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Supporting Information

Computational and Experimental Studies on Copper-Mediated Selective Cascade C-H/N-H Annulation of Electron-Deficient Acrylamide with Arynes

Chao Chen,[†] Yu Hao,[†] Ting-Yu Zhang,[†] Jin-Long Pan,[†] Jun Ding,[†] Heng-Ye Xiang,[†] Man Wang,[†] Tong-Mei Ding,[†] Abing Duan,[*‡] Shu-Yu Zhang[*†]

[†]Sixth People's Hospital South Campus, Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, and School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai, 200240, China

[‡]College of Environmental Science &Technology, Hunan University, Changsha, 410082, China

*E-mail: zhangsy16@sjtu.edu.cn
*E-mail: duanabing@hnu.edu.cn

Contents

1. General information

Solvents: Dichloromethane was distilled from CaH_2, and toluene was distilled from Na before use.

Reagents: All commercial materials were used as received from Energy Chemical or Adamas-beta, Alfa Aesar, TCI and Acros unless otherwise noted. $Cu(OAc)_2$ (99.999%, Alfa Aesar), tetrabutylammonium iodide (TBAI) (98%, Energy), cesium fluoride (CsF) (99%, Adamas-beta), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (97%, Energy) were used in the Cu-mediated annulation reactions. O_2 is purchased from Wetry in 99.999% purity.

Reactions: All reactions were performed in oven-dried glassware under an atmosphere of oxygen unless otherwise noted. All yields reported were averages of at least two experimental runs.

Chromatography: Thin layer chromatography (TLC) was carried out on silica gel 60 F254 pre-coated glass plates. Visualization was detected by irradiation with UV light (254 nm), or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Flash chromatography was carried out on 200 – 300 mesh silica gel, eluting with a mixture of petroleum ether (b.p. 60 – 90 °C) and ethyl acetate.

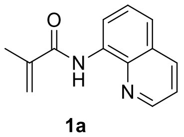
NMR Spectroscope: ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III HD 400 or 500 spectrometer, operating at 400 (or 500) MHz and 100 (or 125) MHz respectively. Chemical shifts (δ) were given in parts per million (ppm), and referenced relative to residual solvent $CHCl_3$ (7.26 ppm) in $CDCl_3$, or tetramethylsilane (0.00 ppm) as an internal standard for ^1H NMR spectra and deuterated solvent $CDCl_3$ (77.0 ppm) for ^{13}C NMR spectra. Coupling constants (J) were reported in hertz (Hz). The following abbreviations are used to indicate the multiplicity of the signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and associated combinations, e.g. dd = doublet of doublets.

Mass Spectrometry: High-resolution mass spectra (HRMS) were obtained on a Waters ACQUITYTM UPLC & Q-TOF MS Premier using the electrospray ionization (ESI) technique.

X-Ray: X-ray diffraction data were collected on a Bruker D8 VENTURE diffractometer or a Bruker APEX-II CCD diffractometer.

2. Preparation of substrates

1) Acrylamides below were prepared according to literature procedures. [1-4]



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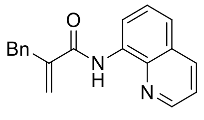

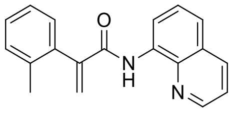

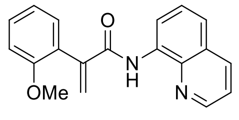

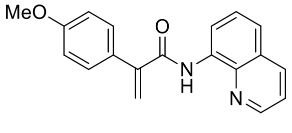

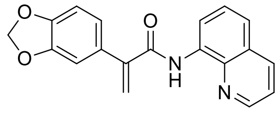

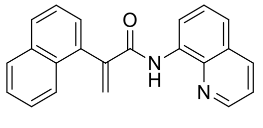

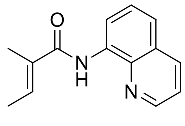

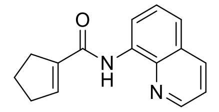

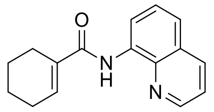

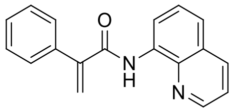

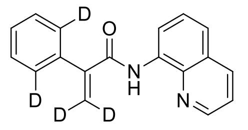

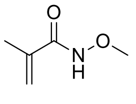

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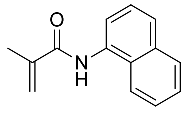
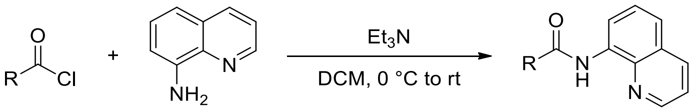


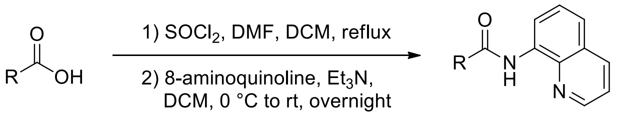
1c

General procedure A:



According to literature procedure [5], to a solution of 8-aminoquinoline (10 mmol, 1.0 equiv.) in dry DCM at 0 °C was added acyl chloride (12mmol, 1.2 equiv.) and Et_3N (15 mmol, 1.5 equiv.). Then the reaction mixture was stirred overnight at room temperature. Saturated $NaHCO_3$ solution was added and the mixture was extracted with DCM (20 mL × 3). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to give the corresponding amide.

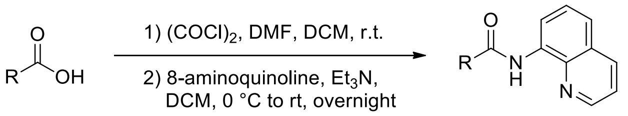
General procedure B:



According to literature procedure [6], a solution of acid (10 mmol, 1.0 equiv), $SOCl_2$

(11 mmol, 1.1 equiv) and DMF (3 drops) in DCM (20 mL) was heated to reflux for 5 hours, and the reaction mixture was concentrated *in vacuo*. And the residue was dissolved in DCM (20 mL), 8-aminoquinoline (9 mmol, 0.9 equiv) and Et_3N (13 mmol, 1.3 equiv) was added at 0 °C, and then stirred overnight at room temperature. Saturated $NaHCO_3$ solution was added and the mixture was extracted with DCM (20 mL × 3). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to give the corresponding amide.

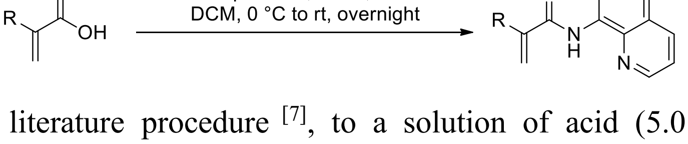
General procedure C:



To an oven-dried 50 mL flask, corresponding acid (252 mg, 2 mmol), DMF (2 drops) and DCM (10 mL) were added. Oxalyl chloride (2.4 mmol, 1.2equiv.) was added dropwise at 0 °C resulting in vigorous stirring. The mixture was stirred overnight at room temperature, and the solvent was then condensed in vacuo. The resulting acid chloride was used immediately without further purification.

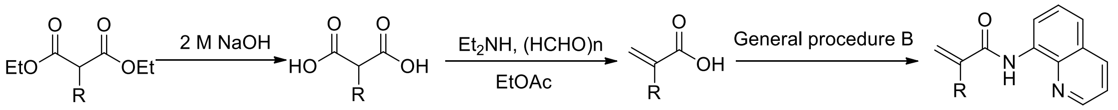
To another oven-dried 50 mL flask, 8-aminoquinoline (346 mg, 2.4 mmol, 1.2 equiv.), Et_3N (4 mmol, 2 equiv.) and DCM (10 mL) were added. A solution of the acid chloride in DCM (5 mL) was added dropwise to the solution at 0 °C, and the solution was then warmed to room temperature. After stirring overnight, the reaction system was quenched with sat. aq. $NaHCO_3$ (20 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers and brine (30 mL), were dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by flash column chromatography to give the corresponding amide.

General procedure D:



According to literature procedure [7], to a solution of acid (5.0 mmol) and 8-aminoquinoline (1.0 equiv., 5.0 mmol) in anhydrous CH_2Cl_2 (20 mL) were added EDCI (1.5 equiv., 7.5 mmol) and DMAP (0.2 equiv., 1 mmol). The reaction mixture was stirred at room temperature overnight, diluted with CH_2Cl_2 (60 mL), washed with aq HCl (1 M, 2 × 30mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography gave the corresponding aminoquinoline carboxamide compound.

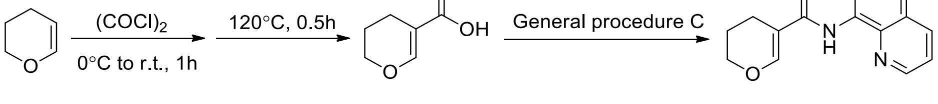
General procedure E:



According to a modified literature procedure [8], to the substituted malonate (synthesized by the treatment of diethylmalonate with base and the corresponding alkyl bromide/ iodide in DMF) was added 2 M NaOH (2.67 eq), and the resulting mixture was stirred vigorously and refluxed for 2 h. The resulting solution was cooled to rt and extracted with hexane (2x) and the aqueous layer was then acidified to pH 1 with aq HCl. The resulting solution was then extracted with EtOAc (3x), the combined organics washed with brine, dried ($MgSO_4$) and the volatiles removed in vacuo to afford the corresponding diacid which was used crude in the next step.

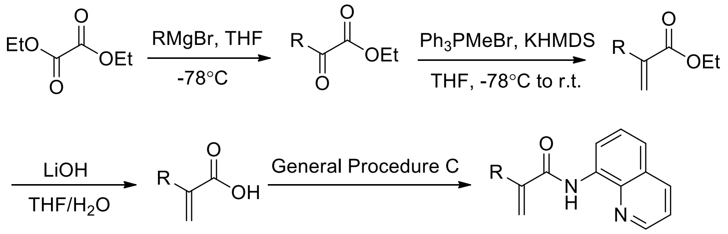
The crude diacid was dissolved in EtOAc (0.75 M) and the resulting solution was cooled to 0 °C, followed by the dropwise addition of diethylamine (1.01 eq) and subsequent addition of paraformaldehyde (1.5 eq). The resulting suspension was refluxed for 2 hours and then the reaction mixture was cooled to 0 °C, diluted with H_2O (0.6 mL/mmol diacid) and acidified to pH 1 with concentrated HCl. The aqueous layer was then extracted with EtOAc (3x) and the combined organics washed with brine, dried ($MgSO_4$) and the volatiles removed in vacuo to afford the crude acid, which was further used to synthesize the corresponding acrylamide by **General procedure B**.

General procedure F:



According to a modified literature procedure [9], oxalyl chloride (3.60 mL, 41.5 mmol) was cooled to 0 °C, and 3,4-dihydro-2H-pyran (1, 2.50 mL, 27.7 mmol) was added. The solution was slowly warmed to ambient temperature and stirring was continued for 1 h. Excess oxalyl chloride was evaporated in vacuo at 30 °C. The mixture was then heated to 120°C for 0.5 h, cooled to ambient temperature, and poured into an ice-cold aqueous solution of Na_2CO_3. The alkaline solution was extracted with dichloromethane, and then acidified with hydrochloric acid (6 M). The aqueous layer was extracted with dichloromethane, and the organic solution was dried with $MgSO_4$, filtered, and evaporated to yield the acid as a colorless solid, which was further used to synthesize the corresponding acrylamide by **General procedure C**.

General procedure G:

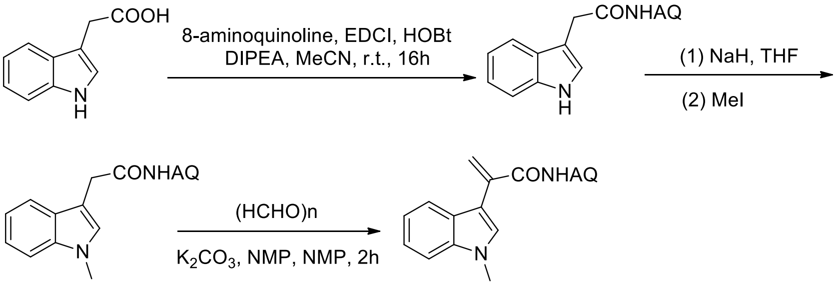


According to a modified literature procedure [10], to a solution of diethyl oxalate (5 mmol) in THF (5mL) at -78 °C was dropwise added fresh Grignard reagents prepared from corresponding aryl bromide) over 1 h. After stirring for 1 h at -78 °C, the mixture was warmed to room temperature and quenched with 2N HCl (10 mL). The aqueous layer was extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried over $MgSO_4$. The volatile compounds were removed in vacuo and the crude α-ketoesters were directly used in the next step without further purification.

An oven-dried 50 mL two-neck RBF was charged with methyl triphenylphosphonium bromide (5 mmol) and dry THF (10 mL). The flask was cooled to -78 °C and KHMDS (5 mmol, 1M in THF) was dropwise added to the solution under N_2 atmosphere. After stirring 15 minutes, the mixture was warmed up to room temperature and stirred for 1 hour, at which point the resulted yellow solution was recooled to -78 °C followed with the addition of crude α-ketoesters obtained in last step. After stirring for 1 hour at -78 °C, the mixture was warmed up to room temperature and the progress of the reaction was monitored using TLC. Once the reaction finished, 2N HCl (10 mL) was added followed by extraction with ethyl acetate (2×20 mL), and drying over $MgSO_4$. The organic solvent was evaporated and the residue was subjected to column chromatography on silica gel to deliver the α-substituted ethyl acrylate derivatives.

An 50 mL RBF was charged with α-substituted ethyl acrylate derivatives (1 eq.), LiOH (5 eq.), THF/H_2O (1:1, 0.25 M) sequentially. The reaction flask was subjected to a 80 °C preheated oil bath and stirred overnight, at which time the resulting mixture was cooled down to room temperature and extracted with diethyl ether. The aqueous phase was acidified with 2N HCl and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$. The volatile compounds were removed in vacuo to afford α-substituted acrylic acids, which were further used to synthesize the corresponding acrylamide by **General procedure C**.

General procedure H:

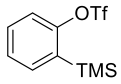


According to a modified literature procedure [11], to a solution of indole acetic acid (10 mmol), aniline (10 mmol), HOBt (12 mmol) in acetonitrile (40 mL), EDC.HCl (13 mmol) followed by DIPEA (30 mmol) was added, and mixture was stirred for 16 h at ambient temperature. The reaction mixture was evaporated to dryness, diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ solution (25 mL), H_2O (25 mL), brine (25 mL), and dried over Na_2SO_4. The crude material obtained after removal of solvent was purified by column chromatography to afford corresponding amide.

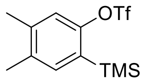
The amide was dissolved in THF (10 mL) was added in NaH (1.1 equiv.) which dissolved in THF (20 mL) at 0°C. After addition, the mixture was warmed to room temperature and stirred for 1 h. The reaction was cooled in ice bath again and MeI (1.2 equiv.) was added. After 6 hours the solvent THF was then evaporated and the resulting solid was dissolved in chloroform (60 mL) and water (30 mL × 3) was afterwards added. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrate in vacuum. The resulting residue was purified by flash column chromatography to give the corresponding amide.

To a solution of the obtained amide (1.0 equiv) in N-methyl pyrrolidone (NMP) was added paraformaldehyde (3.0 equiv) and K_2CO_3 (2.0 equiv). The reaction mixture was stirred at 90 °C for 3 h. After cooling to room temperature, water was added and the mixture was extracted with Et_2O (3 times). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by flash column chromatography to give the corresponding acrylamide.

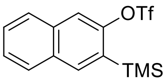
2) The substrates of benzyne precursors **2a**, **2b**, **2c**, **2d** and **2f** were purchased from Energy Chemicals or TCI, and benzyne precursor **2e** were prepared according to the literature procedure. [12]



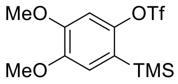
2a



2b



2c



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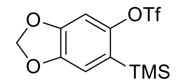
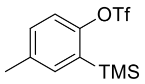
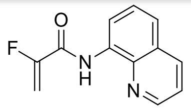


2e



2f



4a

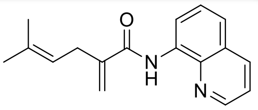
R_f = 0.4, 25% EtOAc in petroleum ether

Prepared according to General Procedure D. Purification of the crude product by flash column chromatography afforded the amide **4a** as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.83 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.79 (dd, *J* =5.1, 3.8 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6Hz, 1H), 7.55-7.54 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.87 (dd, *J* =47.0, 3.4 Hz, 1H), 5.29 (dd, *J* = 14.9, 3.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7 (d, *J* =11.6 Hz), 156.5 (d, *J* = 231.2 Hz), 148.6, 138.6, 136.2, 133.3, 127.9, 127.1, 122.6, 121.8, 117.1, 99.6 (d, *J* = 15.3 Hz).

HRMS (ESI) *m/z* calculated for $C_{12}H_{10}FN_2O$ [M+H$^+$] 217.0772, found 217.0781.



5a

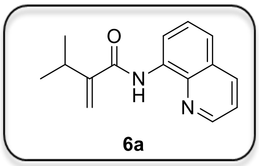
R_f = 0.4, 25% EtOAc in petroleum ether

Prepared according to General Procedure E. Purification of the crude product by flash column chromatography afforded the amide **5a** as yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 10.33 (s, 1H), 8.84 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.14 (dd, *J* =8.3, 1.7 Hz, 1H), 7.56-7.48 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.04 (d, *J* = 0.4 Hz), 5.51 (s, 1H), 5.30-5.27 (m, 1H), 3.22 (d, *J* = 7.1 Hz, 2H), 1.78 (d, *J*= 0.8 Hz, 3H), 1.73 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 166.6, 148.1, 144.5, 138.7, 136.2, 134.8, 134.6, 127.9, 127.4, 121.51, 125.48, 120.4, 119.5, 116.5, 30.9, 25.8, 17.8.

HRMS (ESI) *m/z* calculated for $C_{17}H_{19}N_2O$ [M+H$^+$] 267.1492, found 267.1498.



6a

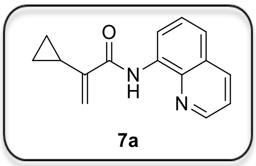
R$_f$ = 0.4, 25% EtOAc in petroleum ether

Prepared according to General Procedure E. Purification of the crude product by flash column chromatography afforded the amide **6a** as pale yellow solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 10.29 (s, 1H), 8.85-8.81 (m, 2H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.58-7.50 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.88 (s, 1H), 5.46 (d, *J* = 1.4 Hz, 1H), 3.07-3.00 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 167.8, 152.9, 148.2, 138.6, 136.3, 134.6, 127.9, 127.4, 121.6, 121.5, 116.4, 115.2, 29.7, 21.5.

HRMS (ESI) *m/z* calculated for $C_{15}H_{17}N_2O$ [M+H$^+$] 241.1335, found 241.1337.



7a

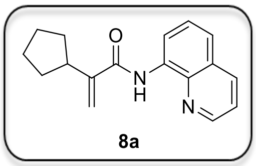
R$_f$ = 0.4, 25% EtOAc in petroleum ether

Prepared according to General Procedure G. Purification of the crude product by flash column chromatography afforded the amide **7a** as colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 10.87 (s, 1H), 8.88 (dd, *J* = 7.5, 1.3 Hz, 1H), 8.82 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.58-7.51 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.21 (s, 1H), 5.42 (s, 1H), 1.86-1.81 (m, 1H), 1.08-1.04 (m, 2H), 0.74-0.70 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 148.3, 145.1, 138.9, 136.3, 134.6, 128.0, 127.5, 121.61, 121.57, 120.3, 116.6, 12.5, 6.6.

HRMS (ESI) *m/z* calculated for $C_{15}H_{15}N_2O$ [M+H$^+$] 239.1179, found 239.1189.



8a

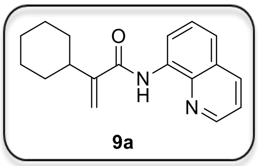
R$_f$ = 0.4, 25% EtOAc in petroleum ether

Prepared according to General Procedure E. Purification of the crude product by flash column chromatography afforded the amide **8a** as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.83 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.81-8.79 (m, 1H), 8.14 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.56-7.48 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.91 (s, 1H), 5.48 (d, *J* = 1.5 Hz, 1H), 3.11-3.03 (m, 1H), 2.07-1.99 (m, 2H), 1.79-1.63 (m, 4H), 1.58-1.49 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 149.8, 148.1, 138.5, 136.2, 134.5, 127.8, 127.3, 121.5, 121.4, 116.3, 115.8, 41.7, 31.6, 24.8.

HRMS (ESI) *m/z* calculated for $C_{17}H_{19}N_2O$ [M+H$^+$] 267.1492, found 267.1498.



9a

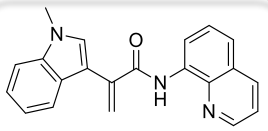
R$_f$ = 0.4, 25% EtOAc in petroleum ether

Prepared according to General Procedure E. Purification of the crude product by flash column chromatography afforded the amide **9a** as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.84-8.81 (m, 2H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.57-7.50 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.86 (s, 1H), 5.41 (d, *J*=1.4 Hz, 1H), 2.69-2.64 (m, 1H), 1.96-1.93 (m, 2H), 1.83-1.80 (m, 2H), 1.76-1.73 (m, 1H), 1.47-1.38 (m, 2H), 1.28-1.18 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 152.1, 148.2, 138.6, 136.3, 134.6, 127.9, 127.4, 121.6, 121.5, 116.4, 115.4, 39.5, 32.2, 26.5, 26.2.

HRMS (ESI) *m/z* calculated for $C_{18}H_{21}N_2O$ [M+H$^+$] 281.1648, found 281.1666.



10a

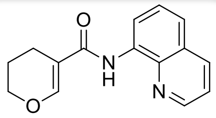
R_f = 0.4, 25% EtOAc in petroleum ether

Prepared according to General Procedure H. Purification of the crude product by flash column chromatography afforded the amide **10a** as yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.94 (dd, *J* = 7.5, 1.3 Hz, 1H), 8.63 (dd, *J* = 4.2, 1.7 Hz,1H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.61-7.57 (m, 1H), 7.53 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.47 (s, 1H), 7.41-7.38 (m, 2H), 7.33-7.29 (m, 1H), 7.22-7.18 (m, 1H), 6.30 (d, *J* = 1.0 Hz, 1H), 5.99 (d, *J* = 1.0 Hz, 1H), 3.86 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 148.2, 138.8, 138.7, 137.3, 136.2, 134.7, 129.5, 127.9, 127.4, 126.7, 122.3, 121.7, 121.5, 120.2, 118.8, 116.7, 111.0, 109.6, 33.0.

HRMS (ESI) *m/z* calculated for $C_{21}H_{18}N_3O$ [M+H$^+$] 328.1444, found 328.1454.



11a

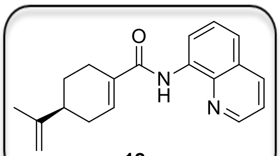
R_f = 0.4, 25% EtOAc in petroleum ether

Prepared according to General Procedure F. Purification of the crude product by flash column chromatography afforded the amide **11a** as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.81-8.79 (m, 2H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.72 (s, 1H), 7.55-7.52 (m, 1H), 7.47 (dd, *J* = 10.3, 1.4 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.13-4.10 (m, 2H), 2.56 (td, *J* = 6.3, 1.1 Hz, 2H), 2.05-2.00 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 152.6, 148.0, 138.7, 136.3, 134.8, 127.9, 127.5, 121.5, 121.0, 116.3, 109.2, 66.3, 21.3, 19.6.

HRMS (ESI) *m/z* calculated for $C_{15}H_{15}N_2O_2$ [M+H$^+$] 255.1128, found 255.1125.



12a

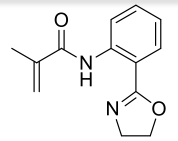
R_f = 0.4, 25% EtOAc in petroleum ether

Prepared according to General Procedure B. Purification of the crude product by flash column chromatography afforded the amide **12a** as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.87-8.83 (m, 2H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.59-7.50 (m, 2H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.99-6.98 (m, 1H), 4.81 (d, *J* = 8.4 Hz, 2H), 2.75-2.71 (m, 1H), 2.58-2.43 (m, 2H), 2.31-2.18 (m, 2H), 2.07-2.02 (m, 1H), 1.81 (s, 3H), 1.67-1.57 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 148.8, 148.1, 138.7, 136.3, 134.6, 134.2, 133.8, 127.9, 127.5, 121.5, 121.3, 116.4, 109.2, 40.2, 31.0, 27.1, 24.8, 20.8.

HRMS (ESI) *m/z* calculated for $C_{19}H_{21}N_2O$ [M+H$^+$] 293.1648, found 293.1666.



1e

R$_f$ = 0.4, 25% EtOAc in petroleum ether

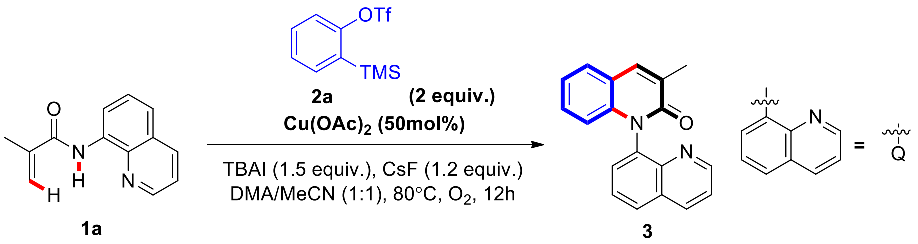
Prepared according to General Procedure A. Purification of the crude product by flash column chromatography afforded the amide **1e** as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.53 (s, 1H), 8.84 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.85 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.48-7.44 (m, 1H), 7.06 (td, *J* = 7.6, 0.9 Hz, 1H), 6.00 (s, 1H), 5.50 (dd, *J* = 1.4, 0.9 Hz, 1H), 4.38-4.34 (m, 2H), 4.13-4.10 (m, 2H), 2.09 (dd, *J* = 1.3, 0.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 164.6, 141.0, 139.9, 132.4, 129.1, 122.2, 120.9, 119.6, 113.3, 66.1, 54.6, 18.7.

HRMS (ESI) *m/z* calculated for $C_{13}H_{15}N_2O_2$ [M+H$^+$] 231.1128, found 231.1130.

3. Experimental details and characterization data

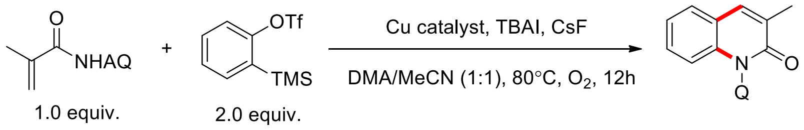


General Procedure for Cu-mediated cascade C-H/N-H annulation of acrylamide with arynes: A mixture of amide **1a** (42.5 mg, 0.2 mmol), $Cu(OAc)_2$ (18.3 mg, 0.1 mmol, 50 mol %), TBAI (111 mg, 0.3 mmol, 1.5 equiv.), CsF (36.5mg, 0.24 mmol, 1.2 equiv.)

and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (120mg, 2.0 equiv) in DMA (1 mL)/MeCN (1mL) in 10-mL glass vial (purged with O_2, sealed with PTFE cap) was heated at 80 °C for 12 hours. The reaction mixture was cooled to room temperature and diluted with EtOAc (20mL), and then the organic layer was washed with water (20mL × 3). The aqueous phase was extracted with EtOAc (20 mL × 2), and the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to give the annulation product **3** in 68% (38.8mg) isolated yield.

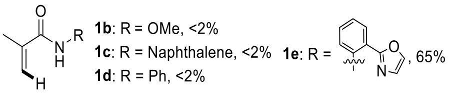
Gram scale reaction: A mixture of amide 1a (1.698 g, 8.0 mmol, 1 equiv.), $Cu(OAc)_2$ (740 mg, 4 mmol, 0.5 equiv.), TBAI (4.44 g, 12.0 mmol, 1.5 equiv.) and CsF (1.460 g, 9.6 mmol, 1.2 equiv.) in DMA (40.0 mL)/MeCN (40.0 mL) in a 250 mL three-necks flask purged with O_2 and then 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (3.6 mL, 12 mmol, 1.5 equiv.) was added under constant oxygen with two stainless steel needles. The mixture was heated at 80°C for 6 hours, and then was cooled to rt. The resulting residue was treated as the small scale above and purified by silica gel flash chromatography to give the annulation product **3** (1.50g, 65% isolated yield) as pale brown solid.

Optimization of Reaction Conditions[a]

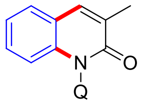


entry	reagents (equiv.)	yield [b](%)
1	$Cu(OAc)_2$ (0.35), CsF (1.2), TBAB (0.5), O_2	17
2	$Cu(OAc)_2$ (0.5), CsF (1.2), TBAB (0.5), O_2	24
3	$Cu(OAc)_2$ (0.5), **NaF (1.2)**, TBAB (0.5), O_2	5
4	$Cu(OAc)_2$ (0.5), **KF (1.2)**, TBAB (0.5), O_2	16
5	$Cu(OAc)_2$ (0.5), CsF (1.2), **TBAI (0.5)**, O_2	63
6	$Cu(OAc)_2$ (0.5), **CsF (2.4)**, TBAI (1.5), O_2	36
7	**$Cu(OAc)_2$ (0.5), CsF (1.2), TBAI (1.5), O_2**	**72(68)**[c]
8	**$Cu(OAc)_2$ (1.0)**, CsF (1.2), TBAI (1.5), O_2	63

9	$Cu(OAc)_2$ (0.5), CsF (1.2), TBAI (1.5), **Ar**	11
10	**$Pd(OAc)_2$ (0.2),** CsF (1.2), TBAI (1.5), O_2	<2
11	$Pd(OAc)_2$ (0.2), CsF (1.2), TBAI (1.5), AgOAc (2.0)	12
12	$Pd(OAc)_2$ (0.2), CsF (1.2), TBAI (1.5), $K_2S_2O_8$ (2.0)	15



[a] All screening reactions were carried out in a 10 mL glass vial with a PTFE-lined cap on a 0.2 mmol scale. [b] Yields are based on ^1H NMR analysis of the reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield in parentheses. TBAB = tetra-n-butylammonium bromide, TBAI = tetra-n-butylammonium iodide, DMA = N,N-dimethylaceta-mide.



3

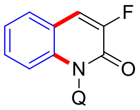
R_f = 0.4, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **3** as pale yellow solid in 67% yield (38.8 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.26 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.01 (dd, *J* = 7.3, 2.4 Hz,1H), 7.76 (s, 1H), 7.74-7.70 (m, 2H), 7.58-7.56 (m, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.19-7.12 (m, 2H), 6.43-6.40 (m, 1H), 2.33 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 151.4, 144.4, 140.6, 136.9, 136.3, 135.9, 130.5, 130.3, 129.7, 129.3, 128.7, 127.4, 126.7, 122.0, 121.9, 120.6, 115.6, 17.4.

HRMS (ESI) *m/z* calculated for $C_{19}H_{15}N_2O$ $[M+H^+]$ 287.1179, found 287.1185.



4

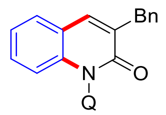
R_f = 0.4, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **4** as white solid in 39% yield (22 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.26 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.05-8.02 (m, 1H), 7.76-7.73 (m, 2H), 7.62-7.59 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.22-7.19 (m, 2H), 6.47-6.44 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6 (d, *J* = 26.8 Hz), 151.5, 150.9 (d, *J* = 253.5 Hz), 144.0, 138.6, 136.3, 134.5 (d, *J* = 1.1 Hz), 130.2, 129.9, 129.8, 129.0 (d, *J* = 2.7 Hz), 128.0 (d, *J* = 6.2 Hz), 126.6, 122.9, 122.1, 119.1 (d, *J* = 17.0 Hz), 118.7 (d, *J* = 7.4 Hz), 115.9.

HRMS (ESI) *m/z* calculated for $C_{18}H_{12}FN_2O$ [M+H$^+$] 291.0928, found 291.0938.



5

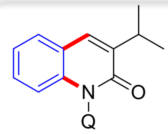
R_f = 0.4, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **5** as white solid in 72% yield (52.3 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.27 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.02 (dd, *J* = 7.0, 2.7 Hz, 1H), 7.76-7.71 (m, 2H), 7.51-7.49 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.40-7.35 (m, 4H), 7.29-7.26 (m, 1H), 7.18-7.15 (m, 1H), 7.13-7.10 (m, 1H), 6.43 (d, *J* = 8.3 Hz, 1H), 4.10 (d, *J* = 16.3 Hz, 1H), 4.01 (d, *J* = 16.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 151.4, 144.4, 140.5, 139.1, 136.8, 136.3, 135.9, 133.9, 130.3, 129.73, 129.65, 129.35, 129.1, 128.5, 127.9, 126.7, 126.3, 122.0, 121.9, 120.4, 115.5, 36.6.

HRMS (ESI) *m/z* calculated for $C_{25}H_{19}N_2O$ [M+H$^+$] 363.1492, found 363.1497.



6

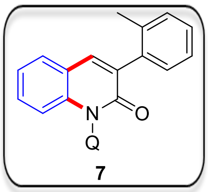
R_f = 0.3, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **6** as white solid in 52% yield (32.6 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.26 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.02-7.99 (m, 1H), 7.74 (d, *J* = 2.2 Hz, 1H), 7.73-7.72 (m, 2H), 7.64-7.60 (m, 1H), 7.42 (dd, J = 8.3, 4.2 Hz, 1H), 7.19-7.13 (m, 2H), 6.45-6.39 (m, 1H), 3.38-3.32 (m, 1H), 1.34 (d, J = 4.2 Hz, 3H), 1.32 (d, J = 4.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 151.3, 144.4, 140.1, 136.2, 136.1, 133.4, 130.3, 129.7, 129.2, 128.8, 127.8, 126.7, 121.91, 121.86, 120.5, 115.4, 28.0, 22.0, 21.7.

HRMS (ESI) *m/z* calculated for $C_{21}H_{19}N_2O$ [M+H$^+$] 315.1492, found 315.1501.



7

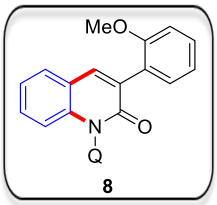
R$_f$ = 0.4, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **7** as white solid in 58% yield (41.2 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (dd, J = 4.2, 1.7 Hz, 1H), 8.22 (dd, J = 8.3, 1.7 Hz, 1H), 7.98 (dd, J = 8.1, 1.5 Hz, 1H), 7.86 (s, 1H), 7.76 (dd, J = 7.3, 1.5 Hz, 1H), 7.72-7.69 (m, 1H), 7.65 (dd, J = 7.7, 1.5 Hz, 1H), 7.40-7.36 (m, 2H), 7.27-7.20 (m, 4H), 7.19-7.16 (m, 1H), 6.52 (d, J = 8.4 Hz, 1H), 2.34 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 151.2, 144.3, 141.3, 138.9, 137.4, 136.5, 136.2, 135.8, 134.4, 130.3, 130.1, 129.8, 129.72, 129.69, 129.3, 128.4, 128.0, 126.6, 125.4, 122.1, 121.9, 120.3, 115.7, 20.1.

HRMS (ESI) *m/z* calculated for $C_{25}H_{19}N_2O$ [M+H$^+$] 363.1492, found 363.1496.



8

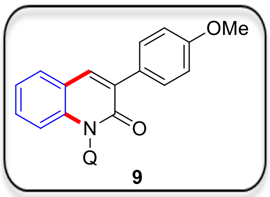
R$_f$ = 0.1, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **8** as white solid in 54% yield (40.7 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (dd, J = 4.2, 1.7 Hz, 1H), 8.25 (dd, J = 8.3, 1.7 Hz, 1H), 8.00-7.99 (m, 2H), 7.78 (dd, J = 7.3, 1.5 Hz, 1H), 7.74-7.71 (m, 1H), 7.66 (dd, J = 7.7, 1.5 Hz, 1H), 7.52 (dd, J = 7.5, 1.7 Hz, 1H), 7.42 (dd, J = 8.3, 4.2 Hz, 1H), 7.34-7.31 (m, 1H), 7.24-7.20 (m, 1H), 7.19-7.16 (m, 1H), 7.00 (td, J = 7.5, 1.0 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 3.82 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 157.4, 151.3, 144.4, 141.2, 139.5, 136.2, 136.0, 131.4, 130.7, 130.4, 129.7, 129.5, 129.3, 129.2, 128.4, 126.7, 125.7, 122.0, 121.8, 120.5, 120.2, 115.6, 111.1, 55.8.

HRMS (ESI) *m/z* calculated for $C_{25}H_{19}N_2O_2$ [M+H$^+$] 379.1441, found 379.1439.



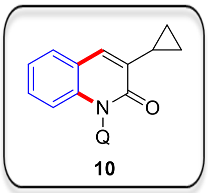
R_f = 0.4, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **9** as white solid in 56% yield (42 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, *J* = 3.3 Hz, 1H), 8.27 (d, *J* = 8.3 Hz, 1H), 8.02 (dd, *J* = 7.2, 2.3 Hz, 1H), 8.01 (s, 1H), 7.80-7.79 (m, 2H), 7.77-7.73 (m, 2H), 7.69-7.67 (m, 1H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.22-7.17 (m, 2H), 6.94 (d, *J* = 8.7 Hz, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 3.83 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 159.5, 151.3, 144.3, 140.7, 136.6, 136.2, 136.0, 131.9, 130.30, 130.25, 129.7, 129.4, 129.3, 128.8, 128.3, 126.6, 122.1, 121.8, 120.7, 115.6, 113.4, 55.2.

HRMS (ESI) *m/z* calculated for $C_{25}H_{19}N_2O_2$ [M+H$^+$] 379.1441, found 379.1448.



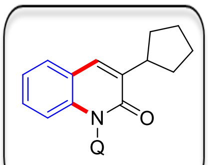
R_f = 0.4, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **10** as pale yellow solid in 64% yield (40 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.27 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.02 (dd, *J* = 6.7, 3.0 Hz, 1H), 7.76-7.71 (m, 2H), 7.56-7.54 (m, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.38 (s, 1H), 7.16-7.11 (m, 2H), 6.42-6.39 (m, 1H), 2.35-2.29 (m, 1H), 1.05-0.98 (m, 2H), 0.90-0.84 (m, 1H), 0.82-0.78 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 151.4, 144.4, 139.9, 136.3, 136.0, 135.9, 131.4, 130.3, 129.7, 129.3, 128.6, 127.5, 126.7, 122.0, 121.9, 120.5, 115.5, 10.8, 8.5, 8.1.

HRMS (ESI) *m/z* calculated for $C_{21}H_{17}N_2O$ [M+H$^+$] 313.1335, found 313.1341.



11

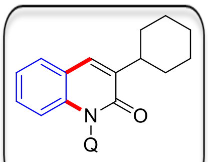
R$_f$ = 0.4, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **11** as pale yellow solid in 72% yield (49 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.25 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.02-7.98 (m, 1H), 7.74 (s, 2H), 7.73 (s, 1H), 7.61-7.59 (m, 1H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.18-7.12 (m, 2H), 6.43-6.41 (m, 1H), 3.40-3.32 (m, 1H), 2.20-2.09 (m, 2H), 1.84-1.63 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 151.3, 144.3, 140.1, 137.9, 136.2, 136.0, 133.7, 130.3, 129.7, 129.2, 128.7, 127.7, 126.7, 121.9, 121.8, 120.5, 115.4.

HRMS (ESI) *m/z* calculated for $C_{23}H_{21}N_2O$ [M+H$^+$] 363.1492, found 363.1496.



12

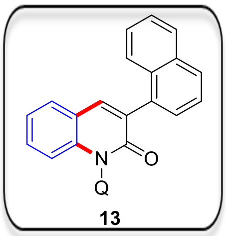
R$_f$ = 0.4, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **12** as white solid in 77% yield (54 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.25 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.02-7.98 (m, 1H), 7.75-7.71 (m, 2H), 7.69 (s, 1H), 7.63-7.59 (m, 1H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.19-7.13 (m ,2H), 6.46-6.44 (m, 1H), 3.06-3.00 (m, 1H), 2.11-2.05 (m, 2H), 1.87-1.84 (m, 2H), 1.79-1.76 (m, 1H), 1.51-1.24 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 151.3, 144.3, 140.0, 139.2, 136.2, 136.1, 133.8, 130.2, 129.6, 129.1, 128.7, 127.8, 126.6, 121.9, 120.6, 115.4, 37.8, 32.7, 32.2, 26.73, 26.69, 26.3.

HRMS (ESI) *m/z* calculated for $C_{24}H_{23}N_2O$ [M+H$^+$] 355.1805, found 355.1800.



13

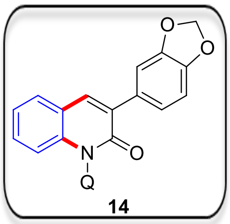
R$_f$ = 0.3, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **13** as yellow solid in 46% yield (36.7 mg).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.91 (s, 1H), 8.25 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.06-7.98 (m, 3H), 7.89-7.85 (m, 3H), 7.75-7.64 (m, 3H), 7.55-7.51 (m, 1H), 7.45 (s, 3H), 7.32-7.28 (m, 1H), 7.25-7.21 (m, 1H), 6.63 (d, *J* = 6.7 Hz, 1H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 162.0, 151.2, 144.2, 141.4, 140.2, 139.8, 136.2, 135.7, 134.9, 134.4, 133.4, 132.5, 132.0, 130.3, 129.9, 129.7, 129.3,128.5, 128.0, 127.3, 126.5, 126.0, 125.6, 125.2, 122.2, 121.9, 120.3, 115.7.

HRMS (ESI) *m/z* calculated for $C_{28}H_{19}N_2O$ [M+H$^+$] 399.1492, found 399.1494.



14

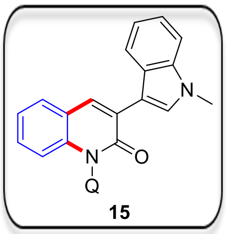
R$_f$ = 0.3, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **14** as pale yellow solid in 53% yield (41.4 mg).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.27 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.03 (dd, *J* = 6.2, 3.5 Hz, 1H), 7.99 (s, 1H), 7.77-7.73 (m, 2H), 7.69-7.67 (m, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz,1H), 7.39 (d, *J* = 1.7 Hz, 1H), 7.32 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.24-7.16 (m, 2H), 6.86 (d, *J* =8.1 Hz, 1H), 6.47-6.45 (m, 1H), 5.96 (s, 2H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 161.8, 151.4, 147.5, 147.3, 144.3, 140.8, 137.1, 136.3, 135.9, 132.0, 130.4, 130.3, 129.7, 129.6, 129.4, 128.4, 126.7, 123.0, 122.2, 121.9, 120.6, 115.6, 109.8, 108.0, 101.0.

HRMS (ESI) *m/z* calculated for $C_{25}H_{17}N_2O_3$ [M+H$^+$] 393.1234, found 393.1229.



15

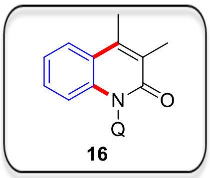
R_f = 0.4, 50% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **15** as white solid in 42% yield (34 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 3.0 Hz, 1H), 8.48 (s, 1H), 8.29-8.27 (m, 2H), 8.19-8.17 (m, 1H), 8.04 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.80-7.75 (m, 3H), 7.43 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.42-7.39 (m, 1H), 7.34-7.28 (m, 2H), 7.24-7.17 (m, 2H), 6.49-6.47 (m, 1H), 3.78 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 151.5, 144.4, 139.3, 136.9, 136.4, 136.3, 132.9, 132.7, 130.2, 129.8, 129.3, 128.4, 127.8, 126.9, 126.8, 126.7, 122.2, 121.9, 121.7, 121.2, 120.2, 119.9, 115.5, 109.7, 109.1, 32.9.

HRMS (ESI) *m/z* calculated for $C_{27}H_{20}N_3O$ [M+H$^+$] 402.1601, found 402.1608.



16

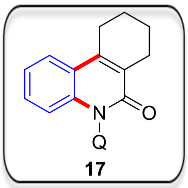
R_f = 0.1, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **16** as white solid in 44% yield (26.4 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.26 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.01 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.82-7.80 (m, 1H), 7.75-7.68 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.21-7.14 (m, 2H), 6.45-6.43 (m, 1H), 2.58 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 151.4, 144.5, 142.3, 139.7, 136.3, 136.2, 130.4, 129.7, 129.2, 128.7, 127.6, 126.7, 124.6, 121.9, 121.8, 121.4, 115.9, 15.7, 13.6.

HRMS (ESI) *m/z* calculated for $C_{20}H_{17}N_2O$ [M+H$^+$] 301.1335, found 301.1340.



17

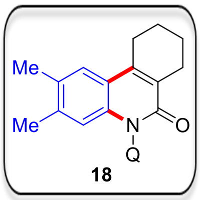
R_f = 0.4, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **17** as white solid in 56% yield (38.1 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.27 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.01 (dd, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.79-7.68 (m, 3H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.20-7.13 (m, 2H), 6.46-6.42 (m, 1H), 2.98 (t, *J* = 6.0 Hz, 2H), 2.77-2.67 (m, 2H), 1.99-1.92 (m, 2H), 1.89-1.86 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 151.4, 144.5, 143.0, 139.4, 136.3, 136.0, 130.5, 129.7, 129.2, 128.9, 128.5, 126.7, 123.3, 121.8, 121.7, 121.0, 115.9, 25.7, 24.3, 22.0, 21.9.

HRMS (ESI) *m/z* calculated for $C_{22}H_{19}N_2O$ [M+H$^+$] 327.1492, found 327.1494.



18

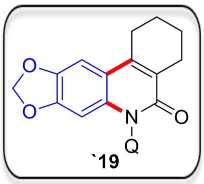
R_f = 0.3, 50% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **18** as white solid in 71% yield (50 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.27 (d, *J* = 8.2 Hz, 1H), 8.01 (d, *J* = 7.4 Hz, 1H), 7.74-7.69 (m, 2H), 7.50 (s, 1H), 7.42 (dd, *J* = 7.7, 2.6 Hz, 1H), 6.21 (s, 1H), 2.96-2.94 (m, 2H), 2.71 (s, 2H), 2.29 (s, 3H), 2.05 (s, 3H), 1.94-1.86 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 151.2, 144.6, 142.8, 137.8, 137.7, 136.2, 130.4, 130.3, 129.6, 129.0, 127.6, 126.6, 123.7, 121.7, 119.0, 116.3, 25.7, 24.1, 22.0, 21.9, 20.0, 19.3.

HRMS (ESI) *m/z* calculated for $C_{24}H_{23}N_2O$ [M+H$^+$] 355.1805, found 355.1806.



`19

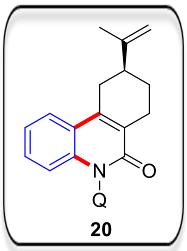
R_f = 0.2, 50% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **19** as yellow solid in 53% yield (39.1 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.25 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.99 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.73-7.66 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.16 (s, 1H), 5.91 (s, 1H), 5.90 (d, *J* = 1.2 Hz, 1H), 5.87 (d, *J* = 1.2 Hz, 1H), 2.88-2.85 (m, 2H), 2.71-2.68 (m, 2H), 1.96-1.89 (m, 2H), 1.86-1.80 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 151.5, 148.6, 144.4, 143.4, 142.8, 136.3, 136.0, 130.4, 129.7, 129.3, 126.7, 126.6, 121.8, 115.4, 101.7, 101.4, 96.8, 26.3, 24.1, 22.1, 21.9.

HRMS (ESI) *m/z* calculated for $C_{23}H_{19}N_2O_3$ [M+H$^+$] 371.1390, found 371.1403.



20

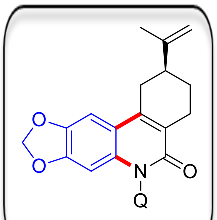
R_f = 0.15, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **20** as pale yellow solid (including two diastereoisomers) in 63% yield (46.1 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (d, J = 4.1 Hz, 1H), 8.26 (d, *J* = 8.3 Hz, 1H), 8.01 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.81-7.78 (m, 1H), 7.75-7.69 (m, 2H), 7.42 (ddd, *J* = 8.3, 4.2, 2.0 Hz, 1H), 7.20-7.15 (m, 2H), 6.47-6.43 (m, 1H), 4.92-4.89 (m, 2H), 3.22-3.18 (m, 1H), 3.08-2.97 (m, 1H), 2.84-2.77 (m, 1H), 2.68-2.57 (m, 1H), 2.53-2.46 (m, 1H), 2.12-2.10 (m, 1H), 1.90 (s, 3H), 1.72-1.63 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.24, 162.22, 151.4, 151.41, 149.05, 148.90, 144.60, 144.53, 142.64, 142.58, 139.64, 136.30, 136.28, 136.06, 135.98, 130.52, 130.45, 129.74, 129.71, 129.25, 128.61, 128.51, 128.47, 126.74, 126.70, 123.34, 123.32, 121.83, 120.82, 120.79, 115.99, 115.94, 109.73, 109.69, 40.92, 40.55, 31.25, 31.17, 26.95, 26.88, 25.00, 24.68, 20.79, 20.66.

HRMS (ESI) *m/z* calculated for $C_{25}H_{23}N_2O$ [M+H$^+$] 367.1805, found 367.1811.



21

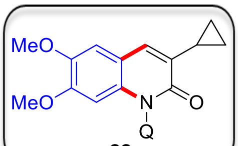
R_f = 0.15, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **21** as pale yellow solid (containing two diastereoisomers) in 61% yield (51 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85-8.84 (m, 1H), 8.26 (d, *J* = 8.3 Hz, 1H), 8.00 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.74-7.66 (m, 2H), 7.43 (ddd, *J* = 8.3, 4.2, 1.6 Hz, 1H), 7.18 (d, *J* = 3.8 Hz, 1H), 5.93-5.88 (m, 3H), 4.90-4.86 (m, 2H), 3.09-2.93 (m, 2H), 2.75-2.68 (m,1H), 2.64-2.42 (m, 2H), 2.10-2.07 (m, 1H), 1.89 (s, 3H), 1.69-1.59 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.11, 162.09, 151.45, 151.43, 148.97, 148.83, 148.68, 144.39, 144.32, 143.48, 142.39, 142.32, 136.31, 136.28, 136.24, 136.23, 136.21, 130.37, 130.30, 129.73, 129.71, 129.30, 126.71, 126.67, 126.13, 126.09, 121.84, 121.82, 115.21, 115.16, 109.69, 109.65, 101.63, 101.40, 96.85, 96.80, 40.95, 40.57, 31.71, 31.63, 26.91, 26.85, 24.83, 24.52, 20.72, 20.60.

HRMS (ESI) *m/z* calculated for $C_{26}H_{23}N_2O_3$ [M+H$^+$] 411.1703, found 411.1704.



22

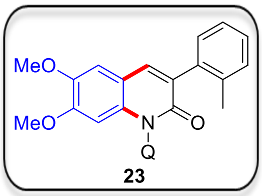
R_f = 0.1, 50% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **22** as pale yellow solid in 85% yield (63.3 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.25 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.02-7.99 (m, 1H), 7.75-7.71 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.30 (s, 1H), 6.96 (s, 1H), 5.87 (s, 1H), 3.90 (s, 3H), 3.41 (s, 3H), 2.30-2.25 (m, 1H), 1.02-0.95 (m, 2H), 0.85-0.79 (m, 1H), 0.76-0.70 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 151.4, 150.6, 145.1, 144.3, 136.2, 136.1, 135.2, 133.2, 131.1, 130.2, 129.6, 129.3, 126.6, 121.9, 113.7, 108.5, 98.7, 56.1, 55.6, 10.7, 8.2, 7.7.

HRMS (ESI) *m/z* calculated for $C_{23}H_{21}N_2O_3$ [M+H$^+$] 373.1547, found 373.1546.



23

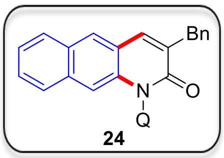
$R_f = 0.2$, 50% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **23** as pale grey solid in 70% yield (58.9 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.26 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.01 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.80-7.72 (m, 3H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.38-7.36 (m, 1H), 7.24-7.19 (m, 3H), 7.05 (s, 1H), 6.00 (s, 1H), 3.94 (s, 3H), 3.47 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 151.5, 151.3, 145.3, 144.2, 138.4, 137.4, 136.83, 136.80, 136.2, 136.0, 131.7, 130.2, 130.1, 129.7, 129.6, 129.3, 127.7, 126.5, 125.4, 121.9, 113.5, 109.1, 98.7, 56.2, 55.7, 20.0.

HRMS (ESI) *m/z* calculated for $C_{27}H_{23}N_2O_3$ [M+H$^+$] 423.1703, found 423.1693.



24

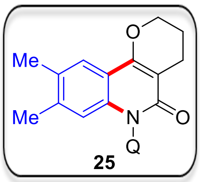
$R_f = 0.4$, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **24** as pale yellow solid in 67% yield (55.2 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.30 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.09-8.05 (m, 1H), 8.00 (s, 1H), 7.84-7.77 (m, 3H), 7.58 (s, 1H), 7.45-7.38 (m, 6H), 7.35-7.29 (m, 3H), 6.78 (s, 1H), 4.14 (d, *J* = 16.5 Hz, 1H), 4.05 (d, *J* = 16.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 151.4, 144.4, 138.9, 138.4, 136.6, 136.3, 136.0, 134.3, 133.3, 130.5, 129.8, 129.7, 129.4, 128.9, 128.6, 127.8, 127.3, 127.1, 126.80, 126.79, 126.4, 124.5, 121.9, 121.1, 111.5, 36.7.

HRMS (ESI) *m/z* calculated for $C_{29}H_{21}N_2O$ [M+H$^+$] 413.1648, found 413.1653.


25

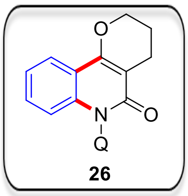
R$_f$ = 0.15, 50% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **25** as white solid in 64% yield (45.4 mg).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.84 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.25 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.99 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.73-7.67 (m, 3H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.19 (s, 1H), 4.40 (t, *J* = 5.2 Hz, 2H), 2.71-2.67 (m, 2H), 2.27 (s, 3H), 2.14-2.08 (m, 2H), 2.05 (s, 3H),

^{13}C NMR (100 MHz, CDCl$_3$) δ 163.5, 157.6, 151.3, 144.8, 139.1, 138.1, 136.3, 136.1, 130.7, 130.3, 129.6, 129.1, 126.6, 122.4, 121.7, 116.1, 113.9, 106.2, 67.1, 21.5, 20.3, 19.4, 19.2.

HRMS (ESI) *m/z* calculated for $C_{23}H_{21}N_2O_2$ [M+H$^+$] 357.1598, found 357.1595.


26

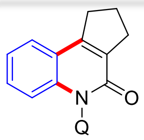
R$_f$ = 0.3, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **26** as yellow solid in 50% yield (32 mg).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.83 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.26 (dd, *J* =8.3, 1.7 Hz, 1H), 8.01-7.96 (m, 2H), 7.74-7.69 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.20-7.13 (m, 2H), 6.42-6.40 (m, 1H), 4.41 (t, *J* = 5.3 Hz, 2H), 2.73-2.69 (m, 2H), 2.16-2.08 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 163.6, 157.6, 151.4, 144.7, 139.7, 136.3, 135.8, 130.7, 129.7, 129.6, 129.2, 126.7, 122.4, 121.8, 121.5, 116.0, 115.5, 107.1, 67.1, 21.4, 19.4.

HRMS (ESI) *m/z* calculated for $C_{21}H_{17}N_2O_2$ [M+H$^+$] 329.1285, found 329.1295.



27

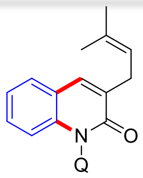
R_f = 0.3, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **27** as white solid in 40% yield (26.4 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.27 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.01 (dd, *J* = 7.7, 1.9 Hz,1H), 7.75-7.69 (m, 2H), 7.62-7.58 (m, 1H), 7..42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.20-7.15 (m, 2H), 6.47-6.43 (m, 1H), 3.25 (t, *J* = 7.7 Hz, 2H), 3.13-3.00 (m, 2H), 2.31-2.23 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 151.5, 151.4, 144.6, 141.4, 136.3, 135.9, 133.5, 130.6, 129.7, 129.3, 128.9, 126.7, 125.1, 121.83, 121.81, 119.4, 116.1.

HRMS (ESI) *m/z* calculated for $C_{21}H_{17}N_2O$ [M+H$^+$] 313.1335, found 313.1351.



28

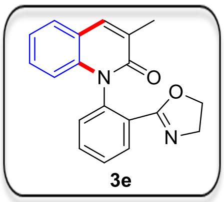
R_f = 0.3, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **28** as yellow and amorphous cream in 63% yield (43 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.25 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.02-7.98 (m, 1H), 7.75-7.71 (m, 2H), 7.69 (s, 1H), 7.61-7.59 (m, 1H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.19-7.12 (m, 2H), 6.45-6.40 (m,1H), 5.49-5.45 (m, 1H), 3.49-3.37 (m, 2H), 1.85 (s, 3H), 1.75 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 151.4, 144.4, 140.3, 136.3, 136.0, 135.6, 134.6, 133.4, 130.3, 129.7, 129.3, 128.8, 127.7, 126.7, 121.94,121.87, 120.6, 120.5, 115.5, 28.9, 25.9, 17.9.

HRMS (ESI) *m/z* calculated for $C_{23}H_{21}N_2O$ [M+H$^+$] 341.1648, found 341.1643.



3e

R_f = 0.4, 50% EtOAc in petroleum ether

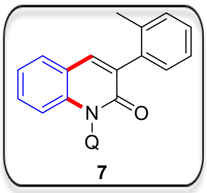
Purification of the crude product by flash column chromatography afforded the annulation product **3e** as pale yellow solid in 65% yield (41.8 mg).

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.19 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.68-7.65 (m, 2H), 7.57 (td, *J* = 7.7, 1.1 Hz, 1H), 7.51 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.30 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.24-7.21 (m, 1H), 7.15-7.12 (m, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 4.09-4.04 (m, 1H), 3.92-3.87 (m, 1H), 3.76-3.64 (m, 2H), 2.28 (d, *J* = 1.1 Hz, 3H).

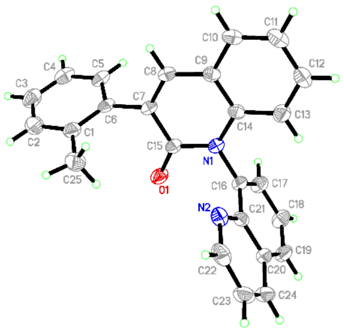
^{13}C NMR (125 MHz, CDCl$_3$) δ 163.2, 140.1, 137.1, 136.3, 132.5, 131.6, 130.4, 128.9, 128.7, 127.2, 126.7, 121.8, 120.5, 115.0, 67.2, 54.8, 17.3.

HRMS (ESI) *m/z* calculated for $C_{19}H_{17}N_2O_2$ [M+H$^+$] 305.1285, found 305.1275.

4. X-ray structure of compound 7



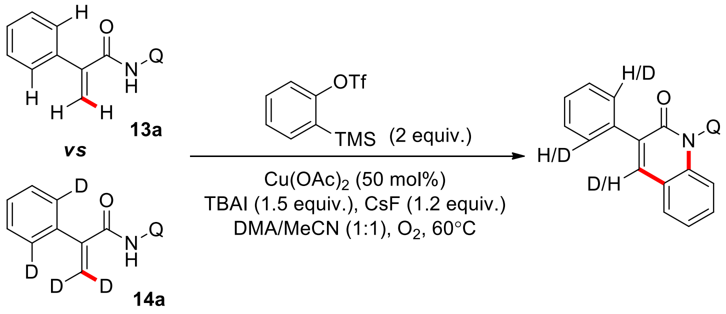
7



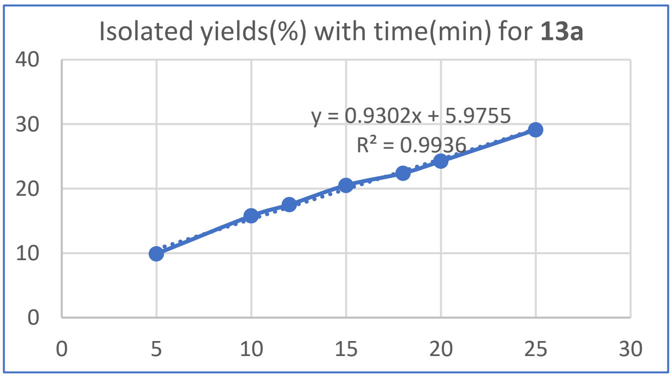
A colorless block shaped crystal of **7** ($C_{25}H_{18}N_2O$) was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 173(2) K, on a Bruker D8 VENTURE CMOS photon 100 diffractometer with helios mx multilayer monochrmator Cu-Kα radiation (λ = 1.54178 Å). The X-ray crystallographic files, in CIF format, are available from the Cambridge Crystallographic Data Centre on quoting the deposition numbers **CCDC 1858672** for **7**. Copies of the data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (Fax: +44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

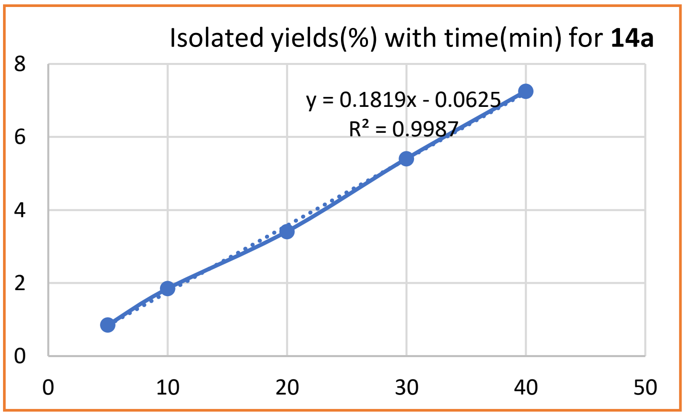
5. Preliminary mechanistic studies

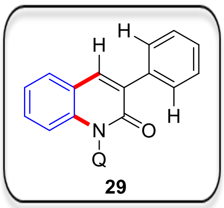
a) Parallel experiments of the annulation of substrate 13a and 14a with 2-(trimethylsilyl)phenyltrifluoromethanesulfonate (Aryne Precursor)



Substrate **13a** or **14a** was subjected to the annulation reaction with 2-(trimethylsilyl)-phenyltrifluoromethanesulfonate under the general reaction condition (the temperature was decreased to 60 ºC from 80 ºC for the purpose of reducing the reaction rate). Data collecting method: at specified reaction time, the reaction vial was quenched and isolated by silica gel flash chromatography. Average data of four repeating experiments were used. k_H/k_D (~5.1) was estimated based on the ratio of annulation yield.







29

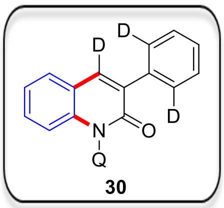
R_f = 0.4, 33% EtOAc in petroleum ether

Purification of the crude product by flash column chromatography afforded the annulation product **29** as pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.22 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.02 (s, 1H), 7.98 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.83-7.81 (m, 2H), 7.75-7.69 (m, 2H), 7.66 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.40-7.37 (m, 3H), 7.34-7.31 (m, 1H), 7.22-7.18 (m, 1H), 7.17-7.14 (m, 1H), 6.46 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 151.3, 144.3, 141.0, 137.7, 136.3, 136.2, 135.9, 132.4, 130.2, 129.7, 129.3, 129.1, 128.4, 127.92, 127.89, 126.6, 122.1, 121.8, 120.6, 115.6.

HRMS (ESI) *m/z* calculated for $C_{24}H_{17}N_2O$ [M+H$^+$] 349.1335, found 349.1339.



30

R_f = 0.4, 33% EtOAc in petroleum ether

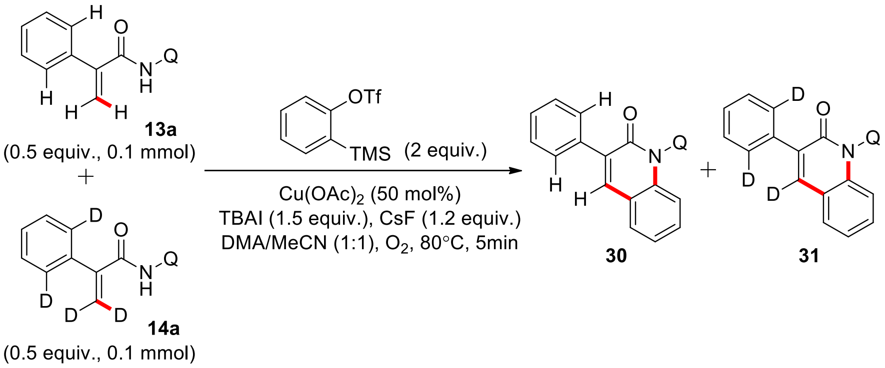
Purification of the crude product by flash column chromatography afforded the annulation product **30** as pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.27 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.03 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.79-7.73 (m, 2H), 7.70 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.45-7.40 (m, 3H), 7.36-7.33 (m, 1H), 7.25-7.17 (m, 2H), 6.49-6.47 (m, 1H).

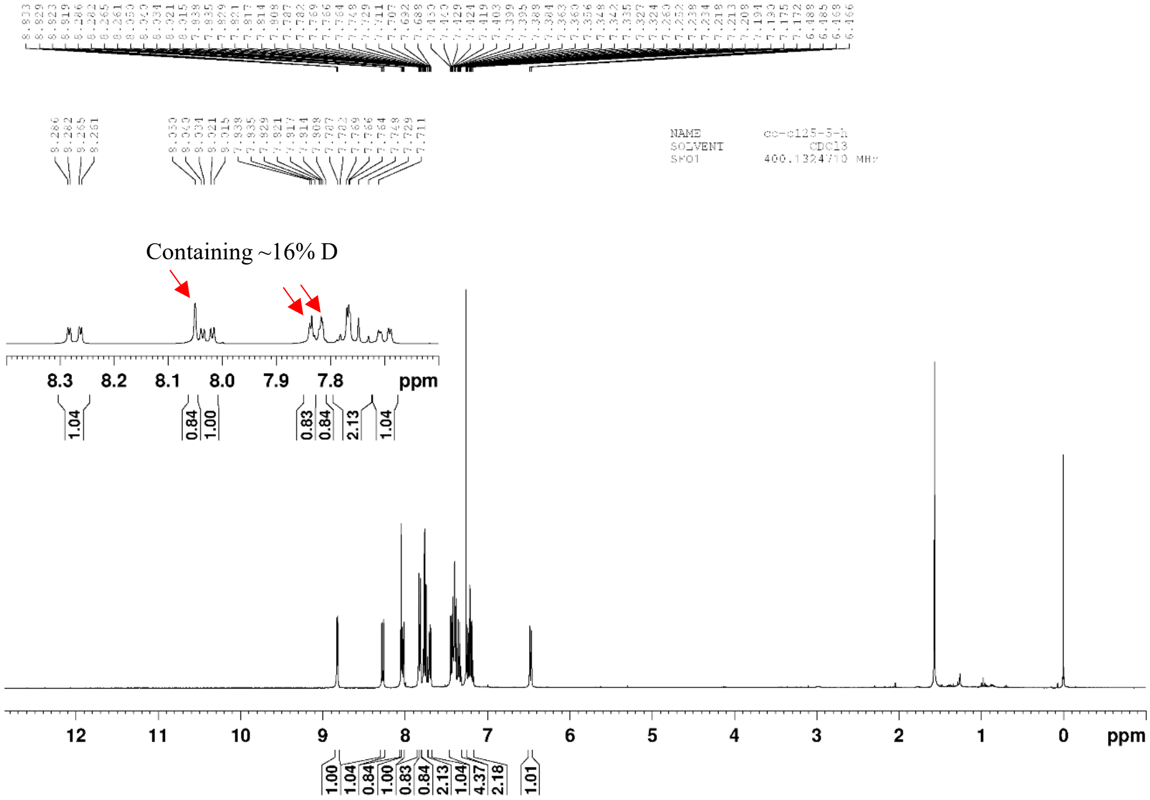
^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 151.4, 144.3, 141.0, 137.0 (d, *J* = 22.3 Hz), 136.3, 136.2, 135.9, 132.4, 130.3, 129.7, 129.4, 129.1, 128.8 (d, *J* = 24.6 Hz), 128.4, 128.0, 127.8, 126.7, 122.2, 121.9, 120.6, 115.7.

HRMS (ESI) *m/z* calculated for $C_{24}H_{14}D_3N_2O$ [M+H$^+$] 352.1524, found 352.1520.

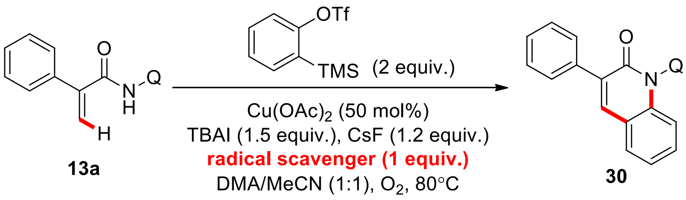
b) Intermolecular Competitive Experiments

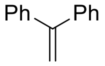


The same equivalent of substrate **13a** and **14a** (both 0.5 equiv.) was subjected to the annulation reaction with 2-(trimethylsilyl)-phenyltrifluoromethanesulfonate under the general reaction condition for 5 min. Data collecting method: at specified reaction time, the reaction vial was quenched and isolated by silica gel flash chromatography. k_H/k_D (~5.2) was estimated based on the ratio of annulation yield.



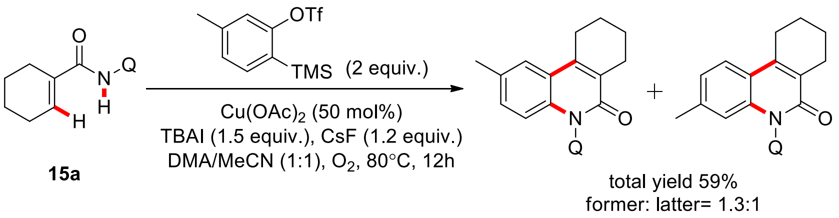
c) Radical trapping experiments



Entry	Radical scavenger (1 equiv.)	Isolated yield of **30**
1	\	40%
2	Tempo	34%
3	BHT	33%
4	Ph-S-S-Ph	29%
5		31%

A mixture of amide **13a** (55.3 mg, 0.2 mmol, 1 equiv.), $Cu(OAc)_2$ (18.2 mg, 0.1mmol, 0.5 equiv.), TBAI (111 mg, 0.3 mmol, 1.5 equiv.), CsF (36.5 mg, 0.24 mmol, 1.2 equiv.), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (120 mg, 2 equiv.) and free radical inhibitor (1 equiv.) in DMA (1.0 mL)/MeCN (1.0 mL) in a 10 mL glass vial (purged with O_2, sealed with PTFE cap) was heated at 80°C for 12 hours. The reaction mixture was cooled to RT. The resulting residue was purified by silica gel flash chromatography to give the annulation product. Undiminished yield indicates that no radical intermediates were generated possibly.

d) The study on generation of benzyne



A mixture of amide **15a** (50.5 mg, 0.2 mmol, 1 equiv.), $Cu(OAc)_2$ (18.2 mg, 0.1mmol, 0.5 equiv.), TBAI (111 mg, 0.3 mmol, 1.5 equiv.), CsF (36.5 mg, 0.24 mmol, 1.2 equiv.), and 5-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (122 mg, 2 equiv.) in DMA (1.0 mL)/MeCN (1.0 mL) in a 10 mL glass vial (purged with O_2, sealed with PTFE cap) was heated at 80°C for 12 hours. The reaction mixture was cooled to RT. The resulting residue was purified by silica gel flash chromatography to give the annulation mix product in 59% isolated yield with ratio = 1.3:1, which indicates that benzyne is generated in situ from 2-(trimethylsilyl)phenyl trifluoromethane-sulfonate indeed.

6. Computational details

The density functional theory (DFT) calculations were performed using Gaussian 09, Revision D.01[13]. The geometry optimizations were conducted using the B3LYP functional[14], with SDD basis set[15] for Copper and 6-31G(d) basis set for the other atoms. To confirm whether each optimized stationary point is an energy minimum or a transition state, as well as evaluate the zero-point vibrational energy and thermal corrections at 298 K, the vibrational frequencies were computed at the same level of theory as for the geometry optimizations. On the basis of the gas-phase optimized structures, the single-point energies and solvent effects were evaluated with the M06 functional[16], SDD basis set for Copper, and 6-311+G(d,p) basis set for other atoms. The solvation energies were calculated using the self-consistent reaction field (SCRF) with the SMD model[17], and acetonitrile was chosen as the solvent for consistency with the experiment. Intrinsic reaction coordinate (IRC) calculations were undertaken to ensure transitions states connected the correct reactants and products. Energies reported are free energies in kcal/mol. Geometries of the optimized structures shown were displayed with CYLview[18].

7. Supplementary Computation Data

Cartesian coordinates, electronic energies and free energies of all stationary points. Numbers (and values) of imaginary frequencies of all transition structures.

1a

B3LYP/6-31G(d)(SDD)(gas) Energy = -687.3528283
B3LYP/6-31G(d)(SDD) (gas) Free Energy= -687.168666
M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -687.0476231
B3LYP/6-31G(d) (SDD)(gas) Geometry

C	-3.56707	-1.80318	0.13241
C	-3.7458	-0.44055	0.06187
C	-2.61798	0.417	0.00453
C	-1.33353	-0.20616	0.02388
C	-2.24837	-2.31541	0.14533
H	-3.68648	2.30261	-0.08335
H	-4.41211	-2.48332	0.17758
H	-4.74308	-0.00687	0.04968
C	-2.70751	1.83091	-0.06918
C	-0.14984	0.60802	-0.03121
H	-2.08269	-3.39045	0.20046
C	-0.27253	1.98653	-0.10154
C	-1.55511	2.58235	-0.12008

H	-1.61896	3.66568	-0.1755
N	-1.17045	-1.55646	0.09303
N	1.05405	-0.09835	-0.0132
C	2.33821	0.39416	-0.02277
O	2.61117	1.59105	0.00616
C	3.42691	-0.64786	-0.06265
C	4.72832	-0.21424	0.55848
H	5.5021	-0.97594	0.42781
H	5.06465	0.72461	0.10724
H	4.60705	-0.01817	1.63113
C	3.26262	-1.82559	-0.67922
H	4.07238	-2.5485	-0.734
H	0.62026	2.59474	-0.13757
H	2.33828	-2.10408	-1.17778
H	0.91406	-1.10104	0.06701

Cu(OAc)$_2$

B3LYP/6-31G(d)(SDD)(gas) Energy = -654.3756845

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -654.312718

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -654.2919521

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	2.57607	-0.00062	0.00051
H	2.97303	1.01544	-0.0049
H	2.93414	-0.53615	0.88591
H	2.93528	-0.54658	-0.87795
C	1.0602	0.00848	-0.00013
O	0.44136	-1.10609	-0.00022
O	0.43742	1.11871	-0.00008
Cu	-1.29967	-0.00279	-0.0001

Com

B3LYP/6-31G(d)(SDD)(gas) Energy = -1341.728513

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -1341.481384

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -1341.339575

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	3.75377	1.45975	0.96368
C	4.25401	0.27926	0.4645
C	3.38144	-0.67991	-0.10775
C	1.98762	-0.36068	-0.16573
C	2.35912	1.66237	0.93997
H	4.88982	-2.16826	-0.55107
H	4.39881	2.21498	1.39947
H	5.31924	0.06554	0.50267
C	3.83213	-1.92666	-0.60732
C	1.08246	-1.25495	-0.81898
H	1.91721	2.55418	1.37545

C	1.56179	-2.47409	-1.26852
C	2.92686	-2.81204	-1.14795
H	3.26289	-3.7754	-1.52016
N	1.51543	0.78899	0.41152
N	-0.24982	-0.83457	-1.02802
C	-1.34074	-1.6975	-0.96479
O	-1.26187	-2.81439	-0.46468
C	-2.64357	-1.18276	-1.50945
C	-3.86842	-1.77749	-0.86352
H	-4.7764	-1.47305	-1.39198
H	-3.80545	-2.86993	-0.85084
H	-3.94662	-1.44246	0.17809
C	-2.69851	-0.33211	-2.54301
H	-3.65794	-0.02528	-2.95264
H	0.87317	-3.17083	-1.72924
H	-1.81898	0.09452	-3.01214
H	-0.35919	0.10595	-1.45518
Cu	-0.46126	0.91627	0.89901
O	-0.3858	-0.49649	2.3273
O	-0.81597	2.58296	0.03798
C	-0.6636	2.7064	-1.24364
C	-1.65878	-0.43842	2.4256
C	-0.93308	4.10604	-1.77374
H	-1.99113	4.35093	-1.62812
H	-0.35109	4.84269	-1.21074
H	-0.68814	4.16515	-2.83567
C	-2.4016	-1.38506	3.32589
H	-2.52166	-2.33828	2.79746
H	-1.82463	-1.57484	4.23453
H	-3.38926	-0.98963	3.57167
O	-0.33936	1.79111	-2.02055
O	-2.27187	0.41536	1.70635

TS1

B3LYP/6-31G(d)(SDD)(gas) Energy = -1341.716565

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -1341.451046

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -1341.350467

Number of Imaginary Frequencies = 1 (-938.20)

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	3.20347	-2.64922	-0.42673
C	4.04721	-1.55964	-0.44105
C	3.51801	-0.24611	-0.37131
C	2.10002	-0.11992	-0.27285
C	1.81057	-2.43605	-0.3482
H	5.38527	0.84871	-0.48114

H	3.58584	-3.66274	-0.48241
H	5.12394	-1.69334	-0.51046
C	4.30485	0.93179	-0.40337
C	1.47999	1.15645	-0.18913
H	1.10235	-3.25907	-0.35427
C	2.28492	2.28031	-0.23157
C	3.68958	2.16387	-0.34161
H	4.28836	3.06956	-0.37103
N	1.29132	-1.22188	-0.27227
N	0.06294	1.19341	0.01372
C	-0.66074	2.08663	-0.82654
O	-0.17947	2.52331	-1.86241
C	-2.05958	2.45636	-0.42776
C	-2.98299	2.73368	-1.58692
H	-3.94752	3.11065	-1.2344
H	-2.53734	3.46292	-2.27049
H	-3.15744	1.81426	-2.15819
C	-2.41848	2.63291	0.85074
H	-3.4197	2.98186	1.09281
H	1.83075	3.26339	-0.18444
H	-1.75417	2.44901	1.6872
H	-0.14889	1.14079	1.24136
Cu	-0.65833	-0.78731	-0.17076
O	-1.41484	-2.5422	-0.87112
O	-1.03737	-1.04451	1.94225
C	-0.74645	-0.16254	2.78478
C	-2.50528	-1.92809	-1.12083
C	-1.0174	-0.41695	4.2553
H	-1.91645	0.13638	4.55211
H	-1.1814	-1.48054	4.43787
H	-0.18845	-0.04525	4.86416
C	-3.71218	-2.67461	-1.62108
H	-3.40797	-3.5446	-2.20772
H	-4.28961	-3.0277	-0.75843
H	-4.35012	-2.01477	-2.21346
O	-0.24118	0.98677	2.49637
O	-2.55451	-0.67481	-0.90242

I

B3LYP/6-31G(d)(SDD)(gas) Energy =	-1112.621896
B3LYP/6-31G(d)(SDD) (gas) Free Energy=	-1112.408044
M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy =	-1112.30852

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	-2.38435	-3.00831	-0.59561
C	-3.43523	-2.17074	-0.28167

C	-3.20228	-0.80243	0.00485
C	-1.85061	-0.35532	-0.04241
C	-1.07617	-2.48397	-0.62322
H	-5.25263	-0.18806	0.36333
H	-2.54494	-4.05735	-0.82043
H	-4.45368	-2.55046	-0.25388
C	-4.21699	0.13672	0.32137
C	-1.49823	1.00933	0.22077
H	-0.21286	-3.0964	-0.86535
C	-2.52759	1.89857	0.51715
C	-3.86787	1.44878	0.56524
H	-4.64287	2.17207	0.80458
N	-0.83217	-1.21066	-0.35558
N	-0.13589	1.27167	0.13525
C	0.40873	2.52545	0.08901
O	-0.1899	3.59853	0.16833
C	1.90296	2.48821	-0.14718
C	2.41968	3.47967	-1.15207
H	3.50991	3.44577	-1.23059
H	1.98791	3.29838	-2.14499
H	2.10676	4.48676	-0.8557
C	2.69183	1.64431	0.54803
H	2.32281	1.02934	1.36555
Cu	0.95999	-0.25815	-0.21274
H	-2.2868	2.93602	0.70245
H	3.76488	1.60795	0.37357
O	2.1679	-1.64358	-0.71341
C	2.66942	-2.00377	0.43718
C	3.70502	-3.10833	0.39617
H	3.28628	-3.99677	-0.08829
H	4.56206	-2.78757	-0.20607
H	4.03646	-3.35696	1.40565
O	2.31243	-1.46402	1.49712

TS2

B3LYP/6-31G(d)(SDD)(gas) Energy = -1112.582932

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -1112.371666

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -1112.272202

Number of Imaginary Frequencies = 1 (-1191.76)

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	-2.52217	-3.00127	-0.53059
C	-3.54805	-2.14622	-0.18441
C	-3.28408	-0.77794	0.07425
C	-1.93056	-0.34836	-0.04793
C	-1.20997	-2.49416	-0.62043

H	-5.30751	-0.14183	0.5323
H	-2.70512	-4.05188	-0.73075
H	-4.56908	-2.51192	-0.10514
C	-4.27215	0.17263	0.43724
C	-1.55472	1.01956	0.18806
H	-0.36758	-3.1311	-0.87321
C	-2.55922	1.91873	0.54482
C	-3.89756	1.48228	0.66263
H	-4.65291	2.21214	0.94257
N	-0.93162	-1.21836	-0.39317
N	-0.21206	1.26597	0.01073
C	0.42171	2.47418	0.11251
O	-0.08788	3.54755	0.43968
C	1.87243	2.36284	-0.3121
C	2.51485	3.66353	-0.70531
H	3.57003	3.53167	-0.96046
H	1.99444	4.1143	-1.56064
H	2.424	4.38388	0.11578
C	2.46696	1.14651	-0.37579
H	3.45448	1.12504	-0.85243
Cu	0.8926	-0.25835	-0.39113
H	-2.29167	2.95061	0.72858
H	2.72586	0.10428	0.57229
O	3.26318	-0.82485	1.14088
C	2.9229	-1.89391	0.51786
C	3.7226	-3.13976	0.81075
H	3.76924	-3.30017	1.89214
H	3.28153	-4.00728	0.31797
H	4.75012	-2.99788	0.45846
O	1.97304	-1.9418	-0.31642

II

B3LYP/6-31G(d)(SDD)(gas) Energy = -883.4840085

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -883.324134

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -883.2329541

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	3.48633	-1.77642	-0.00002
C	3.82464	-0.43949	-0.00002
C	2.81619	0.55598	0.00001
C	1.4619	0.10679	0.00004
C	2.12508	-2.1356	0.
H	4.10662	2.29844	-0.00001
H	4.24401	-2.5528	-0.00003
H	4.8682	-0.13413	-0.00003
C	3.07842	1.9489	0.00001

C	0.36874	1.0472	0.00007
H	1.82395	-3.17934	-0.00001
C	0.67532	2.40961	0.00005
C	2.0193	2.83642	0.00002
H	2.21947	3.90484	0.00001
N	1.14944	-1.23375	0.00003
N	-0.86303	0.45847	0.00014
C	-2.12572	1.00817	-0.00002
O	-2.36995	2.21269	-0.00005
C	-3.18557	-0.07151	-0.00005
C	-4.61418	0.40272	-0.00008
H	-5.31207	-0.44019	-0.00034
H	-4.81625	1.02894	0.8776
H	-4.81607	1.02938	-0.87747
C	-2.76453	-1.35197	-0.00008
H	-3.4853	-2.17223	-0.00014
Cu	-0.8529	-1.46292	-0.00001
H	-0.13922	3.12245	0.00007

INT1

B3LYP/6-31G(d)(SDD)(gas) Energy = -1114.44682

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -1114.216511

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -1114.068641

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	-0.87605	-3.66226	-0.07995
C	-2.23694	-3.43809	-0.0878
C	-2.74368	-2.11495	-0.06122
C	-1.78687	-1.06042	-0.02974
C	0.00298	-2.56106	-0.04705
H	-4.86402	-2.57531	-0.08637
H	-0.46869	-4.66764	-0.09817
H	-2.93445	-4.2719	-0.11285
C	-4.12244	-1.78214	-0.06265
C	-2.18877	0.31549	0.00167
H	1.08007	-2.69309	-0.03061
C	-3.55379	0.59931	-0.00018
C	-4.49578	-0.45288	-0.03268
H	-5.55196	-0.19596	-0.03335
N	-0.43628	-1.31013	-0.02445
N	-1.12816	1.19272	0.02993
C	-1.17932	2.56576	0.05745
O	-2.19014	3.26308	0.06777
C	0.22349	3.12337	0.07149
C	0.37413	4.61872	0.10498
H	1.42593	4.9196	0.10824

H	-0.12415	5.07059	-0.76097
H	-0.11658	5.02924	0.99562
C	1.22801	2.23829	0.05147
H	2.28383	2.48688	0.06009
Cu	0.60902	0.42388	0.01486
H	-3.87348	1.63255	0.02379
C	4.97043	-1.39514	0.08966
C	4.56545	-0.66917	-1.03621
C	3.30436	-0.06379	-1.09122
C	2.41848	-0.20345	-0.00261
C	2.87818	-0.91299	1.06156
C	4.10697	-1.53098	1.18931
H	5.95807	-1.84967	0.12054
H	5.24234	-0.56686	-1.8808
H	3.01611	0.50651	-1.97162
H	4.40477	-2.08197	2.0774

TS3

B3LYP/6-31G(d)(SDD)(gas) Energy = -1114.419886

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -1114.189278

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -1114.043081

Number of Imaginary Frequencies = 1 (-430.22)

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	-2.2191	-3.32633	-0.22751
C	-3.37875	-2.64171	0.07069
C	-3.36298	-1.23076	0.19563
C	-2.11416	-0.57762	-0.01597
C	-1.0218	-2.60463	-0.40059
H	-5.45666	-0.9282	0.67604
H	-2.20826	-4.40696	-0.32266
H	-4.31413	-3.17632	0.21738
C	-4.49808	-0.4433	0.51619
C	-1.99112	0.8493	0.08036
H	-0.08696	-3.11296	-0.60963
C	-3.12979	1.58418	0.41111
C	-4.36139	0.92705	0.6228
H	-5.22929	1.53103	0.8747
N	-0.96988	-1.28258	-0.30488
N	-0.72082	1.30737	-0.17559
C	-0.22818	2.57896	0.04776
O	-0.87645	3.55212	0.43087
C	1.22343	2.62789	-0.30626
C	1.92213	3.95466	-0.25628
H	2.88555	3.92689	-0.7752
H	1.29045	4.73328	-0.69833

H	2.10367	4.2539	0.78544
C	1.80857	1.4569	-0.72018
H	2.66361	1.40015	-1.38
Cu	0.58881	-0.01958	-0.52711
H	-3.04733	2.65888	0.50434
C	4.66436	-1.58764	0.98515
C	3.91317	-2.57461	0.33618
C	2.68866	-2.2711	-0.27774
C	2.2381	-0.94525	-0.23619
C	3.01596	-0.00812	0.3908
C	4.22087	-0.254	1.02353
H	5.60953	-1.85224	1.4545
H	4.28652	-3.59547	0.30486
H	2.13006	-3.05781	-0.78054
H	4.80488	0.5199	1.51458

INT2

B3LYP/6-31G(d)(SDD)(gas) Energy = -1114.50852

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -1114.274264

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -1114.134724

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	-2.83209	-3.16793	0.18769
C	-3.90616	-2.30544	0.1243
C	-3.6943	-0.9087	0.01274
C	-2.34265	-0.459	-0.03508
C	-1.52657	-2.63734	0.14258
H	-5.77138	-0.28358	-0.00732
H	-2.97108	-4.24051	0.27365
H	-4.92421	-2.68565	0.16102
C	-4.73867	0.0514	-0.044
C	-2.03734	0.94273	-0.15085
H	-0.65557	-3.28432	0.19403
C	-3.09091	1.8506	-0.19311
C	-4.42684	1.3924	-0.13895
H	-5.22773	2.12611	-0.17701
N	-1.28962	-1.33767	0.03753
N	-0.68641	1.20313	-0.20398
C	-0.04407	2.40843	-0.09275
O	-0.52191	3.53794	-0.04493
C	1.42976	2.06453	0.13247
C	2.00098	2.47825	1.45784
H	2.02645	3.57461	1.50013
H	1.365	2.14929	2.29002
H	3.01092	2.08786	1.60337
C	2.05381	1.24161	-0.76439

H	1.61942	1.17475	-1.76534
Cu	0.5294	-0.31269	-0.06013
H	-2.86526	2.90718	-0.26758
C	5.20152	-0.90522	-0.20905
C	4.54542	-2.06995	0.19755
C	3.14661	-2.10904	0.28707
C	2.38465	-0.97818	-0.02371
C	3.07754	0.18842	-0.43107
C	4.46596	0.24018	-0.53539
H	6.28653	-0.88854	-0.27484
H	5.12753	-2.95492	0.44578
H	2.66482	-3.03101	0.60872
H	4.96967	1.14836	-0.85969

INT3

B3LYP/6-31G(d)(SDD)(gas) Energy = -1342.960967

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -1342.684164

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -1342.53769

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	-3.04214	-2.59884	-1.51104
C	-4.08502	-1.77325	-1.15588
C	-3.81432	-0.47401	-0.65562
C	-2.44475	-0.09231	-0.55117
C	-1.71644	-2.12381	-1.37509
H	-5.8656	0.14527	-0.32097
H	-3.21746	-3.60105	-1.8893
H	-5.11704	-2.10366	-1.24839
C	-4.82208	0.44054	-0.24781
C	-2.10406	1.2091	-0.03421
H	-0.87141	-2.75738	-1.6282
C	-3.12113	2.07637	0.35644
C	-4.47177	1.68276	0.24071
H	-5.24717	2.37939	0.54775
N	-1.42521	-0.91817	-0.91925
N	-0.75412	1.47654	-0.02755
C	-0.12538	2.65778	0.22013
O	-0.56715	3.77478	0.47804
C	1.35688	2.31275	0.18063
C	2.19485	2.71111	1.35412
H	2.17234	3.80723	1.41636
H	1.76639	2.33832	2.29184
H	3.22795	2.36984	1.26283
C	1.81587	1.60117	-0.92442
H	1.2228	1.63852	-1.8386
Cu	0.66198	0.07931	0.06191

H	-2.85694	3.05936	0.72648
C	5.09089	-0.41593	-1.19494
C	4.58291	-1.56949	-0.58298
C	3.26108	-1.63274	-0.1144
C	2.4938	-0.48753	-0.27462
C	2.98686	0.66341	-0.87786
C	4.29201	0.71991	-1.36529
H	6.11831	-0.40744	-1.54868
H	5.22358	-2.44109	-0.47172
H	2.85345	-2.53136	0.33302
H	4.67515	1.61049	-1.85791
C	-0.13891	-2.7875	2.99102
H	-0.09988	-3.87759	2.95252
H	-1.15308	-2.46173	3.24515
H	0.52861	-2.41587	3.77512
C	0.26638	-2.20752	1.63542
O	0.27818	-0.89903	1.64451
O	0.53457	-2.92972	0.67818

TS4

B3LYP/6-31G(d)(SDD)(gas) Energy = -1342.956032
B3LYP/6-31G(d)(SDD) (gas) Free Energy= -1342.678099
M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -1342.524316
Number of Imaginary Frequencies = 1 (-102.85)
B3LYP/6-31G(d) (SDD)(gas) Geometry

C	-3.05674	-2.8192	-1.13882
C	-4.11879	-1.95211	-0.99712
C	-3.88641	-0.60881	-0.6111
C	-2.53285	-0.21773	-0.39458
C	-1.75073	-2.34327	-0.89622
H	-5.95513	0.04212	-0.58176
H	-3.20598	-3.85449	-1.42818
H	-5.13888	-2.28497	-1.17429
C	-4.92295	0.34351	-0.42401
C	-2.22016	1.13915	-0.00128
H	-0.88738	-2.99727	-0.96539
C	-3.27829	2.03926	0.17439
C	-4.61033	1.63216	-0.0376
H	-5.40644	2.35704	0.10961
N	-1.49758	-1.08938	-0.54393
N	-0.87922	1.39782	0.11961
C	-0.3406	2.62472	0.49106
O	-0.9224	3.61643	0.92538
C	1.16447	2.50256	0.36905
C	1.99367	2.82783	1.57497

H	1.8321	3.87903	1.8445
H	1.68534	2.22853	2.44114
H	3.05872	2.66371	1.39231
C	1.61276	1.96955	-0.79666
H	0.90114	1.92132	-1.62034
Cu	0.492	-0.12644	0.05321
H	-3.05028	3.05097	0.48245
C	4.88024	0.10583	-1.63785
C	4.42526	-1.17327	-1.3048
C	3.13823	-1.37234	-0.77843
C	2.34025	-0.24732	-0.64502
C	2.76832	1.04032	-0.96472
C	4.053	1.22274	-1.47951
H	5.88587	0.23293	-2.02943
H	5.07515	-2.03364	-1.44485
H	2.78329	-2.35849	-0.50204
H	4.3944	2.21764	-1.75521
C	1.33668	-2.87754	3.02446
H	0.66459	-2.42662	3.76068
H	2.36121	-2.62093	3.31508
H	1.21688	-3.96232	3.01947
C	1.04854	-2.3245	1.6316
O	1.04599	-1.01221	1.6141
O	0.8631	-3.05624	0.66259

III

B3LYP/6-31G(d)(SDD)(gas) Energy = -1343.021584

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -1342.74121

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -1341.438159

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	-3.68079	2.43668	0.04507
C	-4.4306	1.32893	0.38322
C	-3.8247	0.04996	0.45679
C	-2.43331	-0.02082	0.16129
C	-2.30525	2.27628	-0.22109
H	-5.56149	-1.10563	1.05626
H	-4.12598	3.42427	-0.01305
H	-5.49143	1.42524	0.60133
C	-4.50239	-1.14243	0.81748
C	-1.71499	-1.25811	0.19843
H	-1.66606	3.11812	-0.46844
C	-2.41722	-2.40014	0.57036
C	-3.79798	-2.32601	0.87214
H	-4.30973	-3.24179	1.15521
N	-1.71657	1.09287	-0.16731

N	-0.36863	-1.17216	-0.19452
C	0.25518	-2.23142	-0.82288
O	-0.27475	-3.33724	-0.9462
C	1.59059	-2.01508	-1.48607
C	1.68225	-2.66205	-2.84769
H	2.69127	-2.56805	-3.25965
H	1.40945	-3.71991	-2.78778
H	0.9819	-2.189	-3.54837
C	2.67461	-1.46567	-0.90854
H	3.61685	-1.53181	-1.45205
Cu	0.26513	0.59466	-0.06698
H	-1.90767	-3.35124	0.59901
C	1.86342	0.55448	2.21556
C	1.78891	0.0045	0.94172
C	2.7643	-0.8403	0.41537
C	3.89919	-1.07376	1.22231
C	4.00375	-0.53658	2.50149
C	2.98167	0.26978	3.00747
H	1.09407	1.22623	2.58408
H	4.68955	-1.71021	0.83075
H	4.88238	-0.74613	3.10533
H	3.0573	0.70084	4.00221
O	0.88552	2.37359	0.03501
C	1.3376	2.63794	-1.17042
O	1.27961	1.82368	-2.09408
C	1.94888	4.01892	-1.32462
H	2.90435	4.05173	-0.78888
H	2.11997	4.23445	-2.38082
H	1.30117	4.78198	-0.88199

TS5

B3LYP/6-31G(d)(SDD)(gas) Energy = -1343.019521

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -1342.739954

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -1342.591895

Number of Imaginary Frequencies = 1 (-148.75)

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	-3.77795	2.10941	0.67341
C	-4.40504	0.91014	0.4199
C	-3.64833	-0.21393	0.00086
C	-2.23767	-0.0333	-0.13841
C	-2.37628	2.18814	0.51281
H	-5.29067	-1.61817	-0.17692
H	-4.33492	2.98436	0.9928
H	-5.48147	0.80871	0.5358
C	-4.21762	-1.48079	-0.27877

C	-1.40576	-1.12222	-0.56409
H	-1.84364	3.11613	0.70752
C	-2.00589	-2.3511	-0.81348
C	-3.4007	-2.51784	-0.67408
H	-3.82903	-3.49294	-0.88856
N	-1.63965	1.1622	0.12732
N	-0.02592	-0.88053	-0.68491
C	0.78553	-1.58903	-1.56452
O	0.33092	-2.32198	-2.4409
C	2.27087	-1.43917	-1.42543
C	3.0394	-1.65954	-2.7027
H	4.11806	-1.62974	-2.5226
H	2.7728	-2.62175	-3.15078
H	2.78946	-0.88795	-3.44147
C	2.89736	-1.31877	-0.23174
H	3.98285	-1.4092	-0.21353
Cu	0.57138	0.82139	-0.10749
H	-1.39893	-3.17932	-1.15087
C	0.27424	-0.5173	2.37862
C	0.99615	-0.54374	1.19175
C	2.24765	-1.15739	1.0642
C	2.84261	-1.63553	2.24844
C	2.16829	-1.57509	3.46508
C	0.88133	-1.03128	3.52947
H	-0.71111	-0.06679	2.4267
H	3.83104	-2.08563	2.19083
H	2.63827	-1.96538	4.36314
H	0.35053	-0.98733	4.47668
O	1.53328	2.41844	0.52014
C	1.52168	2.9577	-0.64997
O	0.98569	2.34717	-1.61168
C	2.16571	4.31334	-0.82532
H	3.24282	4.23054	-0.64252
H	1.99555	4.69153	-1.83494
H	1.76489	5.01561	-0.08732

3

B3LYP/6-31G(d)(SDD)(gas) Energy = -917.214459

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -916.975382

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -916.7953286

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	-2.35824	1.91689	-0.21236
C	-3.18311	0.85584	-0.38865
C	-2.75282	-0.49901	-0.17444
C	-1.41676	-0.73077	0.23882

C	-0.96835	1.70628	0.21676
H	-4.63419	-1.40615	-0.68085
H	-4.21141	1.01724	-0.7085
C	-3.61168	-1.59812	-0.36429
C	-0.97738	-2.05059	0.44704
C	-1.84816	-3.11387	0.24875
C	-3.1728	-2.89599	-0.15715
H	-3.84566	-3.73476	-0.30849
N	-0.58017	0.36821	0.44047
H	-1.4909	-4.12696	0.41244
C	-2.76516	3.34475	-0.43502
H	-2.62814	3.93586	0.47789
H	-2.13294	3.81293	-1.19829
H	-3.81108	3.41317	-0.7494
O	-0.17244	2.62407	0.39223
C	0.7961	0.17486	0.8075
C	1.77331	-0.00164	-0.21803
C	1.16651	0.18199	2.13283
C	3.14182	-0.16674	0.16899
C	2.52092	0.01336	2.50603
H	0.4053	0.32944	2.89261
C	2.29247	-0.17012	-2.44598
C	4.094	-0.33492	-0.86883
C	3.49017	-0.15575	1.54459
H	2.78826	0.02533	3.55856
C	3.67458	-0.33495	-2.17734
H	1.94155	-0.17232	-3.47757
H	5.14367	-0.46024	-0.61334
H	4.53335	-0.28087	1.82469
H	4.37517	-0.45937	-2.99744
N	1.37037	-0.01094	-1.5186
H	0.04271	-2.23586	0.76145

CuOAc

B3LYP/6-31G(d)(SDD)(gas) Energy = -425.8400597

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -425.820393

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -425.844801

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	2.57607	-0.00062	0.00051
H	2.97303	1.01544	-0.0049
H	2.93414	-0.53615	0.88591
H	2.93528	-0.54658	-0.87795
C	1.0602	0.00848	-0.00013
O	0.44136	-1.10609	-0.00022
O	0.43742	1.11871	-0.00008

Cu	-1.29967	-0.00279	-0.0001

HOAc

B3LYP/6-31G(d)(SDD)(gas) Energy = -229.081787

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -229.046993

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -229.040396

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	1.39743	-0.10974	0.
H	1.91803	0.84811	-0.00008
H	1.68424	-0.69155	0.88218
H	1.68431	-0.69177	-0.88201
C	-0.09242	0.1263	-0.00009
O	-0.77825	-1.0471	0.00003
H	-1.72329	-0.80422	0.00009
O	-0.64592	1.20211	0.00002

C6H4

B3LYP/6-31G(d)(SDD)(gas) Energy = -230.909948

B3LYP/6-31G(d)(SDD) (gas) Free Energy= -230.86198

M06/6-311+G(d,p)(SDD)/SMD (acetonitrile) Energy = -230.7897532

B3LYP/6-31G(d) (SDD)(gas) Geometry

C	-1.46142	-0.13359	-0.00006
C	-0.7036	1.05852	0.00001
C	0.70362	1.0585	0.00001
C	1.46142	-0.13362	-0.00006
C	0.62548	-1.23765	0.00005
C	-0.62551	-1.23765	0.00005
H	-2.54667	-0.13465	-0.00002
H	-1.22912	2.01115	0.00007
H	1.22916	2.01113	0.00007
H	2.54667	-0.1347	-0.00002

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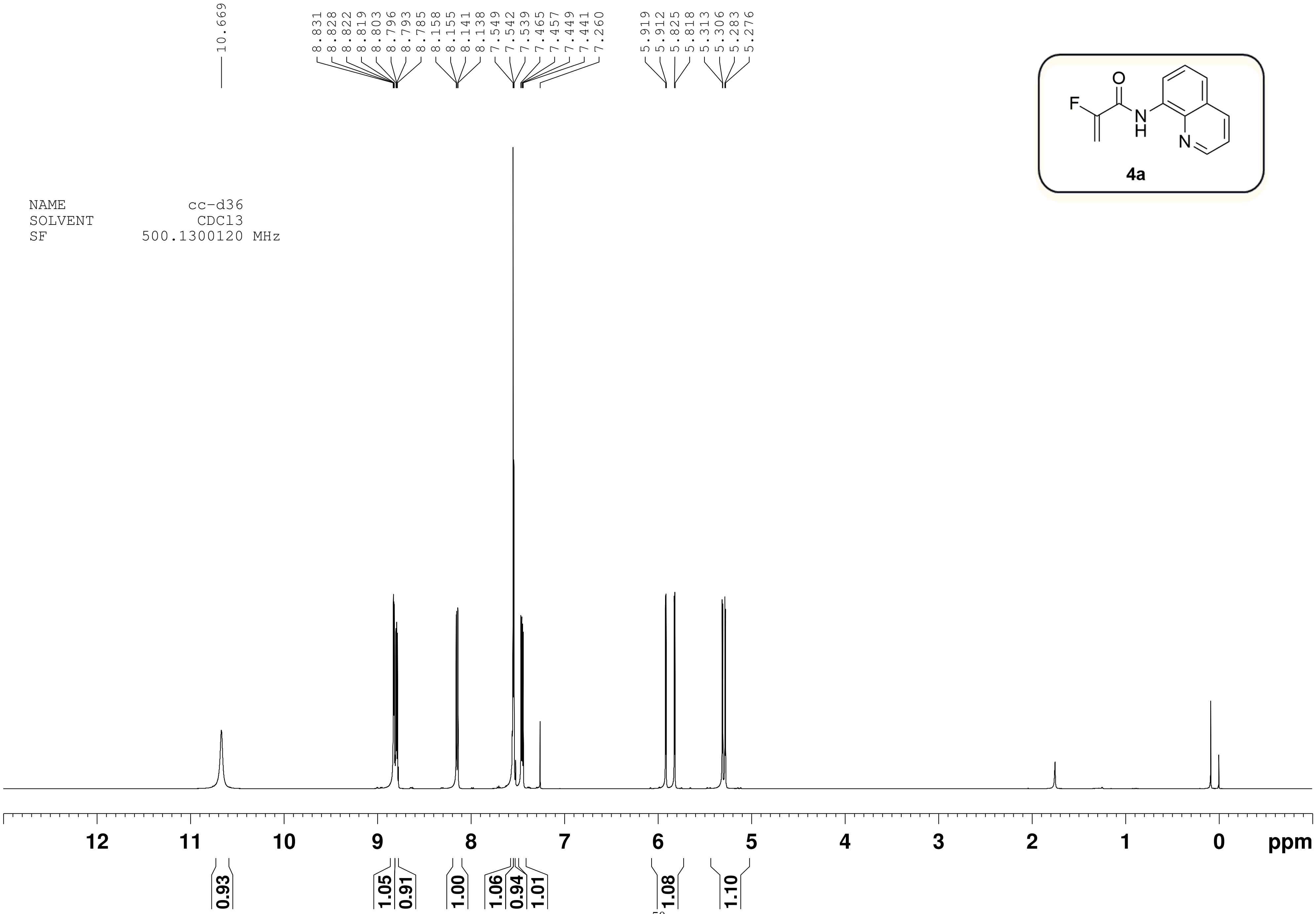
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8.141
8.138
7.549
7.542
7.539
7.465
7.457
7.449
7.441
7.260
5.919
5.912
5.825
5.818
5.313
5.306
5.283
5.276
NAME cc-d36
SOLVENT CDCl3
SF 500.1300120 MHz
F
O
N
H
N
4a
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.93
1.05
0.91
1.00
1.06
0.94
1.01
1.08
1.10

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SFO1        125.7703643 MHz
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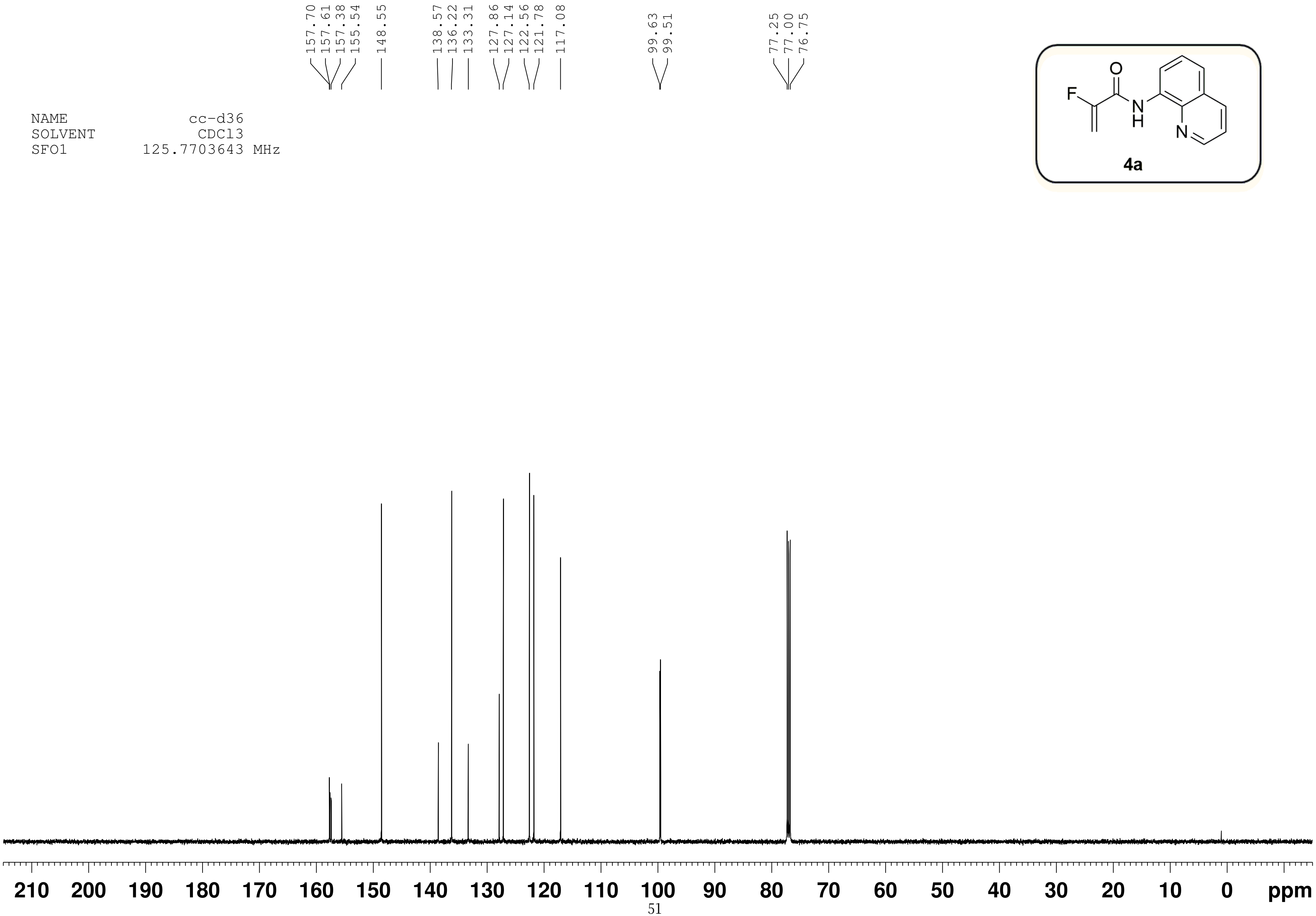

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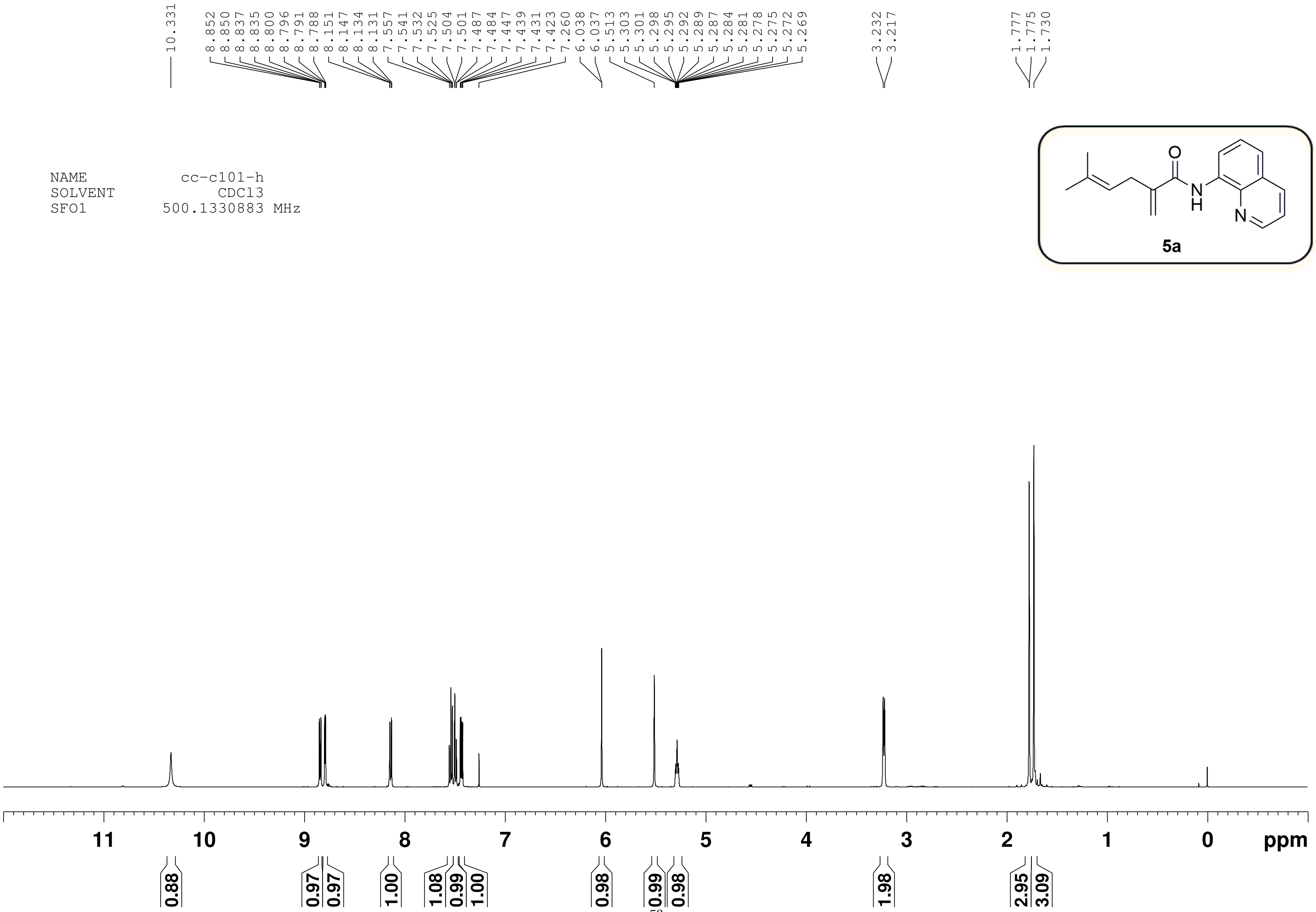

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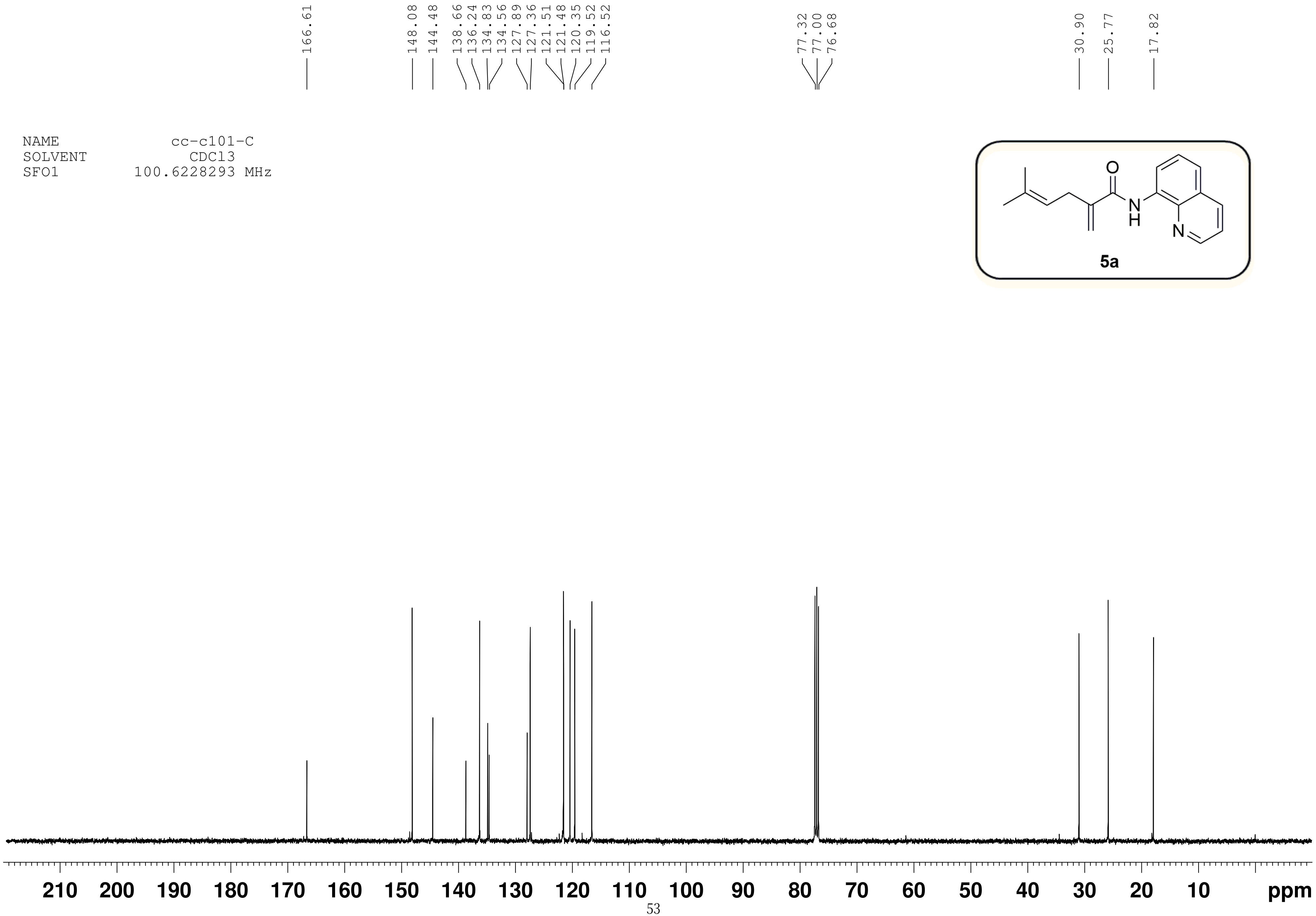

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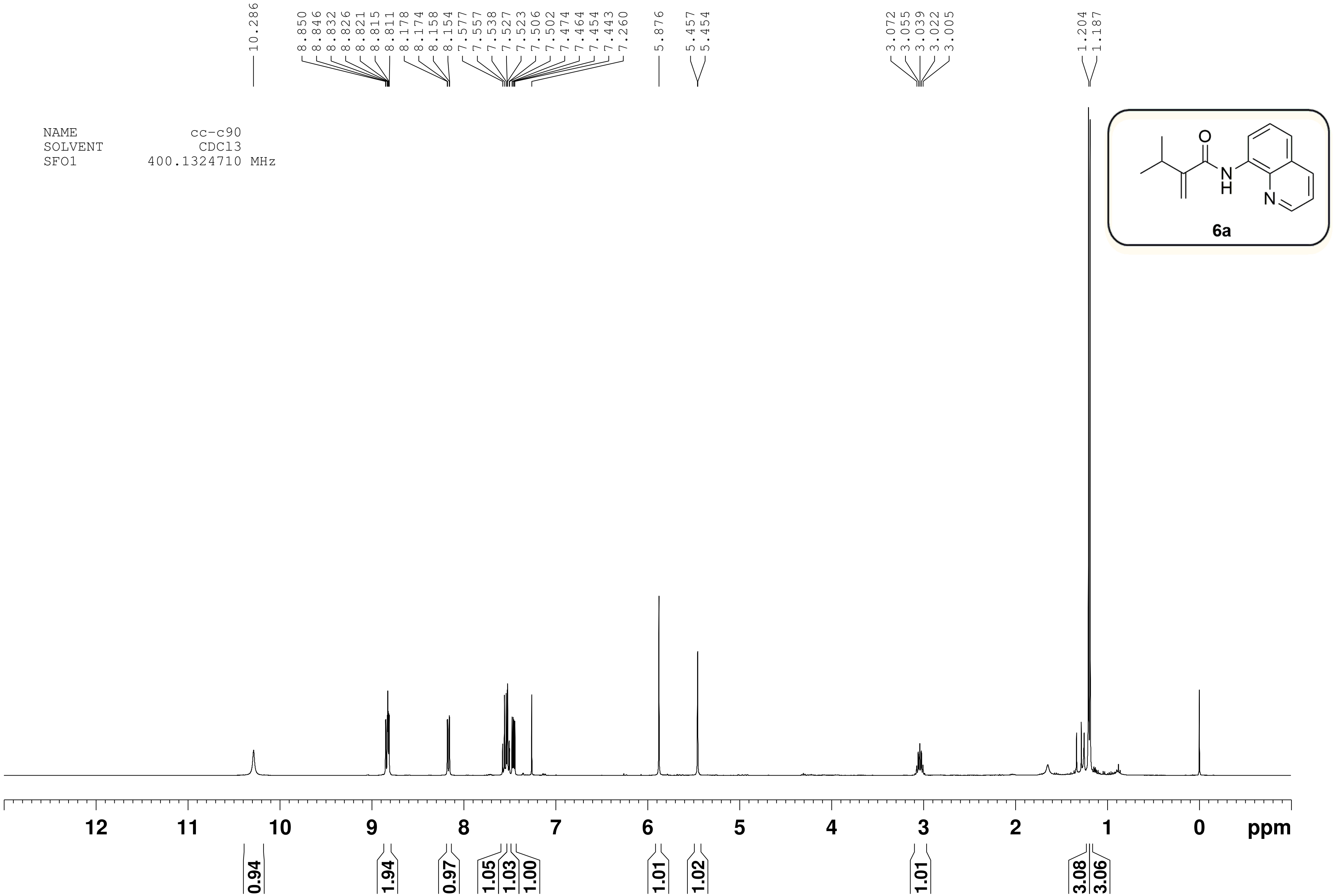
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7.577
7.557
7.538
7.527
7.523
7.506
7.502
7.474
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7.454
7.443
7.260
5.876
5.457
5.454
3.072
3.055
3.039
3.022
3.005
1.204
1.187
NAME cc-c90
SOLVENT CDCl3
SFO1 400.1324710 MHz
O
N
H
N
6a
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
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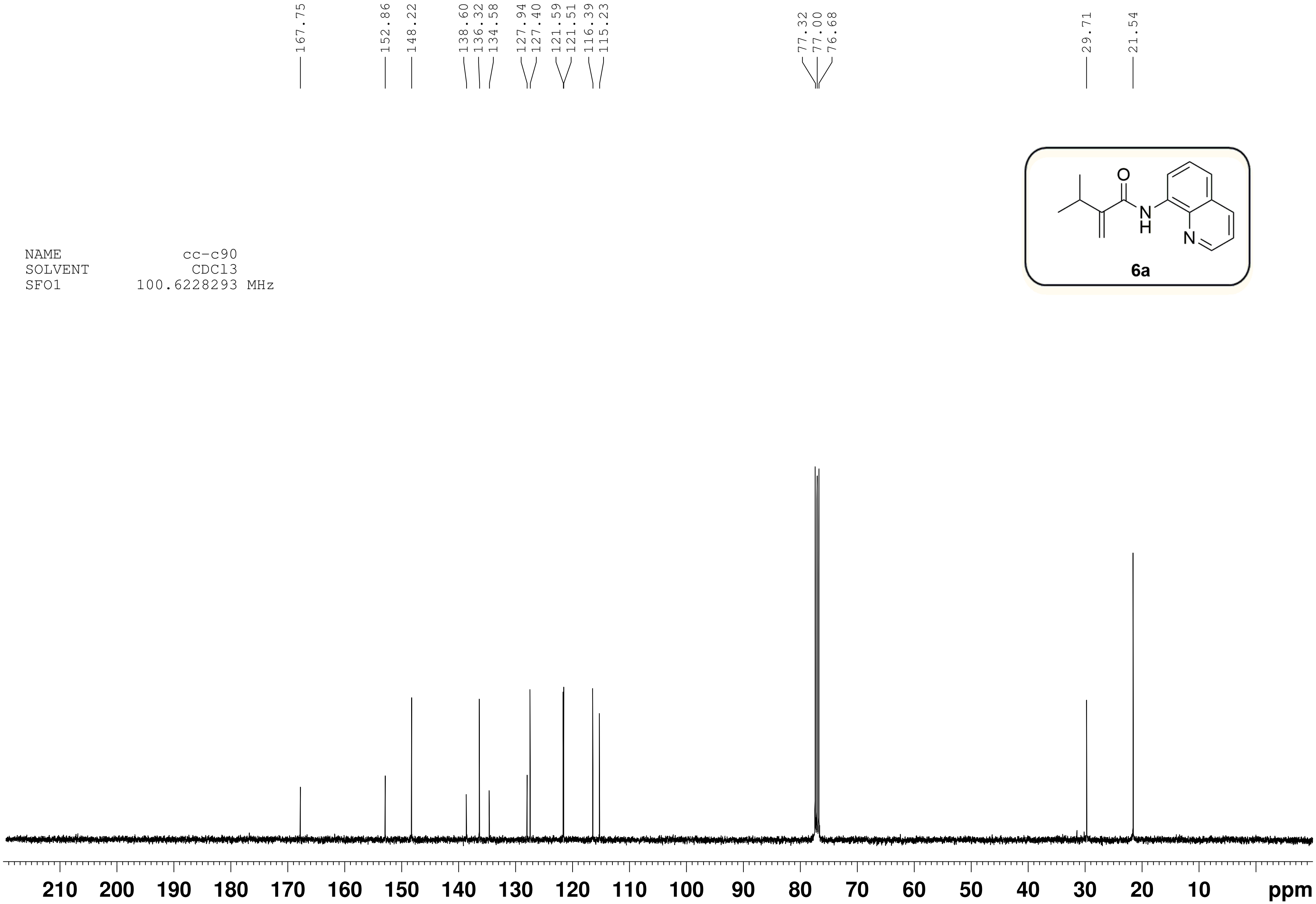
1.03
1.00
1.01
1.02
1.01
3.08
3.06



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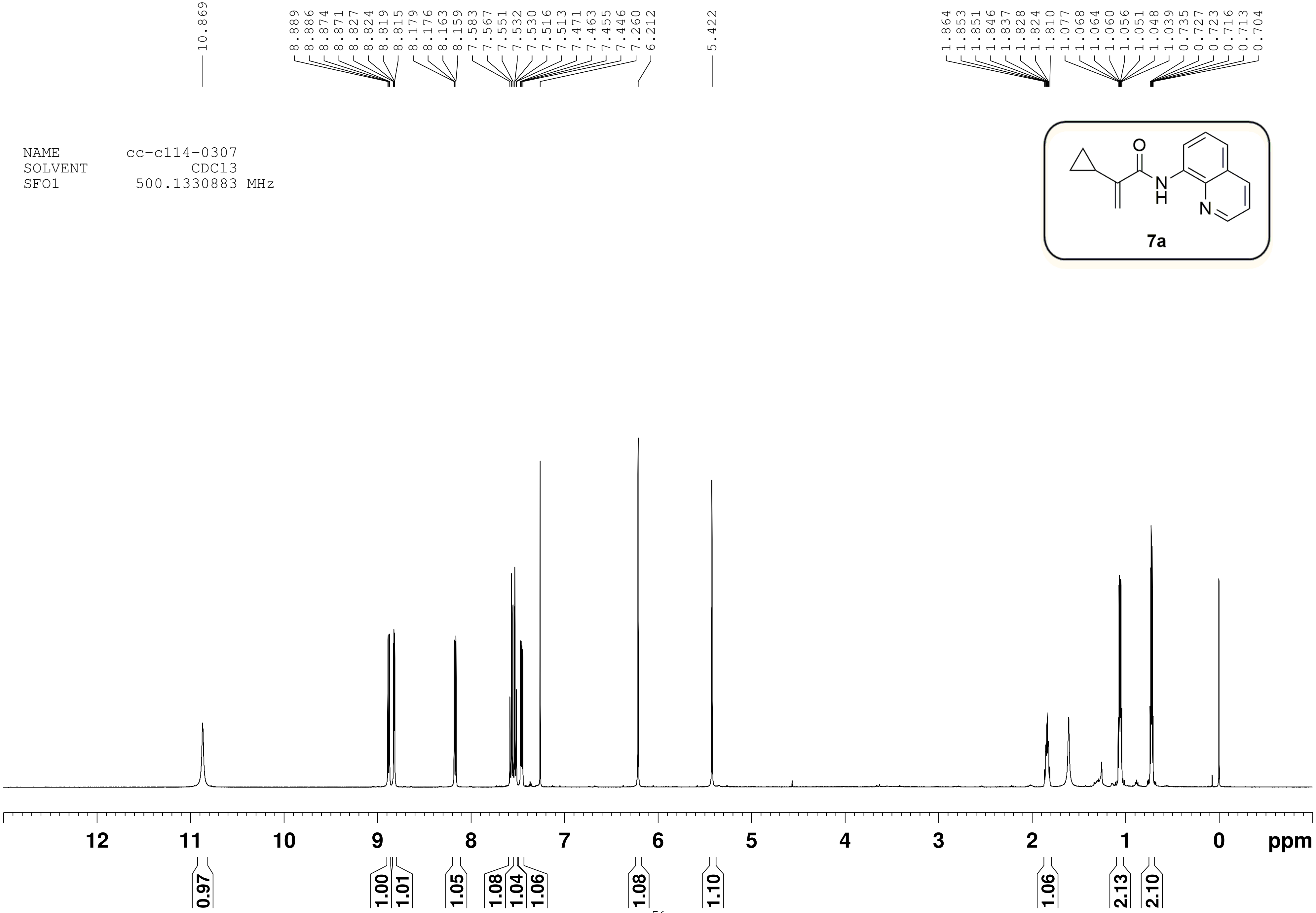

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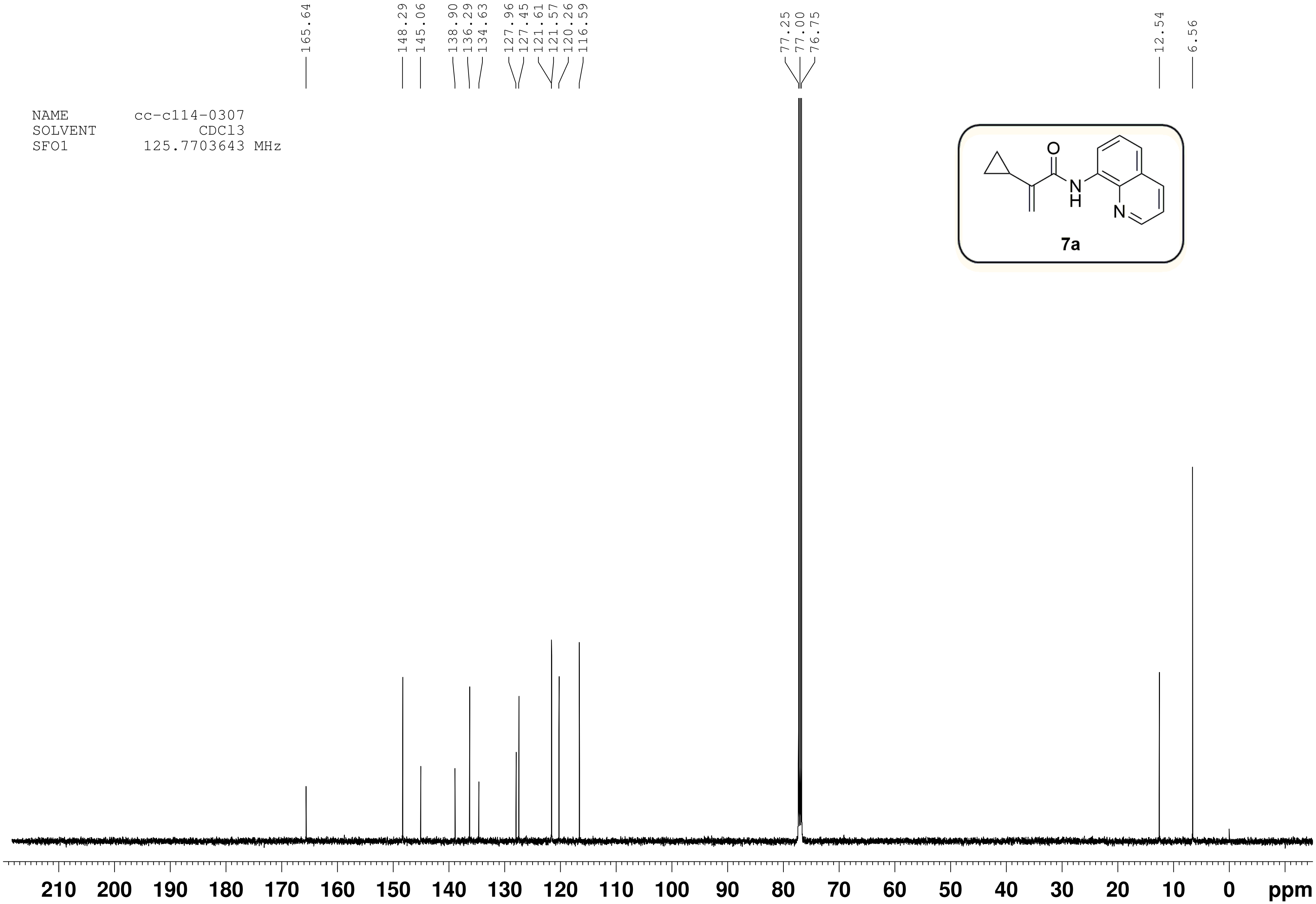

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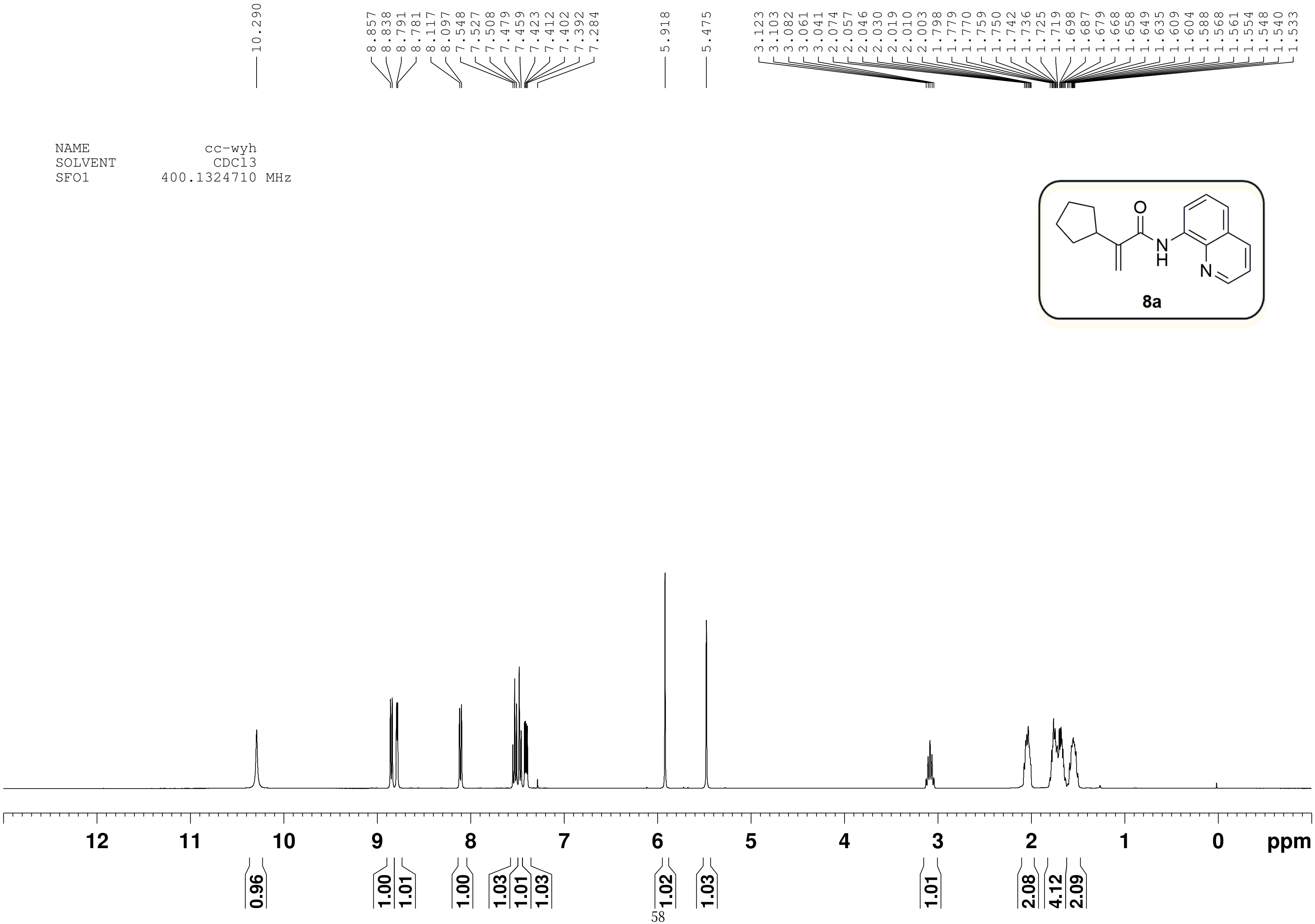
7a



8a

NAME cc-wyh
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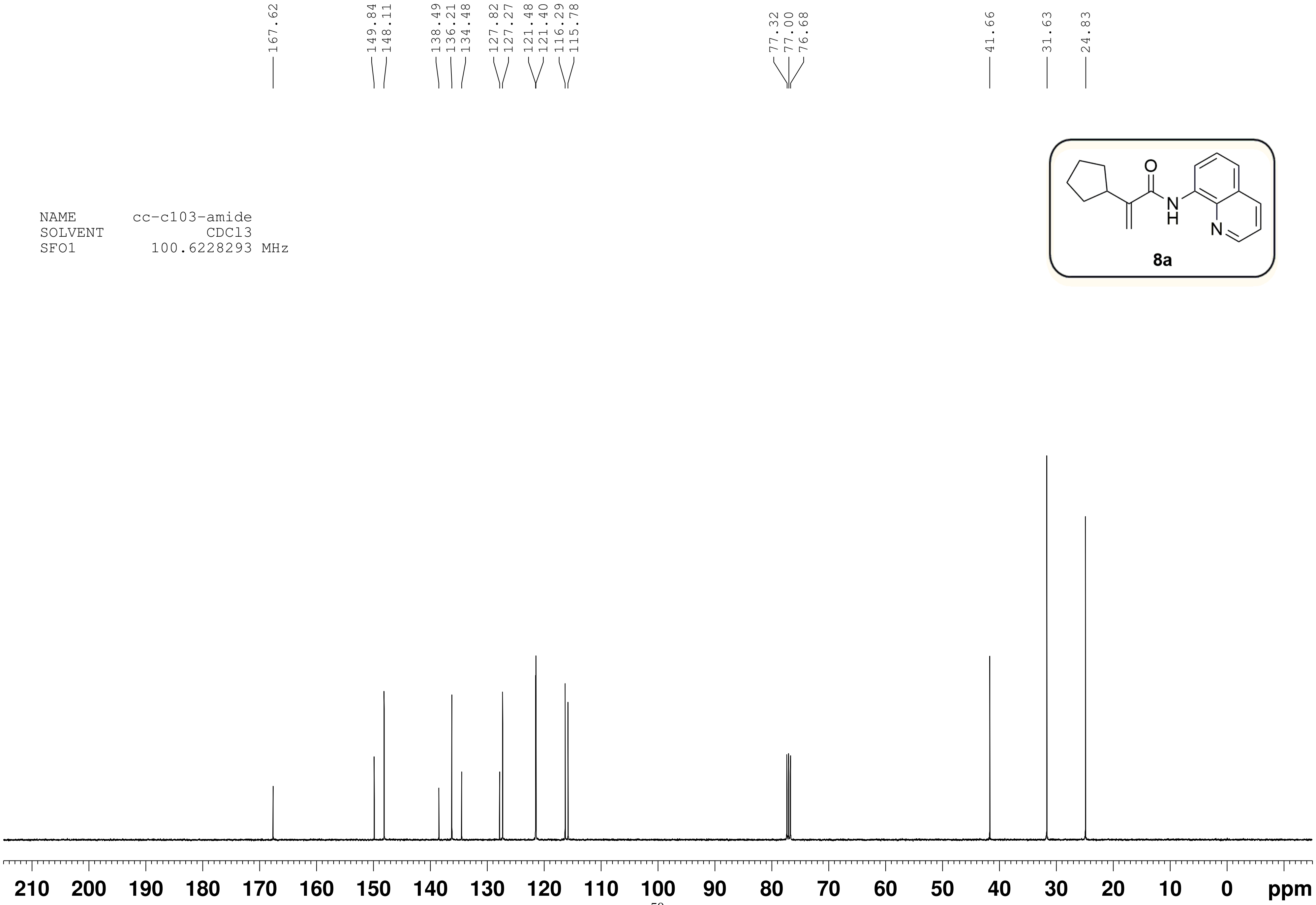
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77.32
77.00
76.68
41.66
31.63
24.83
NAME cc-c103-amide
SOLVENT CDCl3
SFO1 100.6228293 MHz
O
N
H
N
8a
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200
190
180
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130
120
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70
60
50
40
30
20
10
0
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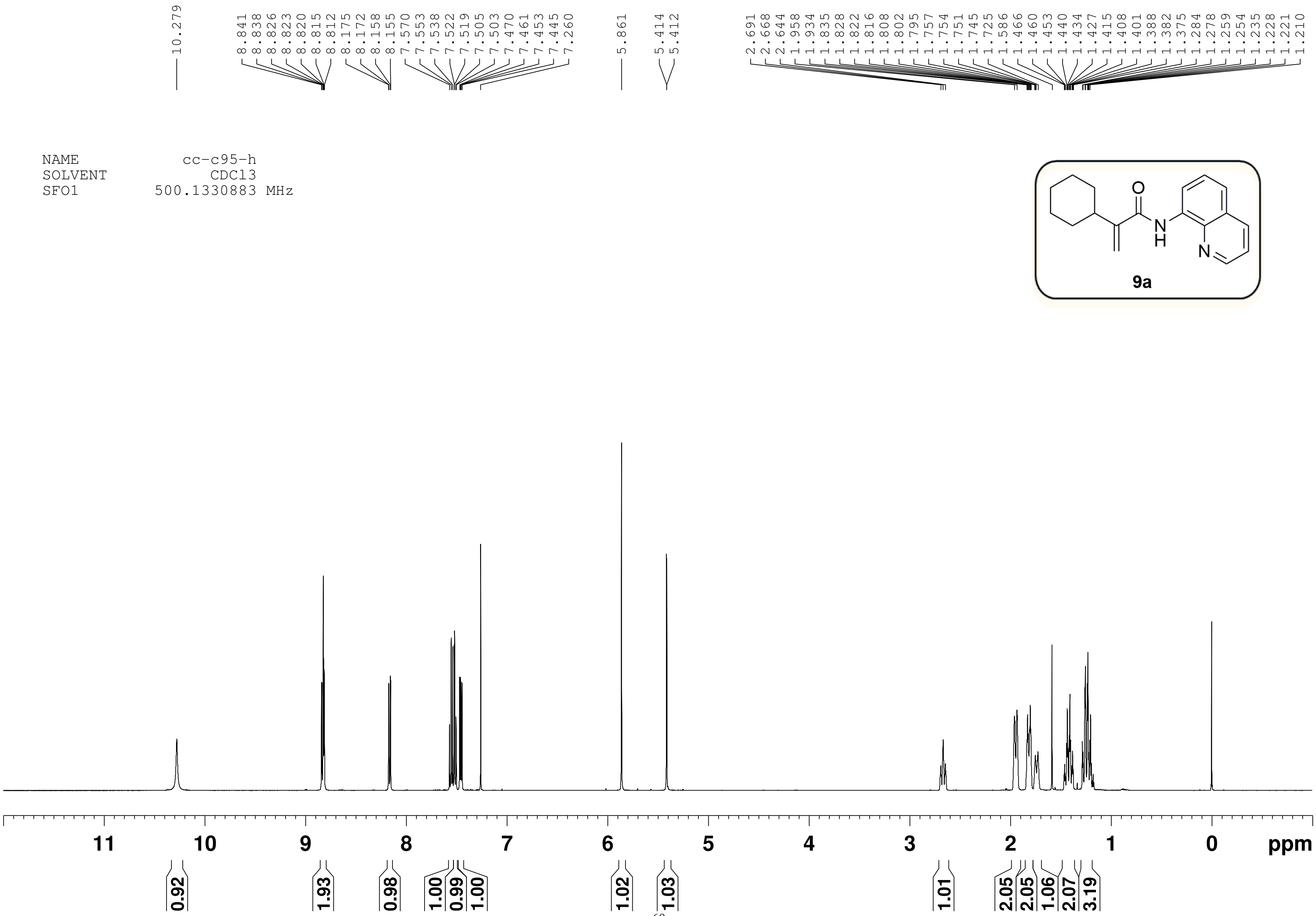

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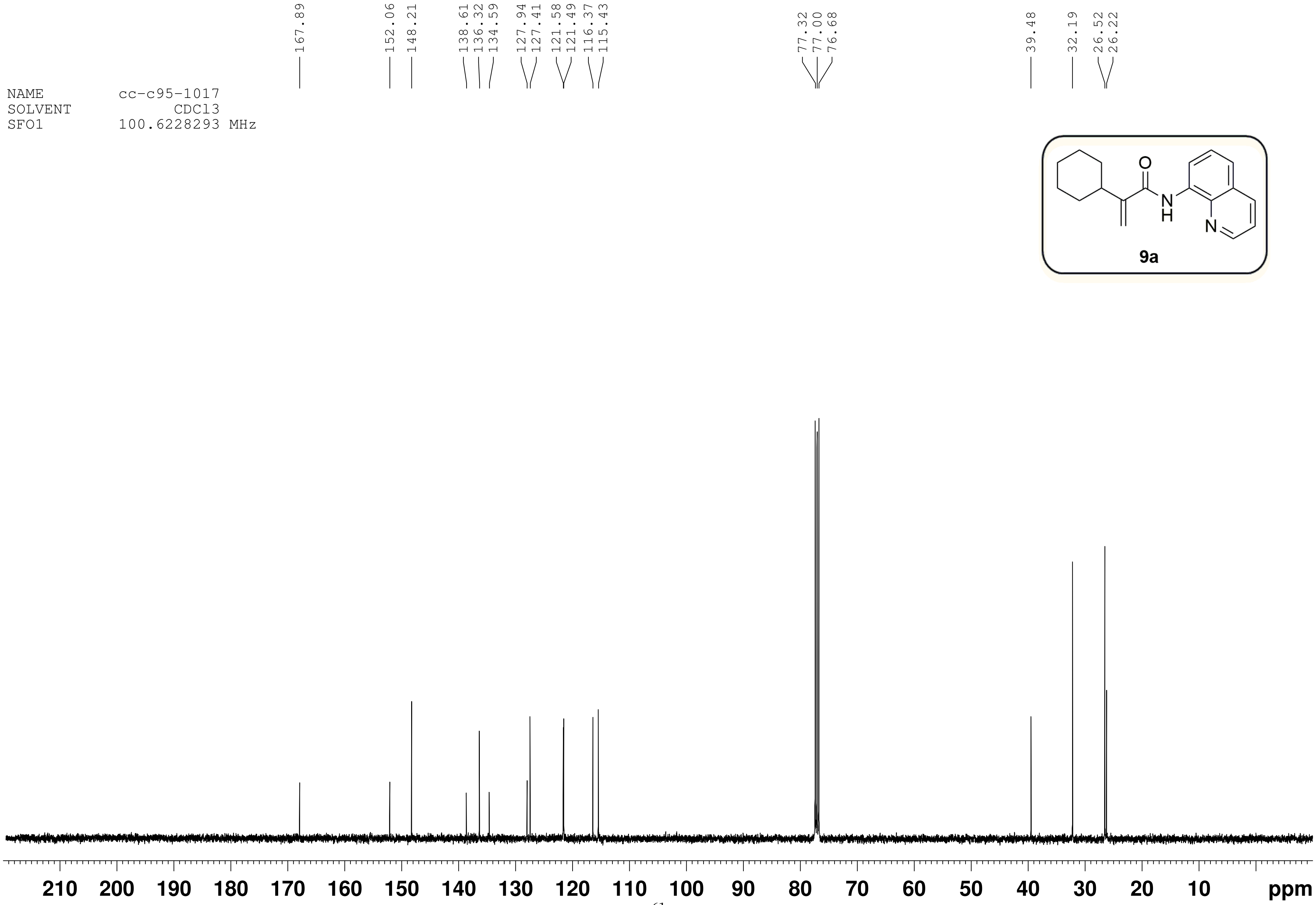
9a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127.41
121.58
121.49
116.37
115.43
77.32
77.00
76.68
39.48
32.19
26.52
26.22
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N
H
N
210
200
190
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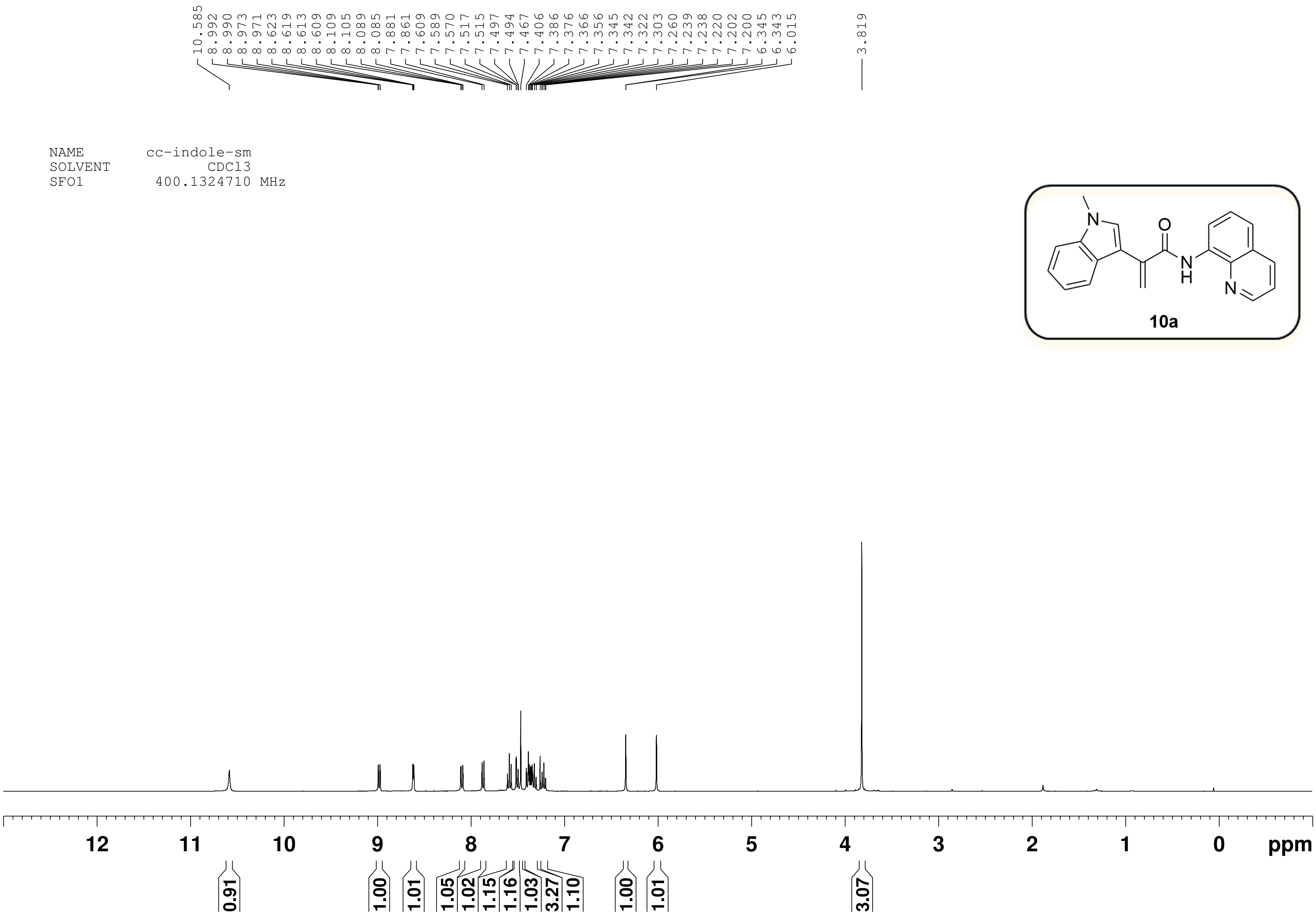
50
40
30
20
10
ppm

9a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7.589
7.570
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7.322
7.303
7.260
7.239
7.238
7.220
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6.343
6.015
3.819
NAME cc-indole-sm
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O
N
H
N
12
11
10
9
8
7
6
5
4
3
2
1
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ppm
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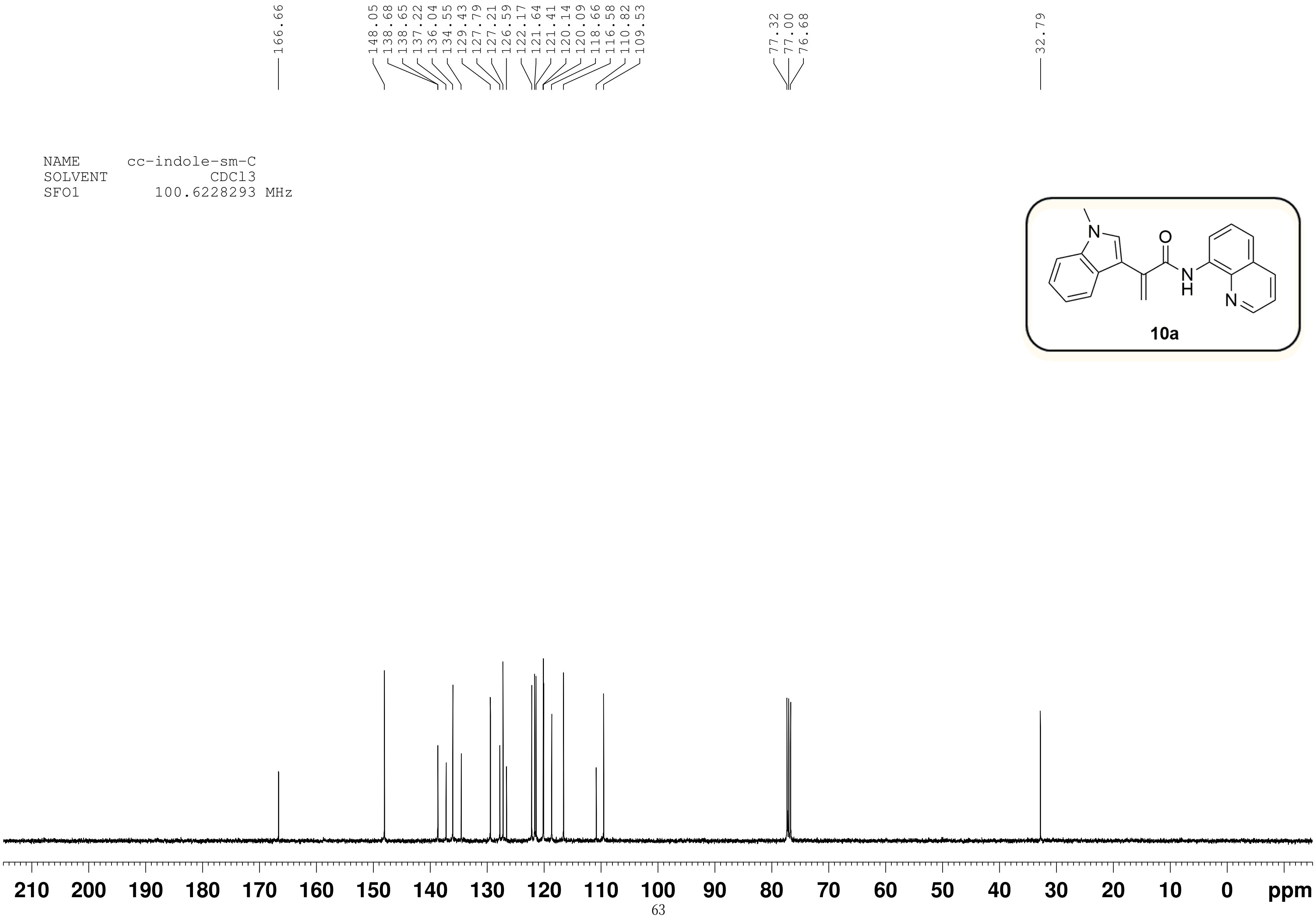
1.01
3.07

10a



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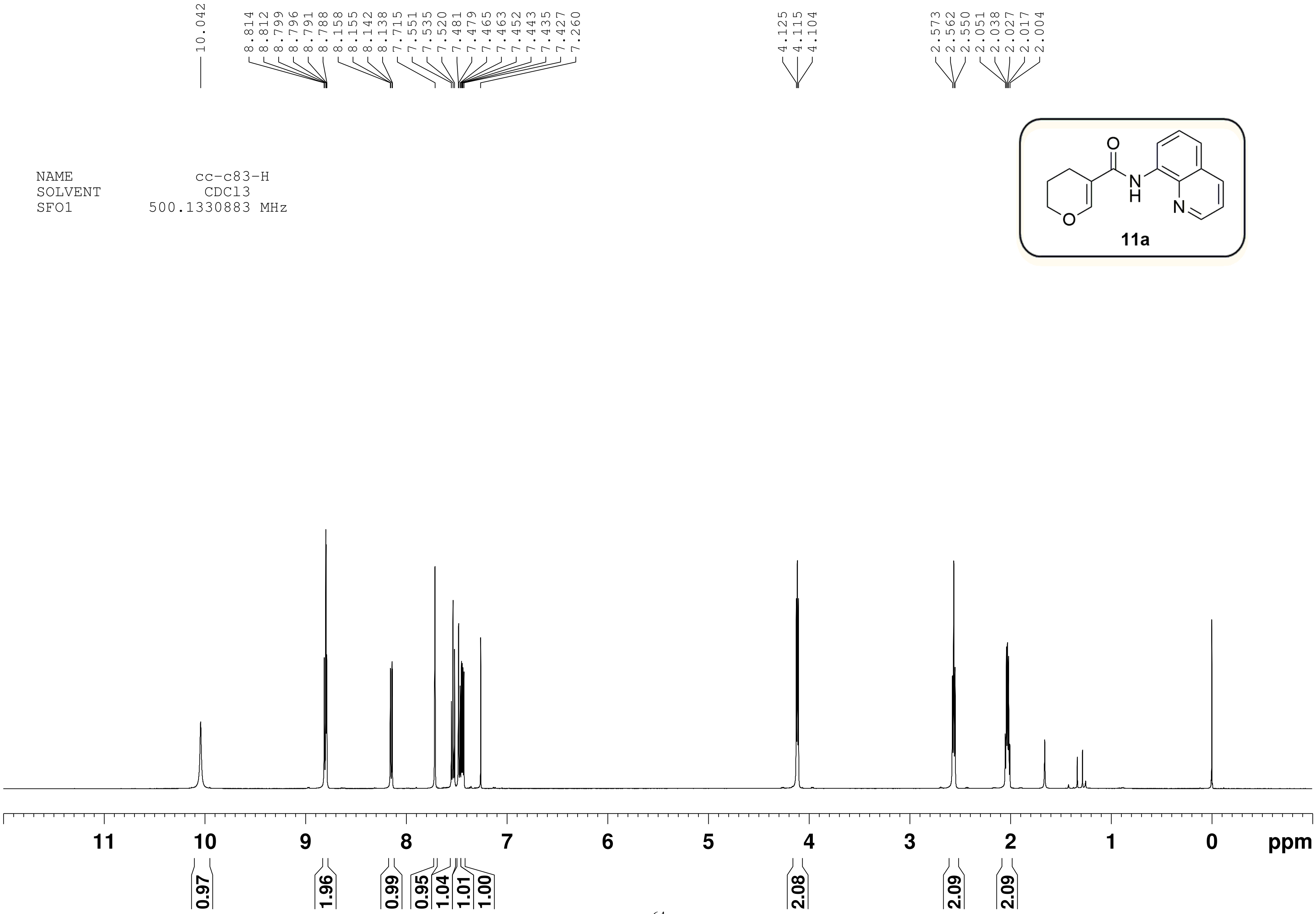

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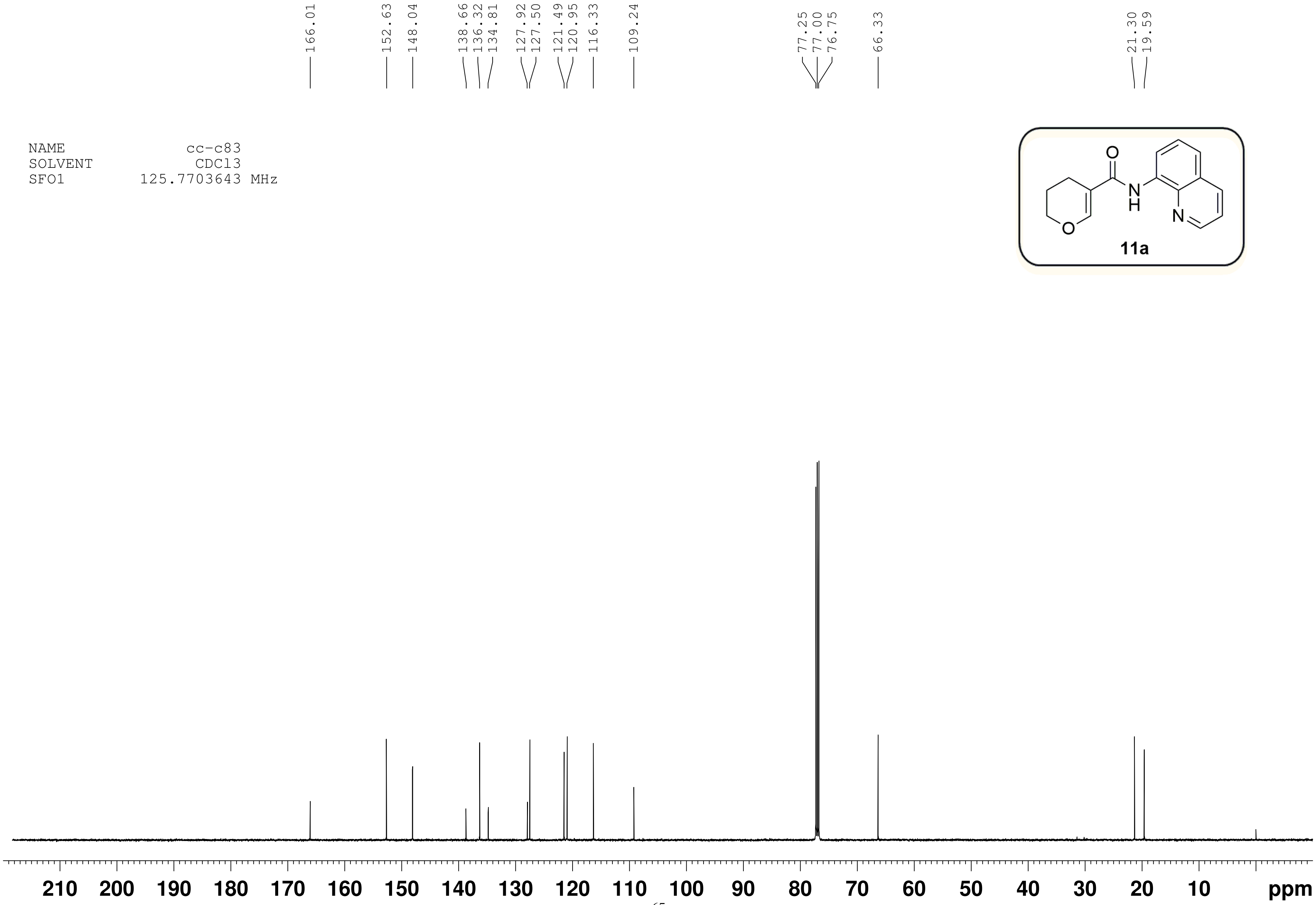

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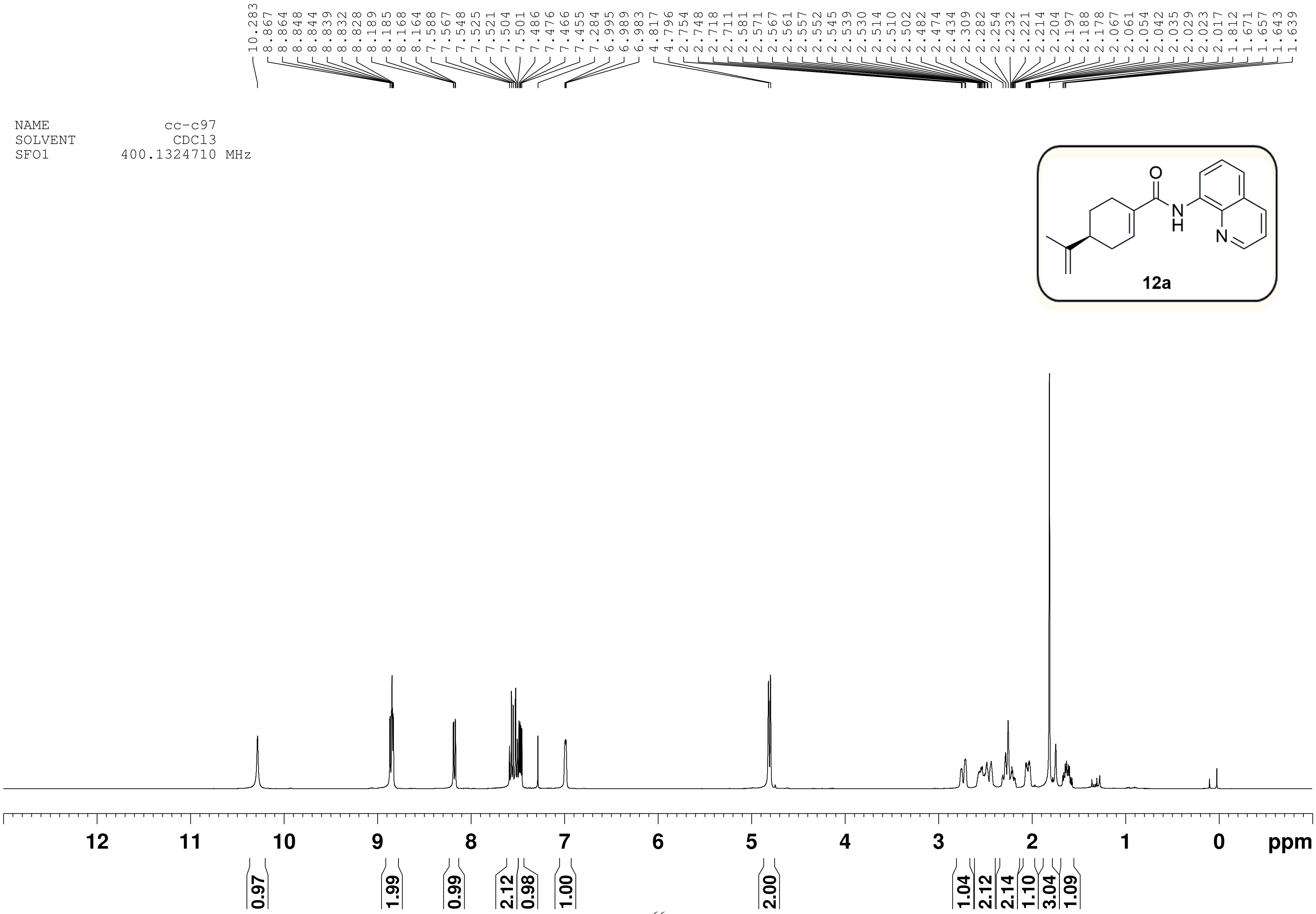
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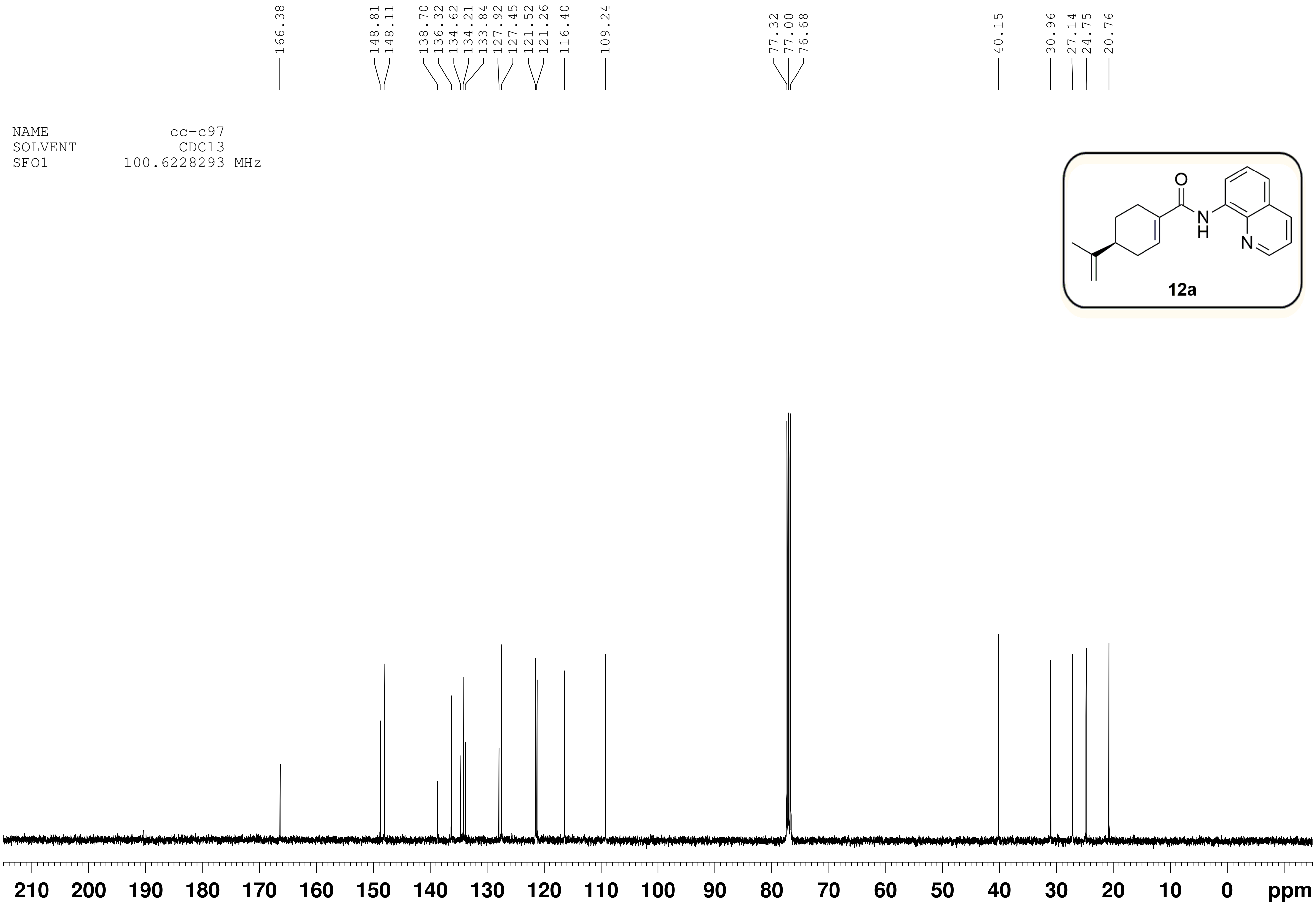
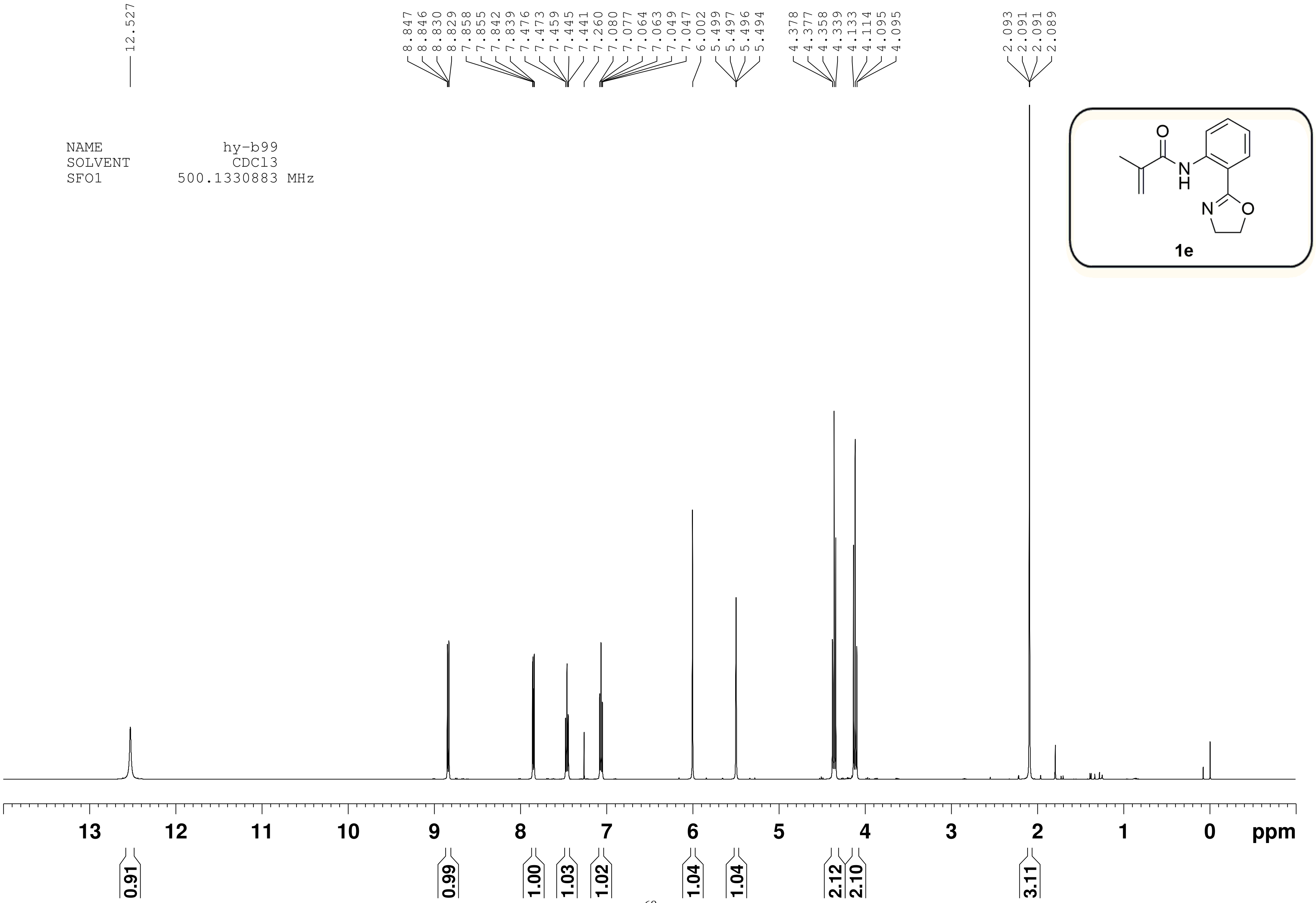
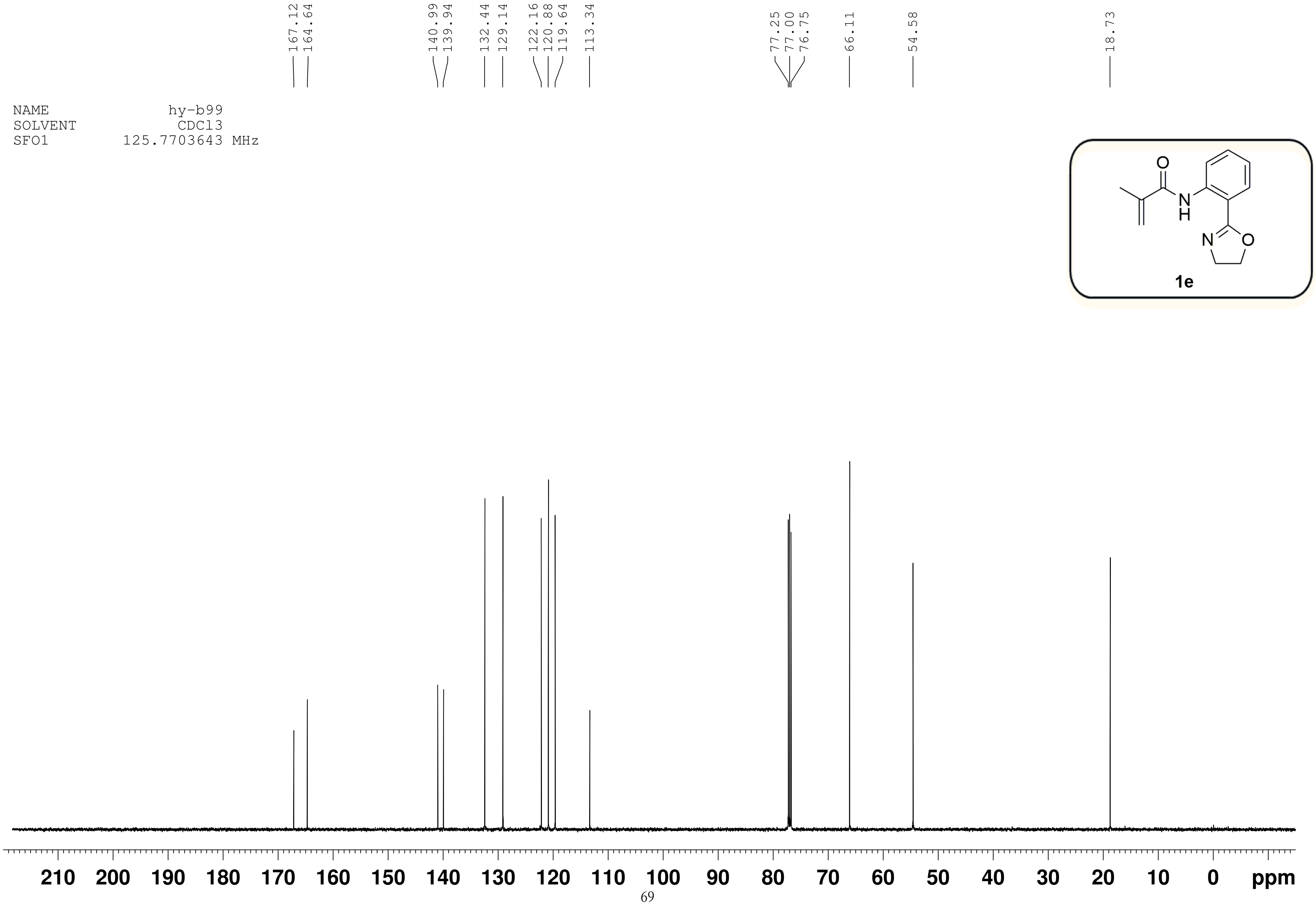
8.168
8.164
7.588
7.567
7.548
7.525
7.521
7.504
7.501
7.486
7.476
7.466
7.455
7.284
6.995
6.989
6.983
4.817
4.796
2.754
2.748
2.718
2.711
2.581
2.571
2.567
2.561
2.557
2.552
2.545
2.539
2.530
2.514
2.510
2.502
2.482
2.474
2.434
2.309
2.282
2.254
2.232
2.221
2.214
2.204
2.197
2.188
2.178
2.067
2.061
2.054
2.042
2.035
2.029
2.023
2.017
1.812
1.671
1.657
1.643
1.639
NAME cc-c97
SOLVENT CDCl3
SFO1 400.1324710 MHz
O
N
H
N
12a
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.97
1.99
0.99
2.12
0.98
1.00
2.00
1.04
2.12
2.14
1.10
3.04
1.09


166.38
148.81
148.11
138.70
136.32
134.62
134.21
133.84
127.92
127.45
121.52
121.26
116.40
109.24
77.32
77.00
76.68
40.15
30.96
27.14
24.75
20.76
NAME cc-c97
SOLVENT CDCl3
SFO1 100.6228293 MHz
O
N
H
N
12a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

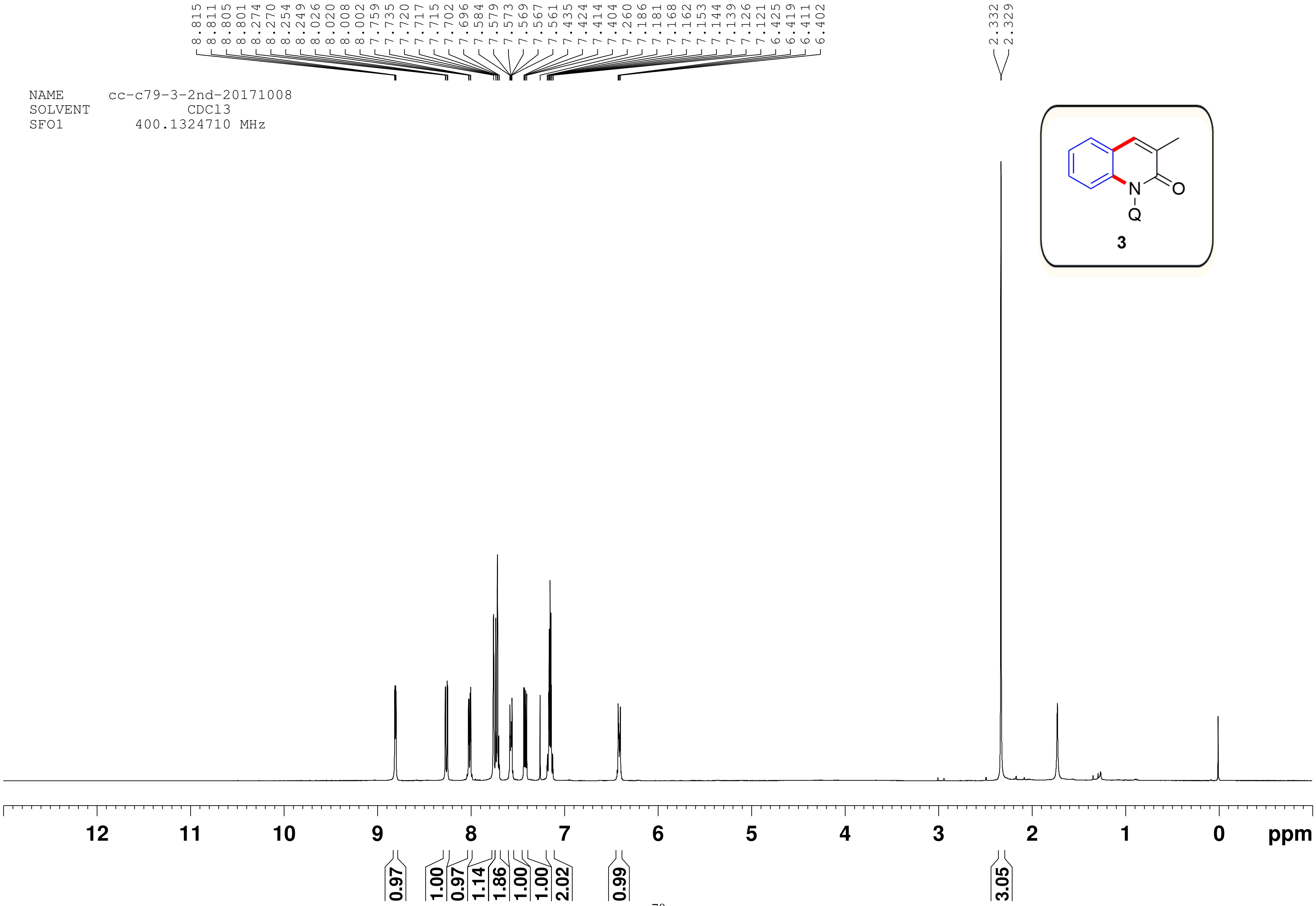


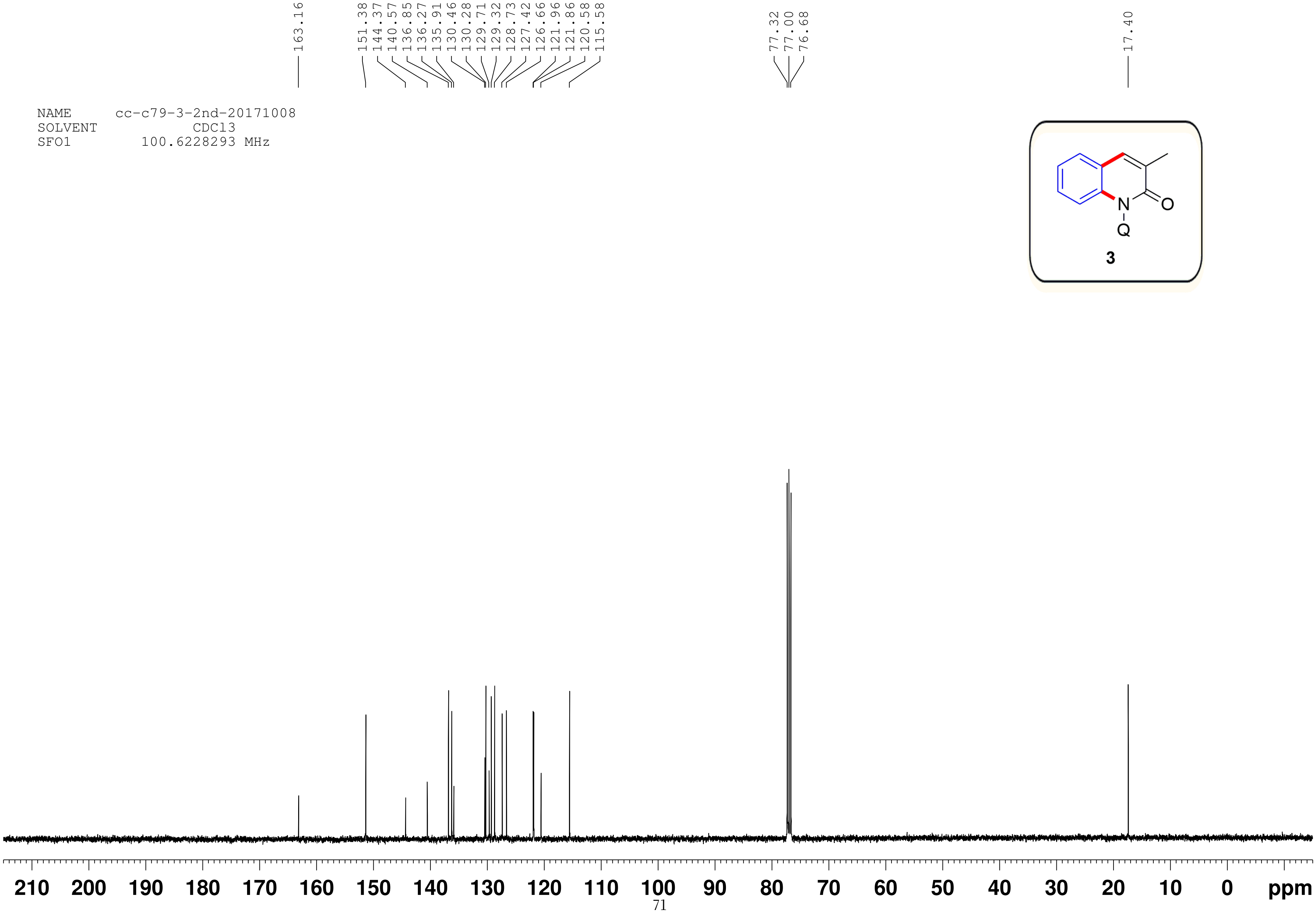
```
NAME            hy-b99
SOLVENT          CDCl3
SFO1    500.1330883 MHz
```

1e

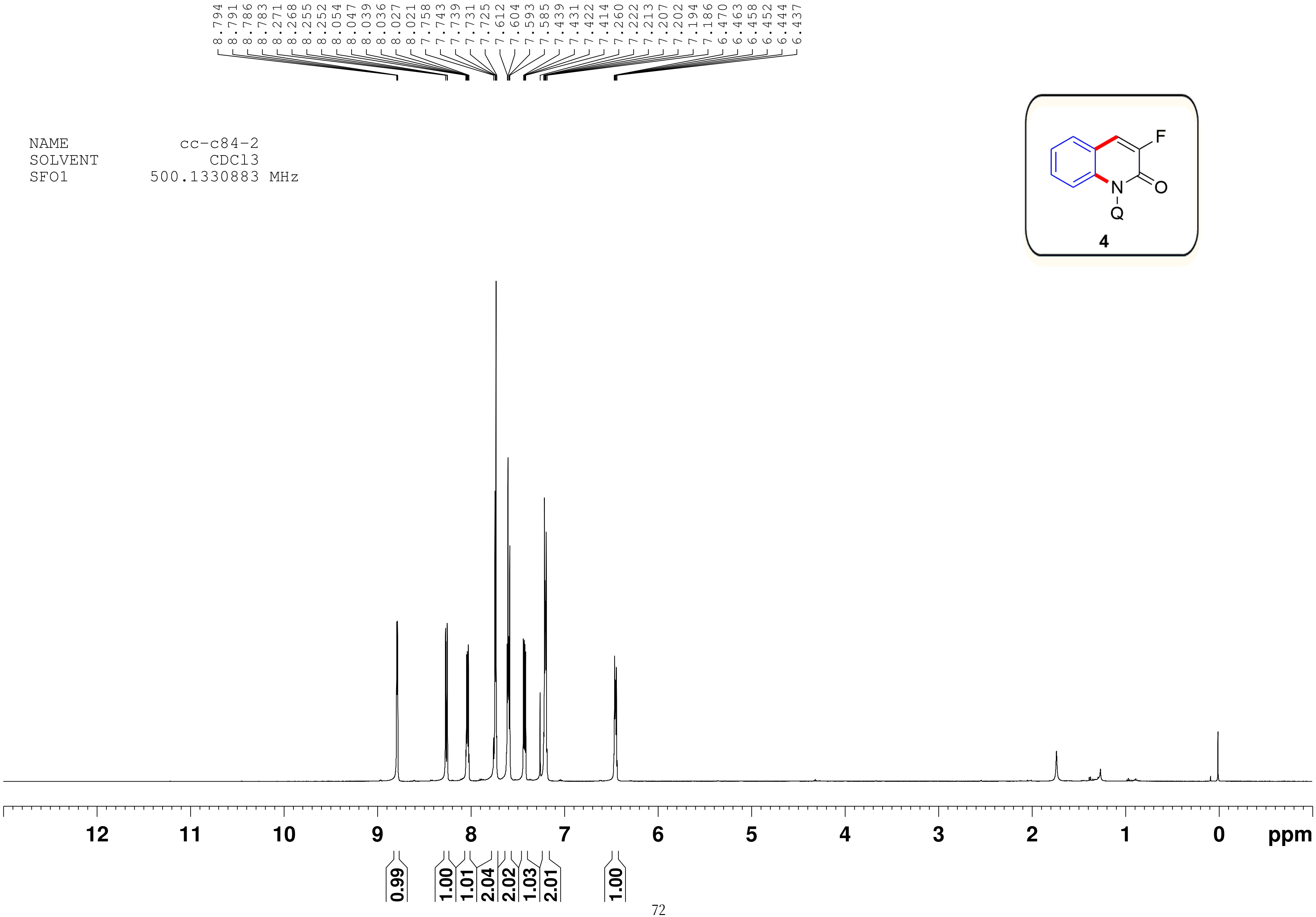

167.12
164.64
140.99
139.94
132.44
129.14
122.16
120.88
119.64
113.34
77.25
77.00
76.75
66.11
54.58
18.73
NAME hy-b99
SOLVENT CDCl3
SFO1 125.7703643 MHz
O
N
H
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

1e

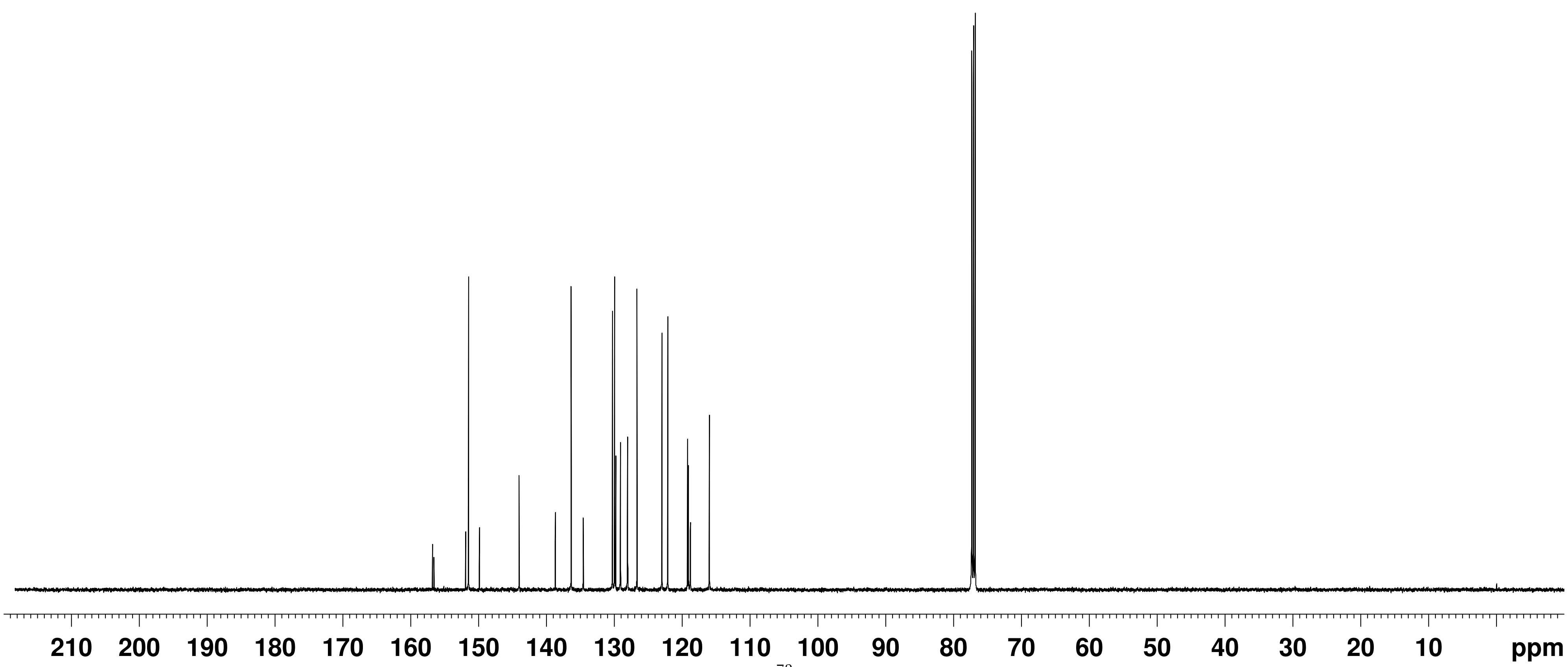

NAME cc-c79-3-2nd-20171008
SOLVENT CDCl3
SFO1 400.1324710 MHz
8.815
8.811
8.805
8.801
8.274
8.270
8.254
8.249
8.026
8.020
8.008
8.002
7.759
7.735
7.720
7.717
7.715
7.702
7.696
7.584
7.579
7.573
7.569
7.567
7.561
7.435
7.424
7.414
7.404
7.260
7.186
7.181
7.168
7.162
7.153
7.144
7.139
7.126
7.121
6.425
6.419
6.411
6.402
2.332
2.329
N
O
Q
3
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.97
1.00
0.97
1.14
1.86
1.00
1.00
2.02
0.99
3.05

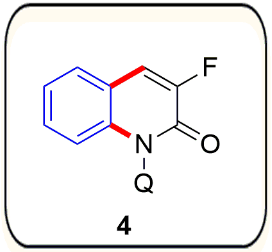

163.16
151.38
144.37
140.57
136.85
136.27
135.91
130.46
130.28
129.71
129.32
128.73
127.42
126.66
121.96
121.86
120.58
115.58
77.32
77.00
76.68
17.40
NAME cc-c79-3-2nd-20171008
SOLVENT CDCl3
SFO1 100.6228293 MHz
N
O
Q
3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

NAME cc-c84-2
SOLVENT CDCl3
SFO1 500.1330883 MHz



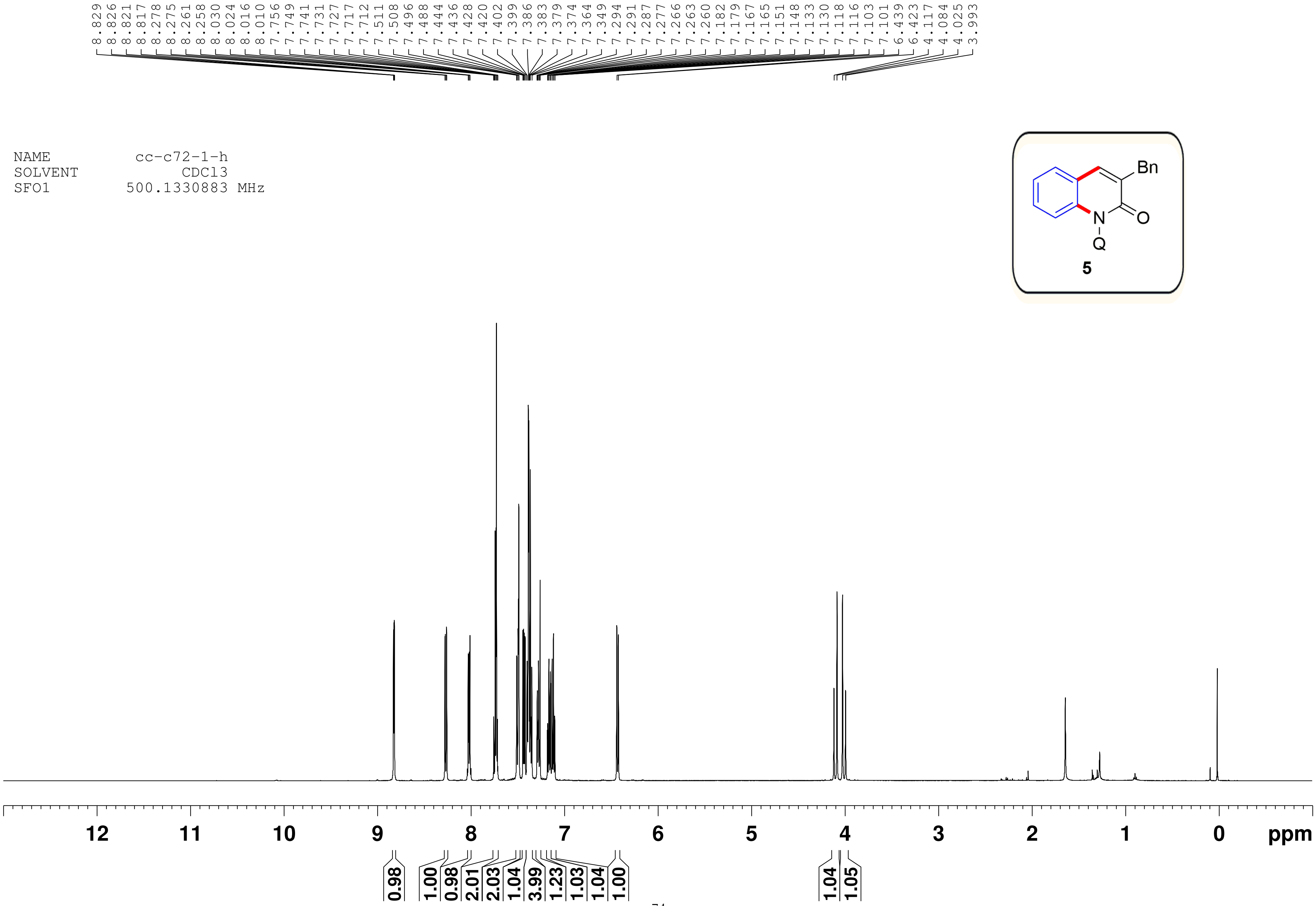
```
NAME              cc-c84-2
SOLVENT              CDCl3
SFO1        125.7703643 MHz
```



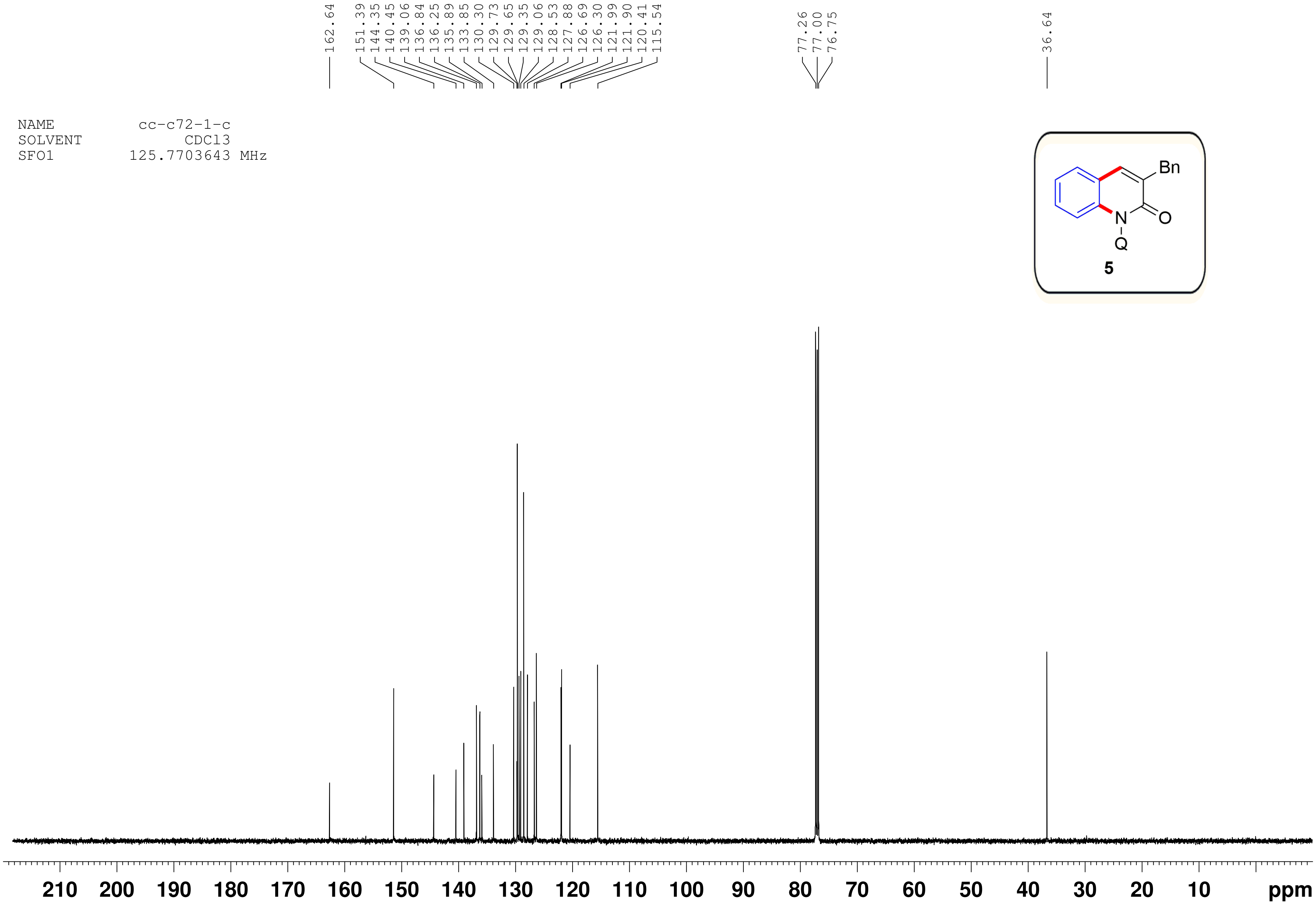


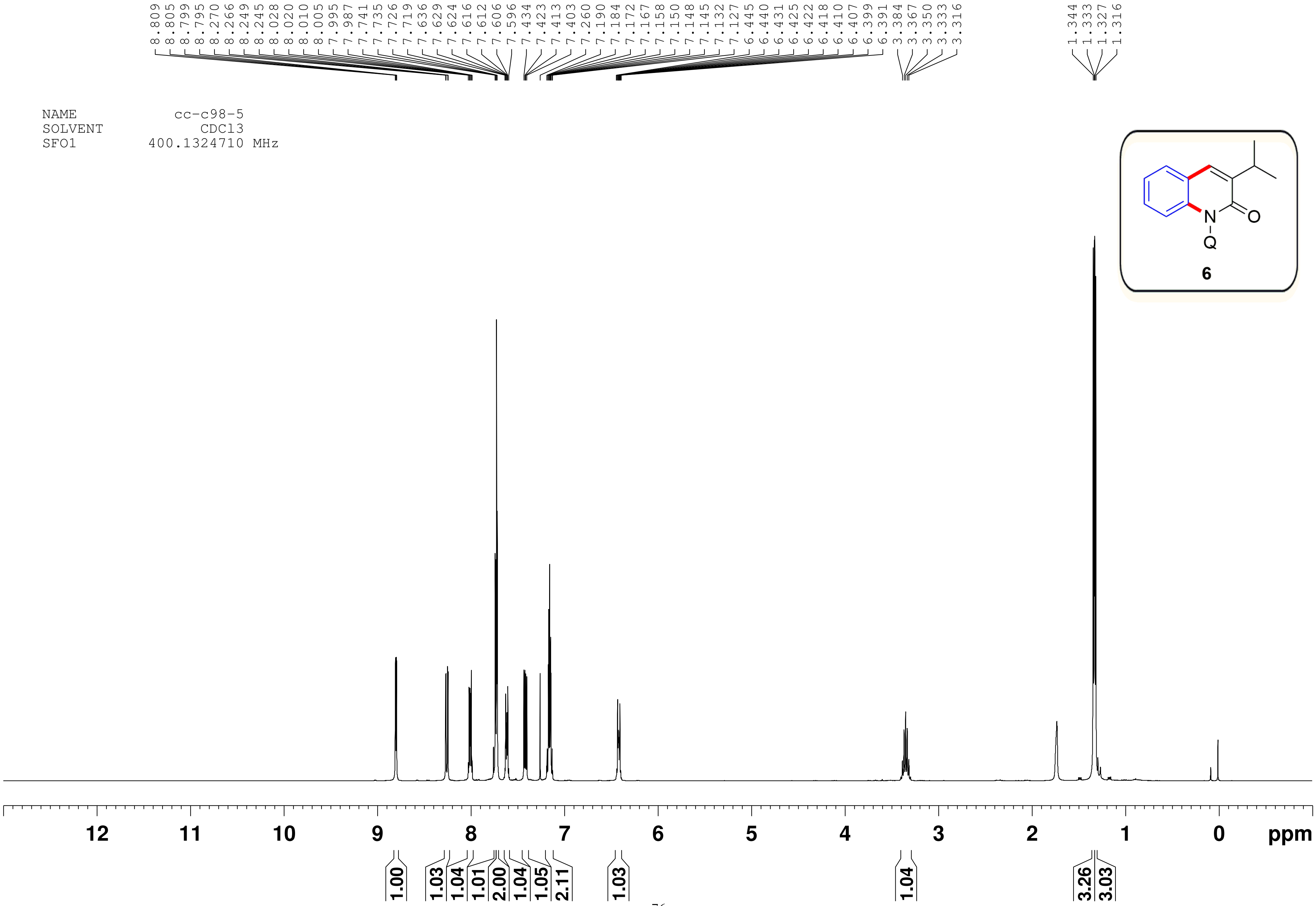
4

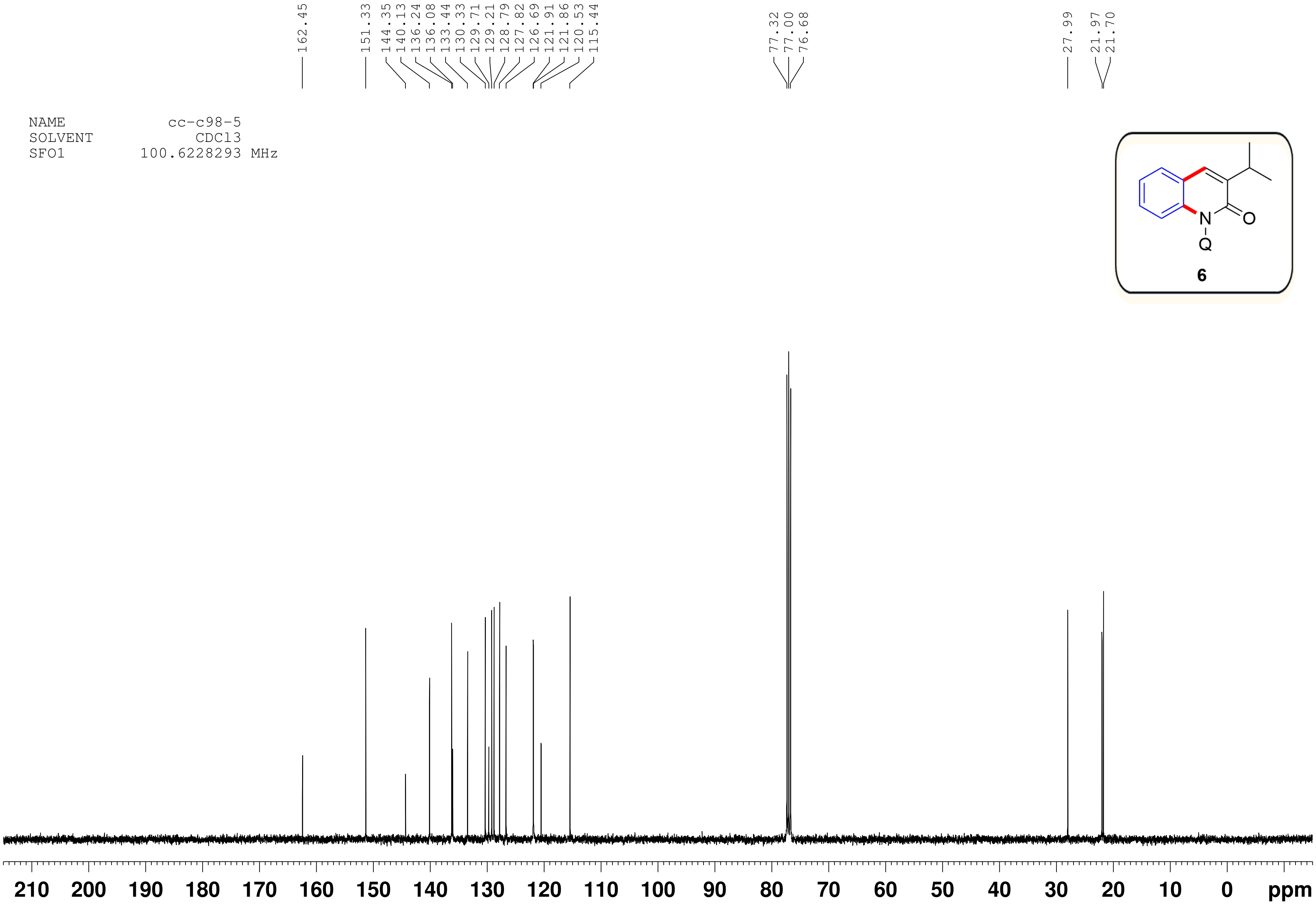
NAME cc-c72-1-h
SOLVENT CDCl3
SFO1 500.1330883 MHz



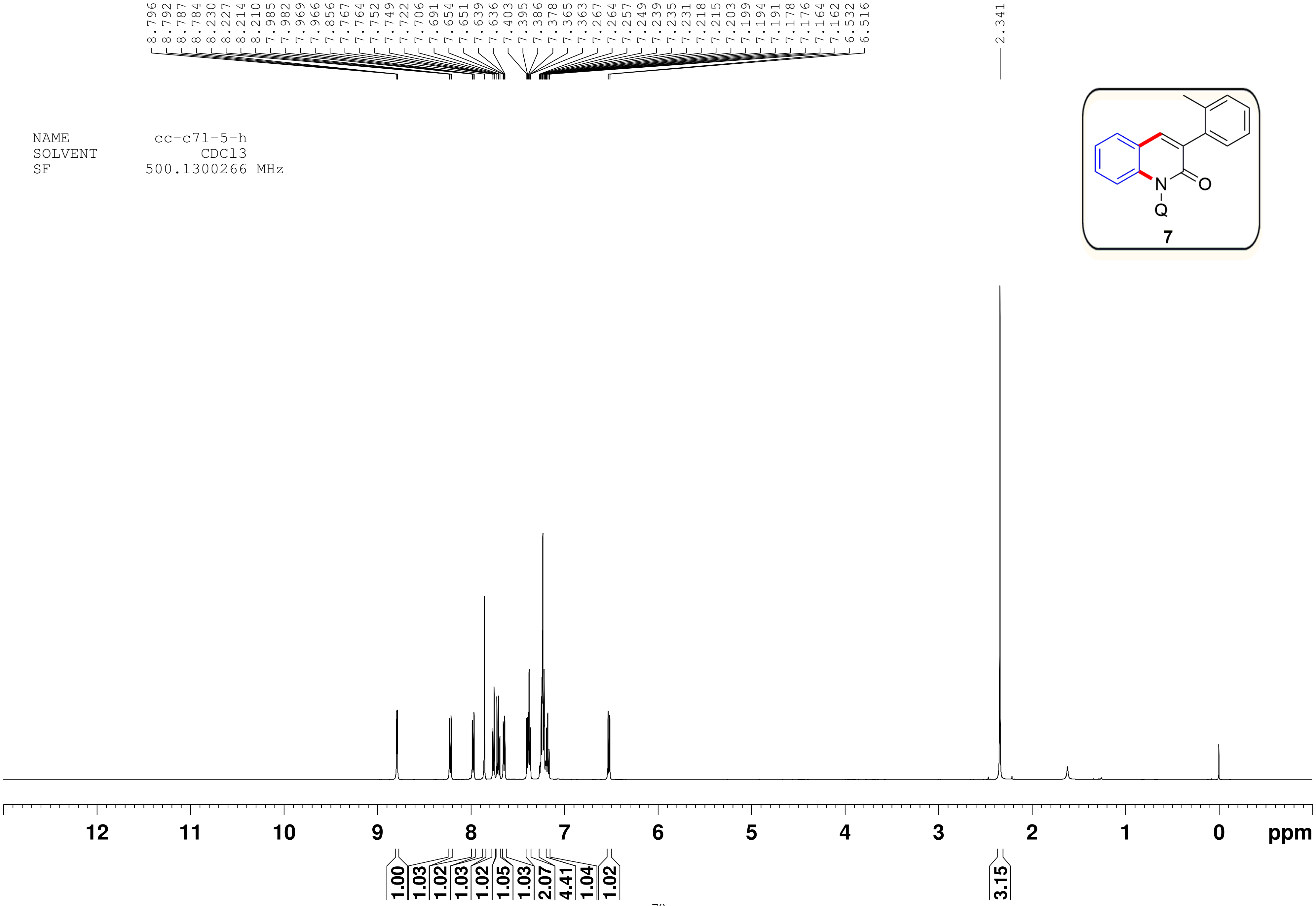
NAME cc-c72-1-c
SOLVENT CDCl3
SFO1 125.7703643 MHz



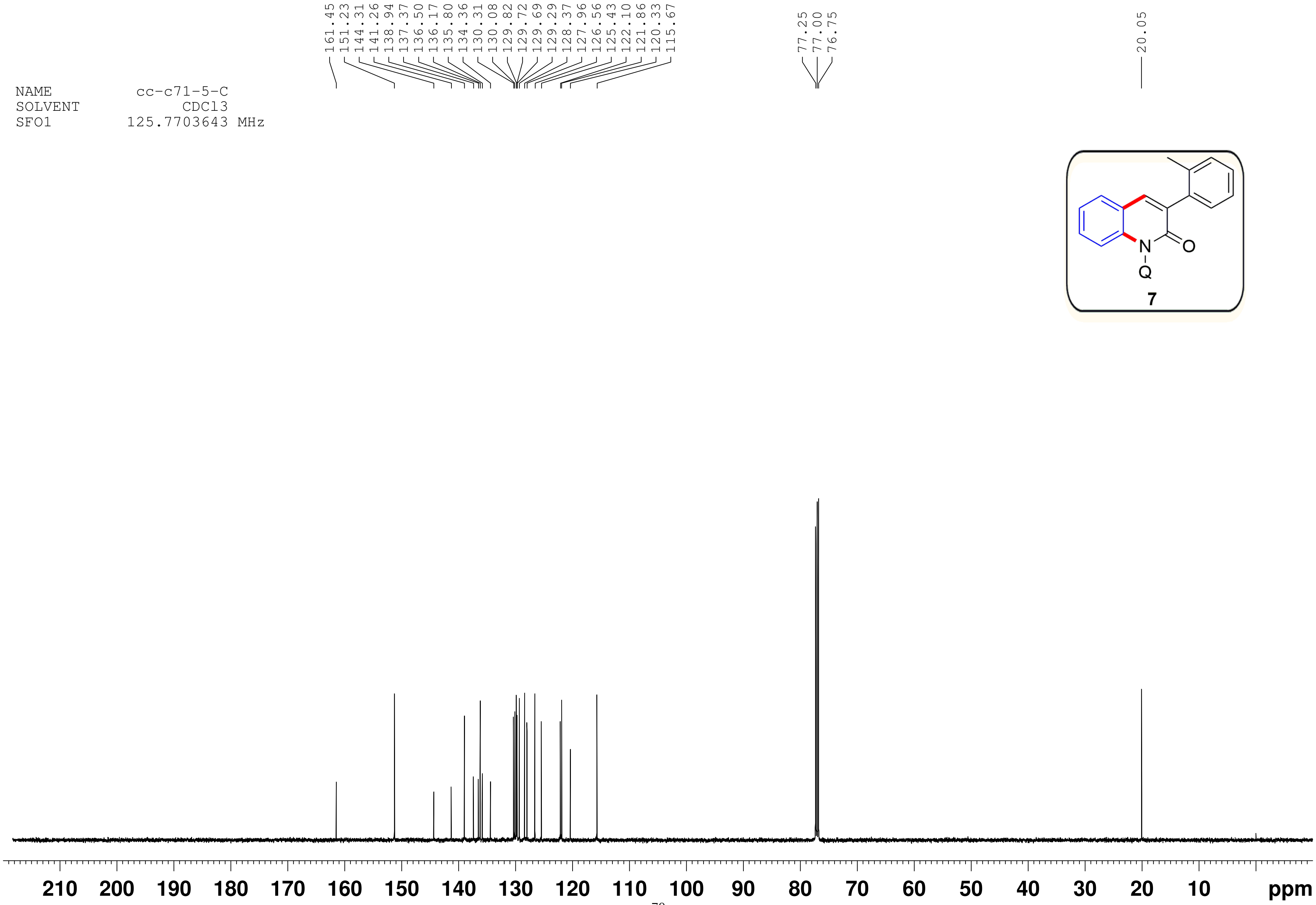

8.809
8.805
8.799
8.795
8.270
8.266
8.249
8.245
8.028
8.020
8.010
8.005
7.995
7.987
7.741
7.735
7.726
7.719
7.636
7.629
7.624
7.616
7.612
7.606
7.596
7.434
7.423
7.413
7.403
7.260
7.190
7.184
7.172
7.167
7.158
7.150
7.148
7.145
7.132
7.127
6.445
6.440
6.431
6.425
6.422
6.418
6.410
6.407
6.399
6.391
3.384
3.367
3.350
3.333
3.316
1.344
1.333
1.327
1.316
NAME cc-c98-5
SOLVENT CDCl3
SFO1 400.1324710 MHz
N
O
Q
6
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.03
1.04
1.01
2.00
1.04
1.05
2.11
1.03
1.04
3.26
3.03

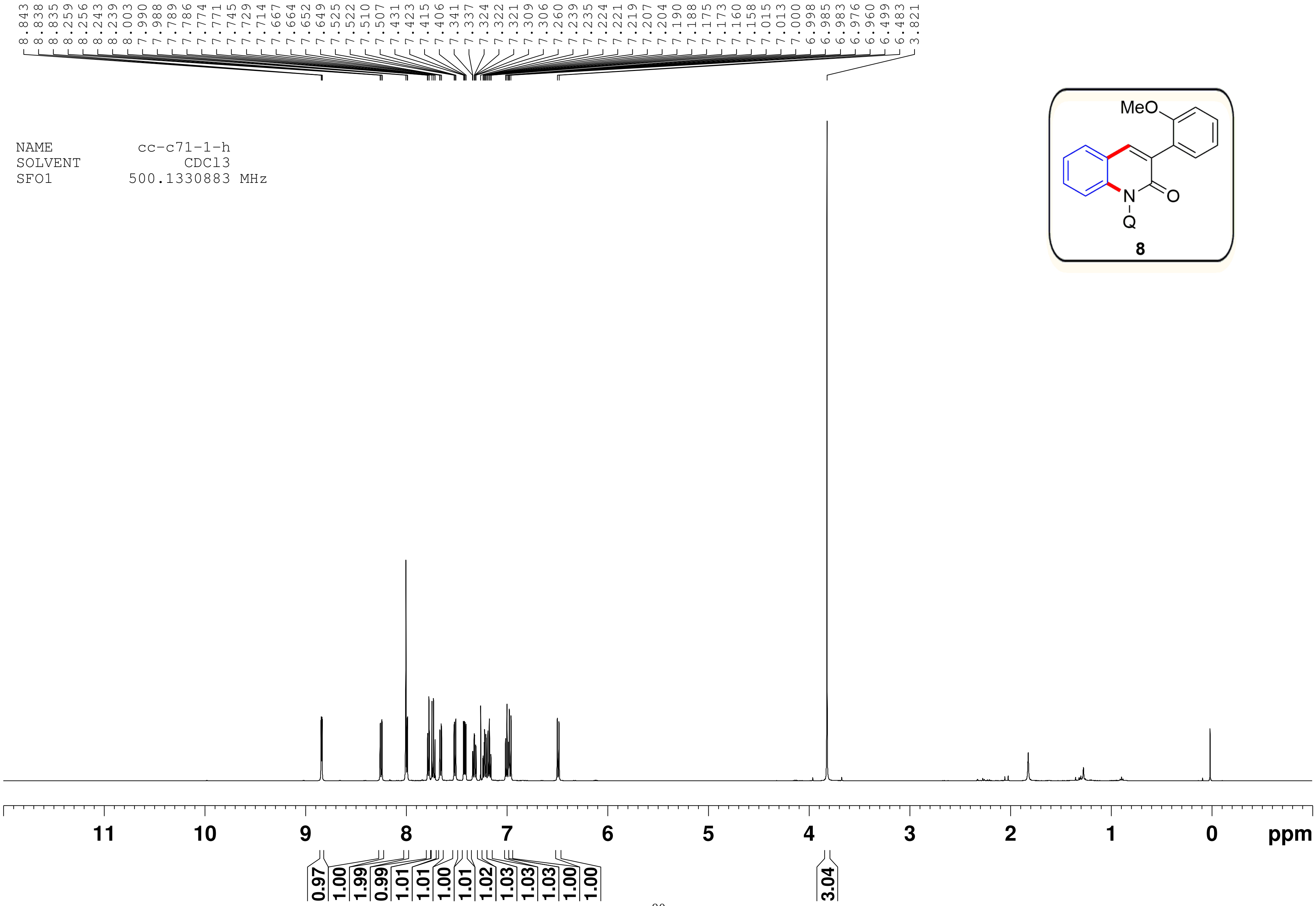

162.45
151.33
144.35
140.13
136.24
136.08
133.44
130.33
129.71
129.21
128.79
127.82
126.69
121.91
121.86
120.53
115.44
77.32
77.00
76.68
27.99
21.97
21.70
NAME cc-c98-5
SOLVENT CDCl3
SFO1 100.6228293 MHz
N
O
Q
6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

```
NAME         cc-c71-5-h
SOLVENT           CDCl3
SF         500.1300266 MHz
```

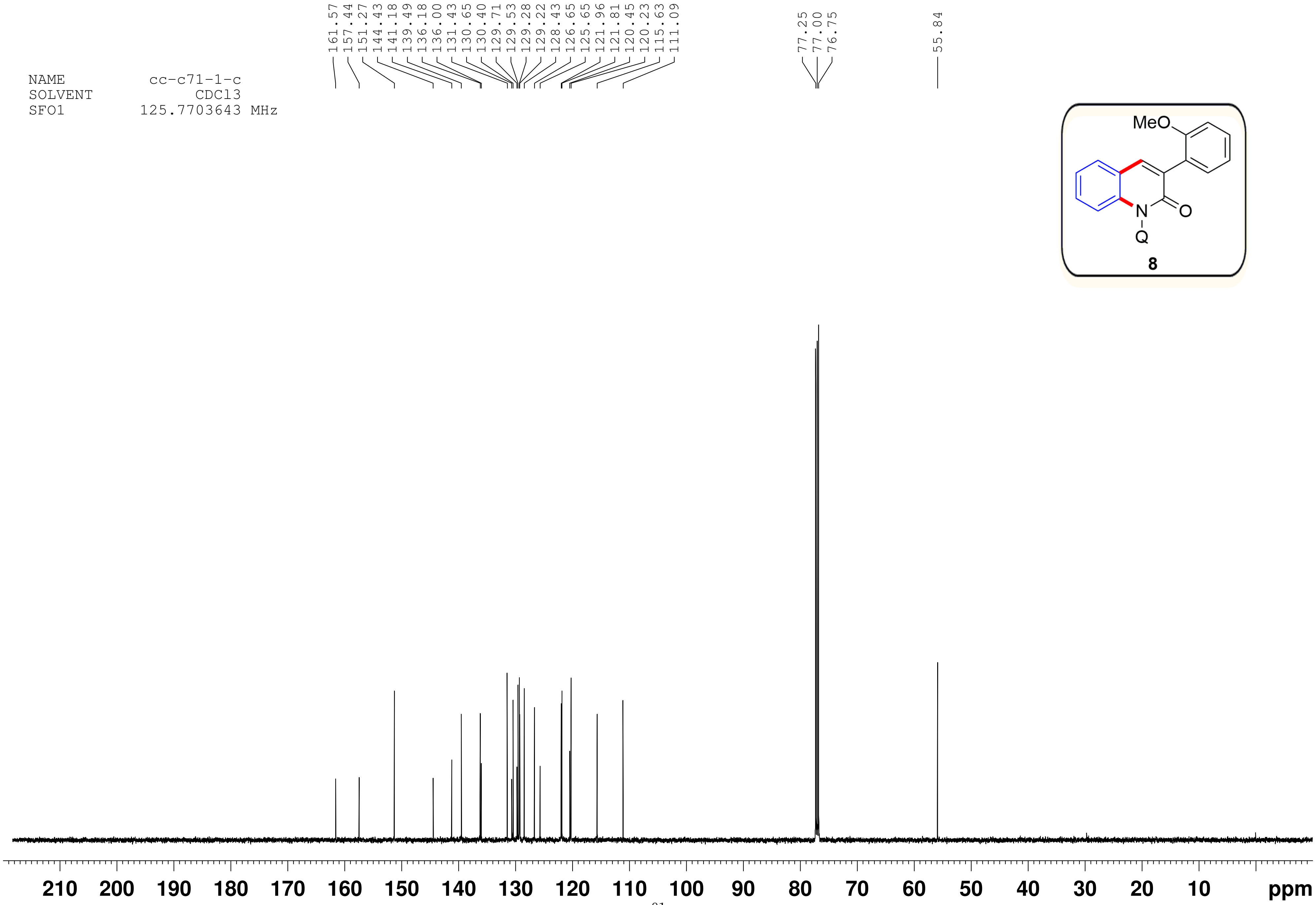


7

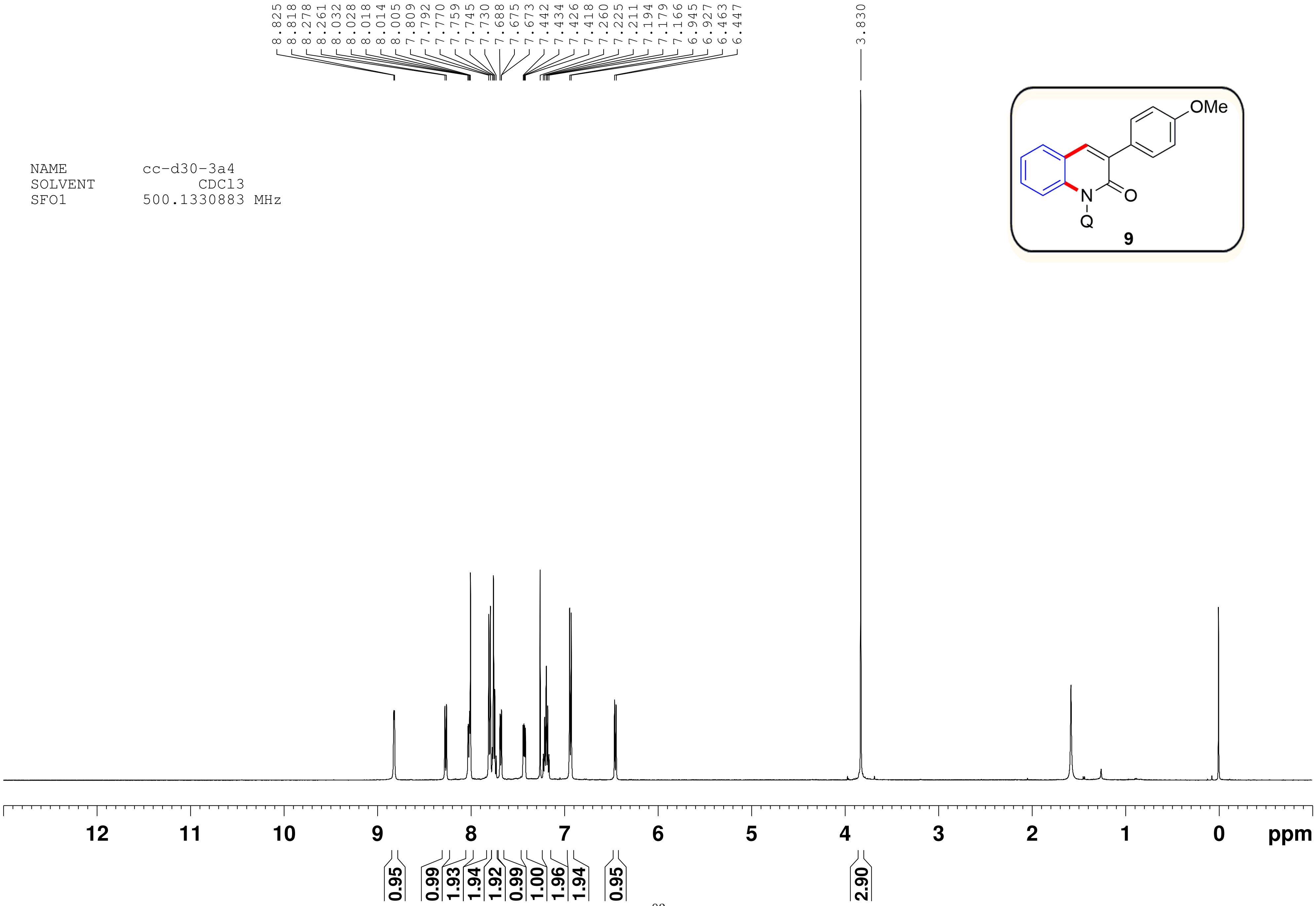

161.45
151.23
144.31
141.26
138.94
137.37
136.50
136.17
135.80
134.36
130.31
130.08
129.82
129.72
129.69
129.29
128.37
127.96
126.56
125.43
122.10
121.86
120.33
115.67
77.25
77.00
76.75
20.05
NAME cc-c71-5-C
SOLVENT CDCl3
SFO1 125.7703643 MHz
N
O
Q
7
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


8.843
8.838
8.835
8.259
8.256
8.243
8.239
8.003
7.990
7.988
7.789
7.786
7.774
7.771
7.745
7.729
7.714
7.667
7.664
7.652
7.649
7.525
7.522
7.510
7.507
7.431
7.423
7.415
7.406
7.341
7.337
7.324
7.322
7.321
7.309
7.306
7.260
7.239
7.235
7.224
7.221
7.219
7.207
7.204
7.190
7.188
7.175
7.173
7.160
7.158
7.015
7.013
7.000
6.998
6.985
6.983
6.976
6.960
6.499
6.483
3.821
NAME cc-c71-1-h
SOLVENT CDCl3
SFO1 500.1330883 MHz
MeO
N
O
Q
8
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.97
1.00
1.99
0.99
1.01
1.01
1.00
1.01
1.02
1.03
1.03
1.03
1.00
1.00
3.04

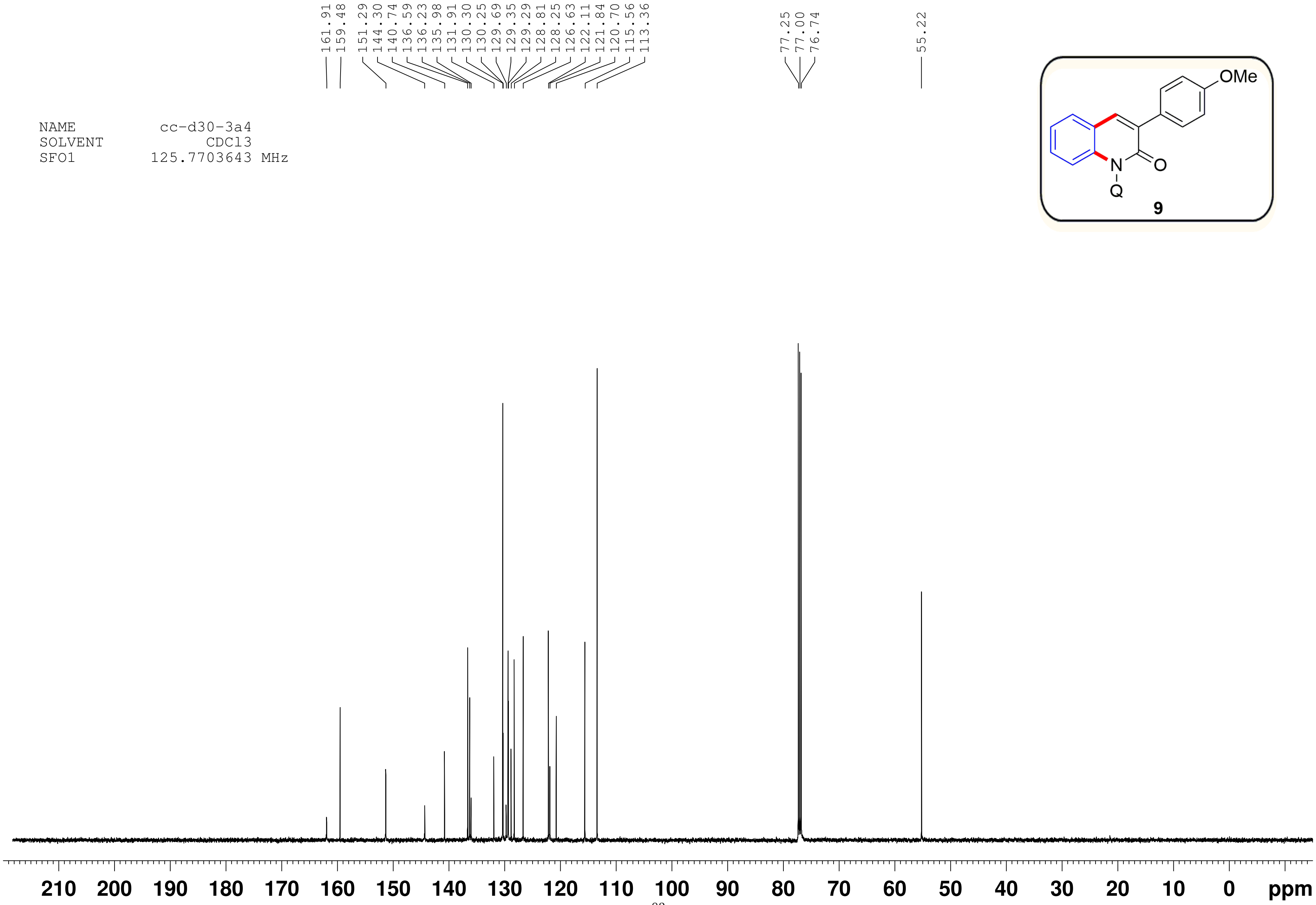
NAME cc-c71-1-c
SOLVENT CDCl3
SFO1 125.7703643 MHz

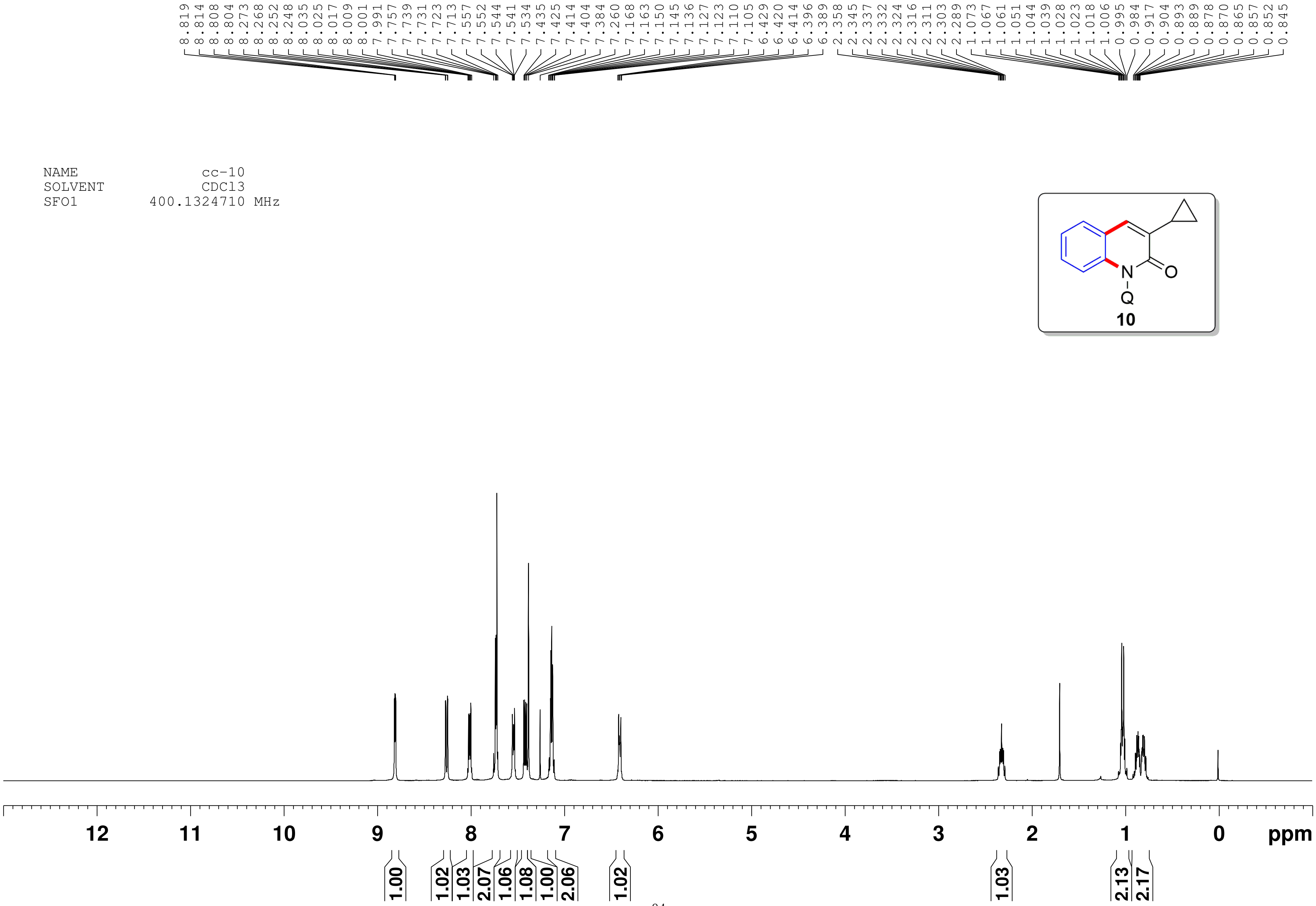


NAME cc-d30-3a4
SOLVENT CDCl3
SFO1 500.1330883 MHz



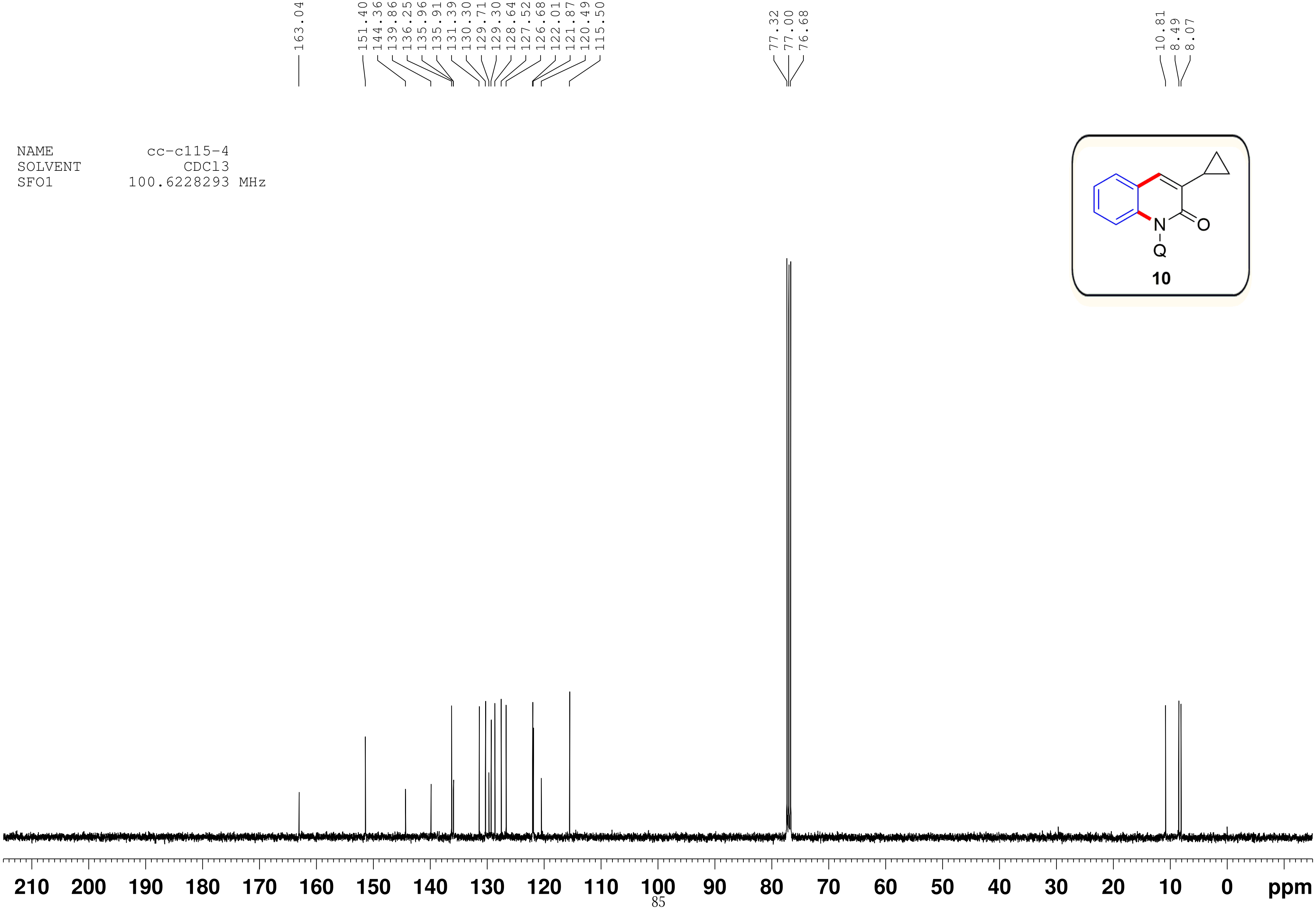
```
NAME          cc-d30-3a4
SOLVENT            CDCl3
SFO1        125.7703643 MHz
```





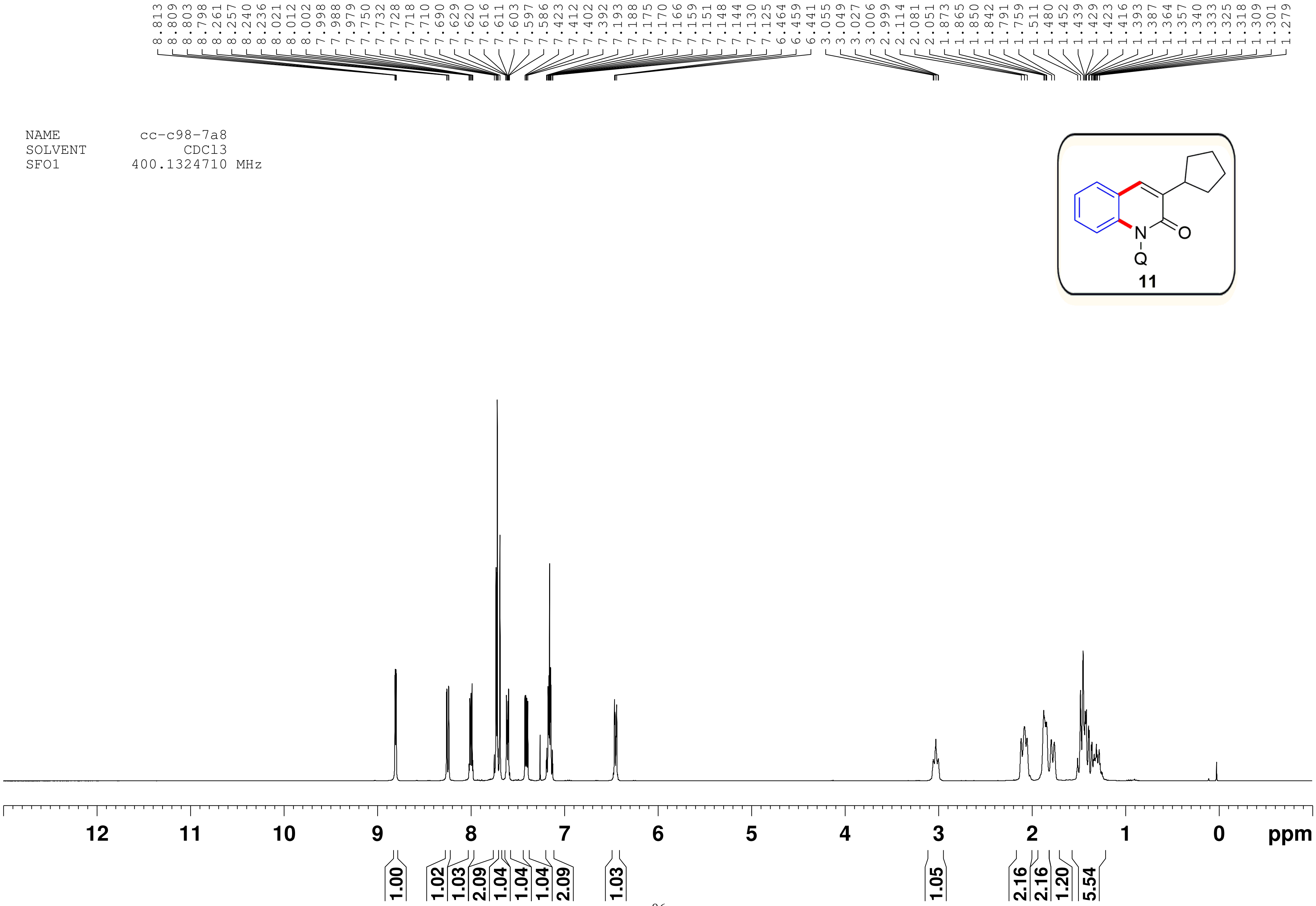
NAME cc-10
SOLVENT CDCl3
SFO1 400.1324710 MHz

NAME cc-c115-4
SOLVENT CDCl3
SFO1 100.6228293 MHz

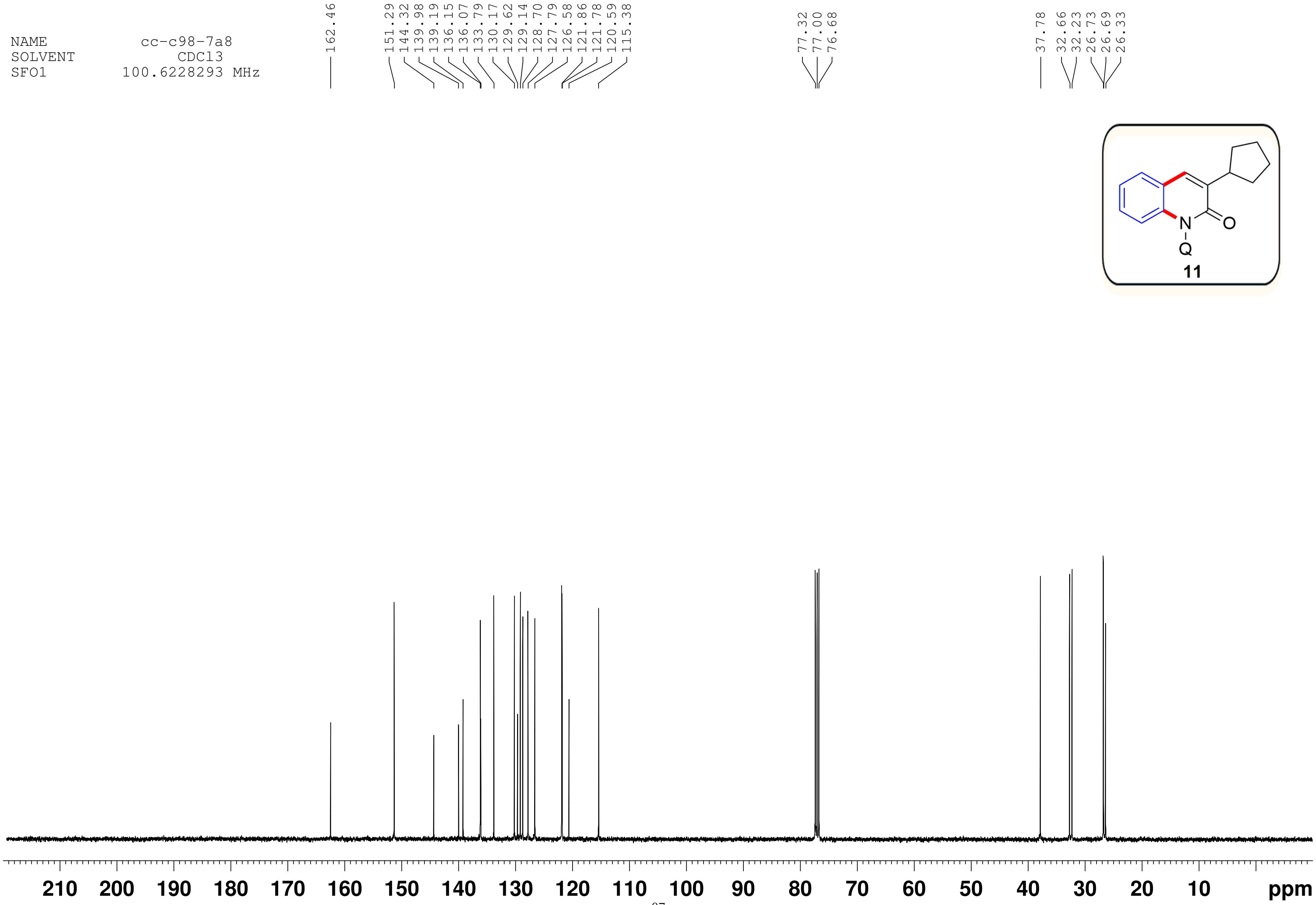


10

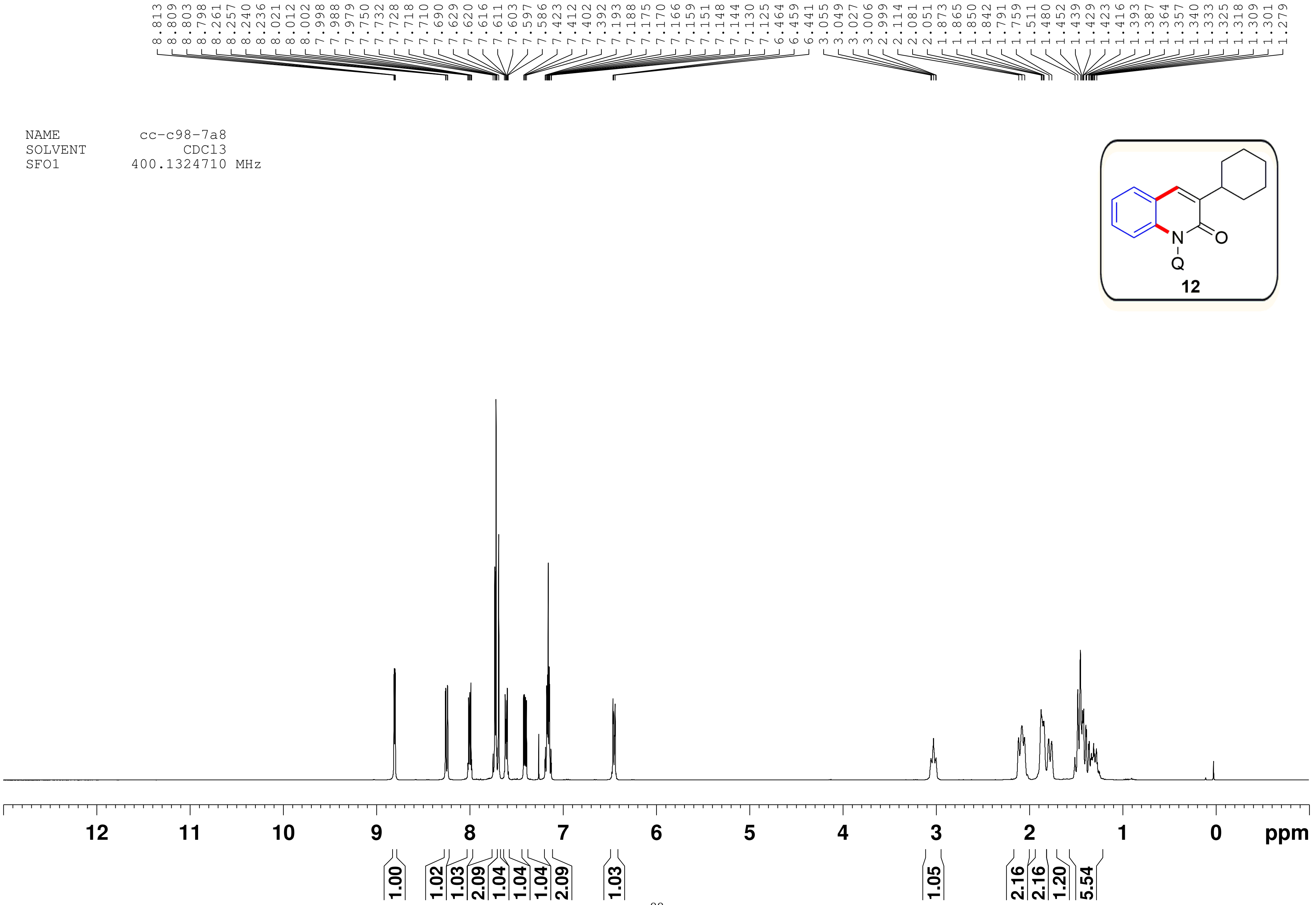
NAME cc-c98-7a8
SOLVENT CDCl3
SFO1 400.1324710 MHz

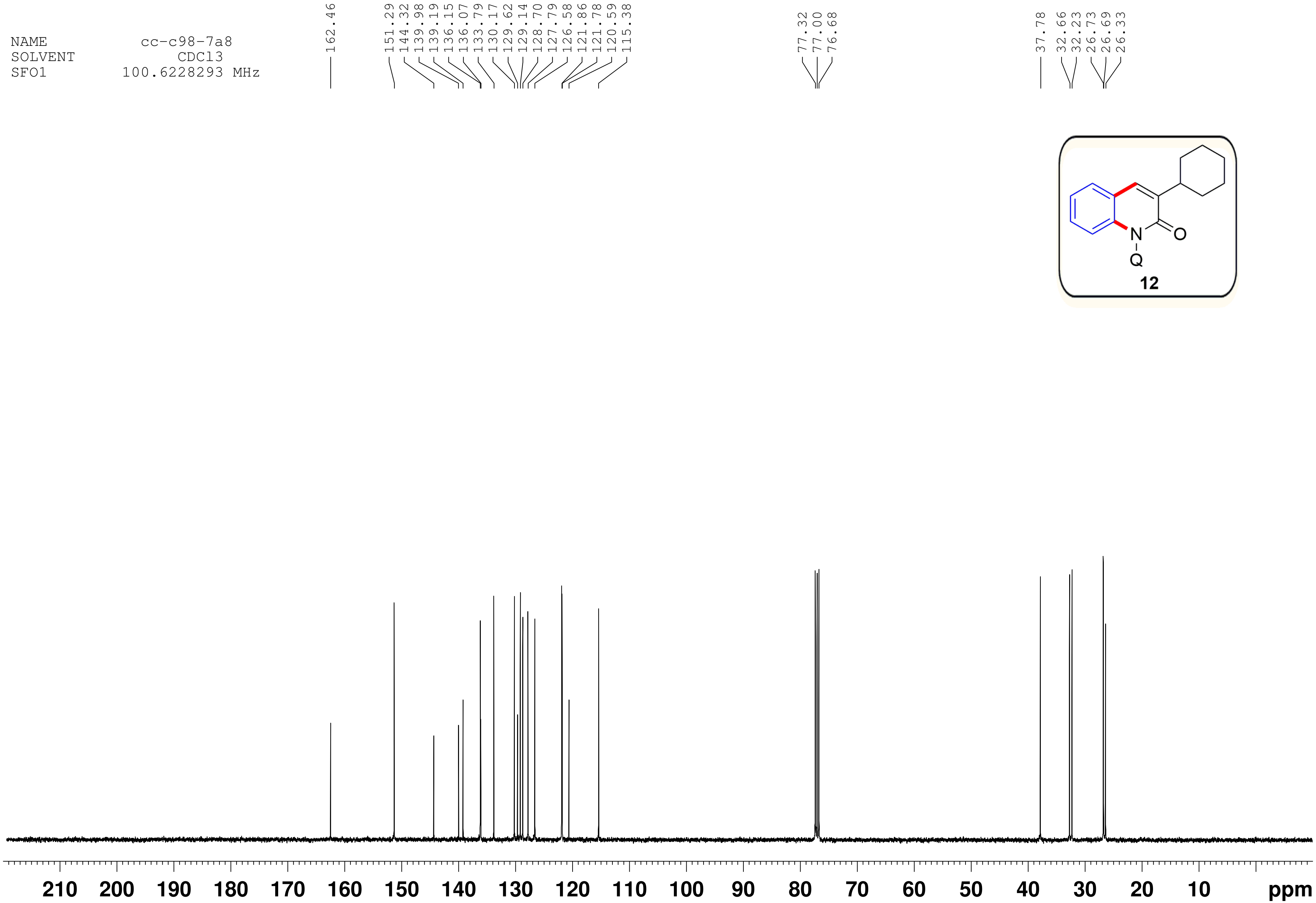


11

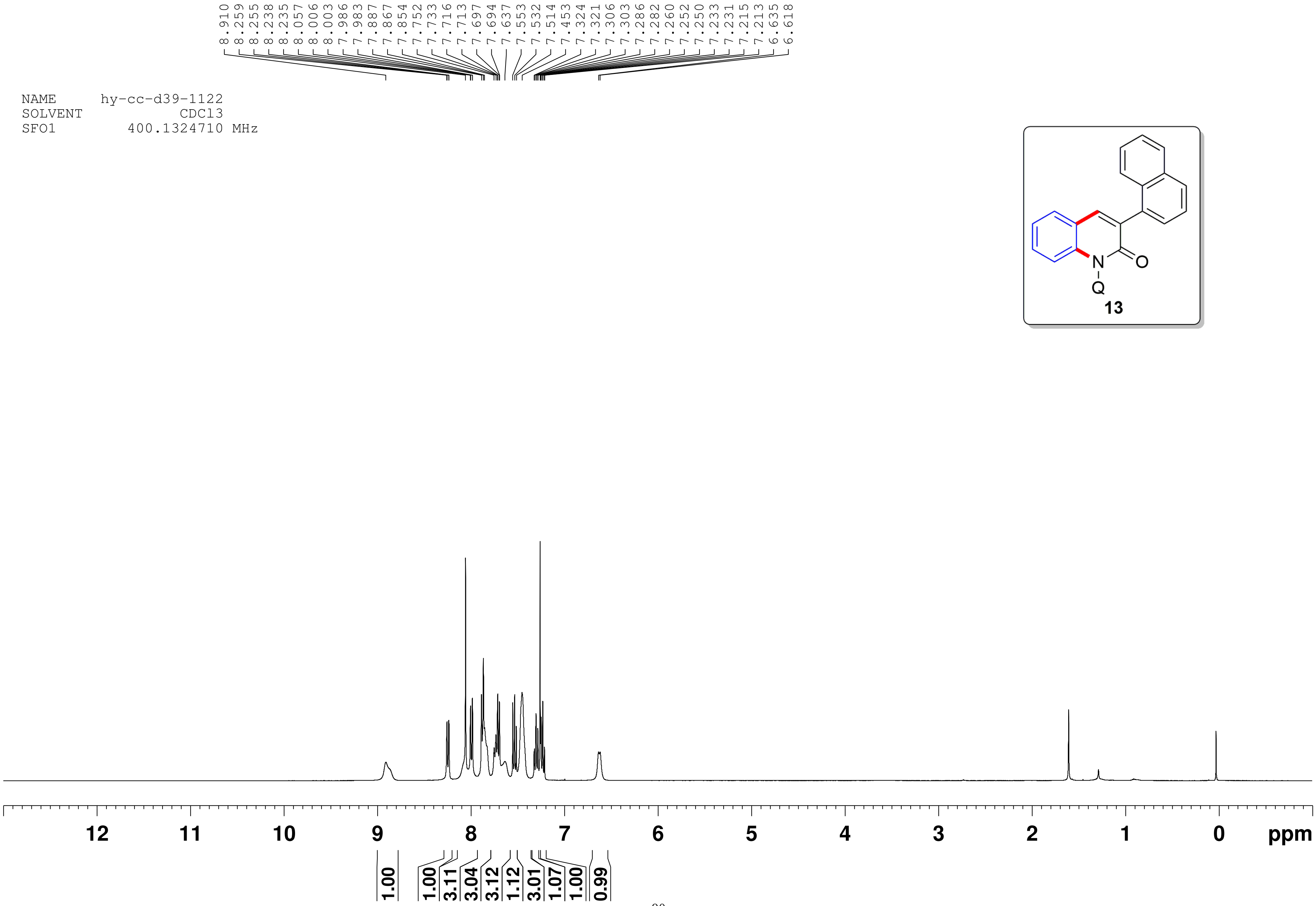

NAME cc-c98-7a8
SOLVENT CDCl3
SFO1 100.6228293 MHz
162.46
151.29
144.32
139.98
139.19
136.15
136.07
133.79
130.17
129.62
129.14
128.70
127.79
126.58
121.86
121.78
120.59
115.38
77.32
77.00
76.68
37.78
32.66
32.23
26.73
26.69
26.33
N
O
Q
11
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

NAME cc-c98-7a8
SOLVENT CDCl3
SFO1 400.1324710 MHz



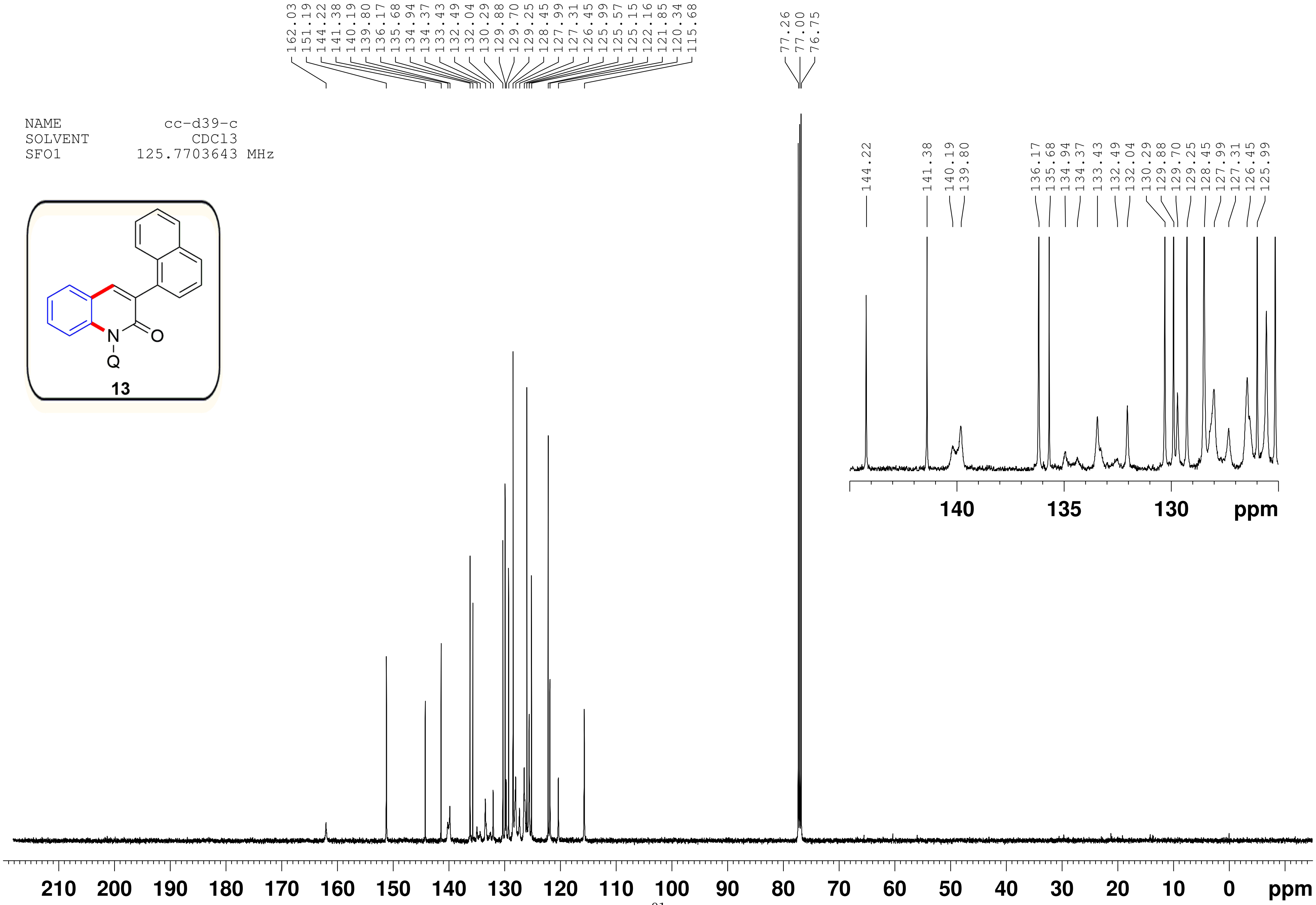

NAME cc-c98-7a8
SOLVENT CDCl3
SFO1 100.6228293 MHz
162.46
151.29
144.32
139.98
139.19
136.15
136.07
133.79
130.17
129.62
129.14
128.70
127.79
126.58
121.86
121.78
120.59
115.38
77.32
77.00
76.68
37.78
32.66
32.23
26.73
26.69
26.33
N
O
Q
12
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

NAME hy-cc-d39-1122
SOLVENT CDCl3
SFO1 400.1324710 MHz

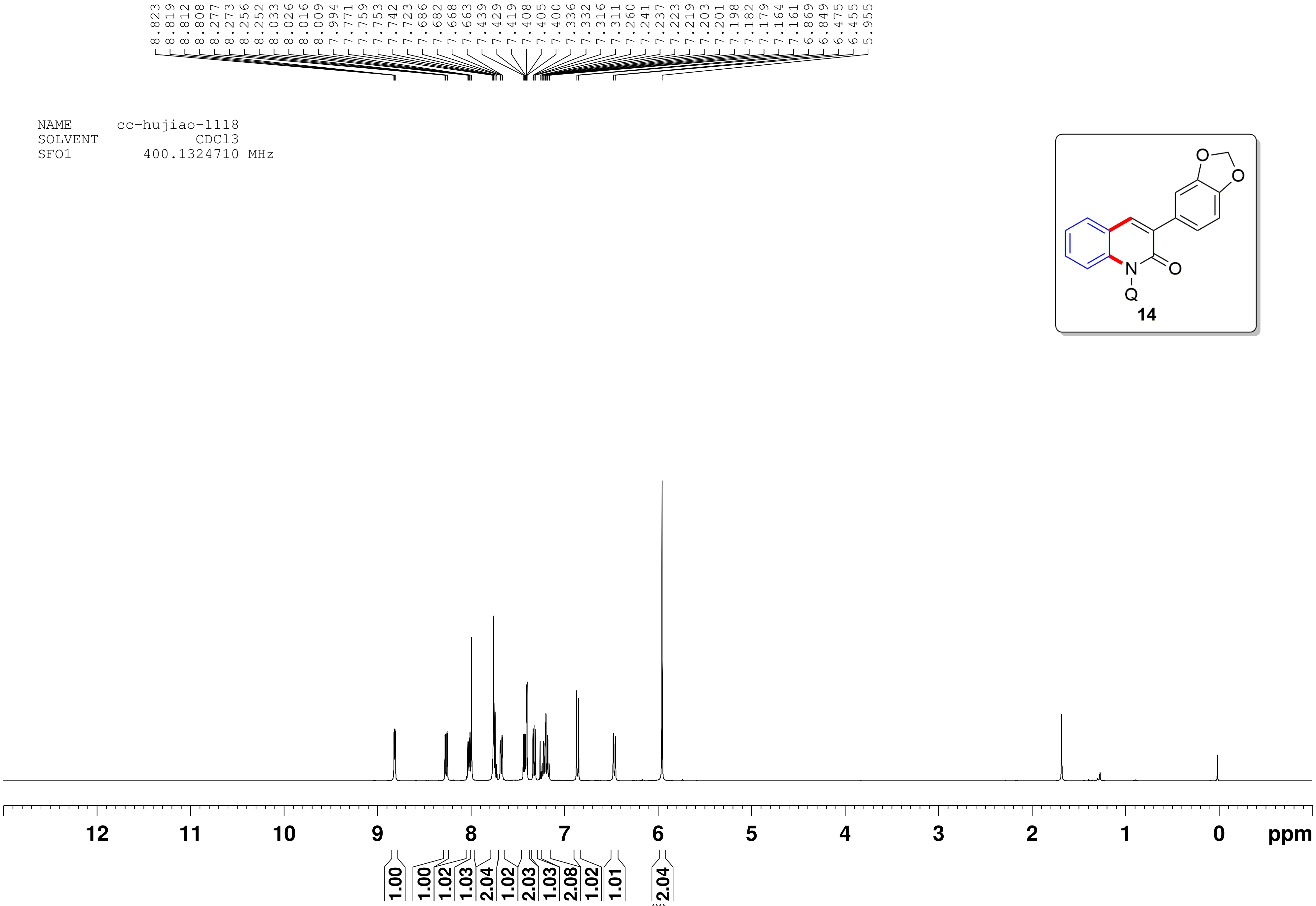


13

```
NAME             cc-d39-c
SOLVENT             CDCl3
SFO1        125.7703643 MHz
```

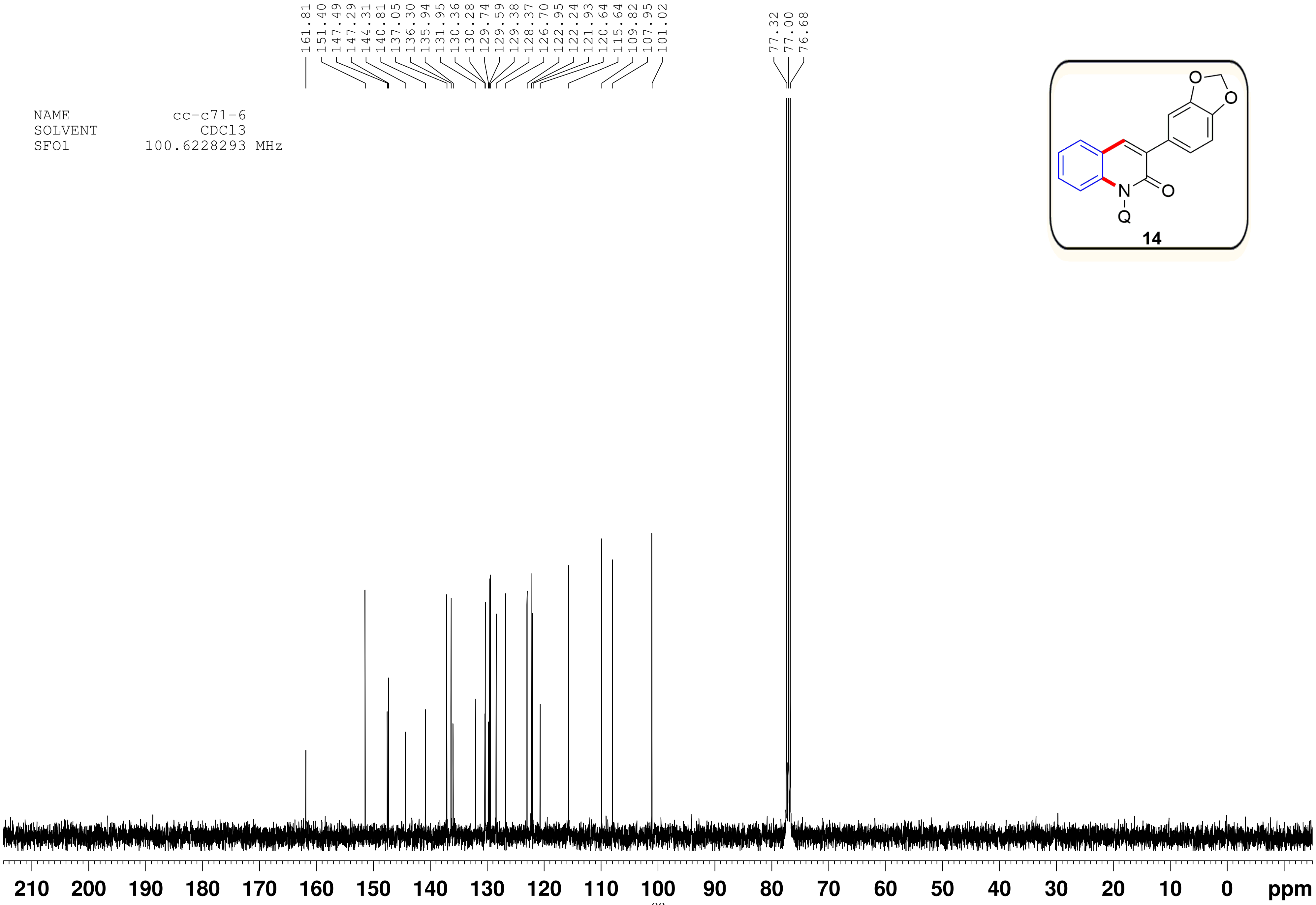


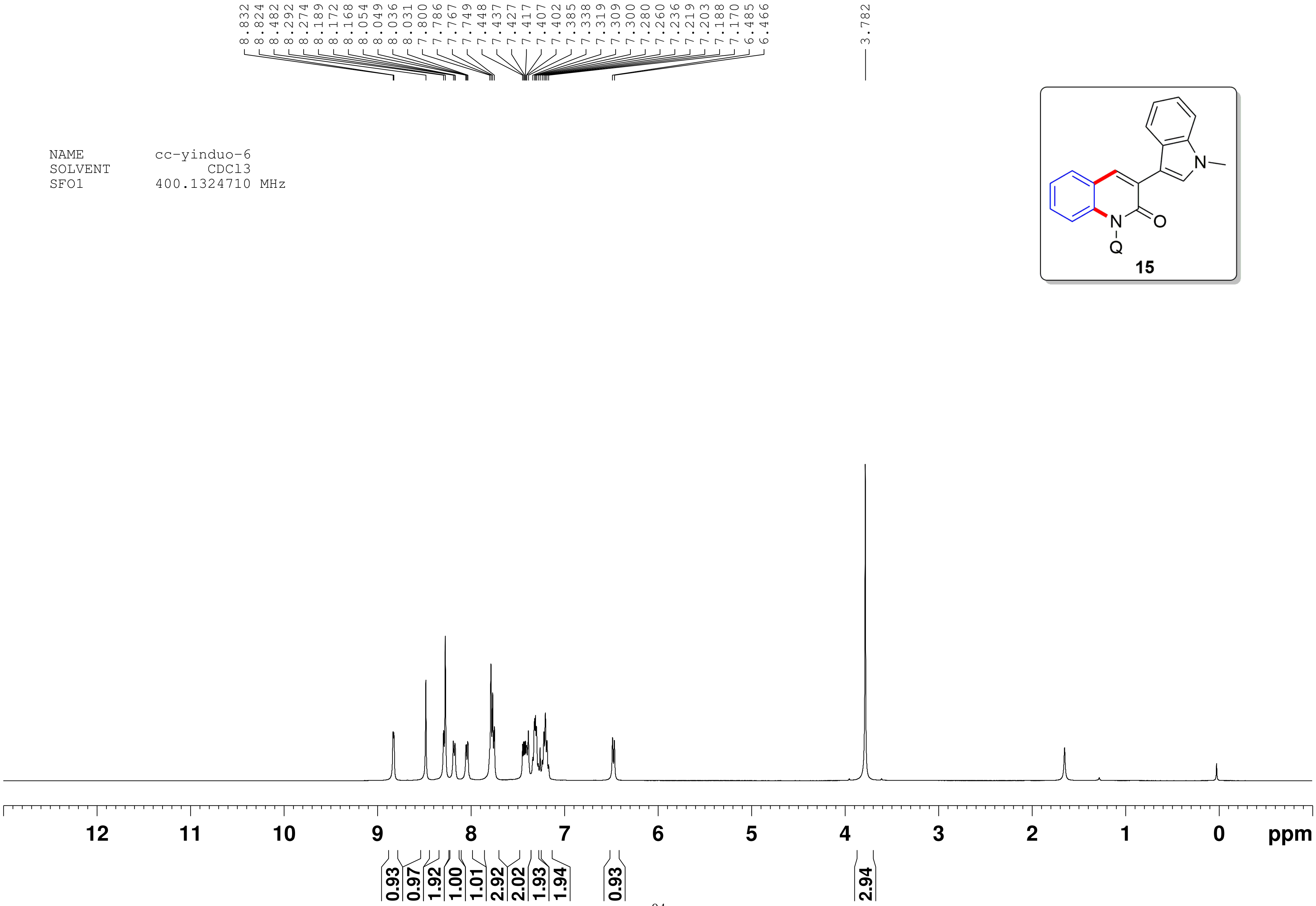
13



NAME cc-hujiao-1118
SOLVENT CDCl3
SFO1 400.1324710 MHz

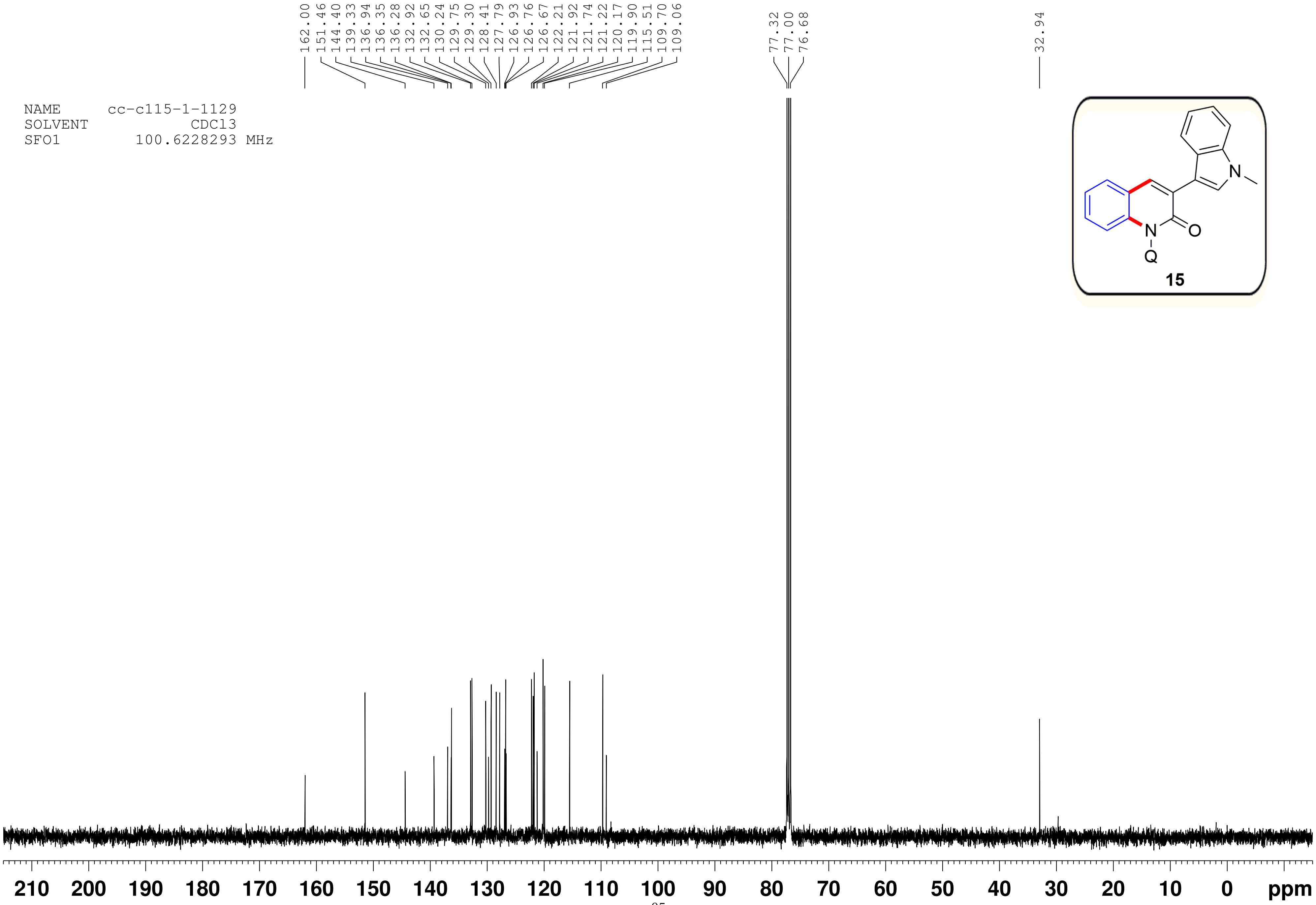
NAME cc-c71-6
SOLVENT CDCl3
SFO1 100.6228293 MHz





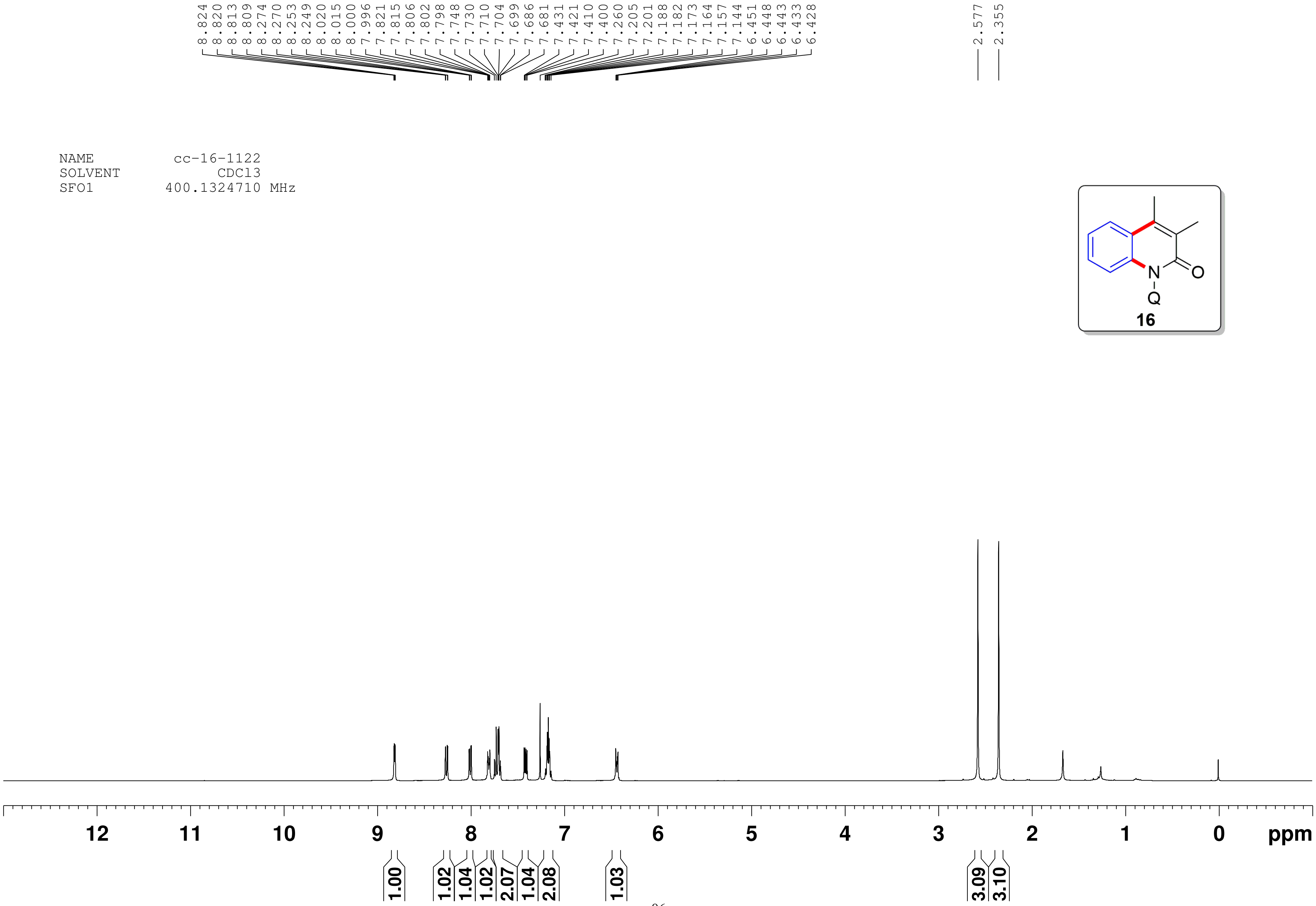
NAME cc-yinduo-6
SOLVENT CDCl3
SFO1 400.1324710 MHz

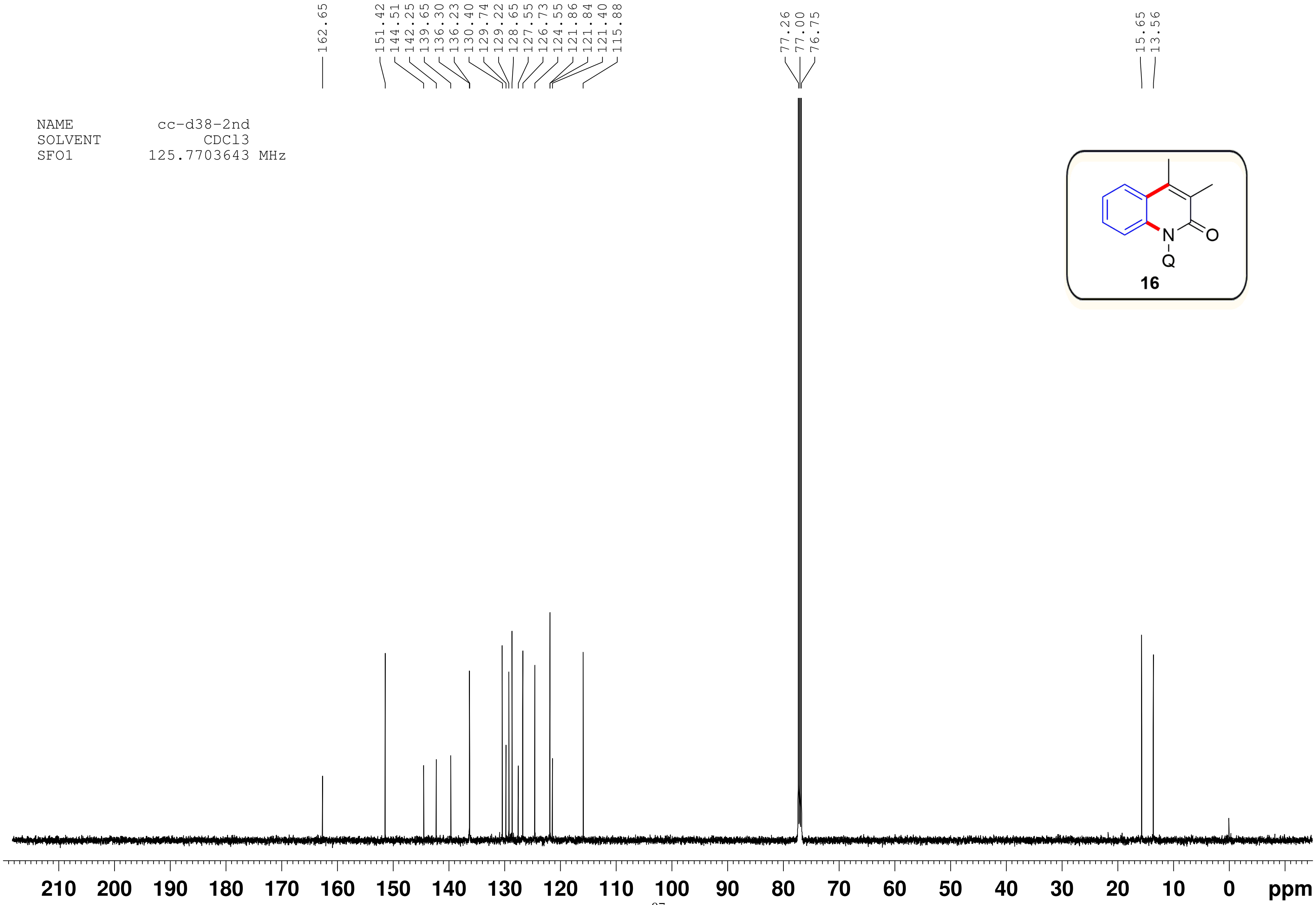
NAME cc-c115-1-1129
SOLVENT CDCl3
SFO1 100.6228293 MHz

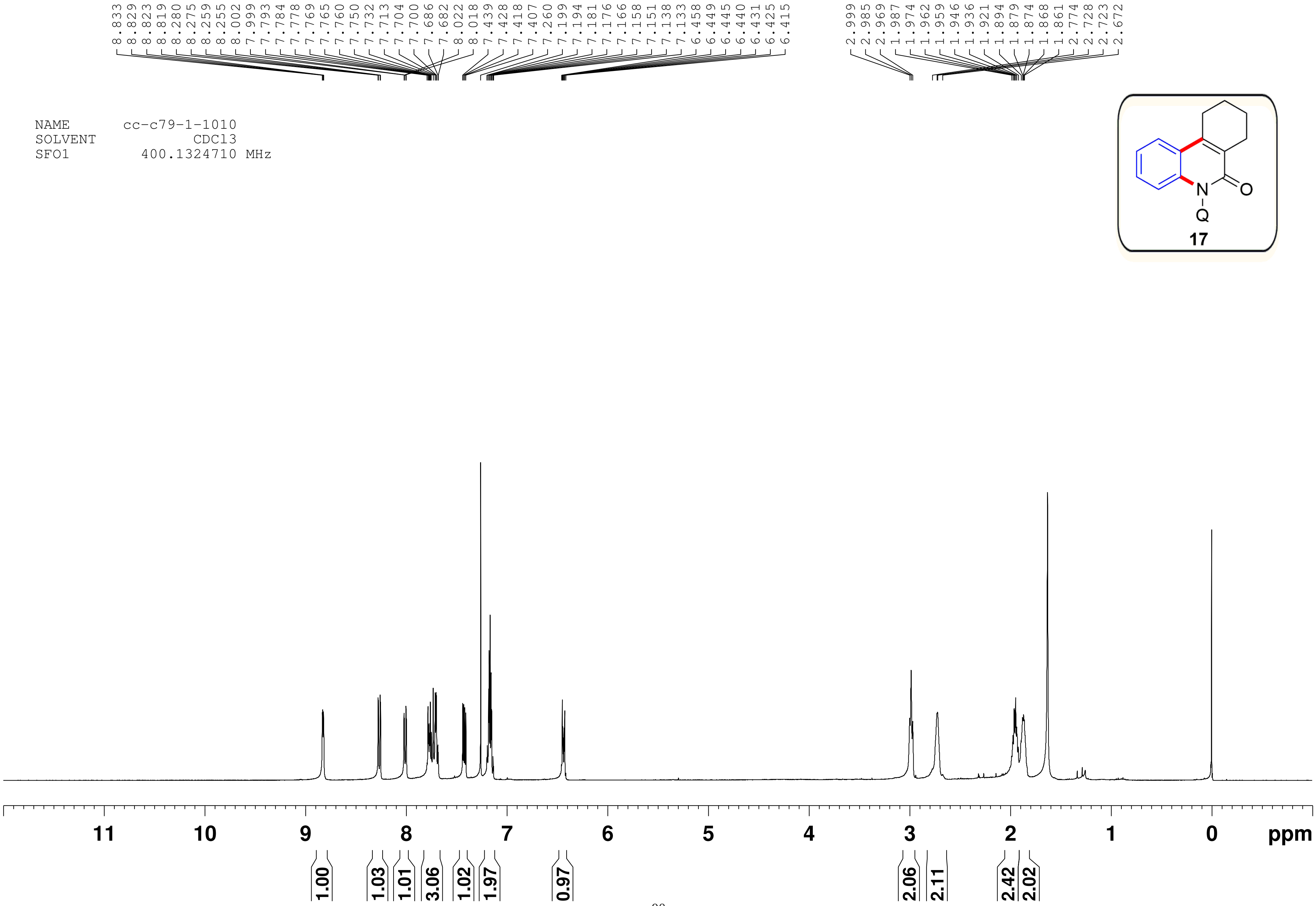


15

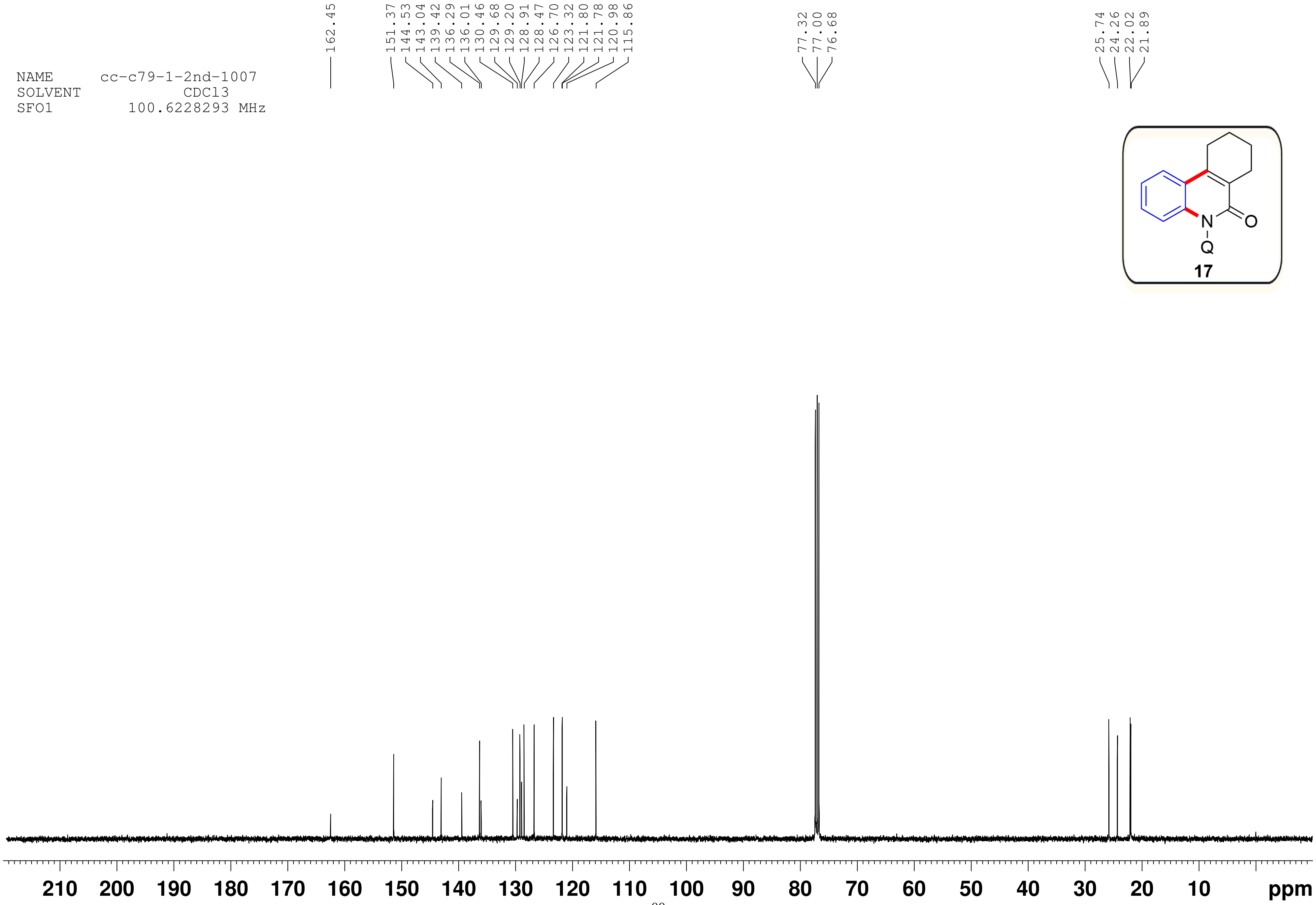
NAME cc-16-1122
SOLVENT CDCl3
SFO1 400.1324710 MHz




162.65
151.42
144.51
142.25
139.65
136.30
136.23
130.40
129.74
129.22
128.65
127.55
126.73
124.55
121.86
121.84
121.40
115.88
77.26
77.00
76.75
15.65
13.56
NAME cc-d38-2nd
SOLVENT CDCl3
SFO1 125.7703643 MHz
N
O
Q
16
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

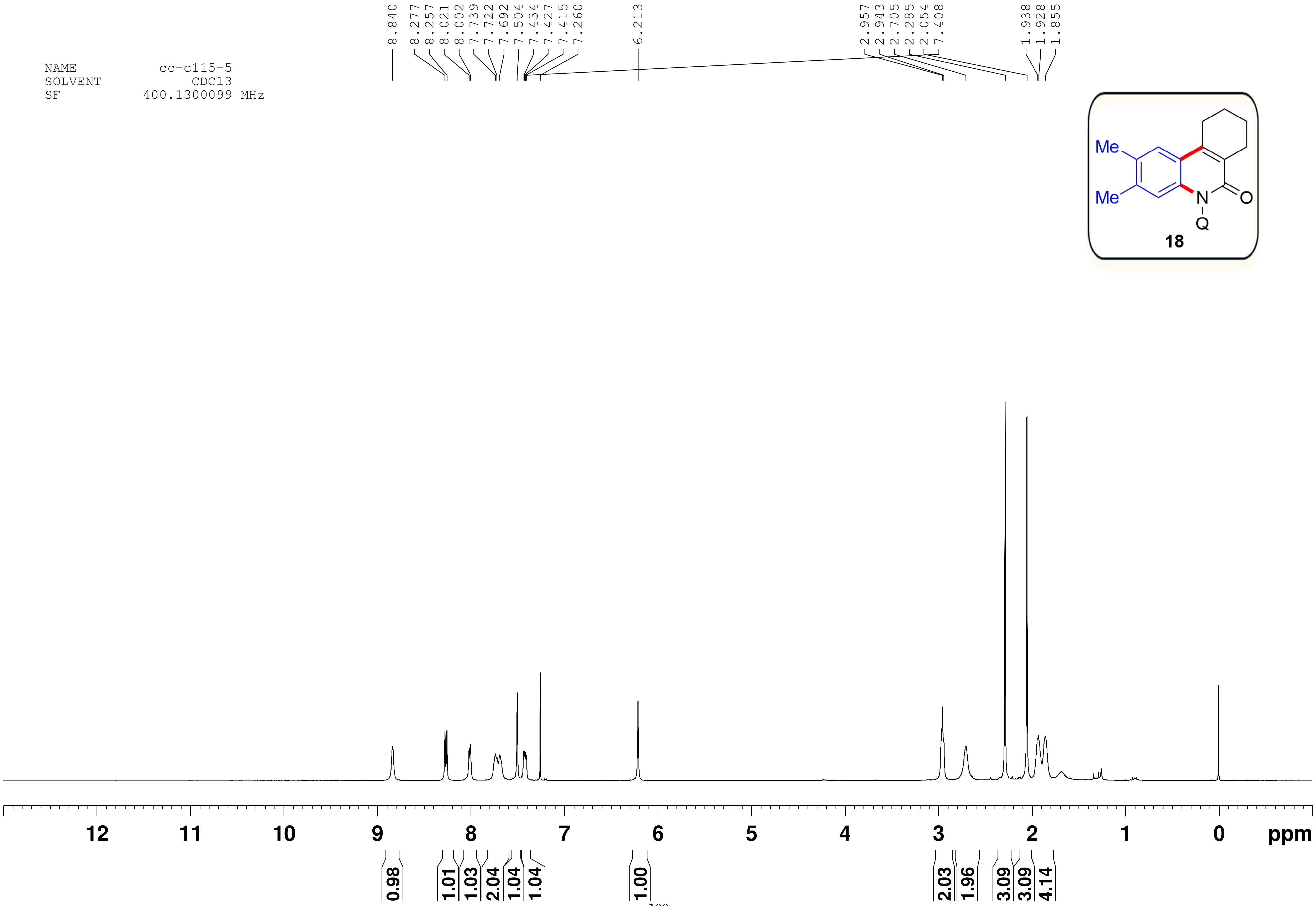


NAME cc-c79-1-1010
SOLVENT CDCl3
SFO1 400.1324710 MHz


NAME cc-c79-1-2nd-1007
SOLVENT CDCl3
SFO1 100.6228293 MHz

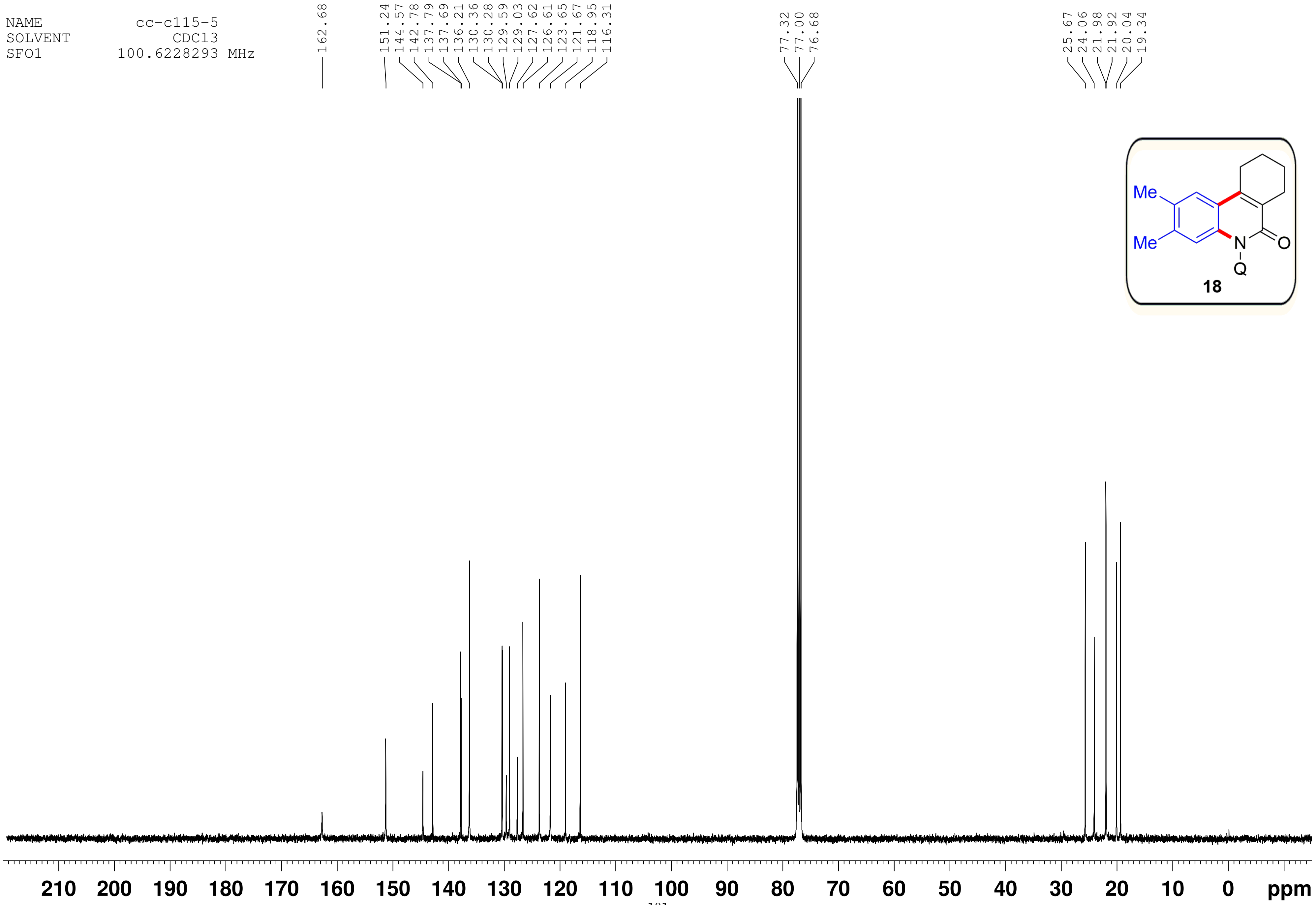
17

NAME cc-c115-5
SOLVENT CDCl3
SF 400.1300099 MHz

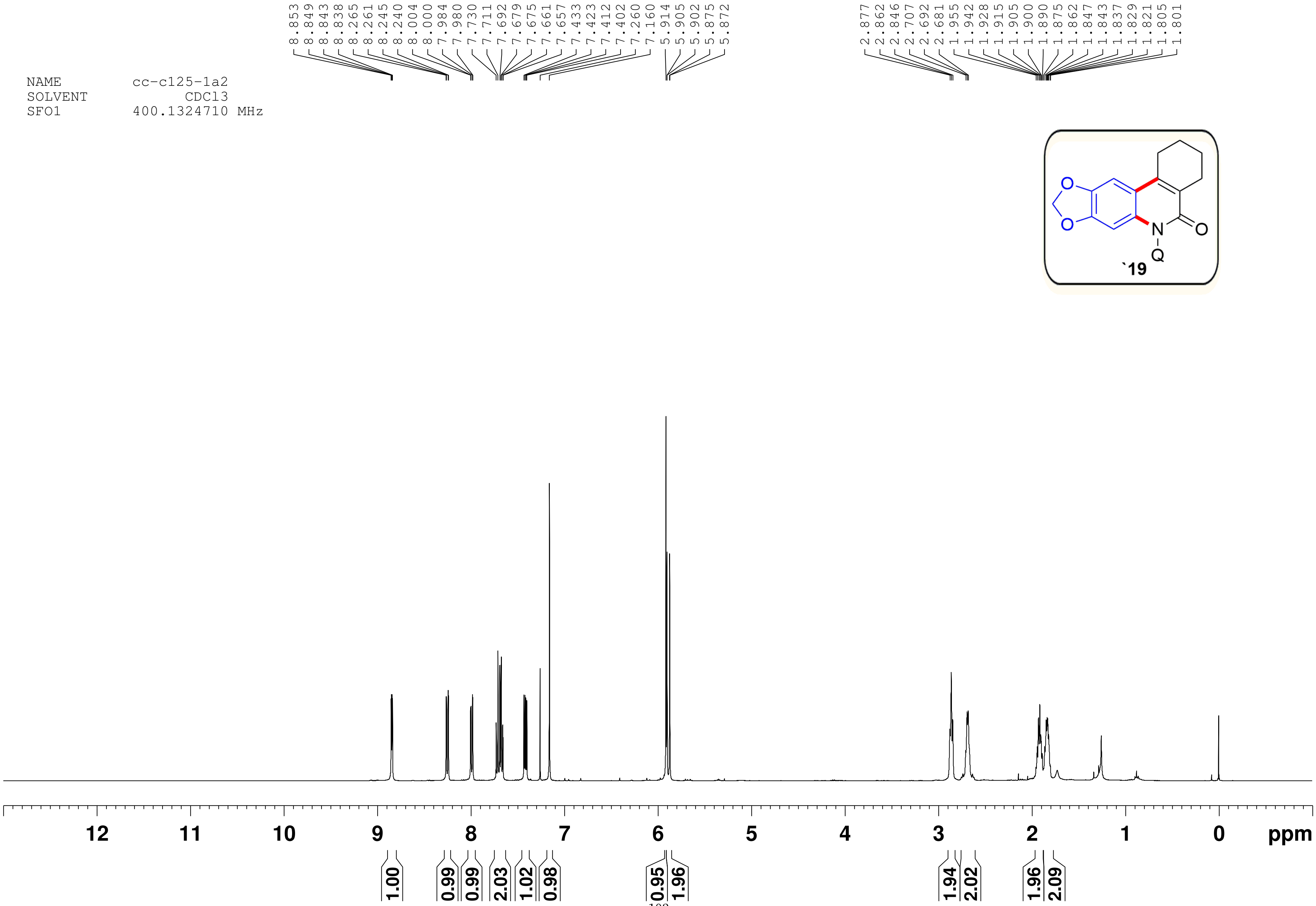


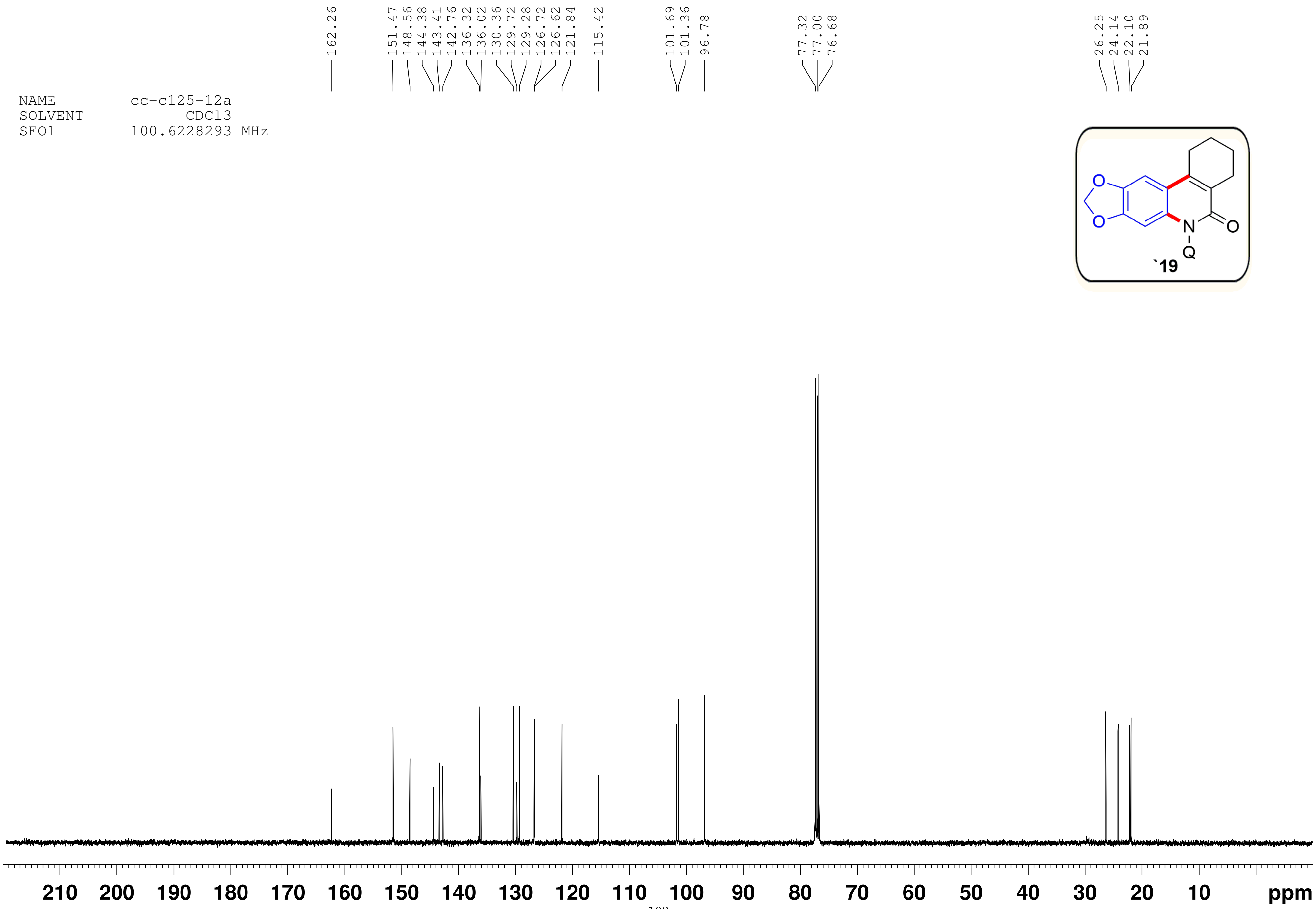
18

NAME cc-c115-5
SOLVENT CDCl3
SFO1 100.6228293 MHz

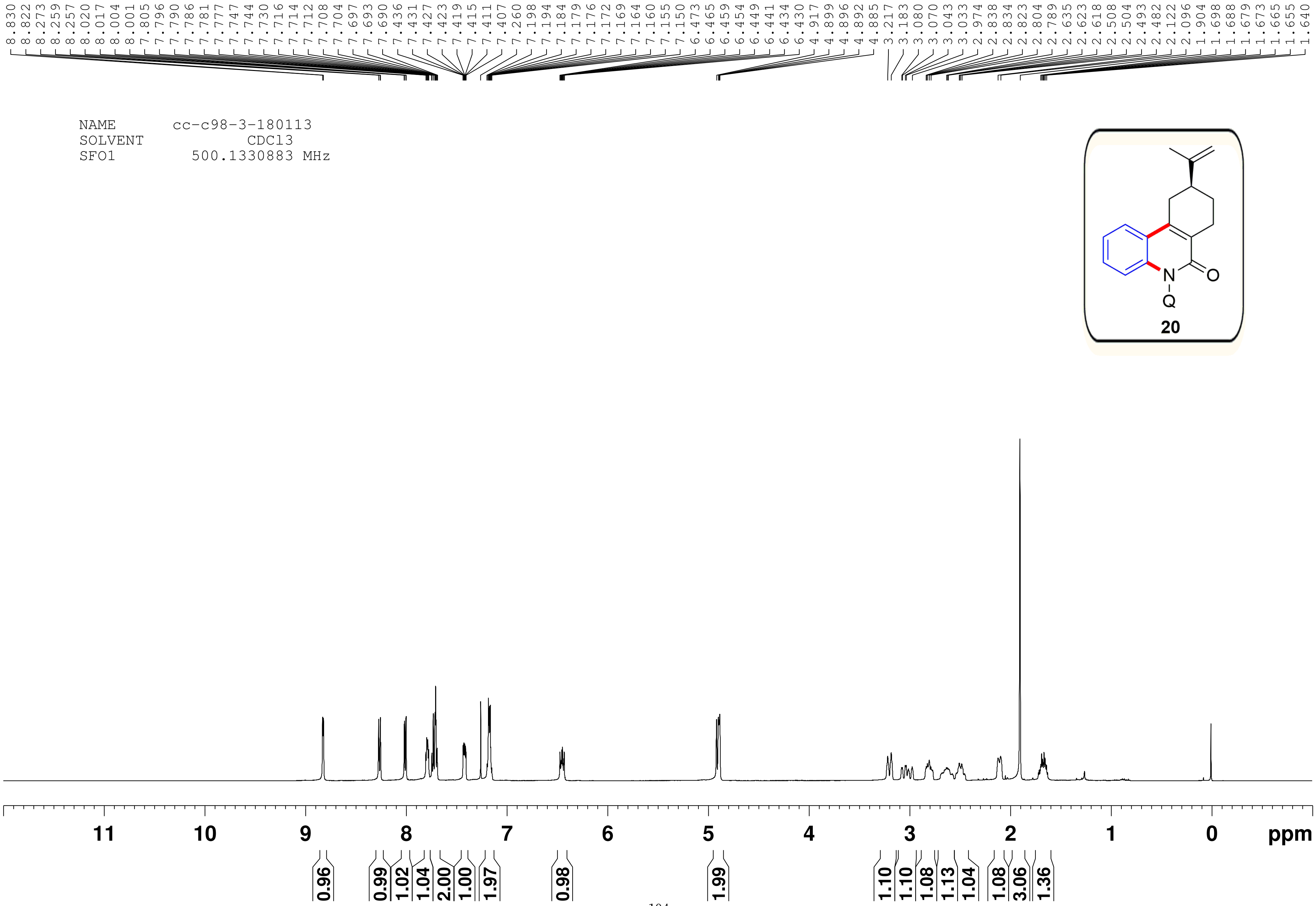


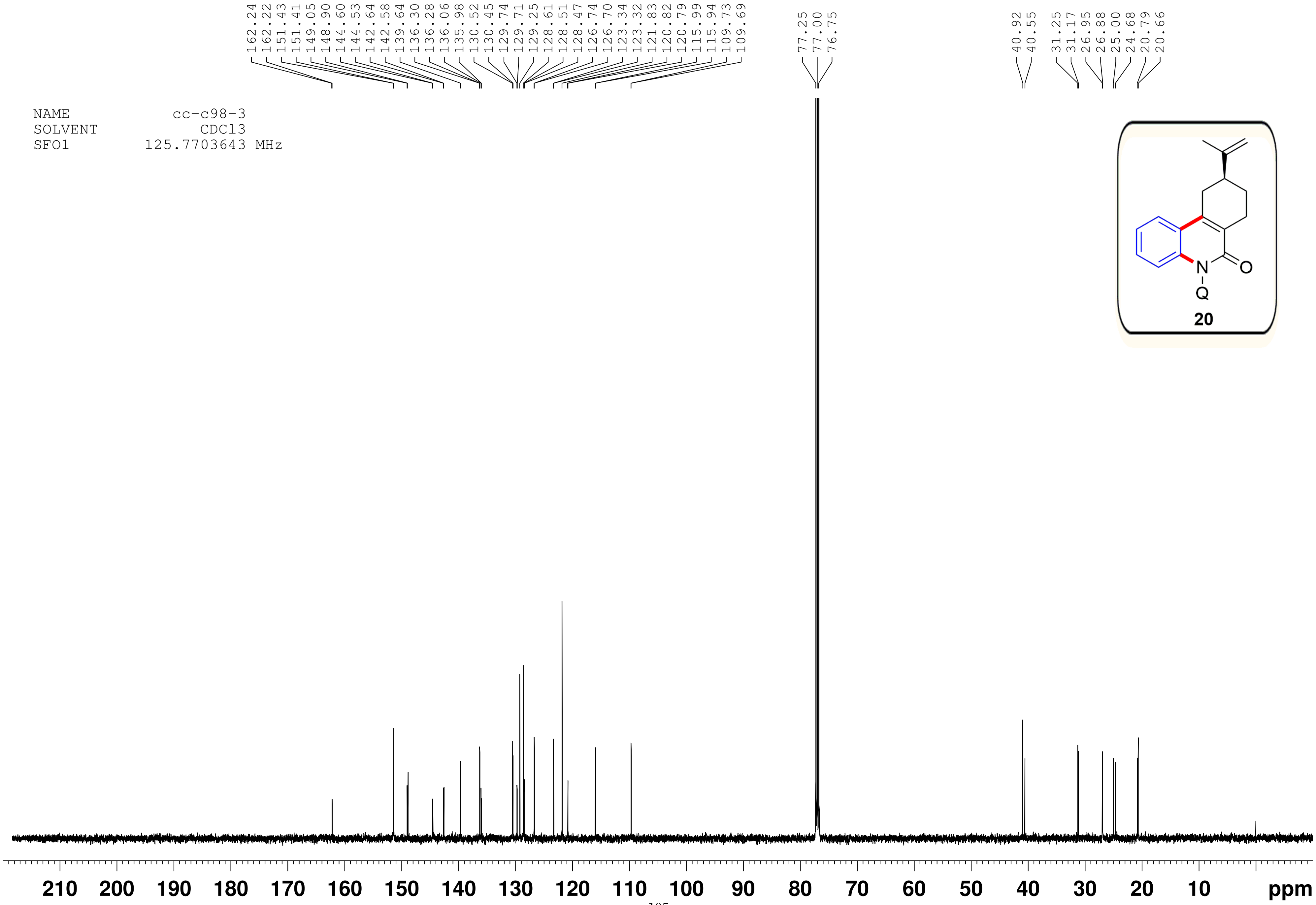
```
NAME          cc-c125-1a2
SOLVENT              CDCl3
SFO1          400.1324710 MHz
```

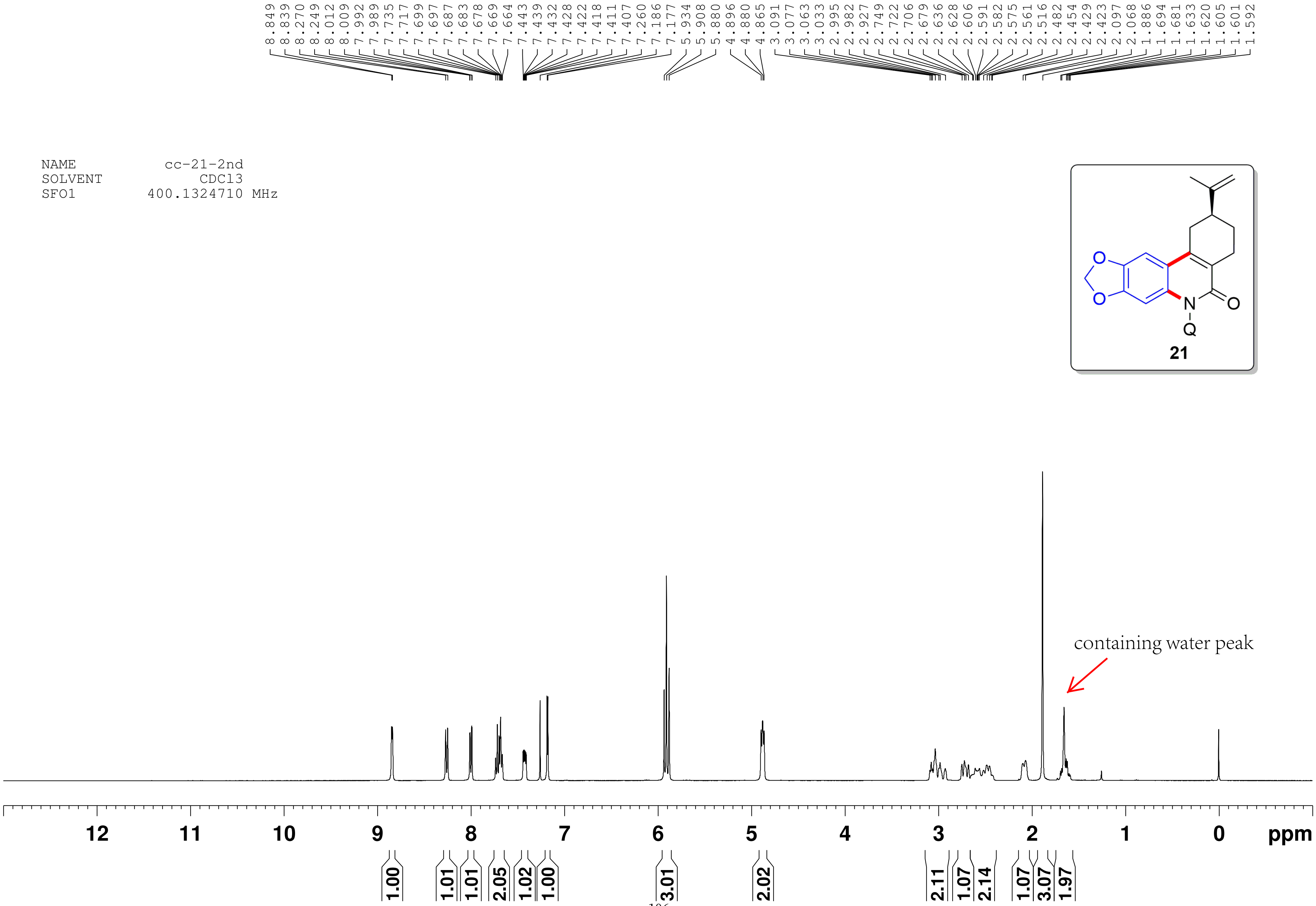




NAME cc-c125-12a
SOLVENT CDCl3
SFO1 100.6228293 MHz


8.830
8.822
8.273
8.259
8.257
8.020
8.017
8.004
8.001
7.805
7.796
7.790
7.786
7.781
7.777
7.747
7.744
7.730
7.716
7.714
7.712
7.708
7.704
7.697
7.693
7.690
7.436
7.431
7.427
7.423
7.419
7.415
7.411
7.407
7.260
7.198
7.194
7.184
7.179
7.176
7.172
7.169
7.164
7.160
7.155
7.150
6.473
6.465
6.459
6.454
6.449
6.441
6.434
6.430
4.917
4.899
4.896
4.892
4.885
3.217
3.183
3.080
3.070
3.043
3.033
2.974
2.838
2.834
2.823
2.804
2.789
2.635
2.623
2.618
2.508
2.504
2.493
2.482
2.122
2.096
1.904
1.698
1.688
1.679
1.673
1.665
1.655
1.640
NAME cc-c98-3-180113
SOLVENT CDCl3
SFO1 500.1330883 MHz
N
O
Q
20
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.96
0.99
1.02
1.04
2.00
1.00
1.97
0.98
1.99
1.10
1.10
1.08
1.13
1.04
1.08
3.06
1.36


162.24
162.22
151.43
151.41
149.05
148.90
144.60
144.53
142.64
142.58
139.64
136.30
136.28
136.06
135.98
130.52
130.45
129.74
129.71
129.25
128.61
128.51
128.47
126.74
126.70
123.34
123.32
121.83
120.82
120.79
115.99
115.94
109.73
109.69
77.25
77.00
76.75
40.92
40.55
31.25
31.17
26.95
26.88
25.00
24.68
20.79
20.66
NAME cc-c98-3
SOLVENT CDCl3
SFO1 125.7703643 MHz
N
O
Q
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

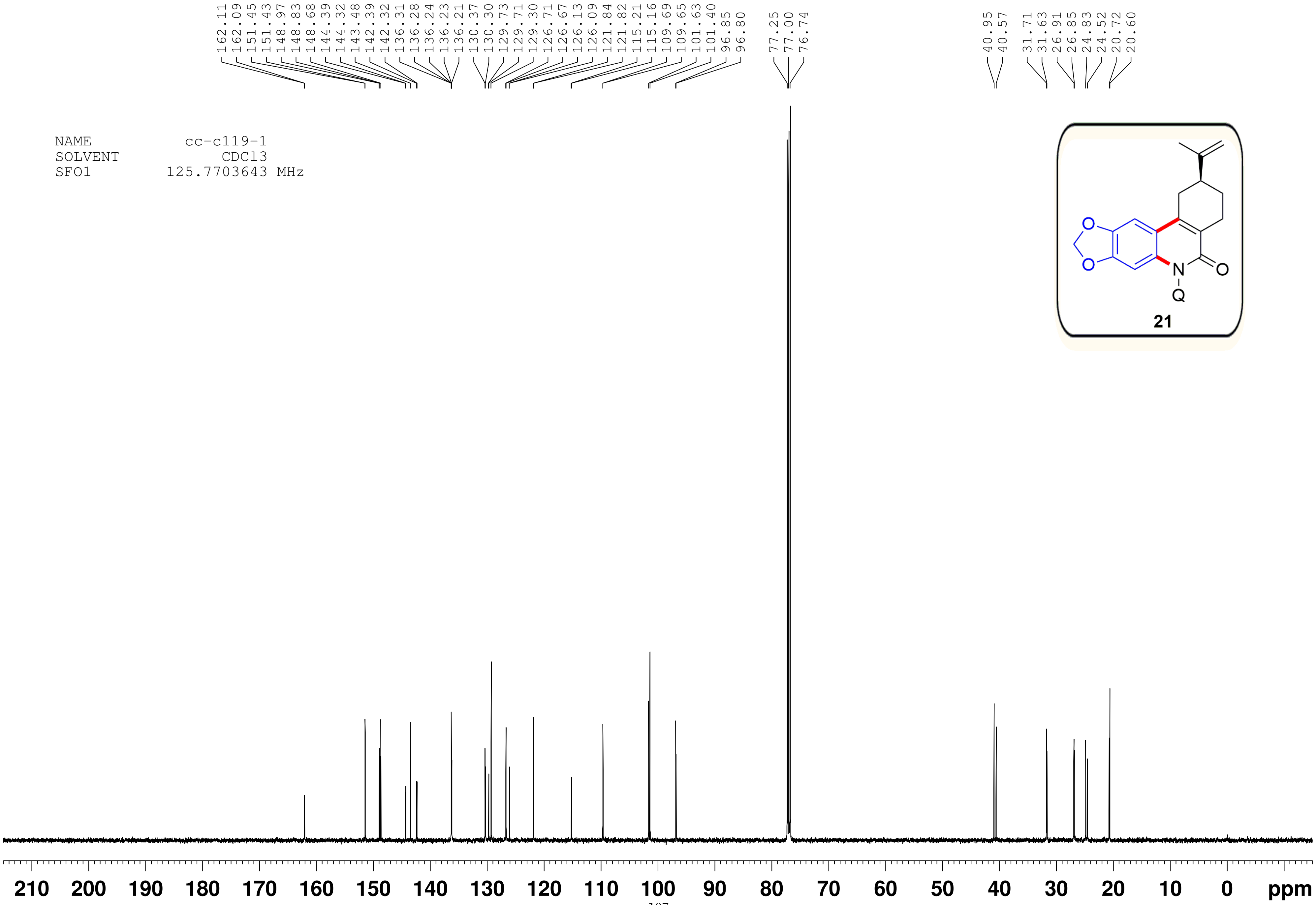


```
NAME          cc-21-2nd
SOLVENT           CDCl3
SFO1       400.1324710 MHz
```

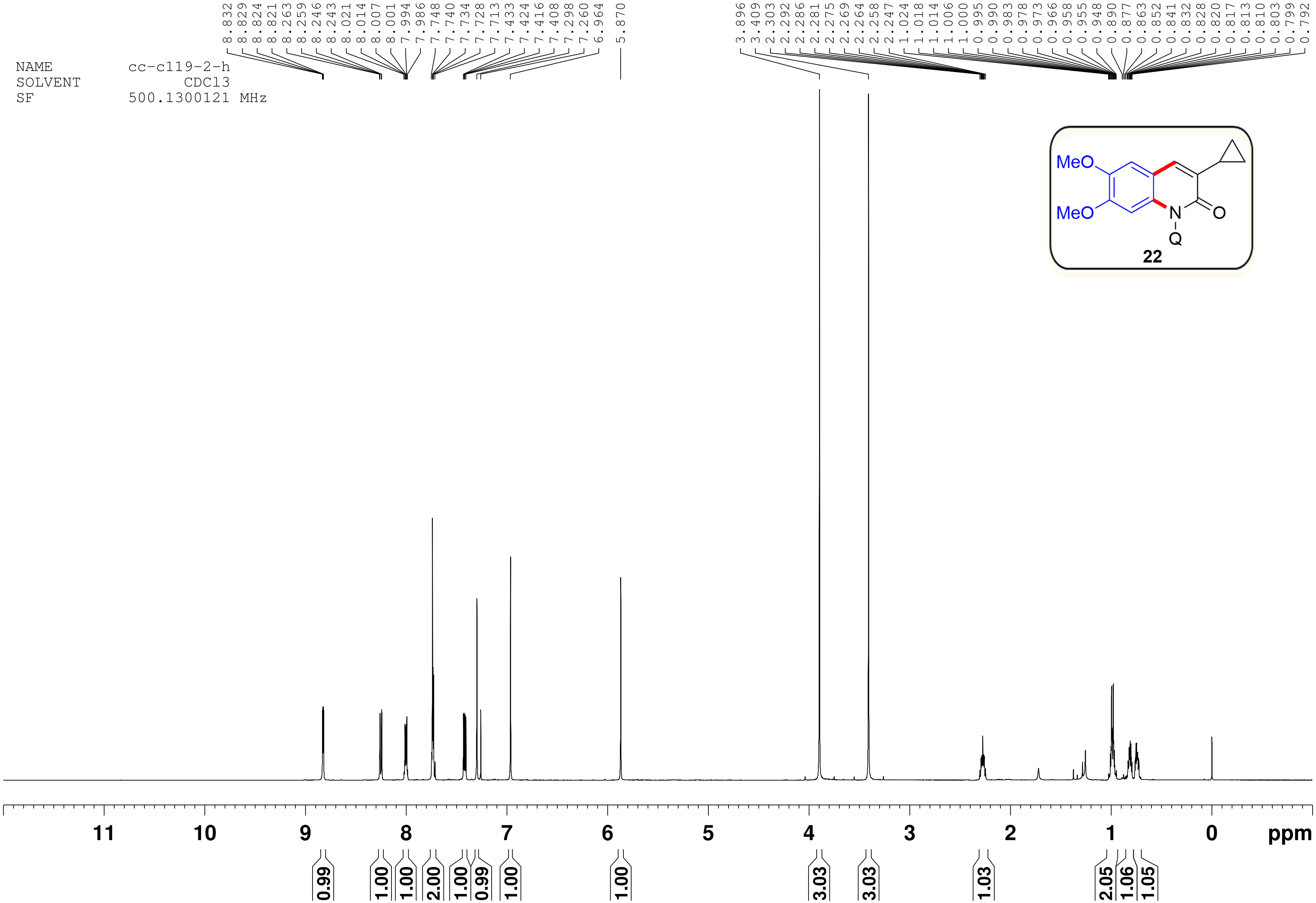
21

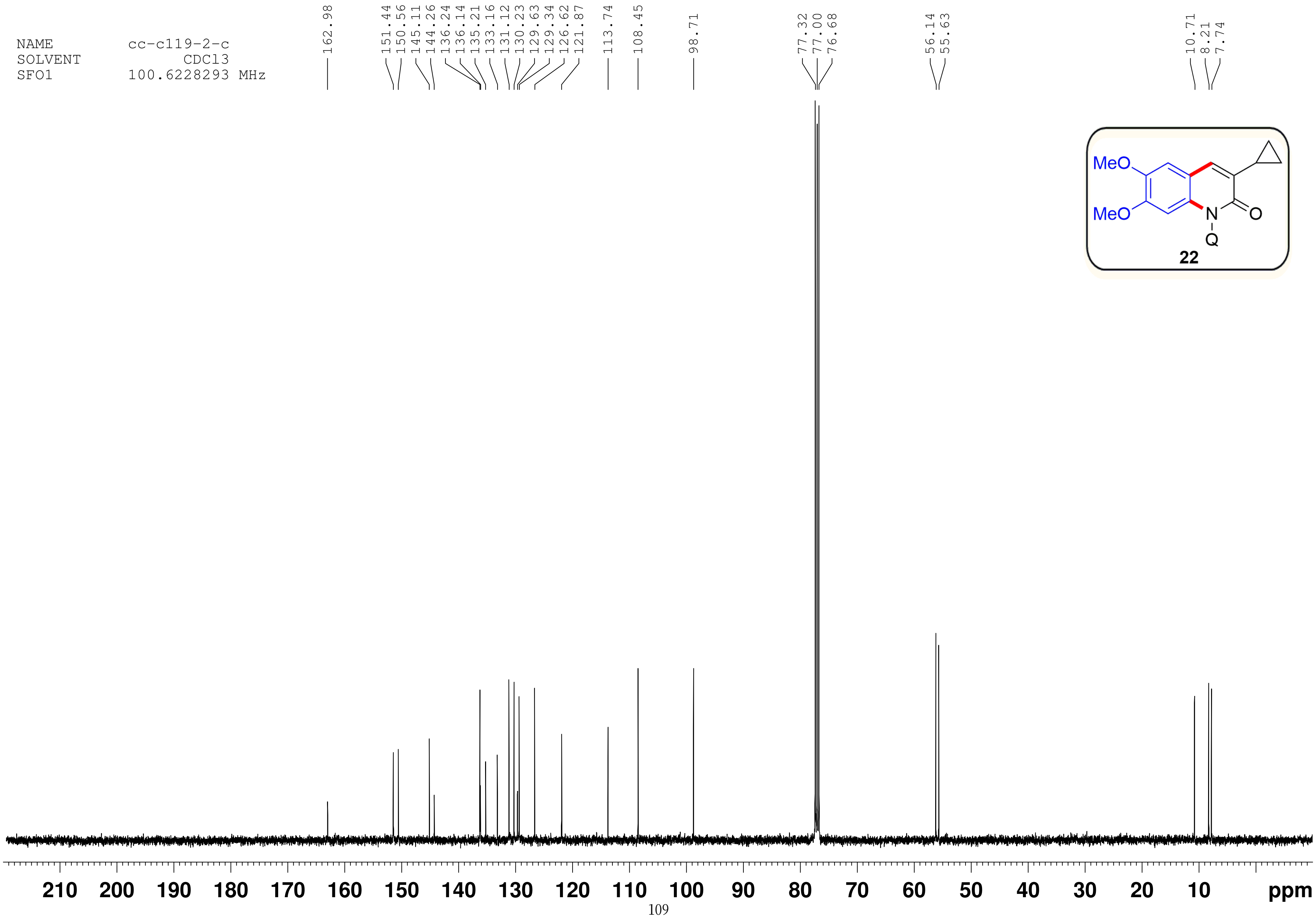
containing water peak

NAME cc-c119-1
SOLVENT CDCl3
SFO1 125.7703643 MHz

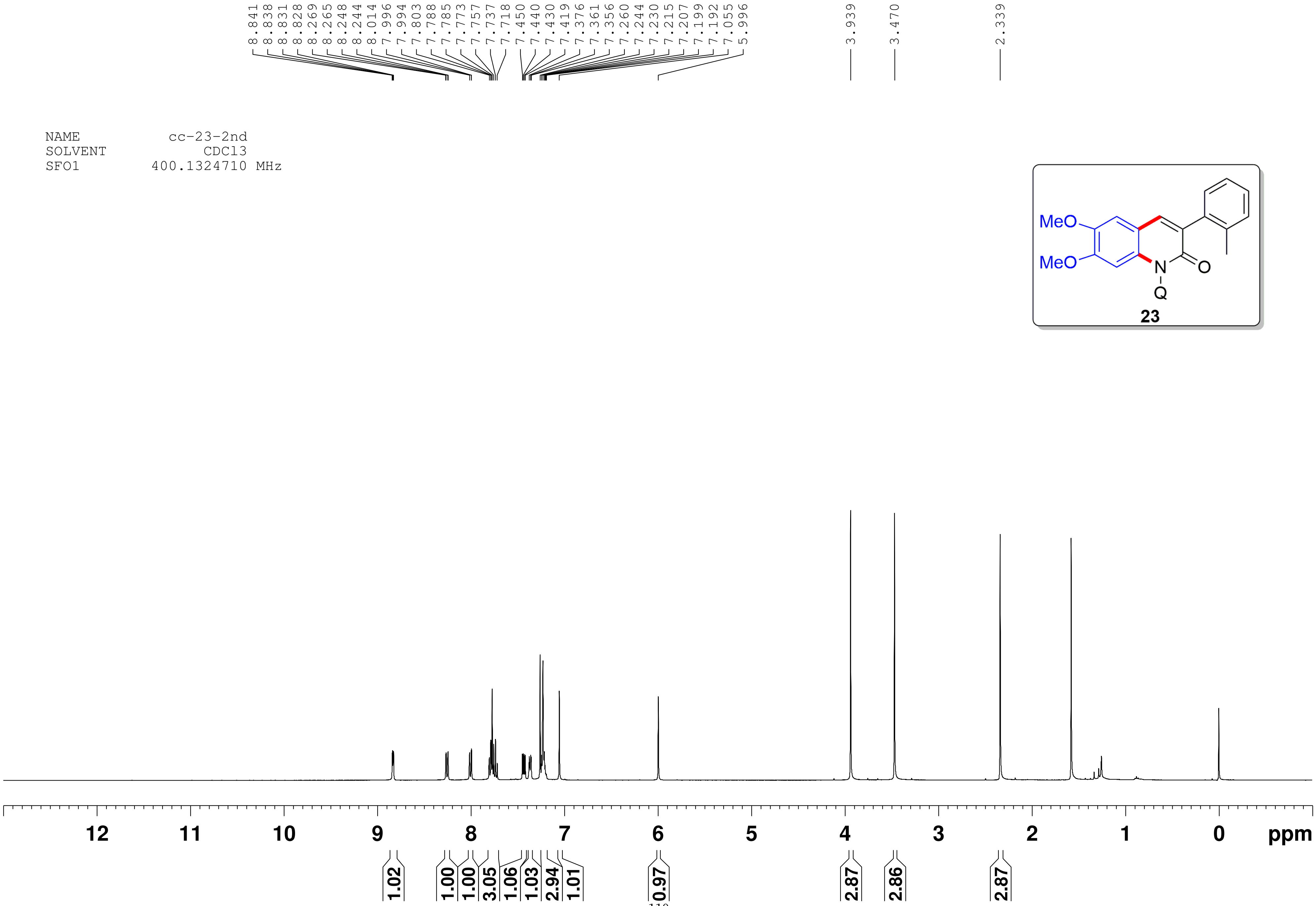


21

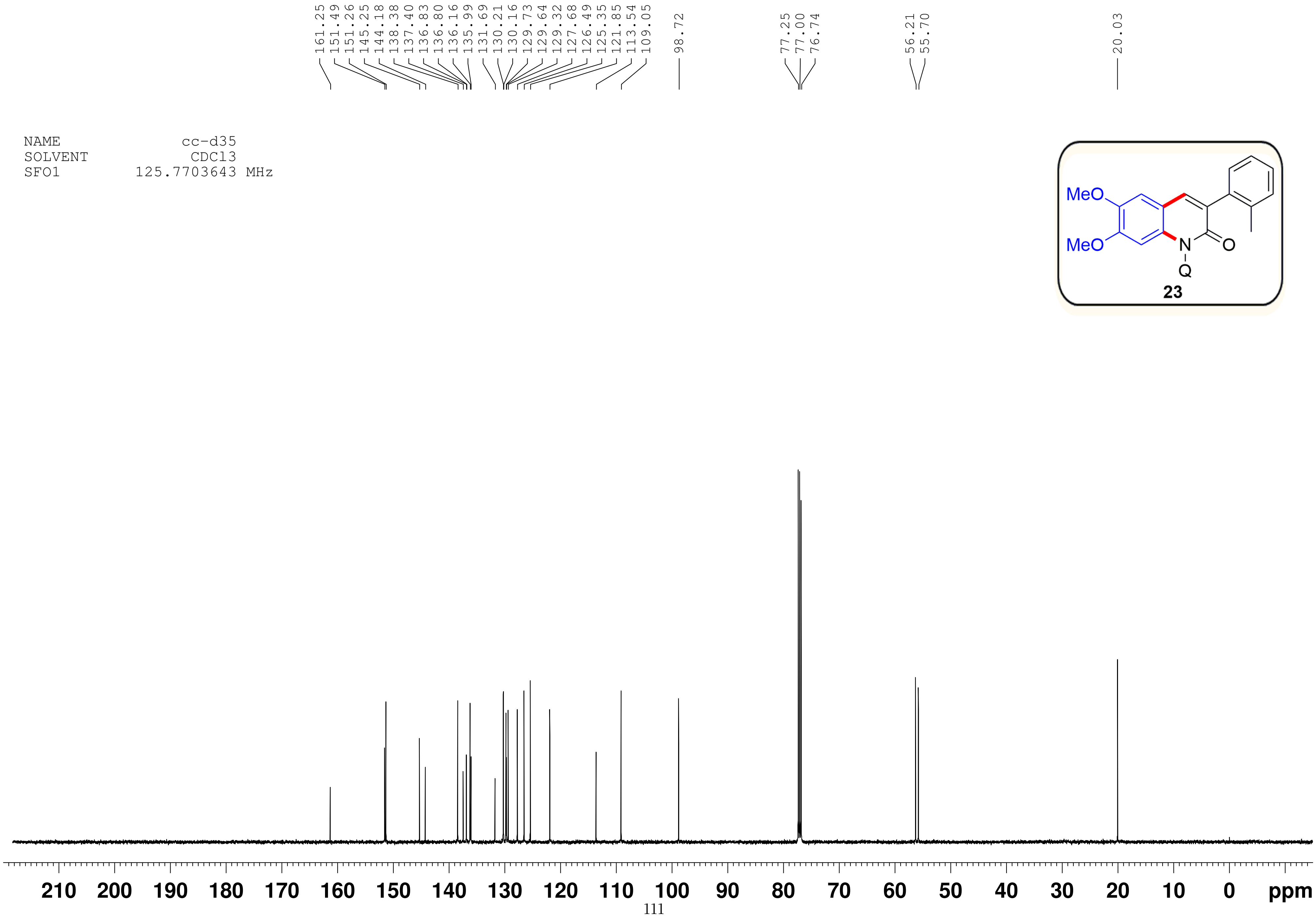

NAME cc-c119-2-h
SOLVENT CDCl3
SF 500.1300121 MHz


NAME cc-c119-2-c
SOLVENT CDCl3
SFO1 100.6228293 MHz
162.98
151.44
150.56
145.11
144.26
136.24
136.14
135.21
133.16
131.12
130.23
129.63
129.34
126.62
121.87
113.74
108.45
98.71
77.32
77.00
76.68
56.14
55.63
10.71
8.21
7.74
MeO
MeO
N
O
Q
22
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

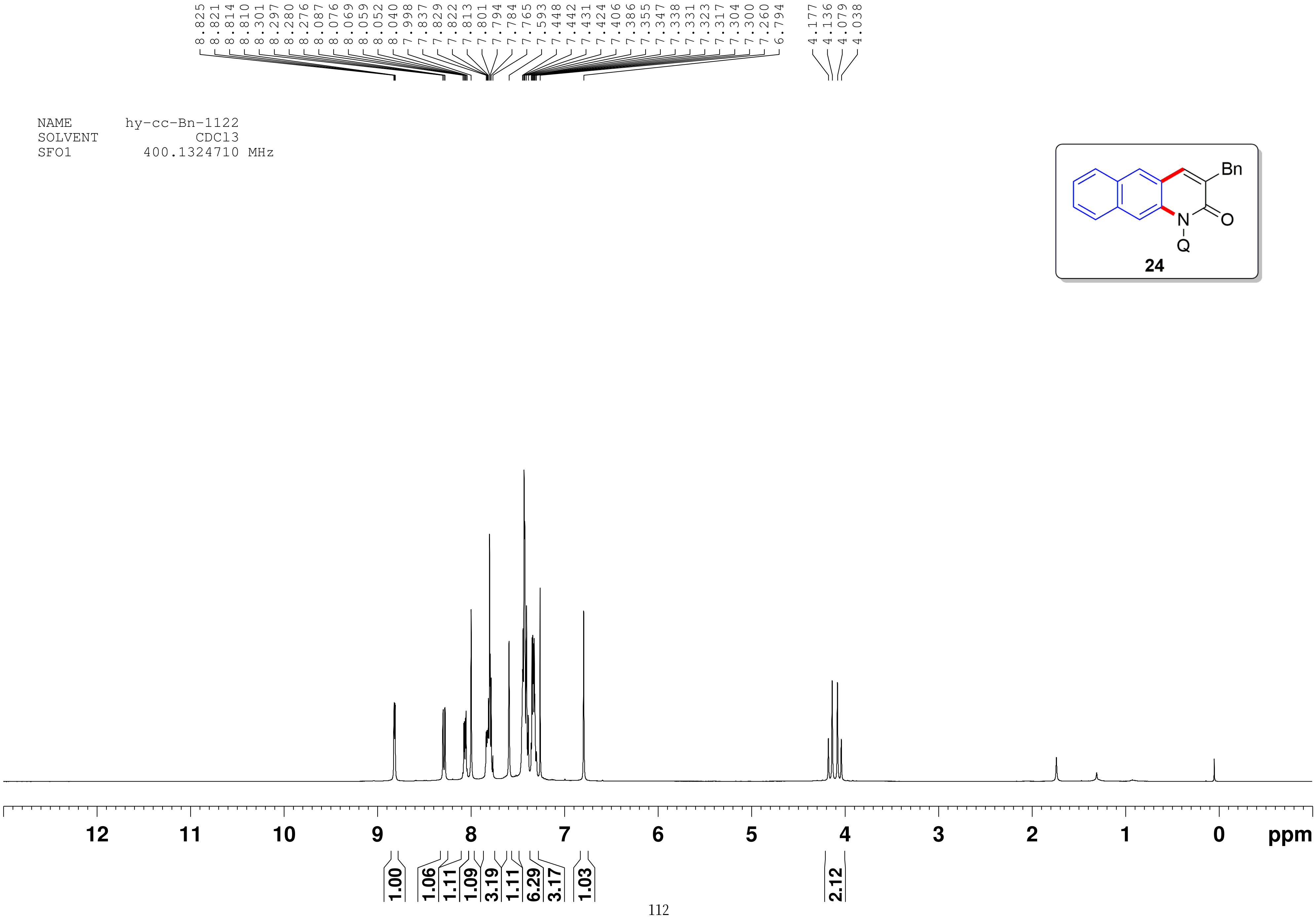
NAME cc-23-2nd
SOLVENT CDCl3
SFO1 400.1324710 MHz



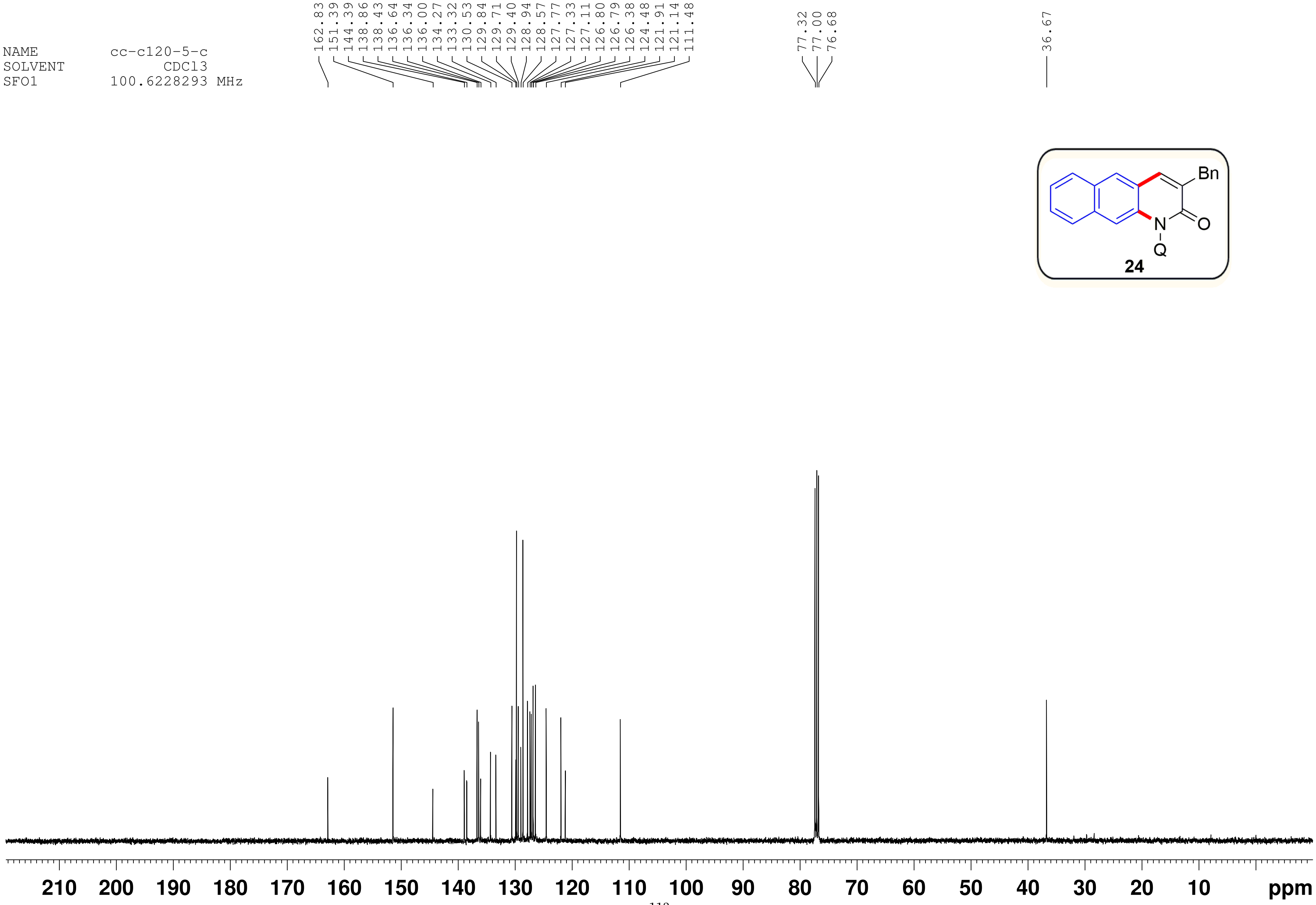
NAME cc-d35
SOLVENT CDCl3
SFO1 125.7703643 MHz



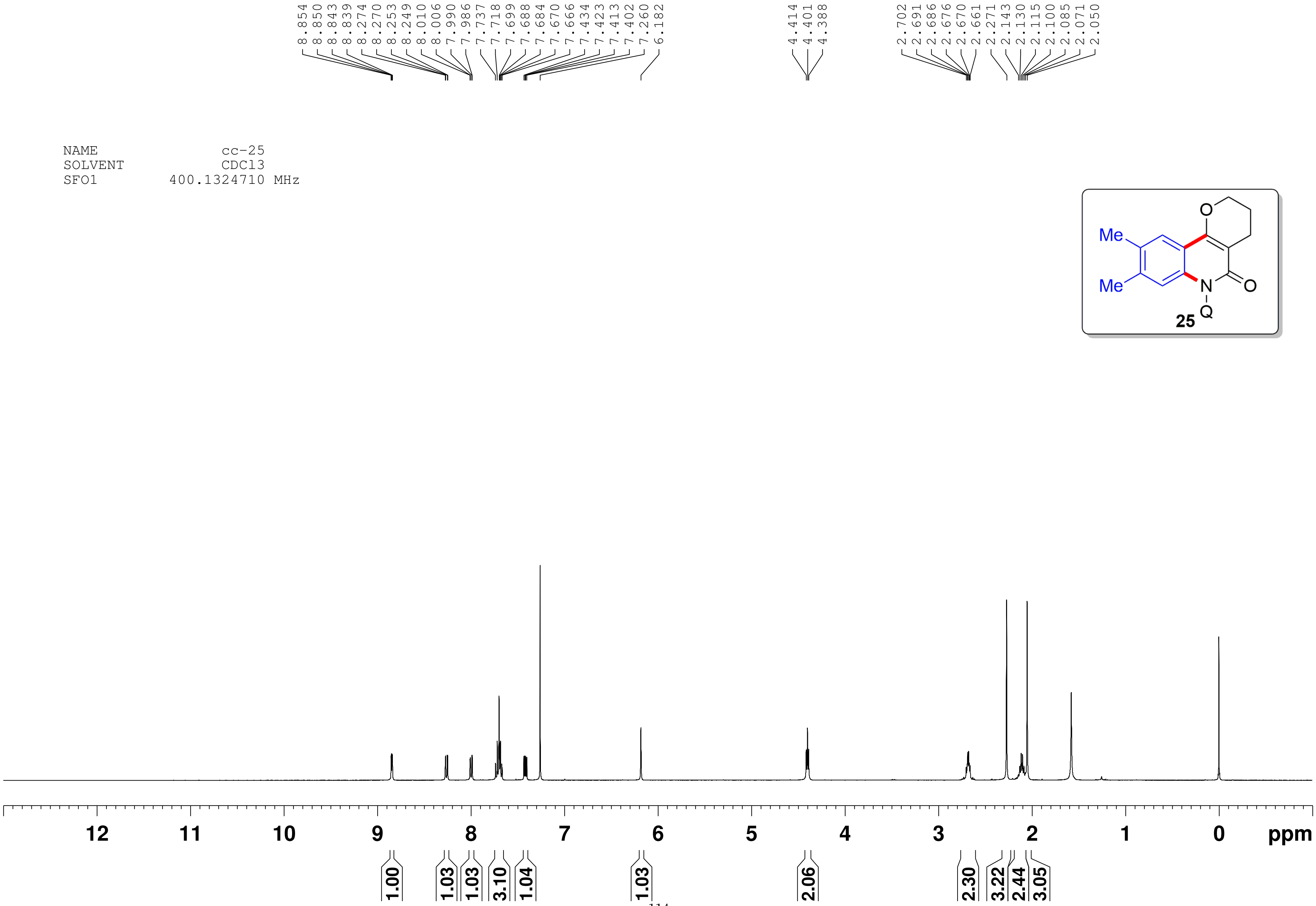
NAME hy-cc-Bn-1122
SOLVENT CDCl3
SFO1 400.1324710 MHz



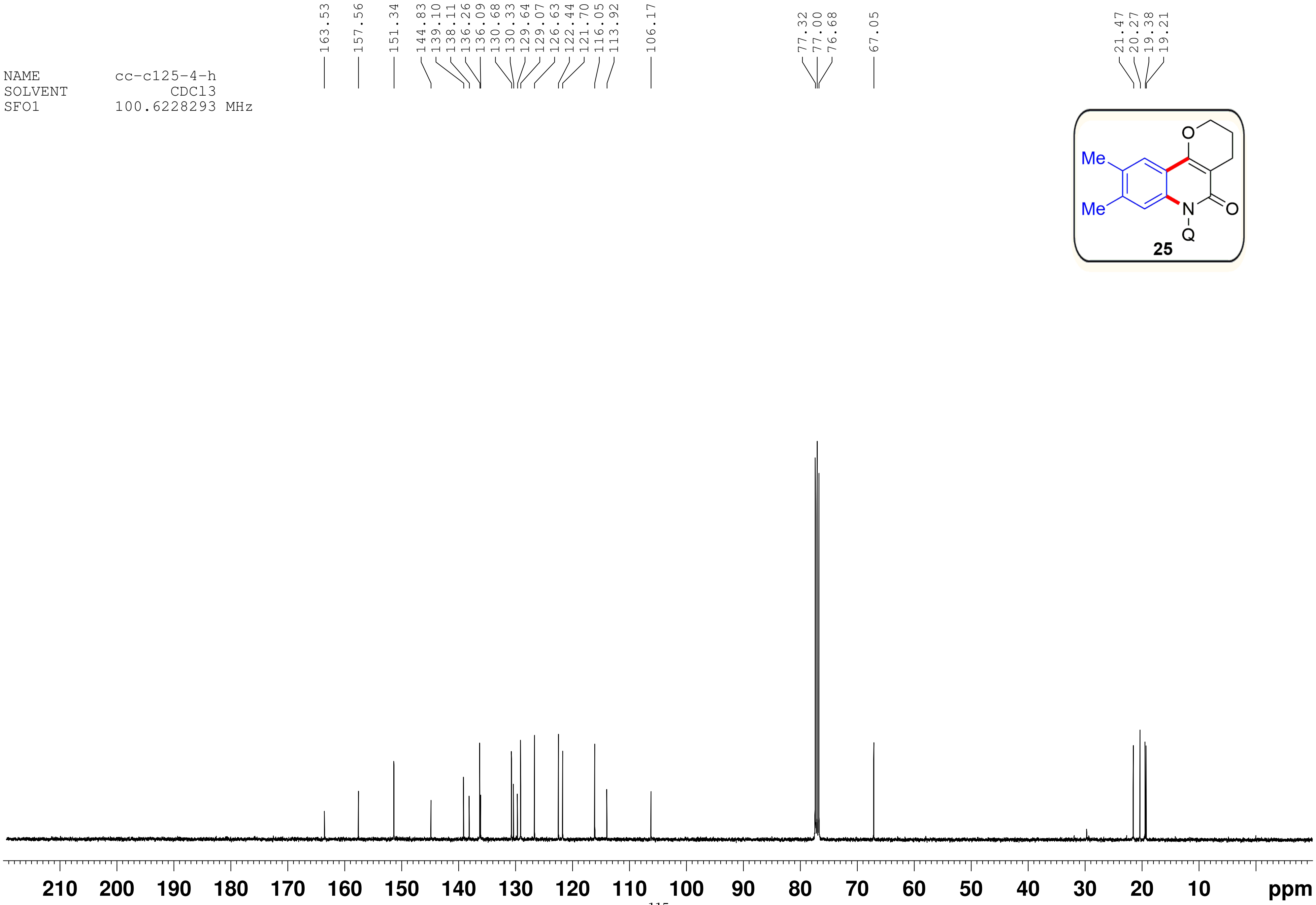
NAME	cc-c120-5-c
SOLVENT	CDCl3
SFO1	100.6228293 MHz

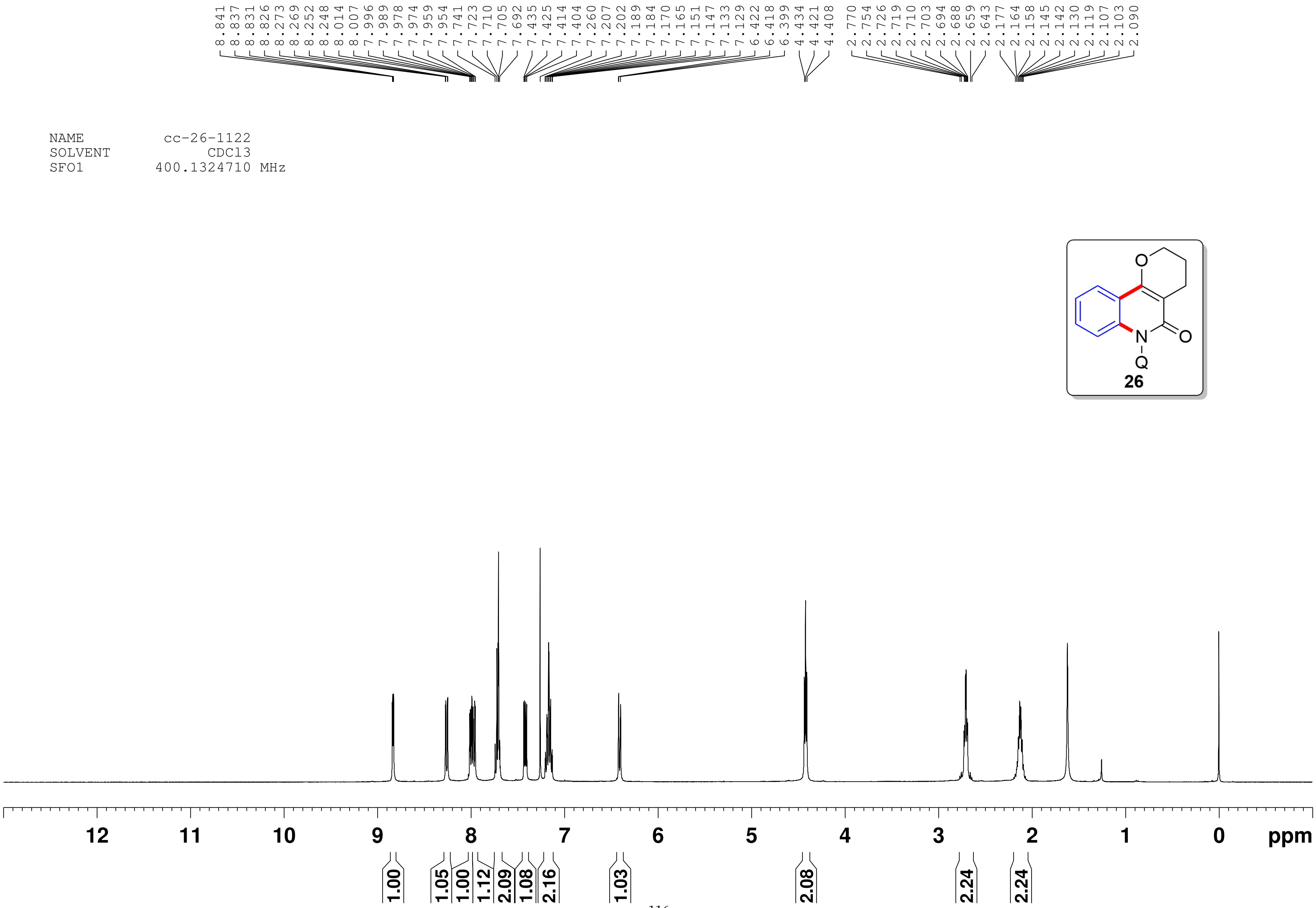


NAME cc-25
SOLVENT CDCl3
SFO1 400.1324710 MHz

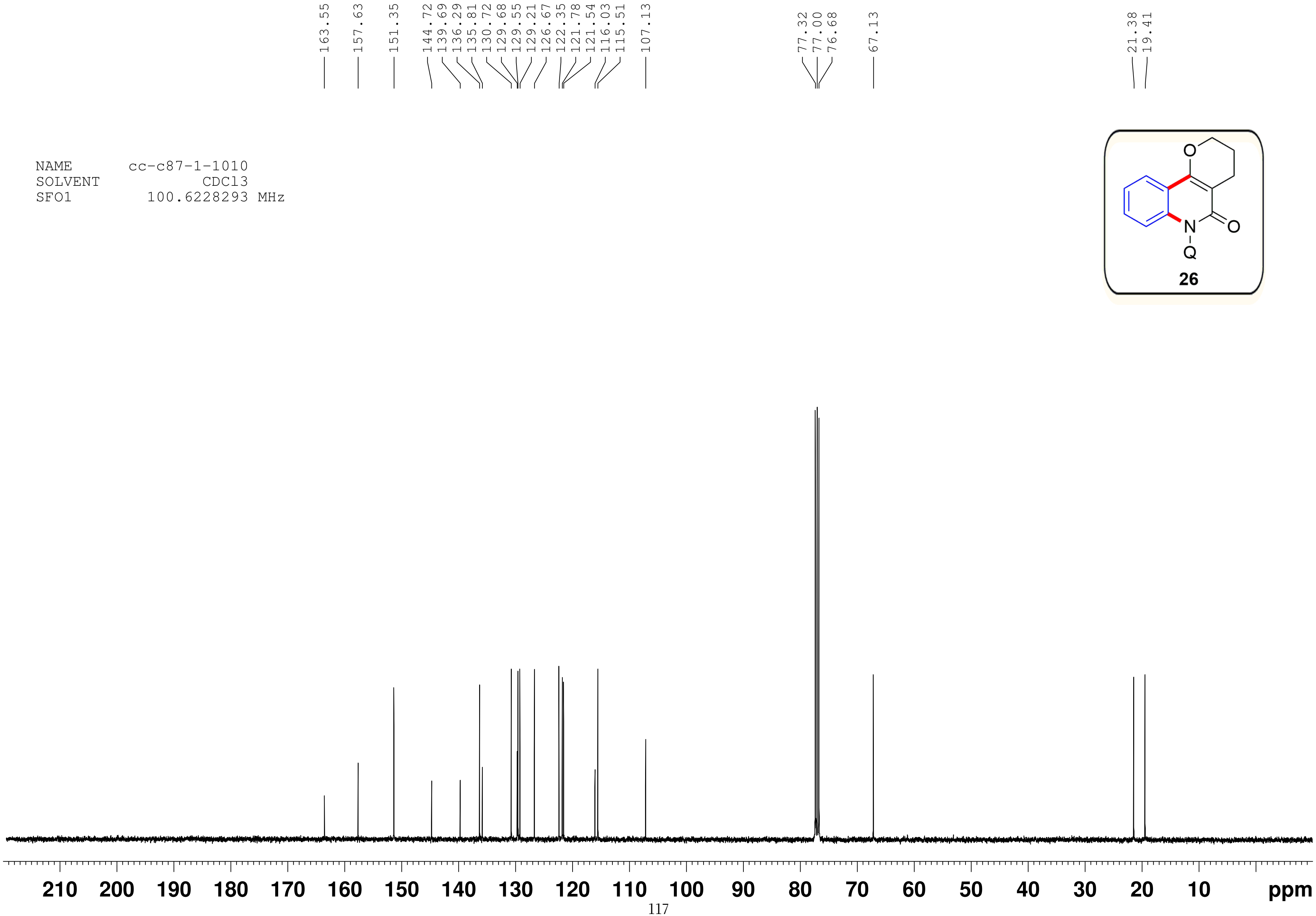


NAME cc-c125-4-h
SOLVENT CDCl3
SFO1 100.6228293 MHz



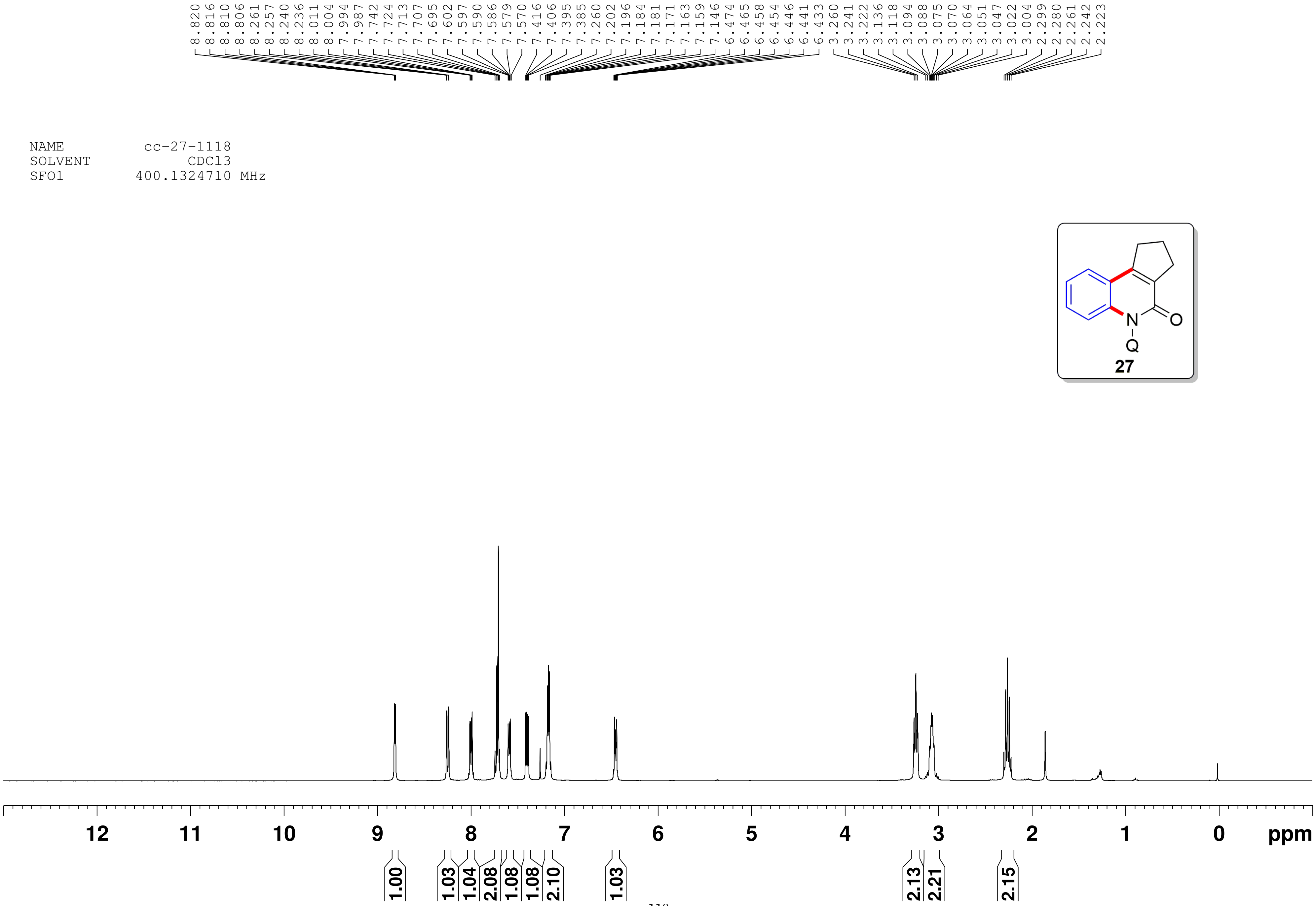


NAME cc-26-1122
SOLVENT CDCl3
SFO1 400.1324710 MHz


163.55
157.63
151.35
144.72
139.69
136.29
135.81
130.72
129.68
129.55
129.21
126.67
122.35
121.78
121.54
116.03
115.51
107.13
77.32
77.00
76.68
67.13
21.38
19.41
NAME cc-c87-1-1010
SOLVENT CDCl3
SFO1 100.6228293 MHz
O
N
O
Q
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

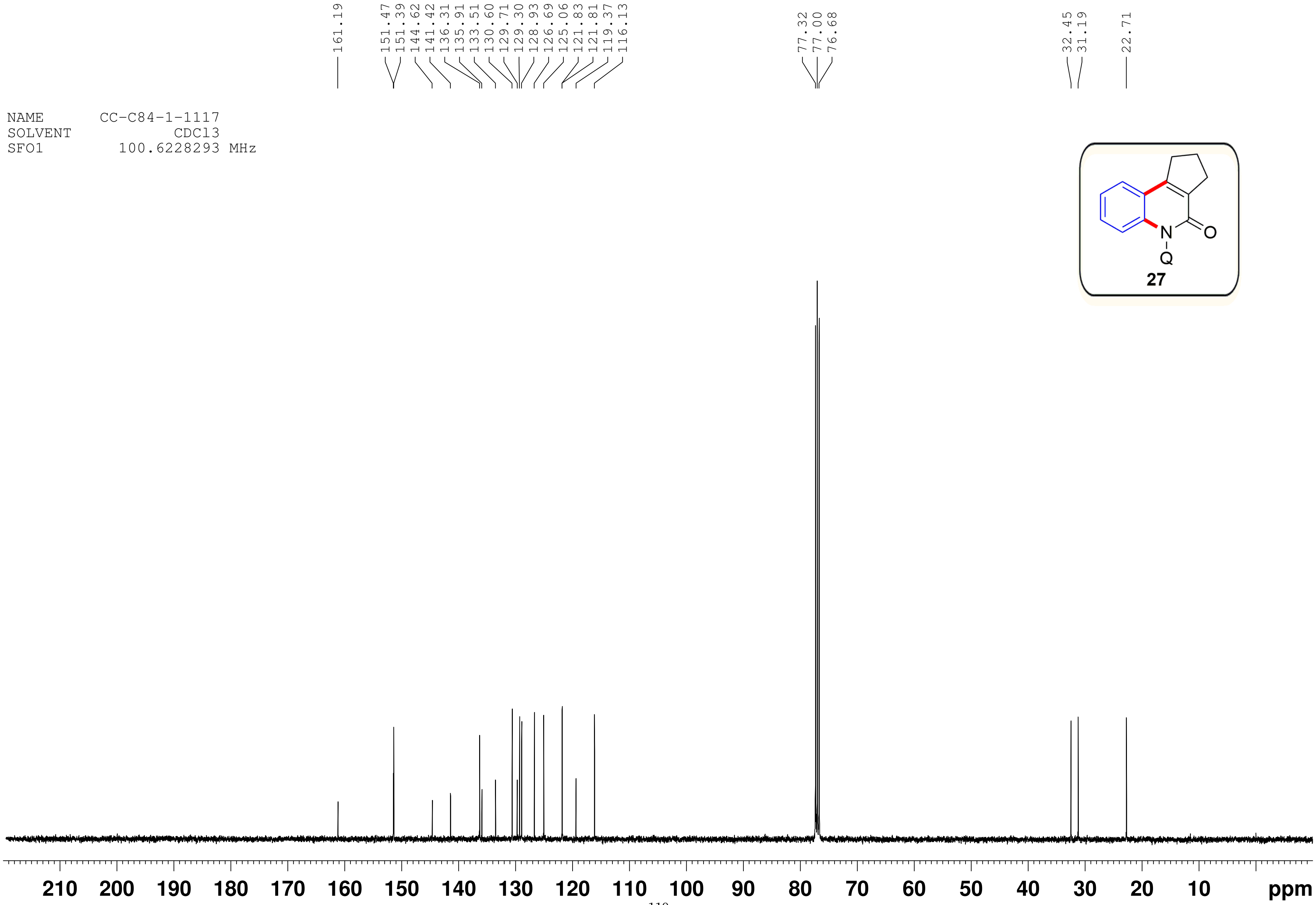
26

NAME cc-27-1118
SOLVENT CDCl3
SFO1 400.1324710 MHz

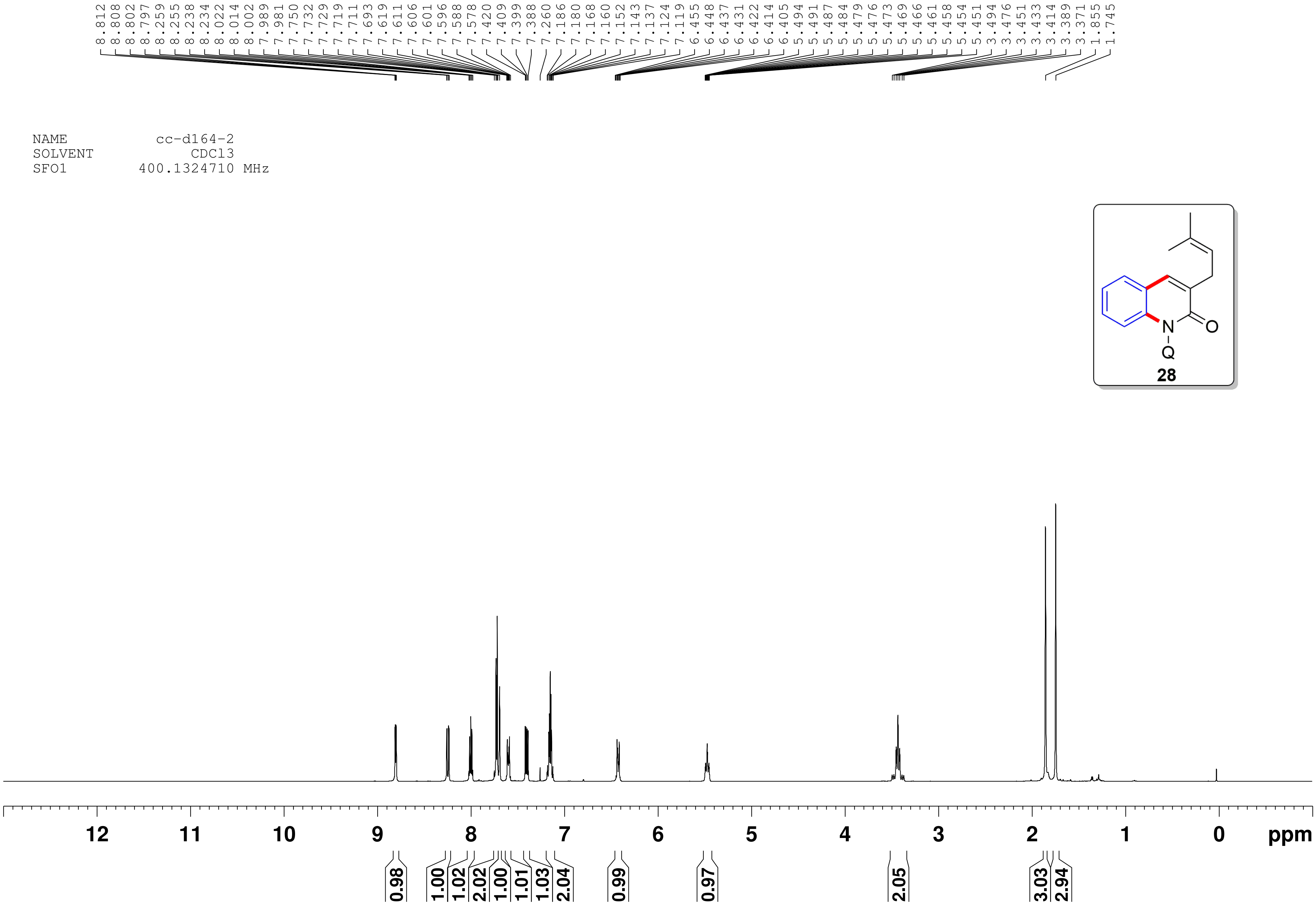


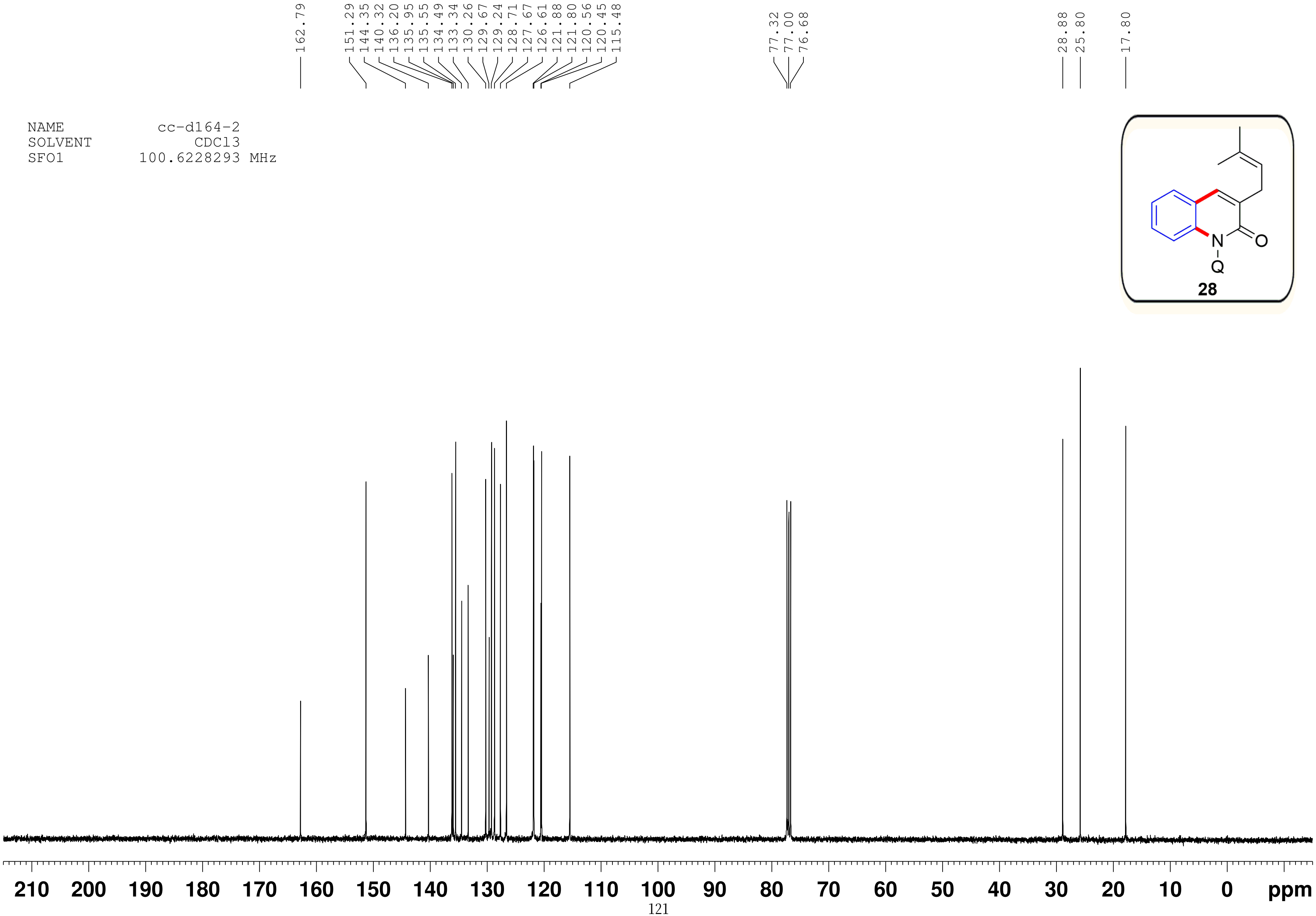
27

NAME CC-C84-1-1117
SOLVENT CDCl3
SFO1 100.6228293 MHz



27

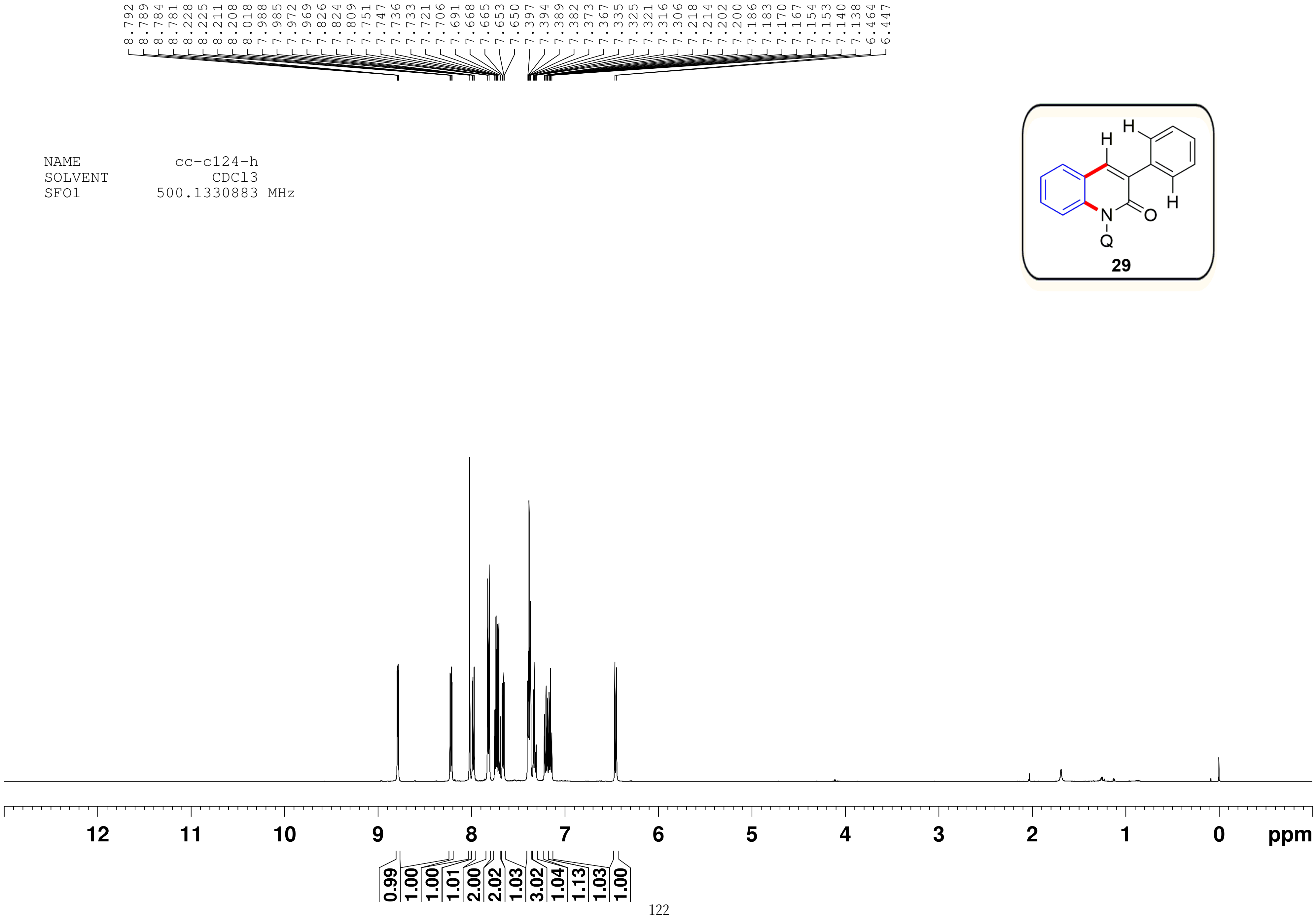

8.812
8.808
8.802
8.797
8.259
8.255
8.238
8.234
8.022
8.014
8.002
7.989
7.981
7.750
7.732
7.729
7.719
7.711
7.693
7.619
7.611
7.606
7.601
7.596
7.588
7.578
7.420
7.409
7.399
7.388
7.260
7.186
7.180
7.168
7.160
7.152
7.143
7.137
7.124
7.119
6.455
6.448
6.437
6.431
6.422
6.414
6.405
5.494
5.491
5.487
5.484
5.479
5.476
5.473
5.469
5.466
5.461
5.458
5.454
5.451
3.494
3.476
3.451
3.433
3.414
3.389
3.371
1.855
1.745
NAME cc-d164-2
SOLVENT CDCl3
SFO1 400.1324710 MHz
N
O
Q
28
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.98
1.00
1.02
2.02
1.00
1.01
1.03
2.04
0.99
0.97
2.05
3.03
2.94



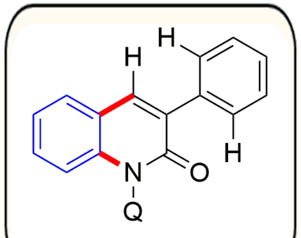
NAME cc-d164-2
SOLVENT CDCl3
SFO1 100.6228293 MHz

NAME cc-c124-h
SOLVENT CDCl3
SFO1 500.1330883 MHz

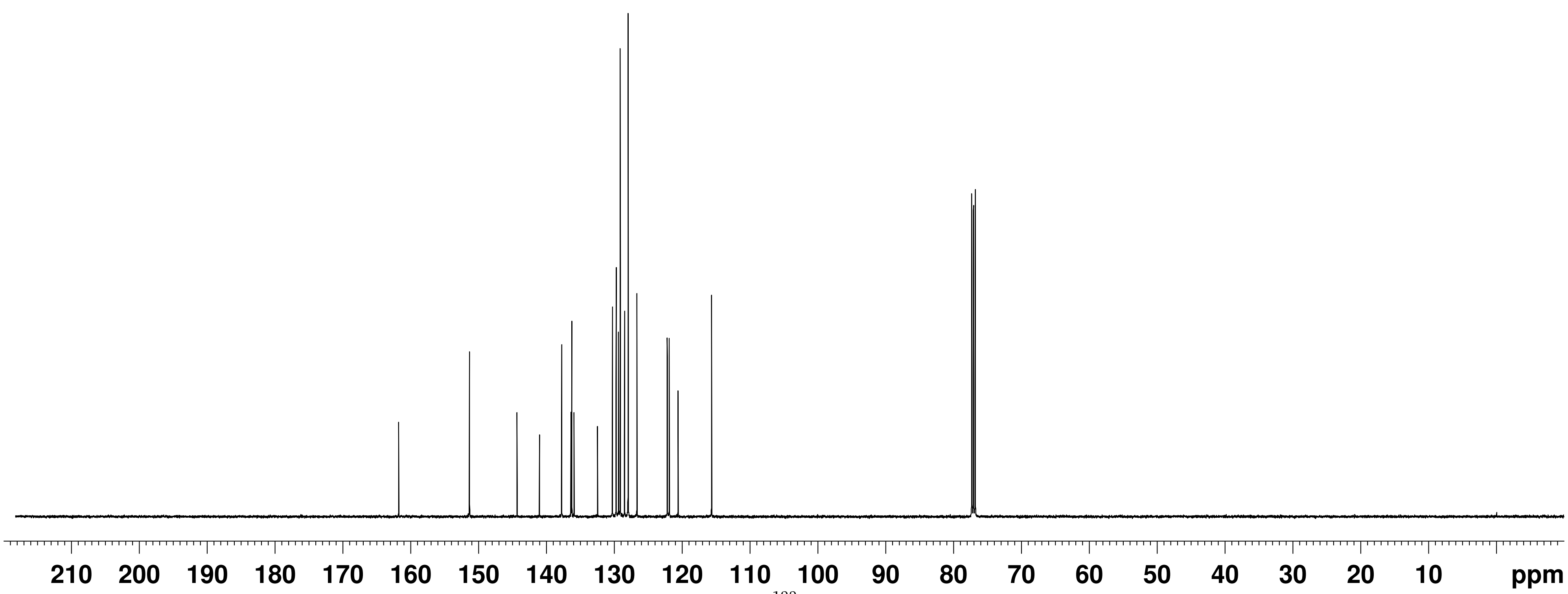
29



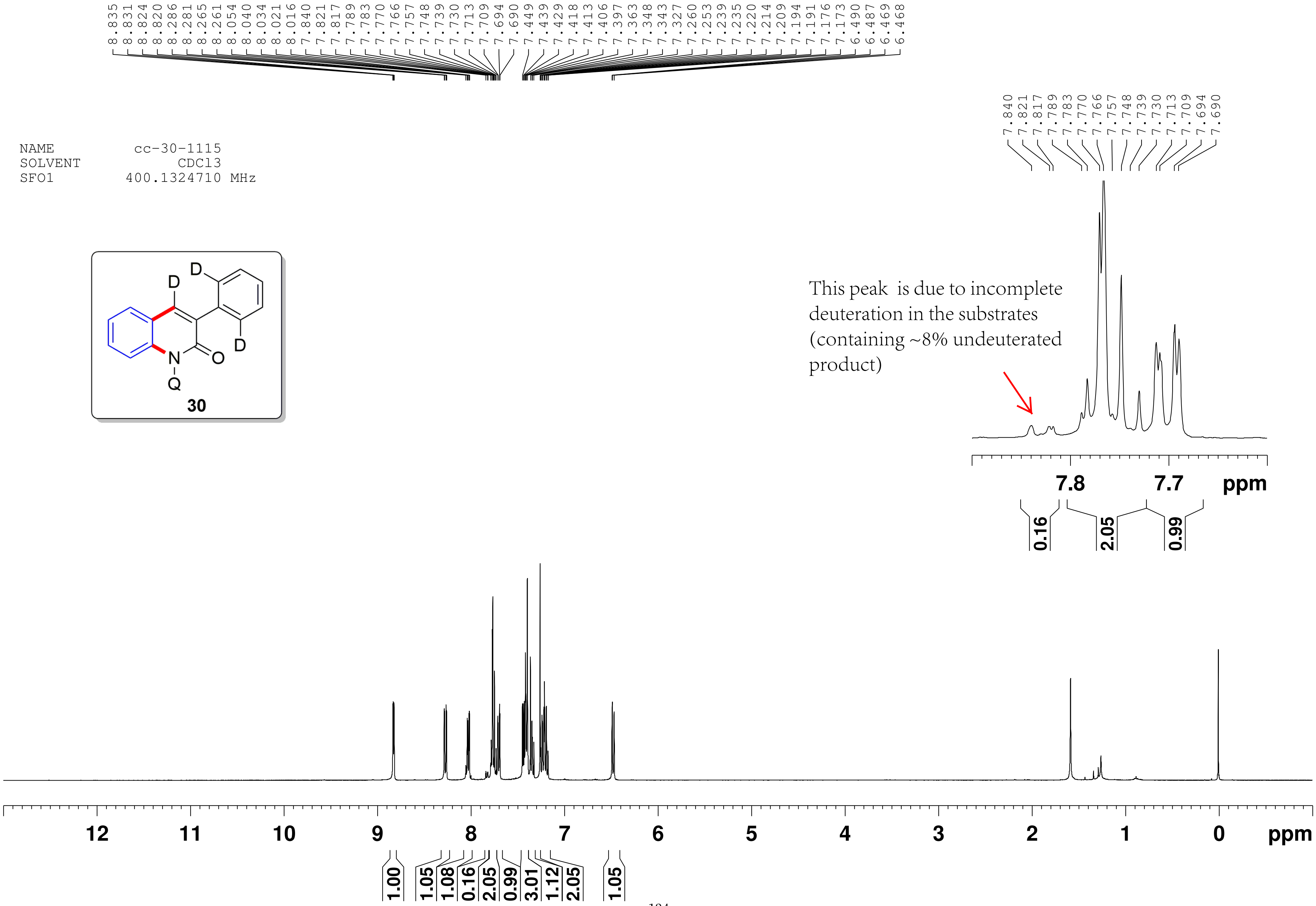
```
NAME            cc-c124-h
SOLVENT             CDCl3
SFO1       125.7703643 MHz
```



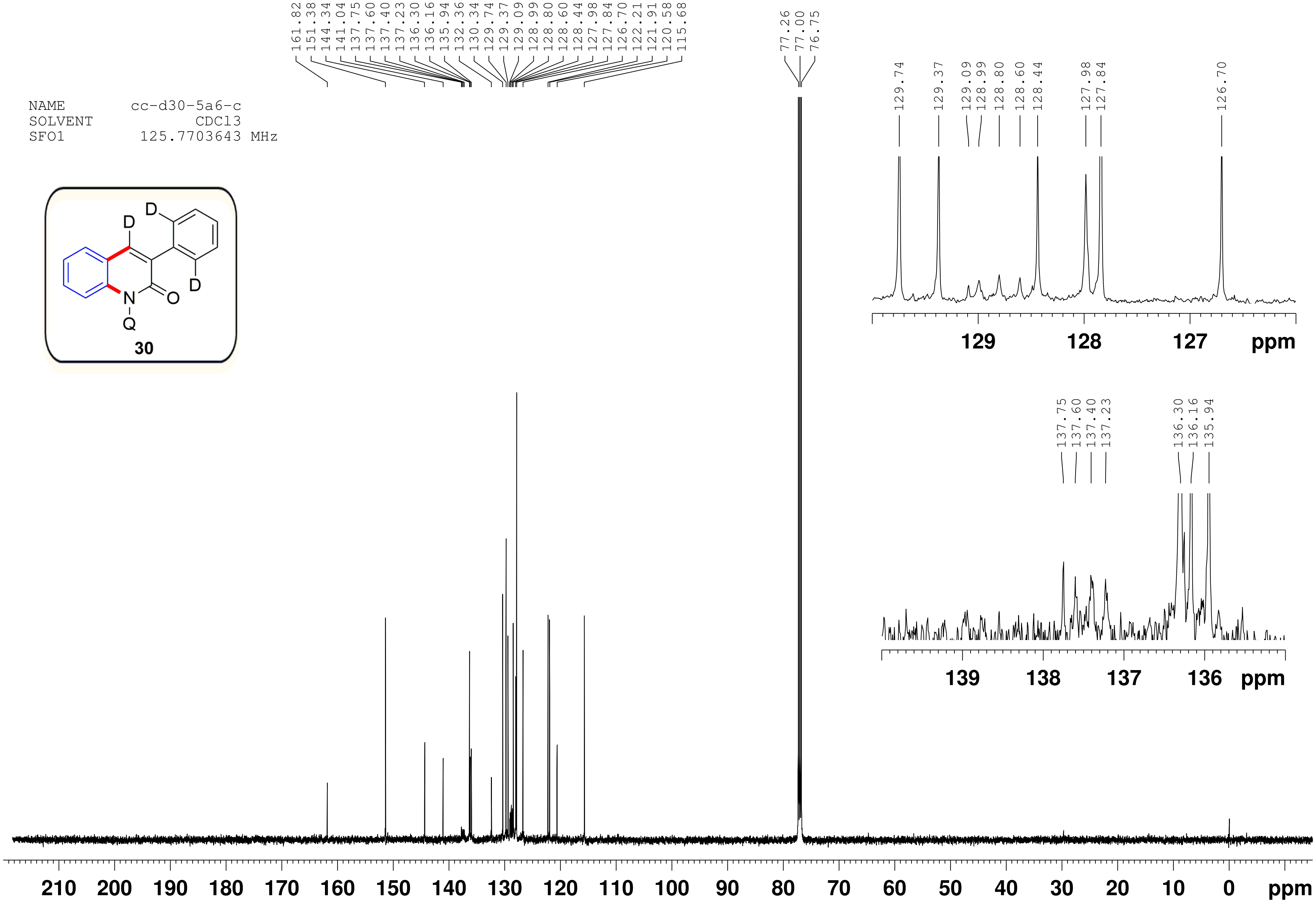
29

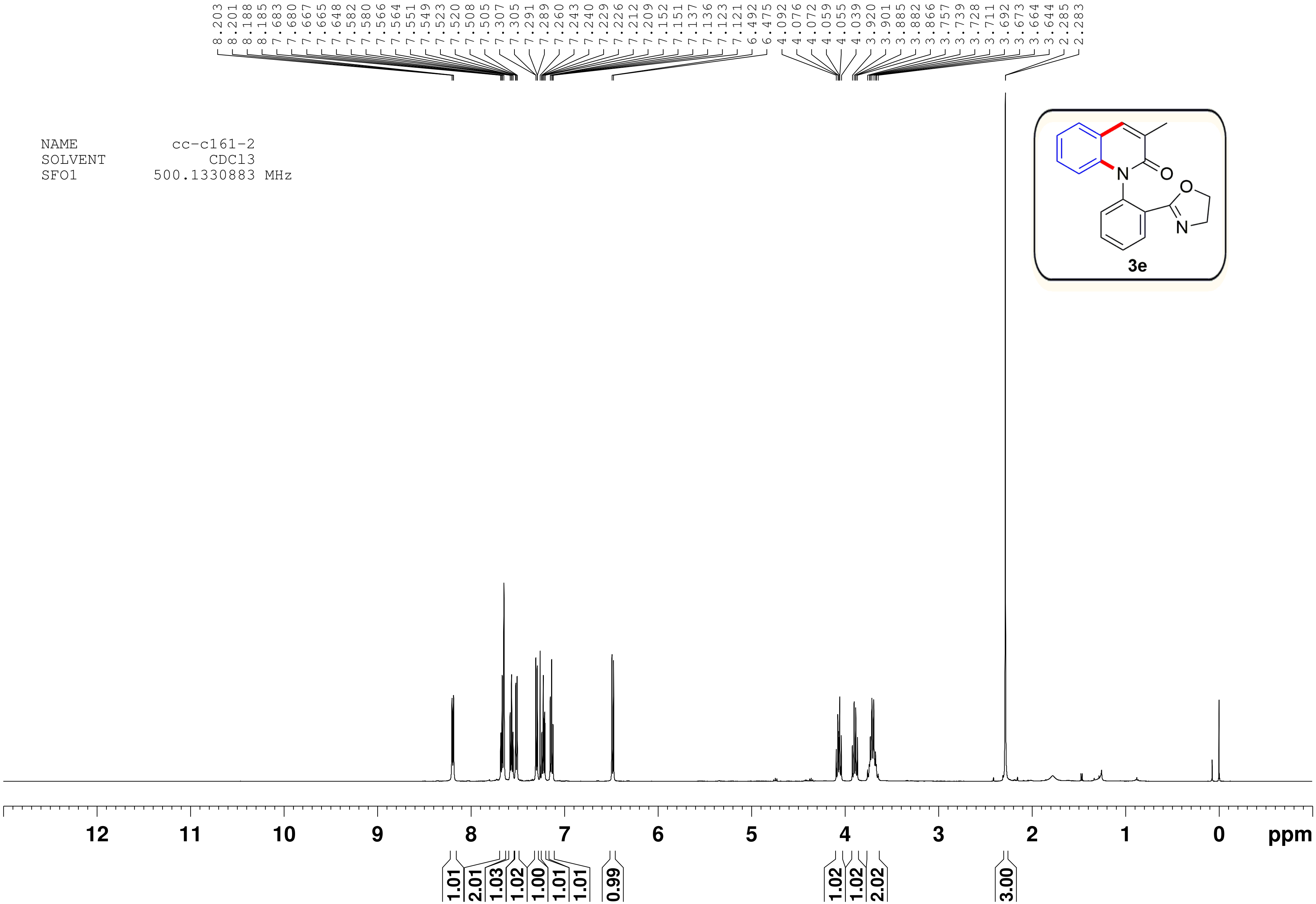


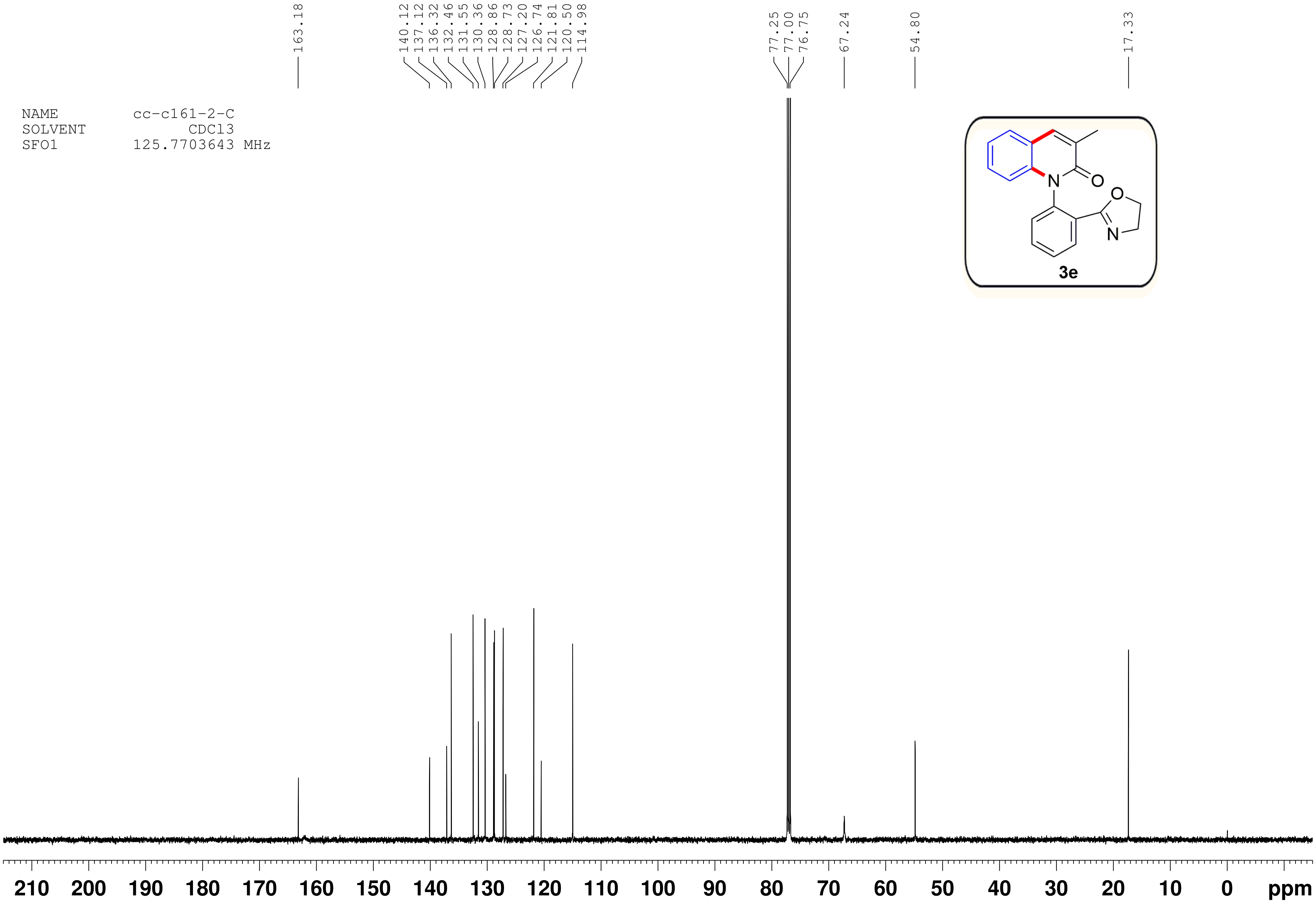
NAME cc-30-1115
SOLVENT CDCl3
SFO1 400.1324710 MHz



This peak is due to incomplete deuteration in the substrates (containing ~8% undeuterated product)


NAME cc-d30-5a6-c
SOLVENT CDCl3
SFO1 125.7703643 MHz
D
D
D
N
O
Q
30
161.82
151.38
144.34
141.04
137.75
137.60
137.40
137.23
136.30
136.16
135.94
132.36
130.34
129.74
129.37
129.09
128.99
128.80
128.60
128.44
127.98
127.84
126.70
122.21
121.91
120.58
115.68
77.26
77.00
76.75
129.74
129.37
129.09
128.99
128.80
128.60
128.44
127.98
127.84
126.70
129
128
127
ppm
137.75
137.60
137.40
137.23
136.30
136.16
135.94
139
138
137
136
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


8.203
8.201
8.188
8.185
7.683
7.680
7.667
7.665
7.648
7.582
7.580
7.566
7.564
7.551
7.549
7.523
7.520
7.508
7.505
7.307
7.305
7.291
7.289
7.260
7.243
7.240
7.229
7.226
7.212
7.209
7.152
7.151
7.137
7.136
7.123
7.121
6.492
6.475
4.092
4.076
4.072
4.059
4.055
4.039
3.920
3.901
3.885
3.882
3.866
3.757
3.739
3.728
3.711
3.692
3.673
3.664
3.644
2.285
2.283
NAME cc-c161-2
SOLVENT CDCl3
SFO1 500.1330883 MHz
N
O
O
N
3e
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.01
2.01
1.03
1.02
1.00
1.01
1.01
0.99
1.02
1.02
2.02
3.00


163.18
140.12
137.12
136.32
132.46
131.55
130.36
128.86
128.73
127.20
126.74
121.81
120.50
114.98
77.25
77.00
76.75
67.24
54.80
17.33
NAME cc-c161-2-C
SOLVENT CDCl3
SFO1 125.7703643 MHz
N
O
O
N
3e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm