
Compound 6



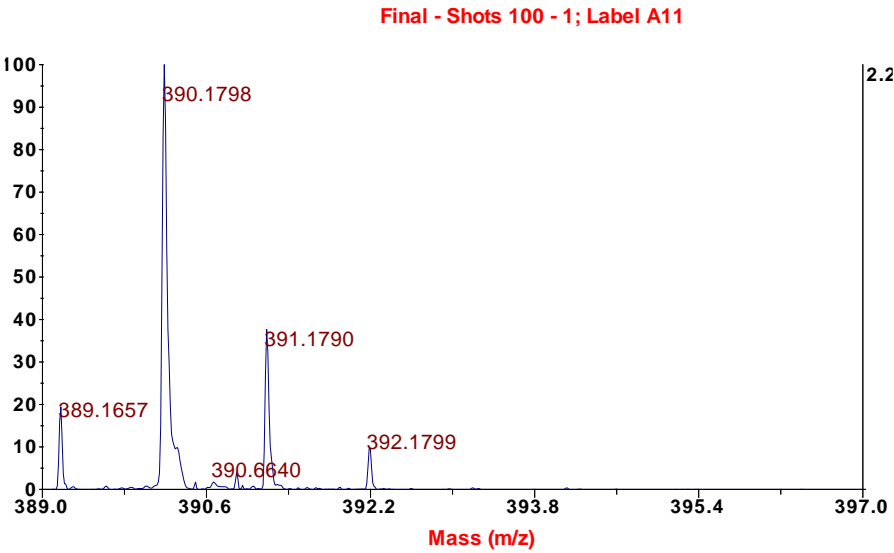
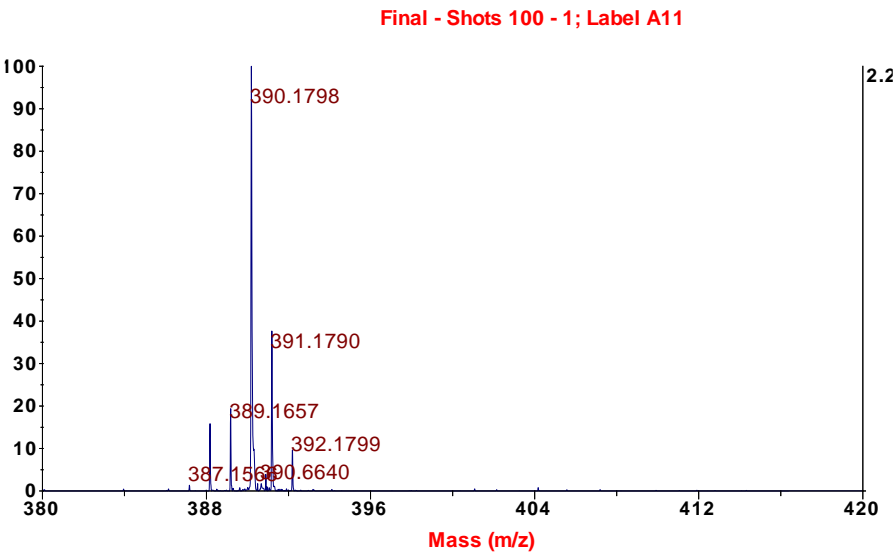
Compound 7



Compound 8

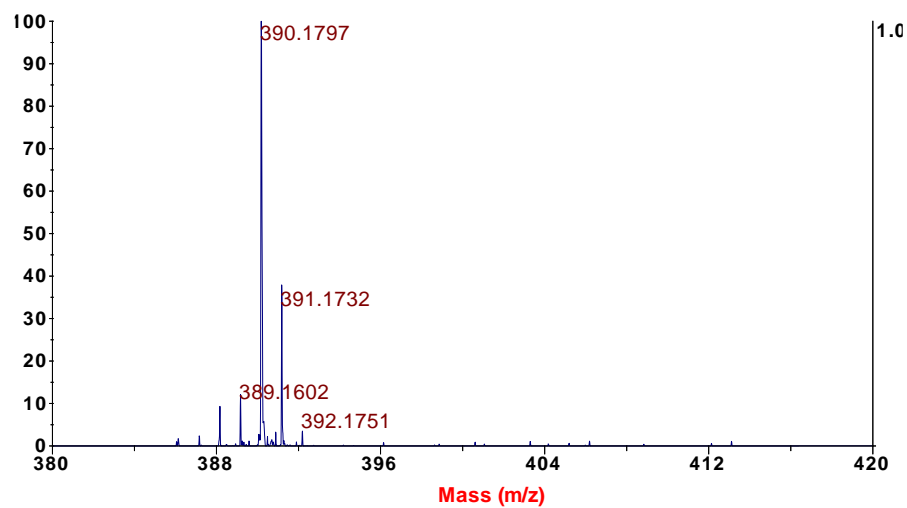


Compound 9

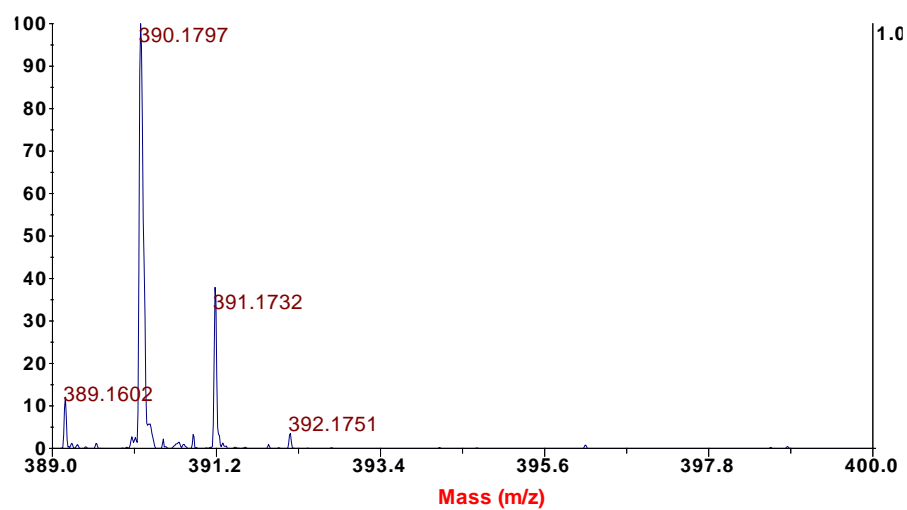


Compound 10

Final - Shots 100 - 1; Label A15

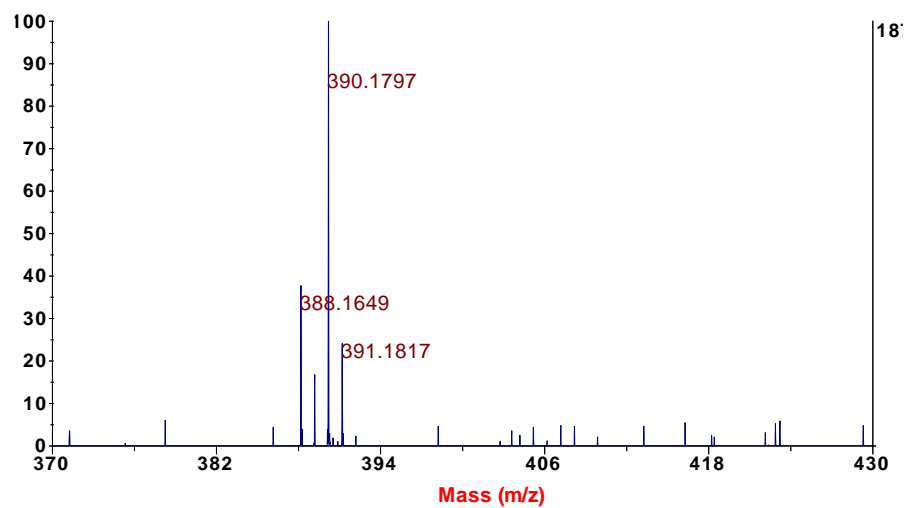


Final - Shots 100 - 1; Label A15

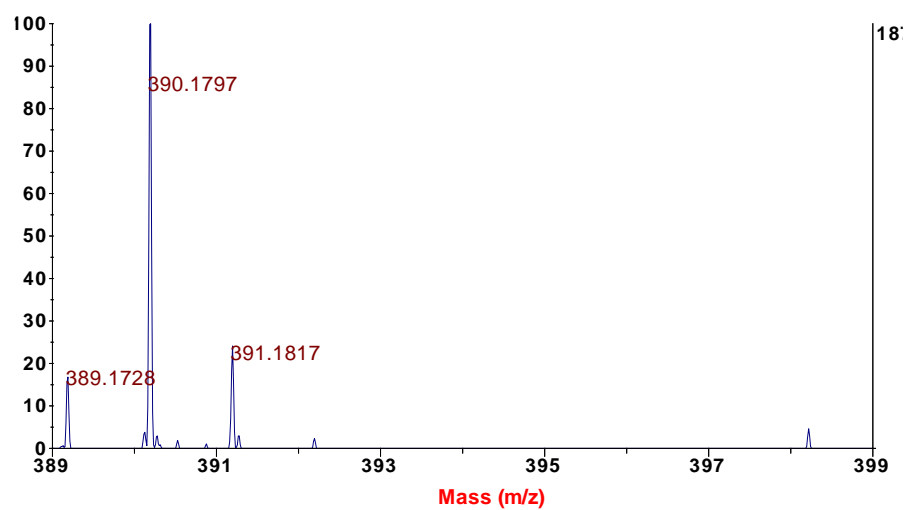


Compound 11

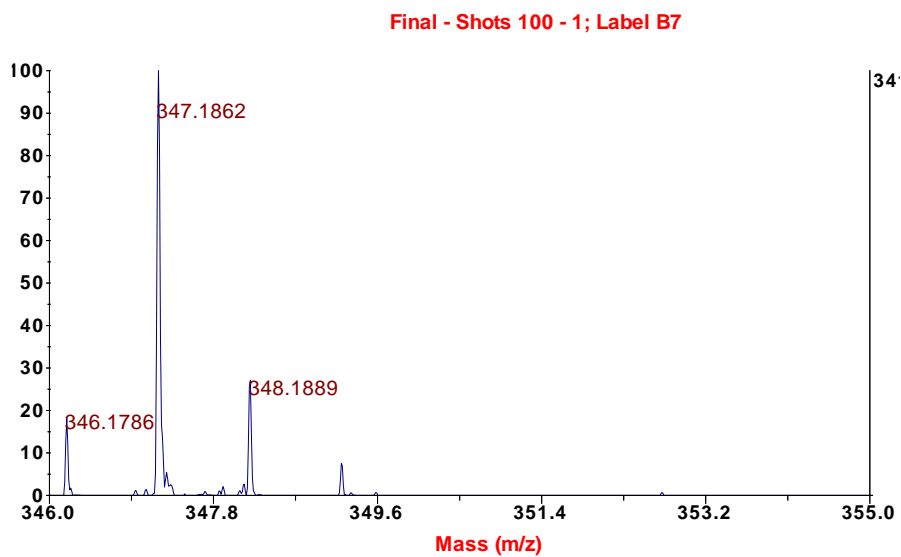
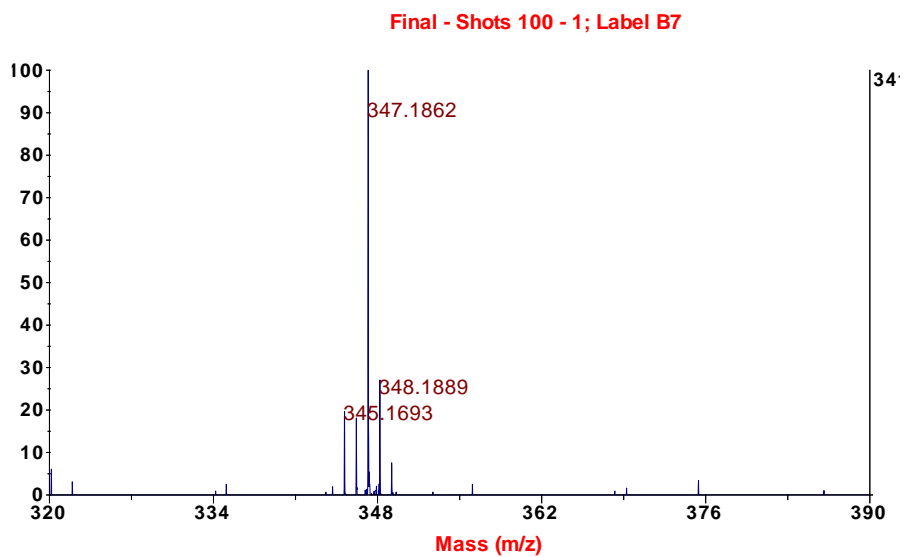
Final - Shots 100 - 1; Label A19



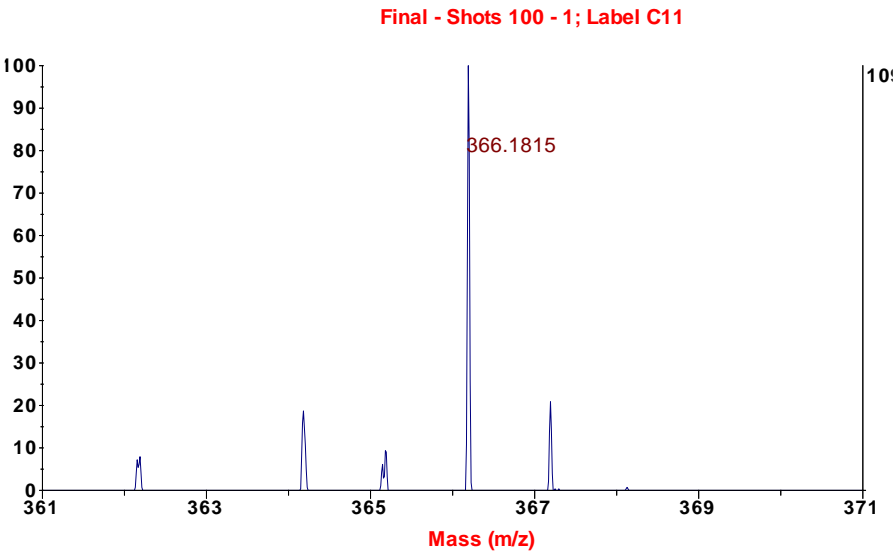
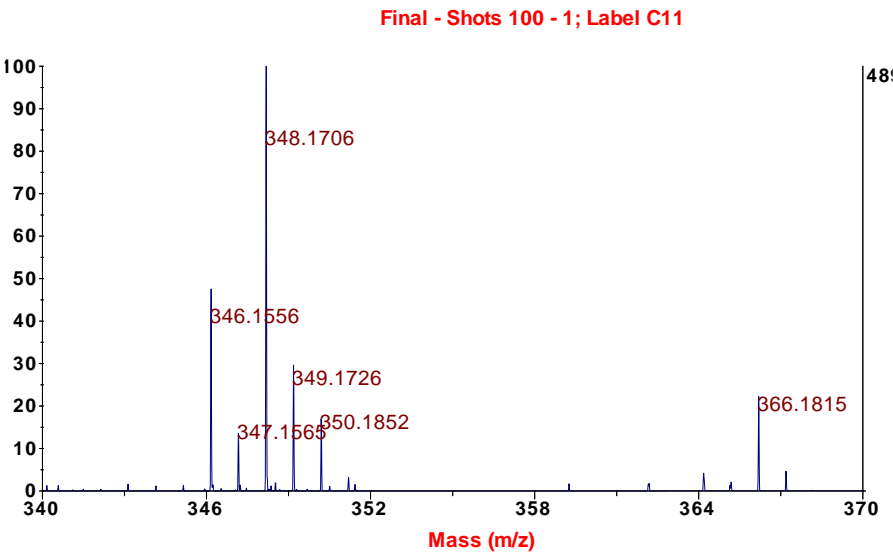
Final - Shots 100 - 1; Label A19



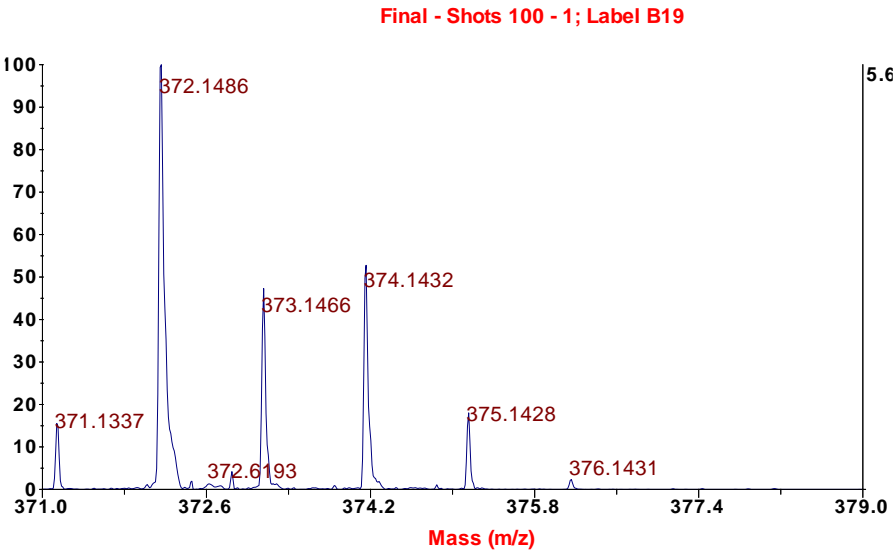
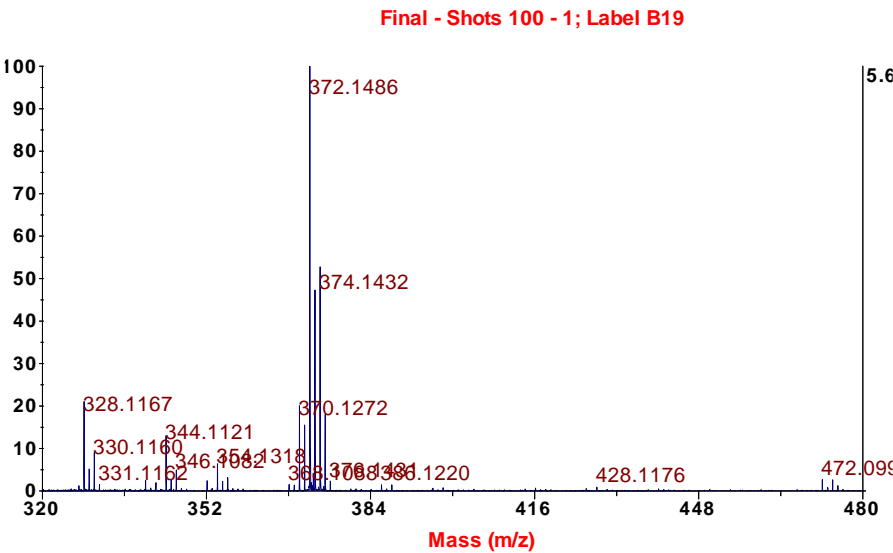
Compound 12



Compound 13



Compound 14



2. List of interactions between tested compounds and cholinesterases

2.1. List of interactions between derivatives **1** – **14** and AChE

Interactions between compound **AMQ** and AChE.

Amino acid	Non-bonding interactions
Glu202	H39, hydrogen bond; electrostatic-salt bridge; attractive charge
Ser203	O19, hydrogen bond-conventional hydrogen bond
Glu202	H40, hydrogen bond-carbon hydrogen bond
Tyr341	N7, electrostatic- π -cation
Trp86	N21, electrostatic- π -cation
Trp86	N21, electrostatic- π -cation
Asp74	AMQ , electrostatic- π -anion
Trp286	AMQ , hydrophobic- π - π stacked
Phe338	AMQ , hydrophobic- π - π stacked
Tyr341	AMQ , hydrophobic- π - π stacked
Trp286	AMQ , hydrophobic- π -alkyl
Trp286	AMQ , hydrophobic- π -alkyl

Interactions between compound **1** and AChE.

Amino acid	Non-bonding interactions
Glu202	N21, electrostatic-attractive charge
Ser203	O19, hydrogen bond-conventional hydrogen bond
Tyr341	N7, electrostatic- π -cation
Trp86	N21, electrostatic- π -cation
Trp86	N21, electrostatic- π -cation
Asp74	1 , electrostatic- π -anion
Trp86	H41, hydrophobic- π -sigma
Trp286	1 , hydrophobic- π - π stacked
Phe338	1 , hydrophobic- π - π stacked
Tyr341	1 , hydrophobic- π - π stacked
Tyr341	1 , hydrophobic- π - π stacked

Interactions between compound **2** and AChE.

Amino acid	Non-bonding interactions
HOH752	F14, hydrogen bond; halogen–water hydrogen bonds; conventional hydrogen bond; halogen (fluorine)
HOH772	F14, hydrogen bond; halogen–water hydrogen bonds; conventional hydrogen bond; halogen (fluorine)
HOH809	H41, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Ser203	H32, hydrogen bond-conventional hydrogen bond
Arg296	H48, hydrogen bond-carbon hydrogen bond
Gly120	F15, halogen-halogen (fluorine)
Gu202	F13, halogen-halogen (fluorine)
Gu202	F15, halogen-halogen (fluorine)
Tyr124	H42, hydrogen bond; electrostatic- π -cation; π -donor hydrogen bond
Tyr124	2 , other- π -lone pair
Trp86	2 , hydrophobic- π - π T-shaped
Trp86	2 , hydrophobic- π - π T-shaped
His447	2 , hydrophobic- π - π T-shaped
His447	2 , hydrophobic- π - π T-shaped
Trp286	C12, hydrophobic- π -alkyl
Trp286	C12, hydrophobic- π -alkyl

Interactions between compound **3** and AChE.

Amino acid	Non-bonding interactions
Glu202	H39, hydrogen bond; electrostatic-salt bridge; attractive charge
Gly121	O20, hydrogen bond-conventional hydrogen bond
Ser203	O20, hydrogen bond-conventional hydrogen bond

Ser203	O20, hydrogen bond-carbon hydrogen bond
Glu202	H40, hydrogen bond-carbon hydrogen bond
Glu202	H46, hydrogen bond-carbon hydrogen bond
Tyr341	N7, electrostatic- π -cation
Trp86	N22, electrostatic- π -cation
Trp86	N22, electrostatic- π -cation
Trp286	3 , hydrophobic- π - π stacked
Phe338	3 , hydrophobic- π - π stacked

Interactions between compound **4** and AChE.

Amino acid	Non-bonding interactions
HOH771	N7, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH883	N7, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Asp74	H33, hydrogen bond-conventional hydrogen bond
Tyr337	H40, hydrogen bond-conventional hydrogen bond
Tyr337	H38, hydrogen bond-carbon hydrogen bond
Trp86	N20, electrostatic- π -cation
Tyr72	N25, electrostatic- π -cation
Trp286	N25, electrostatic- π -cation
Trp286	N25, electrostatic- π -cation
Trp286	O27, electrostatic- π -anion
Tyr124	4 , other- π -lone pair
Trp286	4 , hydrophobic- π - π stacked
Tyr341	4 , hydrophobic- π - π stacked
Tyr124	4 , hydrophobic- π - π T-shaped

Interactions between compound **5** and AChE.

Amino acid	Non-bonding interactions
Asp74	H30, hydrogen bond; electrostatic-salt bridge; attractive charge
Glu202	N20, electrostatic-attractive charge
Gly121	O18, hydrogen bond-conventional hydrogen bond
Gly122	O18, hydrogen bond-conventional hydrogen bond
Ser203	O18, hydrogen bond-conventional hydrogen bond
Ser203	O18, hydrogen bond-carbon hydrogen bond
Asp74	H31, hydrogen bond-carbon hydrogen bond
Glu202	H45, hydrogen bond-carbon hydrogen bond
Glu202	H46, hydrogen bond-carbon hydrogen bond
Tyr341	N7, electrostatic- π -cation
Trp86	N20, electrostatic- π -cation
Tyr124	5 , other- π -lone pair
Trp286	C26, hydrophobic- π -alkyl

Interactions between compound **6** and AChE.

Amino acid	Non-bonding interactions
Asp74	H29, hydrogen bond; electrostatic-salt bridge; attractive charge
Glu202	N20, electrostatic-attractive charge
Gly121	O18, hydrogen bond-conventional hydrogen bond
His447	H36, hydrogen bond-conventional hydrogen bond
Asp74	H30, hydrogen bond-carbon hydrogen bond
Tyr341	N7, electrostatic- π -cation
Trp86	N20, electrostatic- π -cation
Trp86	N20, electrostatic- π -cation
Tyr124	6 , other- π -lone pair
Tyr124	6 , hydrophobic- π - π T-shaped

Interactions between compound **7** and AChE.

Amino acid	Non-bonding interactions
Asp74	H29, hydrogen bond; electrostatic-salt bridge; attractive charge
Glu202	N20, electrostatic-attractive charge

Gly121	O18, hydrogen bond-conventional hydrogen bond
Gly122	O18, hydrogen bond-conventional hydrogen bond
Ser203	H36, hydrogen bond-conventional hydrogen bond
Asp74	H30, hydrogen bond-carbon hydrogen bond
Glu202	H41, hydrogen bond-carbon hydrogen bond
Arg296	F25, halogen-halogen (fluorine)
Tyr341	N7, electrostatic- π -cation
Trp86	N20, electrostatic- π -cation
Trp86	N20, electrostatic- π -cation
Tyr124	7, other- π -lone pair
Tyr124	7, hydrophobic- π - π T-shaped
Phe338	7, hydrophobic- π - π T-shaped

Interactions between compound **8** and AChE.

Amino acid	Non-bonding interactions
Glu202	N20, electrostatic-attractive charge
HOH809	F25, hydrogen bond; halogen–water hydrogen bonds; conventional hydrogen bond; halogen (fluorine)
Trp86	N20, electrostatic- π -cation
Trp86	N20, electrostatic- π -cation
Trp86	H45, hydrophobic- π -sigma
Trp286	8, hydrophobic- π - π stacked
Phe338	8, hydrophobic- π - π stacked
Tyr341	8, hydrophobic- π - π stacked
Tyr341	8, hydrophobic- π - π stacked

Interactions between compound **9** and AChE.

Amino acid	Non-bonding interactions
Glu202	N20, electrostatic-attractive charge
HOH718	F26, hydrogen bond; halogen–water hydrogen bonds; conventional hydrogen bond; halogen (fluorine)
Gly121	O18, hydrogen bond-conventional hydrogen bond
Ser203	O18, hydrogen bond-conventional hydrogen bond
Trp286	F27, hydrogen bond-carbon hydrogen bond
Arg296	F28, halogen-halogen (fluorine)
Trp86	N20, electrostatic- π -cation
Trp86	N20, electrostatic- π -cation
Tyr341	H32, hydrogen bond; electrostatic- π -cation; π -donor hydrogen bond
Phe338	9, hydrophobic- π - π T-shaped
Tyr341	9, hydrophobic- π - π T-shaped
Tyr341	9, hydrophobic- π - π T-shaped
Tyr124	C25, hydrophobic- π -alkyl

Interactions between compound **10** and AChE.

Amino acid	Non-bonding interactions
Asp74	H35, hydrogen bond-conventional hydrogen bond
Trp286	N7, electrostatic- π -cation
Trp86	N20, electrostatic- π -cation
Tyr124	10, other- π -lone pair
Trp286	10, hydrophobic- π - π stacked
Trp286	10, hydrophobic- π - π stacked
Trp286	10, hydrophobic- π - π stacked
Trp286	10, hydrophobic- π - π stacked
Tyr341	10, hydrophobic- π - π stacked
Tyr124	10, hydrophobic- π - π T-shaped
Trp286	C25, hydrophobic- π -alkyl
Trp286	C25, hydrophobic- π -alkyl

Interactions between compound **11** and AChE.

Amino acid	Non-bonding interactions
Tyr337	O18, hydrogen bond-conventional hydrogen bond
Tyr124	H40, hydrogen bond-conventional hydrogen bond
Glu285	F27, halogen-halogen (fluorine)
Glu285	F28, halogen-halogen (fluorine)
Tyr341	O18, electrostatic- π -anion
Tyr124	11 , other- π -lone pair
Tyr72	11 , hydrophobic- π - π stacked
Tyr72	11 , hydrophobic- π - π stacked
Trp286	11 , hydrophobic- π - π stacked
Tyr72	C25, hydrophobic- π -alkyl
Tyr124	C25, hydrophobic- π -alkyl

Interactions between compound **12** and AChE.

Amino acid	Non-bonding interactions
Glu202	N20, electrostatic-attractive charge
Glu202	H40, hydrogen bond-conventional hydrogen bond
Glu202	H47, hydrogen bond-carbon hydrogen bond
Tyr341	N7, electrostatic- π -cation
Trp86	N20, electrostatic- π -cation
Tyr124	12 , hydrogen bond- π -donor hydrogen bond
Trp286	12 , hydrophobic- π - π stacked
Tyr341	12 , hydrophobic- π - π stacked
Tyr124	12 , hydrophobic- π - π T-shaped

Interactions between compound **13** and AChE.

Amino acid	Non-bonding interactions
Asp74	N7, electrostatic-attractive charge
HOH809	O26, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH883	O27, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH809	H34, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Tyr337	O18, hydrogen bond-conventional hydrogen bond
Tyr124	H40, hydrogen bond-conventional hydrogen bond
Trp286	N7, electrostatic- π -cation
Trp286	N7, electrostatic- π -cation
Asp74	13 , electrostatic- π -anion
Tyr124	13 , other- π -lone pair
Trp286	13 , hydrophobic- π - π stacked
Trp286	13 , hydrophobic- π - π stacked
Trp286	13 , hydrophobic- π - π stacked
Trp286	13 , hydrophobic- π - π stacked
Tyr72	13 , hydrophobic- π - π T-shaped
Tyr124	13 , hydrophobic- π - π T-shaped

Interactions between compound **14** and AChE.

Amino acid	Non-bonding interactions
Asp74	N21, electrostatic-attractive charge
HOH809	H39, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Tyr124	O19, hydrogen bond-conventional hydrogen bond
Asp74	H37, hydrogen bond-conventional hydrogen bond
Phe338	O26, hydrogen bond-carbon hydrogen bond
Tyr124	H38, hydrogen bond-carbon hydrogen bond
Tyr124	H41, hydrogen bond-carbon hydrogen bond
Tyr337	H47, hydrogen bond-carbon hydrogen bond
Tyr341	H50, hydrogen bond- π -donor hydrogen bond
Tyr72	14 , hydrophobic- π - π stacked
Trp286	14 , hydrophobic- π - π stacked
Trp286	14 , hydrophobic- π - π stacked
Trp286	14 , hydrophobic- π - π T-shaped

2.2. List of interactions between derivatives **1** – **14** and BChE

Interactions between compound **AMQ** and BChE.

Amino acid	Non-bonding interactions
Glu197	N21, electrostatic-attractive charge
HOH825	H36, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Ser287	H29, hydrogen bond-conventional hydrogen bond
Ser287	H30, hydrogen bond-carbon hydrogen bond
Trp82	N21, electrostatic- π -cation
Trp82	H39, hydrogen bond; electrostatic- π -cation; π -donor hydrogen bond
Phe329	AMQ , hydrophobic- π - π T-shaped
Gly116;Gly117	AMQ , hydrophobic-amide- π stacked
Leu286	C112, hydrophobic-alkyl
Trp231	C112, hydrophobic- π -alkyl
Trp231	C112, hydrophobic- π -alkyl
Phe398	C112, hydrophobic- π -alkyl
Leu286	AMQ , hydrophobic- π -alkyl

Interactions between compound **1** and BChE.

Amino acid	Non-bonding interactions
Glu197	N21, electrostatic-attractive charge
HOH786	O19, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH825	H36, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Ser287	H29, hydrogen bond-conventional hydrogen bond
Gln119	H29, hydrogen bond-conventional hydrogen bond
Ser287	H30, hydrogen bond-carbon hydrogen bond
Trp82	N21, electrostatic- π -cation
Trp82	N21, electrostatic- π -cation
Trp231	1 , hydrophobic- π - π T-shaped
Phe329	1 , hydrophobic- π - π T-shaped
Leu286	1 , hydrophobic- π -alkyl

Interactions between compound **2** and BChE.

Amino acid	Non-bonding interactions
HOH706	H43, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Ser287	H39, hydrogen bond-conventional hydrogen bond
Gly117	O22, hydrogen bond-conventional hydrogen bond
Phe329	N7, electrostatic- π -cation
Trp231	N24, electrostatic- π -cation
Trp231	N24, electrostatic- π -cation
Phe329	2 , hydrophobic- π - π stacked
Trp82	C12, hydrophobic- π -alkyl
Trp82	C12, hydrophobic- π -alkyl
Ala328	2 , hydrophobic- π -alkyl

Interactions between compound **3** and BChE.

Amino acid	Non-bonding interactions
Glu197	N22, electrostatic-attractive charge
HOH786	O20, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH831	O20, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Ser287	H30, hydrogen bond-conventional hydrogen bond
Trp82	N22, electrostatic- π -cation
Trp82	N22, electrostatic- π -cation
Phe329	3 , hydrophobic- π - π stacked
Phe329	3 , hydrophobic- π - π T-shaped

Interactions between compound **4** and BChE.

Amino acid	Non-bonding interactions
Asp70	N20, electrostatic-attractive charge
HOH825	H38, hydrogen bond-water hydrogen bond; carbon hydrogen bond

HOH825	H40, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Gln119	O26, hydrogen bond-conventional hydrogen bond
His438	H33, hydrogen bond-conventional hydrogen bond
Tyr332	N20, electrostatic- π -cation
Trp82	H37, hydrogen bond- π -donor hydrogen bond
Trp82	4 , hydrophobic- π - π T-shaped
Trp82	4 , hydrophobic- π - π T-shaped
Trp231	4 , hydrophobic- π - π T-shaped
Trp231	4 , hydrophobic- π - π T-shaped
Phe329	4 , hydrophobic- π - π T-shaped
Phe329	4 , hydrophobic- π - π T-shaped
Gly116;Gly117	4 , hydrophobic-amide- π stacked
Gly116;Gly117	4 , hydrophobic-amide- π stacked
Leu286	4 , hydrophobic- π -alkyl

Interactions between compound **5** and BChE.

Amino acid	Non-bonding interactions
Glu197	N20, electrostatic-attractive charge
HOH786	O18, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH831	O18, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Ser287	H30, hydrogen bond-conventional hydrogen bond
Trp82	N20, electrostatic- π -cation
Trp82	N20, electrostatic- π -cation
Phe329	5 , hydrophobic- π - π T-shaped
Leu286	C26, hydrophobic-alkyl
Trp231	C26, hydrophobic- π -alkyl
Trp231	C26, hydrophobic- π -alkyl
Phe398	C26, hydrophobic- π -alkyl

Interactions between compound **6** and BChE.

Amino acid	Non-bonding interactions
HOH825	H39, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Gln119	H29, hydrogen bond-conventional hydrogen bond
Ser198	H32, hydrogen bond-conventional hydrogen bond
His438	H32, hydrogen bond-conventional hydrogen bond
Gln119	H30, hydrogen bond-carbon hydrogen bond
Trp82	O18, hydrogen bond-carbon hydrogen bond
Trp82	6 hydrophobic- π - π T-shaped
Trp82	6 , hydrophobic- π - π T-shaped
Trp231	6 , hydrophobic- π - π T-shaped
Trp231	6 , hydrophobic- π - π T-shaped
Phe329	6 , hydrophobic- π - π T-shaped
His438	6 , hydrophobic- π - π T-shaped
Gly116;Gly117	6 , hydrophobic-amide- π stacked
Leu286	6 , hydrophobic- π -alkyl

Interactions between compound **7** and BChE.

Amino acid	Non-bonding interactions
Glu197	N20, electrostatic-attractive charge
HOH786	O18, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH825	H36, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Ser287	H29, hydrogen bond-conventional hydrogen bond
Ser198	F25, hydrogen bond-carbon hydrogen bond
Ser287	H30, hydrogen bond-carbon hydrogen bond
Trp82	N20, electrostatic- π -cation
Trp82	H39, hydrogen bond; electrostatic- π -cation; π -donor hydrogen bond
Trp231	7 , hydrophobic- π - π T-shaped
Trp231	7 , hydrophobic- π - π T-shaped
Phe329	7 , hydrophobic- π - π T-shaped
Gly116;Gly117	7 , hydrophobic-amide- π stacked
Leu286	7 , hydrophobic- π -alkyl

Interactions between compound **8** and BChE.

Amino acid	Non-bonding interactions
Glu197	N20, electrostatic-attractive charge
HOH709	O18, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Ser287	H29, hydrogen bond-carbon hydrogen bond
Ser198	H44, hydrogen bond-conventional hydrogen bond
Glu197	H45, hydrogen bond-conventional hydrogen bond
Trp82	N20, electrostatic- π -cation
Trp231	8 , hydrophobic- π - π T-shaped
Trp231	8 , hydrophobic- π - π T-shaped
Leu286	8 , hydrophobic- π -alkyl
Leu286	8 , hydrophobic- π -alkyl

Interactions between compound **9** and BChE.

Amino acid	Non-bonding interactions
HOH786	O18, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Ser198	F28, hydrogen bond; halogen-carbon hydrogen bond; halogen (fluorine)
Ser287	H32, hydrogen bond-conventional hydrogen bond
Pro285	H35, hydrogen bond-conventional hydrogen bond
His438	F28, halogen-halogen (fluorine)
Trp82	N20, electrostatic- π -cation
Trp82	N20, electrostatic- π -cation
Trp82	O18, electrostatic- π -anion
Trp82	O18, electrostatic- π -anion
Tyr332	9 , hydrophobic- π - π T-shaped
Leu286	C25, hydrophobic-alkyl
Trp231	C25, hydrophobic- π -alkyl
Trp231	C25, hydrophobic- π -alkyl
Phe398	C25, hydrophobic- π -alkyl
Leu286	9 , hydrophobic- π -alkyl

Interactions between compound **10** and BChE.

Amino acid	Non-bonding interactions
Asp70	N7, electrostatic-attractive charge
HOH806	F27, hydrogen bond; halogen-water hydrogen bonds; conventional hydrogen bond; halogen (fluorine)
HOH806	H32, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Ser198	O18, hydrogen bond-conventional hydrogen bond
Asp70	H33, hydrogen bond-carbon hydrogen bond
HOH930	10 , other- π -lone pair
Gly116;Gly117	10 , hydrophobic-amide- π stacked

Interactions between compound **11** and BChE.

Amino acid	Non-bonding interactions
HOH771	O18, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH930	F26, hydrogen bond; halogen-water hydrogen bonds; conventional hydrogen bond; halogen (fluorine)
HOH709	F28, hydrogen bond; halogen-water hydrogen bonds; conventional hydrogen bond; halogen (fluorine)
HOH825	H40, hydrogen bond-water hydrogen bond; conventional hydrogen bond
His438	H34, hydrogen bond-conventional hydrogen bond
Gln119	F27, halogen-halogen (fluorine)
Gln119	F28, halogen-halogen (fluorine)
Trp82	N20, electrostatic- π -cation
Glu197	11 , electrostatic- π -anion
Trp82	11 , hydrophobic- π - π T-shaped
Trp82	11 , hydrophobic- π - π T-shaped
Trp231	11 , hydrophobic- π - π T-shaped
Trp231	11 , hydrophobic- π - π T-shaped
Phe329	11 , hydrophobic- π - π T-shaped
Phe329	11 , hydrophobic- π - π T-shaped
Gly116;Gly117	11 , hydrophobic-amide- π stacked

Leu286	11 , hydrophobic- π -alkyl
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Interactions between compound **12** and BChE.

Amino acid	Non-bonding interactions
Glu197	N20, electrostatic-attractive charge
HOH709	N26, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH825	H37, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Thr120	N26, hydrogen bond-conventional hydrogen bond
Leu286	H30, hydrogen bond-conventional hydrogen bond
Trp231	N7, electrostatic- π -cation
Trp231	N7, electrostatic- π -cation
Trp82	N20, electrostatic- π -cation
Trp82	N20, electrostatic- π -cation
Trp231	12 , hydrophobic- π - π T-shaped
Phe329	12 , hydrophobic- π - π T-shaped
Gly116;Gly117	12 , hydrophobic-amide- π stacked
Leu286	12 , hydrophobic- π -alkyl

Interactions between compound **13** and BChE.

Amino acid	Non-bonding interactions
Glu197	N20, electrostatic-attractive charge
HOH736	O18, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH706	O26, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Ser198	O26, hydrogen bond-conventional hydrogen bond
Leu286	H31, hydrogen bond-conventional hydrogen bond
His438	O27, hydrogen bond-carbon hydrogen bond
Ser287	H32, hydrogen bond-carbon hydrogen bond
Glu197	H47, hydrogen bond-carbon hydrogen bond
Trp82	N20, electrostatic- π -cation
Trp82	N20, electrostatic- π -cation
Trp231	13 , hydrophobic- π - π T-shaped
Trp231	13 , hydrophobic- π - π T-shaped
Phe329	13 , hydrophobic- π - π T-shaped
Phe329	13 , hydrophobic- π - π T-shaped
Gly116;Gly117	13 , hydrophobic-amide- π stacked
Leu286	13 , hydrophobic- π -alkyl

Interactions between compound **14** and BChE.

Amino acid	Non-bonding interactions
HOH825	H38, hydrogen bond-water hydrogen bond; carbon hydrogen bond
HOH825	H40, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH910	H50, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Leu286	H30, hydrogen bond-conventional hydrogen bond
Ser198	H33, hydrogen bond-conventional hydrogen bond
His438	H33, hydrogen bond-conventional hydrogen bond
Asp70	H47, hydrogen bond-carbon hydrogen bond
Trp231	N7, electrostatic- π -cation
Trp231	N7, electrostatic- π -cation
Tyr332	N21, electrostatic- π -cation
Trp82	H37, hydrogen bond- π -donor hydrogen bond
His438	14 , hydrophobic- π - π stacked
Trp231	14 , hydrophobic- π - π T-shaped
Trp231	14 , hydrophobic- π - π T-shaped
Phe329	14 , hydrophobic- π - π T-shaped
Phe329	14 , hydrophobic- π - π T-shaped
Gly116;Gly117	14 , hydrophobic-amide- π stacked
Gly116;Gly117	14 , hydrophobic-amide- π stacked
Leu286	14 , hydrophobic- π -alkyl

3. Metal chelation study

3.1. UV/Vis spectra of compounds, metals and compounds–biometal mixtures

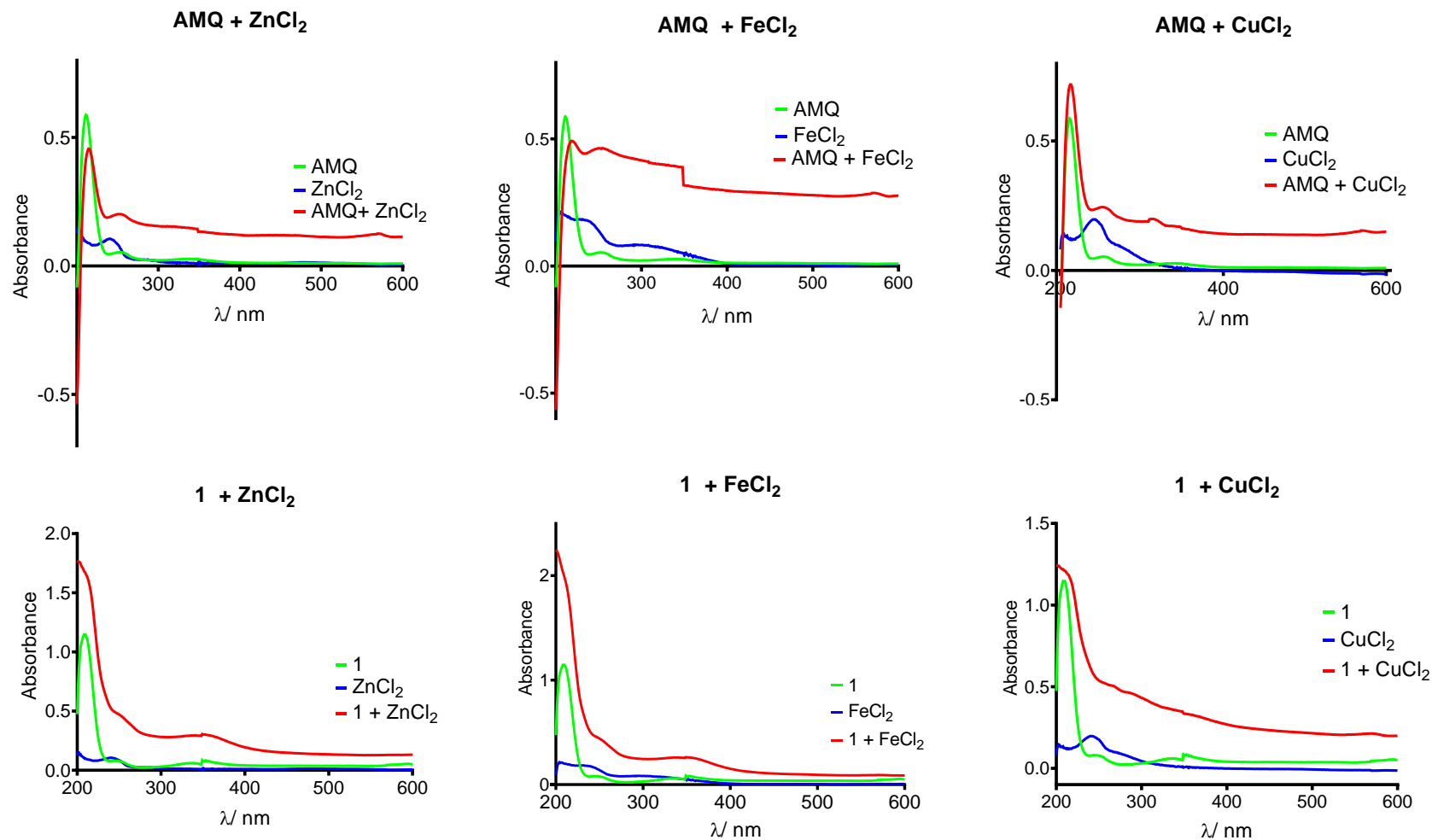


Figure S1. UV/Vis spectra of compounds (AMQ-1), metals (Zn²⁺, Fe²⁺ and Cu²⁺) and compound–biometal mixtures: compound is represented by green line, metal (Zn²⁺, Fe²⁺ or Cu²⁺) is represented by blue line, while the compound–biometal mixture is represented by red line.

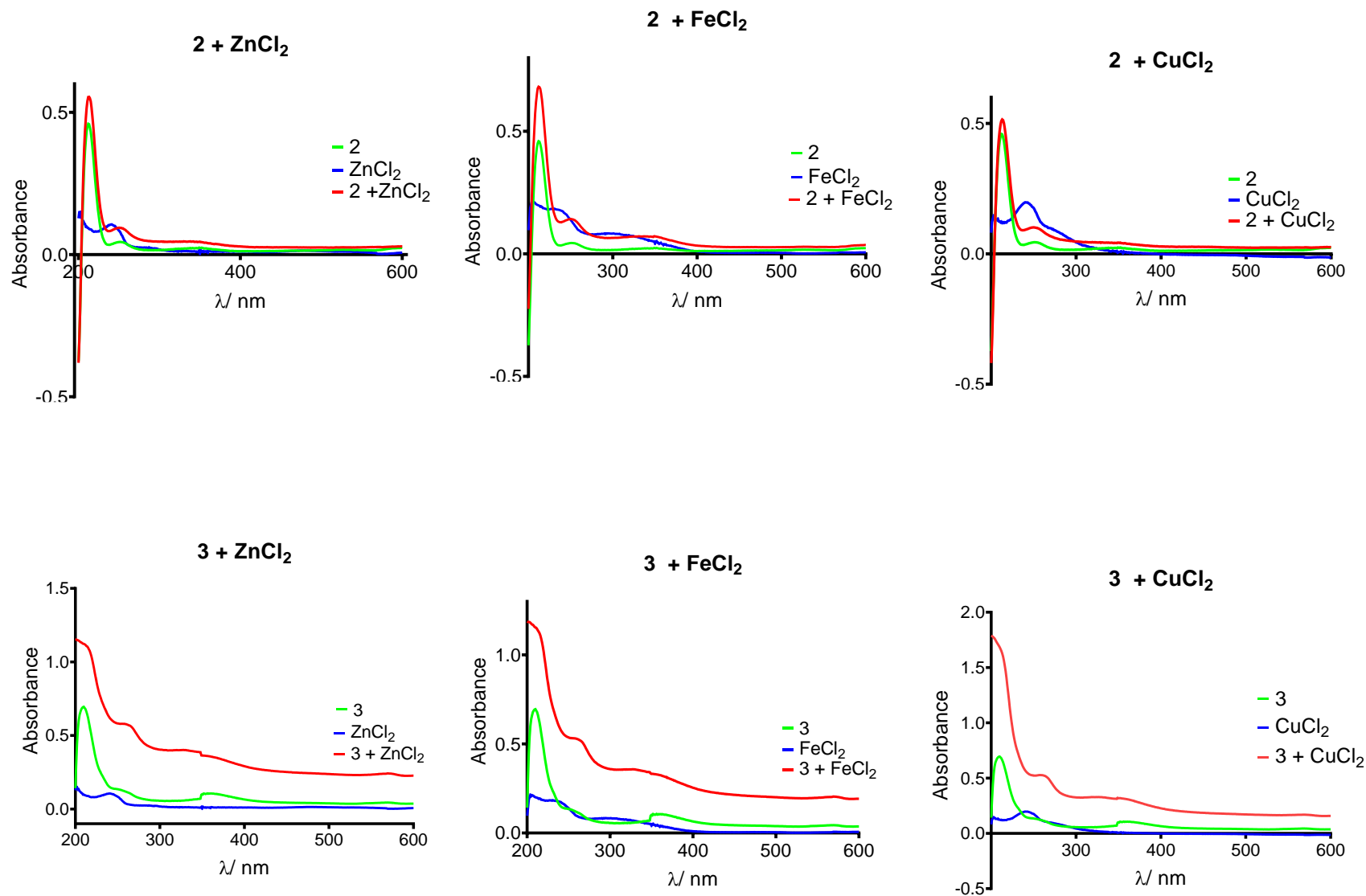


Figure S2. UV/Vis spectra of compounds (**2-3**), metals (Zn²⁺, Fe²⁺ and Cu²⁺) and compound–biometal mixtures: compound is represented by green line, metal (Zn²⁺, Fe²⁺ or Cu²⁺) is represented by blue line, while the compound–biometal mixture is represented by red line.

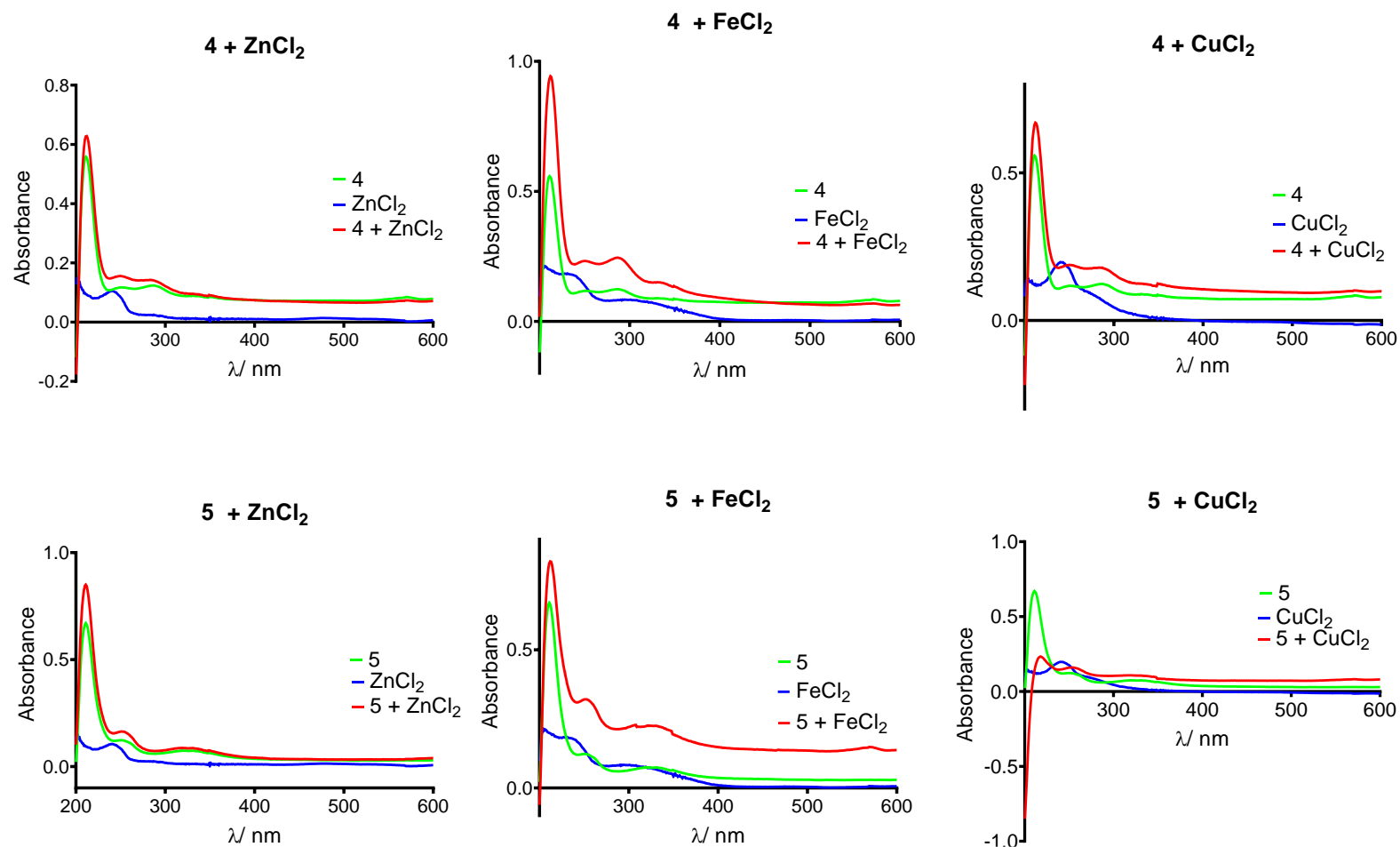


Figure S3. UV/Vis spectra of compounds (**4-5**), metals (Zn²⁺, Fe²⁺ and Cu²⁺) and compound–biometal mixtures: compound is represented by green line, metal (Zn²⁺, Fe²⁺ or Cu²⁺) is represented by blue line, while the compound–biometal mixture is represented by red line.

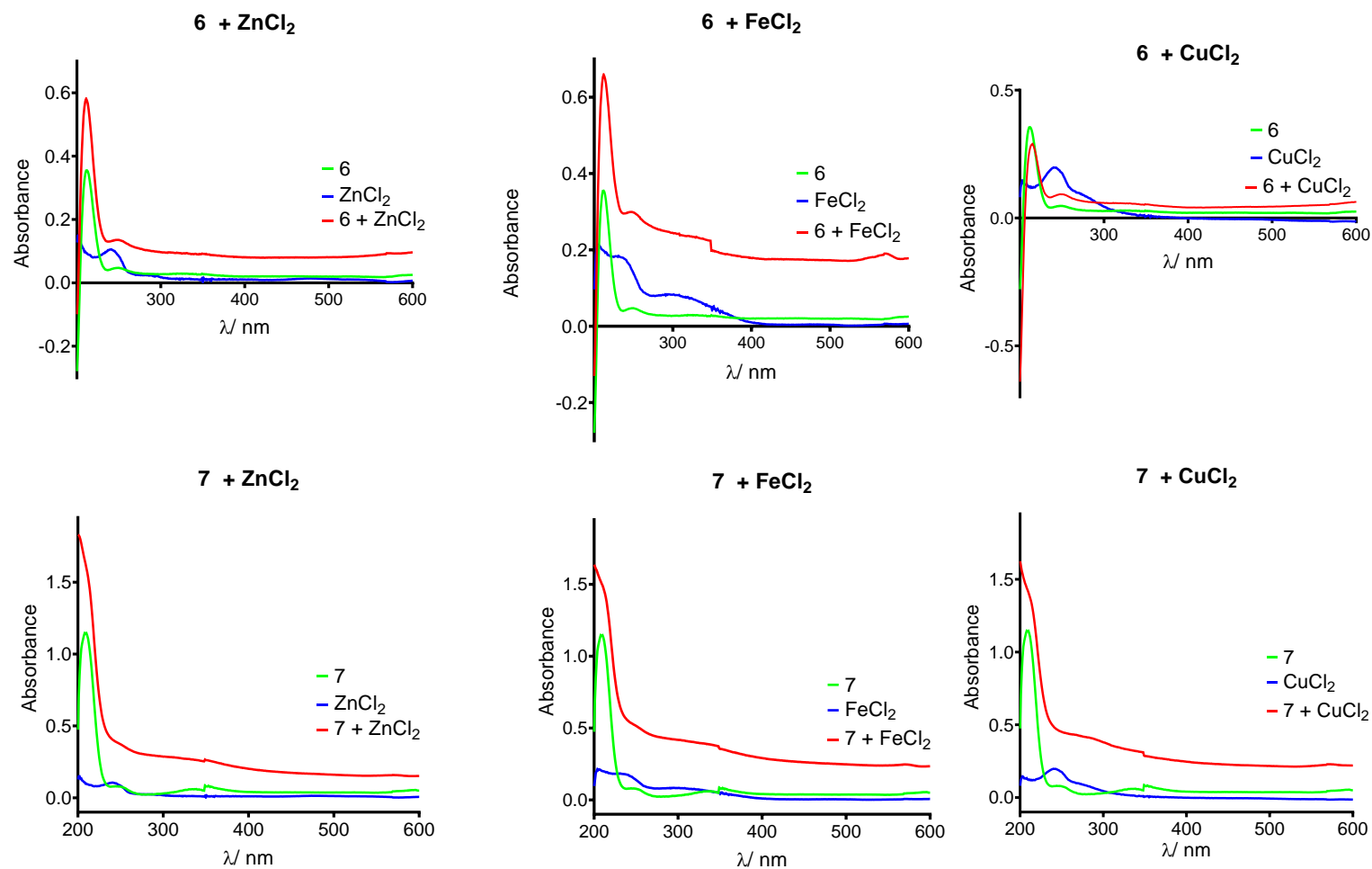


Figure S4. UV/Vis spectra of compounds (**6-7**), metals (Zn²⁺, Fe²⁺ and Cu²⁺) and compound–biometal mixtures: compound is represented by green line, metal (Zn²⁺, Fe²⁺ or Cu²⁺) is represented by blue line, while the compound–biometal mixture is represented by red line.

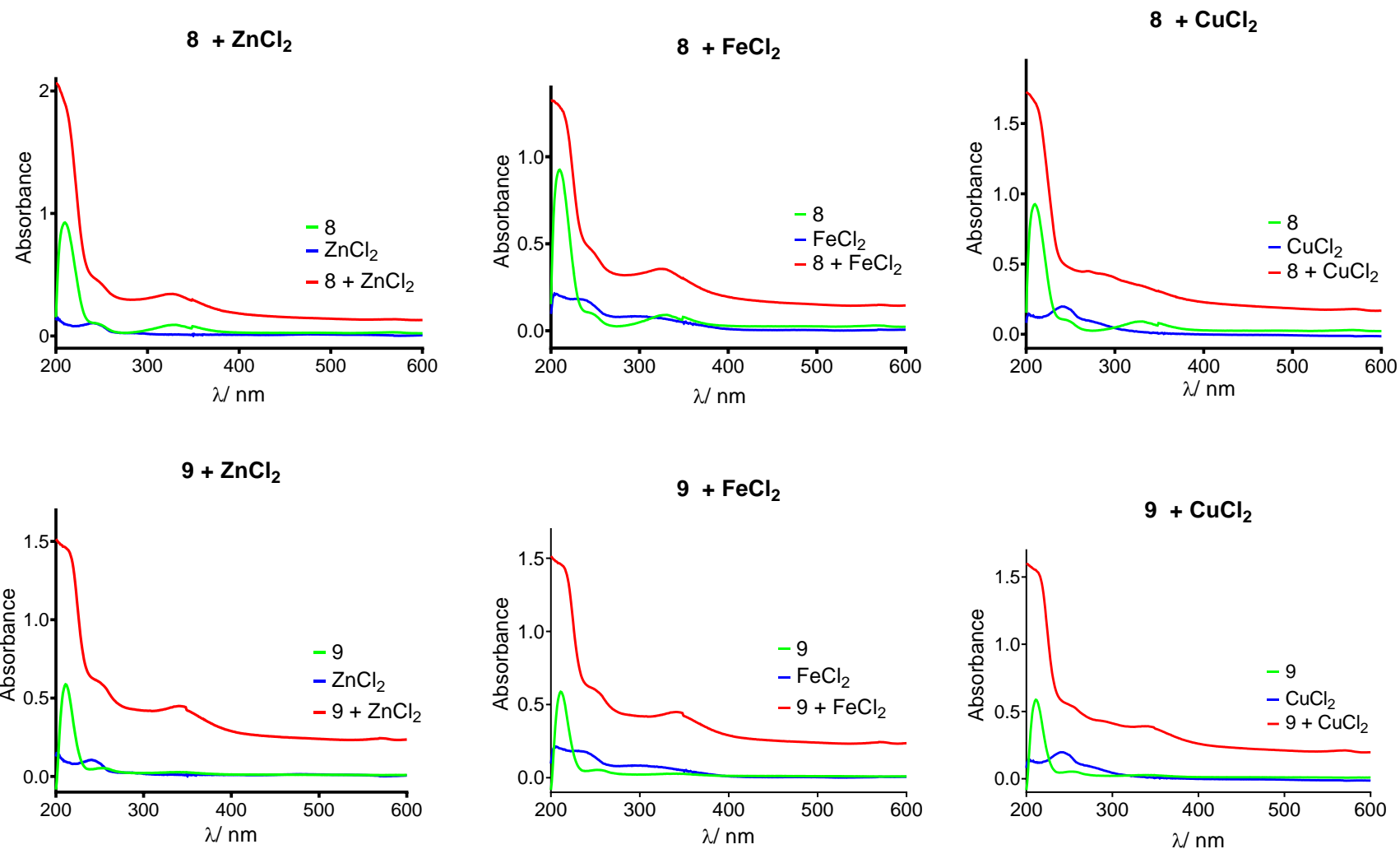


Figure S5. UV/Vis spectra of compounds (**8-9**), metals (Zn²⁺, Fe²⁺ and Cu²⁺) and compound–biometal mixtures: compound is represented by green line, metal (Zn²⁺, Fe²⁺ or Cu²⁺) is represented by blue line, while the compound–biometal mixture is represented by red line.

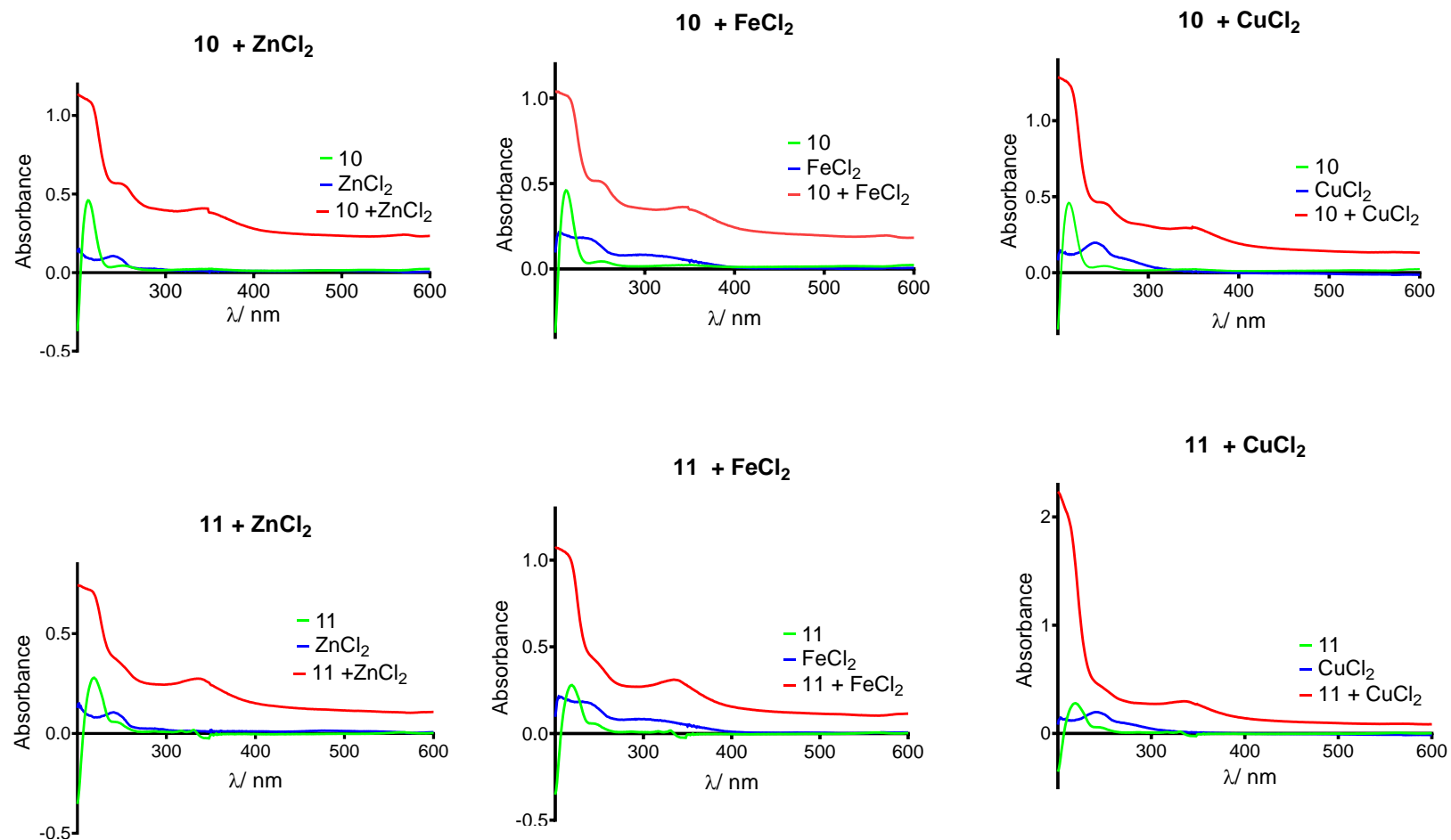


Figure S6. UV/Vis spectra of compounds (**10-11**), metals (Zn^{2+} , Fe^{2+} and Cu^{2+}) and compound–biometal mixtures: compound is represented by green line, metal (Zn^{2+} , Fe^{2+} or Cu^{2+}) is represented by blue line, while the compound–biometal mixture is represented by red line.

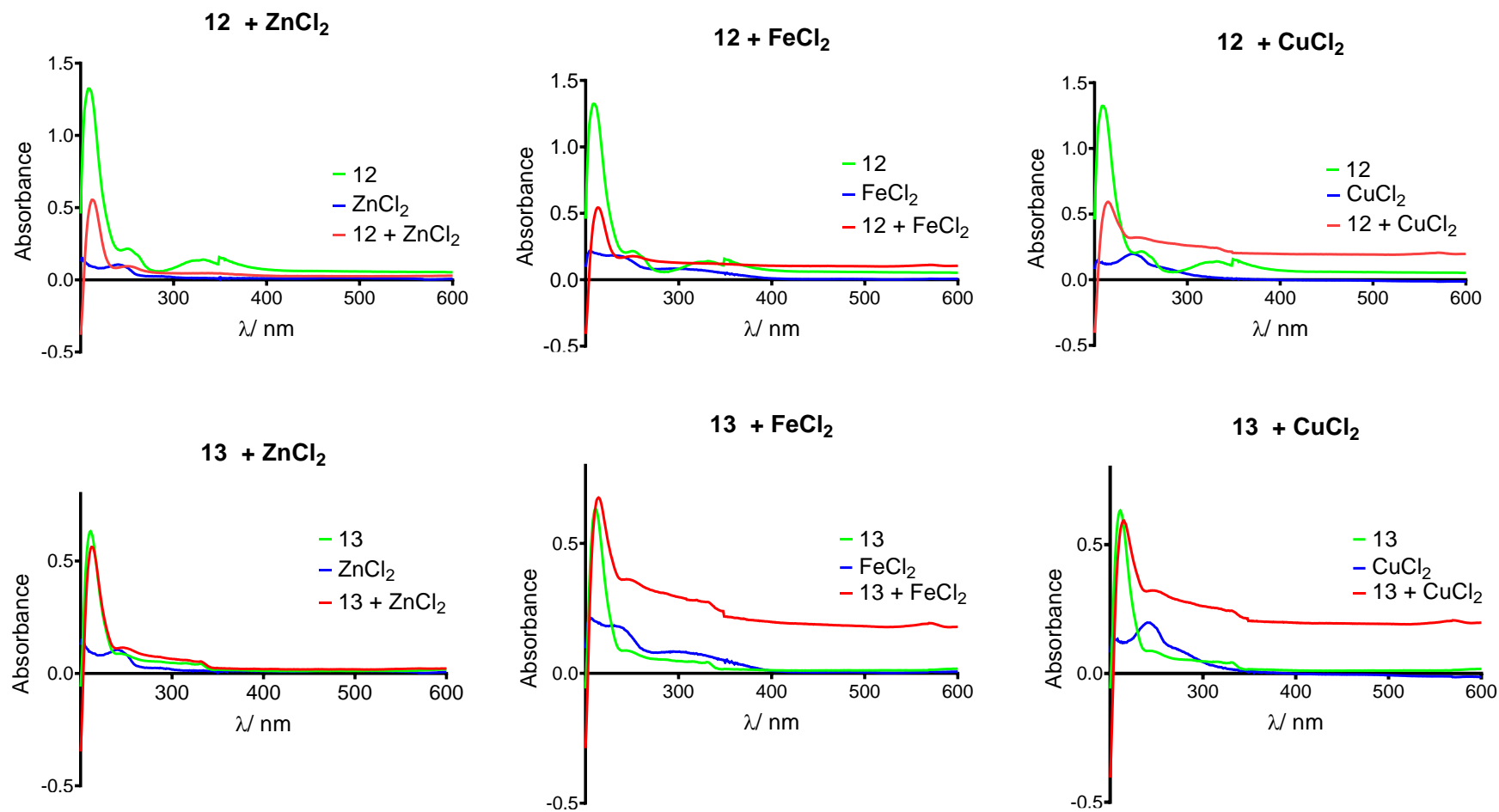


Figure S7. UV/Vis spectra of compounds (**12-13**), metals (Zn^{2+} , Fe^{2+} and Cu^{2+}) and compound–biometal mixtures: compound is represented by green line, metal (Zn^{2+} , Fe^{2+} or Cu^{2+}) is represented by blue line, while the compound–biometal mixture is represented by red line.

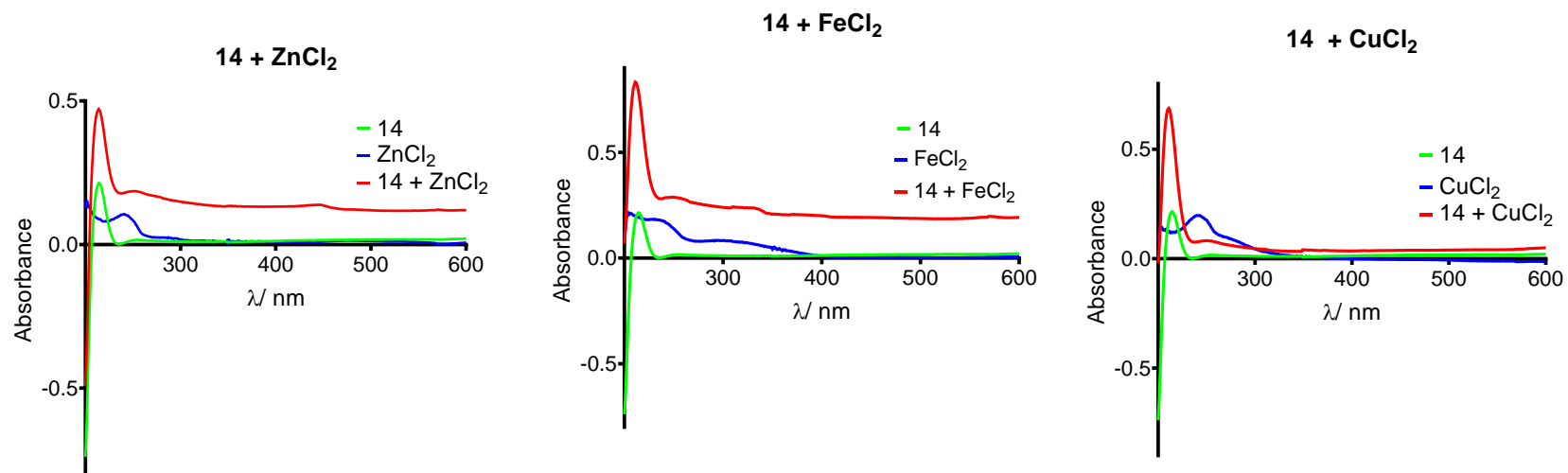


Figure S8. UV/Vis spectra of compound (**14**), metals (Zn^{2+} , Fe^{2+} and Cu^{2+}) and compound–biometal mixtures: compound is represented by green line, metal (Zn^{2+} , Fe^{2+} or Cu^{2+}) is represented by blue line, while the compound–biometal mixture is represented by red line.

3.2. Differential UV/VIS spectra of the compounds-biometal mixtures

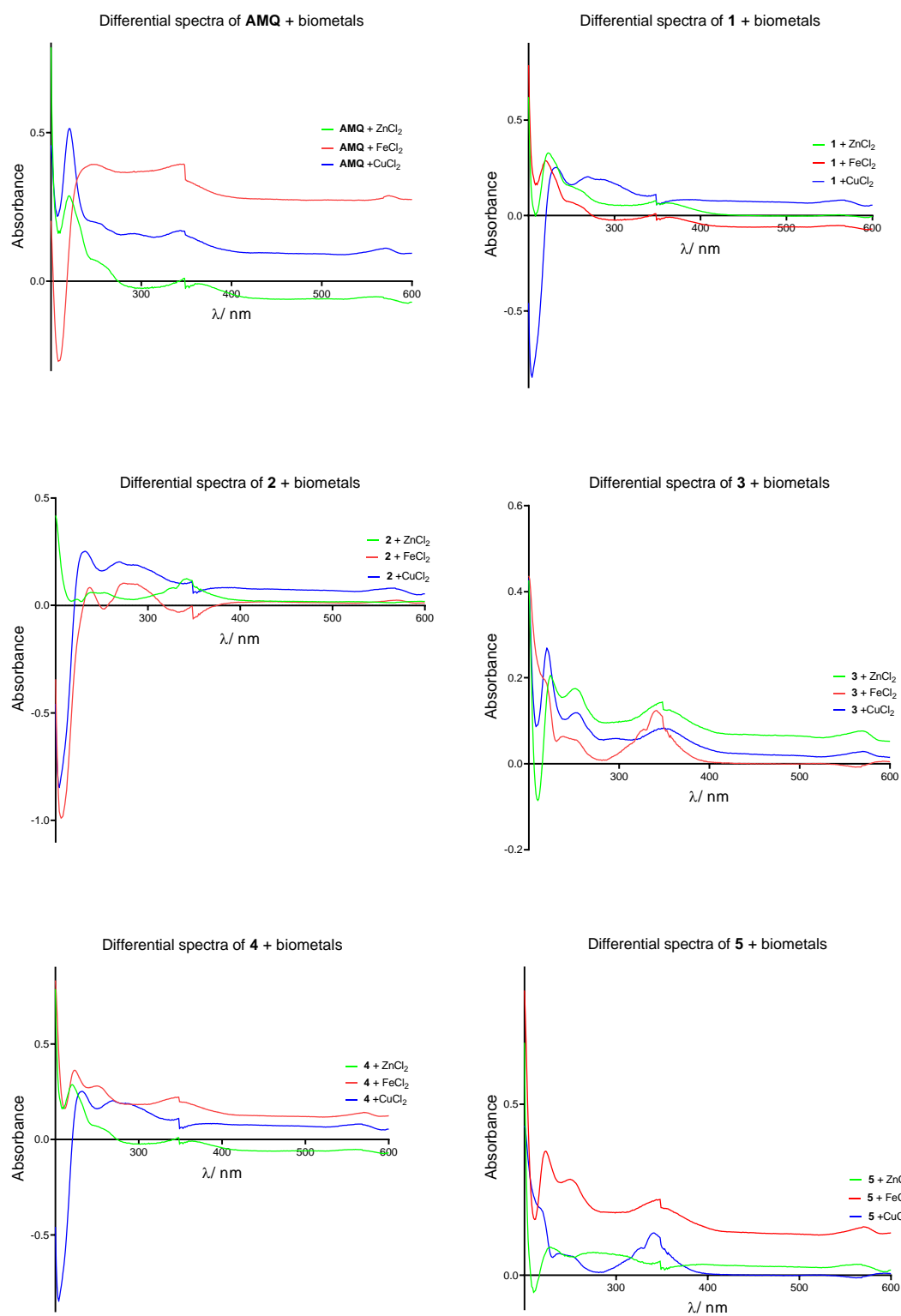


Figure S9. Differential UV/VIS spectra of the compound–biometal mixtures for compounds **AMQ-5**.

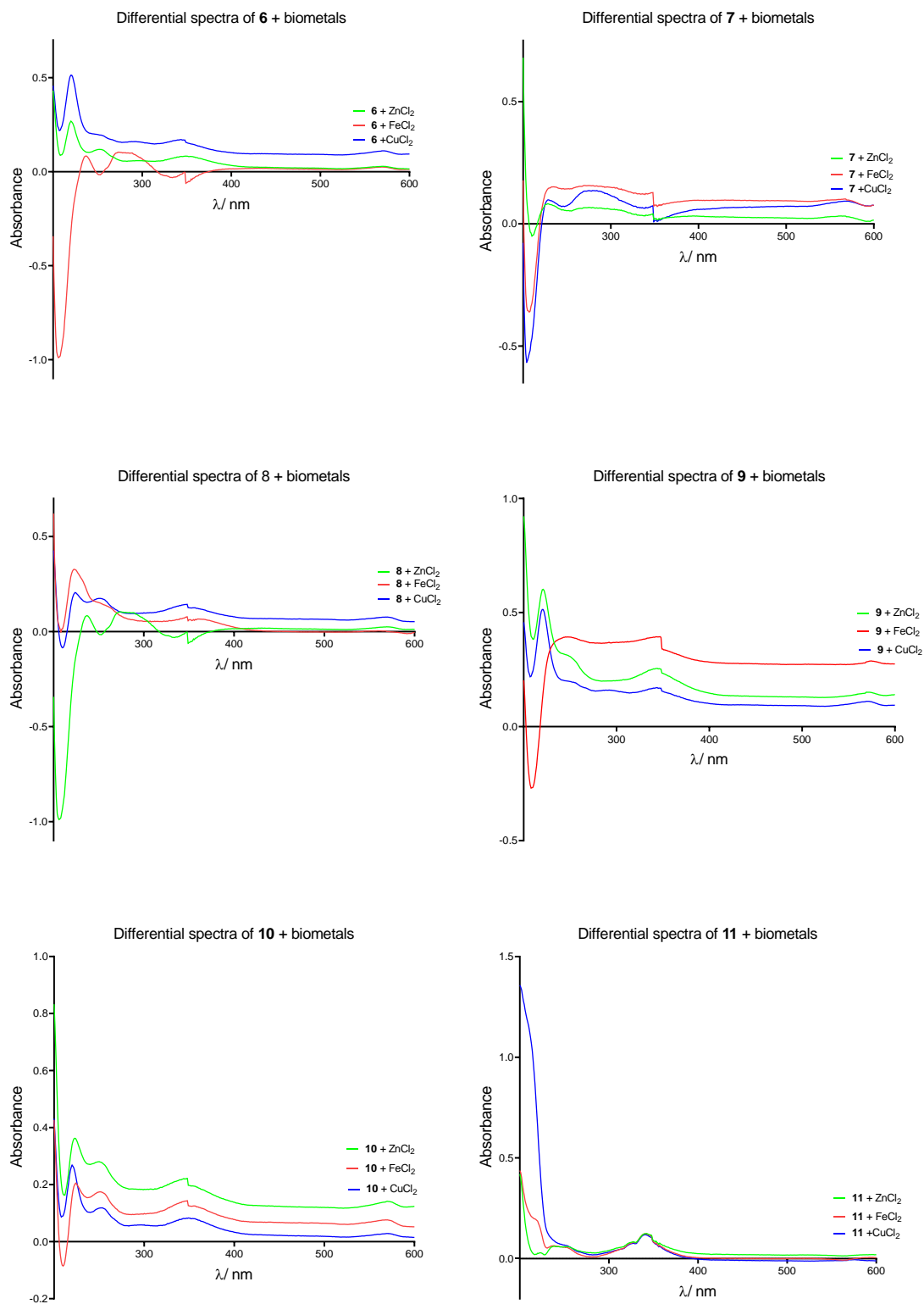


Figure S10. Differential UV/VIS spectra of the compound–biometal mixtures for compounds **6-11**.

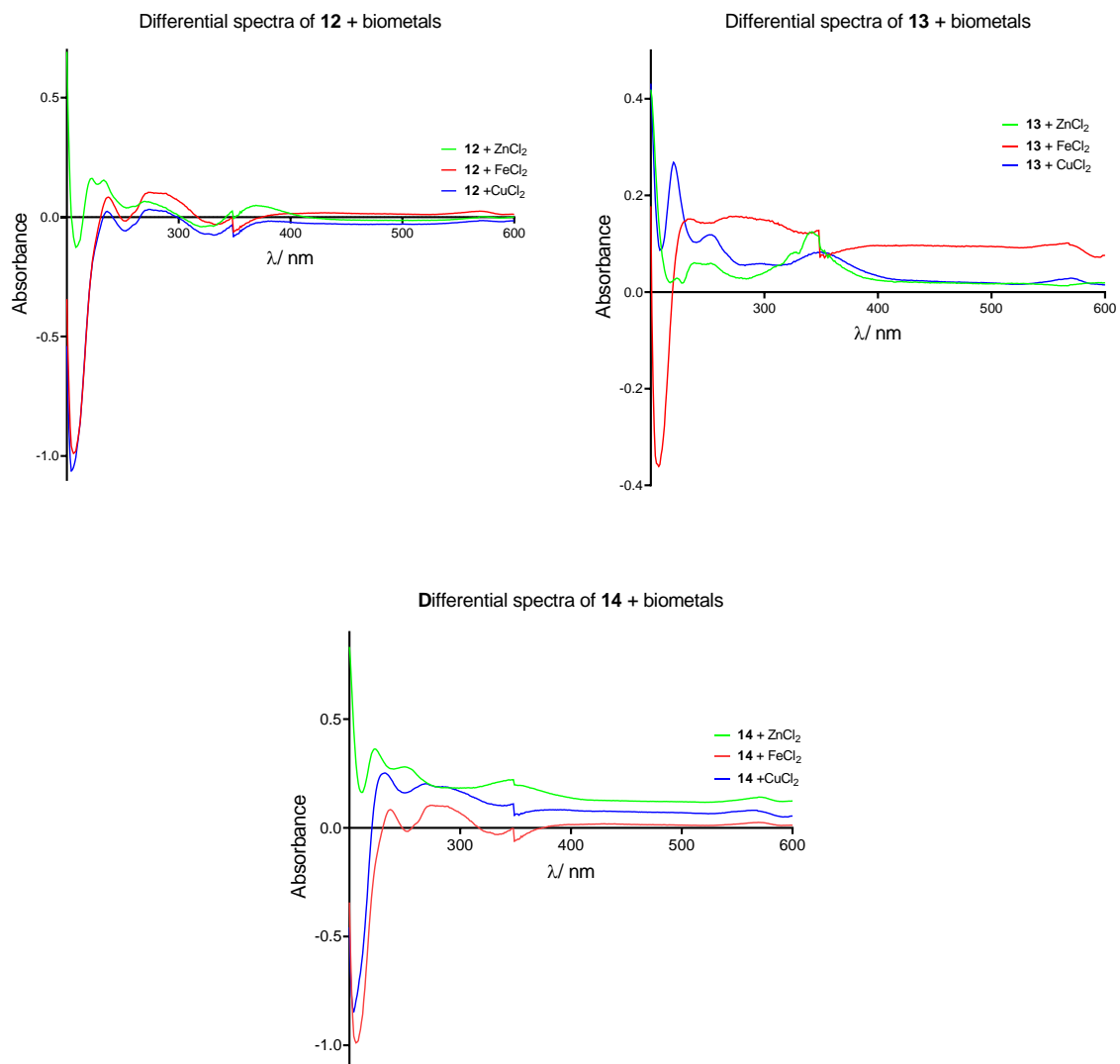


Figure S11. Differential UV/VIS spectra of the compound–biomaterial mixtures for compounds **12-14**.

4. In silico calculations

Table S1. Calculated physiochemical properties (molecular weight, MW; lipophilicity coefficient, logP; number of hydrogen bond donors, HBD; and number of hydrogen bond acceptors, HBA; rotatable bonds, RB; polar surface area, PSA) of aminoquinolines.

Compound	MW/10	logP	HBD	HBA	RB	PSA/10
AMQ	3.559	3.735	2	4	6	4.839
1	3.394	3.273	2	4	6	4.839
2	3.894	4.008	2	4	7	4.839
3	3.464	2.816	2	5	6	7.218
4	3.464	2.816	2	5	6	7.218
5	3.515	2.06	2	5	7	5.762
6	3.214	3.129	2	4	6	4.839
7	3.339	3.274	2	4	6	4.839
8	3.339	3.274	2	4	6	4.839
9	3.894	4.007	2	4	7	4.839
10	3.894	4.009	2	4	7	4.839
11	3.894	4.394	2	4	7	4.839
12	3.464	2.816	2	5	6	7.218
13	3.654	0.969	3	6	7	8.569
14	3.514	2.968	3	5	7	8.569
Recommended values	5	5	5	5	10	9

Table S2. In silico estimated % of compounds that will be absorbed through the human intestine.

Compound	Human intestinal absorption %
AMQ	99.4
1	99.2
2	99.4
3	97.4
4	99.7
5	98.6
6	99.2
7	99.2
8	99.2
9	99.5
10	99.5
11	99.6
12	97.3
13	92.8
14	98.5

References

1. Nsumiwa, S., Kuter, D., Wittlin, S., Chibale, K., Egan, T. J. Structure–activity relationships for ferriprotoporphyrin IX association and β -hematin inhibition by 4-aminoquinolines using experimental and ab initio methods. *Bioorgan Med Chem* **2013**, 21 (13), 3738-3748. doi: 10.1016/j.bmc.2013.04.040