Transition-Metal-Free Synthesis of Phenanthridinones from Biaryl-2-Oxamic Acid under Radical conditions

Ming Yuan[†], Li Chen[†], Junwei Wang[‡], Shenjie Chen[†], Kongchao Wang[†], Yongbo Xue[†], Guangmin Yao[†], Zengwei Luo,*[†] and Yonghui Zhang*[†]

Hubei Key Laboratory of Natural Medicinal Chemistry and Resource Evaluation, School of Pharmacy, Tongji Medical College, Huazhong University of Science and Technology, Huazhong University of Science and Technology, Wuhan 430030, P. R. China and Institute of Clinical Pharmacy, Union Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022，China

zhangyh@mails.tjmu.edu.cn

luozengwei@hust.edu.cn

(Supporting Information)

CONTENTS:

1. General Information.

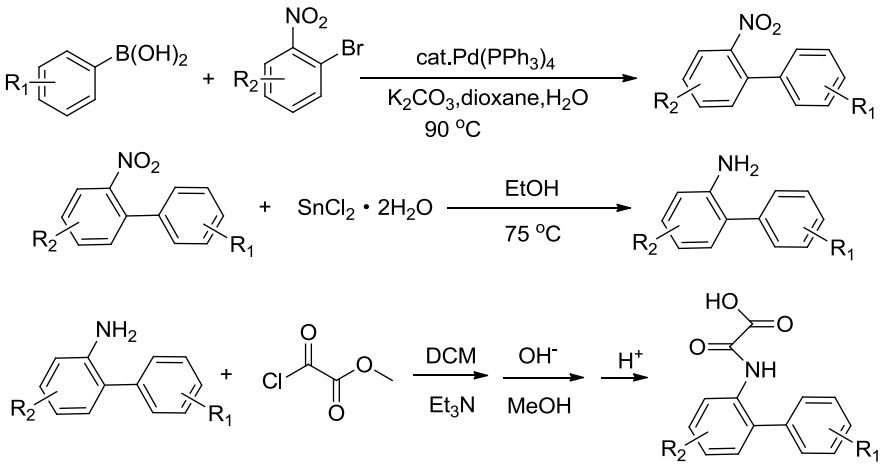
All NMR spectra were recorded on a Bruker 400Hz in DMSO-D_6 or $CDCl_3$, NMR chemical shifts are reported in ppm referenced to the solvent peaks of $CDCl_3$ (7.26 ppm for ^1H and 77.16 (± 0.06) ppm for ^{13}C, respectively) or DMSO-D_6 (2.50 ppm for ^1H and 39.50 ppm for ^{13}C, respectively). High-resolution electrospray ionization mass spectra (HRESIMS) were carried out in the positive ion mode on a Thermo Fisher LC-LTQ-Orbitrap XL spectrometer.

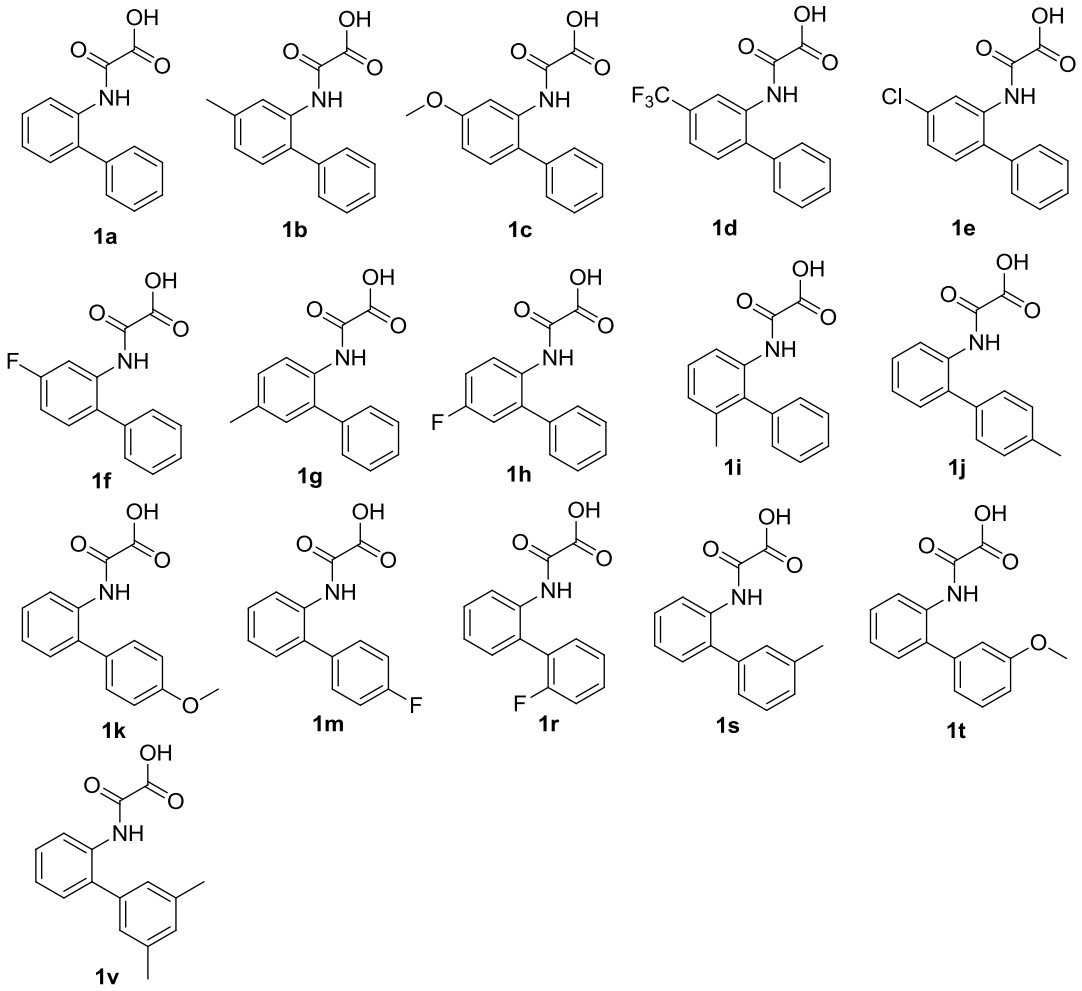
Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Sodium persulfate (98% purity) was purchased from Sigma-Aldrich Co. LLC. Silica gel (200-300 mesh size) was used for column chromatography. TLC analysis of reaction mixtures was performed using silica gel plates. Phenanthridinones **2a**-**2w**, isoindolinone **5** and isoquinolinone **6** were prepared according to following procedures.

2. General Procedure for Synthesis of Phenanthridinones:

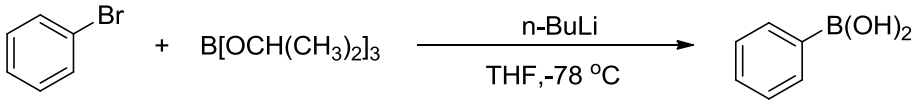
2.1 General Procedure for Synthesis of Biphenyl-2-oxamic Acid

Method A:

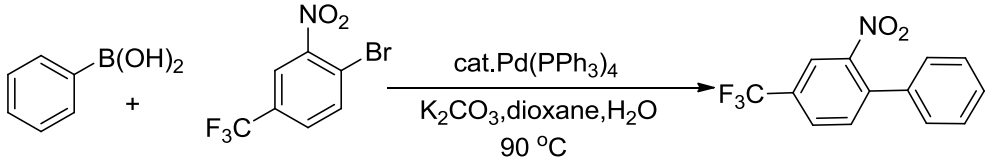




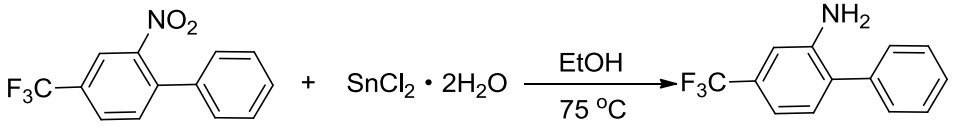
Representative Procedure for Method A above: Synthesis of 1d.



To a solution of bromobenzene (2.24 g, 14.28 mmol, 1.0 equiv) in THF (40 mL) was added n-BuLi (2.5M in hexane, 6.28 mL, 15.71 mmol, 1.1 equiv) at -78 ºC under nitrogen. After the mixture was stirred for 15 min at -78 ºC, triisopropyl borate (4.97 mL, 21.43 mmol, 1.5 equiv) was added in one portion. Then, the mixture was warmed to 25 ºC and was stirred for 20 min, and quenched with HCl solution. After that, THF was removed under vacuum and the residual solution was extracted with EtOAc, dried (Na_2SO_4) and evaporated to obtain the crude phenylboronic acid that was used without further purification.[1]

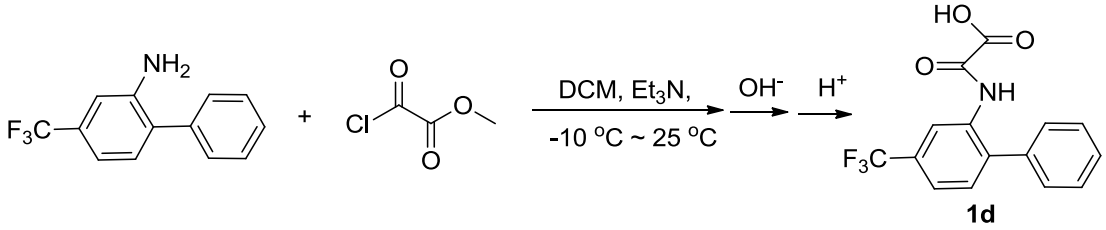


To 30 mL of a solution (v:v = 2:1, Dioxane/H_2O) containing 1-bromo-2-nitro-4-(trifluoromethyl)benzene (1.13 mL, 7.41 mmol, 1.0 equiv), and K_2CO_3 (2.04 g, 14.82 mmol, 2.0 equiv) were added phenylboronic acid (1.08 g, 8.89 mmol, 1.2 equiv) and the reaction mixture was stirred for 2 min. $Pd(PPh_3)_4$ (428 mg, 0.37 mmol, 0.05 equiv) was then added and the flask was flushed with Ar, sealed and allowed to stir at 90 ºC for 12 h. The reaction mixture was evaporated and extracted with ethyl ether. The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield crude product, which was purified by flash chromatography on silica gel using petroleum ether as eluent affording 2-nitro-4-(trifluoromethyl)-1,1'-biphenyl (1.78 g, 76.2%).[2-4]



To 40 mL of a EtOH solution containing 2-nitro-4-(trifluoromethyl)-1,1'-biphenyl (1.5 g, 5.62 mmol, 1.0 equiv) was added stannous chloride dehydrate (6.35 g, 28.09 mmol, 5.0 equiv) and the reaction mixture was stirred at 75 ºC for 5 h. The reaction mixture was evaporated and extracted with ethyl ether and NaOH solution. The resulted suspension was then filtered with Celite. The filter cake was washed with ethyl ether while the filtrate was extracted with ethyl ether. The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the

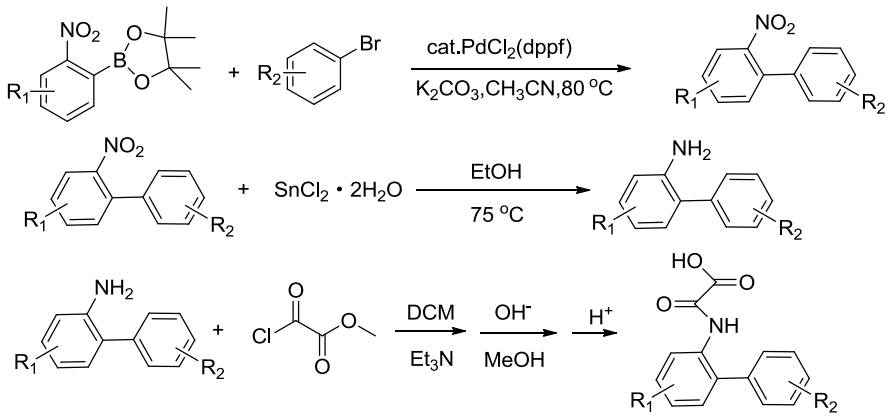
crude product, which was purified by flash chromatography on silica gel using petroleum ether as eluent affording 4-(trifluoromethyl)-[1,1'-biphenyl]-2-amine (1.06 g, 79.6%).[5]

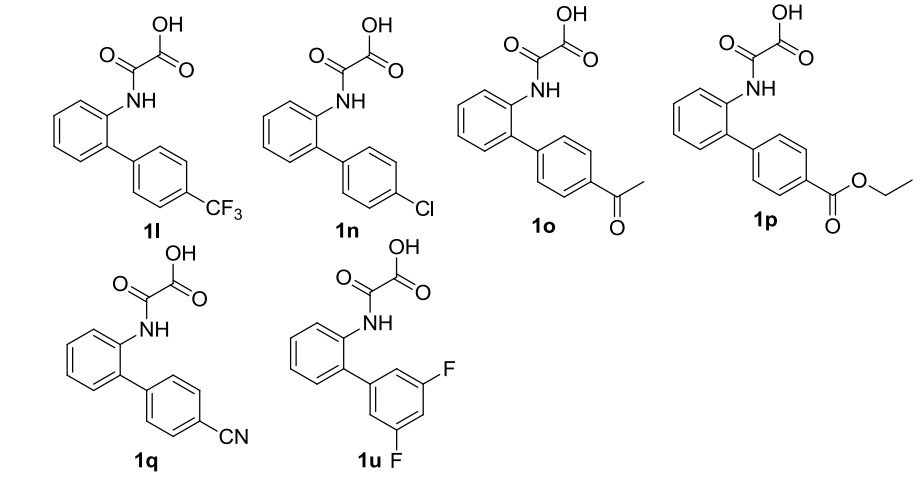


1d

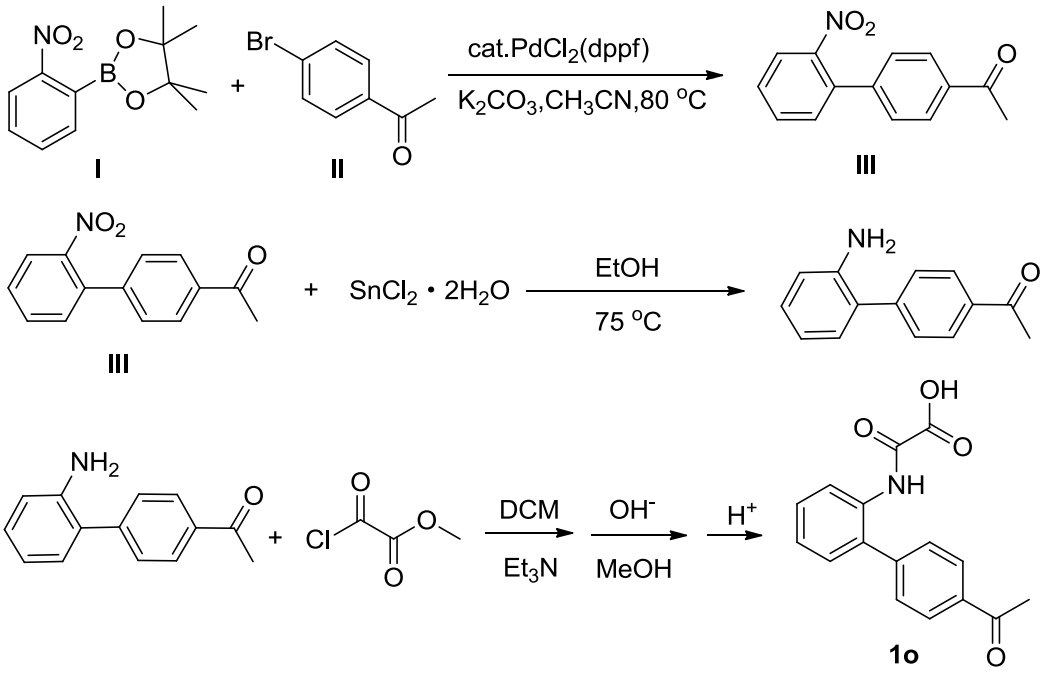
To 10 mL of a CH_2Cl_2 solution containing 4-(trifluoromethyl)-[1,1'-biphenyl]-2-amine (1.07 g, 4.51 mmol, 1.0 equiv) was added TEA (3 mL). The three-necked bottle was purged with Ar and followed by chloroglyoxylic acid methyl ester (0.49 mL, 5.42 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) at -10 ºC dropwise. After addition, the solution was warmed to 25 ºC and stirred for 1 h. The mixture was washed successively with 10% HCl, extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrate to syrup. The residue was dissolved in MeOH and stirred with NaOH solution for 30 min at 25 ºC. After that, the suspension was neutralized with HCl solution, and then extracted with ethyl ether. The combined ether layers were dried (Na_2SO_4) and the solvent was then evaporated to give **1d** (1.05g, 75.3%). **1a, 1b, 1c, 1e, 1f, 1g, 1h, 1i, 1j, 1k, 1m, 1r, 1s, 1t** and **1u** were also produced according to this method.

Method B:





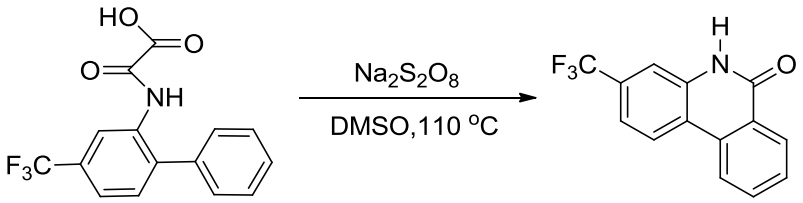
Representative Procedure for Method B above: Synthesis of 1o.



To a solution of compound **I** (1.03g, 4.15 mmol) and **II** (0.82g, 4.15 mmol) in 40 ml of CH_3CN was added 1.72 g (12.45 mmol) of K_2CO_3 followed by 0.15 g (0.21 mmol) $PdCl_2$(dppf) under Ar with stirring. The mixture was refluxed for several hours

until the material disappeared. The reaction mixture was cooled to room temperature. The CH_3CN was removed by rotary evaporation. The residue was poured into water and extracted with EA. The organic layer was dried with Na_2SO_4, filtered and the solvent was removed by rotary evaporation. The product was isolated by flash chromatography on silica gel using PE as eluent affording **III** (0.72 g, 72.1%).[4] Compound **III** was then treated with the same reduction and acidification procedure as depicted in **Method A** providing target compound **1o**. **1l**, **1n, 1p, 1q** and **1u** were also produced according to this method.

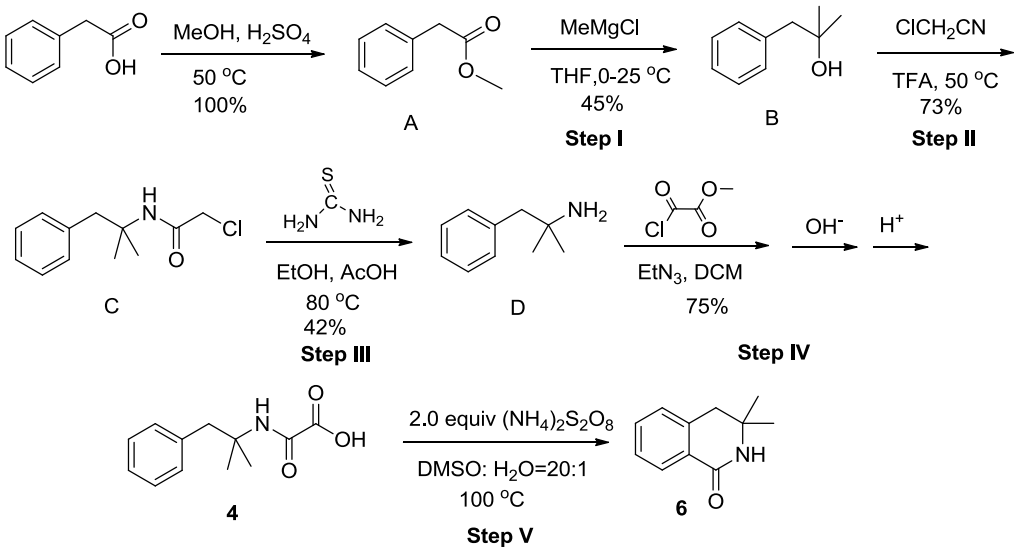
2.2 Typical Procedure for Synthesis of the Phenanthridinnes (2d for instance)

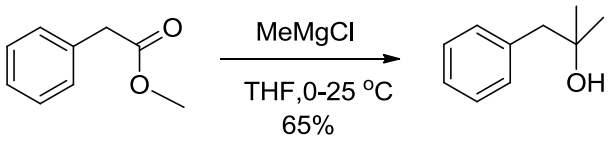


1d **2d**

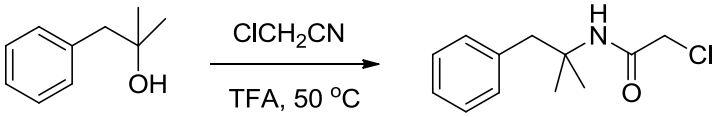
To a 50 mL flask was added $Na_2S_2O_8$ (308 mg, 1.30 mmol, 2.0 equiv), **1d** (200 mg, 0.65 mmol, 1 equiv) and DMSO (20.0 mL). The mixture was stirred at 110 ºC for 36 h. After completion of reaction, reaction mixture was poured over water (120 mL), extracted with ethyl acetate (30 mL × 3), dried over Na_2SO_4, and evaporated under vacuum on rotary evaporator. Obtained crude product was purified by column chromatography on silica gel using PE-EtOAc (10: 1) to give **2d** (130 mg, 76.4%).

3. Synthesis of Isoindolinone and Isoquinolinone



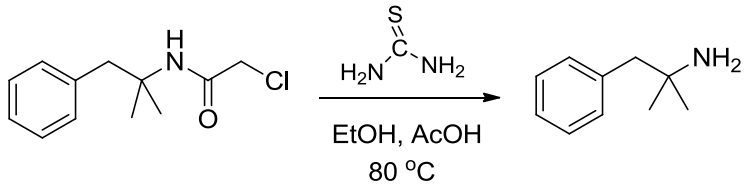


Methylmagnesium chloride (3.0 M solution in THF, 26.6 mL, 80.0 mmol) was added to a solution of methyl 2-phenylacetate (3.0 g, 20.0 mmol) in THF (30 mL) at 0 °C and stirred at room temperature for 2 h. Saturated aqueous NH_4Cl (10 mL) was added to the reaction mixture at 0 °C and the aqueous phase was extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by silica gel column chromatography (petroleum ether) to give 2-methyl-1-phenylpropan-2-ol (colourless oil, 1.3 g, 43.3%).[6]

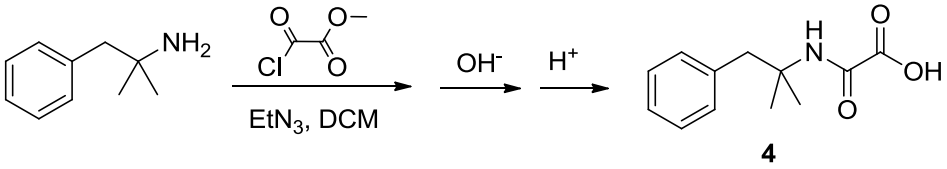


To a stirred solution of the above obtained alcohol (1.3 g, 8.6 mmol) in trifluoroacetic acid (20 mL) in a 50 mL three-necked round bottom flask was added 2-chloroethanenitrile (1.3g, 17.3mmol). The resulting solution was stirred at 50 °C for 9 h to complete the reaction. Cold aqueous $KHCO_3$ solution was poured into the reaction mixture to neutralize the acid. The solution was then extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by silica gel column chromatography using PE-EtOAc (10:1) as eluent to give

2-chloro-N-(2-methyl-1-phenylpropan-2-yl)acetamide (colourless oil, 1.5 g, 77.3%).[7]

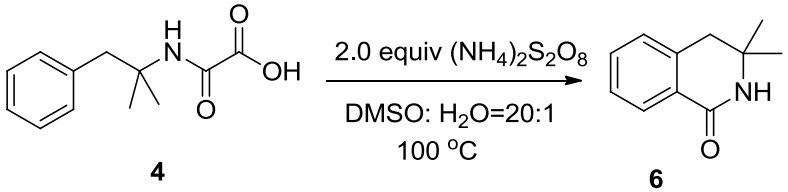


To a solution of the above obtained acetamide (1.5 g, 6.6 mmol) and thiourea (0.6 g, 7.88 mmol) in 10 mL of ethanol was added 1.5 mL of acetic acid. The reaction mixture was stirred and refluxed for 10 h. After completion of reaction, the mixture was filtered and the filter was washed with EA for three times. The washings were combined with the filtrate and aqueous $NaHCO_3$ was used to basify the combined solution. The basic solution was extracted successively with ethyl acetate (20 mL × 3). The combined organic layer was dried over Na_2SO_4 and concentrated to provide the crude product 2-methyl-1-phenylpropan-2-amine (yellow oil, 0.54 g) that was used without further purification.



4

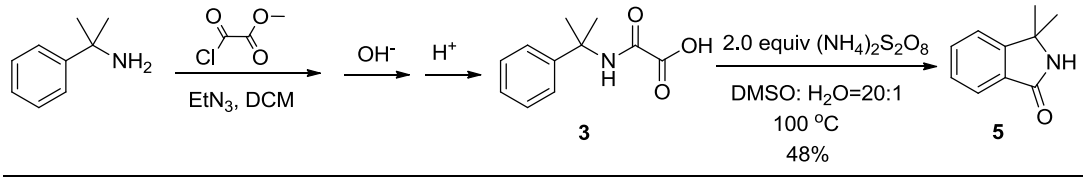
To 5 mL of a CH_2Cl_2 solution containing the above obtained crude product amine (0.2 g) was added TEA (0.37 mL). The three-necked bottle was purged with Ar and followed by chloroglyoxylic acid methyl ester (0.18 mL, 5.42 mmol) at -10 ºC dropwise. After addition, the solution was warmed to 25 ºC and stirred for 1 h. The mixture was washed successively with 10% HCl, extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrate to syrup. The residue was dissolved in MeOH and stirred with NaOH solution for 30 min at 25 ºC. After that, the suspension was neutralized with HCl solution, and then extracted with ethyl ether. The combined ether layers were dried (Na_2SO_4) and the solvent was then evaporated to give product **4** (pale yellow oil, 220 mg, 75.2%).



4 **6**

To a 50 mL flask was added $(NH_4)_2S_2O_8$ (412 mg, 1.81 mmol, 2.0 equiv), compound **4** (200 mg, 0.95 mmol, 1 equiv), DMSO (20 mL) and H_2O (1mL). The

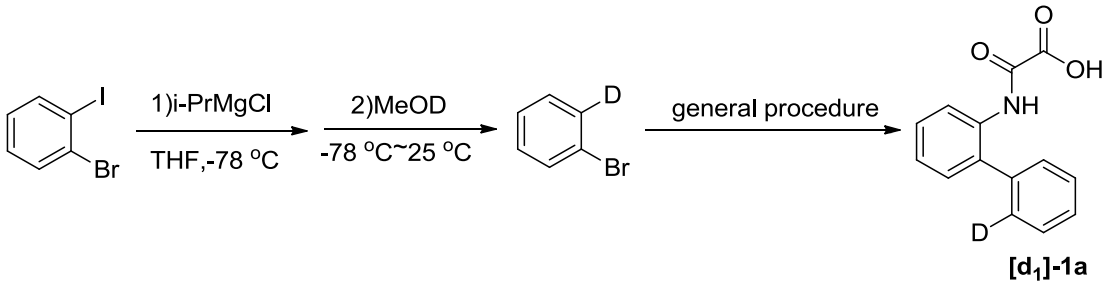
mixture was stirred at 100 ºC for 36 h. After completion of reaction, reaction mixture was poured over water (120 mL), extracted with ethyl acetate (30 mL × 3), dried over Na_2SO_4, and evaporated under vacuum on rotary evaporator. Obtained crude product was purified by column chromatography on silica gel using PE-EtOAc (5: 1) to give **6** (70 mg, 42.2%).



With 2-phenylpropan-2-amine as the starting material**, 3** and **5** were also produced according to the above mentioned method.

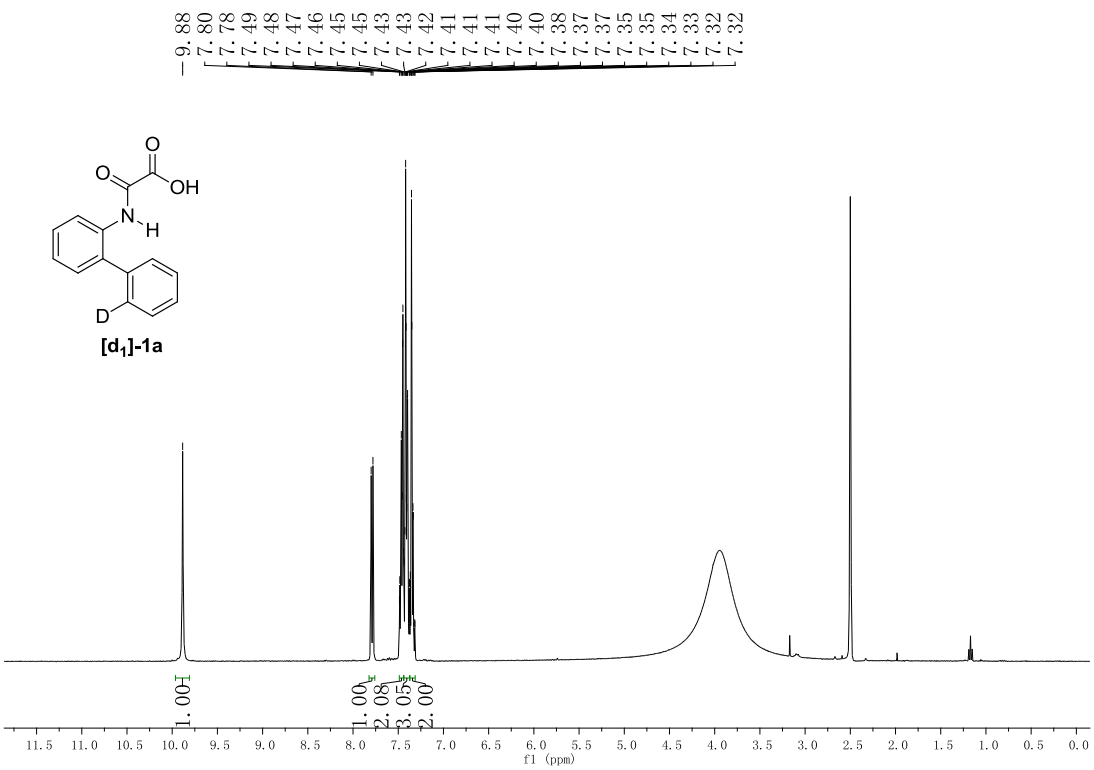
4. Mechanistic Studies

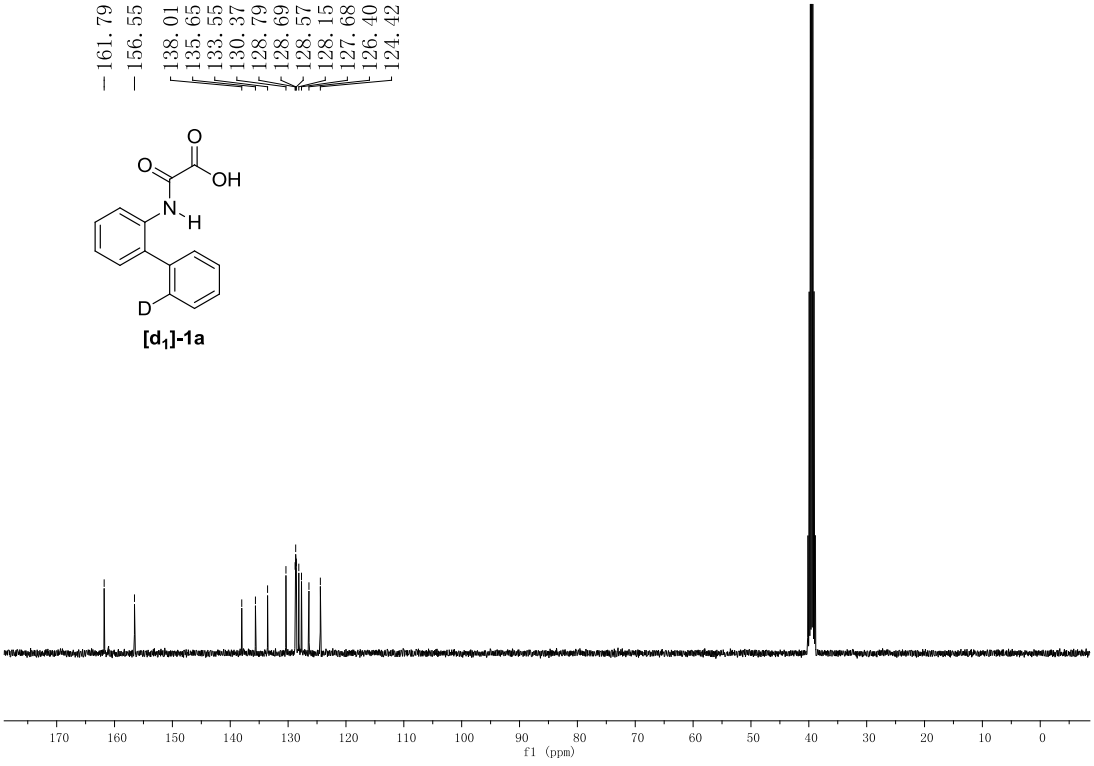
4.1 Synthesis of Compound [d_1]-1a



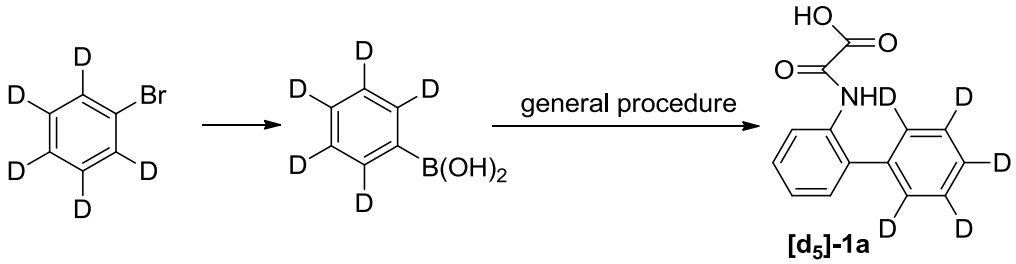
[d_1]-1a

To a solution of 1-bromo-2-iodobenzene (6 g, 21.2 mmol) in a mixture of THF and Et_2O (100 mL, 1:1) at -78 °C was added drop-wise isopropyl magnesium chloride (1 M in THF, 22.3 mL, 22.3 mmol). The mixture was stirred at that temperature for 2 h and then CD_3OD (2.7 mL, 66.3 mmol) was added. The solution was slowly warmed to room temperature. Aqueous HCl (10% aq., 120 mL) was added and the resulting mixture was stirred for 30 minutes at room temperature. The aqueous layer was extracted with Et_2O. The pure 2-deuterio bromobenzene was obtained by distillation.[8] With 2-deuterio bromobenzene as a starting material, through the general procedure mentioned for **1d**, the desired product **[d_1]-1a** was finally obtained. More than 98% deuterium incorporation was observed in ^{1}H-NMR.

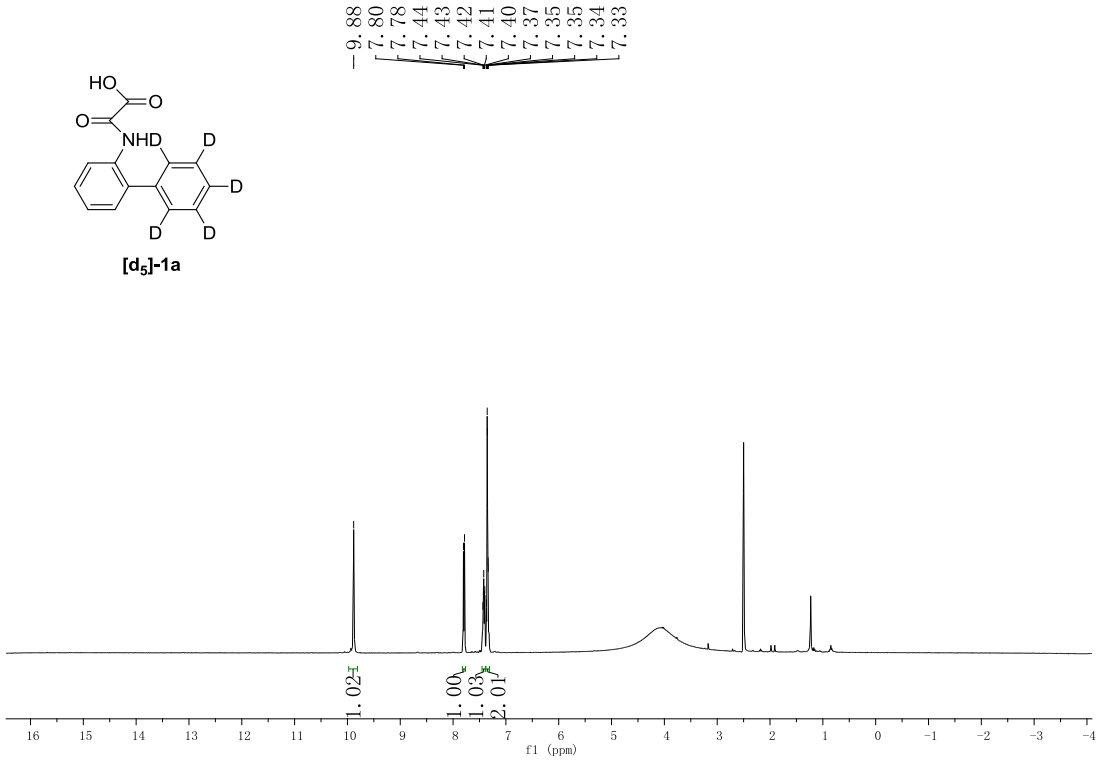




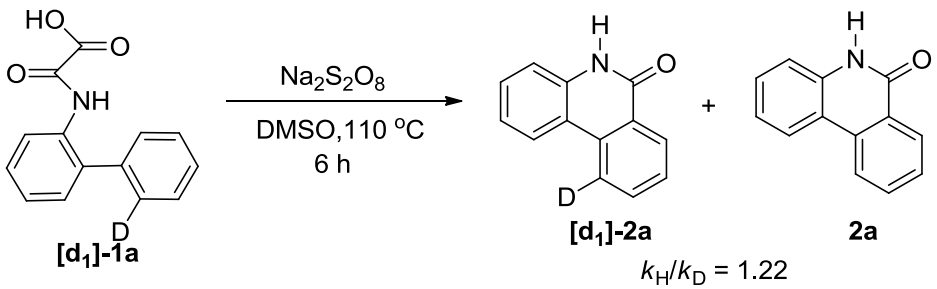
4.2 Synthesis of Compound [d_5]-1a



With D_5-bromobenzene as a starting material, through the general procedure mentioned above, the desired product [**d_5]-1a** was finally obtained. More than 98% deuterium incorporation was observed in ^{1}H-NMR.

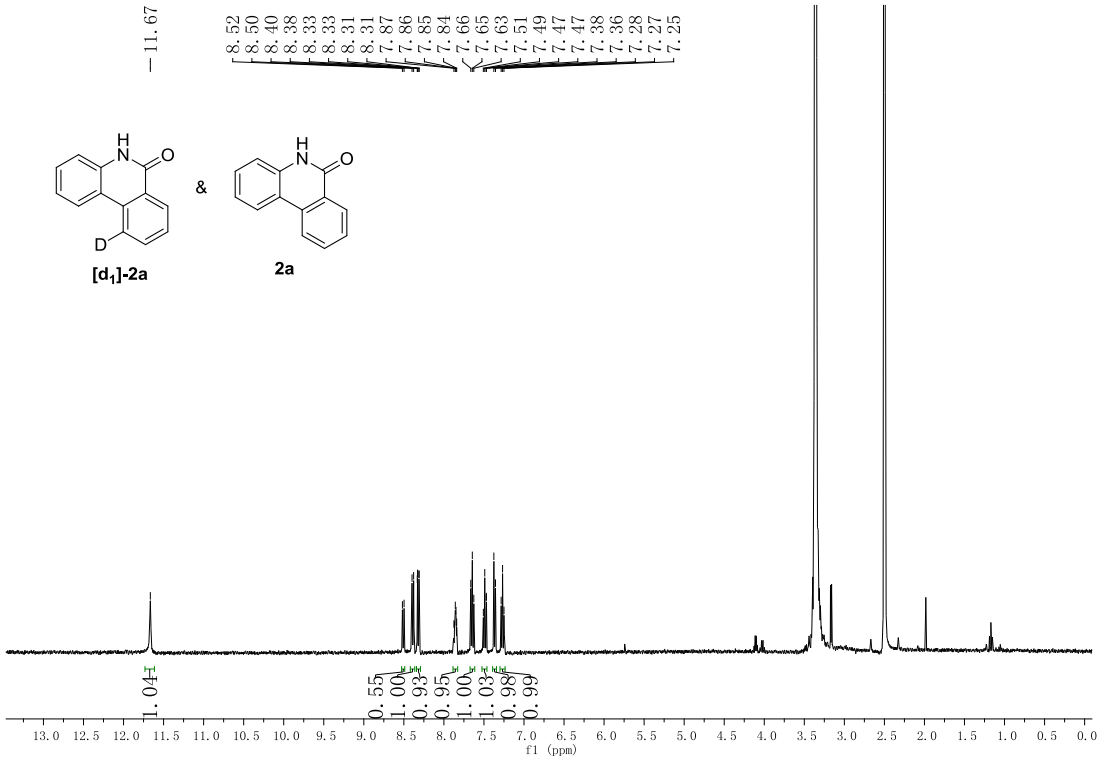


4.3 Intramolecular Kinetic Isotope Effect (KIE) of [d_1]-1a:

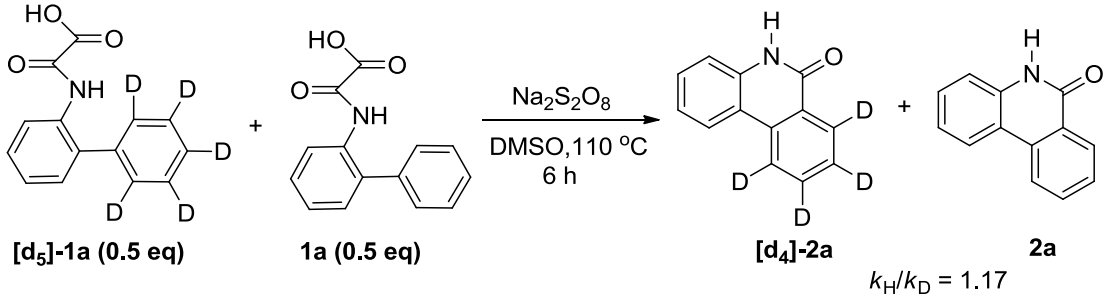


To a 50 mL flask was added $Na_2S_2O_8$ (395 mg, 1.66 mmol, 2.0 equiv), **[d_1]-1a** (200 mg, 0.83 mmol, 1.0 equiv) and DMSO (20 mL). The mixture was heated at 110 °C and stirred for 6 h. At the end of the reaction, the mixture was poured over

water (120 mL), extracted with ethyl acetate (3 × 30 mL) subsequently, dried over Na_2SO_4, and evaporated under vacuum on rotary evaporator. Obtained crude product was purified by column chromatography on silica gel using PE-EtOAc (10:1) as eluent to afford **2a** and **[d_1]-2a** product mixture (60 mg, 37%). The intramolecular kinetic isotopic effect k_H/k_D = 1.22 was determined by ^{1}H-NMR (integration of a doublet at δ 8.39 for 1 H of **2a** and integration of a doublet at δ 8.51 for 1 H of **2a** and **[d_1]-2a** to give intermolecular KIE k_H/k_D = 1.22).

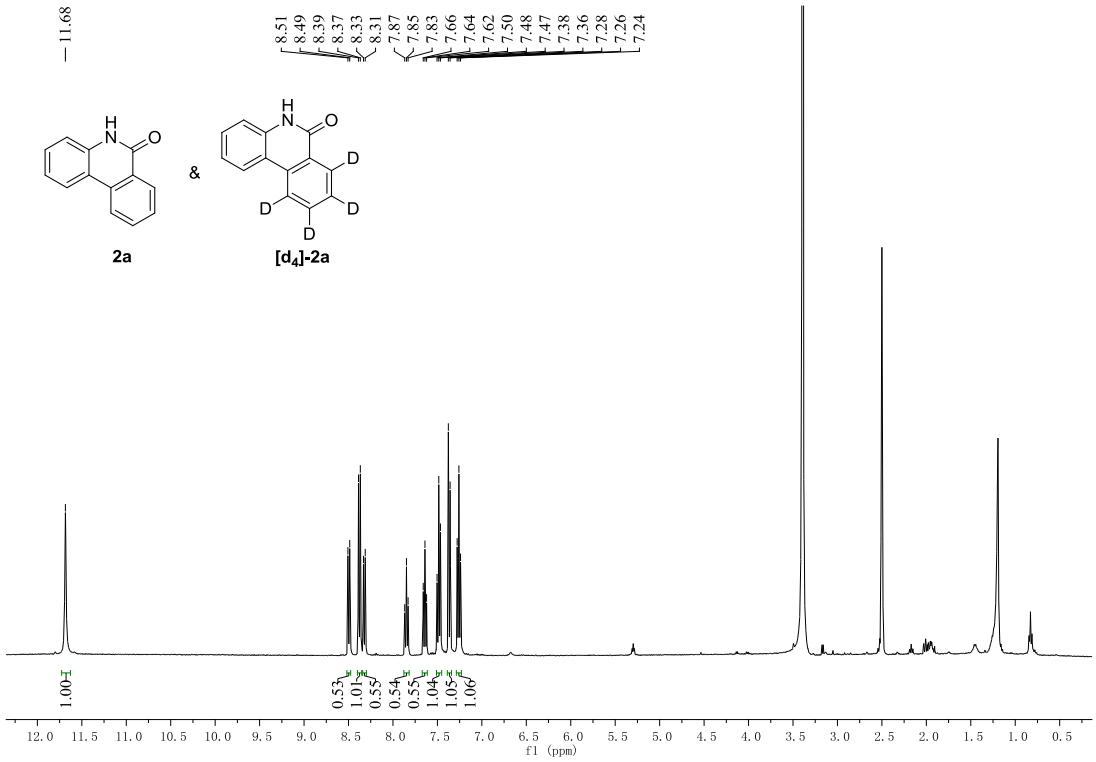


4.4 The Kinetic Isotope Effect (KIE) of Intermolecular Competition Experiments between 1a and [d_5]-1a:

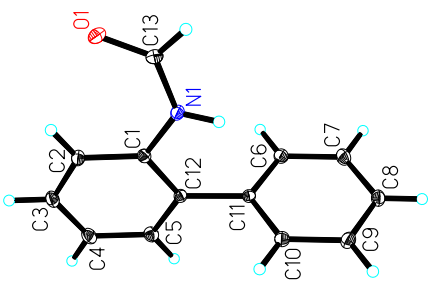


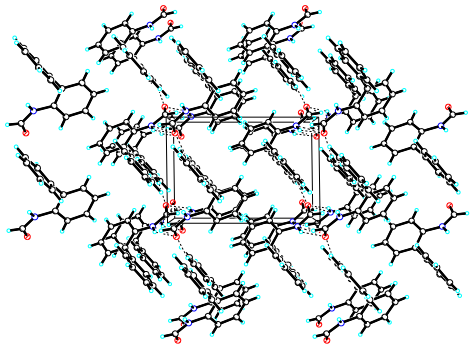
To a 50 mL flask was added $Na_2S_2O_8$ (400 mg, 1.68 mmol, 2.0 equiv), **1a** (100mg, 0.42 mmol, 0.5 equiv), [**d_5]-1a** (102 mg, 0.42 mmol, 0.5 equiv) and DMSO (20 mL). The formed mixture was heated at 110 °C for 6 h. At the end of the reaction, the

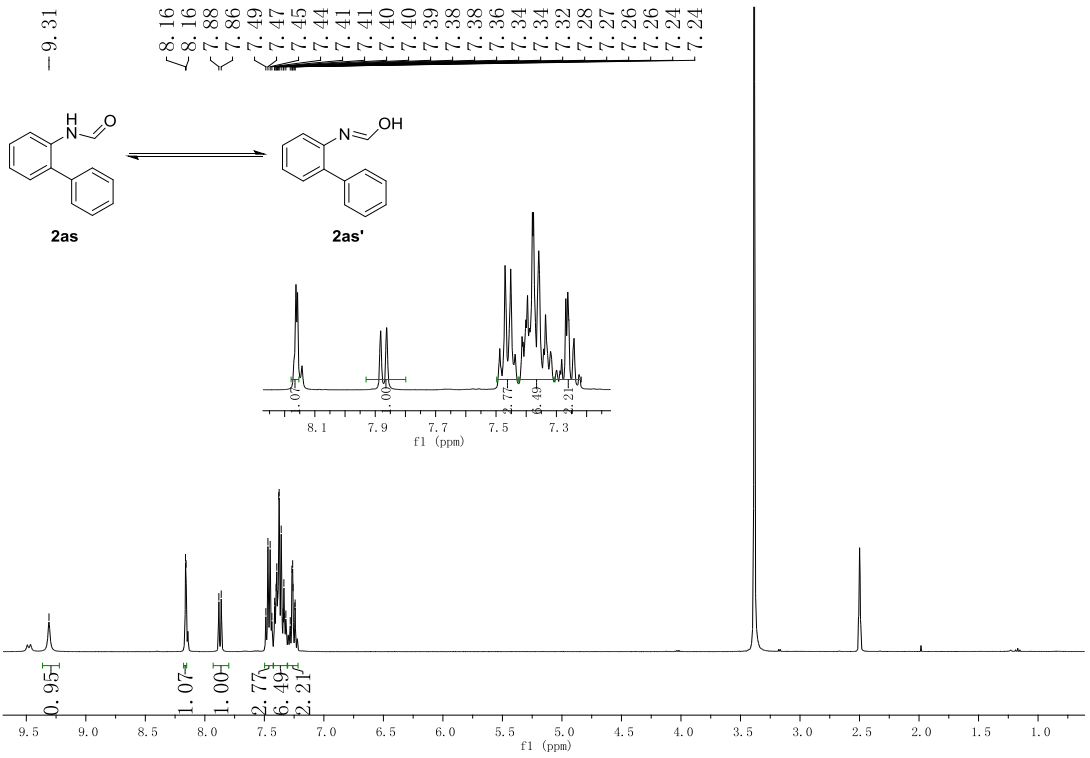
mixture was poured over water (120 mL), extracted with ethyl acetate (3 × 30 mL) subsequently, dried over Na_2SO_4, and evaporated under vacuo on rotary evaporator. Obtained crude product was purified by column chromatography on silica gel using PE-EtOAc (10:1) as eluent to afford **2a** and **[d_4]-2a** product mixture (51 mg, 30%). The intermolecular kinetic isotopic effect k_H/k_D = 1.17 was determined by ^{1}H-NMR.

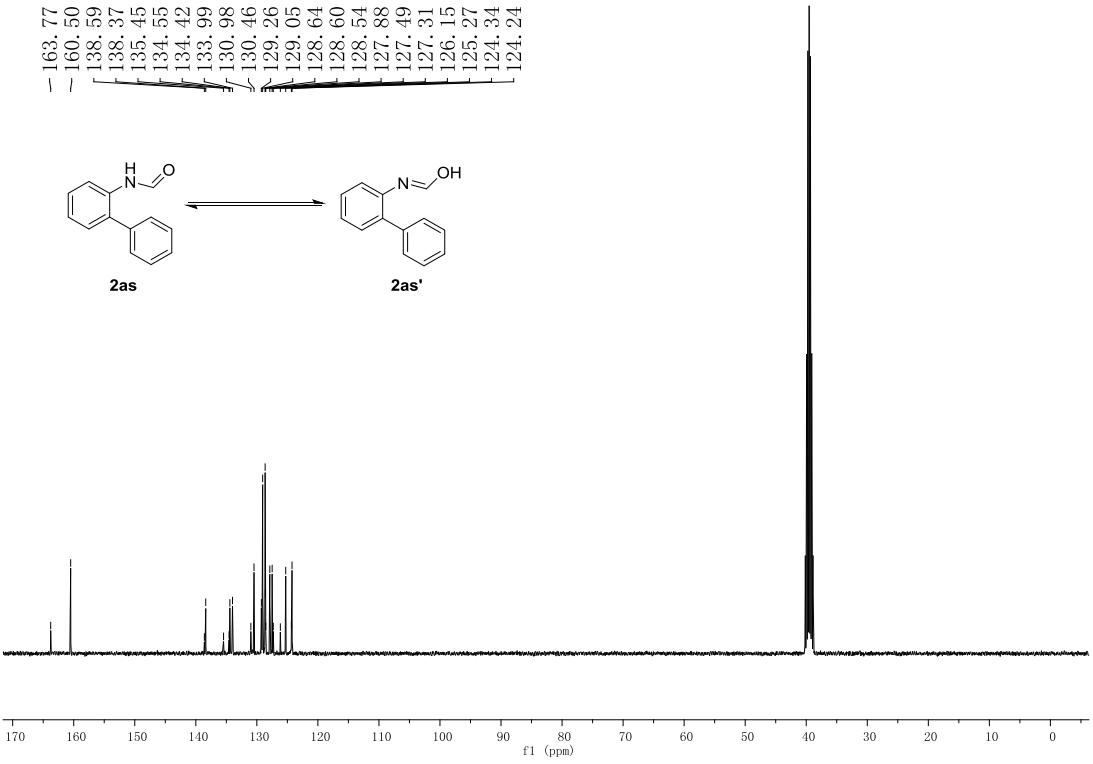


4.5 Crystal Structure, ^{1}H NMR and ^{13}C NMR of Compound 2as






9.31
8.16
8.16
7.88
7.86
7.49
7.47
7.45
7.44
7.41
7.41
7.40
7.40
7.39
7.38
7.38
7.36
7.34
7.34
7.32
7.28
7.27
7.26
7.24
7.24
2as
2as'
0.95
1.07
1.00
2.77
6.49
2.21
f1 (ppm)


163.77
160.50
138.59
138.37
135.45
134.55
134.42
133.99
130.98
130.46
129.26
129.05
128.64
128.60
128.54
127.88
127.49
127.31
126.15
125.27
124.34
124.24
2as
2as'
f1 (ppm)

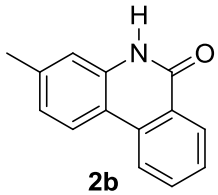
5. Experimental Procedures and Characterization of Products

Phenanthridin-6(5H)-one (**2a)**

2a

The reaction of **1a** (200 mg, 0.829 mmol), $Na_2S_2O_8$ (395 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2a** (127 mg, 79.4%) with standard workup and purification. **2a** (yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.54 – 8.44 (m, 1H), 8.41 – 8.35 (m, 1H), 8.34 – 8.28 (m, 1H), 7.88 – 7.80 (m, 1H), 7.68 – 7.60 (m, 1H), 7.52 – 7.44 (m, 1H), 7.40 – 7.33 (m, 1H), 7.29 – 7.22 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.83, 136.56, 134.26, 132.81, 129.58, 127.93, 127.48, 125.69, 123.26, 122.62, 122.28, 117.56, 116.12. HRMS m/z (ESI) calcd for $C_{13}H_{10}NO$ $(M + H)^+$ 196.0762, found 196.0739.

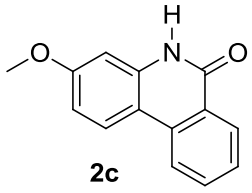
3-methylphenanthridin-6(5H)-one (**2b**)



2b

The reaction of **1b** (200 mg, 0.784 mmol), $Na_2S_2O_8$ (373 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2b** (100 mg, 61.3%) with standard workup and purification. **2b** (white solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H), 8.44 (d, *J* = 8.1 Hz, 1H), 8.33 – 8.23 (m, 2H), 7.82 (td, *J* = 8.2, 4.0 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.15 (s, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.42, 139.85, 137.04, 134.82, 133.19, 127.88, 125.73, 123.98, 123.62, 122.81, 116.42, 115.68, 21.56. HRMS m/z (ESI) calcd for $C_{14}H_{12}NO$ $(M + H)^+$ 210.0913, found 210.0894.

3-methoxyphenanthridin-6(5H)-one (**2c**)

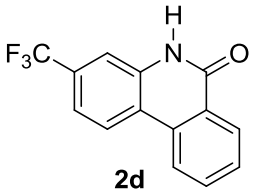


2c

The reaction of **1c** (200 mg, 0.738 mmol), $Na_2S_2O_8$ (351 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2c** (141 mg, 85.3%) with standard workup and purification. **2c** (yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 8.35 (d, *J* = 8.1 Hz, 1H), 8.29 – 8.23 (m, 2H), 7.78 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.57 – 7.51 (m, 1H), 6.89 (d, *J* = 2.5 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.14, 160.29, 138.07, 134.52, 132.74, 127.42, 126.69, 124.72, 124.42, 121.99, 111.11, 110.12, 99.52, 55.27. HRMS m/z (ESI) calcd for

$C_{14}H_{12}NO_2$ $(M + H)^+$ 226.0862, found 226.0841.

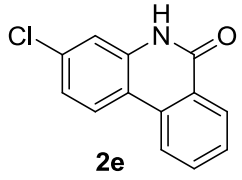
3-(trifluoromethyl)phenanthridin-6(5H)-one (**2d**)



2d

The reaction of **1d** (200 mg, 0.647 mmol), $Na_2S_2O_8$ (308 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2d** (130 mg, 76.4%) with standard workup and purification. **2d** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.58 (dd, *J* = 11.5, 8.4 Hz, 2H), 8.34 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.93 – 7.87 (m, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.67 (s, 1H), 7.56 – 7.51 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.68, 136.65, 133.13, 132.99, 129.46, 129.22, 129.15, 127.55, 126.64 (q, J = 272.5 Hz), 126.29, 124.69, 123.33, 120.79, 118.13 (q, J = 3.4 Hz), 112.78 (q, J = 4.2Hz). HRMS m/z (ESI) calcd for $C_{14}H_9F_3NO$ $(M + H)^+$ 264.0605, found 264.0630.

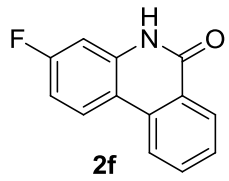
3-chlorophenanthridin-6(5H)-one (**2e**)



2e

The reaction of **1e** (200 mg, 0.726 mmol), $Na_2S_2O_8$ (345 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2e** (156 mg, 93.4%) with standard workup and purification. **2e** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 8.46 (d, *J* = 8.2 Hz, 1H), 8.38 (d, *J* = 8.7 Hz, 1H), 8.30 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.88 – 7.82 (m, 1H), 7.68 – 7.63 (m, 1H), 7.38 (d, *J* = 2.1 Hz, 1H), 7.27 (dd, *J* = 8.6, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.81, 137.64, 133.72, 133.52, 133.05, 128.32, 127.51, 125.49, 125.27, 122.80, 122.16, 116.56, 115.31. HRMS m/z (ESI) calcd for $C_{13}H_9ClNO$ $(M + H)^+$ 230.0367, found 230.0345.

3-fluorophenanthridin-6(5H)-one (**2f**)

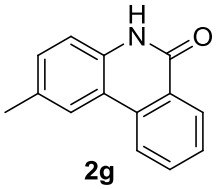


2f

The reaction of **1f** (200 mg, 0.772 mmol), $Na_2S_2O_8$ (367 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2f** (95 mg, 57.9%) with standard workup and purification. **2f** (white solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 8.43 (t, *J* = 8.7 Hz, 2H), 8.29 (d, *J* = 7.9 Hz, 1H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.14 – 7.07 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.44 (d, *J* = 245.5 Hz), 160.95,

138.10 (d, *J* = 11.7 Hz), 133.76, 132.97, 127.77, 127.46, 125.81 (d, *J* = 10.1 Hz), 125.01, 122.60, 114.45, 109.83 (d, *J* = 22.6 Hz), 102.04 (d, *J* = 25.3 Hz). HRMS m/z (ESI) calcd for $C_{13}H_9FNO$ $(M + H)^+$ 214.0662, found 214.0642.

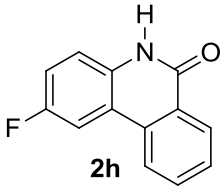
2-methylphenanthridin-6(5H)-one (**2g**)



2g

The reaction of **1g** (200 mg, 0.784 mmol), $Na_2S_2O_8$ (373 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2g** (117 mg, 72.3%) with standard workup and purification. **2g** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1H), 8.47 (d, *J* = 8.1 Hz, 1H), 8.31 (dd, *J* = 7.9, 1.1 Hz, 1H), 8.18 (s, 1H), 7.86 – 7.80 (m, 1H), 7.65 – 7.59 (m, 1H), 7.30 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.67, 134.39, 134.20, 132.65, 131.22, 130.55, 127.73, 127.46, 125.73, 123.02, 122.52, 117.38, 115.99, 20.69. HRMS m/z (ESI) calcd for $C_{14}H_{12}NO$ $(M + H)^+$ 210.0913, found 210.0894.

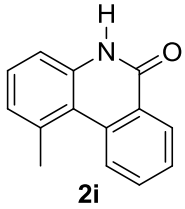
2-fluorophenanthridin-6(5H)-one (**2h**)



2h

The reaction of **1h** (200 mg, 0.772 mmol), $Na_2S_2O_8$ (367 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2h** (110 mg, 67.1%) with standard workup and purification. **2h** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 8.50 (d, *J* = 8.1 Hz, 1H), 8.32 (dd, *J* = 7.9, 0.8 Hz, 1H), 8.27 – 8.21 (m, 1H), 7.89 – 7.81 (m, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.41 – 7.32 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.51, 157.81 (d, *J* = 237.5 Hz), 133.55 (d, *J* = 3.0 Hz), 133.15 (d, *J* = 1.2 Hz), 132.79, 128.54, 127.46, 125.83, 123.17, 118.83 (d, *J* = 8.4 Hz), 117.74 (d, *J* = 8.5 Hz), 117.14 (d, *J* = 24.1 Hz), 109.13 (d, *J* = 24.0 Hz). HRMS m/z (ESI) calcd for $C_{13}H_9FNO$ $(M + H)^+$ 214.0662, found 214.0642.

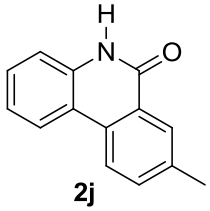
1-methylphenanthridin-6(5H)-one (**2i**)



2i

The reaction of **1i** (200 mg, 0.784 mmol), $Na_2S_2O_8$ (373 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2i** (127 mg, 77.9%) with standard workup and purification. **2i** (yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (s, 1H), 8.56 (d, *J* = 8.4 Hz, 1H), 8.42 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 2.88 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.51, 136.66, 134.87, 134.38, 131.22, 127.59, 126.63, 126.18, 125.81, 125.77, 125.59, 115.89, 113.79, 24.80. HRMS m/z (ESI) calcd for $C_{14}H_{12}NO$ $(M + H)^+$ 210.0913, found 210.0894.

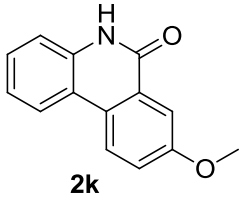
8-methylphenanthridin-6(5H)-one (**2j**)



2j

The reaction of **1j** (200 mg, 0.784 mmol), $Na_2S_2O_8$ (373 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2j** (134 mg, 81.7%) with standard workup and purification. **2j** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H), 8.34 (dd, *J* = 19.8, 8.1 Hz, 2H), 8.12 (s, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.81, 137.58, 136.20, 133.93, 131.82, 129.06, 127.21, 125.60, 122.95, 122.60, 122.19, 117.68, 116.02, 20.93. HRMS m/z (ESI) calcd for $C_{13}H_9FNO$ $(M + H)^+$ 214.0662, found 214.0642. HRMS m/z (ESI) calcd for $C_{14}H_{12}NO$ $(M + H)^+$ 210.0913, found 210.0894.

8-methoxyphenanthridin-6(5H)-one (**2k**)

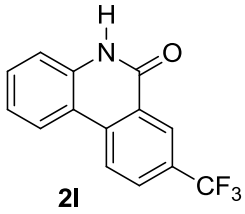


2k

The reaction of **1k** (200 mg, 0.738 mmol), $Na_2S_2O_8$ (351 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2k** (122 mg, 73.6%) with standard workup and purification. **2k** (white solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 8.42 (d, *J* = 9.0 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 2.8 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.26 – 7.20 (m, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.65, 159.07, 135.50, 128.52, 127.72, 127.13, 124.62, 122.68, 122.38, 121.69, 117.78, 116.05, 108.75, 55.51. HRMS m/z (ESI) calcd for

$C_{14}H_{12}NO_2$ $(M + H)^+$ 226.0862, found 226.0841.

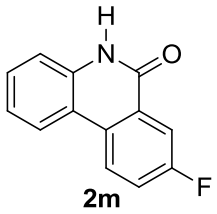
8-(trifluoromethyl)phenanthridin-6(5H)-one (**2l**)



2l

The reaction of **1l** (200 mg, 0.647 mmol), $Na_2S_2O_8$ (308 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2l** (106 mg, 63.1%) with standard workup and purification. **2l** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.71 (d, *J* = 8.5 Hz, 1H), 8.54 (s, 1H), 8.43 (d, *J* = 8.1 Hz, 1H), 8.13 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.93, 137.57, 137.26, 130.92, 128.63 (q, *J* = 3.2 Hz), 127.75, 126.69 (q, *J* = 279.2 Hz), 125.82, 124.39 (q, *J* = 4.2 Hz), 124.31, 124.03, 122.64. HRMS m/z (ESI) calcd for $C_{14}H_9F_3NO$ $(M + H)^+$ 264.0605, found 264.0630.

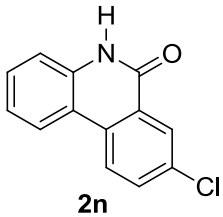
8-fluorophenanthridin-6(5H)-one (**2m**)



2m

The reaction of **1m** (200 mg, 0.772 mmol), $Na_2S_2O_8$ (367 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2m** (95 mg, 57.8%) with standard workup and purification. **2m** (white solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.59 (dd, *J* = 9.0, 5.1 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 7.97 (dd, *J* = 9.3, 2.9 Hz, 1H), 7.73 (td, *J* = 8.7, 2.9 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.30 – 7.24 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.55 (d, *J* = 246.2 Hz), 159.90 (d, *J* = 2.9 Hz), 136.04, 131.07 (d, *J* = 2.5 Hz), 129.47, 127.64 (d, *J* = 7.6 Hz), 125.87 (d, *J* = 8.0 Hz), 123.27, 122.49, 120.96 (d, *J* = 22.9 Hz), 117.06, 116.18, 112.48 (d, *J* = 22.5 Hz). HRMS m/z (ESI) calcd for $C_{13}H_9FNO$ $(M + H)^+$ 214.0662, found 214.0642.

8-chlorophenanthridin-6(5H)-one (**2n**)

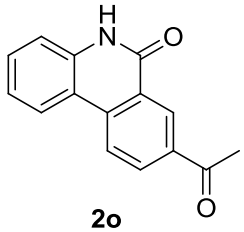


2n

The reaction of **1n** (200 mg, 0.725 mmol), $Na_2S_2O_8$ (345 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2n** (123 mg, 74.2%) with standard workup and purification. **2n** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.52 (d, *J*

= 8.8 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 2.4 Hz, 1H), 7.87 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.54 – 7.47 (m, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.30 – 7.24 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.68, 136.45, 133.07, 132.73, 132.69, 129.96, 127.15, 126.55, 125.15, 123.41, 122.51, 116.85, 116.23. HRMS m/z (ESI) calcd for $C_{13}H_9ClNO$ $(M + H)^+$ 230.0367, found 230.0345.

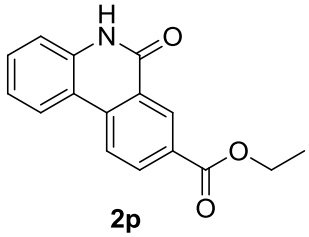
8-acetylphenanthridin-6(5H)-one(**2o**)



2o

The reaction of **1o** (200 mg, 0.707 mmol), $Na_2S_2O_8$ (336 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2o** (70 mg, 42.2%) with standard workup and purification. **2o** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (s, 1H), 9.06 – 8.68 (m, 1H), 8.61 (d, *J* = 8.5 Hz, 1H), 8.43 (d, *J* = 7.5 Hz, 1H), 8.31 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.38 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.33 – 7.26 (m, 1H), 2.70 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.98, 160.51, 137.87, 137.35, 135.54, 131.27, 130.80, 128.04, 125.56, 124.08, 123.25, 122.53, 116.87, 116.29, 26.76. HRMS m/z (ESI) calcd for $C_{15}H_{12}NO_2$ $(M + H)^+$ 238.0862, found 238.0860.

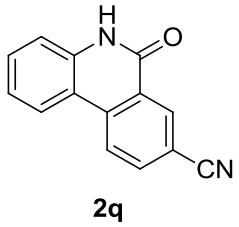
ethyl 6-oxo-5,6-dihydrophenanthridine-8-carboxylate(**2p**)



2p

The reaction of **1p** (170 mg, 0.543 mmol), $Na_2S_2O_8$ (260 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2p** (74 mg, 50.9%) with standard workup and purification. **2p** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (d, *J* = 1.9 Hz, 1H), 8.62 (d, *J* = 8.5 Hz, 1H), 8.42 (d, *J* = 7.8 Hz, 1H), 8.30 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.41 – 7.36 (m, 1H), 7.32 – 7.27 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.00, 160.34, 137.98, 137.34, 132.30, 130.83, 128.81, 125.63, 124.04, 123.37, 122.56, 116.82, 116.33, 61.10, 14.15. HRMS m/z (ESI) calcd for $C_{16}H_{13}NNaO_3$ $(M + Na)^+$ 290.0787, found 290.0783.

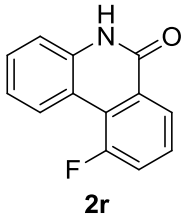
6-oxo-5,6-dihydrophenanthridine-8-carbonitrile(**2q**)



2q

The reaction of **1q** (200 mg, 0.752 mmol), $Na_2S_2O_8$ (357 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2q** (64 mg, 39.4%) with standard workup and purification. **2q** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (d, *J* = 8.5 Hz, 1H), 8.62 (d, *J* = 1.7 Hz, 1H), 8.44 (d, *J* = 7.4 Hz, 1H), 8.22 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.41 – 7.37 (m, 1H), 7.33 – 7.28 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.46, 137.90, 137.50, 134.91, 132.15, 131.34, 126.03, 124.30, 124.23, 122.74, 118.35, 116.43, 110.28. HRMS m/z (ESI) calcd for $C_{14}H_9N_2O$ $(M + H)^+$ 221.0738, found 221.0715.

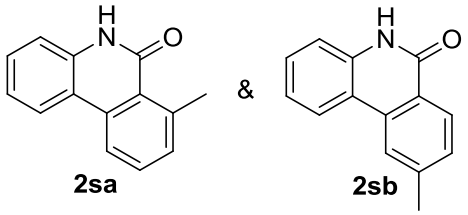
10-fluorophenanthridin-6(5H)-one (**2r**)



2r

The reaction of **1r** (200 mg, 0.772 mmol), $Na_2S_2O_8$ (367 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2r** (101 mg, 62.1 %) with standard workup and purification. **2r** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.48 (d, *J* = 8.1 Hz, 1H), 8.23 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.74 (ddd, *J* = 13.6, 8.0, 1.3 Hz, 1H), 7.66 (td, *J* = 7.9, 5.1 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.28 (t, *J* = 7.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.12, 160.07 (d, *J* = 252.0 Hz), 137.07, 130.32, 129.23 (d, *J* = 9.7 Hz), 128.68, 127.49, 127.26 , 124.40 (d, *J* = 3.2 Hz), 123.16, 120.64 (d, *J* = 23.9 Hz), 116.70. HRMS m/z (ESI) calcd for $C_{13}H_9FNO$ $(M + H)^+$ 214.0662, found 214.0642.

7-methylphenanthridin-6(5H)-one (**2sa**) & 9-methylphenanthridin-6(5H)-one (**2sb**)

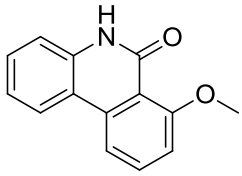


2sa **2sb**

The reaction of **1s** (200 mg, 0.784 mmol), $Na_2S_2O_8$ (373 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2sa** (88 mg, 53.9%) and **2sb** (25 mg, 15.3%) with standard workup and purification, which can be separated easily by column chromatography. **2sa** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6)

δ 11.41 (s, 1H), 8.34 (dd, *J* = 11.4, 8.3 Hz, 2H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 2.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.02, 141.25, 136.69, 135.78, 131.91, 131.28, 129.45, 123.85, 123.50, 121.94, 120.75, 117.73, 115.45, 23.76. HRMS m/z (ESI) calcd for $C_{14}H_{12}NO$ $(M + H)^+$ 210.0913, found 210.0894. **2sb** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 8.36 (d, *J* = 7.9 Hz, 1H), 8.31 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.36 – 7.33 (m, 1H), 7.27 – 7.22 (m, 1H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.85, 143.04, 136.73, 134.28, 129.45, 129.18, 127.50, 123.42, 123.21, 122.51, 122.17, 117.55, 116.09, 21.57. HRMS m/z (ESI) calcd for $C_{14}H_{12}NO$ $(M + H)^+$ 210.0913, found 210.0894.

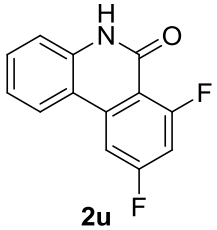
7-methoxyphenanthridin-6(5H)-one (**2t**)



2t

The reaction of **1t** (200 mg, 0.738 mmol), $Na_2S_2O_8$ (351 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2t** (104 mg, 62.9%) with standard workup and purification, which can be separated easily by column chromatography. **2t** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.27 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.72 (t, *J* = 8.2 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.18 (dd, *J* = 10.2, 4.6 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.97, 159.47, 137.11, 137.07, 133.52, 129.70, 123.74, 121.75, 117.13, 115.30, 114.76, 114.33, 110.79, 55.93. HRMS m/z (ESI) calcd for $C_{14}H_{12}NO_2$ $(M + H)^+$ 226.0862, found 226.0841.

7,9-difluorophenanthridin-6(5H)-one (**2u**)

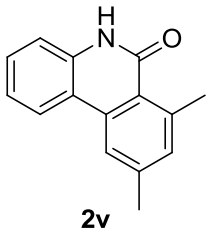


2u

The reaction of **1u** (200 mg, 0.722 mmol), $Na_2S_2O_8$ (341 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2u** (100 mg, 60.2%) with standard workup and purification. **2u** (white solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (s, 1H), 8.35 (d, *J* = 7.9 Hz, 1H), 8.22 (d, *J* = 9.7 Hz, 1H), 7.55 – 7.49 (m, 1H), 7.43 (ddd, *J* = 11.7, 9.2, 2.4 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.26 – 7.21 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.06 – 161.62 (m), 157.80 (d, J = 4.1 Hz), 139.26 – 139.08 (m), 137.13, 131.03,

124.32, 122.37, 116.16 (t, J = 3.2 Hz), 115.92, 111.79 – 111.65 (m), 105.46 – 105.12 (m), 104.51 (t, J = 26.3 Hz). HRMS m/z (ESI) calcd for $C_{13}H_7F_2NNaO$ $(M + Na)^+$ 254.0387, found 254.0385.

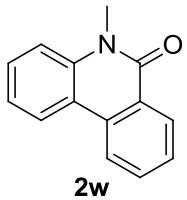
7,9-dimethylphenanthridin-6(5H)-one (**2v**)



2v

The reaction of **1v** (200 mg, 0.742 mmol), $Na_2S_2O_8$ (351 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2v** (88 mg, 53.6%) with standard workup and purification. **2v** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (s, 1H), 8.31 (d, *J* = 7.9 Hz, 1H), 8.17 (s, 1H), 7.46 – 7.39 (m, 1H), 7.29 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.24 – 7.16 (m, 2H), 2.81 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.44, 142.39, 141.51, 137.26, 136.26, 132.95, 129.77, 123.91, 122.27, 121.97, 121.19, 118.13, 115.85, 24.03, 21.69. HRMS m/z (ESI) calcd for $C_{15}H_{14}NO$ $(M + H)^+$ 224.1075, found 224.1053.

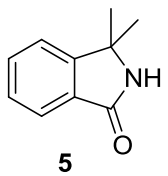
5-ethylphenanthridin-6(5H)-one (**2w**)



2w

The reaction of **1w** (200 mg, 0.781 mmol), $Na_2S_2O_8$ (380 mg, 2.0 equiv) in DMSO (20 mL) under 110 ºC afforded **2w** (58 mg, 35.4%) with standard workup and purification. **2w** (pale yellow solid): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, *J* = 8.2 Hz, 1H), 8.47 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.36 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.83 (ddd, *J* = 8.3, 7.2, 1.5 Hz, 1H), 7.66 – 7.54 (m, 3H), 7.35 (ddd, *J* = 8.2, 6.8, 1.5 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.34, 137.61, 133.17, 132.71, 129.91, 128.11, 128.04, 124.88, 123.52, 122.51, 122.37, 118.37, 115.56, 29.68. HRMS m/z (ESI) calcd for $C_{14}H_{12}NO$ $(M + H)^+$ 210.0913, found 210.0905.

3,3-dimethylisoindolin-1-one (**5**)

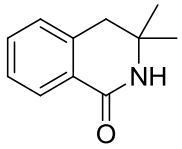


5

The reaction of compound **3** (200 mg, 0.966 mmol), $(NH_4)_2S_2O_8$ (440 mg, 2.0 equiv) in a mixture solvent of DMSO (20 mL) and H_2O (1 mL) under 100 ºC afforded **5** (75 mg, 48.1%) with standard workup and purification. Compound **5** (pale yellow oil): ^{1}H NMR (400 MHz, MeOD) δ 7.73 (d, J = 7.5 Hz, 1H), 7.62 (td, J = 7.5, 1.1 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.47 (td, J

= 7.5, 1.1 Hz, 1H). ^{13}C NMR (100 MHz, MeOD) δ 171.52, 155.02, 133.50, 131.66, 129.17, 124.42, 122.39, 60.59, 27.51. HRMS m/z (ESI) calcd for $C_{10}H_{12}NO$ $(M + H)^+$ 162.0913, found 162.0893.

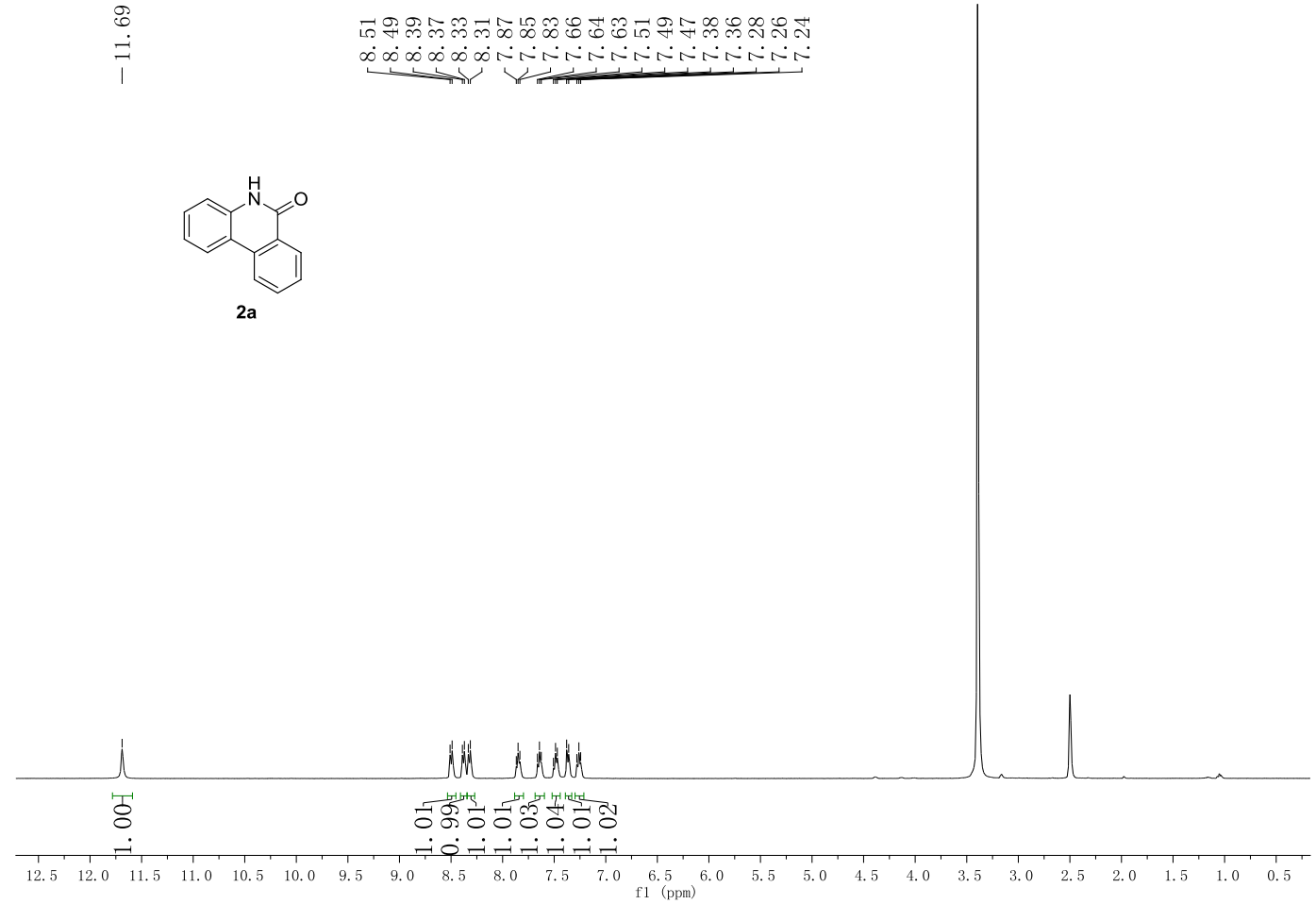
3,3-dimethyl-3,4-dihydroisoquinolin-1(2H)-one (**6**)

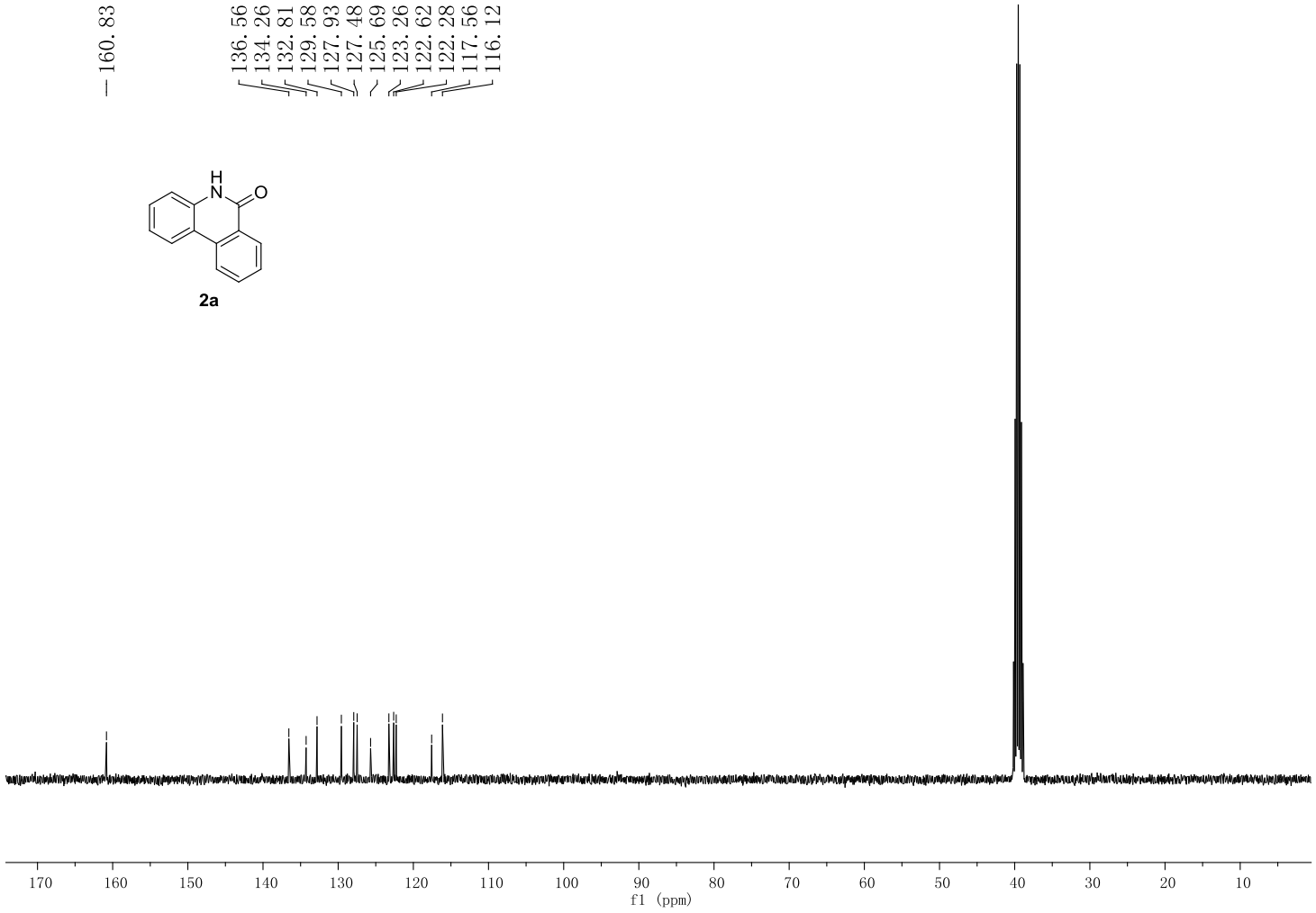


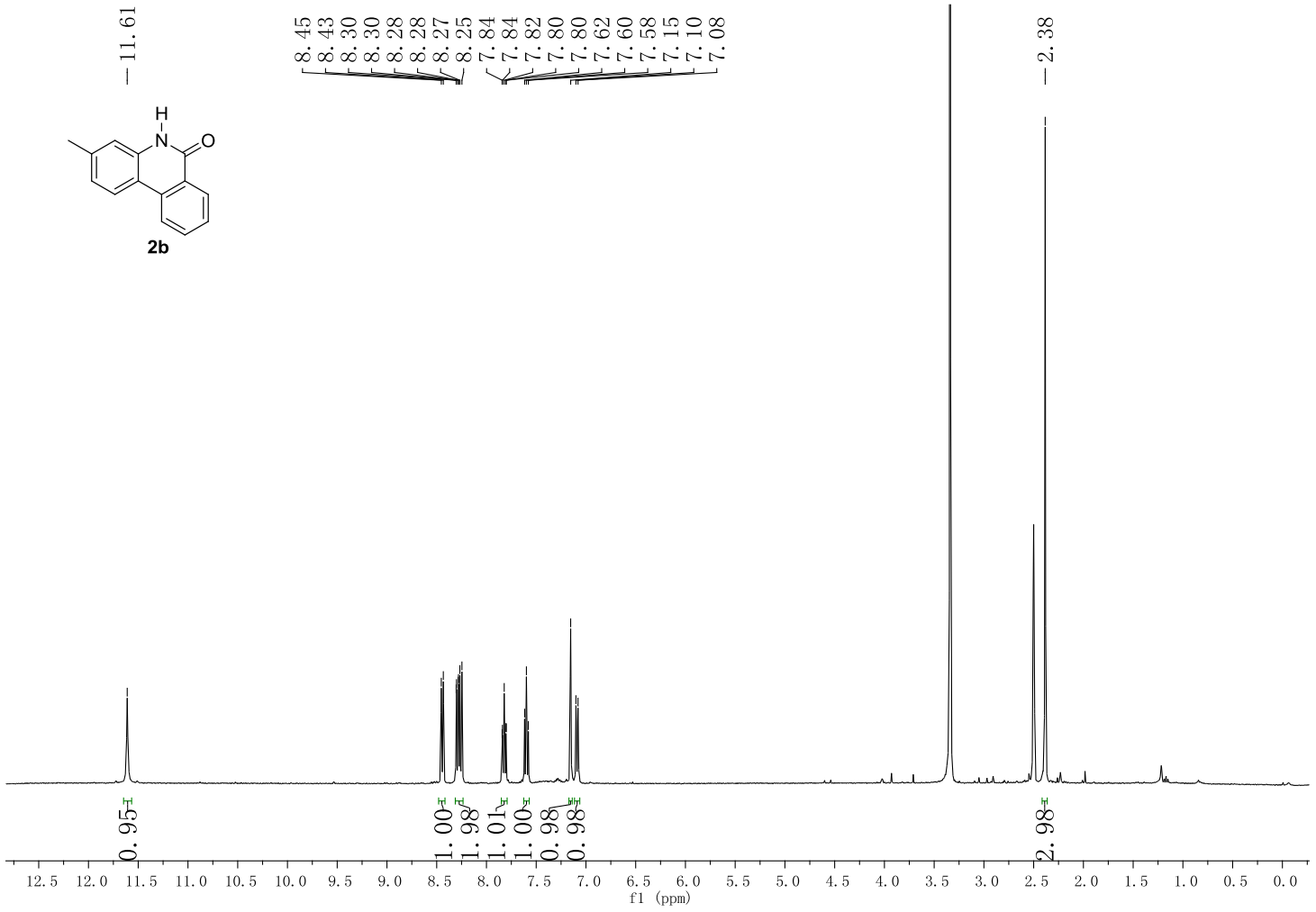
6

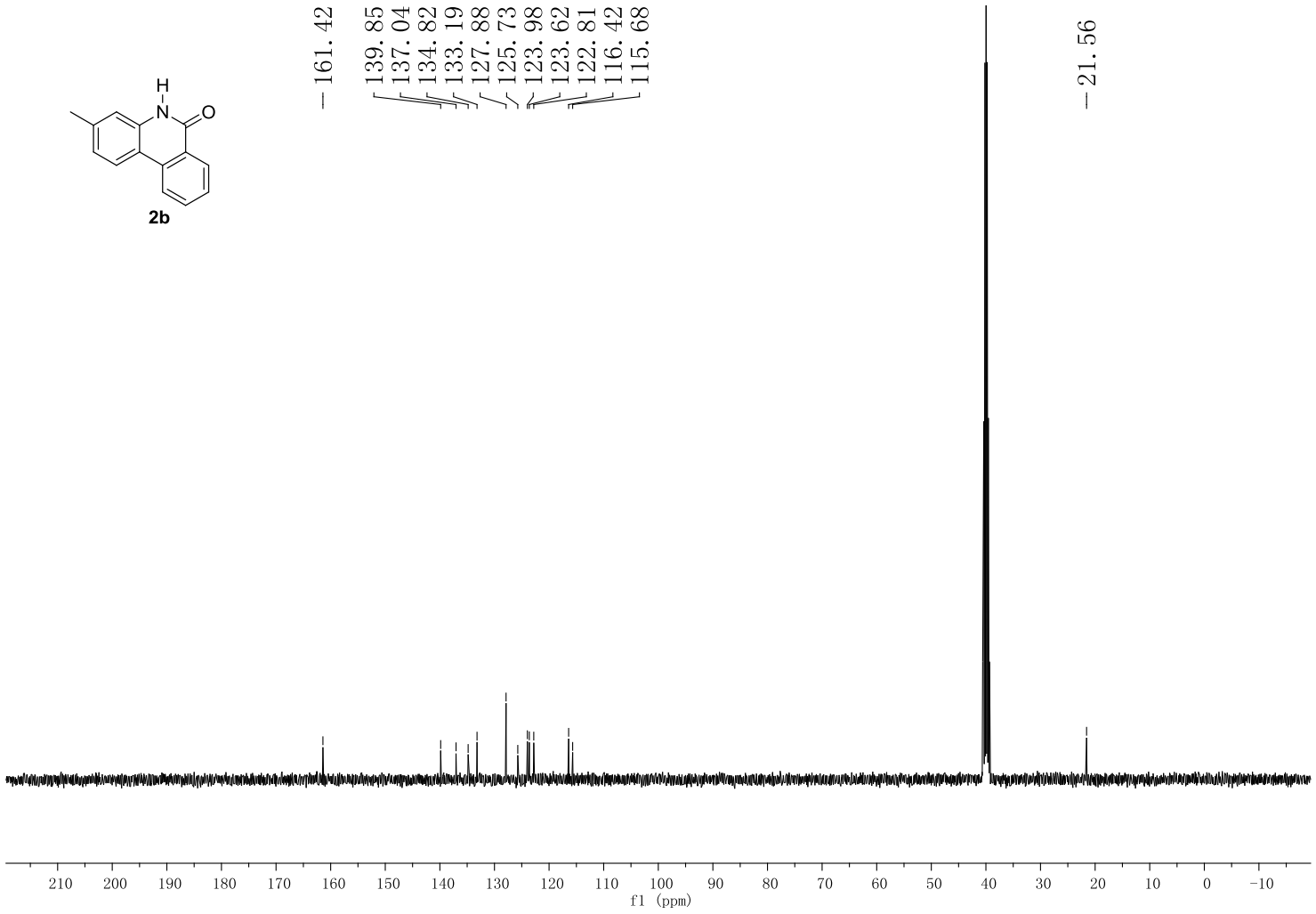
The reaction of compound **4** (200 mg, 0.951 mmol), $(NH_4)_2S_2O_8$ (412 mg, 2.0 equiv) in a mixture solvent of DMSO (20 mL) and H_2O (1 mL) under 100 ºC afforded **6** (70 mg, 42.2%) with standard workup and purification. Compound **6** (pale yellow oil): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.45 (td, *J* = 7.5, 1.4 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 2.93 (s, 2H), 1.31 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.62, 137.68, 132.49, 128.07, 127.99, 127.16, 52.28, 41.80, 29.10. HRMS m/z (ESI) calcd for $C_{11}H_{13}NONa$ $(M + Na)^+$ 198.0889, found 198.0899.

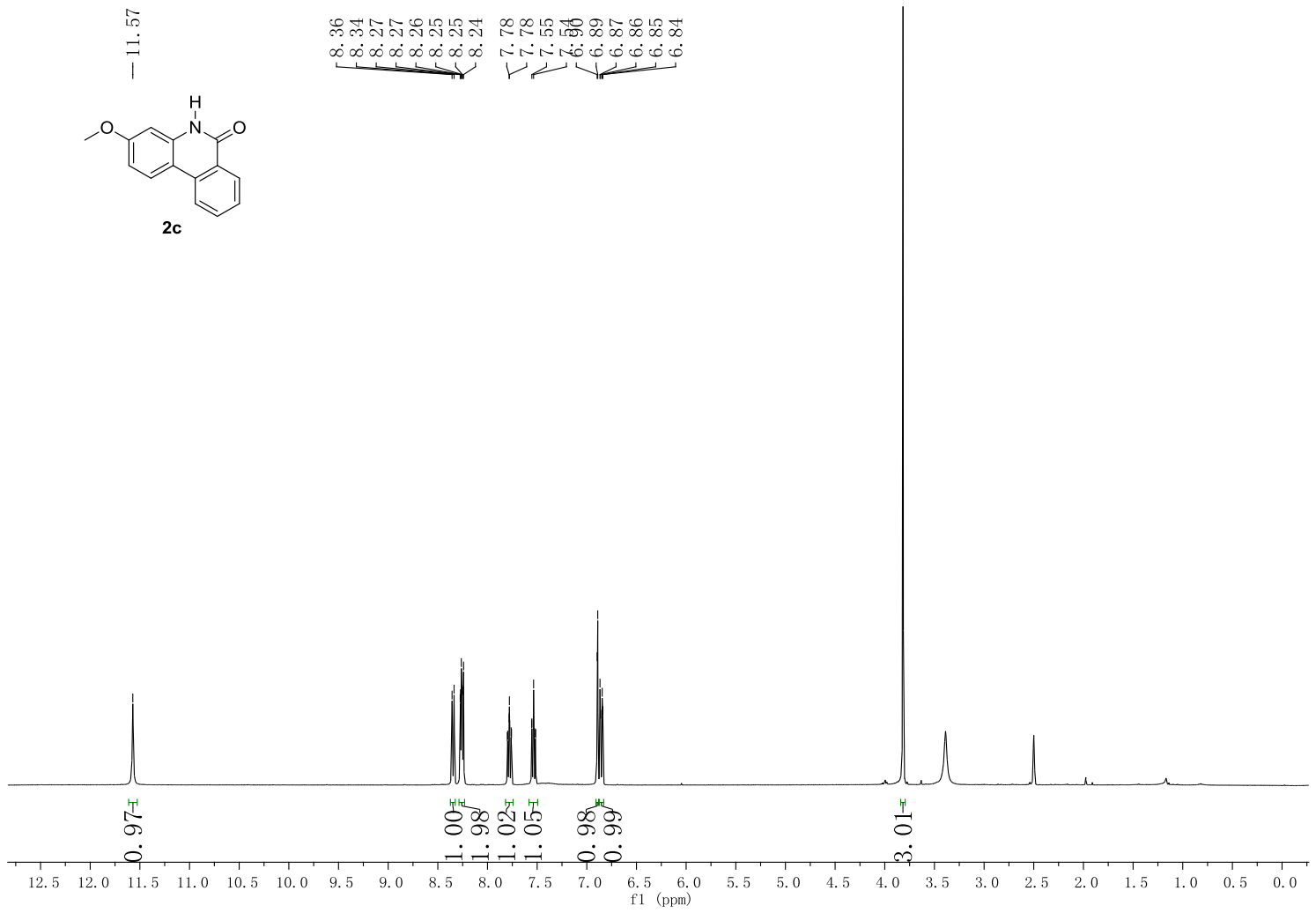
6. ^{1}H NMR and ^{13}C NMR Spectra Copies of all Products

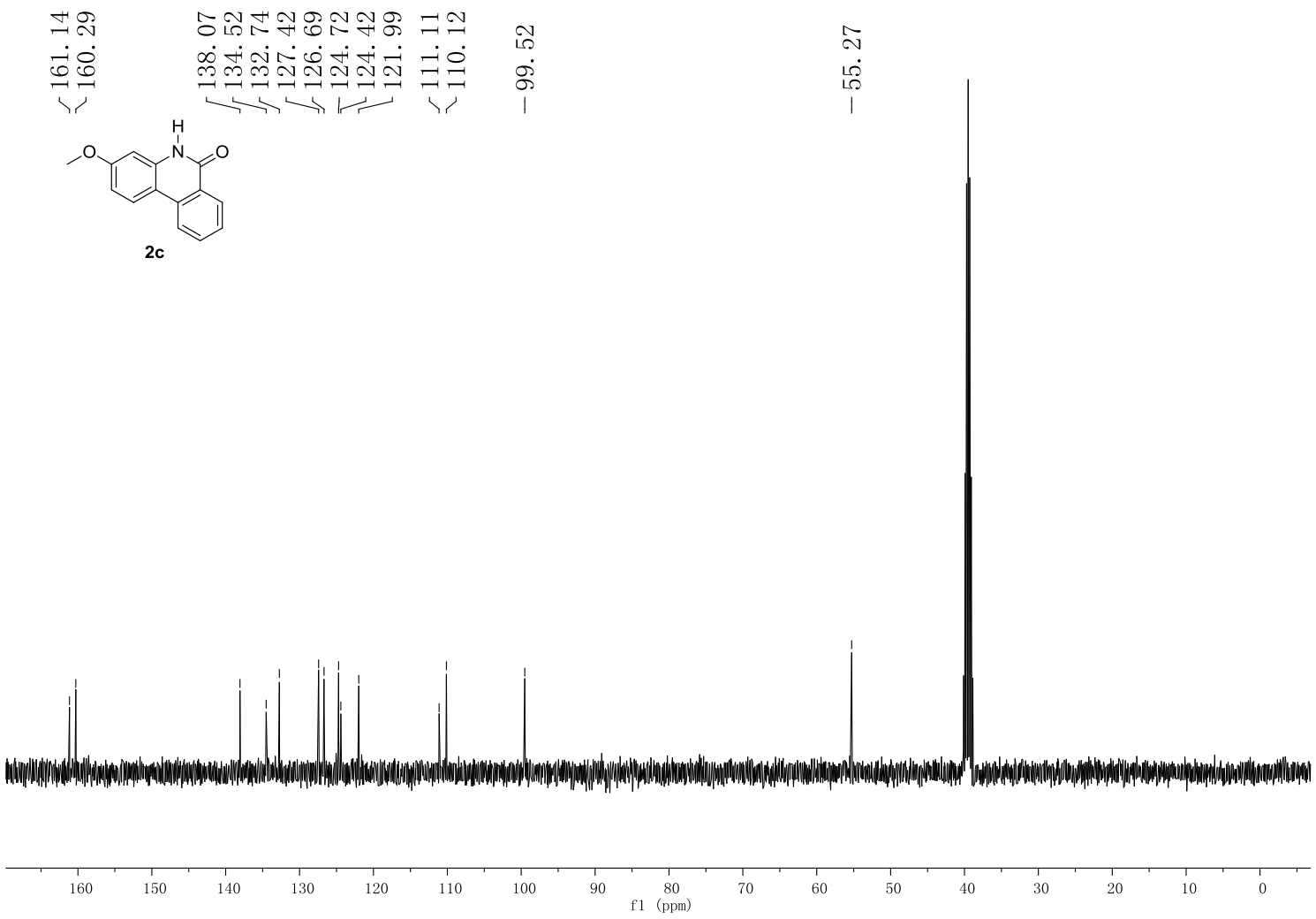


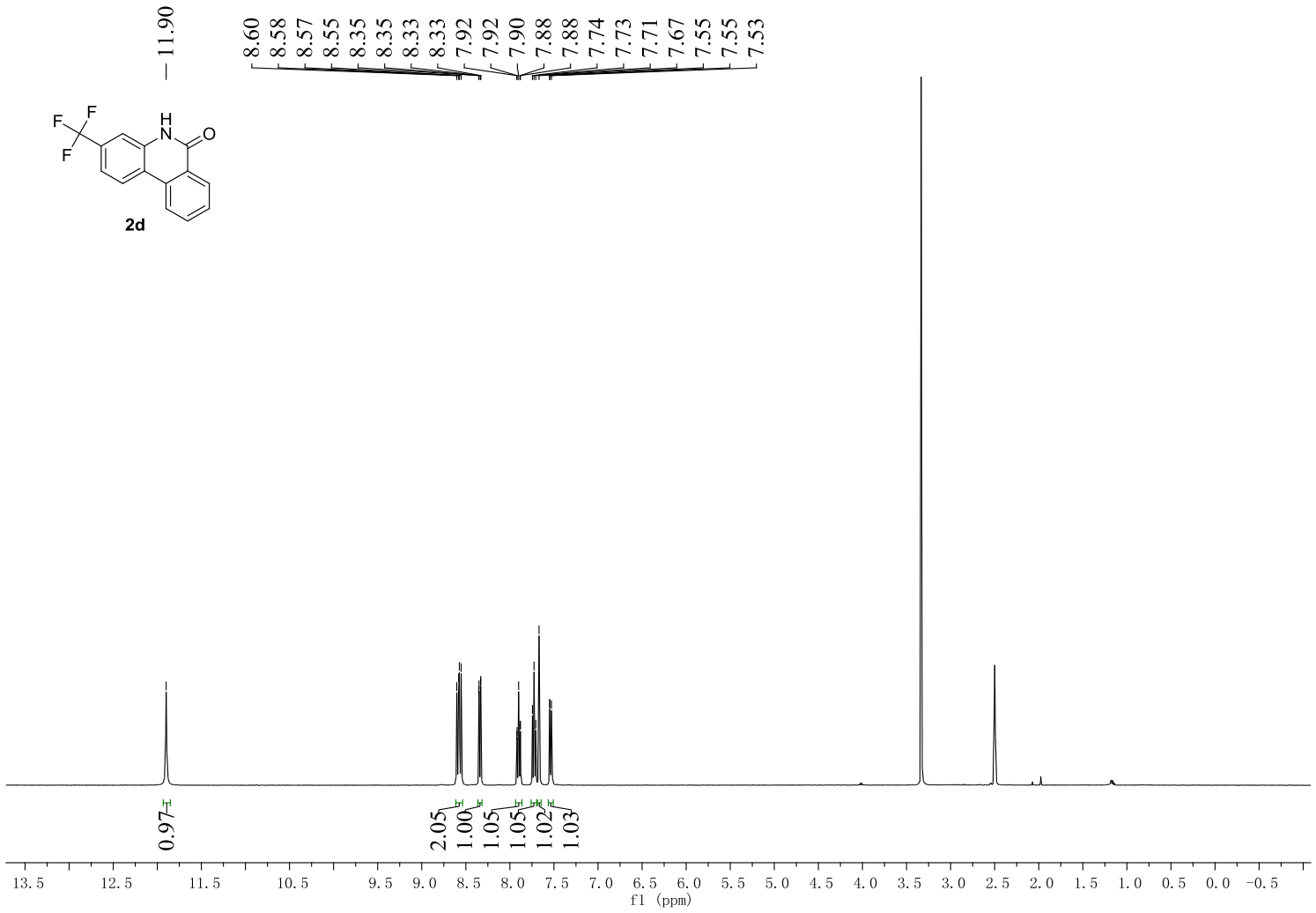

160.83
136.56
134.26
132.81
129.58
127.93
127.48
125.69
123.26
122.62
122.28
117.56
116.12
H
N
O
2a
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

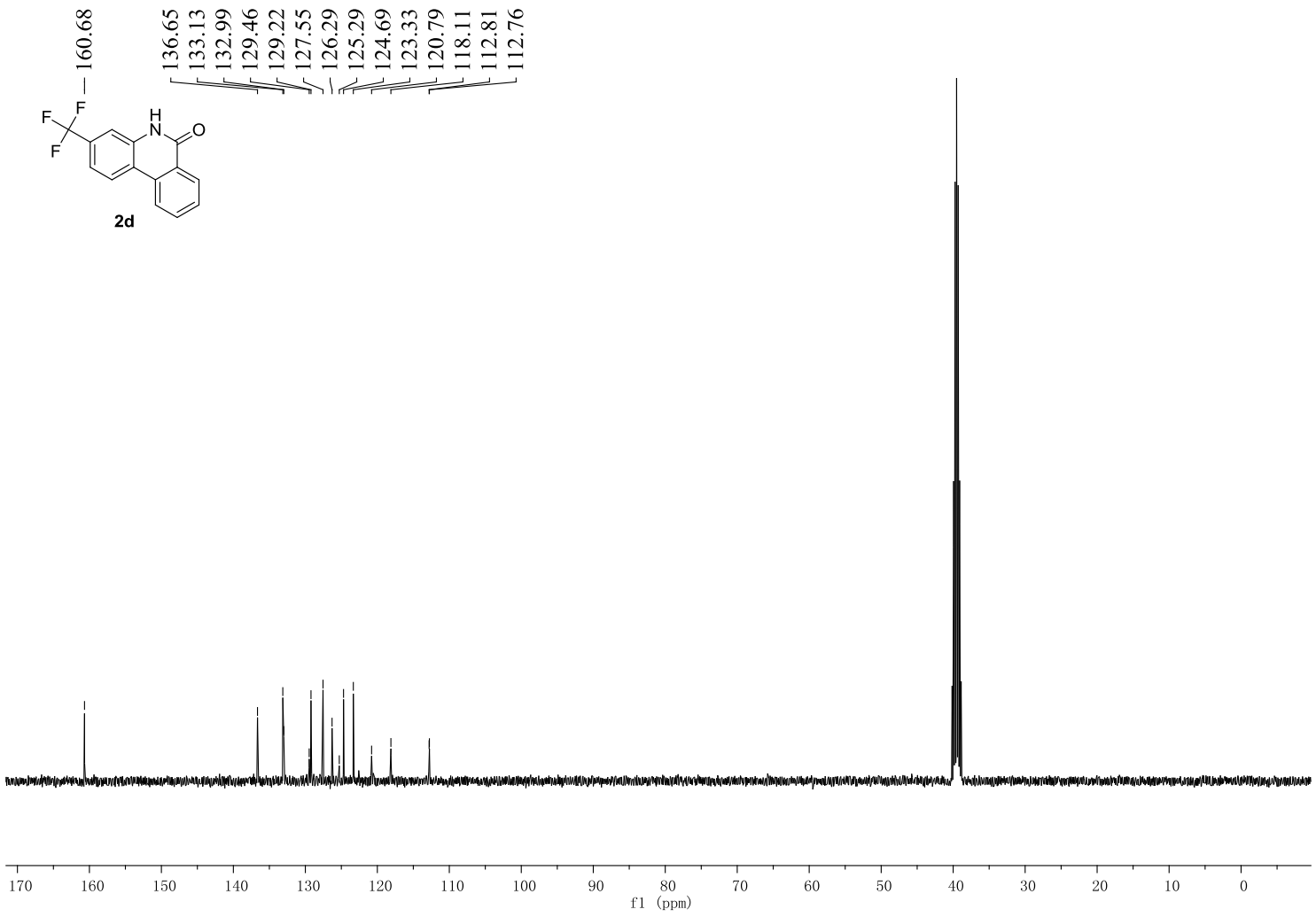

11.61
8.45
8.43
8.30
8.30
8.28
8.28
8.27
8.25
7.84
7.84
7.82
7.80
7.80
7.62
7.60
7.58
7.15
7.10
7.08
2.38
H
N
O
2b
0.95
1.00
1.98
1.01
1.00
0.98
0.98
2.98
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

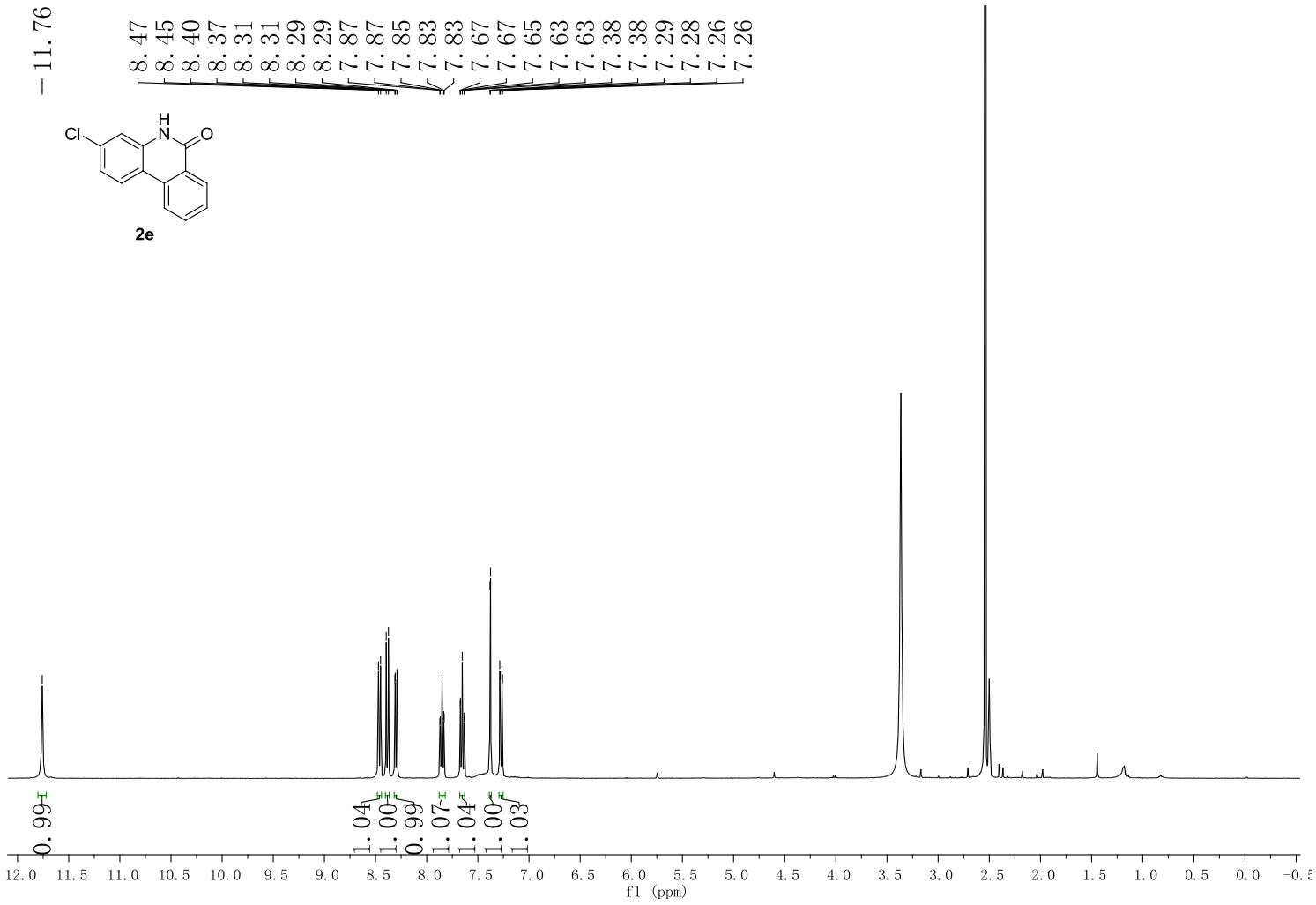

161.42
139.85
137.04
134.82
133.19
127.88
125.73
123.98
123.62
122.81
116.42
115.68
21.56
H
N
O
2b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

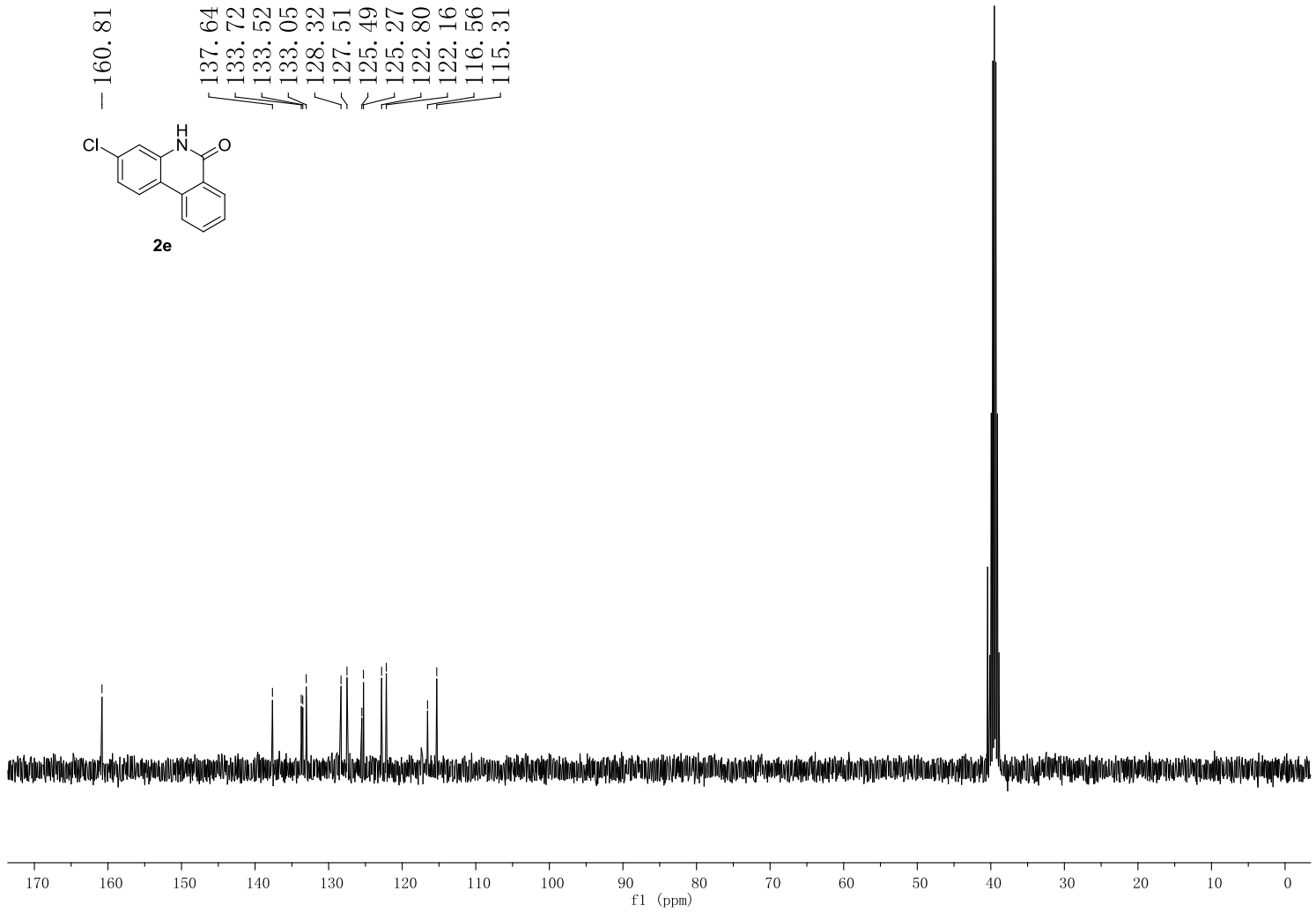

11.57
8.36
8.34
8.27
8.27
8.26
8.25
8.25
8.24
7.78
7.78
7.55
7.54
6.90
6.89
6.87
6.86
6.85
6.84
H
N
O
O
2c
0.97
1.00
1.98
1.02
1.05
0.98
0.99
3.01
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

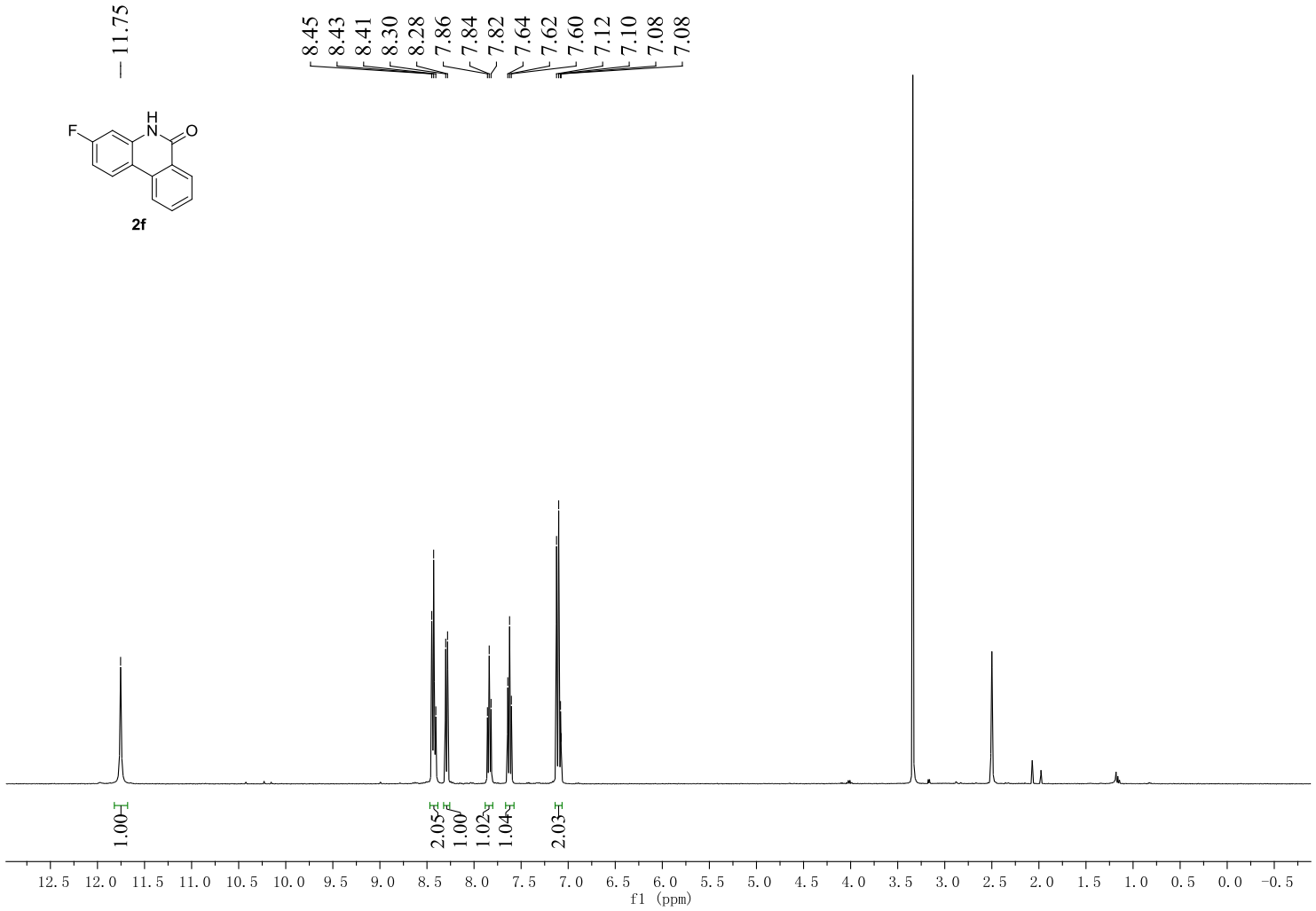

161.14
160.29
138.07
134.52
132.74
127.42
126.69
124.72
124.42
121.99
111.11
110.12
99.52
55.27
H
N
O
O
2c
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

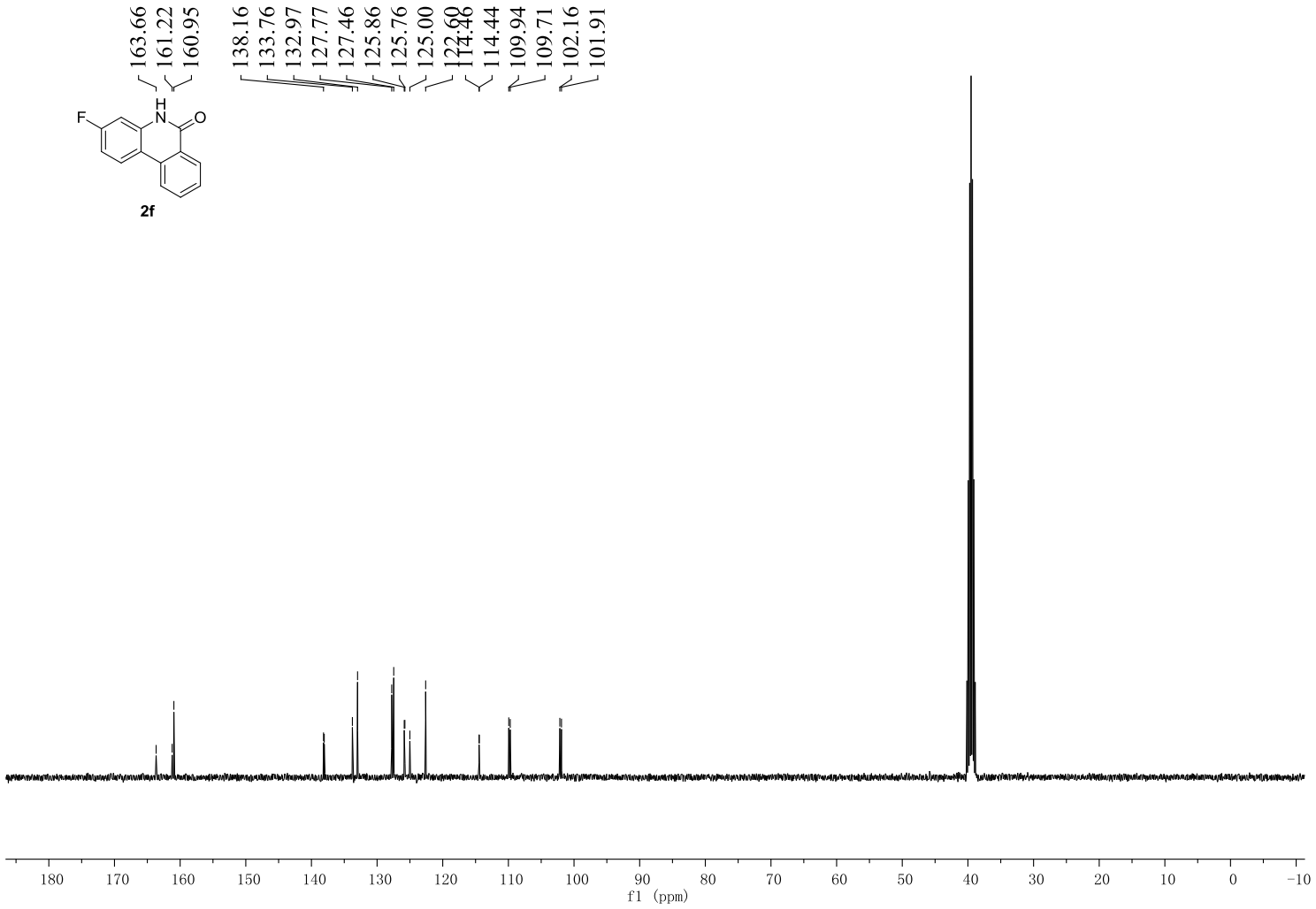

11.90
8.60
8.58
8.57
8.55
8.35
8.35
8.33
8.33
7.92
7.92
7.90
7.88
7.88
7.74
7.73
7.71
7.67
7.55
7.55
7.53
F
F
F
H
N
O
2d
0.97
2.05
1.00
1.05
1.05
1.02
1.03
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

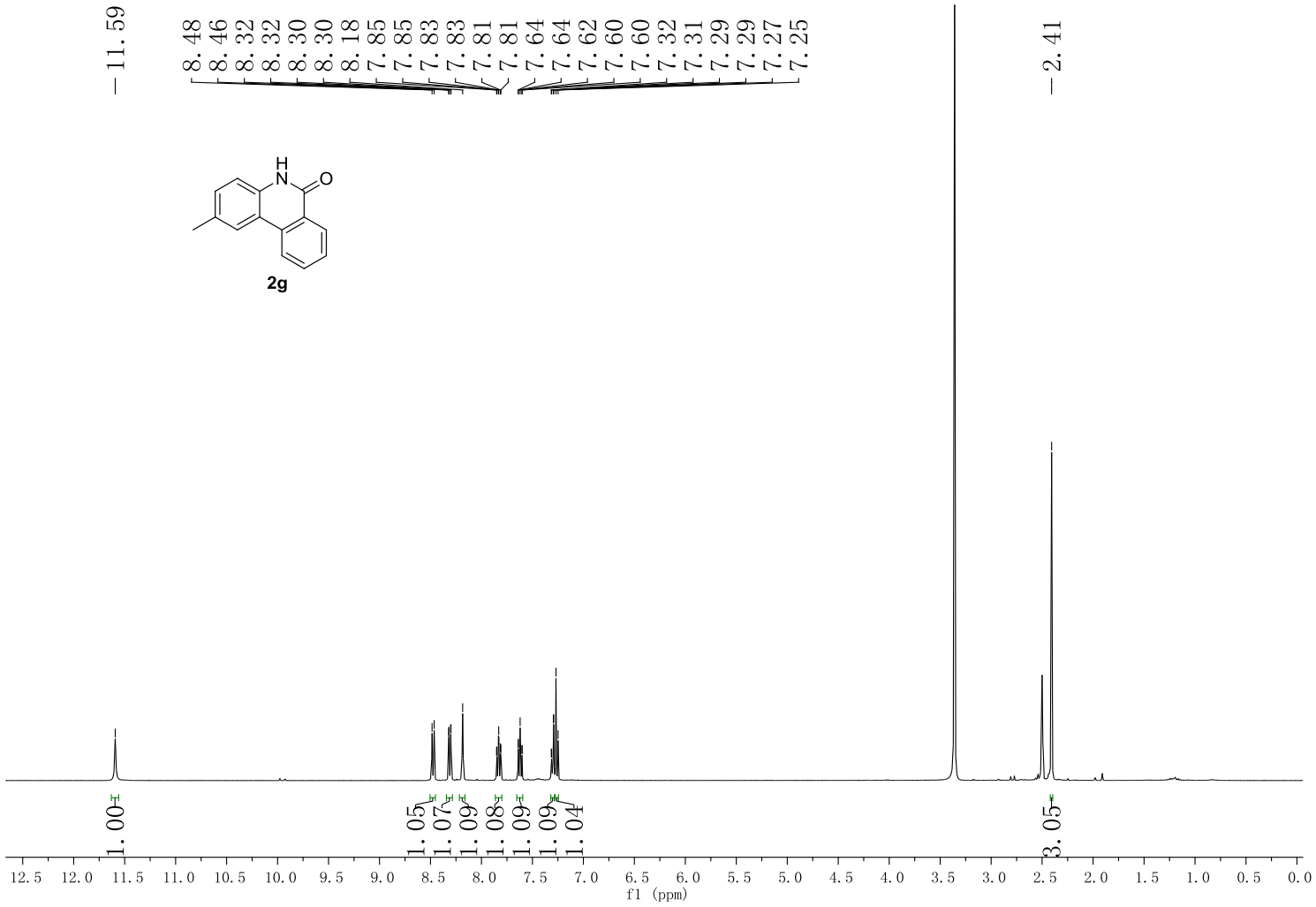

160.68
136.65
133.13
132.99
129.46
129.22
127.55
126.29
125.29
124.69
123.33
120.79
118.11
112.81
112.76
F
F
F
H
N
O
2d
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

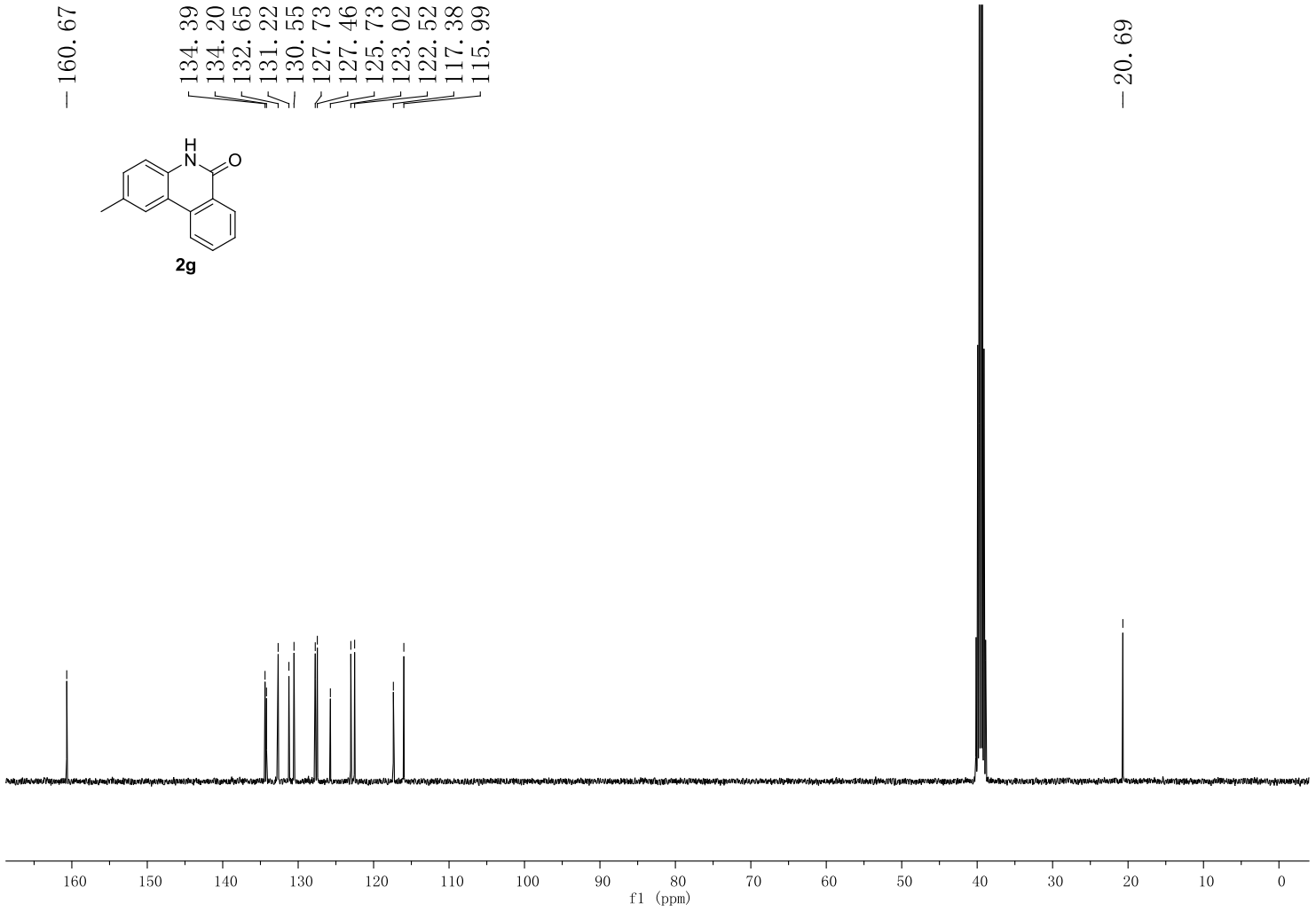

11.76
8.47
8.45
8.40
8.37
8.31
8.31
8.29
8.29
7.87
7.87
7.85
7.83
7.83
7.67
7.67
7.65
7.63
7.63
7.38
7.38
7.29
7.28
7.26
7.26
Cl
H
N
O
2e
0.99
1.04
1.00
0.99
1.07
1.04
1.00
1.03
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

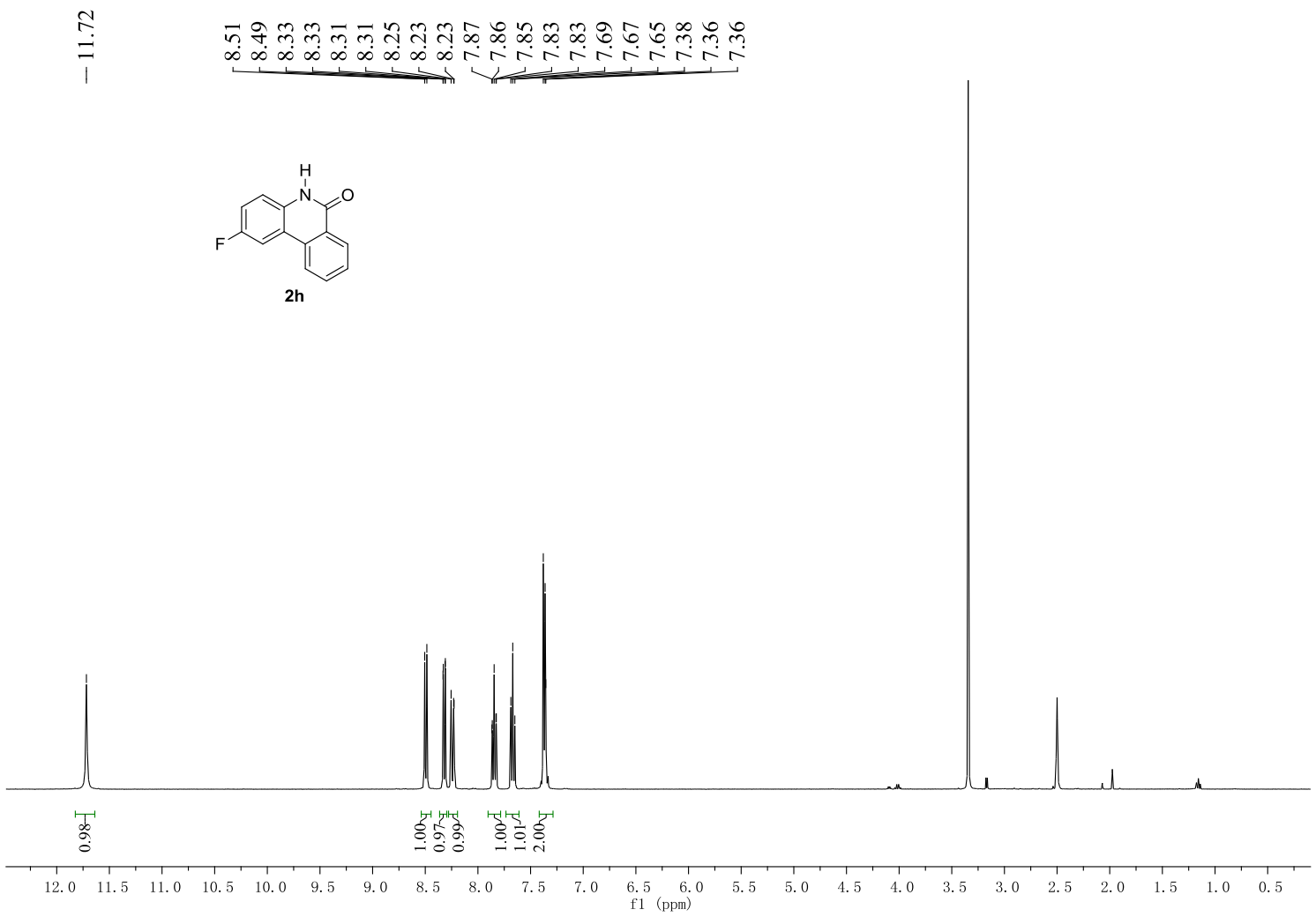

160.81
137.64
133.72
133.52
133.05
128.32
127.51
125.49
125.27
122.80
122.16
116.56
115.31
Cl
H
N
O
2e
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

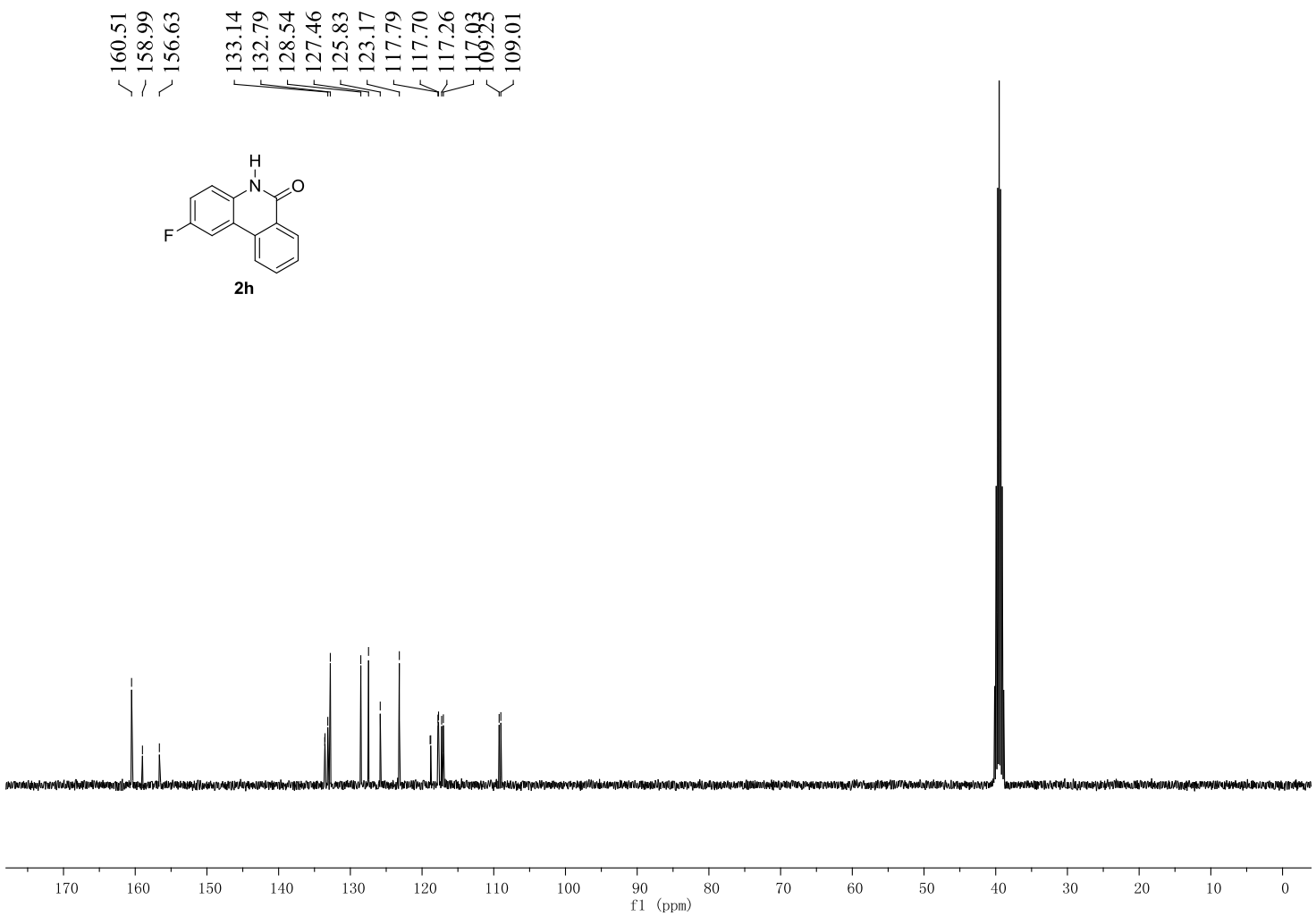

11.75
8.45
8.43
8.41
8.30
8.28
7.86
7.84
7.82
7.64
7.62
7.60
7.12
7.10
7.08
7.08
F
H
N
O
2f
1.00
2.05
1.00
1.02
1.04
2.03
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

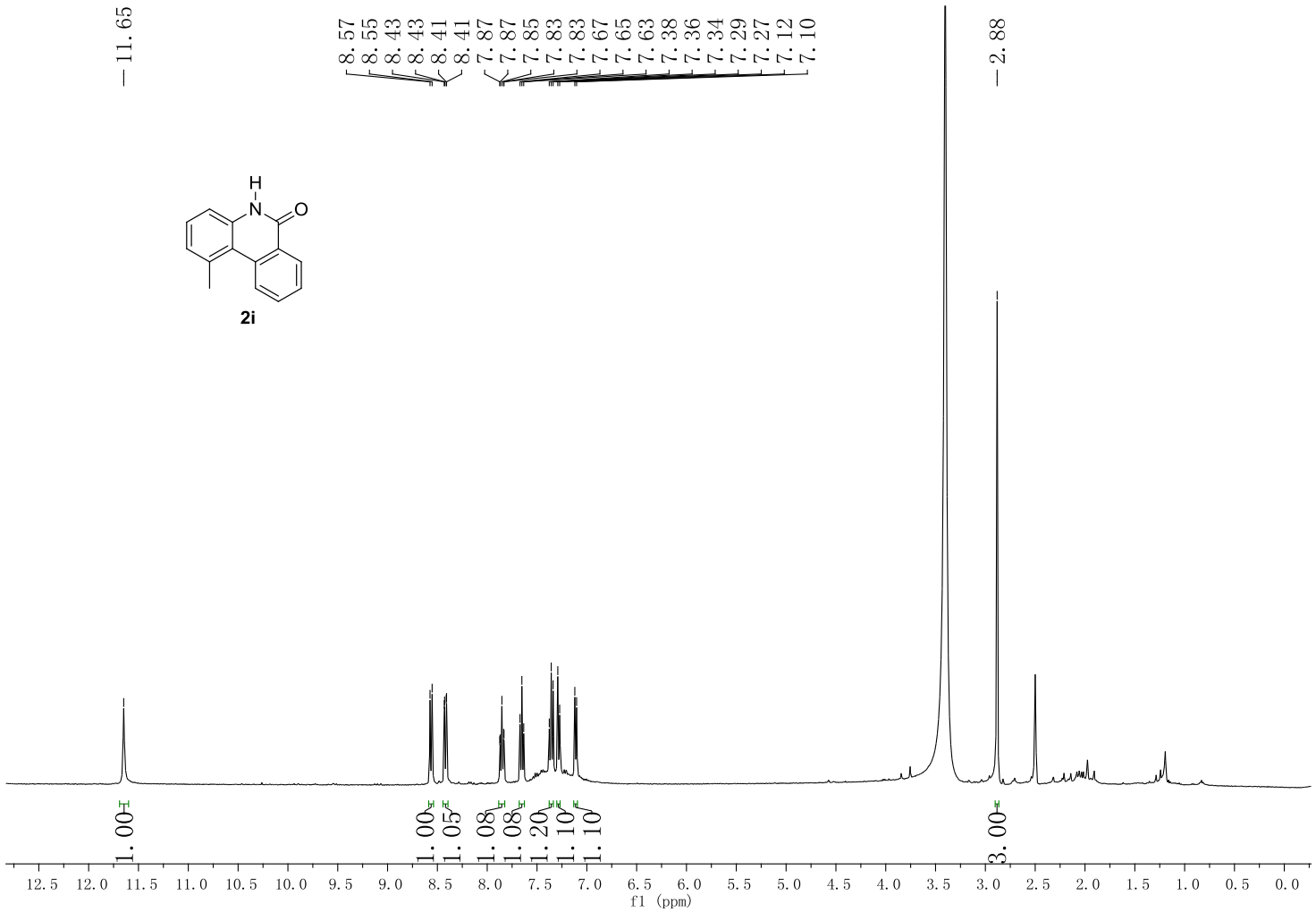

163.66
161.22
160.95
138.16
133.76
132.97
127.77
127.46
125.86
125.76
125.00
122.60
114.46
114.44
109.94
109.71
102.16
101.91
F
H
N
O
2f
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

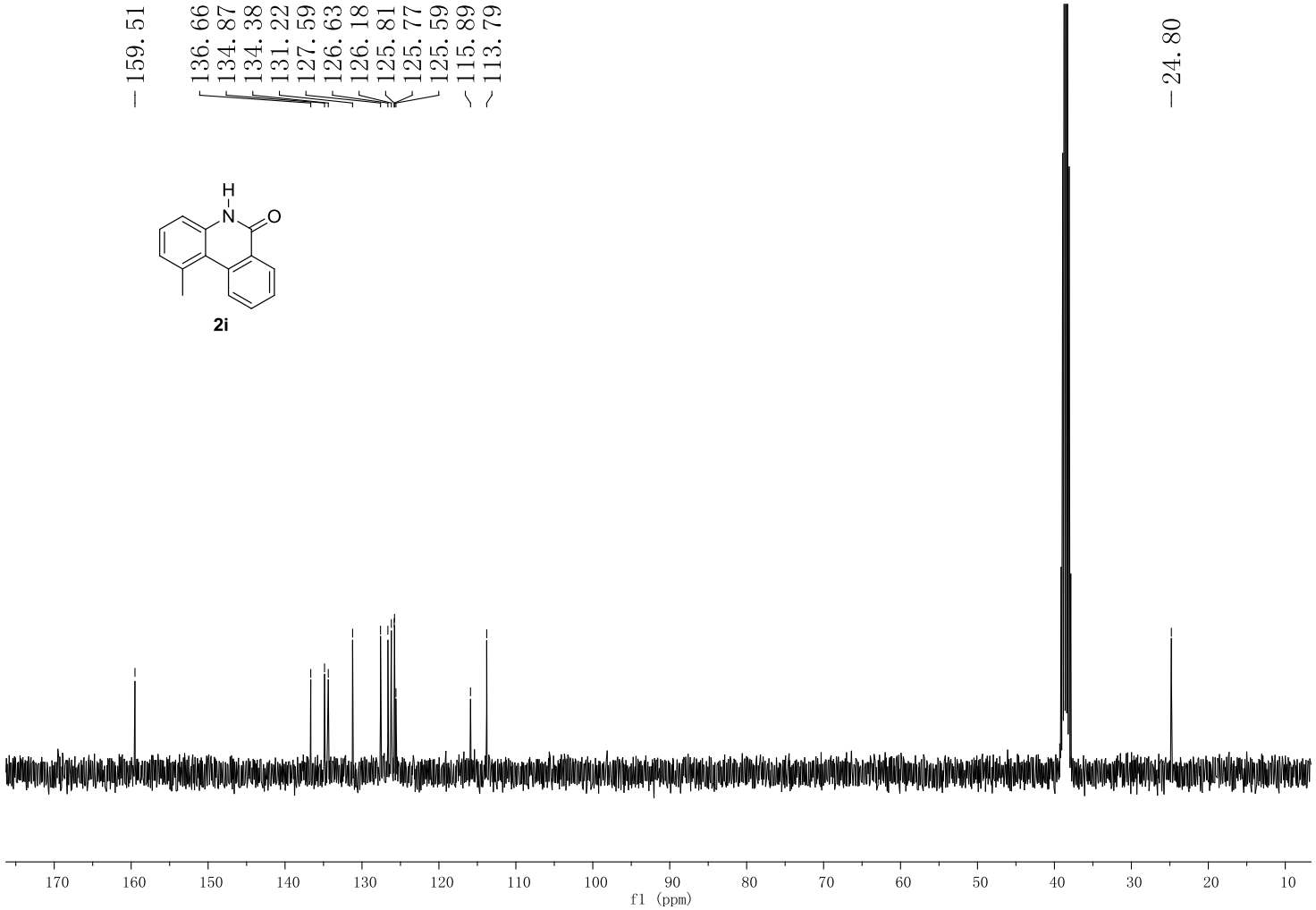

11.59
8.48
8.46
8.32
8.32
8.30
8.30
8.18
7.85
7.85
7.83
7.83
7.81
7.81
7.64
7.64
7.62
7.60
7.60
7.32
7.31
7.29
7.29
7.27
7.25
2.41
H
N
O
2g
1.00
1.05
1.07
1.09
1.08
1.09
1.09
1.04
3.05
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

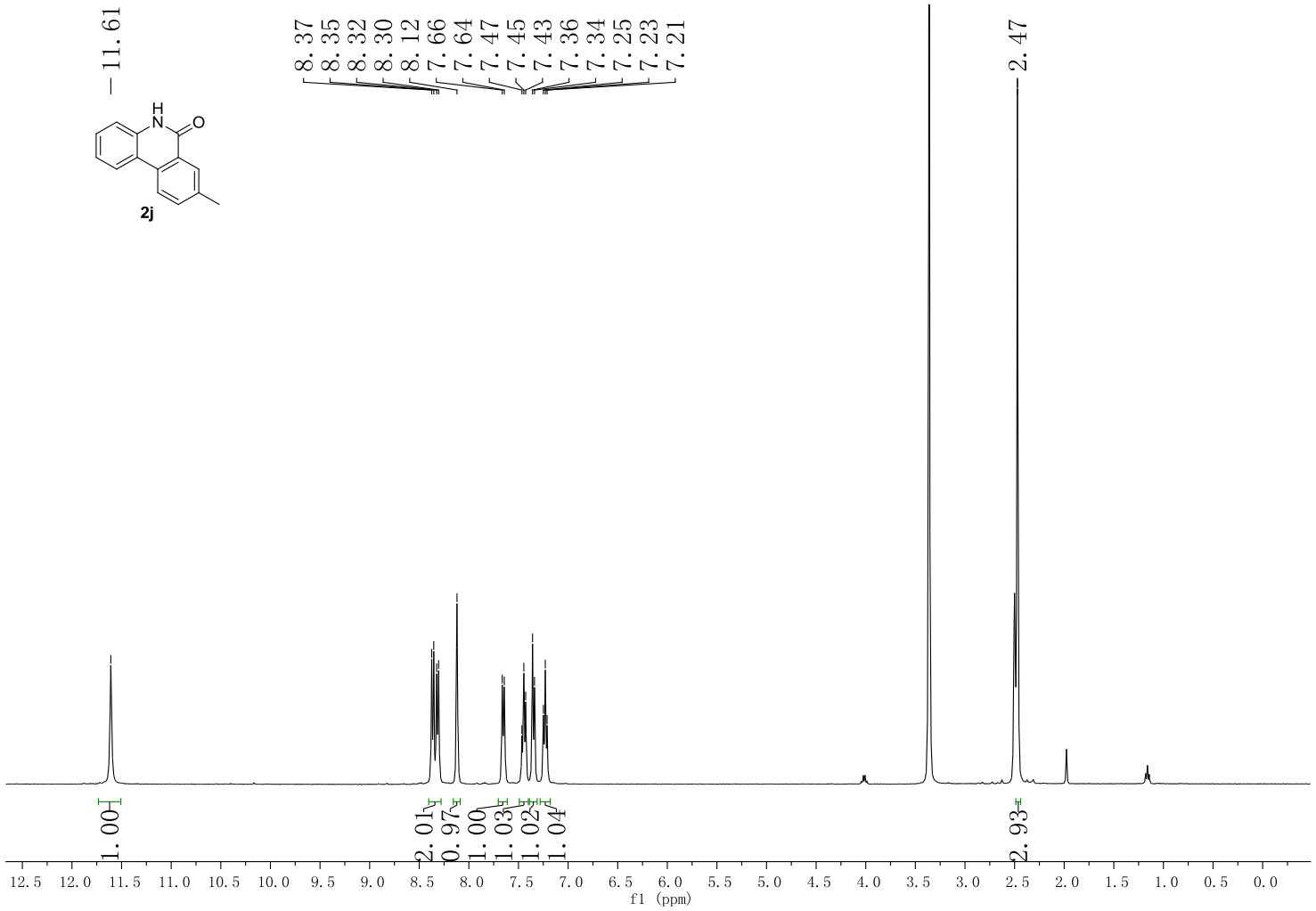

160.67
134.39
134.20
132.65
131.22
130.55
127.73
127.46
125.73
123.02
122.52
117.38
115.99
20.69
H
N
O
2g
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

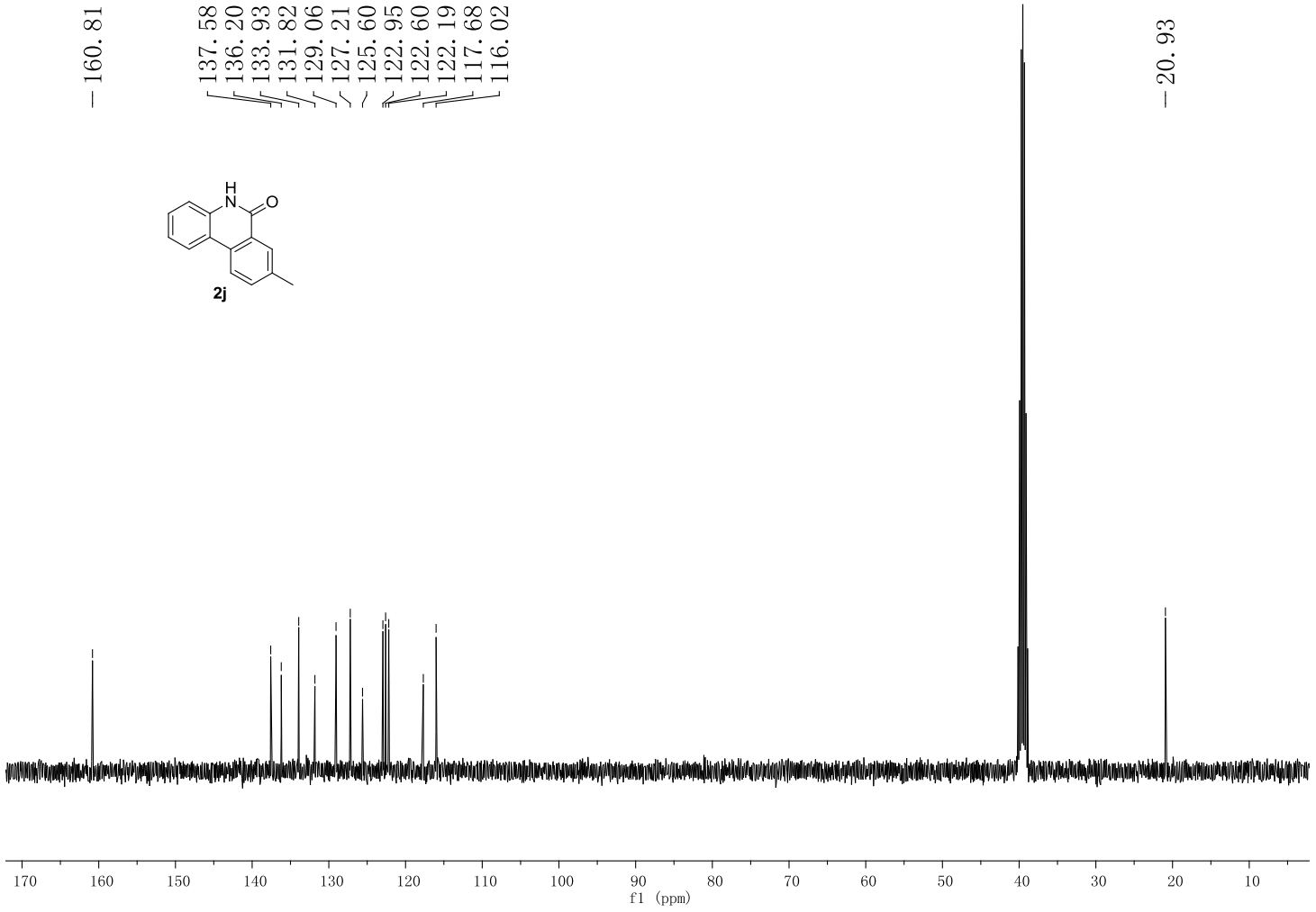

11.72
8.51
8.49
8.33
8.33
8.31
8.31
8.25
8.23
8.23
7.87
7.86
7.85
7.83
7.83
7.69
7.67
7.65
7.38
7.36
7.36
H
N
O
F
2h
0.98
1.00
0.97
0.99
1.00
1.01
2.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

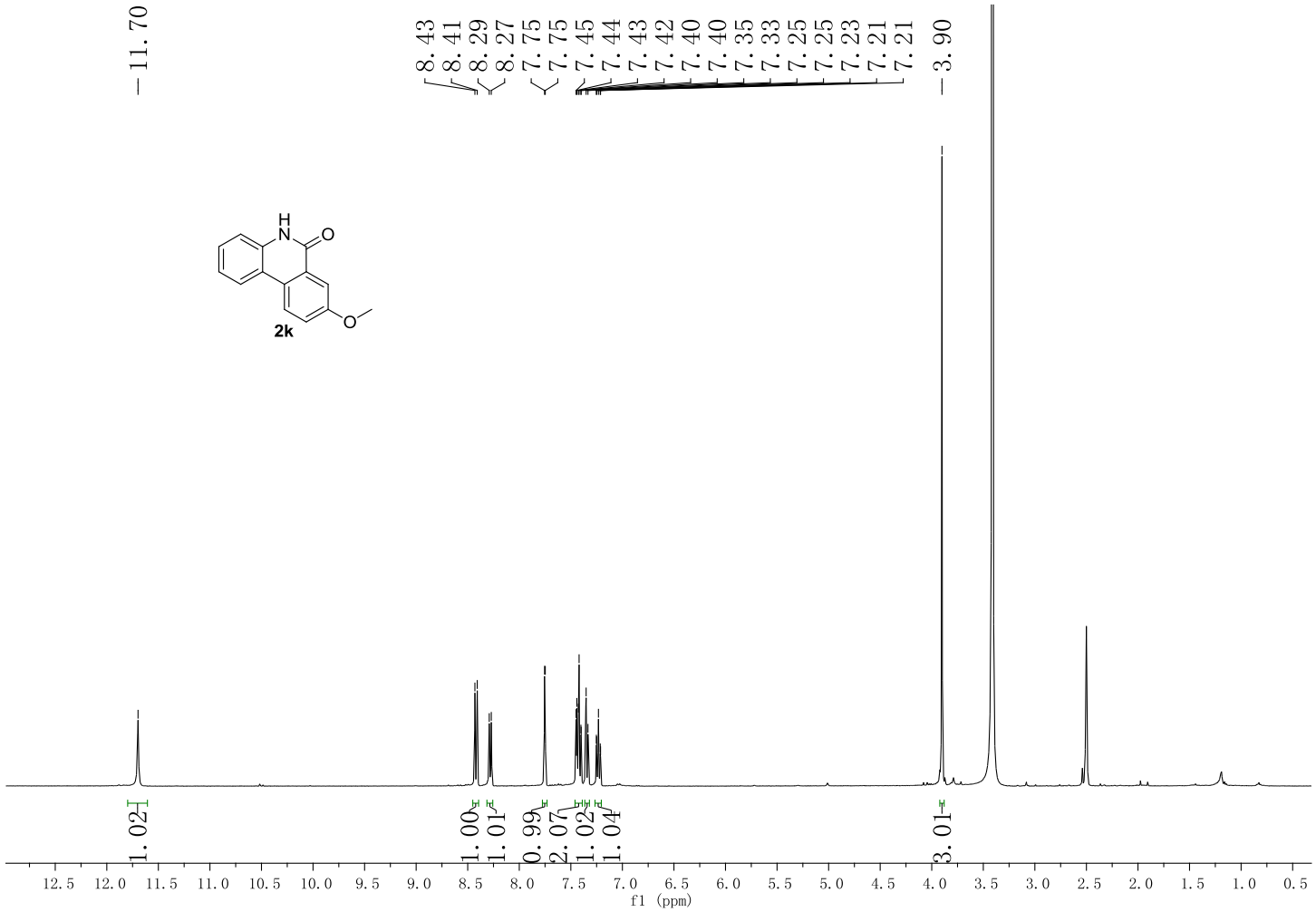

160.51
158.99
156.63
133.14
132.79
128.54
127.46
125.83
123.17
117.79
117.70
117.26
117.03
109.25
109.01
H
N
O
F
2h
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

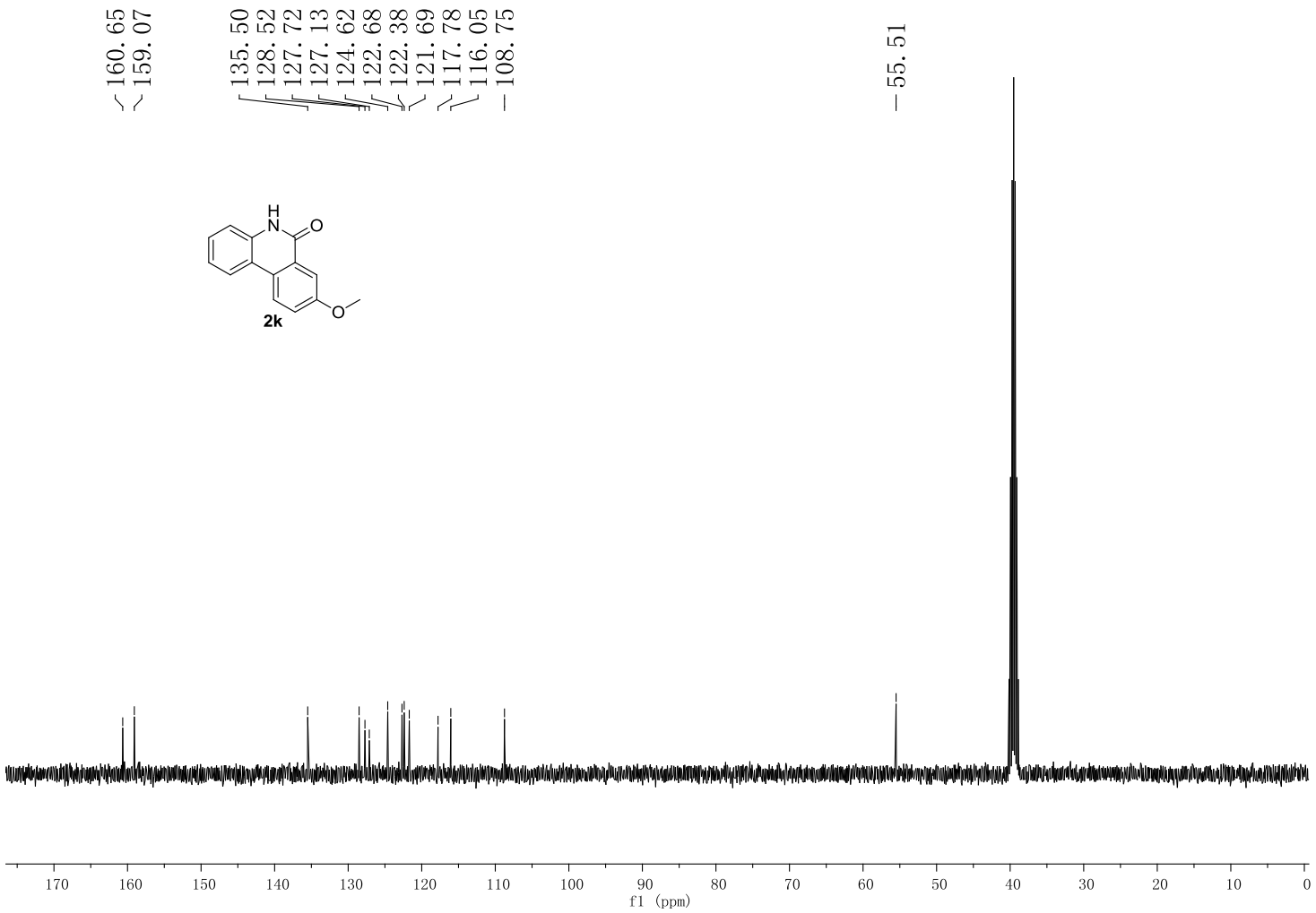

11.65
8.57
8.55
8.43
8.43
8.41
8.41
7.87
7.87
7.85
7.83
7.83
7.67
7.65
7.63
7.38
7.36
7.34
7.29
7.27
7.12
7.10
2.88
H
N
O
2i
1.00
1.00
1.05
1.08
1.08
1.20
1.10
1.10
3.00
f1 (ppm)

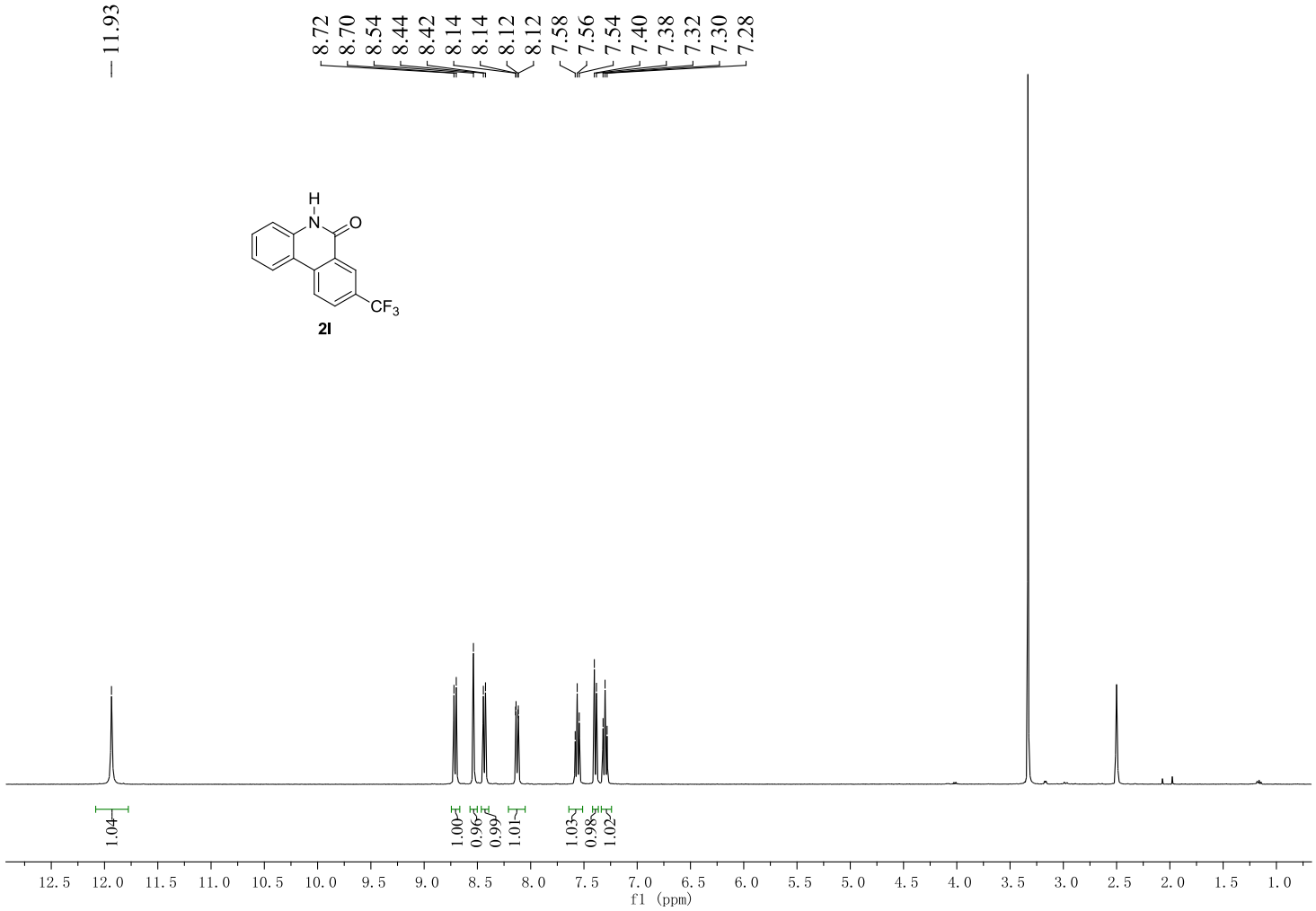

159.51
136.66
134.87
134.38
131.22
127.59
126.63
126.18
125.81
125.77
125.59
115.89
113.79
24.80
H
N
O
2i
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

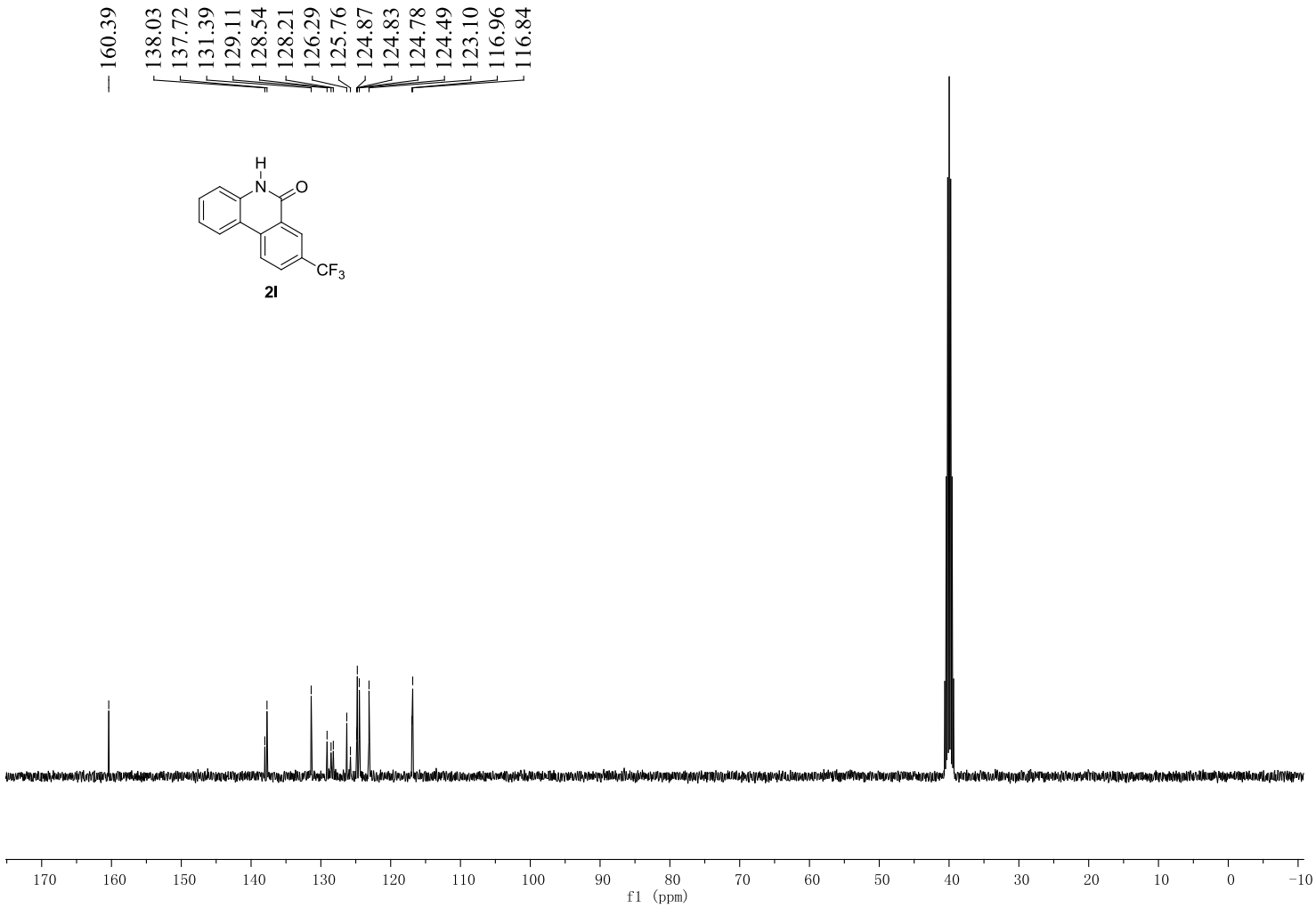

11.61
8.37
8.35
8.32
8.30
8.12
7.66
7.64
7.47
7.45
7.43
7.36
7.34
7.25
7.23
7.21
2.47
2j
1.00
2.01
0.97
1.00
1.03
1.02
1.04
2.93
f1 (ppm)

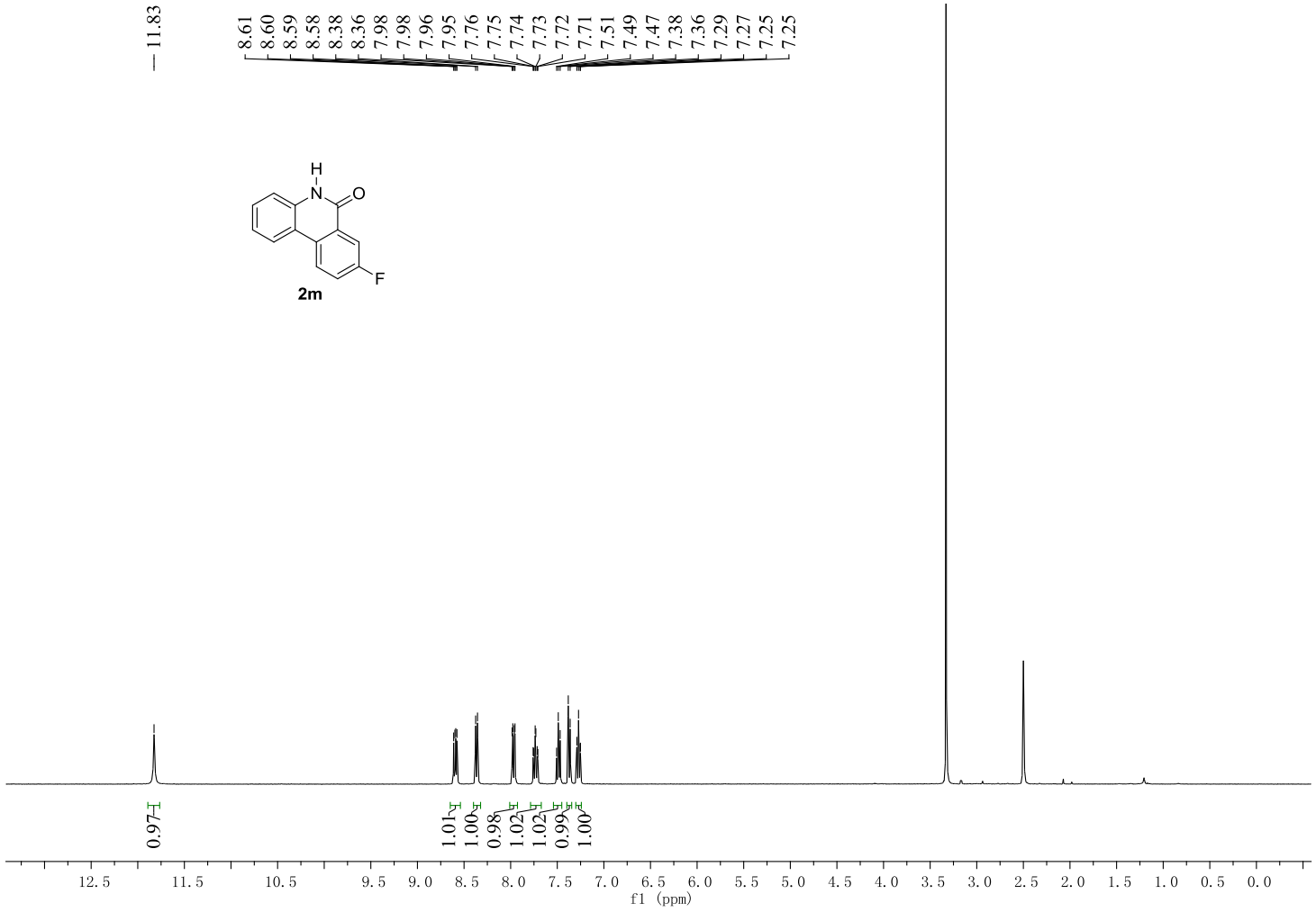

160.81
137.58
136.20
133.93
131.82
129.06
127.21
125.60
122.95
122.60
122.19
117.68
116.02
20.93
H
N
O
2j
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

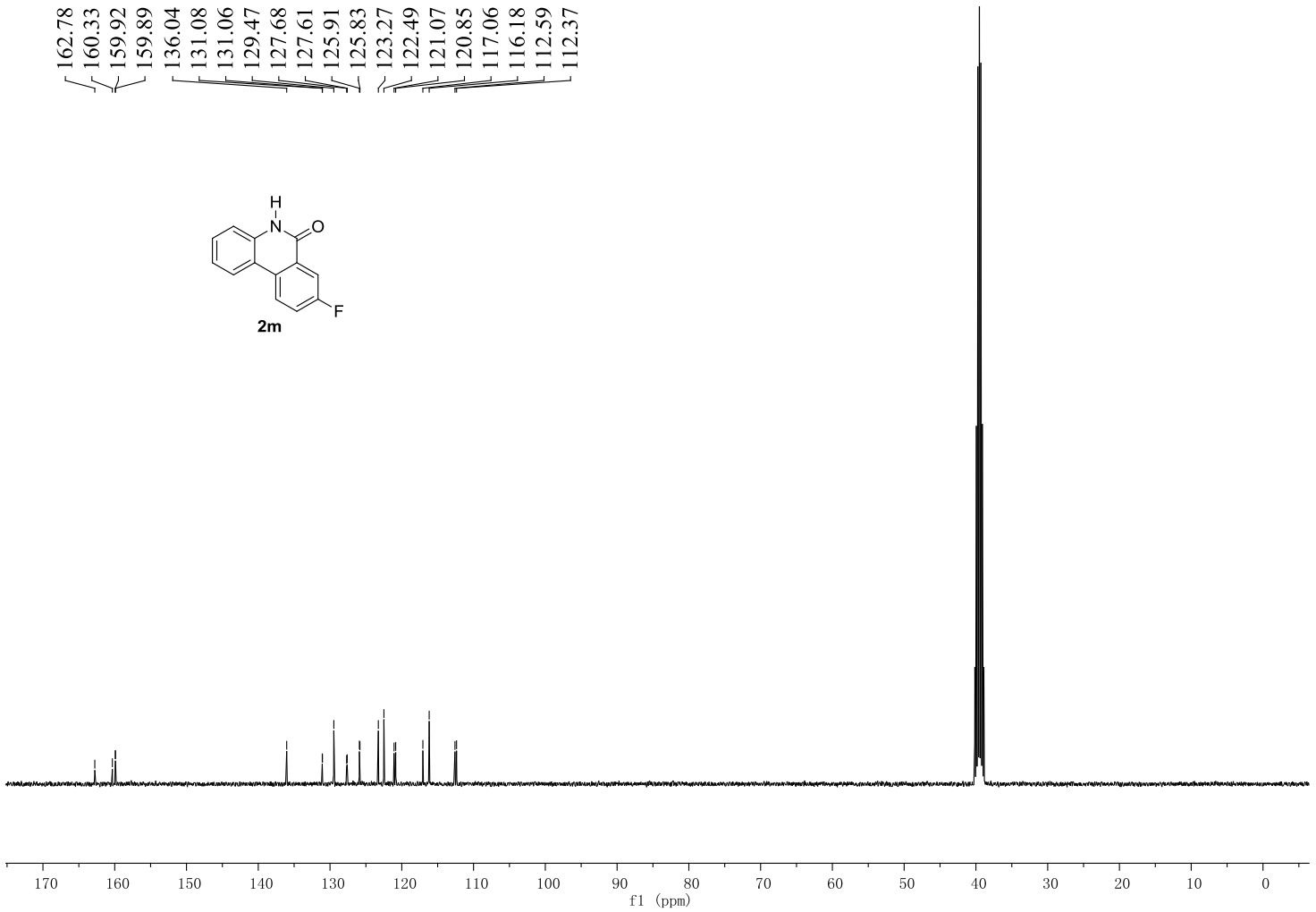

11.70
8.43
8.41
8.29
8.27
7.75
7.75
7.45
7.44
7.43
7.42
7.40
7.40
7.35
7.33
7.25
7.25
7.23
7.21
7.21
3.90
2k
1.02
1.00
1.01
0.99
2.07
1.02
1.04
3.01
f1 (ppm)

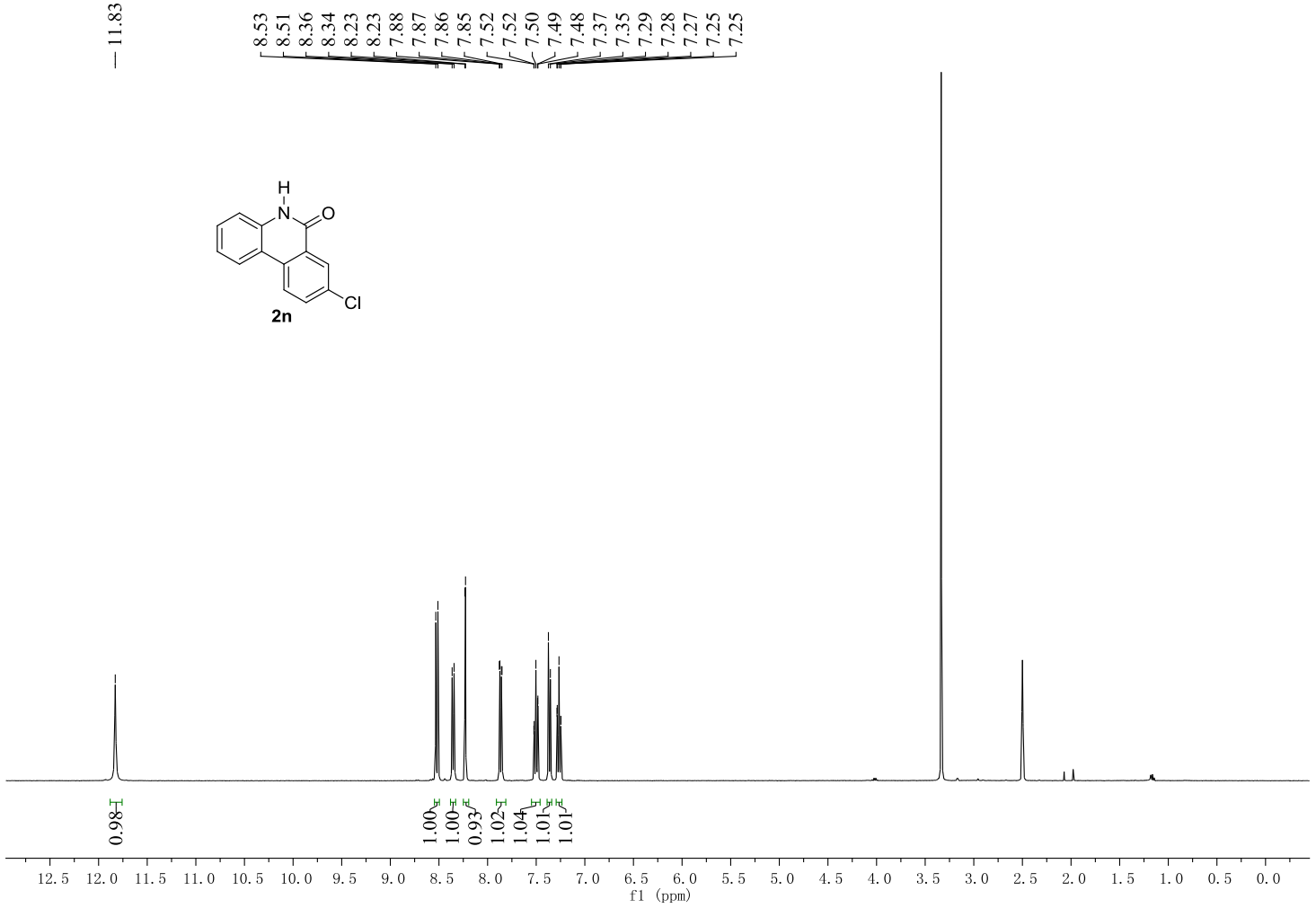

160.65
159.07
135.50
128.52
127.72
127.13
124.62
122.68
122.38
121.69
117.78
116.05
108.75
55.51
2k
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

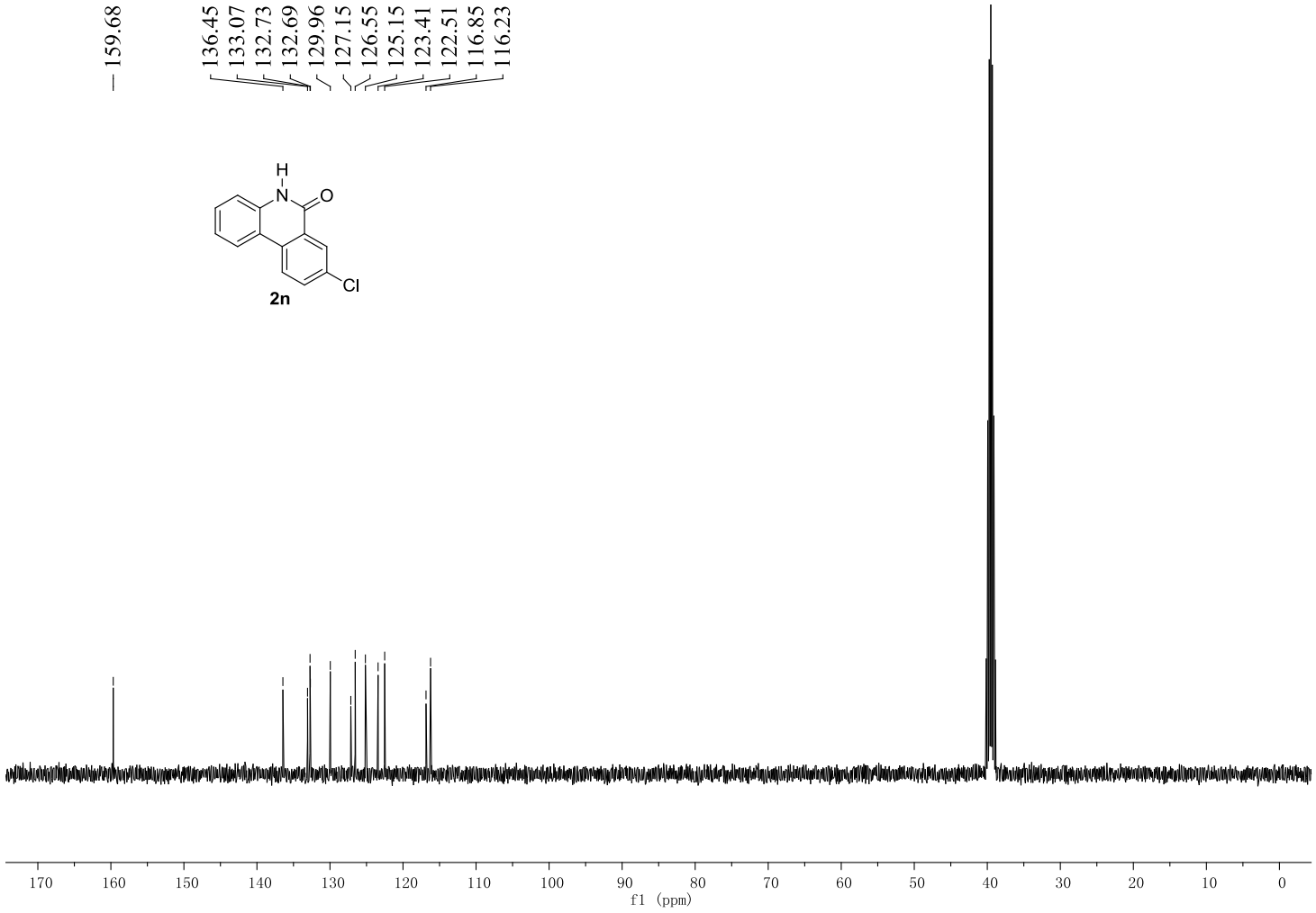

11.93
8.72
8.70
8.54
8.44
8.42
8.14
8.14
8.12
8.12
7.58
7.56
7.54
7.40
7.38
7.32
7.30
7.28
H
N
O
CF3
2l
1.04
1.00
0.96
0.99
1.01
1.03
0.98
1.02
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

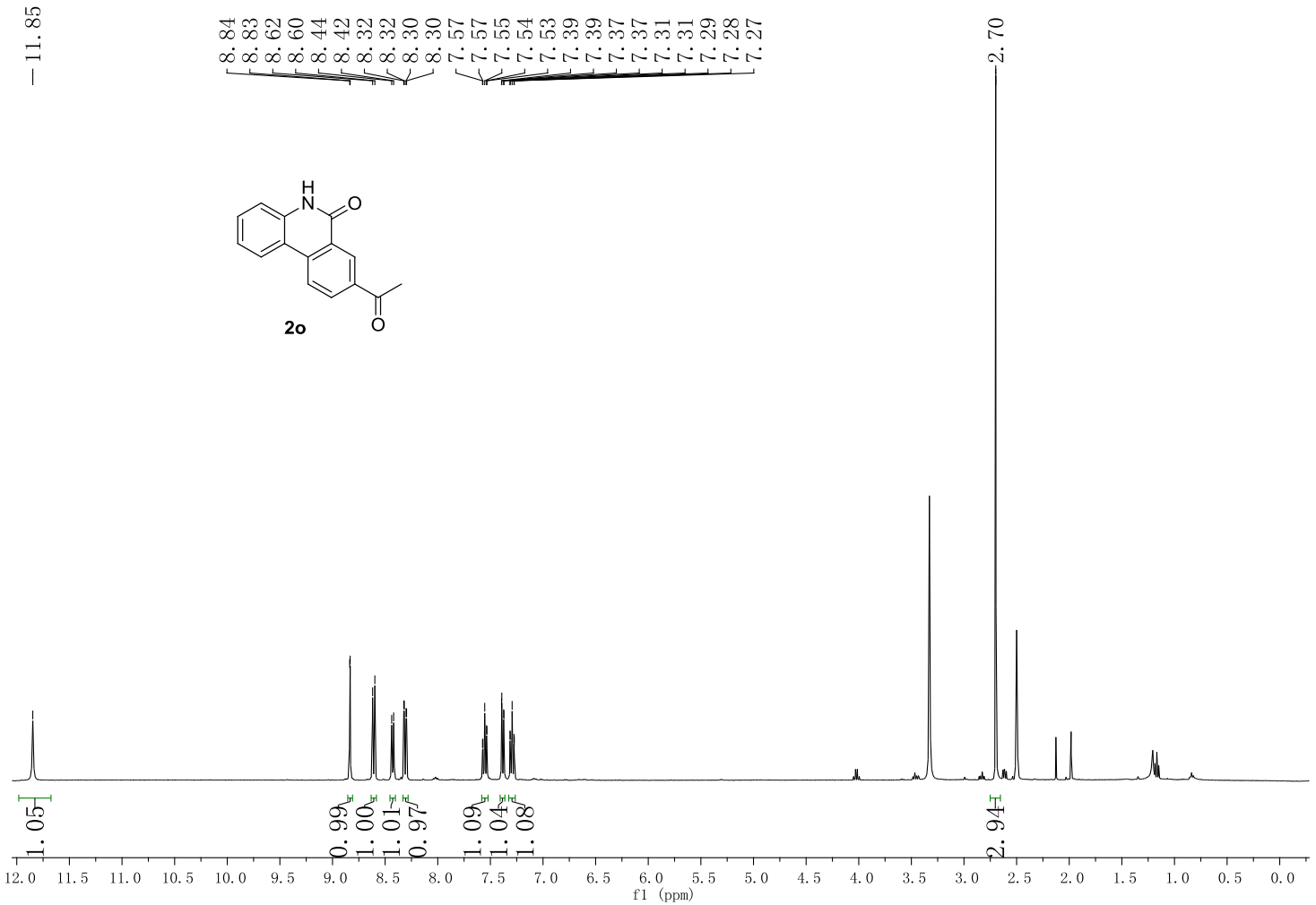

160.39
138.03
137.72
131.39
129.11
128.54
128.21
126.29
125.76
124.87
124.83
124.78
124.49
123.10
116.96
116.84
H
N
O
CF3
2l
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

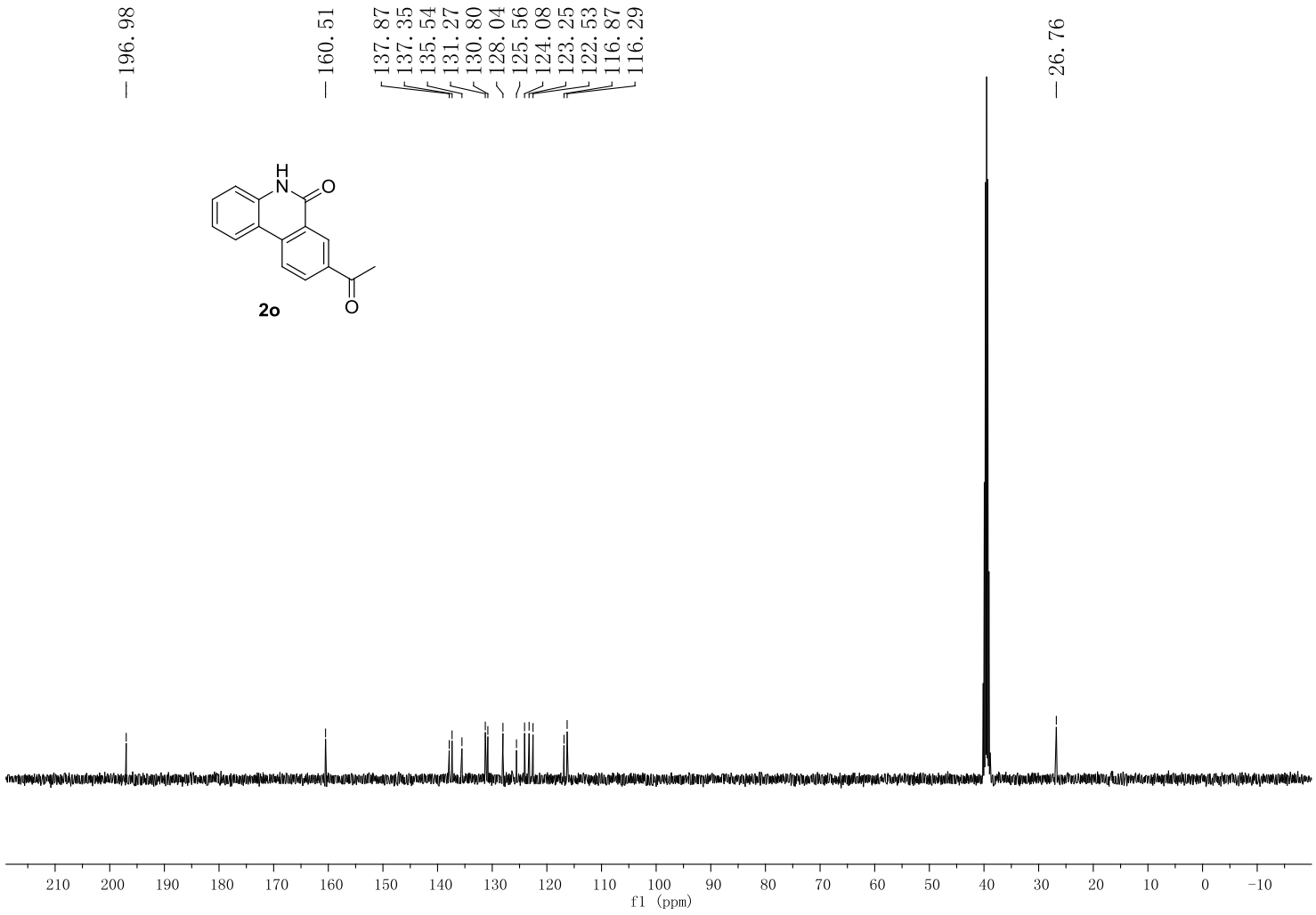

11.83
8.61
8.60
8.59
8.58
8.38
8.36
7.98
7.98
7.96
7.95
7.76
7.75
7.74
7.73
7.72
7.71
7.51
7.49
7.47
7.38
7.36
7.29
7.27
7.25
7.25
H
N
O
F
2m
0.97
1.01
1.00
0.98
1.02
1.02
0.99
1.00
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

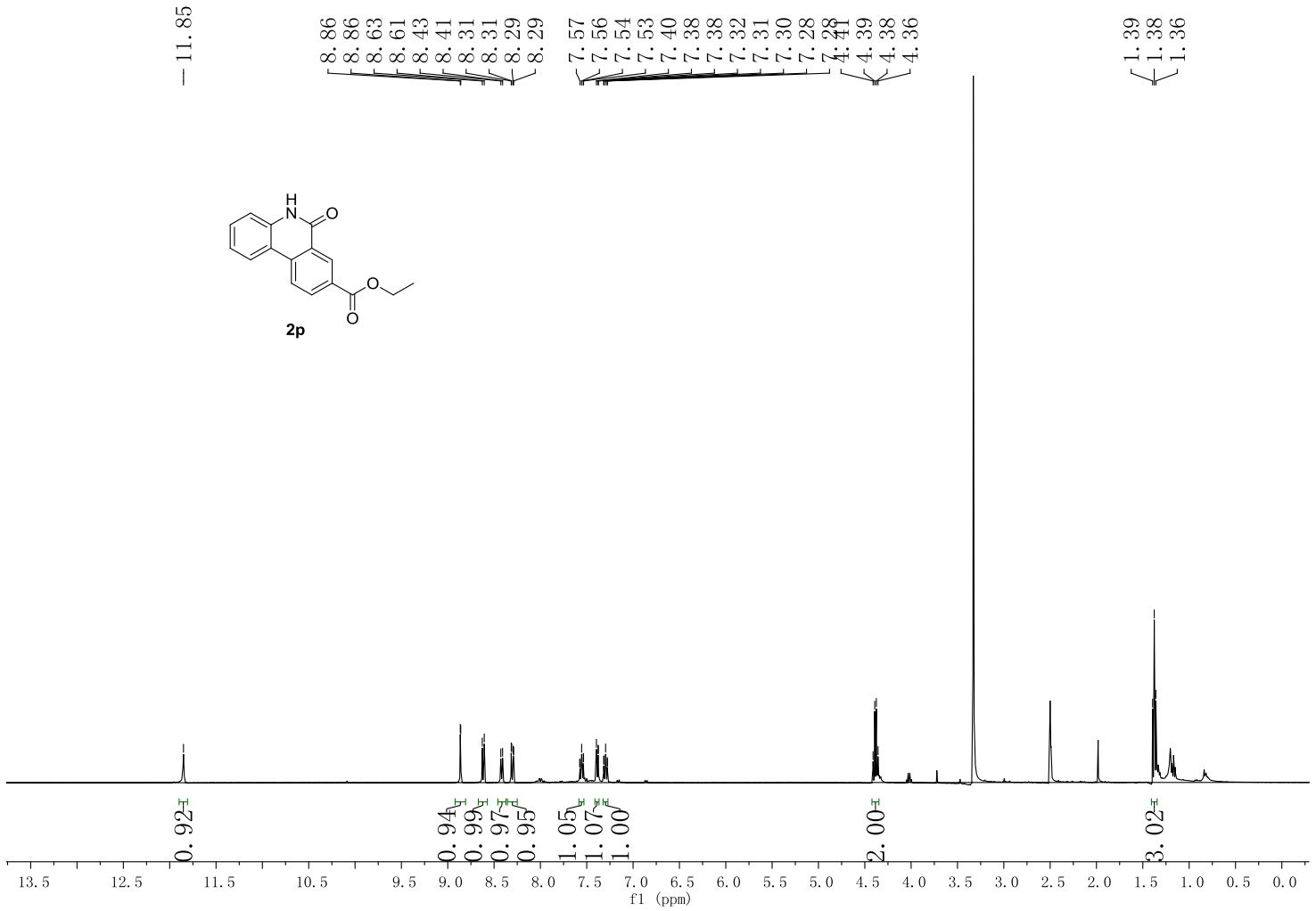

162.78
160.33
159.92
159.89
136.04
131.08
131.06
129.47
127.68
127.61
125.91
125.83
123.27
122.49
121.07
120.85
117.06
116.18
112.59
112.37
H
N
O
F
2m
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

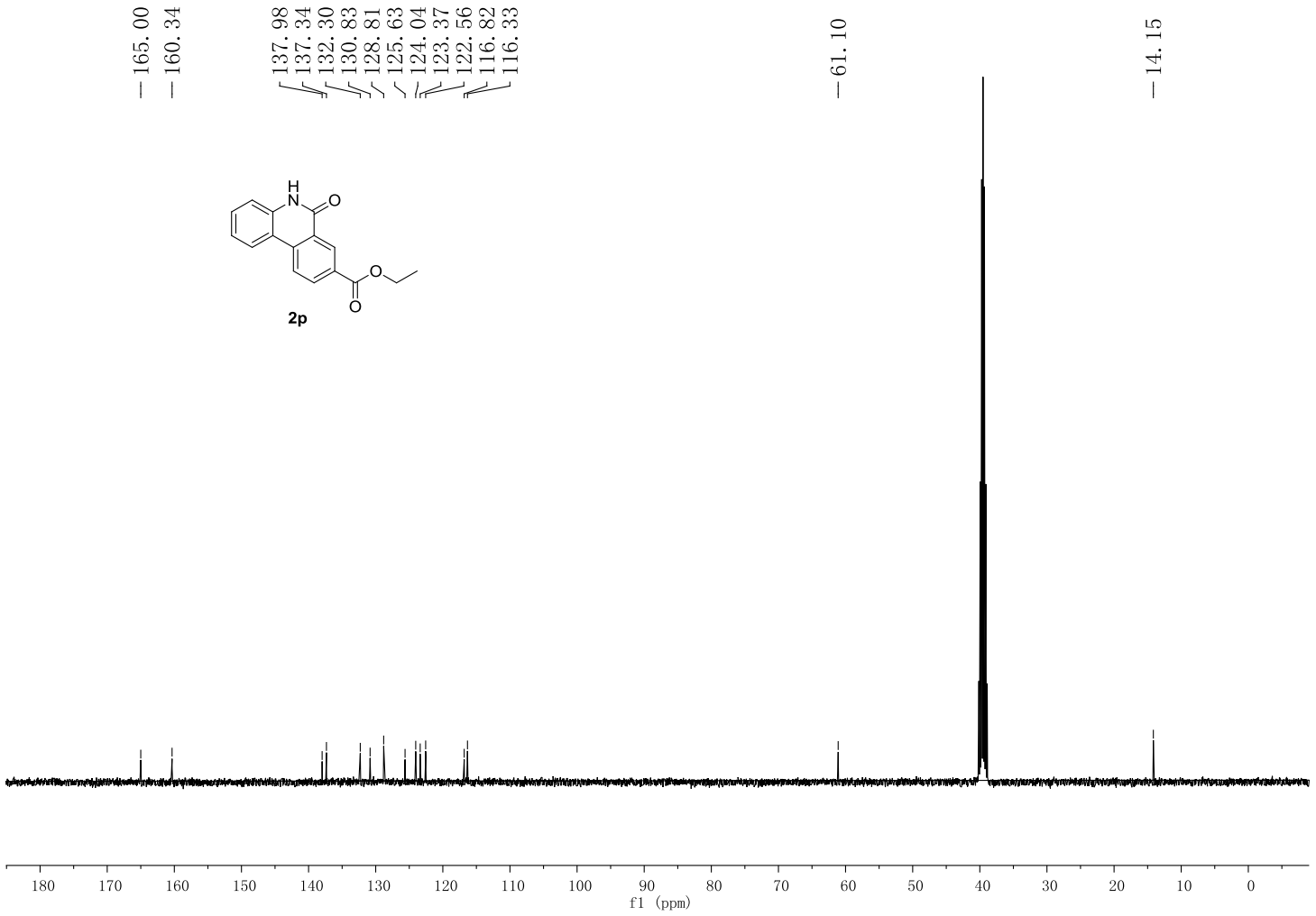

11.83
8.53
8.51
8.36
8.34
8.23
8.23
7.88
7.87
7.86
7.85
7.52
7.52
7.50
7.49
7.48
7.37
7.35
7.29
7.28
7.27
7.25
7.25
H
N
O
Cl
2n
0.98
1.00
1.00
0.93
1.02
1.04
1.01
1.01
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

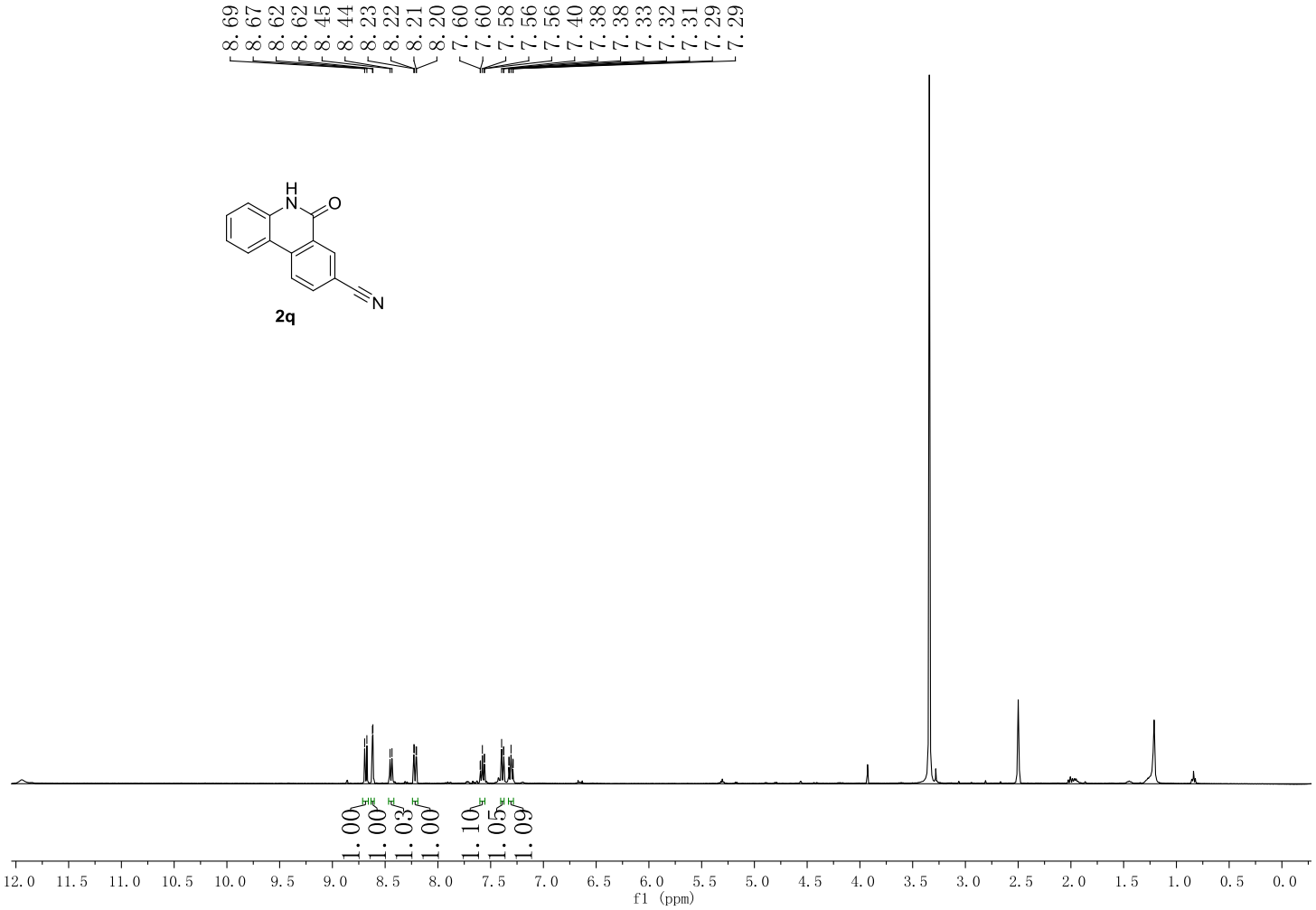

159.68
136.45
133.07
132.73
132.69
129.96
127.15
126.55
125.15
123.41
122.51
116.85
116.23
H
N
O
Cl
2n
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

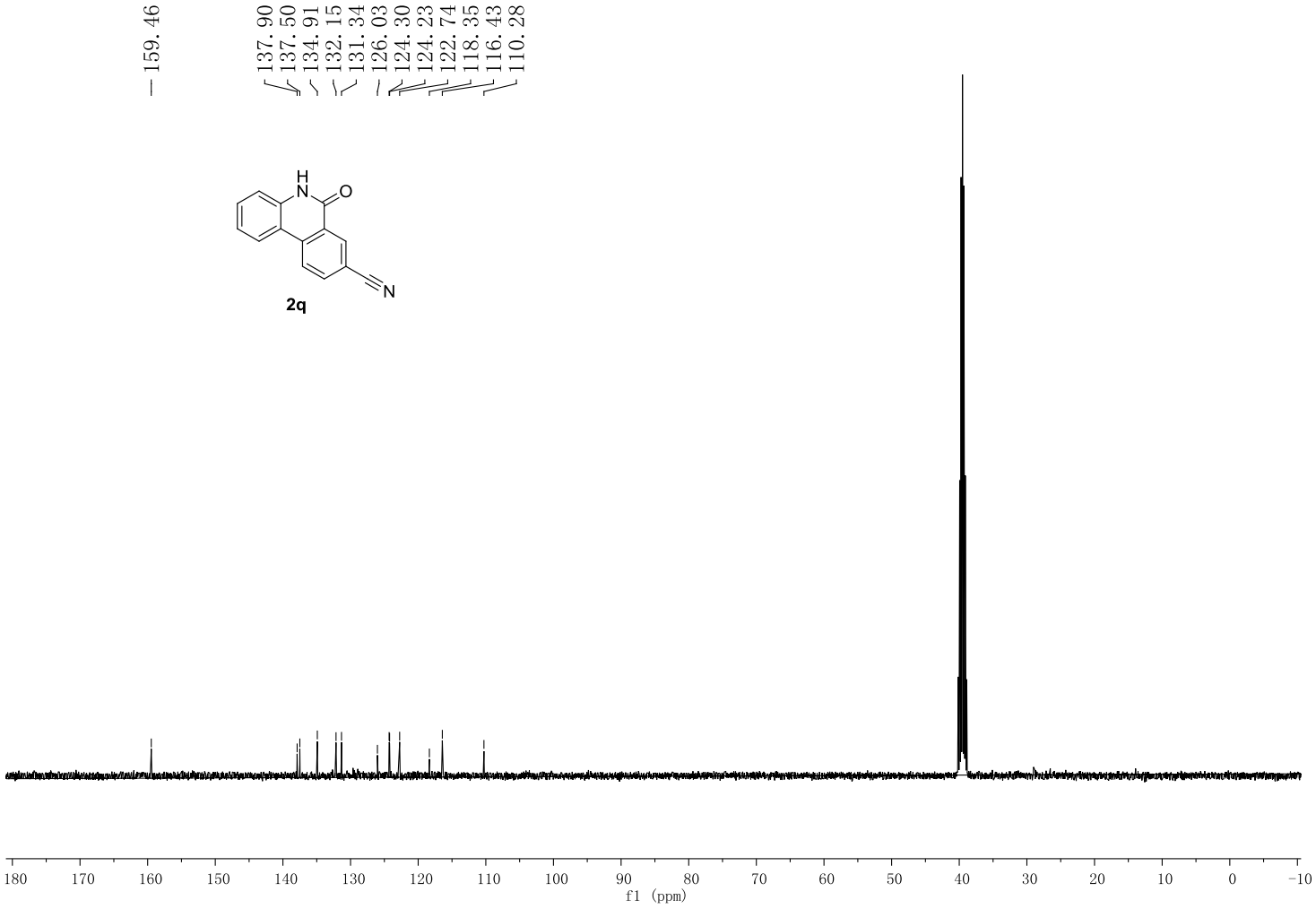

11.85
8.84
8.83
8.62
8.60
8.44
8.42
8.32
8.32
8.30
8.30
7.57
7.57
7.55
7.54
7.53
7.39
7.39
7.37
7.37
7.31
7.31
7.29
7.28
7.27
2.70
2o
1.05
0.99
1.00
1.01
0.97
1.09
1.04
1.08
2.94
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

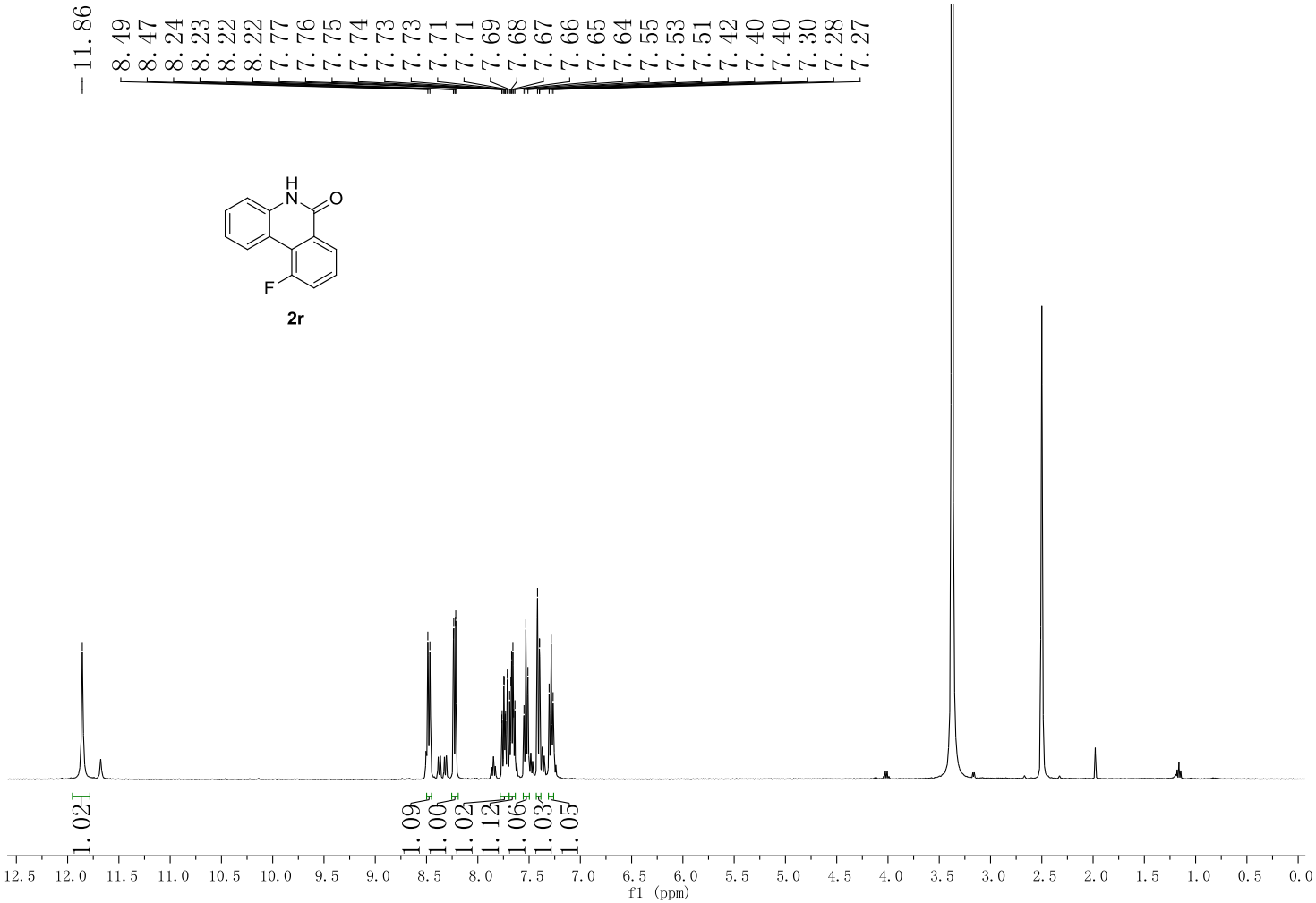

196.98
160.51
137.87
137.35
135.54
131.27
130.80
128.04
125.56
124.08
123.25
122.53
116.87
116.29
26.76
2o
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

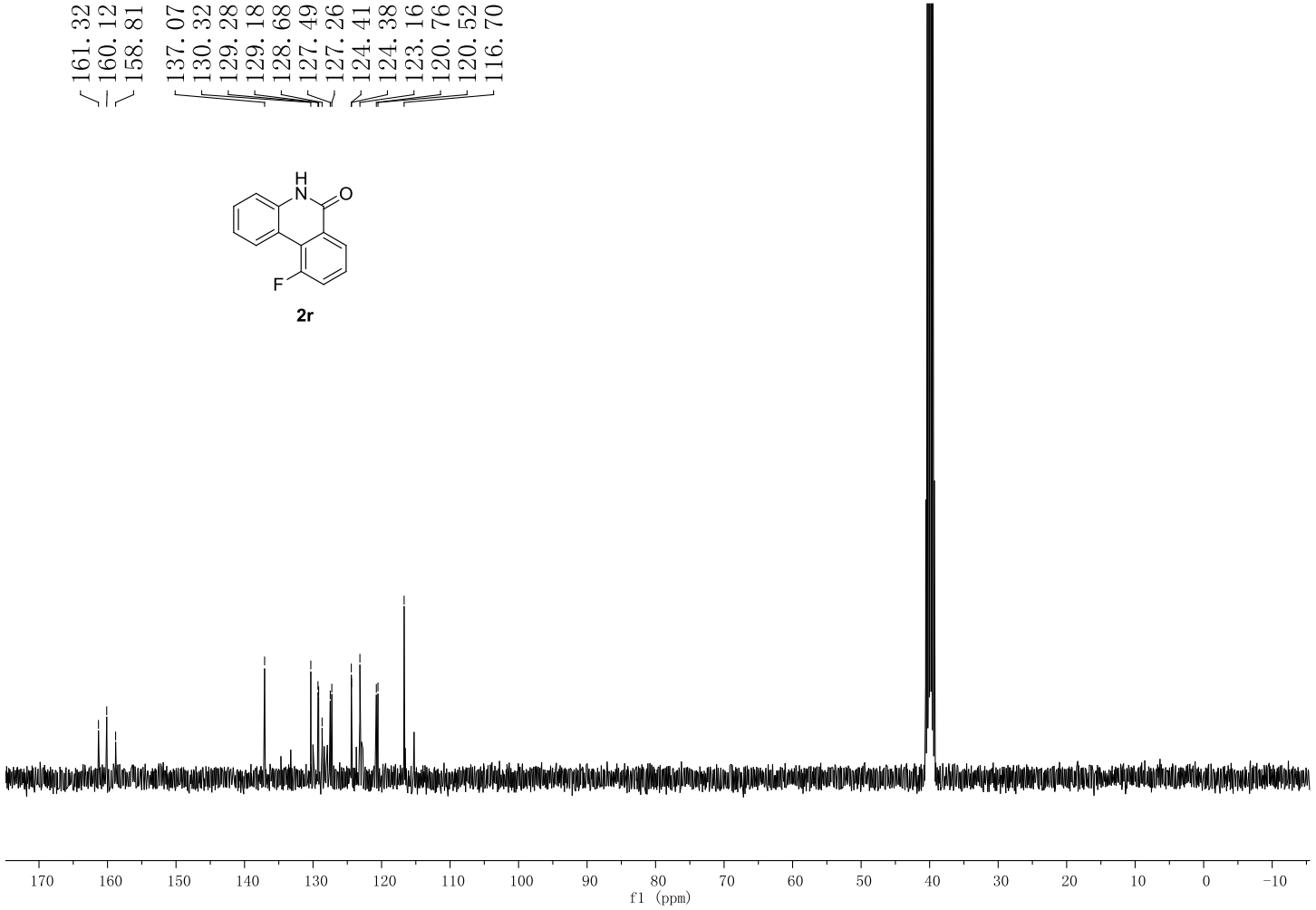

11.85
8.86
8.86
8.63
8.61
8.43
8.41
8.31
8.31
8.29
8.29
7.57
7.56
7.54
7.53
7.40
7.38
7.38
7.32
7.31
7.30
7.28
7.28
4.41
4.39
4.38
4.36
1.39
1.38
1.36
2p
0.92
0.94
0.99
0.97
0.95
1.05
1.07
1.00
2.00
3.02
f1 (ppm)

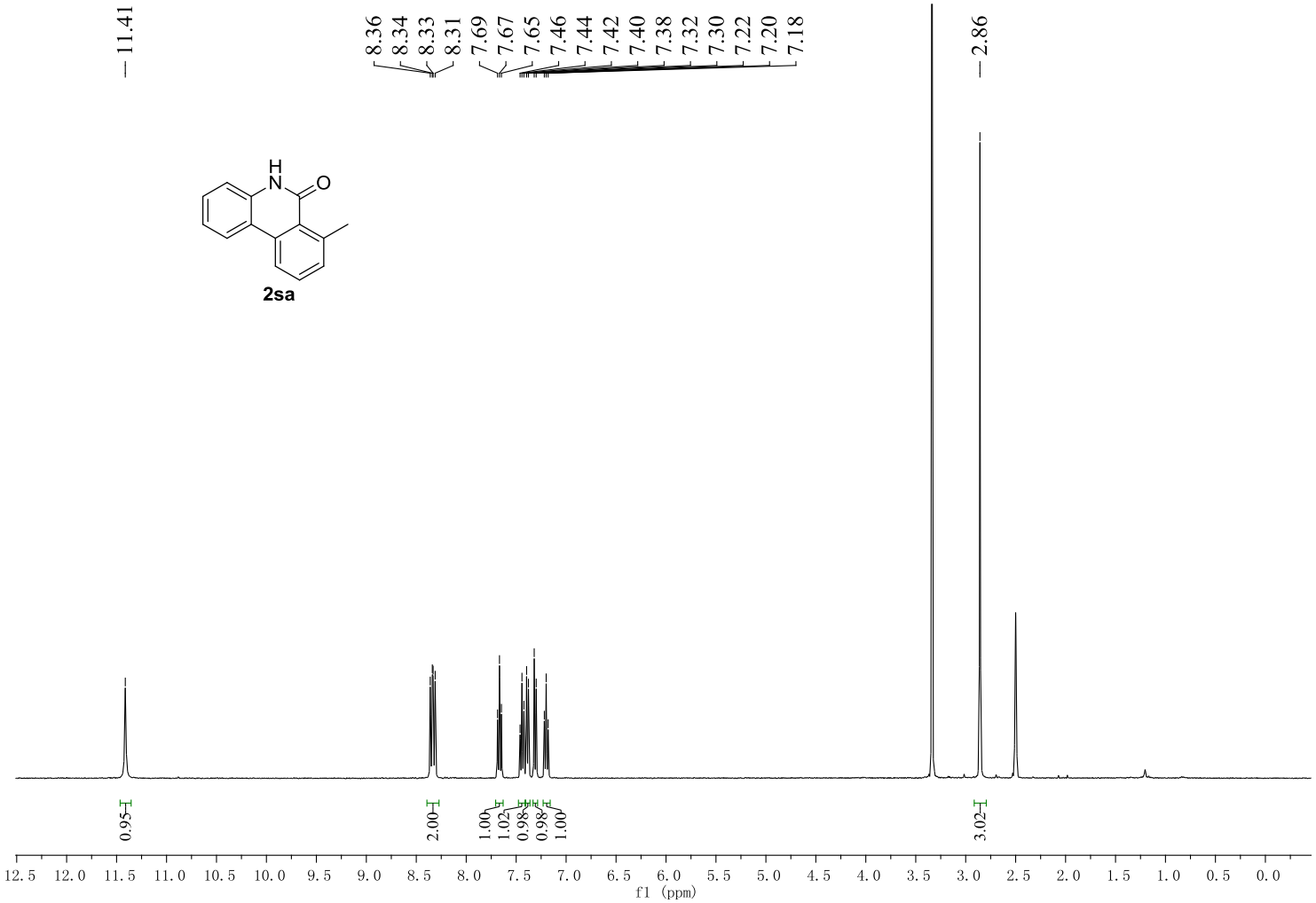

165.00
160.34
137.98
137.34
132.30
130.83
128.81
125.63
124.04
123.37
122.56
116.82
116.33
61.10
14.15
H
N
O
O
O
2p
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

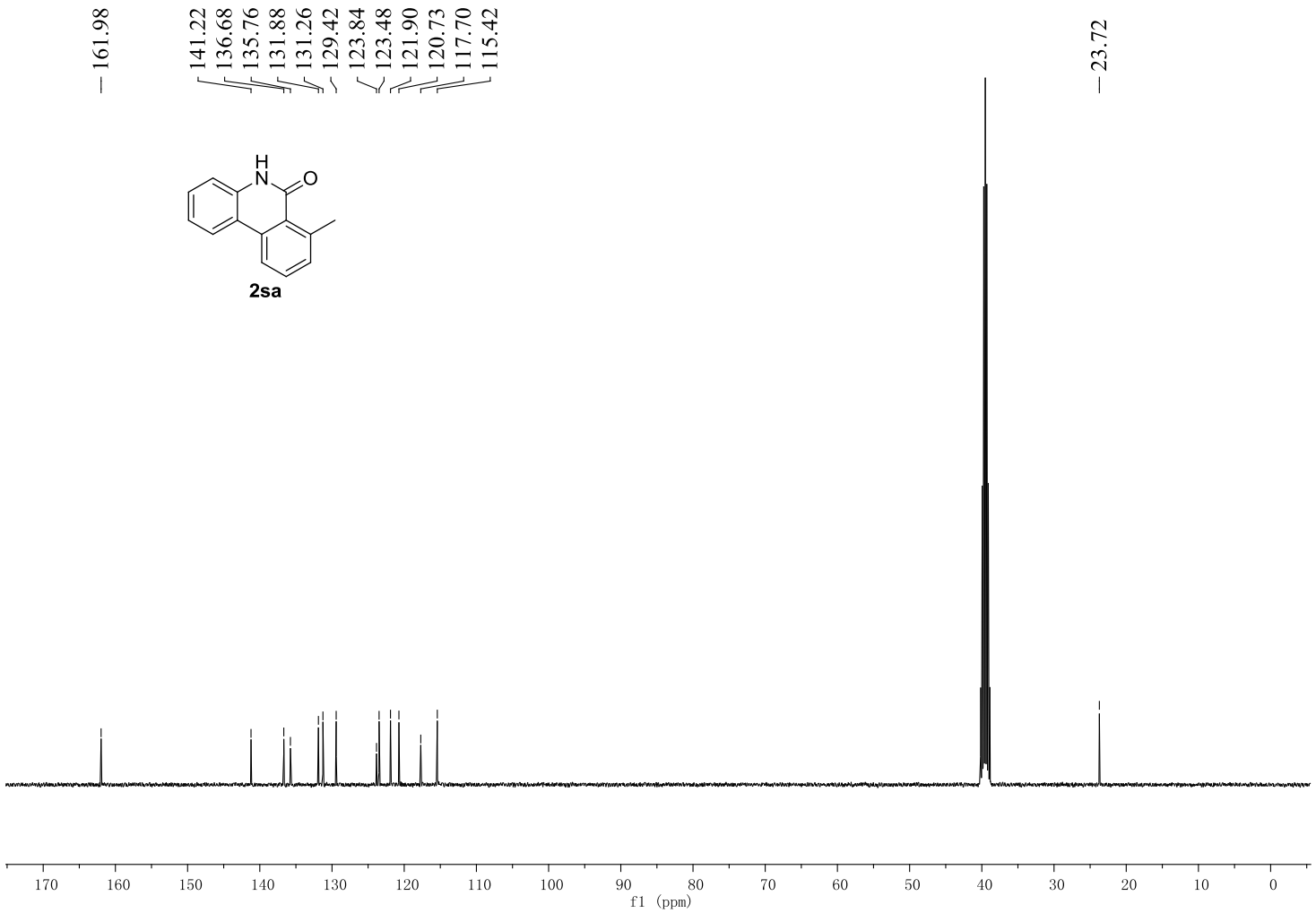

8.69
8.67
8.62
8.62
8.45
8.44
8.23
8.22
8.21
8.20
7.60
7.60
7.58
7.56
7.56
7.40
7.38
7.38
7.33
7.32
7.31
7.29
7.29
H
N
O
N
2q
1.00
1.00
1.03
1.00
1.10
1.05
1.09
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

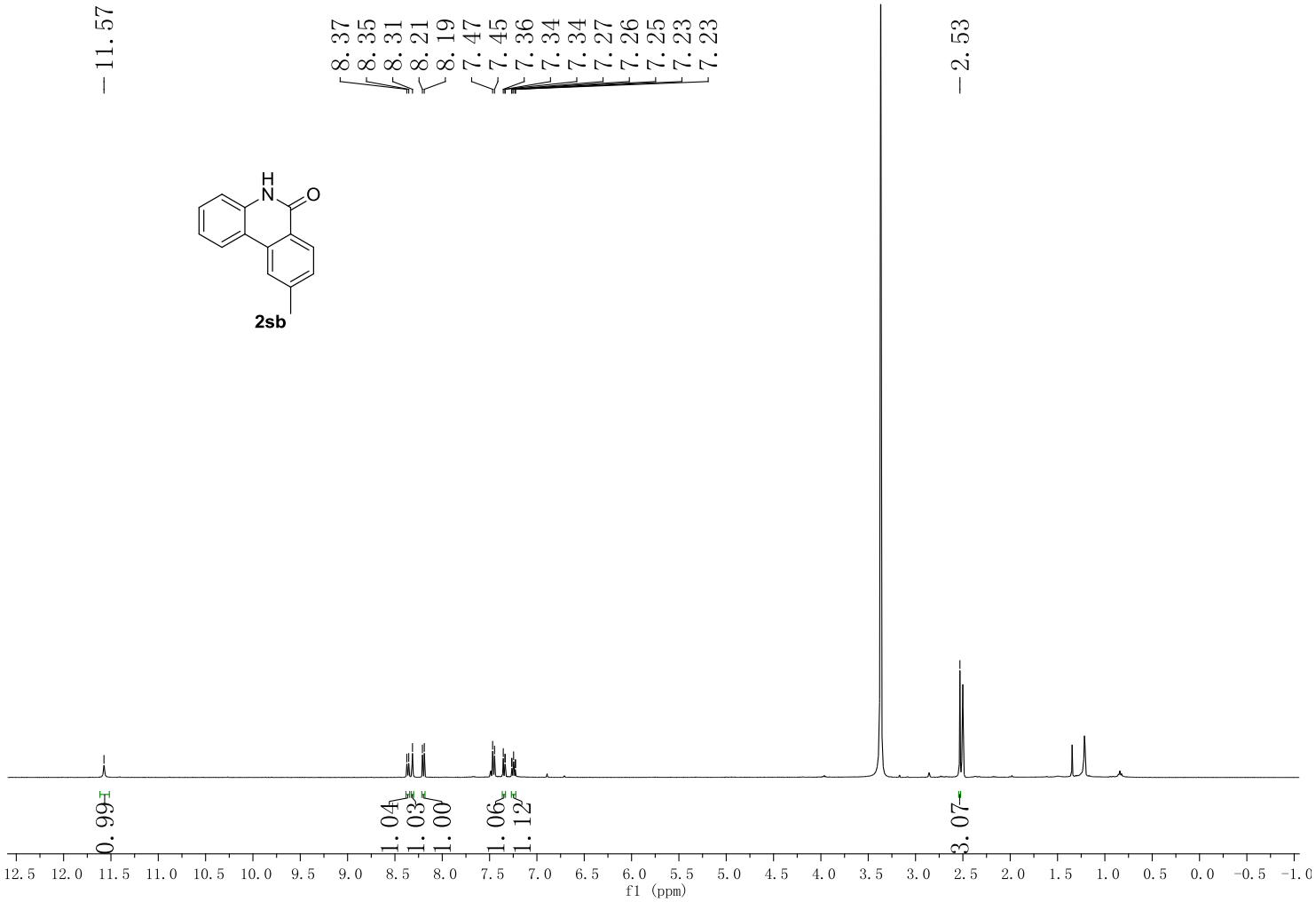

159.46
137.90
137.50
134.91
132.15
131.34
126.03
124.30
124.23
122.74
118.35
116.43
110.28
H
N
O
N
2q
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

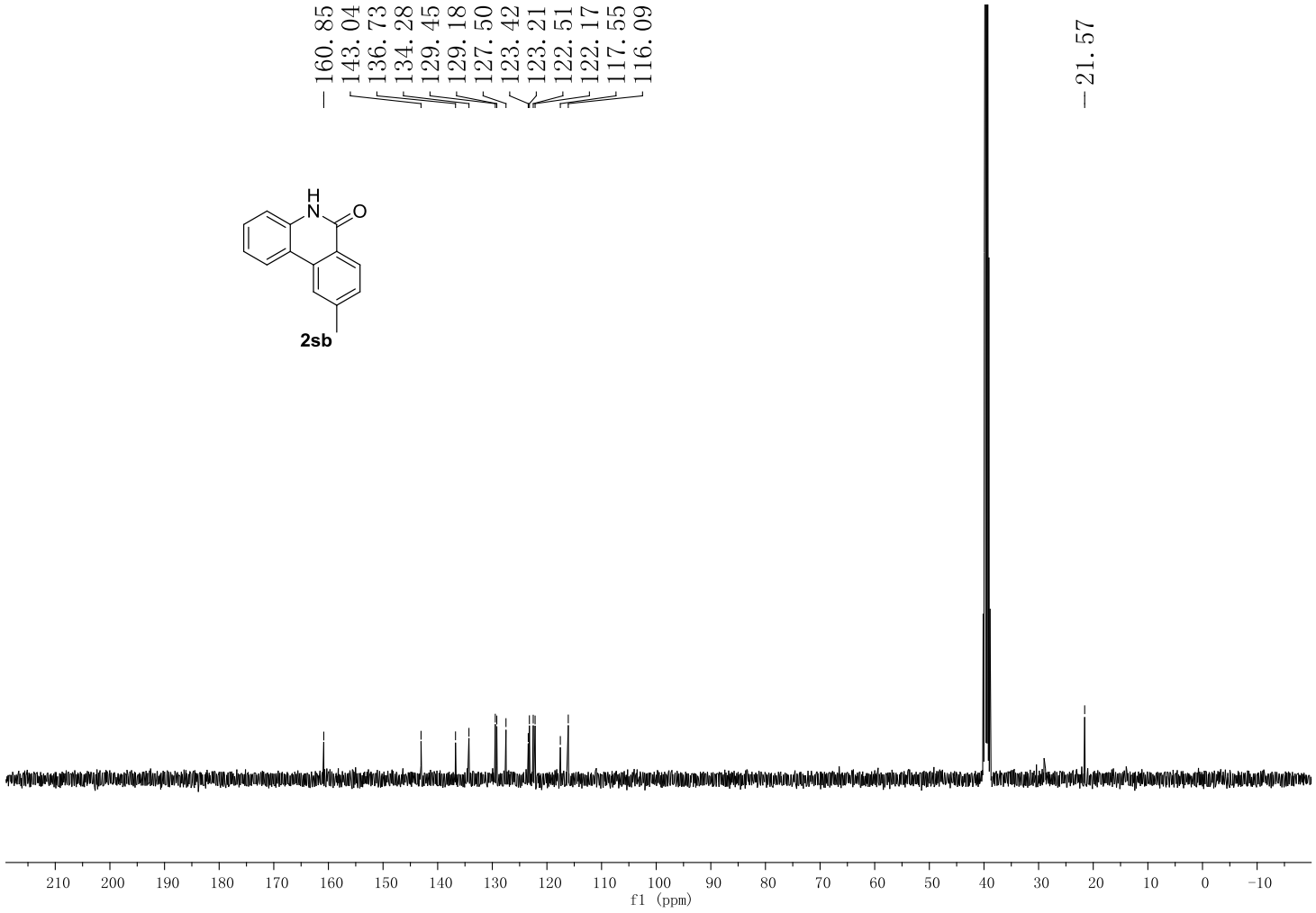

11.86
8.49
8.47
8.24
8.23
8.22
8.22
7.77
7.76
7.75
7.74
7.73
7.73
7.71
7.71
7.69
7.68
7.67
7.66
7.65
7.64
7.55
7.53
7.51
7.42
7.40
7.40
7.30
7.28
7.27
H
N
O
F
2r
1.02
1.09
1.00
1.02
1.12
1.06
1.03
1.05
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

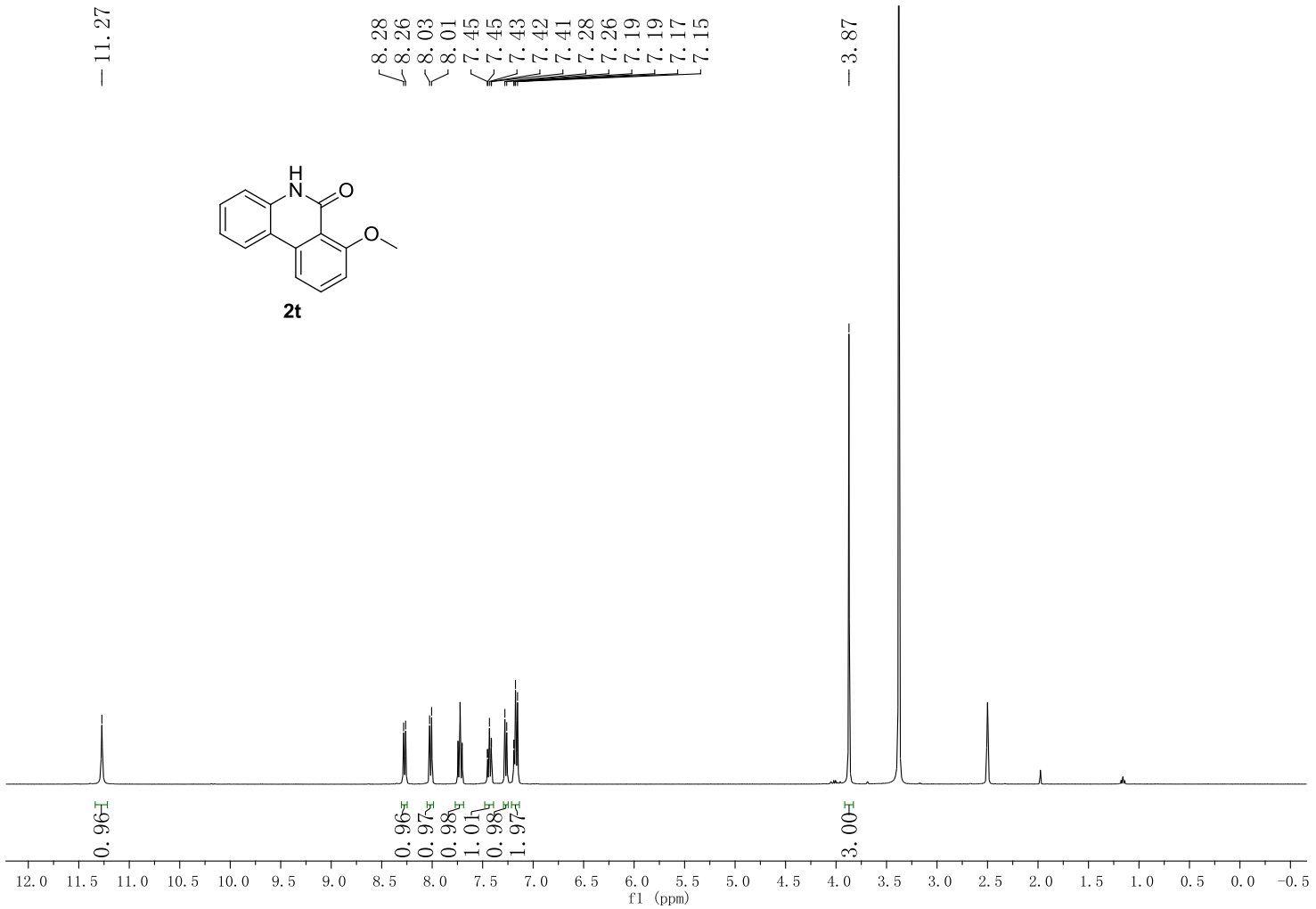

161.32
160.12
158.81
137.07
130.32
129.28
129.18
128.68
127.49
127.26
124.41
124.38
123.16
120.76
120.52
116.70
H
N
O
F
2r
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

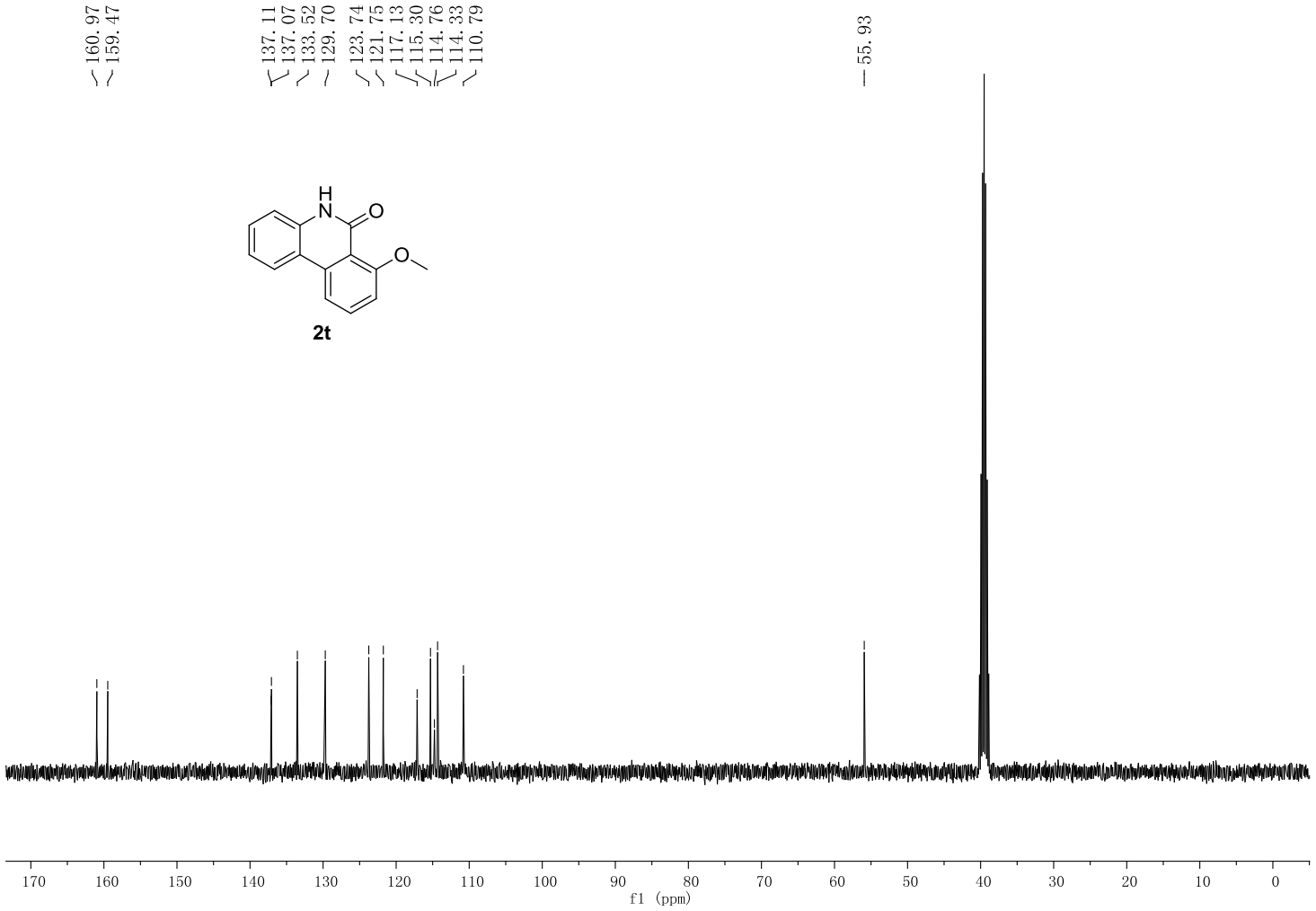

11.41
8.36
8.34
8.33
8.31
7.69
7.67
7.65
7.46
7.44
7.42
7.40
7.38
7.32
7.30
7.22
7.20
7.18
2.86
H
N
O
2sa
0.95
2.00
1.00
1.02
0.98
0.98
1.00
3.02
f1 (ppm)

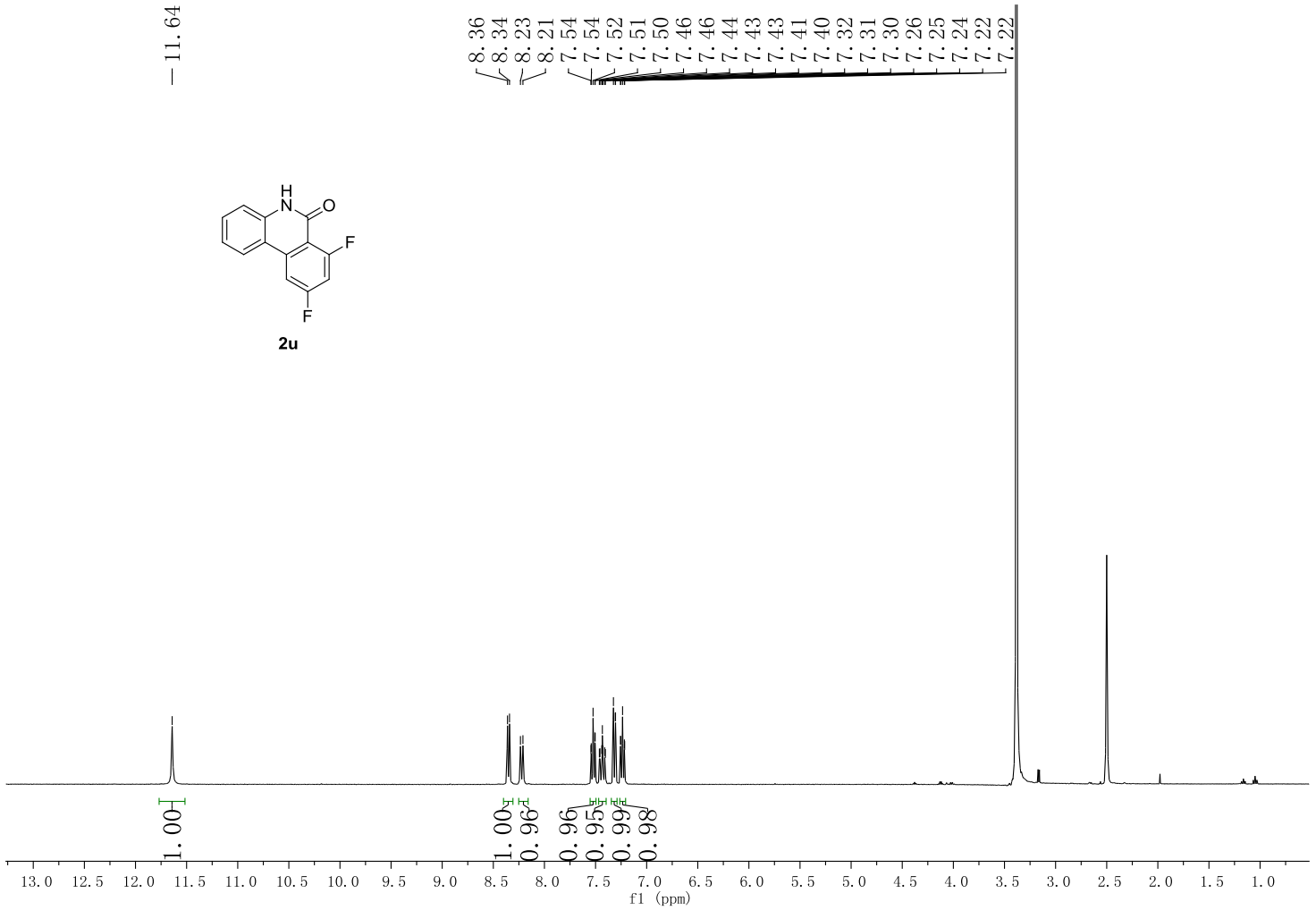

161.98
141.22
136.68
135.76
131.88
131.26
129.42
123.84
123.48
121.90
120.73
117.70
115.42
23.72
H
N
O
2sa
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

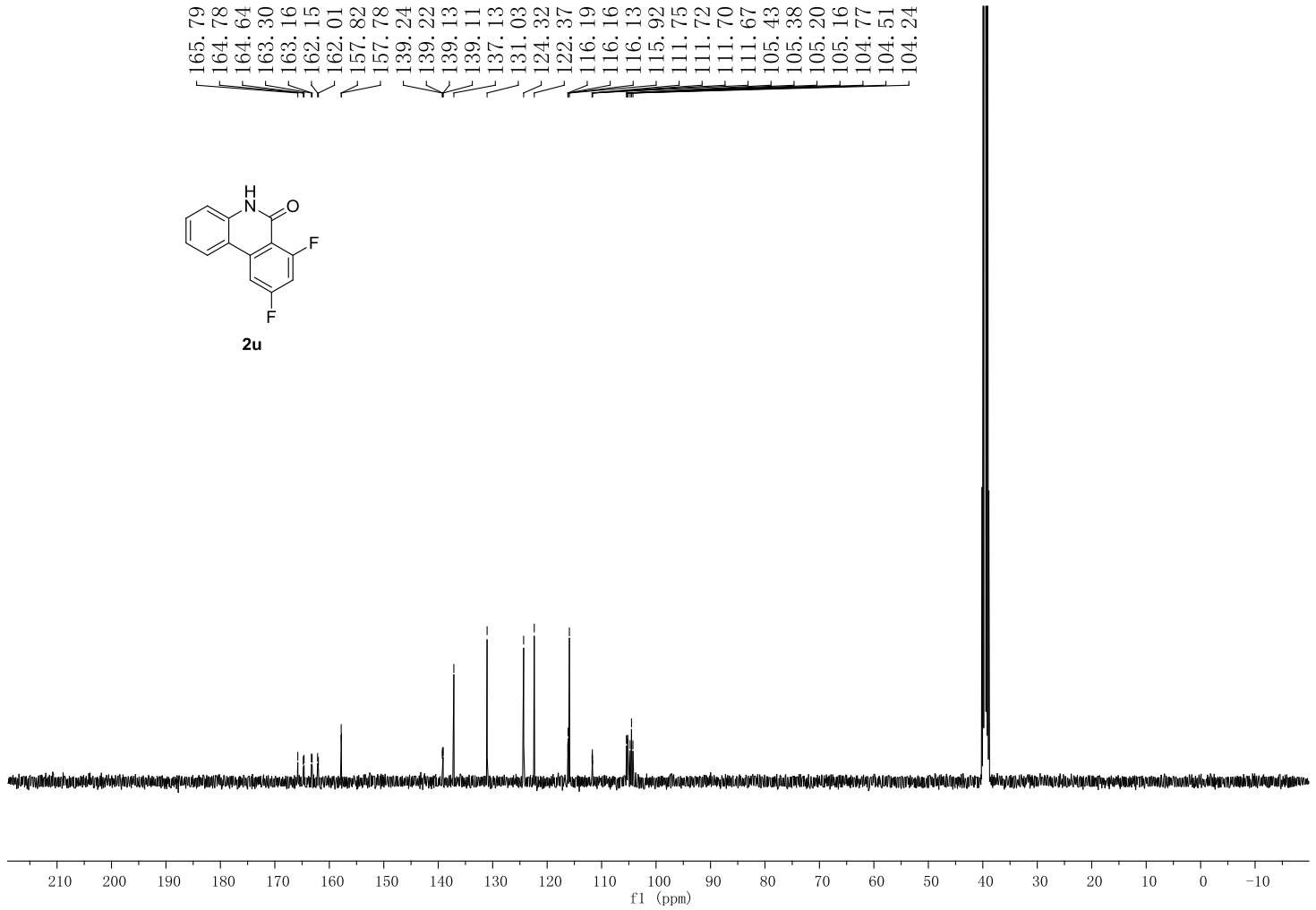

11.57
8.37
8.35
8.31
8.21
8.19
7.47
7.45
7.36
7.34
7.34
7.27
7.26
7.25
7.23
7.23
2.53
H
N
O
2sb
0.99
1.04
1.03
1.00
1.06
1.12
3.07
f1 (ppm)

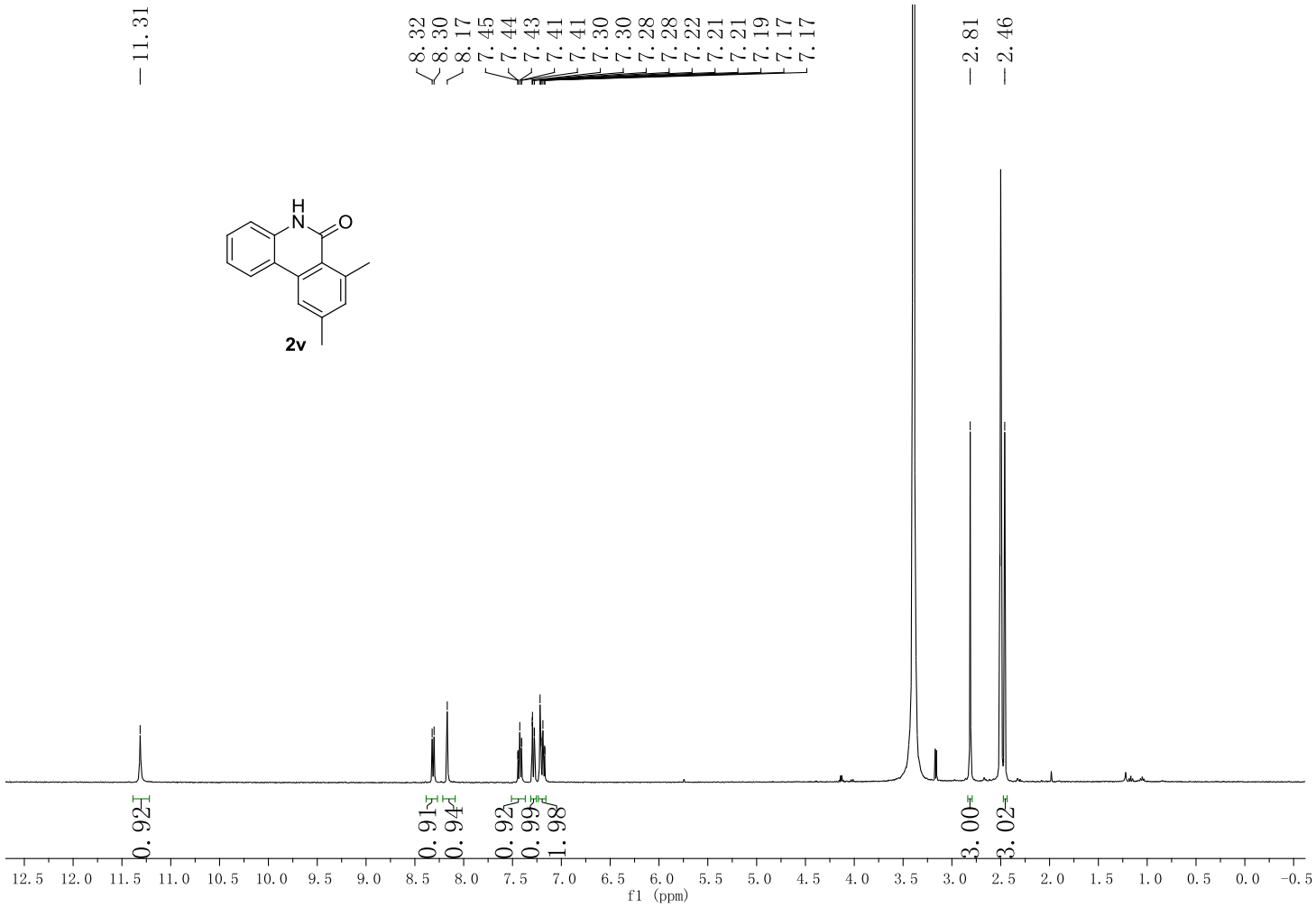

160.85
143.04
136.73
134.28
129.45
129.18
127.50
123.42
123.21
122.51
122.17
117.55
116.09
21.57
H
N
O
2sb
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

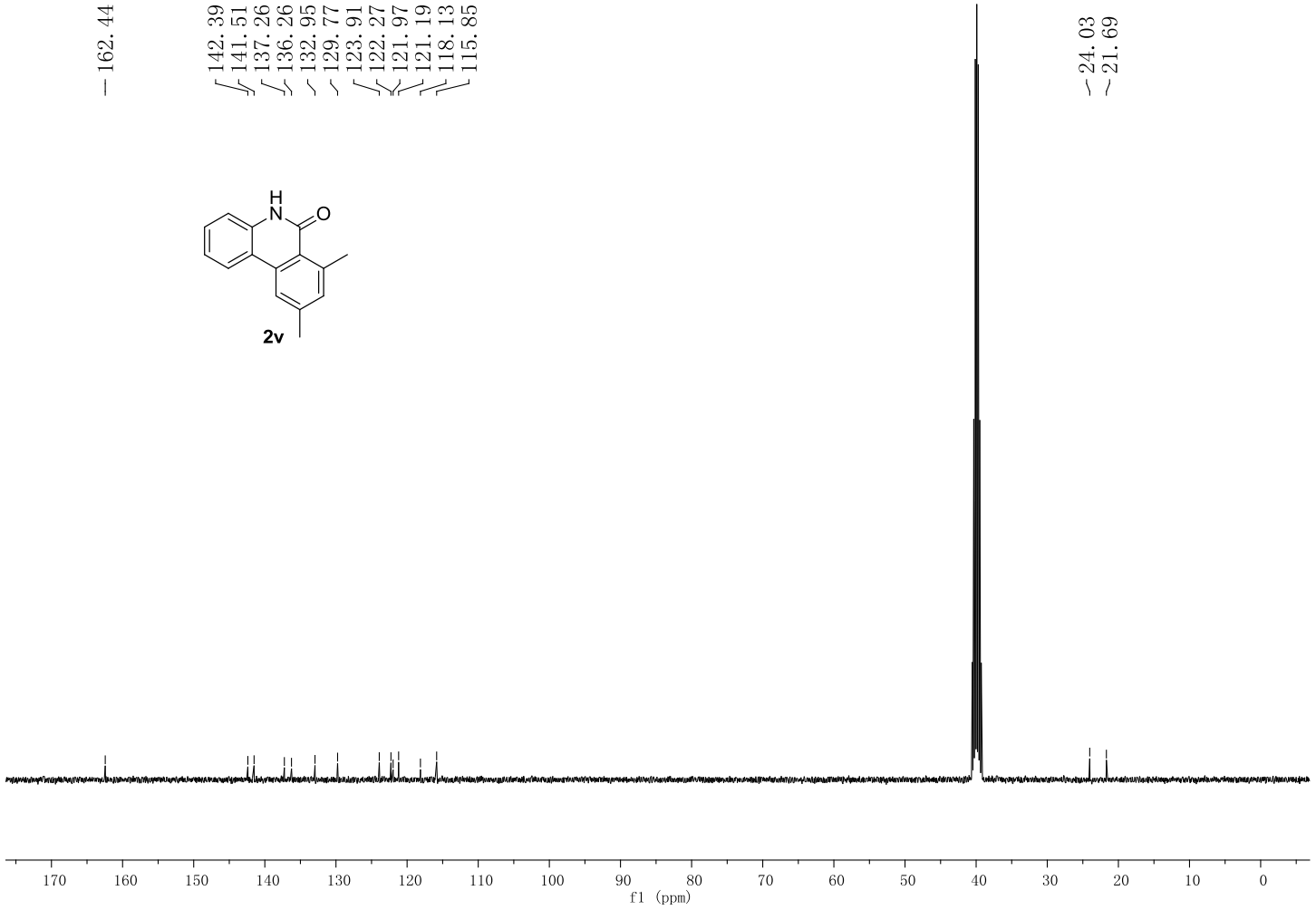

11.27
8.28
8.26
8.03
8.01
7.45
7.45
7.43
7.42
7.41
7.28
7.26
7.19
7.19
7.17
7.15
3.87
H
N
O
O
2t
0.96
0.96
0.97
0.98
1.01
0.98
1.97
3.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

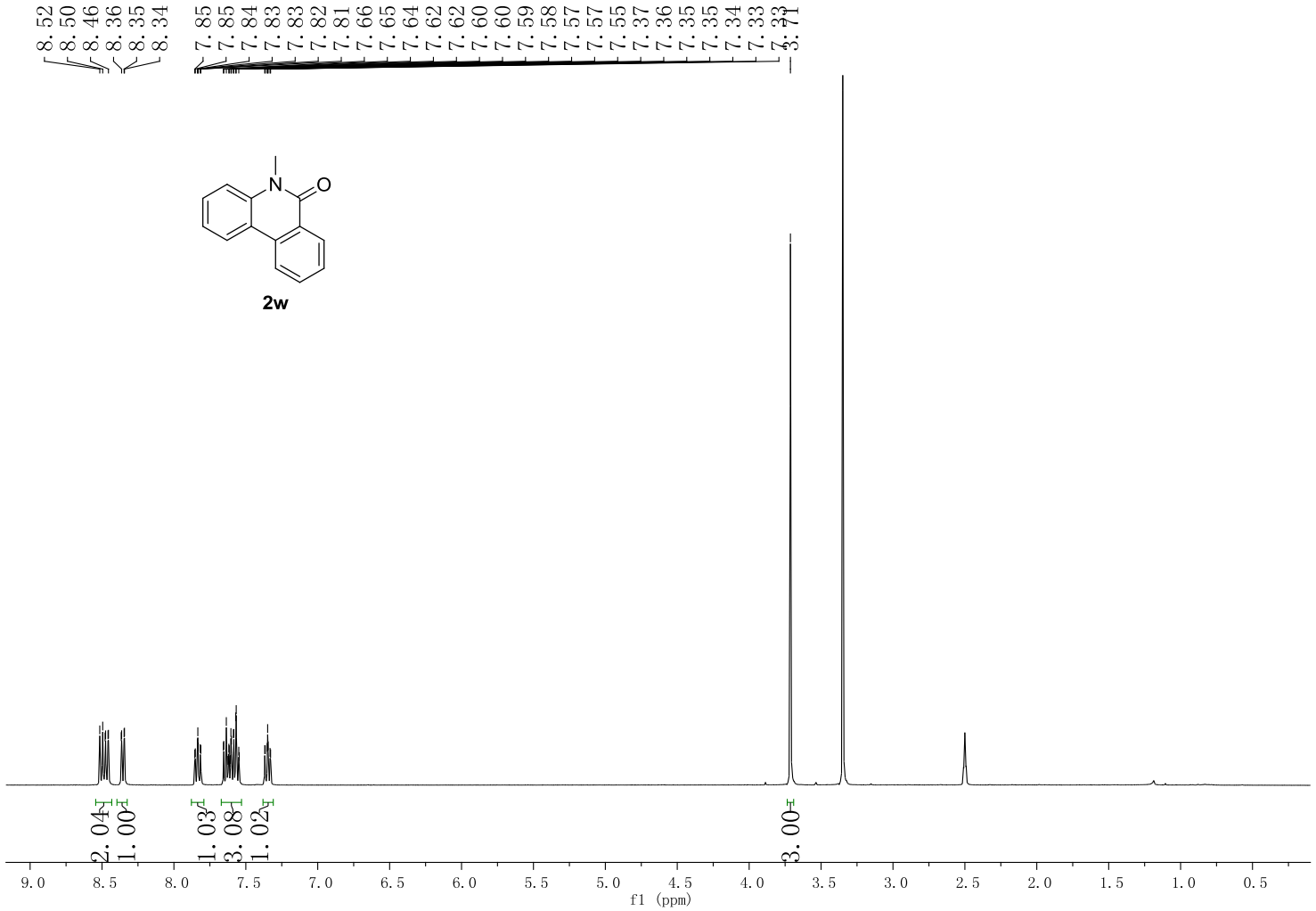

160.97
159.47
137.11
137.07
133.52
129.70
123.74
121.75
117.13
115.30
114.76
114.33
110.79
55.93
H
N
O
O
2t
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

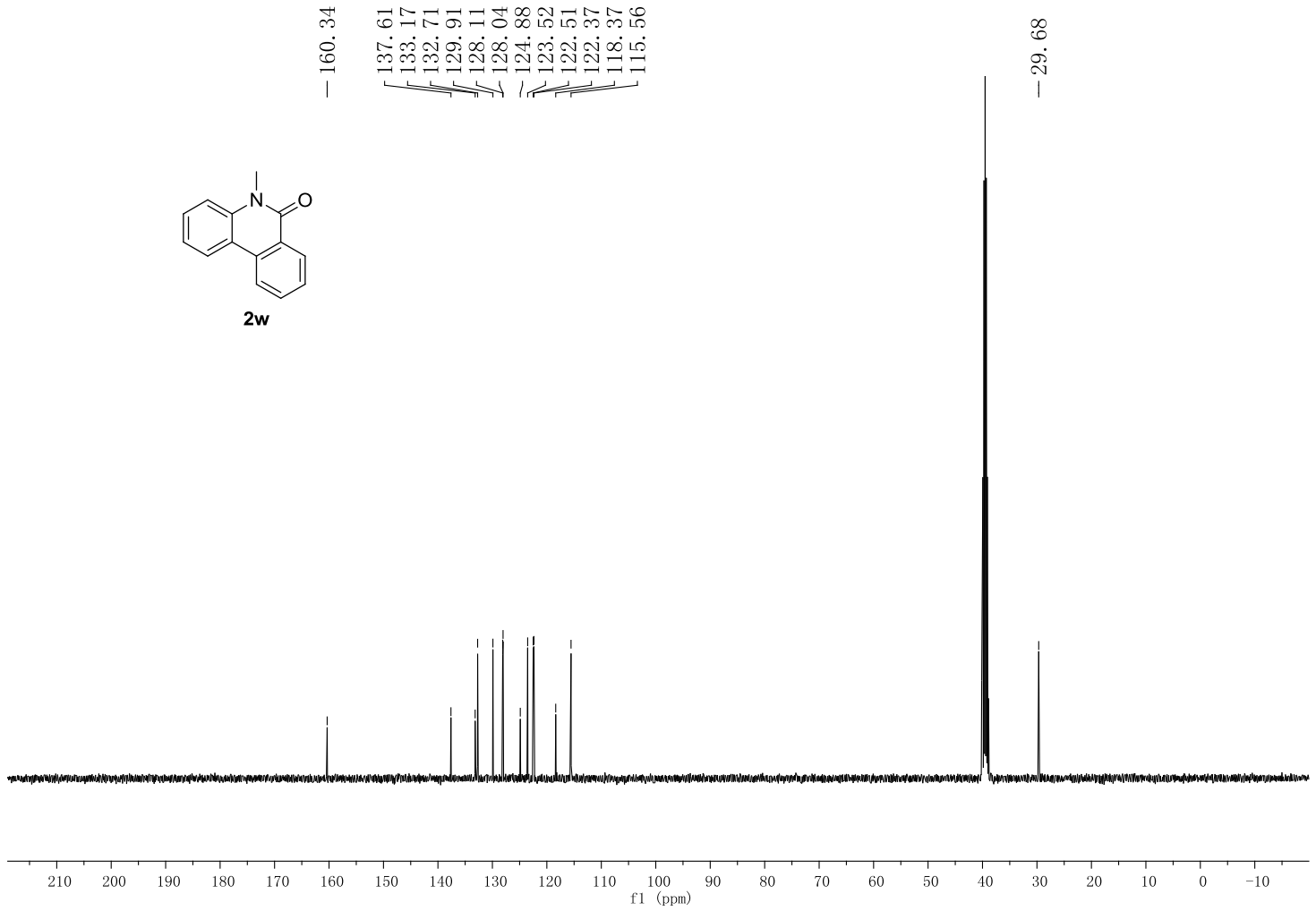

11.64
8.36
8.34
8.23
8.21
7.54
7.54
7.52
7.51
7.50
7.46
7.46
7.44
7.43
7.43
7.41
7.40
7.32
7.31
7.30
7.26
7.25
7.24
7.22
7.22
H
N
O
F
F
2u
1.00
1.00
0.96
0.96
0.95
0.99
0.98
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

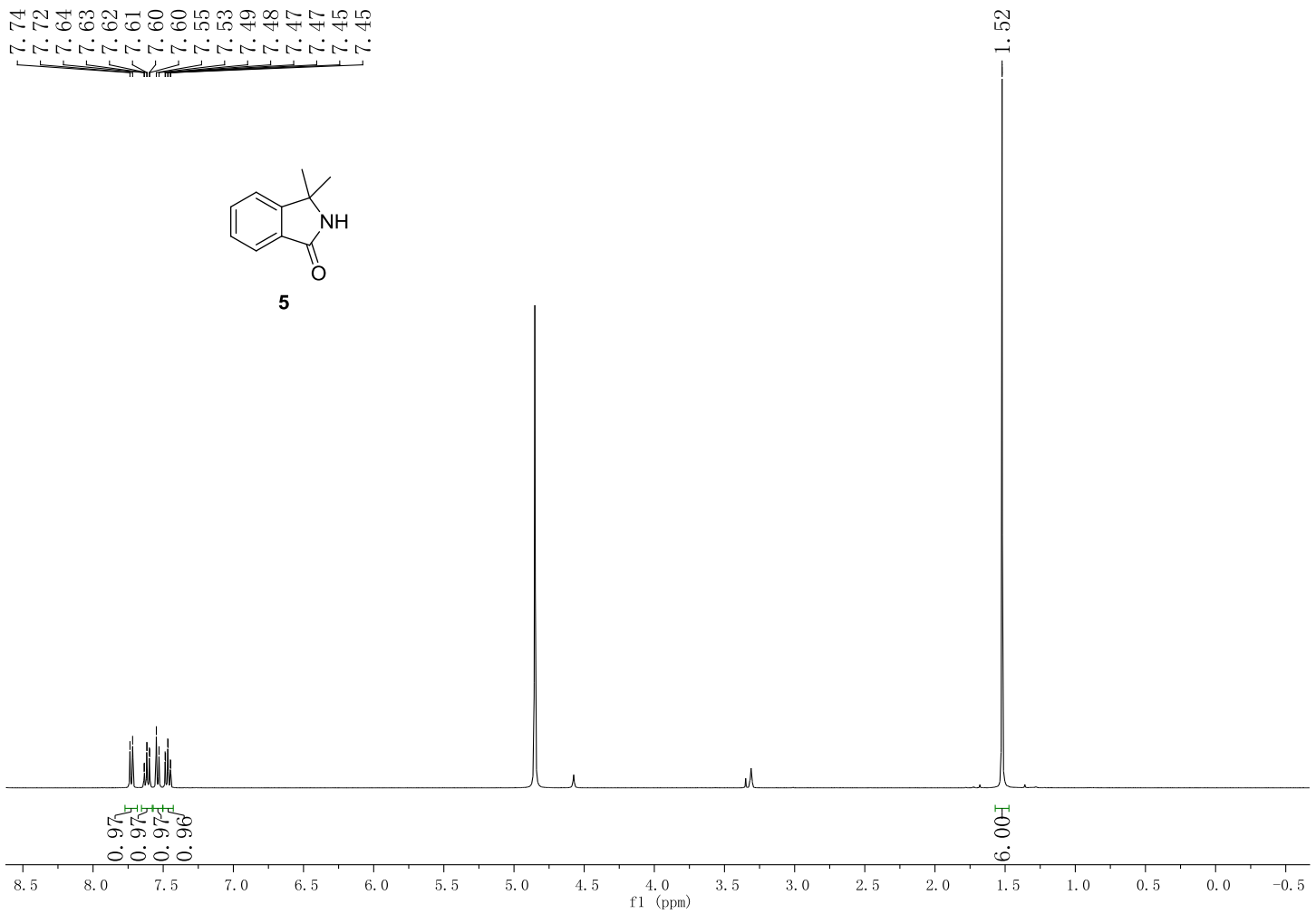

165.79
164.78
164.64
163.30
163.16
162.15
162.01
157.82
157.78
139.24
139.22
139.13
139.11
137.13
131.03
124.32
122.37
116.19
116.16
116.13
115.92
111.75
111.72
111.70
111.67
105.43
105.38
105.20
105.16
104.77
104.51
104.24
H
N
O
F
F
2u
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

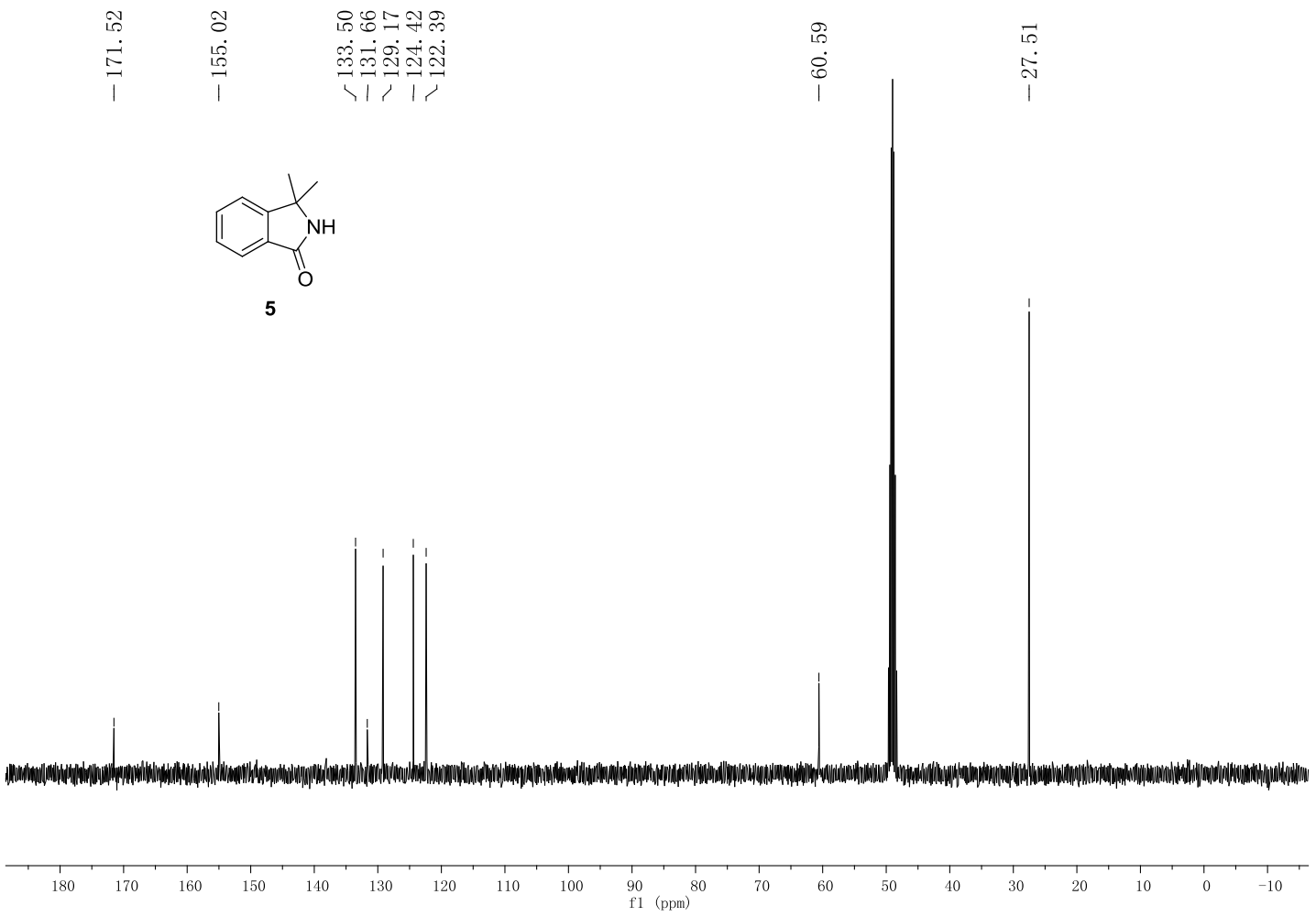

11.31
8.32
8.30
8.17
7.45
7.44
7.43
7.41
7.41
7.30
7.30
7.28
7.28
7.22
7.21
7.21
7.19
7.17
7.17
2.81
2.46
2v
0.92
0.91
0.94
0.92
0.99
1.98
3.00
3.02
f1 (ppm)

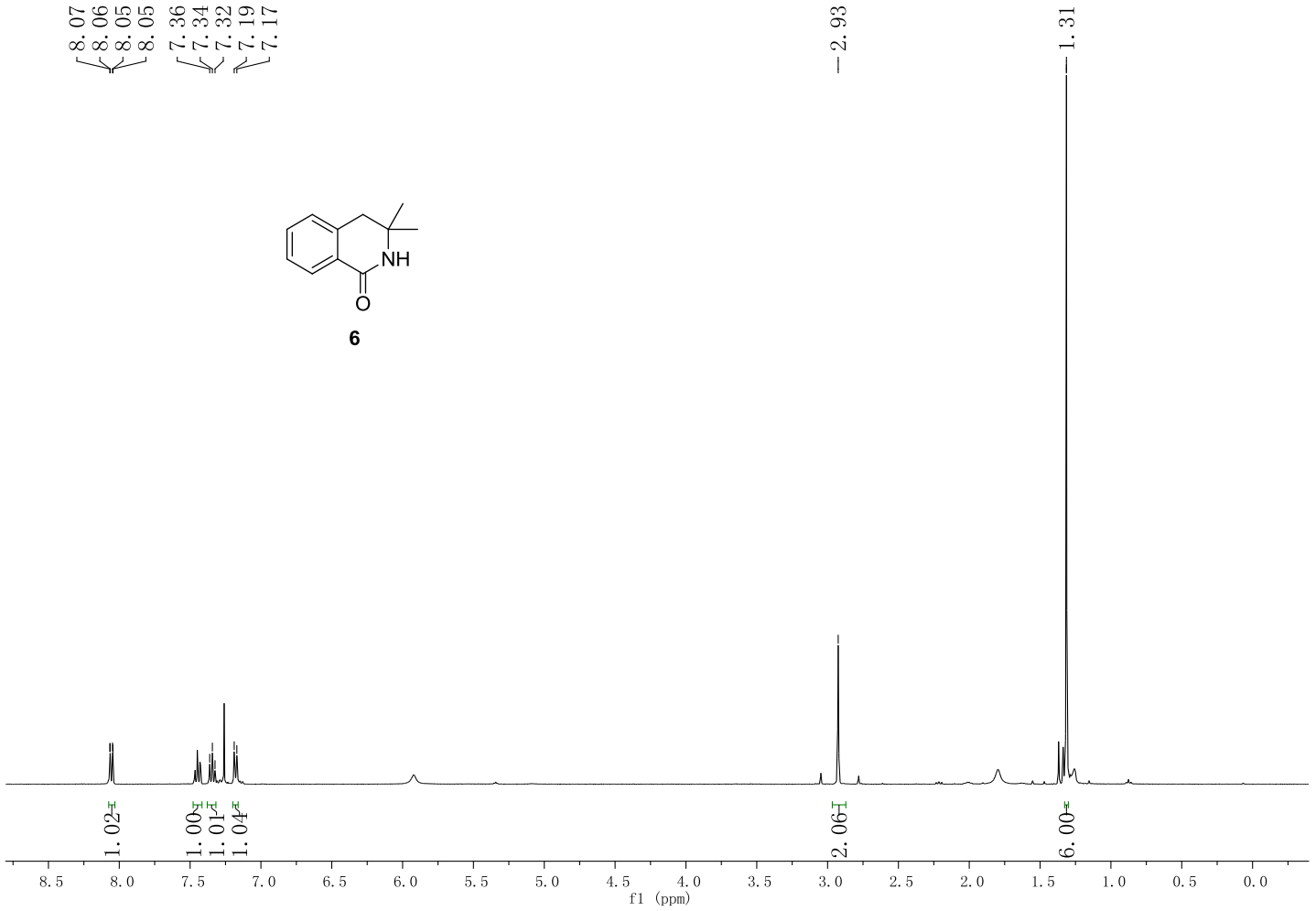

162.44
142.39
141.51
137.26
136.26
132.95
129.77
123.91
122.27
121.97
121.19
118.13
115.85
24.03
21.69
H
N
O
2v
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

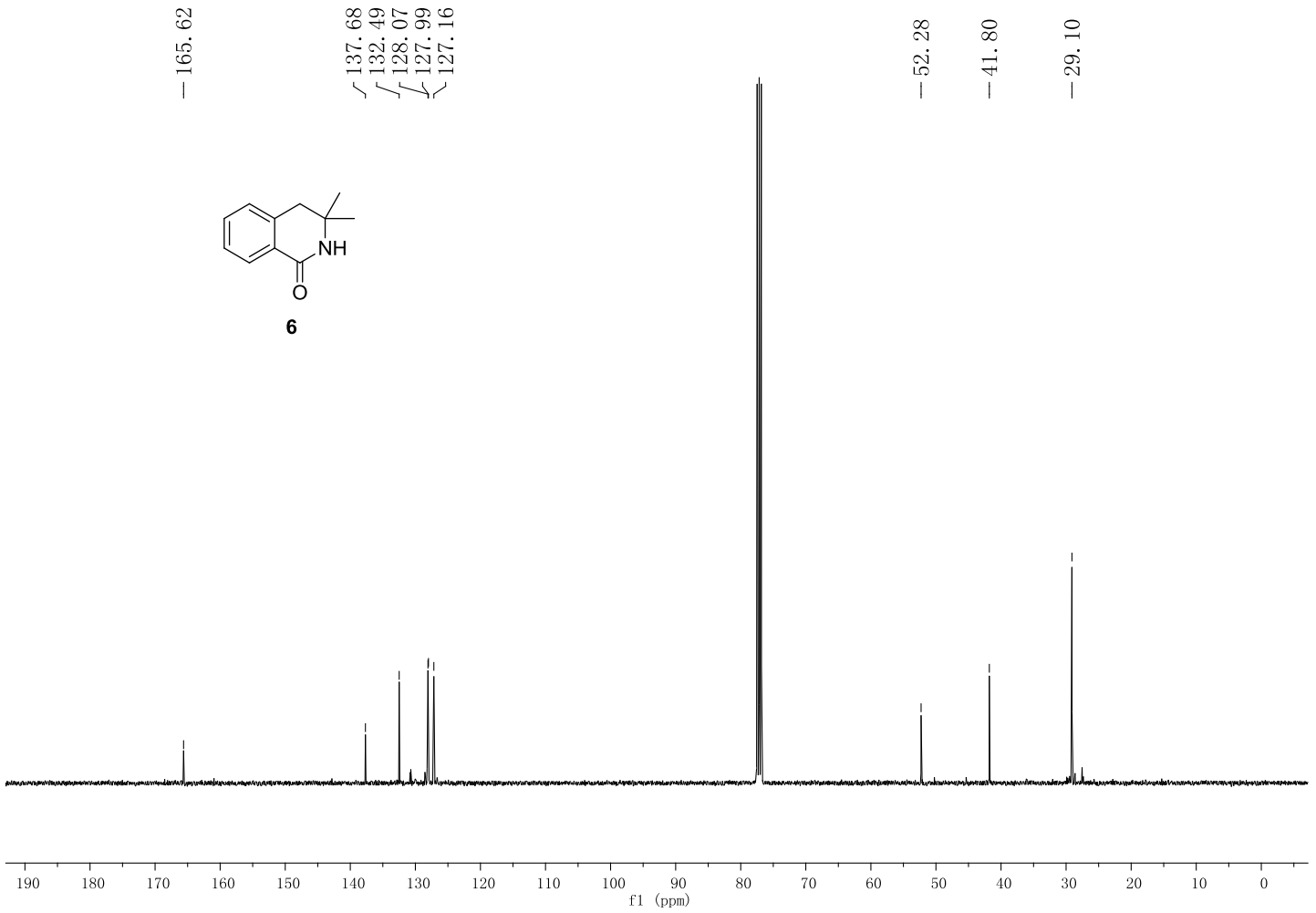

8.52
8.50
8.46
8.36
8.35
8.34
7.85
7.85
7.84
7.83
7.83
7.82
7.81
7.66
7.65
7.64
7.62
7.62
7.60
7.60
7.59
7.58
7.57
7.57
7.55
7.37
7.36
7.35
7.35
7.34
7.33
7.33
3.71
N
O
2w
2.04
1.00
1.03
3.08
1.02
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


160.34
137.61
133.17
132.71
129.91
128.11
128.04
124.88
123.52
122.51
122.37
118.37
115.56
29.68
N
O
2w
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.74
7.72
7.64
7.63
7.62
7.61
7.60
7.60
7.55
7.53
7.49
7.48
7.47
7.47
7.45
7.45
1.52
NH
O
5
0.97
0.97
0.97
0.96
6.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


171.52
155.02
133.50
131.66
129.17
124.42
122.39
60.59
27.51
NH
O
5
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)


8.07
8.06
8.05
8.05
7.36
7.34
7.32
7.19
7.17
2.93
1.31
NH
O
6
1.02
1.00
1.01
1.04
2.06
6.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


165.62
137.68
132.49
128.07
127.99
127.16
52.28
41.80
29.10
NH
O
6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

References

(1). Wan, C.-W.; Burghart, A.; Chen, J.; Bergström, F.; Johansson, L. B. Å.; Wolford, M. F.; Kim, T. G.; Topp, M. R.; Hochstrasser, R. M.; Burgess, K., *Chem. Eur. J.* **2003,** *9*, 4430-4441.

(2). Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V.; Josephy, P. D., *J. Org. Chem.* **1991,** *56*, 3763-3768.

(3). Ishiyama, T.; Murata, M.; Miyaura, N., *J. Org. Chem.* **1995,** *60*, 7508-7510.

(4). Urawa, Y.; Naka, H.; Miyazawa, M.; Souda, S.; Ogura, K., *J. Organomet. Chem.* **2002,** *653*, 269-278.

(5). Krapcho, J.; Turk, C. F.; Piala, J. J., *J. Med. Chem.* **1968,** *11*, 361-364.

(6). Inamoto, K.; Arai, Y.; Hiroya, K.; Doi, T., *Chem Commun* **2008**, 5529-31.

(7). Reddy, K. L., *Tetrahedron Lett.* **2003,** *44*, 1453-1455.

(8). Gandeepan, P.; Cheng, C.-H., *J. Am. Chem. Soc.* **2012,** *134*, 5738-5741.