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Graphical Abstract

Copper-catalyzed C–N cross-coupling of aryl halides and amines in water in the presence of ligand derived from oxalyl dihydrazide: scope and limitation

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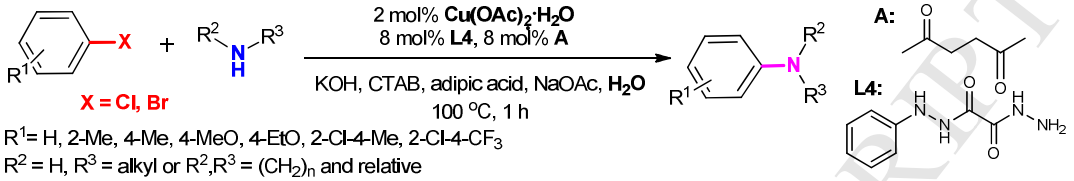

R^1= H, 2-Me, 4-Me, 4-MeO, 4-EtO, 2-Cl-4-Me, 2-Cl-4-CF_3

R^2 = H, R^3 = alkyl or R^2,R^3 = $(CH_2)_n$ and relative

Copper-catalyzed C–N bond cross-coupling of aryl halides and amines in water in the presence of ligand derived from oxalyl dihydrazide: scope and limitation

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Keywords: C−N bond cross-coupling, Copper catalysis, Aryl bromides, Catalysis in aqueous media

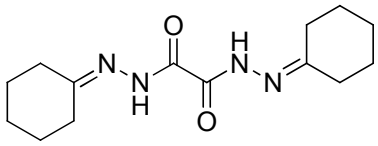
Abstract

An efficient and convenient method has been developed for the copper-catalyzed C–N bond cross-coupling of aryl bromides with electron-donor substituents and aliphatic amines in water. The new ligand system *N*-phenyloxalyl bishydrazide~~L~~/hexane-2,5-dione has been shown to be considerably more efficient in the copper-catalyzed C–N bond cross-coupling reaction as compared to the ligands described in the literature and allowed decreasing of the catalyst amount (up to 2 mol%) to achieve ~~the~~ acceptable yields of isolated products (46–84%). Acceptor substituted aryl bromides, aryl bromides with substituents in the *ortho*-position, and some aryl dichlorides can undergo the C–N cross-coupling under the developed conditions, but their reactivity is lower.

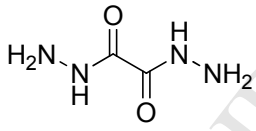
1. Introduction

C–N bond cross-couplings catalyzed by transition metal complexes represent an irreplaceable tool for C–N bond formation in contemporary organic synthesis.[1] The copper-mediated processes, such as Ullmann and Goldberg reactions, were discovered in the beginning of the last century but became broadly applicable only recently when scientists managed to considerably improve classical reactions conditions. Thus, numerous copper-containing catalytic systems have been designed which allow the synthesis of important pharmaceutical intermediates[2,3] and natural products [4] via C–N bond cross-coupling. The use of an appropriate ligand was found to be as essential for the success in a ~~of~~ protocol as the use of an appropriate base, solvent and other components of the reaction mixtures.[5] As a result, researchers have gained the opportunity to modify the reaction conditions of copper-catalyzed C–N bond cross-coupling reactions by many ways that has led to the creation of various protocols. Most of these processes are carried out in common organic solvents like 2-propanol,[6] DMF,[7] DMSO,[8] toluene,[9] and NMP,[10] but recently copper-catalyzed C–N bond cross-coupling was found to proceed in aqueous media.[11] Water as a solvent requires the use of special ligands for the implementation of the couplings of aryl halides and amines. Oxalyl dihydrazide derivatives and their nearest equivalents allow C–N bond cross-coupling in aqueous media in the presence of a phase transfer

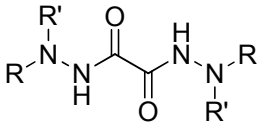
catalyst. Thus, the system of CuO (25 mol%)/*bis*(cyclohexanone)oxalyldihydrazone (**L1**) (50 mol%) was first to be successfully used for the coupling of aryl halides and amines in an aqueous solution.[12] Then, the protocols for microwave-assisted coupling reactions of aryl halides with anilines and aliphatic amines in water were elaborated using CuO (5 mol%) with $(CONHNR'R'')_2$ (**L2**)(25 mol%)[13] or $(CONHNH_2)_2$ (**L3**) (50 mol%)/ketone (100 mol%).[14] Also, pyrrole-2-carbohydrazides (25 mol%) were found to be effective ligands for copper-catalyzed C–N bond coupling reactions in water with CuI (5 mol%).[15]



L1 (Wan et al. *Synthesis* **2006**, 3955)

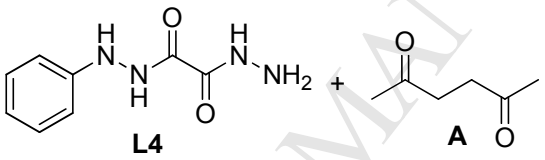


L3 (Wan et al. *Eur. J. Org. Chem.* **2010**, 3219)



R = *c*-C_6H_{11}, *c*-C_5H_9, Ad, Ph, Me, *i*-Pr, *i*-Bu, $CH_3(CH_2)_3CH(CH_3)$, Bn, $PhCH(CH_3)$, 4-$MeOC_6H_4CH(CH_3)$, 4-$NO_2C_6H_4CH(CH_3)$; R' = H, Me

L2 (Wan et al. *Appl. Organometal. Chem.* **2011**, *25*, 341; Wan et al. *Eur. J. Org. Chem.* **2009**, 635)



L4 **A**

(Boyarskiy et al. *Russ. Chem. Bull*. **2012,** *61*, 1009 and ***this work***)

Recently, we described the system of Cu(II)/$PhNHNHCOCONHNH_2$(**L4**)/ hexane-2,5-dione (**A**) which successfully catalyzes the arylation of aniline and substituted anilines with several aryl bromides.[16] Unlike the aforementioned methods for the coupling in water, only 2 mol% of the copper source and 8 mol% of **L4** and 8 mol% of additive **A** were used in our method.

Herein, we report the application of this catalytic system for the cross-coupling of a wide range of aryl halides with 5- and 6-membered saturated N-heterocyclic compounds and aliphatic amines in aqueous media. Only 2 mol% of the copper source and 8 mol% of *N'*-phenyloxalyl bishydrazide (**L4**) and 8 mol% of additive hexane-2,5-dione (**A**) should be used to achieve good isolated yields. Furthermore, scope and limitation of the reaction are discussed.

2. Results and Discussion

Copper-catalyzed arylation of aliphatic amines and, especially saturated *N*-heterocyclic compounds is considerably more interesting than the arylation of anilines. In the published data,[12–15] the yield of the product is always lower in the case of arylation of morpholine than aniline (even at a ratio of amine: aryl bromide is of 4). It can be concluded that the optimum conditions for the arylation of aniline and saturated *N*-heterocyclic compounds are different.

We carried out the $Cu(OAc)_2 \cdot H_2O$/**L4**/**A**-catalyzed reaction of 4-bromotoluene with morpholine in water for 1 h under the conditions described for the arylation of anilines: 4-bromotoluene (1 mmol), morpholine (130 mol%), $Cu(OAc)_2 \cdot H_2O$ (2 mol%), ligand **L4** (8 mol%), TBAB (20 mol%), KOH (200 mol%), water (500 mg/1 mmol ArBr), 100 °C, 1 h. The yield of *N*-(4-methylphenyl)morpholine (**8**) was only a 5% (**Table 1**, entry 1) vs. 66% for the prototype reaction of bromobenzene with aniline. Consequently, there is a need to adapt the reaction conditions taking into account aliphatic amines features. The reaction of 4-bromotoluene with morpholine was chosen as a model process to optimize the reaction conditions.

Morpholine is a stronger nucleophile than aniline but its concentration in organic phase (where the cross-coupling reaction proceeds) is low as compared with aniline under the reaction conditions. This inherent fact could result in the decrease of the rate of reaction. To minimize the extraction of morpholine from the organic phase we reduced the amount of water in the reaction mixture from 500 mg to 100 mg on 1 mmol ArBr. Indeed, the yield of the target product increased from 5% ~~up~~ to 36% (**Table 1**, entry 2).

Inorganic bases in C–N bond-forming~~ation~~ reactions are employed to facilitate the deprotonation /coordination of the nucleophile. However, they suffer from ~~demerits~~ deficiencies, such as low solubility and/or low reactivity in organic phase. For the coupling reaction in two-phase system containing water, phase transfer catalysts (PTC) are used to facilitate the hydroxyl ion transfer from the aqueous to the organic phase. It is well known that tetra-*n*-butylammonium bromide (TBAB) can transfer only a trace amount of hydroxyl ions to the organic phase (as tetra-*n*-butylammonium hydroxide (TBAH)) from water in a two-phase system (containing KOH and organic solvent (toluene, CH_2Cl_2).[17] To overcome these drawbacks, organic ionic bases have been introduced as new and promising promoters for coupling reactions.[18] These are quaternary ammonium or phosphonium salts with basic anions which are relatively well soluble in organic solvents and, more importantly, their ~~resulting~~ solutions have a relatively high electrical conductivity, therefore there is an appreciable quantity of free ions along with the ion pairs. For example, tetrabutylammonium adipate was advantageously used as a base for copper-catalyzed C–N bond cross-coupling of aryl iodides with benzylamine at room temperature in DMF with 20 mol% of *L*-proline as a ligand.[18]

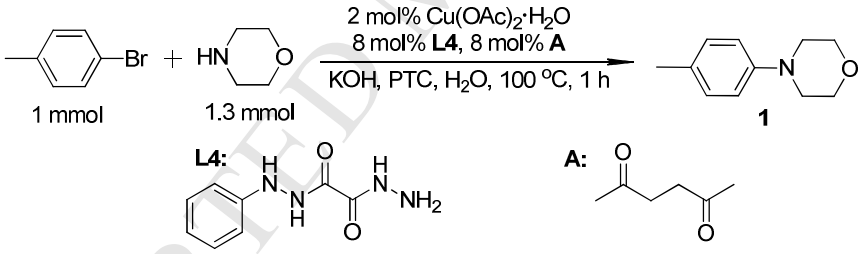
We applied the same approach ~~for~~ to our reactions in two-phase systems containing water. The use of ionic organic bases in stoichiometric amounts was rejected for economic reasons, as their synthesis is carried out by neutralizing expensive TBAH with a carboxylic acid. The addition of adipic acid (30 mol%) to the reaction mixture led to the formation of potassium adipate *in situ* which resulted in an increase of the yield of the desired product up to 72% for 1 h (**Table 1**, entries 3, 4). Cetyltrimethylammonium bromide (CTAB) in a combination with potassium adipate was found to be a more active base than TBAB/potassium adipate and triethylbenzylammonium chloride (TEBA)/potassium adipate (**Table 1**, entries 5, 6, 7). These data ~~are~~ can be well explained by that quaternary ammonium cations of a large volume ~~form salts having~~ possess higher conductivity in an organic solvent.[18] The combination of potassium adipate with surfactants such as potassium stearate and sodium dodecyl sulfate (SDS) (**Table 1**, entries 8, 9) was less successful. The addition of sodium acetate led to a further increase in the

yield (87%), which was probably due to the cooperative action of cetyltrimethylammonium adipate and cetyltrimethylammonium acetate as bases (**Table 1**, entry 10).

What was interesting that CuO applied for the coupling of aryl bromides with anilines in the works[12–15] did not catalyze the reaction with morpholine (**Table 1**, entry 11). The use of 3 mol% of $Cu(OAc)_2 \cdot H_2O$ did not lead to an increase of the yield of the target product (**Table 1**, entry 12). A 85% yield was obtained for 2 hours when 1 mol% of $Cu(OAc)_2 \cdot H_2O$, 4 mol% of **L4**, and 4 mol% of **A** were used (**Table 1**, entry 13). The use of 0.5 mol% of $Cu(OAc)_2 \cdot H_2O$ for the coupling reaction resulted in a 63% yield (**Table 1**, entry 14). According to this data, TON of ~~copper acetate~~ $Cu(OAc)_2$ reached 126, TOF 0.018 s^{-1}, which indicated a significant improvement of the catalytic activity of the investigated system, as compared with the previously studied analogues.[12–15] As a result, the optimal conditions for copper-catalyzed arylation of morpholine were obtained: $Cu(OAc)_2 \cdot H_2O$ (2 mol%), ligand (**L4**) (8 mol%), CTAB (10 mol%), KOH (200 mol%), water (100 mg/1 mmol ArBr), morpholine (130 mol%), adipic acid (30 mol%), NaOAc (60 mol%), 100 °C, 1 h. Thus, on the example the chosen model reaction it was shown that the change of the quantity of water and the modification of the base with the PTC allow an increase of the yield from 5 to 87%. The fact that aliphatic and saturated heterocyclic amines are weaker NH-acids than anilines explains that they require stronger bases.

Table 1

Copper-catalyzed C–N bond cross-coupling of 4-bromotoluene with morpholine – the optimization of reaction conditions[a]



Entry	KOH (mol%)	PTC (mol%)	Additive (mol%)	Yield,[b%]
1[c]	200	TBAB (20)	–	5
2	200	TBAB (20)	–	36
3	260	TBAB (20)	Adipic acid (30)	72
4	260	TBAB (20)	Adipic acid (15)	64
5	260	TBAB (10)	Adipic acid (30)	63
6	260	CTAB (10)	Adipic acid (30)	79
7	260	TEBA (10)	Adipic acid (30)	12

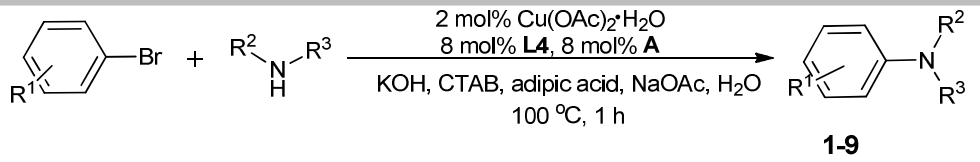
8	260	Potassium stearate (10)	Adipic acid (30)	42
9	260	SDS (20)	Adipic acid (30)	78
10	200	CTAB (10)	Adipic acid (30), NaOAc (60)	87
11[d]	260	CTAB (10)	Adipic acid (30)	0
12[e]	200	CTAB (10)	Adipic acid (30), NaOAc (60)	86
13[f]	200	CTAB (10)	Adipic acid (30), NaOAc (60)	85
14[g]	200	CTAB (10)	Adipic acid (30), NaOAc (60)	63

[a]Reaction conditions: 4-bromotoluene (1 mmol), morpholine (1.3 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.02 mmol), **L4** (0.08 mmol), **A** (0.08 mmol), PTC, additives, KOH, H_2O (100 mg), 100 °C ~~(100 mg)~~, 1 h. [b]Determined by GC analysis (internal standard – biphenyl). [c] 500 mg of H_2O. [d]2 mol% CuO instead of $Cu(OAc)_2 \cdot H_2O$. [e]3 mol% $Cu(OAc)_2 \cdot H_2O$. [f]1 mol% $Cu(OAc)_2 \cdot H_2O$, 4 mol% **L4**, 4 mol% **A**, 2 h. [g]0.5 mol% $Cu(OAc)_2 \cdot H_2O$, 4 mol% **L4**, 4 mol% **A**, 2 h.

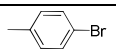
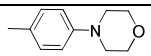
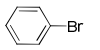
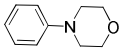
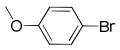
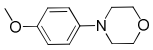
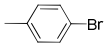
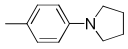
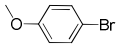
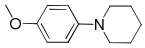
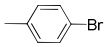
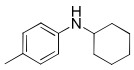
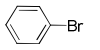
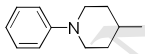
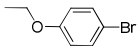
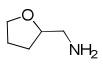
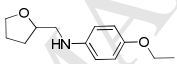
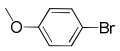
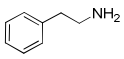
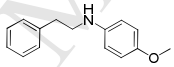
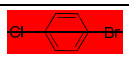
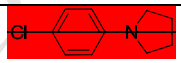
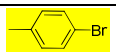
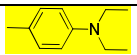
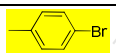
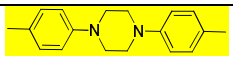
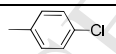
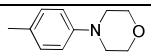
We applied ~~a~~ the new protocol for the cross-coupling of aryl bromides and *N*-heterocyclic compounds and aliphatic amines to establish its scope (**Table 2**). As shown, morpholine, pyrrolidine, piperidine, cyclohexanamine, 4-methylpiperidine, (tetrahydrofuran-2-yl)methanamine, and 2-phenylethanamine reacted with aryl bromides giving the products **1–9** in good to moderate yields.

Table 2

$Cu(OAc)_2 \cdot H_2O$/**L4**/**A**-catalyzed cross-coupling of aryl bromides and heterocyclic and aliphatic amines on a 5 mmol scale[a]



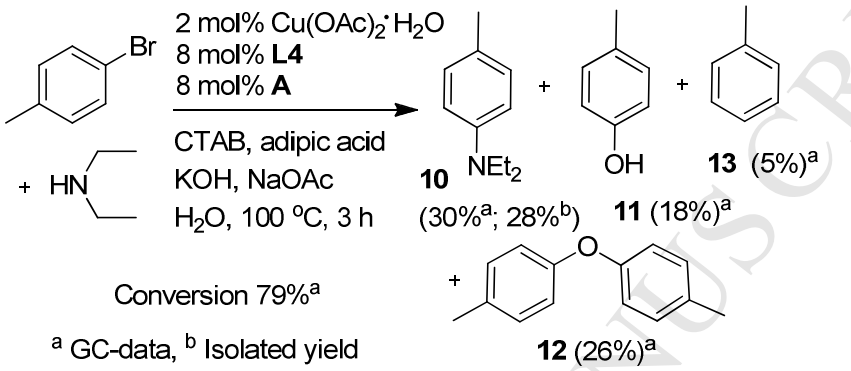
1-9

Entry	ArBr	Amine	Product		Time, h	Yield,[b]%
1				(**1**)	1.5	75
2				(**2**)	1.5	71
3				(**3**)	2	70
4				(**4**)	3	51
5				(**5**)	3	84
6				(**6**)	3	80
7				(**7**)	3	72
8				(**8**)	3	72
9				(**9**)	3	72
~~10~~				~~(10)~~	~~3~~	~~46~~[e]
10				(**10**)	3	28
11				(**14**)	3	68
12				(**1**)	3	*ca.* 0.2[c]
13				(***ortho*-1**)	3	22[c]

[a]Reaction conditions: aryl bromide (5 mmol), amine (6.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol), **L4** (0.4 mmol), **A** (0.4 mmol), CTAB (0.5 mmol), adipic acid (1.5 mmol), NaOAc (3 mmol), KOH (10 mmol), H_2O (0.5 mL), 100 °C, 1 h. [b]Yields of isolated products. [c]GC data, the product was identified by GC-MS

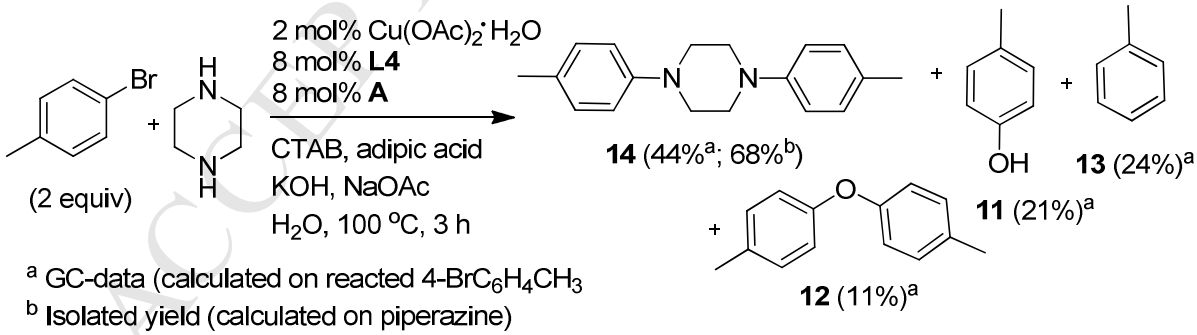
Aryl bromides with donor substituents readily reacted with amines to give the products with good yields as shown in **Table 2** (Entries 1−9). Our results are the best for copper-catalyzed C–N bond cross-coupling of donor-substituted bromobenzenes with aliphatic amines up to data so far. The reaction of 4-bromotoluene with diethylamine gave only a 28% yield of the corresponding C–N coupling product **10**. The rate of the desired reaction may be slowed due to high volatility of the amine (boiling point 55 °C), so that a significant part of the reagent was in the gas phase. In addition, products of the side reactions as C−O cross-coupling (**11, 12**) and hydrodehalogenation of aryl bromide (**13**) were detected in that reaction mixture (Scheme 1).

Scheme 1



A similar pattern was observed for the reaction of piperazine with 2 equivalents of 4-bromotoluene (Scheme 2). Althogh the appreciable amount of the by-products **11–13** was detected by GC desired product **14** was isolated from the reaction mixture with a good yield.

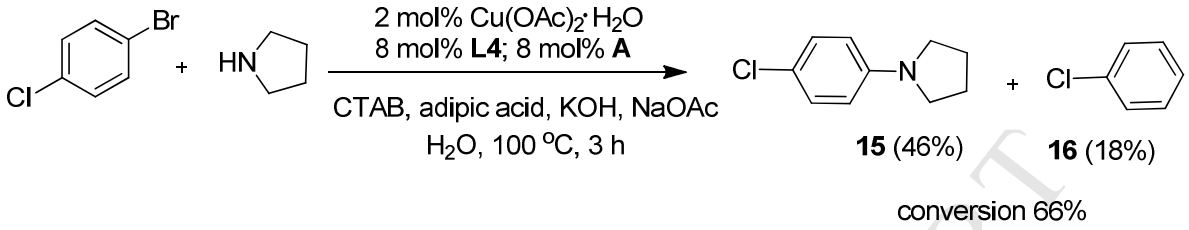
Scheme 2



The reaction of aryl bromides with acceptor substituents (4-Cl) surprisingly led to lower yields of the amination products at the same reaction conditions ~~(Entry 10)~~. The reason is that the reaction selectivity decreases drastically for these substrates that ~~This fact~~ can be demonstrated ~~on~~ by the ~~example of the~~ reaction of 4-chlorobromobenzene with pyrrolidine (**Scheme ~~13~~**), ~~The reaction produced~~ which gave only a 46% of product ~~**10**~~ **15** ~~for~~ after 3 hours. Chlorobenzene ~~**11**~~

16 found in a large amount in the case of this process was formed probably via reductive hydrodehalogenation of 4-chlorobromobenzene.

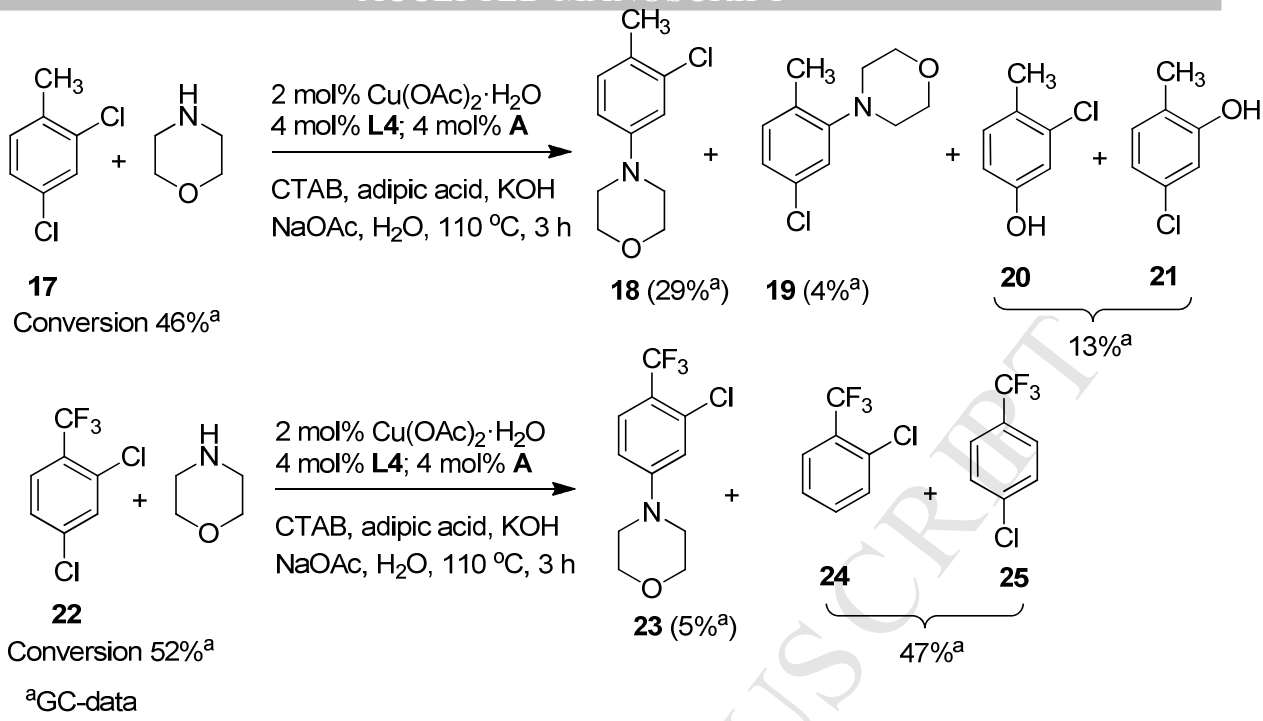
Scheme ~~1~~ 3



The absence of the chlorine atom substitution product in the reaction mixture shows small reactivity of aryl chlorides in this reaction. We confirmed this also on an example of 4-chlorotoluene, which yields only a trace amount of the amination product (Entry 12). Also it is evident~~ly~~ from ~~the~~ **Table 2** that *ortho*-bromotoluene is less reactive than the *para*-isomer ~~in~~ under the applied conditions (Entry 13). In order to study the *ortho*-effect of substituents in more detail, we measured the regioselectivity of the amination for substituted dichlorobenzenes, which usually are more reactive in couplings than monochlorobenzenes.[19,20] ~~This approach to *ortho*-effect studying was developed by us early previously for cobalt-catalyzed methoxycarbonylation of aryl halides[19,20] and for palladium-catalyzed cross-couplings.[21] The essence is to make a difference between the chlorine atoms due to an additional substituent into the dichlorobenzene molecule. This method has the advantage in compareison with the inter-substrate selectivity measurement, since it minimizes the influence of extraneous factors.~~

The amination of substituted dichlorobenzenes **~~12~~17** and **~~17~~22** with morpholine was carried out under the standard conditions up to a low conversion (40%–50%). Analysis of the reactions mixtures by GC-MS and ^{1}H NMR showed that the reaction occurred in both cases ~~although the amination products yields are low~~ with low yields of the amination products (**Scheme ~~2~~4**)(the yields are calculated based on GC data). The resulting substituted *N*-phenylmorpholines were isolated and their structures were determined by NMR analysis. For both compounds **~~12~~17** and **~~17~~22** the substituent directs the amination into position 4 ~~previously regardless its own nature~~ (see **Scheme ~~2~~4**). Thus, the regioselectivity study indicates ~~thus~~ the universal inhibitory effect of *ortho*-substituents (both the donor and acceptor).

Scheme 2 4



As well as for aryl bromides, the yield of the amination products in the case of the substrate with a donor substituent (~~12~~**17**) substantially exceeds that of the acceptor-substituted substrate (~~17~~**22**). ~~We believe the reason is that the amination and the reduction were catalyzed by different catalytic species.~~ Perhaps, substrates with donor substituents are not capable to be activated by the catalytic species that catalyze hydrodehalogenation of aryl halides, therefore only the amination reaction proceeds with these substrates.

3. Conclusion

To summarize, we have developed an efficient and convenient method for the copper-catalyzed C–N bond cross-coupling of aryl bromides and aliphatic amines in water. The new ligand system **L**/hexane-2,5-dione has been ~~proved~~ found considerably more efficient in the copper-catalyzed C–N cross-coupling reaction as compared to the ligands described in the literature that allowed decreasing of the catalyst amount to achieve ~~the~~ acceptable yields of the isolated products. The ~~found~~ developed catalytic system is more suitable for amination of aryl bromides with electron-donor substituents, although acceptor substituted aryl bromides also react. Aryl bromides with substituents in the *ortho*-position, along with ~~and~~ some aryl dichlorides undergo cross-coupling under the same conditions ~~mentioned above~~ but their reactivity is lower.

4. Experimental section

4.1. General chemical procedures

All reagents (except for ligand **L4**) were obtained commercially and used without further purification. Commercial KOH was used (Reakhim, reagent grade, 85%). Ligand **L4** was synthesized according to the methods described in our previous work.[21] Solvents were purified

according to the standard procedures.[22] ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II+ 400 MHz (UltraShield Magnet) spectrometer at room temperature. Chemical shifts are reported in δ (ppm downfield from tetramethylsilane). Spectra in $CDCl_3$ are referenced to the residual solvent peaks at δ 7.27 (^{1}H) and 77.00 (^{13}C). Spectra in DMSO-d_6 и DMSO-d_6+CCl_4 (1:2) are referenced to the residual solvent peaks at δ 2.50 (^{1}H) and 39.52 (^{13}C). 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. GC-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. Melting points were determined on a capillary melting point apparatus and not corrected.

4.2. C–N bond coupling reaction of 4-bromotoluene with morpholine on a 1 mmol scale

A 8 mL screw cap test tube was charged with ~~the required amounts of~~ $Cu(OAc)_2 \cdot H_2O$ (4 mg, 0.02 mmol, 2 mol%), ligand **L4** (15.6 mg, 0.08 mmol, 8 mol%), additive **A** - hexane-2,5-dione (9.2 mg, 0.08 mmol, 8 mol%), adipic acid (73 mg, 0.3 mmol, 30 mol%), NaOAc (49 mg, 0.6 mmol, 60 mol%), KOH (169 mg, 2.6 mmol, 260 mol%) , PTC – TBAB (64.5 mg, 0.2 mmol, 20 mol%) or CTAB (36.4 mg, 0.1 mmol, 10 mol%), H_2O (100 mg), morpholine (115 mg, 1.3 mmol, 130 mol%) and 4-bromotoluene (170 mg, 1 mmol). Argon (flow rate 5−7 mL/min) was bubbled through the resulting mixture for 5 min and it was stirred at 100 °C for the required time. Then the reaction mixture was cooled to room temperature and extracted with EtOAc (5 mL). The samples of organic phase (0.1–0.2 mL) were separated, dried with anhydrous Na_2SO_4, filtered and analyzed by GC.

4.3. General procedure for C–N bond coupling reaction of aryl bromides with 5- and 6-membered saturated N-heterocyclic compounds and aliphatic amines on a 5 mmol scale

A 15 mL screw cap test tube was charged with $Cu(OAc)_2 \cdot H_2O$ (20 mg, 0.1 mmol, 2 mol%), **L4** (78 mg, 0.4 mmol, 8 mol%), hexane-2,5-dione (46 mg, 0.4 mmol, 8 mol%), KOH (650 mg, 10 mmol, 200 mol%), adipic acid (219 mg, 1.5 mmol, 30 mol%), NaOAc (246 mg, 3 mmol, 60 mol%), CTAB (182 mg, 0.5 mmol, 10 mol%), H_2O (0.5 mL), aryl bromide (5 mmol) and amine (6.5 mmol, 130 mol%). Argon (flow rate 5−7 mL/min) was bubbled through the resulting mixture for 5 min. The reaction mixture was stirred in a closed test tube at 100 °C for 3–4 h until complete consumption of starting material as monitored by TLC (eluent–hexane), then cooled to room temperature and diluted with EtOAc (30 mL). The EtOAc solution was purified by flash-chromatography, washed with water (3×10 mL), and dried with anhydrous Na_2SO_4. Then EtOAc was evaporated under reduced pressure and the residue was recrystallized from hexane (substances **1–4**) or aq. EtOH (substances **5–9**). In a case of the substances **5**, **7–9** the residue was dissolved in diethyl ether. Aq. HCl (37%) was added dropwise to the resulting solution until pH 3−4. The formed precipitate was filtered, washed with diethyl ether (10 mL) and dried at 50 °C.

***N*-(4-Methylphenyl)morpholine** (**1**).[23] Pale brown solid (666 mg, 75%), mp 44–45 °C (from hexane) (lit. 47.3–48 °C) ^{1}H NMR (DMSO-d_6+CCl_4 (1:2), 400 MHz, ppm): δ 7.00 (d, *J*=8.4 Hz, 2H), 6.76 (d, *J*=8.4 Hz, 2H), 3.76 (t, *J*=4.8 Hz, 4H), 3.05 (t, *J*=4.8 Hz, 4H), 2.26 (s, 3H). ^{13}C NMR (DMSO-d_6+CCl_4 (1:2), 101 MHz, ppm): δ 148.6, 128.9, 127.8, 115.2, 65.9, 49.0, 19.9. HR-MS (ESI+): calcd for $C_{11}H_{16}NO$ $[M+H]^+$: 178.1226; found 178.1226.

***N*-Phenylmorpholine** (**2**).[23] Pale brown solid (579 mg, 71%), mp 55–56 °C (from hexane)(lit. 52.5-53.4 °C). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.34–7.28 (m, 2H), 6.97–6.91 (m, 3H), 3.90 (t, *J*=4.8 Hz, 4H), 3.19 (t, *J*=4.8 Hz, 4H). ^{13}C NMR ($CDCl_3$, 101 MHz, ppm): δ 151.3, 129.2, 120.1, 115.6, 66.9, 49.4. HR-MS (ESI+): calcd for $C_{10}H_{14}NO$ $[M+H]^+$: 164.1070; found 164.1072.

***N*-(4-Methoxyphenyl)morpholine** (**3**).[24] Pale brown solid (680 mg, 70%), mp 70–72 °C (from hexane)(lit. 71-72 °C). ^{1}H NMR (DMSO-d_6+CCl_4 (1:2), 400 MHz, ppm): δ 6.82 (d, *J*=9.1 Hz, 2H), 6.76 (d, *J*=9.1 Hz, 2H), 3.76 (t, *J*=4.8 Hz, 4H), 3.73 (s, 3H), 2.99 (t, *J*=4.8 Hz, 4H). ^{13}C NMR (DMSO-d_6+CCl_4 (1:2), 101 MHz, ppm): δ 153.1, 145.0, 116.9, 113.7, 66.0, 54.6, 50.0. HR-MS (ESI+): calcd for $C_{11}H_{16}NO_2$ $[M+H]^+$: 194.1176; found 194.1186.

***N*-(4-methylphenyl)pyrrolidine** (**4**).[25] Brown solid (415 mg, 51%), mp 40–42 °C (from hexane)(lit. 40-42 °C). ^{1}H NMR (DMSO-d_6+CCl_4 (1:2), 400 MHz, ppm): δ 6.92 (d, *J*=8.0 Hz, 2H), 6.40 (d, *J*=8.0 Hz, 2H), 3.24 (t, *J*=6.4 Hz, 4H), 2.24 (s, 3H), 2.02 (t, *J*=6.4 Hz, 4H). ^{13}C NMR (DMSO-d_6+CCl_4 (1:2), 101 MHz, ppm): δ 145.3, 128.9, 123.1, 111.2, 47.1, 24.8, 19.8. HR-MS (ESI+): calcd for $C_{11}H_{16}N$ $[M+H]^+$: 162.1277; found 162.1280.

***N*-(4-Methoxyphenyl)piperidine hydrochloride** (**5**).[26] Brown solid (958 mg, 84%), mp 185–187 °C (from 85% EtOH) (lit. 186-187 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.73 (br. s, 1H), 7.84 (d, *J*=8.9 Hz, 2H), 6.97 (d, *J*=8.9 Hz, 2H), 3.83 (s, 3H), 3.62 (d, *J*=11.4 Hz, 2H), 3.23 (dd, *J*=22.3 Hz, 10.5 Hz, 2H), 2.72 (q, *J*=13.4 Hz, 2H), 2.02 (d, *J*=13.4 Hz, 1H), 1.92 (d, *J*=14.4 Hz, 2H), 1.57–1.47 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz, ppm): δ 160.2, 135.6, 122.7, 115.2, 57.6, 55.7, 23.0, 21.7. HR-MS (ESI+): calcd for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1383; found 192.1386.

***N*-Cyclohexyl-4-methylaniline** (**6**).[27] Brown solid (749 mg, 79%), mp 43–44 °C (from 85% EtOH) (lit. 40-41 °C). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 6.99 (d, *J*=8.3 Hz, 1H), 6.56 (d, *J*=8.3 Hz, 1H), 3.56 (br.s, 1H), 3.28–3.21 (m, 1H), 2.26 (s, 3H), 2.10–2.06 (m, 2H), 1.80–1.75 (m, 2H), 1.69–1.64 (m, 1H), 1.44–1.33 (m, 2H), 1.29–1.11 (m, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz, ppm): δ 145.1, 129.8, 126.2, 113.5, 52.1, 33.6, 26.0, 25.1, 20.4. HR-MS (ESI+): calcd for $C_{13}H_{20}N$ $[M+H]^+$: 190.1590; found 190.1592.

4-Methyl-(*N*-phenyl)piperidine hydrochloride (**7**). Pale brown solid (762mg, 72%), mp 155–157 °C (from 85% EtOH). ^{1}H NMR (DMSO-d_6+CCl_4 (1:2), 400 MHz, ppm): δ 13.75 (br. s, 1H), 8.04 (m, 2H), 7.52–7.43 (m, 3H), 3.64 (m, 2H), 3.46–3.44 (m, 2H), 2.18 (m, 2H), 1.91–1.87 (m, 3H), 1.09 (d, J= 6.0 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz, ppm):δ 143.1, 129.2, 121.5, 95.5, 55.2, 30.4, 27.4, 20.8. HR-MS (ESI+): calcd for $C_{12}H_{18}N$ $[M+H]^+$: 176.1434; found 176.1437.

4-Ethoxy-*N*-((tetrahydrofuran-2-yl)methyl)aniline hydrochloride (**8**). Brown solid (929 mg, 72%), mp 98–100 °C (from 85% EtOH). ^{1}H NMR (DMSO-d_6+CCl_4 (1:2), 400 MHz, ppm): δ

11.48 (br.s, 2H), 7.51 (d, *J*=8.8 Hz, 2H), 6.93 (d, *J*=8.8 Hz, 2H), 4.27 (m, 1H), 4.03 (q, *J*=6.9 Hz, 2H), 3.90 (dd, *J*=14.3, 7.4 Hz, 1H), 3.77 (dd, *J*=14.3, 7.3 Hz, 1H), 3.25 (dd, *J*=12.7, 3.4 Hz, 1H), 3.16 (dd, *J*=12.7, 8.8 Hz, 1H), 2.10–2.02 (m, 1H), 2.00–1.85 (m, 2H), 1.70–1.61 (m, 1H), 1.40 (t, *J*=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz, ppm): δ 159.2, 127.9, 124.9, 115.3, 72.9, 68.3, 63.8, 56.1, 29.4, 25.4, 14.7. HR-MS (ESI+): calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$: 222.1489; found 222.1495.

4-Methoxy-*N*-phenethylaniline hydrochloride (**9**).[28] Pale pink solid (941 mg, 71%), mp 127–129 °C (from 85% EtOH) (lit. 127-129 °C). ^{1}H NMR (DMSO-d_6+CCl_4 (1:2), 400 MHz, ppm): δ 11.68 (br. s, 2H), 7.60 (d, *J*=8.9 Hz, 2H), 7.28–7.18 (m, 5H), 6.98 (d, *J*= 8.9 Hz, 2H), 3.81 (s, 3H), 3.39 (dd, *J*=10.4, 6.5 Hz, 2H), 3.12 (dd, *J*=10.4, 6.5 Hz, 2H). ^{13}C NMR (DMSO-d_6+CCl_4 (1:2), 101 MHz, ppm): δ 159.1, 136.7, 128.7, 128.4, 128.0, 126.2, 124.2, 114.6, 55.0, 52.5, 31.3. HR-MS (ESI+): calcd for $C_{15}H_{18}NO$ $[M+H]^+$: 228.1383; found 228.1383.

N-(4-methylphenyl)diethylamine (10).[29] Yellow oil (228 mg, 28%). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.08 (d, *J*=8.2 Hz, 2H), 6.69 (d, *J*= 8.0 Hz, 2H), 3.37 (q, *J*= 6.9 Hz, 4H), 2.30 (s, 3H), 1.2 (t, *J*= 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz, ppm): δ 145.9 (C), 129.8 (2CH), 124.8 (2CH), 112.6 (C), 44.6 (2C, CH_2), 20.2 (CH_3), 12.6 (2C, CH_3). HR-MS (ESI+): calcd for $C_{11}H_{17}N$ $[M+H]^+$: 164.1434; found 164.1442.

1,4-bis(4-methylphenyl)piperazine (14).[30] Prepared according to General procedure 4.3 from 2.5 mmol piperazine (molar ratio of 4-bromotoluene and piperazine 2:1). Light brown solid (450 mg, 68%), mp 191−192 °C (lit. 189−191 °C). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.14 (d, *J*=8.4 Hz, 4H), 6.94 (d, *J*= 8.4 Hz, 4H), 3.32 (s, 8H), 2.32 (s, 6H), ^{13}C NMR ($CDCl_3$, 101 MHz, ppm): δ 149.2 (C), 129.7, 129.6, 116.7, 50.1, 20.5 (C, CH_3). HR-MS (ESI+): calcd for $C_{18}H_{23}N_2$ $[M+H]^+$: 267.1856; found 267.1856.

4.4. General procedure for C–N bond coupling reaction of aryl chlorides with morpholine

A 8 mL screw cap test tube was charged with $Cu(OAc)_2 \cdot H_2O$ (12 mg, 0.06 mmol, 2 mol%), **L** (25 mg, 0.12 mmol, 4 mol%), hexane-2,5-dione (18 mg, 0.12 mmol, 4 mol%), KOH (85%) (225 mg, 3.3 mmol, 110 mol%), adipic acid (70 mg, 0.45 mmol, 15 mol%), NaOAc (78 mg, 0.9 mmol, 30 mol%), CTAB (60 mg, 0.15 mmol, 5 mol%), H_2O (0.3 mL), corresponding aryl chloride (3 mmol) and morpholine (350 mg, 3.9 mmol, 130 mol%). Argon (flow rate 5−7 mL/min) was bubbled through the resulting mixture for 5 min. The reaction mixture was stirred in a closed test tube at 110 °C for 3 h, then cooled to room temperature and diluted with EtOAc (30 mL). The EtOAc solution was washed with water (2 × 30 mL), dried with anhydrous Na_2SO_4, filtered and analyzed by GC and GC-MS. Then EtOAc was evaporated under reduced pressure and the residue was chromatographed with using a SiO_2 column (EtOAc/hexane 1:5 or petroleum ether (40–70 °C)/EtOAc 9:1).

4-(3-Chloro-4-methylphenyl)morpholine (1318):

Dark yellow oil (90 mg, 14%). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.13 (d, *J*=8.4 Hz, 1H, H-5), 6.92 (d, *J*=2.6 Hz, 1H, H-2), 6.75 (dd, *J*=8.4 Hz, *J*=2.6 Hz, 1H, H-6), 3.87 (t, *J*=4.8 Hz, 4H),

3.13 (t, *J*=4.8 Hz, 4H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz, ppm): δ 150.49 (C), 134.87 (C), 131.19 (CH), 127.10 (C), 116.30 (CH), 114.30 (CH), 66.80 (CH_2O), 49.40 (CH_2N), 18.99 (C, CH_3). MS, *m/z* (%): 211 (M^+, 68%), 153 (100%). HR-MS (ESI+): calcd for $C_{11}H_{15}ClNO$: 212.0837 $[M+H]^+$; found 212.0836.

4-(5-Chloro-2-methylphenyl)morpholine (1419):

Brown oil (20 mg, 3%). Purity (^{1}H NMR data): *ca.* 90%. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.12 (d, *J*=8.7 Hz, 1H, H-3), 6.99 (m, 2H, H-4 and H-6), 3.87 (t, *J*=4.6 Hz, 4H), 2.91 (t, *J*=4.6 Hz, 4H), 2.29 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 101 MHz, ppm): δ 152.32 (C), 132.06 (CH), 131.85 (C), 130.84 (C), 123.26 (CH), 119.48 (CH), 67.28 (CH_2O), 52.02 (CH_2N), 17.48 (C, CH_3). MS, *m/z* (%): 211 (M^+, 100%), 153 (99%). HR-MS (ESI+): calcd for $C_{11}H_{15}ClNO$: 212.0837 $[M+H]^+$; found 212.0824.

4-(3-Chloro-4-trifluoromethylphenyl)morpholine (1823):

Brown oil (41 mg, 5%). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.54 (d, *J*=8.9 Hz, 1H, H-5), 6.95 (d, *J*=2.4 Hz, 1H, H-2), 6.77 (dd, *J*=8.9 Hz, *J*=2.4 Hz, 1H, H-6), 3.87 (t, *J*=4.9 Hz, 4H), 3.26 (t, *J*=4.9 Hz, 4H). ^{13}C NMR ($CDCl_3$, 101 MHz, ppm): δ 153.80 (C), 133.32 (br.s, C-Cl), 128.35 (q, *J*=5.2 Hz, CH), 123.41 (q, *J*=271.4 Hz, C-F), 118.20 (q, *J*=31.8 Hz, C), 116.46 (CH), 111.70 (CH), 66.44 ($2CH_2O$), 47.62 ($2CH_2N$). MS, *m/z* (%): 265 (M^+, 79%), 207 (100%). HR-MS (ESI+): calcd for $C_{11}H_{12}ClF_3NO$: 266.0554 $[M+H]^+$; found 266.0555.

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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Supplementary Material

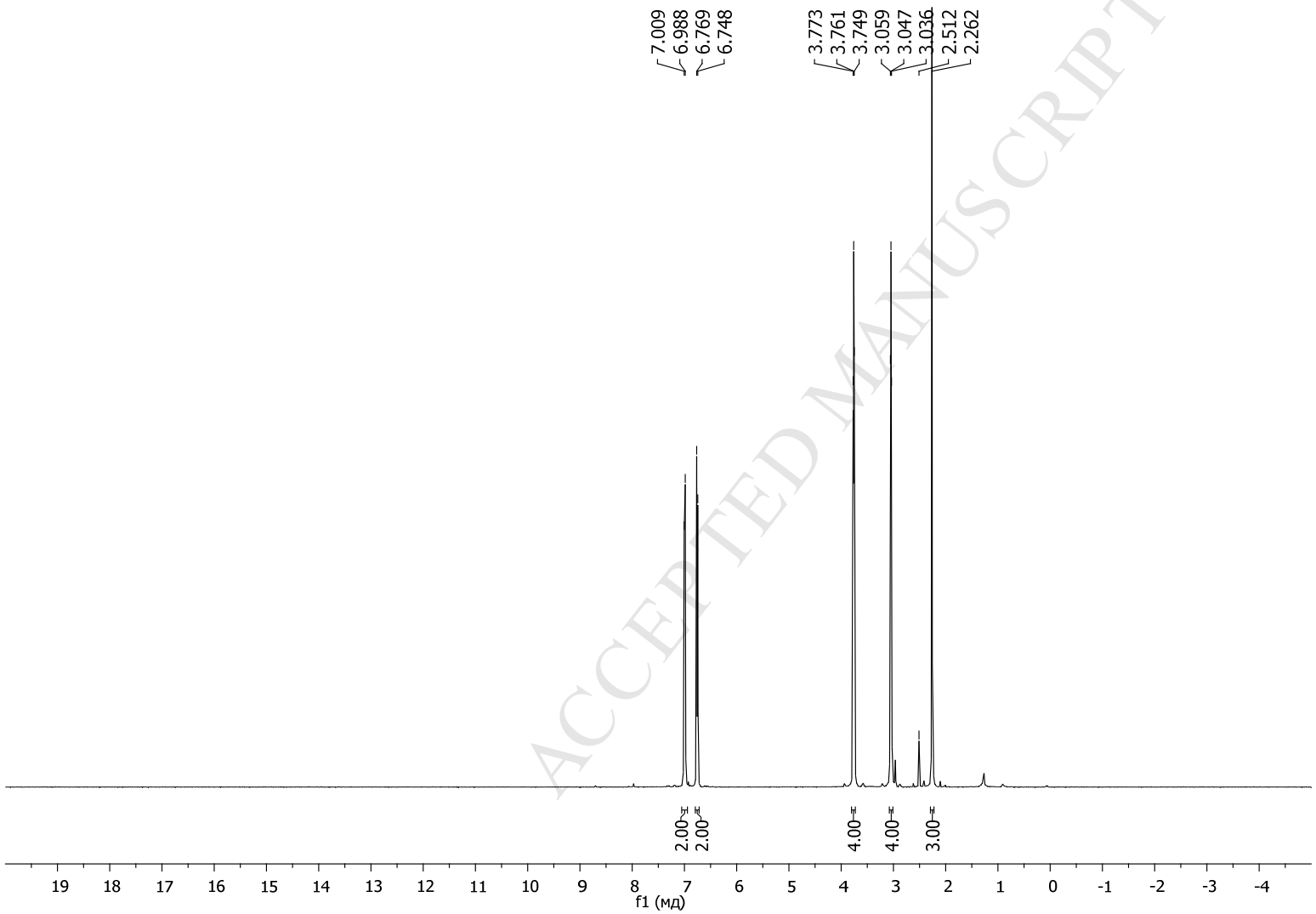
Copper-catalyzed C–N cross-coupling of aryl bromides and amines in water in the presence of ligand derived from oxalyl dihydrazide: scope and limitation

Daria V. Kurandina, Eugene V. Eliseenkov, Tatyana S. Khaibulova, Alexander A. Petrov, Vadim P. Boyarskiy

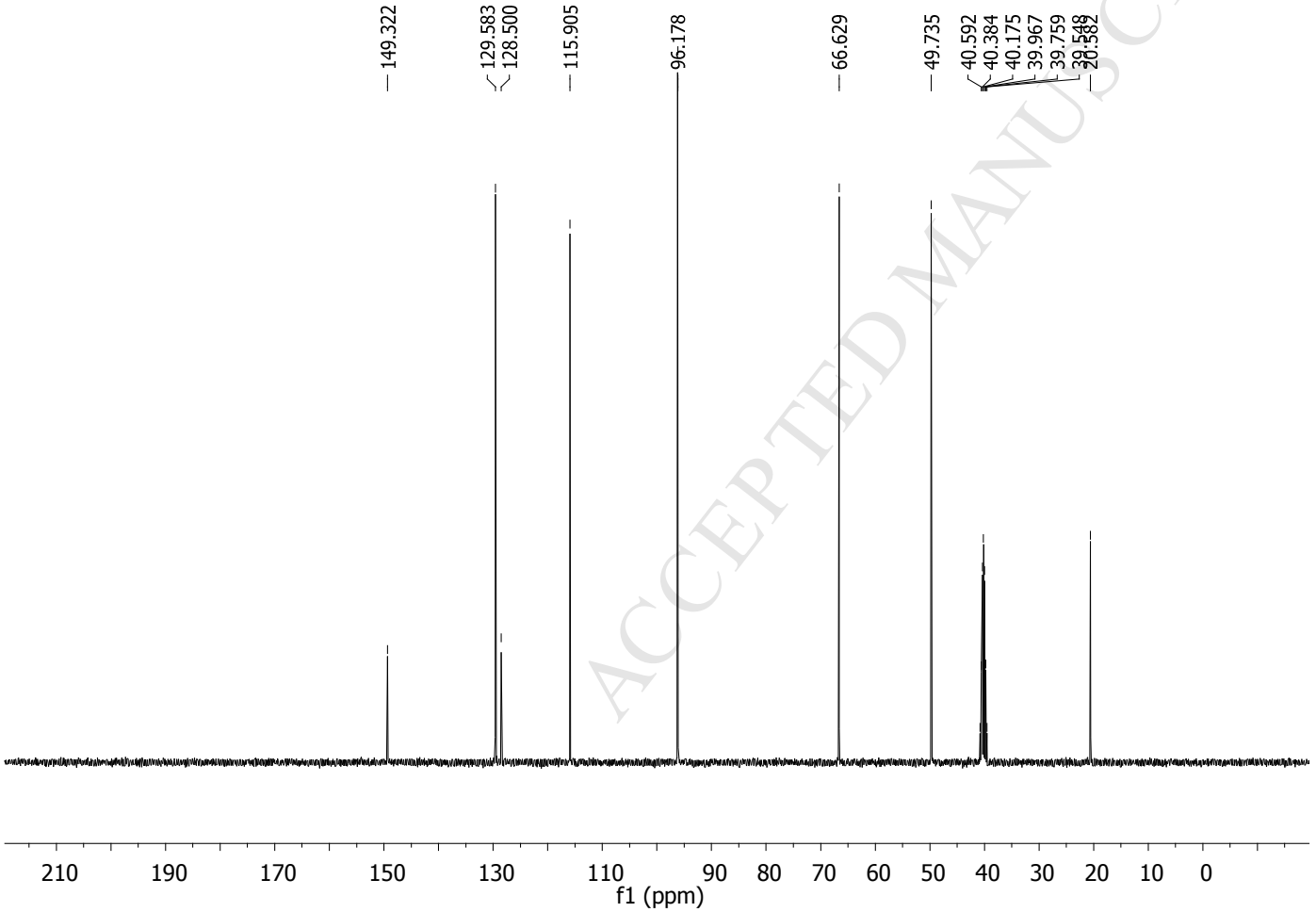
General chemical procedures

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II+ 400 MHz (UltraShield Magnet) spectrometer at room temperature. Chemical shifts are reported in δ (ppm downfield from tetramethylsilane). Spectra in $CDCl_3$ are referenced to the residual solvent peaks at δ 7.27 (^{1}H) and 77.00 (^{13}C). Spectra in DMSO-d_6 are referenced to the residual solvent peaks at δ 2.50 (^{1}H) and 39.52 (^{13}C). 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 mm) capillary column. GS-MS analysis was conducted on a **S**himadzu GCMS QP-2010 SE spectrometer equipped with an electron impact ionization source and Rtx-5MS (30 m×0.32 mm×0.25 mm) capillary column. Mass spectra were recorded on a Bruker micrOTOF spectrometer equipped with an electrospray ionization (ESI) source.

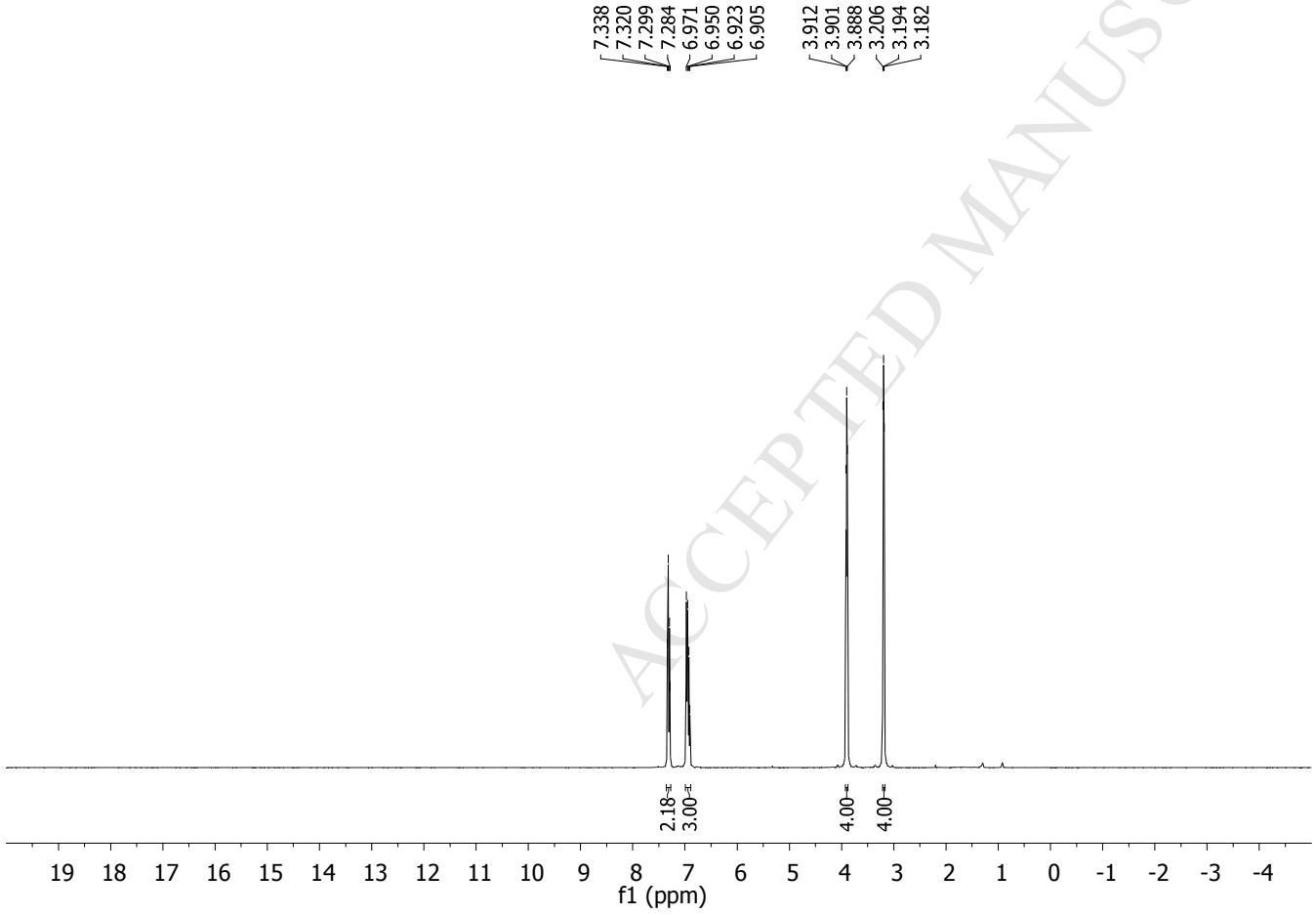
^{1}H NMR of *N*-(4-methylphenyl)morpholine (**1**) (400.13 MHz, DMSO-d_6+CCl_4)



^{13}C NMR of *N*-(4-methylphenyl)morpholine (**1**) (100.61 MHz, DMSO-d_6+CCl_4)



^{1}H NMR of *N*-phenylmorpholine (**2**) (400.13 MHz, $CDCl_3$)



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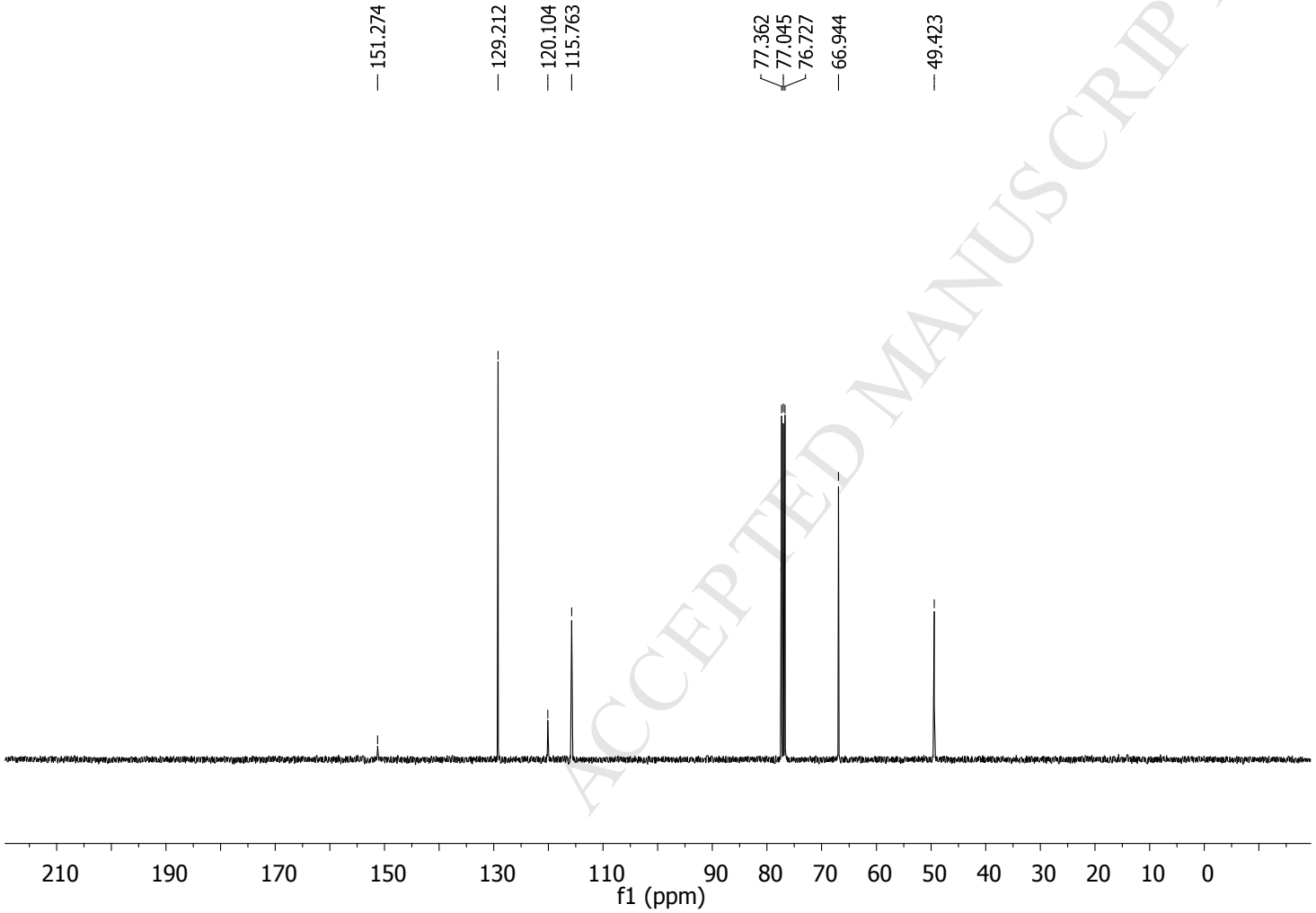
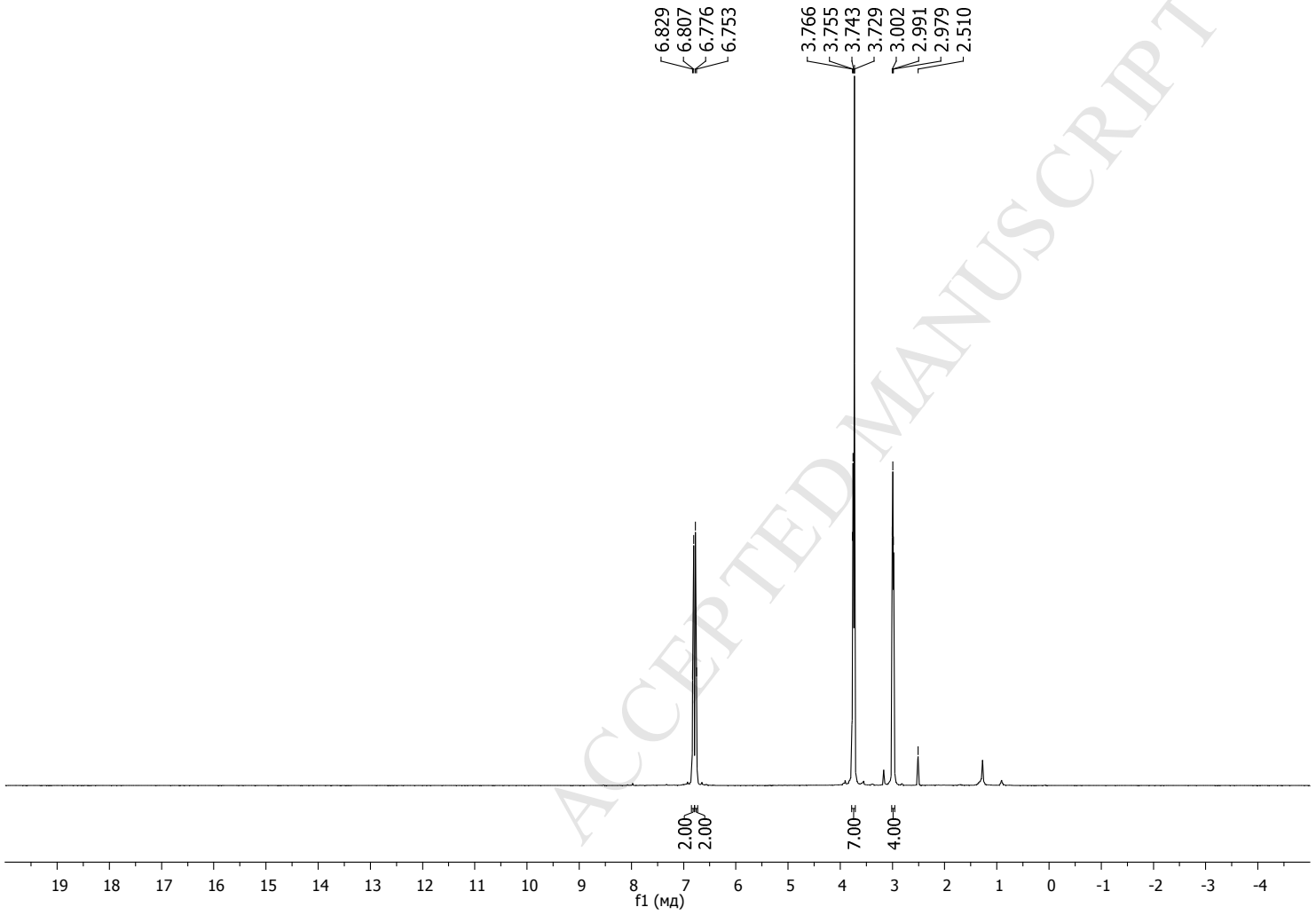


^{1}H NMR of *N*-(4-methoxyphenyl)morpholine (**3**) (400.13 MHz, DMSO-d_6+CCl_4)



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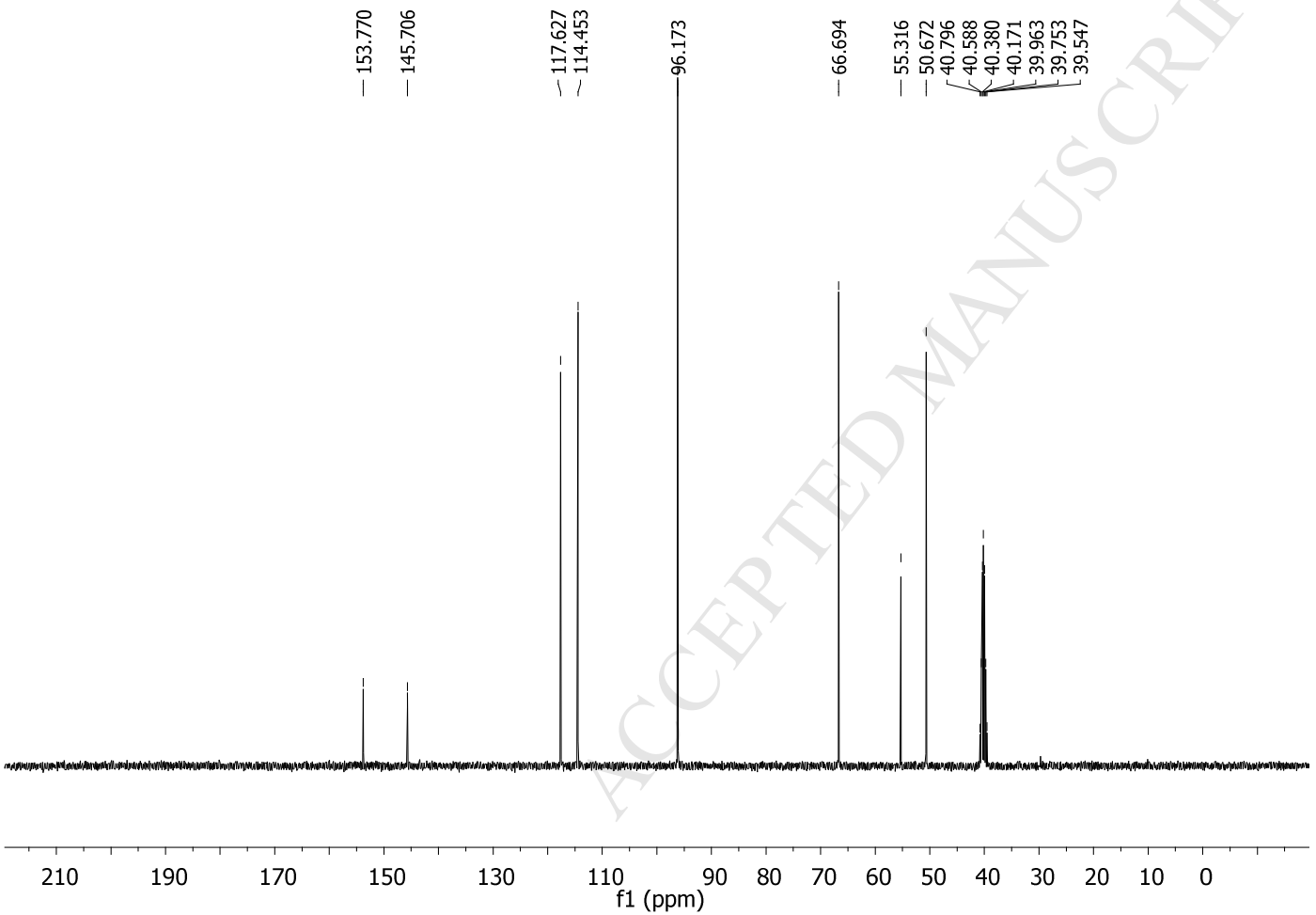

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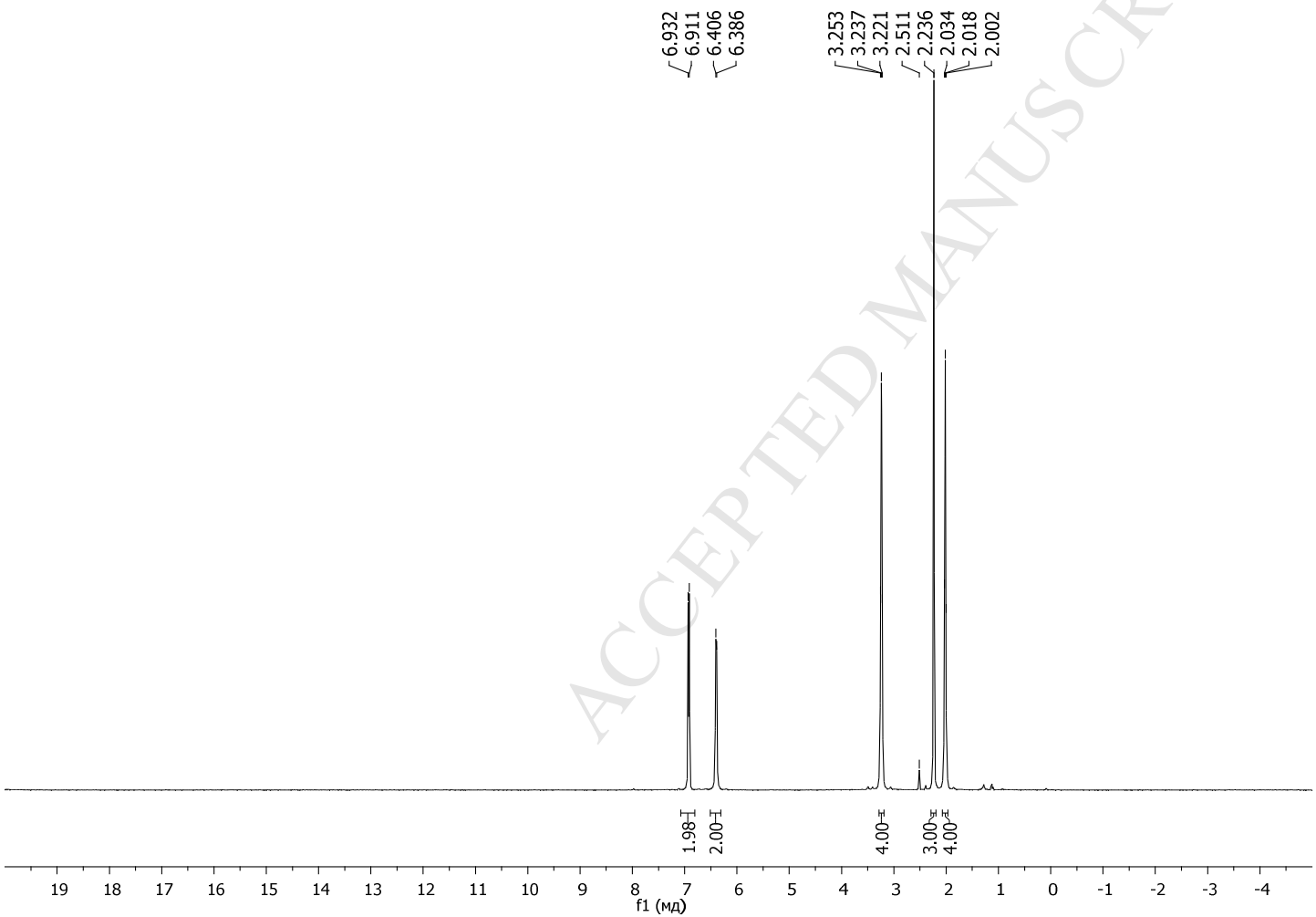
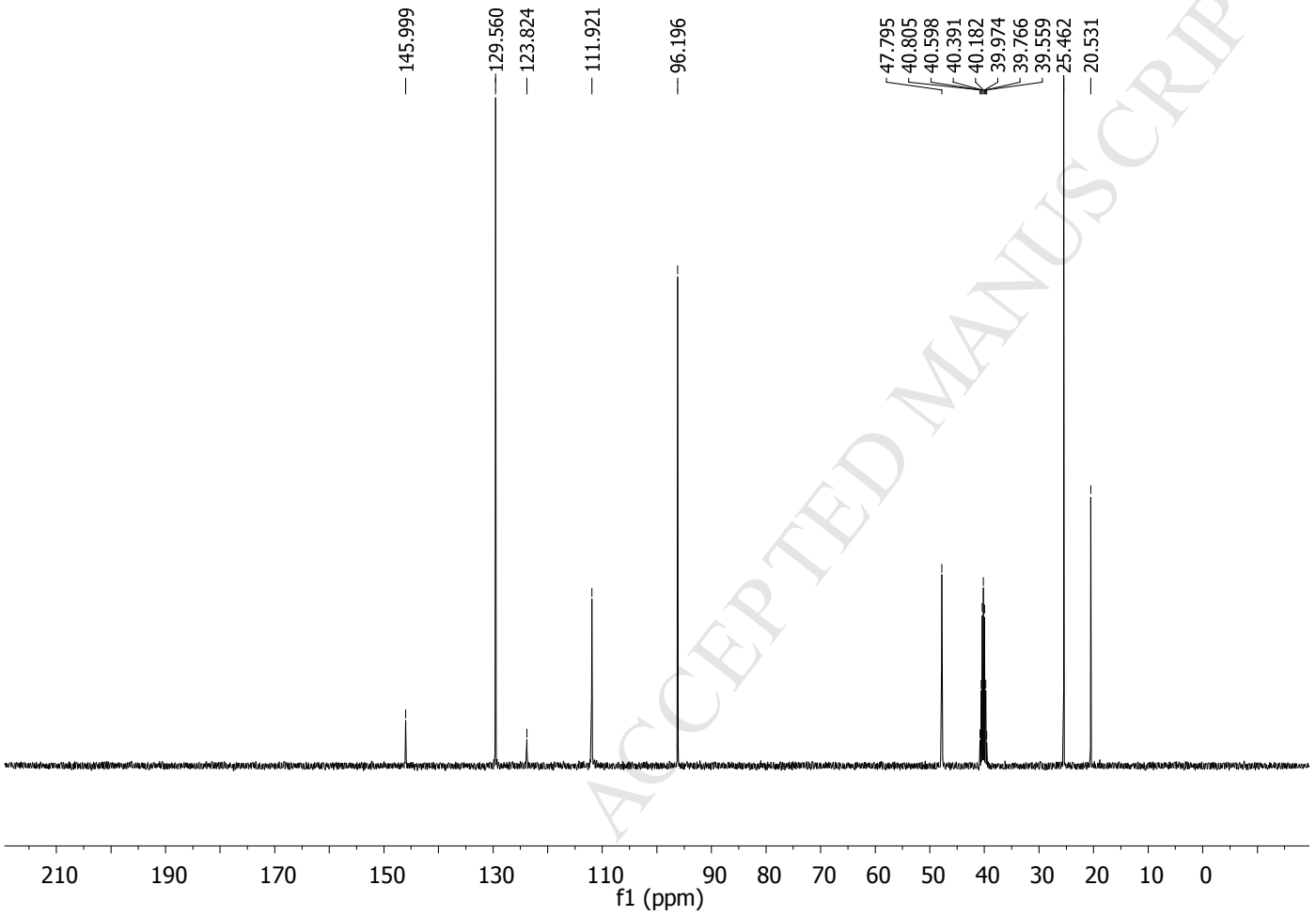
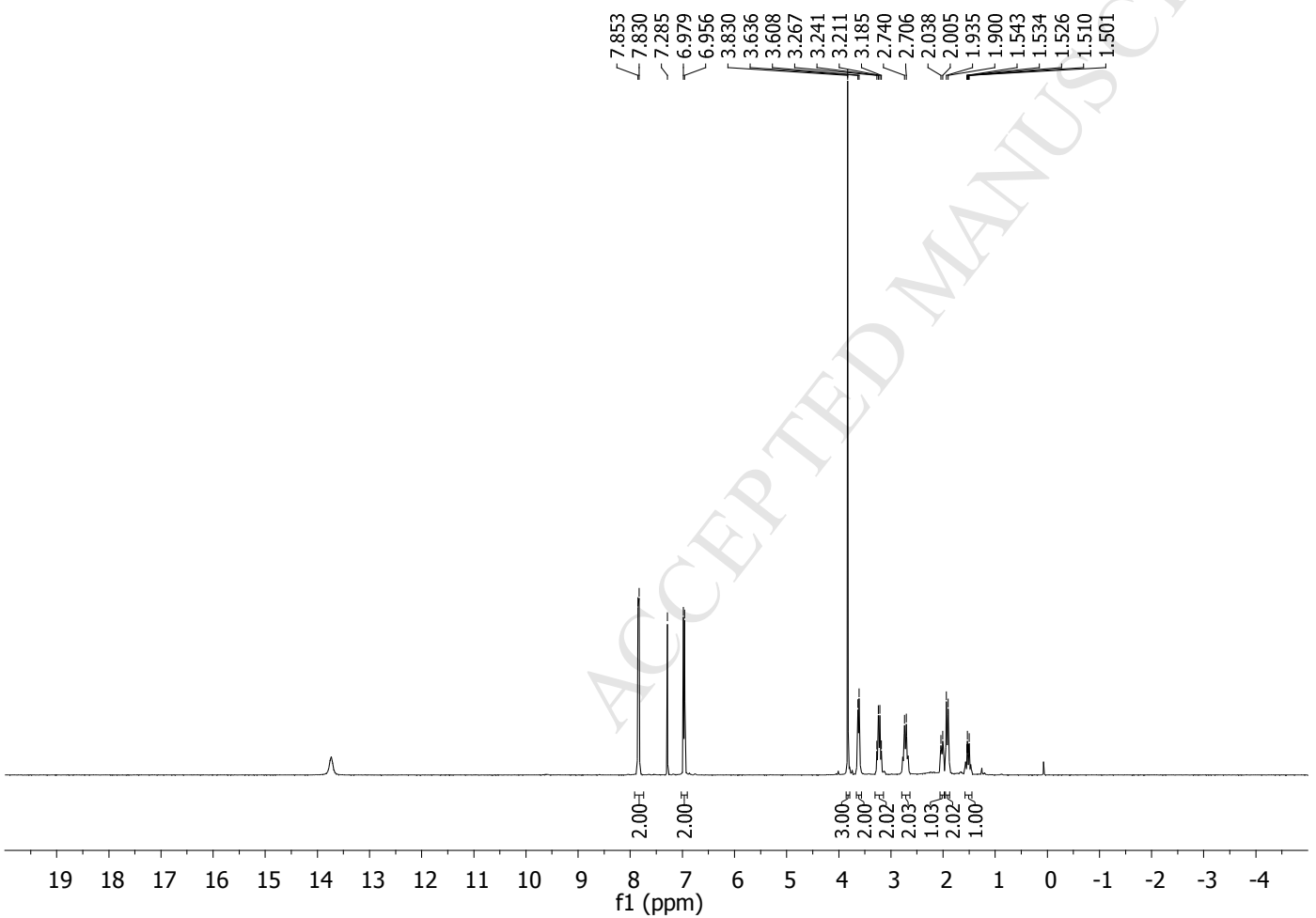
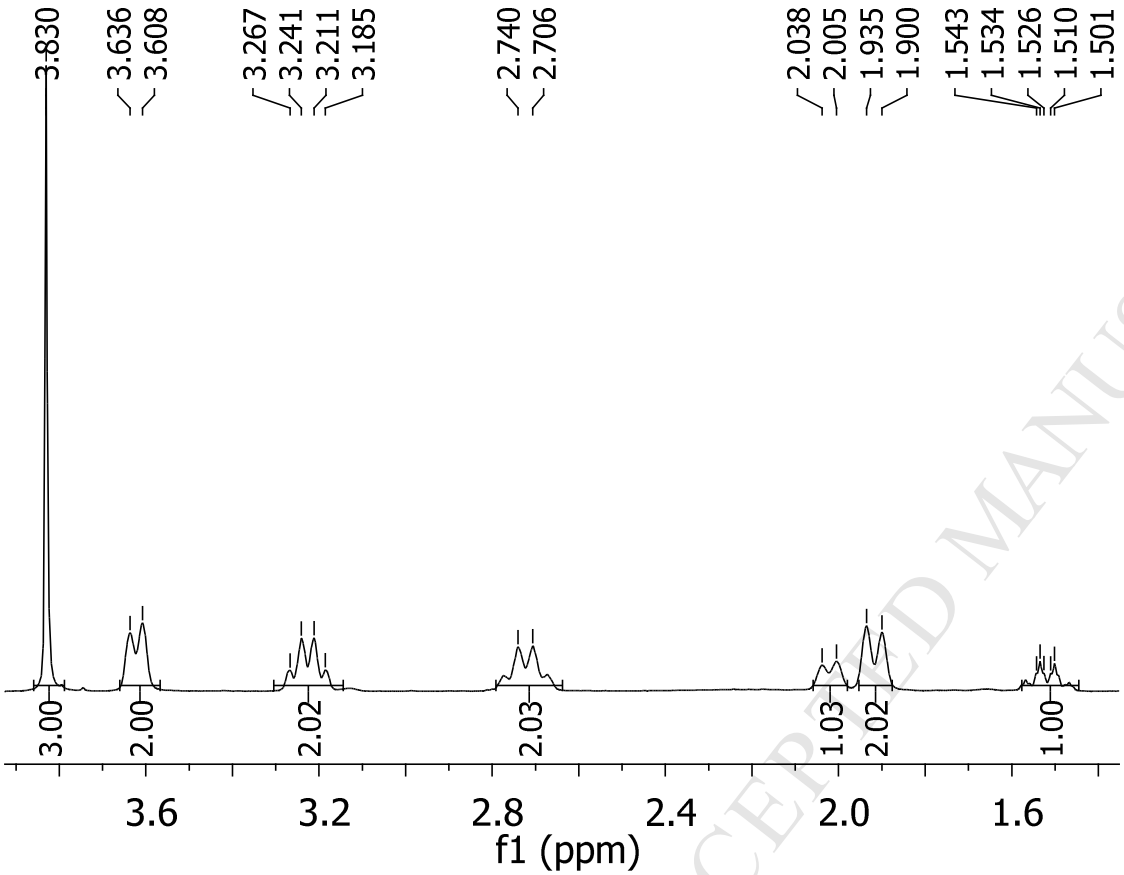


^{13}C NMR of *N*-(4-methylphenyl)pyrrolidine (**4**) (100.61 MHz, DMSO-d_6+CCl_4)



^{1}H NMR of *N*-(4-methoxyphenyl)piperidine hydrochloride (**5**) (400.13 MHz, $CDCl_3$)





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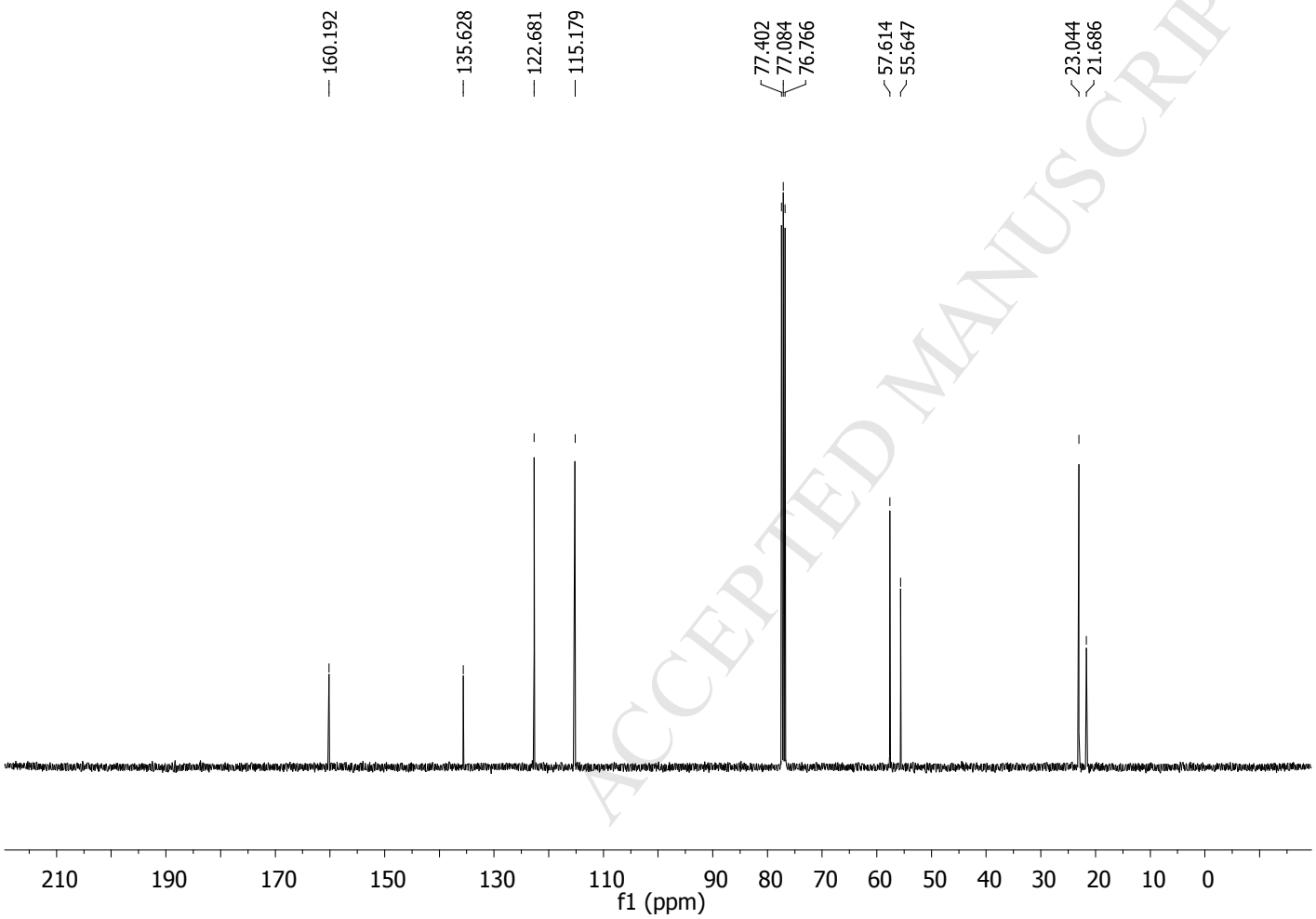
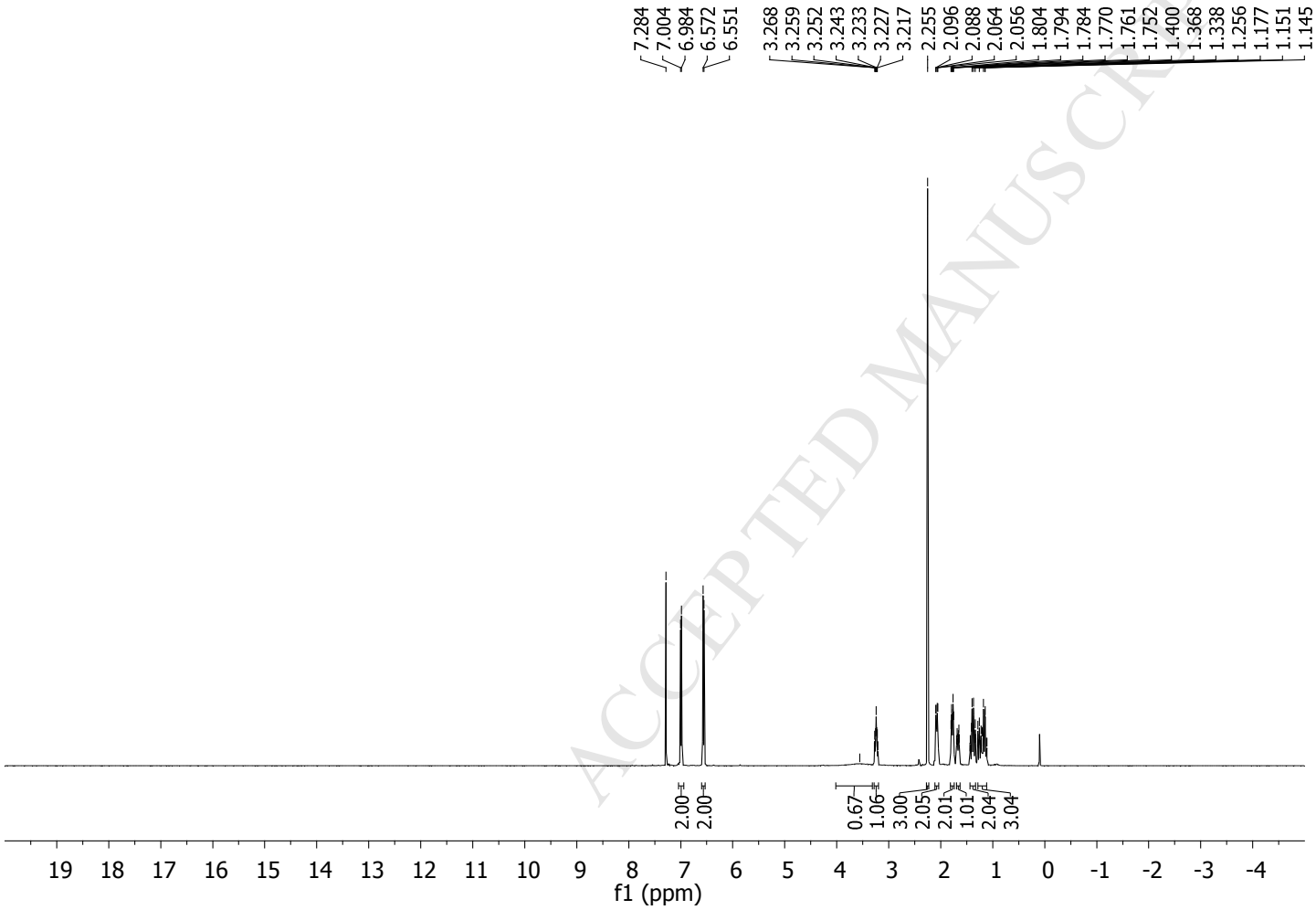
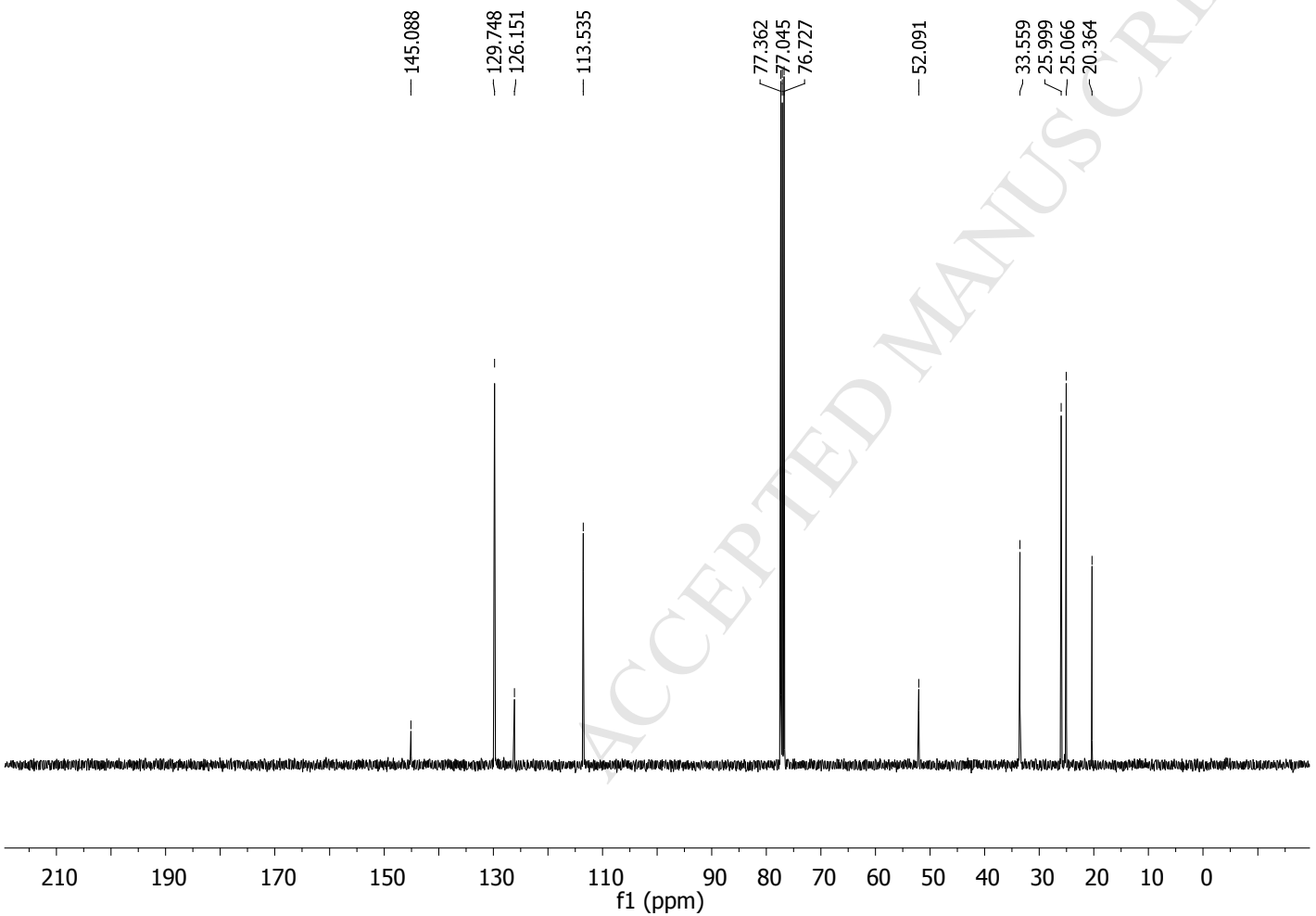


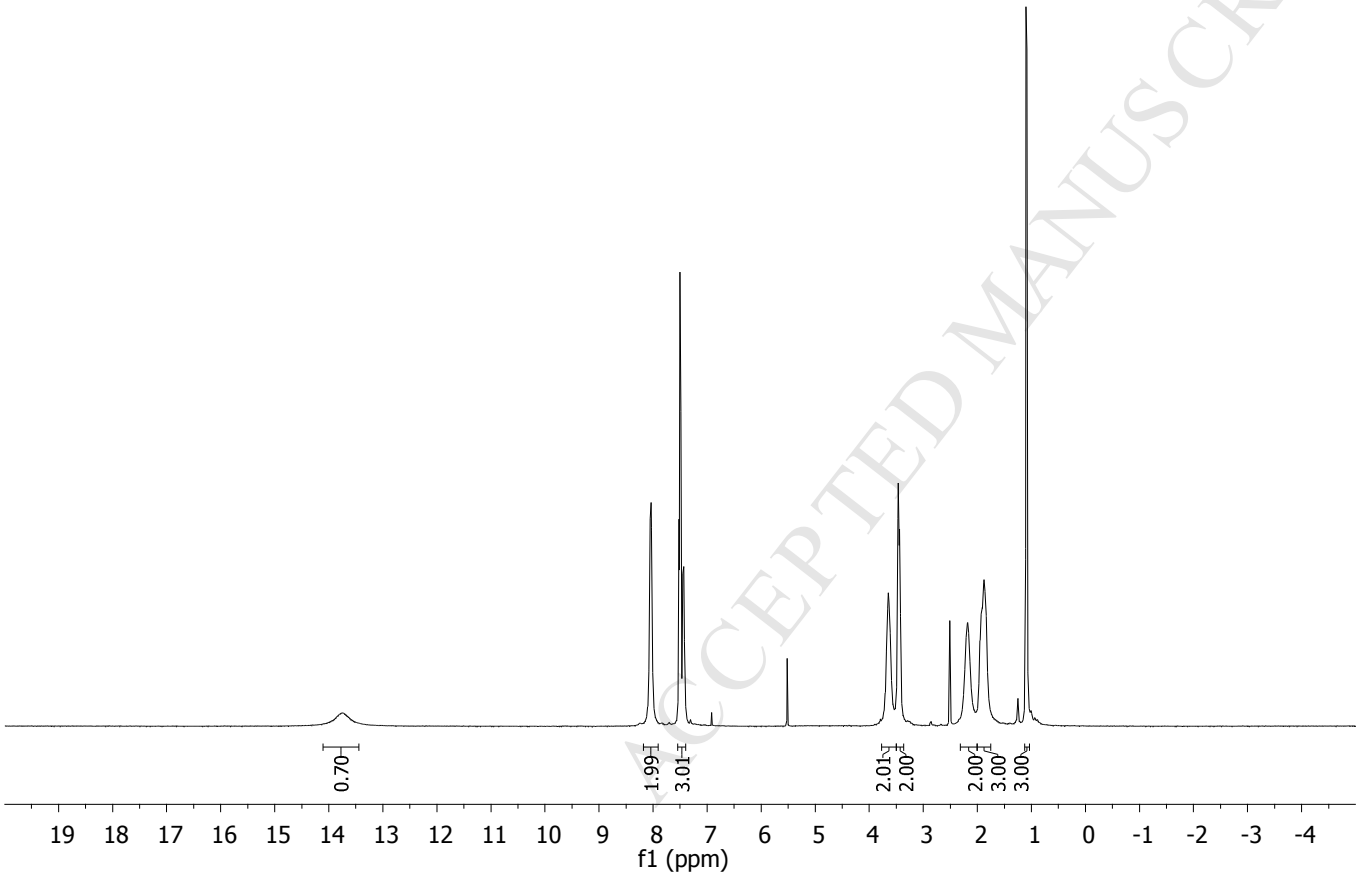
^{1}H NMR of *N*-cyclohexyl-4-methylaniline (**6**) (400.13 MHz, $CDCl_3$)



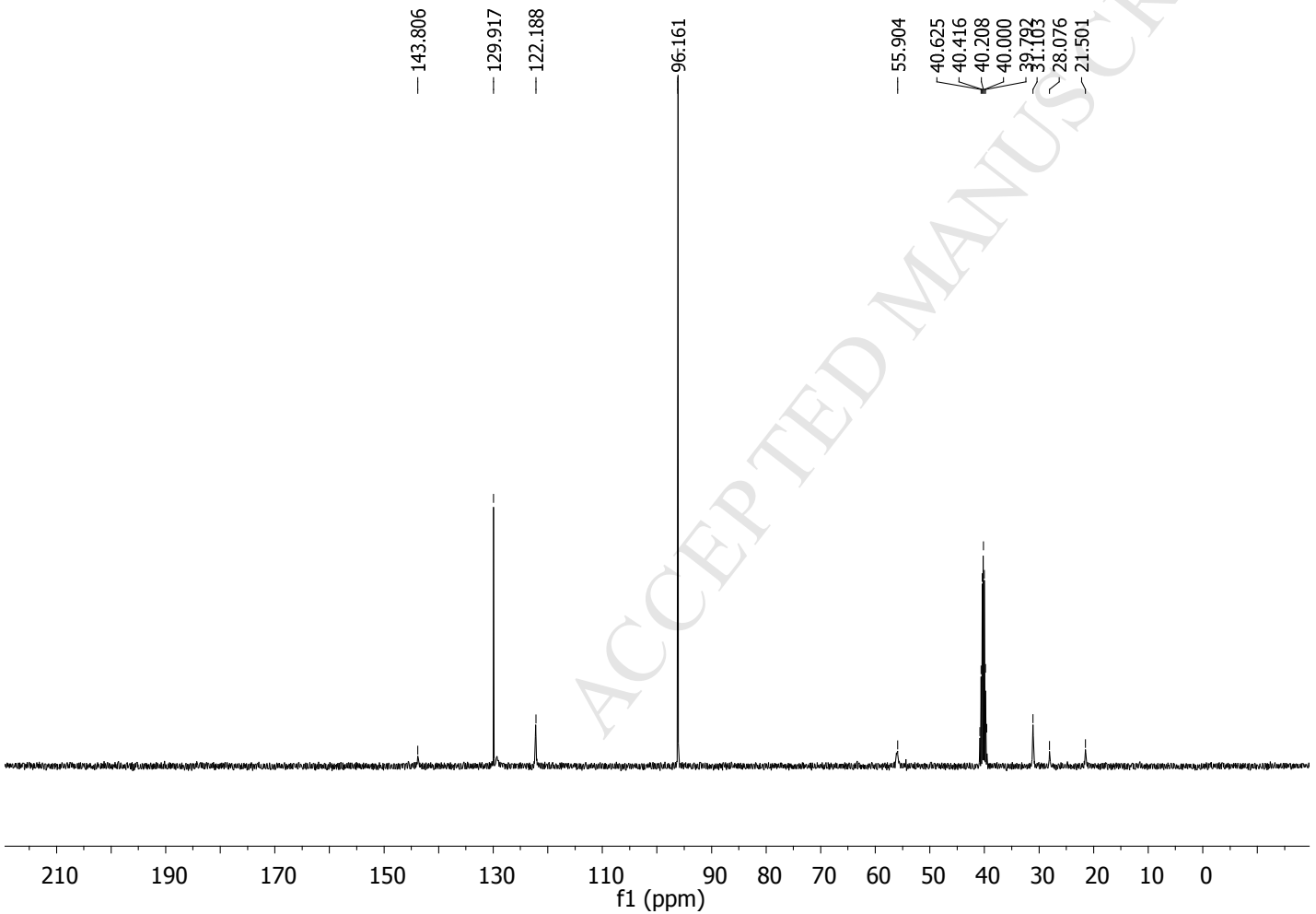
^{13}C NMR of *N*-cyclohexyl-4-methylaniline (**6**) (100.61 MHz, $CDCl_3$)



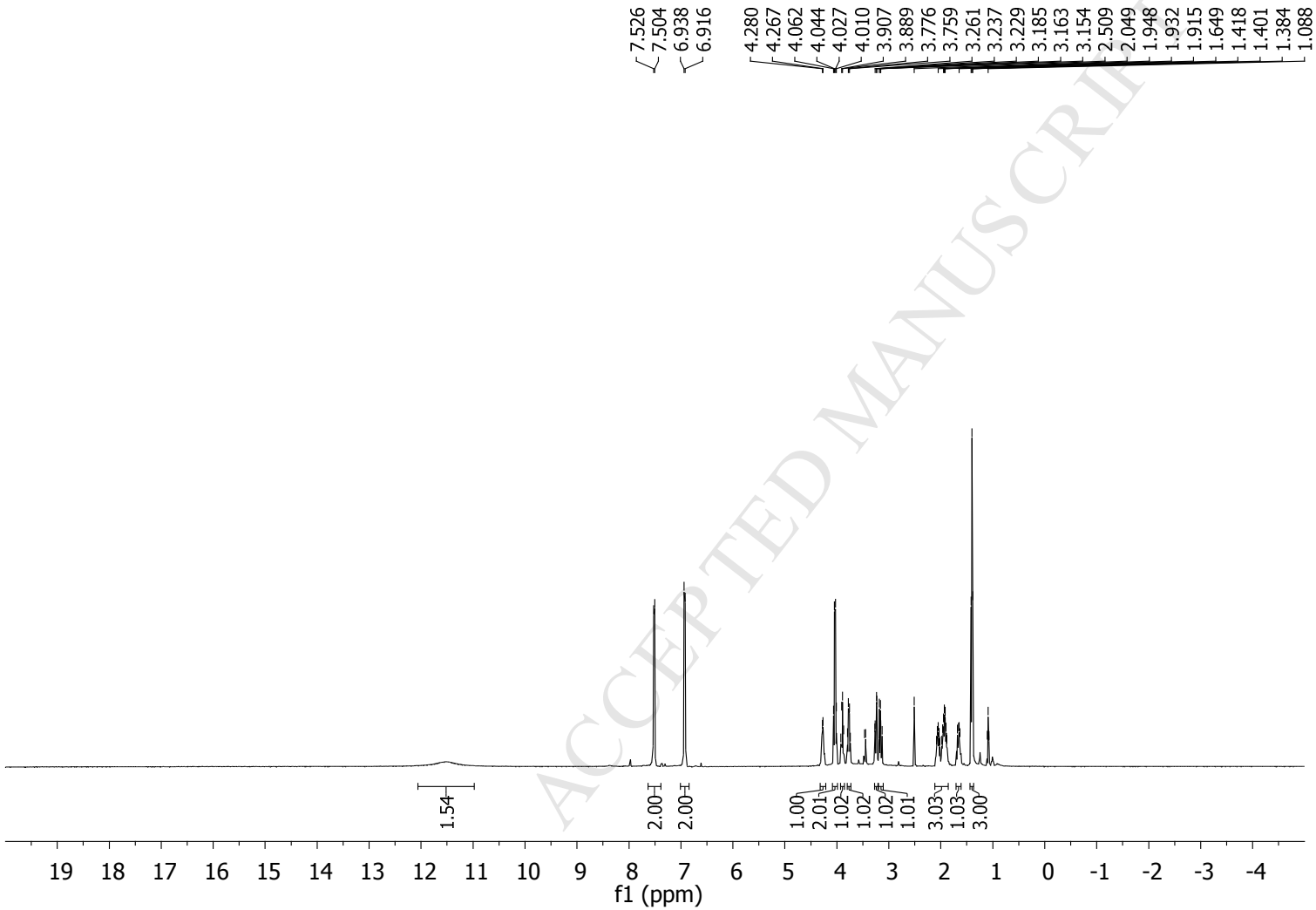
^{1}H NMR of 4-methyl-(*N*-phenyl)piperidine hydrochloride (**7**) (400.13 MHz, $CDCl_3$)

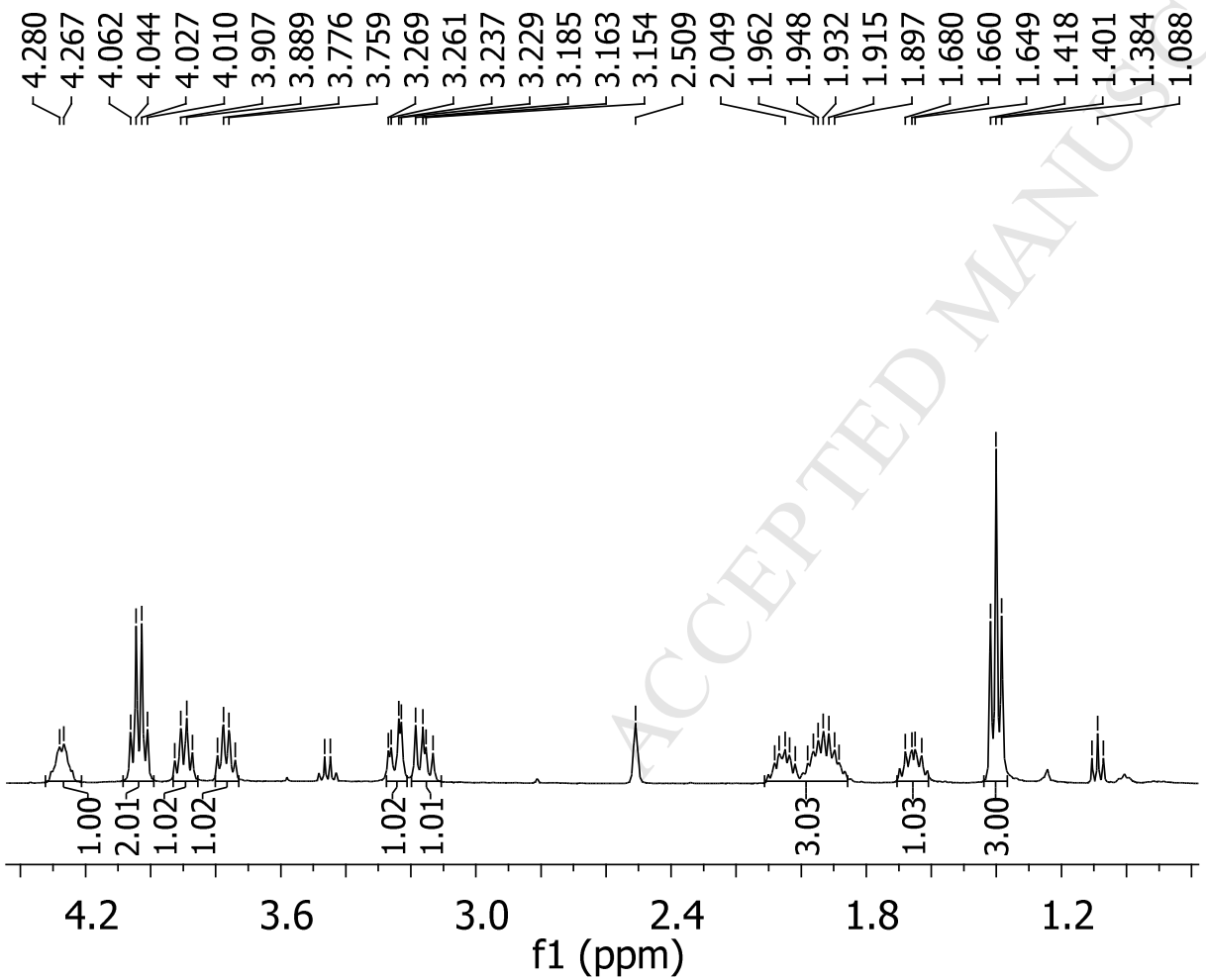


^{13}C NMR of 4-methyl-(*N*-phenyl)piperidine hydrochloride (**7**) (100.61 MHz, DMSO-d_6+CCl_4)

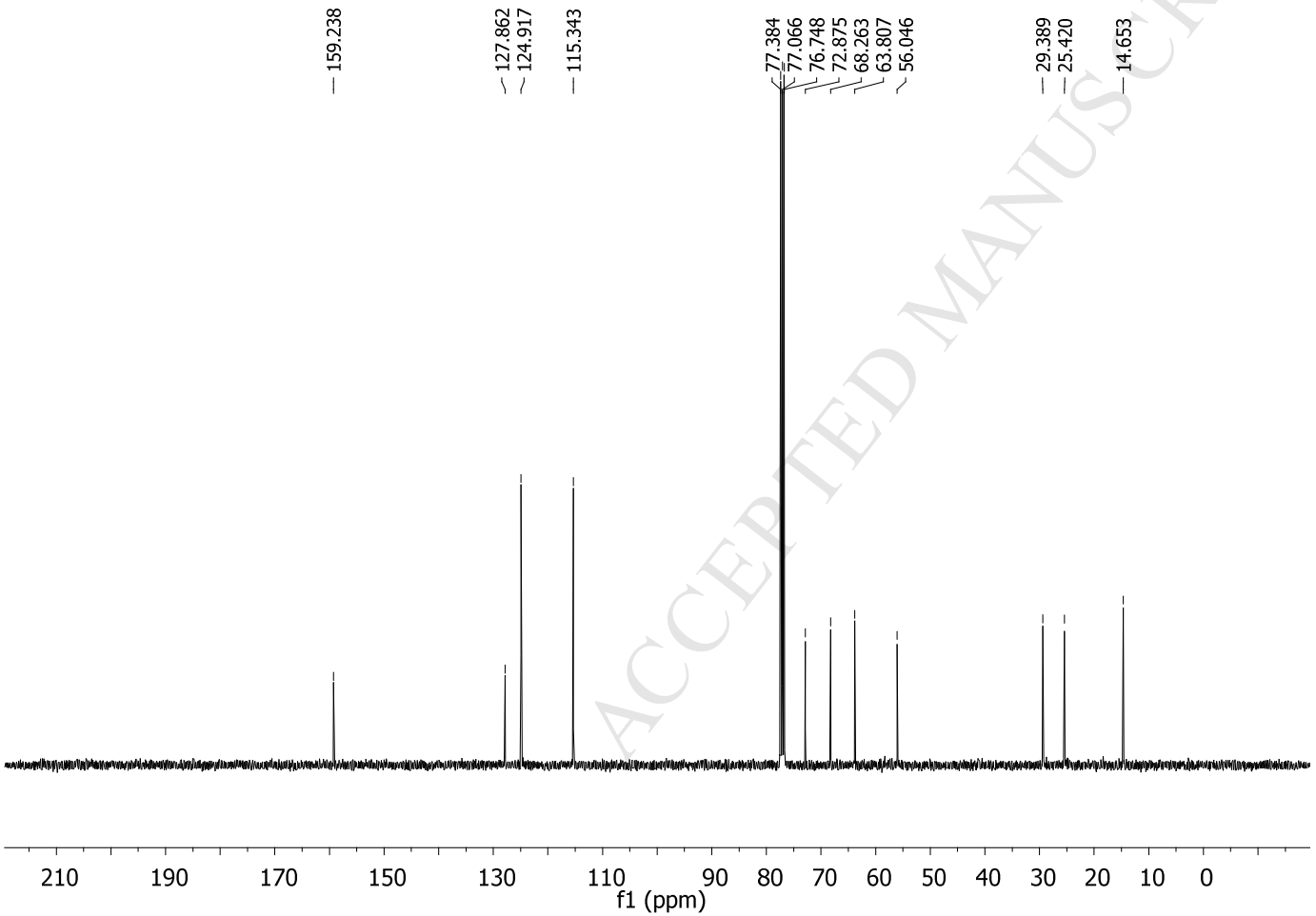


^{1}H NMR of 4-ethoxy-*N*-((tetrahydrofuran-2-yl)methyl)aniline hydrochloride (**8**) (400.13 MHz, DMSO-d_6+CCl_4)

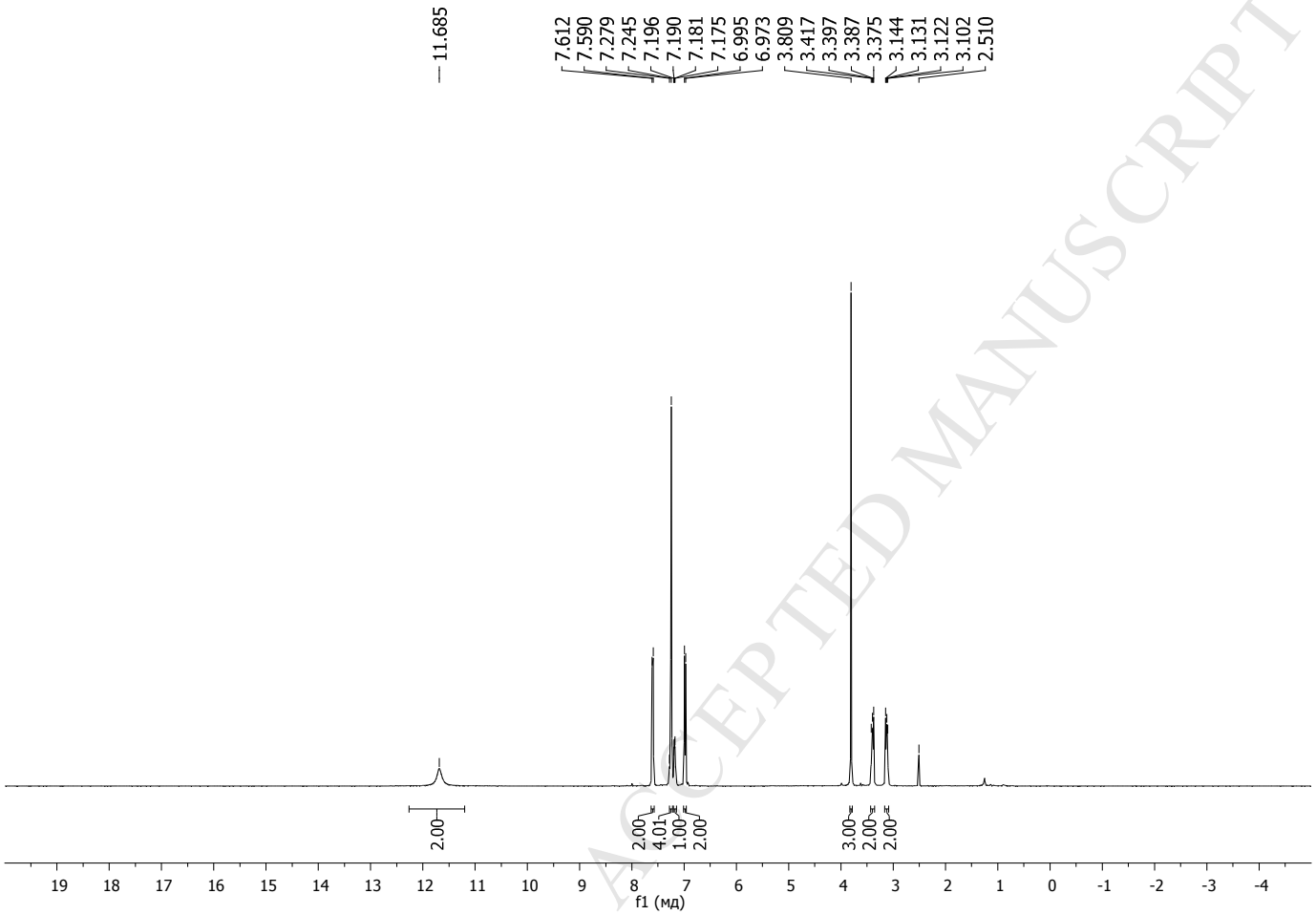




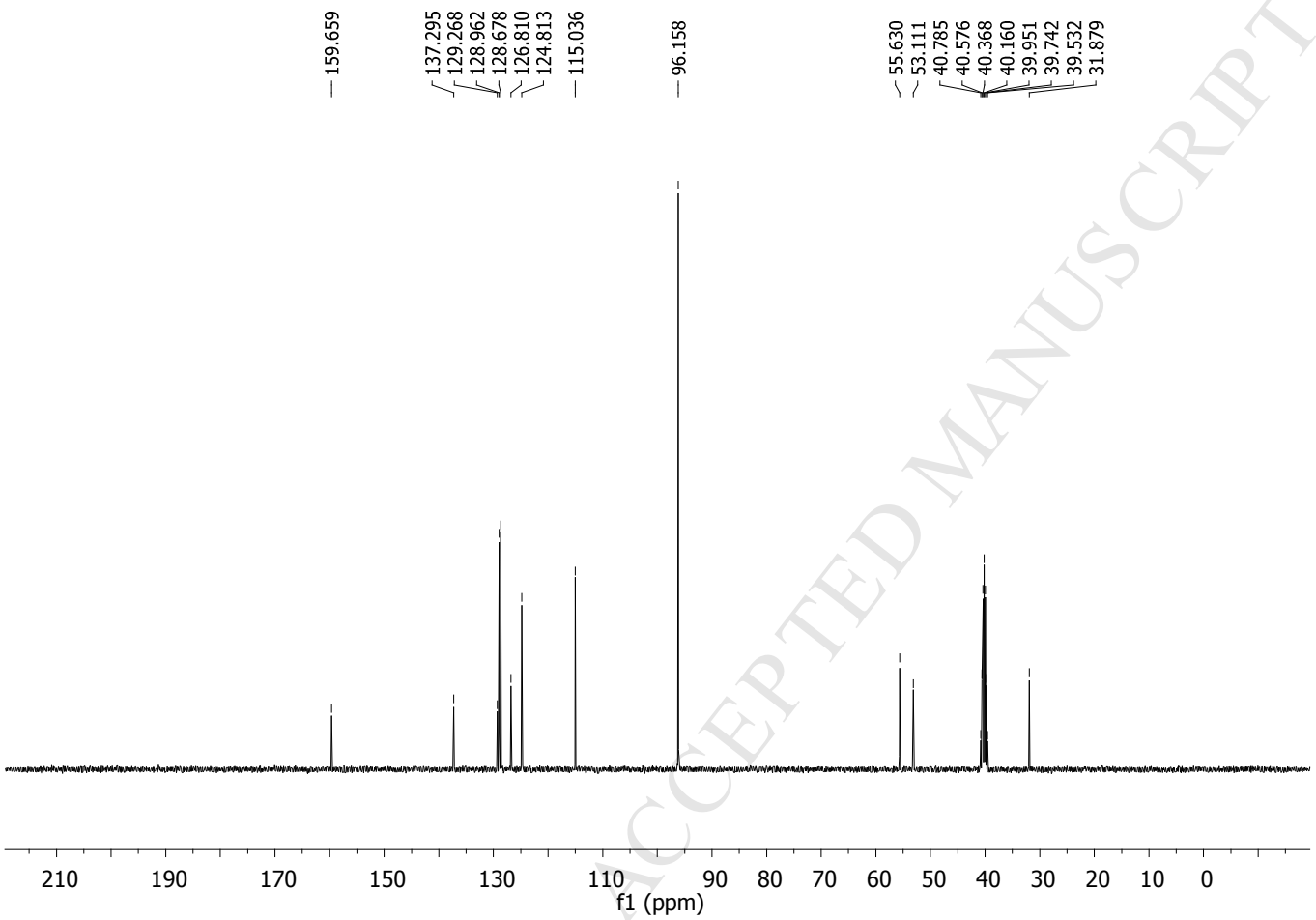
^{13}C NMR of 4-ethoxy-*N*-((tetrahydrofuran-2-yl)methyl)aniline hydrochloride (**8**) (100.61 MHz, $CDCl_3$)



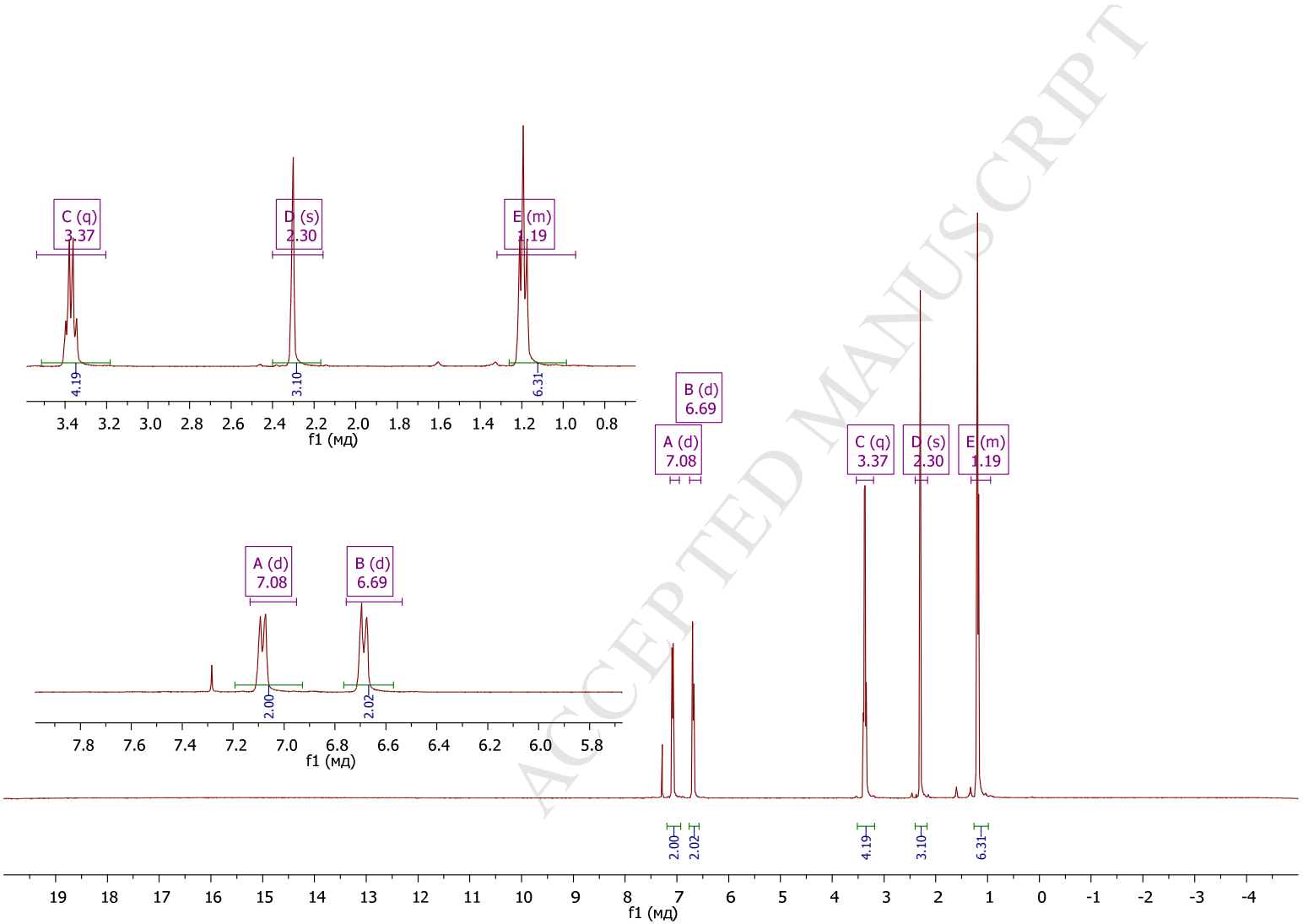
^{1}H NMR of 4-methoxy-*N*-phenethylaniline hydrochloride (**9**) (400.13 MHz, DMSO-d_6+CCl_4)



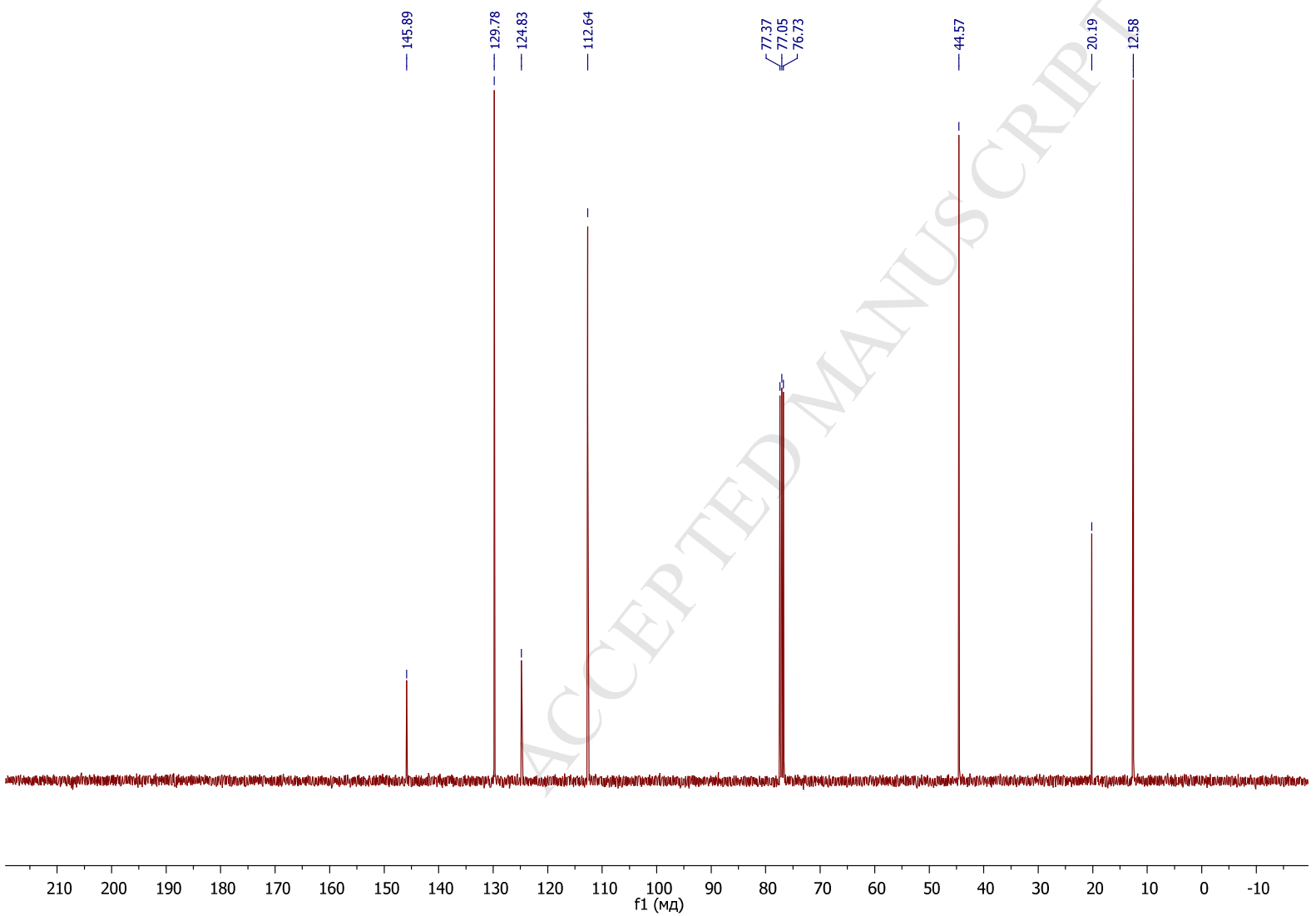
^{13}C NMR of 4-methoxy-*N*-phenethylaniline hydrochloride (**9**) (100.61 MHz, DMSO-d_6+CCl_4)



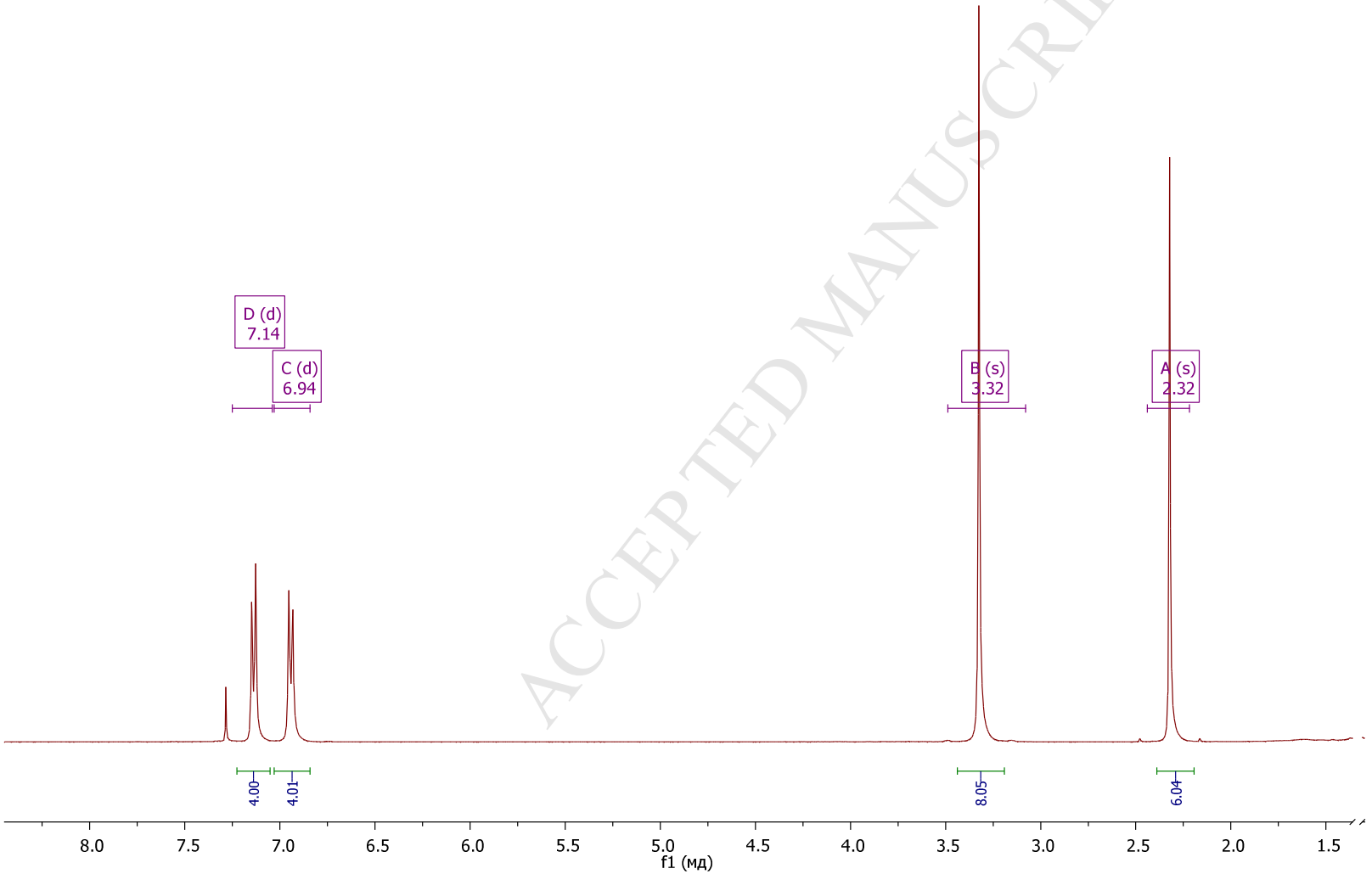
^{1}H NMR of N-(4-methylphenyl)diethylamine (**10**) (400.13 MHz, $CDCl_3$)



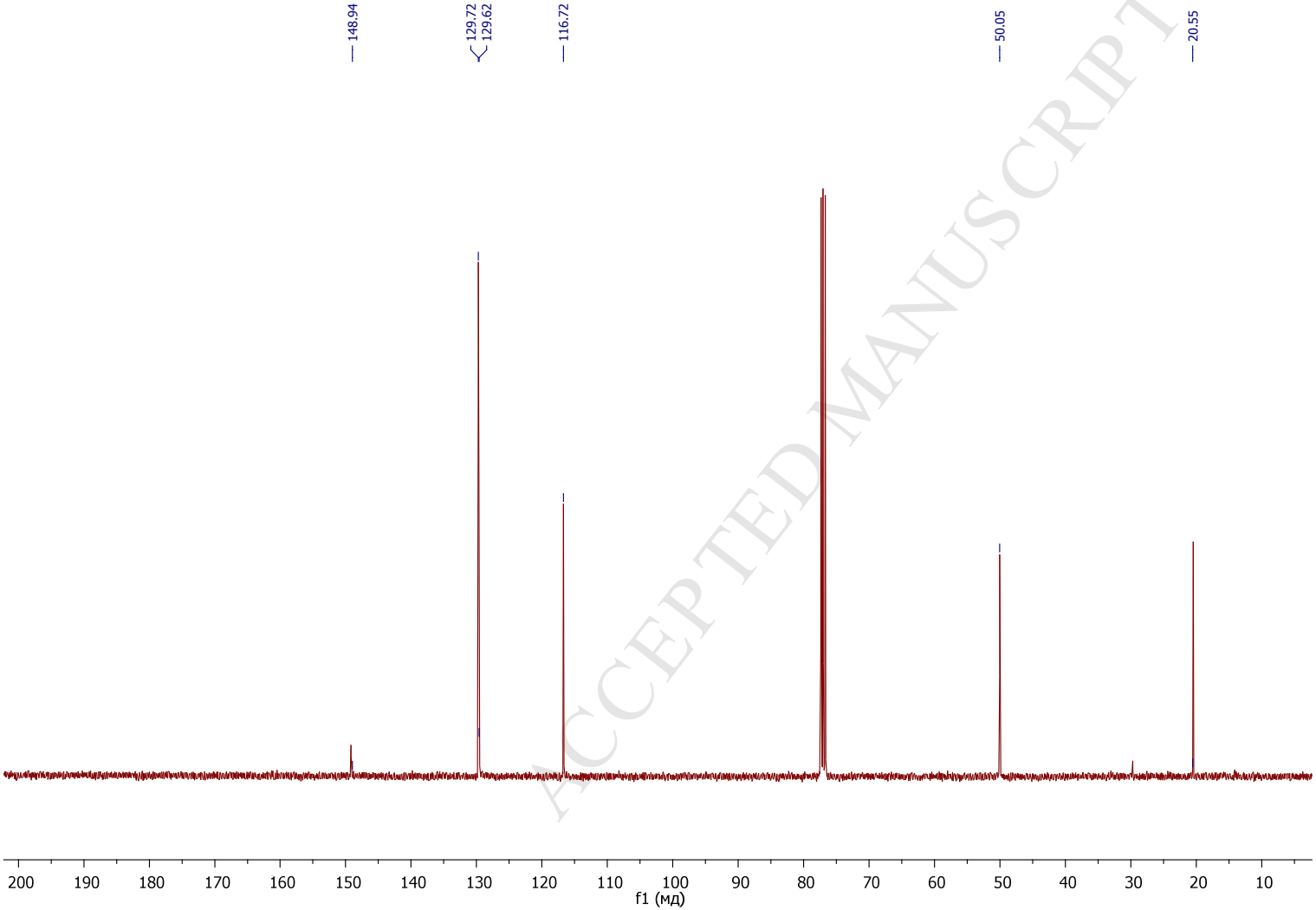
^{13}C NMR of N-(4-methylphenyl)diethylamine (**10**) (100.61 MHz, $CDCl_3$)



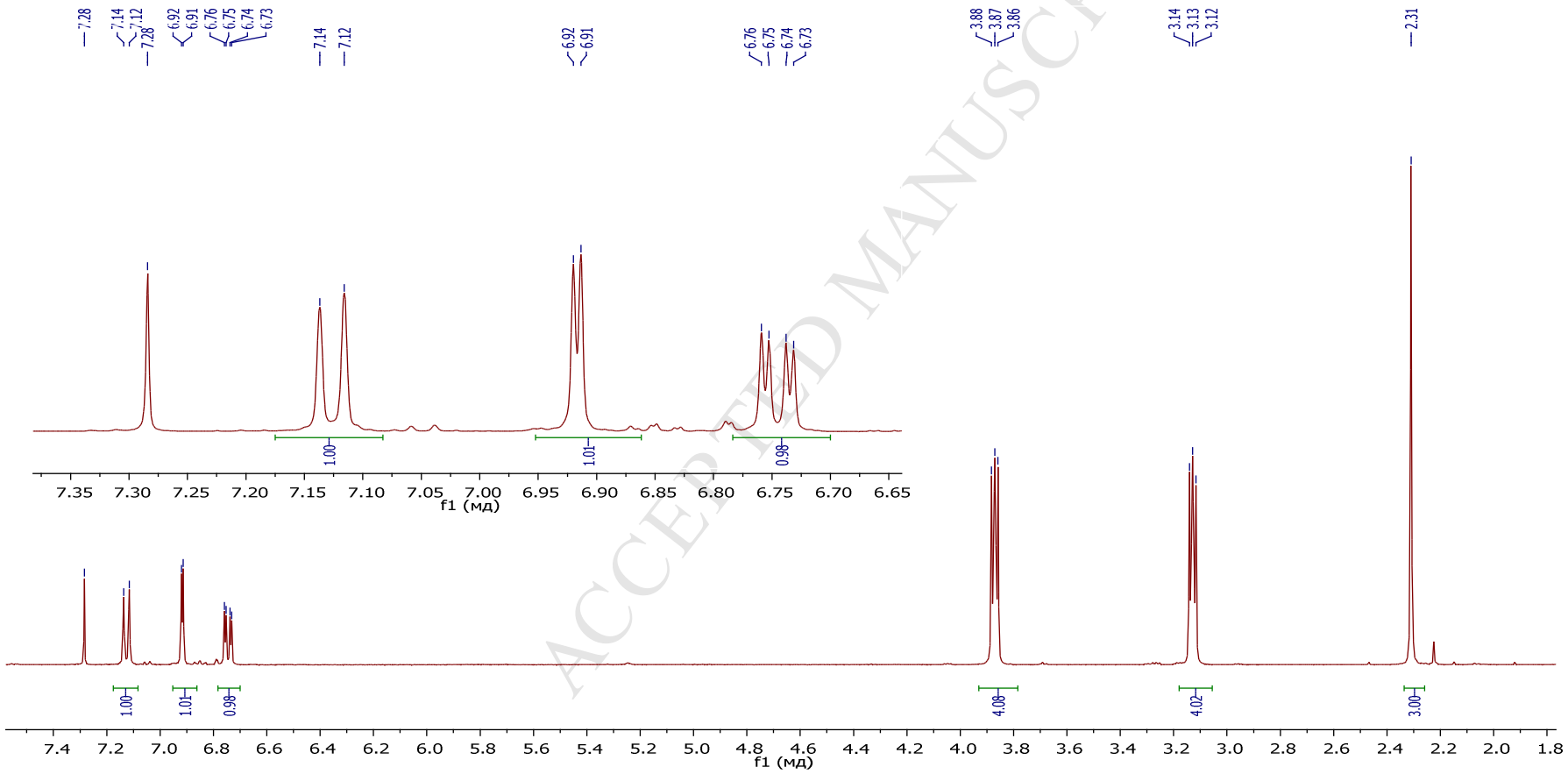
^{1}H NMR of 1,4-bis(4-methylphenyl)piperazine **(14)** (400.13 MHz, $CDCl_3$)



^{13}C NMR of 1,4-bis(4-methylphenyl)piperazine **(14)** (100.61 MHz, $CDCl_3$)



^{1}H NMR of 4-(3-chloro-4-methylphenyl)morpholine (**18**) (400.13 MHz, $CDCl_3$)



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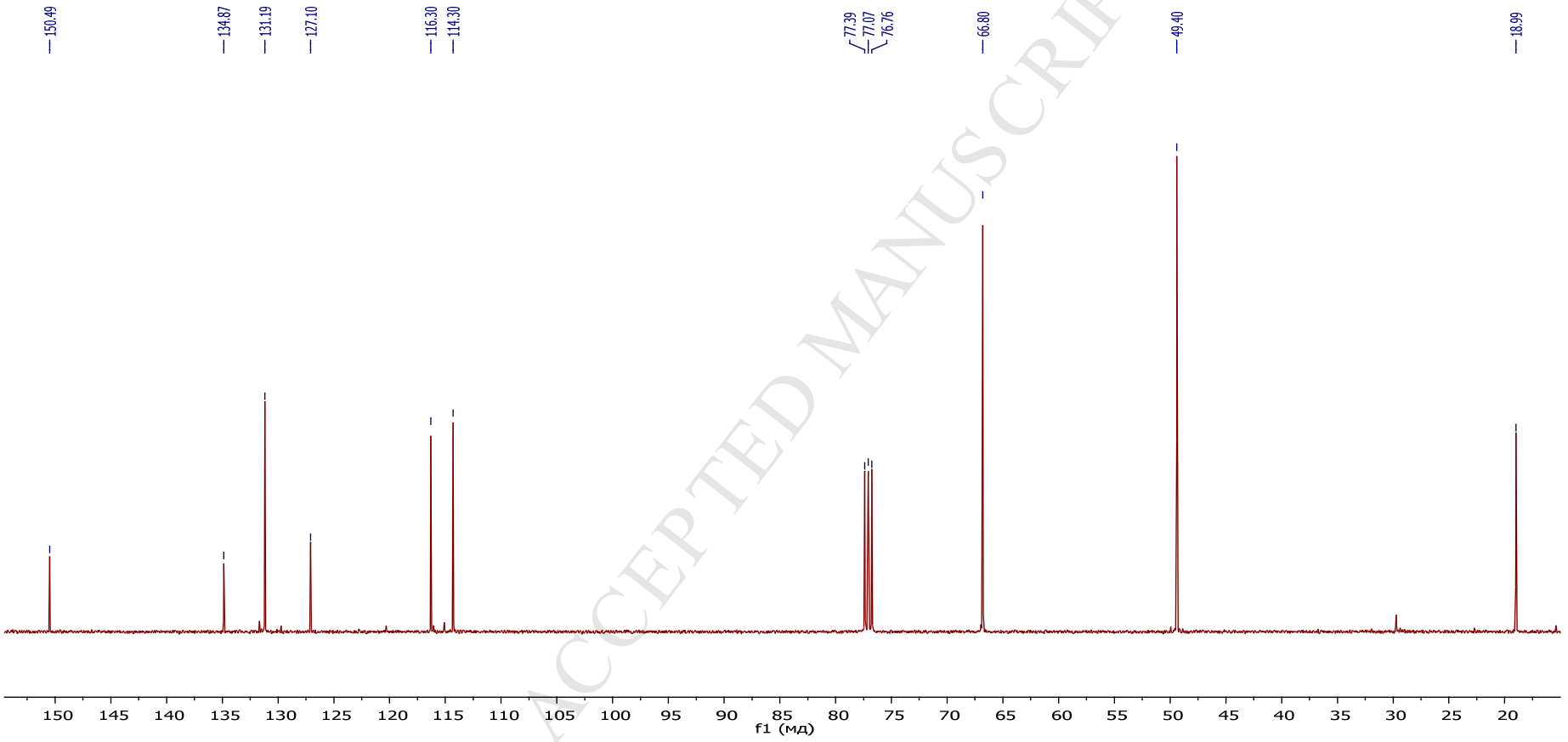
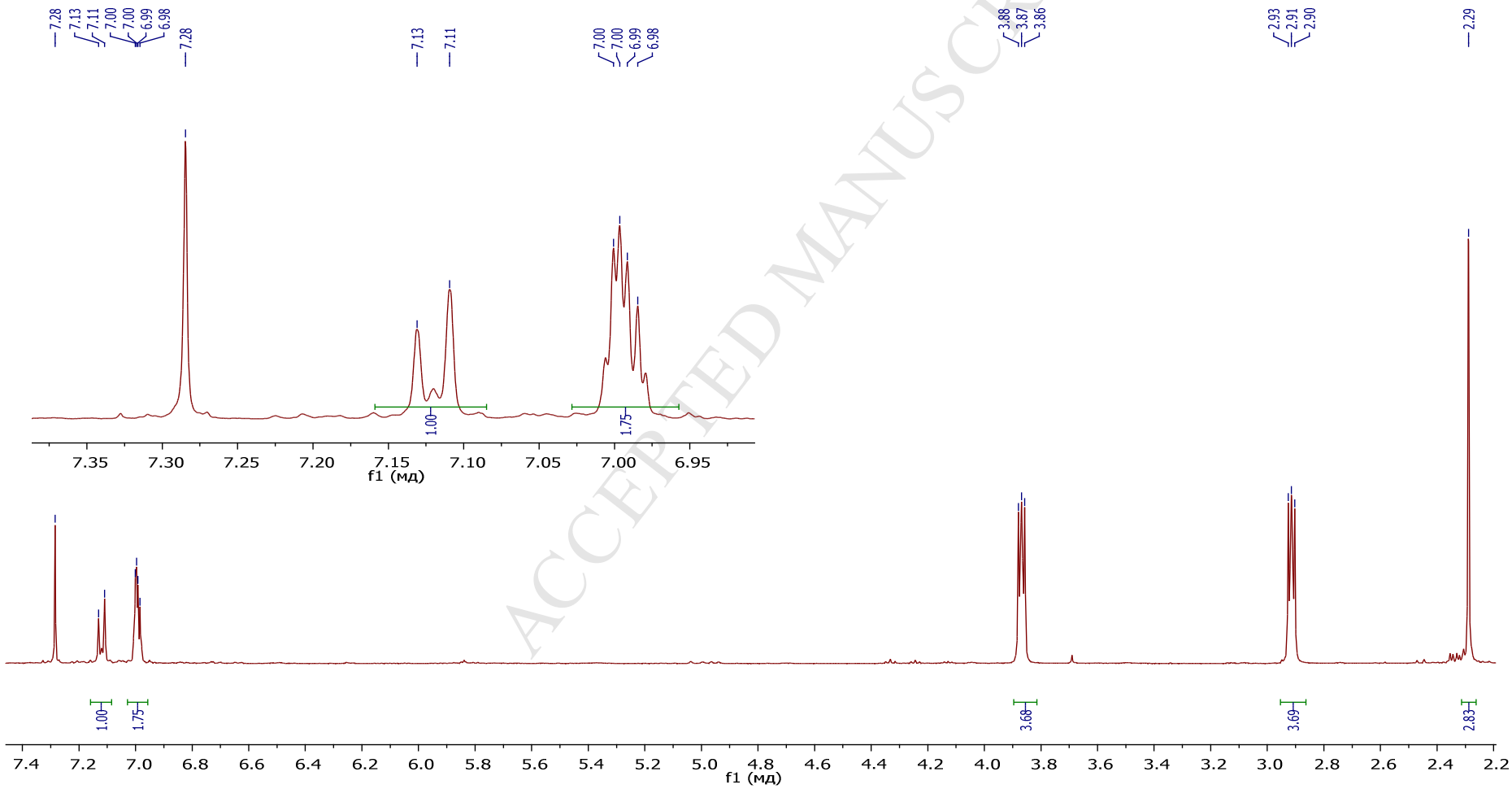
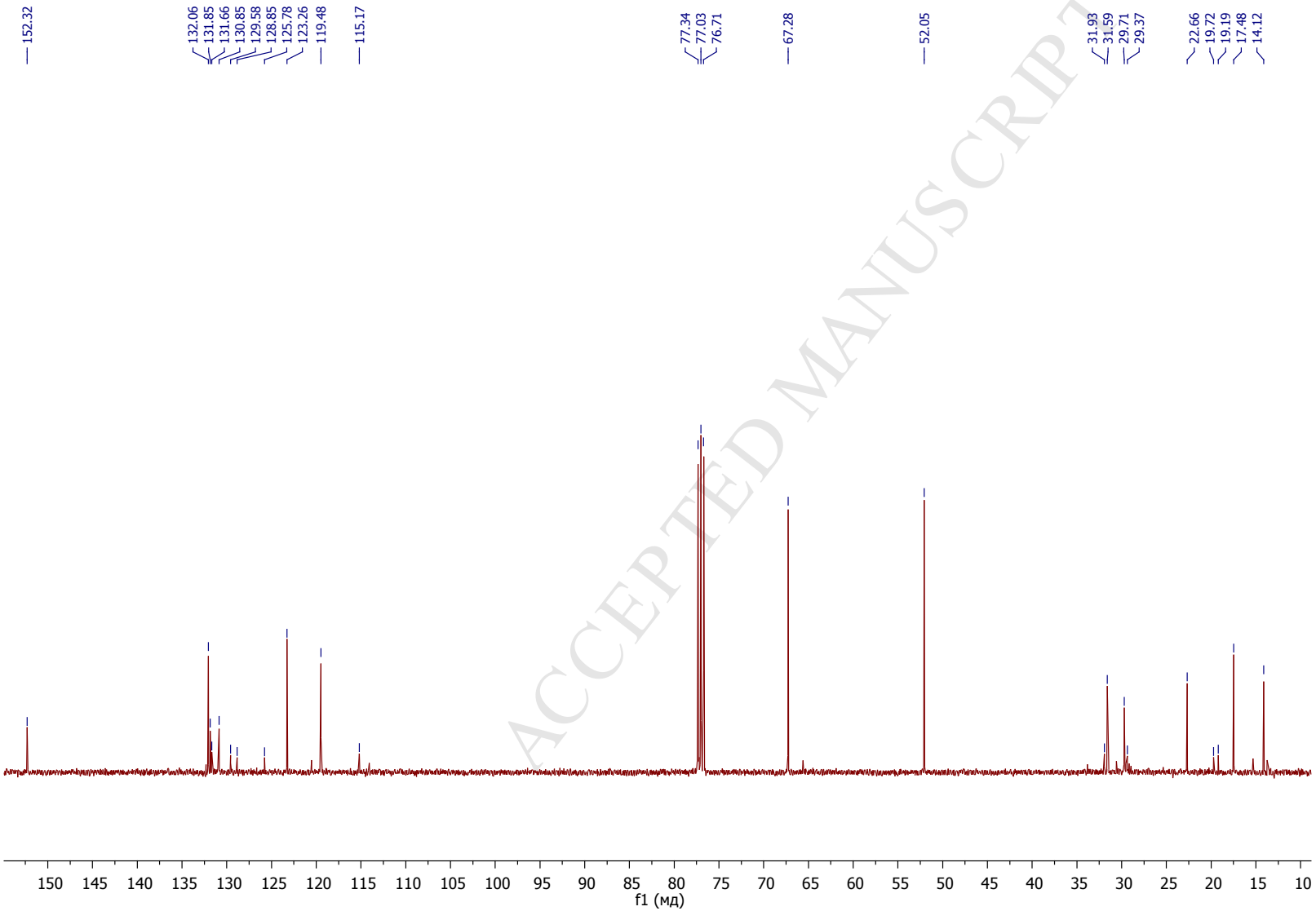


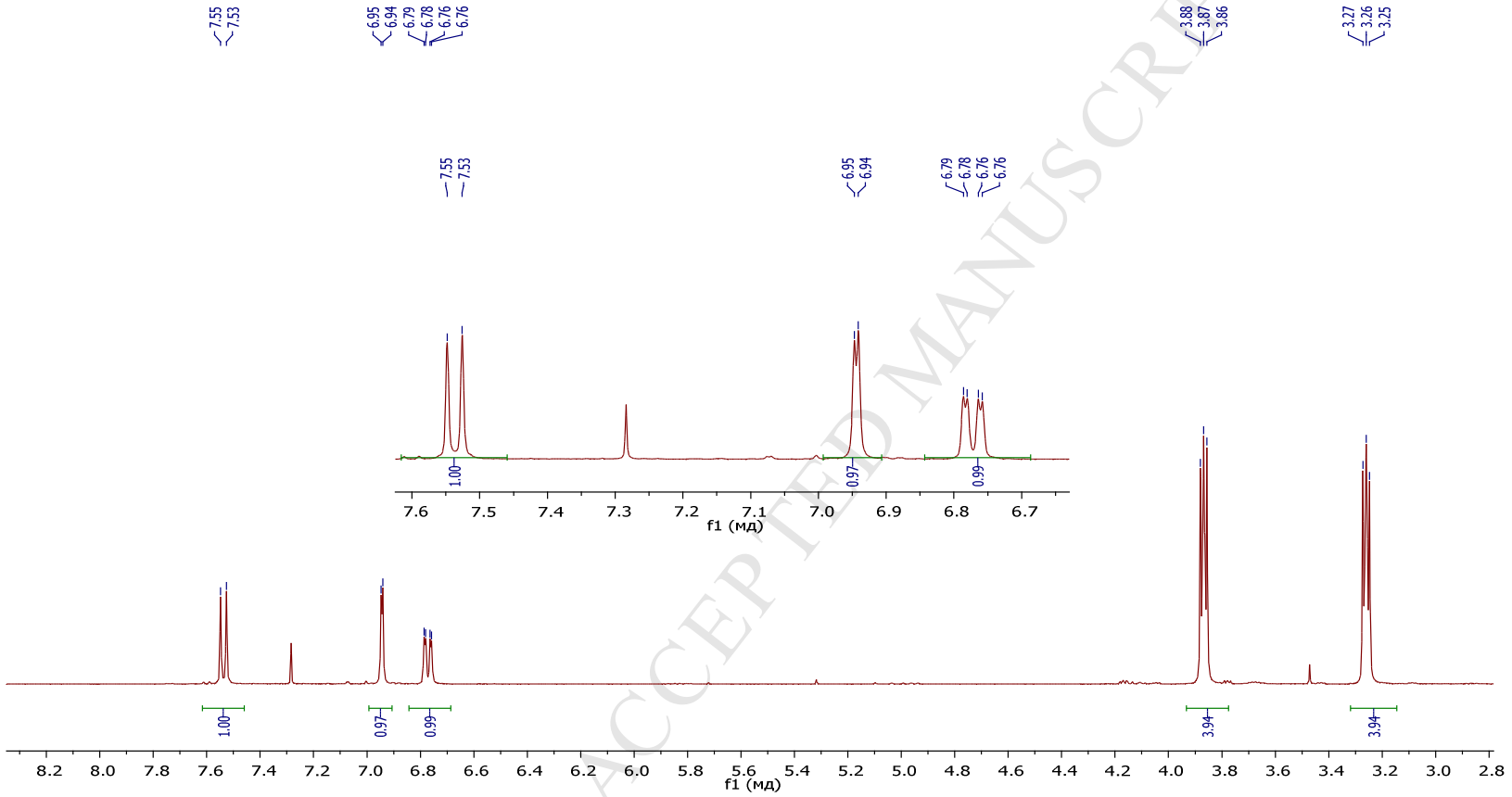
^{1}H NMR of 4-(5-chloro-2-methylphenyl)morpholine (**19**) (400.13 MHz, $CDCl_3$)



^{13}C NMR of 4-(5-chloro-2-methylphenyl)morpholine (**19**) (100.61 MHz, $CDCl_3$)



^{1}H NMR of 4-(3-chloro-4-trifluoromethylphenyl)morpholine (**23**) (400.13 MHz, $CDCl_3$)



^{13}C NMR of 4-(3-chloro-4-trifluoromethylphenyl)morpholine (**23**) (100.61 MHz, $CDCl_3$)