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PII: S0040-4020(14)00569-9

DOI: 10.1016/j.tet.2014.04.048

Reference: TET 25498

To appear in: *Tetrahedron*

Received Date: 22 January 2014

Revised Date: 31 March 2014

Accepted Date: 14 April 2014

Please cite this article as: Kurandina DV, Eliseenkov EV, Ilyin PV, Boyarskiy VP, Facile and convenient synthesis of aryl hydrazines via copper-catalyzed C–N cross-coupling of aryl halides and hydrazine hydrate, *Tetrahedron* (2014), doi: 10.1016/j.tet.2014.04.048.

Graphical Abstract

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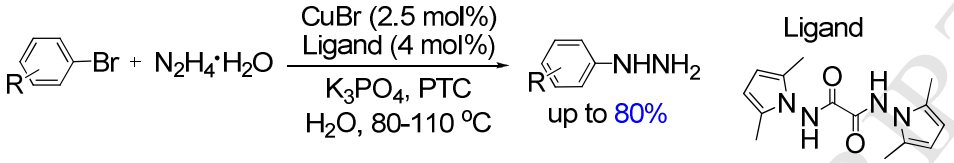
Department of Chemistry, Saint-Petersburg State University, Saint-Petersburg 198504, Russia



Facile and convenient synthesis of aryl hydrazines via copper-catalyzed C–N cross-coupling of aryl halides and hydrazine hydrate

Daria V. Kurandina*, Eugene V. Eliseenkov, Petr V. Ilyin, Vadim P. Boyarskiy

Department of Chemistry, Saint Petersburg State University, Saint-Petersburg 198504, Russia

*Corresponding author. Tel.: +7 981 724-71-46; fax: +7 981 724-71-46. E-mail address: dashakura@gmail.com (Daria V. Kurandina)

Keywords: C−N cross-coupling reaction, Copper catalysis, Hydrazine hydrate, Aryl bromides, Preparation of aryl hydrazines

ABSTRACT

An efficient and convenient method for the synthesis of aryl hydrazines has been developed via copper-catalyzed cross-coupling of aryl bromides and hydrazine with a readily accessible ligand and water as a solvent. The multigram scale procedure is applicable to aryl bromides bearing both moderately electron-donating and electron-withdrawing substituents in the aromatic nucleus. No column chromatography is required to obtain aryl hydrazine hydrochlorides in good yields.

1. Introduction

Aryl hydrazines are widely used as intermediates in the synthesis of various nitrogen-containing heterocyclic systems such as indoles,[1] indazoles,[2] arylpyrazoles,[3] and aryltriazoles.[4] These heterocyclic compounds are of biological and medicinal interest.[5] Preparation of aryl hydrazines is typically carried out via the reduction of the corresponding diazonium salts with tin(II) compounds[6] or alkali metal bisulfites,[7] but these methods have substantial drawbacks. Firstly, they involve the generation of unstable diazonium intermediates which makes this method dangerous at multigram use. Secondly, they produce large volumes of toxic aqueous wastes. Furthermore, yields of aryl hydrazines can be decreased because their deamination is often facile under the reaction conditions, especially for aryl hydrazines with donor substituents.[8] The alternative classical method for the synthesis of aryl hydrazines is based on nucleophilic aromatic substitution of aryl halides with hydrazine. However, such uncatalyzed processes can be applied only for strongly electron-deficient substrates.[9]

Over the last years palladium and copper-catalyzed cross-coupling reactions of aryl halides and amines – Buchwald-Hartwig reactions[10] and modified Ullmann reactions,[11] respectively – have represented the most effective instruments for the construction of new C−N bonds in aromatic systems. Perhaps, because hydrazine is a strong reducing agent capable of destroying a metal-containing system, its derivatives such as benzophenone hydrazone[12] and BOC-hydrazines[13] have been used in palladium-catalyzed cross-coupling in several studies. Stradiotto *et al*. have recently reported the first palladium-catalyzed method for synthesis of aryl hydrazines from hydrazine.[14] While this protocol has obvious advantages, as compared to the classical methods for the synthesis of aryl hydrazines, a number of drawbacks restricts its applicability. To illustrate, the reactions were conducted in a nitrogen-filled glovebox with the high loading of an

expensive catalyst (1.5−10 mol% of [{Pd(cinnamyl)Cl}$_2$] and 4.5−6 mol% of the ligand Mor-DalPhos).

Copper-catalyzed C–N couplings of aryl halides with amines (Ullmann reaction), which can be performed with cheap catalysts and often do not require inert atmosphere, have recently become as popular as Buchwald−Hartwig reactions.[15] Although tremendous progress has been achieved in the field of Ullmann reactions over the past decades, only one paper describing the cross-coupling of unprotected hydrazine with aryl halides catalyzed by copper has been published.[16] The authors performed the coupling reactions of hydrazine and aryl iodides with 10 mol% CuI as a catalyst, PEG−400 as a solvent and 200 mol% K_3PO_4 as a base in a sealed tube at 120 °C for 6 h. The apparent disadvantages of this method are a large amount of PEG−400 (2 mL/1 mmol ArI) and excess hydrazine (1 mL of 85% aqueous hydrazine/1 mmol ArI) obstructing the isolation of product from the reaction mixtures. Furthermore, all of aryl hydrazines (except for phenylhydrazine) had to be transformed into their *N*-tosyl derivatives in order to be isolated. All of these factors appear to restrict the synthetic utility of the method described.

The objective of our work was to design a new and more efficient method of aryl hydrazines synthesis using copper-catalyzed C–N cross-coupling reaction of hydrazine with aryl halides. It has been recently found that copper catalysts containing oxalyl dihydrazide derivatives $(CONHNR'R'')_2$ as ligands allow C–N cross-coupling processes in water in the presence of phase transfer catalysts (PTCs).[17-20] For example, the catalytic systems of Cu(0,I,II)/$(CONHNH_2)_2$(**L1**)/hexane-2,5-dione(**A1**)[17] and Cu(0,II)/$PhNHNHCOCONHNH_2$(**L2**)/hexane-2,5-dione(**A1**)[19] were successfully applied for arylation of anilines. Inspired by these results, we used the ligand systems based on the derivatives of oxalyl dihydrazide for copper-catalyzed arylation of hydrazine. As an extension of their applicability for catalysis in water, we are the first to report a new method for the synthesis of aryl hydrazines hydrochlorides via copper-catalyzed cross-coupling of aryl bromides with hydrazine in an aqueous solution.

2. Results and discussion

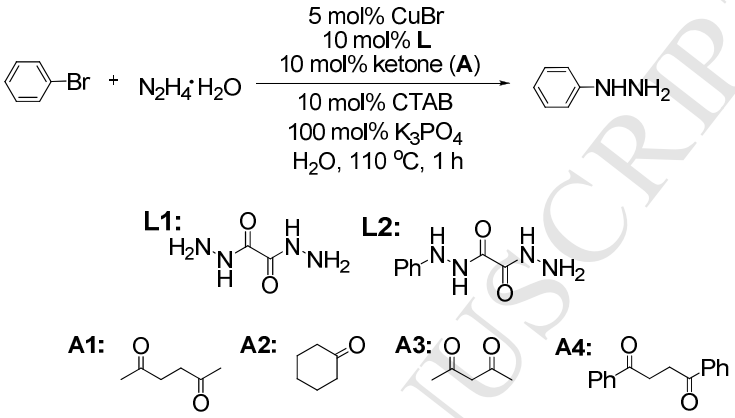
The reaction of bromobenzene with hydrazine hydrate was chosen as a model process for the study. We carried out the CuBr/**L1**/**A1**-catalyzed reaction of bromobenzene with hydrazine hydrate for 1 h and detected that the conversion of bromobenzene was 96% and the yield of phenylhydrazine was 73%.[21] In addition, aniline (3%), which was the by-product formed by deamination of phenylhydrazine, was found in the reaction mixture (Table 1, entry 1). As we suppose based on the data of Pd-catalyzed C–N cross-coupling of aryl halides with hydrazine,[14] the rest of the starting material was turned into benzene, whose yield we did not determine in the optimization experiments.

We optimized the reaction conditions by screening the ligand systems of $RNHNHCOCONHNH_2$ (ligand **L)**/ketone (additive **A**) (Table 1). Initially, it is worth to note that the reaction did not proceed without addition of the ligand system (Table 1, entry 2). At the same time, the ligand system did not catalyze this process without a copper source (Table 1, entry 3). The ligand **L1** and the additive **A1** did not work properly without each other (Table 1, entry 4, 5). The ligand system of **L1**/**A1** proved to be slightly more active than the ligand system of **L2**/**A1** (Table 1, entries 1, 6). However, the drawback of the ligand system of **L2**/**A1** was that **L2** reacted with hydrazine to give an additional amount of phenylhydrazine. This was proven by the reaction of

1-bromo-4-methoxybenzene with hydrazine hydrate where phenylhydrazine was found in the reaction mixture. Therefore, our further investigation was concentrated on the ligand systems composed of **L1** and different mono- and dicarbonyl compounds as additives. The additives such as cyclohexanone (**A2**) (entry 7), pentane-2,4-dione (**A3**) (entry 8), and 1,4-diphenylbutane-1,4-dione (**A4**) (entry 9) proved to be less efficient than hexane-2,5-dione (**A1**).

Table 1

Cross-coupling of bromobenzene and hydrazine hydrate using different ketones as components of the ligand system[a]



Entry	L+A	Conversion,[b] %	Yield of $PhNHNH_2$,[b] %	Yield of $PhNH_2$,[b] %
1	**L1+A1**	96	73	3
2	–	3	0	0
3[c]	**L1+A1**	0	0	0
4	**L1**	38	9	0
5	**A1**	6	0	0
6	**L2+A1**	90	69	4
7	**L1+A2**	13	9	0
8	**L1+A3**	24	9	0
9	**L1+A4**	4	3	0

[a] Reaction conditions: bromobenzene (1 mmol), $N_2H_4 \cdot H_2O$ (2 mmol), CuBr (0.05 mmol), L (0.1 mmol), A (0.1 mmol), CTAB (0.1 mmol), K_3PO_4 (1 mmol), H_2O (50 mg), 110 °C, 1 h.

[b] Determined by GC analysis (internal standard – 4-chloro-1-methoxybenzene, that is stable under the reaction condition). Conversion is based on consumption of bromobenzene.

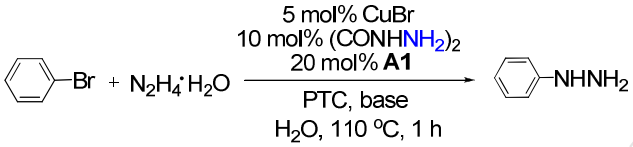
[c] without any copper source.

To optimize the reaction conditions we varied the hydrazine hydrate amount, base, and PTC (Table 2). The optimal amount of hydrazine hydrate was found to be 200 mol% (Table 2, entries 1–3). The bases which were used (Table 2, entries 2, 4–8) led to high conversions of bromobenzene, but the yield of the target product was maximal with K_3PO_4 and decreased markedly when KOH, K_2CO_3, K_2HPO_4 or Na_3PO_4 were applied. This decrease was probably a result of hydrolysis of bromobenzene[22] (in addition to the previously mentioned reduction). Selectivity was maximal in the case of K_3PO_4 possibly due to its strong basity (pKa = 12.3 for the conjugate acid) and low nucleophilicity.[23] Cetyltrimethylammonium bromide (CTAB) or tetrabutylammonium bromide (TBAB) was applied as a PTC with near equal efficiency for the model reaction (Table 2, entries 2, 9). The reaction proceeded without a PTC (Table 2, entry 10),

however, the conversion of the substrate and selectivity of the process were less than in the presence of a PTC. Further, the reaction showed similar level of efficiency at the lower PTC loadings (5 mol% and 2 mol%) (Table 2, entries 11, 12).

Table 2

$CuBr/(CONHNH_2)_2$/hexane-2,5-dione-catalyzed cross-coupling of bromobenzene and hydrazine hydrate: optimization of the reaction conditions[a]



Entry	X	Amount of $N_2H_4 \cdot H_2O$ (mol%)	PTC (mol%)	Base	Conversion,[b] %	Yield of $PhNHNH_2$,[b] %	Yield of $PhNH_2$[b], %
1	Br	400	CTAB (10)	K_3PO_4	92	65	4
2	Br	200	CTAB (10)	K_3PO_4	96	73	3
3	Br	110	CTAB (10)	K_3PO_4	100	24	14
4[c]	Br	200	CTAB (10)	K_3PO_4	98	46	11
5	Br	200	CTAB (10)	KOH	97	46	3
6	Br	200	CTAB (10)	K_2CO_3	79	25	2
7	Br	200	CTAB (10)	$K_2HPO_4 \cdot 3H_2O$	95	54	8
8	Br	200	CTAB (10)	Na_3PO_4	95	44	3
9	Br	200	TBAB (10)	K_3PO_4	100	72	3
10	Br	200	-	K_3PO_4	83	55	2
11	Br	200	CTAB (5)	K_3PO_4	100	73	3
12	Br	200	CTAB (2)	K_3PO_4	100	70	3
13	I	200	CTAB (10)	K_3PO_4	95	68	1
14[d]	Cl	200	CTAB (10)	K_3PO_4	0	0	0

[a] Reaction conditions: bromobenzene (1 mmol), $N_2H_4 \cdot H_2O$ (2 mmol), CuBr (0.05 mmol), $(CONHNH_2)_2$ (0.1 mmol), **A1** (0.2 mmol), PTC (0.1 mmol), base (1 mmol), H_2O (50 mg), 110 °C, 1 h.

[b] Determined by GC analysis (internal standard–4-chloro-1-methoxybenzene). Conversion is based on consumption of aryl bromide.

[c] 50 mol% K_3PO_4.

[d] 8 h, 120 °C.

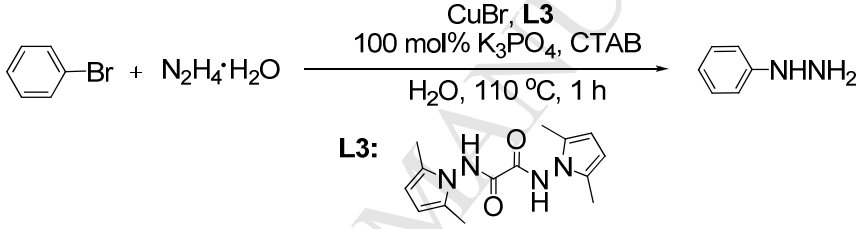
The reactivity of chlorobenzene and iodobenzene was compared with that of bromobenzene (Table 3, entries 2, 13, 14). The reaction of iodobenzene produced approximately the same yield of the product and the conversion of the substrate as the reaction of bromobenzene. In contrast, chlorobenzene was inert in this process even under more drastic reaction conditions (8 h, 120 °C).

It is known that hexane-2,5-dione can react with oxalyl dihydrazide to give *N*,*N*′-bis(2,5-dimethylpyrrol-1-yl)oxalamide (**L3**) via a Paal-Knorr reaction.[24] We synthesized **L3** from **L1** and **A1** and compared the catalytic activity of CuBr/**L3** with that of CuBr/**L1**/**A1** in the reaction of hydrazine hydrate with bromobenzene. The yield of phenylhydrazine increased from 73% up to 86% in the reaction when CuBr/**L3** was used (Table 3, entry 1). The optimization experiments with this catalytic system (Table 3) showed its enhanced activity as compared with CuBr/**L1**/**A1**. The amount of CuBr and **L3** could be diminished down to 2.5 mol% and 4 mol%, respectively,

without a loss of phenylhydrazine yield (Table 3, entry 2). A moderate yield of the target product (66%) was obtained in the reaction with 0.6 mol% of CuBr and 1.2 mol% of **L3** (Table 3, entry 4). In addition, arylation of hydrazine could proceed at room temperature but with a relatively low yield of the target phenylhydrazine (21%) at a moderate conversion of bromobenzene (59%) (Table 3, entry 6). Presumably, reductive hydrodehalogenation of bromobenzene is the main process at room temperature. The same problem occurred for the reaction of chlorobenzene with hydrazine hydrate where the yield of phenylhydrazine was 19% while the conversion of chlorobenzene was 70% after 7 h at 130 °C (Table 3, entry 7). The amount of CTAB could be reduced from 10 mol% to 3 mol% without lowering the yield of phenylhydrazine (Table 3, entry 8). Besides, CTAB, as a phase transfer catalyst, was superior to TBAB and tetrabutylammonium hydroxide (TBAH) (Table 3, entries 8–10). Cu(0), Cu(I) and Cu(II) were active as catalysts for the cross-coupling with hydrazine (Table 3, entries 8, 11–12). As a result, the optimal conditions for copper-catalyzed arylation of hydrazine were obtained: CuBr (2.5 mol%), ligand (**L3**) (4 mol%), CTAB (3 mol%), K_3PO_4 (100 mol%), water (50 mg/1 mmol ArBr), hydrazine hydrate (200 mol%), 110 °C, and 1 h.

Table 3

CuBr/**L3**-catalyzed cross-coupling of bromobenzene and hydrazine hydrate: optimization of the reaction conditions[a]



Entry	Copper source	Copper/**L3** (mol%)	PTC	Amount of PTC (mol%)	T, °C	Conversion,[b] %	Yield of $PhNHNH_2$,[b] %	Yield of $PhNH_2$,[b] %
1	CuBr	5/10	CTAB	10	110	100	86	3
2	CuBr	2.5/4	CTAB	10	110	99	85	4
3	CuBr	1.2/2.5	CTAB	10	110	97	73	2
4	CuBr	0.6/1.2	CTAB	10	110	80	66	2
5	CuBr	0.3/0.6	CTAB	10	110	49	38	1
6[c]	CuBr	5/10	CTAB	10	25	59	21	0
7[d]	CuBr	5/10	CTAB	10	130	70	19	0
8	CuBr	2.5/4	CTAB	3	110	99	84	3
9	CuBr	2.5/4	TBAB	3	110	97	77	3
10	CuBr	2.5/4	TBAH	3	110	98	65	4
11	$Cu(OAc)_2 \cdot H_2O$	2.5/4	CTAB	3	110	98	87	5
12	Cu	2.5/4	CTAB	3	110	95	80	5

[a]Reaction conditions: bromobenzene (1 mmol), $N_2H_4 \cdot H_2O$ (2 mmol), CuBr, **L3**, PTC, K_3PO_4 (1 mmol), H_2O (50 mg), 1 h.

[b] Determined by GC analysis (internal standard–4-chloro-1-methoxybenzene). Conversion is based on consumption of aryl bromide.

[c] The reaction was run for 72 h.

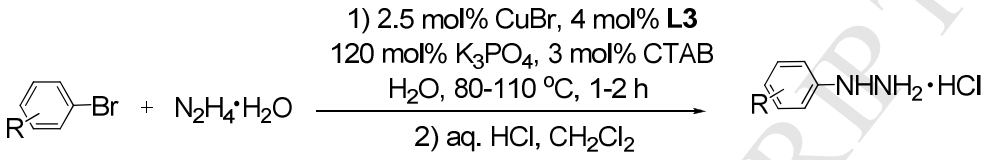
[d] Reaction conditions: chlorobenzene (1 mmol), $N_2H_4 \cdot H_2O$ (2 mmol), CuBr (0.05 mmol), **L3** (0.1 mmol), CTAB (0.1 mmol), K_3PO_4 (1.5 mmol), H_2O (50 mg), 7 h.

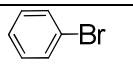
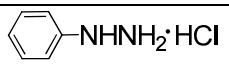
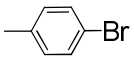
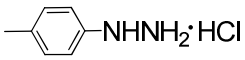
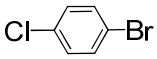
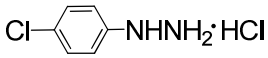
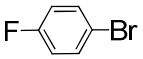
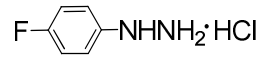
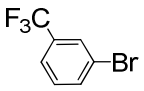
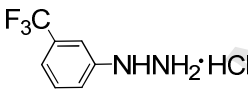
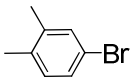
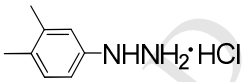
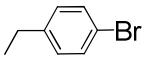
To establish the scope of this protocol, a number of aryl bromides were coupled with hydrazine under the optimal conditions and the corresponding aryl hydrazines were transformed into hydrochloride salts to be isolated. Aryl bromides with moderately electron-donating *meta*- or *para*- substituents, as well as with electron-withdrawing

meta- or *para*-substituents, reacted with hydrazine to give good isolated yields of the products (Table 4, entries 1–7). The strong electron-donating substituents in a substrate like 4-MeO and 4-EtO led to large amounts of the corresponding anilines in the isolated aryl hydrazine hydrochlorides. The method of column chromatography was found to be inapplicable for aryl hydrazines with donor substituents because they were quickly oxidized by oxygen in the air.[25] Aryl hydrazine hydrochlorides can be separated from the corresponding aniline hydrochlorides by recrystallization but with considerable losses in isolated yield.

Table 4

CuBr/**L3** –catalyzed cross-coupling of aryl bromides and hydrazine hydrate on a 10 mmol scale[a]



Entry	ArBr	Product	Time, h	T, °C	Yield of $ArNHNH_2 \cdot HCl$,[b] %
1			1	110	71
2[c]			1	110	73
			2	80	70
3			1.5	110	80
4			1	110	75
5			1	110	70
6			2	80	52
7			2	80	55

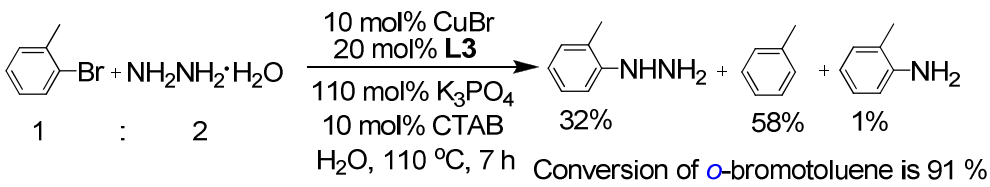
[a] Reaction conditions: aryl bromide (10 mmol), $N_2H_4 \cdot H_2O$ (20 mmol), CuBr (0.25 mmol), **L3** (0.4 mmol), CTAB (0.3 mmol), K_3PO_4 (12 mmol), H_2O (500 mg), 80–110 °C, 1–2 h.

[b] Yields of isolated products.

[c] The reaction at 110 °C was run on a 300 mmol scale.

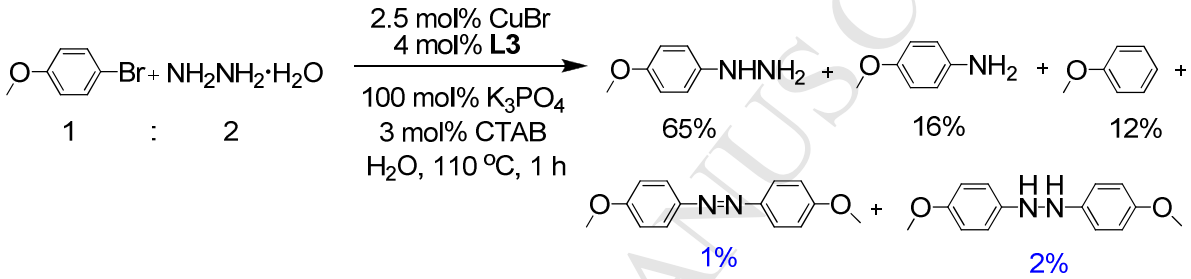
Also, we have investigated C–N cross-coupling of *ortho*-substituted aryl bromides with hydrazine on the example of the reaction with *o*-bromotoluene (Scheme 1). This reaction, performed by **Method 4.5** from Experimental section, produced the corresponding aryl hydrazine with only 32% yield after 7 h and with a high loading of the catalyst. Toluene was found to be the main product in the reaction of *o*-bromotoluene and hydrazine hydrate (yield of 58%).

Scheme 1



In order to determine the nature of the side reactions in C–N cross-coupling of aryl bromides with hydrazine, the coupling of $N_2H_4 \cdot H_2O$ and 1-bromo-4-methoxybenzene (Scheme 2) was carried out by **Method 4.5** from Experimental section and then analyzed by GC and GC-MS. 4-Methoxyphenylhydrazine, 4-methoxyaniline, and anisole were detected in the reaction mixture, as well as trace amounts of 1,2-bis(4-methoxyphenyl)diazene and *N*,*N*′-bis(4-methoxyphenyl)hydrazine. 4-Methoxyaniline (16%) and anisole (12%) formed through known side reactions[14] – metal-mediated N−N bond cleavage in 4-methoxyphenylhydrazine and reductive hydrodehalogenation of 1-bromo-4-methoxybenzene, respectively. A low yield of *N*,*N*′-bis(4-methoxyphenyl)hydrazine (2% at 100% conversion of aryl bromide) indicates the high monoarylation/diaryltion selectivity in this process. The possible explanation of this fact is lower nucleophilicity of aryl hydrazine as compared with hydrazine. The trace amount of 1,2-bis(4-methoxyphenyl)diazene (1%) was presumably formed by oxidation of *N*,*N*′-bis(4-methoxyphenyl)hydrazine by oxygen in the air.

Scheme 2



3. Conclusion

To summarize, we have developed an efficient method for the synthesis of aryl hydrazines with electron-withdrawing and moderately electron-donating substituents via C–N cross-coupling of aryl bromides and hydrazine in water with 2.5 mol% of CuBr and 4 mol% of the ligand. This method is attractive due to a few reasons. Firstly, it can be applied for both aryl iodides and bromides. Secondly, the catalytic system employed is easily accessible and inexpensive. Finally, the isolation of products can be readily performed without column chromatography, which is essential for large scale syntheses.

4. Experimental section

4.1. General chemical procedures

All reagents (except for ligands of **L2, L3** and additive **A4**) and solvents were obtained commercially and used without further purification. Ligands **L2, L3** and additive **A4** were synthesized according to the methods described below. Hydrazine hydrate (100%), and K_3PO_4 (> 98 wt% pure) were from Acros Organics and Sigma, respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance II+ 400 MHz (UltraShield Magnet) spectrometer at room temperature. GC analysis was performed on a Chromatec Crystal 5000.2 chromatograph equipped with a flame ionization detector and a VRH-1 (10 m×0.53 mm×2.65 μm) capillary column. GS-MS analysis was conducted on a Shimadzu GCMS QP-2010 SE spectrometer equipped with an electron impact ionization source and Rtx-5MS (30 m×0.32 mm×0.25 μm)

capillary column. Mass spectra were recorded on a Bruker micrOTOF spectrometer equipped with an electrospray ionization (ESI) source. For this analysis species were dissolved in methanol. Infrared spectra (4000−400 cm^{-1}) were recorded on a Shimadzu FTIR-8400S instrument as KBr pellets. The IR data is reported within 4000–1400 cm^{-1}. Melting points were determined on a capillary melting point apparatus and not corrected.

4.2. Synthesis of 1,4-diphenyl-butane-1,4-dione (A4)[26]

Additive **A4** was prepared according to the previously described protocol[26] by the reaction of acetophenone with α-chloroacetophenone. White solid (62%), mp 144−145 °C (ethyl acetate) (lit.[26]: 144–145 °C); IR (KBr) ν (cm^{-1}): 2966, 2905, 1686–1676, 1593, 1574, 1447. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 8.03 (d, *J* = 7.2 Hz, 4H), 7.60 (t, *J* = 7.3 Hz, 2H), 7.53–7.49 (m, 4H), 3.41 (s, 4H). ^{13}C NMR (DMSO-d_6+CCl_4, 101 MHz, ppm) δ 199.2, 137.0, 133.7, 129.2, 128.4, 32.8. HRMS (ESI^+): calcd for $C_{16}H_{15}O_2$ $[M+H]^+$: 239.1072; found 239.1069.

4.3. Synthesis of *N′*-phenyl oxalyl dihydrazide (L2)[27]

Diethyl oxalate (200 mL, 1.47 mol) and phenylhydrazine (80 mL, 0.814 mol) were dissolved in ethanol (300 mL) in a 1 L flask with a reflux condenser. The reaction mixture was stirred at reflux for 30 min, and then the solution cooled to 50–60 °C and quickly filtered from a precipitate of $(PhNHNHCO)_2$. After cooling the filtrate to room temperature, a precipitate of PhNHNHCOCOOEt was filtered off, washed with water and dried at room temperature (79.6 g, 47%). Then PhNHNHCOCOOEt (20.8 g, 0.1 mol) of and $N_2H_4{\cdot}H_2O$ (98%) (6.4 g, 0.13 mol) were dissolved in ethanol (100 mL) in a 500 mL flask with a reflux condenser. The reaction mixture was stirred at reflux for 1 h, and then cooled to room temperature. A precipitate of **L2** was filtered off, washed with ethanol and dried at 100 °C in the air. Pale yellow solid (18.4 g, 95%), mp 209−210 °C (ethanol) (lit.[27]: 205–206 °C); IR (KBr) ν (cm^{-1}): 3619−2879, 2812, 1932, 1845, 1772, 1703−1585, 1519, 1472.^{1}H NMR (DMSO-d_6+CCl_4, 400 MHz, ppm): δ 10.33 (d, *J* = 2.6 Hz, 1H), 9.95 (s, 1H), 7.60 (d, *J* = 2.6 Hz, 1H), 7.13–7.10 (m, 2H), 6.75–6.69 (m, 3H), 4.41 (s, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz, ppm): δ 160.2, 158.2, 148.9, 129.2, 119.3, 112.8. HRMS (ESI^+): calcd for $C_8H_{10}N_4NaO_2$ $[M+Na]^+$: 217.0702; found 217.0698.

4.4. Synthesis of *N, N′*-bis(2,5-dimethylpyrrol-1-yl)oxalamide (L3)[24]

Hexane-2,5-dione (13.7 g, 0.12 mol) was added to a suspension of oxalyl dihydrazide (11.8 g, 0.1 mol) in acetic acid (100 mL) in a 500 mL flask equipped with a reflux condenser. The reaction mixture was refluxed for 2 h, cooled to room temperature, and the formed precipitate was filtered off, washed with water and dried at 100 °C. Pale yellow solid (14.8 g, 54%), mp 275−276 °C (ethanol); IR (KBr) ν (cm^{-1}): 3428, 3282−3168, 3109, 2987, 2917, 2856, 1724−1676, 1636, 1526, 1482.^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 9.38 (s, 2H), 5.89 (s, 4H), 2.16 (s, 12H). ^{13}C NMR ($CDCl_3$, 101 MHz, ppm): δ 157.4, 127.6, 105.0, 11.1. HRMS (ESI^+): calcd for $C_{14}H_{18}N_4NaO_2$ $[M+Na]^+$: 297.1328; found 297.1323.

4.5. General procedure for C–N coupling reaction of aryl halides and hydrazine hydrate on a 1 mmol scale (see Tables 1, 2, 3, Schemes 1, 2)

Required amounts of CuBr, ligand, PTC and water were mixed in a 8 mL screw cap test tube. After aryl halide (1 mmol) and 10 mol% of the required amount of base were added, the

resulting mixture was stirred at the required temperature (bath temperature) for 10 min. The remaining quantity of base and the required amount of $N_2H_4 \cdot H_2O$ were added. The reaction mixture was stirred in a closed test tube at required temperature for 1 h, then cooled to room temperature and extracted with EtOAc (5 mL). Samples of the organic phase (0.1–0.2 mL) were separated, dried with anhydrous Na_2SO_4, and analyzed by GC.

4.6. General procedure for C–N coupling reaction of aryl bromides and hydrazine hydrate on a 10 mmol scale

CuBr (36 mg, 0.25 mmol, 2.5 mol%), **L3** (110 mg, 0.4 mmol, 4 mol%), H_2O (0.5 mL), and K_3PO_4 (254 mg, 1.2 mmol) were mixed in a 15 mL screw cap test tube. After CTAB (110 mg, 0.3 mmol, 3 mol%) and aryl bromide (10 mmol) were added, the resulting mixture was stirred at 80−110 °C (bath temperature) for 10 min. Then K_3PO_4 (2.29 g, 10.8 mmol) and $N_2H_4 \cdot H_2O$ (1 g, 20 mmol) were added and argon (flow rate 5−7 mL/min) was bubbled through the reaction mixture for 5 min.[28] The reaction mixture was stirred in a closed test tube at 80−110 °C (bath temperature) for 1−2 h until complete consumption of starting material was observed as monitored by TLC (eluent–hexane), then cooled to room temperature and diluted with CH_2Cl_2 (50 mL). The resulting solution was filtered and washed with brine (2×25 mL). Aq. HCl (37%) was added to the CH_2Cl_2 solution dropwise until pH 3−4. The formed precipitate was filtered, washed with CH_2Cl_2 (15 mL) and dried at room temperature. NMR spectra of certain synthesized aryl hydrazine hydrochlorides showed that they contained 1–5 mol% of the corresponding aniline hydrochlorides as impurities (see Supplementary Material). Analytical samples of aryl hydrazine hydrochlorides were purified via precipitation from methanol solution by adding two–three volumes of diethyl ether.

4-Chlorophenylhydrazine hydrochloride[29]

Pale pink solid (1.42 g, 80%), mp 222–224 °C (lit.[29]: 218 °C); IR (KBr) ν (cm^{-1}): 3207, 3156−2763, 2682, 1996, 1876, 1583. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 10.41 (s, 3H), 8.49 (s, 1H, br), 7.31 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz, ppm): δ 145.0, 129.1, 125.5, 116.6. HRMS (ESI^+): calcd for $C_6H_8ClN_2$ $[M–Cl]^+$: 143.0376; found 143.0378.

4-Fluorophenylhydrazine hydrochloride[29]

Pale pink solid (1.22 g, 75%), mp 243−245 °C (lit.[29]: 252–253 °C); IR (KBr) ν (cm^{-1}): 3211, 3162−2784, 2720−2473, 2131, 2034, 1955, 1876, 1589, 1516, 1494. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 10.36 (s, 3H), 7.13–7.05 (m, 4H). ^{13}C NMR (DMSO-d_6, 101 MHz, ppm): δ 157.9 (d, $^1J_{CF}$ = 237.4 Hz), 142.4 (d, $^4J_{CF}$ = 2.0 Hz), 117.06 (d, $^3J_{CF}$ = 7.8 Hz), 115.9 (d, $^2J_{CF}$ = 22.6 Hz). HRMS (ESI^+): calcd for $C_6H_8FN_2$ $[M–Cl]^+$: 127.0672; found 127.0669.

3-(Trifluoromethyl)phenylhydrazine hydrochloride[30]

Pale yellow solid, (1.48 g, 70%) mp 230−232 °C (lit.[30]: 224–225 °C); IR (KBr) ν (cm^{-1}): 3205, 3158–2755, 2668, 2061, 1999, 1955, 1881, 1591, 1494. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 10.52 (s, 3H), 8.77 (s, 1H, br), 7.52–7.48 (m, 1H), 7.34 (s, 1H), 7.28–7.24 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz, ppm): δ 146.8, 130.5, 130.2 (q, $^2J_{CF}$ = 31.6 Hz), 124.6 (q, $^1J_{CF}$ = 272.4

Hz), 118.6 , 117.9 (q, $^3J_{CF}$ = 3.7 Hz), 110.9 (q, $^3J_{CF}$ = 3.9 Hz). HRMS (ESI$^+$): calcd for $C_7H_8F_3N_2$ [M–Cl]$^+$: 177.0640; found 177.0638.

Phenylhydrazine hydrochloride[31]

Pale yellow solid (1.02 g, 71%), mp 256–258 °C (lit.[31]: 250– 252 °C); IR (KBr) ν (cm^{-1}): 3210, 3153−2774, 2682, 2000, 1920, 1848, 1765, 1609, 1587, 1523, 1494. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 10.37 (s, 3H), 8.34 (s, 1H, br), 7.27–7.23 (m, 2H), 7.02 (d, *J* = 7.6 Hz, 2H), 6.92 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz, ppm): δ 146.0, 129.4, 121.9, 115.0. HRMS (ESI$^+$): calcd for $C_6H_9N_2$ [M–Cl]$^+$: 109.0766; found 109.0761.

4-Methylphenylhydrazine hydrochloride[8]

Pale yellow solid (1.11 g, 70%), mp 220–222 °C (lit.[8]:222–235 °C); IR (KBr) ν (cm^{-1}): 3221, 3162−2761, 2690, 2008, 1880, 1587, 1519, 1494. ^{1}H NMR (DMSO-d_6+CCl_4, 400 MHz, ppm): δ 10.28 (s, 3H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 2.27 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz, ppm): δ 143.6, 130.9, 129.7, 115.4, 20.7. HRMS (ESI$^+$): calcd for $C_7H_{11}N_2$ [M–Cl]$^+$: 123.0922; found 123.0919.

3,4-Dimethylphenylhydrazine hydrochloride[32]

Pale brown solid (894 mg, 52%), mp 205−206 °C (lit.[32]:197 °C); IR (KBr) ν (cm^{-1}): 3153−2217, 2016, 1915, 1851, 1749, 1597, 1509, 1448. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 10.22 (s, 3H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.83 (s, 1H), 6.76 (dd, *J* = 8.1, 1.7 Hz, 1H), 2.15 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz, ppm): δ 143.9, 137.1, 130.2, 129.7, 116.7, 112.7, 20.1, 19.0. HRMS (ESI$^+$): calcd for $C_8H_{13}N_2$ [M–Cl]$^+$: 137.1079; found 137.1076.

4-Ethylphenylhydrazine hydrochloride[33]

Pale brown solid (947 mg, 55%), mp 208−210 °C (lit.[33]: 200 °C); IR (KBr) ν (cm^{-1}): 3232, 3162−2747, 2686, 1947, 1889, 1591, 1568, 1535, 1513. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 10.30 (s, 3H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 2.50 (q, *J* = 7.6 Hz, 2H), 1.11 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz, ppm): δ 143.8, 137.4, 128.6, 115.4, 27.9, 16.4. HRMS (ESI$^+$): calcd for $C_8H_{13}N_2$ [M–Cl]$^+$: 137.1079; found 137.1075.

4.7. Typical procedure for C–N coupling reaction of 4-bromotoluene and hydrazine on a 300 mmol scale. Preparative synthesis of 4-tolylhydrazine hydrochloride

CuBr (1.1 g, 7.5 mmol, 2.5 mol%), **L3** (3.3 g, 12 mmol, 4 mol%), H_2O (15 mL) and $K_3PO_4 \cdot 7H_2O$ (12.2 g, 36 mmol) were mixed in a 250 mL flask. After CTAB (3.3 g, 9 mmol) and 4-bromotoluene (51.3 g, 300 mmol) were added, the resulting mixture was stirred at 110 °C for 10 min. Then $K_3PO_4 \cdot 7H_2O$ (109.5 g, 324 mmol) and $N_2H_4 \cdot H_2O$ (98%) (30 g, 600 mmol) were added. The reaction mixture was stirred at 110 °C for 1 h until complete consumption of starting material as monitored by TLC (eluent–hexane), then cooled to room temperature and diluted with CH_2Cl_2 (300 mL). The resulting solution was filtered and washed with brine (2×100 mL). HCl (37%) were added to the CH_2Cl_2 solution dropwise until pH 3−4. The formed precipitate was filtered off, washed with CH_2Cl_2 and dried at room temperature (34.6 g, 73%).

Supplementary data

Acknowledgments

The authors thank the Russian Foundation for Basic Research (Grant 14-03-00297a) and Saint Petersburg State University (Grant 12.38.195.2014) for financial support of this work. Studies were performed at Center for Magnetic Resonance and Center for Chemical Analysis and Material Research of Saint Petersburg State University.

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21. The system of CuBr and $(CONHNR'R'')_2$ could successfully catalyze arylation of hydrazine due to the special preparation of the reaction mixtures, as described in the experimental section.

22. Phenols are well-known by-products in copper-catalyzed C−N cross-coupling reactions of amines with aryl bromides in the presence of KOH.[17] We have demonstrated that copper-catalyzed reaction of aryl bromides and hydrazine with K_3PO_4 as a base gives no detectable (GC analysis) amounts of the corresponding phenols.

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28. Inert reaction atmosphere is not necessary for C–N cross-coupling of aryl bromides with hydrazine. However, it is desirable to remove the air from a reaction vessel by bubbling argon before the reaction in order to avoid oxidation of aryl hydrazines.

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Supplementary Material

Facile and convenient copper-catalyzed synthesis of aryl hydrazines via C–N cross-coupling of aryl halides and hydrazine hydrate

Daria V. Kurandina, Eugene V. Eliseenkov, Petr V. Ilyin, Vadim P. Boyarskiy

General chemical procedures

All reagents (except for ligands of **L2, L3** and additive **A4**) and solvents were obtained commercially and used without further purification. Ligands **L2, L3** and additive **A4** were synthesized according to the methods described below. Hydrazine hydrate (100%), and K_3PO_4 (> 98 wt% pure) were from Acros Organics and Sigma, respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance II+ 400 MHz (UltraShield Magnet) spectrometer at room temperature. GC analysis was performed on a Chromatec Crystal 5000.2 chromatograph equipped with a flame ionization detector and a VRH-1 (10 m×0.53 mm×2.65 μm) capillary column. GS-MS analysis was conducted on a Shimadzu GCMS QP-2010 SE spectrometer equipped with an electron impact ionization source and Rtx-5MS (30 m×0.32 mm×0.25 μm) capillary column. Mass spectra were recorded on a Bruker micrOTOF spectrometer equipped with an electrospray ionization (ESI) source. For this analysis species were dissolved in methanol. Infrared spectra (4000−400 cm^{-1}) were recorded on a Shimadzu FTIR-8400S instrument as KBr pellets. Melting points were determined on a capillary melting point apparatus and not corrected.

General procedure for C–N coupling reaction of aryl bromides and hydrazine hydrate on a 10 mmol scale

CuBr[1] (36 mg, 0.25 mmol, 2.5 mol%), **L3** (110 mg, 0.4 mmol, 4 mol%), H_2O[2] (0.5 mL), and K_3PO_4[3] (254 mg, 1.2 mmol) were mixed in a 15 ml screw cap test tube. After CTAB (110 mg, 0.3 mmol, 3 mol%) and aryl bromide (10 mmol) were added, the resulting mixture was stirred at 80−110 °C (bath temperature) for 10 min. Then K_3PO_4 (2.29 g, 10.8 mmol) and $N_2H_4{\cdot}H_2O$ (1 g, 20 mmol) were added and argon (flow rate 5−7 mL/min) was bubbled through the reaction mixture for 5 min.[4] The reaction mixture was stirred in a closed test tube at 80−110 °C (bath temperature) for 1−2 h until complete consumption of starting material as monitored by TLC (hexane as an eluent), then cooled to room temperature and diluted with CH_2Cl_2 (50 mL). The resulting solution was filtered and washed with brine (2×25 mL). Aq. HCl (37%) was added to the CH_2Cl_2 solution dropwise until pH 3−4. The formed precipitate was filtered, washed with CH_2Cl_2 (15 mL) and dried at room temperature.

[1]Although CuBr, $Cu(OAc)_2{\cdot}H_2O$ and Cu have showed nearly the same activity as catalysts, we have chosen CuBr for preparative syntheses for the following reasons. CuBr led to more reproductive results than Cu and a less amount of aniline than $Cu(OAc)_2{\cdot}H_2O$.

[2]It is important to add H_2O initially to the reaction mixture in order to compose the catalytic system of ligand and copper in basic aqueous medium before $N_2H_4 \cdot H_2O$ addition.

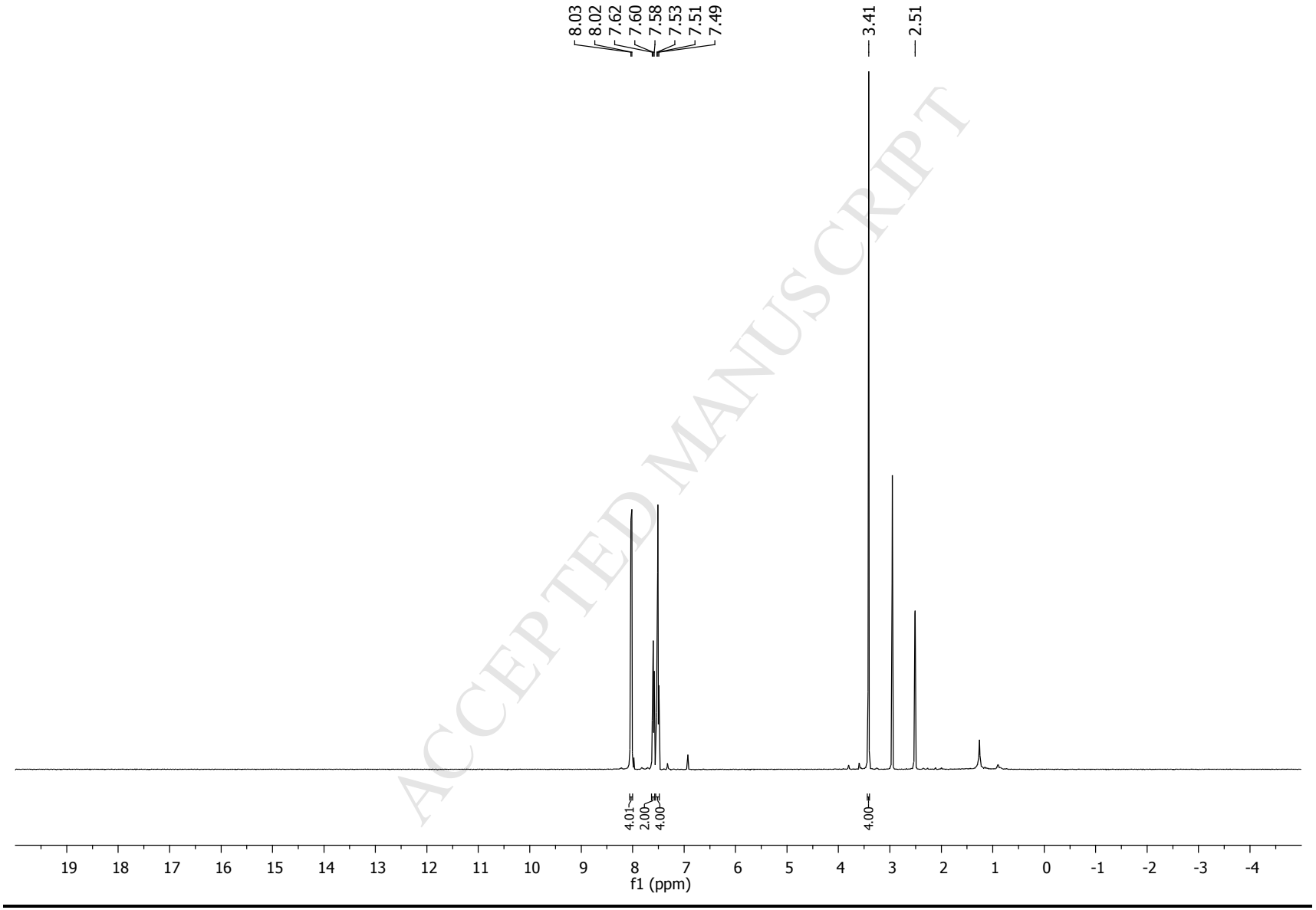
[3] We used 120 mol% K_3PO_4 for preparative syntheses of aryl hydrazines because KH_2PO_4 formed during the reaction led to worse results than K_3PO_4.

[4]Inert reaction atmosphere is desirable to prevent oxidation of aryl hydrazine by oxygen in the air.

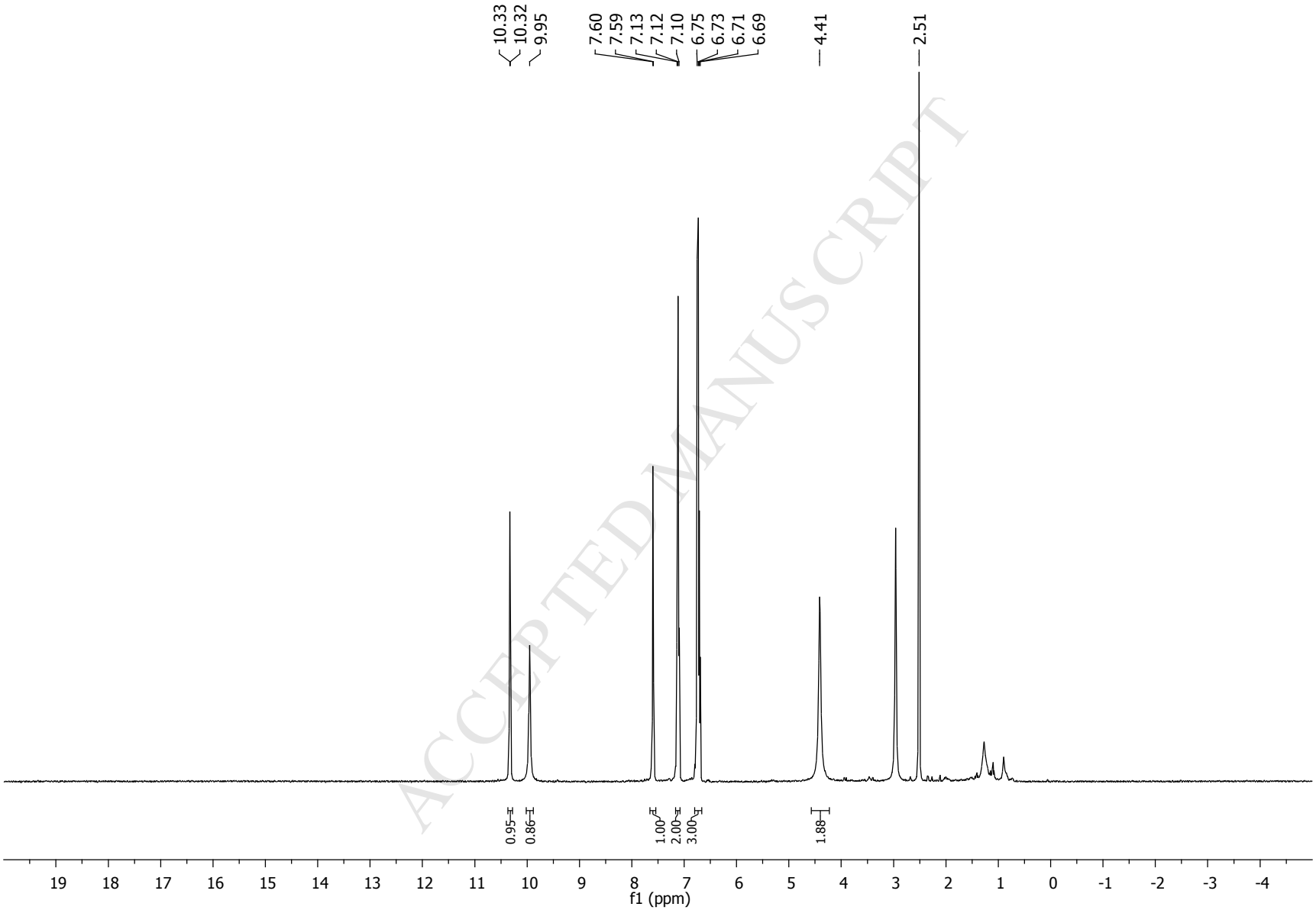
In order to prevent the destruction of the catalytic system, hydrazine hydrate should be the last to be added to the reaction mixture. The reproducible results were obtained only if the catalytic system was initially prepared before performing the reaction.

^{1}H NMR and ^{13}C NMR spectra

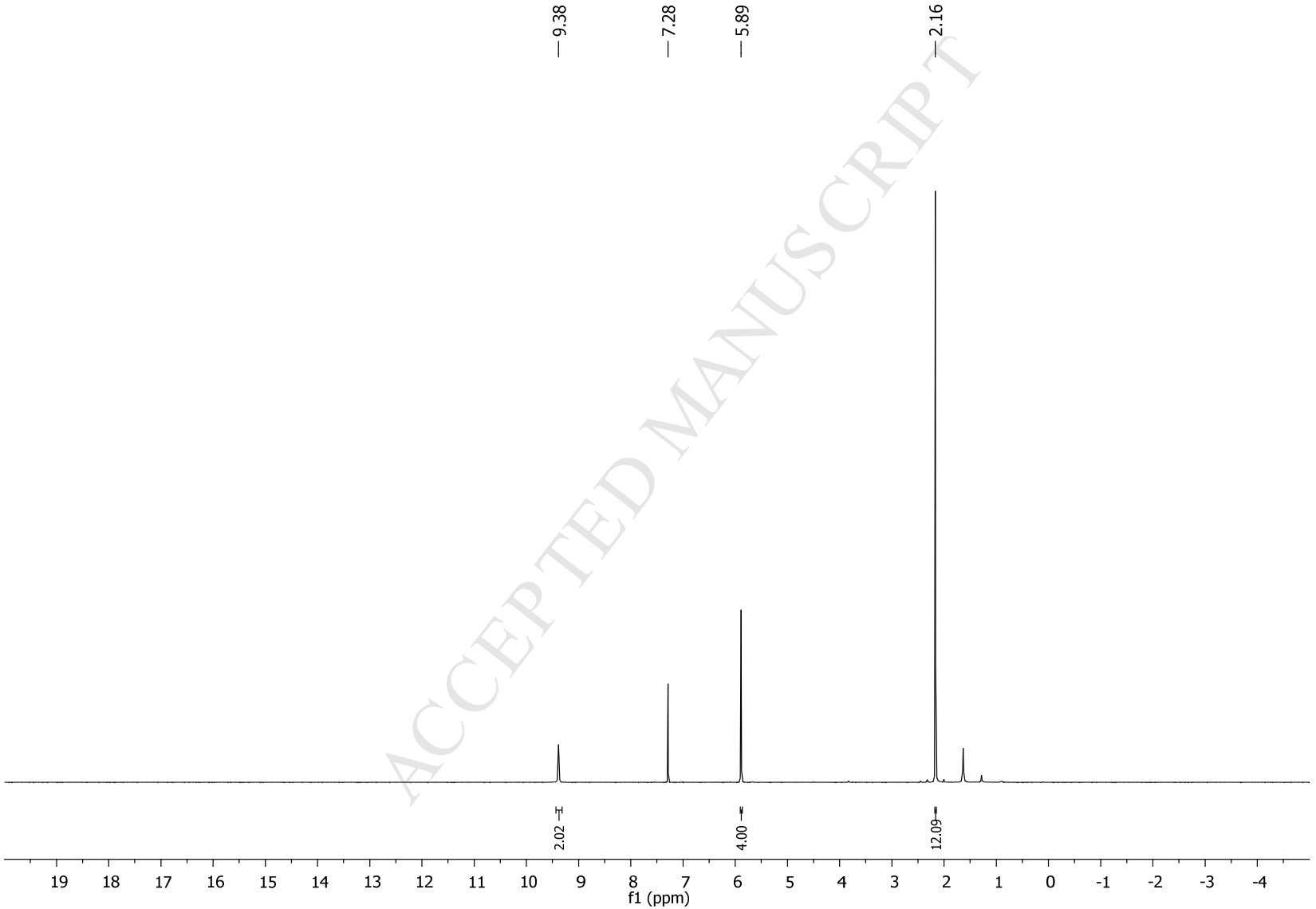
^{1}H NMR of 1,4-diphenylbutane-1,4-dione (400.13 MHz, Solvent – DMSO-d_6 + CCl_4, T = 297 K)



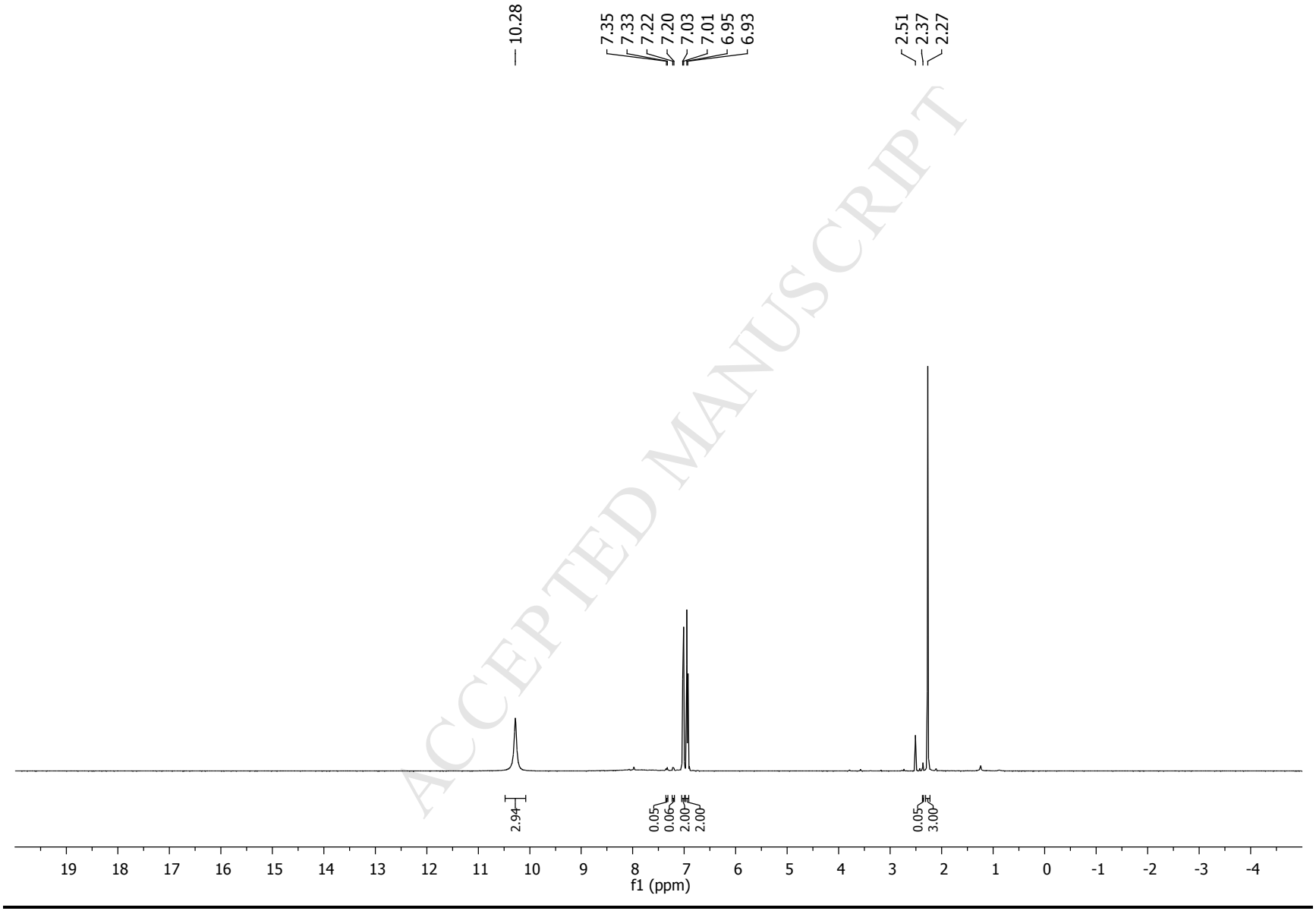
^{1}H NMR of N′-phenyl oxalyl dihydrazide (400.13 MHz, Solvent – DMSO-d_6+CCl_4, T = 298 K)



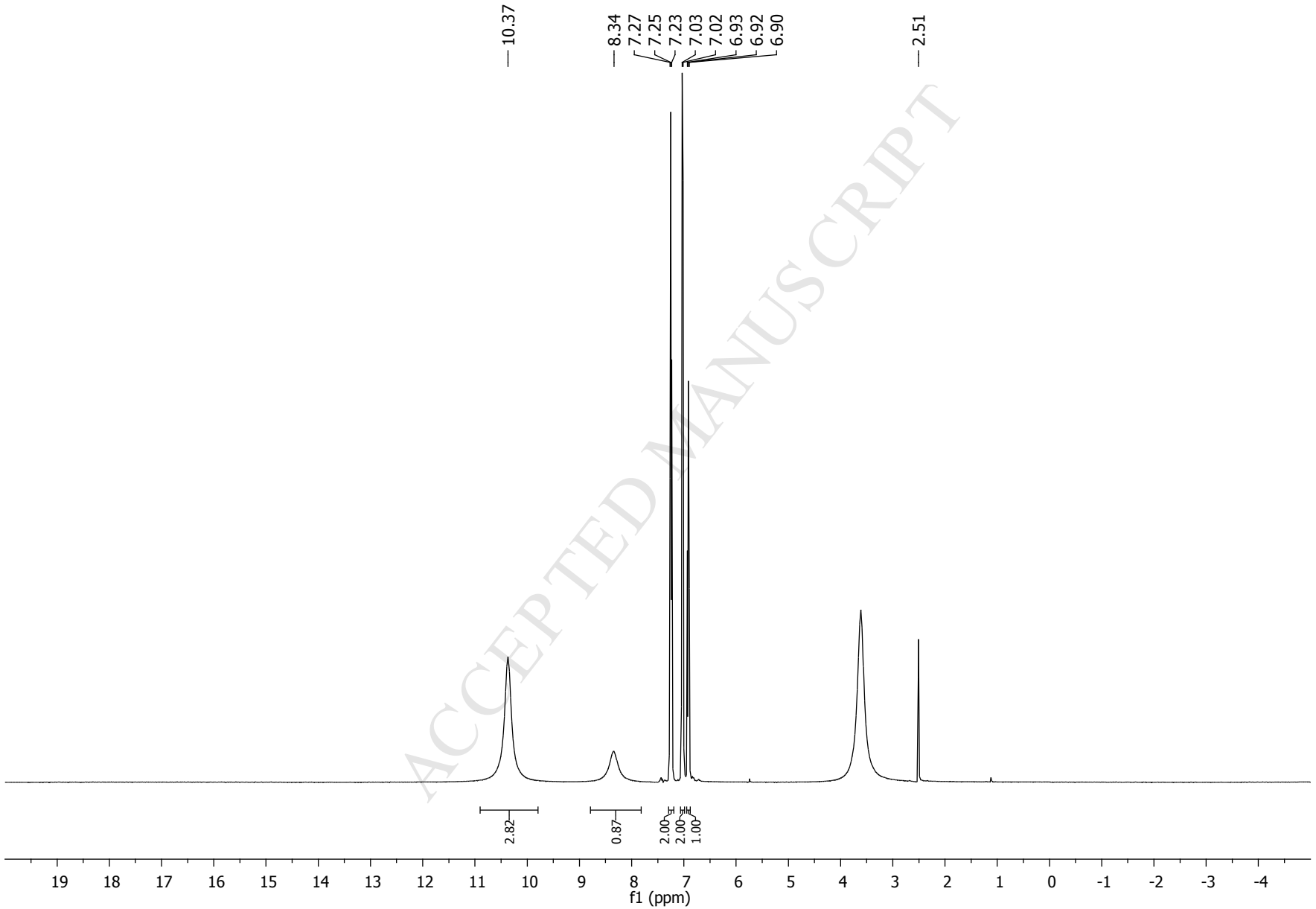
^{1}H NMR of N,N'-bis(2,5-dimethylpyrrol-1-yl)oxalamide (400.13 MHz, Solvent – $CDCl_3$, T = 298 K)



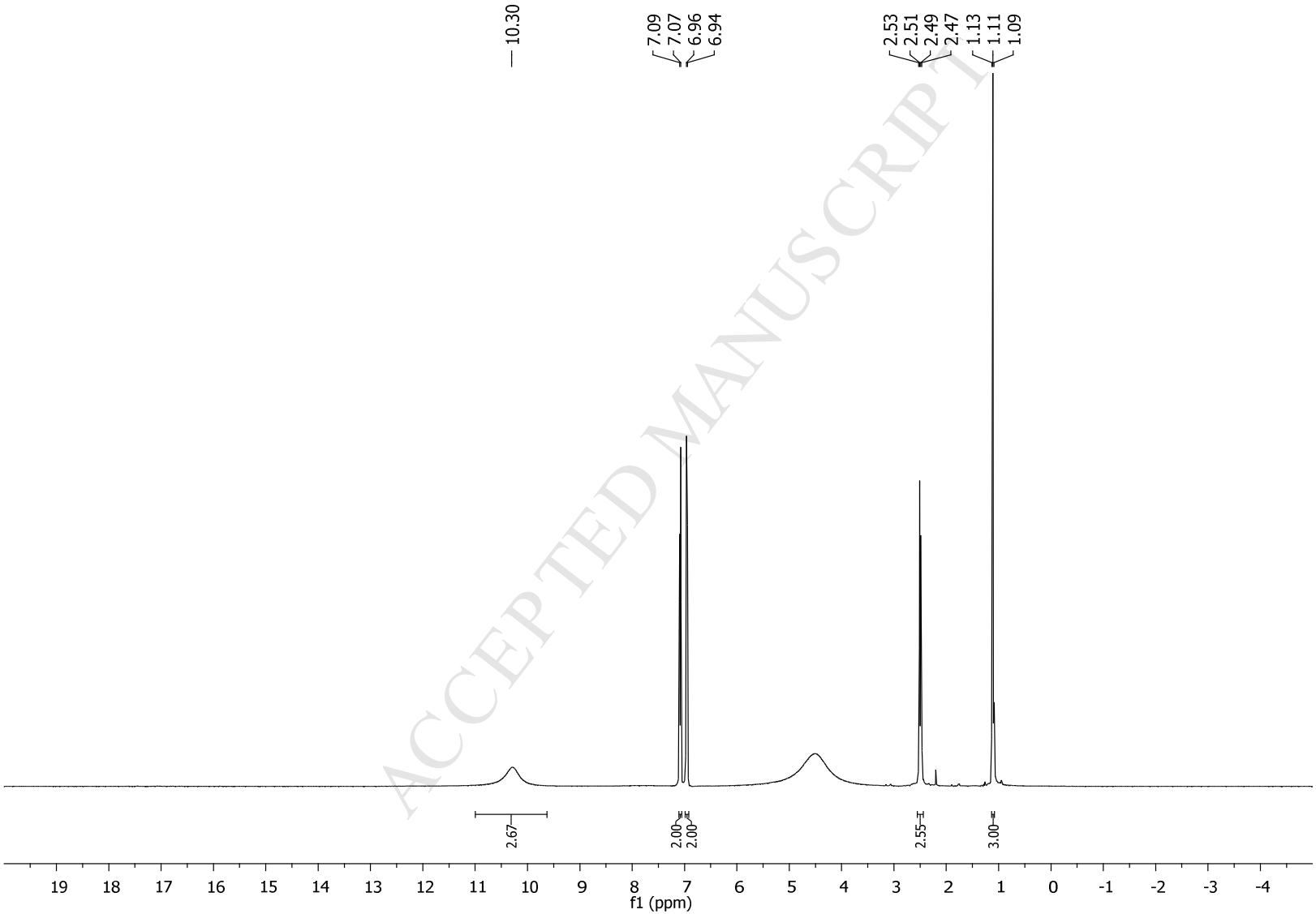
^{1}H NMR of 4-methylphenylhydrazine hydrochloride (400.13 MHz, Solvent – DMSO-d_6 + CCl_4, T = 298 K)



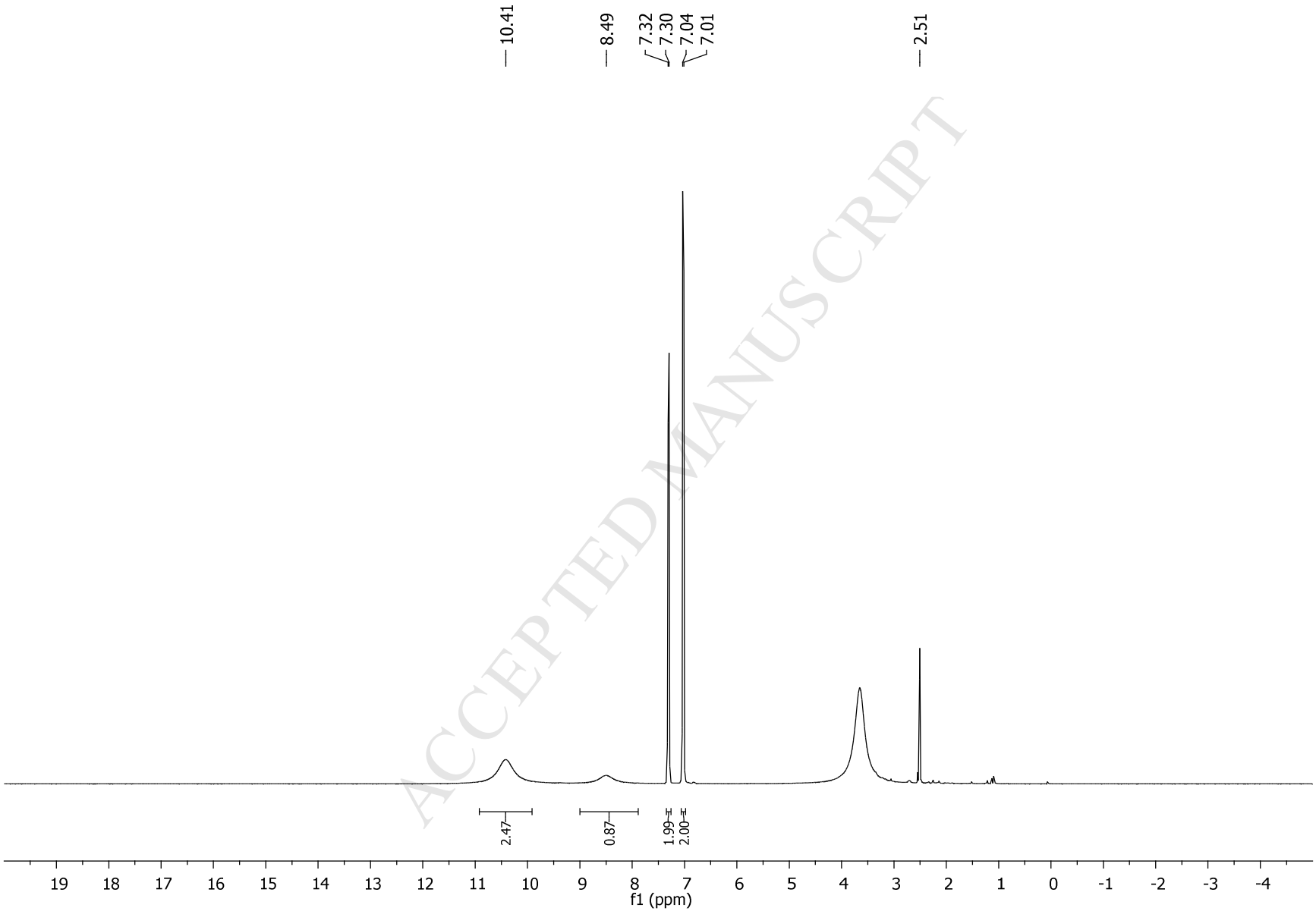
^{1}H NMR of phenylhydrazine hydrochloride (400.13 MHz, Solvent – DMSO-d_6, T = 296 K)



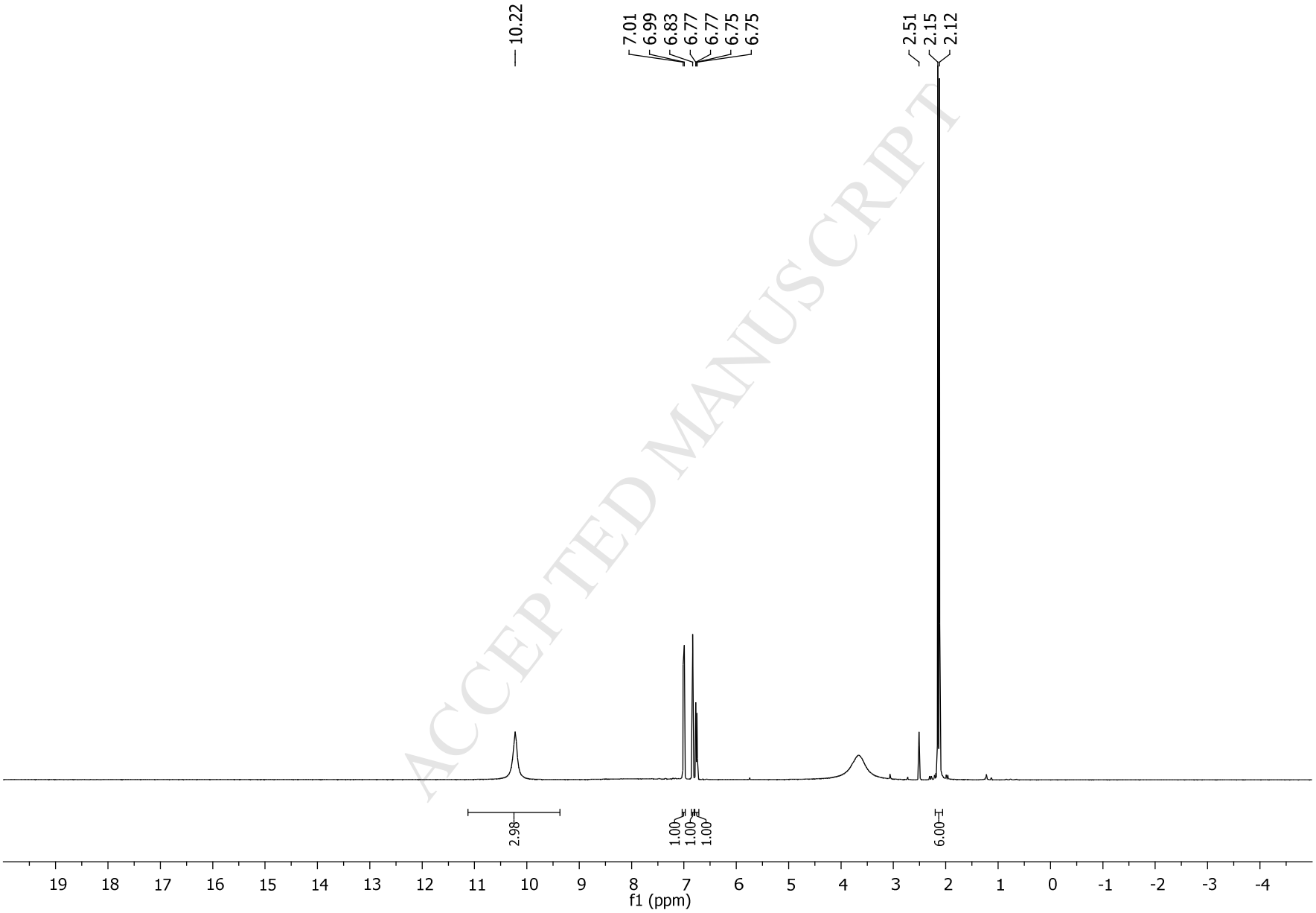
^{1}H NMR of 4-ethylphenylhydrazine hydrochloride (400.13 MHz, Solvent – DMSO-d_6, T = 296 K)



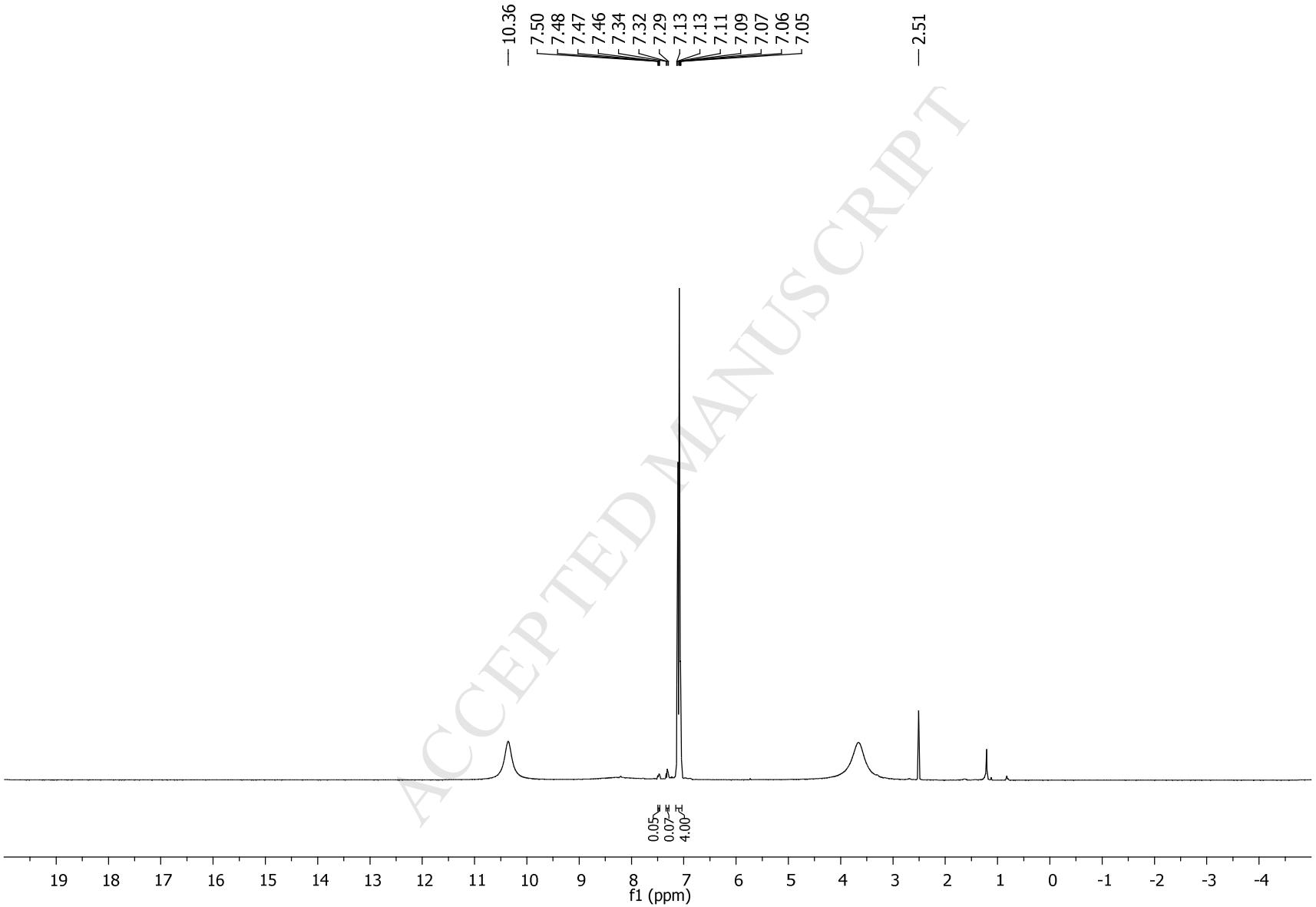
^{1}H NMR of 4-chlorophenylhydrazine hydrochloride (400.13 MHz, Solvent – DMSO-d_6, T = 298 K)



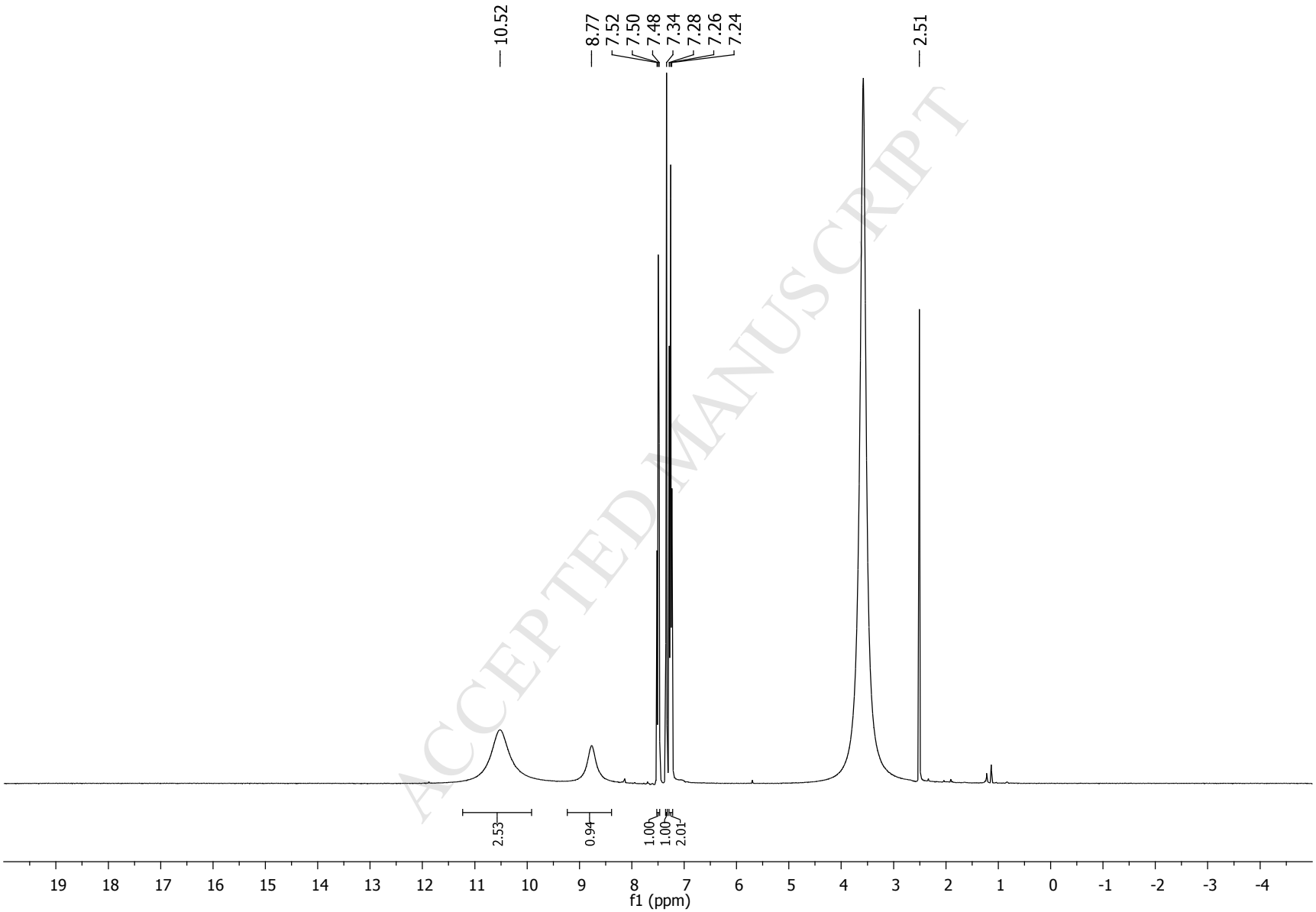
^{1}H NMR of 3,4-dimethylphenylhydrazine hydrochloride (400.13 MHz, Solvent – DMSO-d_6, T = 297 K)



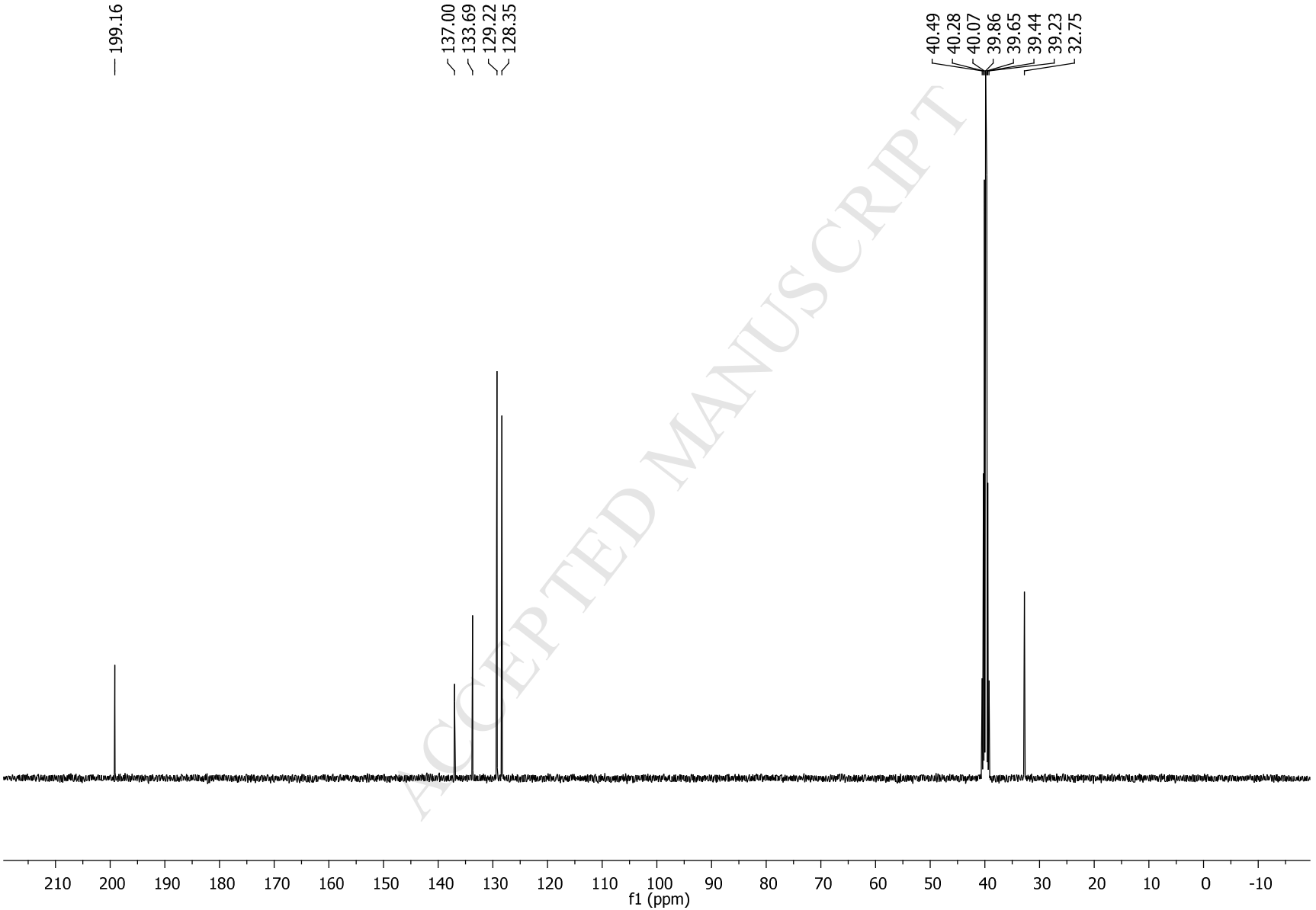
^{1}H NMR of 4-fluorophenylhydrazine hydrochloride (400.13 MHz, Solvent – DMSO-d_6, T = 297 K)



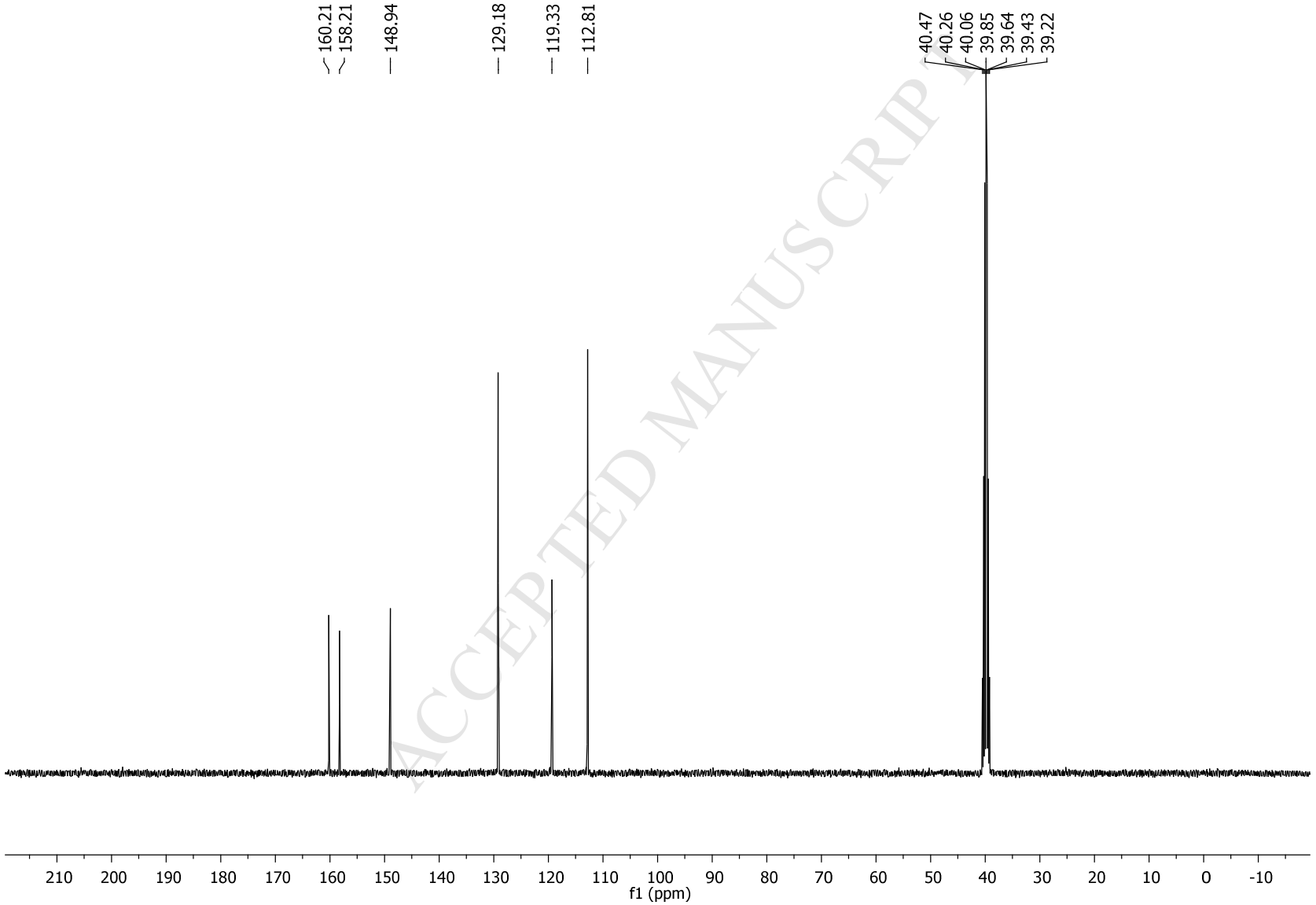
^{1}H NMR of 3-(trifluoromethyl)phenylhydrazine hydrochloride (100.61 MHz, Solvent – DMSO-d_6, T = 297 K)



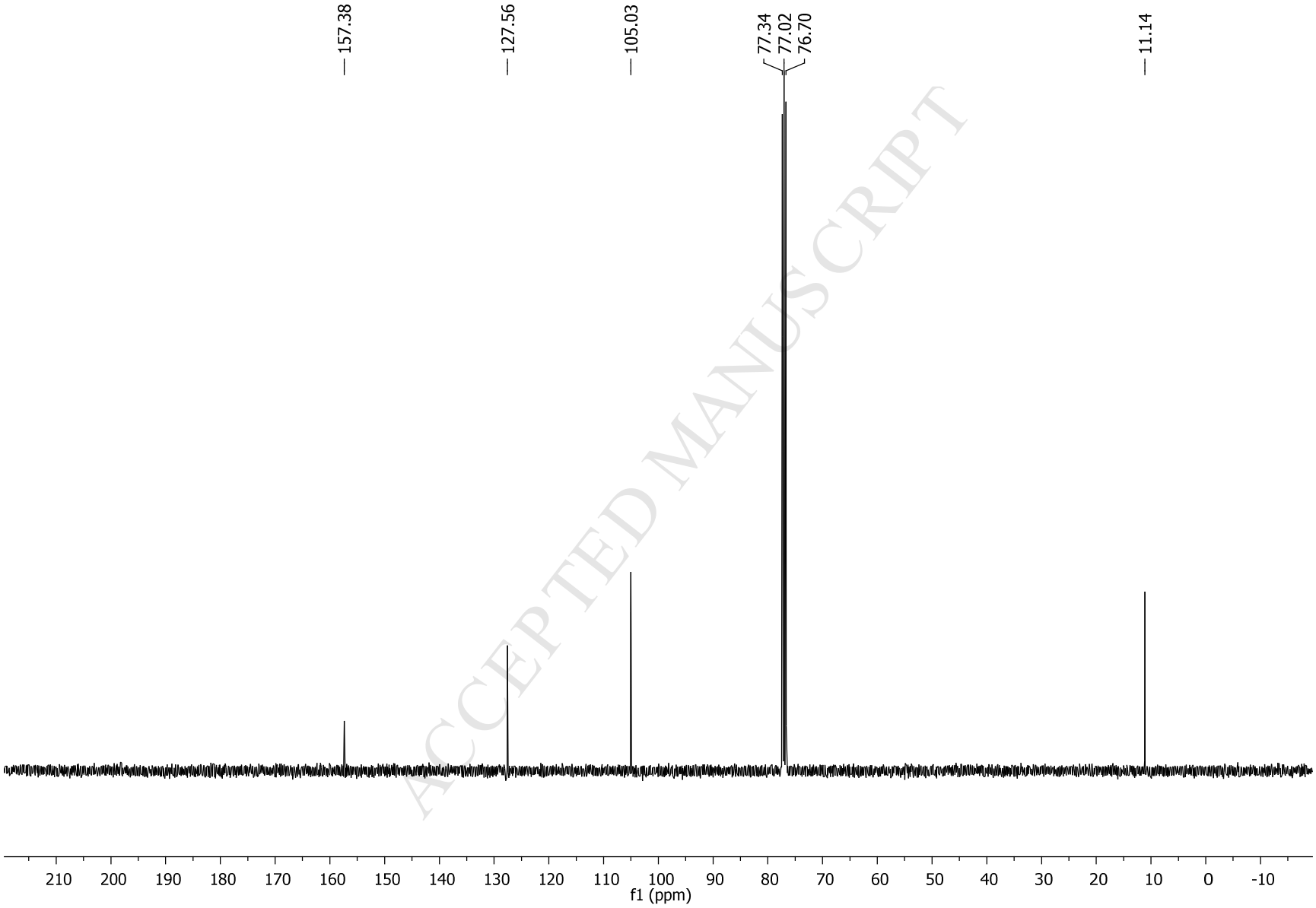
^{13}C NMR of 1,4-diphenyl-1,4-butanedione (100.61 MHz, Solvent – DMSO-d_6, T = 298 K)



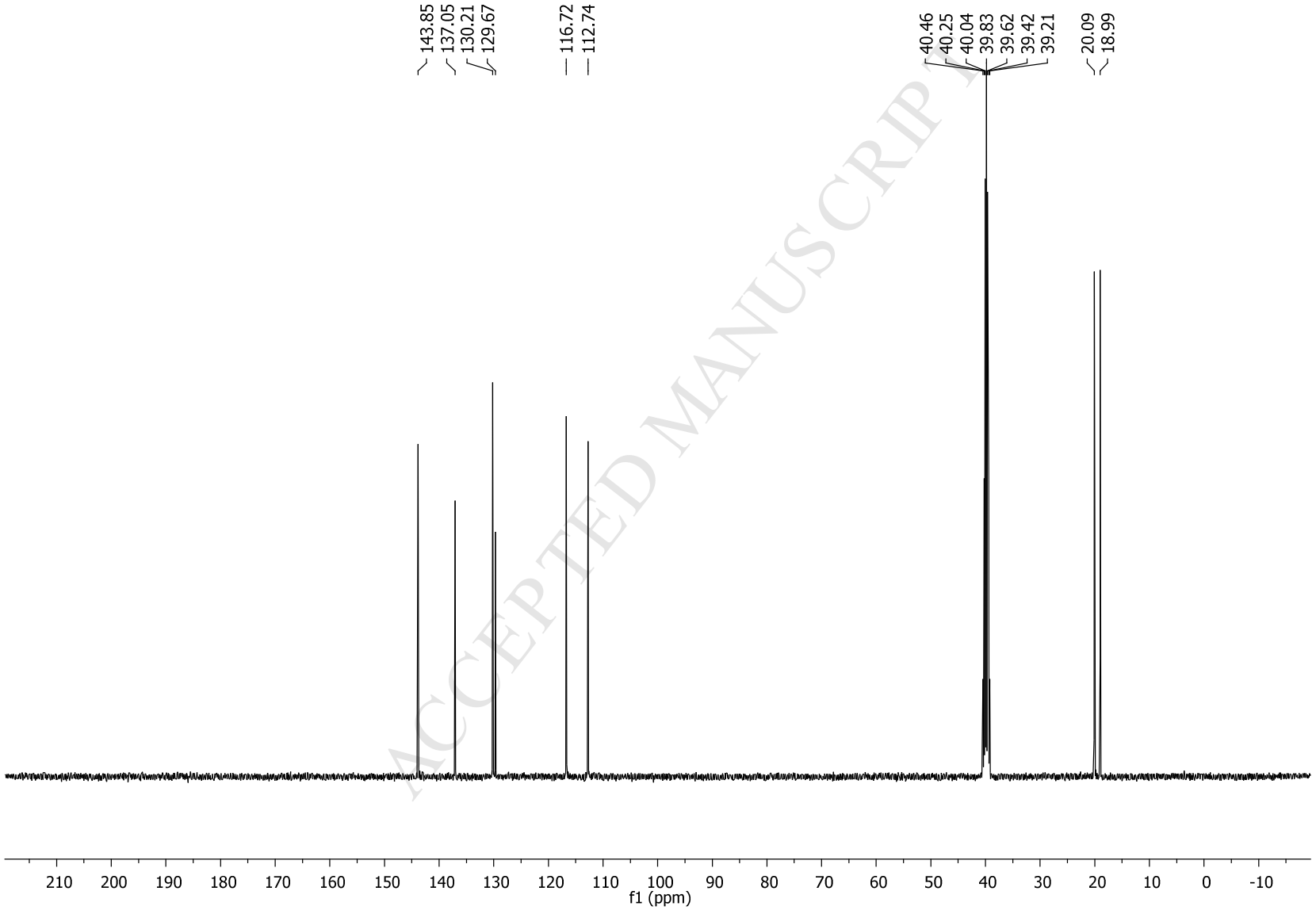
^{13}C NMR of N′-phenyl oxalyl dihydrazide (100.61 MHz, Solvent – DMSO-d_6, T = 299 K)



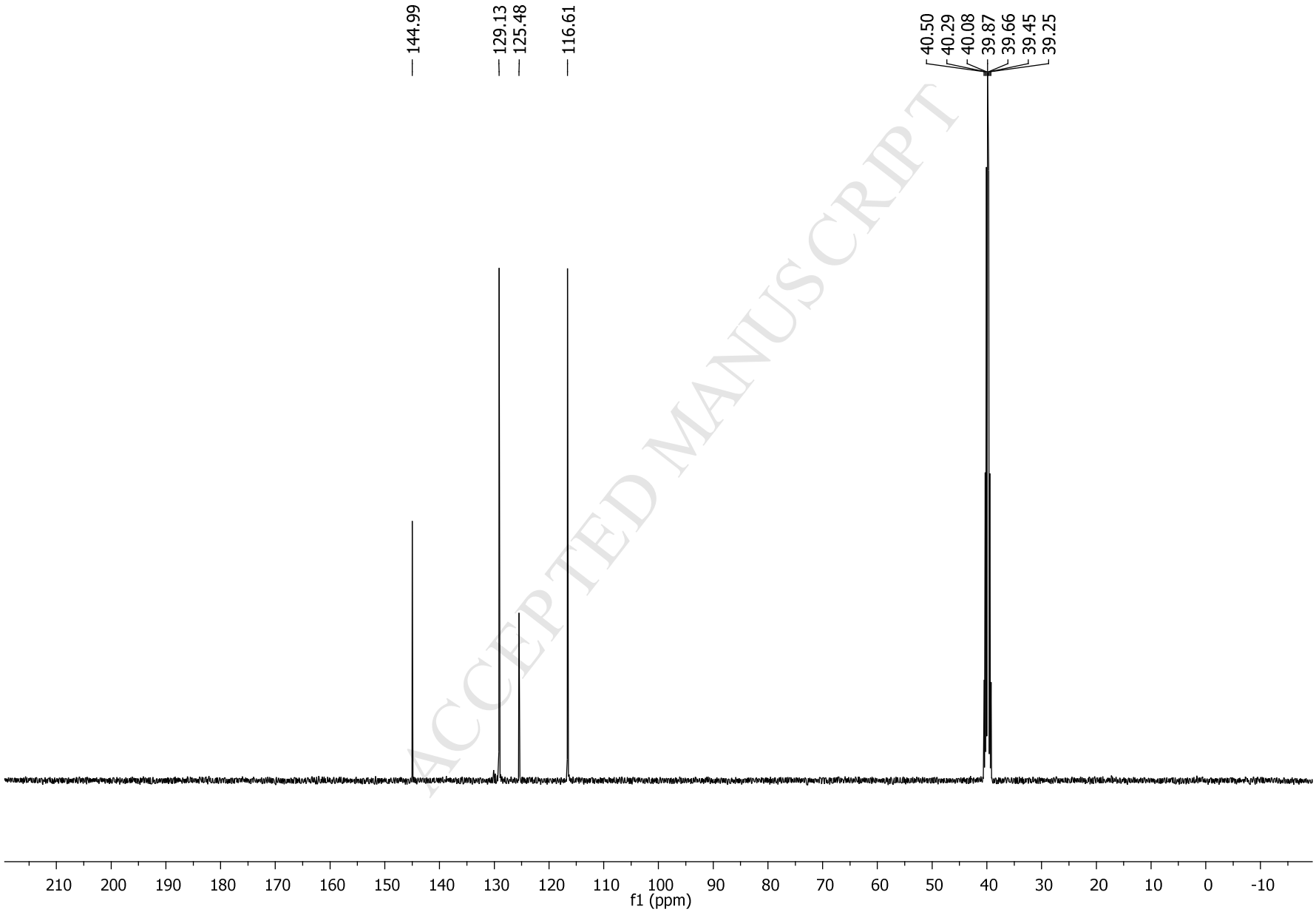
^{13}C NMR of N,N'-bis(2,5-dimethylpyrrol-1-yl)oxalamide (100.61 MHz, Solvent – $CDCl_3$, T = 299 K)



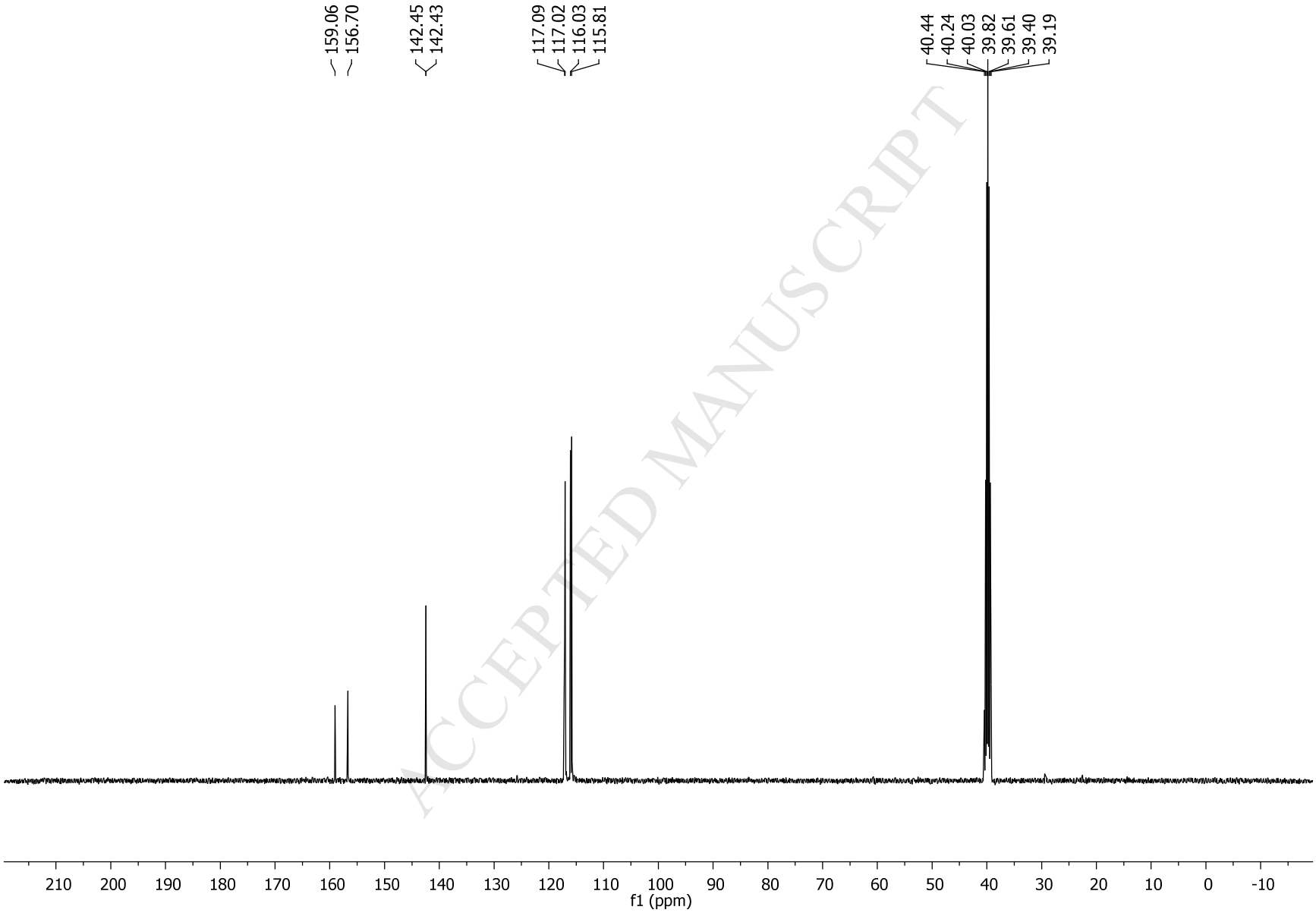
^{13}C NMR of 3,4-dimethylphenylhydrazine hydrochloride (100.61 MHz, Solvent – DMSO-d_6, T = 297 K)



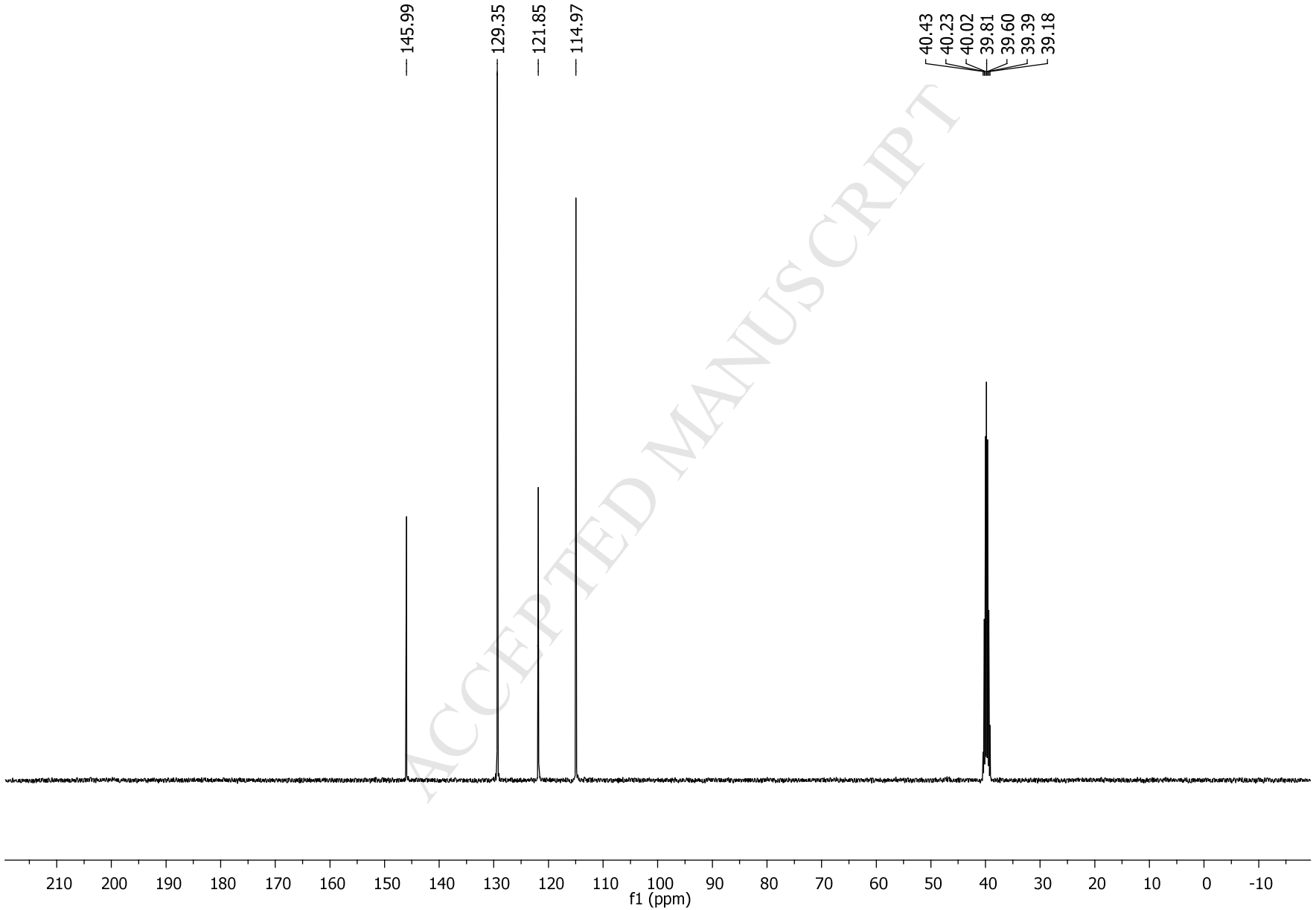
^{13}C NMR of 4-chlorophenylhydrazine hydrochloride (100.61 MHz, Solvent – DMSO-d_6, T = 298 K)



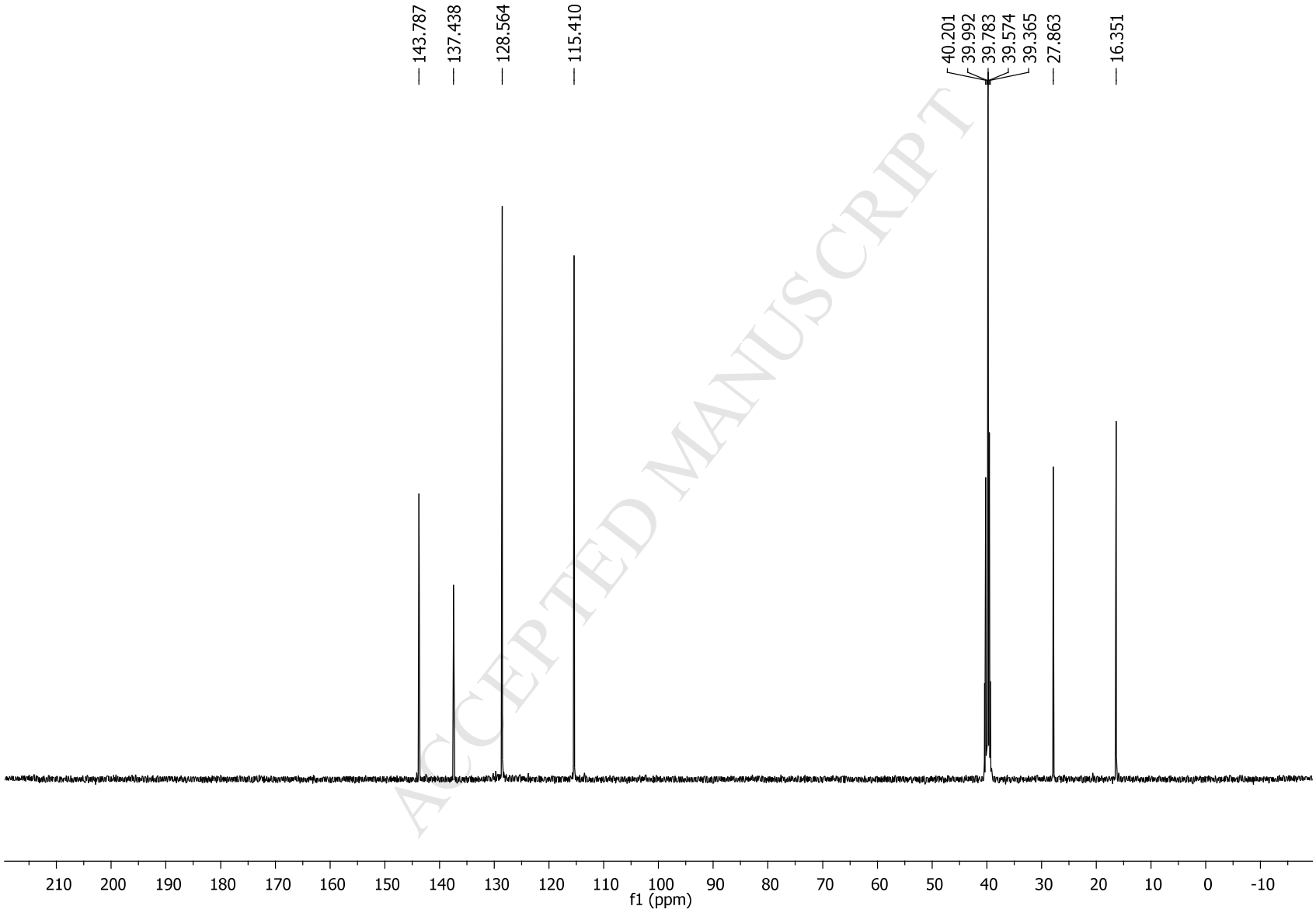
^{13}C NMR of 4-fluorophenylhydrazine hydrochloride (100.61 MHz, Solvent – DMSO-d_6, T = 298 K)



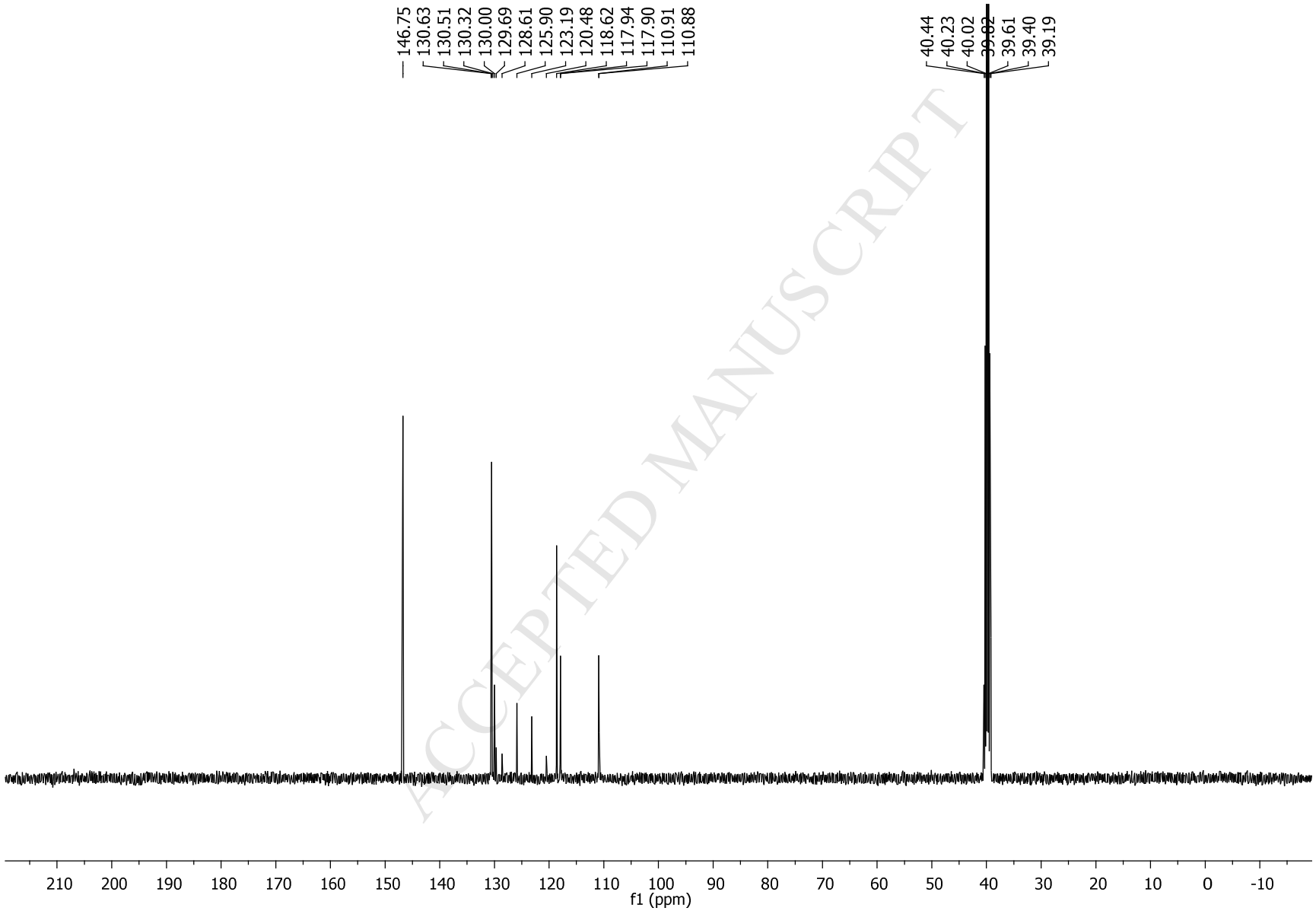
^{13}C NMR of phenylhydrazine hydrochloride (100.61 MHz, Solvent – DMSO-d_6, T = 297 K)



^{13}C NMR of 4-ethylphenylhydrazine hydrochloride (100.61 MHz, Solvent – DMSO-d_6, T = 297 K)



^{13}C NMR of (3-(trifluoromethyl)phenyl)hydrazine hydrochloride (100.61 MHz, Solvent – DMSO-d_6, T = 297 K)



^{13}C NMR of 4-methylphenyl hydrazine hydrochloride (100.61 MHz, Solvent – DMSO-d_6, T = 297 K)