Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Fe^{III}/ TBHP mediated remote C-O bond construction of 8-aminoquinolines: access to methoxylation and cyanomethoxylation

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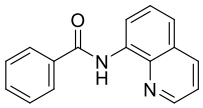
Contents

1. General information[1]

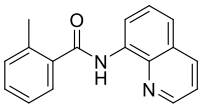
All reagents, starting materials, and solvents were purchased from commercial sources and used without treatment unless otherwise indicated. All the solvents were dried and newly distilled. NMR spectra were obtained on a Bruker AMX 400 system using chloroform-d as deuterated solvents. The ^{1}H-NMR spectra were recorded at 400 MHz in $CDCl_3$, and the ^{13}C-NMR spectra were recorded at 101 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 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.



1a



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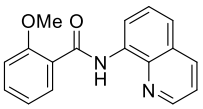

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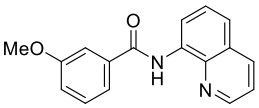

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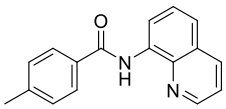

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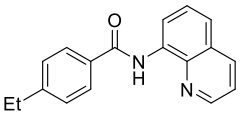

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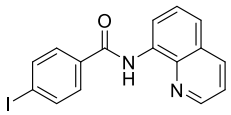

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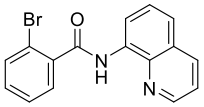

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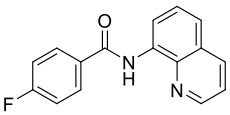

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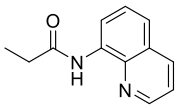

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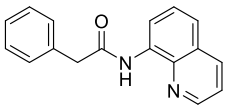

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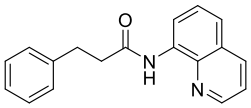

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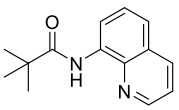

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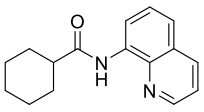

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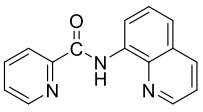

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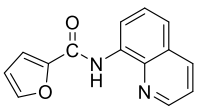

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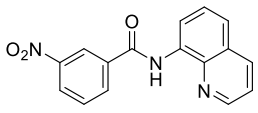

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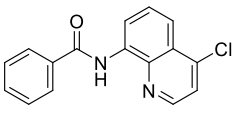

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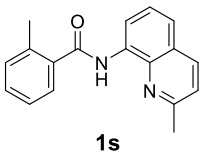


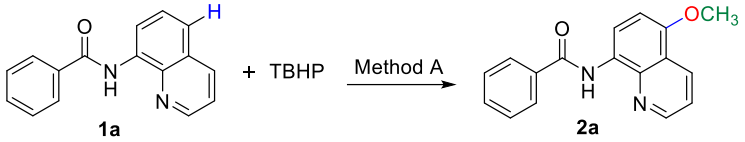
1s

[a] indolin-2-one **1r** and **1s** were purchased from *Energy Chemical.*

3. Experimental section

3.1 Optimization of reaction conditions

Table S1 Optimization for selective methoxylation reaction of 8-aminoquinolines[a]

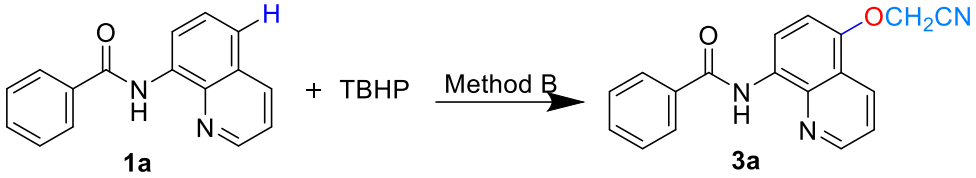


1a **2a**

Entry	T(℃)	catalyst	solvent	t (h)	additive	yield[b]
1	140	dppf($NiCl_2$)	$PhCF_3$	4		27
2	80	dppf($NiCl_2$)	$PhCF_3$	4		trace
3	100	dppf($NiCl_2$)	$PhCF_3$	4		6
4	120	dppf($NiCl_2$)	$PhCF_3$	4		17
5	150	dppf($NiCl_2$)	$PhCF_3$	4		25
6	140	$NiCl_2$	$PhCF_3$	4		n.r.
7	140	$FeCl_3$	$PhCF_3$	4		36
8	140	$K_3Fe(CN)_6$	$PhCF_3$	4		n.r.
9	140	FeF_2	$PhCF_3$	4		trace
10	140	$FeCl_2$	$PhCF_3$	4		22
11	140	$Ni(OTf)_2$	$PhCF_3$	4		n.r.
12	140	$NiSO_4$	$PhCF_3$	4		n.r.
13	140	$Sc(OTf)_3$	$PhCF_3$	4		n.r.
14	140	$CeCl_3$	$PhCF_3$	4		n.r.
15	140	$FeCl_3$	DMSO	4		trace
16	140	$FeCl_3$	DCM	4		6
17	140	$FeCl_3$	CH_3CN	4		26/24[c]
18	140	$FeCl_3$	EtOH	4		n.r.
19	140	$FeCl_3$	DMF	4		n.r.
20	140	$FeCl_3$	DCE	4		n.r.
21	140	$FeCl_3$	toluene	4		n.r.
22	140	$FeCl_3$	TFE	4		45
23	140	$FeCl_3$	TFE	8		47
24	140	$FeCl_3$	TFE	12		46
25[d]	140	$FeCl_3$	TFE	8		39
26[e]	140	$FeCl_3$	TFE	8		46
27	140	$FeCl_3$	TFE	8	PPh_3 (2.0 eq)	48
28	140	$FeCl_3$	TFE	8	PivOH (0.2 eq)	64
29	140	$FeCl_3$	TFE	8	PivOH (0.5 eq)	67
30	**140**	**$FeCl_3$**	**TFE**	**8**	**PivOH (1.0 eq)**	**69**
31	140	$FeCl_3$	TFE	8	PivOH (2.0 eq)	61
32[f]	140	$FeCl_3$	TFE	8	PivOH (2.0 eq)	61
33[g]	140	$FeCl_3$	TFE	8	PivOH (2.0 eq)	61
34	140	$FeCl_3$	TFE	8	$NaHCO_3$ (2.0 eq)	34
35[h]	140	$FeCl_3$	TFE	8	PivOH (1.0 eq)	16
36	130	$FeCl_3$	TFE	8	PivOH (1.0 eq)	64
37	120	$FeCl_3$	TFE	8	PivOH (1.0 eq)	52

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), TBHP (70% in water, 4.0 equiv), catalyst (5 mol%), solvent (1.5 mL), in sealed tube (10 mL). [b] Isolated yield. [c] 24% yield of C-5 cyanomethylation by-product. [d] TBHP (5.0-6.0mol/L in decane, 4.0 eq). [e] $FeCl_3$ (10 mol%). [f] under N_2. [g] under O_2. [h] DTBP (4.0 eq) instead of TBHP.

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



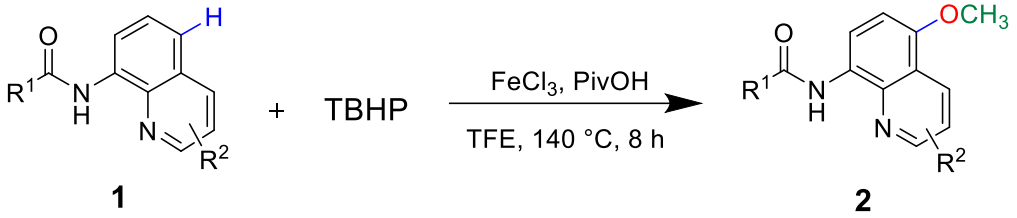
1a **3a**

Entry	T(℃)	catalyst	solvent	additive	t (h)	yield[b]
1	70	$FeCl_2$	CH_3CN		12	6
2	70	$FeCl_3$	CH_3CN		12	8
3	80	$FeCl_3$	CH_3CN		12	17
3	85	$FeCl_3$	CH_3CN		12	18
4	90	$FeCl_3$	CH_3CN		12	18/6[c]
5	100	$FeCl_3$	CH_3CN		12	24/16[c]
6	80	FeF_2	CH_3CN		12	n.r.
7	80	$NiCl_2$	CH_3CN		12	n.r.
8	80	$NiSO_4$	CH_3CN		12	n.r.
9	80	$CoCl_2$	CH_3CN		12	n.r.
10	80	$FeCl_3$	CH_3CN/TFE (1/1)		12	6
11	80	$FeCl_3$	CH_3CN /$PhCF_3$ (1/1)		12	8
12	80	$FeCl_3$	CH_3CN		8	14
13	80	$FeCl_3$	CH_3CN		24	33
14	80	$FeCl_3$	CH_3CN		48	32
15[d]	80	$FeCl_3$	CH_3CN		24	42
16[d]	80	$FeCl_3$ (5 mol%)	CH_3CN		24	16
17[d]	80	$FeCl_3$	CH_3CN	PivOH (2.0 eq)	24	35
18[d]	80	$FeCl_3$	CH_3CN	$NaHCO_3$ (2.0 eq)	24	trace
19[d]	80	$FeCl_3$	CH_3CN	N_2	24	37
20[d]	80	$FeCl_3$	CH_3CN	O_2	24	38
21[d]	80	$FeCl_3$/$FeCl_2$ (5/5 mol%)	CH_3CN		24	41
22[d]	80	$FeCl_3$ (20 mol%)	CH_3CN		24	39
23[d, e]	80	$FeCl_3$	CH_3CN		24	trace
24[d, f]	80	$FeCl_3$	CH_3CN		24	41
24[g]	80	$FeCl_3$	CH_3CN		24	25
24[h]	80	$FeCl_3$	CH_3CN		24	39
24[g]	**85**	**$FeCl_3$**	**CH_3CN (3 mL)**		**24**	**50**

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), TBHP (70% in water, 0.4 mmol, 4.0 equiv), catalyst (10 mol%), solvent (1.5 mL), in sealed tube (10 mL). [b] Isolated yield. [c] yield of C-5 methoxylation by-product. [d] TBHP (5.0-6.0 mol/L in decane, 4.0 eq). [e] DTBP (4.0 eq) instead of TBHP. [f] **1a** (0.5 mmol, 1.0 equiv). [g] TBHP (5.0-6.0 mol/L in decane, 8.0 eq). [h] TBHP (5.0-6.0 mol/L in decane, 2.0 eq).

3.2 General procedure

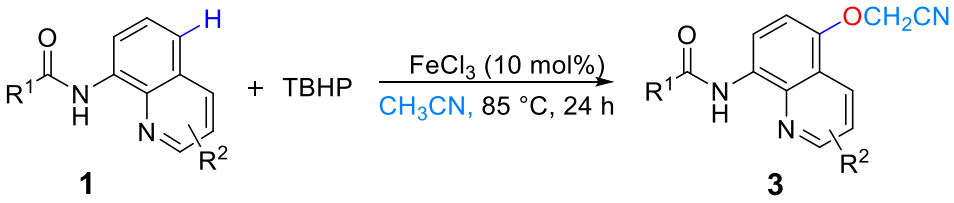
3.2.1 General procedure for C-5 methoxylation



1 2

1 (0.20 mmol, 1.0 equiv), TBHP (4.0 equiv, 70% in water), $FeCl_3$ (5 mol%), PivOH (1.0 eq) were mixed in TFE (1.5 mL) and stirred in a dried sealed tube (10 mL) at 140 °C for 8 h. After completion of the reaction (TLC monitored), it was cooled to room temperature and quenched with 1 mol/L Na_2SO_3 solution (10 mL, for removal of excess TBHP). Then the mixture was extracted with ethyl acetate (3 x 5 mL) and the organic layer was transferred to a round bottom flask after being 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**.

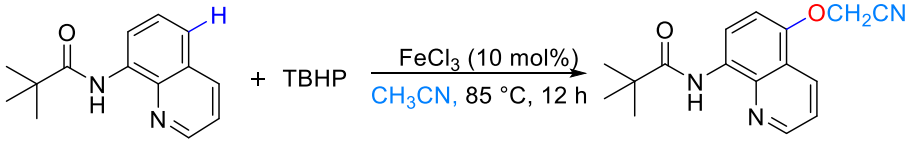
3.2.2 General procedure for C-5 cyanomethoxylation



1 3

1 (0.20 mmol, 1.0 equiv), TBHP (8.0 equiv, 5-6 mol/L in decane), $FeCl_3$ (10 mol%) were mixed in CH_3CN (3.0 mL) and stirred in a dried sealed tube (10 mL) at 85 °C for 24 h. After completion of the reaction (TLC monitored), it was cooled to room temperature and quenched with with 1 mol/L Na_2SO_3 solution (10 mL, for removal of excess TBHP). Then the mixture was extracted with ethyl acetate (3 x 5 mL) and the organic layer was transferred to a round bottom flask after being dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure and further purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate gradient), yielding the target products **2**.

3.2.3 General procedure for gram-scale reaction of cyanomethoxylation

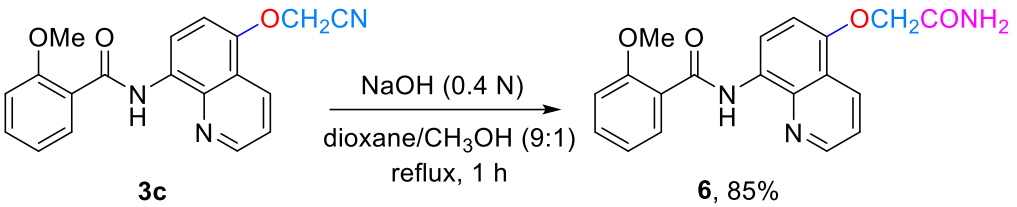


1m (5.0 mmol, 1.14 g) **3m** (46%, 0.65 g)

1m (5.0 mmol, 1.0 equiv), TBHP (5-6 mol/L in decane, 2.0 mL), $FeCl_3$ (10 mol%) were mixed in CH_3CN (10.0 mL) and stirred in a dried sealed tube at 85 °C for 12 h. After completion of the

reaction (TLC monitored), it was cooled to room temperature and quenched with with 1 mol/L Na_2SO_3 solution (20 mL, for removal of excess TBHP). Then the mixture was extracted with ethyl acetate (3 x 20 mL) and the organic layer was transferred to a round bottom flask after being dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure and further purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate gradient), yielding the target product **3m** 0.65g.

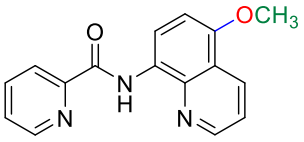
3.2.4 General procedure for the transformation of cyanomethoxylation compound



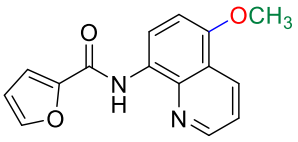
3c **6**, 85%

3c (0.5 mmol), NaOH (2 mmol, dissolved in 0.5 mL CH_3OH) were mixed in dioxane (4.5 mL) and the mixture was refluxed at 80 °C for 1 h. The course of the reaction was monitored by TLC analysis. Then the reaction mixture was cooled and evaporated to dryness, diluted with ethyl acetate and washed with water. The organic phase was concentrated after being dried over anhydrous Na_2SO_4 and purified by column chromatography chromatography (SiO_2, petroleum ether/ethyl acetate gradient), yielding amide **6** with 149 mg.

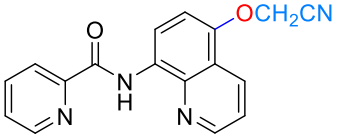
4 Tolerance of this alkoxylation strategy to heteroaryl carboxamides substrates



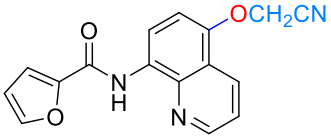
2o, n.r.



2p, trace



3o, n.r.



3p, n.r.

5. The single crystal X-ray diffraction data

5.1 Methoxylation product N-[5-(methoxyl)-8-quinolinyl]-2- phenyl-propionamide 2l

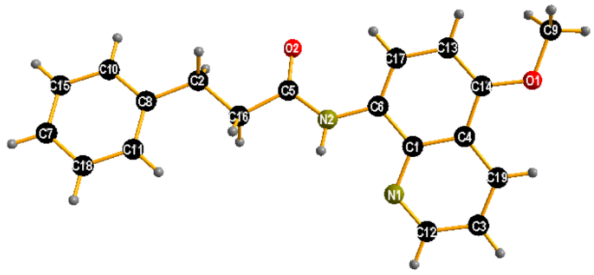


Table S3 Crystal data and structure refinement for **2l**

Bond precision: C-C = 0.0051 A Wavelength = 26.474(3)

Cell: a = 5.3192(6) b = 10.9600(14) c = 26.474(3)

alpha = 90 beta =90 gamma = 90

Temperature: 180 K

	Calculated	Reported
Volume	1543.4(3)	1543.4(3)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C_{19} H_{18} N_2 O_2	C_{19} H_{18} N_2 O_2
Sum formula	C_{19} H_{18} N_2 O_2	C_{19} H_{18} N_2 O_2
Mr	306.35	306.35
Dx (g · cm^{-3})	1.318	1.318
Z	4	4
Mu (mm^{-1})	0.087	0.087
F000	648.0	648.0
F000'	648.27	

h, k, lmax 6,13,31 6,13,31

Nref 2798 2204

Tmin, Tmax 0.978,0.989 0.542,0.745

Tmin' 0.978

Correction method = # Reported T Limits: Tmin = 0.542, Tmax = 0.745,

AbsCorr = MULTI-SCAN

Data completeness = 0.788 Theta(max) = 25.234

R(reflections) = 0.0705(1575) wR2(reflections)= 0.1949(2204)

S = 1.025 Npar = 209

5.2 Cyanomethoxylation product N-[5-(cyanomethoxyl)-8-quinolinyl]-2,2-dimethyl- propionamide 3m

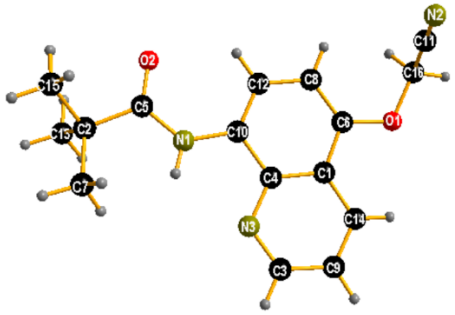


Table S4 Crystal data and structure refinement for **3m**

Bond precision: C-C = 0.0024 A Wavelength = 0.71073

Cell: a=7.8041(6) b=21.7738(13) c=9.3578(8)

alpha=90 beta=112.022(3) gamma=90

Temperature: 180 K

	Calculated	Reported
Volume	1474.11(19)	1474.11(19)
Space group	P 21/c	P 1 21/c 1

Hall group	-P 2ybc	-P 2ybc
Moiety formula	C_{16} H_{17} N_3 O_2	C_{16} H_{17} N_3 O_2
Sum formula	C_{16} H_{17} N_3 O_2	C_{16} H_{17} N_3 O_2
Mr	283.33	283.32
Dx (g • cm^{-3})	1.277	1.277
Z	4	4
Mu (mm^{-1})	0.086	0.086
F000	600.0	600.0
F000'	600.25	
h,k,lmax	9,25,11	9,25,11
Nref	2621	2607
Tmin,Tmax	0.983,0.987	0.638,0.745
Tmin'	0.981	

Correction method= # Reported T Limits: Tmin=0.638, Tmax=0.745

AbsCorr = MULTI-SCAN

Data completeness= 0.995 Theta(max)= 25.068

R(reflections)= 0.0405(2005) wR2(reflections)= 0.1197(2607)

S = 1.079 Npar= 193

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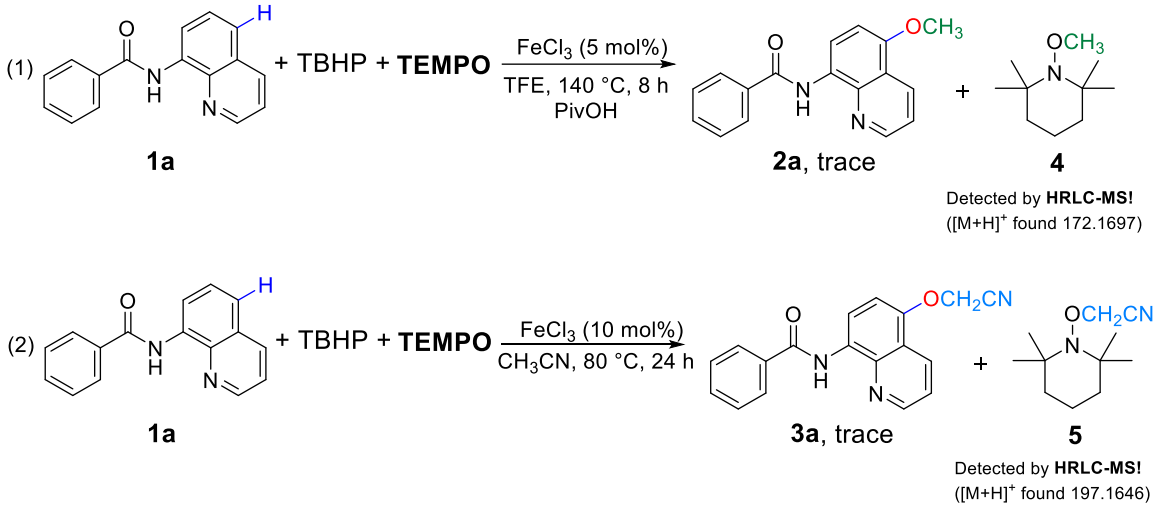
6. Mechanism investigation

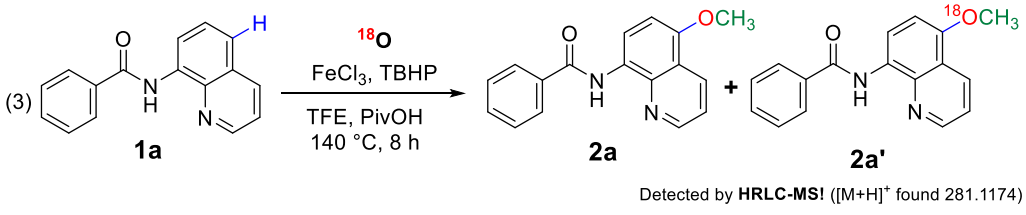
6.1 Control experiments

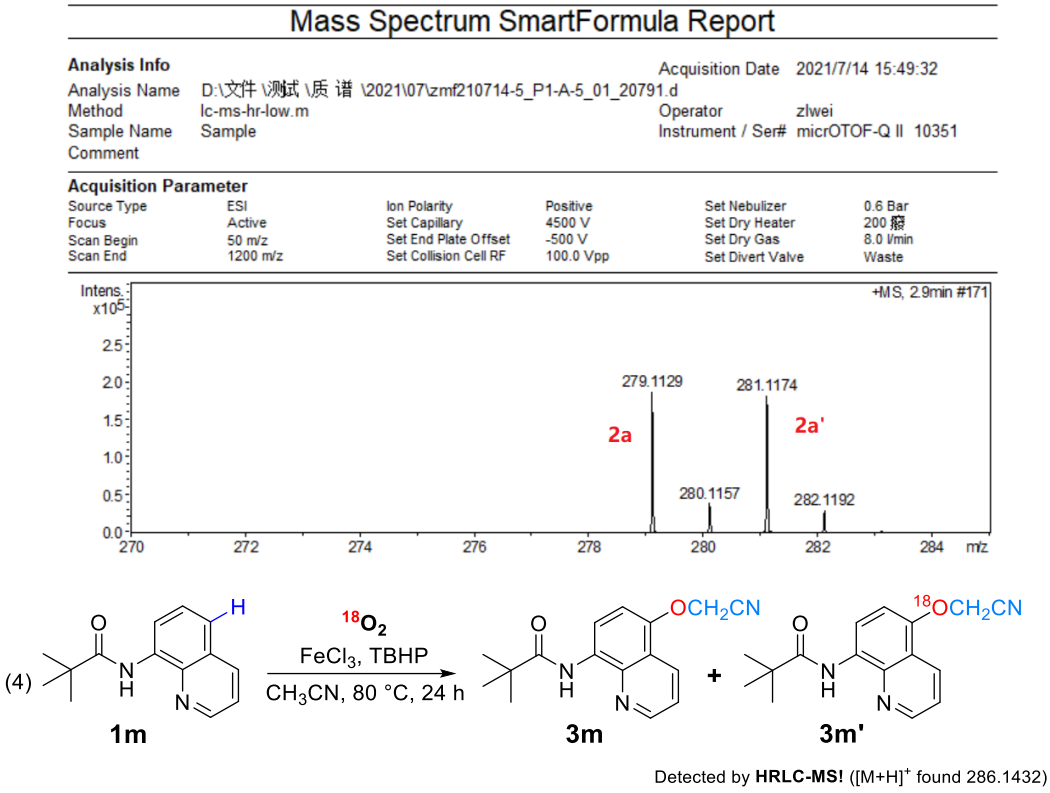


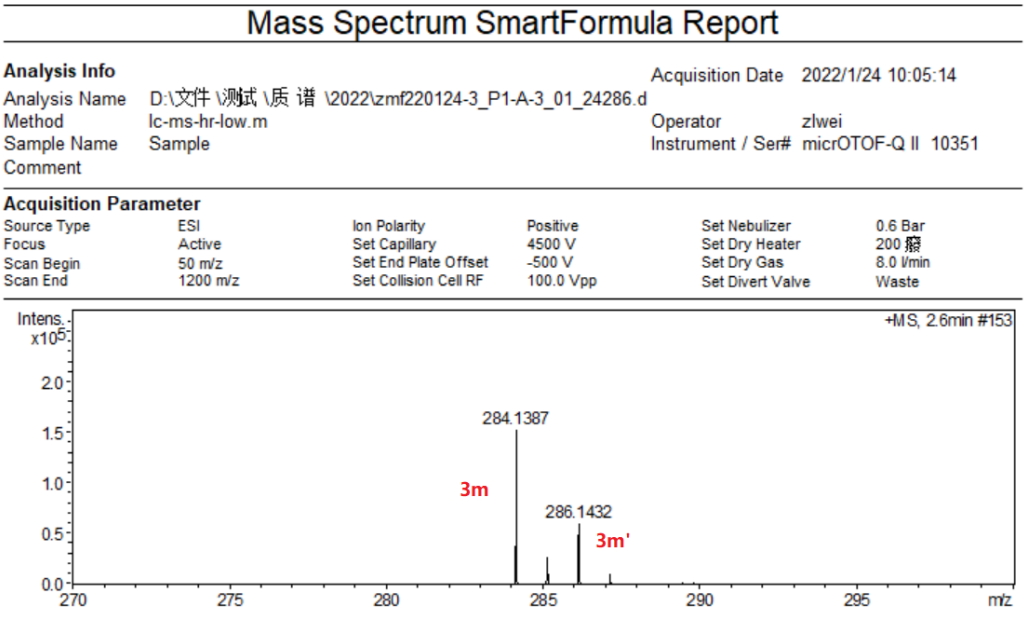
(1) **1a** (0.10 mmol, 1.0 equiv), TBHP (4.0 equiv, 70% in water), $FeCl_3$ (5 mol%), PivOH (2.0 equiv), Tempo (3.0 equiv) were mixed in TFE (1.5 mL) and stirred in a dried sealed tube (10 mL) at 140 °C for 8 h. After completion of the reaction (TLC monitored), it was cooled to room temperature and quenched with a saturated solution of Na_2SO_3 (10 mL, for removal of excess TBHP). Then the mixture was extracted with ethyl acetate (3 x 5 mL) and the organic layer was transferred to a round bottom flask after being dried over anhydrous Na_2SO_4. The mixture was then filtered by flash chromatography (SiO_2, petroleum ethyl acetate gradient) and detected by LC-HRMS.

(2) **1a** (0.10 mmol, 1.0 equiv), TBHP (4.0 equiv, 5-6 mol/L in decane), $FeCl_3$ (10 mol%), Tempo (3.0 equiv) were mixed in CH_3CN (1.5 mL) and stirred in a dried sealed tube (10 mL) at 80 °C for 24 h. After completion of the reaction (TLC monitored), it was cooled to room temperature and quenched with a saturated solution of Na_2SO_3 (10 mL, for removal of excess TBHP). Then the mixture was extracted with ethyl acetate (3 x 5 mL) and the organic layer was transferred to a round bottom flask after being dried over anhydrous Na_2SO_4. The mixture was then filtered by flash chromatography (SiO_2, petroleum ethyl acetate gradient) and detected by LC-HRMS.

6.2 $^{18}O_2$ Isotope labeling experiments







Scheme S1 Investigation of the radical pathway

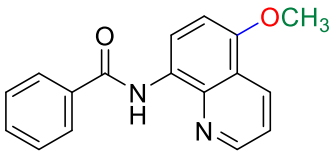
(3) **1a** (0.10 mmol, 1.0 equiv), TBHP (4.0 equiv, 70% in water), $FeCl_3$ (5 mol%), were mixed in TFE (1.5 mL) under $^{18}O_2$ and stirred in a dried schelenk tube (10 mL) at 140 °C for 8 h. After completion of the reaction (TLC monitored), it was cooled to room temperature and quenched with a saturated solution of Na_2SO_3 (10 mL, for removal of excess TBHP). Then the mixture was **extracted** with ethyl acetate (3 x 5 mL) and the organic layer was transferred to a round bottom flask after being dried over anhydrous Na_2SO_4. The mixture was then filtered by flash

chromatography (SiO_2, petroleum ethyl acetate gradient) and detected by LC-HRMS (**2a**: **2a'** = 1:1).

(4) **1a** (0.10 mmol, 1.0 equiv), TBHP (4.0 equiv, 5-6 mol/L in decane), $FeCl_3$ (10 mol%), Tempo (3.0 equiv) were mixed in CH_3CN (1.5 mL) under $^{18}O_2$ and stirred in a dried schelenk tube (10 mL) at 80 °C for 24 h. After completion of the reaction (TLC monitored), it was cooled to room temperature and quenched with a saturated solution of Na_2SO_3 (10 mL, for removal of excess TBHP). Then the mixture was extracted with ethyl acetate (3 x 5 mL) and the organic layer was transferred to a round bottom flask after being dried over anhydrous Na_2SO_4. The mixture was then filtered by flash chromatography (SiO_2, petroleum ethyl acetate gradient) and detected by LC-HRMS (**3m**: **3m'** = 2.5:1).

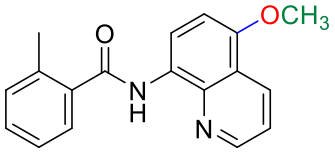
7. Characterization data of products

2a



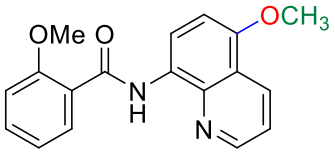
White solid, isolated yield: 69%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.87 (dd, *J* = 4.9, 3.7 Hz, 2H), 8.61 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.10 – 8.05 (m, 2H), 7.58 – 7.51 (m, 3H), 7.47 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 4.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.13 (s), 150.44 (s), 148.75 (s), 139.47 (s), 135.37 (s), 131.61 (s), 131.32 (s), 128.75 (s), 128.01 (s), 127.20 (s), 120.80 (s), 120.52 (s), 116.72 (s), 104.39 (s), 55.80 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{15}N_2O_2$: 279.1128, found: 279.1134.

2b



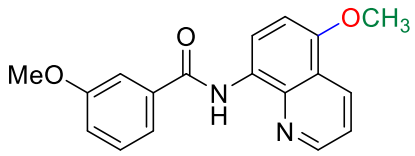
White solid, isolated yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.86 (d, *J* = 8.5 Hz, 1H), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.59 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.44 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.31 (t, *J* = 7.4 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 1H), 4.02 (s, 3H), 2.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.89 (s), 150.50 (s), 148.72 (s), 139.33 (s), 136.89 (s), 136.57 (s), 131.30 (d, *J* = 1.5 Hz), 130.13 (s), 128.19 (s), 127.25 (s), 125.97 (s), 120.78 (s), 120.52 (s), 116.70 (s), 104.33 (s), 55.84 (s), 20.21 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{18}H_{17}N_2O_2$: 293.1285, found: 293.1284.

2c



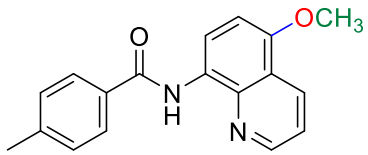
White solid, isolated yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.97 (d, *J* = 8.6 Hz, 1H), 8.89 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.60 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.36 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.52 – 7.48 (m, 1H), 7.45 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 4.20 (s, 3H), 4.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.69 (s), 150.27 (d, *J* = 4.2 Hz), 148.73 (s), 139.95 (s), 132.86 (s), 132.25 (s), 131.10 (s), 129.19 (s), 121.27 (s), 120.56 (s), 117.47 (s), 111.56 (s), 104.61 (s), 56.12 (s), 55.78 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{18}H_{17}N_2O_3$: 309.1234, found: 309.1243.

2d



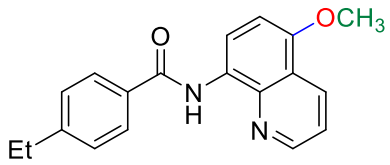
White solid, isolated yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.87 – 8.82 (m, 2H), 8.59 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.62 (dd, *J* = 4.3, 2.4 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.10 (dd, *J* = 7.9, 2.5 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 4.01 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.94 (s), 159.95 (s), 150.46 (s), 148.77 (s), 139.46 (s), 136.86 (s), 131.30 (s), 129.73 (s), 127.98 (s), 120.81 (s), 120.51 (s), 118.99 (s), 117.80 (s), 116.71 (s), 112.56 (s), 104.36 (s), 55.80 (s), 55.51 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{18}H_{17}N_2O_3$: 309.1234, found: 309.1238.

2e



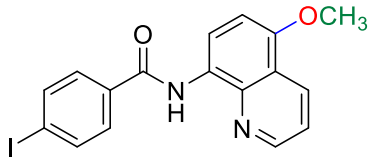
White solid, isolated yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.88 – 8.83 (m, 2H), 8.60 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 2H), 7.46 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 1H), 4.01 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.14 (s), 150.33 (s), 148.71 (s), 142.05 (s), 139.47 (s), 132.55 (s), 131.31 (s), 129.41 (s), 128.13 (s), 127.21 (s), 120.77 (s), 120.53 (s), 116.65 (s), 104.44 (s), 55.80 (s), 21.55 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{18}H_{17}N_2O_2$: 293.1285, found: 293.1284.

2f



White solid, isolated yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.86 (dd, *J* = 5.0, 3.5 Hz, 2H), 8.60 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 2H), 7.46 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 1H), 4.01 (d, *J* = 7.6 Hz, 3H), 2.75 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.17 (s), 150.33 (s), 150.11 (s), 148.69 (s), 148.26 (s), 139.49 (s), 132.83 (s), 131.30 (s), 128.20 (d, *J* = 4.9 Hz), 127.30 (s), 120.75 (s), 116.64 (s), 104.46 (s), 55.81 (s), 28.86 (s), 15.36 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{19}H_{19}N_2O_2$: 307.1442, found: 307.1441.

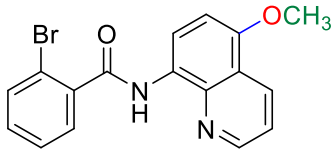
2g



White solid, isolated yield: 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.90 – 8.83 (m, 2H), 8.63 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.50 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 4.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.80 (s), 139.42 (s),

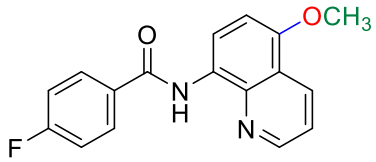
137.96 (s), 134.81 (s), 131.40 (s), 128.79 (s), 120.86 (s), 116.84 (s), 104.36 (s), 55.81 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{14}IN_2O_2$: 405.0094, found: 405.0091.

2h



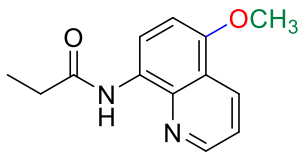
White solid, isolated yield: 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.87 (d, *J* = 8.5 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.59 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.69 (ddd, *J* = 10.1, 7.8, 1.4 Hz, 2H), 7.46 – 7.41 (m, 2H), 7.36 – 7.31 (m, 1H), 6.91 – 6.88 (m, 1H), 4.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.77 (s), 148.81 (s), 133.63 (s), 131.32 (d, *J* = 2.5 Hz), 129.53 (s), 127.69 (d, *J* = 14.8 Hz), 120.84 (s), 120.51 (s), 119.77 (s), 117.12 (s), 104.29 (s), 55.85 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{14}BrN_2O_2$: 357.0233, 359.0213, found: 357.0238, 359.0217.

2i



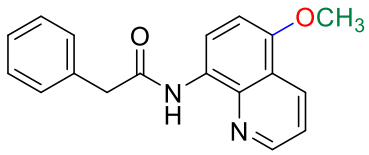
White solid, isolated yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.83 (ddd, *J* = 13.6, 6.8, 5.1 Hz, 2H), 8.59 (dt, *J* = 8.4, 1.8 Hz, 1H), 8.07 (dd, *J* = 8.3, 5.5 Hz, 2H), 7.46 (ddd, *J* = 8.4, 4.2, 1.8 Hz, 1H), 7.21 (dd, *J* = 12.7, 4.6 Hz, 2H), 6.88 (dd, *J* = 8.6, 1.8 Hz, 1H), 4.00 (d, *J* = 1.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.85 (d, *J* = 252.9 Hz), 164.00 (s), 150.51 (s), 148.76 (s), 139.40 (s), 131.53 (d, *J* = 3.2 Hz), 131.38 (s), 129.53 (d, *J* = 9.0 Hz), 127.83 (s), 120.84 (s), 120.53 (s), 116.73 (s), 115.78 (d, *J* = 21.9 Hz), 104.35 (s), 55.80 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{14}FN_2O_2$: 297.1034, found: 297.1035.

2j



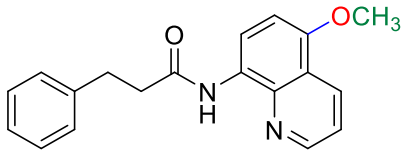
White solid, isolated yield: 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 8.84 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.73 (d, *J* = 8.5 Hz, 1H), 8.61 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.47 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 4.02 (s, 3H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.36 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.12 (s), 148.54 (s), 131.30 (s), 128.00 (s), 120.67 (s), 116.56 (s), 104.38 (s), 55.76 (s), 31.17 (s), 9.88 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{13}H_{15}N_2O_2$: 231.1129, found: 231.1126.

2k



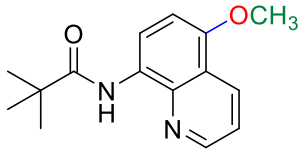
White solid, isolated yield: 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.70 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.67 (d, *J* = 8.5 Hz, 1H), 8.53 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.45 – 7.37 (m, 5H), 7.35 – 7.30 (m, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 3.97 (s, 3H), 3.87 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.10 (s), 150.32 (s), 148.61 (s), 134.89 (s), 131.17 (s), 129.55 (s), 128.93 (s), 127.83 (s), 127.25 (s), 120.64 (s), 120.35 (s), 116.53 (s), 104.25 (s), 55.75 (s), 45.26 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{18}H_{17}N_2O_2$: 293.1285, found: 293.1283.

2l



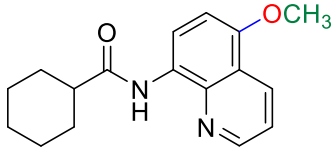
White solid, isolated yield: 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 8.81 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.73 (d, *J* = 8.5 Hz, 1H), 8.60 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.46 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.32 (d, *J* = 4.4 Hz, 4H), 7.23 (dq, *J* = 8.8, 4.2 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 4.02 (s, 3H), 3.20 – 3.14 (m, 2H), 2.91 – 2.86 (m, 2H). ^{13}CNMR (101 MHz, $CDCl_3$) δ 170.34 (s), 150.23 (s), 148.55 (s), 144.90 (s), 140.90 (s), 131.27 (s), 128.47 (d, *J* = 12.8 Hz), 127.89 (s), 126.19 (s), 120.68 (s), 120.43 (s), 116.68 (s), 104.37 (s), 55.78 (s), 39.68 (s), 31.61 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{19}H_{19}N_2O_2$: 307.1442, found: 307.1442.

2m



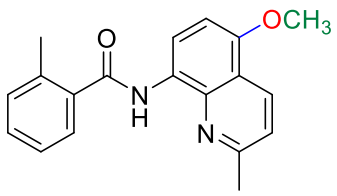
White solid, isolated yield: 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.71 (d, *J* = 8.5 Hz, 1H), 8.56 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.43 (dd, *J* = 8.4, 4.3 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 3.98 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.85 (s), 150.06 (s), 148.67 (s), 131.19 (s), 120.64 (s), 116.28 (s), 104.36 (s), 55.76 (s), 40.18 (s), 27.79 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{15}H_{19}N_2O_2$: 259.1441, found: 259.1440.

2n



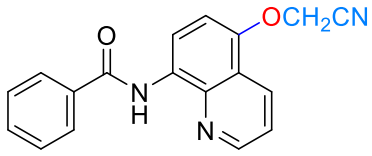
White solid, isolated yield: 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.72 (d, *J* = 8.5 Hz, 1H), 8.57 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.44 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 3.98 (d, *J* = 8.0 Hz, 3H), 2.45 (tt, *J* = 11.7, 3.5 Hz, 1H), 2.07 (d, *J* = 13.3 Hz, 2H), 1.91 – 1.84 (m, 2H), 1.76 – 1.60 (m, 3H), 1.34 (ddd, *J* = 22.0, 12.5, 9.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.51 (s), 150.05 (s), 148.56 (s), 139.17 (s), 131.26 (s), 128.09 (s), 120.66 (s), 120.42 (s), 116.52 (s), 104.38 (s), 55.77 (s), 46.85 (s, 2C), 29.82 (s), 25.82 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{21}N_2O_2$: 285.1598, found: 285.1605.

2s



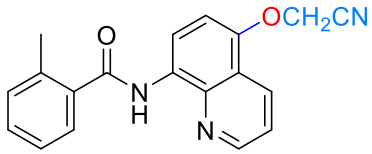
yellow solid, isolated yield: 54%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.82 (d, *J* = 8.5 Hz, 1H), 8.46 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 7.4 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.35 – 7.29 (m, 3H), 6.83 (d, *J* = 8.5 Hz, 1H), 4.00 (s, 3H), 2.68 (s, 3H), 2.62 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.70 (s), 157.79 (s), 150.61 (s), 138.82 (s), 136.55 (s), 131.33 (s), 131.30 (s), 130.10 (s), 127.67 (s), 127.43 (s), 126.22 (s), 126.00 (s), 121.51 (s), 118.51 (s), 116.64 (s), 103.50 (s), 55.75 (s), 25.24 (s), 20.34 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{19}H_{19}N_2O_2$: 307.1442, found: 307.1440.

3a



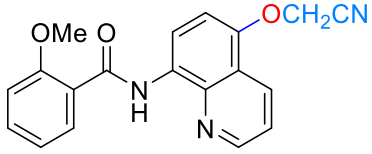
White solid, isolated yield: 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.91 (dd, *J* = 5.0, 3.4 Hz, 2H), 8.58 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.08 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.60 – 7.53 (m, 4H), 7.03 (d, *J* = 8.6 Hz, 1H), 5.00 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.72 (s), 149.26 (s), 146.98 (s), 140.26 (s), 131.86 (s), 130.91 (s), 130.30 (s), 129.55 (s), 128.83 (s), 127.24 (s), 121.84 (s), 121.60 (s), 120.48 (s), 115.84 (s), 106.75 (s), 54.13 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{18}H_{14}N_3O_2$: 304.1081, found: 304.1076.

3b



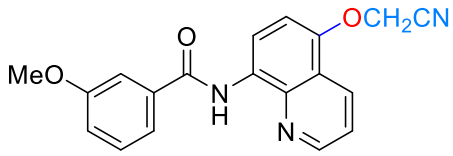
White solid, isolated yield: 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.91 (d, *J* = 8.5 Hz, 1H), 8.83 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.56 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.67 (d, *J* = 7.4 Hz, 1H), 7.52 (dd, *J* = 8.5, 4.3 Hz, 1H), 7.41 (t, *J* = 6.8 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 1H), 5.00 (s, 2H), 2.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.07 (s), 149.23 (s), 140.05 (s), 139.27 (s), 136.69 (s), 136.54 (s), 135.71 (s), 134.74 (s), 131.39 (s), 130.85 (s), 130.44 (s), 130.36 (s), 127.25 (s), 126.03 (s), 121.57 (s), 115.80 (s), 106.68 (s), 54.13 (s), 20.23 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{19}H_{16}N_3O_2$: 318.1237, found: 318.1232.

3c



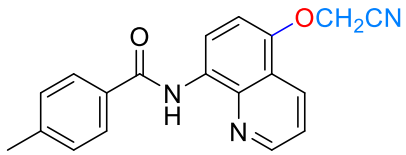
White solid, isolated yield: 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.25 (s, 1H), 9.02 (d, *J* = 8.6 Hz, 1H), 8.96 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.59 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.38 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 5.01 (s, 2H), 4.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.45 (s), 157.71 (s), 149.21 (s), 146.81 (s), 139.87 (s), 133.16 (s), 132.33 (s), 131.43 (s), 130.69 (s), 122.21 (s), 121.35 (s), 120.48 (s), 120.29 (s), 116.55 (s), 115.39 (s), 111.59 (s), 106.91 (s), 56.15 (s), 54.15 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{19}H_{16}N_3O_3$: 334.1186, found: 334.1189.

3d



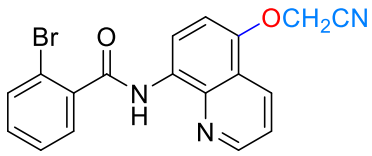
White solid, isolated yield: 44%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.89 (d, *J* = 8.3 Hz, 2H), 8.57 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.63 (d, *J* = 6.3 Hz, 2H), 7.54 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.46 (t, *J* = 8.1 Hz, 1H), 7.13 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 5.00 (s, 2H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.17 (s), 156.45 (s), 153.60 (s), 149.28 (s), 136.54 (s), 132.51 (s), 130.89 (s), 130.26 (s), 129.81 (s), 128.58 (s), 121.61 (s), 118.89 (d, *J* = 24.3 Hz), 118.67 – 118.22 (m), 118.02 (s), 115.83 (s), 112.62 (s), 106.70 (s), 55.54 (s), 54.11 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{19}H_{16}N_3O_3$: 334.1186, found: 334.1191.

3e



White solid, isolated yield: 44%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.90 (dd, *J* = 7.0, 4.7 Hz, 2H), 8.57 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 2H), 7.54 (dd, *J* = 8.4, 4.1 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 1H), 4.99 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.35 (s), 149.21 (s), 146.87 (s), 142.37 (s), 139.40 (s), 130.89 (s), 129.48 (s), 127.76 (s), 127.29 (d, *J* = 8.6 Hz), 121.56 (s), 115.75 (s), 106.77 (s), 54.13 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{19}H_{16}N_3O_2$: 318.1237, found: 318.1220.

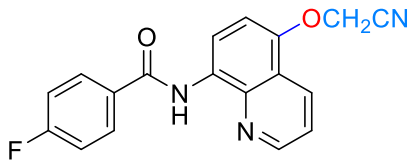
3h



White solid, isolated yield: 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.92 (d, *J* = 8.6 Hz, 1H), 8.85 (d, *J* = 2.7 Hz, 1H), 8.57 (d, *J* = 7.0 Hz, 1H), 7.70 (t, *J* = 6.8 Hz, 2H), 7.53 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 6.9 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 5.00 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.22 (s), 149.32 (s), 147.27 (s), 136.44 (s), 133.71 (s), 131.54 (s), 130.96 (d, *J* = 19.3 Hz), 130.18 – 130.11 (m), 129.80 (d, *J* = 42.1 Hz), 127.82 (d, *J* = 26.3 Hz), 121.63 (s), 118.98 (s),

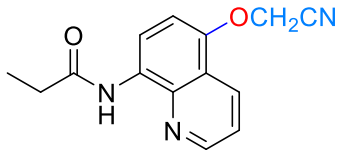
116.21 (s), 111.91 (s), 106.57 (s), 54.10 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{18}H_{13}BrN_3O_2$: 382.0186, 384.0165, found: 382.0188, 384.0173.

3i



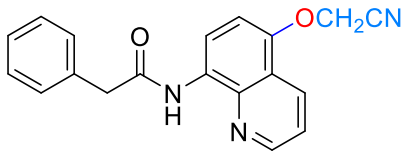
White solid, isolated yield: 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.90 (dd, *J* = 14.8, 6.4 Hz, 2H), 8.58 (d, *J* = 8.5 Hz, 1H), 8.09 (dd, *J* = 7.4, 5.3 Hz, 2H), 7.56 (dd, *J* = 8.5, 4.3 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 1H), 5.00 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.99 (d, *J* = 252.5 Hz), 164.23 (s), 149.28 (s), 147.05 (s), 139.35 (s), 131.21 (d, *J* = 3.1 Hz), 130.97 (s), 130.09 (s), 129.61 (d, *J* = 9.0 Hz), 121.64 (s), 120.48 (s), 115.89 (d, *J* = 22.0 Hz), 115.87 (s), 114.75 (s), 106.69 (s), 54.10 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{18}H_{13}FN_3O_2$: 322.0986, found: 322.0989.

3j



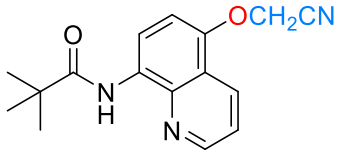
White solid, isolated yield: 43%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 8.86 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.75 (d, *J* = 8.6 Hz, 1H), 8.54 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.51 (dd, *J* = 8.5, 4.2 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 4.96 (s, 2H), 2.59 (q, *J* = 7.6 Hz, 2H), 1.34 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.34 (s), 149.05 (s), 146.67 (s), 130.84 (s), 130.28 (s), 126.08 (s), 121.46 (s), 120.39 (s), 115.64 (s), 114.78 (s), 106.78 (s), 54.13 (s), 31.17 (s), 9.78 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{14}H_{14}N_3O_2$: 256.1081, found: 256.1082.

3k



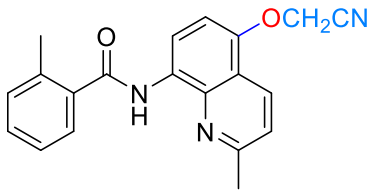
White solid, isolated yield: 36%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.74 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.71 (d, *J* = 8.6 Hz, 1H), 8.49 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.45 (dt, *J* = 13.7, 5.6 Hz, 5H), 7.34 (d, *J* = 6.5 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 4.94 (s, 2H), 3.88 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.10 (s), 150.32 (s), 148.61 (s), 134.89 (s), 131.17 (s), 129.55 (s), 129.55 (s), 128.93 (s), 127.83 (s), 127.25 (s), 120.64 (s), 120.35 (s), 116.53 (s), 104.25 (s), 55.75 (s), 45.26 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{19}H_{16}N_3O_2$: 318.1237, found: 318.1235.

3m



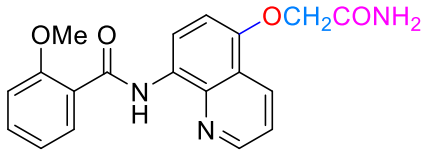
White solid, isolated yield: 59%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.87 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.75 (d, *J* = 8.6 Hz, 1H), 8.54 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.51 (dd, *J* = 8.5, 4.2 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 4.96 (s, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.12 (s), 149.17 (s), 146.63 (s), 139.40 (s), 130.78 (s), 121.43 (s), 115.41 (s), 114.81 (s), 106.75 (s), 54.12 (s), 40.26 (s), 27.74 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{18}N_3O_2$: 284.1394, found: 284.1392.

3s



White solid, isolated yield: 34%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.86 (d, *J* = 8.6 Hz, 1H), 8.42 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.38 (ddd, *J* = 18.1, 15.0, 7.1 Hz, 4H), 6.94 (d, *J* = 8.6 Hz, 1H), 4.97 (s, 2H), 2.71 (s, 3H), 2.62 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.38 (s), 158.49 (s), 147.17 (s), 138.79 (s), 136.66 (s), 131.42 (s), 130.86 (s), 130.24 (d, *J* = 14.4 Hz), 129.86 (s), 127.41 (s), 126.07 (s), 122.35 (s), 118.50 (s), 115.80 (s), 114.87 (s), 105.79 (s), 54.11 (s), 25.30 (s), 20.34 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{20}H_{18}N_3O_2$: 332.1394, found: 332.1392.

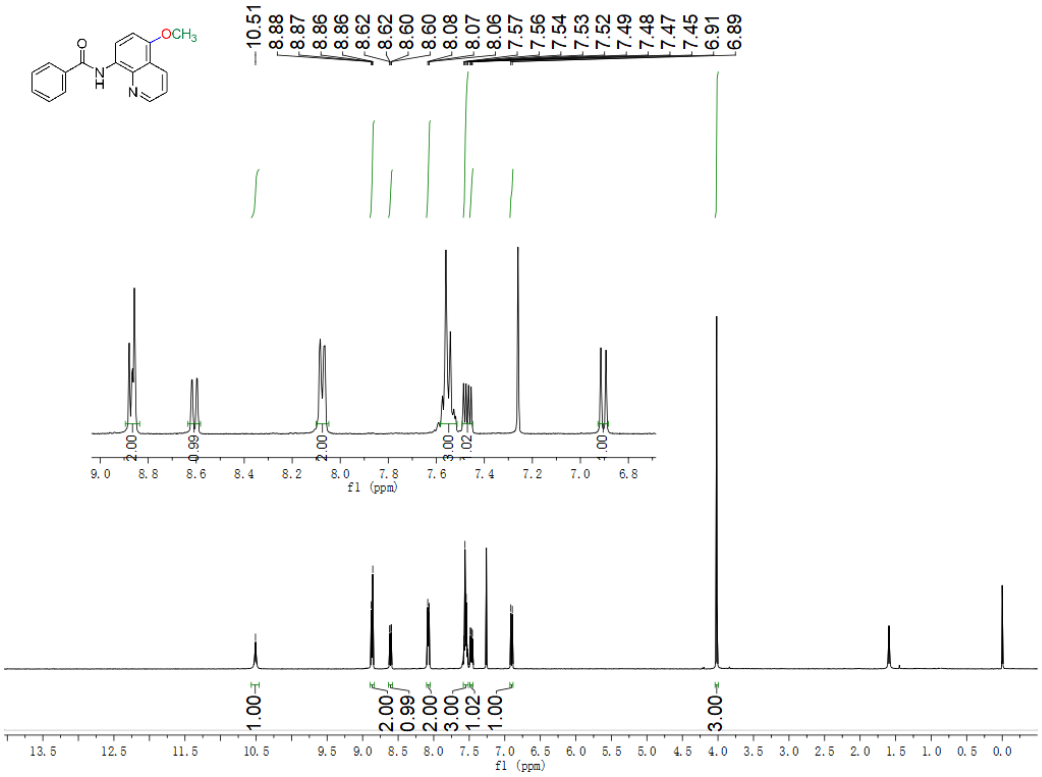
6

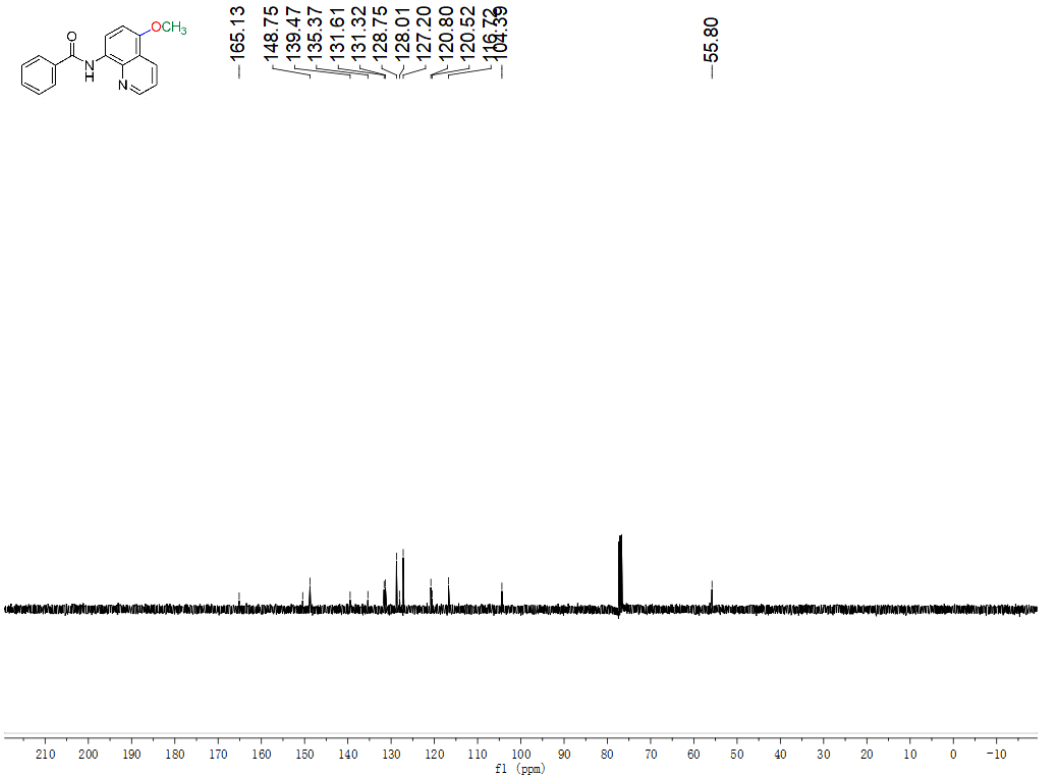


White solid, isolated yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.22 (s, 1H), 9.02 – 8.96 (m, 2H), 8.60 (d, *J* = 8.2 Hz, 1H), 8.38 (d, *J* = 7.6 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.20 – 7.16 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.55 (s, 1H), 5.68 (s, 1H), 4.76 (s, 2H), 4.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.21 (s), 163.42 (s), 157.62 (s), 149.36 (s), 146.89 (s), 139.81 (s), 133.16 (s), 132.27 (s), 131.30 (s), 130.81 (s), 122.21 (s), 121.35 (s), 120.48 (s), 120.29 (s), 116.40 (s), 111.41 (s), 106.21 (s) 67.95 (s), 54.15 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{19}H_{18}N_3O_4$: 352.1292, found: 352.1290.

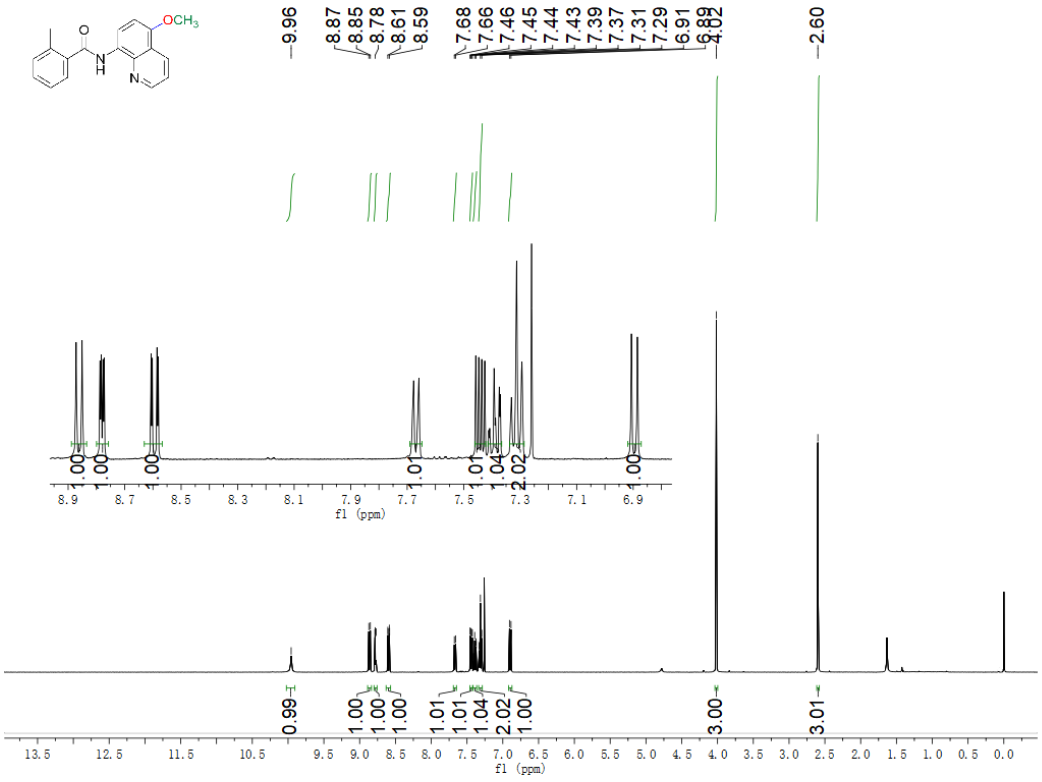
7. ^{1}H and ^{13}C NMR spectra

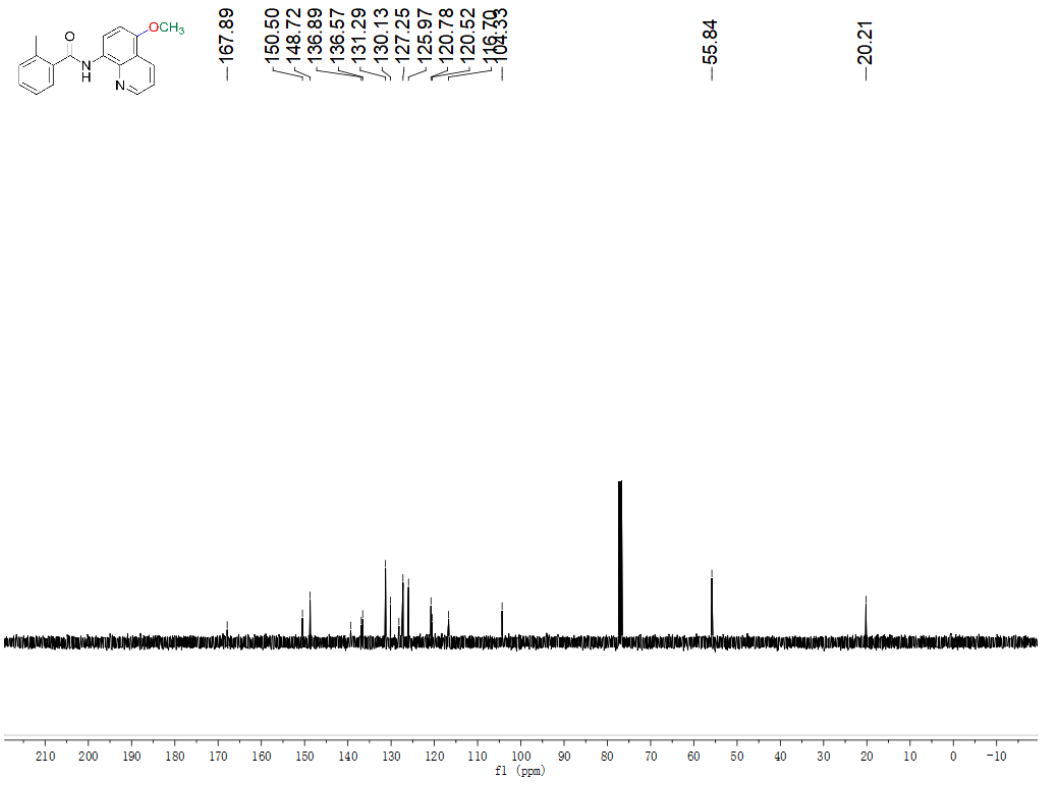
2a



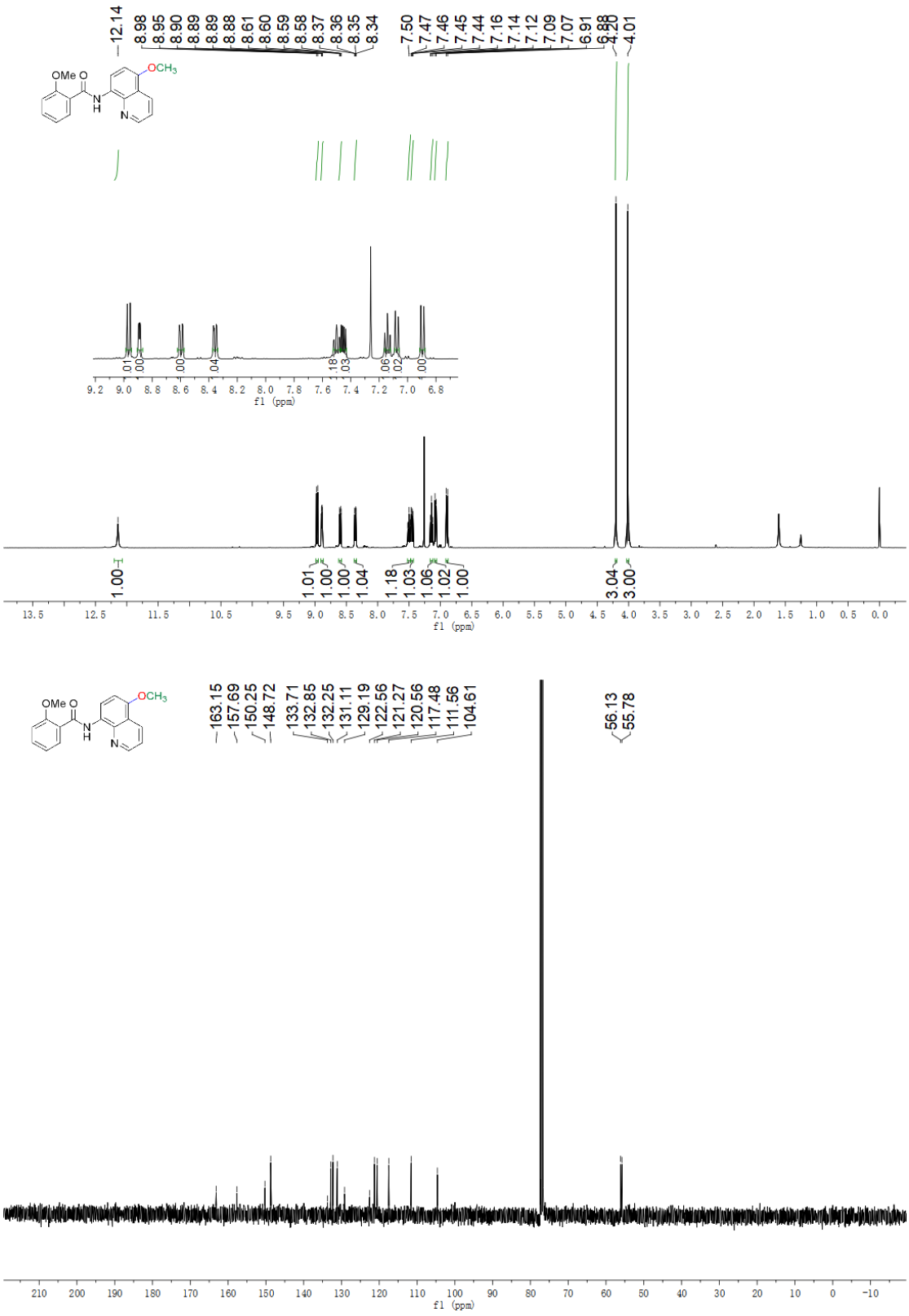


2b

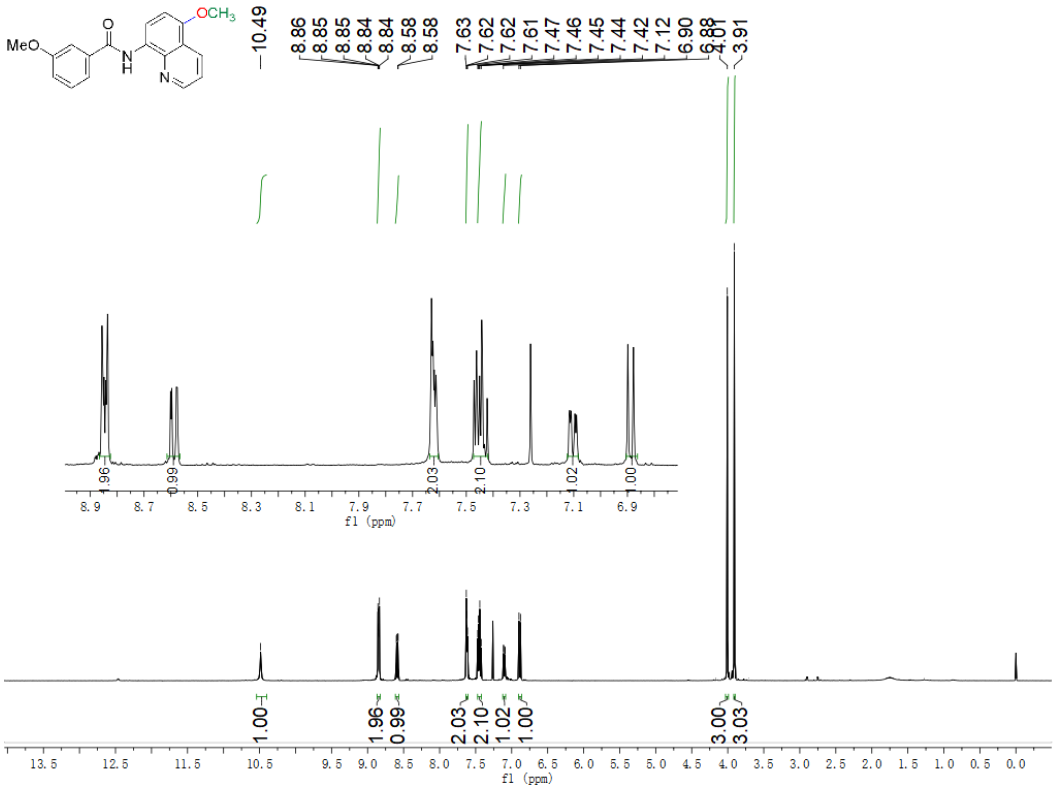

OCH3
O
N
H
9.96
8.87
8.85
8.78
8.61
8.59
7.68
7.66
7.46
7.45
7.44
7.43
7.39
7.37
7.31
7.29
6.91
6.89
4.02
2.60
f1 (ppm)

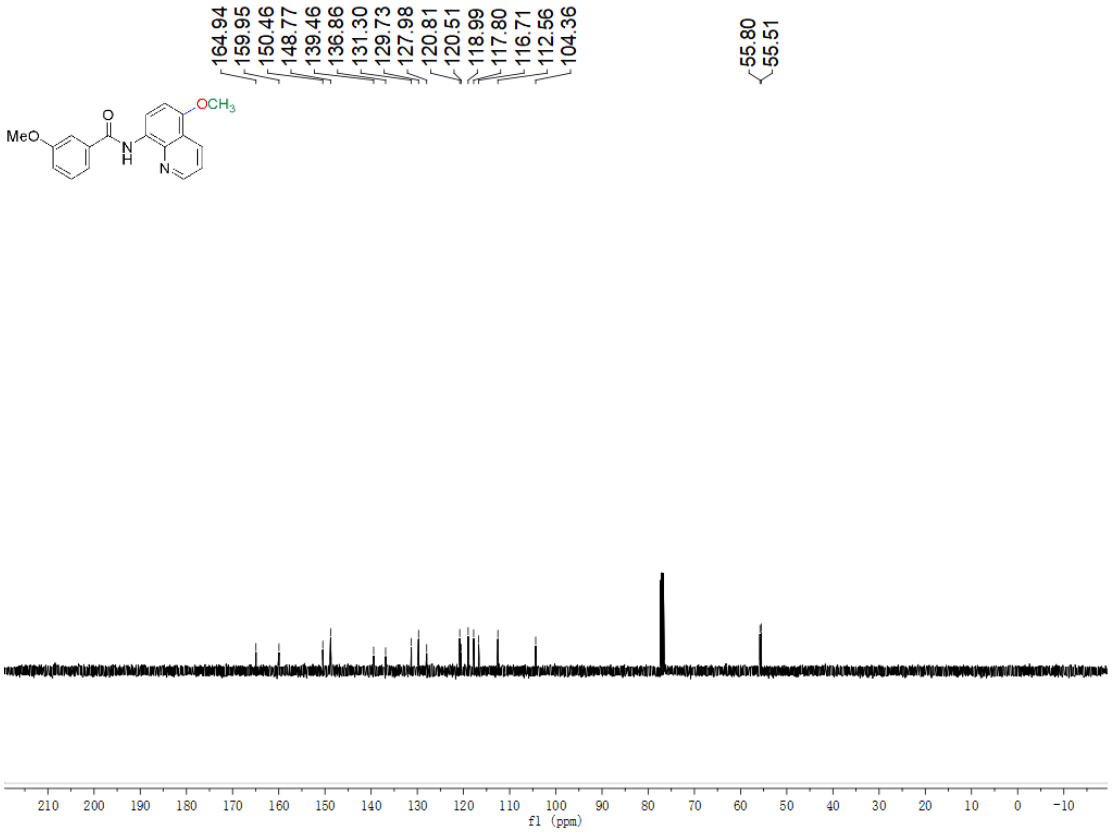

OCH3
O
N
H
167.89
150.50
148.72
136.89
136.57
131.29
130.13
127.25
125.97
120.78
120.52
116.70
104.33
55.84
20.21
f1 (ppm)

2c

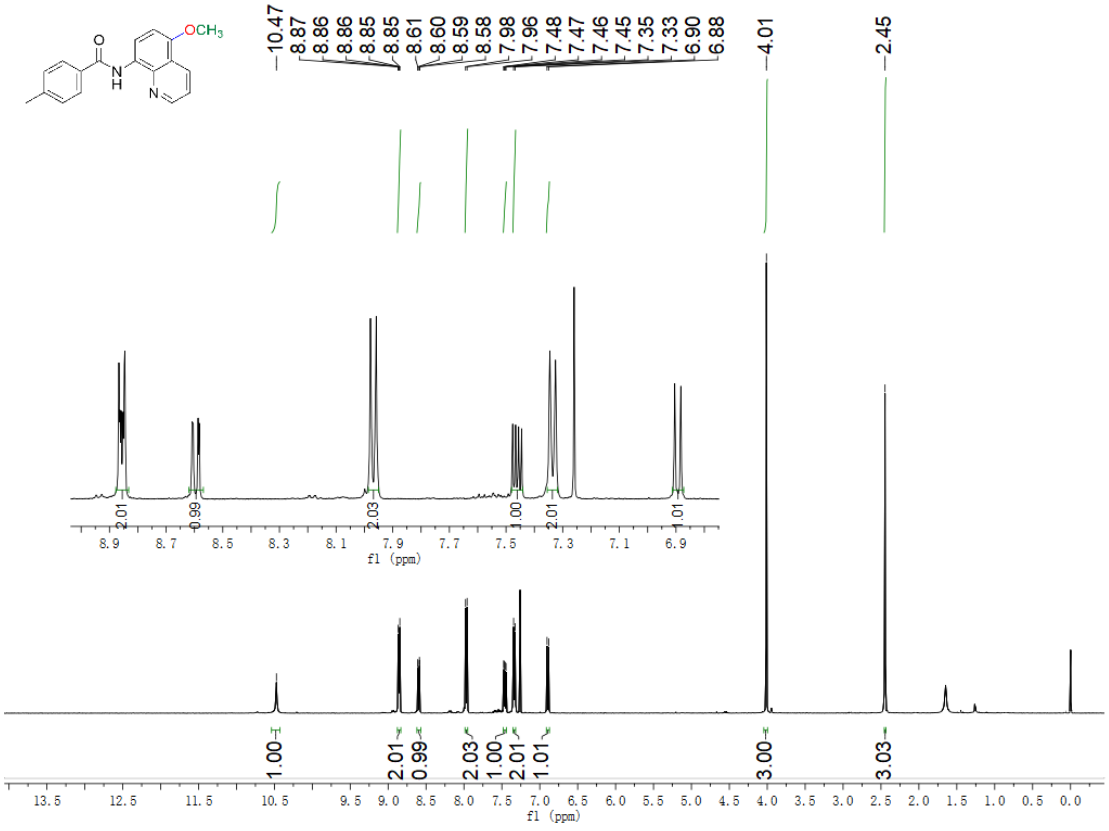

12.14
8.98
8.95
8.90
8.89
8.89
8.88
8.61
8.60
8.59
8.58
8.37
8.36
8.35
8.34
7.50
7.47
7.46
7.45
7.44
7.16
7.14
7.12
7.09
7.07
6.91
6.88
4.20
4.01
OMe O
OCH3
N
H
f1 (ppm)
1.00
1.01
1.00
1.00
1.04
1.18
1.03
1.06
1.02
1.00
3.04
3.00
163.15
157.69
150.25
148.72
133.71
132.85
132.25
131.11
129.19
122.56
121.27
120.56
117.48
111.56
104.61
56.13
55.78

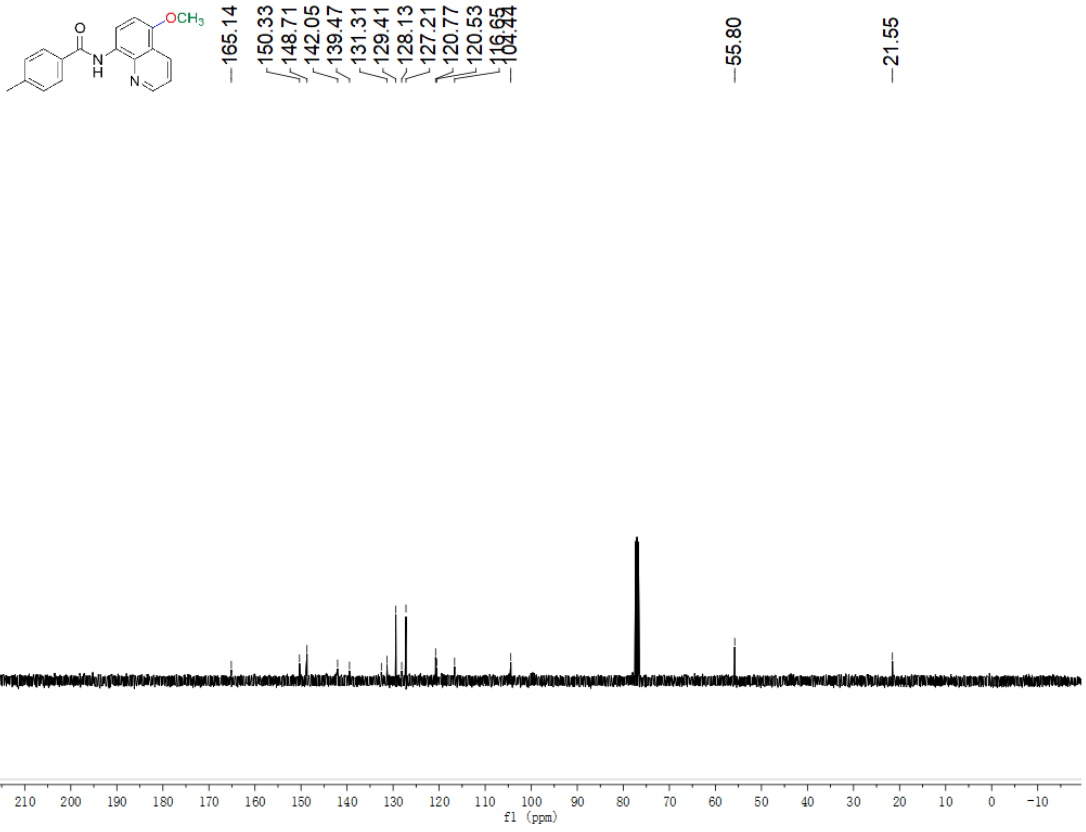
2d


MeO
OCH3
10.49
8.86
8.85
8.85
8.84
8.84
8.58
8.58
7.63
7.62
7.62
7.61
7.47
7.46
7.45
7.44
7.42
7.12
6.90
6.88
4.01
3.91
1.96
0.99
2.03
2.10
1.02
1.00
f1 (ppm)
1.00
1.96
0.99
2.03
2.10
1.02
1.00
3.00
3.03

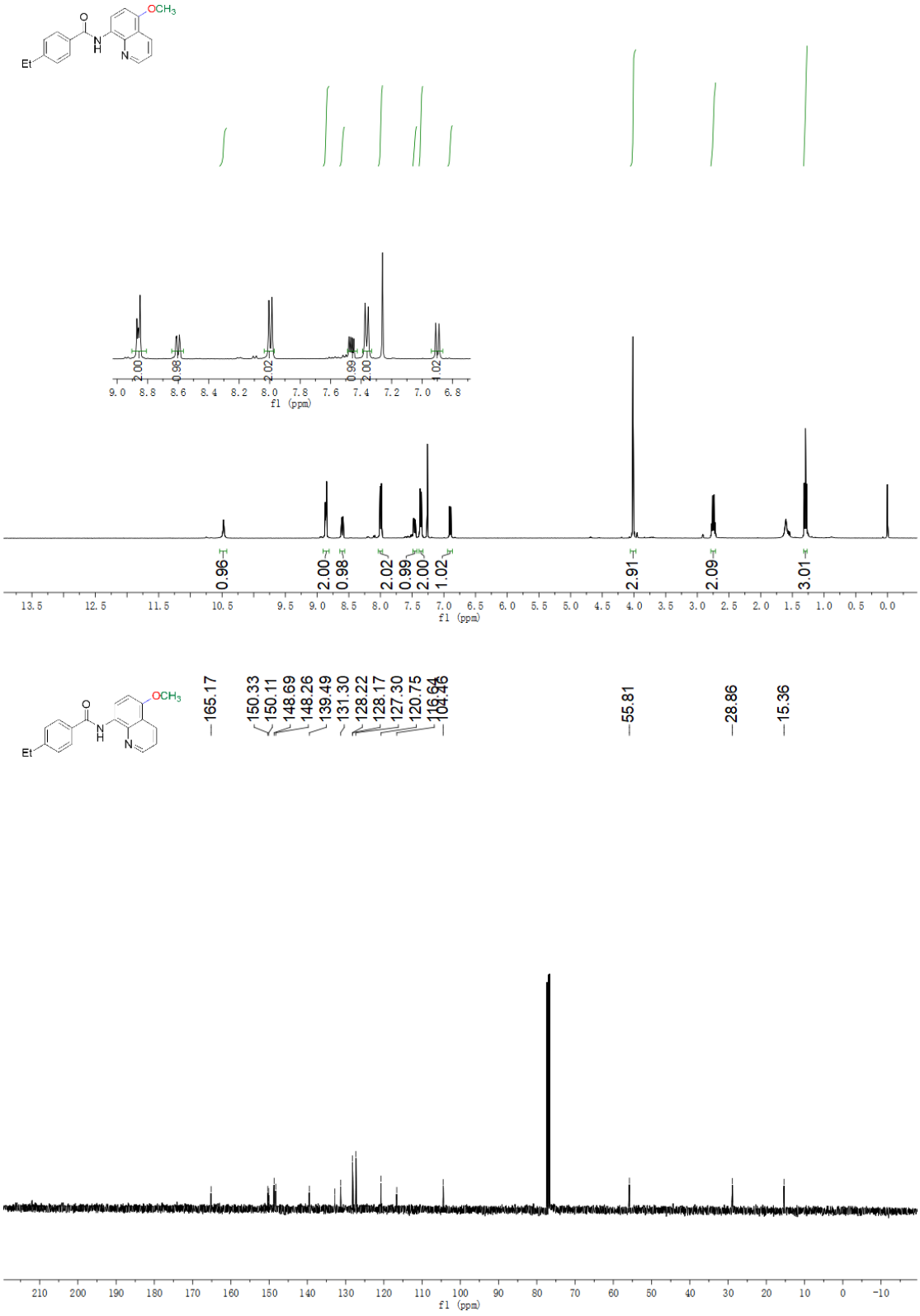

164.94
159.95
150.46
148.77
139.46
136.86
131.30
129.73
127.98
120.81
120.51
118.99
117.80
116.71
112.56
104.36
55.80
55.51
MeO
OCH3
f1 (ppm)

2e

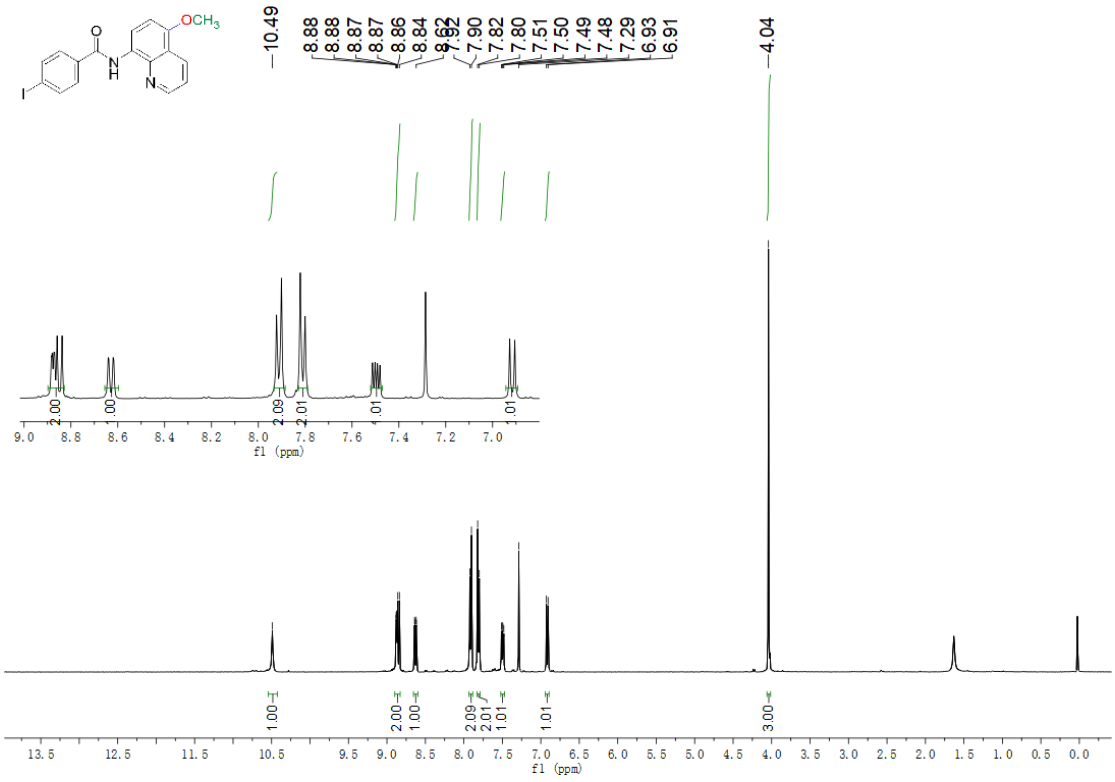

OCH3
O
N
H
N
10.47
8.87
8.86
8.86
8.85
8.85
8.61
8.60
8.59
8.58
7.98
7.96
7.48
7.47
7.46
7.45
7.35
7.33
6.90
6.88
4.01
2.45
2.01
0.99
2.03
1.00
2.01
1.01
f1 (ppm)
1.00
2.01
0.99
2.03
1.00
2.01
1.01
3.00
3.03
f1 (ppm)

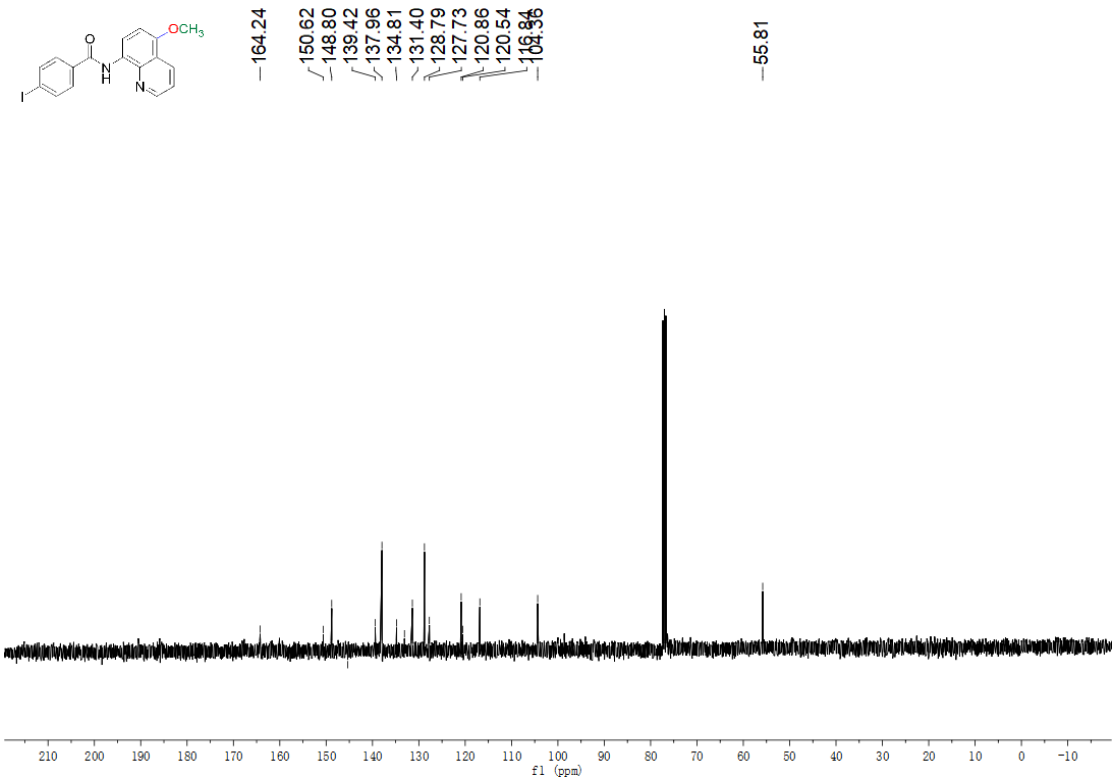

OCH3
O
N
H
N
165.14
150.33
148.71
142.05
139.47
131.31
129.41
128.13
127.21
120.77
120.53
116.65
104.44
55.80
21.55
f1 (ppm)

2f

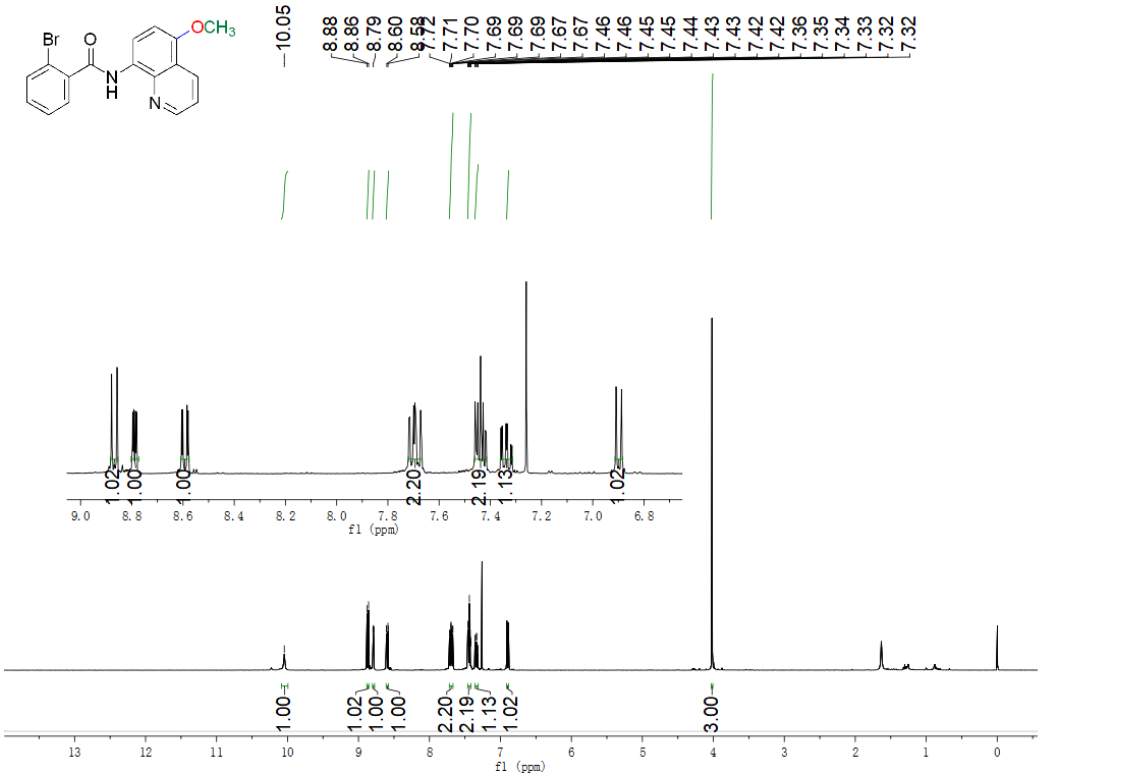

OCH3
Et
2.00
0.98
2.02
0.99
2.00
1.02
f1 (ppm)
0.96
2.00
0.98
2.02
0.99
2.00
1.02
2.91
2.09
3.01
f1 (ppm)
OCH3
Et
165.17
150.33
150.11
148.69
148.26
139.49
131.30
128.22
128.17
127.30
120.75
116.64
104.46
55.81
28.86
15.36
f1 (ppm)

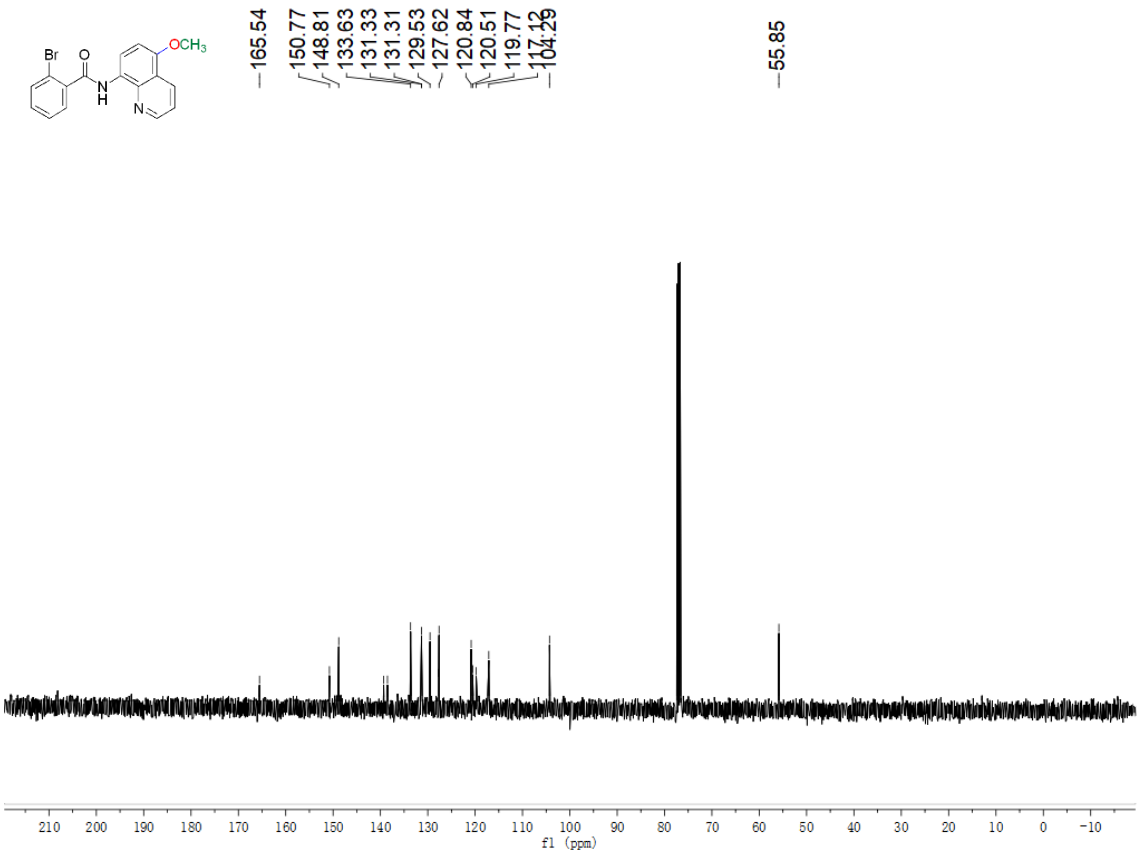
2g


OCH3
O
N
H
I
10.49
8.88
8.88
8.87
8.87
8.86
8.84
8.62
7.92
7.90
7.82
7.80
7.51
7.50
7.49
7.48
7.29
6.93
6.91
4.04
2.00
1.00
1.00
2.09
2.01
1.01
1.01
f1 (ppm)
3.00

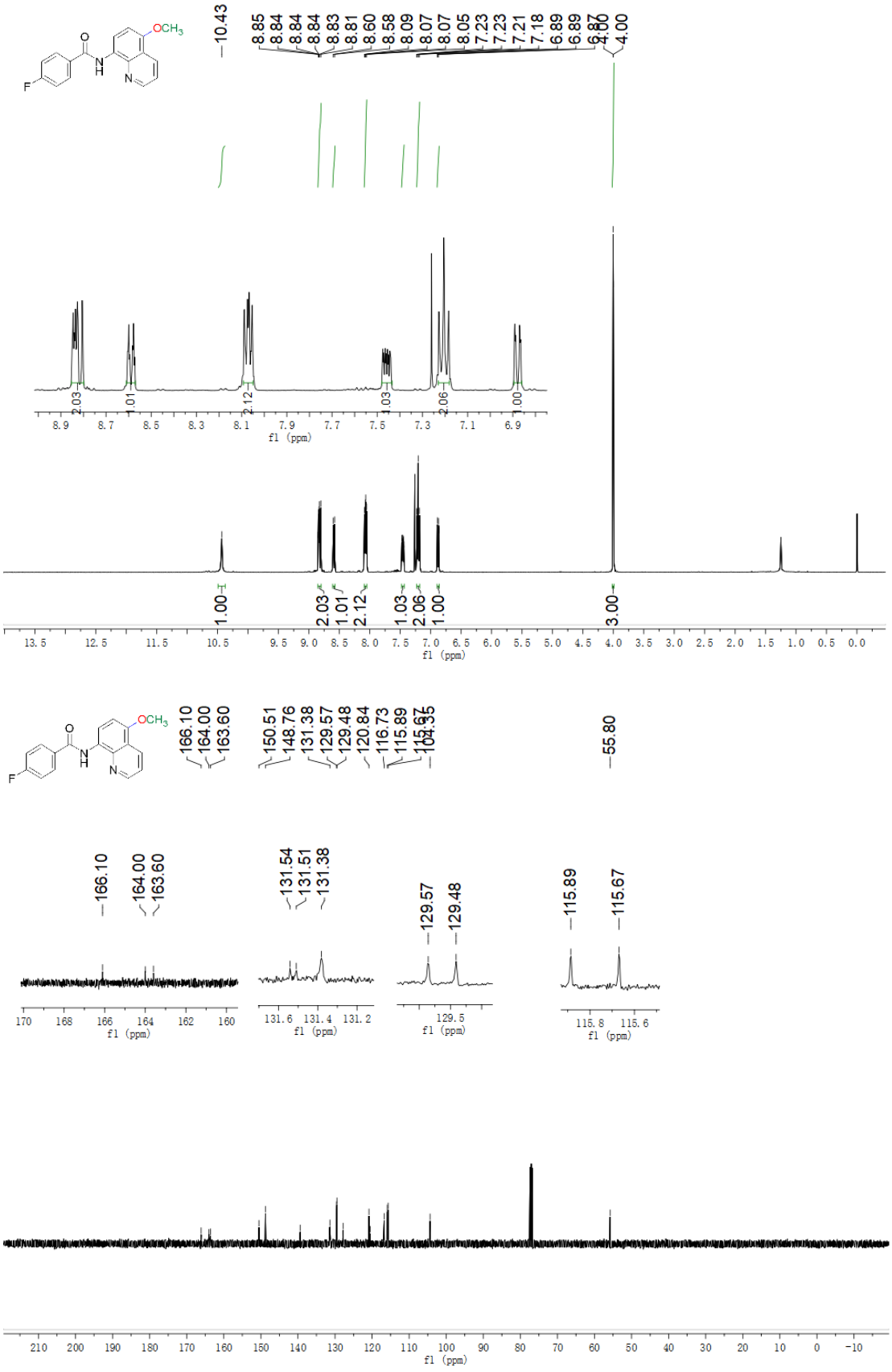

OCH3
O
N
H
I
164.24
150.62
148.80
139.42
137.96
134.81
131.40
128.79
127.73
120.86
120.54
55.81
f1 (ppm)

2h

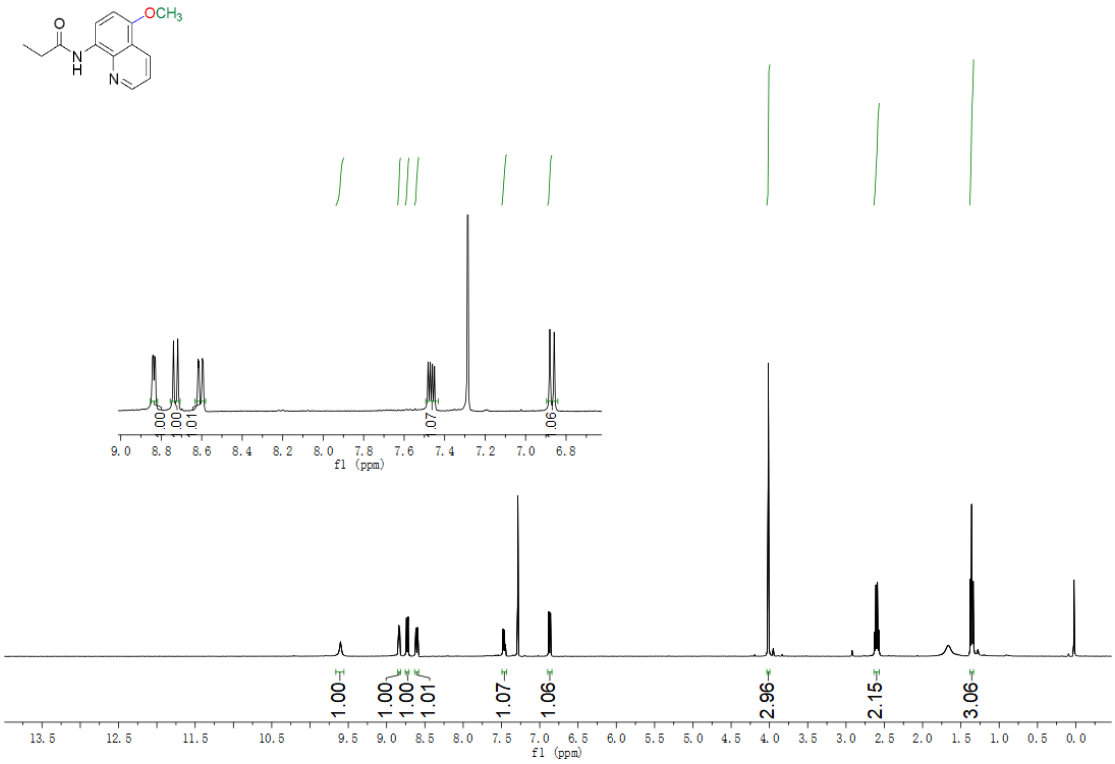

Br
O
N
H
OCH3
10.05
8.88
8.86
8.79
8.60
7.71
7.70
7.69
7.69
7.69
7.67
7.67
7.46
7.46
7.45
7.45
7.44
7.43
7.43
7.42
7.42
7.36
7.35
7.34
7.33
7.32
7.32
1.02
1.00
1.00
2.20
2.19
1.13
1.02
f1 (ppm)
1.00
1.02
1.00
1.00
2.20
2.19
1.13
1.02
3.00
f1 (ppm)

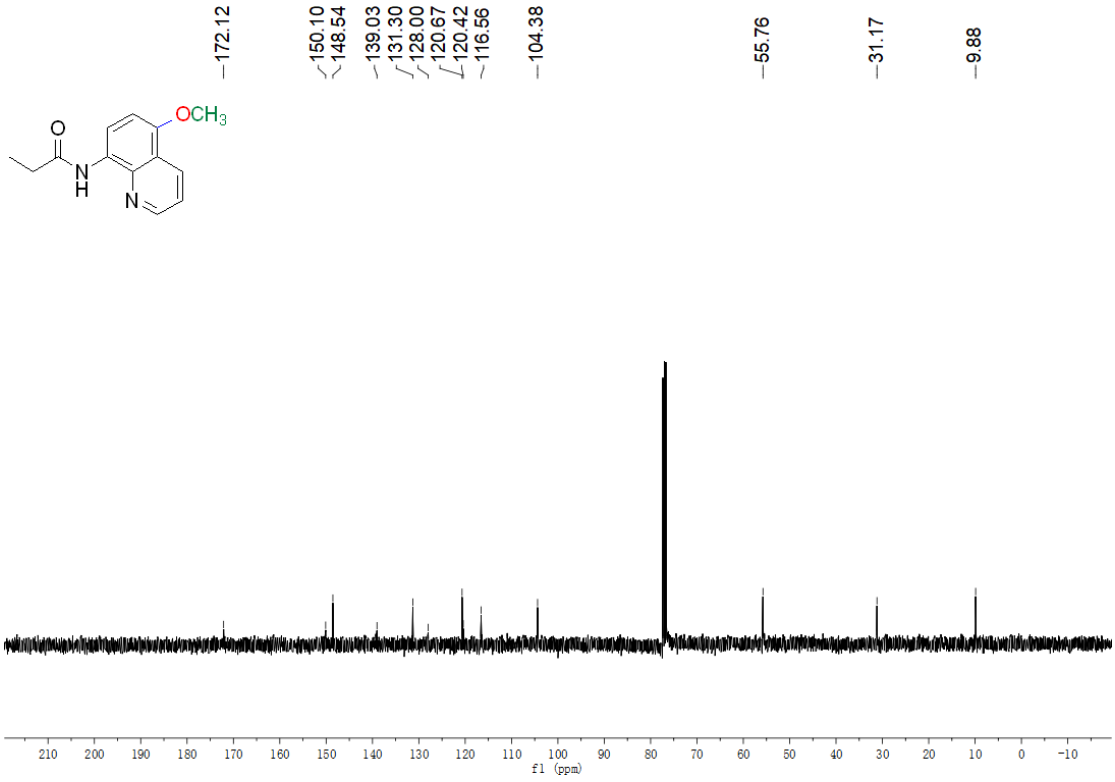

Br
O
N
H
OCH3
165.54
150.77
148.81
133.63
131.33
131.31
129.53
127.62
120.84
120.51
119.77
117.12
104.29
55.85
f1 (ppm)

2i

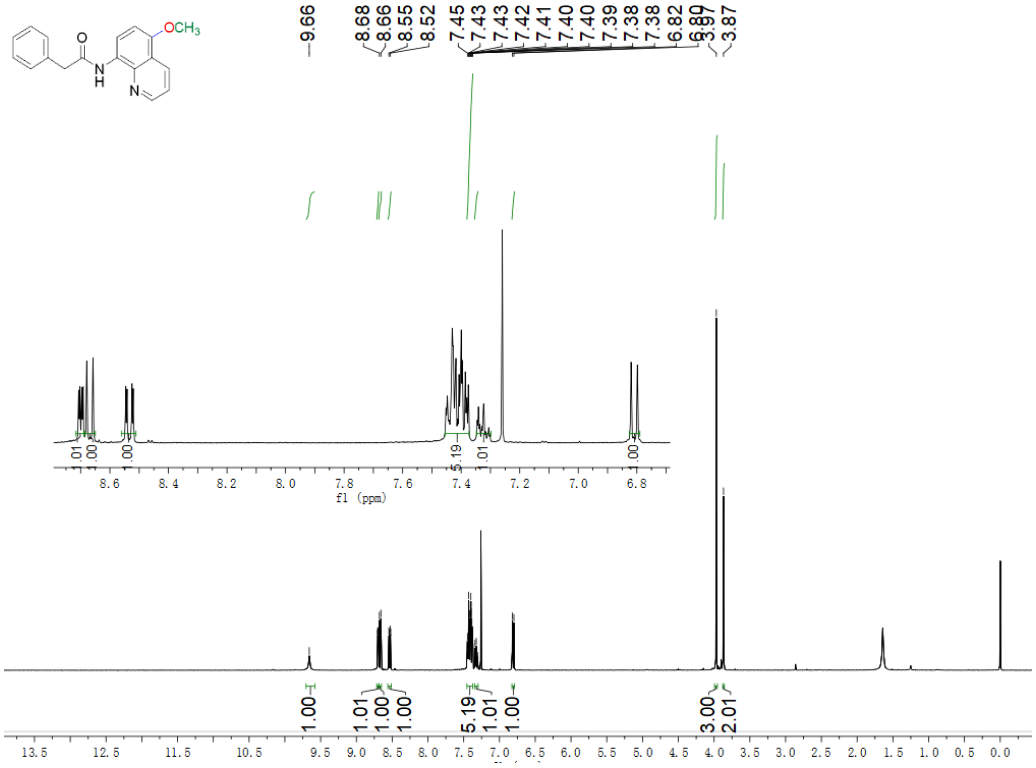

OCH3
F
N
H
O
10.43
8.85
8.84
8.84
8.84
8.83
8.81
8.60
8.58
8.09
8.07
8.07
8.05
7.23
7.23
7.21
7.18
6.89
6.89
6.87
4.00
2.03
1.01
2.12
1.03
2.06
1.00
f1 (ppm)
1.00
2.03
1.01
2.12
1.03
2.06
1.00
3.00
166.10
164.00
163.60
150.51
148.76
131.38
129.57
129.48
120.84
116.73
115.89
115.67
104.35
55.80
131.54
131.51
131.38
115.89
115.67

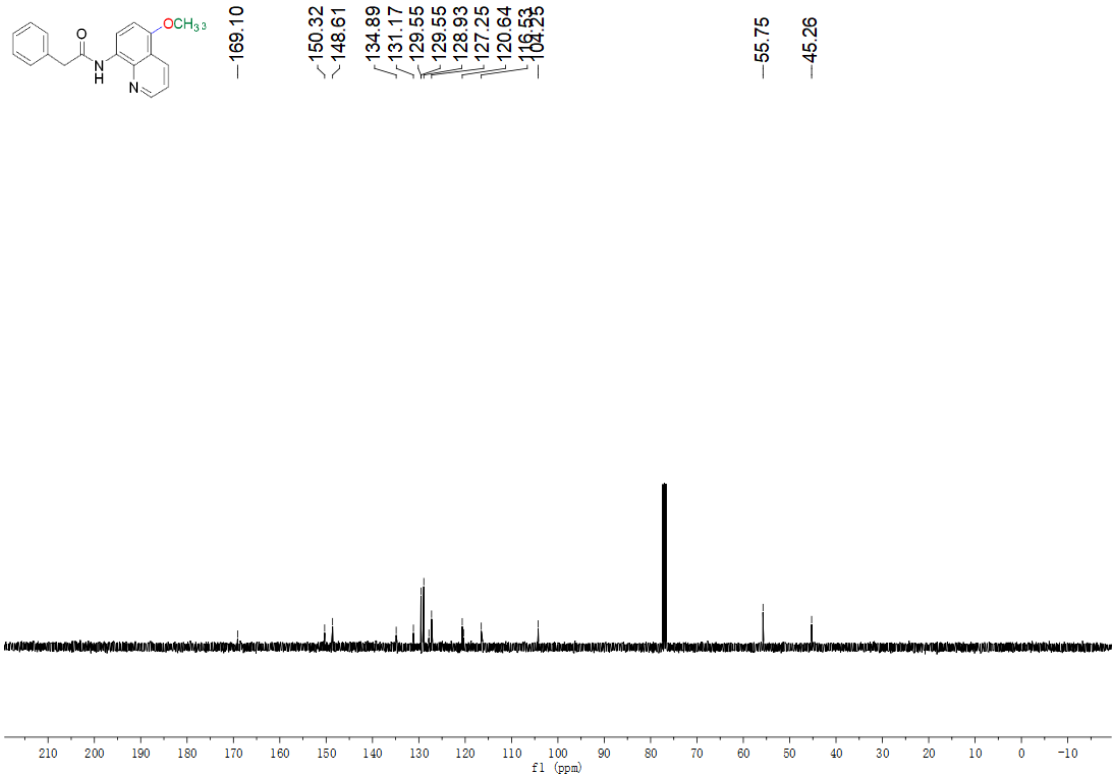
2j


OCH3
O
N
H
N
1.00
1.00
1.00
1.01
1.07
1.06
2.96
2.15
3.06
f1 (ppm)

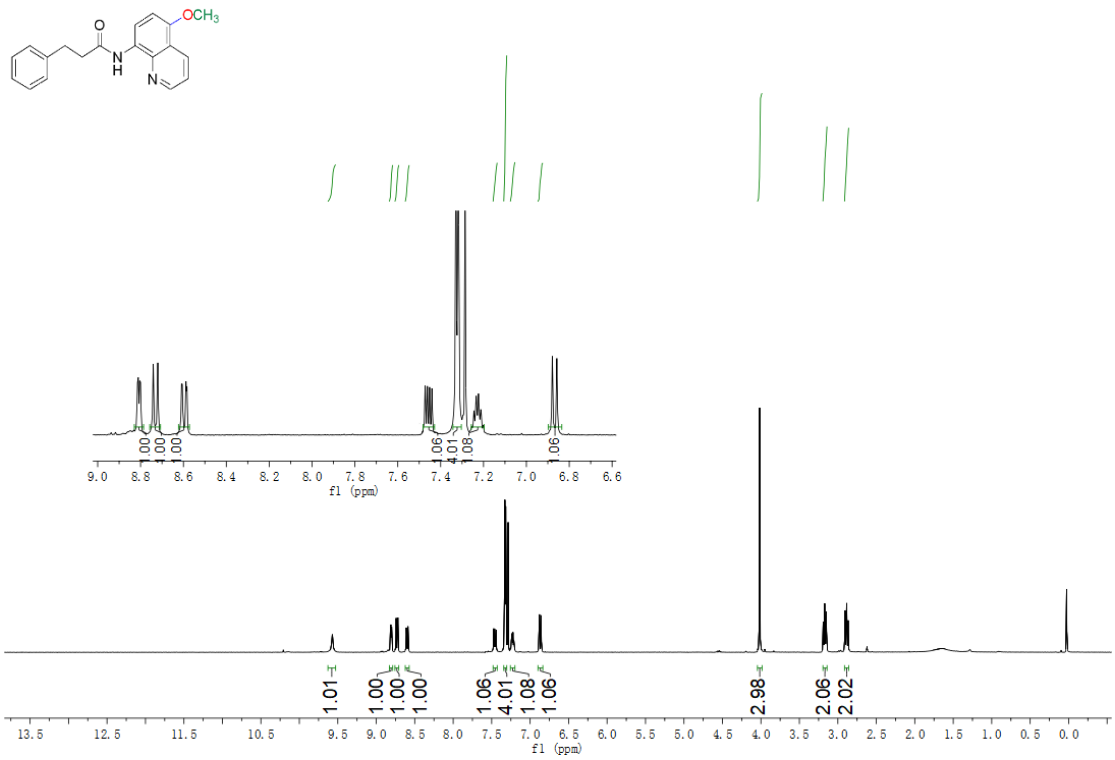

172.12
150.10
148.54
139.03
131.30
128.00
120.67
120.42
116.56
104.38
55.76
31.17
9.88
OCH3
O
N
H
N
f1 (ppm)

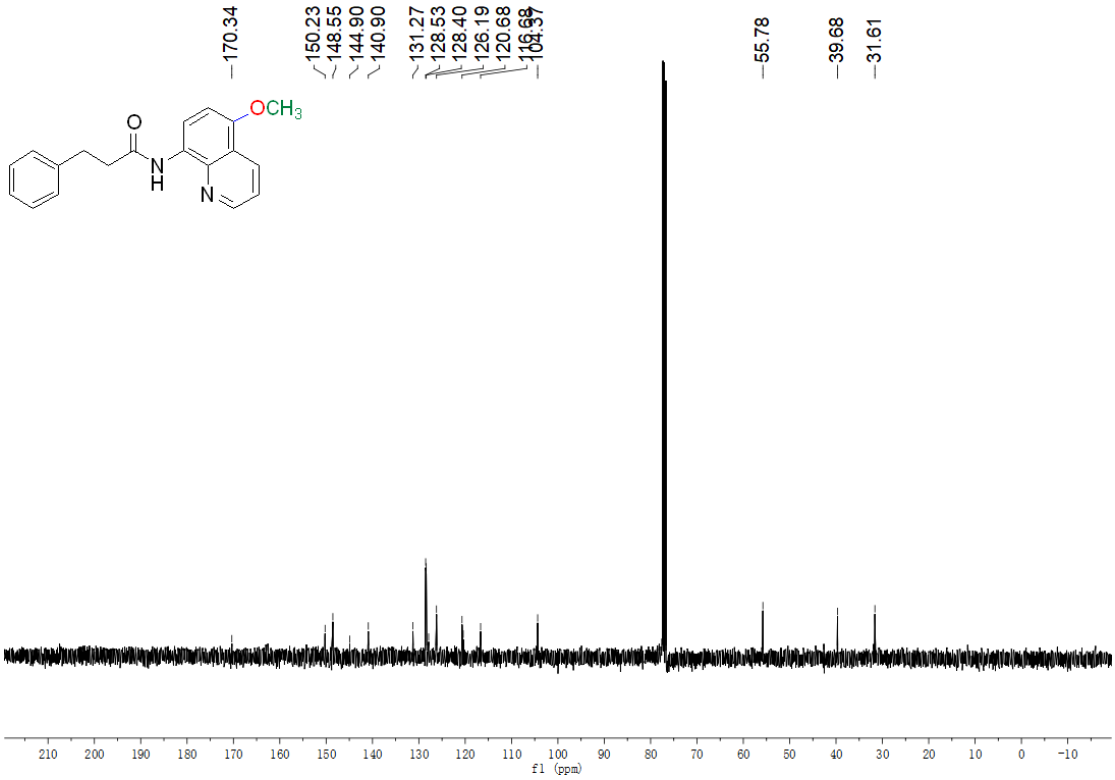
2k


OCH3
9.66
8.68
8.66
8.55
8.52
7.45
7.43
7.43
7.42
7.41
7.40
7.40
7.39
7.38
7.38
6.82
6.80
3.97
3.87
f1 (ppm)

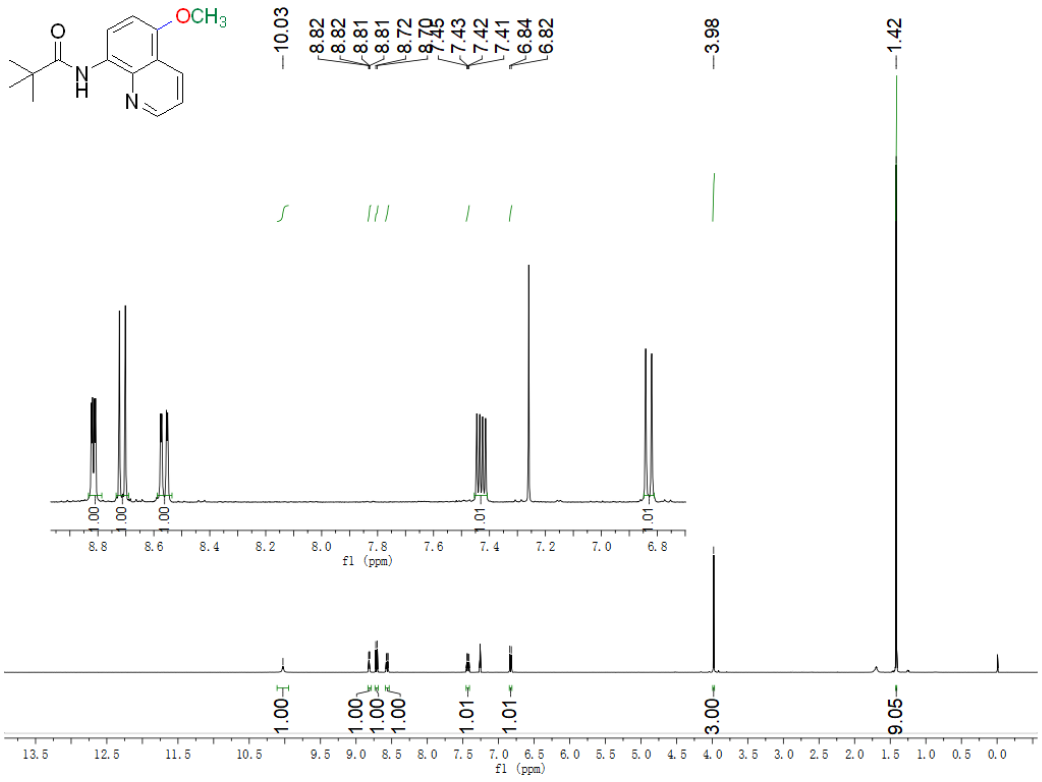

OCH3
169.10
150.32
148.61
134.89
131.17
129.55
129.55
128.93
127.25
120.64
116.53
104.25
55.75
45.26
f1 (ppm)

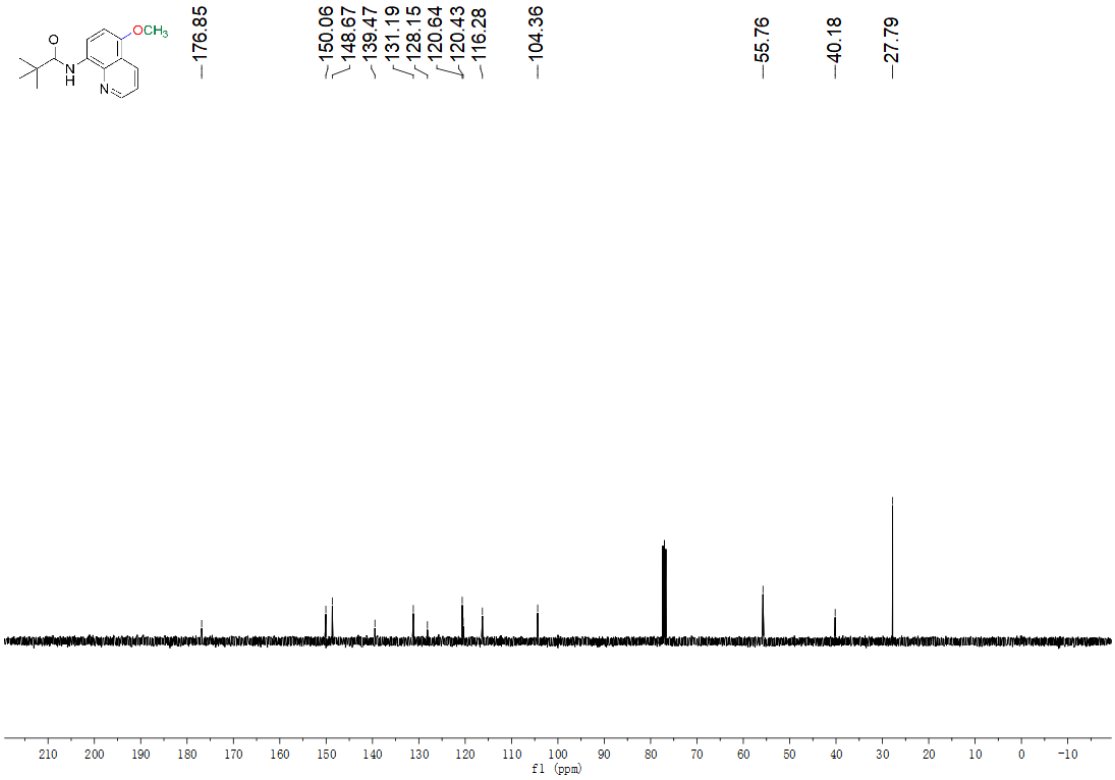
2l


OCH3
O
N
H
N
1.01
1.00
1.00
1.00
1.06
4.01
1.08
1.06
2.98
2.06
2.02
f1 (ppm)

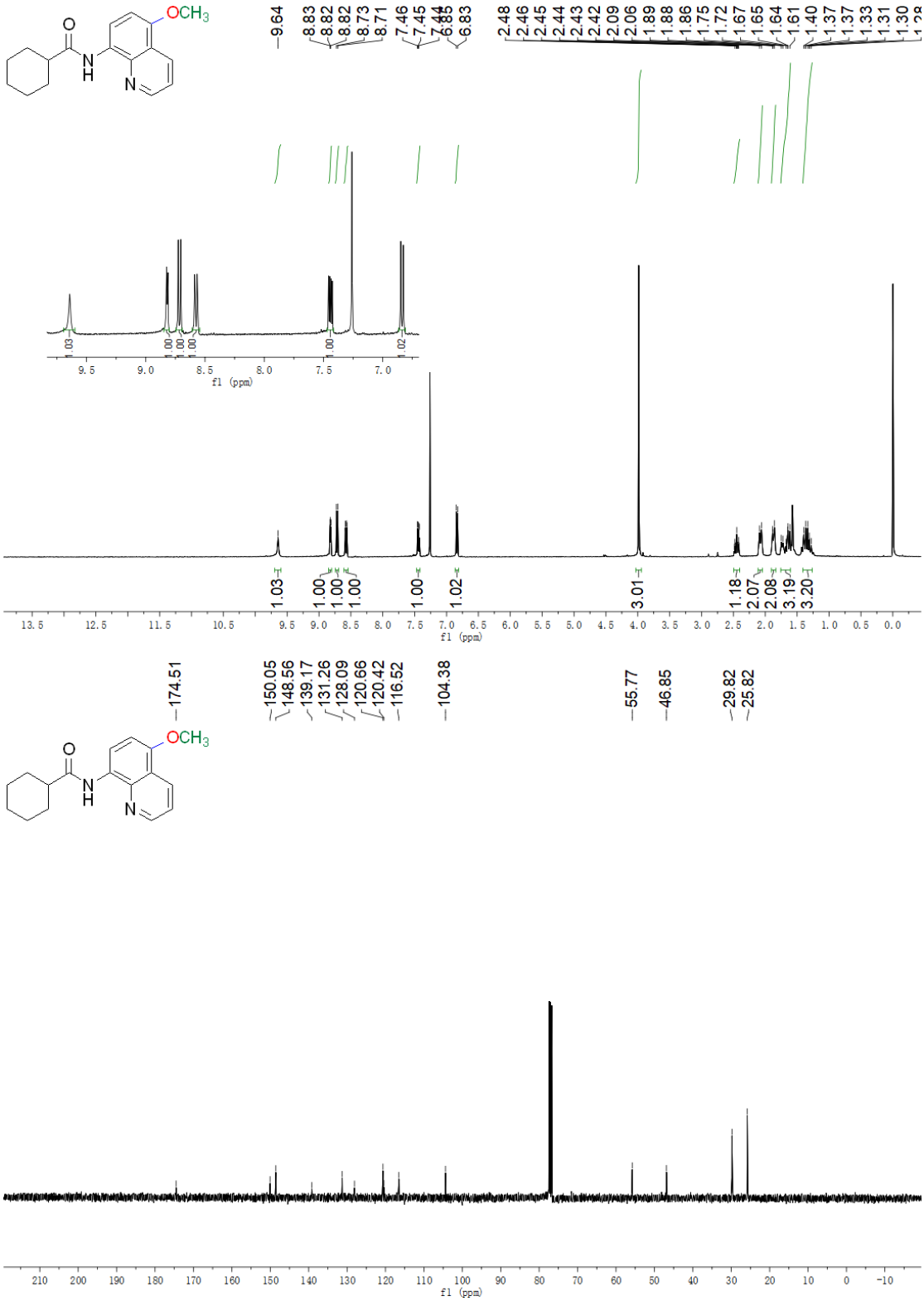

170.34
150.23
148.55
144.90
140.90
131.27
128.53
128.40
126.19
120.68
55.78
39.68
31.61
OCH3
O
N
H
N
f1 (ppm)

2m

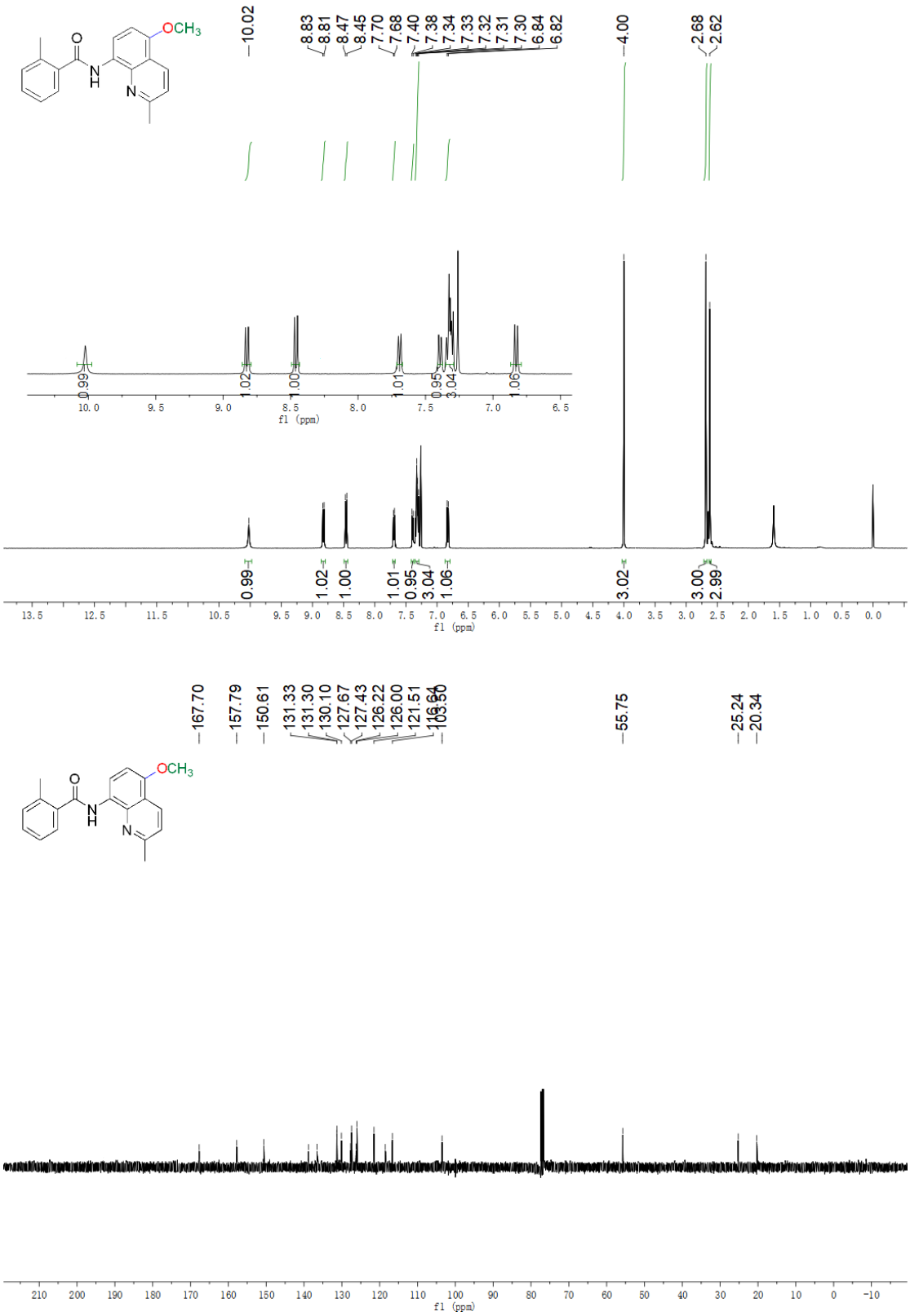

OCH3
O
N
H
N
10.03
8.82
8.82
8.81
8.81
8.72
8.70
7.45
7.43
7.42
7.41
6.84
6.82
3.98
1.42
1.00
1.00
1.00
1.00
1.01
1.01
3.00
9.05
f1 (ppm)


OCH3
O
N
H
N
176.85
150.06
148.67
139.47
131.19
128.15
120.64
120.43
116.28
104.36
55.76
40.18
27.79
f1 (ppm)

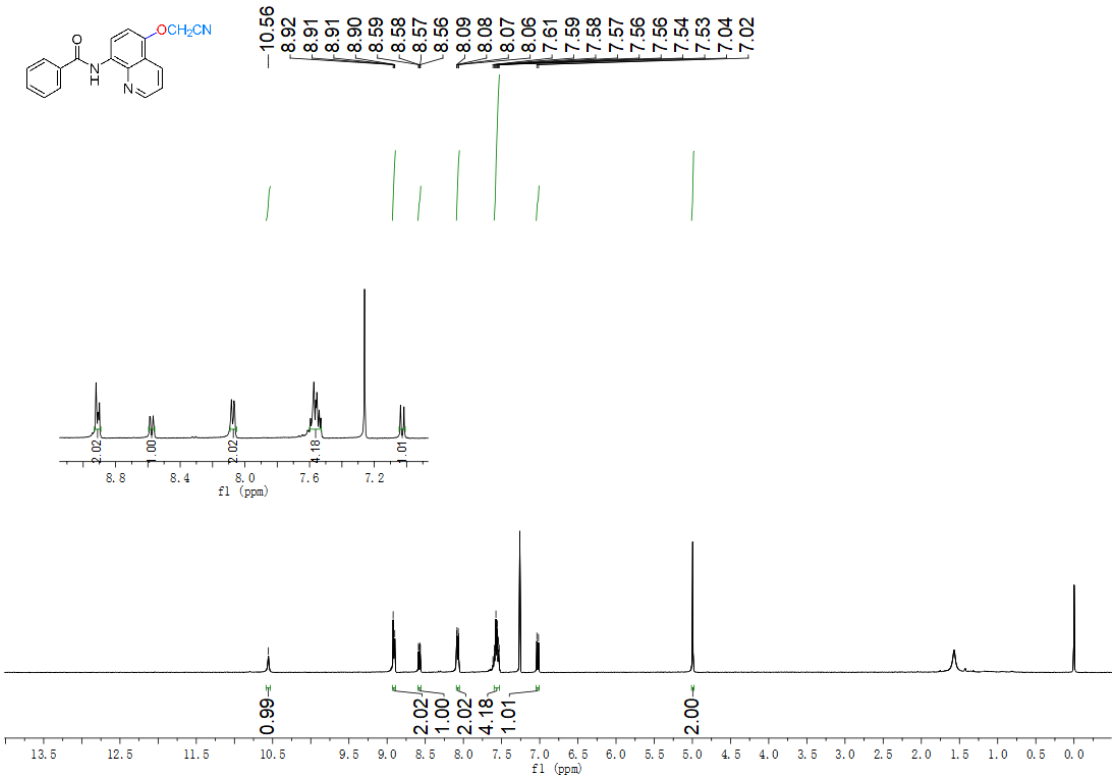
2n

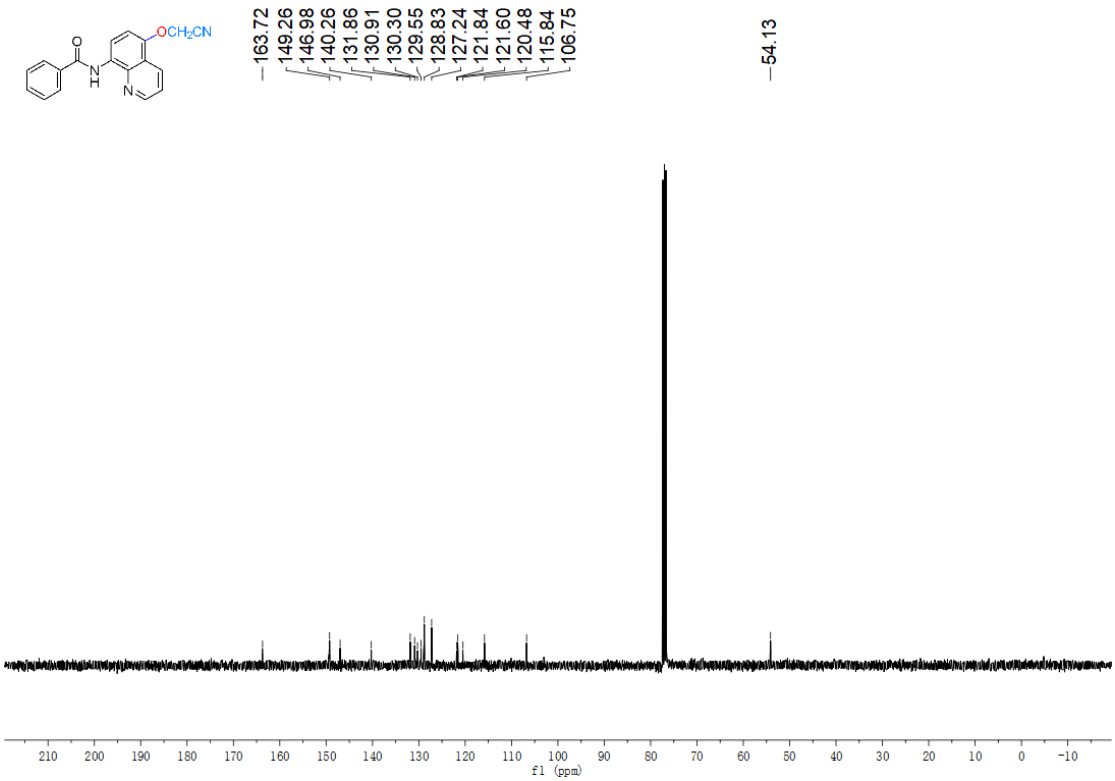

OCH3
O
N
H
N
9.64
8.83
8.82
8.82
8.73
8.71
7.46
7.45
7.44
6.85
6.83
2.48
2.46
2.45
2.44
2.43
2.42
2.09
2.06
1.89
1.88
1.86
1.75
1.72
1.67
1.65
1.64
1.61
1.40
1.37
1.37
1.33
1.31
1.30
1.03
1.00
1.00
1.00
1.00
1.00
1.02
3.01
1.18
2.07
2.08
3.19
3.20
f1 (ppm)
174.51
150.05
148.56
139.17
131.26
128.09
120.66
120.42
116.52
104.38
55.77
46.85
29.82
25.82
f1 (ppm)

2s

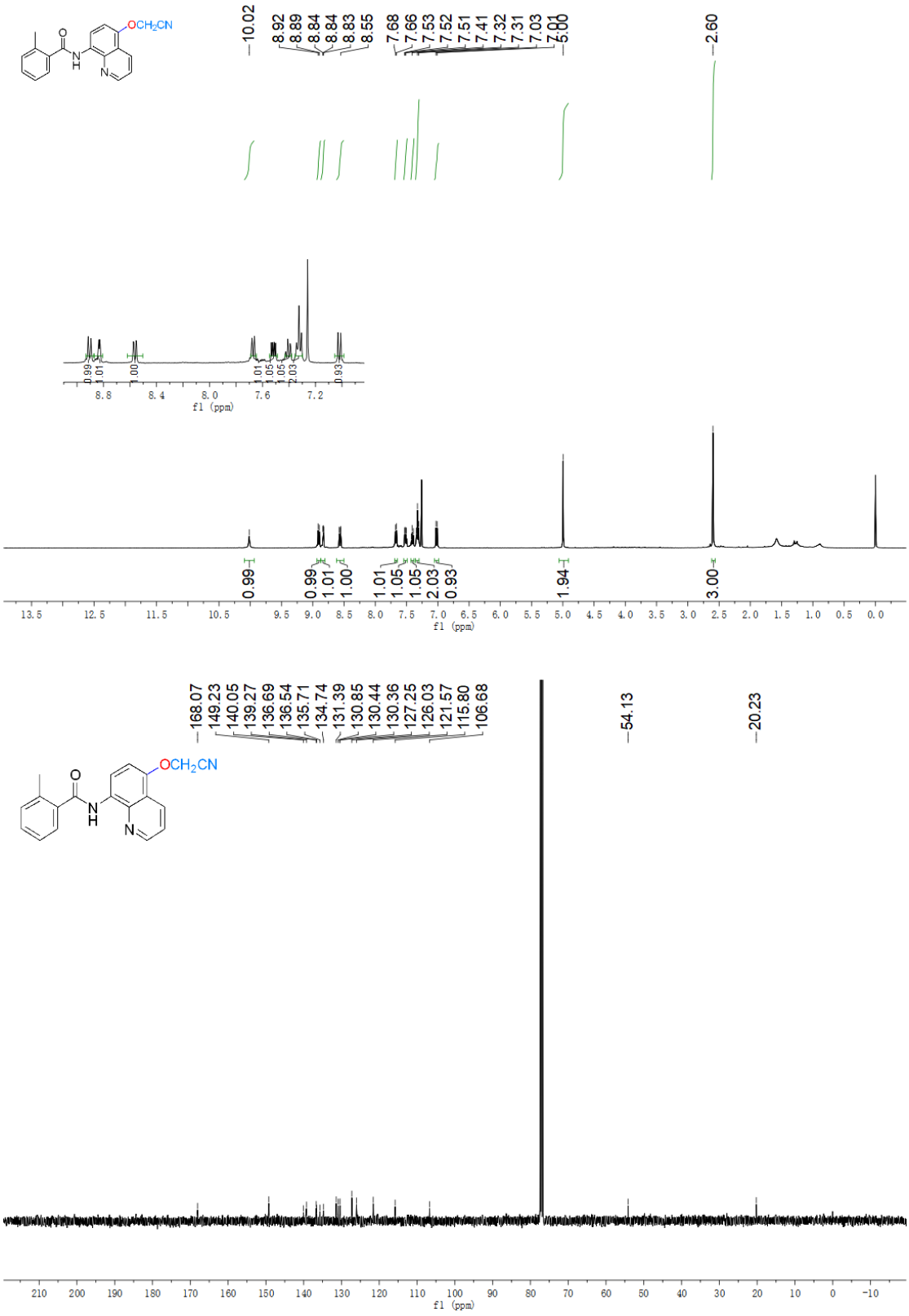

OCH3
O
N
H
N
10.02
8.83
8.81
8.47
8.45
7.70
7.68
7.40
7.38
7.34
7.33
7.32
7.31
7.30
6.84
6.82
4.00
2.68
2.62
0.99
1.02
1.00
1.01
0.95
3.04
1.06
3.02
3.00
2.99
f1 (ppm)
167.70
157.79
150.61
131.33
131.30
130.10
127.67
127.43
126.22
126.00
121.51
116.64
103.50
55.75
25.24
20.34
f1 (ppm)

3a

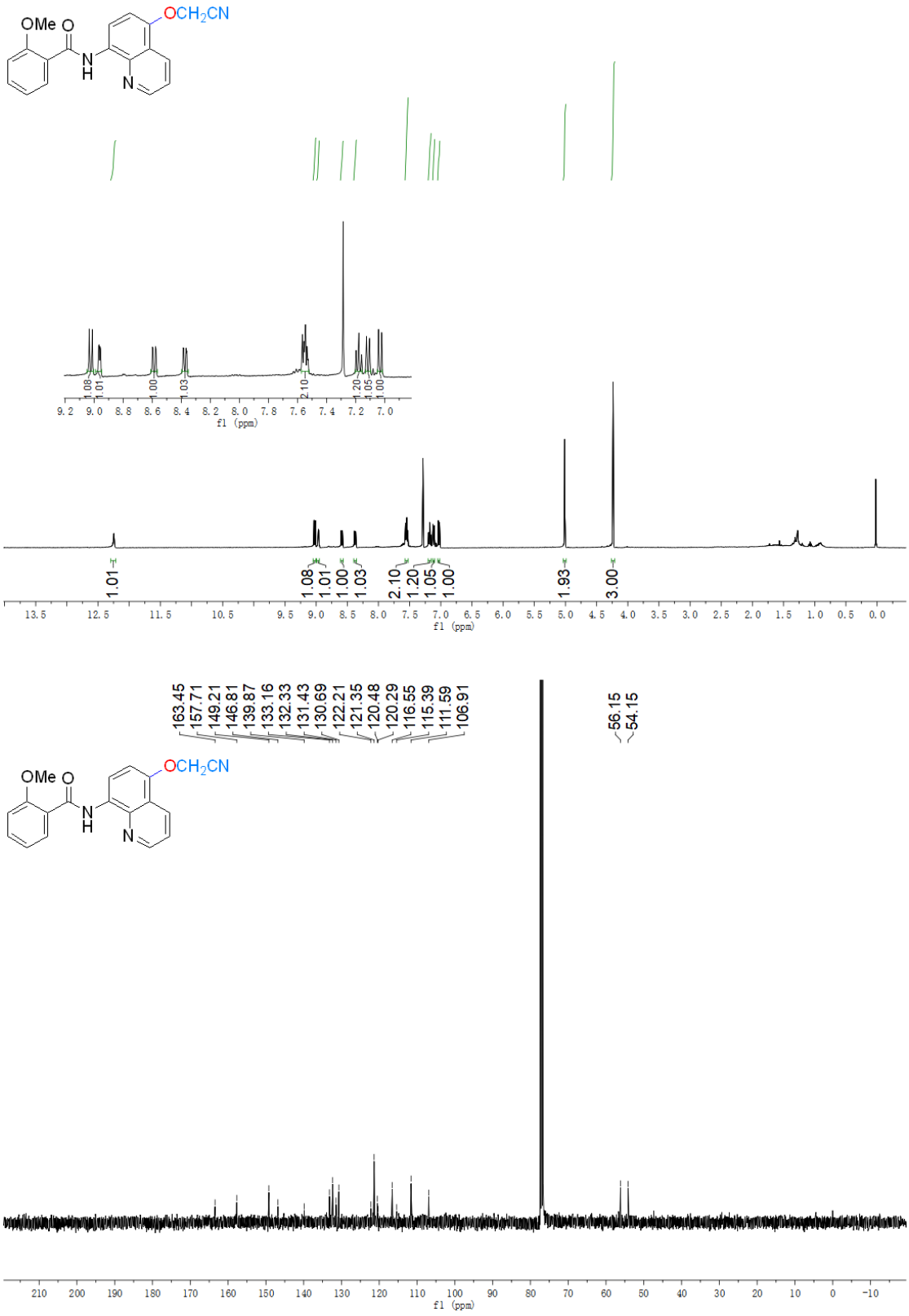

OCH2CN
10.56
8.92
8.91
8.91
8.90
8.59
8.58
8.57
8.56
8.09
8.08
8.07
8.06
7.61
7.59
7.58
7.57
7.56
7.56
7.54
7.53
7.04
7.02
2.02
1.00
2.02
4.18
1.01
2.00
f1 (ppm)


OCH2CN
163.72
149.26
146.98
140.26
131.86
130.91
130.30
129.55
128.83
127.24
121.84
121.60
120.48
115.84
106.75
54.13
f1 (ppm)

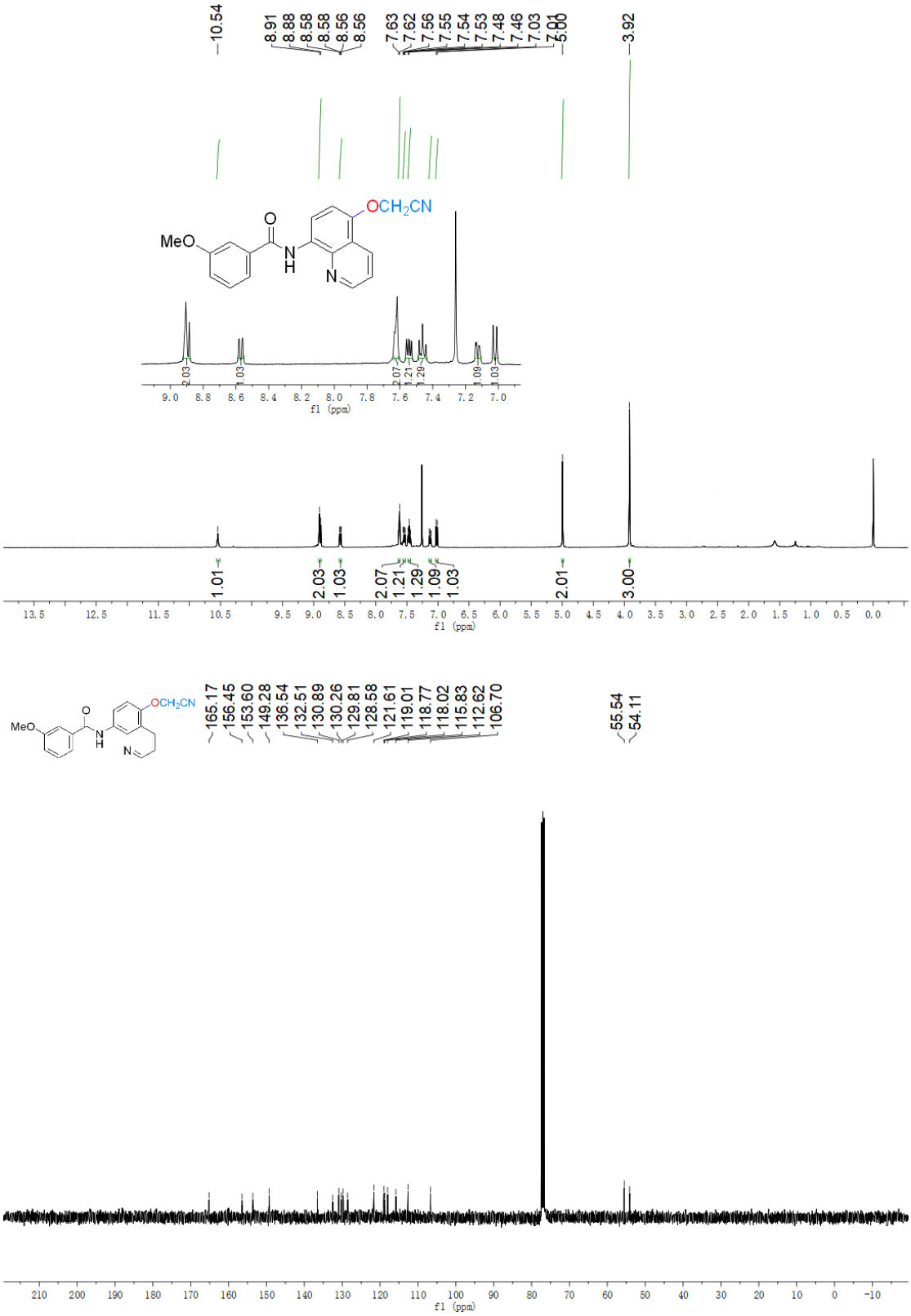
3b


OCH2CN
10.02
8.92
8.89
8.84
8.84
8.83
8.55
7.68
7.66
7.53
7.52
7.51
7.41
7.32
7.31
7.03
7.01
5.00
2.60
0.99
1.01
1.00
1.01
1.05
1.05
2.03
0.93
1.94
3.00
f1 (ppm)
168.07
149.23
140.05
139.27
136.69
136.54
135.71
134.74
131.39
130.85
130.44
130.36
127.25
126.03
121.57
115.80
106.68
54.13
20.23
OCH2CN
f1 (ppm)

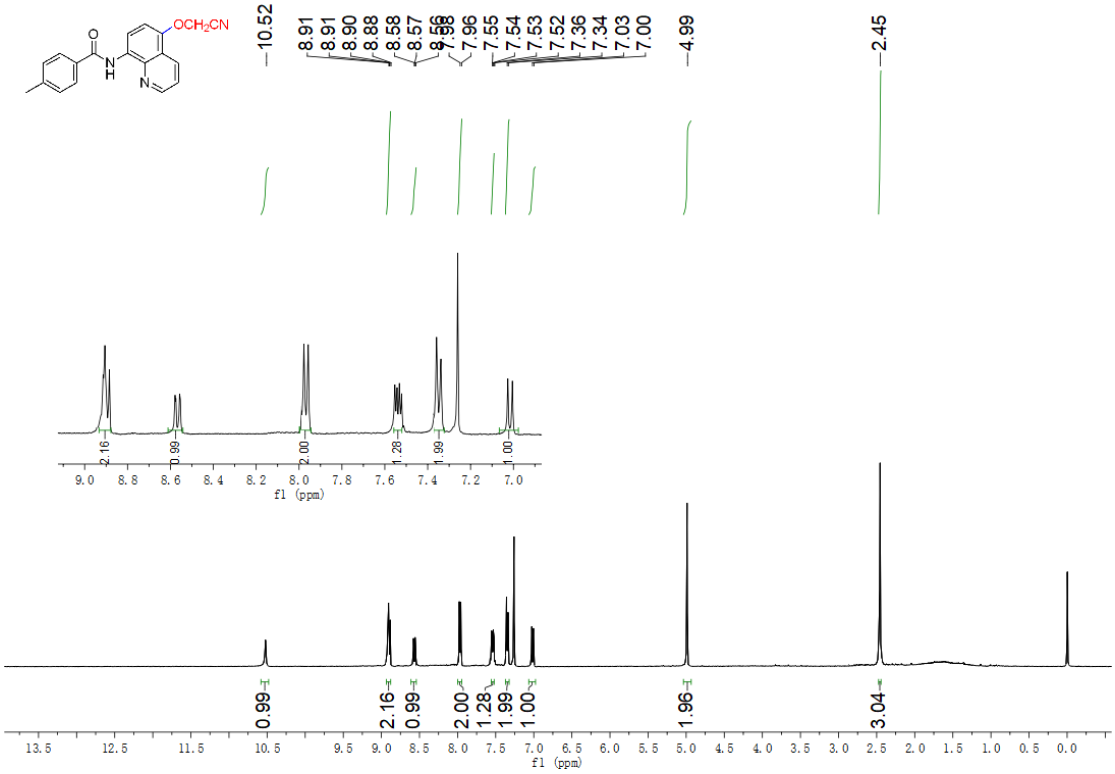
3c

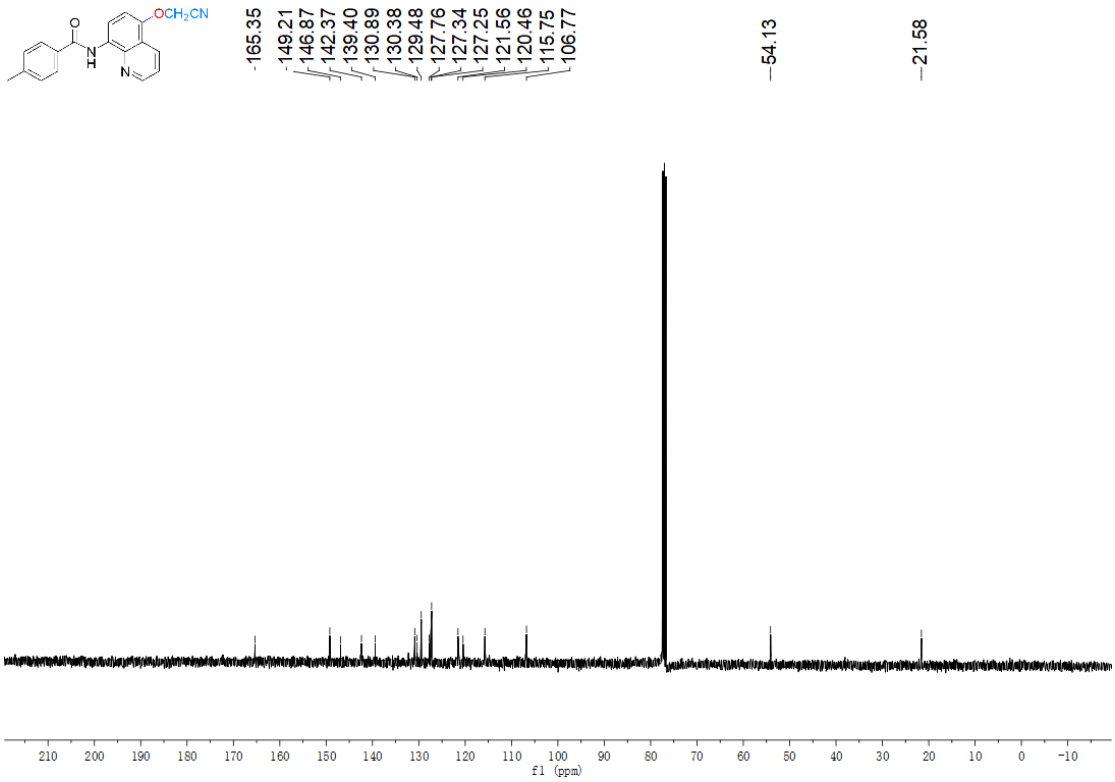

OMe
O
N
H
N
OCH2CN
1.01
1.08
1.01
1.00
1.03
2.10
1.20
1.05
1.00
1.93
3.00
f1 (ppm)
163.45
157.71
149.21
146.81
139.87
133.16
132.33
131.43
130.69
122.21
121.35
120.48
120.29
116.55
115.39
111.59
106.91
56.15
54.15
f1 (ppm)

3d

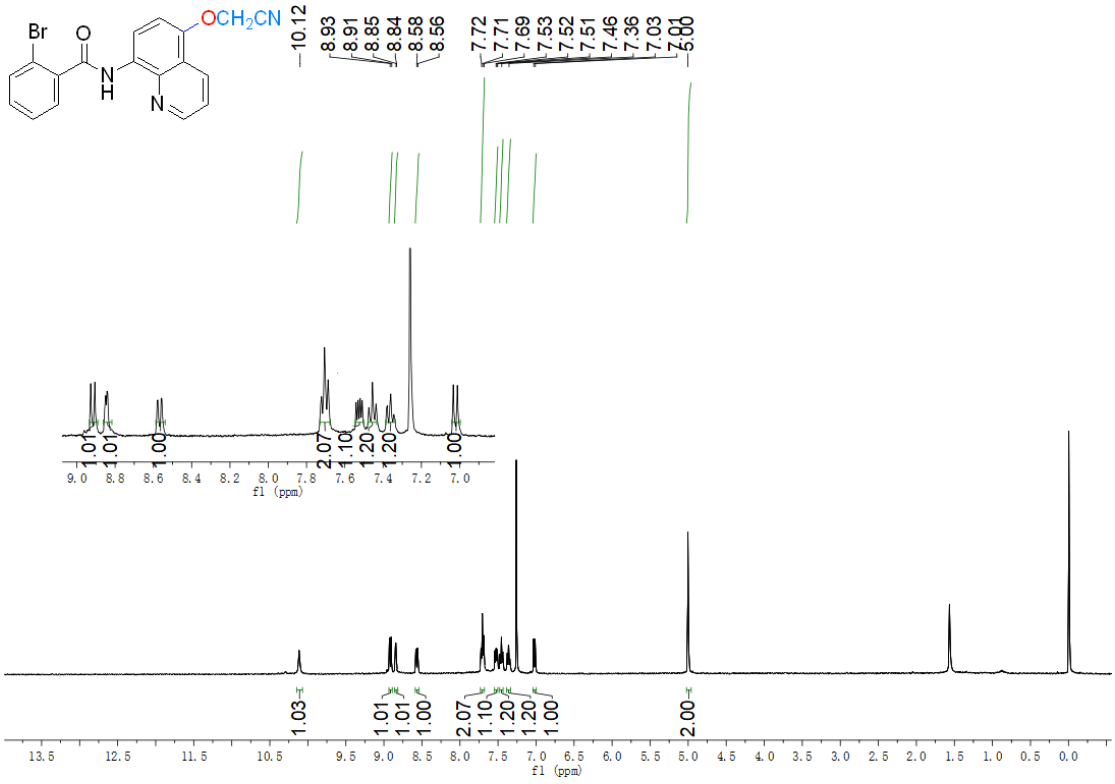

10.54
8.91
8.88
8.58
8.58
8.56
8.56
7.63
7.62
7.56
7.55
7.54
7.53
7.48
7.46
7.03
7.00
5.00
3.92
OCH2CN
MeO
O
N
H
N
f1 (ppm)
1.01
2.03
1.03
2.07
1.21
1.29
1.09
1.03
2.01
3.00
165.17
156.45
153.60
149.28
136.54
132.51
130.89
130.26
129.81
128.58
121.61
119.01
118.77
118.02
115.83
112.62
106.70
55.54
54.11

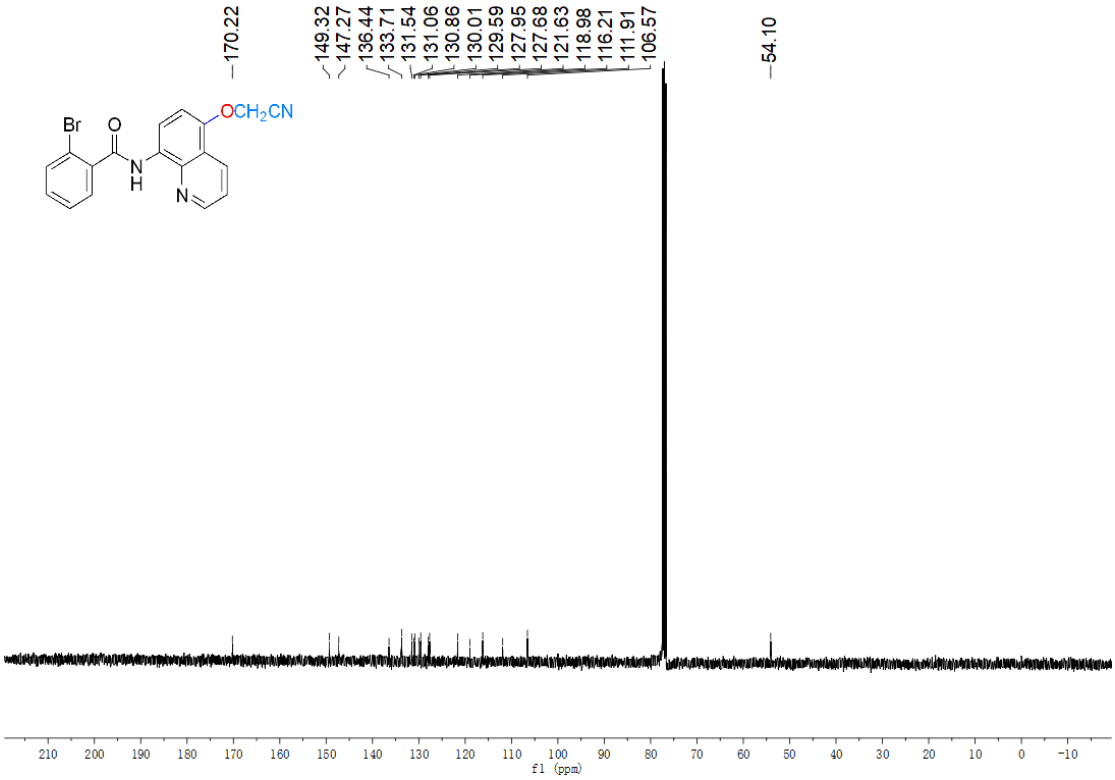
3e


OCH2CN
10.52
8.91
8.91
8.90
8.88
8.58
8.57
7.96
7.55
7.54
7.53
7.52
7.36
7.34
7.03
7.00
4.99
2.45
0.99
2.16
0.99
2.00
1.28
1.99
1.00
1.96
3.04
f1 (ppm)

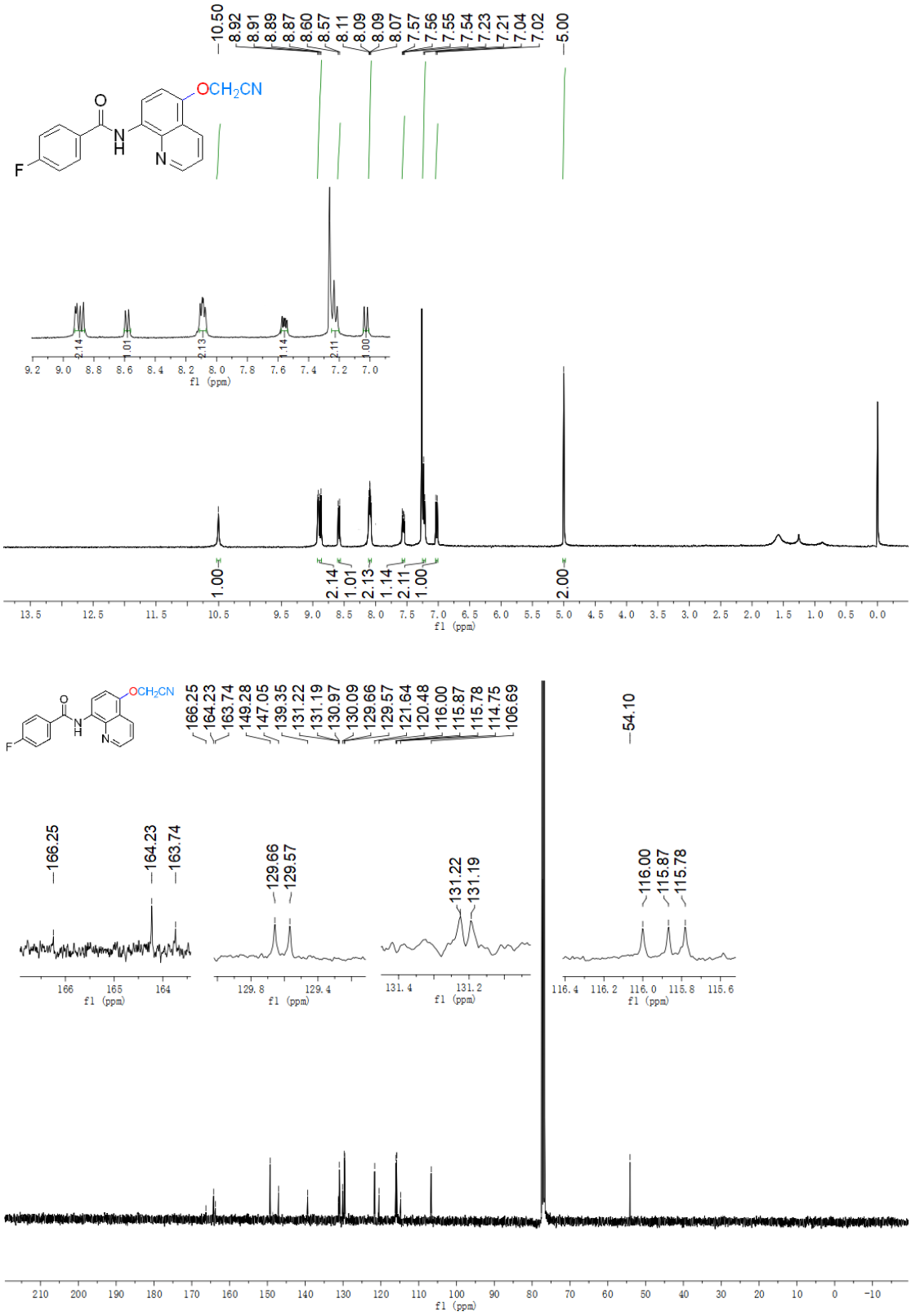

OCH2CN
165.35
149.21
146.87
142.37
139.40
130.89
130.38
129.48
127.76
127.34
127.25
121.56
120.46
115.75
106.77
54.13
21.58
f1 (ppm)

3h

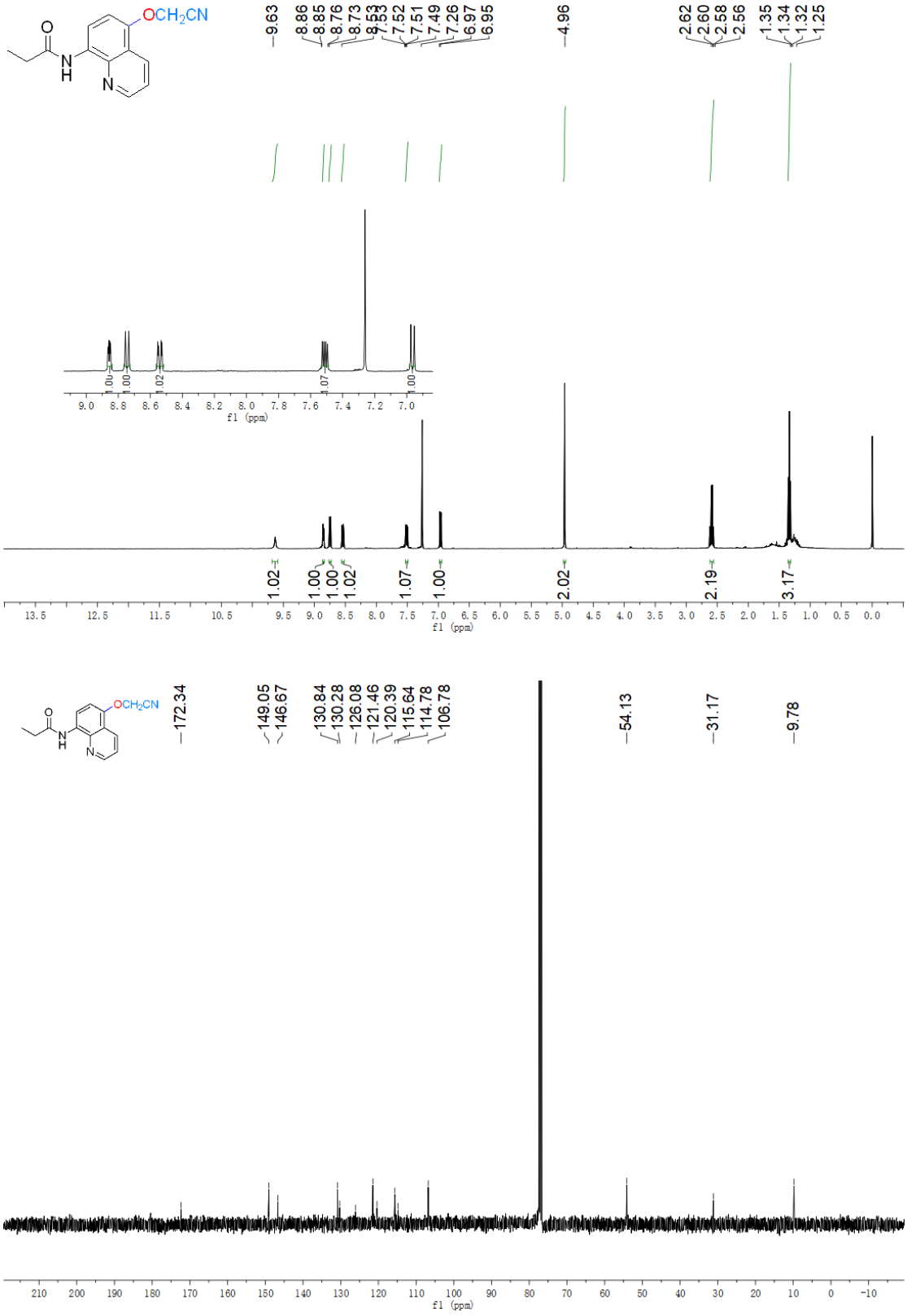

Br
O
N
H
N
OCH2CN
10.12
8.93
8.91
8.85
8.84
8.58
8.56
7.72
7.71
7.69
7.53
7.52
7.51
7.46
7.36
7.03
7.01
5.00
1.03
1.01
1.01
1.00
2.07
1.10
1.20
1.20
1.00
2.00
f1 (ppm)


Br
O
N
H
N
OCH2CN
170.22
149.32
147.27
136.44
133.71
131.54
131.06
130.86
130.01
129.59
127.95
127.68
121.63
118.98
116.21
111.91
106.57
54.10
f1 (ppm)

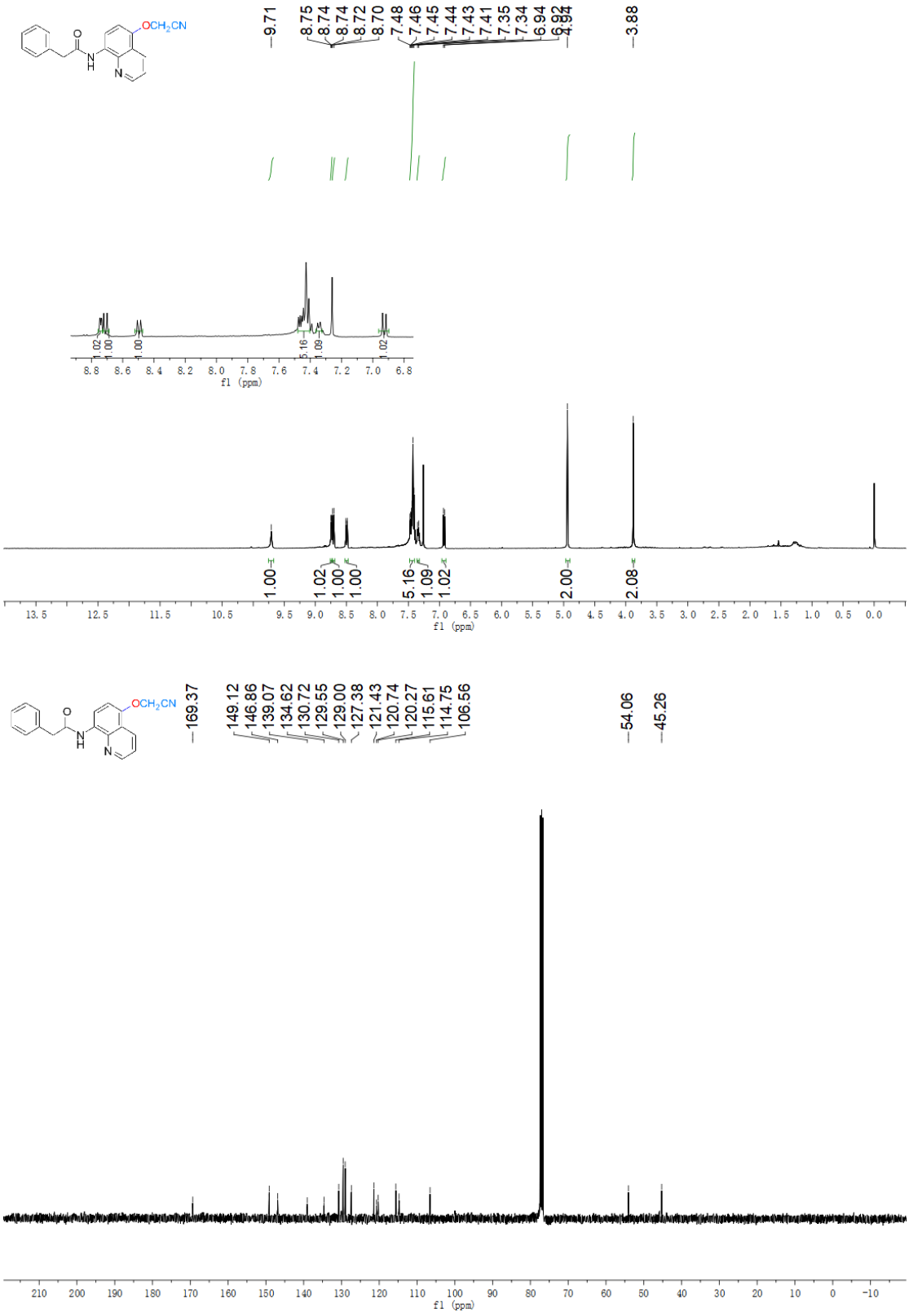
3i


10.50
8.92
8.91
8.89
8.87
8.60
8.57
8.11
8.09
8.09
8.07
7.57
7.56
7.55
7.54
7.23
7.21
7.04
7.02
5.00
OCH2CN
O
N
H
N
F
1.00
2.14
1.01
2.13
1.14
2.11
1.00
2.00
f1 (ppm)
166.25
164.23
163.74
149.28
147.05
139.35
131.22
131.19
130.97
130.09
129.66
129.57
121.64
120.48
116.00
115.87
115.78
114.75
106.69
54.10
f1 (ppm)

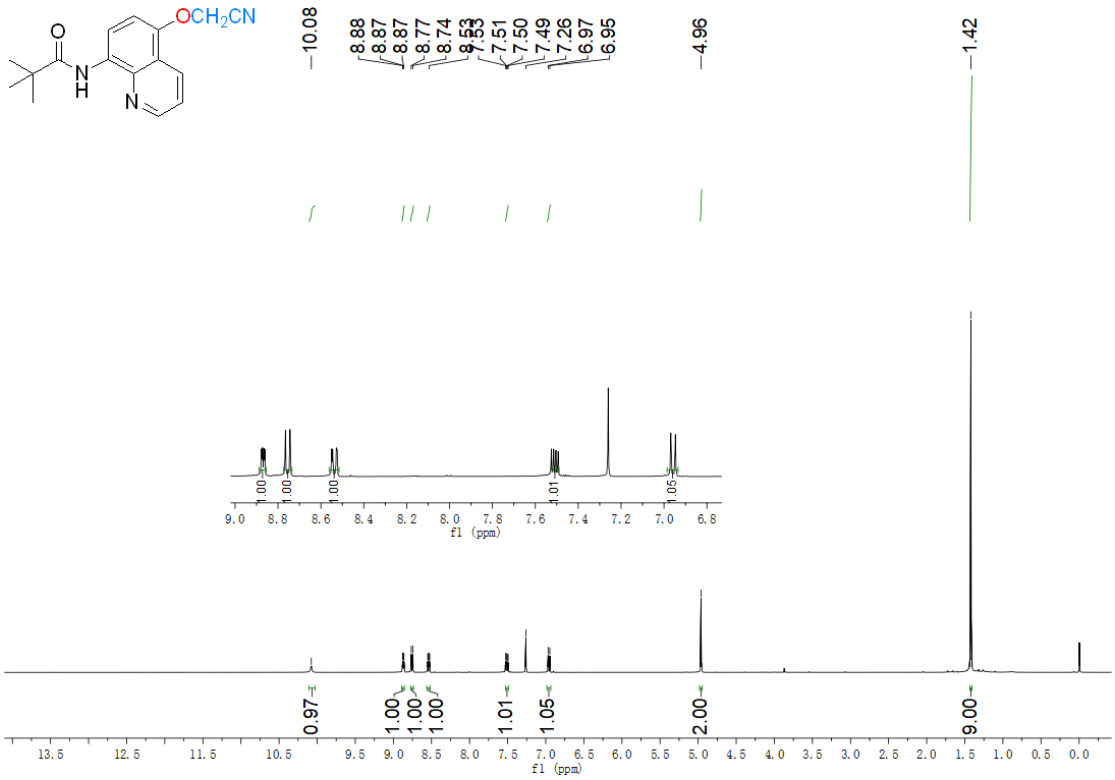
3j

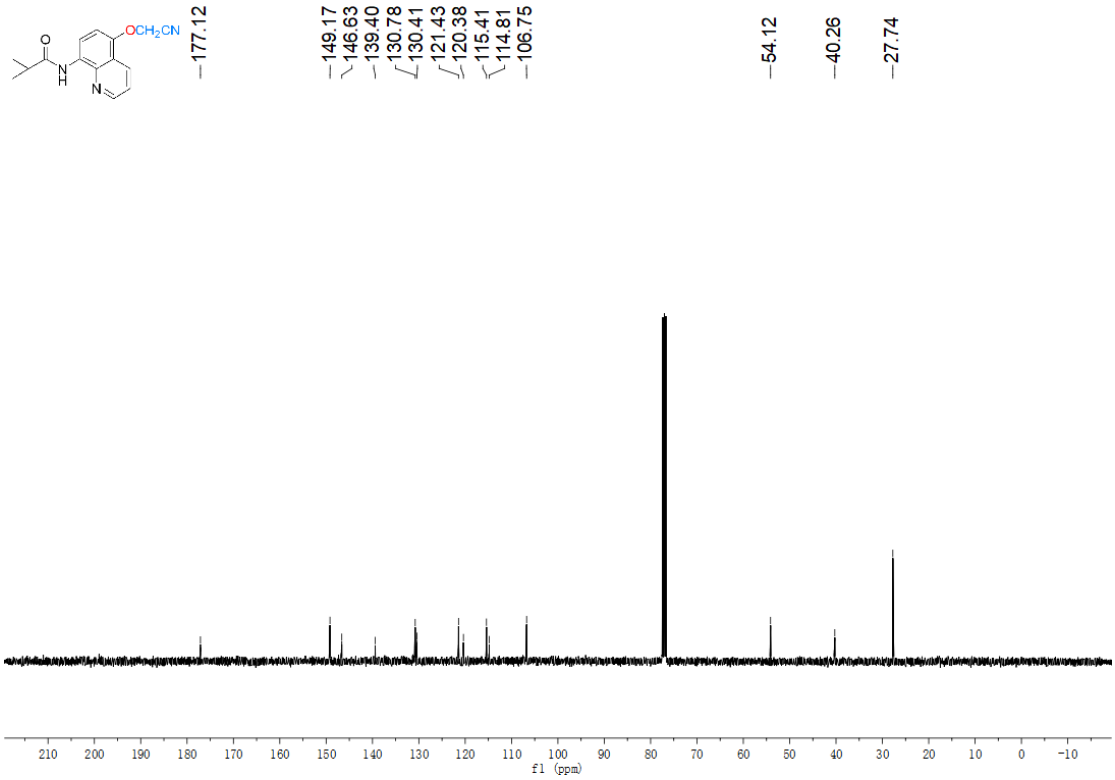

OCH2CN
9.63
8.86
8.85
8.76
8.73
8.53
7.52
7.51
7.49
7.26
6.97
6.95
4.96
2.62
2.60
2.58
2.56
1.35
1.34
1.32
1.25
1.02
1.00
1.00
1.02
1.07
1.00
2.02
2.19
3.17
f1 (ppm)
172.34
149.05
146.67
130.84
130.28
126.08
121.46
120.39
115.64
114.78
106.78
54.13
31.17
9.78
f1 (ppm)

3k


OCH2CN
9.71
8.75
8.74
8.74
8.72
8.70
7.48
7.46
7.45
7.44
7.43
7.41
7.35
7.34
6.94
6.92
4.94
3.88
1.00
1.02
1.00
1.00
5.16
1.09
1.02
2.00
2.08
f1 (ppm)
OCH2CN
169.37
149.12
146.86
139.07
134.62
130.72
129.55
129.00
127.38
121.43
120.74
120.27
115.61
114.75
106.56
54.06
45.26
f1 (ppm)

3m

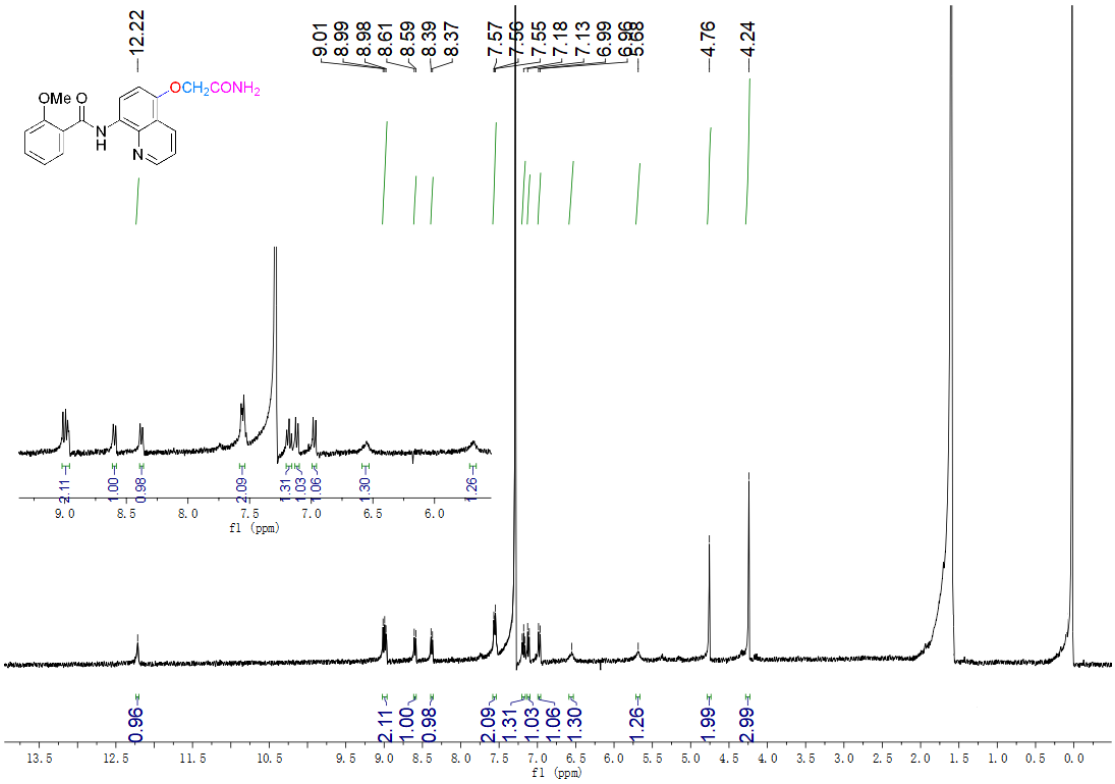

OCH2CN
10.08
8.88
8.87
8.87
8.77
8.74
8.53
7.51
7.50
7.49
7.26
6.97
6.95
4.96
1.42
0.97
1.00
1.00
1.00
1.01
1.05
2.00
9.00
f1 (ppm)

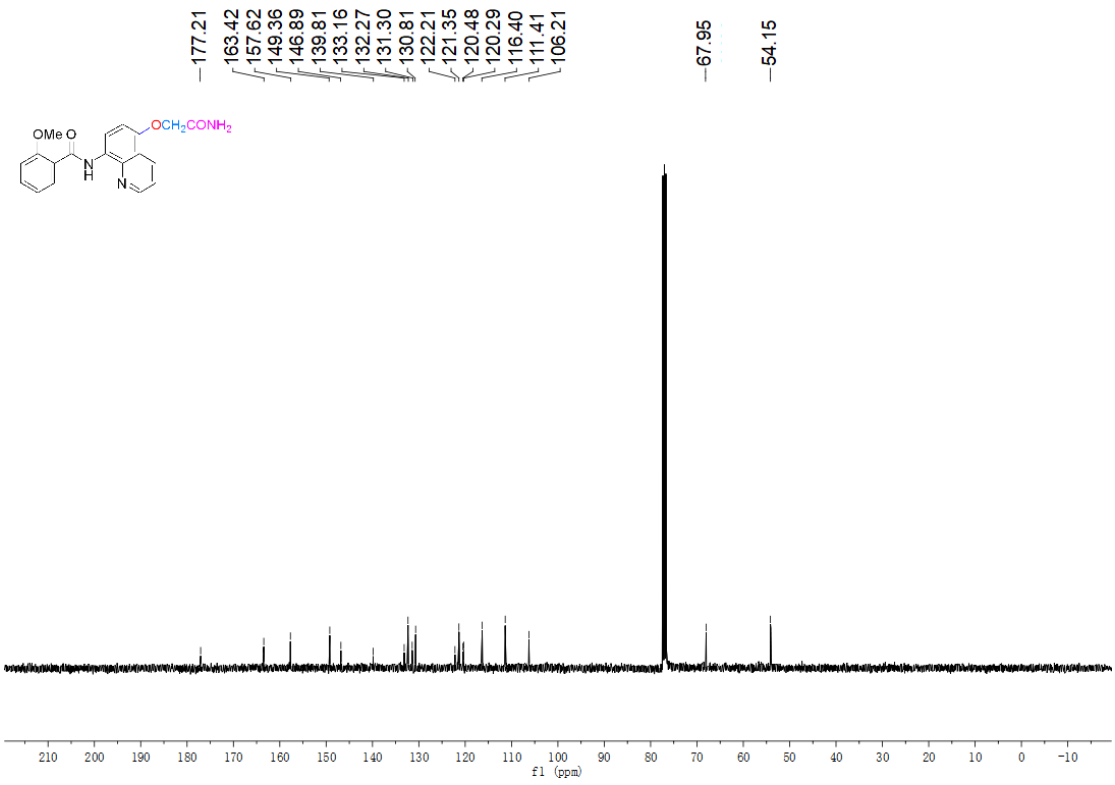

OCH2CN
177.12
149.17
146.63
139.40
130.78
130.41
121.43
120.38
115.41
114.81
106.75
54.12
40.26
27.74
f1 (ppm)

3s


OCH2CN
10.07
8.87
8.85
8.43
8.41
7.70
7.68
7.42
7.38
7.36
7.36
7.34
7.32
6.95
6.93
4.97
2.71
2.62
1.00
1.00
1.01
4.39
1.02
2.00
3.00
3.02
f1 (ppm)
165.38
158.49
147.17
138.79
136.66
131.42
130.86
130.31
130.17
129.86
127.41
126.07
122.35
118.50
115.80
114.87
105.79
54.11
25.30
20.34
OCH2CN
f1 (ppm)

6


12.22
9.01
8.99
8.98
8.61
8.59
8.39
8.37
7.57
7.56
7.55
7.18
7.13
6.99
6.96
6.68
4.76
4.24
OMe O
OCH2CONH2
N
H
N
0.96
2.11
1.00
0.98
2.09
1.31
1.03
1.06
1.30
1.26
1.99
2.99
f1 (ppm)


177.21
163.42
157.62
149.36
146.89
139.81
133.16
132.27
131.30
130.81
122.21
121.35
120.48
120.29
116.40
111.41
106.21
67.95
54.15
OMe O
OCH2CONH2
N
H
N
f1 (ppm)