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Copper-catalyzed α-C−H amidation of simple ethers through C(sp^3)−H/N−H cross dehydrogenative coupling

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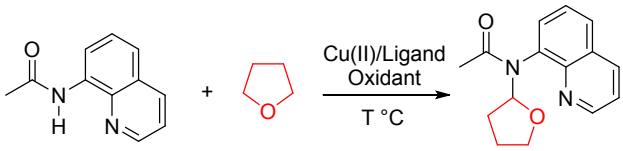
Optimization process data in detail

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

entry	Cu(II) (20 mol%)	oxidant (equiv)	ligand (20 mol%)	T (˚C)	yield (%)[b]
1	$Cu(OAc)_2$	TBHP (1.2)		65	56
2	$CuCl_2$	TBHP (1.2)		65	n.d.
3	$CuBr_2$	TBHP (1.2)		65	trace
4	CuF_2	TBHP (1.2)		65	5
5	$Cu(OTf)_2$	TBHP (1.2)		65	n.d.
6	$Cu(OTFA)_2$	TBHP (1.2)		65	6
7	CuI	TBHP (1.2)		65	trace
8	CuCl	TBHP (1.2)		65	5.
9	CuBr	TBHP (1.2)		65	9
10	$Cu(OAc)_2$	TBHP (2)		65	65
11	$Cu(OAc)_2$	TBHP (2.5)		65	72
12	$Cu(OAc)_2$	TBHP (3)		65	69
13	$Cu(OAc)_2$	DTBP (2)		65	n.d.
14	$Cu(OAc)_2$	Oxone (2)		65	n.d.
15	$Cu(OAc)_2$	$K_2S_2O_8$ (2)		65	n.d.
16	$Cu(OAc)_2$	$PhI(OPiv)_2$ (2)		65	32
17	$Cu(OAc)_2$	PhIO(2)		65	15
18	$Cu(OAc)_2$	BQ(2)		65	n.d.
19	$Cu(OAc)_2$	NMO(2)		65	n.d.
20	$Cu(OAc)_2$	AgOAc(2)		65	n.d.
21	$Cu(OAc)_2$	H_2O_2(2)		65	n.d.
22[c]	$Cu(OAc)_2$	TBHP (2.5)		65	56
23	$Cu(OAc)_2$	TBHP (2.5)	1,10-phenanthroline	65	41
24	$Cu(OAc)_2$	TBHP (2.5)	2,2'-bypyridine	65	50
25	$Cu(OAc)_2$	TBHP (2.5)	D-proline	65	61
26	$Cu(OAc)_2$	TBHP (2.5)	PPh_3	65	56
27	$Cu(OAc)_2$	TBHP (2.5)	pyridine	65	77
28	$Cu(OAc)_2$	TBHP (2.5)	4-tert-butlylpyridine	65	70
29	**$Cu(OAc)_2$**	**TBHP (2.5)**	**4-methylpyridine**	**65**	**80**
30	$Cu(OAc)_2$	TBHP (2.5)	2,4,6-trimethylpyridine	65	69

31	$Cu(OAc)_2$	TBHP (2.5)	4-methylpyridine (40)	65	79
32	$Cu(OAc)_2$	TBHP (2.5)	4-methylpyridine	45	49
33	$Cu(OAc)_2$	TBHP (2.5)	4-methylpyridine	85	68
34[d]	$Cu(OAc)_2$	TBHP (2.5)	4-methylpyridine	65	72
35[e]	$Cu(OAc)_2$	TBHP (2.5)	4-methylpyridine	65	81
36[f]	$Cu(OAc)_2$	TBHP (2.5)	4-methylpyridine	65	69

[a]Reaction conditions: *N*-(8-quinolyl)acetamide (**1a**) (0.2 mmol), Cu(II) catalyst (20 mol%), ligand (20 mol%), oxidant in THF (**2a**) (2.0 mL) stirring under air for 8 h. [b]Isolated yields. [c]With 10 mol% $Cu(OAc)_2$. [d]4 h. [e]12 h. [f]In 1 mL THF.

Experimental Section

Instrumentation and chemicals

^{1}H NMR, ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer with $CDCl_3$ as the solvent and TMS as an internal standard, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Melting points were measured by SGW X-4A microscopic apparatus. The X-ray crystallography was measured on Bruker D8 VENTURE PHOTON instrument. HRMS-ESI were measured by Q Exactive LC/HRMS spectrometer. Dichloromethane, ethyl acetate and hexane were used for column chromatography without further purification. All solvents and chemicals were obtained from commercial sources and used as received unless otherwise noted. All the *N*-(8-quinolyl)amides were synthesized through the coupling between corresponding aryl or alkyl acids and 8-aminoquinoline according to literature procedures.[1]

Experimental procedures

General procedure for the copper-catalyzed α-C−H amidation of ethers with *N*-(8-quinolyl)amides. A mixture of *N*-(8-quinolyl)amide (0.2 mmol), $Cu(OAc)_2$ (20 mol%), 4-methylpyridine (20 mol%)and TBHP(2.5equiv) were added into a vial containing a stirring bar and sealed with a Teflon-lined cap. Then THF (2 mL) was introduced. The resulting mixture was stirred at 65 °C for 8 h. After reaction the mixture was added into H_2O (25 mL) and extracted with ethyl acetate (10 mL) for three times. The combined organic layer was dried over anhydrous $MgSO_4$ and filtered. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (ethyl acetate/hexane) to afford the pure product.

Characterization Data

N-(8-quinolyl)-*N*-(2-tetrahydrofuryl)acetamide (**3aa**)

Light brown solid, mp 101–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00–1.08 (m, 1H), 1.52–1.62 (m, 2H), 1.68 (s, 3H), 1.95–2.04 (m, 1H), 3.64–3.70 (m, 2H), 6.75–6.78 (m, 1H), 7.48 (dd, *J* = 4.00 Hz, *J* = 7.84 Hz, 1H), 7.59–7.62 (m, 1H), 7.83–7.84 (m, 1H), 7.89–7.91 (m, 1H), 8.23–8.25 (m, 1H), 8.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 25.0, 28.6, 68.0, 85.4, 121.7, 126.5, 128.8, 129.1, 131.8, 136.3, 136.7, 145.8, 151.2, 171.9; HRMS-ESI (m/z): calcd for $C_{15}H_{17}N_2O_2$ ($M+H^+$): 257.1285, found 257.1281.

N-(8-quinolyl)-*N*-(2-tetrahydrofuryl)propionamide (**3ba**)

Light yellow solid, mp 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94–0.98 (m, 3H), 1.00–1.06 (m, 1H), 1.51–1.64 (m, 2H), 1.80–1.88 (m, 2H), 1.94–2.01 (m, 1H), 3.64–3.70 (m, 2H), 6.78–6.81 (m, 1H), 7.47 (dd, *J* = 4.12 Hz, *J* = 8.08 Hz, 1H), 7.58–7.62 (m, 1H), 7.82–7.83 (m, 1H), 7.89–7.91 (m, 1H), 8.23–8.25 (m, 1H), 8.98–8.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.3, 25.1, 28.2, 28.5, 67.9, 85.5, 121.7, 126.5, 128.8, 129.1, 132.0, 136.3, 136.4, 145.9, 151.2, 175.1; HRMS-ESI (m/z): calcd for $C_{16}H_{19}N_2O_2$ ($M+H^+$): 271.1441, found 271.1443.

N-(8-quinolyl)-*N*-(2-tetrahydrofuryl)butyramide (**3ca**)

Light yellow solid, mp 99–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68–0.72 (m, 3H), 0.97–1.03 (m, 1H), 1.51–1.57 (m, 4H), 1.77–1.81 (m, 2H), 1.94–2.00 (m, 1H), 3.64–3.69 (m, 2H), 6.78–6.81 (m, 1H), 7.48 (dd, *J* = 4.12 Hz, *J* = 8.12 Hz, 1H), 7.59–7.62 (m, 1H), 7.81–7.83 (m, 1H), 7.90–7.92 (m, 1H), 8.23–8.25 (m, 1H), 8.98–8.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 18.4, 25.0, 28.5, 36.8, 67.9, 85.5, 121.7, 126.4, 128.7, 129.1, 132.0, 136.3, 136.4, 145.9, 151.1, 174.2; HRMS-ESI (m/z): calcd for $C_{17}H_{21}N_2O_2$ ($M+H^+$): 285.1598, found 285.1601.

N-(8-quinolyl)-*N*-(2-tetrahydrofuryl)-3-phenylpropenamide (**3da**)

Light brown solid, mp 99–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97–0.99 (m, 1H), 1.54–1.58 (m, 2H), 1.95–2.01 (m, 1H), 2.11–2.15 (m, 2H), 2.87–2.92 (m, 2H), 3.60–3.70 (m, 2H), 6.80 (t, *J* = 5.36 Hz, 1H), 6.89–6.91 (m, 2H), 7.06–7.13 (m, 3H), 7.45 (dd, *J* = 4.16 Hz, *J* = 8.12 Hz, 1H), 7.53–7.57 (m, 1H), 7.70–7.72 (m, 1H), 7.85–7.87 (m, 1H), 8.19–8.21 (m, 1H), 8.96–8.97 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 28.6, 31.5, 37.0, 68.0, 85.7, 121.7, 125.7, 126.5, 128.2, 128.3, 128.9, 129.1, 132.0, 136.1, 136.4, 141.5, 145.8, 151.2, 173.5; HRMS-ESI (m/z): calcd for $C_{22}H_{23}N_2O_2$ ($M+H^+$): 347.1754, found 347.1751.

N-(8-quinolyl)-*N*-(2-tetrahydrofuryl)isobutyramide (**3ea**)

Yellow solid, mp 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94–0.98 (m, 6H), 1.56 (s, 2H), 1.93–1.99 (m, 2H), 2.26–2.32 (m, 1H), 3.65–3.66 (m, 2H), 6.77 (s, 1H), 7.47 (s, 1H), 7.58–7.62 (m, 1H), 7.83–7.91 (m, 2H), 8.22–8.24 (m, 1H), 8.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 20.4, 25.0, 28.5, 67.9, 85.6, 121.7, 126.4, 128.6, 129.0, 131.8, 136.3, 136.4, 146.0, 151.1, 178.8; HRMS-ESI (m/z): calcd for $C_{17}H_{21}N_2O_2$ ($M+H^+$): 285.1598, found 285.1596.

N-(8-quinolyl)-*N*-(2-tetrahydrofuryl)cyclopropanecarboxamide (**3fa**)

Light yellow solid, mp 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.31–0.33 (m, 1H), 0.41–0.45 (m, 1H), 0.83–0.89 (m, 1H), 0.99–1.05 (m, 3H), 1.55–1.65 (m, 2H), 1.98–2.02 (m, 1H), 3.68–3.71 (m, 2H), 6.76–6.79 (m, 1H), 7.48 (dd, J = 4.04 Hz, J = 7.96 Hz, 1H), 7.60–7.64 (m, 1H), 7.90–7.92 (m, 2H), 8.23–8.25 (m, 1H), 9.00–9.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.5, 8.7, 13.7, 25.1, 28.5, 67.9, 85.7, 121.7, 126.5, 128.7, 129.1, 132.2, 136.2, 136.5, 146.2, 151.1, 175.0; HRMS-ESI (m/z): calcd for $C_{17}H_{19}N_2O_2$ ($M+H^+$): 283.1441, found 283.1445.

N-(8-quinolyl)-*N*-(2-tetrahydrofuryl)cyclohexanecarboxamide (**3ga**)

Light yellow solid, mp 162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.59–0.73 (m, 2H), 0.94–0.98 (m, 1H), 1.04–1.14 (m, 1H), 1.38–1.43 (m, 2H), 1.55–1.66 (m, 8H), 1.93–1.99 (m, 1H), 3.62–3.67 (m, 2H), 6.75–6.77 (m, 1H), 7.48 (dd, J = 3.92 Hz, J = 7.88 Hz, 1H), 7.58–7.62 (m, 1H), 7.81–7.83 (m, 1H), 7.89–7.91 (m, 1H), 8.23–8.25 (m, 1H), 8.96–8.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 25.2, 25.6, 25.7, 28.5, 28.6, 30.2, 43.6, 67.9, 85.6, 121.7, 126.4, 128.6, 128.9, 131.7, 136.3, 136.4, 146.1, 151.1, 177.7; HRMS-ESI (m/z): calcd for $C_{20}H_{25}N_2O_2$ ($M+H^+$): 325.1911, found 325.1914.

N-(8-quinolyl)-*N*-(2-tetrahydrofuryl)benzamide (**3ha**)

Light yellow solid, mp 139–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–0.89 (m, 1H), 0.98–1.06

(m, 1H), 1.63 (s, 1H), 1.83 (s, 1H), 2.15–2.20 (m, 1H), 3.72–3.73 (m, 2H), 6.82–6.95 (m, 3H), 7.34–7.35 (m, 3H), 7.50–7.51 (m, 1H), 7.70 (s, 1H), 7.93 (s, 1H), 8.01 (s, 1H), 8.89 (m, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 31.9, 68.4, 87.5, 121.4, 126.0, 126.9, 127.4, 128.0, 128.2, 128.7, 129.1, 131.7, 135.9, 137.3, 145.3, 150.4, 172.6; HRMS-ESI (m/z): calcd for $C_{20}H_{19}N_2O_2$ ($M+H^+$): 319.1441, found 319.1445.

N-(8-quinolyl)-*N*-(2-tetrahydrofuryl) -4-methylbenzamide (**3ia**)

White solid, mp 133–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80–0.92 (m, 1H), 0.94–1.00 (m, 1H), 1.62–1.63 (m, 2H), 1.81–1.83 (m, 2H), 3.72 (s, 3H), 6.70–6.80 (m, 2H), 7.29–7.31 (m, 2H), 7.49–7.52 (m, 2H), 7.71–7.77 (m, 2H), 7.91–7.92 (m, 1H), 7.99–8.03 (m, 1H), 8.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 25.1, 31.9, 68.3, 87.5, 121.3, 126.1, 126.3, 127.7, 128.2, 128.7, 131.6, 134.4, 135.9, 137.5, 139.2, 145.4, 150.4, 172.7; HRMS-ESI (m/z): calcd for $C_{21}H_{21}N_2O_2$ ($M+H^+$): 333.1598, found 333.1595.

N-(8-quinolyl)-*N*-(2-tetrahydrofuryl)-4-methoxybenzamide (**3ja**)

White solid, mp 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80–0.89 (m, 1H), 0.98–1.06 (m, 1H), 1.56–1.63 (m, 1H), 1.81–1.82 (m, 1H), 2.14–2.15 (m, 1H), 3.61 (s, 3H), 3.72 (s, 2H), 6.44–6.51 (m, 2H), 6.70–6.78 (m, 1H), 7.32–7.40 (m, 2H), 7.49–7.53 (m, 1H), 7.71–7.73 (m, 1H), 7.91 (s, 1H), 8.04 (s, 1H), 8.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 31.9, 55.0, 68.3, 87.8, 112.4, 121.3, 126.1, 128.1, 128.8, 129.7, 130.1, 131.5, 135.9, 137.7, 145.3, 150.4, 160.2, 172.3; HRMS-ESI (m/z): calcd for $C_{21}H_{21}N_2O_3$ ($M+H^+$): 349.1547, found 349.1543.

N-(8-quinolyl)-*N*-(2-tetrahydrofuryl)-4-chlorobenzamide (**3ka**)

White solid, mp 82–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–0.89 (m, 1H), 0.97–0.99 (m, 1H), 1.58–1.64 (m, 2H), 2.13–2.14 (m, 1H), 3.71–3.72 (m, 2H), 6.69–6.78 (m, 1H), 6.88–6.94 (m, 2H), 7.31 (s, 2H), 7.50–7.54 (m, 1H), 7.73–7.74 (m, 1H), 7.87–7.93 (m, 1H), 8.04–8.09 (m, 1H), 8.87 (m, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 31.9, 68.5, 87.6, 121.5, 126.1, 127.2, 128.4, 128.8, 129.5, 131.5, 135.1, 135.8, 136.0, 136.9, 145.1, 150.5, 171.5; HRMS-ESI (m/z): calcd for $C_{20}H_{18}ClN_2O_2$ ($M+H^+$): 353.1051, found 353.1055.

N-(8-quinolyl)-*N*-(2-tetrahydrofuryl)-4-bromobenzamide (**3la**)

White solid, mp 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–0.89 (m, 1H), 0.97–0.99 (m, 1H), 1.58–1.63 (m, 2H), 2.12–2.14 (m, 1H), 3.71–3.72 (m, 2H), 6.72–6.77 (m, 1H), 6.98–7.13 (m, 2H), 7.23 (s, 1H), 7.33 (s, 1H), 7.50–7.54 (m, 1H), 7.73–7.74 (m, 1H), 7.89–7.93 (m, 1H), 8.05–8.09 (m, 1H), 8.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 31.9, 68.5, 87.6, 121.5, 123.5, 126.1, 128.5, 128.8, 129.7, 130.2, 131.5, 136.0, 136.3, 136.9, 145.1, 150.5, 171.6; HRMS-ESI (m/z): calcd for $C_{20}H_{18}BrN_2O_2$ ($M+H^+$): 397.0546, found 397.0542.

N-(5-methyl-2-tetrahydrofuryl)-*N*-(8-quinolyl)butyramide (**3cb**)

Light brown solid, mp 86–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.67–0.71 (m, 3H), 0.83–0.89 (m, 2H), 1.14 (d, *J* = 5.92 Hz, 3H), 1.48–1.56 (m, 3H), 1.76–1.79 (m, 2H), 2.06–2.14 (m, 1H), 3.79 (q, *J* = 6.16 Hz, 1H), 6.85 (t, *J* = 6.32 Hz, 1H), 7.46 (dd, *J* = 3.92 Hz, *J* = 7.64 Hz, 1H), 7.58–7.62 (m, 1H), 7.84–7.90 (m, 2H), 8.21–8.23 (m, 1H), 8.96–8.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 18.4, 21.5, 28.9, 32.7, 36.9, 75.3, 85.5, 121.6, 126.5, 128.7, 129.1, 132.1, 136.3, 136.5, 146.0, 151.1, 174.2 ; HRMS-ESI (m/z): calcd for $C_{18}H_{23}N_2O_2$ ($M+H^+$): 299.1754, found 299.1758.

N-(8-quinolyl)-*N*-(2-tetrahydropyranyl)butyramide (**3cc**)

Light yellow solid, mp 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (t, *J* = 7.40 Hz, 3H), 1.31–1.40 (m, 2H), 1.51–1.60 (m, 6H), 1.78–1.82 (m, 2H), 3.70–3.78 (m, 1H), 4.05–4.09 (m, 1H), 6.01–6.05 (m, 1H), 7.46 (dd, *J* = 4.16 Hz, *J* = 8.28 Hz, 1H), 7.59–7.63 (m, 1H), 7.83–7.85 (m, 1H), 7.88–7.90 (m, 1H), 8.21–8.24 (m, 1H), 8.95–8.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 18.3, 23.3, 25.3, 28.6, 36.8, 68.1, 82.4, 121.6, 126.5, 128.6, 129.1, 131.4, 136.3, 136.8, 145.8, 150.9, 174.0 ; HRMS-ESI (m/z): calcd for $C_{18}H_{23}N_2O_2$ ($M+H^+$): 299.1754, found 299.1749.

N-(1,4-dioxan-2-yl)-*N*-(8-quinolyl)butyramide (**3cd**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (t, *J* = 7.36 Hz, 3H), 1.54 (q, *J* = 7.32 Hz, 2H), 1.77–1.81 (m, 2H), 3.21–3.26 (m, 1H), 3.53–3.56 (m, 1H), 3.66–3.70 (m, 1H), 3.78–3.81 (m, 1H), 3.87–3.90 (m, 1H), 3.99–4.05 (m, 1H), 6.24–6.27 (m, 1H), 7.48 (dd, *J* = 4.04 Hz, *J* = 8.08 Hz, 1H), 7.61–7.64 (m, 1H), 7.82–7.84 (m, 1H), 7.91–7.93 (m, 1H), 8.23–8.25 (m, 1H), 8.94–8.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 18.3, 65.6, 66.1, 67.0, 67.9, 78.9, 121.8, 126.4, 129.0, 129.1,

131.7, 135.8, 136.4, 145.6, 151.1, 174.3; HRMS-ESI (m/z): calcd for $C_{17}H_{21}N_2O_3$ ($M+H^+$): 301.1547, found 301.1545.

N-(1,3-dioxolan-2-yl)-*N*-(8-quinolyl)butyramide (**3ce**)

White solid, mp 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.69–0.72 (m, 3H), 1.51–1.56 (m, 2H), 1.72–1.85 (m, 2H), 3.80–3.81 (m, 2H), 3.86–3.89 (m, 2H), 6.91 (t, *J* = 4.68 Hz, 1H), 7.48 (dd, *J* = 4.16 Hz, *J* = 8.24 Hz, 1H), 7.58–7.63 (m, 1H), 7.76–7.78 (m, 1H), 7.90–7.92 (m, 1H), 8.23–8.25 (m, 1H), 8.95–8.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 18.3, 36.6, 65.4, 67.1, 81.6, 121.8, 126.5, 129.1, 129.2, 132.0, 135.4, 136.5, 145.7, 151.2, 174.8; HRMS-ESI (m/z): calcd for $C_{16}H_{19}N_2O_3$ ($M+H^+$): 287.1390, found 287.1394.

N-(1-ethoxyethyl)-*N*-(8-quinolyl)butyramide (**3cf**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (t, *J* = 7.40 Hz, 3H), 0.89–0.90 (m, 3H), 1.34 (t, *J* = 7.04 Hz, 3H), 1.53–1.59 (m, 2H), 1.78–1.94 (m, 2H), 3.72–3.80 (m, 1H), 3.86–3.94 (m, 1H), 6.47 (q, *J* = 6.16 Hz, 1H), 7.44 (dd, *J* = 4.16 Hz, *J* = 8.28 Hz, 1H), 7.58–7.63 (m, 2H), 7.86–7.88 (m, 1H), 8.20–8.22 (m, 1H), 8.93–8.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 15.3, 18.5, 18.7, 36.9, 63.2, 79.6, 121.6, 126.5, 128.4, 129.1, 130.4, 135.9, 136.2, 145.8, 150.8, 174.9; HRMS-ESI (m/z): calcd for $C_{17}H_{23}N_2O_2$ ($M+H^+$): 287.1754, found 287.1758.

N-(1-butoxybutyl)-*N*-(8-quinolyl)butyramide (**3cg**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68–0.74 (m, 6H), 0.82–0.89 (m, 2H), 0.98 (t, *J* = 7.28 Hz, 3H), 1.34–1.41 (m, 2H), 1.45–1.50 (m, 2H), 1.53–1.60 (m, 2H), 1.66–1.71 (m, 2H), 1.76–1.84 (m, 1H), 1.89–1.96 (m, 1H), 3.64–3.70 (m, 1H), 3.85–3.90 (m, 1H), 6.25–6.28 (m, 1H), 7.44 (dd, *J* = 4.12 Hz, *J* = 8.20 Hz, 1H), 7.57–7.60 (m, 2H), 7.84–7.86 (m, 1H), 8.19–8.21 (m, 1H), 8.93–8.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 13.7, 14.0, 18.7, 19.0, 19.6, 31.9, 34.7, 36.9, 68.2, 83.7, 121.5, 126.5, 128.2, 129.0, 130.1, 136.2, 136.5, 145.8, 150.7, 175.0; HRMS-ESI (m/z): calcd for $C_{21}H_{31}N_2O_2$ ($M+H^+$): 343.2380, found 343.2376.

N-(*tert*-butoxymethyl)-*N*-(8-quinolyl)butyramide (**3ch**)

White solid, mp 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71–0.74 (m, 3H), 1.20 (s, 9H),

1.53–1.58 (m, 2H), 1.76–1.84 (m, 1H), 1.89–1.97 (m, 1H), 4.44 (d, *J* = 9.52 Hz, 1H), 6.10 (d, *J* = 9.56 Hz, 1H), 7.46 (dd, *J* = 3.56 Hz, *J* = 7.36 Hz, 1H), 7.57–7.61 (m, 1H), 7.75–7.76 (m, 1H), 7.86–7.88 (m, 1H), 8.20–8.22 (m, 1H), 8.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 18.4, 28.0, 36.5, 71.4, 73.9, 121.7, 126.3, 128.4, 129.4, 130.9, 136.3, 138.7, 144.5, 150.9, 173.7; HRMS-ESI (m/z): calcd for $C_{18}H_{25}N_2O_2$ ($M+H^+$): 301.1911, found 301.1914.

N-((2-methoxyethoxy)methyl)-*N*-(8-quinolyl)butyramide (**3ci**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72–0.76 (m, 3H), 1.54–1.59 (m, 2H), 1.86–1.99 (m, 2H), 3.36 (s, 3H), 3.55–3.57 (m, 2H), 3.93–3.94 (m, 2H), 4.83 (d, *J* = 10.44 Hz, 1H), 5.80 (d, *J* = 10.48 Hz, 1H), 7.46 (dd, *J* = 3.96 Hz, *J* = 8.00 Hz, 1H), 7.57–7.61 (m, 1H), 7.69–7.70 (m, 1H), 7.86–7.88 (m, 1H), 8.20–8.22 (m, 1H), 8.93–8.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 18.5, 36.3, 58.9, 68.0, 71.8, 77.8, 121.8, 126.5, 128.5, 129.5, 130.2, 136.3, 138.9, 144.5, 153.0, 175.1; HRMS-ESI (m/z): calcd for $C_{17}H_{23}N_2O_3$ ($M+H^+$): 303.1703, found 303.1707.

N-(1,2-dimethoxyethyl)-*N*-(8-quinolyl)butyramide (**3ci'**)

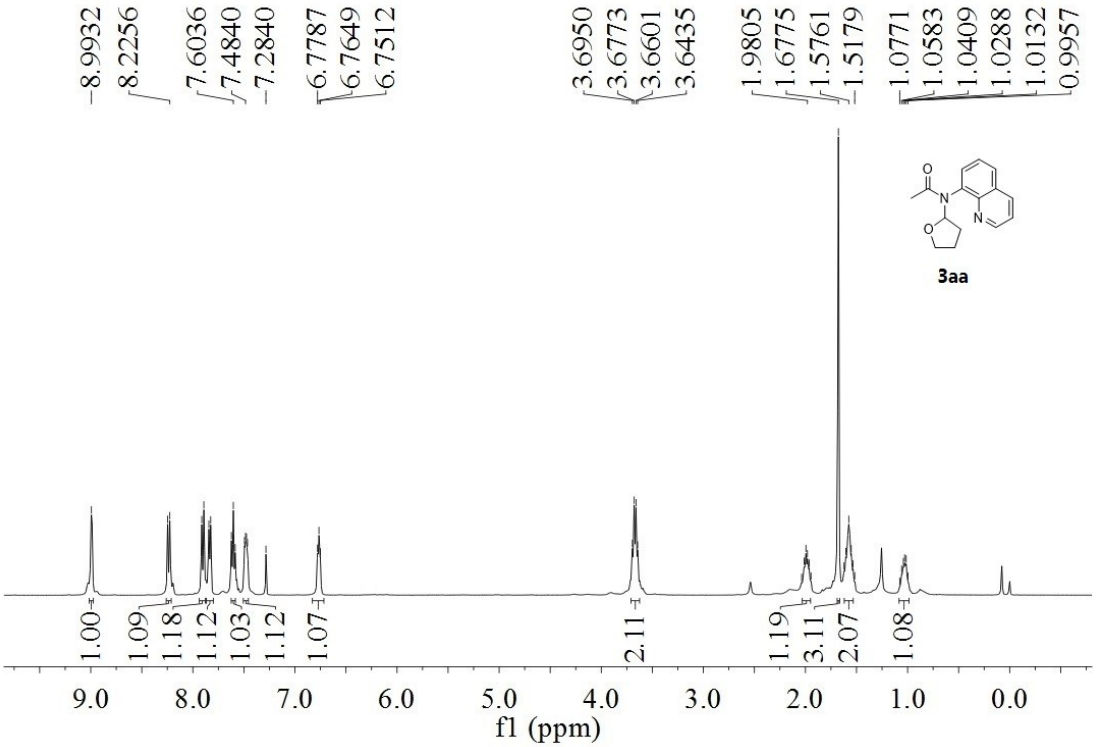
Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71–0.75 (m, 3H), 1.54–1.60 (m, 2H), 1.83–1.92 (m, 2H), 3.09 (s, 3H), 3.39–3.44 (m, 2H), 3.66 (s, 3H), 6.38 (d, *J* = 8.24 Hz, 1H), 7.46 (dd, *J* = 4.08 Hz, *J* = 8.24 Hz, 1H), 7.58–7.61 (m, 2H), 7.86–7.88 (m, 1H), 8.21–8.23 (m, 1H), 8.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 18.6, 36.5, 56.4, 58.9, 72.5, 83.4, 121.7, 126.5, 128.5, 129.1, 130.3, 136.3, 138.9, 145.5, 150.8, 175.1; HRMS-ESI (m/z): calcd for $C_{17}H_{23}N_2O_3$ ($M+H^+$): 303.1703, found 303.1706.

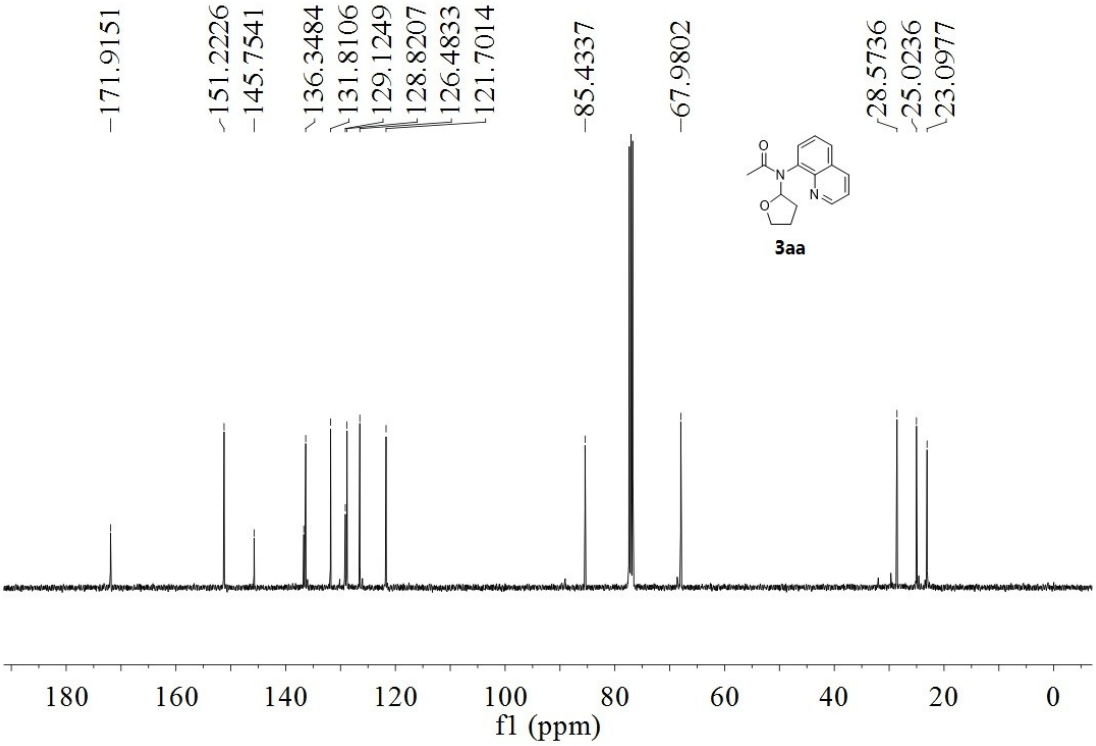
2,6-Di-*tert*-butyl-4-((2-tetrahydrofuranyl)methyl)phenol (**7**)

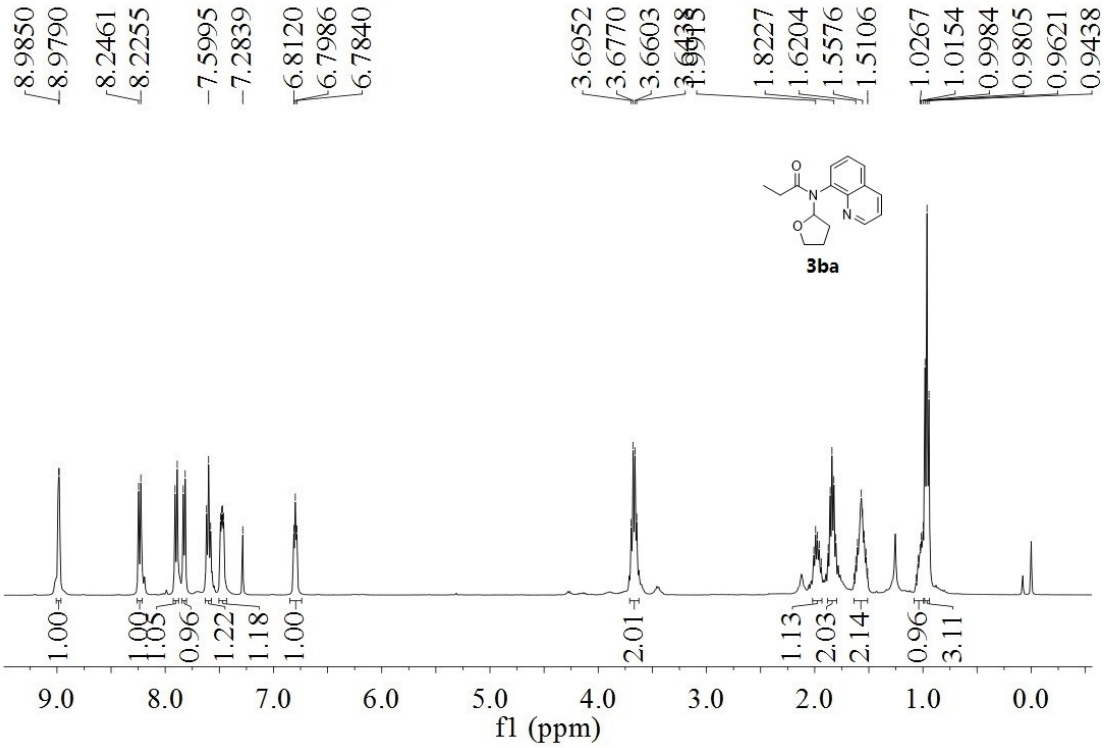
Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.23 (m, 9H), 1.24 (m, 9H), 1.30 (m, 3H), 1.66–1.84 (m, 3H), 3.75–3.84 (m, 2H), 3.90 (t, *J* = 6.52 Hz, 1H), 6.39 (s, 1H), 6.57 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.6, 26.5, 27.4, 29.4, 29.6, 34.7, 34.9, 43.9, 69.0, 84.8, 142.8, 143.8, 147.0, 148.1, 186.6; HRMS-ESI (m/z): calcd for $C_{19}H_{31}O_2$ ($M+H^+$): 291.2319, found: 291.2320.

[1] Y. Wang, Y. Wang, K. Jiang, Q. Zhang and D. Li, *Org. Biomol. Chem.,* 2016, **14**, 10180.

Copies of ^{1}H and ^{13}C NMR spectra



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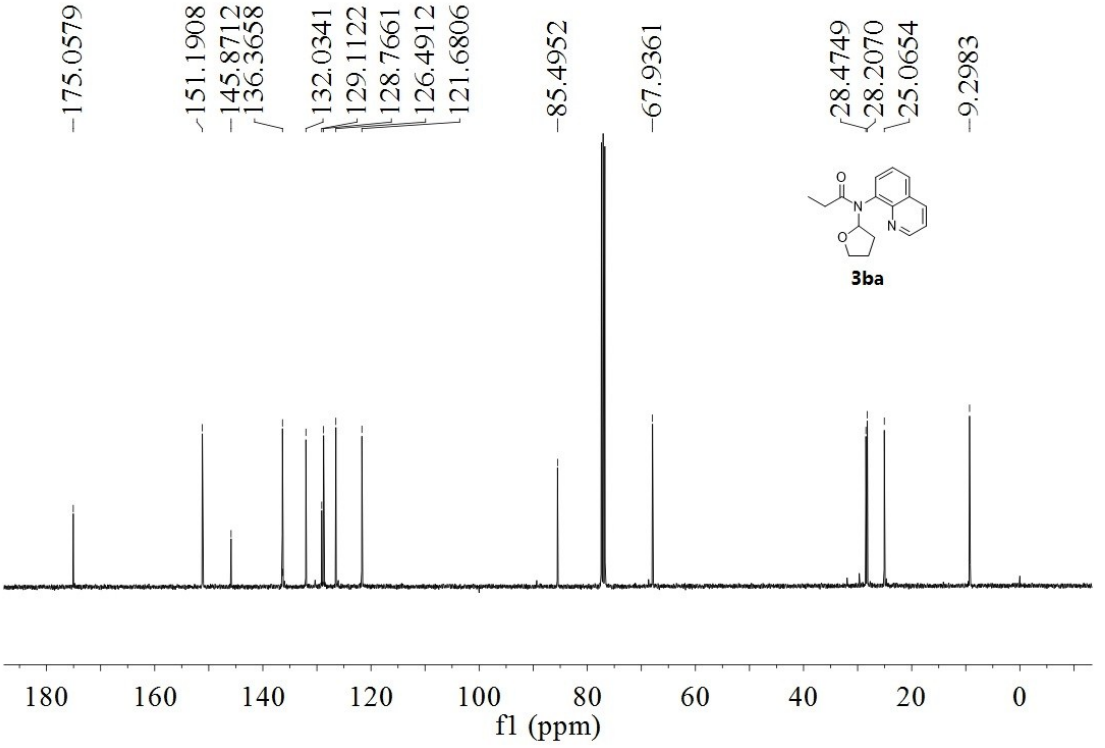
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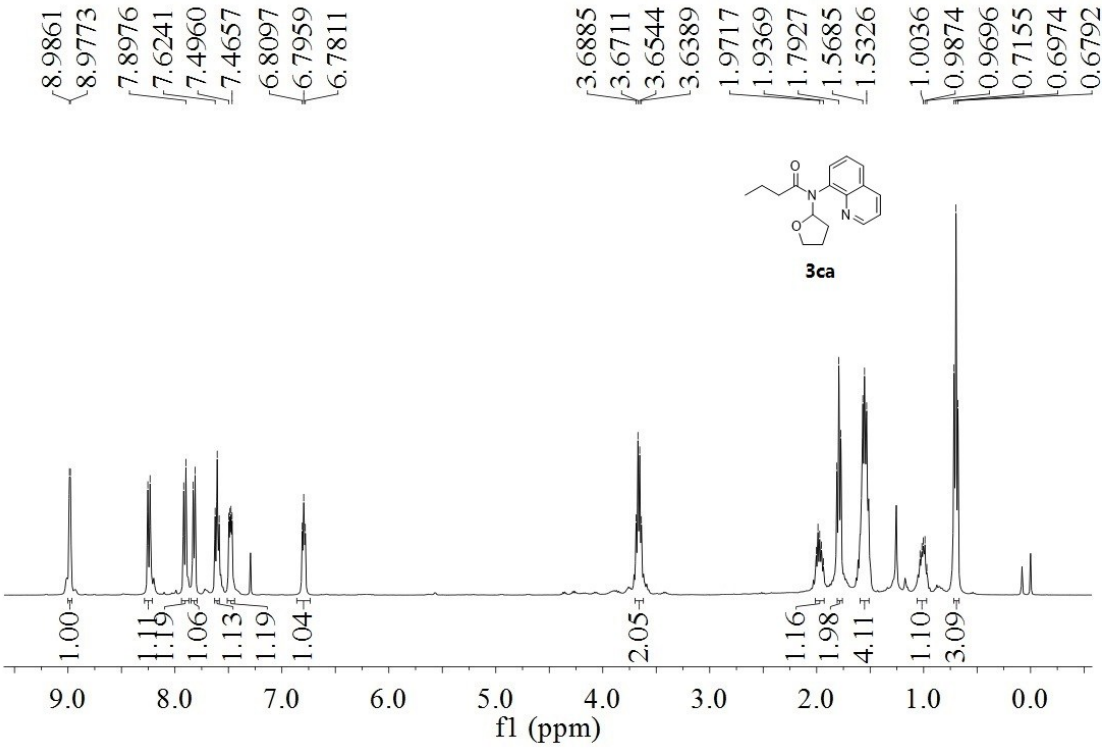
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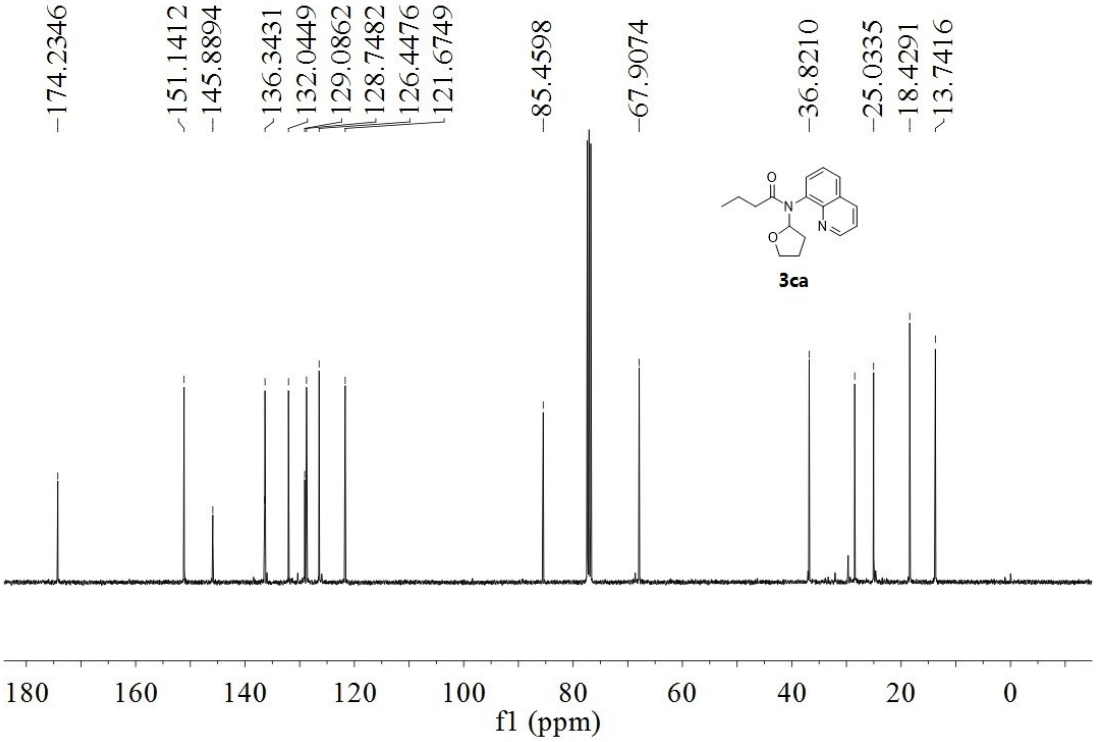
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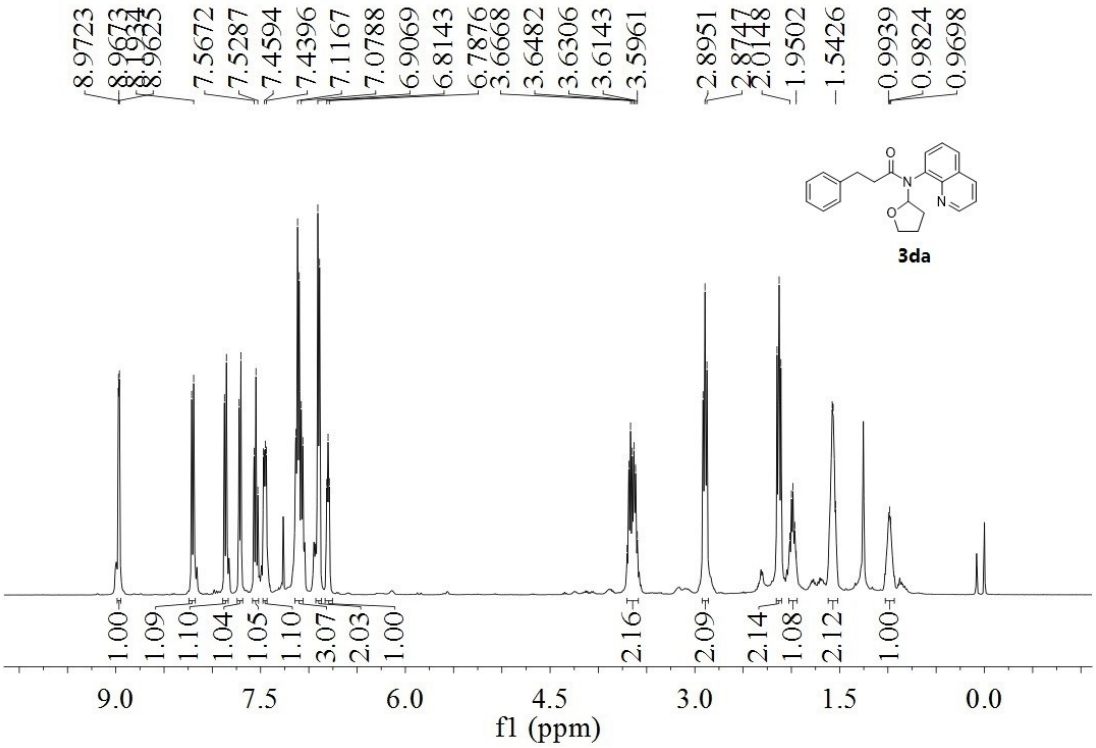
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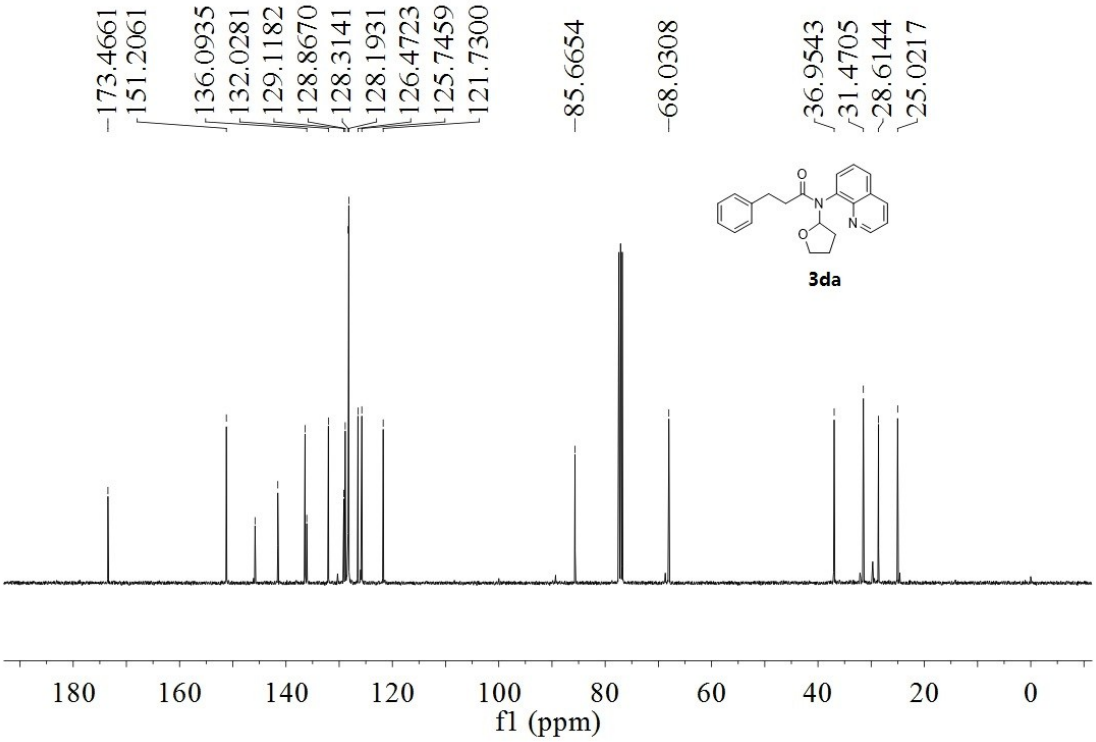
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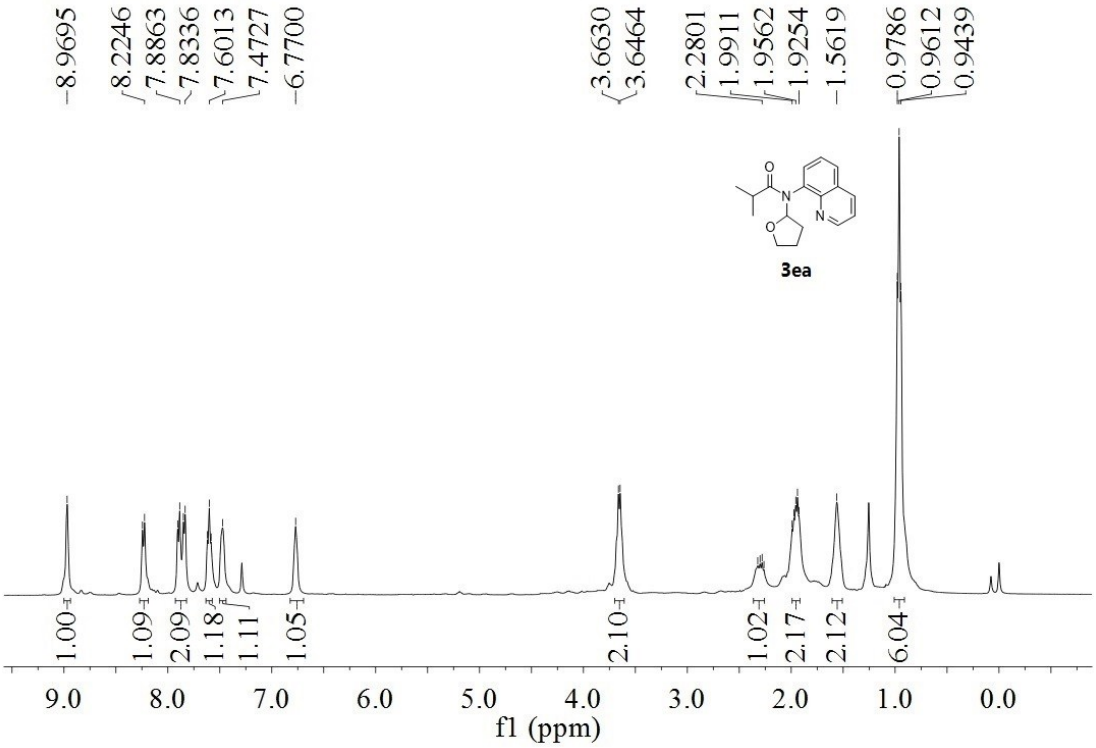
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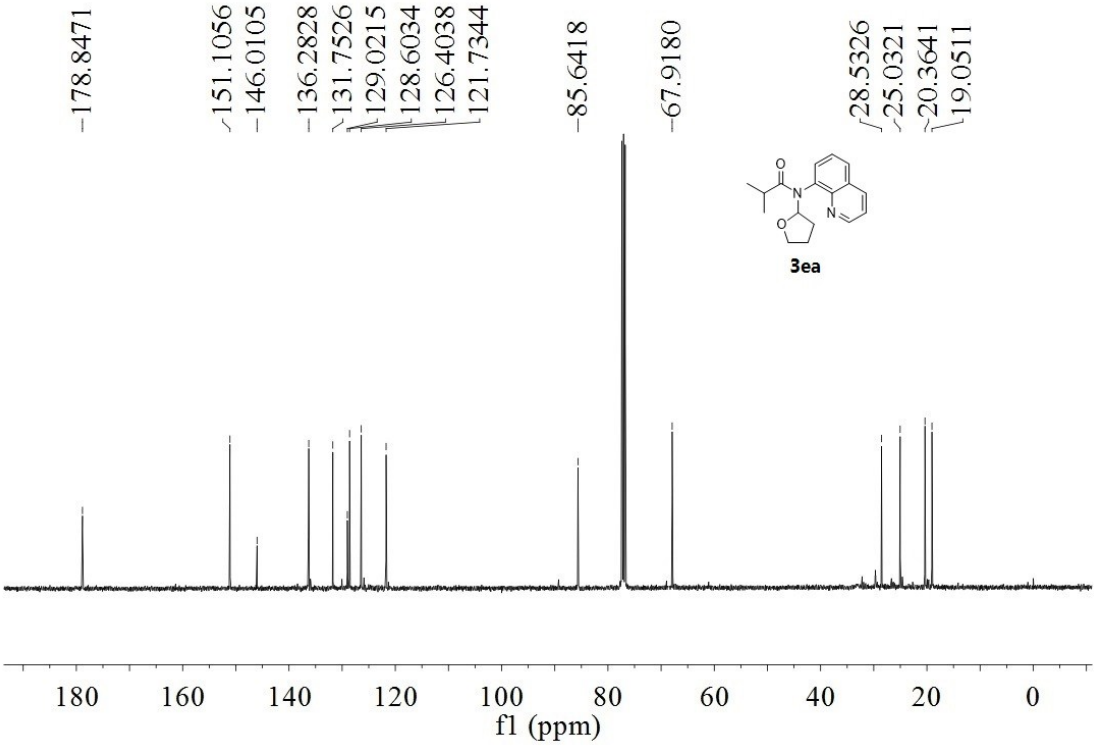
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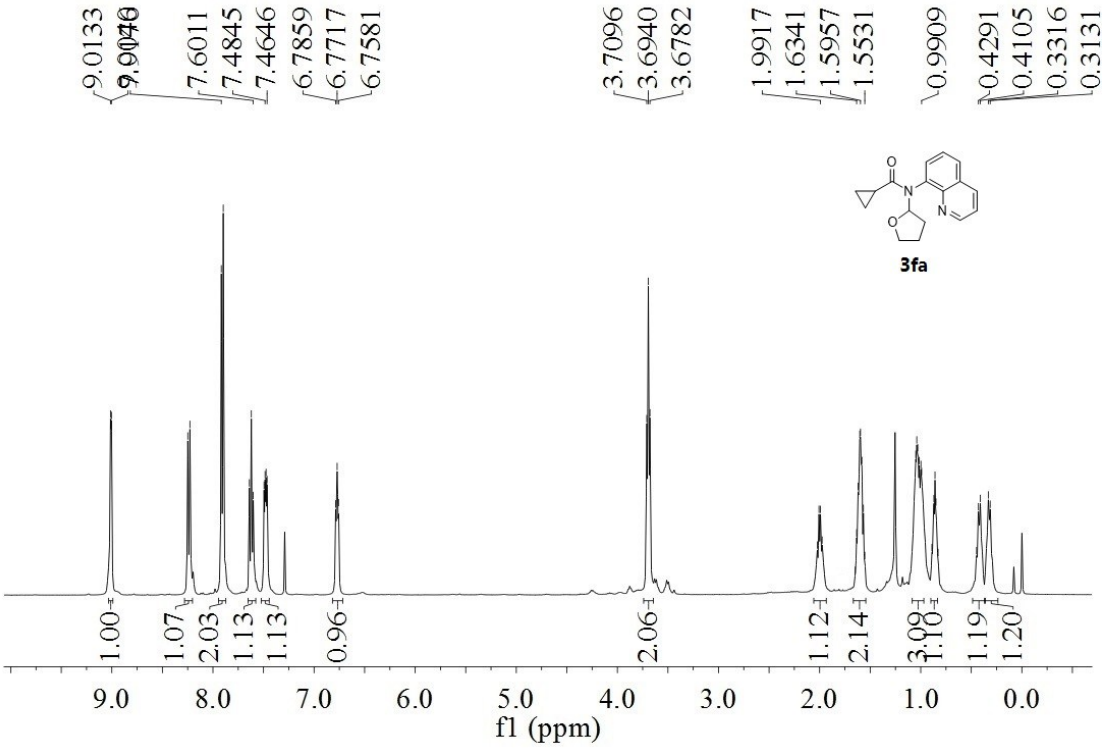
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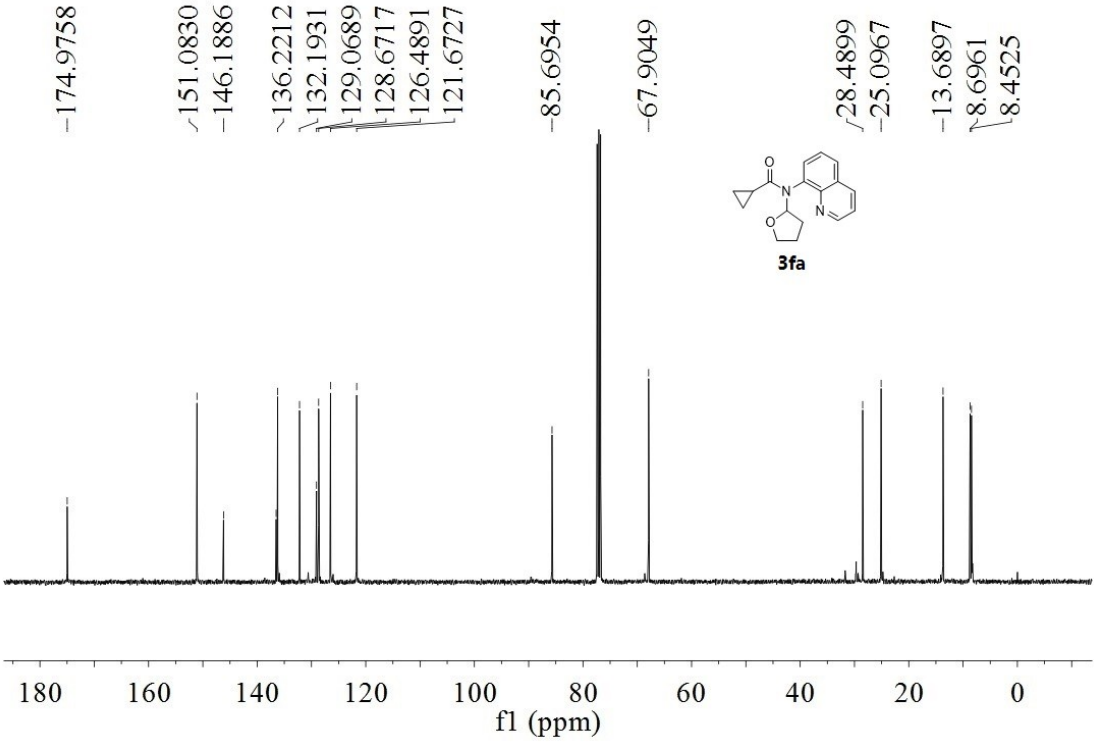
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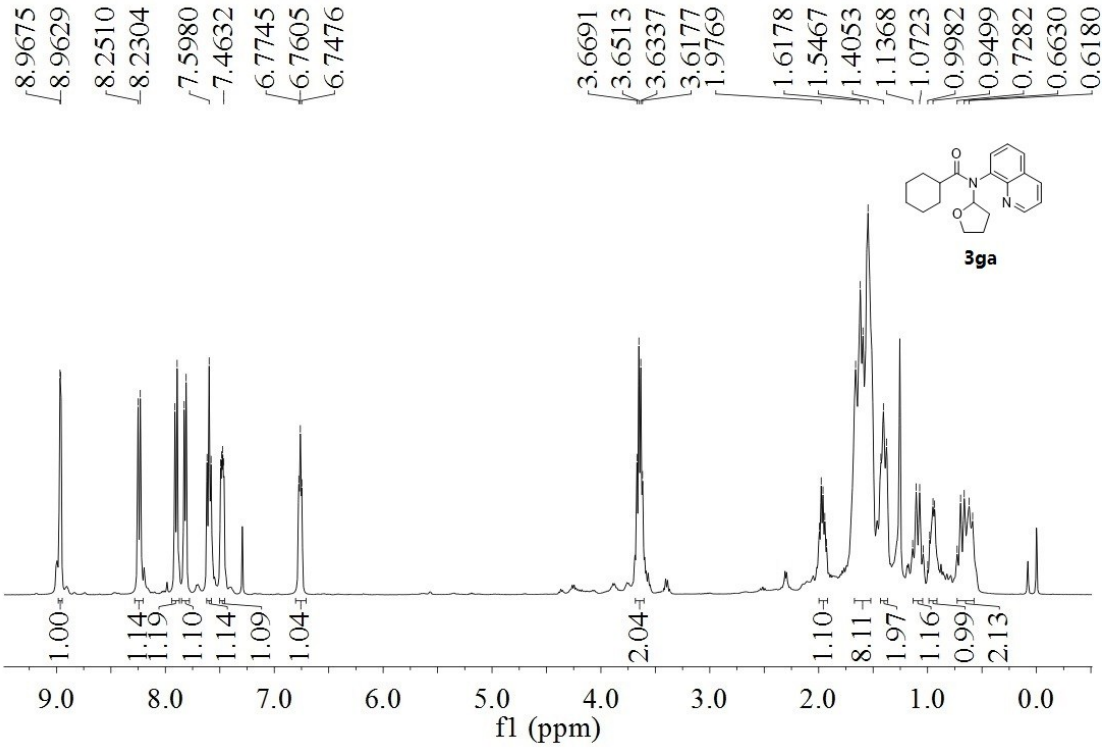
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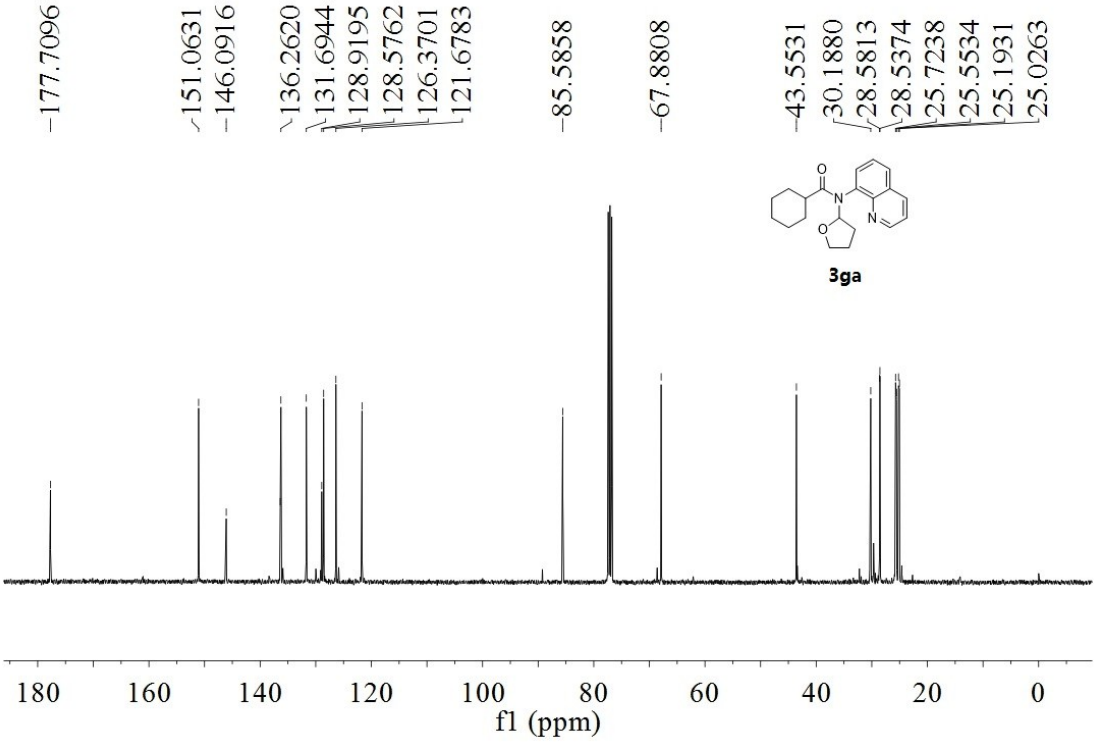
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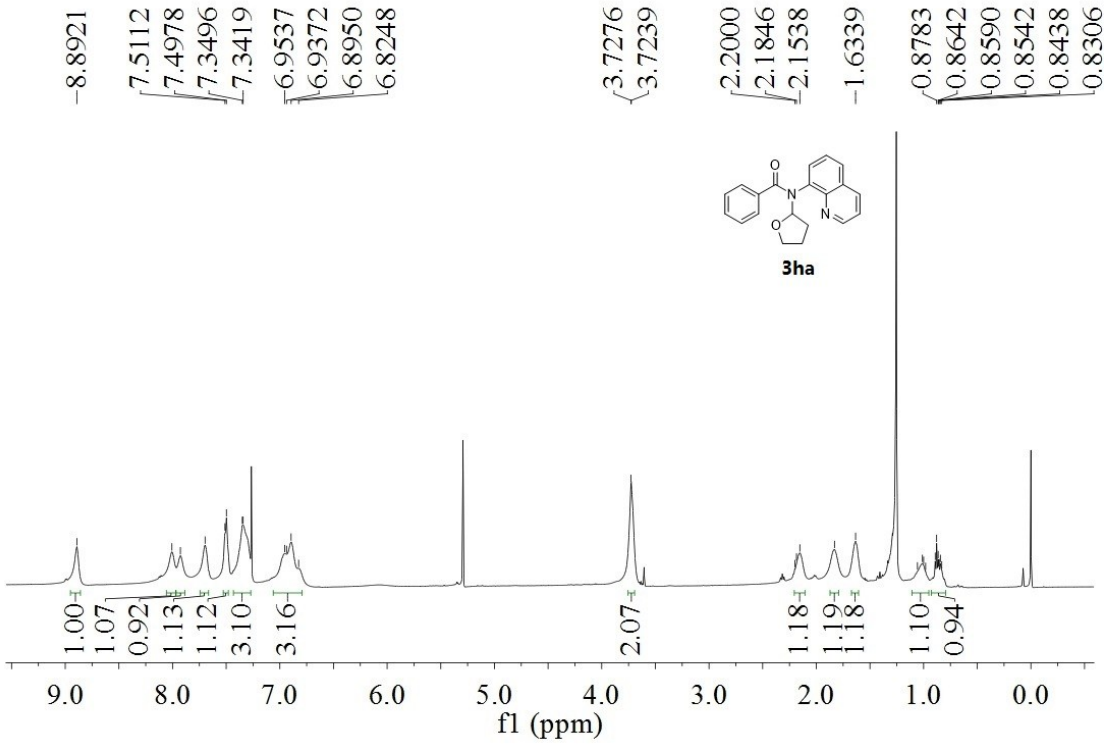
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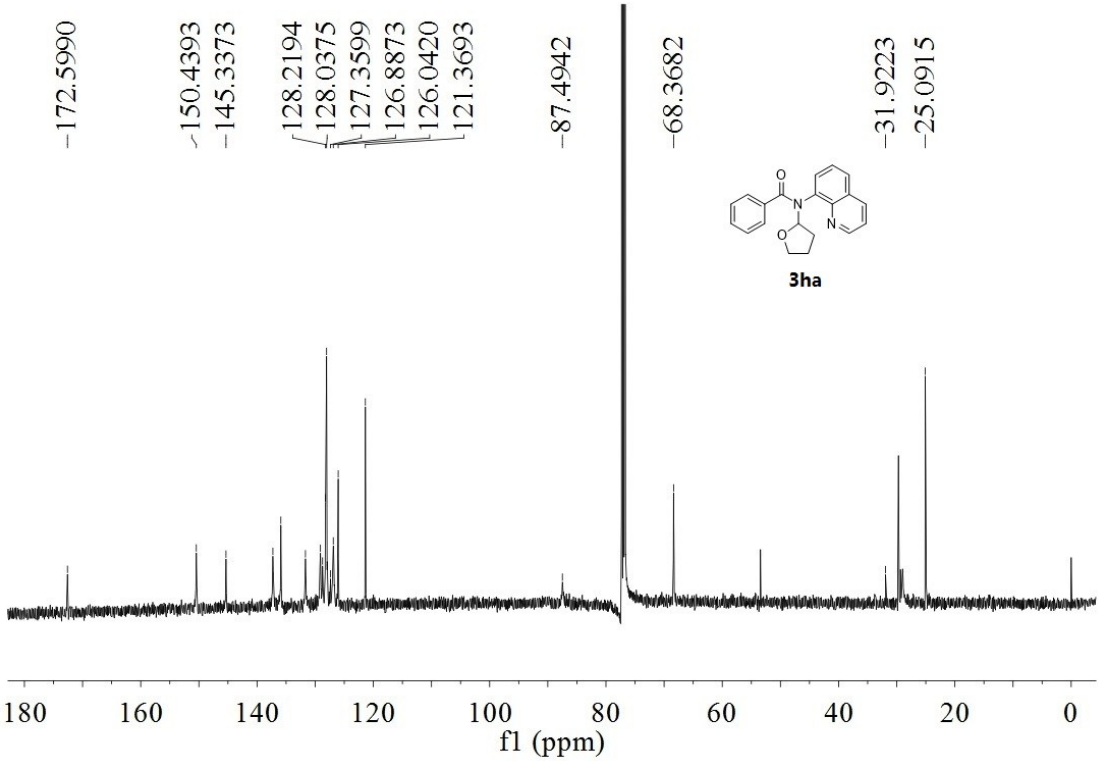
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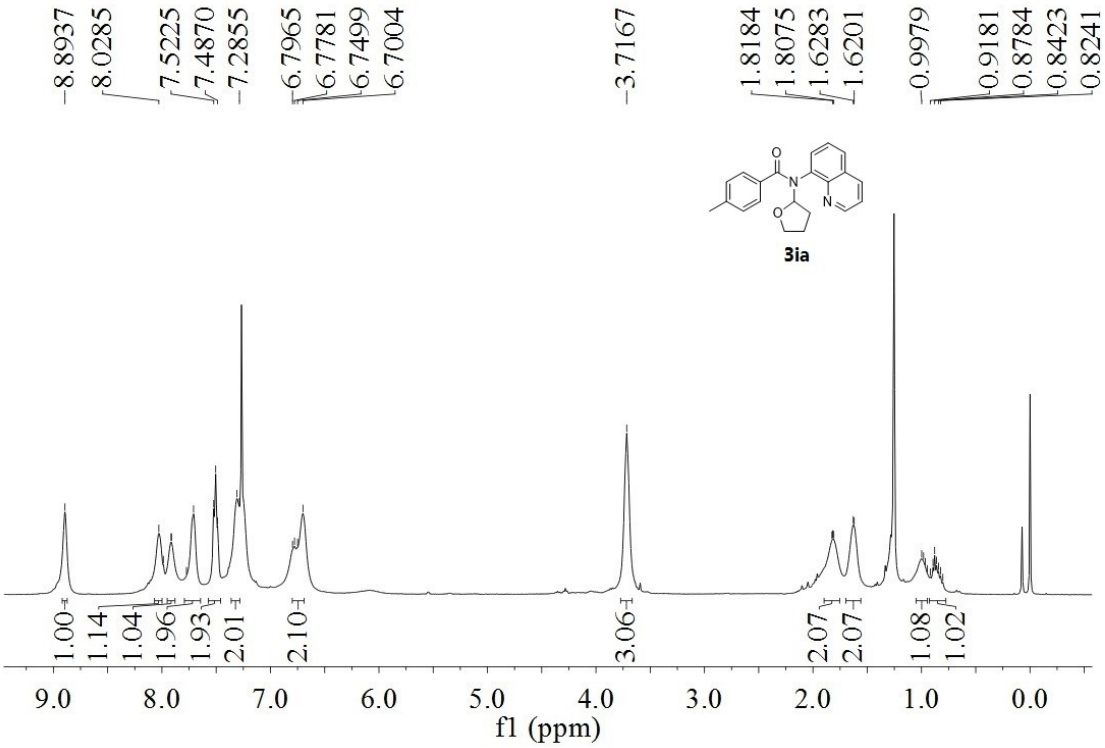
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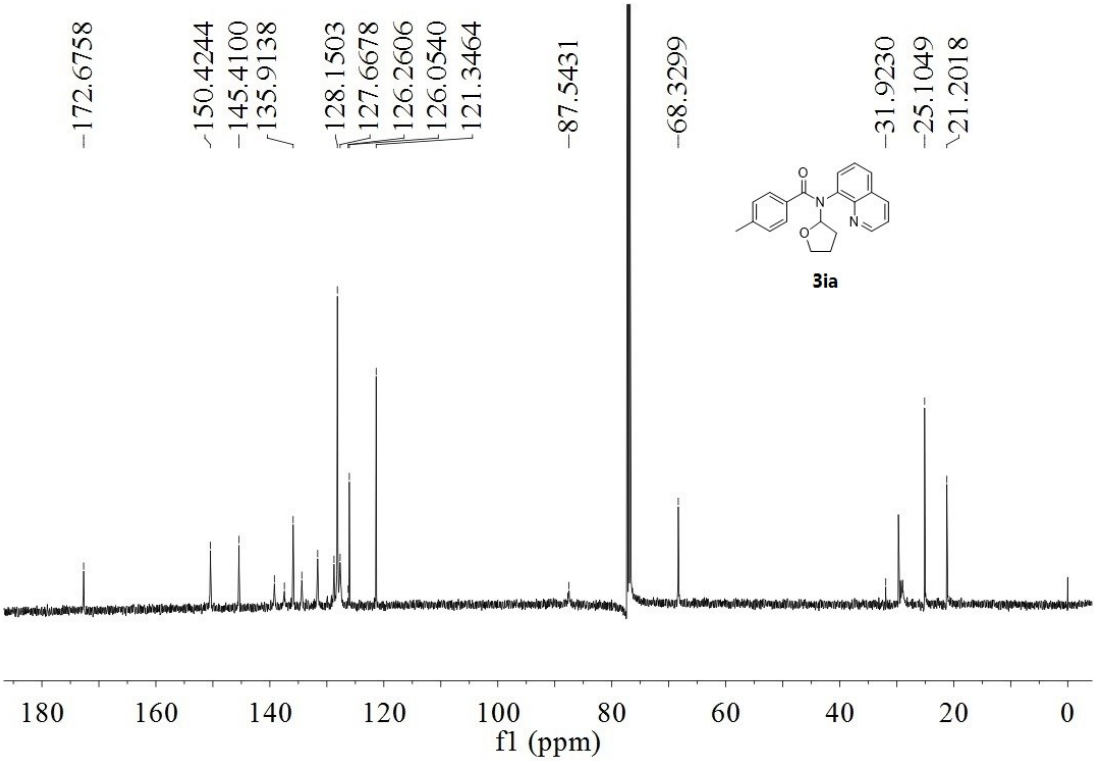
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126.0540
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68.3299
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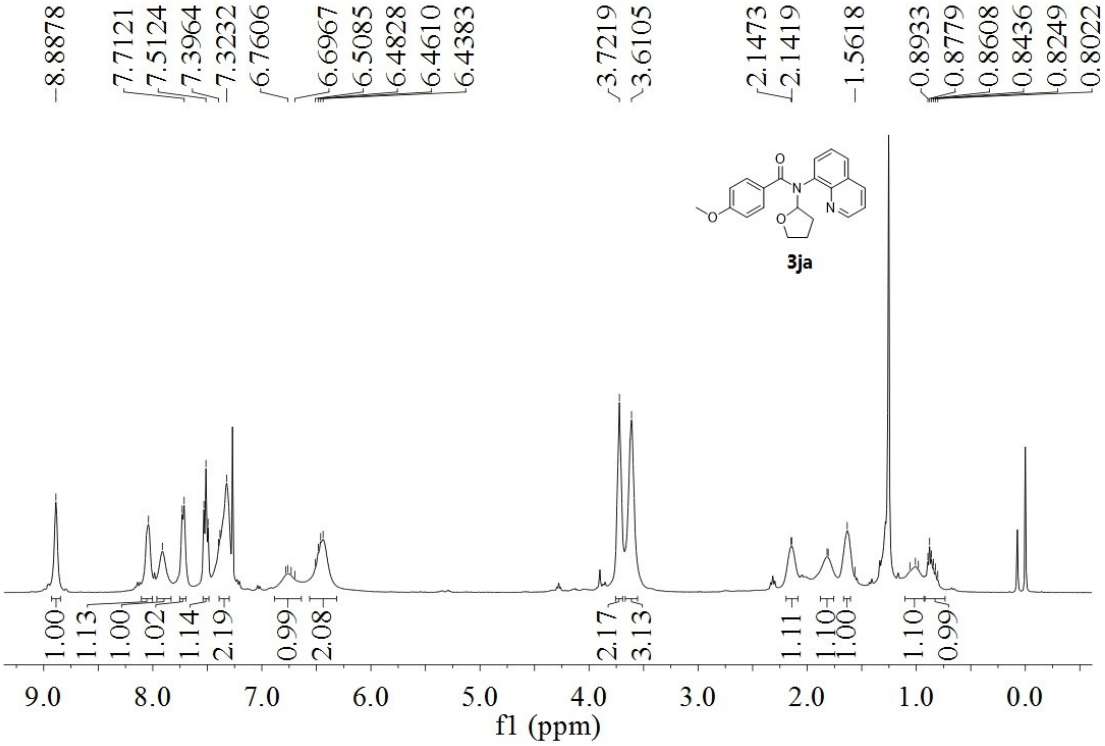
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6.4383
3.7219
3.6105
2.1473
2.1419
1.5618
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0.8779
0.8608
0.8436
0.8249
0.8022
3ja
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1.13
1.00
1.02
1.14
2.19
0.99
2.08
2.17
3.13
1.11
1.10
1.00
1.10
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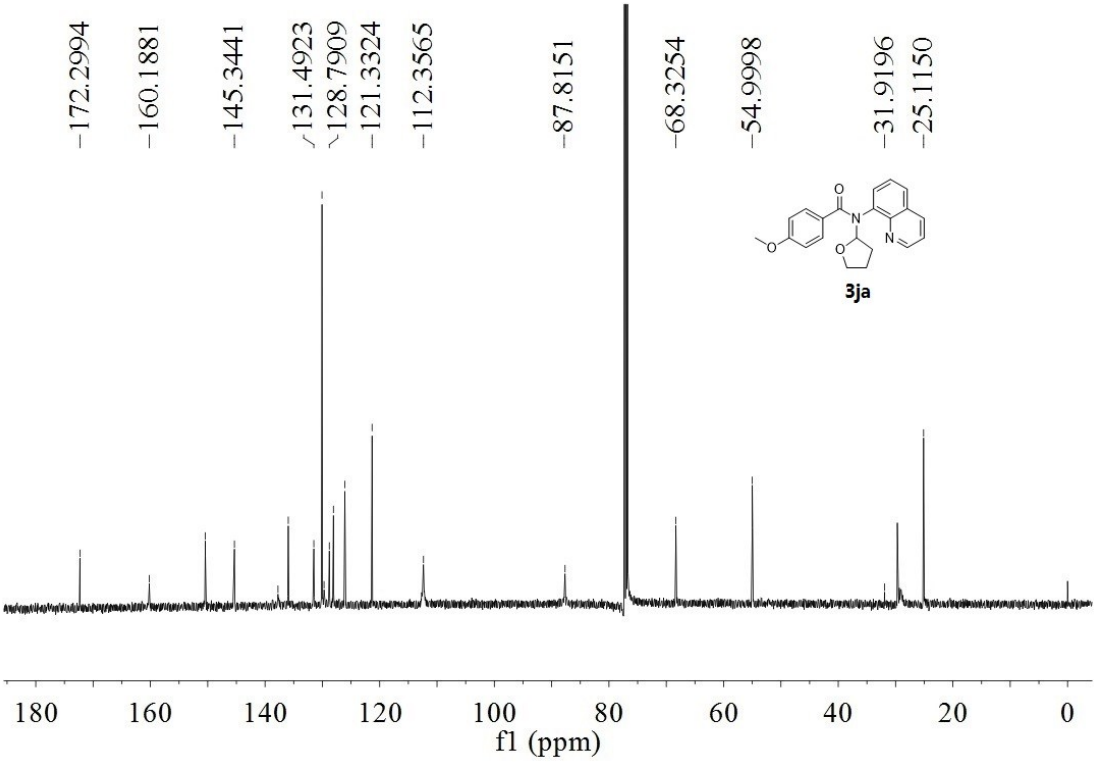
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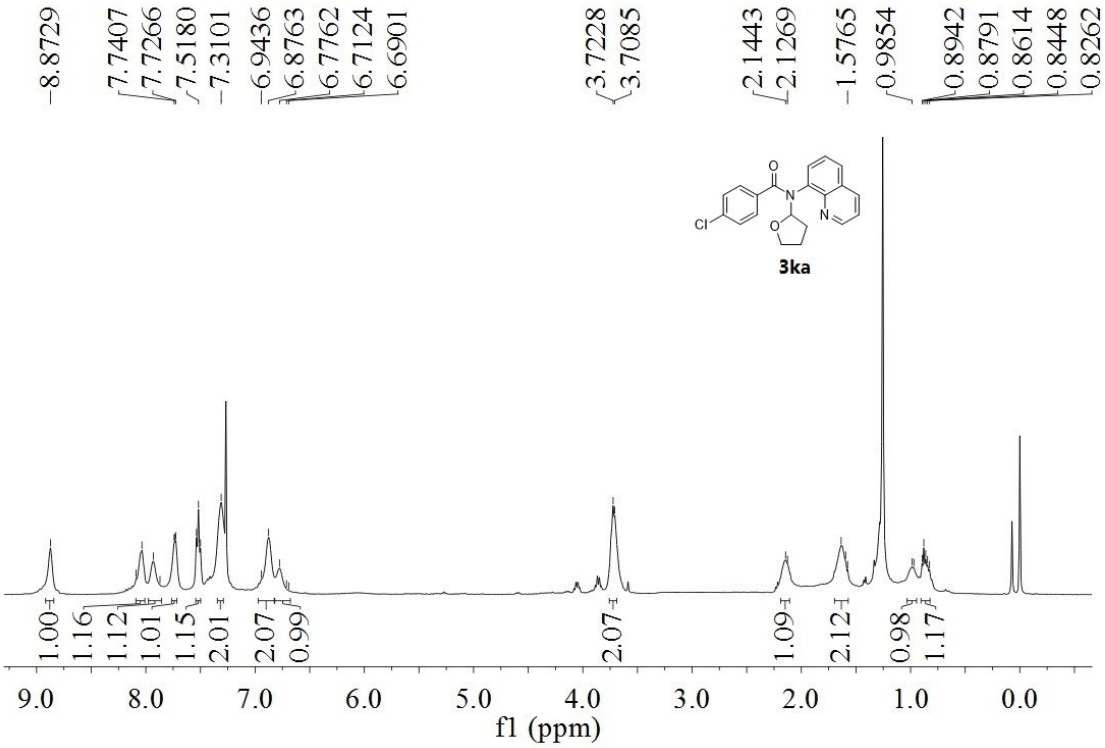
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3.7228
3.7085
2.1443
2.1269
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1.16
1.12
1.01
1.15
2.01
2.07
0.99
2.07
1.09
2.12
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1.17
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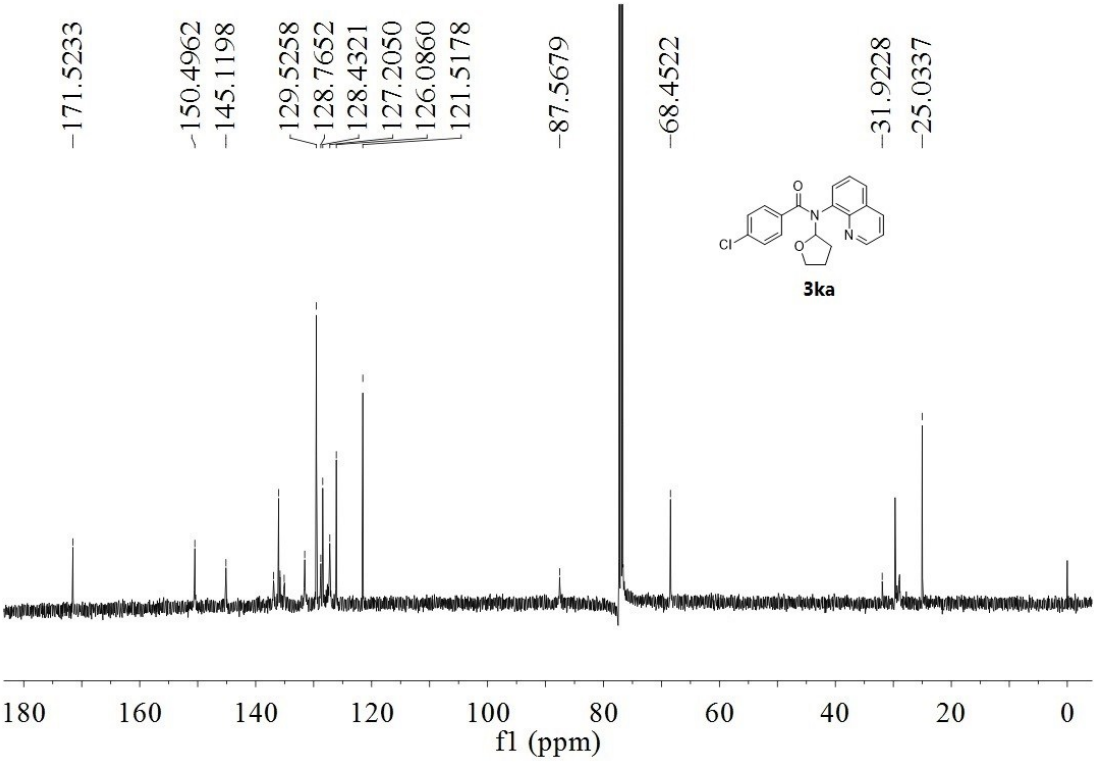
3ka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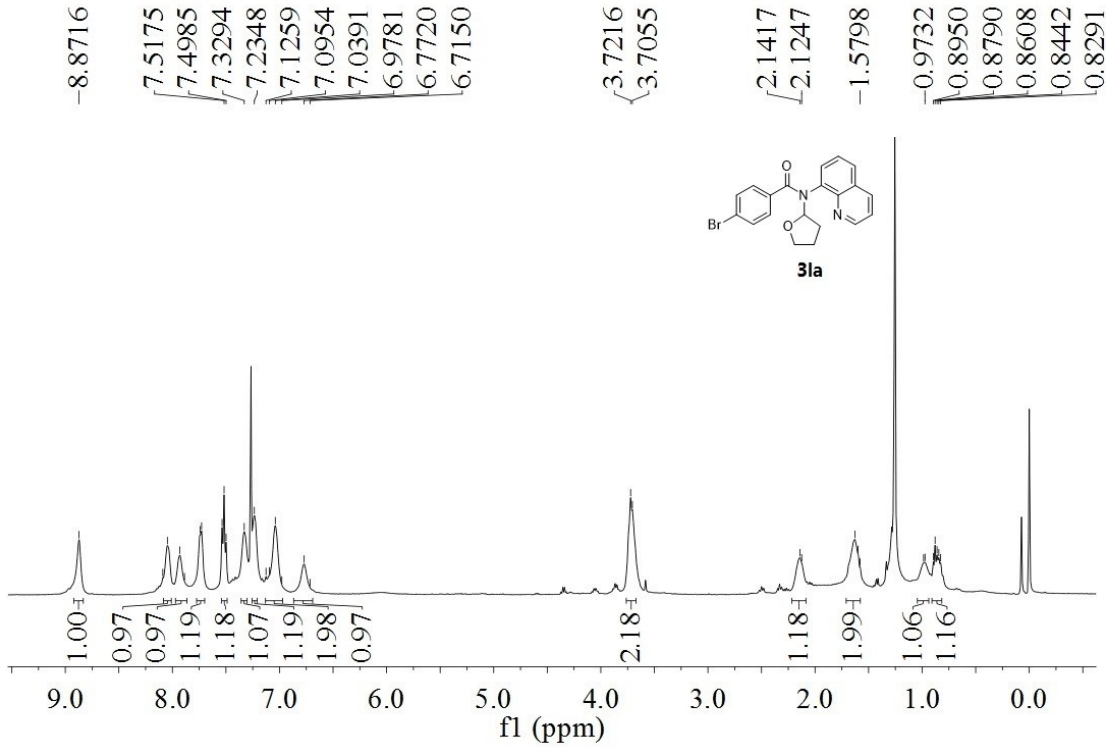
3ka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6.7150
3.7216
3.7055
2.1417
2.1247
1.5798
0.9732
0.8950
0.8790
0.8608
0.8442
0.8291
1.00
0.97
0.97
1.19
1.18
1.07
1.19
1.98
0.97
2.18
1.18
1.99
1.06
1.16
9.0
8.0
7.0
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N
O
N
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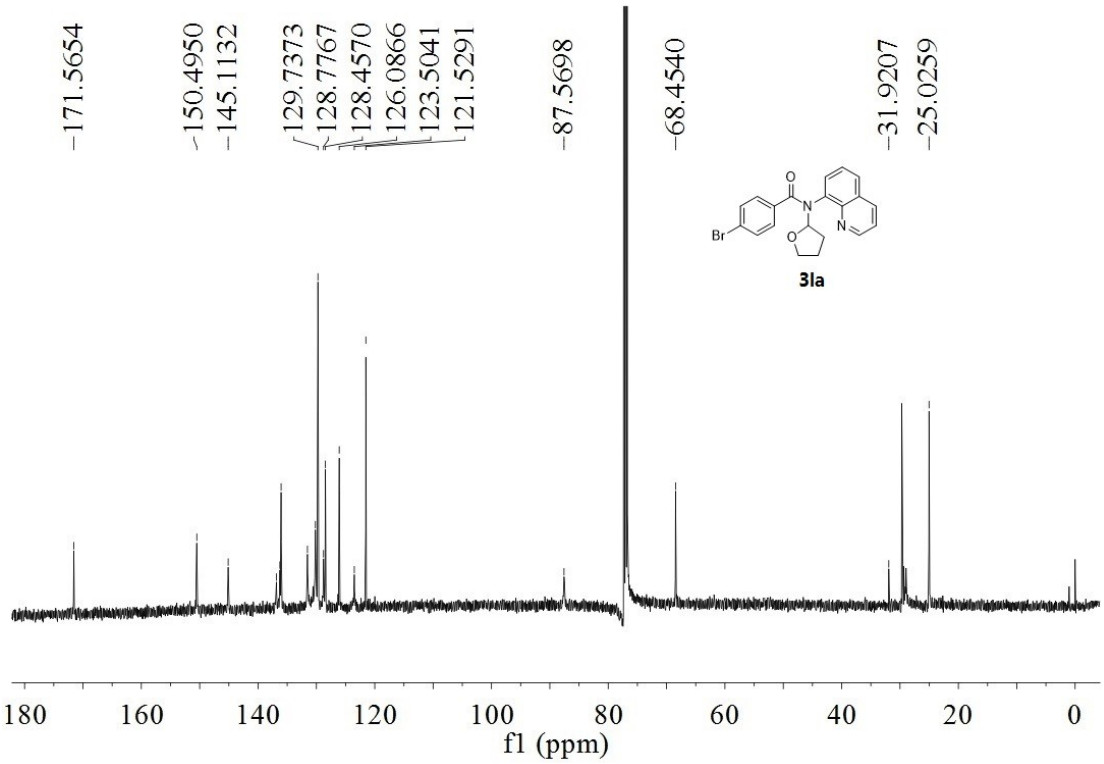
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31.9207
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N
O
N
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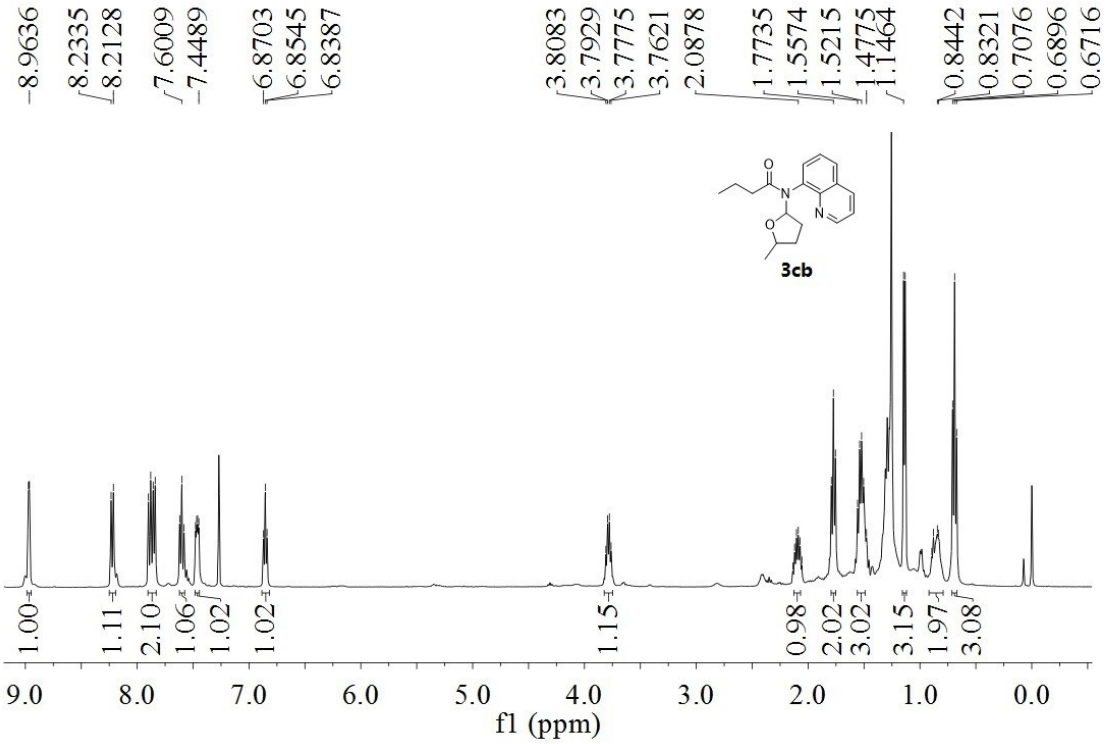
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6.8545
6.8387
3.8083
3.7929
3.7775
3.7621
2.0878
1.7735
1.5574
1.5215
1.4775
1.1464
0.8442
0.8321
0.7076
0.6896
0.6716
3cb
1.00
1.11
2.10
1.06
1.02
1.02
1.15
0.98
2.02
3.02
3.15
1.97
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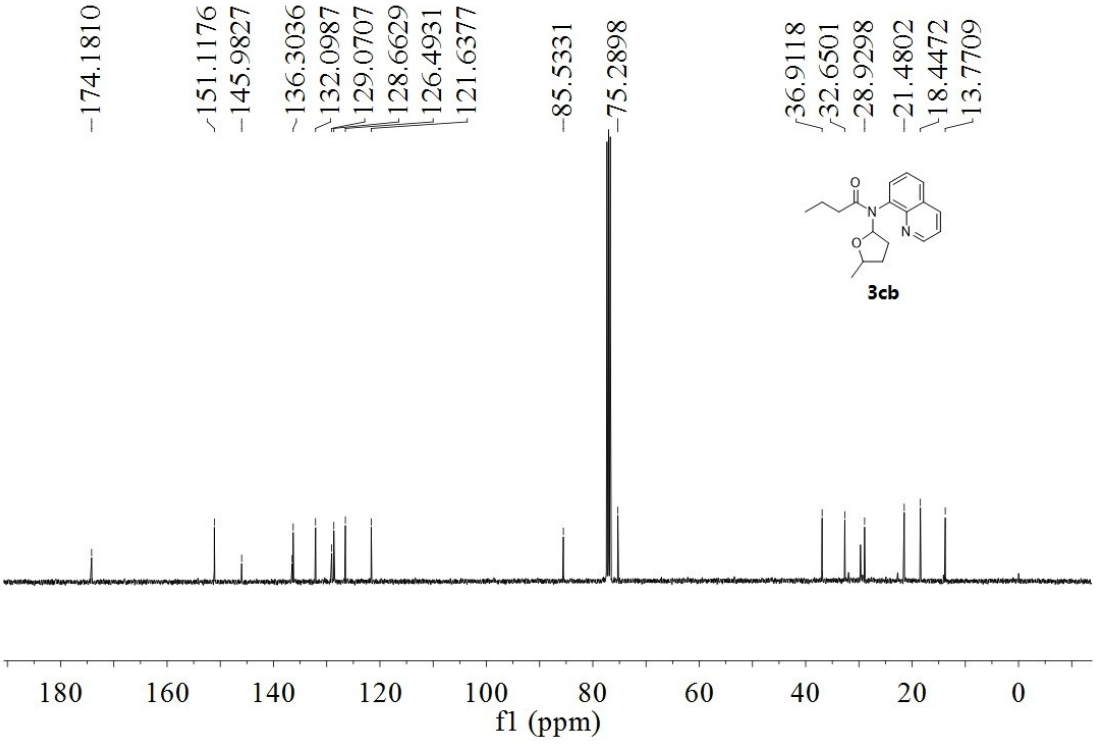
f1 (ppm)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129.0707
128.6629
126.4931
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85.5331
75.2898
36.9118
32.6501
28.9298
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100
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20
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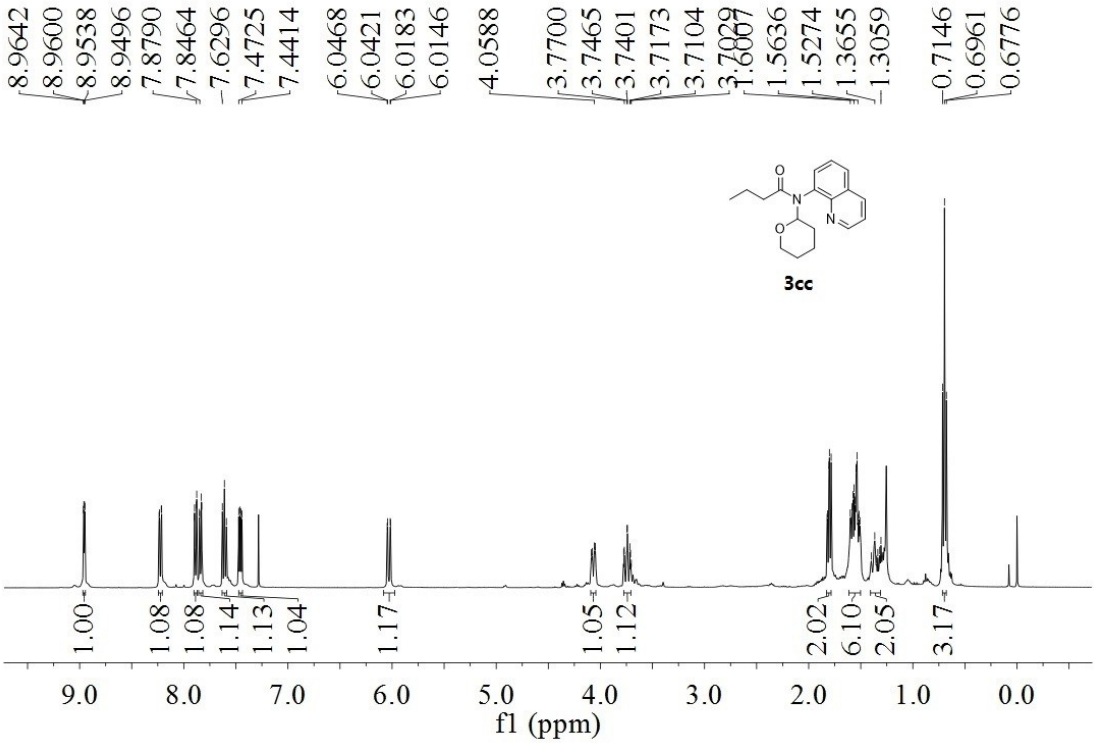
f1 (ppm)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3.7401
3.7173
3.7104
3.7029
3.7007
1.5636
1.5274
1.3655
1.3059
0.7146
0.6961
0.6776
3cc
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1.08
1.08
1.14
1.13
1.04
1.17
1.05
1.12
2.02
6.10
2.05
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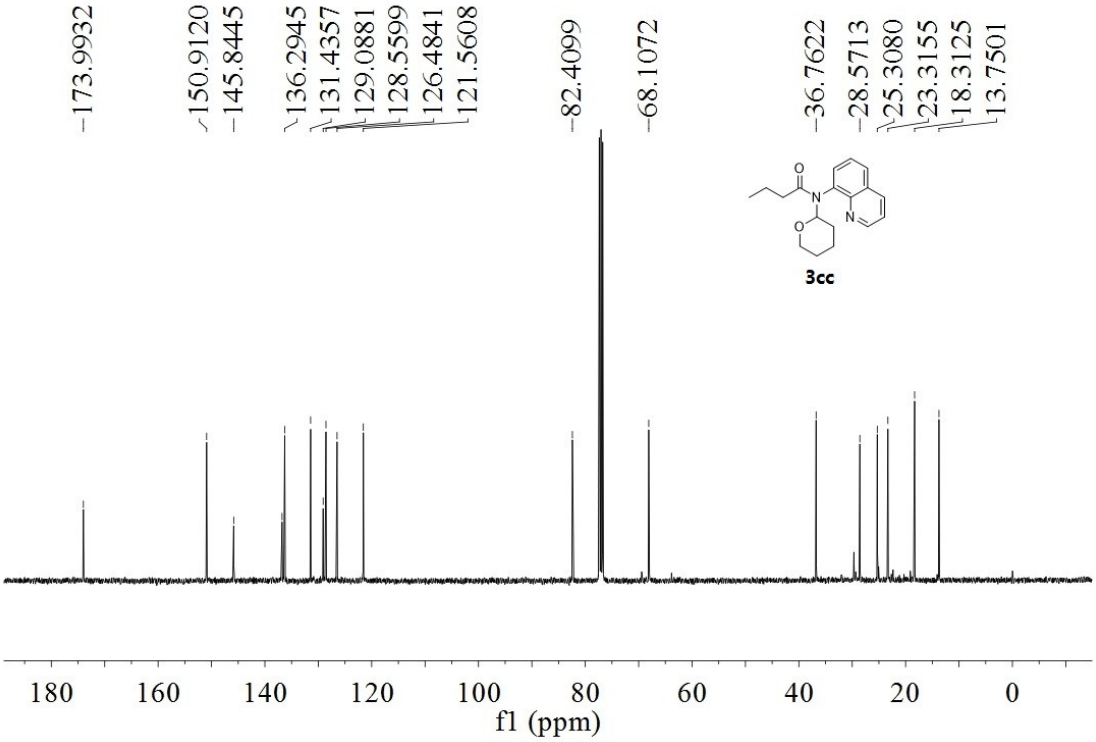
0.0
f1 (ppm)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28.5713
25.3080
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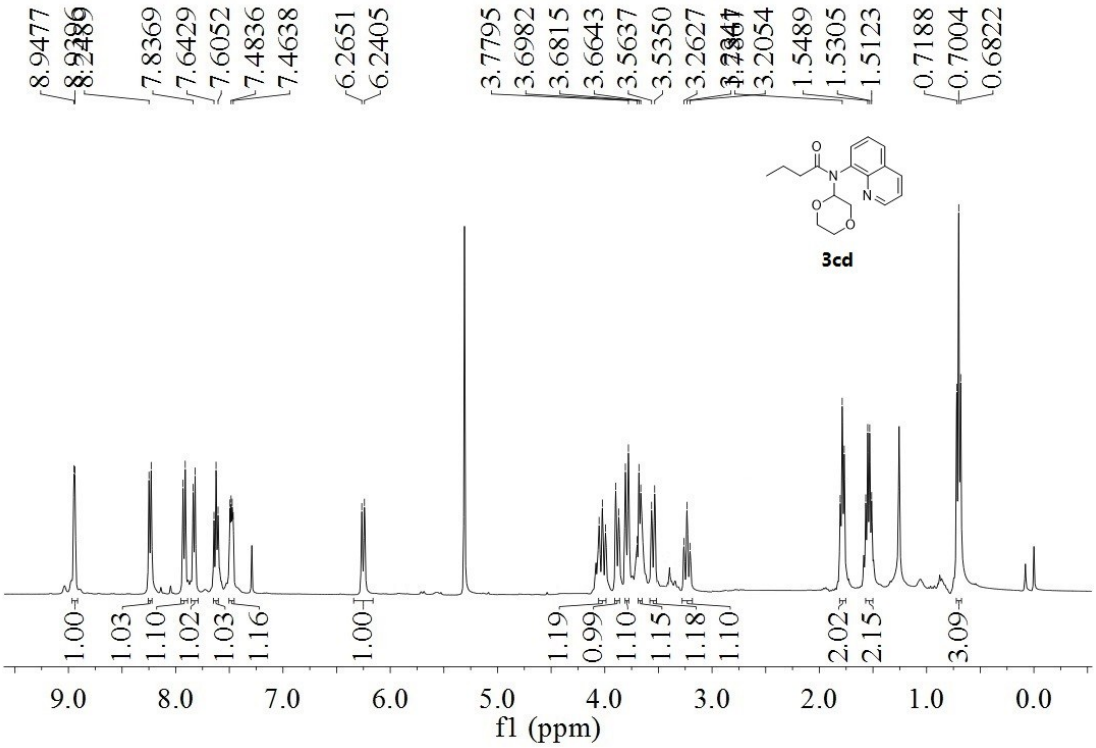
20
0
f1 (ppm)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3.6815
3.6643
3.5637
3.5350
3.2627
3.2054
1.5489
1.5305
1.5123
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0.6822
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1.02
1.03
1.16
1.00
1.19
0.99
1.10
1.15
1.18
1.10
2.02
2.15
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7.0
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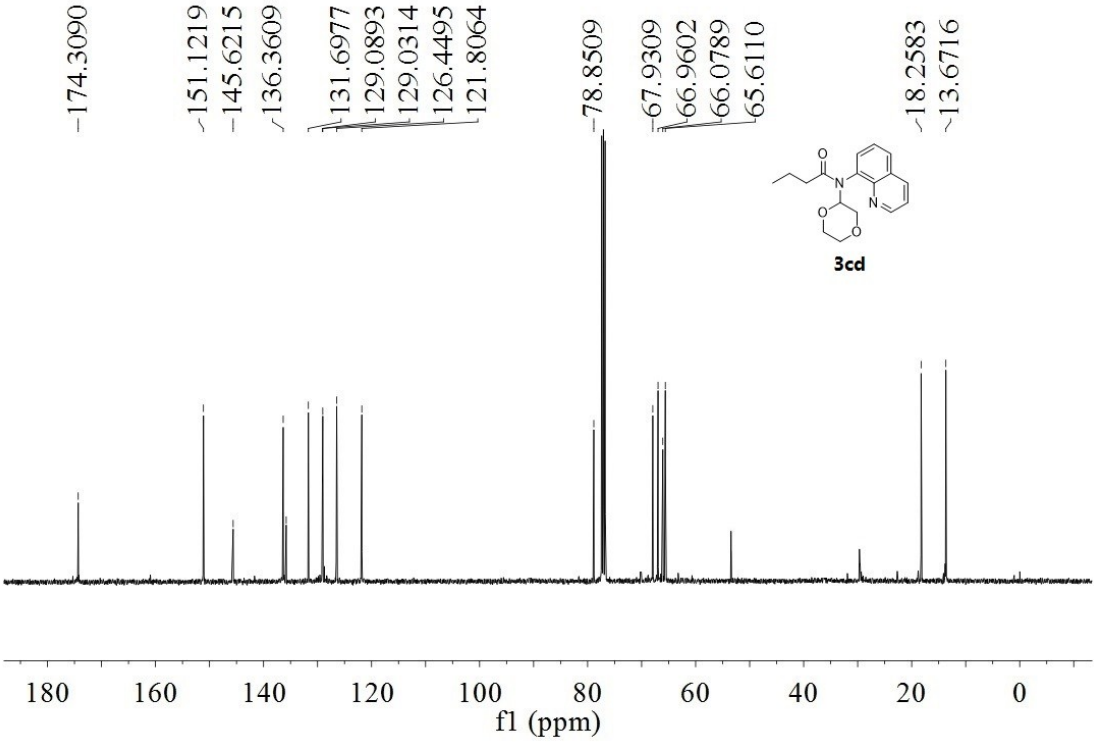
f1 (ppm)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66.9602
66.0789
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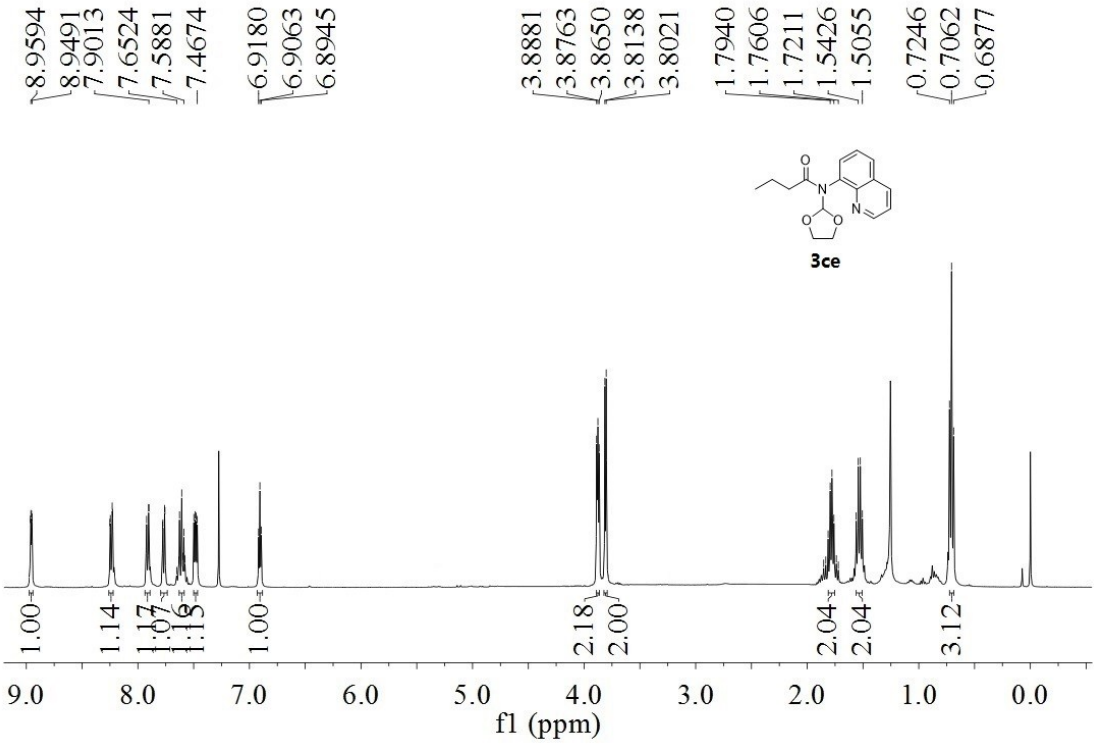
f1 (ppm)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3.8650
3.8138
3.8021
1.7940
1.7606
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1.5426
1.5055
0.7246
0.7062
0.6877
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1.17
1.07
1.16
1.15
1.00
2.18
2.00
2.04
2.04
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5.0
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2.0
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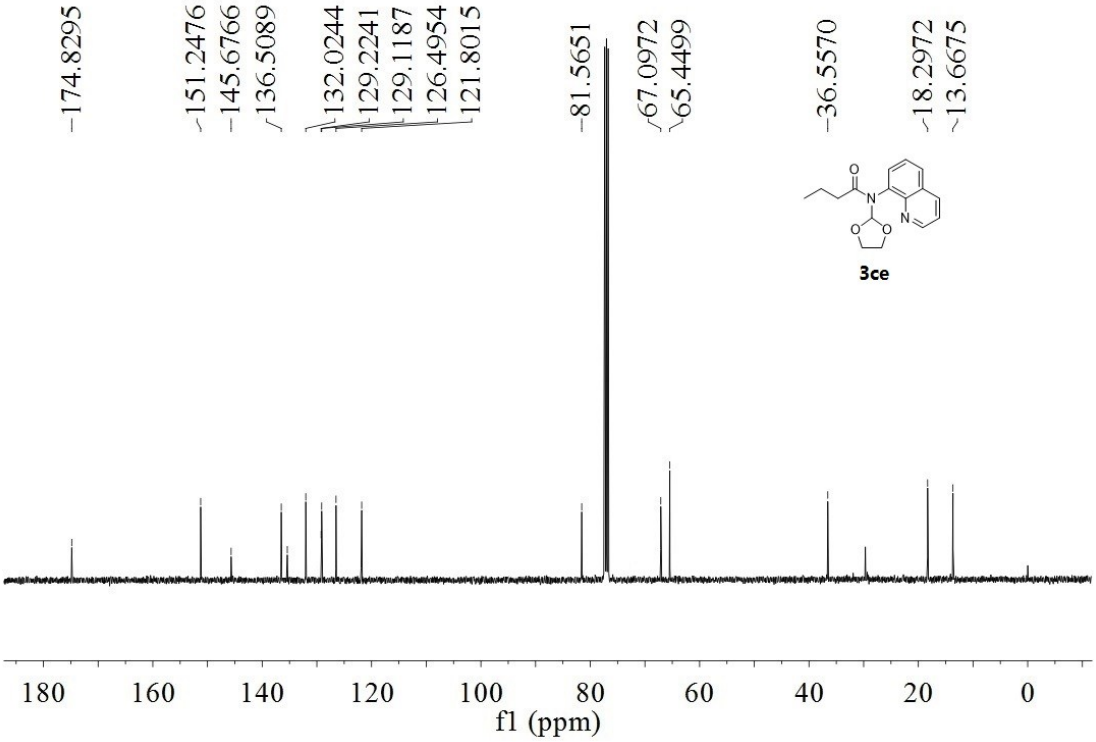
0.0
f1 (ppm)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100
80
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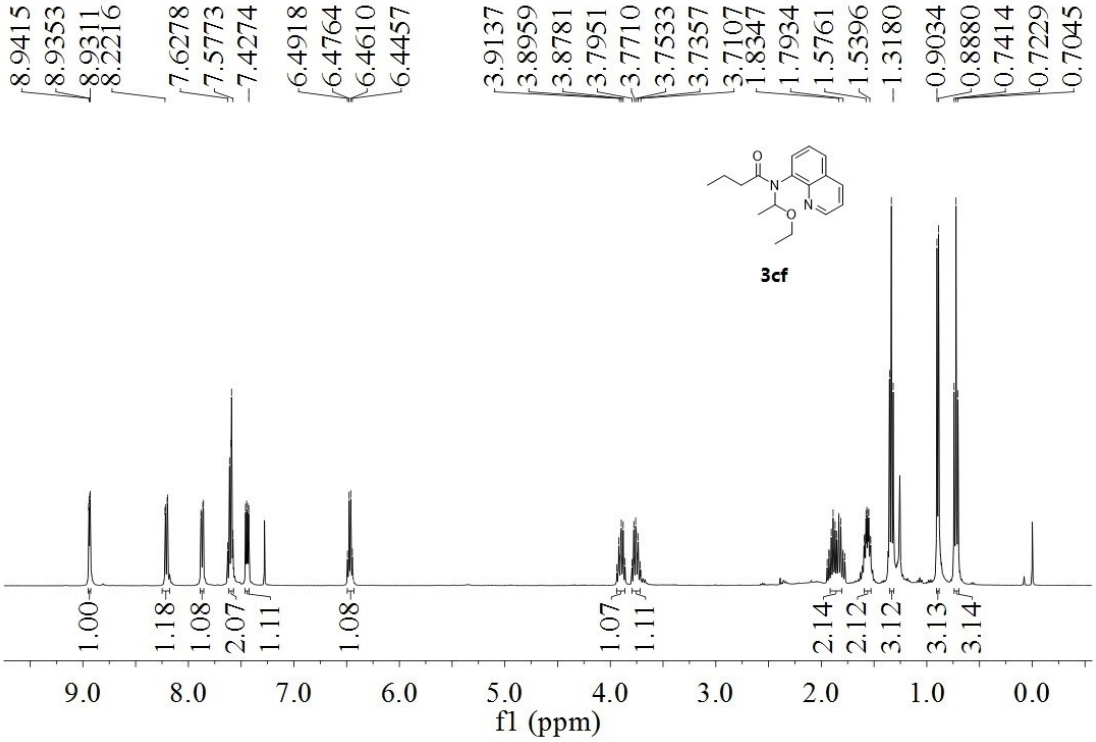
f1 (ppm)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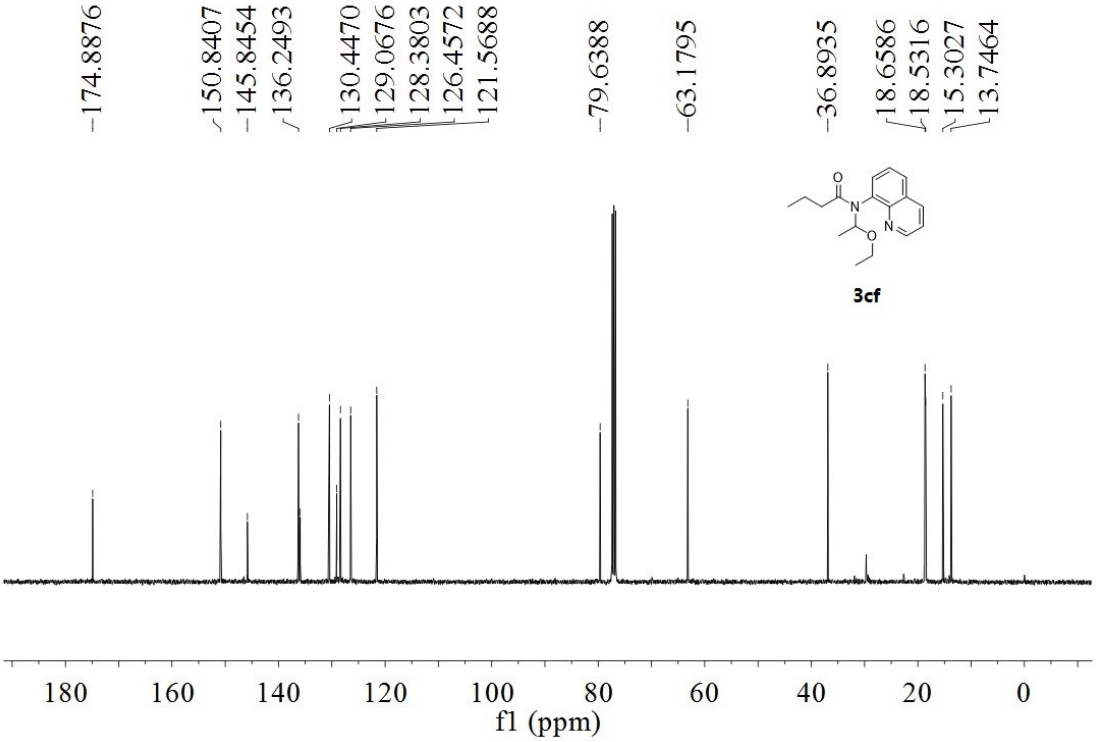
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36.8935
18.6586
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140
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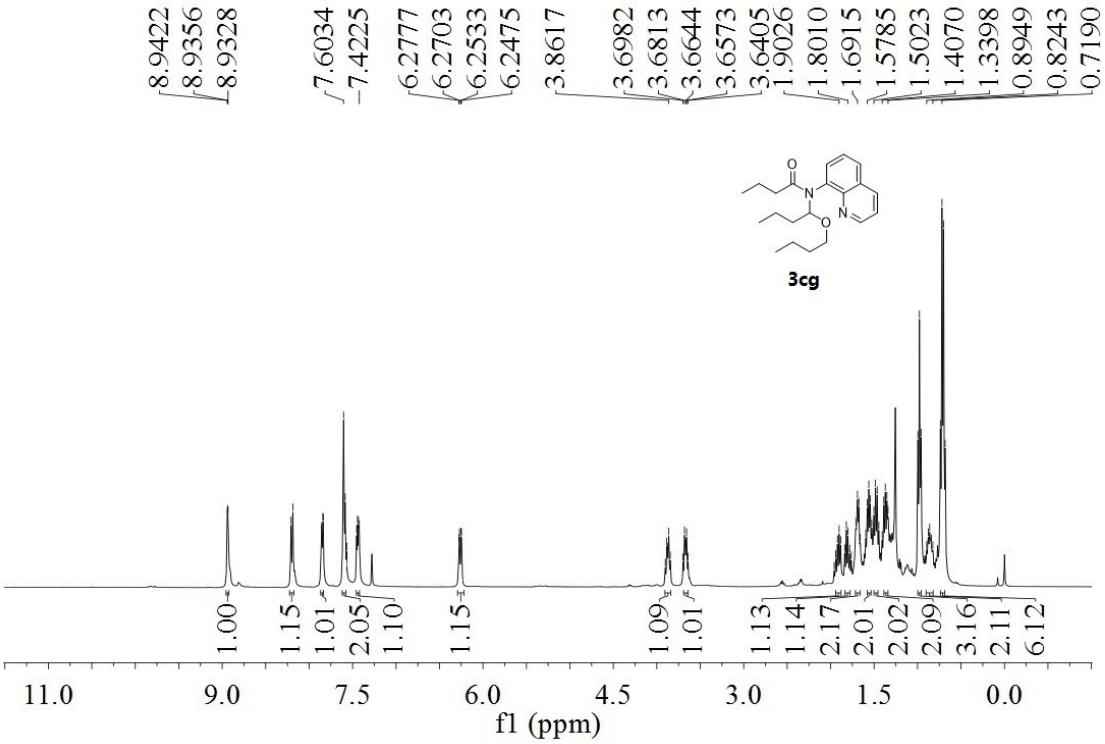
f1 (ppm)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3.6813
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3.6573
3.6405
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1.3398
0.8949
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1.01
2.05
1.10
1.15
1.09
1.01
1.13
1.14
2.17
2.01
2.02
2.09
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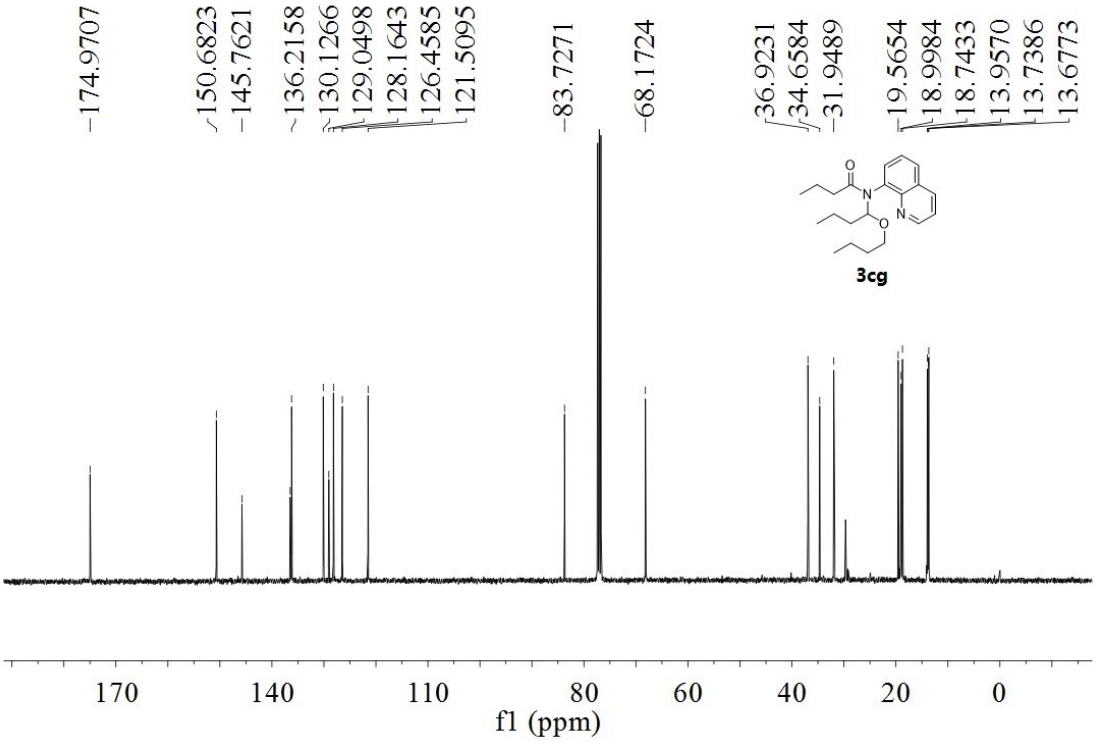
f1 (ppm)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68.1724
36.9231
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31.9489
19.5654
18.9984
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20
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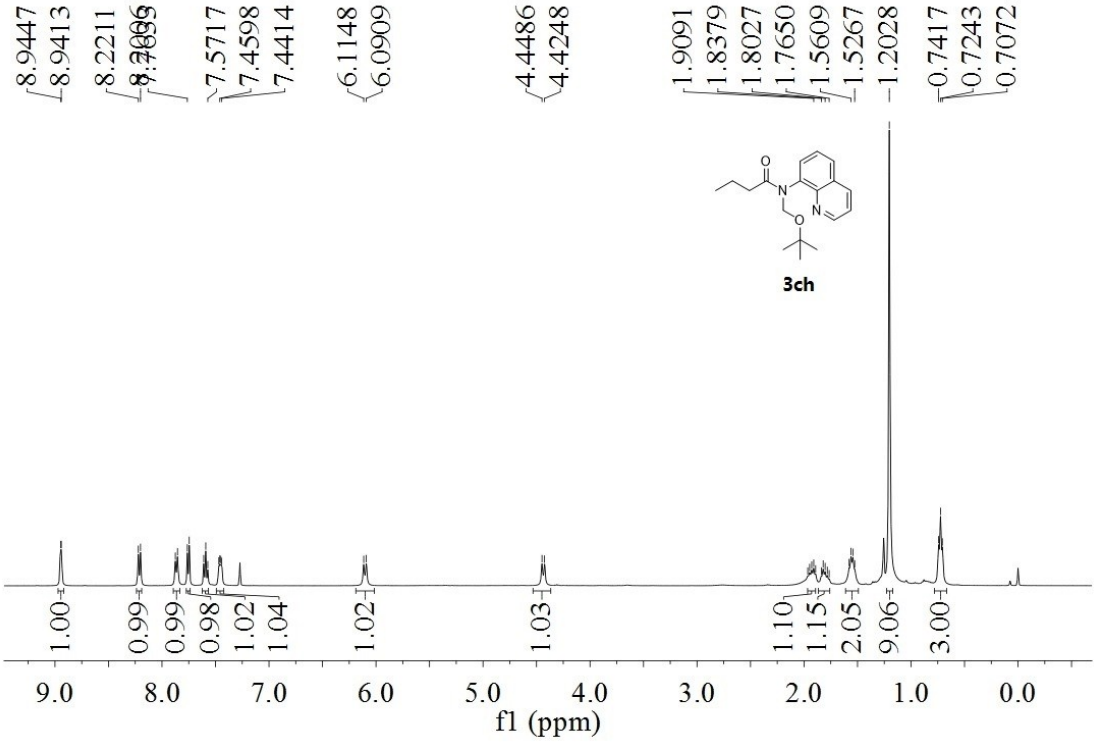
f1 (ppm)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1.04
1.02
1.03
1.10
1.15
2.05
9.06
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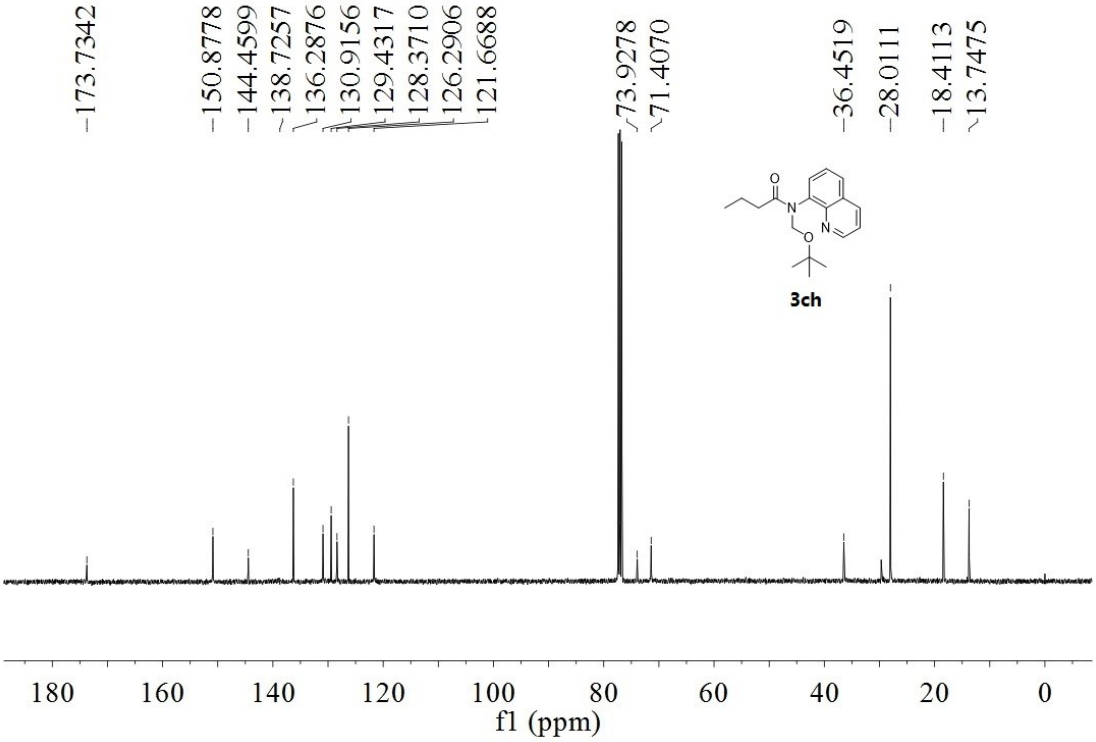
f1 (ppm)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71.4070
36.4519
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20
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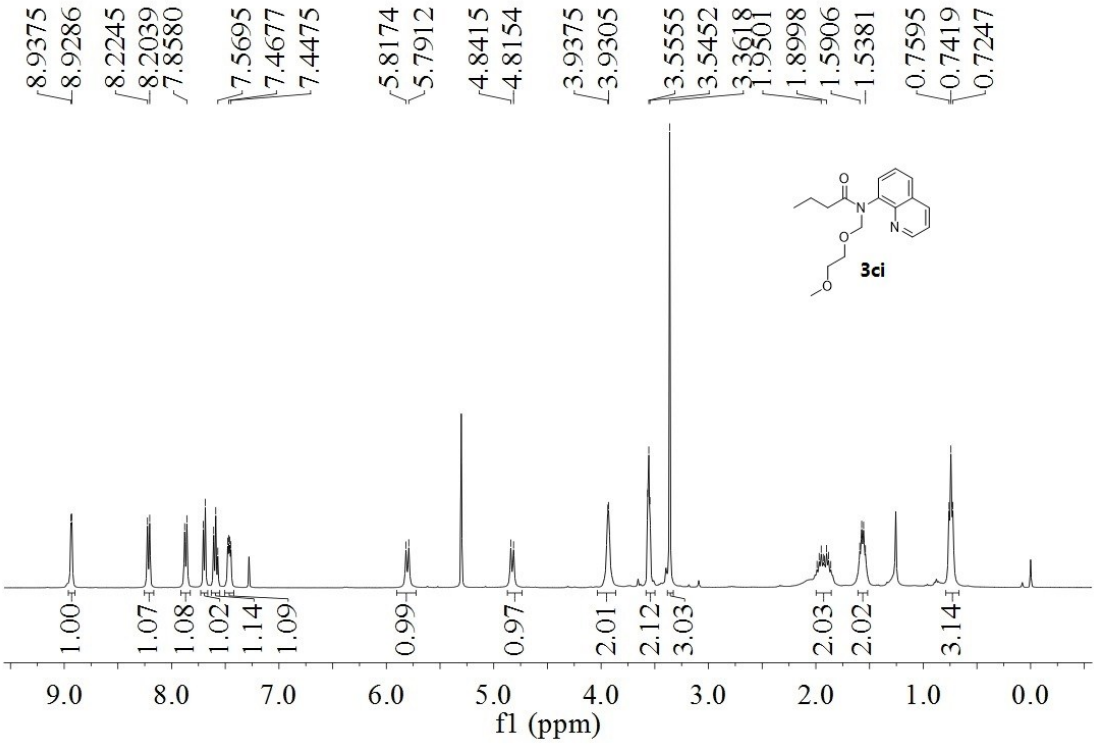
f1 (ppm)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1.00
1.07
1.08
1.02
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1.09
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2.01
2.12
3.03
2.03
2.02
3.14
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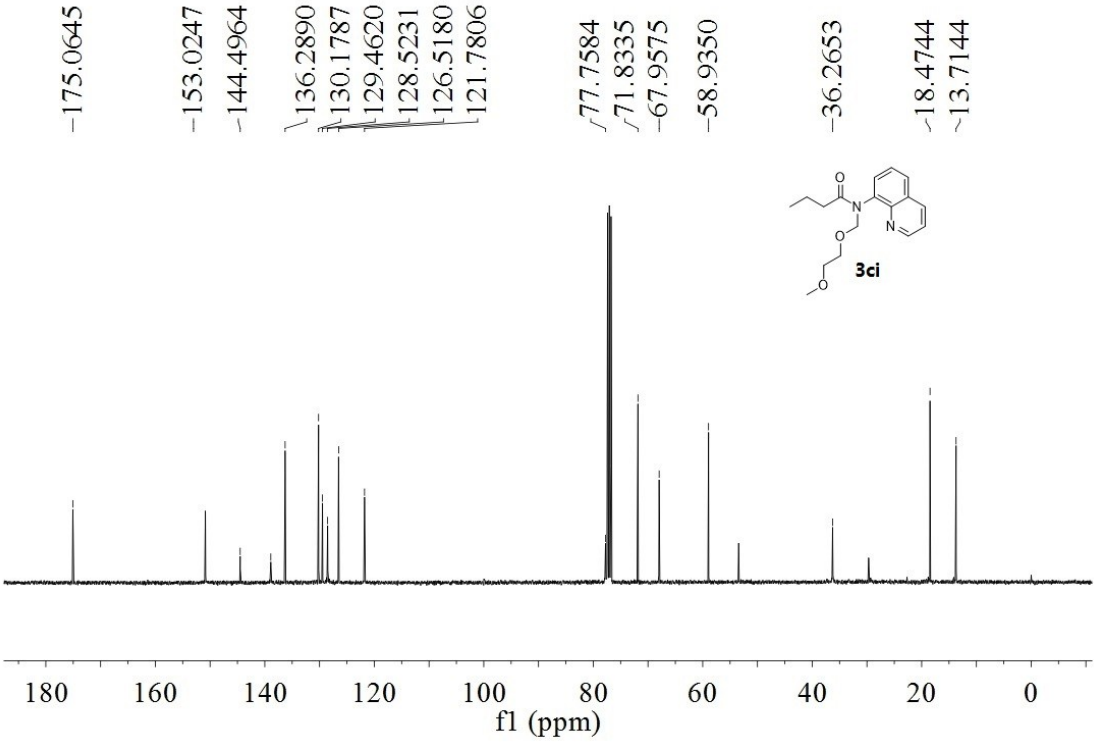
f1 (ppm)
3ci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67.9575
58.9350
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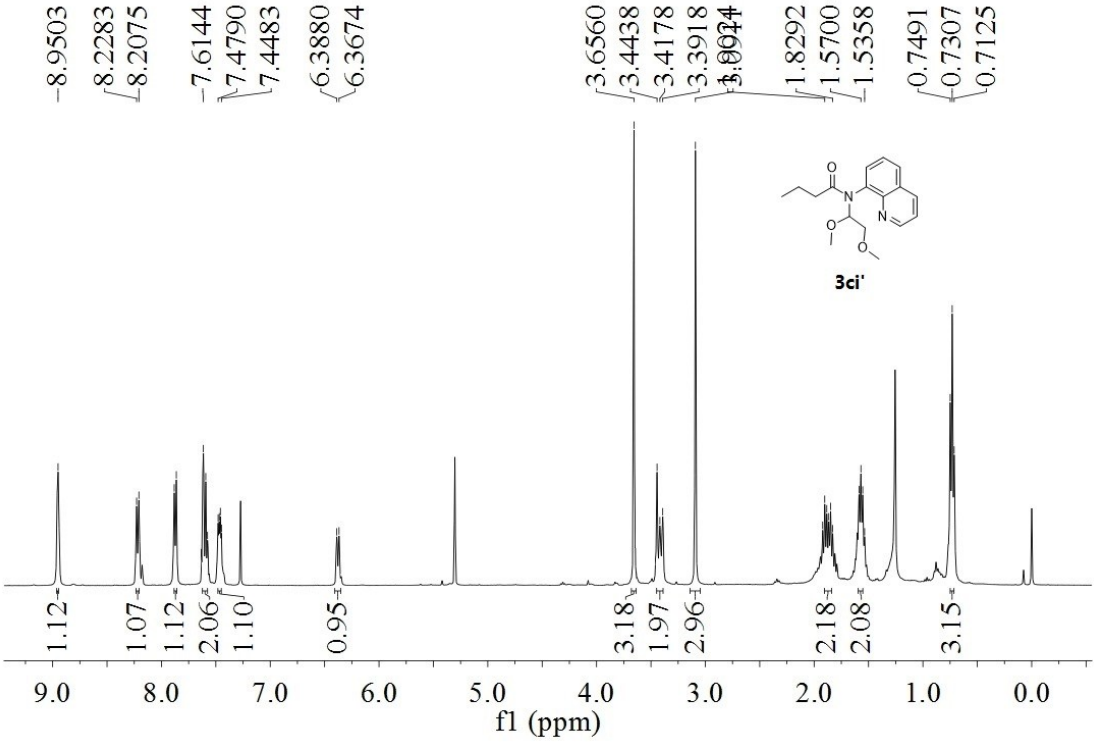
140
120
100
80
60
40
20
0
f1 (ppm)
3ci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1.07
1.12
2.06
1.10
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1.97
2.96
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2.08
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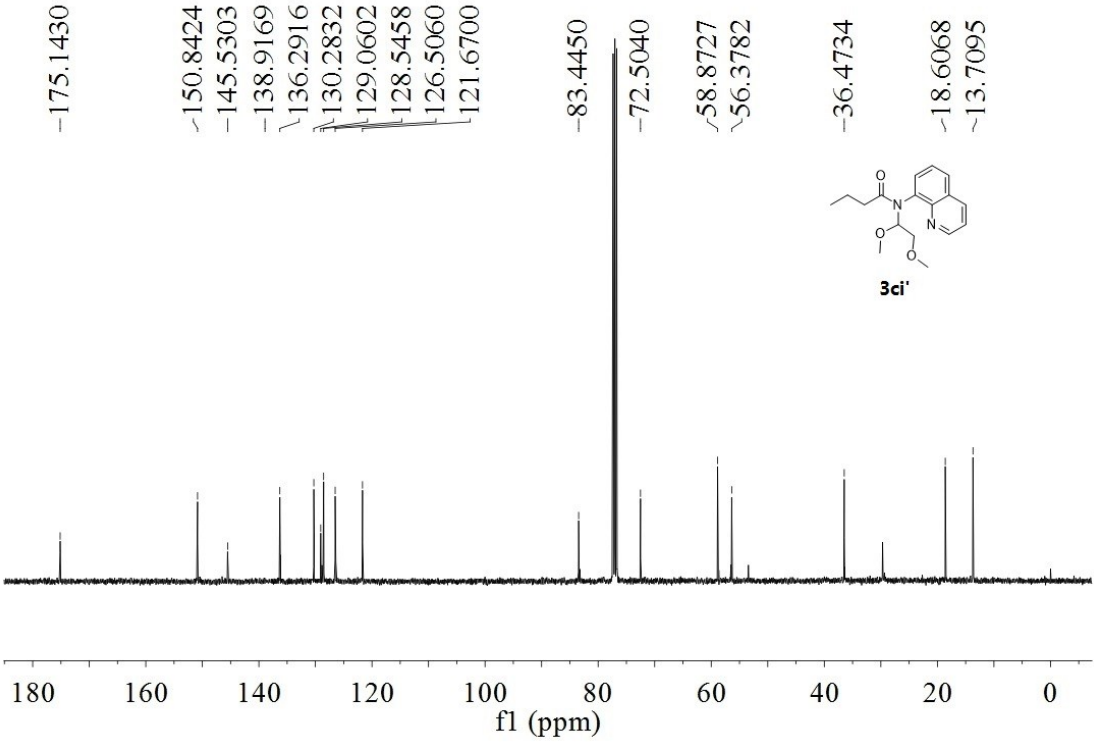
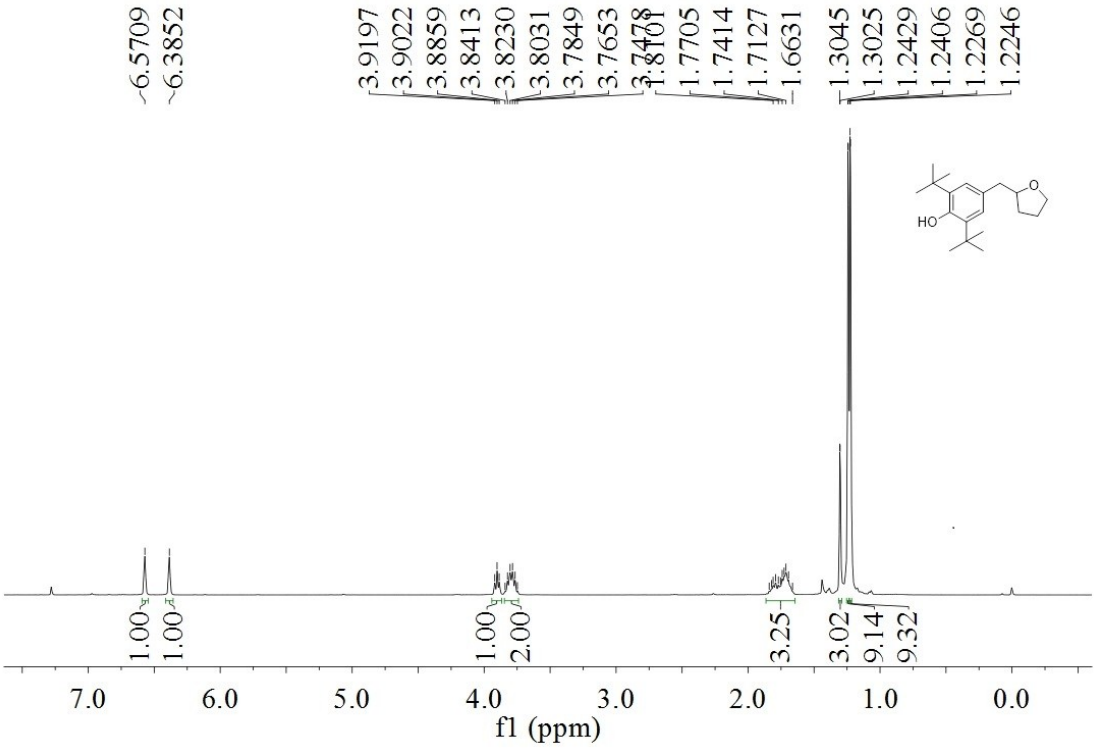
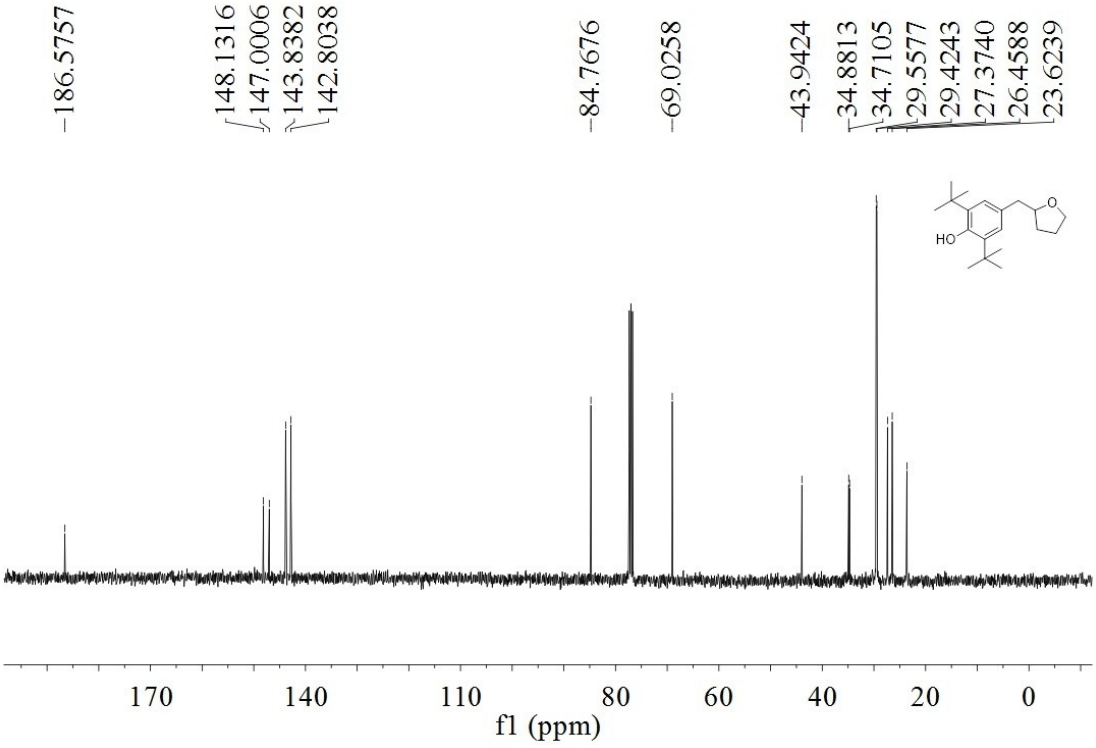
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


175.1430
150.8424
145.5303
138.9169
136.2916
130.2832
129.0602
128.5458
126.5060
121.6700
83.4450
72.5040
58.8727
56.3782
36.4734
18.6068
13.7095
3ci'
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


6.5709
6.3852
3.9197
3.9022
3.8859
3.8413
3.8230
3.8031
3.7849
3.7653
3.7478
3.8101
1.7705
1.7414
1.7127
1.6631
1.3045
1.3025
1.2429
1.2406
1.2269
1.2246
HO
O
1.00
1.00
1.00
2.00
3.25
3.02
9.14
9.32
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


186.5757
148.1316
147.0006
143.8382
142.8038
84.7676
69.0258
43.9424
34.8813
34.7105
29.5577
29.4243
27.3740
26.4588
23.6239
HO
O
170
140
110
80
60
40
20
0
f1 (ppm)