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Supporting Information

Metal-free site-selective C-H Cyanoalkylation of 8-Aminoquinoline and Aniline-derived Amides with Azobisisobutyronitrile

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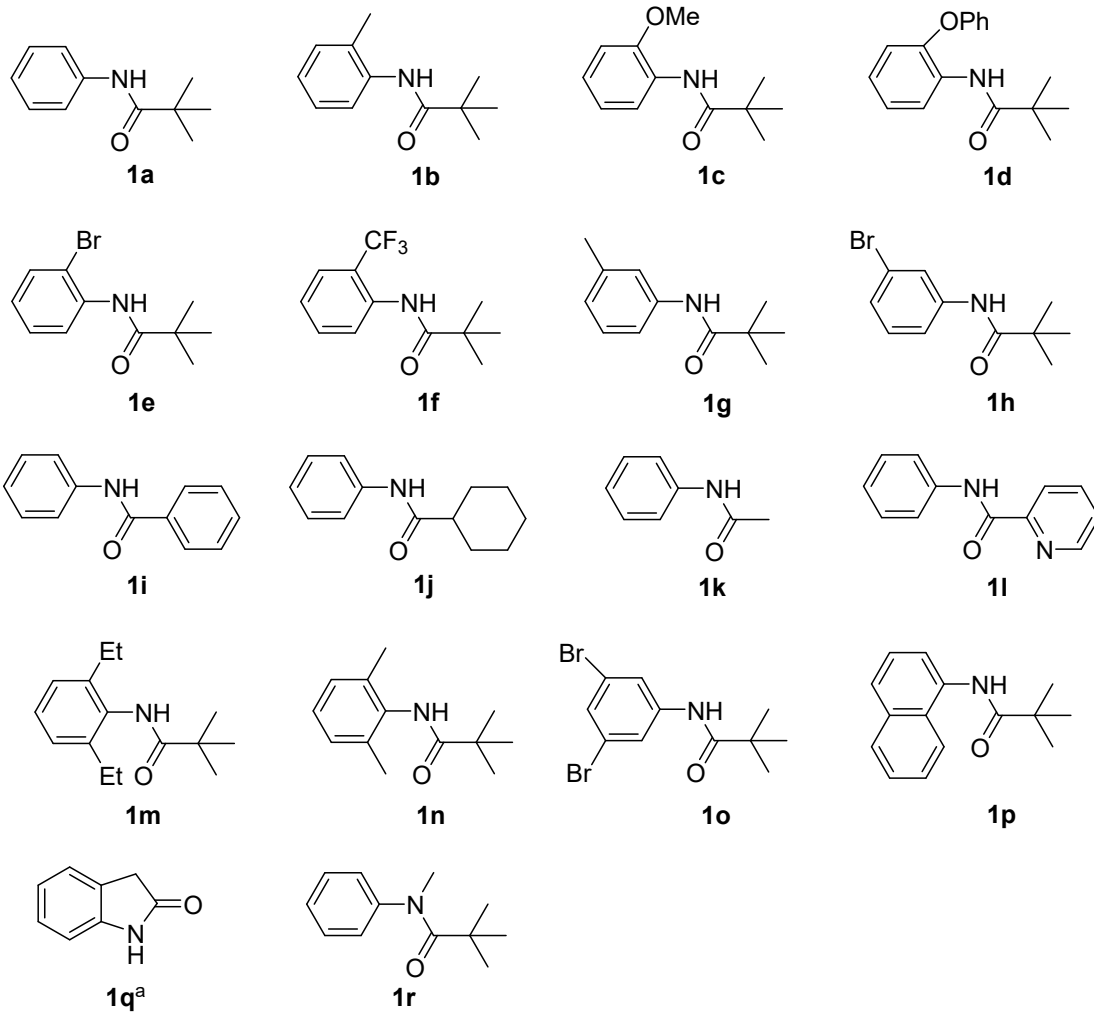
Contents

1. General information[1]

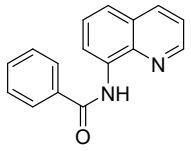
All reagents, starting materials, and solvents were purchased from commercial sources and used without treatment unless otherwise indicated. All the solvents were dried and newly distilled. NMR spectra were obtained on a Bruker AMX 400 system using chloroform-d as deuterated solvents. The ^{1}H-NMR spectra were recorded at 400 MHz in $CDCl_3$, and the ^{13}C-NMR spectra were recorded at 100 MHz in $CDCl_3$. All shifts were given in ppm. All coupling constants (*J* values) were reported in Hertz (Hz). High-Resolution Liquid Chromatography-Mass Spectrometry was recorded on the Bruker MicrOTOF QII. Column chromatography was performed on silica gel 100-200 mesh or 200-300 mesh. Ethyl acetate and petroleum ether were used for column chromatography.

2. Preparation of starting materials[1]

Preparation of starting materials: Aromatic amine (5.0 mmol, 1.0 equiv) was dissolved in 10 mL of dichloromethane and cooled to 0 ℃ using an ice bath. NEt_3 (6.0 mmol, 1.2 equiv) was added to the aniline solution followed by the corresponding acid chloride (6.0 mmol, 1.2 equiv) dropwise. The mixture was stirred for 10 h at room temperature. Then, the mixture was washed with sat. $NaHCO_3$ (50 mL), and was extracted with dichloromethane for three times (3 x 40 mL). The organic layer was dried over Na_2SO_4. After filtration and evaporation, the amides were purified by column chromatography through silica gel.



[a] indolin-2-one **1q** was purchased from *Energy Chemical.*



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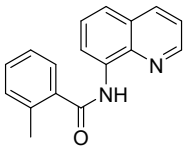

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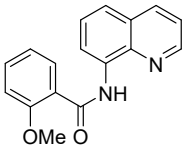

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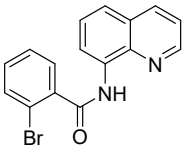

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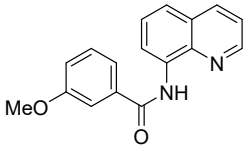

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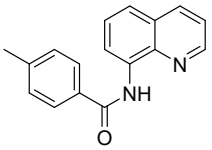

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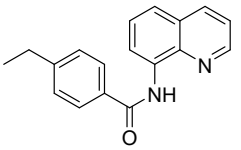

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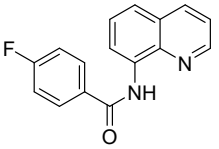

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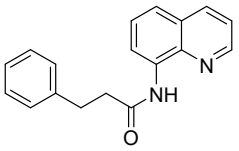

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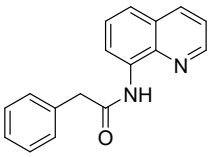

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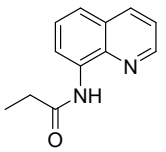

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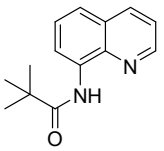

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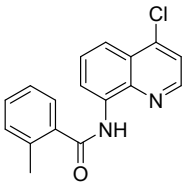
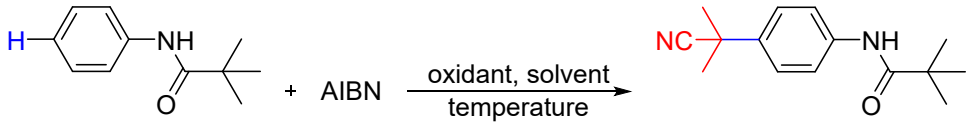


3m

3. Experimental section

3.1 Optimization of reaction conditions

Table S1 Optimization for selective cyanoalkylation reaction of aniline amides [a]

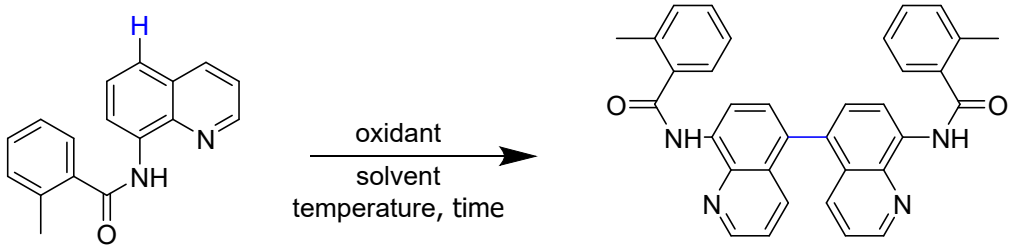


1a **2a**

Entry	Oxidant (eq)	Solvent [b]	Temp(℃)	Yield [c] (%)
1	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	120	87
2	$(NH_4)_2S_2O_8$(2.0)	CH_3CN/H_2O	120	81
3	$PhI(OAc)_2$(2.0)	CH_3CN/H_2O	120	26
4	TBHP(2.0)	CH_3CN/H_2	120	Trace
5	$K_2S_2O_8$(2.0)	CH_3CN	120	Trace
6	$K_2S_2O_8$(2.0)	H_2O	120	13
7	$K_2S_2O_8$(2.0)	DMF	120	Trace
8	$K_2S_2O_8$(2.0)	CH_3CN/DMSO	120	9
9[d]	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	120	15
10[e]	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	120	46
11	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	90	43
12	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	100	55
13	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	110	79
14	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	130	85
15	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	140	32
16	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	150	11
17	$K_2S_2O_8$(1.7)	CH_3CN/H_2O	120	87
18	$K_2S_2O_8$(1.5)	CH_3CN/H_2O	120	84
19	$K_2S_2O_8$(2.5)	CH_3CN/ H_2O	120	69
20[f]	**$K_2S_2O_8$(1.7)**	**CH_3CN/H_2O**	**120**	**89**
21[g]	$K_2S_2O_8$(1.7)	CH_3CN/H_2O	120	86
22[h]	$K_2S_2O_8$(1.7)	CH_3CN/H_2O	120	74
23[i]	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	120	78
24[j]	$K_2S_2O_8$(2.0)	CH_3CN/H_2O	120	75

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), AIBN (0.3 mmol, 1.5 equiv), oxidant (0.4 mmol, 2.0 equiv), solvent (2.0 mL), in sealed tube for 1 h. [b] solvents mentioned are mixed at a ratio of 1:1 unless otherwise specified. [c] Isolated yield. [d] CH_3CN/H_20=0.5/1.5. [e] CH_3CN/H_20=1.5/0.5. [f] AIBN (1.3 equiv). [g] AIBN (1.2 equiv). [h] AIBN (2.0 equiv). [i] AcOH (3.0 equiv). [j] Na_2CO_3 (3.0 equiv).

Table S2 Optimization for dimerization reaction of quinoline amides [a]

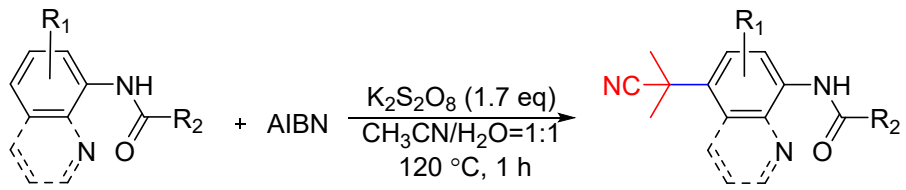


3b **9b**

Entry	Oxidant (eq)	Solvent	Temp (℃)	Time (h)	Yield [b] (%)
1[c]	$K_2S_2O_8$(1.7)	MeCN/H_2O(1/1)	100	12	6
2	$K_2S_2O_8$(1.7)	MeCN/H_2O(1/1)	100	12	6
3	$(NH_4)_2S_2O_8$(1.7)	MeCN/H_2O(1/1)	100	12	trace
4	TBHP(1.7)	MeCN/H_2O(1/1)	100	12	n.r
5	$PhI(OAc)_2$(1.7)	MeCN/H_2O(1/1)	100	12	trace
6	$K_2S_2O_8$(1.7)	MeCN/H_2O(1/1)	100	4	8
7	$K_2S_2O_8$(1.7)	MeCN/H_2O(1.5/0.5)	100	4	27
8	$K_2S_2O_8$(1.7)	MeCN/H_2O(0.5/1.5)	100	4	<5
9	$K_2S_2O_8$(1.7)	MeCN/DMSO(1/1)	100	4	11
10	$K_2S_2O_8$(1.7)	DMSO	100	4	39
11	$K_2S_2O_8$(1.7)	DCE	100	4	n.r
12	$K_2S_2O_8$(1.7)	DMF	100	4	n.r
13	$K_2S_2O_8$(1.7)	DMSO /H_2O (1/1)	100	4	15
14	$K_2S_2O_8$(1.7)	DMSO	120	4	28
15	$K_2S_2O_8$(1.7)	DMSO	80	4	22
16	$K_2S_2O_8$(1.2)	DMSO	100	4	24
17	**$K_2S_2O_8$(2.0)**	**DMSO**	**100**	**4**	**52**
18	$K_2S_2O_8$(3.0)	DMSO	100	4	49
19[d]	$K_2S_2O_8$(2.0)	DMSO	100	4	25
20[e]	$K_2S_2O_8$(2.0)	DMSO	100	4	12

[a] Reaction conditions: **3b** (0.2 mmol, 1.0 equiv), solvent (2.0 mL), in sealed tube. [b] Isolated yield. [c] CF_3SO_3Na (0.4 mmol, 2.0 equiv), [d] Na_2CO_3 (3.0 equiv). [e] PivOH (3.0 eq)

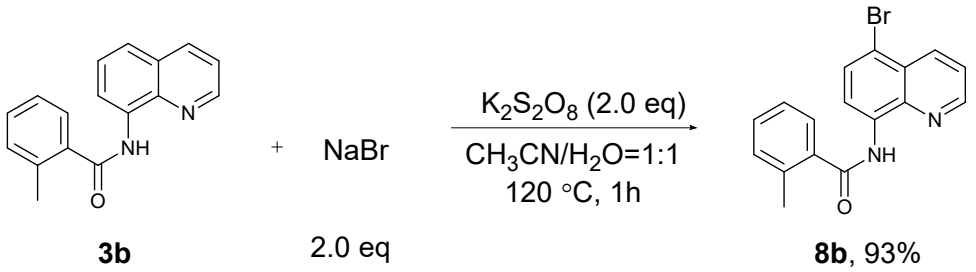
3.2 General procedure for cyanoalkylation of aniline and 8-aminoquinoline amides[2]



1 or **3** 1.3 eq **2** or **4**

1 or **3** (0.20 mmol, 1.0 equiv), AIBN (0.26 mmol, 1.3 equiv), $K_2S_2O_8$ (0.34 mmol, 1.7 equiv) were mixed in CH_3CN/H_2O=1:1 (2.0 mL) and stirred in a dried sealed tube under air atmosphere at 120 °C for 1 h. After completion of the reaction (TLC monitored), it was cooled to room temperature and washed with sat. NaCl (10 mL), and was extracted with ethyl acetate for three times (3 x 5 mL). The organic layer was then transferred to a round bottom flask after dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure and further purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate gradient), yielding the target products **2** or **4**.

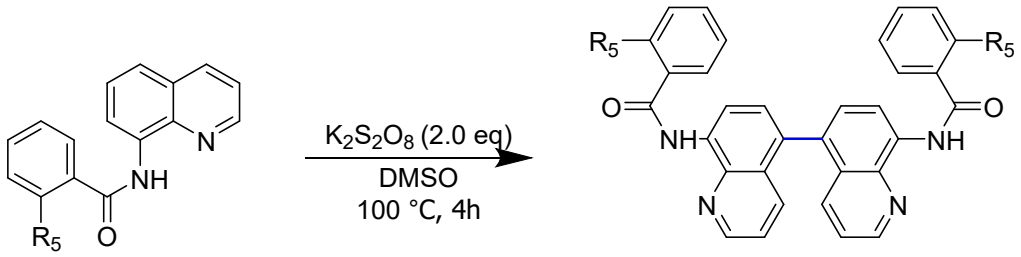
3.3 General procedure for bromination of 3b[3]



3b **8b**, 93%

3b (0.20 mmol, 1.0 equiv), NaBr (0.4 mmol, 2.0 equiv), $K_2S_2O_8$ (0.4 mmol, 2.0 equiv) were mixed in CH_3CN/H_2O=1:1 (2.0 mL) and stirred in a dried sealed tube under air atmosphere at 120 °C for 1 h. After completion of the reaction (TLC monitored), it was cooled to room temperature and washed with sat. NaCl (10 mL), and was extracted with ethyl acetate for three times (3 x 5 mL). The organic layer was then transferred to a round bottom flask after dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure and further purified by flash chromatography (SiO2, petroleum ether/ethyl acetate gradient), yielding the target products **8b**.

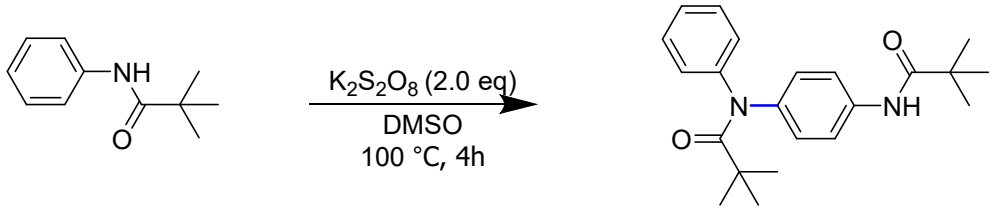
3.4 General procedure for dimerization of 3a and 3b[4]



3a; **3b** **9a**,48%; **9b**,52%

3a or **3b** (0.20 mmol, 1.0 equiv), $K_2S_2O_8$ (0.40 mmol, 2.0 equiv) were mixed in DMSO (2.0 mL) and stirred in a dried sealed tube under air atmosphere at 100 °C for 4 h. After completion of the reaction (TLC monitored), it was cooled to room temperature and washed with sat. NaCl (10 mL), and was extracted with dichloromethane for three times (3 x 5 mL). The organic layer was then transferred to a round bottom flask after dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure and further purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate gradient), yielding the target products **9**.

3.5 General procedure for para-C4-amidation of 1a[5]



1a **10**, 42%

1a (0.20 mmol, 1.0 equiv), $K_2S_2O_8$ (0.40 mmol, 2.0 equiv) were mixed in DMSO (2.0 mL) and stirred in a dried sealed tube under air atmosphere at 100 °C for 4 h. After completion of the reaction (TLC monitored), it was cooled to room temperature and washed with sat. NaCl (10 mL), and was extracted with dichloromethane for three times (3 x 5 mL). The organic layer was then transferred to a round bottom flask after dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure and further purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate gradient), yielding the target products **10**.

4. The single crystal X-ray diffraction studies of N-(5-(2-cyanopropan-2-yl) quinolin-8-yl)-2-methylbenzamide 4d

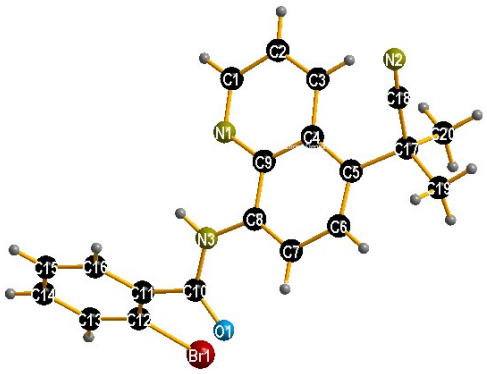


Table S3 Crystal data and structure refinement for **4d**

Bond precision: C-C = 0.0025 A Wavelength = 0.71073

Cell: a = 13.4703(3) b = 14.2884(3) c = 9.0192(2)

alpha = 90 beta = 97.198 (1) gamma = 90

Temperature: 180 K

	Calculated	Reported
Volume	1722.24(7)	1722.24(7)
Space group	P 21/c	P 1 21/c 1

Hall group	-P 2ybc	-P 2ybc
Moiety formula	$C_{20}H_{16}BrN_3O$	$C_{20}H_{16}BrN_3O$
Sum formula	$C_{20}H_{16}BrN_3O$	$C_{20}H_{16}BrN_3O$
Mr	394.26	394.27
Dx ($g \cdot cm^{-3}$)	1.520	1.521
Z	4	4
Mu (mm^{-1})	2.399	2.400
F000	800.0	800.0
F000'	799.12	
h, k, lmax	16,17,10	16,17,10
Nref	3050	3013
Tmin, Tmax	0.787, 0.825	0.616, 0.745
Tmin'	0.787	

Correction method = # Reported T Limits: Tmin = 0.616, Tmax = 0.745,

AbsCorr = MULTI-SCAN

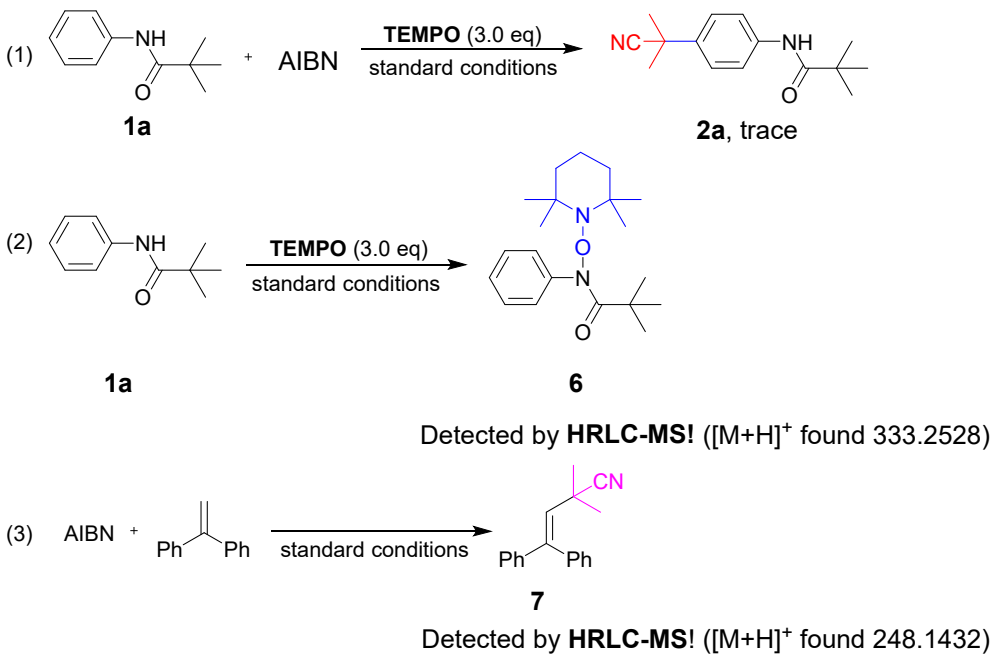
Data completeness = 0.988 Theta(max) = 25.040

R(reflections) = 0.0221 (2770) wR2(reflections)= 0.0574 (3013)

S = 1.046 Npar = 228

5. Mechanism investigation

To gain insight into the reaction mechanism, some control experiments were carried out (Scheme S1). Only a trace of the desired products **2a** was obtained in the presence of radical scavenger TEMPO (1). In addition, the TEMPO adduct **6** was detected by HRLC-MS, which implied the involvement of free radical in the reaction pathway (2). Furthermore, we tried to capture cyanopropyl radical by using 3.0 equiv. of 1, 1-diphenylethylene, and radical coupling product **7** was detected via HRLC-MS. (3).



Scheme S1 Investigation of the radical pathway

Several aniline substrates were undertaken under the standard conditions (Figure S1). The aniline substrates **1m-1o** with C2-H and C3-H substituted on the same side are not effective for the reaction, suggesting that a smooth hydrogen atom transfer path from C4 to N is important to the reaction. Besides, the naphthylamide substrate **1p** and indolin-2-one **1q** were also inactive in the reaction. Sulfonamide derivative **3n** failed to get the expected product, which probably due to the acid intolerance of the sulfonyl group, but C5-H was replaced by cyanoalkyl group Unexpectedly, N-methylpivalanilide **1r** obtained the *para*-C-functionalized product **2a** in a moderate 45% yield. This may be because the N-C bond is fragile (with bond energy 305 kJ/mol *vs.* 389 kJ/mol of N-H bond), which makes the methyl group easy to leave in the presence of the strong oxidant $K_2S_2O_8$.

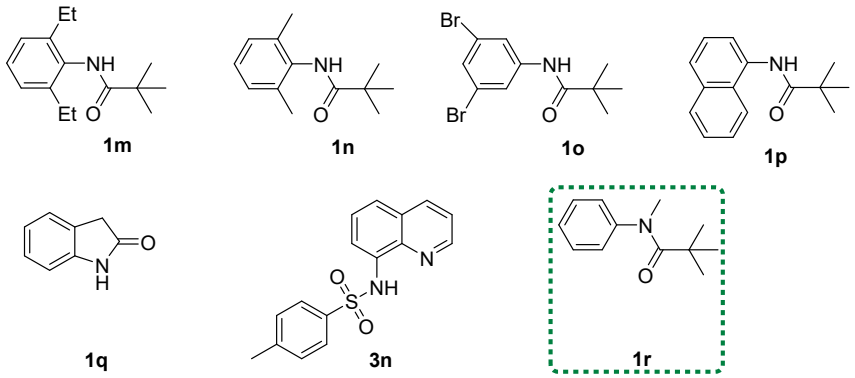
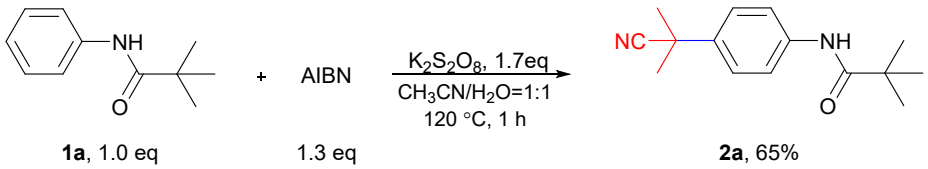


Figure S1 Screening substrates

6. Exploration of further application

6.1 Scaled-up experiment [a]

The scaled-up experiment was carried out by using **1a** as substrate, and 65% yield could be obtained, which indicated its potential applications.



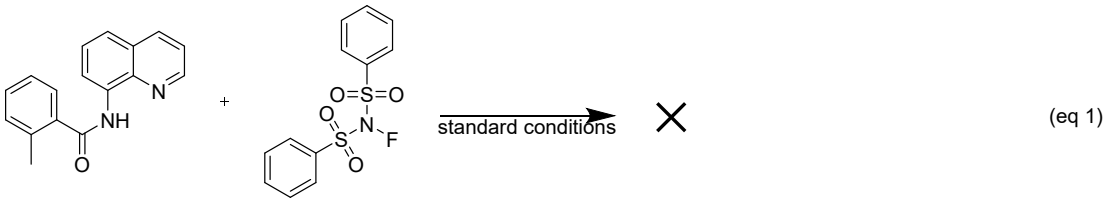
1a, 1.0 eq 1.3 eq **2a**, 65%

Scheme S2 Gram-scaled experiment

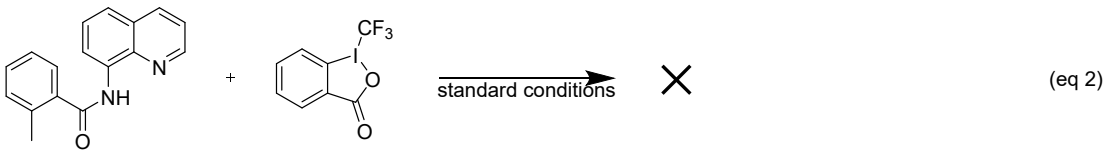
[a] Reaction conditions: **1a** (0.71 g, 4.0 mmol), AIBN (0.85 g, 5.2 mmol), $K_2S_2O_8$ (1.84g, 6.8 mmol), H_2O (5.0 mL), MeCN (5.0 mL), 120 ℃, in sealed tube for 1 h.

6.2 Exploration of compatibility with other free radicals [a]

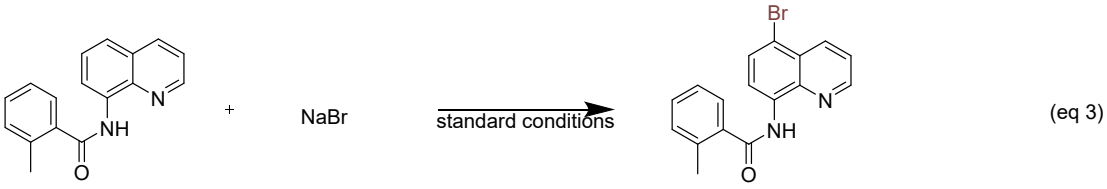
The synthetic utility of this direct C-H activation procedure was implemented with **3b** as the substrate. Delightly, the para-bromo-substituted product **8b** was obtained with 93% yield readily when an inexpensive inorganic salts NaBr as bromine source reagent (Scheme S3, eq 3). Interestingly, a dimerization product **9b** was found when the experiment was carried out without any radical reagents (eq 5, proved by NMR and HRLC-MS (SI)).



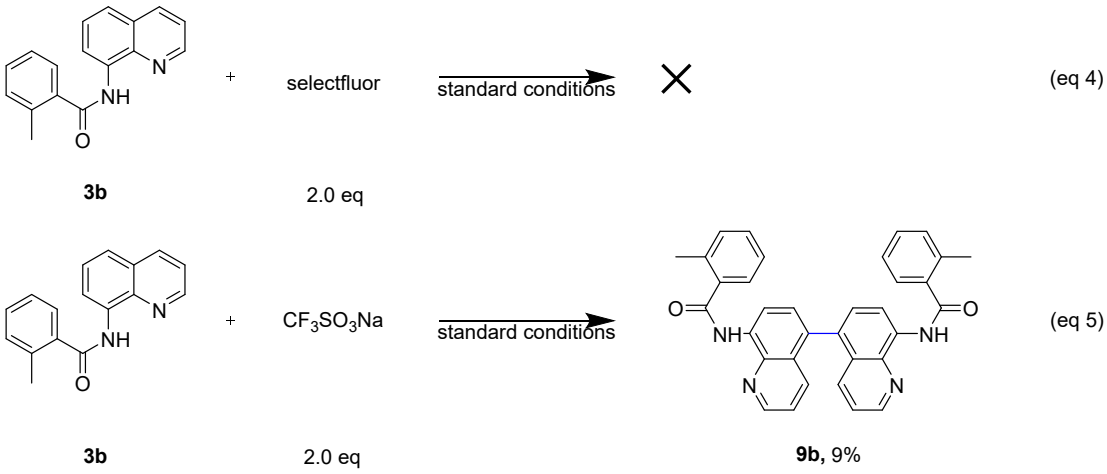
3b NFSI, 2.0 eq



3b 2.0 eq



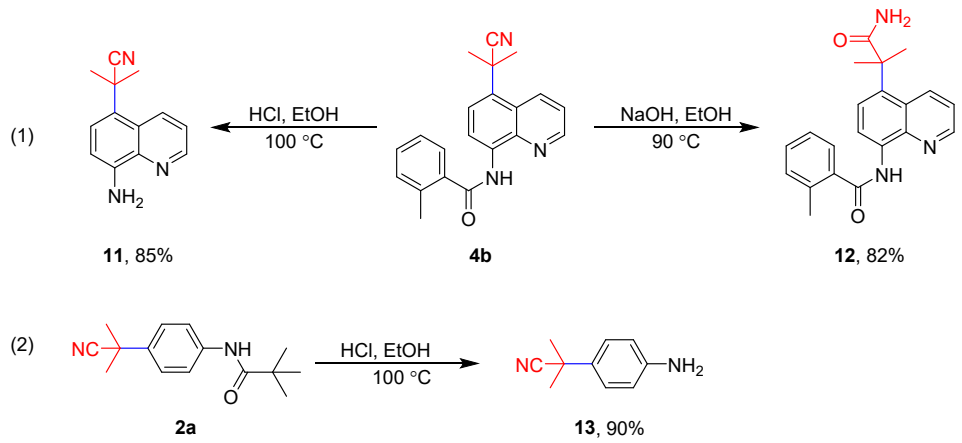
3b 2.0 eq **8b**, 93%



[a] standard conditions: **3b** (0.2 mmol), $K_2S_2O_8$ (0.34 mmol), CH_3CN (1 mL), H_2O (1 mL), 120 ℃, 1 h.

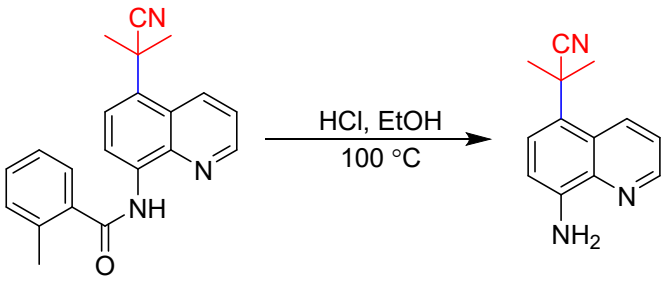
Scheme S3 Exploration of compatibility with other free radicals

6.3 Synthetic transformations of 4b and 2a[1c]



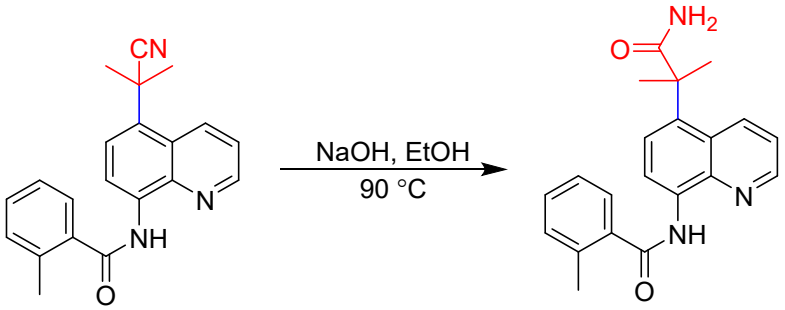
Scheme S4 Functional groups transformation.

To demonstrate the potential application, the transformations of the products were also investigated (Scheme S4). Upon treatment of **4b** with HCl or NaOH in EtOH for 12 h, the corresponding amide derivatives **11** and **12** were obtained in 85% yield and 82% yield, respectively. In addition, the acyl group is easily removed from **2a** by simple acid hydrolysis, giving the corresponding product **13** in 90% yield.



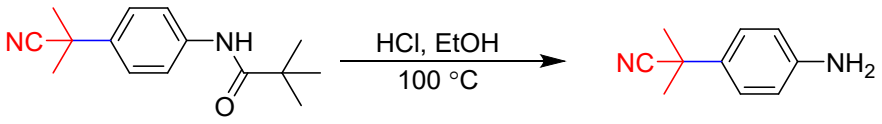
4b **11**, 85%

To a solution of **4b** (0.2 mmol, 1.0 equiv) in 4.0 mL of EtOH, concentrated HCl (2.0 mL) was added. The mixture was stirred at 100 °C for 12 h. Upon completion of room temperature and evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (petroleum ether/EtOAc=5:1) to afford pure **11** as a pale yellow solid in 85% yield.



4b **12**, 82%

To a solution of **4b** (0.2 mmol, 1.0 equiv) in 2.0 mL of EtOH, NaOH (0.8 mmol, 4.0 equiv) was added. The mixture was stirred at 90 °C for 12 h. Upon completion of room temperature and evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (petroleum ether/EtOAc=2:1) to afford pure **12** as a white solid in 82% yield.

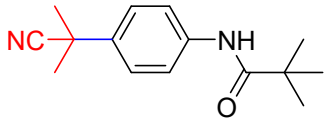


2a **13**, 90%

To a solution of **2a** (0.20 mmol, 1.0 equiv) in 2.0 mL of EtOH, HCl (0.8 mmol, 4.0 equiv) was added. The mixture was stirred at 100 °C for 12 h. Upon completion of room temperature and evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (petroleum ether/EtOAc=2:1) to afford pure **13** in 90% yield.

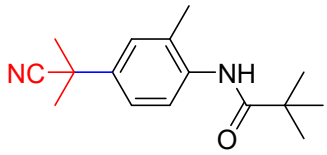
7. Characterization data of products

2a:



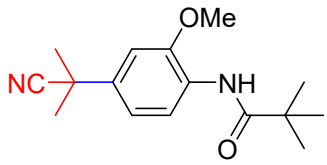
White solid, isolated yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.35 (s, 1H), 1.71 (s, 6H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.74 (s), 137.63 (s), 137.05 (s), 125.68 (s), 124.56 (s), 120.32 (s), 39.65 (s), 36.73 (s), 29.16 (s), 27.60 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{15}H_{21}N_2O$: 245.1648, found: 245.1645.

2b:



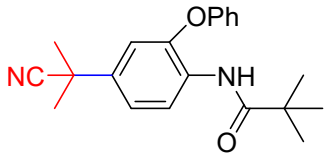
White solid, isolated yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 2.2 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.24 (s, 1H), 2.28 (s, 3H), 1.70 (s, 6H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.63 (s), 137.68 (s), 135.40 (s), 129.81 (s), 127.15 (s), 124.53 (s), 123.50 (s), 123.06 (s), 39.58 (s), 36.61 (s), 29.04 (s), 27.55 (s), 17.75 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{23}N_2O$: 259.1805, found: 259.1814.

2c:



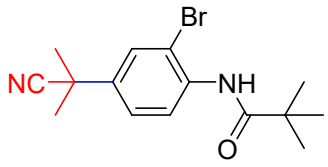
White solid, isolated yield: 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.4 Hz, 1H), 8.09 (s, 1H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.5, 2.1 Hz, 1H), 3.94 (s, 3H), 1.71 (s, 6H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.60 (s), 148.12 (s), 136.55 (s), 127.37 (s), 124.59 (s), 119.61 (s), 117.13 (s), 107.18 (s), 55.98 (s), 39.99 (s), 37.02 (s), 29.17 (s), 27.58 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{23}N_2O_2$: 275.1754, found: 275.1742.

2d:



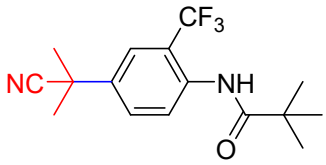
White solid, isolated yield: 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.6 Hz, 1H), 7.92 (s, 1H), 7.40 – 7.33 (m, 2H), 7.24 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 2.2 Hz, 1H), 6.97 (dd, *J* = 8.6, 0.9 Hz, 2H), 1.66 (s, 6H), 1.19 (s, 9H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.58 (s), 156.39 (s), 145.18 (s), 137.37 (s), 130.14 (s), 129.90 (s), 124.15 (s), 123.87 (s), 121.47 (s), 121.15 (s), 117.32 (s), 116.00 (s), 39.85 (s), 36.66 (s), 29.01 (s), 27.37 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{21}H_{25}N_2O_2$: 337.1911, found: 337.1909.

2e:



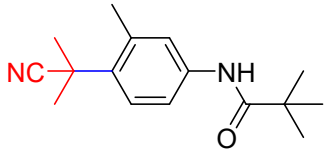
White solid, isolated yield: 54%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.7 Hz, 1H), 8.01 (s, 1H), 7.65 (d, *J* = 2.3 Hz, 1H), 7.39 (dd, *J* = 8.7, 2.3 Hz, 1H), 1.70 (s, 6H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.69 (s), 138.13 (s), 135.46 (s), 128.91 (s), 125.05 (s), 123.88 (s), 121.89 (s), 121.43 (s), 39.28 (s), 28.97 (s), 27.49 (s), 23.27 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{15}H_{20}BrN_2O$: 323.0754, 325.0733, found: 323.0761, 325.0739.

2f:



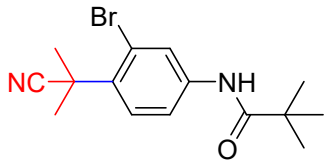
White solid, isolated yield: 37%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.6 Hz, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 1.73 (s, 6H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.74 (s), 137.48 (s), 135.37 (s), 129.62 (s), 127.94, 125.22, 122.51, 119.79 (q, *J* = 274 Hz, 1 H), 124.81, 123.70 (q apparent d, *J* = 37.4 Hz, 1H), 122.75 (q, *J* = 5.4 Hz), 121.41 (s), 119.07 (s), 28.96 (s), 27.28 (s), 25.12 (s), 23.36 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{20}F_3N_2O$: 313.1522, found: 313.1543.

2g:



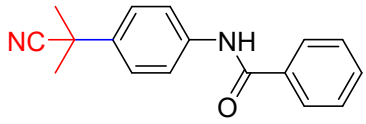
White solid, isolated yield: 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.32 (s, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 2.61 (s, 3H), 1.76 (s, 6H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.88 (s), 137.71 (s), 137.12 (s), 133.66 (s), 125.41 (s), 124.59 (s), 123.78 (s), 117.75 (s), 39.65 (s), 34.57 (s), 28.26 (s), 27.58 (s), 21.13 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{23}N_2O$: 259.1805, found: 259.1814.

2h:



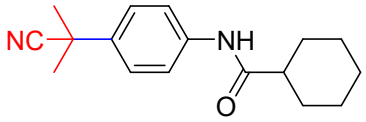
White solid, isolated yield: 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 2.2 Hz, 1H), 7.55 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.44 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 1.86 (s, 6H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.93 (s), 138.86 (s), 133.49 (s), 127.36 (s), 126.37 (s), 123.50 (s), 122.53 (s), 118.97 (s), 39.76 (s), 36.93 (s), 27.60 (s), 27.52 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{15}H_{20}BrN_2O$: 323.0754，325.0733, found: 323.0761, 325.0743.

2i:



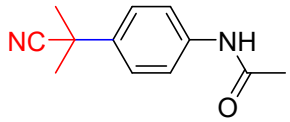
White solid, isolated yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.12 – 8.04 (m, 2H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.60 – 7.51 (m, 3H), 7.47 – 7.42 (m, 1H), 7.40 – 7.30 (m, 2H), 1.76 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.10 (s), 132.28 (s), 129.83 (s), 129.17 (s), 128.88 (d, *J* = 17.2 Hz), 127.29 (t, *J* = 16.2 Hz), 125.82 (s), 124.95 (s), 120.62 (s), 29.17 (s), 27.29 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{17}N_2O$: 265.1335, found: 265.1331.

2j:



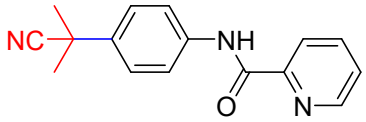
White solid, isolated yield: 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 2.23 (dd, *J* = 13.3, 10.0 Hz, 1H), 1.94 (d, *J* = 13.1 Hz, 2H), 1.83 (d, *J* = 9.5 Hz, 2H), 1.70 (s, 6H), 1.53 (d, *J* = 11.9 Hz, 2H), 1.38 – 1.22 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.54 (s), 129.82 (s), 129.02 (s), 125.70 (s), 124.82 (s), 120.07 (s), 29.63 (s), 29.57 (s), 29.15 (s), 27.32 (s), 25.71 (s), 25.65 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{23}N_2O$: 271.1805, found: 271.1803.

2k:



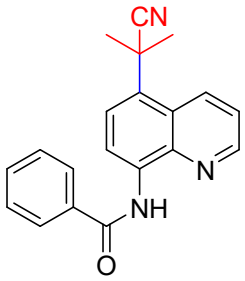
White solid, isolated yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 2.17 (s, 3H), 1.70 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.61 (s), 137.98 (s), 136.65 (s), 125.49 (s), 124.67 (s), 120.40 (s), 36.62 (s), 28.99 (s), 24.18 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{12}H_{15}N_2O$: 203.1179, found: 203.1193.

2l:



White solid, isolated yield: 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.62 (d, *J* = 4.6 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.91 (td, *J* = 7.6, 0.8 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.49 (m, 3H), 1.73 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.10 (s), 149.56 (s), 148.01 (s), 137.76 (s), 137.24 (d, *J* = 13.0 Hz), 126.62 (s), 125.87 (s), 124.56 (s), 122.46 (s), 120.02 (s), 36.79 (s), 29.19 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{16}N_3O$: 266.1288, found: 266.1295.

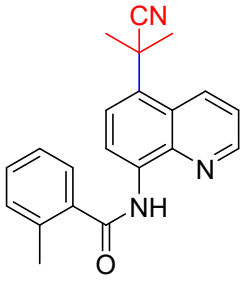
4a:



White solid, isolated yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.89 (s, 1H), 8.96 (dd, *J* = 8.8, 1.1 Hz, 1H), 8.94 – 8.87 (m, 2H), 8.09 (d, *J* = 6.7 Hz, 2H), 7.66 – 7.62 (m, 1H), 7.62 – 7.56 (m, 4H), 1.97 (s,

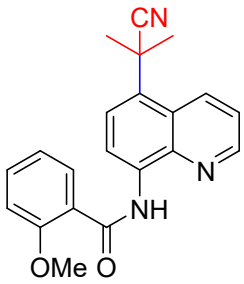
6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.53 (s), 147.92 (s), 139.57 (s), 135.26 (s), 134.90 (s), 133.24 (s), 132.03 (s), 129.74 (s), 128.86 (s), 127.32 (s), 125.32 (s), 124.84 (s), 124.22 (s), 121.59 (s), 115.37 (s), 33.93 (s), 28.89 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{20}H_{18}N_3O$: 316.1444, found: 316.1453.

4b:



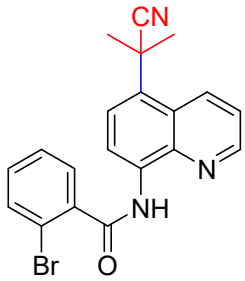
White solid, isolated yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.94 (d, *J* = 8.1 Hz, 1H), 8.89 (d, *J* = 8.3 Hz, 1H), 8.84 (d, *J* = 3.9 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.34 (m, 2H), 2.60 (s, 3H), 1.96 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.28 (s), 147.89 (s), 139.43 (s), 136.76 (s), 136.40 (s), 135.42 (s), 133.19 (s), 131.45 (s), 130.49 (s), 129.84 (s), 127.29 (s), 126.07 (s), 125.32 (s), 124.82 (s), 124.15 (s), 121.56 (s), 115.33 (s), 33.93 (s), 28.91 (s), 20.25 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{21}H_{20}N_3O$: 330.1601, found: 330.1600.

4c:



White solid, isolated yield: 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.46 (s, 1H), 8.98 (d, *J* = 8.3 Hz, 1H), 8.93 (d, *J* = 1.7 Hz, 1H), 8.92 (s, 1H), 8.34 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.57 – 7.50 (m, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 4.20 (s, 3H), 1.95 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.78 (s), 157.78 (s), 147.82 (s), 140.06 (s), 136.47 (s), 133.33 (s), 133.01 (s), 132.39 (s), 129.33 (s), 125.37 (s), 124.96 (s), 124.37 (s), 122.16 (s), 121.34 (s), 121.31 (s), 116.12 (s), 111.63 (s), 56.15 (s), 33.88 (s), 28.91 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{21}H_{20}N_3O_2$: 346.1550, found: 346.1561.

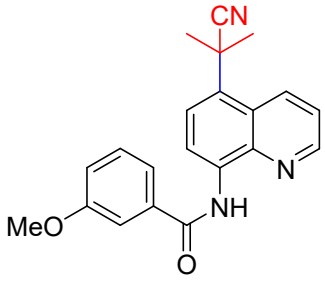
4d:



Brown solid, isolated yield: 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.94 (dd, *J* = 8.8, 1.4 Hz, 1H), 8.90 (d, *J* = 8.3 Hz, 1H), 8.84 (dd, *J* = 4.1, 1.4 Hz, 1H), 7.71 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.68 (dd, *J* = 8.0 , 0.8 Hz, 1H), 7.59-7.57 (m, 1H), 7.58(t, J=4.4 Hz, 1H), 7.44 (td, *J* = 7.5, 1.0 Hz, 1H), 7.35 (td, *J* = 7.8, 1.7 Hz, 1H), 1.95 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.05 (s), 148.01 (s), 139.37 (s), 138.07

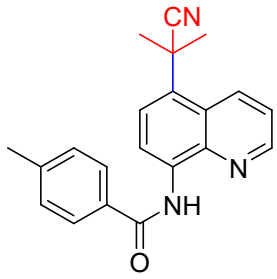
(s), 134.97 (s), 133.73 (s), 133.19 (s), 131.66 (s), 130.29 (s), 129.60 (s), 127.72 (s), 125.31 (s), 124.78 (s), 124.14 (s), 121.65 (s), 119.67 (s), 115.74 (s), 33.95 (s), 28.89 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{20}H_{17}BrN_3O$: 394.0550, 396.0529, found: 394.0564, 396.0545.

4e:



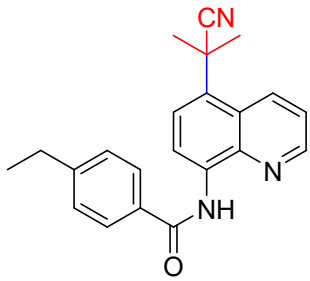
White solid, isolated yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.85 (s, 1H), 8.93 (d, J = 8.8 Hz, 1H), 8.89 (d, J = 3.9 Hz, 1H), 8.87 (d, J = 8.4 Hz, 1H), 7.61 (dd, J = 12.7, 5.3 Hz, 3H), 7.56 (d, J = 8.3 Hz, 1H), 7.45 (t, J = 8.1 Hz, 1H), 7.15 – 7.09 (m, 1H), 3.90 (s, 3H), 1.95 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.36 (s), 160.01 (s), 147.96 (s), 139.52 (s), 136.33 (s), 135.18 (s), 133.21 (s), 129.81 (d, J = 8.7 Hz), 125.29 (s), 124.84 (s), 124.20 (s), 121.61 (s), 119.08 (s), 118.15 (s), 115.37 (s), 112.73 (s), 55.53 (s), 33.92 (s), 28.87 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{21}H_{20}N_3O_2$: 346.1550, found: 346.1566.

4f:



White solid, isolated yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.85 (s, 1H), 8.94 (dd, J = 8.7, 1.5 Hz, 1H), 8.91 (dd, J = 4.2, 1.4 Hz, 1H), 8.89 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.62 (dd, J = 8.7, 4.2 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 7.9 Hz, 2H), 2.46 (s, 3H), 1.96 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.88 (s), 142.59 (s), 139.58 (s), 135.36 (s), 133.22 (s), 132.09 (s), 129.54 (d, J = 2.6 Hz), 127.34 (s), 124.24 (s), 121.56 (s), 115.30 (s), 33.91 (s), 28.90 (s), 21.60 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{21}H_{19}N_3O$: 330.1601, found: 330.1593.

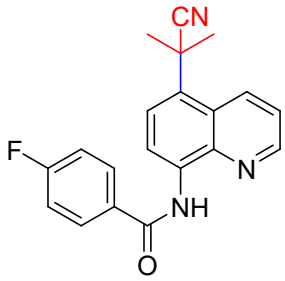
4g:



White solid, isolated yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.85 (s, 1H), 8.94 (d, J = 8.8 Hz, 1H), 8.91 (d, 1H), 8.89 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.61 (dd, J = 8.7, 4.1 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 2.75 (q, J = 7.6 Hz, 2H), 1.95 (s, 6H), 1.30 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.81 (s), 137.47 (s), 135.34 (s), 129.63 (s), 125.22 (s), 124.79 (s),

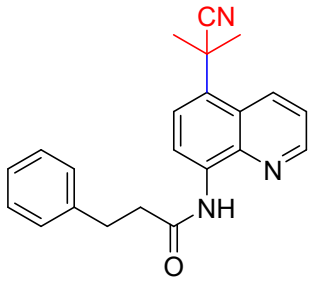
123.72 (s), 122.76 (d, J = 5.5 Hz), 121.43 (s), 119.10 (s), 28.98 (s), 27.29 (s), 25.14 (s), 23.39 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{22}H_{22}N_3O$: 344.1757, found: 344.1749.

4h：



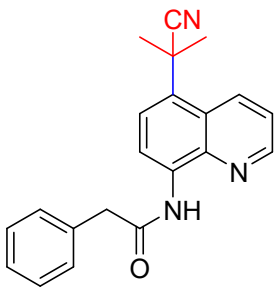
White solid, isolated yield: 43%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.83 (s, 1H), 8.96 (dd, J = 8.8, 1.4 Hz, 1H), 8.92 (dd, J = 4.1, 1.4 Hz, 1H), 8.86 (d, J = 8.3 Hz, 1H), 8.13 – 8.07 (m, 2H), 7.64 (dd, J = 8.7, 4.2 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.22 (dd, J = 6.7, 4.8 Hz, 2H), 1.96 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.47 (s), 147.95 (s), 139.53 (s), 135.10 (s), 133.31 (s), 132.86 (d, J = 9.7 Hz, 1H), 131.09 (d, J = 3.2 Hz, 1H), 129.90 (s), 129.73 (d, J = 9.0 Hz, 1H), 125.34 (s), 124.80 (s), 124.21 (s), 121.64 (s), 115.94 (d, J = 21.8 Hz, 1H), 115.83 – 115.74 (m), 115.62 (s), 115.41 (s), 33.94 (s), 28.89 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{20}H_{17}FN_3O$: 334.1350, found: 334.1375.

4i：



White solid, isolated yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.91 (d, J = 8.8 Hz, 1H), 8.85 – 8.81 (m, 1H), 8.74 (d, J = 8.3 Hz, 1H), 7.58 (dd, J = 8.7, 4.1 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 4.3 Hz, 4H), 7.21 (dd, J = 8.4, 4.2 Hz, 1H), 3.15 (t, J = 7.8 Hz, 2H), 2.90 (t, J = 7.8 Hz, 2H), 1.93 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.96 (s), 147.71 (s), 140.64 (s), 139.09 (s), 135.07 (s), 133.15 (s), 129.51 (s), 128.49 (d, J = 19.2 Hz), 126.30 (s), 125.21 (s), 124.15 (s), 121.48 (s), 115.31 (s), 39.74 (s), 33.87 (s), 31.42 (s), 28.87 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{22}H_{22}N_3O$: 344.1757, found: 344.1767.

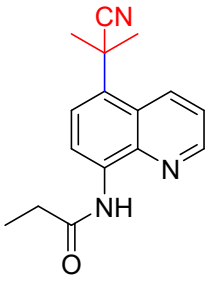
4j：



White solid, isolated yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.87 (d, J = 8.8 Hz, 1H), 8.74 (d, J = 4.1 Hz, 1H), 8.71 (d, J = 8.3 Hz, 1H), 7.54 (dd, J = 8.8, 4.1 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.46 – 7.38 (m, 4H), 7.37 – 7.31 (m, 1H), 3.90 (s, 2H), 1.91 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$)

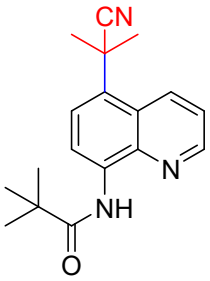
δ 169.68 (s), 147.76 (s), 139.22 (s), 135.04 (s), 134.52 (s), 133.07 (s), 129.65 (s), 129.54 (s), 129.02 (s), 127.41 (s), 125.15 (s), 124.80 (s), 124.06 (s), 121.42 (s), 115.14 (s), 45.38 (s), 33.86 (s), 28.85 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{21}H_{20}N_3O$: 330.1601, found: 330.1608.

4k：



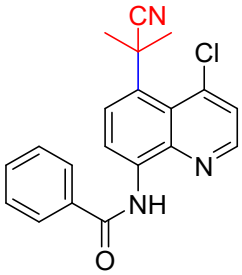
White solid, isolated yield: 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.91 (d, *J* = 8.7 Hz, 1H), 8.85 (d, *J* = 3.6 Hz, 1H), 8.73 (d, *J* = 8.3 Hz, 1H), 7.58 (dd, *J* = 8.7, 4.1 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 2.60 (q, *J* = 7.5 Hz, 2H), 1.93 (s, 6H), 1.33 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.64 (s), 147.70 (s), 139.14 (s), 135.22 (s), 133.16 (s), 129.32 (s), 125.22 (s), 124.85 (s), 124.18 (s), 121.45 (s), 115.17 (s), 77.37 (s), 77.06 (s), 76.74 (s), 33.86 (s), 31.26 (s), 28.87 (s), 9.69 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{18}N_3O$: 268.1444, found: 268.1452.

4l：



White solid, isolated yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.91 (d, *J* = 8.8 Hz, 1H), 8.87 (dd, *J* = 4.0, 1.0 Hz, 1H), 8.74 (d, *J* = 8.3 Hz, 1H), 7.59 (dd, *J* = 8.7, 4.2 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 1.93 (s, 6H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.44 (s), 147.83 (s), 135.37 (s), 133.14 (s), 129.26 (s), 125.24 (s), 124.87 (s), 124.17 (s), 121.42 (s), 115.02 (s), 40.41 (s), 33.86 (s), 28.89 (s), 27.71 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{18}H_{22}N_3O$: 296.1757, found: 296.1764.

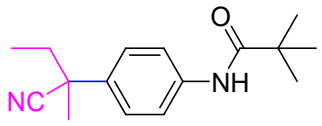
4m



White solid, isolated yield: 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.93 (d, *J* = 8.5 Hz, 1H), 8.71 (d, *J* = 4.6 Hz, 1H), 8.06 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.71 (d, *J* = 4.6 Hz, 1H), 7.62 – 7.56 (m, 3H), 2.06 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.37 (s), 148.83 (s), 144.68 (s), 139.35 (s), 131.86 (s), 131.36 (s), 130.51 (s), 129.70 (s), 128.82 (s), 127.26 (s), 123.58 (s), 123.40

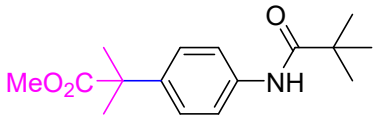
(s), 121.56 (s), 116.19 (s), 116.06 (s), 72.69 (s), 27.53 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{20}H_{16}ClN_3O_2$: 366.1004, found: 366.1003.

2aa



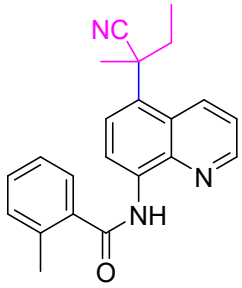
White solid, isolated yield: 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.6 Hz, 2H), 7.39 (s, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 1.99 – 1.86 (m, 2H), 1.68 (s, 3H), 1.31 (s, 9H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.87 (s), 137.66 (s), 135.56 (s), 126.05 (s), 123.50 (s), 120.39 (s), 42.77 (s), 39.63 (s), 35.19 (s), 27.57 (s), 27.27 (s), 9.82 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{23}N_2O$: 259.1805, found: 259.1810.

2ab



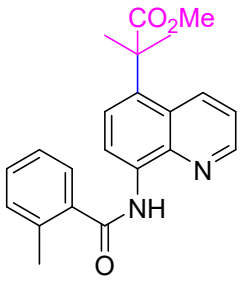
White solid, isolated yield: 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 3H), 3.63 (s, 3H), 1.56 (s, 6H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.22 (s), 176.59 (s), 140.42 (s), 136.63 (s), 126.22 (s), 119.96 (s), 52.21 (s), 46.04 (s), 39.57 (s), 27.62 (s), 26.49 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{24}NO_3$: 278.1751, found: 258.1759.

4ba



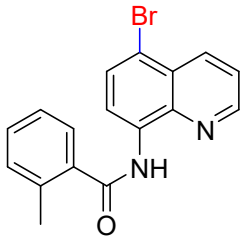
White solid, isolated yield: 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.92 (t, *J* = 8.9 Hz, 2H), 8.82 (d, *J* = 4.0 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 2.61 (s, 3H), 2.38 (dq, *J* = 14.5, 7.3 Hz, 1H), 2.10 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.94 (s, 3H), 1.10 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.27 (s), 147.85 (s), 139.44 (s), 136.76 (s), 136.40 (s), 135.30 (s), 133.11 (s), 131.45 (s), 130.49 (s), 128.91 (s), 127.29 (s), 126.07 (s), 125.31 (d, *J* = 18.0 Hz), 124.10 (s), 121.45 (s), 115.31 (s), 39.55 (s), 33.74 (s), 25.74 (s), 20.26 (s), 9.53 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{22}H_{22}N_3O$: 344.1757, found: 344.1760.

4bb



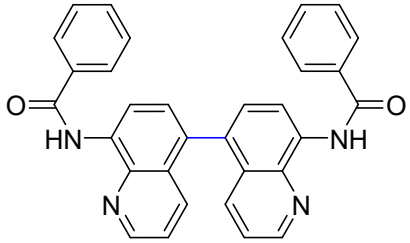
White solid, isolated yield: 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.90 (d, *J* = 8.2 Hz, 1H), 8.75 (d, *J* = 4.0 Hz, 1H), 8.22 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 3.59 (s, 3H), 2.60 (s, 3H), 1.76 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.99 (s), 168.16 (s), 147.42 (s), 139.34 (s), 136.68 (s), 136.66 (s), 134.97 (s), 134.14 (s), 132.75 (s), 131.37 (s), 130.33 (s), 127.26 (s), 126.12 (s), 126.03 (s), 124.01 (s), 121.31 (s), 115.79 (s), 52.51 (s), 45.85 (s), 27.55 (s), 20.22 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{22}H_{23}N_2O_3$: 363.1703, found: 363.1710.

8b



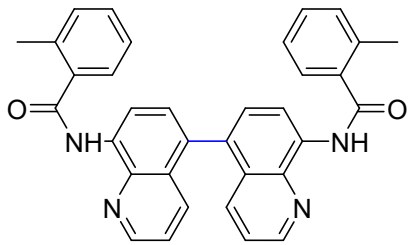
White solid, isolated yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.84 (d, *J* = 8.4 Hz, 1H), 8.79 (d, *J* = 3.9 Hz, 1H), 8.53 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 1H), 7.56 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 2.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.13 (s), 148.76 (s), 139.29 (s), 136.81 (s), 136.30 (s), 136.00 (s), 134.65 (s), 131.48 (s), 130.93 (s), 130.52 (s), 127.25 (s), 126.07 (s), 122.73 (s), 116.99 (s), 114.50 (s), 20.27 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{14}BrN_2O$: 341.0284,343.0264, found: 341.0274, 343.0248.

9a



White solid, isolated yield: 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.91 (s, 1H), 9.07 (d, *J* = 7.9 Hz, 1H), 8.89 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.15 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.85 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.67 – 7.57 (m, 4H), 7.37 (dd, *J* = 8.5, 4.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.60 (s), 148.34 (s), 138.71 (s), 135.00 (d, *J* = 18.4 Hz), 134.60 (s), 131.99 (s), 130.77 (s), 129.64 (s), 128.88 (s), 127.38 (s), 121.89 (s), 116.09 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{32}H_{23}N_4O_2$: 495.1816, found:495.1828.

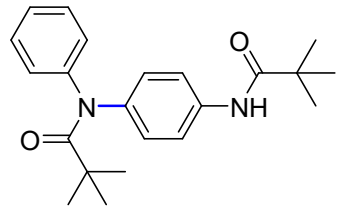
9b



White solid, isolated yield: 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 9.06 (d, *J* = 7.9 Hz, 1H), 8.80 (dd, *J* = 4.0, 1.3 Hz, 1H), 7.83 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.35 (dt, *J* = 8.7, 6.2 Hz, 3H), 2.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.33 (s), 148.33 (s), 138.54 (s), 136.79 (s), 136.55 (s), 134.79 (d, *J* = 9.4 Hz), 131.47 (s), 130.85 (s),

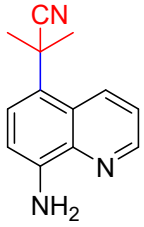
130.47 (s), 129.57 (s), 127.76 (s), 127.33 (s), 126.10 (s), 121.87 (s), 116.03 (s), 20.31 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{34}H_{27}N_4O_2$: 523.2129, found: 523.2117.

10



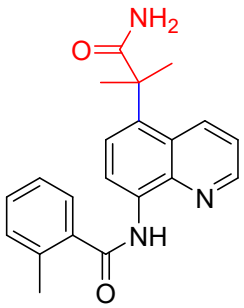
White solid, isolated yield: 42%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.7 Hz, 2H), 7.32 (t, J = 7.6 Hz, 3H), 7.23 – 7.17 (m, 5H), 1.30 (s, 9H), 1.14 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.53 (s), 176.65 (s), 144.54 (s), 140.18 (s), 136.82 (s), 129.02 (d, J = 10.6 Hz), 128.16 (s), 126.78 (s), 120.51 (s), 41.65 (s), 39.63 (s), 29.67 (s), 27.61 (d, J = 6.1 Hz). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{22}H_{29}N_2O_2$: 353.2224, found: 353.2226.

11



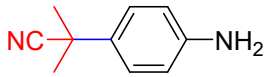
Pale yellow solid, isolated yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (dd, J = 10.2, 1.8 Hz, 2H), 7.51 (dd, J = 8.7, 4.2 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 5.20 (s, 2H), 1.90 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.58 (s), 145.52 (s), 139.28 (s), 136.57 (s), 130.20 (s), 127.24 (s), 125.97 (s), 122.84 (s), 121.14 (s), 113.11 (s), 73.33 (s), 25.70 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{13}H_{14}N_3O$: 228.1131, found: 228.1128.

12



White solid, isolated yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.84 (d, J = 8.6 Hz, 1H), 8.80 (dd, J = 4.1, 1.4 Hz, 1H), 8.53 (dd, J = 8.5, 1.4 Hz, 1H), 7.66 (d, J = 7.3 Hz, 1H), 7.49 (dd, J = 8.5, 4.2 Hz, 1H), 7.40 (t, J = 7.3 Hz, 1H), 7.32 (t, J = 7.2 Hz, 2H), 7.10 (d, J = 8.5 Hz, 1H), 6.70 (s, 1H), 5.56 (s, 1H), 2.60 (s, 3H), 1.64 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ: 180.48 (s), 168.27 (s), 147.85 (s), 139.50 (s), 136.70 (s), 136.46 (s), 134.81 (s), 134.70 (s), 134.04 (s), 131.43 (s), 130.45 (s), 127.27 (s), 126.24 (s), 126.06 (s), 124.70 (s), 121.51 (s), 115.56 (s), 46.45 (s), 27.88 (s), 20.24 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{21}H_{22}N_3O_2$: 348.1707, found: 348.1705.

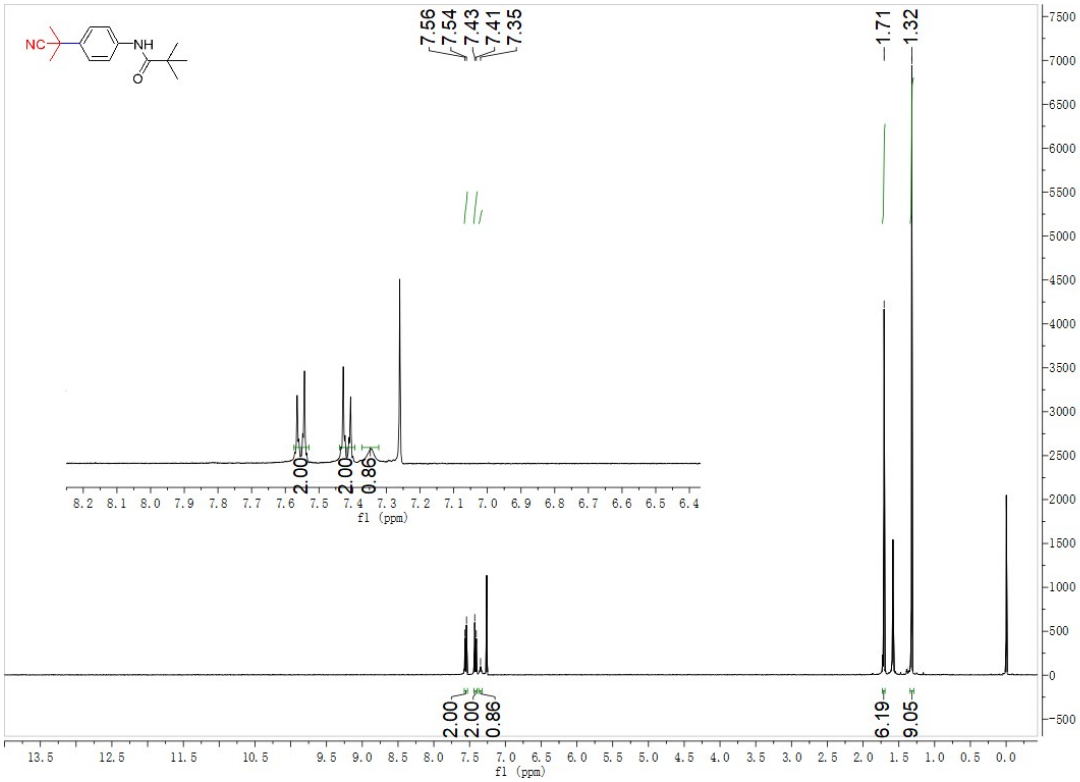
13

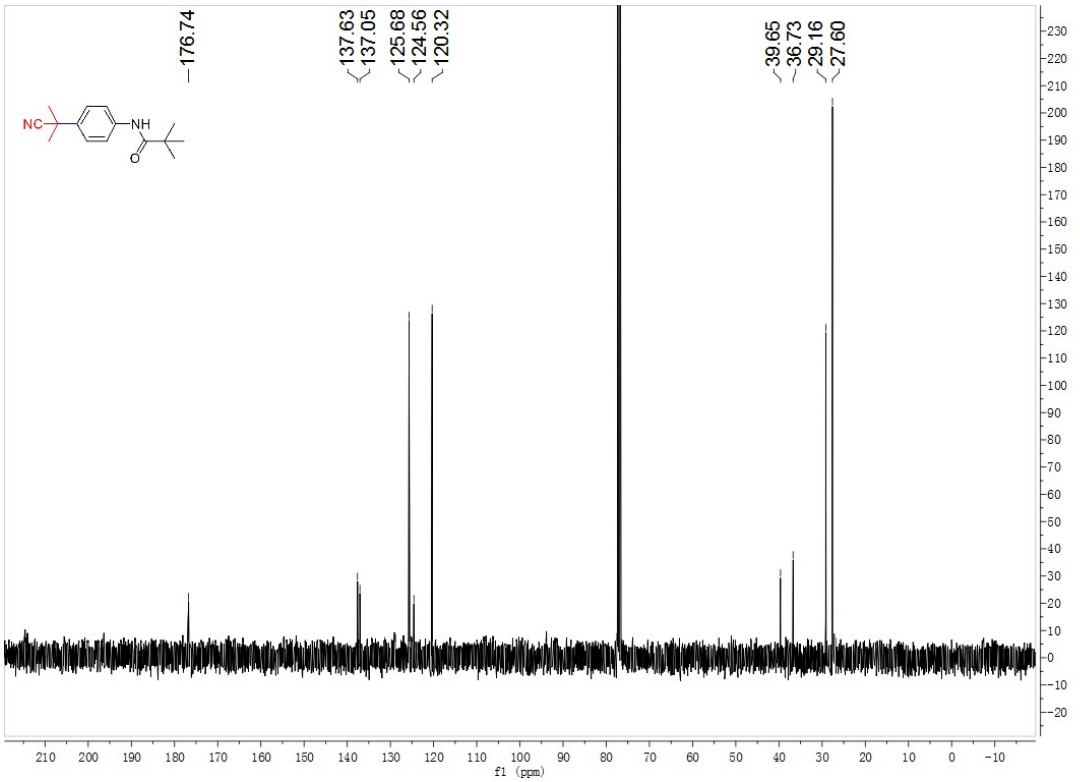


Pale yellow solid, isolated yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.71 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 2H), 1.71 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 146.98 (s), 144.62 (s), 139.17 (s), 132.70 (s), 125.99 (s), 125.29 (s), 124.21 (s), 123.53 (s), 121.23 (s), 108.18 (s), 33.63 (s), 28.92 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{13}H_{14}N_3$: 212.1182, found: 212.1180.

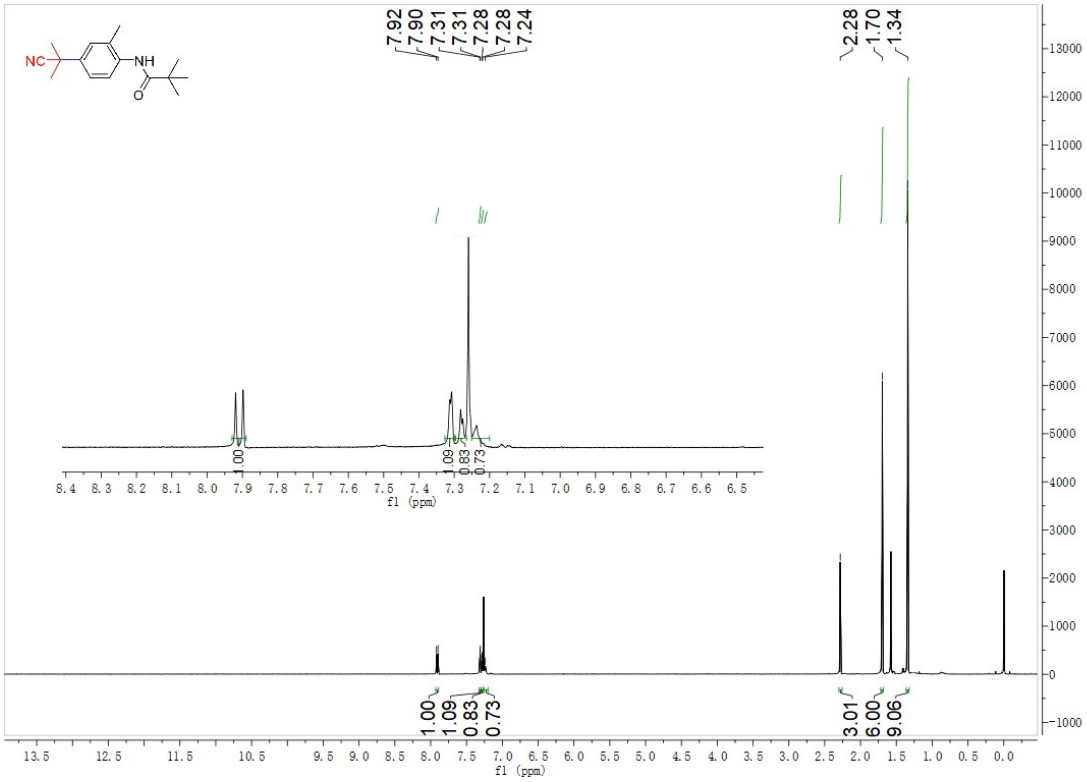
8. ^{1}H and ^{13}C NMR Spectra

2a





2b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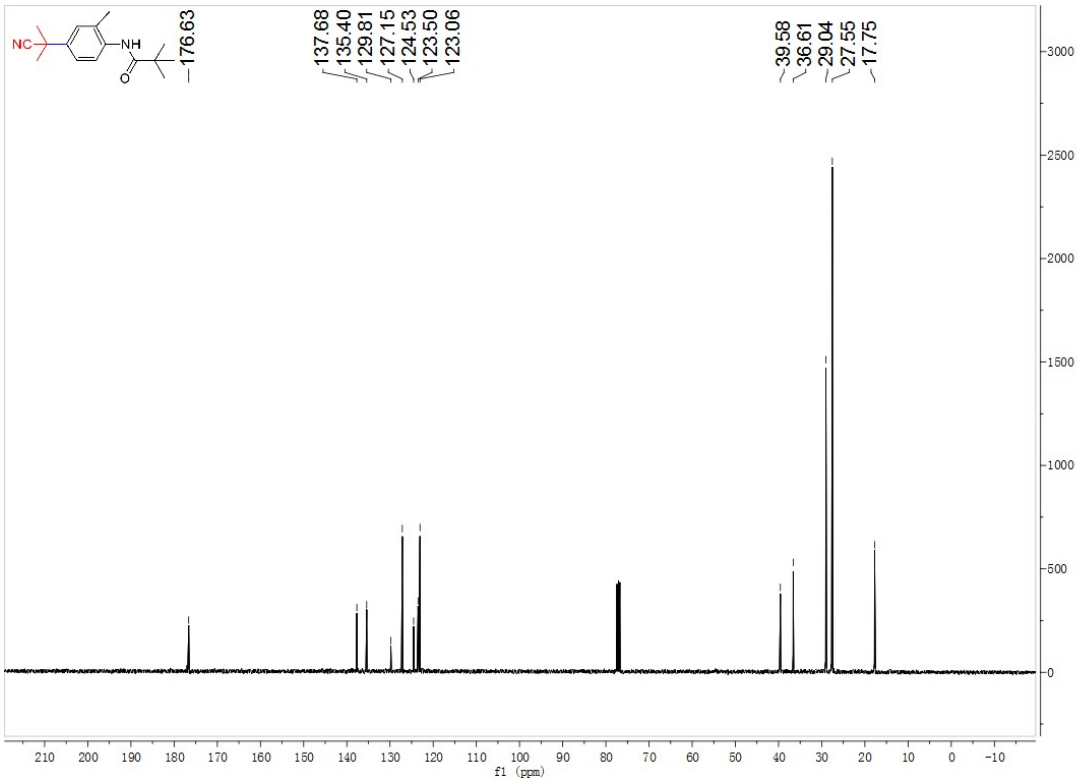
7.31
7.31
7.28
7.28
7.24
2.28
1.70
1.34
1.00
1.09
0.83
0.73
3.01
6.00
9.06
f1 (ppm)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NH
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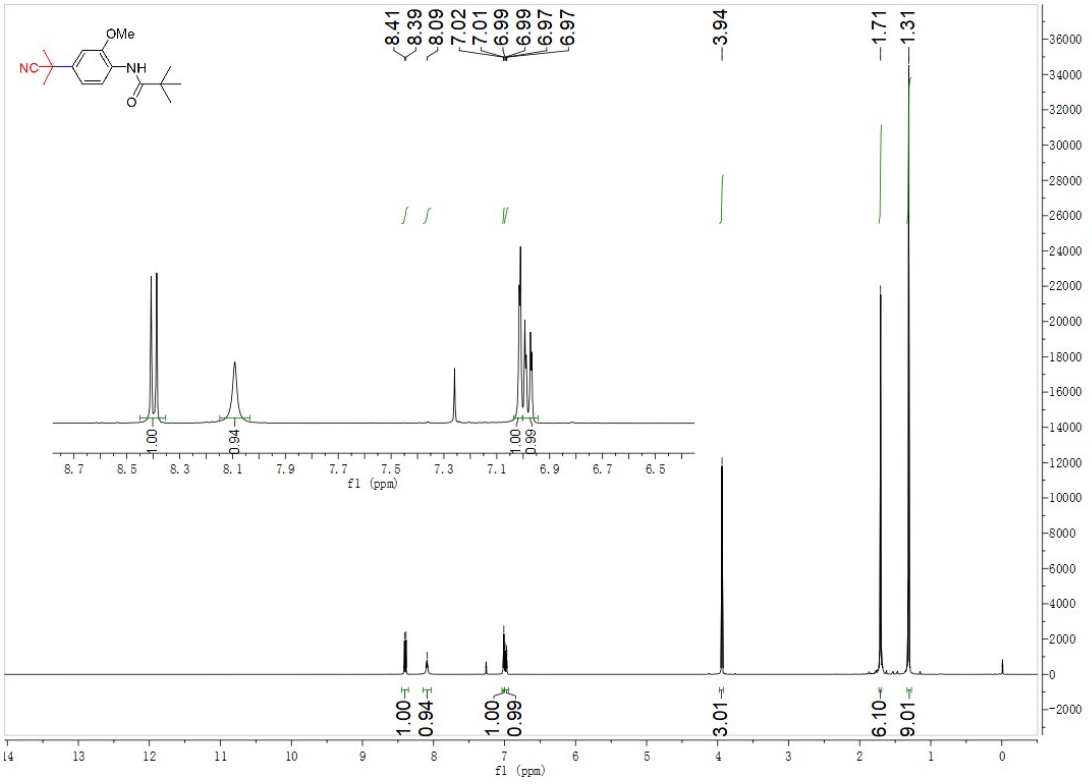
f1 (ppm)

2c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O
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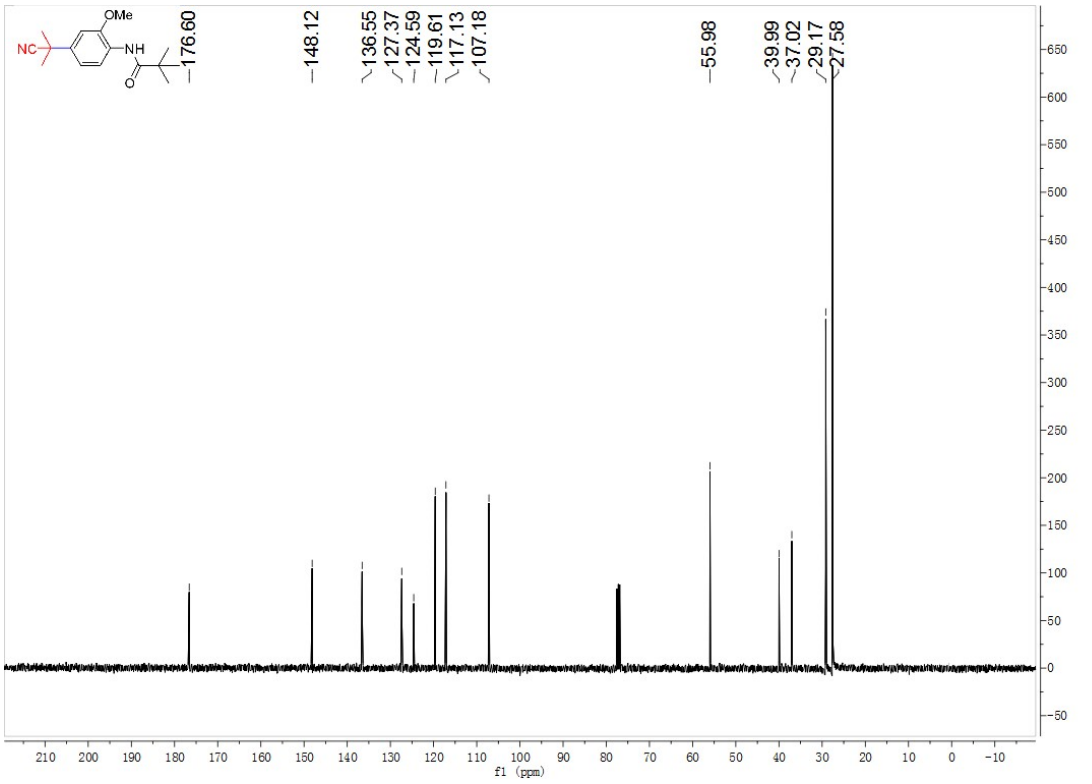
8.39
8.09
7.02
7.01
6.99
6.99
6.97
6.97
3.94
1.71
1.31
1.00
0.94
1.00
0.99
f1 (ppm)
3.01
6.10
9.01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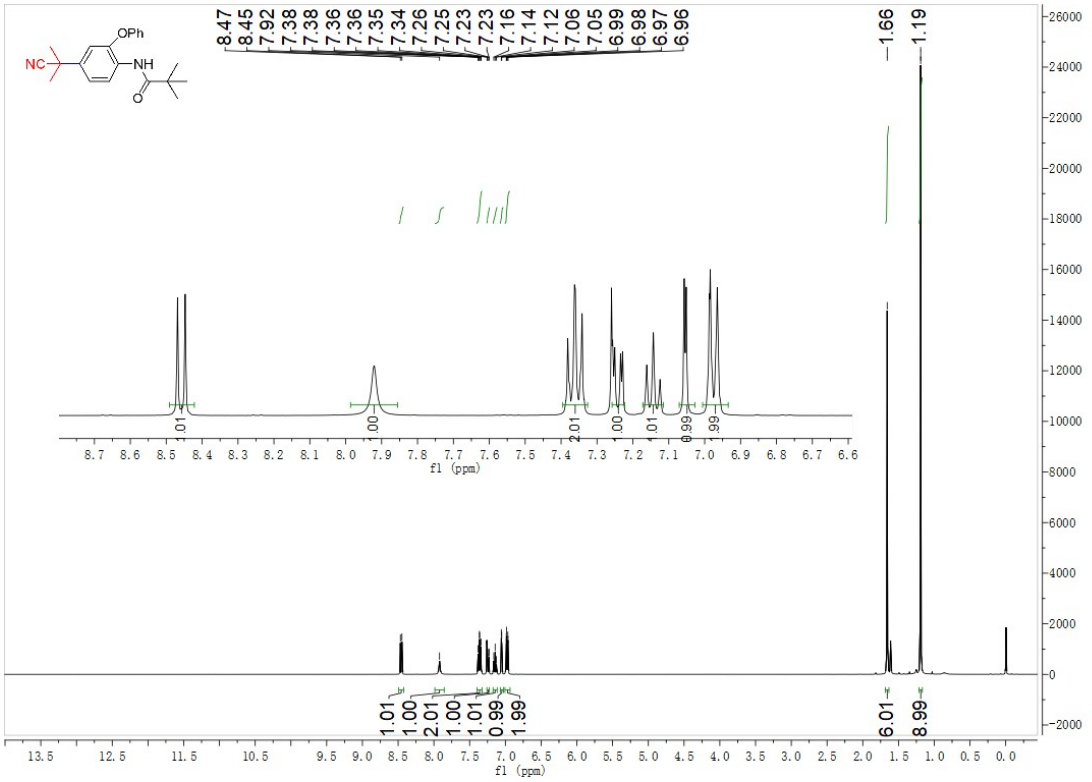
29.17
27.58
f1 (ppm)

2d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O
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8.45
7.92
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7.38
7.36
7.36
7.35
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7.26
7.25
7.23
7.23
7.16
7.14
7.12
7.06
7.05
6.99
6.98
6.97
6.96
1.66
1.19
1.01
1.00
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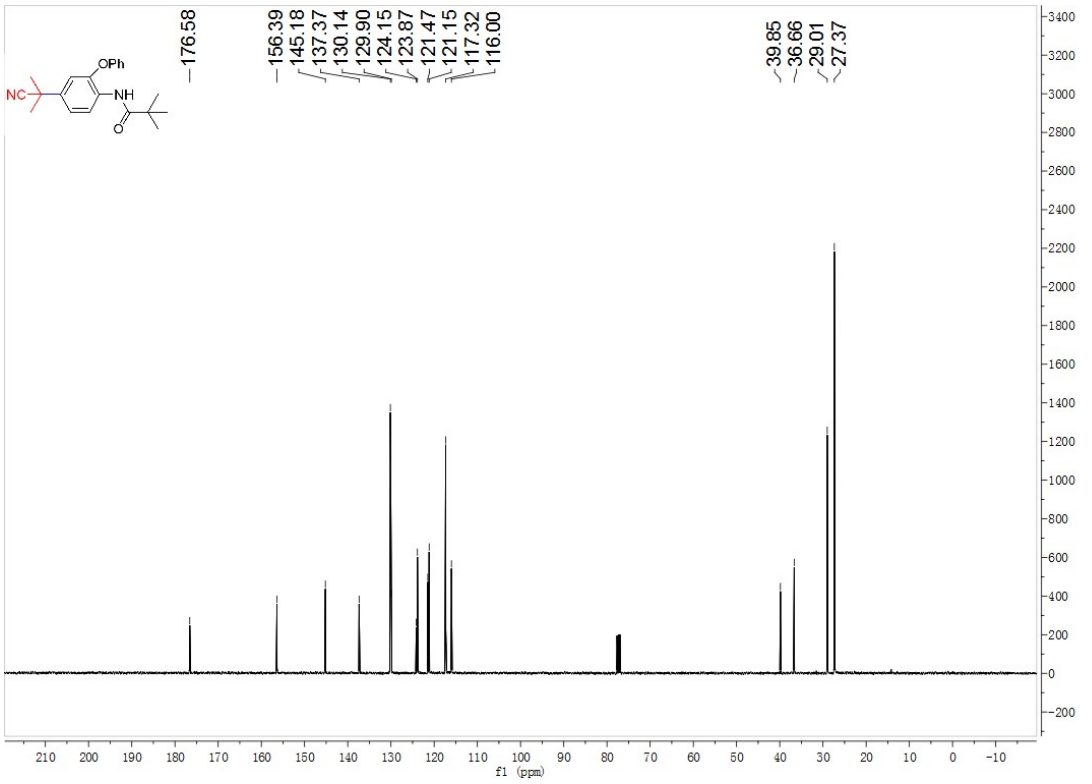
1.00
1.01
0.99
1.99
6.01
8.99
f1 (ppm)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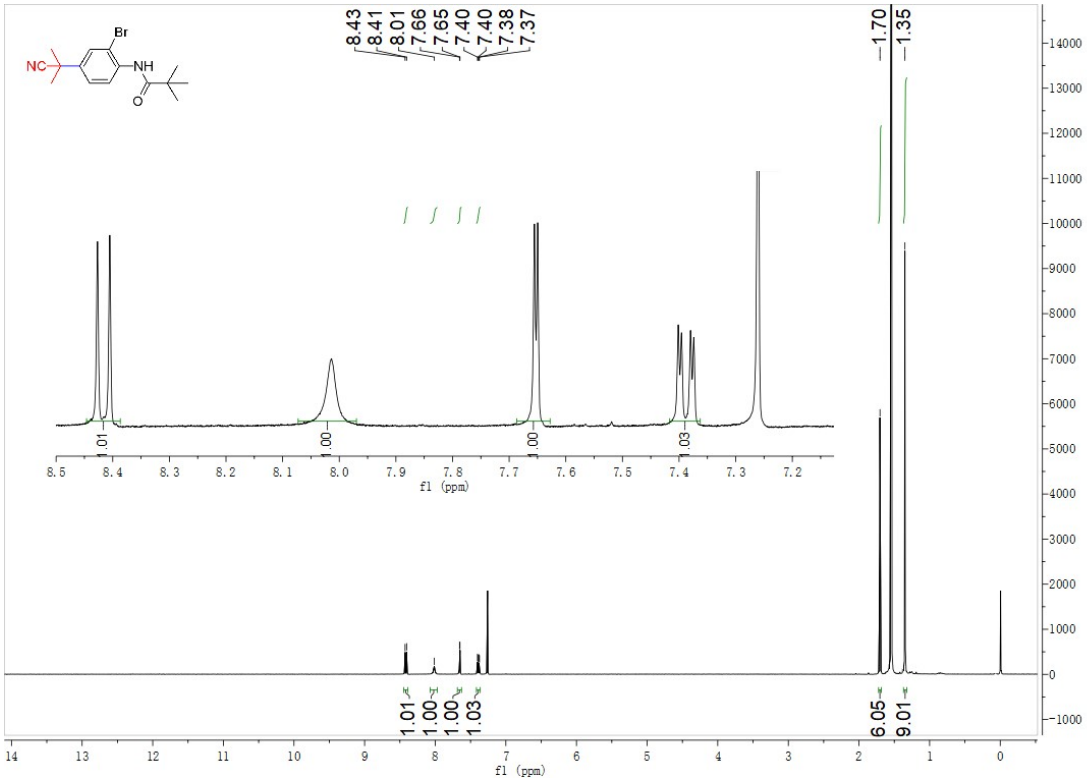
121.15
117.32
116.00
39.85
36.66
29.01
27.37
f1 (ppm)

2e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O
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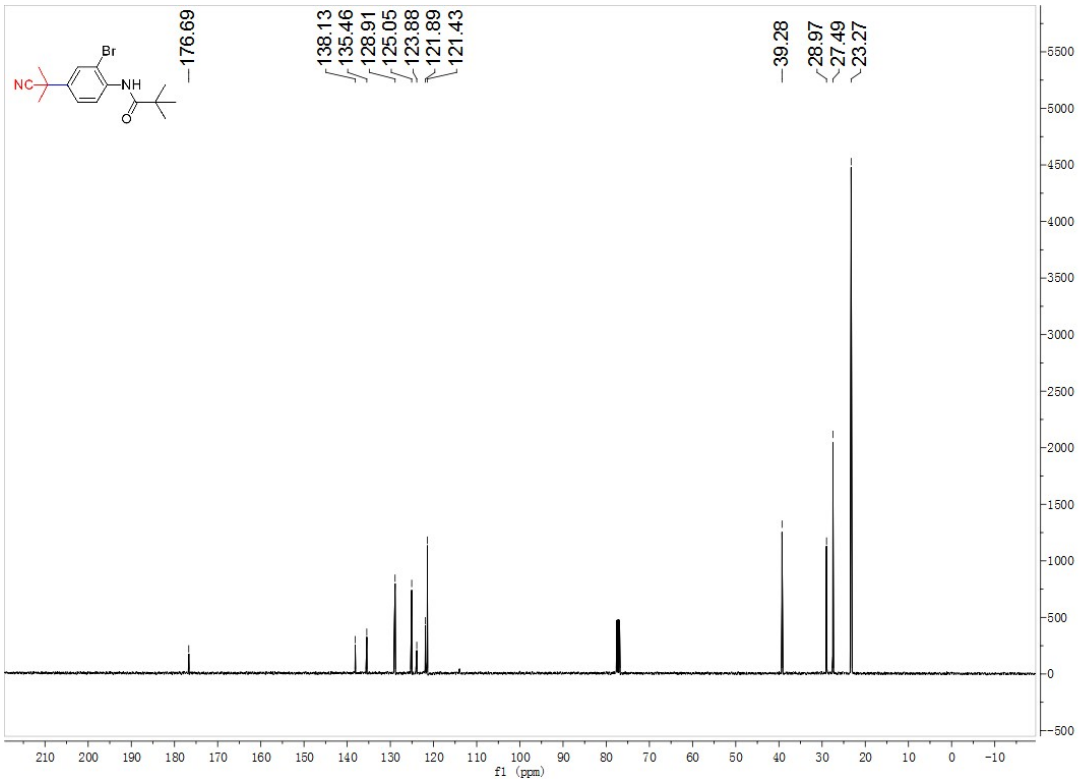
1.00
1.03
6.05
9.01
f1 (ppm)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121.43
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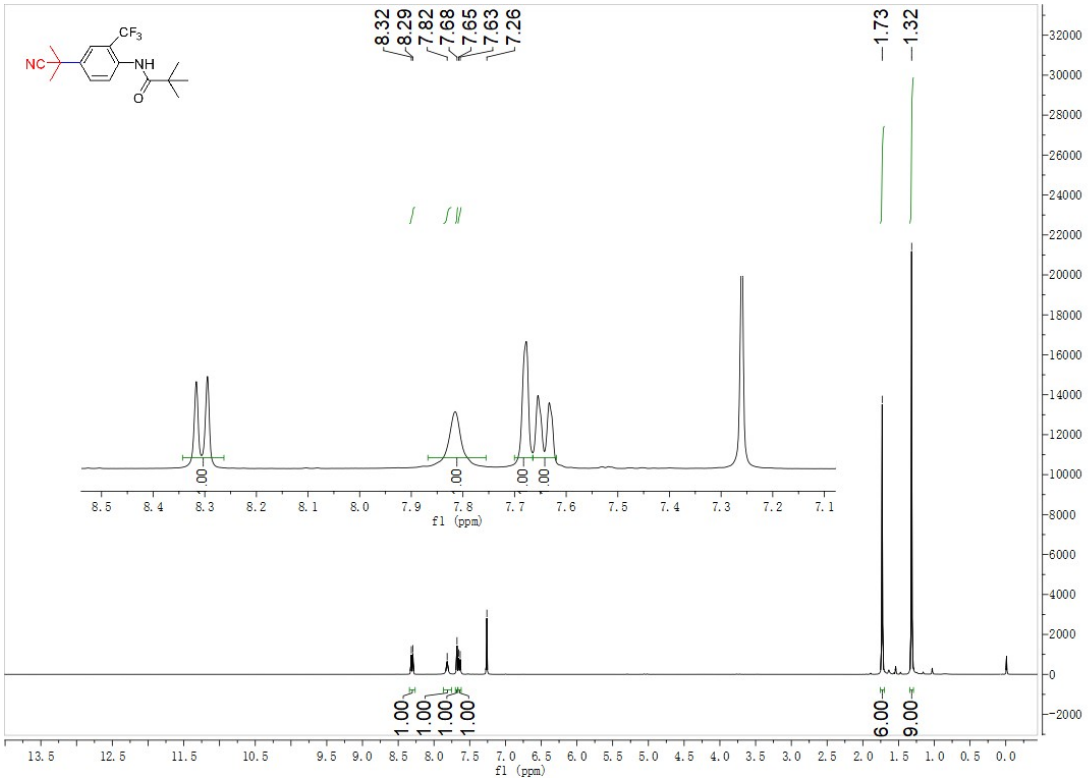
27.49
23.27
f1 (ppm)

2f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8.29
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7.63
7.26
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1.32
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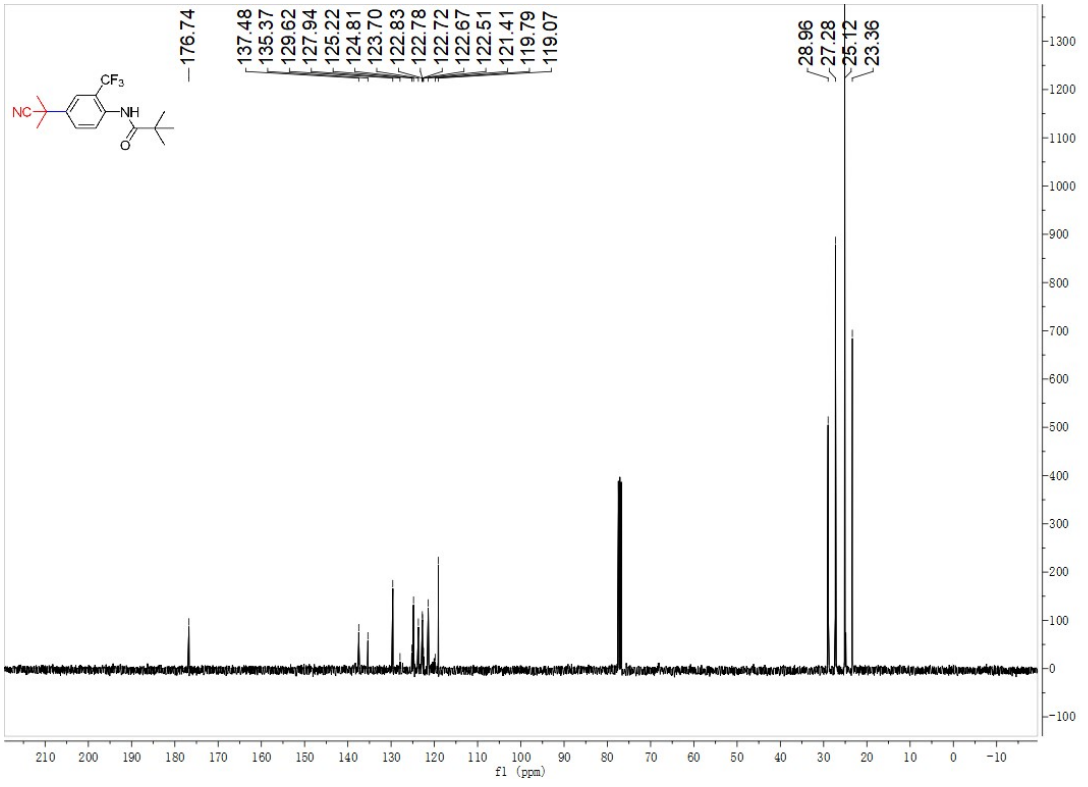
1.00
1.00
1.00
6.00
9.00
f1 (ppm)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123.70
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122.78
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121.41
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119.07
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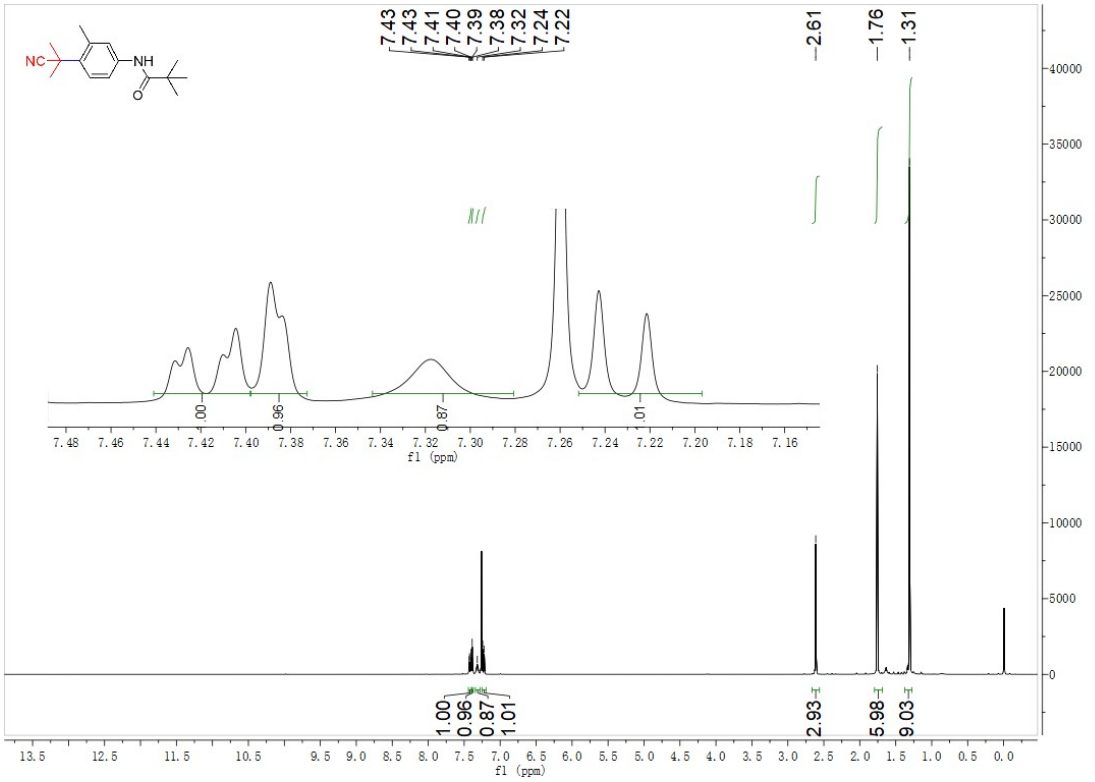
27.28
25.12
23.36
f1 (ppm)

2g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O
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7.38
7.32
7.24
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0.87
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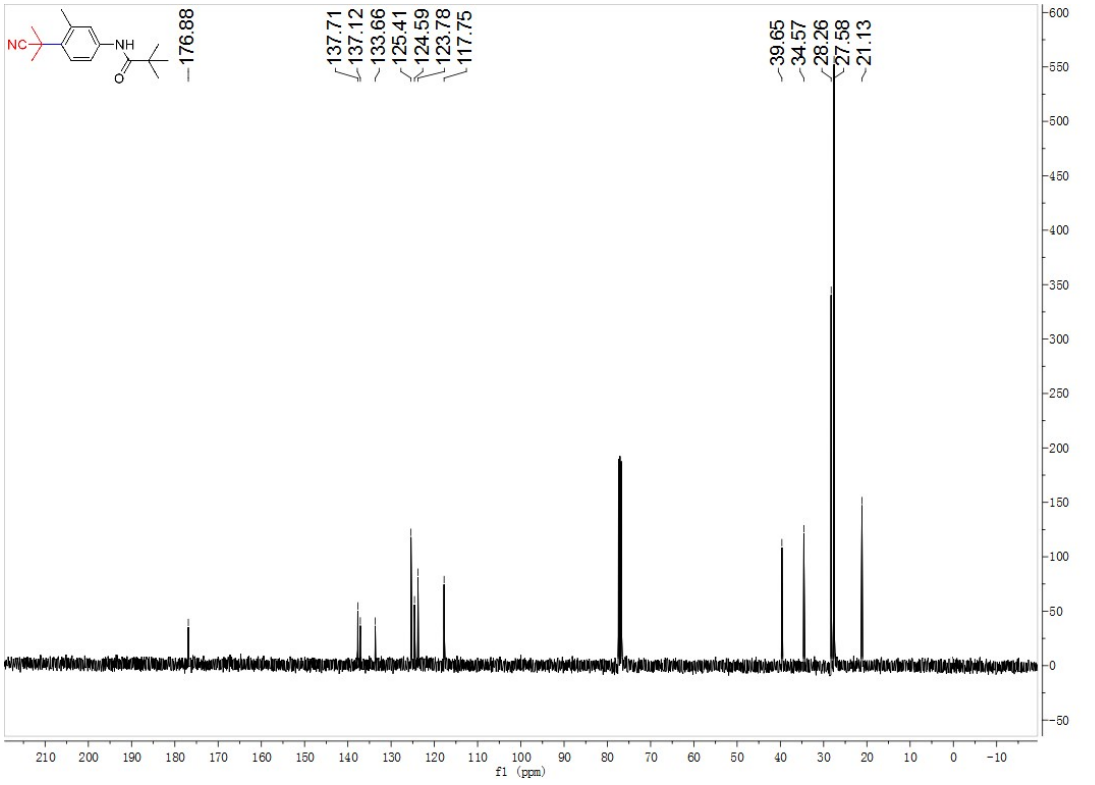
5.98
9.03
f1 (ppm)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O
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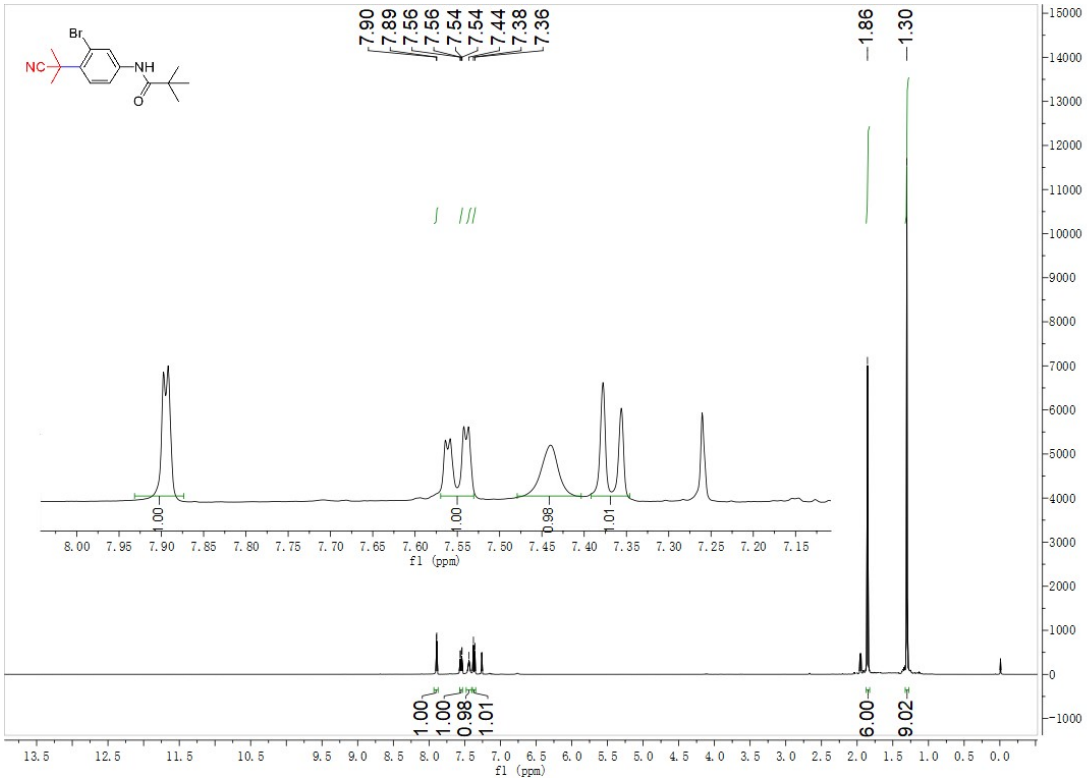
28.26
27.58
21.13
f1 (ppm)

2h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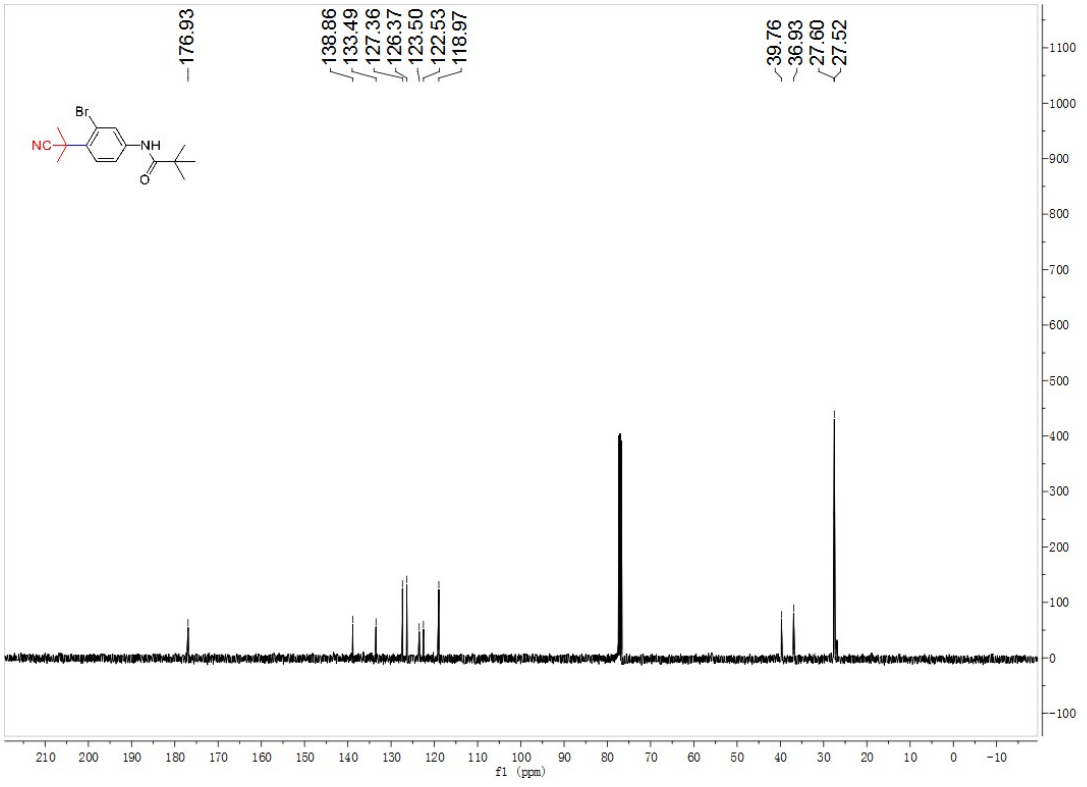
1.00
0.98
1.01
6.00
9.02
fl (ppm)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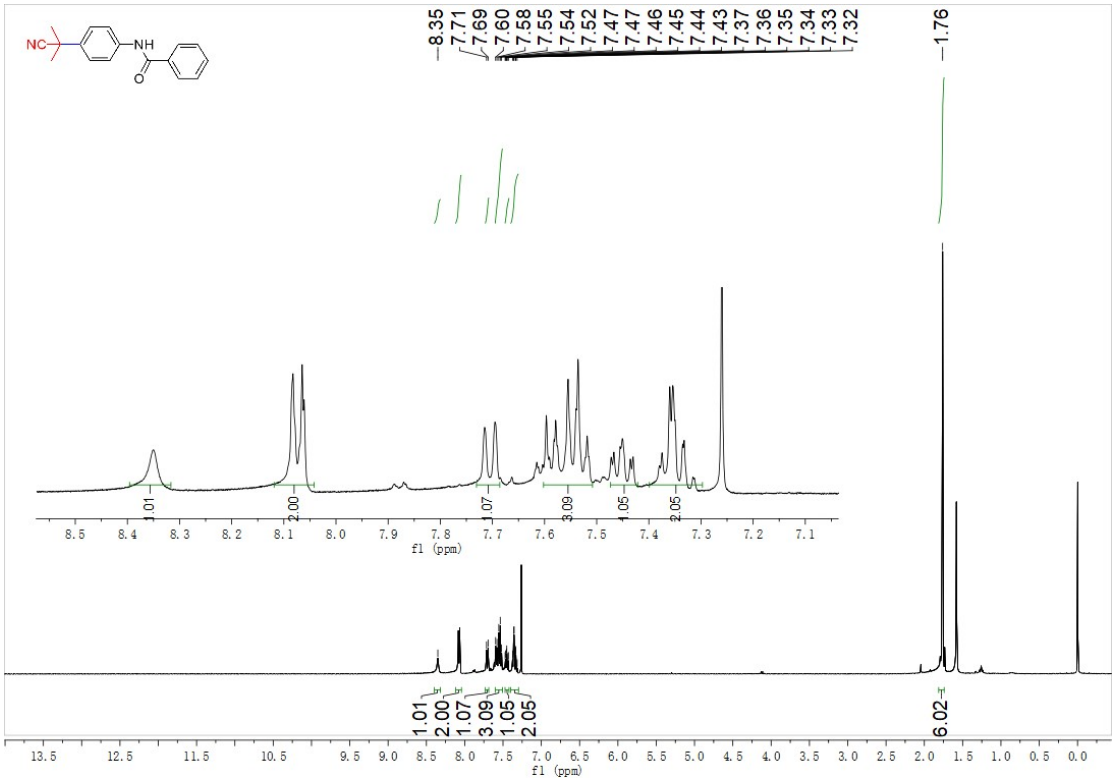
27.52
fl (ppm)

2i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7.55
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7.47
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7.46
7.45
7.44
7.43
7.37
7.36
7.35
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1.76
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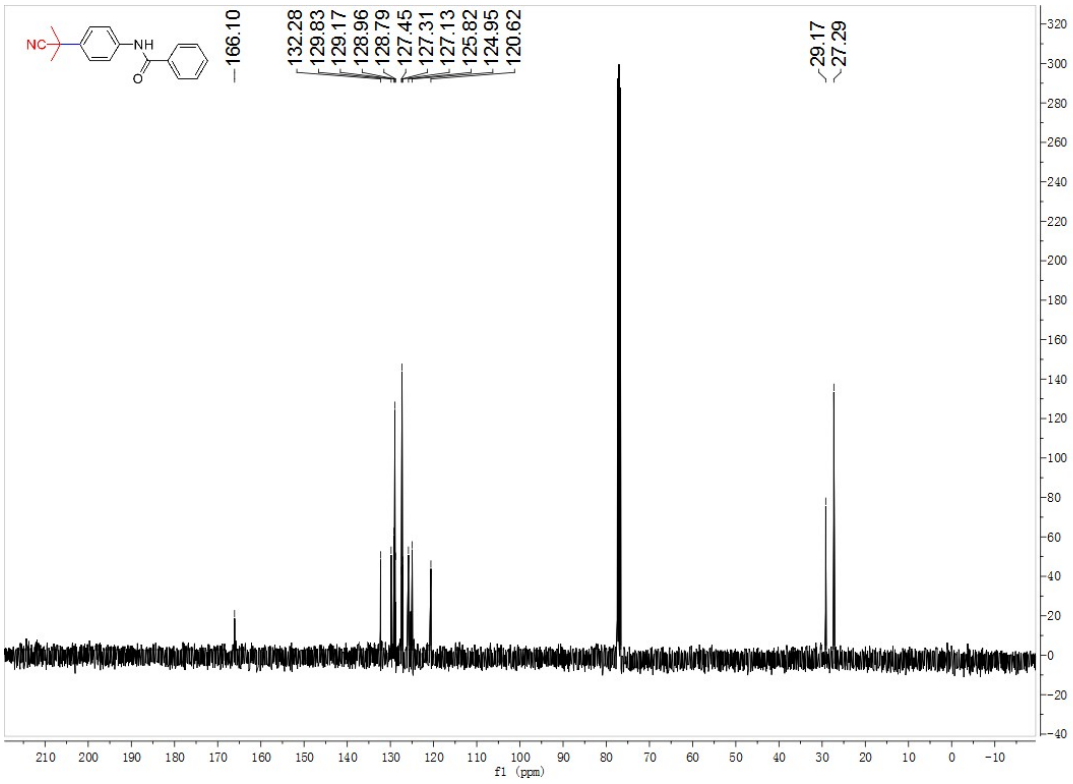
1.07
3.09
1.05
2.05
6.02
f1 (ppm)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129.17
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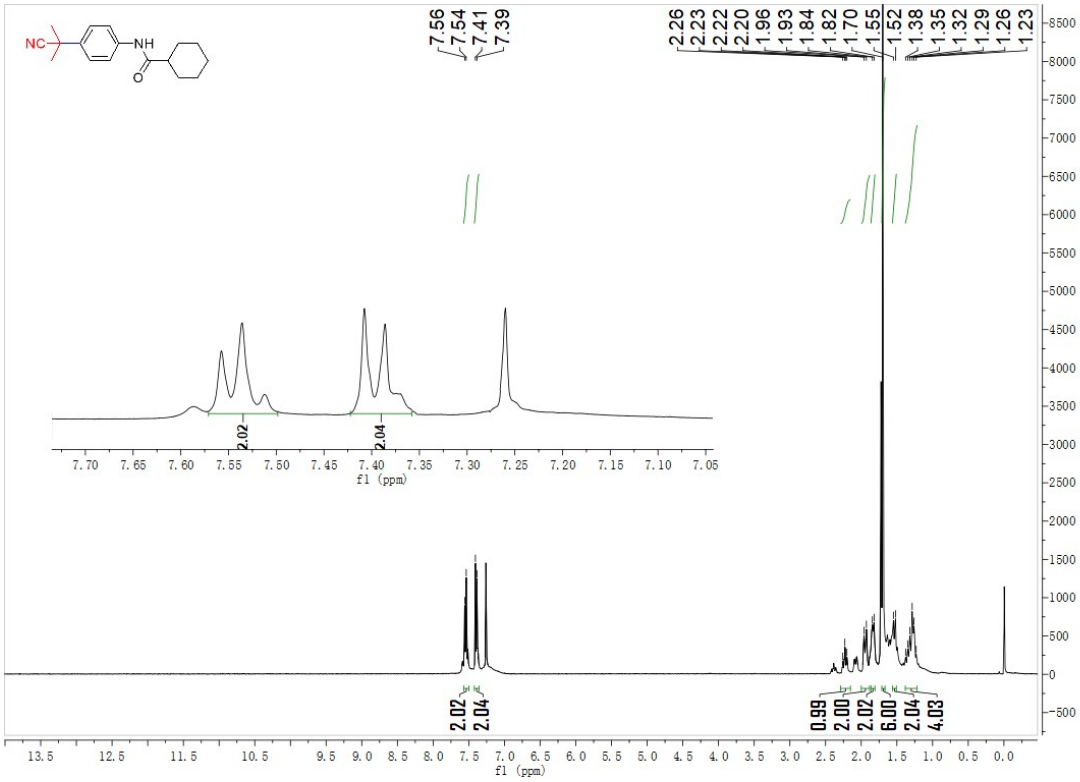
120.62
29.17
27.29
f1 (ppm)

2j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NH
O
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7.39
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2.20
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1.93
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1.70
1.55
1.52
1.38
1.35
1.32
1.29
1.26
1.23
2.02
2.04
f1 (ppm)
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2.00
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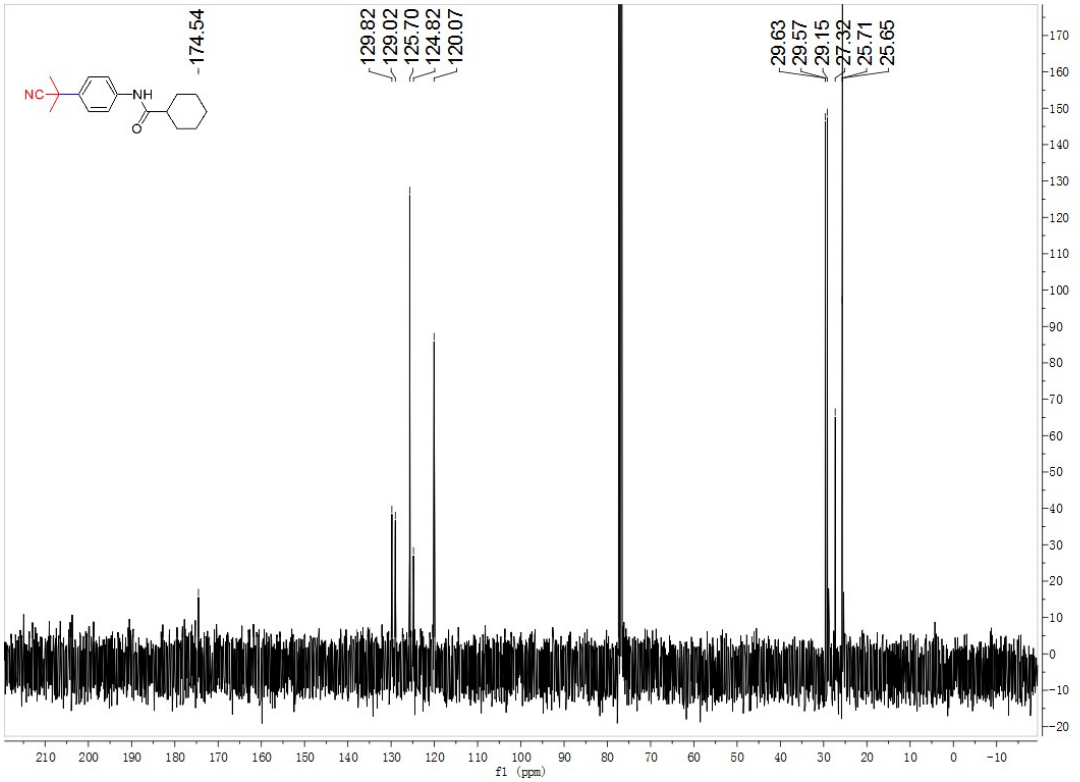
6.00
2.04
4.03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O
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120.07
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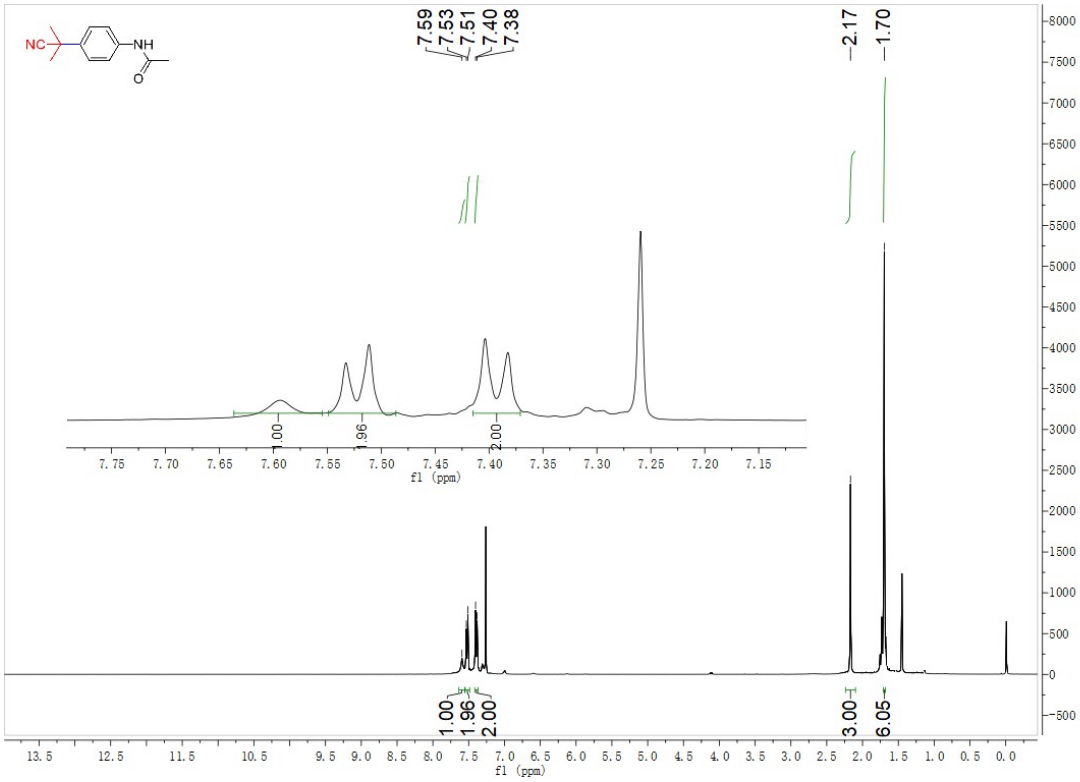
f1 (ppm)

2k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1.00
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2.00
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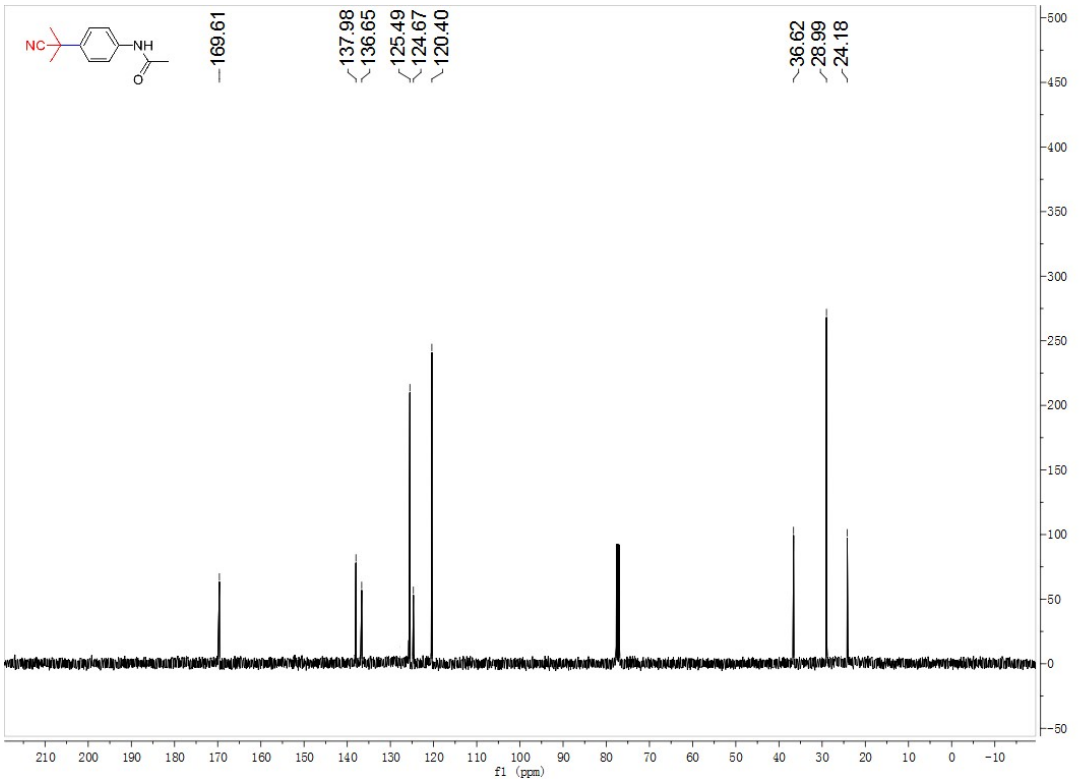
f1 (ppm)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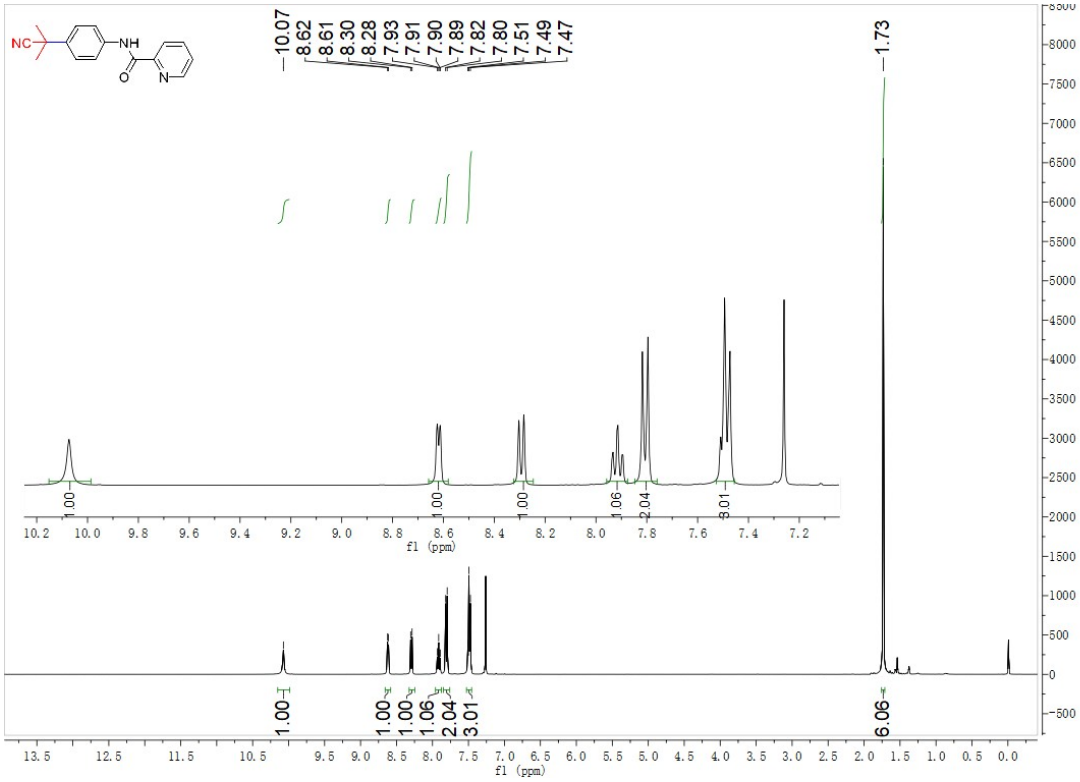
2l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O
N
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7.93
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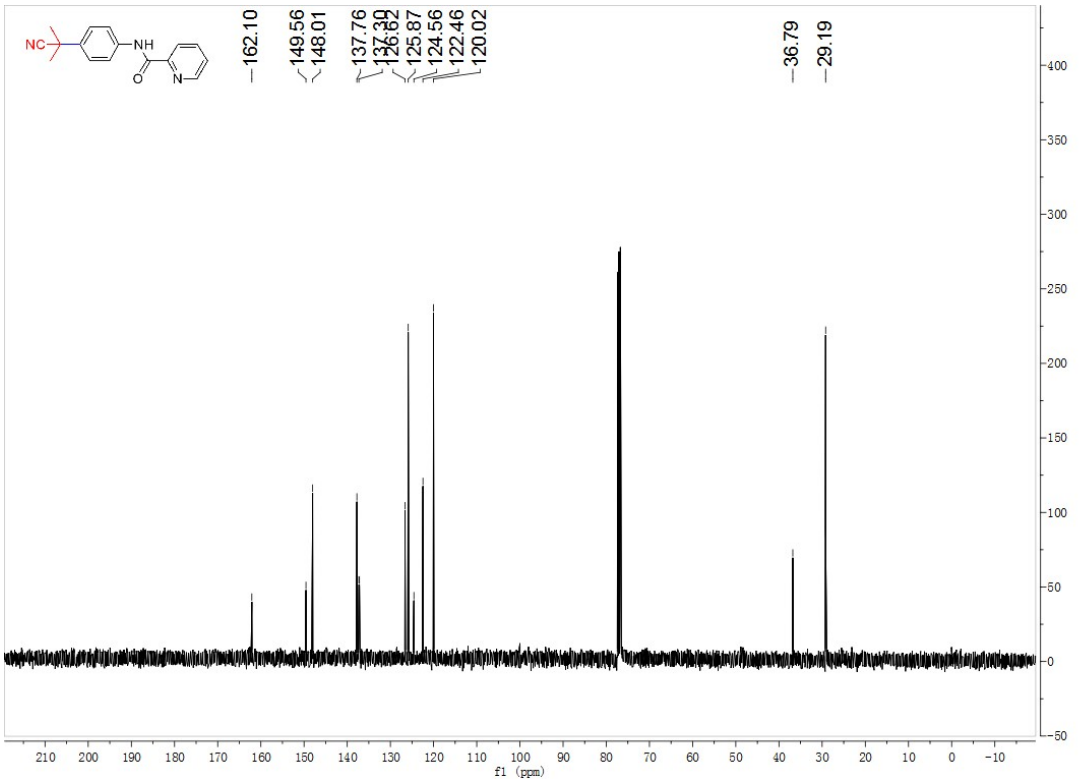
1.06
2.04
3.01
6.06
f1 (ppm)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O
N
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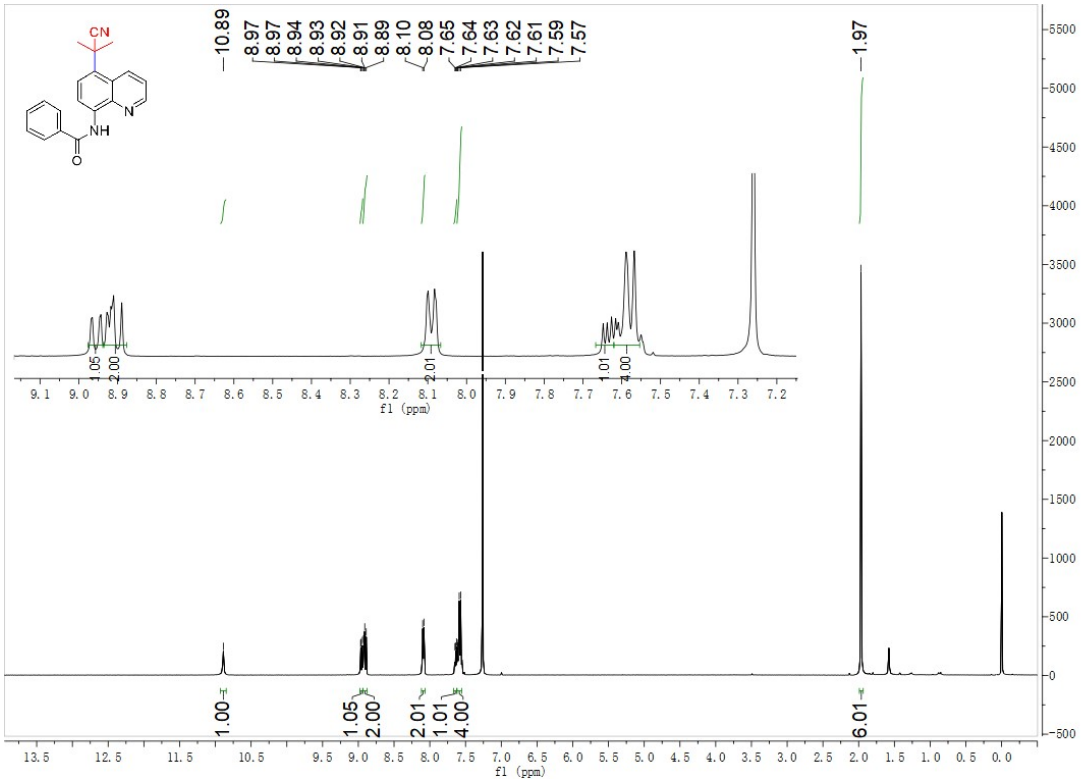
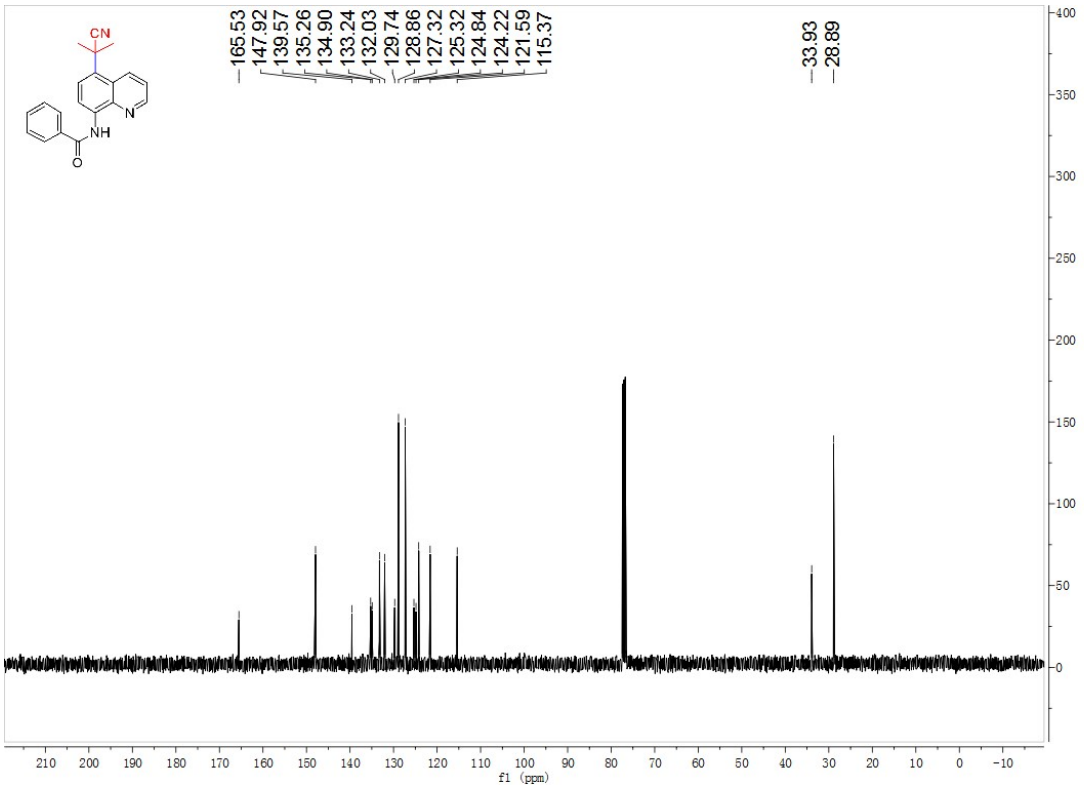
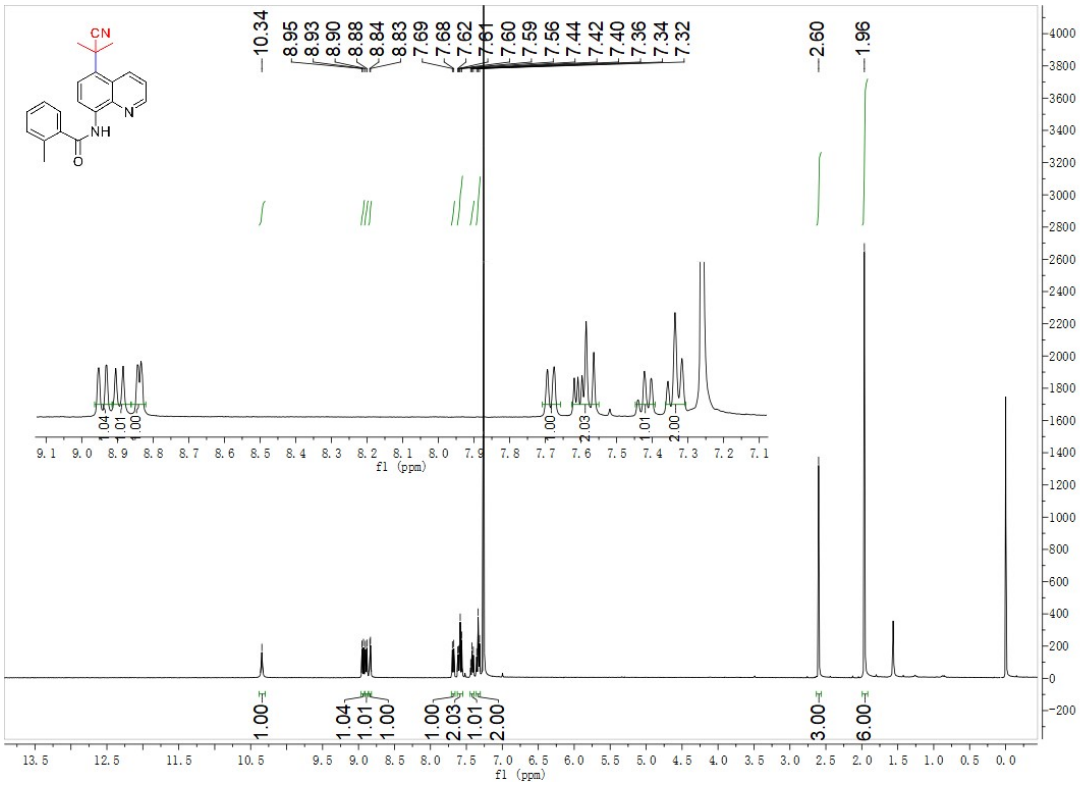
137.30
126.62
125.87
124.56
122.46
120.02
36.79
29.19
f1 (ppm)

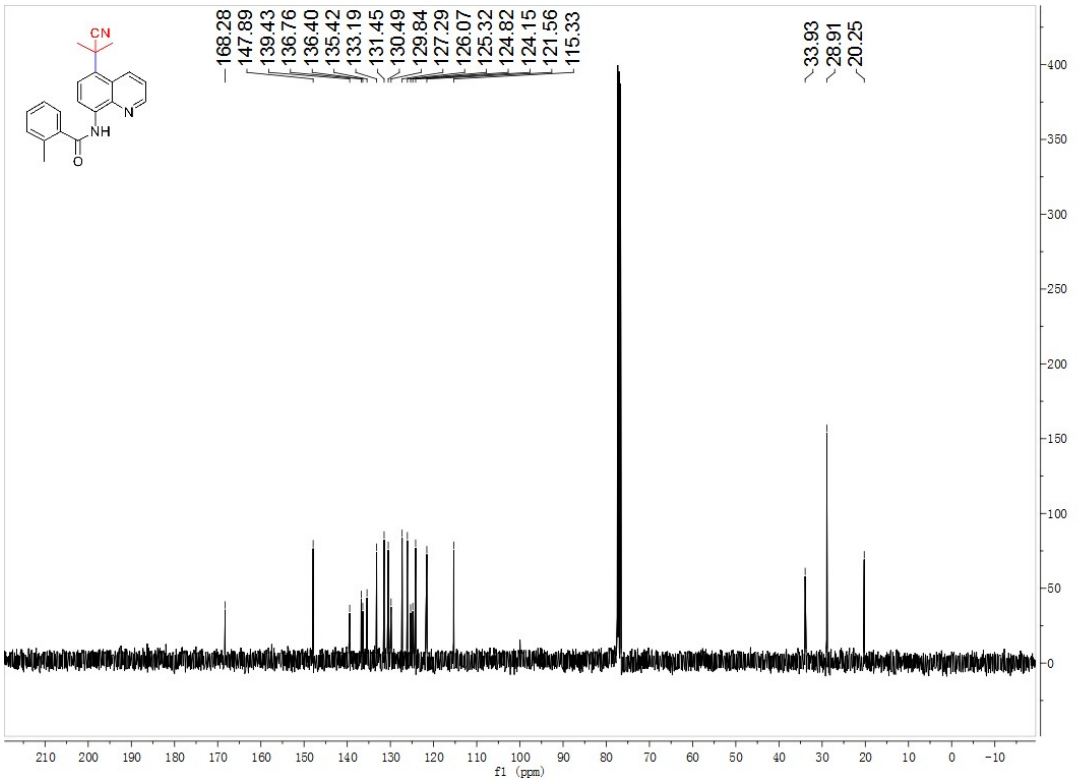
4a


CN
NH
O
N
10.89
8.97
8.97
8.94
8.93
8.92
8.91
8.89
8.10
8.08
7.65
7.64
7.63
7.62
7.61
7.59
7.57
1.97
1.05
2.00
2.01
1.01
4.00
f1 (ppm)
1.00
1.05
2.00
2.01
1.01
4.00
6.01

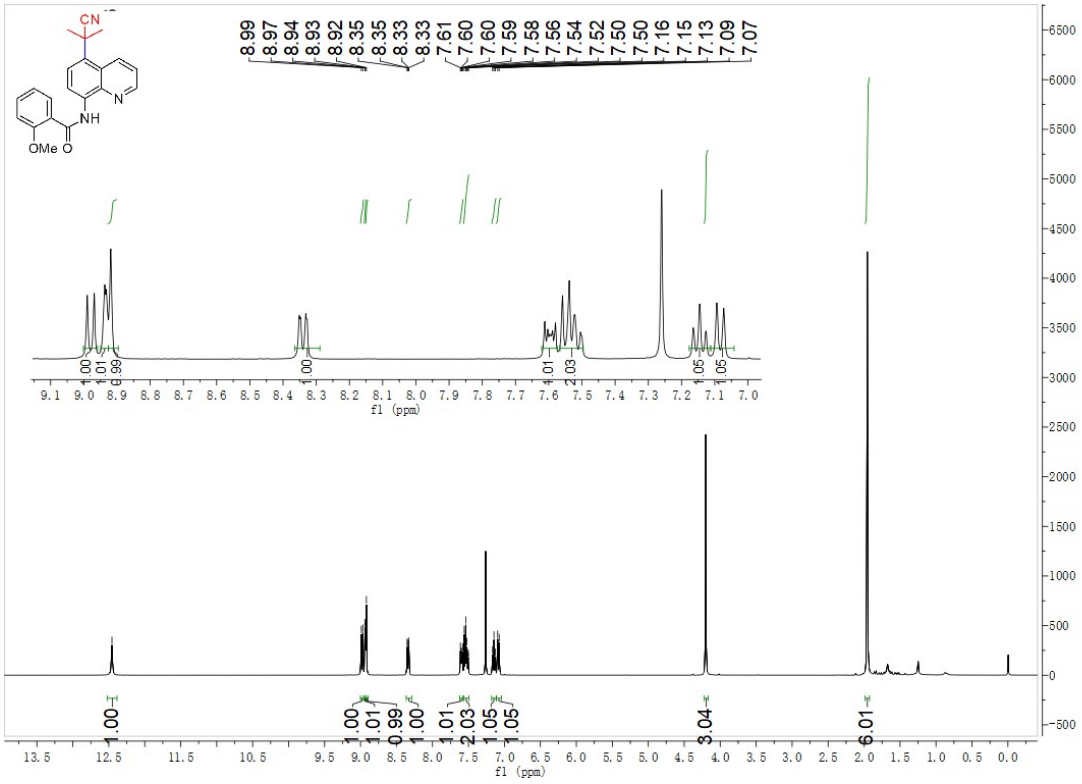

CN
NH
O
N
165.53
147.92
139.57
135.26
134.90
133.24
132.03
129.74
128.86
127.32
125.32
124.84
124.22
121.59
115.37
33.93
28.89
f1 (ppm)

4b


CN
NH
O
N
10.34
8.95
8.93
8.90
8.88
8.84
8.83
7.69
7.68
7.62
7.61
7.60
7.59
7.56
7.44
7.42
7.40
7.36
7.34
7.32
2.60
1.96
1.00
1.04
1.01
1.00
1.00
2.03
1.01
2.00
3.00
6.00
f1 (ppm)


CN
NH
O
N
168.28
147.89
139.43
136.76
136.40
135.42
133.19
131.45
130.49
129.84
127.29
126.07
125.32
124.82
124.15
121.56
115.33
33.93
28.91
20.25
f1 (ppm)

4c


CN
NH
OMe O
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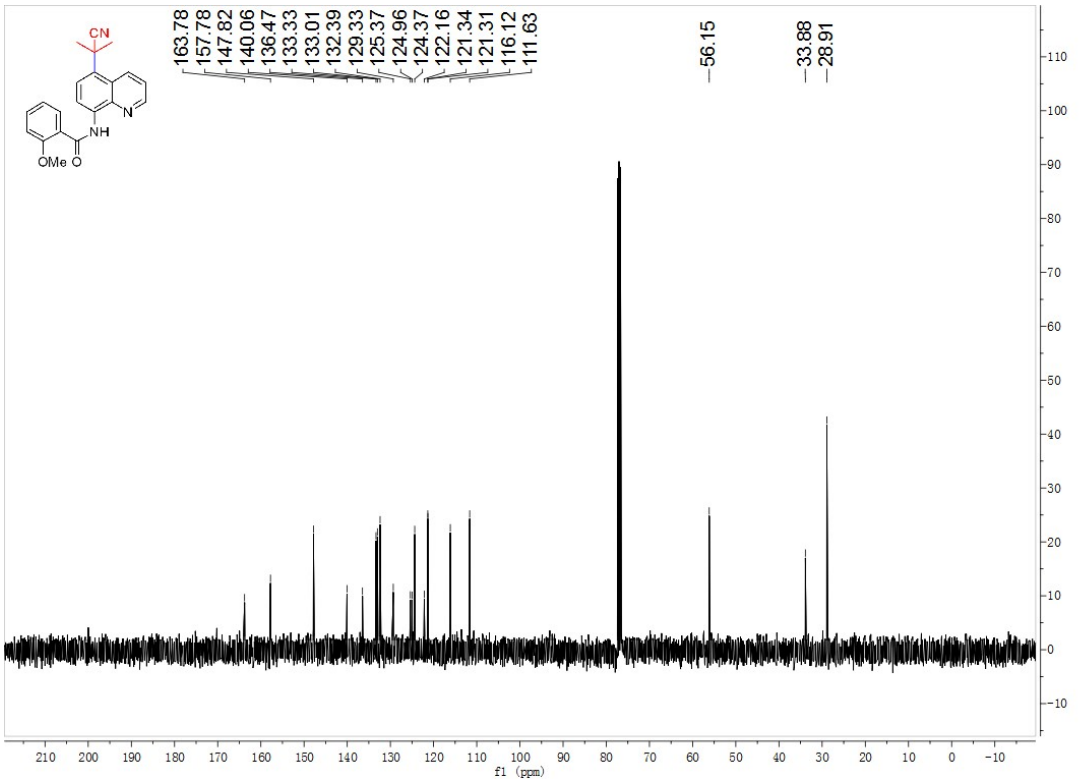
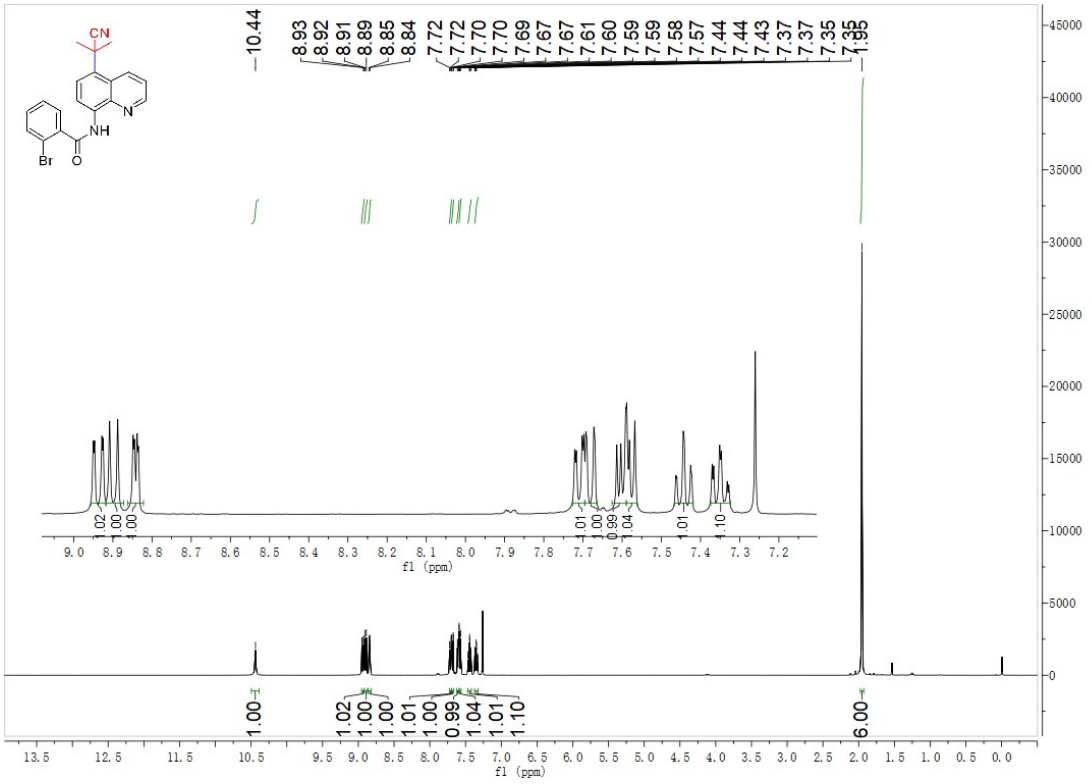
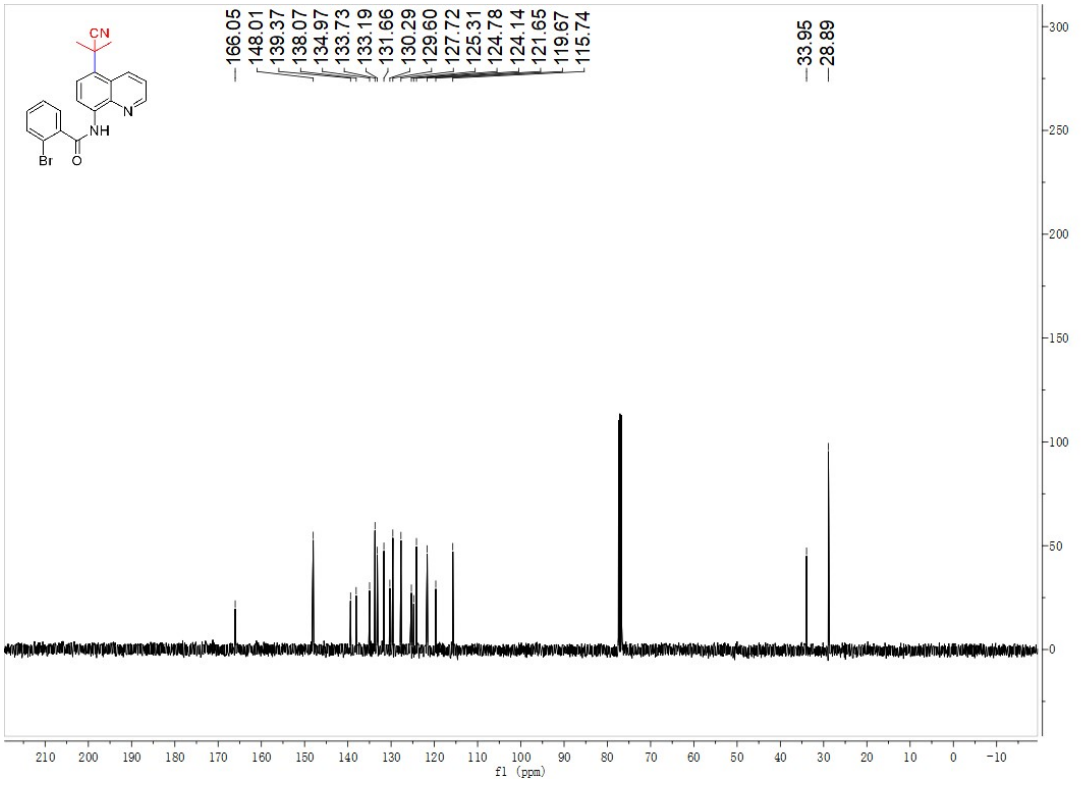
8.97
8.94
8.93
8.92
8.35
8.35
8.33
8.33
7.61
7.60
7.60
7.59
7.58
7.56
7.54
7.52
7.50
7.50
7.16
7.15
7.13
7.09
7.07
1.00
1.01
0.99
1.00
1.01
2.03
1.05
1.05
3.04
6.01
f1 (ppm)

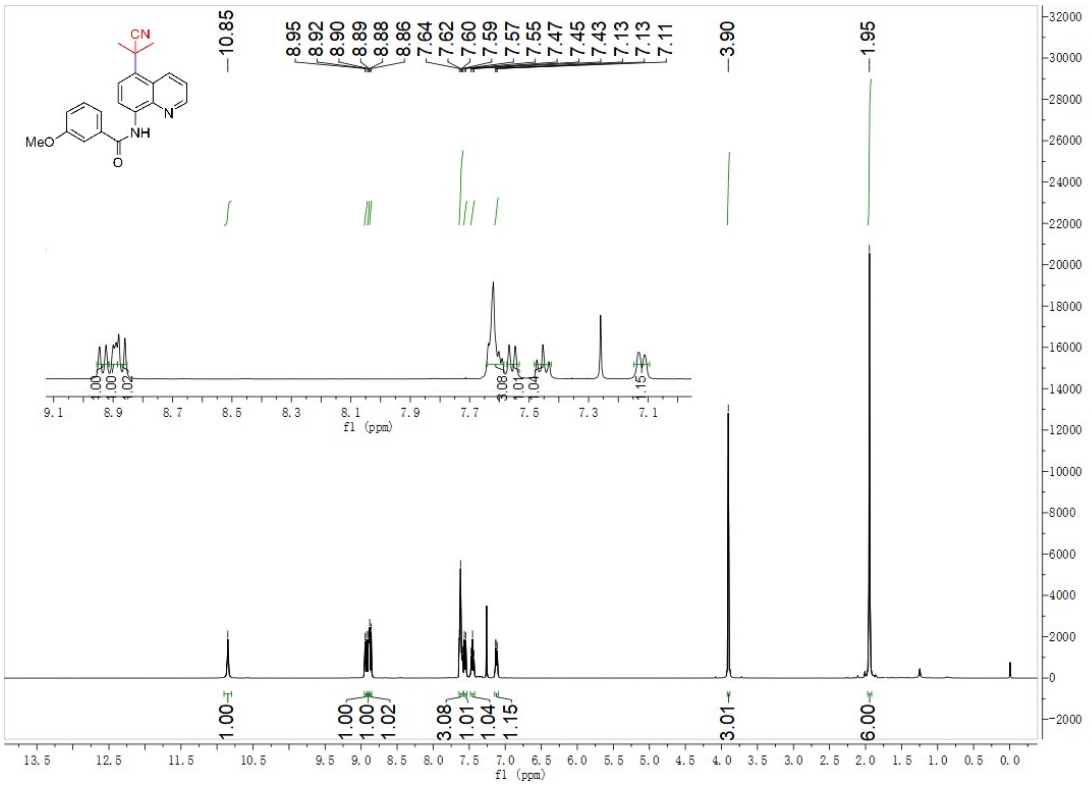

CN
NH
OMe O
163.78
157.78
147.82
140.06
136.47
133.33
133.01
132.39
129.33
125.37
124.96
124.37
122.16
121.34
121.31
116.12
111.63
56.15
33.88
28.91
f1 (ppm)

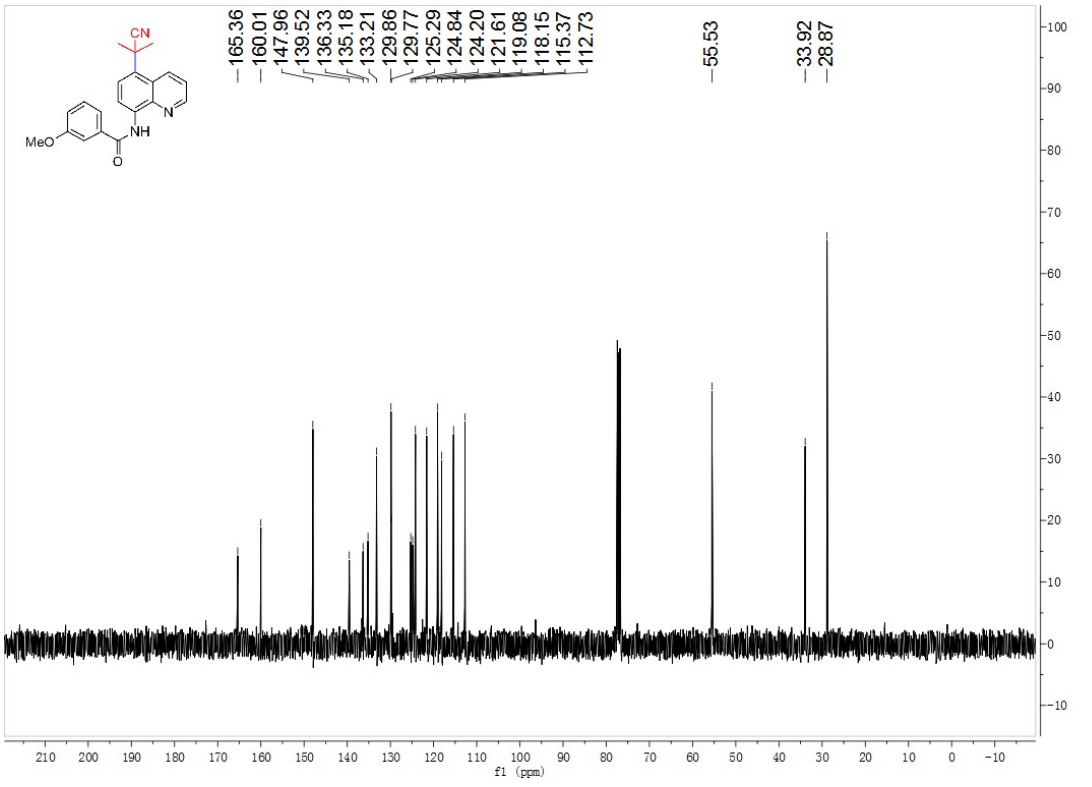
4d


10.44
8.93
8.92
8.91
8.89
8.85
8.84
7.72
7.72
7.70
7.70
7.69
7.67
7.67
7.61
7.60
7.59
7.59
7.58
7.57
7.44
7.44
7.43
7.37
7.37
7.35
7.35
1.00
1.02
1.00
1.00
1.01
1.00
0.99
1.04
1.01
1.10
6.00
f1 (ppm)

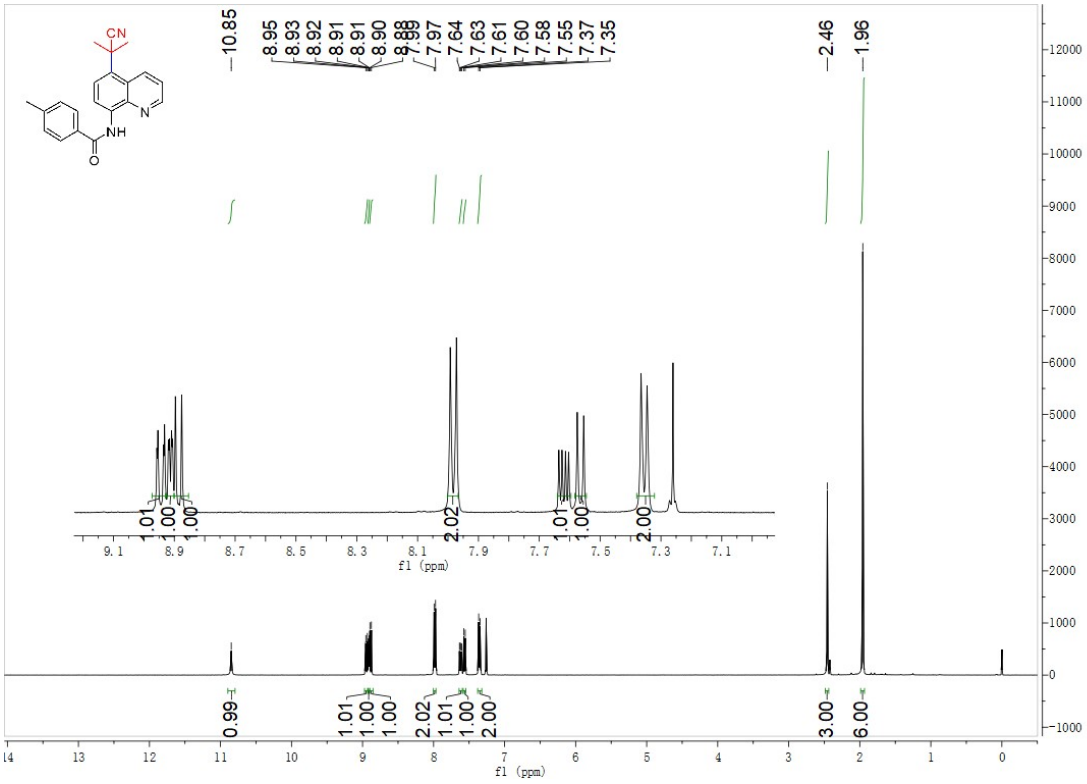

166.05
148.01
139.37
138.07
134.97
133.73
133.19
131.66
130.29
129.60
127.72
125.31
124.78
124.14
121.65
119.67
115.74
33.95
28.89
f1 (ppm)

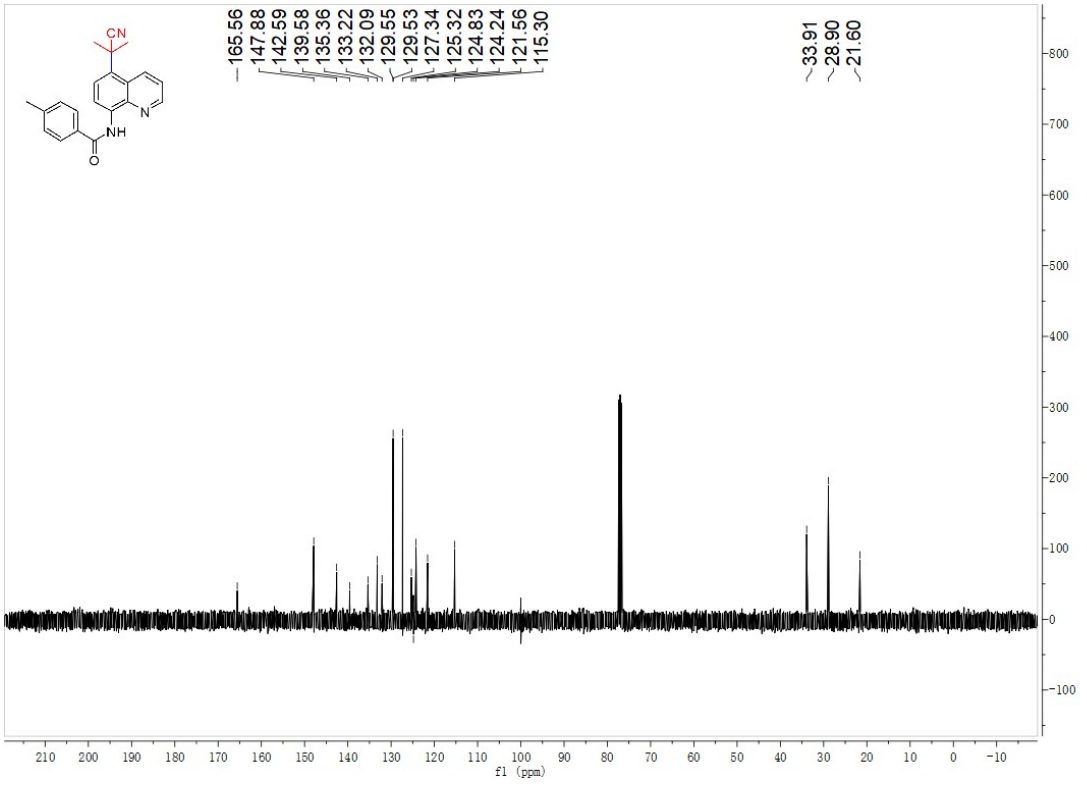
4e


CN
MeO
NH
O
N
10.85
8.95
8.92
8.90
8.89
8.88
8.86
7.64
7.62
7.60
7.59
7.57
7.55
7.47
7.45
7.43
7.13
7.13
7.11
3.90
1.95
1.00
1.00
1.00
1.02
3.08
1.01
1.04
1.15
3.01
6.00
f1 (ppm)

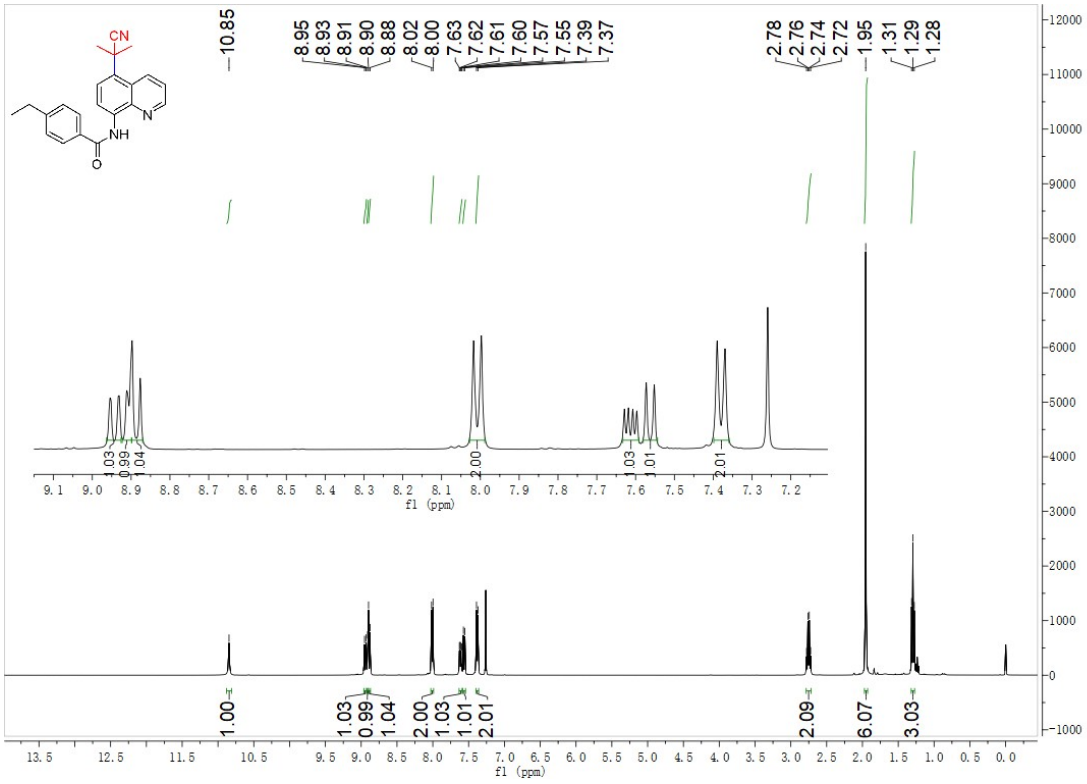

CN
MeO
NH
O
N
165.36
160.01
147.96
139.52
136.33
135.18
133.21
129.86
129.77
125.29
124.84
124.20
121.61
119.08
118.15
115.37
112.73
55.53
33.92
28.87
f1 (ppm)

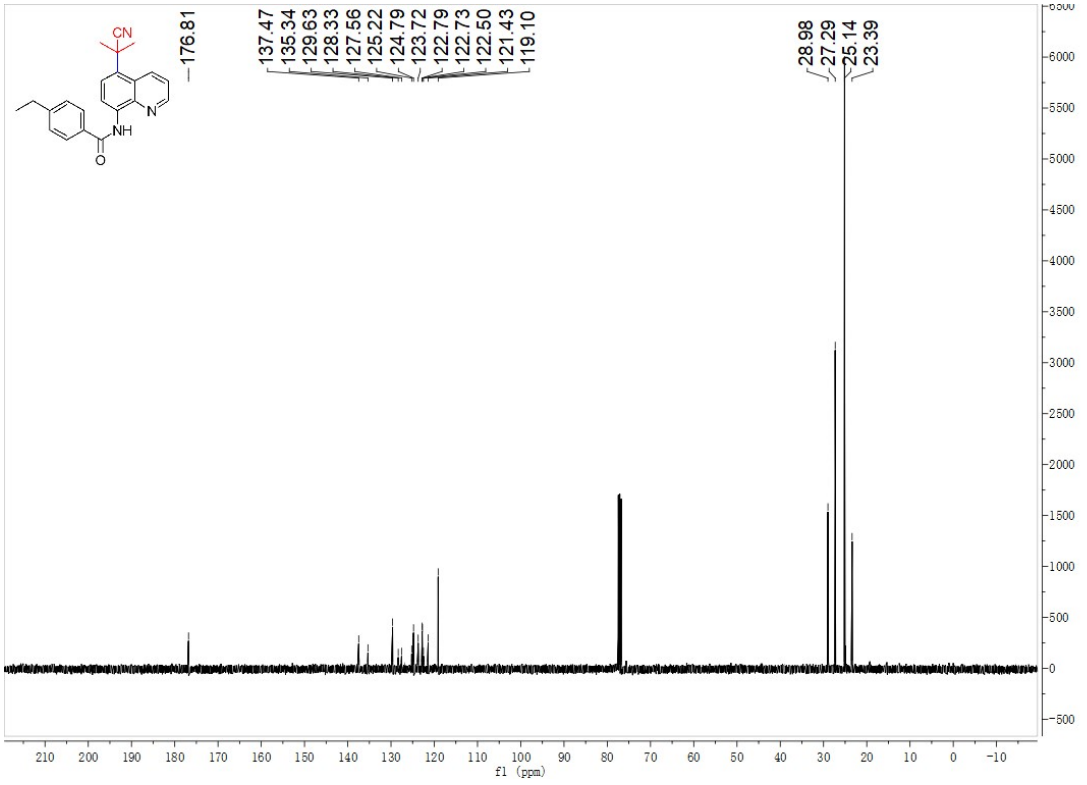
4f


CN
NH
O
N
10.85
8.95
8.93
8.92
8.91
8.91
8.90
7.97
7.64
7.63
7.61
7.60
7.58
7.55
7.37
7.35
2.46
1.96
f1 (ppm)

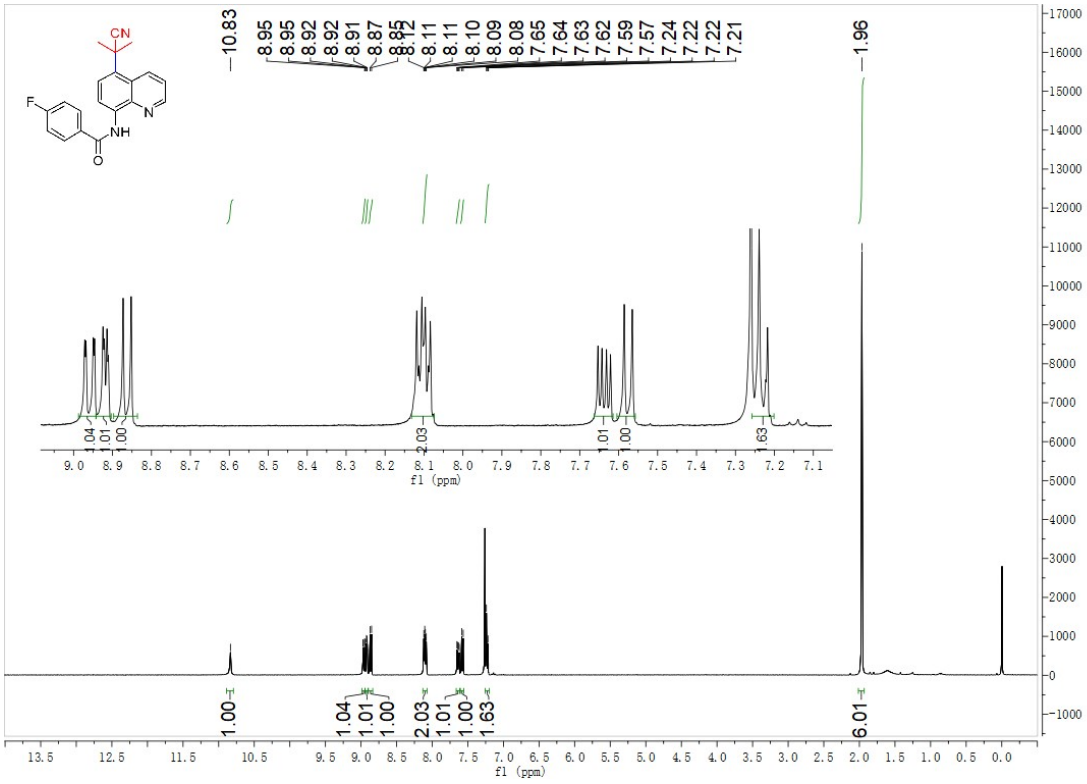

CN
NH
O
N
165.56
147.88
142.59
139.58
135.36
133.22
132.09
129.55
129.53
127.34
125.32
124.83
124.24
121.56
115.30
33.91
28.90
21.60
f1 (ppm)

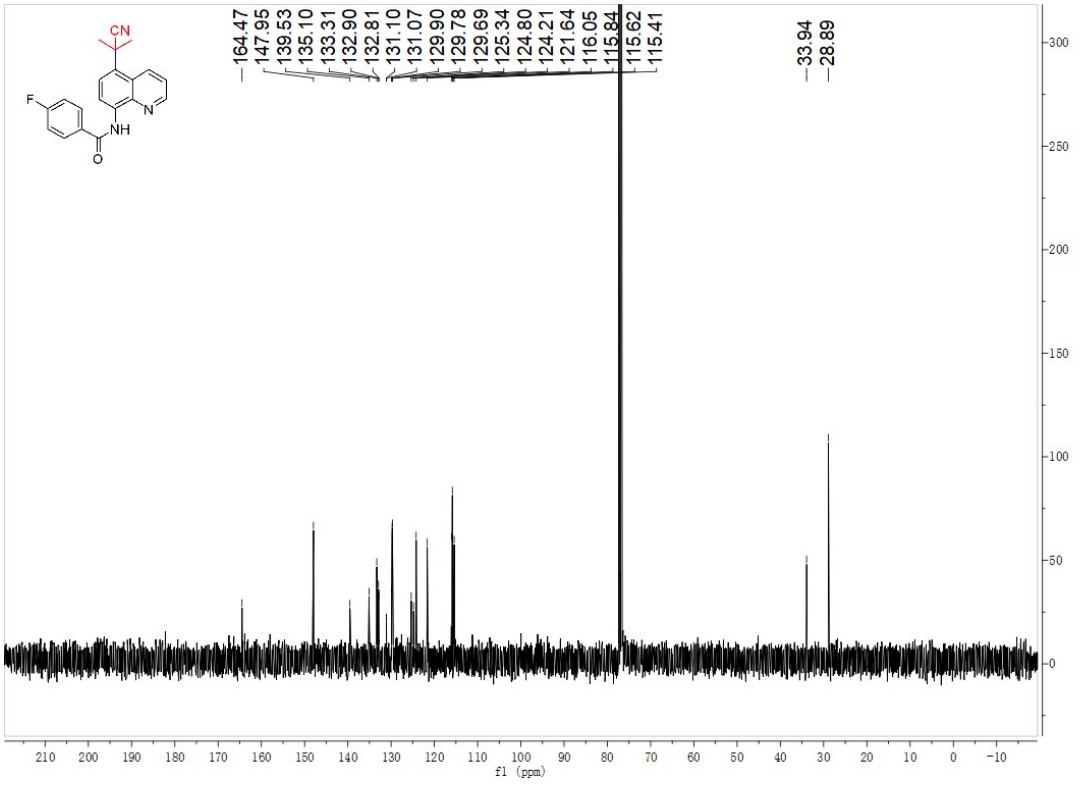
4g


CN
NH
O
N
10.85
8.95
8.93
8.91
8.90
8.88
8.02
8.00
7.63
7.62
7.61
7.60
7.57
7.55
7.39
7.37
2.78
2.76
2.74
2.72
1.95
1.31
1.29
1.28
1.03
0.99
1.04
2.00
1.03
1.01
2.01
f1 (ppm)
1.00
1.03
0.99
1.04
2.00
1.03
1.01
2.01
2.09
6.07
3.03
f1 (ppm)

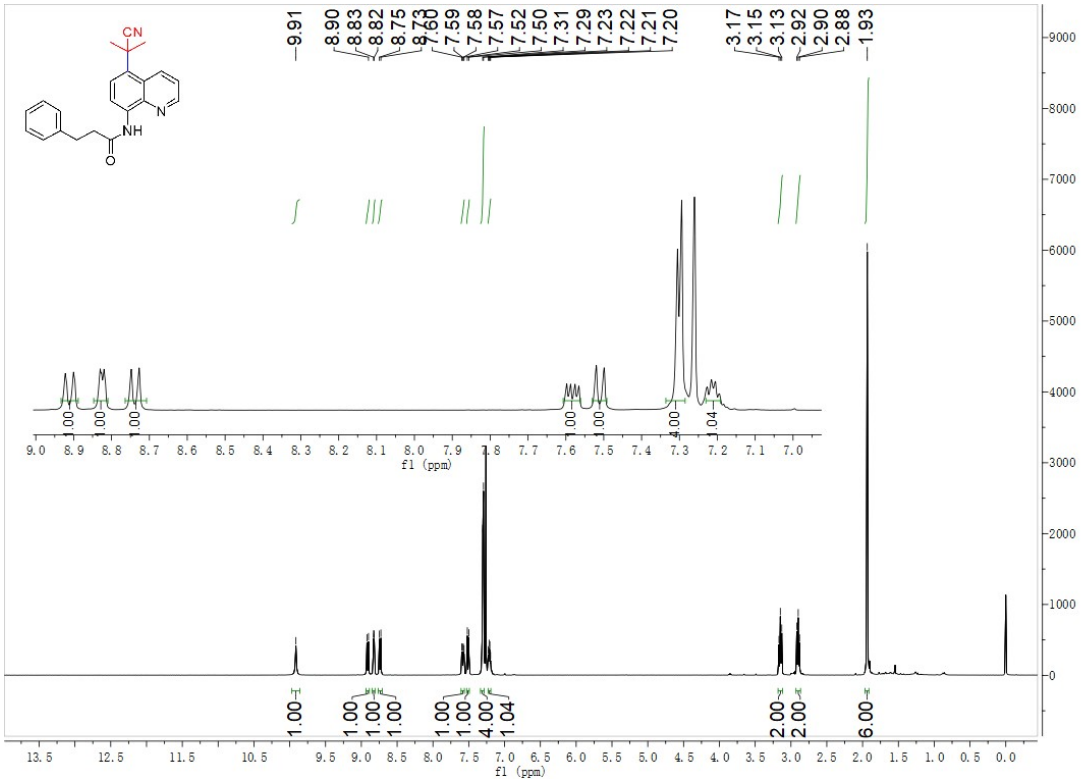

CN
NH
O
N
176.81
137.47
135.34
129.63
128.33
127.56
125.22
124.79
123.72
122.79
122.73
122.50
121.43
119.10
28.98
27.29
25.14
23.39
f1 (ppm)

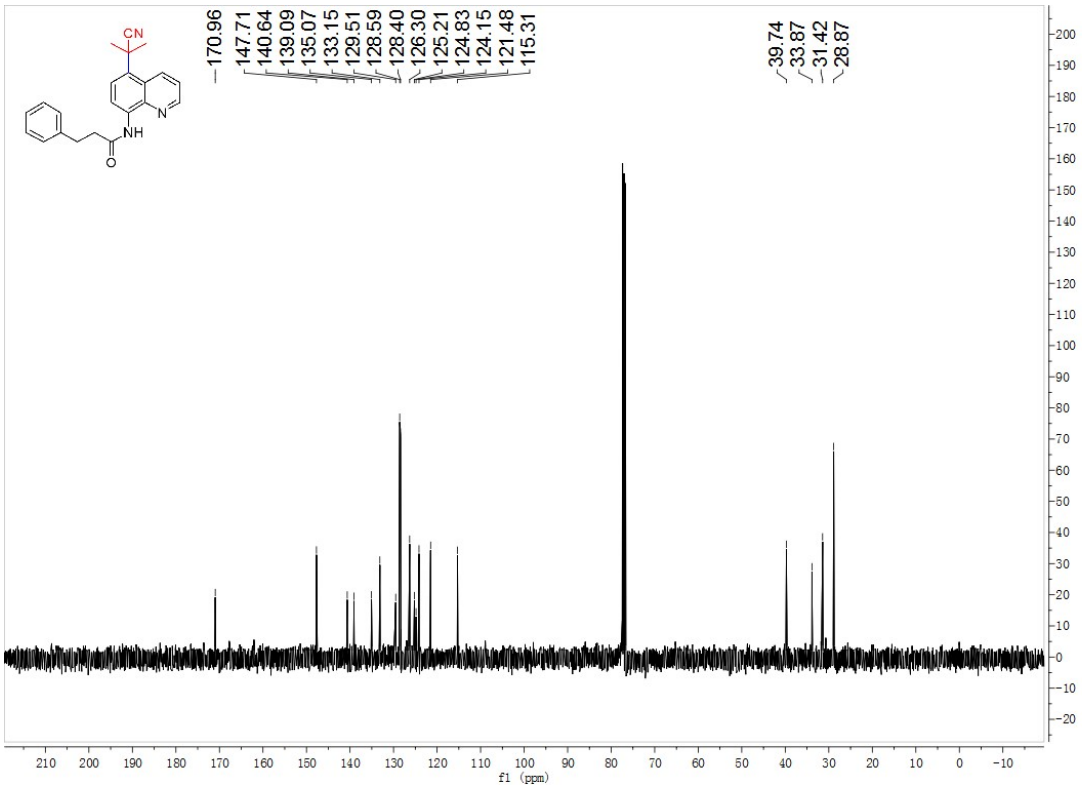
4h


CN
F
NH
O
N
10.83
8.95
8.95
8.92
8.92
8.91
8.87
8.85
8.12
8.11
8.11
8.10
8.09
8.08
7.65
7.64
7.63
7.62
7.59
7.57
7.24
7.22
7.22
7.21
1.96
1.04
1.01
1.00
2.03
1.01
1.00
1.63
6.01
f1 (ppm)

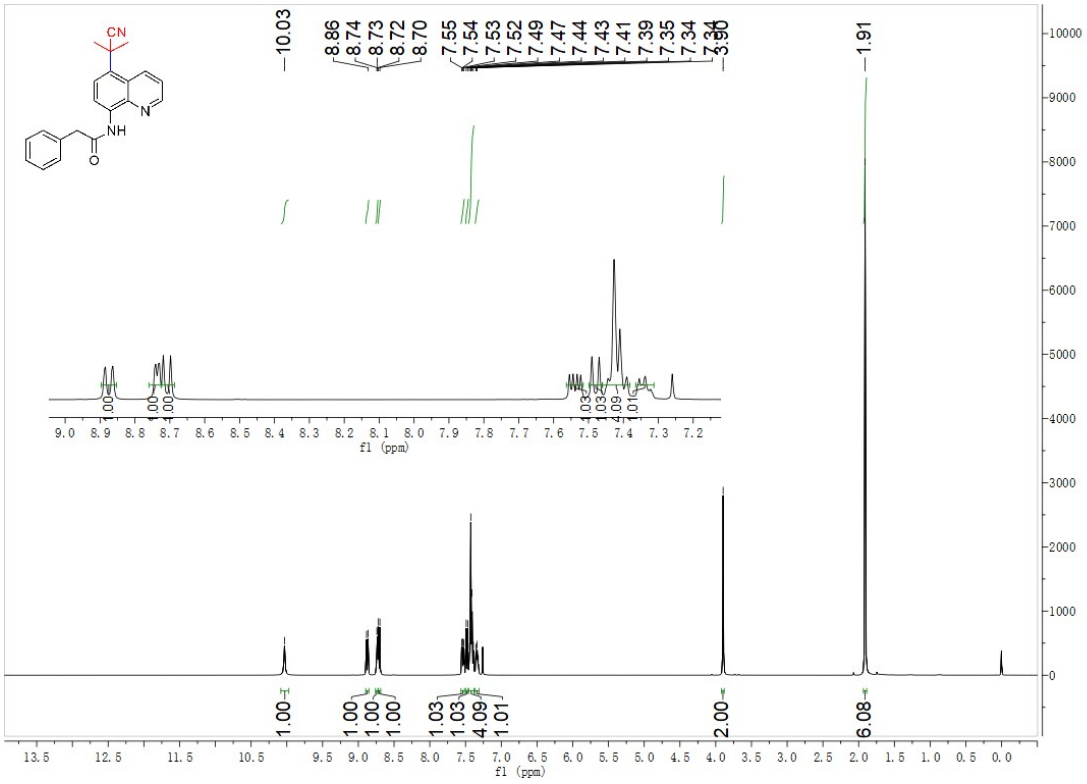

CN
F
NH
O
N
164.47
147.95
139.53
135.10
133.31
132.90
132.81
131.10
131.07
129.90
129.78
129.69
125.34
124.80
124.21
121.64
116.05
115.84
115.62
115.41
33.94
28.89
f1 (ppm)

4i


9.91
8.90
8.83
8.82
8.75
8.73
7.60
7.59
7.58
7.57
7.52
7.50
7.31
7.29
7.23
7.22
7.21
7.20
3.17
3.15
3.13
2.92
2.90
2.88
1.93
CN
NH
O
N
f1 (ppm)


170.96
147.71
140.64
139.09
135.07
133.15
129.51
128.59
128.40
126.30
125.21
124.83
124.15
121.48
115.31
39.74
33.87
31.42
28.87
CN
NH
O
N
f1 (ppm)

4j


CN
N
NH
O
10.03
8.86
8.74
8.73
8.72
8.70
7.55
7.54
7.53
7.52
7.49
7.47
7.44
7.43
7.41
7.39
7.35
7.34
7.34
7.30
1.91
1.00
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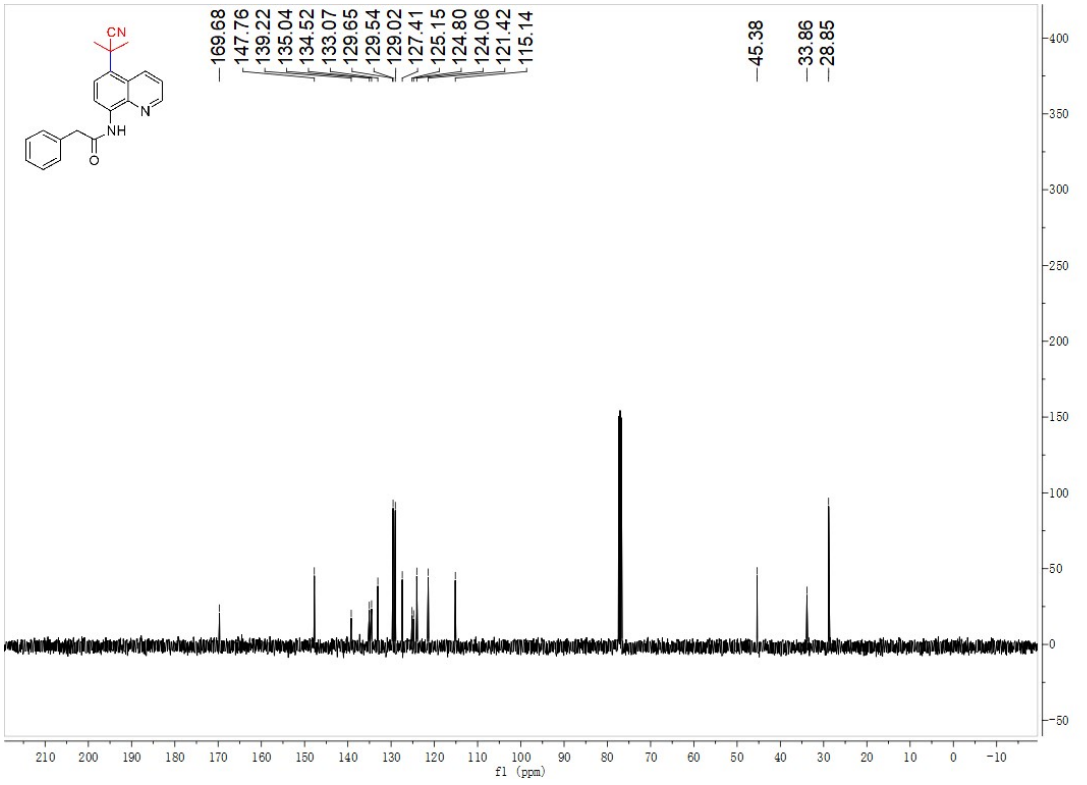
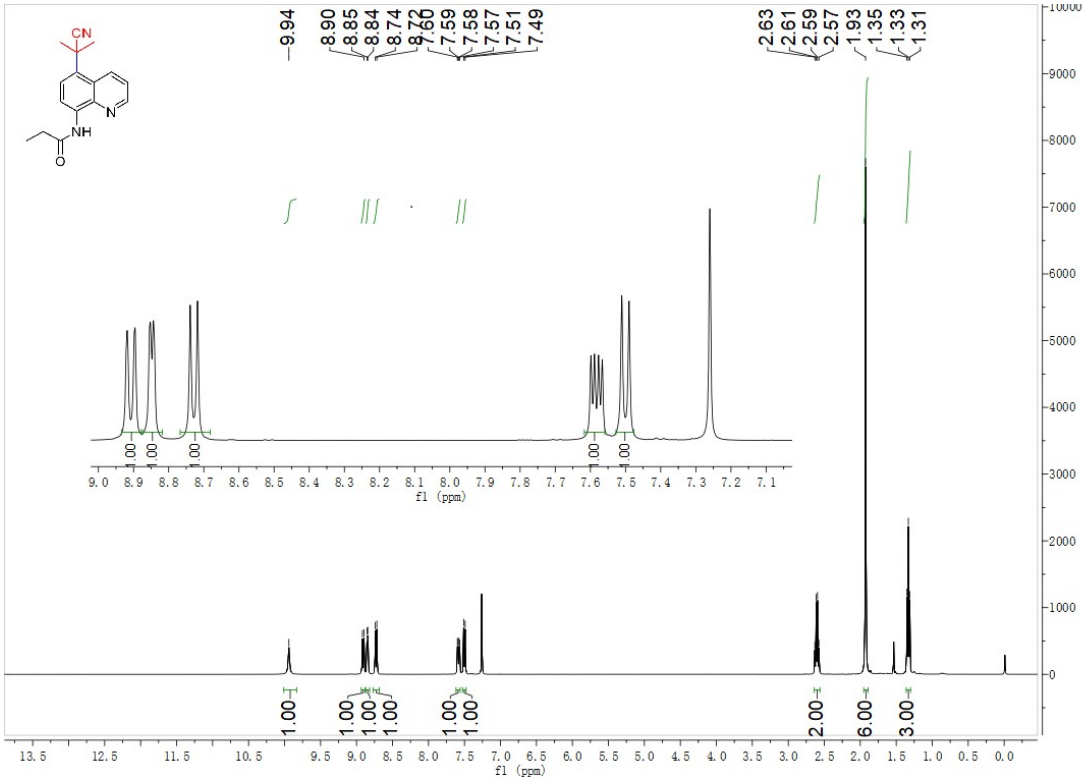
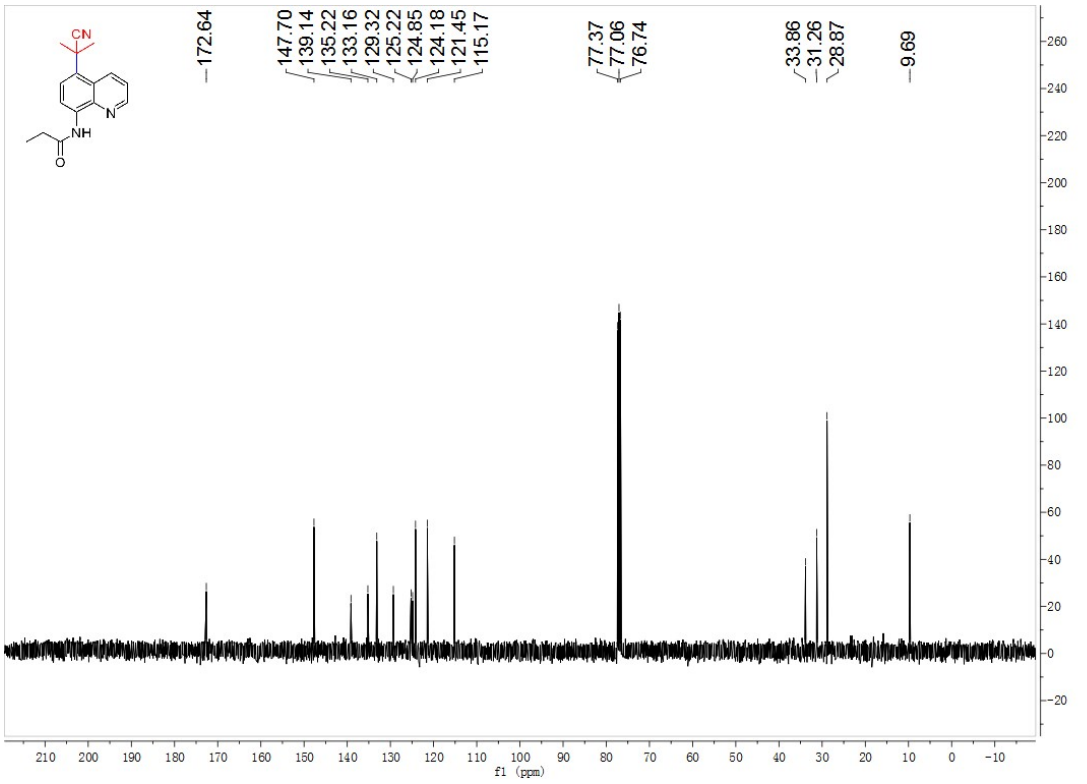
1.00
1.00
1.03
1.03
4.09
1.01
2.00
6.08
f1 (ppm)

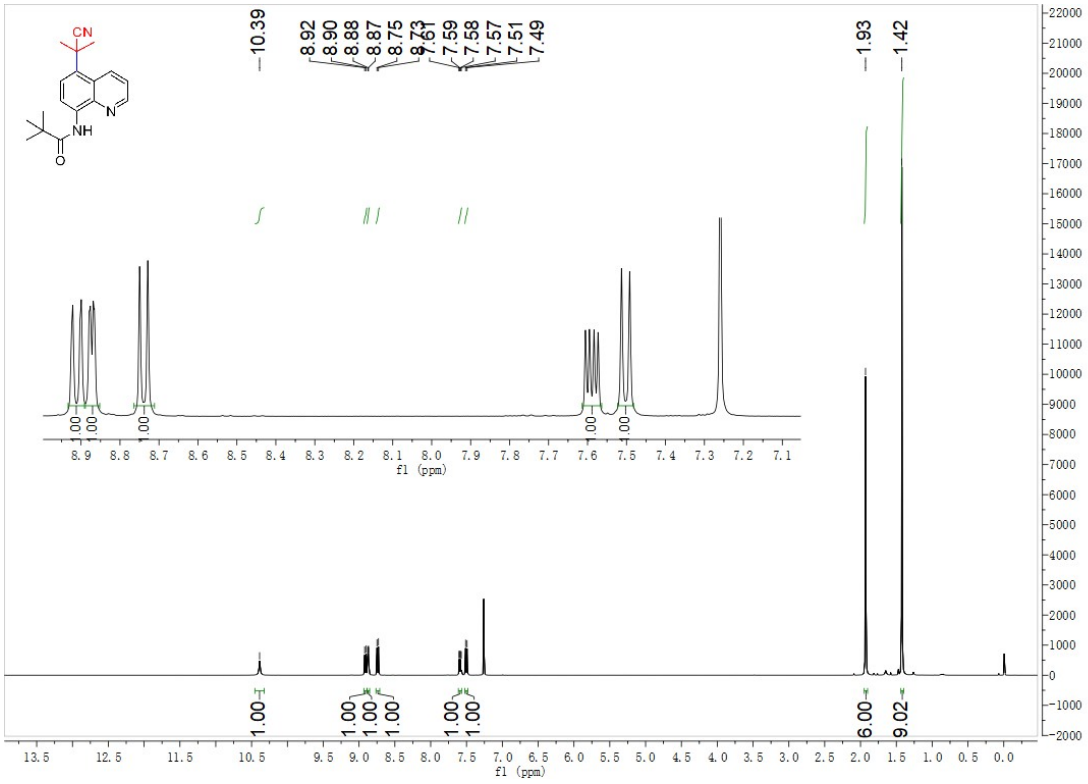

CN
N
NH
O
169.68
147.76
139.22
135.04
134.52
133.07
129.65
129.54
129.02
127.41
125.15
124.80
124.06
121.42
115.14
45.38
33.86
28.85
f1 (ppm)

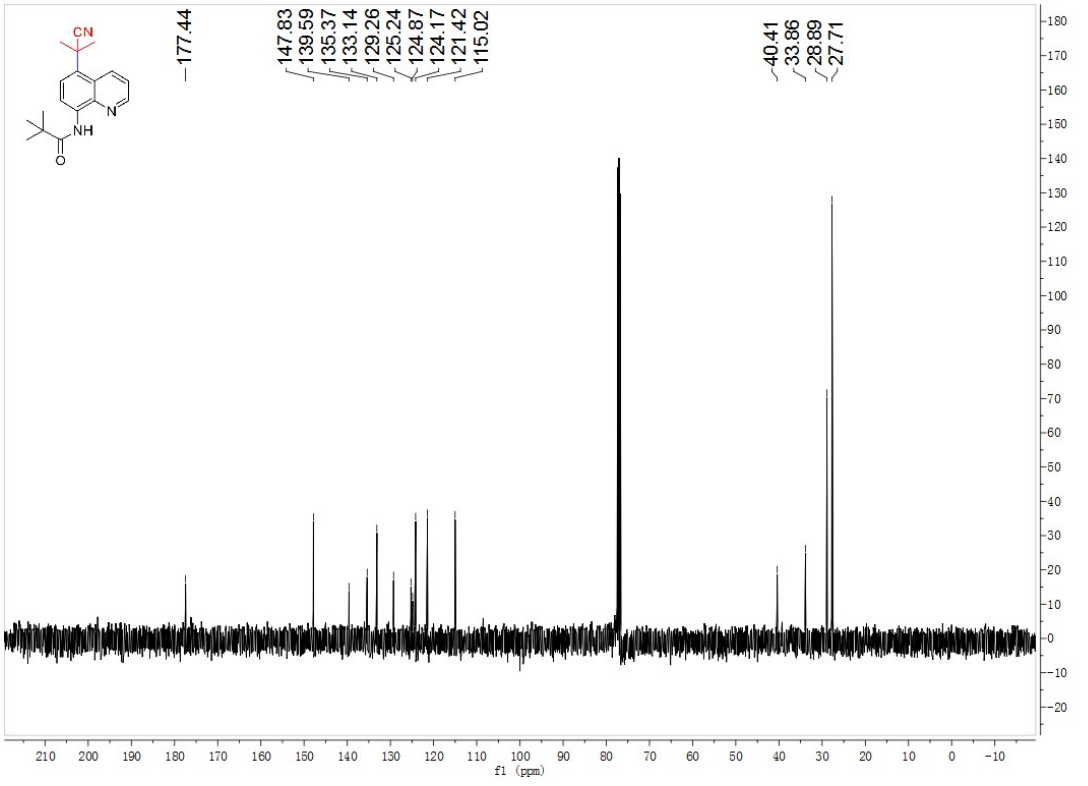
4k


9.94
8.90
8.85
8.84
8.74
8.72
7.60
7.59
7.58
7.57
7.51
7.49
2.63
2.61
2.59
2.57
1.93
1.35
1.33
1.31
f1 (ppm)

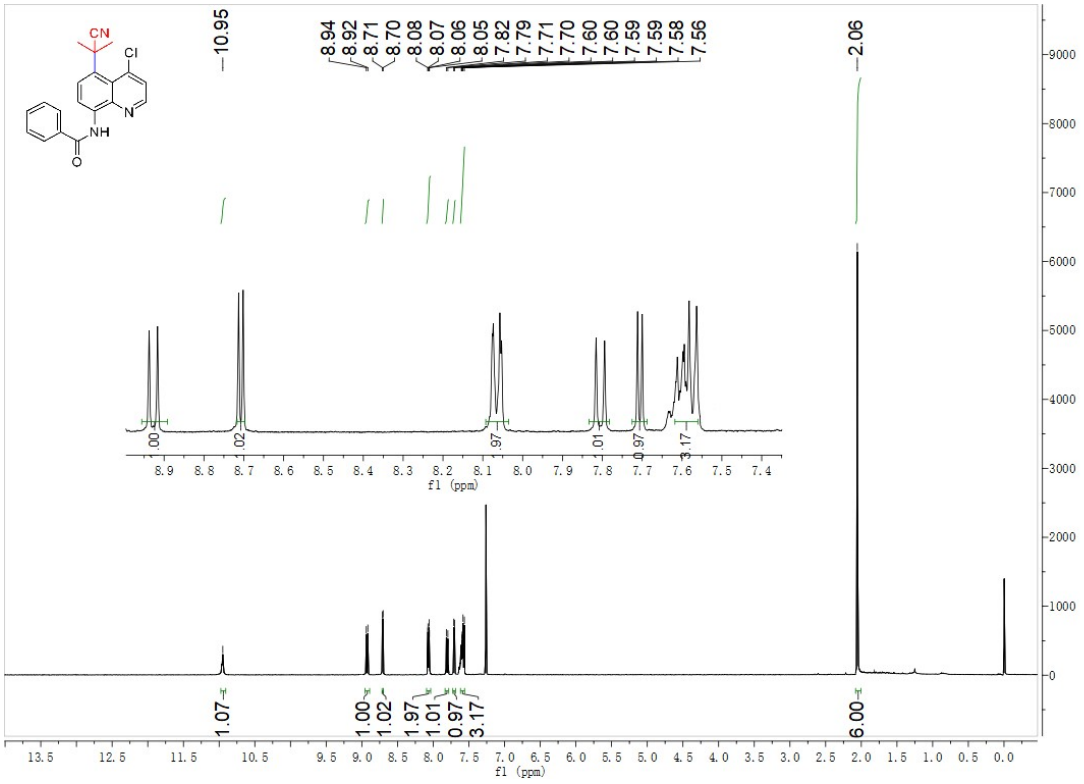

172.64
147.70
139.14
135.22
133.16
129.32
125.22
124.85
124.18
121.45
115.17
77.37
77.06
76.74
33.86
31.26
28.87
9.69
f1 (ppm)

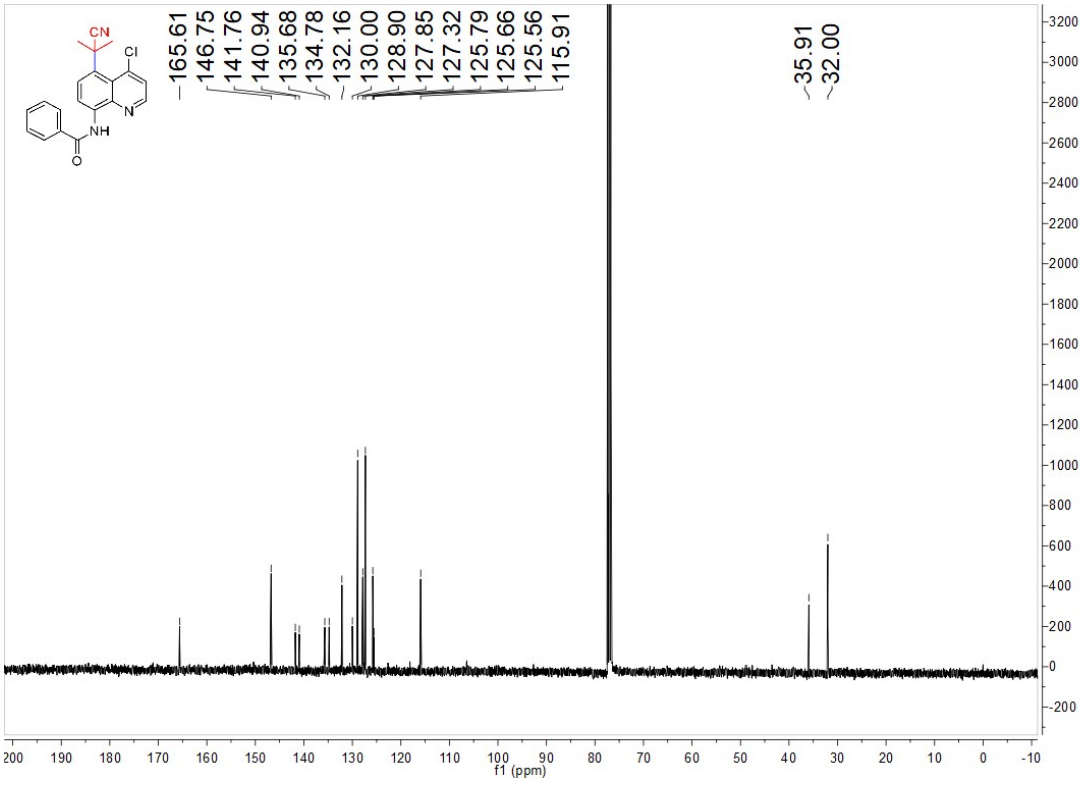
4l


CN
NH
O
N
10.39
8.92
8.90
8.88
8.87
8.75
8.73
7.61
7.59
7.58
7.57
7.51
7.49
1.93
1.42
1.00
1.00
1.00
1.00
1.00
1.00
6.00
9.02
f1 (ppm)

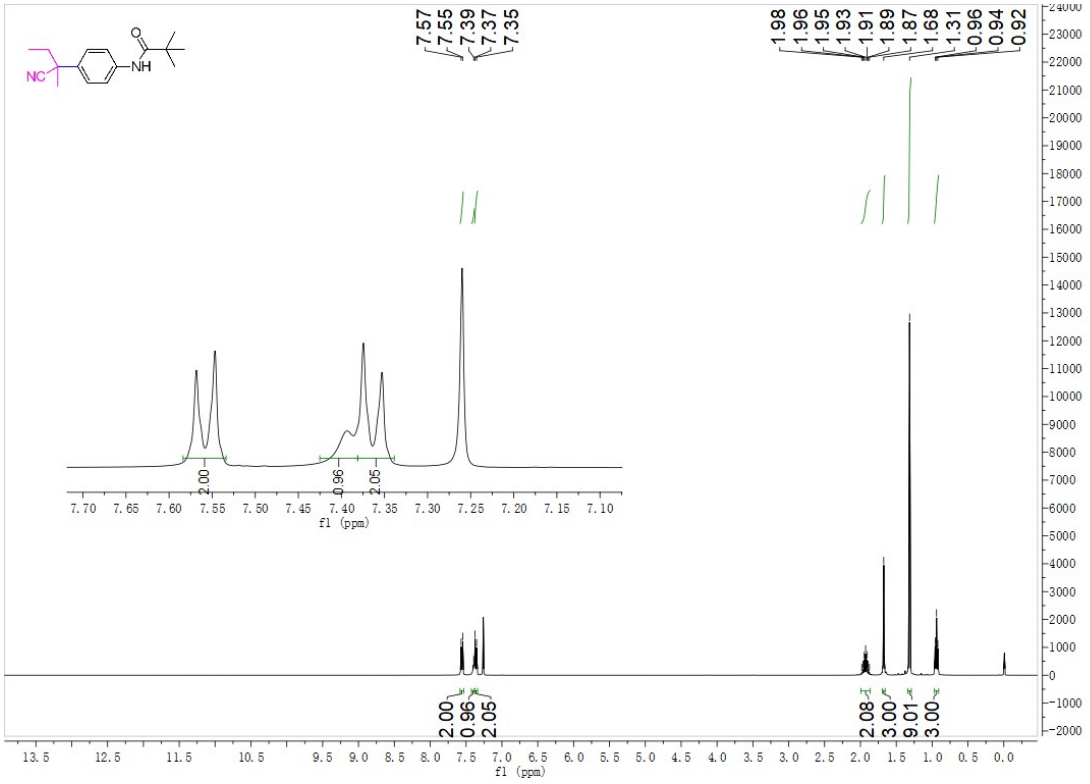

CN
NH
O
N
177.44
147.83
139.59
135.37
133.14
129.26
125.24
124.87
124.17
121.42
115.02
40.41
33.86
28.89
27.71
f1 (ppm)

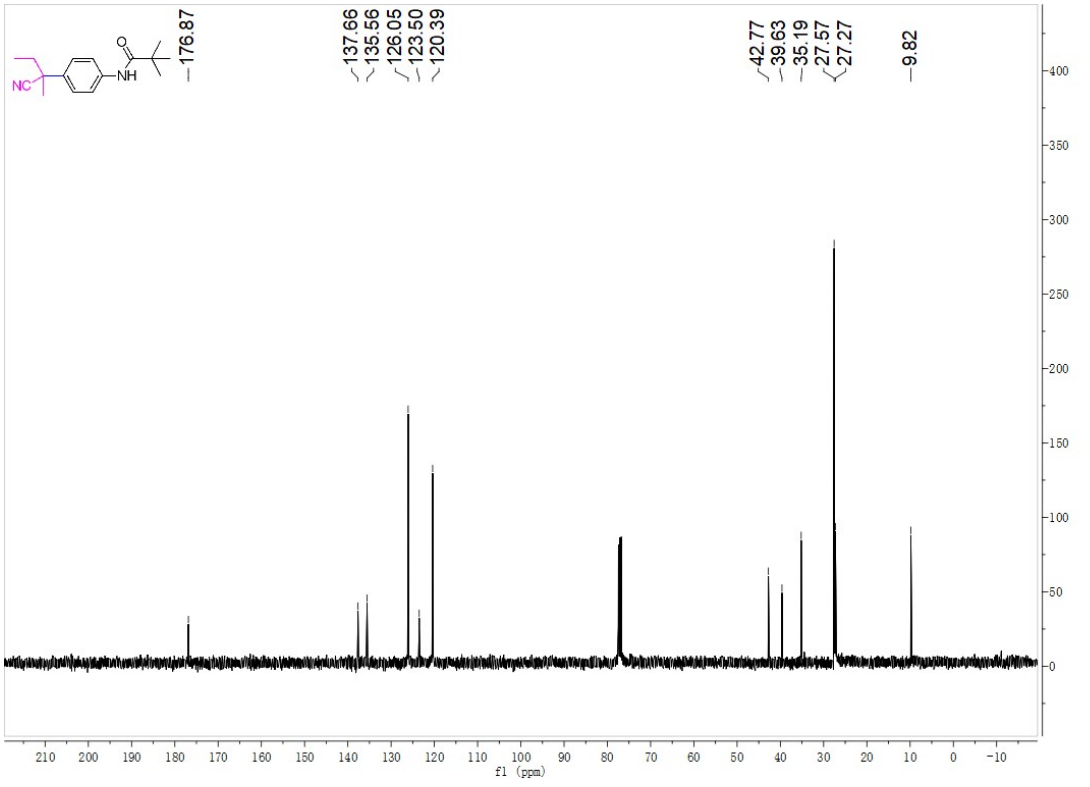
4m


CN
Cl
N
NH
O
10.95
8.94
8.92
8.71
8.70
8.08
8.07
8.06
8.05
7.82
7.79
7.71
7.70
7.60
7.59
7.59
7.58
7.56
2.06
f1 (ppm)
1.07
1.00
1.02
1.97
1.01
0.97
3.17
6.00

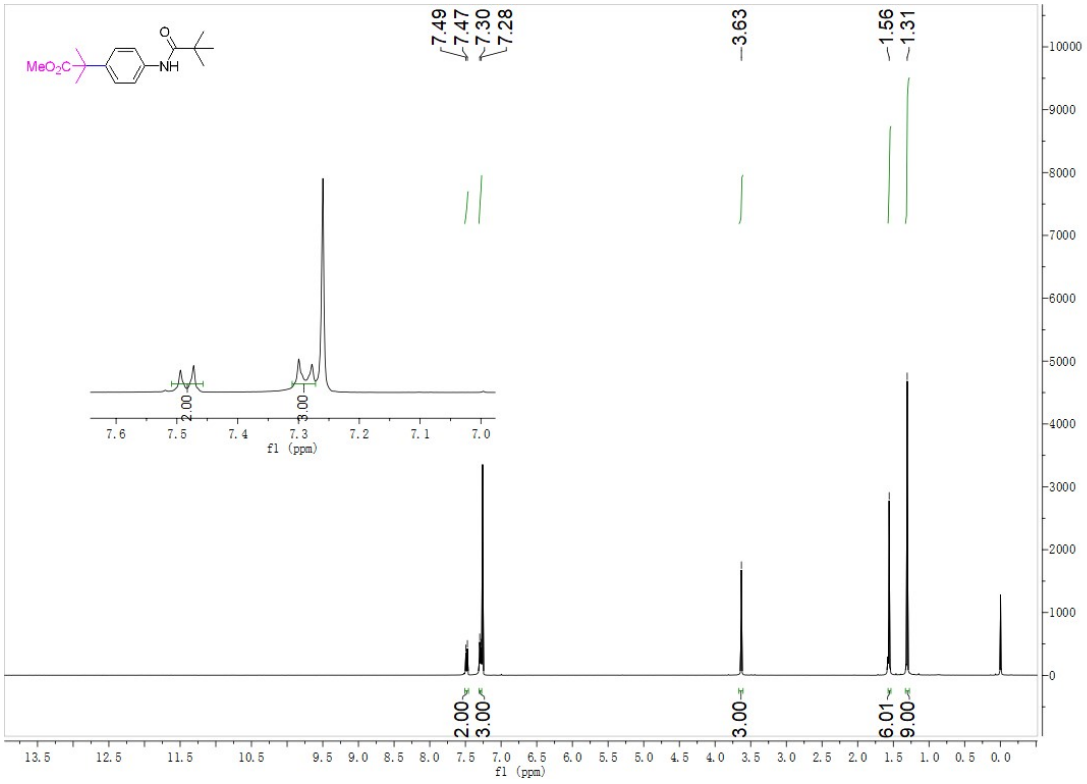

CN
Cl
N
NH
O
165.61
146.75
141.76
140.94
135.68
134.78
132.16
130.00
128.90
127.85
127.32
125.79
125.66
125.56
115.91
35.91
32.00
f1 (ppm)

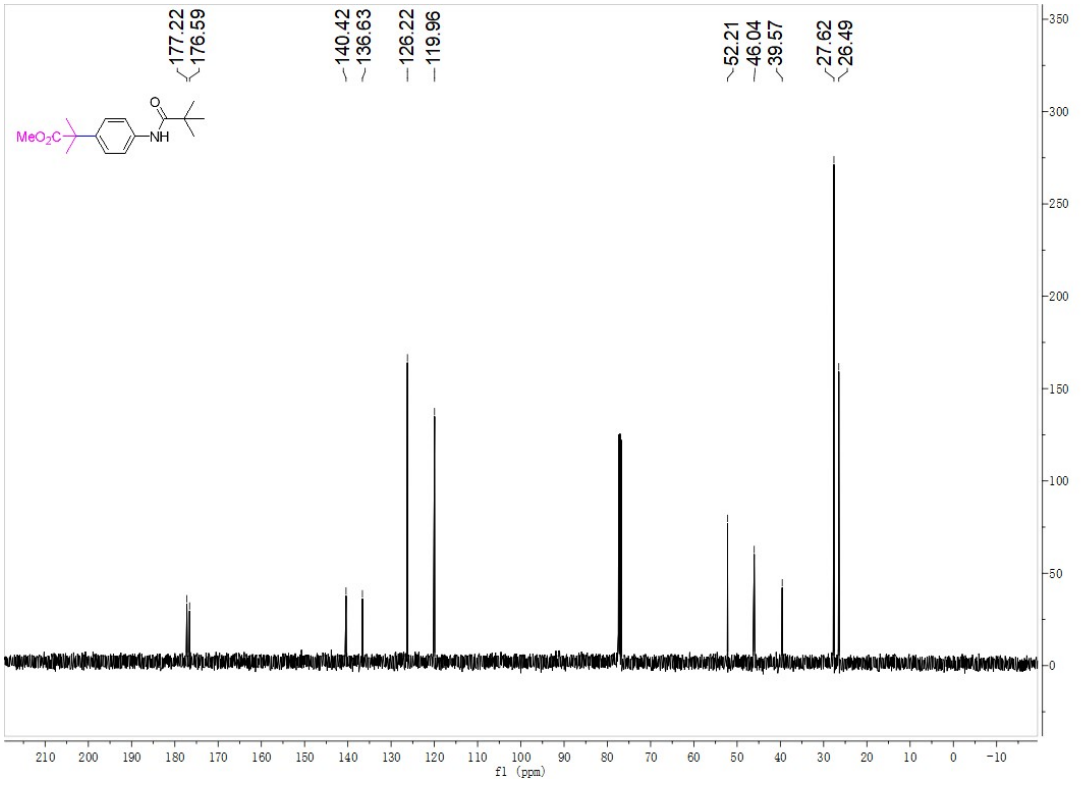
2aa


7.57
7.55
7.39
7.37
7.35
1.98
1.96
1.95
1.93
1.91
1.89
1.87
1.68
1.31
0.96
0.94
0.92
2.00
0.96
2.05
2.08
3.00
9.01
3.00
f1 (ppm)

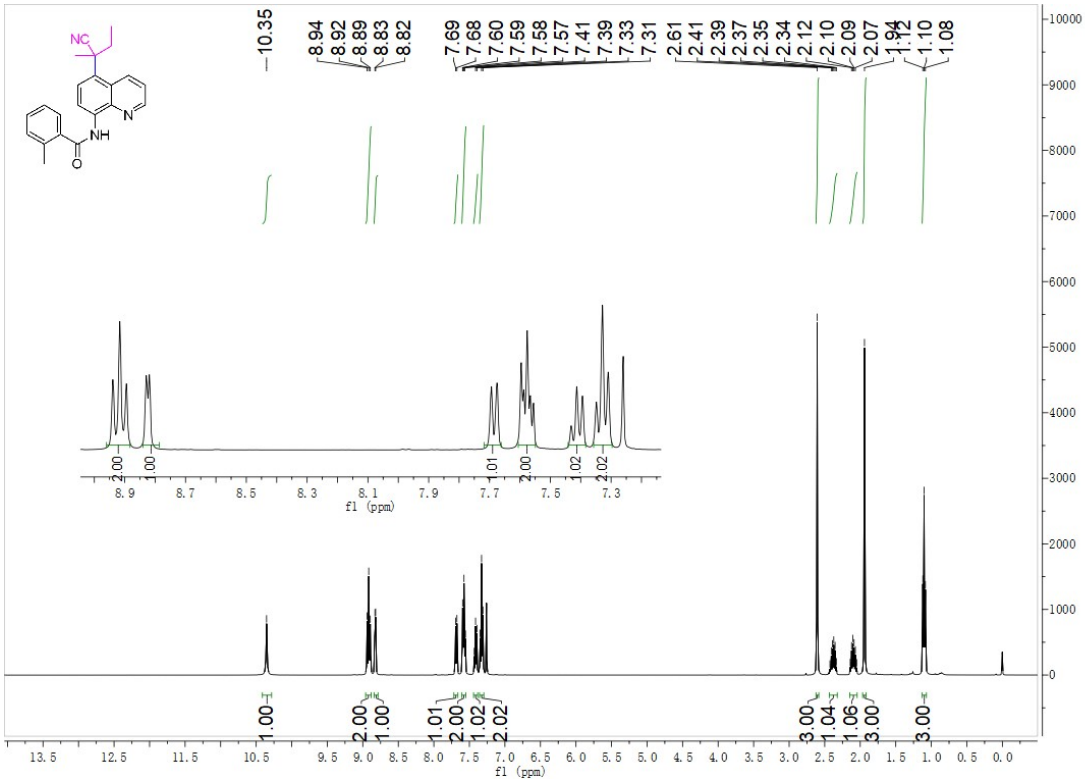

176.87
137.66
135.56
126.05
123.50
120.39
42.77
39.63
35.19
27.57
27.27
9.82
f1 (ppm)

2ab


7.49
7.47
7.30
7.28
3.63
1.56
1.31
MeO2C
NH
2.00
3.00
f1 (ppm)
2.00
3.00
6.01
9.00


177.22
176.59
140.42
136.63
126.22
119.96
52.21
46.04
39.57
27.62
26.49
MeO2C
NH
f1 (ppm)

4ba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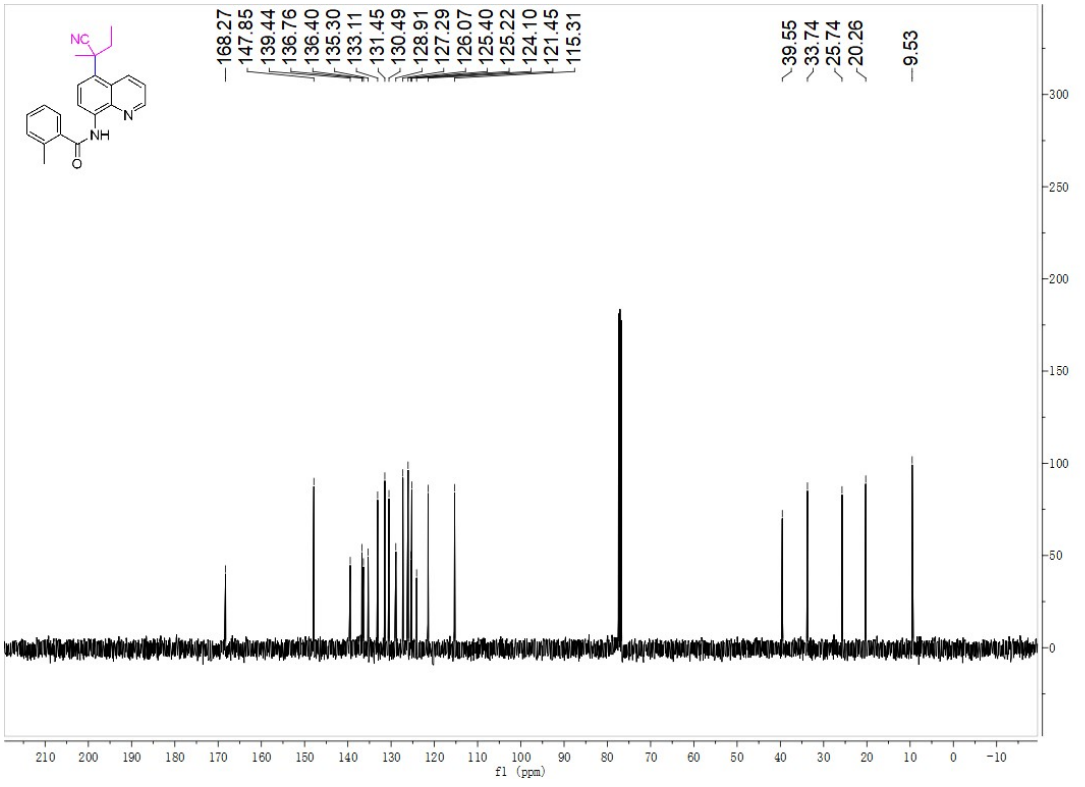
8.94
8.92
8.89
8.83
8.82
7.69
7.68
7.60
7.59
7.58
7.57
7.41
7.39
7.33
7.31
2.61
2.41
2.39
2.37
2.35
2.34
2.12
2.10
2.09
2.07
1.94
1.12
1.10
1.08
f1 (ppm)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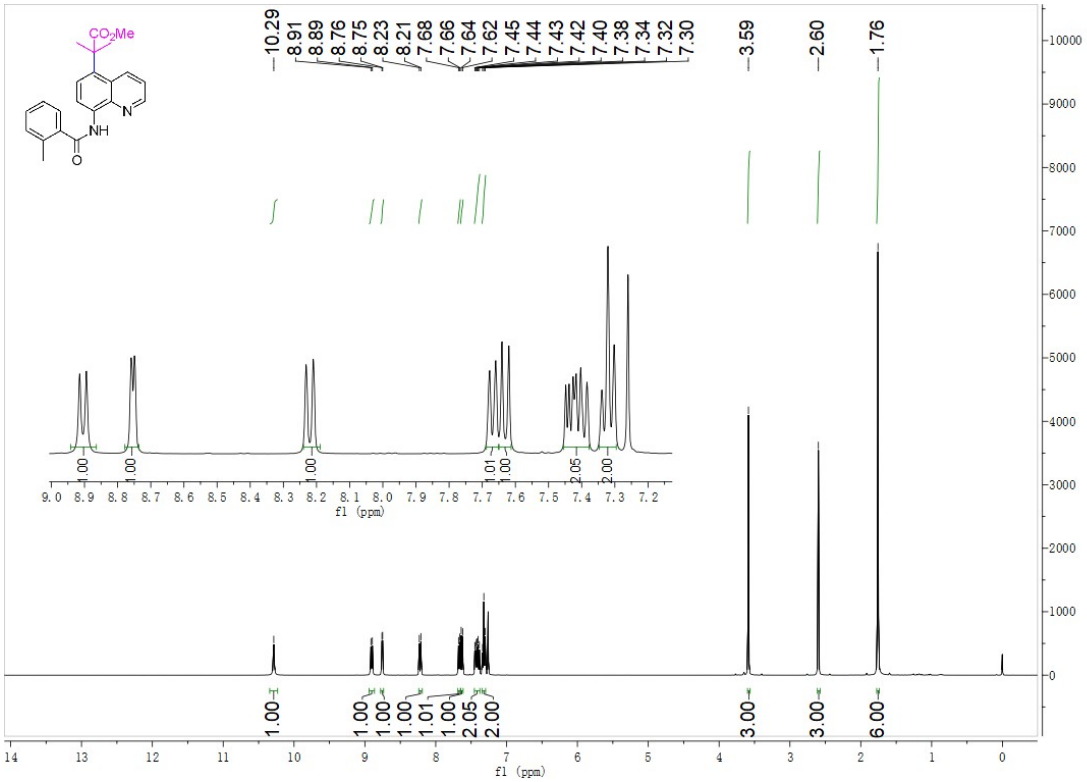
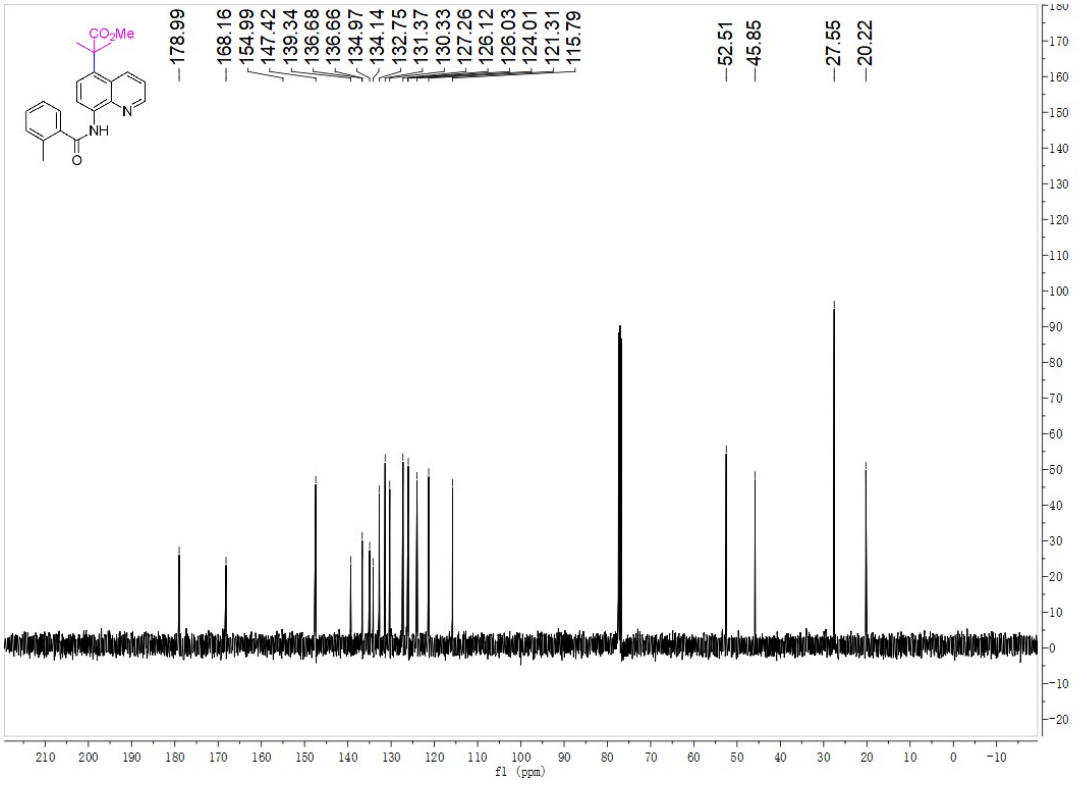
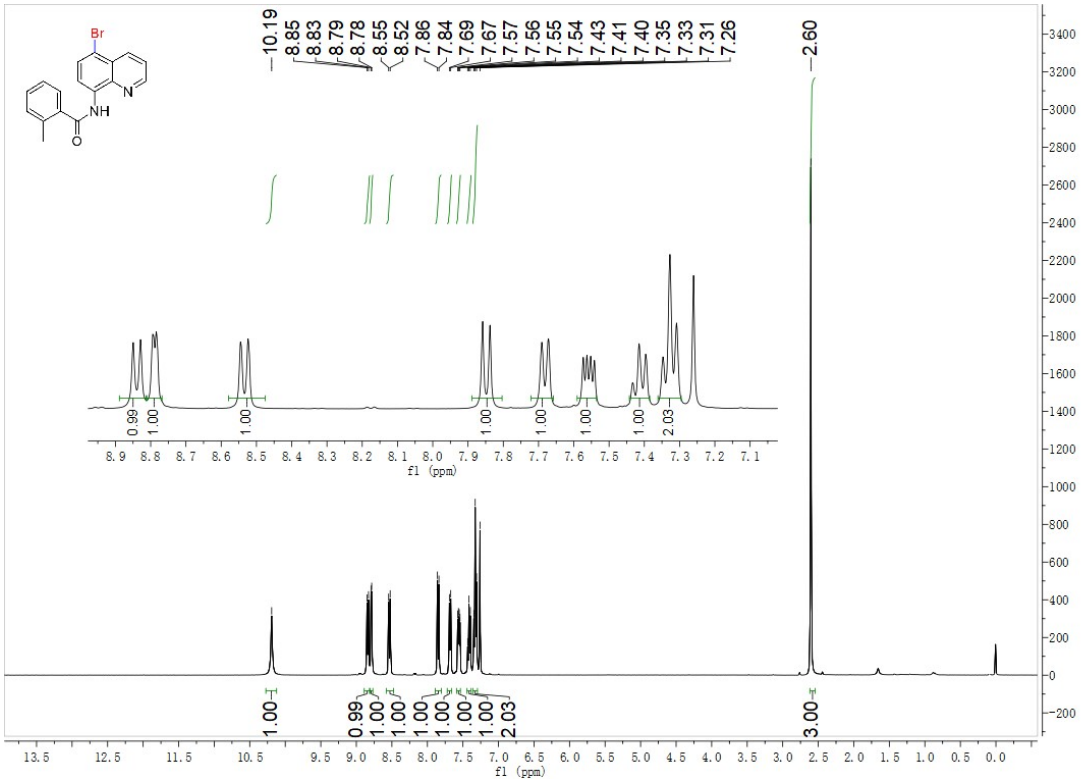
147.85
139.44
136.76
136.40
135.30
133.11
131.45
130.49
128.91
127.29
126.07
125.40
125.22
124.10
121.45
115.31
39.55
33.74
25.74
20.26
9.53
f1 (ppm)

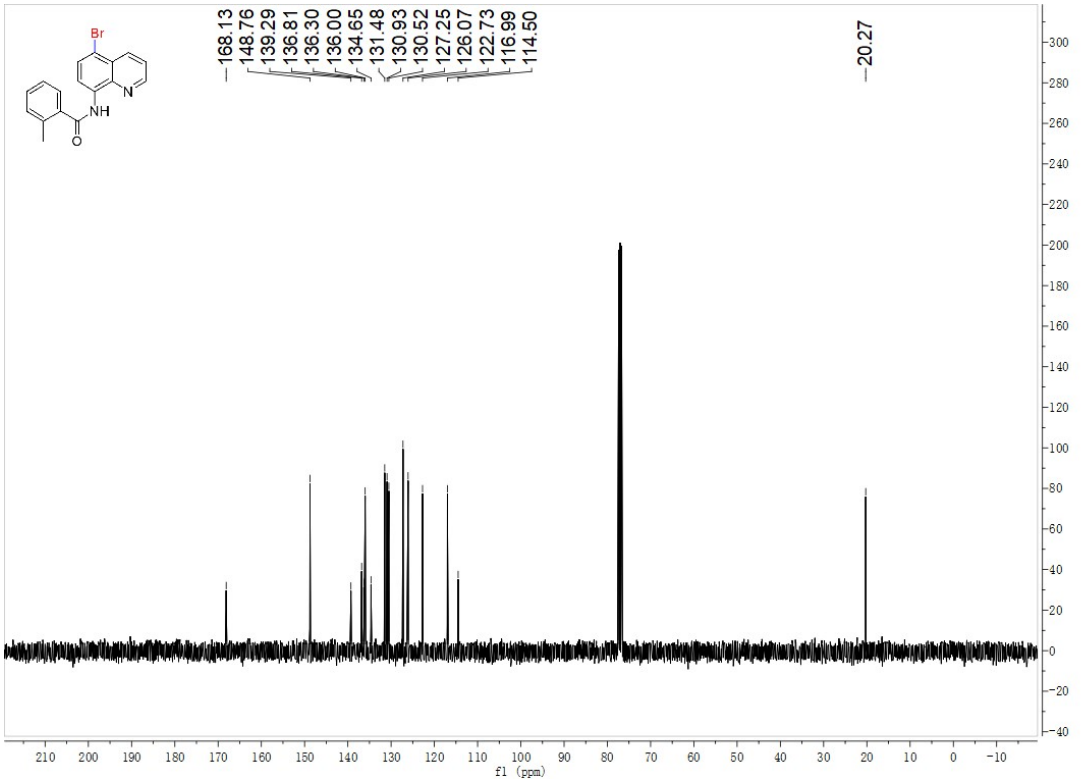
4bb


10.29
8.91
8.89
8.76
8.75
8.23
8.21
7.68
7.66
7.64
7.62
7.45
7.44
7.43
7.42
7.40
7.38
7.34
7.32
7.30
3.59
2.60
1.76
f1 (ppm)

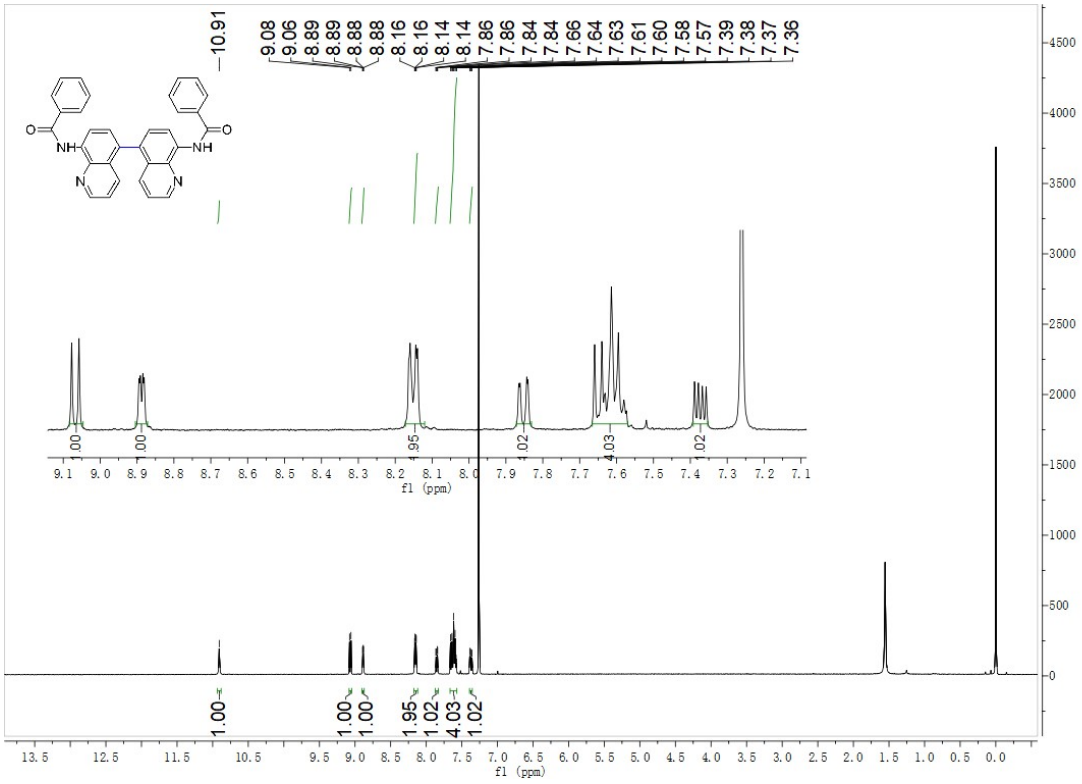

178.99
168.16
154.99
147.42
139.34
136.68
136.66
134.97
134.14
132.75
131.37
130.33
127.26
126.12
126.03
124.01
121.31
115.79
52.51
45.85
27.55
20.22
f1 (ppm)

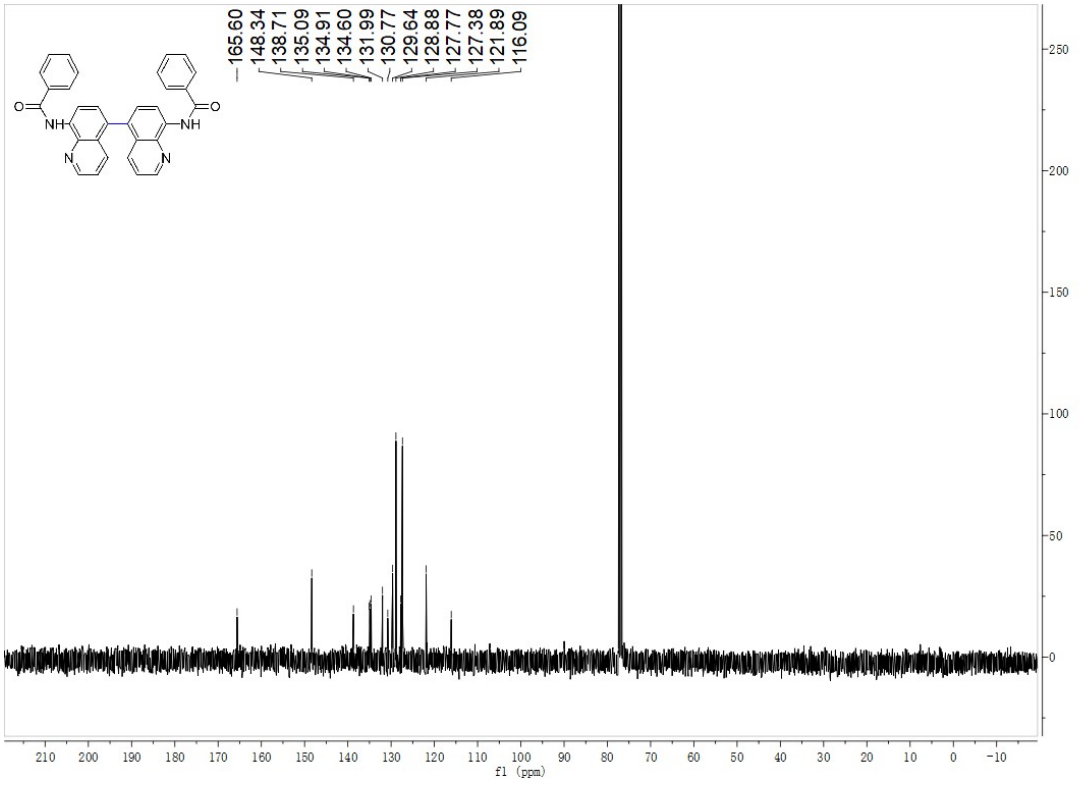
8b


Br
NH
O
N
10.19
8.85
8.83
8.79
8.78
8.55
8.52
7.86
7.84
7.69
7.67
7.57
7.56
7.55
7.54
7.43
7.41
7.40
7.35
7.33
7.31
7.26
2.60
0.99
1.00
1.00
1.00
1.00
1.00
1.00
1.00
2.03
3.00
f1 (ppm)

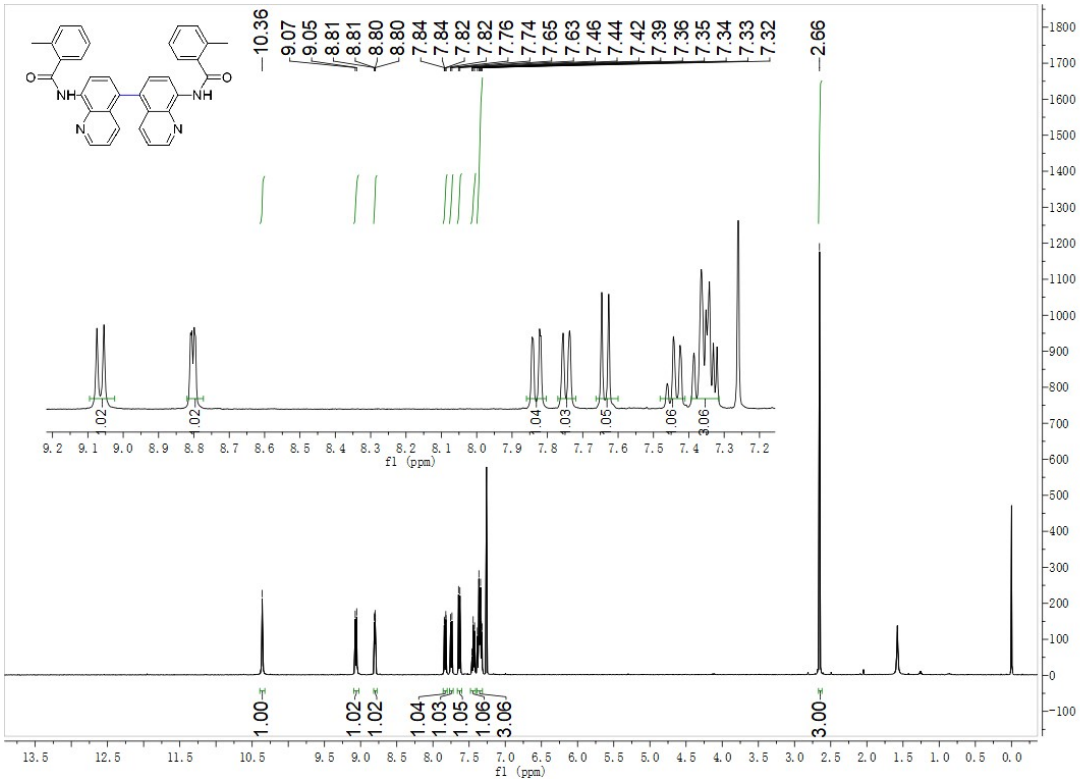

Br
NH
O
N
168.13
148.76
139.29
136.81
136.30
136.00
134.65
131.48
130.93
130.52
127.25
126.07
122.73
116.99
114.50
20.27
f1 (ppm)

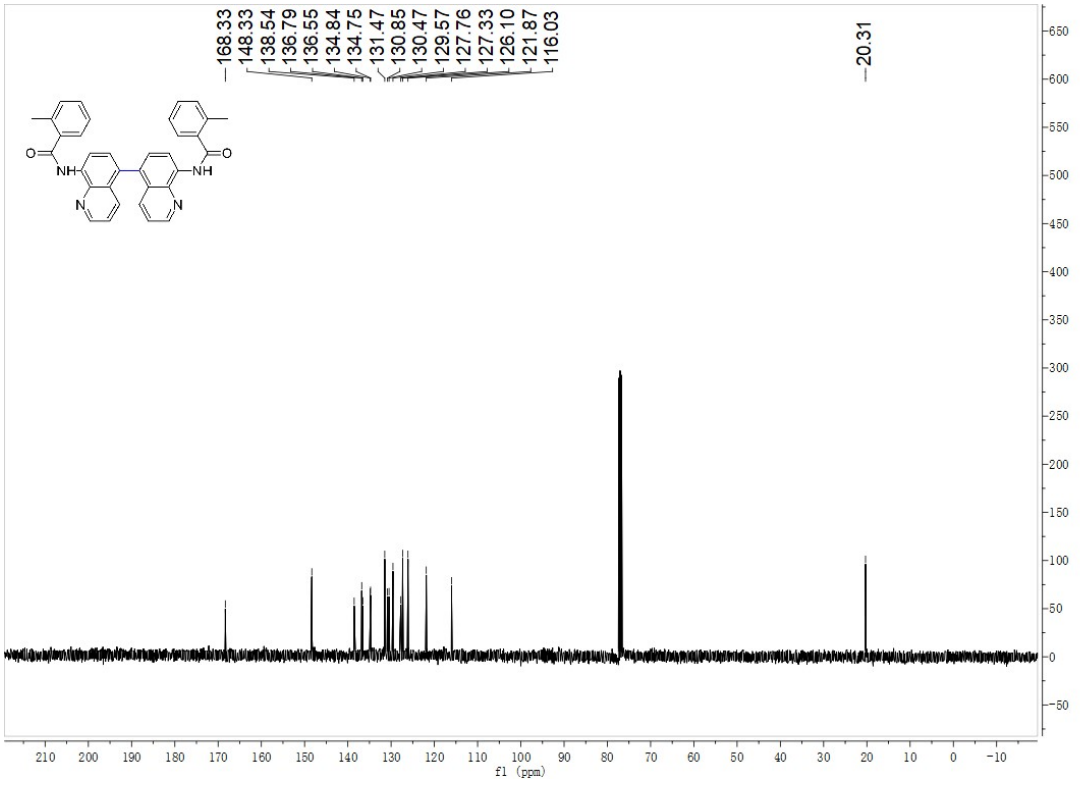
9a


10.91
9.08
9.06
8.89
8.89
8.88
8.88
8.16
8.16
8.14
8.14
7.86
7.86
7.84
7.84
7.66
7.64
7.63
7.61
7.60
7.58
7.57
7.39
7.38
7.37
7.36
NH
NH
N
N
1.00
1.00
1.95
1.02
4.03
1.02
f1 (ppm)

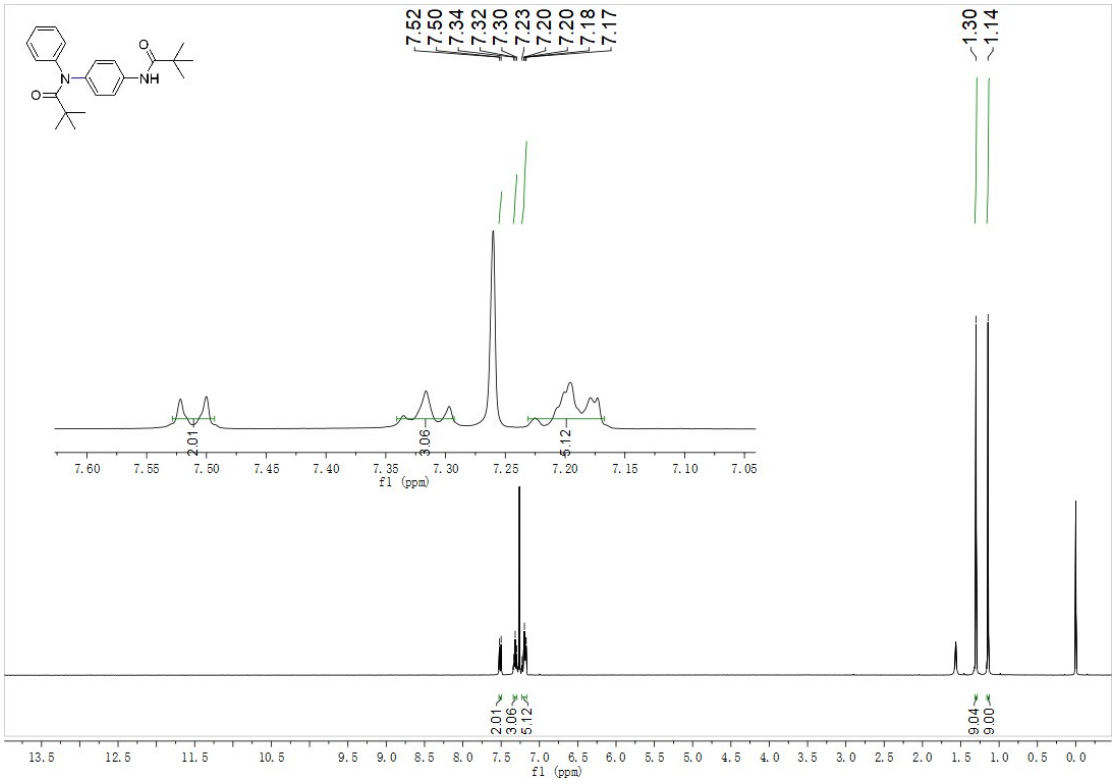

165.60
148.34
138.71
135.09
134.91
134.60
131.99
130.77
129.64
128.88
127.77
127.38
121.89
116.09
NH
NH
N
N
f1 (ppm)

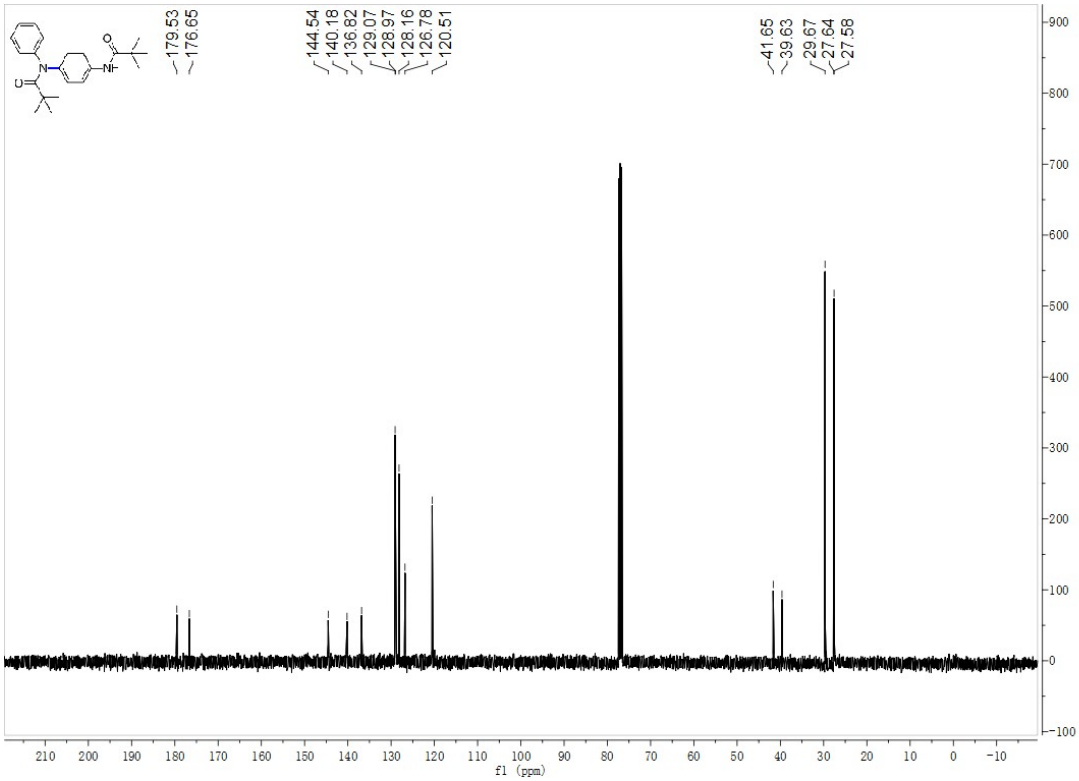
9b


10.36
9.07
9.05
8.81
8.81
8.80
8.80
7.84
7.84
7.82
7.82
7.76
7.74
7.65
7.63
7.46
7.44
7.42
7.39
7.36
7.35
7.34
7.33
7.32
2.66
1.00
1.02
1.02
1.04
1.03
1.05
1.06
3.06
3.00
f1 (ppm)

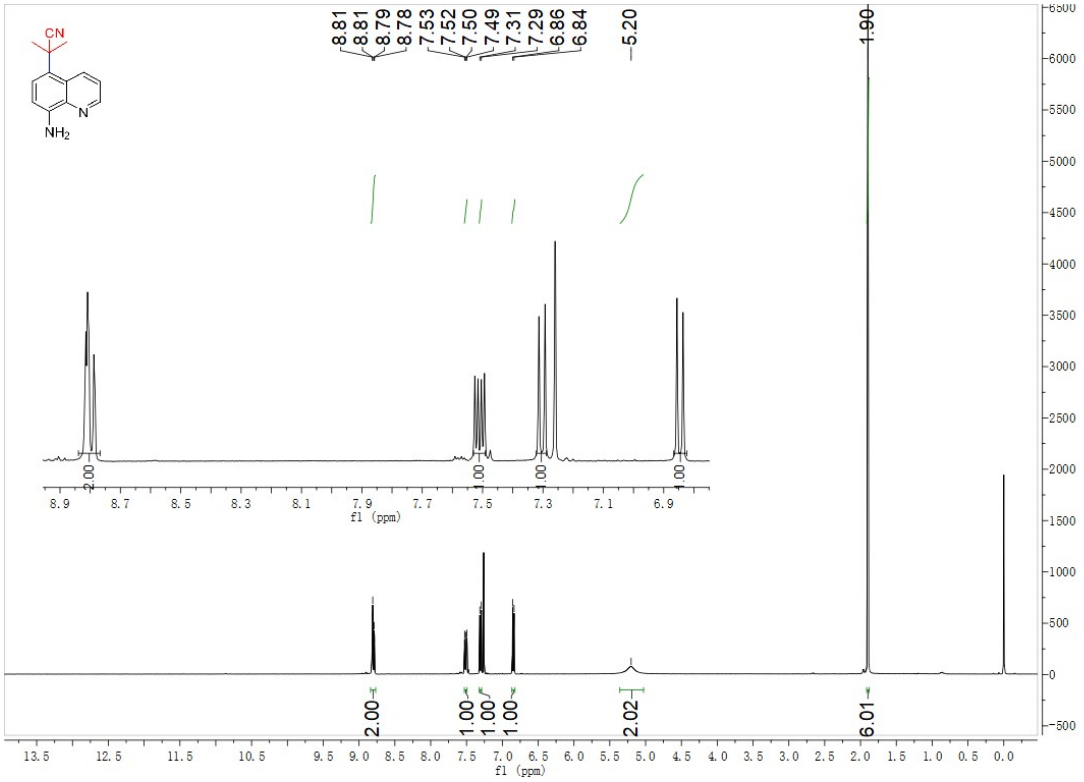

168.33
148.33
138.54
136.79
136.55
134.84
134.75
131.47
130.85
130.47
129.57
127.76
127.33
126.10
121.87
116.03
20.31
f1 (ppm)

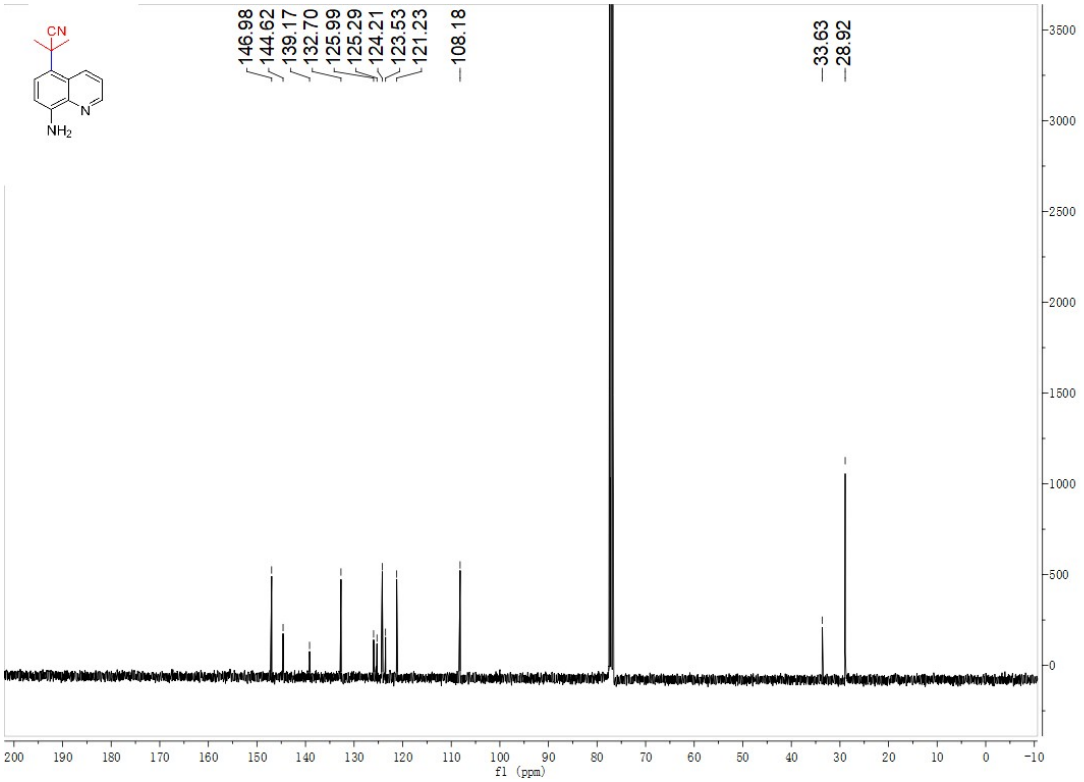
10


7.52
7.50
7.34
7.32
7.30
7.23
7.20
7.20
7.18
7.17
1.30
1.14
2.01
3.06
5.12
9.04
9.00
f1 (ppm)

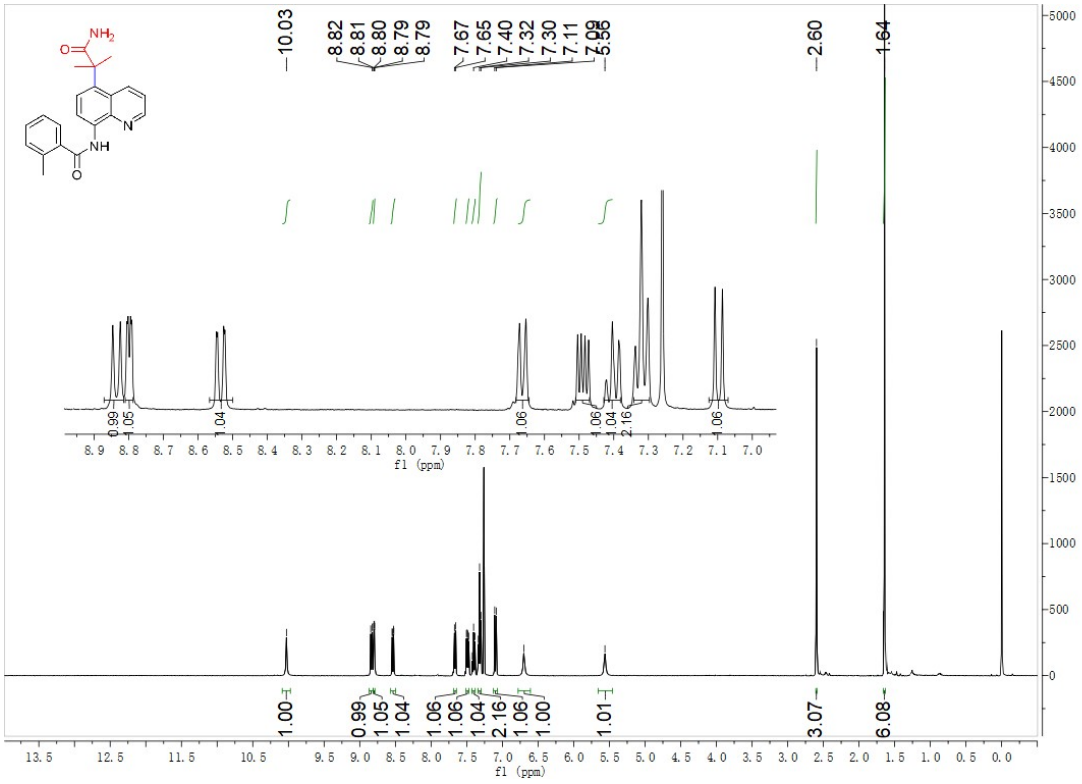

179.53
176.65
144.54
140.18
136.82
129.07
128.97
128.16
126.78
120.51
41.65
39.63
29.67
27.64
27.58
f1 (ppm)

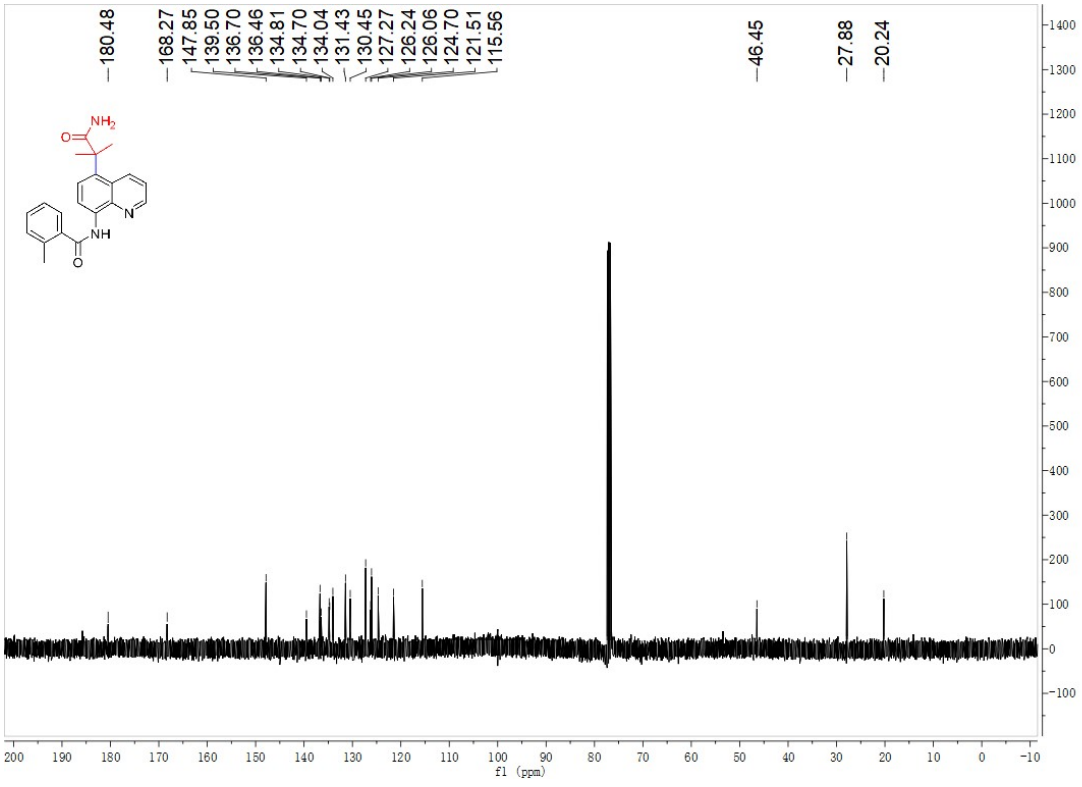
11


CN
NH2
8.81
8.81
8.79
8.78
7.53
7.52
7.50
7.49
7.31
7.29
6.86
6.84
5.20
1.90
2.00
1.00
1.00
1.00
2.02
6.01
f1 (ppm)

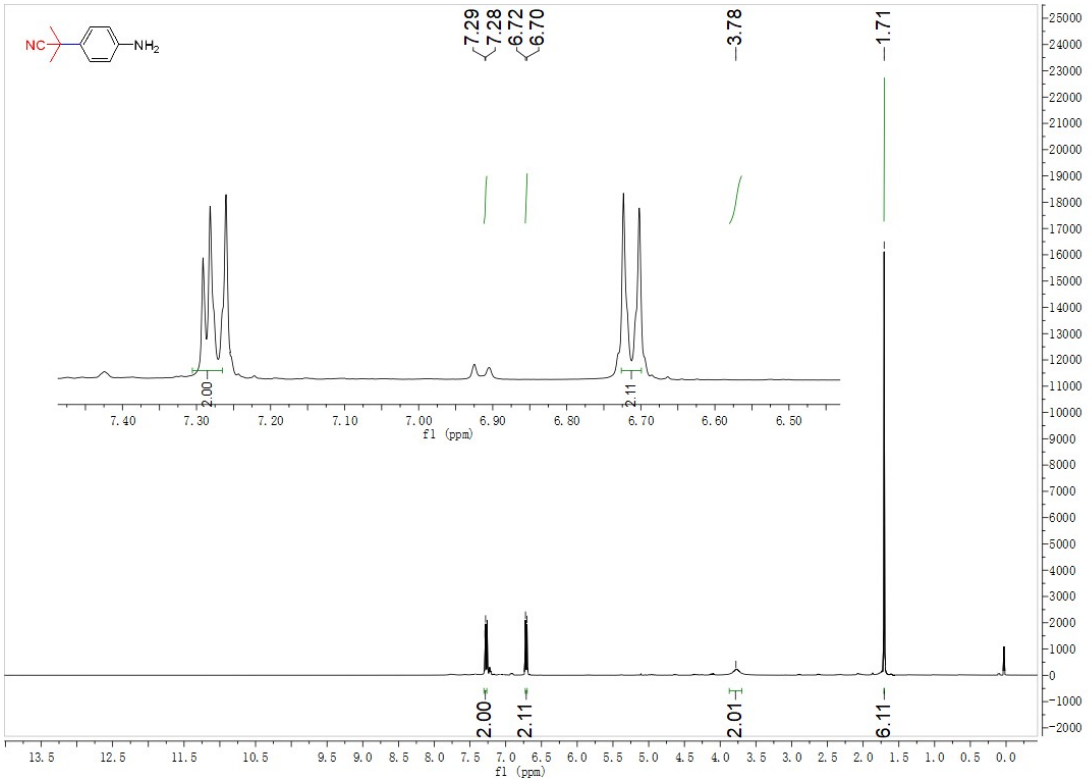

CN
NH2
146.98
144.62
139.17
132.70
125.99
125.29
124.21
123.53
121.23
108.18
33.63
28.92
f1 (ppm)

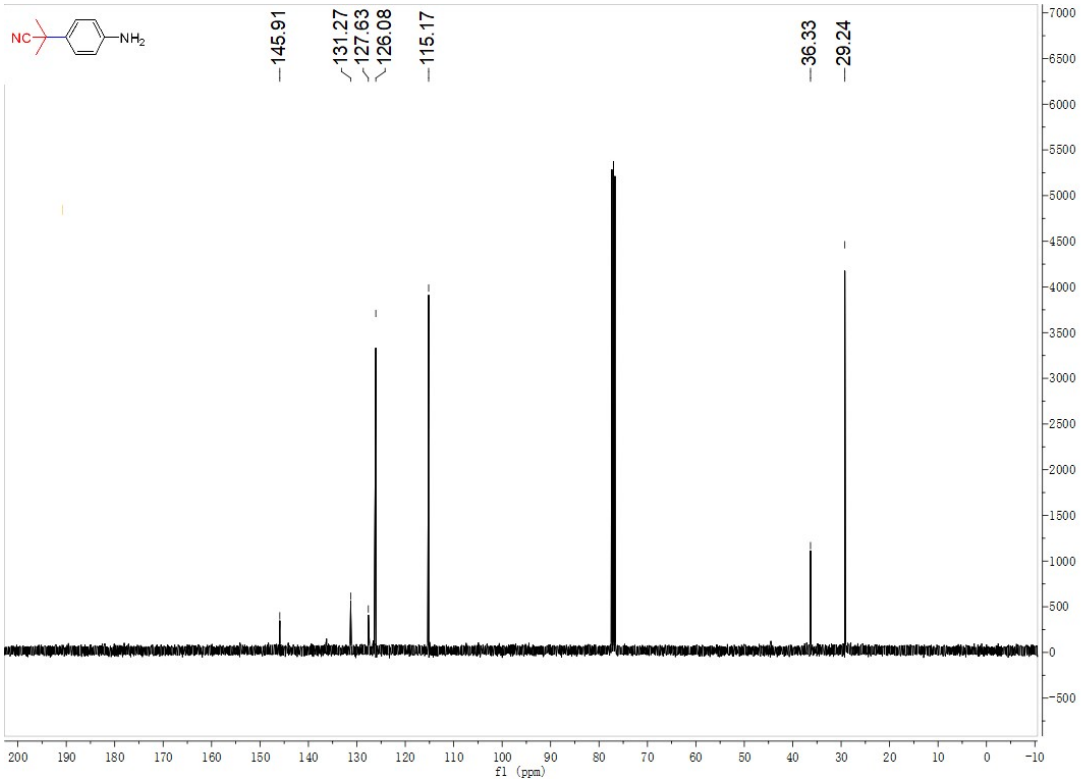
12


10.03
8.82
8.81
8.80
8.79
8.79
7.67
7.65
7.40
7.32
7.30
7.11
7.09
5.56
2.60
1.64
NH2
O
NH
O
N
f1 (ppm)


180.48
168.27
147.85
139.50
136.70
136.46
134.81
134.70
134.04
131.43
130.45
127.27
126.24
126.06
124.70
121.51
115.56
46.45
27.88
20.24
NH2
O
NH
O
N
f1 (ppm)

13


NC
NH2
7.29
7.28
6.72
6.70
3.78
1.71
2.00
2.11
2.01
6.11
f1 (ppm)


NC
NH2
145.91
131.27
127.63
126.08
115.17
36.33
29.24
f1 (ppm)

9. References

1. (a) G. Liao, H. M. Chen and B. F. Shi, *Chem Commun (Camb)*, 2018, **54**, 10859-10862; (b) L. D. Tran, J. Roane and O. Daugulis, *Angew Chem Int Ed Engl*, 2013, **52**, 6043-6046; (c) C. Wen, R. Zhong, Z. Qin, M. Zhao and J. Li, *Chem Commun (Camb)*, 2020, **56**, 9529-9532; (d) Y. Zhang, C. Wen and J. Li, *Org Biomol Chem*, 2018, **16**, 1912-1920.
2. (a) S. Mandal, T. Bera, G. Dubey, J. Saha and J. K. Laha, *ACS Catalysis*, 2018, **8**, 5085-5144; (b) H. Shen, Z. Liu, P. Zhang, X. Tan, Z. Zhang and C. Li, *J Am Chem Soc*, 2017, **139**, 9843-9846.
3. J. Xu, X. Zhu, G. Zhou, B. Ying, P. Ye, L. Su, C. Shen and P. Zhang, *Org Biomol Chem*, 2016, **14**, 3016-3021.
4. M. D. Reddy, F. R. Fronczek and E. B. Watkins, *Org Lett*, 2016, **18**, 5620-5623.
5. A. B. Viveki, D. N. Garad, R. G. Gonnade and S. B. Mhaske, *Chem Commun (Camb)*, 2020, **56**, 1565-1568.