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Graphical Abstract

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Chunyin Zhu[a,b,*], Wei Wei[a], Peng Du[a] and Xiaobing Wan[a,*]

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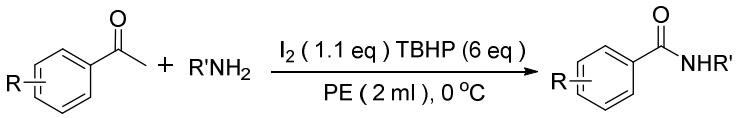

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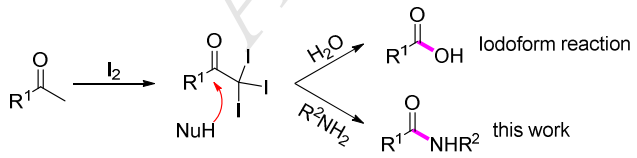
A metal-free oxidative coupling of methyl ketones and primary amines to amides has been developed. The reaction tolerates a variety of functional groups, and is operationally simple. The reaction is proposed to go through a radical pathway to form the triiodomethyl ketone intermediate and the amide is formed by the nucleophilic attack of amine on triiodomethyl ketone carbonyl.

1. Introduction

The amides are important structural motif found in biomolecules (peptides), polymers, natural products and pharmaceuticals, and serve as useful intermediates for synthetic organic chemistry.[1] Routinely, they were prepared by coupling reaction of activated carboxylic acid and amines, thus requiring stoichiometric coupling reagent and/or generating large amounts of waste products.[2] Due to the growing focus on economic and environmental issue, much attention has been paid to development of catalytic systems for the amides synthesis under mild conditions. As results, a variety of powerful methods, such as the Beckmann rearrangement, [3] the Staudinger reaction, [4] the Schmidt reaction,[5] transamidation of primary amides,[6] catalytic acylation of amines with carboxylic acids,[7] hydroamination of alkynes,[8] direct amidation of unactivated carboxylic acids and amines,[9] aminocarbonylation of aryl halides,[10] oxidative amidation of aldehydes[11] or alcohols,[12] and oxidative amidation of alkynes with amines and azides,[13] have offered attractive alternatives for amides synthesis.



Scheme 1 Design for amides synthesis.

The iodoform reaction, reaction of methyl ketone and iodine, is one of the oldest reactions in synthetic organic chemistry.[14] While the iodoform reaction has been widely used to prepare carboxylic acids and test for the *a*-methyl carbonyl group, few expansion has been developed since its discovery.[15] Also ketones are very common and readily available starting material in chemistry. So we envisioned replacement of H_2O with amine would provide a simple and practical method for amides synthesis from reaction of ketones with amines under oxidizing conditions (Scheme 1).

2. Results and discussion.

To test the viability of amines in the proposed iodoform reaction, a mixture of acetophenone and n-butyl amine was treated with oxidant in different solvents (Table 1). As can be seen in Table 1, no desired product was detected in DMSO, acetic acid or dioxane (entries 7, 9 and 11), and only trace amount of product in isopropanol, dichloroethane, toluene, acetonitrile and DMF (entries 2-6), but the reactions in ethyl acetate, water, nitromethane and PE (petroleum ether) were able to show significant amount of desired amide product (entries 1, 8, 10 and 12). The highest yield was obtained from the reaction in PE using 1.1 equivalents of I_2 and 6.0 equivalents of TBHP (tert-Butyl hydroperoxide) as oxidant. Further investigation demonstrated that both I_2 and oxidant were indispensable for the reaction (entries 13 and 21) and it would require stoichiometric amount of I_2 to get a decent yield (entries 13-16). Also it was found TBHP was better oxidant over H_2O_2, mCPBA (3-Chloroperbenzoic acid), Oxone and O_2 (entries 12-15), and 6.0 equivalents was needed for the optimal condtion (entries 22-24).

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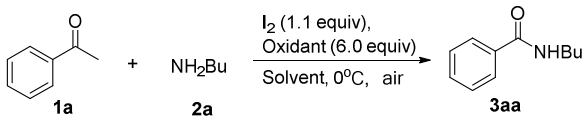
Table 1.

Optimization of Reaction Conditions[a]



entry	solv.	oxidant	yield[b] (%)
1	EA	TBHP	75
2	IPA	TBHP	trace
3	DCE	TBHP	trace
4	PhMe	TBHP	trace
5	MeCN	TBHP	trace
6	DMF	TBHP	trace
7	DMSO	TBHP	N.D.[c]
8	H_2O	TBHP	73
9	HOAc	TBHP	N.D.
10	$MeNO_2$	TBHP	35
11	Dioxane	TBHP	N.D.
12	PE	TBHP	85
13[d]	PE	TBHP	trace
14[e]	PE	TBHP	44
15	PE	TBHP	85
16[f]	PE	TBHP	84
17	PE	H_2O_2	trace
18	PE	mCPBA	trace
19	PE	Oxone	N.D.
20	PE	O2	trace
21	PE	-	N.D.
22[g]	PE	TBHP	54
23[h]	PE	TBHP	82
24[i]	PE	TBHP	84

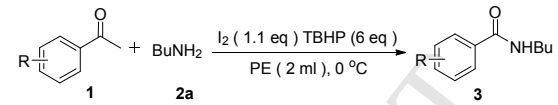
[a]0.5 mmol of acetophenone, 2.0 mmol of $BuNH_2$, 0.55 mmol of I_2 3.0 mmol of oxidant, 2.0 mL of solvent. [b]isolated yiled. [c]not detected. [d]without I_2. [e]0.5 equiv. of I_2. [f]1.5 equiv. of I_2. [g]2.0 equiv. TBHP. [h]4.0 equiv. TBHP. [i]8.0 equiv. TBHP.

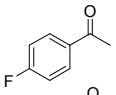
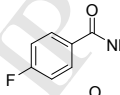
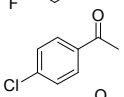
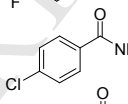
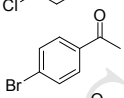
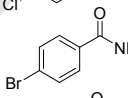
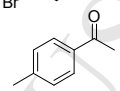
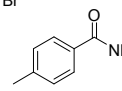
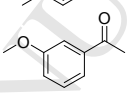
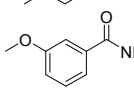
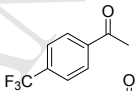
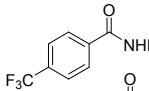
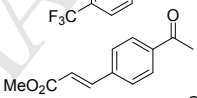
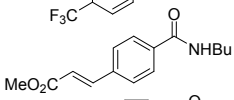
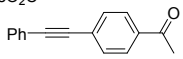
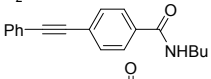
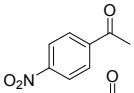
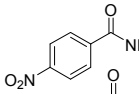
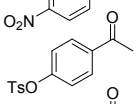
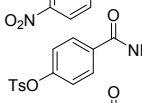
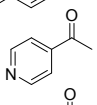
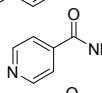
With the optimum conditions in hand, we explored the scope of the reaction of n-butyl amine with various ketone (Table 2). We were pleased to find that our reaction conditions provided the desired amide products across a range of substituted aryl methyl ketone (entries 1-10, Table 2). Both electron-rich (entries 4 and 5, Table 2) and electron-deficient aryl substituted ketones (entries 6 and 9, Table 2) were compatible, and fluoro, chloro, bromo, tosyl groups were tolerated in the reaction (entries 1-3 and 10, Table 2), which could be used for further functionalization through transition-metal-catalyzed cross-coupling. Notably, both alkene and alkyne group could survive the oxidizing reagents, resulting in good yield for the amide (entries 7 and 8, Table 2). Also, the reaction worked smoothly for the substrates with hetero aromatic rings, for example, pyridine, thiophene and furan (entries 7-13, Table 2).

Subsequently, the scope of amines was studied (Table 3). The reaction was examined for several amines under the optimized reaction conditions. In all the cases the reaction worked smoothly, giving the corresponding amide in good yields with good functional group tolerance. Interestingly, when both amine and alcohol groups are present, the reaction gave amide product exclusively, showing excellent chemo-selectivity (entry 4, Table 3)

Table 2.

Substrate scope for ketones [a]



entry	1	product	isolated yield
1	 1b	 3ba	83 %
2	 1c	 3ca	80 %
3	 1d	 3da	82%
4	 1e	 3ea	75 %
5	 1f	 3fa	78 %
6	 1g	 3ga	82 %
7	 1h	 3ha	76 %
8	 1i	 3ia	80 %
9	 1j	 3ja	79 %
10	 1k	 3ka	55 %
11	 1l	 3la	64 %
12	 1m	 3ma	83 %
13	 1n	 3na	86 %

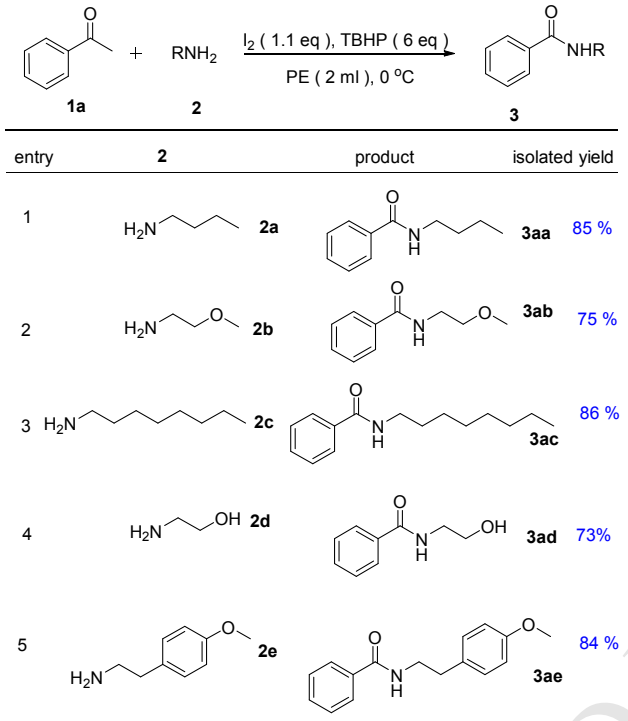
[a]0.5 mmol of ketone, 2.0 mmol of $BuNH_2$, 0.55 mmol of I_2, 3.0 mmol of TBHP, 2.0 mL of solvent.

Interestingly, in most of the experiments, a distinctive color change from black to yellow was observed and at the end of the reaction, there would form a layer of precipitate which is conformed to be iodoform by ^1H and ^{13}C NMR (eq 1, scheme 2).[16] Also, under the same condition, iodomethyl ketone **4** was transformed to amide with 79% yield (eq 2, scheme 2), indicating iodomethyl ketone could be an intermediate for the reaction. Based on the observations, we proposed the reaction should go through triiodoketone intermediate which would be likely formed through a radical pathway instead of an anion one as the case of traditional haloform reaction (scheme 3), since this reaction took place in PE under a neutral environment, which usually would not favor an anion reaction. Also TBHP is believed to work through radical pathway in a lot of reactions. So, in this reaction,

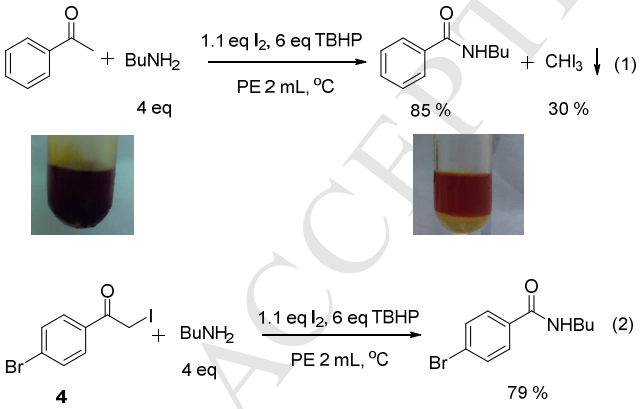
the starting methyl ketone would be converted to a methylene radical which could abstract an iodo from iodine, resulting in the formation of monoiodomethyl ketone. Repeating this process twice would generate the triiodomethyl intermediate. Finally nucleophilic attack of amine on the carbonyl carbon atom would form the desired amide product along with iodoform.

Table 3.

Substrate scope for amines [a]



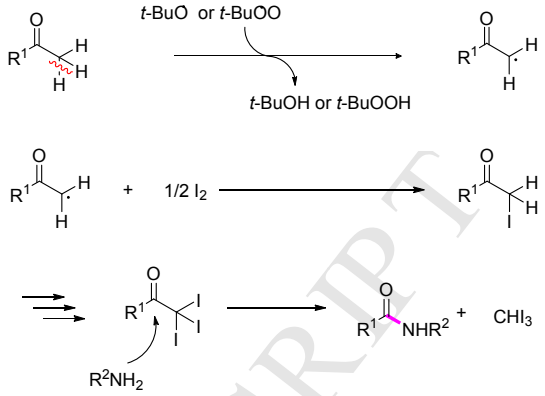
[a]0.5 mmol of acetophenone, 2.0 mmol of amine, 0.55 mmol of I_2, 3.0 mmol of TBHP, 2.0 mL of solvent.



Scheme 2 Investigations into the reaction mechanism

3. Conclusion.

In summary, we have described an oxidative coupling of methyl ketones with primary amines to give amides in good to excellent yields. The reaction is proposed to go through a radical pathway to form the triiodomethyl ketone intermediate. And the reaction makes direct use of simple and abundant starting materials without requiring transition metal catalysts. In view of the wide functional group tolerance, the ease of conducting such reactions, and the mild reaction conditions, we envision this protocol will be widely adapted in synthetic chemistry



Scheme 3 Plausible mechanism

4. Experimental section

4.1. General

All manipulations were carried out under air atmosphere. I_2 and TBHP (70% aqueous solution) were purchased from Sigma-Aldrich. Column chromatography was generally performed on silica gel (300-400 mesh) and reactions were monitored by thin layer chromatography (TLC) using UV light to visualize the course of the reactions. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data were recorded on Varian 400 M spectrometers using $CDCl_3$ as solvent at room temperature. The chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. ^{1}H NMR spectra was recorded with tetramethylsilane (δ = 0.00 ppm) as internal reference; ^{13}C NMR spectra was recorded with $CDCl_3$ (δ = 77.00 ppm) as internal reference. IR, MS, and HRMS were performed by the State-authorized Analytical Center in Soochow University.

4.2 General procedures for amides 3

Methyl ketones (0.5 mmol), ammines (2.0 mmol), I_2 (0.55 mmol, 110 mol %), TBHP (6.0 equiv, 70% aqueous solution 401 uL), and 2.0 mL of PE, were added to a tube under air. The reaction mixture was stirred at 0°C for 12 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution, extracted repeatedly with ethyl acetate, dried over Na_2SO_4. It was then removal of the organic solvent in vacuum and followed by flash silica gel column chromatographic purification afforded product with Petroleum/Ethyl acetate mixtures.

*4.2.1 N-butylbenzamide (**3aa**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 – 7.76 (m, 2H), 7.48 – 7.44 (m, 1H), 7.40 – 7.37 (m, 2H), 6.62 (s, 1H), 3.44 – 3.39 (m, 2H), 1.61 – 1.54 (m, 2H), 1.43 – 1.33 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 134.7, 131.1, 128.3, 126.8, 39.7, 31.6, 20.1, 13.6; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{11}H_{16}NO$: 178, found: 178; IR (KBr, cm^{-1}): ν 1641.

*4.2.2 N-butyl-4-fluorobenzamide (**3ba**).* ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.79 (d, *J* = 6.2 Hz, 2H), 7.08 (d, *J* = 6.2 Hz, 2H), 6.52 (s, 1H), 3.45 – 3.40 (m, 2H), 1.58 – 1.55 (m, 1H), 1.43 – 1.35 (m, 1H), 0.94 (t, *J* = 9.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 166.1, 162.8, 130.9, 129.2, 129.1, 115.5, 115.2, 39.8, 31.6, 20.1, 13.7; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{11}H_{15}FNO$: 196, found: 196; IR (KBr, cm^{-1}): ν 1632.

*4.2.3 N-butyl-4-chlorobenzamide (**3ca**).* ^{1}H NMR ($CDCl_3$, 300 MHz): δ7.71 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 6.89 (s, 1H), 3.42 – 3.36 (m, 2H), 1.57 – 1.52 (m, 2H), 1.37 – 1.32 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ166.6, 137.3, 133.1, 128.5, 128.3, 39.8, 31.5, 20.0, 13.6; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{11}H_{15}ClNO$: 212, found: 212; IR (KBr, cm^{-1}): ν 1630.

*4.2.4 4-bromo-N-butylbenzamide (**3da**).* ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 6.88 (s, 3H), 3.42 – 3.35 (m, 2H), 1.56 – 1.51 (m, 2H), 1.37 – 1.32 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.7, 133.5, 131.5, 128.5, 125.7, 39.8, 31.5, 20.0, 13.7; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{11}H_{15}BrNO$: 256, found: 256; $C_{11}H_{15}BrNO$: 258, found: 258; IR (KBr, cm^{-1}): ν 1635.

*4.2.5 N-butyl-4-methylbenzamide (**3ea**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.63 (s, 1H), 3.43 – 3.38 (m, 2H), 2.37 (s, 3H), 1.60 – 1.53 (m, 2H), 1.42 – 1.34 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4, 141.5, 131.9, 129.0, 126.8, 39.7, 31.6, 21.3, 20.1, 13.7; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{12}H_{18}NO$: 192, found: 192; IR (KBr, cm^{-1}): ν 1636.

*4.2.6 N-butyl-3-methoxybenzamide (**3fa**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 – 7.36 (m, 1H), 7.32 – 7.26 (m, 2H), 7.01 – 6.98 (m, 1H), 6.66 (s, 1H), 3.80 (s, 3H), 3.43 – 3.38 (m, 2H), 1.61 – 1.53 (m, 2H), 1.42 – 1.33 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4, 159.5, 136.1, 129.3, 118.6, 117.3, 112.1, 55.2, 39.7, 31.5, 20.0, 13.6; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{12}H_{18}NO_2$: 208, found: 208; IR (KBr, cm^{-1}): ν 1643.

*4.2.7 N-butyl-4-(trifluoromethyl)benzamide (**3ga**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 6.92 (s, 1H), 3.45 – 3.40 (m, 2H), 1.59 – 1.55 (m, 2H), 1.41 – 1.35 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4, 138.0, 133.0, 132.7, 127.4, 125.4, 125.3, 125.3, 124.9, 122.2, 40.0, 31.5, 20.1, 13.6; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{12}H_{15}F_3NO$: 246, found: 246; IR (KBr, cm^{-1}): ν 1632.

*4.2.8 (E)-methyl 3-(4-(butylcarbamoyl)phenyl)acrylate (**3ha**).* ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 16.0 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 6.99 (s, 3H), 6.45 (d, *J* = 16.0 Hz, 1H), 3.80 (s, 3H), 3.45 – 3.40 (m, 2H), 1.63 – 1.55 (m, 2H), 1.43 – 1.33 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9, 166.7, 143.4, 136.7, 136.0, 127.8, 127.4, 119.2, 51.7, 39.8, 31.5, 20.0, 13.6; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{15}H_{20}NO_3$: 262, found: 262; IR (KBr, cm^{-1}): ν 1717, 1629.

*4.2.9 N-butyl-4-(phenylethynyl)benzamide (**3ia**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.55 – 7.52 (m, 4H), 7.34 – 7.33 (m, 2H), 6.64 (s, 3H), 3.44 – 3.39 (m, 2H), 1.62 – 1.54 (m, 2H), 1.43 – 1.34 (m, H), 0.94 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ166.9, 134.0, 131.6, 131.5, 128.5, 128.3, 126.9, 126.2, 122.6, 91.5, 88.5, 39.82, 31.6, 20.1, 13.7; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{19}H_{20}NO$: 278, found: 278; IR (KBr, cm^{-1}): ν 1633.

*4.2.10 N-butyl-4-nitrobenzamide (**3ja**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.02 (s, 1H), 3.47 – 3.42 (m, *J* = 13.1, 7.1 Hz, 2H), 1.65 – 1.57 (m, 2H), 1.44 – 1.35 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 149.2, 140.3, 128.1, 123.5, 40.1, 31.4, 20.0, 13.6; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{11}H_{15}N_2O_3$: 223, found: 223; IR (KBr, cm^{-1}): ν 1636.

*4.2.11 4-(butylcarbamoyl)phenyl 4-methylbenzenesulfonate (**3ka**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 – 7.66 (m, 4H), 7.32 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.68 – 6.66 (m, 3H), 3.41 – 3.36 (m, 2H), 2.44 (s, 3H), 1.58 – 1.52 (m, 2H), 1.41 – 1.31 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ166.2, 151.4, 145.7, 133.5, 131.7, 129.8, 128.5, 128.3, 122.2, 39.8, 31.4, 21.6, 20.0, 13.6; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{18}H_{22}NO_4S$: 348, found: 348; IR (KBr, cm^{-1}): ν 1639.

*4.2.12 N-butylisonicotinamide (**3la**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ8.67 (d, *J* = 5.3 Hz, 2H), 7.64 (d, *J* = 5.3 Hz, 2H), 7.17 (s, 1H), 3.46 – 3.41 (m, 2H), 1.63 – 1.55 (m, 2H), 1.41 – 1.36 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 150.0, 141.9, 121.0, 39.8, 31.3, 20.0, 13.6; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{10}H_{15}N_2O$: 179, found: 179; IR (KBr, cm^{-1}): ν 1650.

*4.2.13 N-butylthiophene-2-carboxamide (**3ma**).* ^{1}H NMR (CDCl3, 300 MHz): δ 7.59 (d, *J* = 3.0 Hz, 1H), 7.44 (d, *J* = 3.0 Hz, 1H), 7.05 – 7.03 (m, 1H), 6.72 (s, 3H), 3.44 – 3.37 (m, 2H), 1.62 – 1.53 (m, 2H), 1.43 – 1.31 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.0, 139.3, 129.6, 127.7, 127.5, 39.7, 31.6, 20.0, 13.7; MS (ESI) m/z $[M+H]^+$ Calcd for $C_9H_{14}NOS$: 184, found: 184; IR (KBr, cm^{-1}): ν 1634.

*4.2.14 N-butylfuran-2-carboxamide (**3na**).* ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34 (d, *J* = 2.7 Hz, 1H), 7.00 (d, *J* = 2.7 Hz, 1H), 6.50 (s, 1H), 6.40 – 6.37 (m, 1H), 3.35 – 3.31 (m, 2H), 1.49 – 1.47 (m, 2H), 1.33 – 1.28 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.4, 148.1, 143.6, 113.8, 112.0, 38.8, 31.7, 31.5, 20.0, 13.6, 13.5; MS (ESI) m/z $[M+H]^+$ Calcd for $C_9H_{14}NO_2$: 168, found: 168; IR (KBr, cm^{-1}): ν 1649.

*4.2.15 N-(2-methoxyethyl)benzamide (**3ab**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 – 7.78 (m, 2H), 7.49 – 7.45 (m, 1H), 7.42 – 7.38 (m, 2H), 6.85 (s, 1H), 3.65 – 3.61 (m, 2H), 3.56 – 3.53 (m, 2H), 3.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 134.3, 131.2, 128.3, 126.8, 71.0, 58.6, 39.5; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{10}H_{14}NO_2$: 180, found: 180; IR (KBr, cm^{-1}): ν 1644.

*4.2.16 N-octylbenzamide (**3ac**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 – 7.77 (m, 2H), 7.46 – 7.43 (m, 1H), 7.38 – 7.35 (m, 2H), 6.75 (s, 1H), 3.42 – 3.37 (m, 2H), 1.60 – 1.56 (m, 2H), 1.32 – 1.24 (m, 10H), 0.87 (t, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 134.7, 131.0, 128.3, 126.8, 40.0, 31.7, 29.5, 29.2, 29.1, 26.9, 22.5, 14.0; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{15}H_{24}NO$: 234, found: 234; IR (KBr, cm^{-1}): ν 1634.

*4.2.17 N-(2-hydroxyethyl)benzamide (**3ad**).* ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 – 7.63 (m, 2H), 7.36 – 7.31 (m, 1H), 7.25 –

7.20 (m, 2H), 4.21 (s, 1H), 3.65 – 3.61 (m, 2H), 3.45 – 3.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.7, 133.9, 131.5, 128.4, 126.9, 61.5, 42.7; MS (ESI) m/z $[M+H]^+$ Calcd for $C_9H_{12}NO_2$: 166, found: 166; IR (KBr, cm^{-1}): ν 1651.

*4.2.18 N-(4-methoxyphenethyl)benzamide (**3ae**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 – 7.70 (m, 2H), 7.46 – 7.43 (m, 1H), 7.38 – 7.34 (m, 2H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.58 (s, 1H), 3.76 (s, 3H), 3.66 – 3.61 (m, 2H), 2.86 – 2.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.4, 158.1, 134.5, 131.2, 130.8, 129.6, 128.4, 126.7, 113.9, 55.1, 41.3, 34.6; MS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{18}NO_2$: 256, found: 256; IR (KBr, cm^{-1}): ν 1639.

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Supplementary data

Copies of ^{1}H and/or ^{13}C spectra for isolated products. Supplementary data associated with this article can be found online.

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16. Similar phenomenon was reported by Wu *etc.* See ref 15.

Supporting Information
For

Metal free amide synthesis via carbon-carbon bond cleavage

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General Information

All manipulations were carried out under air atmosphere. I_2 and TBHP (70% aqueous solution) were purchased from Sigma-Aldrich. Column chromatography was generally performed on silica gel (300-400 mesh) and reactions were monitored by thin layer chromatography (TLC) using UV light to visualize the course of the reactions. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data were recorded on Varian 400 M spectrometers using $CDCl_3$ as solvent at room temperature. The chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. ^{1}H NMR spectra was recorded with tetramethylsilane (δ = 0.00 ppm) as internal reference; ^{13}C NMR spectra was recorded with $CDCl_3$ (δ = 77.00 ppm) as internal reference. IR, MS, and HRMS were performed by the State-authorized Analytical Center in Soochow University.

General procedures for amides **3**: Methyl ketones (0.5 mmol), ammines (2.0 mmol), I_2 (0.55 mmol, 110 mol %), TBHP (6.0 equiv, 70% aqueous solution 401 uL), and 2.0 mL of PE, were added to a tube under air. The reaction mixture was stirred at 0^{o}C for 12 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution, extracted repeatedly with ethyl acetate, dried over Na_2SO_4. It was then removal of the organic solvent in vacuum and followed by flash silica gel column chromatographic purification afforded product with Petroleum/Ethyl acetate mixtures.

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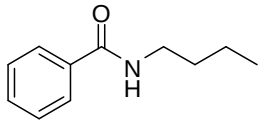
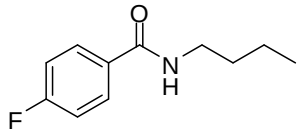
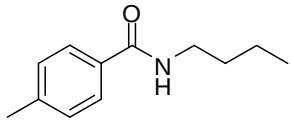


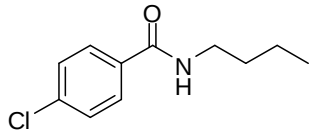
N-butylbenzamide. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 – 7.76 (m, 2H), 7.48 – 7.44 (m, 1H), 7.40 – 7.37 (m, 2H), 6.62 (s, 1H), 3.44 – 3.39 (m, 2H), 1.61 – 1.54 (m, 2H), 1.43 – 1.33 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 134.7, 131.1, 128.3, 126.8, 39.7, 31.6, 20.1, 13.6; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{16}NO$: 178, found: 178; IR (KBr, cm^{-1}): ν 1641.



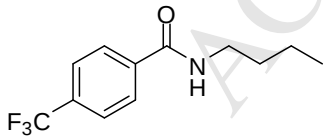
N-butyl-4-fluorobenzamide. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.79 (d, *J* = 6.2 Hz, 2H), 7.08 (d, *J* = 6.2 Hz, 2H), 6.52 (s, 1H), 3.45 – 3.40 (m, 2H), 1.58 – 1.55 (m, 1H), 1.43 – 1.35 (m, 1H), 0.94 (t, *J* = 9.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 166.1, 162.8, 130.9, 129.2, 129.1, 115.5, 115.2, 39.8, 31.6, 20.1, 13.7; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{15}FNO$: 196, found: 196; IR (KBr, cm^{-1}): ν 1632.



N-butyl-4-methylbenzamide. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.63 (s, 1H), 3.43 – 3.38 (m, 2H), 2.37 (s, 3H), 1.60 – 1.53 (m, 2H), 1.42 – 1.34 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4, 141.5, 131.9, 129.0, 126.8, 39.7, 31.6, 21.3, 20.1, 13.7; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{12}H_{18}NO$: 192, found: 192; IR (KBr, cm^{-1}): ν 1636.

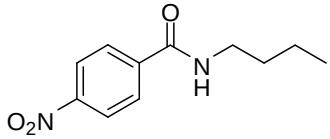


N-butyl-4-chlorobenzamide. ^{1}H NMR ($CDCl_3$, 300 MHz): δ7.71 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 6.89 (s, 1H), 3.42 – 3.36 (m, 2H), 1.57 – 1.52 (m, 2H), 1.37 – 1.32 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ166.6, 137.3, 133.1, 128.5, 128.3, 39.8, 31.5, 20.0, 13.6; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{15}{}^{35}ClNO$: 212, found: 212; IR (KBr, cm^{-1}): ν 1630.

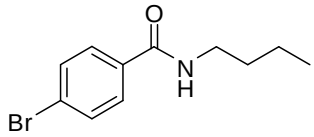


N-butyl-4-(trifluoromethyl)benzamide. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 6.92 (s, 1H), 3.45 – 3.40 (m, 2H), 1.59 – 1.55 (m, 2H), 1.41 – 1.35 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4, 138.0, 133.0, 132.7, 127.4, 125.4, 125.3, 125.3, 124.9,

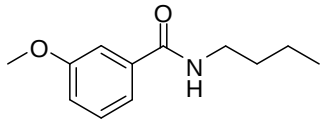
122.2, 40.0, 31.5, 20.1, 13.6; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{12}H_{15}F_3NO$: 246, found: 246; IR (KBr, cm^{-1}): ν 1632.



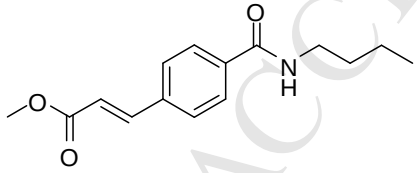
N-butyl-4-nitrobenzamide. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.02 (s, 1H), 3.47 – 3.42 (m, *J* = 13.1, 7.1 Hz, 2H), 1.65 – 1.57 (m, 2H), 1.44 – 1.35 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 149.2, 140.3, 128.1, 123.5, 40.1, 31.4, 20.0, 13.6; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{15}N_2O_3$: 223, found: 223; IR (KBr, cm^{-1}): ν 1636.



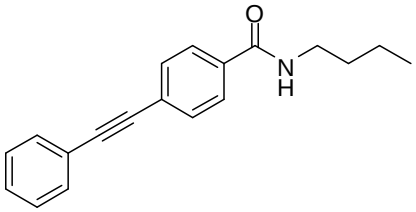
4-bromo-N-butylbenzamide. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 6.88 (s, 3H), 3.42 – 3.35 (m, 2H), 1.56 – 1.51 (m, 2H), 1.37 – 1.32 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.7, 133.5, 131.5, 128.5, 125.7, 39.8, 31.5, 20.0, 13.7; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{15}{}^{79}BrNO$: 256, found: 256; $C_{11}H_{15}{}^{81}BrNO$: 258, found: 258; IR (KBr, cm^{-1}): ν 1635.



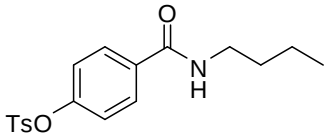
N-butyl-3-methoxybenzamide. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37 – 7.36 (m, 1H), 7.32 – 7.26 (m, 2H), 7.01 – 6.98 (m, 1H), 6.66 (s, 1H), 3.80 (s, 3H), 3.43 – 3.38 (m, 2H), 1.61 – 1.53 (m, 2H), 1.42 – 1.33 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4, 159.5, 136.1, 129.3, 118.6, 117.3, 112.1, 55.2, 39.7, 31.5, 20.0, 13.6; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{12}H_{18}NO_2$: 208, found: 208; IR (KBr, cm^{-1}): ν 1643.



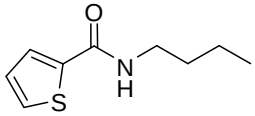
(E)-methyl 3-(4-(butylcarbamoyl)phenyl)acrylate. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 16.0 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 6.99 (s, 3H), 6.45 (d, *J* = 16.0 Hz, 1H), 3.80 (s, 3H), 3.45 – 3.40 (m, 2H), 1.63 – 1.55 (m, 2H), 1.43 – 1.33 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9, 166.7, 143.4, 136.7, 136.0, 127.8, 127.4, 119.2, 51.7, 39.8, 31.5, 20.0, 13.6; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{15}H_{20}NO_3$: 262, found: 262; IR (KBr, cm^{-1}): ν 1717, 1629.



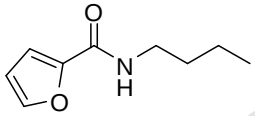
N-butyl-4-(phenylethynyl)benzamide. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.55 – 7.52 (m, 4H), 7.34 – 7.33 (m, 2H), 6.64 (s, 3H), 3.44 – 3.39 (m, 2H), 1.62 – 1.54 (m, 2H), 1.43 – 1.34 (m, H), 0.94 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ166.9, 134.0, 131.6, 131.5, 128.5, 128.3, 126.9, 126.2, 122.6, 91.5, 88.5, 39.82, 31.6, 20.1, 13.7; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{19}H_{20}NO$: 278, found: 278; IR (KBr, cm^{-1}): ν 1633.



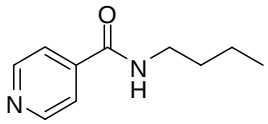
4-(butylcarbamoyl)phenyl 4-methylbenzenesulfonate. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 – 7.66 (m, 4H), 7.32 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.68 – 6.66 (m, 3H), 3.41 – 3.36 (m, 2H), 2.44 (s, 3H), 1.58 – 1.52 (m, 2H), 1.41 – 1.31 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ166.2, 151.4, 145.7, 133.5, 131.7, 129.8, 128.5, 128.3, 122.2, 39.8, 31.4, 21.6, 20.0, 13.6; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{18}H_{22}NO_4S$: 348, found: 348; IR (KBr, cm^{-1}): ν 1639.



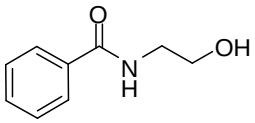
N-butylthiophene-2-carboxamide. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59 (d, *J* = 3.0 Hz, 1H), 7.44 (d, *J* = 3.0 Hz, 1H), 7.05 – 7.03 (m, 1H), 6.72 (s, 3H), 3.44 – 3.37 (m, 2H), 1.62 – 1.53 (m, 2H), 1.43 – 1.31 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.0, 139.3, 129.6, 127.7, 127.5, 39.7, 31.6, 20.0, 13.7; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_9H_{14}NOS$: 184, found: 184; IR (KBr, cm^{-1}): ν 1634.



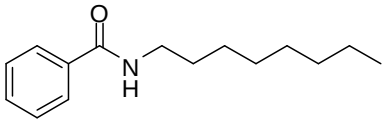
N-butylfuran-2-carboxamide. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34 (d, *J* = 2.7 Hz, 1H), 7.00 (d, *J* = 2.7 Hz, 1H), 6.50 (s, 1H), 6.40 – 6.37 (m, 1H), 3.35 – 3.31 (m, 2H), 1.49 – 1.47 (m, 2H), 1.33 – 1.28 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.4, 148.1, 143.6, 113.8, 112.0, 38.8, 31.7, 31.5, 20.0, 13.6, 13.5; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_9H_{14}NO_2$: 168, found: 168; IR (KBr, cm^{-1}): ν 1649.



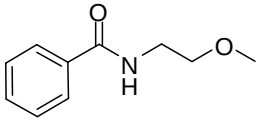
N-butylisonicotinamide. ^{1}H NMR ($CDCl_3$, 400 MHz): δ8.67 (d, *J* = 5.3 Hz, 2H), 7.64 (d, *J* = 5.3 Hz, 2H), 7.17 (s, 1H), 3.46 – 3.41 (m, 2H), 1.63 – 1.55 (m, 2H), 1.41 – 1.36 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 150.0, 141.9, 121.0, 39.8, 31.3, 20.0, 13.6; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{10}H_{15}N_2O$: 179, found: 179; IR (KBr, cm^{-1}): ν 1650.



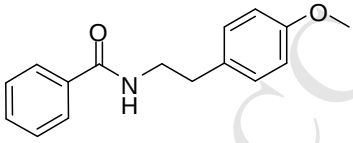
N-(2-hydroxyethyl)benzamide. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 – 7.63 (m, 2H), 7.36 – 7.31 (m, 1H), 7.25 – 7.20 (m, 2H), 4.21 (s, 1H), 3.65 – 3.61 (m, 2H), 3.45 – 3.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.7, 133.9, 131.5, 128.4, 126.9, 61.5, 42.7; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_9H_{12}NO_2$: 166, found: 166; IR (KBr, cm^{-1}): ν 1651.



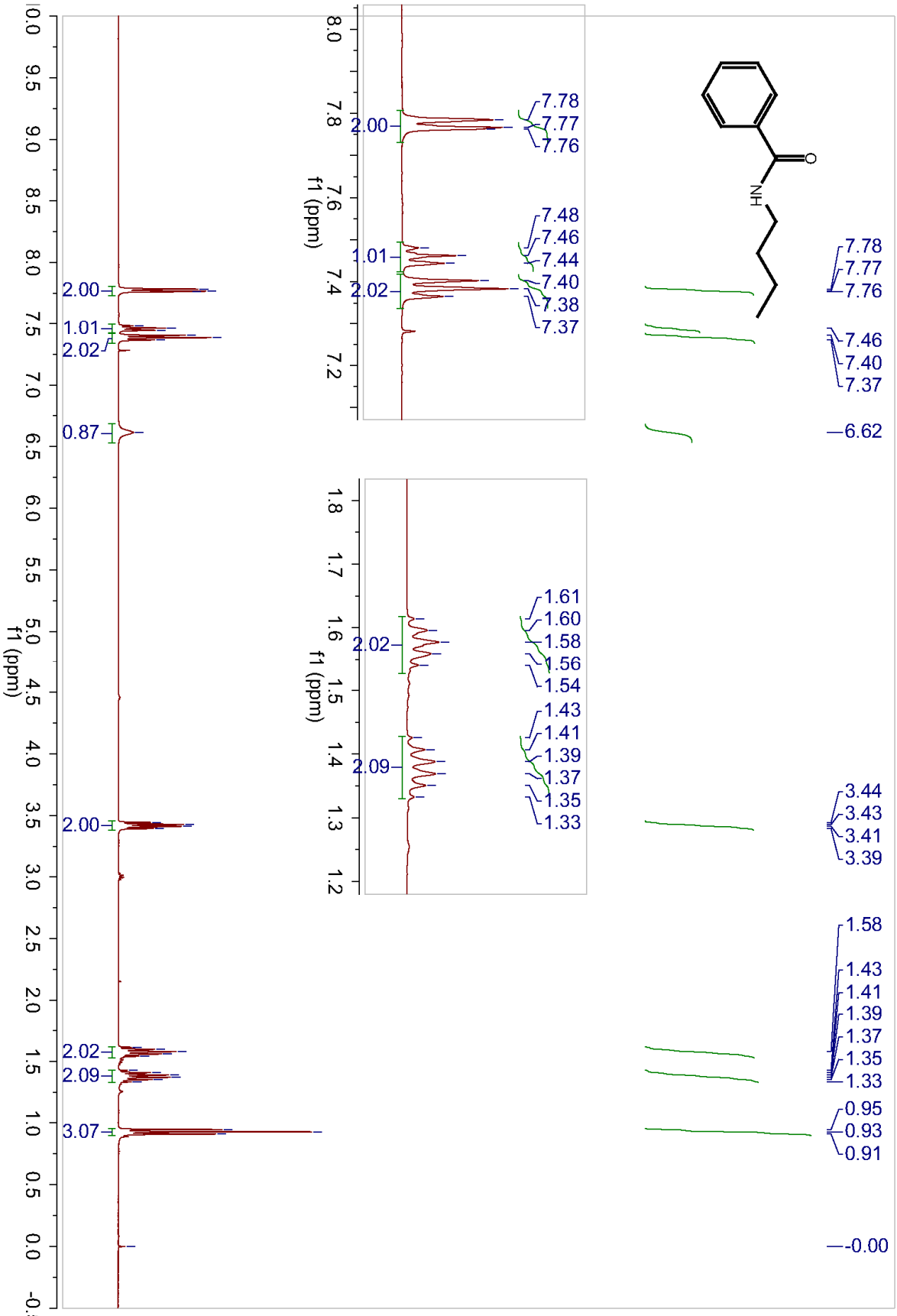
N-octylbenzamide. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 – 7.77 (m, 2H), 7.46 – 7.43 (m, 1H), 7.38 – 7.35 (m, 2H), 6.75 (s, 1H), 3.42 – 3.37 (m, 2H), 1.60 – 1.56 (m, 2H), 1.32 – 1.24 (m, 10H), 0.87 (t, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 134.7, 131.0, 128.3, 126.8, 40.0, 31.7, 29.5, 29.2, 29.1, 26.9, 22.5, 14.0; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{15}H_{24}NO$: 234, found: 234; IR (KBr, cm^{-1}): ν 1634.



N-(2-methoxyethyl)benzamide. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 – 7.78 (m, 2H), 7.49 – 7.45 (m, 1H), 7.42 – 7.38 (m, 2H), 6.85 (s, 1H), 3.65 – 3.61 (m, 2H), 3.56 – 3.53 (m, 2H), 3.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 134.3, 131.2, 128.3, 126.8, 71.0, 58.6, 39.5; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{10}H_{14}NO_2$: 180, found: 180; IR (KBr, cm^{-1}): ν 1644.



N-(4-methoxyphenethyl)benzamide. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 – 7.70 (m, 2H), 7.46 – 7.43 (m, 1H), 7.38 – 7.34 (m, 2H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.58 (s, 1H), 3.76 (s, 3H), 3.66 – 3.61 (m, 2H), 2.86 – 2.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.4, 158.1, 134.5, 131.2, 130.8, 129.6, 128.4, 126.7, 113.9, 55.1, 41.3, 34.6; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{16}H_{18}NO_2$: 256, found: 256; IR (KBr, cm^{-1}): ν 1639.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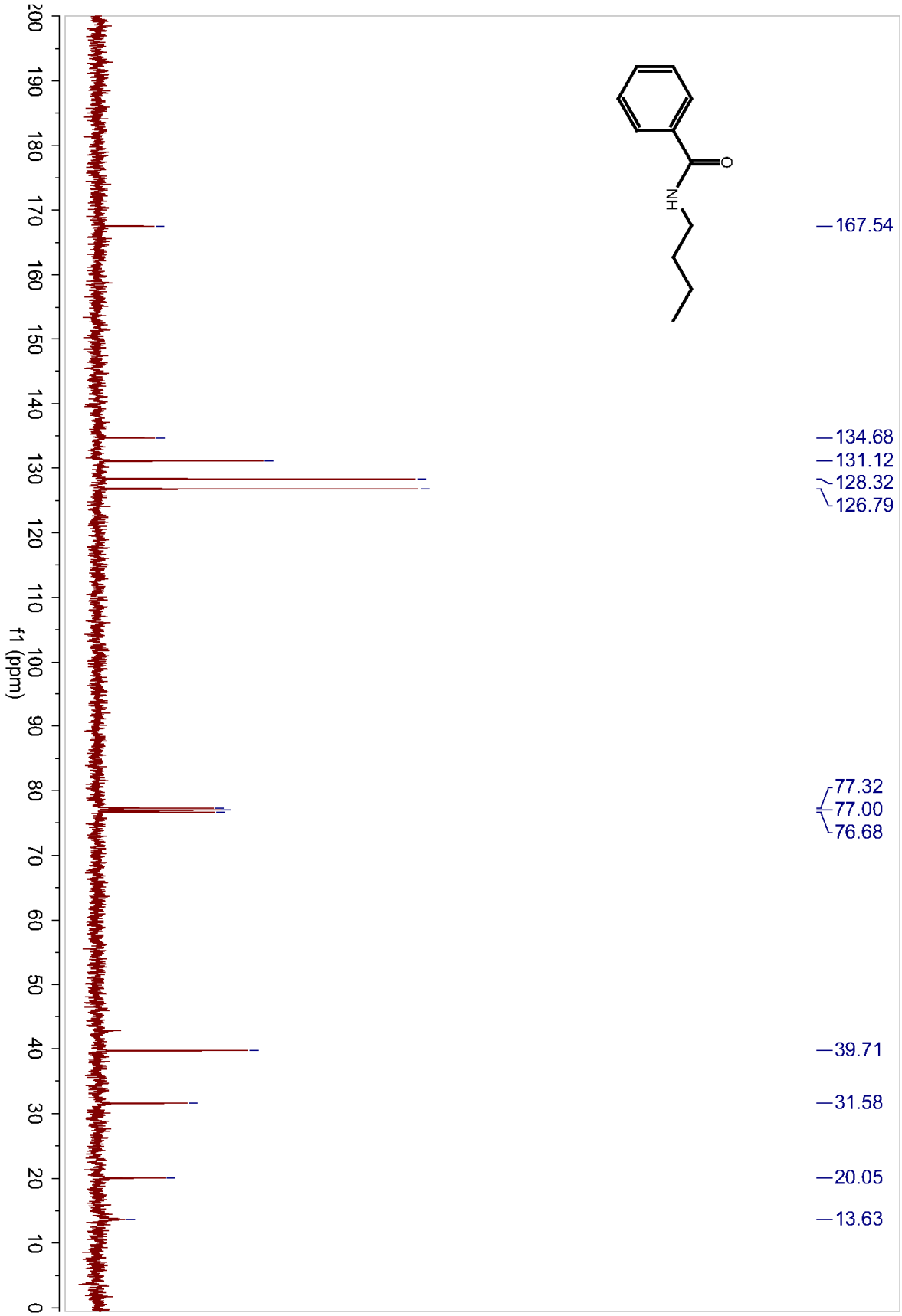
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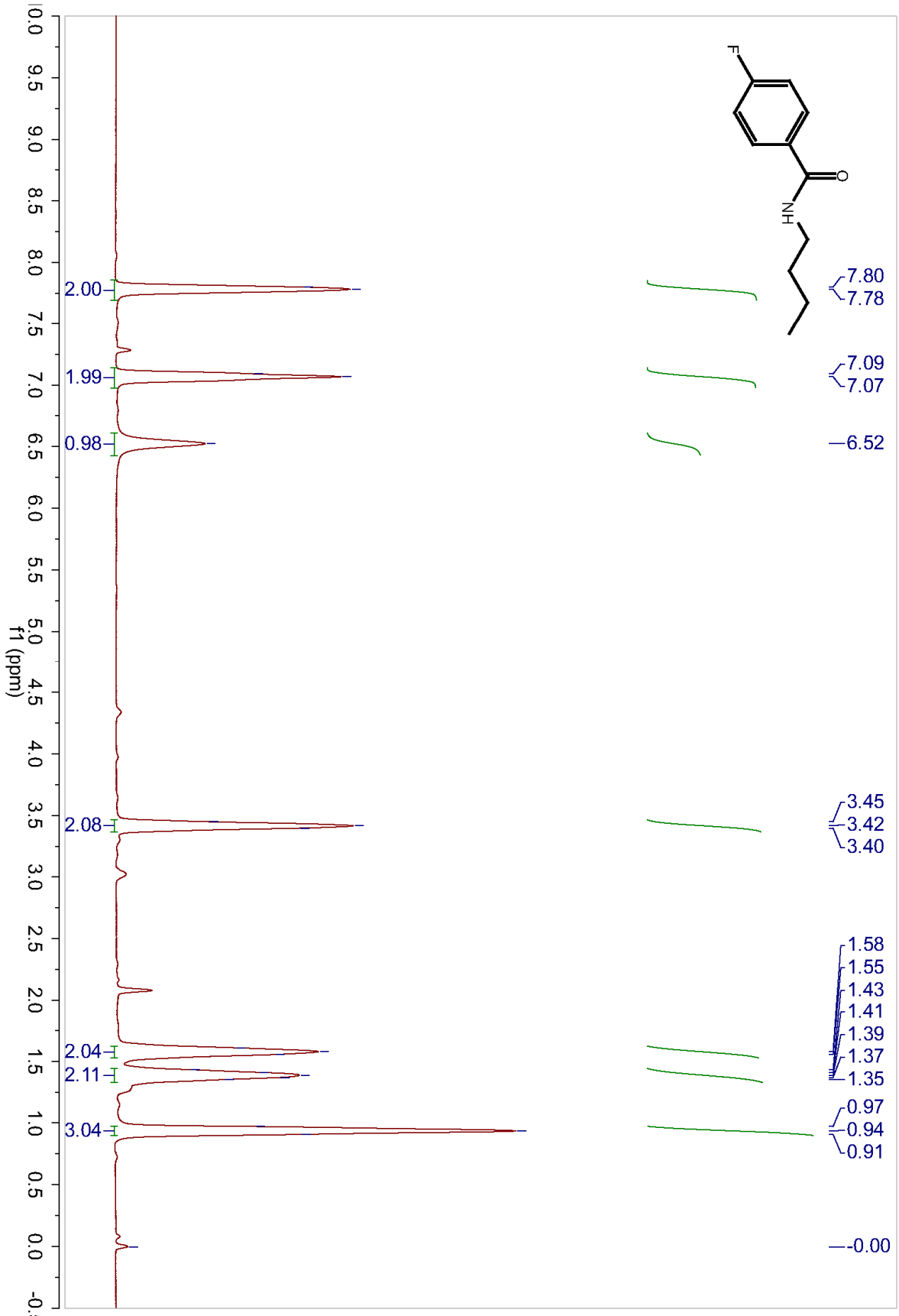
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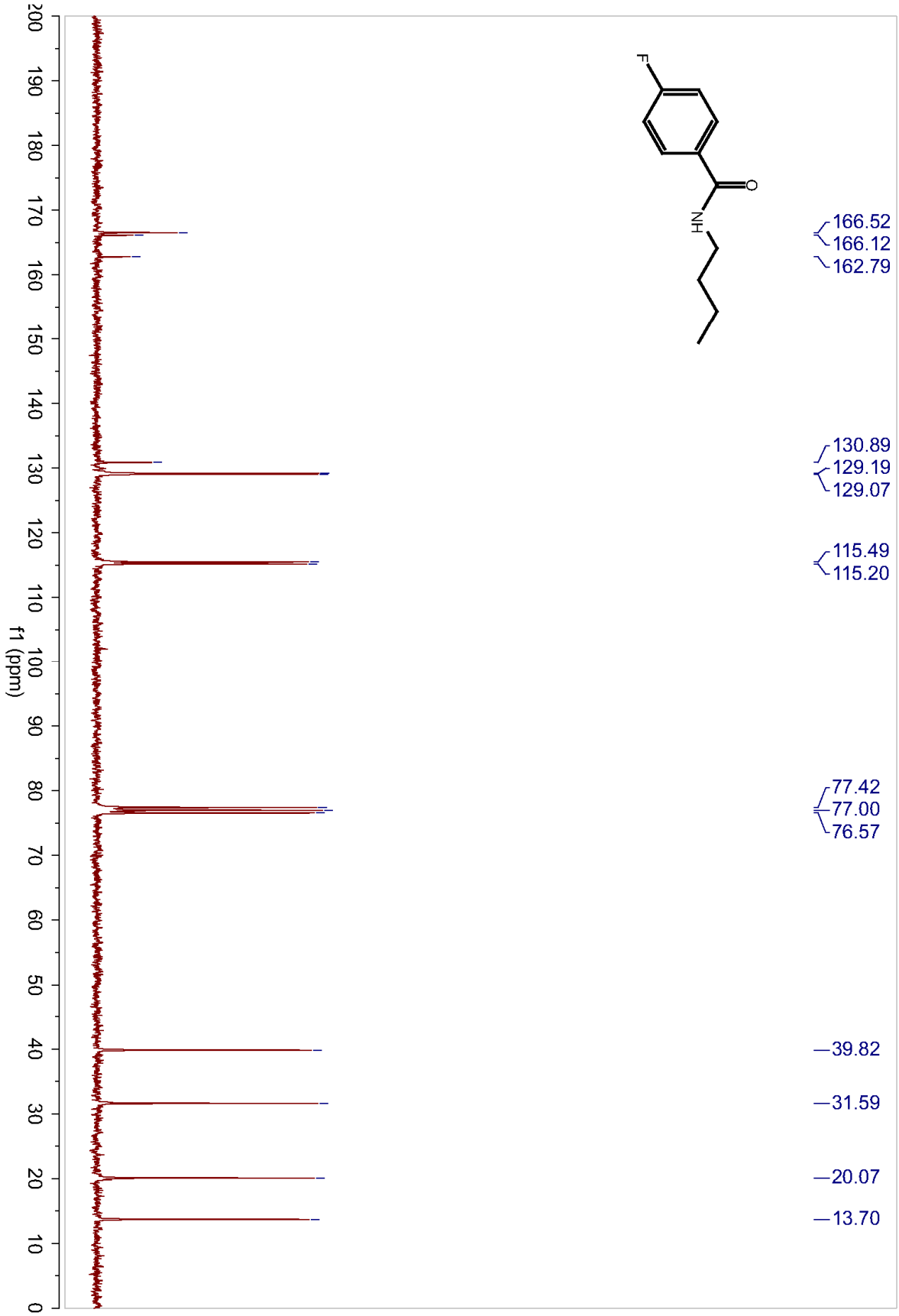
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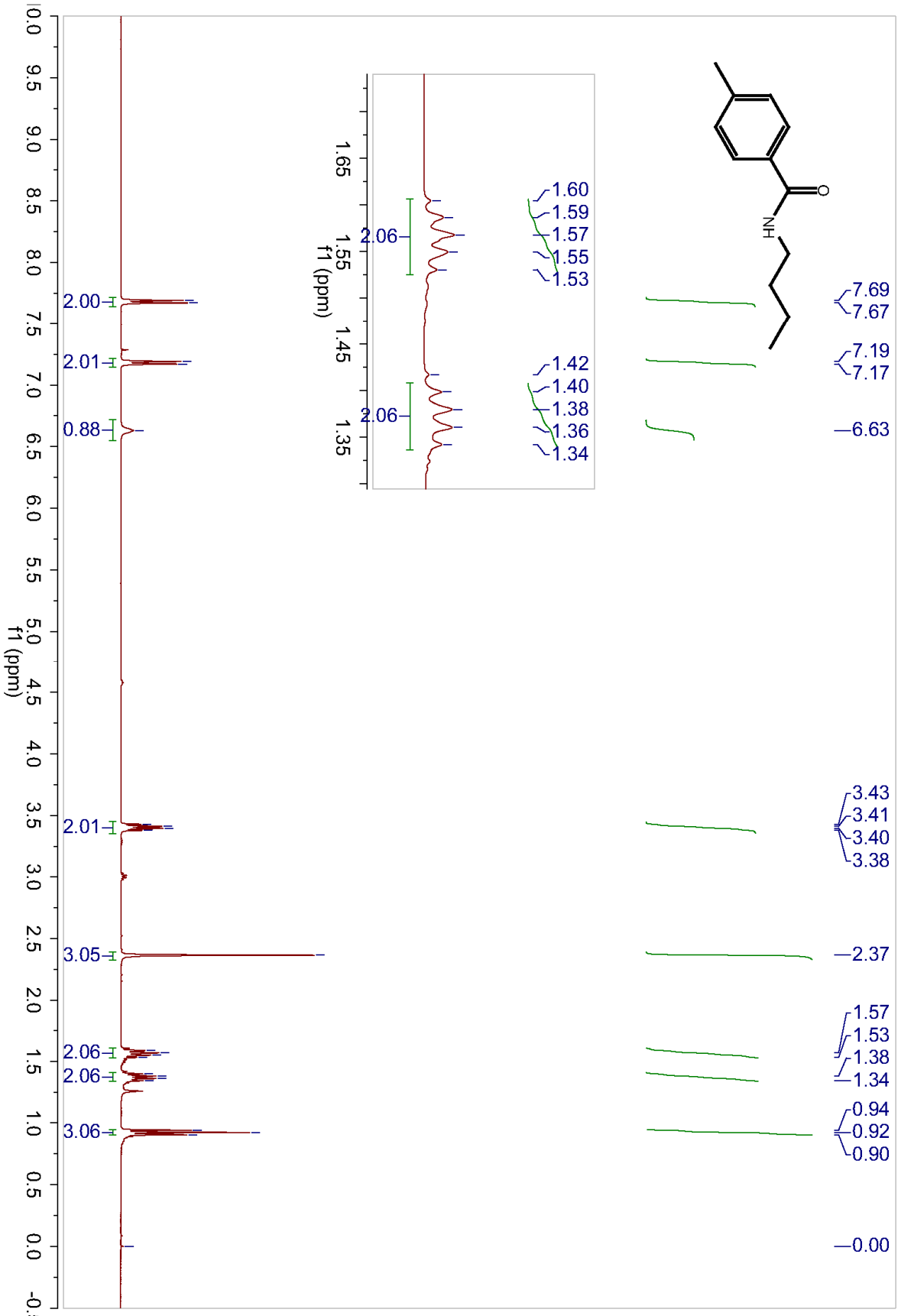
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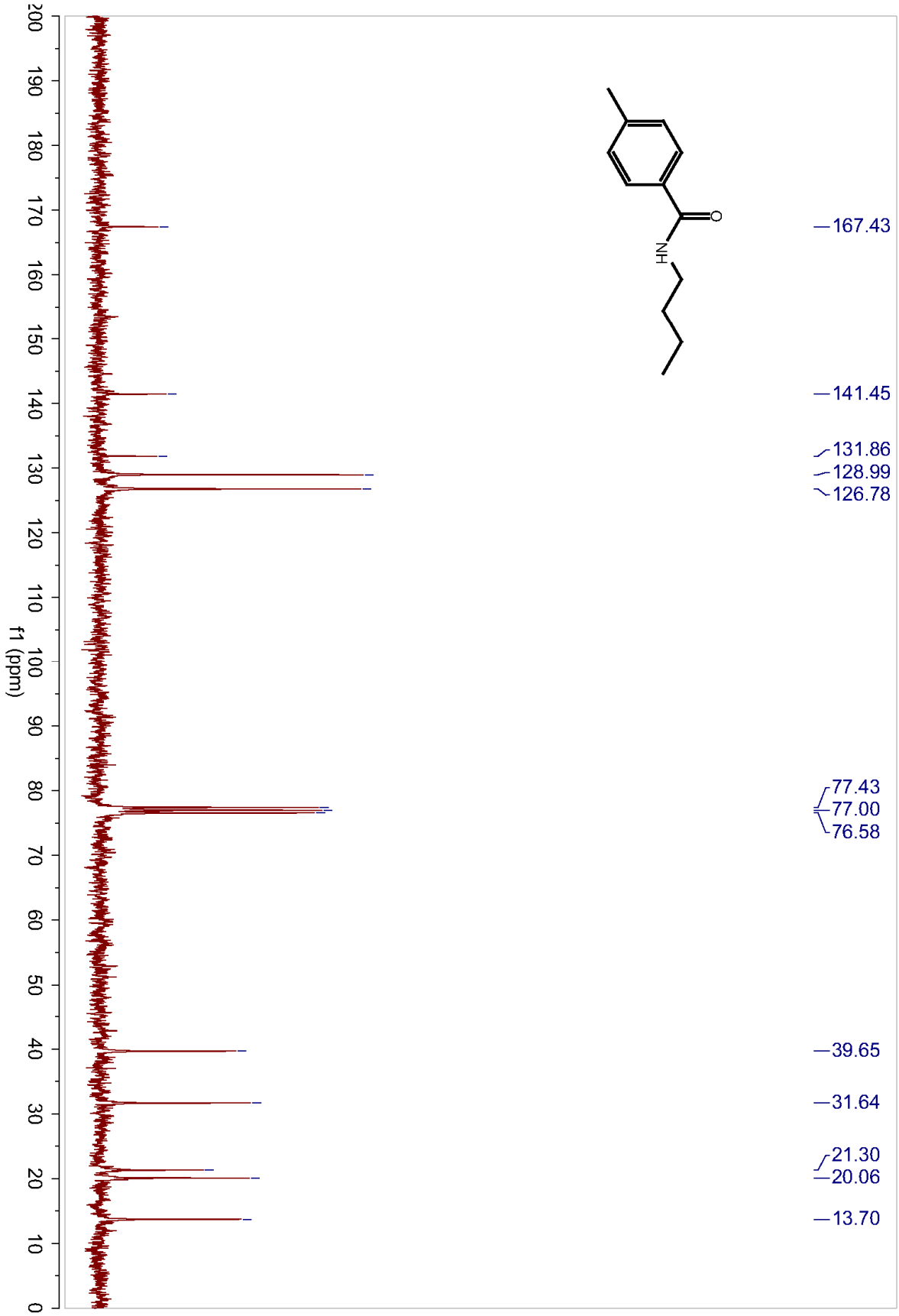
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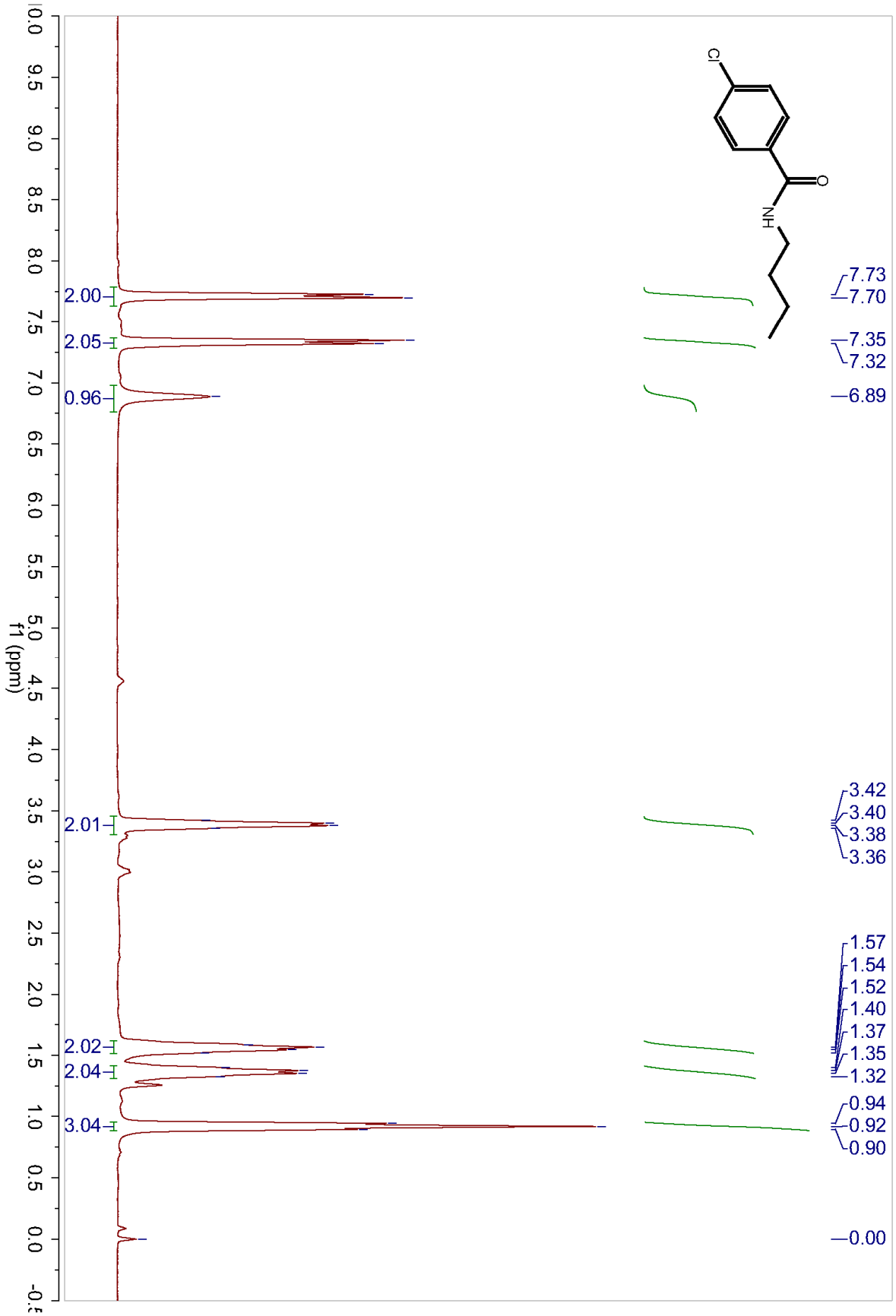
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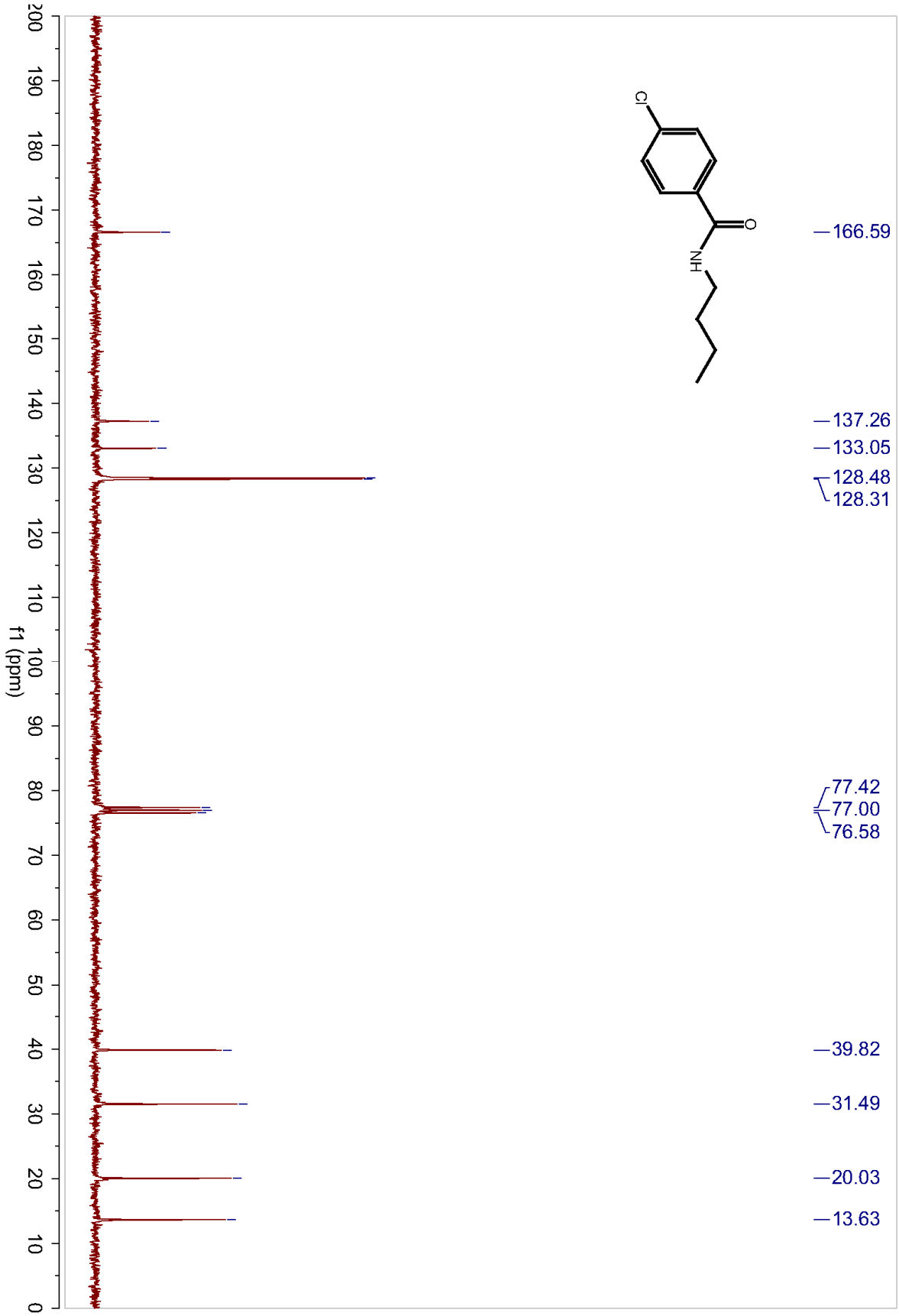
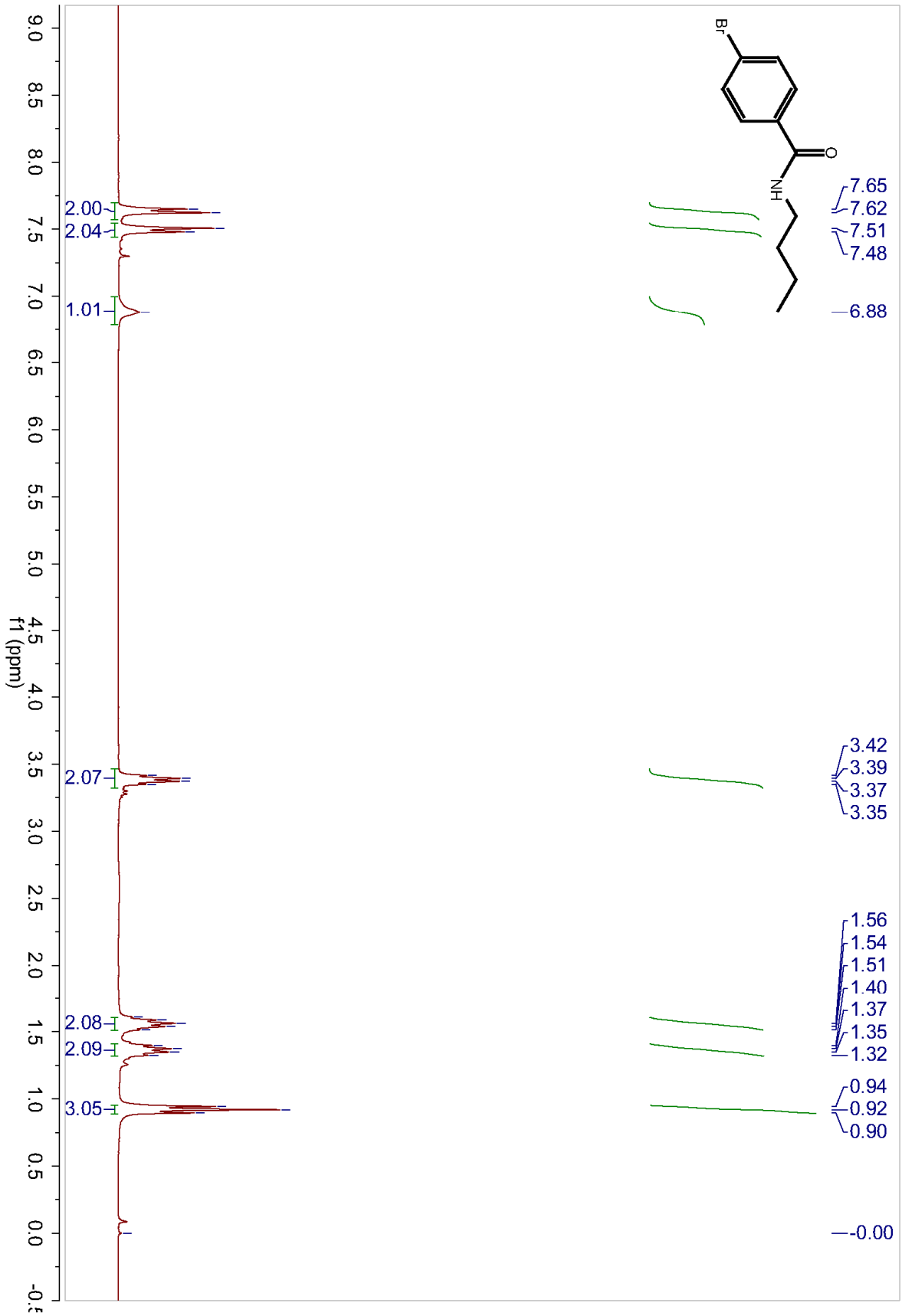
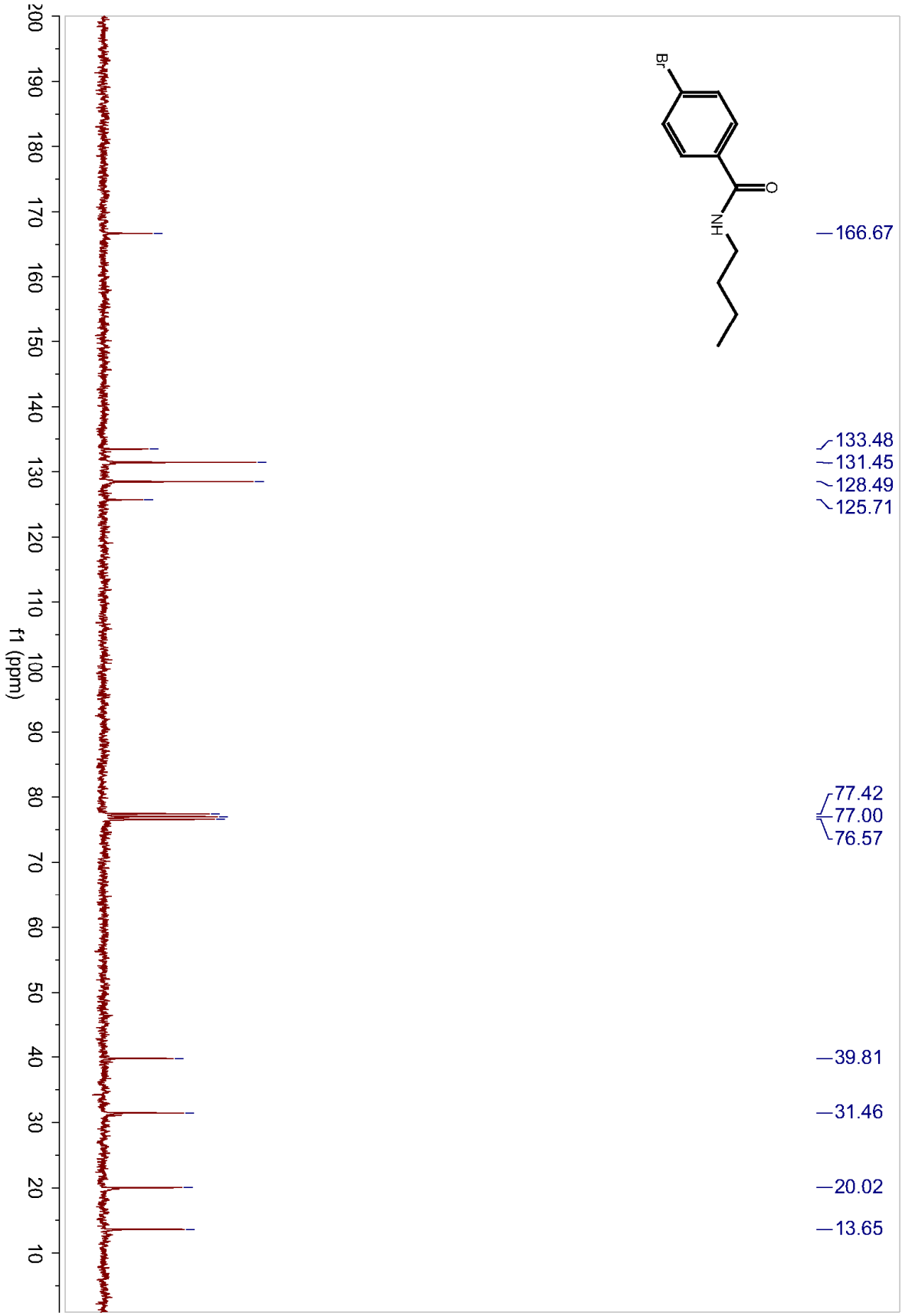
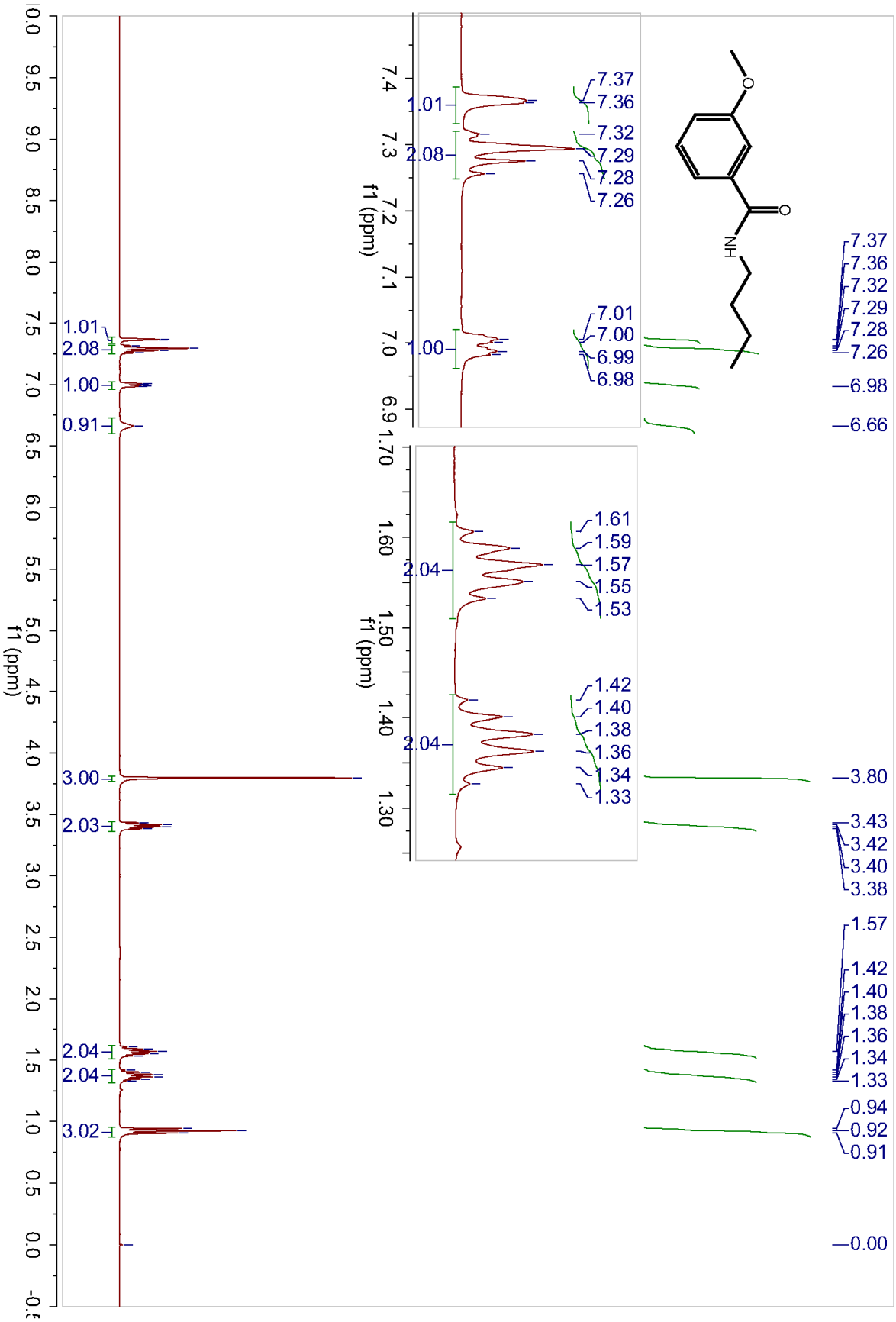
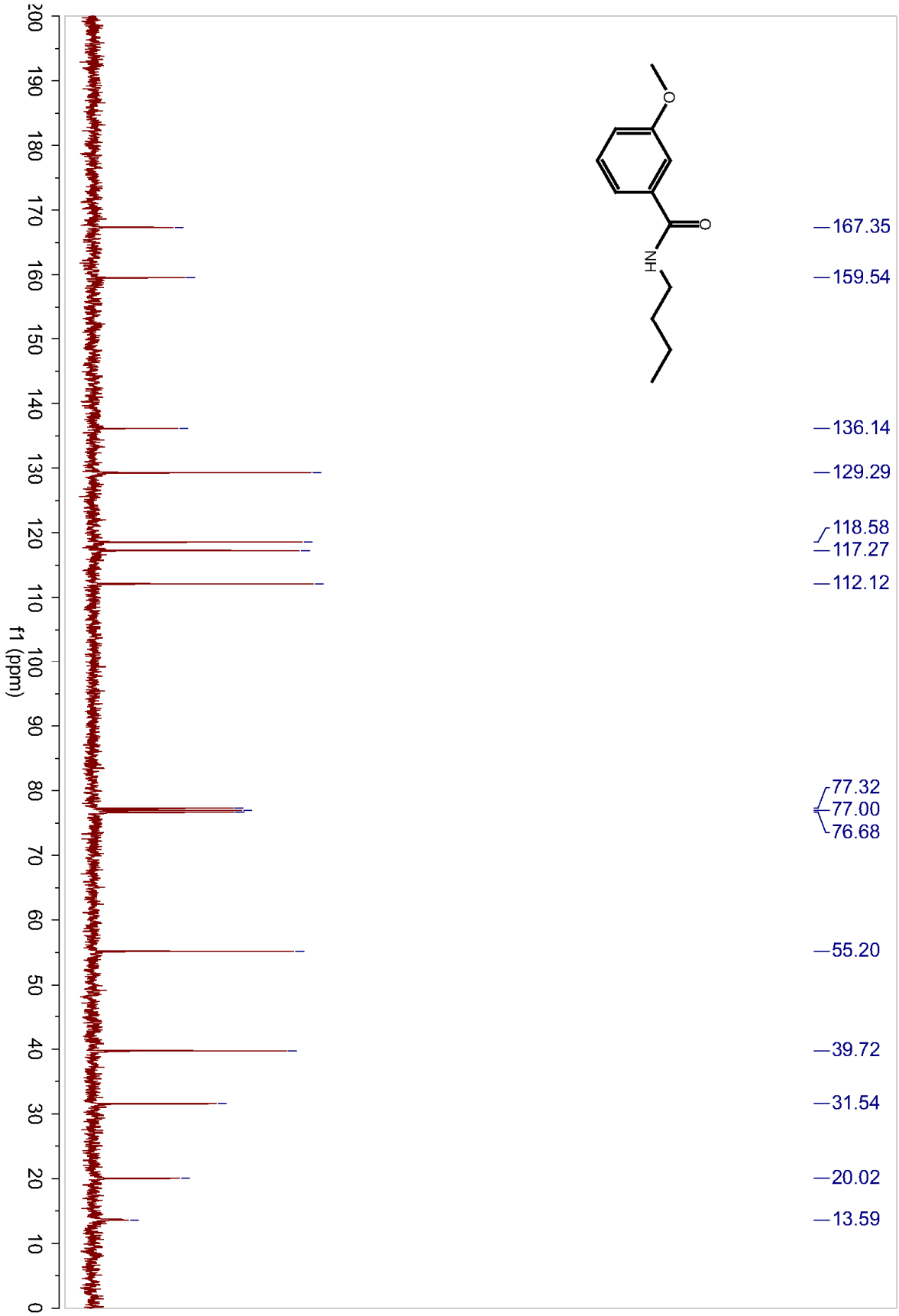
3.36
1.57
1.54
1.52
1.40
1.37
1.35
1.32
0.94
0.92
0.90
0.00
Cl
O
HN

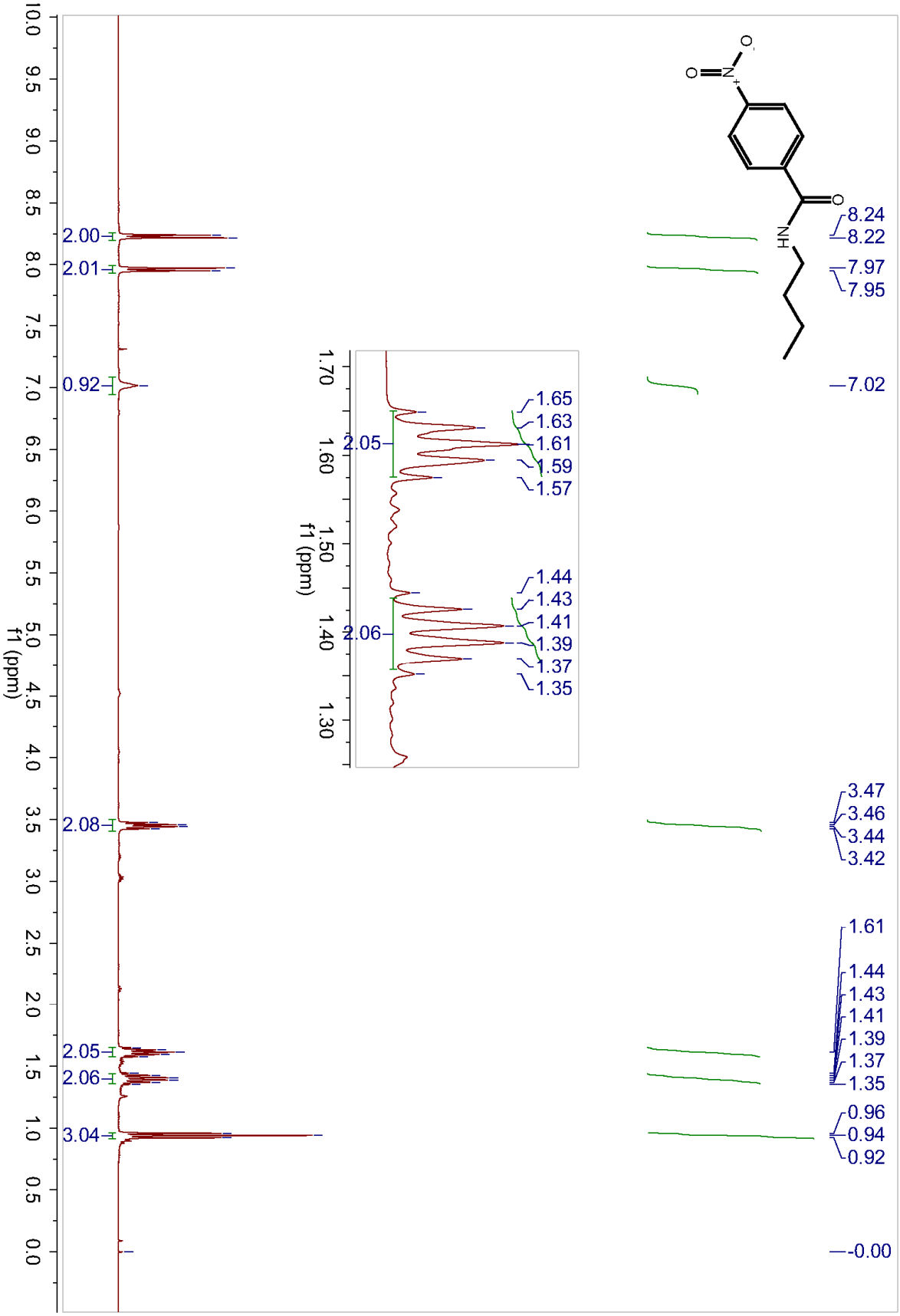

Cl
O
NH
166.59
137.26
133.05
128.48
128.31
77.42
77.00
76.58
39.82
31.49
20.03
13.63
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

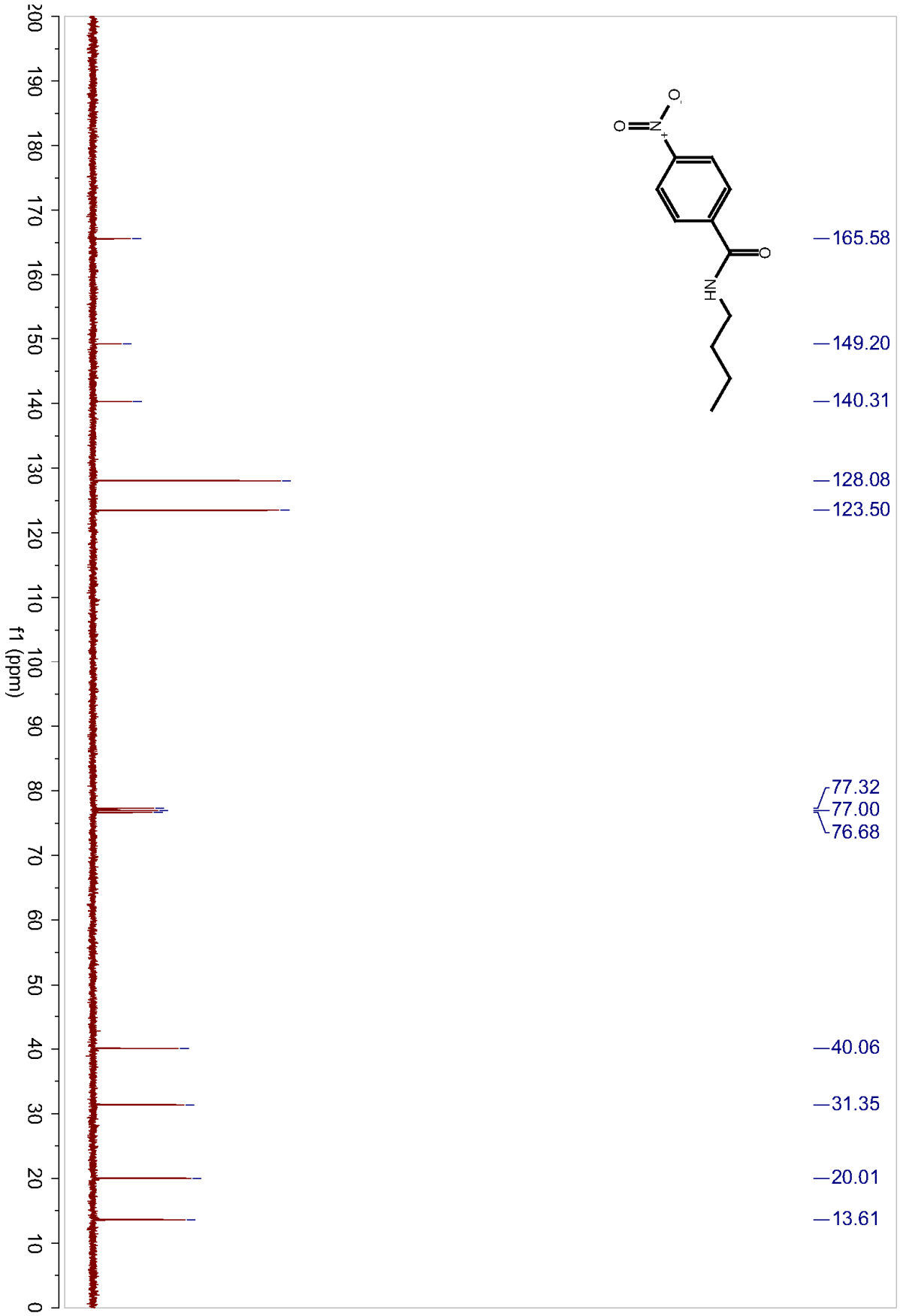

Br
O
NH
7.65
7.62
7.51
7.48
6.88
3.42
3.39
3.37
3.35
1.56
1.54
1.51
1.40
1.37
1.35
1.32
0.94
0.92
0.90
-0.00
2.00
2.04
1.01
2.07
2.08
2.09
3.05
f1 (ppm)

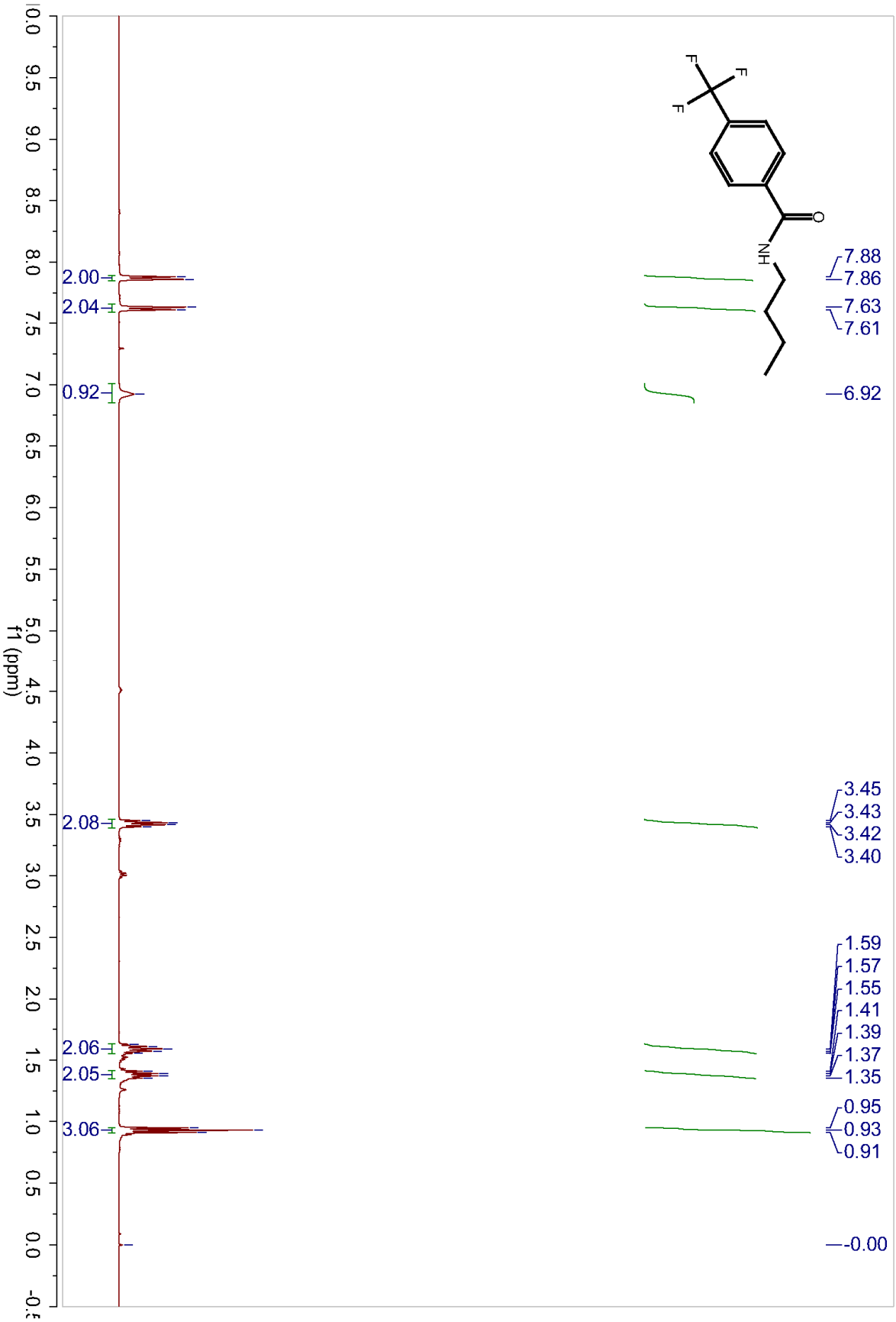

f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Br
O
NH
166.67
133.48
131.45
128.49
125.71
77.42
77.00
76.57
39.81
31.46
20.02
13.65

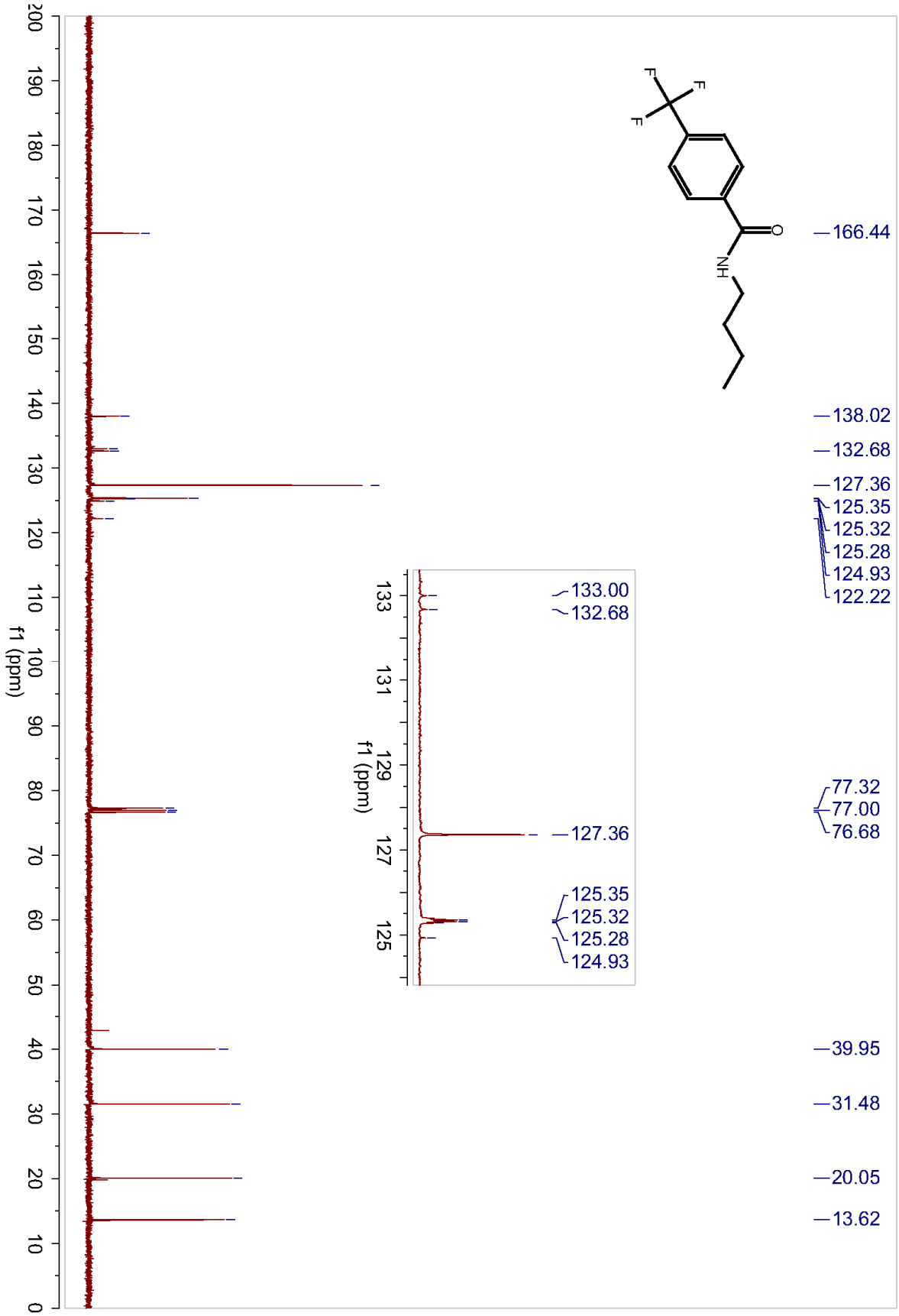

f1 (ppm)
1.01
2.08
1.00
0.91
3.00
2.03
2.04
2.04
3.02
7.37
7.36
7.32
7.29
7.28
7.26
7.01
7.00
6.99
6.98
1.61
1.59
1.57
1.55
1.53
1.42
1.40
1.38
1.36
1.34
1.33
O
NH
O
7.37
7.36
7.32
7.29
7.28
7.26
6.98
6.66
3.80
3.43
3.42
3.40
3.38
1.57
1.42
1.40
1.38
1.36
1.34
1.33
0.94
0.92
0.91
0.00

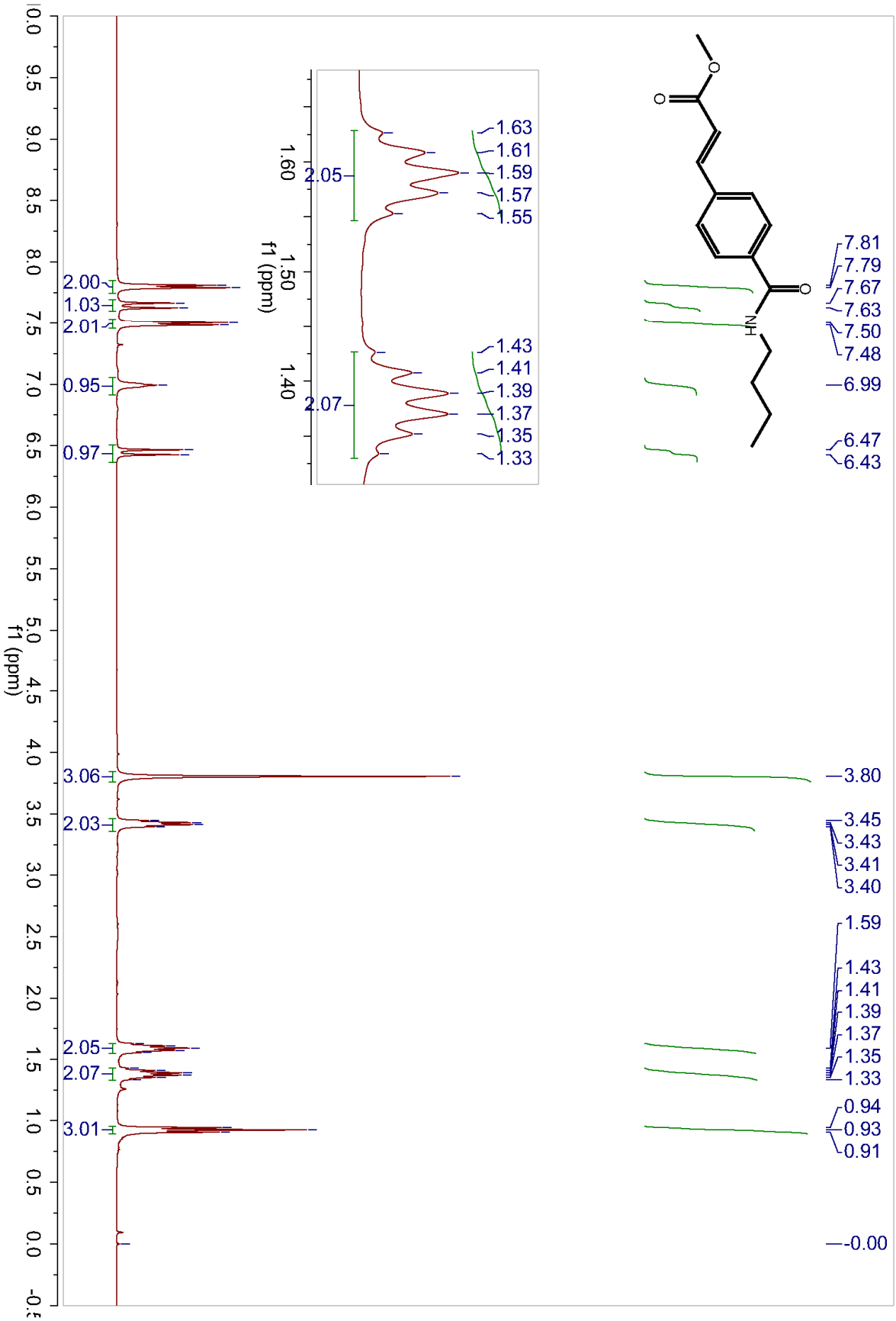

f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
O
O
HN
167.35
159.54
136.14
129.29
118.58
117.27
112.12
77.32
77.00
76.68
55.20
39.72
31.54
20.02
13.59

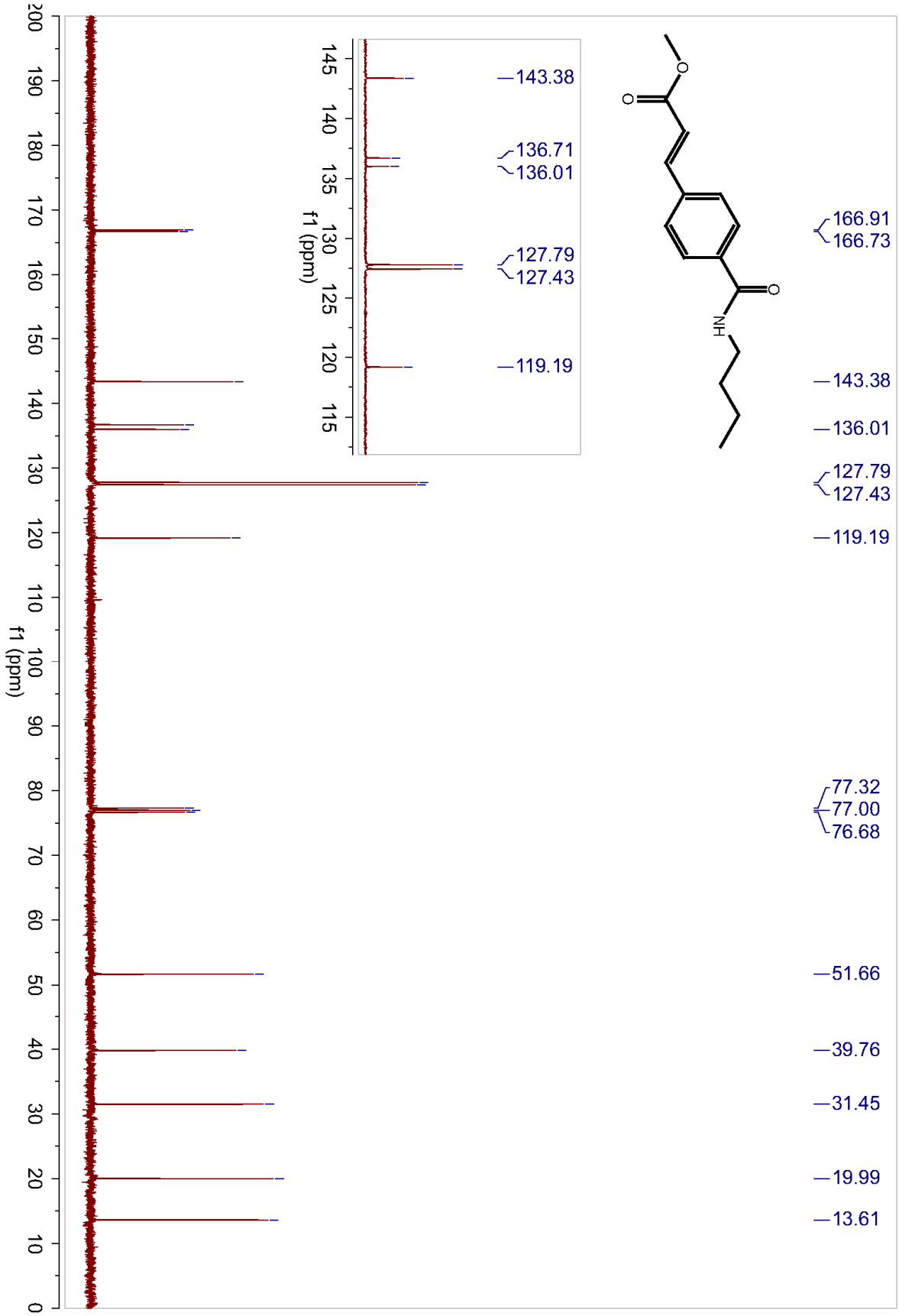

f1 (ppm)
2.00
2.01
0.92
2.08
2.05
2.06
3.04
1.65
1.63
1.61
1.59
1.57
1.44
1.43
1.41
1.39
1.37
1.35
8.24
8.22
7.97
7.95
7.02
3.47
3.46
3.44
3.42
1.61
1.44
1.43
1.41
1.39
1.37
1.35
0.96
0.94
0.92
-0.00
NH


f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
O
O
N
O
HN
O
165.58
149.20
140.31
128.08
123.50
77.32
77.00
76.68
40.06
31.35
20.01
13.61


F
F
F
O
NH
7.88
7.86
7.63
7.61
6.92
3.45
3.43
3.42
3.40
1.59
1.57
1.55
1.41
1.39
1.37
1.35
0.95
0.93
0.91
-0.00
2.00
2.04
0.92
2.08
2.06
2.05
3.06
f1 (ppm)


F
F
F
O
NH
166.44
138.02
132.68
127.36
125.35
125.32
125.28
124.93
122.22
77.32
77.00
76.68
39.95
31.48
20.05
13.62
f1 (ppm)
133.00
132.68
127.36
125.35
125.32
125.28
124.93


f1 (ppm)
2.00
1.03
2.01
0.95
0.97
3.06
2.03
2.05
2.07
3.01
1.60
1.50
1.40
2.05
2.07
1.63
1.61
1.59
1.57
1.55
1.43
1.41
1.39
1.37
1.35
1.33
O
O
NH
O
7.81
7.79
7.67
7.63
7.50
7.48
6.99
6.47
6.43
3.80
3.45
3.43
3.41
3.40
1.59
1.43
1.41
1.39
1.37
1.35
1.33
0.94
0.93
0.91
-0.00


f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
145
140
135
130
125
120
115
143.38
136.71
136.01
127.79
127.43
119.19
O
O
NH
O
166.91
166.73
143.38
136.01
127.79
127.43
119.19
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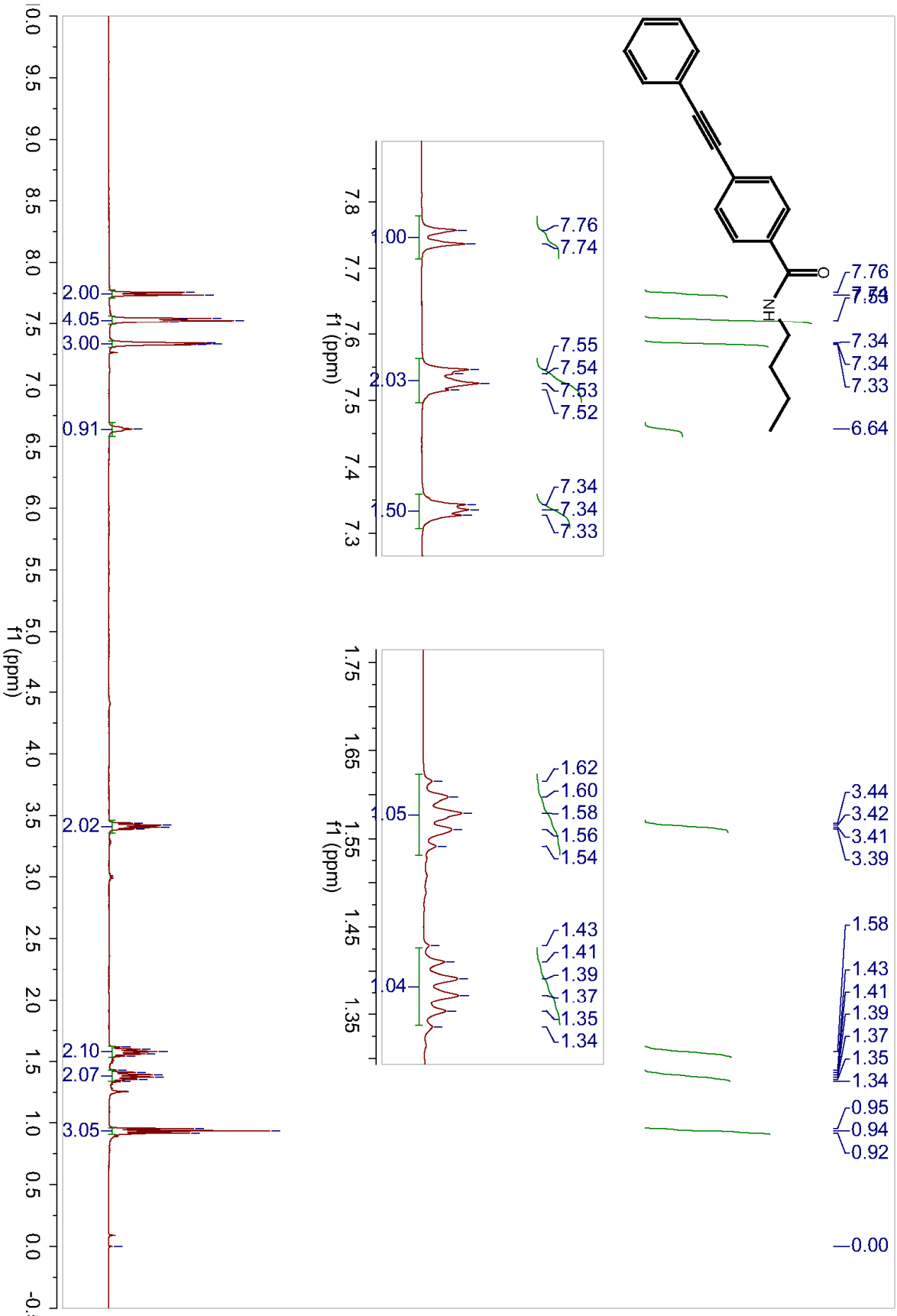
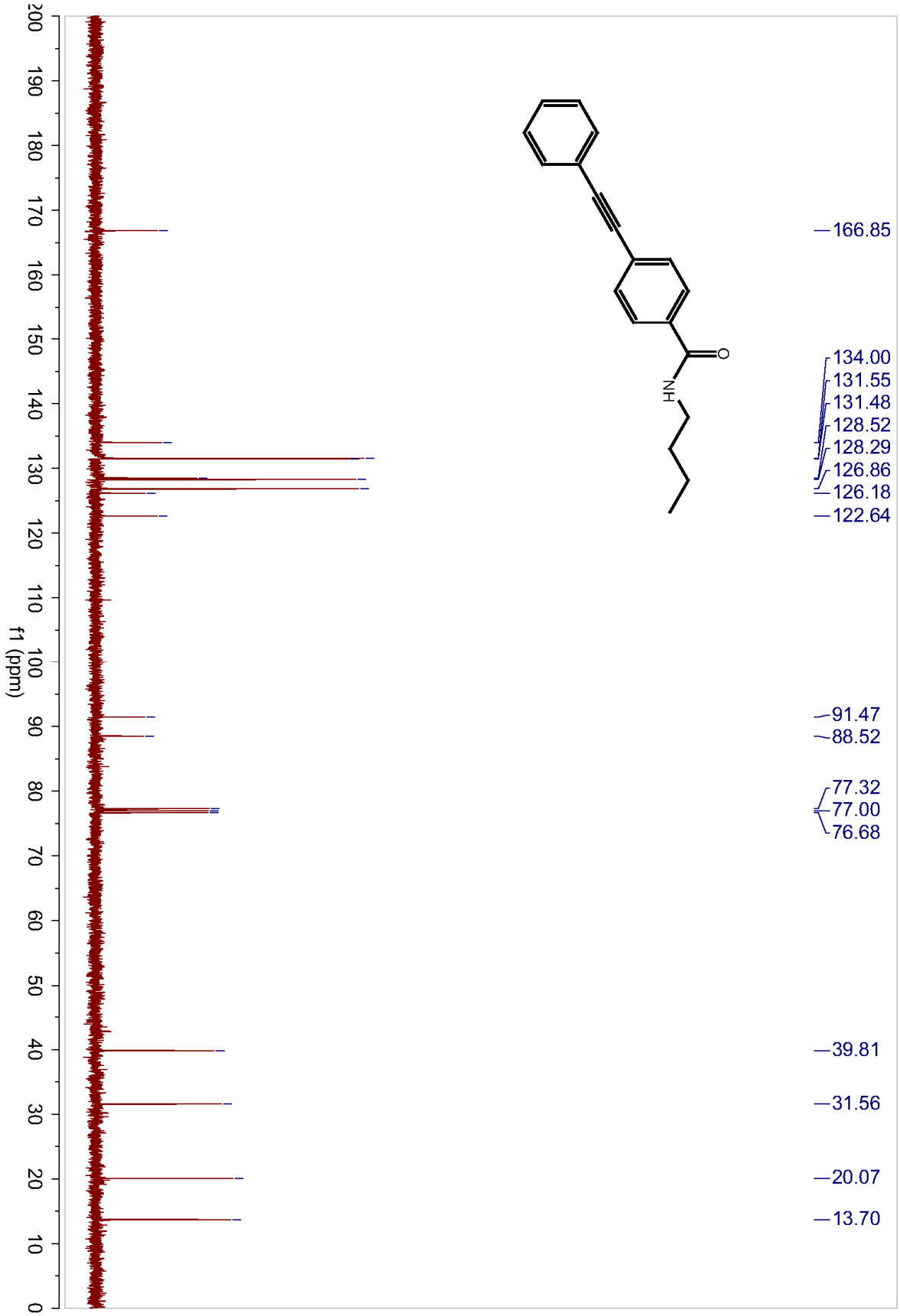
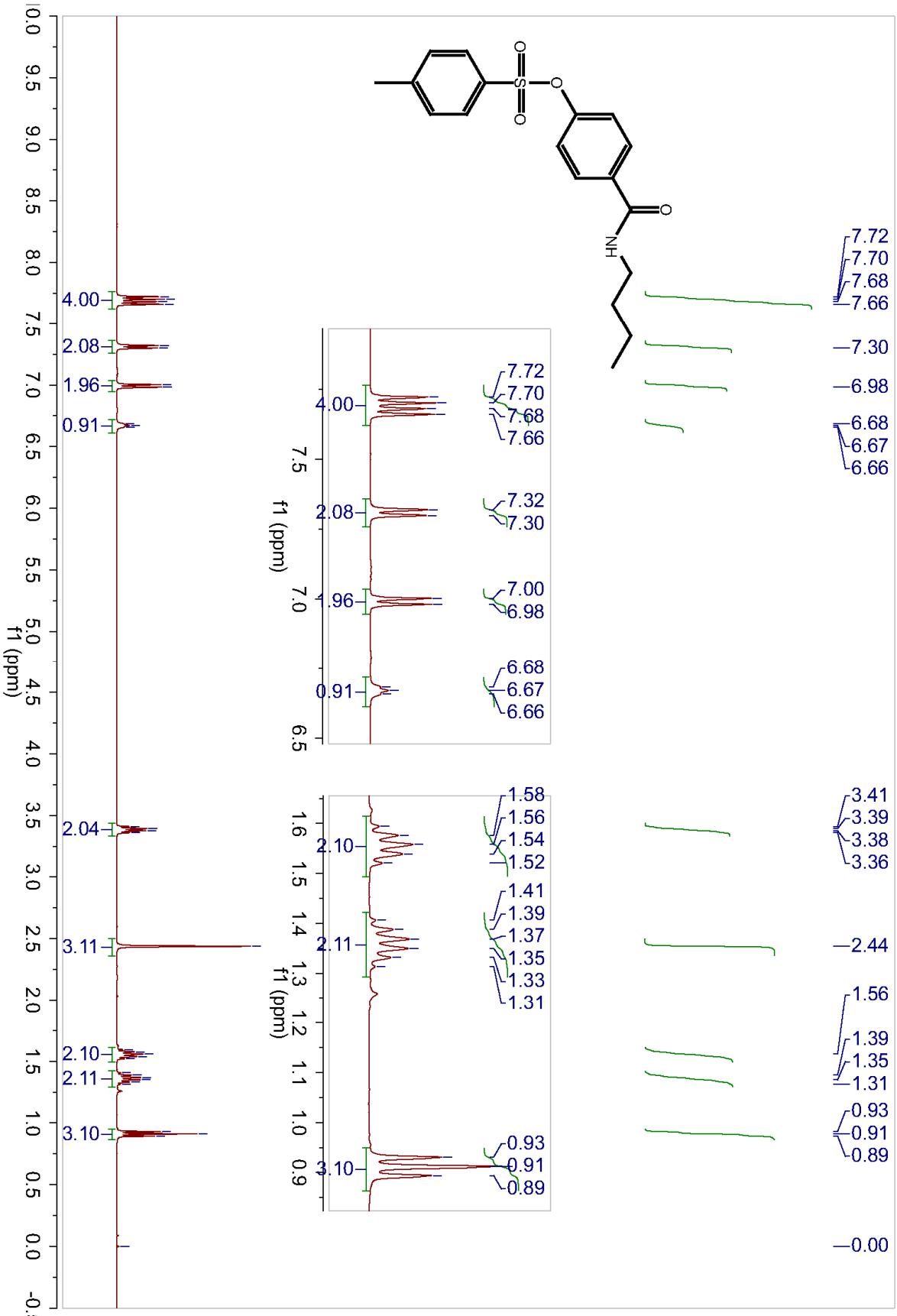
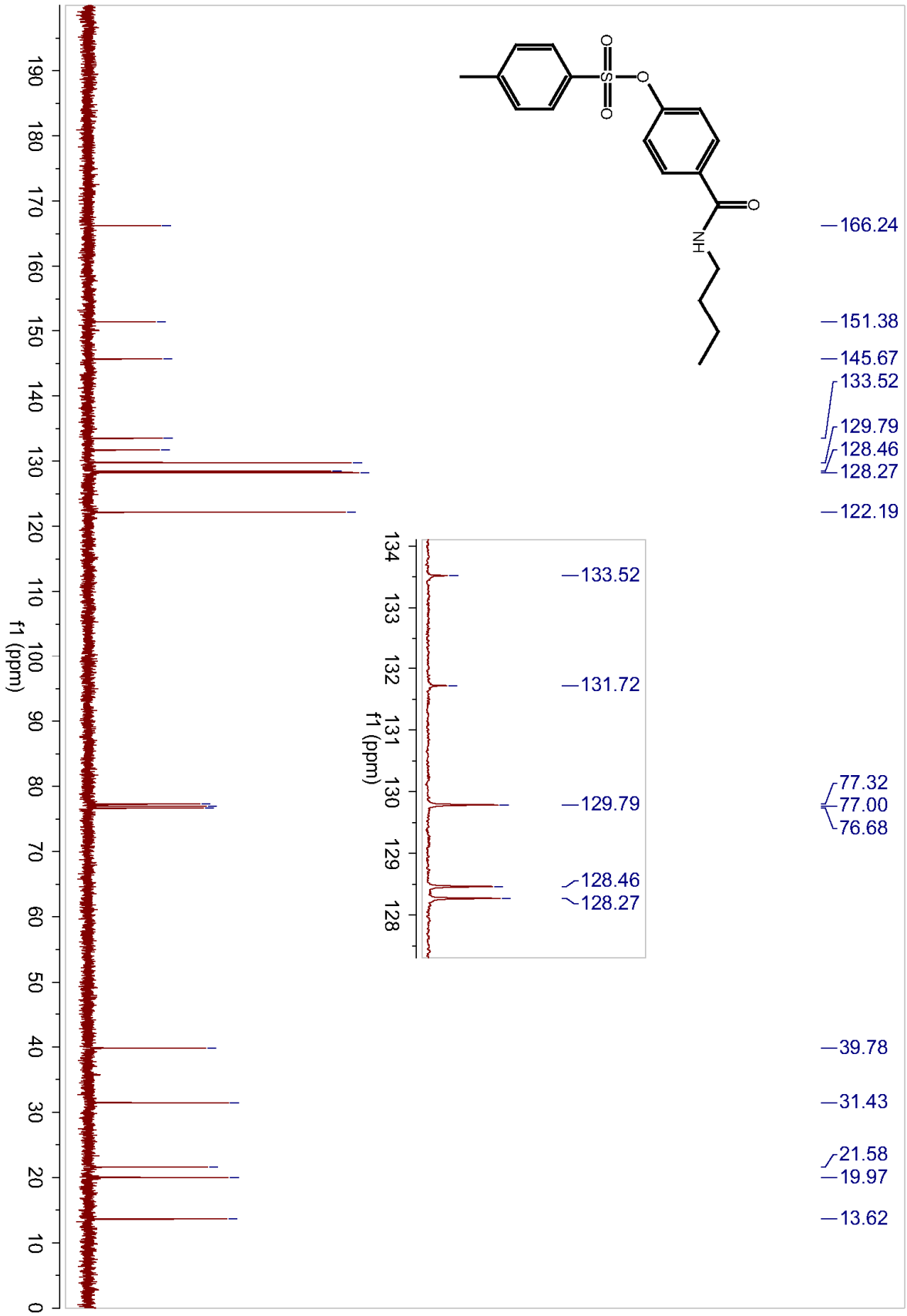
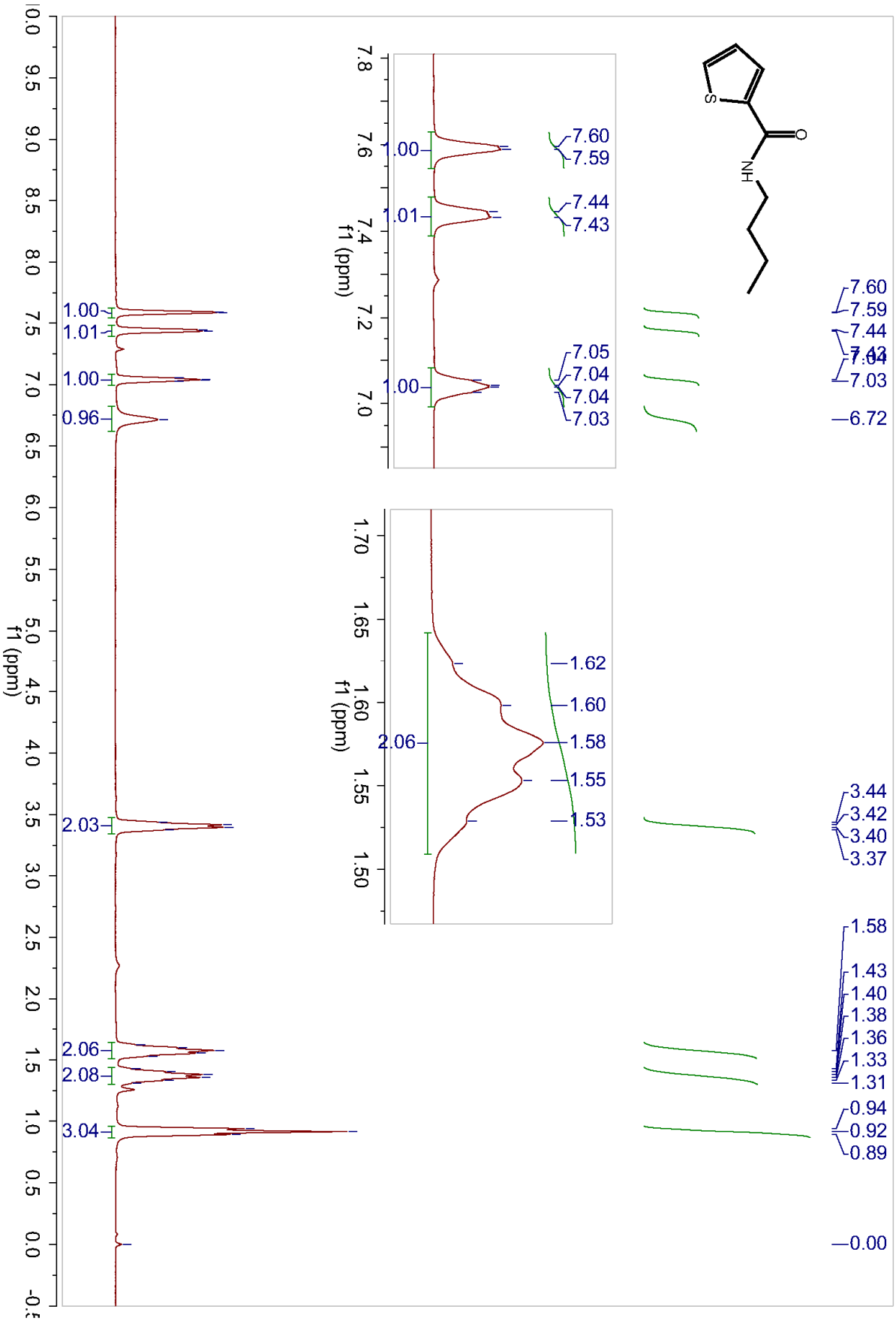
77.00
76.68
51.66
39.76
31.45
19.99
13.61

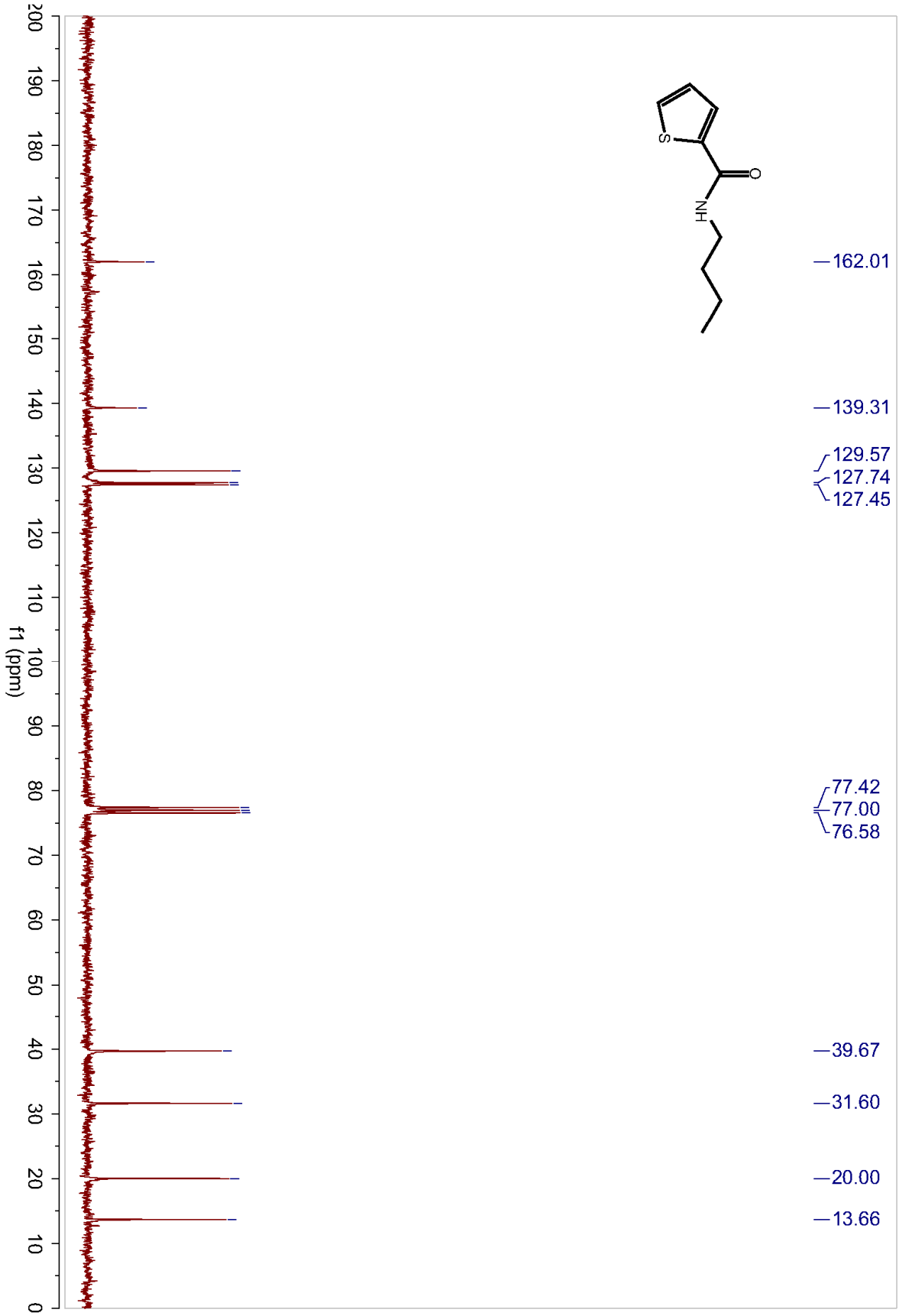

f1 (ppm)
2.00
4.05
3.00
0.91
2.02
2.10
2.07
3.05
1.00
2.03
1.50
7.76
7.74
7.55
7.54
7.53
7.52
7.34
7.34
7.33
1.05
1.04
1.62
1.60
1.58
1.56
1.54
1.43
1.41
1.39
1.37
1.35
1.34
NH
O
7.76
7.74
7.55
7.34
7.34
7.33
6.64
3.44
3.42
3.41
3.39
1.58
1.43
1.41
1.39
1.37
1.35
1.34
0.95
0.94
0.92
0.00

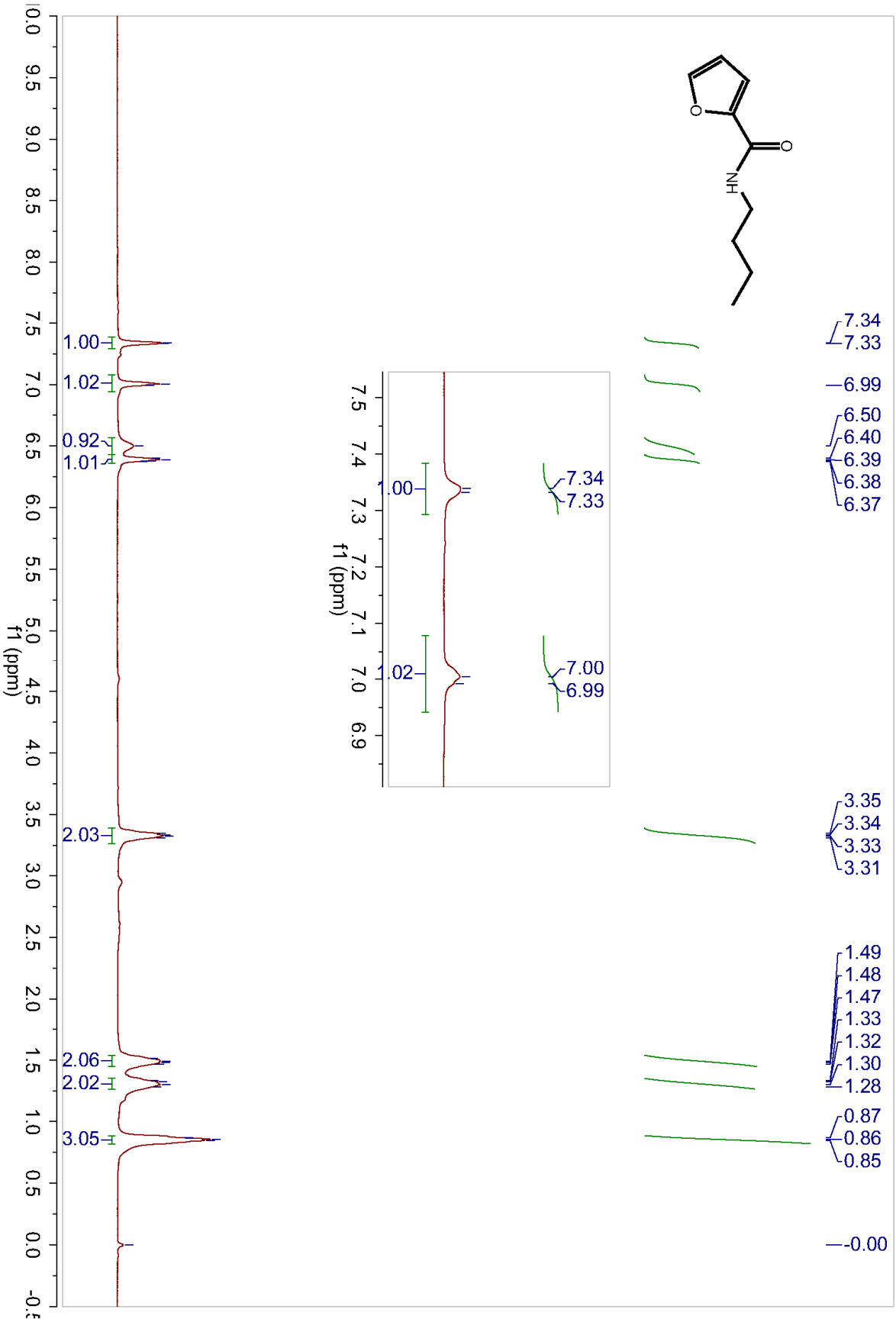

f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
166.85
134.00
131.55
131.48
128.52
128.29
126.86
126.18
122.64
91.47
88.52
77.32
77.00
76.68
39.81
31.56
20.07
13.70
O
HN

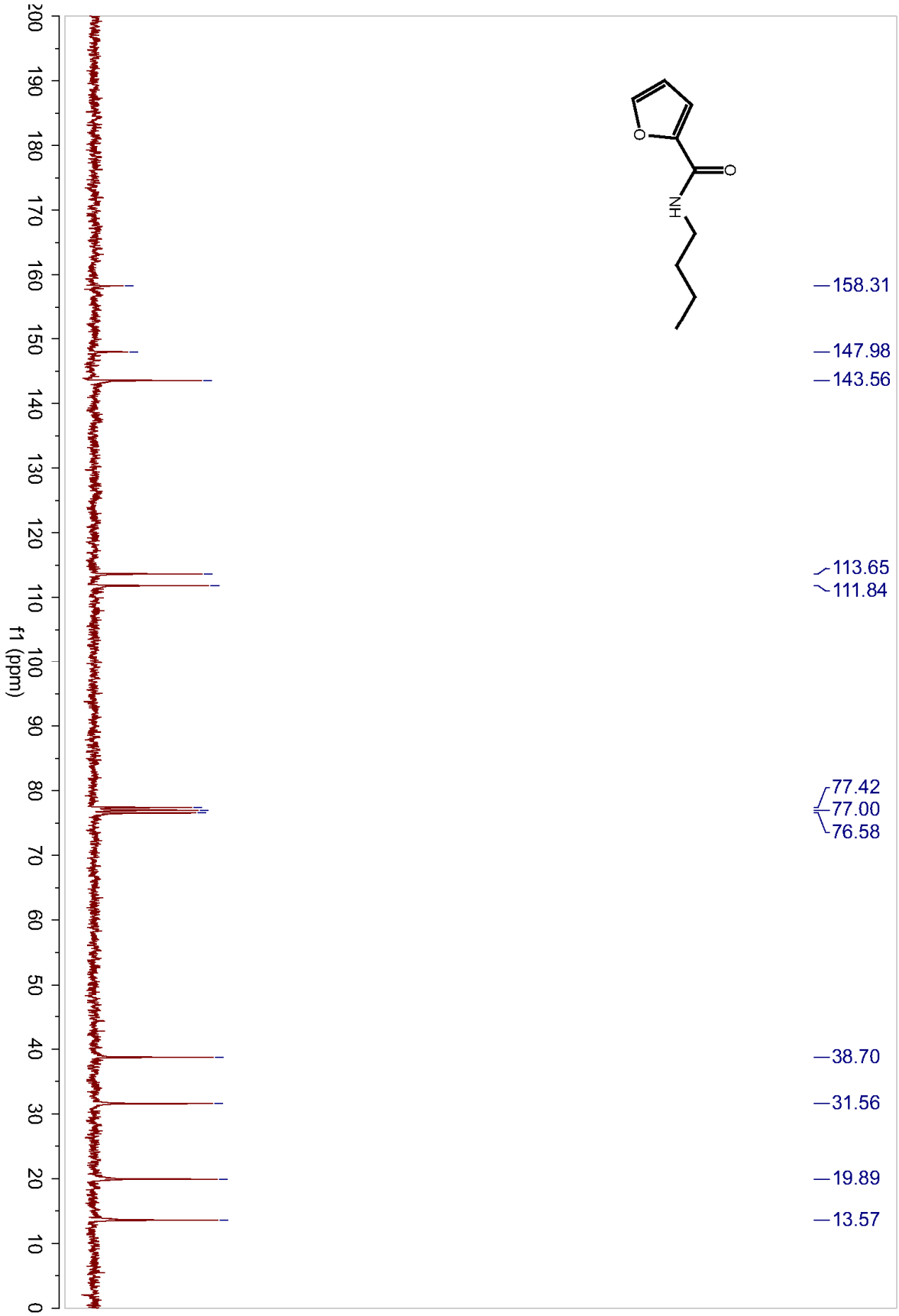

f1 (ppm)
4.00
2.08
1.96
0.91
2.04
3.11
2.10
2.11
3.10
7.72
7.70
7.68
7.66
7.32
7.30
7.00
6.98
6.68
6.67
6.66
1.58
1.56
1.54
1.52
1.41
1.39
1.37
1.35
1.33
1.31
0.93
0.91
0.89
3.41
3.39
3.38
3.36
2.44
0.00
NH

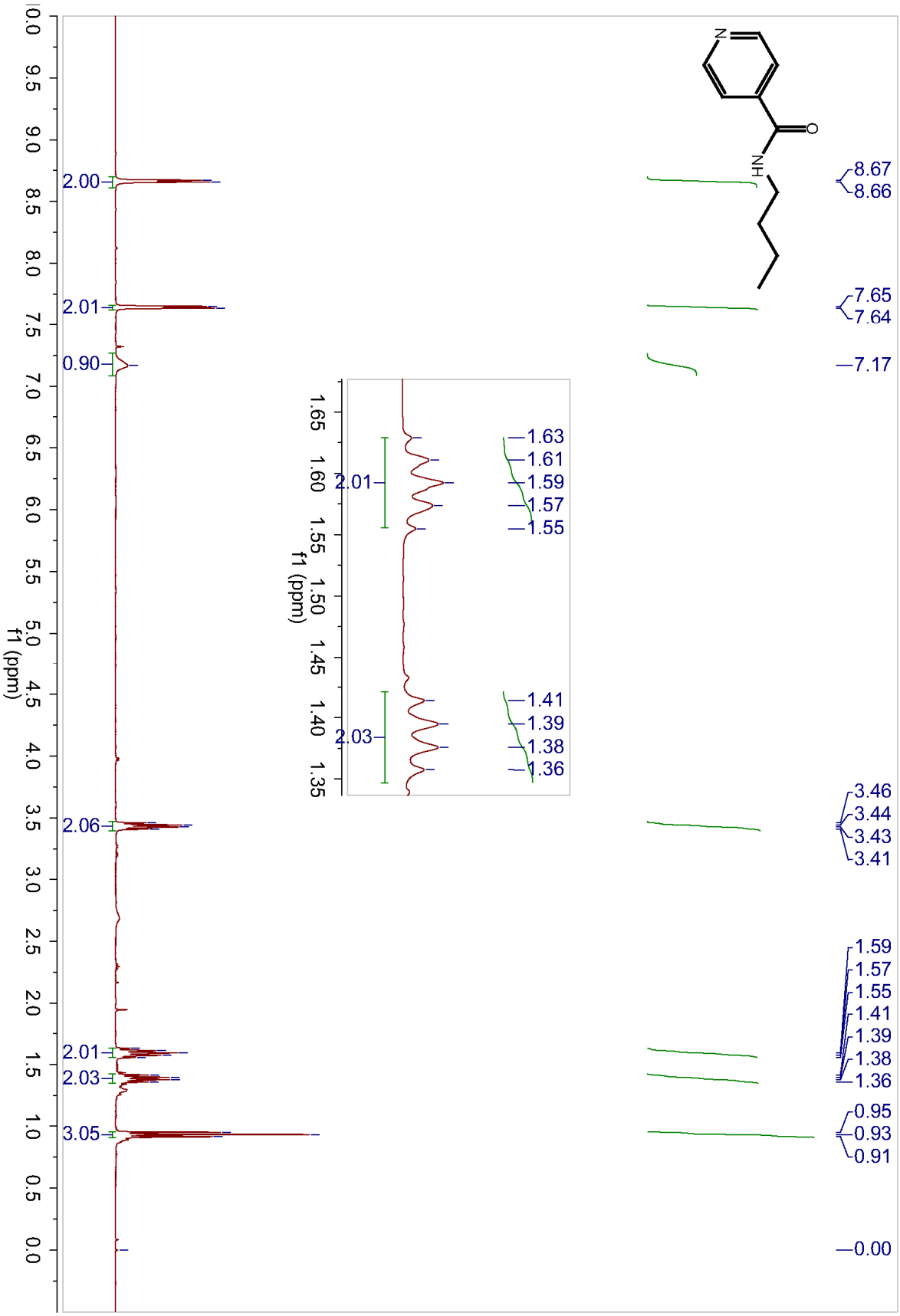

166.24
151.38
145.67
133.52
129.79
128.46
128.27
122.19
77.32
77.00
76.68
39.78
31.43
21.58
19.97
13.62
f1 (ppm)
133.52
131.72
129.79
128.46
128.27
f1 (ppm)

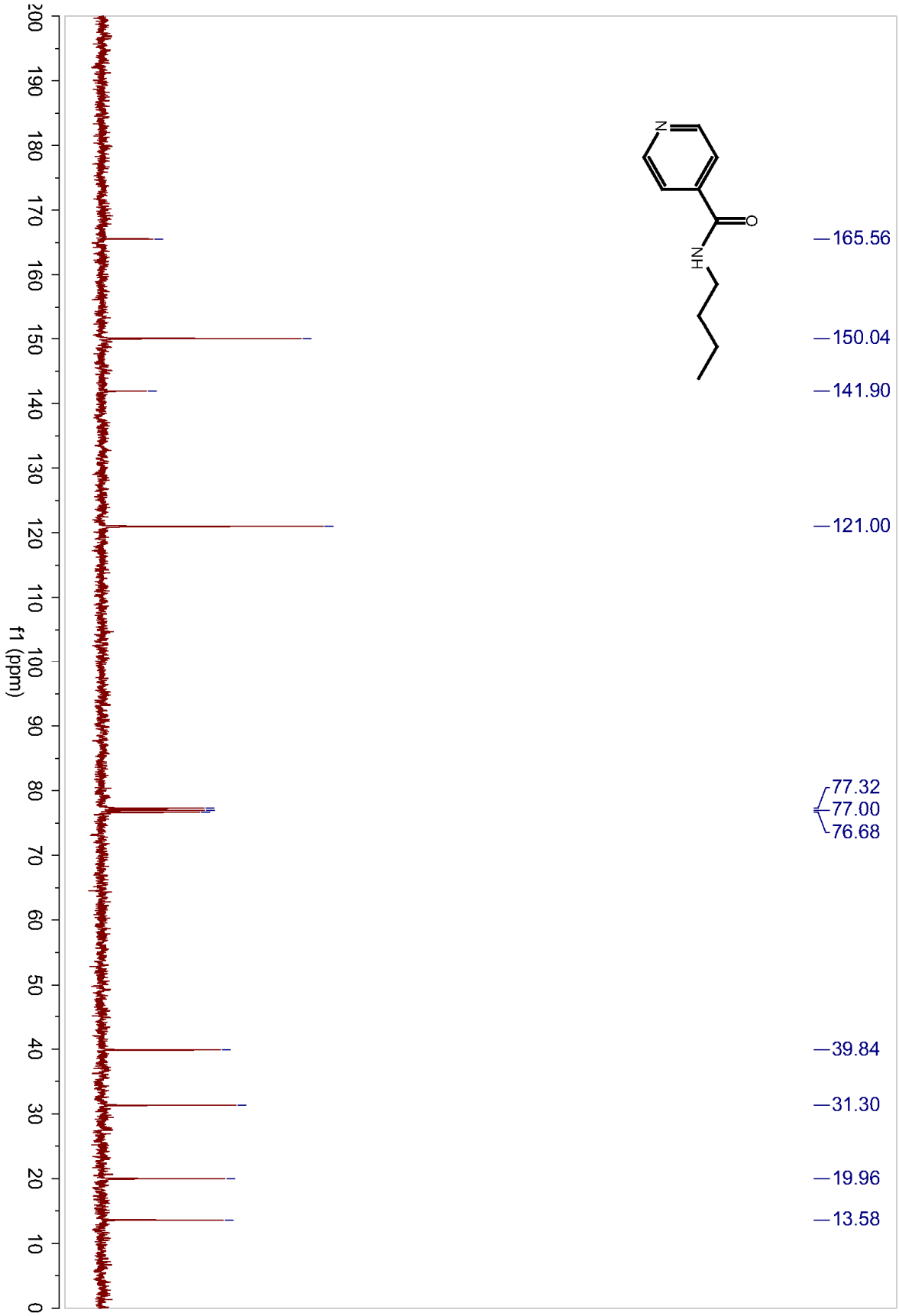

f1 (ppm)
1.00
1.01
1.00
0.96
2.03
2.06
2.08
3.04
7.60
7.59
7.44
7.43
7.05
7.04
7.04
7.03
6.72
3.44
3.42
3.40
3.37
1.62
1.60
1.58
1.55
1.53
1.58
1.43
1.40
1.38
1.36
1.33
1.31
0.94
0.92
0.89
0.00
S
O
NH

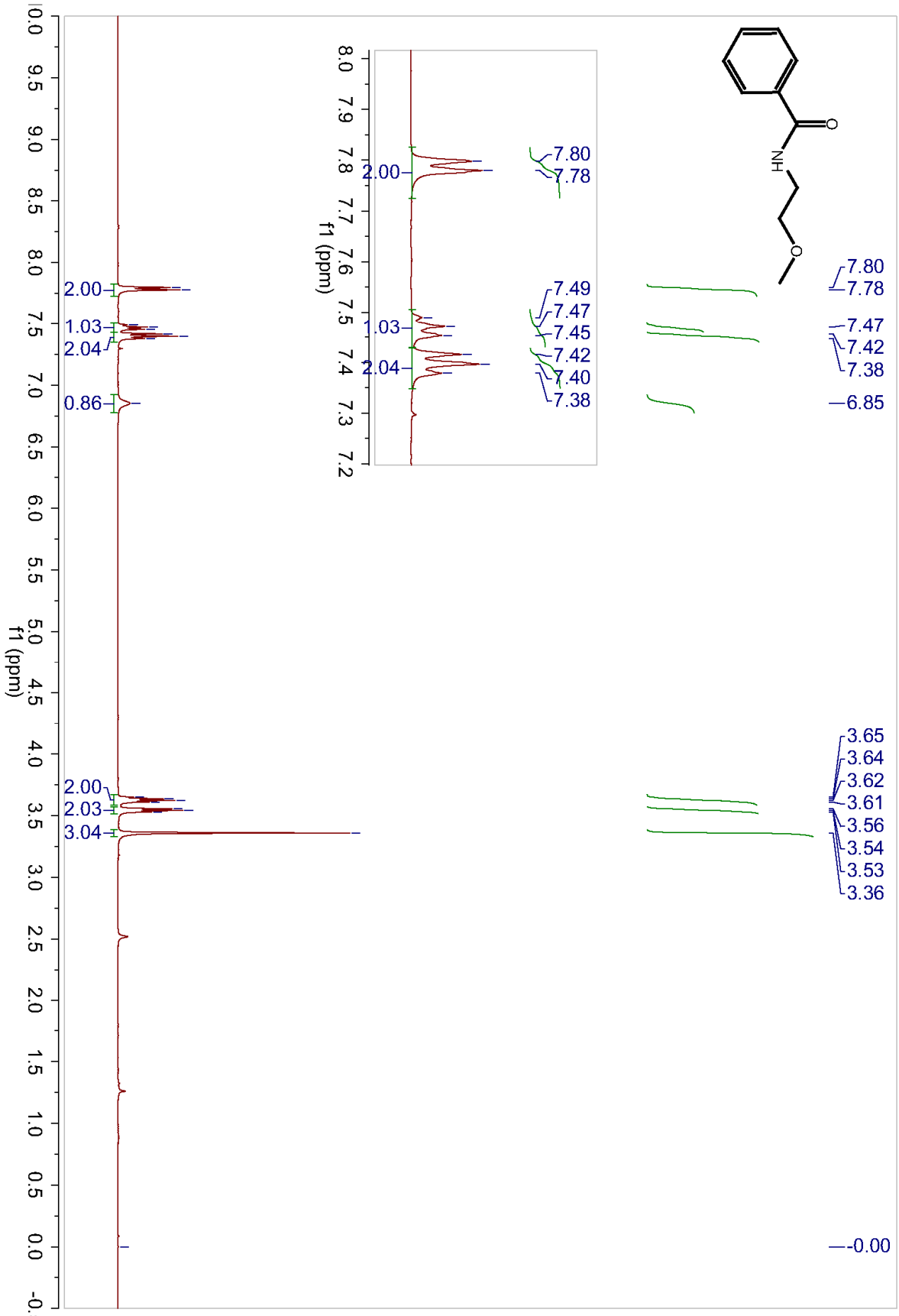

f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
S
O
NH
162.01
139.31
129.57
127.74
127.45
77.42
77.00
76.58
39.67
31.60
20.00
13.66

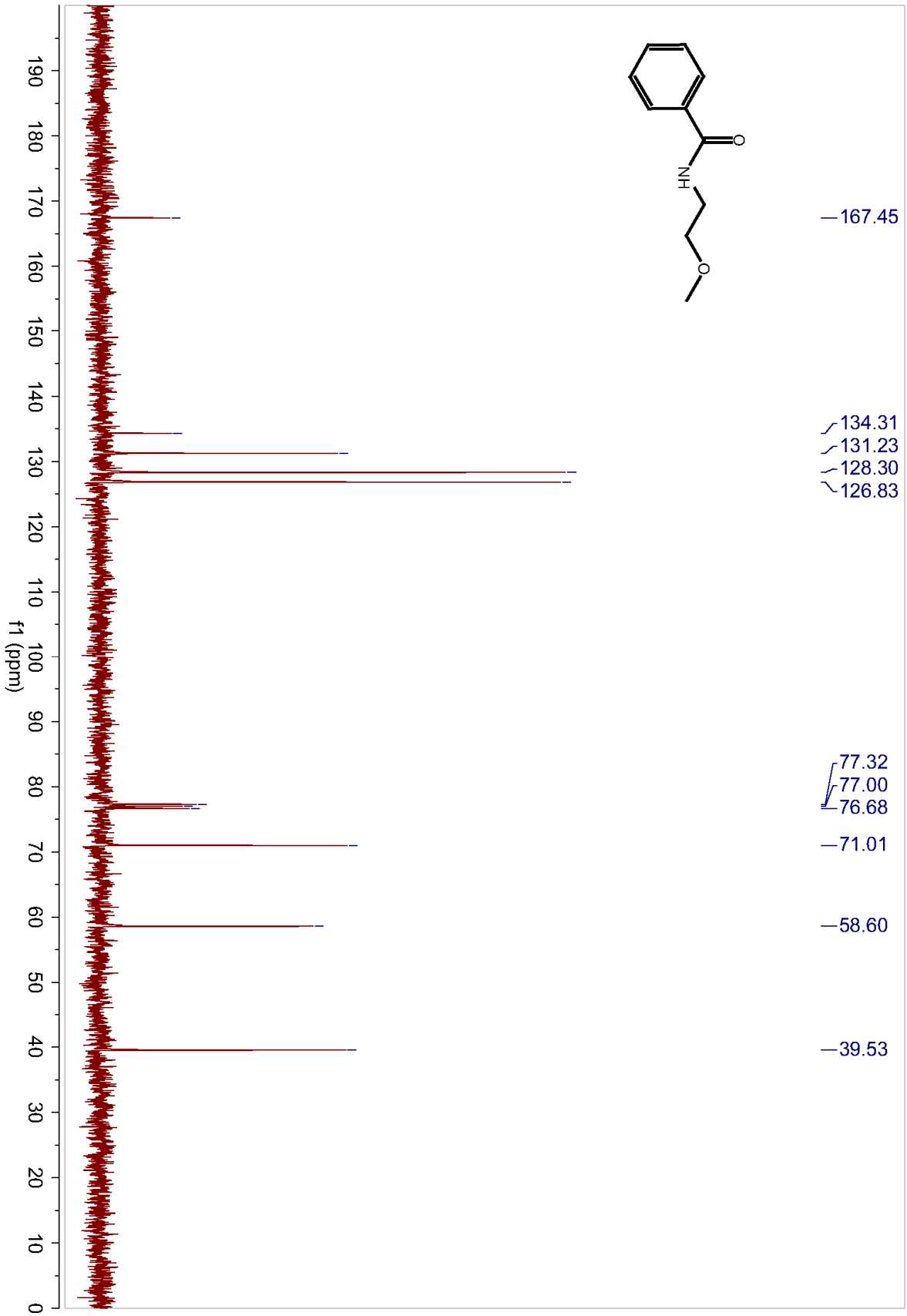

f1 (ppm)
1.00
1.02
0.92
1.01
2.03
2.06
2.02
3.05
7.34
7.33
6.99
6.50
6.40
6.39
6.38
6.37
3.35
3.34
3.33
3.31
1.49
1.48
1.47
1.33
1.32
1.30
1.28
0.87
0.86
0.85
-0.00
O
O
HN

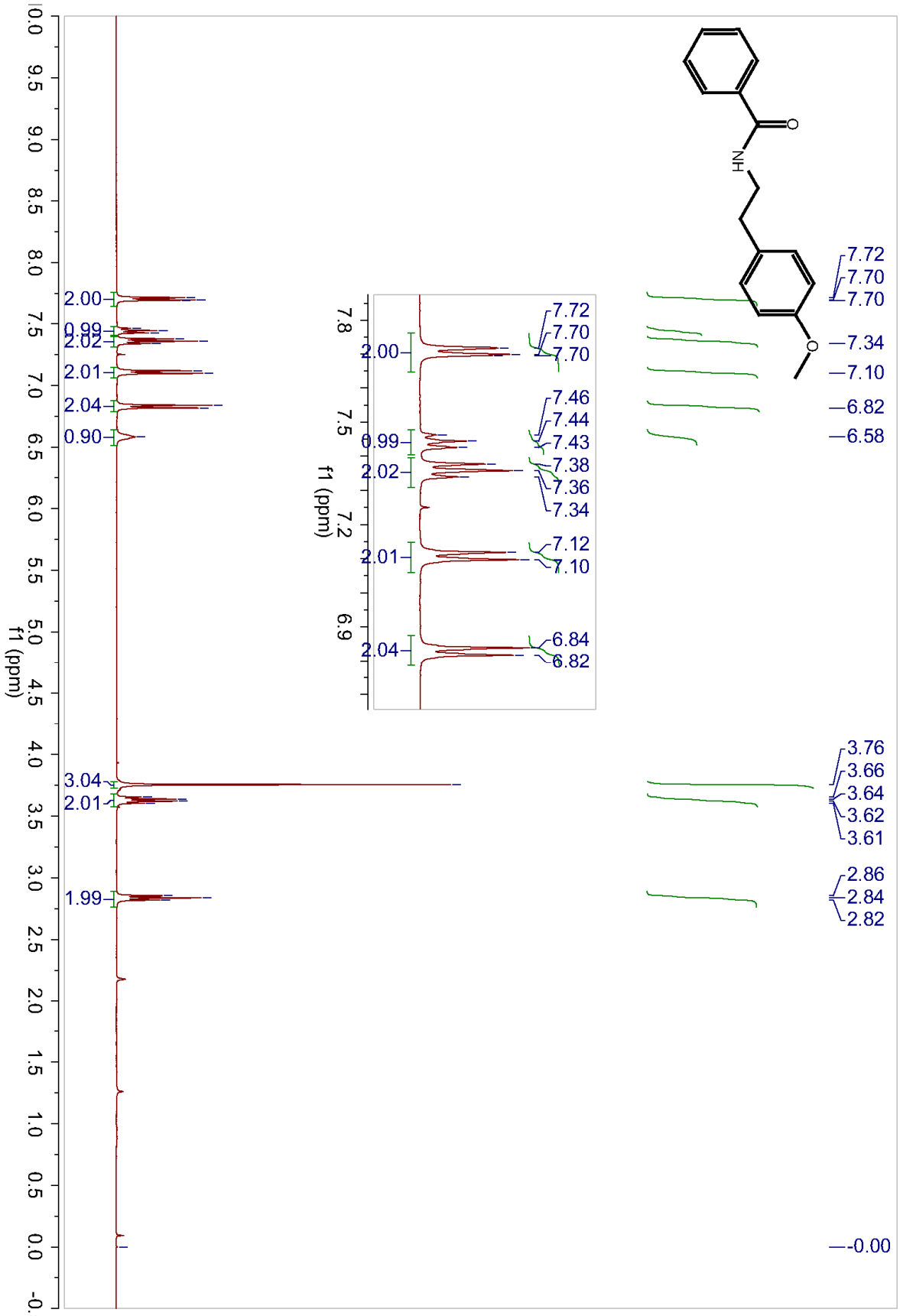

158.31
147.98
143.56
113.65
111.84
77.42
77.00
76.58
38.70
31.56
19.89
13.57
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
O
HN
O

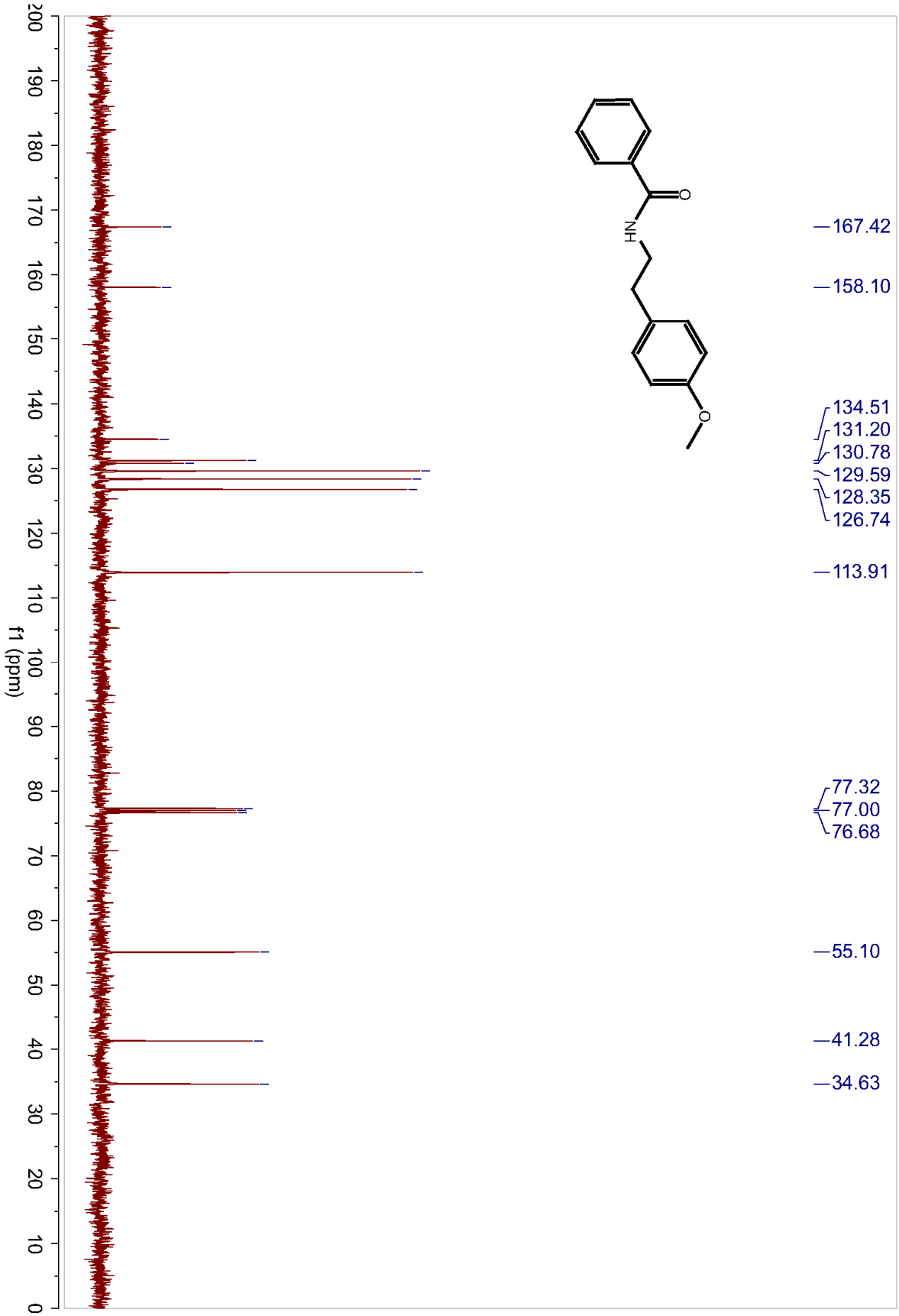

f1 (ppm)
2.00
2.01
0.90
2.06
2.01
2.03
3.05
8.67
8.66
7.65
7.64
7.17
3.46
3.44
3.43
3.41
1.59
1.57
1.55
1.41
1.39
1.38
1.36
0.95
0.93
0.91
0.00
N
NH
O
1.63
1.61
1.59
1.57
1.55
1.41
1.39
1.38
1.36

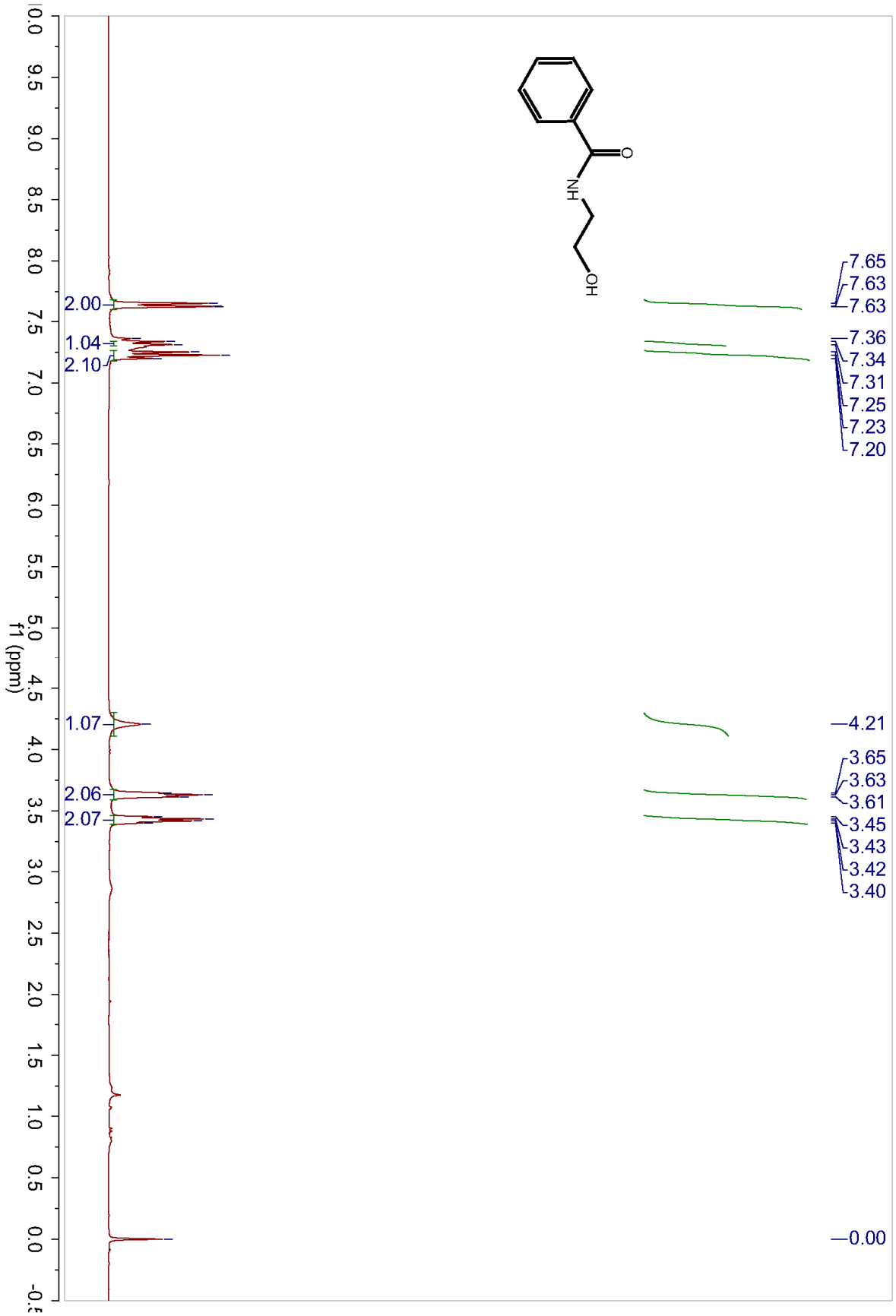

f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
N
O
HN
165.56
150.04
141.90
121.00
77.32
77.00
76.68
39.84
31.30
19.96
13.58

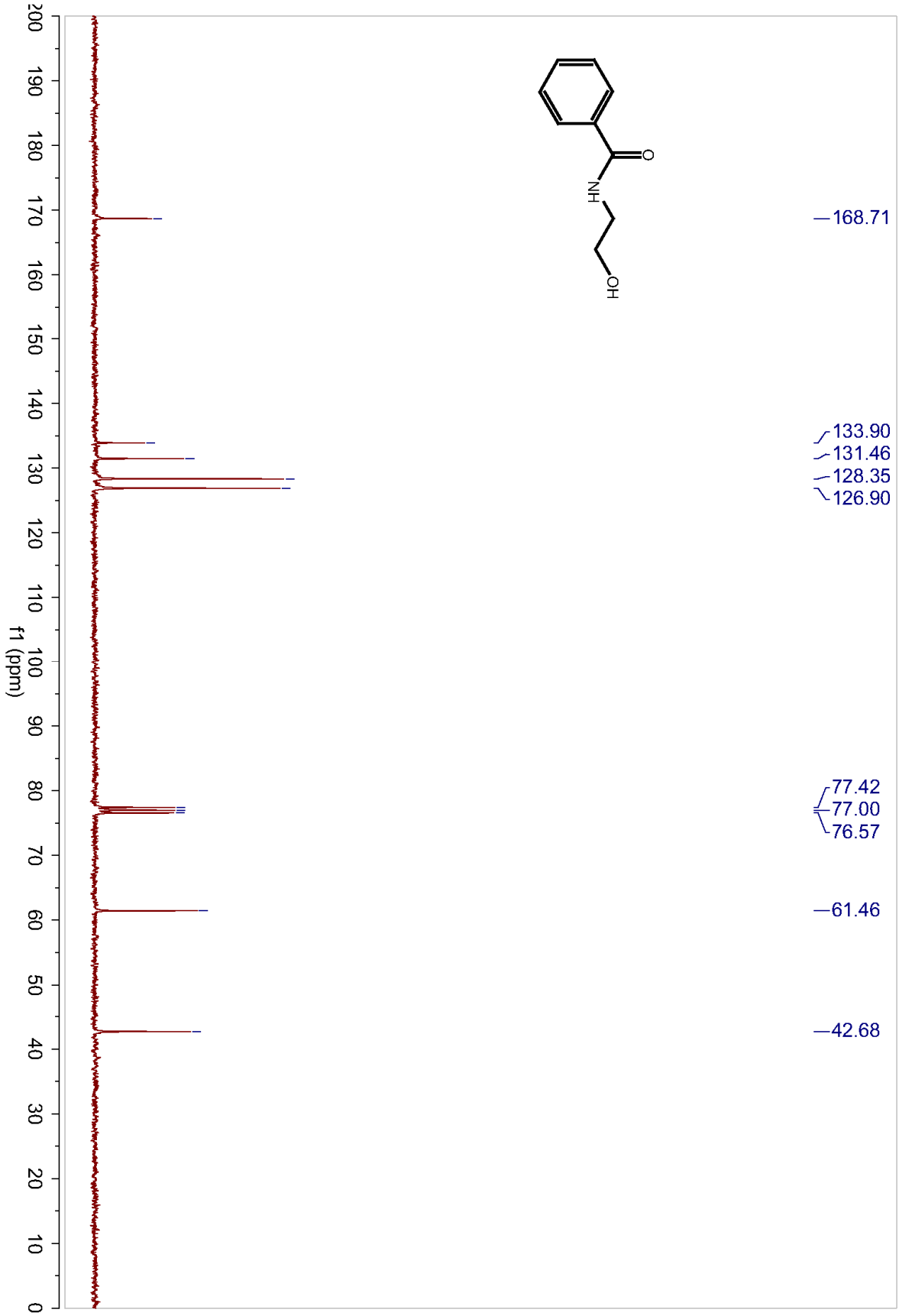

f1 (ppm)
2.00
1.03
2.04
0.86
2.00
2.03
3.04
7.80
7.78
7.49
7.47
7.45
7.42
7.40
7.38
7.80
7.78
7.47
7.42
7.38
6.85
3.65
3.64
3.62
3.61
3.56
3.54
3.53
3.36
-0.00
NH
O
O

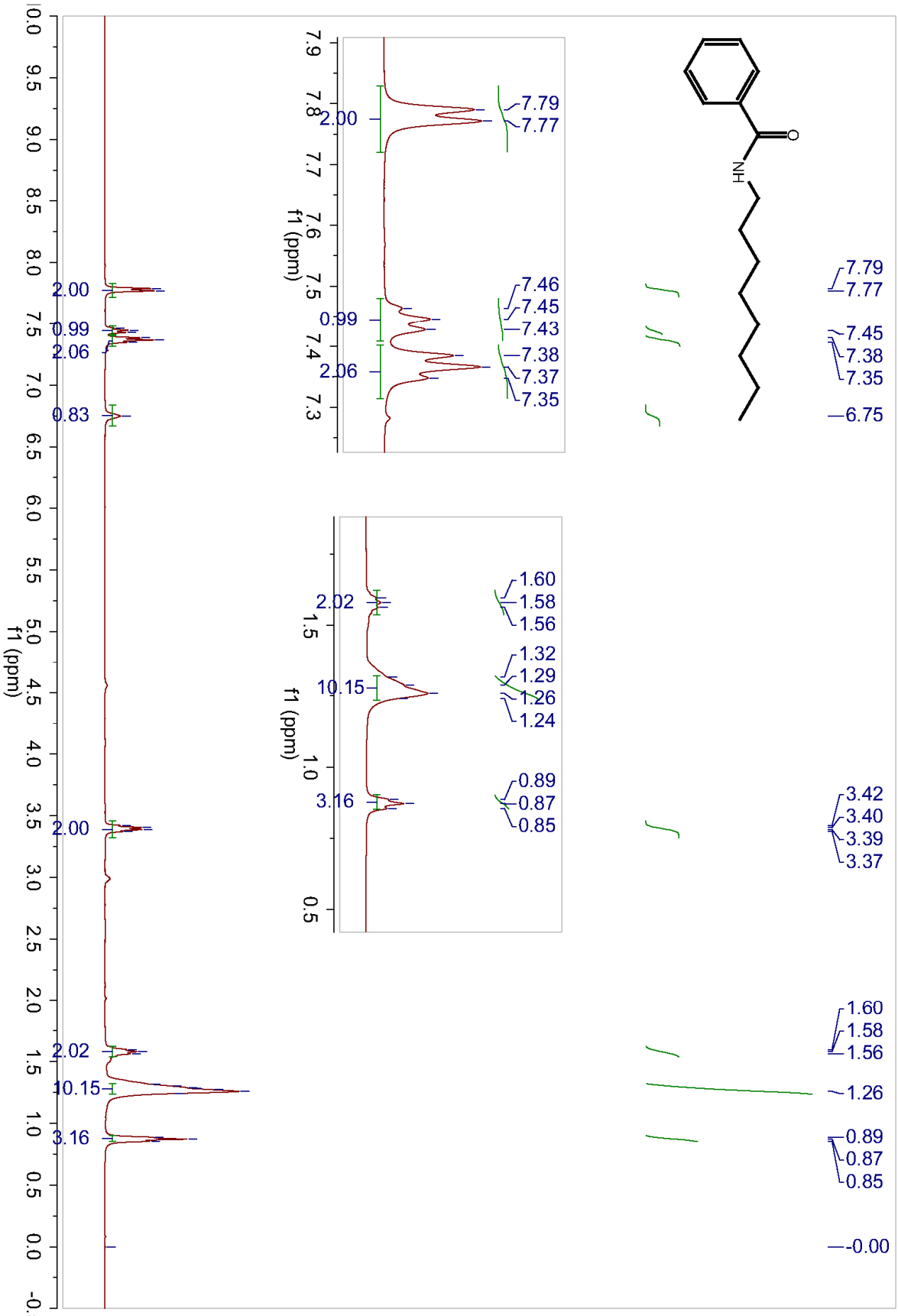

f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
167.45
134.31
131.23
128.30
126.83
77.32
77.00
76.68
71.01
58.60
39.53
HN
O
O

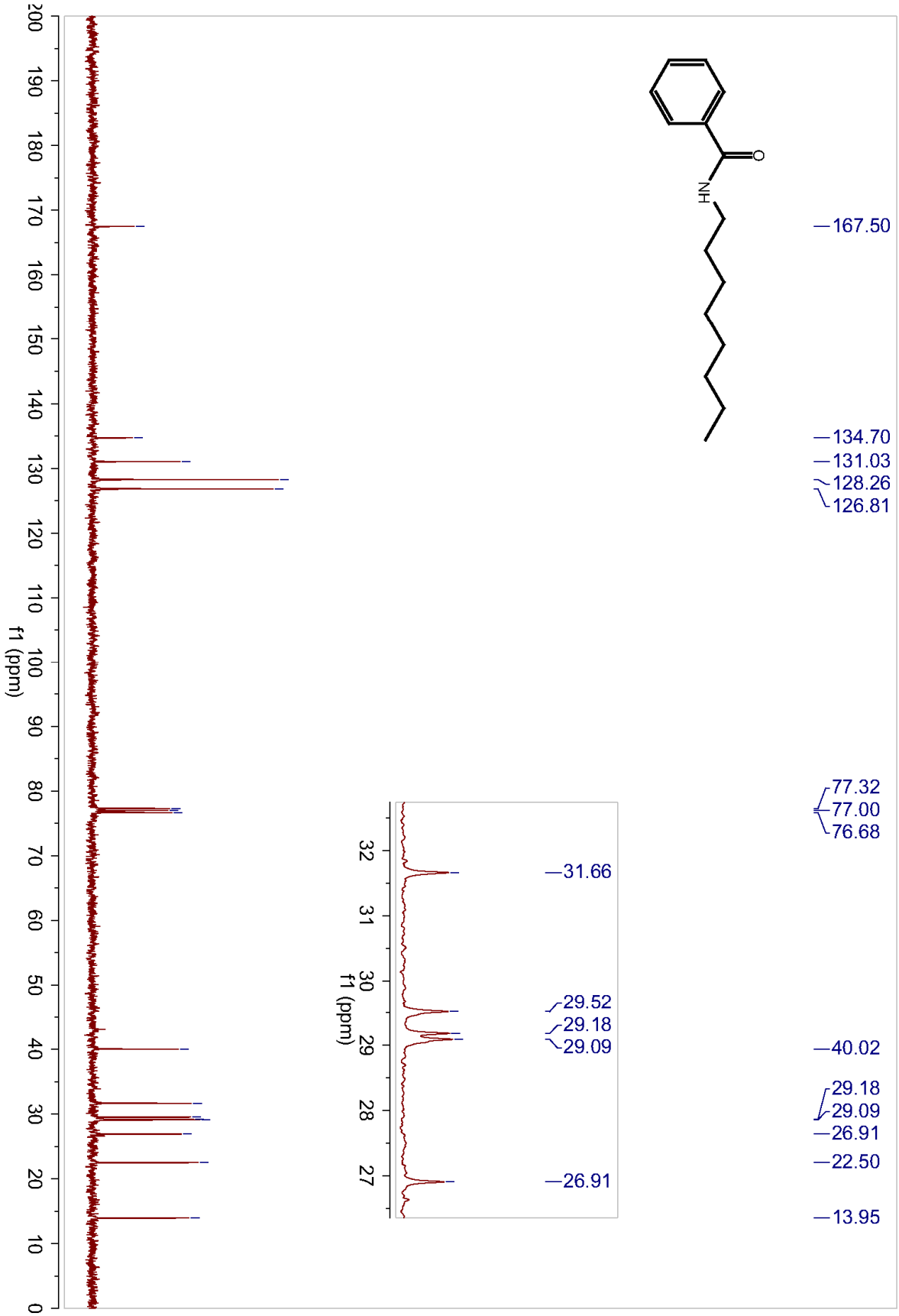

f1 (ppm)
2.00
0.99
2.02
2.01
2.04
0.90
3.04
2.01
1.99
7.72
7.70
7.70
7.46
7.44
7.43
7.38
7.36
7.34
7.12
7.10
6.84
6.82
7.72
7.70
7.70
7.34
7.10
6.82
6.58
3.76
3.66
3.64
3.62
3.61
2.86
2.84
2.82
-0.00
NH
O
O


f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
HN
O
O
167.42
158.10
134.51
131.20
130.78
129.59
128.35
126.74
113.91
77.32
77.00
76.68
55.10
41.28
34.63


f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
2.00
1.04
2.10
1.07
2.06
2.07
O
NH
OH
7.65
7.63
7.63
7.36
7.34
7.31
7.25
7.23
7.20
4.21
3.65
3.63
3.61
3.45
3.43
3.42
3.40
0.00


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
O
NH
OH
168.71
133.90
131.46
128.35
126.90
77.42
77.00
76.57
61.46
42.68


f1 (ppm)
2.00
0.99
2.06
0.83
2.00
2.02
10.15
3.16
7.79
7.77
7.46
7.45
7.43
7.38
7.37
7.35
1.60
1.58
1.56
1.32
1.29
1.26
1.24
0.89
0.87
0.85
HN
O
3.42
3.40
3.39
3.37
6.75
-0.00


f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
NH
O
167.50
134.70
131.03
128.26
126.81
77.32
77.00
76.68
40.02
29.18
29.09
26.91
22.50
13.95
f1 (ppm)
32
31
30
29
28
27
31.66
29.52
29.18
29.09
26.91