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Article

Eco-Friendly Synthesis of 2-Substituted Benzothiazoles Catalyzed by Cetyltrimethyl Ammonium Bromide (CTAB) in Water

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Uma série de benzotiazóis 2-substituídos foi sintetizada pela condensação de 2-aminotiofenol com aldeídos (RCHO: R = Alquil, Aril, Heteroaril, 2-Arilformil) na presença de quantidade catalítica de brometo de cetiltrimetil amônio (CTAB) em água e sem adição de solventes orgânicos e oxidantes. Assim, usando esse protocolo, 2-alquilbenzotiazóis foram sintetizados em altos rendimentos e 2-arilformilbenzotiazóis foram obtidos pela condensação de 2-aminotiofenol com arilformil aldeídos pela primeira vez.

A series of 2-substituted benzothiazoles have been synthesized by the condensation of 2-aminothiophenol with aldehydes (RCHO: R = Alkyl, Aryl, Heteroaryl, 2-Arylformyl) in the presence of a catalytic amount of cetyltrimethyl ammonium bromide (CTAB) "on water" by a one-pot procedure without additional organic solvents and oxidants. Thereinto, 2-alkylbenzothiazoles were synthesized in high yields and 2-arylformylbenzothiazoles were obtained from the condensation of 2-aminothiophenol with arylformyl aldehydes for the first time using the present protocol.

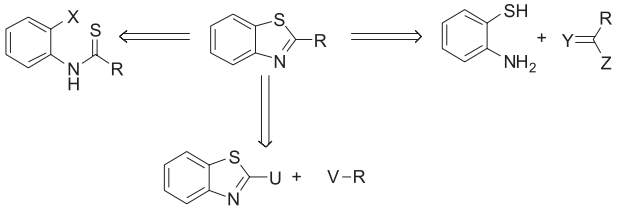
Keywords: 2-alkylbenzothiazole, 2-arylbenzothiazole, 2-arylformylbenzothiazole, cetyltrimethyl ammonium bromide (CTAB), water

Introduction

Benzothiazoles and their derivatives are very important group of heterocyclic bicyclic systems,[1] which play a fundamental role in organic and bioorganic chemistry. They have potent antitumor activity[2-5] and other important pharmaceutical utilities,[6-9] such as their applications for treatment of autoimmune and inflammatory diseases, prevention of solid organ transplant rejection, epilepsy, analgesia, viral infections, cancer, and tuberculosis.[10-16] Also, they can be used in industry as antioxidants and vulcanization accelerators that highlight their synthesis necessity.[17]

The reported methods for the synthesis of 2-substituted benzothiazole (Scheme 1) involve two major routes: the condensation of 2-aminothiophenol with aldehydes,[18-33] carboxylic acids,[6,34] acid chlorides,[35] or esters[36,37] and by the cyclization of thiobenzanilides.[38-45] Some other methods include microwave-mediated reaction of 2-aminothiophenol with β-chlorocinnamaldehydes,[46] palladium-catalyzed Suzuki biaryl coupling of 2-halobenzothiazole with arylboronic acids,[47,48] coupling of benzothiazoles with aryl bromides[49] and the reaction between thiophenols and aromatic nitriles.[50]

However, many of these methodologies are associated with one or more disadvantages such as (*i*) harsh reaction conditions, e.g., heating at 120 °C in xylene catalyzed by



X=H, Cl, Br, I, SMe; Y=O, S, Se; Z=H, OH, OR, NH_2, Cl

U=H, $SnBu_3$, $SnMe_3$, SMe; V=COOH, Br, I, ZnBr

Scheme 1. Strategies for the synthesis of 2-substituded benzothiazoles.

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4-methoxy-TEMPO in presence of oxygen;[18] heating in the presence of excess of PPA at 150-220 °C for 2-4 h[31] or P_2O_5/$MeSO_3H$ at 70 °C for 10 h;[32] microwave-assisted in ionic liquids[23] or using excess of *p*-TsOH adsorbed on SiO_2/K10 and graphite,[27] treatment with stoichiometric amounts of oxidizing agents such as $K_3Fe(CN)_6$ at 90 °C under basic conditions[38] and excess of $Mn(OAc)_3$ in AcOH at 110 °C for 4 h;[41] (*ii*) prolonged reaction time;[32,47] (*iii*) additional reagents/catalysts, high boiling solvents that are difficult to recover;[18,21,28] (*iv*) costly, air sensitive, and toxic substances;[18] (*v*) requirement of excess strong oxidizing agents,[18,19,21] *etc.* In many cases the acidic/metallic wastes are generated and mixed with the effluent water. On the other hand, the condensation reaction of 2-aminothiophenol with aliphatic aldehydes tend to attract little attention.[21,33] Thus, the development of environmentally benign, high yielding, and clean approaches for the synthesis of 2-substituted benzothiazoles is in demand.

The increasing concern about the tight legislation on the maintenance of greenness in synthetic processes[51] led us to develop a method using a reagent that is less hazardous, non-toxic, cheap, and benign to the environment. Water as a reaction medium has gained importance in the development of sustainable chemistry.[52]

As a common catalyst for phase transfer, cetyltrimethyl ammonium bromide (CTAB is able to expedite the reaction between anion or nucleophile and neutral substrate via transferring one phase to another, making them collided with each other frequently.[53]

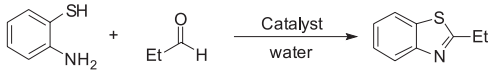
In continuation of our efforts to develop green synthetic routes for the formation of C-C and carbon-heteroatom bond,[54] we herein report a green, simple and practical method for the synthesis of 2-sustituted benzothiazoles from the condensation of 2-aminothiophenol with aldehydes catalyzed by CTAB in water.

Results and Discussion

Initially, we investigated various conditions in the model reaction using 2-aminothiophenol with propionaldehyde in water and the results were summarized in Table 1. The results established that CTAB proved to be a superior catalyst among all the catalysts screened in this transformation. Then, the reaction was investigated with different amounts of CTAB. It was found that the yield was not significantly affected by adding amount of CTAB, 5 mol% of CTAB was sufficient, and excessive amount of catalyst did not increase the yield remarkably (Table 1, entries 6-8).

With the optimal conditions in hand, further investigations were carried out to expand the scope of other alkyl aldehydes and the results were summarized in Table 2. In all cases, it was found that alkyl aldehydes can react well with 2-aminothiophenol in good yields without using extra oxidants. It is noteworthy that the present protocol is superior to the previous method for the synthesis of **3a** by heating in

Table 1. The condensation of 2-aminothiophenol with propionaldehyde under different reaction conditions[a]

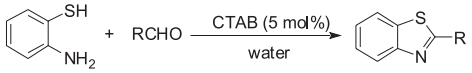


3a

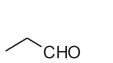
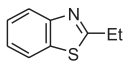
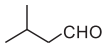
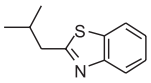
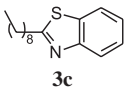
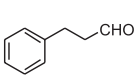
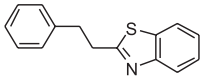
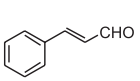
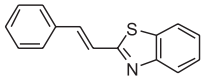
Entry	Catalyst	time / h	Yields / (%)[b]
1	none	8	18
2	SDS[c]	8	39
3	TMAB[c]	8	31
4	TBAF[c]	8	28
5	TEBA[c]	8	41
6	CTAB	8	87
7	CTAB	8	89[d]
8	CTAB	8	89[e]

[a]All reactions were run with 2-aminobenzenethiol (1.1 mmol), propionaldehyde (1 mmol), CTAB (5 mol%, 0.05 mmol) and water (5 mL) at reflux. [b]Isolated yields. [c]Dodecyl sodium sulfate (SDS), Tetramethyl ammonium bromide(TMAB), Tetrabutyl ammonium fluoride(TBAF), Benzyltriethylammonium chloride(TEBA). [d]The load of catalyst was 10 mol%. [e]The load of catalyst was 20 mol%.

Table 2. Synthesis of 2-alkyl benzothiazoles[a]

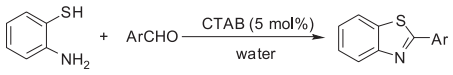


3a-3e

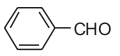
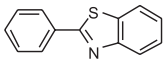
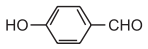
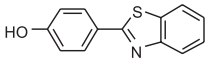
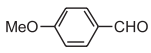
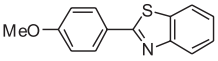
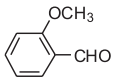
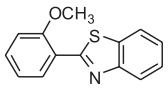
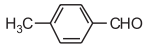
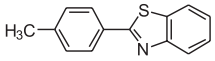
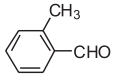
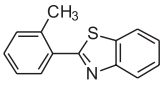
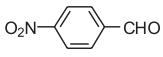
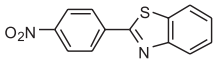
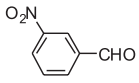
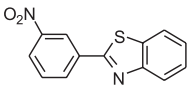
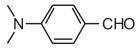
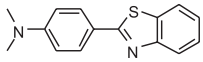
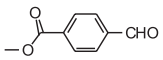
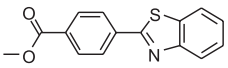
Entry	RCHO	Product	time / h	Yields / (%)[b]
1		 **3a**	8	87
2		 **3b**	8	86
3		 **3c**	8.5	89
4		 **3d**	9	83
5		 **3e**	4	84

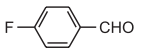
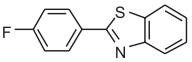
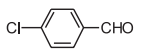
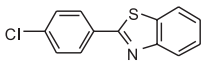
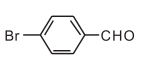
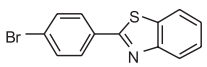
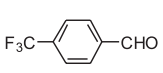
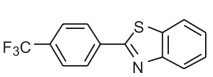
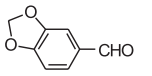
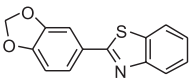
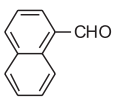
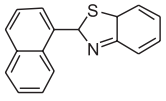
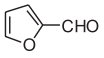
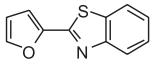
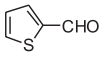
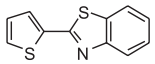
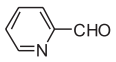
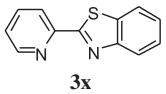
[a]All reactions were run with 2-aminobenzenethiol (1.1 mmol), alkyl aldehydes (1 mmol), CTAB (5 mol%, 0.05 mmol) and water (5 mL) at reflux. [b]Isolated yields.

Table 3. Synthesis of 2-aryl benzothiazoles[a]



3f-3x

Entry	ArCHO	Product	time / h	Yields / (%)[b]
1		 **3f**	1.5	98
2		 **3g**	1	95
3		 **3h**	1.2	97
4		 **3i**	2	89
5		 **3j**	2	88
6		 **3k**	2.5	90
7		 **3l**	7	78
8		 **3m**	6	86
9		 **3n**	2	87
10		 **3o**	3	88

Entry	ArCHO	Product	time / h	Yields / (%)[b]
11		 **3p**	2	91
12		 **3q**	2	93
13		 **3r**	2	96
14		 **3s**	6	85
15		 **3t**	3	80
16		 **3u**	2.5	87
17		 **3v**	3	86
18		 **3w**	3	89
19		 **3x**	3	90

[a]All reactions were run with 2-aminobenzenethiol (1.1 mmol), aryl aldehydes (1 mmol), CTAB (5 mol%, 0.05 mmol) and water (5 mL) at reflux. [b]Isolated yields.

DMF at 100 °C catalyzed by 50 mol% of molecular iodine[21] with the yields of 31% (Table 2, entry 1). Moreover, the 2-styrylbenzothiazole can react well with 2-aminothiophenol in high yield in short time (Table 2, entry 5).

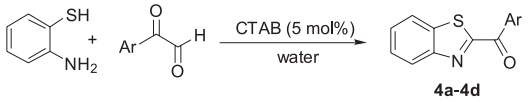
Next, we examined the scope of the reaction of 2-aminothiophenol with a variety of aromatic aldehydes. As shown in Table 3, it was observed that a series of aromatic aldehydes bearing either electron-donating or electron-withdrawing groups on aromatic ring were investigated. The substitution groups on the aromatic ring have no obvious effect on the yields and reaction time under the above optimal conditions. However, aldehydes with strongly electron-withdrawing groups on aromatic ring such as *p*-nitrobenzaldehyde gave the product of **3l** with good yield in a long reaction time (Table 3, entry 7).

Furthermore, we also examined the condensation reaction of heteroaromatic aldehydes such as furfural, 2-thienyl aldehyde, 2-pyridyl aldehydes with 2-aminothiophenol (Table 3, entries 17-19). Similarly, the corresponding products were obtained with excellent yields.

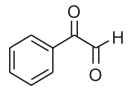
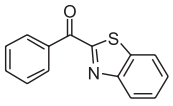
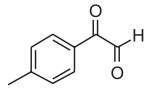
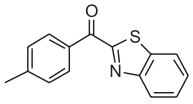
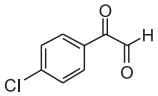
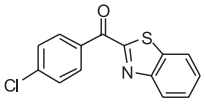
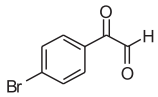
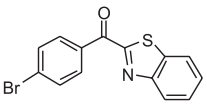
Finally, we examined the reactivity of arylformyl aldehyde with 2-aminothiophenol in the presence of CTAB in water (Table 4). The results showed that arylformyl aldehyde exhibited analogous behavior to that of aromatic

aldehyde and aliphatic aldehyde. To our knowledge, we reported the synthesis of 2-arylformylbenzothiazoles from the condensation of 2-aminothiophenol with arylformyl aldehyde for the first time.

Table 4. Synthesis of 2-arylformylbenzothiazoles[a]



4a-4d

Entry	ArCOCHO	Products	time / h	Yields / (%)[b]
1		 **4a**	4	83
2		 **4b**	4	84
3		 **4c**	4	80
4		 **4d**	4	85

[a]All reactions were run with 2-aminobenzenethiol (1.1 mmol), arylformyl aldehydes (1 mmol), CTAB (5 mol%, 0.05 mmol) and water (5 mL) at reflux. [b]Isolated yields.

A tentative mechanism for the formation of 2-substituted benzothiazoles was proposed. It may be assumed that the bromide ion of cetyltrimethyl ammonium bromide is hydrogen-bonding to –SH increasing the nucleophilicity of sulfur atom, which makes the thiolate anion as a stronger nucleophile towards efficient condensation with aldehydes followed by cyclization. The second step could be a rate determining step. That the actual oxidant is the oxygen of air, wherein in the atmosphere of nitrogen resulted in an extremely sluggish reaction insufficient for complete product formation even after 10 h. While the miceller environment formed by catalytic amount of resolved in water can accelerate the oxidation of thiazoline to thiazole.

In conclusion, we have developed a facile, efficient and green method for the synthesis of 2-substituted benzothiazoles by the condensation of alkyl, aryl, arylformyl aldehydes with 2-aminothiophenol in the presence of CTAB in water. Compared to previous reported methodologies, the present protocol features simple work-up, environmentally benign, high yields with alkyl aldehyde, no requirement of extra oxidants and use of the catalytic amounts of the cheap catalyst. Currently, studies on the extension of this protocol are ongoing in our laboratory.

Experimental

Melting points were recorded on Digital Melting Point Apparatus WRS-1B and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker DPX300 spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts were given in δ relative to TMS, the coupling constants *J* are given in Hz. Mass spectrometric analysis was performed on GC-MS analysis (SHIMADZU GCMS-QP2010).

General procedure for the preparation of 2-substituted benzothiazoles

To a mixture of benzaldehyde (1 mmol) and 2-aminothiophenol (1.1 mmol), CTAB (0.05 mmol, 5 mol%) was added in water (5 mL) under reflux. The reaction was monitored by TLC. After completion of the reaction, the product was extracted with ethyl acetate (3 × 10 mL), the organic layer washed with brine (3 × 10 mL), then dried over Na_2SO_4 and concentrated. The product was separated and purified by column chromatography on silica gel (300-400 mesh) using an ethyl acetate/petroleum ether mixture as the eluent to afford a pure product. When necessary, the products are purified through recrystallization from 95% ethanol.

Acknowledgments

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Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br, as PDF file.

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Eco-Friendly Synthesis of 2-Substituted Benzothiazoles Catalyzed by Cetyltrimethyl Ammonium Bromide (CTAB) in Water

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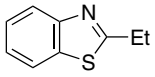
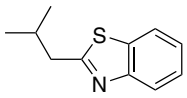
Description of the Products

*2-Ethylbenzothiazole (**3a**)[1]*



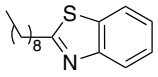
Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-8.00 (m, 4H, ArH), 3.10 (q, *J* 7.6 Hz, 2H, CH_2CH_3), 1.43 (t, *J* 7.6 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 153.2, 135.0, 125.9, 124.6, 122.5, 121.5, 27.8, 13.8; MS (ESI): *m/z* (%) 164 ([M+H]$^+$, 100).

*2-Isobutylbenzothiazole (**3b**)[1]*



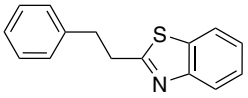
Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-8.01 (m, 1H, ArH), 7.84-7.87 (m, 1H, ArH), 7.43-7.48 (m, 1H, ArH), 7.35-7.38 (m, 1H, ArH), 3.00 (d, *J* 7.2 Hz, 2H, CH_2), 2.25 (m, 1H, $CH(CH_3)_2$), 1.06 (d, *J* 6.6 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 153.2, 135.2, 125.8, 124.6, 122.5, 121.4, 43.2, 29.7, 22.4; MS (ESI): *m/z* (%) 192 ([M+H]$^+$, 100).

*2-Nonylbenzothiazole (**3c**)[2]*



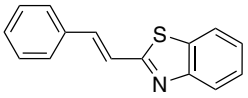
Yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* 7.7 Hz, 1H, ArH), 7.84 (d, *J* 7.7Hz, 1H, ArH), 7.42-7.48 (m, 1H, ArH), 7.32-7.37 (m, 1H, ArH), 3.12 (t, *J* 7.8Hz, 2H, CH_2); 1.83-1.93 (m, 2H, CH_2), 1.27-1.47 (m, 12H, $(CH_2)_6$), 0.88 (t, *J* 6.9 Hz,3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 153.2, 135.1, 125.8, 124.6, 122.5, 121.5, 34.4, 31.8, 29.8, 29.4, 29.3, 29.3, 29.2, 22.7, 14.1; MS (ESI): *m/z* (%) 262 ([M+H]$^+$, 100).

*2-Phenethylbenzothiazole (**3d**)[3]*



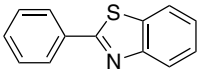
White crystal, mp 54-56 °C (not reported); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* 8.0 Hz, 1H, ArH); 7.85 (d, *J* 8.0 Hz, 1H, ArH); 7.22-7.48 (m, 6H, ArH); 3.45 (t, *J* 6.0 Hz, 2H, CH_2); 3.24 (t, *J* 6.0 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 153.1, 140.1, 135.1, 128.6, 128.4, 126.4, 126.0, 124.7, 122.5, 121.5, 36.0, 35.5; MS (ESI): *m/z* (%) 240 ([M+H]$^+$, 100).

*2-Styrylbenzothiazole (**3e**)[4]*



Yellow crystal, mp 110-112 °C (not reported); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.98 (m, 11 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 153.9, 137.6, 135.4, 134.4, 129.4, 128.9, 127.4, 126.3, 125.3, 123.0, 122.2, 121.5; MS (ESI): *m/z* (%) 238 ([M+H]$^+$, 100).

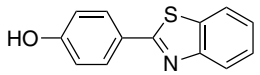
*2-Phenylbenzothiazole (**3f**)[4]*



White solid, mp 111-112 °C (113-114 °C)[4]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-8.12 (m, 3H, ArH), 7.91(d, *J* 7.7 Hz, 1H, ArH), 7.48-7.53 (m, 4H, ArH), 7.40 (d, *J* 7.7 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$,) δ 168.1, 154.1, 135.0, 133.6, 131.0, 129.1, 127.6, 126.3, 125.2, 123.2, 121.6; MS (ESI): *m/z* (%) 212 ([M+H]$^+$, 100).

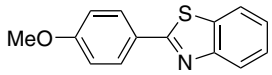
*e-mail: jiuxichen@wzu.edu.cn; huayuewu@wzu.edu.cn

*2-(4-Hydroxyphenyl) benzothiazole (**3g**)*[4]



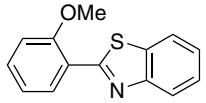
White solid, mp 229-231 °C (227-228 °C)[4]; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89-8.06 (m, 4H, ArH), 7.36-7.50 (m, 2H, ArH), 6.90-6.95(m, 2H, ArH), 3.64 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$,) δ 167.9, 170.1, 154.1, 134.5, 129.5, 126.8, 125.3, 124.4, 122.7, 122.5, 116.5; MS (ESI): *m/z* (%) 228 ([M+H]$^+$, 100).

*2-(4-Methoxyphenyl)benzothiazole (**3h**)*[5]



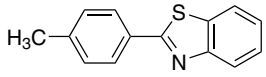
Yellow crystal, mp 120-121 °C (119-121 °C)[5]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04-8.07 (m, 3H, ArH), 7.90 (m, 1H, ArH), 7.48 (d, *J* 7.3 Hz, 1H, ArH), 7.37 (d, *J* 7.3 Hz, 1H, ArH), 7.01-7.04 (m, 2H, ArH), 3.90 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 162.1, 154.4, 135.1, 129.3, 126.6, 126.4, 125.0, 123.0, 121.7, 114.5, 55.6; MS (ESI): *m/z* (%) 242 ([M+H]$^+$, 100).

*2-(2-Methoxyphenyl)-benzothiazole (**3i**)*[1]



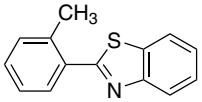
White crystal, mp 120-122 °C (not reported); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03-8.58 (m, 8H, ArH), 4.03 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 156.9, 151.9, 135.8, 131.4, 129.2, 125.6, 124.3, 122.5, 120.9, 120.8, 111.4, 55.4; MS (ESI): *m/z* (%) 242 ([M+H]$^+$, 100).

*2-(4-Methylphenyl)-benzothiazole (**3j**)*[4]



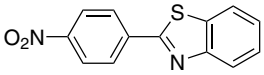
Yellow crystal, mp 85-86°C (84-85°C)[4]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* 8.0 Hz, 1H, ArH), 7.97 (d, *J* 8.0 Hz, 2H, ArH), 7.86 (d, *J* 8.0 Hz, 1H, ArH), 7.44-7.46 (m, 1H, ArH), 7.34-7.37 (m, 1H, ArH), 7.27 (d, *J* 8.0 Hz, 1H, ArH), 2.40 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 154.2, 141.4, 135.0, 131.0, 129.7, 127.5, 126.2, 125.0, 123.0, 121.5, 21.5; MS (ESI): *m/z* (%) 226 ([M+H]$^+$, 100).

*2-(2-Methylphenyl)-benzothiazole (**3k**)*[1]



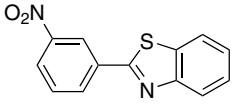
White crystal, mp 53-54 °C (53-54 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1 (d, *J* 8.0 Hz, 1H, ArH), 7.90 (d, *J* 8.0 Hz, 1H, ArH), 7.75 (d, *J* 7.6 Hz, 1H, ArH), 7.50 (d, *J* 7.6 Hz, 1H, ArH), 7.26-7.41 (m, 4H, ArH), 2.65 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 157.2, 152.1, 136.1, 131.7, 129.5, 125.8, 124.5, 122.7, 122.2, 121.2, 121.1, 111.6, 55.6; MS (ESI): *m/z* (%) 226 ([M+H]$^+$, 100).

*2-(4-Nitrophenyl)-benzothiazole (**3l**)*[5]



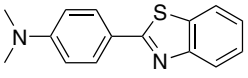
Yellow crystal, mp 231-232 °C (229-230 °C)[5]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-8.38 (m, 8H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 154.1, 149.0, 139.1, 135.5, 128.2, 126.9, 126.2, 124.3, 123.9, 121.8; MS (ESI): *m/z* (%) 257 ([M+H]$^+$, 100).

*2-(3-Nitrophenyl)-benzothiazole (**3m**)*[6]



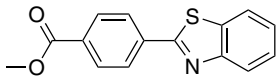
Yellow crystal, mp 185-186 °C (183-185 °C)[6]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-8.95 (m, 8H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 153.8, 148.6, 135.2, 135.1, 132.9, 130.0, 126.8, 126.0, 125.1, 123.7, 122.2, 121.8; MS (ESI): *m/z* (%) 257 ([M+H]$^+$, 100).

*2-(4-N,N-dimethylaminophenyl)benzothiazole (**3n**)*[4]



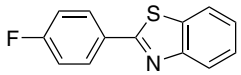
Brown crystal, mp 173-175 °C (176-178 °C)[4]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, *J* 7.0 Hz, *J* 2.0 Hz, 3H, ArH), 7.83-7.86 (m, 1H, ArH), 7.42-7.45 (m, 1H, ArH), 7.3.-7.33 (m, 1H, ArH), 6.74 (dd, *J* 2.0 Hz, *J* 7.0 Hz, 2H, ArH), 3.05 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 154.4, 152.1, 134.5, 128.8, 125.9, 124.1, 122.2, 121.3, 111.6, 40.1; MS (ESI): *m/z* (%) 255 ([M+H]$^+$, 100).

*2-(4-Methoxycarbonylphenyl) benzothiazole (**3o**)*[7]



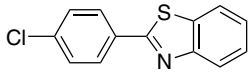
White crystal, mp 166-167 °C (166 °C)[7]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07-8.12 (m, 5H, ArH), 7.87-7.89 (m, 1H, ArH), 7.39-7.50 (m, 2H, ArH), 3.94 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 166.3, 150.4, 137.3, 135.2, 131.9, 130.1, 127.3, 126.5, 125.6, 123.5, 121.6, 52.25; MS (ESI): *m/z* (%) 270 ([M+H]$^+$, 100).

*2-(4-Fluorophenyl)benzothiazole (**3p**)*[5]



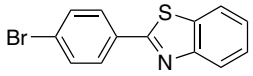
White crystal, mp 98-100 °C (98-99 °C)[5]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-8.07 (m, 3H, ArH), 7.85 (d, *J* 8.0 Hz, 1H, ArH), 7.47 (d, *J* 7.7 Hz, 1H, ArH), 7.35 (d, *J* 7.7 Hz, 1H, ArH), 7.15 (t, *J* 8.0 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 163.0 (d, $^1J_{C\text{-}F}$ 250.3Hz), 154.3, 135.2, 130.1, 129.7 (d, $^3J_{C\text{-}F}$ 7.0 Hz), 129.6, 125.4, 123.4 (d, $^4J_{C\text{-}F}$ 2.9 Hz), 121.7, 116.3 (d, $^2J_{C\text{-}F}$=22.0 Hz); MS (ESI): *m/z* (%) 230 ([M+H]$^+$, 100).

*2-(4-Chlorophenyl)benzothiazole (**3q**)*[8]



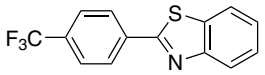
Yellow crystal, mp 113-114°C (113°C)[8]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-8.06 (m, 4H, ArH), 7.35-7.51 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 154.3, 137.2, 135.3, 132.3, 129.5, 128.9, 126.7, 125.6, 123.5, 121.8; MS (ESI): *m/z* (%) 246 ([M+H]$^+$, 100), 248 ([M+2+H]$^+$, 35).

*2-(4-Bromophenyl)benzothiazole (**3r**)*[5]



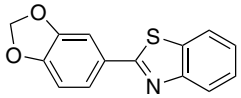
Yellow crystal, mp 131-132 °C (130-131 °C)[5]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-8.08 (m, 8H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 154.1, 135.0, 132.5, 132.2, 128.9, 126.5, 125.5, 125.4, 123.3, 121.6; MS (ESI): *m/z* (%) 291 ([M+H]$^+$, 100), 289 ([M+2+H]$^+$, 97).

*2-(4-(Trifluoromethyl) phenyl) benzothiazole (**3s**)*[9]



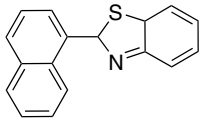
Yellow crystal, mp 160-162 °C (not reported); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08-8.18 (m, 3H, ArH), 7.90(d, *J* 8.1 Hz, 1H, ArH), 7.70 (d, *J* 8.1 Hz, 2H, ArH), 7.39-7.7.54 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 153.9, 136.6, 135.1, 132.3 (q, $^2J_{C\text{-}F}$ 32.8Hz, *C*-CF_3), 127.7, 126.6, 125.8 (q, $^3J_{C\text{-}F}$ 3.8 Hz, *C*H-C-CF_3), 125.7, 124.6 (q, $^1J_{C\text{-}F}$ 270.1 Hz, CF_3), 123.5, 121.7; MS (ESI): *m/z* (%) 280 ([M+H]$^+$, 100).

*2-(Benzo[1, 3] dioxol-5-yl)benzothiazole (**3t**)*[4]



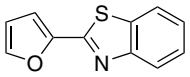
Yellow crystal, mp 125-127 °C (127-128 °C)[4]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* 8.1 Hz, 1H, ArH), 7.90 (d, *J* 8.1 Hz, 1H, ArH), 7.60-7.63 (m, 2H, ArH), 7.46-7.49 (m, 1H, ArH), 7.38-7.41 (m, 1H, ArH), 7.00 (d, *J* 7.8 Hz, 1H, ArH), 6.08 (s, 2H, OCH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 154.1, 150.1, 148.4, 134.9, 128.0, 126.2, 124.9, 122.9, 122.5, 121.5, 108.6, 107.5, 101.7; MS (ESI): *m/z* (%) 256 ([M+H]$^+$, 100).

*2-(Naphthalen-1-yl)benzothiazole (**3u**)*[4]



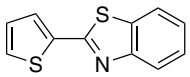
White crystal, mp 125-127°C (126 °C)[4]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (d, *J* 8.3 Hz, 1H, ArH), 8.23 (d, *J* 7.8 Hz, 1H, ArH), 7.95-8.03 (m, 4H, ArH), 7.58-7.63 (m, 4H, ArH), 7.48-7.56 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 154.2, 135.5, 134.1, 131.1, 130.9, 130.7, 129.5, 128.5, 127.7, 126.6, 126.3, 126.0, 125.3, 125.0, 123.6, 121.5; MS (ESI): *m/z* (%) 264 ([M+H]$^+$, 100).

*2-(Furan-2-yl)benzothiazole (**3v**)*[4]



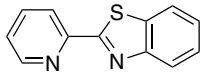
Yellow crystal, mp 102-104 °C (103 °C)[4]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* 8.1 Hz, 1H, ArH), 7.90 (d, *J* 8.1 Hz, 1H, ArH), 7.60 (s, 1H, ArH), 7.46-7.51 (m, 1H, ArH), 7.35-7.40 (m, 1H, ArH), 7.18-7.19 (m, 1H, ArH), 6.59-6.60(m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 153.9, 140.9, 144.9, 134.5, 126.6, 125.3, 123.3, 121.7, 112.7, 111.6; MS (ESI): *m/z* (%) 202 ([M+H]$^+$, 100).

*2-(Thiophen-2-yl)benzothiazole (**3w**)*[1]



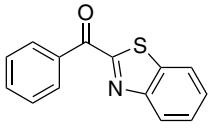
White crystal, mp 99-100 °C (99 °C)[1]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02-8.05 (m, 1H, ArH), 7.84-7.87 (m, 1H, ArH), 7.66 (dd, *J* 3.6 Hz, *J* 1.2 HZ, 1H, ArH), 7.48-7.52 (m, 2H, ArH), 7.37-7.39 (m, 1H, ArH), 7.14 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 153.7, 137.3, 134.7, 129.3, 128.6, 128.0, 126.4, 125.2, 122.9, 121.4; MS (ESI): *m/z* (%) 218 ($[M+H]^+$, 100).

*2-(Pyridin-2-yl) benzothiazole (**3x**)*[4]



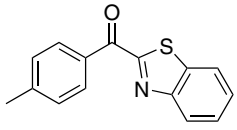
White crystal, mp 136-137 °C (136-137 °C)[4]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64-8.65 (m, 1H, ArH), 8.32-8.35 (m, 1H, ArH), 8.05-8.08 (m, 1H, ArH), 7.91-7.93 (m, 1H, ArH), 7.76-7.79 (m, 1H, ArH), 7.32-7.47 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$,) δ 169.5, 154.5, 151.6, 149.8, 137.1, 136.3, 126.4, 125.8, 125.4, 123.8, 122.2, 120.9; MS (ESI): *m/z* (%) 213 ($[M+H]^+$, 100).

*2-Benzoylbenzothiazole (**4a**)*[10]



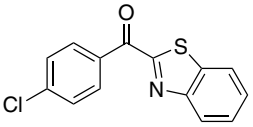
Yellow crystal, mp 98-99 °C (98-99 °C)[10]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55-8.59 (m, 2H, ArH), 8.24-8.27 (m, 1H, ArH), 8.02-8.05 (m, 1H, ArH), 7.54-7.71 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.7, 167.4, 154.2, 137.3, 135.3, 134.2, 131.6, 128.9, 128.0, 127.3, 126.1, 122.5; MS (ESI): *m/z* (%) 240 ($[M+H]^+$, 100).

*2-(4-Methylbenzoyl) benzothiazole (**4b**)*[11]



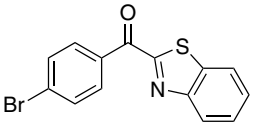
Yellow crystal; mp 96-98 °C (not reported); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47-8.50 (m, 2H, ArH), 8.23-8.26 (m, 1H, ArH), 8.01-8.04 (m, 1H, ArH), 7.52-7.62 (m, 2H, ArH), 7.37 (d, *J* 7.8 Hz, 2H, ArH), 2.47 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 167.4, 153.8, 145.0, 136.9, 132.3, 131.4, 129.2, 127.4, 126.8, 125.6, 122.1, 21.8; MS (ESI): *m/z* (%) 254 ($[M+H]^+$, 100).

*2-(4-chlorobenzoyl)benzothiazole (**4c**)*[12]



White crystal, mp 100-102°C (102-103°C)[12]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.54-8.59 (m, 2H, ArH), 8.23-8.27 (m, 1H, ArH), 8.02-8.05 (m, 1H, ArH), 7.53-7.64 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.9, 166.7, 153.7, 140.5, 137.0, 133.1, 132.7, 128.8, 127.7, 127.0, 125.7, 122.1; MS (ESI): *m/z* (%) 274 ($[M+H]^+$, 100), 276 ($[M+2+H]^+$, 34).

*2-(4-Bromobenzoyl)benzothiazole (**4d**)*[11]



Yellow crystal, mp 123-124 °C (not reported); ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.46-8.49 (m, 2H, ArH), 8.23-8.26 (m, 1H, ArH), 8.02-8.07 (m, 1H, ArH), 7.70-7.73 (m, 2H, ArH), 7.56-7.61 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1, 166.7, 153.8, 137.0, 133.6, 132.7, 131.8, 129.5, 127.8, 127.0, 125.7, 122.2; MS (ESI): *m/z* (%) 317 ($[M+H]^+$, 100), 319 ($[M+2+H]^+$, 98).

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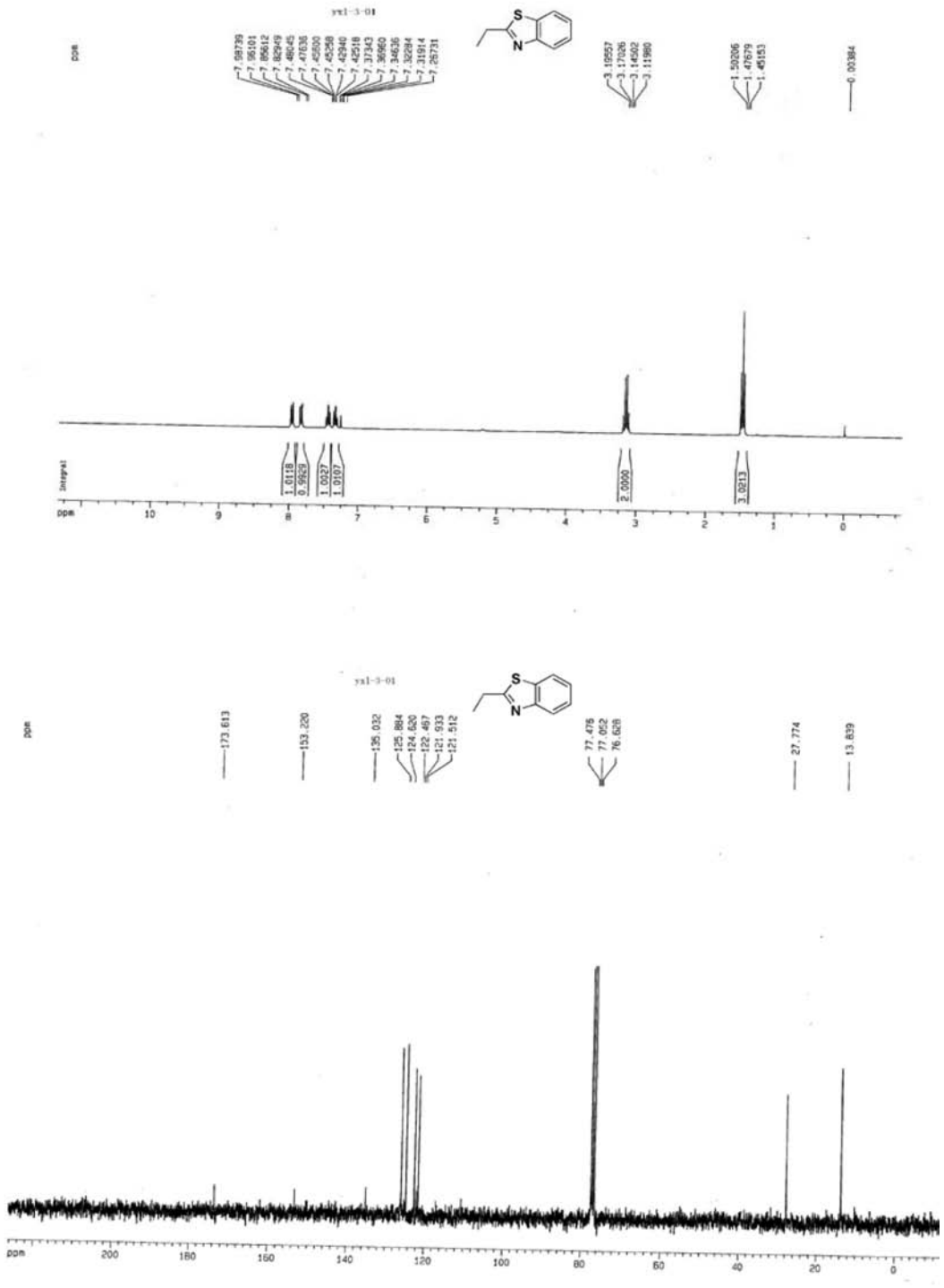

Figure S1. ^{1}H NMR of **3a** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3a** (75 MHz, $CDCl_3$).

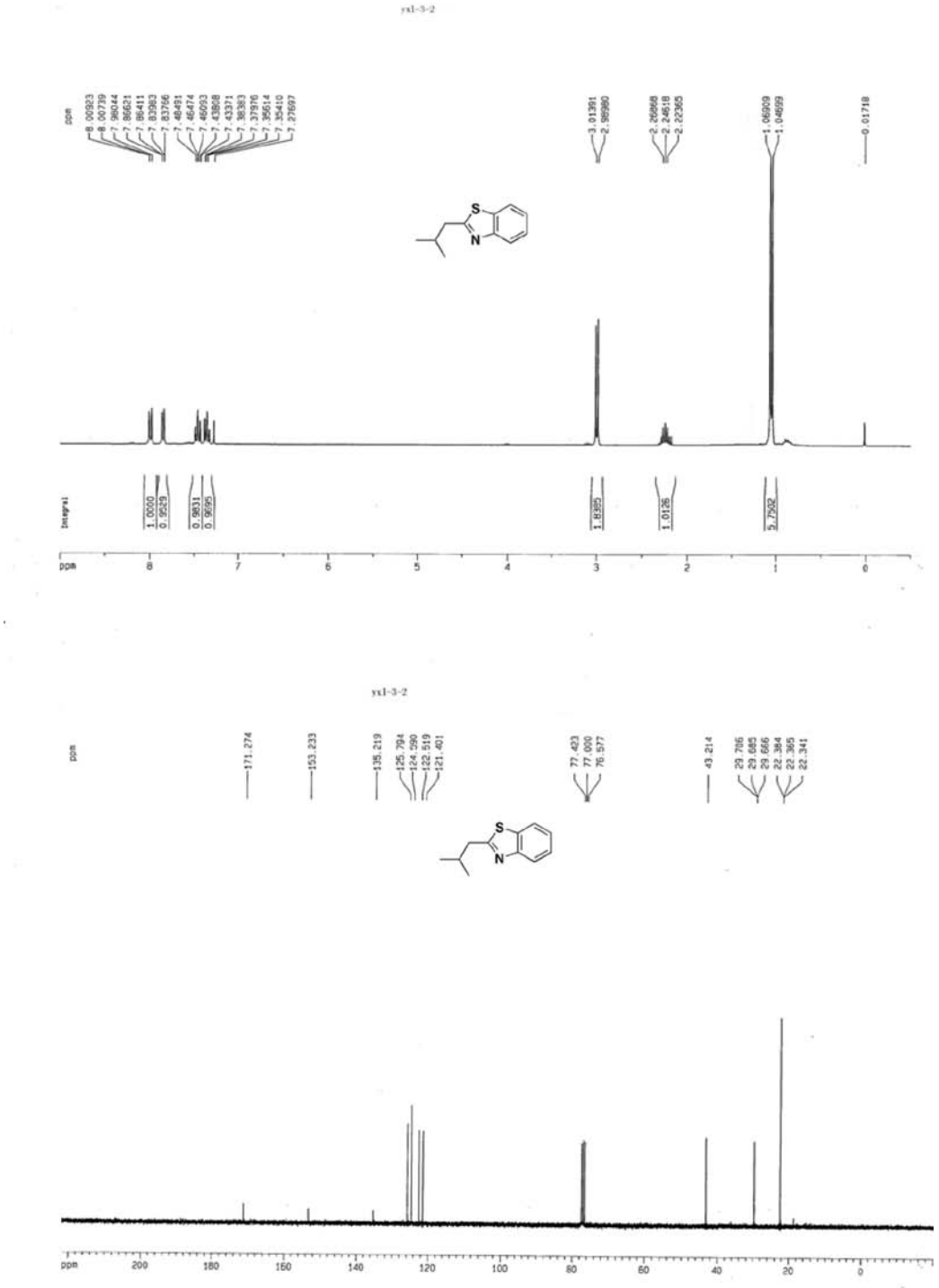

Figure S2. ^{1}H NMR of **3b** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3b** (75 MHz, $CDCl_3$).

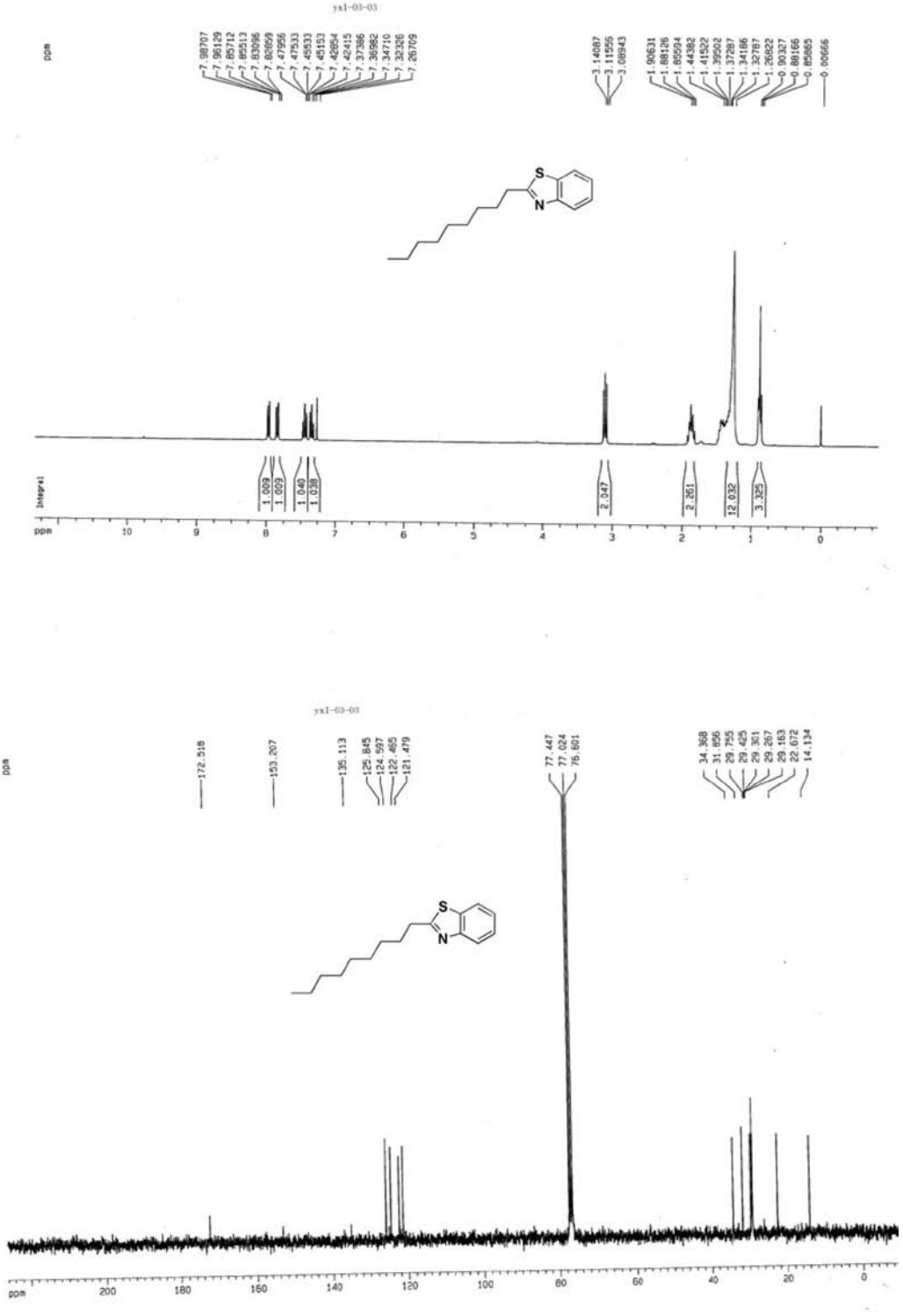

Figure S3. ^{1}H NMR of **3c** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3c** (75 MHz, $CDCl_3$).

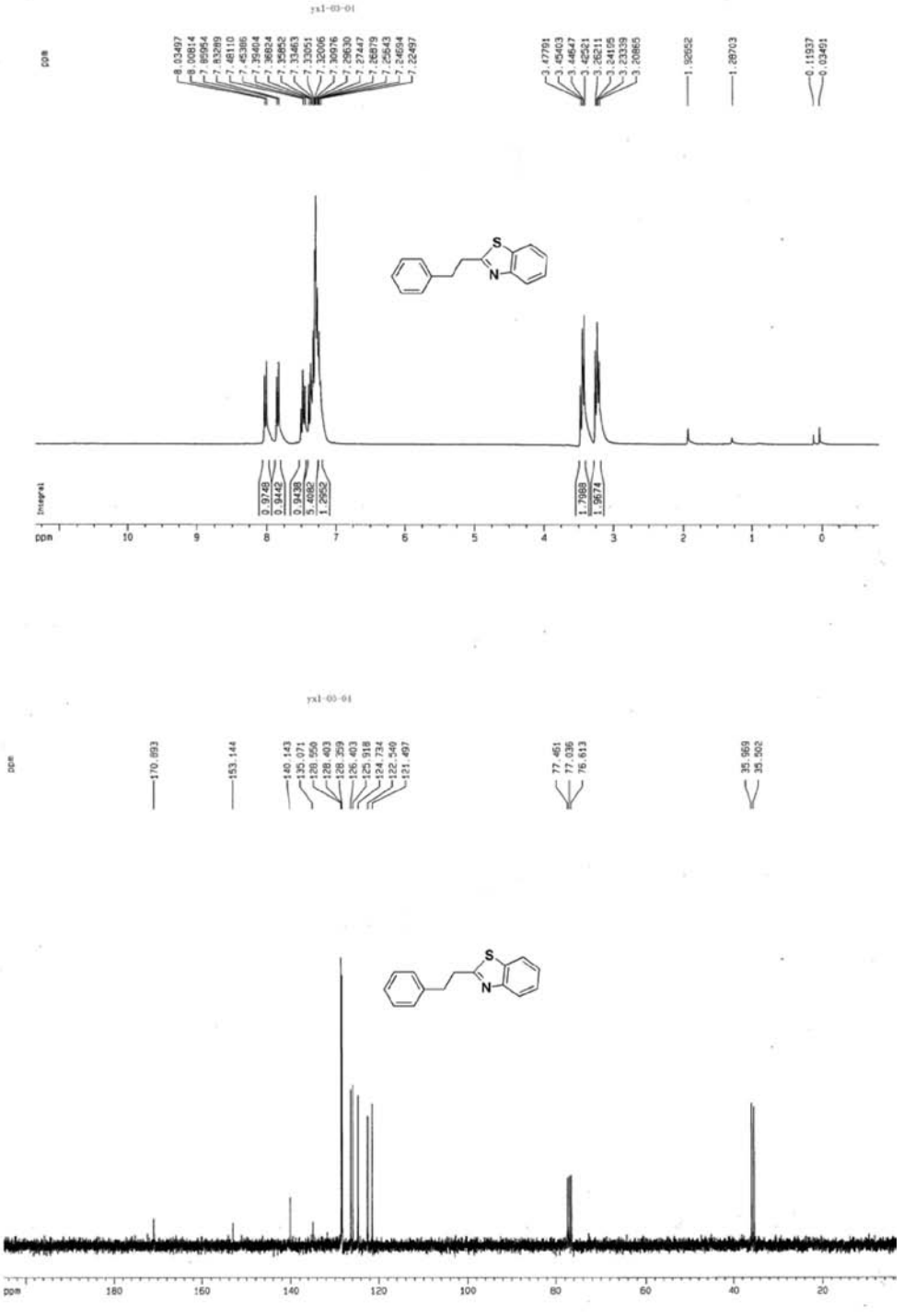

Figure S4. ^{1}H NMR of **3d** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3d** (75 MHz, $CDCl_3$).

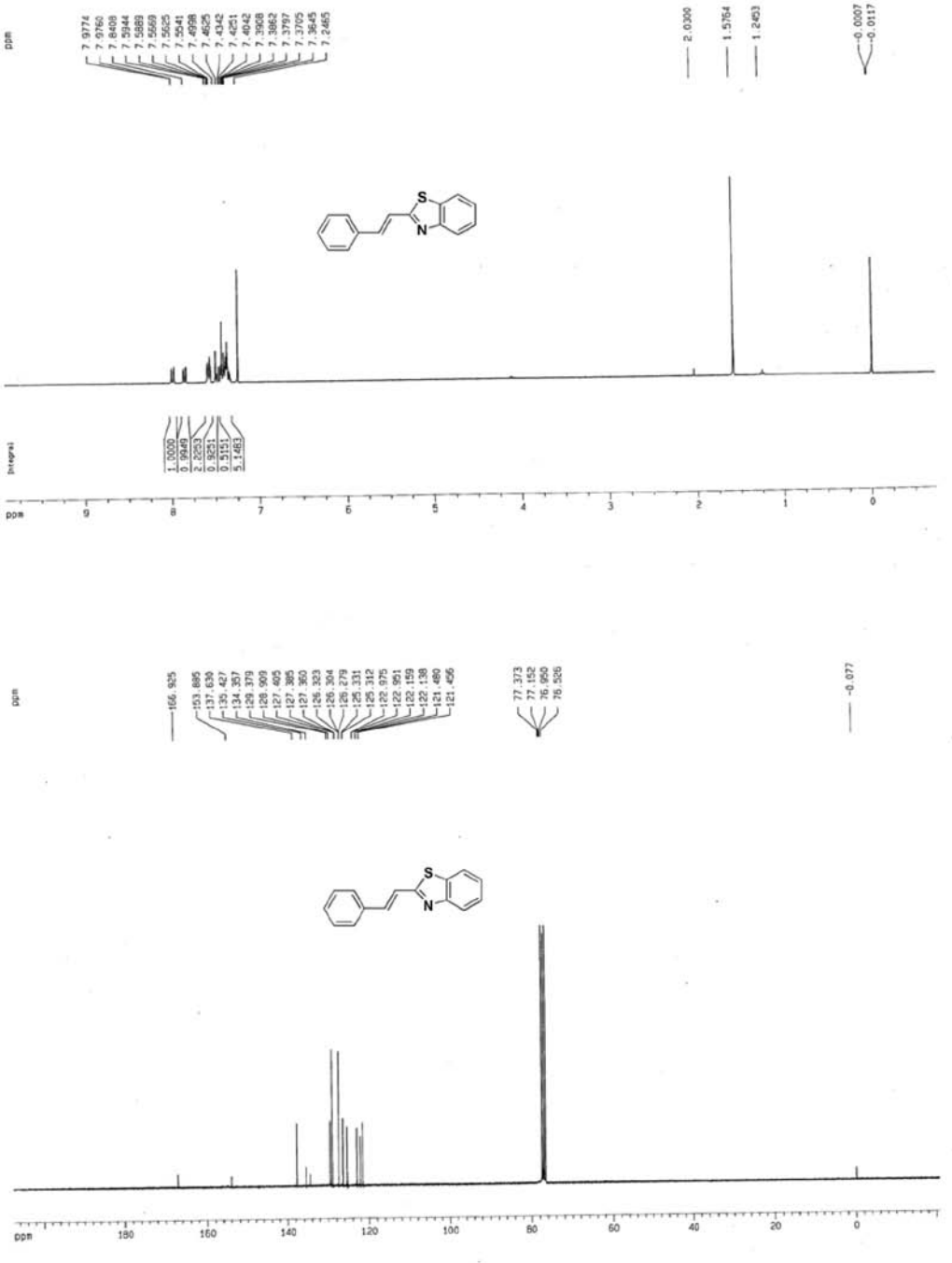

Figure S5. ^{1}H NMR of **3e** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3e** (75 MHz, $CDCl_3$).

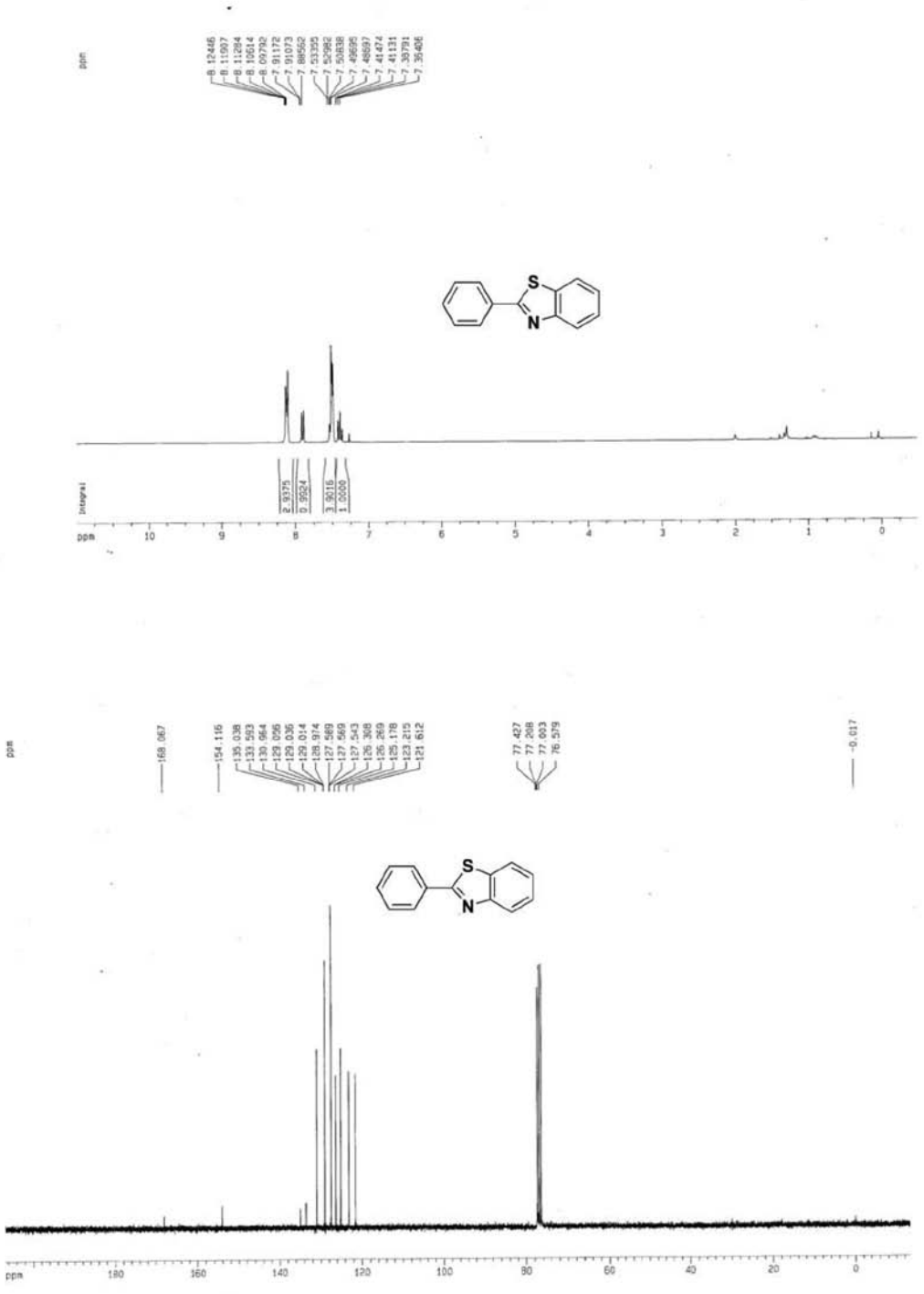

Figure S6. ^{1}H NMR of **3f**(300 MHz, $CDCl_3$) and ^{13}C NMR of **3f** (75 MHz, $CDCl_3$).

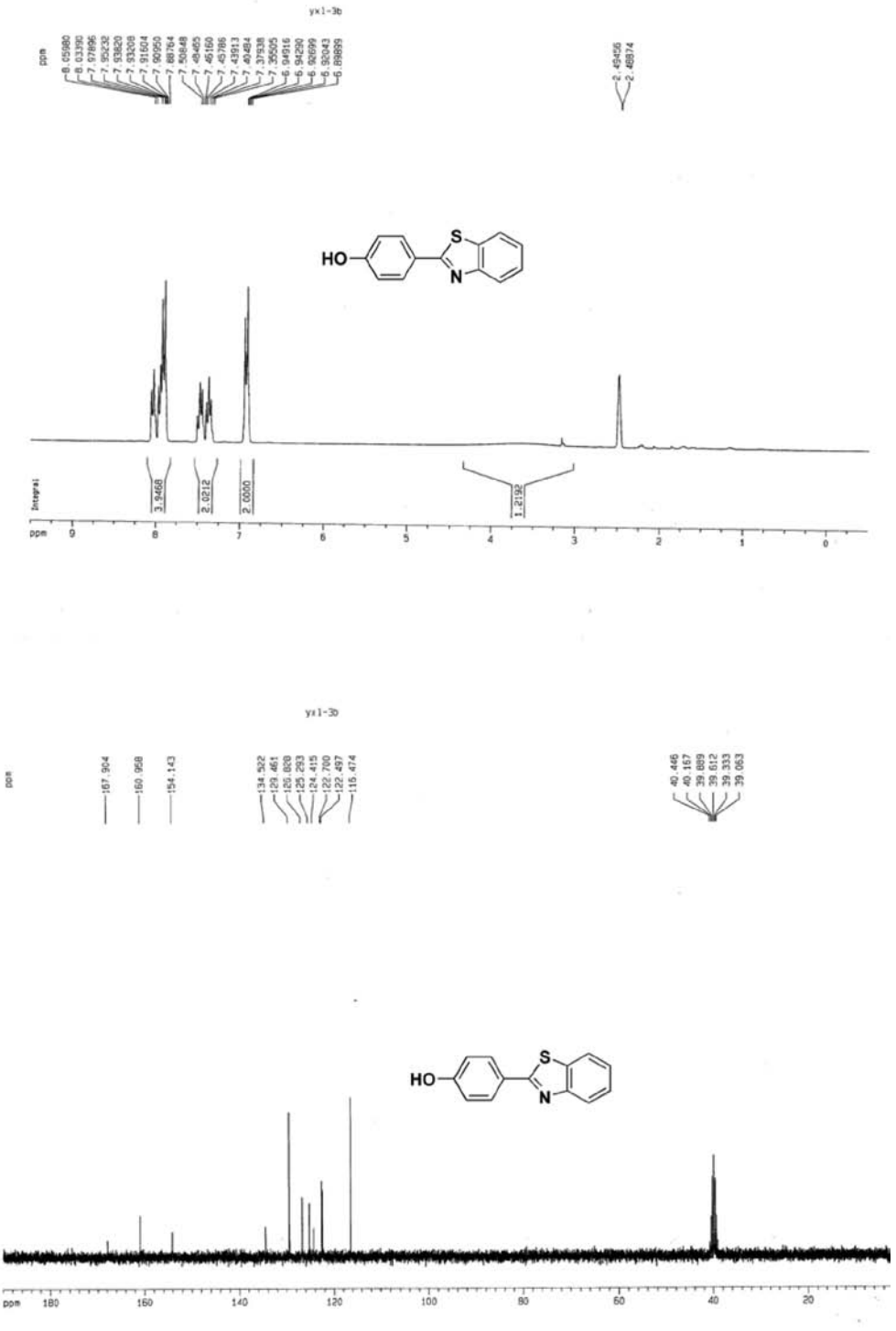

Figure S7. ^{1}H NMR of **3g** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3g** (75 MHz, $CDCl_3$).

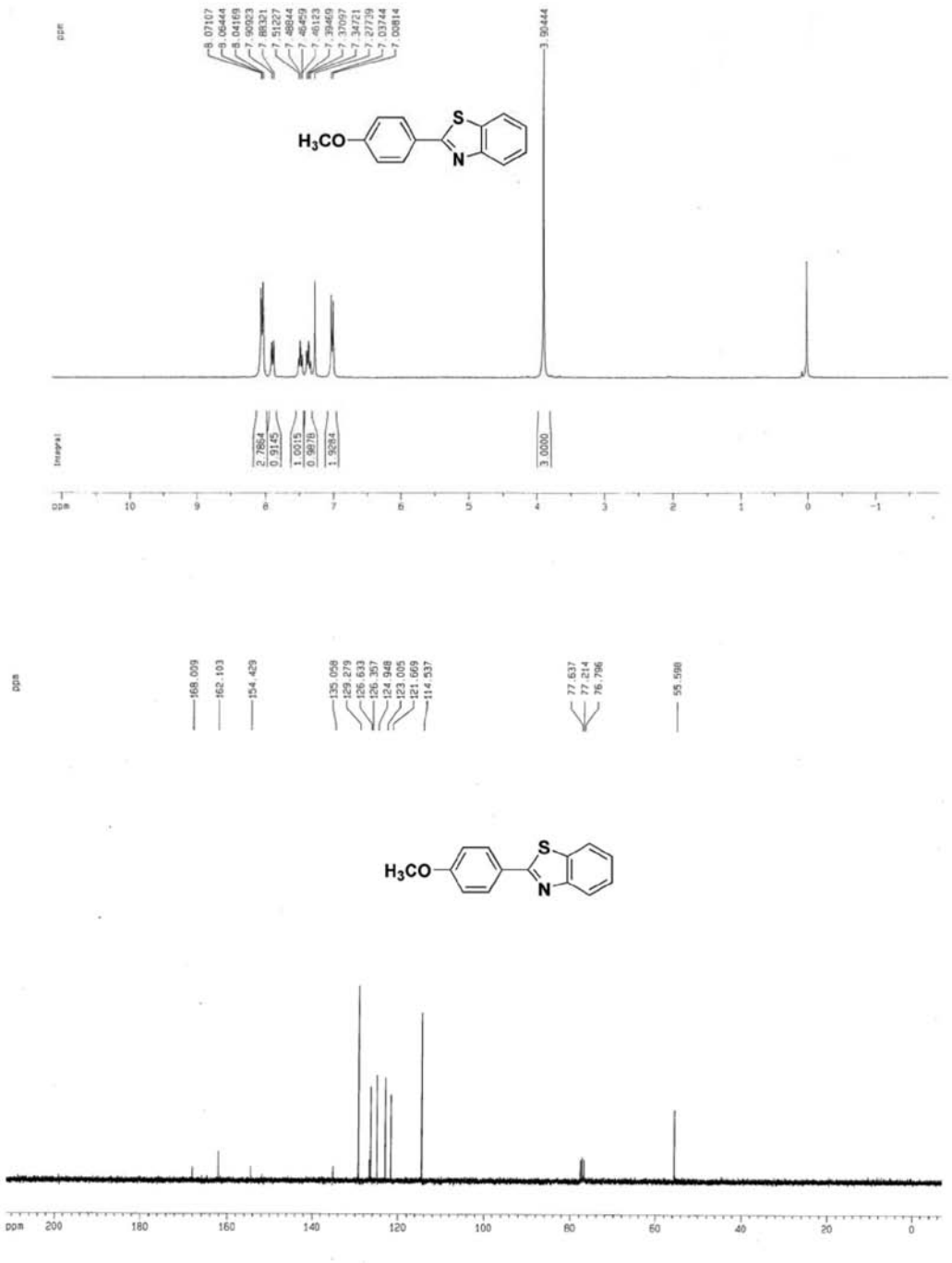

Figure S8. ^{1}H NMR of **3h** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3h** (75 MHz, $CDCl_3$).

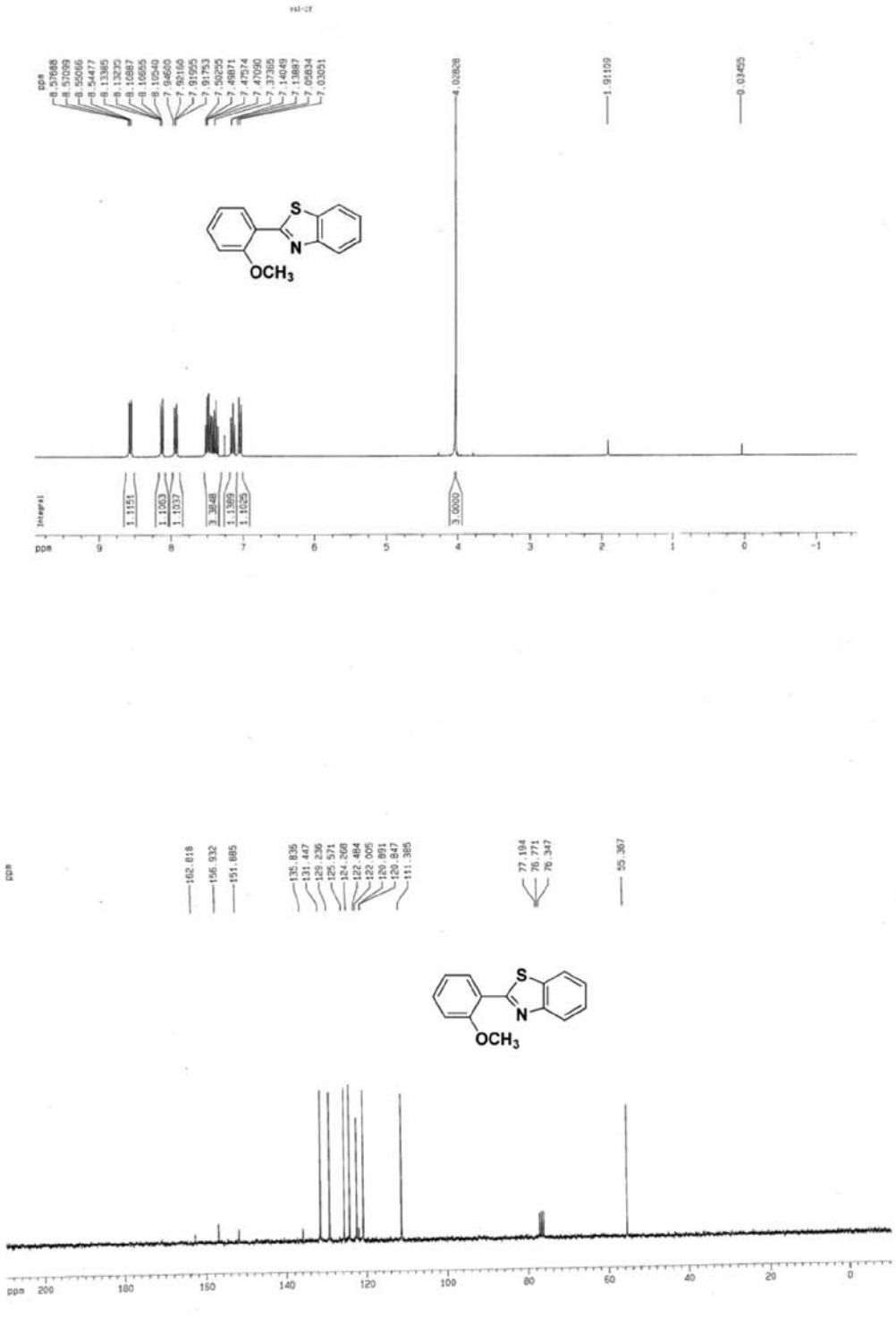

Figure S9. ^{1}H NMR of **3i** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3i** (75 MHz, $CDCl_3$).

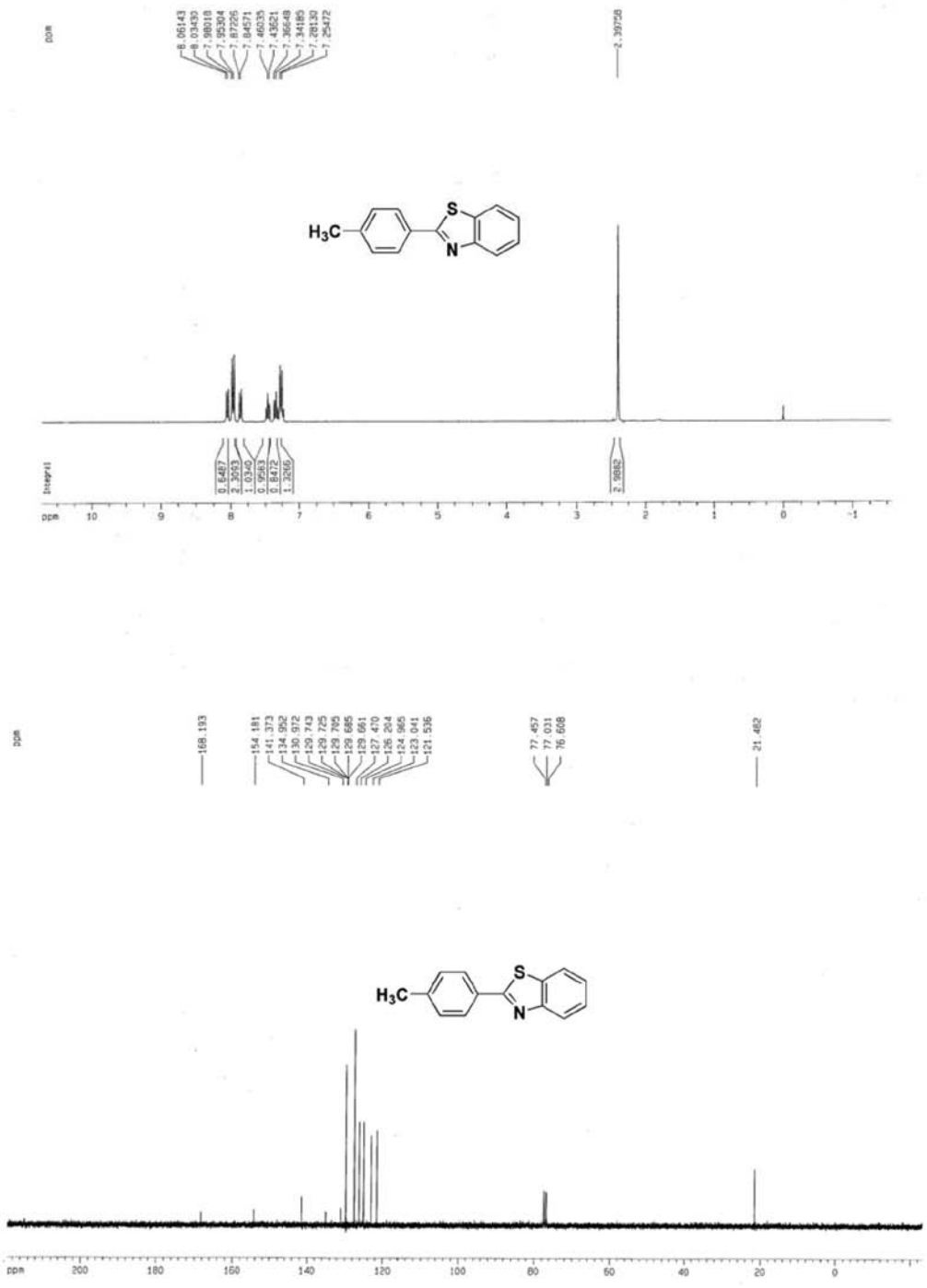

Figure S10. [1]H NMR of **3j** (300 MHz, $CDCl_3$) and [13]C NMR of **3j** (75 MHz, $CDCl_3$).

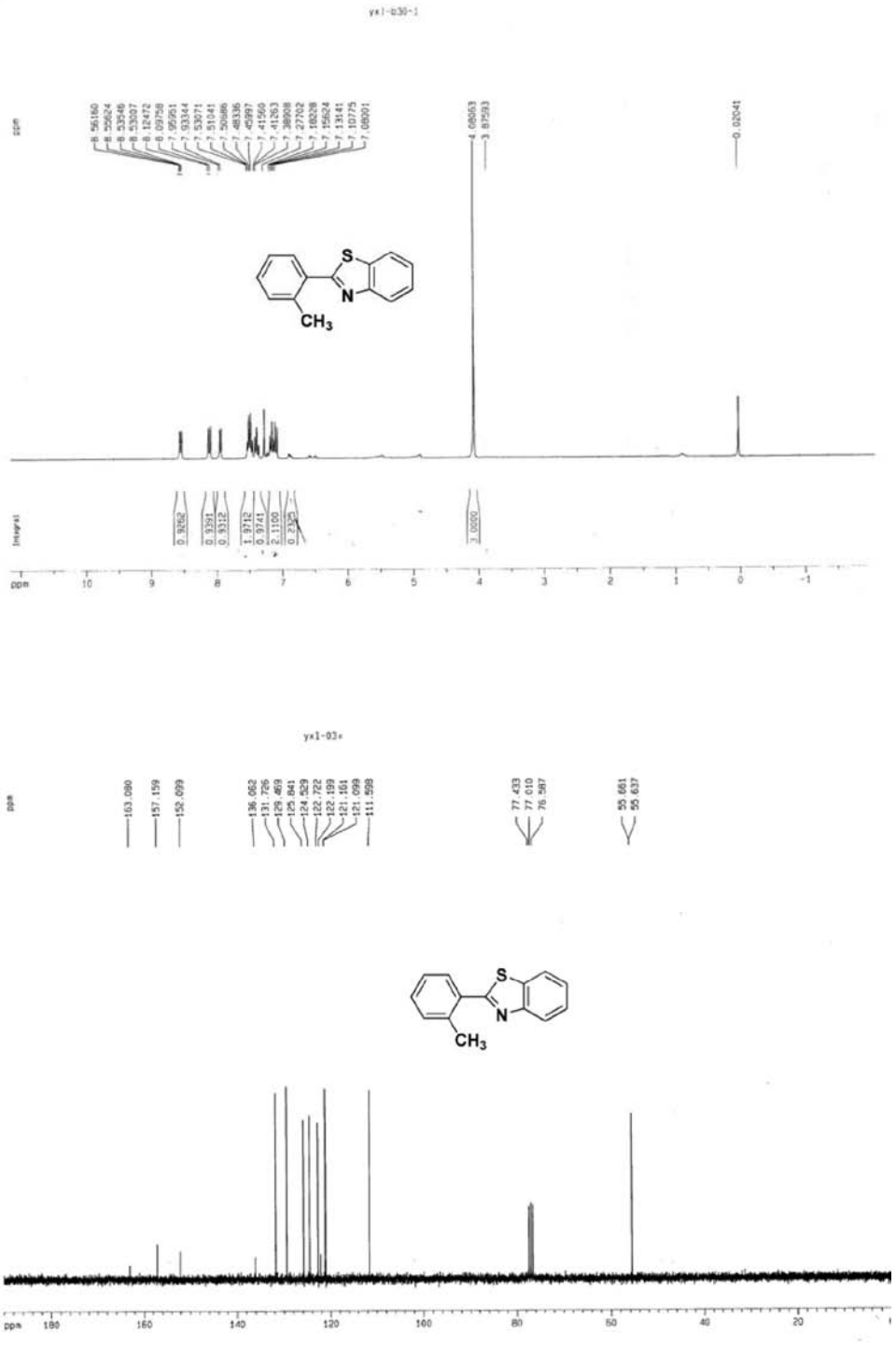

Figure S11. ^{1}H NMR of **3k** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3k** (75 MHz, $CDCl_3$).

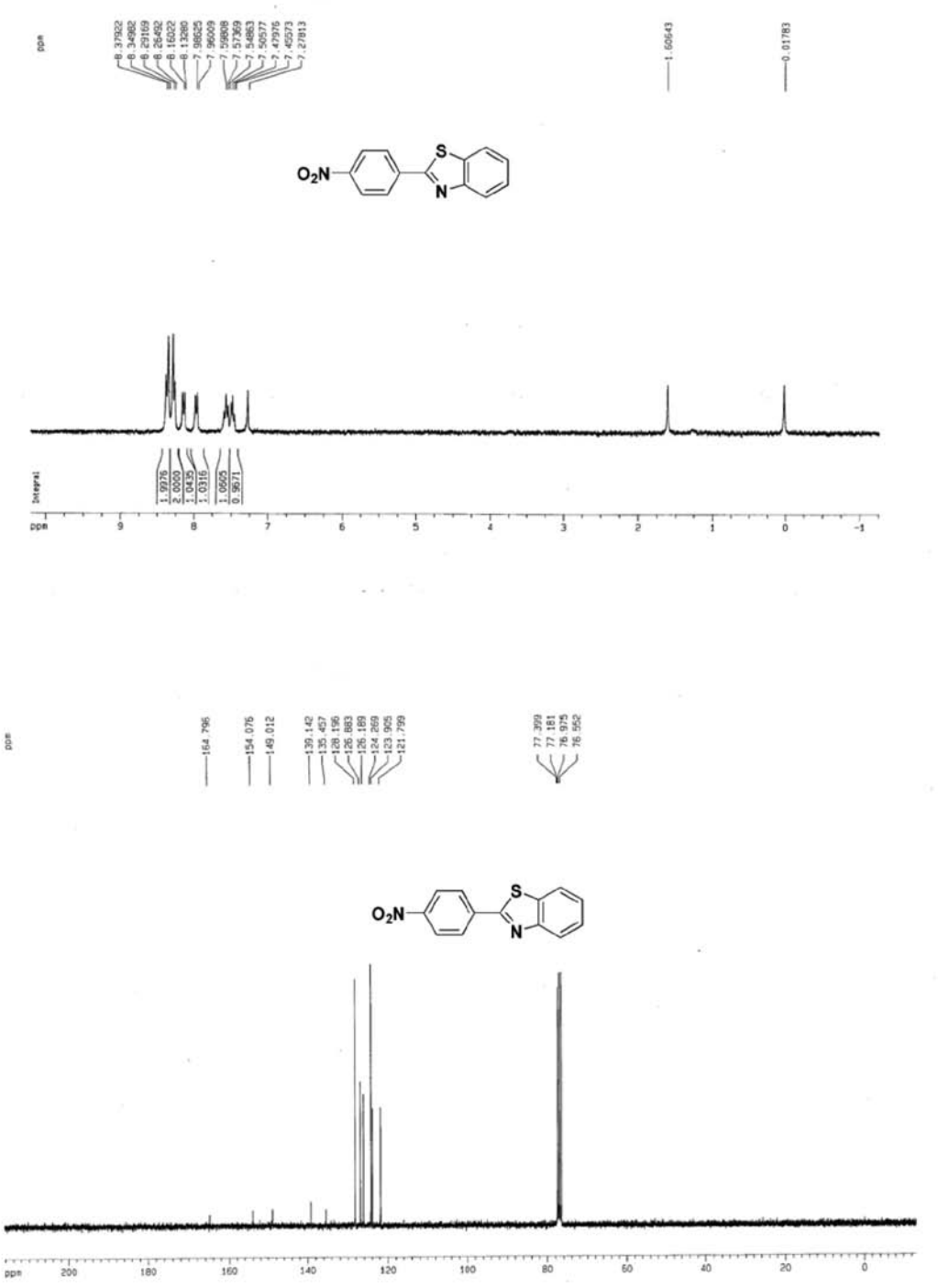

Figure S12. ^{1}H NMR of **3l** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3l** (75 MHz, $CDCl_3$).

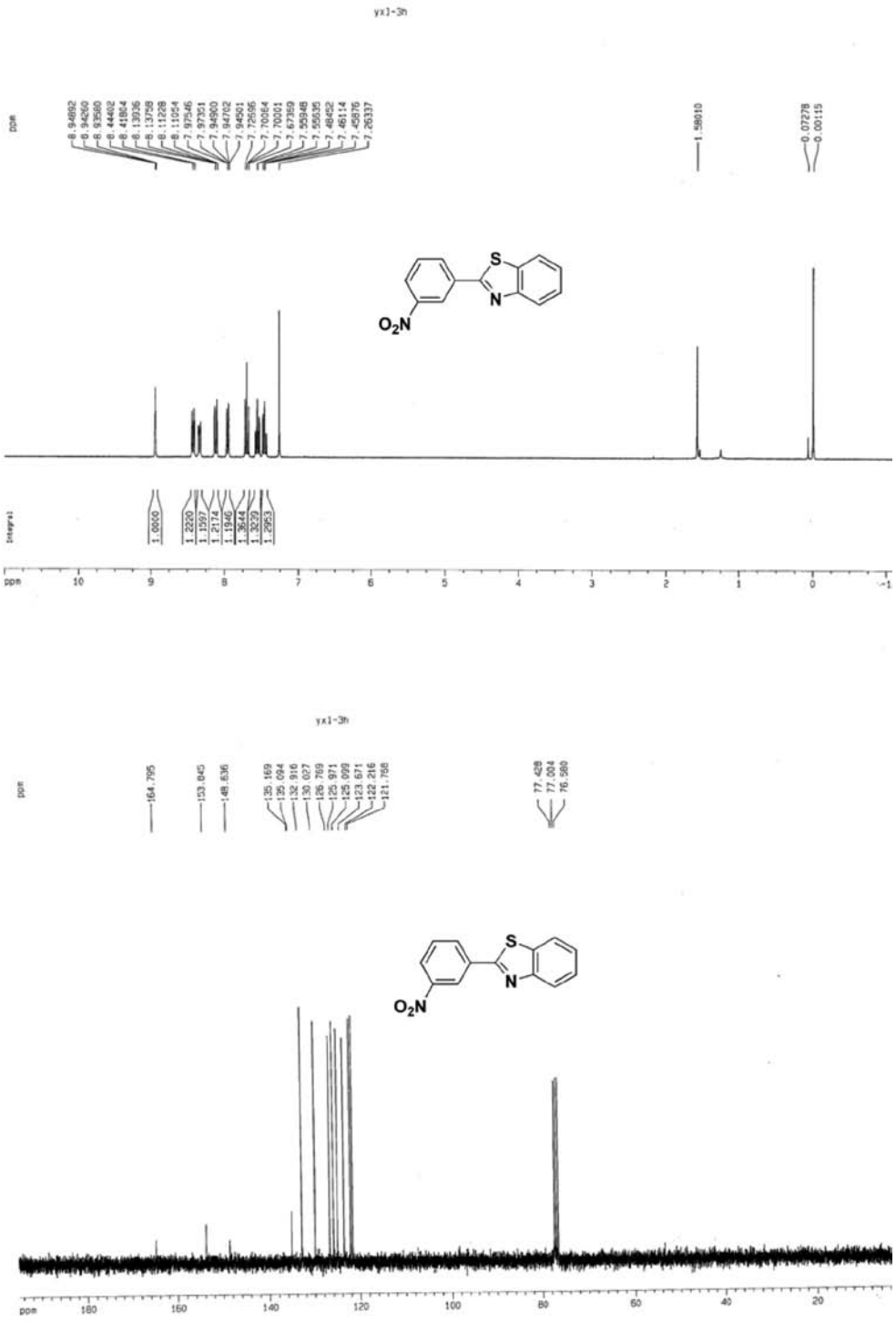

Figure S13. ^{1}H NMR of **3m** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3m** (75 MHz, $CDCl_3$).

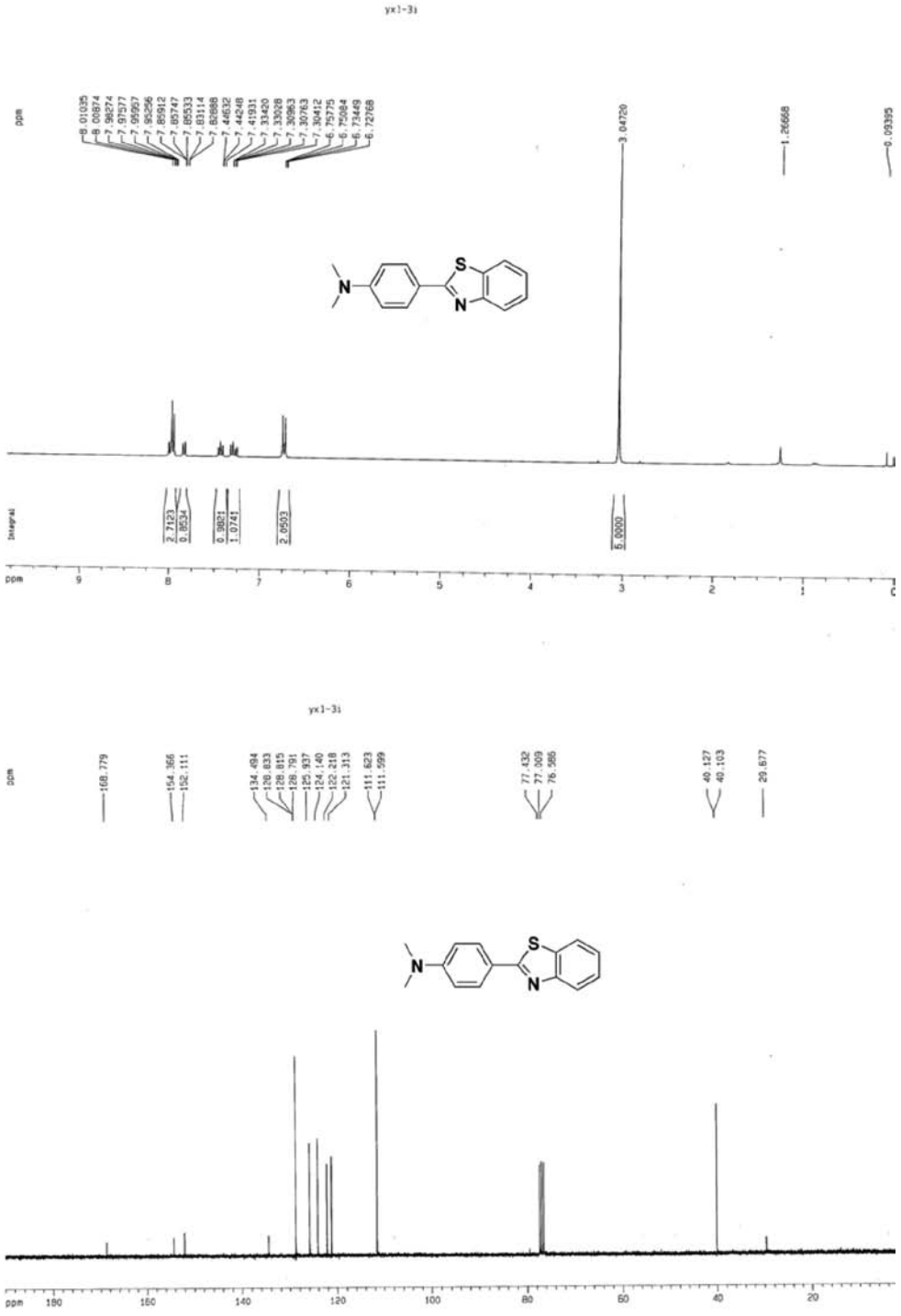

Figure S14. ^{1}H NMR of **3n** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3n** (75 MHz, $CDCl_3$).

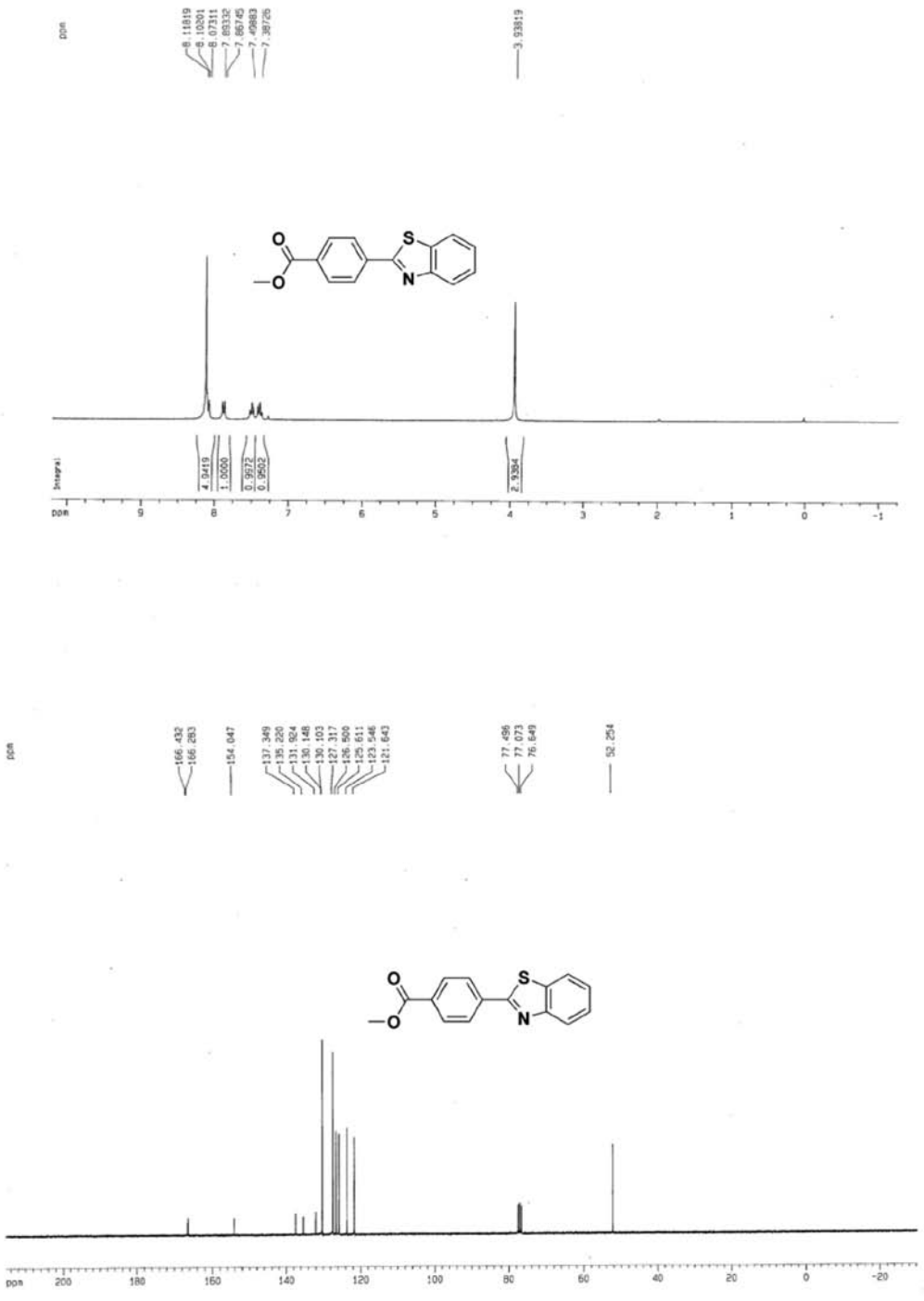

Figure S15. ^{1}H NMR of **3o** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3o** (75 MHz, $CDCl_3$).

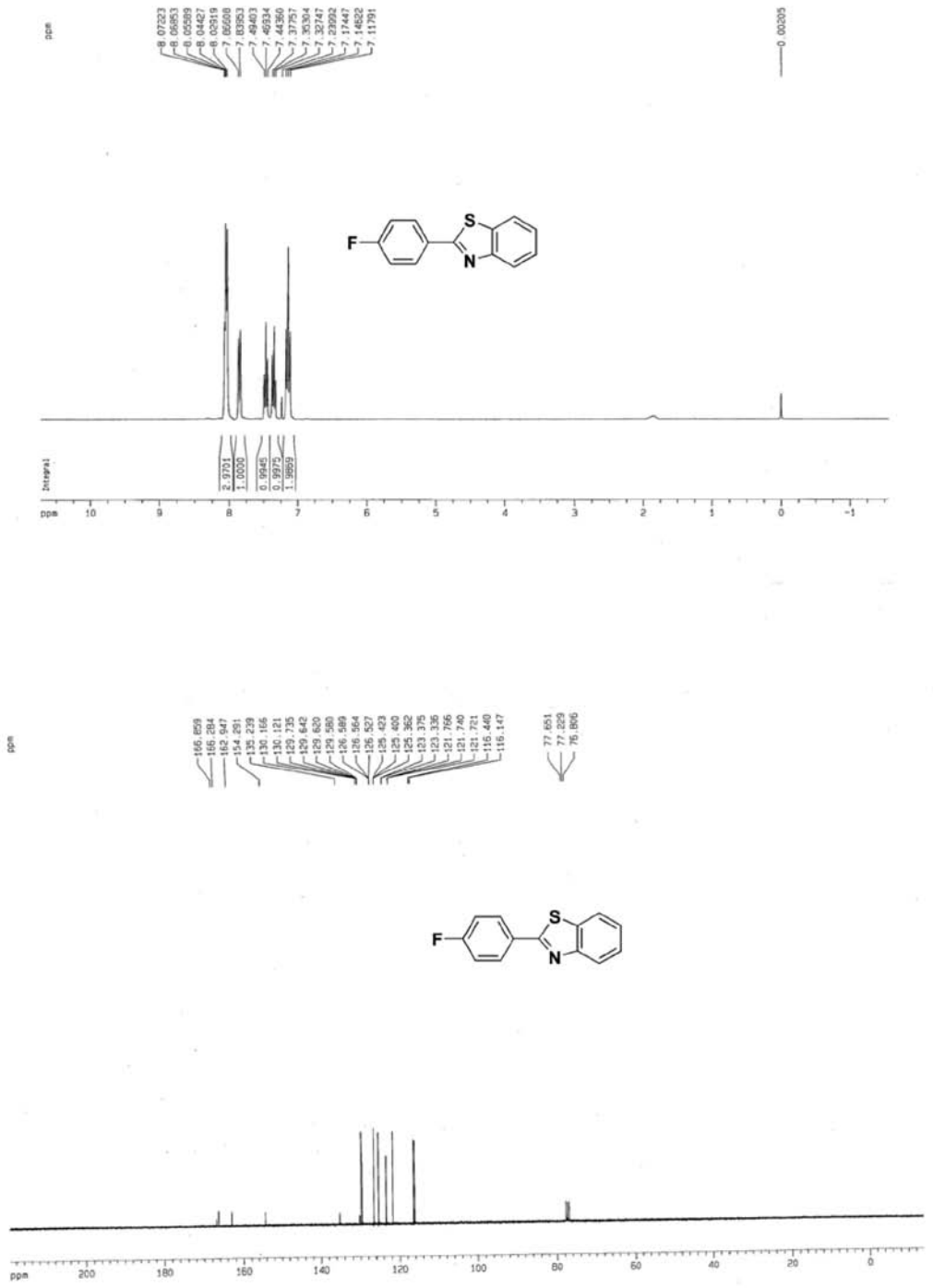

Figure S16. [1]H NMR of **3p** (300 MHz, $CDCl_3$) and [13]C NMR of **3p** (75 MHz, $CDCl_3$).

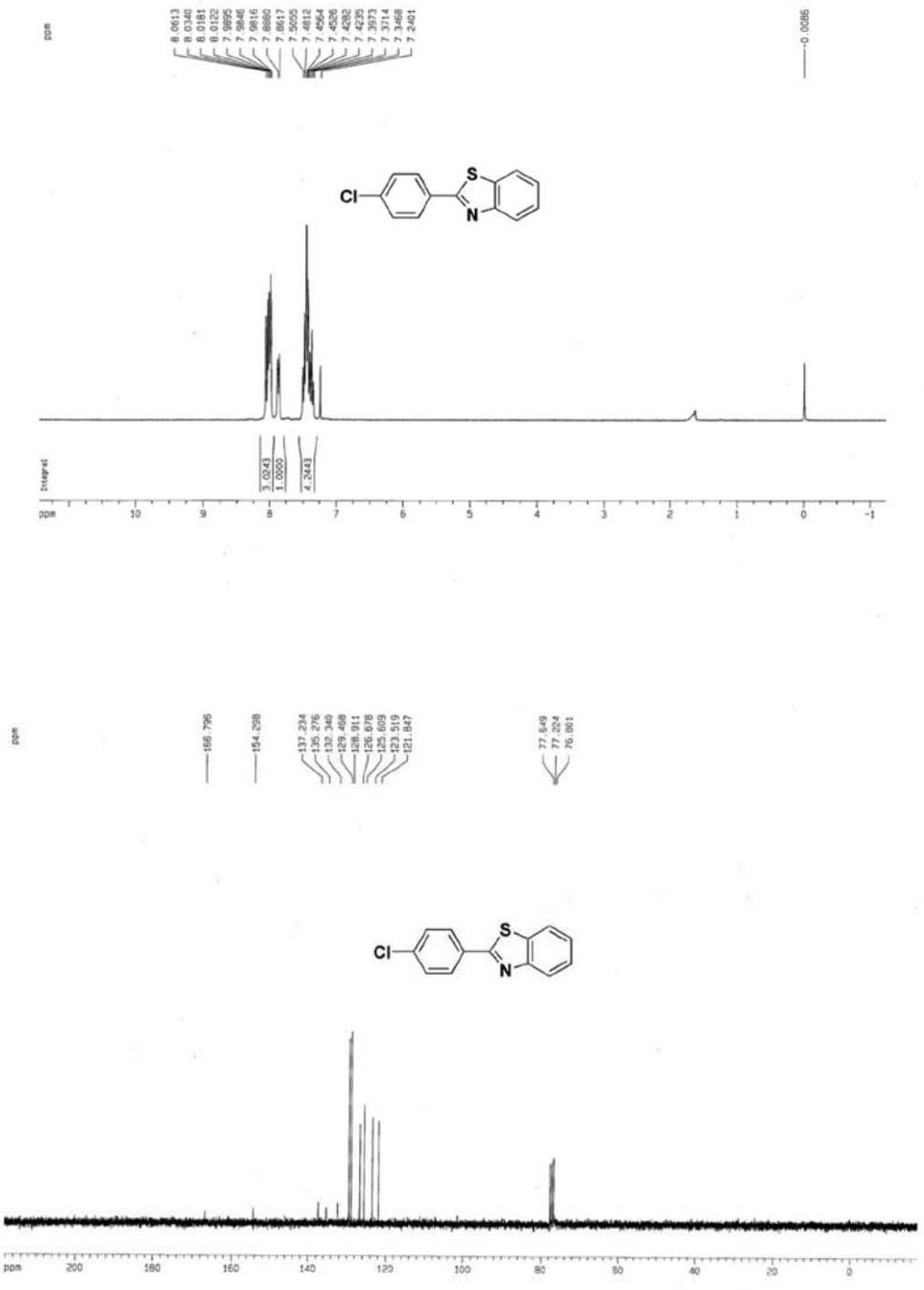

Figure S17. ^{1}H NMR of **3q**(300 MHz, $CDCl_3$) and ^{13}C NMR of **3q** (75 MHz, $CDCl_3$).

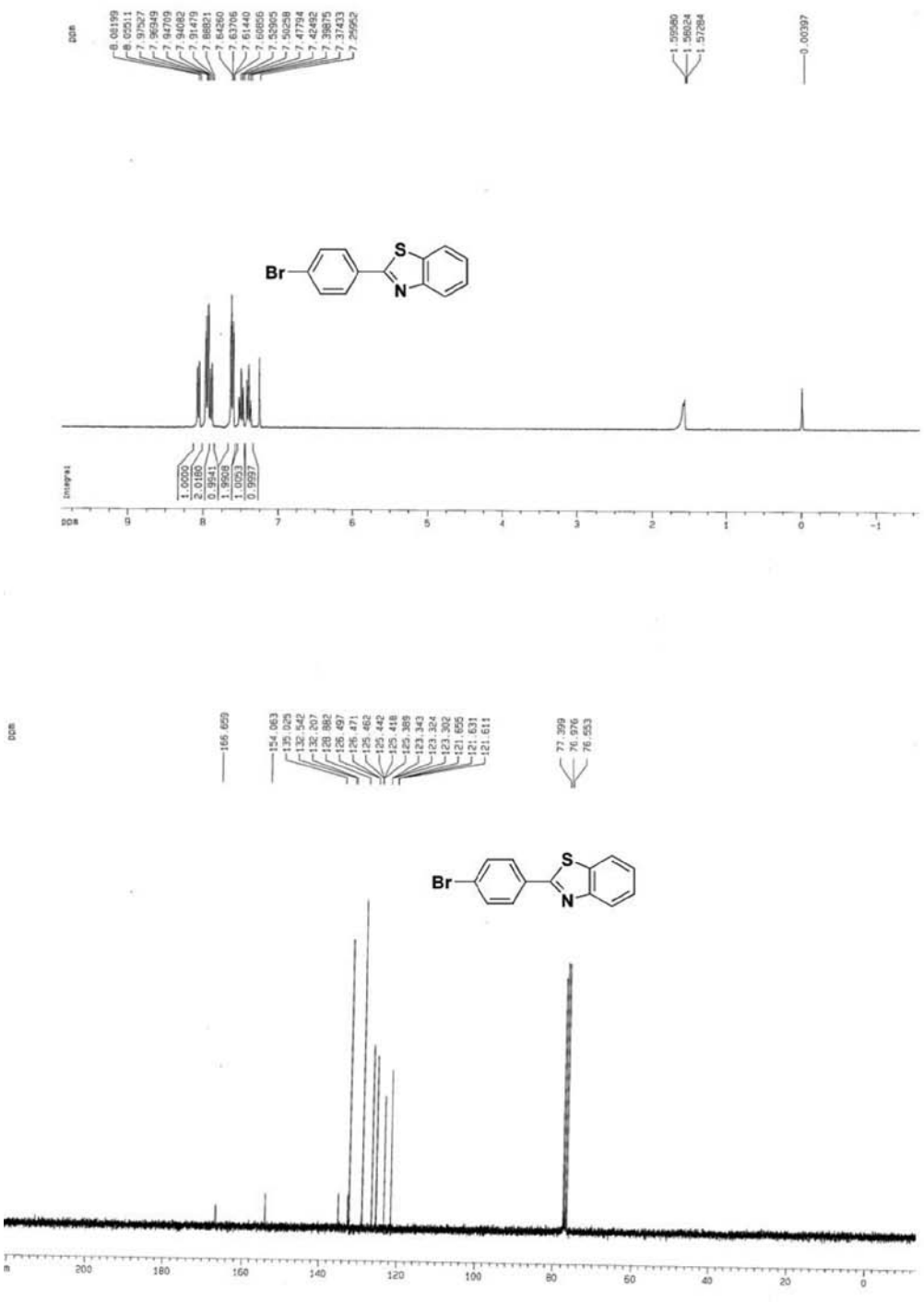

Figure S18. ^{1}H NMR of **3r** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3r** (75 MHz, $CDCl_3$).

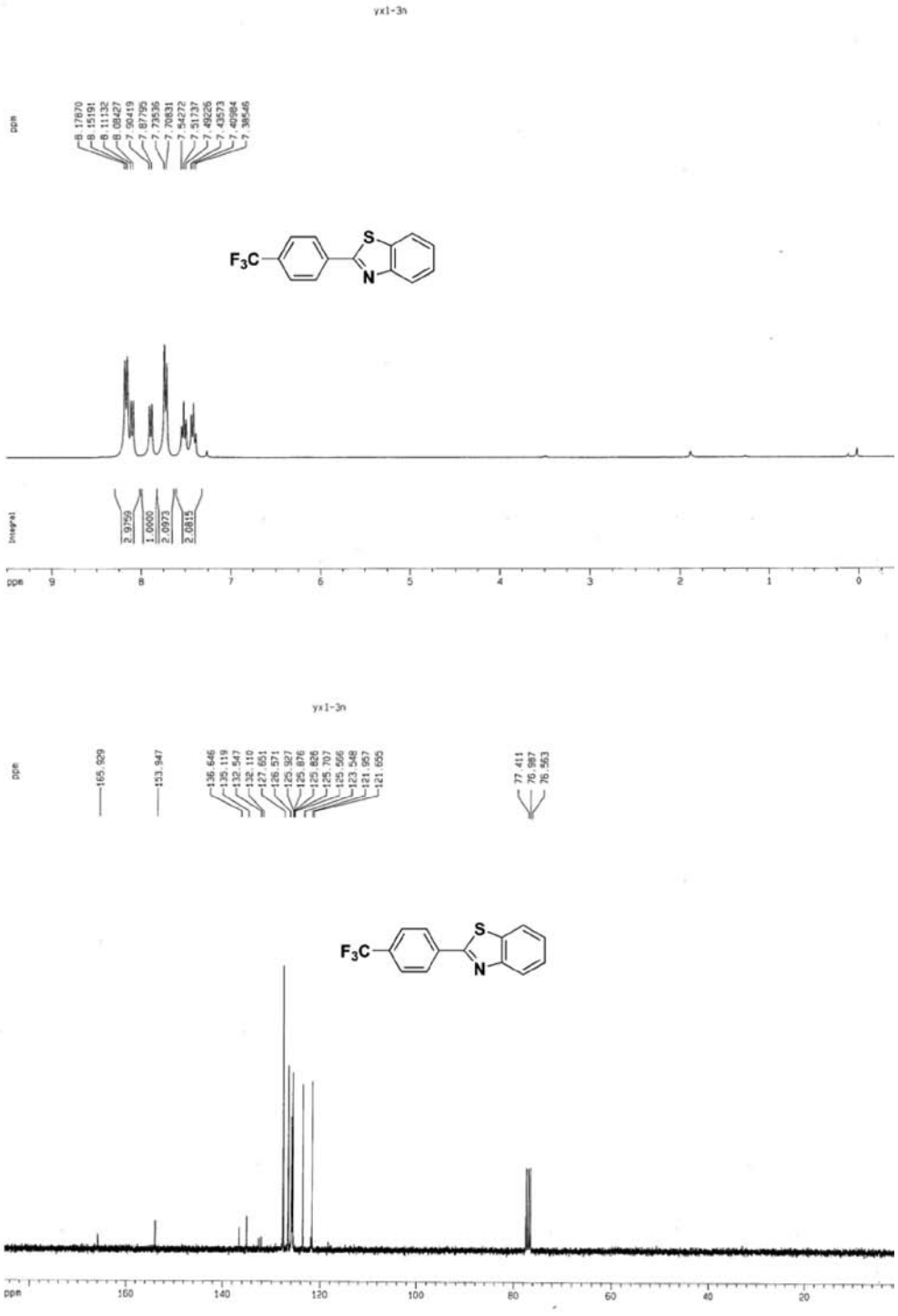

Figure S19. ^{1}H NMR of **3s** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3s** (75 MHz, $CDCl_3$).

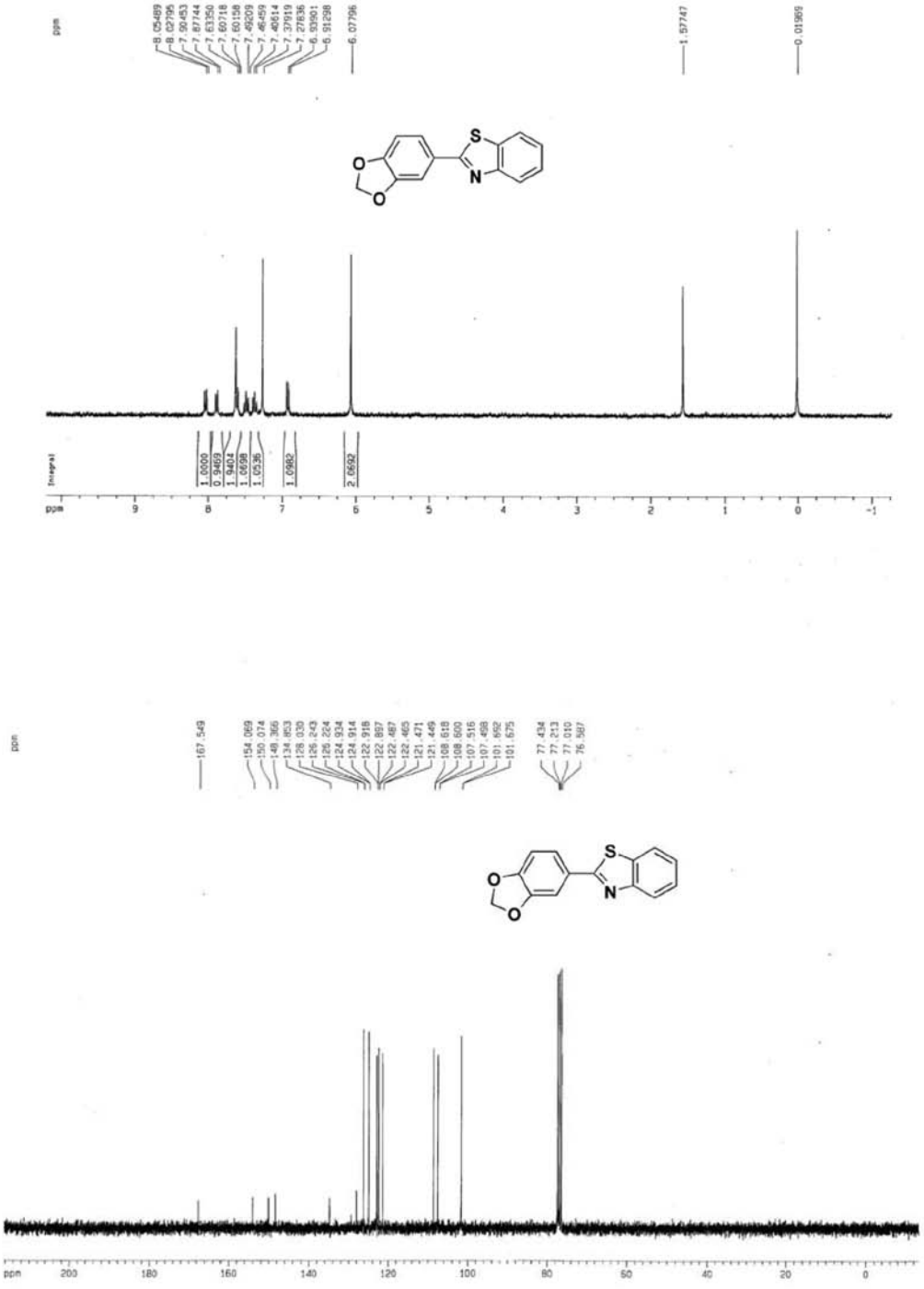

Figure S20. [1]H NMR of **3t** (300 MHz, $CDCl_3$) and [13]C NMR of **3t** (75 MHz, $CDCl_3$).

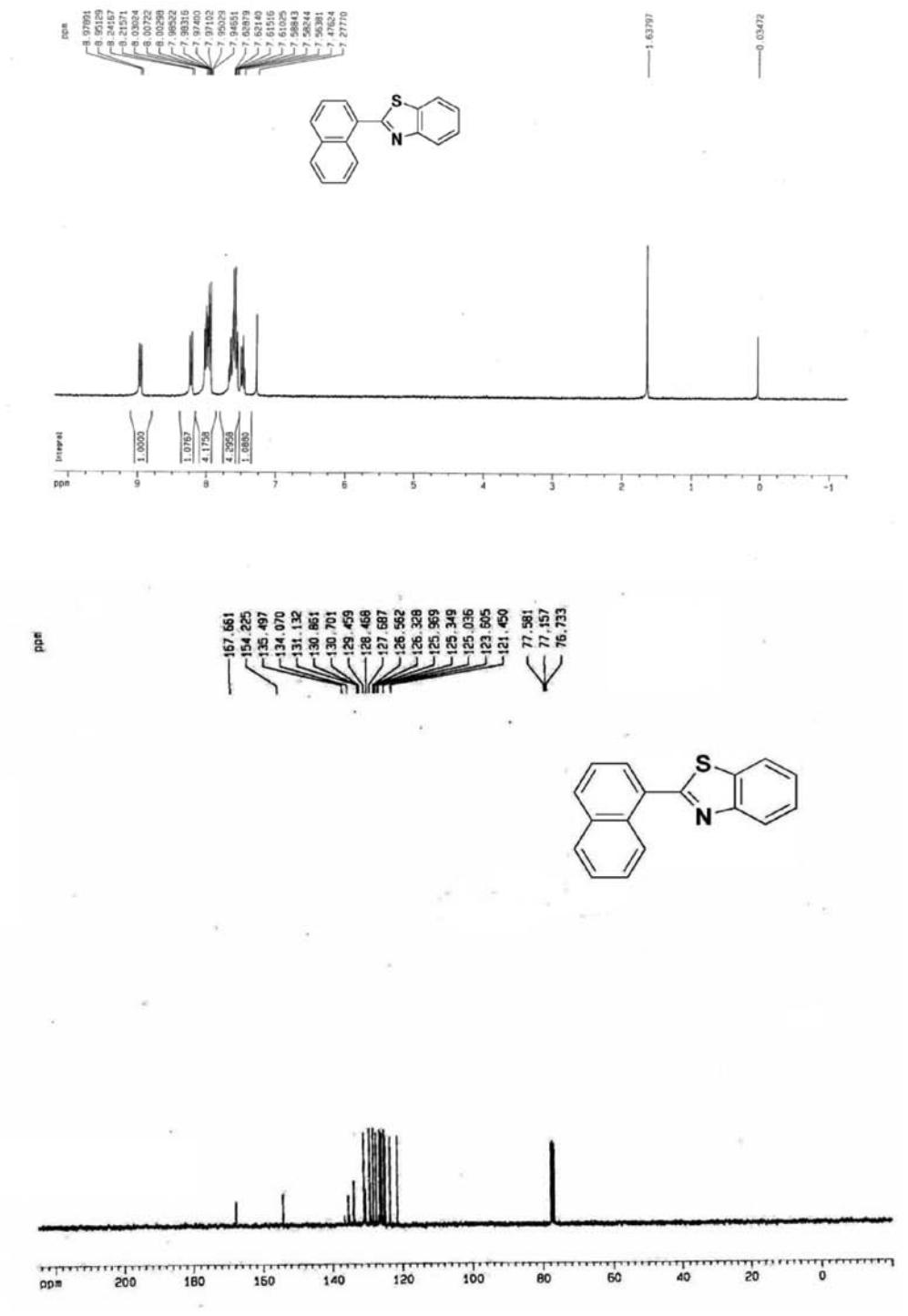

Figure S21. ^{1}H NMR of **3u** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3u** (75 MHz, $CDCl_3$).

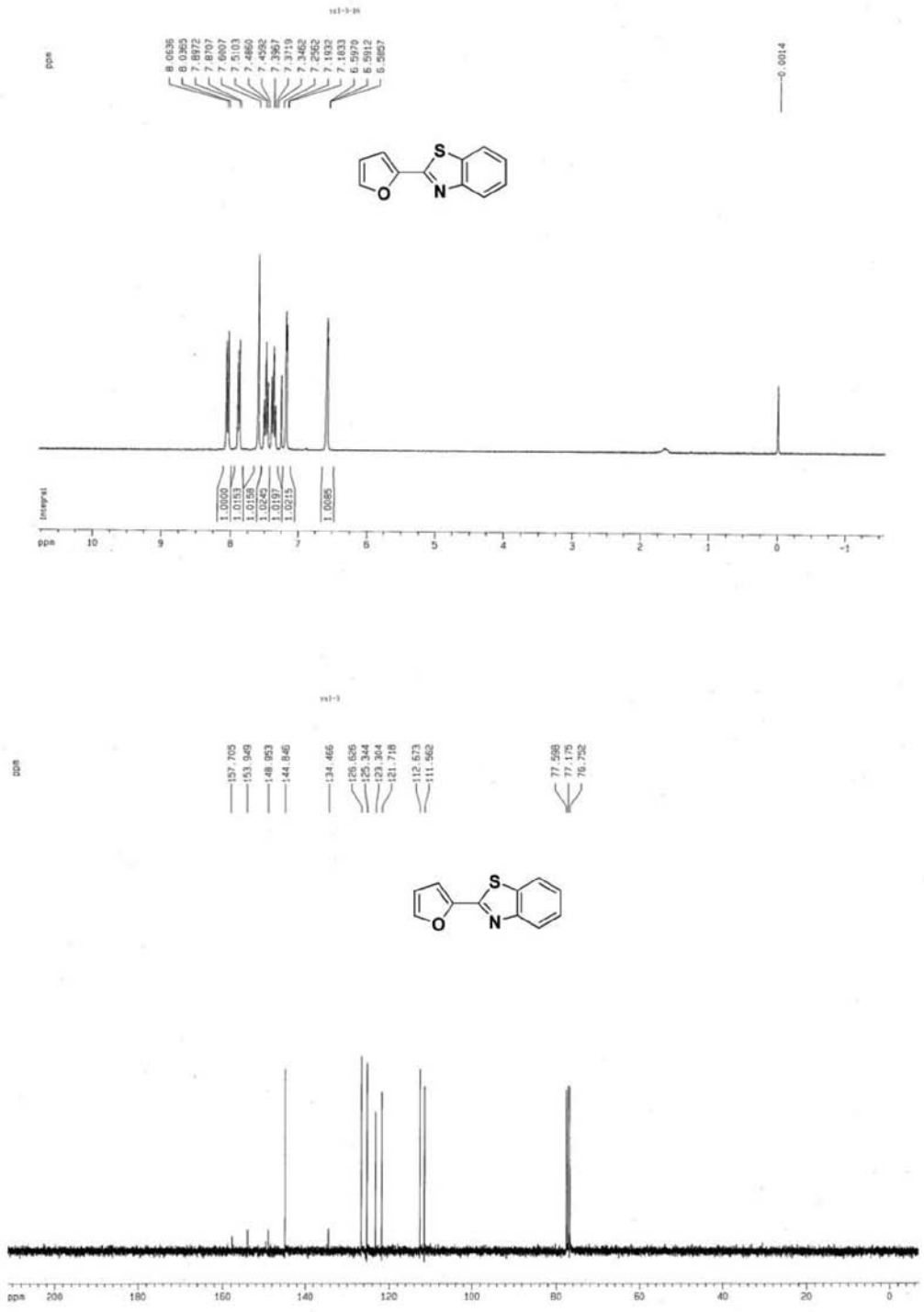

Figure S22. ^{1}H NMR of **3v** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3v** (75 MHz, $CDCl_3$).

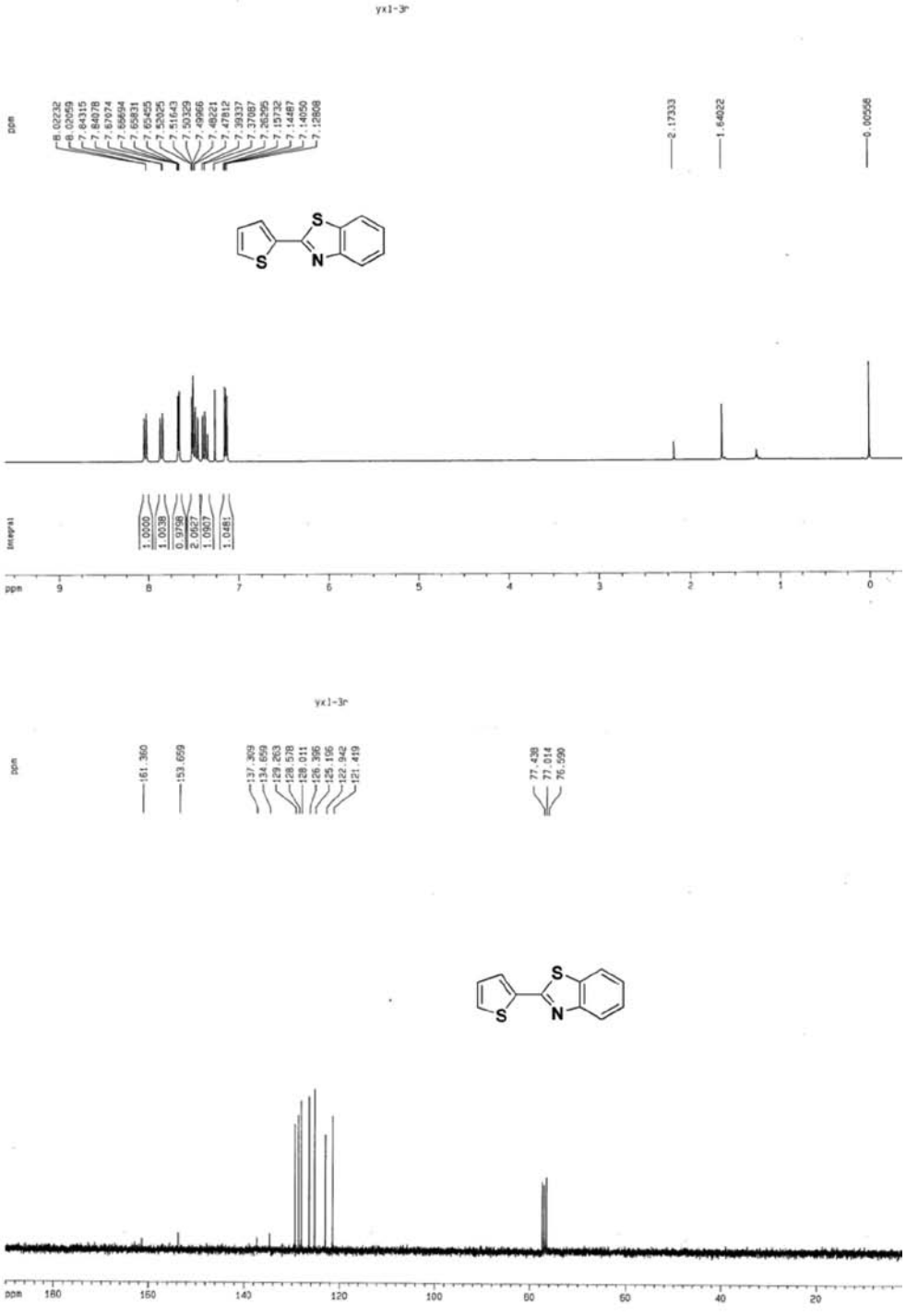

Figure S23. ^{1}H NMR of **3w** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3w** (75 MHz, $CDCl_3$).

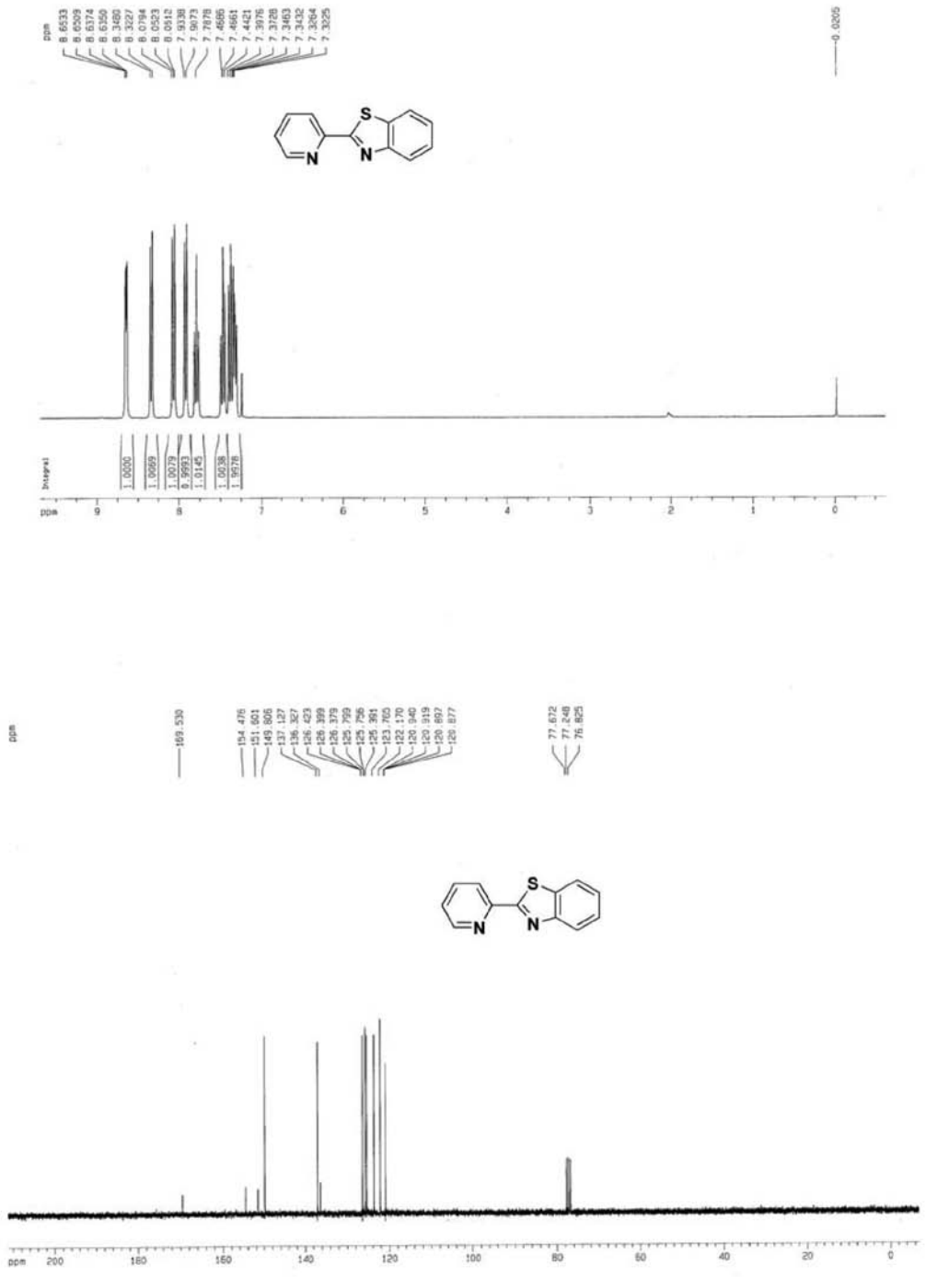

Figure S24. ^{1}H NMR of **3x** (300 MHz, $CDCl_3$) and ^{13}C NMR of **3x** (75 MHz, $CDCl_3$).

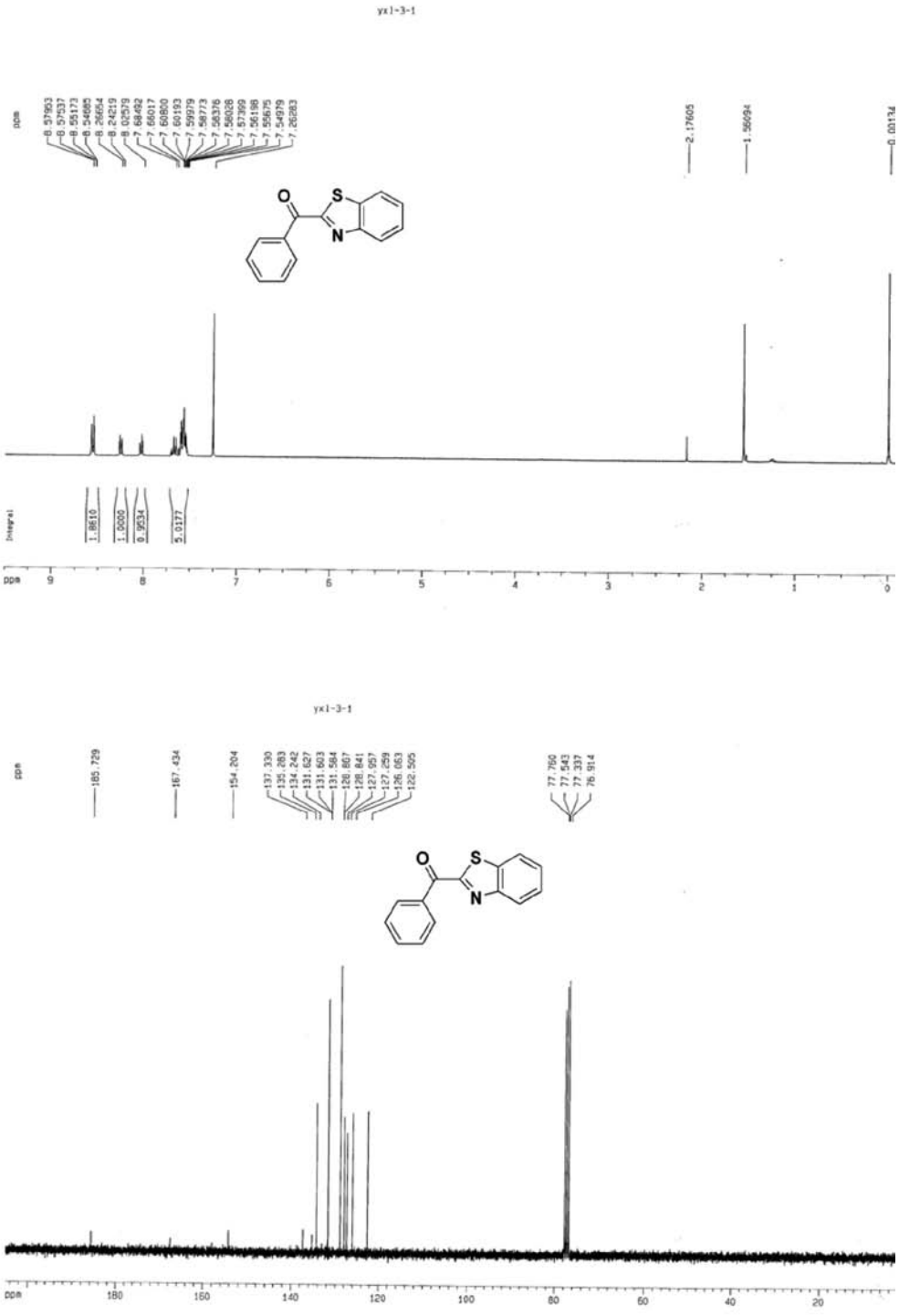

Figure S25. ^{1}H NMR of **4a** (300 MHz, $CDCl_3$) and ^{13}C NMR of**4a** (75 MHz, $CDCl_3$).

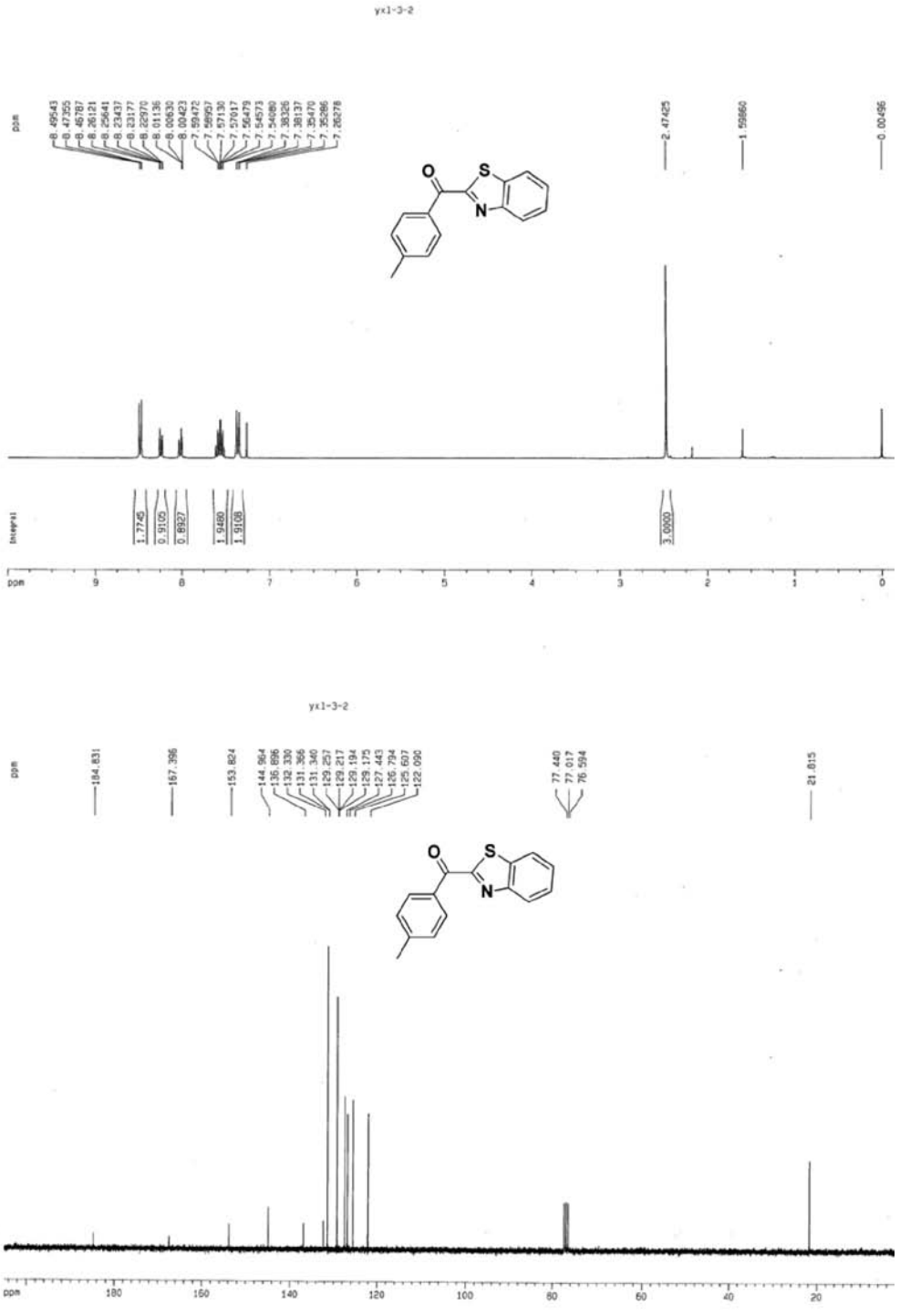

Figure S26. ^{1}H NMR of **4b** (300 MHz, $CDCl_3$) and ^{13}C NMR of **4b** (75 MHz, $CDCl_3$).

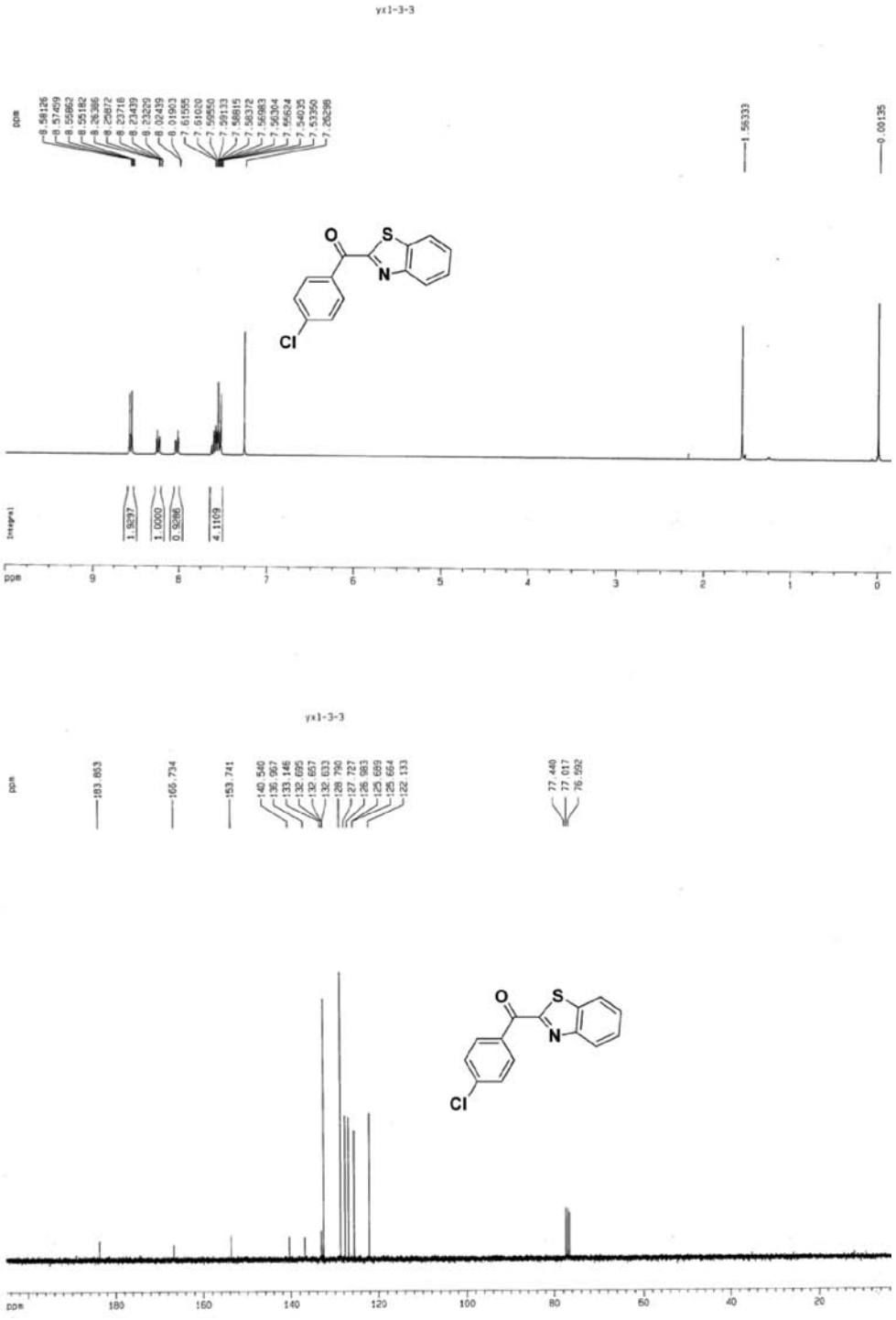

Figure S27. ^{1}H NMR of **4c** (300 MHz, $CDCl_3$) and ^{13}C NMR of **4c** (75 MHz, $CDCl_3$).

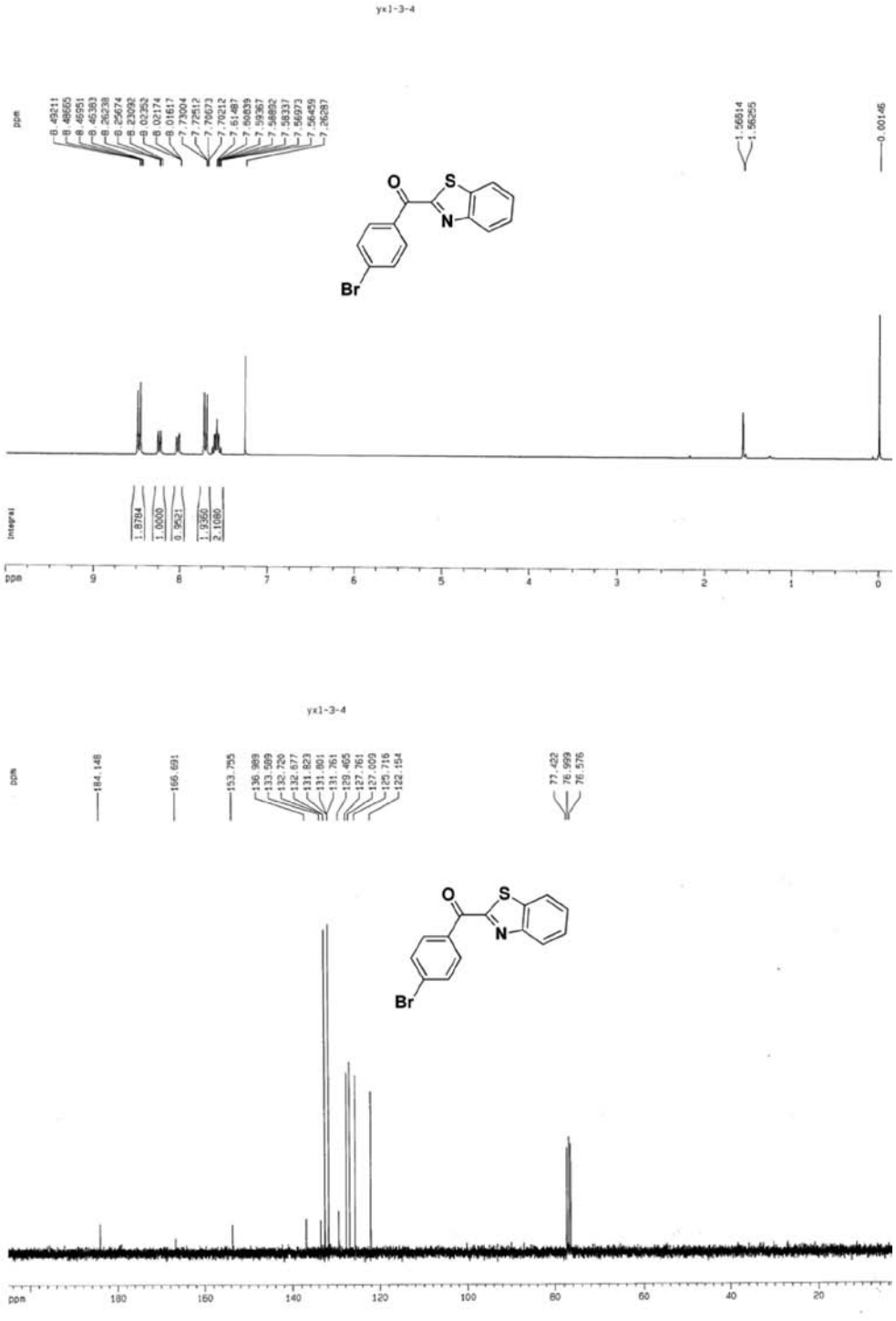

Figure S28. ^{1}H NMR of **4d** (300 MHz, $CDCl_3$) and ^{13}C NMR of **4d** (75 MHz, $CDCl_3$).