

## Synthesis of 2'-(1,2,3-triazoyl)-acetophenones: molecular docking and *in vitro* monoamine oxidase activity inhibition

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## Optimization of conditions

Focused on proceed the studies using the thiourea as ligand to form a new class of 1,2,3-triazoles by CuAAC reactions, the initial conditions were based in a previous report in literature by our research group.<sup>1</sup> Thus, the 2'-azidoacetophenone **1a** and phenylacetylene **2a** were reacted using 10 mol% of CuI as catalyst, thiourea as a ligand (20 mol%), DMSO as solvent, triethylamine as base under 100 °C. After 24 h the desired product **3a** was obtained in 87% yield (Table S1, entry 1). Looking for a better condition, we screened different temperatures from 25 to 120 °C (Table S1, entries 2-7) and we found that 60 °C is the ideal temperature to reaction, generating the compound **3a** in an excellent yield (Table S1, entry 5).

Different polar solvents such as, ethanol, 1,4-dioxane, DMF and water were examined, despite the formation of product in most cases, DMSO was better than the others (Table S1, entry 5 vs. entries 8-12). The use of CuBr or CuBr<sub>2</sub> as other species of copper catalyst resulted in a decrease in the formation of product **3a** (Table S1, entries 13-14). An excellent result was obtained when we used Cu(OAc)<sub>2</sub>, however in view of the price, we choose CuI that is less expensive (Table S1, entry 5 vs. entry 15). Increasing the amount of CuI from 10 to 15 mol% leading to the formation of desired product **3a** in similar yield (94%) (Table1, entry 5 vs. entry 16). Unfortunately, a significant decrease in the yield of **3a** was observed when the amount of the CuI was reduced from 10 to 5 mol% (Table S1, entry 17).

In order to evaluate the base influence, triethylamine was changed to diethylamine and DBU. However, in both cases the compound **3a** was obtained in lower yield compared that reactions using triethylamine (Table S1, entry 5 vs. entries 18-19).

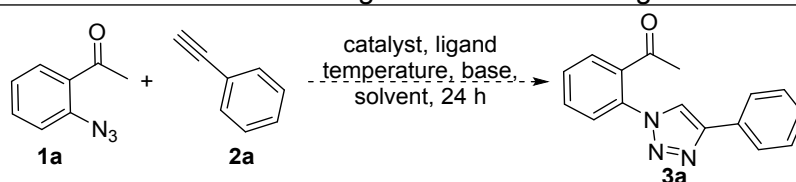
Subsequently, we carried out an experiment using a classic ligand in this type of reaction. However, the use of bipyridine in amount of 20 or 10 mol% yielding the compound **3a** in 60 and 62% yield, respectively. These results suggest that thiourea is the best ligand for this reaction (Table S1, entry 5 vs. entries 20-21).

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<sup>1</sup> G.P. Costa, R. Baldinotti, M.G. Fronza, J.E. Nascimento, Í. Dias, M.S. Sonego, F.K. Seixas, T. Collares, G. Perin, R.G.Jacob, L. Savegnago, D. Alves, *ChemMedChem* 2020, **15**, 610-622

We also examined the load of thiourea in the reaction. A decrease in the yield of compound **3a** was observed when we used 10 mol% of thiourea (Table S1, entry 5 vs. entry 22). The excellent yield relates to the use of this ligand, once when reaction was carried out in the absence of thiourea give the desired product **3a** in only 52% yield, (Table S1, entry 5 vs. entry 23). Finally, when the reaction was performed under air atmosphere, the compound **3a** was obtained with a slight decrease in the yield (85%) (Table S1, entry 24).

**Table S1** Optimization of conditions using conventional heating to form compound **3a**.<sup>a</sup>



Entry	Temp. (°C)	Solvent	Catalyst (mol%)	Yield of <b>3a</b> (%)
1	100	DMSO	CuI (10)	87
2	120	DMSO	CuI (10)	70
3	80	DMSO	CuI (10)	99
4	70	DMSO	CuI (10)	97
<b>5</b>	<b>60</b>	<b>DMSO</b>	<b>CuI (10)</b>	<b>98</b>
6	50	DMSO	CuI (10)	82
7	25	DMSO	CuI (10)	52
8	60	EtOH	CuI (10)	40
9	60	1,4-dioxane	CuI (10)	12
10	60	DMF	CuI (10)	70
11	60	DMSO:H <sub>2</sub> O (3:1)	CuI (10)	95
12	60	H <sub>2</sub> O	CuI (10)	traces
13	60	DMSO	CuBr (10)	60
14	60	DMSO	CuBr <sub>2</sub> (10)	63
15	60	DMSO	Cu(OAc) <sub>2</sub> (10)	95
16	60	DMSO	CuI (15)	94
17	60	DMSO	CuI (5)	12
18 <sup>b</sup>	60	DMSO	CuI (10)	93
19 <sup>c</sup>	60	DMSO	CuI (10)	56
20 <sup>d</sup>	60	DMSO	CuI (10)	60
21 <sup>e</sup>	60	DMSO	CuI (10)	62
22 <sup>f</sup>	60	DMSO	CuI (10)	79
23 <sup>g</sup>	60	DMSO	CuI (10)	52
24 <sup>h</sup>	60	DMSO	CuI (10)	85

<sup>a</sup> Reaction were performed using 2'-azidoacetophenone (**1a**) (0.25 mmol), phenylacetylene (**2a**) (0.25 mmol), thiourea (20 mol%), TEA (0.5 mmol), copper catalyst and solvent (0.5 mL) under N<sub>2</sub> atmosphere. <sup>b</sup> TEA was changed by DEA. <sup>c</sup> TEA was changed by DBU. <sup>d</sup> bipy (20 mol%) was used instead thiourea. <sup>e</sup> bipy (10 mol%) was used instead thiourea. <sup>f</sup> thiourea (10 mol%) was used instead thiourea (20 mol%). <sup>g</sup> reaction without ligand. <sup>h</sup> under air atmosphere.

Since, the use of ultrasound (US) irradiation in organic synthesis (sonochemistry) as an alternative energy source has gained popularity in the past decades. This non-conventional energy source has been proved to be able to

accelerate reactions or even to switch product profiles and selectivity's, as well as also able to reduce the number and amounts of side reaction products. Beyond that, it is generally considered as an environmentally sound energy source, comparatively less energy intensive to conventional heating and microwave irradiation.<sup>2</sup>

Even though of good results, we next turned our attention to reduce the reaction time. Thus, we apply the use of US irradiation as an alternative source of energy using the same reaction conditions previous optimized, and after 30 min of reaction under 40% amplitude, the desired 1,2,3-triazole **3a** was obtained in 60% yield (Table S2, entry 1). Aiming to improve the yield of product **3a**, a mixture of DMSO:H<sub>2</sub>O (3:1) as solvent was used giving the compound 3a in excellent yield (Table S2, entry 2).

Different amplitude of US were screened for this reaction. When 20, 30, 50 or 60% were applied as amplitude, the compound 3a was obtained in 86, 86, 88 and 93% yield, respectively (Table S2, entries 3-6). We observed that when the reaction time was reduced to 20 min the 1,2,3-triazole 3a was obtained in 81% yield (Table S2, entry 7).

**Table S2** Optimization conditions reactional using US.<sup>a</sup>

Entry	Amplitude (%)	Time (min)	Yield of 3a (%)
1	40	30	60
<b>2<sup>b</sup></b>	<b>40</b>	<b>30</b>	<b>97</b>
3 <sup>b</sup>	20	30	86
4 <sup>b</sup>	30	30	86
5 <sup>b</sup>	50	30	88
6 <sup>b</sup>	60	30	93
7 <sup>b</sup>	40	20	81

<sup>a</sup> Reaction was performed with 2'-azidoacetophenone (**1a**) (0.25 mmol), phenylacetylene (**2a**) (0.25 mmol), thiourea (20 mol%), TEA (0.5 mmol), CuI (10 mol%) and DMSO (0.5 mL) under air atmosphere. <sup>b</sup> DMSO was changed by a mixture DMSO:H<sub>2</sub>O (3:1).

<sup>2</sup> a) G. Cravotto, P. Cintas, *Chem. Soc. Rev.* 2006, **35**, 180-196; b) T.J. Mason, *Ultrason. Sonochem.* 2007, **14**, 476-483; c) M. Nüchter, B. Ondruschka, A. Jungnickel, U. Müller, *J. Phys. Org. Chem.* 2000, **13**, 579-586; d) T.J. Mason, *Chem. Soc. Rev.* 1997, **26**, 443-451; e) L. Abenante, F. Penteado, M.M. Vieira, G. Perin, D. Alves, E.J. Lenardão, *Ultrason. Sonochem.* 2018, **49**, 41-46; f) G. Perin, D.R. Araujo, P.C. Nobre, E.J. Lenardão, R.G. Jacob, M.S. Silva, J.A. Roehrs, *PeerJ* 2018, **6**, e4706; g) D.M. Xavier, B.S. Goldani, N. Seus, R.G. Jacob, T. Barcellos, M.W. Paixão, R. Luque, D. Alves, *Ultrason. Sonochem.* 2017, **34**, 107-114.

SELECTED SPECTRA

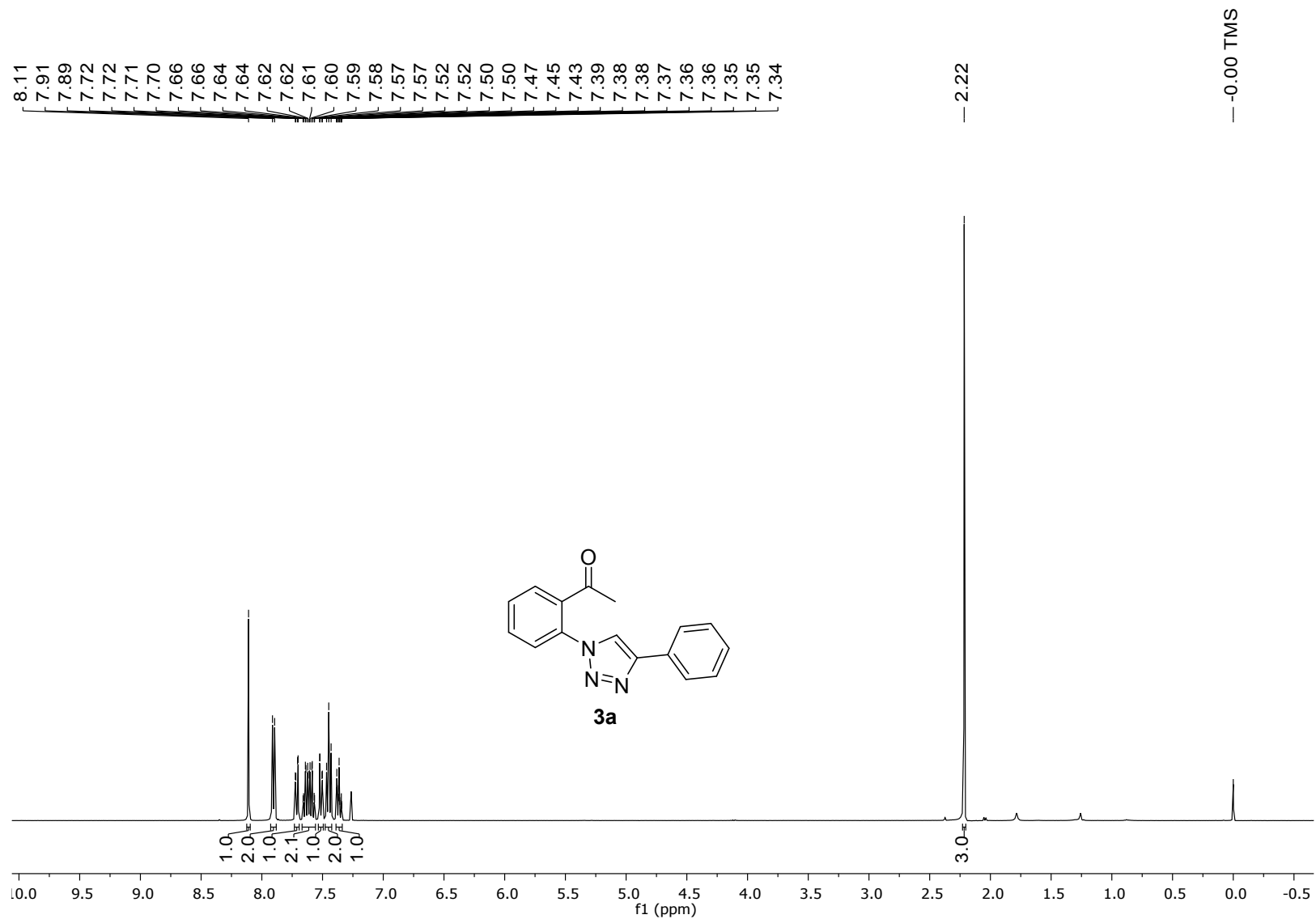


Figure S1: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **3a**.

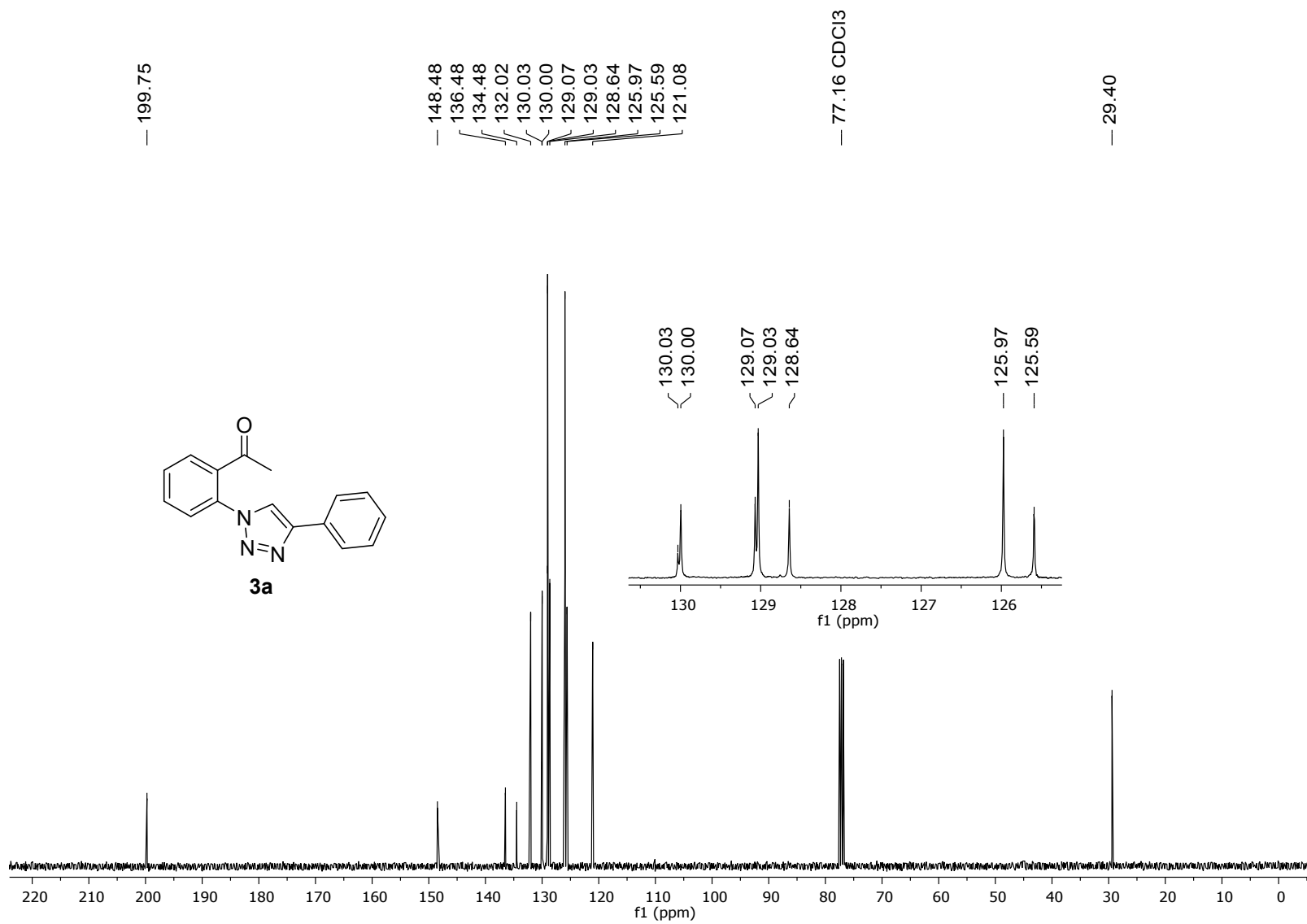
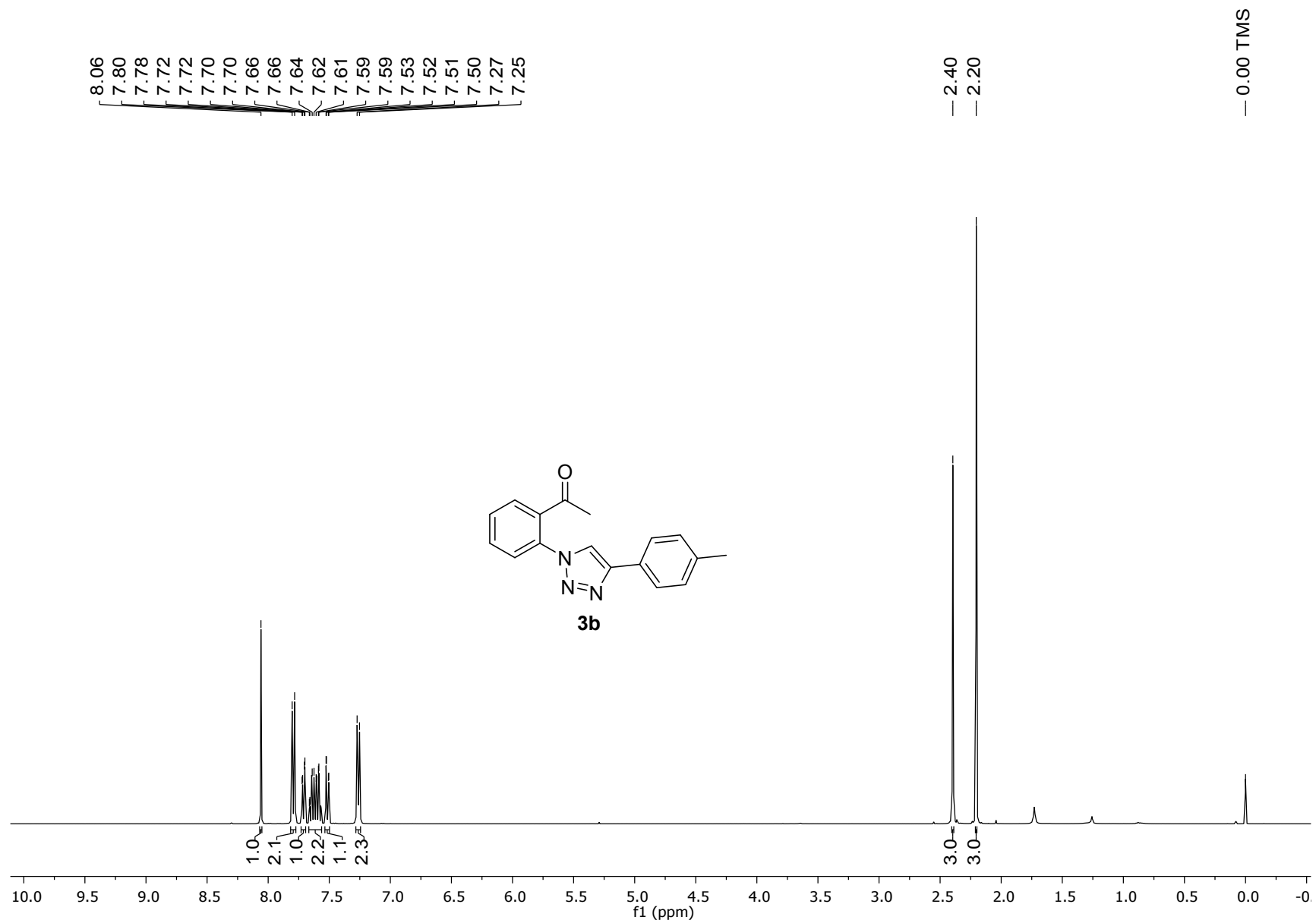


Figure S2:  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3a**.



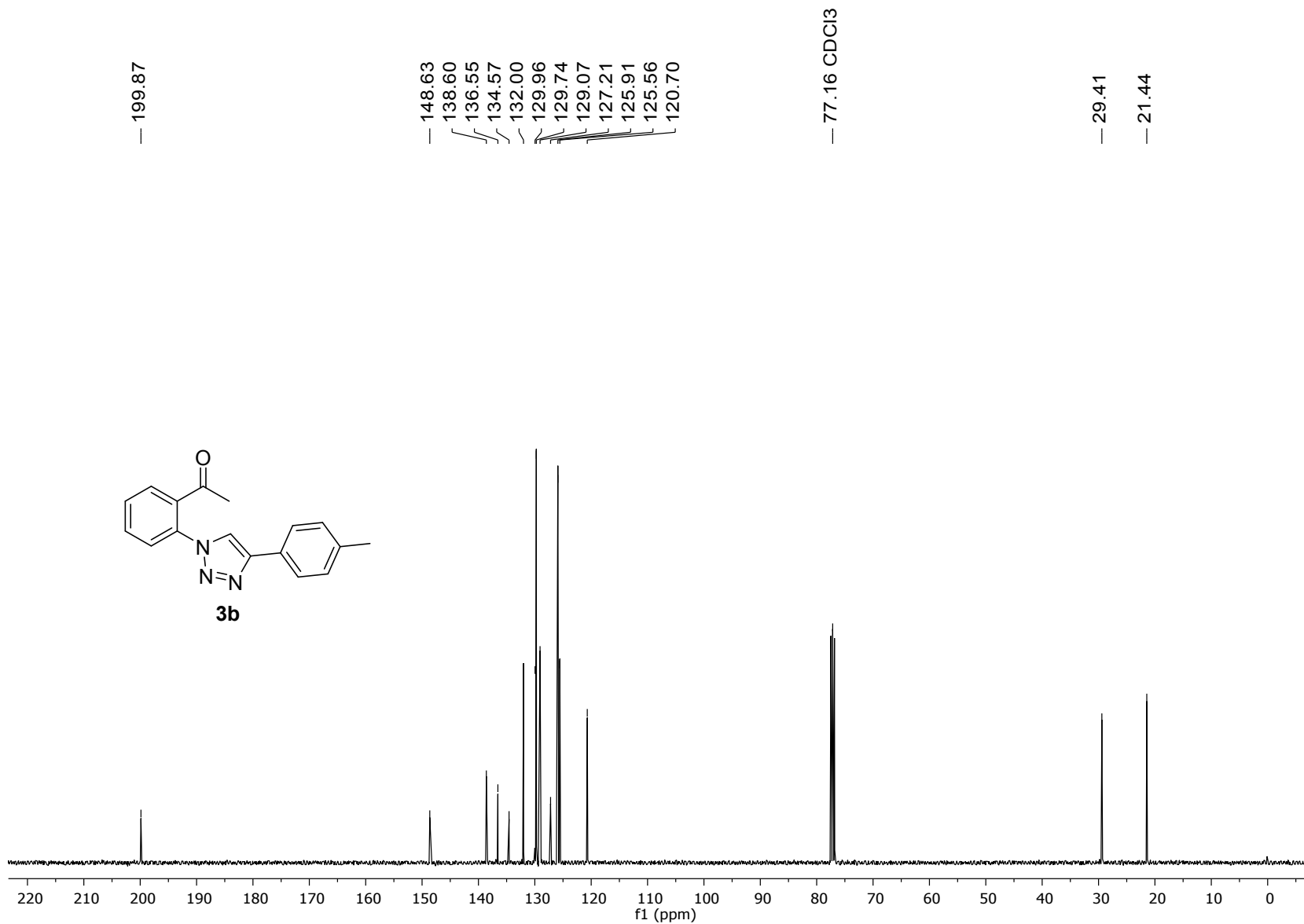
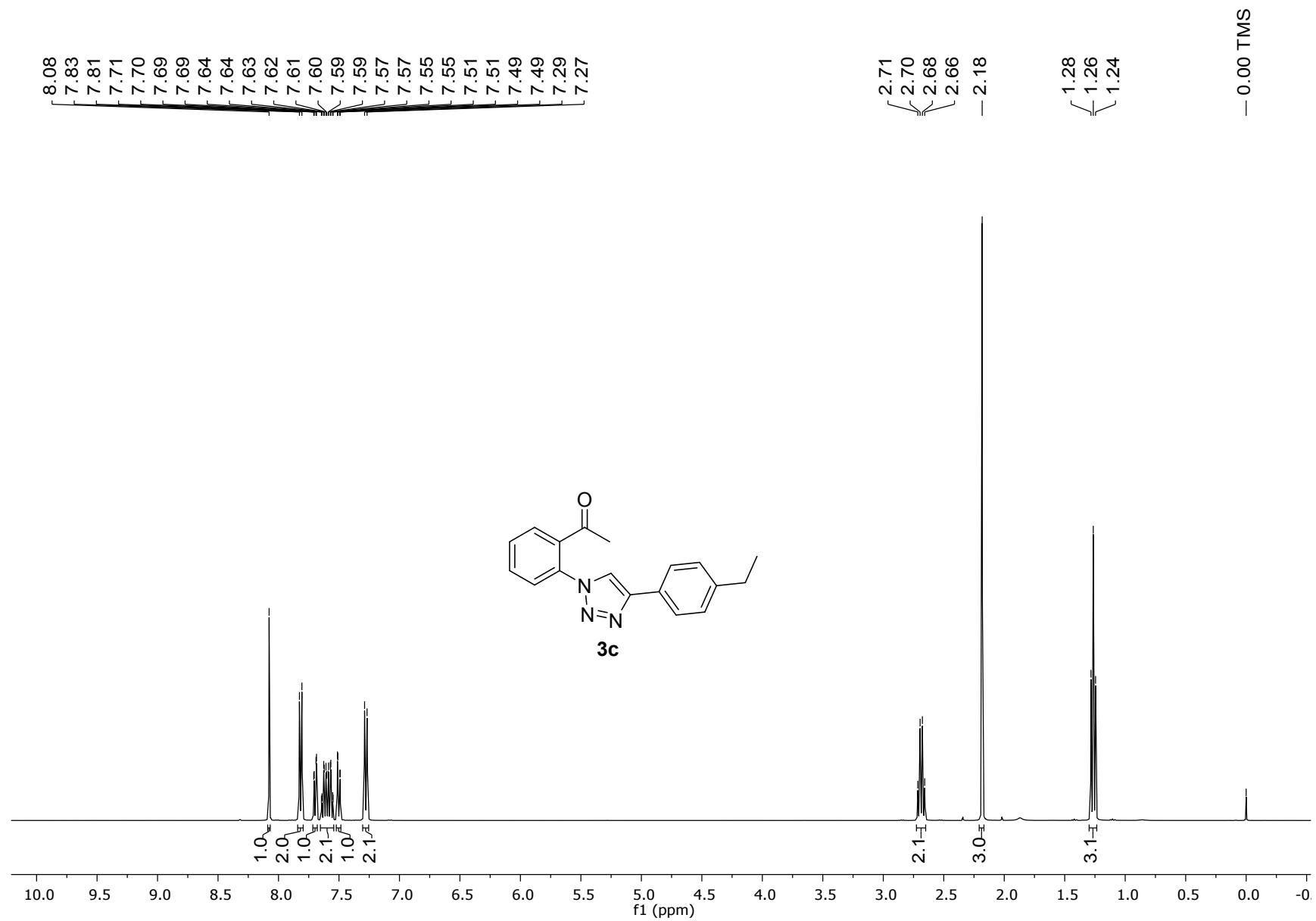


Figure S4:  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3b**.





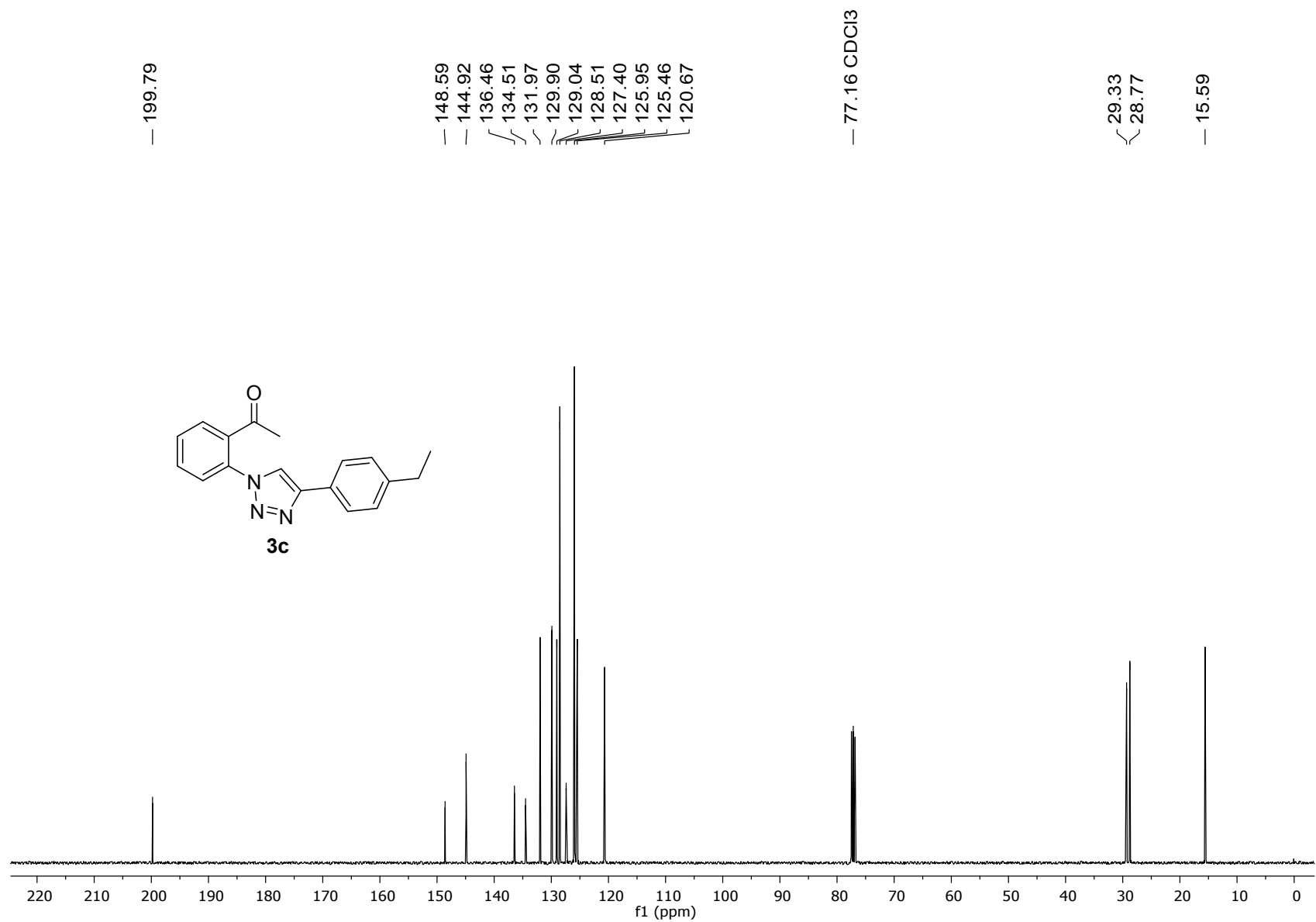
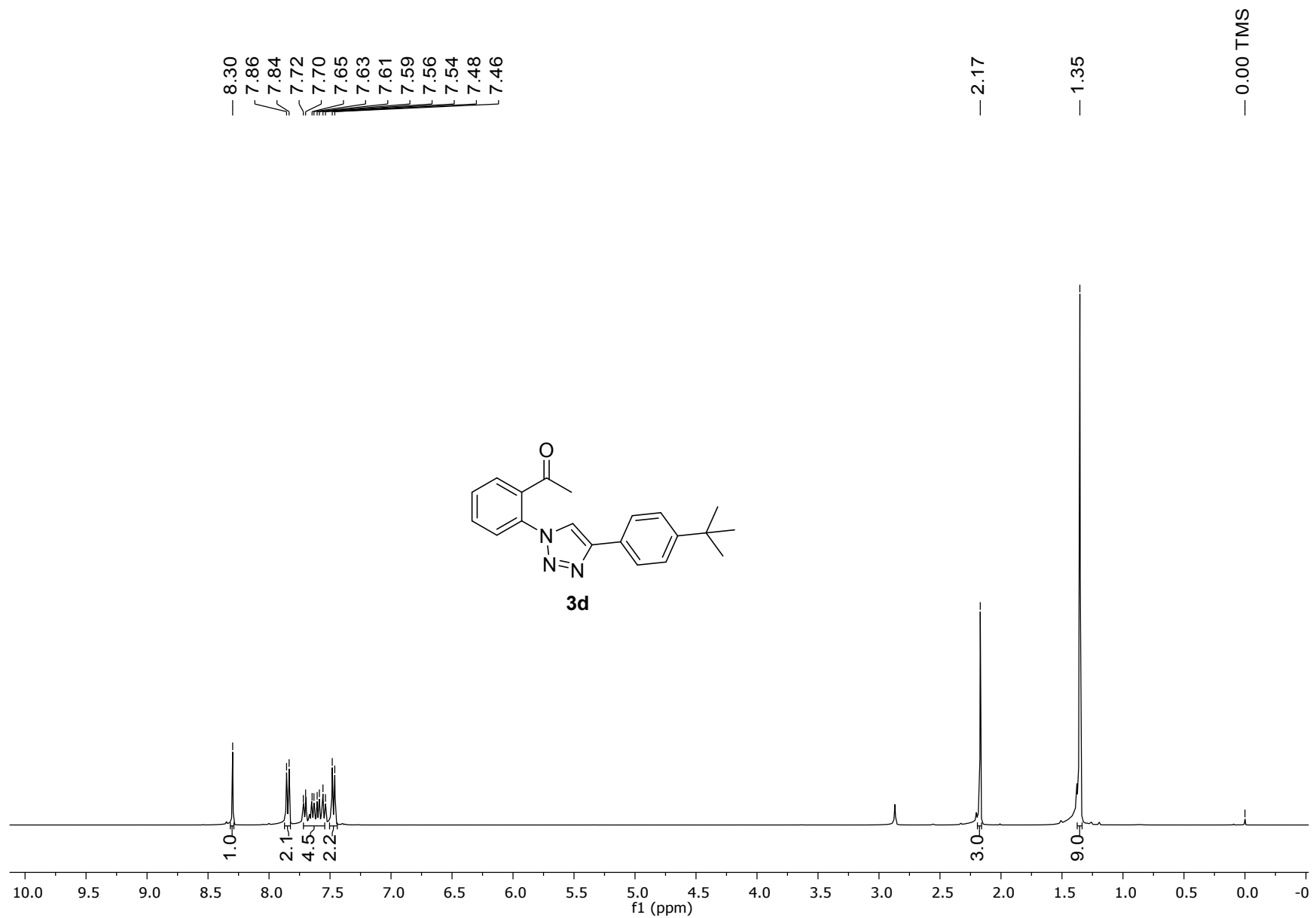


Figure S6:  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3c**.



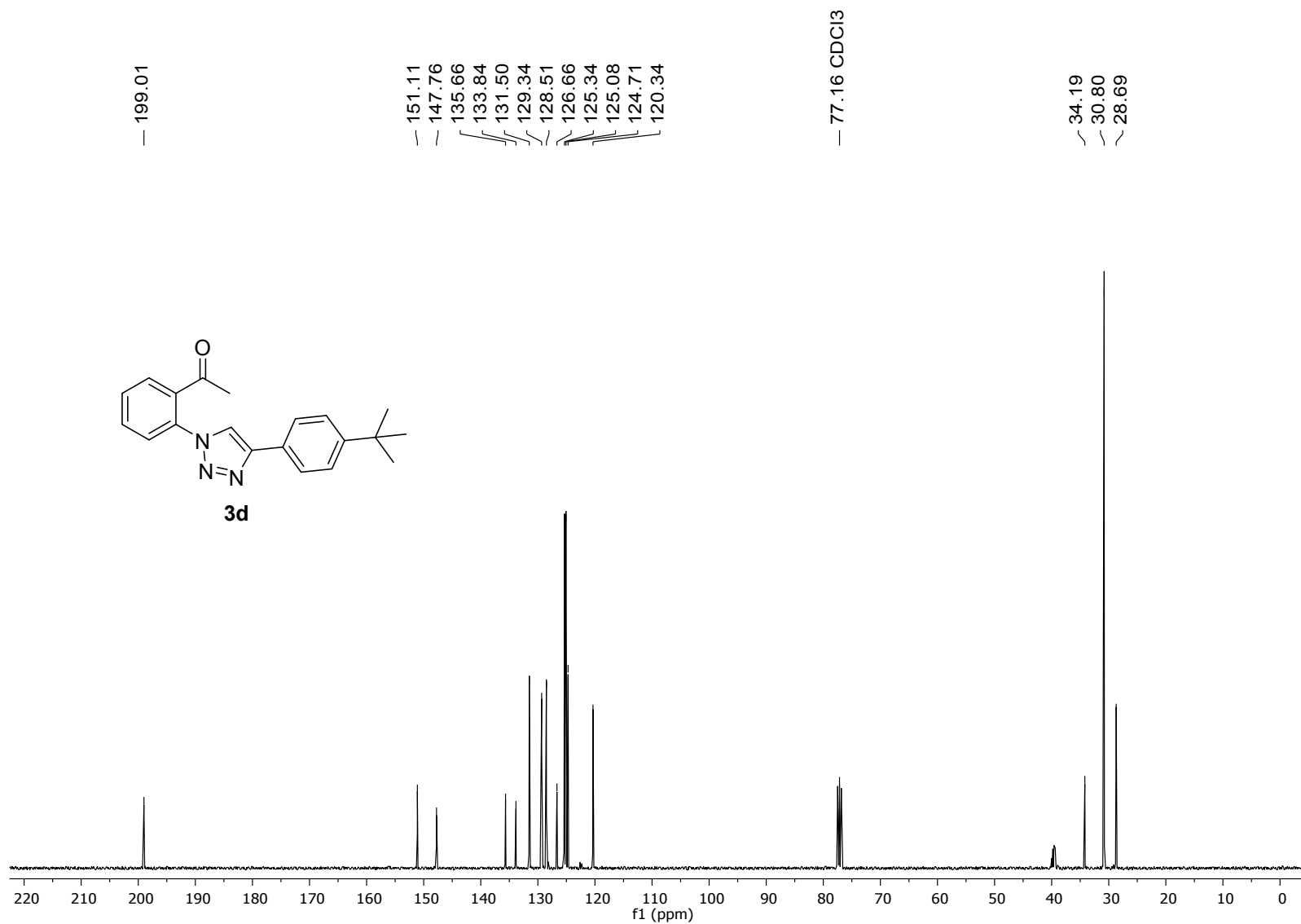


Figure S8:  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3d**.

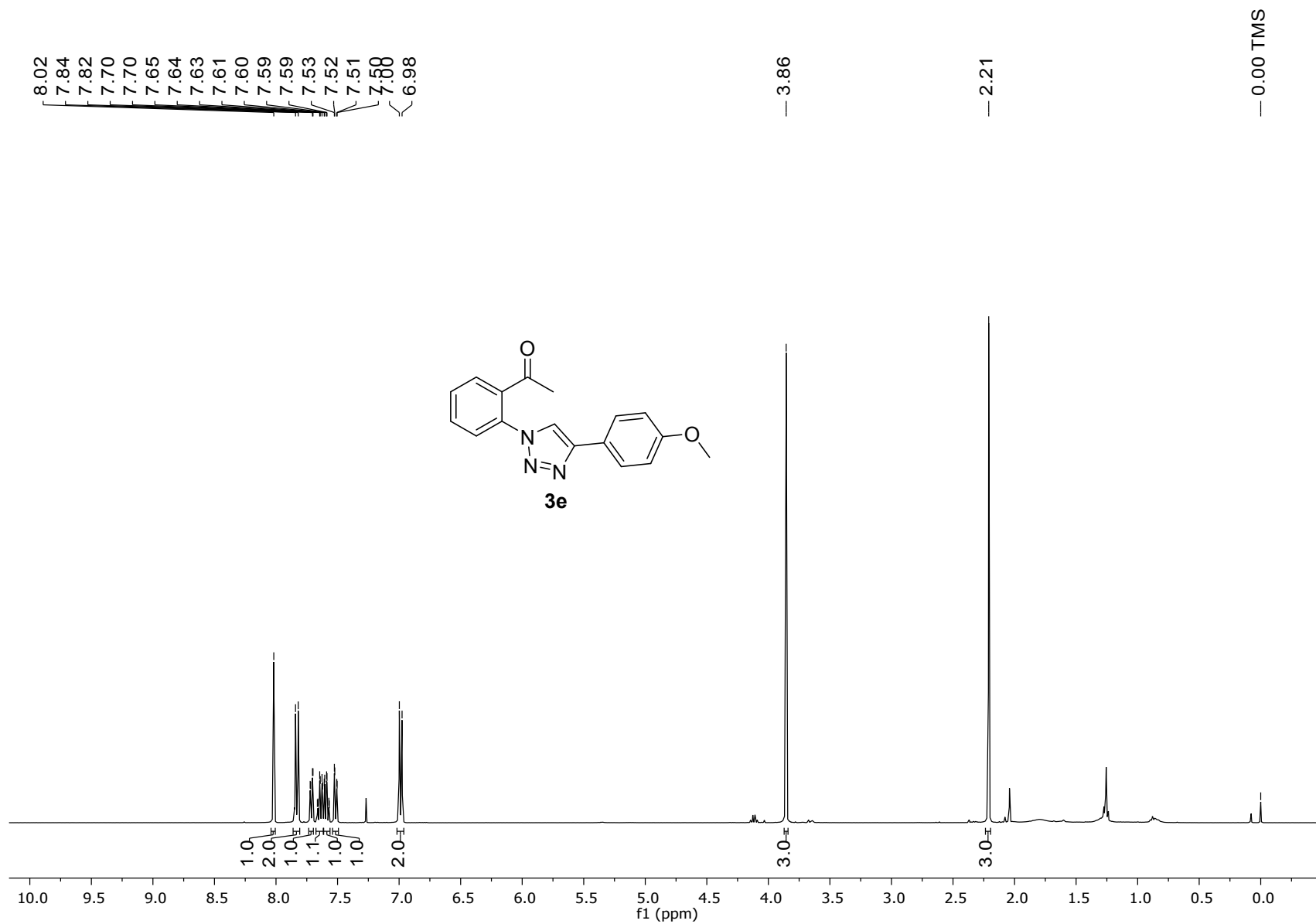


Figure S9: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **3e**.

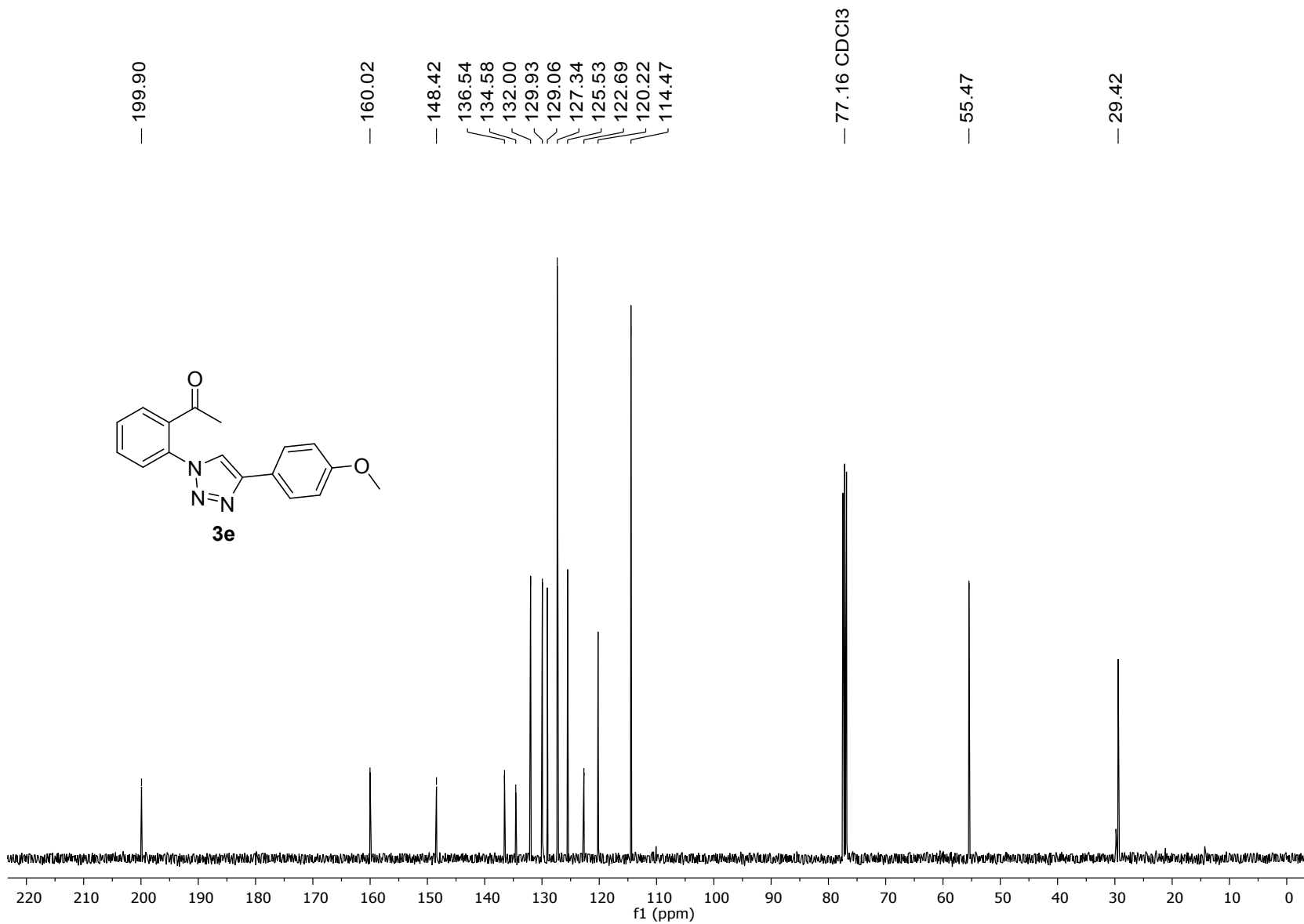


Figure S10:  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3e**.

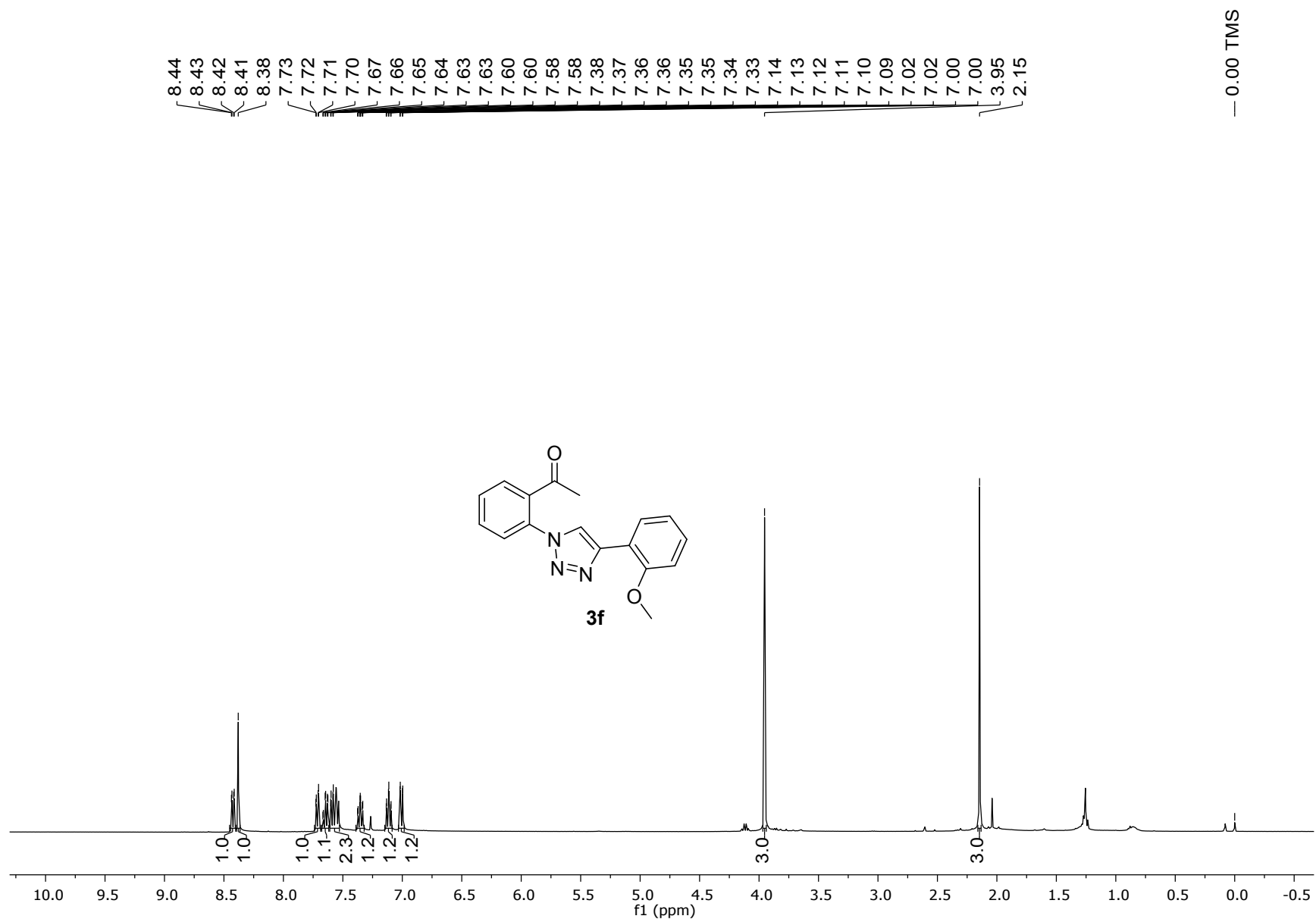


Figure S11:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3f**.

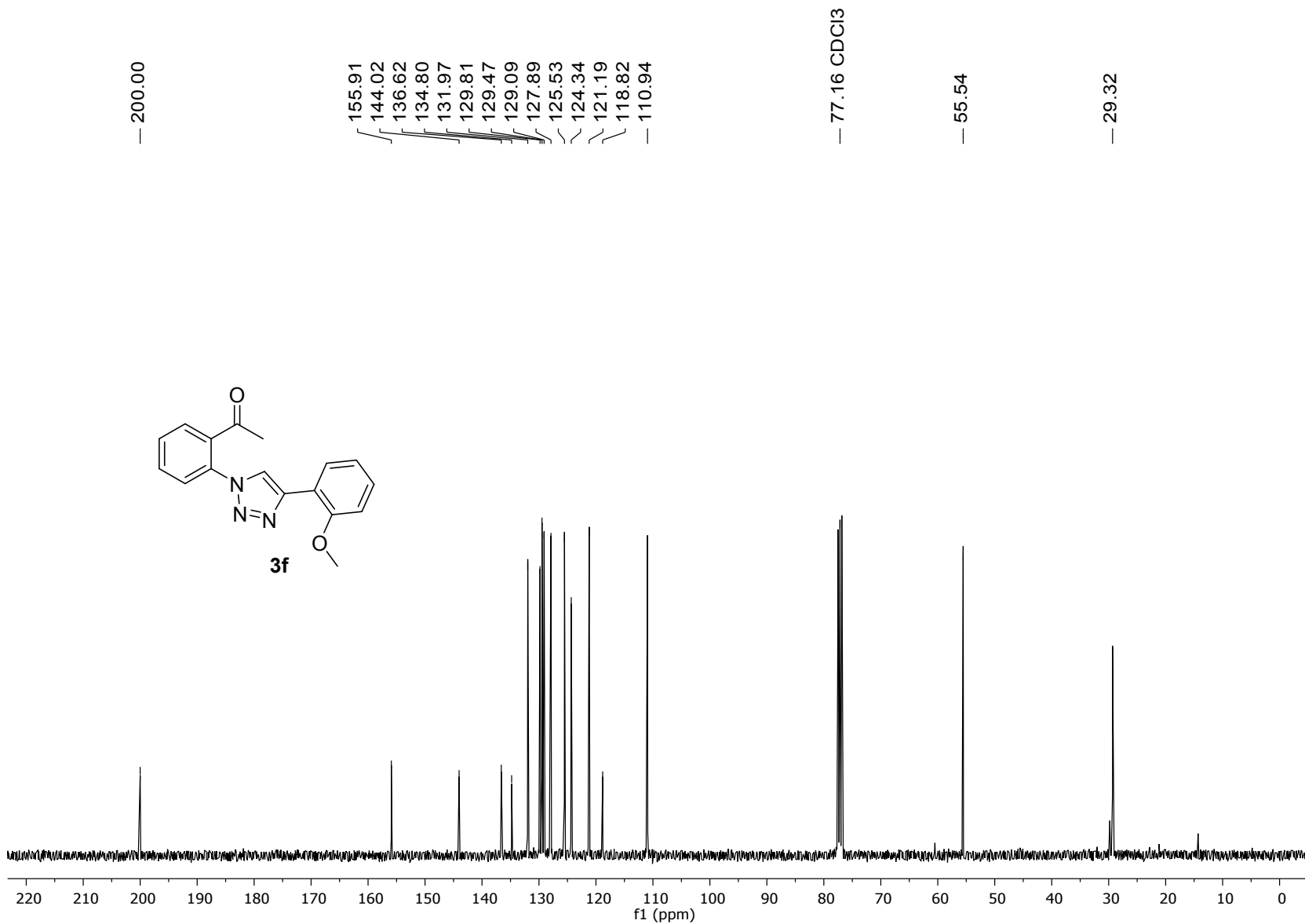


Figure S12:  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3f**.



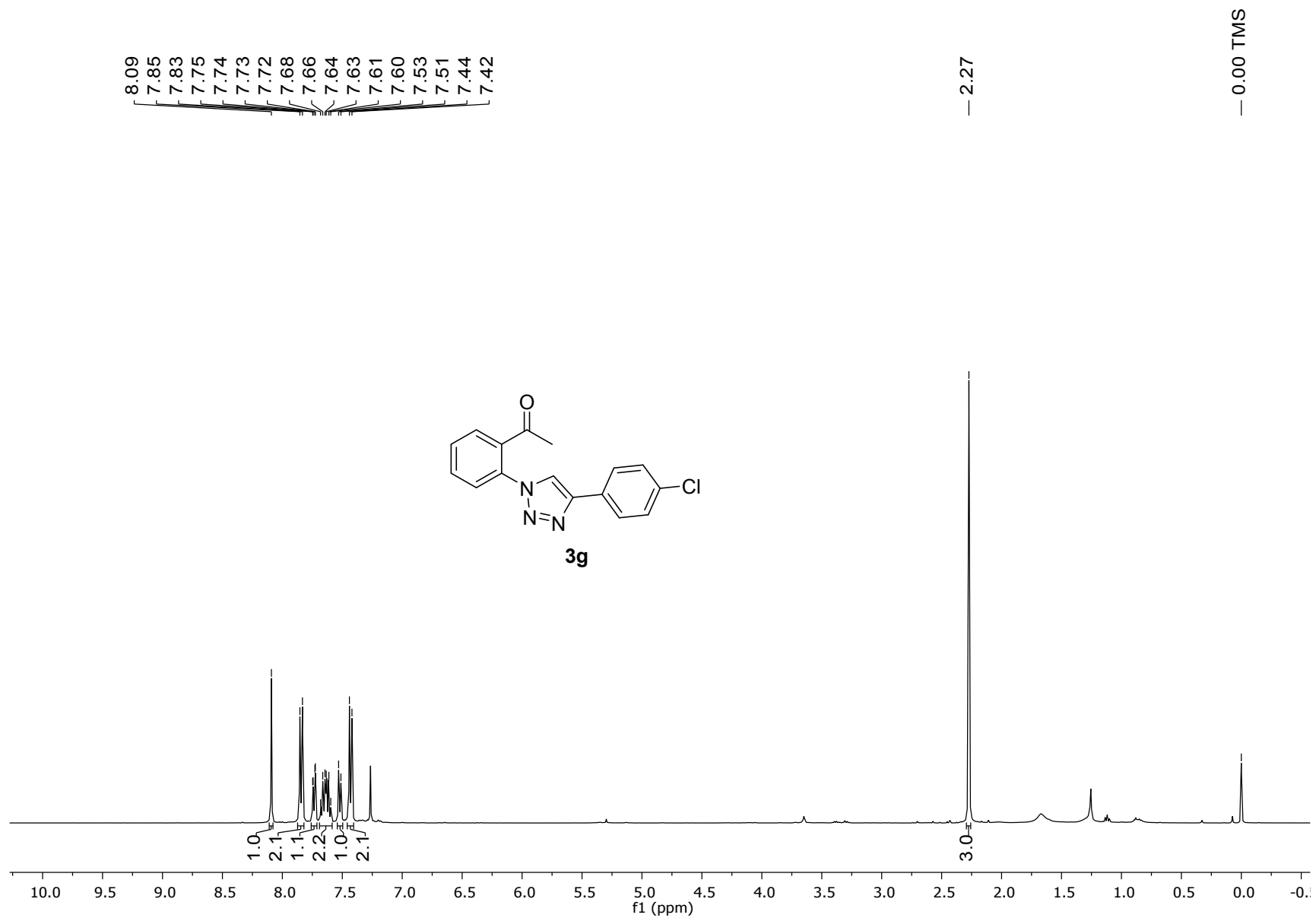


Figure S13: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **3g**.

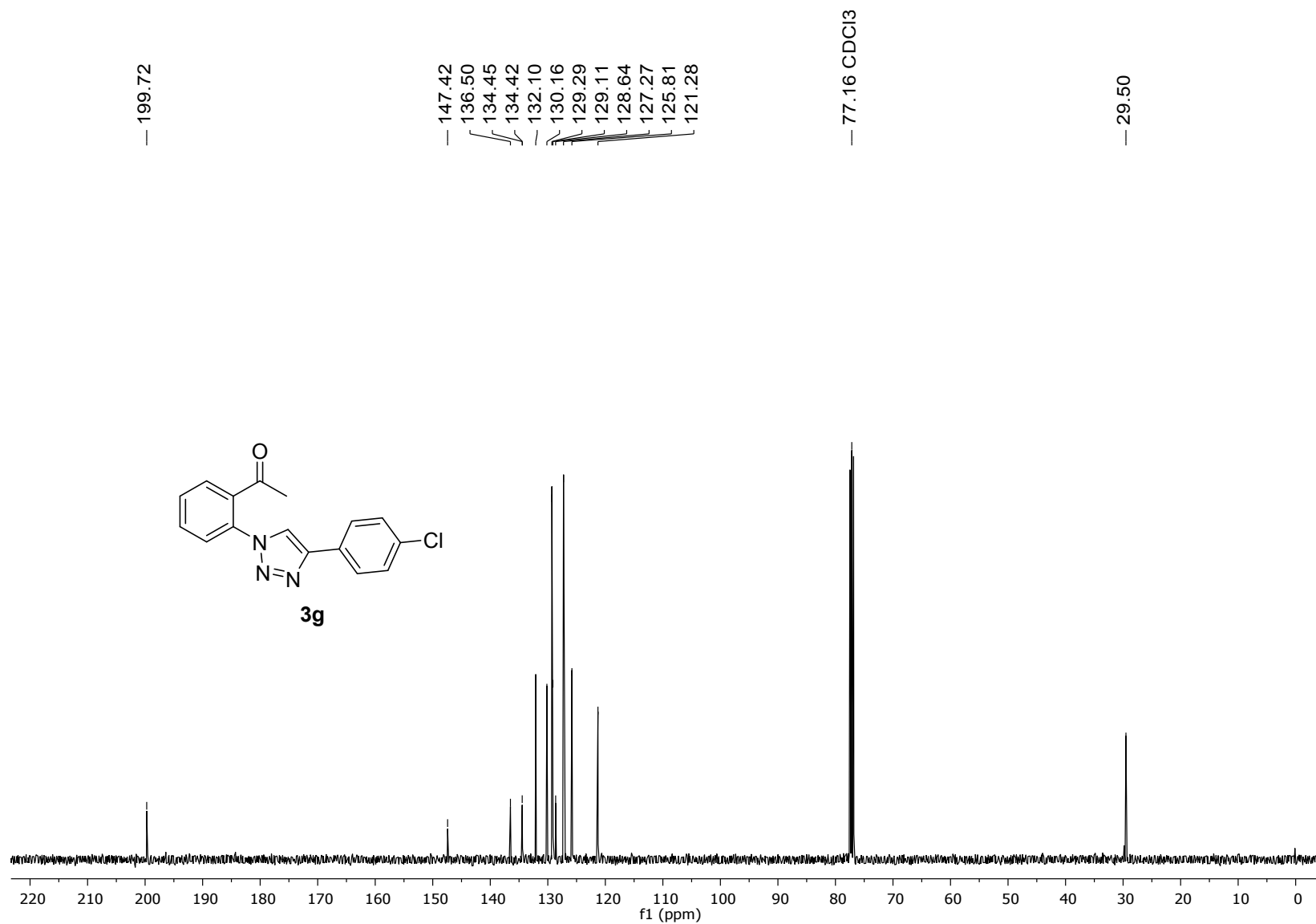


Figure S14:  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3g**.

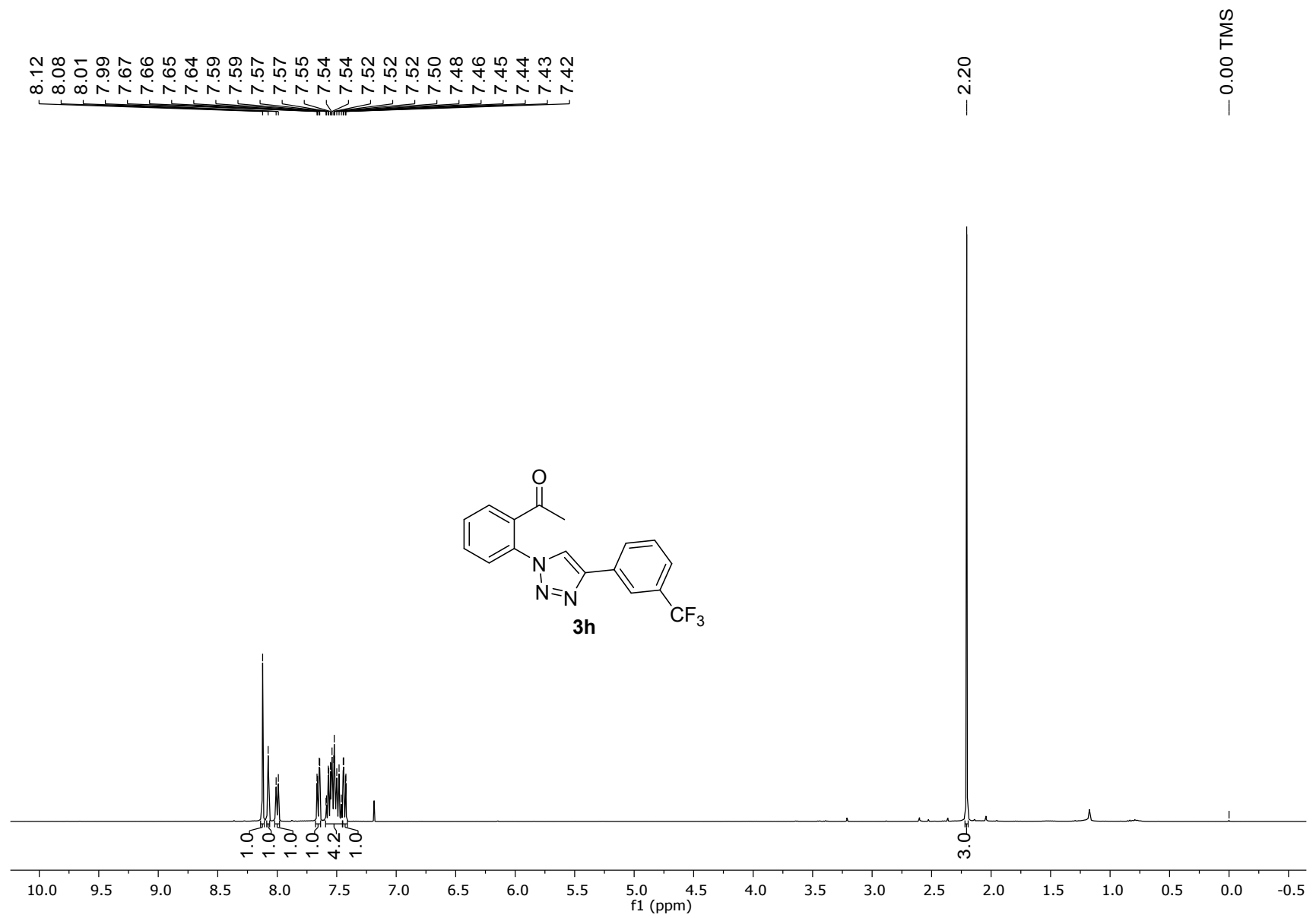


Figure S15: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **3h**.

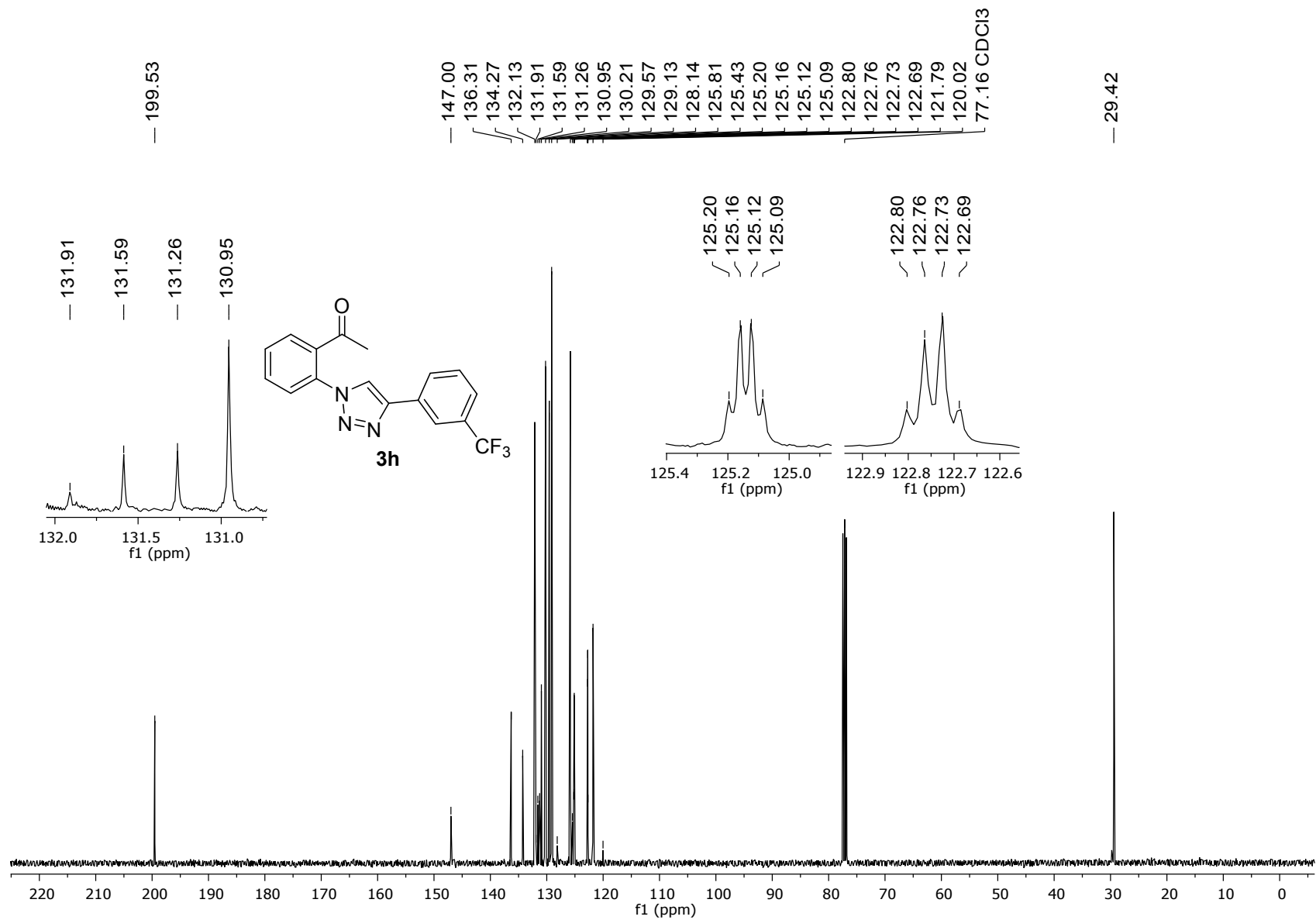


Figure S16: <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) spectrum of compound **3h**.

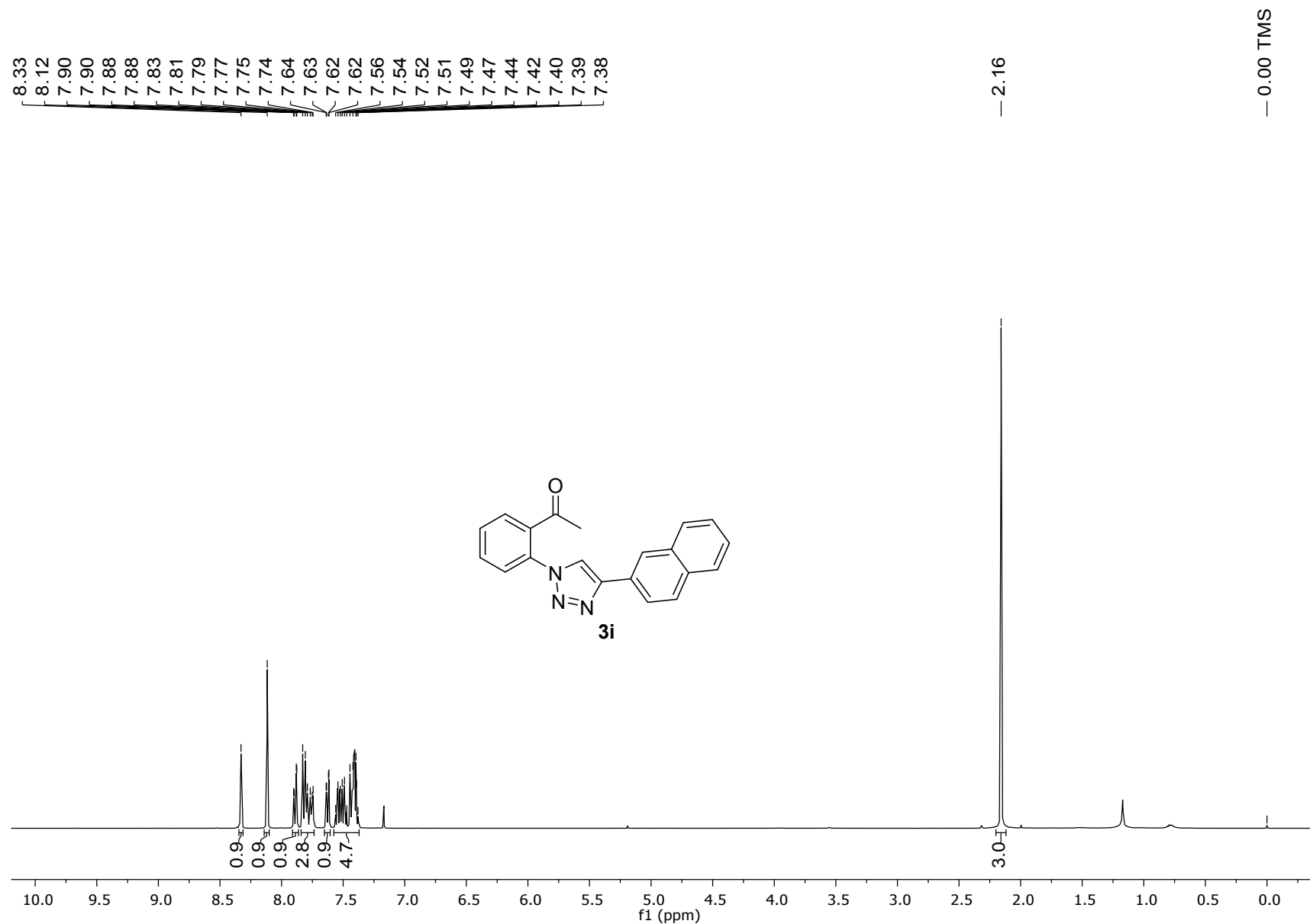


Figure S17: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **3i**.

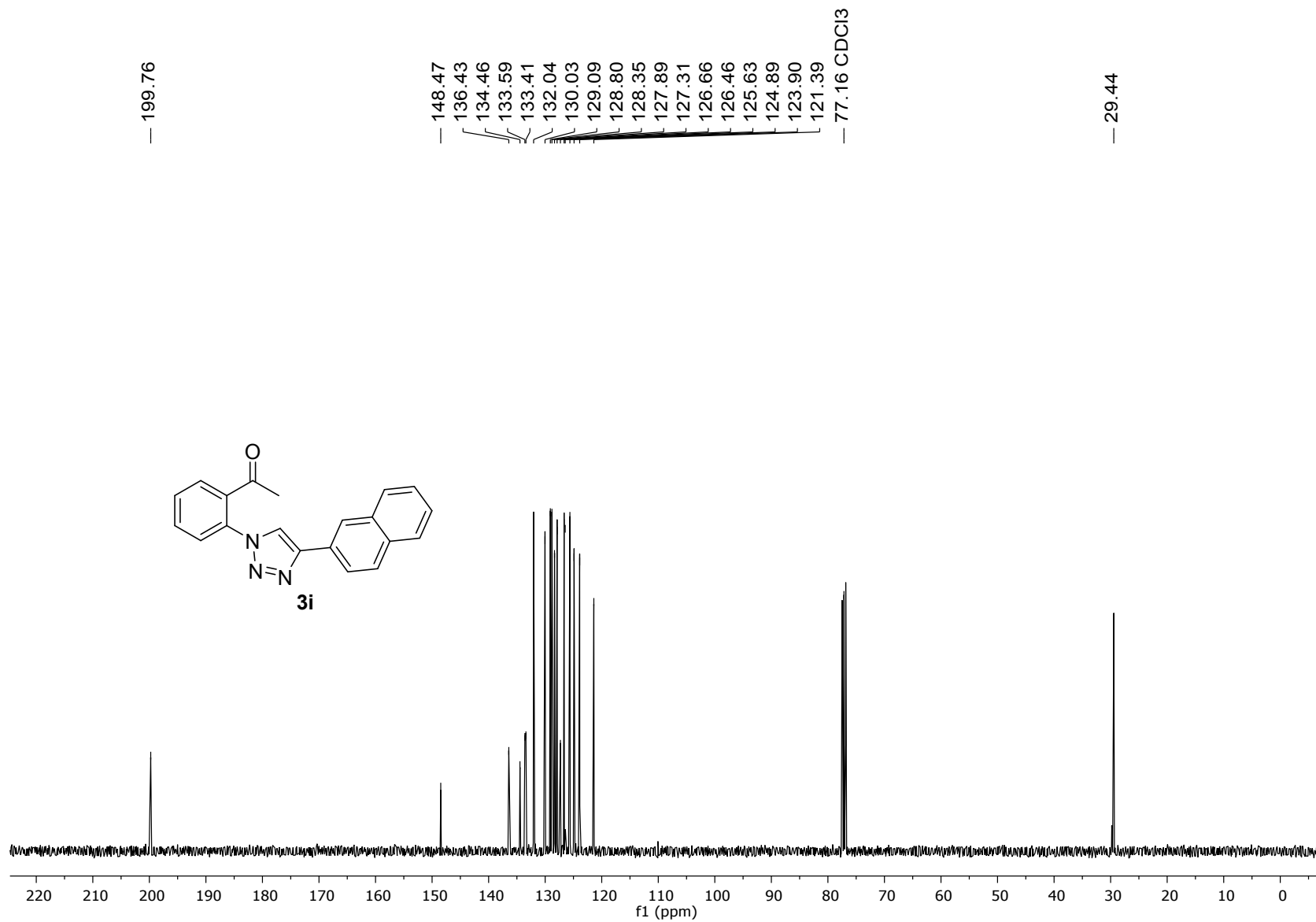


Figure S18:  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3i**.

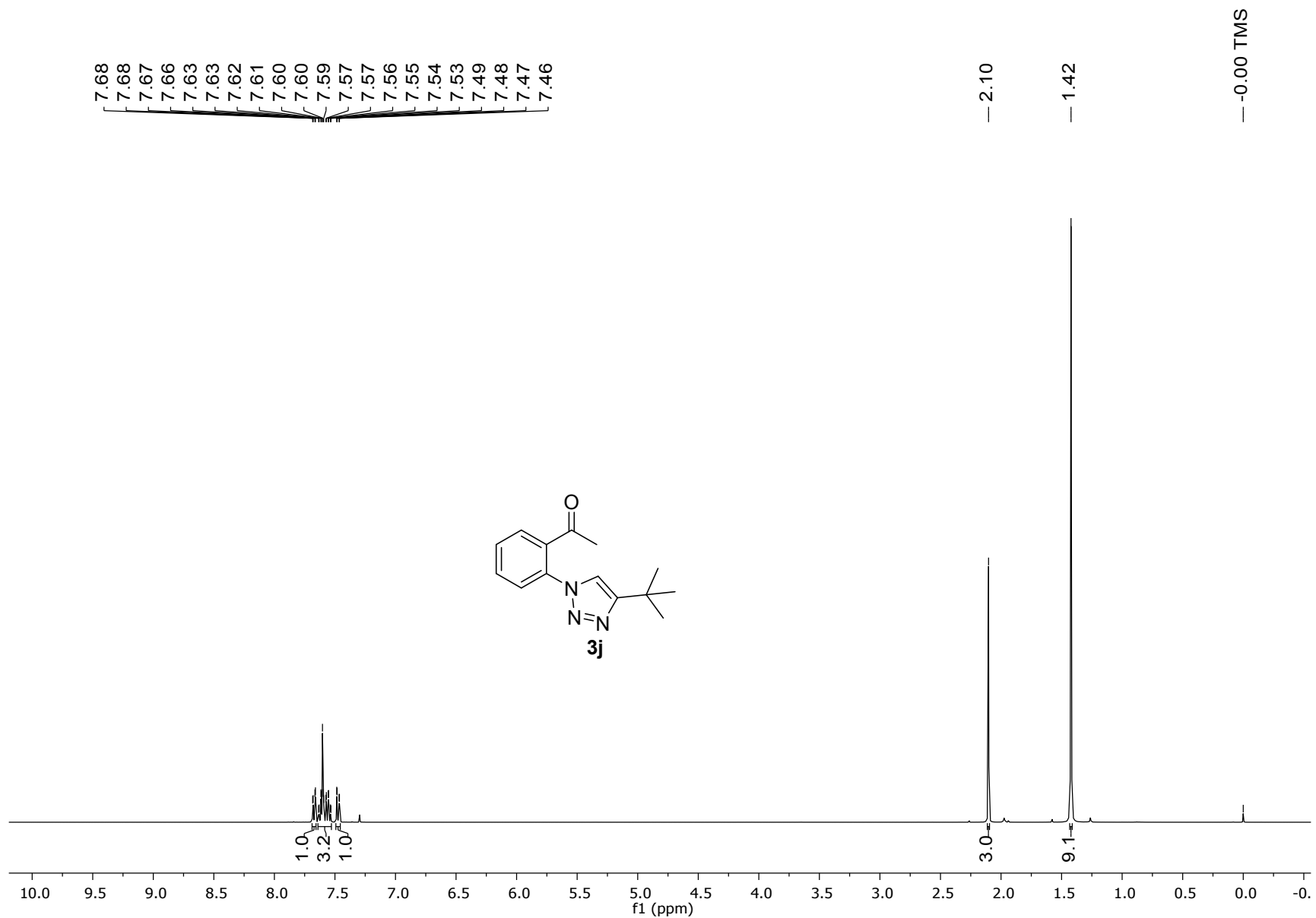


Figure S19: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **3j**.

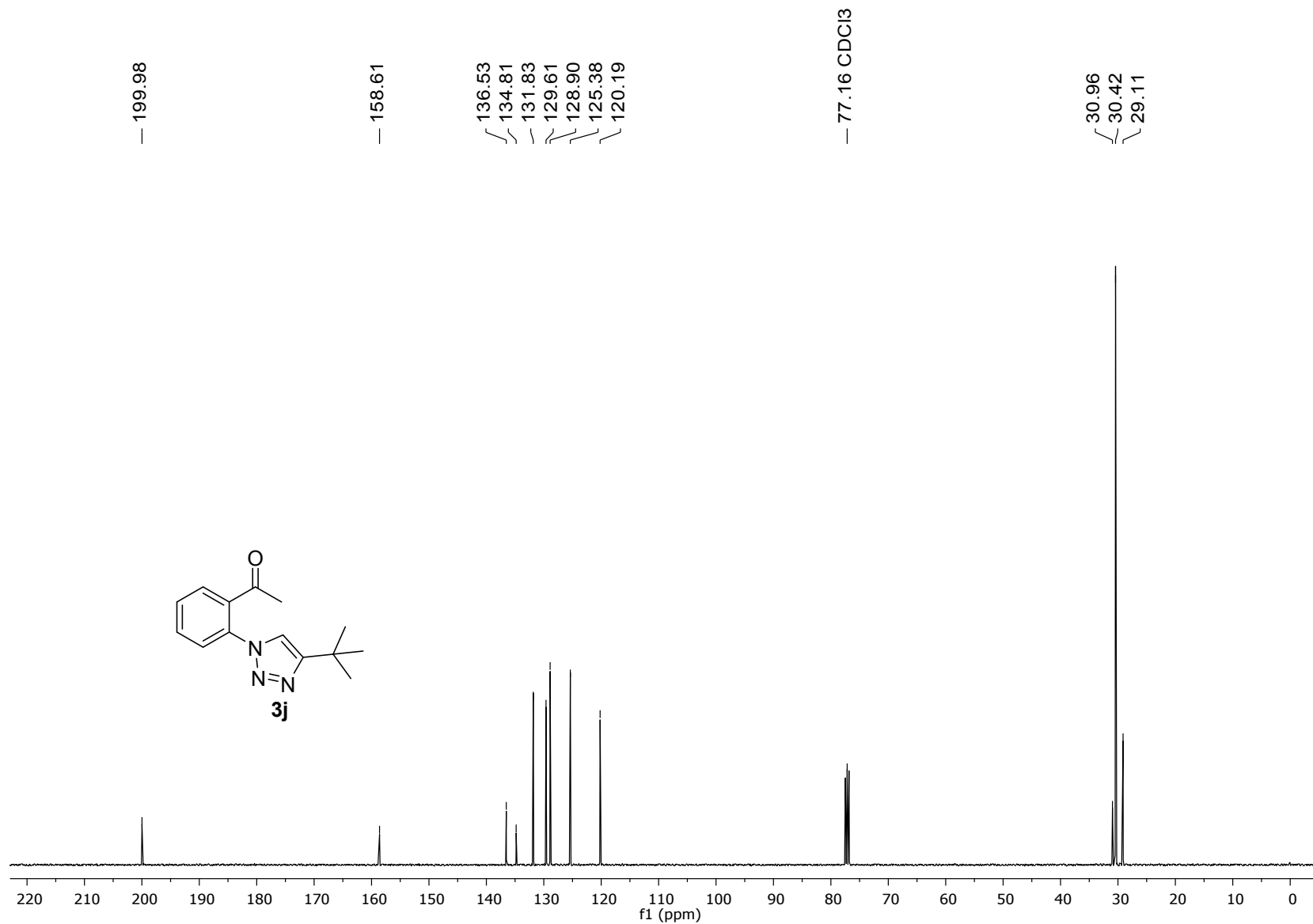
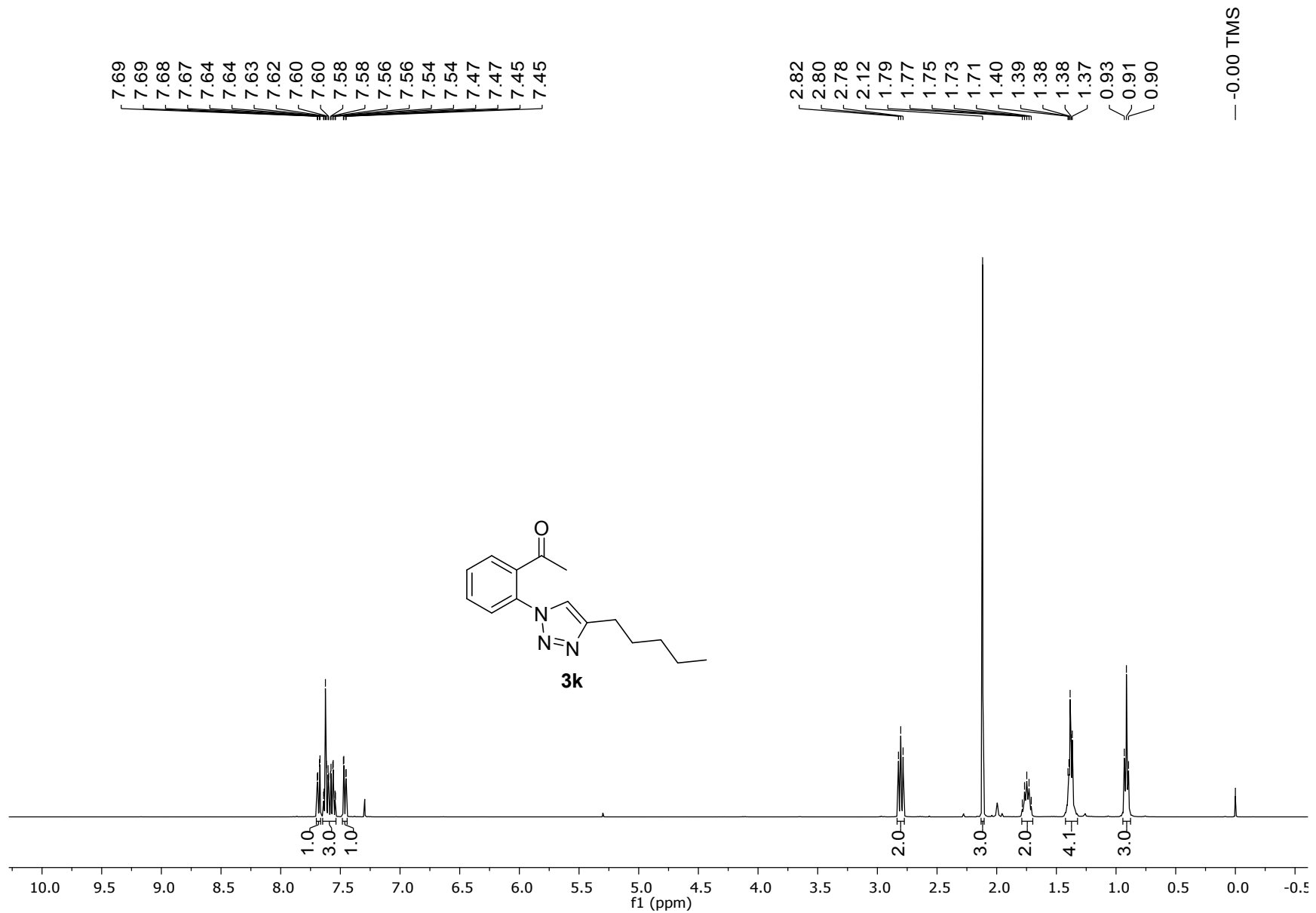


Figure S20:  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3j**.





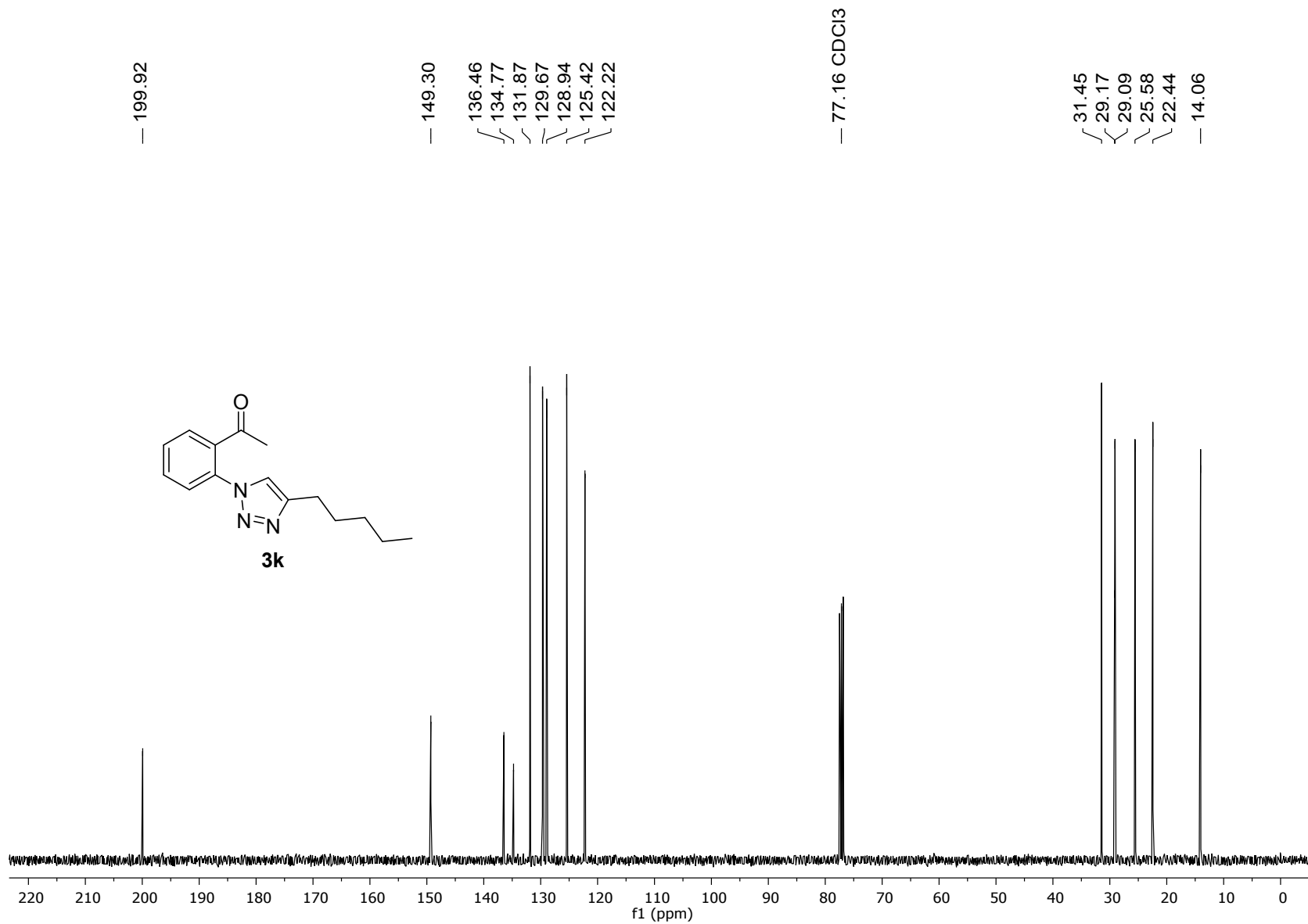
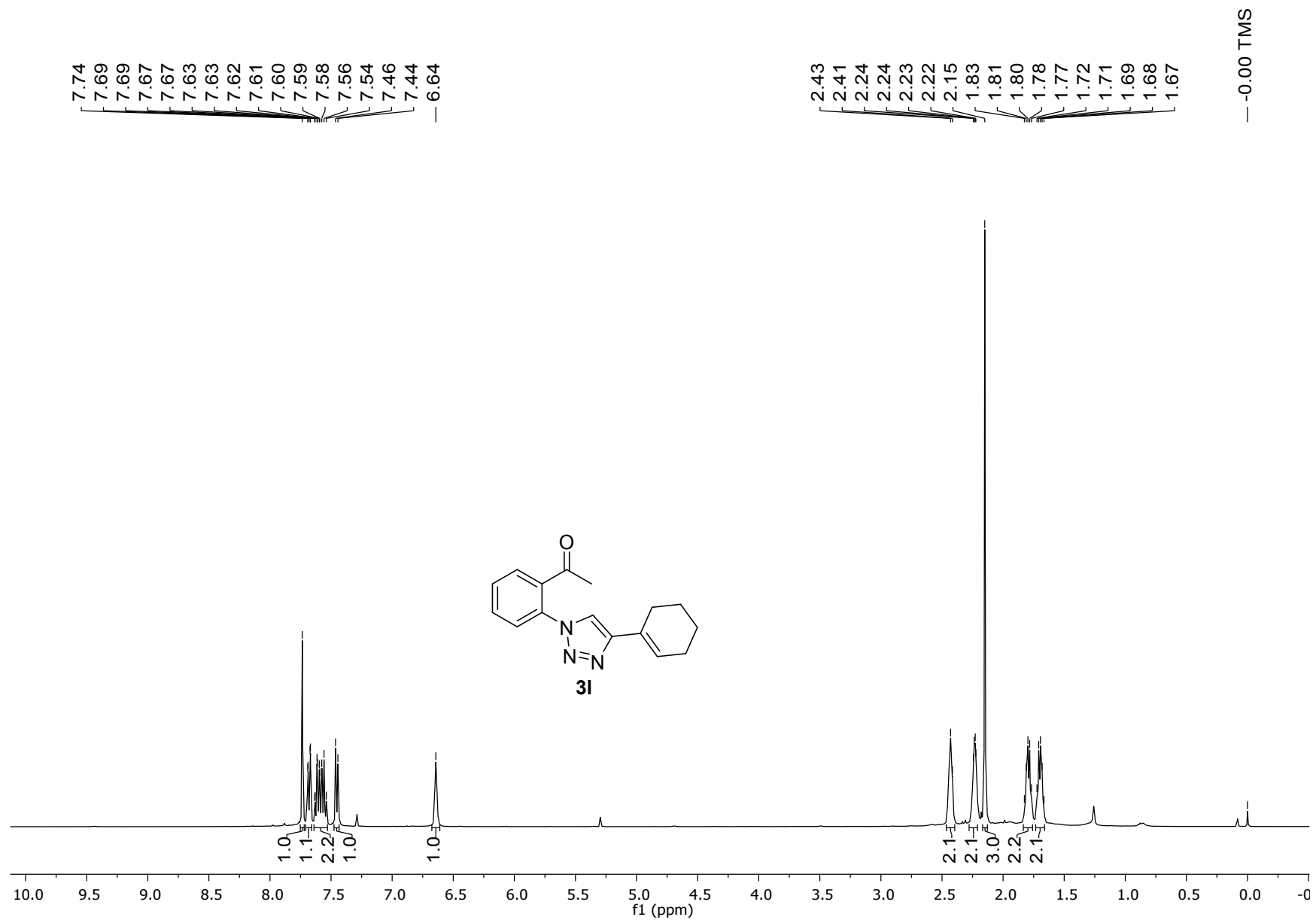


Figure S22:  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3k**.



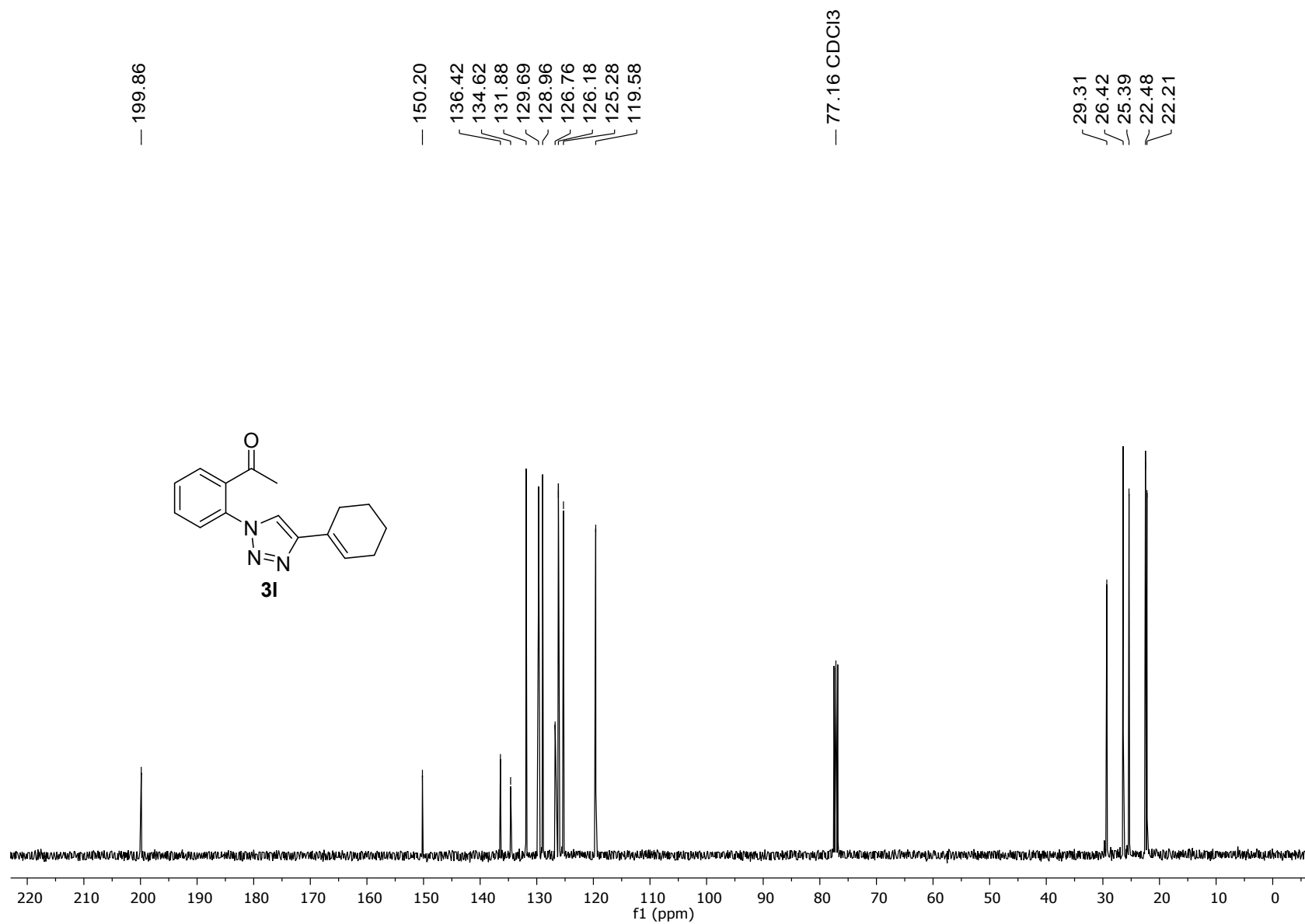
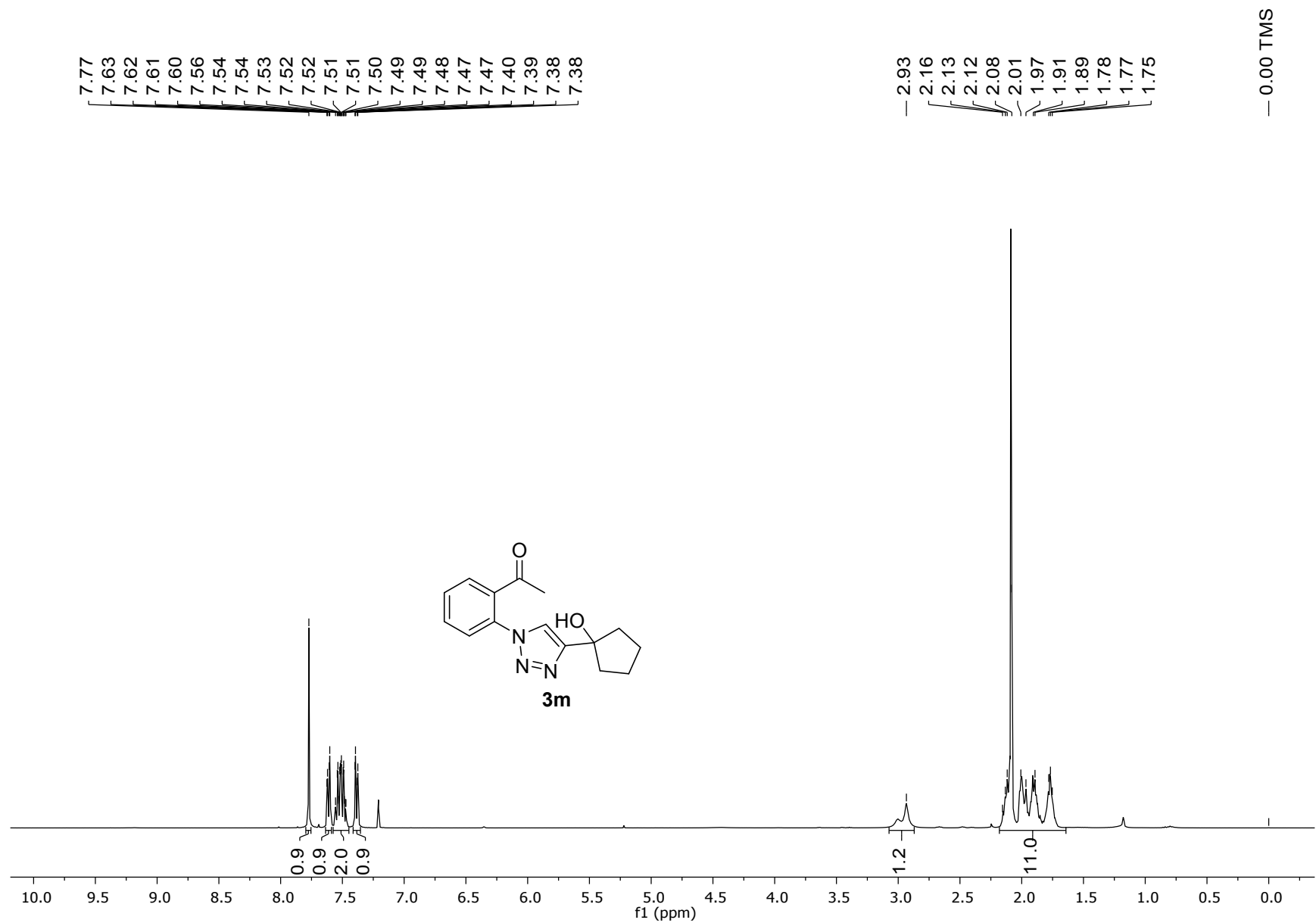


Figure S24:  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **31**.



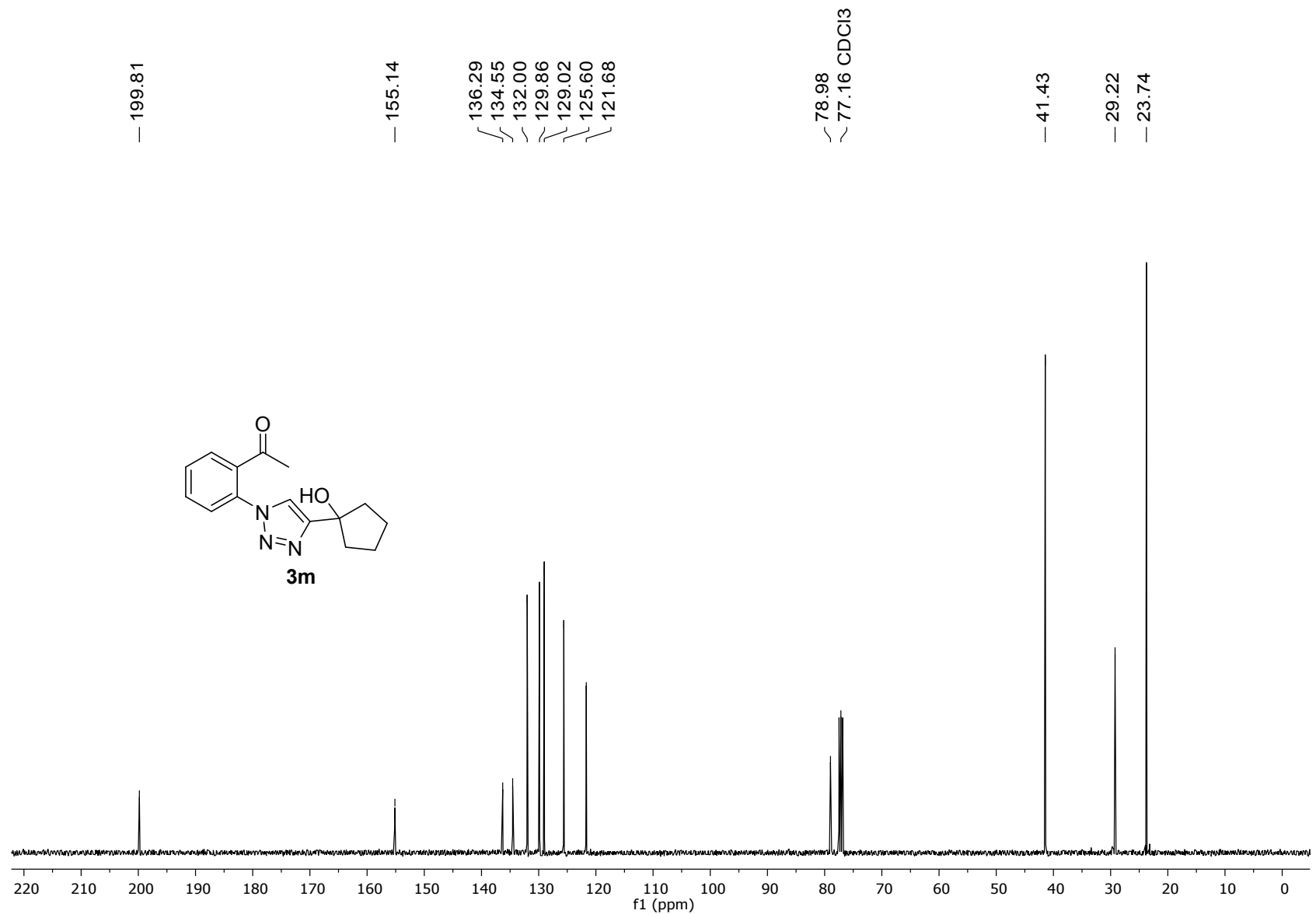


Figure S26:  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3m**.

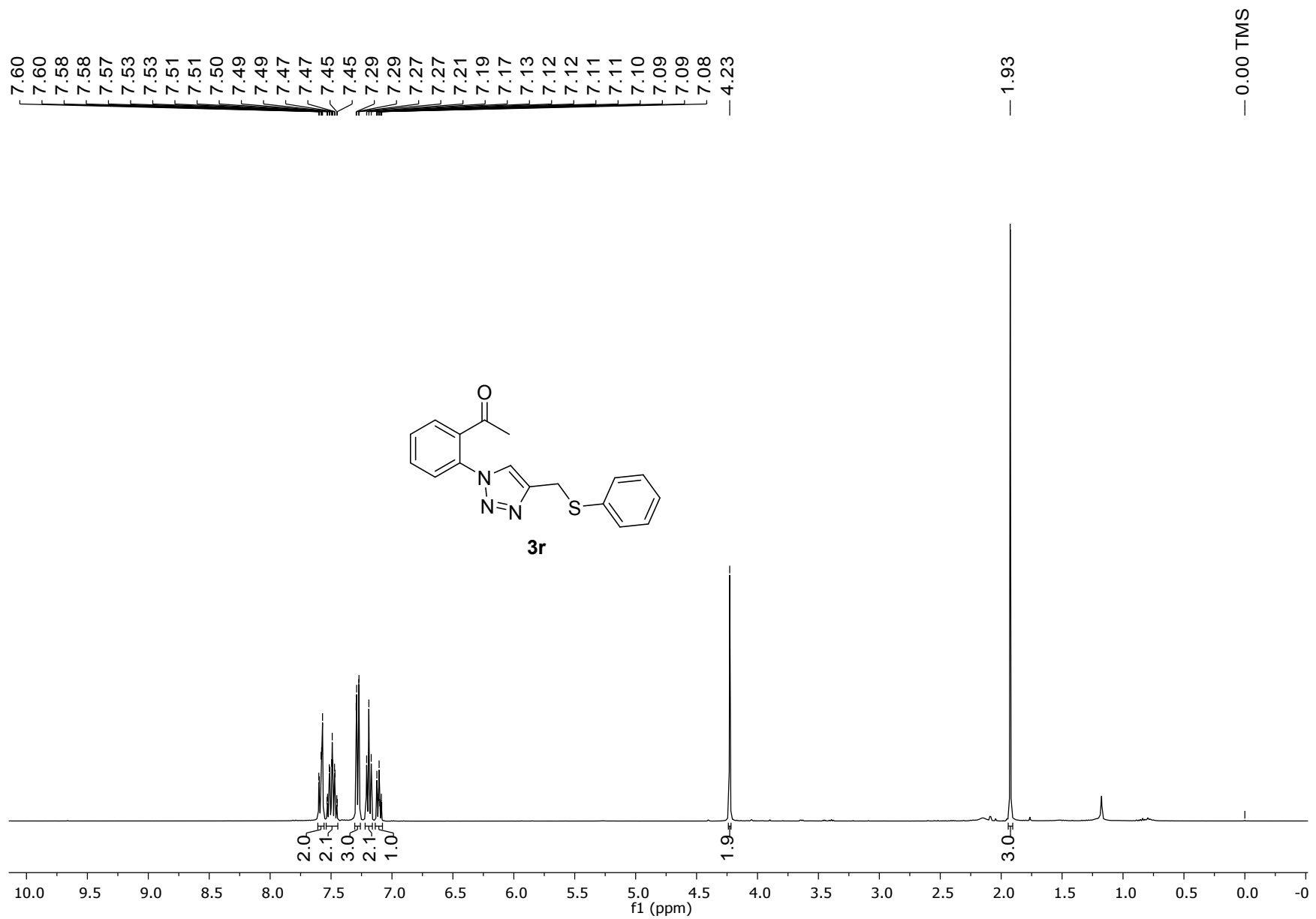


Figure S27: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **3r**.

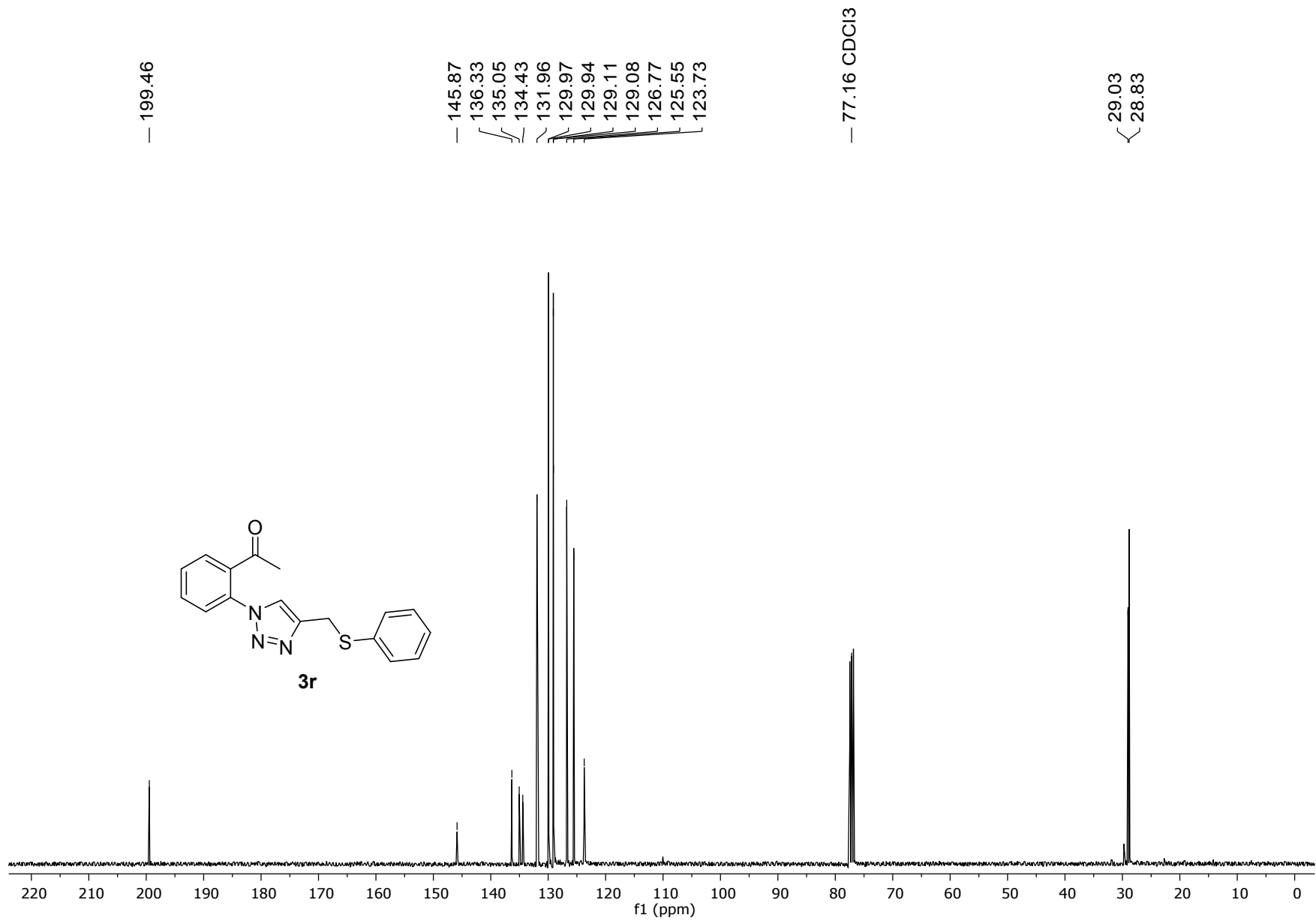
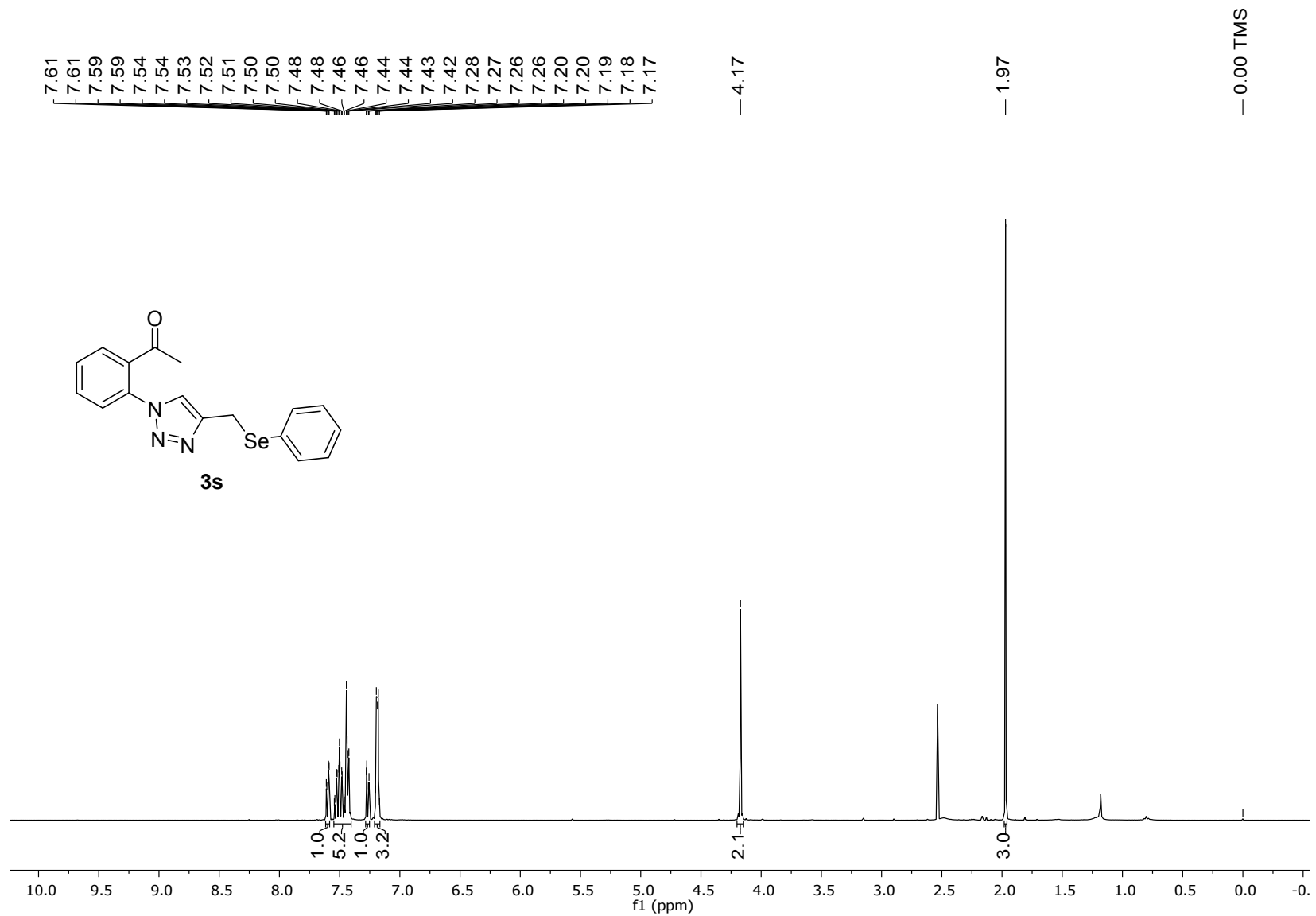


Figure S28:  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3r**.

S32





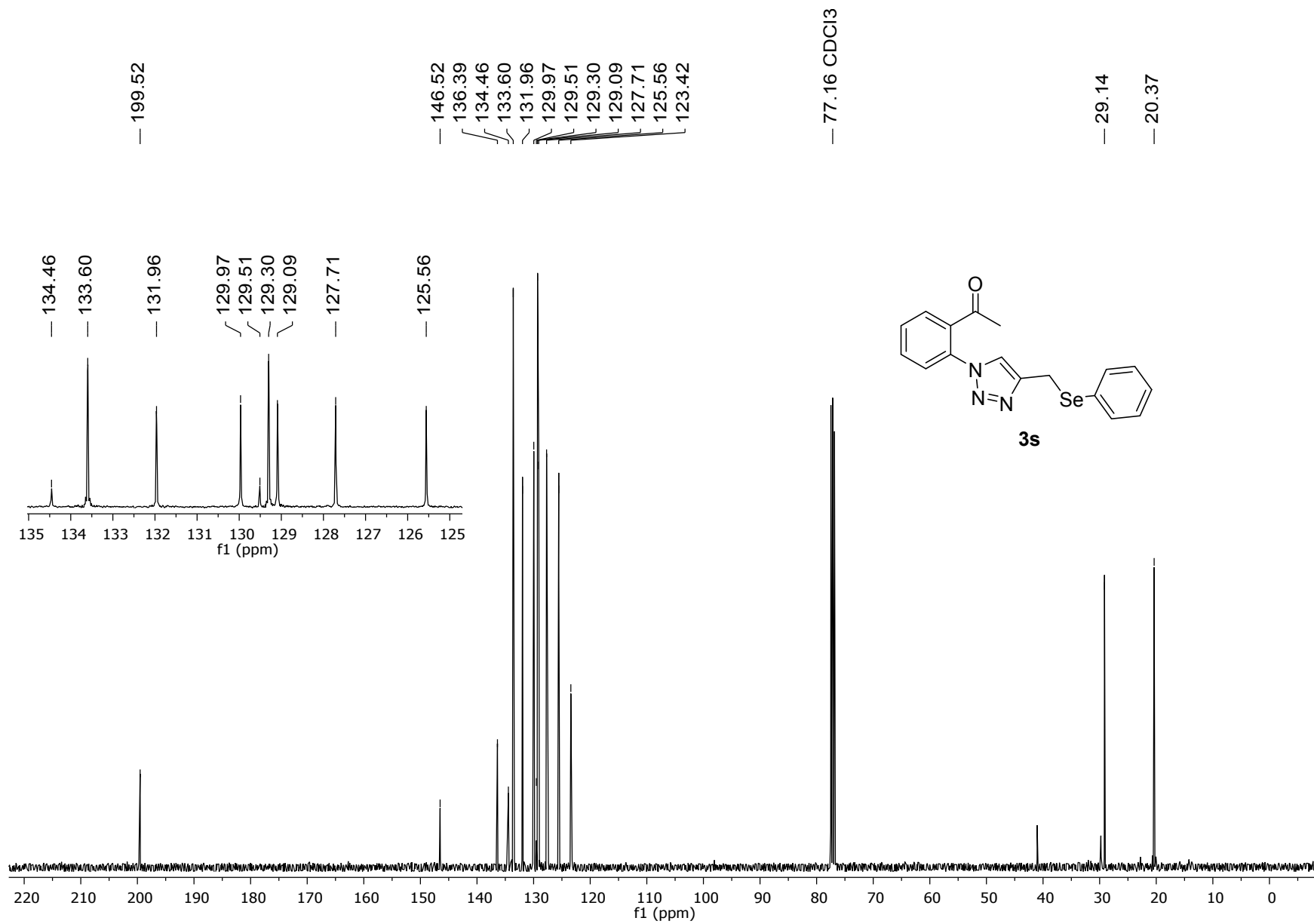


Figure S30: <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) spectrum of compound **3s**.

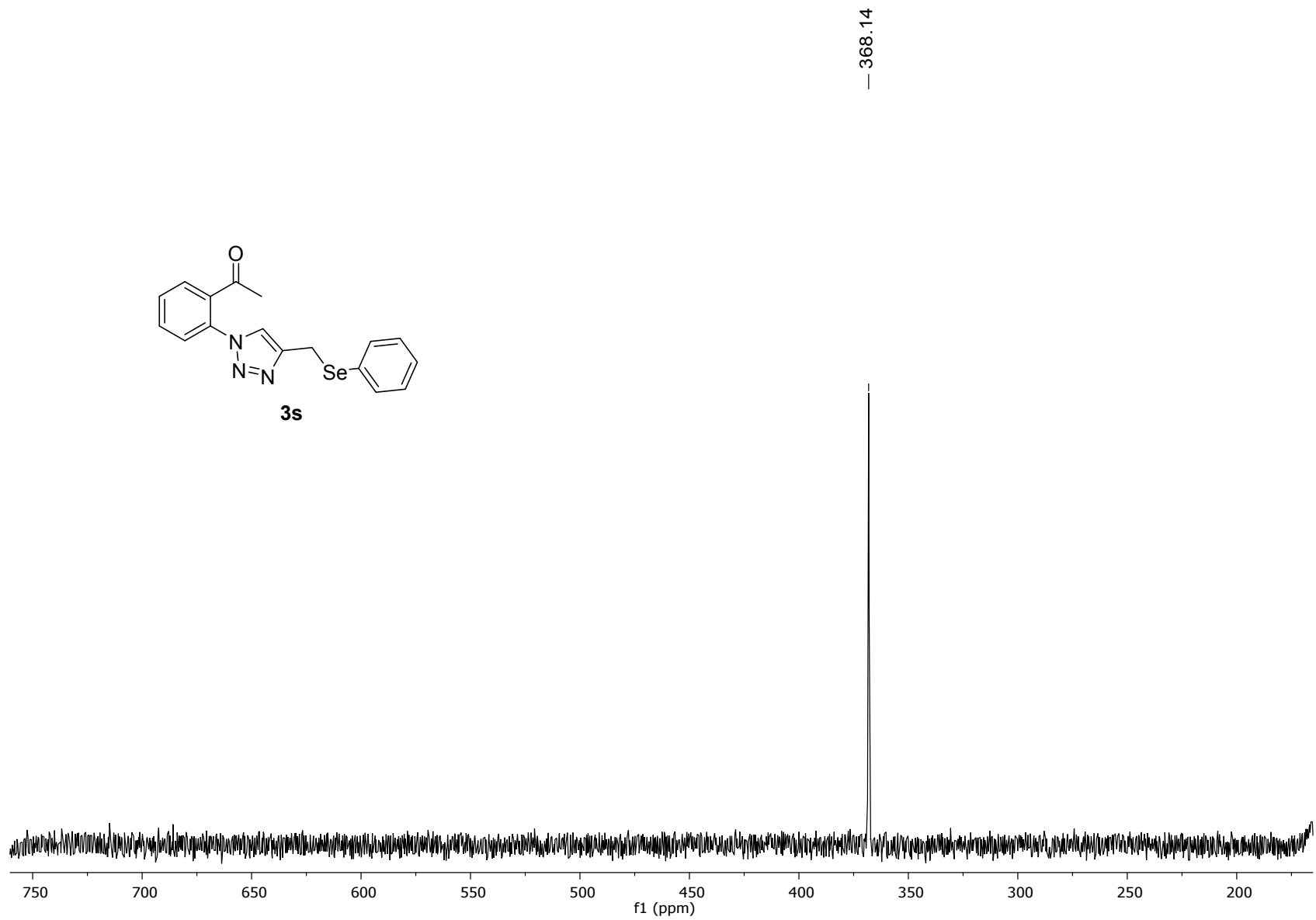


Figure S31:  $^{77}\text{Se}\{^1\text{H}\}$  NMR (76 MHz,  $\text{CDCl}_3$ ) spectrum of compound **3s**.

S35