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Synthesis and Characterization of Azobenzene Derived from 8-aminoquinoline in Aqueous Media

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Abstract: A series of novel 8-(aryldiazenyl)quinolones have been synthesized effectively with excellent yields by using 8-amimoquinoline and a variety of aryldiazonium salts containing electron donating and withdrawing moieties in aqueous media. The structure of the synthesized azo dyes has been characterized by NMR, FTIR, mass spectroscopy, and UV–Vis techniques. The compounds' absorption maxima values are in the range of 427 nm and 445 nm due to π-π* charge transfer transition. It can be evaluated that azobenzenes have more absorbance ability in the strong donor systems.

Keywords: Azo dye, 8-aminoquinoline, aqueous media, diazonium salt, azobenzene

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INTRODUCTION

Azobenzenes are an important class of organic compounds that are widely used as organic dyes (1, 2), protein probes (3, 4), chemosensors (5, 6), cosmetics (7-9), nanotubes (10, 11) and polymers (12-14). Due to the presence of N-N linkages, they have been used for pharmacological applications such as antiviral, anti-inflammatory, antimicrobial, antitumor, antidiabetics, and antituberculotic (15-25). Beyond their potential in these application areas, azo-compounds are mostly used as dyes. Until the late 1800s, all dyes were obtained from natural sources. However, limitation of the natural dye sources led scientists to synthesize dyes with a wide variety of new colors. Azo dyes can be easily prepared by using diazo and coupling components that are generally low-cost materials (26). Due to remarkable stability, light resistance and easy diversification of donor and acceptor groups in the organic compounds, azo dyes are one-step ahead of other dyes (27, 28). Currently, the dyes and pigments market are valued for approximately USD $33 billion (29) and keeping the number and production volume about 70% in mind, azo dyes are the largest class of organic dye around the world (30). Having such a large market share, as a matter of course increases the tendency towards azo dyes.

Quinoline backbones are considered as one of the main classes of heterocyclic chemistry and are found in many natural products, alkaloids, and synthetic molecules (31-33). Quinoline forms the main framework of drugs used clinically in the treatment of many diseases (34). After first discovering chloroquine as an antimalarial drug in 1934, many other analogues were explored such as mefloquine, piperquine, primaquine and amodiaquine (35-39). Also, they are used as antibiotics such as gatifloxacin, moxifloxacin, ciprofloxacin, sparfloxacin, levofloxacin, and norfloxacin (40-42). In addition, due to the formation of stable complexes with many metals, quinolines are known as the best chelating agents (43-48).

In this regard, herein the author reports the simple, efficient synthesis and characterization of 8-(aryldiazenyl)quinolines (**6a-g**) by using 8-

aminoquinoline (**3a**) and aryldiazonium salts (**5a-g**) in aqueous media.

EXPERIMENTAL SECTION

General considerations

All the chemicals used were used as received without further purification. IR spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer. The UV–Visible absorption spectra were carried out with a Shimadzu UV-3600 UV-Vis NIR spectrophotometer in the wavelength range of 200–800 nm. Melting points were determined by using a Stuart melting point apparatus. NMR spectra were recorded on a 500 MHz Varian or Bruker spectrometer. Mass spectra were recorded on a Bruker microflex LT MALDI spectrometer. The spectra are presented in the Supplementary Section at the end of this article.

Synthesis of 8-aminoquinoline **(3a)**

Under an ice bath, sulfuric acid (2.0 mL) was added onto quinoline (5 mmol, 1.0 equiv) then 65% nitric acid (3.0 equiv) were added dropwise and stirred for 4h at rt. The mixture was poured into the ice water and neutralized with NaOH; and then extracted with dichloromethane. After dried over Na_2SO_4 and evaporated in vacuo, used next step without purification(49).

Mixture of nitroquinolines (**2a-b**) and 5% Pd/C was solved in ethanol and suspension was saturated with hydrogen gas under atmospheric pressure at 40 C° until the starting material was consumed. 2 h later, the mixture was filtered and evaporated. The crude product was purified by silica gel column chromatography, eluting with EtOAc in hexanes to yield the desired 8-aminoquinoline **3a** is isolated as a brown solid in a yield of 32% (50).

Obtained as a brown solid (231 mg, 32%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 – 8.60 (m, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.16 (m, 2H), 7.02 (d, *J* = 8.1 Hz, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 4.89 (s, 2H).

General Procedure for Synthesis of Aryl Diazonium Salts (5a-g)

The appropriate aniline (2.0 mmol) and 0.68 mL 50% HBF_4 aq. in 2.0 mL distilled water was placed in an ice bath and the temperature was set to 0 °C then sodium nitrite (2.0 mmol) solution in 1.5 mL distilled water was added dropwise. The reaction was stirred 30 min., precipitate was filtered and washed with water (15 mL) and diethyl ether (15 mL). After final filtration, the compound was dried under low pressure and yielded the desired product (51).

4-tert-butylbenzenediazonium tetrafluoroborate (5a)

Obtained as a white solid (416 mg, 84%); ^{1}H NMR (500 MHz, DMSO-d6) δ 8.58 (d, *J* = 7.3 Hz, 1H), 8.03 (d, *J* = 7.3 Hz, 1H), 1.35 (s, 9H).

4-Trifluoromethylbenzenediazonium tetrafluoroborate (5b)

Obtained as a white solid (462 mg, 89%); ^{1}H NMR (500 MHz, DMSO-d6) δ 8.90 (d, *J* = 8.0 Hz, 2H), 8.42 (d, *J* = 8.0 Hz, 2H).

2-Chlorobenzenediazonium tetrafluoroborate (5c)

Obtained as a white solid (294 mg, 65%); ^{1}H NMR (500 MHz, DMSO-d6) δ 8.85 (d, *J* = 8.1 Hz, 1H), 8.28 (d, *J* = 8.2 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.96 (t, *J* = 6.2 Hz, 1H).

2-Trifluoromethylbenzenediazonium tetrafluoroborate (5d)

Obtained as a white solid (369 mg, 71%); ^{1}H NMR (500 MHz, DMSO-d6) δ 9.08 (d, *J* = 6.6 Hz, 1H), 8.49 (s, 2H), 8.39 – 8.30 (m, 1H).

3-Fluorobenzenediazonium tetrafluoroborate (5e)

Obtained as a white solid (231 mg, 55%); ^{1}H NMR (500 MHz, DMSO-d6) δ 8.67 (d, *J* = 6.0 Hz, 1H), 8.59 (d, *J* = 7.8 Hz, 1H), 8.22 (t, *J* = 7.4 Hz, 1H), 8.09 – 8.01 (m, 1H).

4-Ethynylbenzenediazonium tetrafluoroborate (5f)

Obtained as a pale brown solid (344 mg, 73%); 1H NMR (500 MHz, DMSO-d6) δ 8.67 (d, *J* = 7.9 Hz, 2H), 8.06 (d, *J* = 7.8 Hz, 2H), 5.15 (s, 1H).

4-Fluorobenzenediazonium tetrafluoroborate (5g)

Obtained as a white solid (243 mg, 58%); 1H NMR (500 MHz, DMSO-d6) δ 8.83 – 8.73 (m, 2H), 7.88 (t, J = 8.7 Hz, 2H).

General Procedure for Synthesis of 8-(aryldiazenyl)quinoline (6a-g)

8-aminoquinoline (0.1 mmol, 1.0 equiv) and aryl diazonium salt (0.11 mmol, 1.1 equiv.) was dissolved in 2.0 mL distilled water and stirred 30 min at RT. Extracted with ethyl acetate, dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by silica gel column chromatography, eluting with EtOAc in hexanes to yield the desired product.

(E)-5-((4-(tert-butyl)phenyl)diazenyl) quinolin-8-amine (6a)

Obtained as a reddish-orange solid (28 mg, 92%); mp: 149-151 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (d, *J* = 8.5 Hz, 1H), 8.85 (s, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 7.3 Hz, 3H), 6.97 (d, *J* = 7.5 Hz, 1H), 5.50 (s, 2H), 1.41 (d, *J* = 0.9 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.28, 151.39, 147.82, 147.79, 147.42, 138.43, 137.18, 132.32, 127.98, 125.96, 125.91, 122.22, 122.18, 115.10, 109.02, 34.92, 31.31; IR (neat, cm^{-1}) 3478, 3353, 2952, 2919, 2855, 1615, 1587, 1565, 1508, 1473, 1428, 1174, 1126, 846, 785;

MALDI-TOF *m/z* calcd for $C_{19}H_{21}N_4$ ($[M+H]^+$) 305,177, found 305.336.

(E)-5-((4-(trifluoromethyl)phenyl)diazenyl) quinolin-8-amine (6b)
Obtained as a maroon solid (31 mg, 98%); mp: 137-139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (d, *J* = 6.5 Hz, 1H), 8.85 (s, 1H), 8.14 – 7.95 (m, 3H), 7.78 (d, *J* = 7.0 Hz, 2H), 7.58 (d, *J* = 2.2 Hz, 1H), 7.02 – 6.84 (m, 1H), 5.69 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.33, 148.73, 147.94 (d, *J* = 3.8 Hz), 138.02, 136.89, 132.14, 130.79 (q, *J* = 32.4 Hz), 128.37, 126.62 – 125.81 (m), 125.22, 123.05, 122.86 (d, *J* = 5.4 Hz), 122.54, 116.22, 108.87; IR (neat, cm^{-1}) 3433, 3317, 2951, 2918, 2851, 1609, 1553, 1504, 1475, 1440, 1382, 1154, 1104, 1065, 843; MALDI-TOF *m/z* calcd for $C_{16}H_{12}F_3N_4$ ($[M+H]^+$) 317,101, found 317.139.

(E)-5-((2-chlorophenyl)diazenyl)quinolin-8-amine (6c)
Obtained as an orange solid (25 mg, 89%); mp: 156-158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 9.37 (d, *J* = 8.1 Hz, 1H), 8.85 (s, 1H), 8.13 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.0 Hz, 1H), 7.57 (d, *J* = 4.6 Hz, 2H), 7.35 (t, *J* = 13.9 Hz, 2H), 6.98 (d, *J* = 7.0 Hz, 1H), 5.63 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.49, 148.42, 147.88, 138.55, 137.00, 134.40, 132.47, 130.60, 130.27, 127.79, 127.21 , 122.95, 118.16, 117.67, 108.96; IR (neat, cm^{-1}) 3457, 3301, 2949, 2917, 2845, 1610, 1587, 1508, 1370, 1340, 1244, 1175, 1120, 824, 785, 754; MALDI-TOF *m/z* calcd for $C_{15}H_{12}ClN_4$ ($[M+H]^+$) 283,075, found 282.933.

(E)-5-((2-(trifluoromethyl)phenyl)diazenyl) quinolin-8-amine (6d)
Obtained as a rust solid (30 mg, 95%); mp: 145-147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.85 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.59 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 5.72 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.95, 150.49, 148.69, 147.87, 138.42, 136.85, 132.40 (d, *J* = 4.5 Hz), 128.90, 128.06, 126.71 – 126.25 (m), 125.40, 122.96, 118.26, 116.35, 109.12; IR (neat, cm^{-1}) 3458, 3318, 2952, 2915, 2851, 1621, 1600, 1506, 1424, 1387, 1310, 1238, 1130, 1048, 1032, 815, 791, 751; MALDI-TOF *m/z* calcd for $C_{16}H_{12}F_3N_4$ ($[M+H]^+$) 317,101, found 317.072.

(E)-5-((3-fluorophenyl)diazenyl)quinolin-8-amine (6e)
Obtained as a rust solid (24 mg, 91%); mp: 136-138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.75 (dd, *J* = 4.1, 1.7 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.69 (dd, *J* = 7.9, 0.6 Hz, 1H), 7.62 – 7.52 (m, 1H), 7.48 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.40 (td, *J* = 8.0, 6.1 Hz, 1H), 7.08 – 6.99 (m, 1H), 6.89 – 6.83 (m, 1H), 5.52 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.41, 162.45, 155.06 (d, *J* = 7.1 Hz), 148.35, 147.95, 137.91, 137.02, 132.22, 130.15 (d, *J* = 8.5 Hz), 128.28, 122.75, 120.23 (d, *J* = 2.7 Hz), 116.47, 116.30, 115.87, 108.94, 107.56, 107.38; IR (neat, cm^{-1}) 3430, 3309, 3165, 2951, 2920, 2851, 1729, 1619, 1566, 1508, 1475, 1379, 1335, 1246, 1205, 1100, 965, 866, 780, 682; MALDI-TOF *m/z* calcd for $C_{15}H_{12}FN_4$ ($[M+H]^+$) 267,1046, found 266.992.

(E)-5-((4-ethynylphenyl)diazenyl)quinolin-8-amine (6f)
Obtained as a rust solid (23 mg, 84%); mp: 186-188 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (d, *J* = 8.2 Hz, 1H), 8.85 (s, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.71 – 7.51 (m, 3H), 6.97 (d, *J* = 8.2 Hz, 1H), 5.60 (s, 2H), 3.23 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.09, 148.23, 147.88, 138.23, 137.02, 132.96, 132.22, 128.23, 123.17, 122.65, 122.41, 115.73, 108.96, 83.62, 78.92; IR (neat, cm^{-1}) 3429, 3305, 3177, 2923, 2847, 1719, 1611, 1508, 1378, 1328, 1246, 1192, 839, 790; MALDI-TOF *m/z* calcd for $C_{17}H_{13}N_4$ ($[M+H]^+$) 273,114, found 272.861.

(E)-5-((4-fluorophenyl)diazenyl)quinolin-8-amine (6g)
Obtained as an orange solid (26 mg, 96%); mp: 162-164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (d, *J* = 6.7 Hz, 1H), 8.85 (s, 1H), 8.00 (d, *J* = 21.5 Hz, 3H), 7.57 (d, *J* = 4.3 Hz, 1H), 7.22 (s, 2H), 7.03 – 6.92 (m, 1H), 5.55 (s, 2H); ^{13}C NMR (126 MHz, CDCl3) δ 164.61, 162.61, 149.98, 147.86 (d, J = 5.0 Hz), 147.78, 138.04, 137.09, 132.18, 128.03, 125.03 – 123.91 (m), 122.50 (dd, *J* = 7.9, 5.7 Hz), 115.91 (dd, *J* = 23.3, 6.2 Hz), 115.38 (d, *J* = 5.0 Hz), 108.95; IR (neat, cm^{-1}) 3446, 3321, 2925, 2851, 1615, 1591, 1567, 1510, 1492, 1385, 1334, 1248, 1223, 1184, 847, 788; MALDI-TOF *m/z* calcd for $C_{15}H_{12}FN_4$ ($[M+H]^+$) 267,105, found 266.961.

RESULTS AND DISCUSSION

In this work, novel azobenzenes (**6a-g**) have been synthesized with excellent yields. The synthetic route has been illustrated in Scheme 1. At first, quinoline was nitrated in the presence of nitric acid and sulfuric acid, and a mixture of 5-nitroqoinoline and 8-nitroquinoline (**2a-b**) was obtained. Without any purification, this mixture was subjected for hydrogenolysis in the presence of H_2/Pd and amino quinoline forms (**3a-b**) were attained by full conversion. On the other hand, aniline derivatives were converted to the corresponding diazonium salts (**5a-g**) in single step with good and acceptable yields. Finally, azobenzenes as target products were synthesized by reacting with 8-aminoquinoline (**3a**) and aryl diazonium salts (**5a-g**) in aqueous media at room temperature in facile manner. Diazonium salts with electron donating or withdrawing groups substituted at different positions of benzene gave the target product 8-(aryldiazenyl)quinolines (**6a-g**) quite successfully with exceptional yields. Structural

features of the 8-(aryldiazenyl)quinolines (**6a-g**) were fully elucidated using NMR, UV–Visible absorption spectra and mass spectrometry.

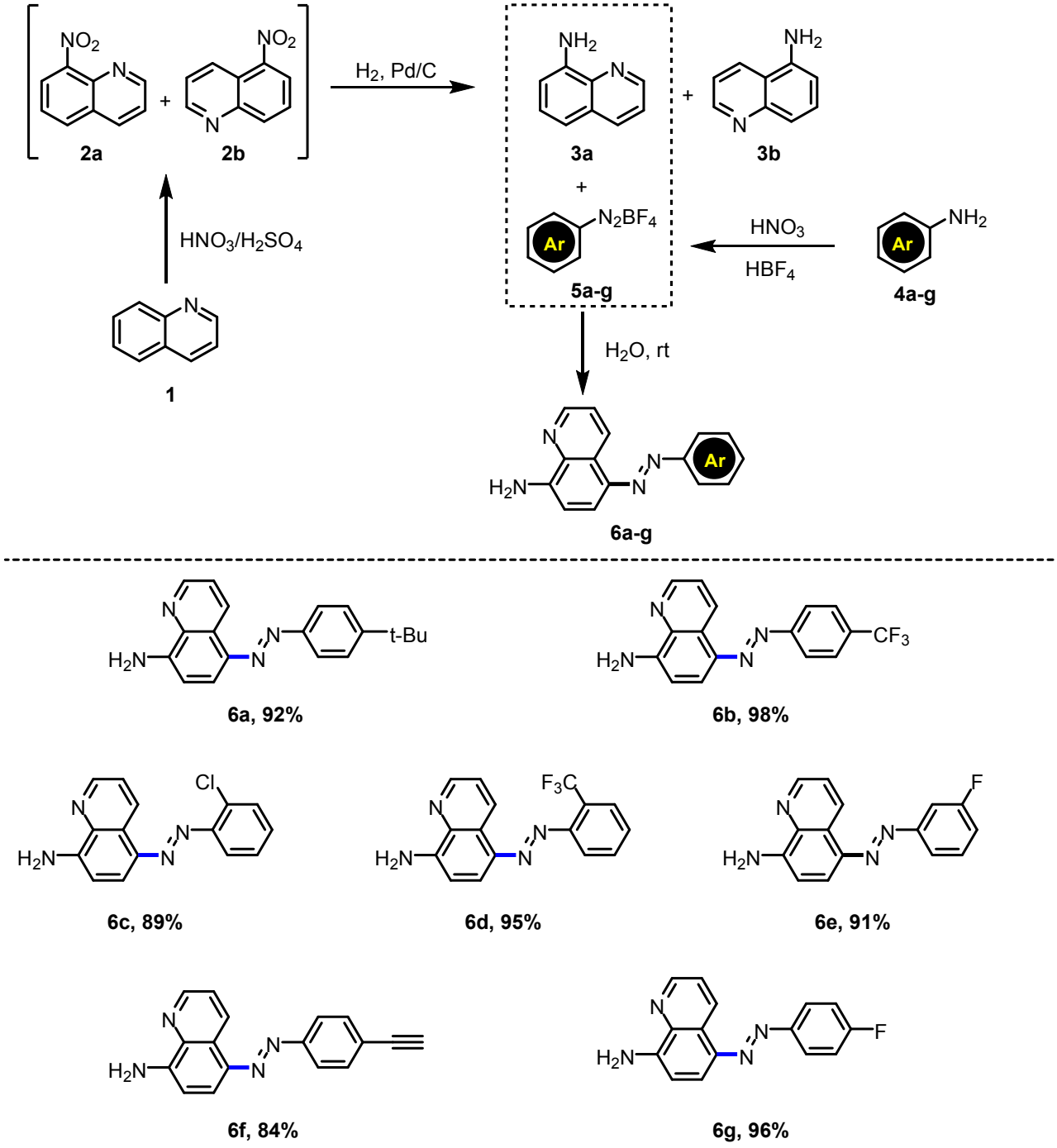

Figure 1: Synthetic route for the preparation of azobenzenes.

UV-Vis spectra of the compounds were collected in acetonitrile solvent with Shimadzu UV-3600 UV-Vis NIR spectrophotometer and they were presented in Figure 2. Their maximal values and molar absorption coefficients were also recorded in Table 1. As seen in Table 1, the absorption maximal values of the compounds are between 427 nm and 445 nm due to π-π* charge transfer transition (52). The absorption bands are slightly shifted to longer wavelengths (redshifted) in the order of **6a**, **6g**, **6c**, **6e**, **6b**, **6d**, and **6f**. Generally, as the electron donor strength increases, the absorption band maximum shifts to longer wavelengths (53); however, here the opposite effects were observed, similar to the literature (54). When their molar absorption coefficient was compared, **6a** had the

biggest molar absorption coefficient and **6f** had the lowest molar absorption coefficient among the compounds presented. It can be concluded that the compounds have more absorbance ability in the strong donor systems.

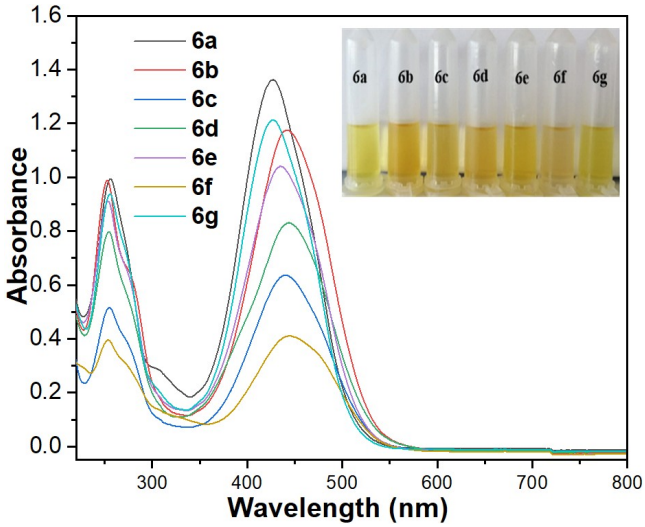

Figure 2: UV-Vis spectrum of the compounds (50 μM) in ACN.

Table 1: Absorption maximal values of the compounds.

Compounds	Absorption Maxima	Molar Absorption Coefficient (ε) ($cm^{-1}M^{-1}$)
6a	427	27,180
6b	442	23,500
6c	430	12,640
6d	442	16,560
6e	435	20,740
6f	445	8,260
6g	428	24,220

CONCLUSION

As a summary, the author hereby discloses the simple, easy and operational synthesis of novel 8-(aryldiazenyl)quinolones and their structural characterization was carried out by varied analytical techniques as NMR, IR, UV-Visible, and mass spectroscopy. The compounds were provided with excellent yields ranging from 89% to 98%. UV-Vis spectrum of the azobenzenes was collected in acetonitrile solvent and maximal values were measured between 427 nm and 445 nm. The molar absorptivity of compounds showed that their electronic transition is by virtue of π–π*. It can be assumed that the compounds have greater absorbance ability in strong donor systems. New azobenzenes with potentially dye and pharmaceutical agents due to the aminoquinoline backbone and diazo unit were brought to the literature.

CONFLICT OF INTEREST

There are no conflicts to declare.

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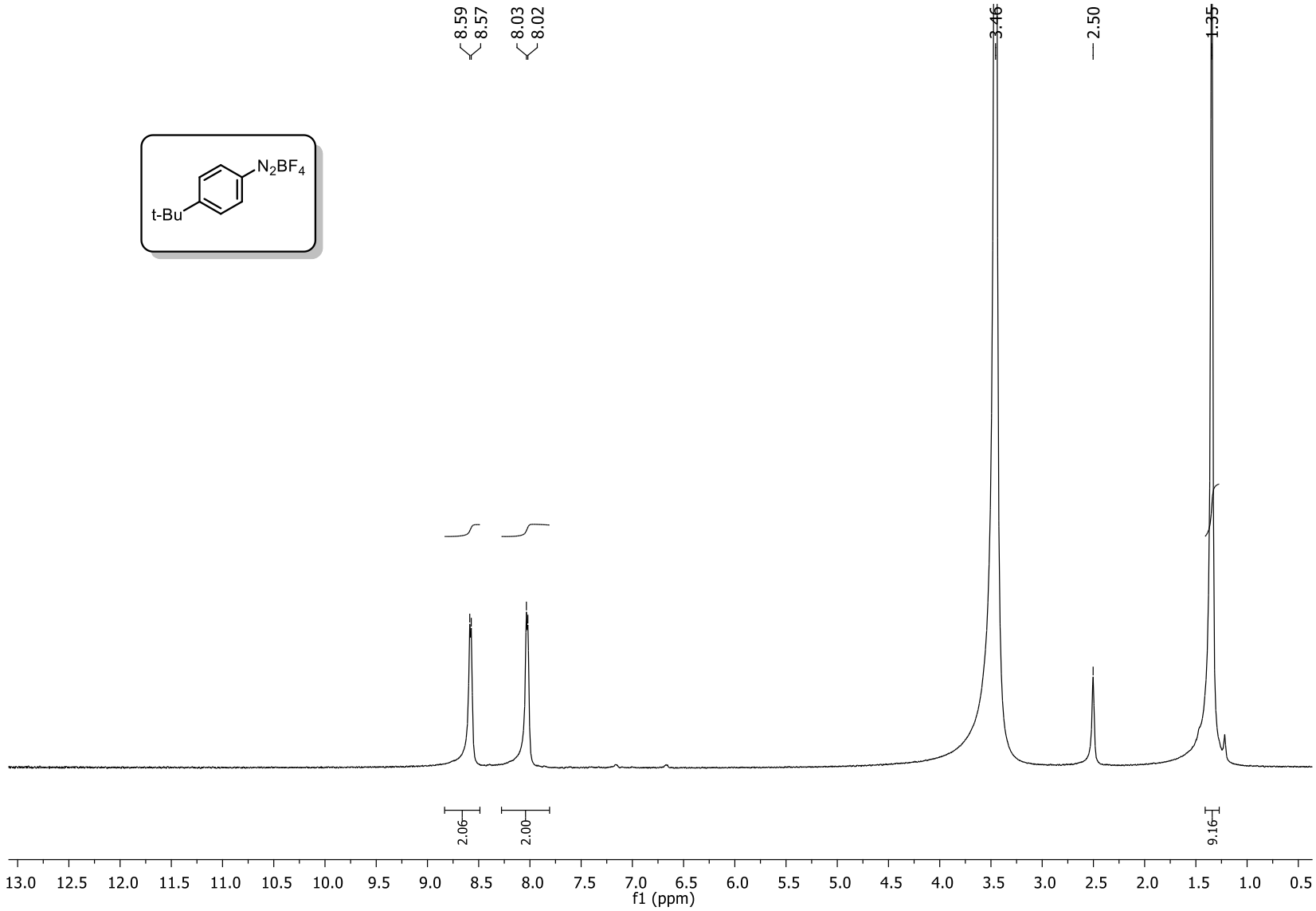
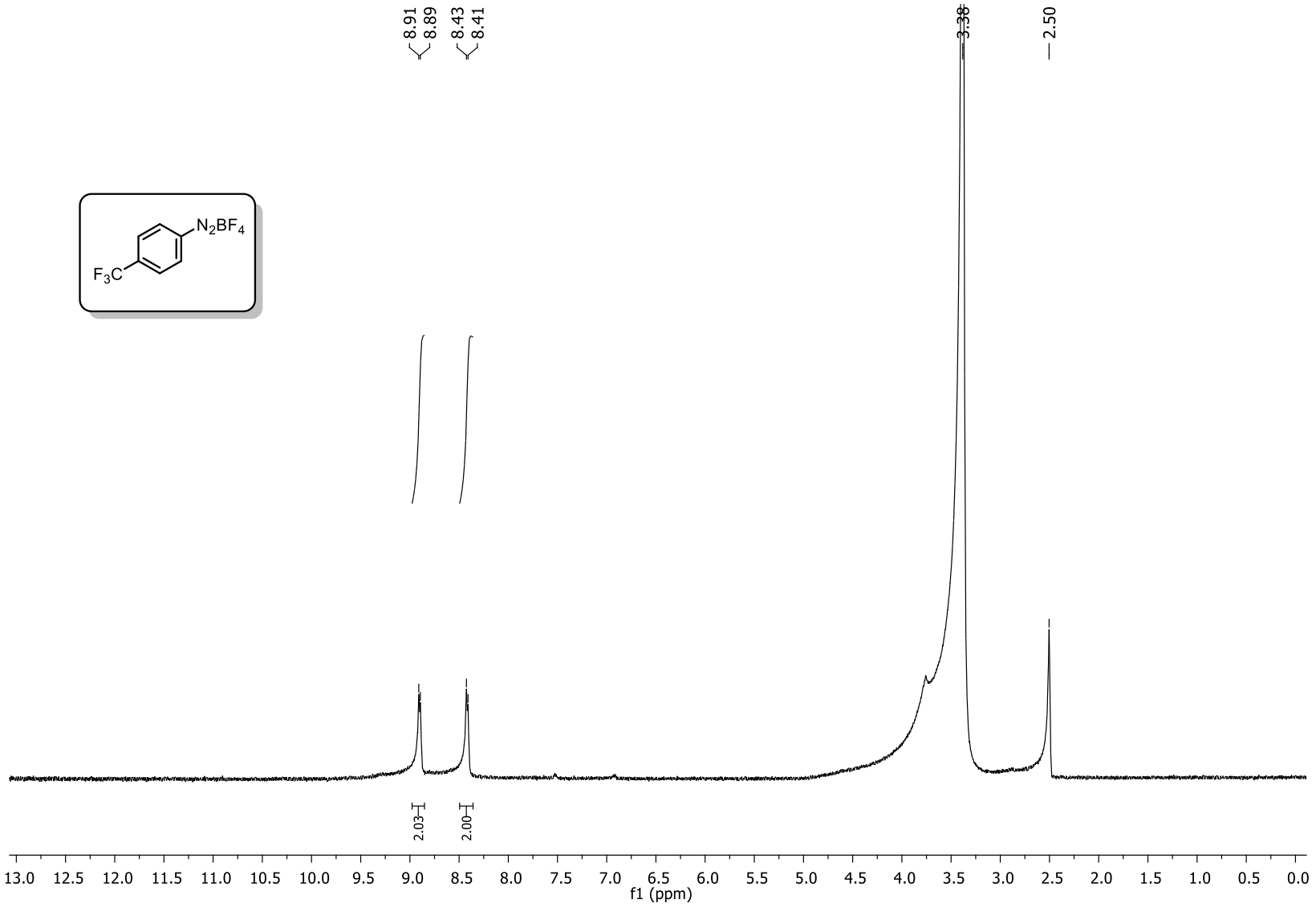
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of 4-tert-butylbenzenediazonium tetrafluoroborate (**5a**)



^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of 4-trifluoromethylbenzenediazonium tetrafluoroborate (**5b**)



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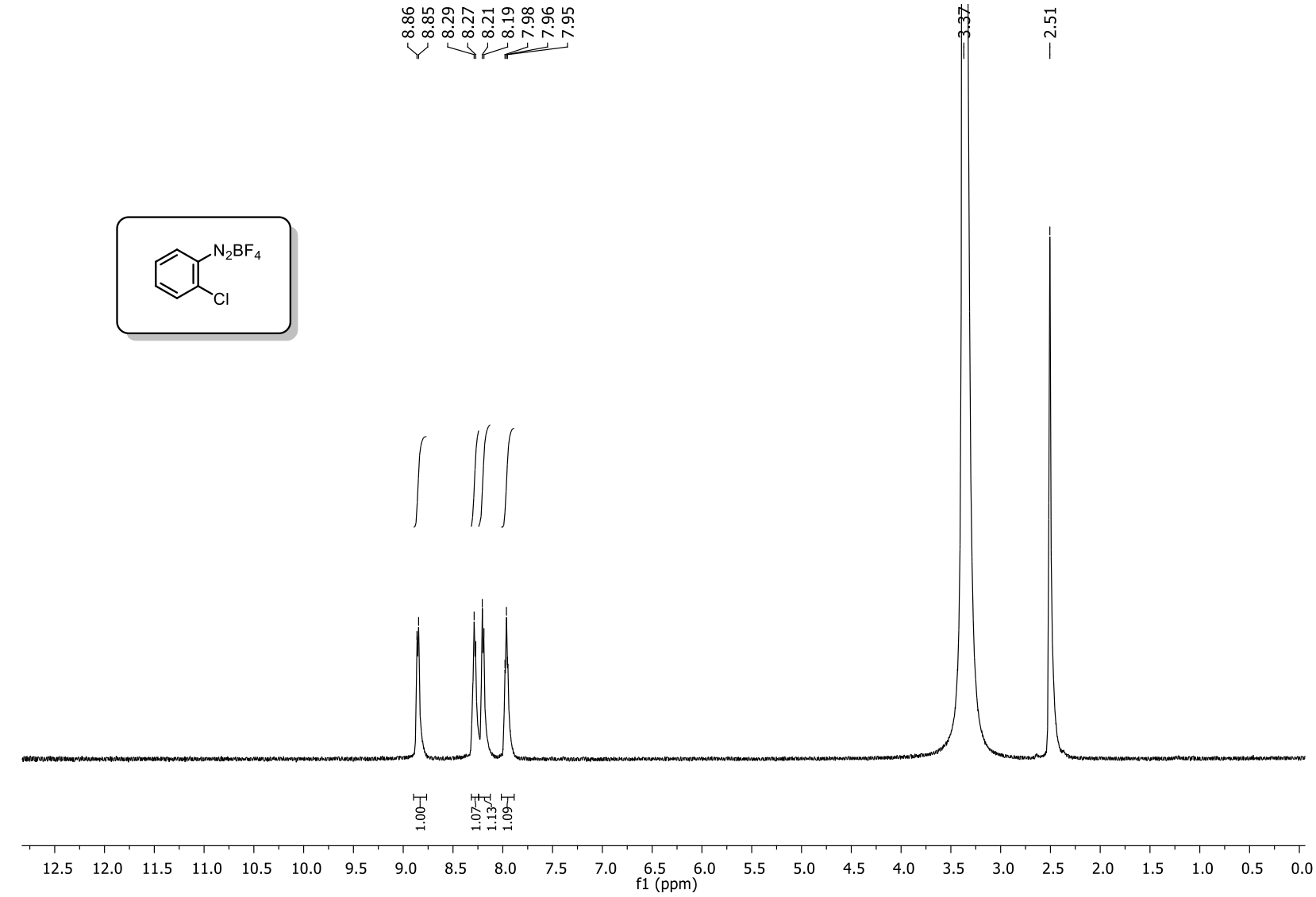
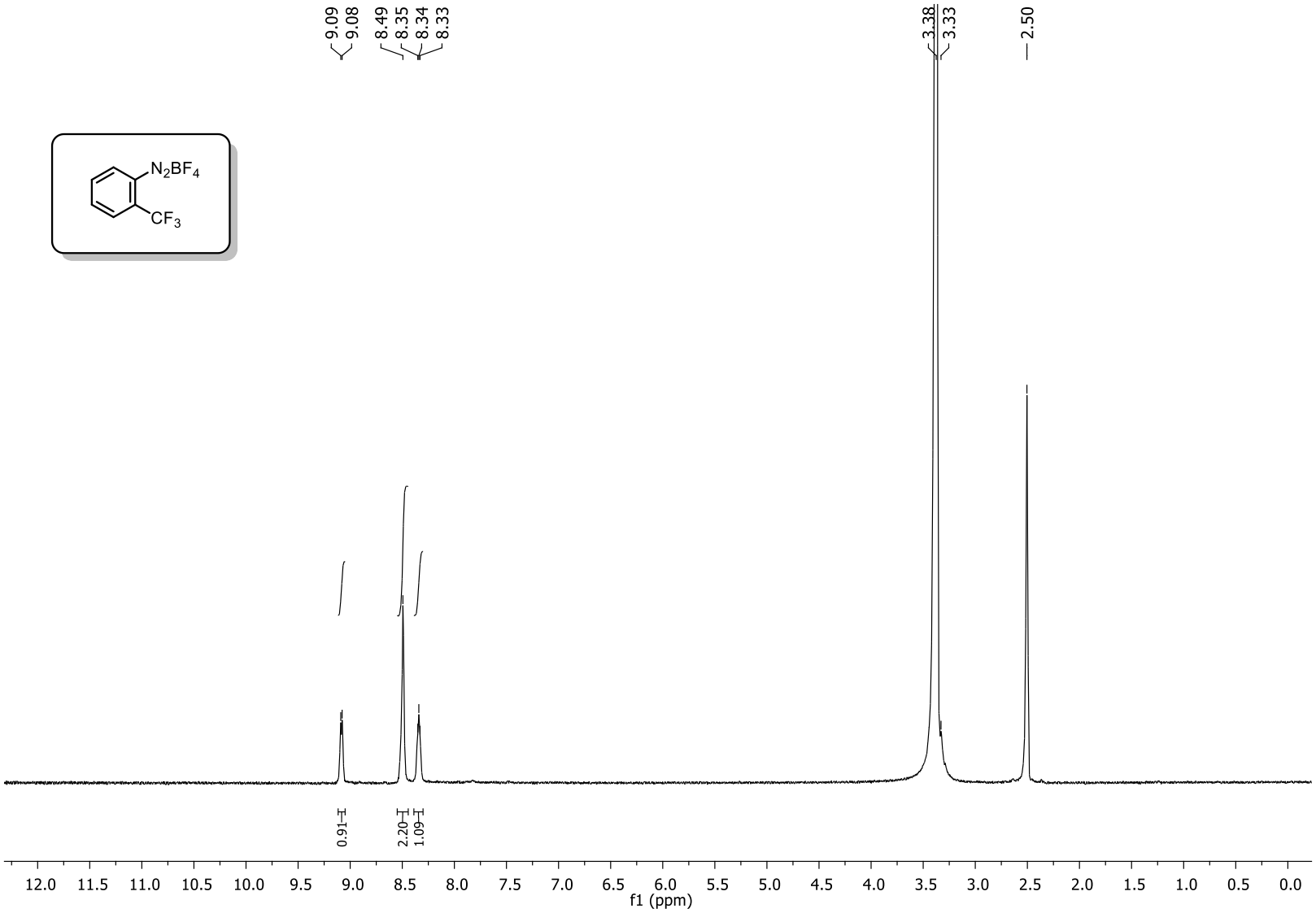
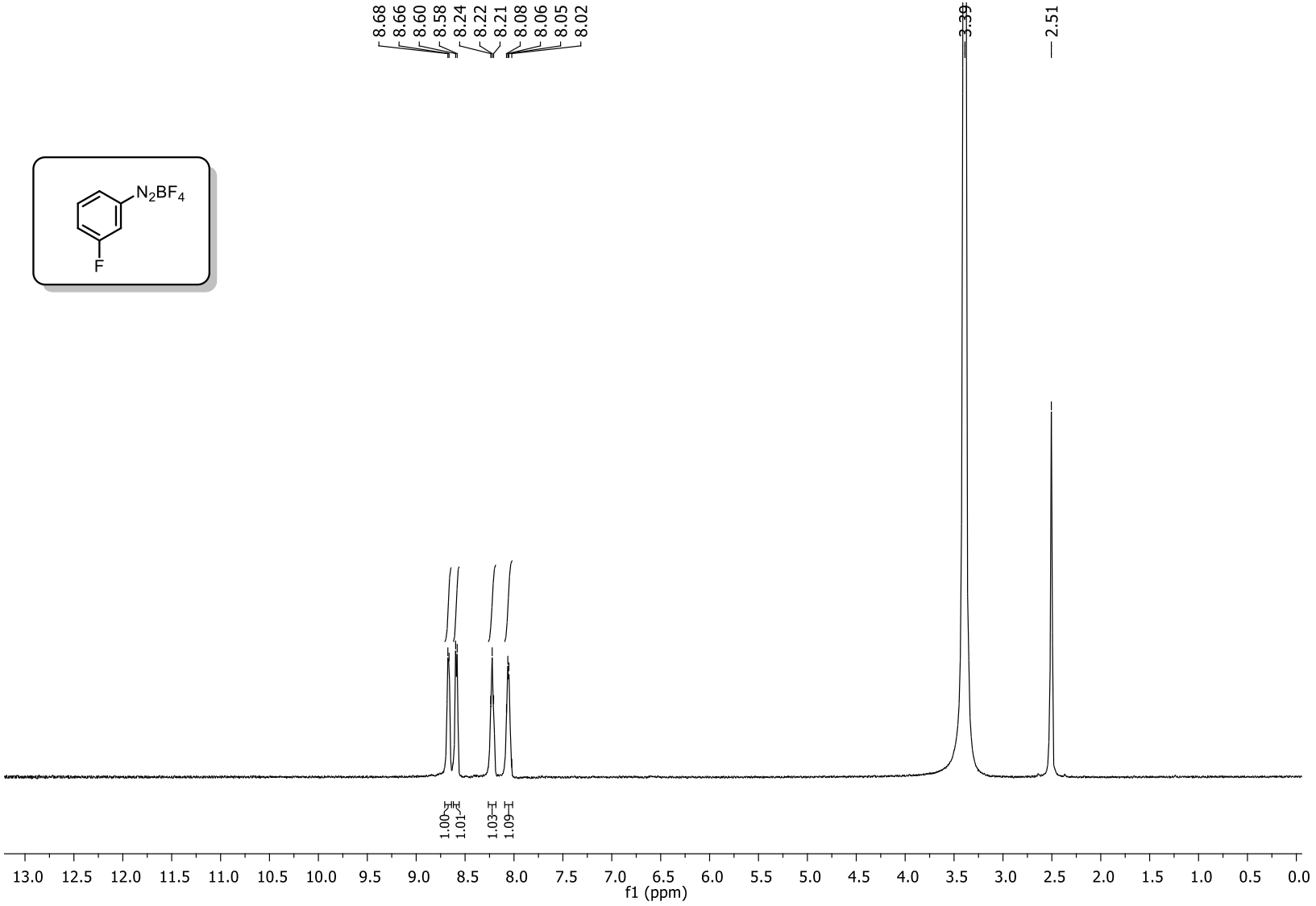


^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of 2-trifluoromethylbenzenediazonium tetrafluoroborate (**5d**)



^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of 3-fluorobenzenediazonium tetrafluoroborate (**5e**)



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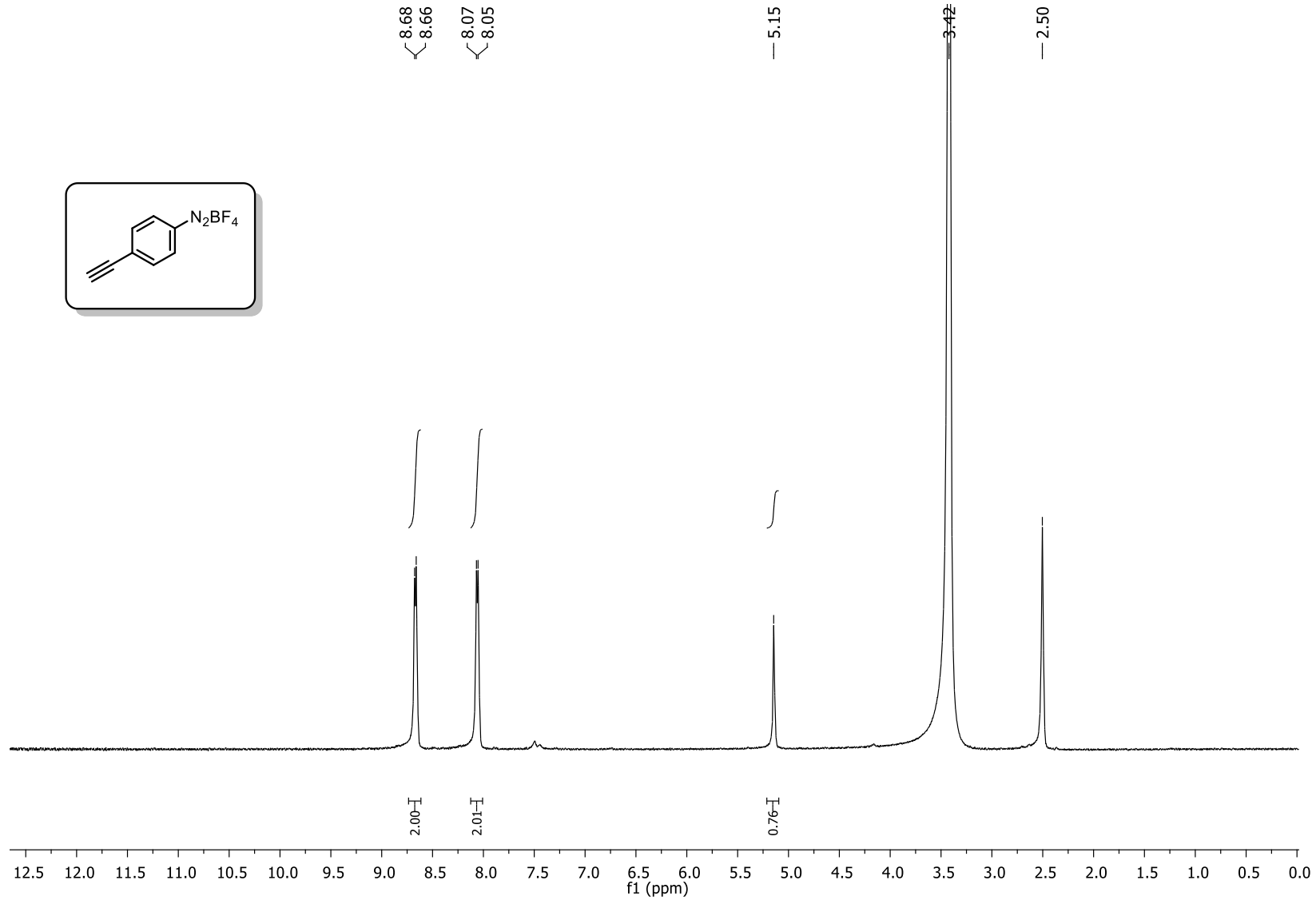

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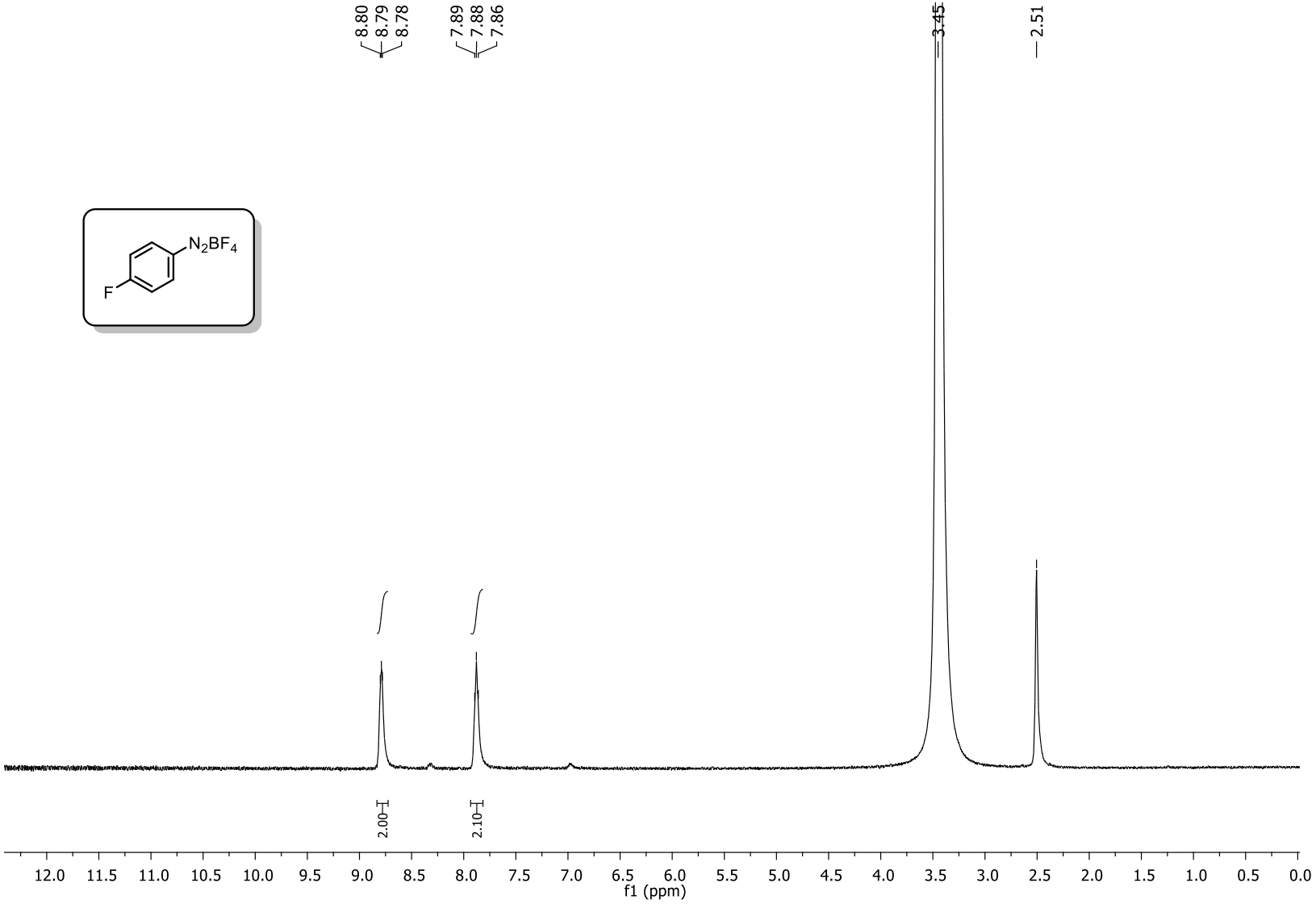

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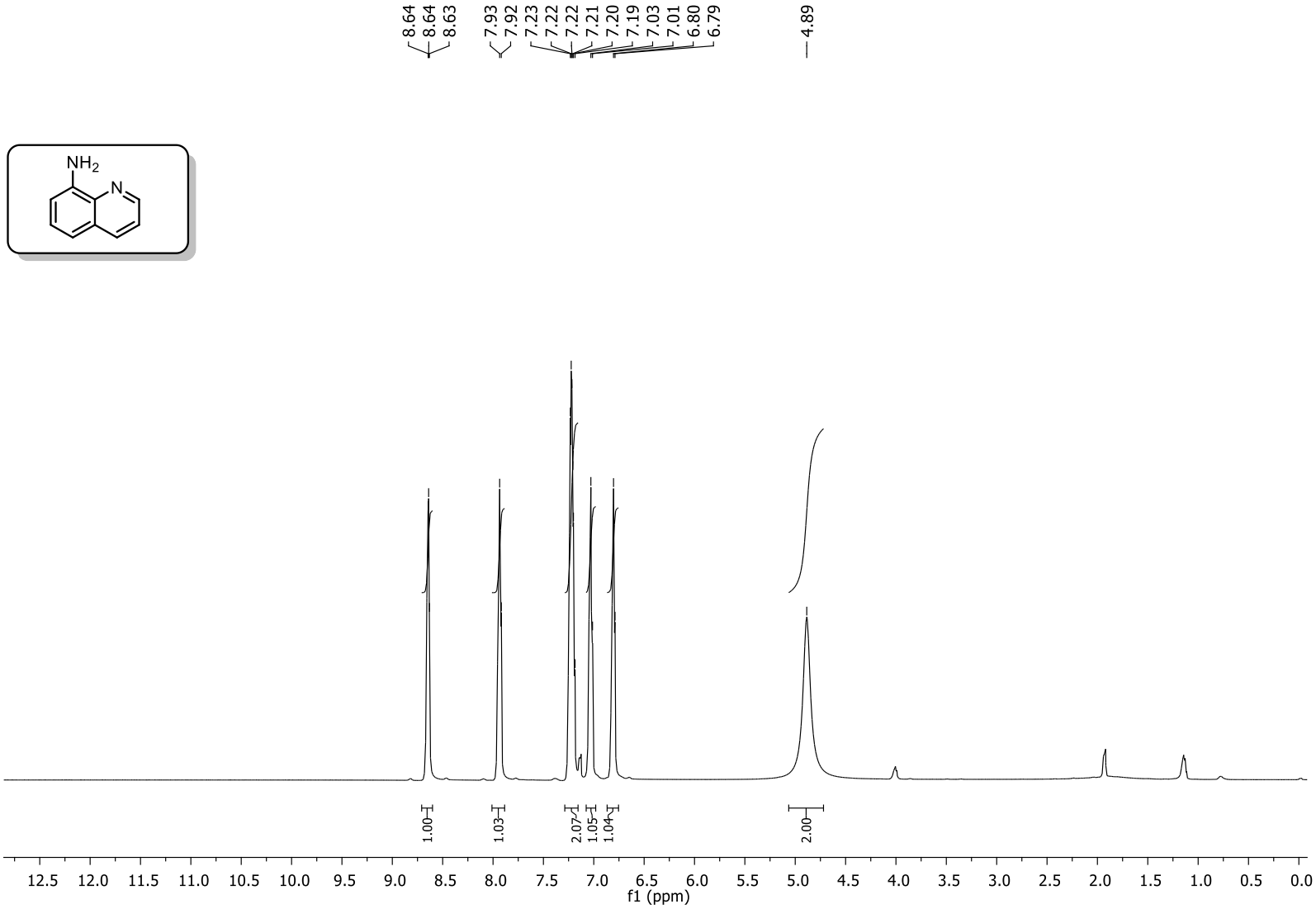
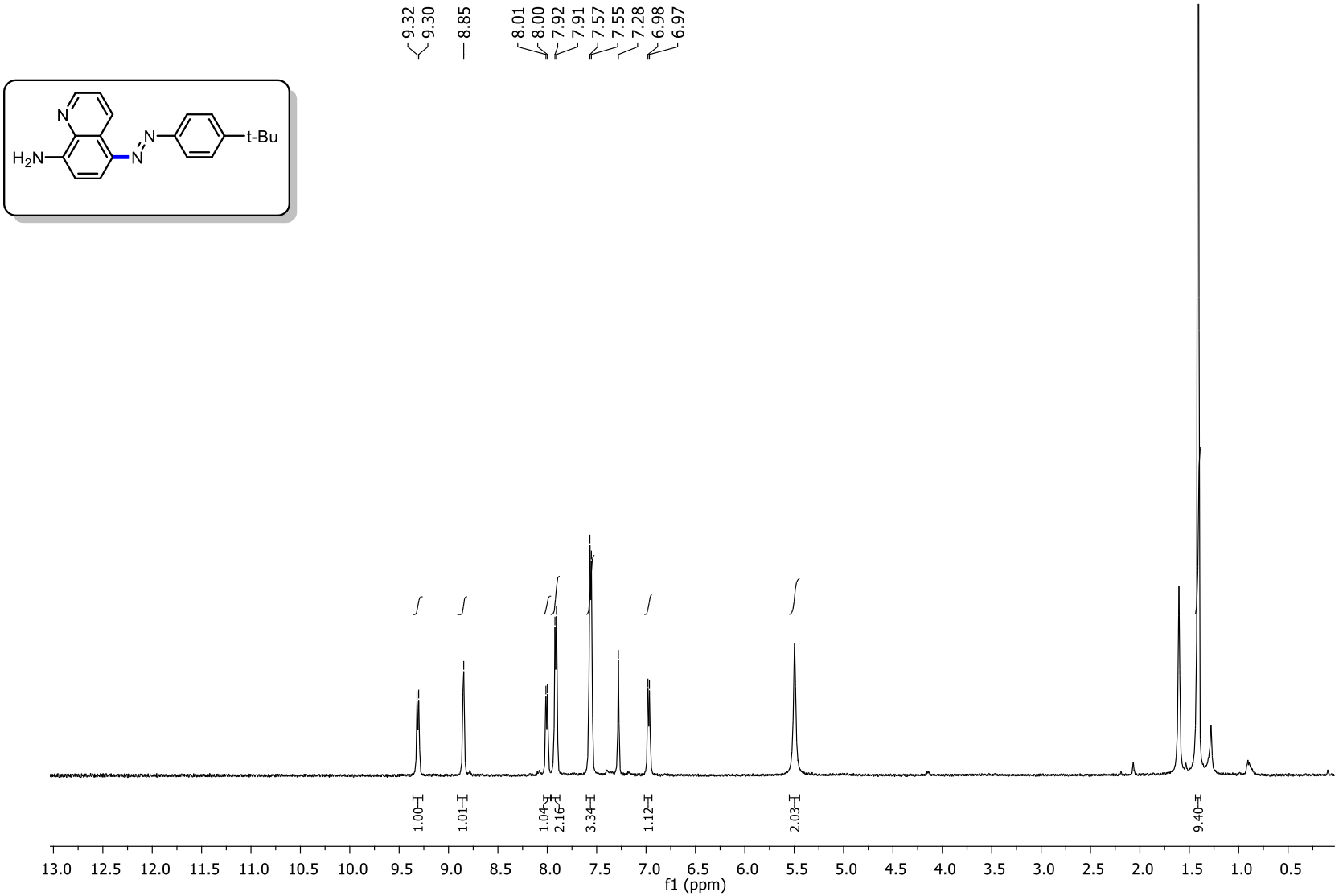
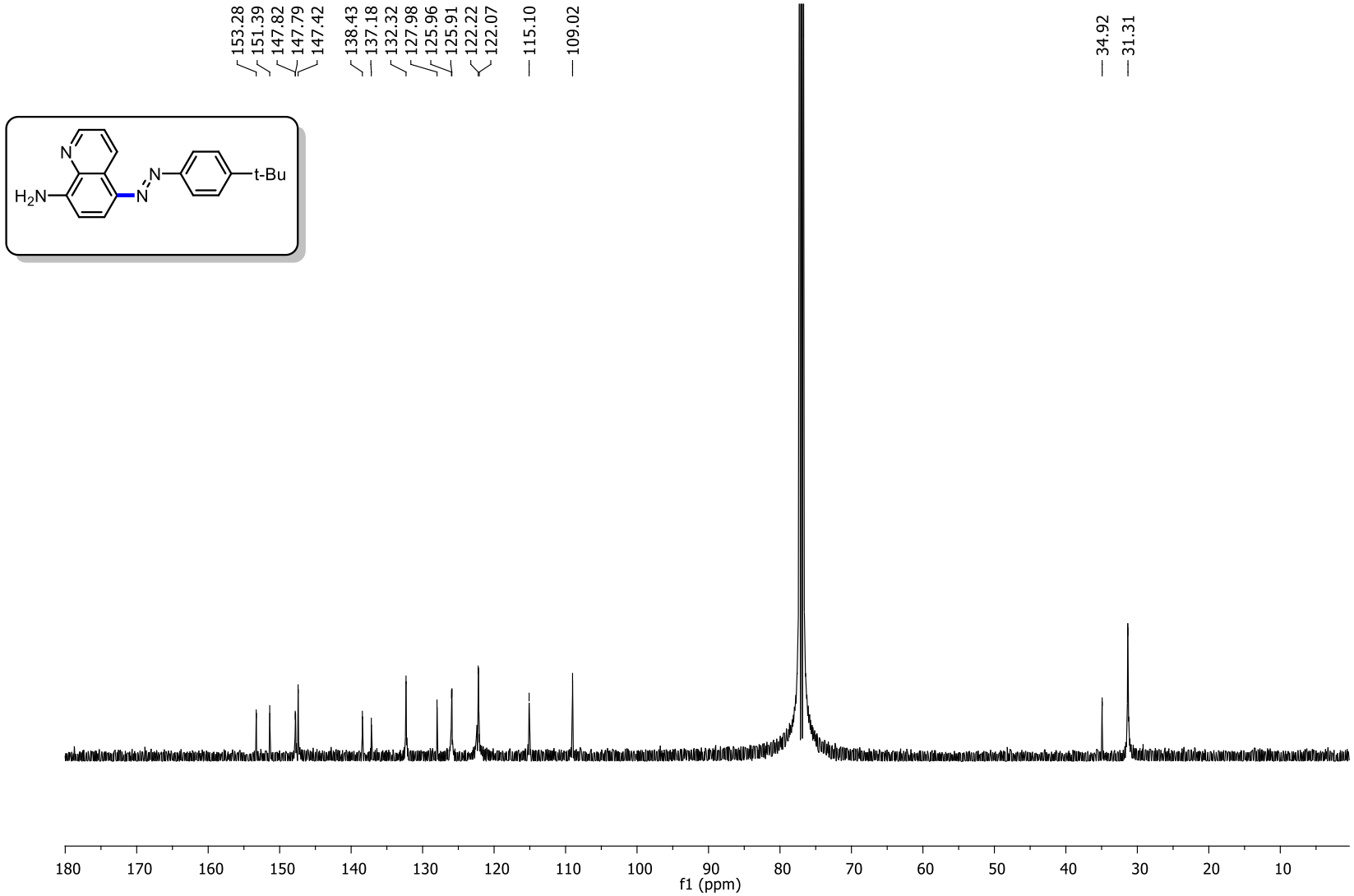


^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of (E)-5-((4-(tert-butyl)phenyl)diazenyl)quinolin-8-amine (**6a**)



^{13}C NMR ($CDCl_3$, 126 MHz) spectrum of (E)-5-((4-(tert-butyl)phenyl)diazenyl)quinolin-8-amine (**6a**)



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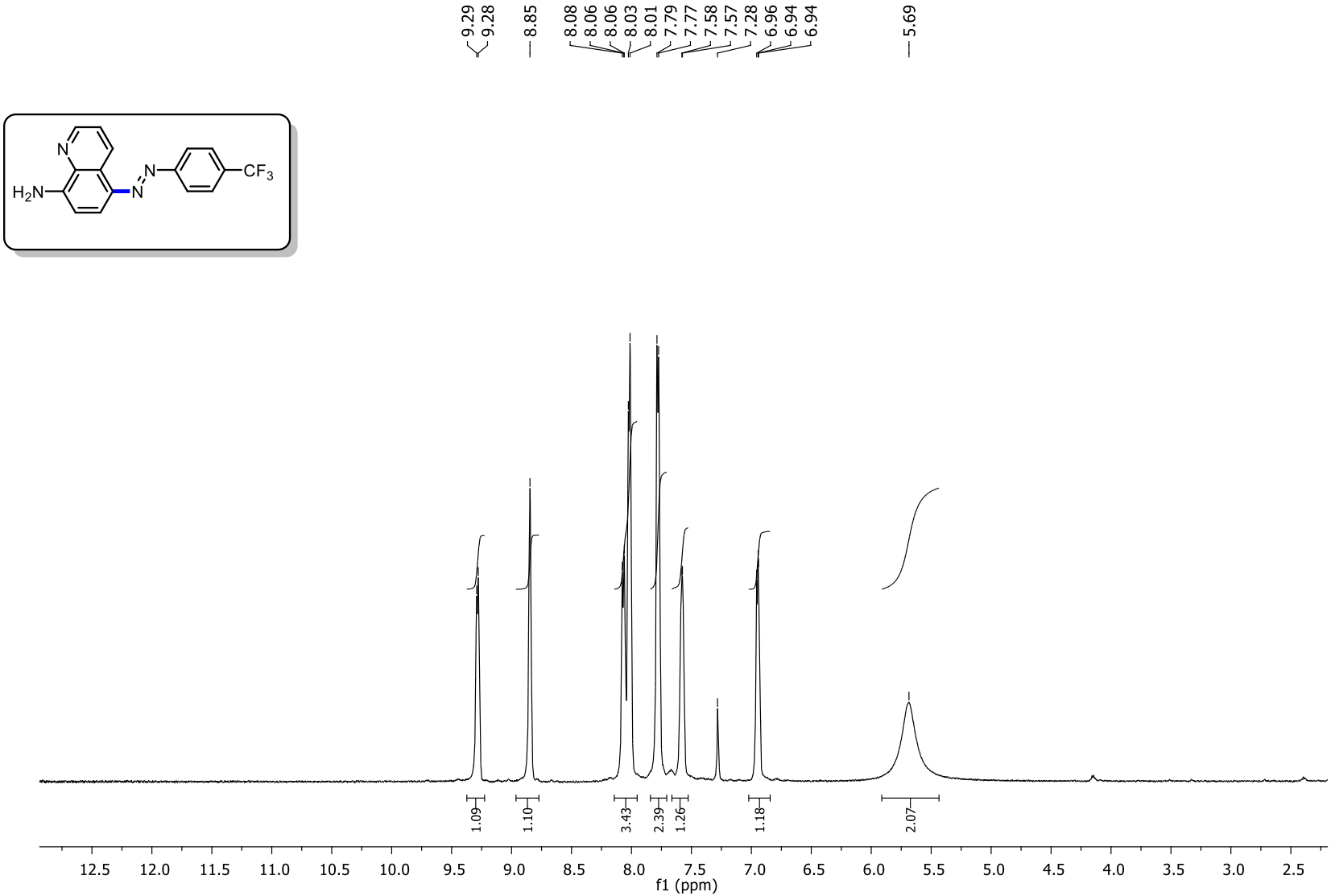
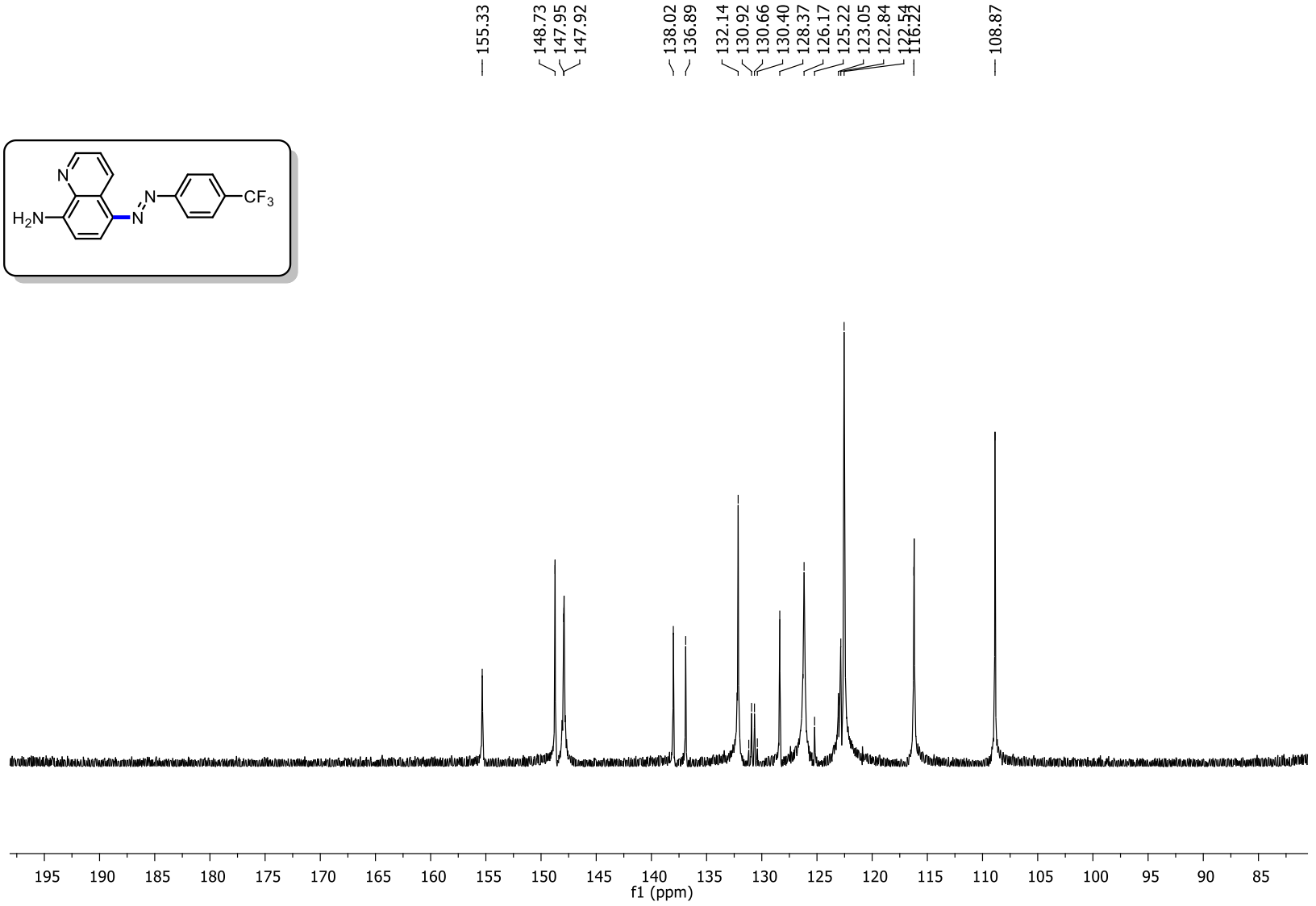
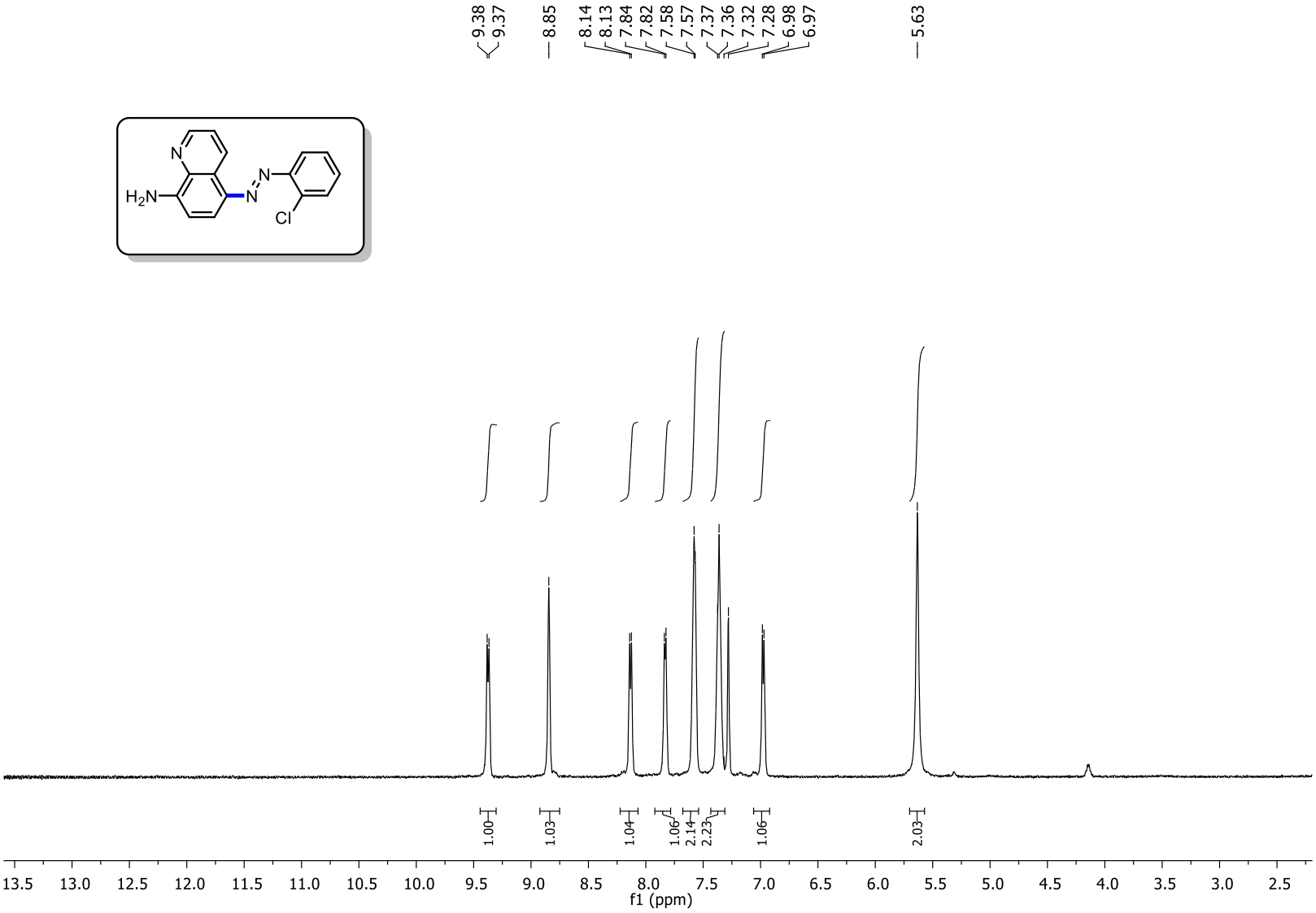


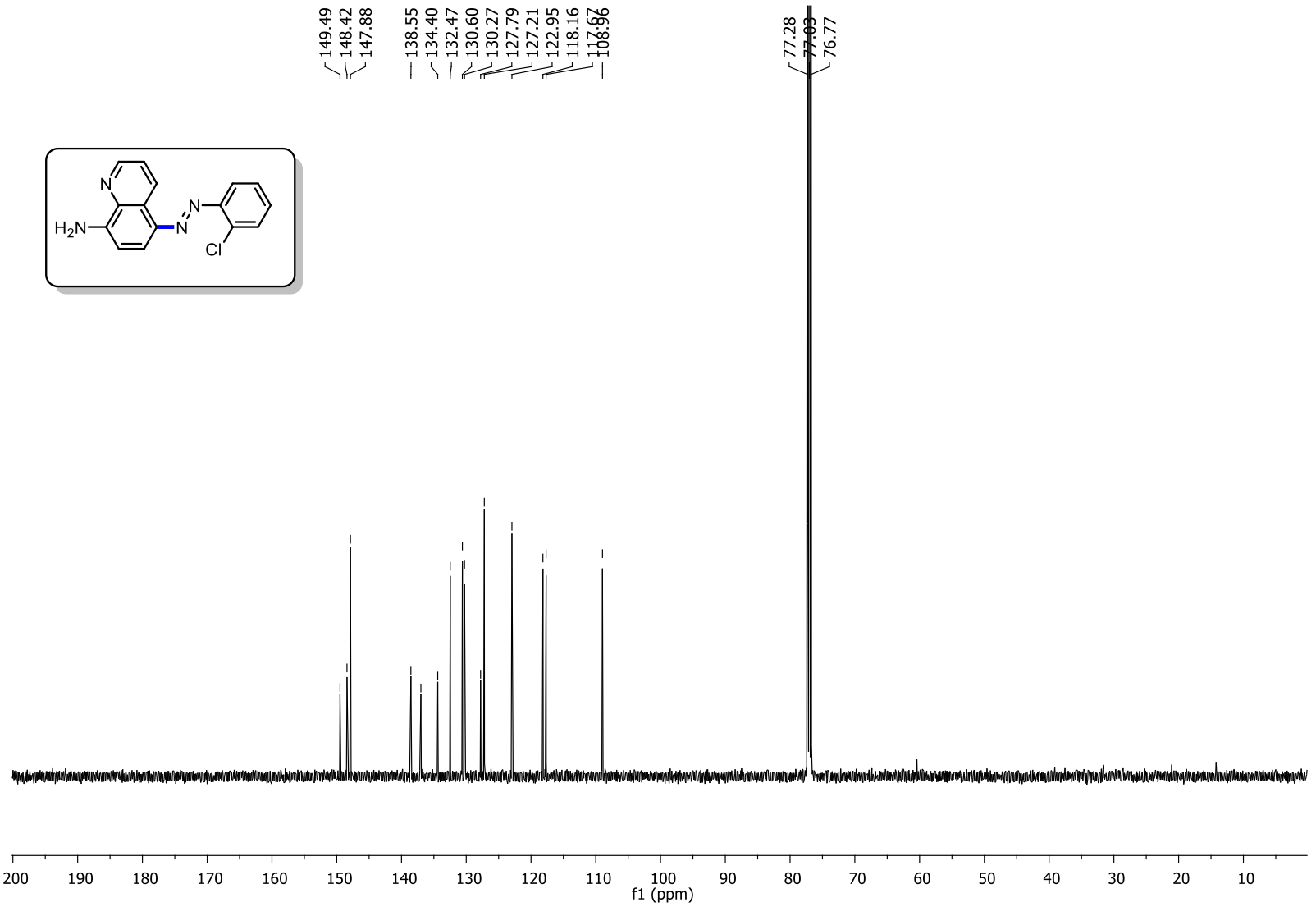
^{13}C NMR ($CDCl_3$, 126 MHz) spectrum of (E)-5-((4-(trifluoromethyl)phenyl)diazenyl)quinolin-8-amine (**6b**)



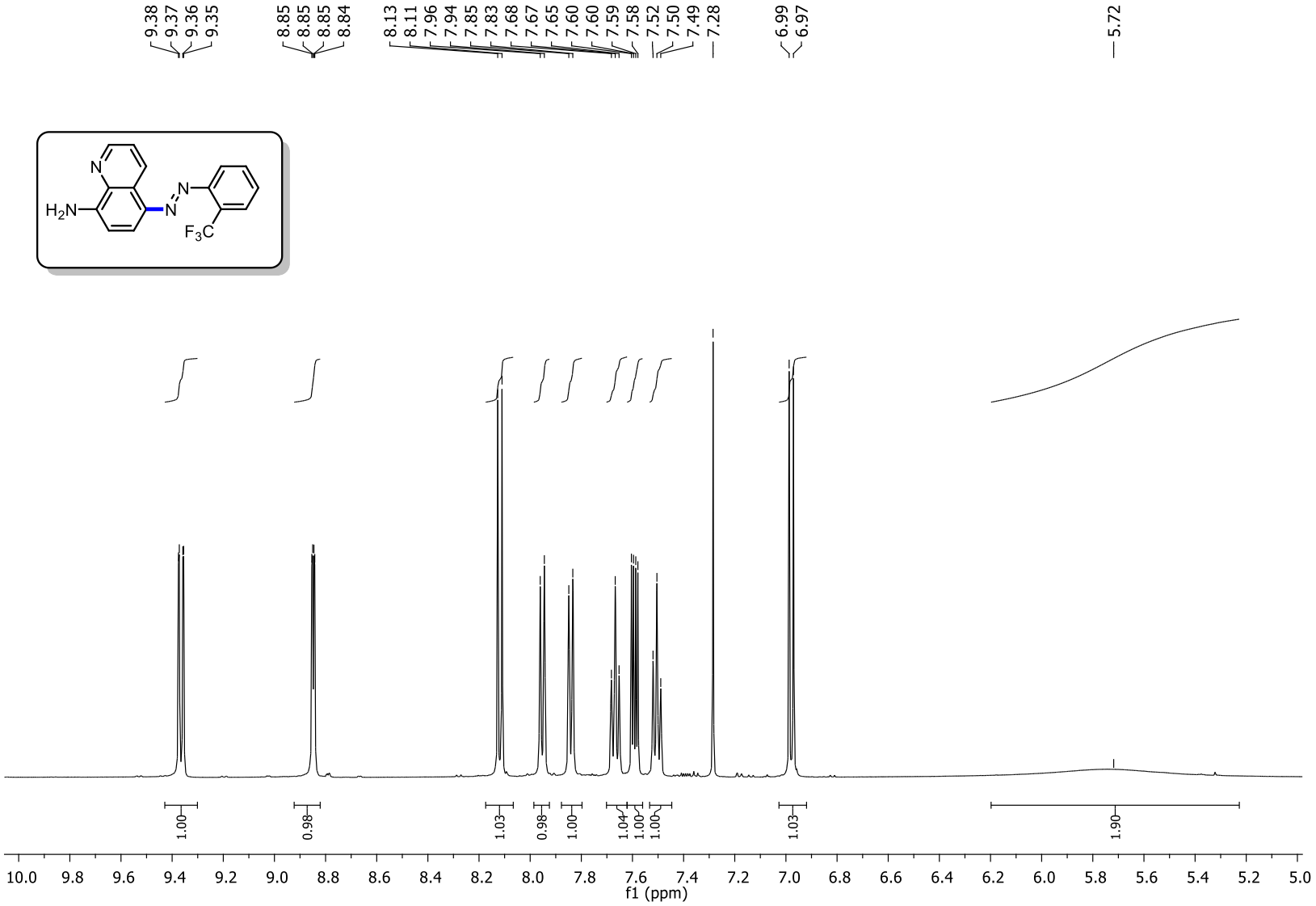
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of (E)-5-((2-chlorophenyl)diazenyl)quinolin-8-amine (**6c**)



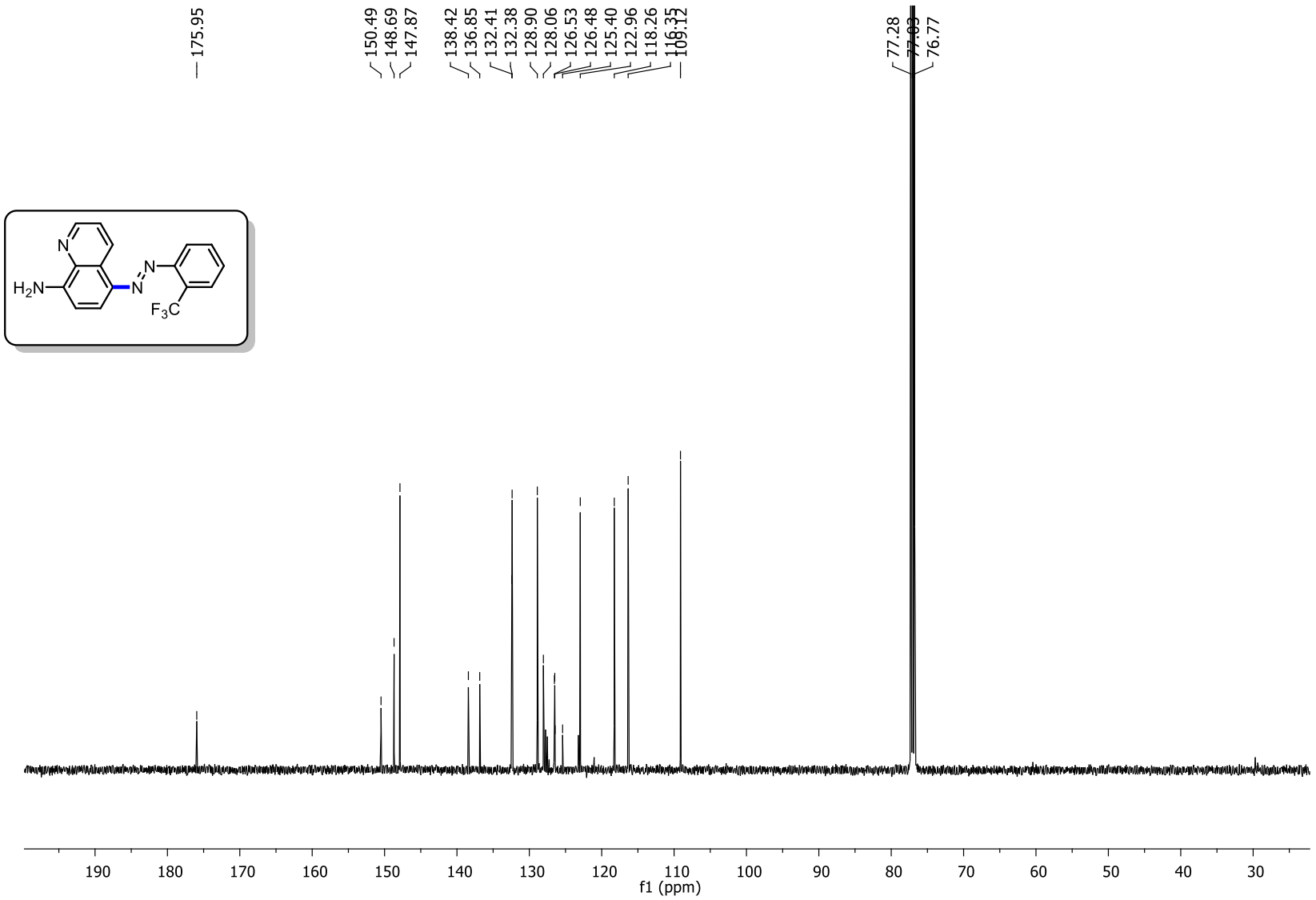
^{13}C NMR ($CDCl_3$, 126 MHz) spectrum of (E)-5-((2-chlorophenyl)diazenyl)quinolin-8-amine (**6c**)



^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of (E)-5-((2-(trifluoromethyl)phenyl)diazenyl)quinolin-8-amine (**6d**)



^{13}C NMR ($CDCl_3$, 126 MHz) spectrum of (E)-5-((2-(trifluoromethyl)phenyl)diazenyl)quinolin-8-amine (**6d**)



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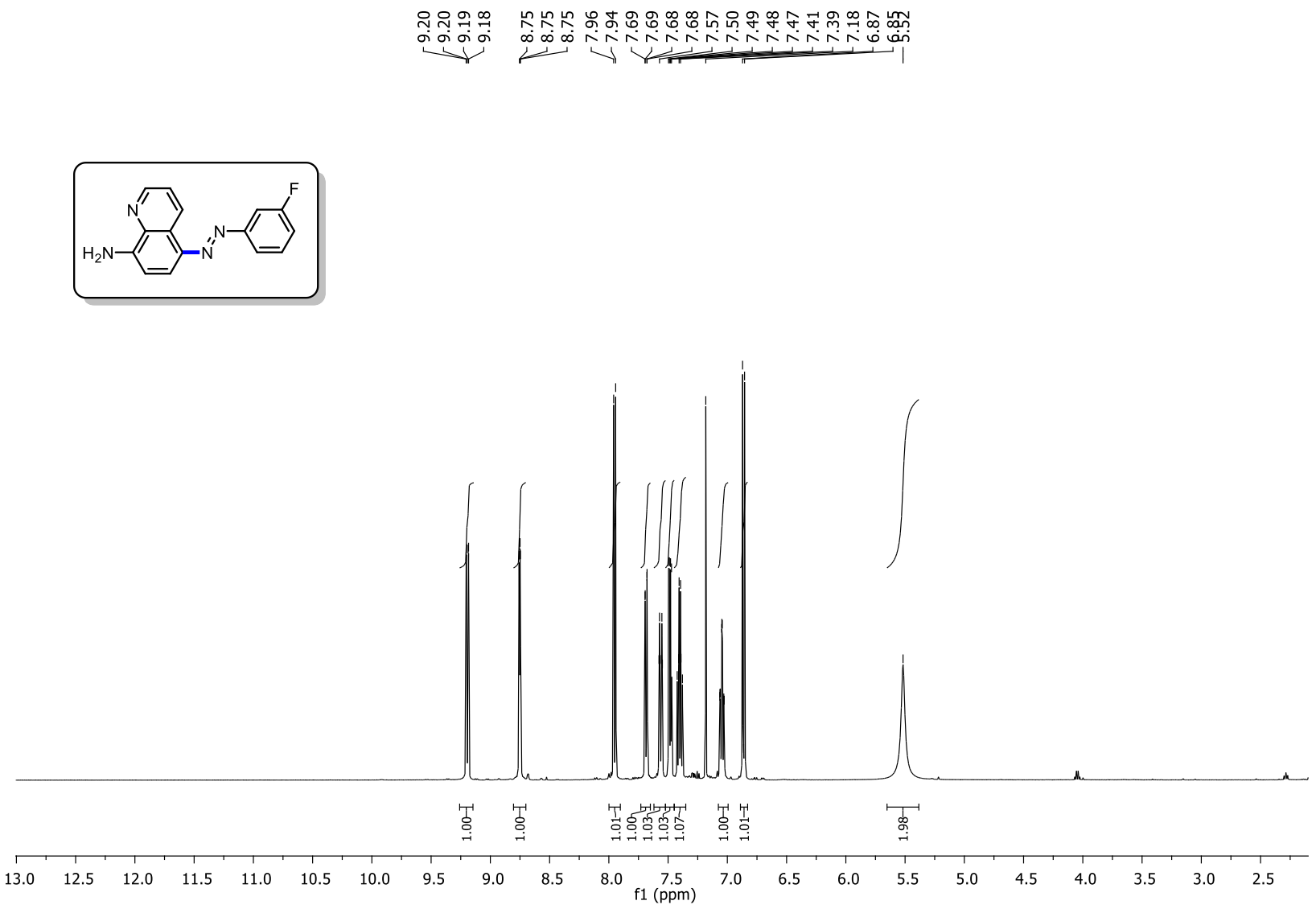
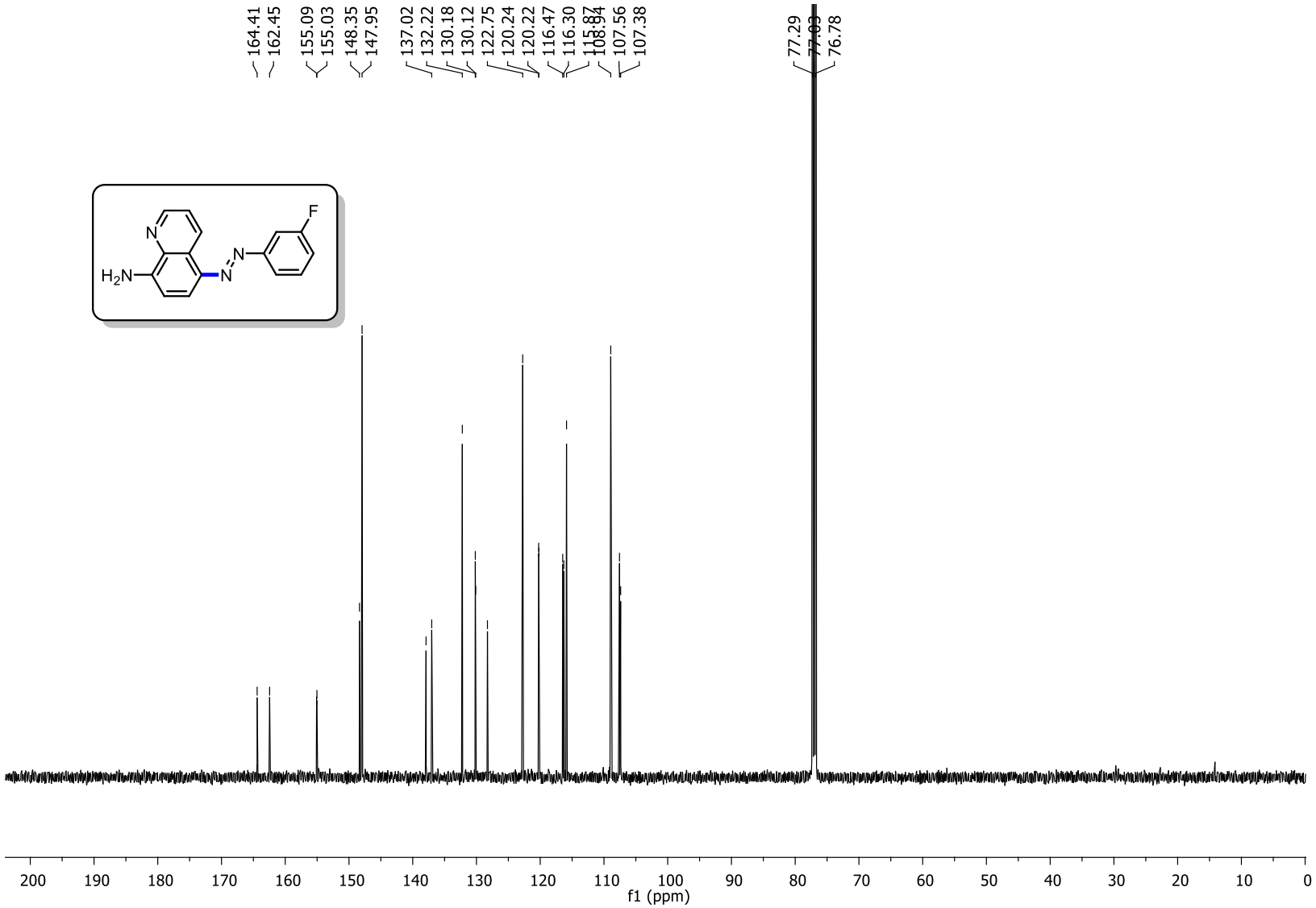
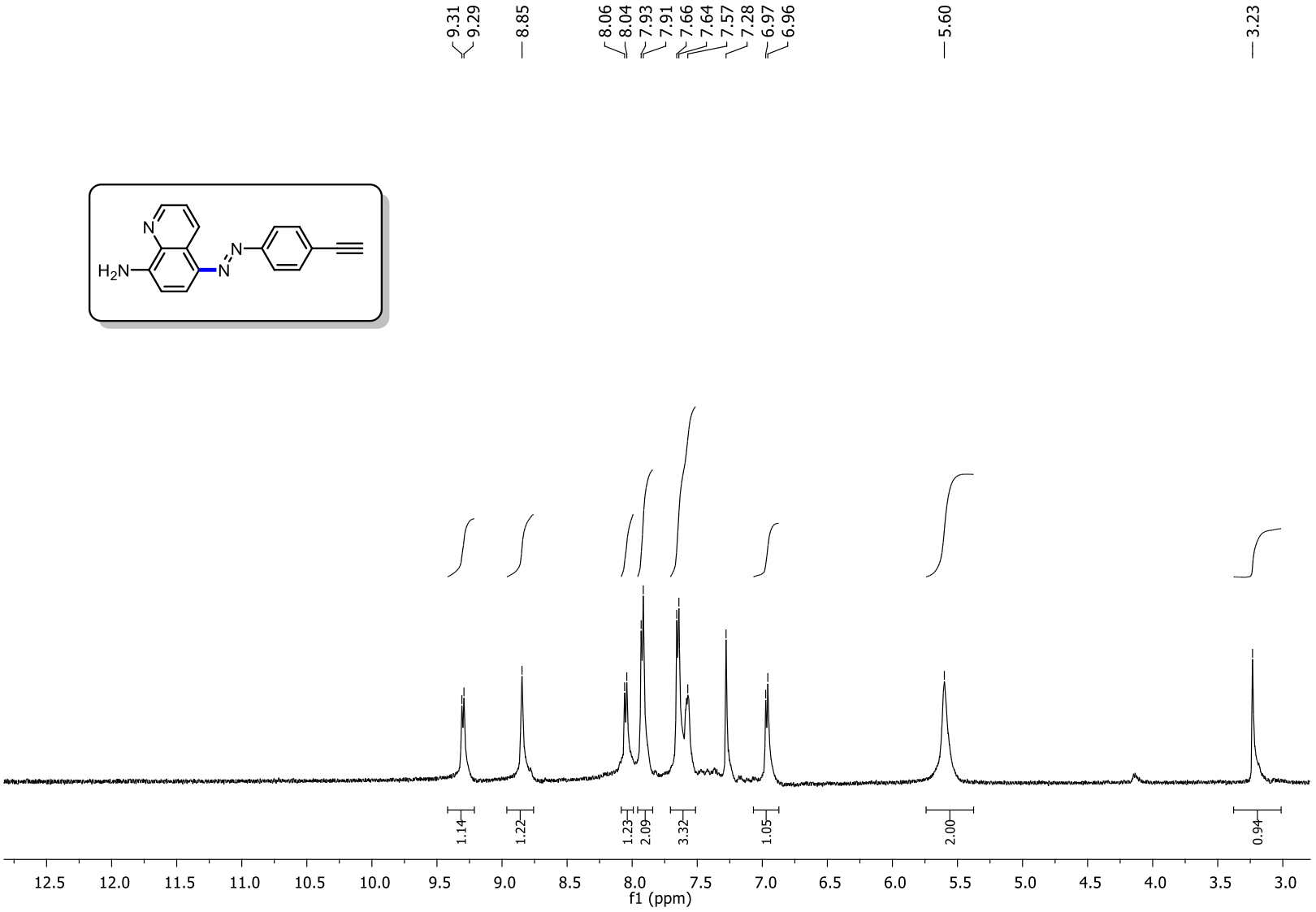


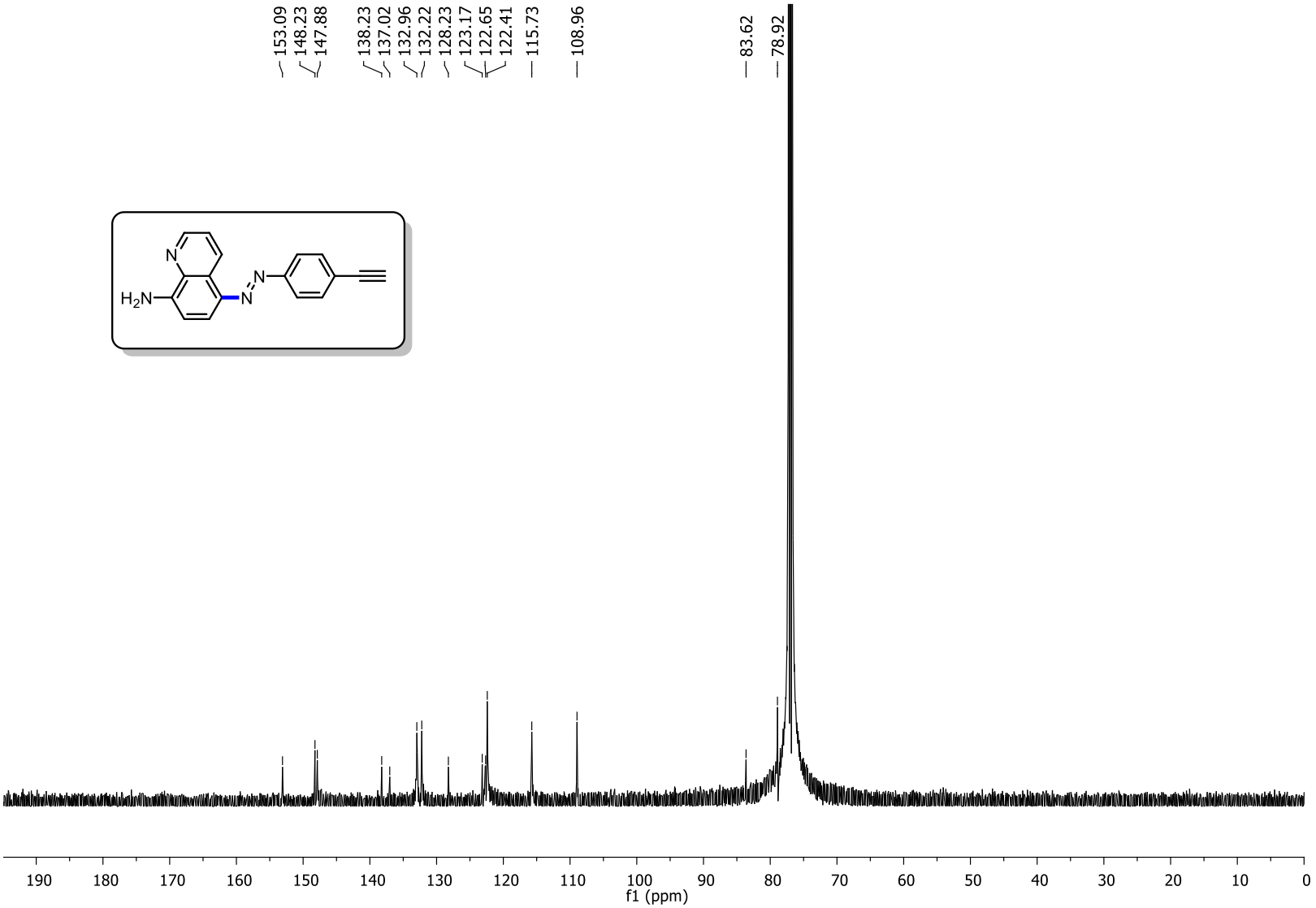
^{13}C NMR ($CDCl_3$, 126 MHz) spectrum of (E)-5-((3-fluorophenyl)diazenyl)quinolin-8-amine (**6e**)



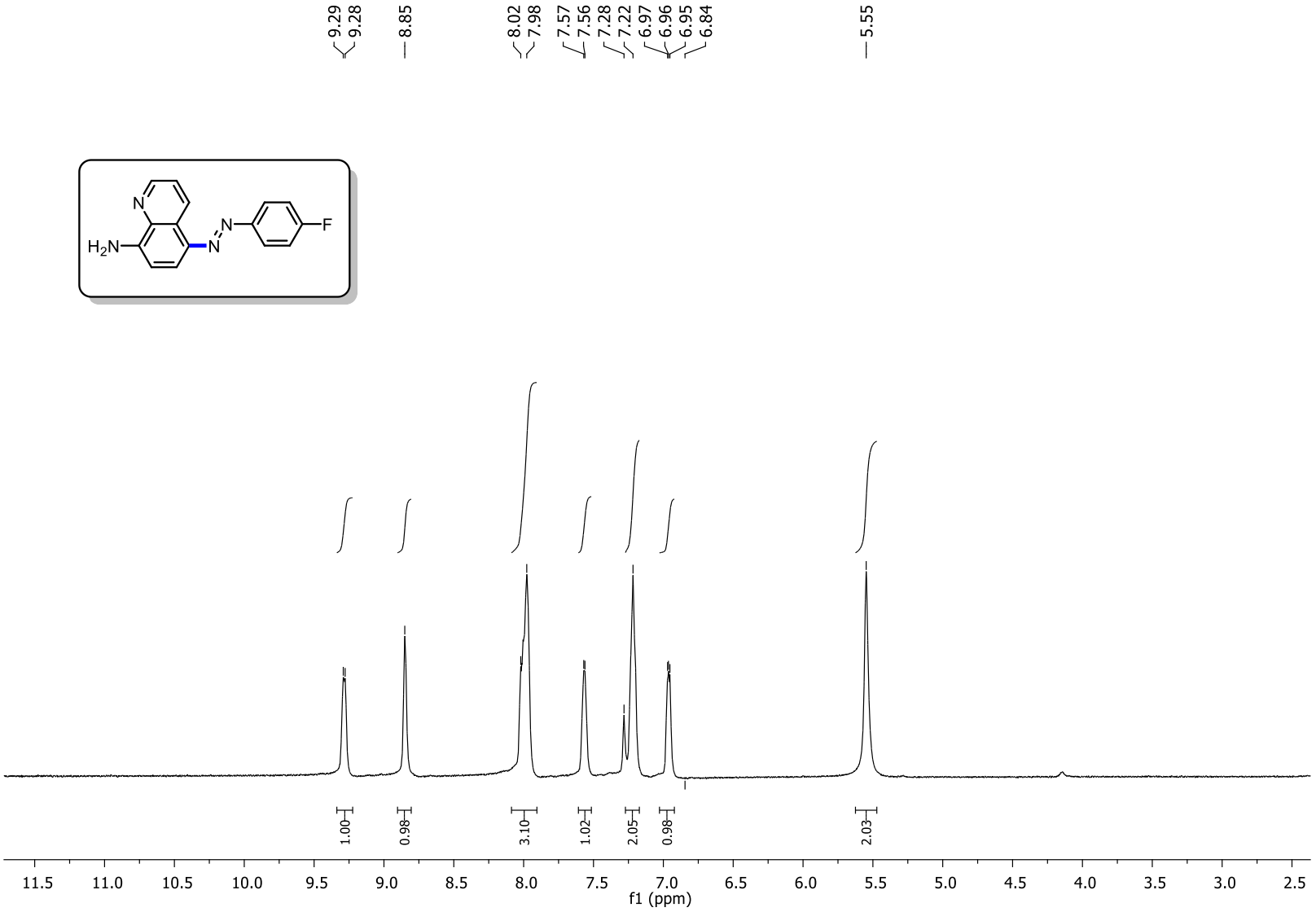
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of (E)-5-((4-ethynylphenyl)diazenyl)quinolin-8-amine (**6f**)



^{13}C NMR ($CDCl_3$, 126 MHz) spectrum of (E)-5-((4-ethynylphenyl)diazenyl)quinolin-8-amine (**6f**)



^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of (E)-5-((4-fluorophenyl)diazenyl)quinolin-8-amine (**6g**)



^{13}C NMR ($CDCl_3$, 126 MHz) spectrum of (E)-5-((4-fluorophenyl)diazenyl)quinolin-8-amine (**6g**)