Electronic Supplementary Information

Iodine-catalyzed oxidative multiple C-H bonds functionalization of isoquinolines with methylarenes: an efficient synthesis of isoquinoline-1,3,4(*2H*)-triones

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I. General information

Unless otherwise noted, all commercially available compounds (Energy-Chemical Company in Shanghai, China) were used as provided without further purification. Dry solvents (toluene) were used as commercially available; Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) or Sorbent Silica Gel 60 F254 plates. The developed chromatography was analyzed by UV lamp (254 nm). High-resolution mass spectra (HRMS) were obtained from a JEOL JMS-700 instrument (ESI). Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 spectrometer at ambient temperature. Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard (chloroform: δ 7.26 ppm). Chemical shifts for ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: δ 77.16 ppm). Data are reported as following: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration.

II. General experimental procedures

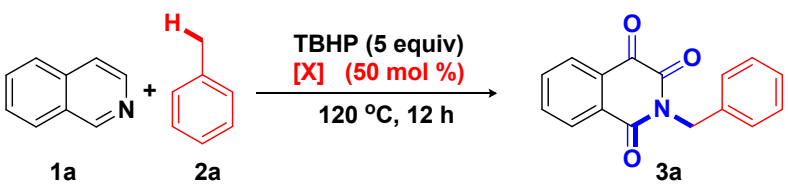
A general experimental procedure is described as following:

Method A: (for 3a-3j, 4b-4e and 5) an oven-dried reaction vessel was successively charged with isoquinoline (**1a**, 0.4 mmol, 1 equiv), iodine (0.1 mmol, 25 mol %.), toluene (**2a**, 3.2 mmol, 8 equiv), TBHP (4.0 mmol, 10 equiv, 70% in water) under air. The vessel was sealed and heated at 110 °C (oil bath temperature) for 24 h. Afterwards the resulting mixture was cooled to room temperature, transferred to silica gel column directly and purified by column chromatography on silica gel with petroleum ether and ethyl acetate (8:1) as eluent to give *N*-benzylisoquinoline-1,3,4(*2H*)-trione (**3a**, 78.7 mg) in 74% yield.

Method B: (for 3k-3n): an oven-dried reaction vessel was successively charged with isoquinoline (**1a**, 0.4 mmol, 1 equiv), iodine (0.1 mmol, 25 mol %.), *p*-xylene (**2k**, 0.8 mmol, 2 equiv), TBHP (4.0 mmol, 10 equiv, 70% in water) and chlorobenzene (1.0 mL) as solvent under air. The vessel was sealed and heated at 110 °C (oil bath temperature) for 24 h. Afterwards the resulting mixture was cooled to room temperature, transferred to silica gel column directly and purified by column chromatography on silica gel with petroleum ether and ethyl acetate (8:1) as eluent to give 2-(4-methylbenzyl)isoquinoline-1,3,4(2H)-trione (**3k**, 67.1 mg) in 60% yield.

III. Condition optimization

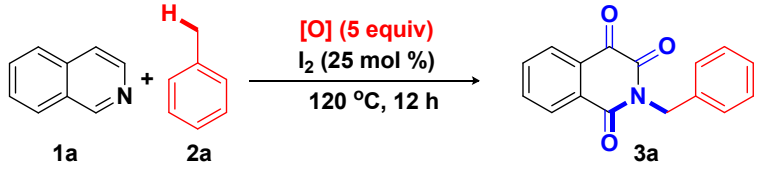
Table S1. Optimization of the catalyst[a]



entry	catalyst (mol %)	yield (%)[b]
1	I_2 (25)	38
2	KI (50)	n.d.
3	NIS (50)	17
4	CuI (50)	n.d.
5	-	n.d.

[a] A solution of **1a** (0.4 mmol, 1 equiv), TBHP (2 mmol, 5 equiv, 70% in H_2O) and toluene (**2a**, 3.2 mmol, 8 equiv) was added with vigorous stirring. The reaction mixture was stirring at 120 °C for 12 h under air. [b] Isolated yields. NIS = *N*-iodosuccinimide, n.d. = not detected.

Table S2. Optimization of the oxidants[a]

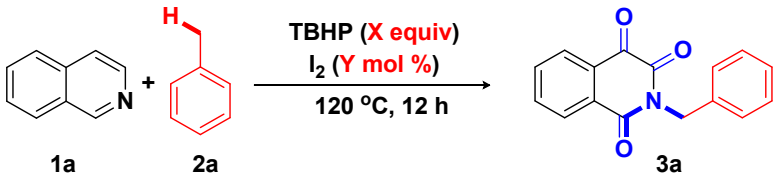


1a 2a 3a

entry	oxidant (equiv)	yield (%)[b]
1[c]	Aqueous TBHP	38
2	TBHP in decane	18
3	TBP	n.d.
3	H_2O_2	n.d.
4	air	n.d.

[a] A solution of **1a** (0.4 mmol, 1 equiv), I_2 (0.1 mmol, 25 mol %), oxidant (2 mmol, 5 equiv) and toluene (**2a**, 3.2 mmol, 8 equiv) was added with vigorous stirring. The reaction mixture was stirring at 120 °C for 12 h under air. [b] Isolated yields; n.d. = not detected. [c] 70% in H_2O.

Table S3. Optimization of the reactants ratio[a]



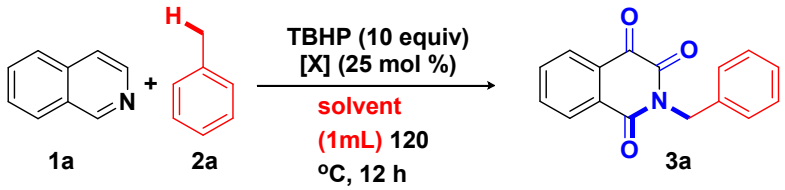
1a 2a 3a

entry	I_2 (X mol %)	TBHP (Y equiv)	yield (%)[b]
1	10	5	12
2	20	5	17
3	30	5	23

4	50	5	13
5	25	5	38
6	25	6	45
7	25	8	54
8	**25**	**10**	**65**
9	25	12	35

[a] A solution of **1a** (0.4 mmol, 1 equiv), TBHP (X equiv, 70% in H_2O), I_2 (Y mol %.) and toluene (**2a**, 3.2 mmol, 8 equiv) was added with vigorous stirring. The reaction mixture was stirring at 120 °C for 12 h under air. [b] Isolated yields.

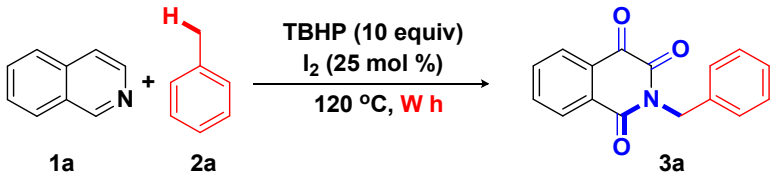
Table S4. Optimization of the solvent[a]



entry	toluene (Z equiv)	solvent	yield (%)[b]
1	11	Chlorobenzene	43
2	8	Chlorobenzene	62
3	5	Chlorobenzene	32
4	2	Chlorobenzene	21
5	8	Acetonitrile	45
6	8	DMSO	n.d.
7	8	*o*-$C_6H_4Cl_2$	48
8	8	DMF	n.d.
9	8	Ethanediol	<10
10	**8**	**-**	**65**
11	11	-	43

[a] A solution of **1a** (0.4 mmol, 1 equiv), I_2 (0.1 mmol, 25 mol %), TBHP (4 mmol, 10 equiv, 70% in H_2O), toluene (**2a** , Z equiv) and solvent (1 mL) was added with vigorous stirring. The reaction mixture was stirring at 120 °C for 12 h under air. [b] Isolated yields, n.d. = not detected.

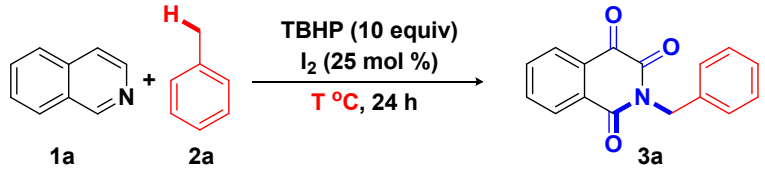
Table S5. Optimization of the reaction time[a]



entry	time (W h)	yield (%)[b]
1	6	40
2	12	65
3	18	67
4	**24**	**71**
5	36	70

[a] A solution of **1a** (0.4 mmol, 1 equiv) and I_2 (0.2 mmol, 50 mol %), TBHP (3.5 equiv, 1.4 mmol, 70% in H_2O) and toluene (**2a**, 3.2mmol , 8 equiv) was added with vigorous stirring. The reaction mixture was stirring at 120 °C for given time under air. [b] Isolated yields.

Table S6. Optimization of the temperature[a]

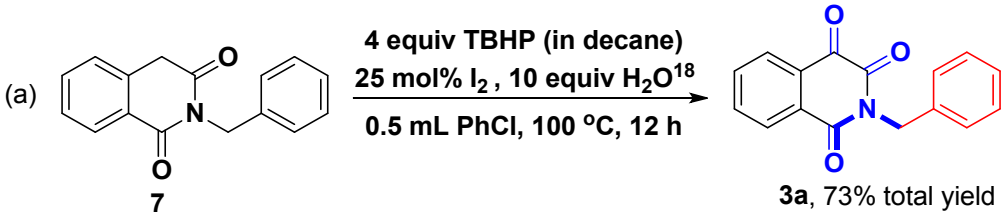


entry	temp (°C)	yield (%)[b]
1	130	54
2	120	71
3	**110**	**74**
4[c]	110	73
5[d]	110	71
6[e]	110	54
7	100	66

[a] A solution of **1a** (0.4 mmol, 1 equiv) and I_2 (0.1 mmol, 25 mol %), TBHP (4 mmol, 10 equiv, 70% in H_2O) and toluene (**2a**, 3.2 mmol, 8 equiv) was added with vigorous stirring. The reaction mixture was stirring at given temperature for 24 h under air. [b] Isolated yields. [c] Under O_2 atmosphere. [d] Under Ar atmosphere. [e] I_2 (0.04 mmol, 10 mol %) was added.

IV. Mechanistic experiments

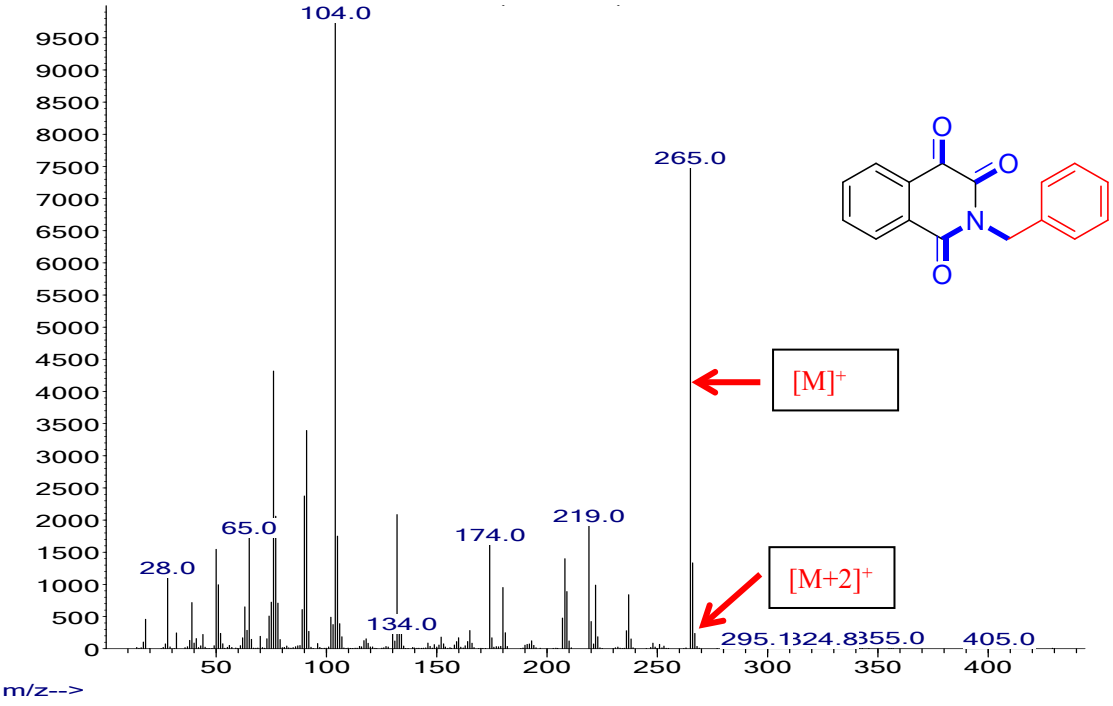
To gain more insight into the reaction mechanism, control experiments were carried out as follows.



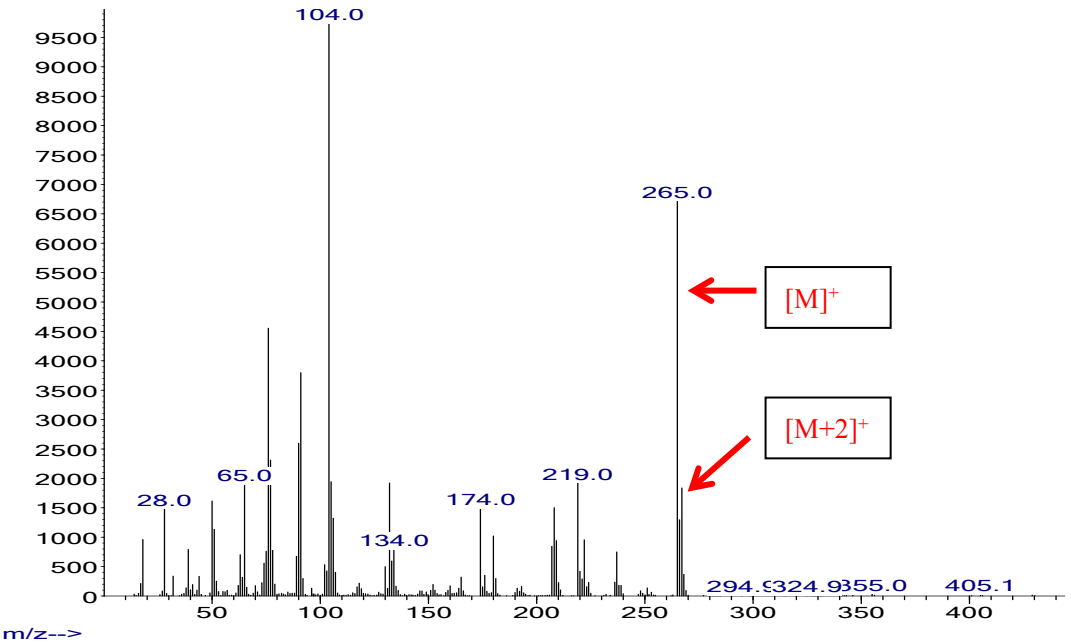
entry	isotope	abundance ratio
		M_{265}: M_{267}
A1	H_2O^{16}	97 : 3
A2	H_2O^{18}	77 : 23
A2'	H_2O^{18}	79 : 21

(a) A mixture of isochroman-1,3-dione (**7**, 0.4 mmol, 1 equiv), iodine (0.1 mmol, 25 mol %.), PhCl (1 mL, dried by CaH_2), TBHP (6 equiv, 5.5 M in dodecane) and H_2O^{16} or H_2O^{18} (4 mmol, 10 equiv) was stirred at 100 °C for 12 h under air. Afterwards the resulting mixture was cooled to room temperature, transferred to silica gel column directly and purified by column chromatography on silica gel with petroleum ether and ethyl acetate (8:1) as eluent to give 2-benzylisoquinoline-1,3,4(2H)-trione (**3a**, 78.4 mg) in 73% yield. When **H_2O^{16}** was added, the percentage composition of $[M+2]^+$ was found to be 3% in entry **A1**. When **H_2O^{18}** was added, the percentage raised to 23% in entry **A2** (parallel test was run to examine operational error, the percentage was found to be 21% in entry **A2')**. All percentages were detected by GC-MS analysis with an EI detector. (The GC-MS were copied as below.)

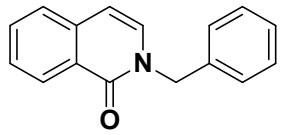
GC-MS of **A1:**



GC-MS of **A2:**

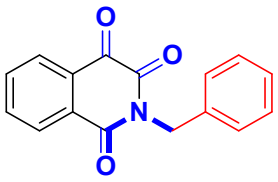


(b)



6

6 equiv TBHP (in decane)
25 mol% I_2 , 10 equiv H_2O^{18}
0.5 mL PhCl, 100 °C, 12 h



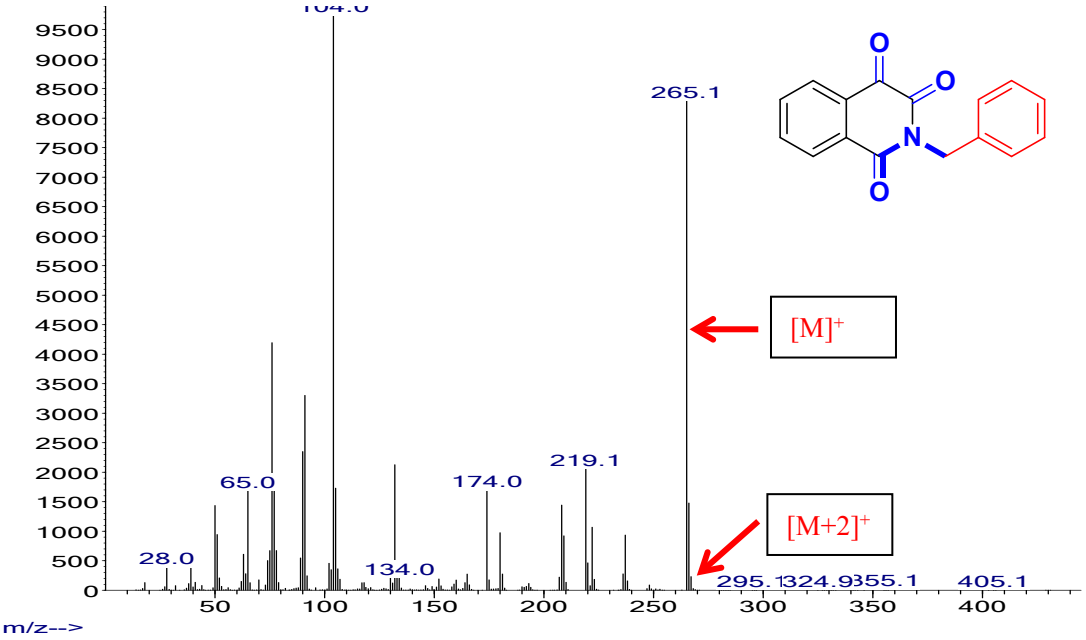
3a, 69% total yield

entry	isotope	abundance ratio M_{265}: M_{267}: M_{269}
B1	H_2O^{16}	97 : 3 : 0
B2	H_2O^{18}	51 : 40 : 9
B2'	H_2O^{18}	46 : 43 : 11

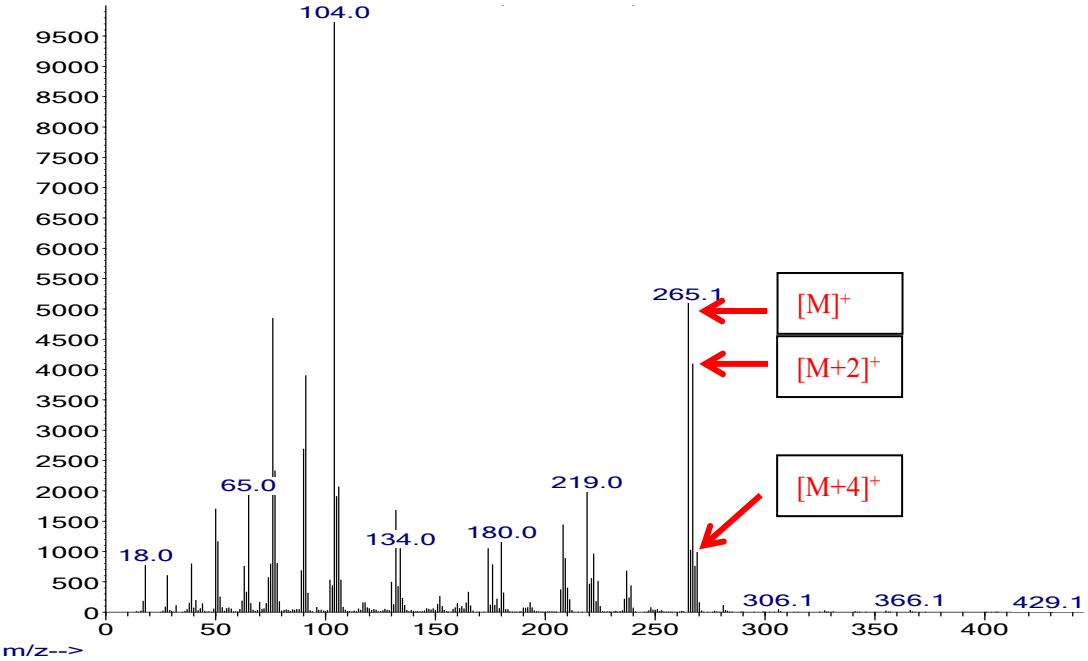
(b) A mixture of 2-benzylisoquinolin-1(*2H*)-one (**6**, 0.4 mmol, 1 equiv), iodine (0.1 mmol, 25 mol %.), PhCl (1 mL, dried by CaH_2), TBHP (4 equiv, 5.5 M in dodecane) and H_2O^{16} or H_2O^{18} (4 mmol, 10 equiv) was stirred at 100 °C for 12 h under air. Afterwards the resulting mixture was cooled to room temperature, transferred to silica gel column directly and purified by column chromatography on silica gel with petroleum ether and ethyl acetate (8:1) as eluent to give 2-benzylisoquinoline-1,3,4(2H)-trione (**3a**, 73.0 mg) in 69% yield. When **H_2O^{16}** was added, the percentage composition of $[M+2]^+$ was found to be 3% and no $[M+4]^+$ was found in entry **B1**. When **H_2O^{18}** was added, the percentage of $[M+2]^+$ **(because of containing one O^{18})** raise to be 40%, $[M+4]^+$ **(because of containing two O^{18})** was found to be 9% in entry **B2** (parallel test was run to examine operational error, the percentage was found to be 46:43:11 in entry **B2')**. All percentages were detected by GC-MS analysis with an EI detector.

(The GC-MS were copied as below.)

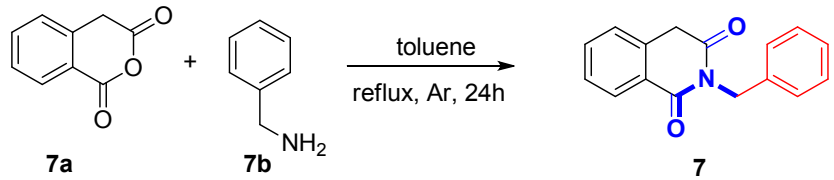
GC-MS of **B1:**



GC-MS of **B2:**



V. Synthesis of intermediate 7 [Ref: Holmes, B.; Lee, J.; Landon, K. A.; Benavides-Serrato, A.; Bashir, T.; Jung, M. E.; Lichtenstein, A.; Gera, J. *J. Biol. Chem.*, 2016, 291, 14146-14159.]



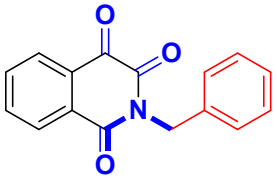
7a **7b** **7**

A mixture of **7a** (isochroman-1,3-dione, 642 mg, 4.0 mmol), **7b** (benzylamine, 1.2 equiv, 514 mg), and toluene (2.5 mL) was refluxed for 24 h under argon. Afterwards the resulting mixture was cooled to room temperature, transferred to silica gel column directly and purified by column chromatography on silica gel with petroleum ether and ethyl acetate (6:1) as eluent to give intermediate **7** in 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.58 (td, *J* = 7.6, 1.2 Hz, 1H), 7.49 – 7.39 (m, 3H), 7.33 – 7.23 (m, 4H), 5.19 (s, 2H), 4.07 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.94, 164.87, 137.13, 134.17, 133.73, 129.30, 129.05, 128.48, 127.78, 127.58, 127.18, 125.40, 43.32, 36.54. MS (EI) m/z (%): 251(100) $[M]^+$, 222(35), 207(30), 146(10), 132(30), 118(65), 91(75).

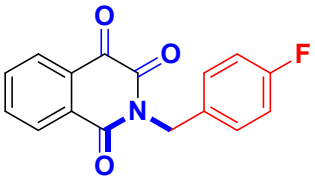
VI. Spectra data of products

(3a) 2-benzylisoquinoline-1,3,4(*2H*)-trione



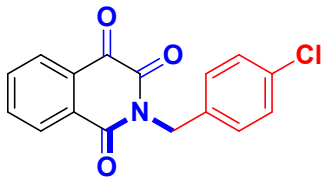
The title compound was prepared according to the general procedure described above by the reaction between isoquinoline (**1a**) with toluene (**2a**), and purified by flash column chromatography as light yellow solid (78.7 mg, 74%). Melting point: 190- 191 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.21 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.90 (td, *J* = 7.6, 1.4 Hz, 1H), 7.83 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.35 – 7.27 (m, 3H), 5.25 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.66, 162.22, 157.03, 136.17, 135.91, 134.58, 130.82, 130.00, 129.86, 129.54, 128.67, 128.12, 127.87, 44.36. IR: 3066, 3032, 2972, 1678, 1584 cm^{-1}. MS (EI) m/z (%):265(90) $[M]^+$, 237(10), 222(20), 207(30), 174(15), 132(20), 104(100), 90(35). HRMS: calcd. for $[M+H]^+$ $C_{16}H_{12}O_3N$: 266.08117, found: 266.08076.

(3b) 2-(4-fluorobenzyl)isoquinoline-1,3,4(*2H*)-trione



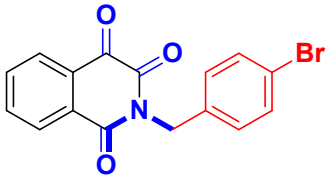
The title compound was prepared according to the general procedure described above by the reaction between isoquinoline (**1a**) with *p*-fluorotoluene (**2b**), and purified by flash column chromatography as light yellow solid (80.7 mg, 71%). Melting point: 210- 211 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.8, 0.8 Hz, 1H), 8.21 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.91 (td, *J* = 7.6, 0.8 Hz, 1H), 7.83 (td, *J* = 7.6, 1.2 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.04 – 6.93 (m, 2H), 5.21 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.65, 162.59 (d, *J* = 245.4 Hz), 162.26, 157.05, 136.25, 134.71, 131.84(d, *J* = 3.2 Hz), 131.65 (d, *J* = 8.1 Hz), 130.93, 130.08, 129.89, 127.99, 115.59(d, *J* = 21.4 Hz), 43.71. IR: 3077, 3046, 2973, 1678, 1595 cm^{-1}. MS (EI) m/z (%): 283(100) $[M]^+$, 255(10), 237(15), 174(20), 132(250, 104(75), 90(20). HRMS: calcd. for $[M+H]^+$ $C_{16}H_{11}O_3NF$: 284.07175, found: 284.07123.

(3c) 2-(4-chlorobenzyl)isoquinoline-1,3,4(*2H*)-trione



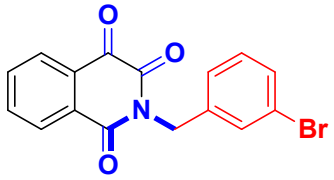
The title compound was prepared according to the general procedure described above by the reaction between isoquinoline (**1a**) with *p*-chlorotoluene (**2c**), and purified by flash column chromatography as light yellow solid (94.3mg, 79%). Melting point: 187- 188 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 7.8, 0.8 Hz, 1H), 8.22 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.91 (td, *J* = 7.6, 1.2 Hz, 1H), 7.84 (td, *J* = 7.6, 1.2 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.20 (s, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 174.57, 162.24, 157.03, 136.27, 134.75, 134.40, 134.13, 131.12, 130.89, 130.08, 129.80, 128.89, 128.01, 43.76. IR: 3077, 3038, 2975, 1680, 1593 cm^{-1}. MS (EI) m/z (%): 299(70)$[M]^+$, 255(15), 236(40), 207(15),174(20), 132(35), 104(100), 90(30). HRMS: calcd. for $[M+H]^+$ $C_{16}H_{11}O_3NCl$: 300.04220, found: 300.04154.

(3d) 2-(4-bromobenzyl)isoquinoline-1,3,4(*2H*)-trione



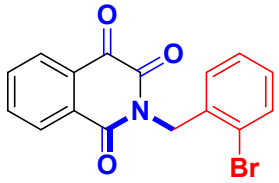
The title compound was prepared according to the general procedure described above by the reaction between isoquinoline (**1a**) with *p*-bromotoluene (**2d**), and purified by flash column chromatography as light yellow solid (105.6 mg, 77%). Melting point: 178- 179 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 8.0, 0.8 Hz, 1H), 8.21 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.91 (td, *J* = 7.6, 1.2 Hz, 1H), 7.84 (td, *J* = 7.6, 1.2 Hz, 1H), 7.47 – 7.32 (m, 4H), 5.19 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.57, 162.25, 157.05, 136.29, 134.92, 134.77, 131.89, 131.43, 130.92, 130.11, 129.82, 128.04, 122.34, 43.85.. IR: 3077, 3038, 2970, 1678, 1595 cm^{-1}. MS (EI) m/z (%):343(60) $[M]^+$, 300(10),236(40), 208(10), 174(20), 132(40), 104(100), 90(50). HRMS: calcd. for $[M+H]^+$ $C_{16}H_{11}O_3NBr$: 343.99168, found: 343.99091.

(3e) 2-(3-bromobenzyl)isoquinoline-1,3,4(*2H*)-trione



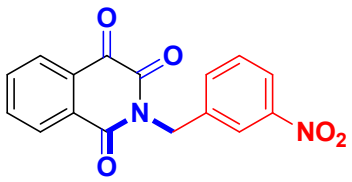
The title compound was prepared according to the general procedure described above by the reaction between isoquinoline (**1a**) with *m*-bromotoluene (**2e**), and purified by flash column chromatography as light yellow solid (104.1 mg, 76%). Melting point: 167- 168 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.22 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.92 (td, *J* = 7.6, 1.4 Hz, 1H), 7.84 (td, *J* = 7.6, 1.2 Hz, 1H), 7.65 (t, *J* = 1.6 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.19 (t, *J* = 7.8 Hz, 1H), 5.20 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.38, 162.27, 157.03, 148.51, 137.76, 136.44, 135.71, 135.00, 130.94, 130.26, 129.82, 129.59, 128.18, 124.48, 123.31, 43.75. IR: 3077, 3043, 2958, 1678, 1590 cm^{-1}. MS (EI) m/z (%): 343(50)$[M]^+$, 300(10), 236(30), 174(15), 132(40), 104(100), 90(40). HRMS: calcd. for $[M+H]^+$ $C_{16}H_{11}O_3NBr$: 343.99168, found: 343.99110.

(3f) 2-(2-bromobenzyl)isoquinoline-1,3,4(*2H*)-trione



The title compound was prepared according to the general procedure described above by the reaction between isoquinoline (**1a**) with *o*-bromotoluene (**2f**), and purified by flash column chromatography as light white solid (94.8 mg, 69%). Melting point: 185- 186 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.6 Hz, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 7.94 (td, *J* = 7.4, 1.0 Hz, 1H), 7.88 (td, *J* = 7.6, 1.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 5.36 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.53, 162.15, 157.09, 136.37, 134.85, 134.55, 133.19, 131.00, 130.21, 129.73, 129.13, 128.09, 127.67, 127.64, 123.09, 44.86. IR: 3077, 2998, 2964, 1669, 1581 cm^{-1}. MS (EI) m/z (%):343(1) $[M]^+$, 264(100), 236(20), 207(5), 130(10), 104(30), 90(10). HRMS: calcd. for $[M+H]^+$ $C_{16}H_{11}O_3NBr$: 343.99168, found: 343.99088.

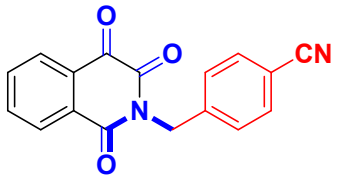
(3g) 2-(3-nitrobenzyl)isoquinoline-1,3,4(*2H*)-trione



The title compound was prepared according to the general procedure described above by the reaction between isoquinoline (**1a**) with *m*-nitrotoulene (**2g**), and purified by flash column chromatography as light yellow solid (70.9 mg, 57%). Melting point: 186- 187 °C.

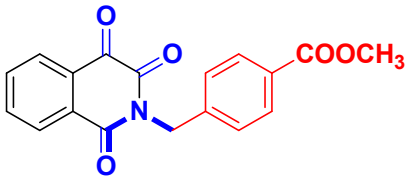
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.35 (t, *J* = 1.8 Hz, 1H), 8.24 (dd, *J* = 7.6, 1.0 Hz, 1H), 8.19 – 8.09 (m, 1H), 7.94 (td, *J* = 7.6, 1.4 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 5.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.47, 162.37, 157.12, 148.58, 137.85, 136.54, 135.82, 135.09, 131.03, 130.35, 129.91, 129.68, 128.28, 124.58, 123.40, 43.84. IR: 3080, 2363, 2329, 1683, 1587, 1533 cm^{-1}. MS (EI) m/z (%): 310(40)$[M]^+$, 265(35), 235(25), 174(10),132(20),104(100), 90(25). HRMS: calcd. for $[M+H]^+$ $C_{16}H_{11}O_5N_2$: 311.06625, found: 311.06549.

(3h) 4-((1,3,4-trioxo-3,4-dihydroisoquinolin-2(*1H*)-yl)methyl)benzonitrile



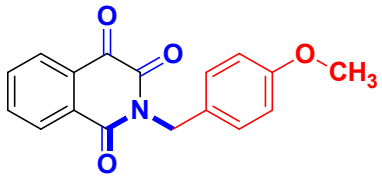
The title compound was prepared according to the general procedure described above by the reaction between isoquinoline (**1a**) with *p*-methylbenzonitrile (**2h**), and purified by flash column chromatography as light white solid (62.5 mg, 54%). Melting point: 226- 227 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.8, 0.8 Hz, 1H), 8.24 (dd, *J* = 7.6, 1.0Hz, 1H), 7.93 (td, *J* = 7.6, 1.2 Hz, 1H), 7.86 (td, *J* = 7.6, 1.2 Hz, 1H), 7.62 (s, 2H), 5.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.36, 162.25, 157.02, 140.96, 136.43, 134.99, 132.61, 130.92, 130.21, 129.60, 128.18, 118.62, 112.18, 44.05. IR: 3077, 2981, 2227, 1714, 1675, 1595 cm^{-1}. MS (EI) m/z (%): 290(70)$[M]^+$, 262(25), 244(10), 174(10), 132(40), 104(100), 90(25). HRMS: calcd. for $[M+H]^+$ $C_{17}H_{11}O_3N_2$: 291.07642, found: 291.07578.

(3i) methyl 4-((1,3,4-trioxo-3,4-dihydroisoquinolin-2(*1H*)-yl)methyl)benzoate



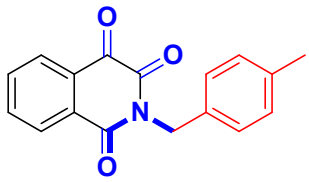
The title compound was prepared according to the general procedure described above by the reaction between isoquinoline (**1a**) with methyl *p*-methylbenzoate (**2i**), and purified by flash column chromatography as light yellow solid (70.8 mg, 55%). Melting point: 197- 198 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.92 (t, *J* = 7.6 Hz, 1H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 5.28 (s, 1H), 3.89 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.53, 166.78, 162.25, 157.05, 140.81, 136.30, 134.80, 130.93, 130.13, 130.04, 129.92, 129.76, 129.33, 128.05, 52.27, 44.15. IR: 3049, 2995, 2944, 2848, 2355, 1717, 1678, 1595 cm^{-1}. MS (EI) m/z (%): 323(100)$[M]^+$, 294(10), 280(15), 264(5), 236(50), 207(15), 174(10), 132(40), 118(10), 104(100),90(40). HRMS: calcd. for $[M+H]^+$ $C_{18}H_{14}O_5N$: 324.08665, found: 324.08589.

(3j) 2-(4-methoxybenzyl)isoquinoline-1,3,4(*2H*)-trione



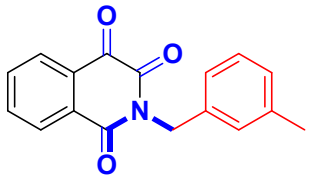
The title compound was prepared according to the general procedure described above by the reaction between isoquinoline (**1a**) with 1-methoxy-4-methylbenzene (**2j**), and purified by flash column chromatography as light yellow solid (56.9 mg, 48%). Melting point: 163- 164 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.20 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.89 (td, *J* = 7.6, 1.0 Hz, 1H), 7.81 (td, *J* = 7.6, 1.2 Hz, 1H), 7.53 – 7.44 (m, 2H), 6.88 – 6.77 (m, 2H), 5.18 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.75, 162.25, 159.42, 157.05, 136.11, 134.52, 131.18, 130.88, 129.96, 128.23, 127.83, 113.98, 55.33, 43.83. IR: 3006, 2978, 2938, 2834, 1672, 1590, 1510 cm^{-1}. MS (EI) m/z (%): 295(90)[M]$^+$, 267(5), 252(15), 224(15), 135(20), 121(100), 104(30), 90(40). HRMS: calcd. for [M+Na]$^+$ $C_{17}H_{13}O_4NNa$: 318.07368, found: 318.07327.

(3k) 2-(4-methylbenzyl)isoquinoline-1,3,4(*2H*)-trione



The title compound was prepared according to the procedure by the reaction between isoquinoline (**1a, 1 equiv**) with *p*-xylene (**2k, 2 equiv**) in chlorobenzene (0.5 mL), and purified by flash column chromatography as light yellow solid (67.1 mg, 60%). Melting point: 222- 223 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.20 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.89 (td, *J* = 7.6, 1.2 Hz, 1H), 7.82 (td, *J* = 7.6, 1.2 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.21 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.74, 162.24, 157.07, 137.96, 136.15, 134.56, 133.03, 130.87, 130.01, 129.58, 129.36, 127.87, 44.16, 21.25. IR: 3043, 2984, 2924, 1714, 1680, 1587, 1516 cm^{-1}. MS (EI) m/z (%): 279(100)[M]$^+$, 26595), 251(5), 236(50), 222(10), 207(50), 174(20), 132(20), 118(30), 104(70), 90(20). HRMS: calcd. for [M+H]$^+$ $C_{17}H_{14}O_3N$: 280.09682, found: 280.09633.

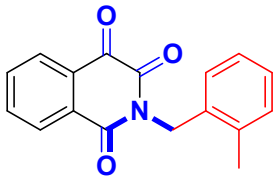
(3l) 2-(3-methylbenzyl)isoquinoline-1,3,4(*2H*)-trione



The title compound was prepared according to the procedure by the reaction between isoquinoline(**1a, 1equiv**) with *m*-xylene (**2l, 2 equiv**) in chlorobenzene(0.5 mL), and purified by flash column chromatography as light yellow solid (75.8 mg, 68%). Melting point: 168- 169 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.21 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.90 (td, *J* = 7.6, 1.4 Hz, 1H), 7.82 (td, *J* = 7.6, 1.2 Hz, 1H), 7.30 (d, *J* = 7.0 Hz, 2H), 7.20 (t, *J* = 7.6 Hz,

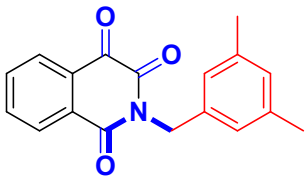
1H), 7.08 (d, *J* = 7.4 Hz, 1H), 5.21 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.72, 162.23, 157.08, 138.41, 136.14, 135.88, 134.56, 130.90, 130.14, 130.03, 129.97, 128.87, 128.58, 127.87, 126.54, 44.37, 21.44. IR: 3057, 2972, 2919, 1709, 1669, 1595 cm^{-1}. MS (EI) m/z (%): 279(100)$[M]^+$, 265(5), 251(7.5), 236(25), 222(10), 207(15), 174(20), 160(10), 132(25), 118(30), 104(100), 90(20). HRMS: calcd. for $[M+H]^+$ $C_{17}H_{14}O_3N$: 280.09682, found: 280.09627.

(3m) 2-(2-methylbenzyl)isoquinoline-1,3,4(*2H*)-trione



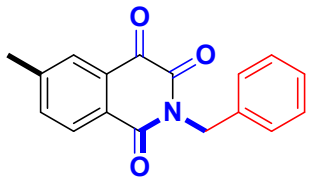
The title compound was prepared according to the procedure by the reaction between isoquinoline (**1a, 1 equiv**) with *o*-xylene (**2m, 2 equiv**) in chlorobenzene (0.5 mL), and purified by flash column chromatography as light yellow solid (71.1 mg, 64%). Melting point: 178- 179 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.25 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.92 (td, *J* = 7.6, 1.4 Hz, 1H), 7.85 (td, *J* = 7.6, 1.4 Hz, 1H), 7.17 – 7.08 (m, 4H), 5.27 (s, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.68, 162.37, 157.24, 136.24, 134.67, 133.81, 130.95, 130.62, 130.12, 129.93, 127.95, 127.67, 126.96, 126.25, 41.89, 19.56. IR: 3083,3018, 2984, 1663, 1584 cm^{-1}. MS (EI) m/z (%): 279(20)$[M]^+$, 251(10),236(5), 207(10),174(15), 160(15), 104(100), 90(10). HRMS: calcd. for $[M+H]^+$ $C_{17}H_{14}O_3N$: 280.09682, found: 280.09630.

(3n) 2-(3,5-dimethylbenzyl)isoquinoline-1,3,4(*2H*)-trione



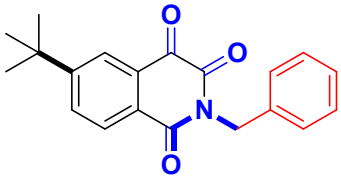
The title compound was prepared according to the procedure by the reaction between isoquinoline (**1a, 1 equiv**) with mesitylene (**2n, 2 equiv**) in chlorobenzene (0.5 mL), and purified by flash column chromatography as light yellow solid (52.7 mg, 45%). Melting point: 191- 192 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.6 Hz, 1H), 8.21 (d, *J* = 7.0 Hz, 1H), 7.90 (t, *J* = 6.8 Hz, 1H), 7.82 (t, *J* = 7.4 Hz, 1H), 7.11 (s, 2H), 6.91 (s, 1H), 5.17 (s, 2H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.71, 162.20, 157.05, 138.25, 136.11, 135.79, 134.50, 130.86, 130.01, 129.98, 129.73, 127.82, 127.17, 44.30, 21.30. IR: 3089, 2924, 2363, 1703, 1675, 1587 cm^{-1}. MS (EI) m/z (%): 293(100)$[M]^+$, 250(25), 222(10), 174915),132(25), 118(20), 104(45), 91(15). HRMS: calcd. for $[M+H]^+$ $C_{18}H_{16}O_3N$:294.11247, found: 294.11192.

(4b) 2-benzyl-6-methylisoquinoline-1,3,4(*2H*)-trione



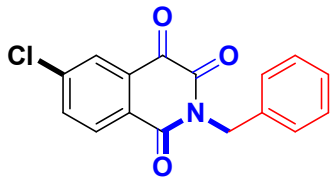
The title compound was prepared according to the general procedure described above by the reaction between 6-methylisoquinoline (**1b**) with toluene (**2a**), and purified by flash column chromatography as light yellow solid (80.4 mg, 72%). Melting point:160-160 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 0.5 Hz, 1H), 7.68 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.23 (m, 3H), 5.23 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.94, 162.31, 157.25, 146.02, 137.06, 136.11, 130.78, 130.11, 129.52, 128.69, 128.09, 127.51, 44.31, 21.79. IR: 3035, 2363, 1714, 1651, 1666, 1601 cm^{-1}. MS (EI) m/z (%): 279(100)[M]$^+$, 251(10), 233(25), 208(10), 188(20), 146(25), 118(100), 105(25), 91(40). HRMS: calcd. for [M+H]$^+$ $C_{17}H_{14}O_3N$: 280.09682, found: 280.09636.

(4c) 2-benzyl-6-(tert-butyl)isoquinoline-1,3,4(2H)-trione



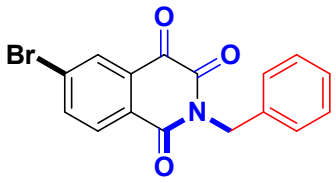
The title compound was prepared according to the general procedure described above by the reaction between 6-tertbutylisoquinoline (**1c**) with toluene (**2a**), and purified by flash column chromatography as light yellow oil (88.2 mg, 69%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.2 Hz, 1H), 8.20 (d, *J* = 2.0 Hz, 1H), 7.91 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.49 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.36 – 7.19 (m, 4H), 5.23 (s, 2H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.01, 162.26, 159.04, 157.33, 136.07, 133.54, 130.65, 130.03, 129.42, 128.64, 128.02, 127.39, 124.64, 44.22, 35.71, 30.96. IR: 2970, 2356, 2332, 1709, 1684, 1600 cm^{-1}. MS (EI) m/z (%): 321(100)[M]$^+$, 293(10), 278(35), 250(10), 208(15), 188(15), 160(90), 131(10), 117(35), 91(35). HRMS: calcd. for [M+H]$^+$ $C_{20}H_{20}O_3N$:322.14337, found: 322.14309.

(4d) 2-benzyl-6-chloroisoquinoline-1,3,4(*2H*)-trione



The title compound was prepared according to the general procedure described above by the reaction between 6-chloroisoquinoline (**1d**) with toluene (**2a**), and purified by flash column chromatography as light yellow solid (80.3 mg, 67%). Melting point: 159- 160 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 7.84 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.50 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.35 – 7.27 (m, 3H), 5.23 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.90, 161.53, 156.62, 141.83, 136.31, 135.76, 131.90, 131.67, 129.62, 128.80, 128.31, 128.17, 127.67, 44.58. IR: 3097, 3069, 3035, 2364, 2335, 1703, 1669, 1581 cm^{-1}. MS (EI) m/z (%): 299(100)[M]$^+$, 271(10), 253(25), 208(30), 166(20), 138(75), 124(15), 110(35). HRMS: calcd. for [M+H]$^+$ $C_{16}H_{11}O_3NCl$: 300.04220, found:300.04166.

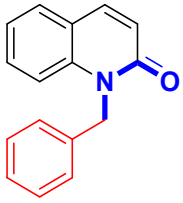
(4e) 2-benzyl-6-bromoisoquinoline-1,3,4(*2H*)-trione



The title compound was prepared according to the general procedure described above by the reaction between 6-bromoisoquinoline (**1e**) with toluene (**2a**), and purified by flash column chromatography as light yellow solid (86.3 mg, 63%). Melting point: 215- 216 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 2.0 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.01 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.49 (d, *J* = 6.4 Hz, 2H), 7.35 – 7.27 (m, 3H), 5.23 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.78, 161.67, 156.51, 139.22, 135.71, 131.79, 131.56, 130.65, 130.12, 129.59, 128.75, 128.54, 128.26, 44.54. IR: 3074, 3032, 1663, 1578 cm^{-1}. MS (EI) m/z (%):345(100)$[M]^+$, 315300(25),286(10), 252(15), 208(25), 182(75), 168(15), 154(25), 130(10), 106(50), 91(80). HRMS: calcd. for $[M+H]^+$ $C_{16}H_{11}O_3NBr$: 343.99168, found: 343.99101.

(5) 1-benzylquinolin-2(*1H*)-one [1]

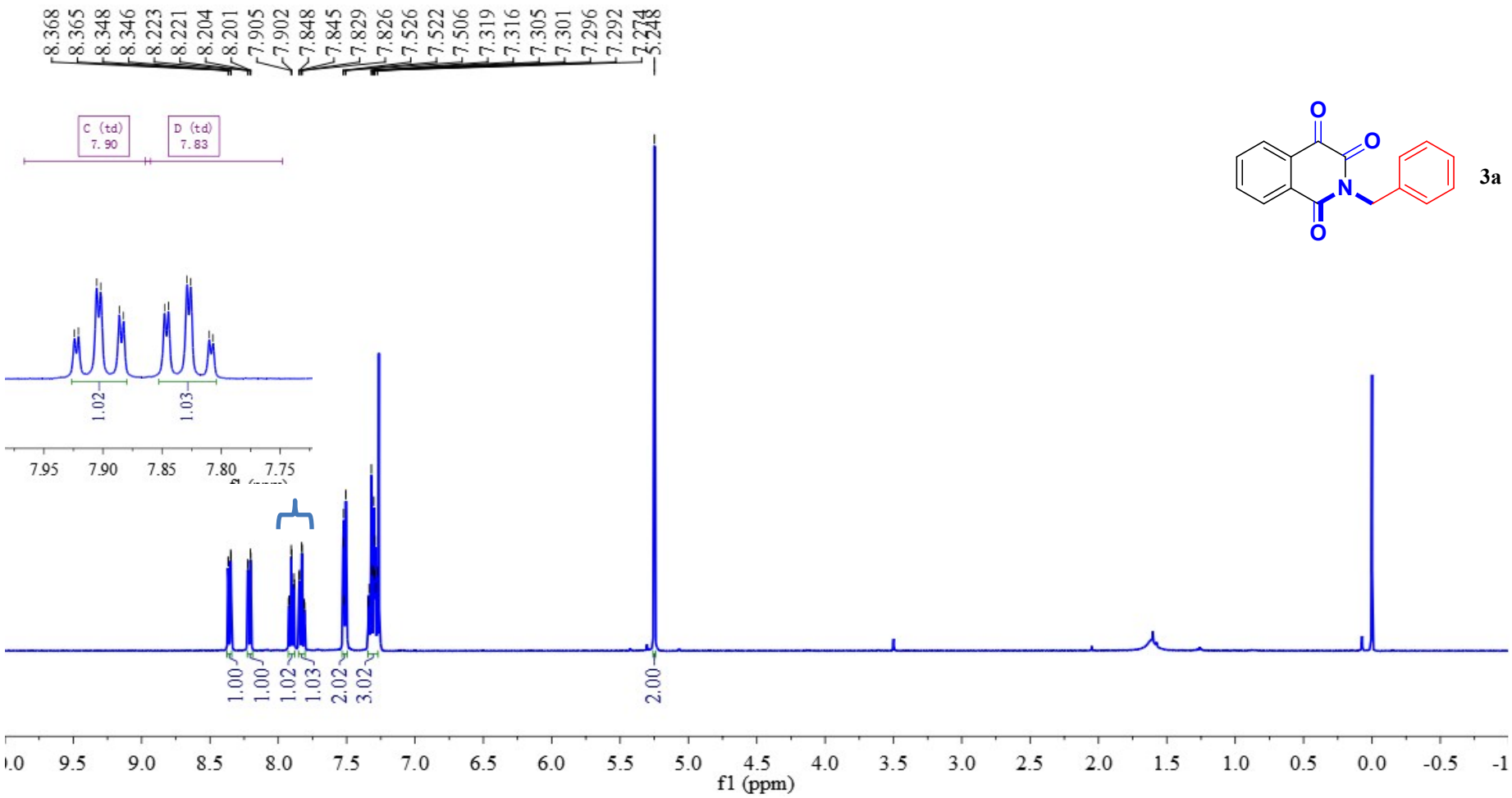


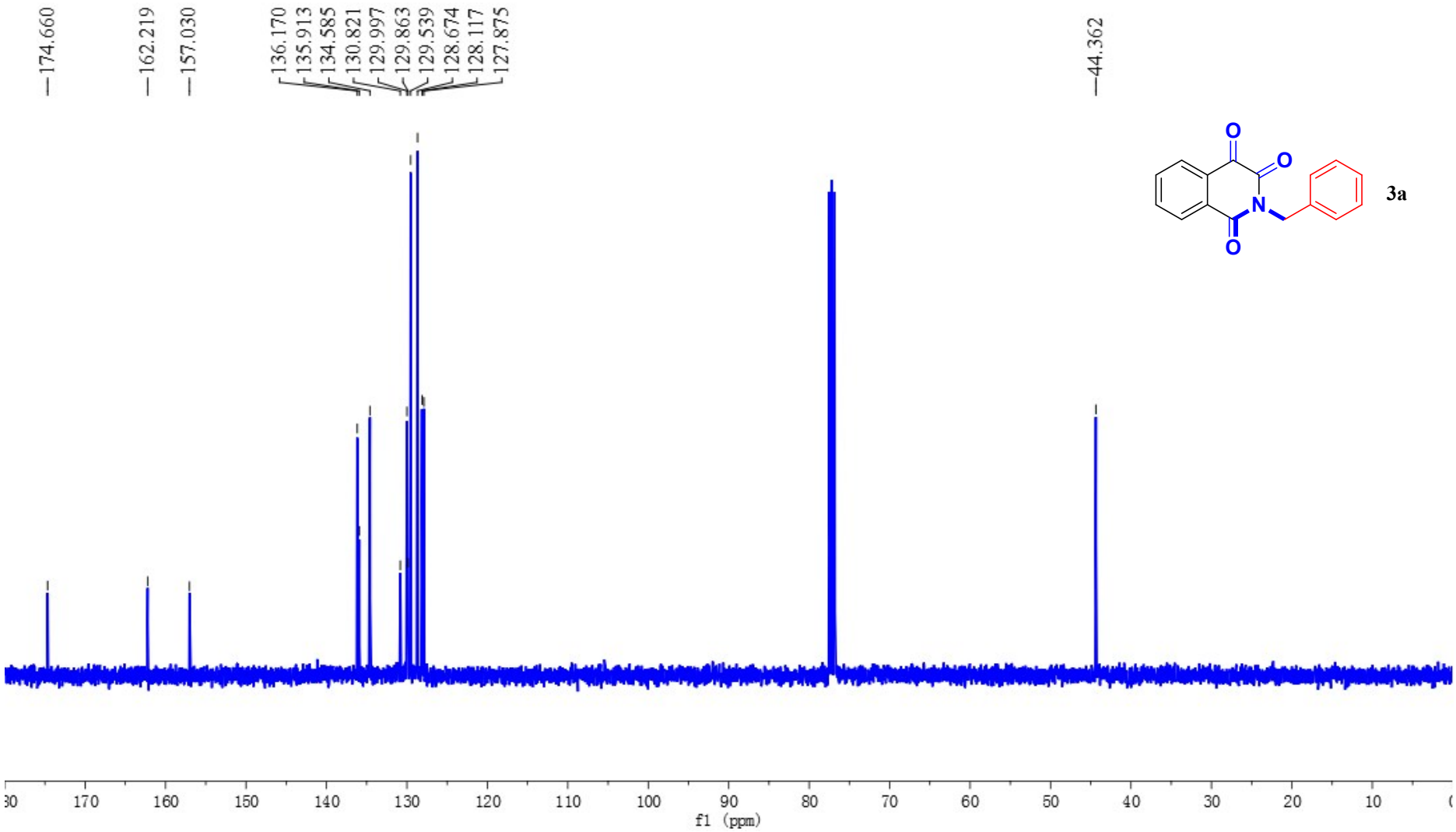
The title compound was prepared according to the general procedure described above by the reaction between quinoline (**1f**) with toluene (**2a**), and purified by flash column chromatography as light red solid. Melting point: 69-70 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 6.4 Hz, 1H), 7.42 (d, *J* = 6.0 Hz, 1H), 7.27-7.22 (m, 7H), 6.82 (d, *J* = 8.8 Hz, 1H), 5.57 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.57, 139.69, 139.36, 136.26, 130.67, 128.85, 128.78, 127.26, 126.55, 122.27, 121.52, 120.92, 115.05, 45.90. IR: 3060, 1651, 1598 cm^{-1}. MS (EI) m/z (%): 65(15), 91(98), 129(80), 158(20), 216(15), 235(100)$[M]^+$.

[1] Lanni, E. L.; Bosscher, M. A.; Ooms, B. D.; Shandro, C. A.; Ellsworth, B. A.; Anderson, C. E. *J. Org. Chem.* **2008**, *73*, 6425.

VII. Copies of 1H and 13C NMR spectra of products

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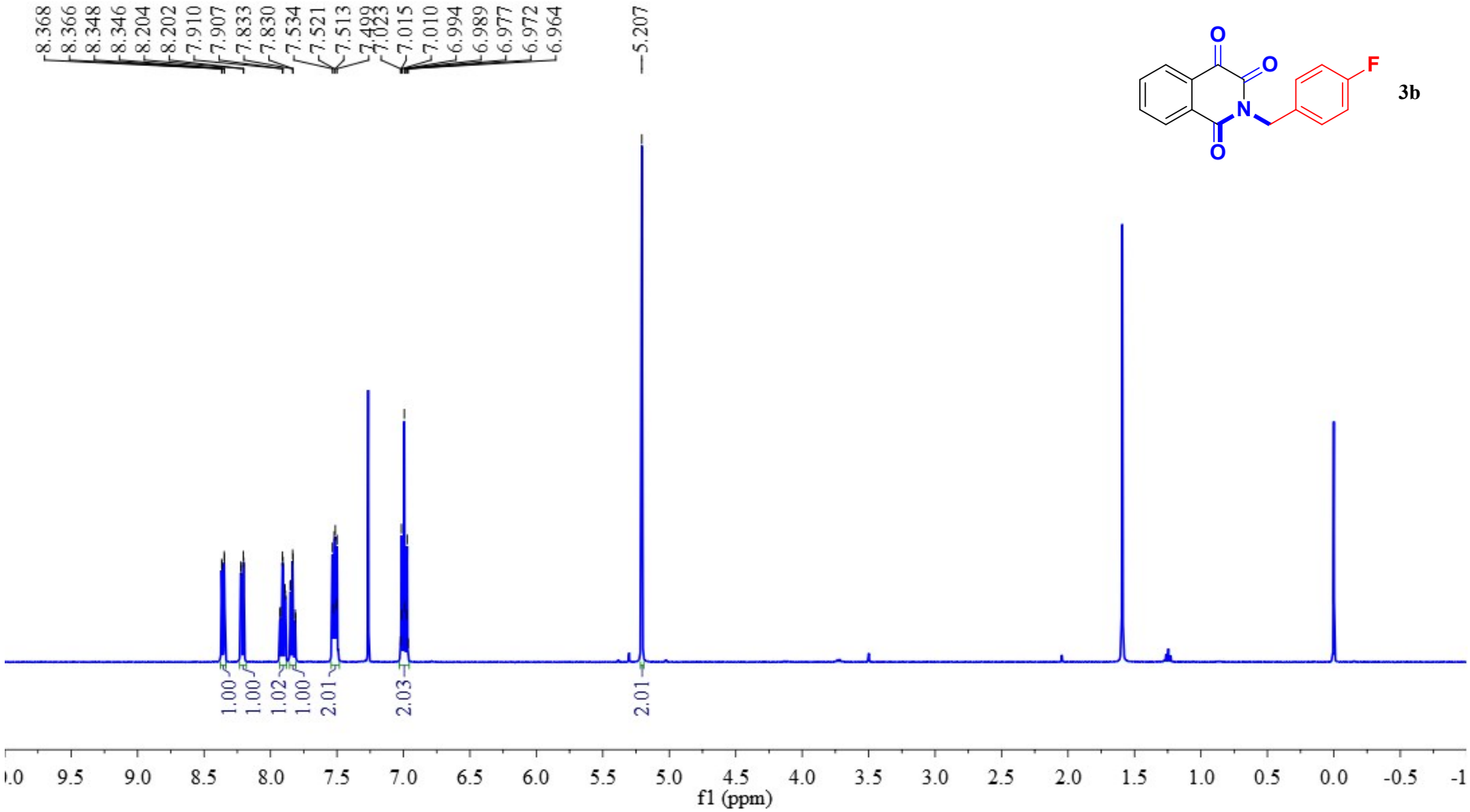
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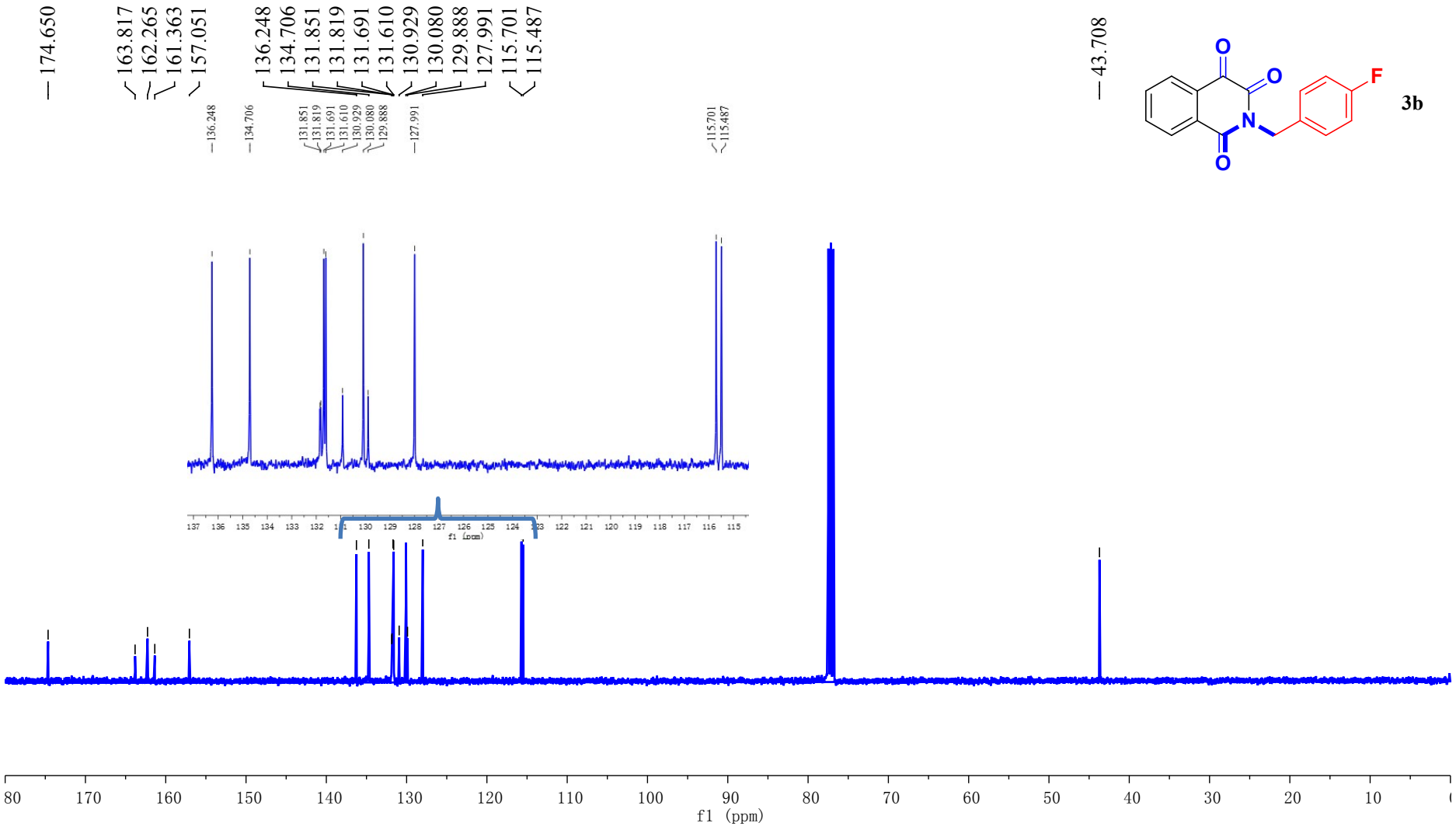
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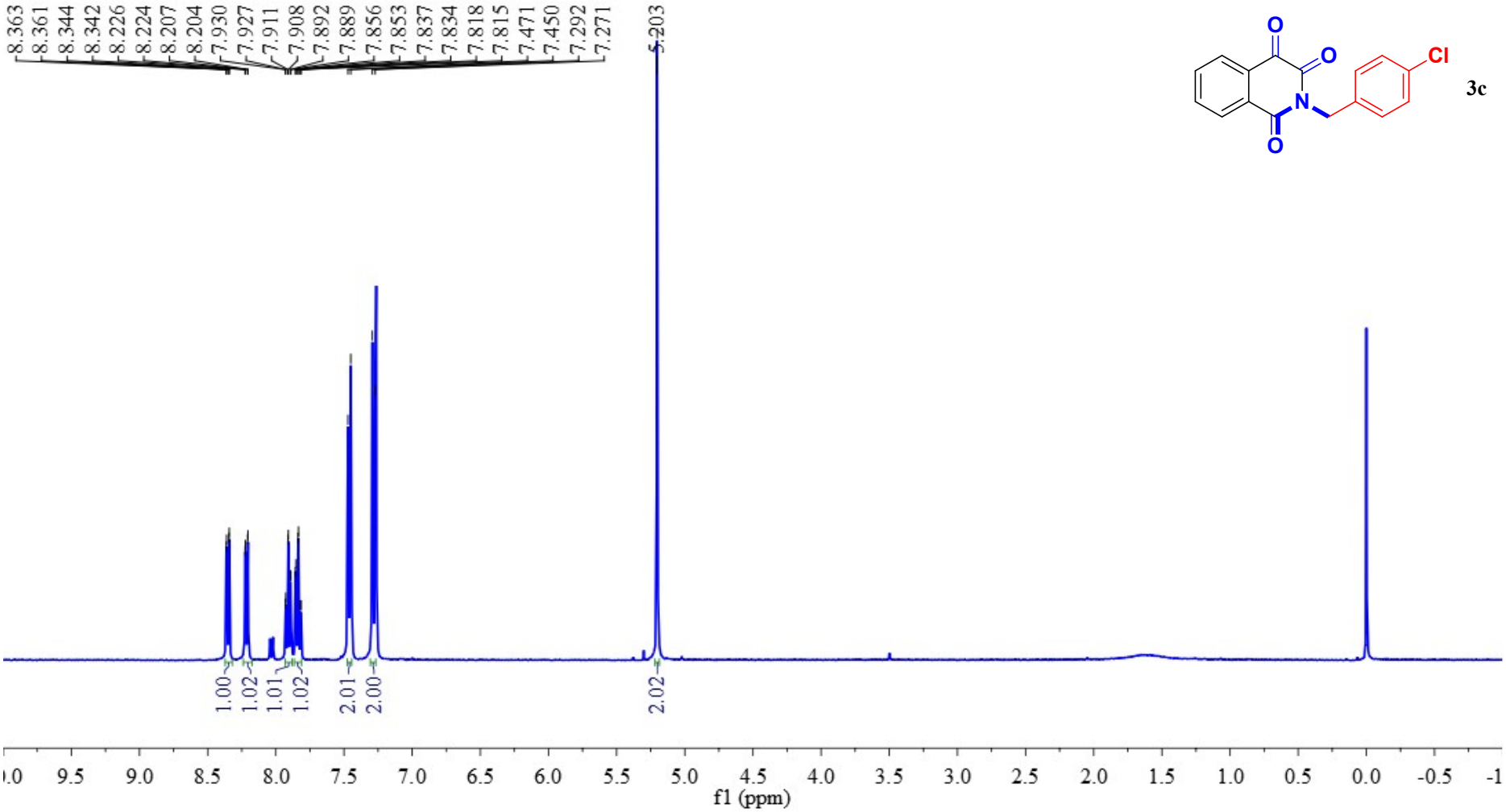
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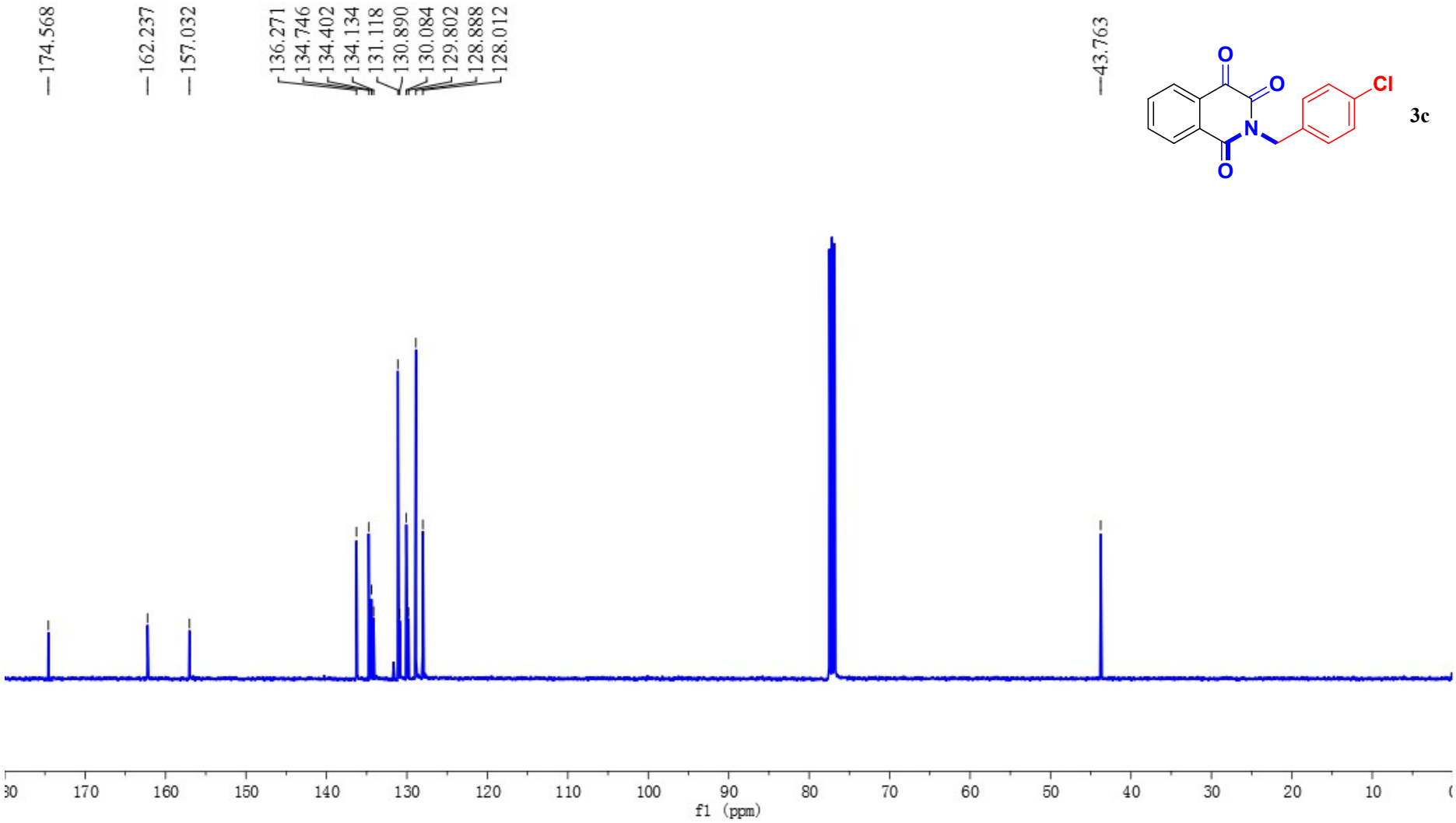
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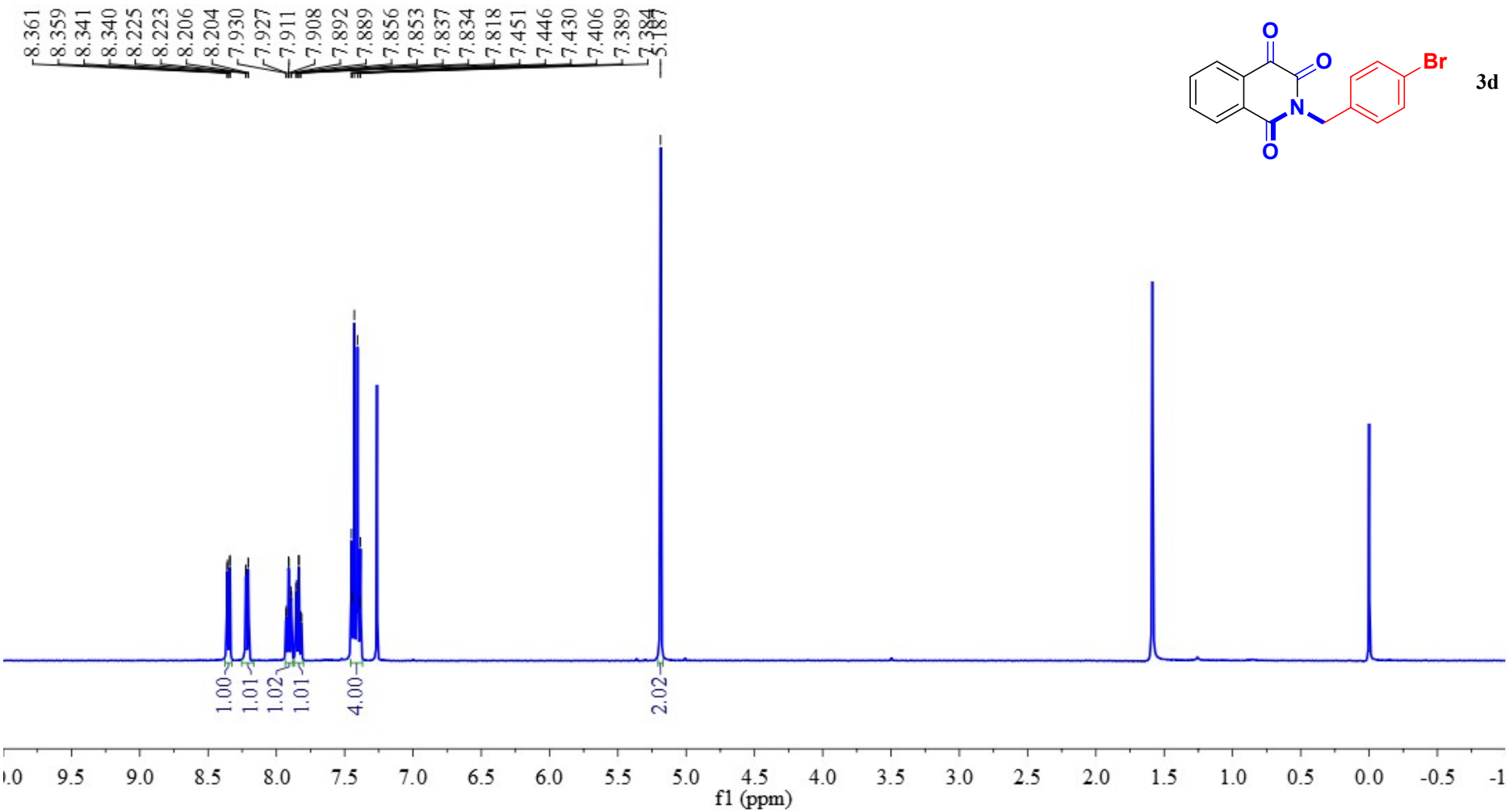
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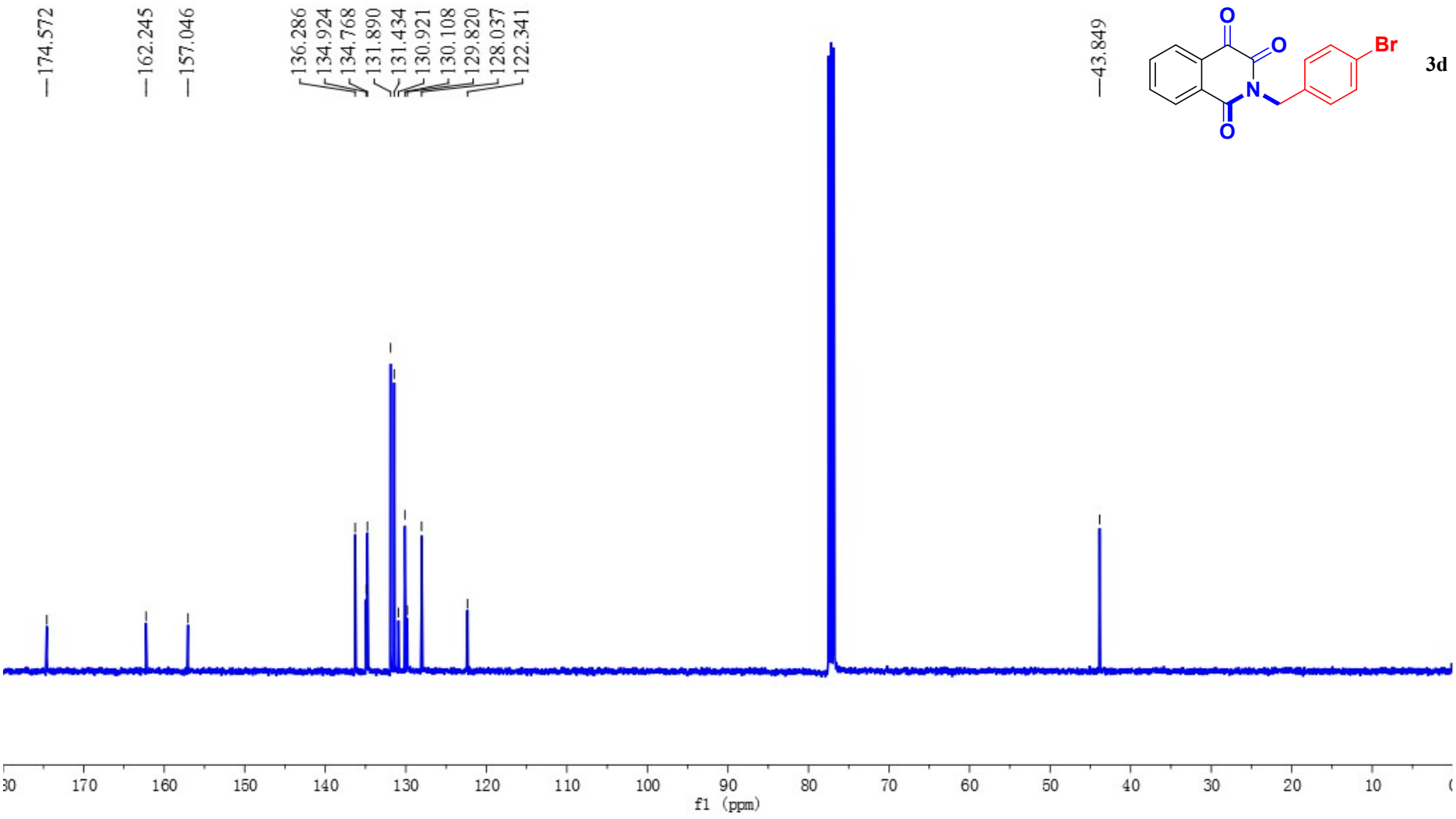
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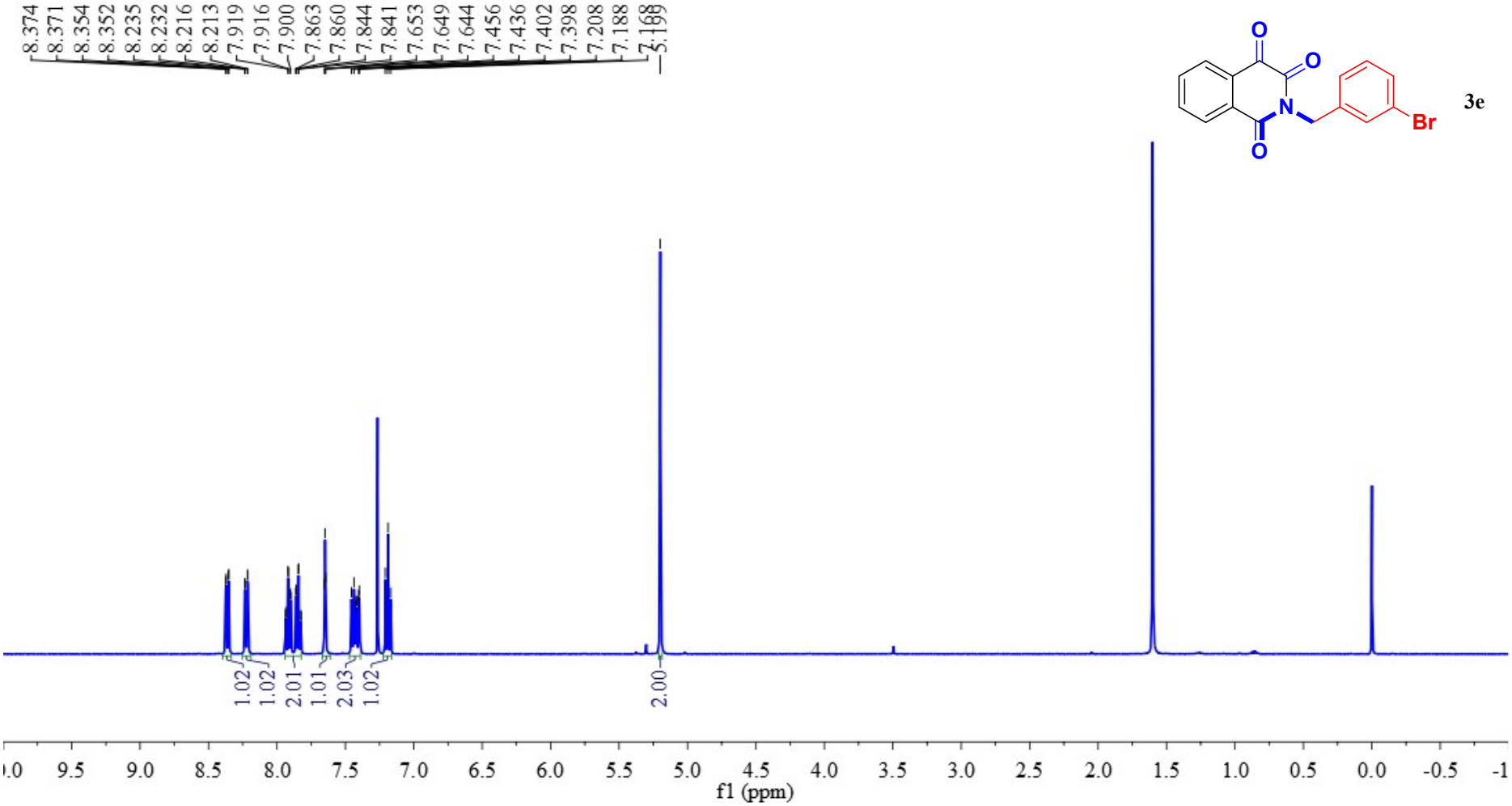
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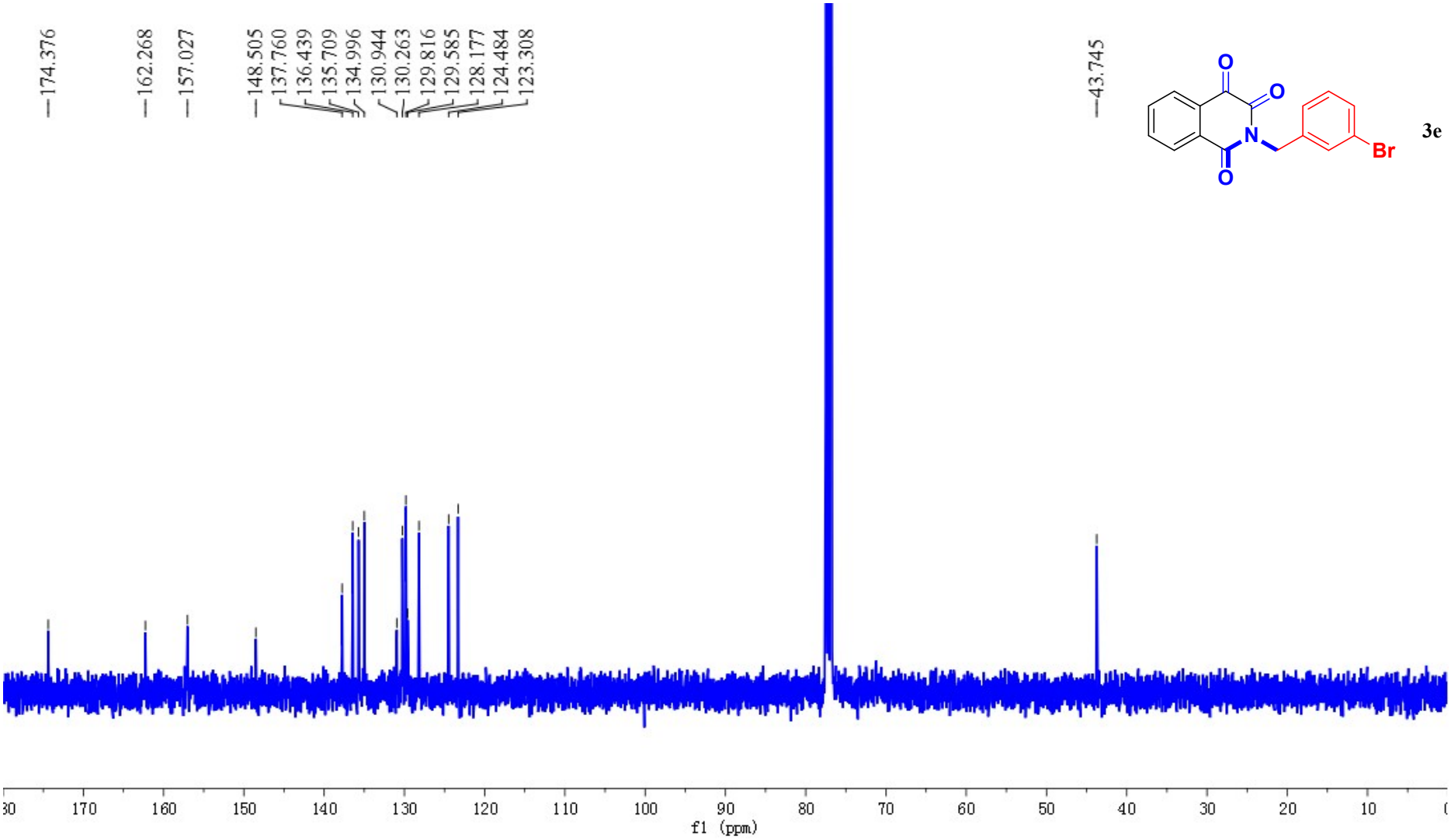
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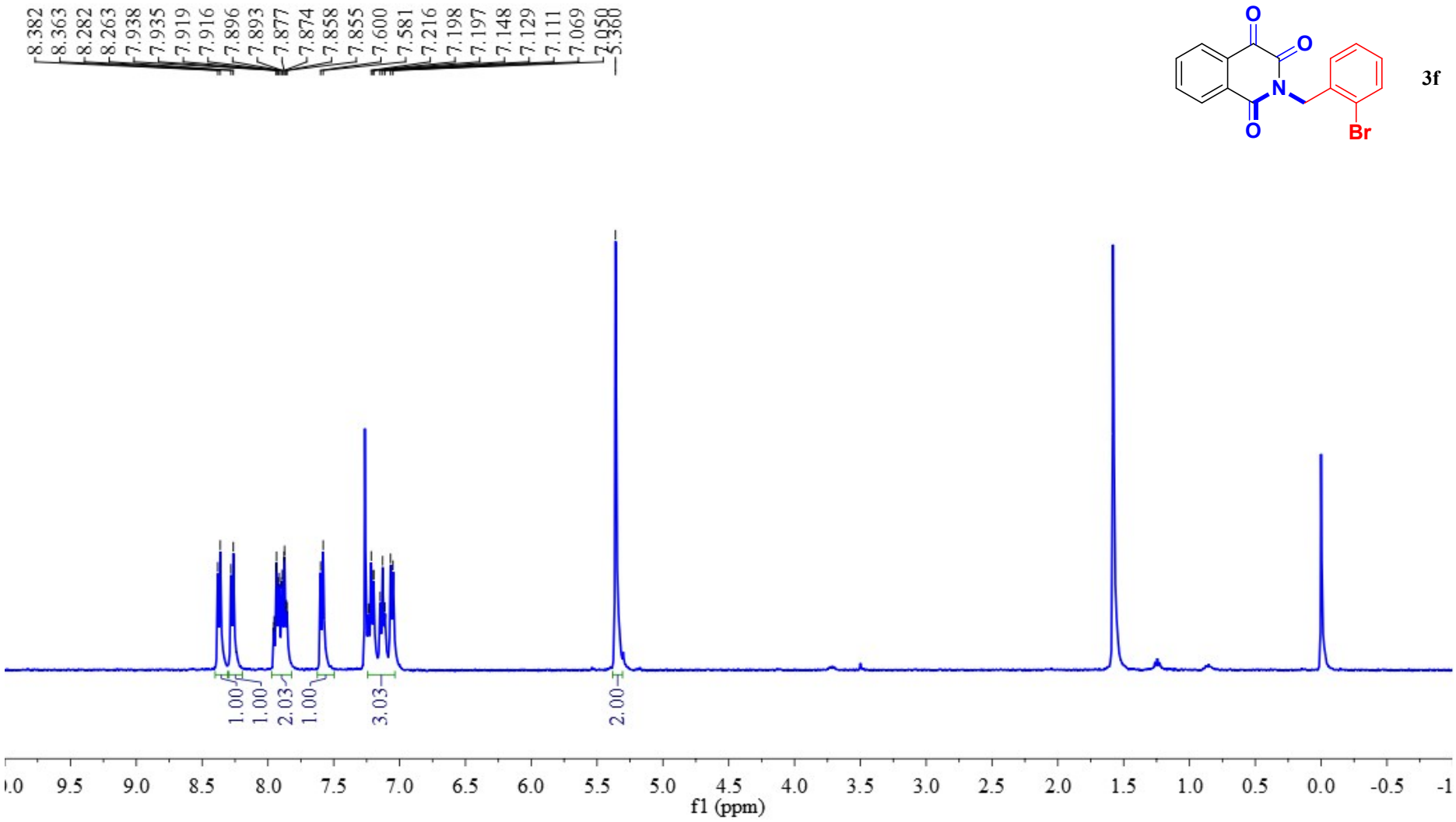
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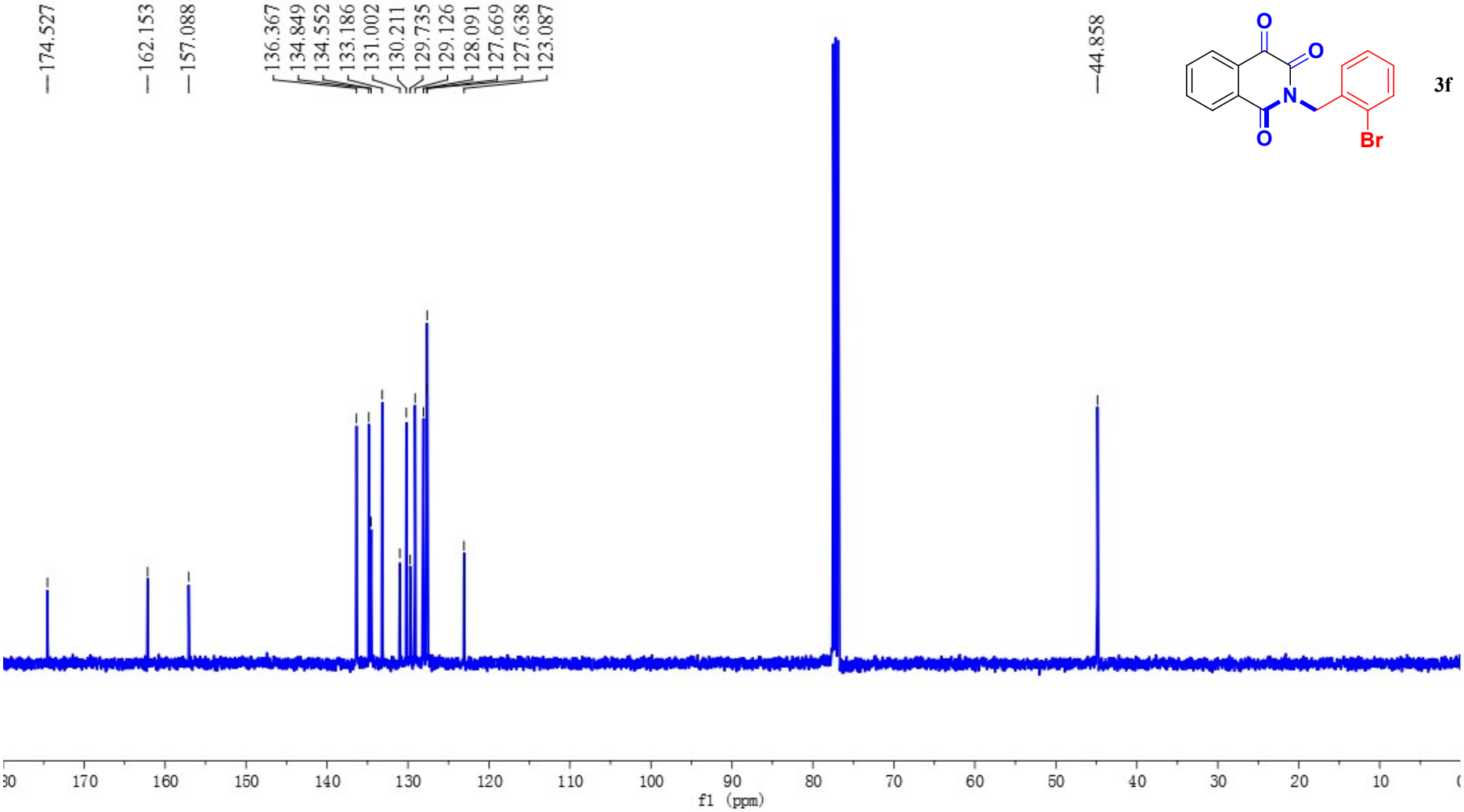
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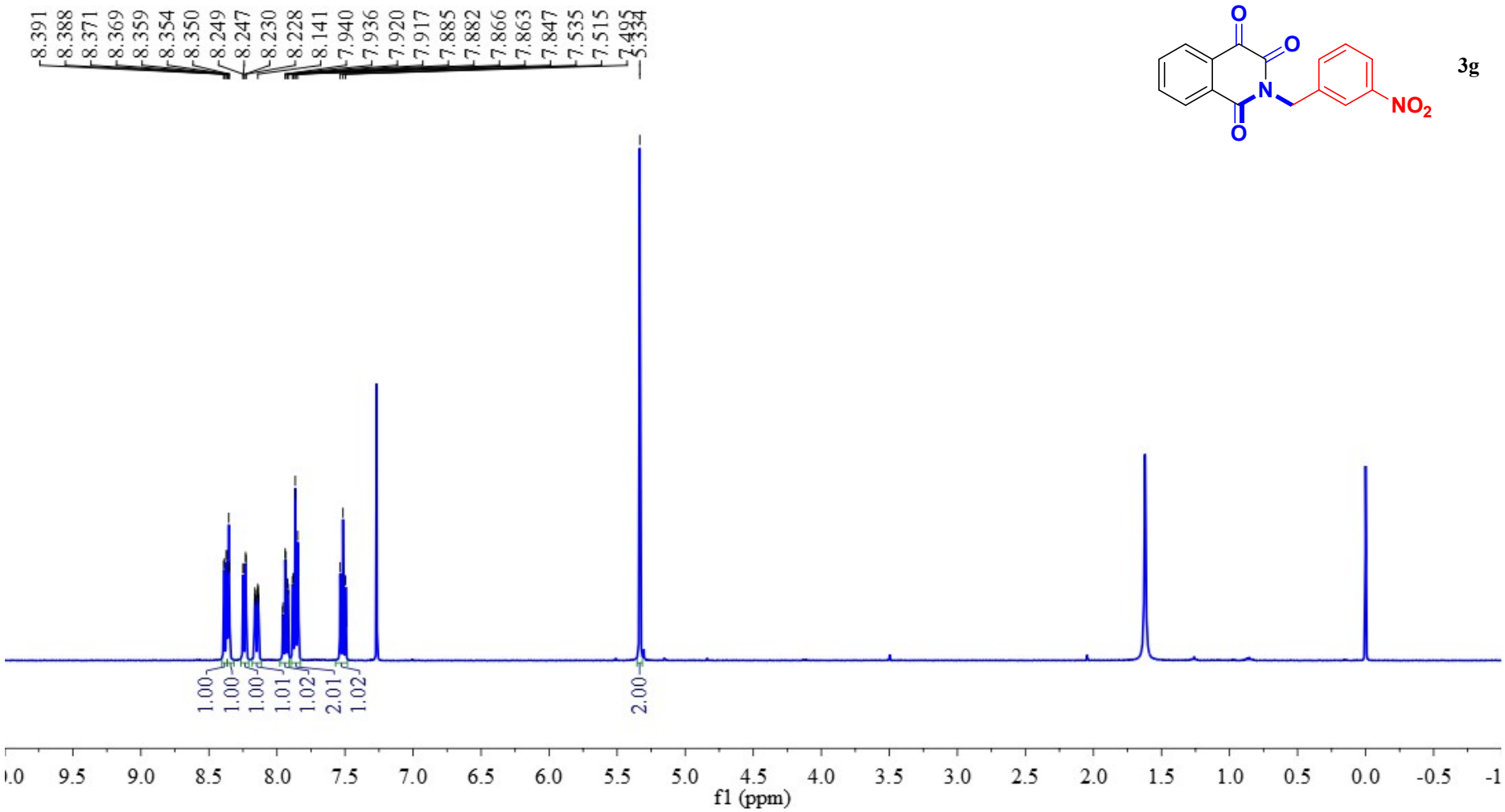
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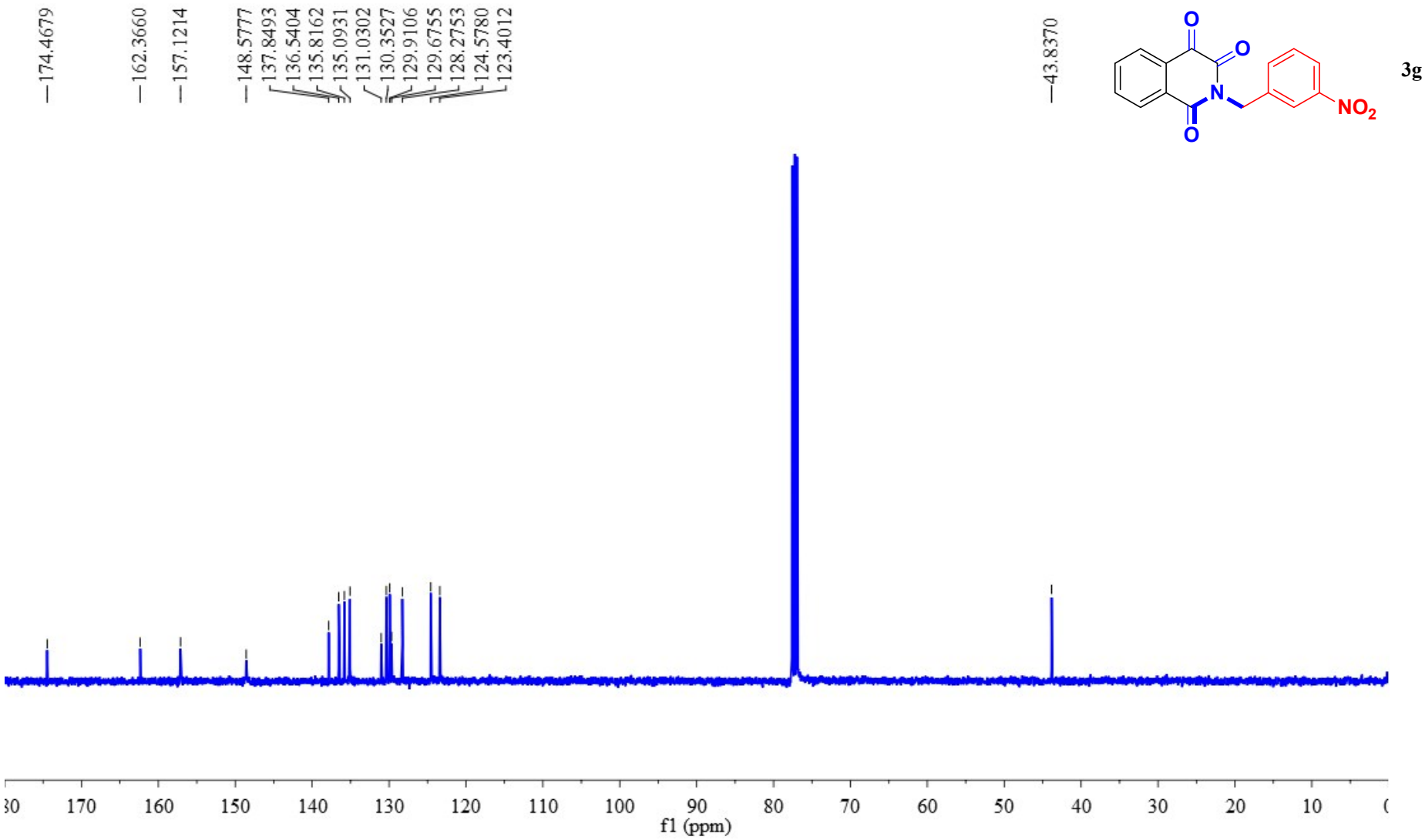
f1 (ppm)
3g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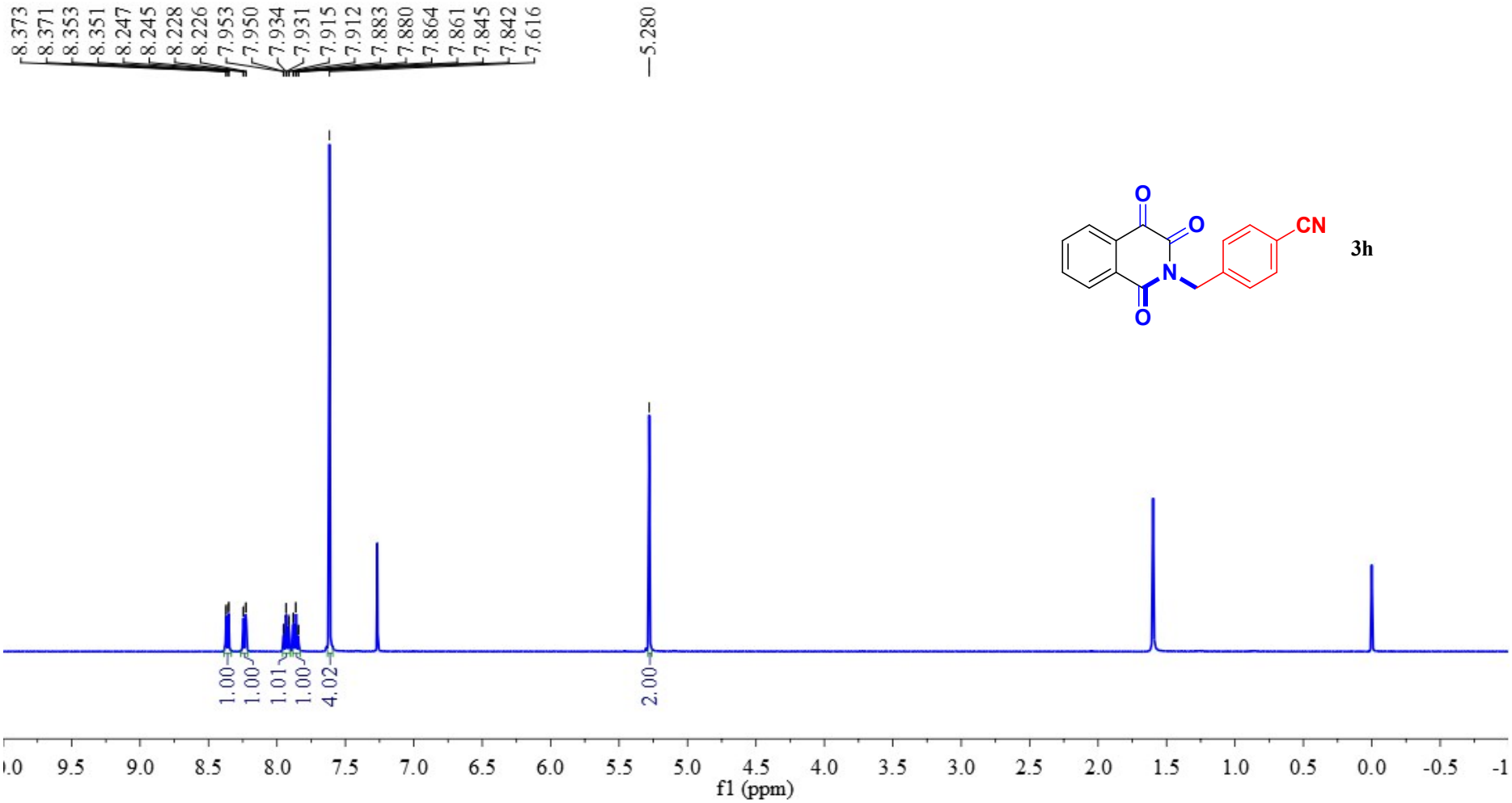
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O
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O
CN
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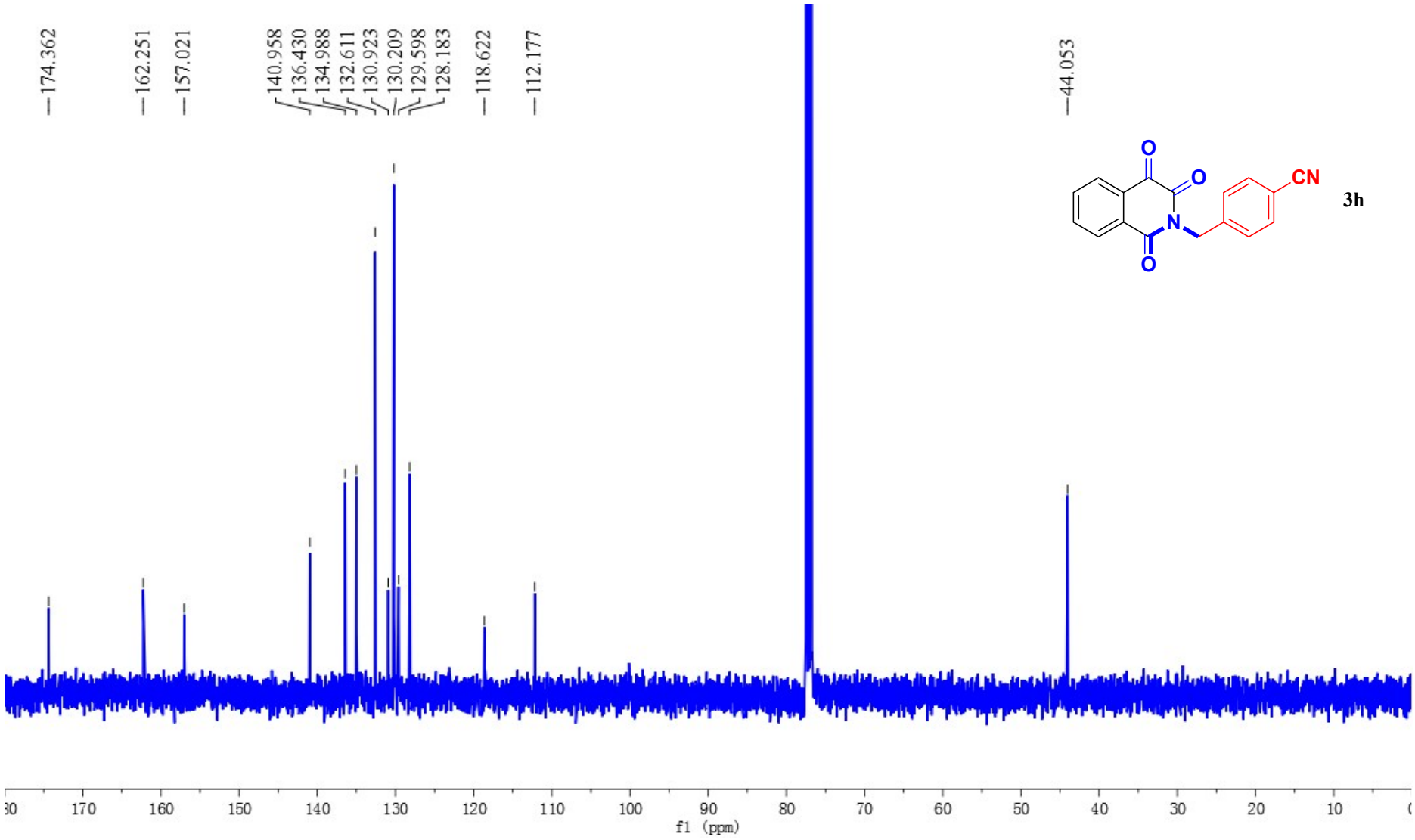
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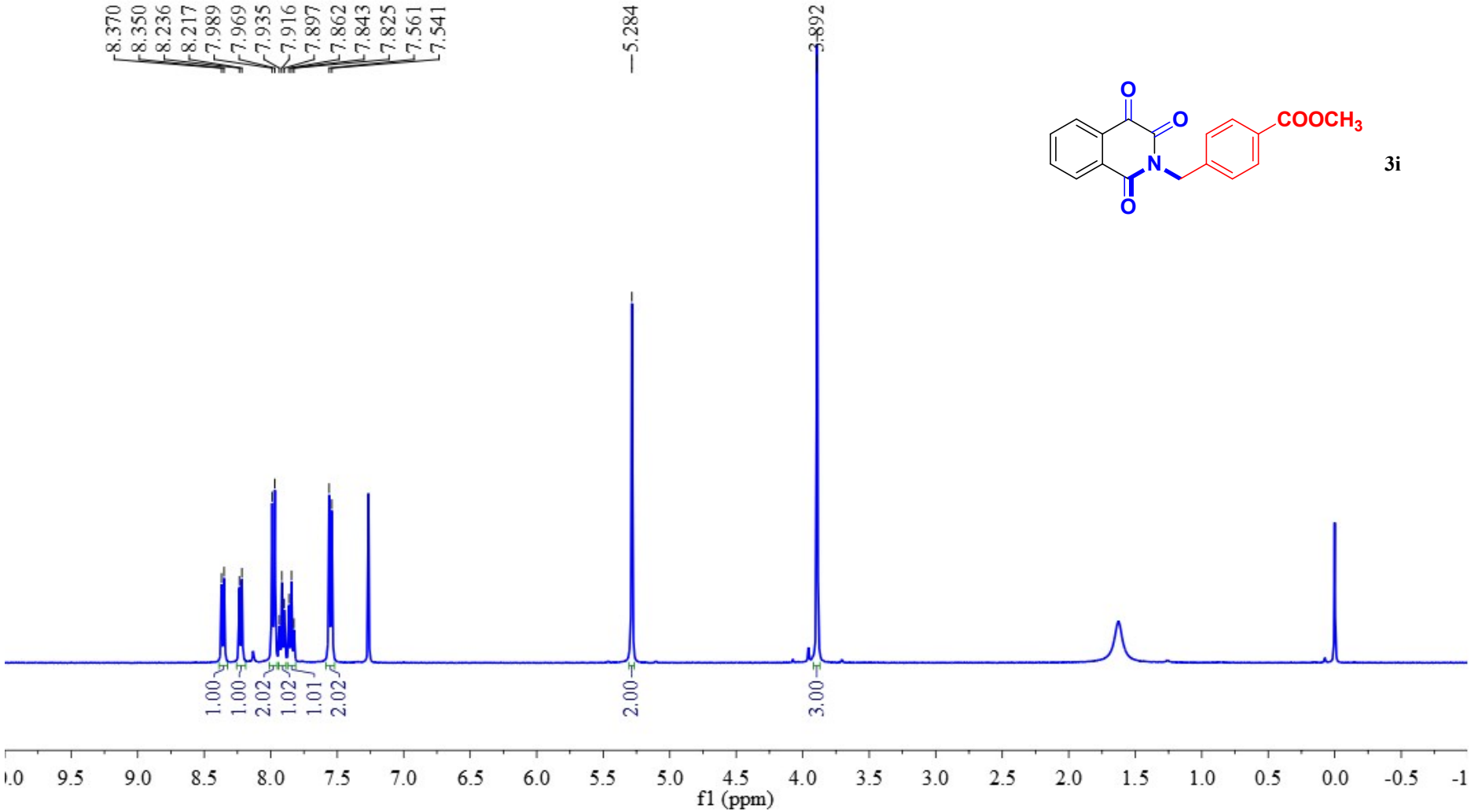
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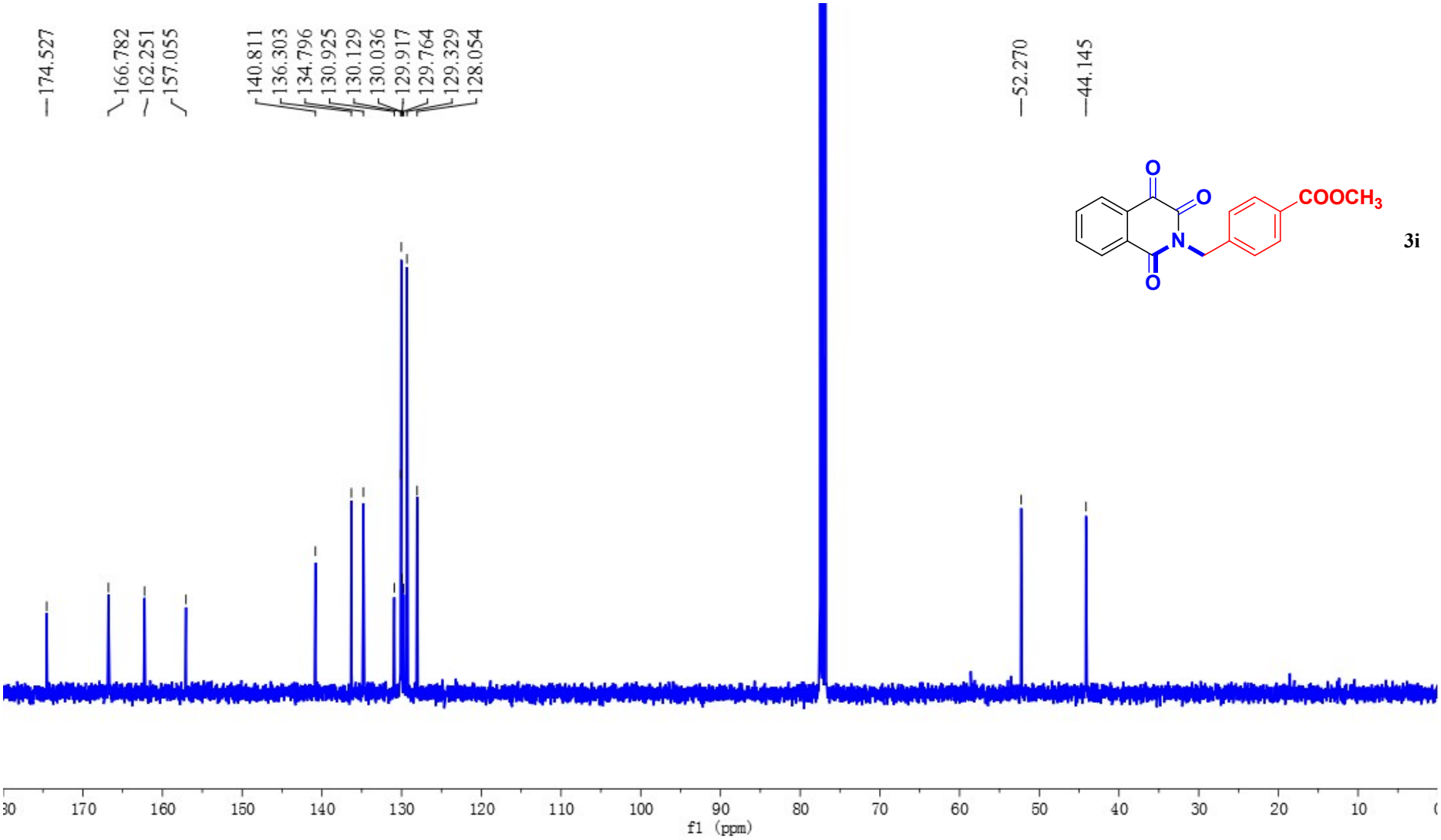
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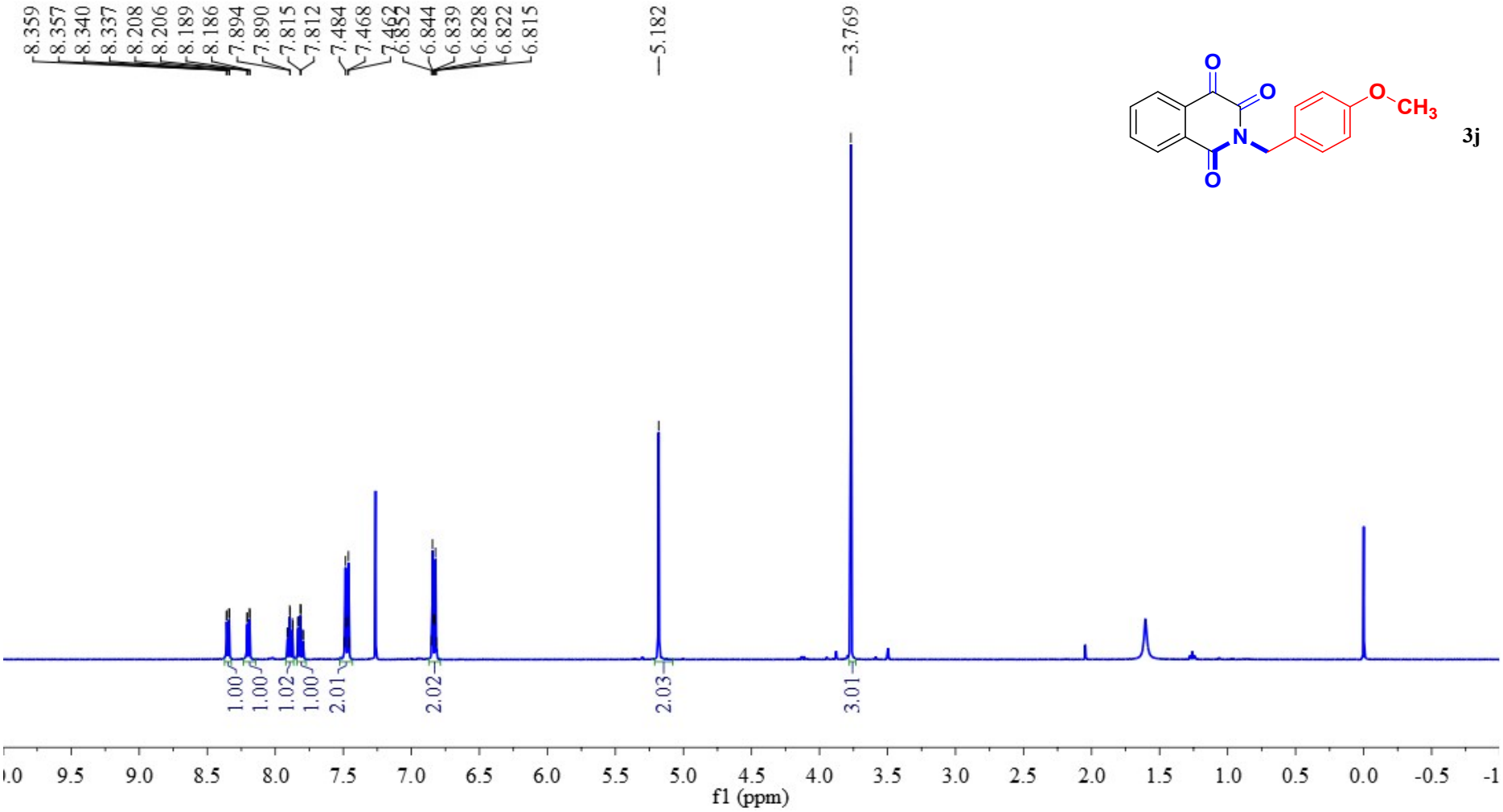
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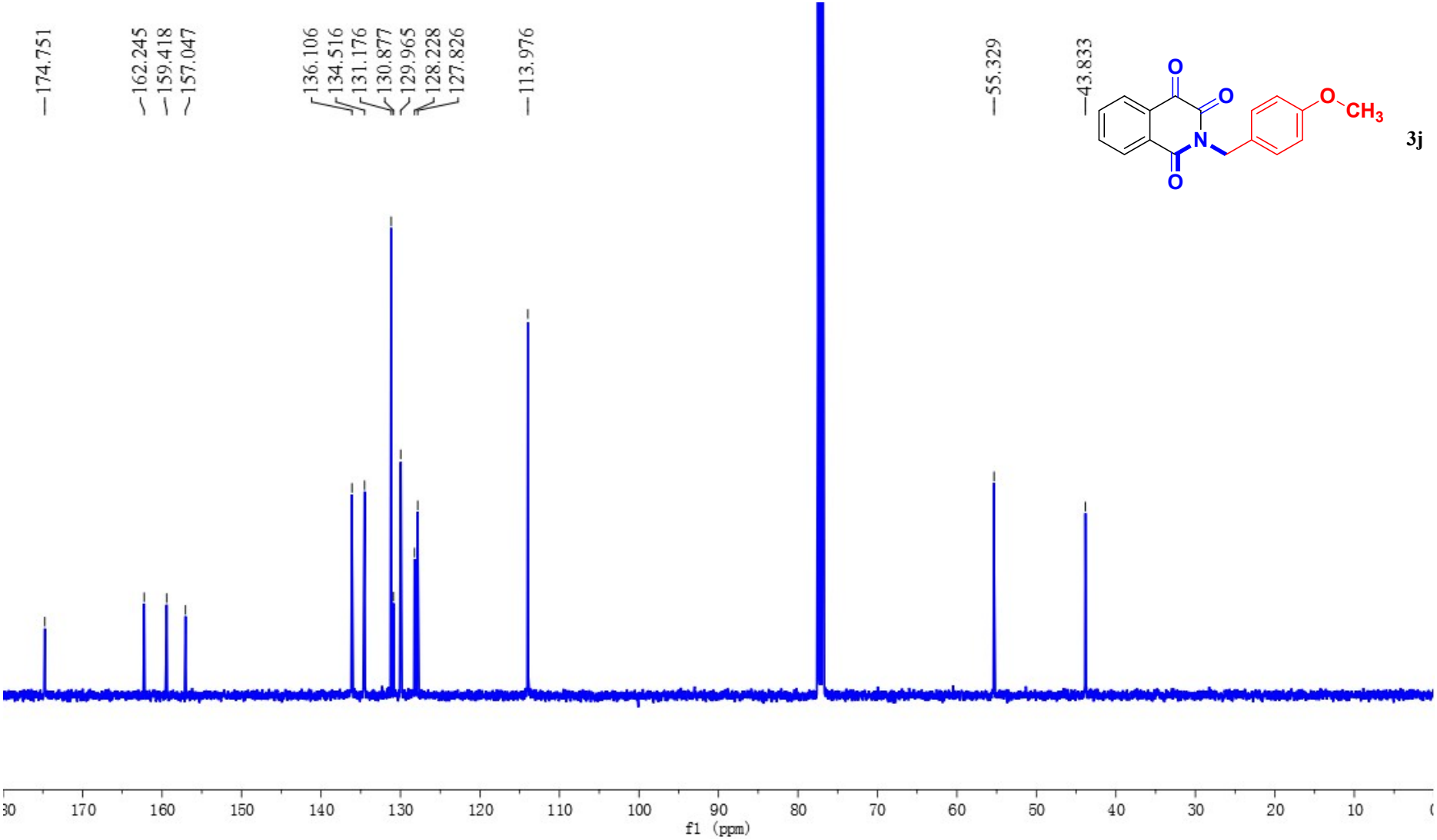
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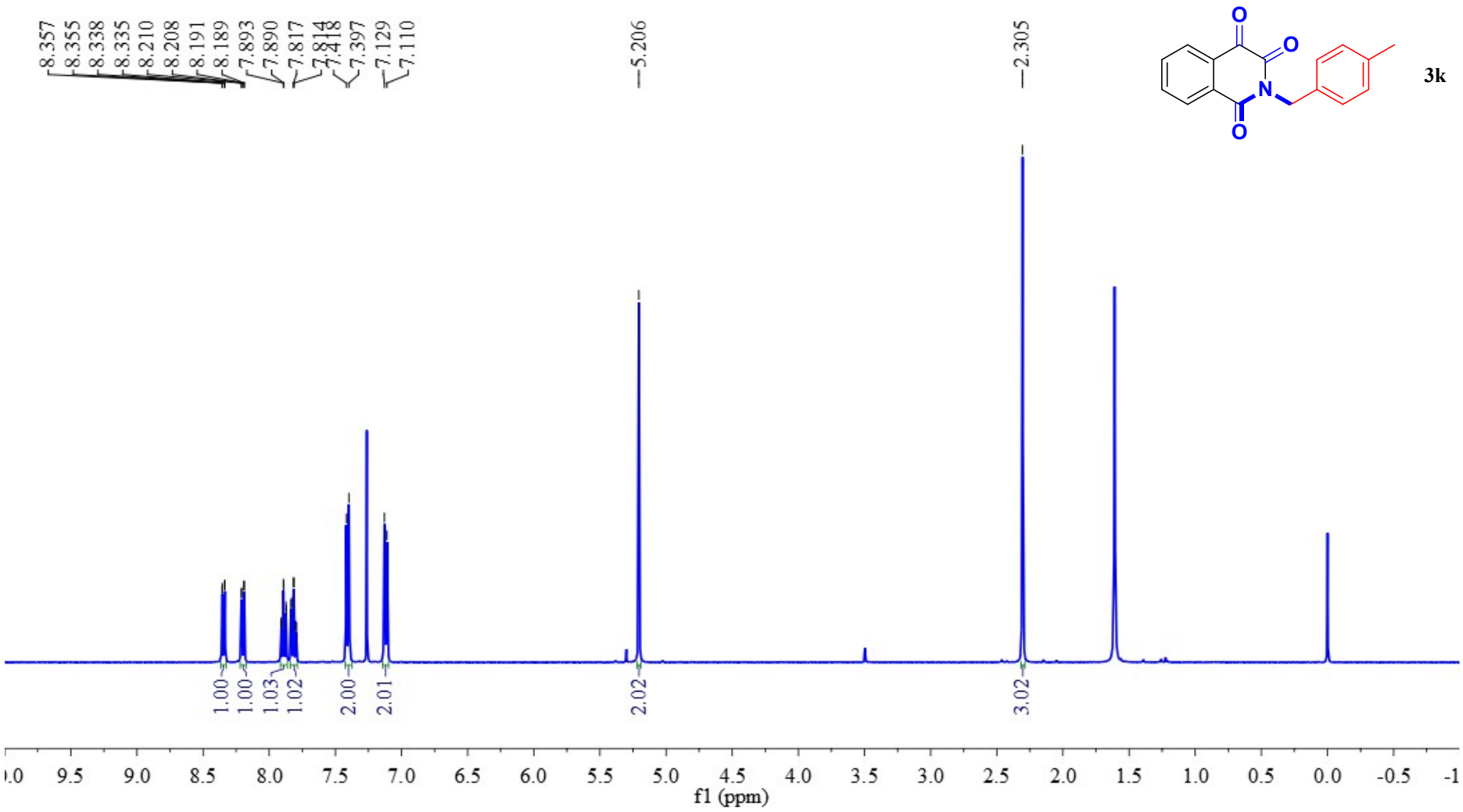
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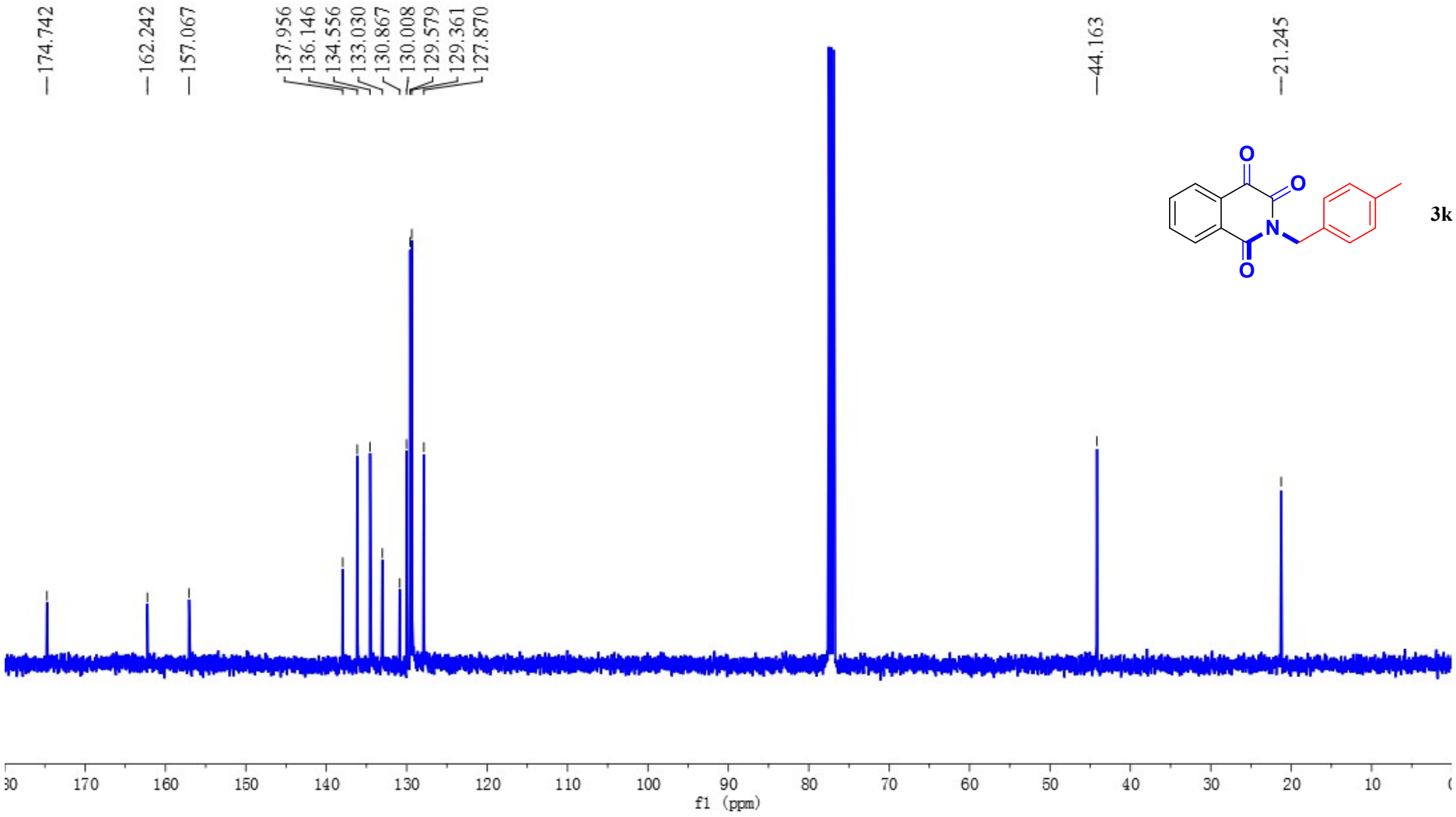
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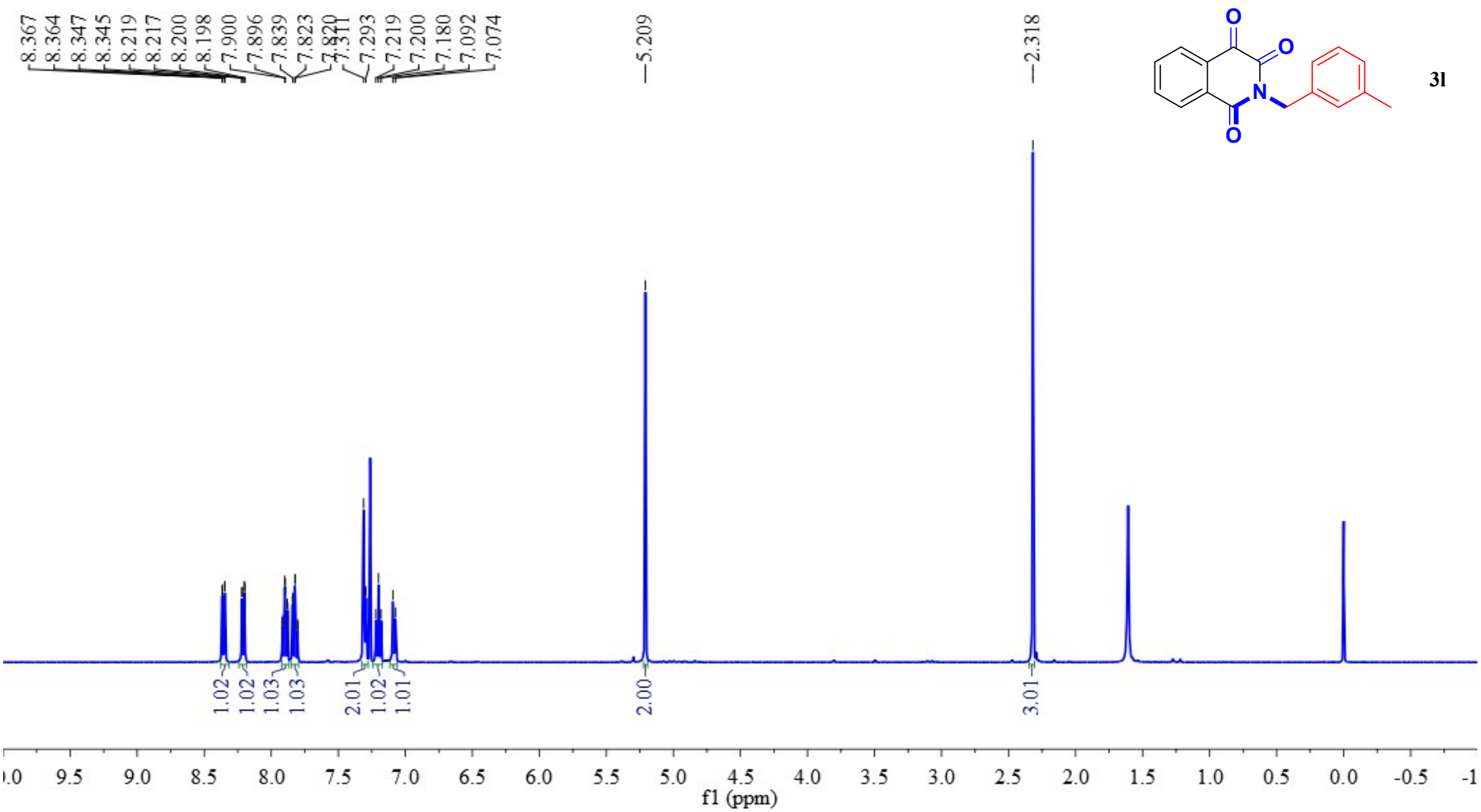
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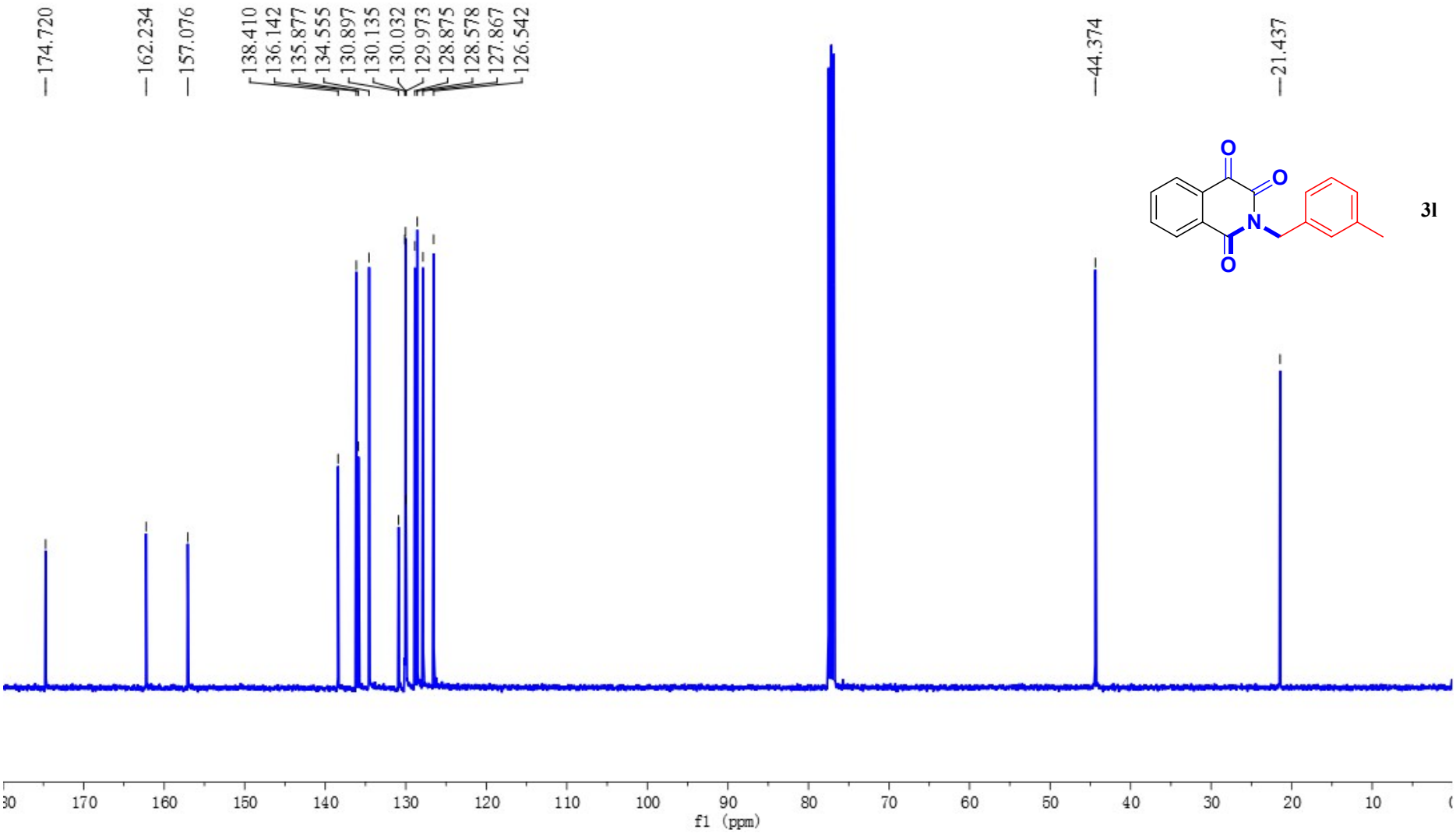
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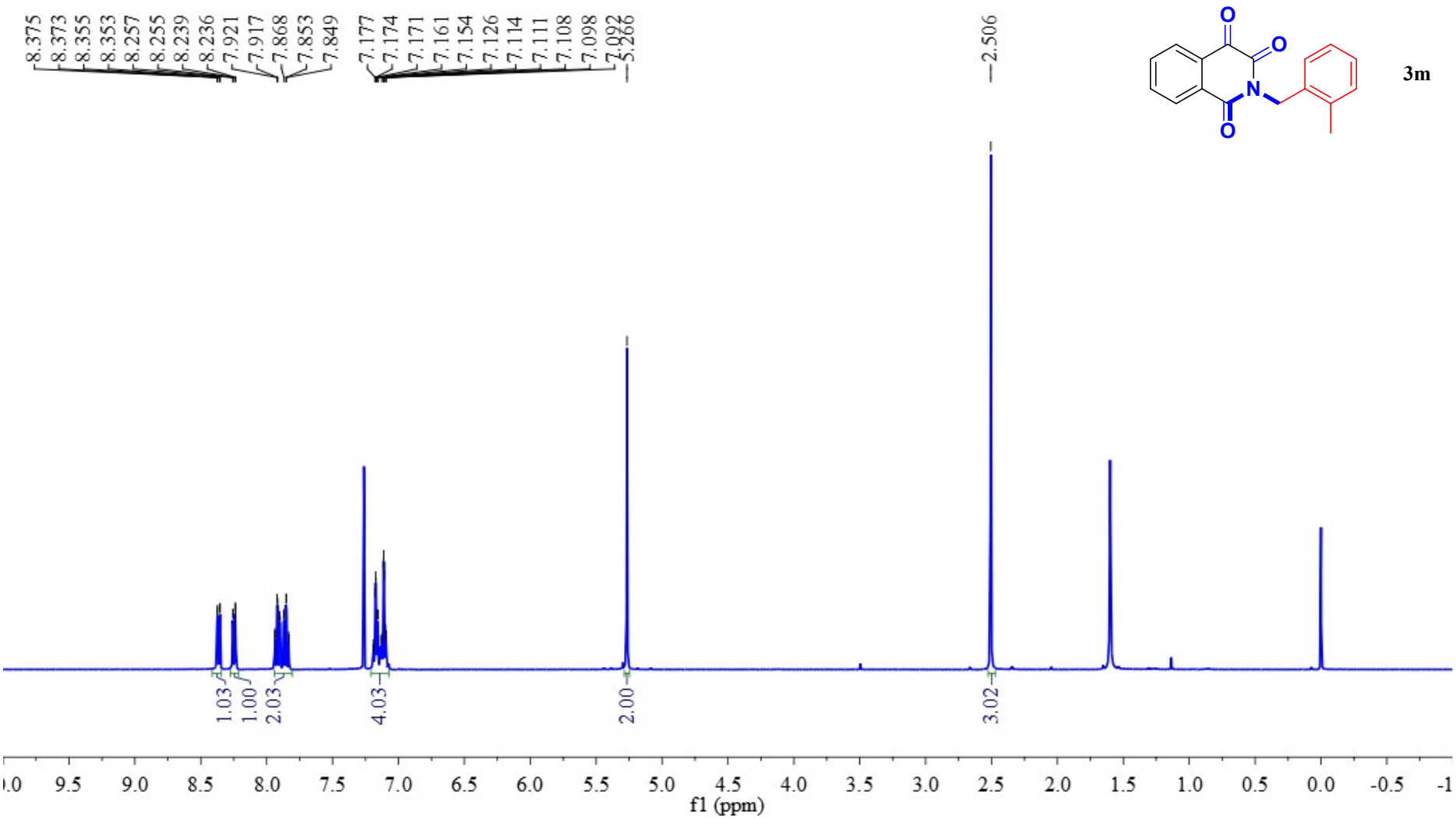
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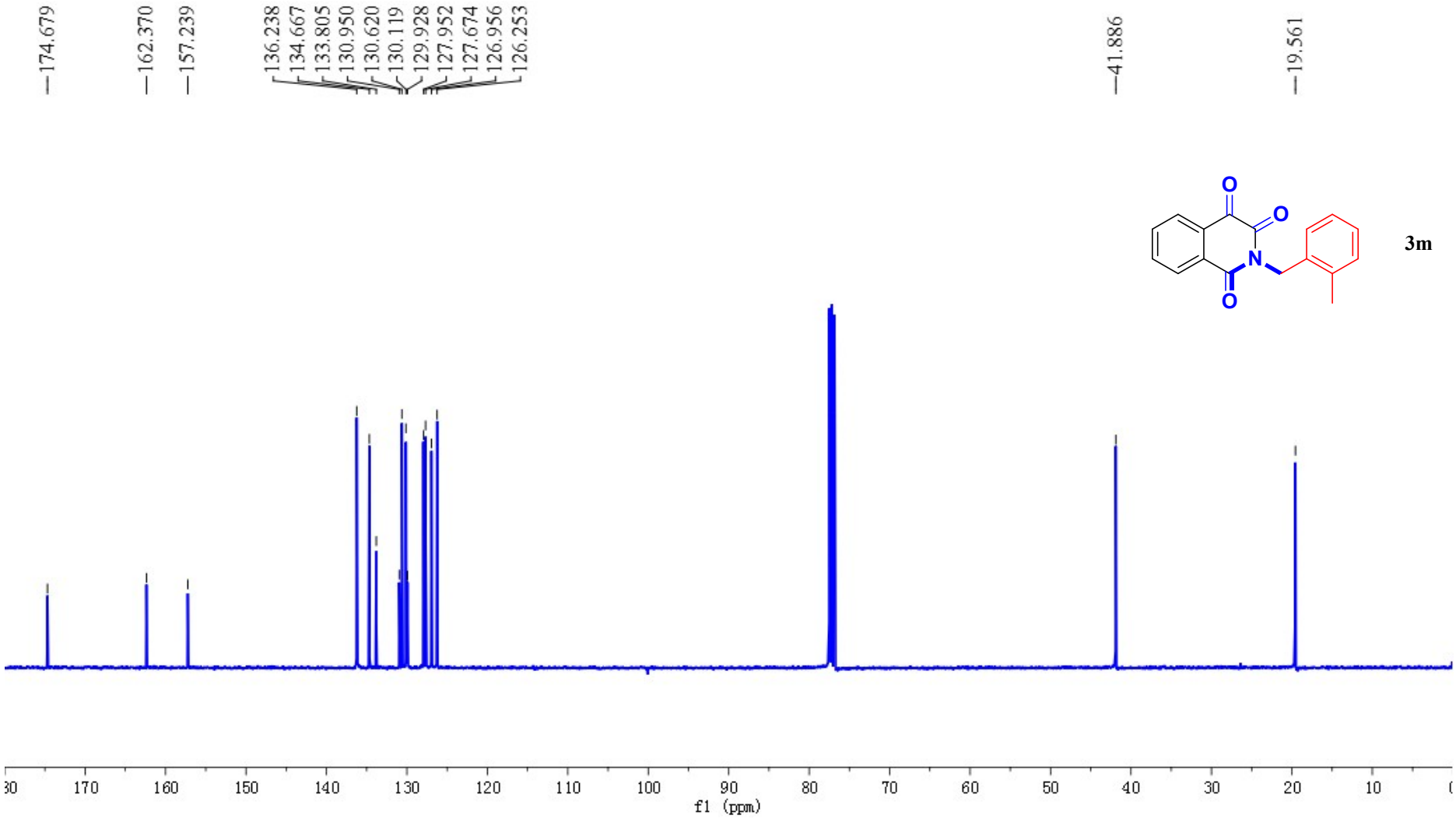
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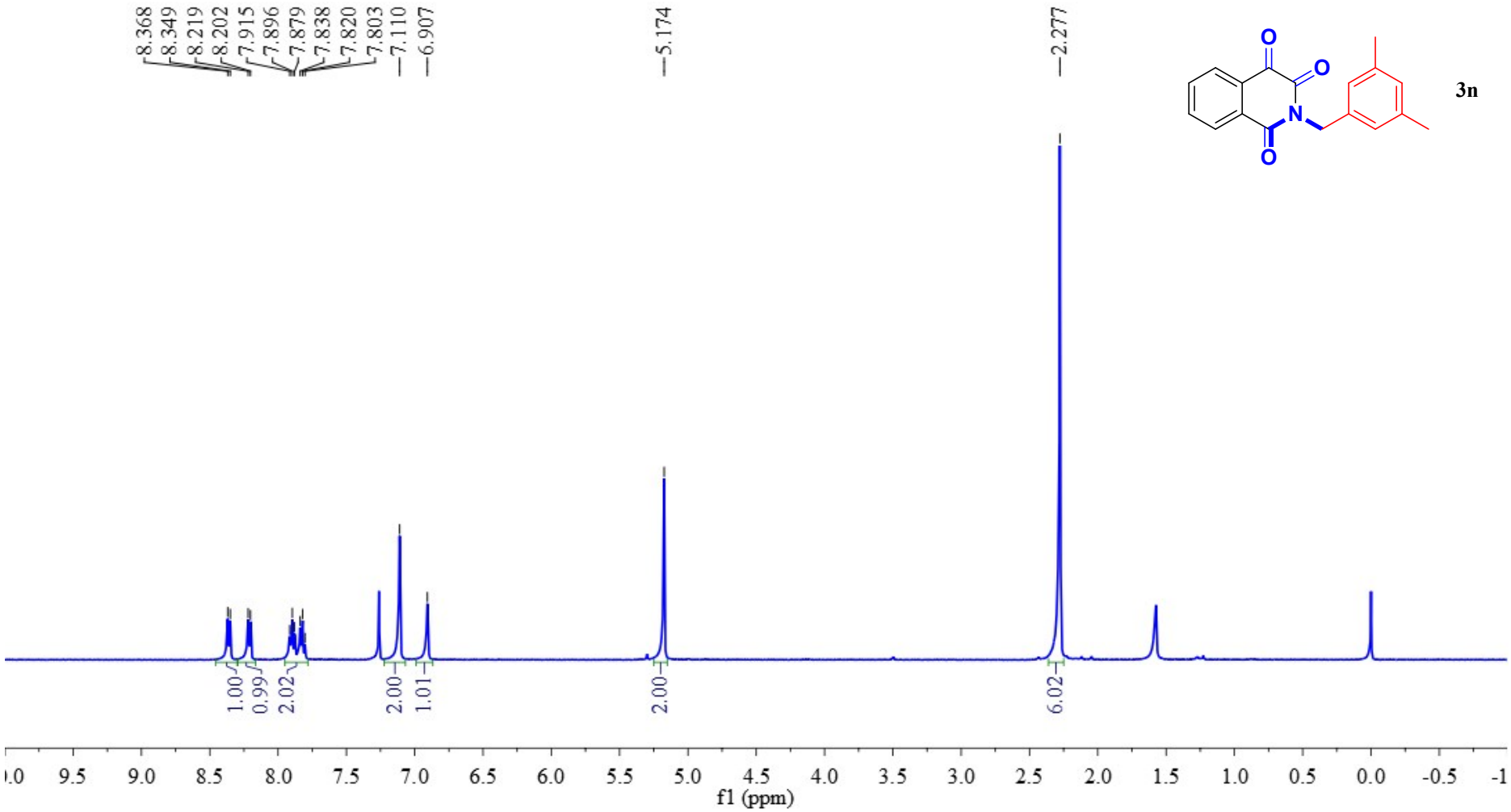
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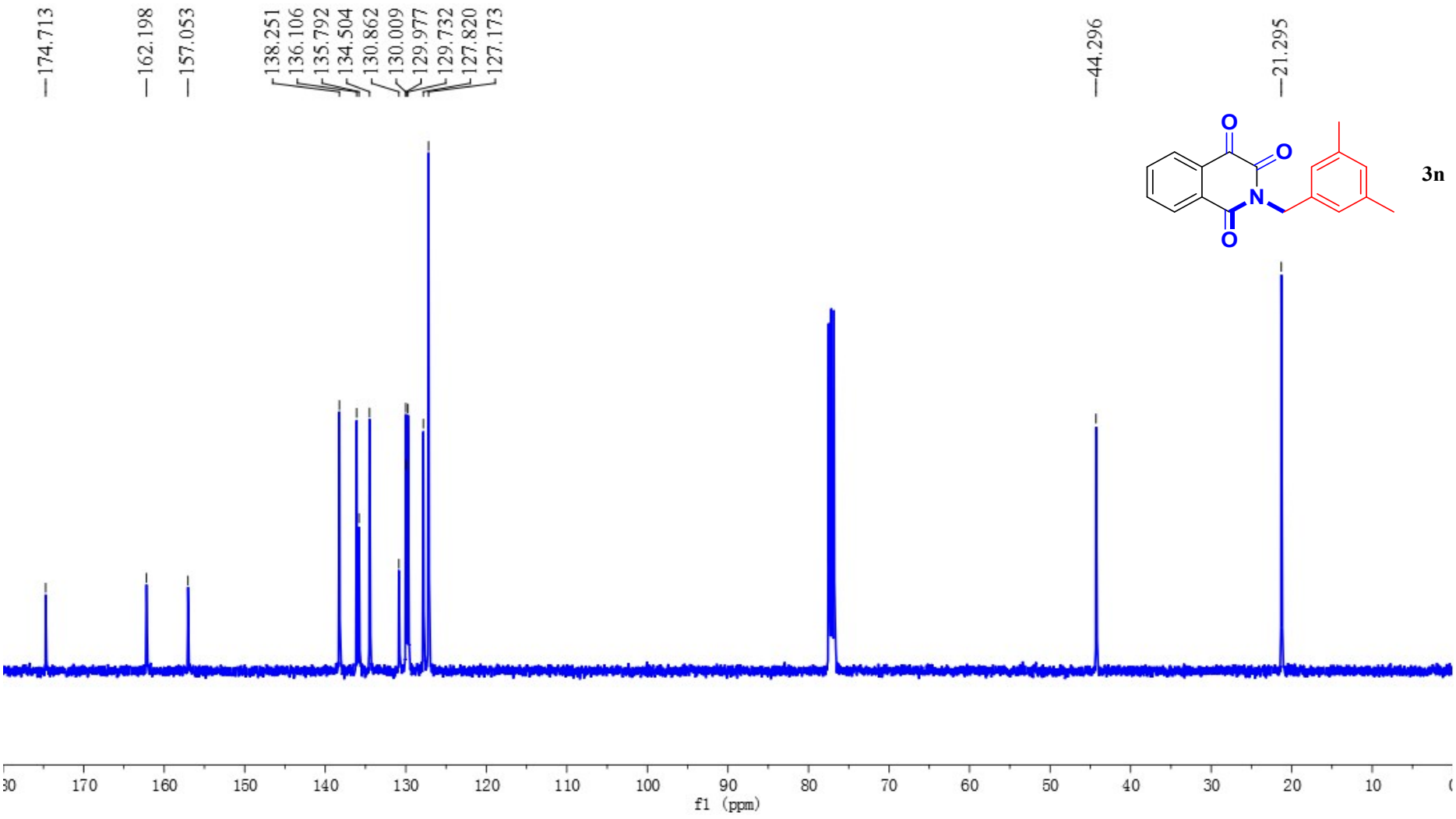
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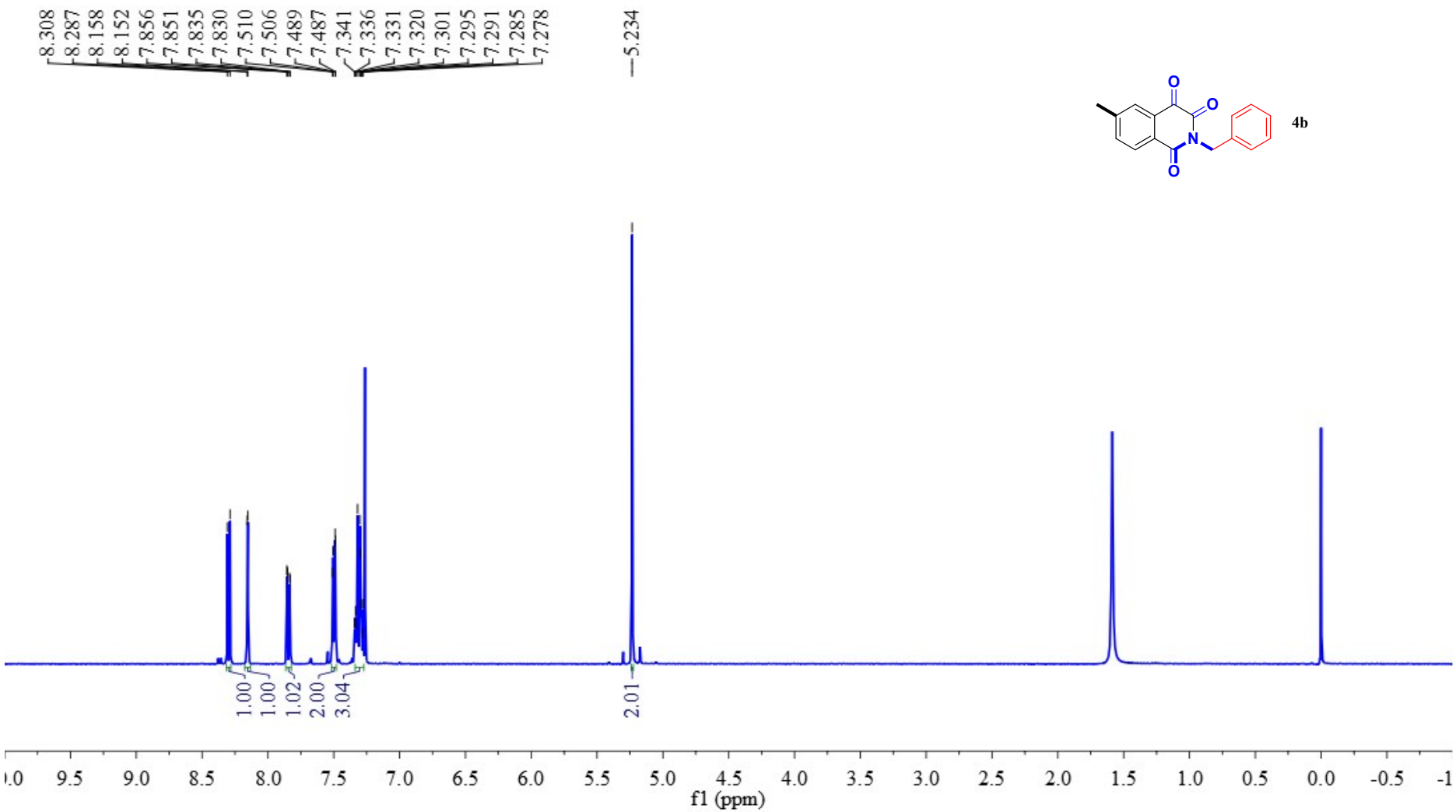
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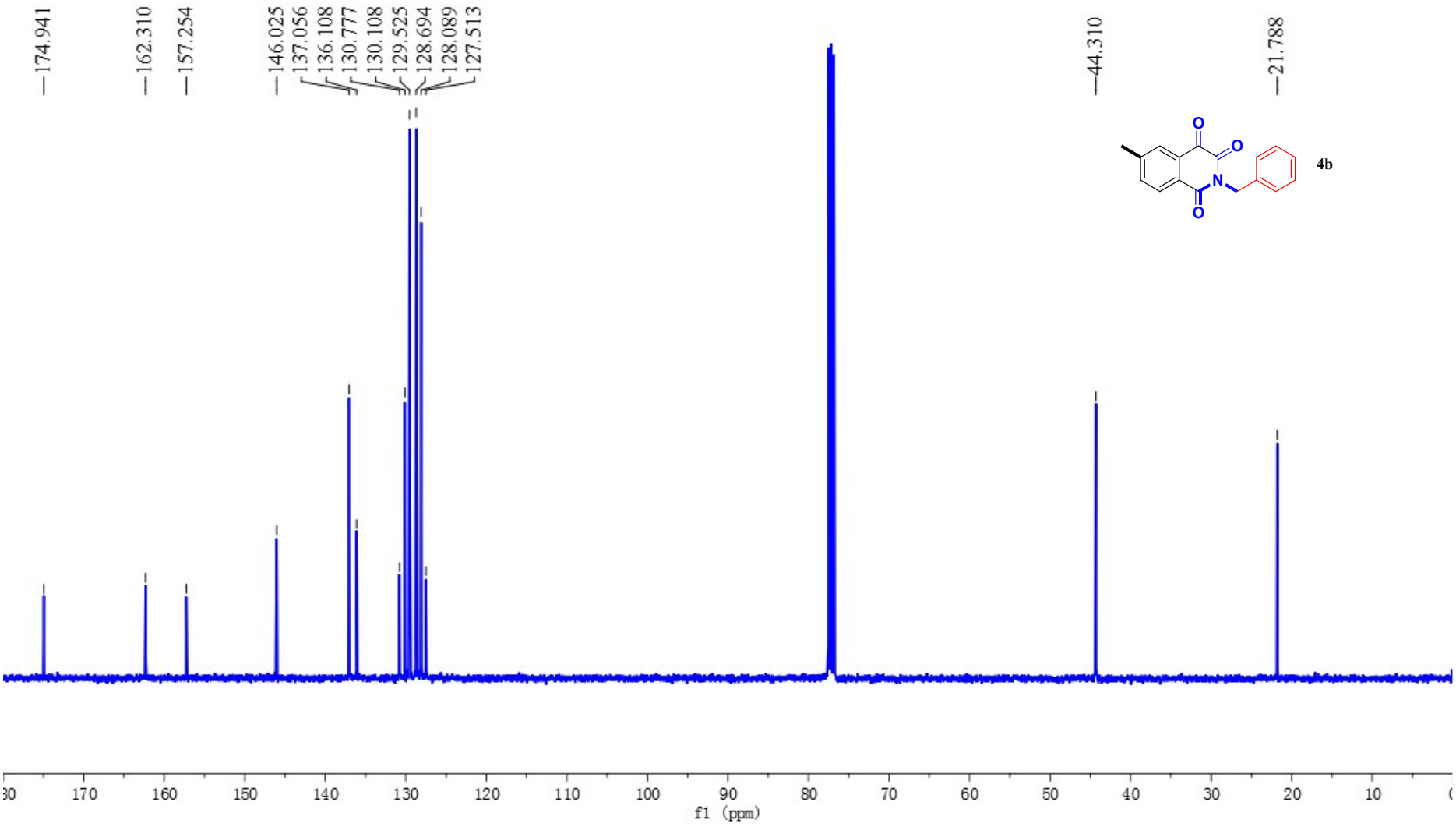
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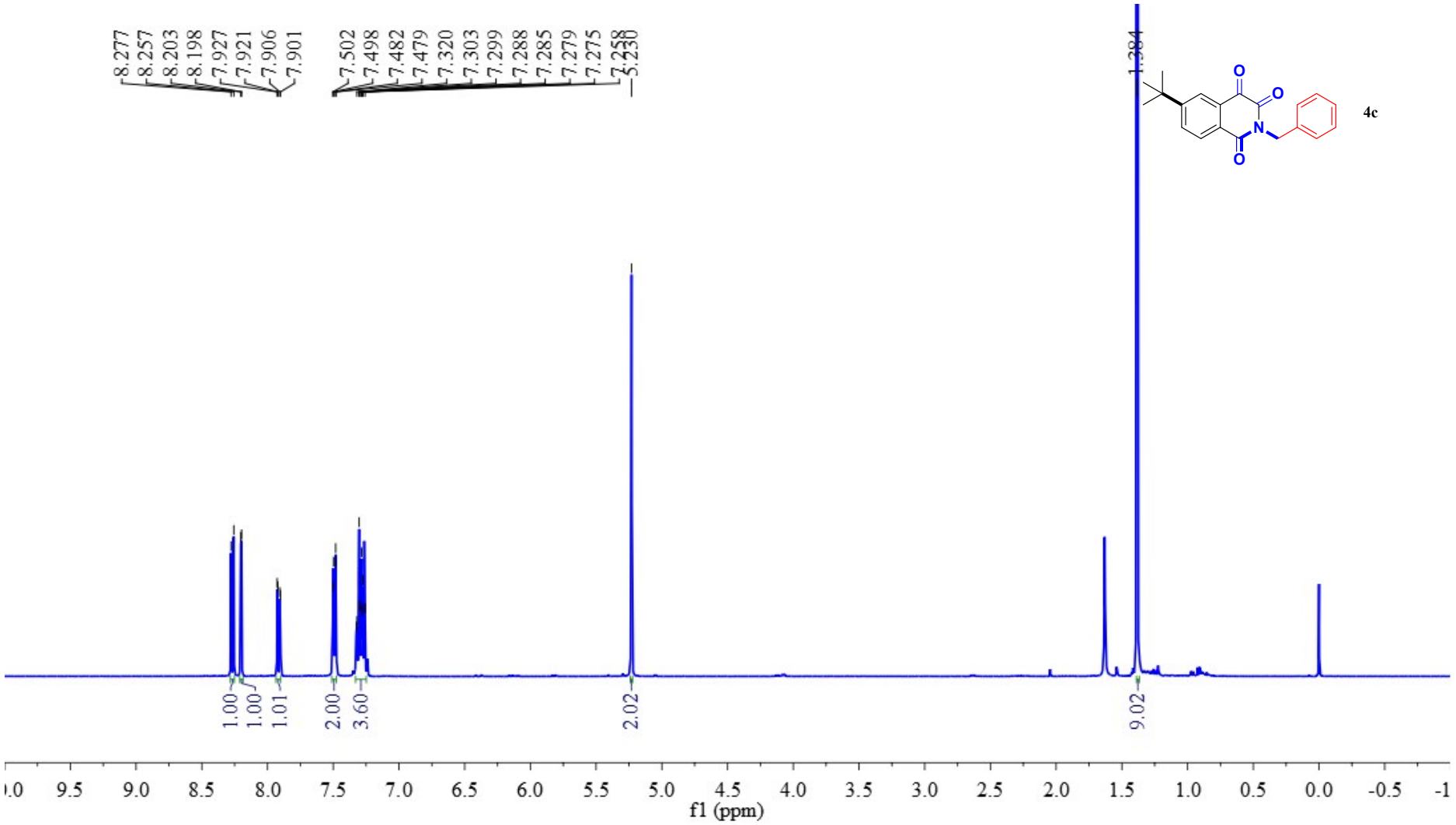
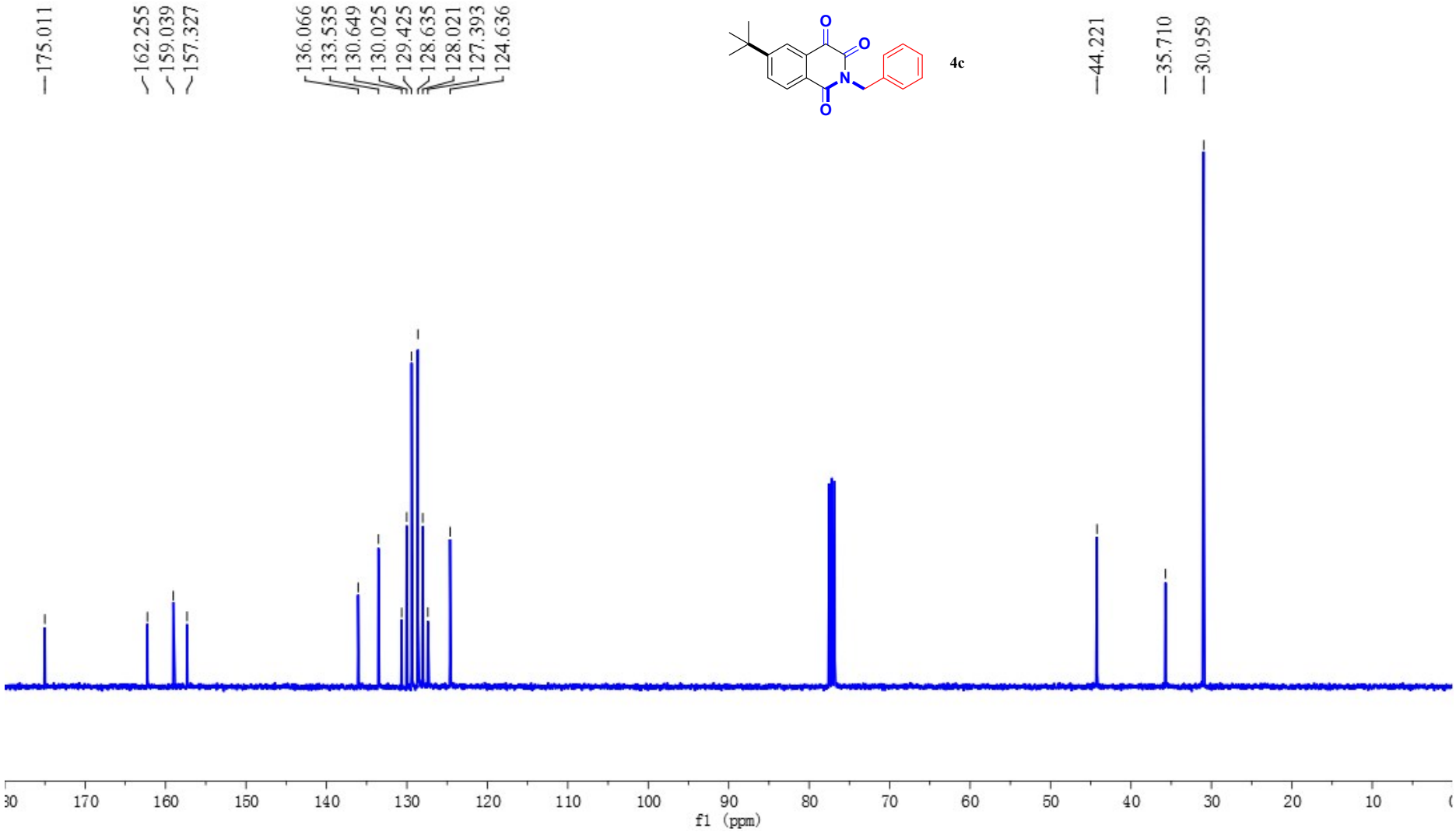
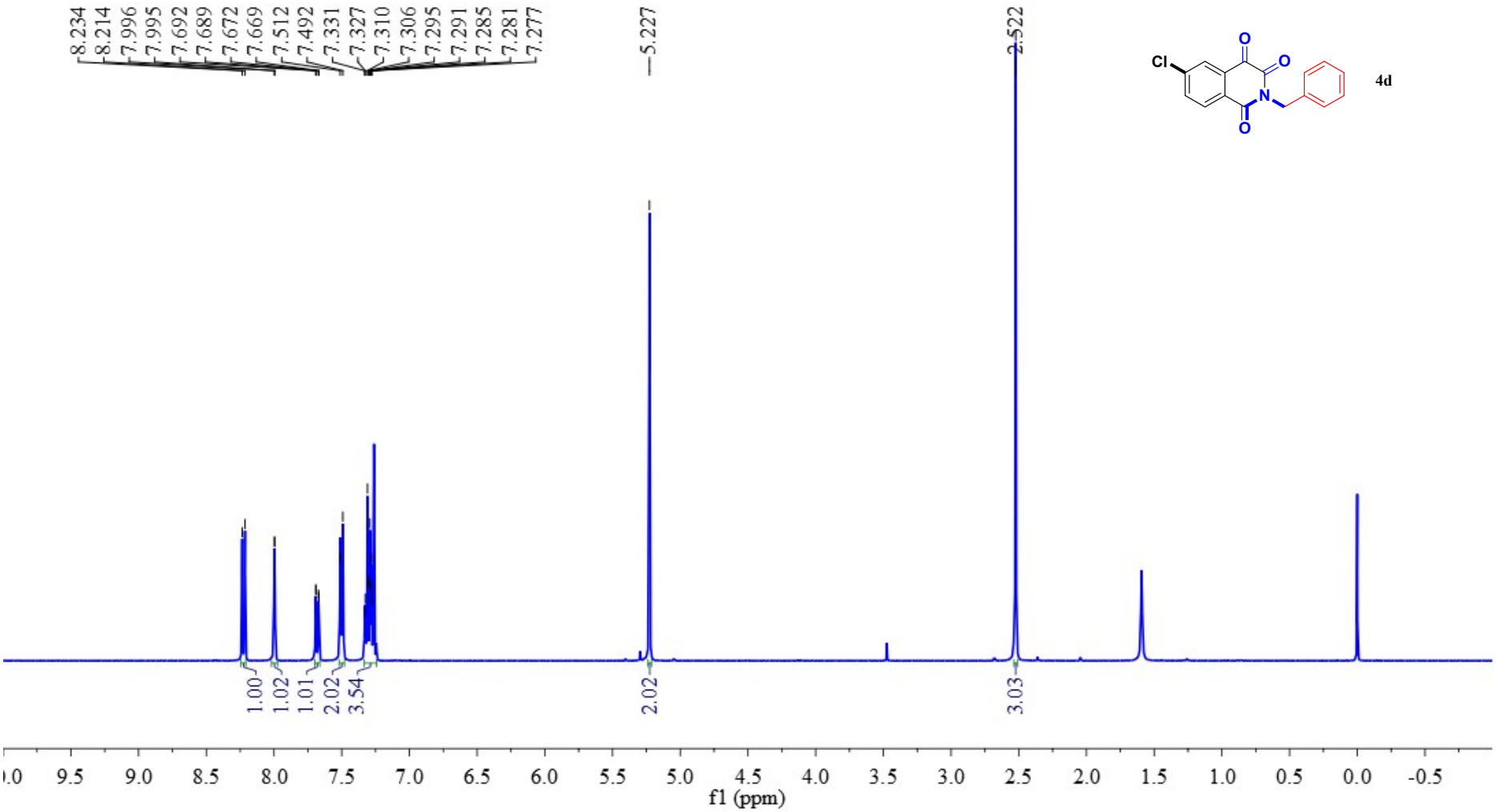
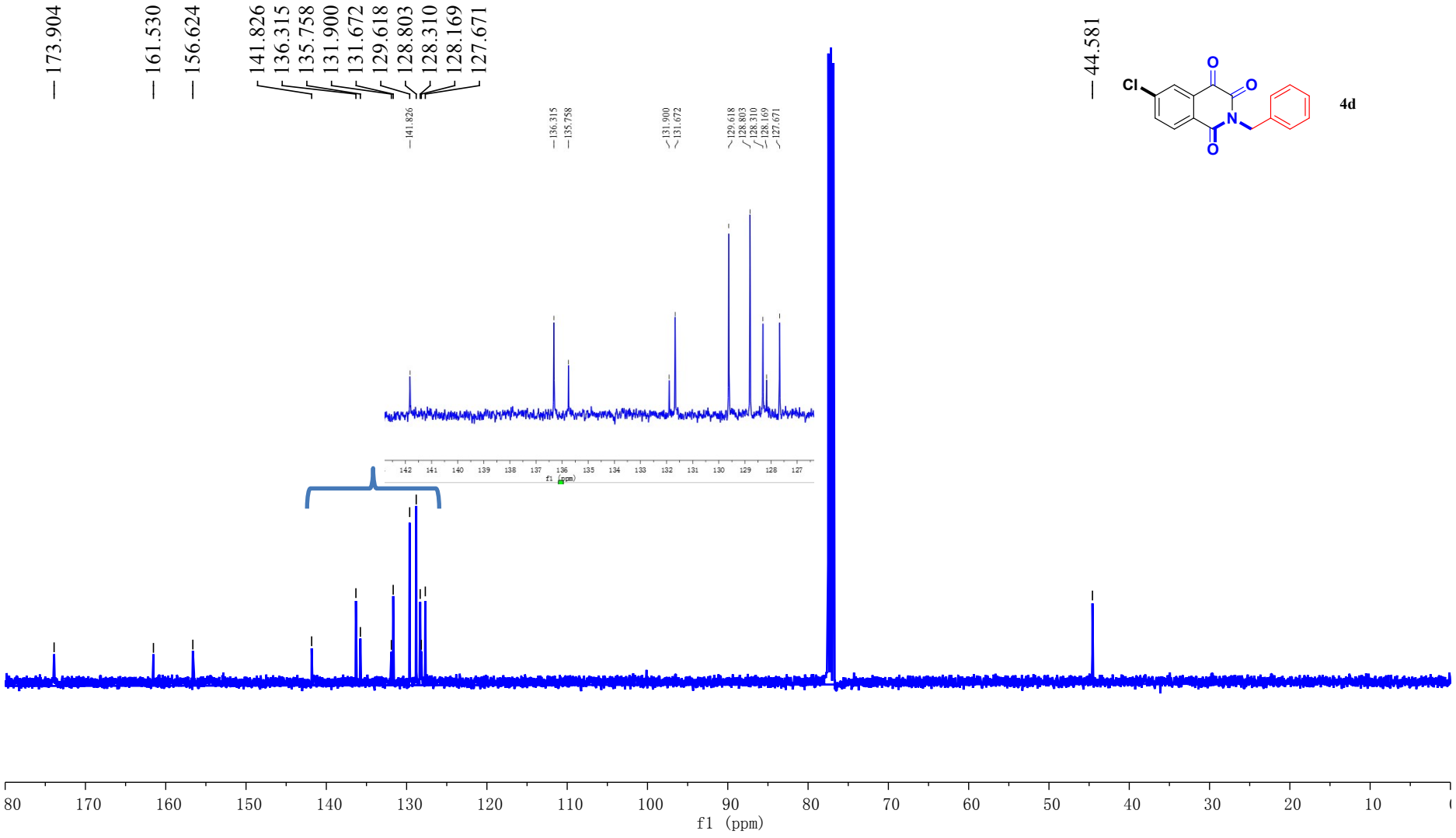
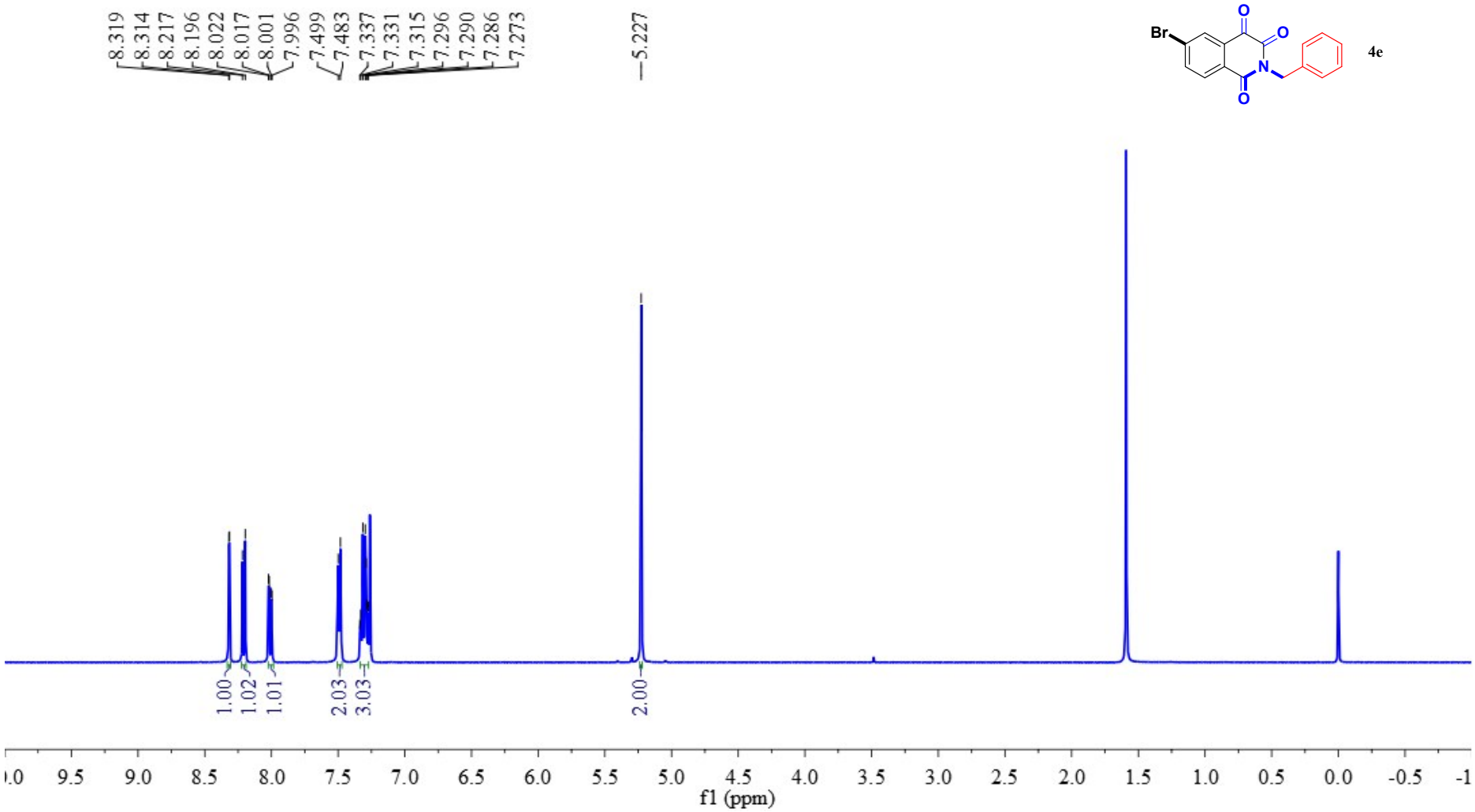
21.788
4b
f1 (ppm)

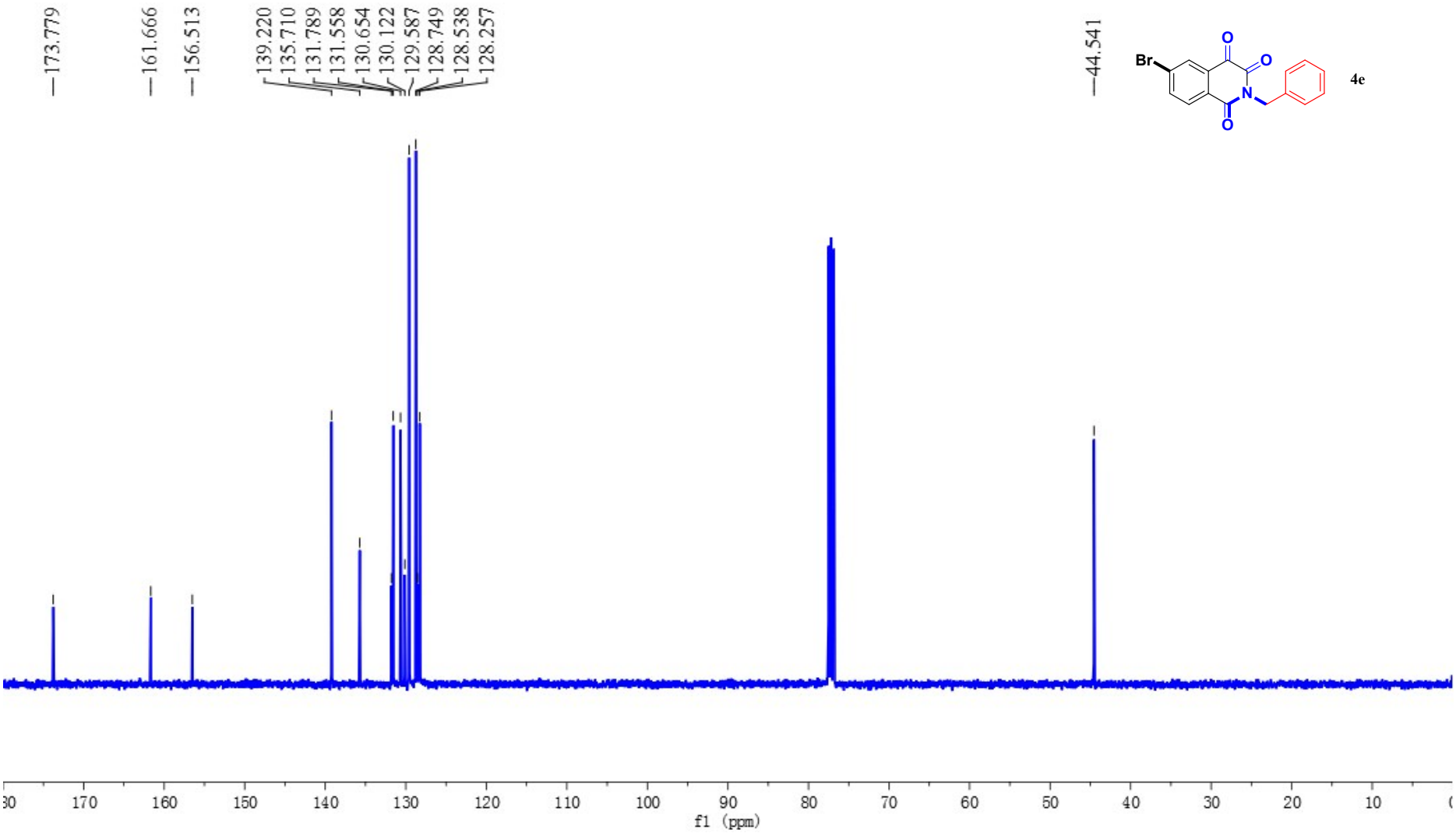

8.277
8.257
8.203
8.198
7.927
7.921
7.906
7.901
7.502
7.498
7.482
7.479
7.320
7.303
7.299
7.288
7.285
7.279
7.275
7.258
7.230
1.384
4c
1.00
1.00
1.01
2.00
3.60
2.02
9.02
f1 (ppm)

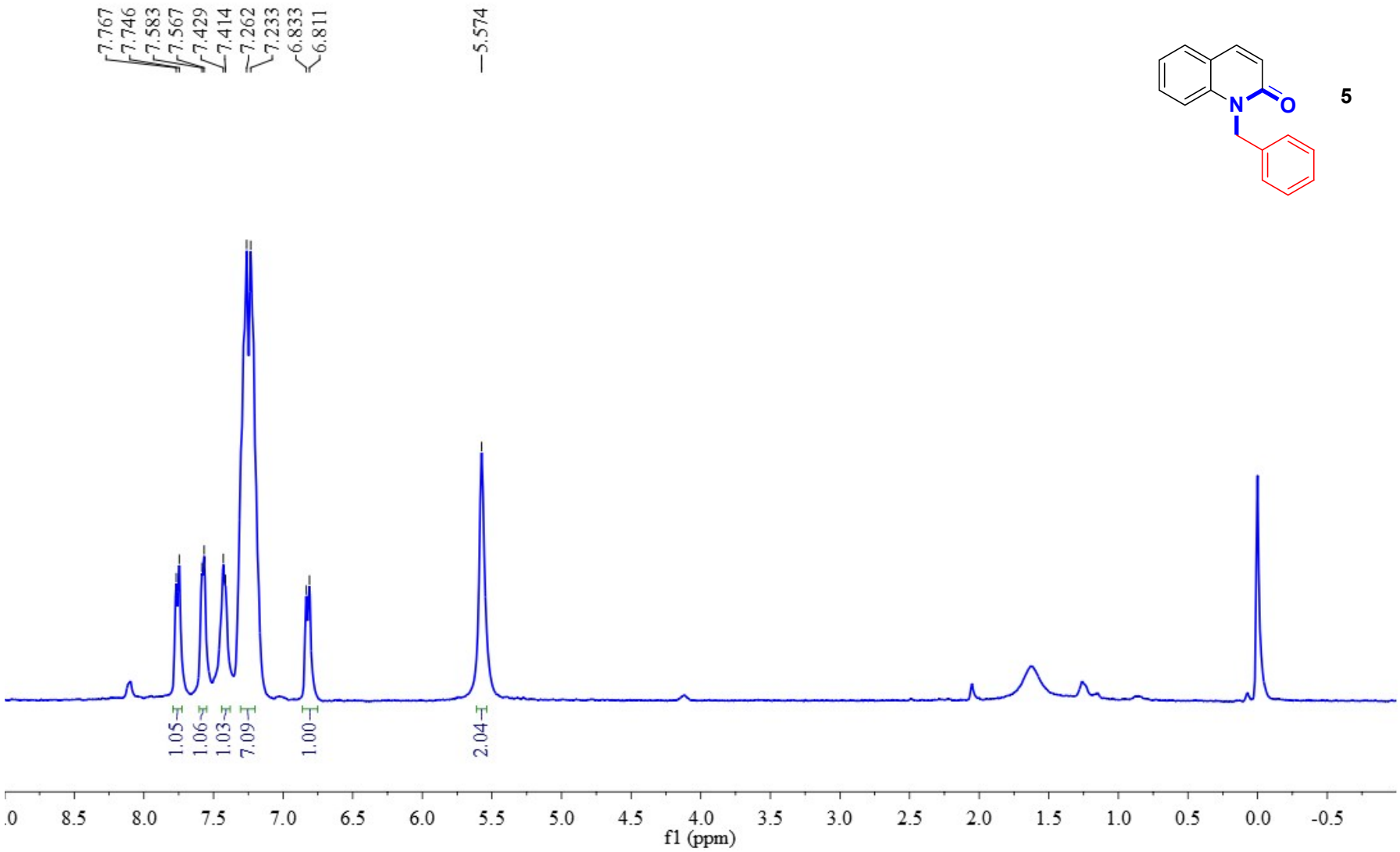

175.011
162.255
159.039
157.327
136.066
133.535
130.649
130.025
129.425
128.635
128.021
127.393
124.636
44.221
35.710
30.959
O
O
N
O
4c
f1 (ppm)


8.234
8.214
7.996
7.995
7.692
7.689
7.672
7.669
7.512
7.492
7.331
7.327
7.310
7.306
7.295
7.291
7.285
7.281
7.277
5.227
2.522
Cl
O
O
N
O
4d
1.00
1.02
1.01
2.02
3.54
2.02
3.03
f1 (ppm)


173.904
161.530
156.624
141.826
136.315
135.758
131.900
131.672
129.618
128.803
128.310
128.169
127.671
44.581
Cl
O
O
N
O
4d
f1 (ppm)

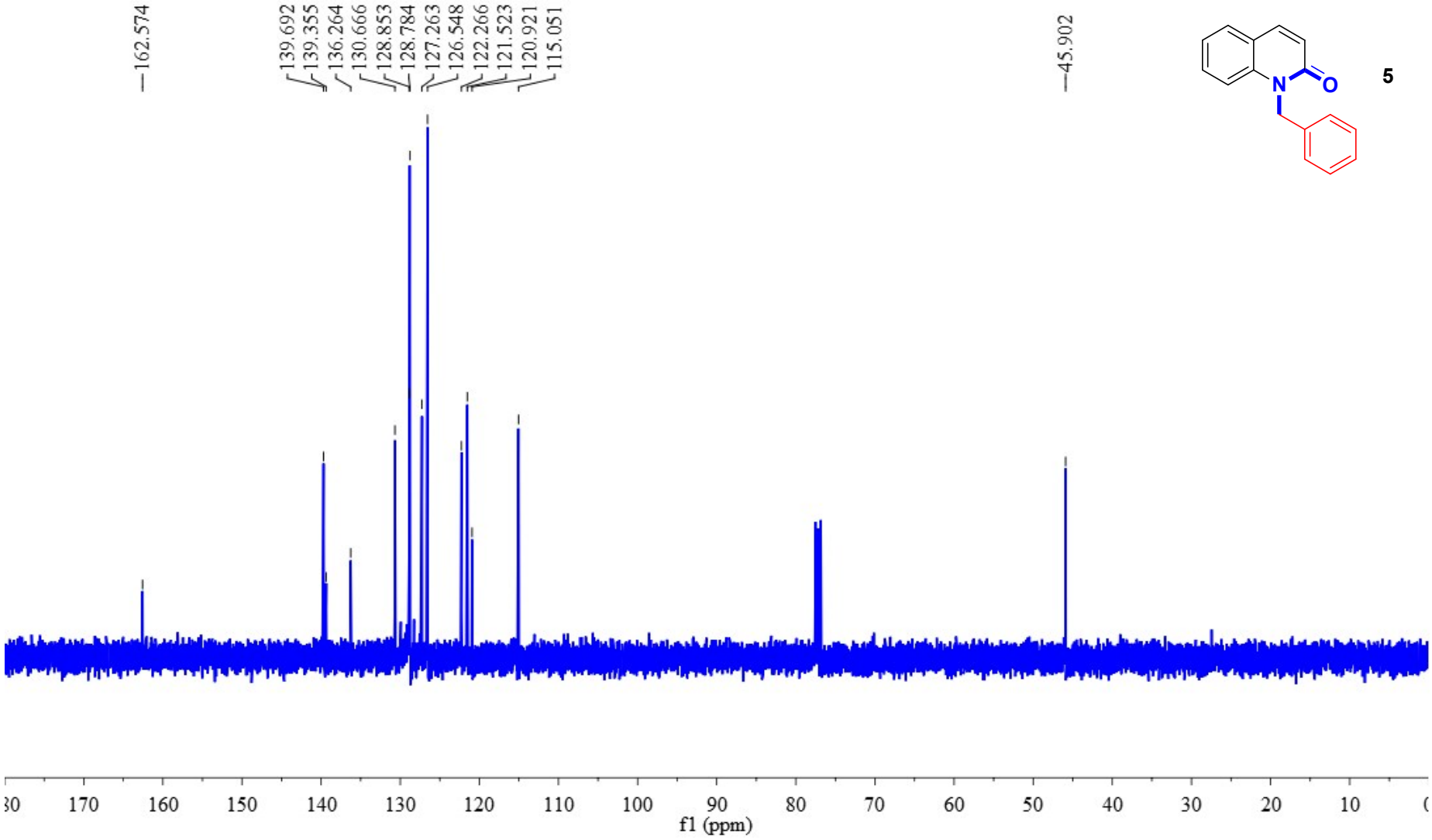

8.319
8.314
8.217
8.196
8.022
8.017
8.001
7.996
7.499
7.483
7.337
7.331
7.315
7.296
7.290
7.286
7.273
5.227
Br
O
O
N
O
4e
1.00
1.02
1.01
2.03
3.03
2.00
f1 (ppm)

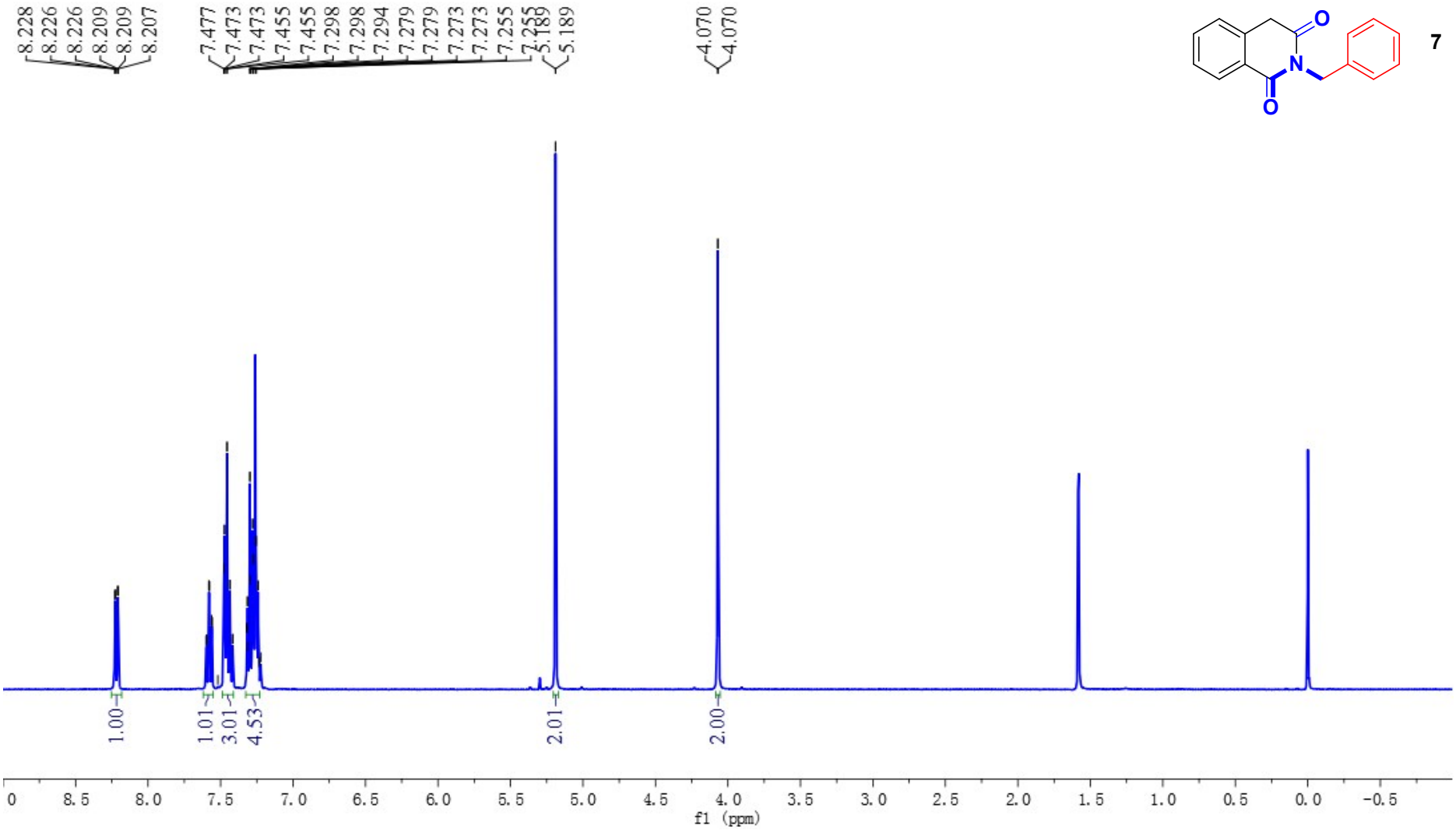

173.779
161.666
156.513
139.220
135.710
131.789
131.558
130.654
130.122
129.587
128.749
128.538
128.257
44.541
Br
O
O
N
O
4e
f1 (ppm)

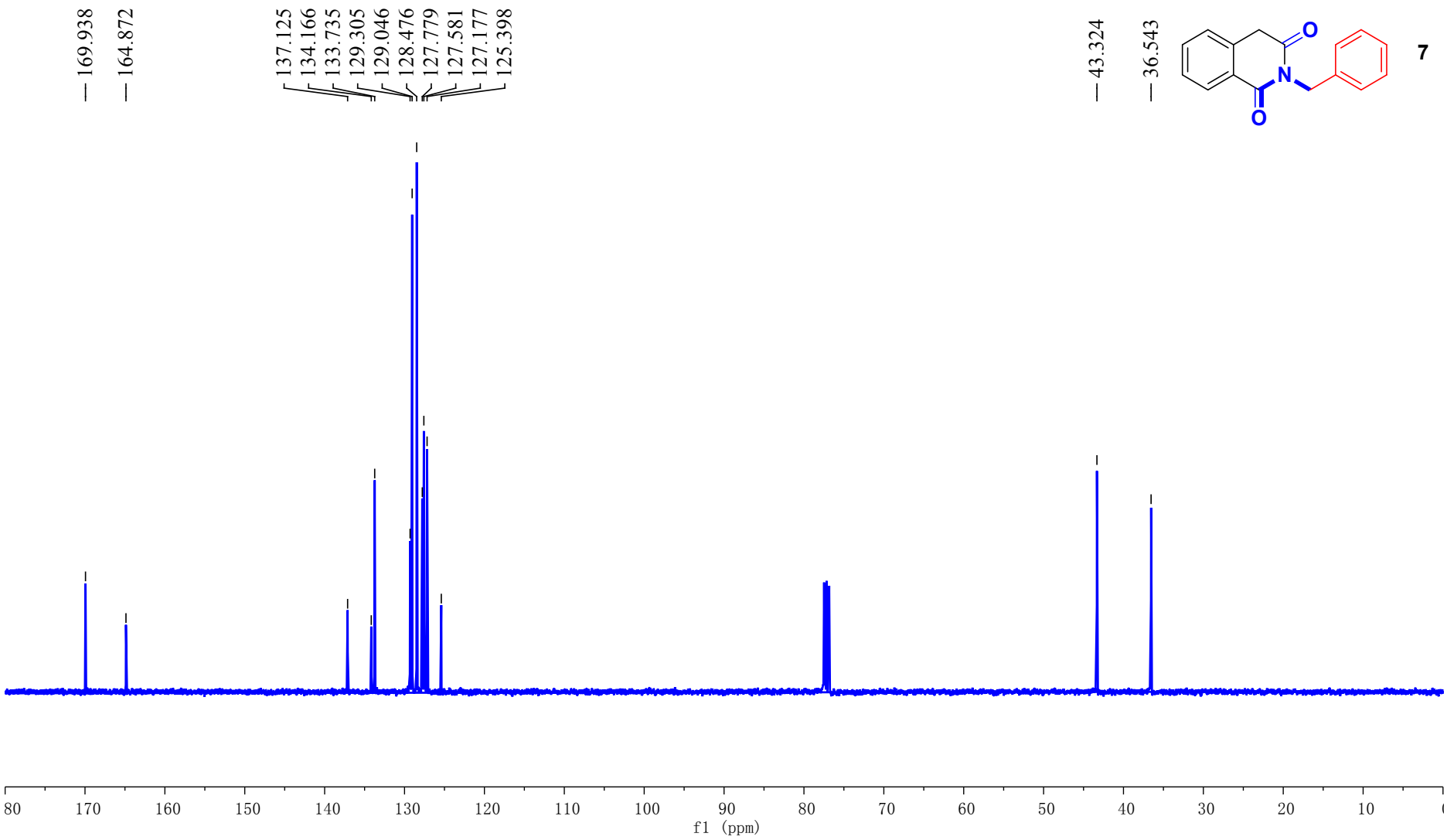

7.767
7.746
7.583
7.567
7.429
7.414
7.262
7.233
6.833
6.811
5.574
1.05
1.06
1.03
7.09
1.00
2.04
f1 (ppm)

N
O

5


162.574
139.692
139.355
136.264
130.666
128.853
128.784
127.263
126.548
122.266
121.523
120.921
115.051
45.902
N
O
5
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


8.228
8.226
8.226
8.209
8.209
8.207
7.477
7.473
7.473
7.455
7.455
7.298
7.298
7.294
7.279
7.279
7.273
7.273
7.255
7.255
5.189
5.189
4.070
4.070
O
N
O
7
1.00
1.01
3.01
4.53
2.01
2.00
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)


169.938
164.872
137.125
134.166
133.735
129.305
129.046
128.476
127.779
127.581
127.177
125.398
43.324
36.543
O
N
O
7
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)