Electronic Supplementary Information

Copper-Catalyzed Intramolecular Iminolactonization Cyclization Reactions of Remote C(sp^3)-H Bonds in Carboxamides

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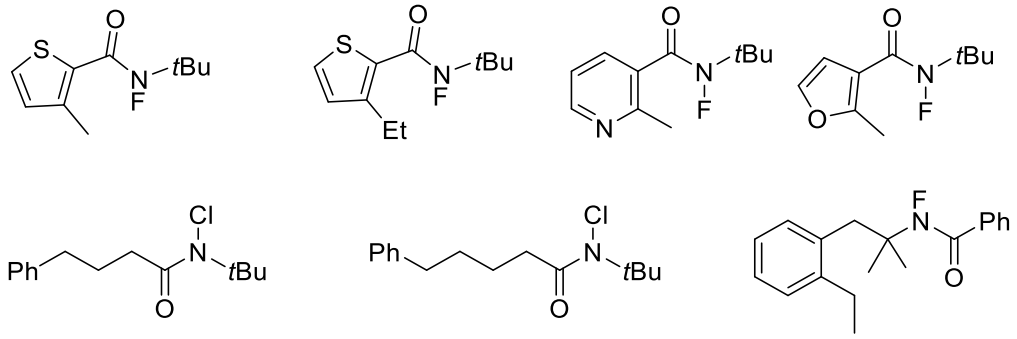
General information

Most of reactions were carried out under argon atmosphere using Schlenk techniques. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. CuI was purchased from Sigma-Aldrich. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 GF254 plates. Flash column chromatography was performed using Tsingdao silica gel (60, particle size 0.040–0.063 mm). Visualization on TLC was achieved by use of UV light (254 nm) or iodine. NMR spectra were recorded on Bruker DRX-400 at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR, respectively, in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. The chemical shifts are expressed in ppm and coupling constants are given in Hz. Data for ^{1}H NMR are recorded as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quarter; p, pentet, m, multiplet; br, broad), coupling constant (Hz), integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Mass spectrometric data were obtained using Bruker Apex IV RTMS.

Unsuccessful substrates



Optimization of the reaction conditions

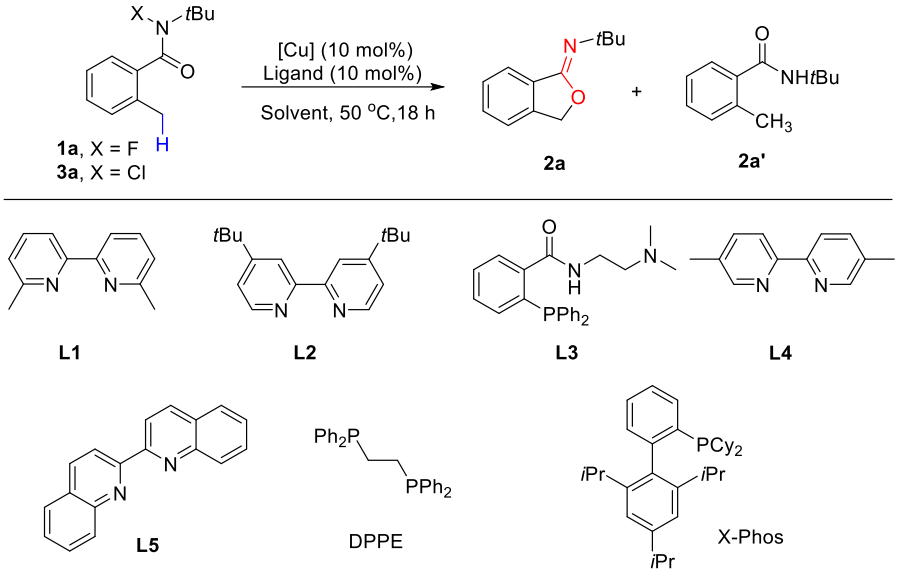


Table S1: Screen of the ligand[a,b]

entry	[Cu]	Ligand	solvent	**2a**	**2a'**
1	CuBr	Phen	THF	56	23
2	CuBr	bpy	THF	68	13
3	CuBr	L1	THF	63	15
4	CuBr	L2	THF	59	18
5	CuBr	L3	THF	60	12
6	CuBr	L4	THF	61	18
7	CuBr	L5	THF	45	27
8	CuBr	PPh_3	THF	26	15
9	CuBr	DPPE	THF	39	20
10	CuBr	X-Phos	THF	36	11
11[c]	CuBr	bpy	THF	56	37

[a]Reaction conditions: **1a** (0.2 mmol), CuBr (10 mol%), and Ligand (10 mol%) in dry THF (1.0 mL) under Ar at 50 ℃ for 18 h. [b]Isolated yield based on **1a**. [c]*N*-chlorocarboxamide **3a** was used.

Table S2: Screen of the catalysts [a,b]

entry	[Cu]	Ligand	solvent	**2a**	**2a'**
1	CuBr	bpy	THF	68	13
2	CuI	bpy	THF	79	<10
3	CuTc	bpy	THF	72	<10
4	CuOAc	bpy	THF	58	14
5	$CuBr{\cdot}Me_2S$	bpy	THF	72	<10
6	CuCl	bpy	THF	61	13
7	$Cu(OTf)_2$	bpy	THF	45	<10
8	Cu_2O	bpy	THF	Trace	Trace
9	AgCl	bpy	THF	Trace	Trace
10	AuCl	bpy	THF	15	<10
11	$PdCl_2$	bpy	THF	25	<10

12	$NiCl_2$	bpy	THF	38	18
13	$Ni(PPh_3)_2Cl_2$	--	THF	45	20
14	$Fe(OTf)_2$	bpy	THF	Trace	Trace
15[c]	CuI	bpy	THF	62	29
16[c,d]	$CuBr{\cdot}Me_2S$	bpy	THF	73	21

[a]Reaction conditions: **1a** (0.2 mmol), [catalyst] (10 mol%), and bpy (10 mol%) in dry THF (1.0 mL) under Ar at 50 ℃ for 18 h. [b]Isolated yield based on **1a**. [c]*N*-chlorocarboxamide **3a** was used. [d]At 30 ℃ for 18 h.

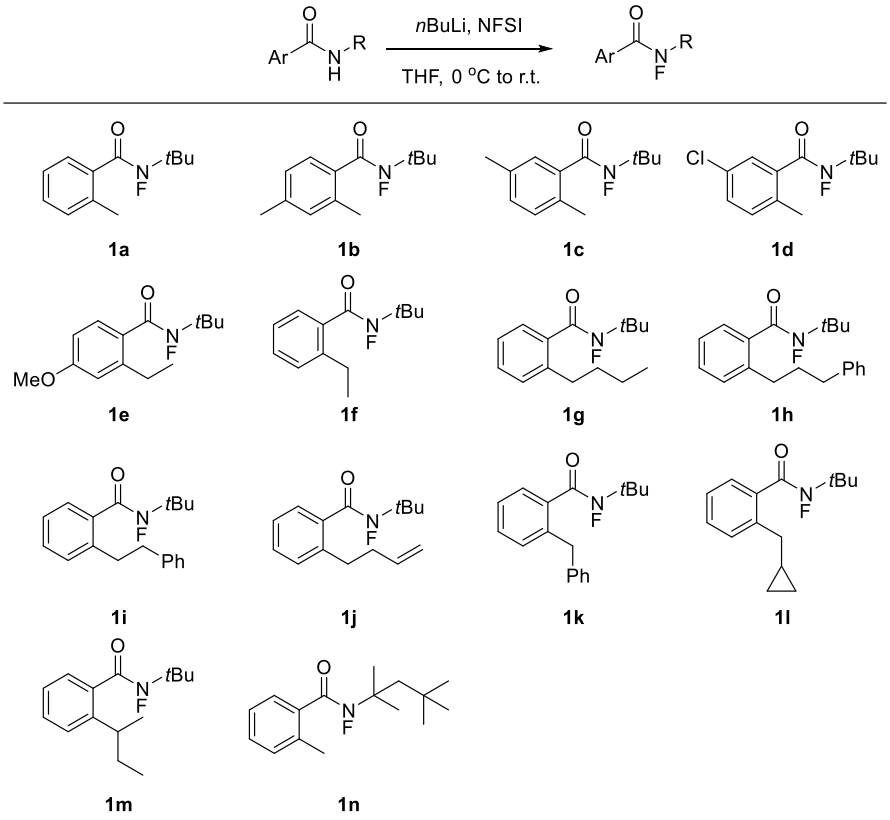
Table S3: Screen of the solvents [a,b]

entry	[Cu]	Ligand	solvent	**2a**	**2a'**
1	CuI	bpy	toluene	64	19
2	CuI	bpy	DME	73	11
3	CuI	bpy	DCE	48	35
4	CuI	bpy	$PhCF_3$	72	<10
5	CuI	bpy	THF	79	<10
6	CuI	bpy	1,4-dioxane	65	24
7	CuI	bpy	H_2O	Trace	Trace
8	CuI	bpy	DMF	61	<10
9	CuI	bpy	Et_2O	69	<10
10	CuI	bpy	DMSO	54	12
11	CuI	bpy	DMA	37	<10

[a]Reaction conditions: **1a** (0.2 mmol), CuI (10 mol%), and bpy (10 mol%) in dry solvent (1.0 mL) under Ar at 50 ℃ for 18 h. [b]Isolated yield based on **1a**.

General procedure for the synthesis of substrates:

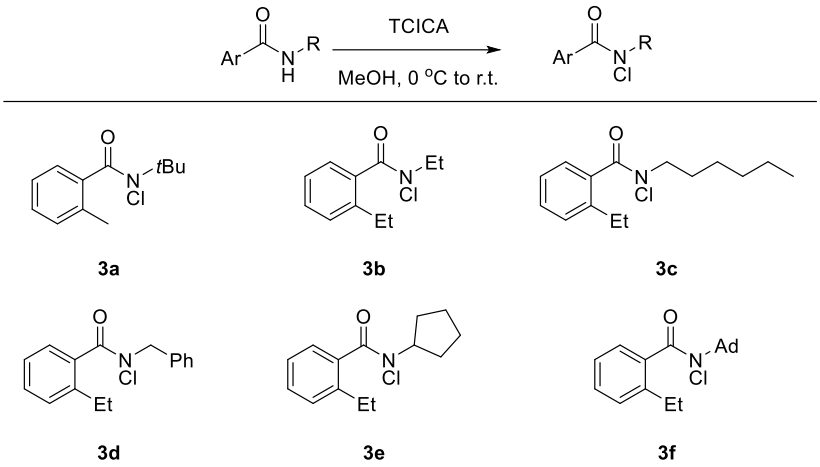
General procedure for the synthesis of *N*-fluorocarboxamides.



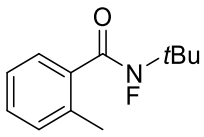
All the *N*-fluorocarboxamides were prepared by *N*-fluorination of their parent carboxamides according to conventional methods.[1,2] To a flame-dried round-bottom flask with a stir bar was added amide (1.0 equiv.). The contents were evacuated and backfilled three times with argon. Anhydrous THF (0.13 M) was added and the stirred solution was cooled on an ice bath for 15 min. *n*-Butyllithium (1.1 equiv., 2.4 M in hexanes) was added dropwise. The reaction was maintained at 0 ℃ for 1.5 h. NFSI (1.5 equiv., 0.6 M in THF) was added dropwise. The reaction was left overnight in the ice bath and allowed to warm to rt. After 10 to 14 h, the reaction was quenched with 1 M aqueous HCl and transferred to a separatory funnel. The crude mixture was diluted with DCM (0.1 M) and water (0.1 M). The organic layer was removed, and the aqueous layer was extracted with DCM. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and then brine, dried with $MgSO_4$, filtered, and concentrated by

rotary evaporation. The residue thus obtained was purified by silica gel column chromatography (15% EtOAc in hexanes) to afford pure fluoroamides.

General procedures for the synthesis of *N*-chlorocarboxamides



All the *N*-chlorocarboxamides were prepared by *N*-chlorination of their parent carboxamides according to conventional methods.[1] A 50 mL foil-wrapped round bottom flask equipped with a stir bar was charged with the corresponding amide (1 equiv.). Methanol (0.33M) was then added and the resulting solution was cooled to 0 ℃ in an ice bath. Trichloroisocyanuric acid (0.5 equiv.) was then added in one portion and the reaction mixture was stirred at room temperature. When the reaction was complete as judged by TLC analysis (typically within 0.5 to 3 hours, note: the formed N-chloroamide is much less polar than the starting amide), the reaction mixture was passed through a short pad of celite and was washed with DCM (30 mL ×3). The filtrate was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (hexanes and ethyl acetate) to afford the *N*-chlorocarboxamides.

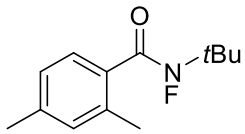


***N*-(*tert*-butyl)-*N*-fluoro-2-methylbenzamide (1a)[1]**

Yellow oil, 585 mg (28% yield, 10.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 2H), 7.24-7.17 (m, 2H), 2.41 (s, 3H), 1.56 (d, J = 2.2 Hz, 9H);**^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.1 (d, J = 10.8 Hz), 135.4 (d, J = 2.4 Hz), 135.1, 130.5, 130.0 (d, J

= 1.4 Hz), 127.2 (d, *J* = 4.4 Hz), 125.4, 64.4 (d, *J* = 10.5 Hz), 27.2 (d, *J* = 5.7 Hz), 19.4; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -64.67.

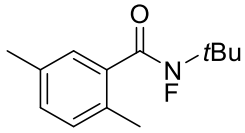
HRMS (ESI) m/z calcd. for $C_{12}H_{17}FNO$ $[M+H]^+$ 210.1289, found 210.1287.



***N*-(*tert*-butyl)-*N*-fluoro-2,4-dimethylbenzamide (1b)[1]**

Yellow oil, 691 mg (31% yield, 10.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.7 Hz, 1H), 7.09-6.95 (m, 2H), 2.37 (s, 3H), 2.32 (s, 3H), 1.53 (d, *J* = 2.0 Hz, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.5 (d, *J* = 10.4 Hz), 140.3, 135.7 (d, *J* = 2.3 Hz), 132.3, 131.4, 127.6 (d, *J* = 4.6 Hz), 126.1, 64.4 (d, *J* = 10.6 Hz), 27.3 (d, *J* = 5.8 Hz), 21.4, 19.5.; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -64.02.

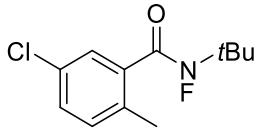
HRMS (ESI) m/z calcd. for $C_{13}H_{19}FNO$ $[M+H]^+$ 224.1445, found 224.1442.



***N*-(*tert*-butyl)-*N*-fluoro-2,5-dimethylbenzamide (1c)[3]**

Yellow oil, 846 mg (38% yield, 10.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.12-7.07 (m, 2H), 2.35 (s, 3H), 2.32 (s, 3H), 1.55 (d, *J* = 1.9 Hz, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2 (d, *J* = 10.8 Hz), 134.9, 132.1 (d, *J* = 2.4 Hz), 130.7, 130.3, 127.5 (d, *J* = 4.2 Hz), 64.3 (d, *J* = 10.5 Hz), 27.2 (d, *J* = 5.7 Hz), 20.8, 18.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -64.82.

HRMS (ESI) m/z calcd. for $C_{13}H_{19}FNO$ $[M+H]^+$ 224.1445, found 224.1442.

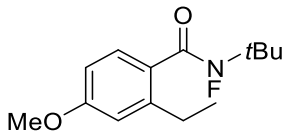


***N*-(*tert*-butyl)-5-chloro-*N*-fluoro-2-methylbenzamide (1d)[3]**

Yellow oil, 772 mg (32% yield, 10.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.25 (m, 2H), 7.14 (d, *J* = 8.2 Hz, 1H), 2.35 (s, 3H), 1.55 (d, *J* = 2.0 Hz, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.2 (d, *J* = 11.1 Hz), 136.4, 133.7 (d, *J* = 2.5 Hz), 131.8, 131.1,

129.8 (d, J = 1.4 Hz), 126.9 (d, J = 4.4 Hz), 64.6 (d, J = 10.4 Hz), 27.1 (d, J = 5.5 Hz), 18.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -64.48.

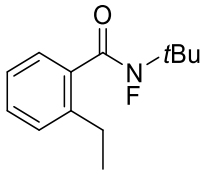
HRMS (ESI) m/z calcd. for $C_{12}H_{15}ClFNONa$ $[M+Na]^+$ 266.0718, found 266.0720.



***N*-(*tert*-butyl)-2-ethyl-*N*-fluoro-4-methoxybenzamide (1e)[4]**

Yellow oil, 998 mg (40% yield, 10.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.5 Hz, 1H), 6.81-6.66 (m, 2H), 3.82 (s, 3H), 2.75 (q, J = 7.6 Hz, 2H), 1.53 (d, J = 1.9 Hz, 9H), 1.24 (t, J = 7.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.3 (d, J = 10.5 Hz), 161.0, 144.7 (d, J = 1.9 Hz), 129.8 (d, J = 5.0 Hz), 126.9, 114.7, 110.4, 64.11 (d, J = 10.6 Hz), 55.2, 27.1 (d, J = 5.7 Hz), 26.4, 15.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.16.

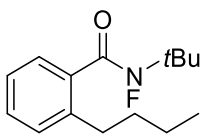
HRMS (ESI) m/z calcd. for $C_{14}H_{21}FNO_2$ $[M+H]^+$ 254.1551, found 254.1547.



***N*-(*tert*-butyl)-2-ethyl-*N*-fluorobenzamide (1f)[4]**

Yellow oil, 694 mg (31% yield, 10.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (td, J = 7.4, 1.4 Hz, 1H), 7.34-7.28 (m, 2H), 7.24 (td, J = 7.4, 1.4 Hz, 1H), 2.77 (q, J = 7.6 Hz, 2H), 1.58 (d, J = 2.0 Hz, 9H), 1.27 (t, J = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.0 (d, J = 10.9 Hz), 141.6 (d, J = 2.2 Hz), 134.6, 130.0 (d, J = 1.1 Hz), 128.9, 127.1 (d, J = 4.4 Hz), 125.4, 64.3 (d, J = 10.5 Hz), 27.1 (d, J = 5.6 Hz), 26.1, 15.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.36.

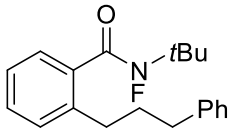
HRMS (ESI) m/z calcd. for $C_{13}H_{19}FNO$ $[M+H]^+$ 224.1445, found 224.1442.



***N*-(*tert*-butyl)-2-butyl-*N*-fluorobenzamide (1g)[4]**

Yellow oil, 453 mg (36% yield, 5.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 2H), 7.26-7.17 (m, 2H), 2.77-2.65 (m, 2H), 1.62-1.56 (m, 2H), 1.55 (d, *J* = 2.0 Hz, 9H), 1.42-1.32 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.0 (d, *J* = 10.9 Hz), 140.4 (d, *J* = 2.1 Hz), 134.8, 129.8, 129.6, 127.2 (d, *J* = 4.3 Hz), 125.3, 64.2 (d, *J* = 10.5 Hz), 33.7, 32.8, 27.2 (d, *J* = 5.6 Hz), 22.7, 13.9; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.35.

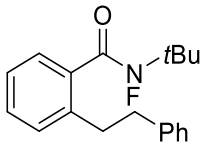
HRMS (ESI) m/z calcd. for $C_{15}H_{23}FNO$ $[M+H]^+$ 252.1758, found 252.1754.



***N*-(*tert*-butyl)-*N*-fluoro-2-(3-phenylpropyl) benzamide (1h)[4]**

Yellow oil, 437 mg (28% yield, 5.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.20 (m, 6H), 7.20-7.14 (m, 3H), 2.79-2.70 (m, 2H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.01-1.90 (m, 2H), 1.52 (d, *J* = 1.8 Hz, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.9 (d, *J* = 10.9 Hz), 142.1, 139.8 (d, *J* = 2.0 Hz), 134.9, 129.9, 129.6, 128.5, 128.3, 127.3 (d, *J* = 4.4 Hz), 125.8, 125.5, 64.3 (d, *J* = 10.4 Hz), 35.8, 33.0, 32.8, 27.1 (d, *J* = 5.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.28.

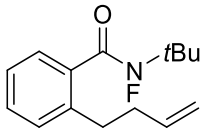
HRMS (ESI) m/z calcd. for $C_{20}H_{25}FNO$ $[M+H]^+$ 314.1915, found 314.1911.



***N*-(*tert*-butyl)-*N*-fluoro-2-phenethylbenzamide (1i)[4]**

Yellow oil, 204 mg (23% yield, 3.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.08 (m, 9H), 3.05-2.96 (m, 2H), 2.96-2.86 (m, 2H), 1.56 (d, *J* = 1.8 Hz, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.9 (d, *J* = 10.8 Hz), 141.7, 139.3 (d, *J* = 2.0 Hz), 134.8, 130.0, 129.9, 128.45, 128.38, 127.5 (d, *J* = 4.5 Hz), 126.0, 125.7, 64.3 (d, *J* = 10.5 Hz), 38.0, 35.5, 27.2 (d, *J* = 5.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.08.

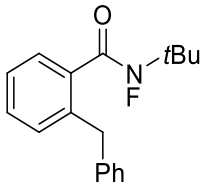
HRMS (ESI) m/z calcd. for $C_{19}H_{23}FNO$ $[M+H]^+$ 300.1758, found 300.1755.



2-(but-3-en-1-yl)-*N*-(*tert*-butyl)-*N*-fluorobenzamide (1j)[4]

Yellow oil, 396 mg (32% yield, 5.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 2H), 7.27-7.18 (m, 2H), 5.90-5.78 (m, 1H), 5.08-5.93 (m, 2H), 2.85-2.75 (m, 2H), 2.43-2.29 (m, 2H), 1.55 (d, *J* = 1.9 Hz, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.8 (d, *J* = 10.9 Hz), 139.3 (d, *J* = 2.1 Hz), 137.9, 134.9, 129.9 (d, *J* = 1.4 Hz), 129.7, 127.3 (d, *J* = 4.4 Hz), 125.6, 115.0, 64.3 (d, *J* = 10.5 Hz), 35.5, 32.5, 27.2 (d, *J* = 5.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.26.

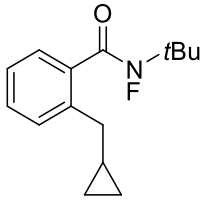
HRMS (ESI) m/z calcd. for $C_{15}H_{21}FNO$ $[M+H]^+$ 250.1602, found 250.1599.



2-benzyl-*N*-(t*ert*-butyl)-*N*-fluorobenzamide (1k)[5]

Yellow oil, 985 mg (35% yield, 10.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.25 (m, 5H), 7.24-7.18 (m, 4H), 4.18 (s, 2H), 1.49 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.5, 140.5, 138.6, 135.0, 130.6, 130.2, 129.2, 128.4, 127.7 (d, *J* = 4.7 Hz), 126.1, 125.9, 64.3, 38.6, 27.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.31.

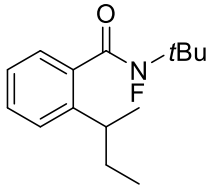
HRMS (ESI) m/z calcd. for $C_{18}H_{21}FNO$ $[M+H]^+$ 286.1602, found 286.1602.



***N*-(*tert*-butyl)-2-(cyclopropylmethyl)-*N*-fluorobenzamide (1l)[1]**

Yellow oil, 394 mg (35% yield, 4.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.7 Hz, 1H), 7.39-7.28 (m, 2H), 7.22 (t, J = 7.3 Hz, 1H), 2.64 (d, *J* = 6.9 Hz, 2H), 1.55 (d, *J* = 1.9 Hz, 9H), 1.08-0.97 (m, 1H), 0.58-0.47 (m, 2H), 0.22 (q, *J* = 5.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.09 (d, J = 10.8 Hz), 139.66 (d, J = 2.0 Hz), 134.87, 130.03, 129.38, 127.15 (d, J = 4.4 Hz), 125.64, 64.46 (d, J = 10.3 Hz), 37.31, 27.32 (d, J = 5.7 Hz), 11.67, 5.01; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.12.

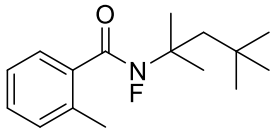
HRMS (ESI) m/z calcd. for $C_{15}H_{21}FNO$ $[M+H]^+$ 250.1602, found 250.1599.



2-(*sec*-butyl)-*N*-(*tert*-butyl)-*N*-fluorobenzamide (1m)

Yellow oil, 406 mg (32% yield, 5.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.37 (m, 1H), 7.33 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.30-7.2 (m, 2H), 2.91-2.86 (m, 1H), 1.76-1.61 (m, 2H), 1.59 (d, *J* = 1.9 Hz, 9H), 1.27 (d, *J* = 6.9 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.15 (d, *J* = 11.3 Hz), 144.9, 135.2, 129.9, 126.6 (d, *J* = 4.1 Hz), 126.0, 125.3, 64.4 (d, *J* = 10.4 Hz), 37.6, 31.0, 27.2 (d, *J* = 5.6 Hz), 22.1, 12.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.74.

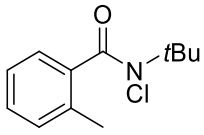
HRMS (ESI) m/z calcd. for $C_{15}H_{23}FNO$ $[M+H]^+$ 252.1758, found 252.1754.



***N*-fluoro-2-methyl-*N*-(2,4,4-trimethylpentan-2-yl) benzamide (1n)[6]**

Yellow oil, 479 mg (37% yield, 5.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.3 Hz, 2H), 7.21 (d, *J* = 7.0 Hz, 2H), 2.42 (s, 3H), 1.93 (s, 2H), 1.63 (s, 6H), 1.11 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.6 (d, *J* = 11.2 Hz), 135.2, 135.1 (d, *J* = 2.4 Hz), 130.3, 129.6, 126.8 (d, *J* = 4.5 Hz), 125.2, 67.9 (d, *J* = 9.6 Hz), 51.1 (d, *J* = 3.6 Hz), 31.4, 31.2, 27.5 (d, *J* = 6.2 Hz), 19.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.52.

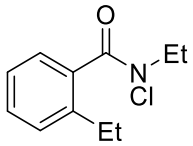
HRMS (ESI) m/z calcd. for $C_{16}H_{25}FNO$ $[M+H]^+$ 266.1915, found 266.1915.



***N*-(*tert*-butyl)-*N*-chloro-2-methylbenzamide (3a)[1]**

Colorless oil, 870 mg (78% yield, 5.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25-7.20 (m, 2H), 7.17 (t, *J* = 7.9 Hz, 2H), 2.35 (s, 3H), 1.60 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.6, 137.8, 134.3, 130.3, 129.1, 126.1, 125.6, 64.5, 28.7, 19.0.

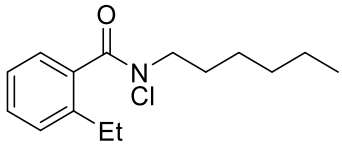
HRMS (ESI) m/z calcd. for $C_{12}H_{17}ClNO$ $[M+H]^+$ 226.0993, found 226.0994.



***N*-chloro-*N*-ethyl-2-methylbenzamide (3b)**

Colorless oil, 763 mg (72% yield, 5.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 1H), 7.31-7.26 (m, 1H), 7.24-7.19 (m, 2H), 3.72-3.60 (m, 2H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.25 (dt, *J* = 12.3, 7.3 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0, 134.1, 129.9, 129.0, 126.1, 125.9, 26.1, 15.2, 13.1.

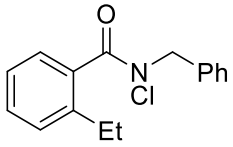
HRMS (ESI) m/z calcd. for $C_{11}H_{15}ClNO$ $[M+H]^+$ 212.0837, found 212.0840.



***N*-chloro-2-ethyl-*N*-hexylbenzamide (3c)**

Colorless oil, 994 mg (75% yield, 5.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 1H), 7.32-7.27 (m, 1H), 7.25-7.16 (m, 2H), 3.61 (s, 2H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.71 (p, *J* = 7.1 Hz, 2H), 1.33-1.15 (m, 9H), 0.87 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0, 134.2, 129.8, 128.9, 126.3, 125.8, 31.3, 27.5, 26.1, 25.7, 22.5, 15.2, 13.9.

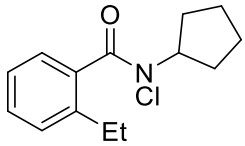
HRMS (ESI) m/z calcd. for $C_{15}H_{23}ClNO$ $[M+H]^+$ 268.1463, found 268.1464.



***N*-benzyl-*N*-chloro-2-ethylbenzamide (3d)**

Colorless oil, 948 mg (69% yield, 5.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.15 (m, 9H), 4.83 (s, 2H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.2, 135.2, 133.8, 130.1, 129.0, 128.8, 128.4, 128.2, 126.5, 125.9, 26.2, 15.2.

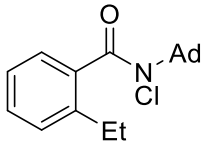
HRMS (ESI) m/z calcd. for $C_{16}H_{17}ClNO$ $[M+H]^+$ 274.0993, found 274.0995.



***N*-chloro-*N*-cyclopentyl-2-ethylbenzamide (3e)**

Colorless oil, 976 mg (78% yield, 5.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (td, *J* = 7.4, 1.6 Hz, 1H), 7.31-7.27 (m, 1H), 7.23 (td, *J* = 7.3, 1.4 Hz, 1H), 7.18 (dd, *J* = 7.6, 1.6 Hz, 1H), 4.49 (s, 1H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.95-1.71 (m, 6H), 1.56-1.40 (m, 2H), 1.23 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.9, 134.8, 129.7, 129.1, 126.0, 126.0, 29.6, 26.1, 24.8, 15.3.

HRMS (ESI) m/z calcd. for $C_{14}H_{19}ClNO$ $[M+H]^+$ 252.1150, found 252.1149.



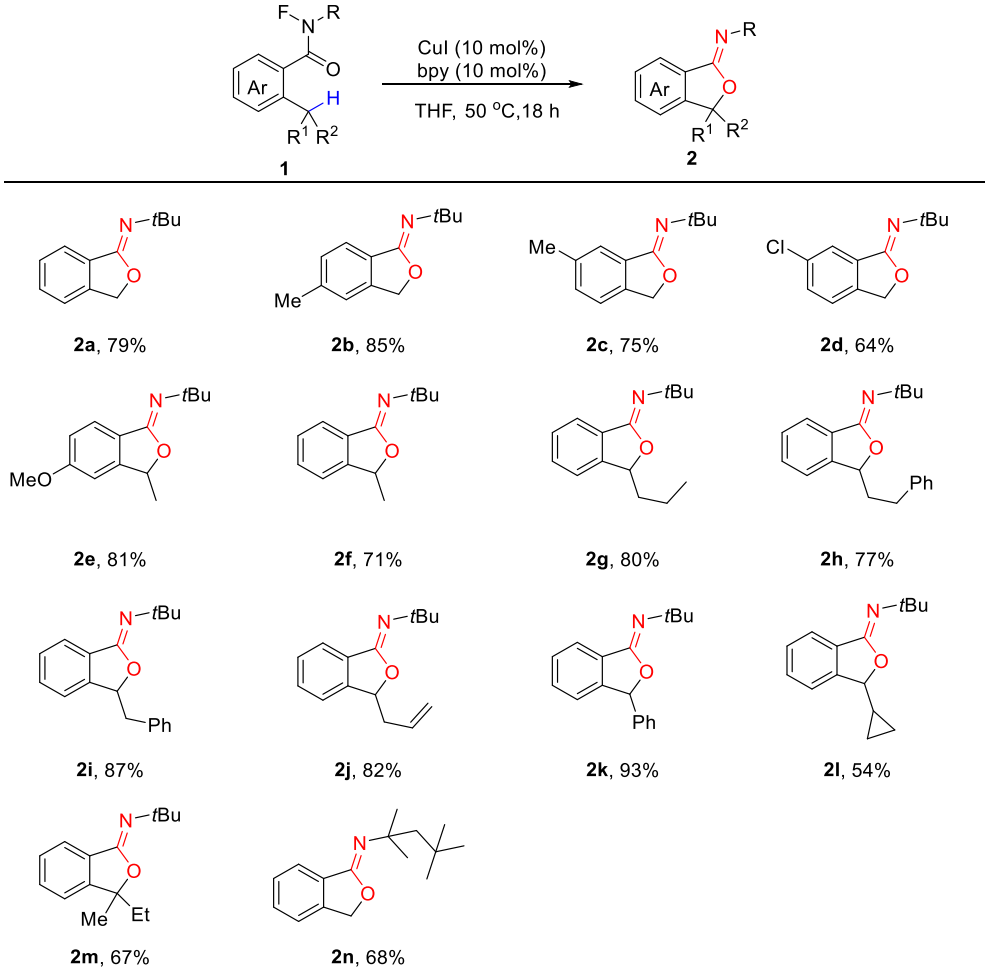
***N*-((3s,5s,7s)-adamantan-1-yl)-*N*-chloro-2-ethylbenzamide (3f)**

Colorless oil, 1.07 g (68% yield, 5.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 1H), 7.25-7.16 (m, 3H), 2.70 (q, *J* = 7.6 Hz, 2H), 2.36 (s, 6H), 2.22-2.16 (m, 3H), 1.71 (q, *J* = 12.3 Hz, 6H), 1.26 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.0, 140.2, 137.8, 129.1, 128.6, 126.1, 125.6, 65.8, 40.7, 36.2, 30.5, 26.0, 15.1.

HRMS (ESI) m/z calcd. for $C_{19}H_{25}ClNO$ $[M+H]^+$ 318.1619, found 318.1615.

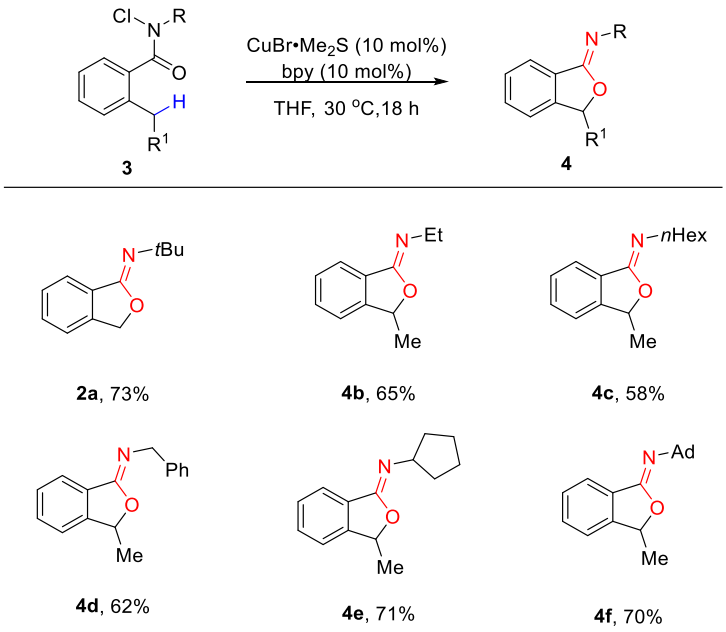
Copper-catalyzed intramolecular iminolactonization cyclization reactions of remote (sp^3)-H bonds in carboxamides

General procedure A:

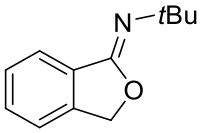


Under argon atmosphere, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with CuI (0.04 mmol, 10 mol%), bpy (0.04mmol, 10 mol%), and anhydrous THF (2.0 mL). Then, *N*-fluorocarboxamide (0.40 mmol, 1.0 equiv.) was sequentially added into the mixture and the reaction mixture was stirred at 50 ℃ for 18 h. Upon completion (monitored by TLC), the precipitate was filtered off and washed by DCM. The filtrate was evaporated and the residue was purified by column chromatography on silica gel to afford the desired product.

General procedure B:



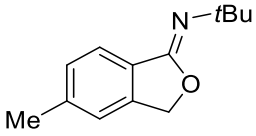
Under argon atmosphere, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with CuBr·Me_2S (0.04 mmol, 10 mol%), bpy (0.04mmol, 10 mol%), and anhydrous THF (2.0 mL). Then, *N*-chlorocarboxamide (0.40 mmol, 1.0 equiv.) was sequentially added into the mixture and the reaction mixture was stirred at rt for 18 h. Upon completion (monitored by TLC), the precipitate was filtered off and washed by DCM. The filtrate was evaporated and the residue was purified by column chromatography on silica gel to afford the desired product.



(*Z*)-*N*-(*tert*-butyl)isobenzofuran-1(3*H*)-imine (2a)[6]

White solid, 59.6 mg (79% yield), mp: 104-106 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) 7.81 (d, *J* = 7.6 Hz, 1H), 7.49-7.44 (m, 1H), 7.42-7.36 (m, 1H), 7.35-7.32 (m, 1H), 5.31 (s, 2H), 1.40 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.0, 142.5, 132.0, 130.9, 128.2, 123.7, 121.1, 72.0, 53.6, 30.1.

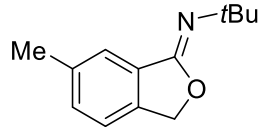
HRMS (ESI) m/z calcd. for $C_{12}H_{16}NO$ $[M+H]^+$ 190.1226, found 190.1226.



(*Z*)-*N*-(*tert*-butyl)-5-methylisobenzofuran-1(3*H*)-imine (2b)

White solid, 68.8 mg (85% yield), mp: 110-114 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.8 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7. 15-7. 11 (m, 1H), 5.26 (s, 2H), 2.42 (s, 3H), 1.40 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.3, 142.9, 141.4, 129.3, 126.6, 123.5, 121.5, 71.9, 53.5, 30.1, 21.7.

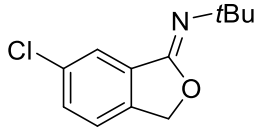
HRMS (ESI) m/z calcd. for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1383, found 204.1380.



(*Z*)-*N*-(*tert*-butyl)-6-methylisobenzofuran-1(3*H*)-imine (2c)

White solid, 60.7 mg (75% yield), mp: 108-110 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.31-7.25 (m, 1H), 7.23-7.19 (m, 1H), 5.27 (s, 2H), 2.39 (s, 3H), 1.40 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.2, 139.7, 138.3, 132.1, 140.0, 123.8, 120.8, 72.0, 53.5, 30.1, 21.1.

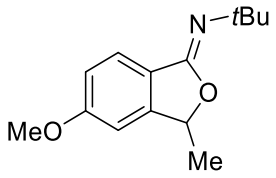
HRMS (ESI) m/z calcd. for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1383, found 204.1380.



(*Z*)-*N*-(*tert*-butyl)-6-chloroisobenzofuran-1(3*H*)-imine (2d)

Colorless oil, 57.1 mg (64% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 1.9 Hz, 1H), 7.43 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.30-7.21 (m, 1H), 5.28 (s, 2H), 1.38 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.3, 140.6, 134.5, 134.1, 131.1, 123.8, 122.4, 71.8, 53.7, 30.0.

HRMS (ESI) m/z calcd. for $C_{12}H_{15}ClNO$ $[M+H]^+$ 224.0837, found 224.0840.

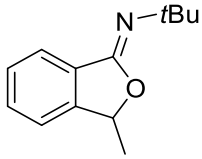


(*Z*)-*N*-(*tert*-butyl)-5-methoxy-3-methylisobenzofuran-1(3*H*)-imine (2e)

White solid, 75.0 mg (81% yield), mp: 123-126 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 -7.22 (m, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 7.02 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.49 (q, *J* = 6.5

Hz, 1H), 3.86 (s, 3H), 1.53 (d, J = 6.5 Hz, 3H), 1.40 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.2, 156.7, 139.6, 133.3, 121.6, 119.9, 105.7, 79.4, 55.7, 53.5, 30.0, 21.5.

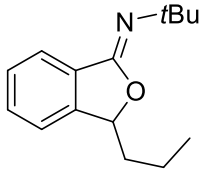
HRMS (ESI) m/z calcd. for $C_{14}H_{20}NO_2$ $[M+H]^+$ 234.1489, found 234.1492.



(*Z*)-*N*-(*tert*-butyl)-3-methylisobenzofuran-1(3*H*)-imine (2f)

Colorless oil, 57.9 mg (71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.6 Hz, 1H), 7.48-7.43 (m, 1H), 7.41-7.35 (m, 1H), 7.29-7.24 (m, 1H), 5.55 (q, J = 6.6 Hz, 1H), 1.56 (d, J = 6.6 Hz, 3H), 1.40 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.6, 147.1, 131.8, 130.9, 128.3, 123.7, 120.8, 79.6, 53.5, 30.0, 21.3.

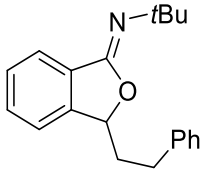
HRMS (ESI) m/z calcd. for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1383, found 204.1380.



(*Z*)-*N*-(*tert*-butyl)-3-propylisobenzofuran-1(3*H*)-imine (2g)

Colorless oil, 73.5 mg (80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.7 Hz, 1H), 7.48-7.42 (m, 1H), 7.40-7.34 (m, 1H), 7.29-7.23 (m, 1H), 5.46 (dd, J = 7.7, 3.9 Hz, 1H), 2.00-1.90 (m, 1H), 1.76-1.61 (m, 1H), 1.57-1.38 (m, 11H), 0.97 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.7, 145.9, 132.2, 130.8, 128.2, 123.6, 120.9, 83.2, 53.5, 37.8, 30.0, 18.3, 14.0.

HRMS (ESI) m/z calcd. for $C_{15}H_{22}NO$ $[M+H]^+$ 232.1696, found 232.1695.

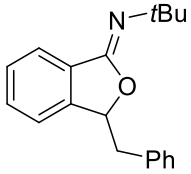


(*Z*)-*N*-(*tert*-butyl)-3-phenethylisobenzofuran-1(3*H*)-imine (2h)

Colorless oil, 89.6 mg (77% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.6, 1.2 Hz, 1H), 7.46-7.41 (m, 1H), 7.40-7.35 (m, 1H), 7.32-7.18 (m, 6H), 5.46 (dd, J = 8.2, 3.6 Hz, 1H), 2.87-2.69 (m, 2H), 2.33-2.24(m, 1H), 2.05-1.93 (m, 1H), 1.45 (s, 9H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 145.6, 141.2, 132.2, 133.0, 128.6, 128.5, 128.4, 126.1, 123.7, 120.9, 82.3, 53.7, 37.5, 31.4, 30.1.

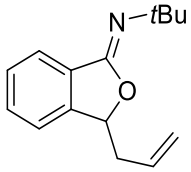
HRMS (ESI) m/z calcd. for $C_{20}H_{24}NO$ $[M+H]^+$ 294.1852, found 294.1852.



(*Z*)-3-benzyl-*N*-(*tert*-butyl)isobenzofuran-1(3*H*)-imine (2i)

Colorless oil, 96.6 mg (87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77-7.73 (m, 1H), 7.43-7.32 (m, 2H), 7.31-7.19 (m, 5H), 7.09-7.04 (m, 1H), 5.67 (t, J = 6.3 Hz, 1H), 3.21-3.08 (m, 2H), 1.38 (s, 9H);**^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.8, 145.0, 136.3, 132.4, 130.6, 129.7, 128.5, 128.4, 126.8, 123.7, 121.5, 83.5, 53.5, 42.0, 30.1.

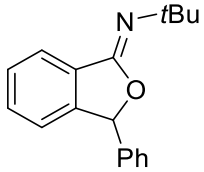
HRMS (ESI) m/z calcd. for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1696, found 280.1700.



(*Z*)-3-allyl-N-(*tert*-butyl)isobenzofuran-1(3*H*)-imine (2j)

Colorless oil, 75.3 mg (82% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83-7.77 (m, 1H), 7.48-7.42 (m, 1H), 7.41-7.36 (m, 1H), 7.32-7.28 (m, 1H), 5.82-5.70 (m, 1H), 5.51 (dd, J = 6.7, 4.8 Hz, 1H), 5.20-5.07 (m, 2H), 2.77-2.67 (m, 1H), 2.61-2.47 (m, 1H), 1.40 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.4, 145.2, 132.4, 132.3, 130.8, 128.4, 123.7, 121.1, 118.8, 82.4, 53.6, 39.9, 30.0.

HRMS (ESI) m/z calcd. for $C_{15}H_{20}NO$ $[M+H]^+$ 230.1539, found 230.1540.

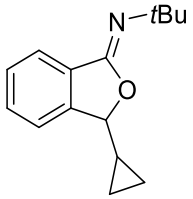


(*Z*)-*N*-(t*ert*-butyl)-3-phenylisobenzofuran-1(3*H*)-imine (2k)

White solid, 98.0 mg (93% yield), mp: 135-138 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86-7.81 (m, 1H), 7.41-7.31 (m, 5H), 7.29-7.25 (m, 2H), 7.15-7.11 (m, 1H), 6.36 (s,

1H), 1.43 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.1, 145.9, 139.3, 131.5, 131.2, 128.8, 128.6, 128.6, 126.5, 123.6, 122.0, 84.9, 53.8, 30.1.

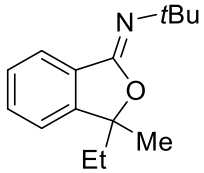
HRMS (ESI) m/z calcd. for $C_{18}H_{20}NO$ $[M+H]^+$ 266.1539, found 230.1541.



(*Z*)-*N*-(*tert*-butyl)-3-cyclopropylisobenzofuran-1(3*H*)-imine (2l)

Colorless oil, 52.7 mg (58% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.49-7.43 (m, 1H), 7.42-7.36 (m, 2H), 4.98 (d, *J* = 7.3 Hz, 1H), 1.40 (s, 9H), 1.17-1.07 (m, 1H), 0.73-0.43 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.1, 144.1, 130.6, 129.3, 126.9, 122.0, 119.8, 84.5, 52.0, 28.4, 13.8, 0.3.

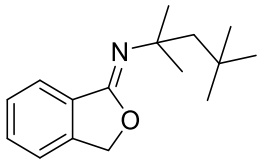
HRMS (ESI) m/z calcd. for $C_{15}H_{20}NO$ $[M+H]^+$ 230.1539, found 230.1540.



(*Z*)-*N*-(*tert*-butyl)-3-ethyl-3-methylisobenzofuran-1(3*H*)-imine (2m)

Colorless oil, 61.4 mg (67% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.47-7.42 (m, 1H), 7.38-7.33 (m, 1H), 7.19 (dd, *J* = 7.5, 1.0 Hz, 1H), 2.05-1.95 (m, 1H), 1.90-1.80 (m, 1H), 1.56 (s, 3H), 1.41 (s, 9H), 0.71 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR (**101 MHz, $CDCl_3$) δ 156.5, 149.2, 132.2, 130.9, 128.2, 123.6, 120.2, 89.3, 53.4, 33.7, 29.9, 26.5, 8.0.

HRMS (ESI) m/z calcd. for $C_{15}H_{22}NO$ $[M+H]^+$ 232.1696, found 232.1695.

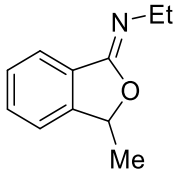


(*Z*)-*N*-(2,4,4-trimethylpentan-2-yl)isobenzofuran-1(3*H*)-imine (2n)

Colorless oil, 66.0 mg (68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 1H), 7.49-7.42 (m, 1H), 7.41-7.35 (m, 1H), 7.34-7.30 (m, 1H), 5.29 (s, 2H), 1.75 (s, 2H), 1.44 (s, 6H), 1.02 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.1, 142.3, 132.5,

130.6, 128.2, 123.7, 121.1, 71.8, 57.3, 55.2, 32.1, 31.9, 30.4.

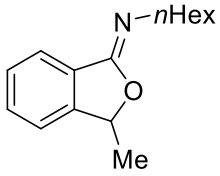
HRMS (ESI) m/z calcd. for $C_{16}H_{24}NO$ $[M+H]^+$ 246.1852, found 246.1853.



(*Z*)-*N*-ethyl-3-methylisobenzofuran-1(3*H*)-imine (4b)

Colorless oil, 45.1 mg (65% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.6 Hz, 1H), 7.52-7.46 (m, 1H), 7.41 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.32-7.28 (m, 1H), 5.56 (q, *J* = 6.6 Hz, 1H), 3.54 (q, *J* = 7.3 Hz, 2H), 1.58 (d, *J* = 6.6 Hz, 3H), 1.28 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 147.7, 131.2, 130.3, 128.5, 123.3, 121.0, 79.8, 41.7, 21.2, 16.0.

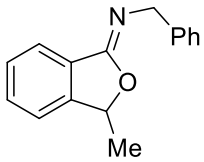
HRMS (ESI) m/z calcd. for $C_{11}H_{14}NO$ $[M+H]^+$ 176.1070, found 176.1070.



(*Z*)-*N*-hexyl-3-methylisobenzofuran-1(3*H*)-imine (4c)

Colorless oil, 53.0 mg (58% yield). **^{1}H NMR** (400 MHz, $CDCl_3$ δ 7.83 (d, *J* = 7.6 Hz, 1H), 7.50-7.46 (m, 1H), 7.41 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.32-7.28 (m, 1H), 5.55 (q, *J* = 6.6 Hz, 1H), 3.50 (t, *J* = 7.4 Hz, 2H), 1.71-1.63 (m, 2H), 1.58 (d, *J* = 6.6 Hz, 3H), 1.44-1.36 (m, 2H), 1.36-1.30 (m, 4H), 0.92-0.86 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.6, 147.7, 131.1, 128.5, 123.3, 120.9, 79.6, 47.4, 31.8, 30.9, 27.3, 22.7, 21.3, 14.1.

HRMS (ESI) m/z calcd. for $C_{15}H_{22}NO$ $[M+H]^+$ 232.1696, found 232.1695.

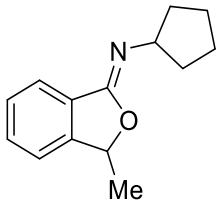


(*Z*)-*N*-benzyl-3-methylisobenzofuran-1(3*H*)-imine (4d)

Colorless oil, 58.1 mg (62% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.53-7.47 (m, 1H), 7.46-7.40 (m, 3H), 7.35-7.29 (m, 3H), 7.25-7.20 (m, 1H), 5.61 (q, *J* = 6.6 Hz, 1H), 4.74 (s, 2H), 1.60 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$)

δ 160.2, 147.9, 140.8, 131.4, 130.2, 128.6, 128.3, 127.9, 126.5, 123.6, 121.0, 80.1, 51.0, 21.2.

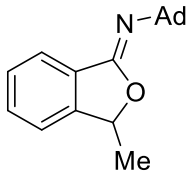
HRMS (ESI) m/z calcd. for $C_{16}H_{16}NO$ $[M+H]^+$ 238.1226, found 238.1227.



(*Z*)-*N*-cyclopentyl-3-methylisobenzofuran-1(3*H*)-imine (4e)

Colorless oil, 60.8 mg (71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 -7.82 (m, 1H), 7.49-7.42 (m, 1H), 7.42-7.36 (m, 1H), 7.30-7.25 (m, 1H), 5.54 (q, *J* = 6.6 Hz, 1H), 4.27-4.20 (m, 1H), 2.05-1.93 (m, 2H), 1.83-1.74 (m, 2H), 1.64-1.53 (m, 7H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.7, 147.7, 131.0, 130.5, 128.4, 123.4, 120.9, 79.5, 57.7, 34.2, 34.1, 24.4, 21.3.

HRMS (ESI) m/z calcd. for $C_{14}H_{18}NO$ $[M+H]^+$ 216.1383, found 216.1384.



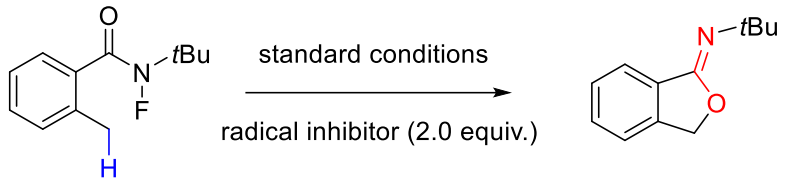
(*Z*)-*N*-((3s,5s,7s)-adamantan-1-yl)-3-methylisobenzofuran-1(3*H*)-imine (4f)

Colorless oil, 77.6 mg (70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96-7.76 (m, 1H), 7.50-7.44 (m, 1H), 7.39 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 5.56 (q, *J* = 6.5 Hz, 1H), 2.16-2.01 (m, 9H), 1.77-1.66 (m, 6H), 1.58 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.9, 147.1, 131.7, 131.1, 128.4, 124.0, 120.8, 79.9, 42.4, 36.8, 29.9, 21.3.

HRMS (ESI) m/z calcd. for $C_{19}H_{24}NO$ $[M+H]^+$ 282.1852, found 282.1852.

Mechanism study

Radical inhibition experiments



1a **2a**

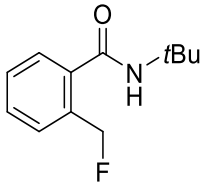
entry	additive	yield
1	no	79%
2	BHT	0
3	TEMPO	0

Under argon atmosphere, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with CuI (0.02 mmol, 10 mol%), bpy (0.02mmol, 10 mol%), additive (0.40 mmol), and anhydrous THF (1.0 mL). Then, *N*-fluorocarocarboxamide **1a** (0.20 mmol) was sequentially added into the mixture and the reaction mixture was stirred at 50 ℃ for 18 h. Then, the precipitate was filtered off and washed by DCM. The reaction mixture was monitored by TLC and the target product **2a** was strongly suppressed when BHT and TEMPO were added in standard condition.

Control experiments

Synthesis of the substrate 5a and 5b:

The substrate **5a** was synthesized according to the literature procedures.[1]



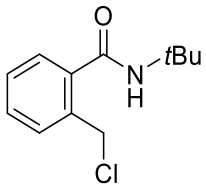
***N*-(*tert*-butyl)-2-(fluoromethyl)benzamide (5a)[1]**

White solid, 161 mg (79% yield, 1.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53-7.41 (m, 3H), 7.41-7.34 (m, 1H), 5.93 (s, 1H), 5.59 (d, J = 48.1 Hz, 2H), 1.46 (s, 9H);**^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.0, 136.6 (d, J = 3.7 Hz), 134.3 (d, J = 16.3 Hz), 130.2,

128.8, 128.7 (d, J = 2.7 Hz), 127.2 82.9 (d, J = 164.2 Hz), 52.0, 28.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -205.45.

HRMS (ESI) m/z calcd. for $C_{12}H_{17}FNO$ $[M+H]^+$ 210.1289, found 210.1287.

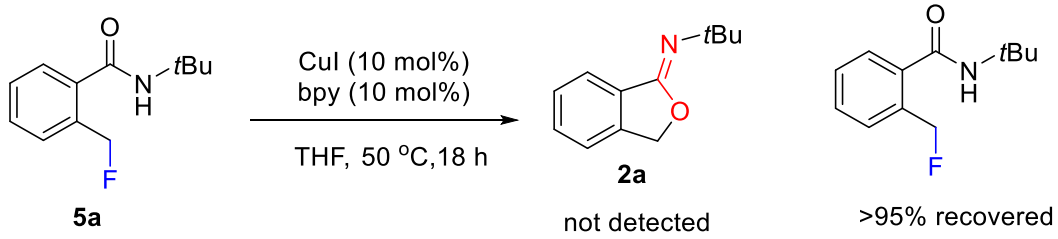
The substrate **5b** was synthesized according to the literature procedures.[6]



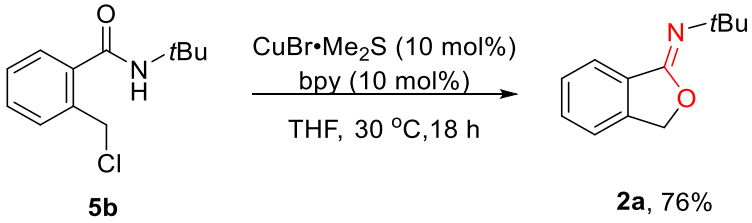
***N*-(*tert*-butyl)-2-(chloromethyl)benzamide (5b)[6]**

White solid, 150 mg (68% yield, 1.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 3H), 7.34-7.26 (m, 1H), 5.93 (s, 1H), 4.74 (s, 2H), 1.45 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.4, 137.8, 134.9, 130.7, 130.1, 128.8, 127.6, 52.2, 44.1, 28.8.

HRMS (ESI) m/z calcd. for $C_{12}H_{17}ClNO$ $[M+H]^+$ 226.0993, found 226.0996.



Under argon atmosphere, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with CuI (0.020 mmol, 10 mol%), bpy (0.020mmol, 10 mol%), and anhydrous THF (1.0 mL). Then, the substrate **5a** (0.20 mmol, 41.8mg) was sequentially added into the mixture and the reaction mixture was stirred at 50 ℃ for 18 h. The reaction mixture was monitored by TLC, the formation of iminolactone **2a** was not observed. The filtrate was evaporated and the residue was purified by column chromatography on silica gel to afford the substrate **5a** (40.7 mg).

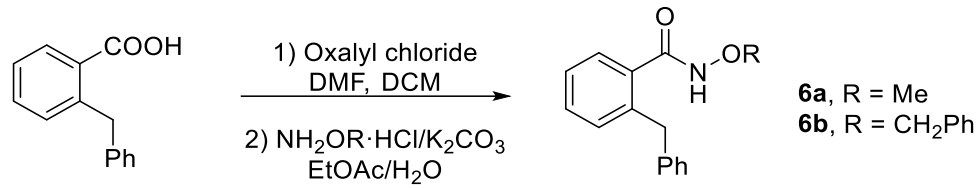


Under argon atmosphere, an oven-dried resealable Schlenk tube equipped with a

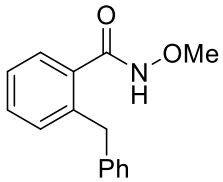
magnetic stir bar was charged with CuBr·Me_2S (0.020 mmol, 10 mol%), bpy (0.020mmol, 10 mol%), and anhydrous THF (1.0 mL). Then, the substrate **5b** (0.20 mmol, 1.0 equiv.) was sequentially added into the mixture and the reaction mixture was stirred at 30 ℃ for 18 h. The reaction mixture was monitored by TLC, the formation of iminolactone **2a** was observed. The filtrate was evaporated and the residue was purified by column chromatography on silica gel to afford the product **2a** (28.5 mg, 76%).

Lactamization of *N*-alkoxycarboxamides

General procedures for the synthesis of *N*-alkoxycarboxamides[7]



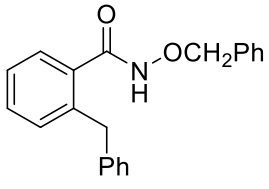
To a solution of the carboxylic acid (1.0 equiv) in dry DCM (0.3 M) at 0 ℃ under Ar was added dropwise oxalyl chloride (1.2 equiv) followed by a catalytic amount of dry DMF (2 drops). The reaction was allowed to stir at rt until completion. The solvent was then removed under reduced pressure to afford the corresponding crude acid chloride. Then the crude acid chloride dissolved in a minimum amount of EtOAc was added dropwise to a biphasic mixture of alkoxyamine hydrochloride (1.2 equiv) and K_2CO_3 (2.0 equiv) in a 2:1 mixture of EtOAc (0.15 M) and H_2O (0.3 M) at 0 ℃. The reaction was allowed to stir at rt overnight. Afterwards, the phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The product was purified on silica gel by eluting with 25:75:1 EtOAc/ petroleum ether /NEt_3.



2-benzyl-*N*-methoxybenzamide (6a)[8]

White solid, 863 mg (71% yield, 5.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.43-7.31 (m, 2H), 7.29-7.20 (m, 4H), 7.20-7.15 (m, 3H), 4.19 (s, 2H), 3.68 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.7, 140.5, 139.9, 132.8, 131.2, 130.8, 129.0, 128.5, 127.7, 126.4, 126.2, 64.5, 38.8.

HRMS (ESI) m/z calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.1176, found 242.1176.

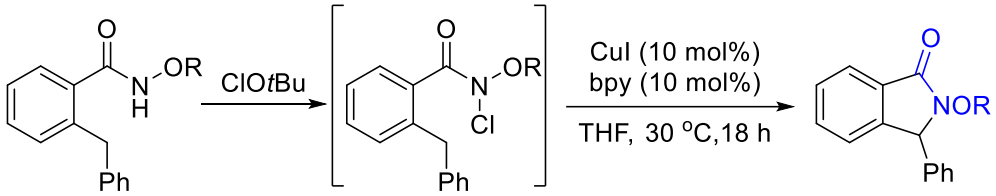


2-benzyl-*N*-(benzyloxy)benzamide (6b)[9]

White solid, 1.17 g (75% yield, 5.0 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.36-7.27 (m, 6H), 7.26-7.21 (m, 3H), 7.20-7.10 (m, 5H), 4.85 (s, 2H), 4.14 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.4, 140.3, 139.8, 135.1, 132.7, 130.9, 130.6, 129.1, 129.0, 128.6, 128.4, 128.3, 127.5, 126.1, 126.0, 78.0, 38.4.

HRMS (ESI) m/z calcd for $C_{21}H_{20}NO_2$ $[M+H]^+$ 318.1489, found 318.1491.

General procedures for the lactamization of *N*-alkoxycarboxamides

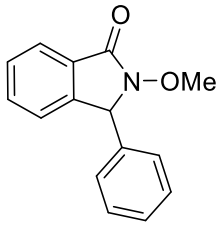


6a, R = Me
6b, R = CH_2Ph

in situ generation of *N*-chlorocarboxamides

7a, 23%
7b, 19%

To a stirred solution of a *N*-alkoxyamide (0.4 mmol) in CH_2C1_2 (2 mL) in an oven-dried resealable Schlenk tube was added slowly *tert*-butyl hypochlorite (0.44 mmol) with cooling. The reaction mixture was stirred at 0 ℃ in the dark until the reaction was complete (the time required was generally less than 20 min). The solvent was evaporated at rt under reduced pressure. Under argon atmosphere, CuI (0.040 mmol, 10 mol%), bpy (0.040mmol, 10 mol%), and anhydrous THF (2.0 mL) were added into the Schlenk tube and the reaction mixture was stirred at 30 ℃ for 18 h. The precipitate was filtered off and washed by DCM. The filtrate was evaporated and the residue was purified by column chromatography on silica gel to afford the desired product.

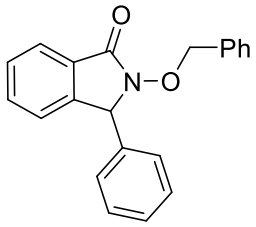


2-methoxy-3-phenylisoindolin-1-one (7a)[8]

White solid, 21.9 mg (23% yield), mp: 126-129 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79-7.68 (m, 1H), 7.46-7.40 (m, 2H), 7.37-7.34 (m, 2H), 7.28-7.25 (m, 2H), 7.21-7.14 (m, 2H), 6.50 (s, 1H), 3.96 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.1, 144.4, 137.6,

131.1, 129.4, 129.3, 129.0, 128.9, 128.4, 128.4, 127.5, 122.5, 121.6, 87.8, 62.8.

HRMS (ESI) m/z calcd for $C_{15}H_{13}NO_2Na$ $[M+Na]^+$ 262.0838, found 262.0833.



2-(benzyloxy)-3-phenylisoindolin-1-one (7b)

White solid, 23.8 mg (19% yield), mp: 135-138 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76-7.67 (m, 1H), 7.49-7.43 (m, 2H), 7.40 -7.31 (m, 7H), 7.27 (m, 3H), 7.19-7.02 (m, 1H), 6.50 (s, 1H), 5.16 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.4, 144.5, 138.0, 137.8, 131.0, 129.2, 128.9, 128.8, 128.5, 128.4, 128.3, 127.8, 127.4, 122.4, 121.8, 87.7, 77.5.

HRMS (ESI) m/z calcd. for $C_{21}H_{18}NO_2$ $[M+H]^+$ 316.1332, found 316.1337.

Supplementary references:

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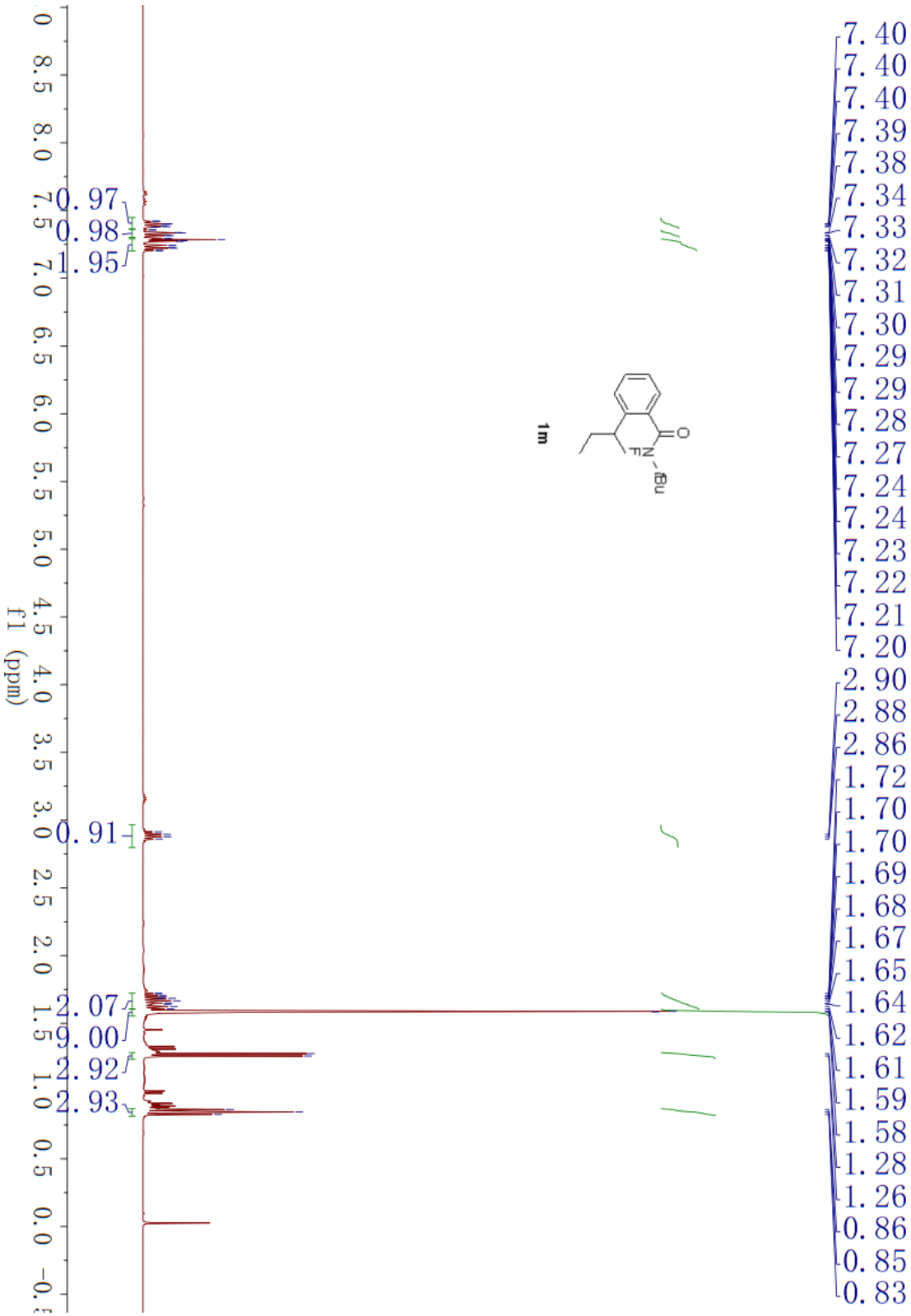
NMR spectra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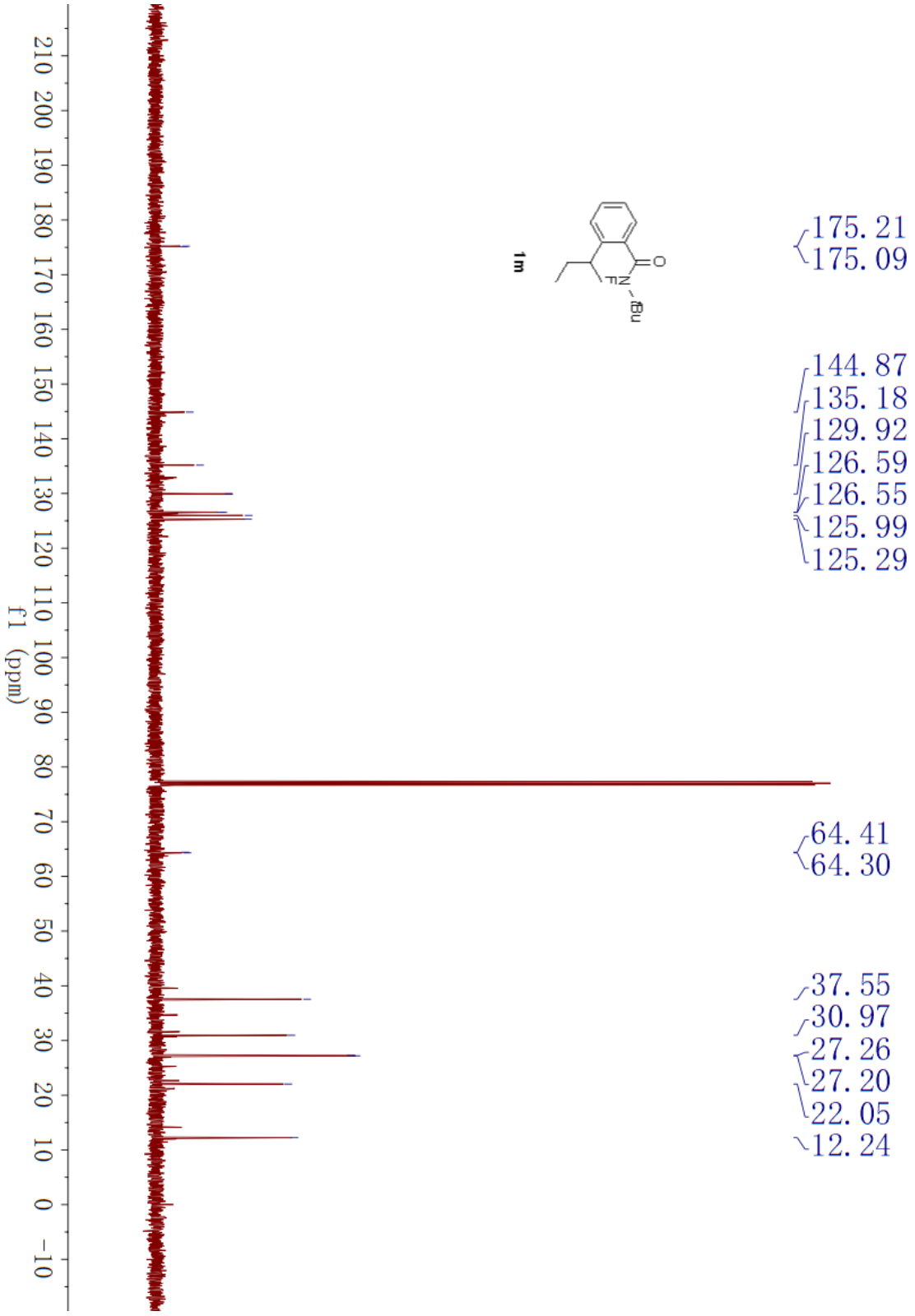
7.28
7.27
7.24
7.24
7.23
7.22
7.21
7.20
2.90
2.88
2.86
1.72
1.70
1.70
1.69
1.68
1.67
1.65
1.64
1.62
1.61
1.59
1.58
1.28
1.26
0.86
0.85
0.83
0.97
0.98
1.95
0.91
2.07
9.00
2.92
2.93
1m
f1 (ppm)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O
N
tBu
175.21
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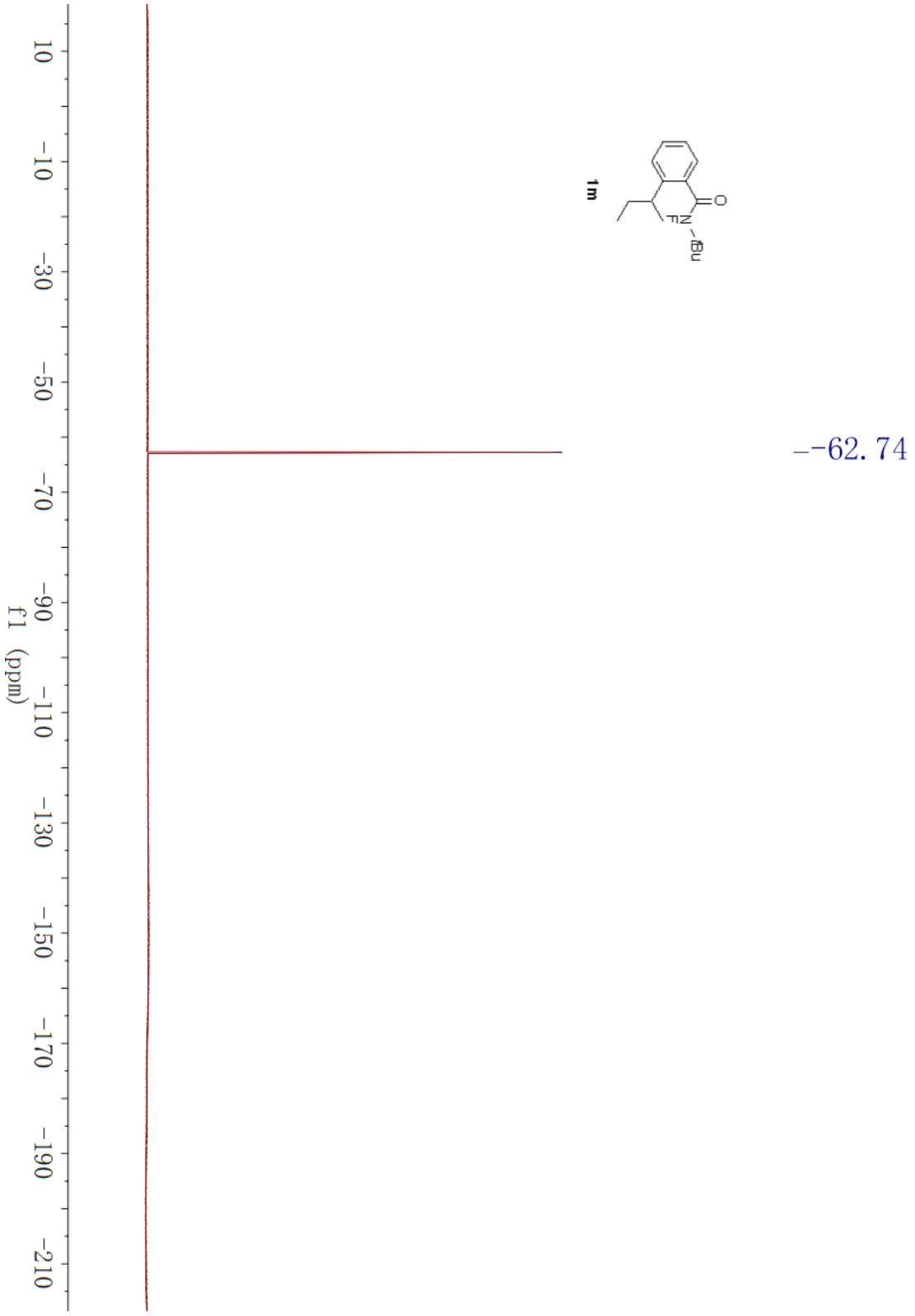
144.87
135.18
129.92
126.59
126.55
125.99
125.29
64.41
64.30
37.55
30.97
27.26
27.20
22.05
12.24
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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f1 (ppm)
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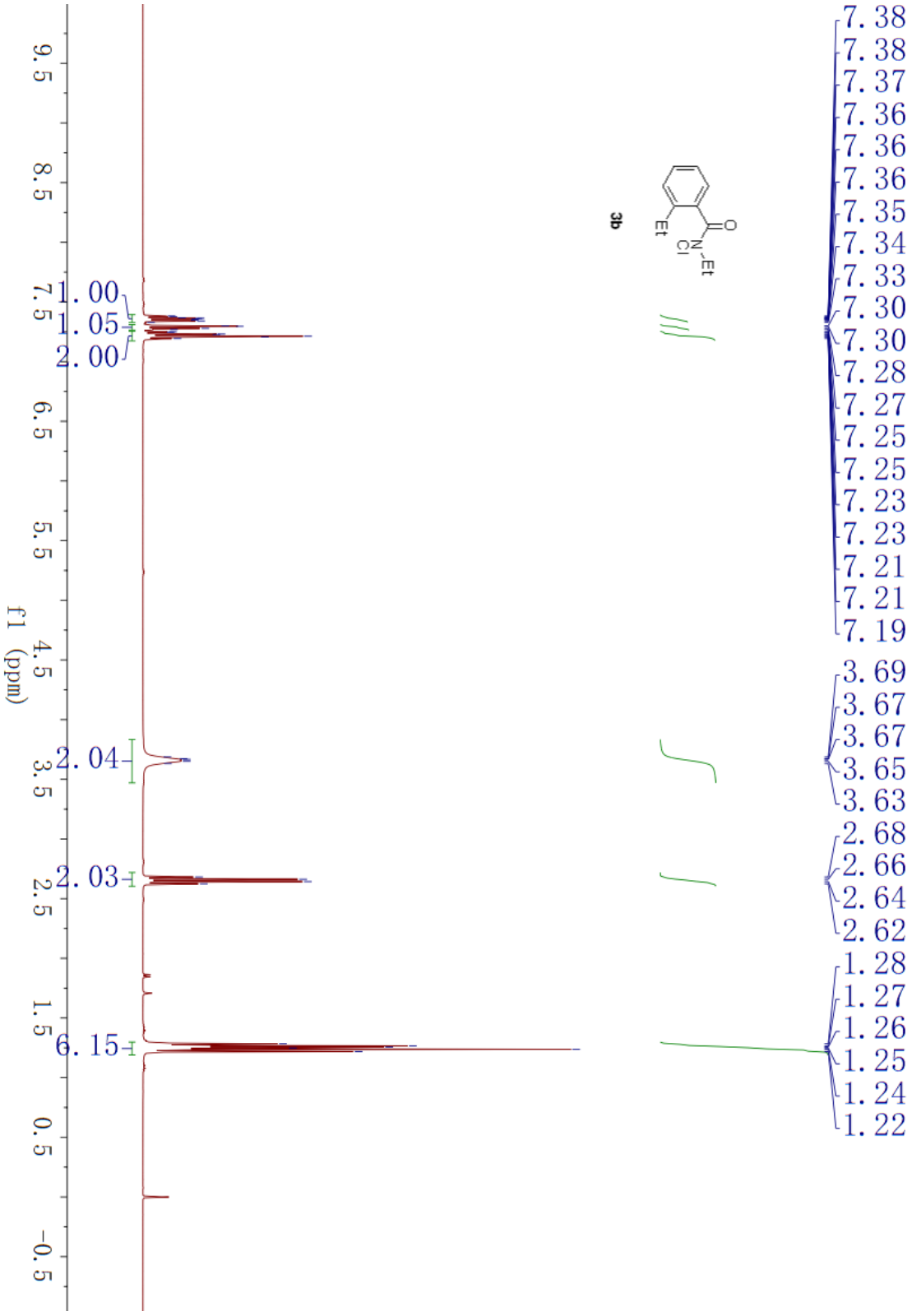
O
N
F
tBu
-62.74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7.36
7.35
7.34
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7.30
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7.21
7.19
3.69
3.67
3.67
3.65
3.63
2.68
2.66
2.64
2.62
1.28
1.27
1.26
1.25
1.24
1.22
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1.05
2.00
2.04
2.03
6.15
f1 (ppm)
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7.5
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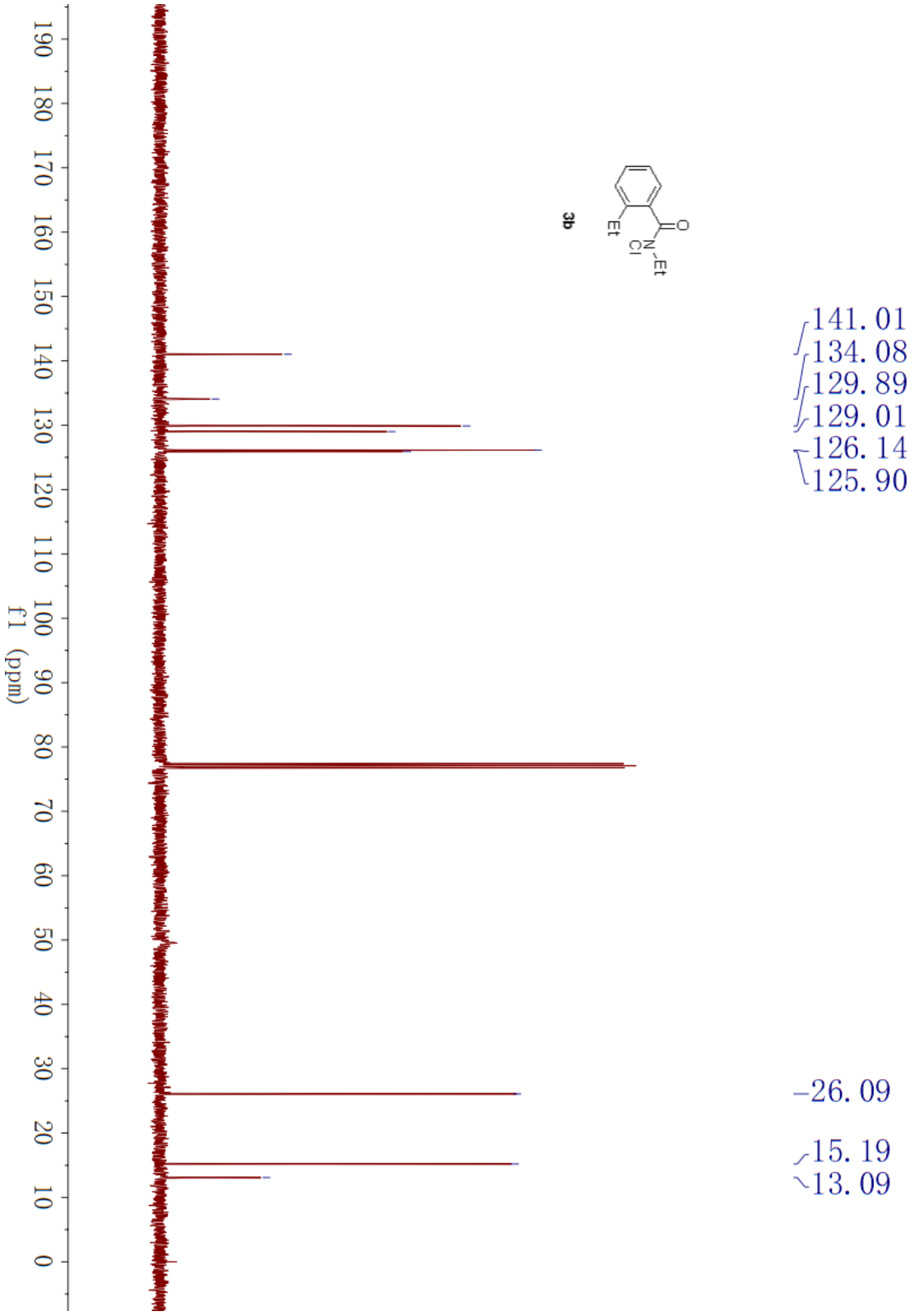
-0.5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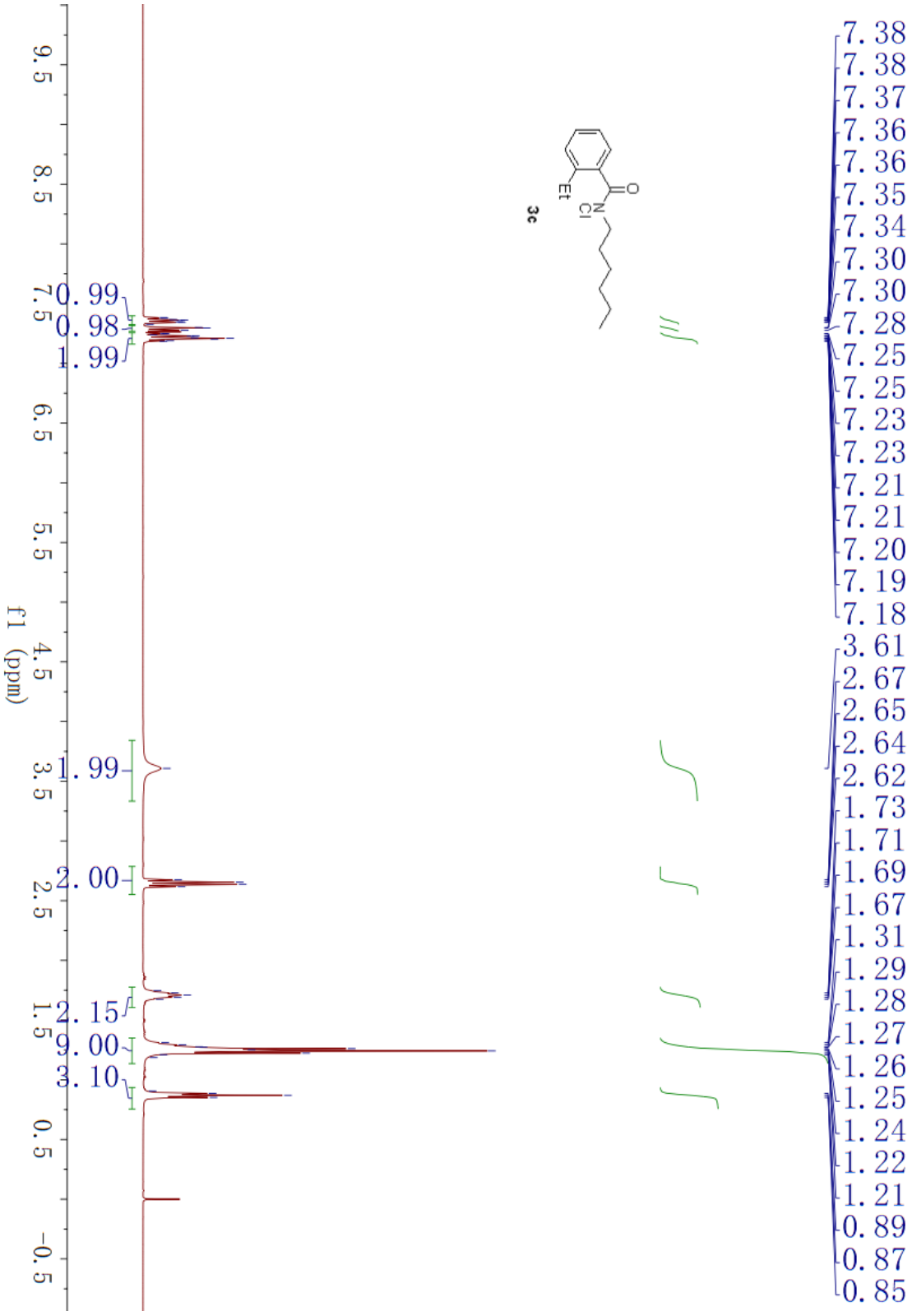
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1.99
2.00
2.15
9.00
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7.38
7.37
7.36
7.36
7.35
7.34
7.30
7.30
7.28
7.25
7.25
7.23
7.23
7.21
7.21
7.20
7.19
7.18
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2.67
2.65
2.64
2.62
1.73
1.71
1.69
1.67
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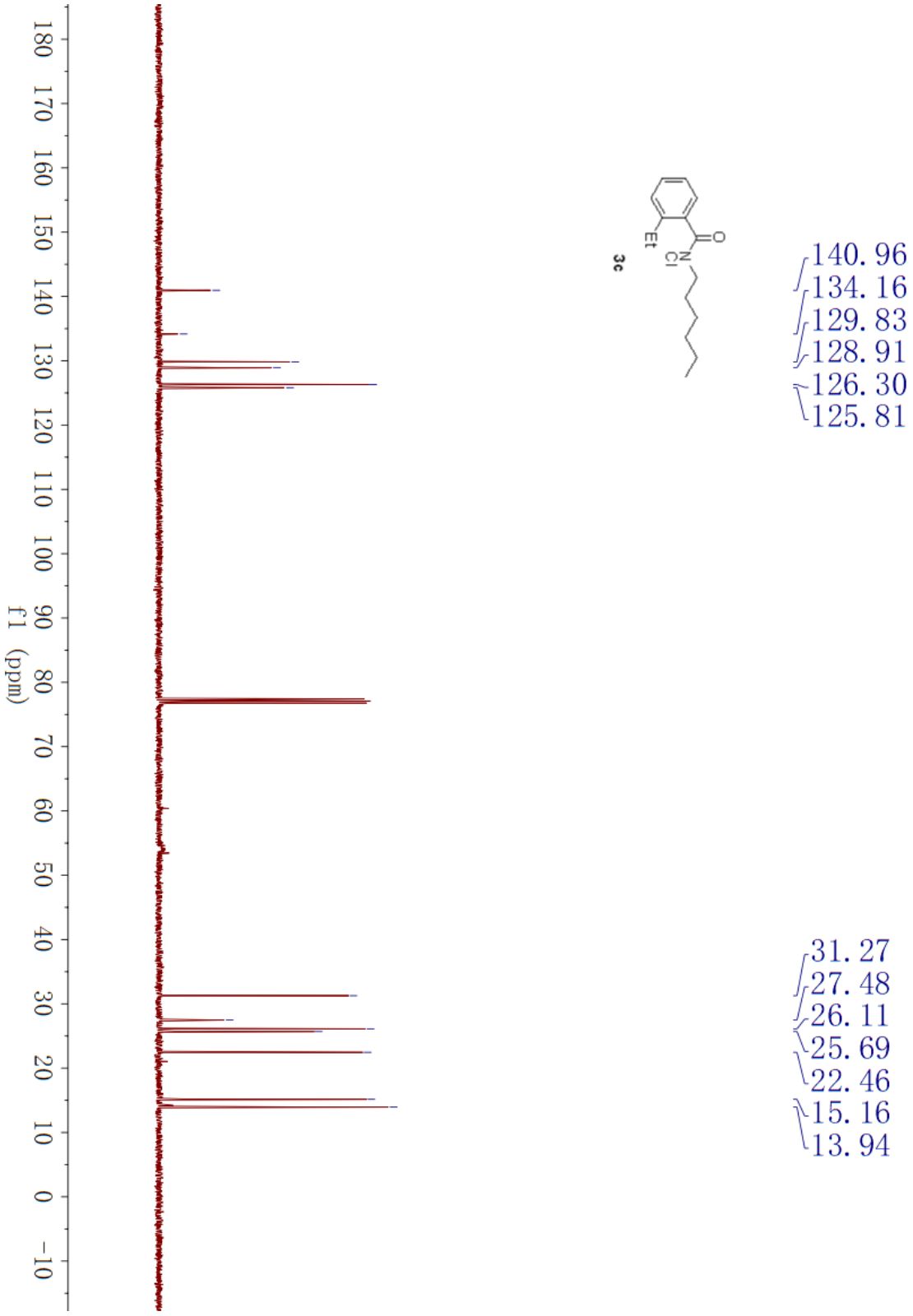
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N
Cl
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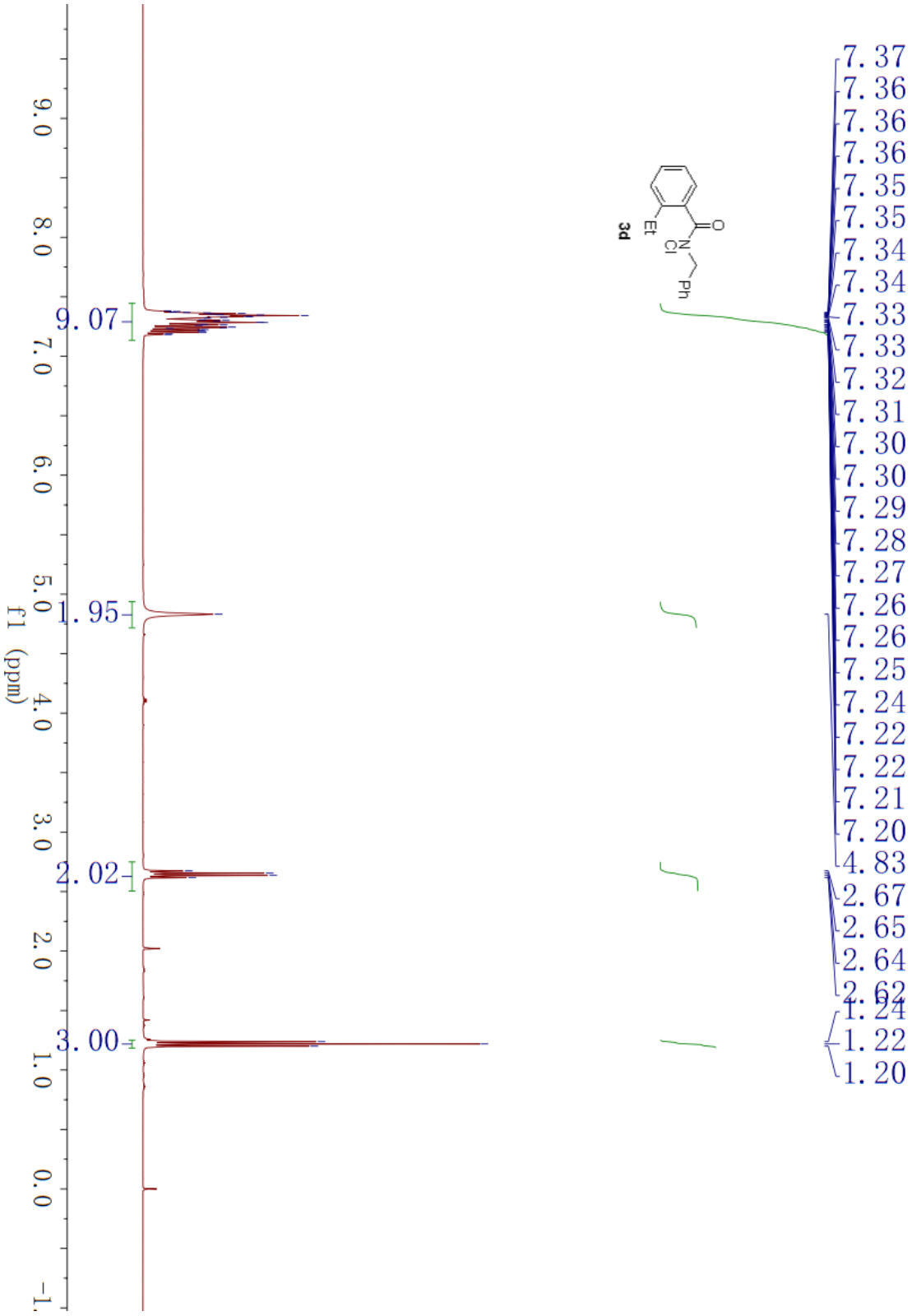
13.94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Cl
Ph
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f1 (ppm)
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7.24
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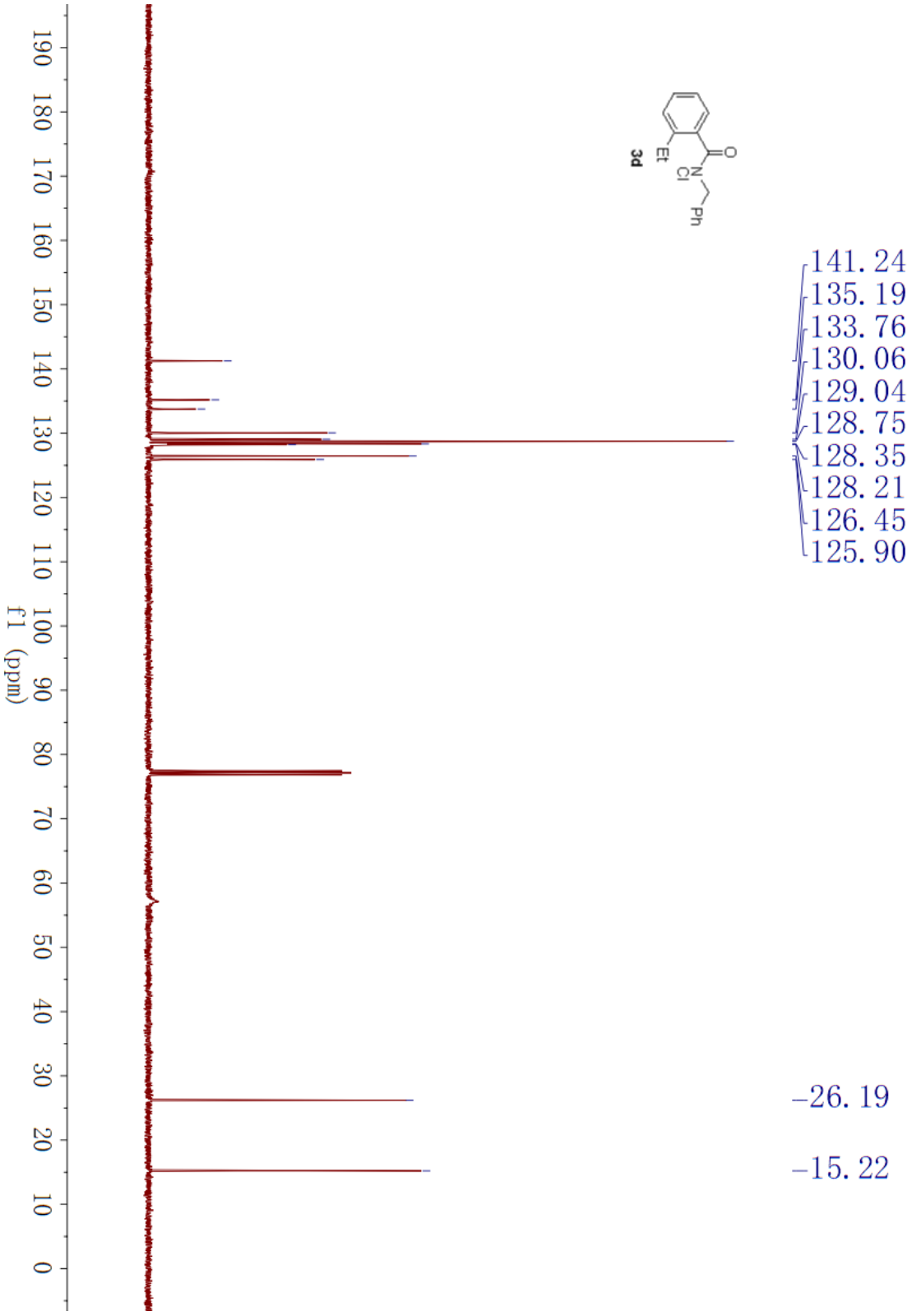
1.20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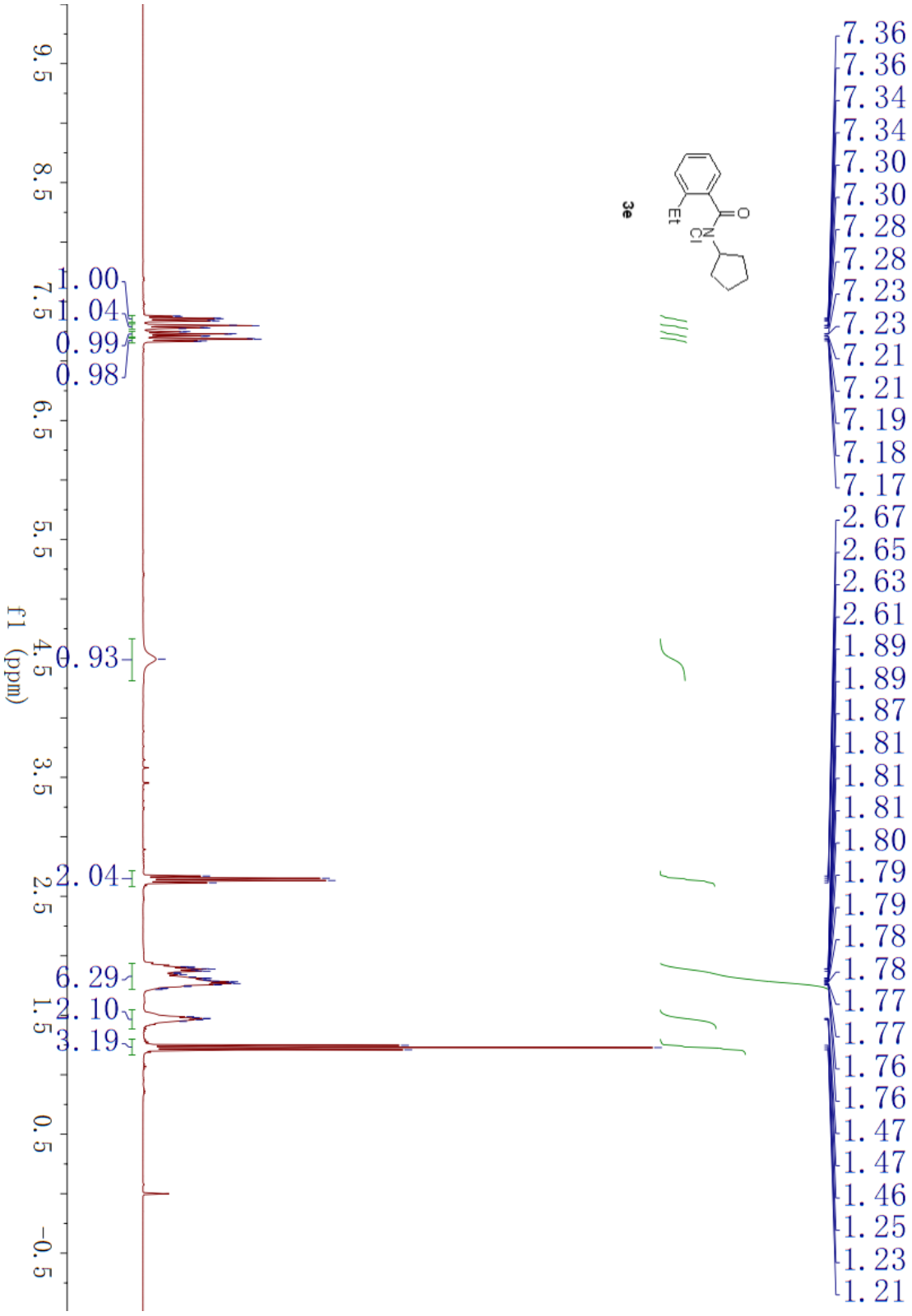
-15.22
f1 (ppm)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N
Cl
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1.04
0.99
0.98
0.93
2.04
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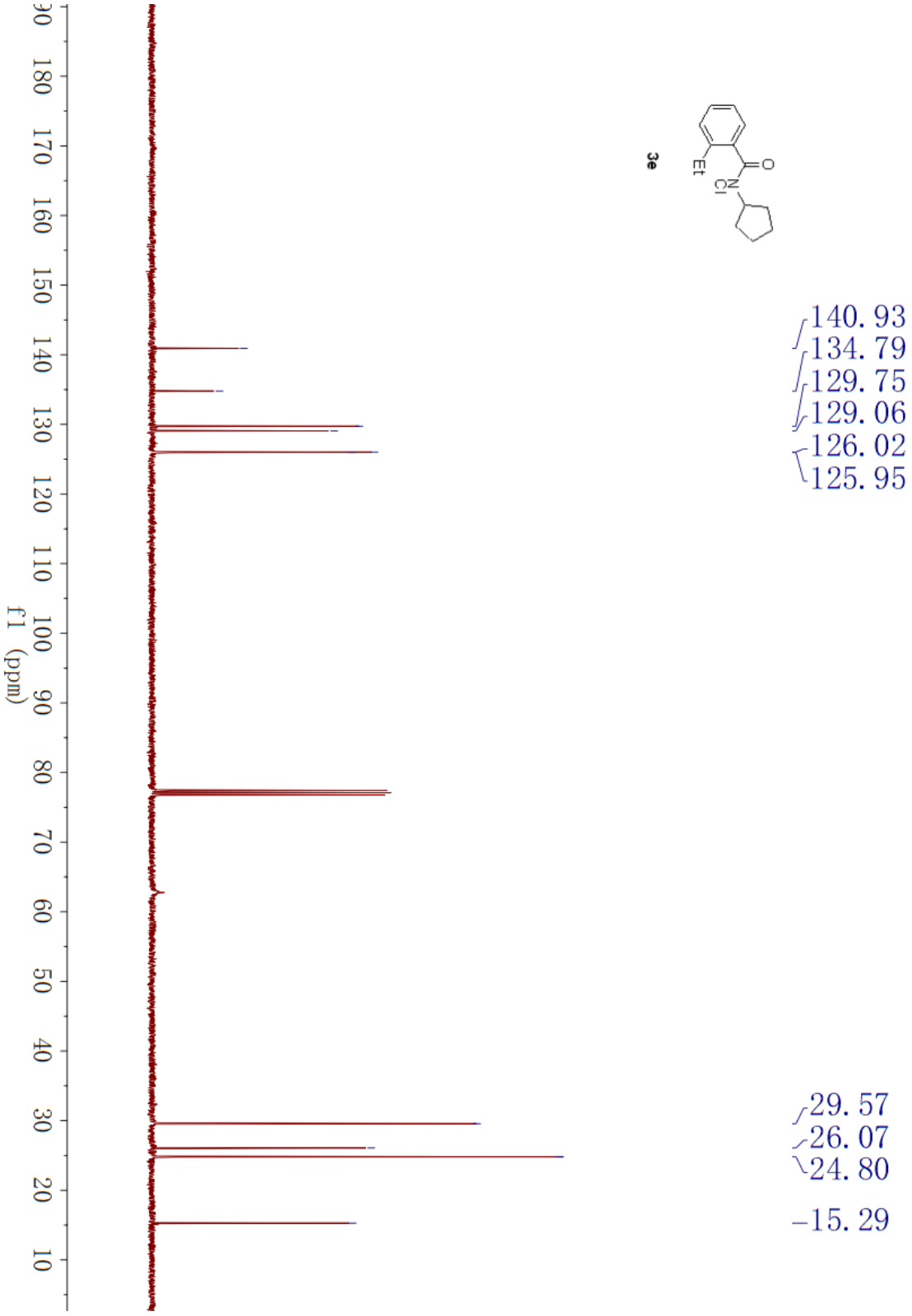
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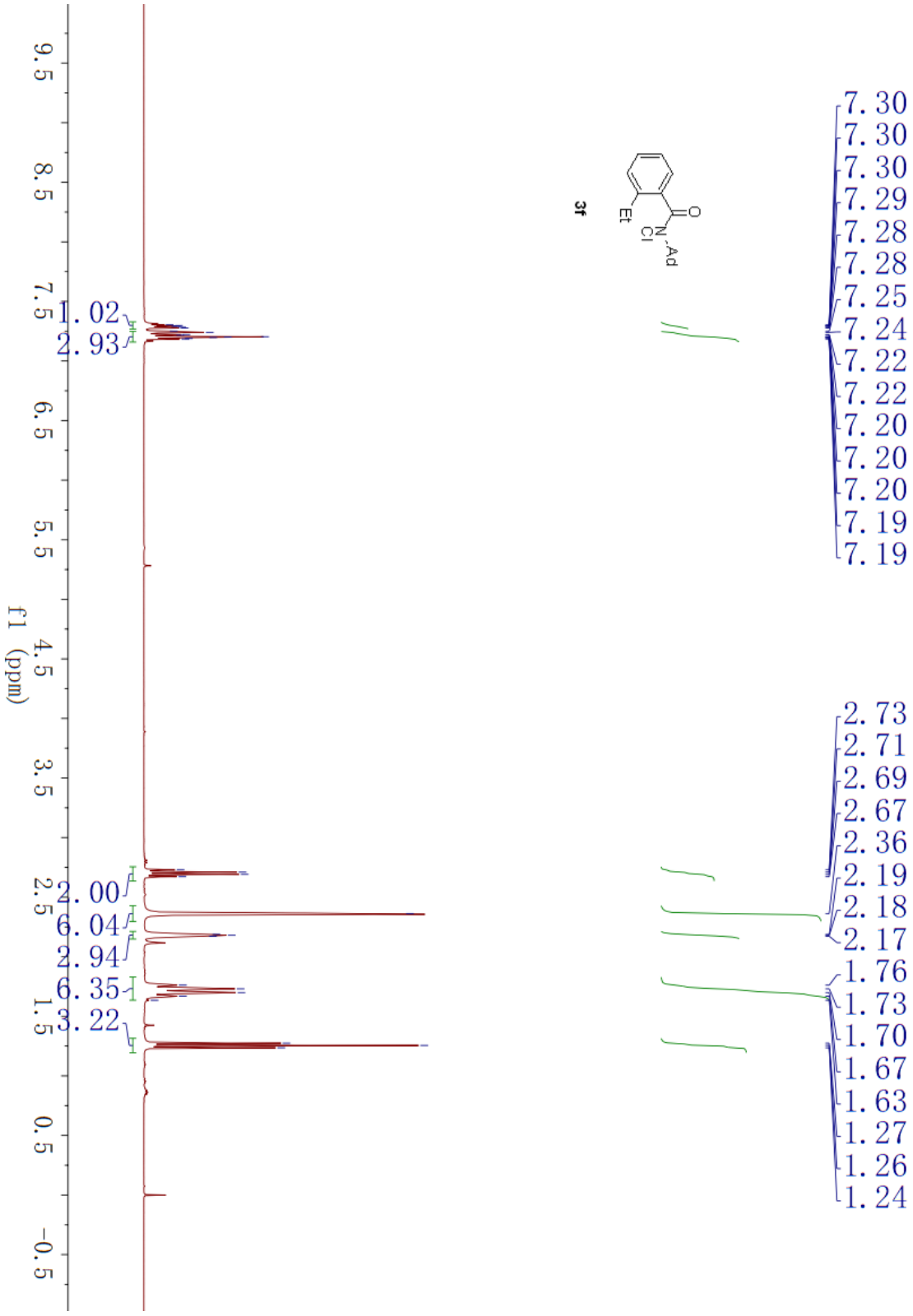
f1 (ppm)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7.20
7.20
7.19
7.19
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2.18
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1.63
1.27
1.26
1.24
1.02
2.93
2.00
6.04
2.94
6.35
3.22
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7.5
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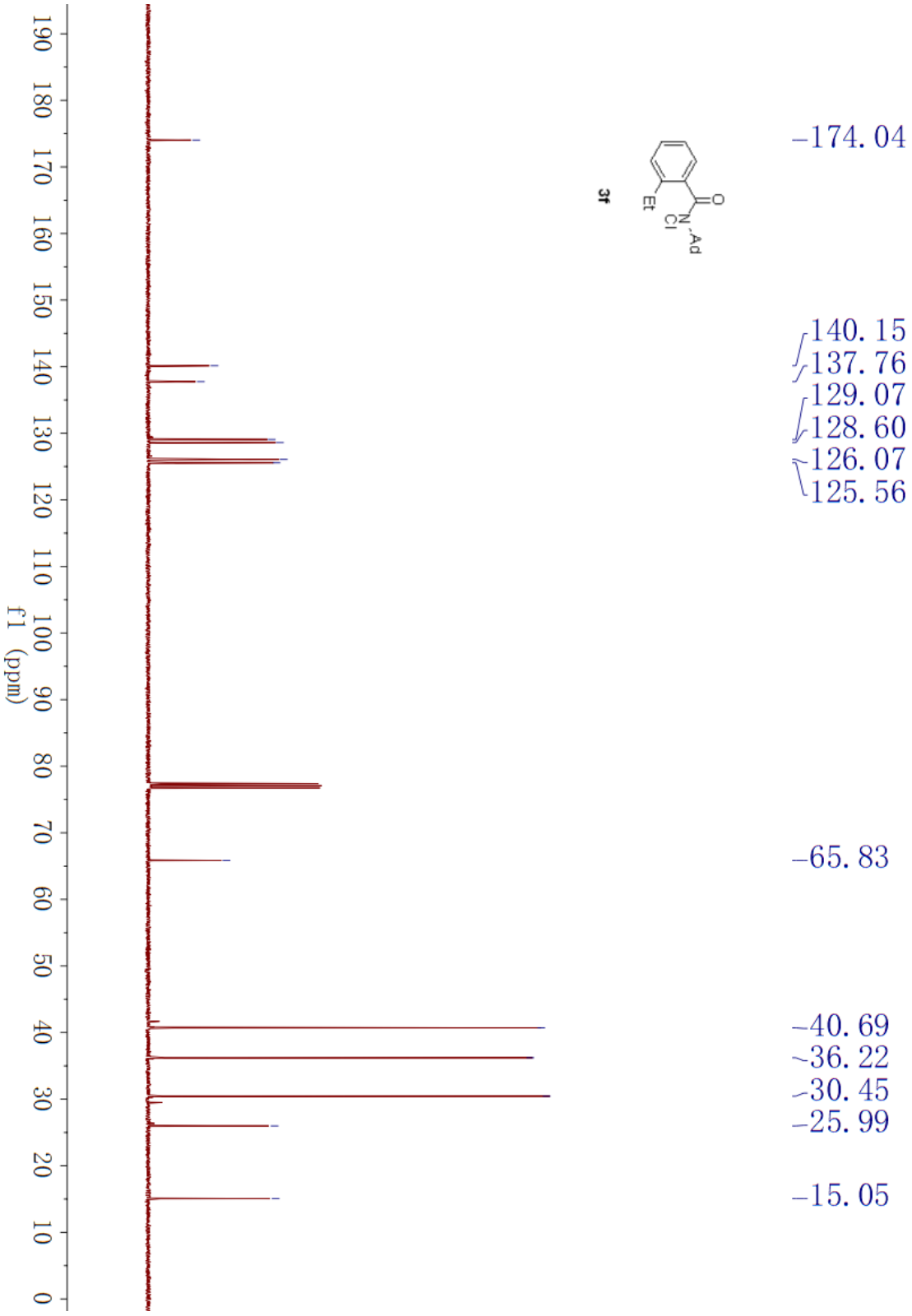
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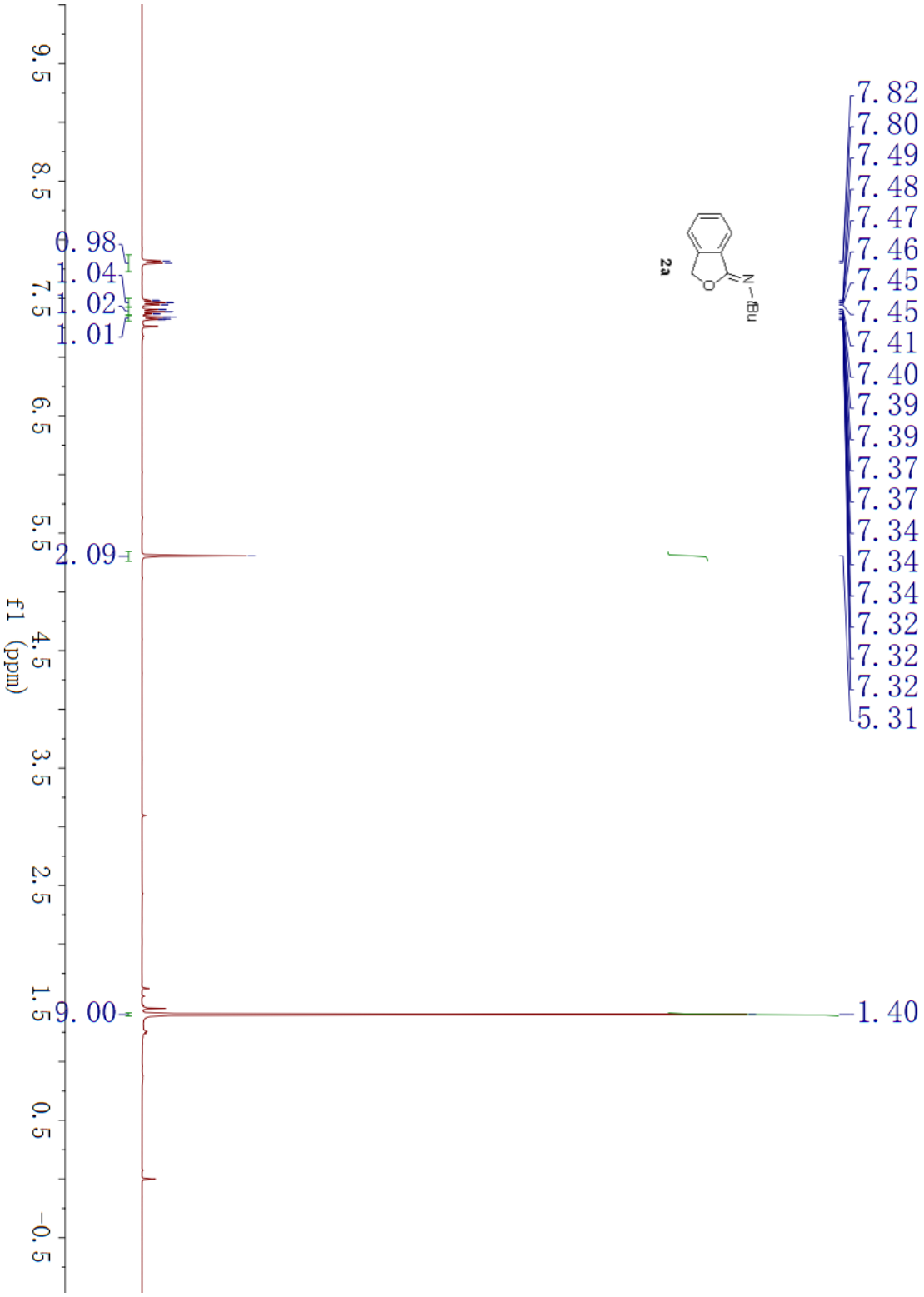
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7.37
7.34
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7.34
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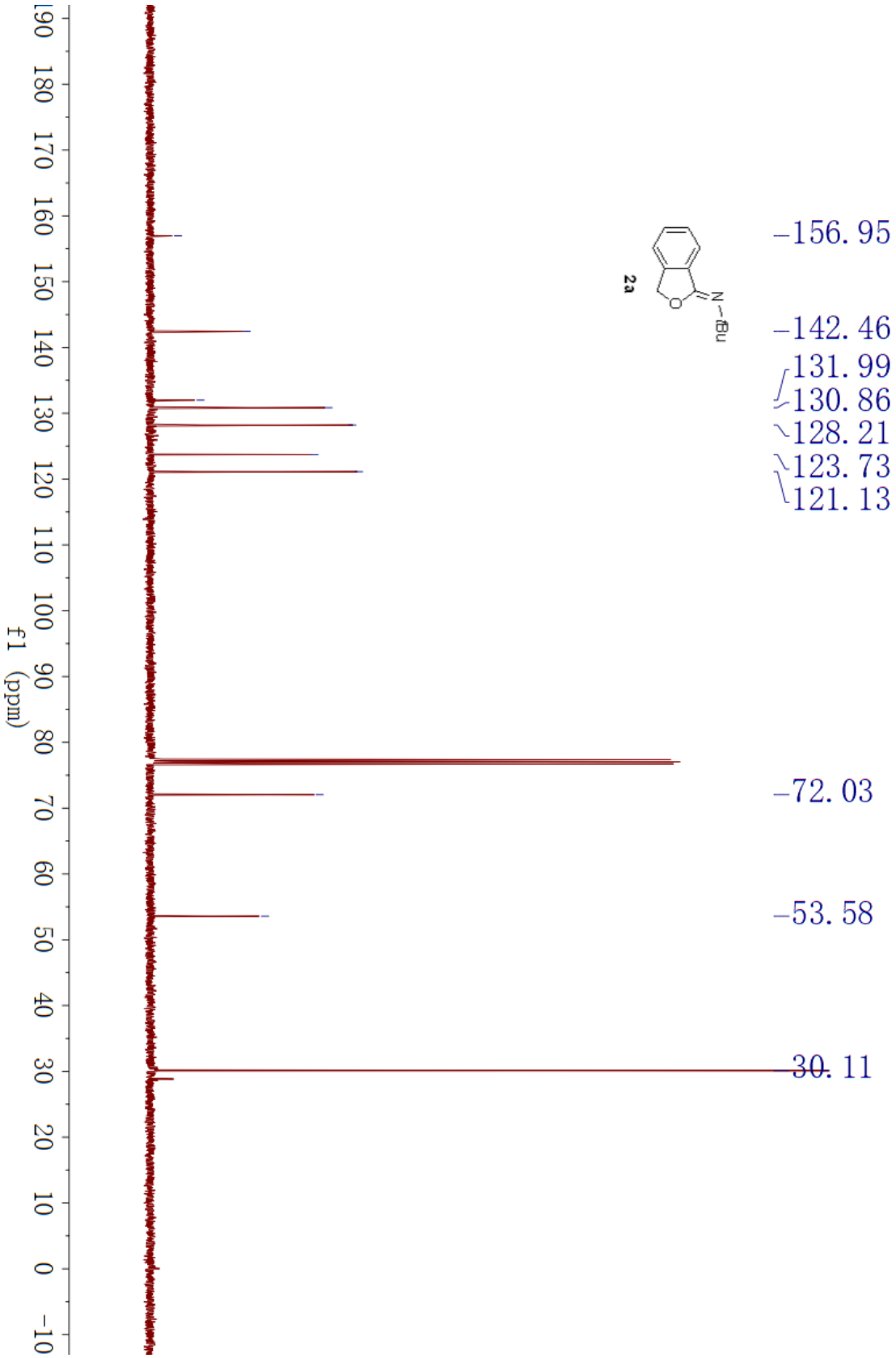
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123.73
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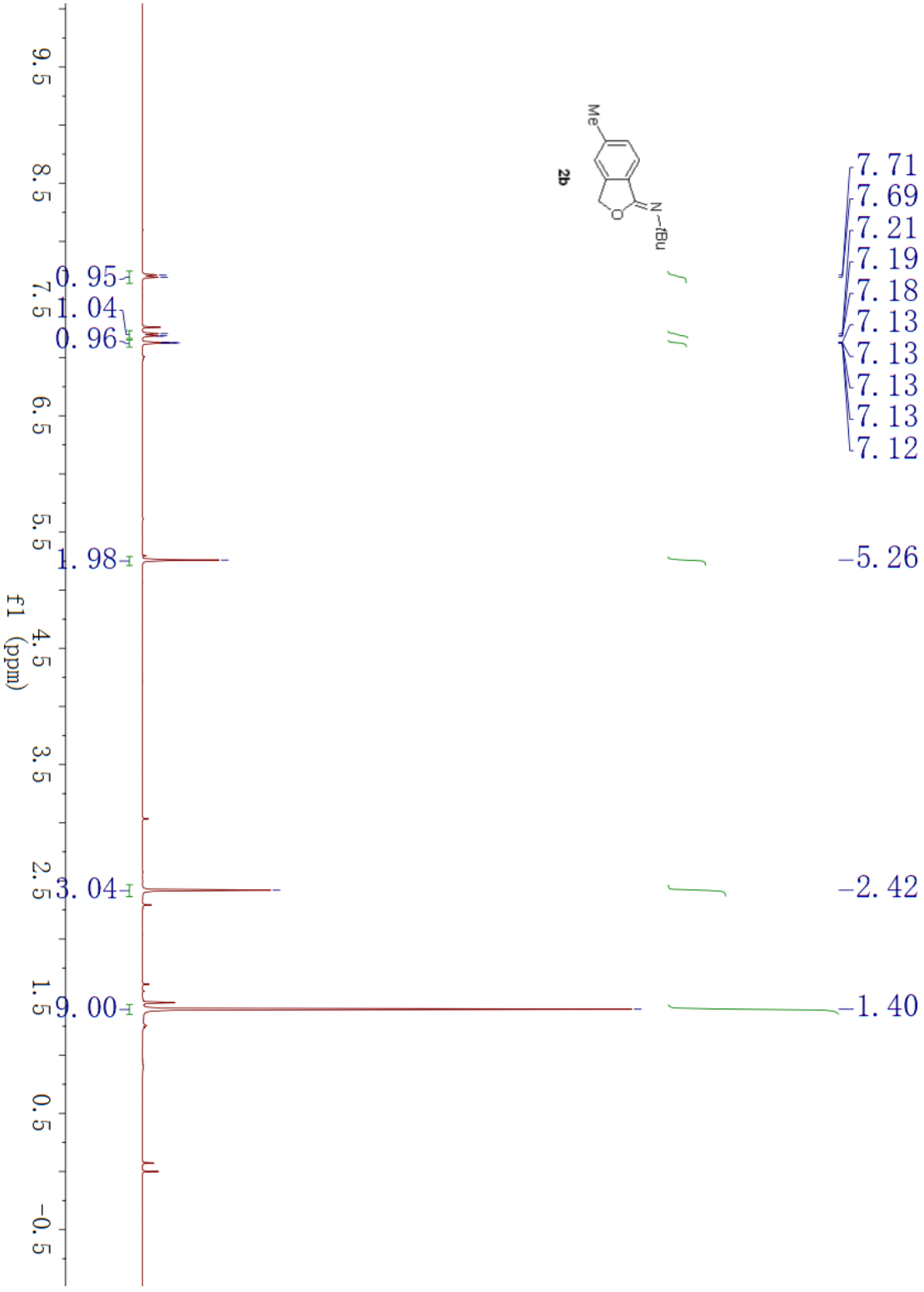
30.11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tBu
O
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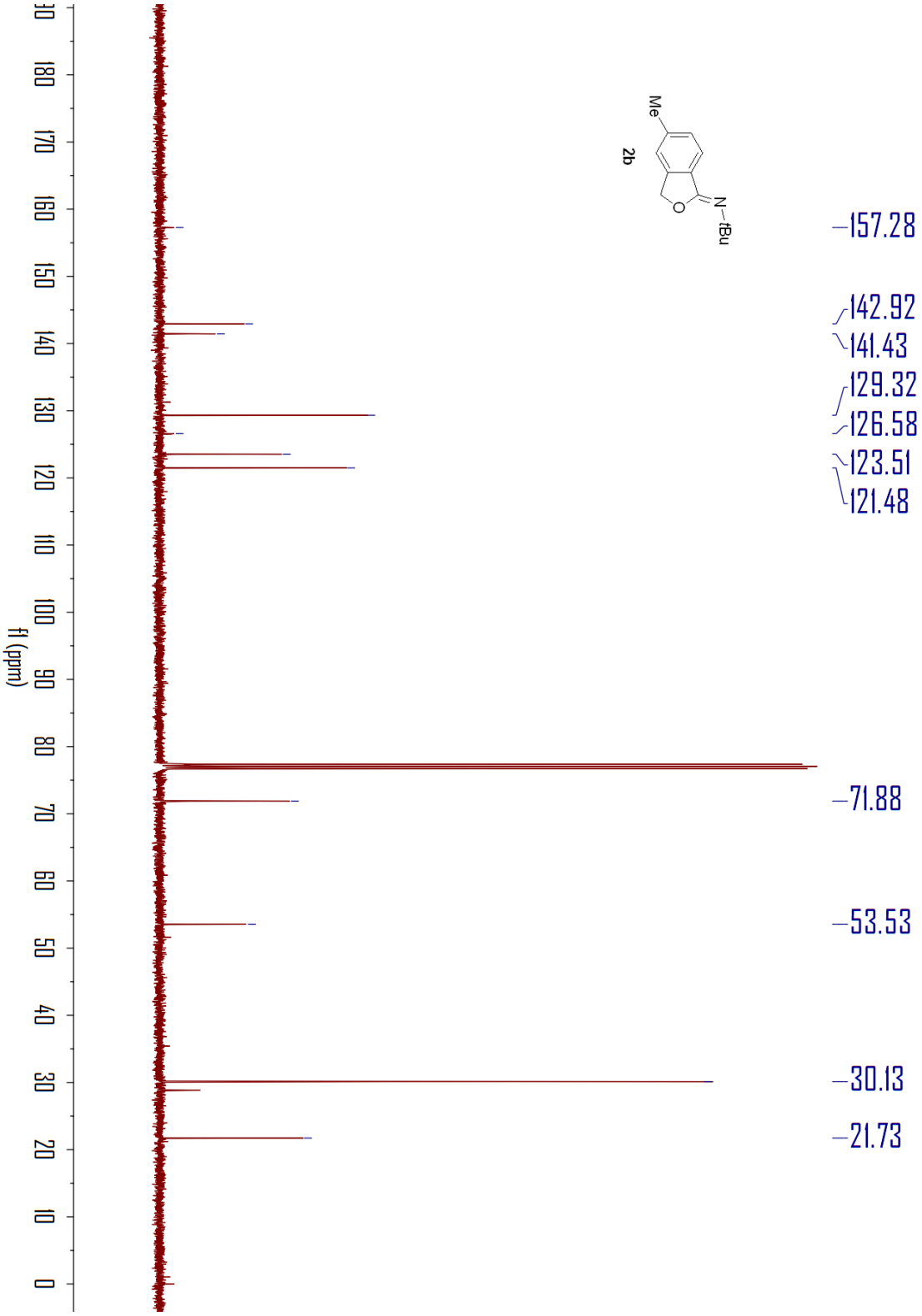
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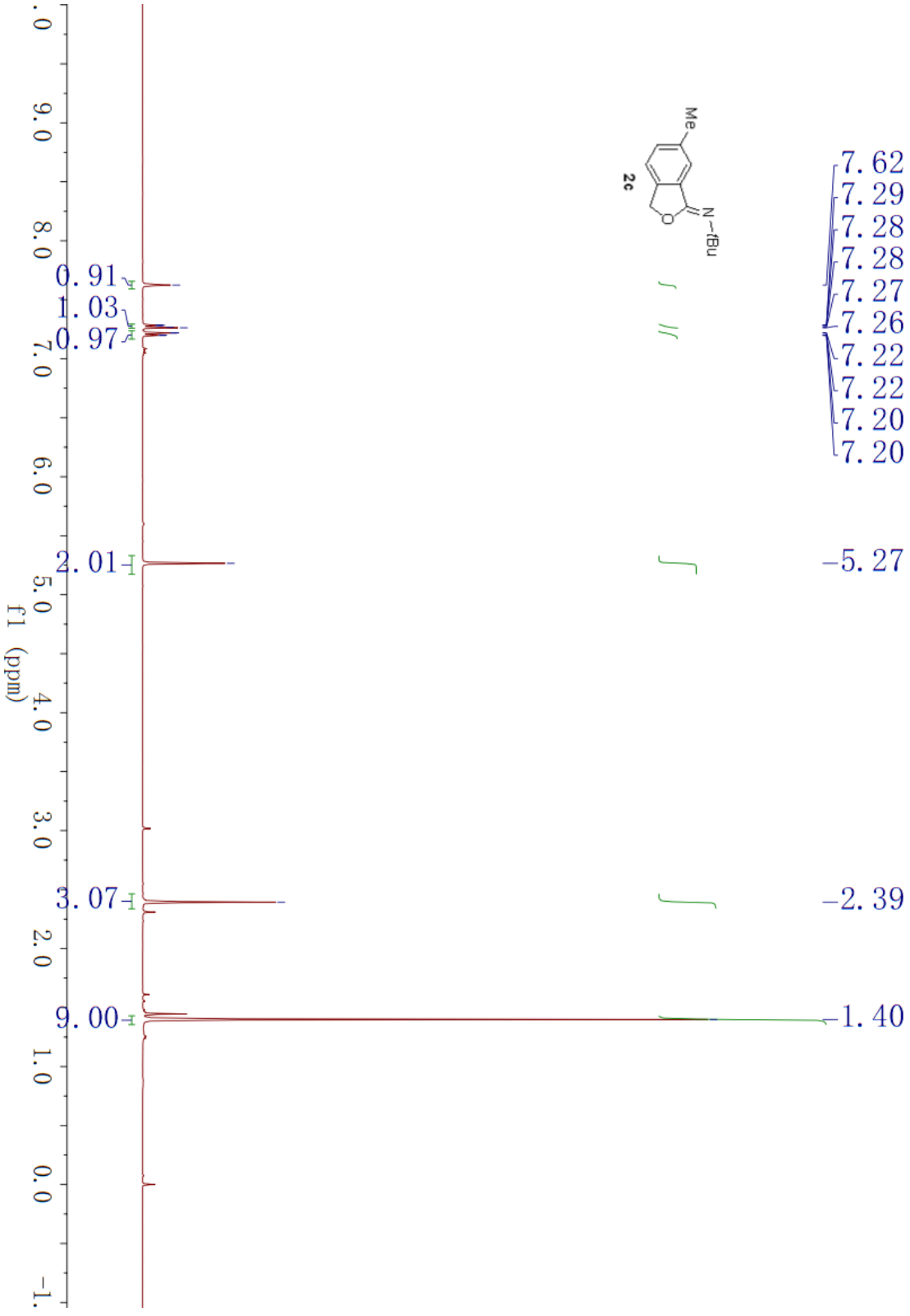
f1 (ppm)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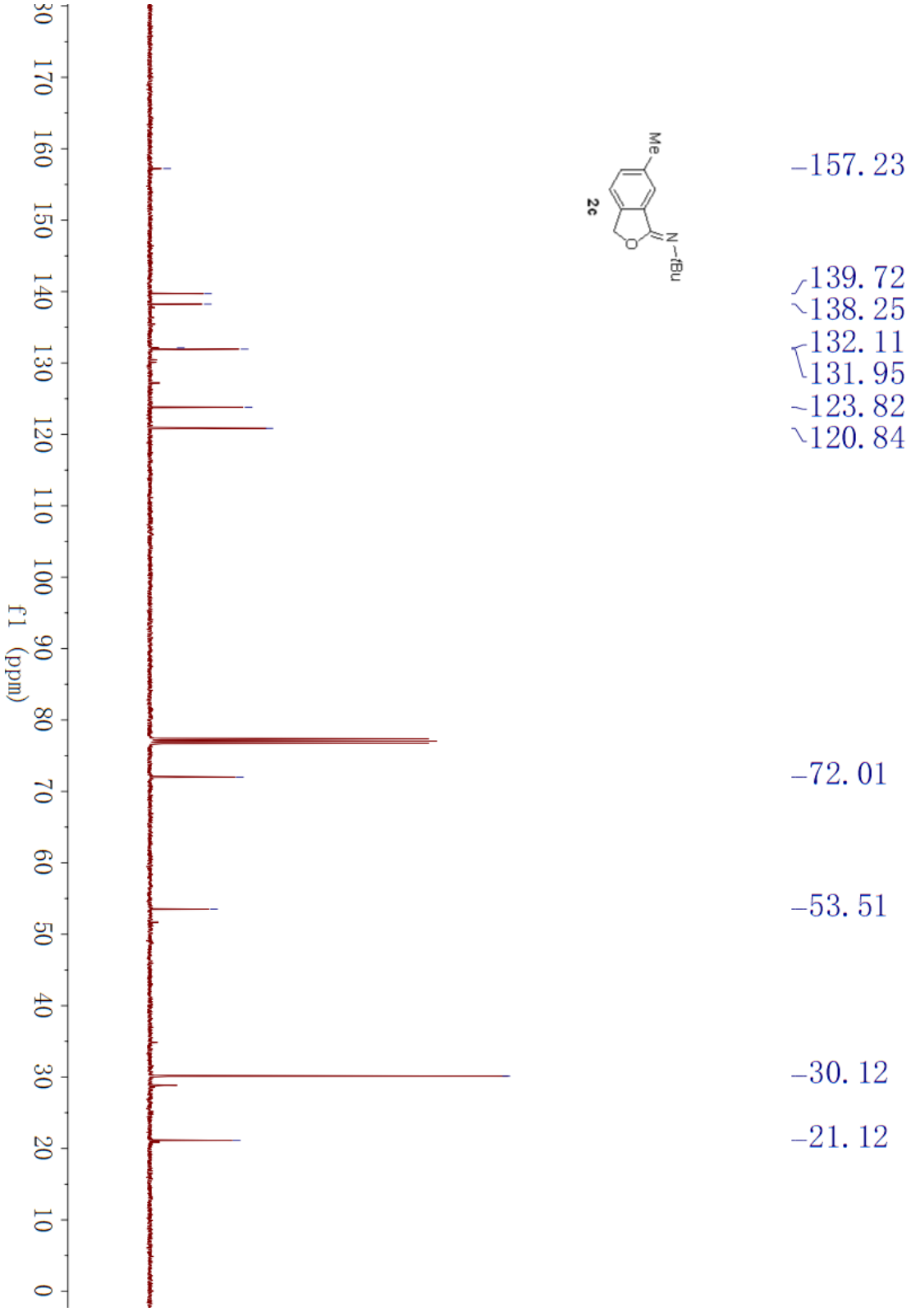
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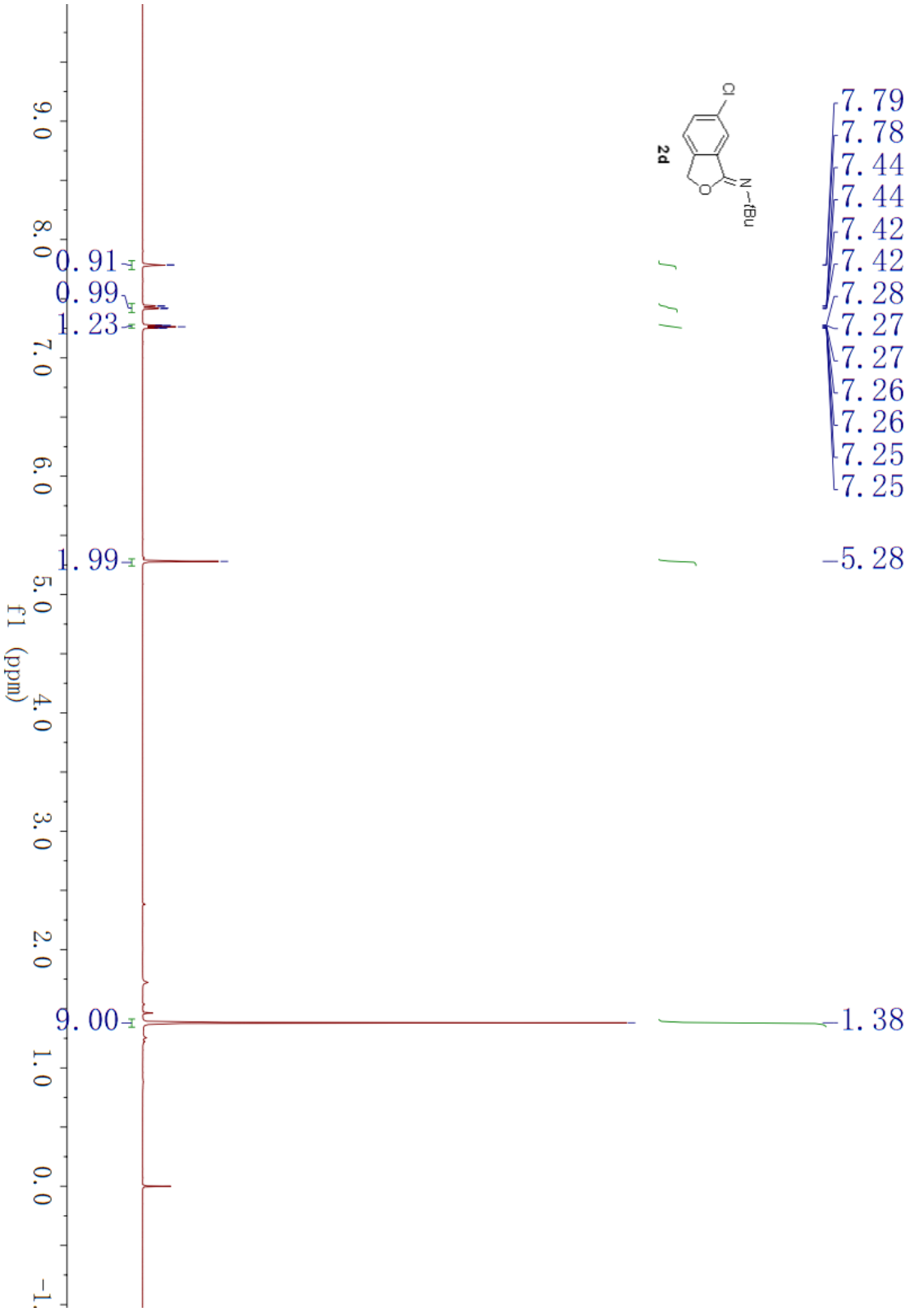
f1 (ppm)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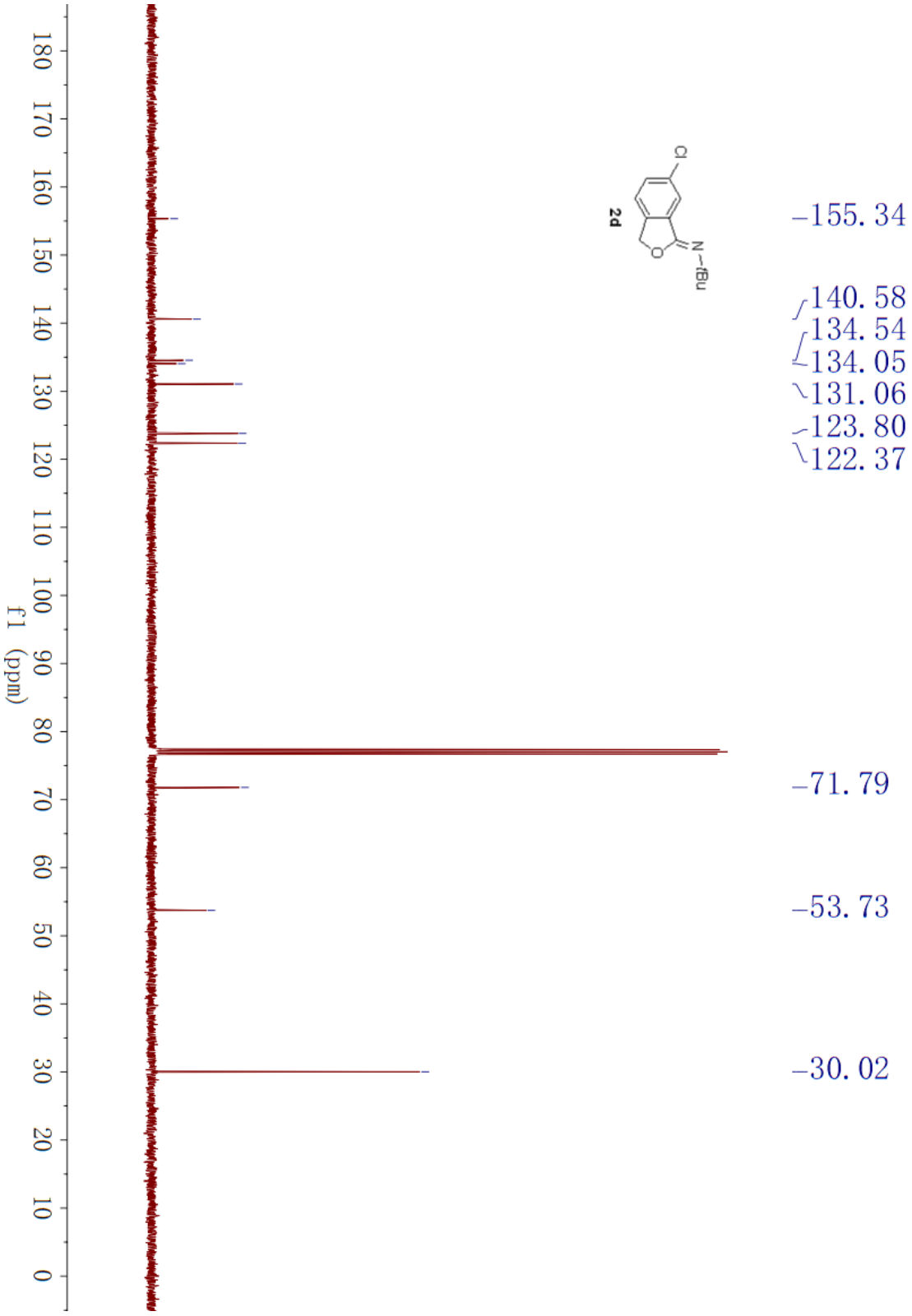
f1 (ppm)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30.02
f1 (ppm)
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20
10
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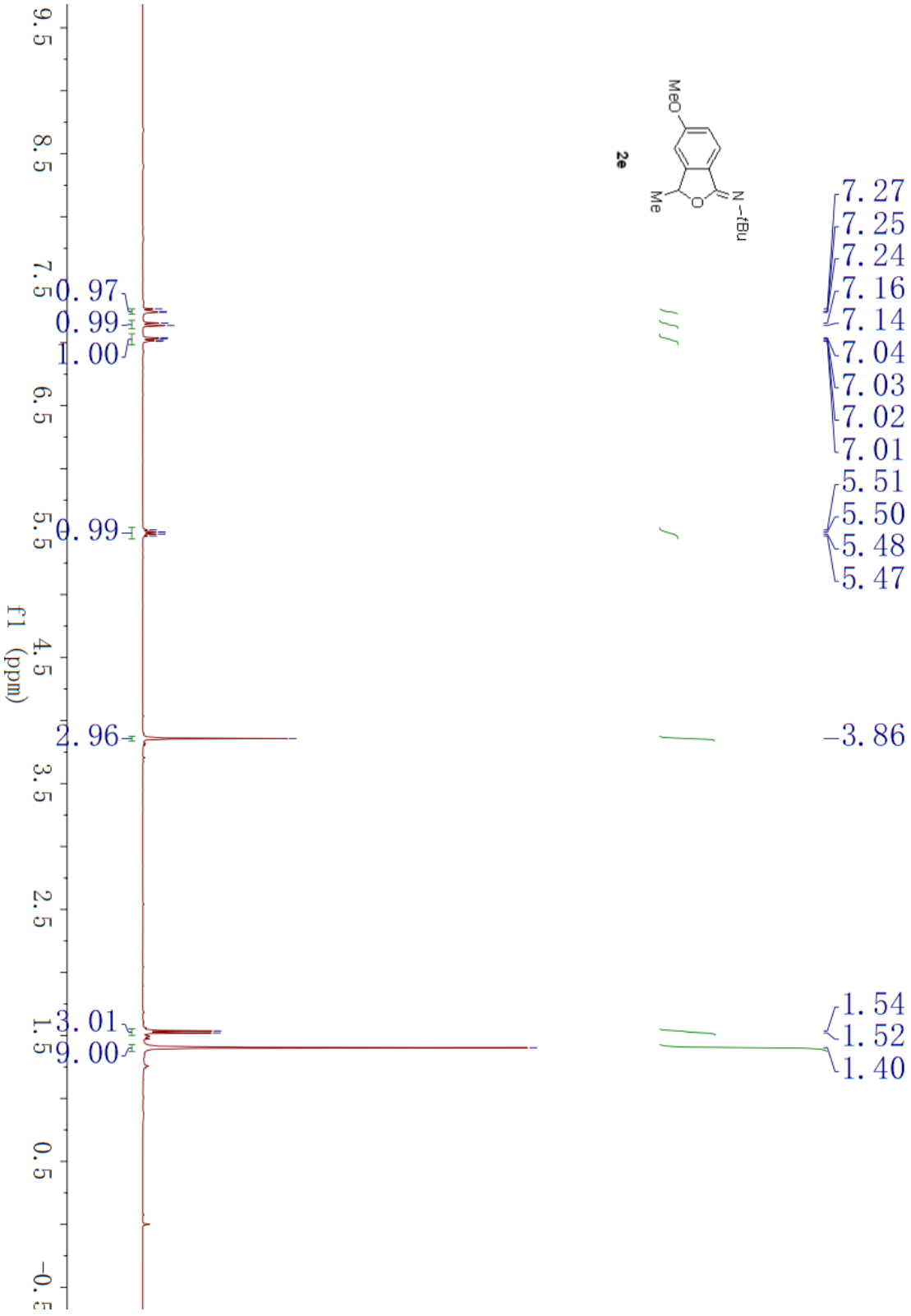
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Me
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7.01
5.51
5.50
5.48
5.47
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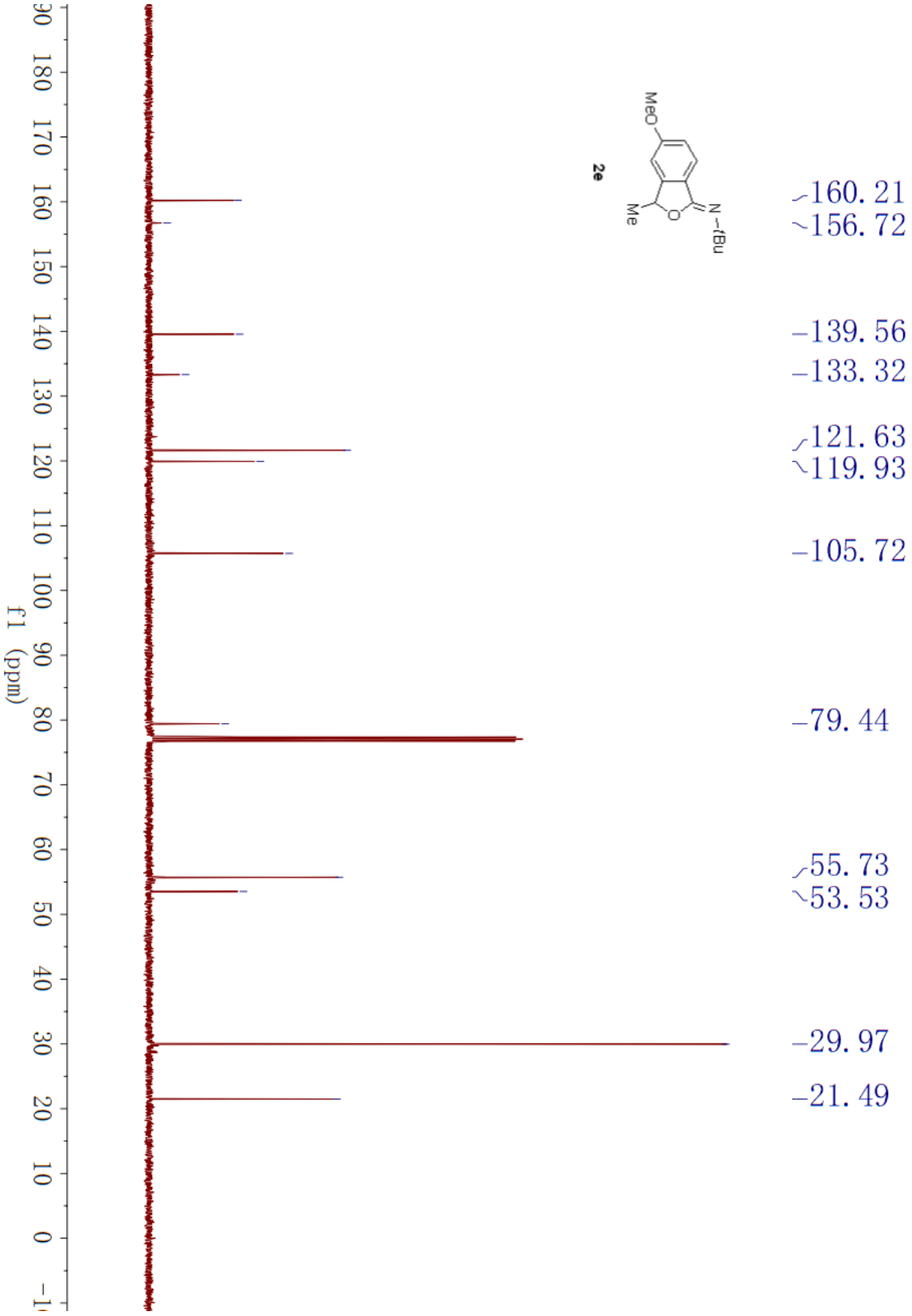
f1 (ppm)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Me
O
N-tBu
2e
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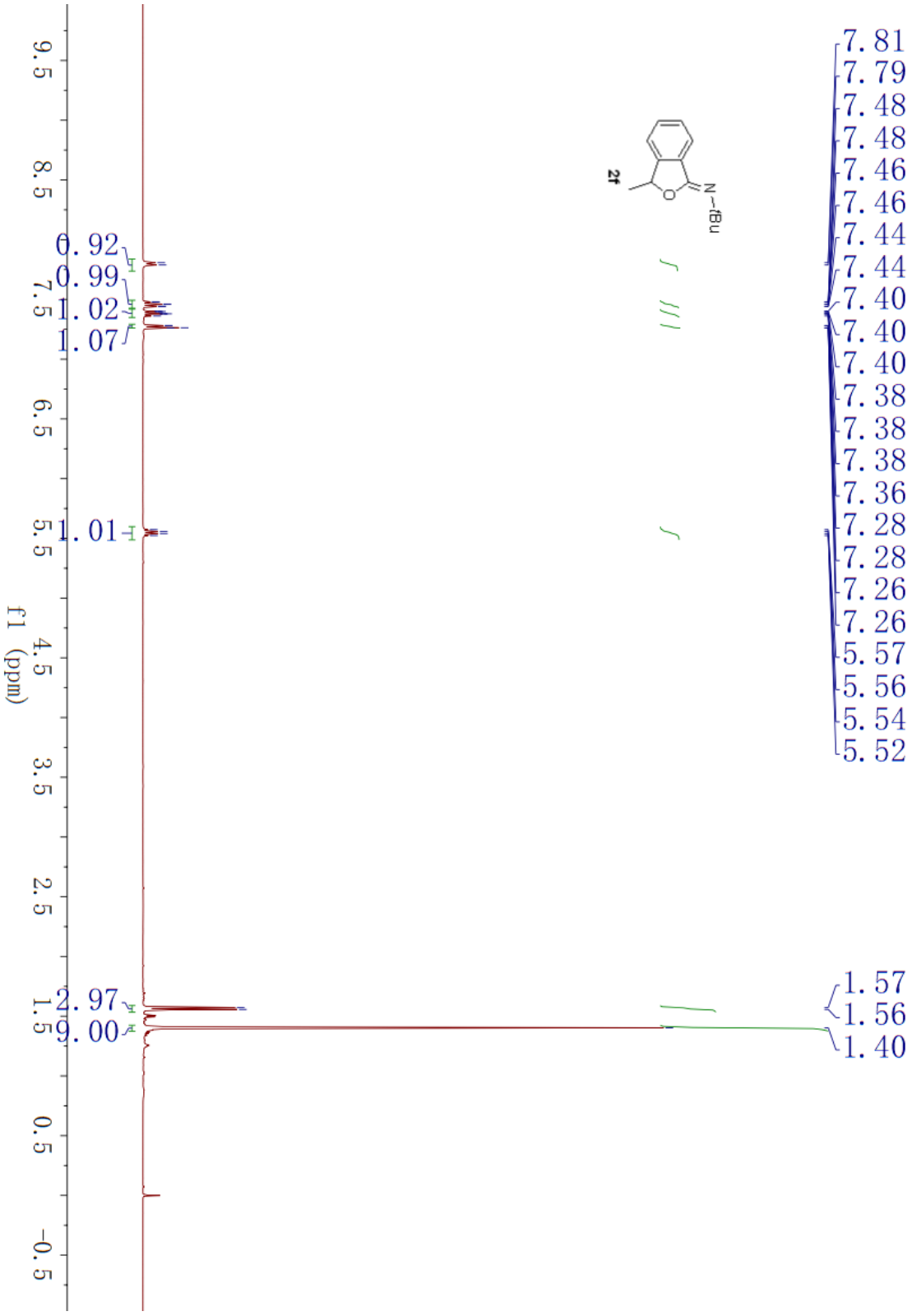
55.73
53.53
29.97
21.49
f1 (ppm)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0.5
-0.5
0.92
0.99
1.02
1.07
1.01
2.97
9.00
7.81
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7.48
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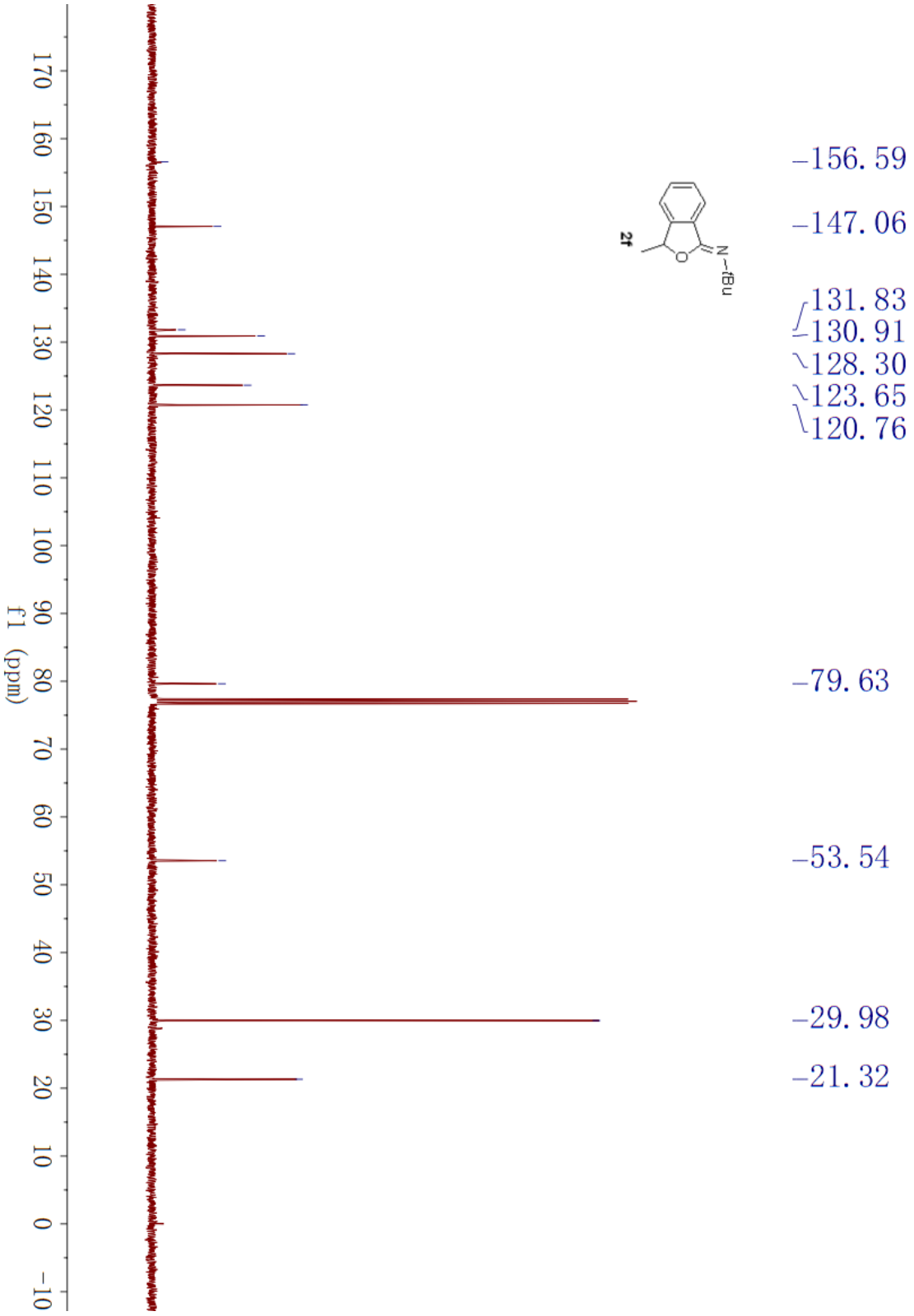
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80
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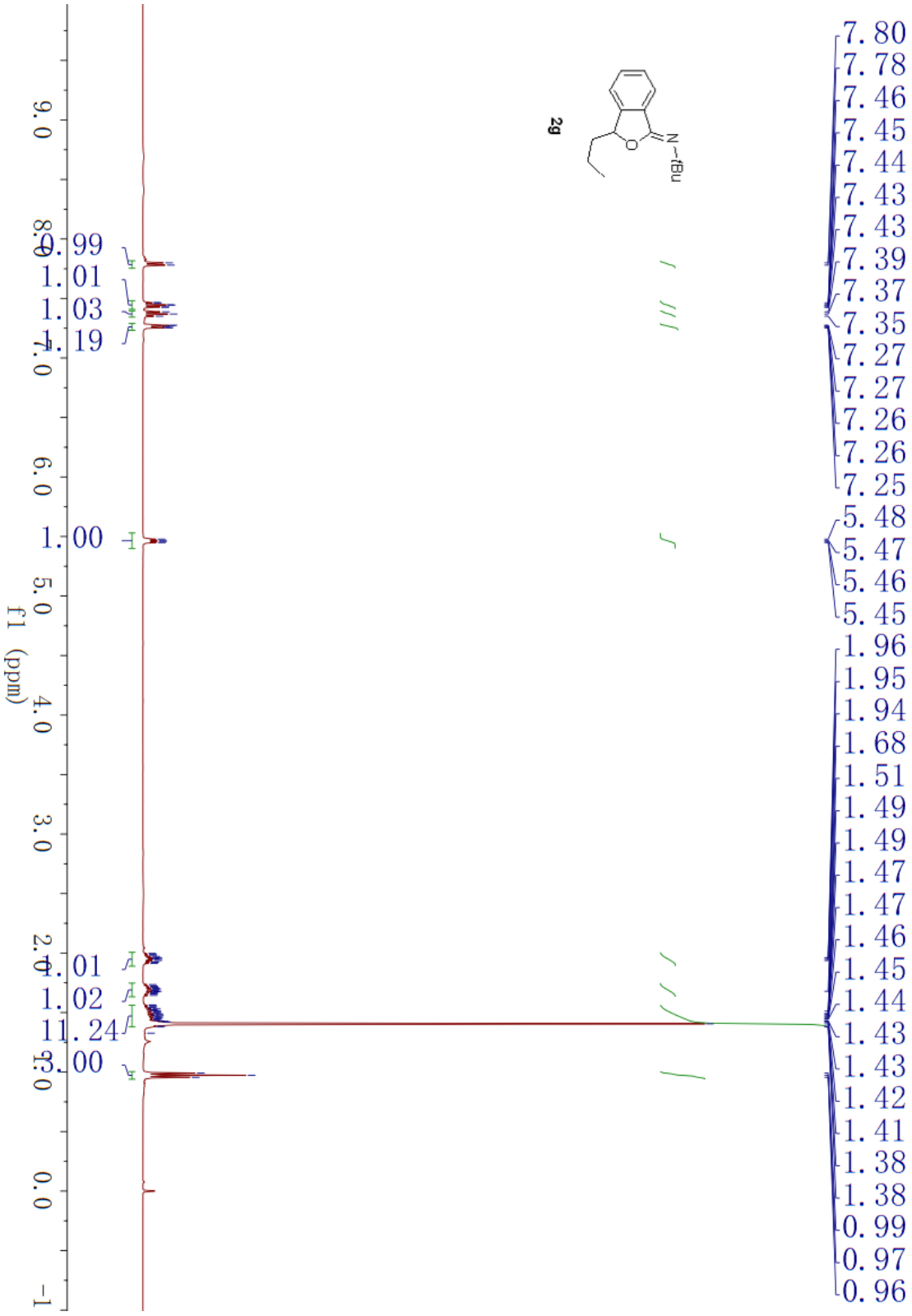
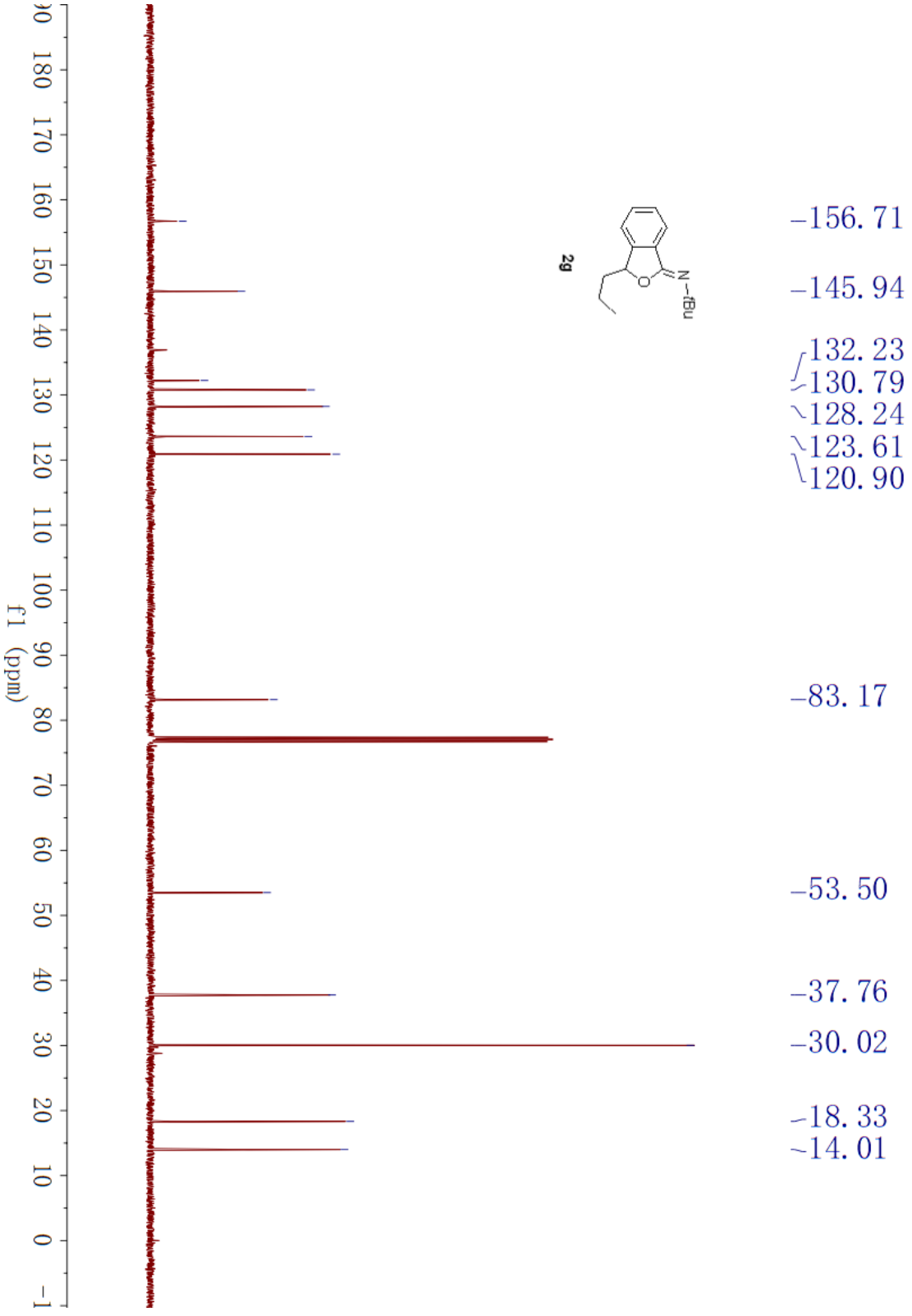
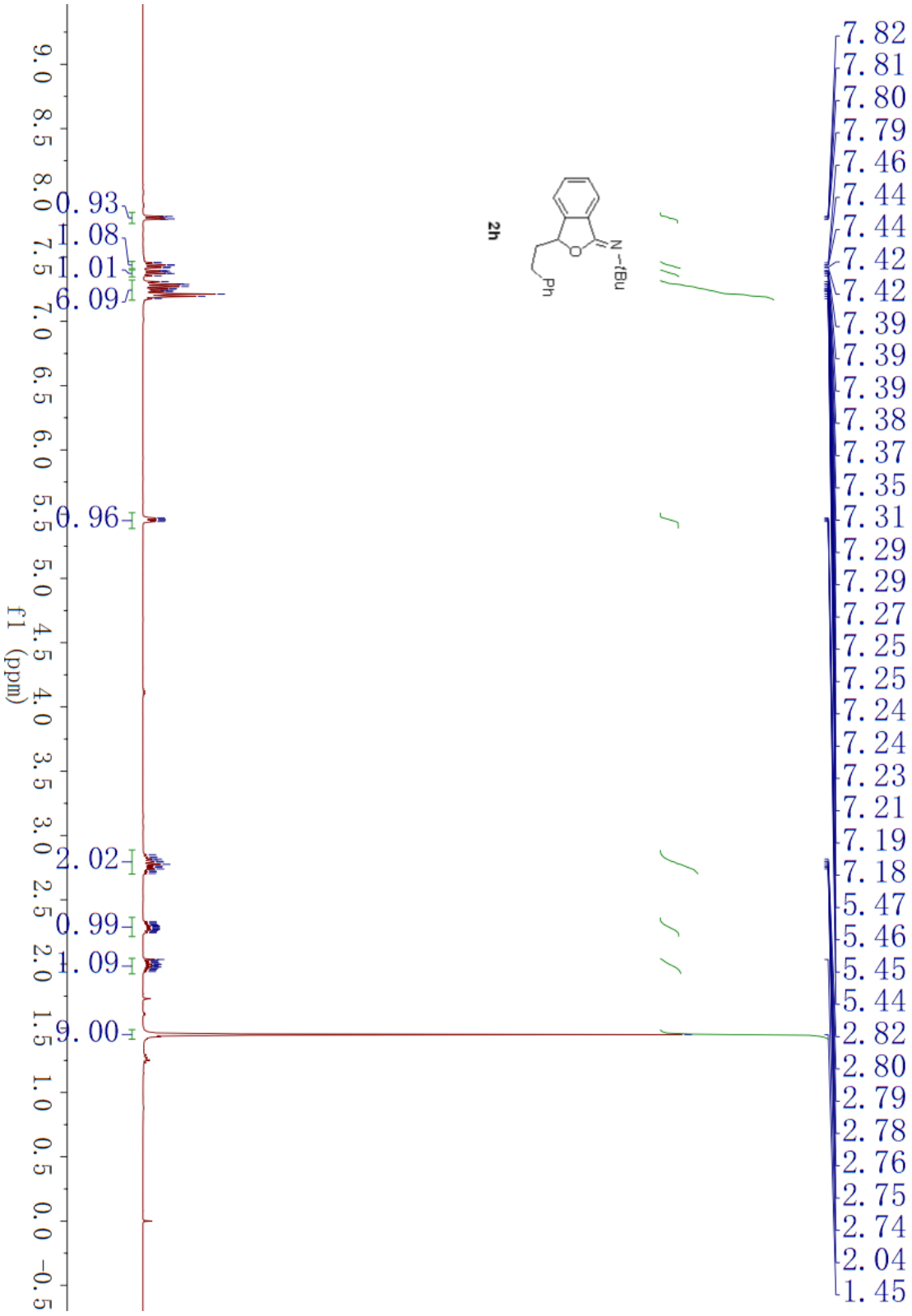
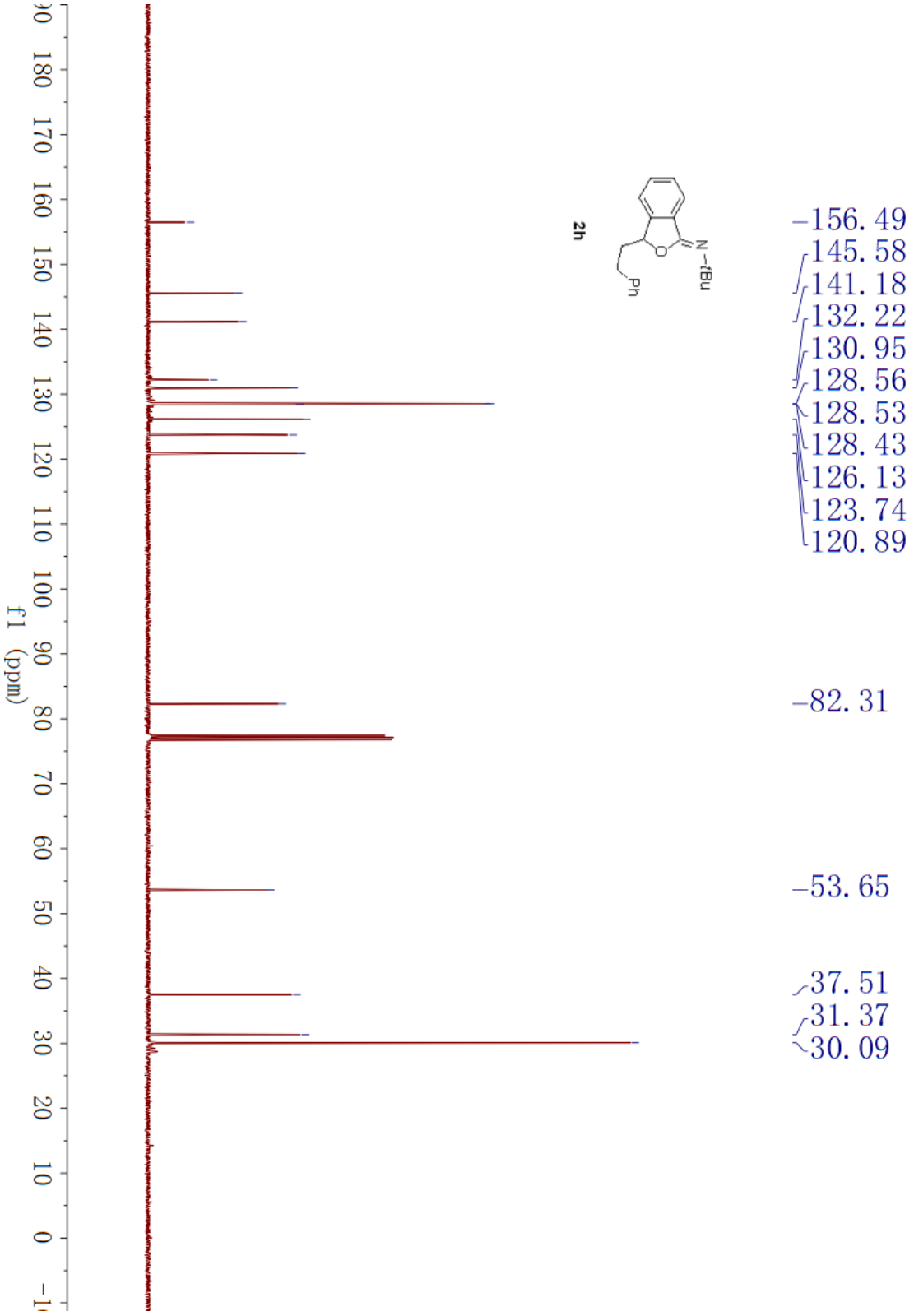
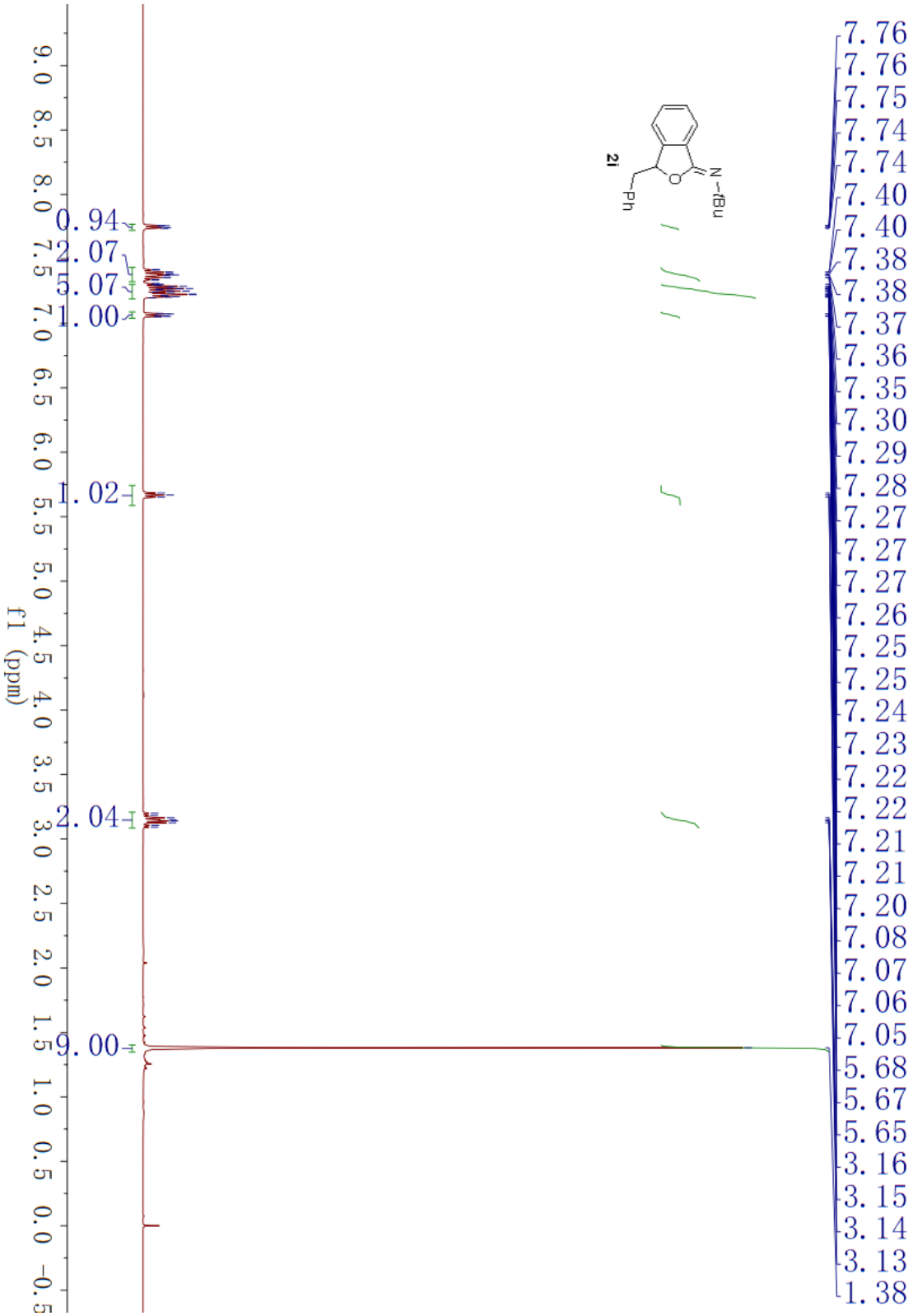
60
50
40
30
20
10
0
-10
f1 (ppm)
2f
N-tBu
156.59
147.06
131.83
130.91
128.30
123.65
120.76
79.63
53.54
29.98
21.32

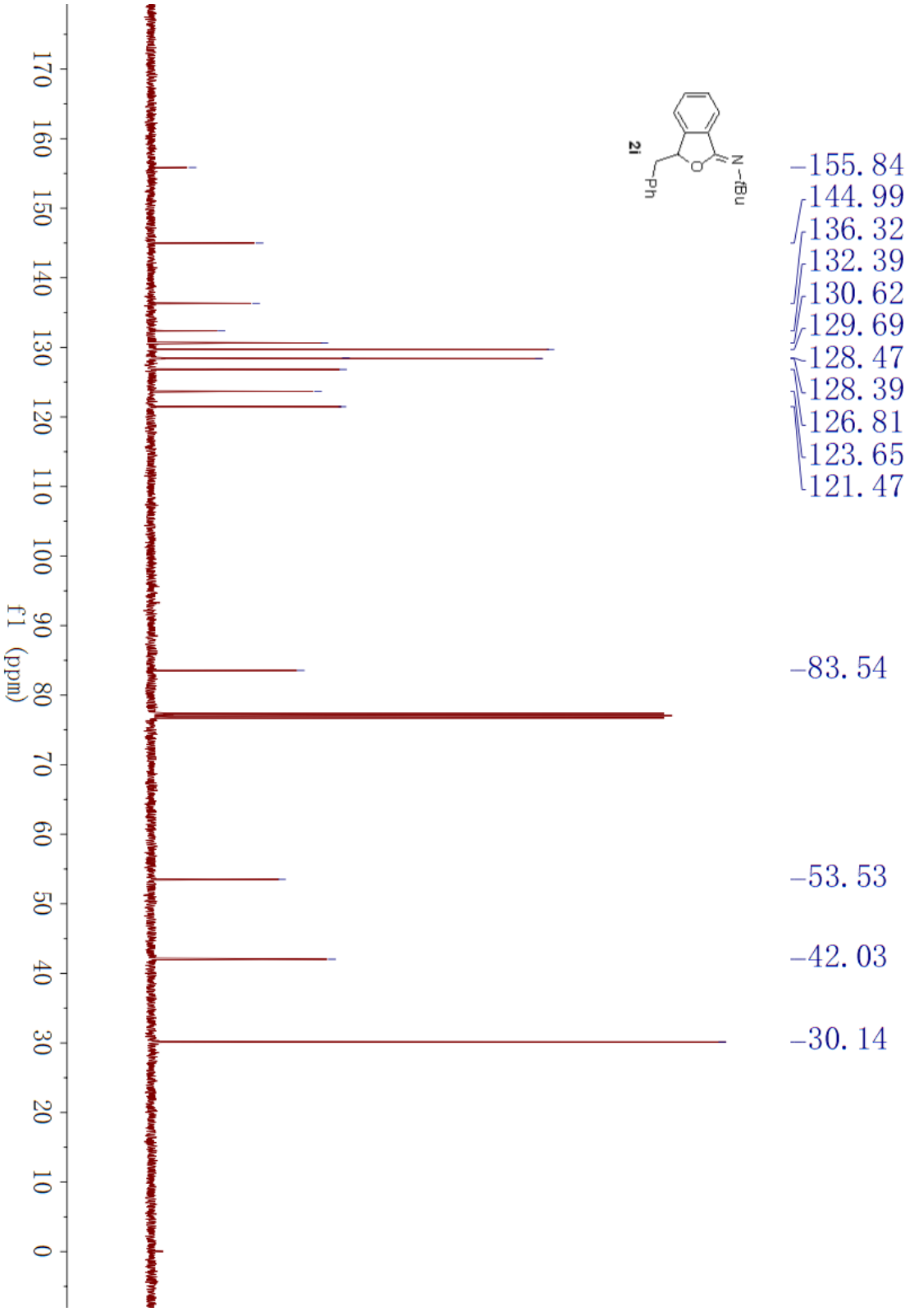

2g
N-tBu
f1 (ppm)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1
0.99
1.01
1.03
1.19
1.00
1.01
1.02
11.24
3.00
7.80
7.78
7.46
7.45
7.44
7.43
7.43
7.39
7.37
7.35
7.27
7.27
7.26
7.26
7.25
5.48
5.47
5.46
5.45
1.96
1.95
1.94
1.68
1.51
1.49
1.49
1.47
1.47
1.46
1.45
1.44
1.43
1.43
1.42
1.41
1.38
1.38
0.99
0.97
0.96

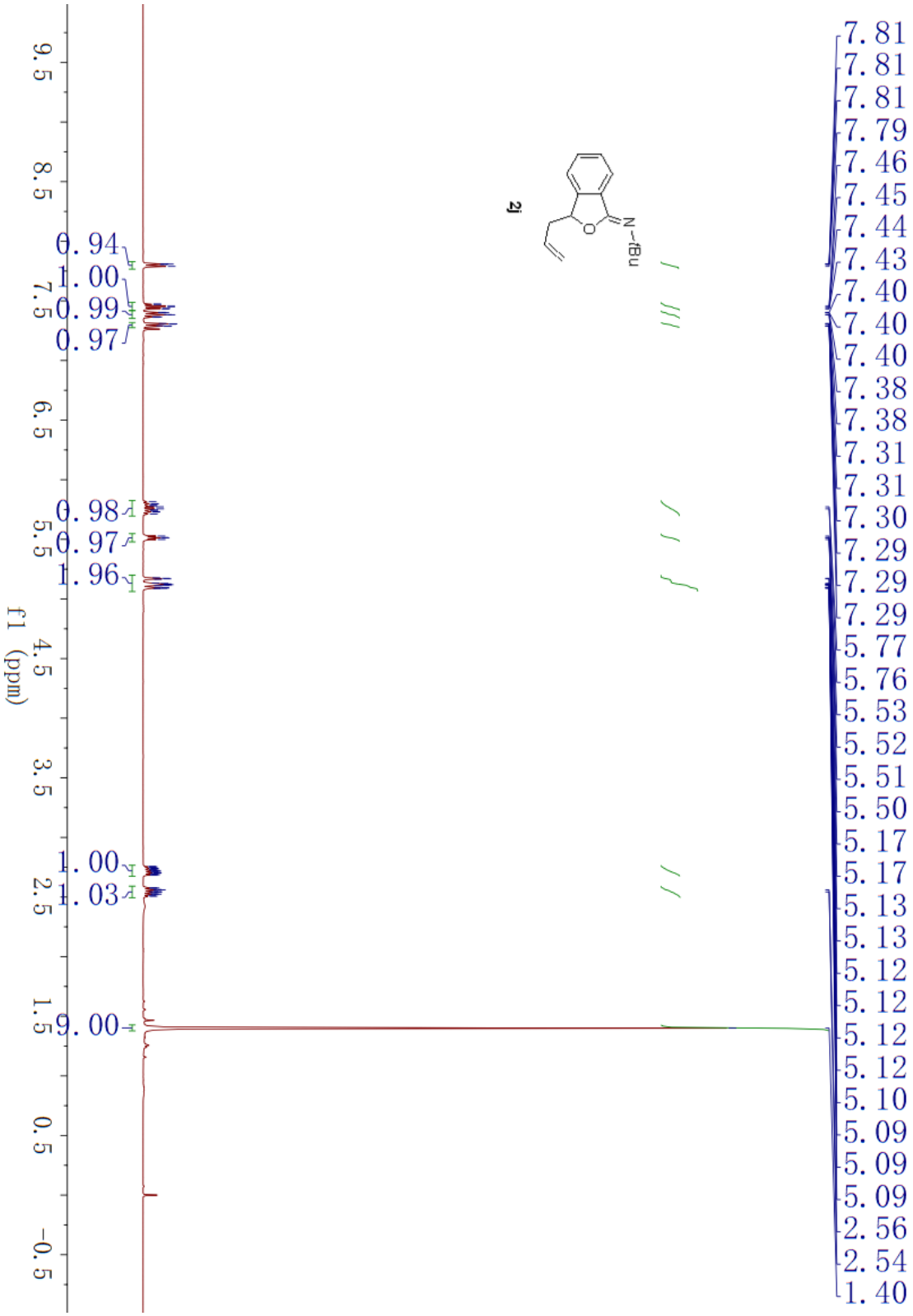

2g
N—tBu
O
-156.71
-145.94
132.23
130.79
128.24
123.61
120.90
-83.17
-53.50
-37.76
-30.02
-18.33
-14.01
f1 (ppm)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

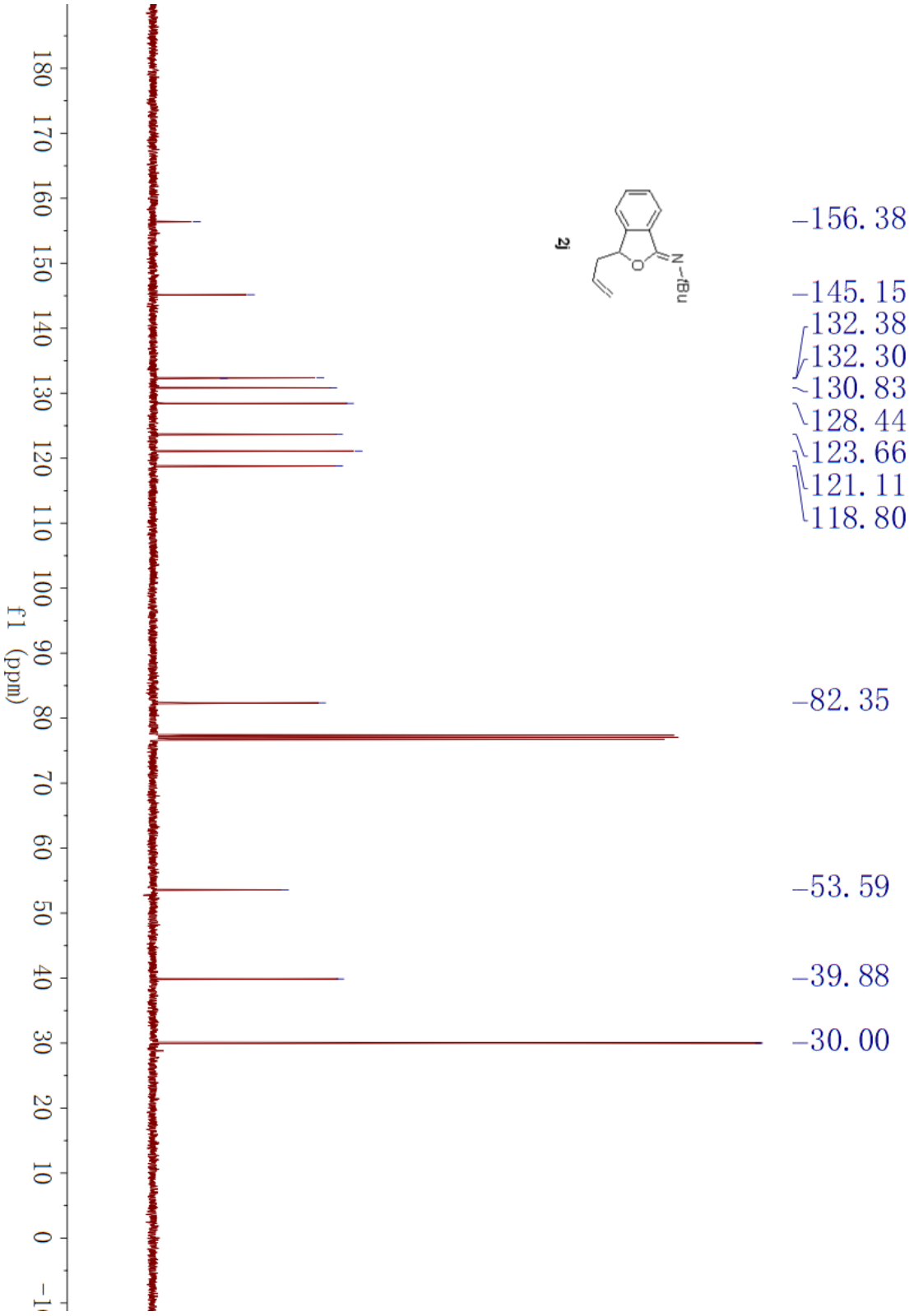

2h
N-tBu
Ph
f1 (ppm)
0.93
1.08
1.01
6.09
0.96
2.02
0.99
1.09
9.00
7.82
7.81
7.80
7.79
7.46
7.44
7.44
7.42
7.42
7.39
7.39
7.39
7.38
7.37
7.35
7.31
7.29
7.29
7.27
7.25
7.25
7.24
7.24
7.23
7.21
7.19
7.18
5.47
5.46
5.45
5.44
2.82
2.80
2.79
2.78
2.76
2.75
2.74
2.04
1.45

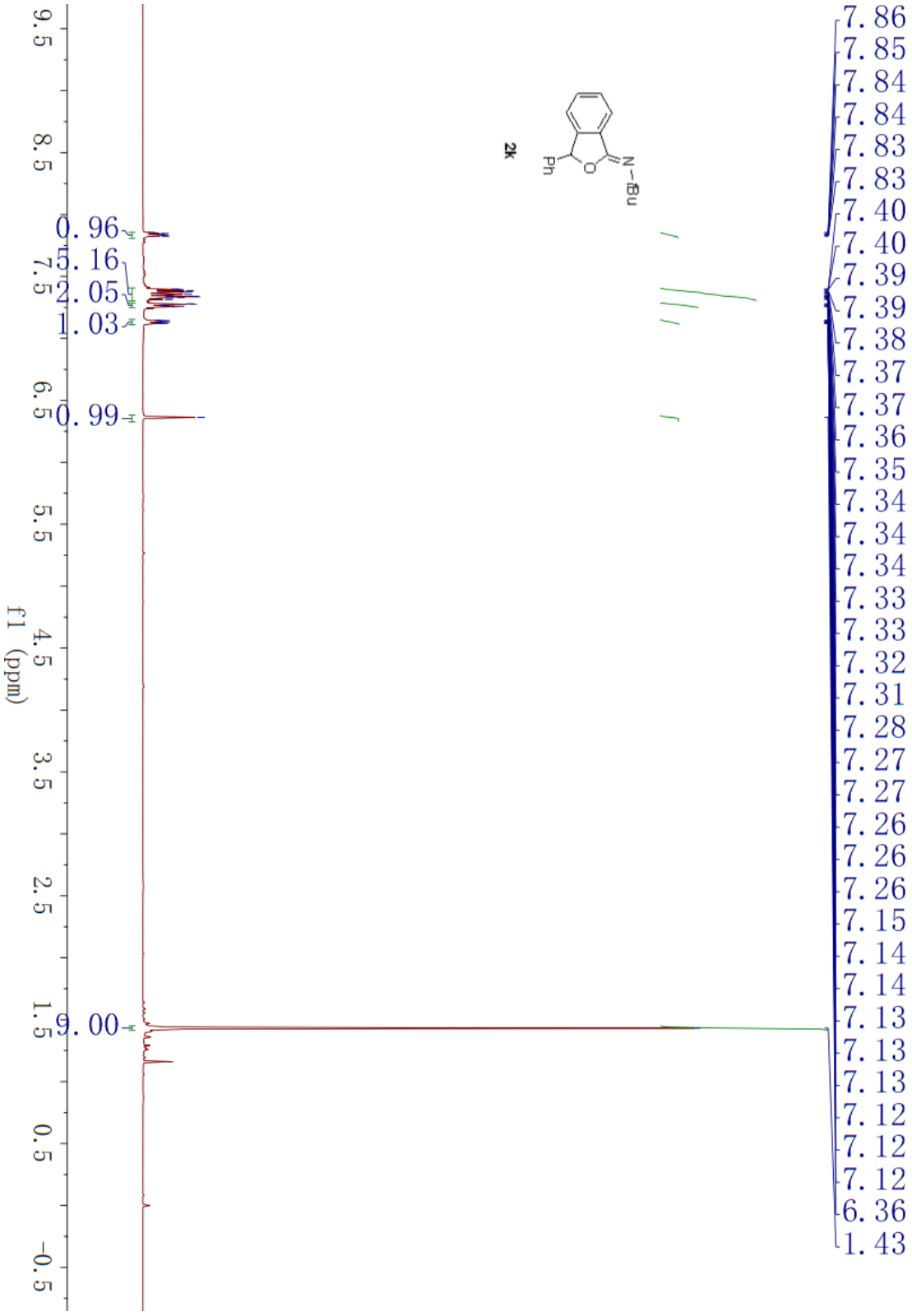

2h
N-tBu
Ph
156.49
145.58
141.18
132.22
130.95
128.56
128.53
128.43
126.13
123.74
120.89
82.31
53.65
37.51
31.37
30.09
f1 (ppm)

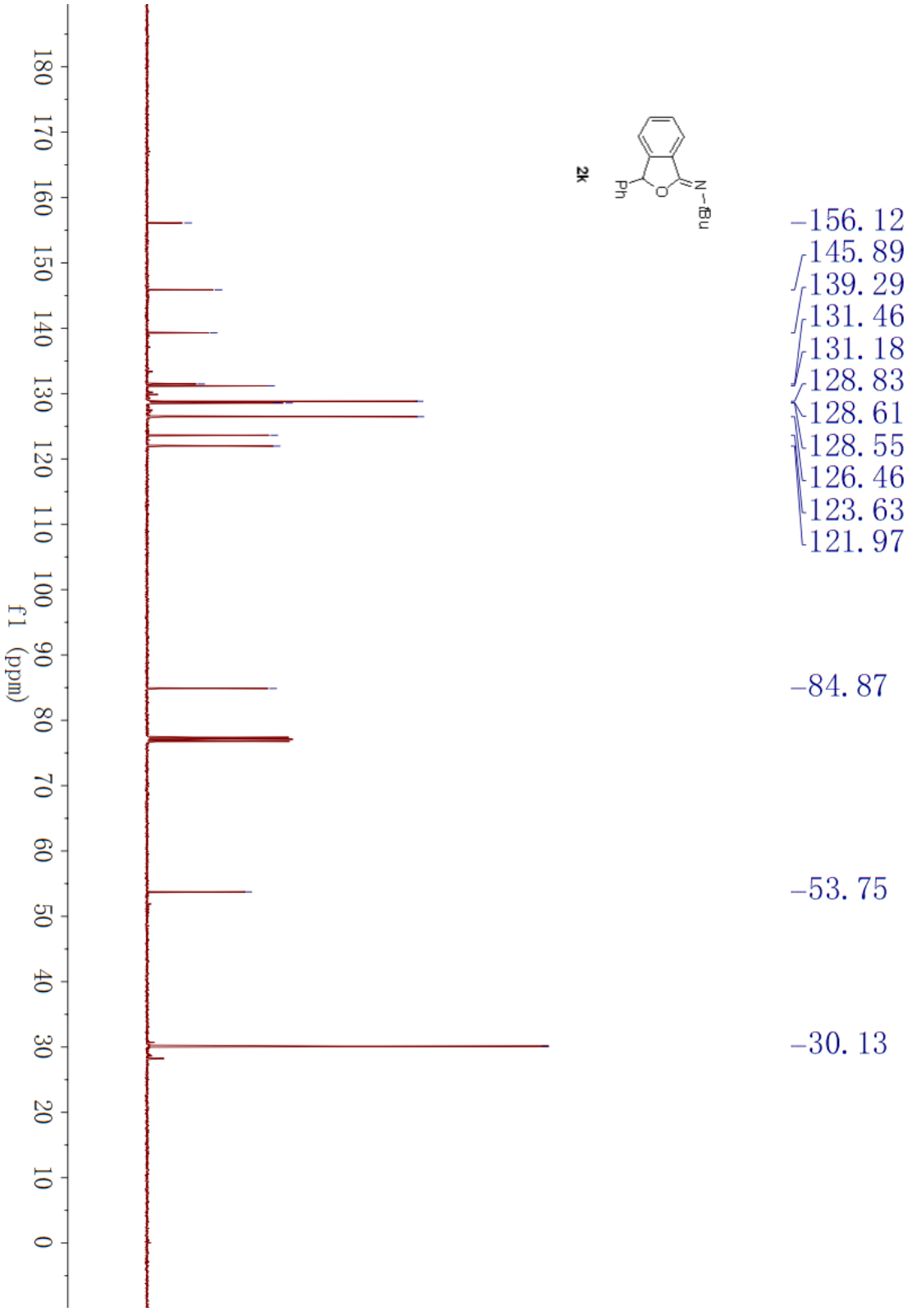

2i
N–tBu
Ph
0.94
2.07
5.07
1.00
1.02
2.04
9.00
f1 (ppm)
7.76
7.76
7.75
7.74
7.74
7.40
7.40
7.38
7.38
7.37
7.36
7.35
7.30
7.29
7.28
7.27
7.27
7.27
7.26
7.25
7.25
7.24
7.23
7.22
7.22
7.21
7.21
7.20
7.08
7.07
7.06
7.05
5.68
5.67
5.65
3.16
3.15
3.14
3.13
1.38

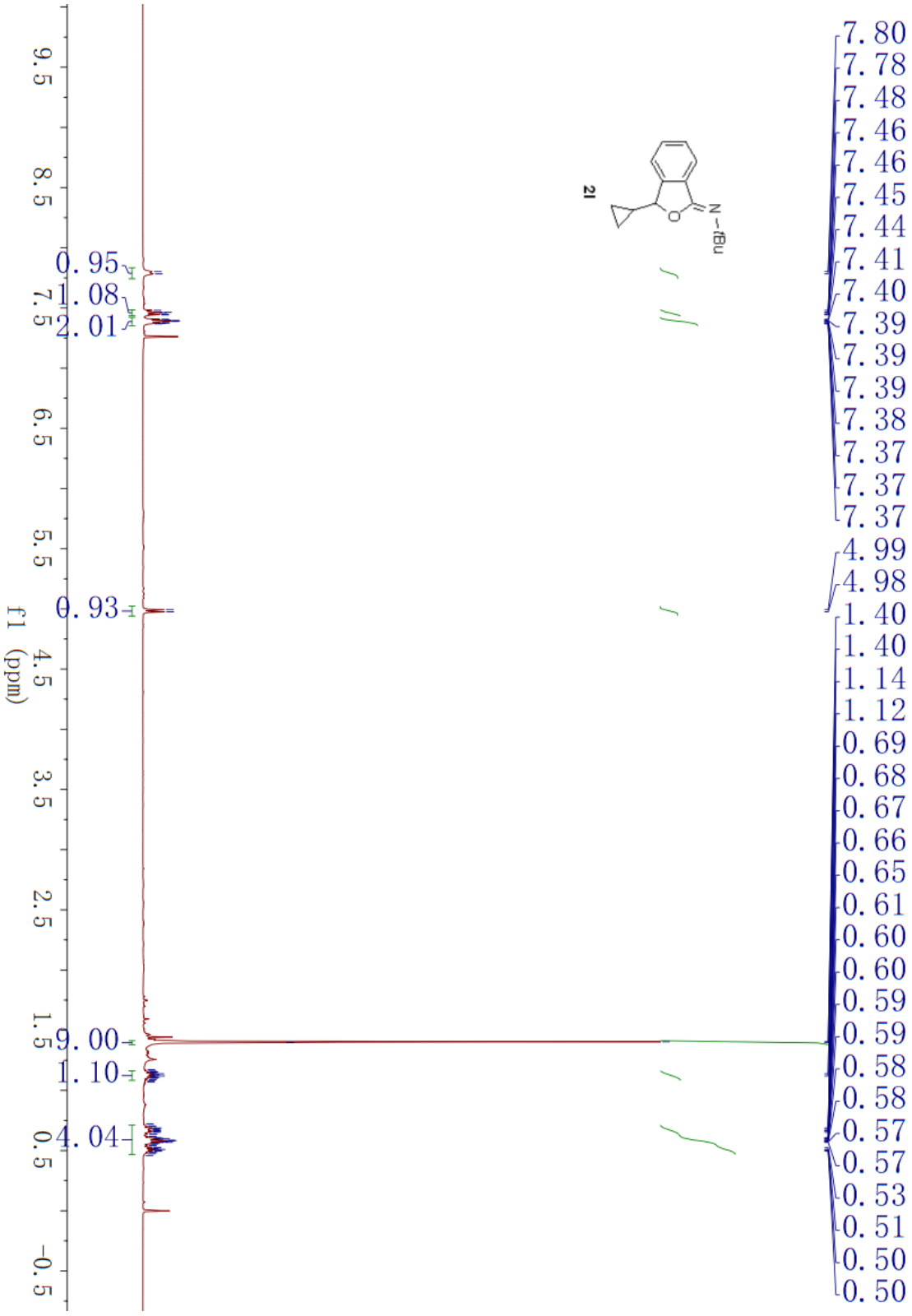

2i
Ph
N-tBu
155.84
144.99
136.32
132.39
130.62
129.69
128.47
128.39
126.81
123.65
121.47
83.54
53.53
42.03
30.14
f1 (ppm)

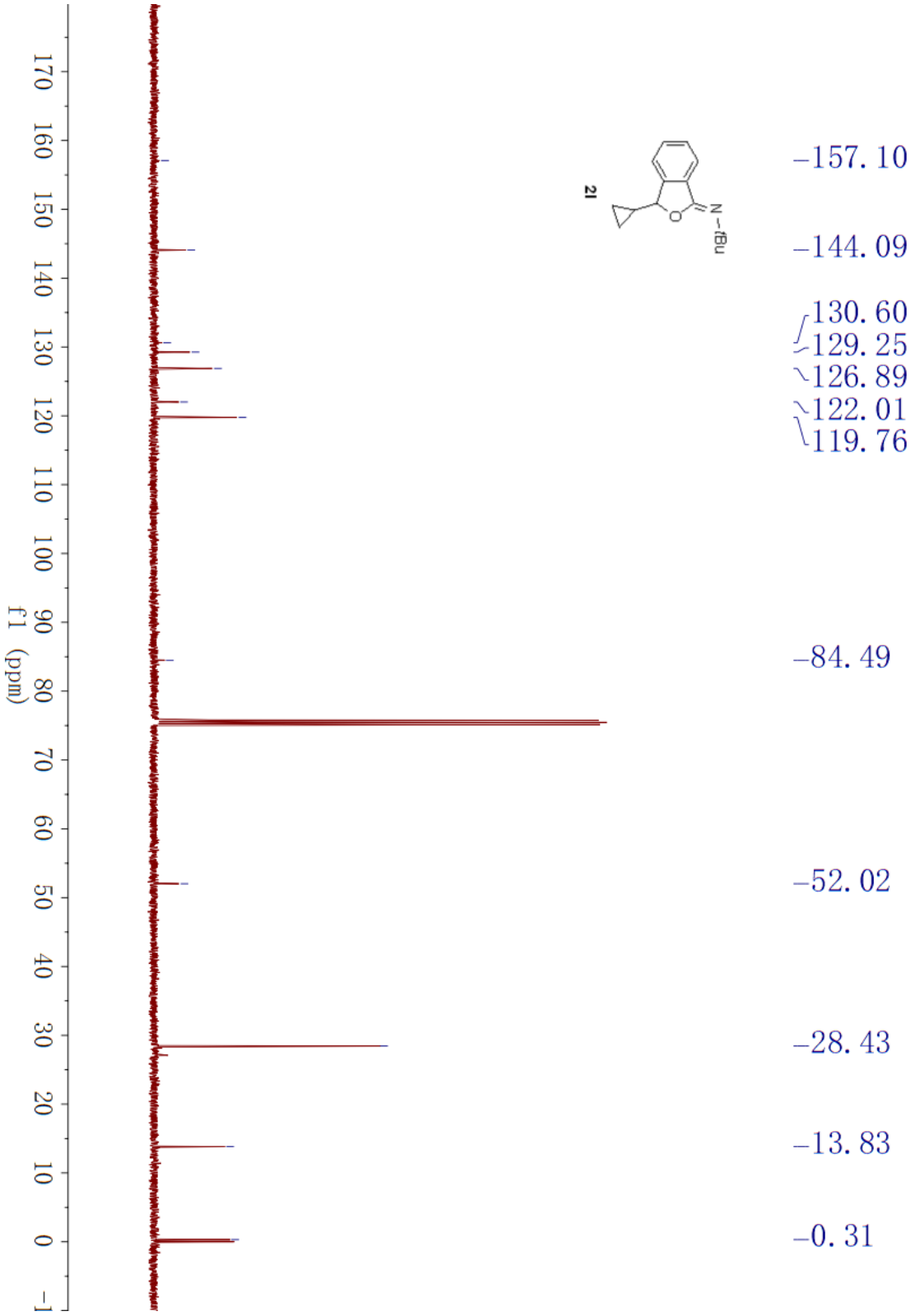

2j
N
tBu
O
f1 (ppm)
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
0.94
1.00
0.99
0.97
0.98
0.97
1.96
1.00
1.03
9.00
7.81
7.81
7.81
7.79
7.46
7.45
7.44
7.43
7.40
7.40
7.40
7.38
7.38
7.31
7.31
7.30
7.29
7.29
7.29
5.77
5.76
5.53
5.52
5.51
5.50
5.17
5.17
5.13
5.13
5.12
5.12
5.12
5.12
5.10
5.09
5.09
5.09
2.56
2.54
1.40

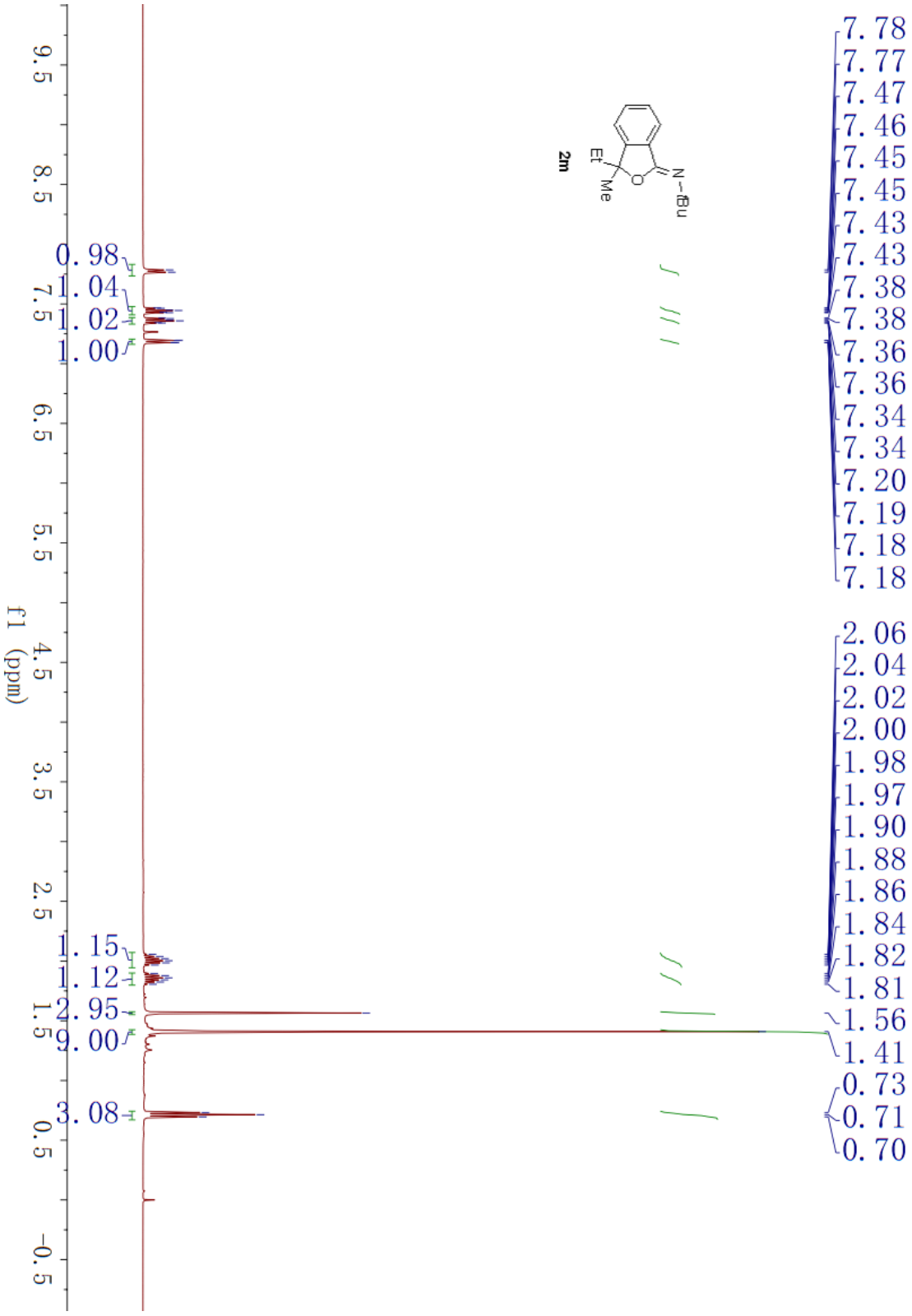

2j
N-tBu
O
-156.38
-145.15
132.38
132.30
130.83
128.44
123.66
121.11
118.80
-82.35
-53.59
-39.88
-30.00
f1 (ppm)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1

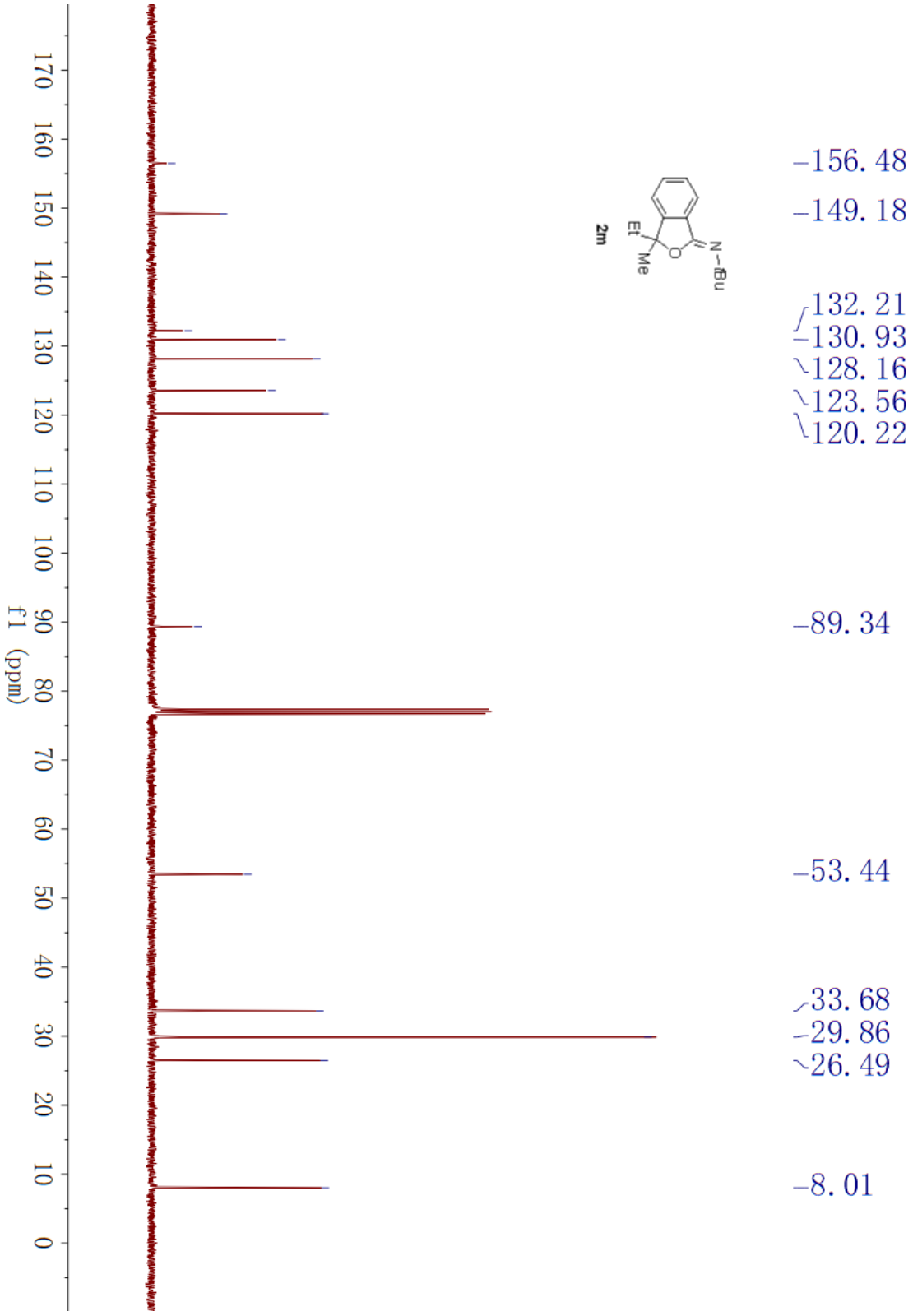

2k
Ph
O
N
tBu
f1 (ppm)
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
0.96
5.16
2.05
1.03
0.99
9.00
7.86
7.85
7.84
7.84
7.83
7.83
7.40
7.40
7.39
7.39
7.38
7.37
7.37
7.36
7.35
7.34
7.34
7.34
7.34
7.33
7.33
7.32
7.31
7.28
7.27
7.27
7.26
7.26
7.26
7.15
7.14
7.14
7.13
7.13
7.13
7.12
7.12
7.12
6.36
1.43

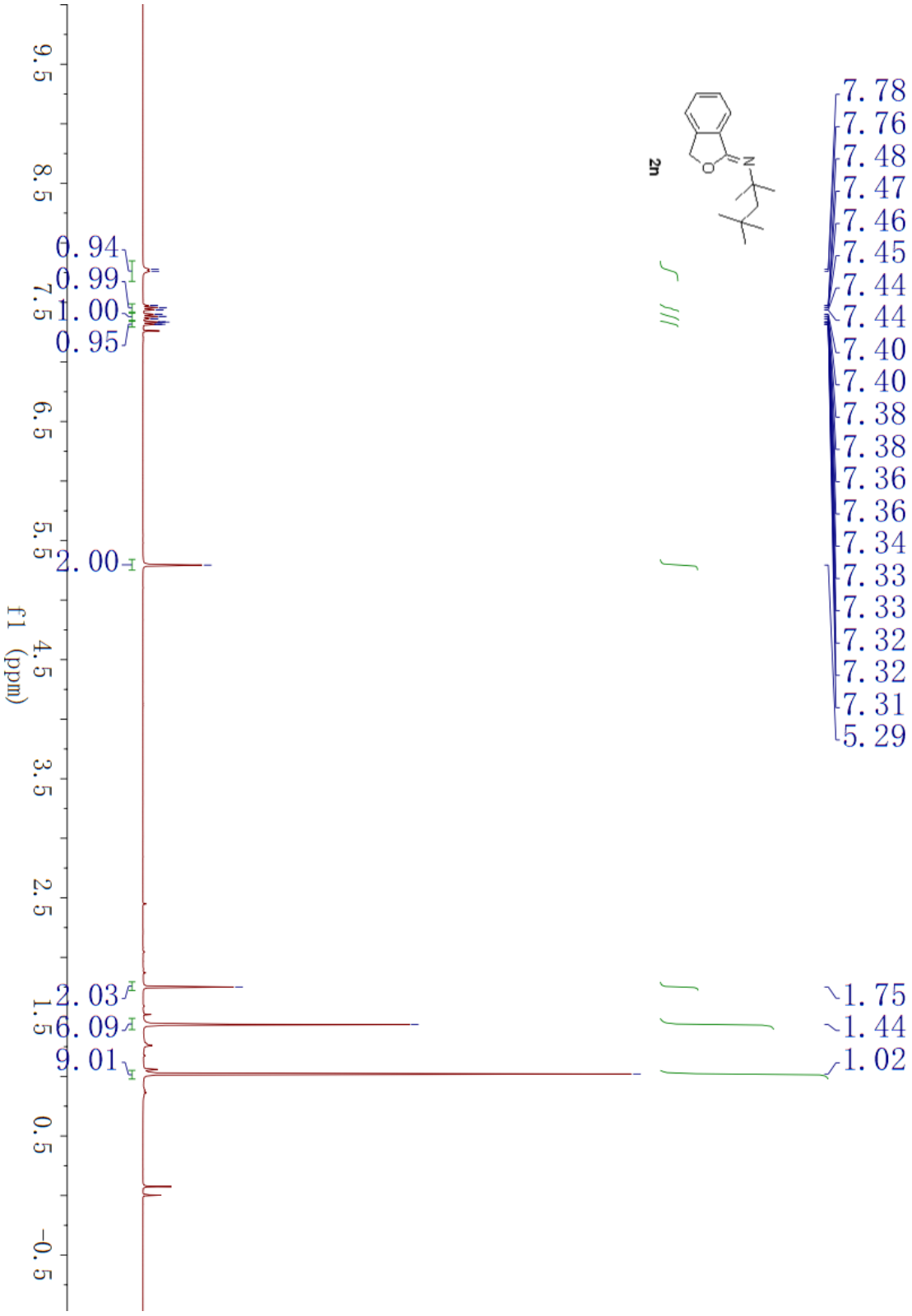

2k
Ph
O
N-tBu
156.12
145.89
139.29
131.46
131.18
128.83
128.61
128.55
126.46
123.63
121.97
84.87
53.75
30.13
f1 (ppm)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

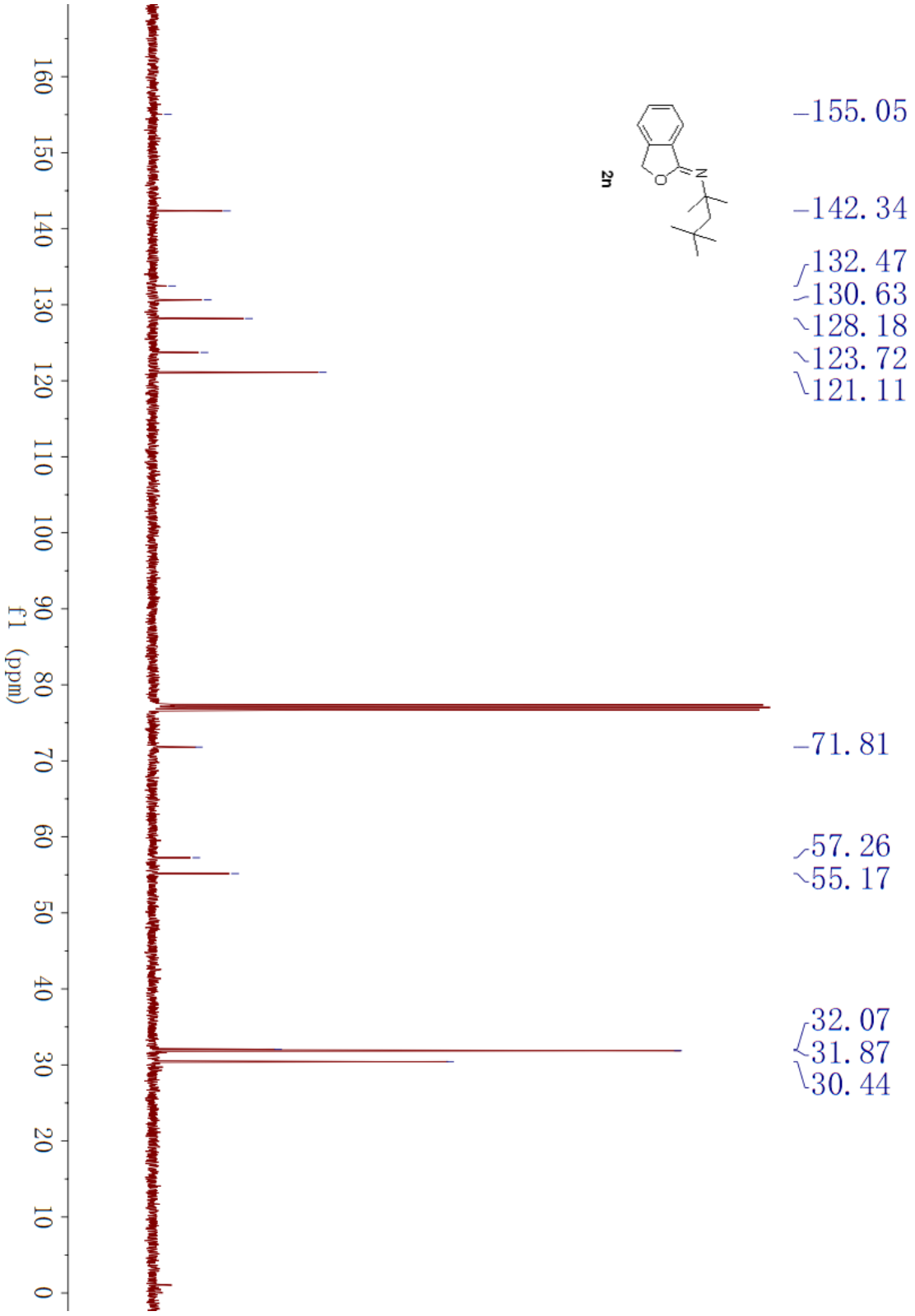

21
N–tBu
f1 (ppm)
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
−0.5
0.95
1.08
2.01
0.93
9.00
1.10
4.04
7.80
7.78
7.48
7.46
7.46
7.45
7.44
7.41
7.40
7.39
7.39
7.39
7.38
7.37
7.37
7.37
4.99
4.98
1.40
1.40
1.14
1.12
0.69
0.68
0.67
0.66
0.65
0.61
0.60
0.60
0.59
0.59
0.58
0.58
0.57
0.57
0.53
0.51
0.50
0.50

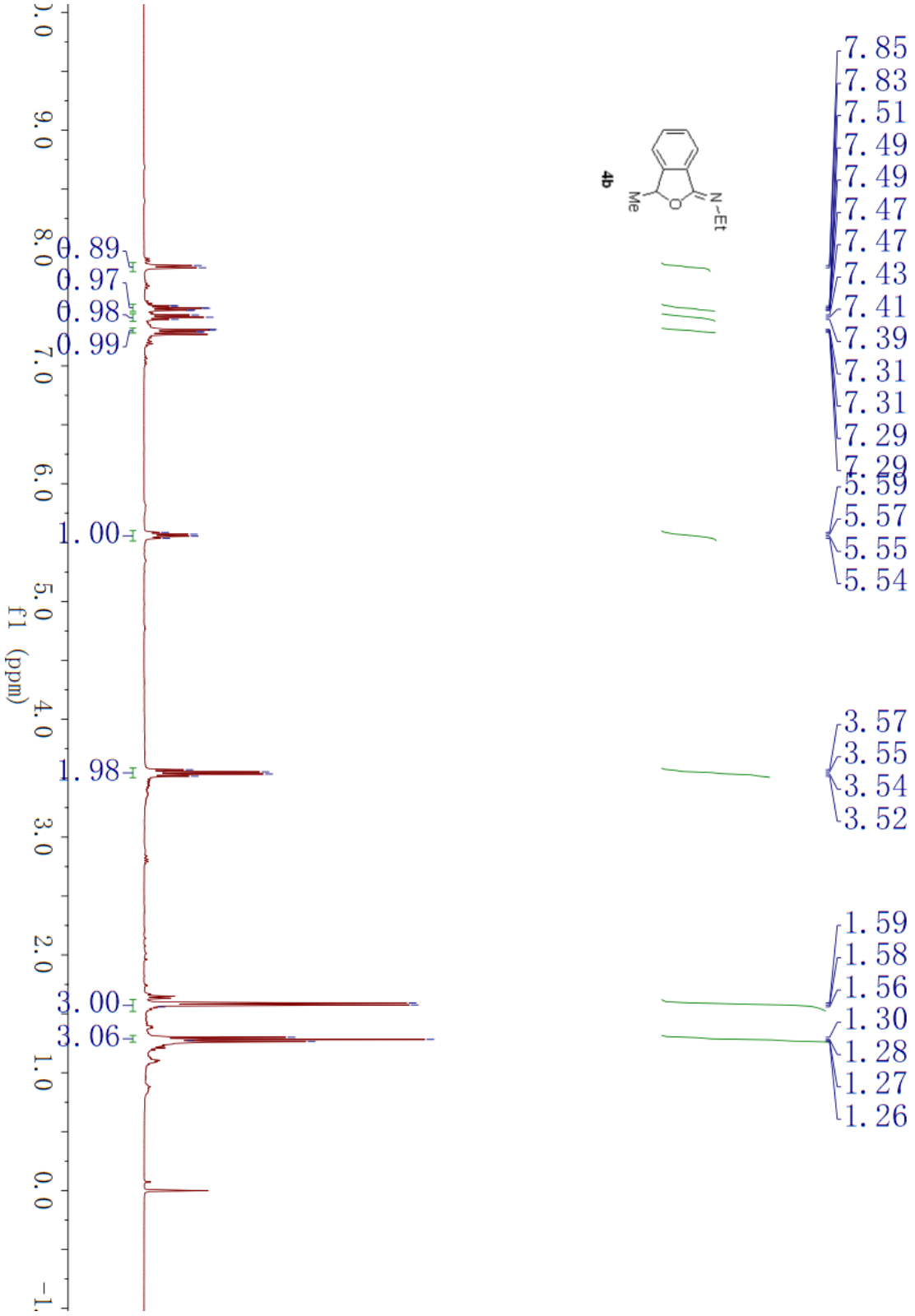

21
N-tBu
157.10
144.09
130.60
129.25
126.89
122.01
119.76
84.49
52.02
28.43
13.83
0.31
f1 (ppm)

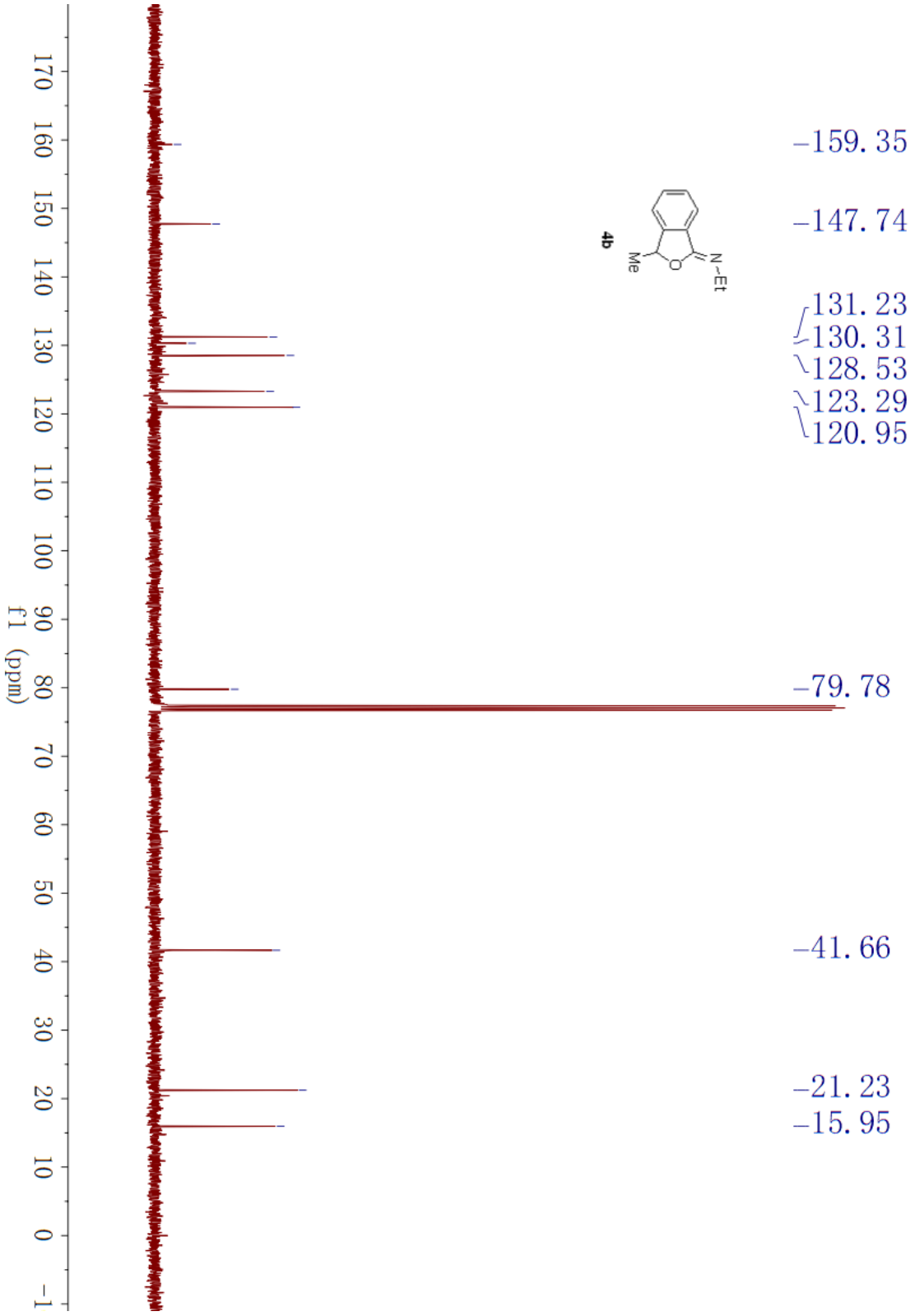

2m
Et
Me
N-tBu
f1 (ppm)
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
0.98
1.04
1.02
1.00
1.15
1.12
2.95
9.00
3.08
7.78
7.77
7.47
7.46
7.45
7.45
7.43
7.43
7.38
7.38
7.36
7.36
7.34
7.34
7.20
7.19
7.18
7.18
2.06
2.04
2.02
2.00
1.98
1.97
1.90
1.88
1.86
1.84
1.82
1.81
1.56
1.41
0.73
0.71
0.70

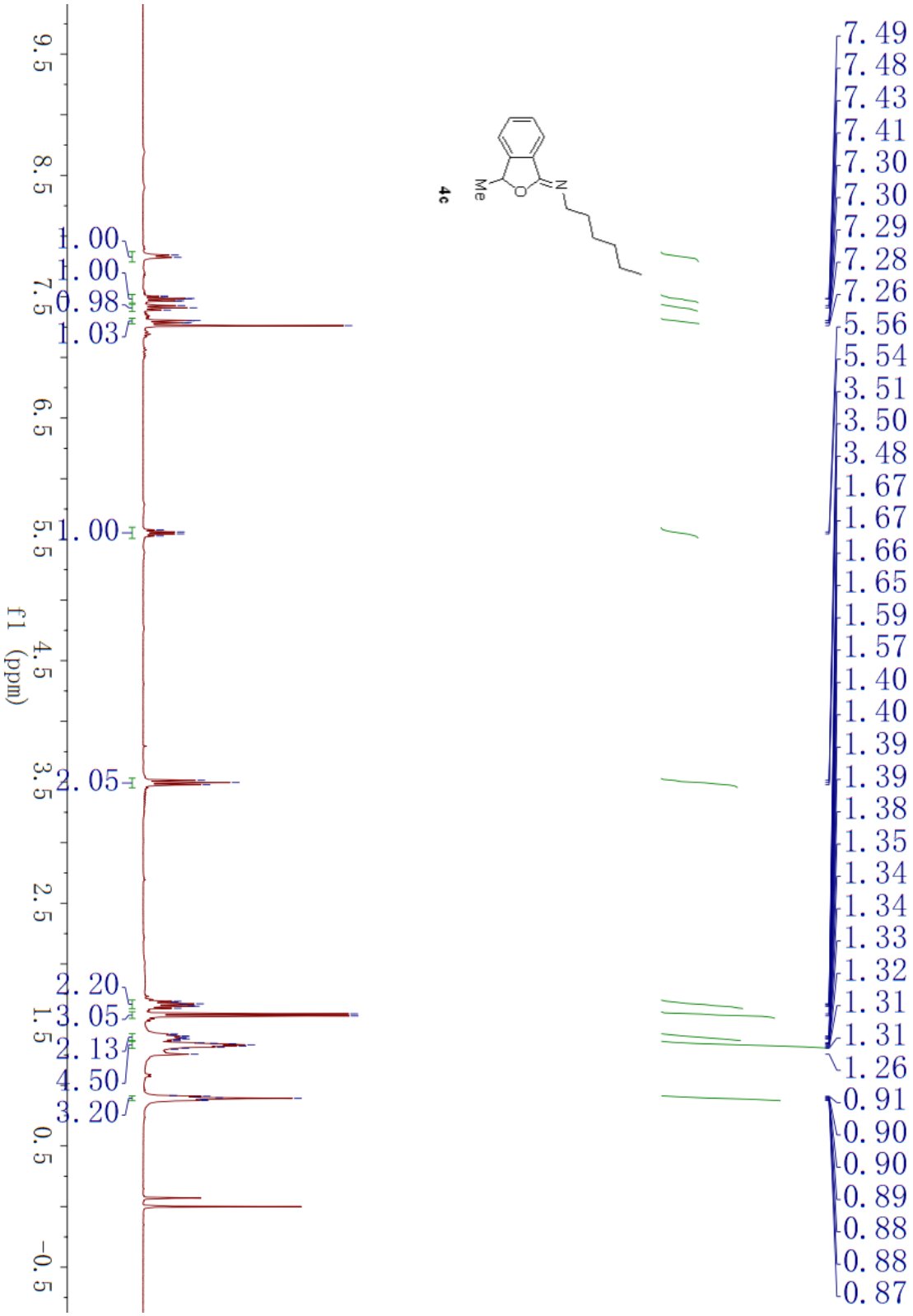

156.48
149.18
132.21
130.93
128.16
123.56
120.22
89.34
53.44
33.68
29.86
26.49
8.01
2m
Et
Me
N-tBu
f1 (ppm)

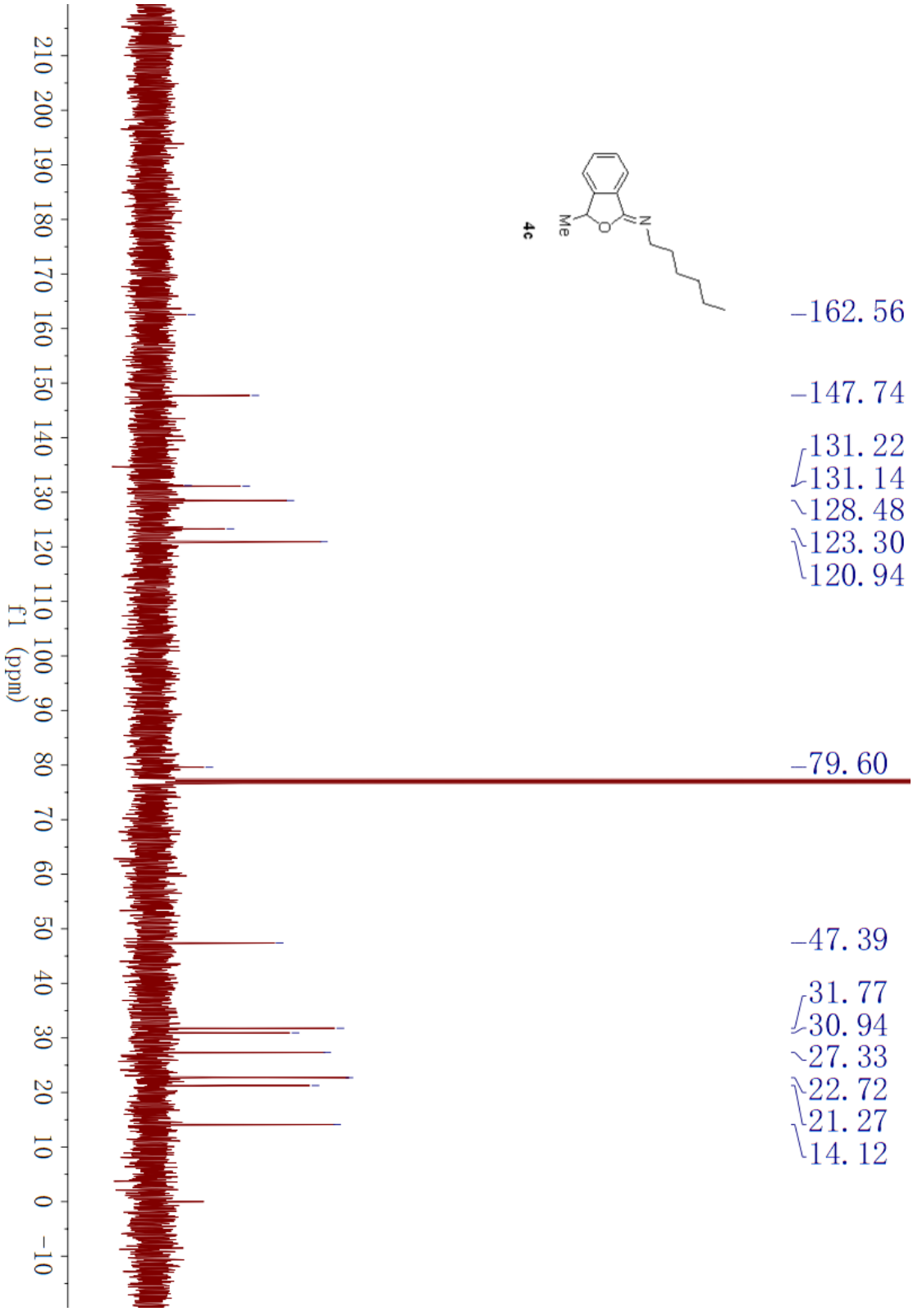

2n
7.78
7.76
7.48
7.47
7.46
7.45
7.44
7.44
7.40
7.40
7.38
7.38
7.36
7.36
7.34
7.33
7.33
7.32
7.32
7.31
5.29
0.94
0.99
1.00
0.95
2.00
2.03
6.09
9.01
1.75
1.44
1.02
f1 (ppm)

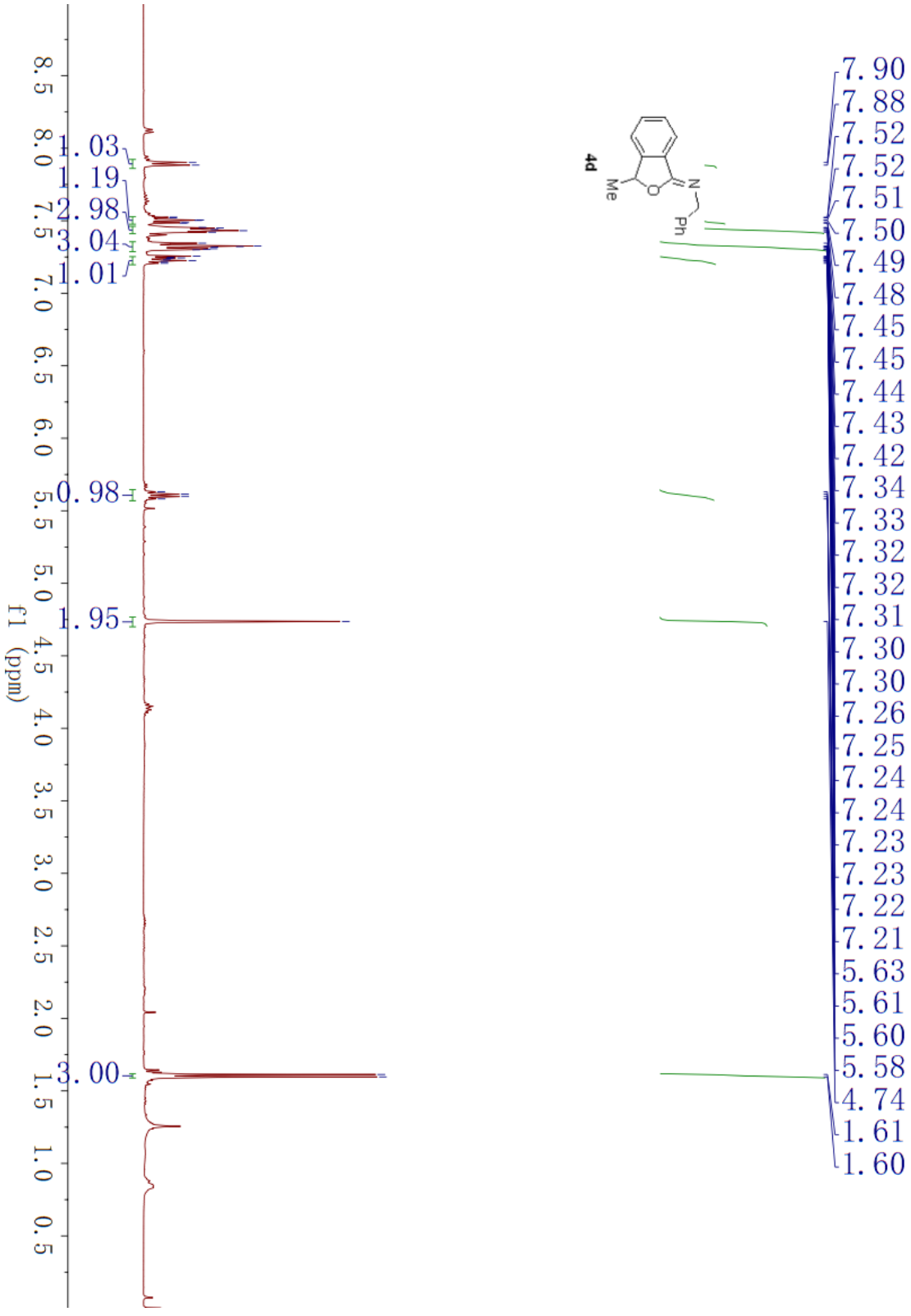

2n
155.05
142.34
132.47
130.63
128.18
123.72
121.11
71.81
57.26
55.17
32.07
31.87
30.44
f1 (ppm)

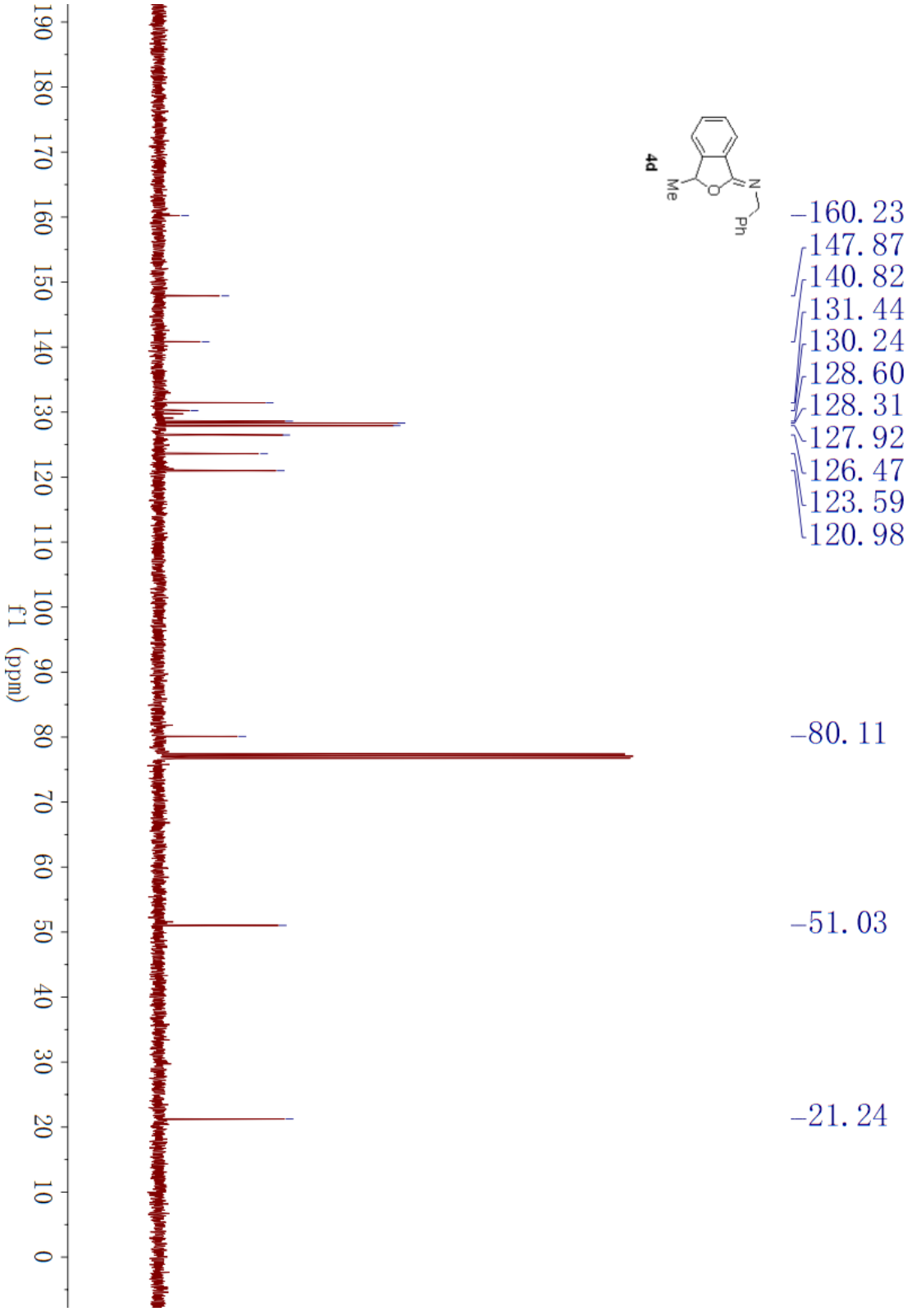

4b
Me
N-Et
7.85
7.83
7.51
7.49
7.49
7.47
7.47
7.43
7.41
7.39
7.31
7.31
7.29
7.29
5.59
5.57
5.55
5.54
3.57
3.55
3.54
3.52
1.59
1.58
1.56
1.30
1.28
1.27
1.26
0.89
0.97
0.98
0.99
1.00
1.98
3.00
3.06
f1 (ppm)

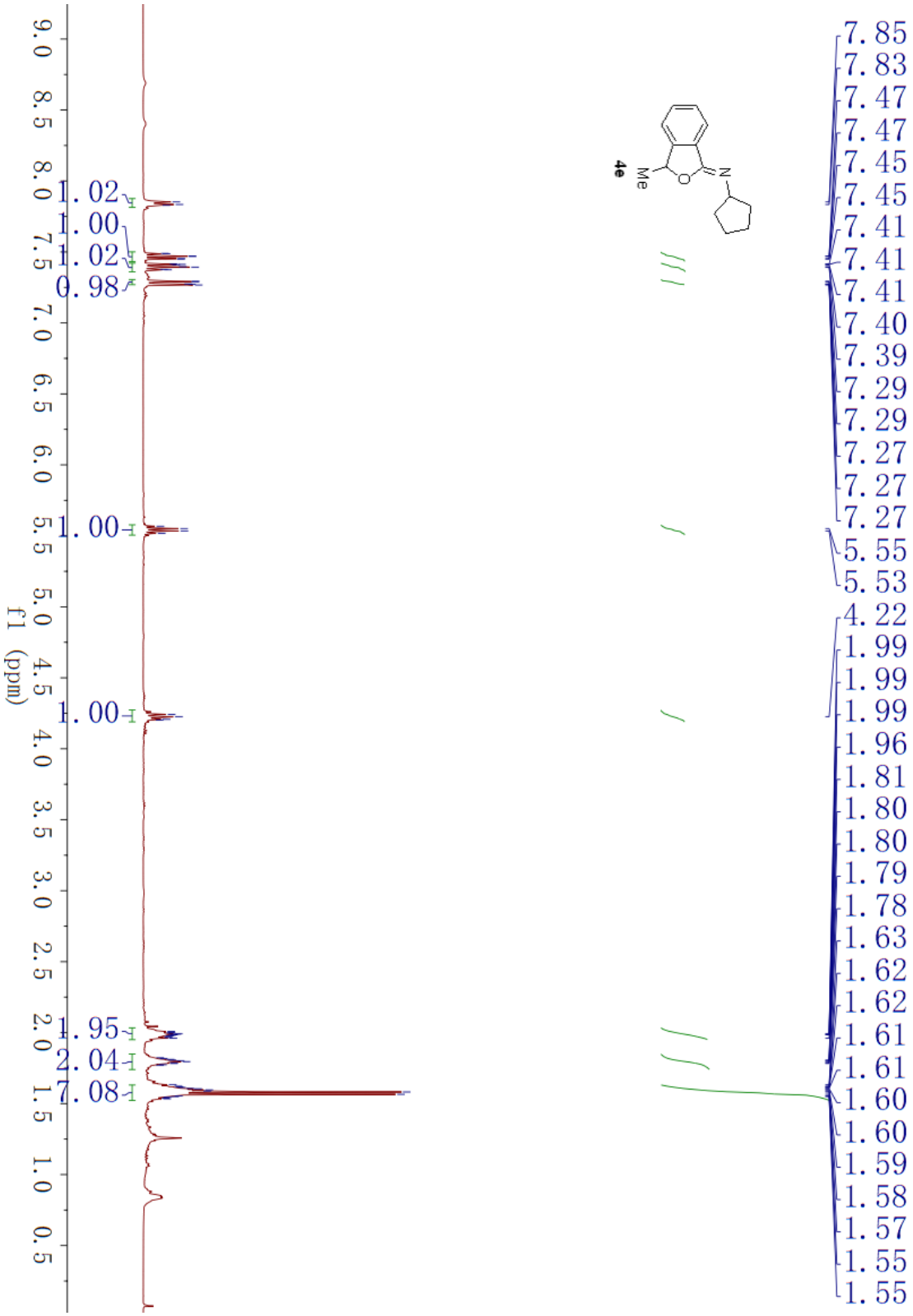

4b
Me
O
N
Et
159.35
147.74
131.23
130.31
128.53
123.29
120.95
79.78
41.66
21.23
15.95
f1 (ppm)

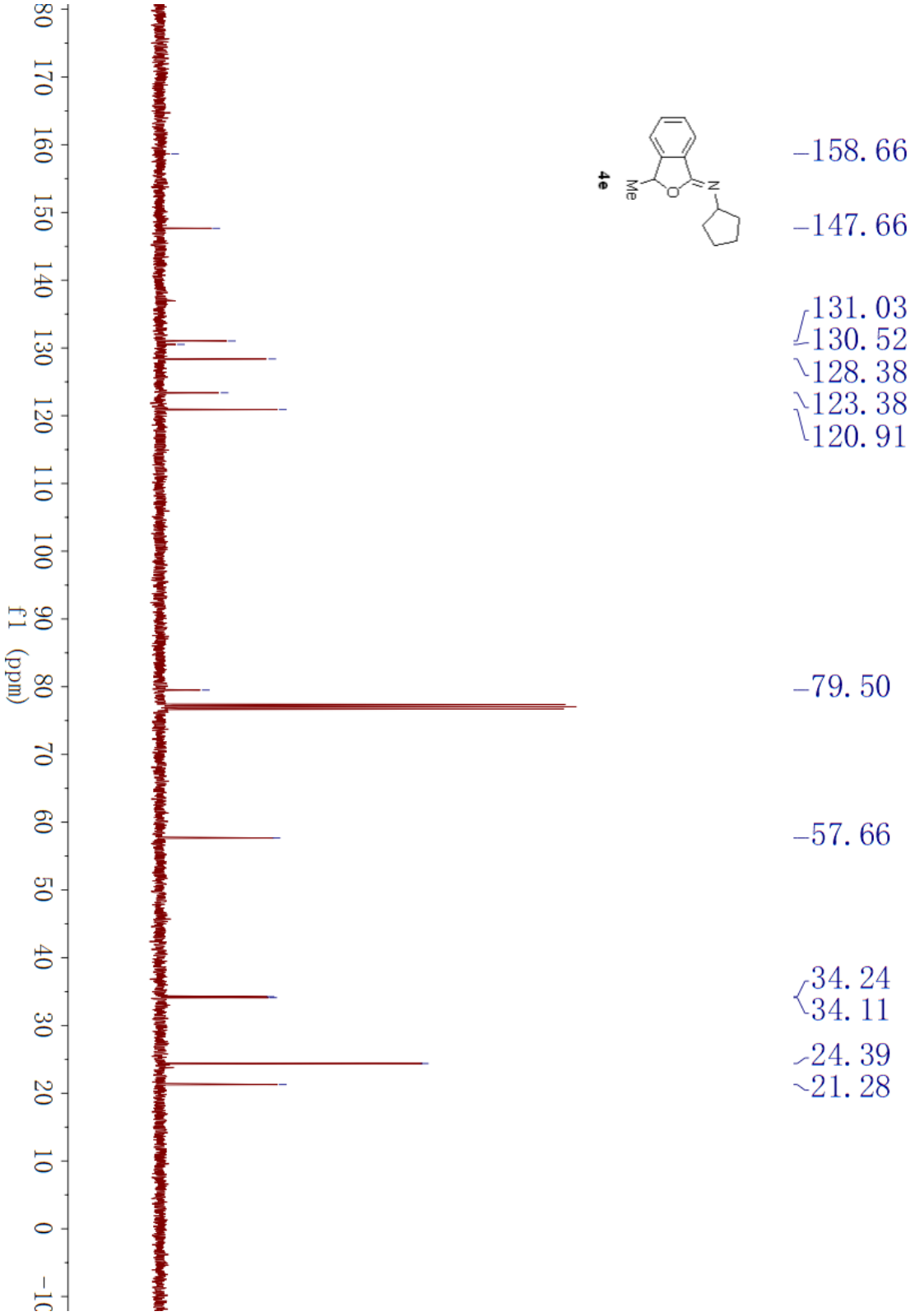

4c
Me
N
O
f1 (ppm)
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
1.00
1.00
0.98
1.03
1.00
2.05
2.20
3.05
2.13
4.50
3.20
7.49
7.48
7.43
7.41
7.30
7.30
7.29
7.28
7.26
5.56
5.54
3.51
3.50
3.48
1.67
1.67
1.66
1.65
1.59
1.57
1.40
1.40
1.39
1.39
1.38
1.35
1.34
1.34
1.33
1.32
1.31
1.31
1.26
0.91
0.90
0.90
0.89
0.88
0.88
0.87

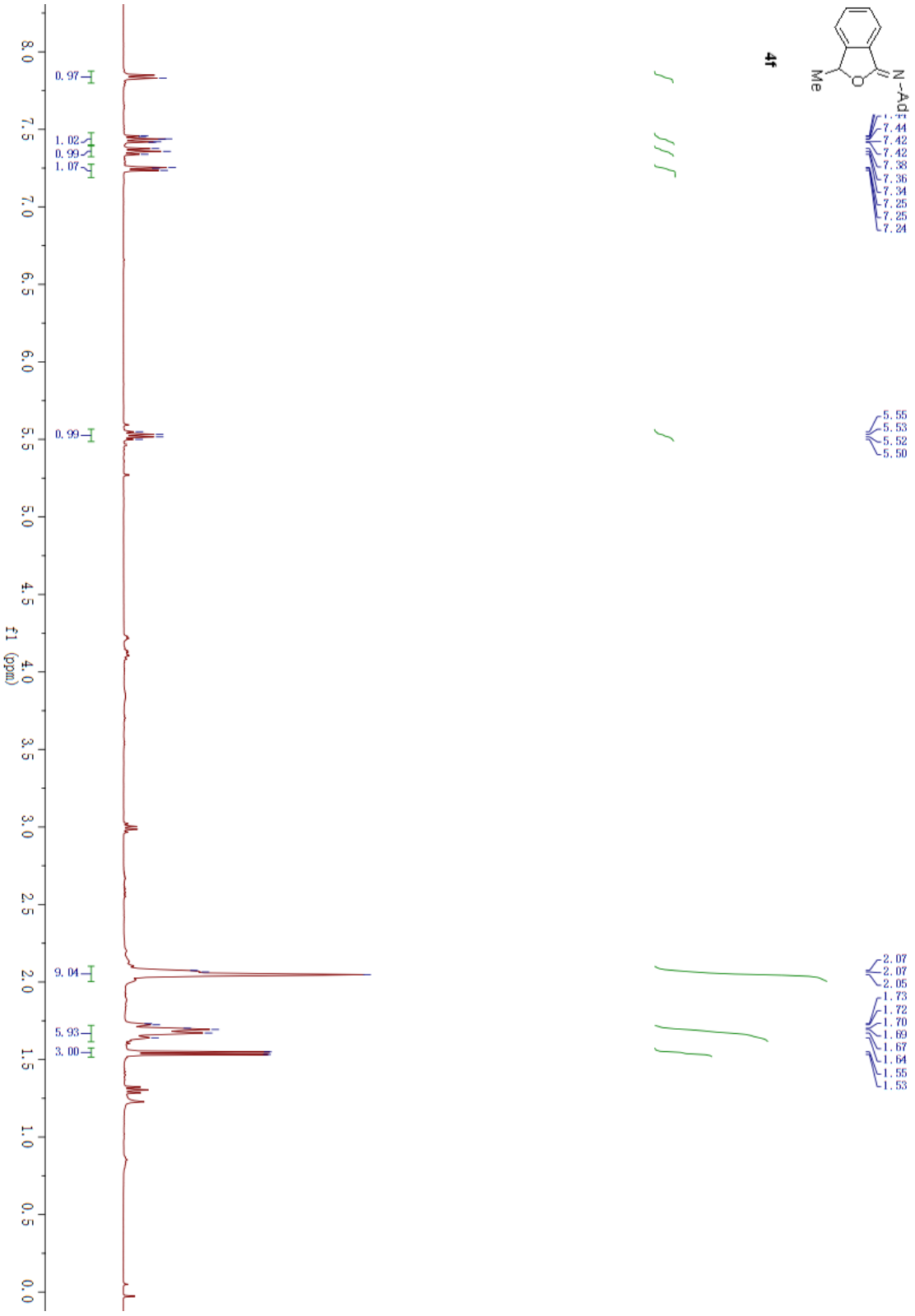

4c
Me
N
O
162.56
147.74
131.22
131.14
128.48
123.30
120.94
79.60
47.39
31.77
30.94
27.33
22.72
21.27
14.12
f1 (ppm)

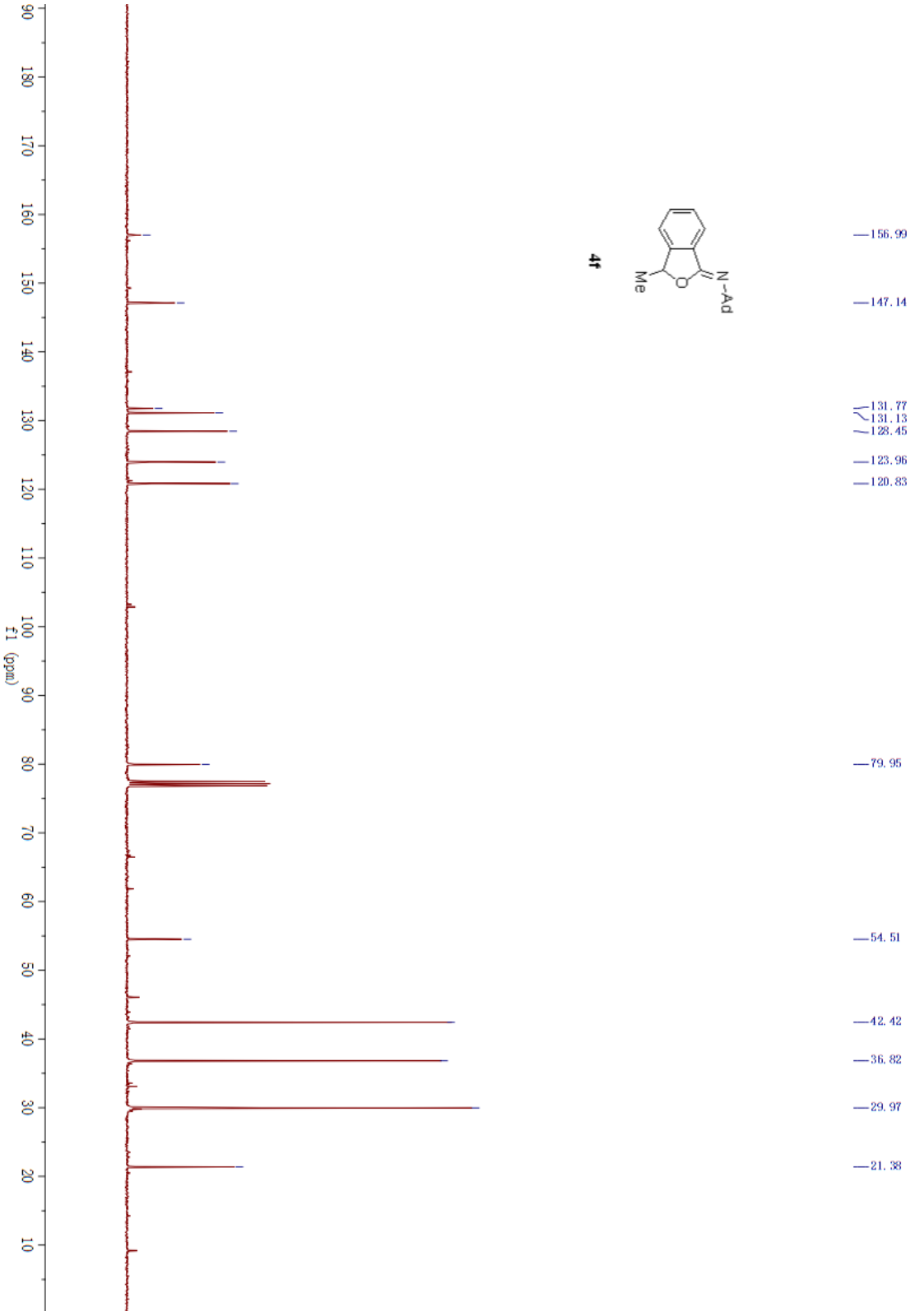

4d
Me
O
N
Ph
7.90
7.88
7.52
7.52
7.51
7.50
7.49
7.48
7.45
7.45
7.44
7.43
7.42
7.34
7.33
7.32
7.32
7.31
7.30
7.30
7.26
7.25
7.24
7.24
7.23
7.23
7.22
7.21
5.63
5.61
5.60
5.58
4.74
1.61
1.60
1.03
1.19
2.98
3.04
1.01
0.98
1.95
3.00
f1 (ppm)

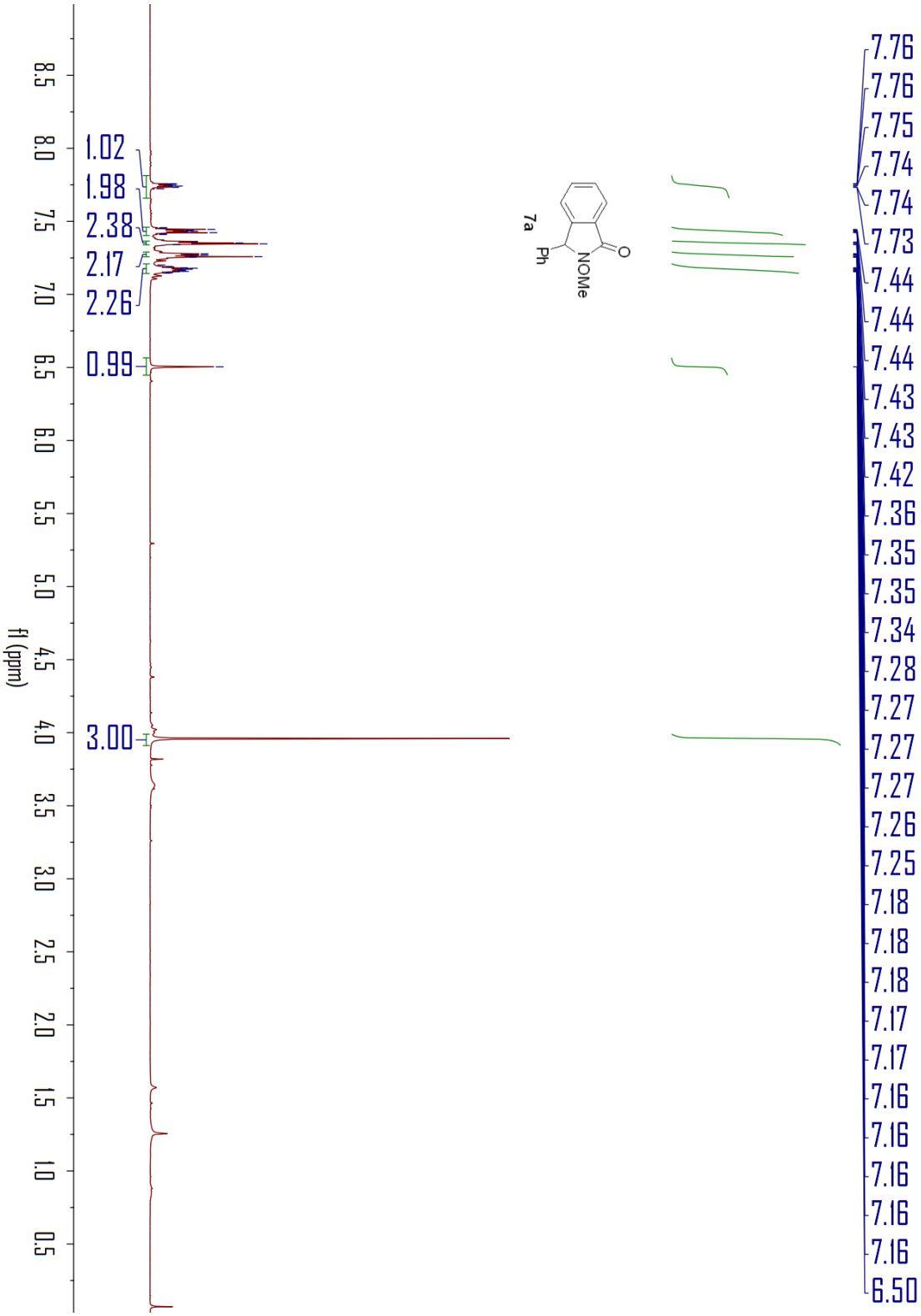

4t
Me
N
Ph
160.23
147.87
140.82
131.44
130.24
128.60
128.31
127.92
126.47
123.59
120.98
80.11
51.03
21.24
f1 (ppm)

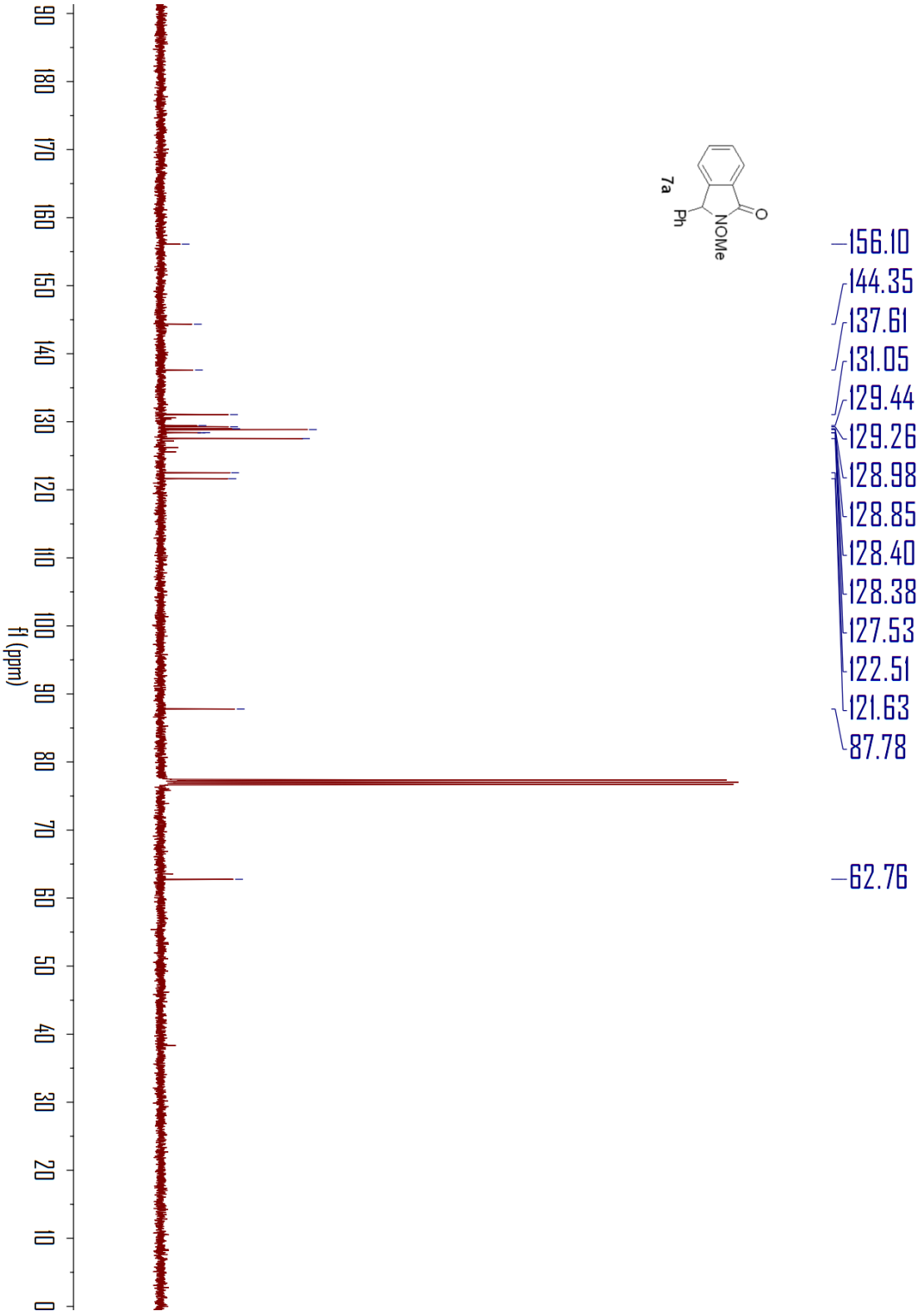

4e
Me
N
O
7.85
7.83
7.47
7.47
7.45
7.45
7.41
7.41
7.41
7.40
7.39
7.29
7.29
7.27
7.27
7.27
5.55
5.53
4.22
1.99
1.99
1.99
1.96
1.81
1.80
1.80
1.79
1.78
1.63
1.62
1.62
1.61
1.61
1.60
1.60
1.59
1.58
1.57
1.55
1.55
1.02
1.00
1.02
0.98
1.00
1.00
1.95
2.04
7.08
f1 (ppm)

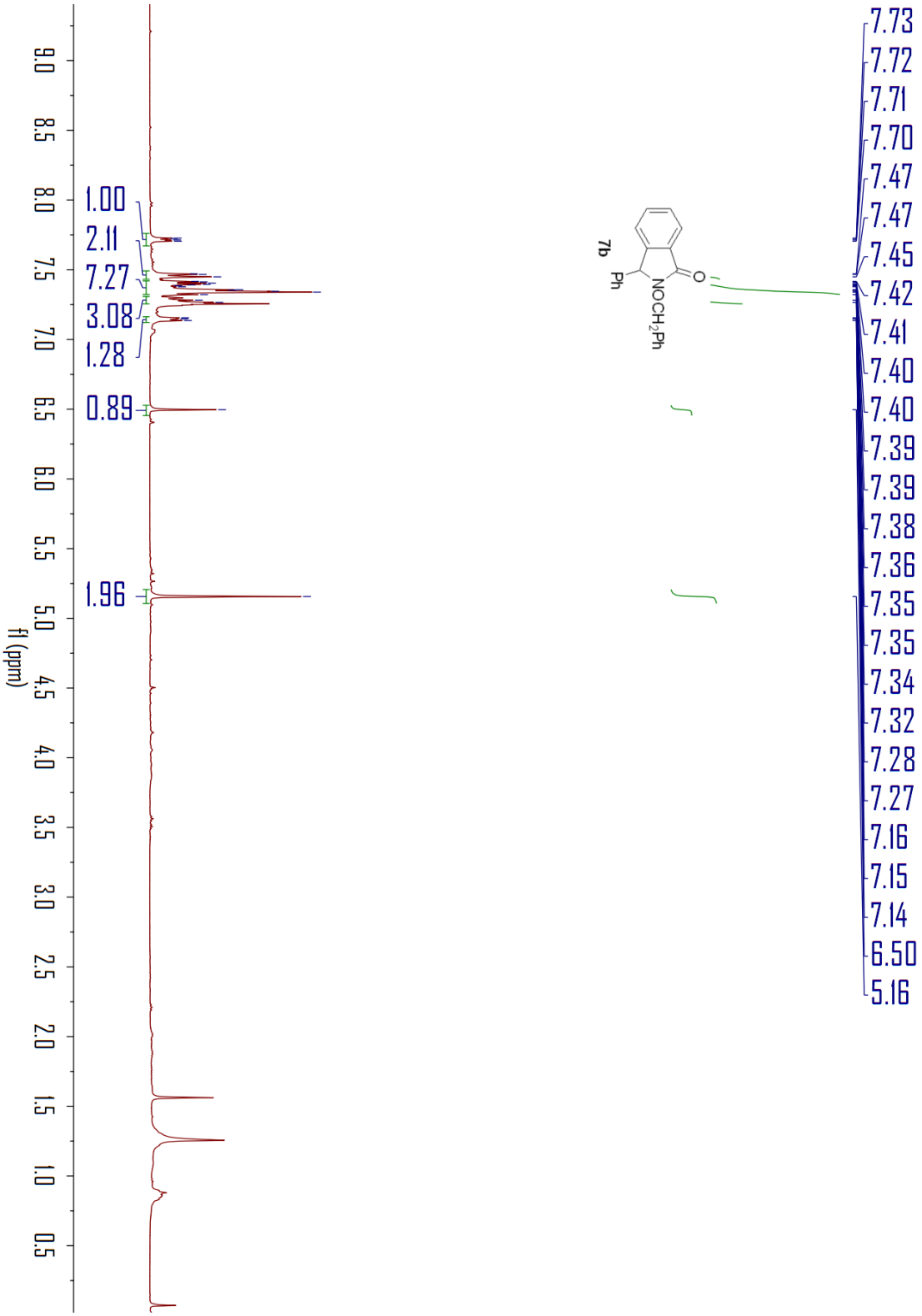

4e
Me
N
O
158.66
147.66
131.03
130.52
128.38
123.38
120.91
79.50
57.66
34.24
34.11
24.39
21.28
f1 (ppm)

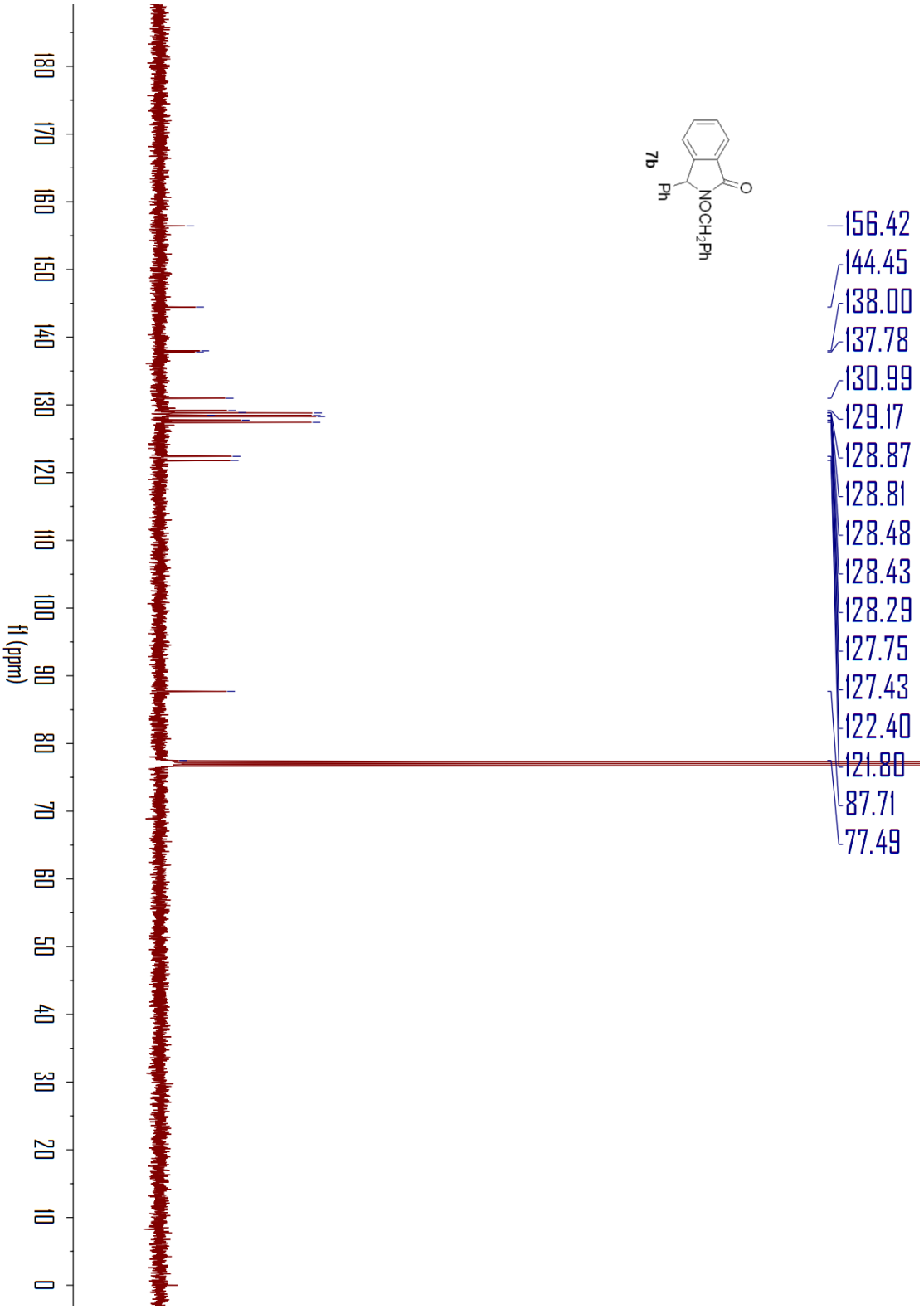

4f
N-Ad
Me
7.44
7.42
7.42
7.38
7.36
7.34
7.25
7.25
7.24
5.55
5.53
5.52
5.50
2.07
2.07
2.05
1.73
1.72
1.70
1.69
1.67
1.64
1.55
1.53
0.97
1.02
0.99
1.07
0.99
9.04
5.93
3.00
f1 (ppm)


4f
N-Ad
Me
156.99
147.14
131.77
131.13
128.45
123.96
120.83
79.95
54.51
42.42
36.82
29.97
21.38
f1 (ppm)


1.02
1.98
2.38
2.17
2.26
0.99
3.00
f1 (ppm)
7a
Ph
NOMe
O
7.76
7.76
7.75
7.74
7.74
7.73
7.44
7.44
7.44
7.43
7.43
7.42
7.36
7.35
7.35
7.34
7.28
7.27
7.27
7.27
7.26
7.25
7.18
7.18
7.18
7.17
7.17
7.16
7.16
7.16
7.16
7.16
6.50


7a
Ph
NOMe
O
156.10
144.35
137.61
131.05
129.44
129.26
128.98
128.85
128.40
128.38
127.53
122.51
121.63
87.78
62.76
f1 (ppm)


1.00
2.11
7.27
3.08
1.28
0.89
1.96
f1 (ppm)
7b
Ph
NOCH2Ph
O
7.73
7.72
7.71
7.70
7.47
7.47
7.45
7.42
7.41
7.40
7.40
7.39
7.39
7.38
7.36
7.35
7.35
7.34
7.32
7.28
7.27
7.16
7.15
7.14
6.50
5.16


7b
Ph
NOCH2Ph
O
156.42
144.45
138.00
137.78
130.99
129.17
128.87
128.81
128.48
128.43
128.29
127.75
127.43
122.40
121.80
87.71
77.49
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0