

Supporting Information  
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# **Nickel-Catalyzed Multicomponent Coupling Reaction of Alkyl halides, Isocyanides and H<sub>2</sub>O: An Expedient Way to Access Alkyl Amides**

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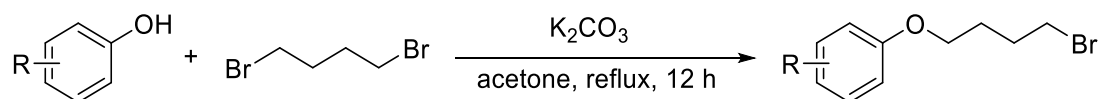
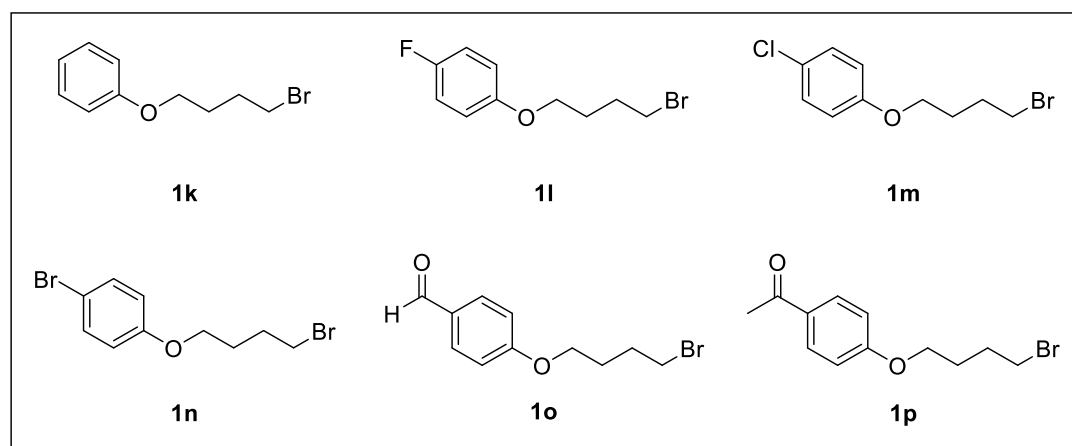
## 1. General Information

Unless otherwise noted, all reactions were conducted in 25 mL flame-dried Schlenk tube under positive nitrogen atmosphere.  $^1\text{H}$  NMR spectra were recorded on 500 MHz Bruker NMR spectrometer. Chemical shifts ( $\delta$ ) were reported as parts per million (ppm) downfield from tetramethylsilane. High resolution mass spectra were recorded on Thermo Q Exactive Plus. Melting points were measured on X4 melting point apparatus and uncorrected. Flash column chromatography was performed on silica gel (200-300 mesh) with the indicated solvent mixtures.

## 2. Preparation of Substrates

### 2.1 General procedure for the preparation of alkyl bromides

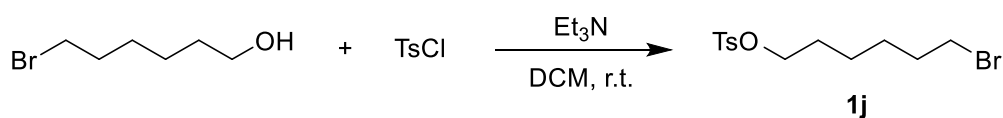
Alkyl halides **1a**, **1b**, **1c**, **1d**, **1e**, **1f**, **1g**, **1h**, **1i**, **1q**, **1r**, **1s**, and **1t** were commercial available and used as received. The other compounds were prepared from known literature.<sup>1</sup>



To a Schlenk tube with a magnetic stirrer under nitrogen were added phenol (5.4 mmol, 1 equiv), 1,4-dibromobutane (21.6 mmol, 4 equiv), potassium carbonate (27 mmol, 5 equiv) were dissolved in 10 mL of dry acetone. The reaction mixture was

refluxed for 12 h. After complete consumption of phenol (monitored by TLC), the reaction mixture was then cooled to room temperature. The reaction mixture was filtered through celite and acetone was evaporated. Aqueous NaOH was added and the reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated with under reduced pressure. The residue was purified by flash column chromatography. Substrates **1k**, **1l**, **1m**, **1n**, **1o** and **1p** were prepared following the general procedure.

## 2.2 General procedure for the preparation of 6-bromo-1-hexyl tosylate<sup>2</sup>.

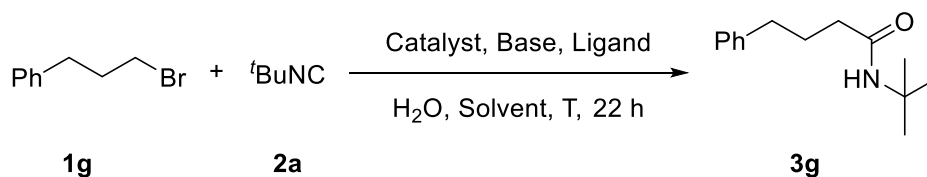


To a Schlenk tube with a magnetic stirrer under nitrogen were added p-toluenesulfonyl chloride (1.5 equiv, 7.50 mmol) dissolved in 10 mL of DCM, and the mixture was brought to 0 °C. Triethylamine (5 equiv, 25.0 mmol) was added, and 2-bromohexanol (1 equiv, 5.0 mmol) was added dropwise. The mixture was stirred for 16 h at room temperature, and the reaction was completed, washed with water (10 mL), brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed and the residue was purified by silica gel column chromatography to afford the pure product **1j** in 75% yield.

## 3. Nickel-Catalyzed Multicomponent Coupling Reaction

### 3.1 Optimization of reaction conditions<sup>a</sup>

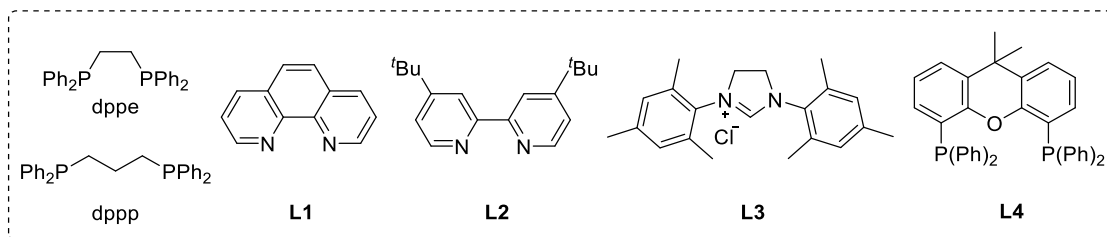
**Table S1.** Survey of the reaction parameters



Entry	Catalyst (mol%)	Base	T (°C)	H <sub>2</sub> O : Solvent (mL/mL)	Ligand (mol%)	Yield (%) <sup>b</sup>
1	NiCl <sub>2</sub> (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : Toluene (0.2/0.3)	dppe (20)	6
2	NiCl <sub>2</sub> (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : Toluene (0.2/0.3)	L1 (20)	ND
3	NiCl <sub>2</sub> (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : Toluene (0.2/0.3)	L2 (20)	ND
4	NiCl <sub>2</sub> (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : Toluene (0.2/0.3)	L3 (20)	ND
5	NiCl <sub>2</sub> (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : Toluene (0.2/0.3)	L4 (20)	27
6	NiCl <sub>2</sub> (dppe) (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : Toluene (0.2/0.3)	- <sup>c</sup>	67
7	Ni(acac) <sub>2</sub> (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : Toluene (0.2/0.3)	- <sup>c</sup>	ND
8	NiCl <sub>2</sub> (dme) (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : Toluene (0.2/0.3)	- <sup>c</sup>	53
9	Ni (COD) <sub>2</sub> (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : Toluene (0.2/0.3)	- <sup>c</sup>	75
10	NiCl <sub>2</sub> (dppp) (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : Toluene (0.2/0.3)	- <sup>c</sup>	90
11	NiCl <sub>2</sub> (dppp) (5)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : Toluene (0.2/0.3)	- <sup>c</sup>	38
12	NiCl <sub>2</sub> (dppp) (2)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : Toluene (0.2/0.3)	- <sup>c</sup>	17
13	NiCl <sub>2</sub> (dppp) (10)	NaOH	150	H <sub>2</sub> O : Toluene (0.2/0.3)	- <sup>c</sup>	85
14	NiCl <sub>2</sub> (dppp) (10)	Na <sub>2</sub> CO <sub>3</sub>	150	H <sub>2</sub> O : Toluene (0.2/0.3)	- <sup>c</sup>	65
15	NiCl <sub>2</sub> (dppp) (10)	NaOEt	150	H <sub>2</sub> O : Toluene (0.2/0.3)	- <sup>c</sup>	26

16	NiCl <sub>2</sub> (dppp) (10)	NaH	150	H <sub>2</sub> O : Toluene (0.2/0.3)	- <sup>c</sup>	23
17	NiCl <sub>2</sub> (dppp) (10)	<sup>t</sup> BuOLi	150	H <sub>2</sub> O : Toluene (0.2/0.3)	- <sup>c</sup>	31
18	NiCl <sub>2</sub> (dppp) (10)	Cs <sub>2</sub> CO <sub>3</sub>	150	H <sub>2</sub> O : Toluene (0.2/0.3)	- <sup>c</sup>	78
19	NiCl <sub>2</sub> (dppp) (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : THF (0.2/0.3)	- <sup>c</sup>	94
20	NiCl <sub>2</sub> (dppp) (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : 1,4-dioxane (0.2/0.3)	- <sup>c</sup>	85
21	NiCl <sub>2</sub> (dppp) (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : DMF(0.2/0.3)	- <sup>c</sup>	35
22	NiCl <sub>2</sub> (dppp) (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : DCM (0.2/0.3)	- <sup>c</sup>	6
23	NiCl <sub>2</sub> (dppp) (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : CH <sub>3</sub> CN (0.2/0.3)	- <sup>c</sup>	97
24	NiCl <sub>2</sub> (dppp) (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : DMSO (0.2/0.3)	- <sup>c</sup>	3
25	NiCl <sub>2</sub> (dppp) (10)	<sup>t</sup> BuONa	150	H <sub>2</sub> O : p-xylene (0.2/0.3)	- <sup>c</sup>	13
26	NiCl <sub>2</sub> (dppp) (10)	<sup>t</sup> BuONa	80	H <sub>2</sub> O : CH <sub>3</sub> CN (0.2/0.3)	- <sup>c</sup>	90
27	NiCl <sub>2</sub> (dppp) (10)	<sup>t</sup> BuONa	60	H <sub>2</sub> O : CH <sub>3</sub> CN (0.2/0.3)	- <sup>c</sup>	90
28	<i>NiCl<sub>2</sub>(dppp)</i> (10)	<i><sup>t</sup>BuONa</i>	40	<i>H<sub>2</sub>O : CH<sub>3</sub>CN (0.2/0.3)</i>	- <sup>c</sup>	92 (90 <sup>d</sup> )
29	NiCl <sub>2</sub> (dppp) (10)	<sup>t</sup> BuONa	25	H <sub>2</sub> O : CH <sub>3</sub> CN (0.2/0.3)	- <sup>c</sup>	88

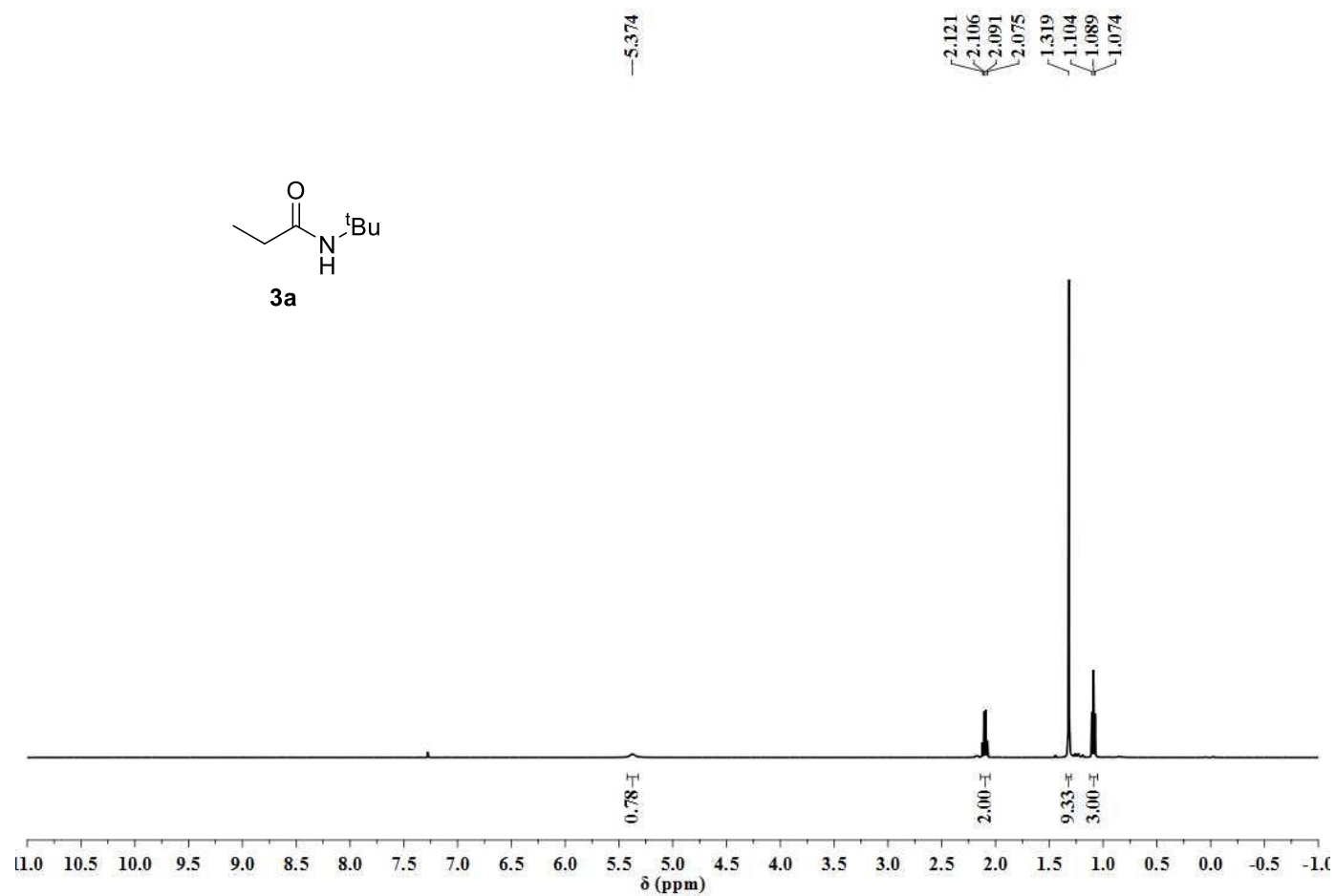
<sup>a</sup>Conditions: **1g** (0.1 mmol), **2a** (0.1 mmol), Catalyst (10 mol%), Base (2 equiv), Solvent (0.3 mL), H<sub>2</sub>O (0.2 mL), 22 h. <sup>b</sup>Yield was estimated by GC analysis using dodecane as an internal standard. <sup>c</sup>No ligand was added. <sup>d</sup>Isolated yield shown in parentheses. ND = Not detected.

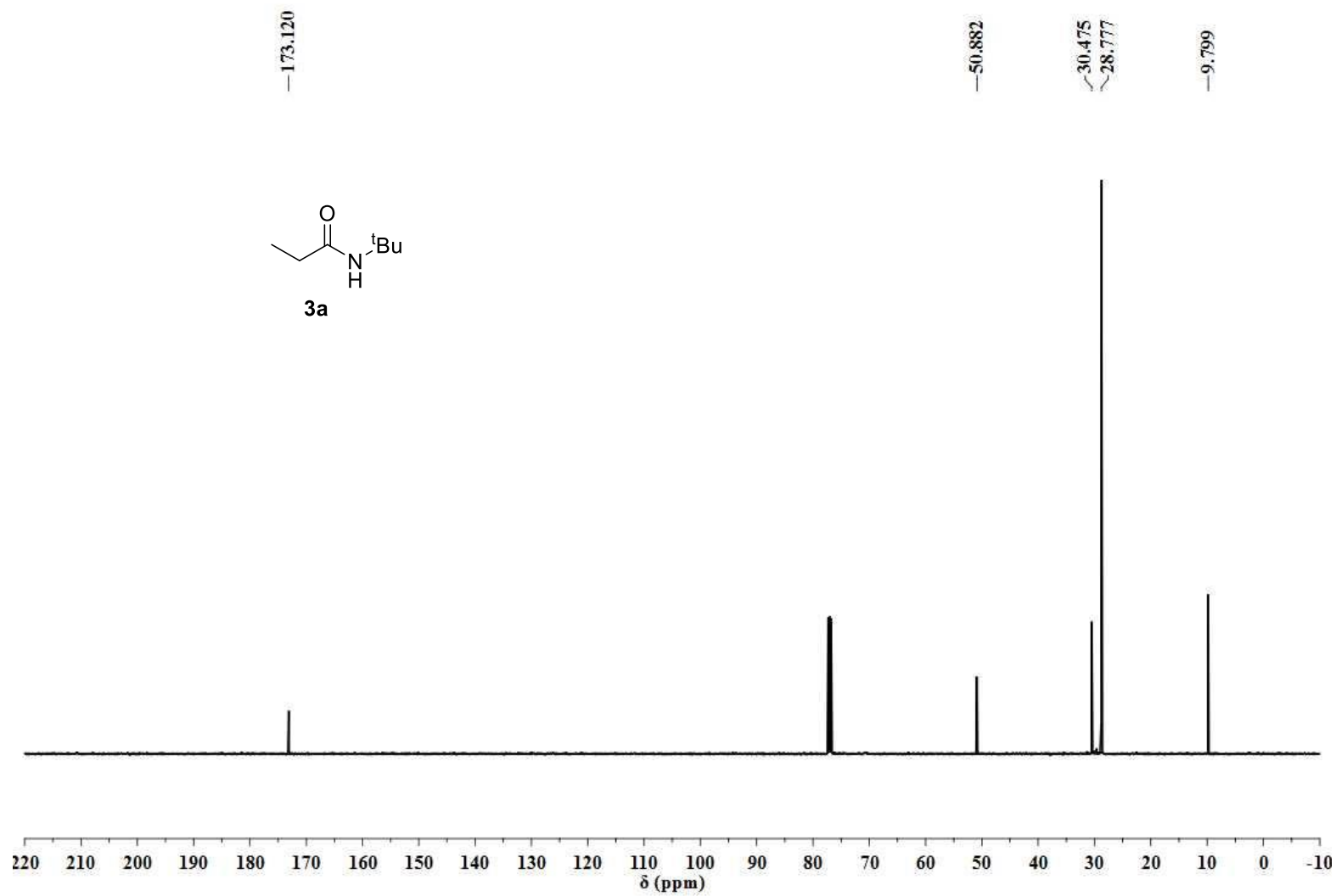


#### 4. References

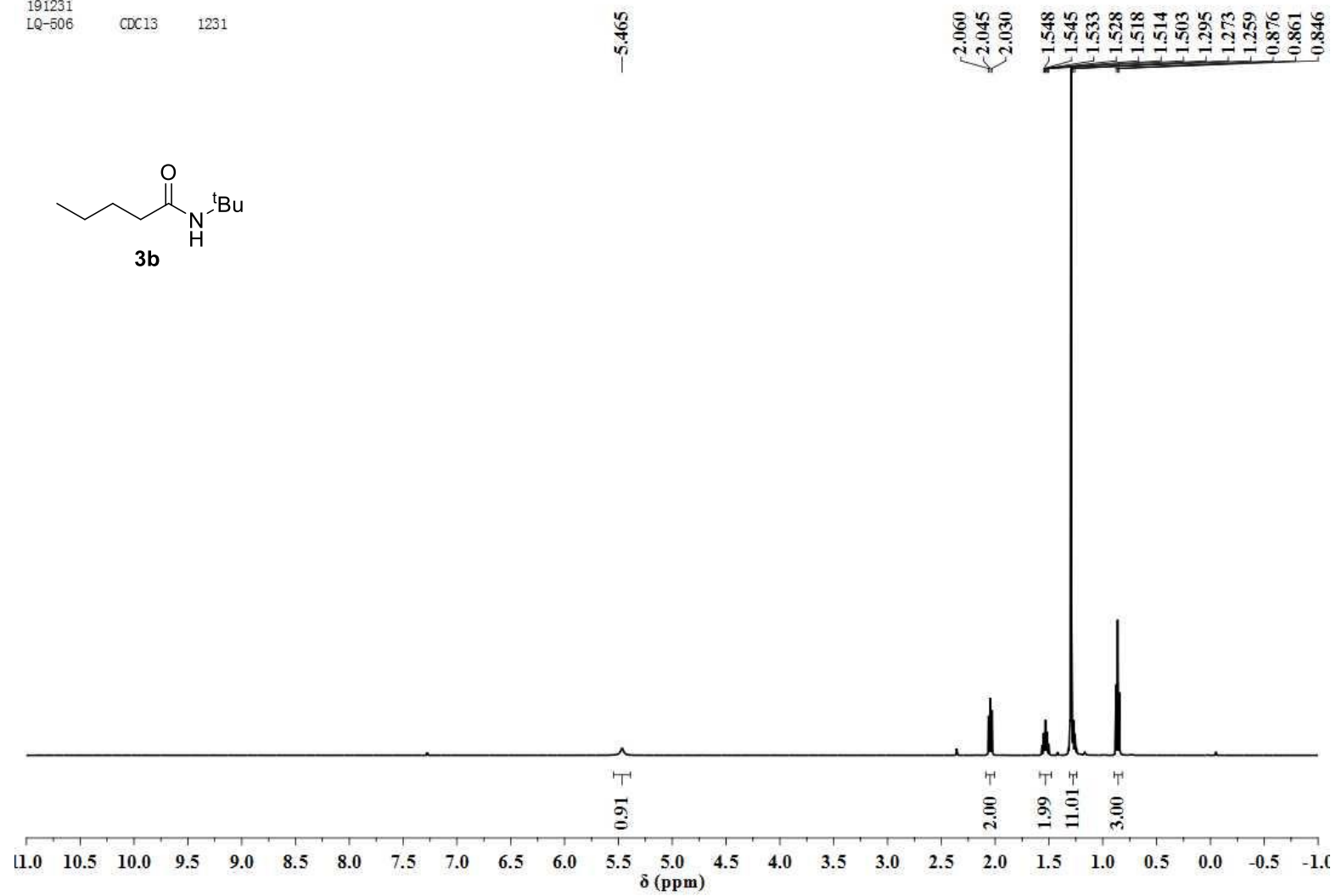
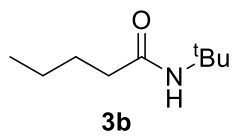
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- [2] H. Savolainen, M. Cantore, N. A. Colabufo, P. H. Elsinga, A. D. Windhorst and G. Luurtsema, *Mol. Pharm.*, **2015**, 12, 2265.

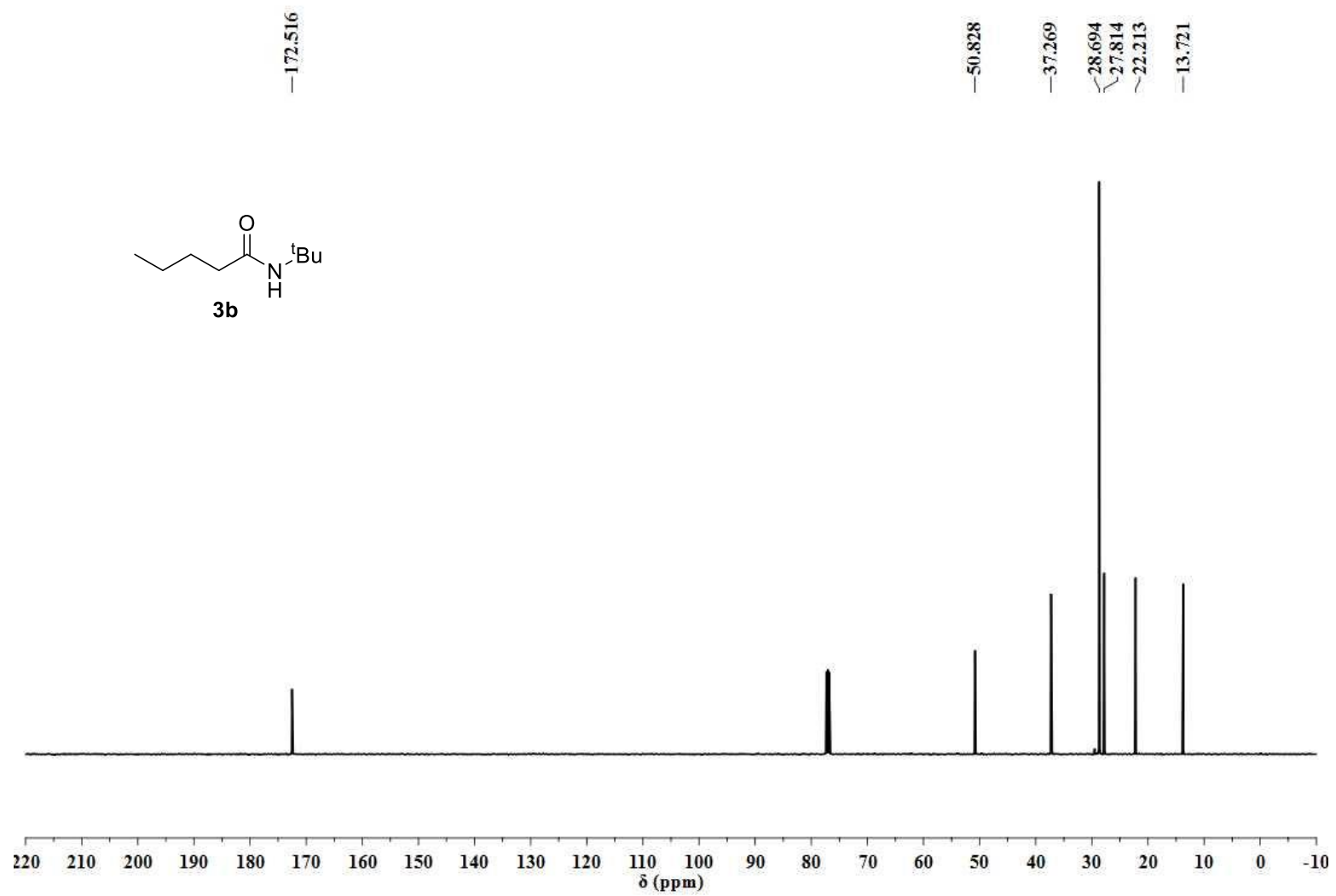
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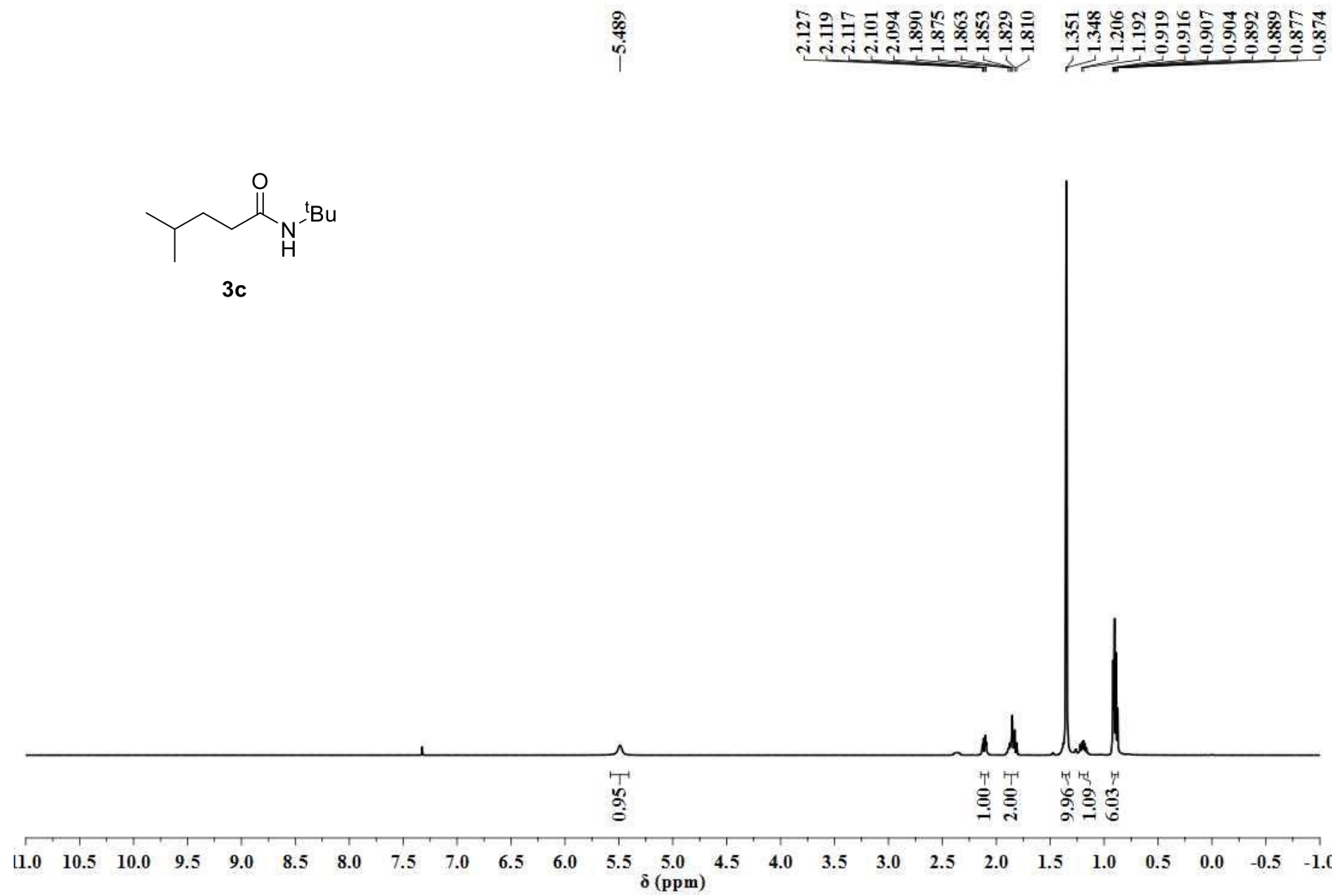
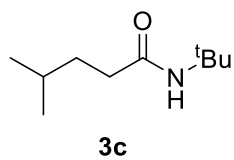


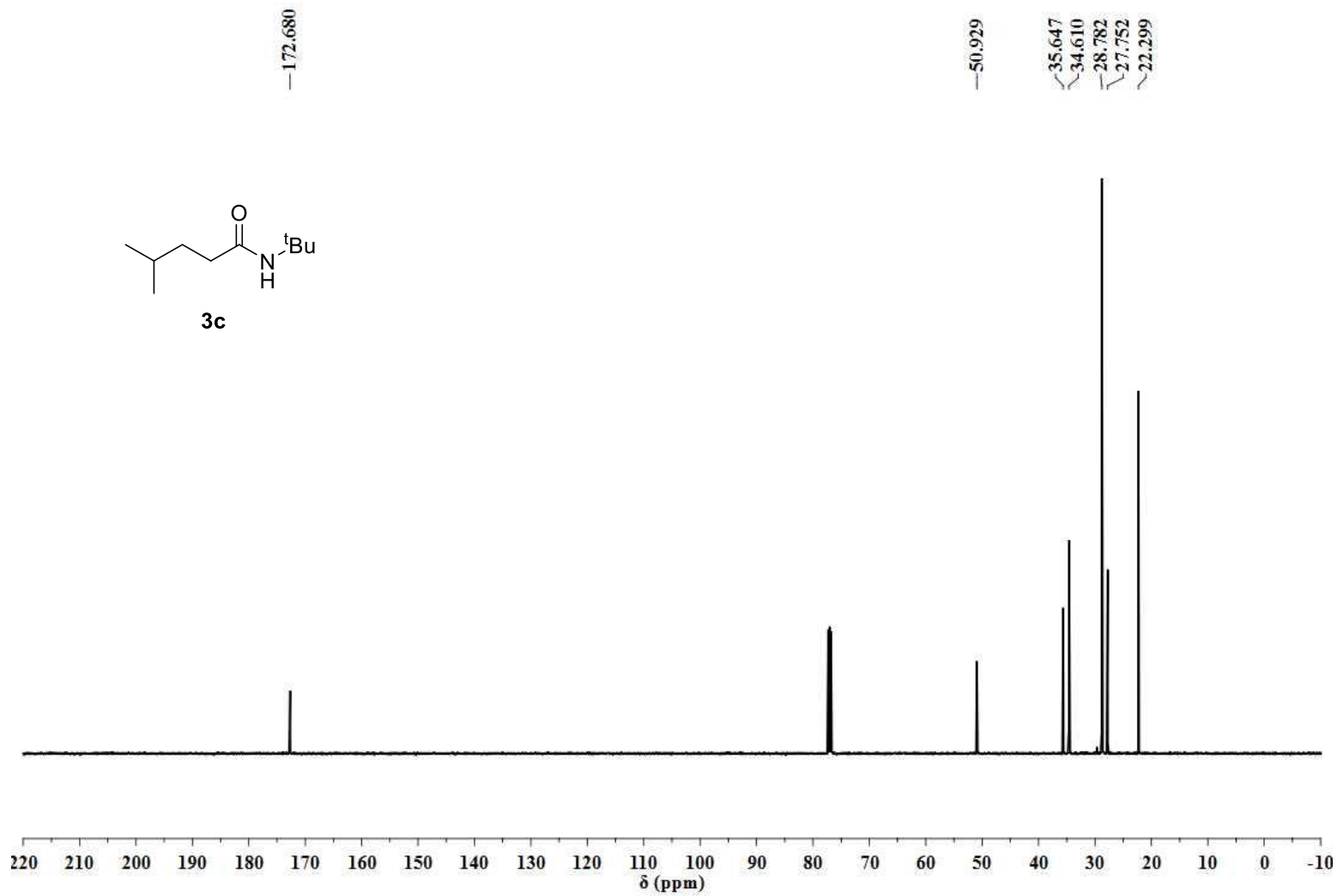
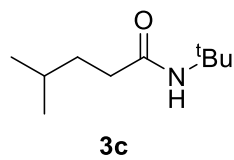


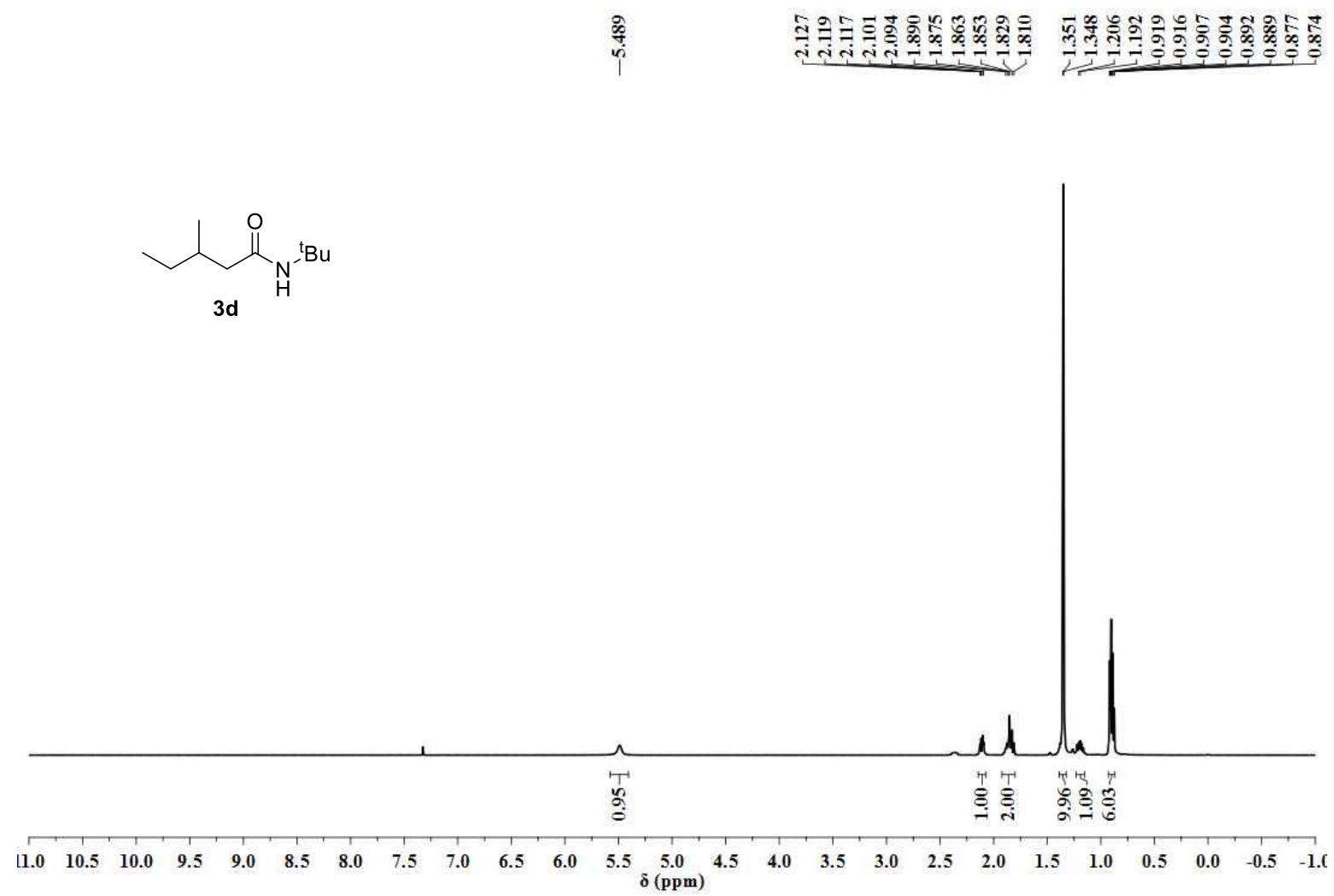
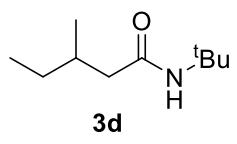
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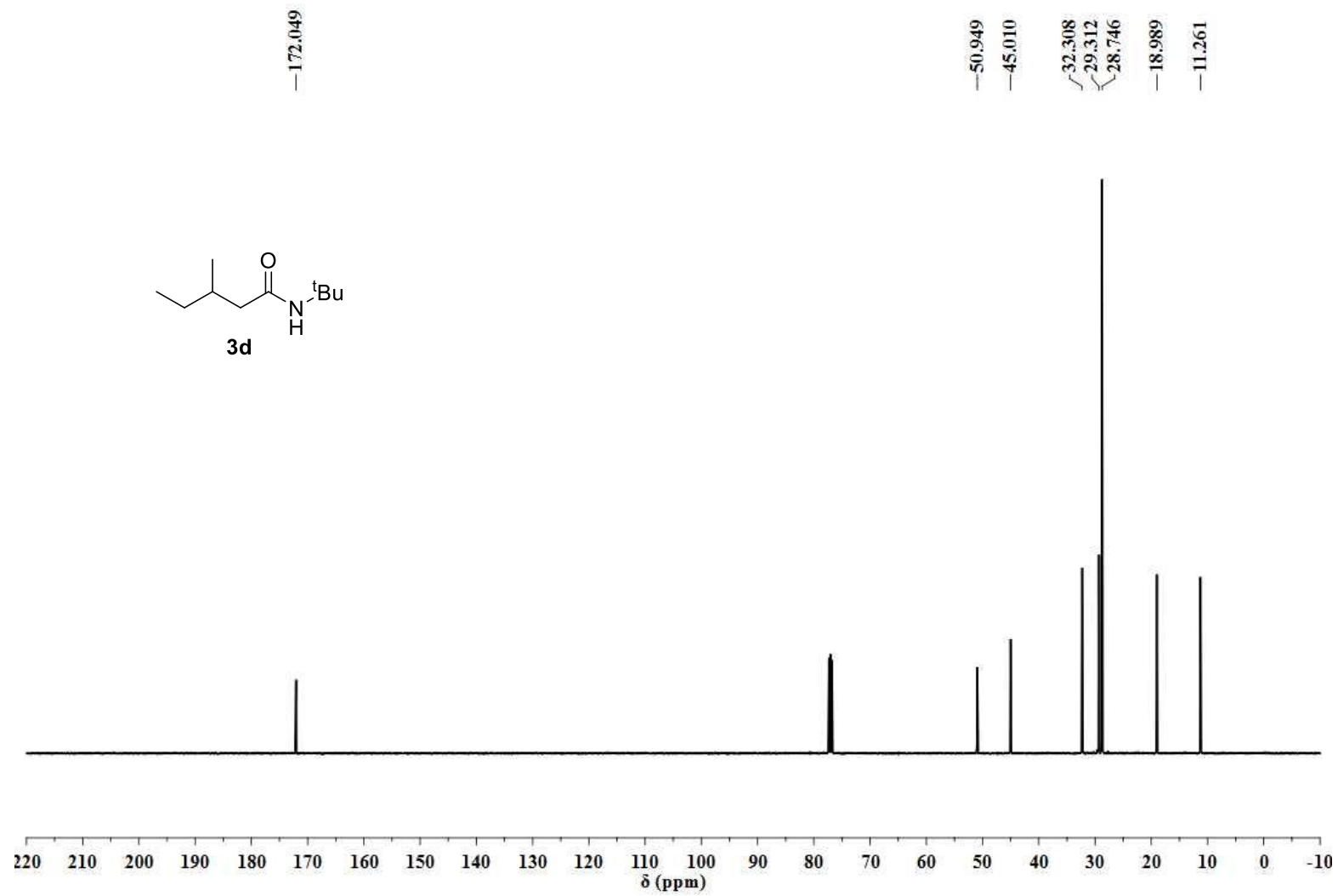


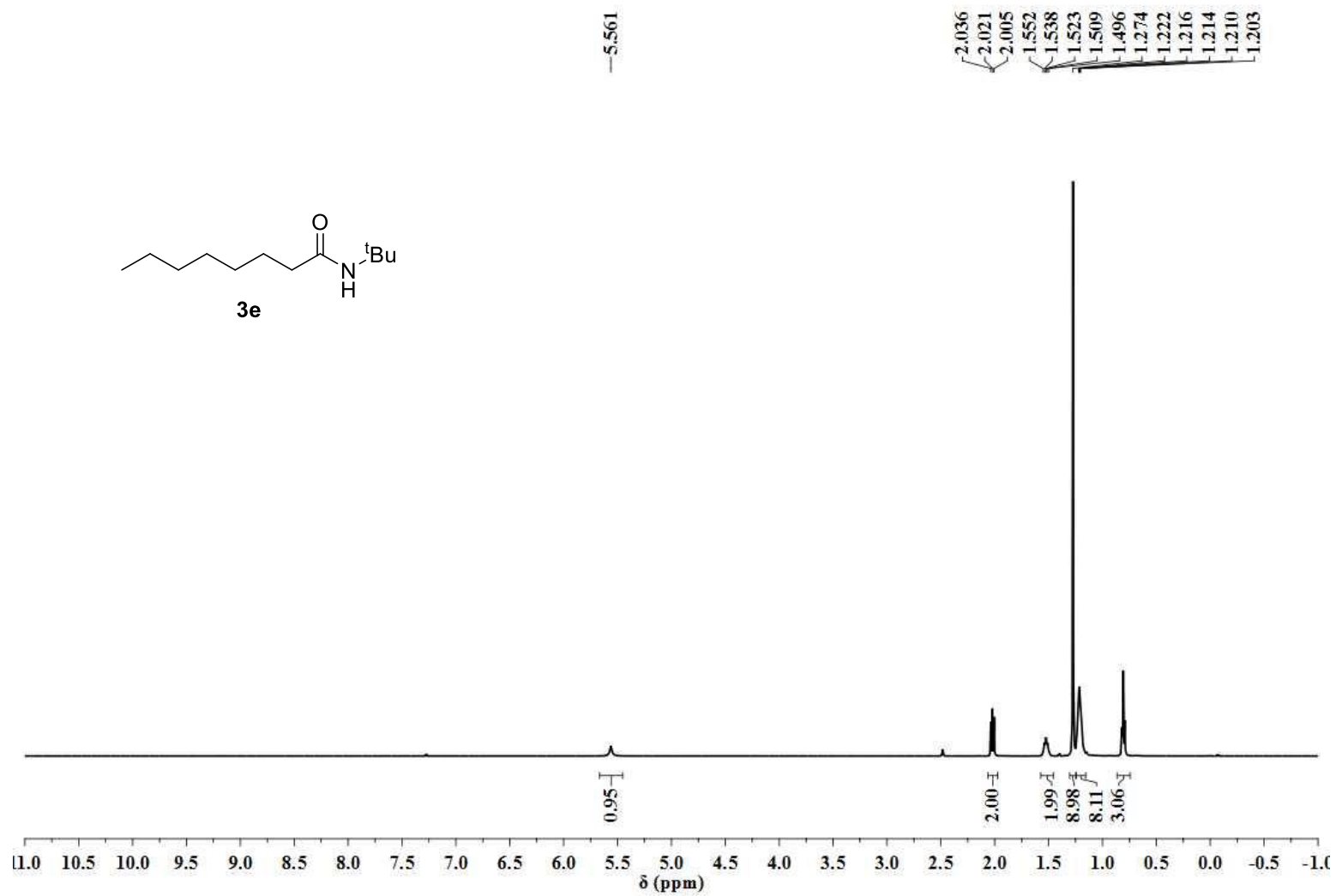
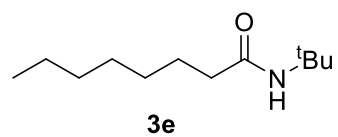


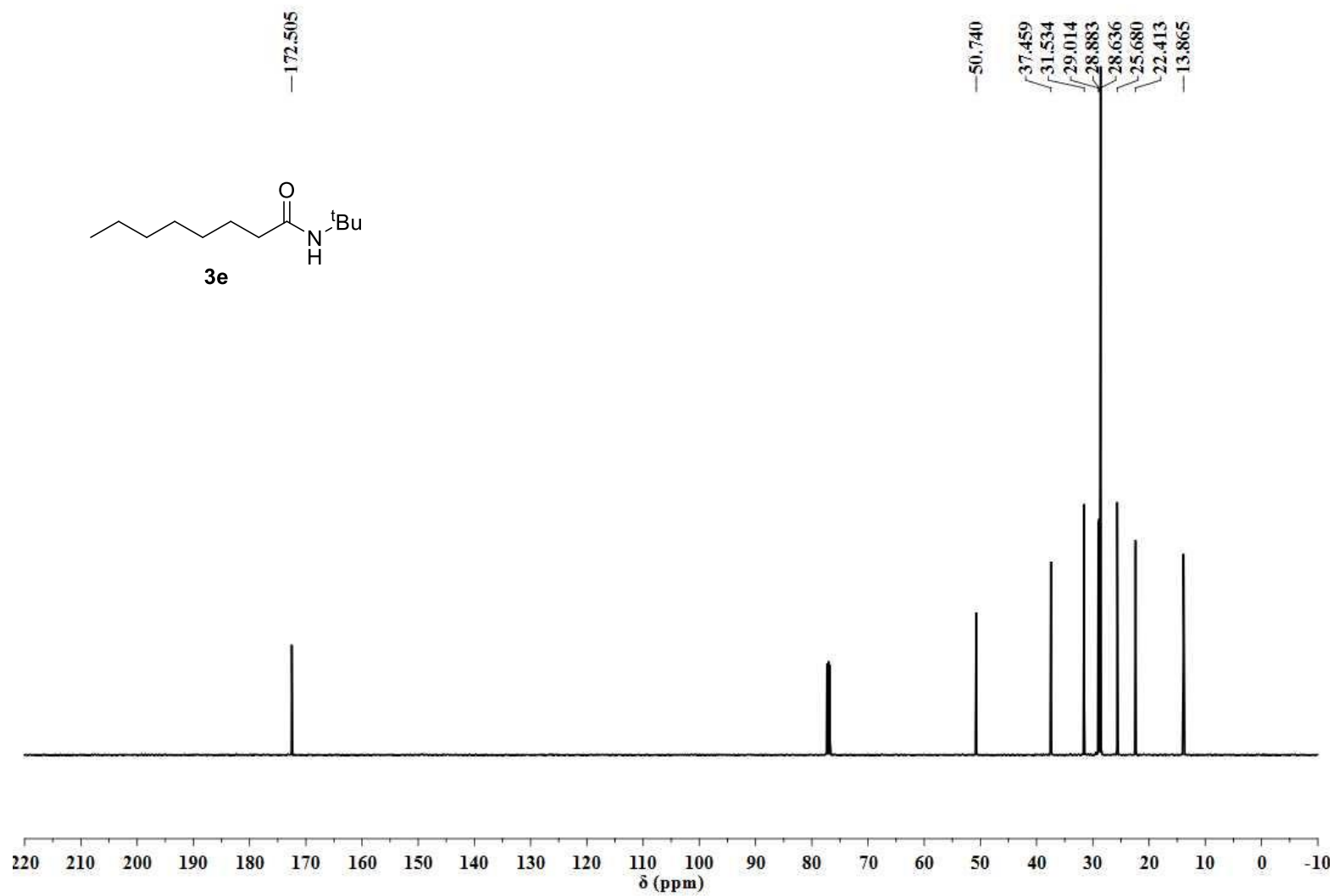


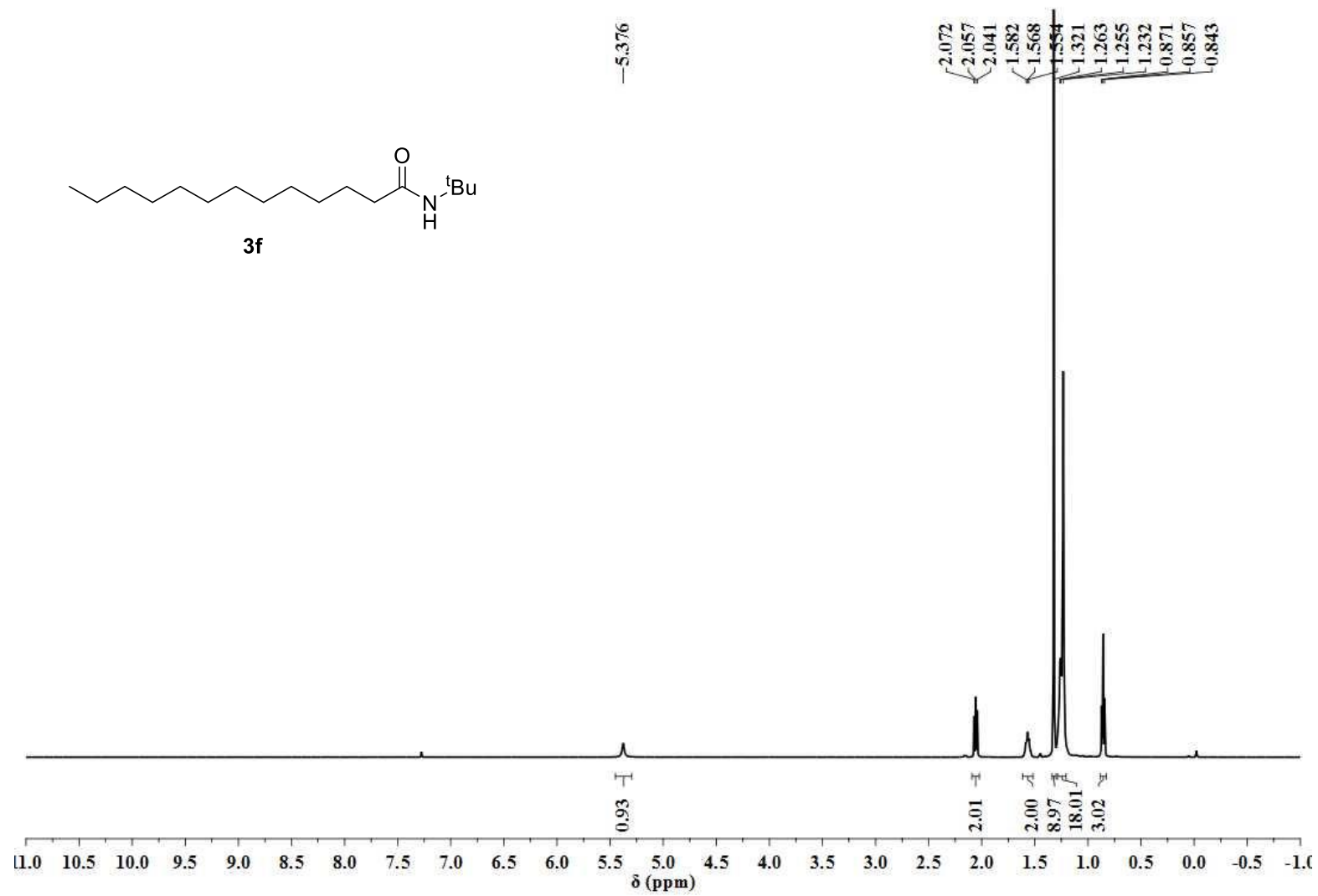
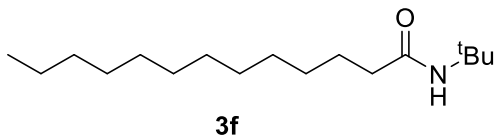


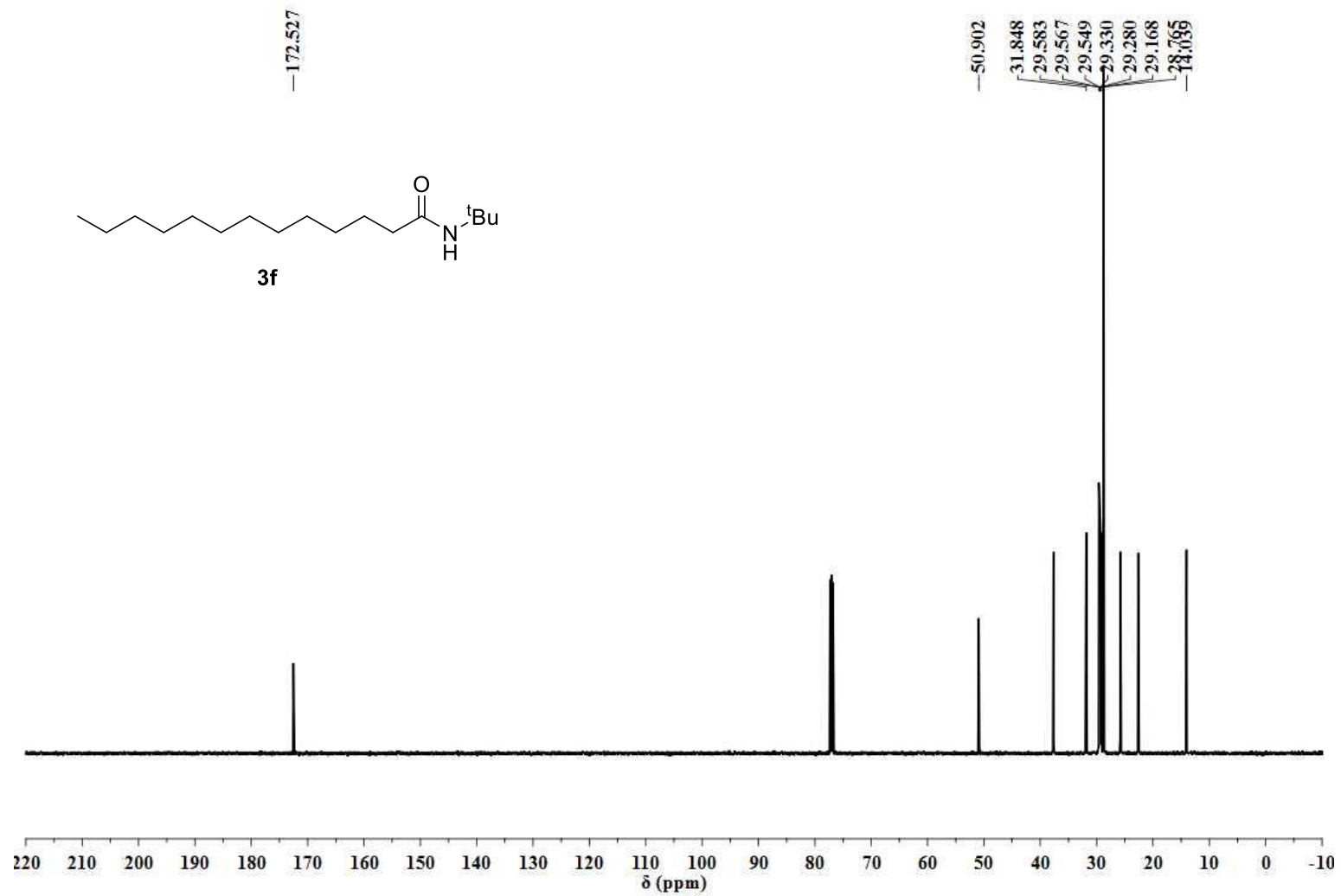


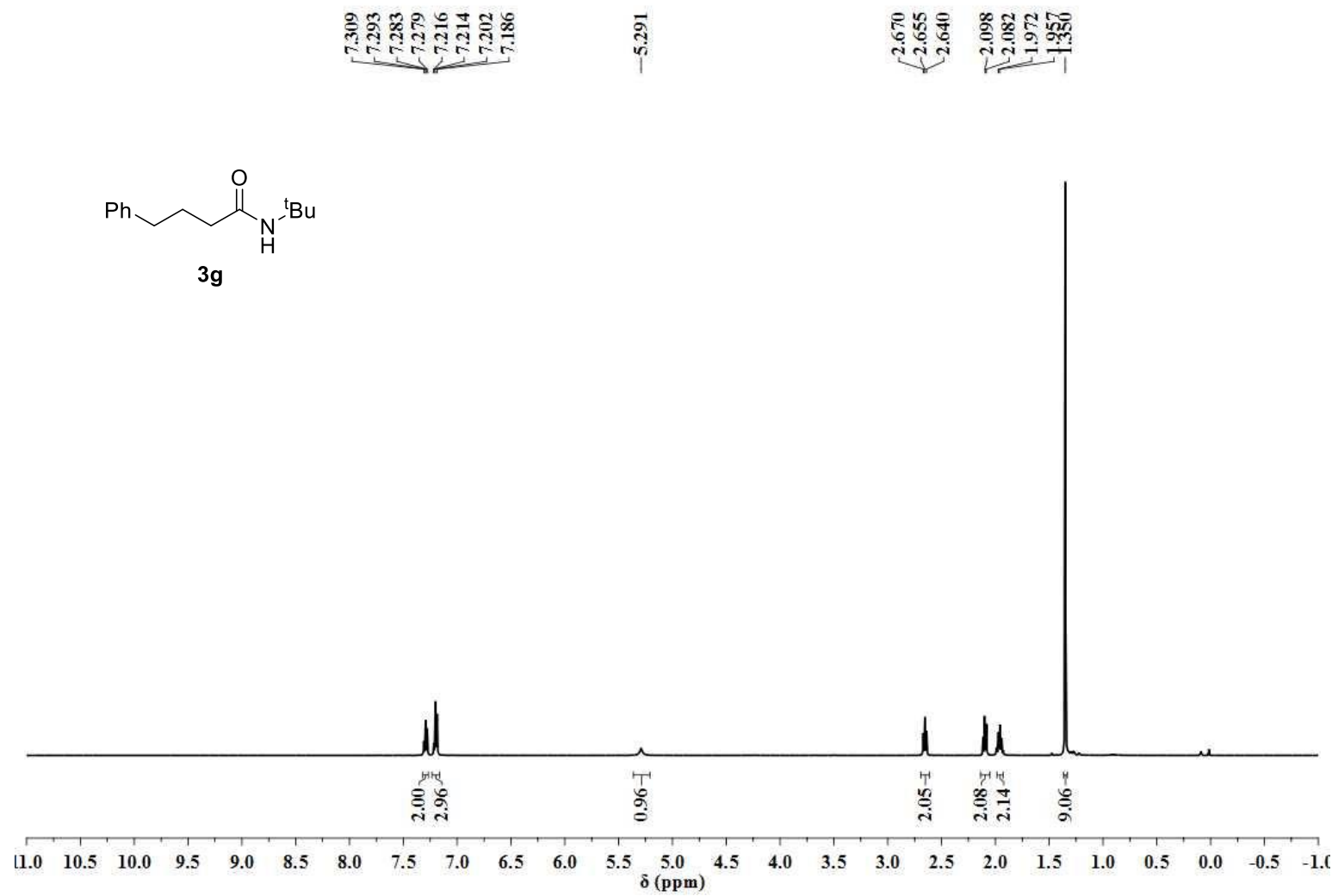


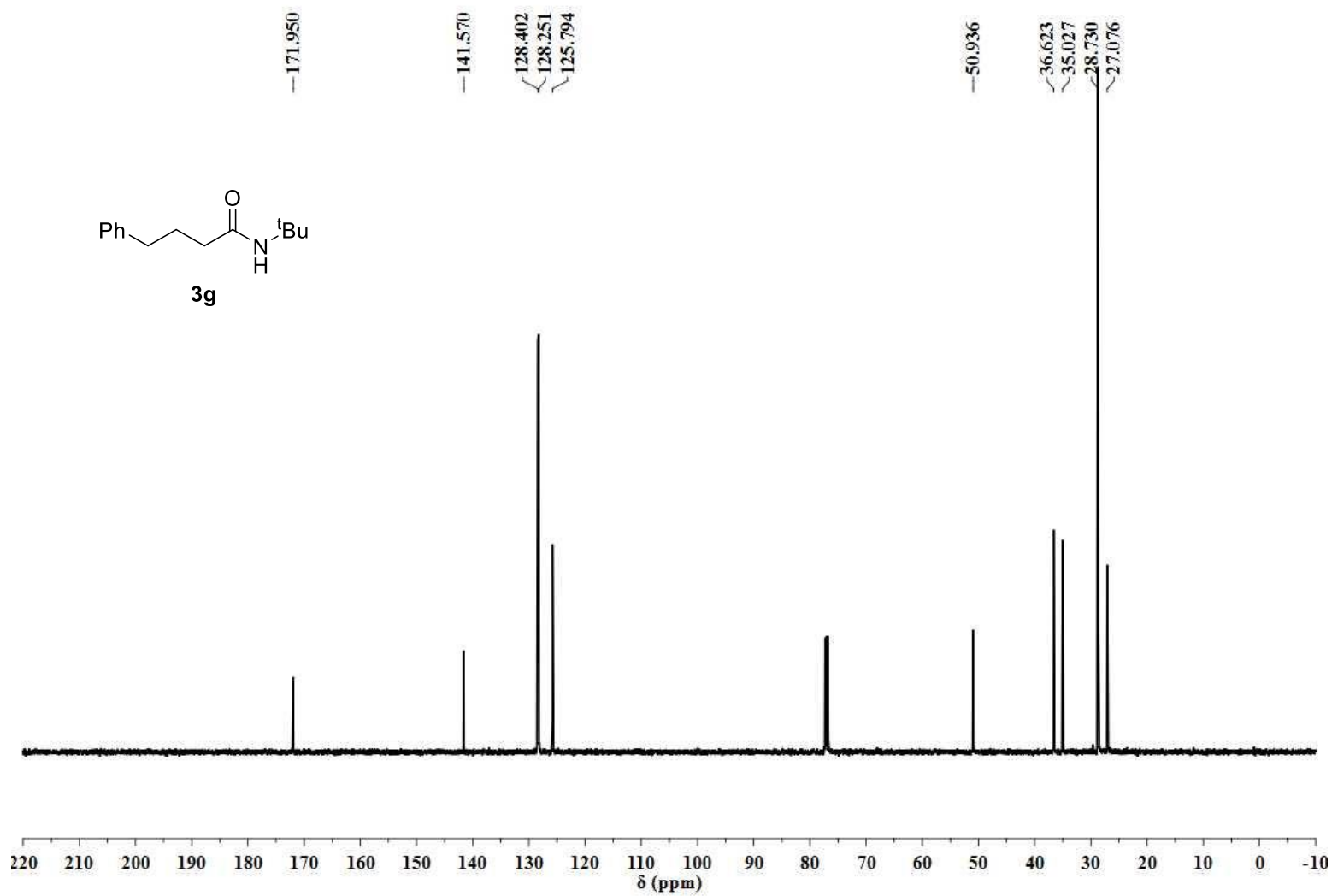


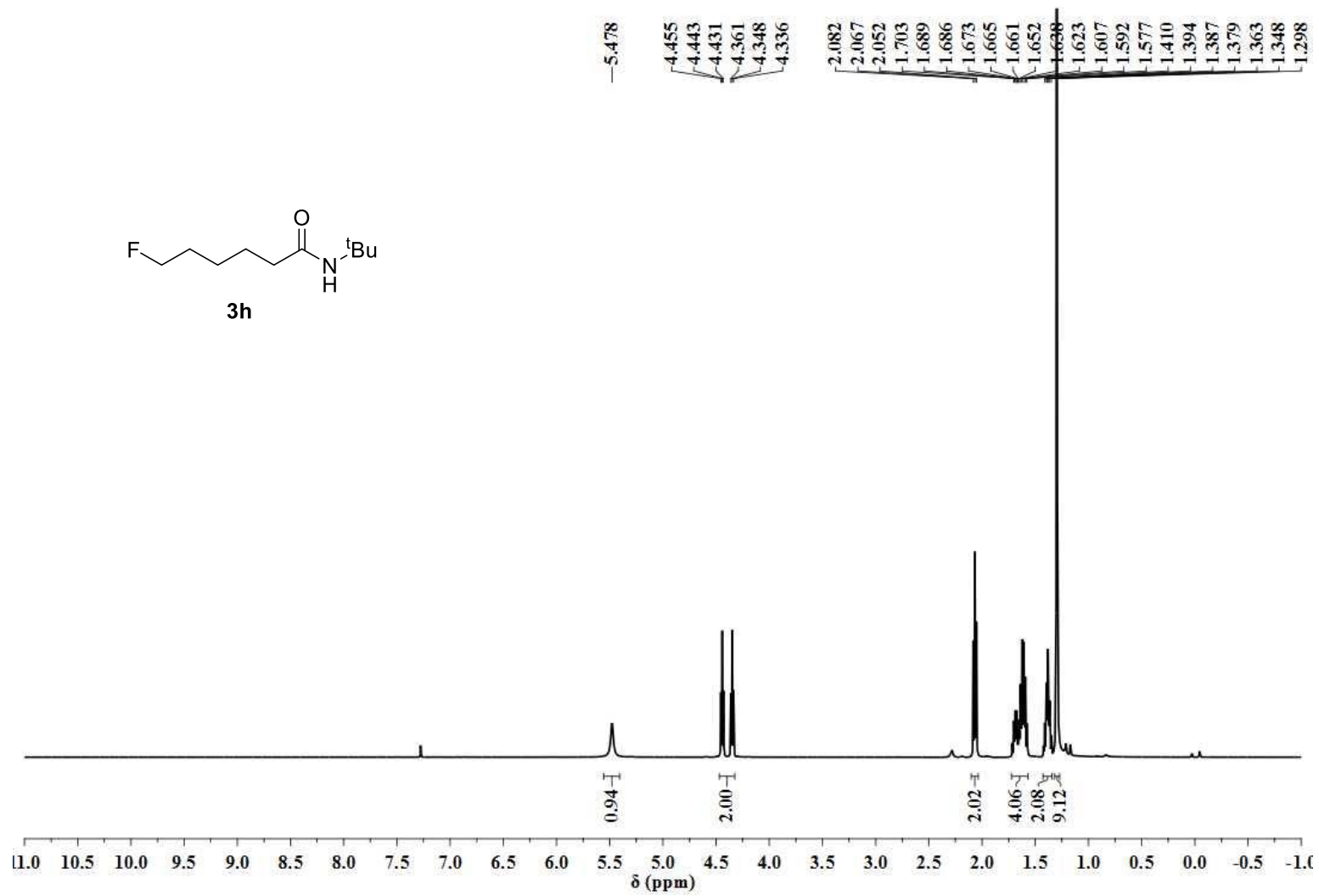
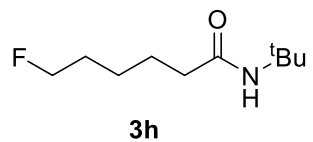


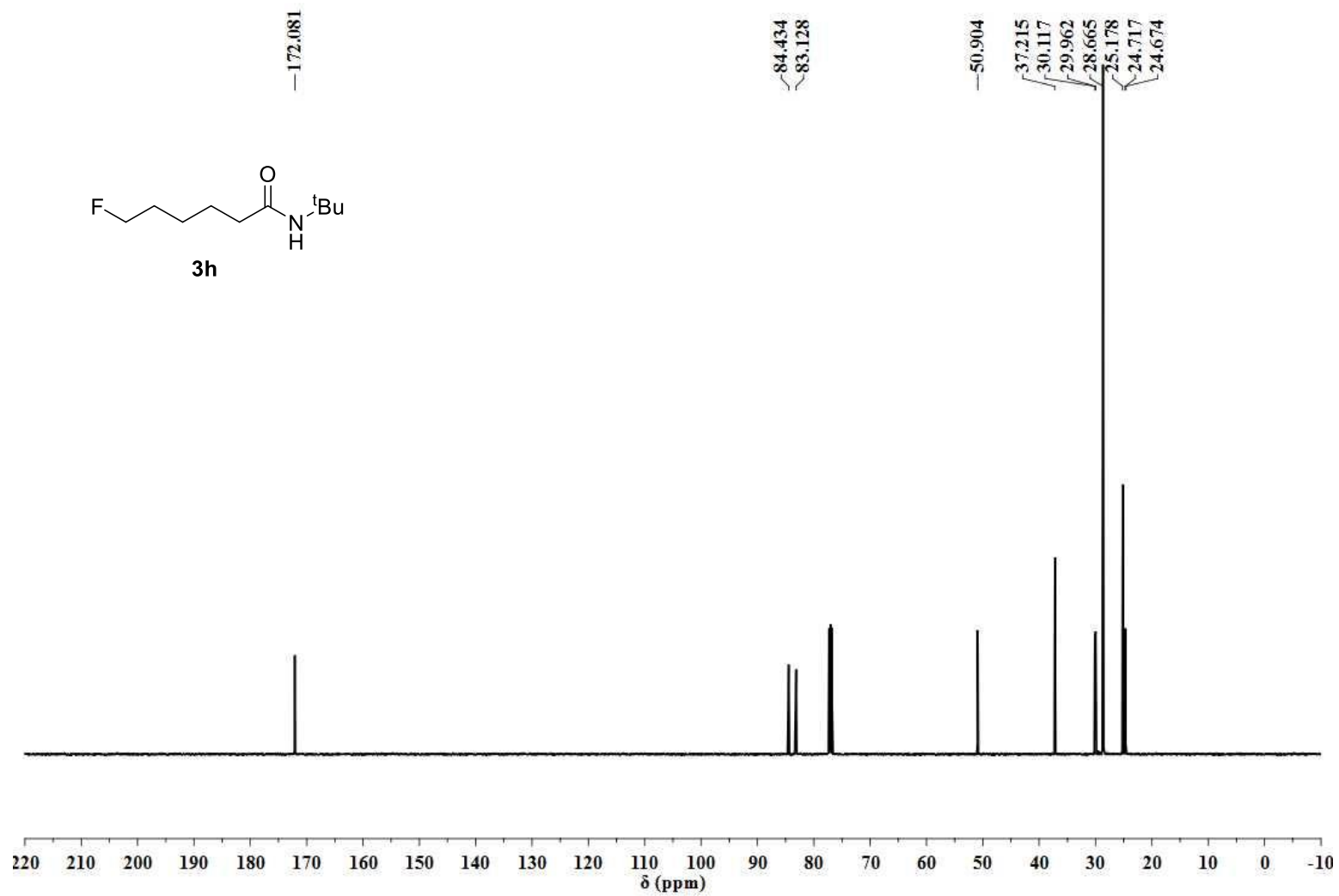


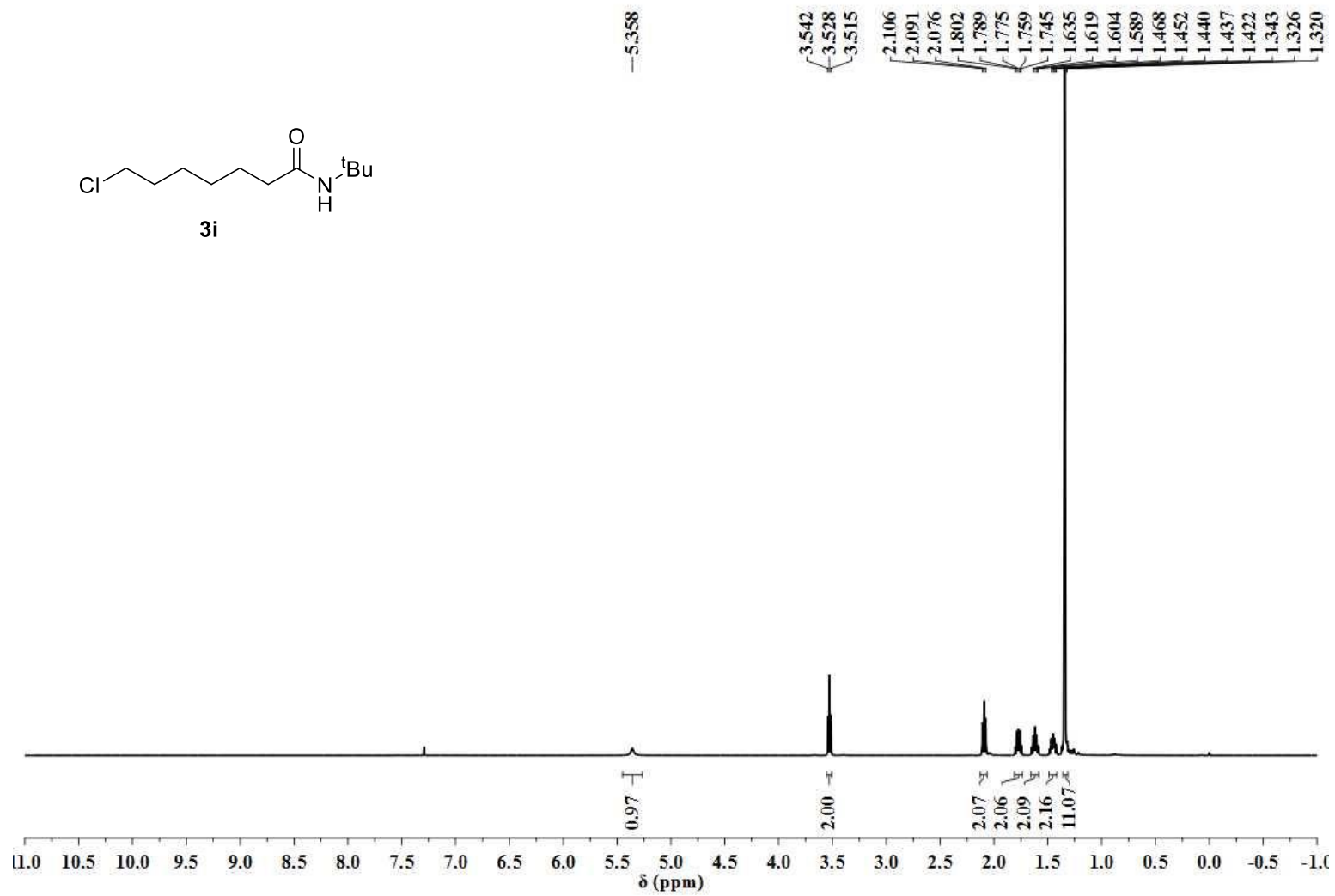
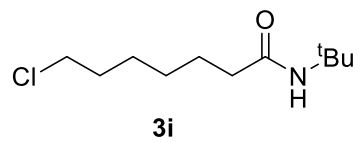


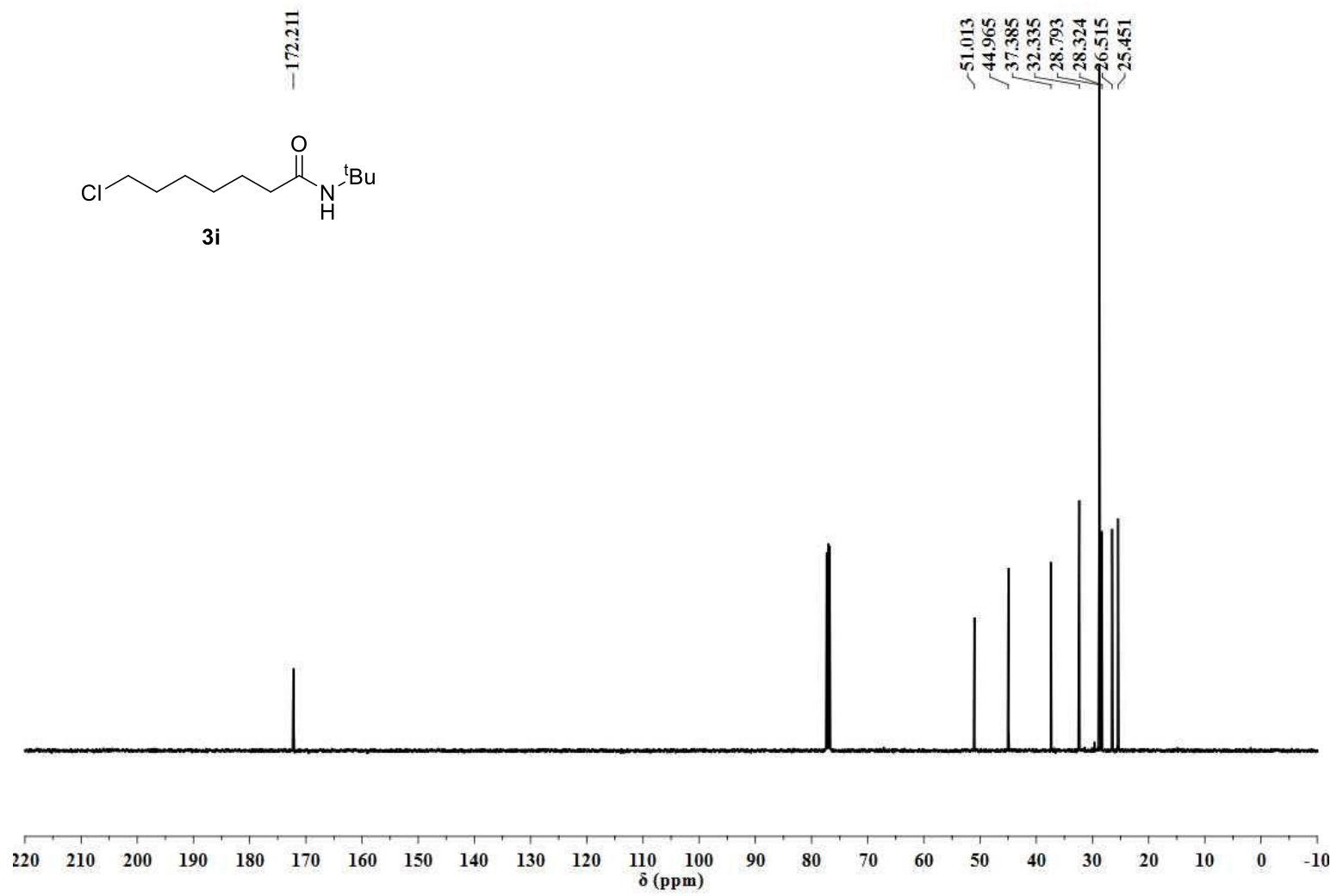


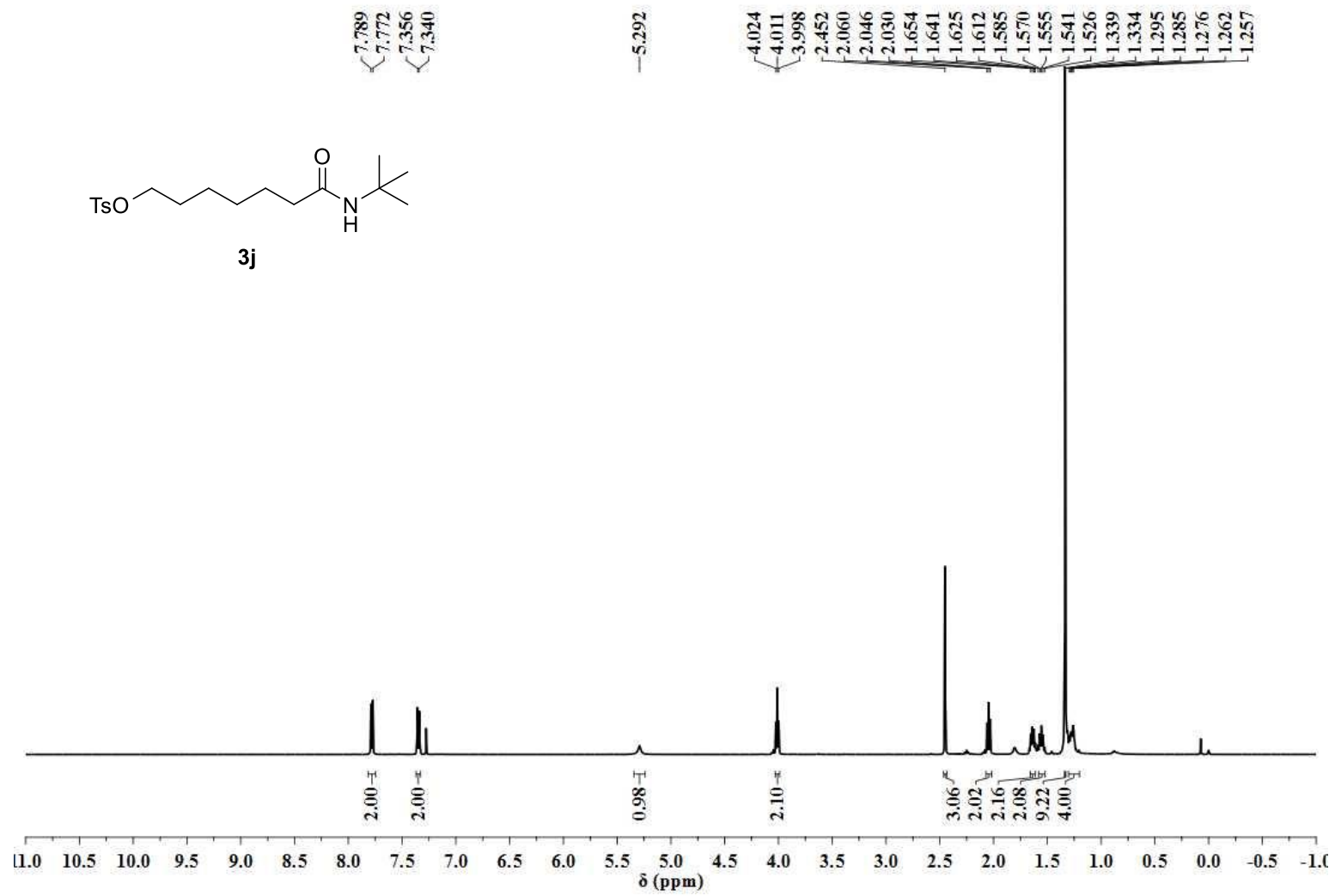


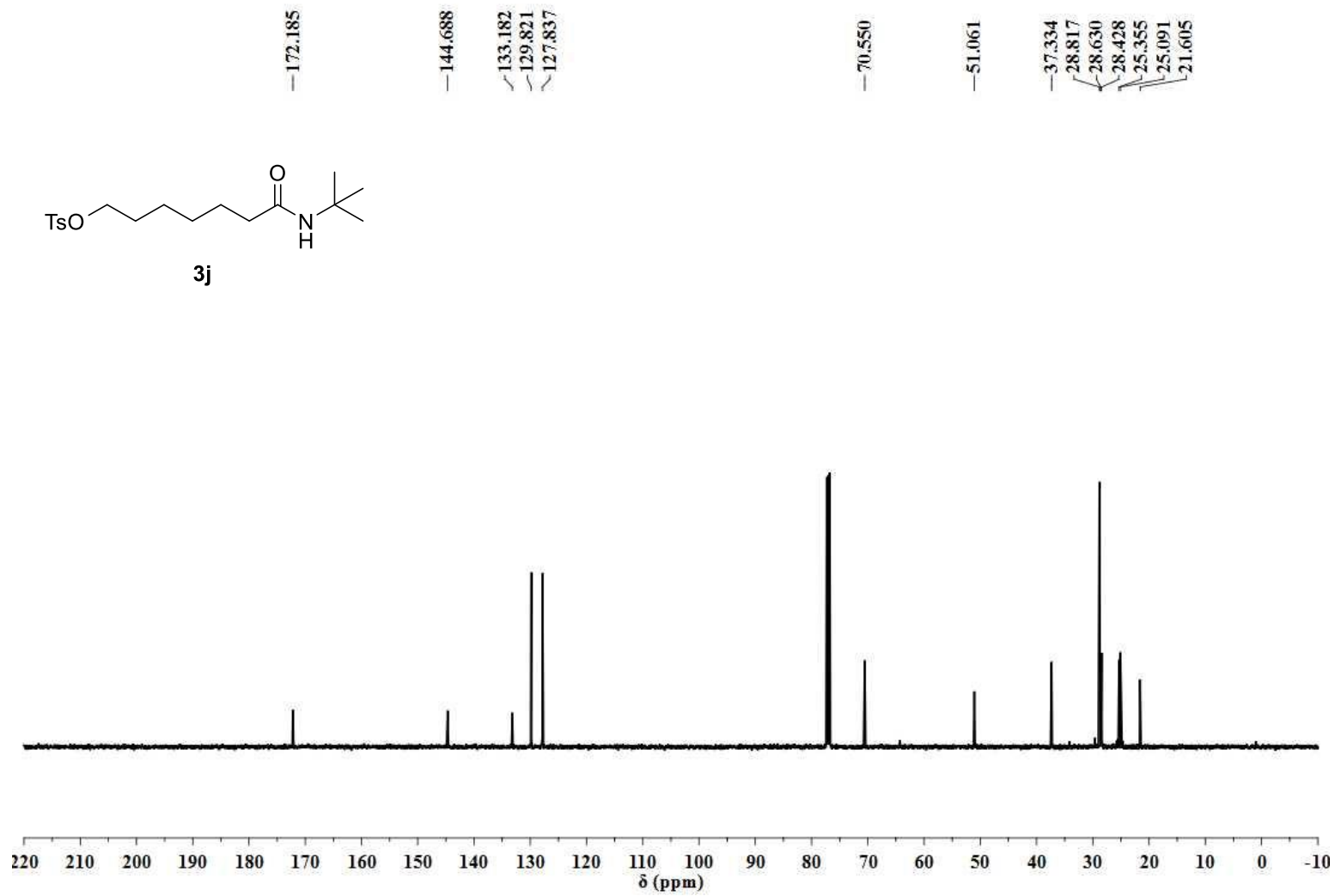


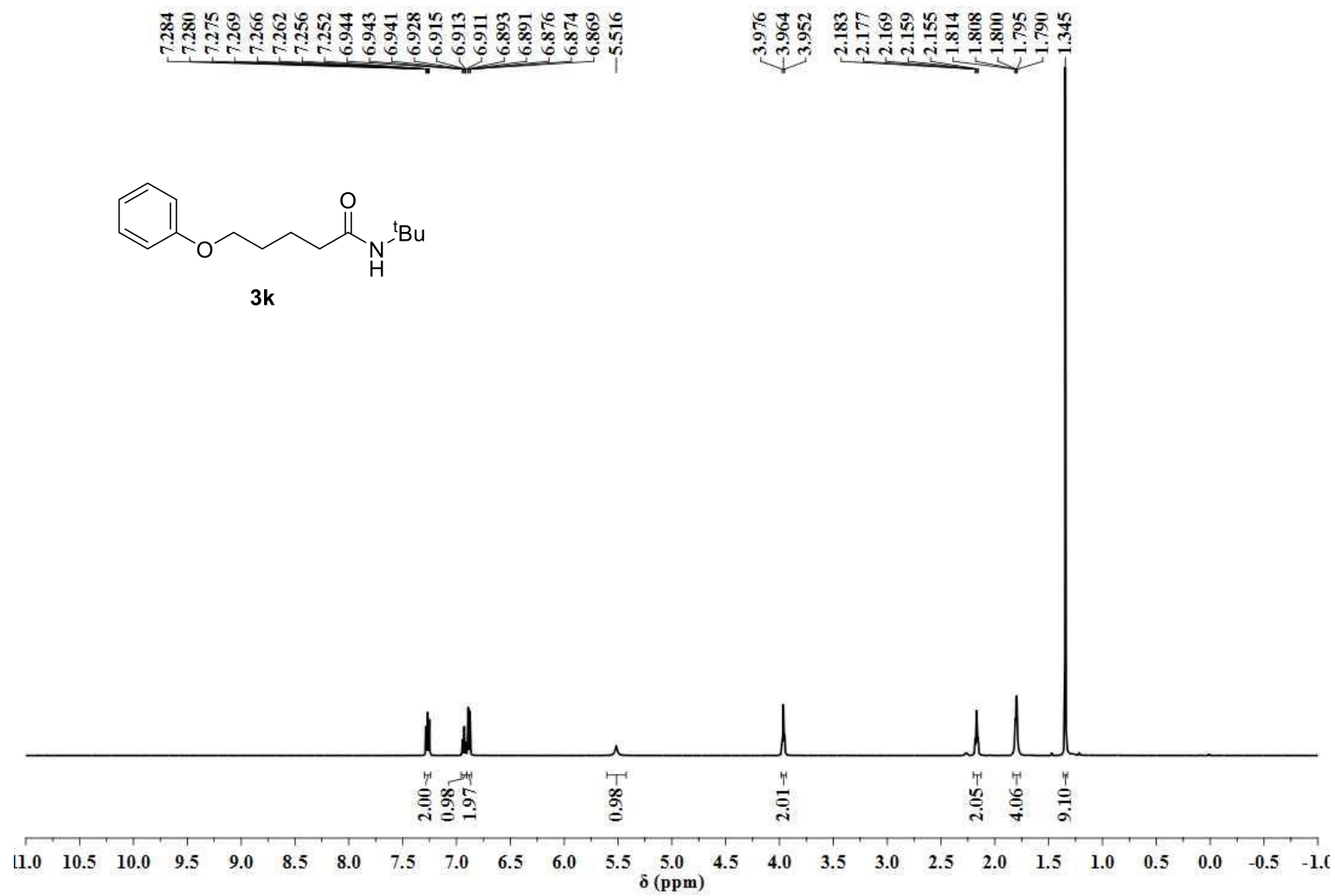


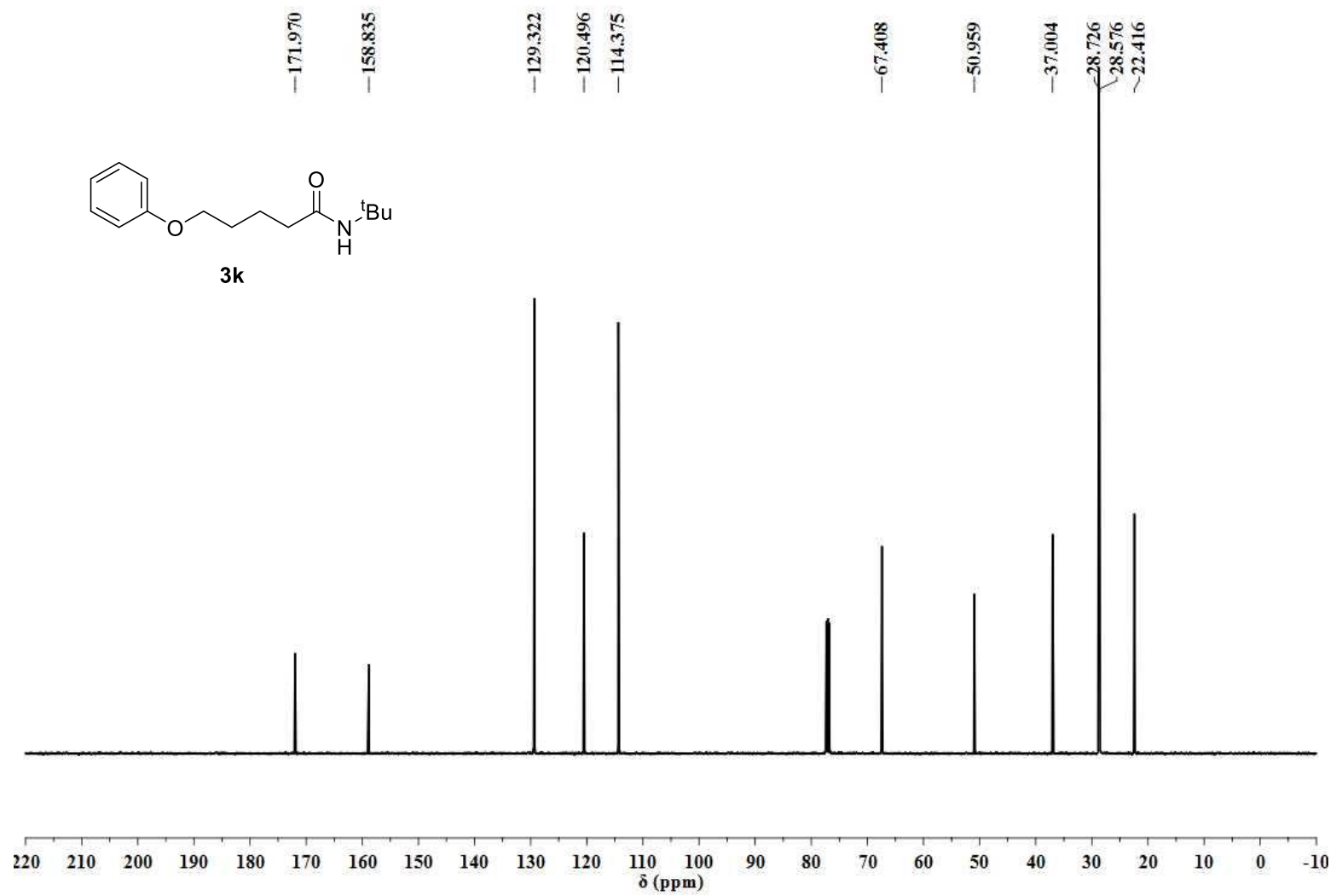


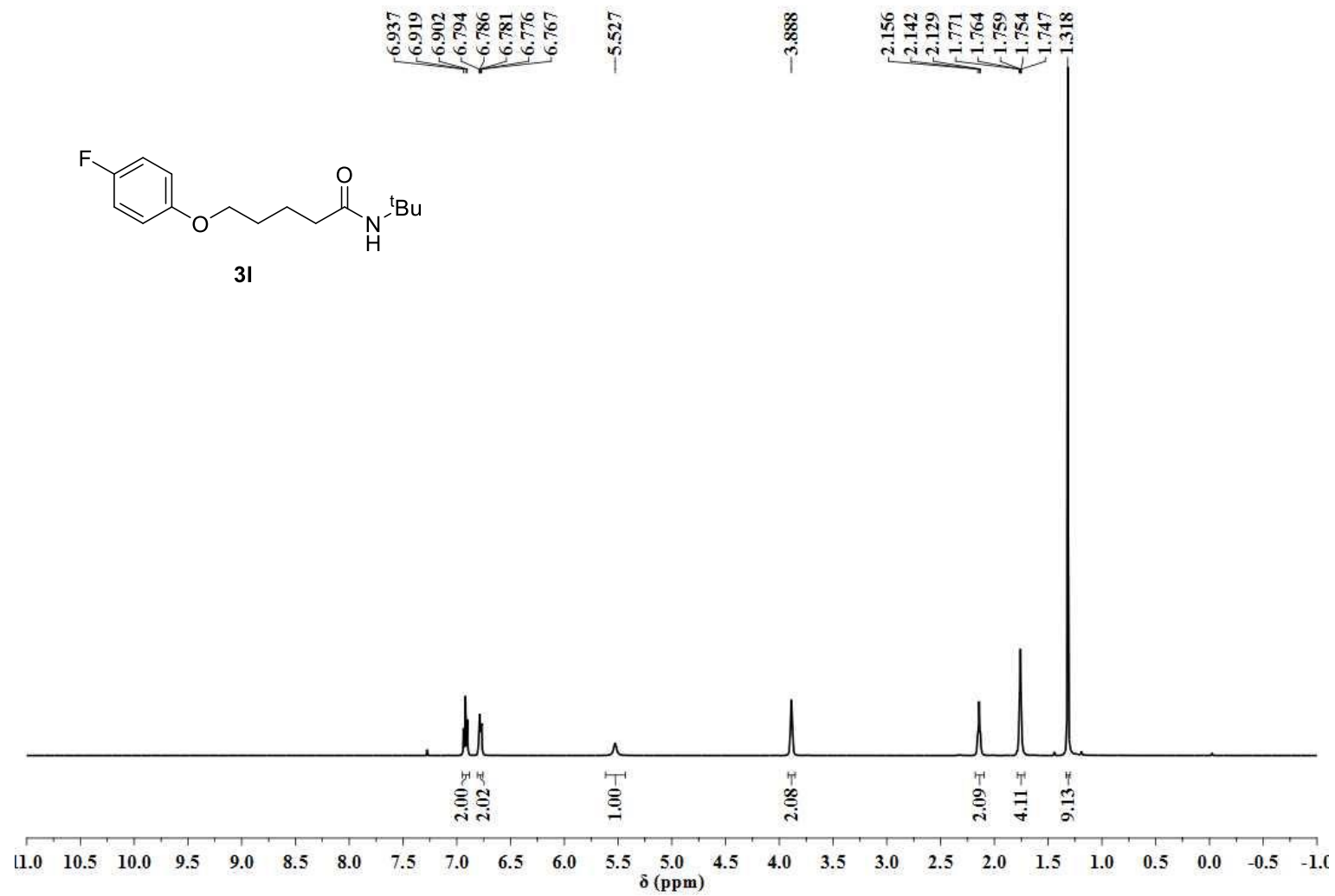


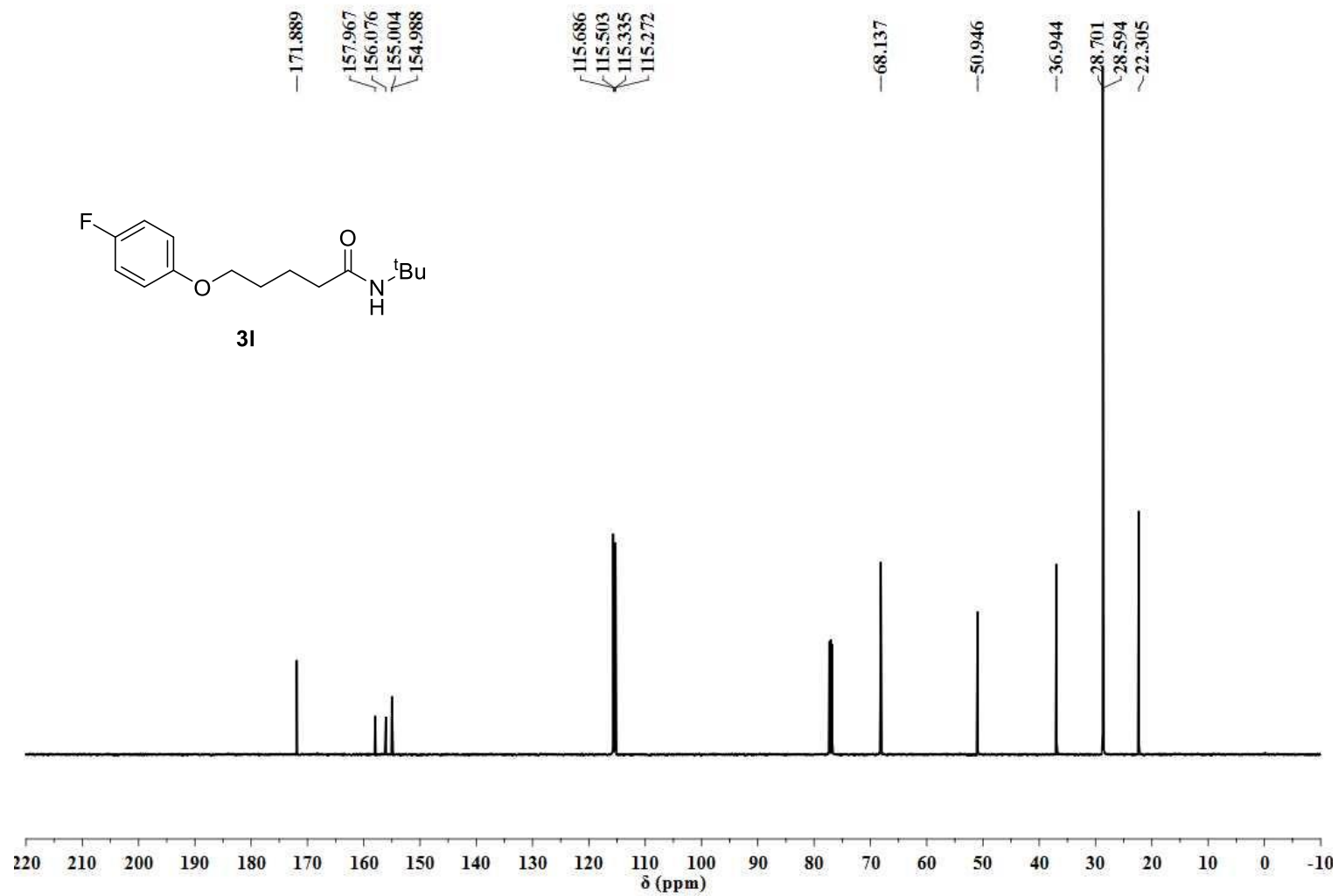


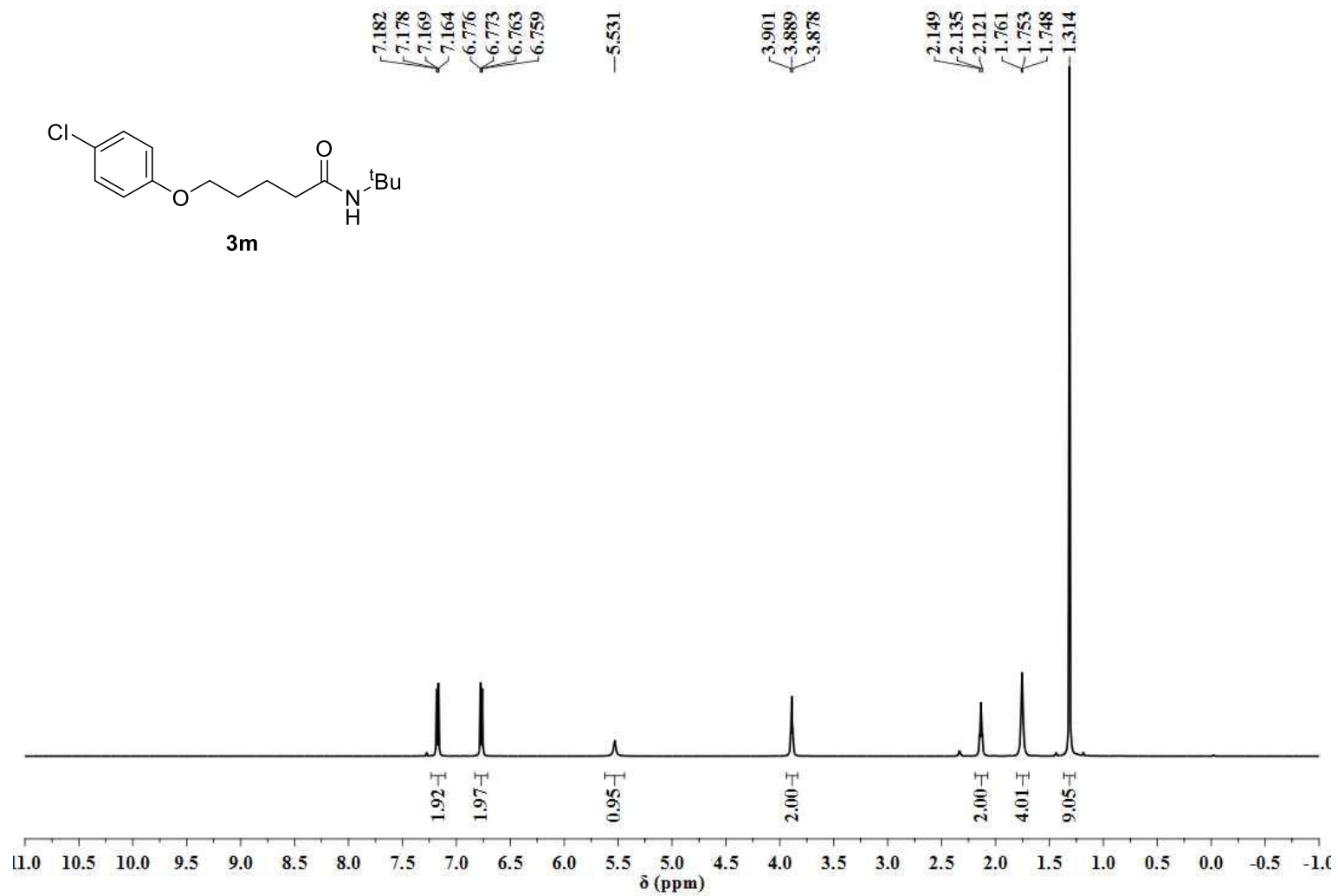


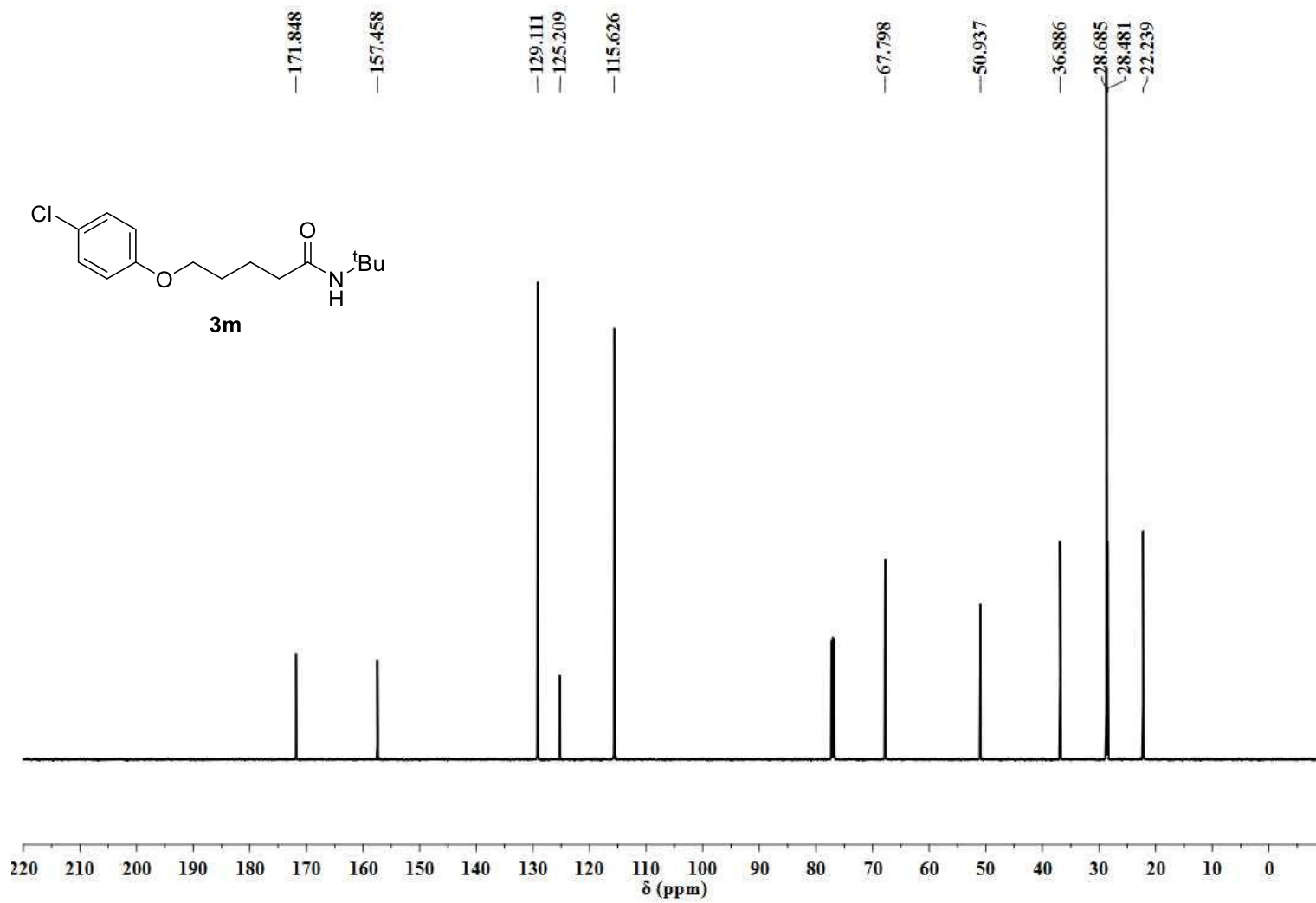


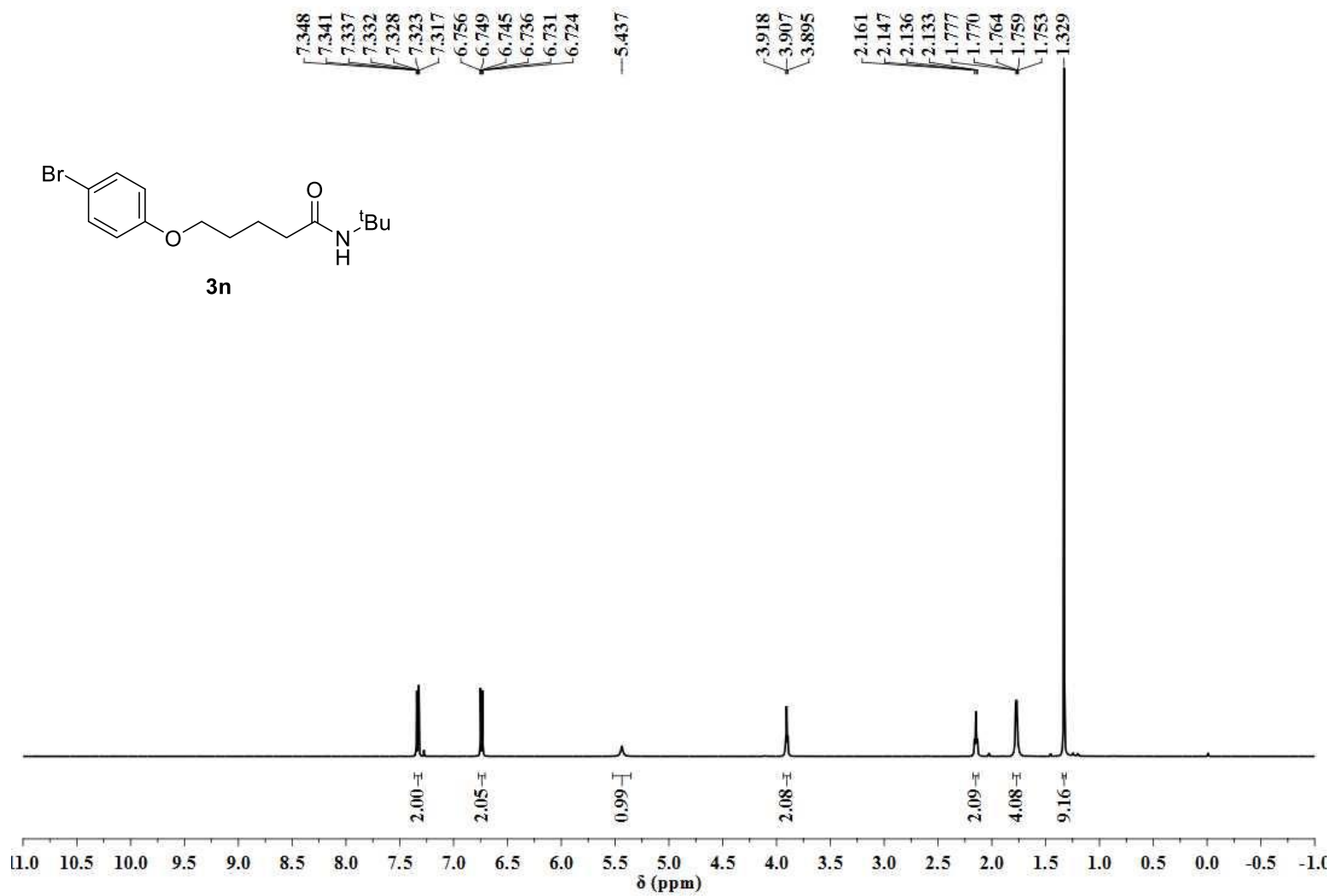


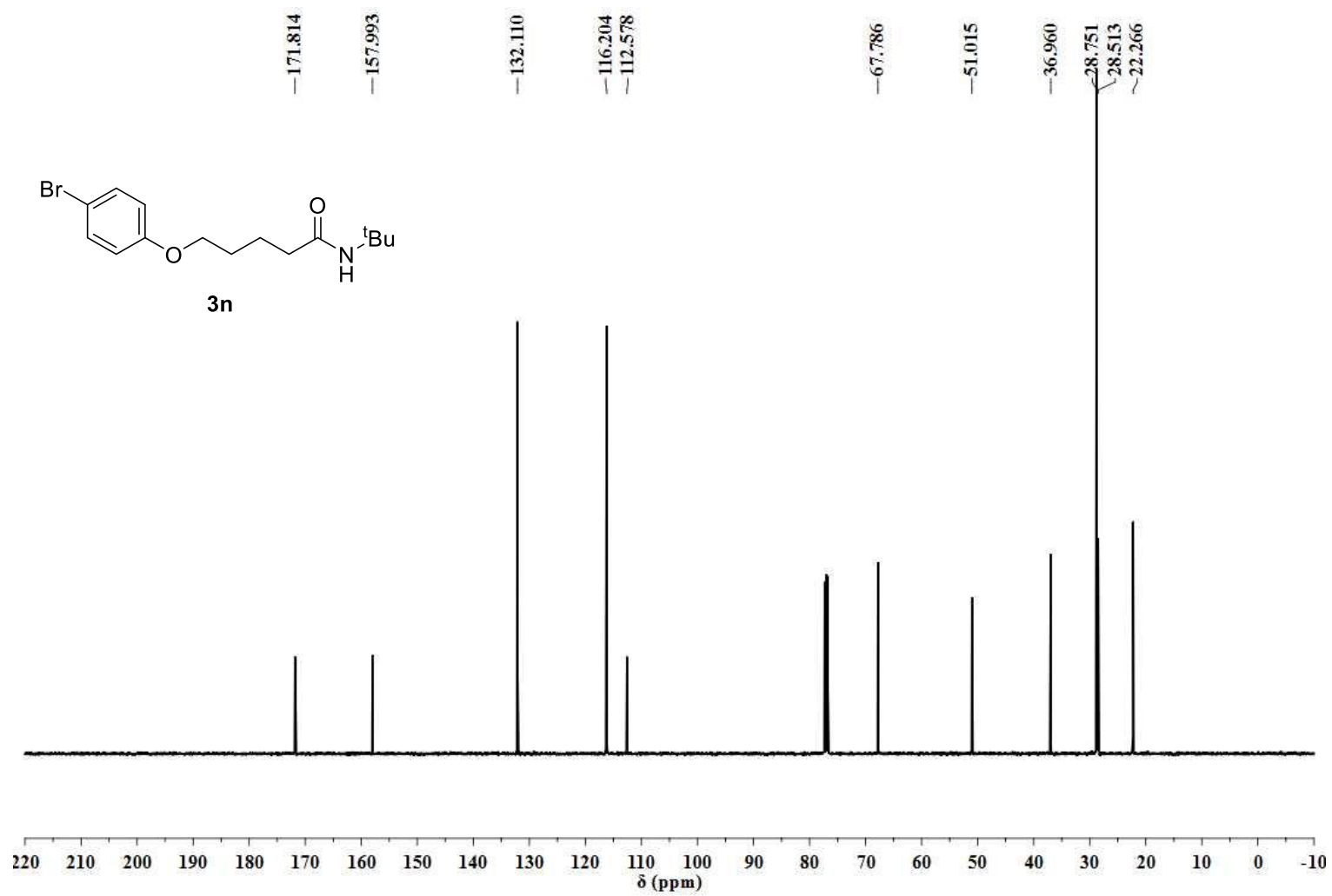


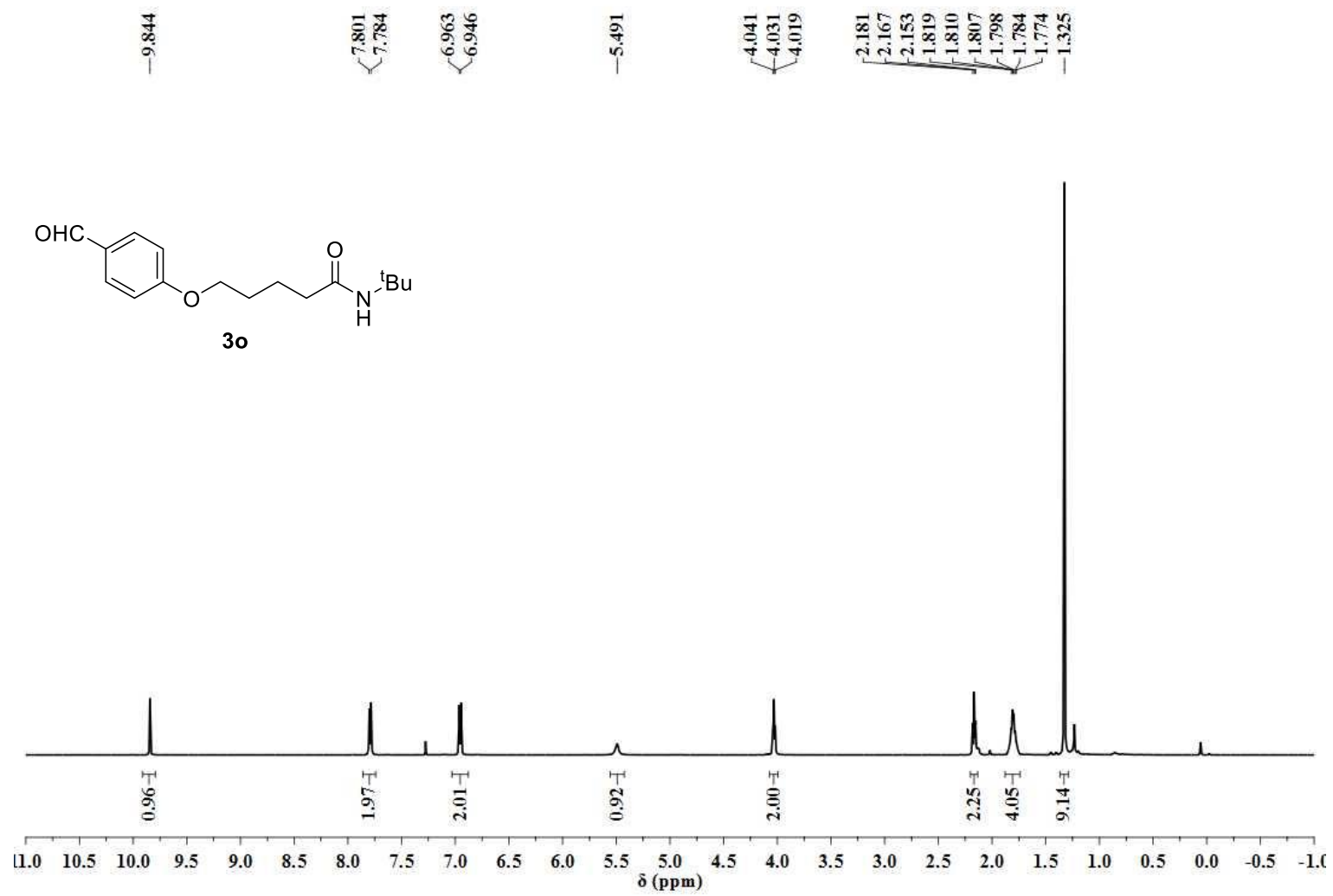


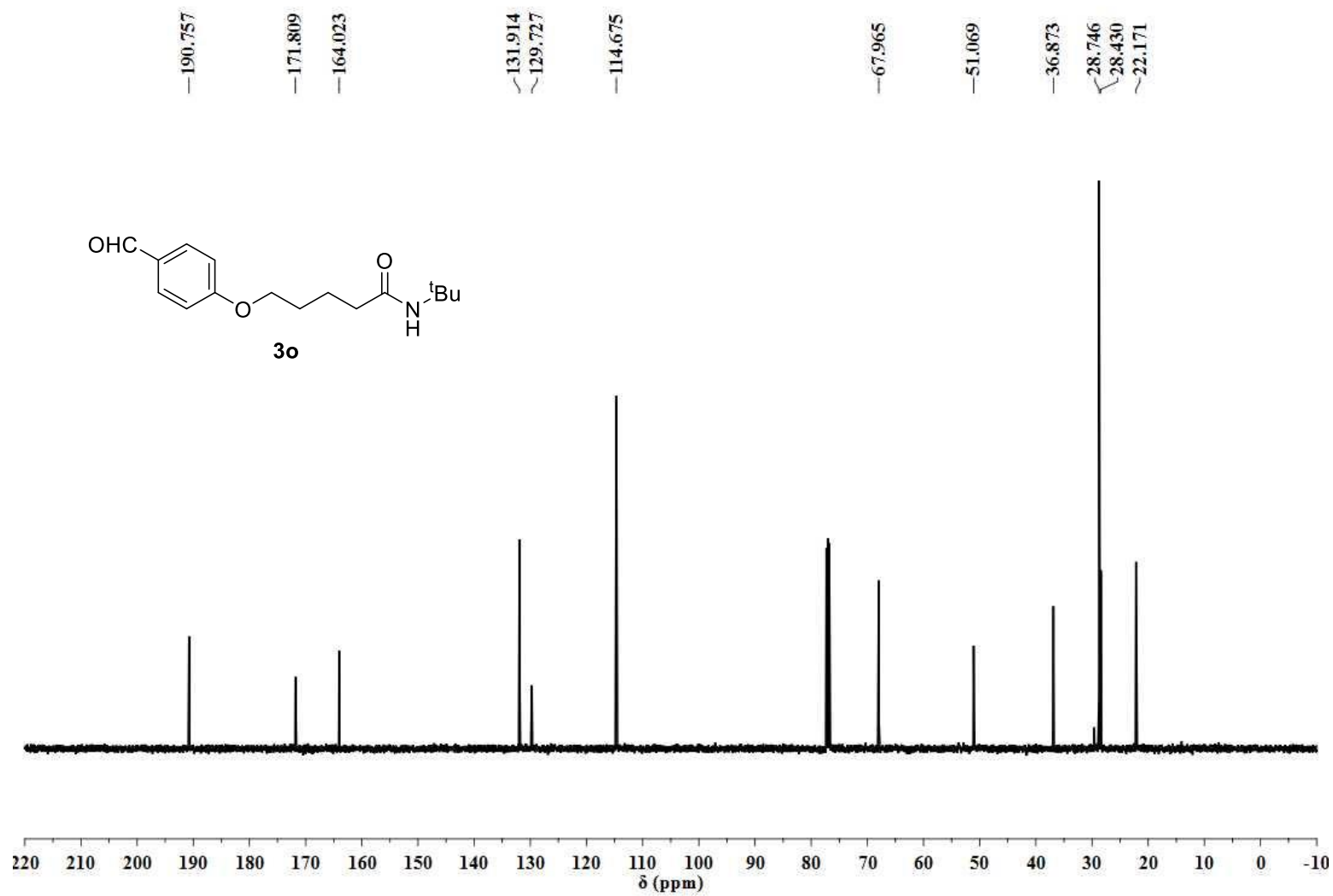


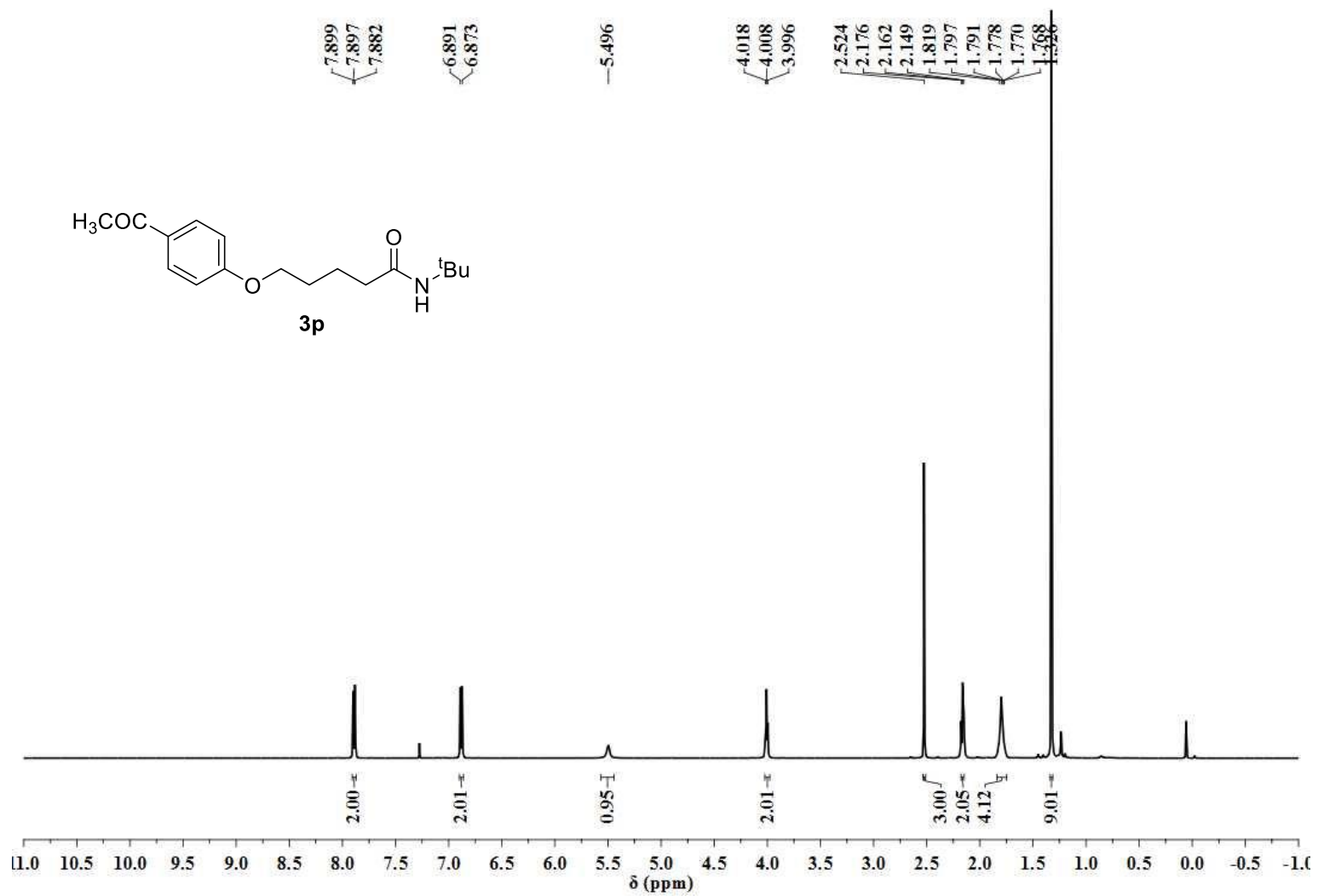


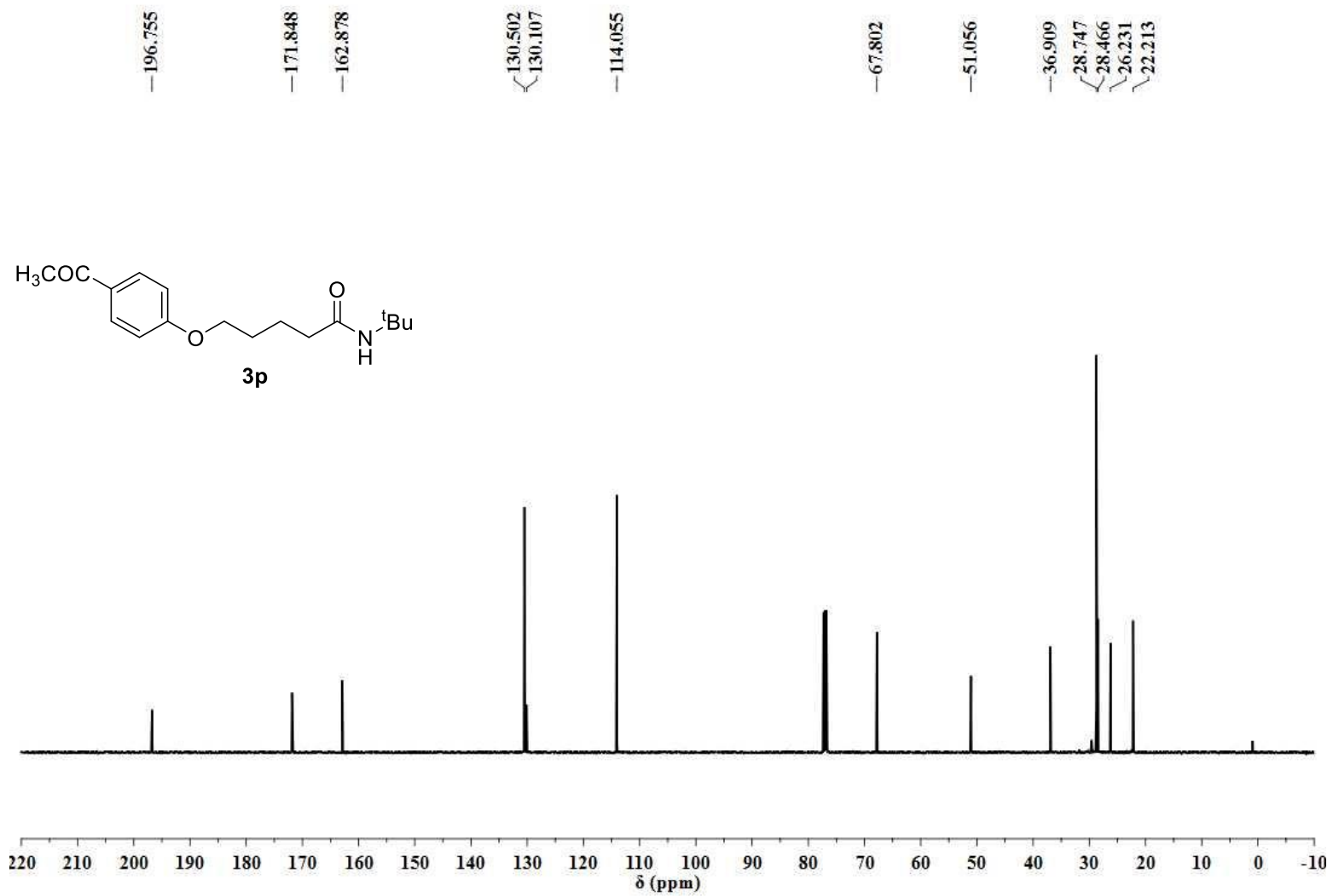


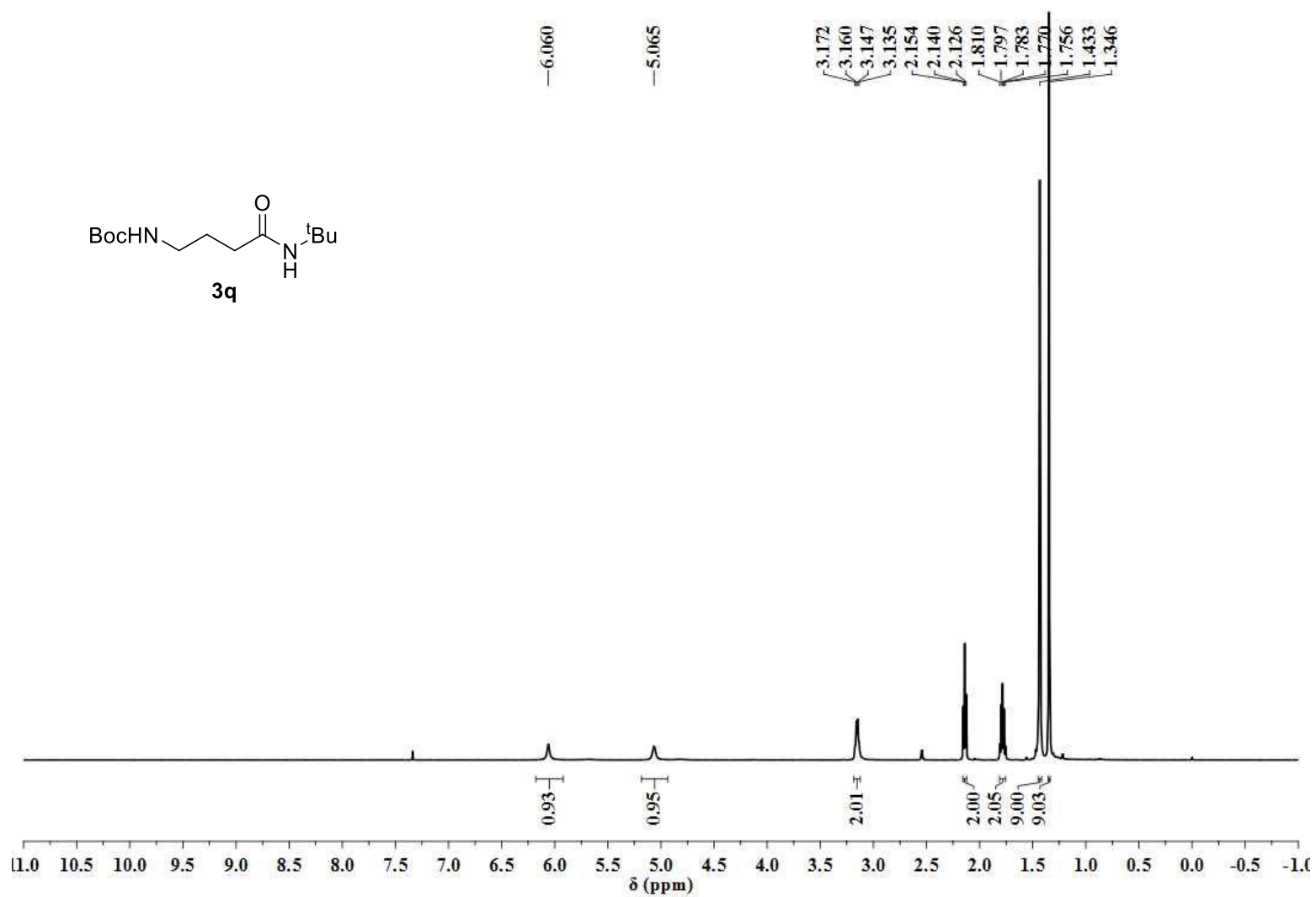
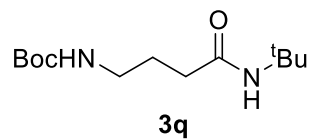


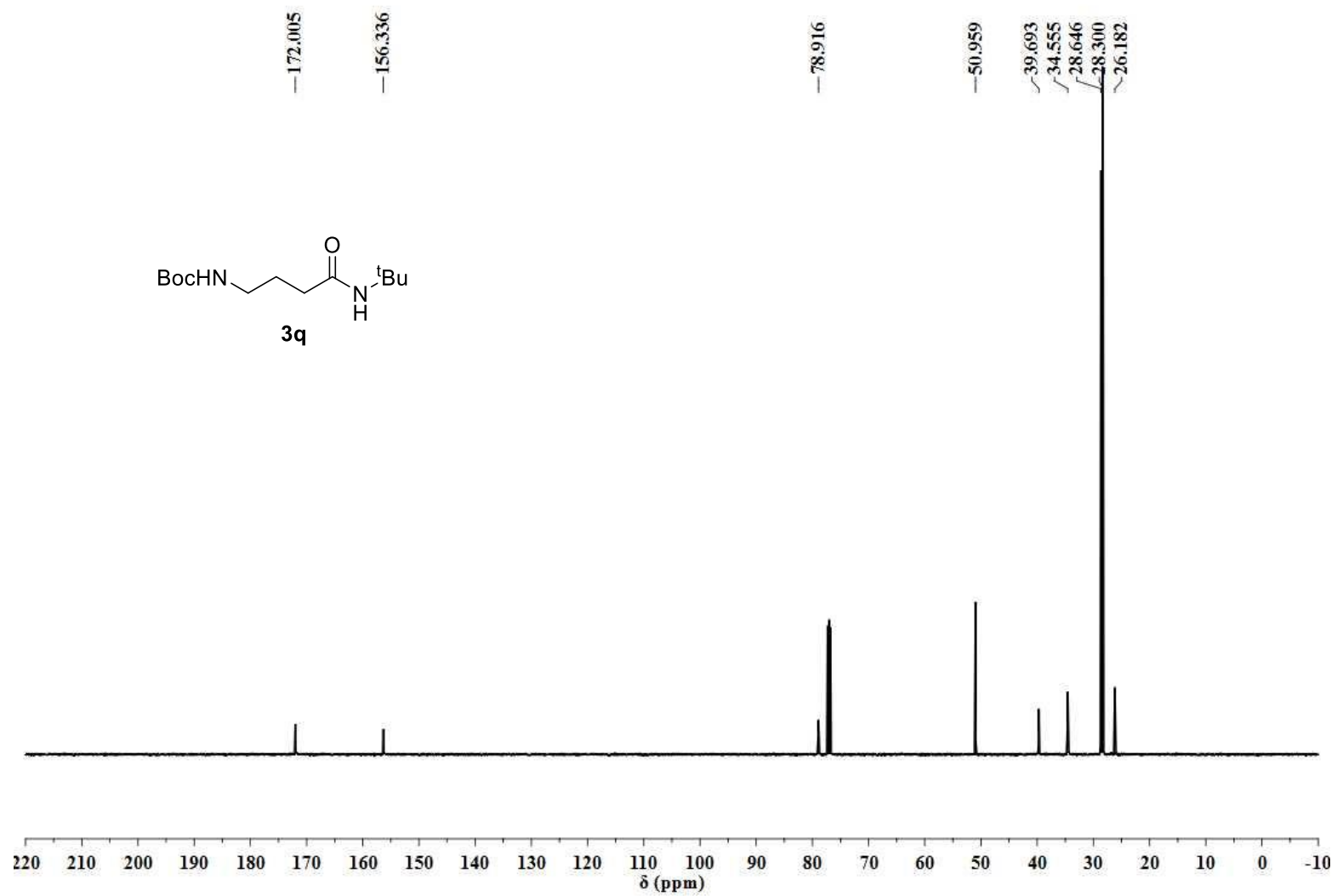
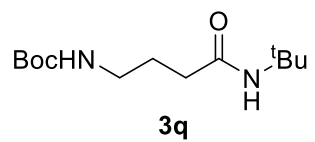


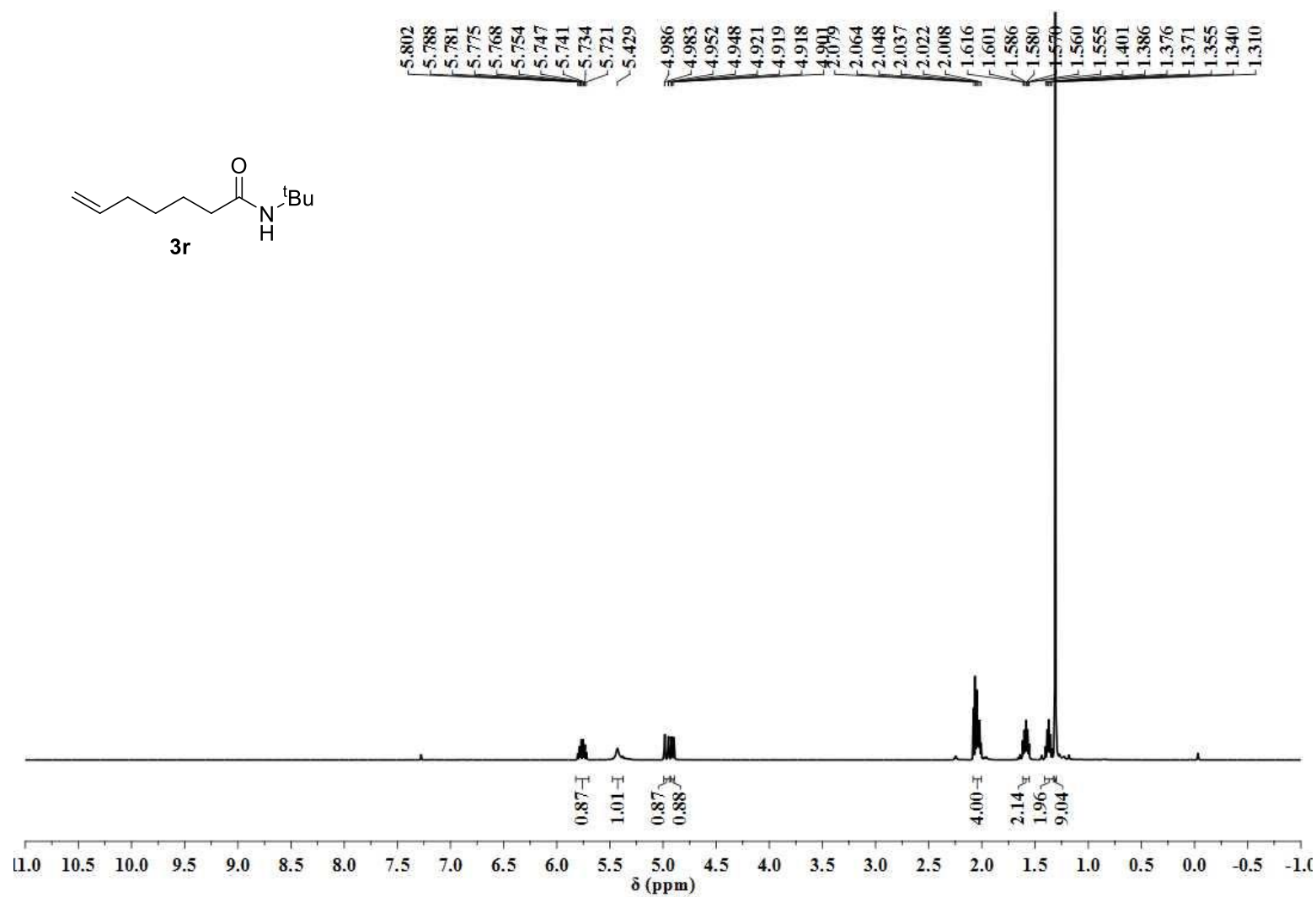
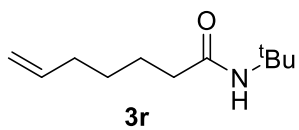


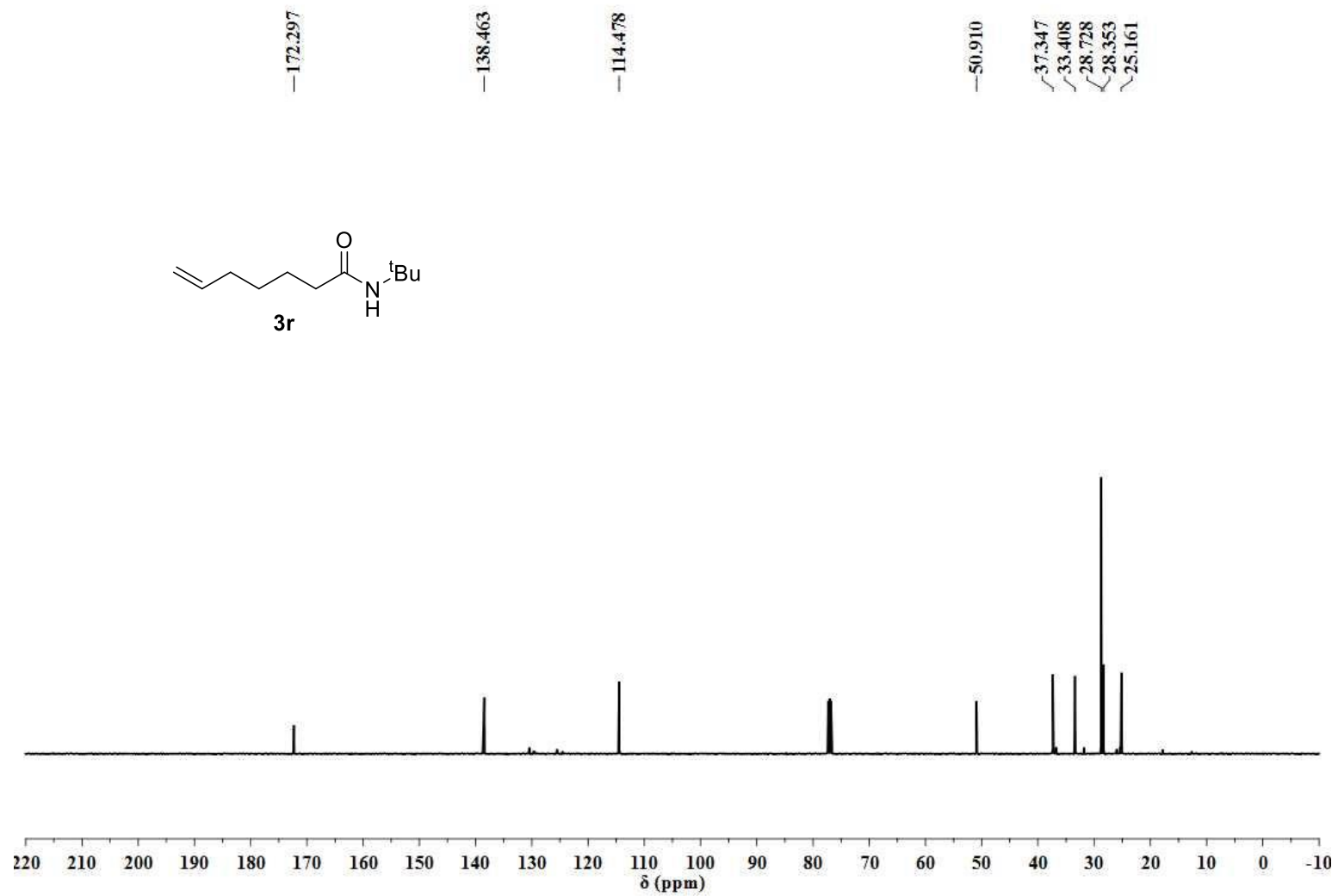
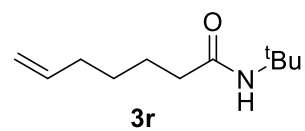


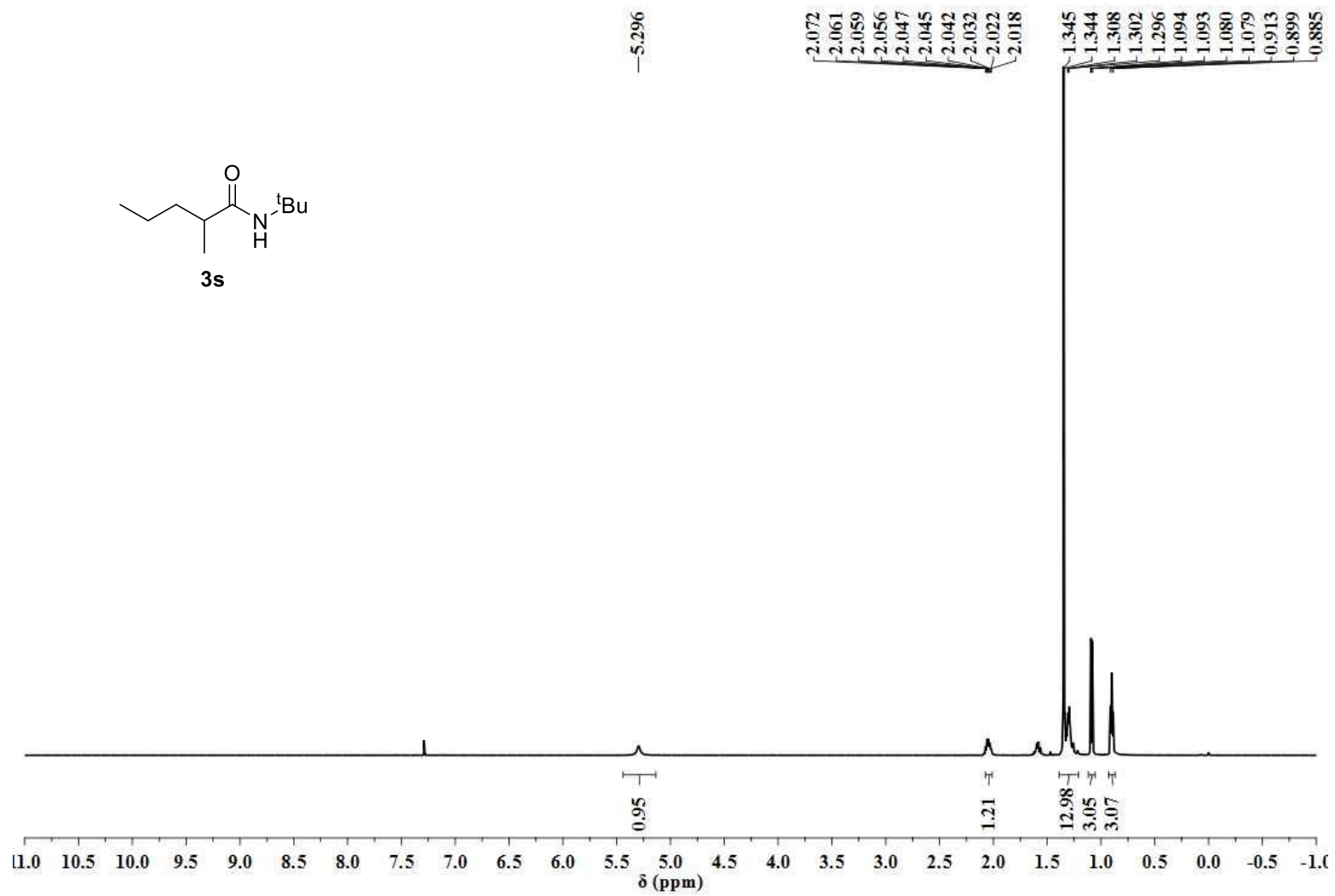
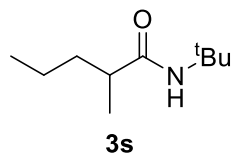


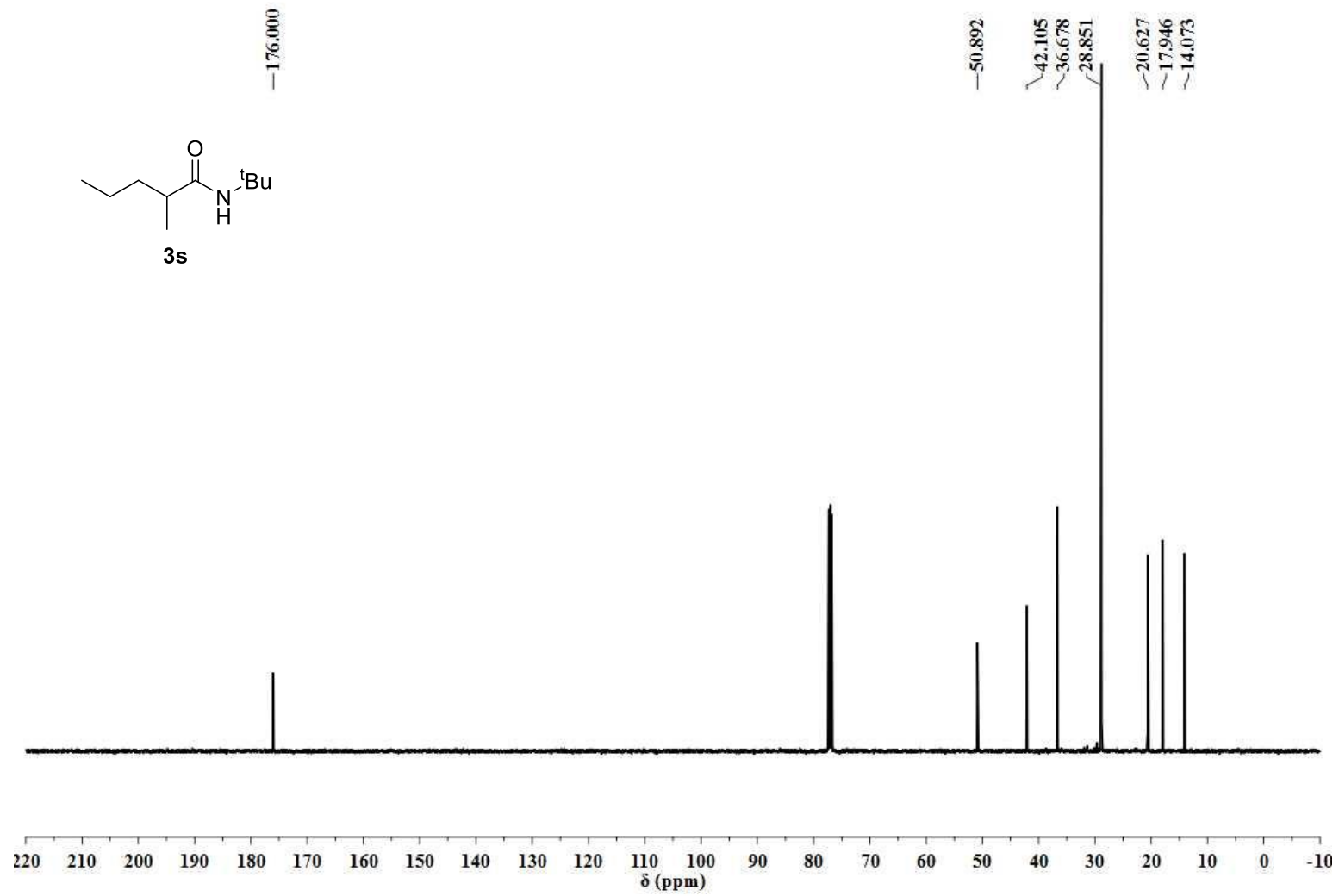


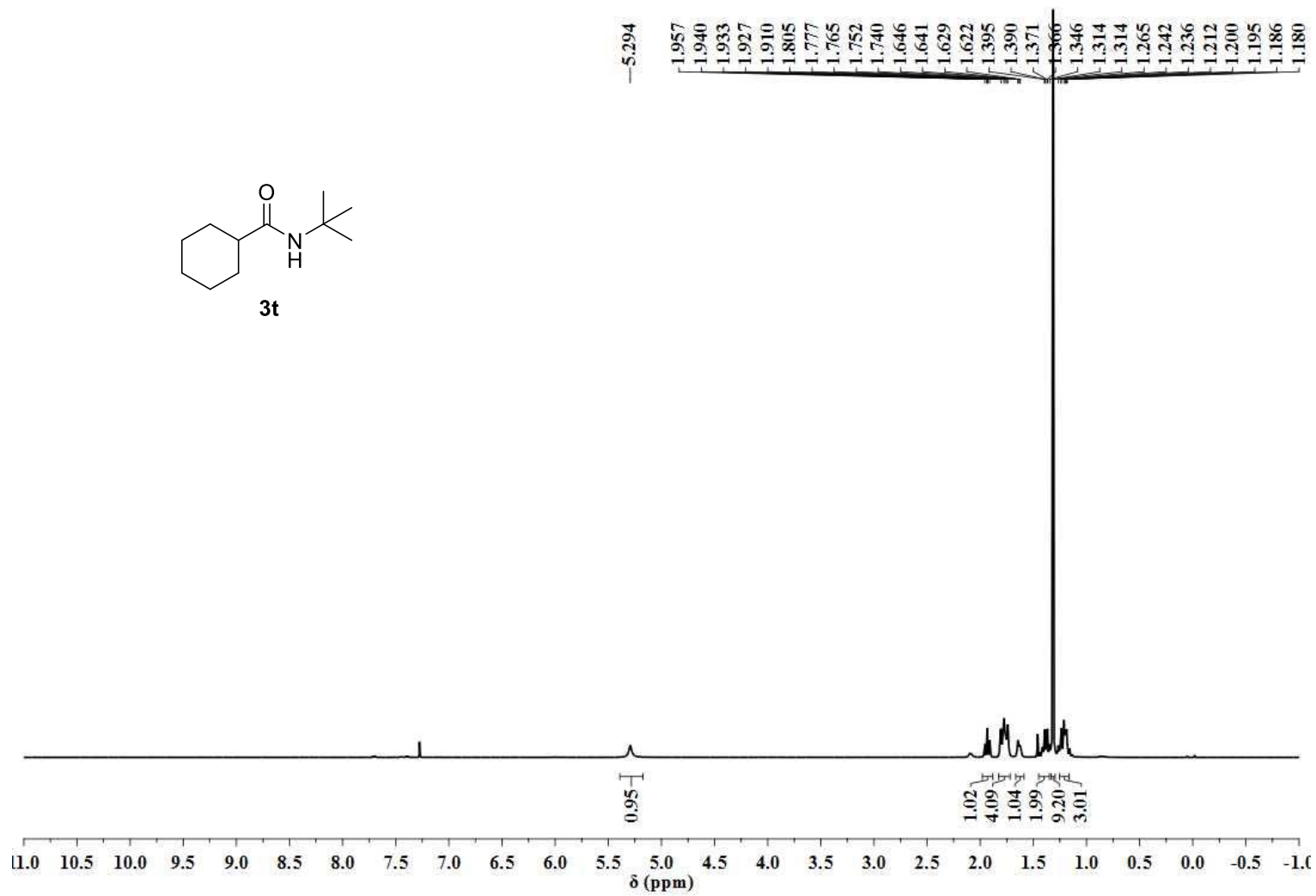
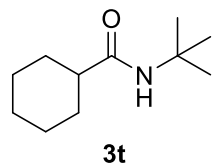


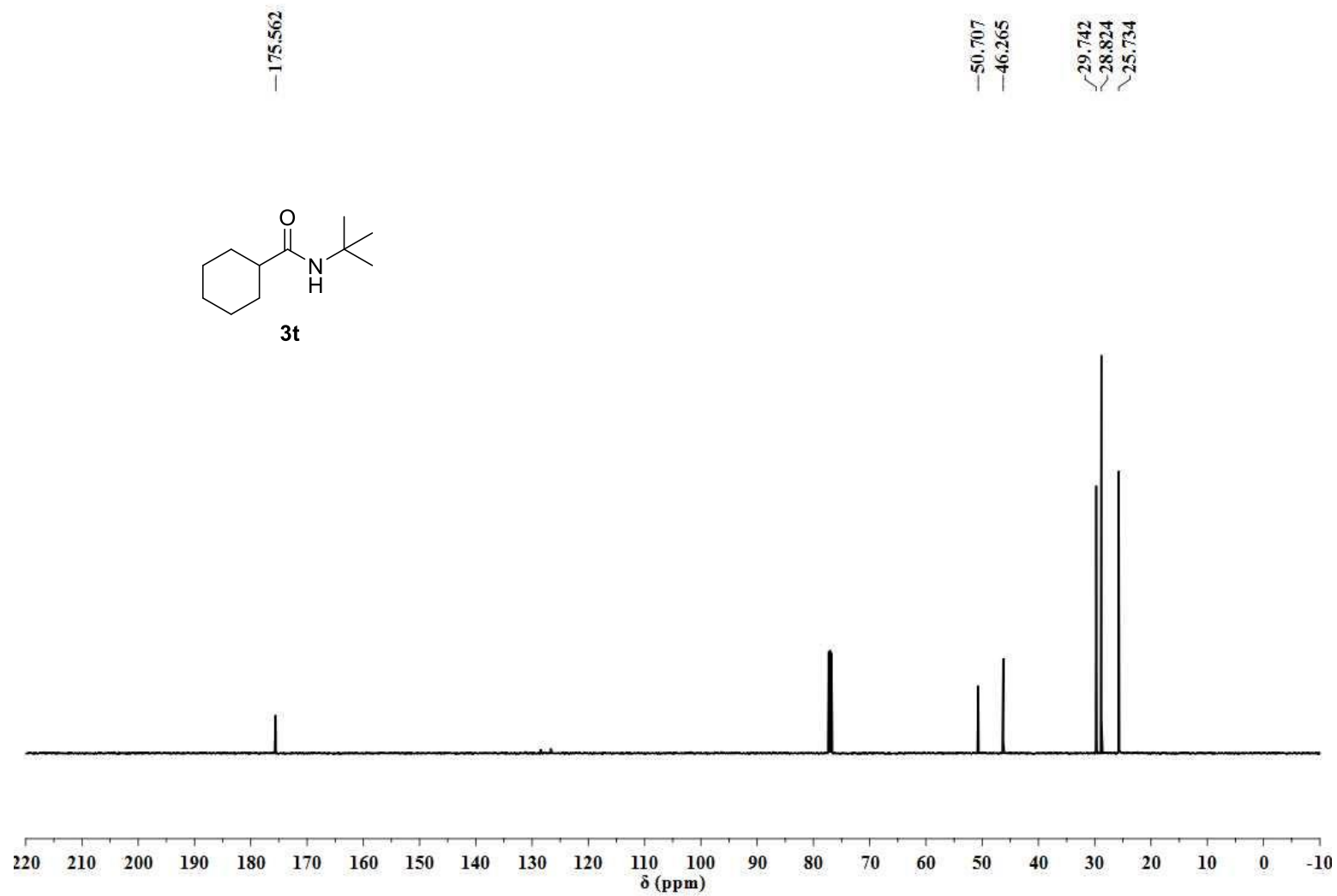
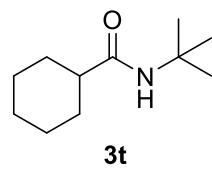


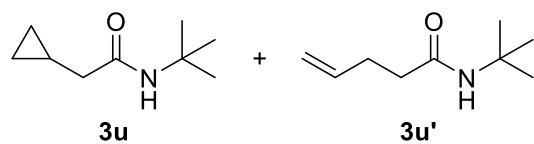












3u : 3u' = 10 : 1

-5.752  
 5.033  
 5.031  
 4.999  
 4.962  
 4.942

2.325  
 2.312  
 2.297  
 2.164  
 2.148  
 2.134  
 2.032  
 2.017  
 1.322  
 1.301  
 -0.915  
 -0.900  
 -0.885  
 -0.561  
 -0.551  
 -0.536  
 -0.525  
 -0.147  
 -0.138  
 -0.128  
 -0.117

