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Palladium-Catalyzed Oxidative Carbamoylation of Isoquinoline *N*-Oxides with Formylamides by Means of Dual C-H Oxidation

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Supporting Information

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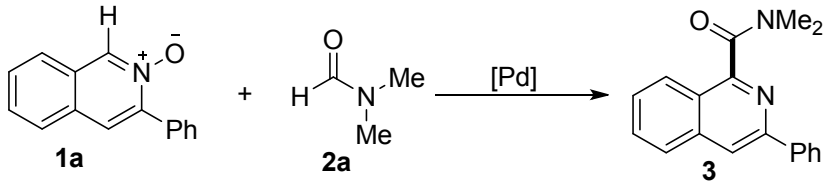
(A) Screening Optimal Conditions [a]

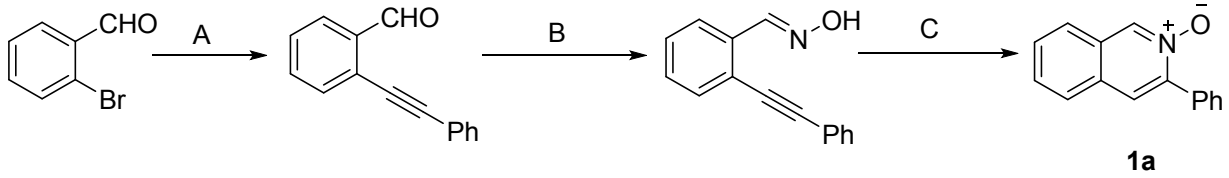


Entry	Catalyst	Additive	Base	Solvent	T(°C)	Yield [%]
1	$Pd(MeCN)_2Cl_2$	—	ZnO	—	120	4
2	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NBr	ZnO	—	120	12
3	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NCl	ZnO	—	120	11
4	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NF	ZnO	—	120	9
5	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	ZnO	—	120	52
6[b]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	—	—	120	62
7	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	—	120	67
8	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	MgO	—	120	35
9	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	CuO	—	120	29
10	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Ag_2O	—	120	40
11	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Fe_2O_3	—	120	47
12	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Al_2O_3	—	120	26
13	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Bu_3N	—	120	37
14	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	LiOAc	—	120	27
15	$PdCl_2$	*n*-Bu_4NOAc	Yb_2O_3	—	120	30
16	$Pd(OAc)_2$	*n*-Bu_4NOAc	Yb_2O_3	—	120	5
17	$Pd(PPh_3)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	—	120	7
18	$Cu(OAc)_2$	*n*-Bu_4NOAc	Yb_2O_3	—	120	nr
19	CuI	*n*-Bu_4NOAc	Yb_2O_3	—	120	nr
20	AgOAc	*n*-Bu_4NOAc	Yb_2O_3	—	120	nr
21[c]	—	*n*-Bu_4NOAc	Yb_2O_3	—	120	0
22[d]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	—	120	trace
22[e]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	—	120	31
23[f]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	—	120	47
24[g]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	DMA	120	56
25[g]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	Toluene	120	70
26[h]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	Toluene	120	55
27[g]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	MeCN	120	44
28[g]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	DMSO	120	44
29[g]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	DCE	120	36
30[g]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	NMP	120	42
31[g]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	THF	120	37
32[g]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	AcOH	120	36
33[g]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	Toluene	130	68
34[g]	$Pd(MeCN)_2Cl_2$	*n*-Bu_4NOAc	Yb_2O_3	Toluene	110	61

[a] Reaction conditions: **1a** (0.5 mmol), DMF (**2a**) (75 equiv), [Pd] (10 mol%), additive (2 equiv) and base (2 equiv) at 120 °C for 24 h under air atmosphere, isolated yields. [b] For 48 h. [c] A reductive product, 3-phenylisoquinoline (**4**), was isolated in 60% yield. [d] Under argon atmosphere. [e] Under O_2 (1 atm). Some unidentified products were observed by GC-MS analysis. [f] DMF (**2a**) (10 equiv) was added. [g] DMF (**2a**) (75 equiv) in solvent (1 mL). [h] DMF (**2a**) (50 equiv) in solvent (1 mL).

(B) Typical Experimental Procedure

(a) Typical Experimental Procedure for the Synthesis of Isoquinoline *N*-oxides Derivatives (1)[1]



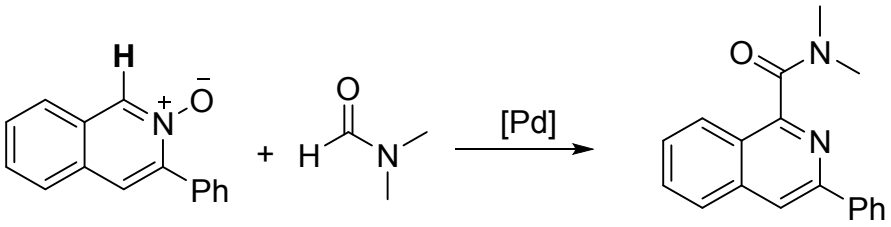
1a

Procedure A: 2-bromobenzaldehyde (0.5 mmol), acetylene (0.7 mmol), $PdCl_2(PPh_3)_2$ (2 mol%), CuI (1 mol%), Et_3N (3 mL), at 50 ^oC for 12 h under N_2 atmosphere.

Procedure B: 2-(phenylethynyl)benzaldehyde (0.5 mmol), $NH_2OH{\cdot}HCl$ (1.5 equiv), MeCN (2 mL), at room temperature for 10-12 h.

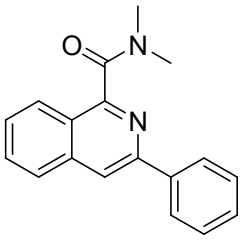
Procedure C: 2-(phenylethynyl)benzaldehyde oxime (0.5 mmol), $ZnCl_2$ (10-20 mol%), dioxane (2 mL), at 110 ^oC for 12 h afforded substrates **1a** in 80% yields. The product was identified by ^1H-NMR, ^{13}C NMR and GC-MS spectra.

(b) Typical Experimental Procedure for the Synthesis of Isoquinoline-1-carboxamides



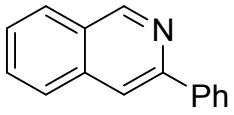
To a Schlenk tube were added isoquinoline *N*-oxides **1** (0.5 mmol) and formylamides **2** (75 equiv), $Pd(MeCN)_2Cl_2$ (10 mol %), *n*-Bu_4NOAc (2 equiv), Yb_2O_3 (2 equiv) and toluene (1 mL). Then the tube was charged with air, and was stirred at room temperature for the indicated time (Tables 1 and 2) until complete consumption of starting material as monitored by TLC and GC-MS analysis. After the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1) to afford the desired isoquinoline-1-carboxamides.

(C) Analytical data for 3-27



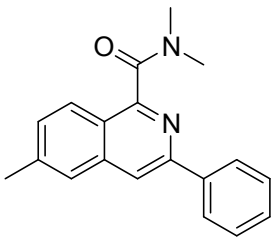
***N*,*N*-Dimethyl-3-phenylisoquinoline-1-carboxamide (3):**

Yellow solid, mp 153.5-155.1 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 8.5 Hz, 2H), 7.99 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.62-7.58 (m, 1H), 7.51-7.46 (m, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 3.21 (s, 3H), 2.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.3, 155.4, 150.0, 139.0, 137.4, 130.8, 128.8, 128.7, 127.7, 127.4, 127.1, 126.0, 124.5, 117.0, 38.5, 35.0; IR (neat, cm^{-1}): 1634, 1590, 1568, 1414, 1129; LRMS (EI 70 ev) m/z (%): 276 (M^+, 31), 205 (100), 219 (72), 204 (60), 176 (12); HRMS (ESI) calcd for $C_{18}H_{17}N_2O$ $(M+H)^+$ 277.1335, found 277.1345.



3-Phenylisoquinoline (4):[2]

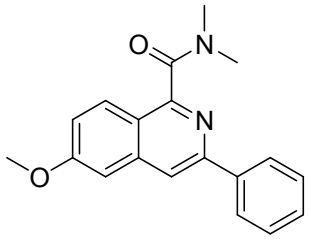
Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.27 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 8.01 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 152.4, 151.3, 139.6, 136.7, 130.5, 128.8, 128.5, 127.8, 127.6, 127.1 (2C), 126.9, 116.5; LRMS (EI 70 ev) *m*/z (%): 205 (M^+, 100), 204 (60), 102 (20), 176 (13), 88 (8).



***N*,*N*,6-Trimethyl-3-phenylisoquinoline-1-carboxamide (5):**

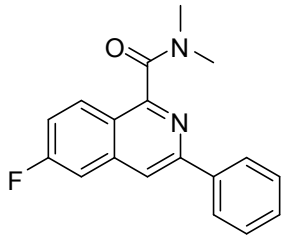
Yellow solid, mp 167.7-169.3 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 7.5 Hz, 2H), 7.90 (s, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.57 (s, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.33-7.30 (m, 2H), 3.20

(s, 3H), 2.83 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5, 155.0, 150.1, 141.3, 139.1, 137.8, 130.1, 128.7, 128.6, 127.1, 126.3, 125.8, 123.0, 116.6, 38.5, 35.0, 22.0; IR (neat, cm^{-1}): 1640, 1455, 1402, 1133, 769; LRMS (EI 70 ev) m/z (%): 290 (M^+, 23), 219 (100), 204 (45), 218 (31), 233 (31); HRMS (ESI) calcd for $C_{19}H_{19}N_2O$ $(M+H)^+$ 291.1492, found 291.1505.



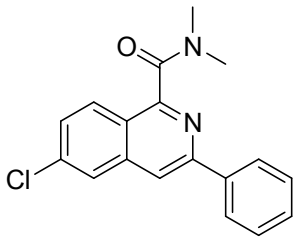
6-Methoxy-*N*,*N*-dimethyl-3-phenylisoquinoline-1-carboxamide (6):

Brown solid, mp 157.7-159.3 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 7.5 Hz, 2H), 7.92 (s, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.31-7.23 (m, 3H), 3.84 (s, 3H), 3.21 (s, 3H), 2.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.6, 158.9, 153.3, 148.1, 139.1, 133.3, 129.0, 128.7, 128.4, 126.8, 125.9, 124.2, 117.1, 103.4, 55.6, 38.7, 35.1; IR (neat, cm^{-1}): 1633, 1498, 1415, 1143, 1029; LRMS (EI 70 ev) m/z (%): 306 (M^+, 31), 235 (100), 249 (29), 191 (26), 220 (23); HRMS (ESI) calcd for $C_{19}H_{19}N_2O_2$ $(M+H)^+$ 307.1441, found 307.1450.



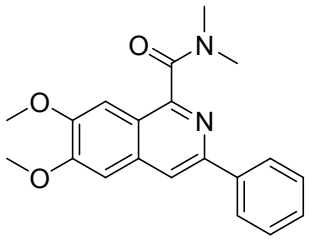
6-Fluoro-*N*,*N*-dimethyl-3-phenylisoquinoline-1-carboxamide (7):

Dark yellow solid, mp 171.5-172.8 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.03-8.00 (m, 3H), 7.95 (s, 1H), 7.44-7.40 (m, 3H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.28-7.24 (m, 1H), 3.22 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.0, 164.5, 162.5, 155.2, 150.8, 139.2, 138.6, 129.2 (d, *J* = 45.5 Hz, 1C), 128.8, 127.1, 126.0, 121.8, 118.2 (d, *J* = 21.3 Hz, 1C), 116.5, 110.6 (d, *J* = 21.3 Hz, 1C), 38.6, 35.0; IR (neat, cm^{-1}): 1627, 1418, 1263, 1124, 895; LRMS (EI 70 ev) m/z (%): 294 (M^+, 21), 223 (100), 222 (59), 237 (27), 77 (7); HRMS (ESI) calcd for $C_{18}H_{16}FN_2O$ $(M+H)^+$ 295.1241, found 295.1249.



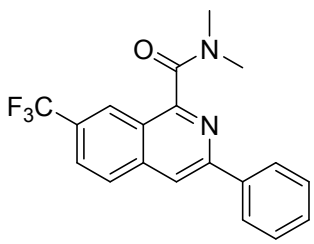
6-Chloro-*N*,*N*-dimethyl-3-phenylisoquinoline-1-carboxamide (8):

Brown solid, mp 164.6-166.6 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 7.5 Hz, 2H), 7.98 (s, 2H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.57-7.55 (m, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 3.23 (s, 3H), 2.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.7, 154.3, 150.2, 138.5, 135.8, 133.5, 132.0, 129.4, 129.0 (2C), 128.8, 127.0, 125.1, 116.7, 38.6, 35.1; IR (neat, cm^{-1}): 1635, 1561, 1401, 1145, 1019; LRMS (EI 70 ev) m/z (%): 312 (M^++2, 11), 310 (M^+, 33), 239 (100), 204 (86), 241 (32); HRMS (ESI) calcd for $C_{18}H_{16}ClN_2O$ $(M+H)^+$ 311.0946, found 311.0956.



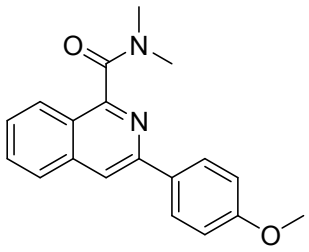
6,7-Dimethoxy-*N*,*N*-dimethyl-3-phenylisoquinoline-1-carboxamide (9):

Dark yellow solid, mp 197.7-199.2 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 7.0 Hz, 2H), 7.88 (s, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.33-7.30 (m, 1H), 7.26 (s, 1H), 7.07 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.22 (s, 3H), 2.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 153.4, 152.3, 150.8, 148.8, 139.4, 134.6, 128.7, 128.4, 126.8, 120.8, 116.2, 105.3, 104.0, 56.2, 56.1, 38.8, 35.2; IR (neat, cm^{-1}): 1637, 1469, 1264, 1138, 1027; LRMS (EI 70 ev) m/z (%): 336 (M^+, 23), 235 (100), 279 (35), 249 (22), 204 (20); HRMS (ESI) calcd for $C_{20}H_{21}N_2O_3$ $(M+H)^+$ 337.1547, found 337.1536.



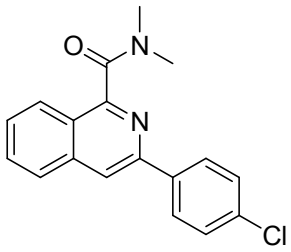
***N*,*N*-Dimethyl-3-phenyl-7-(trifluoromethyl)isoquinoline-1-carboxamide (10):**

Yellow solid, mp 127.8-129.1 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.37 (s, 1H), 8.16 (s, 1H), 8.15 (s, 2H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.54-7.40 (m, 4H), 3.33 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.4, 156.1, 151.8, 138.8, 138.2, 129.4, 128.9, 128.7, 127.2, 126.4 (d, *J* = 3.0 Hz, 1C), 126.2, 124.4, 124.2 (m, 1C), 124.1, 123.6, 116.6, 38.7, 35.2; IR (neat, cm^{-1}): 1634, 1329, 1300, 1168, 1071; LRMS (EI 70 ev) m/z (%): 344 (M^+, 36), 273 (100), 204 (57), 207 (43), 287 (37); HRMS (ESI) calcd for $C_{19}H_{16}F_3N_2O$ $(M+H)^+$ 345.1209, found: 345.1216.



3-(4-Methoxyphenyl)-*N*,*N*-dimethylisoquinoline-1-carboxamide (11):

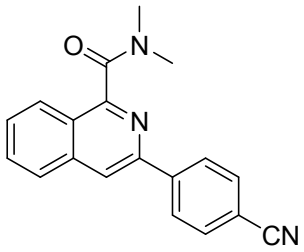
Dark yellow solid, mp 172.1-174.1 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 8.5 Hz, 2H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 3.22 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.4, 160.3, 155.3, 149.8, 137.5, 131.7, 130.7, 128.3, 127.3, 127.2, 126.0, 124.2, 115.9, 114.2, 55.4, 38.5, 35.0; IR (neat, cm^{-1}): 1634, 1514, 1249, 1175, 733; LRMS (EI 70 ev) m/z (%): 306 (M^+, 34), 235 (100), 249 (35), 191 (29), 204 (27); HRMS (ESI) calcd for $C_{19}H_{19}N_2O_2$ $(M+H)^+$ 307.1441, found 307.1451.



3-(4-Chlorophenyl)-*N*,*N*-dimethylisoquinoline-1-carboxamide (12):

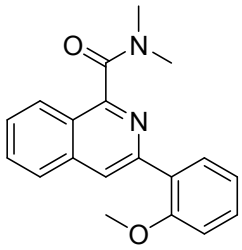
Yellow solid, mp 169.8-171.1 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.03-7.93 (m, 4H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 3.22 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.9, 162.7, 155.8, 149.7, 138.9, 137.3, 130.7, 128.7, 128.6, 127.6, 127.3, 126.9, 124.5, 116.7, 38.4, 35.7; IR (neat, cm^{-1}): 1635, 1527, 1431, 1151, 1021;

LRMS (EI 70 ev) m/z (%): 312 (M^++2, 8), 310 (M^+, 26), 239 (100), 204 (82), 203 (40); HRMS (ESI) calcd for $C_{18}H_{16}ClN_2O$ $(M+H)^+$ 311.0946, found 311.0953.



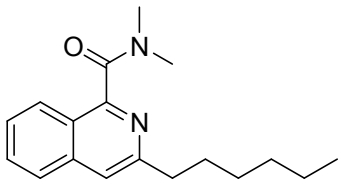
3-(4-Cyanophenyl)-*N*,*N*-dimethylisoquinoline-1-carboxamide (13):

Yellow solid, mp 175.8-177.1 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.20 (d, *J* = 8.5 Hz, 2H), 8.08 (s, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.72-7.69 (m, 3H), 7.58 (t, *J* = 8.0 Hz, 1H), 3.25 (s, 3H), 2.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.1, 170.0, 155.9, 147.7, 143.1, 137.2, 132.6, 131.3, 128.7, 127.7, 127.5, 126.6, 126.1, 118.1, 112.1, 38.5, 35.0; IR (neat, cm^{-1}): 2227, 1671, 1533, 1154, 1028; LRMS (EI 70 ev) m/z (%): 301 (M^+, 45), 239 (100), 253 (55), 191 (31), 241 (22); HRMS (ESI) calcd for $C_{19}H_{16}N_3O$ $(M+H)^+$ 302.1288, found 302.1297.



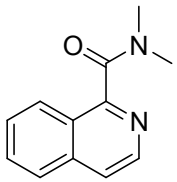
3-(2-Methoxyphenyl)-*N*,*N*-dimethylisoquinoline-1-carboxamide (14):

Yellow solid, mp 147.3-149.1 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.16 (s, 1H), 7.96 (d, *J* = 8.5, 1H), 7.84 (d, *J* = 7.5, 1H), 7.81 (d, *J* = 8.5, 1H), 7.62 (t, *J* = 7.5, 1H), 7.50 (t, *J* = 7.0, 1H), 7.30 (t, *J* = 7.5, 1H), 7.02 (t, *J* = 8.5, 1H), 6.96 (t, *J* = 7.0, 1H), 3.82 (s, 3H), 3.20 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.4, 162.4, 157.2, 154.8, 148.0, 137.0, 131.6, 130.6, 129.7, 127.7, 127.5, 125.9, 124.2, 121.9, 121.1, 111.5, 55.7, 38.5, 35.0; IR (neat, cm^{-1}): 1635, 1491, 1265, 1240, 1023; LRMS (EI 70 ev) m/z (%): 306 (M^+, 36), 235 (100), 249 (32), 189 (22), 207 (14); HRMS (ESI) calcd for $C_{19}H_{19}N_2O_2$ $(M+H)^+$ 307.1441, found 307.1449.



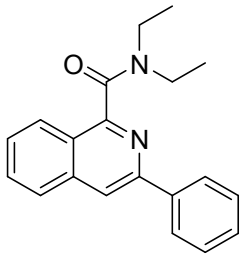
3-Hexyl-*N*,*N*-dimethylisoquinoline-1-carboxamide (15):

Yellow solid, mp 125.7-127.4 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.41 (s, 1H), 3.18 (s, 3H), 2.85 (t, *J* = 8.0 Hz, 2H), 2.77 (s, 3H), 1.74-1.68 (m, 2H), 1.33-1.26 (m, 2H), 1.26-1.20 (m, 4H), 0.80 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5, 162.5, 154.7, 137.2, 130.5, 127.0, 126.6, 125.8, 123.7, 118.7, 38.3, 37.9, 34.9, 31.7, 30.0, 29.0, 22.6, 14.0; IR (neat, cm^{-1}): 1644, 1414, 1402, 1135, 750; LRMS (EI 70 ev) m/z (%): 284 (M^+, 21), 156 (100), 214 (52), 170 (40), 143 (39); HRMS (ESI) calcd for $C_{18}H_{25}N_2O$ $(M+H)^+$ 285.1961, found 285.1971.



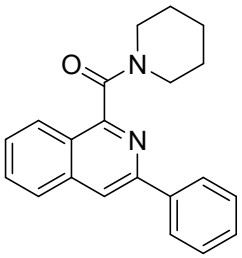
***N*,*N*-Dimethylisoquinoline-1-carboxamide (16):**

Yellow solid, mp 139.2-141.2 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.19 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 3.13 (s, 3H), 3.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.0, 154.1, 146.5, 137.3, 130.1, 129.6, 128.0, 127.7, 127.6, 120.6, 39.1, 35.8; IR (Neat, cm^{-1}): 1633, 1496, 1399, 1123, 1085; LRMS (EI 70 ev) m/z (%): 200 (M^+, 17), 129 (100), 128 (27), 143 (23), 101 (13); HRMS (ESI) calcd for $C_{12}H_{13}N_2O$ $(M+H)^+$ 201.1022, found 201.1030.



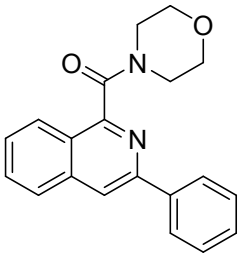
***N*,*N*-Diethyl-3-phenylisoquinoline-1-carboxamide (17):**

Yellow solid, mp 181.9-183.7 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.09 (d, *J* = 7.0 Hz, 2H), 8.01 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 7.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 3.69-3.65 (m, 2H), 3.14-3.10 (m, 2H), 1.34 (t, *J* = 7.0 Hz, 3H), 1.05 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.1, 162.8, 155.9, 149.9, 139.0, 137.5, 130.8, 128.8, 127.7, 127.5, 127.1, 126.1, 124.7, 116.8, 38.6, 35.8, 14.3, 13.2; IR (neat, cm^{-1}): 1634, 1477, 1461, 1378, 1263, 754; LRMS (EI 70 ev) m/z (%): 304 (M^+, 9), 72 (100), 205 (52), 204 (43), 233 (32); HRMS (ESI) calcd for $C_{20}H_{21}N_2O$ $(M+H)^+$ 305.1648, found 305.1657.



(3-Phenylisoquinolin-1-yl)(piperidin-1-yl)methanone (18):

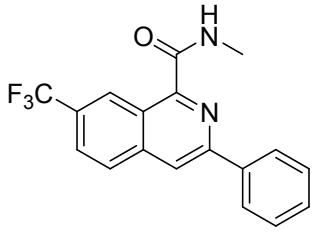
Yellow solid, mp 193.4-195.7 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 7.5 Hz, 2H), 8.02 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.68-7.60 (m, 2H), 7.45-7.42 (m, 2H), 7.35 (t, *J* = 7.0 Hz, 1H), 3.86 (t, *J* = 5.5 Hz, 2H), 3.17 (t, *J* = 5.0 Hz, 2H), 1.77-1.72 (m, 2H), 1.70-1.62 (m, 2H), 1.50-1.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.3, 155.5, 149.7, 138.6, 137.5, 131.1, 129.4, 128.8, 127.8, 127.4, 127.2, 126.2, 124.6, 117.1, 48.1, 42.8, 29.7, 21.0, 14.2; IR (neat, cm^{-1}): 1636, 1507, 1457, 1265, 726; LRMS (EI 70 ev) m/z (%): 316 (M^+, 14), 84 (100), 205 (37), 204 (36), 232 (14); HRMS (ESI) calcd for $C_{21}H_{21}N_2O$ $(M+H)^+$ 317.1648, found: 317.1656.



Morpholino(3-phenylisoquinolin-1-yl)methanone (19):

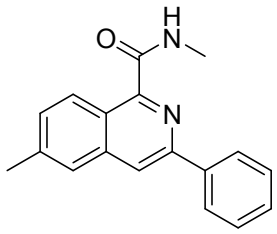
Yellow solid, mp 191.3-193.1 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.06 (d, *J* = 7.5 Hz, 2H), 8.04 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* =

7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 3.93 (t, *J* = 5.0 Hz, 2H), 3.84 (t, *J* = 5.0 Hz, 2H), 3.58 (t, *J* = 5.0 Hz, 2H), 3.33 (t, *J* = 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.7, 154.3, 149.8, 138.6, 137.6, 131.1, 129.0, 128.8, 128.2, 127.5, 127.0, 125.9, 125.3, 117.3, 67.1, 67.0, 47.5, 42.3; IR (neat, cm^{-1}): 1639, 1466, 1440, 1264, 1114; LRMS (EI 70 ev) m/z (%): 318 (M^+, 20), 205 (100), 204 (55), 86 (19), 206 (13); HRMS (ESI) calcd for $C_{20}H_{19}N_2O_2$ $(M+H)^+$ 319.1441, found 319.1451.



***N*-Methyl-3-phenyl-7-(trifluoromethyl)isoquinoline-1-carboxamide (20):**

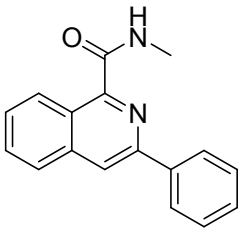
White solid, mp 133.3-135.1 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.97 (s, 1H), 8.24 (brs, 1H), 8.11 (s, 1H), 8.02 (d, *J* = 7.0 Hz, 2H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.76 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 1H), 3.05 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.0, 150.5, 148.7, 139.6, 137.9, 130.1, 129.8, 129.5, 129.0, 128.3, 127.0, 126.5, 126.4 (d, *J* = 9.5 Hz, 1C), 126.3 (d, *J* = 3.0 Hz, 1C), 126.2 (d, *J* = 3.0 Hz, 1C), 125.0, 124.9, 122.8, 119.7, 26.3; IR (neat, cm^{-1}): 2921, 1646, 1553, 1284, 1115, 882; LRMS (EI 70 ev) m/z (%): 330 (M^+, 34), 273 (100), 204 (50), 272 (31), 252 (8), HRMS (ESI) for $C_{18}H_{14}F_3N_2O$ $(M+H)^+$: calcd: 331.1053, found: 331.1061.



***N*,6-Dimethyl-3-phenylisoquinoline-1-carboxamide (21):**

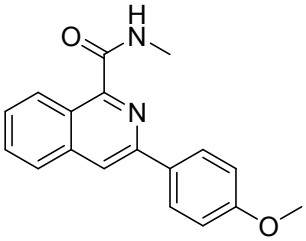
White solid, mp 130.5-132.4 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.41 (d, *J* = 8.5 Hz, 1H), 8.25 (brs, 1H), 8.01-7.99 (m, 3H), 7.54 (s, 1H), 7.44-7.34 (m, 4H), 3.03 (d, *J* = 5.0 Hz, 3H), 2.46 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.9, 148.5, 147.7, 141.0, 138.9, 130.8, 128.8 (2C), 127.7, 127.0, 126.9, 126.0, 124.5, 119.7, 26.4, 21.9; IR (neat, cm^{-1}): 2937, 1662, 1522, 1403, 1284, 774; LRMS (EI 70

ev) m/z (%): 276 (M^+, 35), 219 (100), 204 (50), 218 (30), 203 (10); HRMS (ESI) for $C_{18}H_{17}N_2O$ $(M+H)^+$: calcd: 277.1335, found: 277.1346.



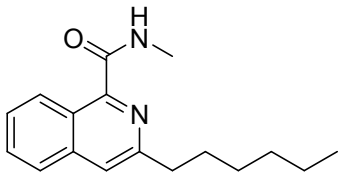
N-Methyl-3-phenylisoquinoline-1-carboxamide (22)

Yellow solid; mp: 135.3-137.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.50 (d, *J* = 8.5 Hz, 1H), 8.22 (brs, 1H), 8.05 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.56-7.51 (m, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 3.02 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.8, 148.5, 148.0, 138.7, 138.4, 130.6, 128.9, 128.4, 128.0, 127.2, 127.1, 126.9, 126.0, 120.2, 26.3; IR (neat): 2912, 1641, 1576, 1421, 1151 cm^{-1}; HRMS (ESI) for $C_{17}H_{15}N_2O$ $(M+H)^+$: calcd: 263.1179, found: 263.1190.



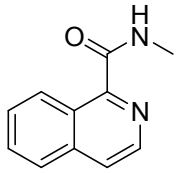
3-(4-Methoxyphenyl)-*N*-methylisoquinoline-1-carboxamide (23):

White solid, mp 169.4-171.1 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.50 (d, *J* = 9.0 Hz, 1H), 8.23 (brs, 1H), 8.01 (s, 1H), 7.97 (d, *J* = 9.0 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.61-7.58 (m, 1H), 7.55-7.52 (m, 1H), 6.97 (d, *J* = 9.0 Hz, 2H), 3.81 (s, 3H), 3.04 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.8, 160.4, 148.3, 147.9, 138.6, 131.3, 130.5, 128.1, 128.0 (2C), 127.0, 125.7, 119.1, 114.3, 55.4, 26.3; IR (neat, cm^{-1}): 3322, 2932, 1640, 1545, 1247, 1175, 834; LRMS (EI 70 ev) m/z (%): 292 (M^+, 75), 235 (100), 220 (63), 236 (21), 191 (14); HRMS (ESI) for $C_{18}H_{17}N_2O_2$ $(M+H)^+$: calcd: 293.1285, found: 293.1292.



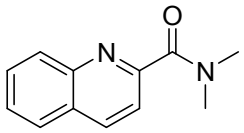
3-Hexyl-*N*-methylisoquinoline-1-carboxamide (24):

Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.48 (d, *J* = 8.5 Hz, 1H), 8.19 (brs, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.58-7.55 (m, 1H), 7.52-7.49 (m, 2H), 3.00 (d, *J* = 5.0 Hz, 3H), 2.83 (t, *J* = 8.0 Hz, 2H), 1.75-1.69 (m, 2H), 1.33-1.29 (m, 2H), 1.28-1.24 (m, 4H), 0.82 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.9, 153.2, 147.6, 138.2, 130.2, 127.8, 127.6, 126.3, 125.4, 121.9, 37.6, 31.7, 29.8, 29.0, 26.2, 22.6, 14.1; IR (neat, cm^{-1}): 2923, 1666, 1520, 1407, 1154, 753; LRMS (EI 70 ev) m/z (%): 270 (M^+, 11), 200 (100), 141 (33), 182 (15), 156 (15); HRMS (ESI) for $C_{17}H_{23}N_2O$ $(M+H)^+$: calcd: 271.1805, found: 271.1796.



***N*-Methylisoquinoline-1-carboxamide (25):**

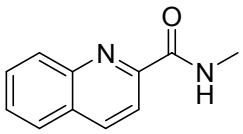
Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.50 (d, *J* = 8.5 Hz, 1H), 8.35 (d, *J* = 5.5 Hz, 1H), 8.09 (brs, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 5.5 Hz, 1H), 7.64-7.57 (m, 2H), 2.99 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.8, 148.5, 140.2, 137.4, 130.4, 128.6, 127.9, 126.9, 126.7, 124.2, 26.2; IR (neat, cm^{-1}): 3058, 1663, 1525, 1409, 1266, 744; LRMS (EI 70 ev) m/z (%): 186 (M^+, 20), 129 (100), 128 (27), 157 (19), 102 (15); HRMS (ESI) for $C_{11}H_{11}N_2O$ $(M+H)^+$: calcd: 187.0866, found: 187.0871.



***N*,*N*-Dimethylquinoline-2-carboxamide (26):[3]**

Yellow solid, mp 132.5-134.1 ^{o}C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.44 (d, *J* = 5.5 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.65-7.61 (m, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 3.20 (s, 3H), 2.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.2, 155.6, 141.6, 136.5, 130.8, 128.1, 127.0, 126.0,

125.4, 121.3, 38.4, 34.9; IR (neat, cm^{-1}): 1635, 1415, 1376, 1125, 750; LRMS (EI 70 ev) m/z (%): 200 (M^+, 21), 129 (100), 128 (34), 143 (25), 101 (9).



***N*-Methylquinoline-2-carboxamide (27):[3]**

White solid, mp 112.7-114.3 °C (uncorrected); ^1H NMR (500 MHz, $CDCl_3$) δ: 8.23-8.19 (m, 3H), 7.99 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.68-7.64 (m, 1H), 7.53-7.50 (m, 1H), 3.01 (d, J = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.1, 149.9, 146.4, 137.4, 130.0, 129.6, 129.3, 127.8, 127.7, 118.8, 26.2; IR (neat, cm^{-1}): 2930, 1660, 1562, 1427, 1410, 795; LRMS (EI 70 ev) m/z (%): 186 (M^+, 26), 129 (100), 128 (27), 157 (16), 101 (13).

(D) References

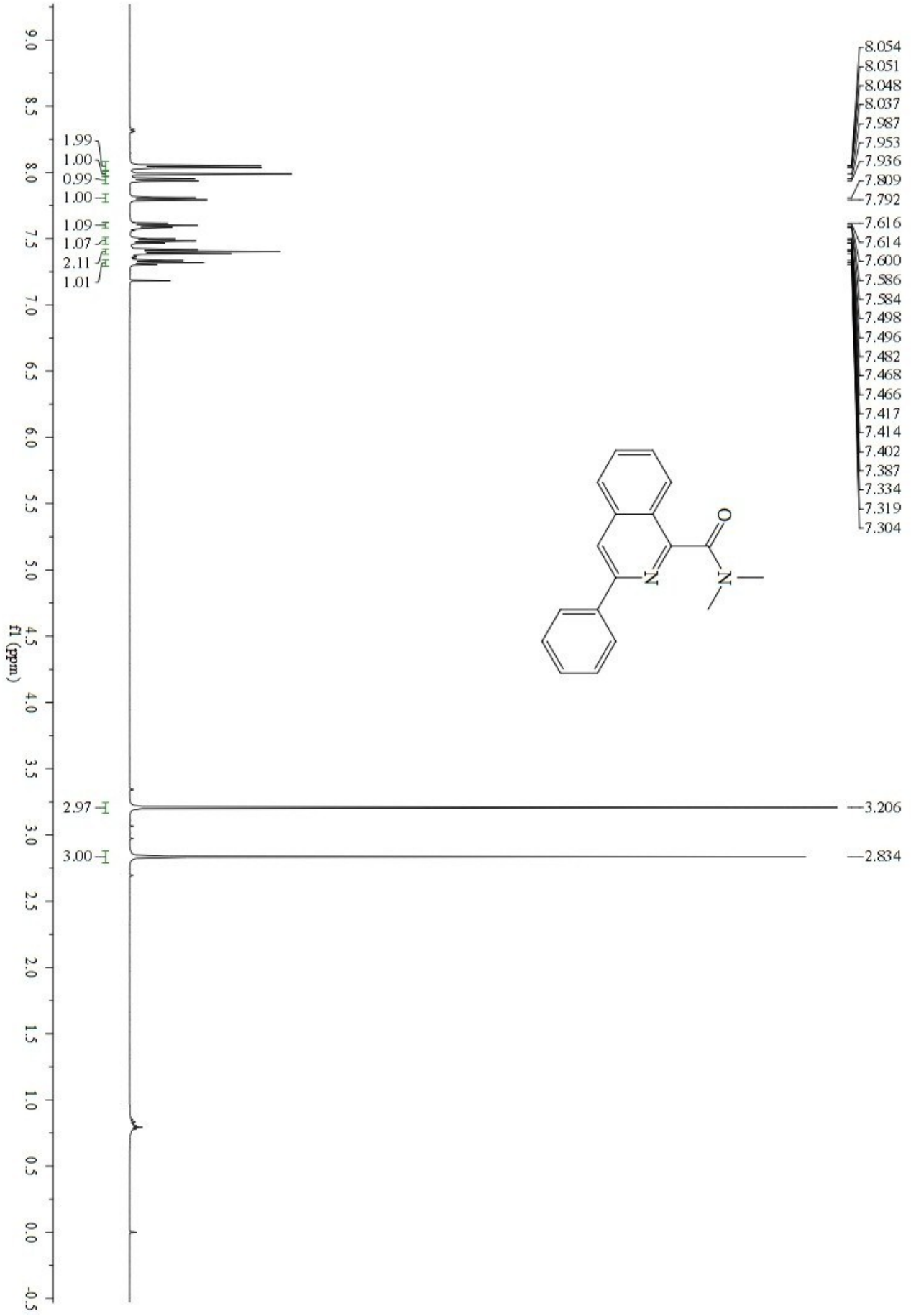
[1] J. Wu, X. Cui, L. Chen, G. Jiang, Y. Wu, *J. Am. Chem. Soc.* **2009**, *131*, 13888 and references cited therein.

[2] E. V. Kuznetsov, I. V. Shcherbakova, V. I. Ushakov, G. N. Dorofeenko, *Russ. J. Org. Chem.* **1977**, *13*, 631-634.

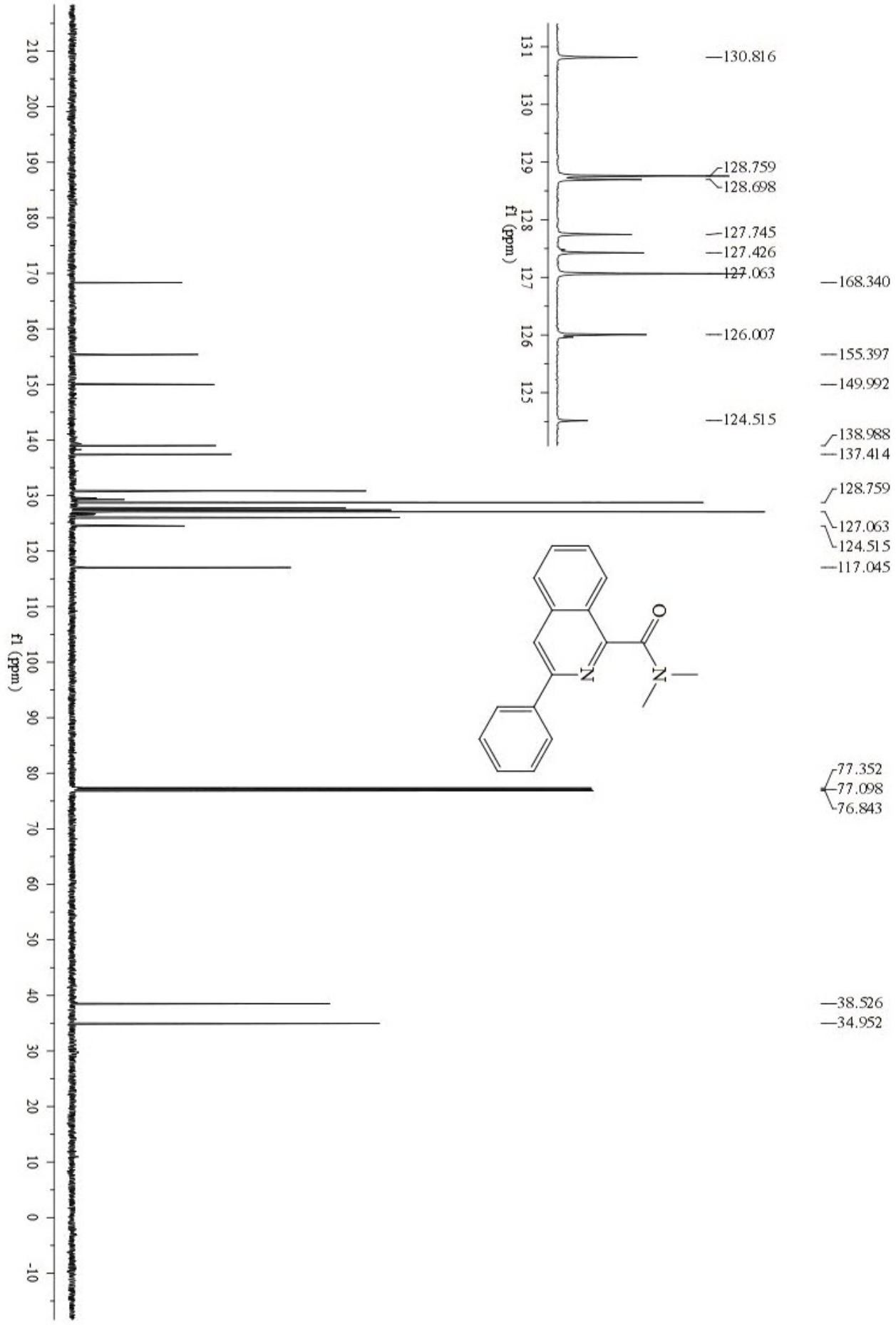
[3] S. Haruki, K. Mamoru, T. Takashi, *Chemical & Pharmaceutical Bulletin*, **1990**, *38*, 2919-2925.

(E) Spectra

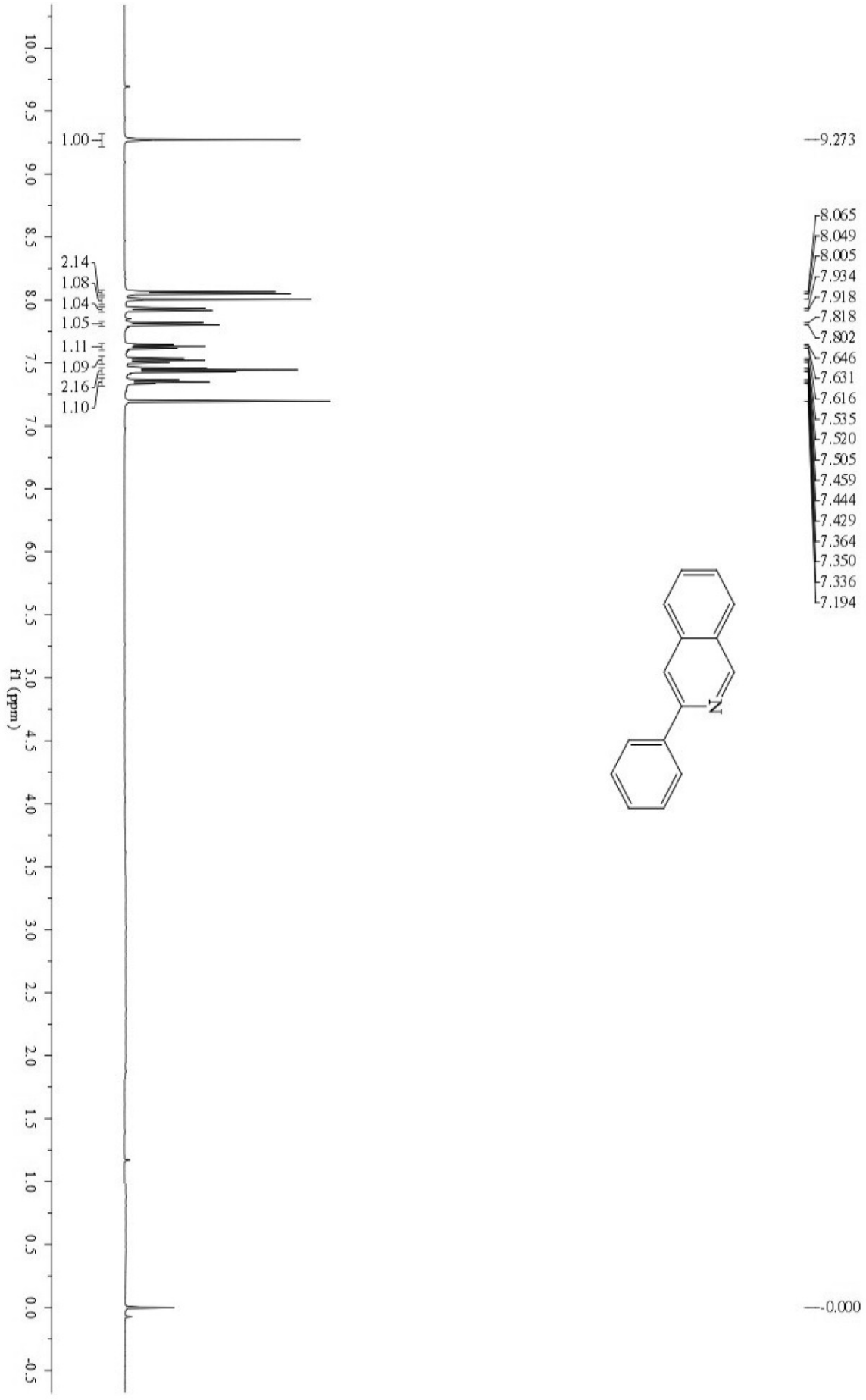
N,*N*-Dimethyl-3-phenylisoquinoline-1-carboxamide (3)



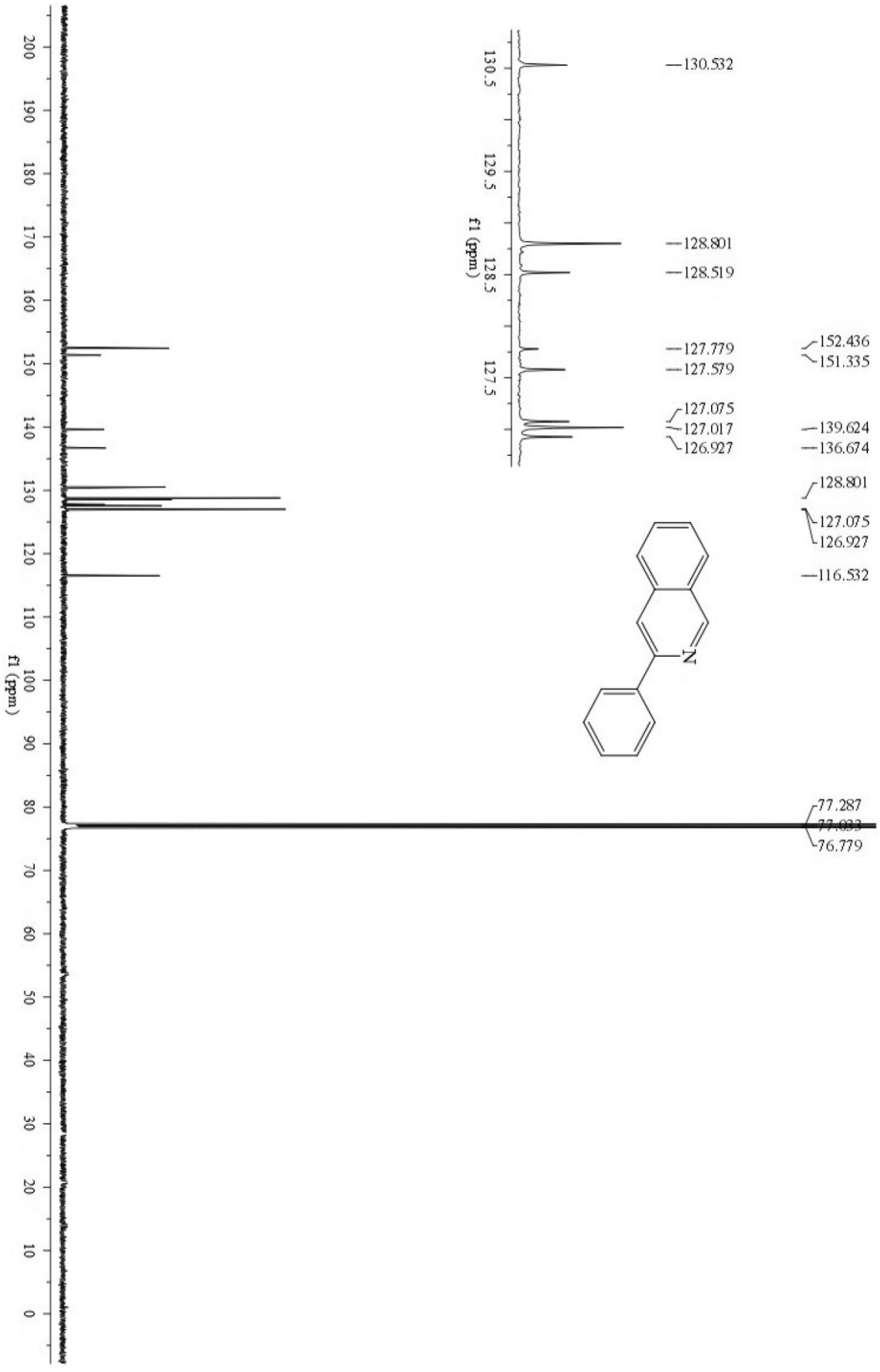
N,*N*-Dimethyl-3-phenylisoquinoline-1-carboxamide (3)



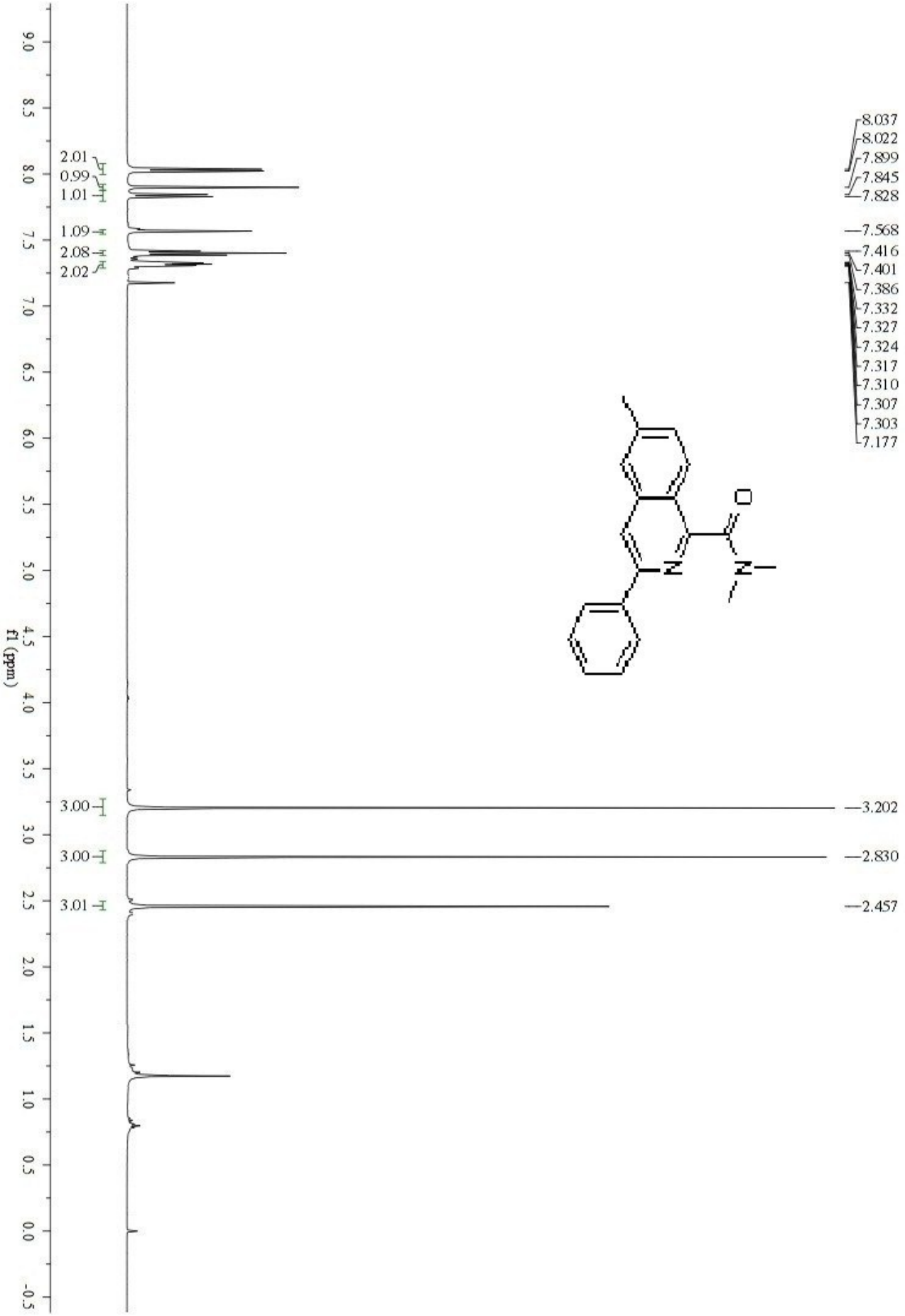
3-Phenylisoquinoline (4)



3-Phenylisoquinoline (4)



N,*N*,6-Trimethyl-3-phenylisoquinoline-1-carboxamide (5)



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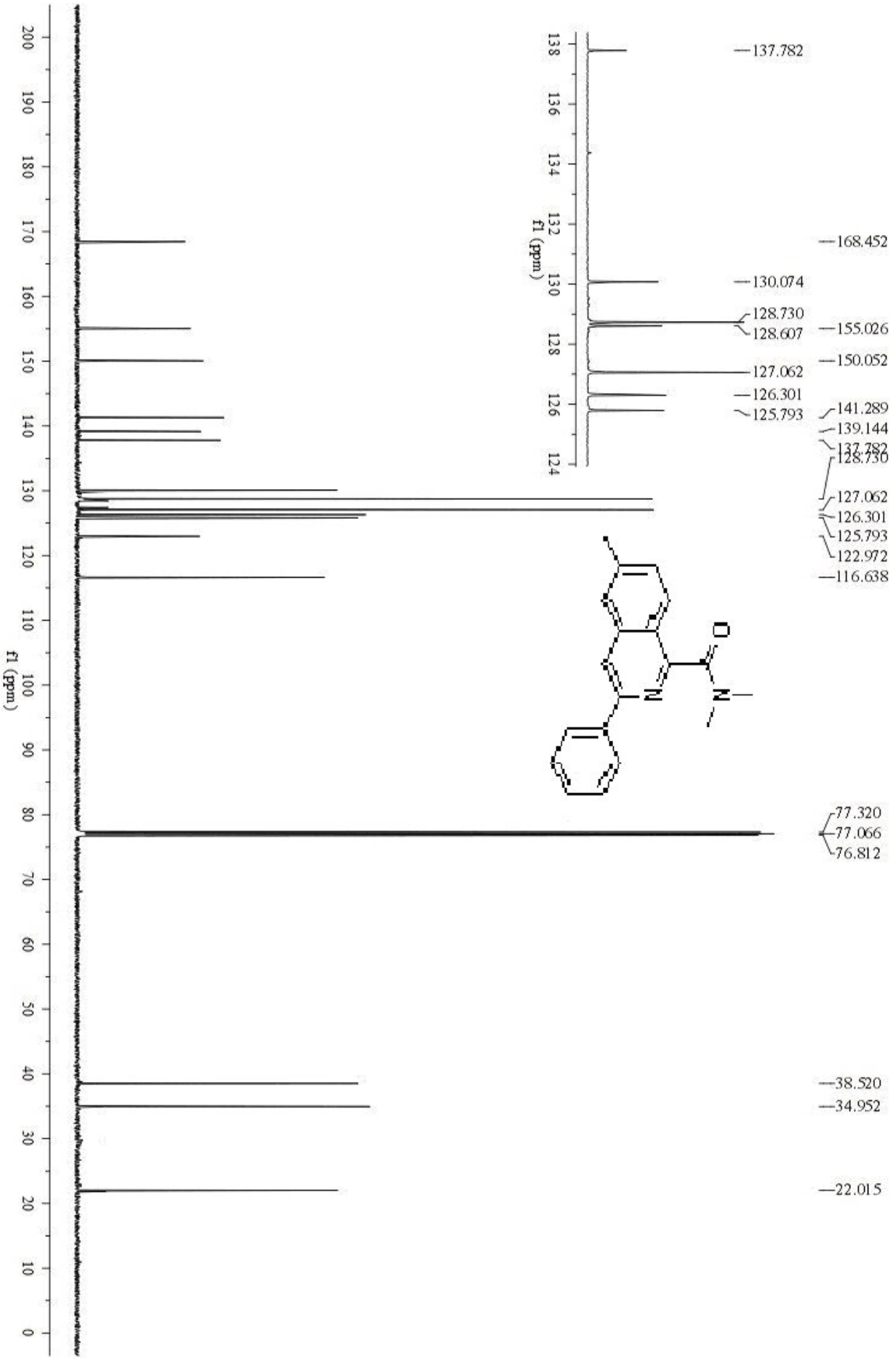
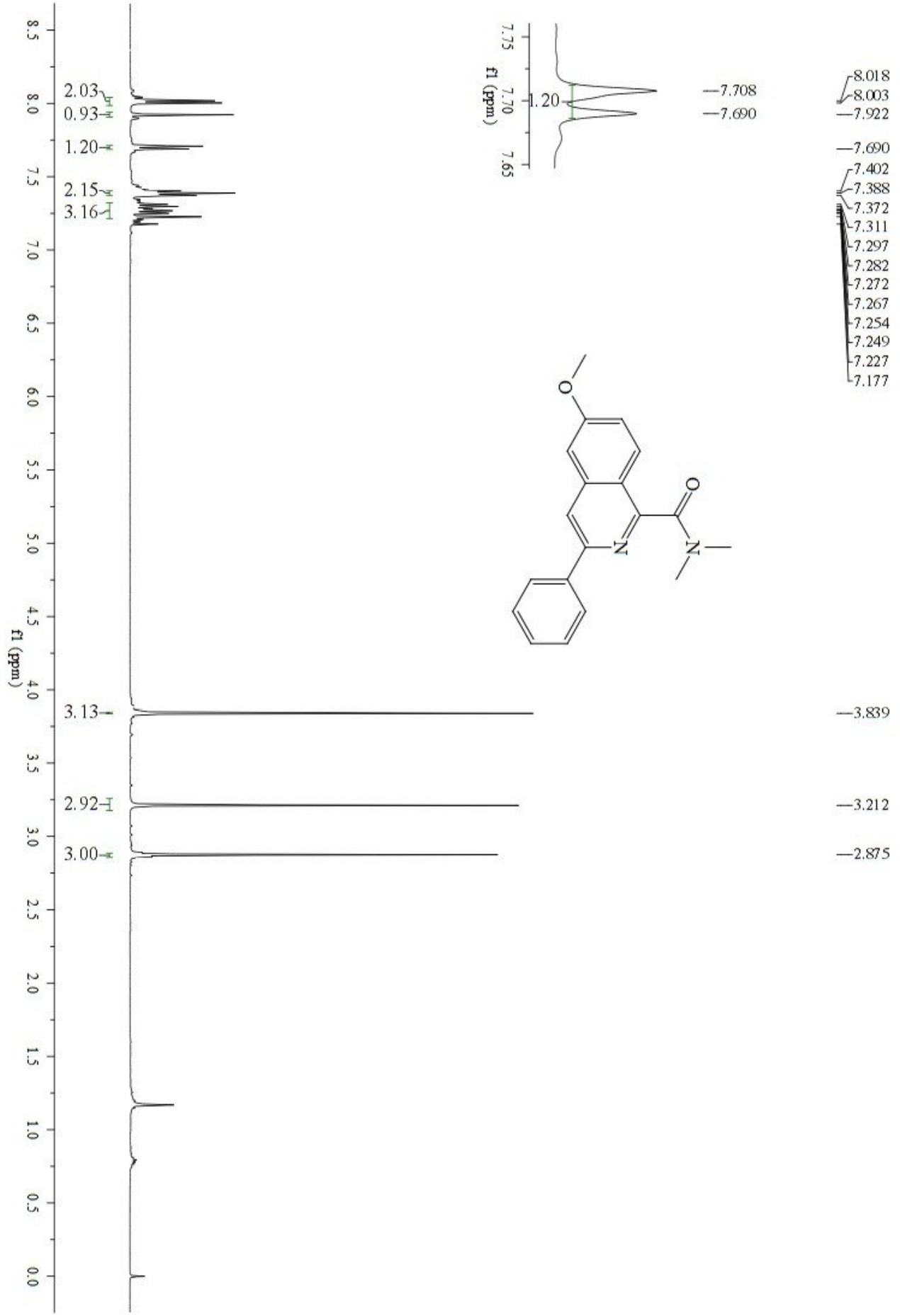


6-Methoxy-*N*,*N*-dimethyl-3-phenylisoquinoline-1-carboxamide (6)



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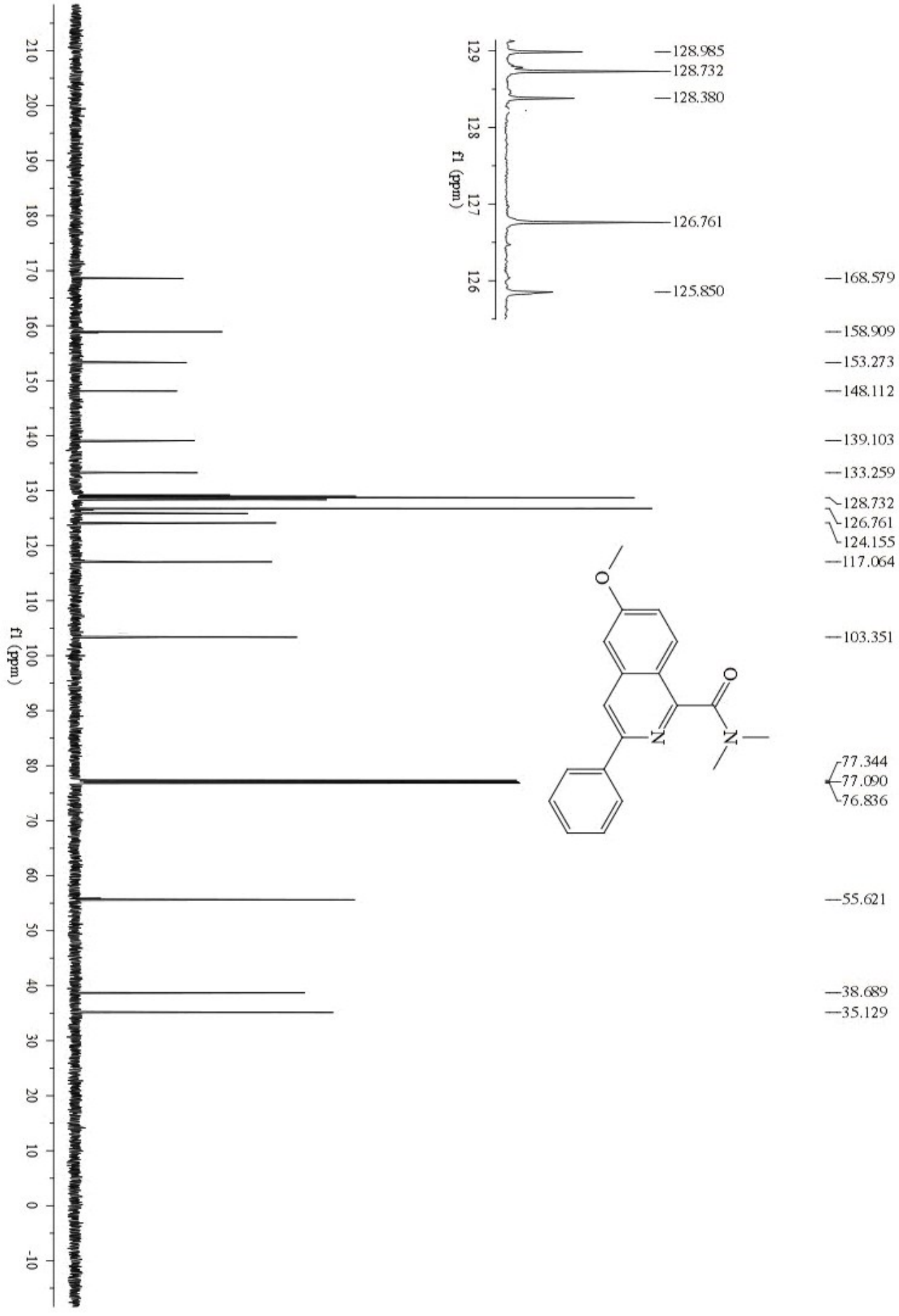
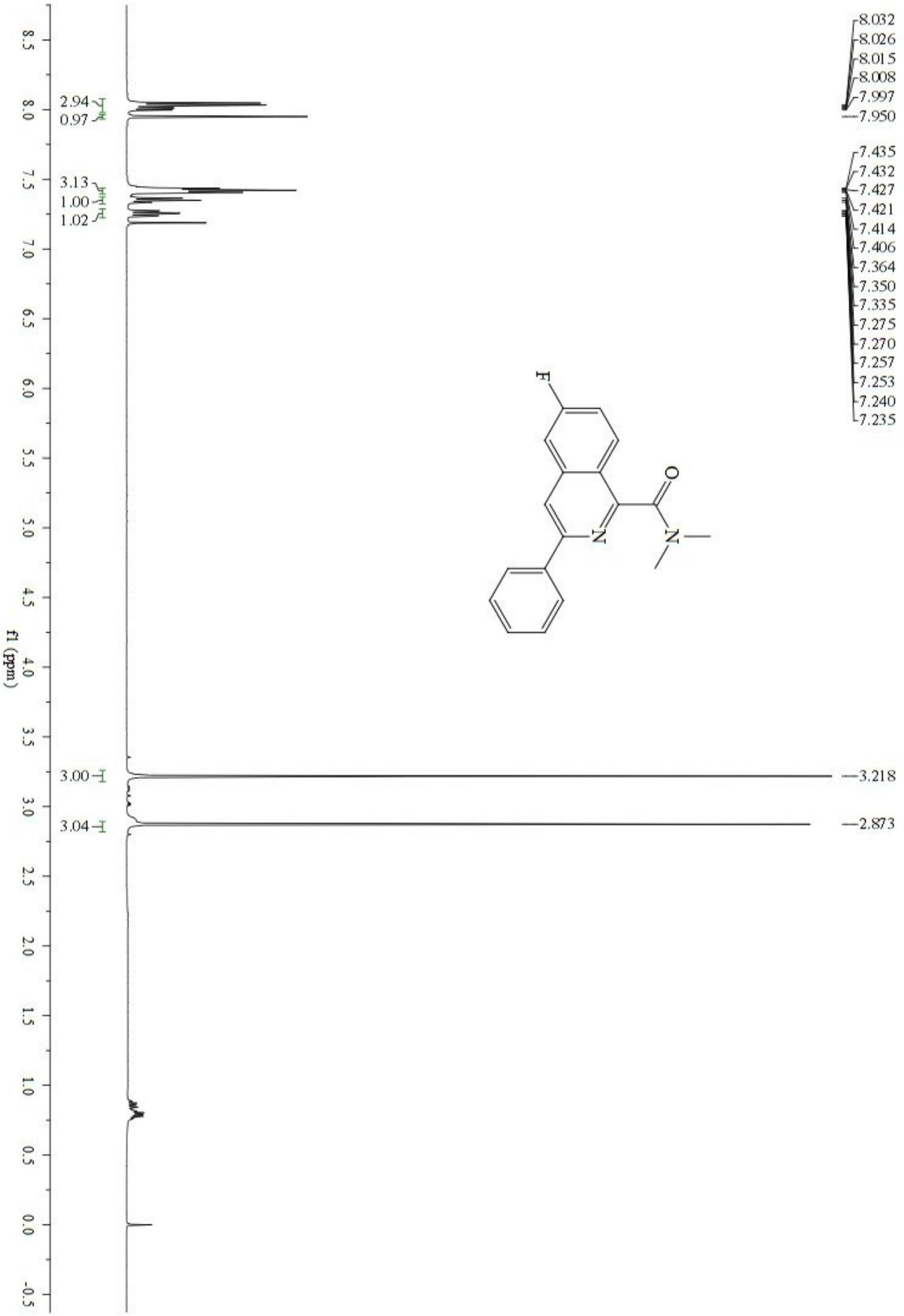


6-Fluoro-*N*,*N*-dimethyl-3-phenylisoquinoline-1-carboxamide (7)



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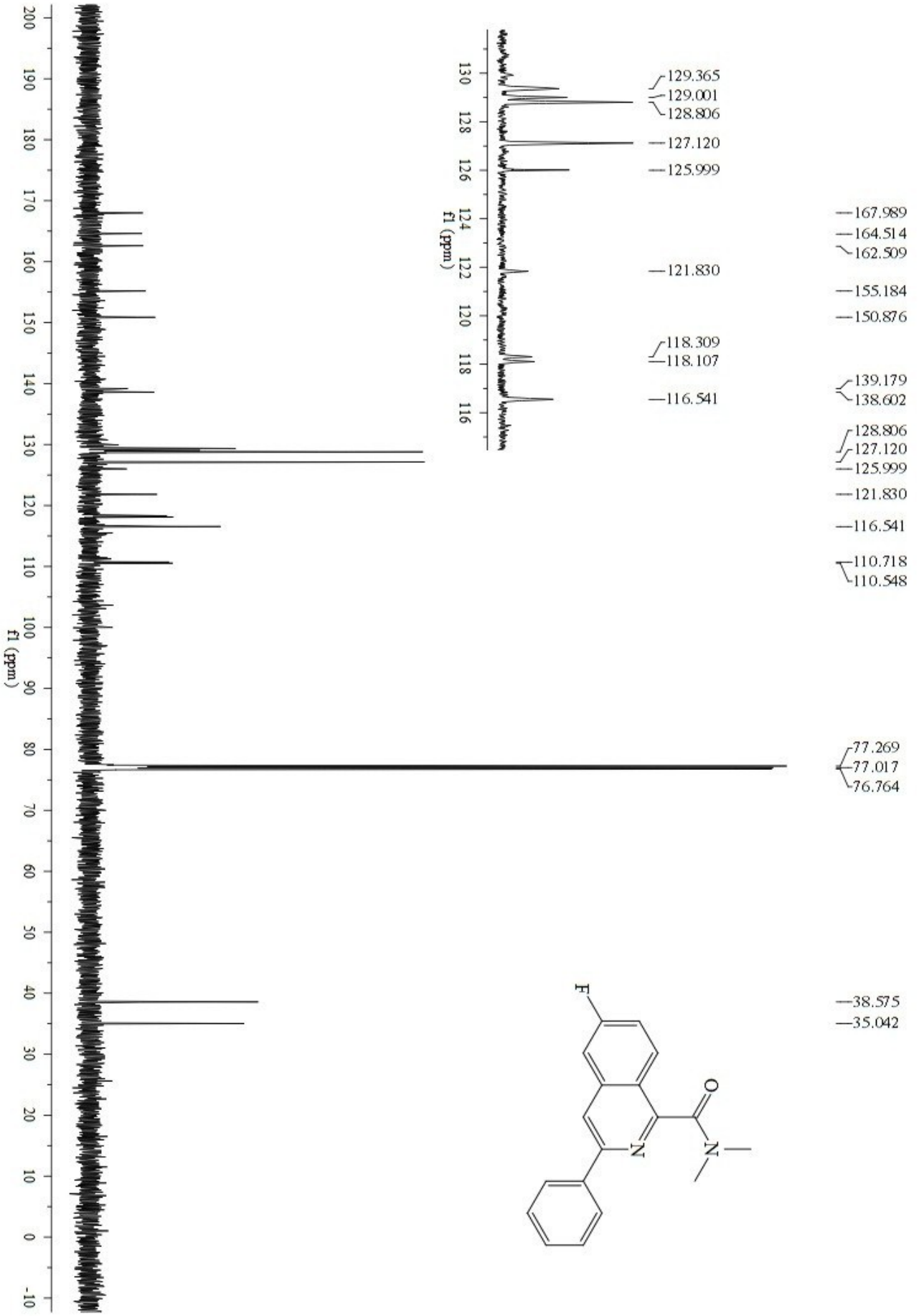
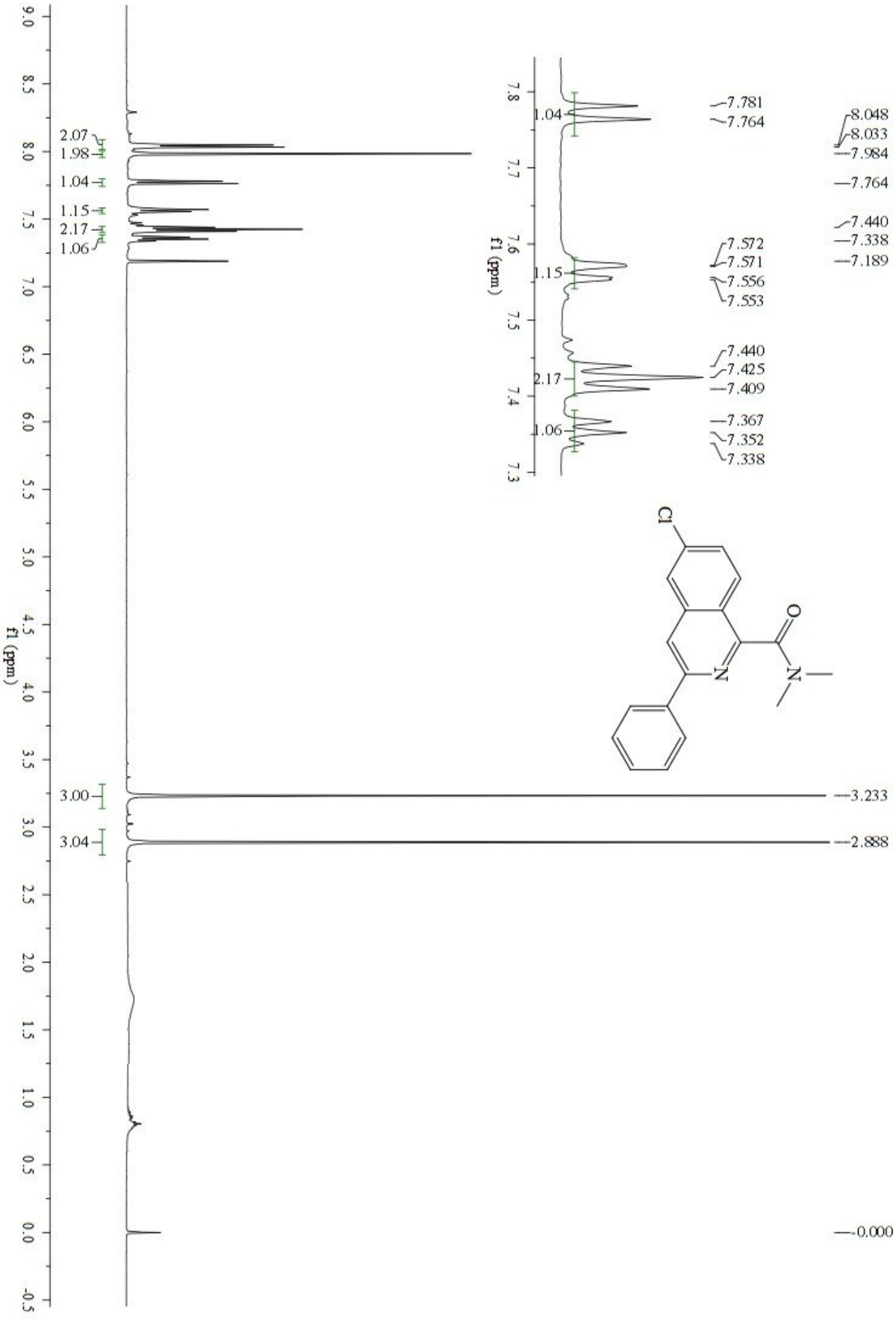


6-Chloro-*N*,*N*-dimethyl-3-phenylisoquinoline-1-carboxamide (8)



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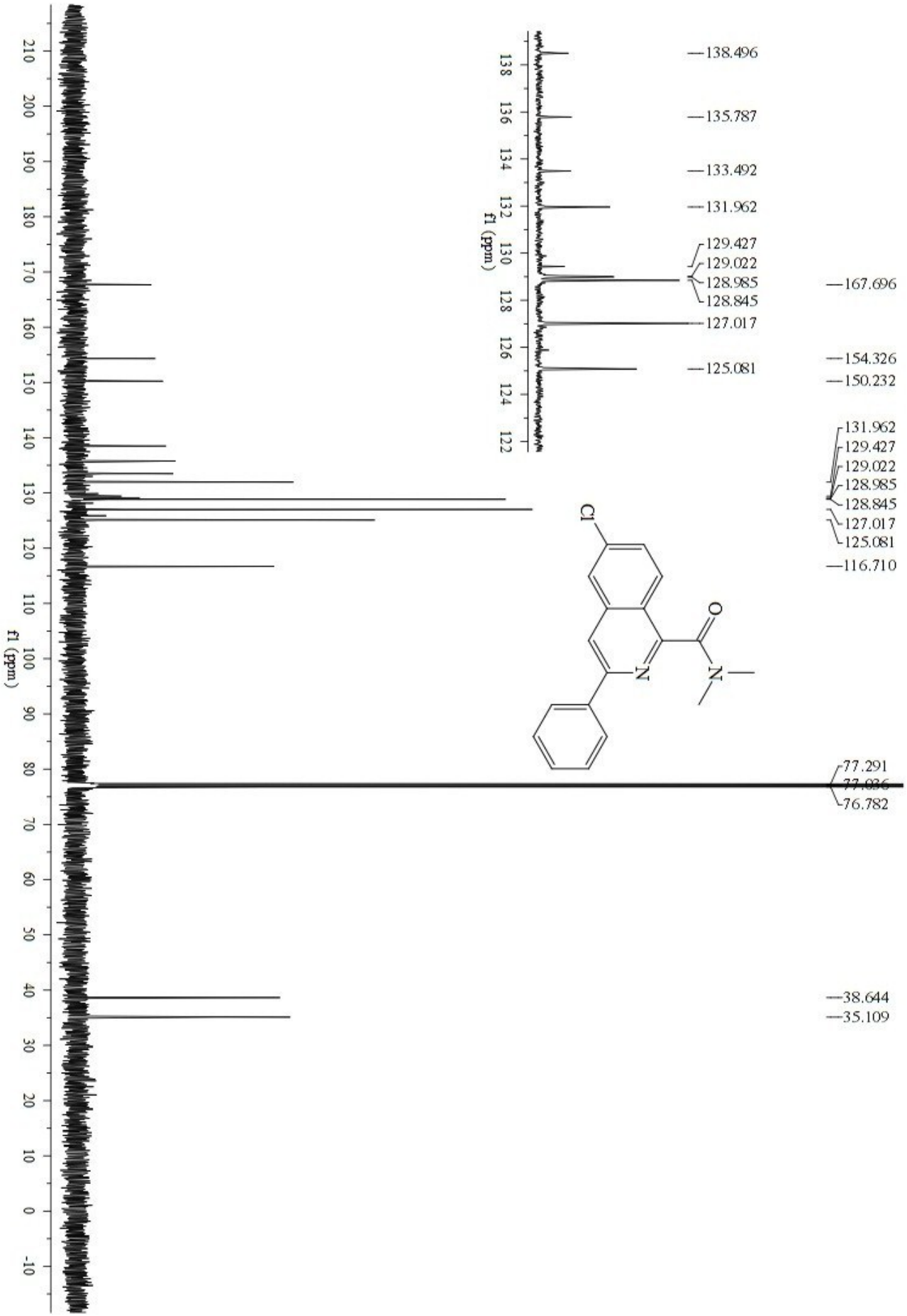
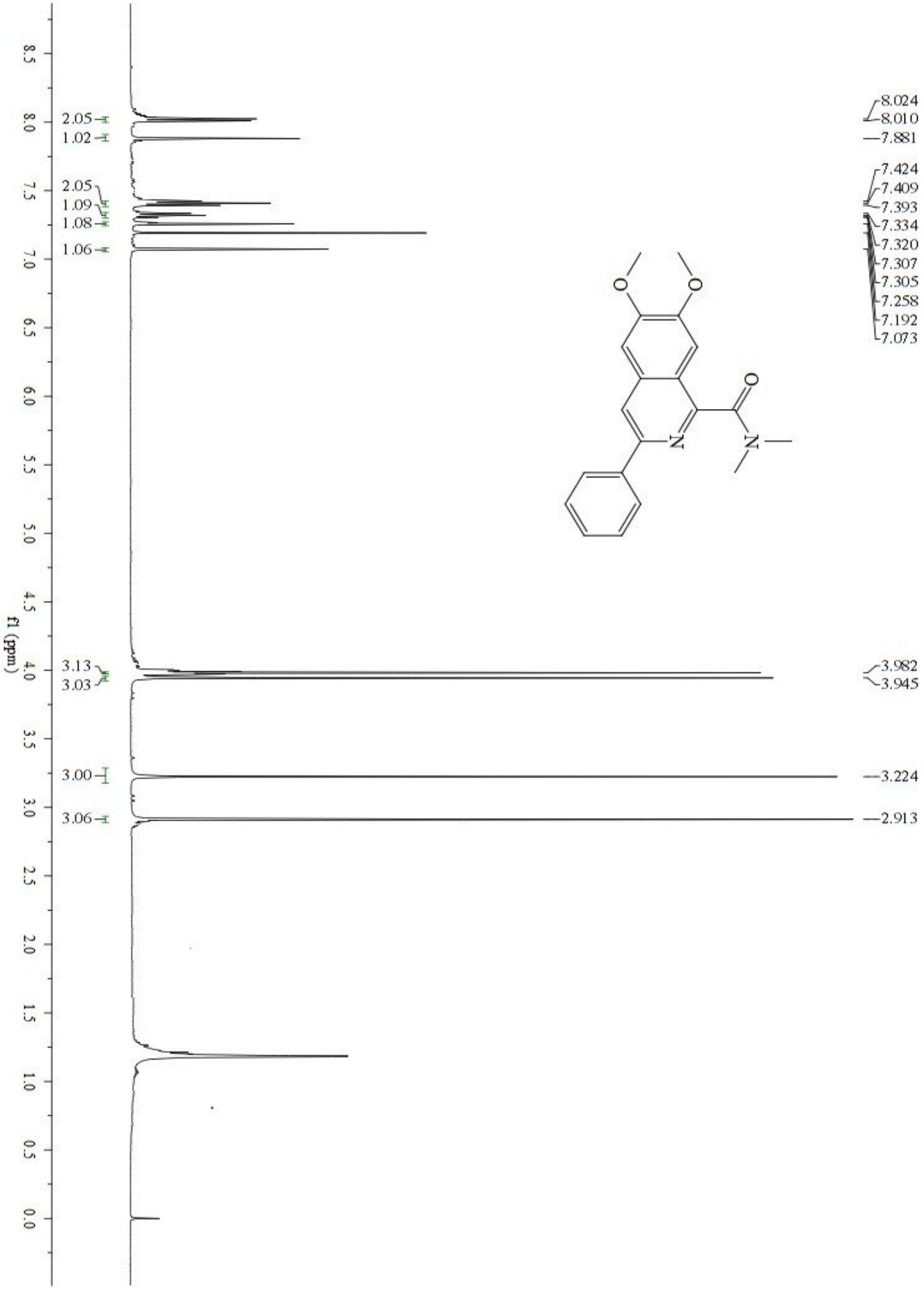


6,7-Dimethoxy-*N*,*N*-dimethyl-3-phenylisoquinoline-1-carboxamide (9)



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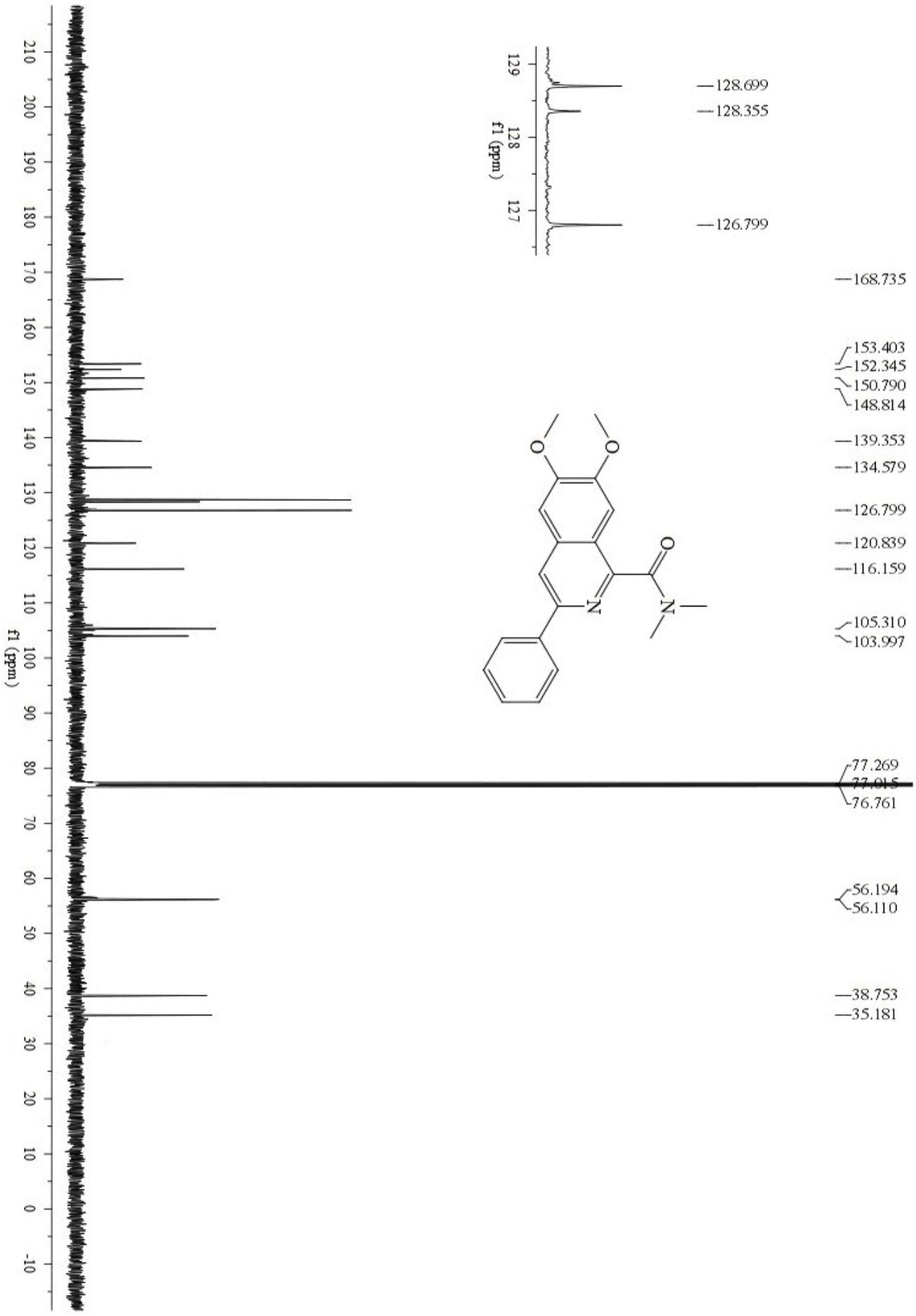
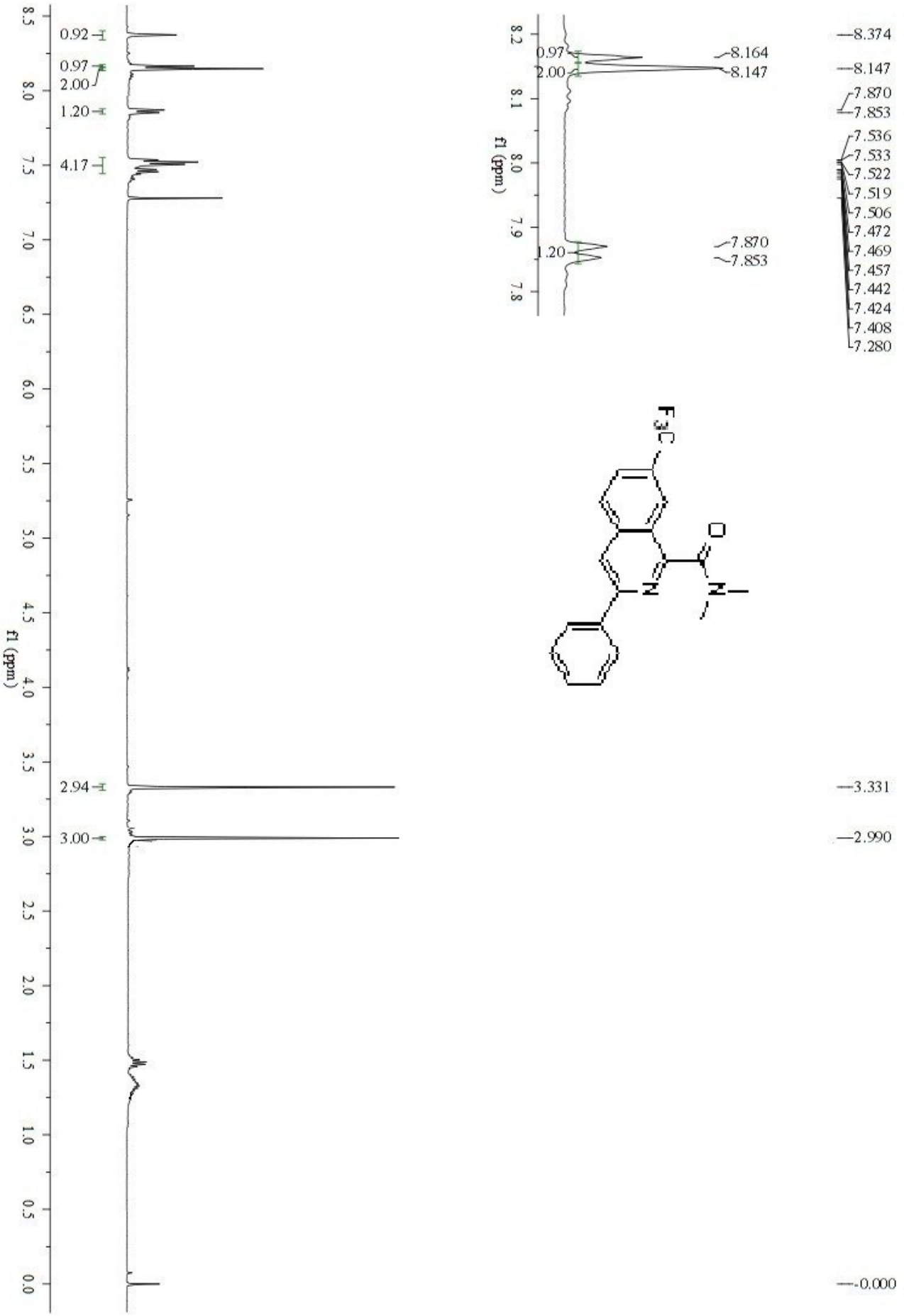
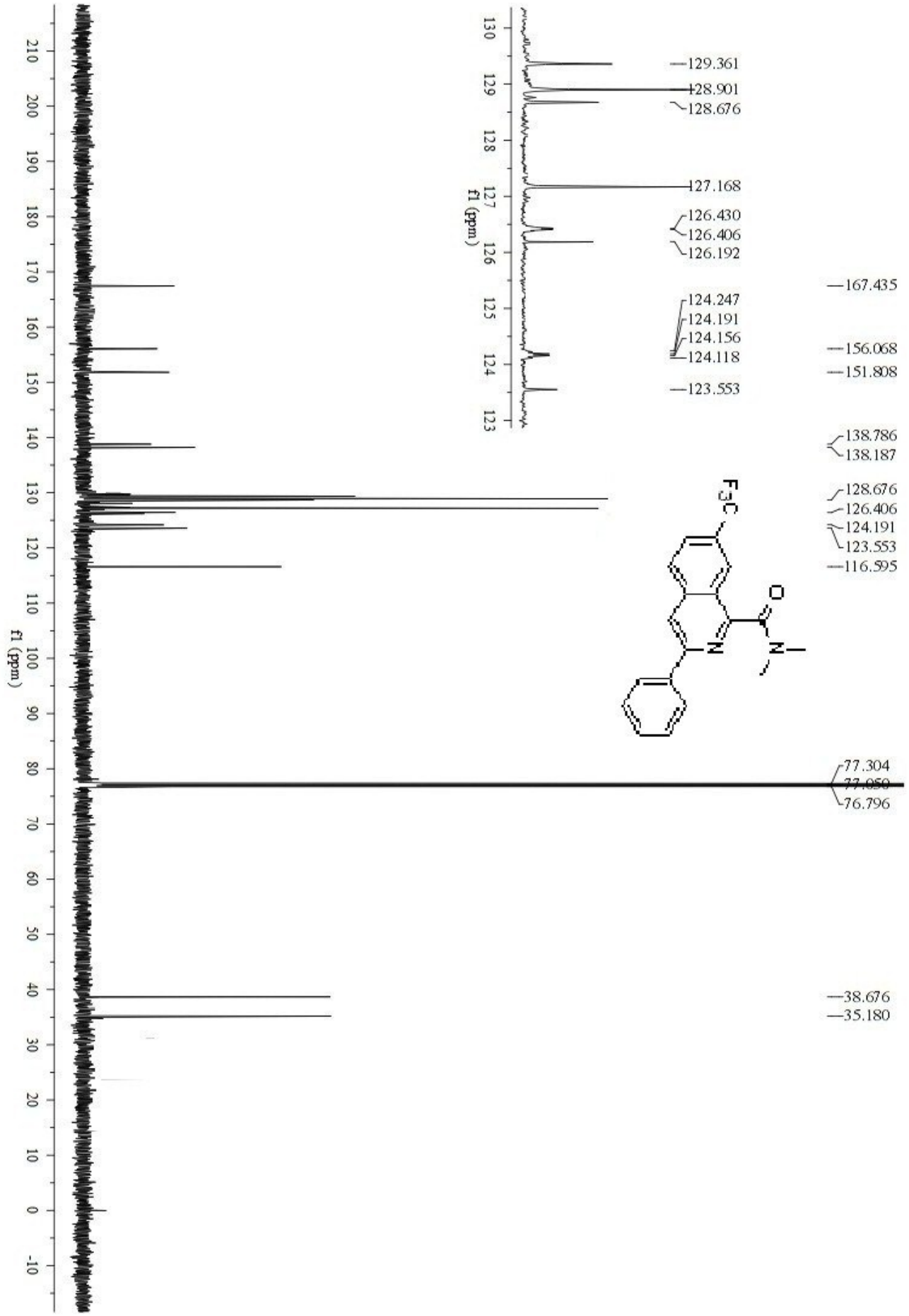


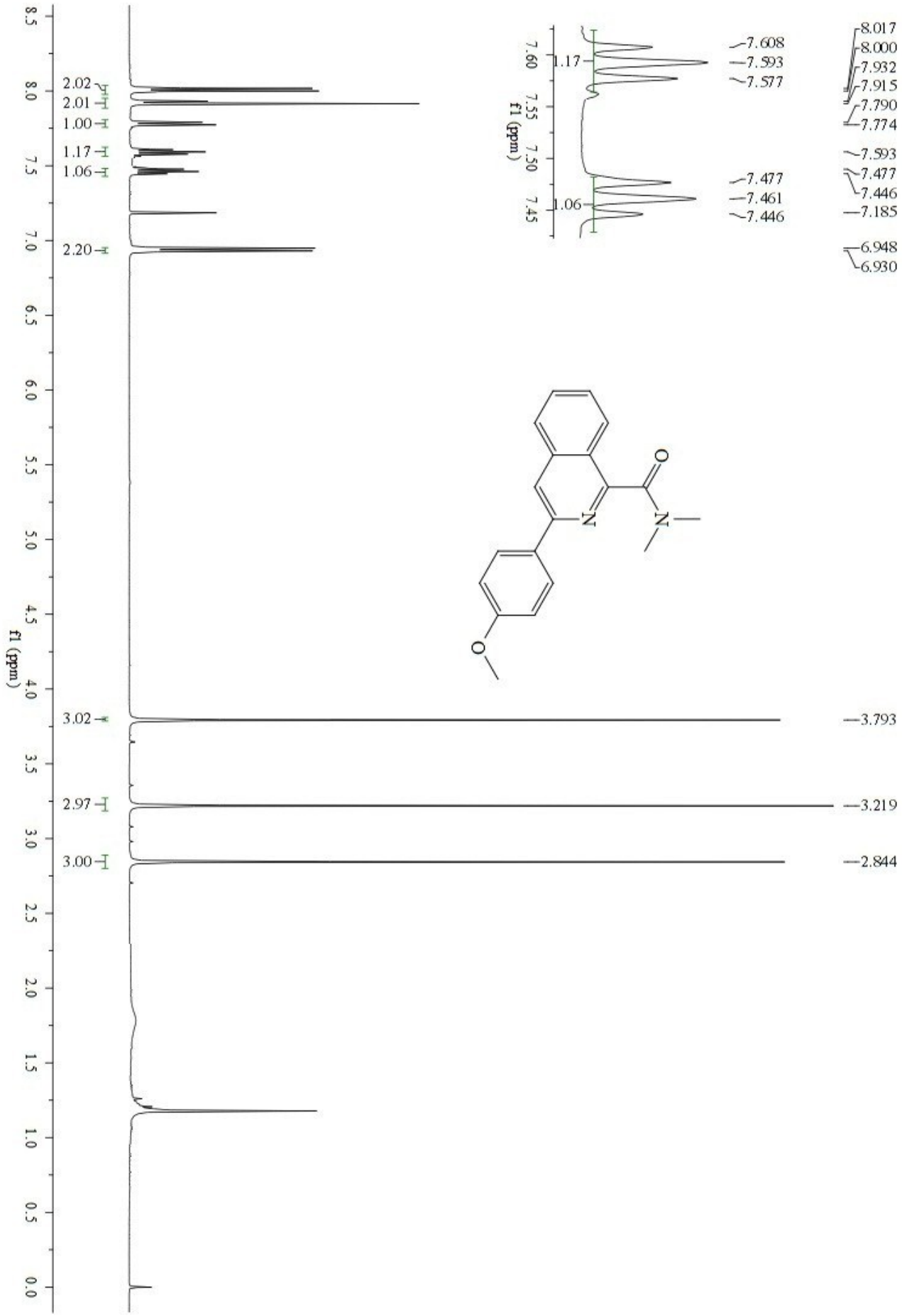
N,*N*-Dimethyl-3-phenyl-7-(trifluoromethyl)isoquinoline-1-carboxamide (10)



N,*N*-Dimethyl-3-phenyl-7-(trifluoromethyl)isoquinoline-1-carboxamide (10)



3-(4-Methoxyphenyl)-*N*,*N*-dimethylisoquinoline-1-carboxamide (11)



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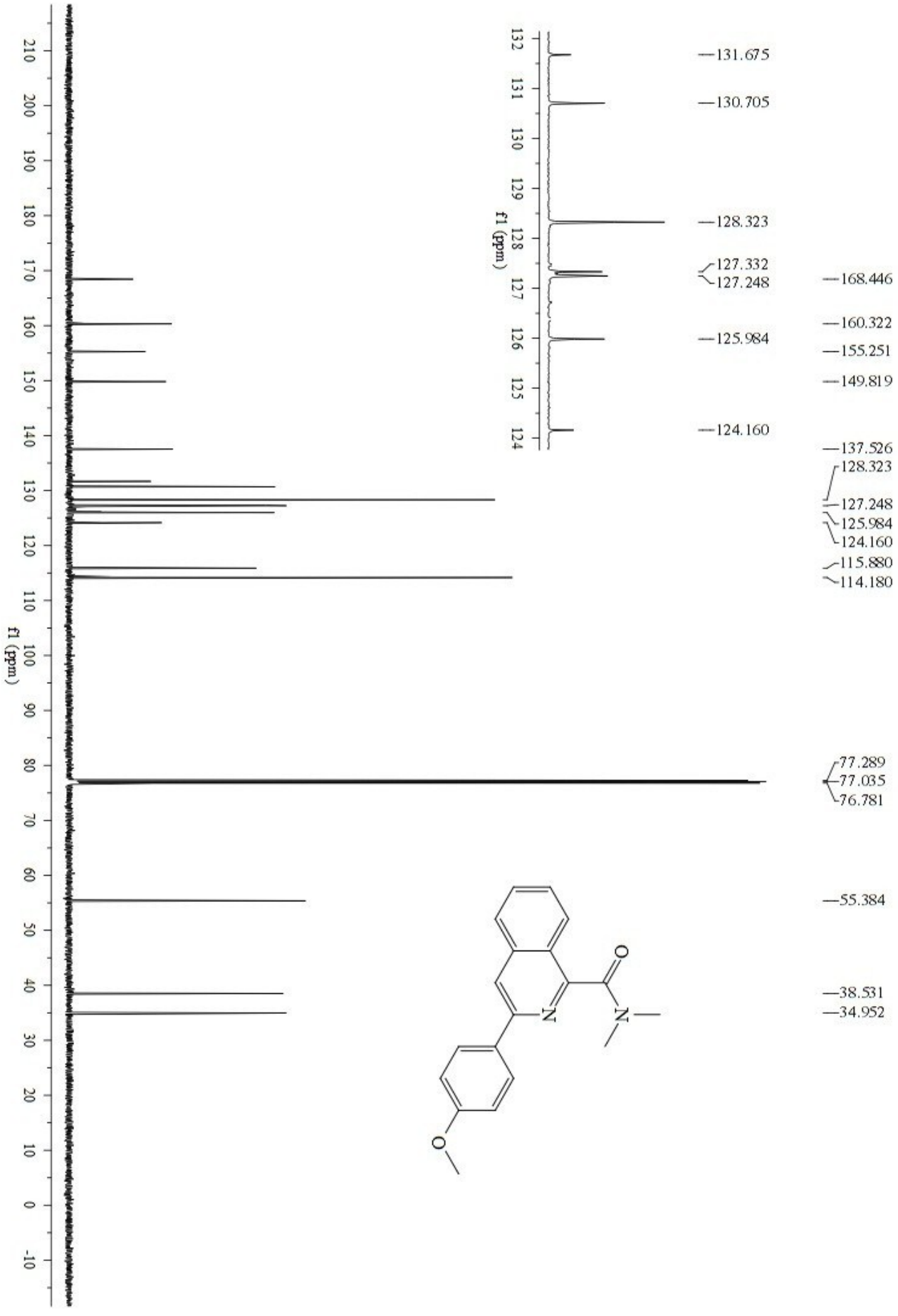
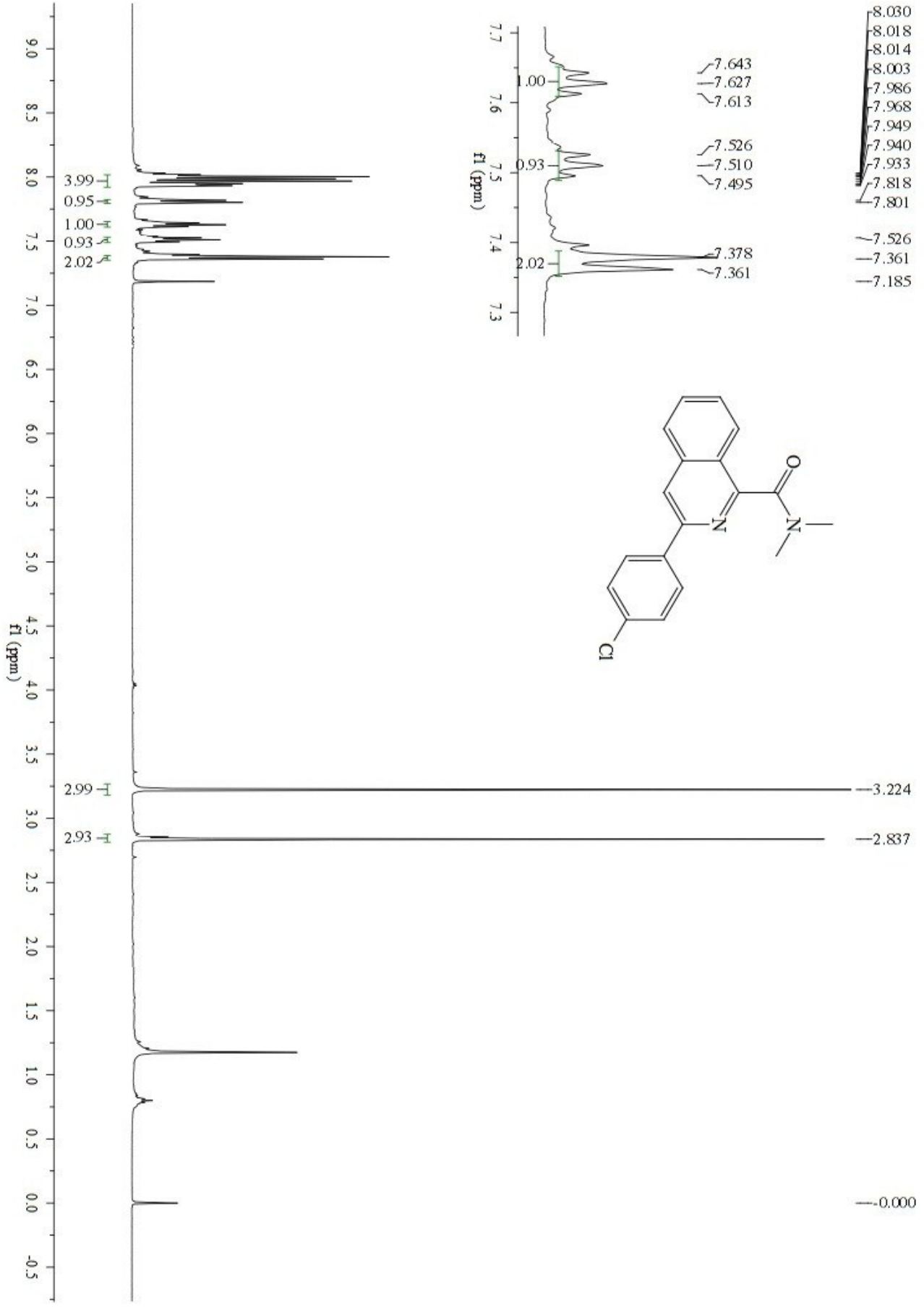
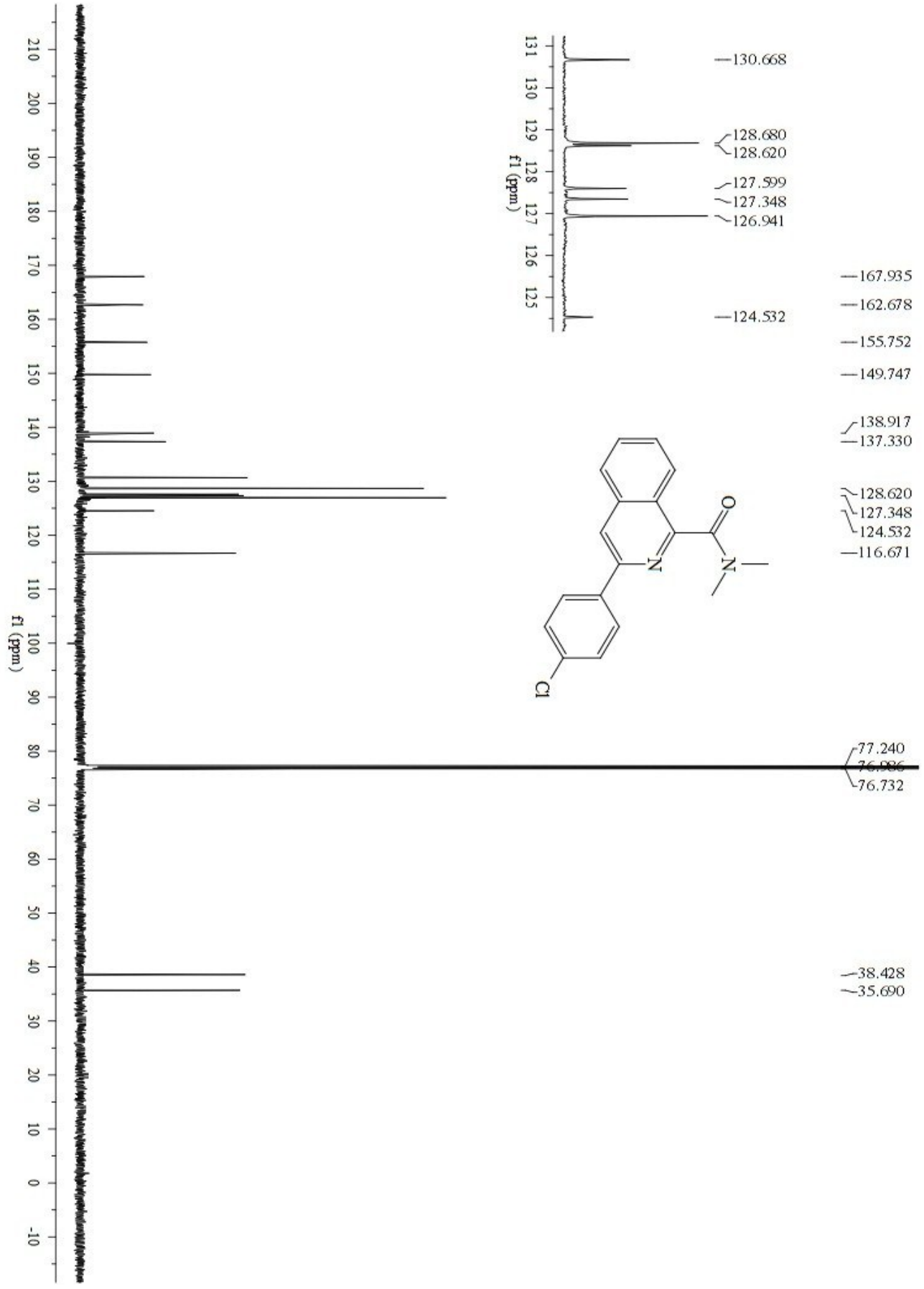


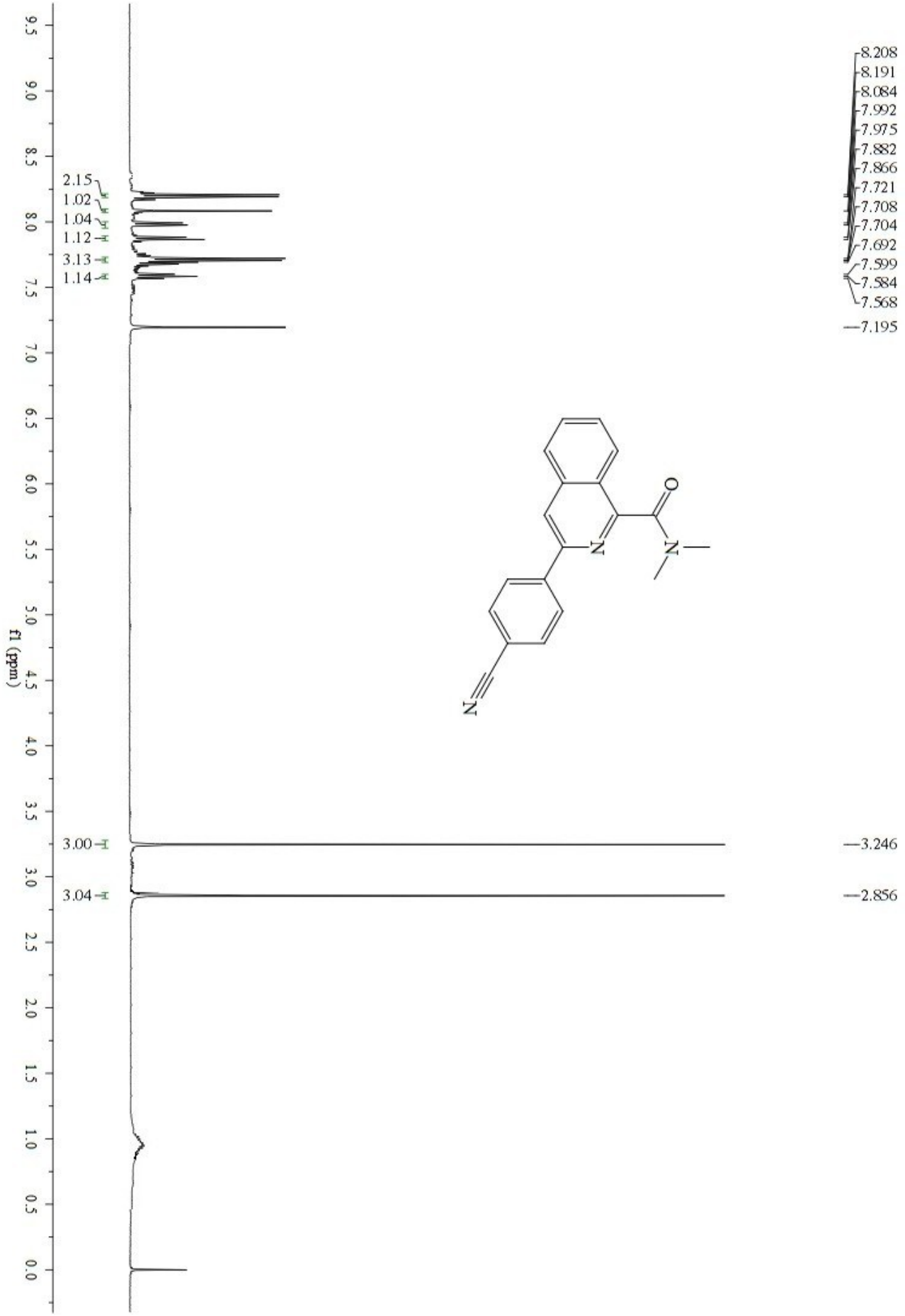
3-(4-Chlorophenyl)-*N*,*N*-dimethylisoquinoline-1-carboxamide (12)



3-(4-Chlorophenyl)-*N*,*N*-dimethylisoquinoline-1-carboxamide (12)



3-(4-Cyanophenyl)-*N*,*N*-dimethylisoquinoline-1-carboxamide (13)



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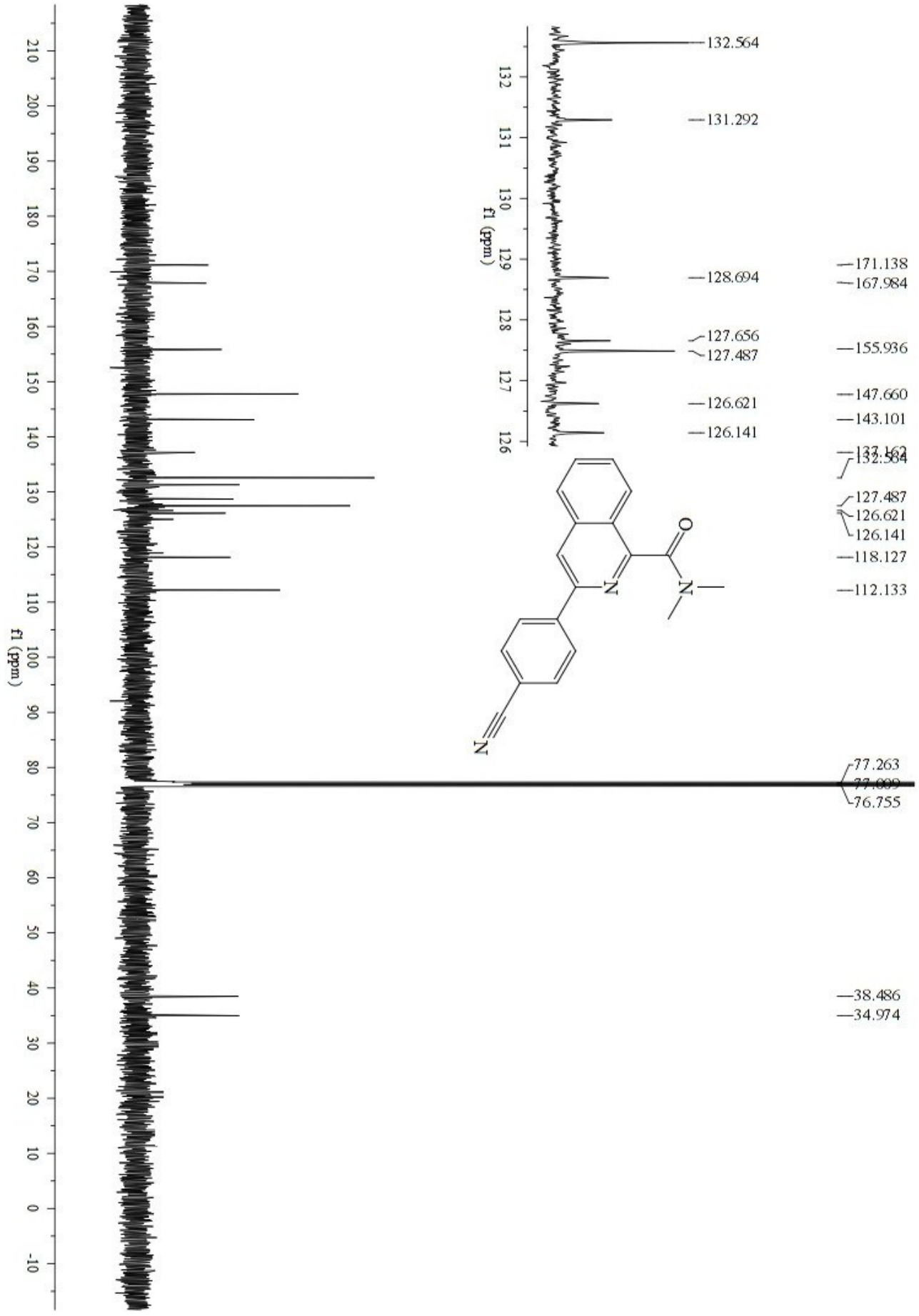
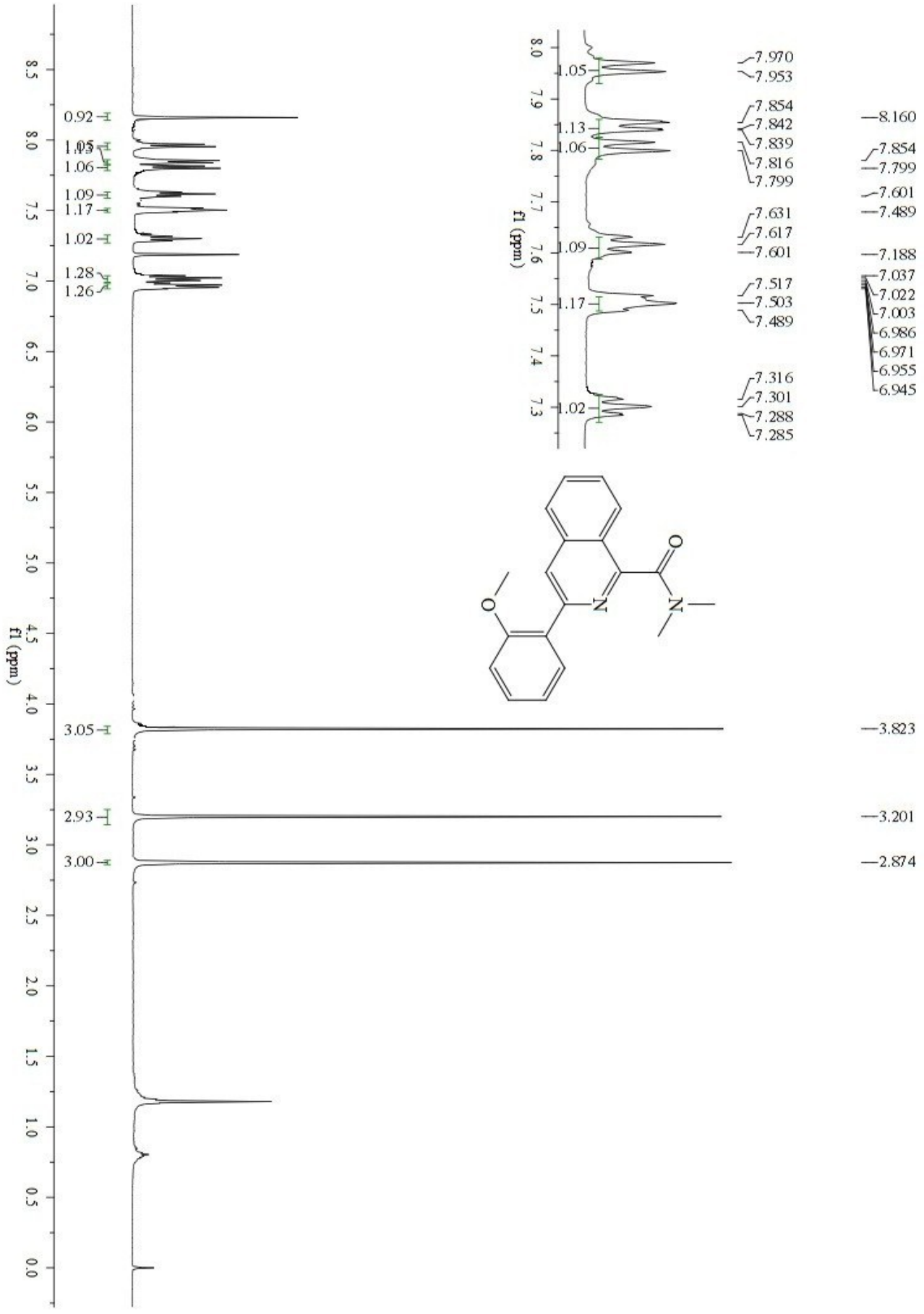


3-(2-Methoxyphenyl)-*N*,*N*-dimethylisoquinoline-1-carboxamide (14)



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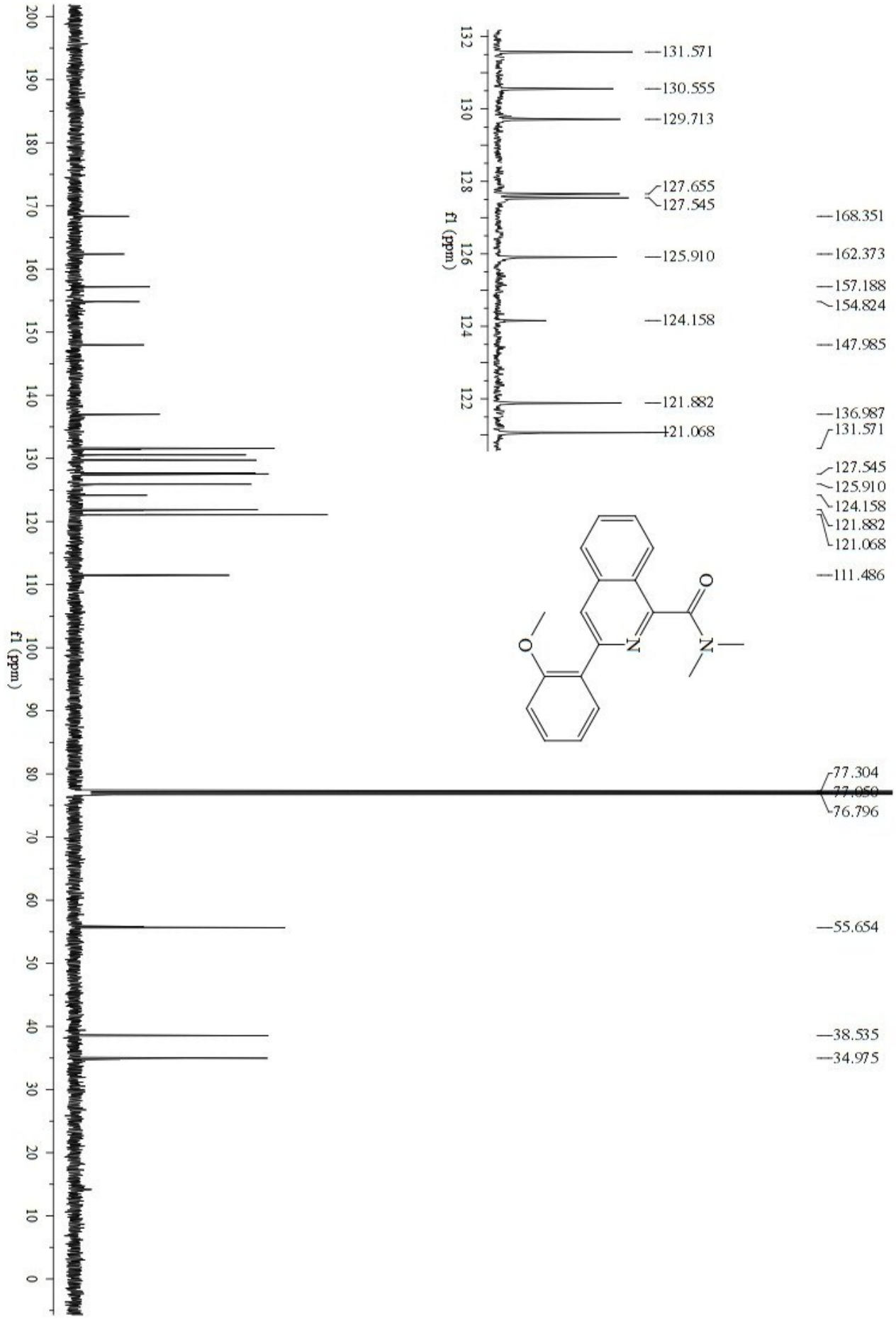
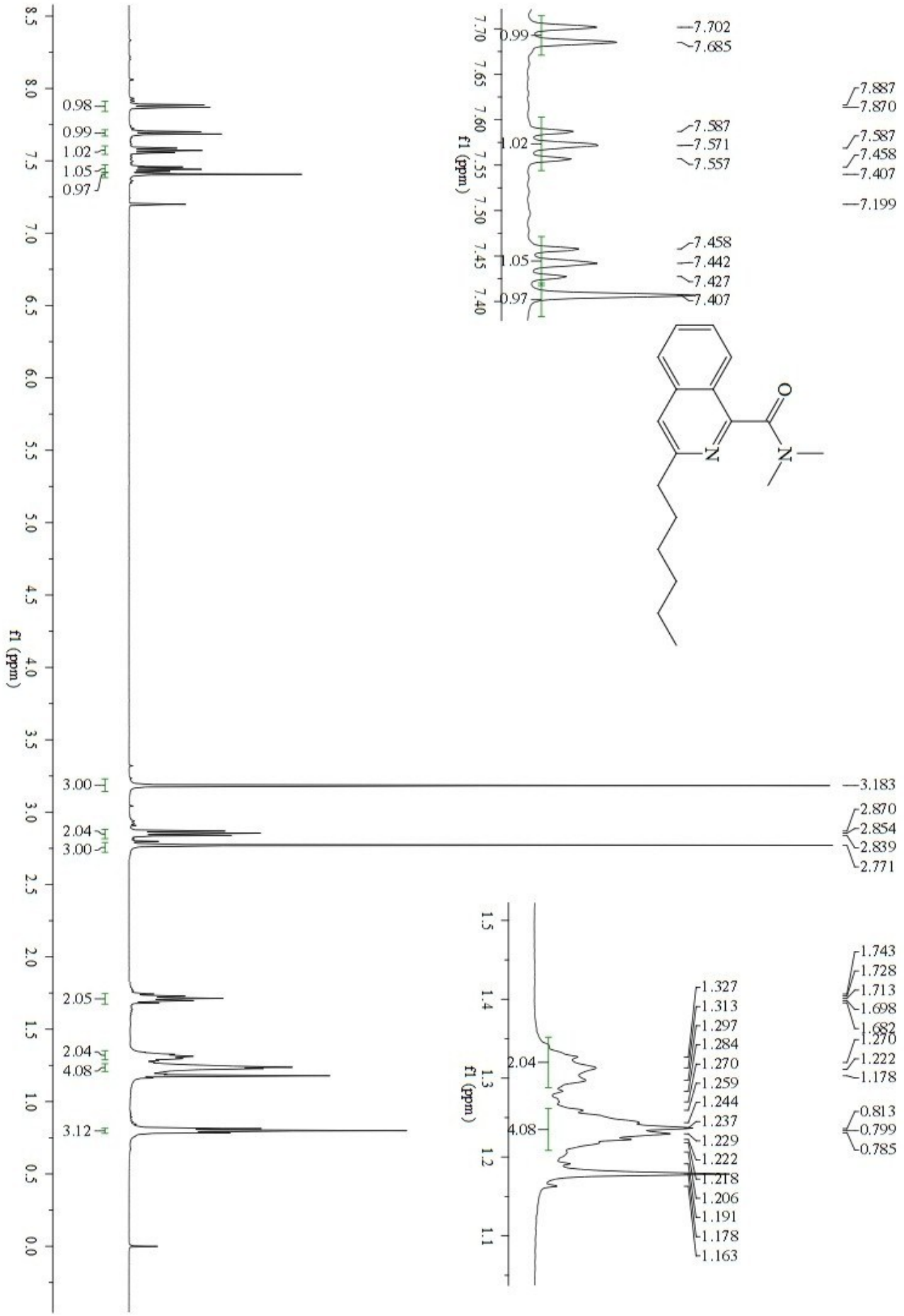


3-Hexyl-*N*,*N*-dimethylisoquinoline-1-carboxamide (15)



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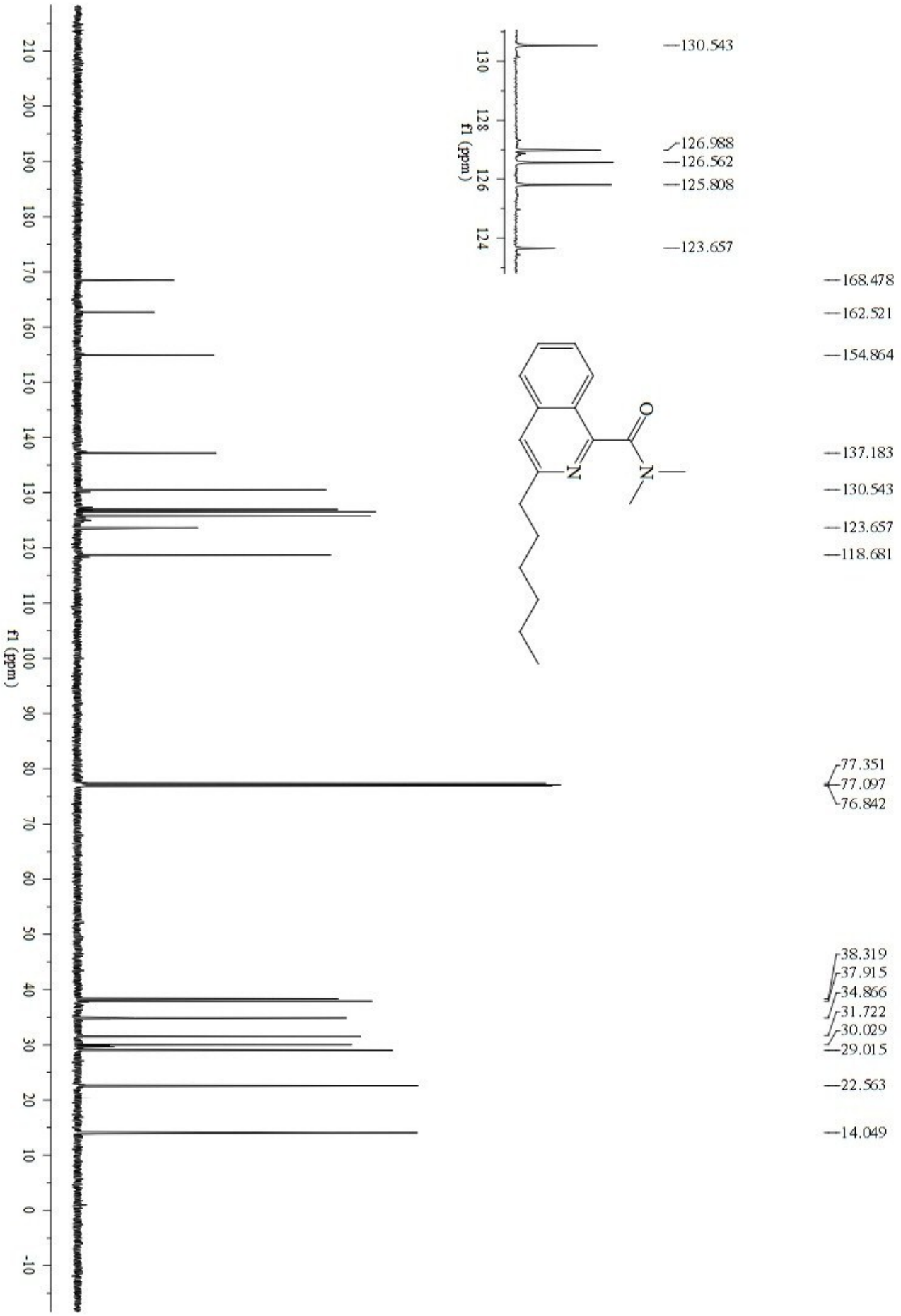
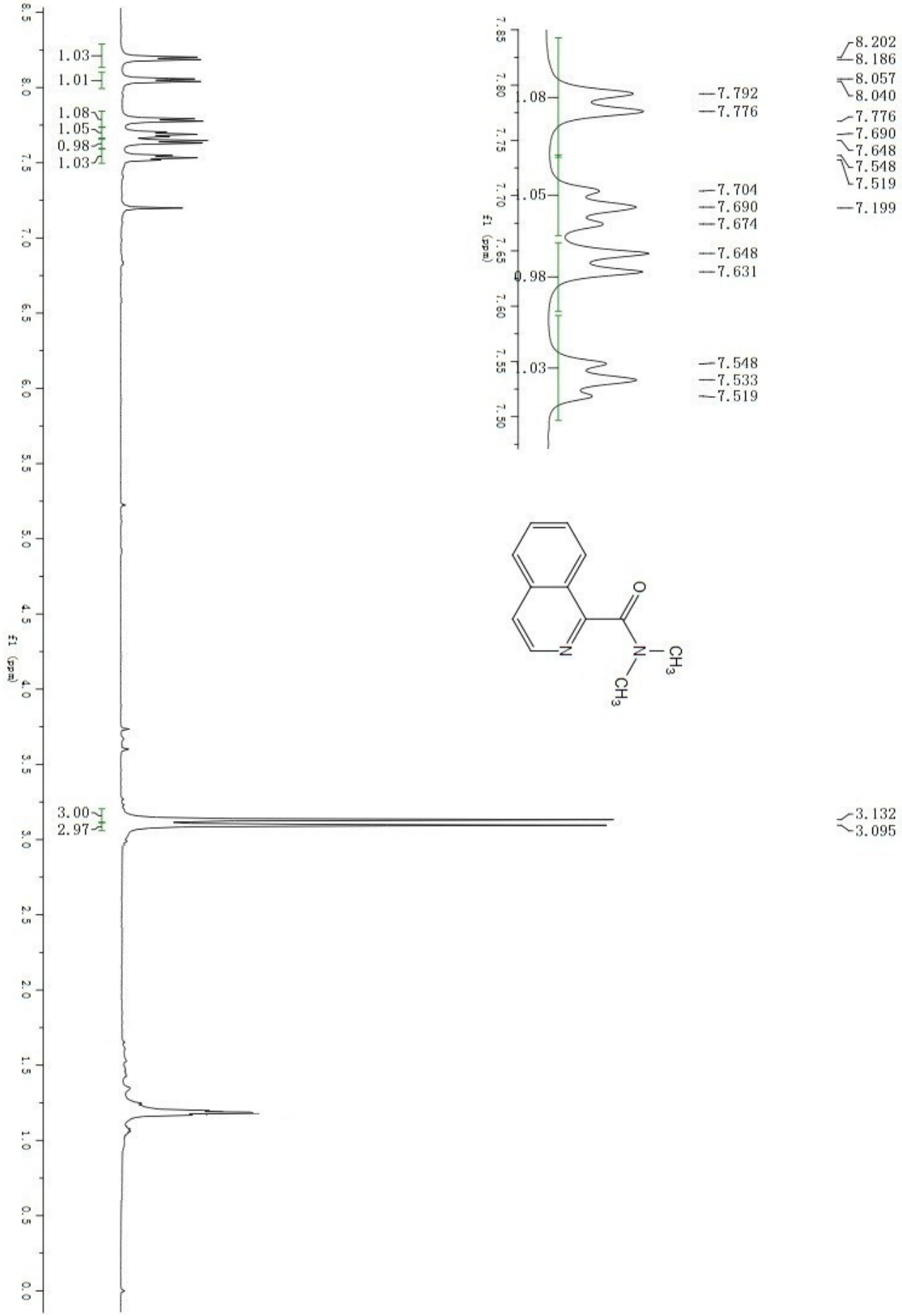


N,*N*-Dimethylisoquinoline-1-carboxamide (16)



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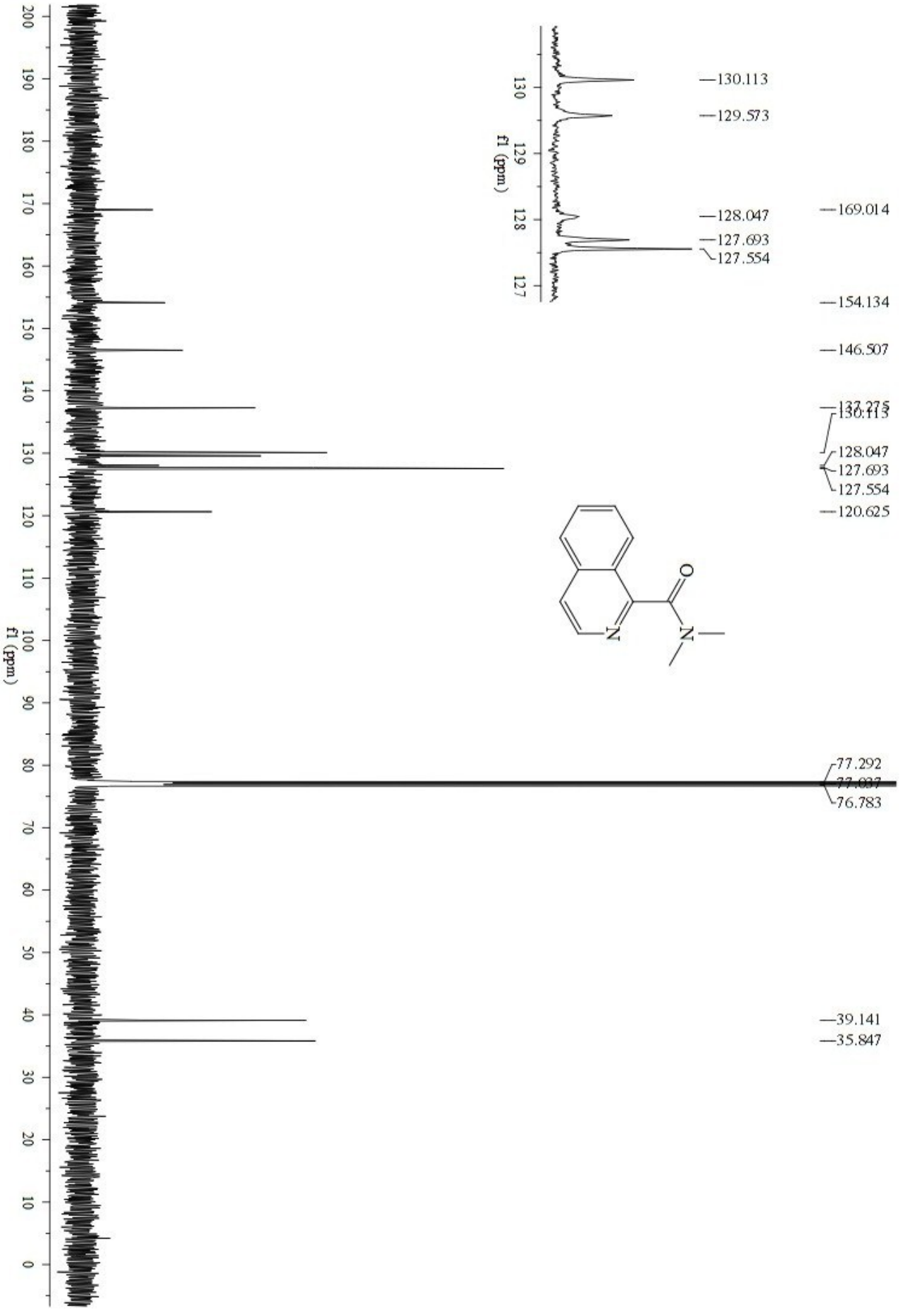
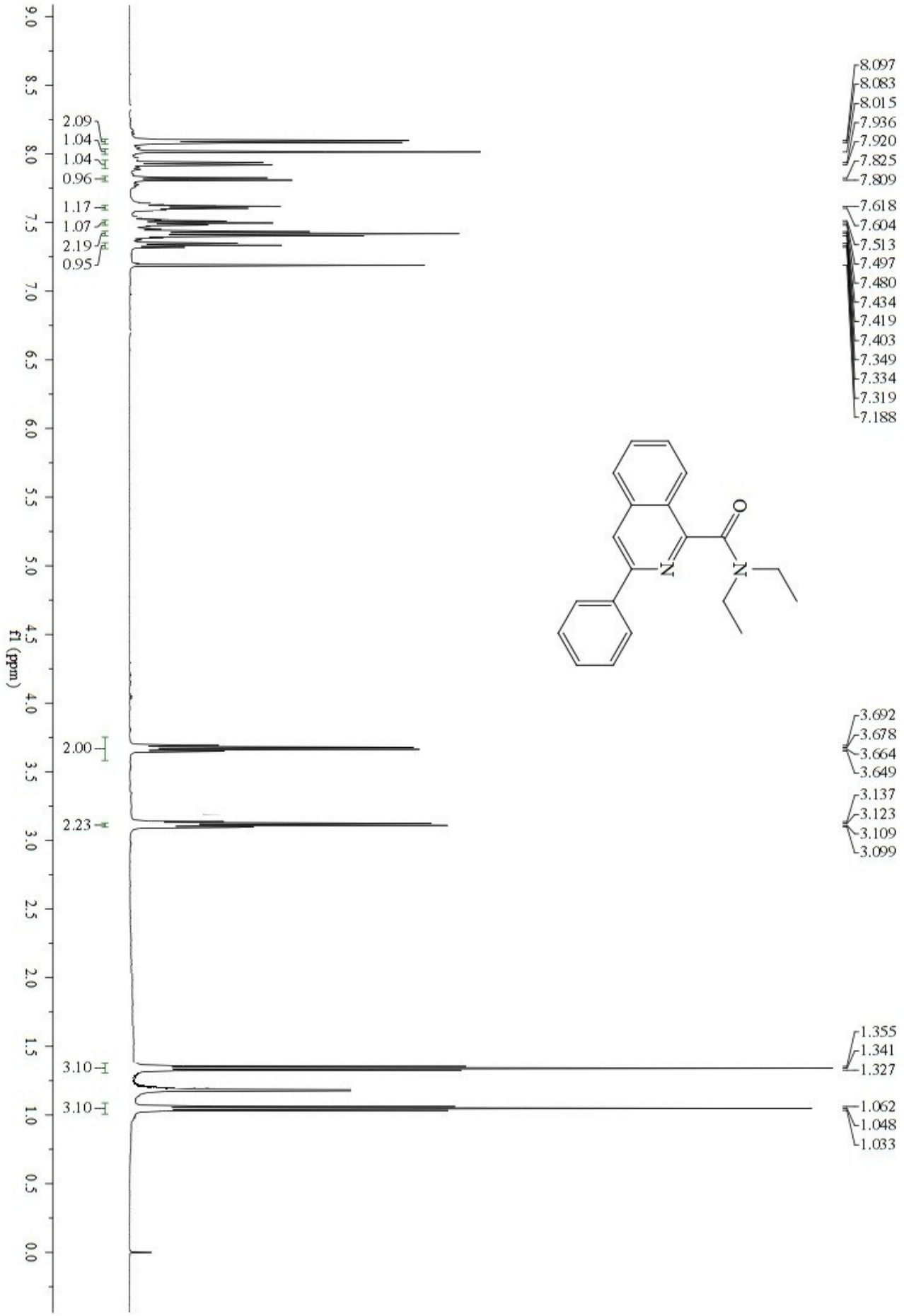


N,*N*-Diethyl-3-phenylisoquinoline-1-carboxamide (17)



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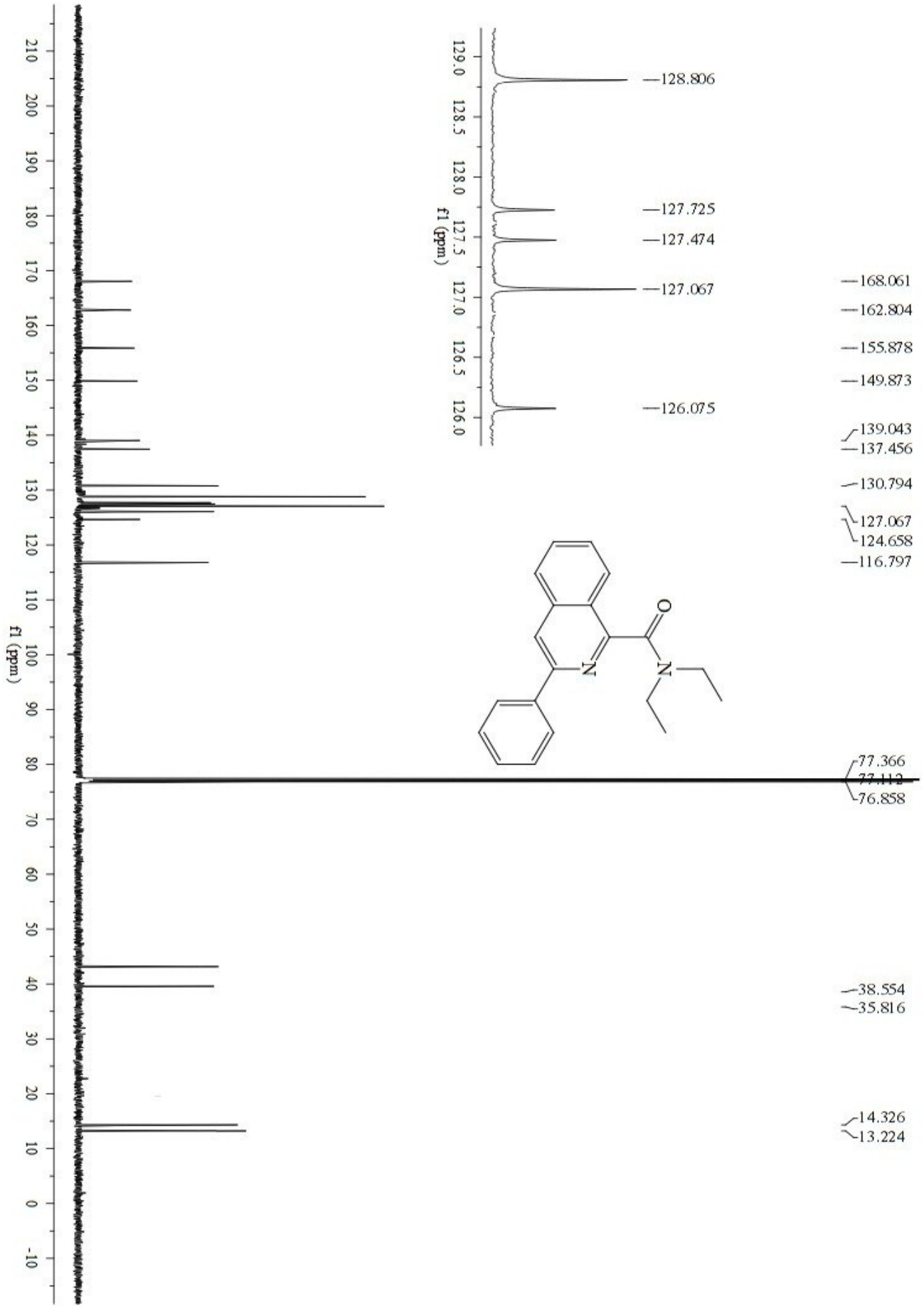
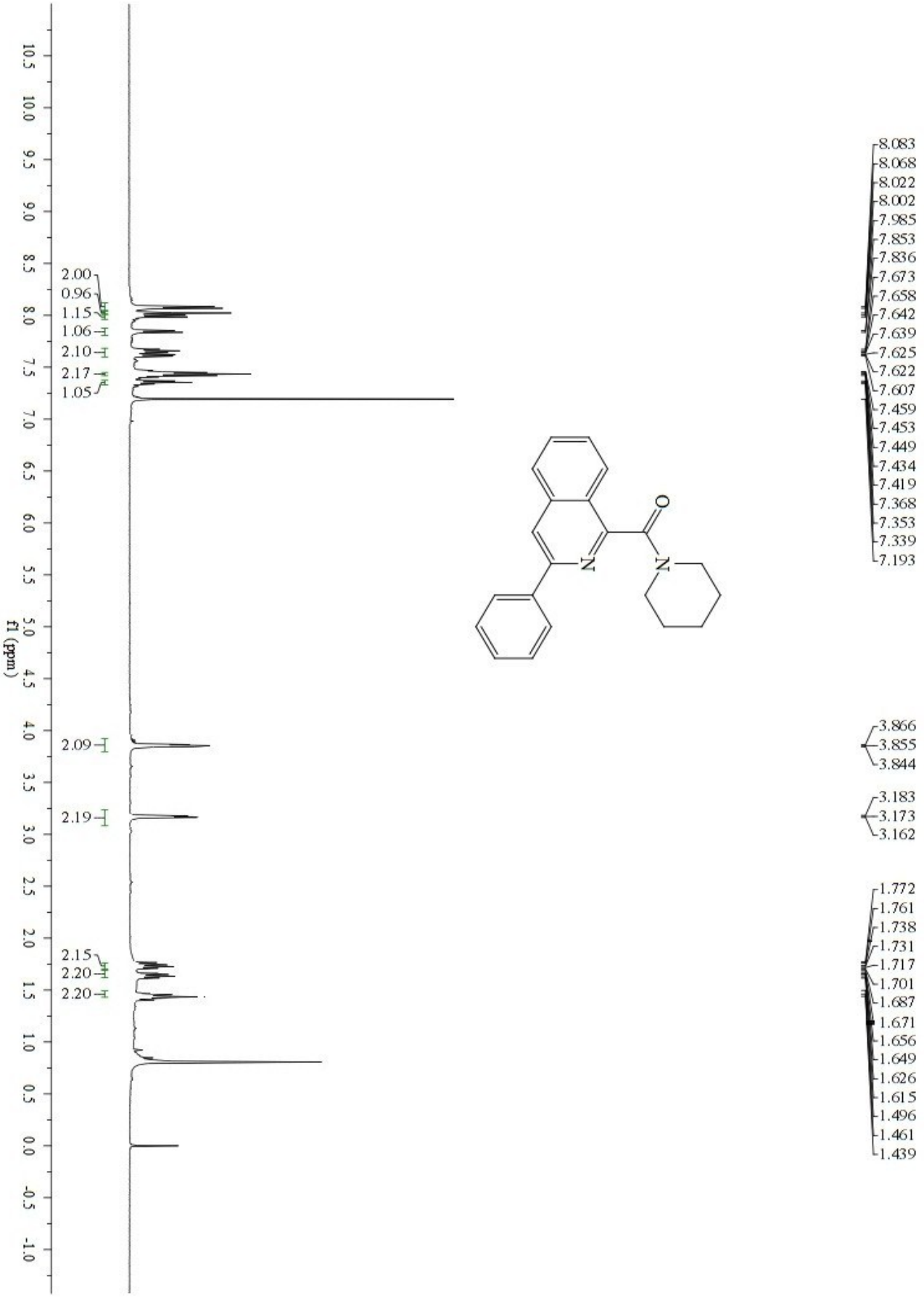
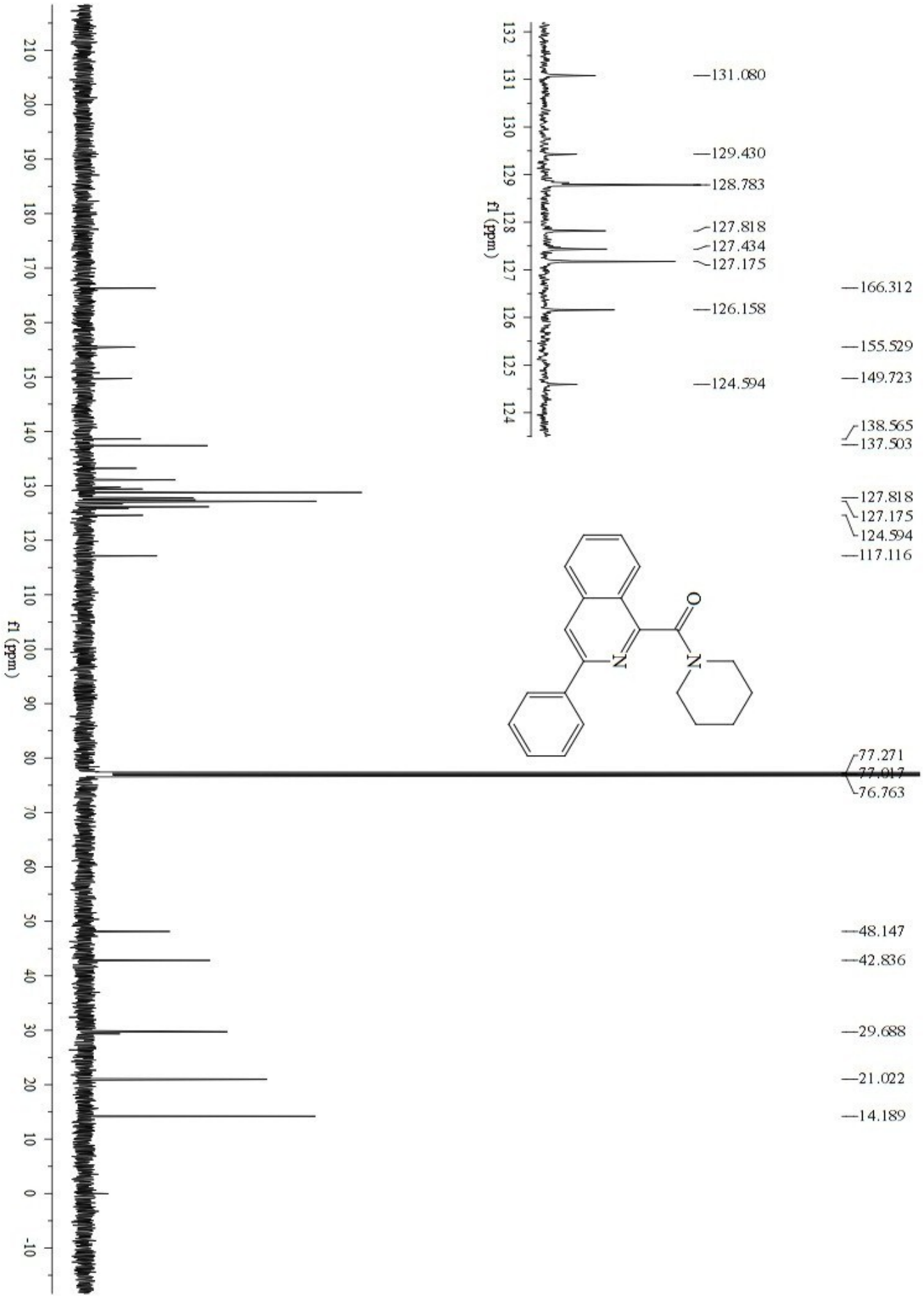


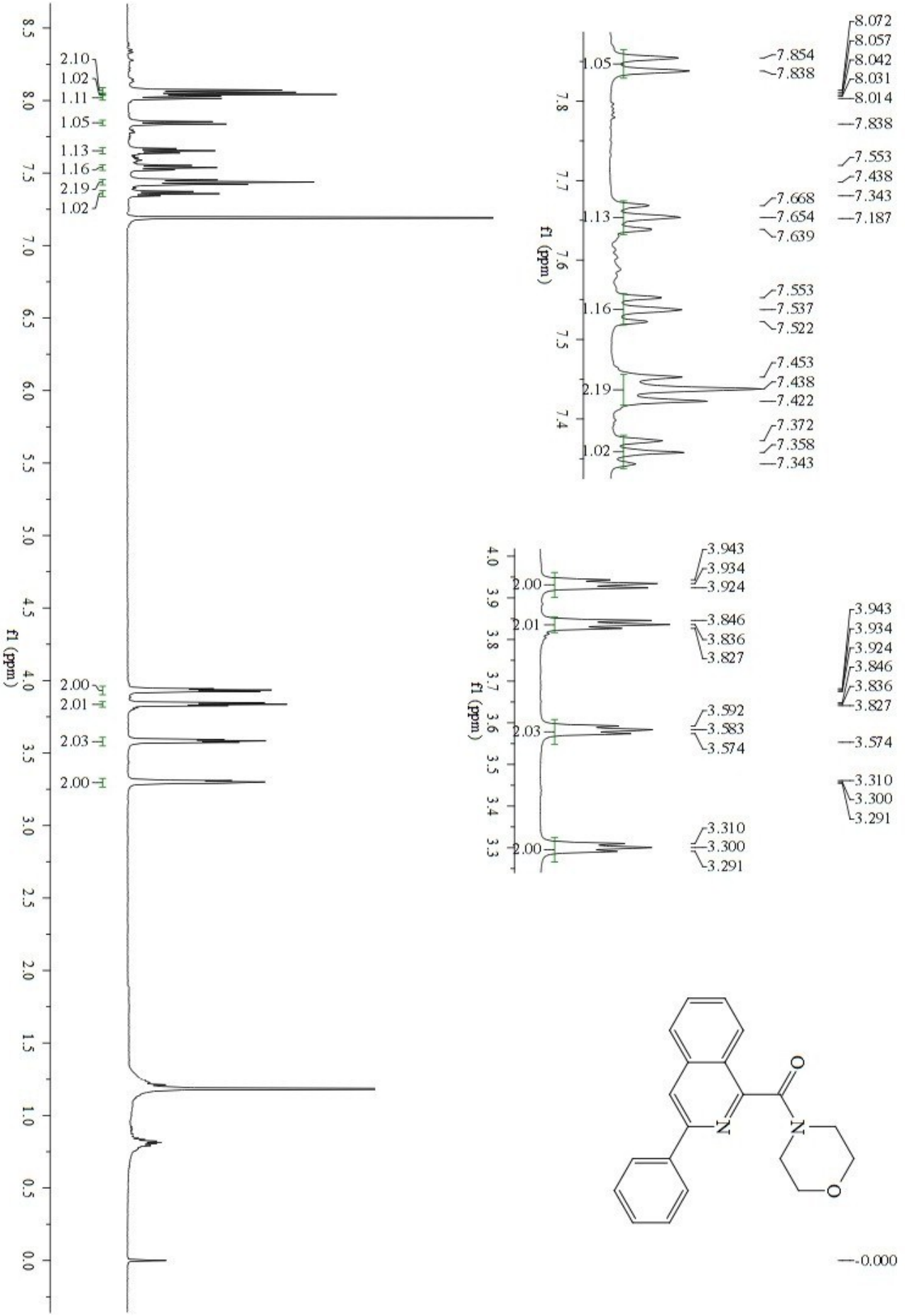
(3-Phenylisoquinolin-1-yl)(piperidin-1-yl)methanone (18)



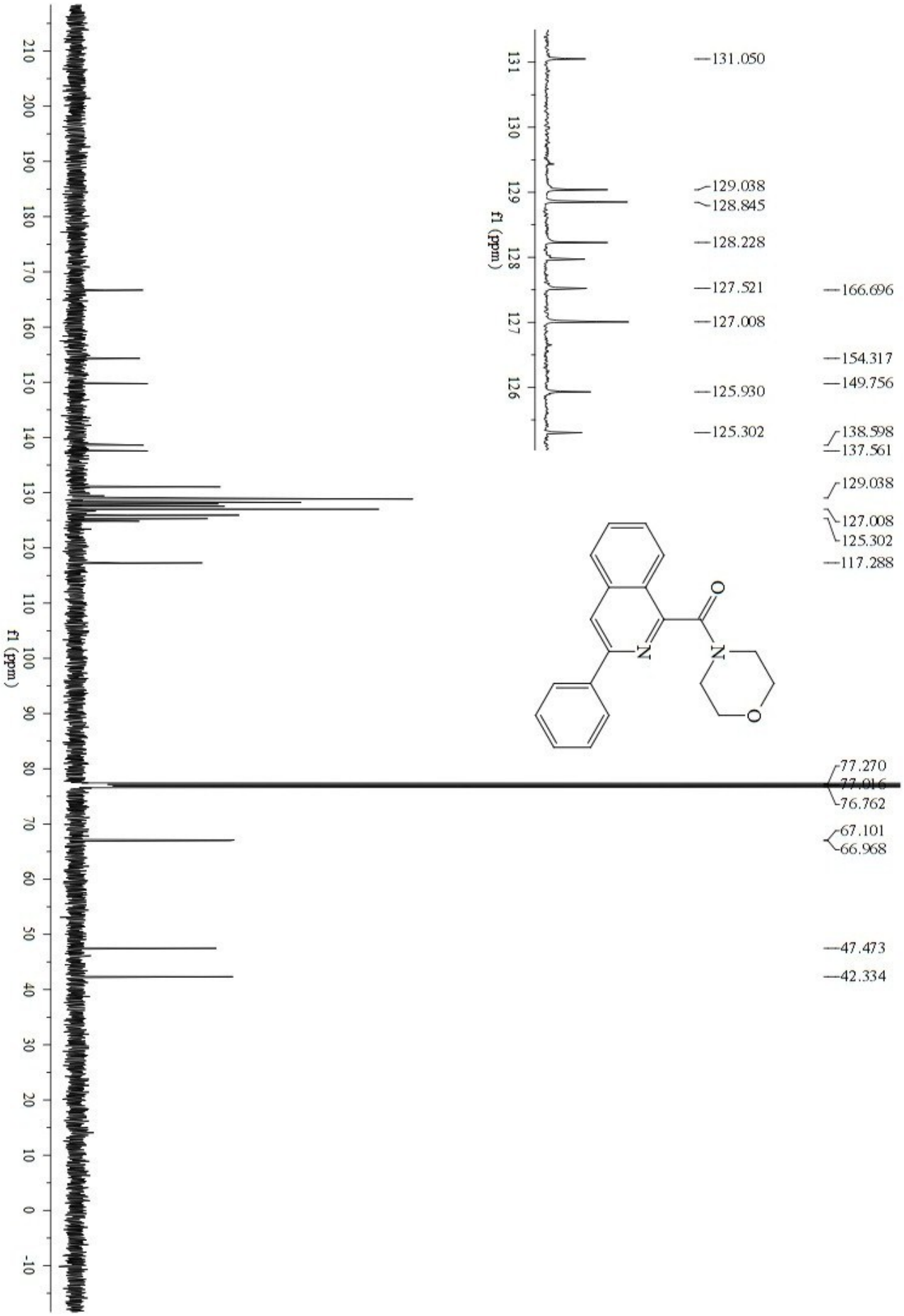
(3-Phenylisoquinolin-1-yl)(piperidin-1-yl)methanone (18)



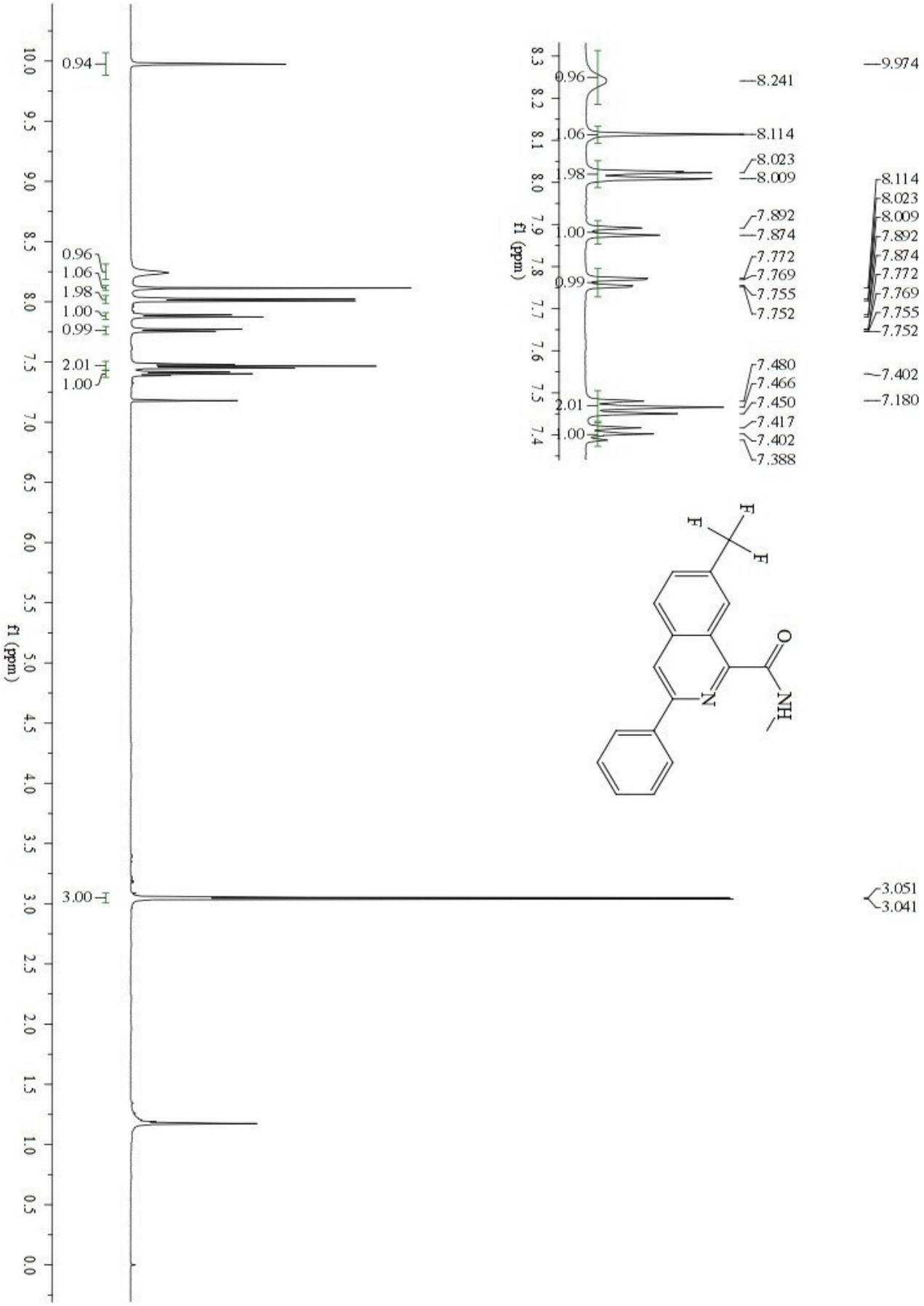
Morpholino(3-phenylisoquinolin-1-yl)methanone (19)



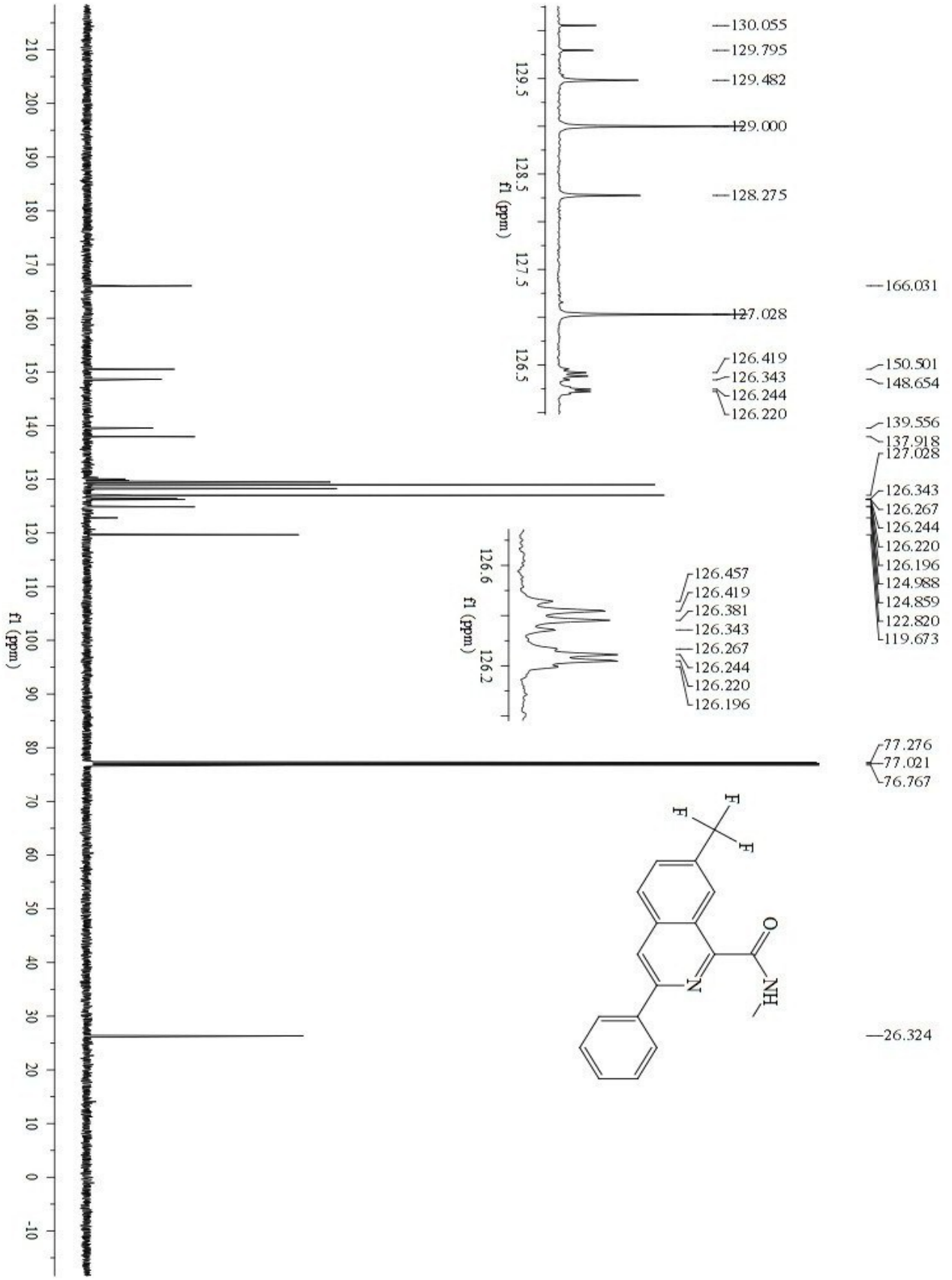
Morpholino(3-phenylisoquinolin-1-yl)methanone (19)



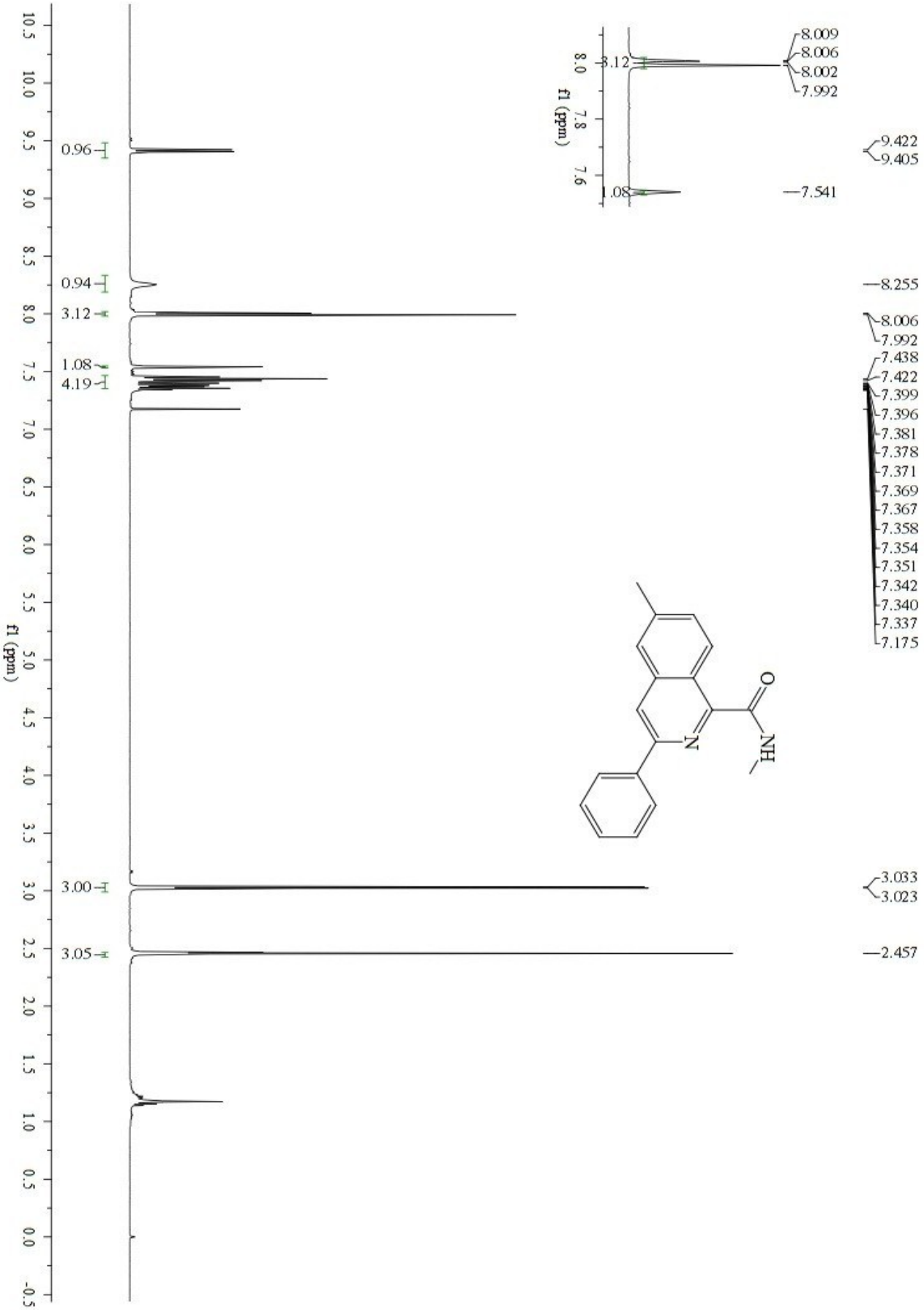
N-Methyl-3-phenyl-7-(trifluoromethyl)isoquinoline-1-carboxamide (20)



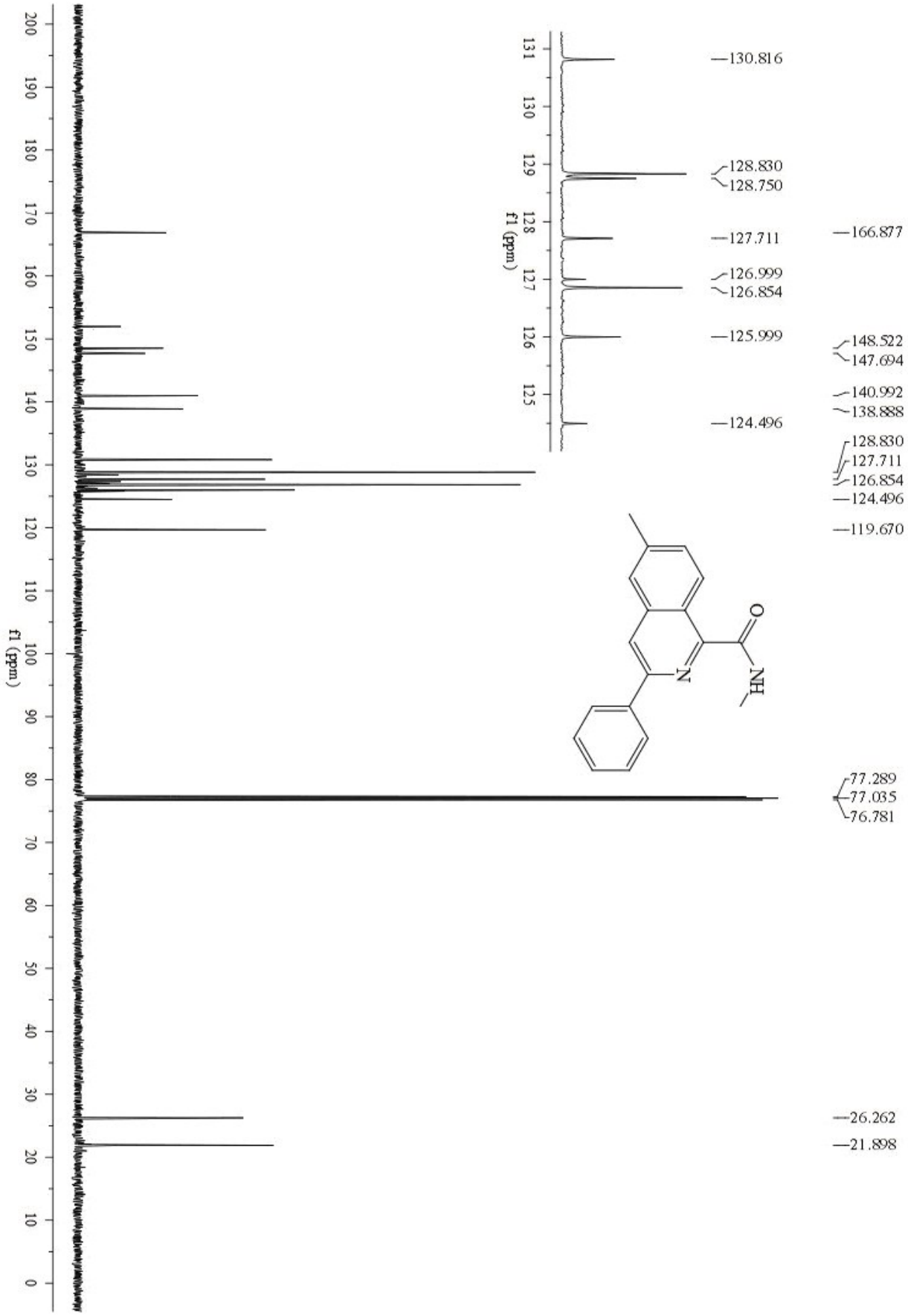
N-Methyl-3-phenyl-7-(trifluoromethyl)isoquinoline-1-carboxamide (20)



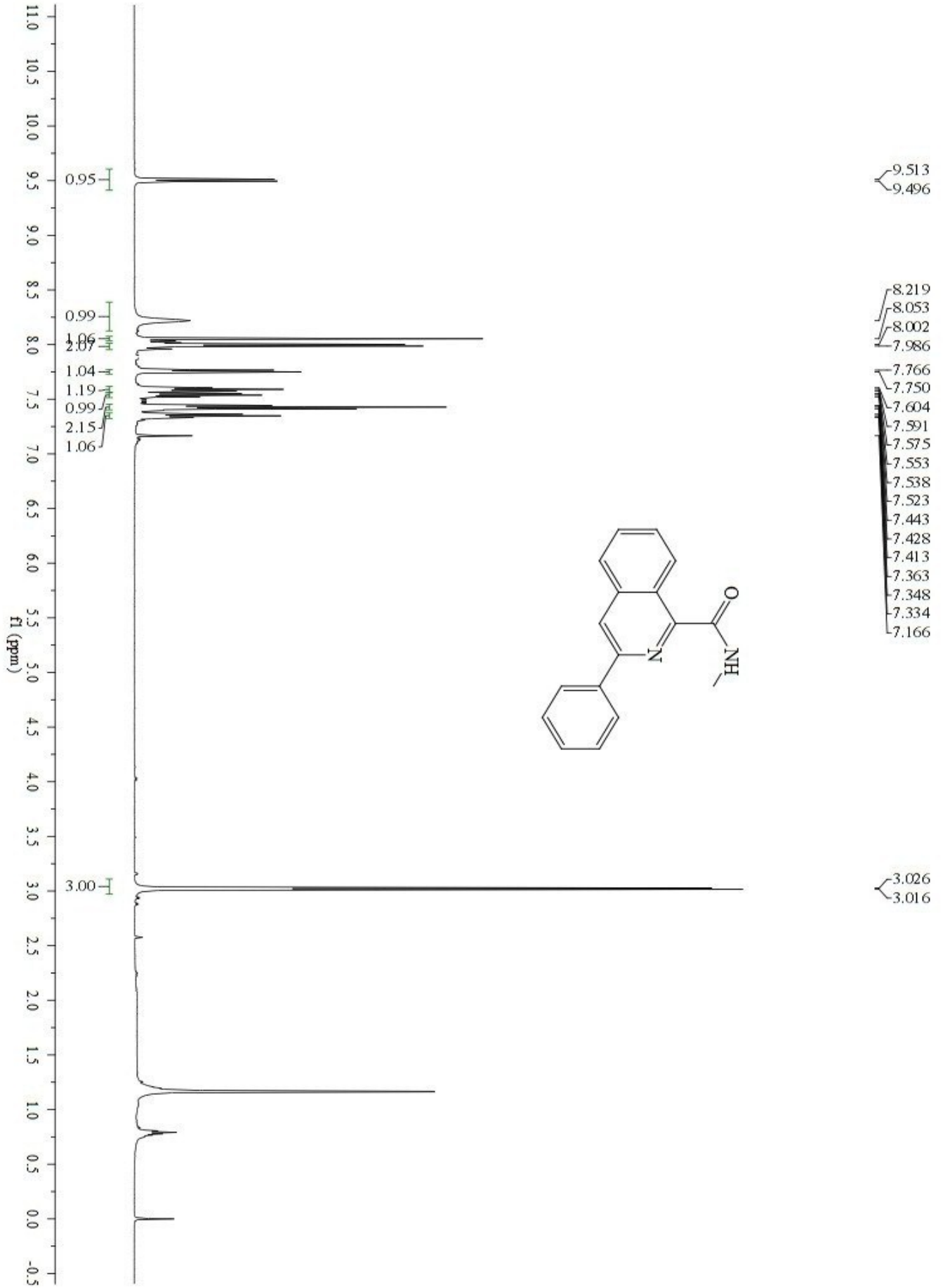
N,6-Dimethyl-3-phenylisoquinoline-1-carboxamide (21)



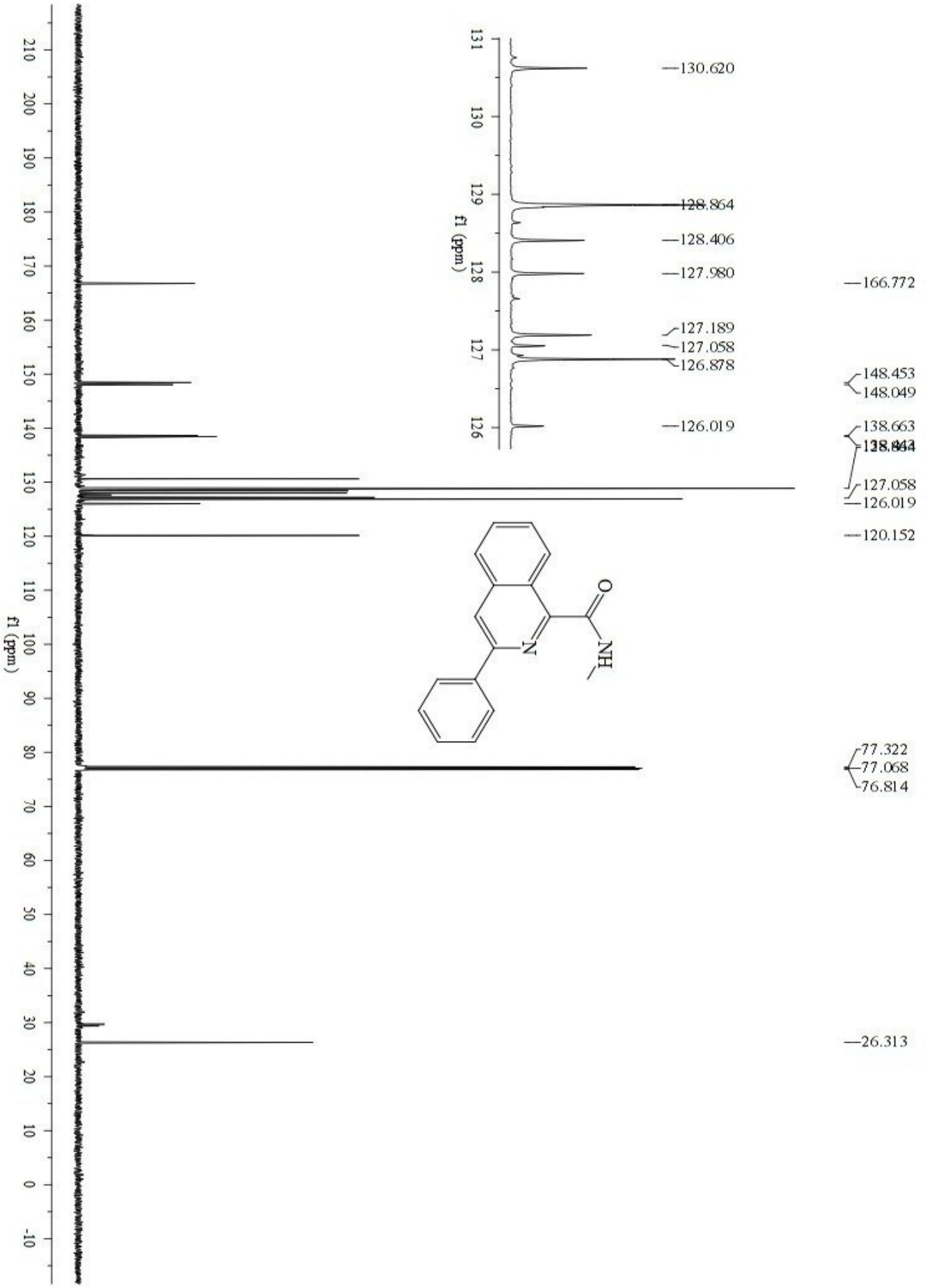
N,6-Dimethyl-3-phenylisoquinoline-1-carboxamide (21)



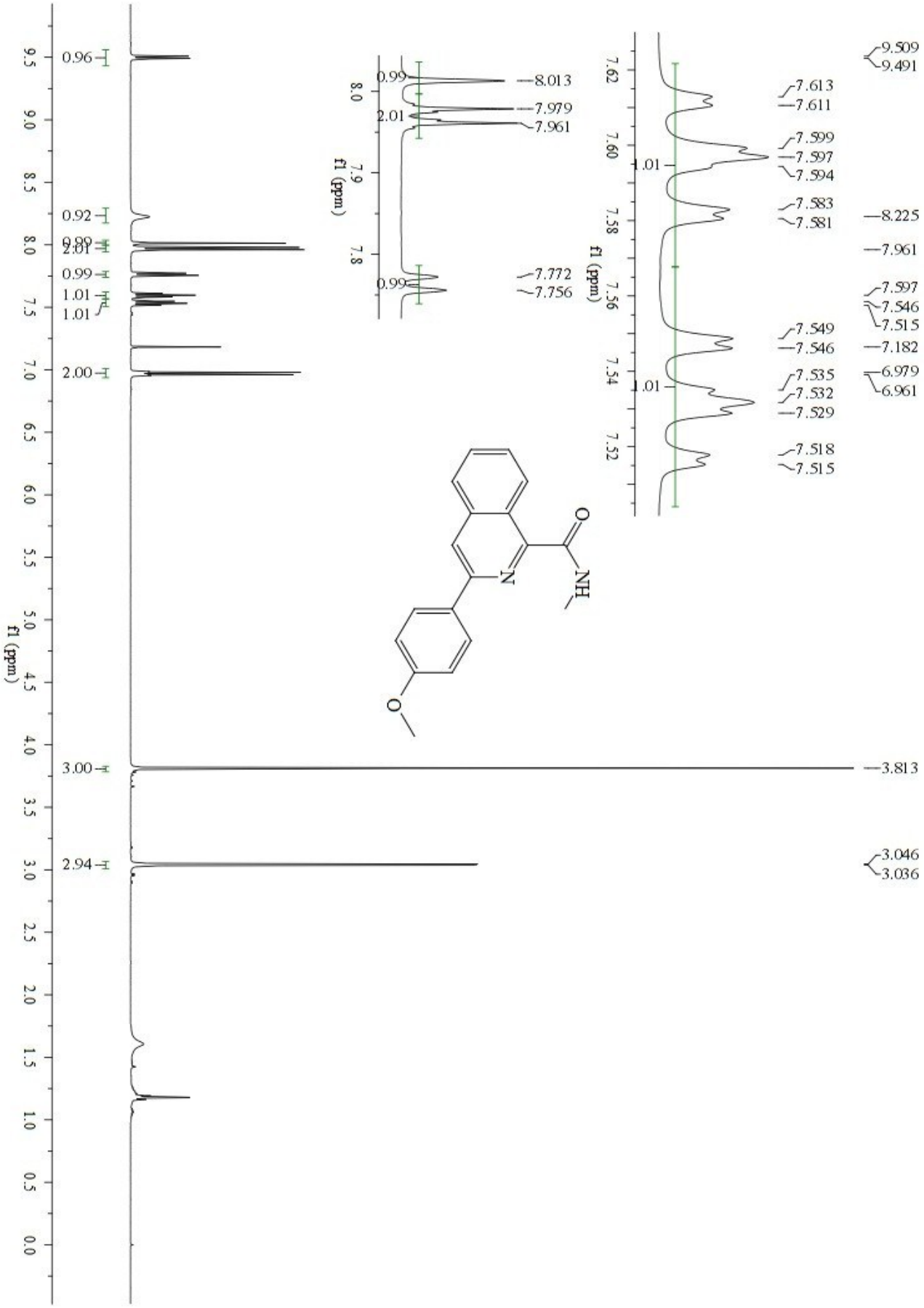
N-Methyl-3-phenylisoquinoline-1-carboxamide (22)



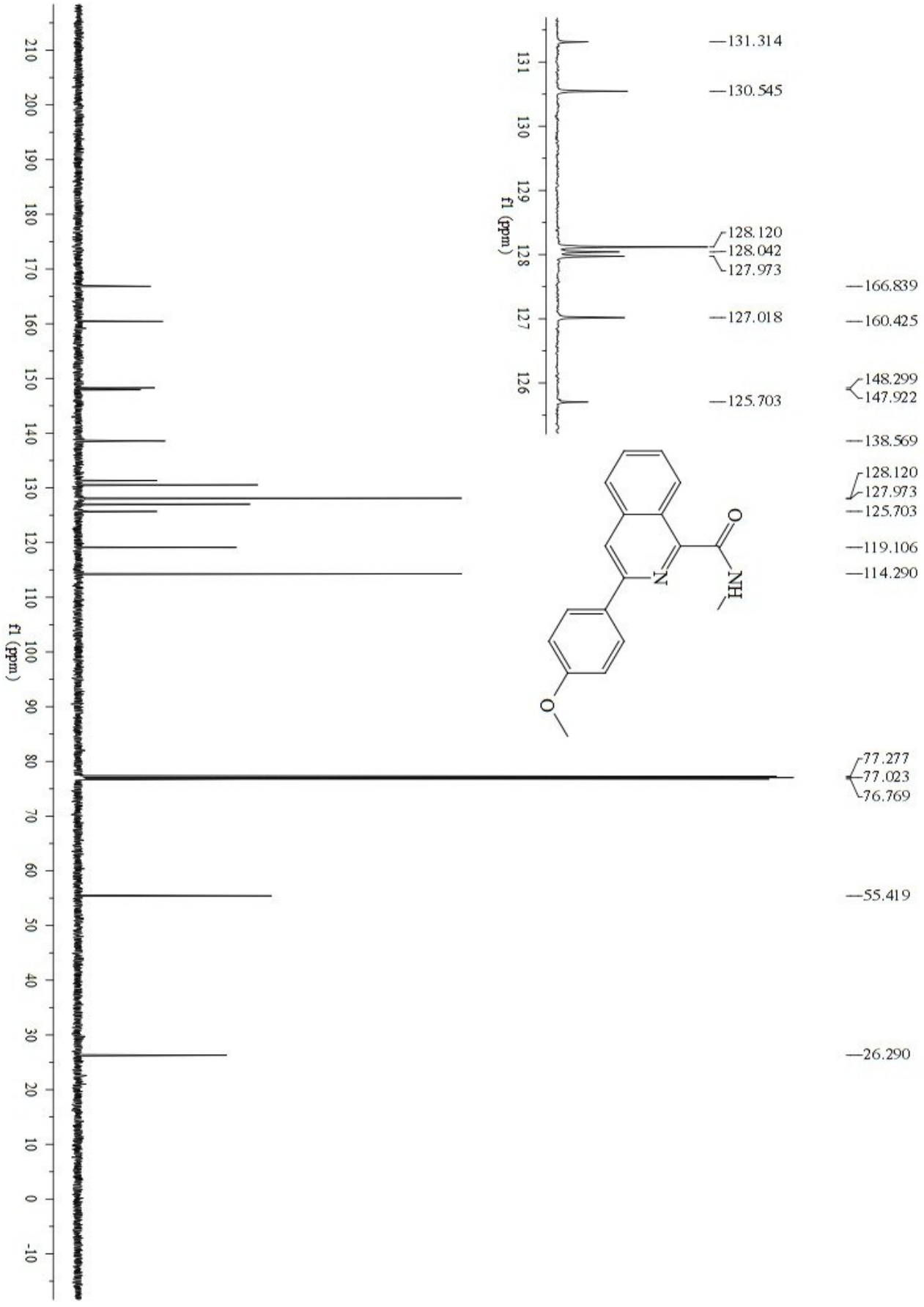
N-Methyl-3-phenylisoquinoline-1-carboxamide (22)



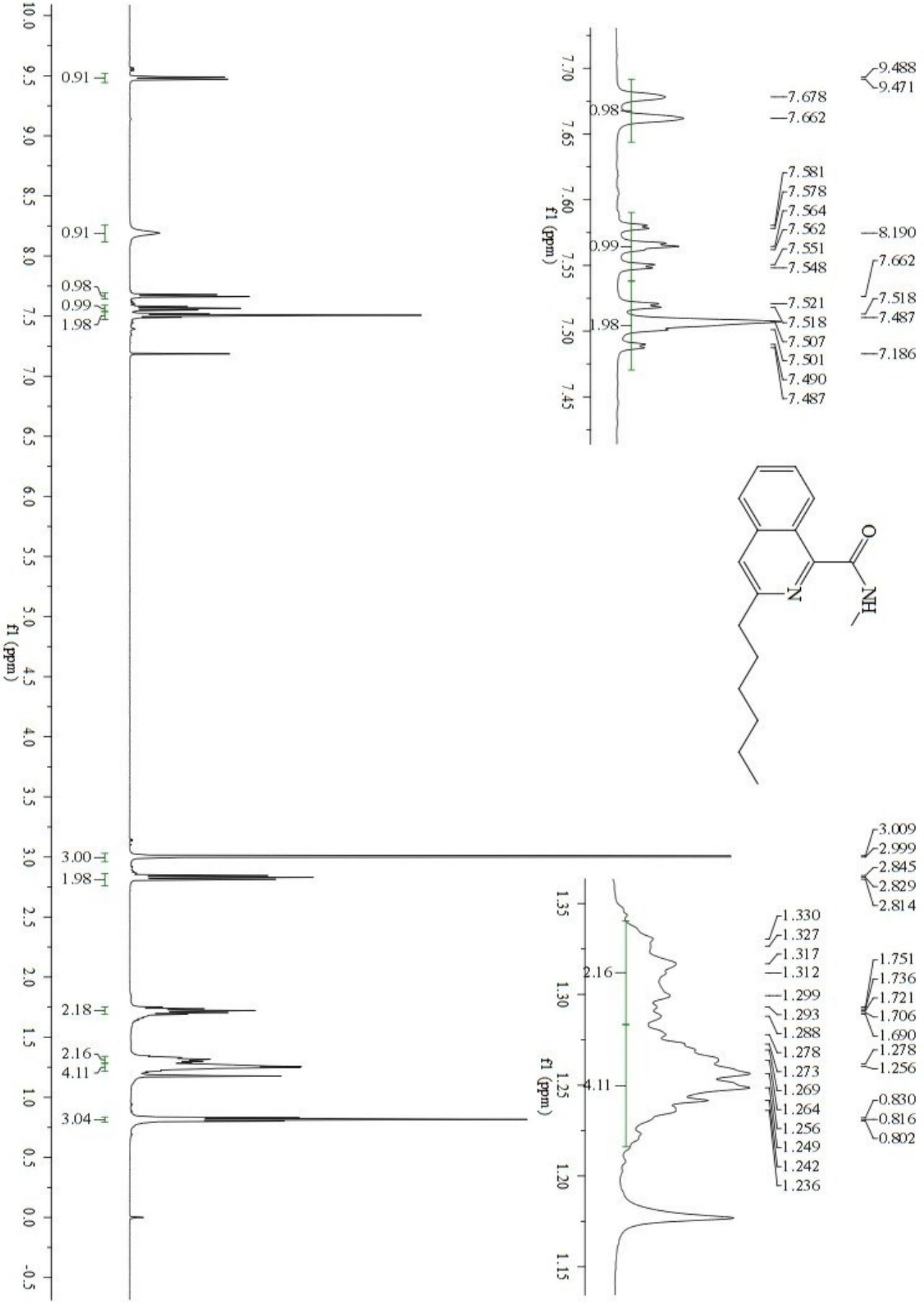
3-(4-Methoxyphenyl)-*N*-methylisoquinoline-1-carboxamide (23)



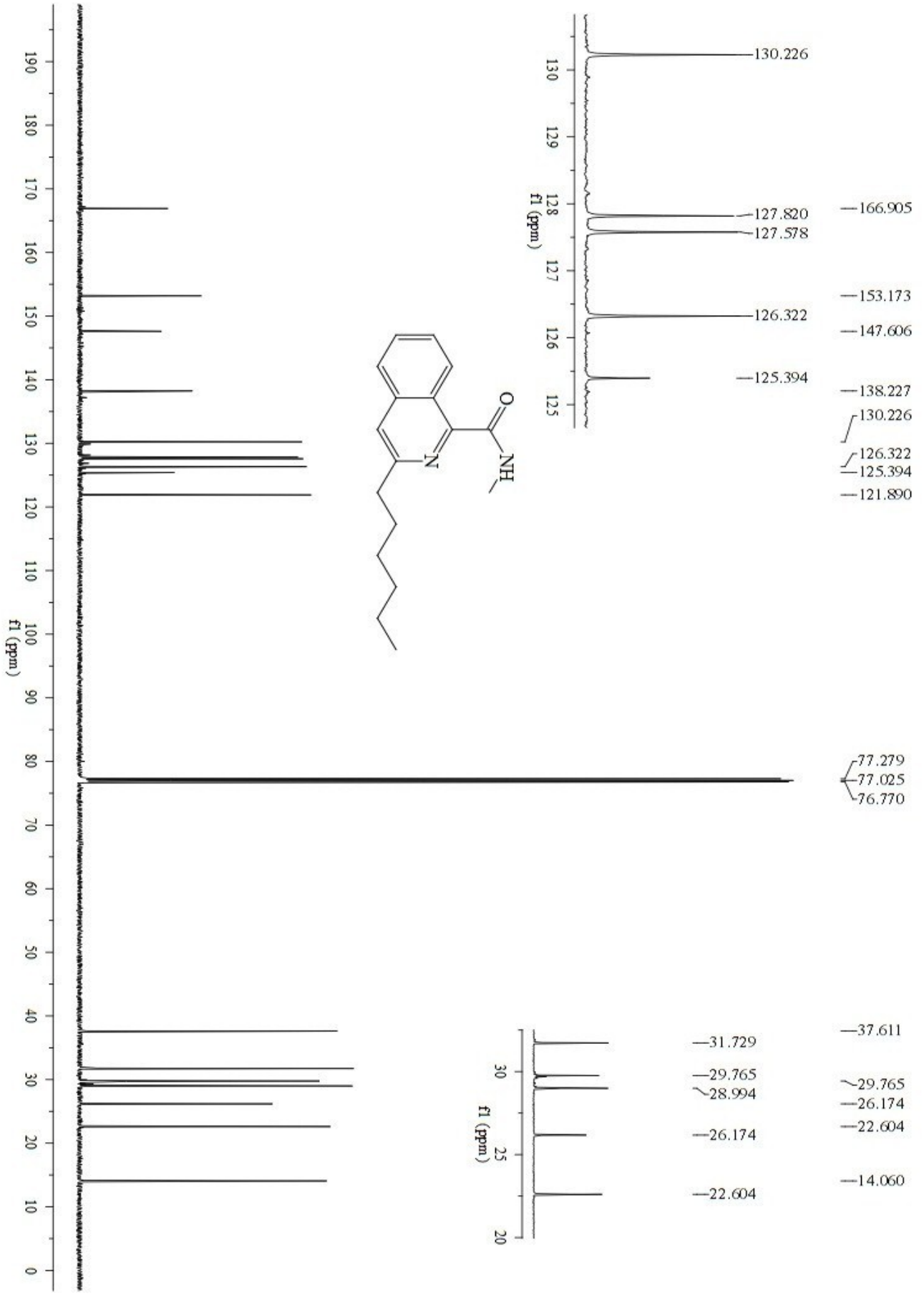
3-(4-Methoxyphenyl)-*N*-methylisoquinoline-1-carboxamide (23)



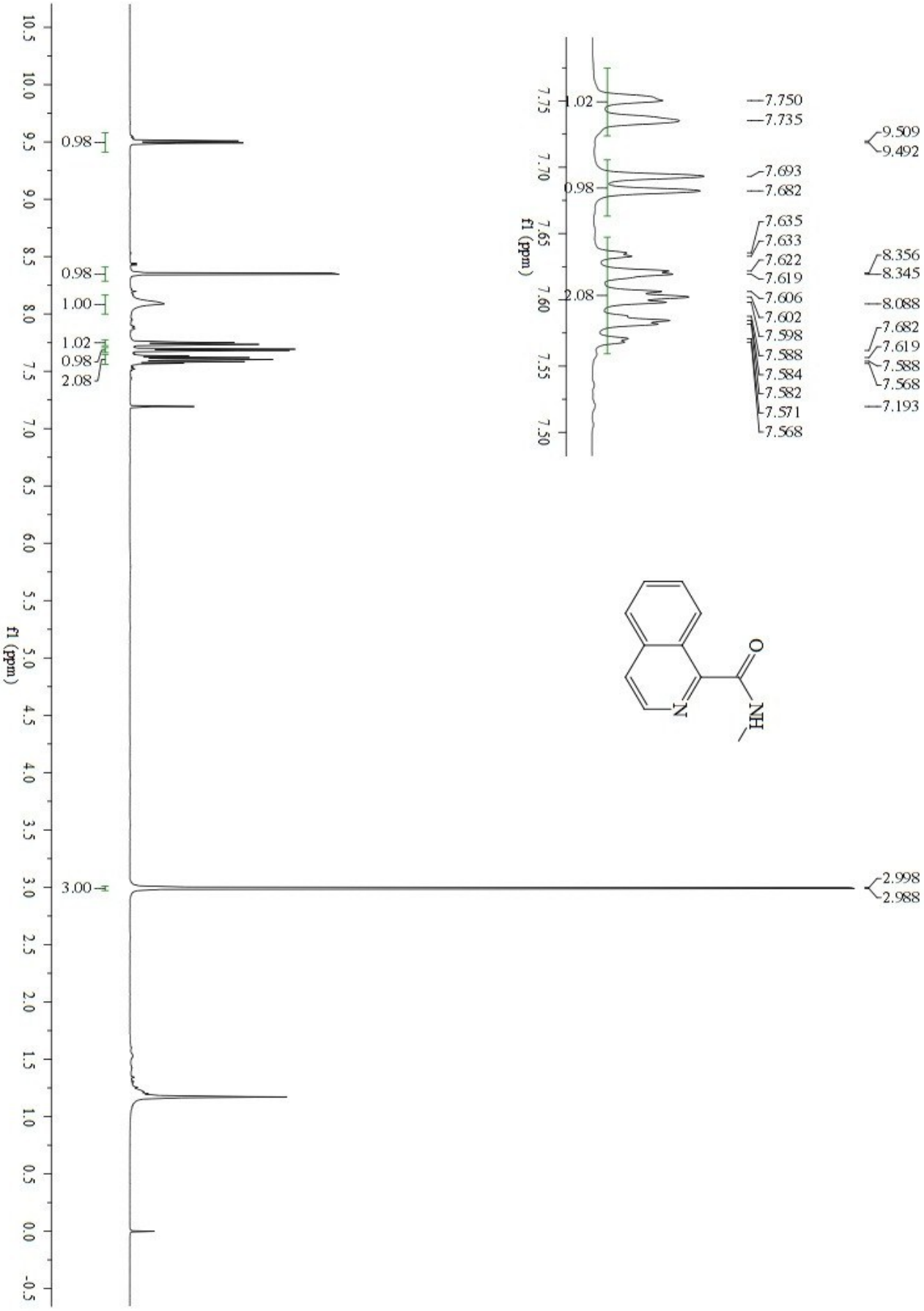
3-Hexyl-*N*-methylisoquinoline-1-carboxamide (24)



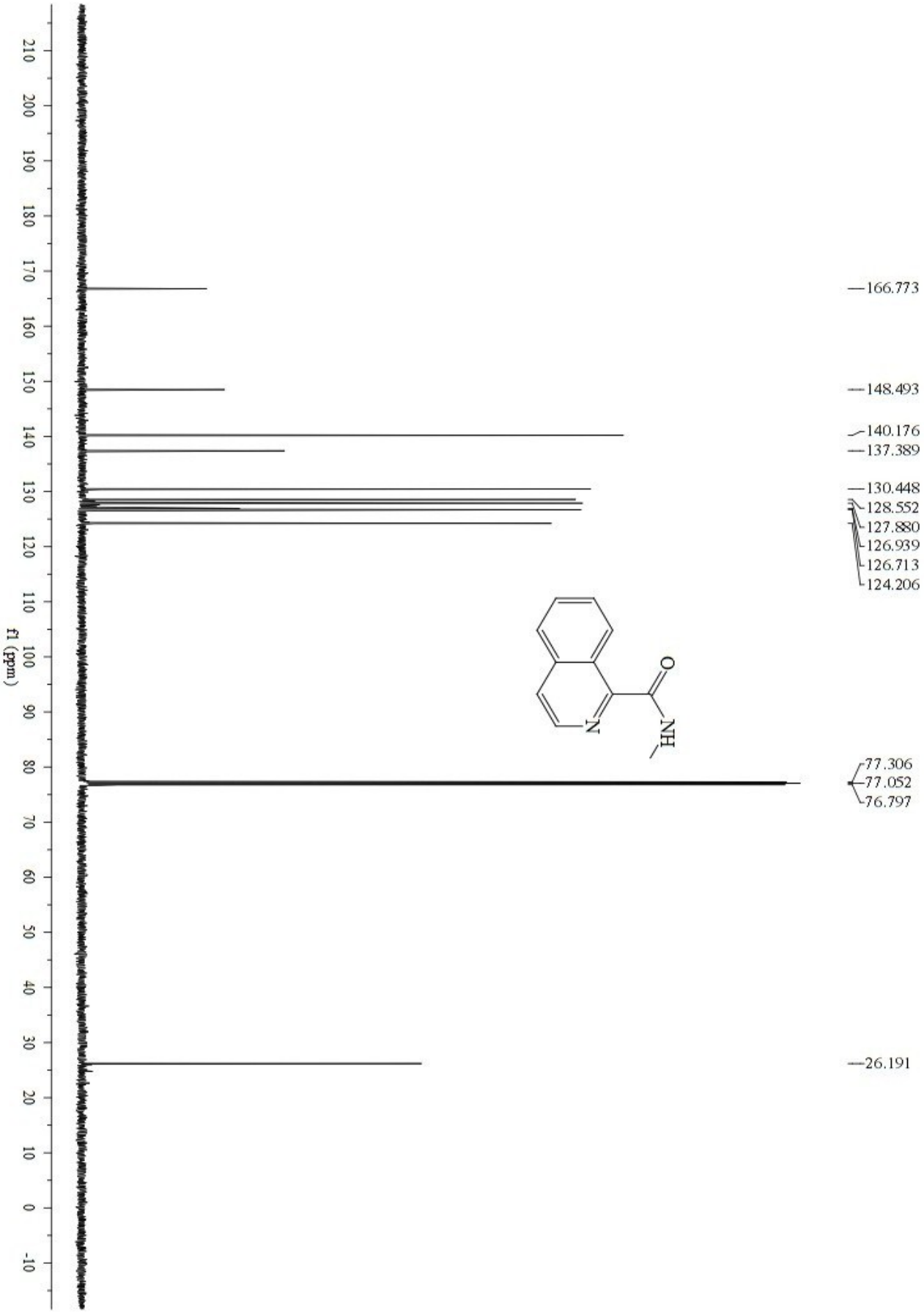
3-Hexyl-*N*-methylisoquinoline-1-carboxamide (24)



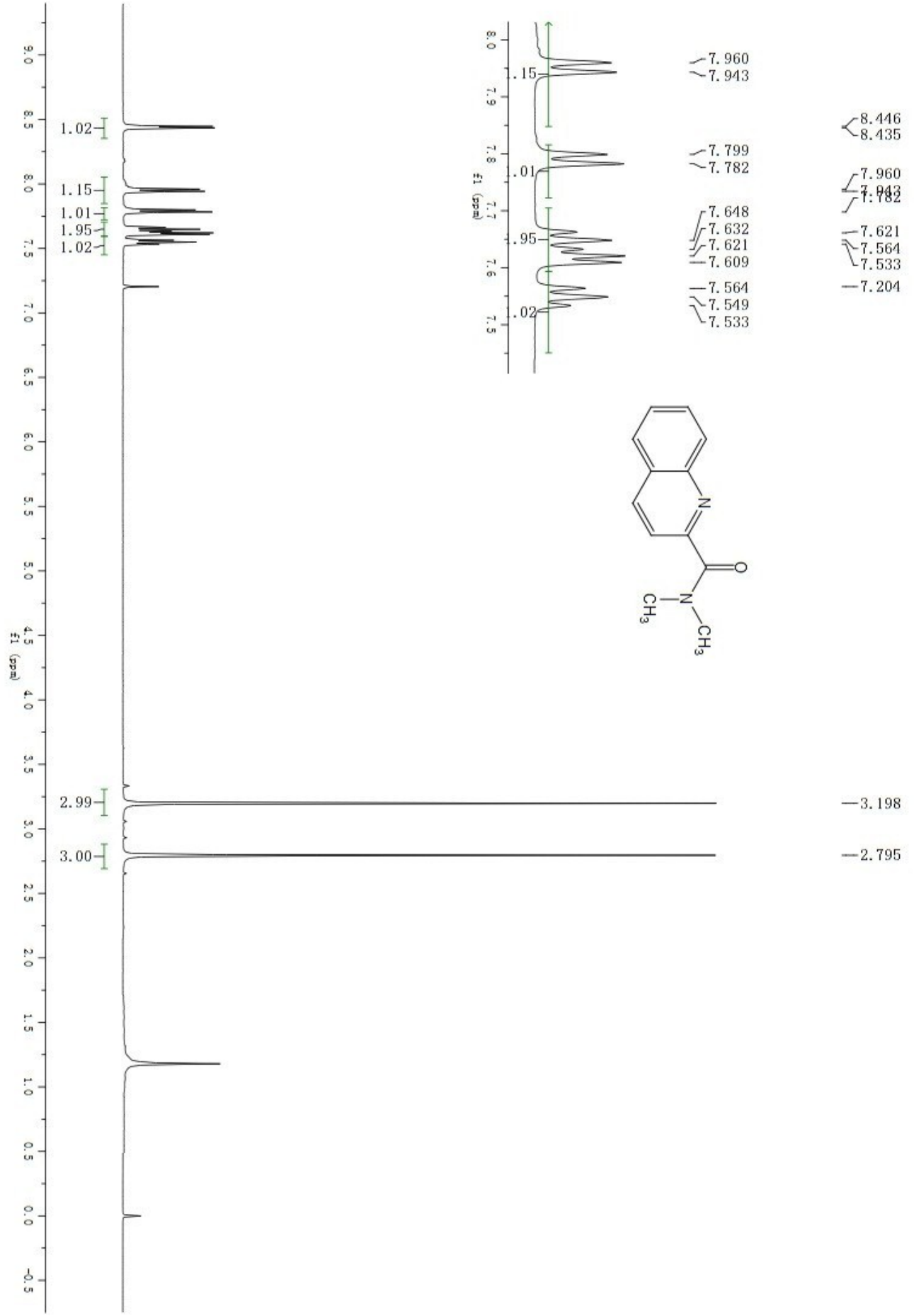
N-Methylisoquinoline-1-carboxamide (25)



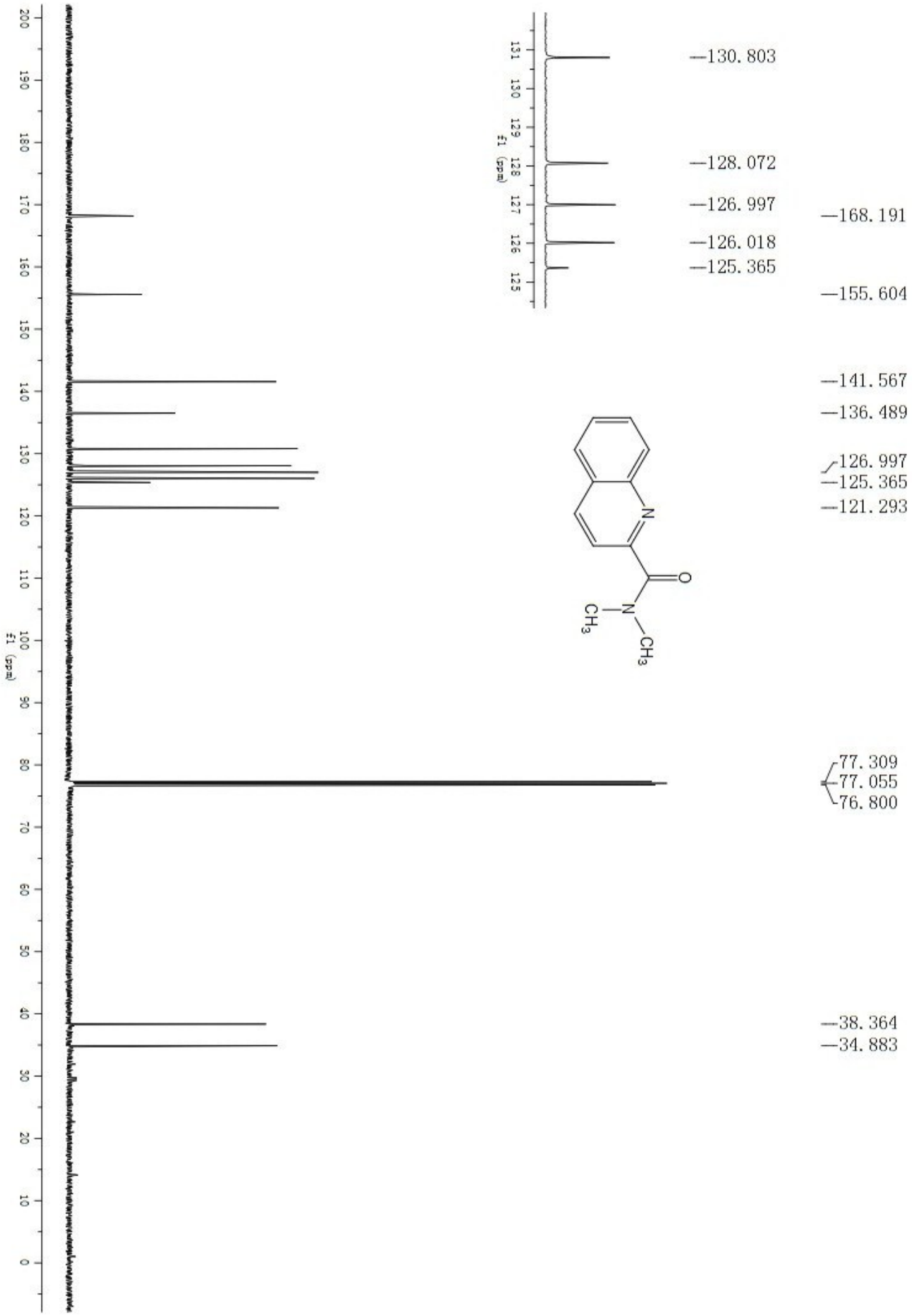
N-Methylisoquinoline-1-carboxamide (25)



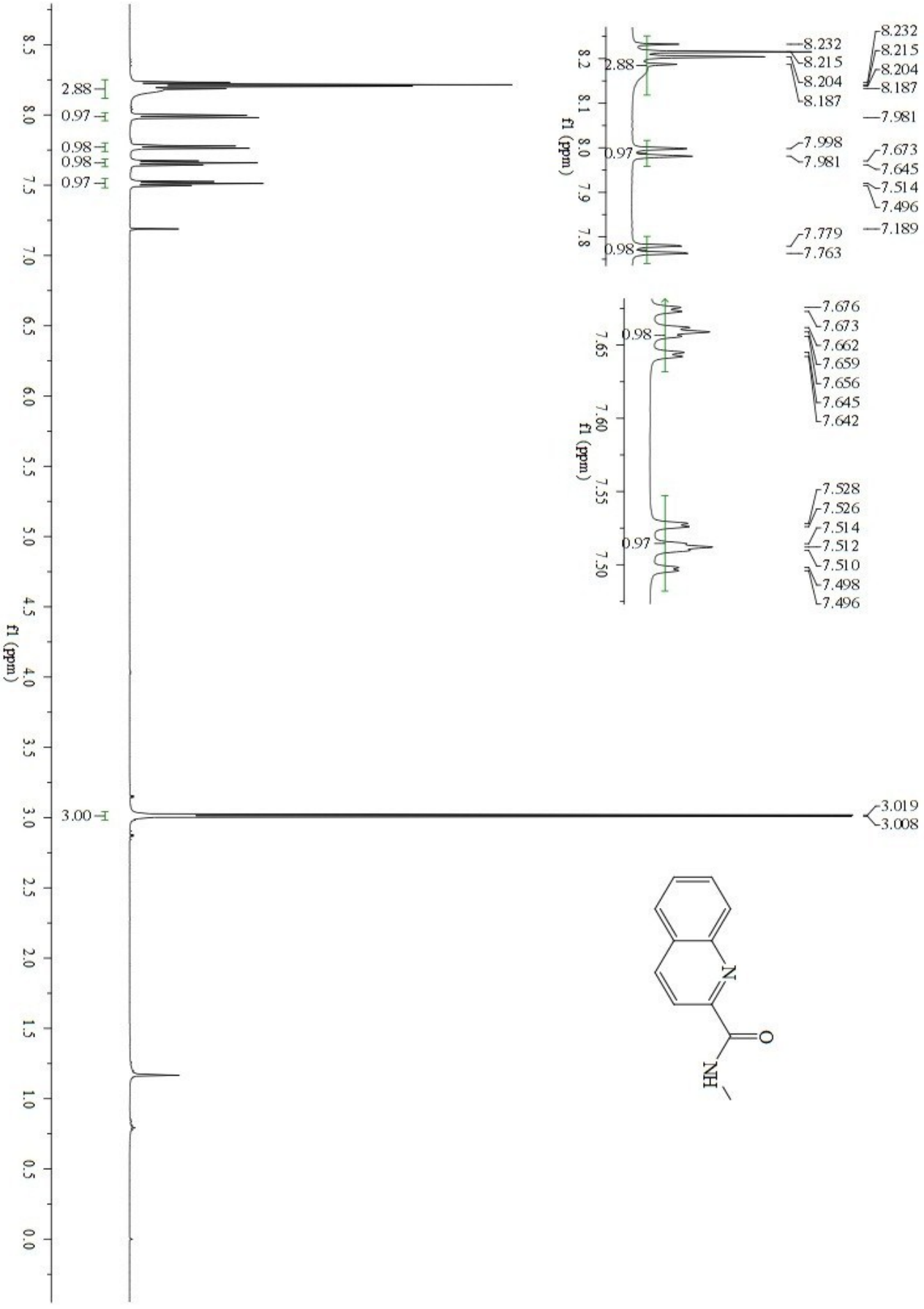
N,*N*-Dimethylquinoline-2-carboxamide (26)



N,*N*-Dimethylquinoline-2-carboxamide (26)



N-Methylquinoline-2-carboxamide (27)



N-Methylquinoline-2-carboxamide (27)