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# Graphical Abstract

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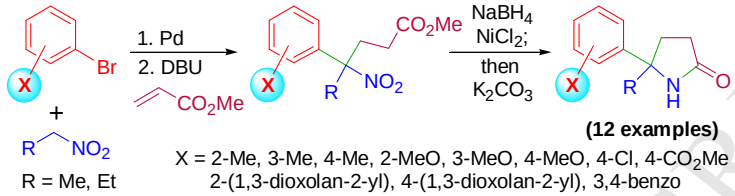


**(12 examples)**

R = Me, Et

X = 2-Me, 3-Me, 4-Me, 2-MeO, 3-MeO, 4-MeO, 4-Cl, 4-$CO_2$Me
2-(1,3-dioxolan-2-yl), 4-(1,3-dioxolan-2-yl), 3,4-benzo

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# Synthesis of 5-alkyl-5-aryl-γ-lactams from 1-aryl-substituted nitroalkanes and methyl acrylate via Michael addition and reductive lactamization

Jingjing Xu[a], Xingyao Li[a], Jinlong Wu[a,*], Wei-Min Dai[a,b,*,†]

[a]Laboratory of Asymmetric Catalysis and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, China
[b]Laboratory of Advanced Catalysis and Synthesis, Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

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ABSTRACT

A general method for accessing 5-alkyl-5-aryl-γ-lactams has been developed using readily available aryl bromides, nitroalkanes, and methyl acrylate as the starting materials. The palladium-catalyzed arylation of nitroalkanes gave the 1-aryl-substituted nitroalkanes which underwent the DBU-mediated Michael addition with methyl acrylate at room temperature to afford the methyl 4-aryl-4-nitroalkanoates. The latter were then subjected to the nitro reduction using $NaBH_4$–$NiCl_2{\cdot}6H_2O$ in MeOH at 0 ºC to furnish, after treatment with aqueous $K_2CO_3$ at room temperature, the 5-alkyl-5-aryl-γ-lactams in good to excellent overall yields. Selected examples of N-alkylation of the γ-lactams were also illustrated.



## 1. Introduction

The γ-lactam (pyrrolidin-2-one) core is a biologically significant structural motif and has been found in many natural products. Figure 1 illustrates some representative structures possessing 5,5-disubstituted γ-lactams **I**. Rolapitant (SCH619734, **1**)[1] and oxazolomycin A (**2**)[2] feature a γ-lactam unit within the spirobicyclic skeleton while salinosporamide A (**3**)[3] and *clasto*-lactacystin β-lactone (**4**, also called omuralide, a transformation product of **5**)[4] contain a fused β-lactone ring onto the C4 and C5 positions of the pyrrolidin-2-one core. Lactacystin (**5**)[5] was known as a prodrug that delivers its biological activity through conversion into **4**. Moreover, the γ-lactam unit has been found in the macrocyclic natural products such as ansalactam A (**6**)[6] and divergolide D (**7**).[7] These γ-lactam-containing natural products exhibit diverse biological activities. Rolapitant (**1**) was reported as a selective and orally active neurokinin NK1 receptor antagonist with centrally-mediated antiemetic effects.[1] Oxazolomycin A (**2**) is the parent member of a family of polyene lactone-lactam antibiotics with potent antiviral, antibacterial and cytotoxic activity. Its broad-spectrum activity has been attributed to its protonophoric properties.[8] Lactacystin (**5**) is known to transform into omuralide (**4**) for penetrating cell and forming covalent bond conjugate with 20S proteasome.[9,10] The compound **4** is also a synthetic intermediate[4b,c] of lactacystin and it is the first molecule as a truly specific inhibitor of the proteasome with enormous potential applications as a therapeutic agent. Salinosporamide A (**3**) shares the same fused bicyclic core with **4** and was found to be about 35 times more potent than **4** in inhibiting proteasomal chymotrypsin-like proteolytic activity against purified 20S proteasome. The compound **3** also possesses cytotoxicity against a number of cancer cell lines with $IC_{50}$/$LC_{50}$ values less than 10 nM.[3] Ansalactam A (**6**) and divergolide D (**7**) are the new members of the ansamycin family of polyketide natural products. The biological activity of ansalactam A (**6**) is not available yet but divergolide D (**7**) was reported to be active against *Mycobacterium vaccae* and *Stapylococcus aureus* and is potent against a panel of 40 tumor cell lines with mean $IC_{50}$ value of 2.4 μM.[7] Moreover, the N-substituted γ-lactams, both natural and synthetic origin, have been reported. Some representative examples include the natural products, bisavenanthramide B,[11] heliotropamine,[12] and nagelamide U and V[13] (all structures not shown), and the synthetic libraries prepared by Shaw and other groups.[14]

* Corresponding authors. Tel./fax: +86 571 89953128; e-mail addresses: wyz@zju.edu.cn (J. Wu); chdai@zju.edu.cn (W.-M. Dai).

† Tel.: +852 23587365; fax: +852 23581594; e-mail address: chdai@ust.hk.

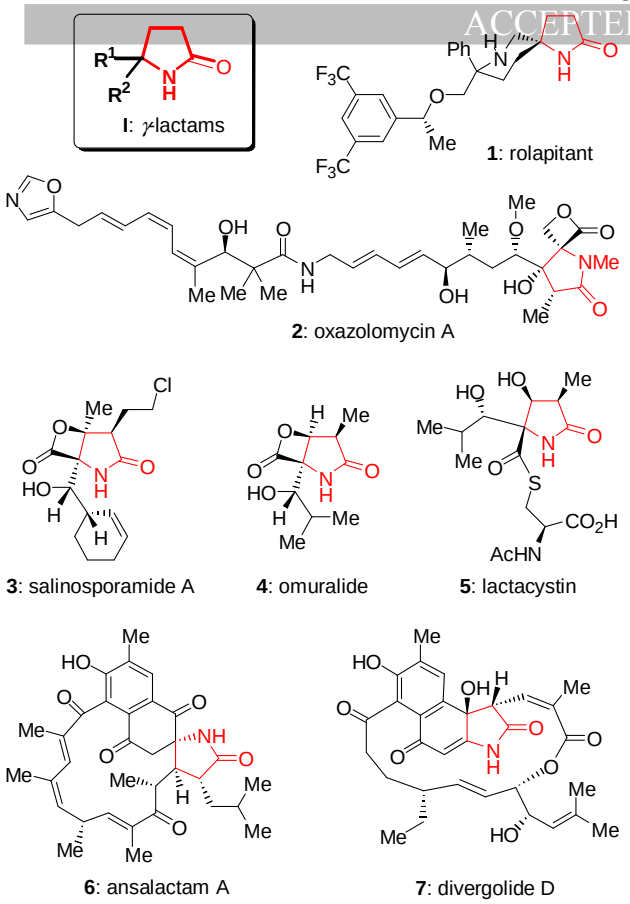



**Figure 1.** Structures of γ-lactam-containing natural products **1**–**7**.

5-Methyl-5-phenylpyrrolidin-2-one (**10**, Figure 2),[15] a cyclic analogue of γ-aminobutyric acid (GABA), was reported to exhibit powerful anticonvulsive action as the inhibitor of γ-aminobutyric acid–α-ketoglutaric acid transaminase.[15a] It was also found to act as an inhibitor of mitochondria protein synthesis and deliver the effect on discrimination learning.[15b] Miller and Goelitz reported a synthesis of **10** from 2-phenylpropionic acid (**8**) via a 7-step sequence, involving formation of the urethane **9** under thermolysis of the corresponding acyl azide (Figure 2a).[16] A Pd–Cu-catalyzed oxidative heteroannulation of *N*-carbamoyl aminoalkynes was used by Vatéle and coworkers for synthesis of

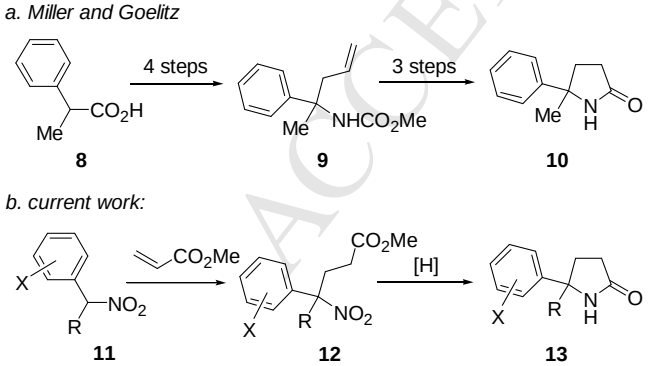


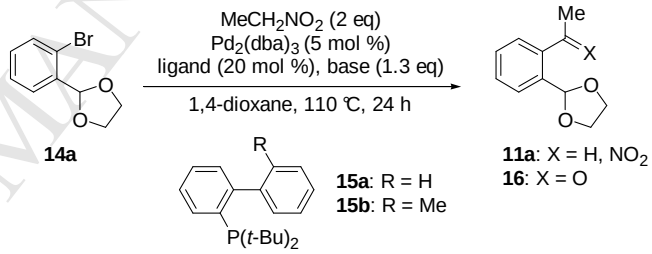

**Figure 2.** Synthetic approaches toward 5-alkyl-5-aryl-γ-lactams **10** and **13**.

5,5-dialkyl, 5,5-spiro-, or 4,5-fused pyrrolidin-2-ones.[17] We envisioned a general synthetic route to the 5-alkyl-5-aryl γ-lactams **13** from the readily available 1-aryl nitroalkanes **11**[18] via Michael addition of **11**[19] with methyl acrylate followed by reductive amidation of the 4-nitrobutyrates **12** (Figure 2b). We report here the results on synthesis of the γ-lactams **13** and the related N-alkylated derivatives.[20–24]

## 2. Results and discussion

The Pd-catalyzed α-arylation of nitroalkanes with both aryl bromides and chlorides has been reported by Vogl and Buchwald using $Cs_2CO_3$ as the base and DME (dimethoxyethane) as the solvent.[18] The sterically demanding substrate **14a** was not used for this type of arylation reaction in the previous study. We used **14a** as the substrate for optimization of the reaction conditions and some representative results are summarized in Table 1. In the presence of 5 mol % $Pd_2(dba)_3$, 20 mol % of the phosphine ligand **15a**, and 2 equivalents of $MeCH_2NO_2$, three bases were examined (entries 1–3, Table 1). After heating at 110 ºC for 24 h in 1,4-dioxane in a closed vial, the desired product **11a** was obtained along with the ketone byproduct **16** and the recovered **14a**. The arylation using these three bases gave about 60% conversion of **14a** and the milder base $K_3PO_4$ provided a better yield (42%) of **11a** with less amount of the ketone **16** in 13% yield (entry 2, Table 1). In the entries 4–6, the phosphine ligand **15b**[18] and the base, $K_3PO_4$, were used to investigate the effect of the catalyst loading on the product yield. With 5 mol % $Pd_2(dba)_3$, the product **11a** was formed in 71% and 67% yields, respectively, when 20 and 10 mol % of **15b** were used (entries 4 and 5, Table 1). Once the loading of $Pd_2(dba)_3$ decreased to 2.5 mol %, a diminished product yield of 50% was obtained with 22% of the recovered **14a** (entry 6, Table 1).

**Table 1**
Screening of reaction conditions for Pd-catalyzed arylation



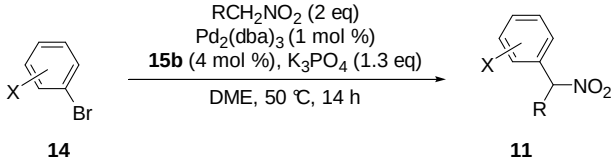

| Entry | Base | Ligand | **14a** (%)[a] | **16** (%)[b] | **11a** (%)[b] |
|---|---|---|---|---|---|
| 1 | $Cs_2CO_3$ | **15a** | 43 | 20 | 18 |
| 2 | $K_3PO_4$ | **15a** | 39 | 13 | 42 |
| 3 | KO*t*-Bu | **15a** | 36 | 19 | 38 |
| 4 | $K_3PO_4$ | **15b** | – [c] | – [c] | 71 |
| 5[d] | $K_3PO_4$ | **15b** | – [c] | – [c] | 67 |
| 6[e] | $K_3PO_4$ | **15b** | 22 | – [c] | 50 |

[a] Recovered substrate after isolation.
[b] Isolated yields. The ketone **16** was formed from **11a** via the Nef reaction.
[c] Not determined.
[d] 5 mol % $Pd_2(dba)_3$ and 10 mol % of **15b** were used. [Pd]/[**15b**] = 1:1.
[e] 2.5 mol % $Pd_2(dba)_3$ and 10 mol % of **15b** were used. [Pd]/[**15b**] = 1:2.

After optimizing the suitable ligand **15b** and the base, $K_3PO_4$, the arylation of nitroethane and nitropropane was performed with a number of aryl bromides **14a**–**k** (Table 2). Presumably due to steric hindrance, the three *ortho*-substituted substrates **14a**,**d**,**g** (entries 1, 4, and 7, Table 2) required a higher palladium loading while other substrates underwent the arylation with 1 mol % $Pd_2(dba)_3$ and 4 mol % the ligand **15b**. After heating in DME at 50 ºC for 14 h (except for entry 1, Table 2), the products **11b**–**l** were produced in 74–97% yields. Our results listed in the entries 3, 9, 11, and 12 in Table 2 are comparable with those obtained by using $Cs_2CO_3$ as the base.[18]

**Table 2**

Results of Pd-catalyzed arylation of nitroalkanes




**14** **11**

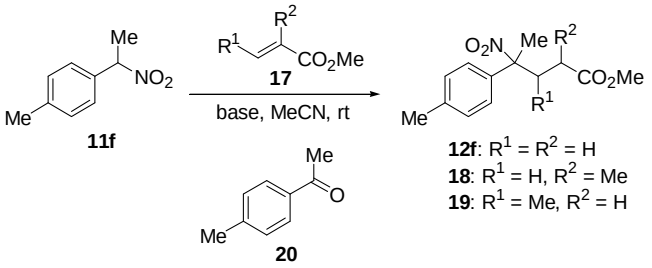
| Entry | **14**: X | R | **11**: Yield (%)[c] |
|---|---|---|---|
| 1[a] | **14a**: 2-(1,3-dioxolan-2-yl) | Me | **11a**: 71 |
| 2 | **14b**: 4-(1,3-dioxolan-2-yl) | Me | **11b**: 82 |
| 3 | **14c**: 3,4-Benzo | Me | **11c**: 89 (96)[d,e] |
| 4[b] | **14d**: 2-Me | Me | **11d**: 87 |
| 5 | **14e**: 3-Me | Me | **11e**: 90 |
| 6 | **14f**: 4-Me | Me | **11f**: 78 |
| 7[b] | **14g**: 2-MeO | Me | **11g**: 91 |
| 8 | **14h**: 3-MeO | Me | **11h**: 97 |
| 9 | **14i**: 4-MeO | Me | **11i**: 74 (94)[d,e] |
| 10 | **14j**: 4-Cl | Me | **11j**: 84 |
| 11 | **14k**: 4-MeO$_2$C | Me | **11k**: 88 (85)[d] |
| 12 | **14k**: 4-MeO$_2$C | Et | **11l**: 87 (86)[d,f] |

[a] Using 5 mol % $Pd_2(dba)_3$ and 20 mol % **15b** in 1,4-dioxane at 110 ˚C for 24 h (taken from entry 4 of Table 1).
[b] Using 5 mol % $Pd_2(dba)_3$ and 10 mol % **15b**.
[c] Isolated yields.
[d] Data given in the parenthesis are taken from ref. 18 using 4 equiv of the nitroalkane and 2.2 equiv of $Cs_2CO_3$ instead of $K_3PO_4$ as the base.
[e] For the yields given in the parenthesis, 1.5 mol % $Pd_2(dba)_3$ and 6 mol % **15b** were used.
[f] For the yield given in the parenthesis, the corresponding chloride was used for the arylation at 60 ºC.

The Michael addition of nitroalkanes with substituted acrylates or the equivalent Michael acceptors has been reported in the literature.[19] With the readily prepared 1-aryl-substituted nitroalkanes **11** in hand, we investigated the Michael addition reaction using the nitro compound **11f** as the substrate (Table 3). It was found that $Et_3N$ failed to promote the Michael addition of **11f** with methyl acrylate (**17a**) at room temperature for 12 h while the same reaction using DBU as the base afforded 94% yield of the desired product **12f** within 1 h (entry 1 vs. entry 2, Table 3). *p*-Tolyl methyl ketone **20** derived from the Nef reaction of **11f** was also isolated from the DBU-mediated reaction in 4% yield. By lowering the amount of DBU to 0.5 equivalent and with an extended reaction time to 2 h, the Nef reaction byproduct could be minimized, giving the desired product **12f** in 97% yield (entry 3, Table 3). However, when only 0.1 equivalent of DBU was used, the Michael addition became sluggish and, after 12 h, the product **12f** was isolated in 20% yield along with 10% of the byproduct **20** (entry 4, Table 3). Two other Michael acceptors, i.e. methyl methacrylate (**17b**) and methyl crotonate (**17c**) were tried using 1.0 equivalent of DBU but the corresponding Michael adducts **18** and **19** were not obtained. Instead, the Nef product **20** was exclusively generated from **11f** in 70 and 71% yields, respectively (entries 5 and 6, Table 3). These results suggest that any substituent at the α or β position of the acrylate renders formation of the nitro-substituted quaternary carbon difficult presumably due to severe steric interaction among the reactants.

**Table 3**

Screening of reaction conditions for the Michael addition of **11f**[a]



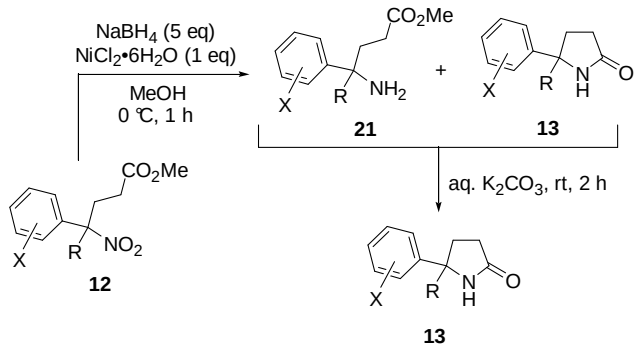

| Entry | $R^1$ | $R^2$ | Base (eq) | *t* (h) | **20** (%)[b,c] | Yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | H | H | $Et_3N$ (2.0) | 12 | – | **12f**: trace |
| 2 | H | H | DBU (1.0) | 1 | 4 | **12f**: 94 |
| 3 | H | H | DBU (0.5) | 2.5 | 1 | **12f**: 97 |
| 4 | H | H | DBU (0.1) | 12 | 10 | **12f**: 20 |
| 5 | H | Me | DBU (1.0) | 4 | 70 | **18**: – |
| 6 | Me | H | DBU (1.0) | 5 | 71 | **19**: – |

[a] Using 2.0 equiv of **17** in MeCN at room temperature.
[b] The Nef reaction product of **11f**.
[c] Isolated yields.

The Michael addition of the 1-aryl-substituted nitroalkanes **11a**–**l** with methyl acrylate (**17a**) was found to be general and efficient in the presence of 0.5 equivalent of DBU in MeCN at room temperature for 2.5 h (Figure 2). Except for the (1,3-dioxolan-2-yl)-substituted substrates **11a**,**b**, excellent yields of 94–98% were obtained for the γ-nitrobutyrates **12c**–**l** (Scheme 1 and entries 3–12, Table 4). The yields for the Michael addition of **11a**,**b** are slightly lower (85–88%) and for the *ortho*-substituted substrate **11a**, 1.0 equiv of DBU and a longer reaction time (21 h) were required (entries 1 and 2, Table 4).

Reduction of aliphatic nitro compounds could be achieved by a variety of combination of $NaBH_4$ with another transition metal species, such as $NaBH_4$–$CoCl_2$,[25] $NaBH_4$–$NiCl_2$,[26] $NaBH_4$–$CuSO_4$,[27] $NaBH_4$–$ZrCl_2$,[28] and $NaBH_4$–Pd/C.[29] We found that the combination of 5.0 equivalents of $NaBH_4$ and 1.0 equivalent of $NiCl_2{\cdot}6H_2O$ could efficiently reduce the nitroalkanes **12** at 0 ºC for 1 h in MeOH to form the corresponding amines **21** with spontaneous formation of the γ-lactams **13** in various ratios under the reduction conditions (Scheme 1). The reaction mixture of **21** and **13**, without separation, was further treated with aqueous $K_2CO_3$ at room temperature for 2 h to afford the γ-lactams **13**. The yields for **13c**–**i** by the one-pot reductive lactamization are 93–99% (entries 3–9, Table 4) while the yields for **13k**,**l** possessing a methyl benzoate moiety are 85–86% (entries 11 and 12, Table 4). In the latter cases, hydrolysis of the methyl benzoate might occur to some extent under the basic conditions. For the 4-chlorophenyl-substituted nitro compound **12j**, although only 0.3 equivalent of $NiCl_2{\cdot}6H_2O$ was used, partial reductive cleavage of the chloro group was observed to form the byproduct **10** as an inseparable mixture with the desired product **13j** in a 11:89 ratio of **10**:**13j** (entry 10, Table 4). It is worthy of mentioning that a reduced amount of $NiCl_2{\cdot}6H_2O$ and a shorter reaction time were beneficial for the reductive lactamization of the acetal-containing **12b** to furnish **13b** in 83% yield (entry 2, Table 4) as compared to 50% yield under the general reaction conditions (data not shown). Finally, from the *ortho*-(1,3-dioxolan-2-yl)-substituted nitroalkane **12a** only 53% yield of the γ-lactam **13a** was formed even though 0.5 equivalent of $NiCl_2{\cdot}6H_2O$ was used for the reduction for only 0.5 h (entry 1,

Table 4), implying that electronic/steric effect(s) of the acetal moiety should be involved.




**Scheme 1.** γ-Lactams **13** from reductive lactamization of γ-nitrobutyrates **12**.

**Table 4**

Synthesis of γ-lactams **13** via Michael addition and reductive lactamization[a]

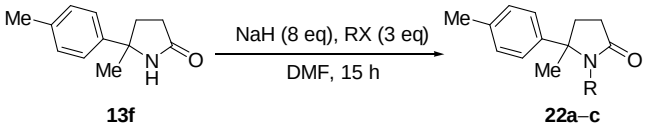
| Entry | X | R | **12**: Yield (%)[b] | **13**: Yield (%)[b] |
|---|---|---|---|---|
| 1 | 2-(1,3-dioxolan-2-yl) | Me | **12a**: 85[c] | **13a**: 53[d] |
| 2 | 4-(1,3-dioxolan-2-yl) | Me | **12b**: 88 | **13b**: 83[e] |
| 3 | 3,4-Benzo | Me | **12c**: 95 | **13c**: 93 |
| 4 | 2-Me | Me | **12d**: 96 | **13d**: 96 |
| 5 | 3-Me | Me | **12e**: 97 | **13e**: 96 |
| 6 | 4-Me | Me | **12f**: 97 | **13f**: 98 |
| 7 | 2-MeO | Me | **12g**: 94 | **13g**: 99 |
| 8 | 3-MeO | Me | **12h**: 97 | **13h**: 97 |
| 9 | 4-MeO | Me | **12i**: 95 | **13i**: 98 |
| 10 | 4-Cl | Me | **12j**: 94 | **13j**: 75[f] |
| 11 | 4-$MeO_2C$ | Me | **12k**: 97 | **13k**: 86 |
| 12 | 4-$MeO_2C$ | Et | **12l**: 98 | **13l**: 85 |

[a] Reaction conditions for the Michael addition of **11**: 2 equiv methyl acrylate **17a**, 0.5 equiv DBU, MeCN, rt, 2.5 h. Reaction conditions for reductive lactamization of **12**: 5 equiv $NaBH_4$, 1 equiv $NiCl_2·6H_2O$, MeOH, 0 ºC, 1 h; then aq. $K_2CO_3$, rt, 2 h.
[b] Isolated yields.
[c] Using 1.0 equiv of DBU for 21 h.
[d] Using 0.5 equiv $NiCl_2·6H_2O$, 0.5 h.
[e] Using 0.3 equiv $NiCl_2·6H_2O$, 0.5 h. 50% yield was obtained under the general reaction conditions.
[f] Using 0.3 equiv $NiCl_2·6H_2O$. An inseparable mixture of **13j** with the dechlorinated byproduct **10** was obtained. **13j**:**10** = 89:11.

Finally, we attempted to N-functionalization of the γ-lactams **13** in order to increase the structural diversity. Unfortunately, the Pd- and Cu-catalyzed arylation[30] of **13f** with iodobenzene failed to give the product presumably due to steric hindrance of the two substituents at the C5 position. In contrast, N-alkylation of **13f** proceeded in the presence of NaH as the base.[31] Methylation of **13f** was initially carried out in a closed vial at 80 ºC in DMF with 1.5 equivalents each of NaH and MeI to give **22a** in 43% yield with 46% conversion of the substrate (entry 1, Table 5). By increasing the amounts of NaH (8 equiv) and MeI (3 equiv), the yield of **22a** was improved significantly (70%) with 84% conversion of **13f** (entry 2, Table 5). When benzyl bromide was used for the reaction at 70 ºC, a higher yield of 83% was obtained for **22b** with 100% conversion of **13f** (entry 3, Table 5). The reaction of allyl bromide with **13f** under the same conditions at 70 ºC resulted in a complex mixture with only trace product **22c**. Fortunately, allylation of **13f** at room temperature afforded the product **22c** in 58% yield (entry 5, Table 5).

**Table 5**

Results of N-alkylation of γ-lactam **13f**[a]




**13f** **22a–c**

| Entry | RX | *T* (ºC) | Conversion (%) | Yield (%)[c] |
|---|---|---|---|---|
| 1 | MeI[b] | 80 | 46 | **22a**: 43 |
| 2 | MeI | 70 | 84 | **22a**: 70 |
| 3 | BnBr | 70 | 100 | **22b**: 83 |
| 4 | AllylBr | 70 | 84 | **22c**: complex |
| 5 | AllylBr | rt | 94 | **22c**: 58 |

[a] Reaction conditions: **13f** (0.25 mmol), NaH (2.0 mmol) in DMF (3.0 mL) in a closed process vial at 60 ºC for 50 min; then RX (0.75 mmol), 15 h at the indicated temperature.
[b] 1.5 equiv each of NaH and MeI were used.
[c] Isolated yields.

## 3. Conclusion

In summary, we have established a general and high-yielding synthesis of 5-alkyl-5-aryl-γ-lactams **13** by Michael addition of 1-aryl-substituted nitroalkanes **11** with methyl acrylate followed by one-pot reductive lactamization of the adducts **12**. Since the palladium-catalyzed α-arylation of nitroalkanes tolerates a variety of aryl bromides/chlorides such as **14**,[18] the above described synthetic protocol offers access to the diversely 5,5-disubstituted γ-lactams **13** from the readily available nitro compounds **11**. The γ-lactams **13** might be used as the candidates for biological studies[15] or as the building blocks for synthesis of much more sophisticated molecular entities.

## 4. Experimental

### 4.1. General methods

$^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ (400 or 500 MHz for $^1H$ and 100, 125, or 150 MHz for $^{13}C$, respectively). IR spectra were taken on an FT-IR spectrophotometer. Mass spectra (MS) were measured by the ESI or EI method. Melting points are uncorrected. Elemental analyses were performed by Zhejiang University. Silica gel plates pre-coated on glass were used for thin-layer chromatography using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Silica gel was used for flash column chromatography. Yields refer to chromatographically and spectroscopically ($^1H$ NMR) homogeneous materials. Reagents were obtained commercially and used as received.

### 4.2. General procedure A for the arylation of nitroalkanes

A dried 10-mL process vial was charged with appropriate amounts of $Pd_2(dba)_3$ and 2-(di-*tert*-butylphosphinyl)-2′-methylbiphenyl (**15b**), and 1.3 equiv of $K_3PO_4$. The vial was sealed with as cap containing a silicon septum. The loaded vial was evacuated and backfilled with nitrogen for three times. Then, aryl bromide **14** (1.0 mmol), nitroalkane (2.0 mmol), and degassed DME (5.0 mL) were added sequentially via a syringe. The resultant mixture was stirred vigorously for 1 min at room temperature, and then at 50 ºC for 14 h. After cooling to ambient temperature the reaction mixture was diluted with EtOAc. The resulting solution was filtered off through a plug of Celite with washing by EtOAc. The combined filtrate was washed with water and brine, dried over anhydrous $Na_2SO_4$, filtered, and condensed

under reduced pressure. The residue was purified by flash column chromatography over silica gel to give the product **11**. The results are found in Table 2.

*4.2.1. 2-[2-(1-Nitroethyl)phenyl][1,3]dioxolane (**11a**).*

Prepared according to the general procedure A in 71% yield as a colorless oil; $R_f$=0.41 (9% EtOAc in hexane); IR (film): 2894, 1557, 1455, 1385, 1360, 1225, 1087, 1061 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.60–7.55 (m, 2H), 7.46–7.39 (m, 2H), 6.22 (q, *J*=6.8 Hz, 1H), 6.05 (s, 1H), 4.19–4.01 (m, 4H), 1.89 (d, *J*=6.8 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 135.7, 134.8, 129.9, 129.5, 127.4, 127.0, 102.5, 81.1, 65.4, 65.2, 20.3; HRMS (+EI) calcd for $C_{11}H_{12}O_2$ 176.0837 ($M^+$–$HNO_2$), found 176.0833.

*4.2.2. 2-[4-(1-Nitroethyl)phenyl][1,3]dioxolane (**11b**).*

Prepared according to the general procedure A in 82% yield as a colorless oil; $R_f$=0.38 (9% EtOAc in hexane); IR (film): 2946, 2884, 1705, 1552, 1386, 1358, 1085, 1042 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J*=8.4 Hz, 2H), 7.48 (d, *J*=8.4 Hz, 2H), 5.82 (s, 1H), 5.62 (q, *J*=7.2 Hz, 1H), 4.14–4.00 (m, 4H), 1.88 (d, *J*=7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 139.8, 136.5, 127.6 (×2) , 127.1 (×2), 103.1, 85.9, 65.4 (×2), 19.6; HRMS (+EI) calcd for $C_{11}H_{12}O_2$ 176.0837 ($M^+$–$HNO_2$), found 176.0837.

*4.2.3. 2-(1-Nitroethyl)naphthalene (**11c**).*[18]

Prepared according to the general procedure A in 89% yield as a crystalline solid; $R_f$=0.43 (9% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.92–7.85 (m, 4H), 7.57–7.53 (m, 3H), 5.79 (q, *J*=6.8, 1H), 1.99 (d, *J*=6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 133.6, 132.9, 132.8, 128.9, 128.2, 127.6, 127.2, 127.0 126.7, 124.0, 86.2, 19.4.

*4.2.4. 1-Methyl-2-(1-nitroethyl)benzene (**11d**).*

Prepared according to the general procedure A in 87% yield as a yellow oil; $R_f$=0.55 (9% EtOAc in hexane ); IR (film): 3069, 2989, 1553, 1494, 1462, 1385, 1359, 1273, 1067, 1046 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.44–7.42 (m, 1H), 7.30–7.19 (m, 3H), 5.88 (q, *J*=7.2 Hz, 1H), 2.42 (s, 3H), 1.87 (d, *J*=6.8 Hz, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 136.5, 134.1, 130.8, 129.4, 126.7, 125.9, 82.1, 19.20, 19.18; HRMS (+EI) calcd for $C_9H_{11}$ 119.0861 ($M^+$–$NO_2$), found 119.0858.

*4.2.5. 1-Methyl-3-(1-nitroethyl)benzene (**11e**).*[32]

Prepared according to the general procedure A in 90% yield as a colorless oil; $R_f$=0.50 (9% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.32–7.21 (m, 4H), 5.58 (q, *J*=6.8 Hz, 1H), 2.38 (s, 3H), 1.88 (d, *J*=6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 139.0, 135.6, 130.6, 129.0, 128.1, 124.5, 86.3, 21.5, 19.6.

*4.2.6. 1-Methyl-4-(1-nitroethyl)benzene (**11f**).*[33]

Prepared according to the general procedure A in 78% yield as a colorless oil; $R_f$=0.56 (9% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J*=8.0 Hz, 2H), 7.22 (d, *J*=8.0 Hz, 2H), 5.60 (q, *J*=6.8 Hz, 1H), 2.38 (s, 3H), 1.88 (d, *J*=6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 139.9, 132.8, 129.7 (×2), 127.4 (×2), 86.0, 21.2, 19.4.

*4.2.7. 1-Methoxy-2-(1-nitroethyl)benzene (**11g**).*

Prepared according to the general procedure A in 91% yield as a colorless oil; $R_f$=0.39 (9% EtOAc in hexane); IR (film): 2943, 1603, 1552, 1495, 1463, 1384, 1355, 1250 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.40–7.36 (m, 2H), 7.03–6.99 (m, 1H), 6.94–6.91 (m, 1H), 5.99 (q, *J*=6.8 Hz, 1H), 3.84 (s, 3H), 1.88 (d, *J*=6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 156.9, 130.7, 127.4, 124.2, 120.7, 110.9, 80.0, 55.5, 18.5; HRMS (+EI) calcd for $C_9H_{11}NO_3$ 181.0739 ($M^+$), found 181.0738.

*4.2.8. 1-Methoxy-3-(1-nitroethyl)benzene (**11h**).*[32]

Prepared according to the general procedure A in 97% yield as a colorless oil; $R_f$=0.40 (9% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J*=8.0 Hz, 1H), 7.03 (d, *J*=7.6 Hz, 1H), 6.99 (t, *J*=2.0 Hz, 1H), 6.94 (dd, *J*=8.0, 2.0 Hz, 1H), 5.58 (q, *J*=6.8 Hz, 1H), 3.82 (s, 3H), 1.88 (d, *J*=6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 159.9, 136.9, 130.0, 119.5, 115.0, 113.0, 86.0, 55.3, 19.4.

*4.2.9. 1-Methoxy-4-(1-nitroethyl)benzene (**11i**).*[18,34]

Prepared according to the general procedure A in 74% yield as a colorless oil; $R_f$=0.38 (9% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J*=8.8 Hz, 2H), 6.91 (d, *J*=8.4 Hz, 2H), 5.57 (q, *J*=6.8 Hz, 1H), 3.80 (s, 3H), 1.86 (d, *J*=6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 160.7, 128.9 (×2), 127.7, 114.3 (×2), 85.8, 55.4, 19.3.

*4.2.10. 1-Chloro-4-(1-nitroethyl)benzene (**11j**).*[32,34]

Prepared according to the general procedure A in 84% yield as a colorless oil; $R_f$=0.39 (9% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.42–7.37 (m, 4H), 5.58 (q, *J*=6.8 Hz, 1H), 1.88 (d, *J*=6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 136.1, 134.0, 129.4 (×2), 129.0 (×2), 85.5, 19.5.

*4.2.11. Methyl 4-(1-nitroethyl)benzoate (**11k**).*[18,34]

Prepared according to the general procedure A in 88% yield as a colorless oil; $R_f$=0.44 (17% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J*=7.2 Hz, 2H), 7.50 (d, *J*=8.0 Hz, 2H), 5.65 (q, *J*=6.8, 1H), 3.90 (d, *J*=0.8 Hz, 3H), 1.88 (dd, *J*=6.8, 0.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 166.3, 140.0, 131.4, 130.3 (×2), 127.5 (×2), 85.7, 52.4, 19.4.

*4.2.12. Methyl 4-(1-nitropropyl)benzoate (**11l**).*[18]

Prepared according to the general procedure A in 87% yield as a colorless oil; $R_f$=0.36 (9% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J*=8.4 Hz, 2H), 7.52 (d, *J*=8.4 Hz, 2H), 5.40 (dd, *J*=8.8, 6.8 Hz, 1H), 3.91 (s, 3H), 2.56–2.45 (m, 1H), 2.16–2.05 (m, 1H), 0.97 (t, *J*=7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 166.3, 139.0, 131.6, 130.3 (×2), 127.9 (×2), 92.6, 52.4, 27.5, 10.6.

### 4.3. General procedure B for the Michael addition of nitroalkanes 11 with methyl arylate

To a solution of **11** (1.0 mmol) and methyl acrylate (2.0 mmol) in MeCN (4.0 mL) at room temperature under a nitrogen atmosphere was added DBU (0.5 mmol). The resultant mixture was stirred at room temperature for 2.5 h. The reaction was quenched with saturated aqueous $NH_4Cl$ solution (20 mL) and the reaction mixture was extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and condensed under reduced pressure. The residue was purified by flash column chromatography over silica gel to afford **12**. The results are found in Table 4.

*4.3.1. Methyl 4-[2-(1,3-dioxolan-2-yl)phenyl]-4-nitropentanoate (**12a**).*

Prepared according to the general procedure B with 1 equiv DBU for 21 h in 85% yield as a colorless oil; $R_f$=0.24 (17% EtOAc in hexane); IR (film): 2993, 2954, 2886, 1743, 1729, 1549, 1538, 1433, 1208, 1174, 1089, 1060 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=7.6 Hz, 1H), 7.46–7.35 (m, 3H), 5.68 (s, 1H), 4.18–4.09 (m, 2H), 4.02–3.93 (m, 2H), 3.65 (s, 3H), 2.87–2.74 (m, 2H), 2.30–2.11 (m, 2H), 2.02 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 172.4, 136.5, 136.0, 129.4, 129.2, 128.9, 126.3, 99.1, 92.4, 65.3 (×2), 51.8, 34.8, 29.5, 27.0; MS (+EI) *m*/*z* 308 ($M^+$–H, 1.51), 263 ($M^+$–$NO_2$, 15), 201 (93), 141 (100);

HRMS (+EI) calcd for $C_{15}H_{18}O_4$ 262.1205 ($M^+$–$HNO_2$), found 262.1203.

### *4.3.2. Methyl 4-[4-(1,3-dioxolan-2-yl)phenyl]-4-nitropentanoate (**12b**)*

Prepared according to the general procedure B in 88% yield as a colorless oil; $R_f$=0.21 (17% EtOAc in hexane); IR (film): 2993, 2953, 2888, 1740, 1729, 1548, 1538, 1199, 1174, 1089, 1019 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J*=8.4 Hz, 2H), 7.38 (d, *J*=8.4 Hz, 2H), 5.81 (s, 1H), 4.12–4.03 (m, 4H), 3.66 (s, 3H), 2.80–2.61 (m, 2H), 2.30–2.26 (m, 2H), 1.95 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 172.3, 139.5, 138.9, 126.9 (×2), 125.3 (×2), 102.7, 92.2, 65.2 (×2), 51.7, 34.4, 29.3, 23.7; MS (+EI) *m/z* 308 ($M^+$–H, 0.34), 263 ($M^+$–$NO_2$, 100); HRMS (+EI) calcd for $C_{15}H_{18}O_4$ 262.1205 ($M^+$–$HNO_2$), found 262.1198.

### *4.3.3. Methyl 4-(Naphthalene-2-yl)-4-nitropentanoate (**12c**)*

Prepared according to the general procedure B in 95% yield as a colorless oil; $R_f$=0.23 (9% EtOAc in hexane); IR (film): 3057, 2993, 2950, 1738, 1729, 1547, 1534, 1436, 1199, 1172 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.87–7.82 (m, 4H), 7.55–7.50 (m, 2H), 7.43 (dd, *J*=8.8, 1.6 Hz, 1H), 3.65 (s, 3H), 2.93–2.77 (m, 2H), 2.33 (t, *J*=8.0 Hz, 2H), 2.07 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 172.5, 135.9, 133.0, 132.7, 128.9, 128.3, 127.5, 127.0, 126.7, 124.9, 122.6, 92.6, 51.8, 34.4, 29.5, 23.8; MS (+EI) *m/z* 241 ($M^+$–$NO_2$, 42), 209 (64), 181 (100); HRMS (+EI) calcd for $C_{16}H_{17}NO_4$ 287.1158 ($M^+$), found 287.1152.

### *4.3.4. Methyl 4-(2-Methylphenyl)-4-nitropentanoate (**12d**)*

Prepared according to the general procedure B in 96% yield as a colorless oil; $R_f$=0.31 (9% EtOAc in hexane); IR (film): 2994, 2953, 1742, 1732, 1547, 1538, 1345, 1201, 1172 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J*=7.5, 2.0 Hz, 1H), 7.29–7.22 (m, 2H), 7.19 (dd, *J*=7.0, 1.0 Hz, 1H), 3.63 (s, 3H), 2.76 (t, *J*=8.0 Hz, 2H), 2.34–2.27 (m, 1H), 2.19 (s, 3H), 2.18–2.11 (m, 1H), 1.96 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 172.4, 136.7, 136.1, 132.8, 128.8, 126.3, 126.2, 92.6, 51.8, 33.4, 29.6, 26.0, 19.9; MS (+EI) *m/z* 205 ($M^+$–$NO_2$, 30), 173 (40), 145 (100); HRMS (+EI) calcd for $C_{13}H_{16}O_2$ 204.1150 ($M^+$–$HNO_2$), found 204.1155.

### *4.3.5. Methyl 4-(3-Methylphenyl)-4-nitropentanoate (**12e**)*

Prepared according to the general procedure B in 97% yield as a colorless oil; $R_f$=0.32 (9% EtOAc in hexane); IR (film): 2997, 2953, 1739, 1541, 1437, 1345, 1201, 1172 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (m, 1H), 7.18–7.14 (m, 3H), 3.66 (s, 3H), 2.80–2.73 (m, 1H), 2.69–2.61 (m, 1H), 2.36 (s, 3H), 2.31–2.27 (m, 2H), 1.94 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 172.5, 138.7, 138.6, 129.6, 128.7, 125.8, 122.2, 92.4, 51.8, 34.4, 29.4, 23.7, 21.4; MS (+ESI) *m/z* 524.8 (2M+$Na^+$, 100), 273.8 (M+$Na^+$, 59); HRMS (+EI) calcd for $C_{13}H_{16}O_2$ 204.1150 ($M^+$–$HNO_2$), found 204.1147.

### *4.3.6. Methyl 4-(4-Methylphenyl)-4-nitropentanoate (**12f**)*

Prepared according to the general procedure B in 97% yield as a colorless oil; $R_f$=0.33 (9% EtOAc in hexane); IR (film): 2997, 2952, 1739, 1541, 1437, 1343, 1197, 1176 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J*=8.4 Hz, 2H), 7.19 (d, *J*=8.4 Hz, 2H), 3.66 (s, 3H), 2.80–2.63 (m, 2H), 2.35 (s, 3H), 2.28 (t, *J*=8.4, Hz, 2H), 1.94 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 172.5, 138.9, 135.8, 129.5 (×2), 125.2 (×2), 92.2, 51.8, 34.4, 29.5, 23.6, 20.9; MS (+ESI) *m/z* 273.8 (M+$Na^+$, 48), 524.8 (2M+$Na^+$, 100); HRMS (+EI) calcd for $C_{13}H_{16}O_2$ 204.1150 ($M^+$–$HNO_2$), found 204.1155.

### *4.3.7. Methyl 4-(2-Methoxyphenyl)-4-nitropentanoate (**12g**)*

Prepared according to the general procedure B in 94% yield as a colorless solid; mp 61–63 ˚C ($CH_2Cl_2$–hexane); $R_f$=0.26 (9% EtOAc in hexane); IR (KBr): 3002, 2951, 1736, 1545, 1491, 1348, 1250, 1199, 1174, 1025 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.36 (td, *J*=8.0, 1.2 Hz, 1H), 7.28 (dd, *J*=8.0, 1.2 Hz, 1H), 7.00 (t, *J*=7.2 Hz, 1H), 6.92 (d, *J*=8.4 Hz, 1H), 3.76 (s, 3H), 3.62 (s, 3H), 2.86–2.79 (m, 1H), 2.72–2.64 (m, 1H), 2.27 (ddd, *J*=16.4, 10.4, 5.2 Hz, 1H), 2.14 (ddd, *J*=16.4, 10.8, 6.0 Hz, 1H), 1.91 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 172.7, 156.7, 130.3, 127.3, 126.8, 120.5, 111.8, 90.5, 55.3, 51.7, 32.3, 29.6, 24.6; MS (+EI) *m/z* 221 ($M^+$–$NO_2$, 41), 189 (43), 161 (100). Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.86; H, 6.44; N, 5.40%.

### *4.3.8. Methyl 4-(3-Methoxyphenyl)-4-nitropentanoate (**12h**)*

Prepared according to the general procedure B in 97% yield as a colorless oil; $R_f$=0.24 (9% EtOAc in hexane); IR (film): 3000, 2953, 1743, 1729, 1602, 1537, 1346, 1201, 1174, 1045 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 1H), 6.94–6.88 (m, 3H), 3.81 (s, 3H), 3.66 (s, 3H), 2.79–2.74 (m, 1H), 2.72–2.62 (m, 1H), 2.29 (t, *J*=8.0 Hz, 2H), 1.94 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 172.4, 159.7, 140.2, 129.8, 117.4, 113.7, 111.7, 92.3, 55.1, 51.7, 34.4, 29.3, 23.6; MS (+EI) *m/z* 221 ($M^+$–$NO_2$, 32), 189 (79), 161 (100); HRMS (+EI) calcd for $C_{13}H_{16}O_3$ 220.1099 ($M^+$–$HNO_2$), found 220.1093.

### *4.3.9. Methyl 4-(4-Methoxyphenyl)-4-nitropentanoate (**12i**)*

Prepared according to the general procedure B in 95% yield as a colorless solid; mp 57–59 ˚C ($CH_2Cl_2$–hexane); $R_f$=0.21 (9% EtOAc in hexane); IR (KBr): 2999, 2954, 1740, 1611, 1538, 1386, 1344, 1258, 1185 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J*=8.8 Hz, 2H), 6.90 (d, *J*=8.8 Hz, 2H), 3.81 (s, 3H), 3.66 (s, 3H), 2.80–2.64 (m, 2H), 2.27 (t, *J*=8.0 Hz, 2H), 1.94 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 172.5, 159.9, 130.5, 126.9 (×2), 114.1 (×2), 91.9, 55.2, 51.8, 34.5, 29.5, 23.5; MS (+EI) *m/z* 221 ($M^+$–$NO_2$, 74), 189 (63), 161 (100). Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.79; H, 6.41; N, 5.40%.

### *4.3.10. Methyl 4-(4-Chlorophenyl)-4-nitropentanoate (**12j**)*

Prepared according to the general procedure B in 94% yield as a colorless oil; $R_f$=0.29 (9% EtOAc in hexane); IR (film): 2997, 2953, 1741, 1727, 1547, 1536, 1495, 1346, 1201, 1173, 1100 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 3.66 (s, 3H), 2.80–2.72 (m, 1H), 2.68–2.60 (m, 1H), 2.28 (t, *J*=8.0 Hz, 2H), 1.94 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 172.3, 137.2, 135.1, 129.0 (×2), 126.9 (×2), 91.9, 51.9, 34.4, 29.3, 23.6; MS (+EI) *m/z* 225 ($M^+$–$NO_2$, 59), 193 (73), 165 (100); HRMS (+EI) calcd for $C_{12}H_{13}O_2Cl$ 224.0604 ($M^+$–$HNO_2$), found 204.0608.

### *4.3.11. Methyl 4-(3-Methoxycarbonyl-1-methyl-1-nitropropyl)benzoate (**12k**)*

Prepared according to the general procedure B in 97% yield as a colorless oil; $R_f$=0.11 (9% EtOAc in hexane); IR (film): 2999, 2954, 1740, 1727, 1544, 1436, 1284, 1196, 1174, 1115 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J*=8.4 Hz, 2H), 7.43 (d, *J*=8.4 Hz, 2H), 3.93 (s, 3H), 3.66 (s, 3H), 2.83–2.76 (m, 1H), 2.70–2.62 (m, 1H), 2.30 (dd, *J*=8.4, 8.0 Hz, 2H), 1.97 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 172.2, 166.1, 143.4, 130.7, 130.1 (×2), 125.4 (×2), 92.3, 52.2, 51.9, 34.4, 29.3, 23.9; MS (+EI) *m/z* 264 ($M^+$–$OCH_3$, 4), 249 ($M^+$–$NO_2$, 19), 217 (100); HRMS (+EI) calcd for $C_{14}H_{16}O_4$ 248.1049 ($M^+$–$HNO_2$), found 248.1047.

*4.3.12. Methyl 4-(1-Ethyl-3-methoxycarbonyl-1-nitropropyl)benzoate (**12l**)*

Prepared according to the general procedure B in 98% yield as a colorless oil; $R_f$=0.14 (9% EtOAc in hexane); IR (film): 2985, 2954, 1740, 1732, 1544, 1436, 1284, 1192, 1115 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J*=8.4 Hz, 2H), 7.37 (d, *J*=8.4 Hz, 2H), 3.93 (s, 3H), 3.64 (s, 3H), 2.73 (t, *J*=8.0 Hz, 2H), 2.55–2.46 (m, 1H), 2.39–2.29 (m, 1H), 2.25–2.09 (m, 2H), 0.88 (t, *J*=7.6 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 172.2, 166.1, 142.6, 130.6, 129.9 (×2), 125.9 (×2), 96.3, 52.2, 51.9, 30.3, 29.3, 28.8, 8.2; MS (+EI) *m/z* 278 ($M^+$–$OCH_3$, 3), 263 ($M^+$–$NO_2$, 11), 231 (100); HRMS (+EI) calcd for $C_{15}H_{18}O_4$ 262.1205 ($M^+$–$HNO_2$), found 262.1208.

### 4.4. General procedure C for the synthesis of γ-lactams 13

To a solution of the nitroalkanes **12** (1.0 mmol) and $NiCl_2·6H_2O$ (1.0 mmol) in MeOH (10 mL) cooled in an ice–water bath (0 ºC) was added $NaBH_4$ (5.0 mmol) slowly. The resultant mixture was stirred at the same temperature for 1 h. The reaction was quenched by adding a solution of $K_2CO_3$ (4.0 mmol) in $H_2O$ (5 mL) followed by stirring at room temperature for 2 h. The mixture was extracted with EtOAc (40 mL×3) and the combined organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and condensed under reduced pressure. The residue was purified by flash column chromatography over silica gel to give the γ-lactams **13**. The results are found in Table 4.

*4.4.1. 5-[2-(1,3-Dioxolan-2-yl)phenyl]-5-methylpyrrolidin-2-one (**13a**)*

Prepared according to the general procedure C in 53% yield using 0.5 equiv $NiCl_2·6H_2O$ and 5 equiv $NaBH_4$ for 0.5 h at 0 ˚C followed by addition of aq $K_2CO_3$. A colorless oil; $R_f$=0.27 (67% EtOAc in hexane); IR (film): 3214 (br), 3068, 2968, 1691, 1394, 1083, 1062 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J*=7.0 Hz, 1H), 7.37–7.28 (m, 3H), 7.01 (br s, 1H), 6.21 (s, 1H), 4.21–4.04 (m, 4H), 2.60–2.51 (m, 1H), 2.47–2.40 (m, 2H), 2.37–2.31 (m, 1H), 1.69 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 177.2, 144.6, 133.8, 129.1, 127.6, 127.2, 125.4, 100.5, 65.4, 65.2, 62.6, 37.6, 31.8, 30.0; MS (+EI) *m/z* 247 ($M^+$, 21), 232 ($M^+$–Me, 28), 189 (100); HRMS (+EI) calcd for $C_{14}H_{17}NO_3$ 247.1208 ($M^+$), found 247.1211.

*4.4.2. 5-[4-(1,3-Dioxolan-2-yl)phenyl]-5-methylpyrrolidin-2-one (**13b**)*

Prepared according to the general procedure C in 83% yield using 0.3 equiv $NiCl_2·6H_2O$ and 5 equiv $NaBH_4$ for 0.5 h at 0 ˚C followed by addition of aq $K_2CO_3$. A colorless solid; mp 134–136 ˚C ($CH_2Cl_2$–hexane); $R_f$=0.29 (67% EtOAc in hexane); IR (KBr): 3171 (br), 3071, 2968, 1716, 1681, 1383, 1363, 1221, 1085 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J*=8.0 Hz, 2H), 7.37 (d, *J*=8.0 Hz, 2H), 6.68 (br s, 1H), 5.80 (s, 1H), 4.16–3.99 (m, 4H), 2.46–2.24 (m, 4H), 1.64 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 177.8, 147.5, 136.7, 126.7 (×2), 124.6 (×2), 103.3, 65.3 (×2), 61.9, 37.5, 30.3, 29.4; MS (+EI) *m/z* 246 ($M^+$–H, 9), 232 ($M^+$–Me, 100); HRMS (+EI) calcd for $C_{14}H_{17}NO_3$ 247.1208 ($M^+$), found 247.1203.

*4.4.3. 5-Methyl-5-(naphthalene-2-yl)pyrrolidin-2-one (**13c**)*

Prepared according to the general procedure C in 93% yield as a colorless solid; mp 142–144 ˚C ($CH_2Cl_2$–hexane); $R_f$=0.13 (50% EtOAc in hexane); IR (KBr): 3179 (br), 3075, 2954, 1694, 1654, 1372, 1312, 1231 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.99–7.96 (m, 1H), 7.85–7.80 (m, 4H), 7.50–7.45 (m, 3H), 2.53–2.27 (m, 4H), 1.73 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 178.1, 143.7, 132.9, 132.2, 128.4, 128.0, 127.3, 126.2, 125.8, 123.2, 122.6, 62.1, 37.1, 30.4, 29.4; MS (+EI) *m/z* 225 ($M^+$, 14), 210 ($M^+$–Me, 100). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.81; H, 6.61; N, 6.27%.

*4.4.4. 5-Methyl-5-(2-methylphenyl)pyrrolidin-2-one (**13d**)*

Prepared according to the general procedure C in 96% yield as a colorless solid; mp 119–120 ˚C ($CH_2Cl_2$–hexane); $R_f$=0.31 (50% EtOAc in hexane); IR (KBr): 3178 (br), 3069, 3003, 1694, 1378, 1248 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.36–7.34 (m, 1H), 7.19–7.16 (m, 3H), 6.73 (br s, 1H), 2.53–2.44 (m, 2H), 2.47 (s, 3H), 2.41–2.33 (m, 2H), 1.69 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 177.5, 143.9, 133.8, 132.5, 126.9, 125.9, 124.6, 62.8, 35.1, 30.2, 29.0, 21.7; MS (+EI) *m/z* 189 ($M^+$, 3), 174 ($M^+$–Me, 100). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.30; H, 8.00; N, 7.45%.

*4.4.5. 5-Methyl-5-(3-methylphenyl)pyrrolidin-2-one (**13e**)*

Prepared according to the general procedure C in 96% yield as a colorless oil; $R_f$=0.37 (50% EtOAc in hexane); IR (film): 3212 (br), 3066, 2971, 1694, 1455, 1378, 1358, 1212 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.25 (t, *J*=7.5 Hz, 1H), 7.16 (s, 1H), 7.15 (d, *J*=7.5 Hz, 1H), 7.08 (d, *J*=7.5 Hz, 1H), 6.40 (br s, 1H), 2.49–2.38 (m, 2H), 2.36 (s, 3H), 2.32–2.22 (m, 2H), 1.65 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 177.9, 146.5, 138.1, 128.4, 127.7, 125.2, 121.5, 61.9, 37.5, 30.4, 29.6, 21.5; MS (+ESI) *m/z* 379.1 ($2M+H^+$, 53), 190.2 ($M+H^+$, 100); HRMS (+EI) calcd for $C_{12}H_{15}NO$ 189.1154 ($M^+$), found 189.1159.

*4.4.6. 5-Methyl-5-(4-methylphenyl)pyrrolidin-2-one (**13f**)*

Prepared according to the general procedure C in 98% yield as a colorless solid; mp 124–126 ˚C ($CH_2Cl_2$–hexane); $R_f$=0.32 (50% EtOAc in hexane); IR (KBr): 3180 (br), 3087, 2978, 1691, 1511, 1380, 1363, 1252 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J*=8.0 Hz, 2H), 7.16 (d, *J*=8.4 Hz, 2H), 6.97 (br s, 1H), 2.49–2.37 (m, 2H), 2.33 (s, 3H), 2.28–2.23 (m, 2H), 1.64 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 178.0, 143.6, 136.4, 129.1 (×2), 124.3 (×2), 61.8, 37.3, 30.4, 29.6, 20.7; MS (+ESI) *m/z* 400.9 ($2M+Na^+$, 100), 211.8 ($M+Na^+$, 9). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.32; H, 7.97; N, 7.51%.

*4.4.7. 5-(2-Methoxyphenyl)-5-methylpyrrolidin-2-one (**13g**)*

Prepared according to the general procedure C in 99% yield as a colorless solid; mp 109–111 ˚C ($CH_2Cl_2$–hexane); $R_f$=0.30 (50% EtOAc in hexane); IR (KBr): 3179 (br), 3077, 2993, 2963, 1695, 1486, 1372, 1246, 1076, 1032 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.26 (td, *J*=8.0, 2.0 Hz, 1H), 7.21 (dd, *J*=8.0, 2.0 Hz, 1H), 6.95 (td, *J*=7.5, 0.5 Hz, 1H), 6.92 (d, *J*=8.0 Hz, 1H), 6.83 (br s, 1H), 3.87 (s, 3H), 2.63–2.57 (m, 1H), 2.50–2.43 (m, 1H), 2.35–2.26 (m, 2H), 1.57 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 177.0, 156.2, 133.3, 128.3, 125.1, 120.5, 111.2, 61.2, 55.0, 34.3, 29.8, 28.1; MS (+EI) *m/z* 205 ($M^+$, 2), 190 ($M^+$–Me, 100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.32; H, 7.37; N, 6.84%.

*4.4.8. 5-(3-Methoxyphenyl)-5-methylpyrrolidin-2-one (**13h**)*

Prepared according to the general procedure C in 97% yield as a colorless oil; $R_f$=0.31 (50% EtOAc in hexane); IR (film): 3212 (br), 3075, 2968, 1681, 1602, 1488, 1288, 1258, 1221, 1044 $cm^{-1}$; $^1H$ NMR 400 MHz, $CDCl_3$) δ 7.27 (t, *J*=8.0 Hz, 1H), 7.00 (br s, 1H), 6.93 (d, *J*=8.0 Hz, 1H), 6.90 (s, 1H), 6.79 (d, *J*=8.0 Hz, 1H), 3.80 (s, 3H), 2.47–2.21 (m, 4H), 1.64 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 178.1, 159.6, 148.3, 129.5, 116.8, 111.7, 110.7, 62.1, 55.1, 37.2, 30.4, 29.6; MS (+EI) *m/z* 205 ($M^+$, 14), 190

($M^+$–Me, 100); HRMS (+EI) calcd for $C_{12}H_{15}NO_2$ 205.1103 ($M^+$), found 205.1107.

#### *4.4.9. 5-(4-Methoxyphenyl)-5-methylpyrrolidin-2-one (**13i**)*

Prepared according to the general procedure C in 98% yield as a colorless solid; mp 136–138 ˚C ($CH_2Cl_2$–hexane); $R_f$=0.24 (50% EtOAc in hexane); IR (KBr): 3178 (br), 3072, 2972, 1694, 1514, 1248, 1182, 1027 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J*=8.4 Hz, 2H), 7.07 (br s, 1H), 6.87 (d, *J*=8.4 Hz, 2H), 3.78 (s, 3H), 2.46–2.32 (m, 2H), 2.26–2.18 (m, 2H), 1.62 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 178.0, 158.2, 138.6, 125.5 (×2), 113.7 (×2), 61.6, 55.0, 37.3, 30.4, 29.5; MS (+EI) *m/z* 205 ($M^+$, 5), 190 ($M^+$–Me, 100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.04; H, 7.24; N, 6.86%.

#### *4.4.10. 5-(4-Chlorophenyl)-5-methylpyrrolidin-2-one (**13j**) and 5-Methyl-5-phenylpyrrolidin-2-one (**10**)*[16]

Prepared according to the general procedure C using 0.3 equiv $NiCl_2 \cdot 6H_2O$ and 5 equiv $NaBH_4$ for 0.5 h at 0 ˚C followed by addition of aq $K_2CO_3$. The product was obtained in 75% yield as a 89:11 inseparable mixture of **13j** with the dechlorinated byproduct **10**. A colorless oil; $R_f$=0.30 (50% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 4.1H), 6.72 (br s, 0.89H), 6.55 (br s, 0.11H), 2.48–2.37 (m, 2H), 2.28–2.22 (m, 2H), 1.66 (s, 0.33H), 1.64 (s, 2.67H).

#### *4.4.11. Methyl 4-(2-Methyl-5-oxo-pyrrolidin-2-yl)benzoate (**13k**)*

Prepared according to the general procedure C in 86% yield as a colorless solid; mp 159–161 ˚C ($CH_2Cl_2$–hexane); $R_f$=0.20 (50% EtOAc in hexane); IR (KBr): 3184 (br), 3070, 2982, 1725, 1687, 1433, 1279, 1107 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J*=8.4 Hz, 2H), 7.44 (d, *J*=8.4 Hz, 2H), 6.59 (br s, 1H), 3.92 (s, 3H), 2.50–2.38 (m, 2H), 2.36–2.24 (m, 2H), 1.68 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 178.1, 166.6, 151.7, 129.8 (×2), 128.7, 124.5 (×2), 62.2, 52.0, 37.1, 30.3, 29.5; MS (+EI) *m/z* 233 ($M^+$, 3), 218 ($M^+$–Me, 100). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.26; H, 6.38; N, 6.09%.

#### *4.4.12. Methyl 4-(2-Ethyl-5-oxo-pyrrolidin-2-yl)benzoate (**13l**)*

Prepared according to the general procedure C in 85% yield as a colorless solid; mp 137–139 ˚C ($CH_2Cl_2$–hexane); $R_f$=0.30 (50% EtOAc in hexane); IR (KBr): 3187 (br), 3079, 2975, 1717, 1691, 1289, 1113 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J*=8.0 Hz, 2H), 7.38 (d, *J*=8.4 Hz, 2H), 6.98 (br s, 1H), 3.92 (s, 3H), 2.48–2.22 (m, 4H), 2.10–1.89 (m, 2H), 0.79 (t, *J*=7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 178.6, 166.7, 150.5, 129.8 (×2), 128.7, 125.0 (×2), 66.1, 52.0, 35.5, 35.4, 30.3, 8.6; MS (+EI) *m/z* 248 (M+$H^+$, 4), 218 ($M^+$–Et, 100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.16; H, 6.79; N, 5.77%.

### 4.5. General procedure D for the N-alkylation of γ-lactam 13f

An oven-dried process vial charged with NaH (60% dispersion in mineral oil; 2 mmol) was sealed with a cap containing a silicon septum. The loaded vial was cooled in an ice–water bath (0 ºC) under nitrogen atmosphere and a solution of **13f** (0.25 mmol) in dry DMF (3 mL) was added via a syringe. The resultant mixture was stirred at 0 ˚C for 10 min and at 60 ˚C for another 50 min. The resultant mixture was cooled to 0 ºC and a solution of the alkyl halide (0.75 mmol) was added via a syringe at 0 ˚C followed by heating at 70 ˚C for 15 h. After cooling to ambient temperature, the reaction mixture was poured into water (30 mL) and extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and condensed under reduced pressure. The residue was purified by flash column chromatography over silica gel to give the N-alkylated products **22a**–**c**. The results are found in Table 5.

#### *4.5.1. 1,5-Dimethyl-5-(4-methylphenyl)pyrrolidin-2-one (**22a**)*

Prepared according to the general procedure D in 70% yield as a colorless oil; $R_f$=0.35 (50% EtOAc in hexane); IR (film): 3025, 2968, 1691, 1681, 1511, 1417, 1385, 1144 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J*=8.0 Hz, 2H), 7.09 (d, *J*=8.0 Hz, 2H), 2.65 (s, 3H), 2.44 (t, *J*=8.0 Hz, 2H), 2.33 (s, 3H), 2.08 (t, *J*=7.6 Hz, 2H), 1.65 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.9, 140.9, 136.6, 129.2 (×2), 124.9 (×2), 65.1, 36.5, 29.4, 25.3, 24.1, 20.6; MS (+EI) *m/z* 203 ($M^+$, 6), 188 ($M^+$–Me, 100); HRMS (+EI) calcd for $C_{13}H_{17}NO$ 203.1310 ($M^+$), found 203.1308.

#### *4.5.2. 1-Benzyl-5-methyl-5-(4-methylphenyl)pyrrolidin-2-one(**22b**)*

Prepared according to the general procedure D in 83% yield as a colorless oil; $R_f$=0.46 (33% EtOAc in hexane); IR (film): 3029, 2975, 2921, 1691, 1679, 1395, 1171, 1153 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.24–7.17 (m, 7H), 7.10 (d, *J*=8.0 Hz, 2H), 4.99 and 3.67 (ABq, *J*=15.0 Hz, 2H), 2.58–2.46 (m, 2H), 2.36 (s, 3H), 2.17–2.07 (m, 2H), 1.46 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 175.8, 141.1, 138.7, 137.0, 129.4 (×2), 128.2 (×2), 127.7 (×2), 126.8, 125.4 (×2), 66.5, 44.3, 37.1, 29.5, 26.4, 20.8; MS (+EI) *m/z* 279 ($M^+$, 37), 264 ($M^+$–Me, 23); HRMS (+EI) calcd for $C_{19}H_{21}NO$ 279.1623 ($M^+$), found 279.1620.

#### *4.5.3. 1-Allyl-5-methyl-5-(4-methylphenyl)pyrrolidin-2-one (**22c**)*

Prepared according to the general procedure D in 58% yield but by reacting with allyl bromide at room temperature for 15 h instead of 70 ˚C. A colorless oil; $R_f$=0.29 (33% EtOAc in hexane); IR (film): 3024, 2976, 2916, 1693, 1681, 1513, 1393 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J*=8.4 Hz, 2H), 7.09 (d, *J*=8.4 Hz, 2H), 5.85–5.75 (m, 1H), 5.07 (dd, *J*=9.6, 1.6 Hz, 1H), 5.04 (d, *J*=0.8 Hz, 1H), 4.17 (ddd, *J*=15.6, 3.2, 1.6 Hz, 1H), 3.27 (dd, *J*=15.6, 6.8 Hz, 1H), 2.51–2.38 (m, 2H), 2.34 (s, 3H), 2.18–2.08 (m, 2H), 1.68 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 175.3, 141.6, 137.0, 134.3, 129.4 (×2), 125.4 (×2), 116.5, 66.3, 43.6, 37.2, 29.5, 26.2, 20.9; MS (+EI) *m/z* 229 ($M^+$, 25), 214 ($M^+$–Me, 100); HRMS (+EI) calcd for $C_{15}H_{19}NO$ 229.1467 ($M^+$), found 229.1461.

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**Supplementary data**

$^1H$ and $^{13}C$ NMR spectra for compounds **11**–**13** are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.00.000.

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# Synthesis of 5-alkyl-5-aryl-γ-lactams from 1-aryl-substituted nitroalkanes and methyl acrylate via Michael addition and reductive lactamization

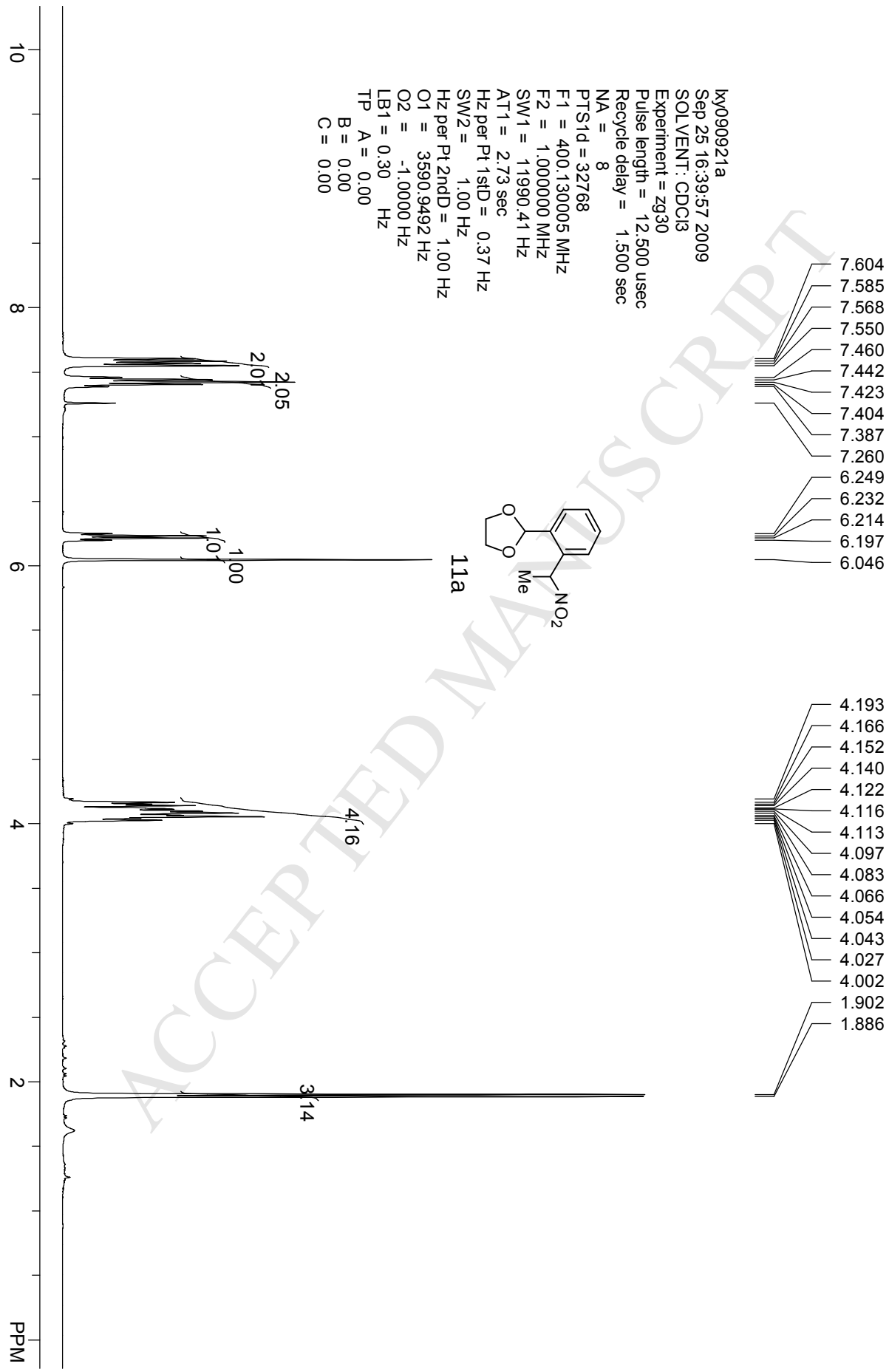
Jingjing Xu[a], Xingyao Li[a], Jinlong Wu[a,*], Wei-Min Dai[a,b,*,†]

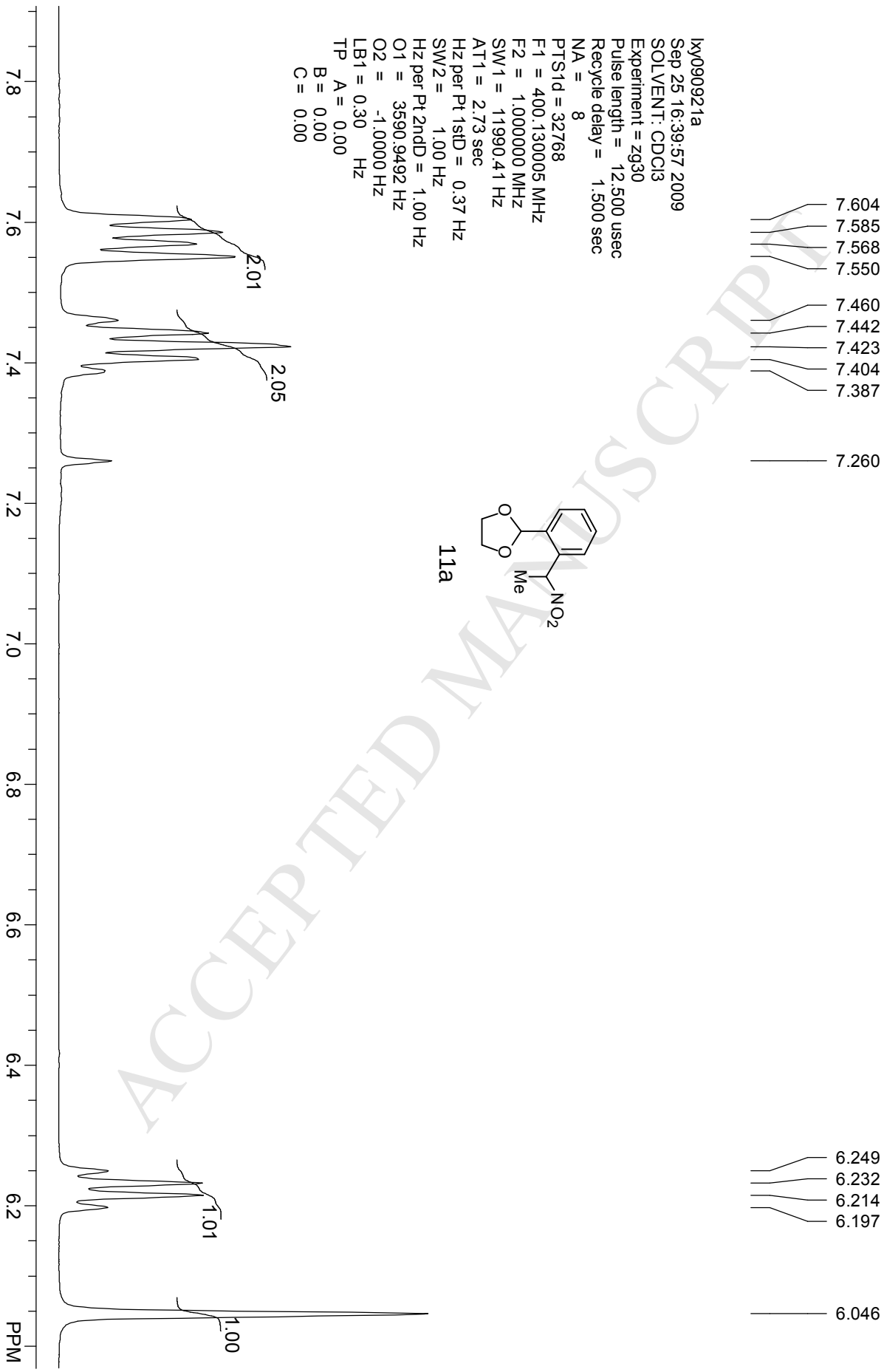
[a]*Laboratory of Asymmetric Catalysis and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, China*
[b]*Laboratory of Advanced Catalysis and Synthesis, Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China*

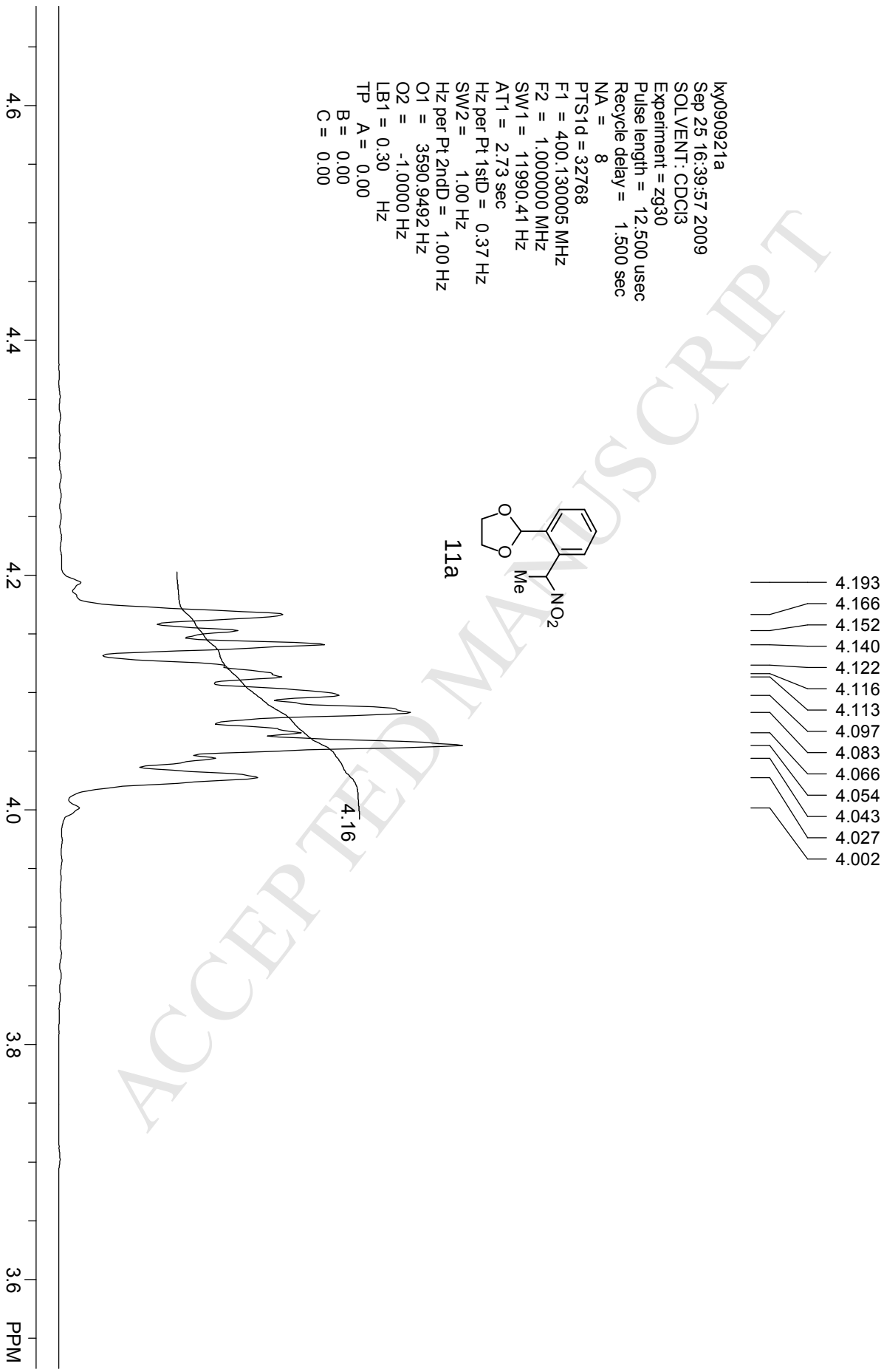
∗ Corresponding authors. Tel./fax: +86 571 89953128; e-mail addresses: wyz@zju.edu.cn (J. Wu); chdai@zju.edu.cn (W.-M. Dai)
† Tel.: +852 23587365; fax: +852 23581594; e-mail address: chdai@ust.hk.

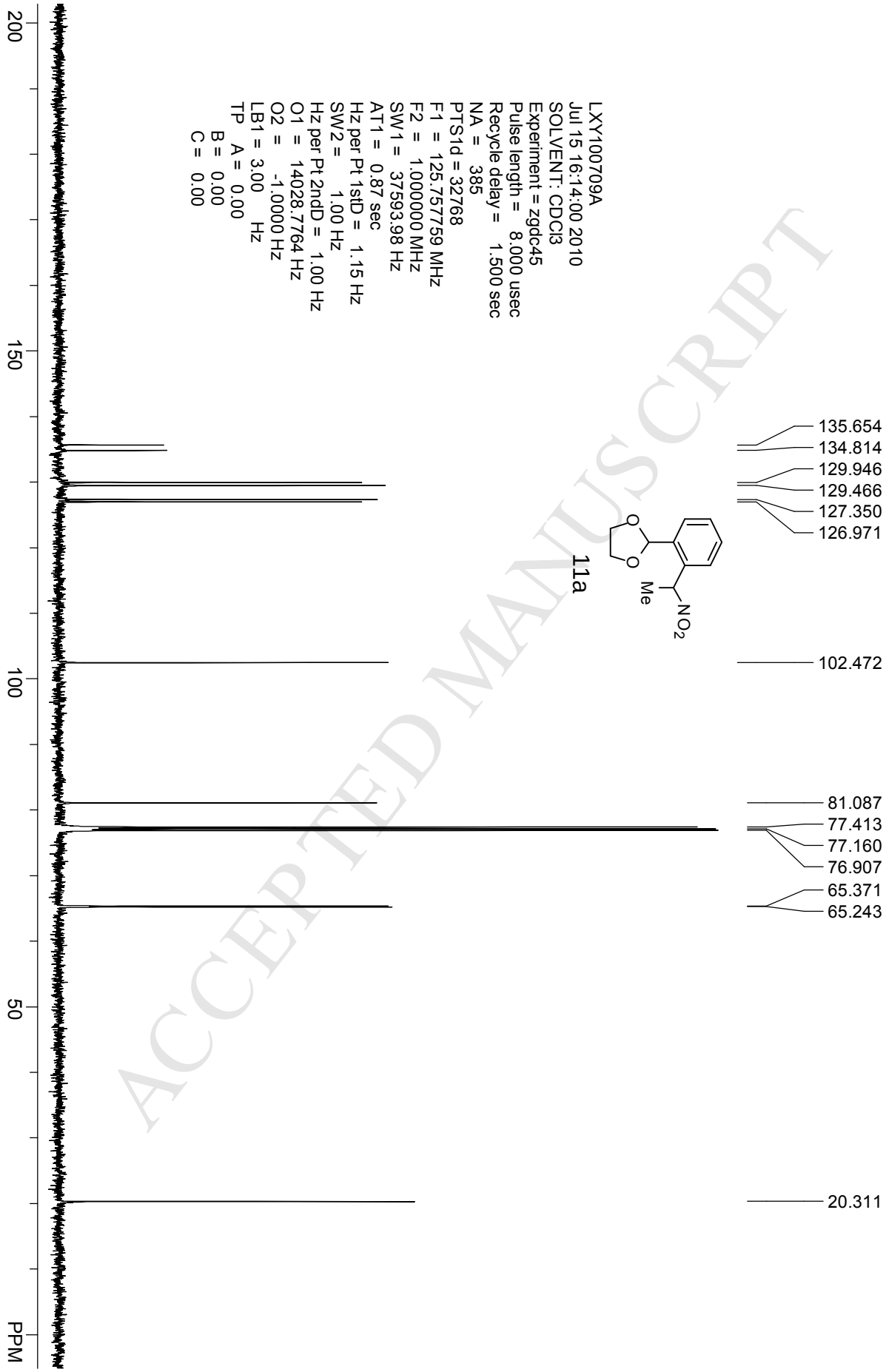
## Supporting Information

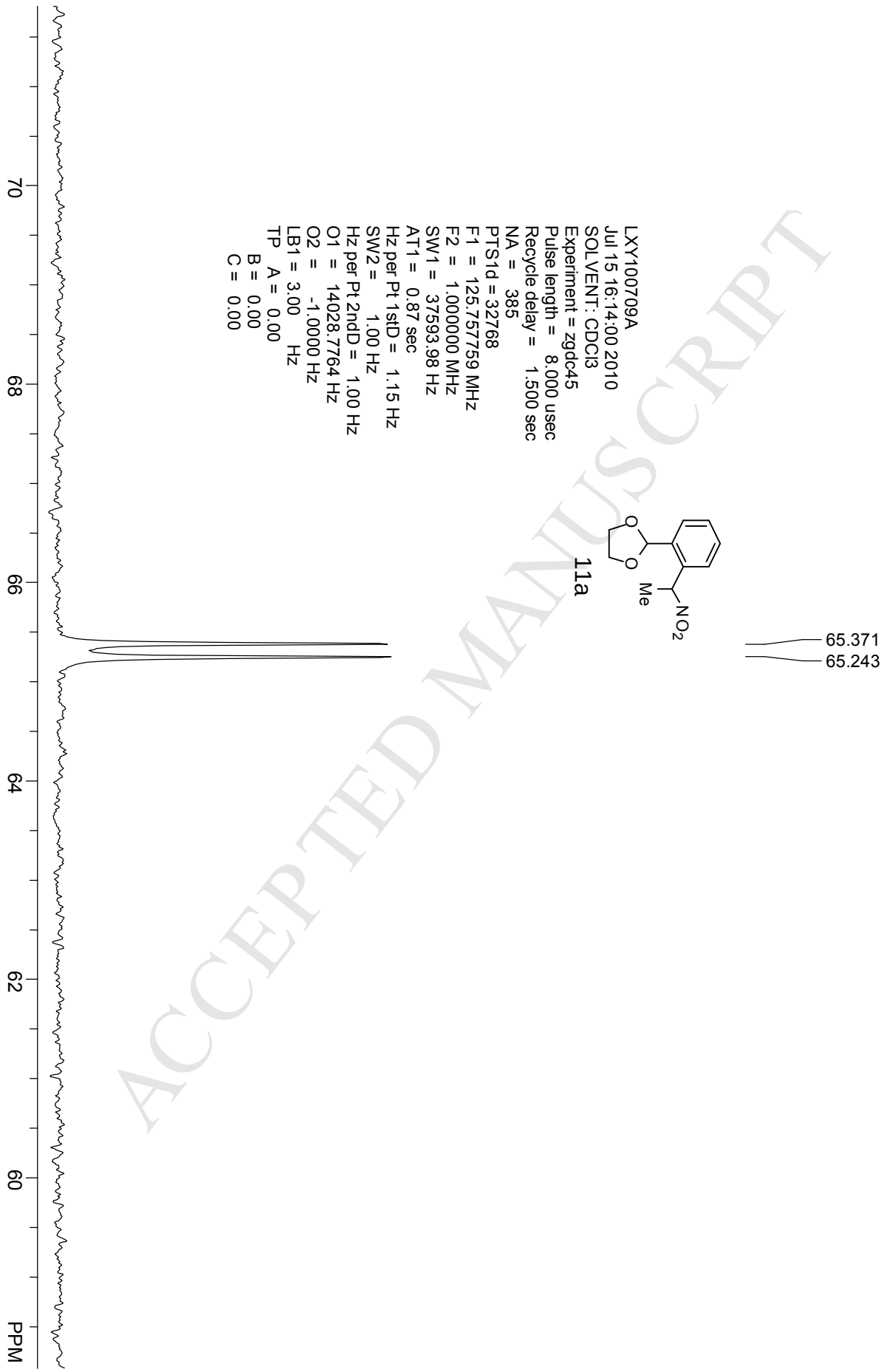
Copies of $^{1}H$ and $^{13}C$ NMR Spectra for Compounds **11a**–**l**, **12a**–**l**, **13a**–**l**, and **22a**–**c**.

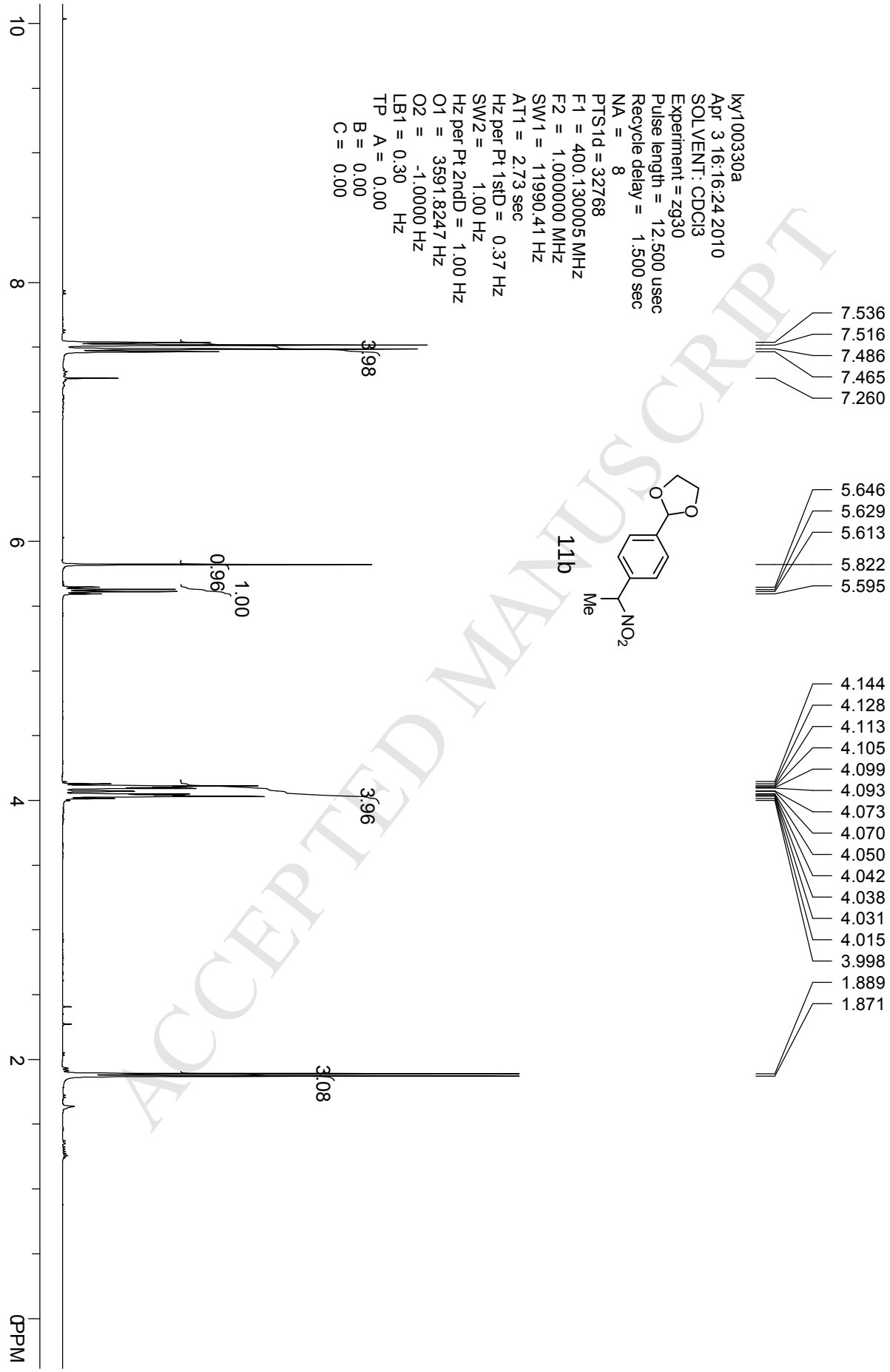


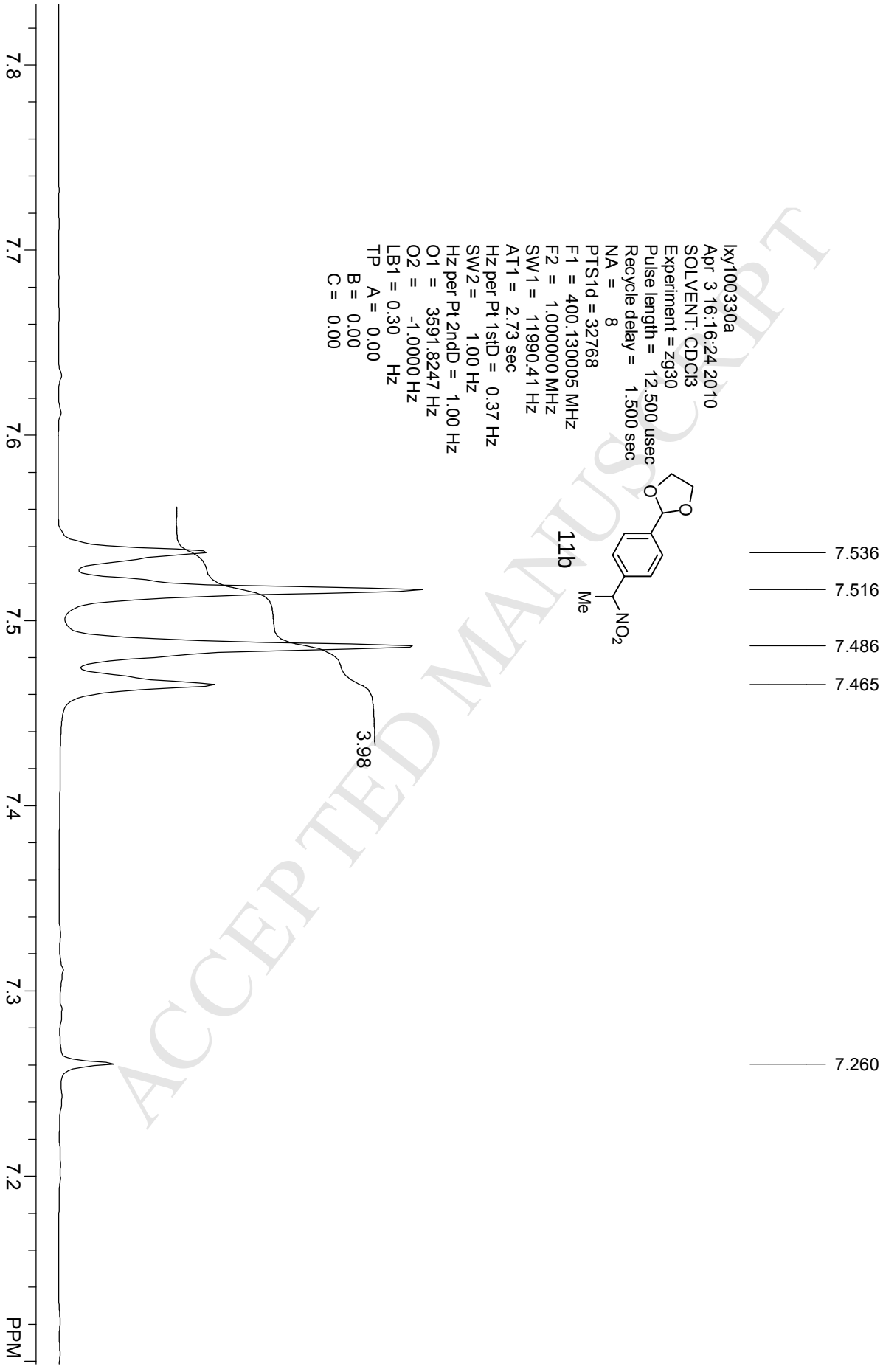


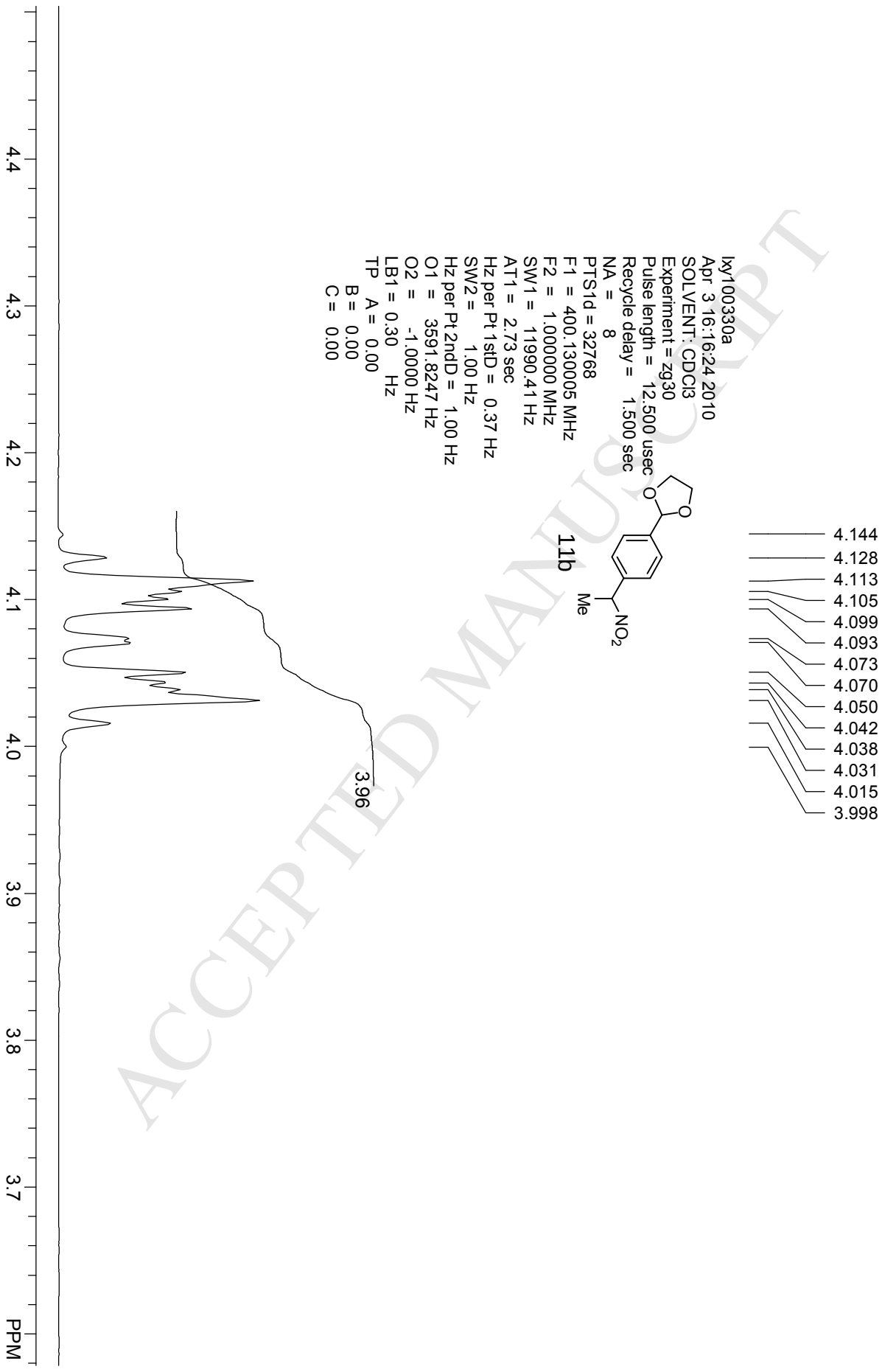


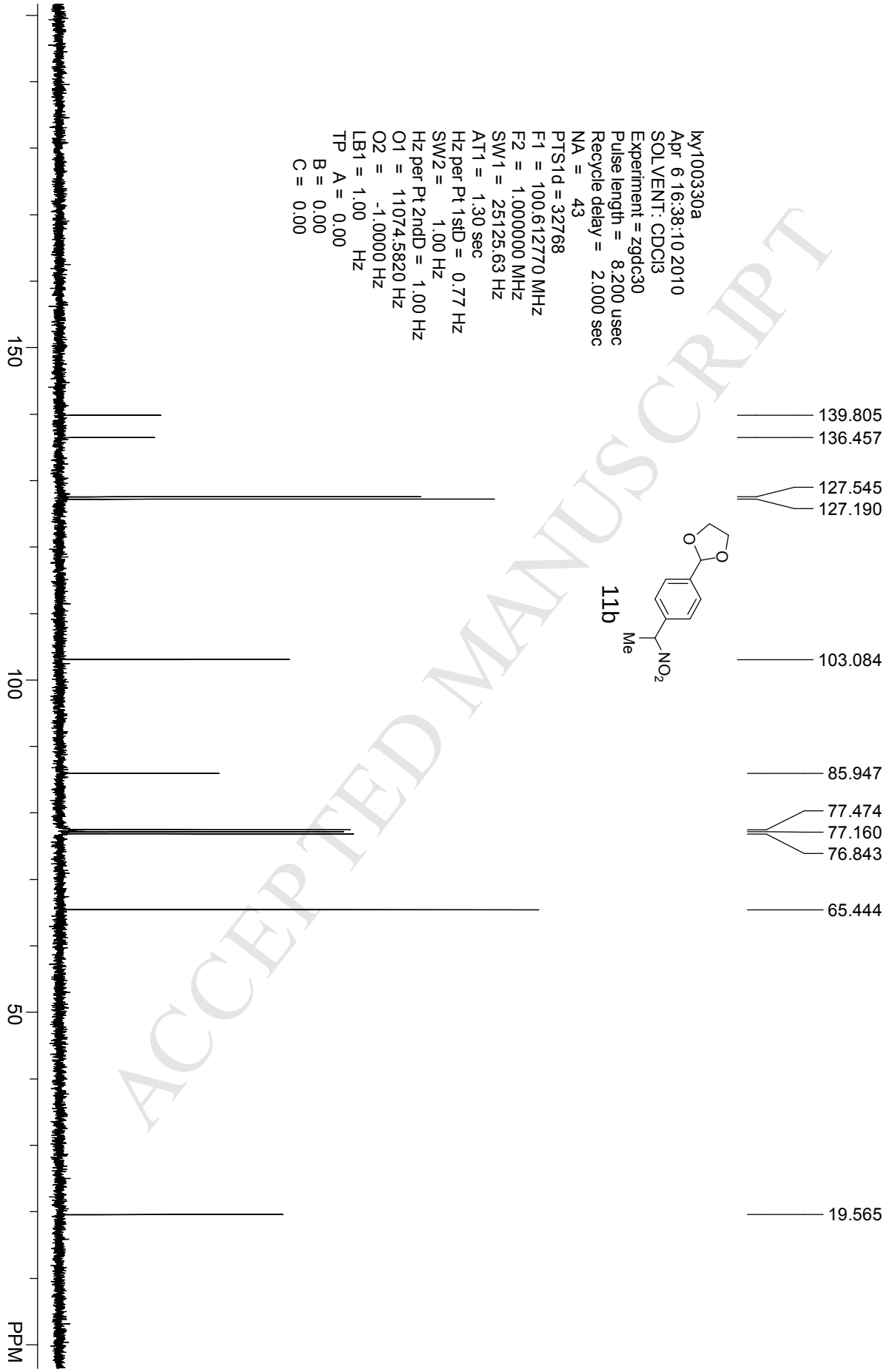


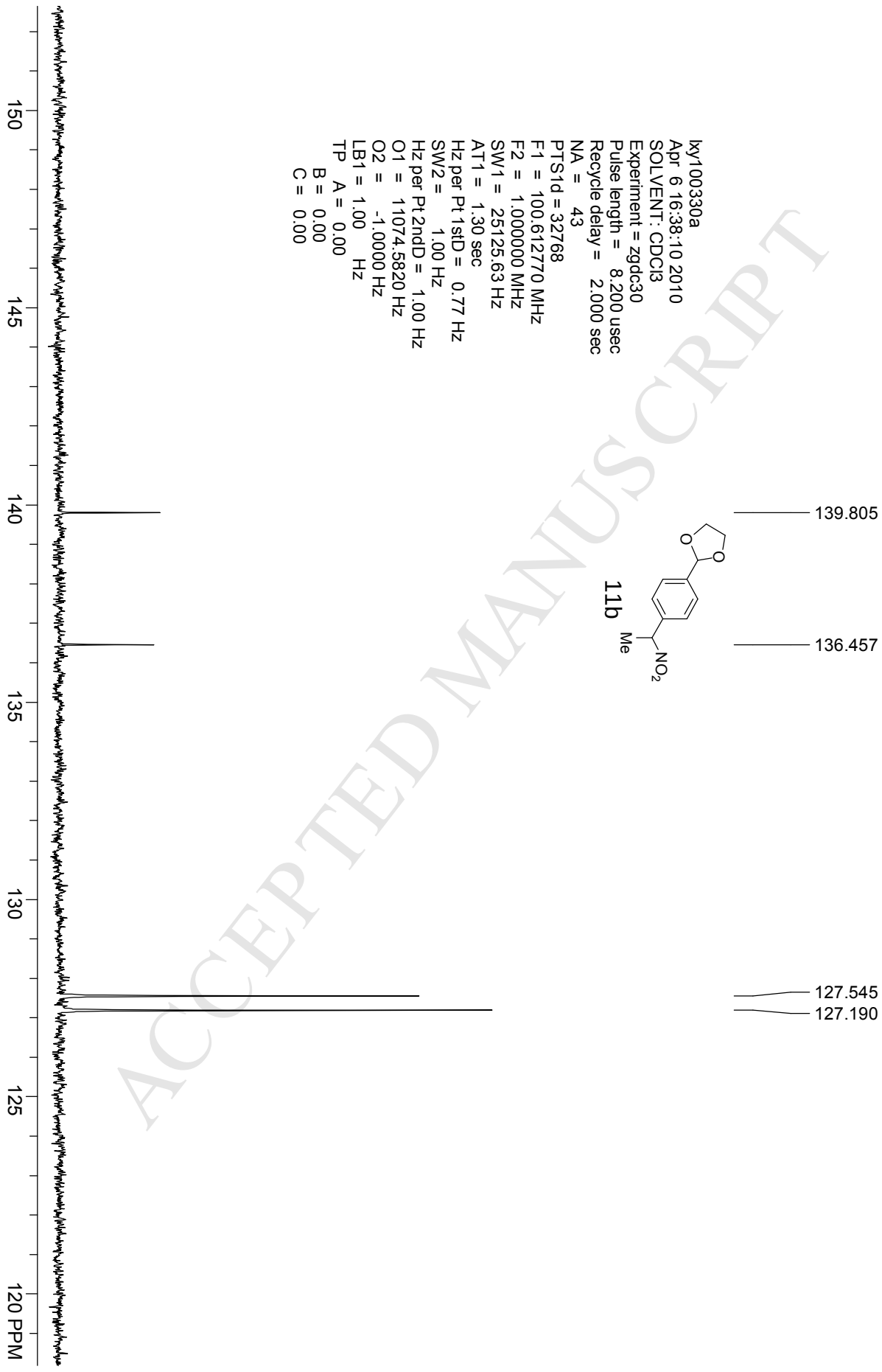


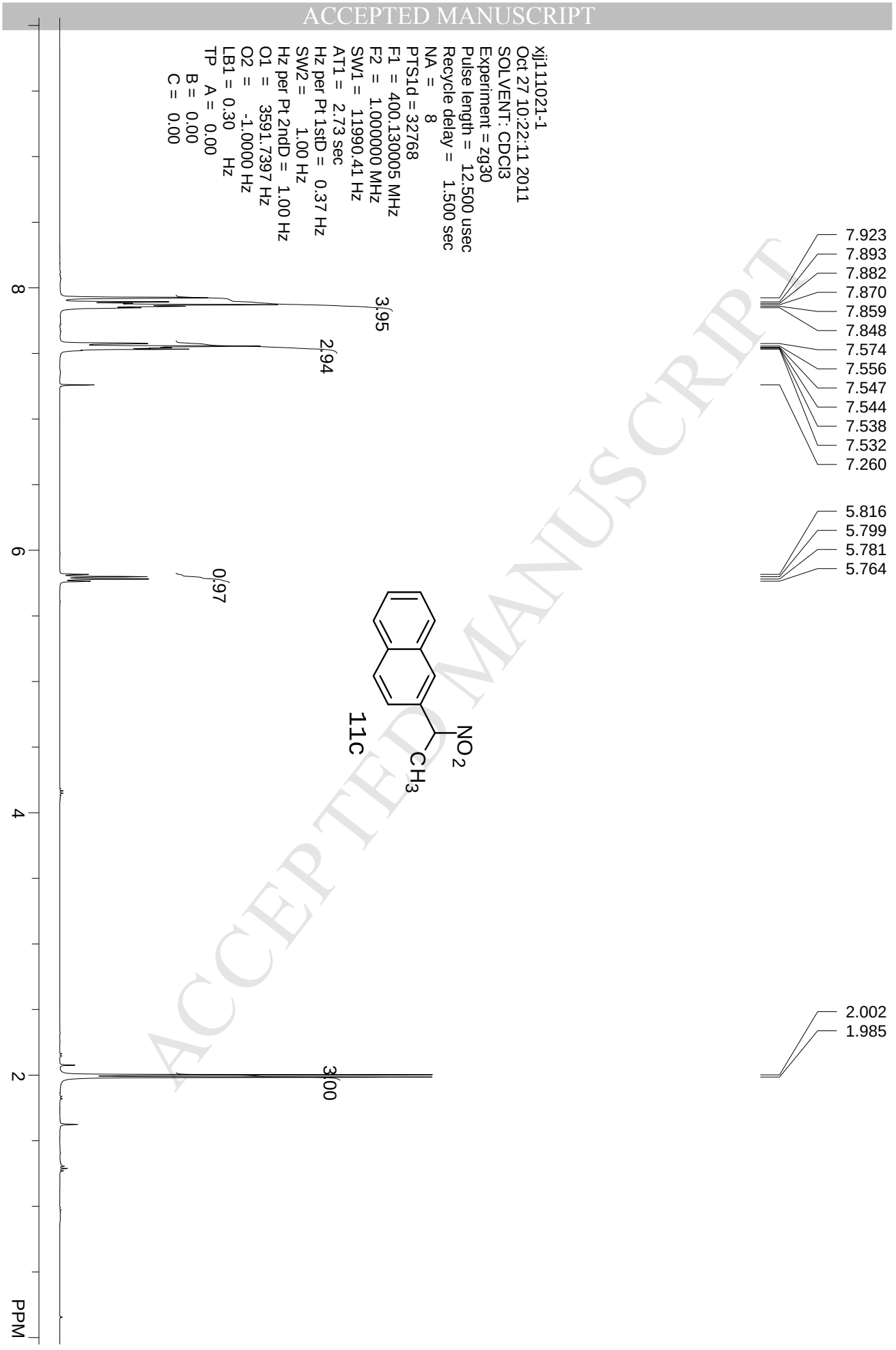


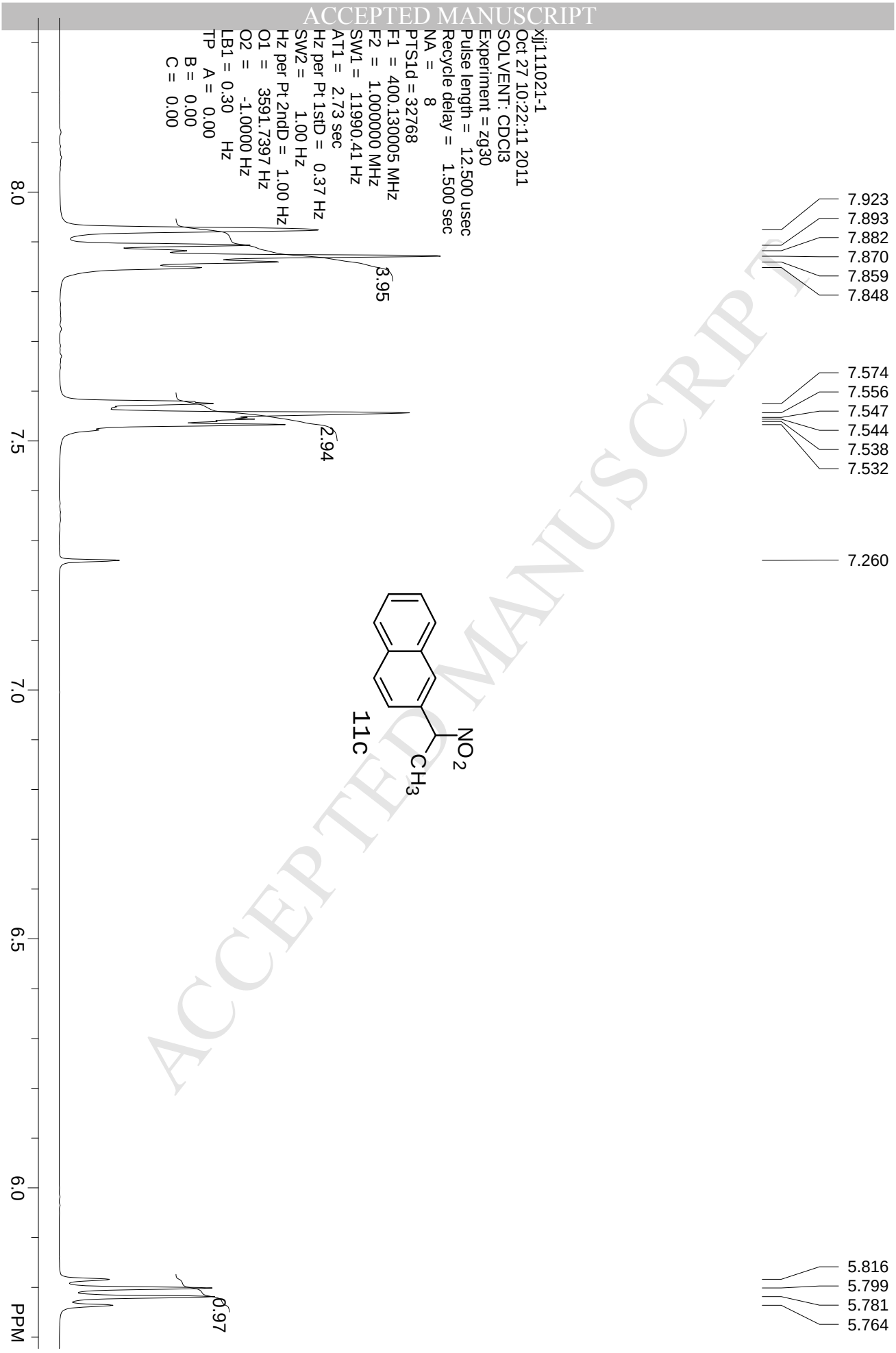


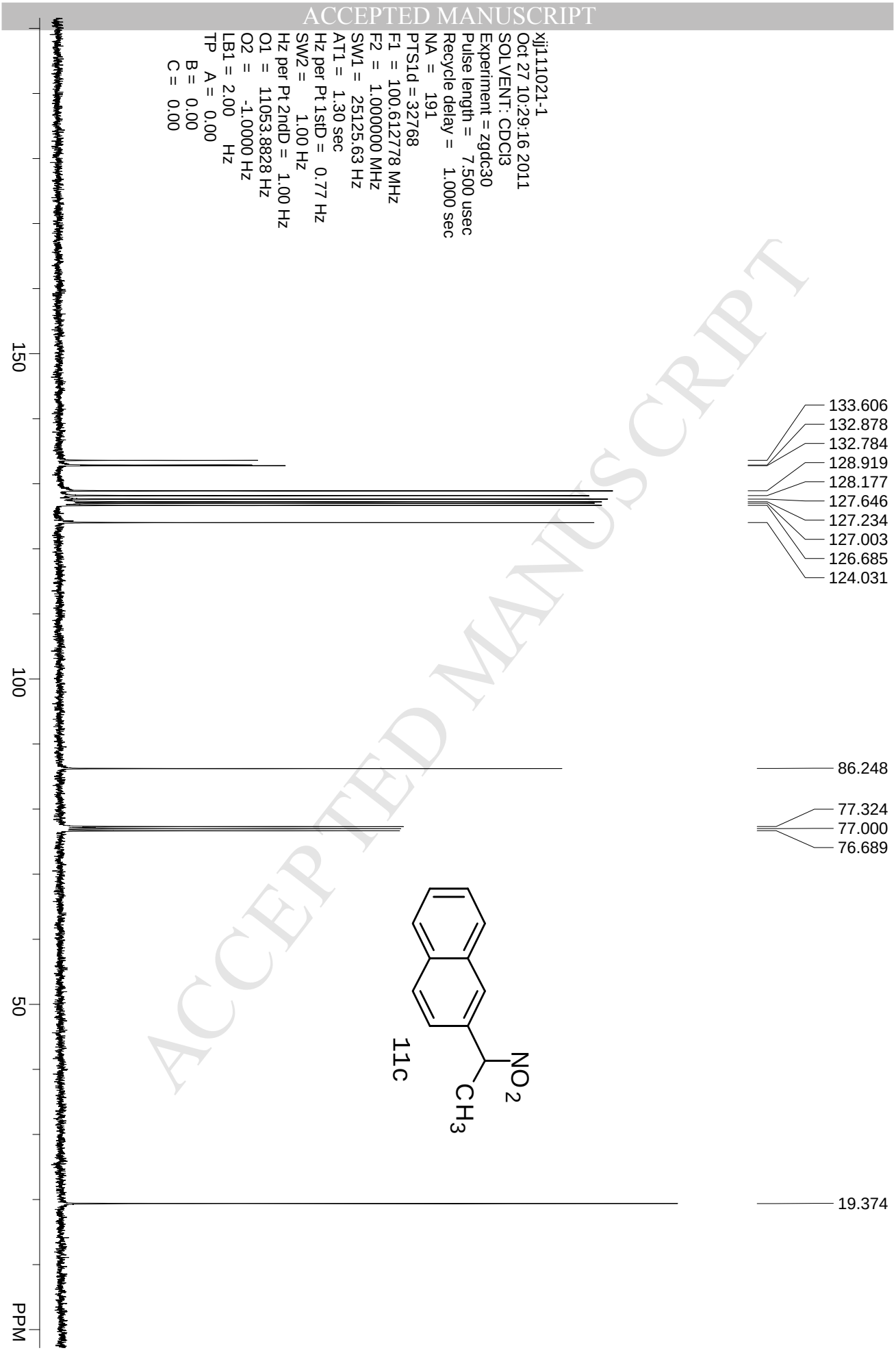


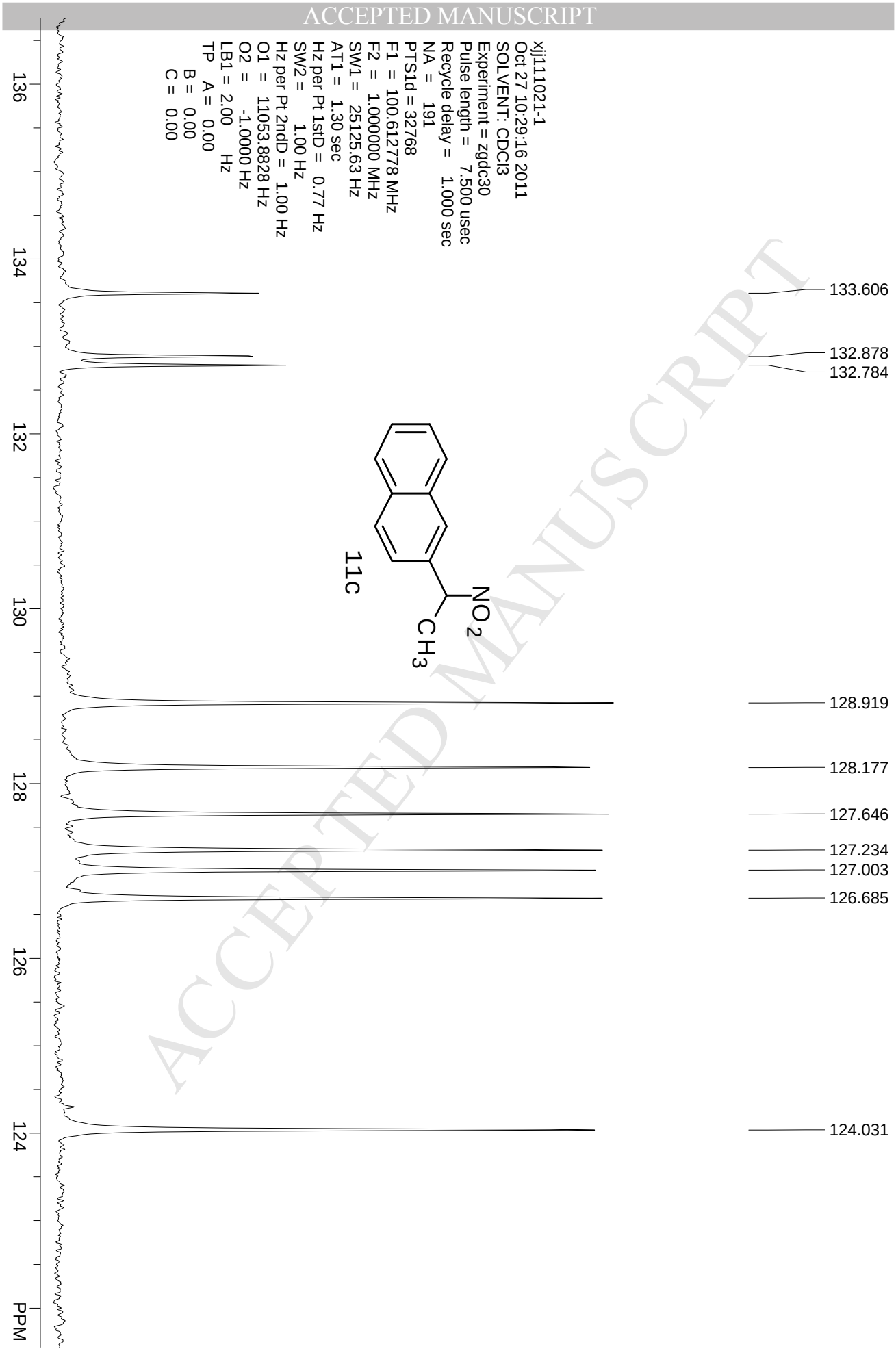


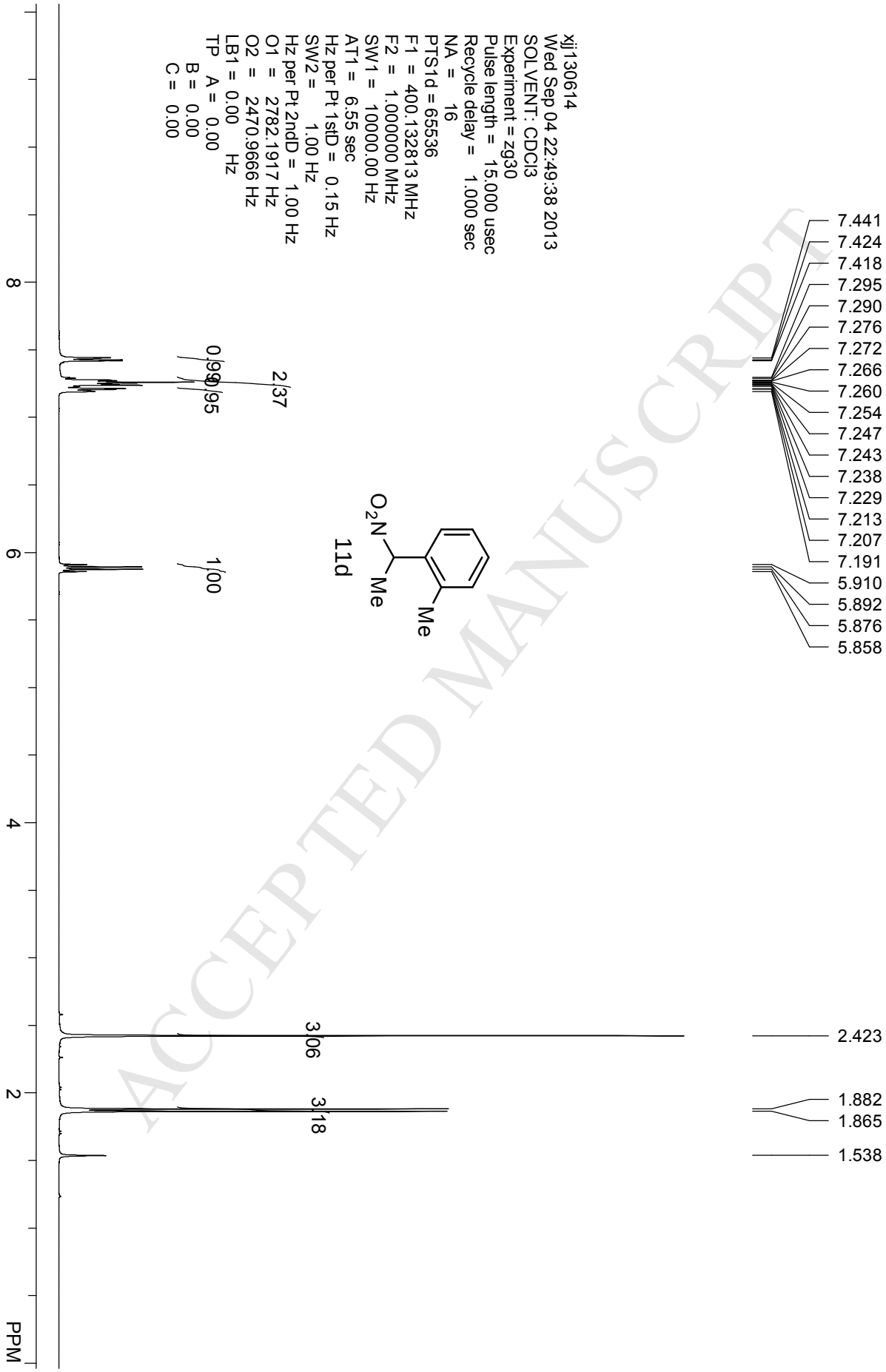


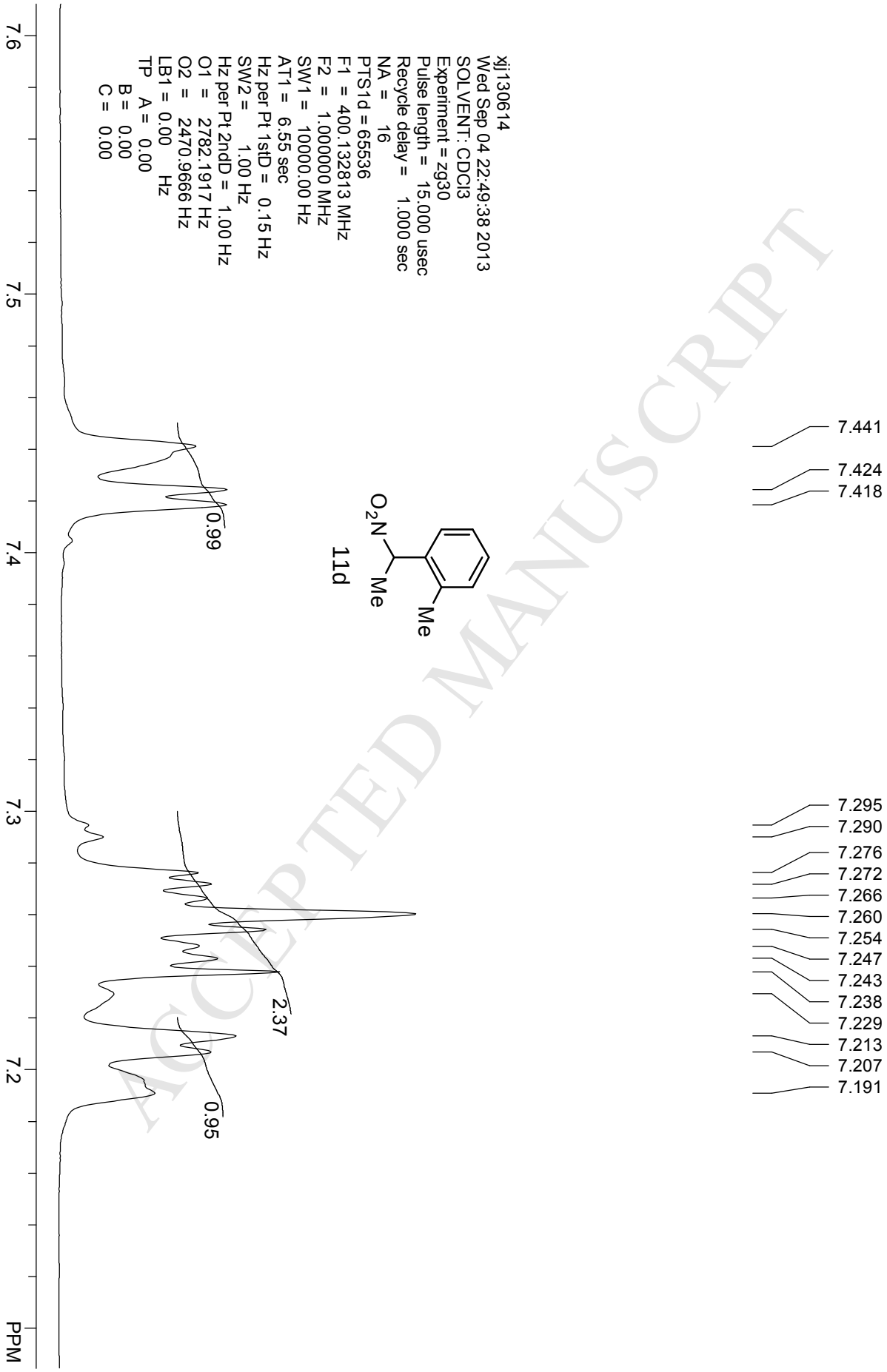


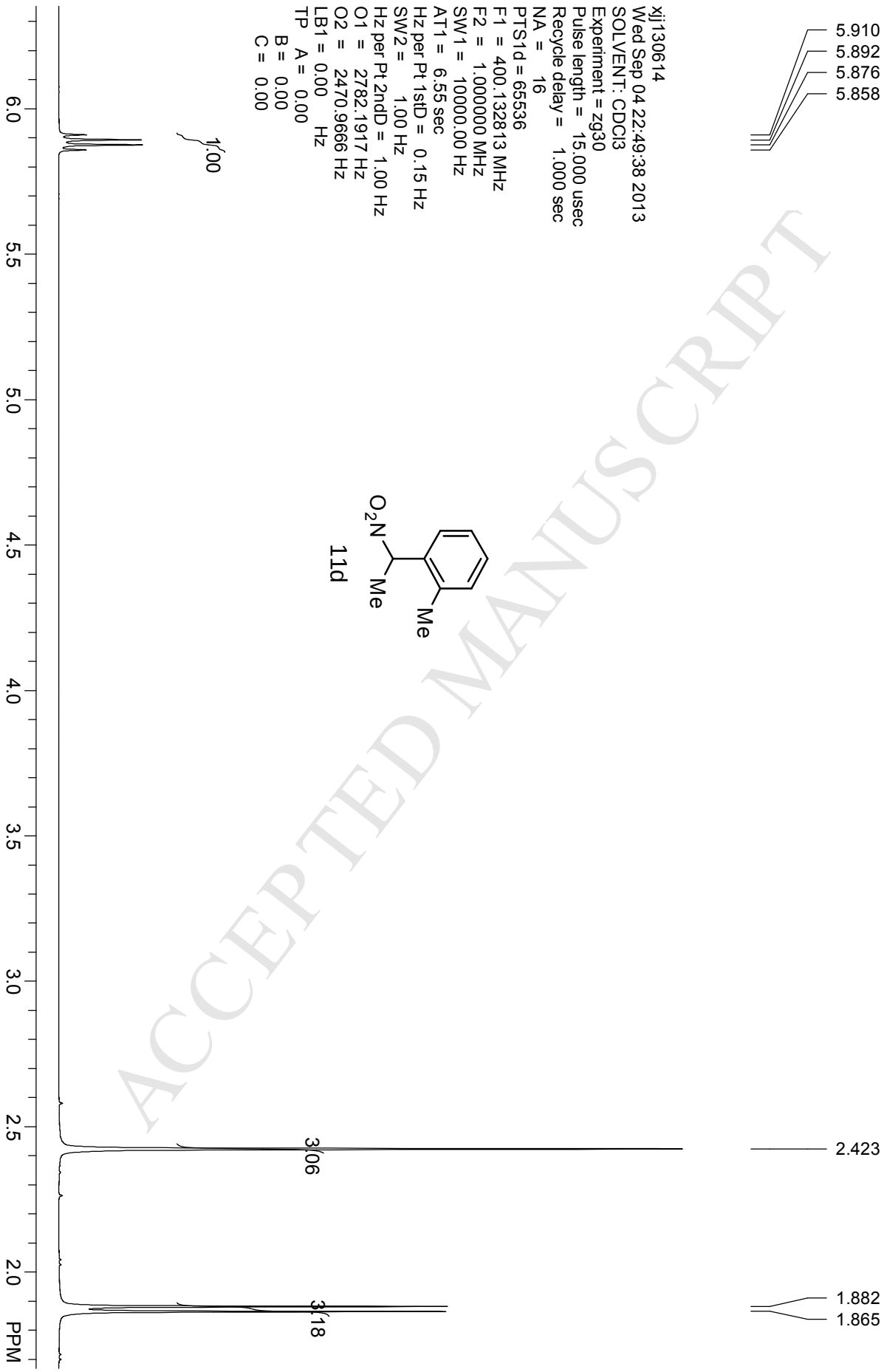












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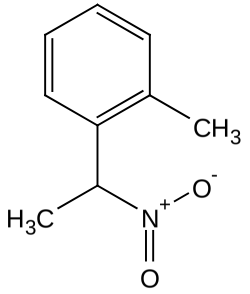


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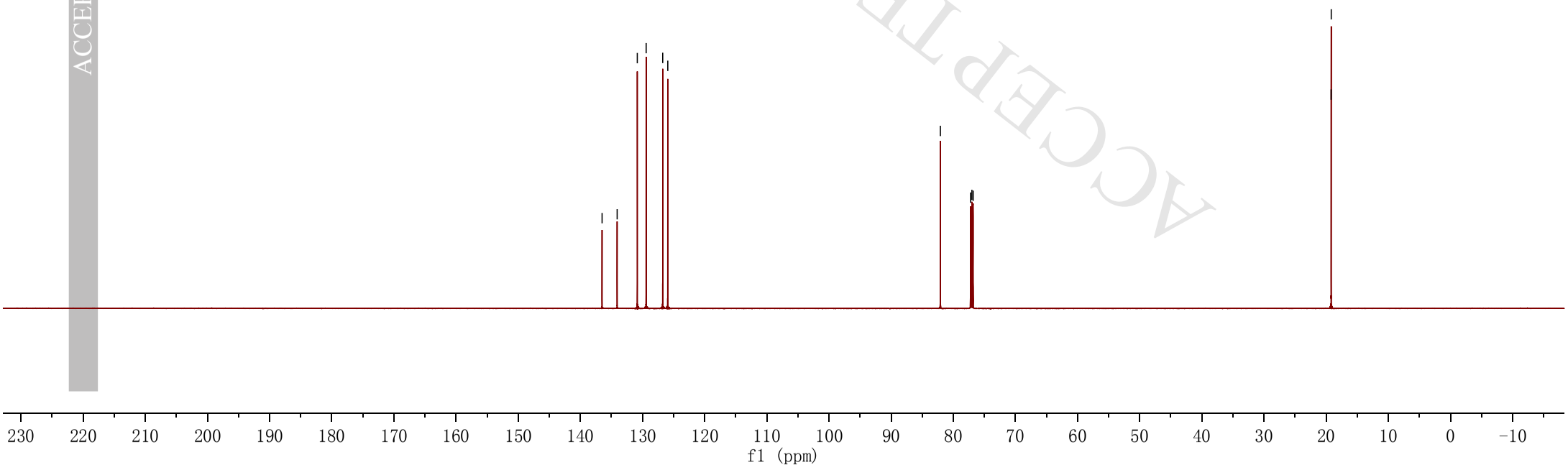

| | Parameter | Value |
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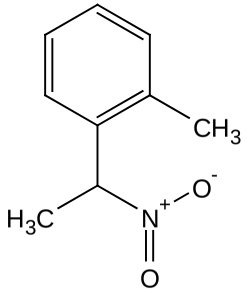


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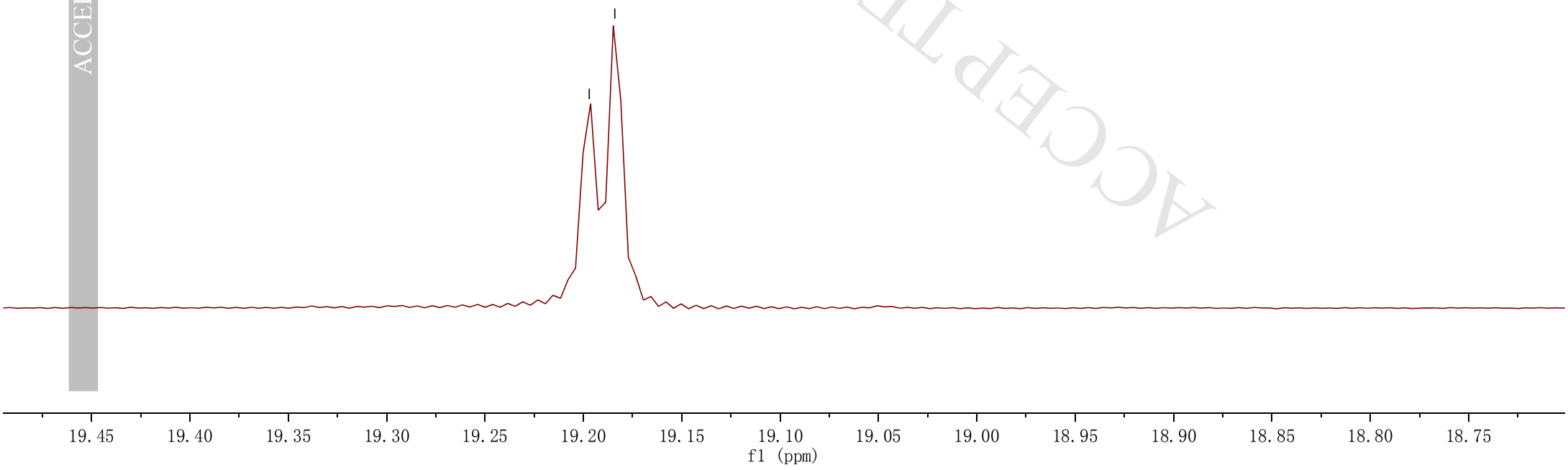

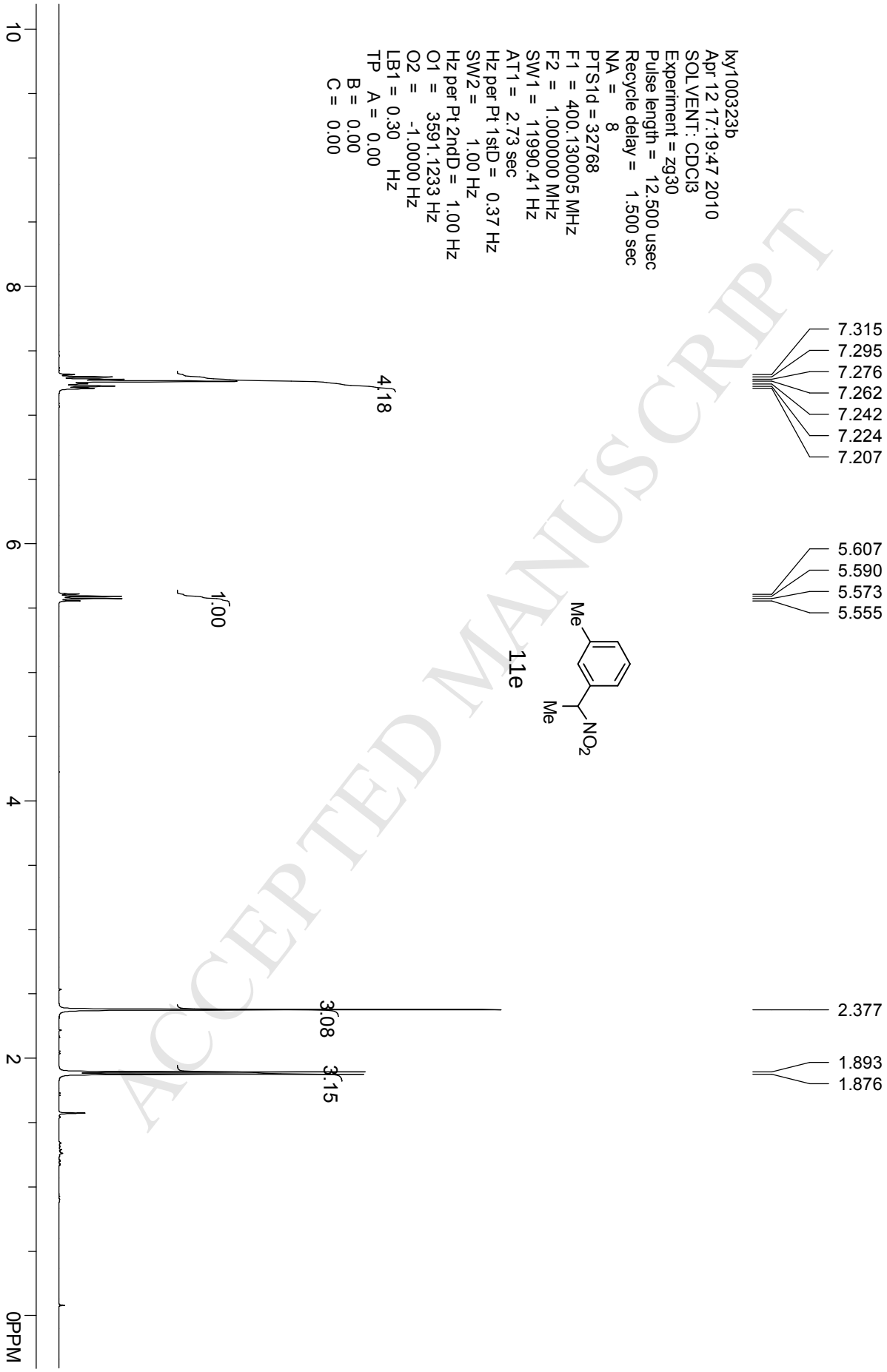

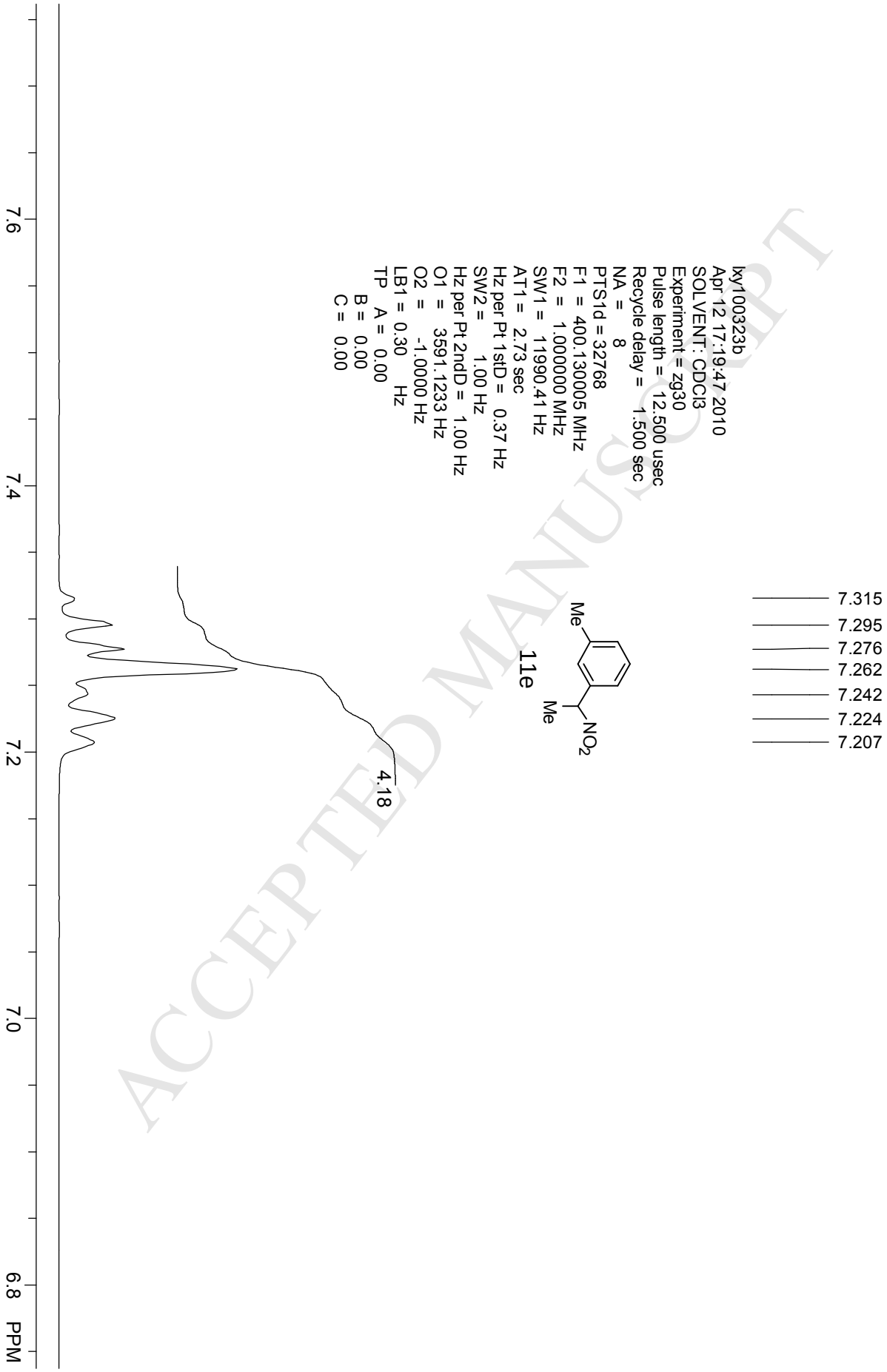

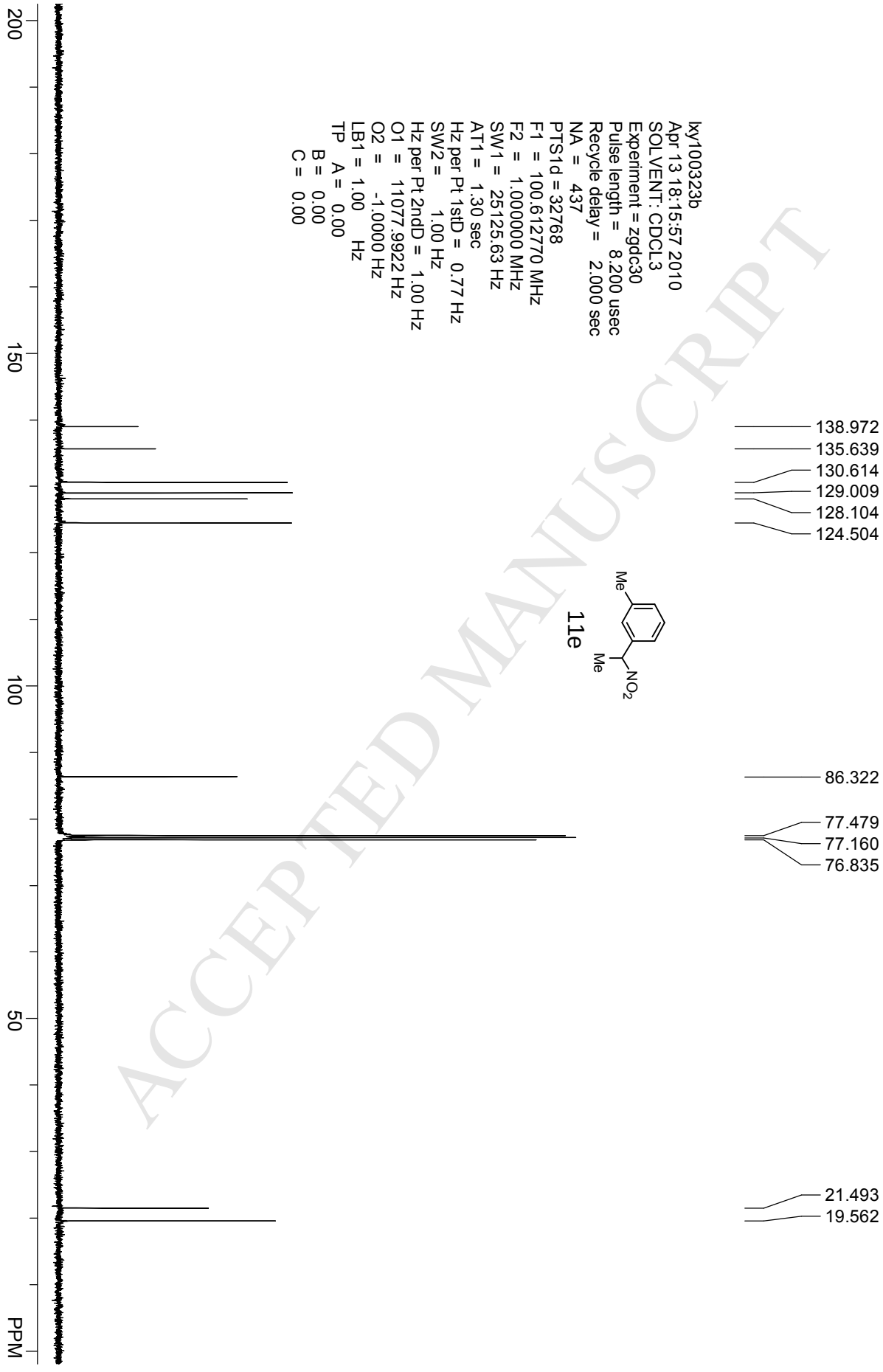

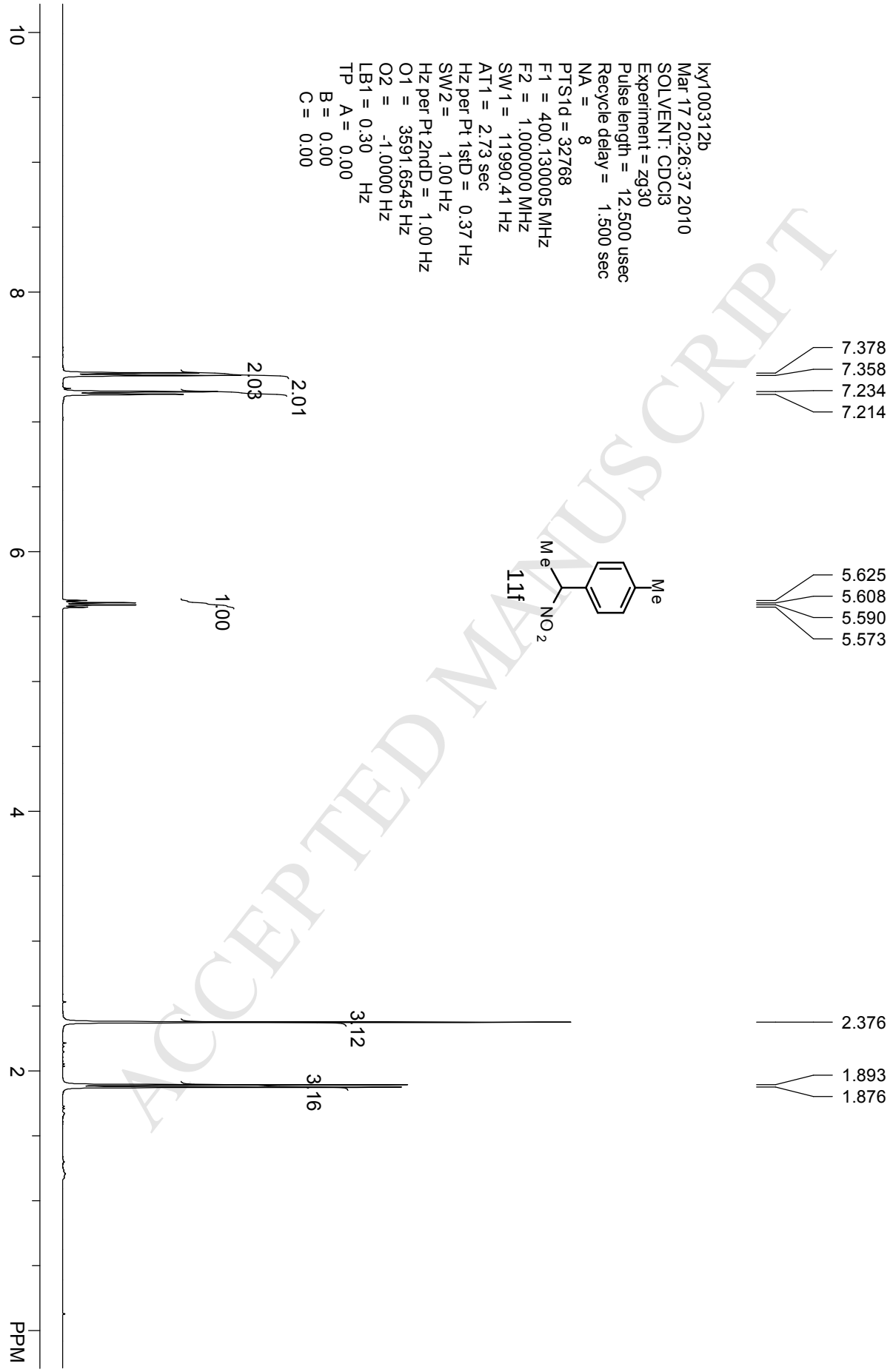

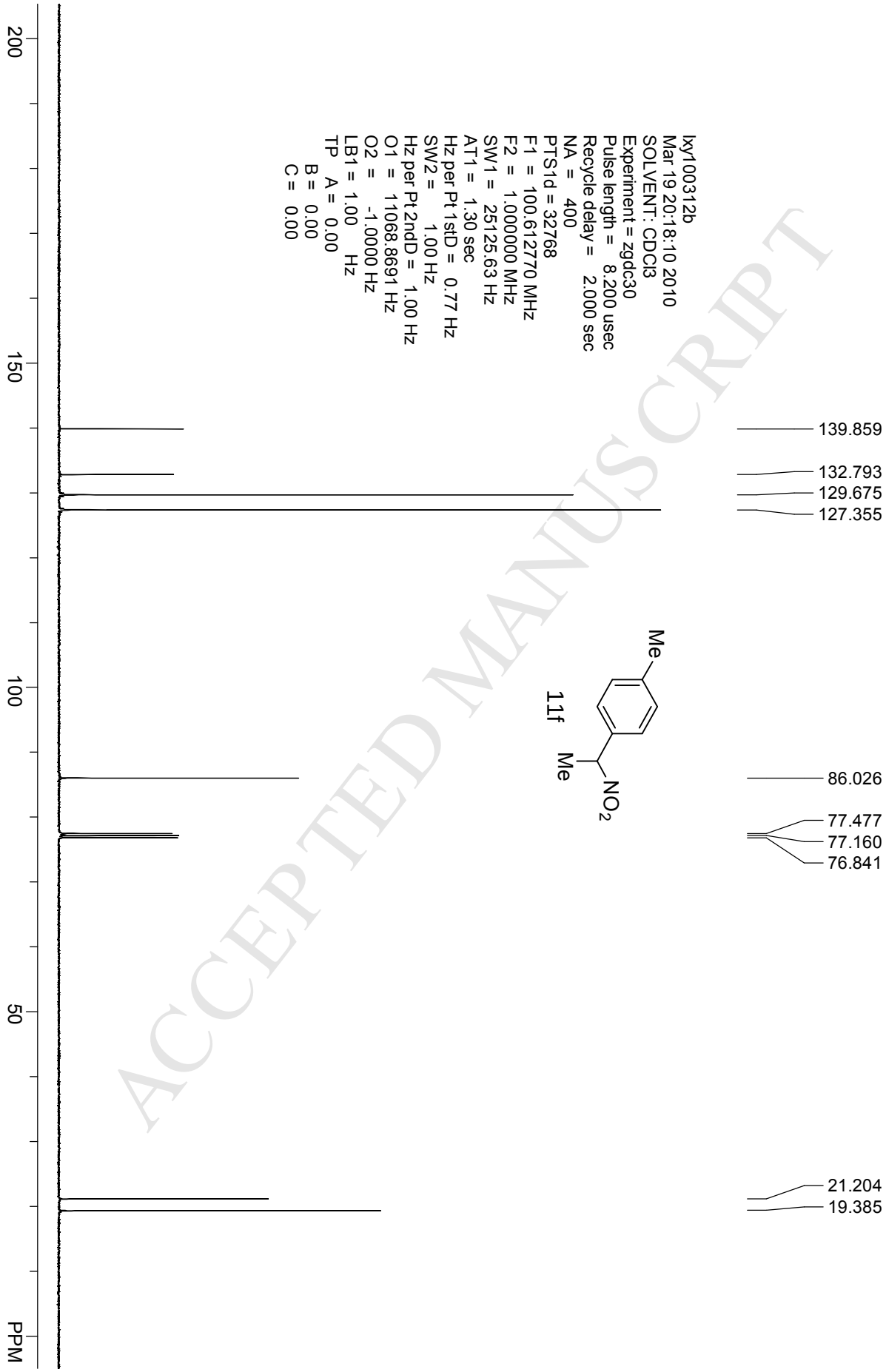

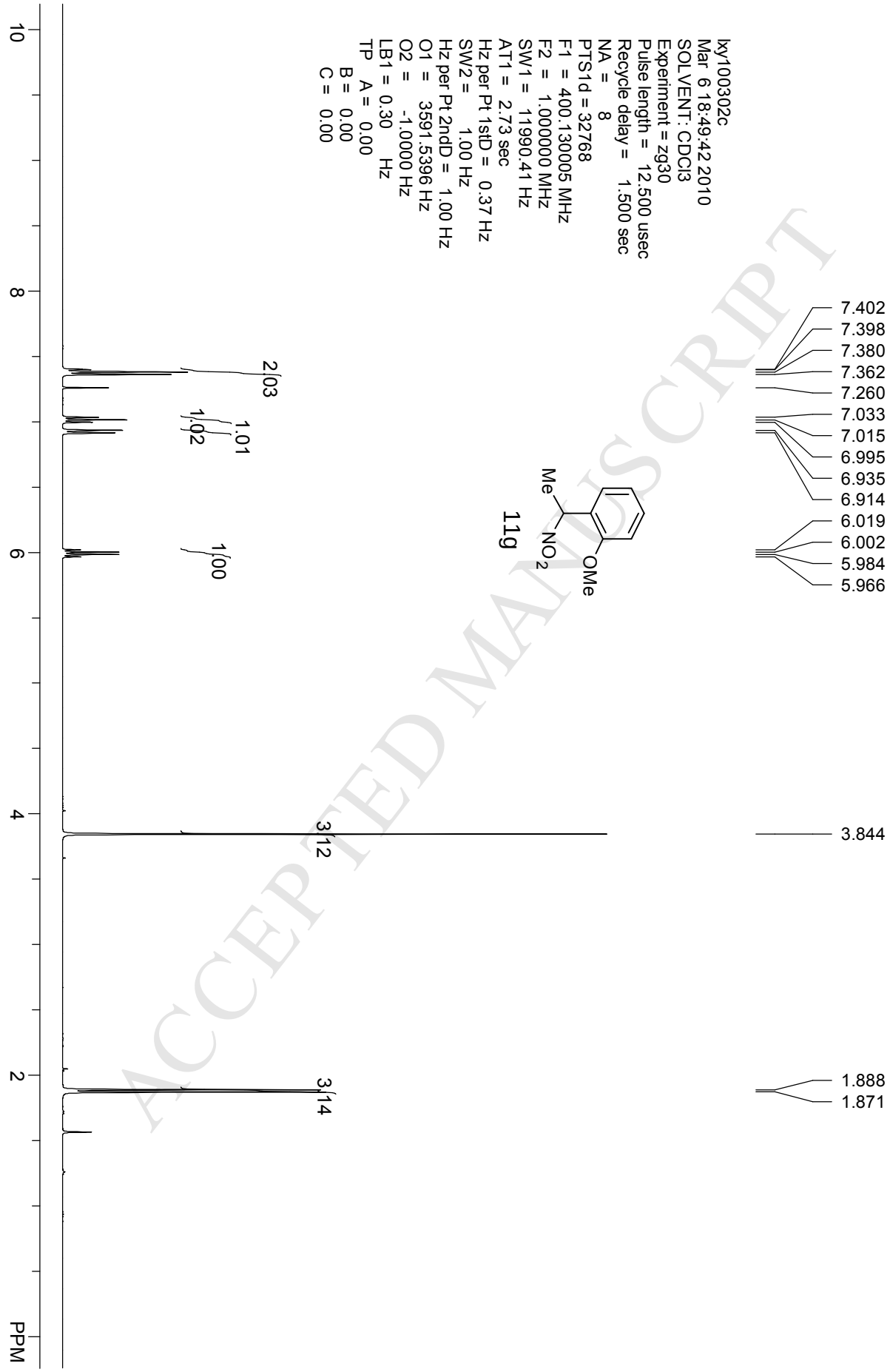

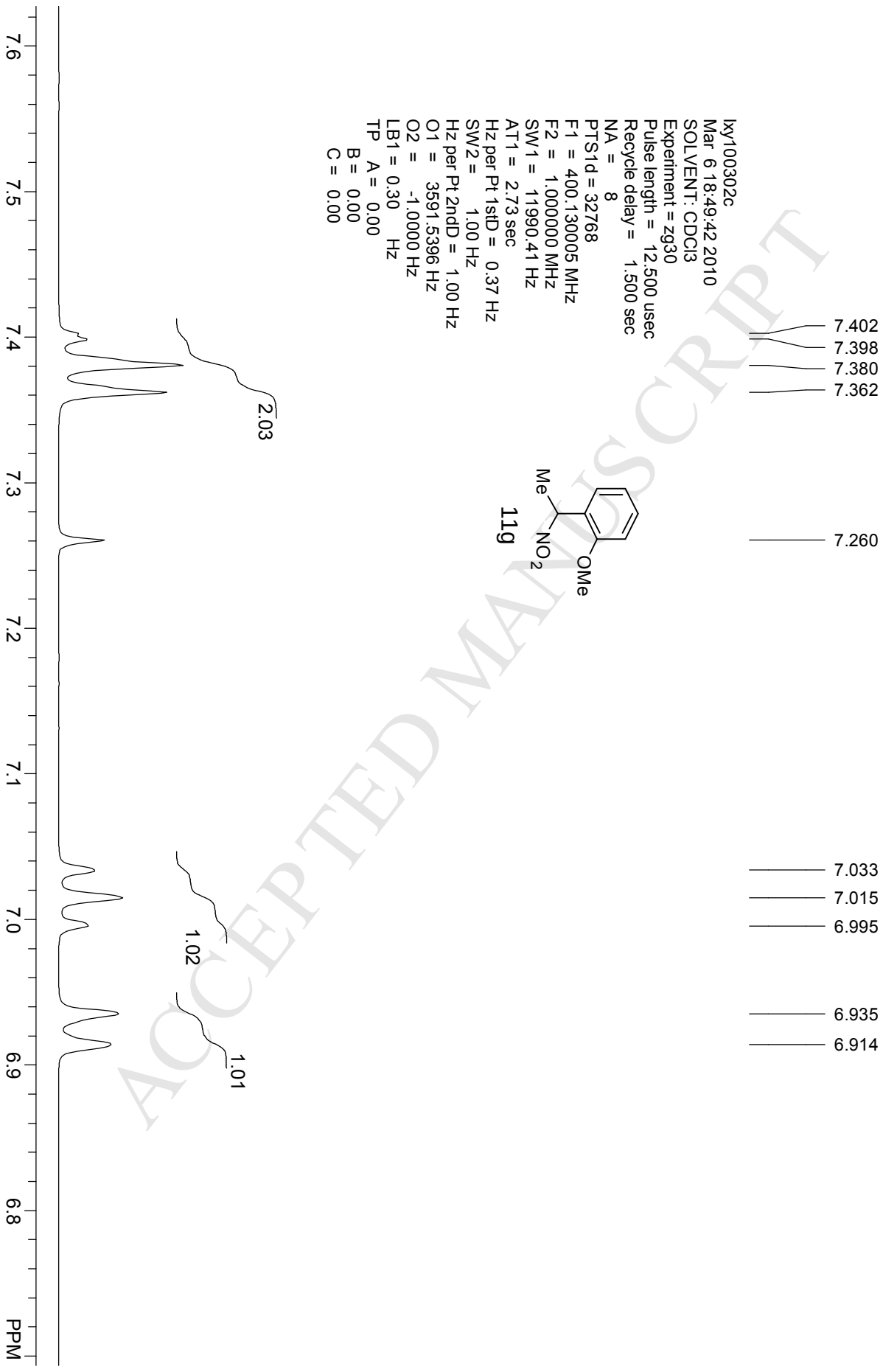

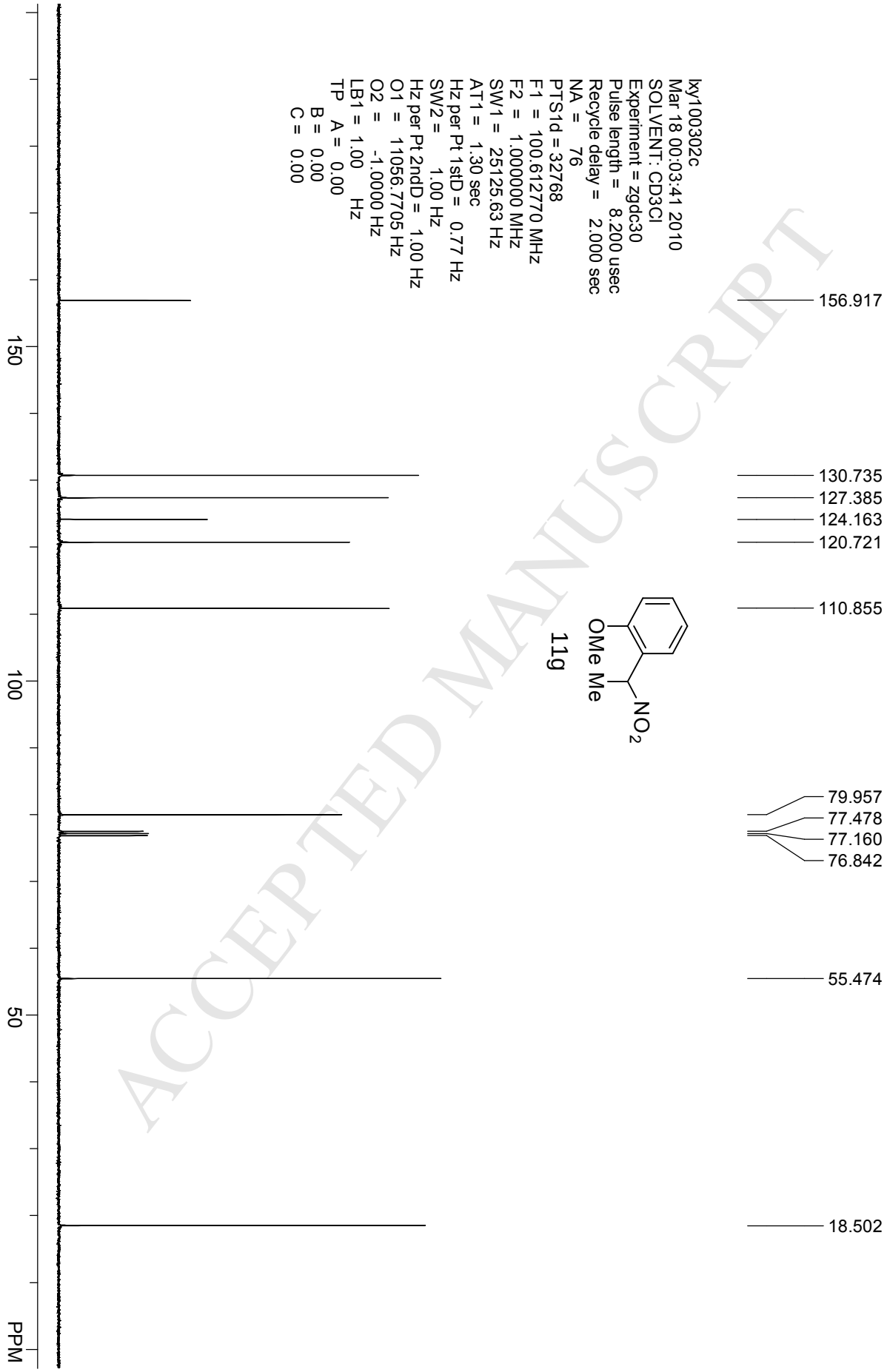

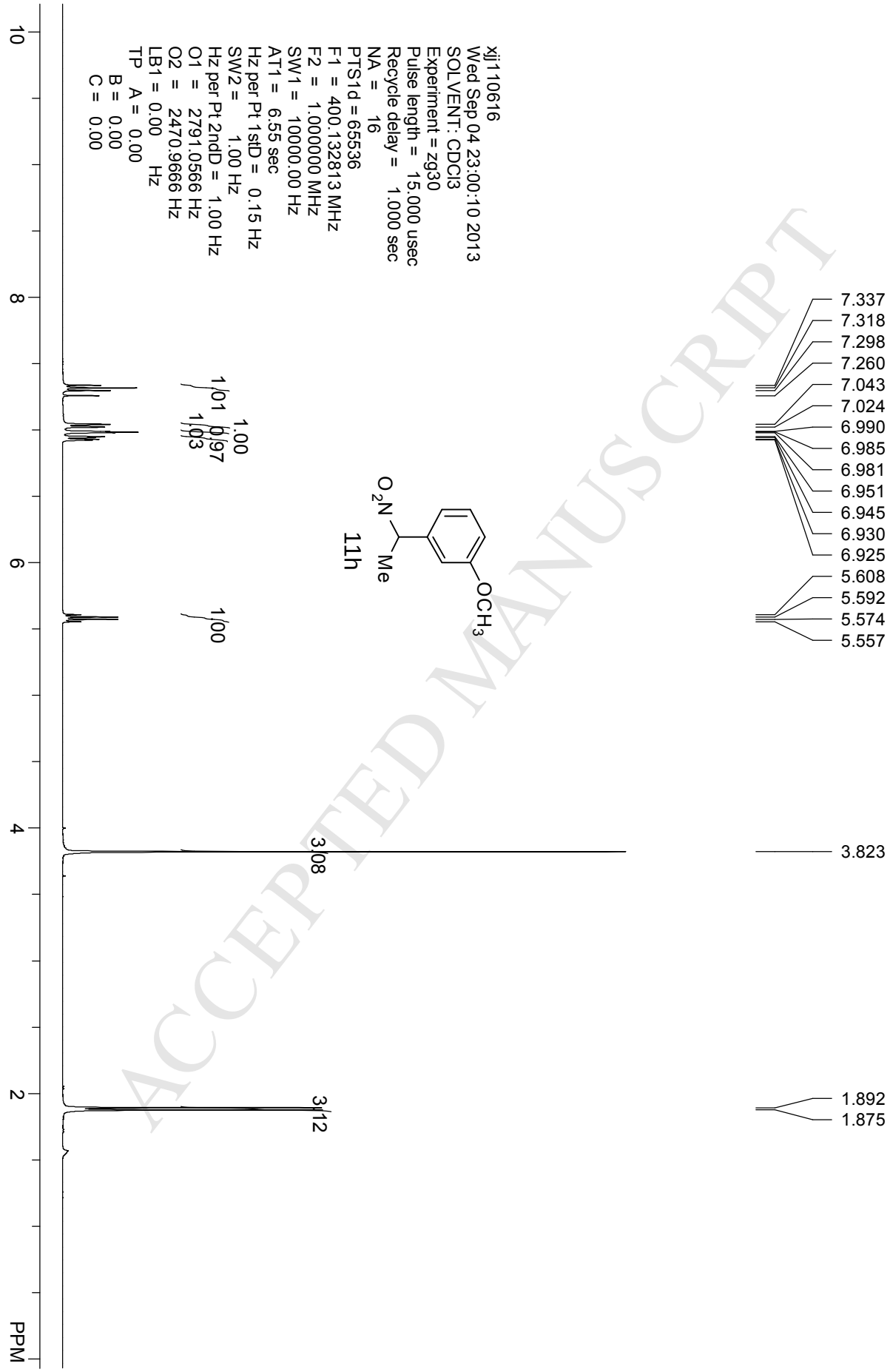

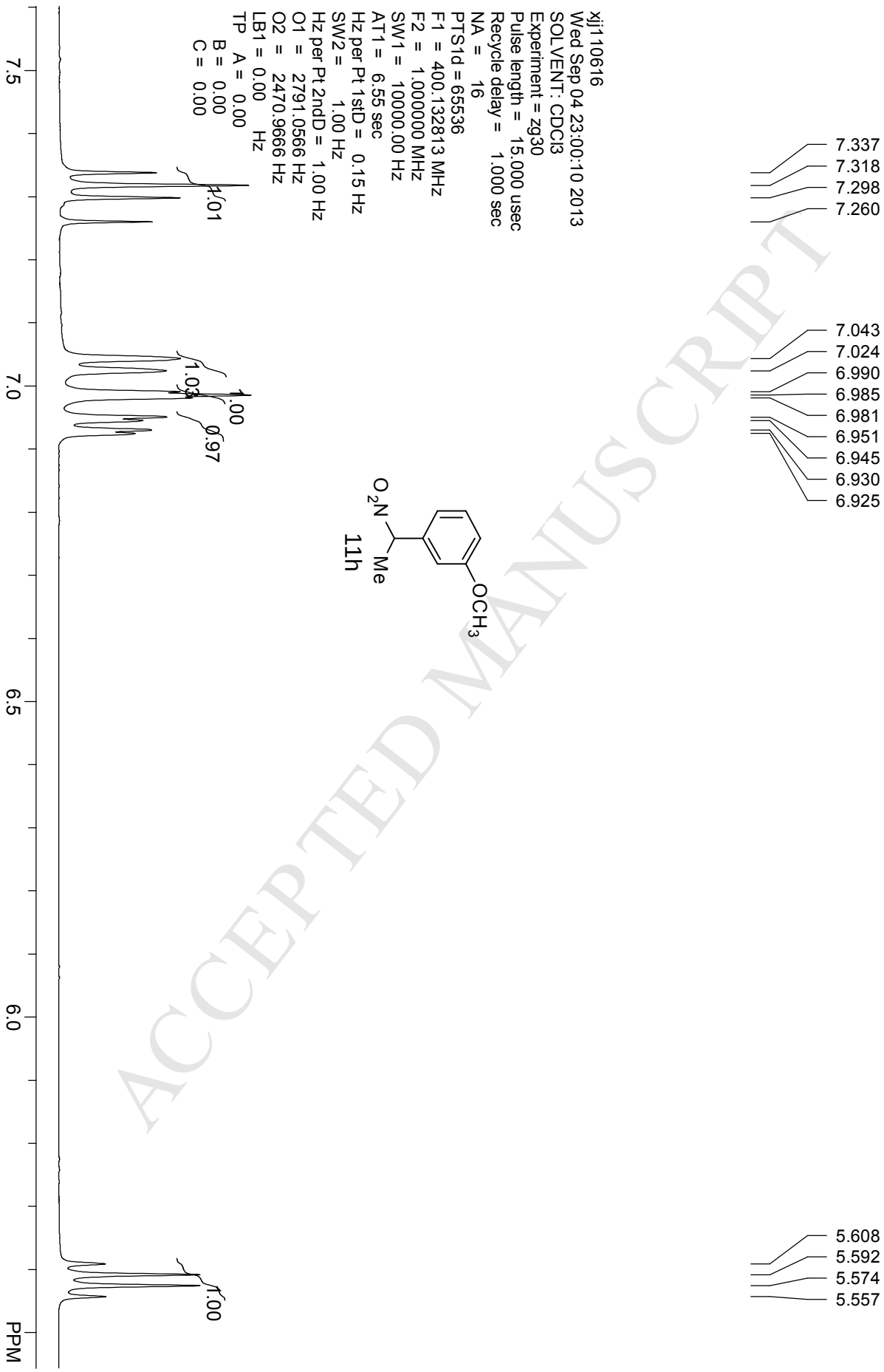

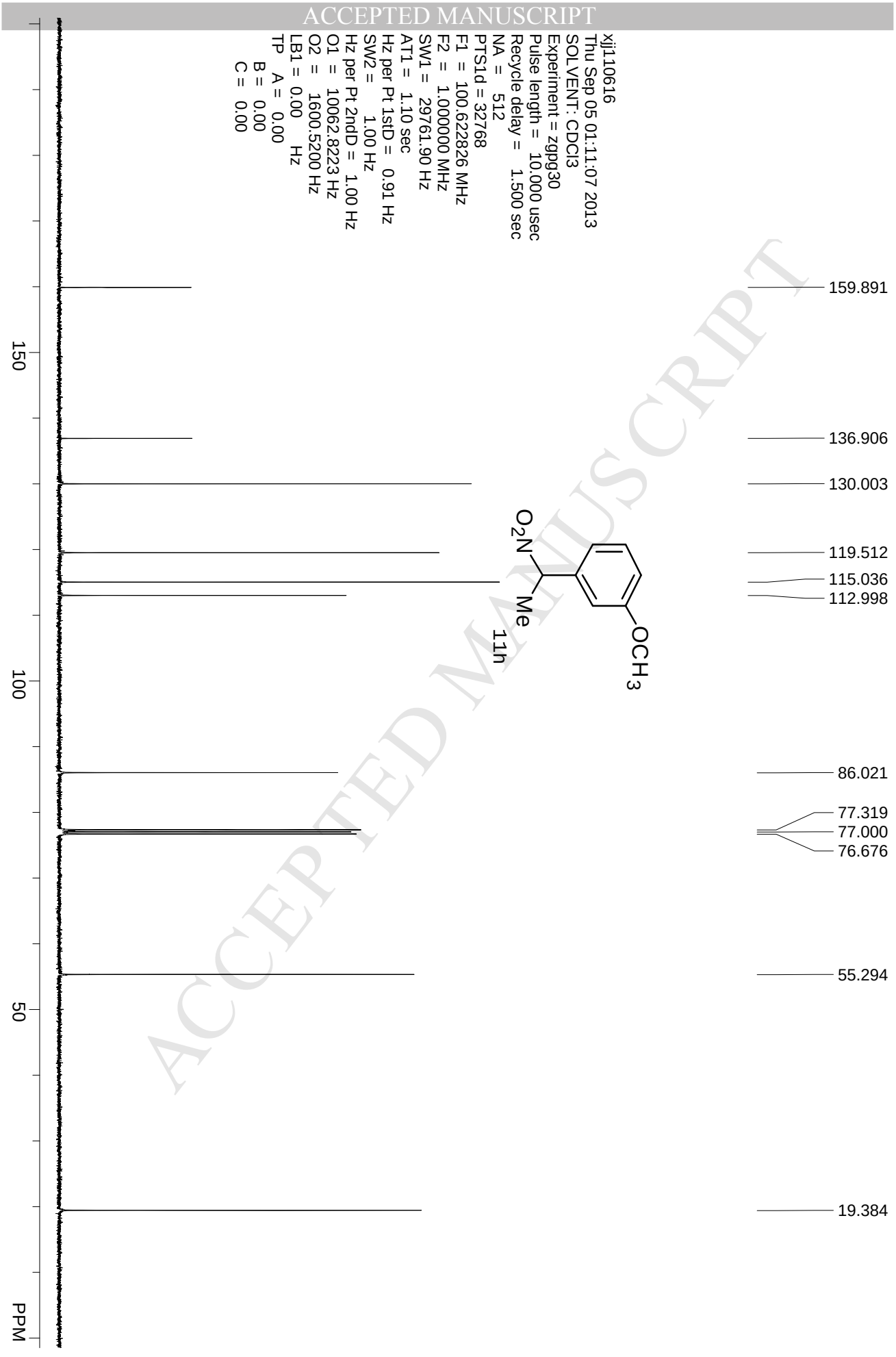

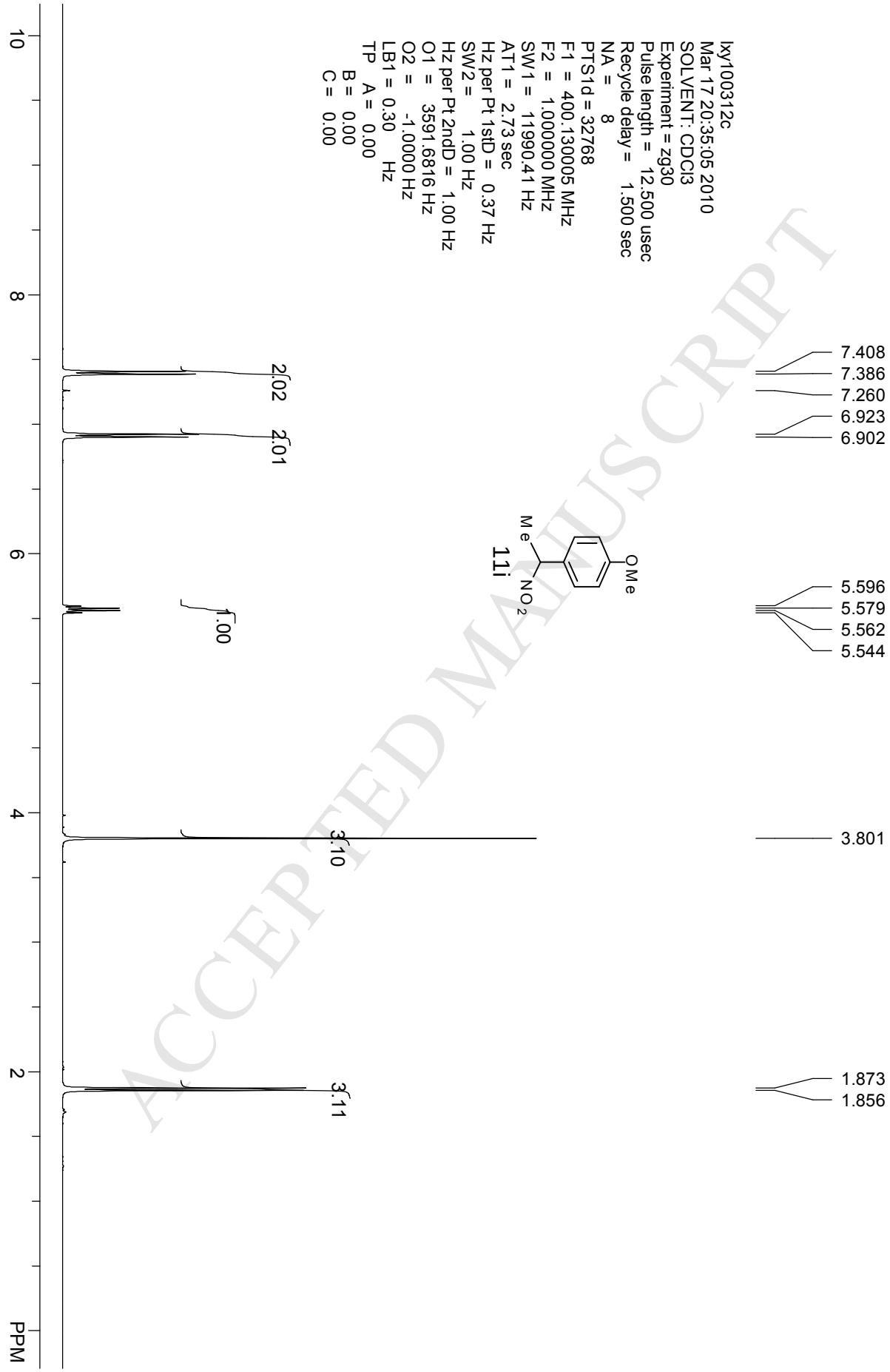

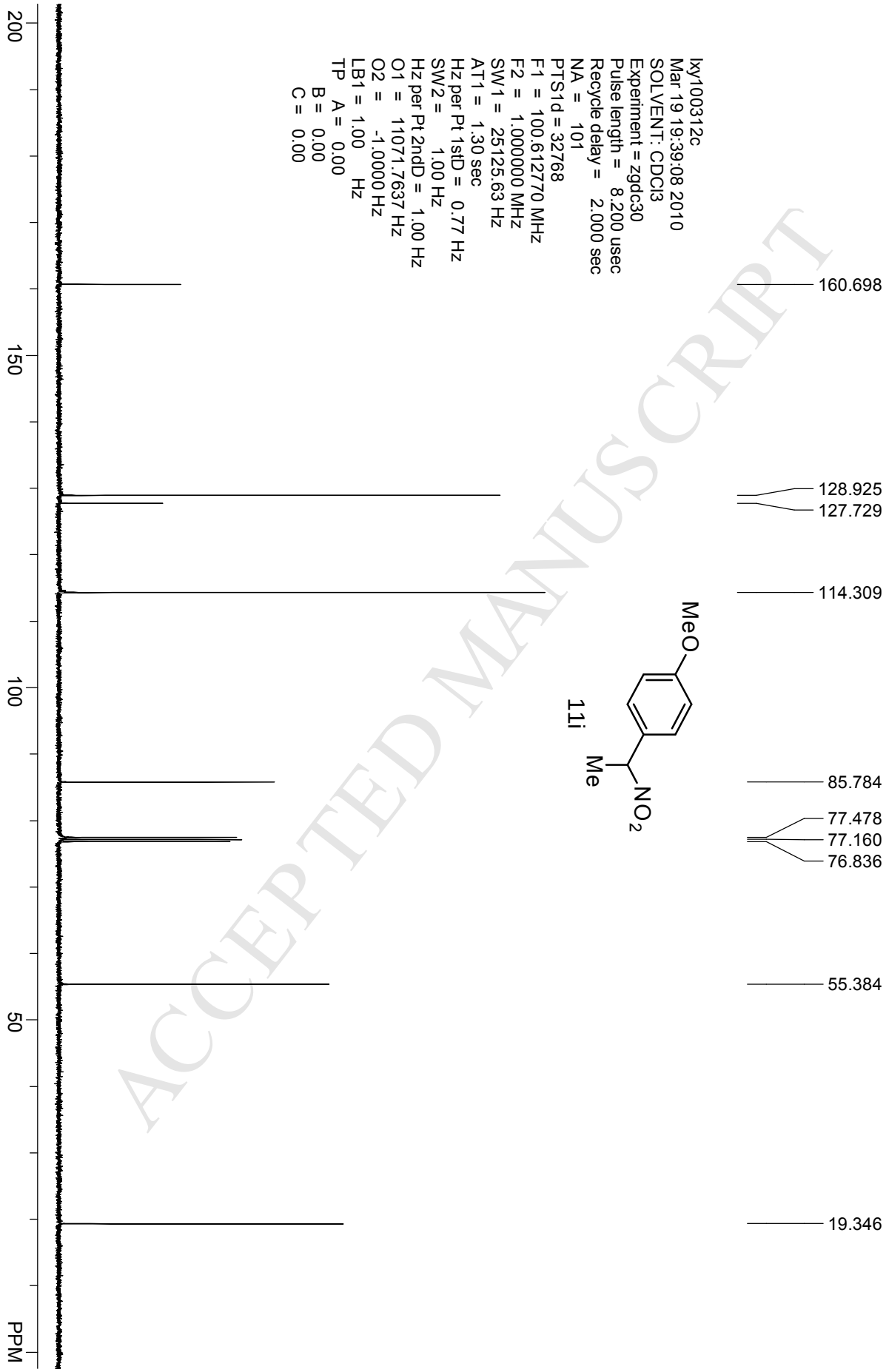

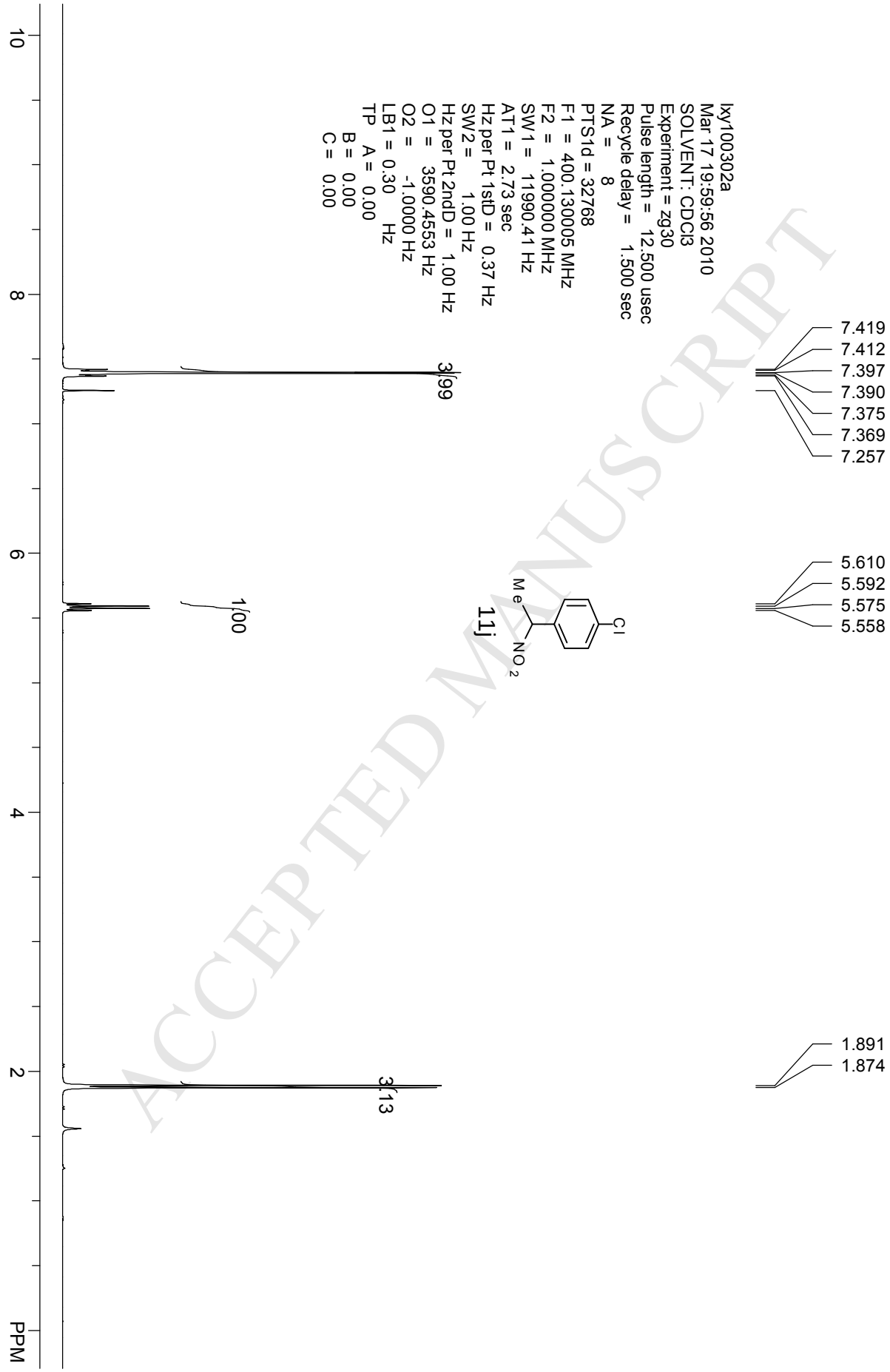

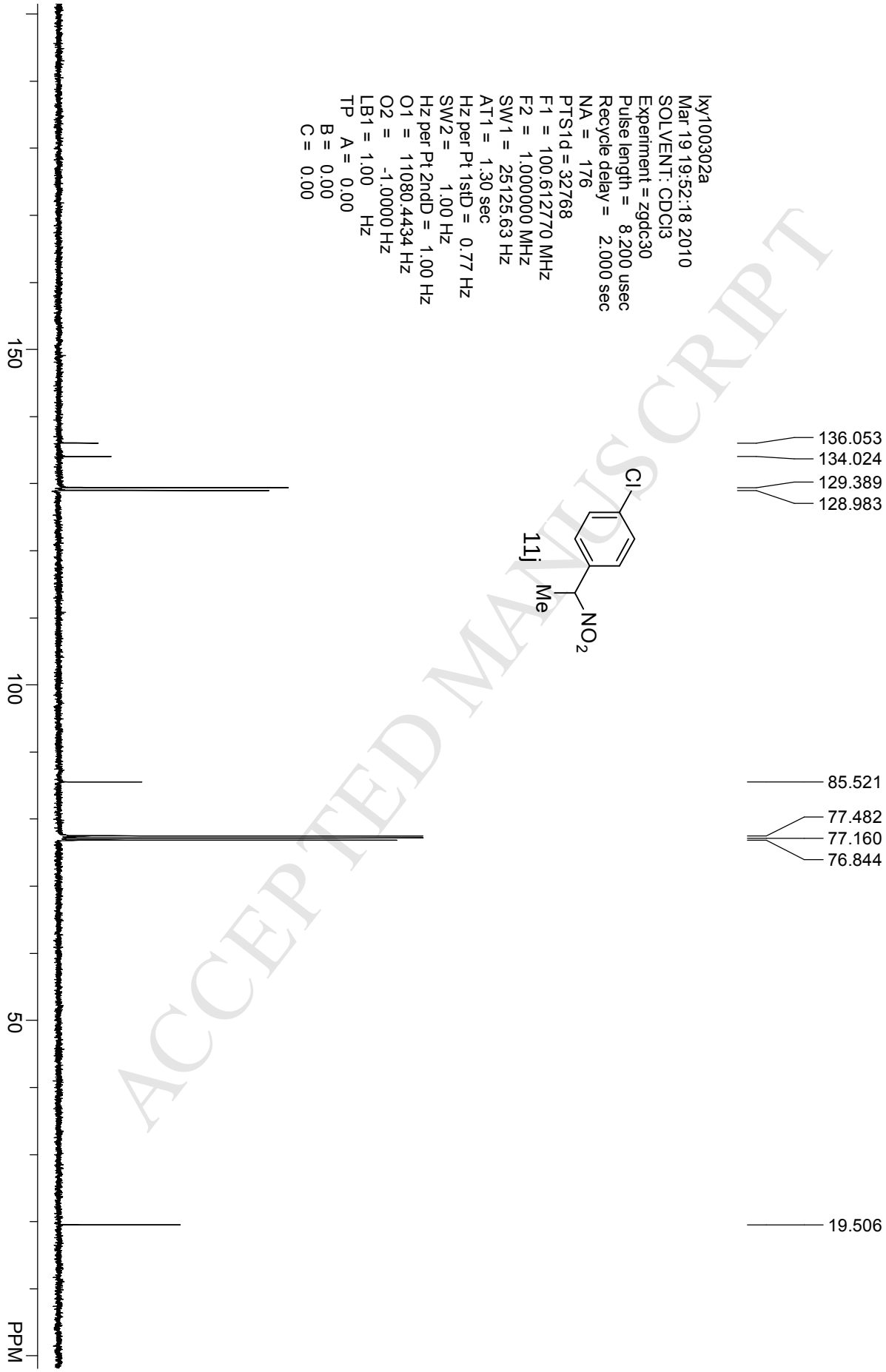

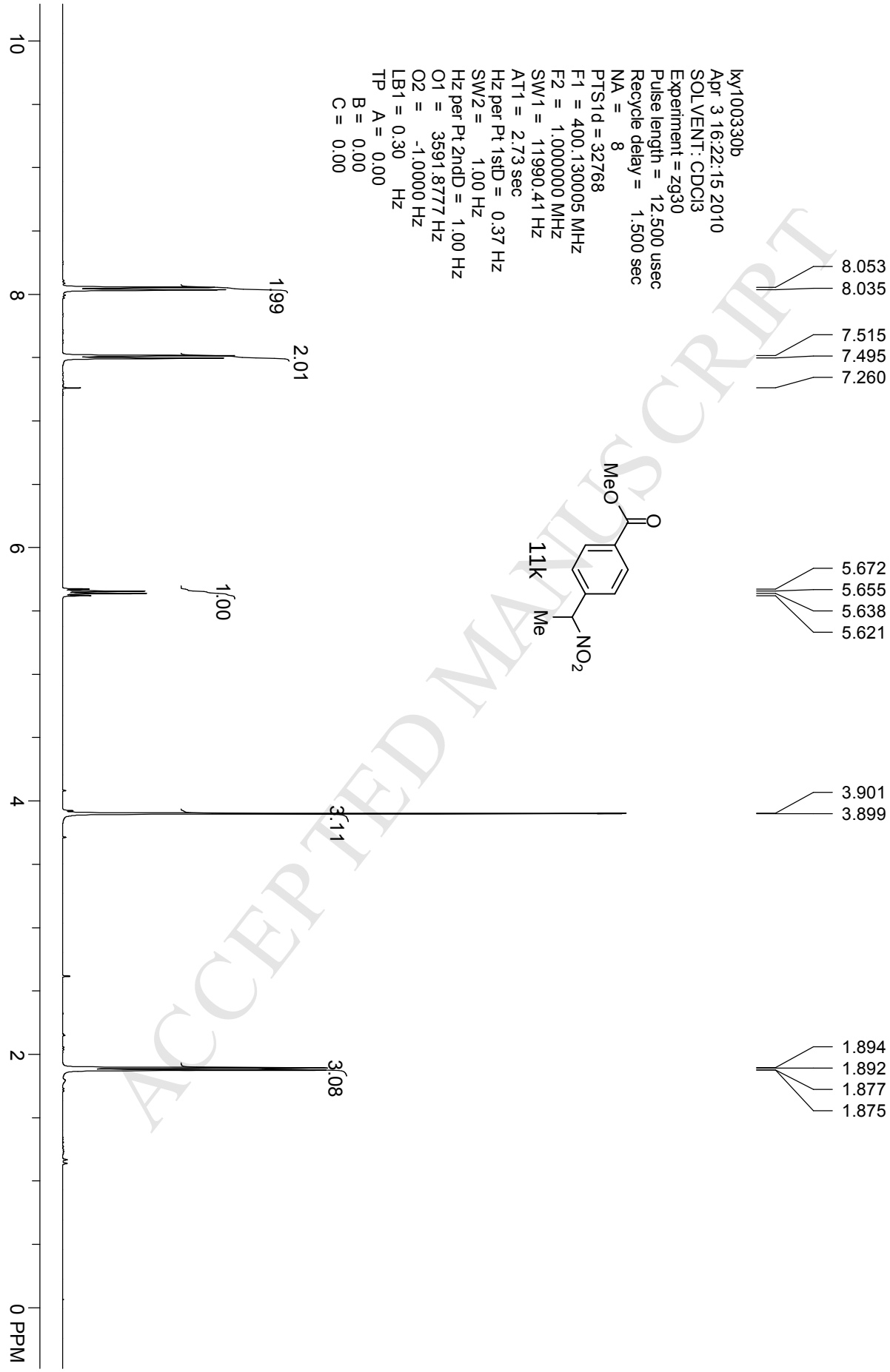

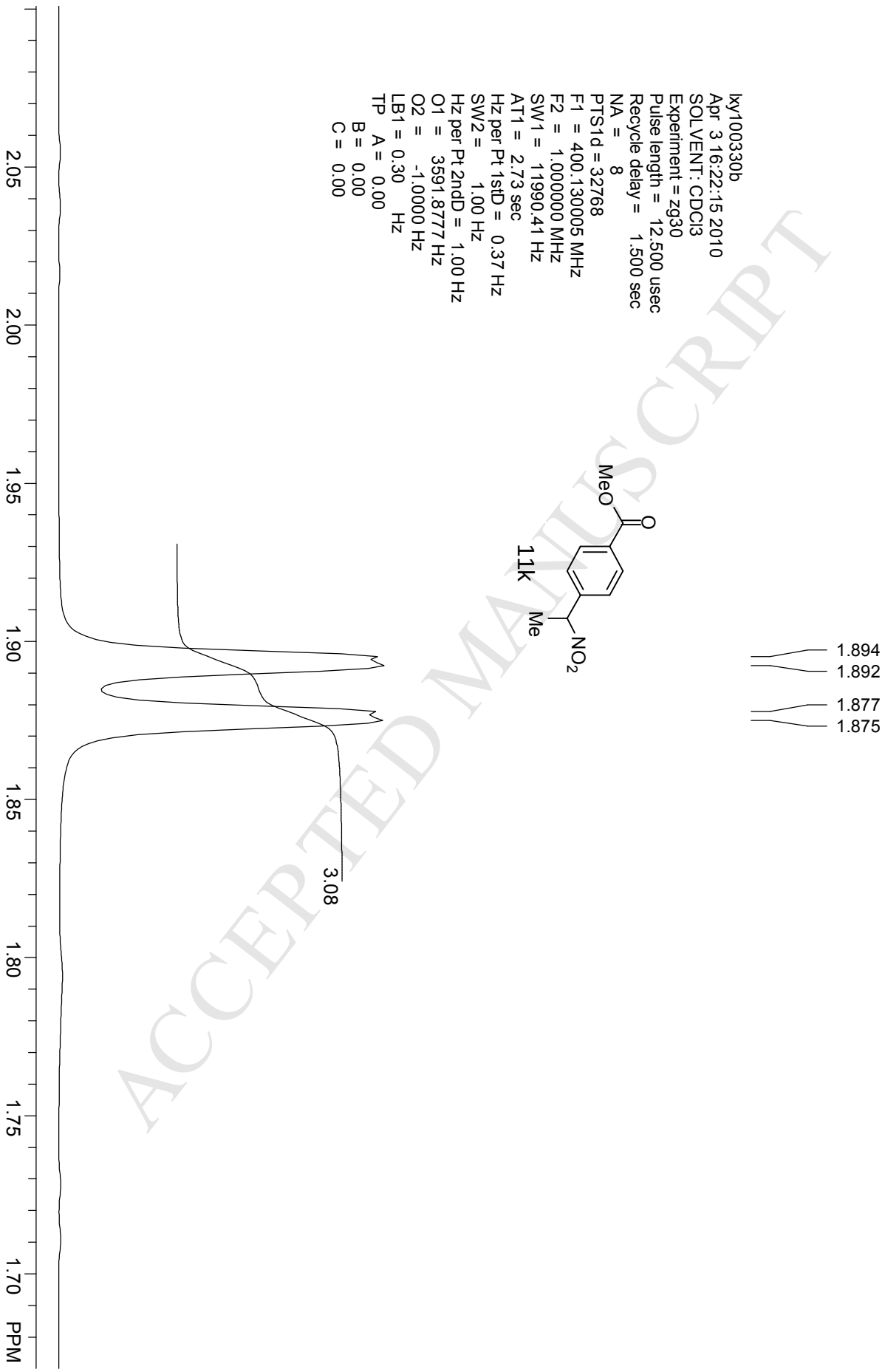


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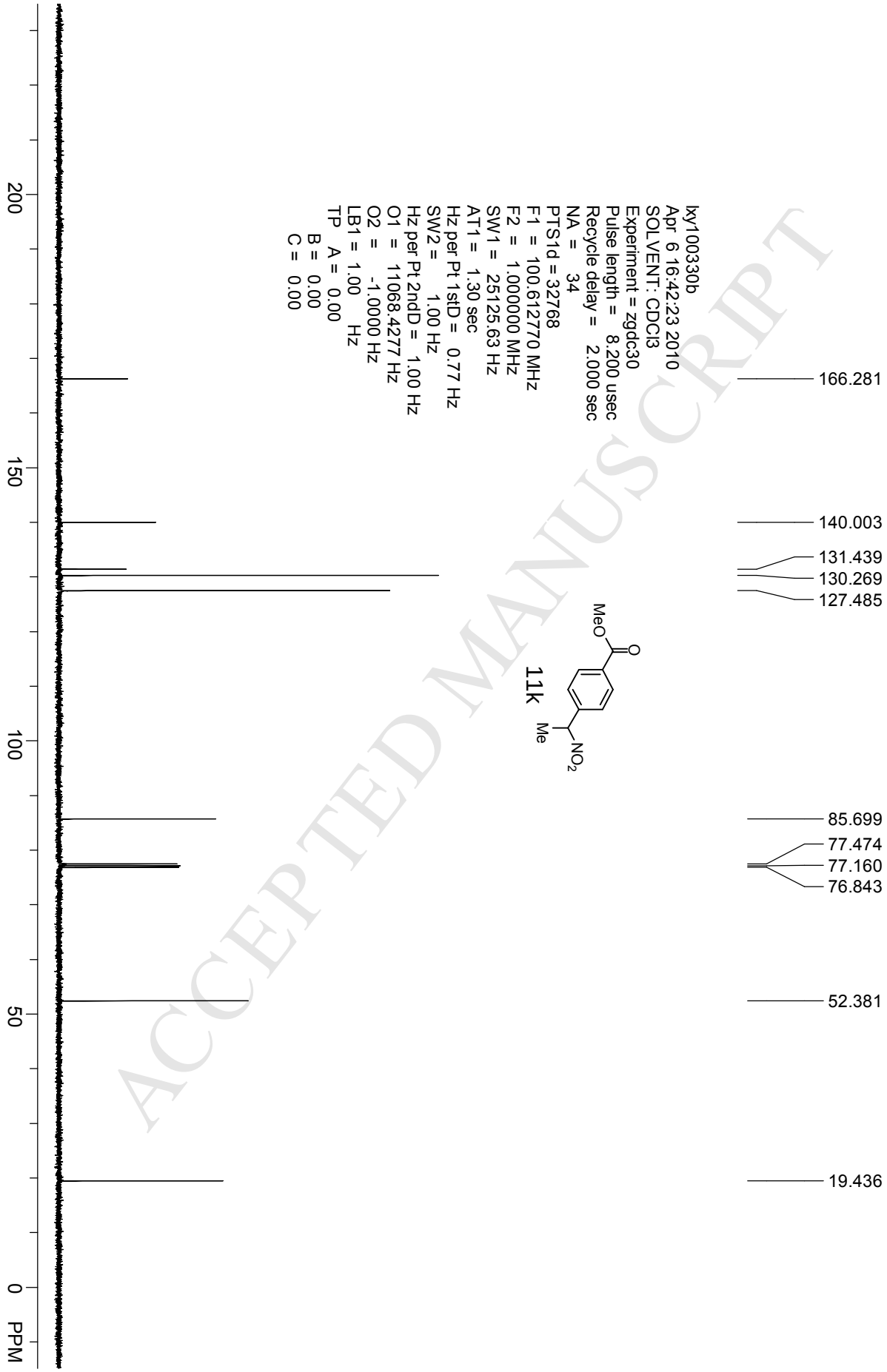

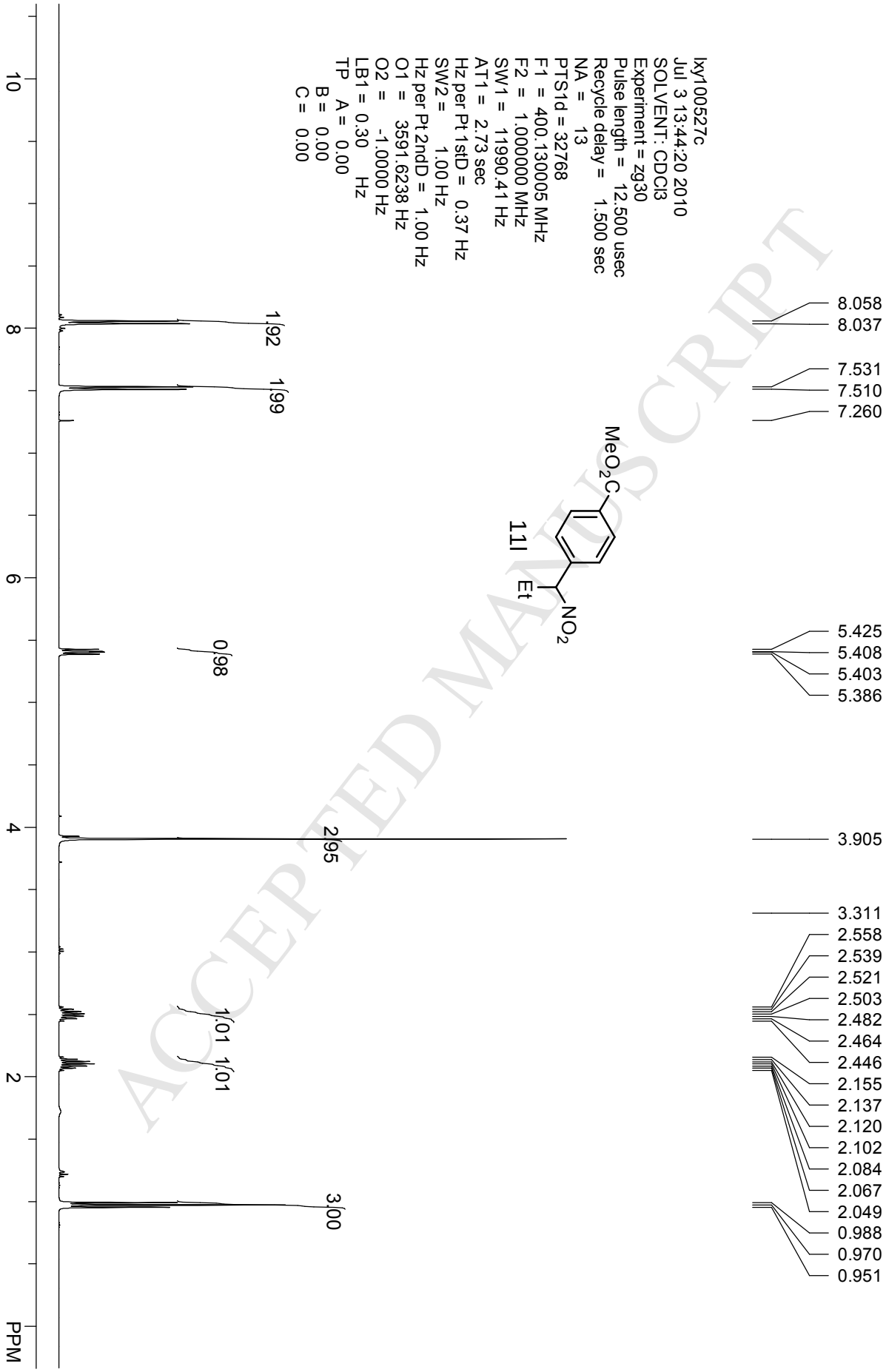

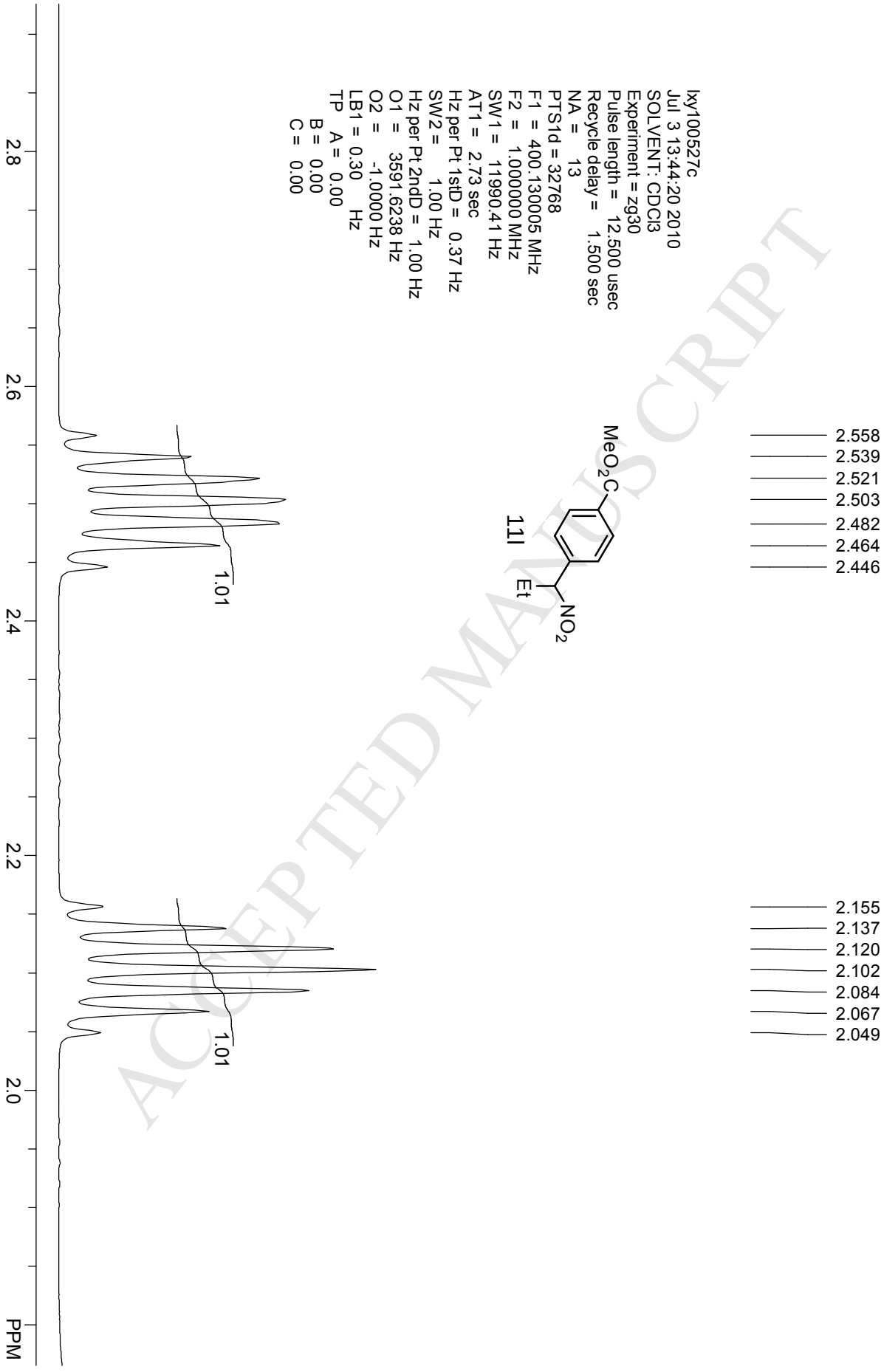

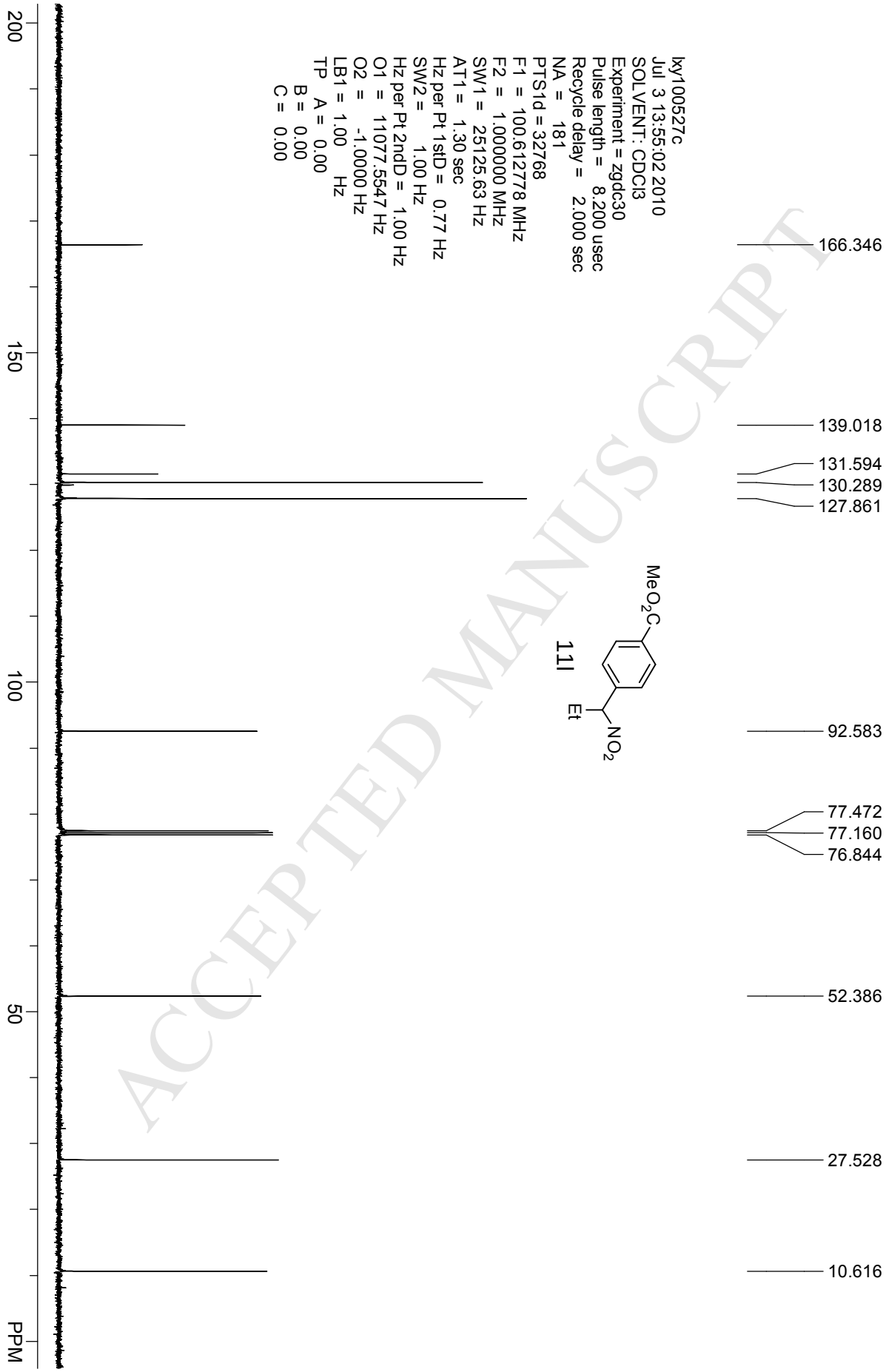

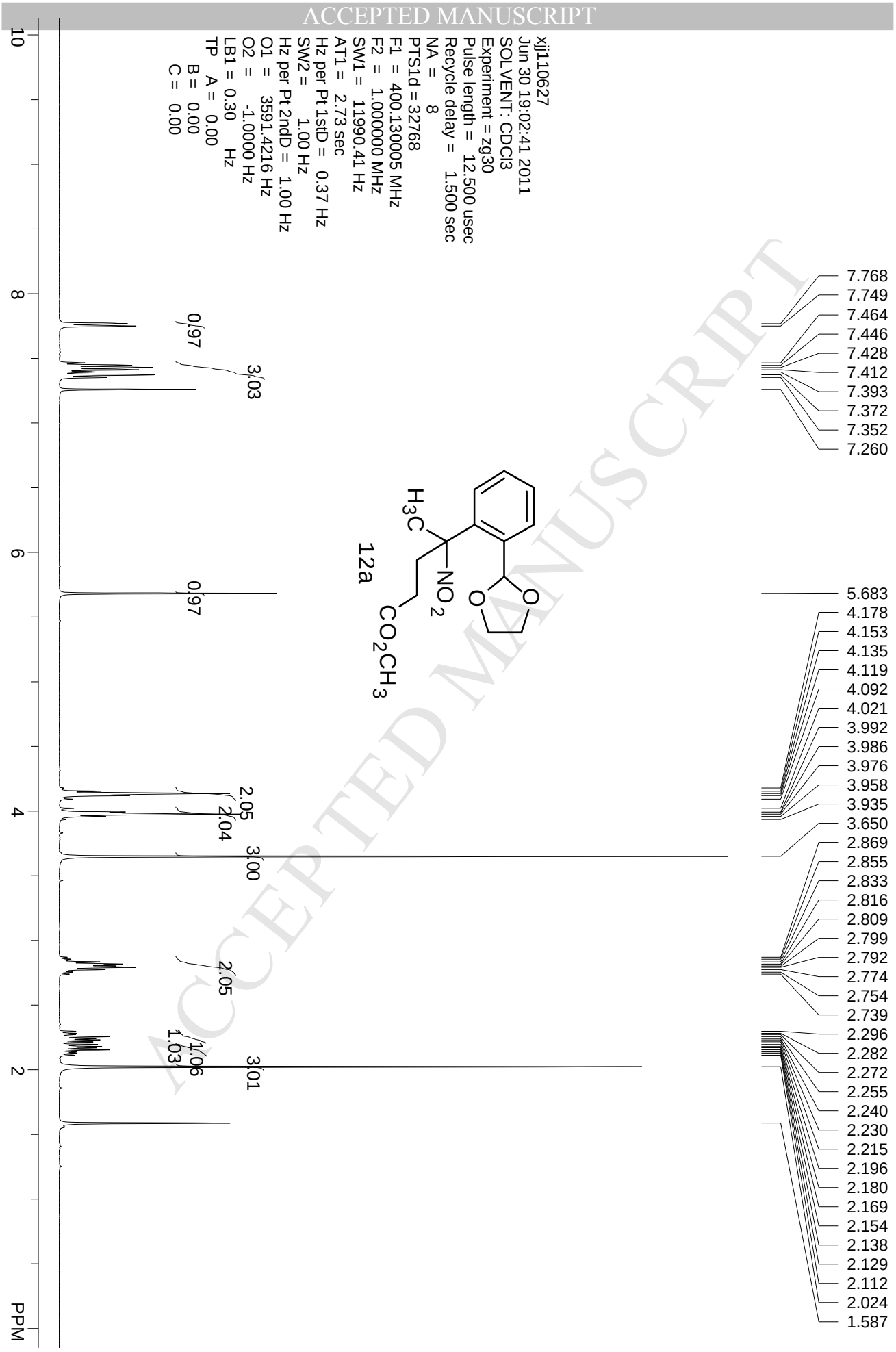

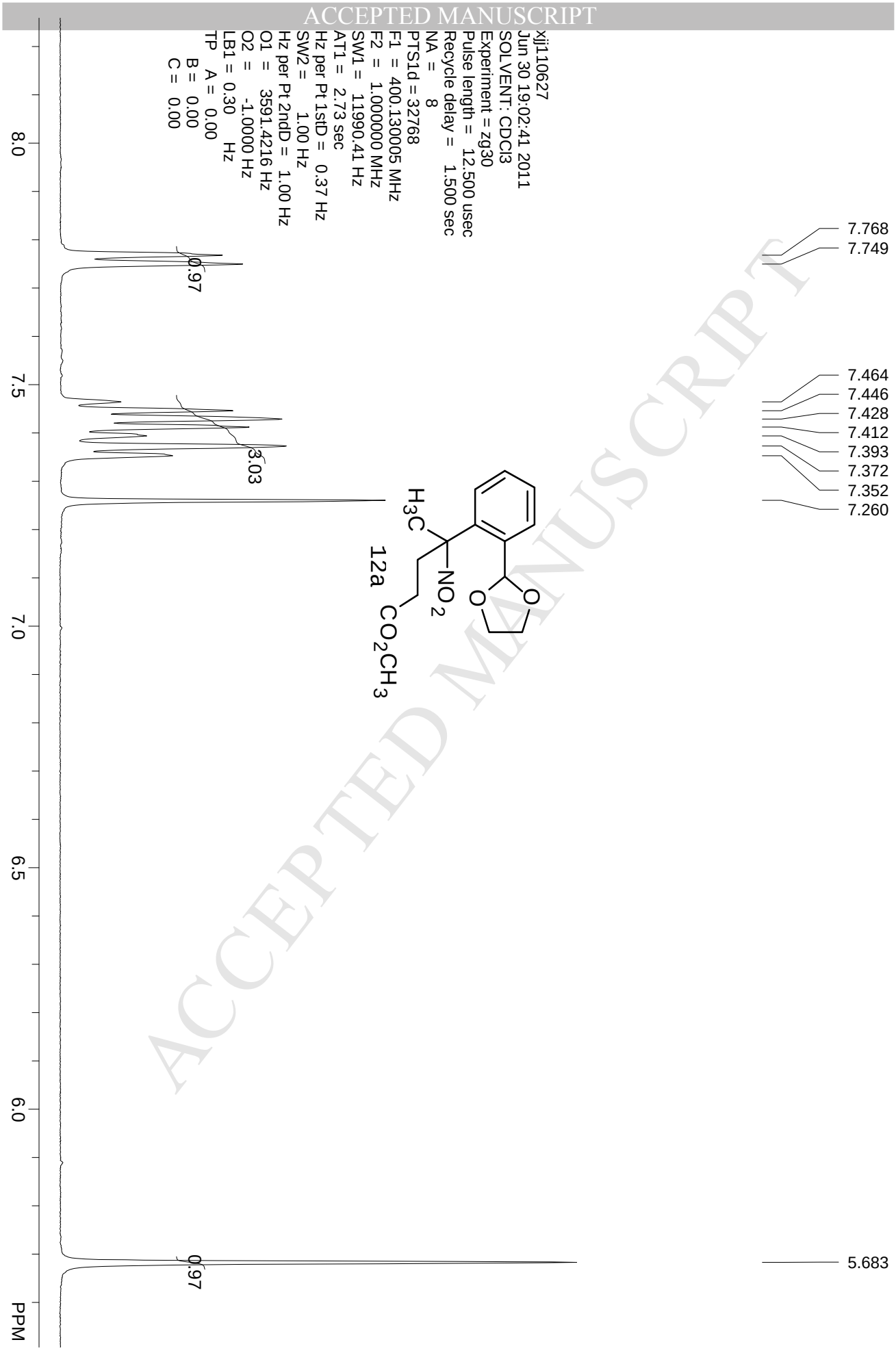

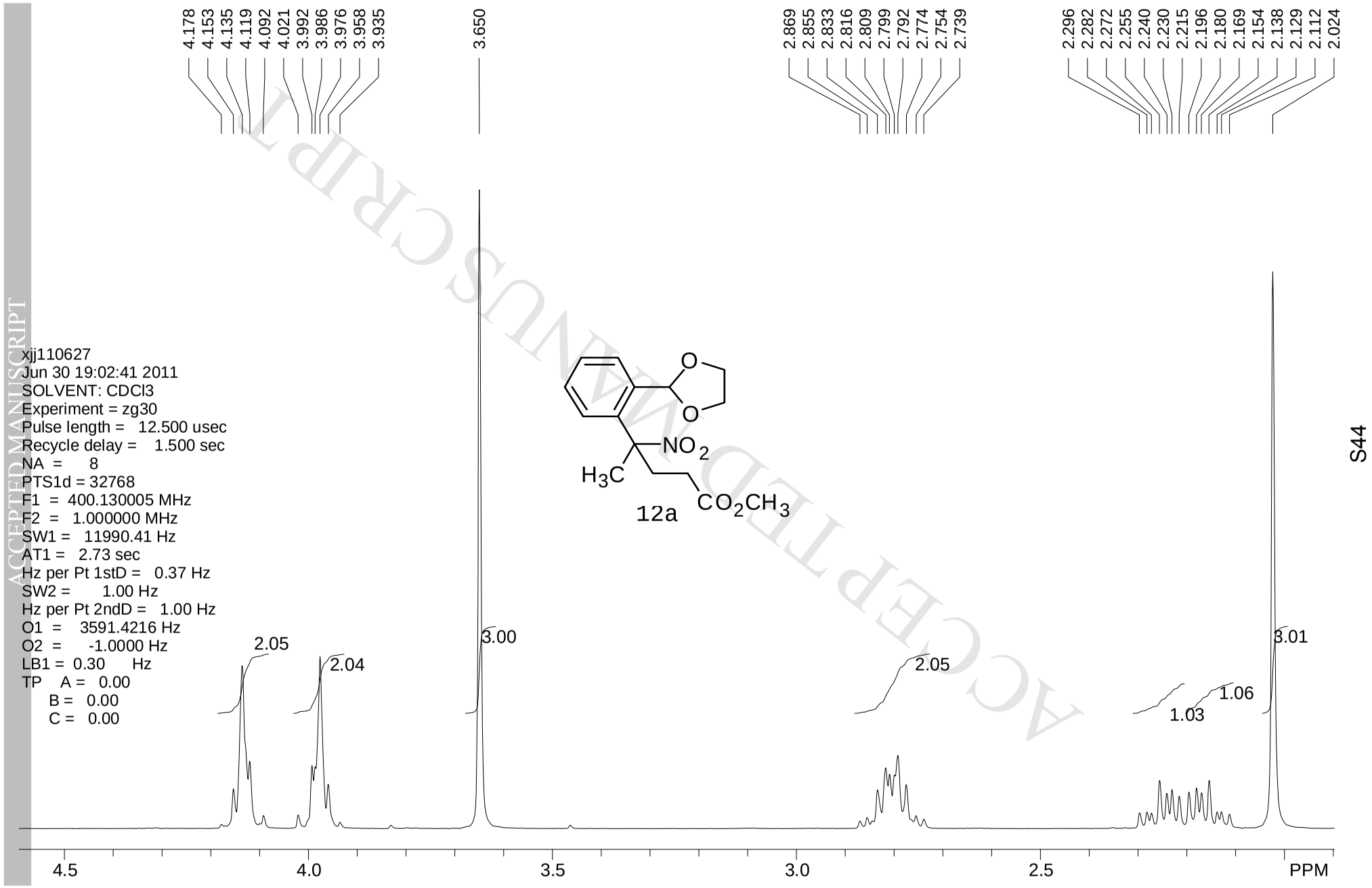

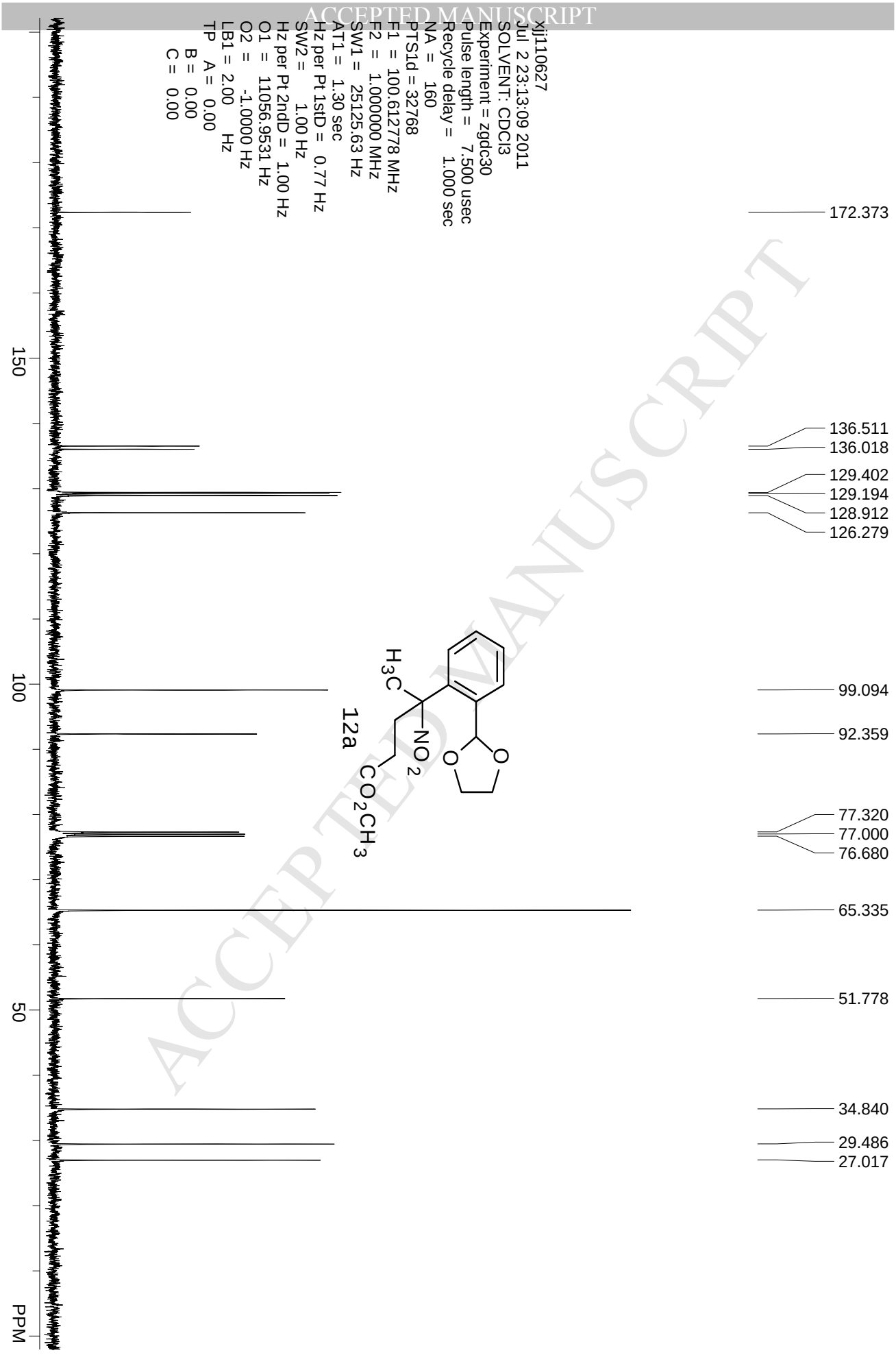

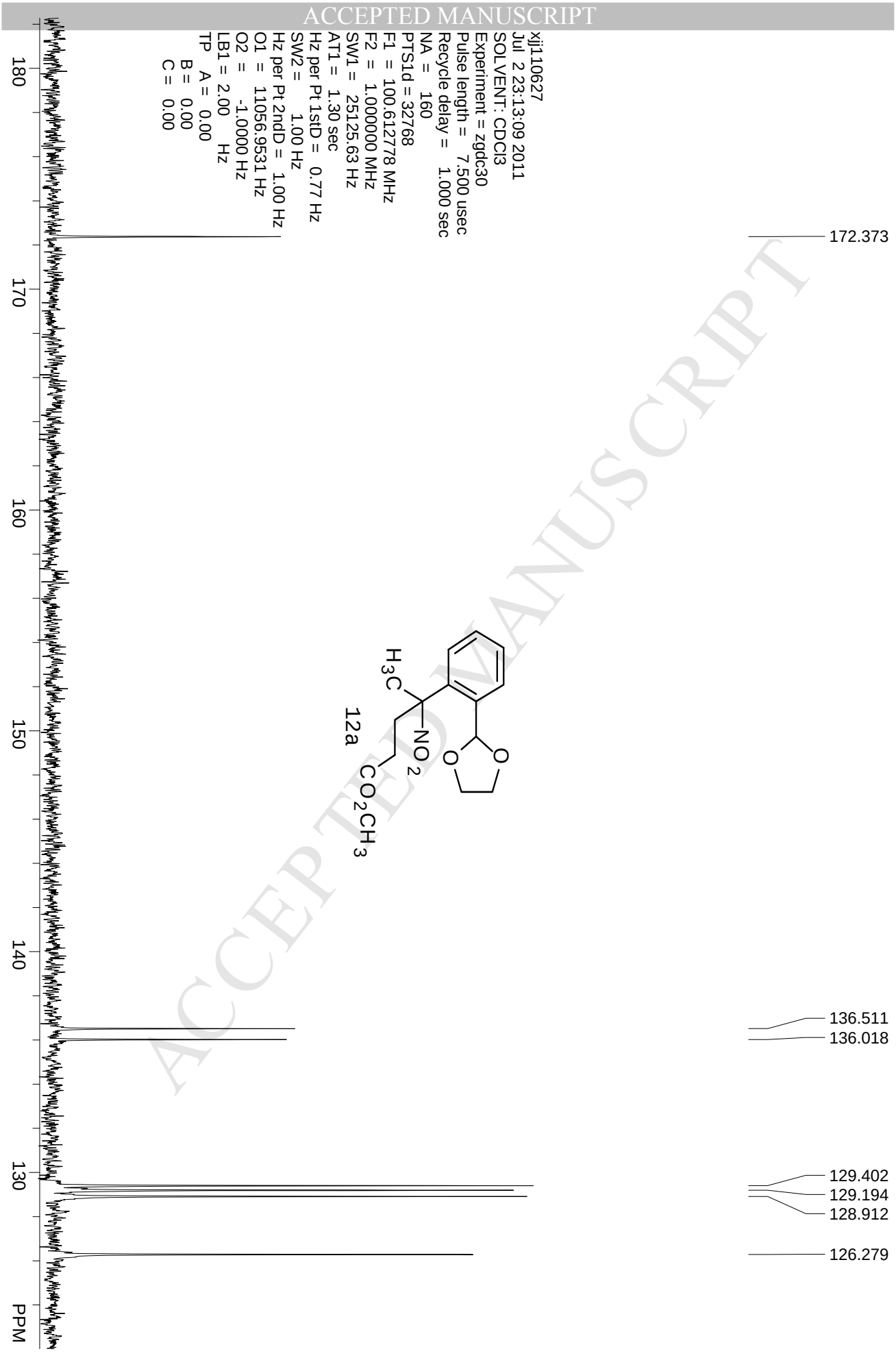

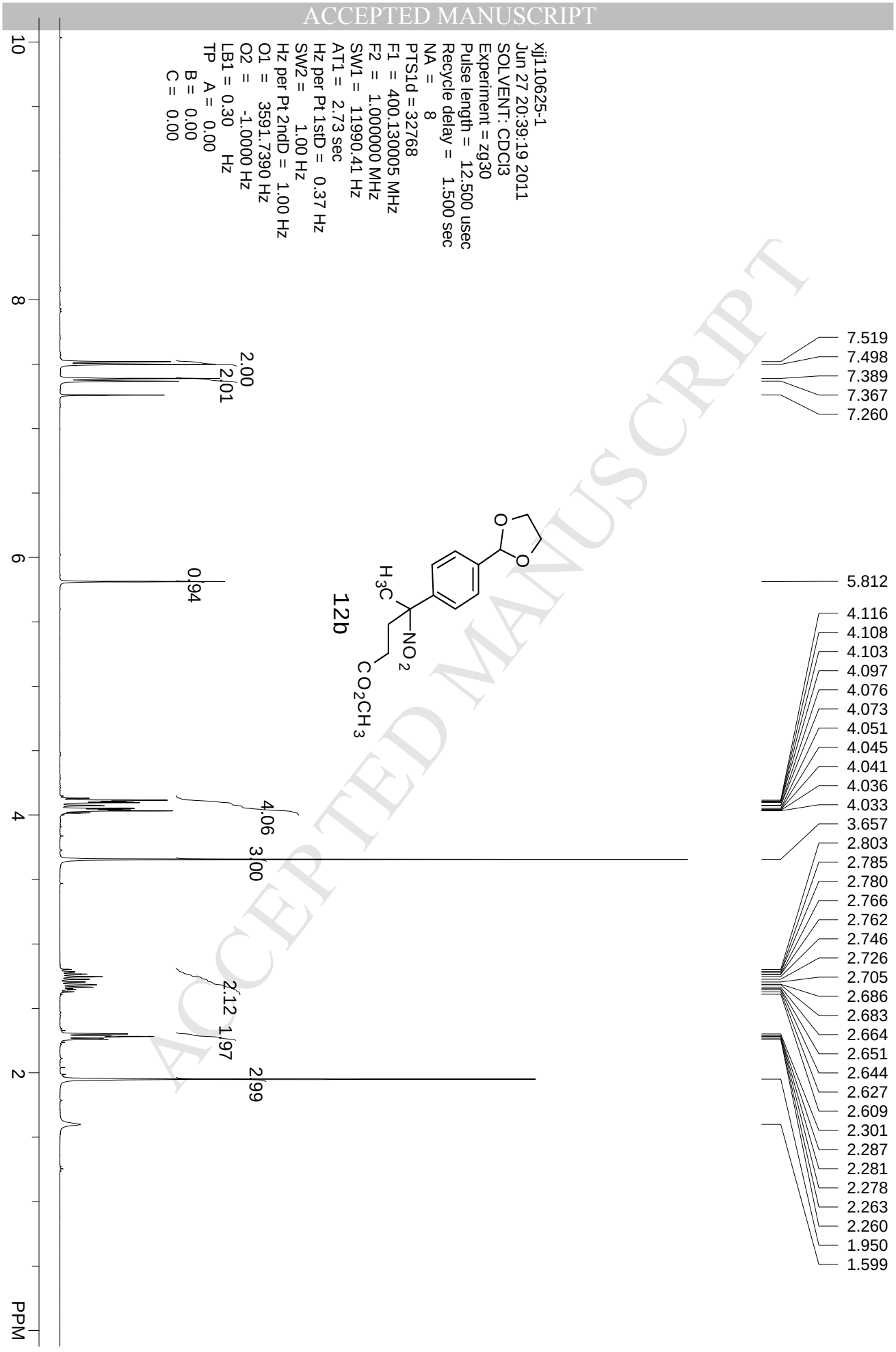

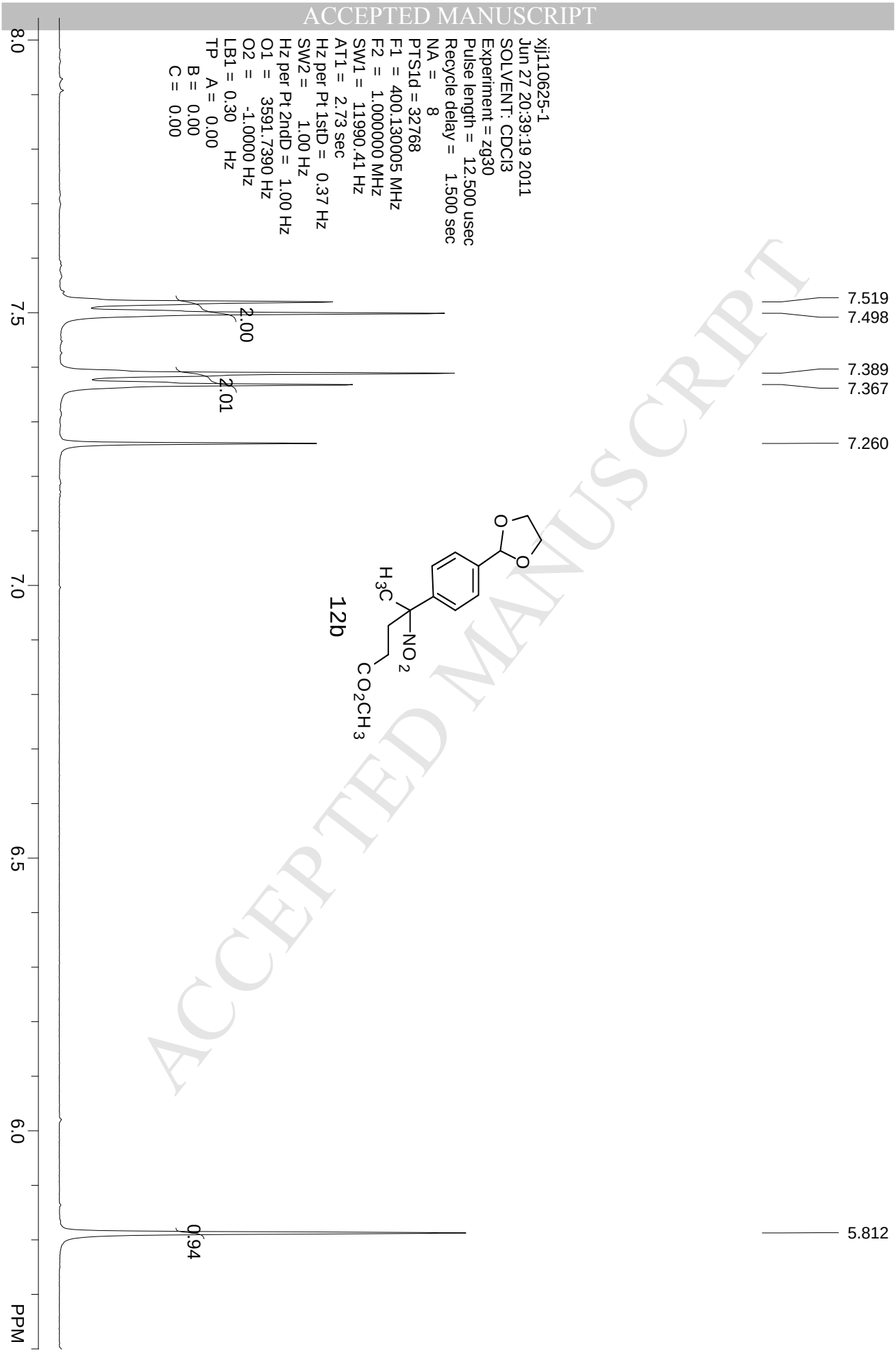

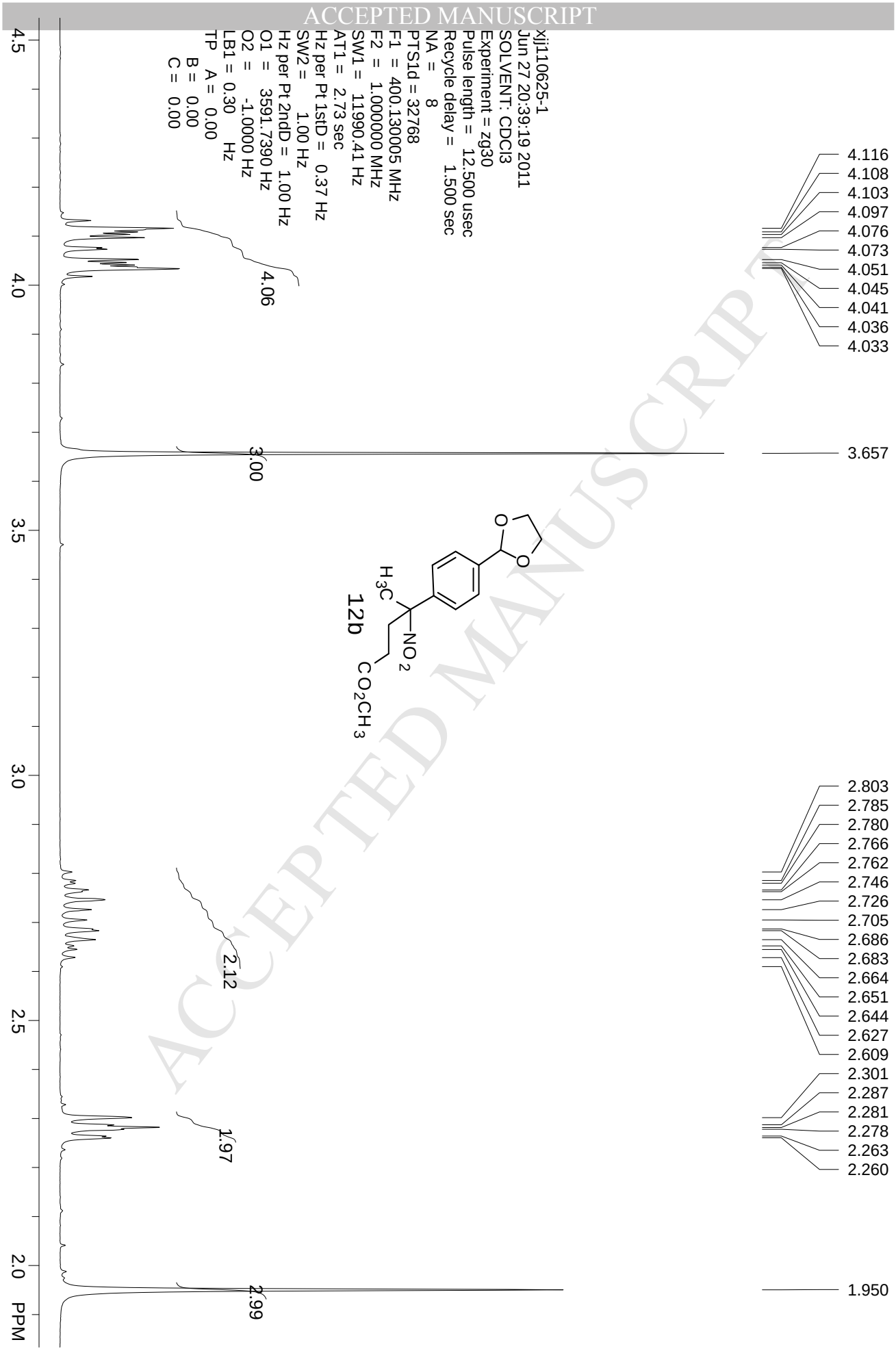

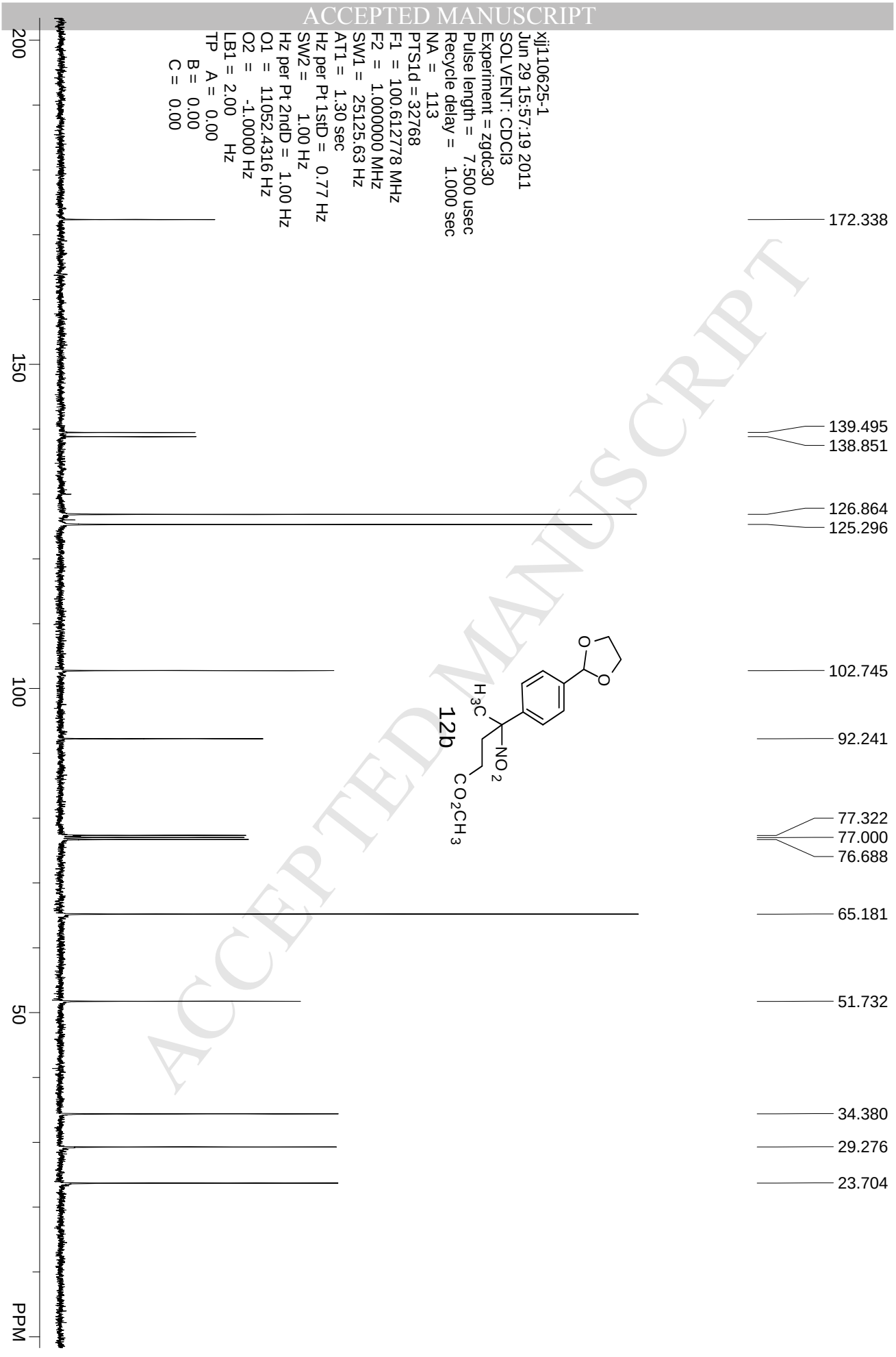

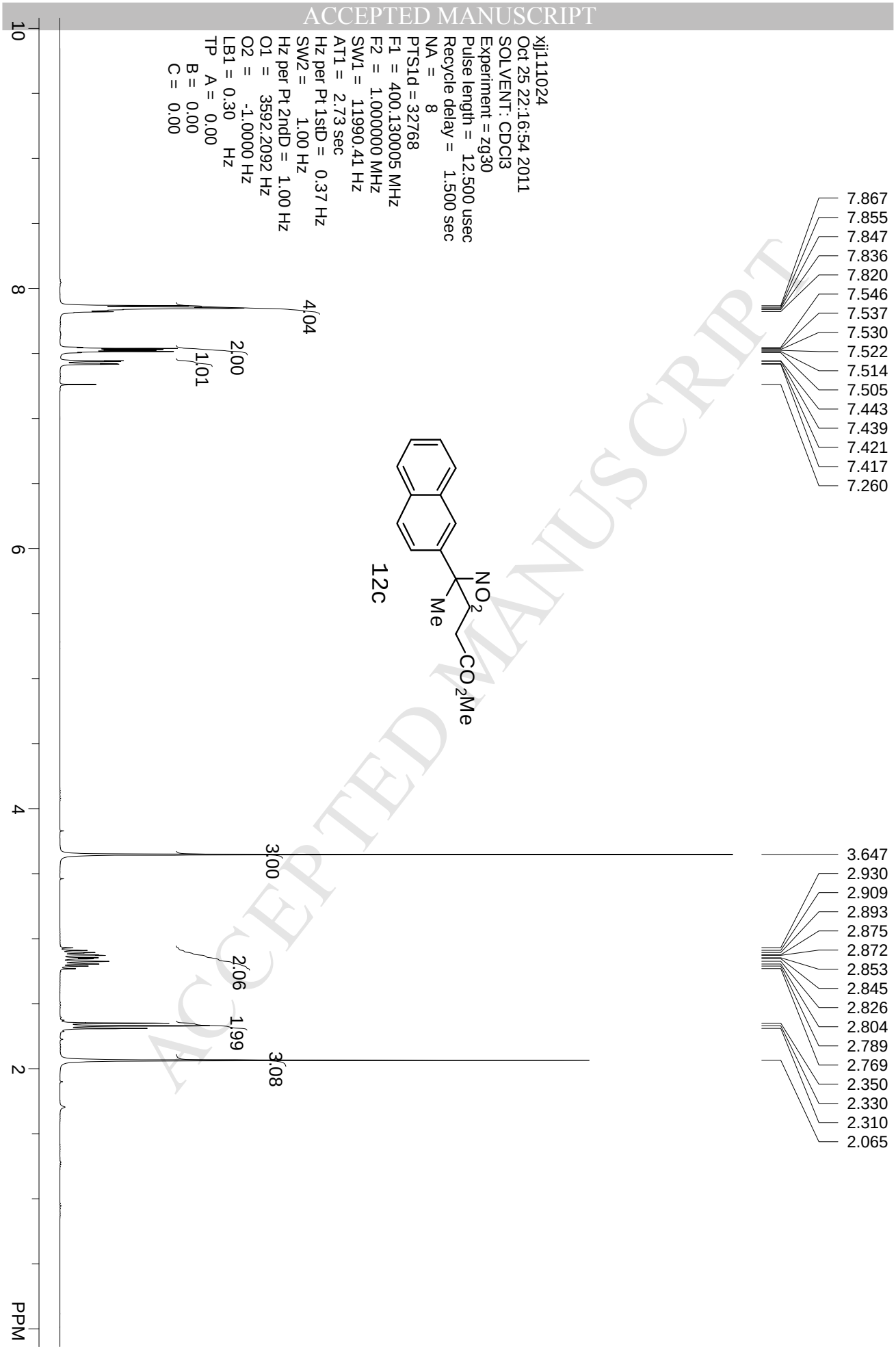

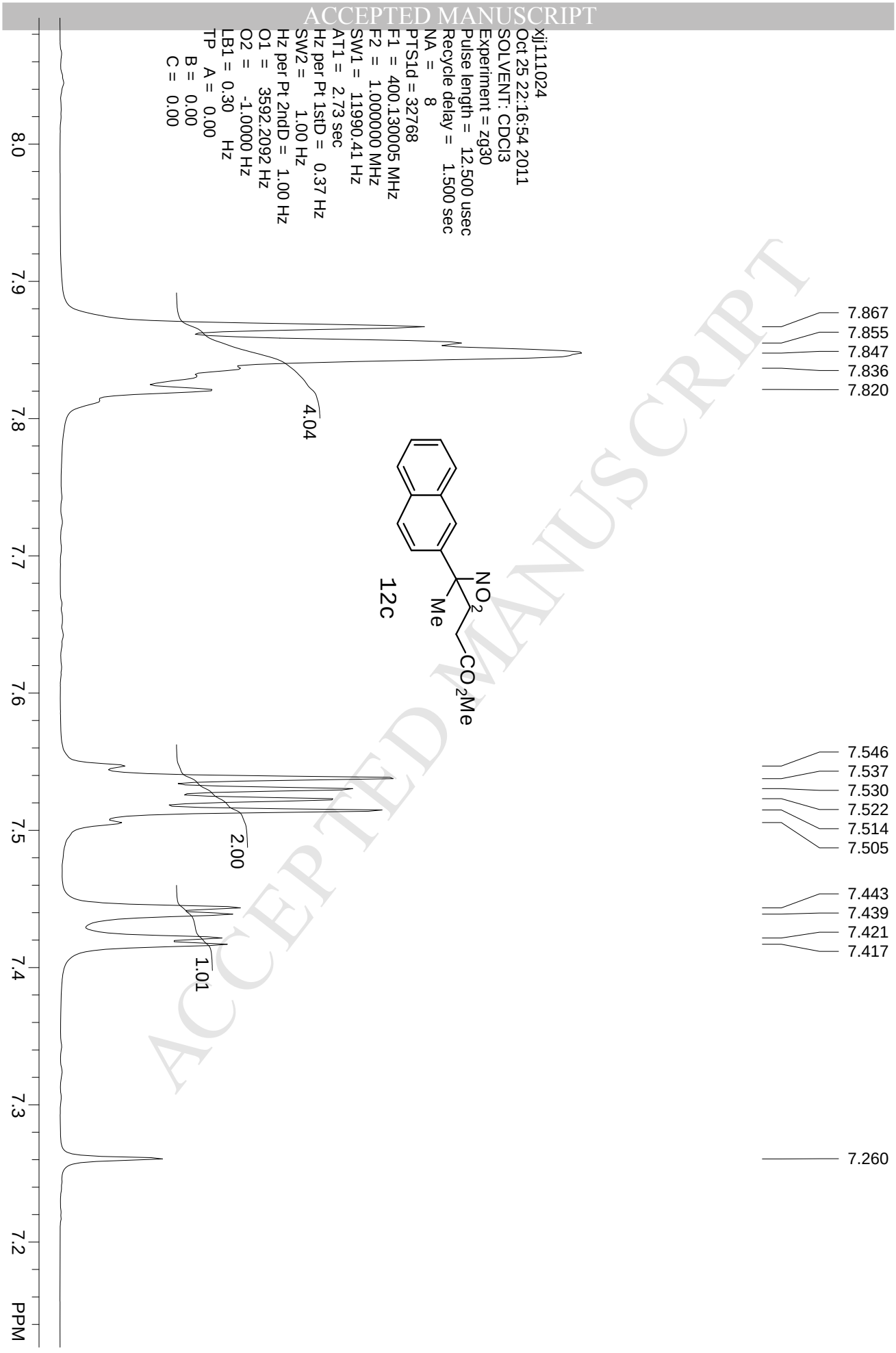

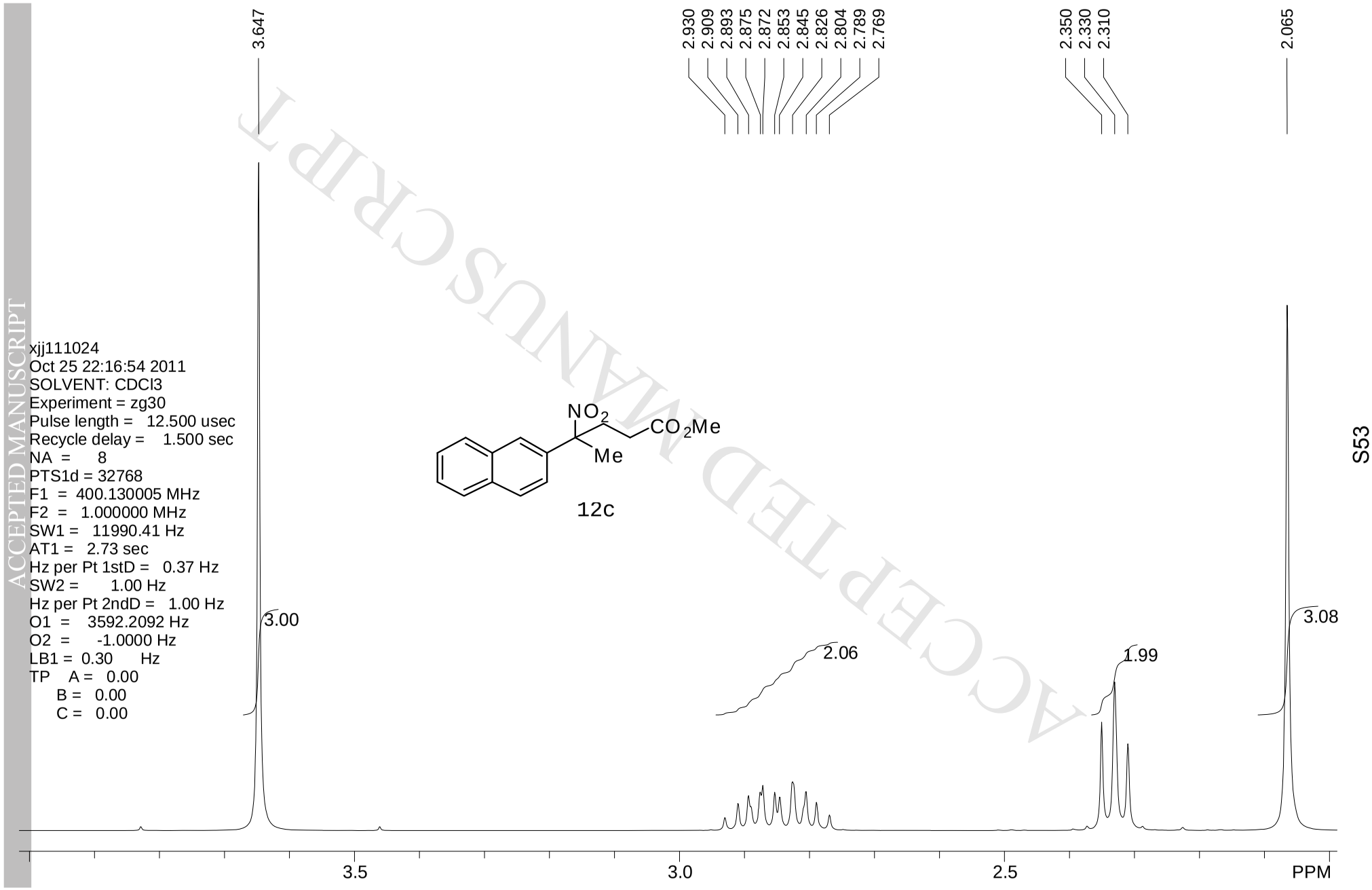

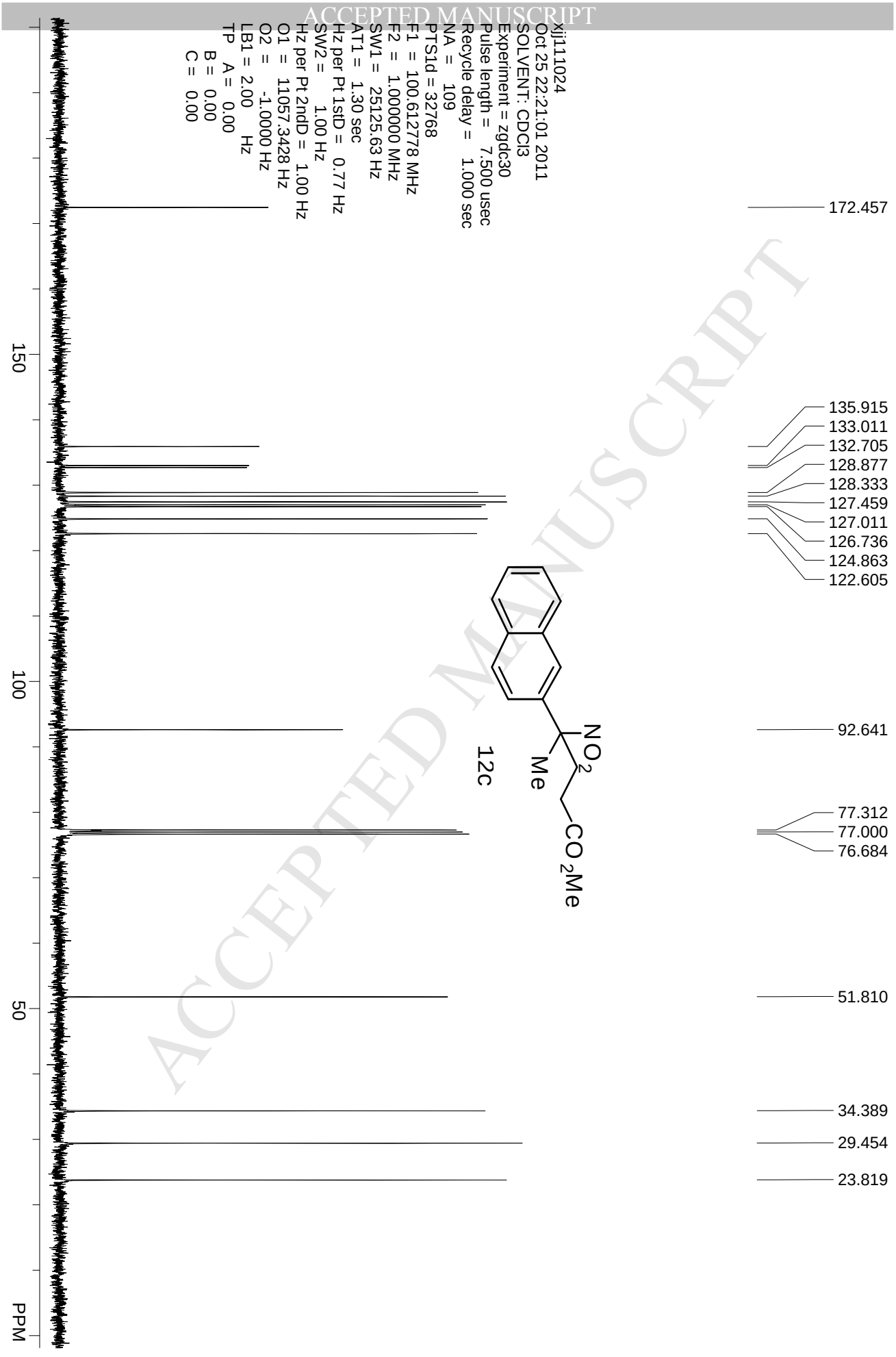

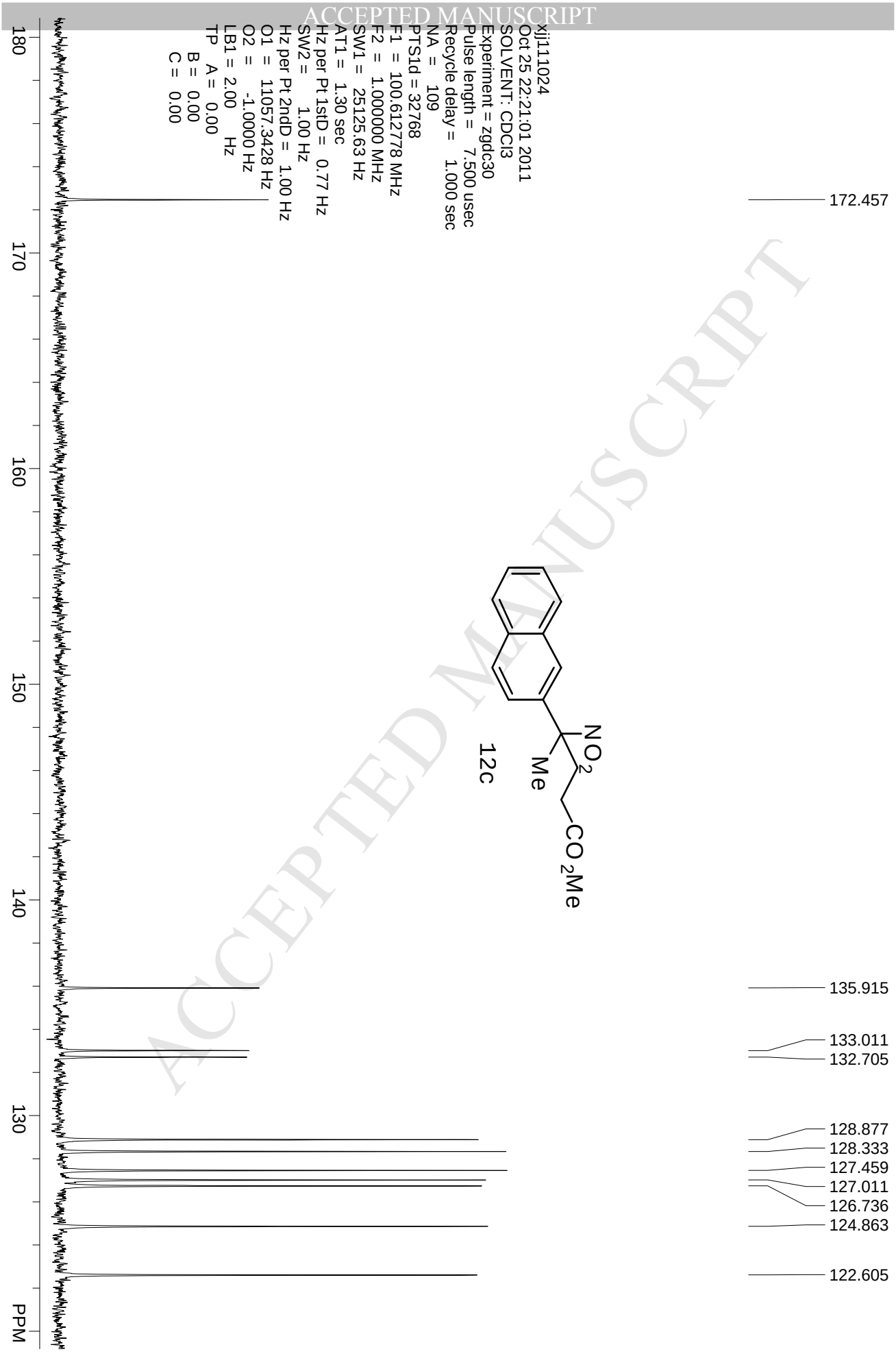

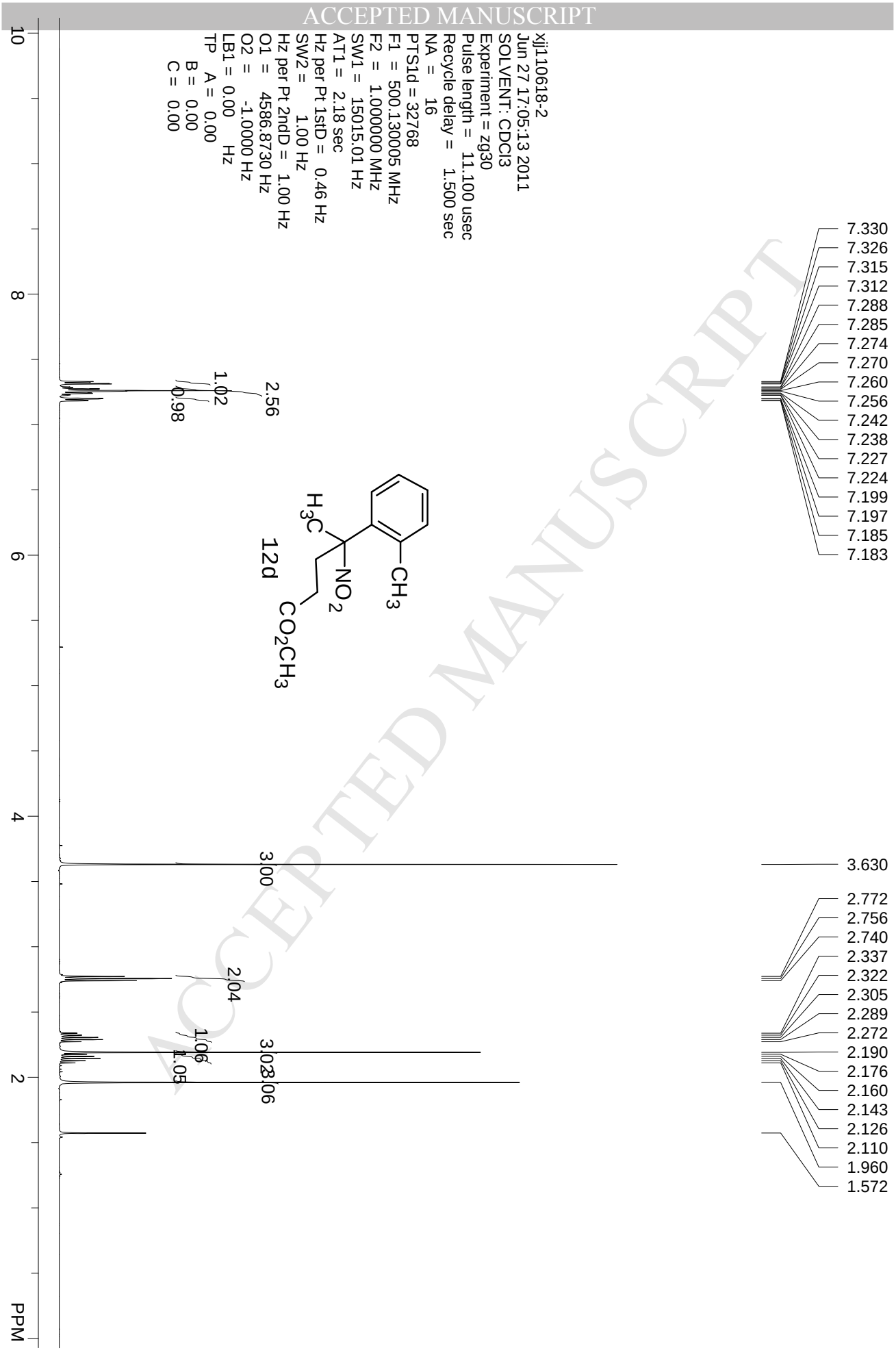

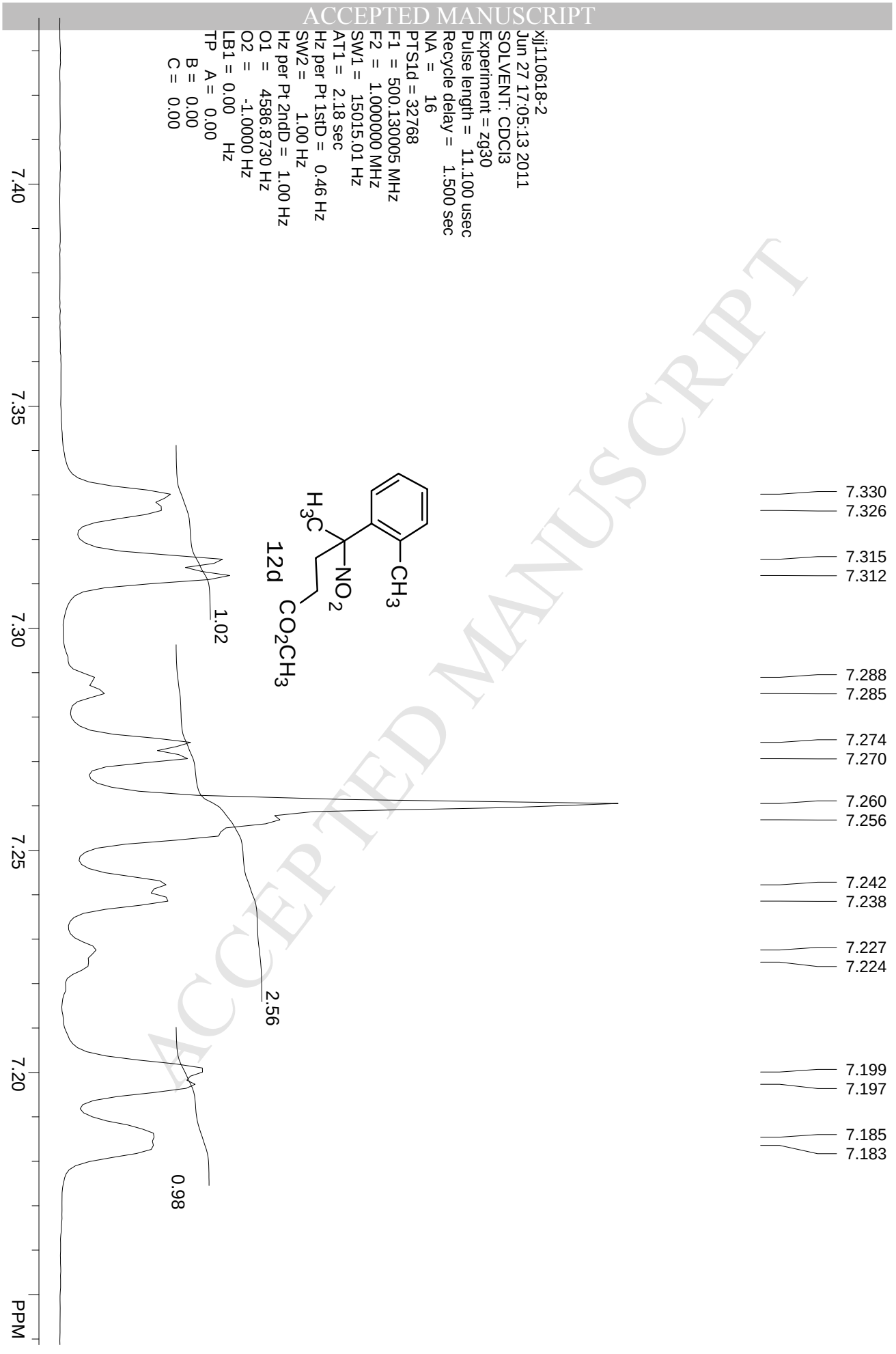

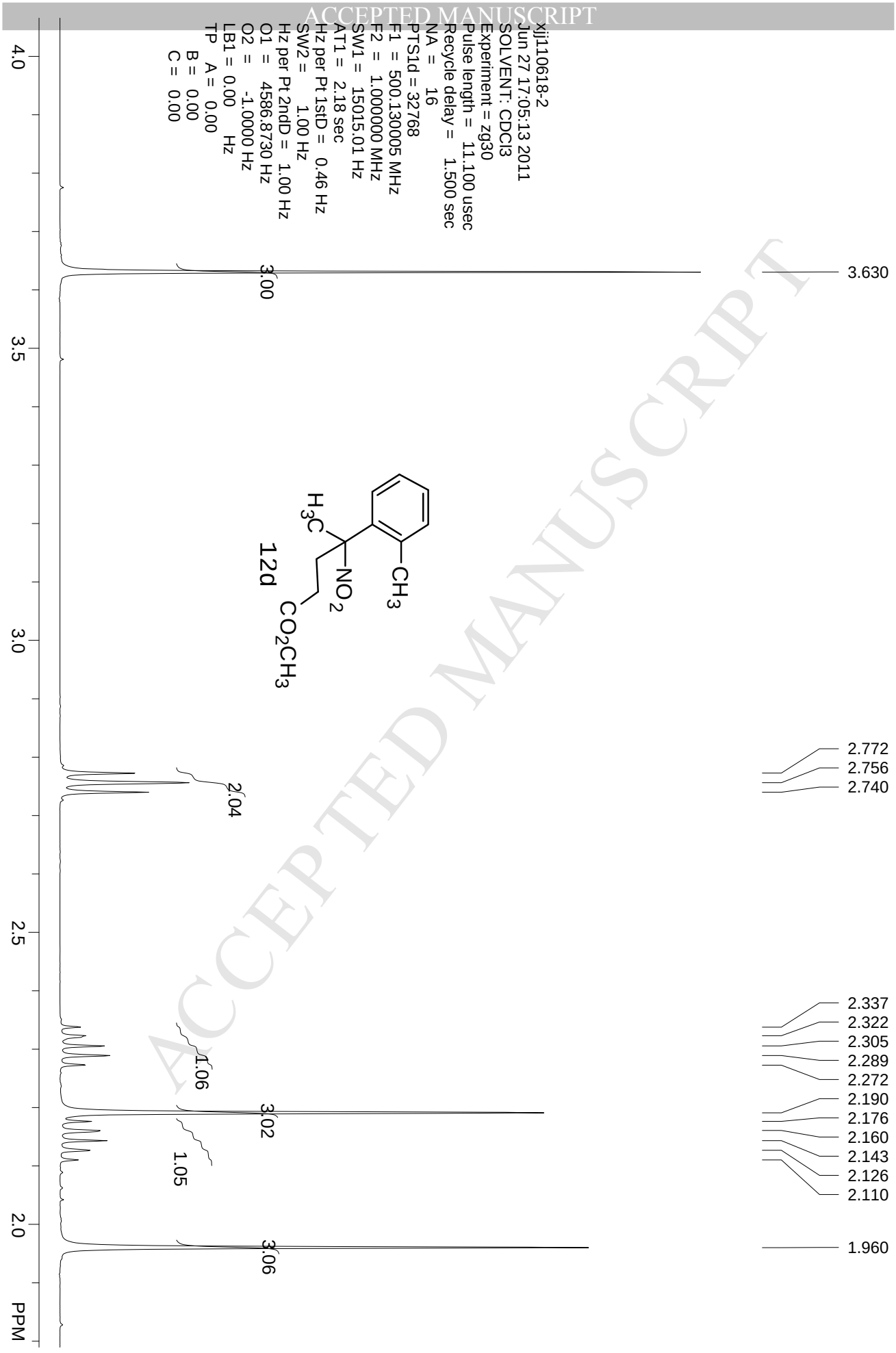

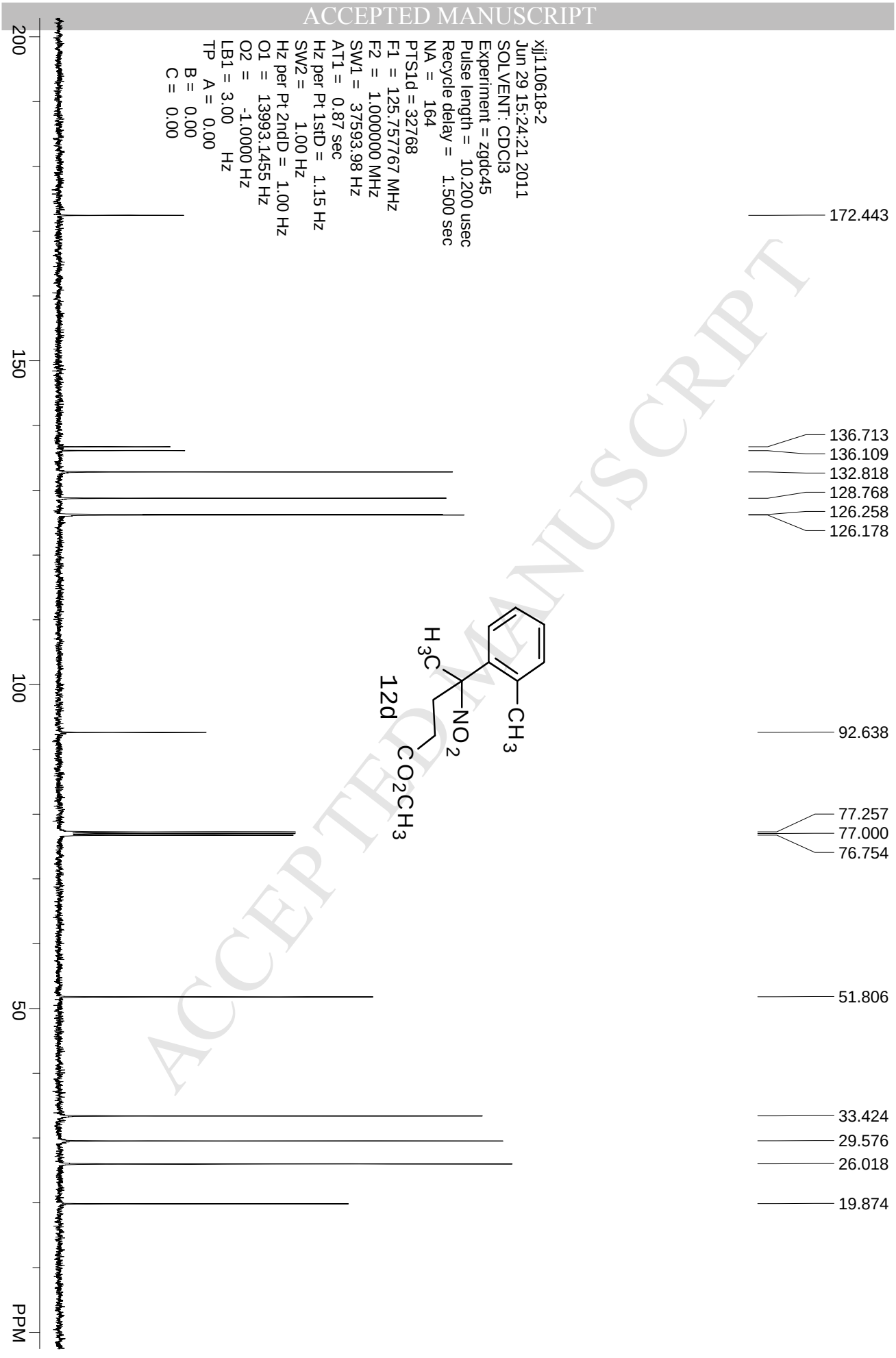

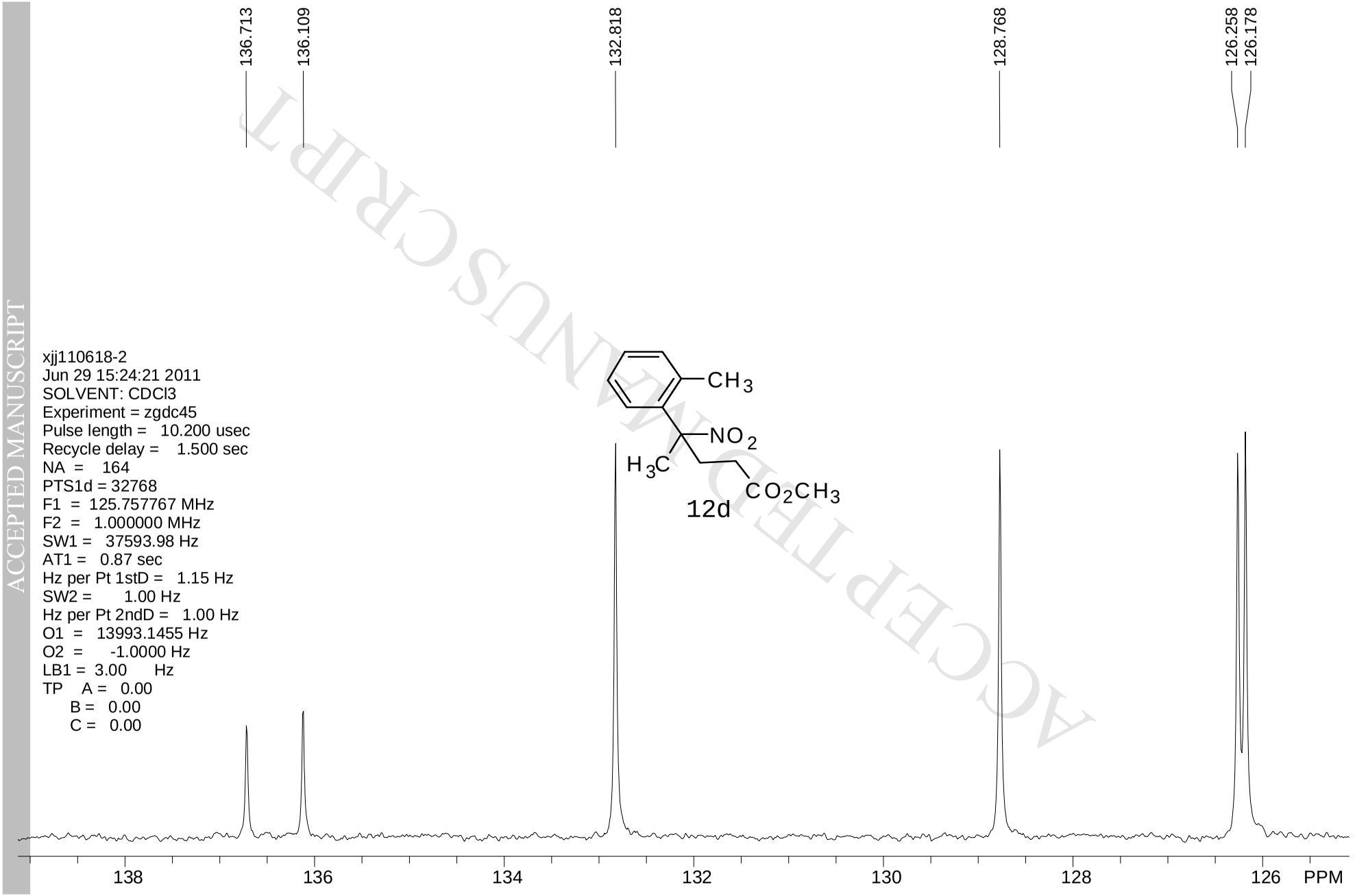

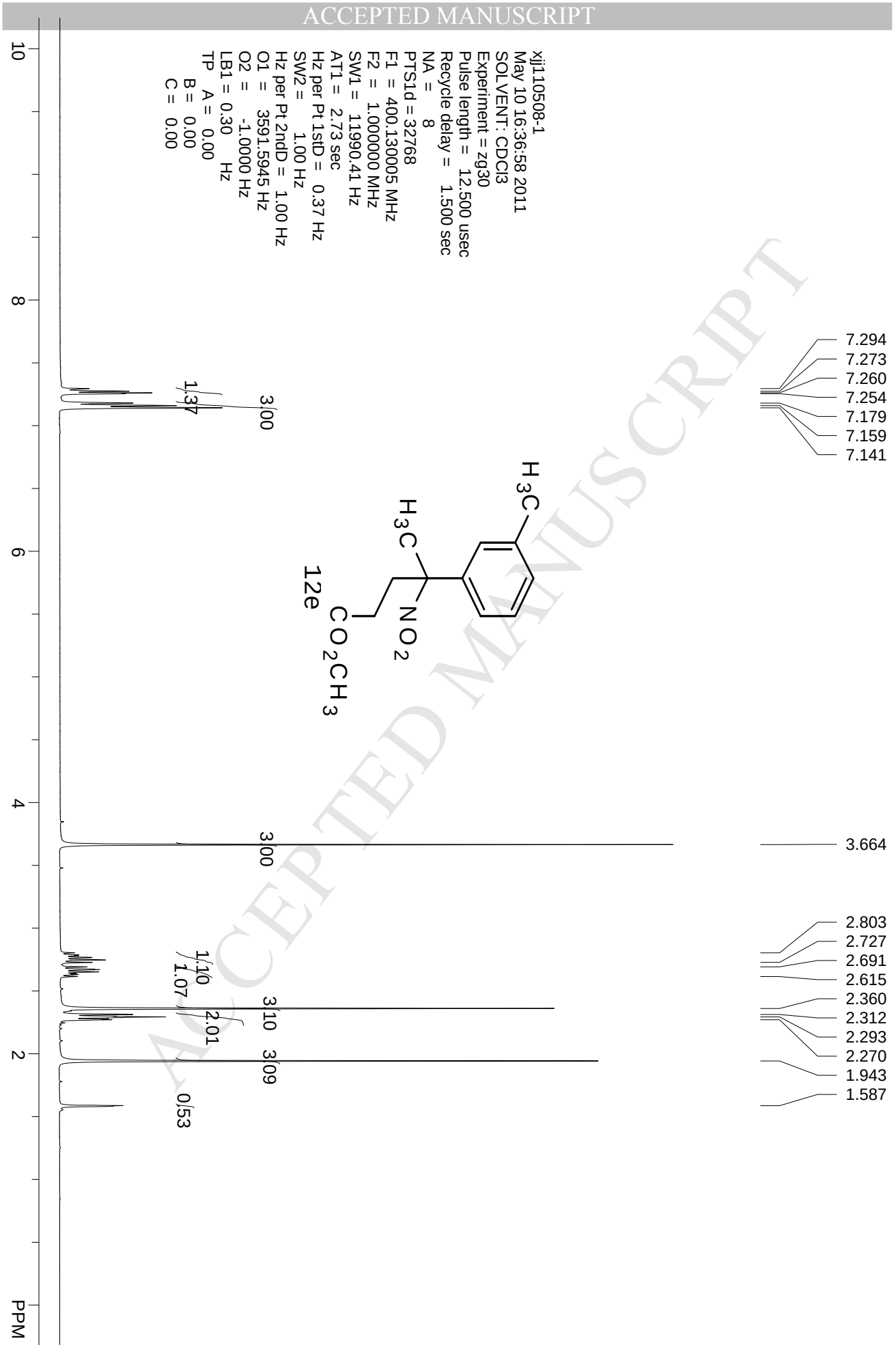

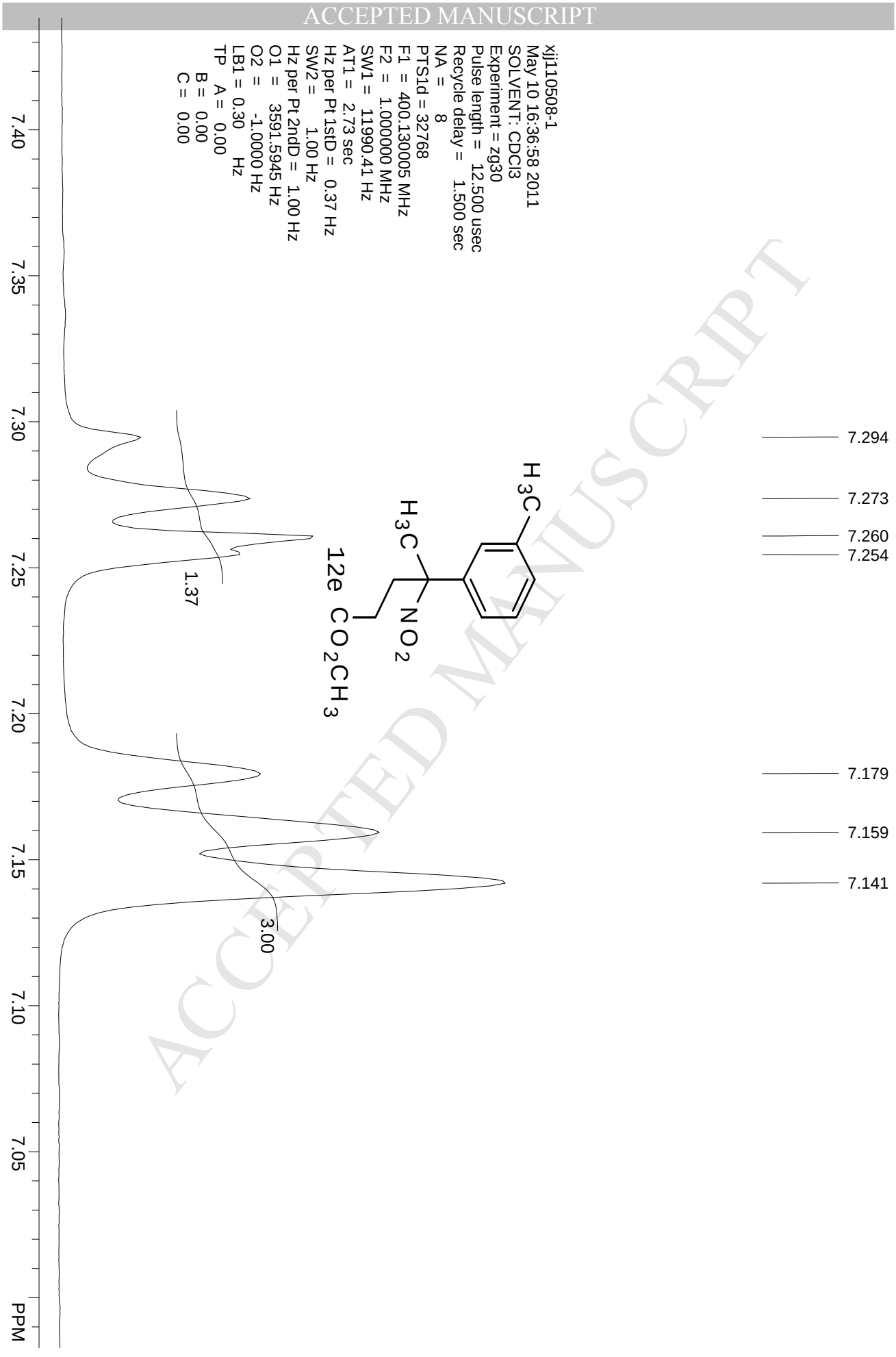

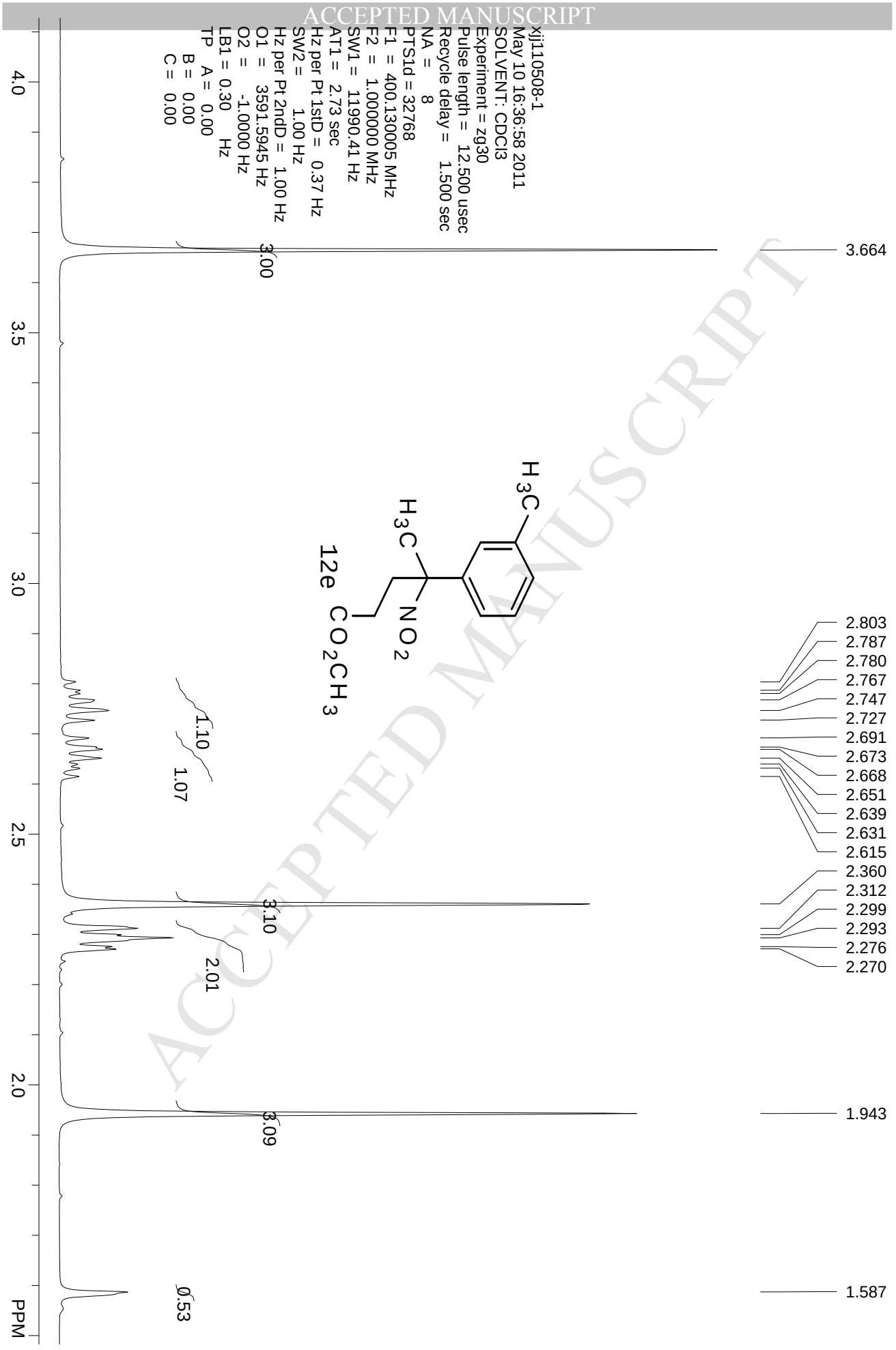

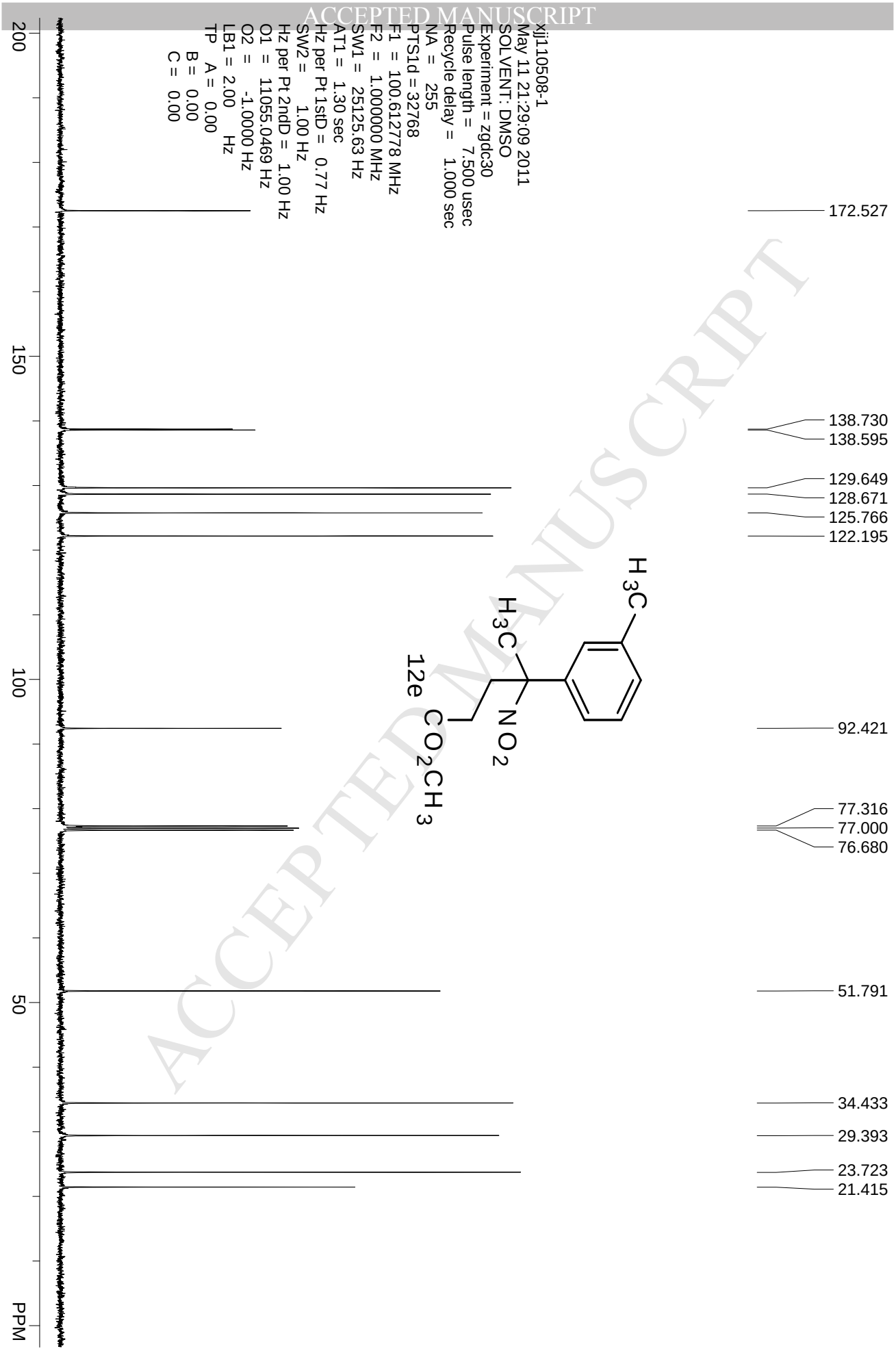

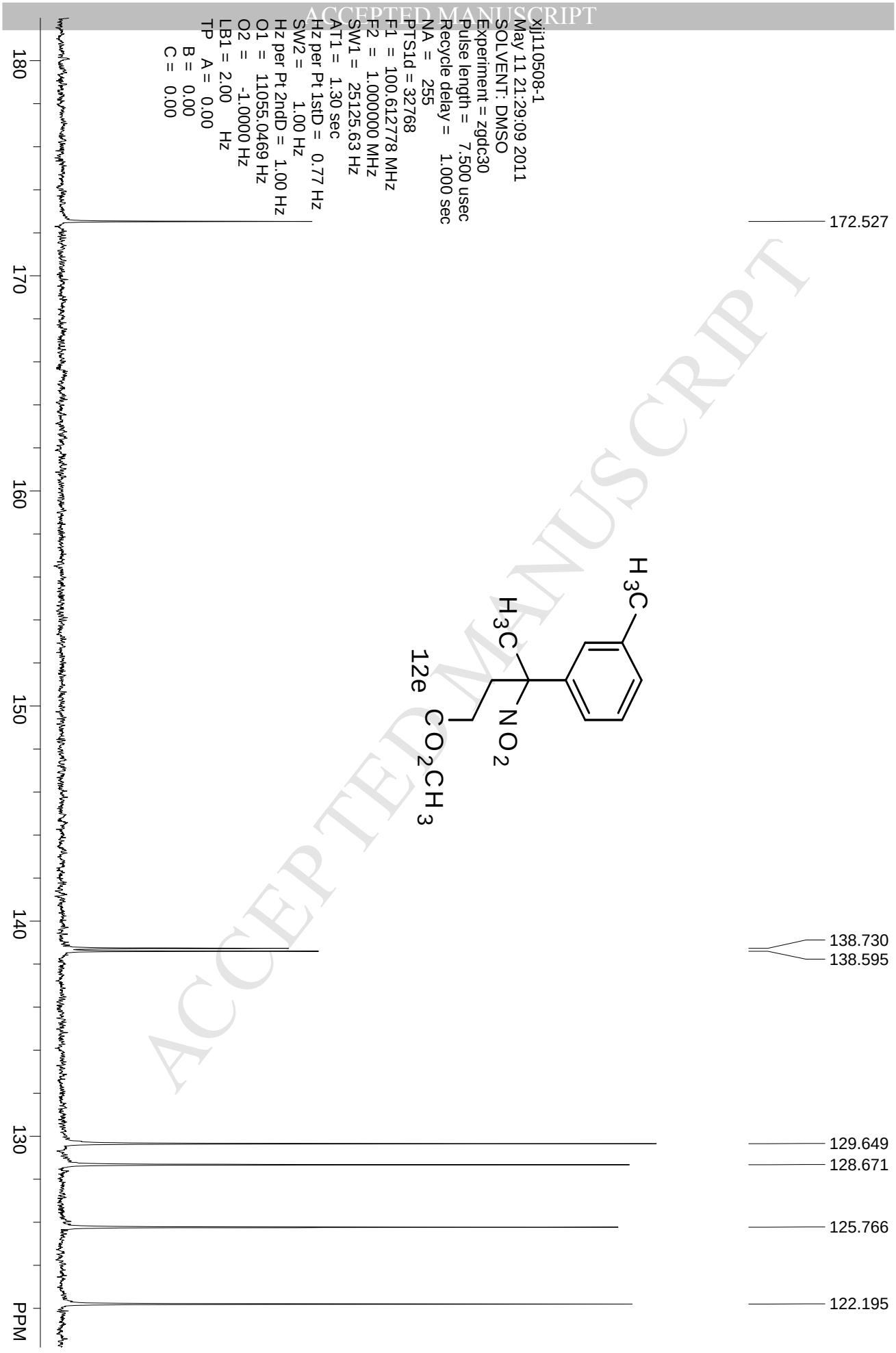

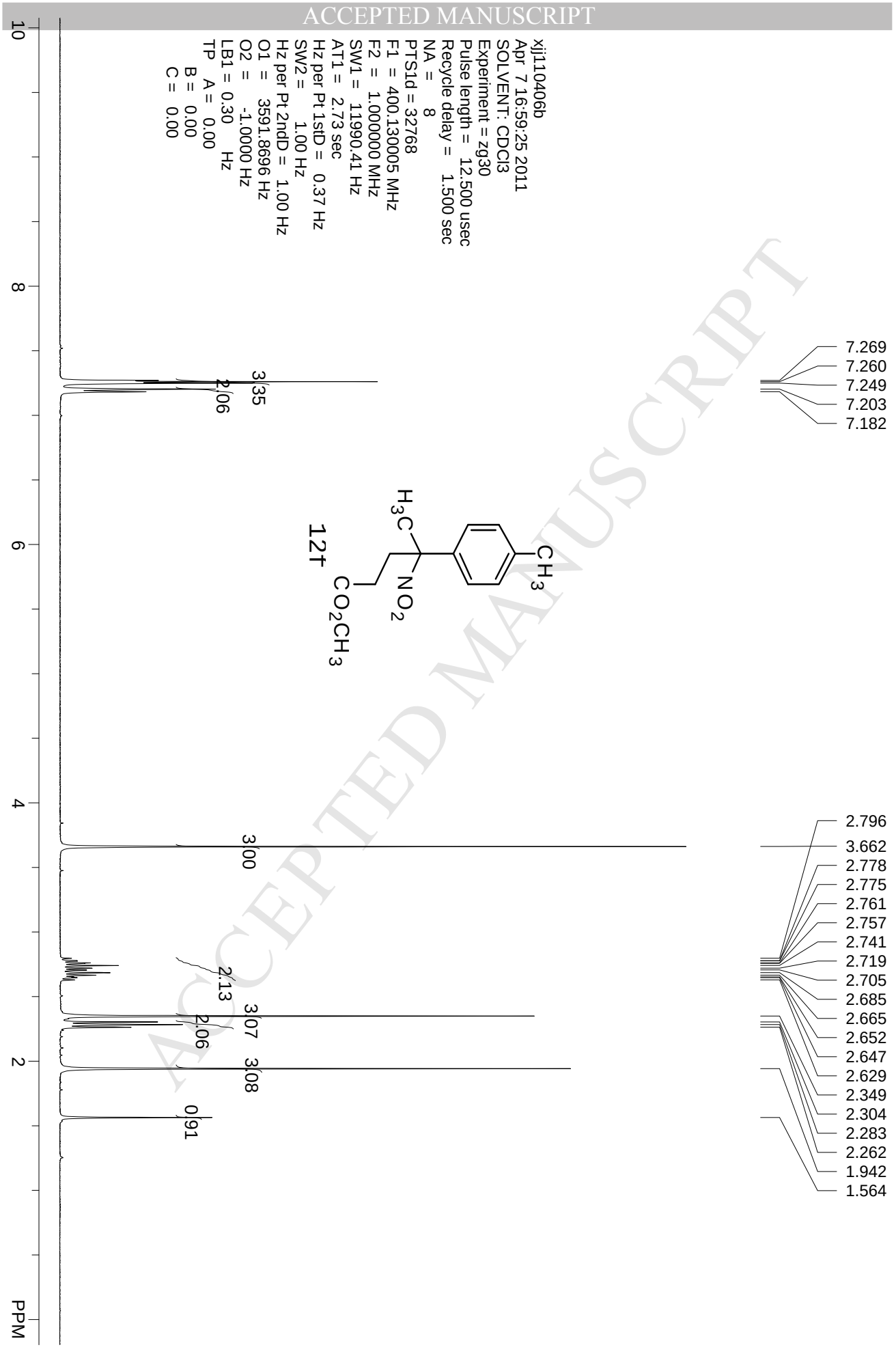

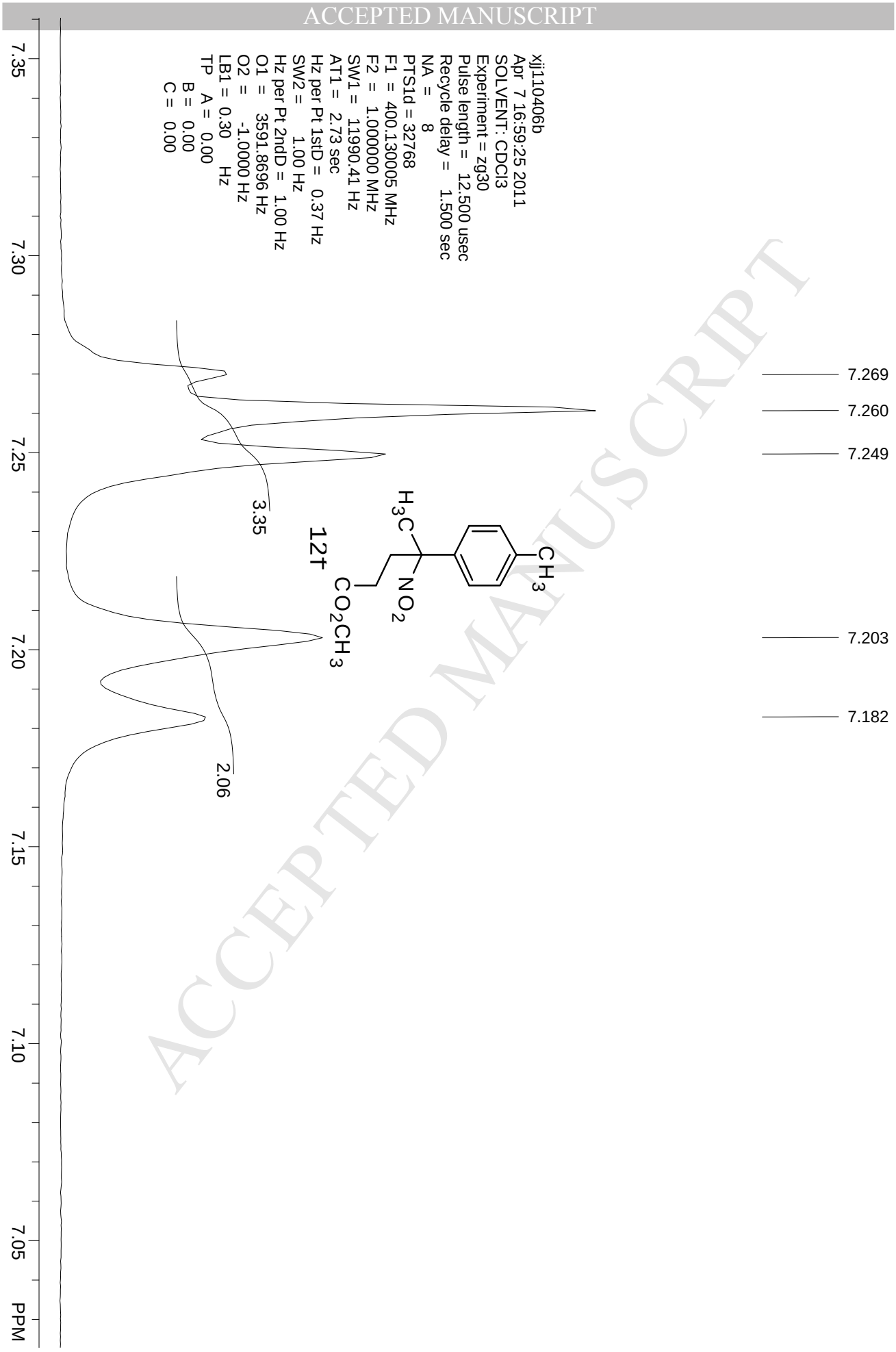

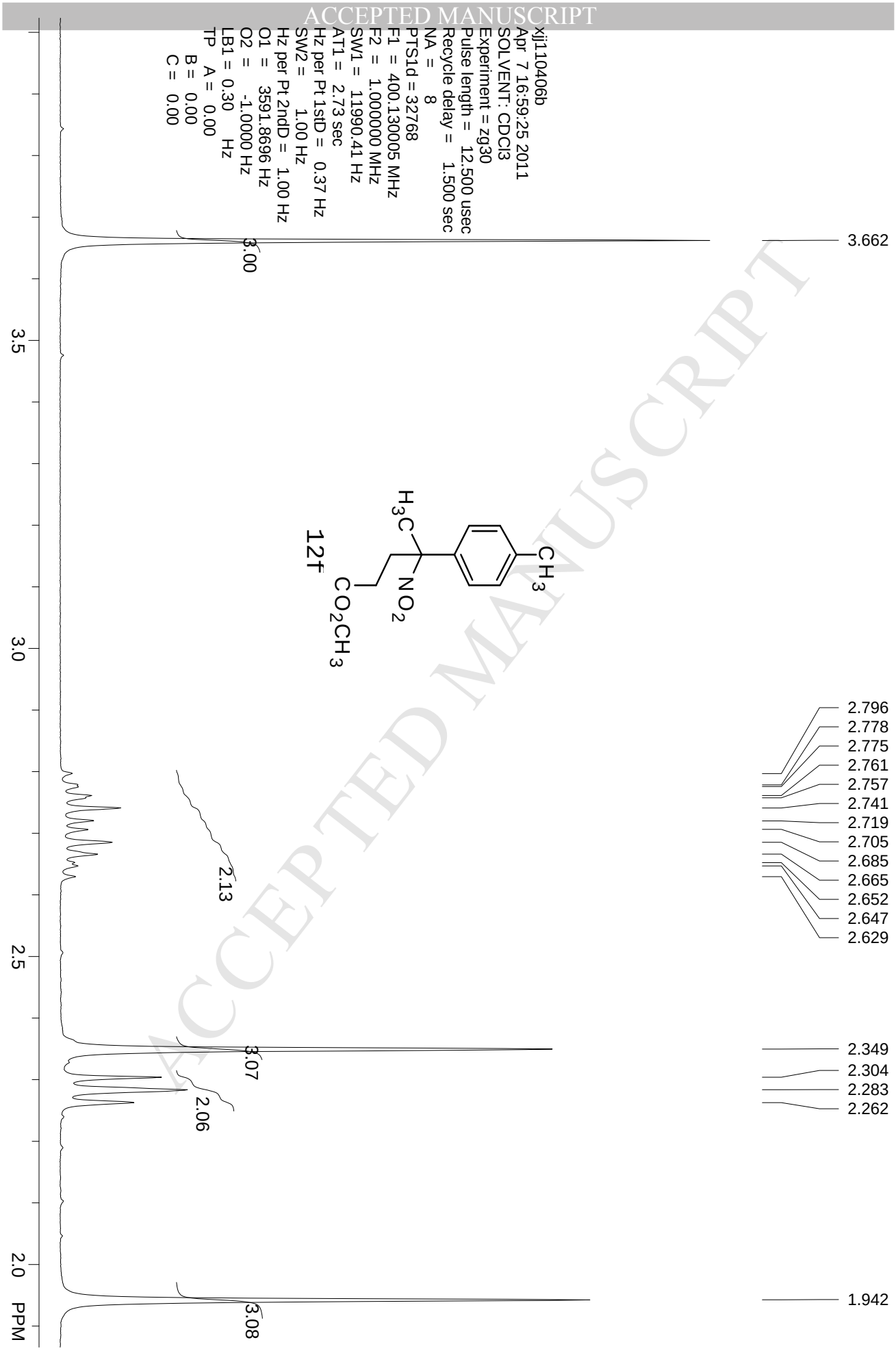

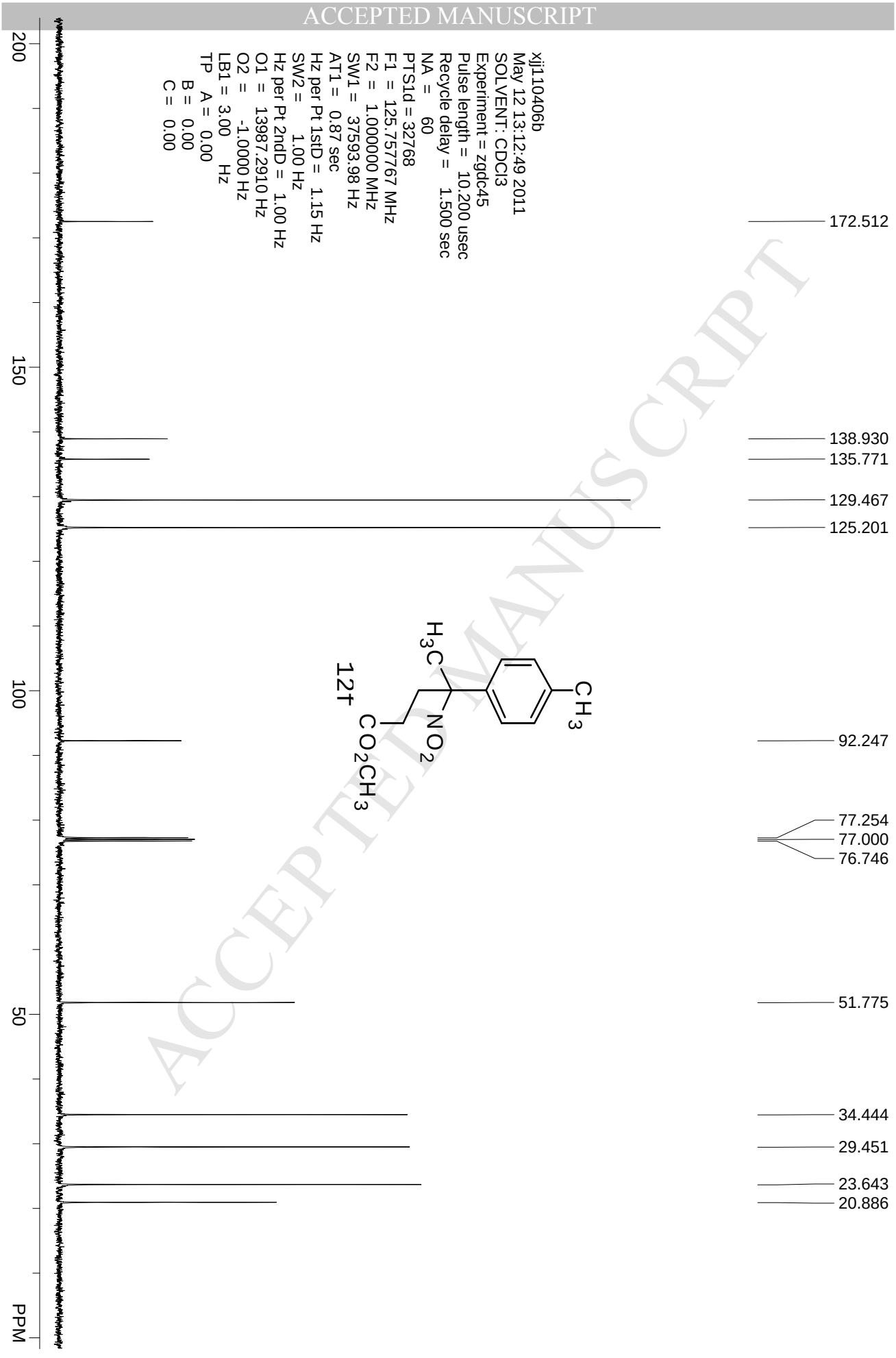

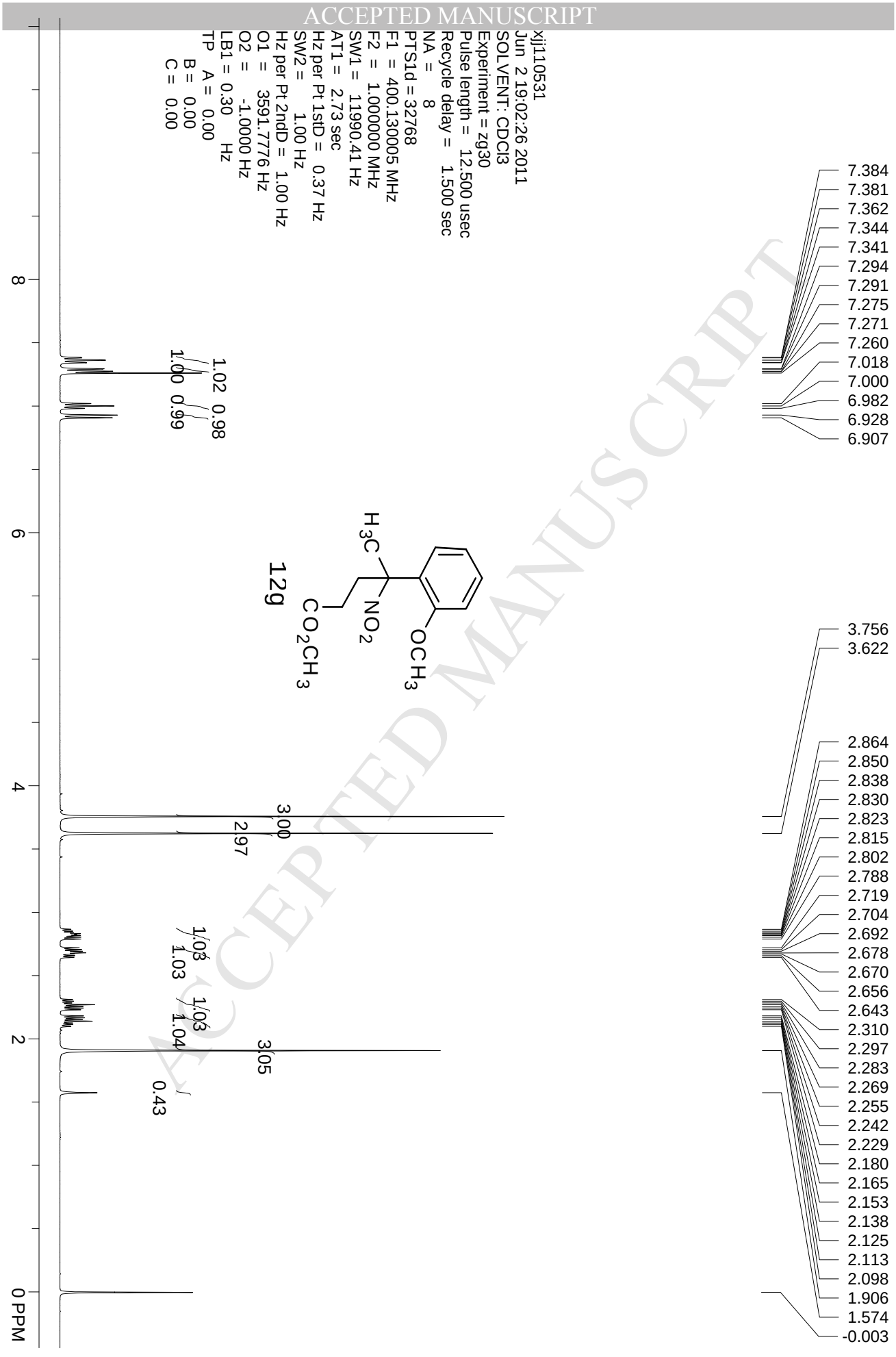

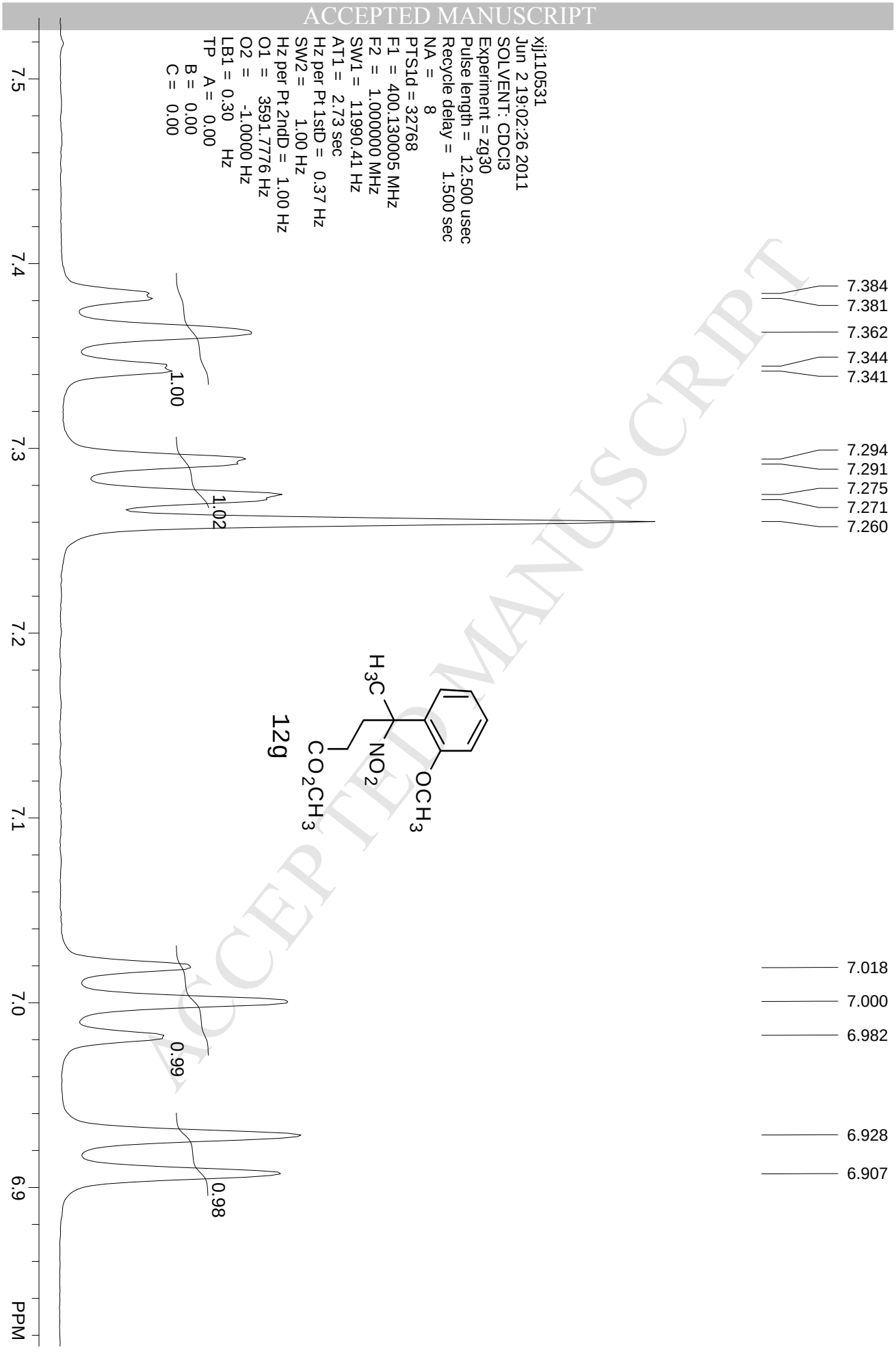

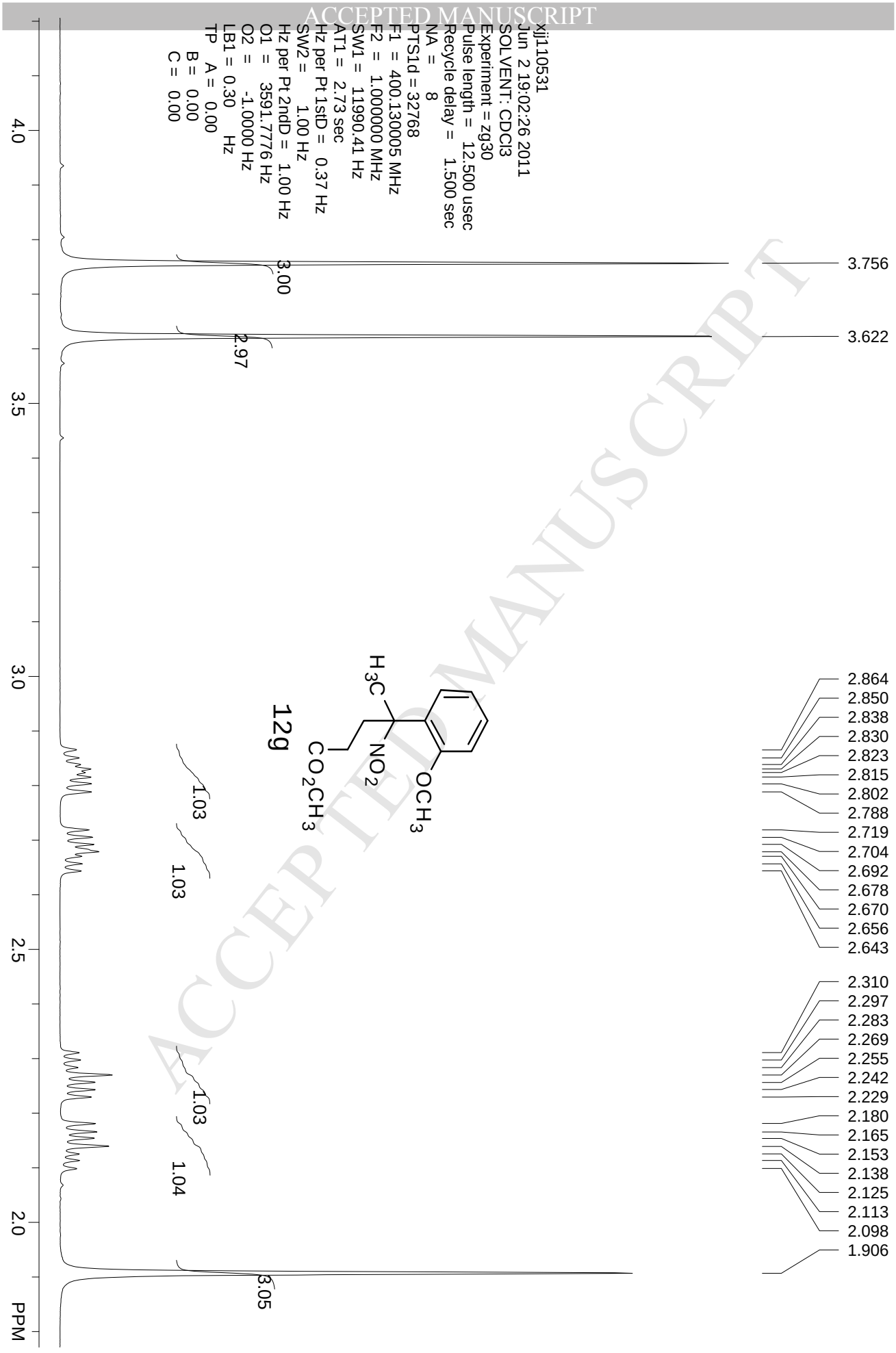

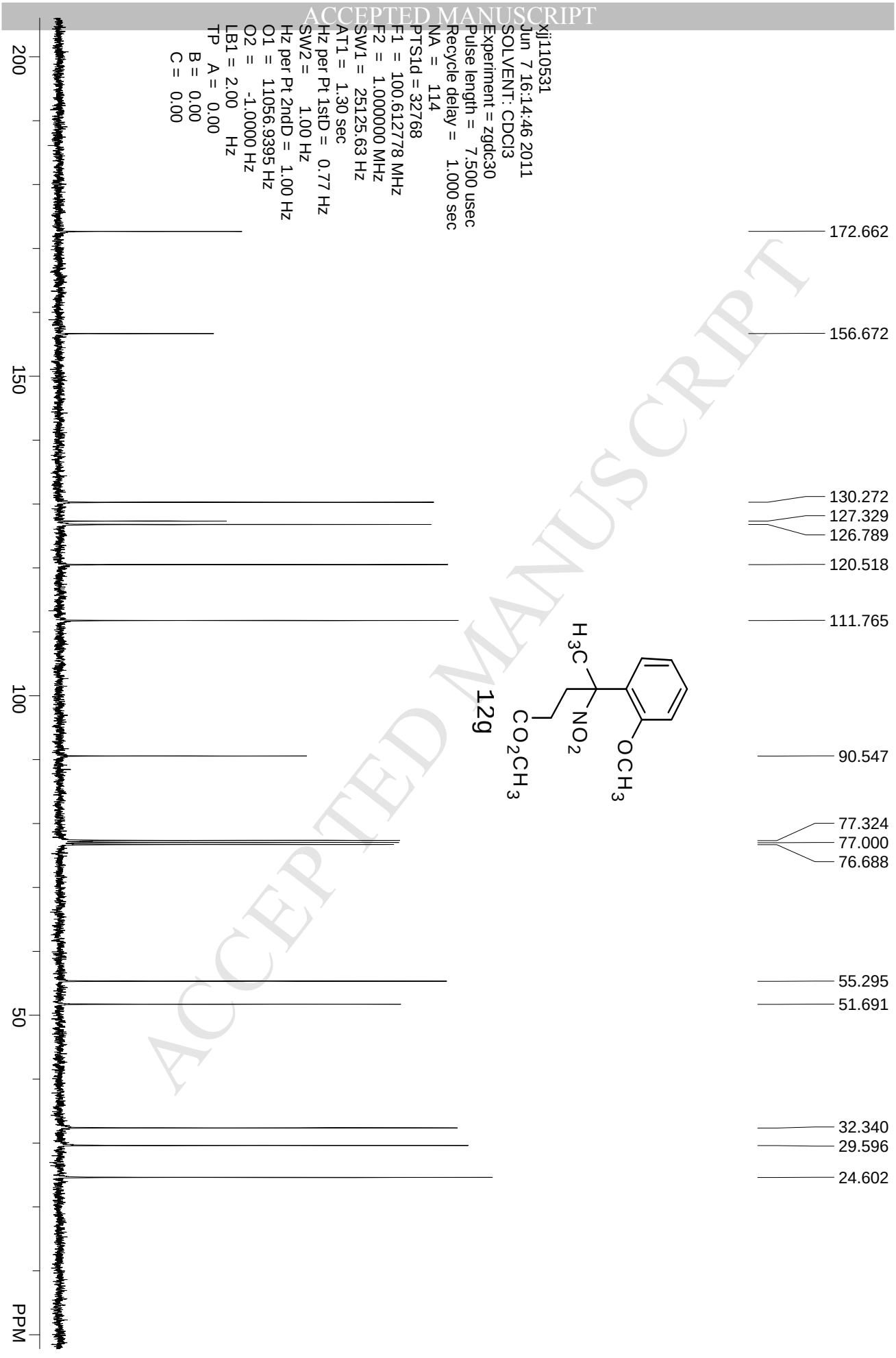

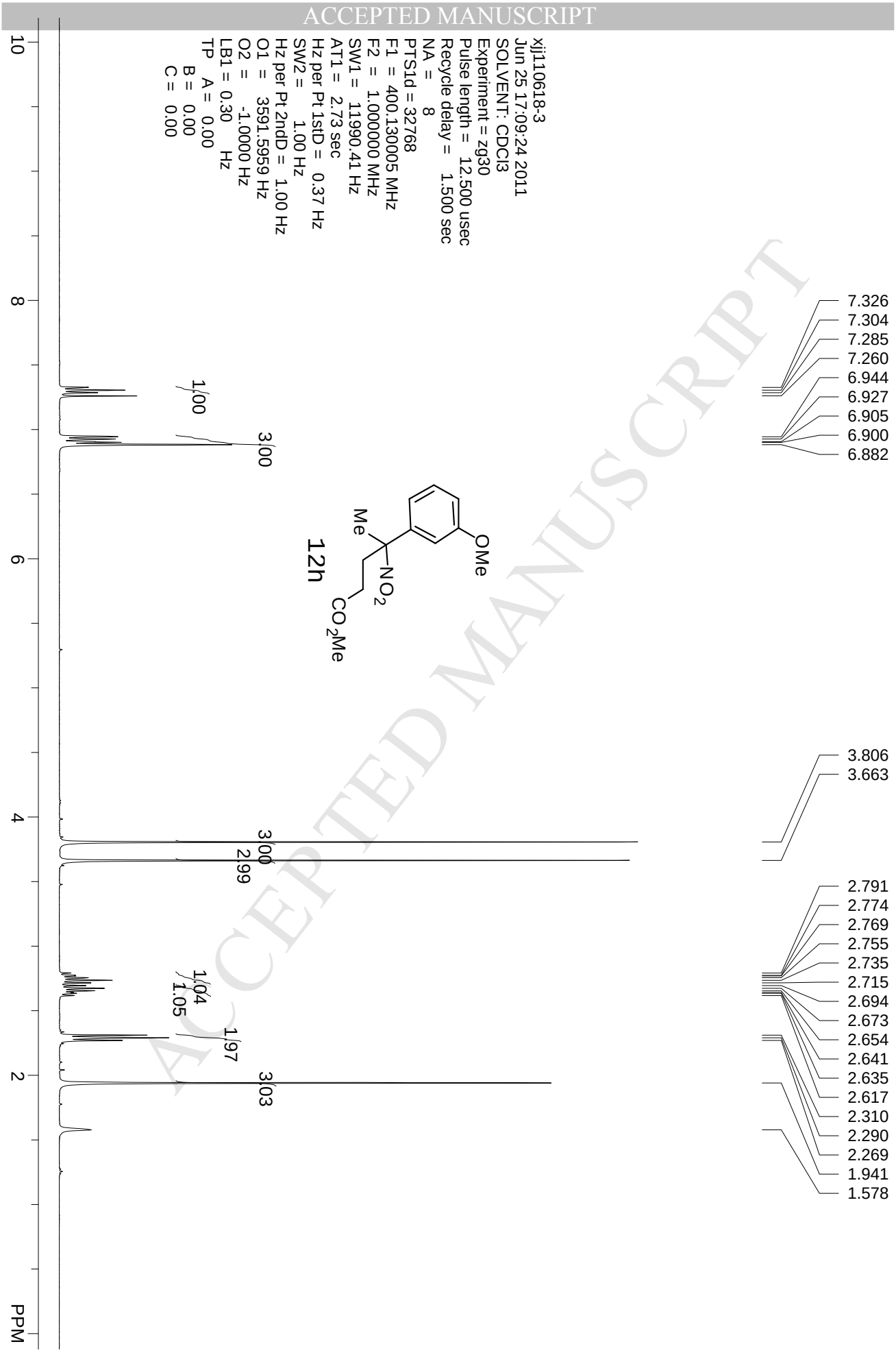

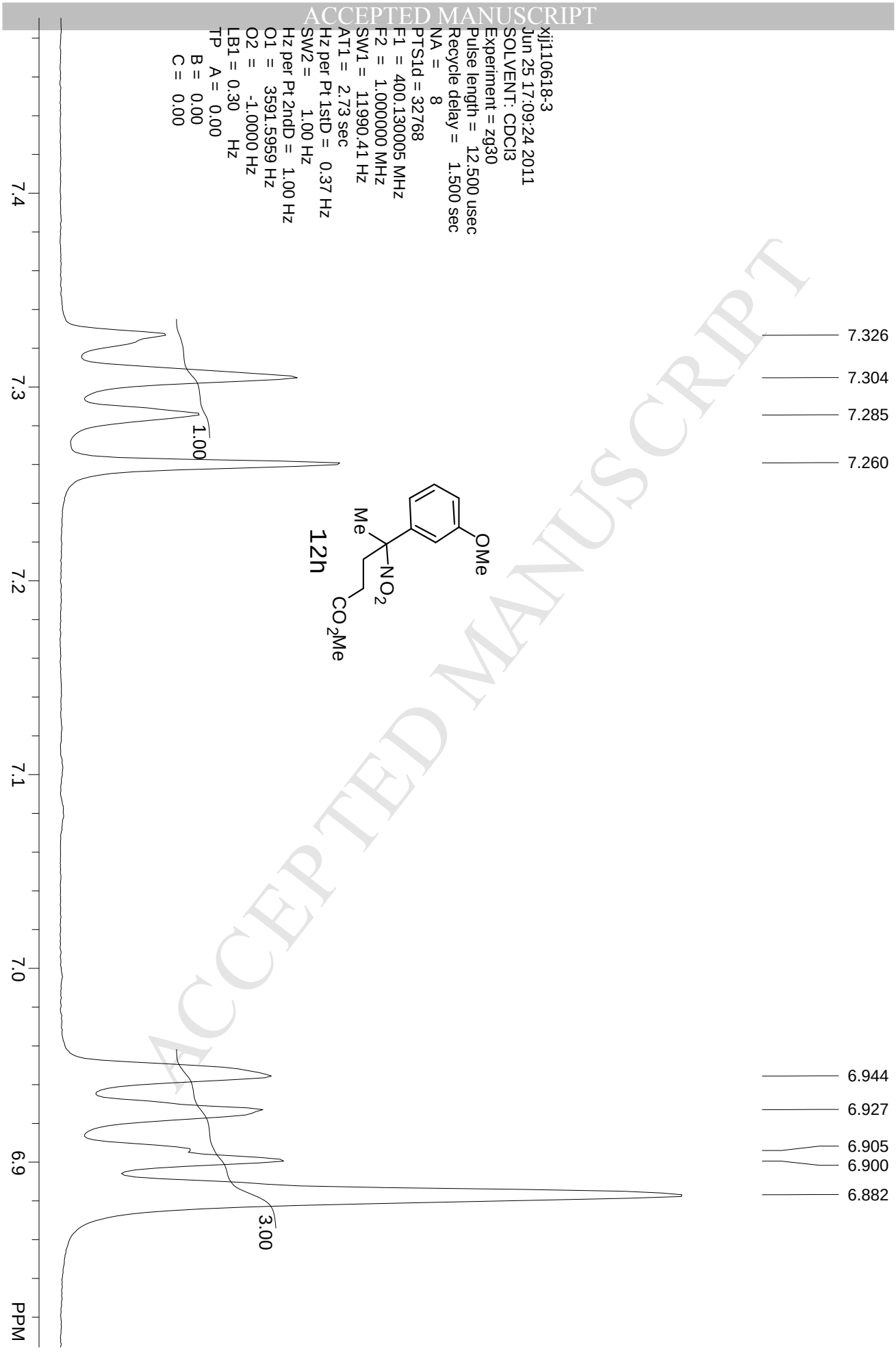

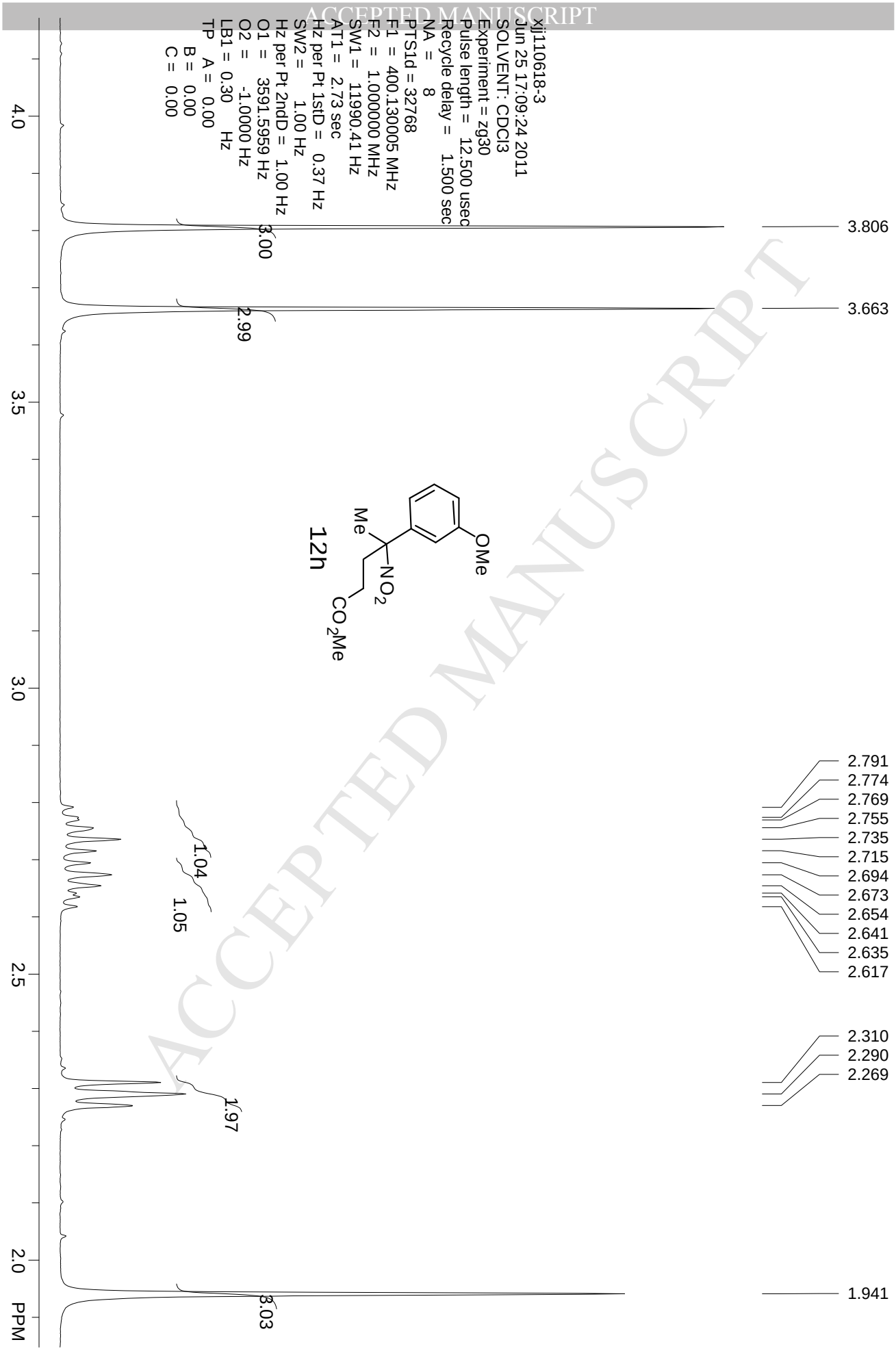

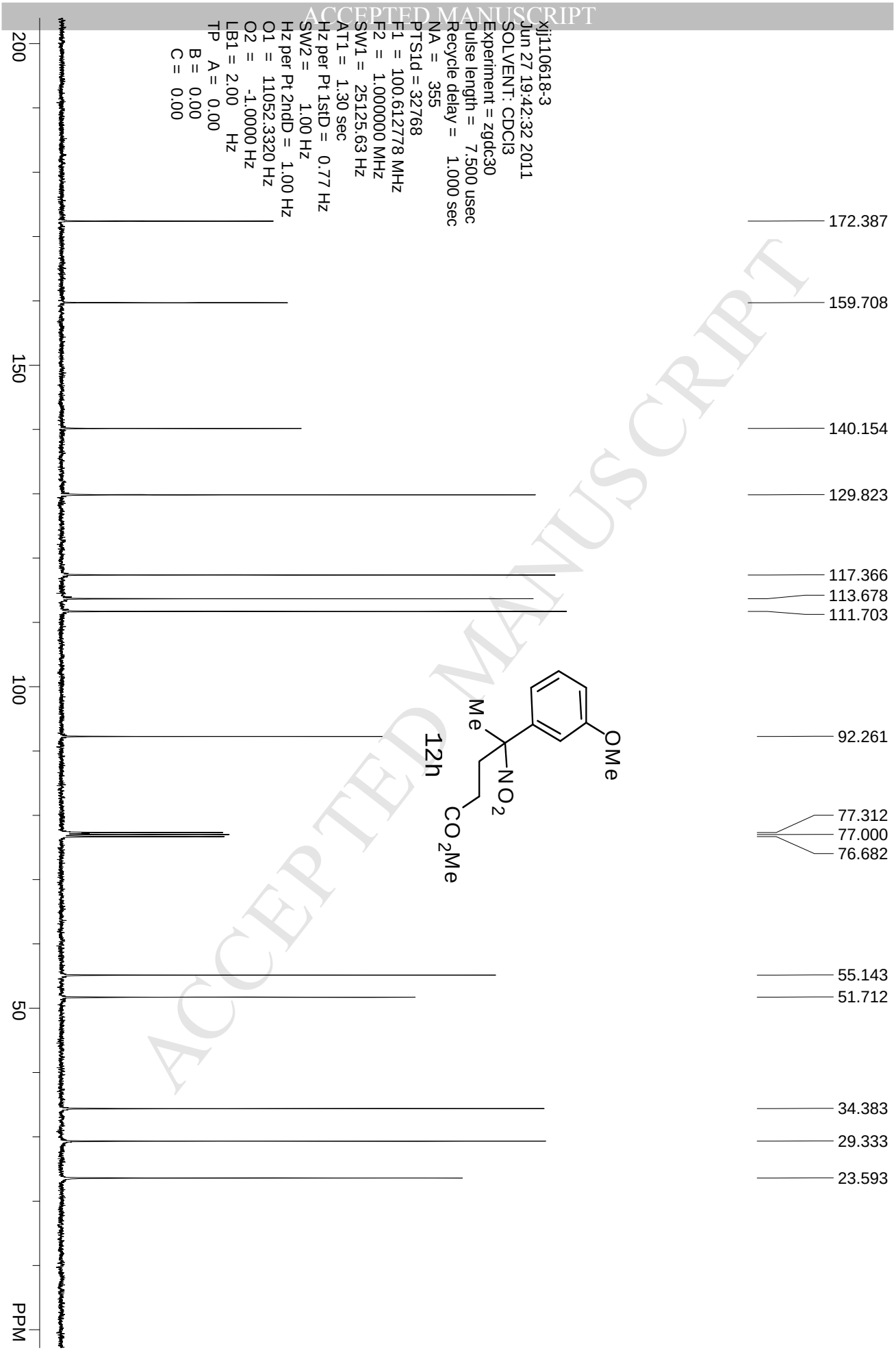

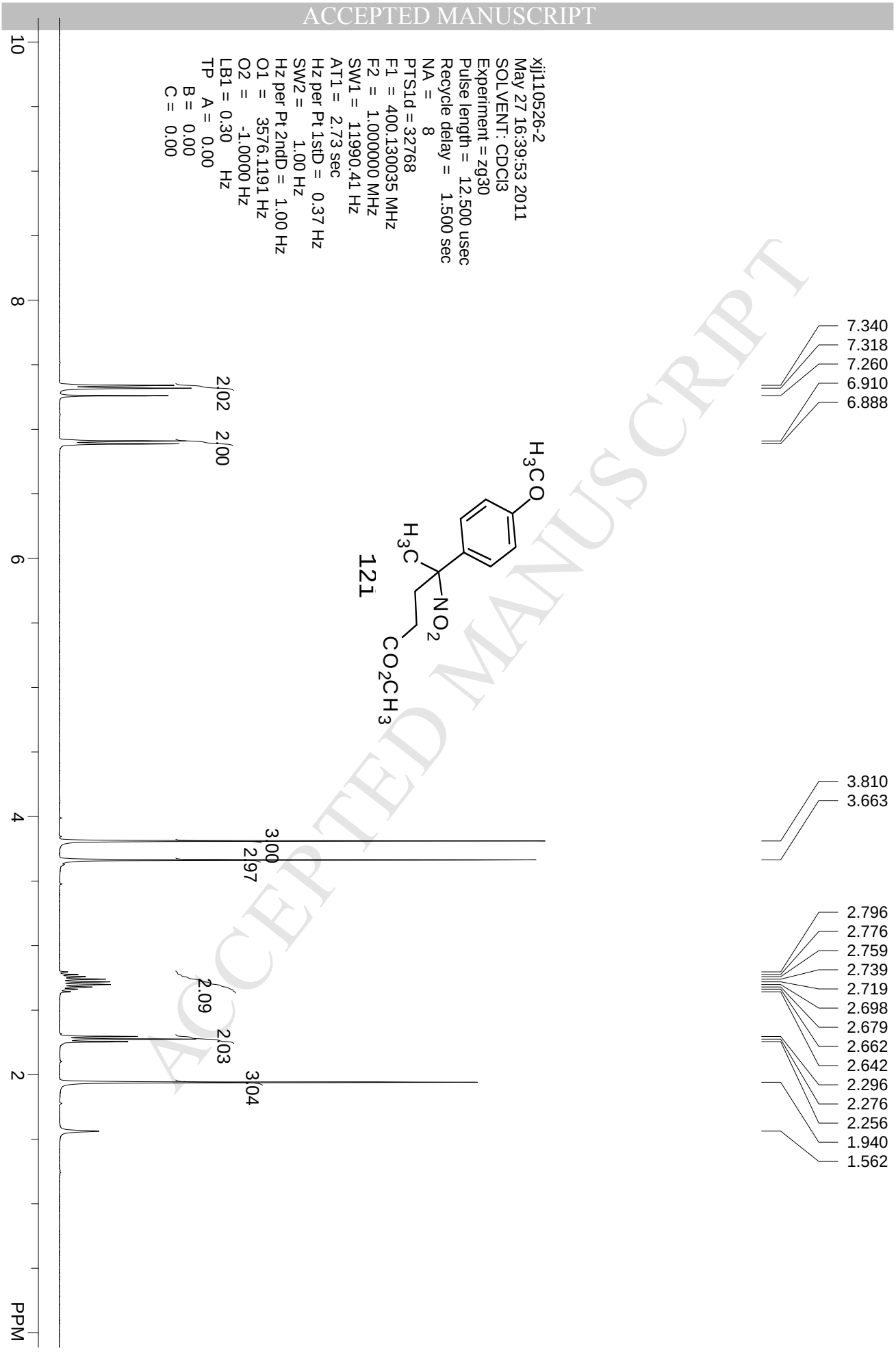

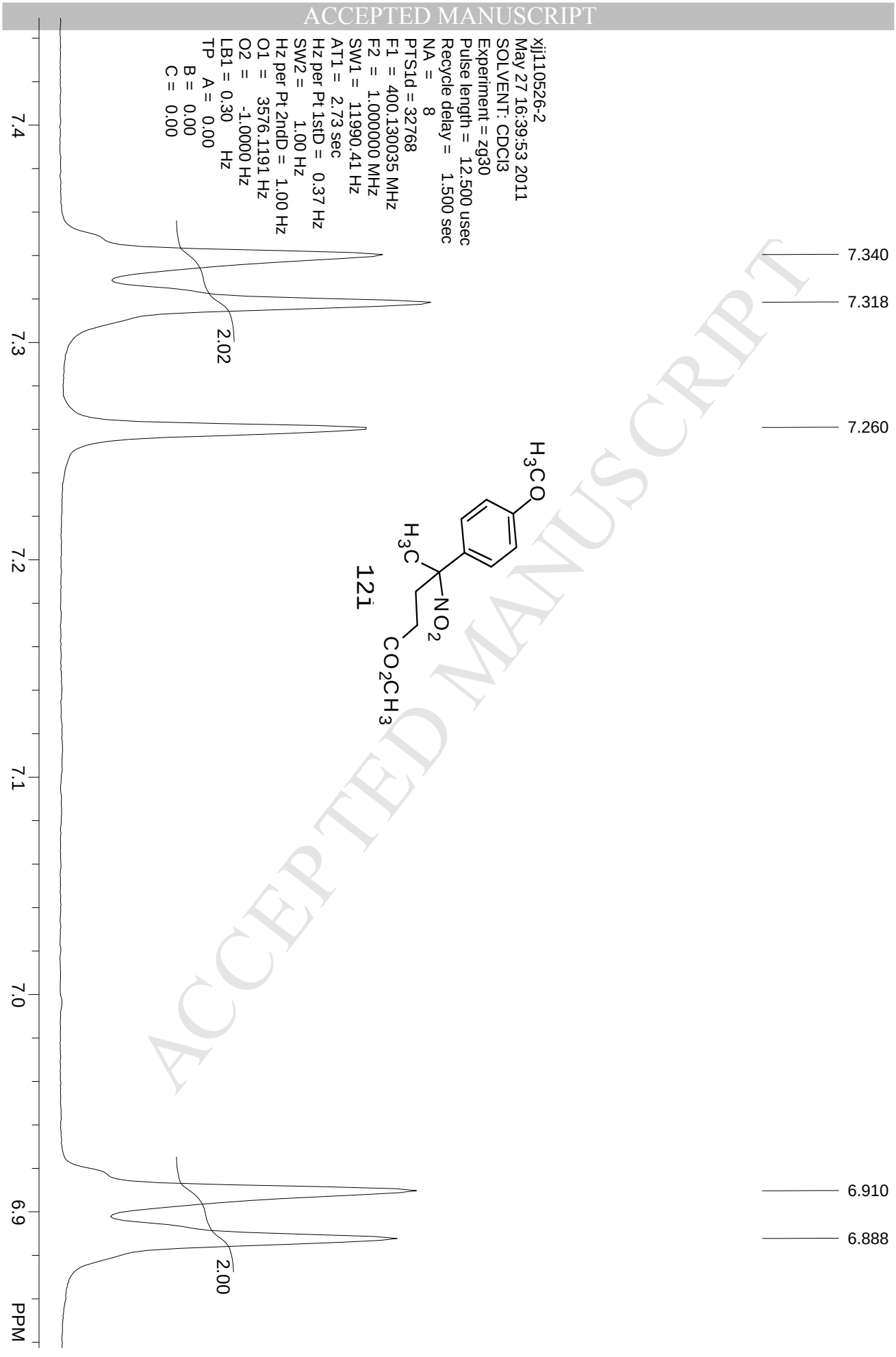

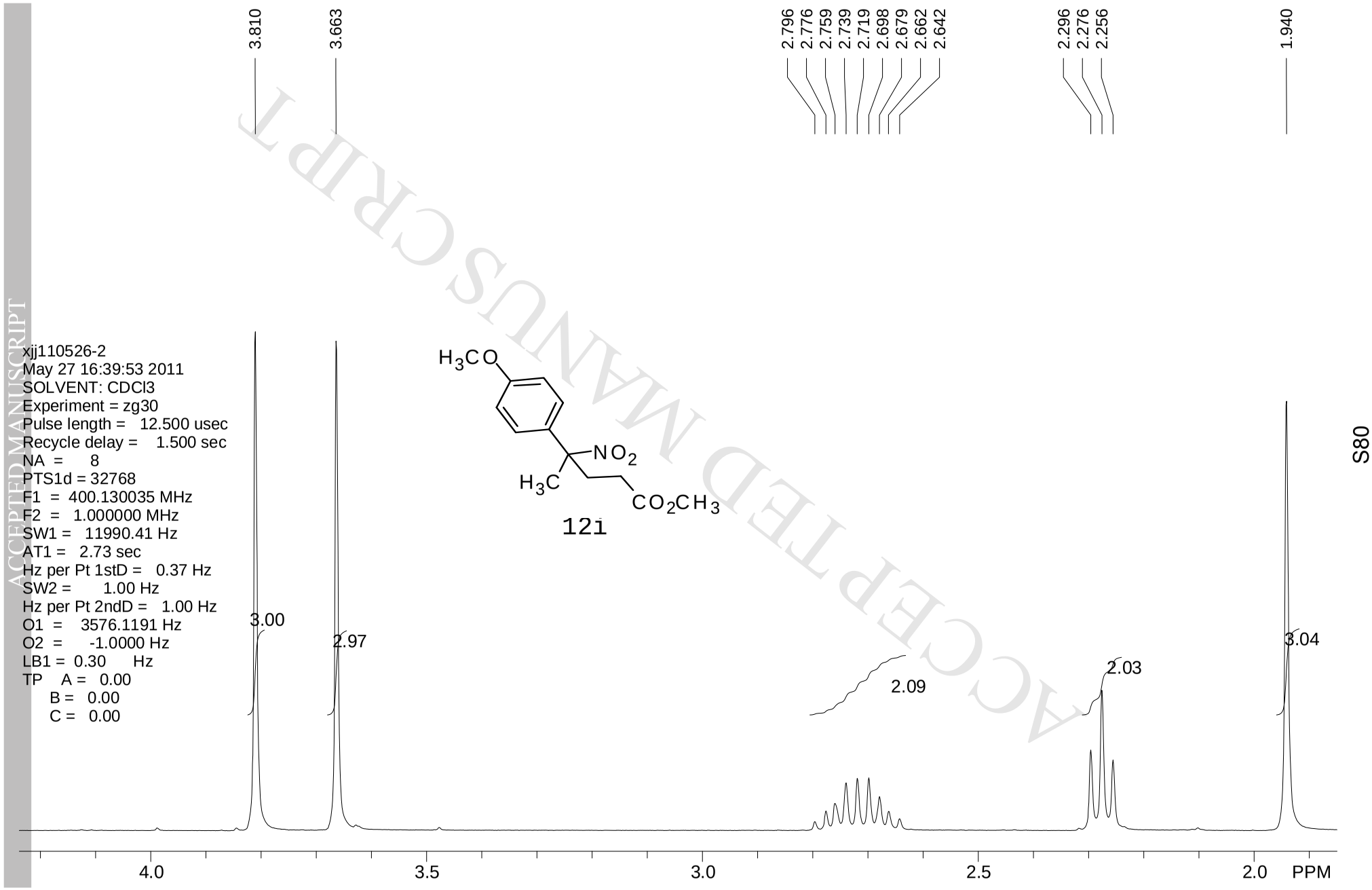

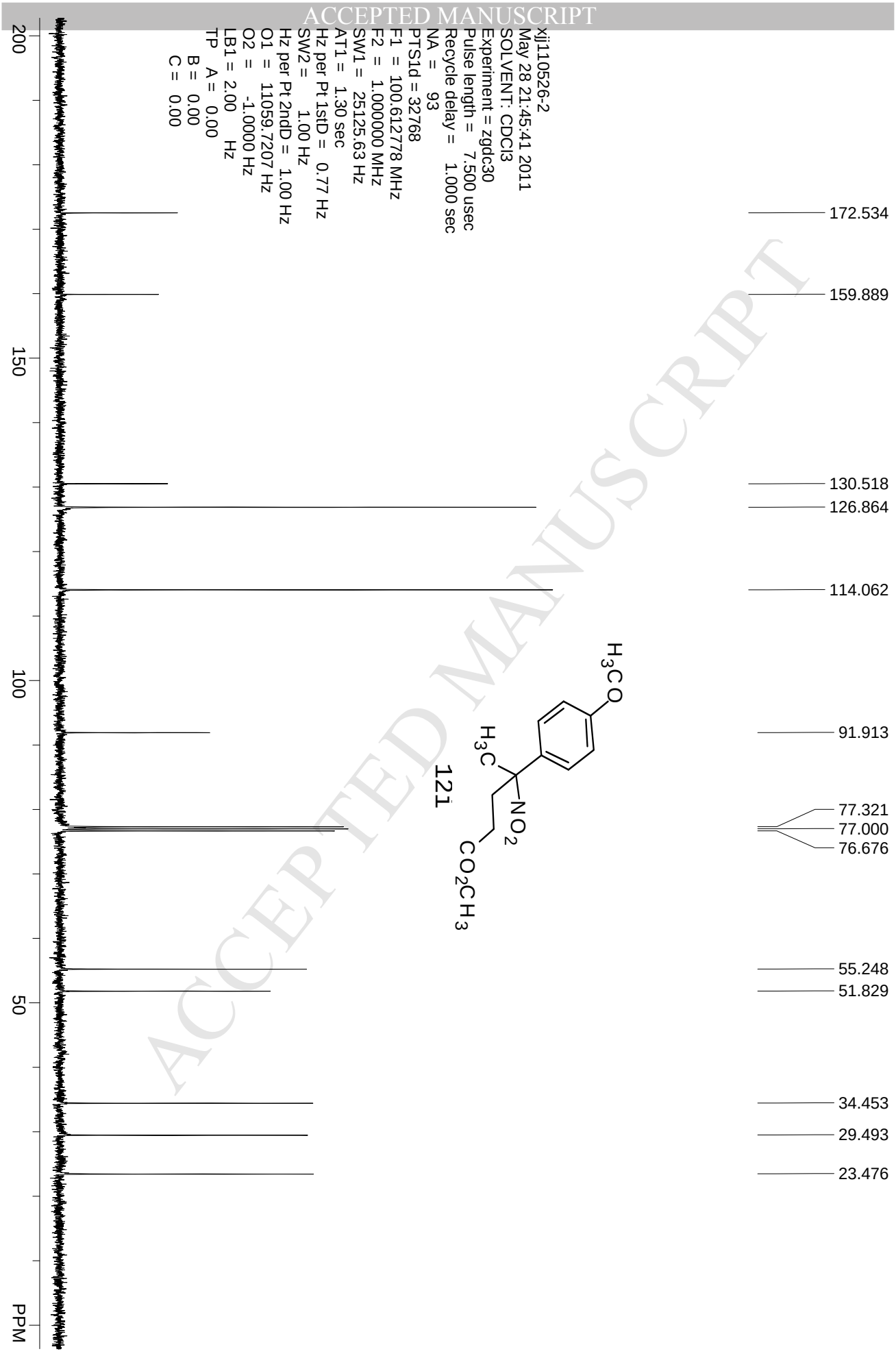

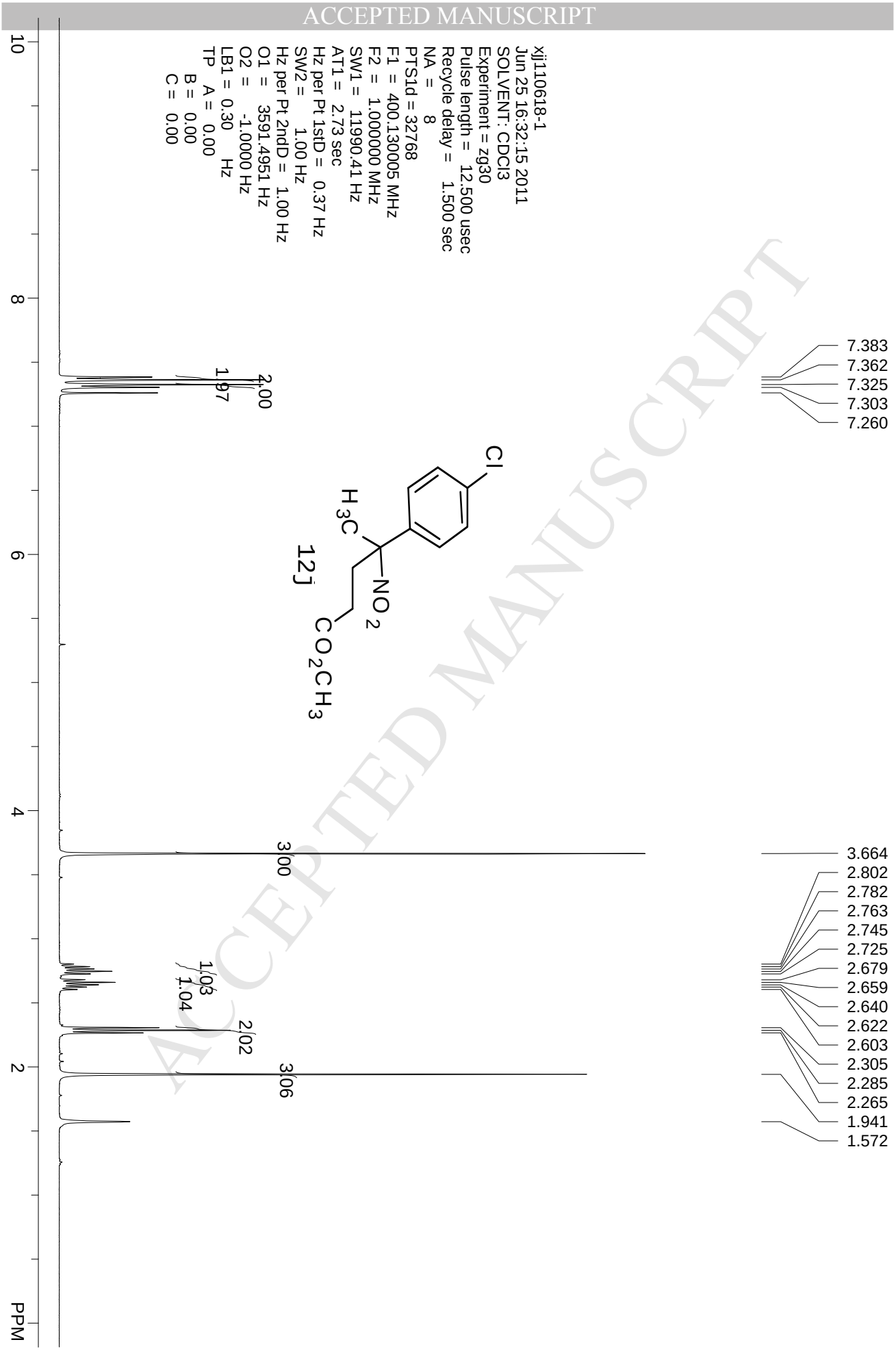

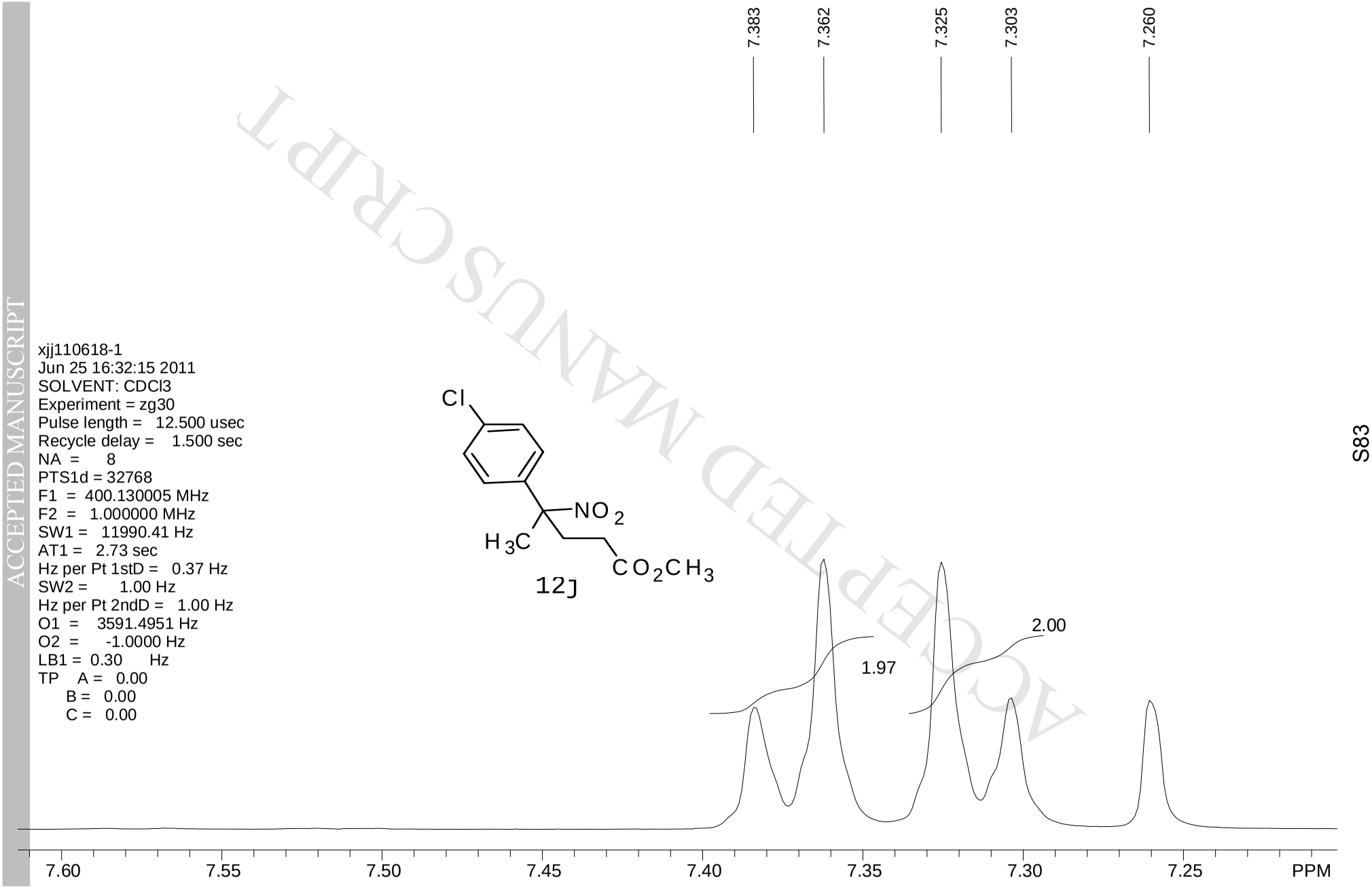

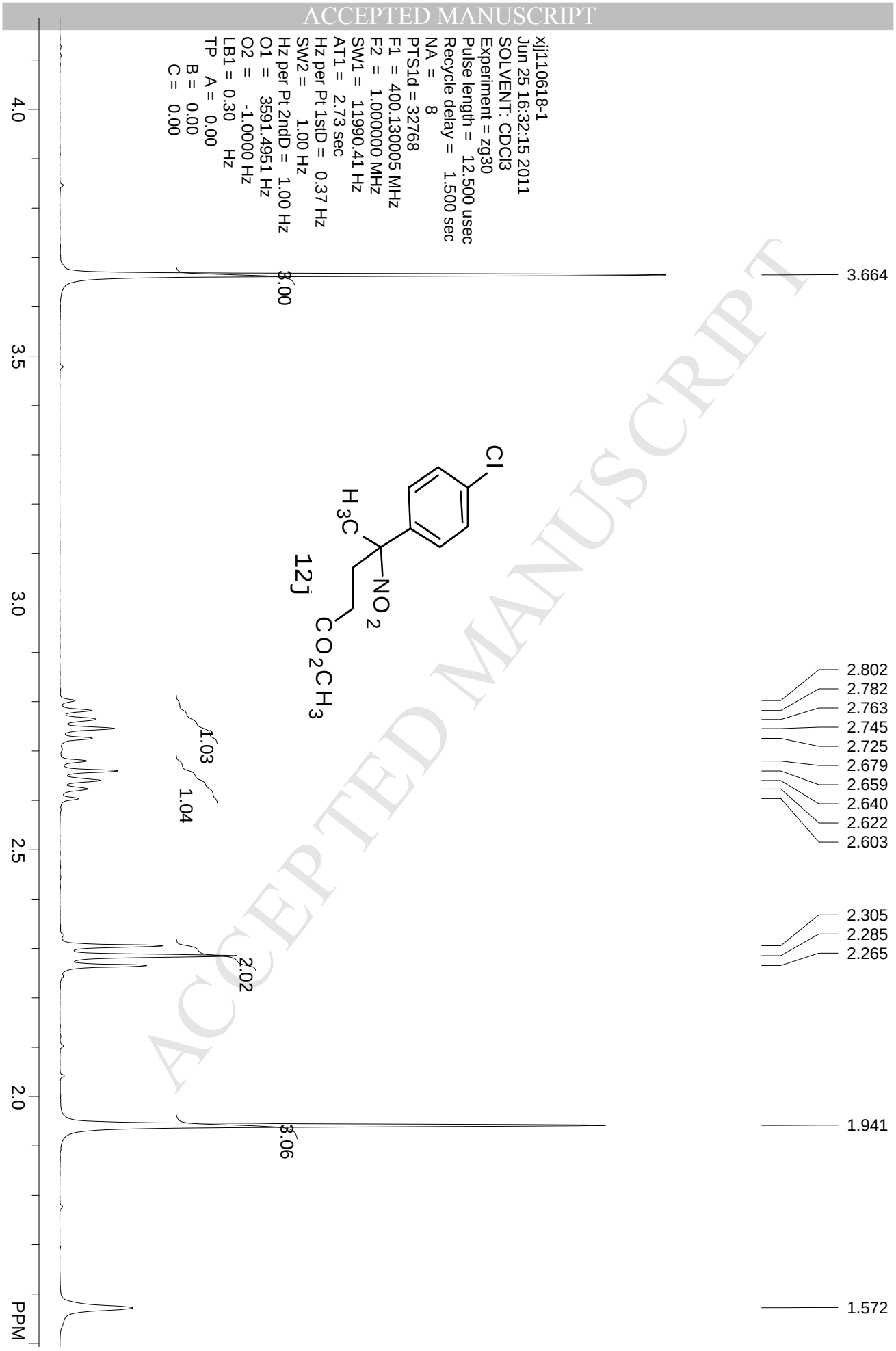

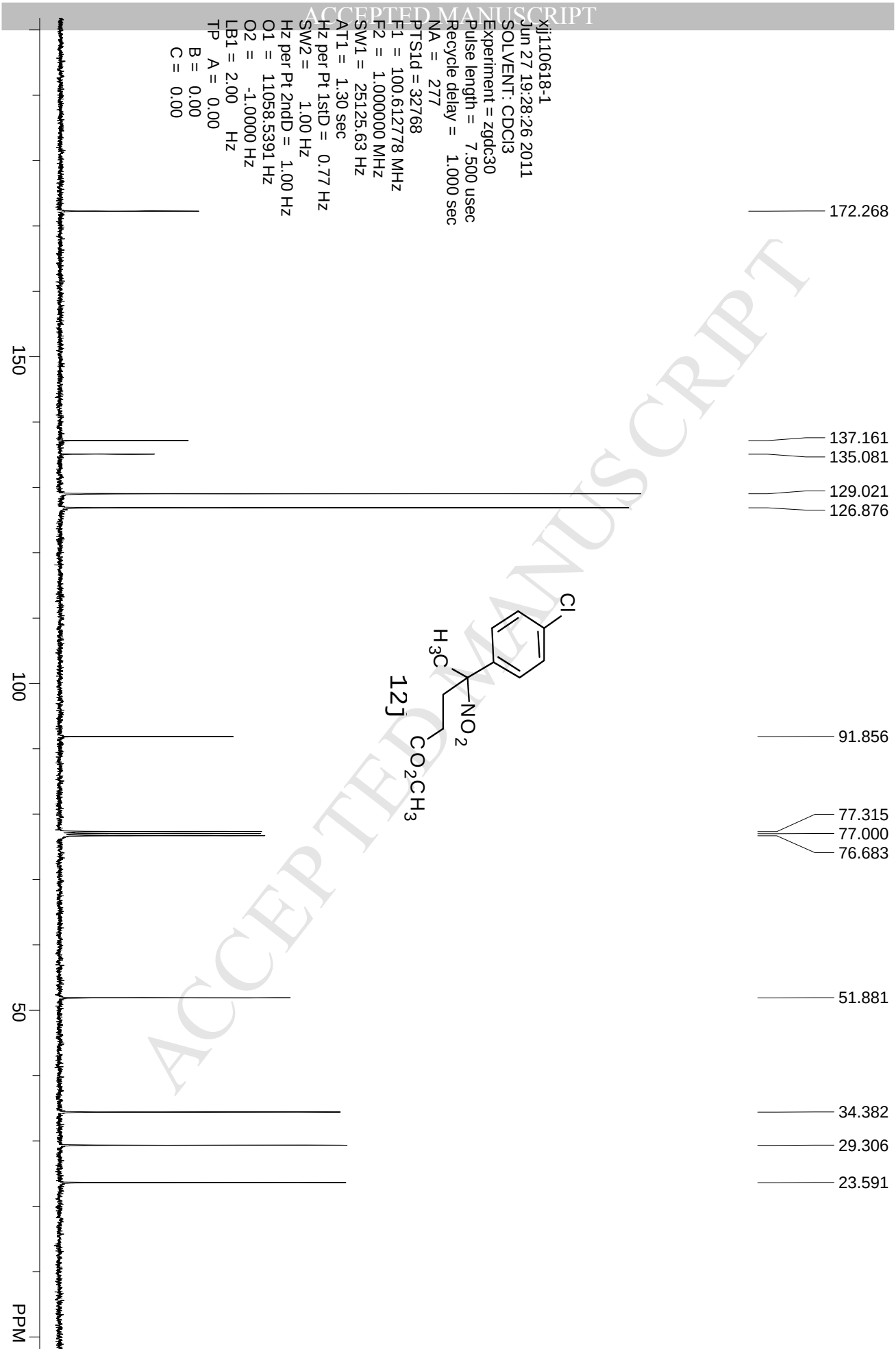

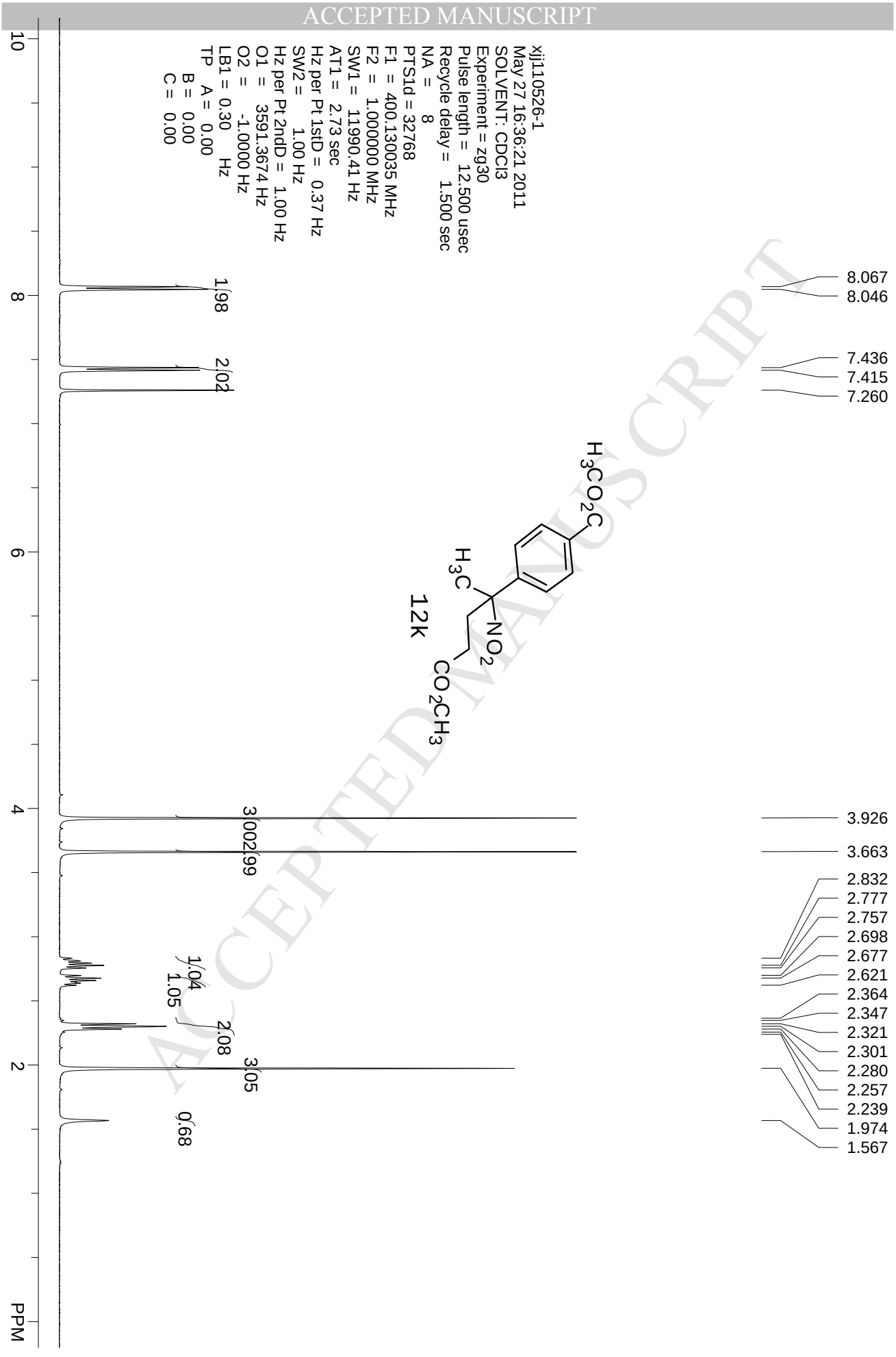

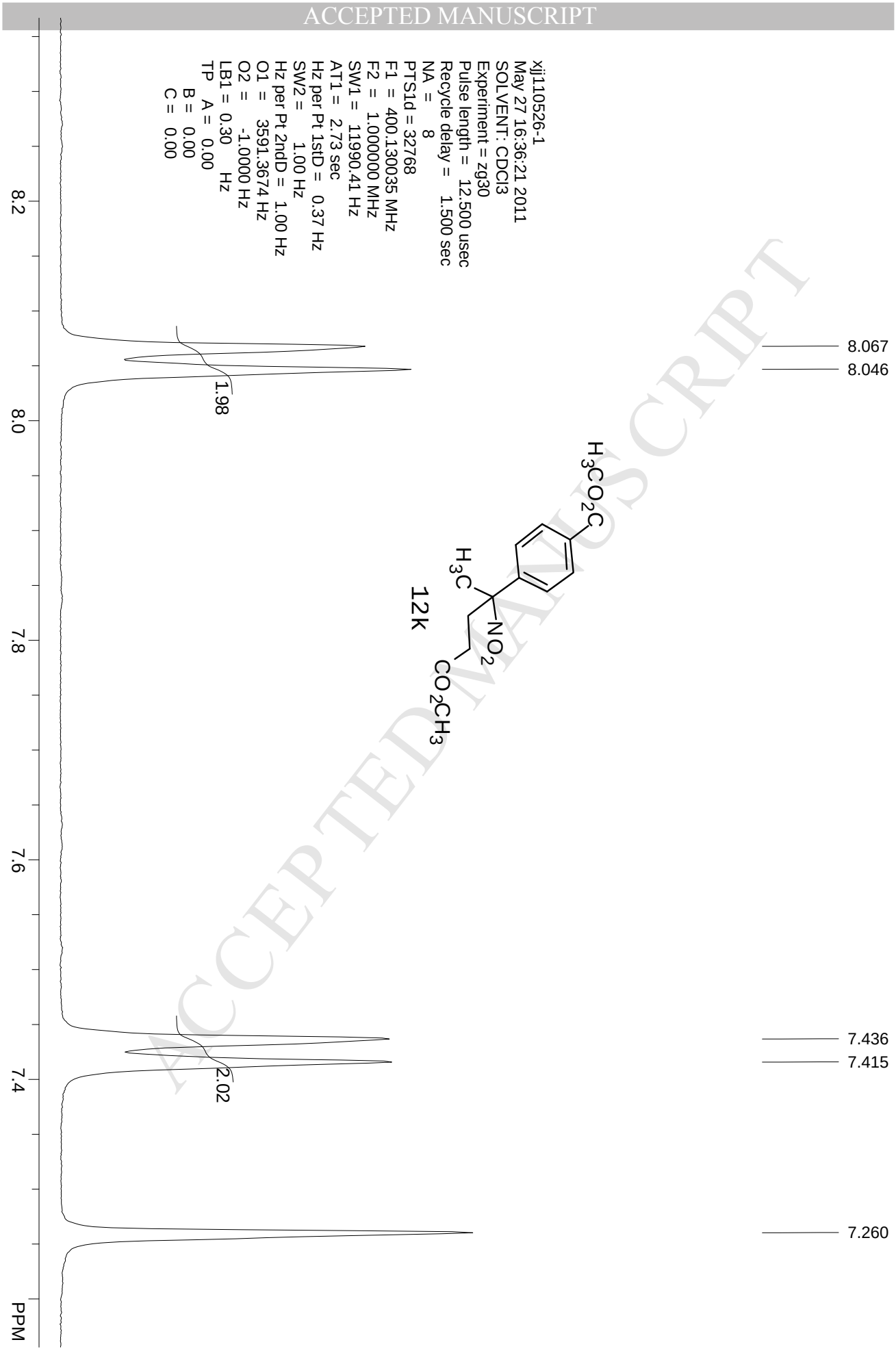

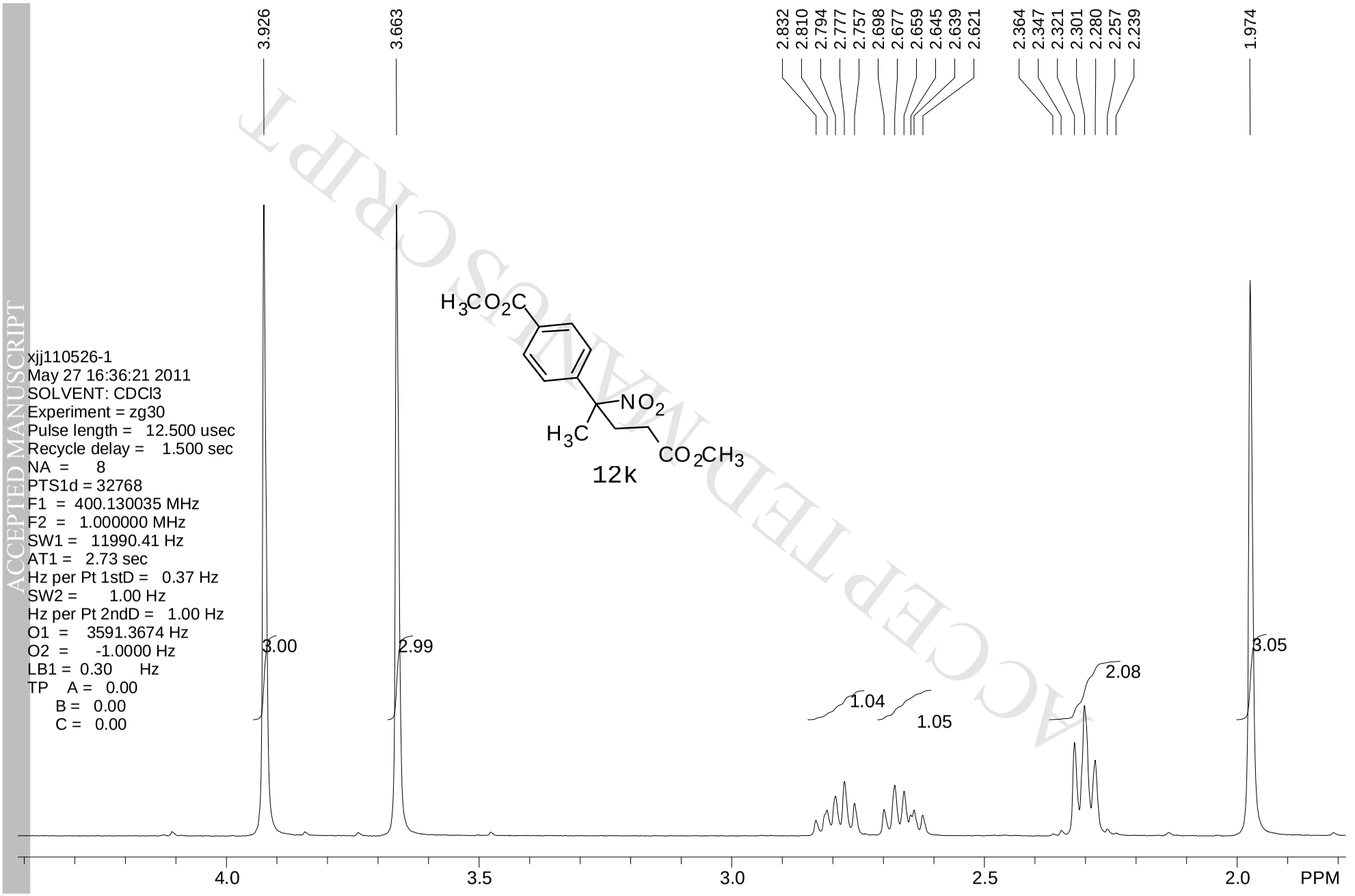

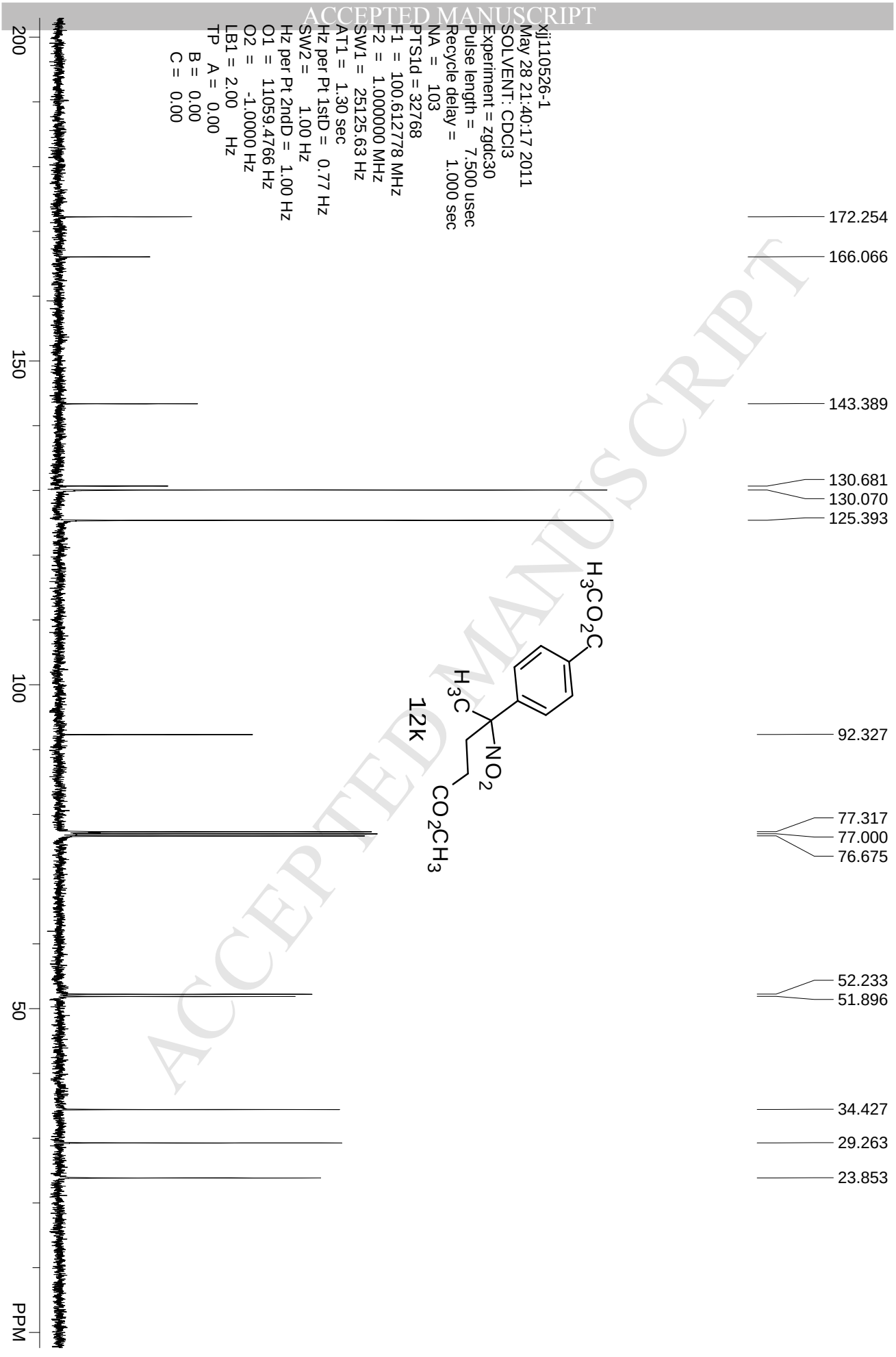

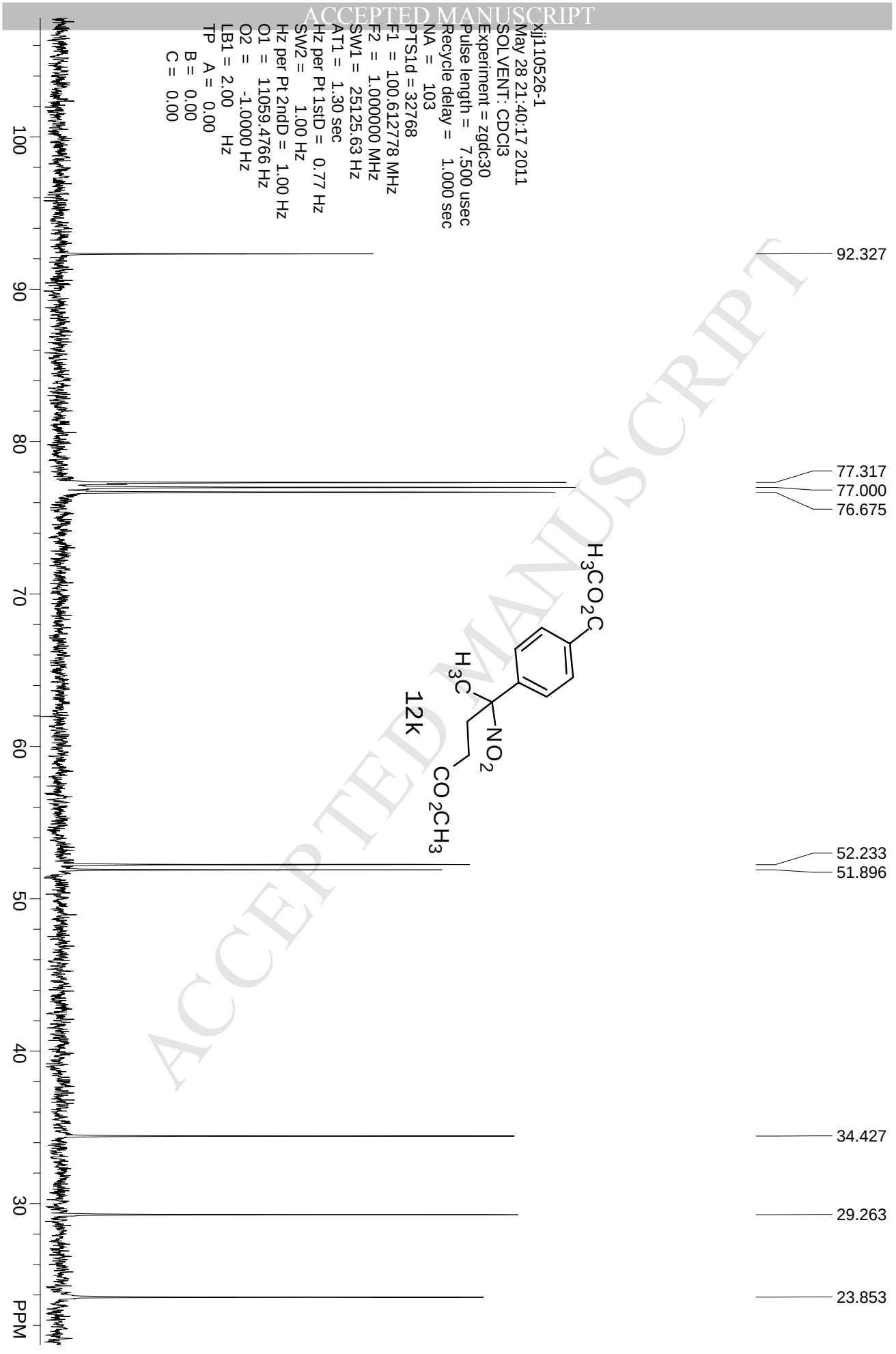

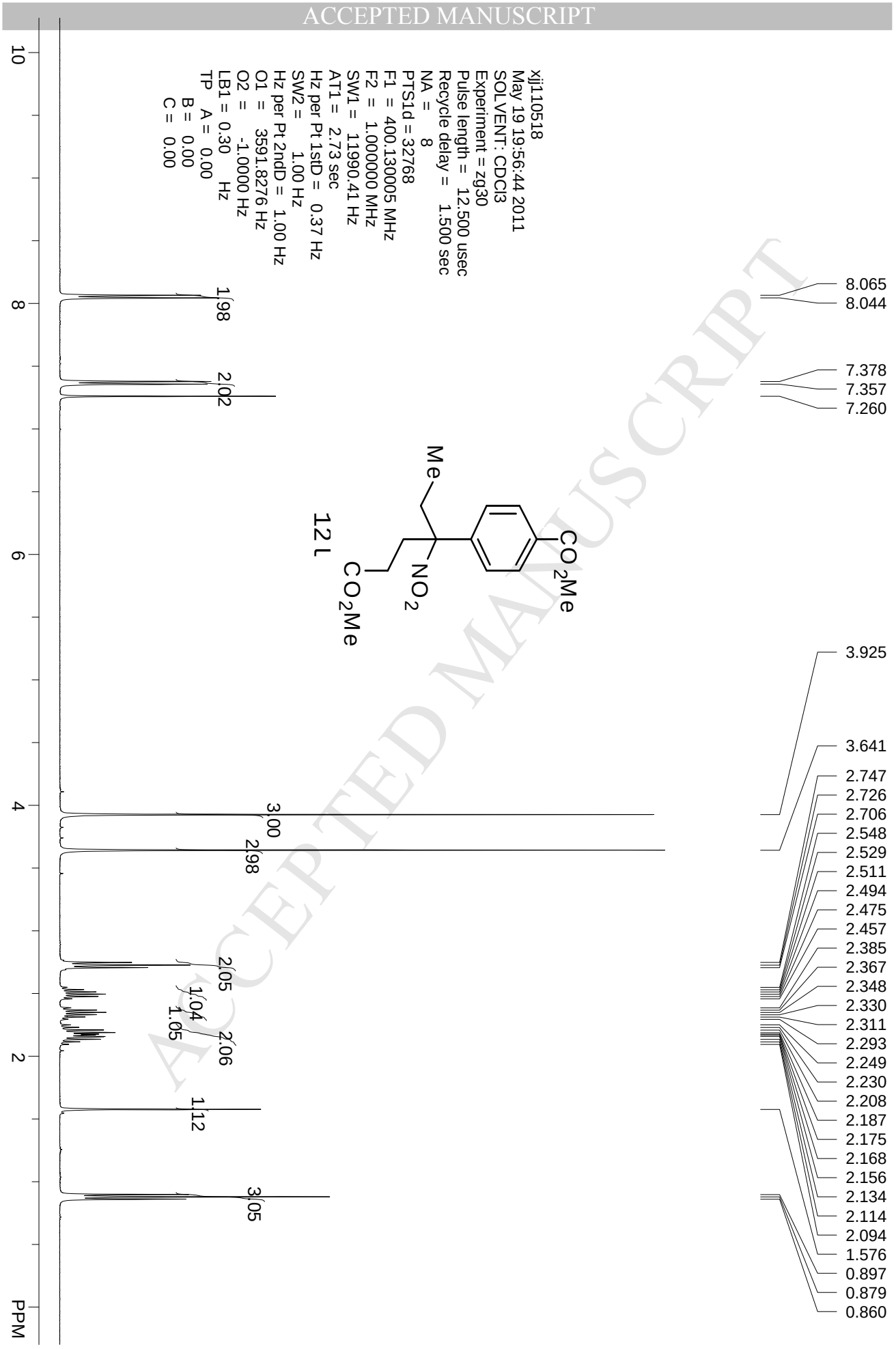

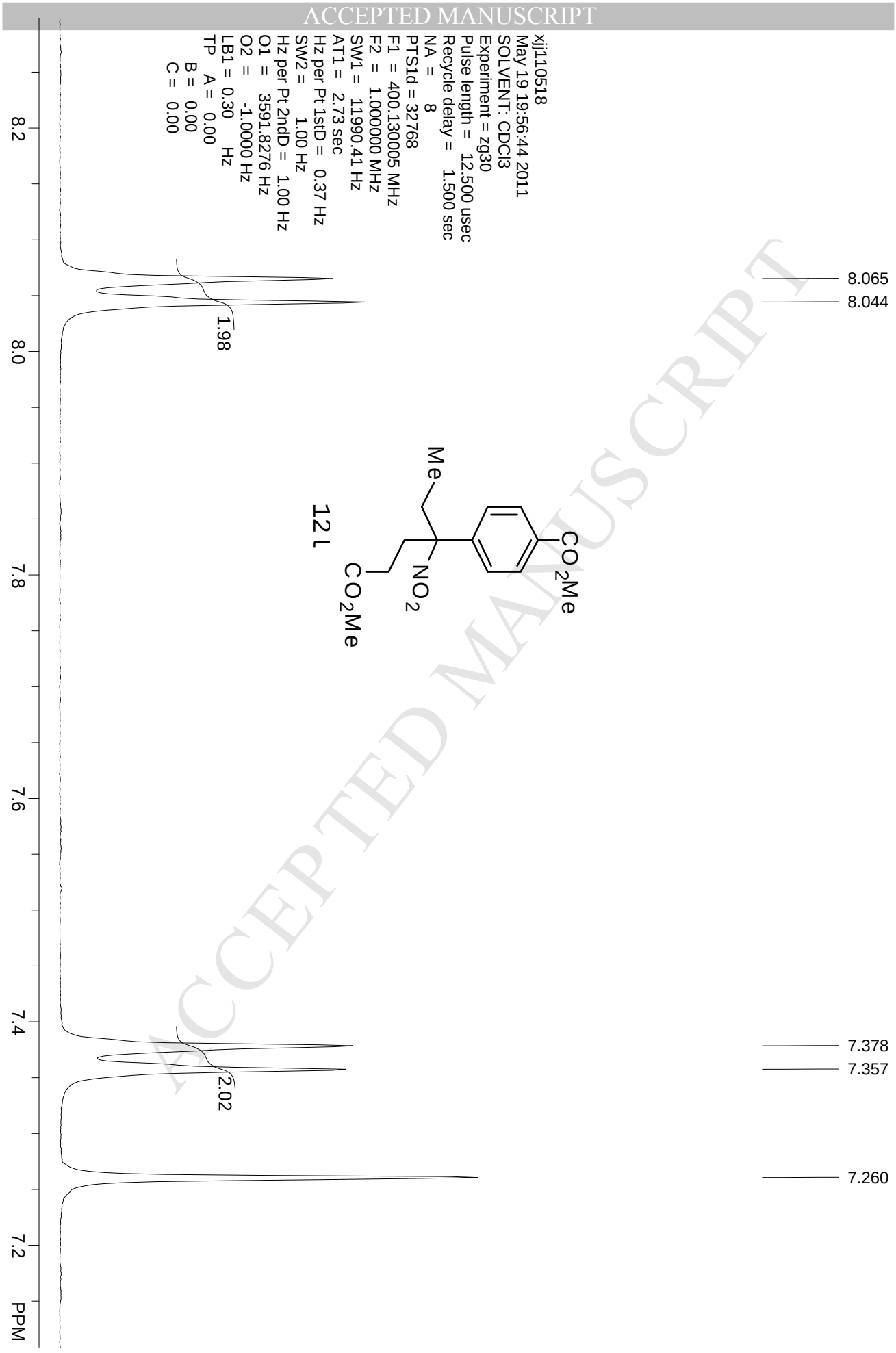

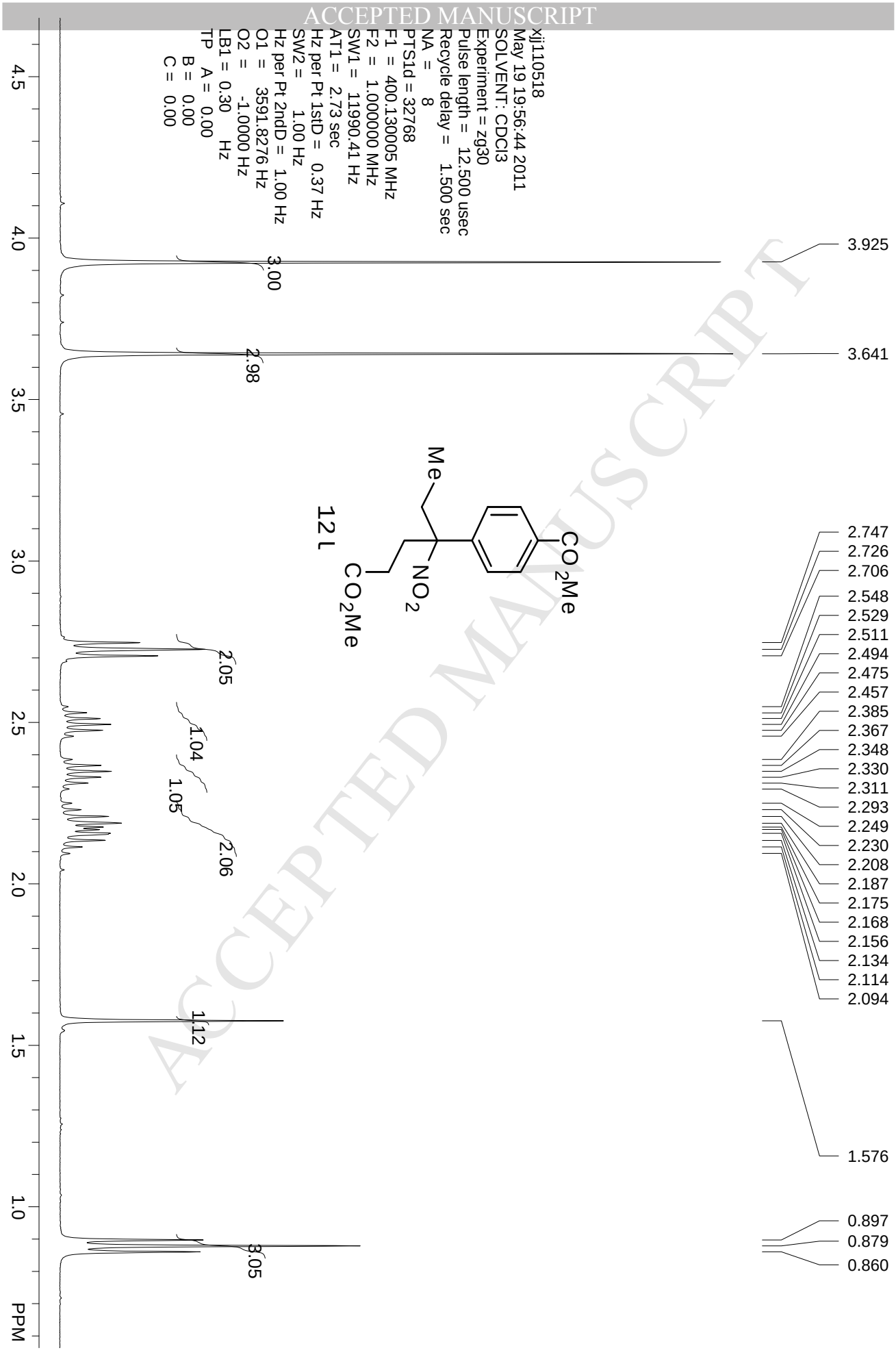

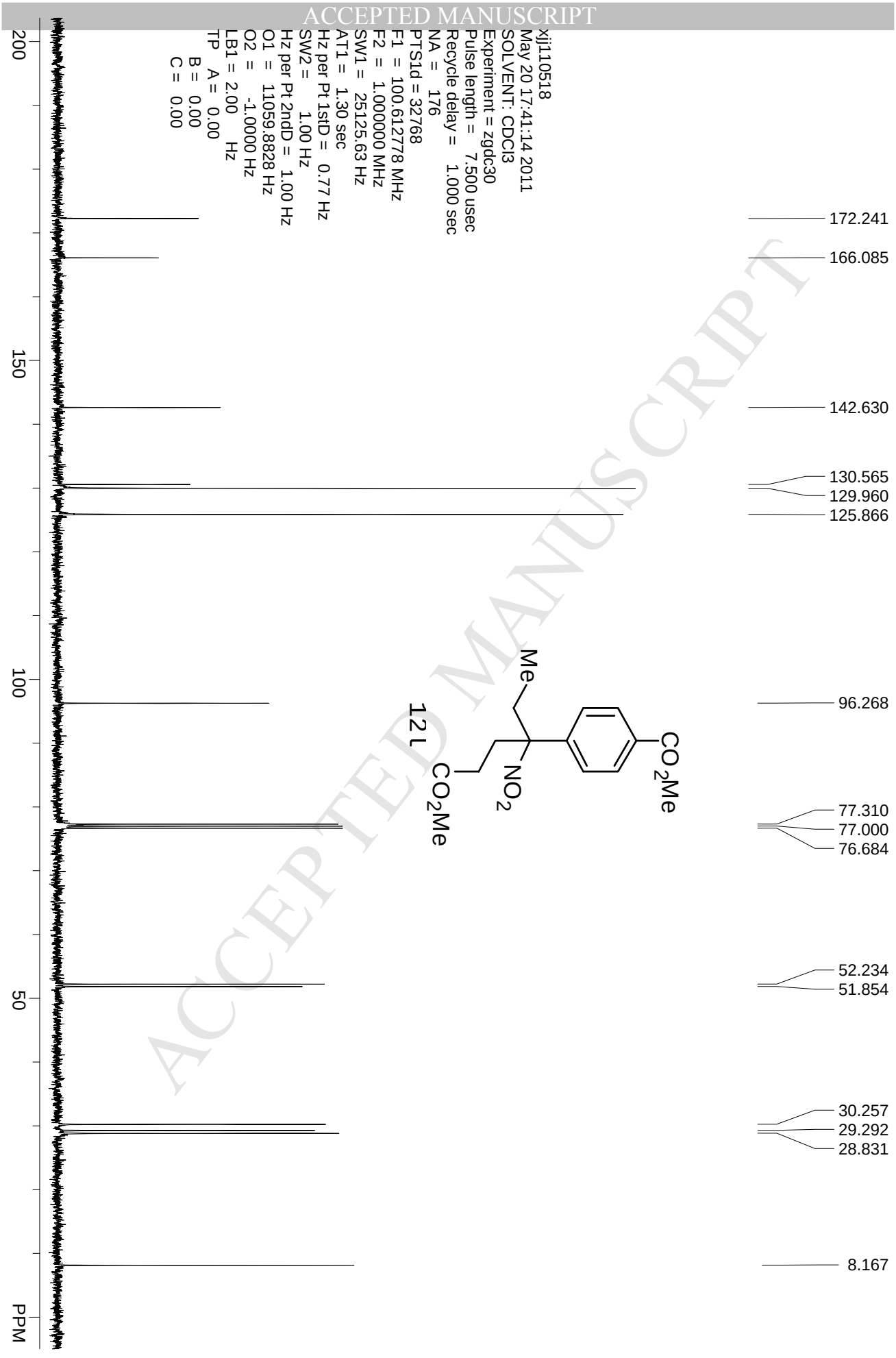

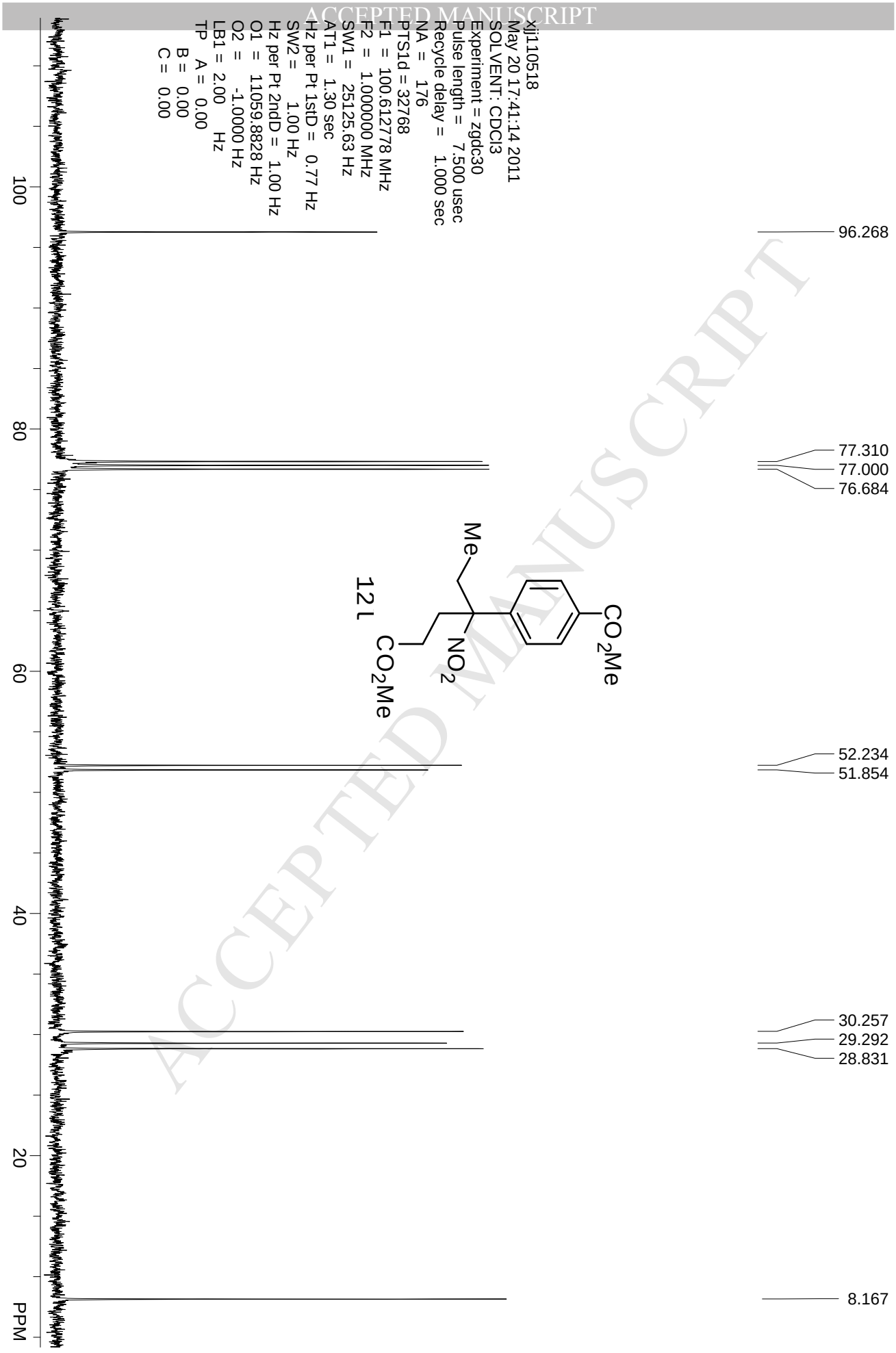

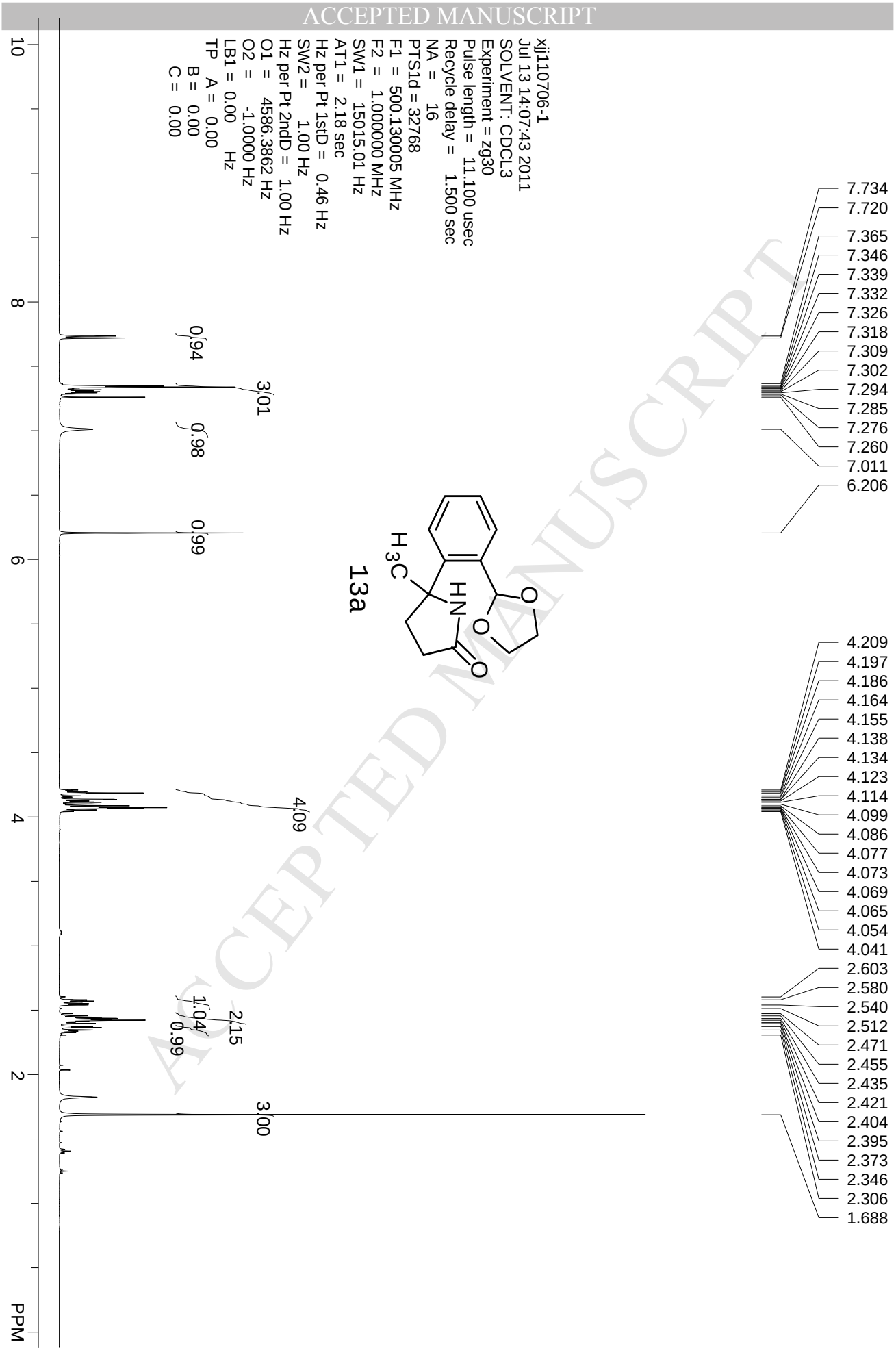


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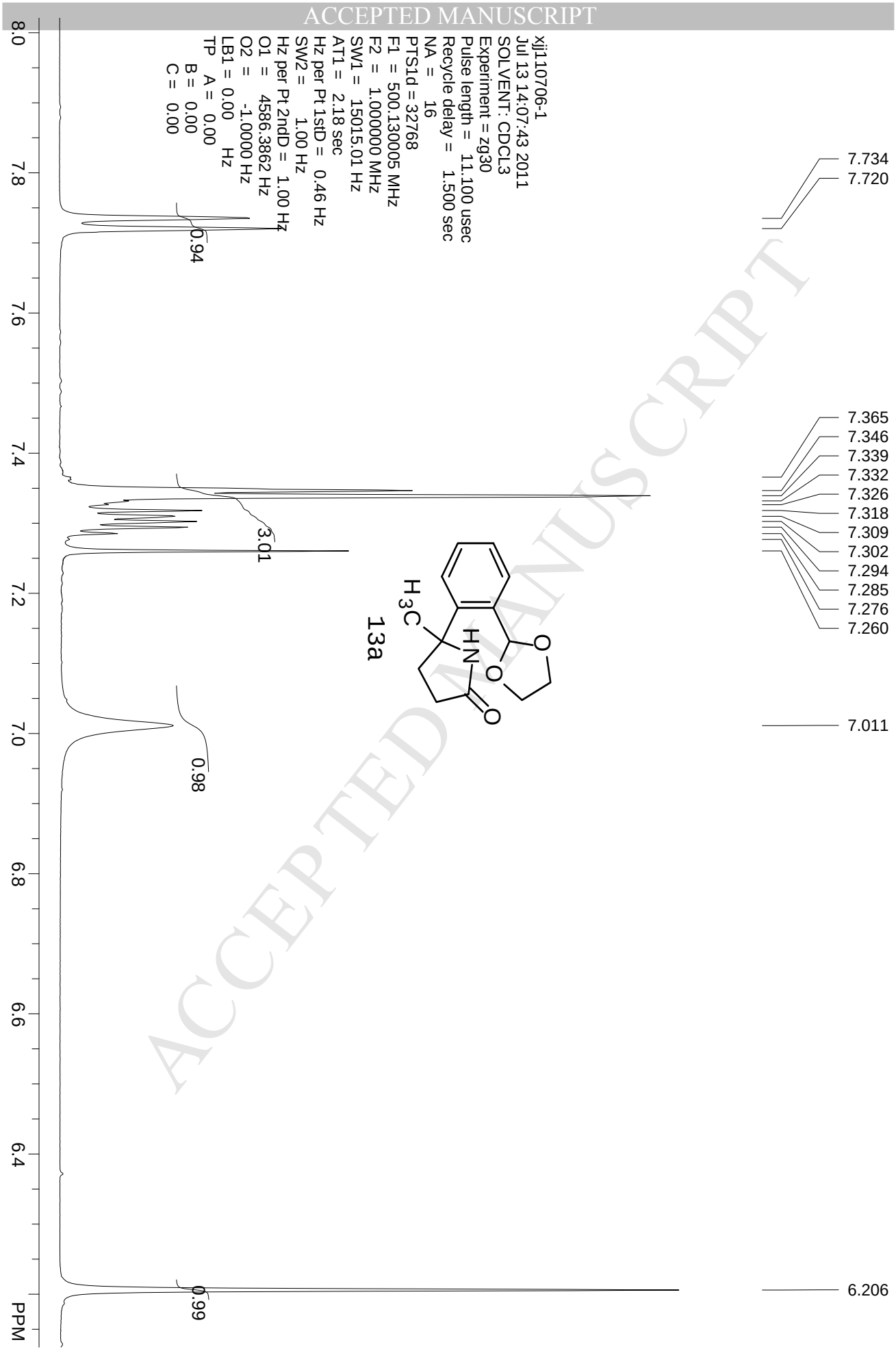

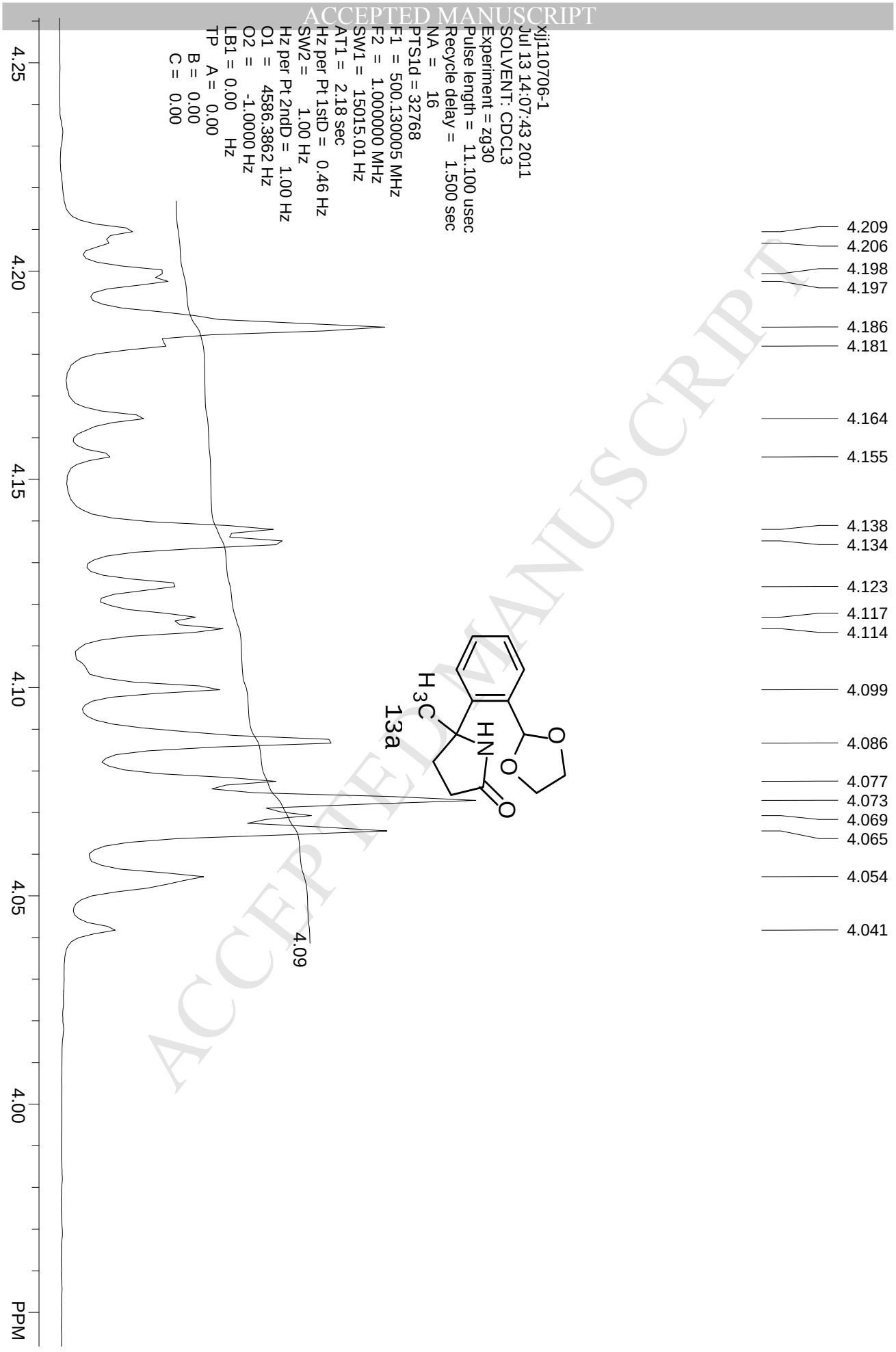

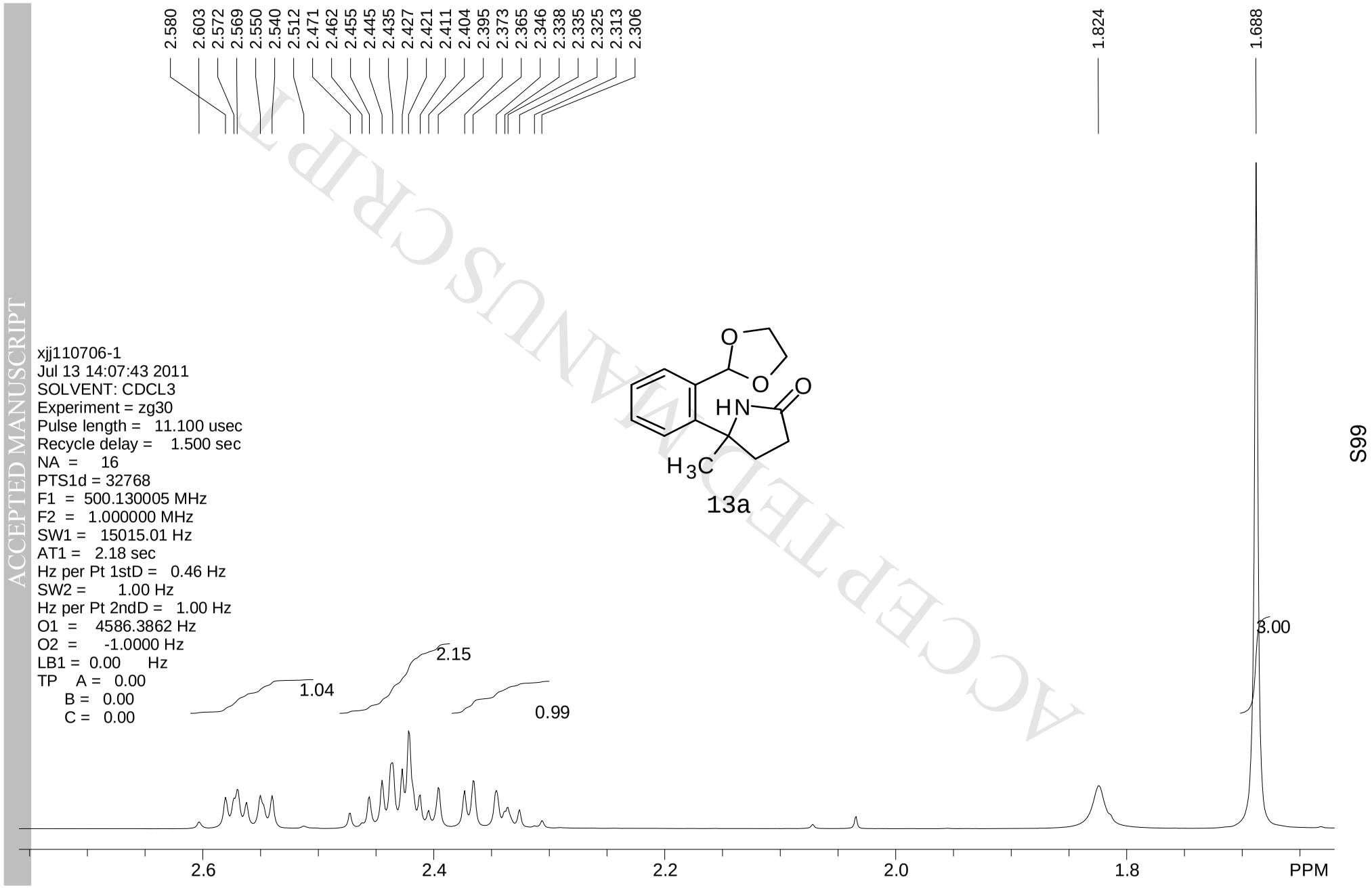

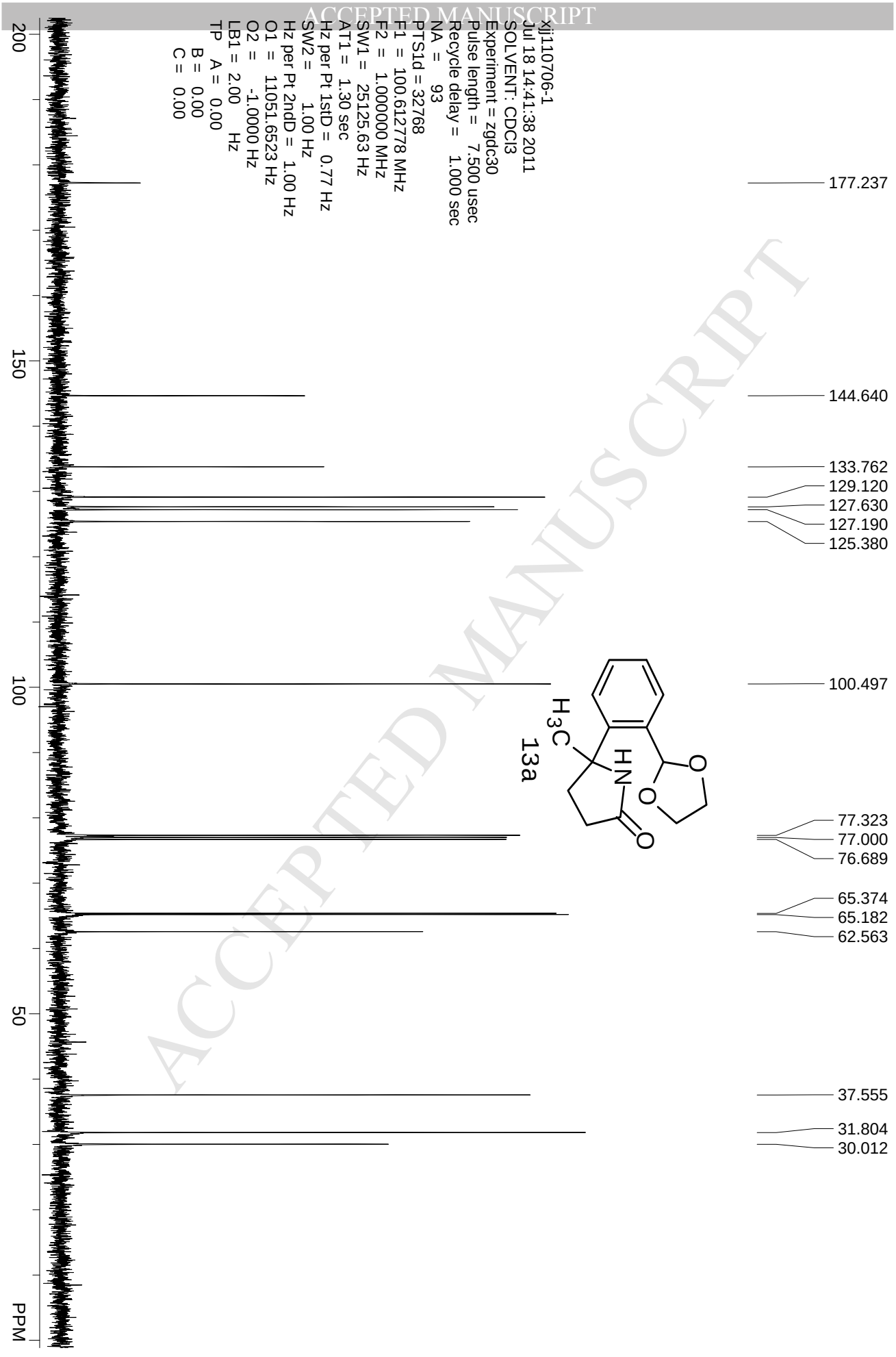

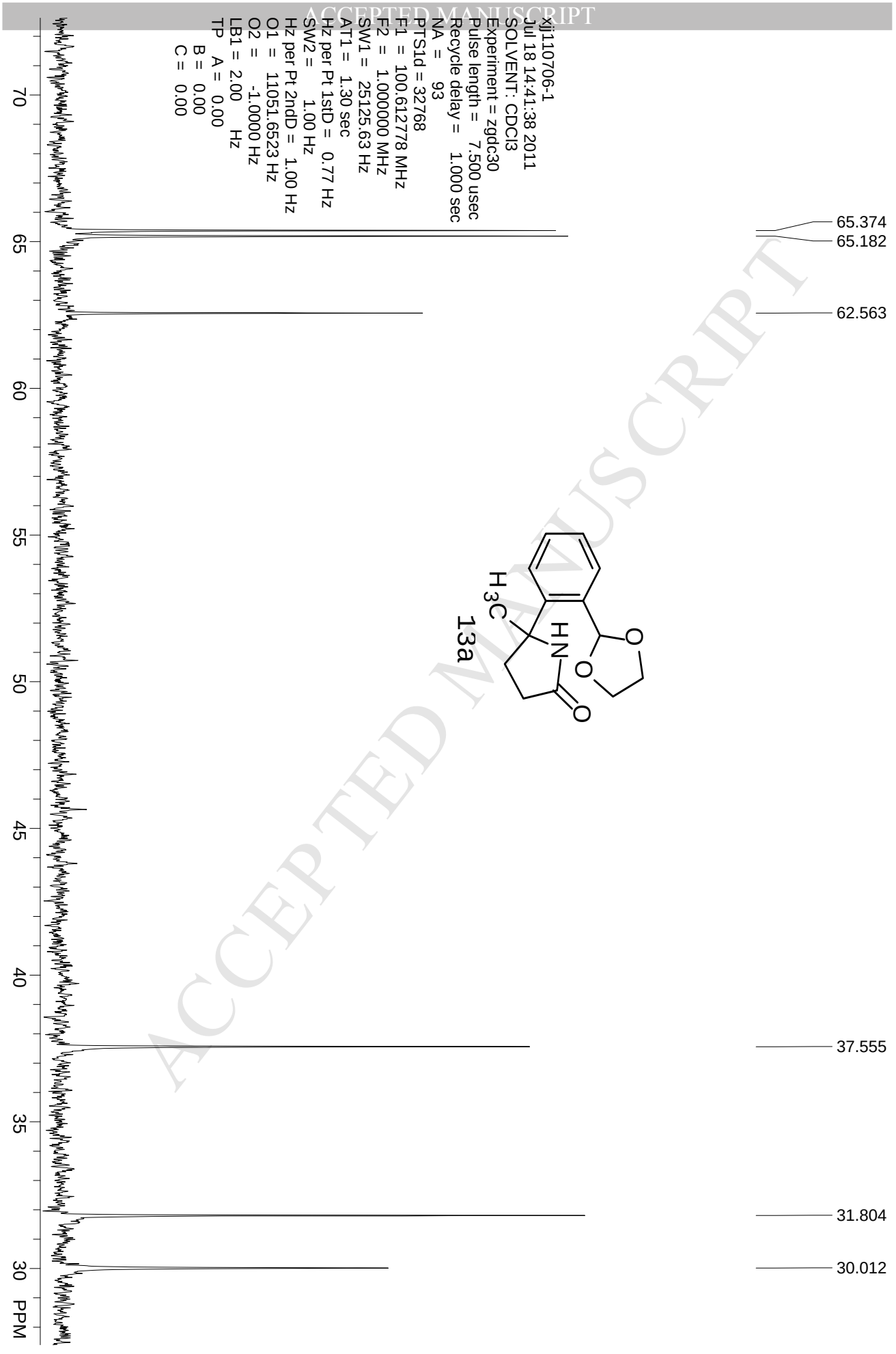

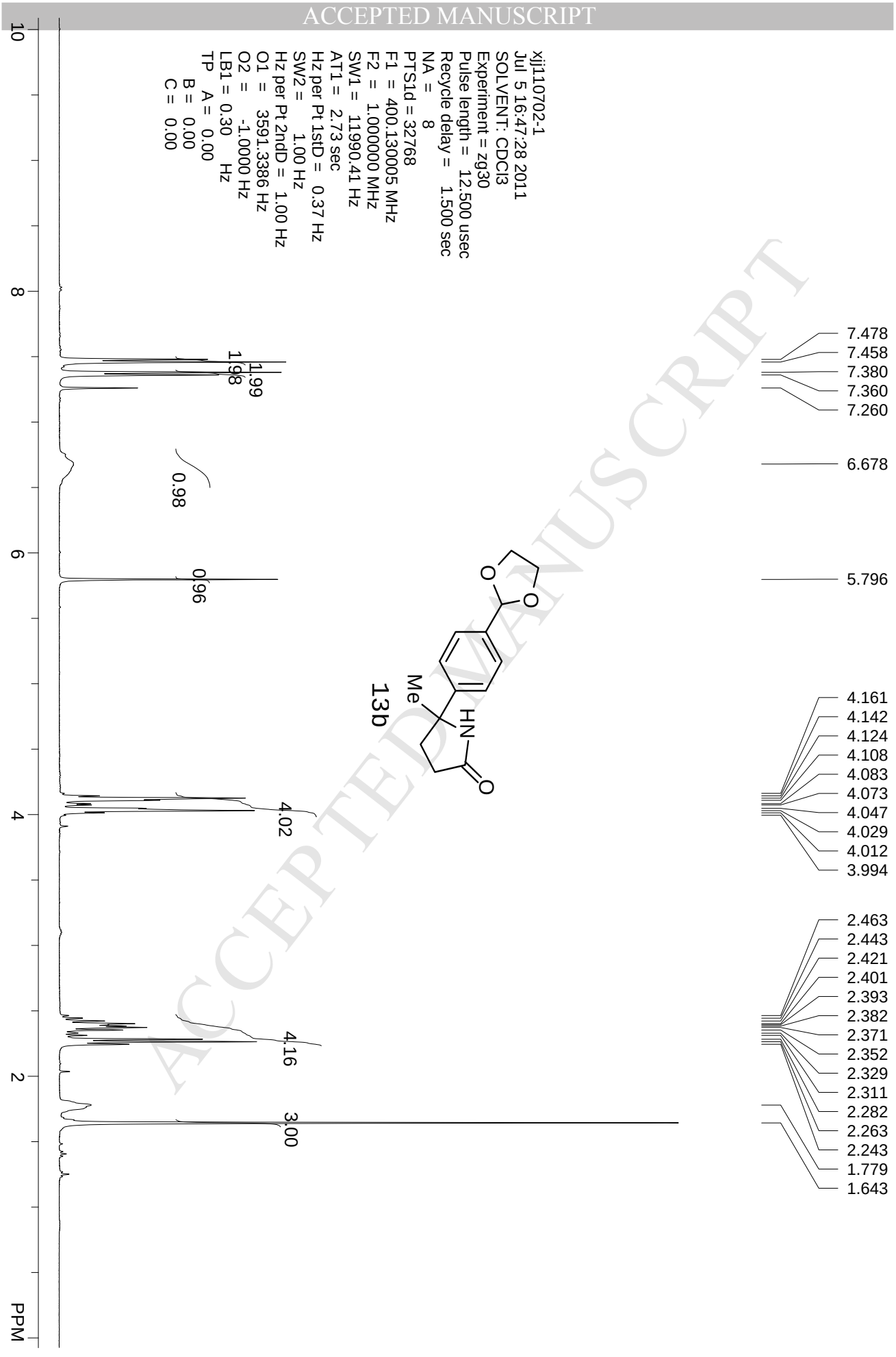

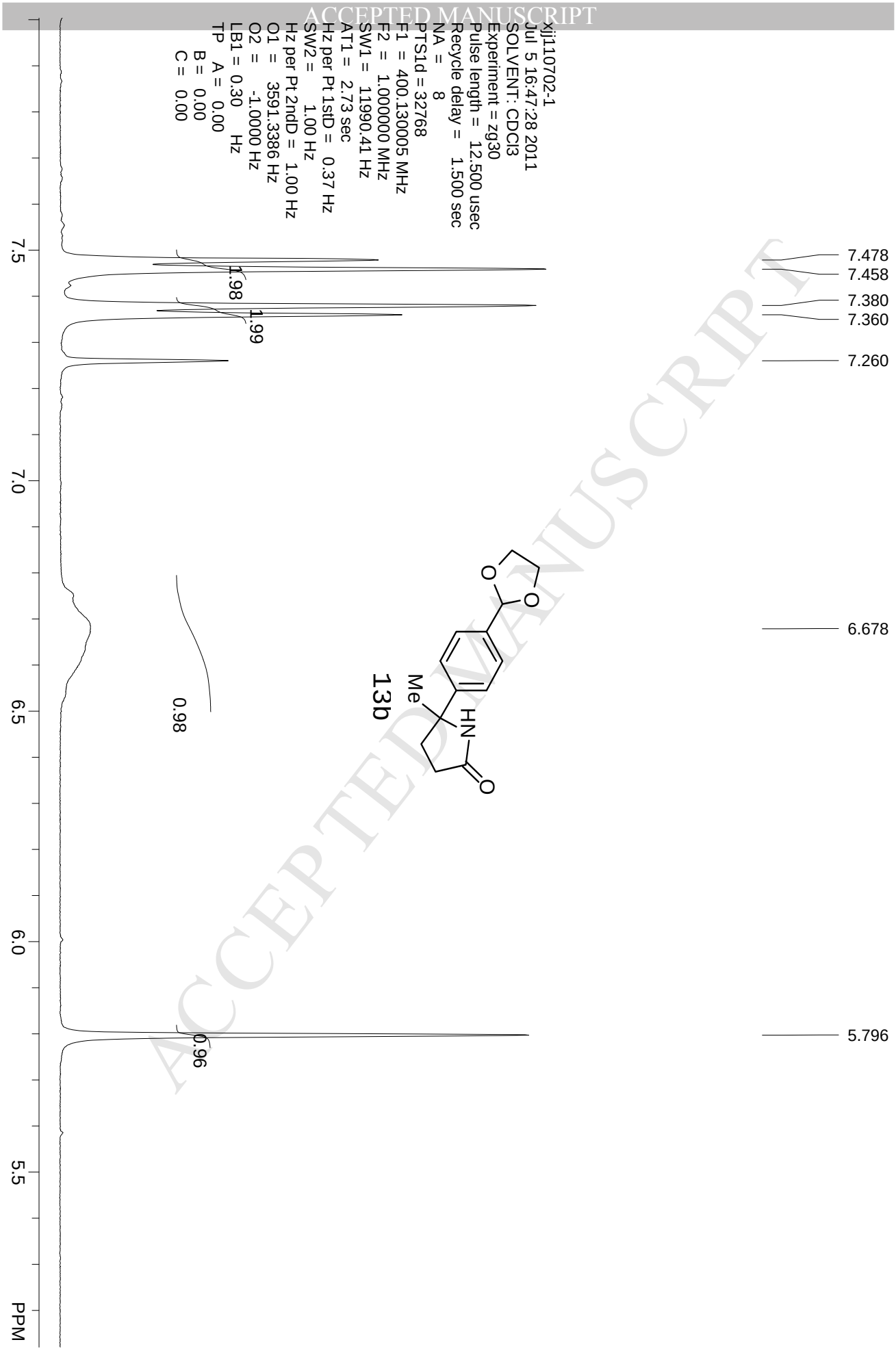

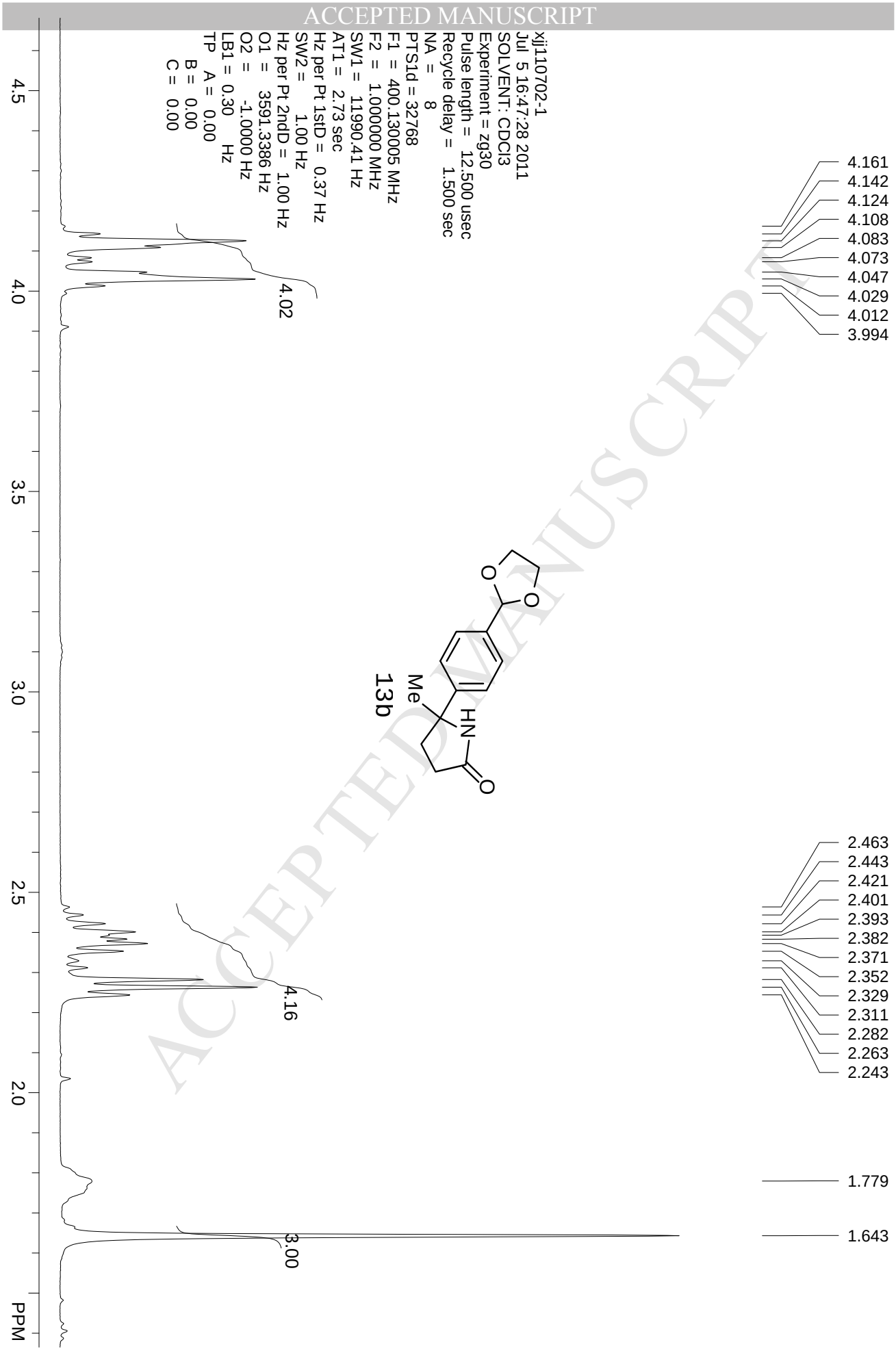

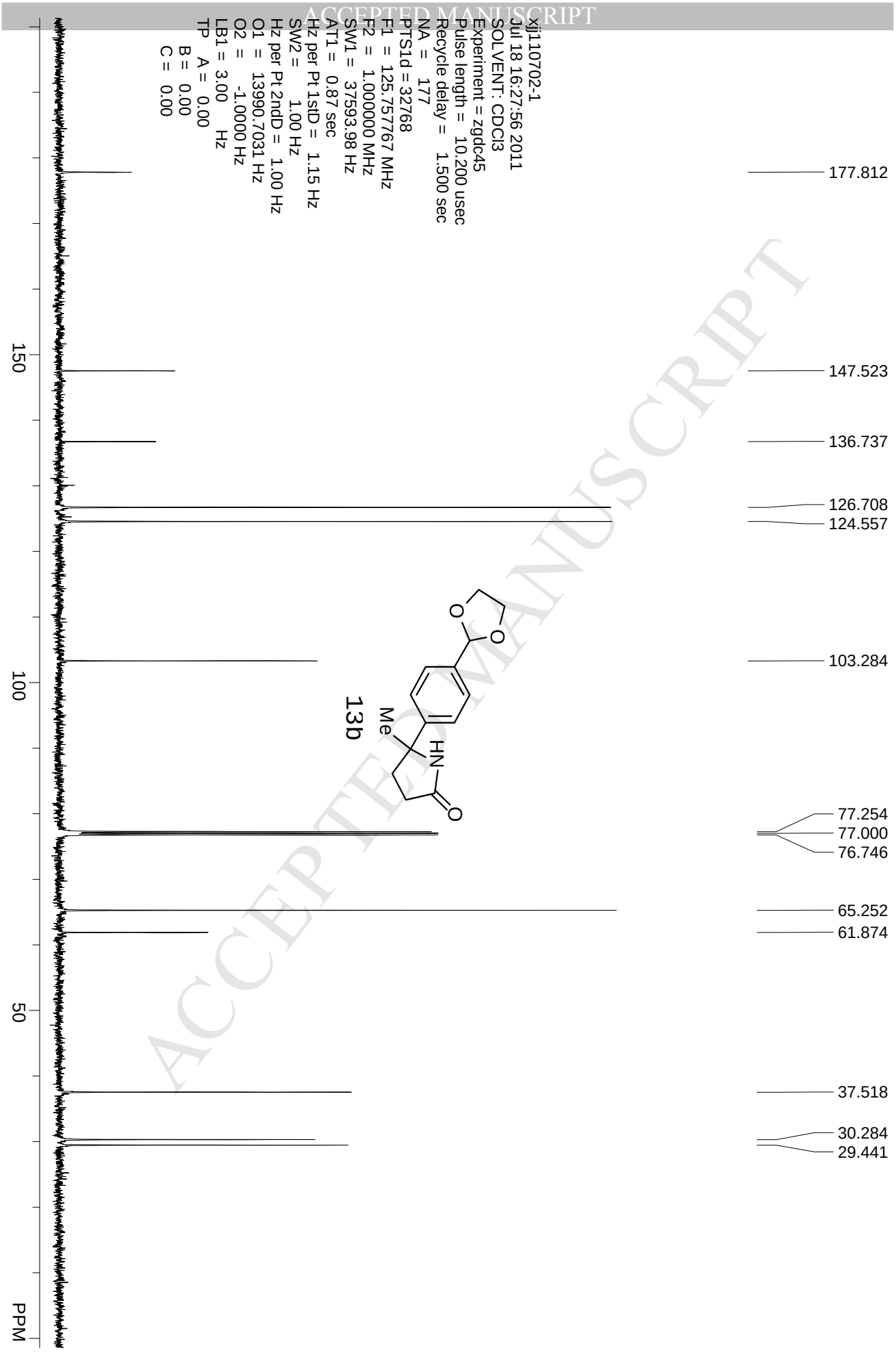

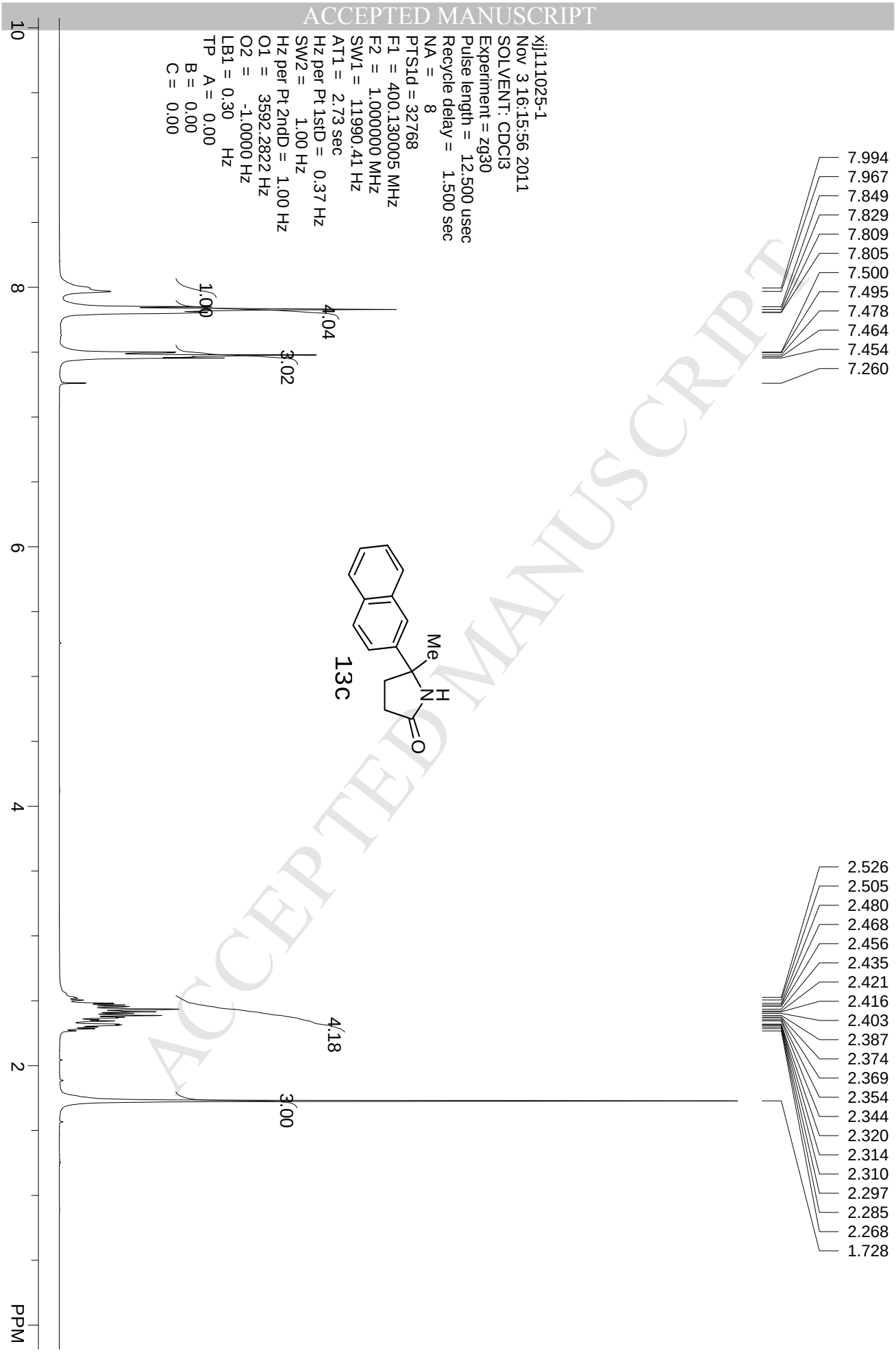

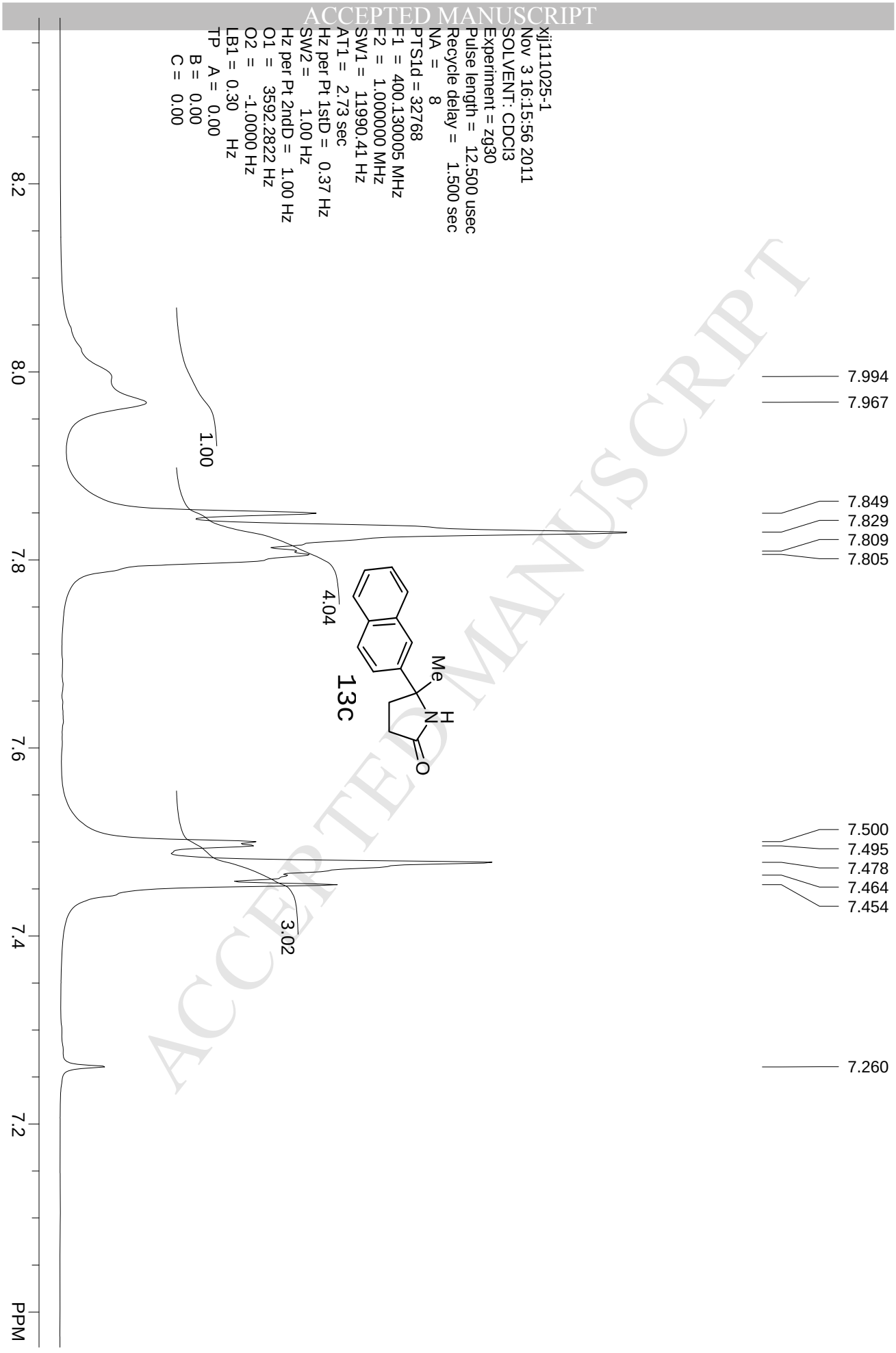

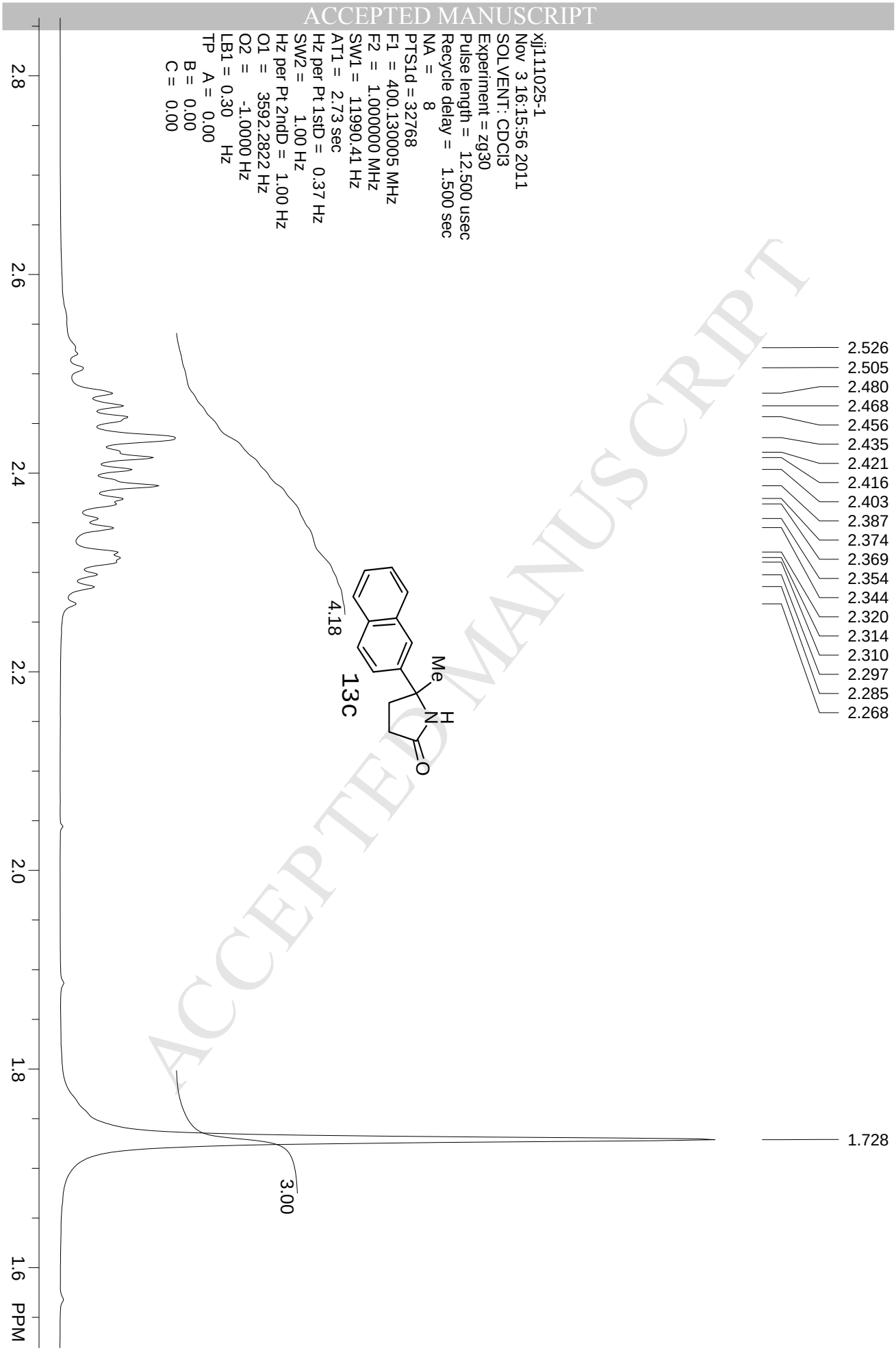

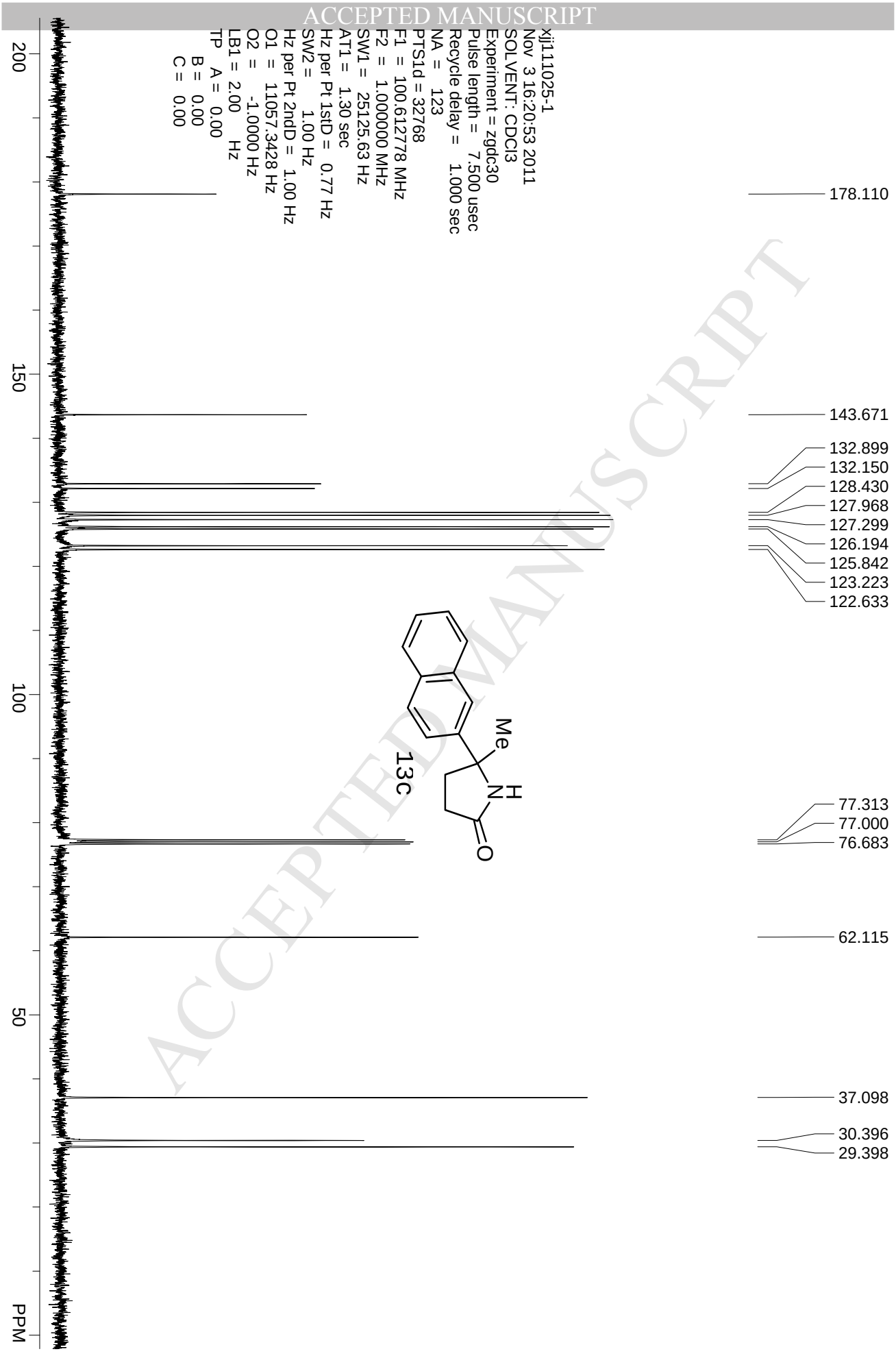

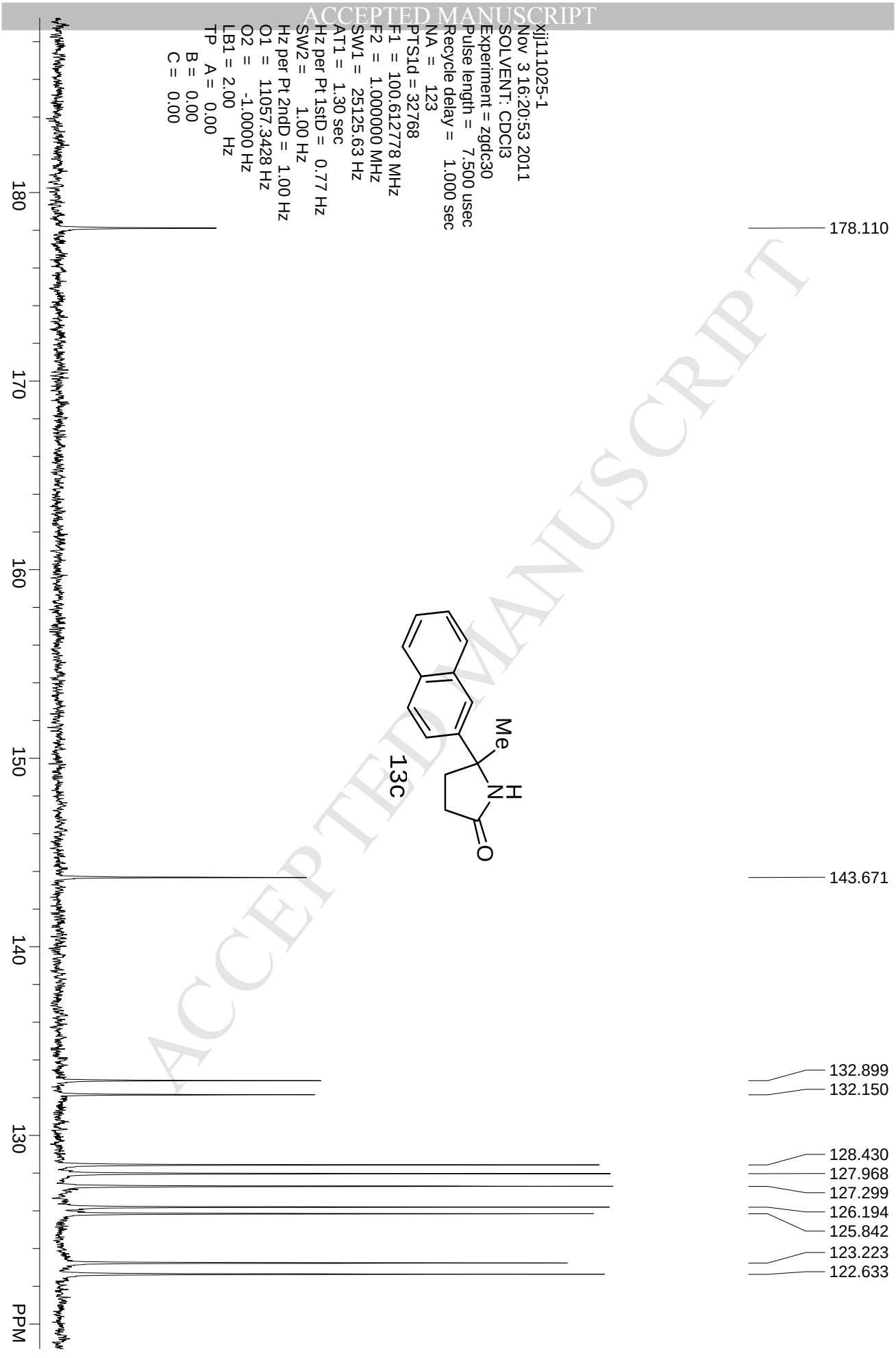

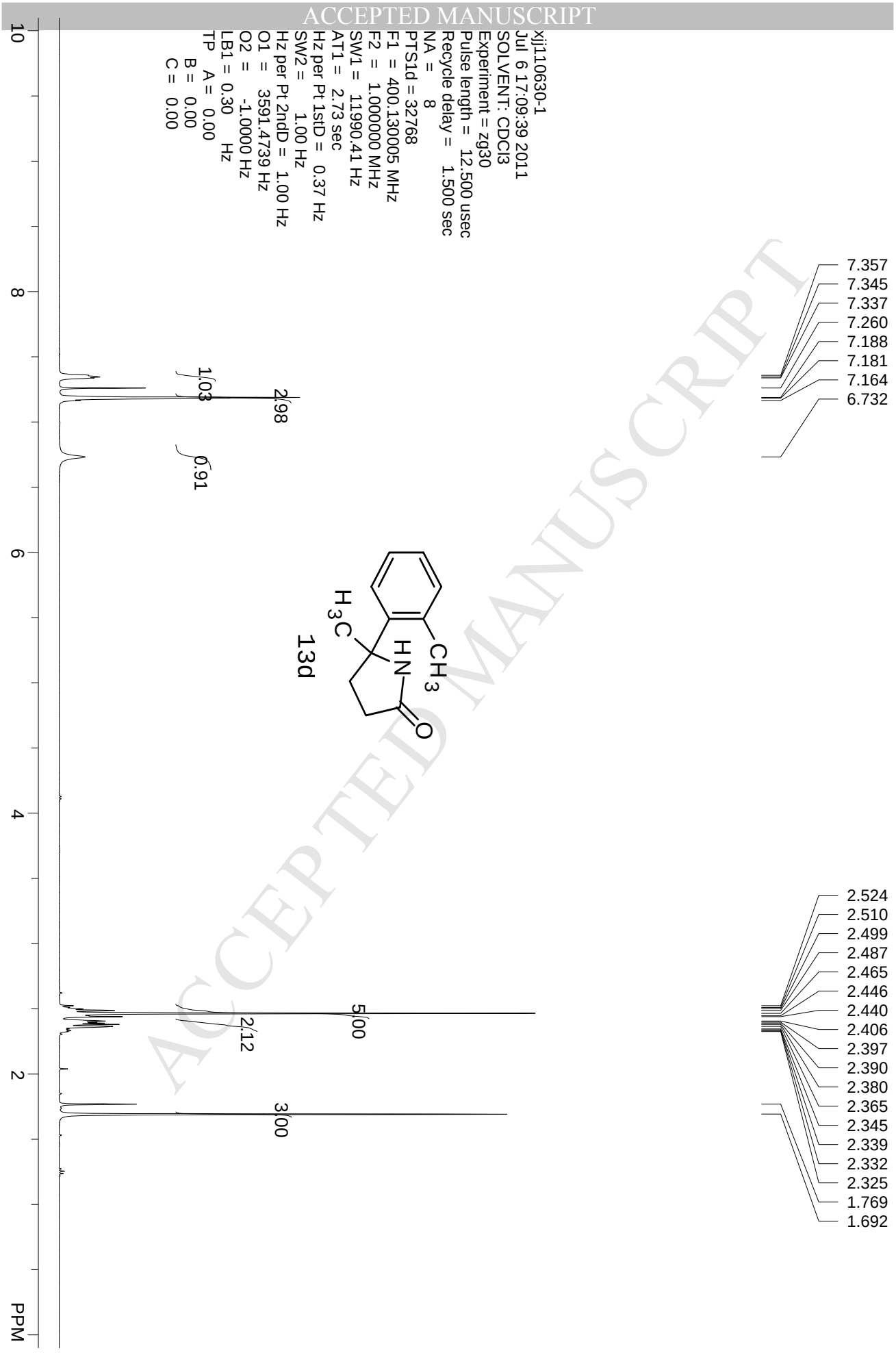

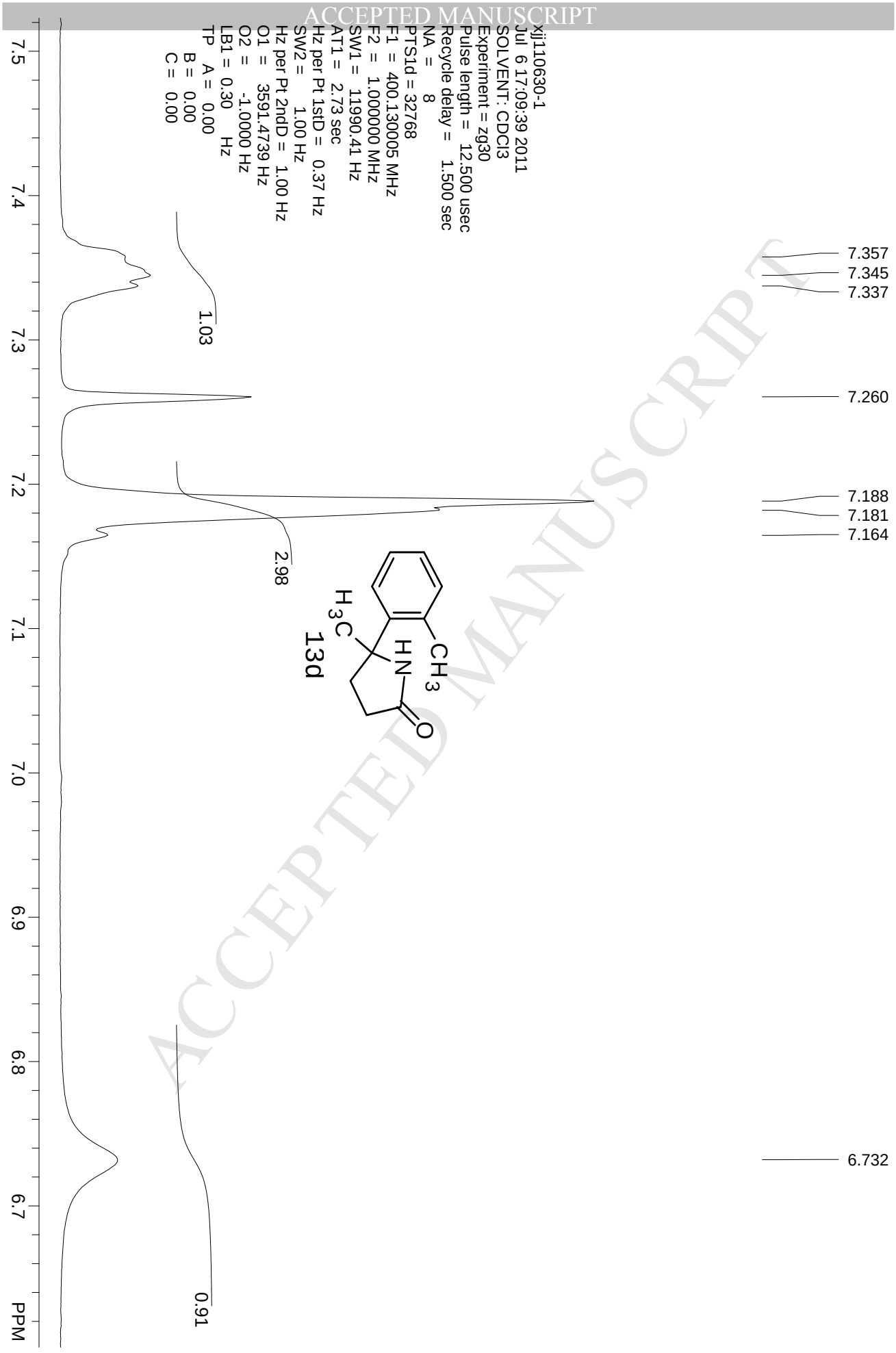

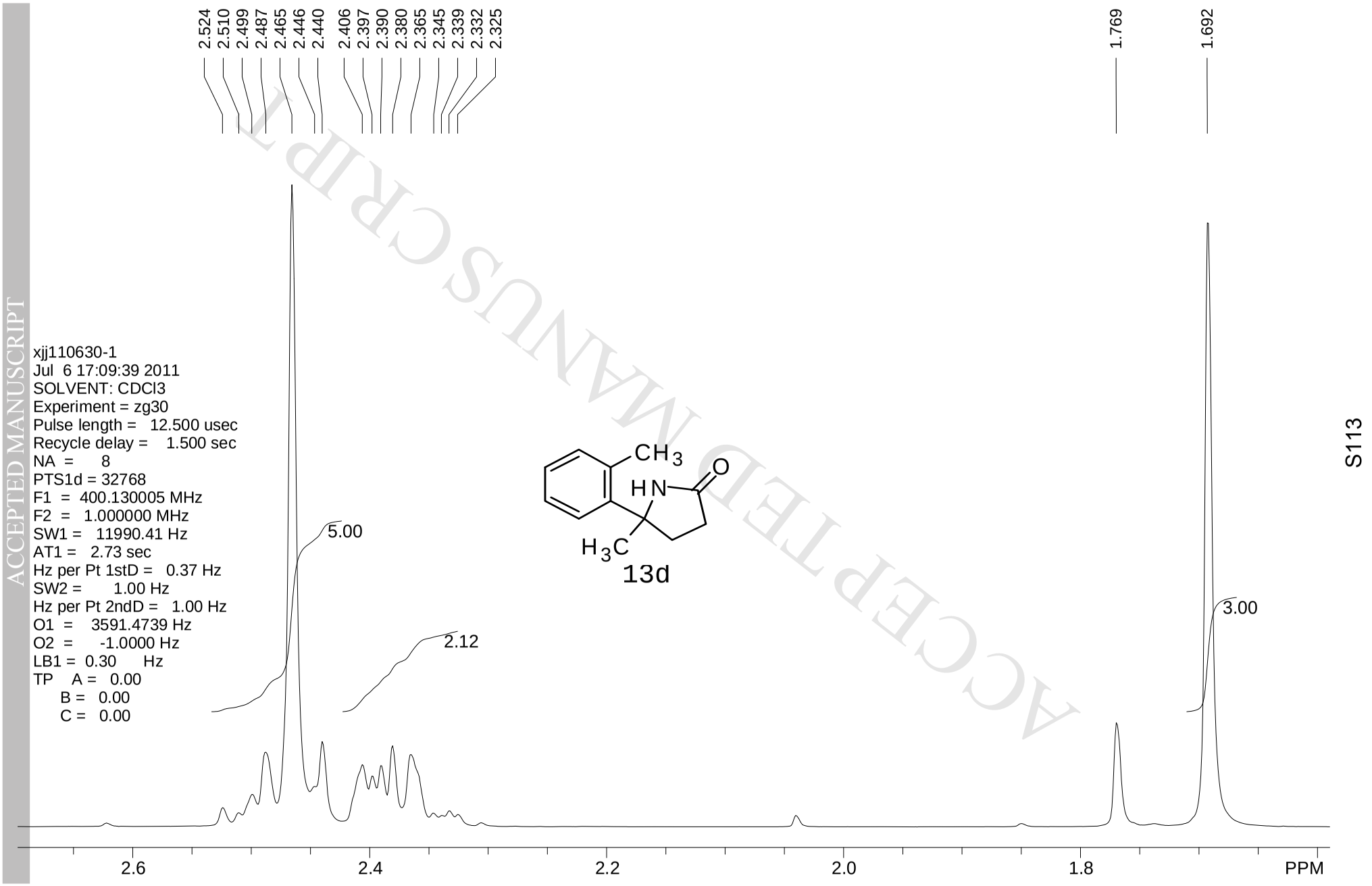

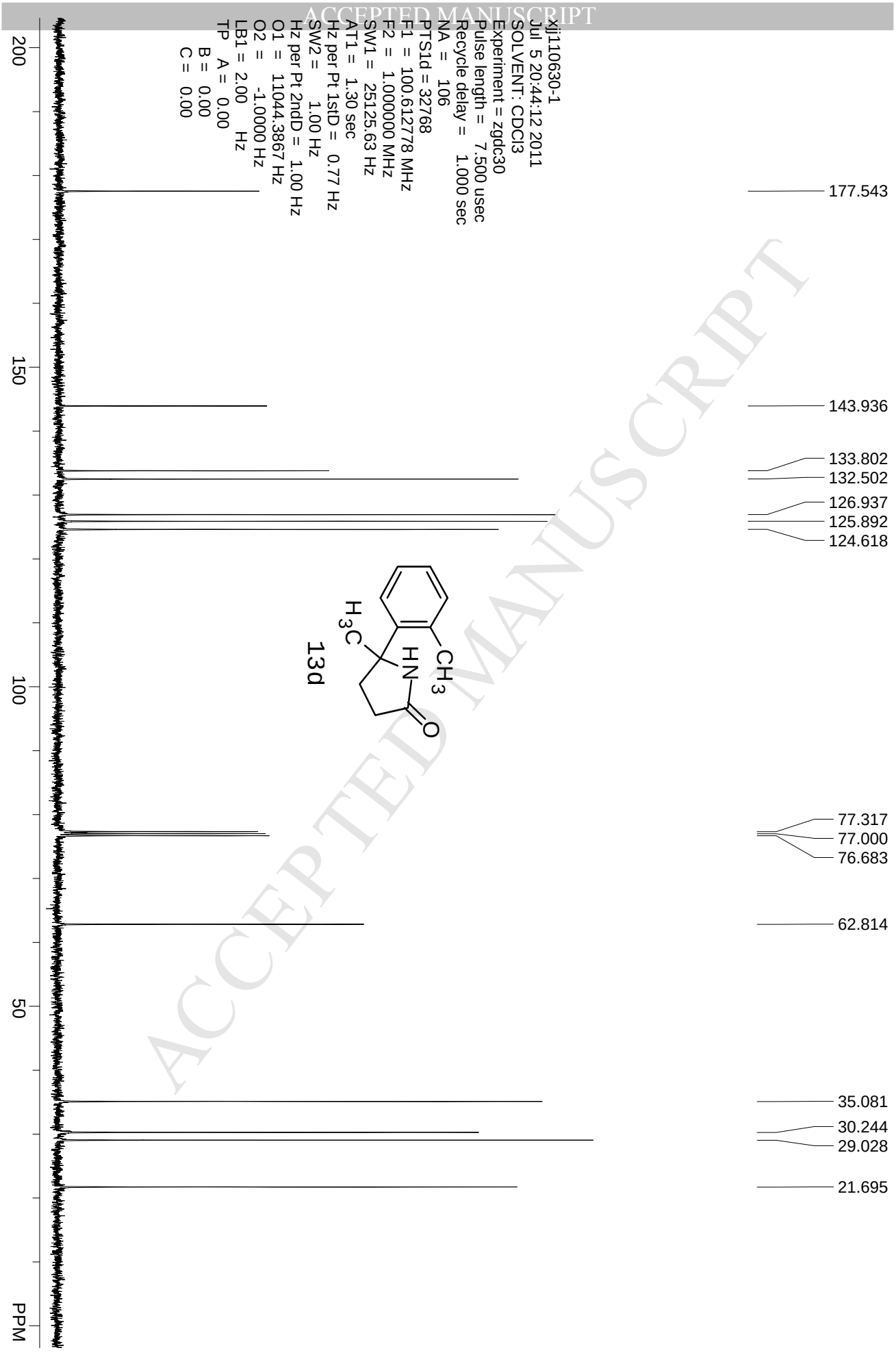

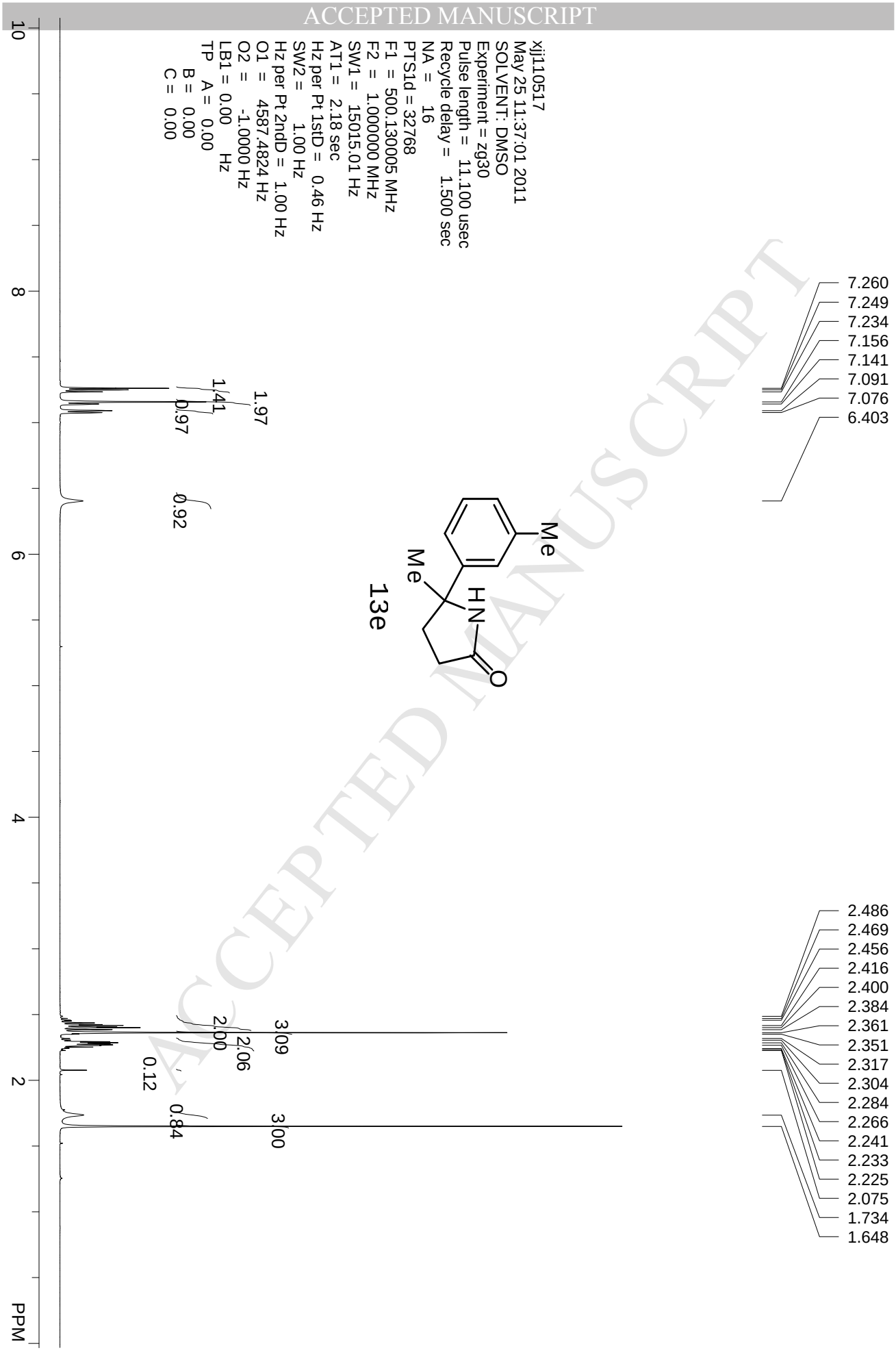

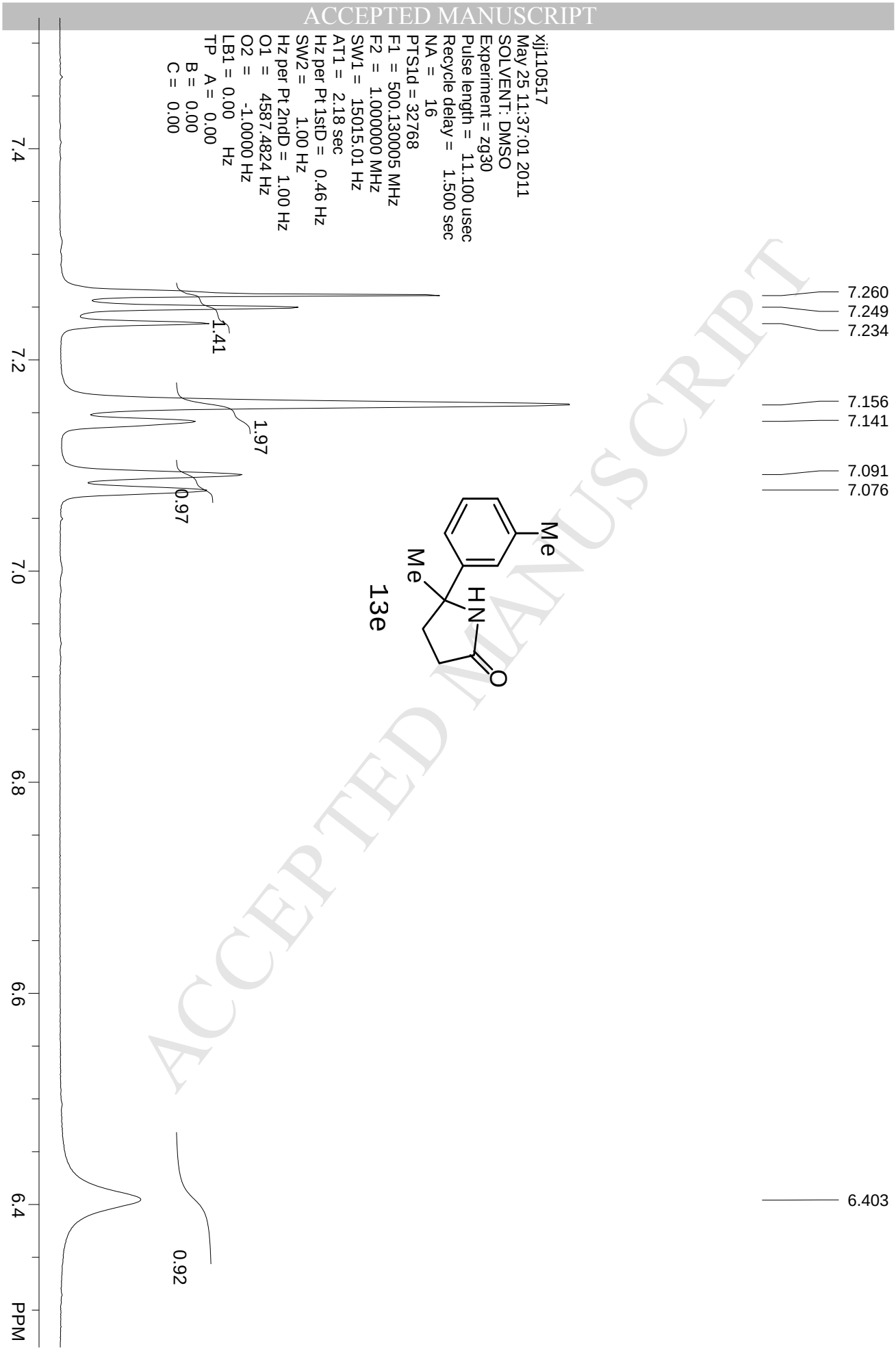

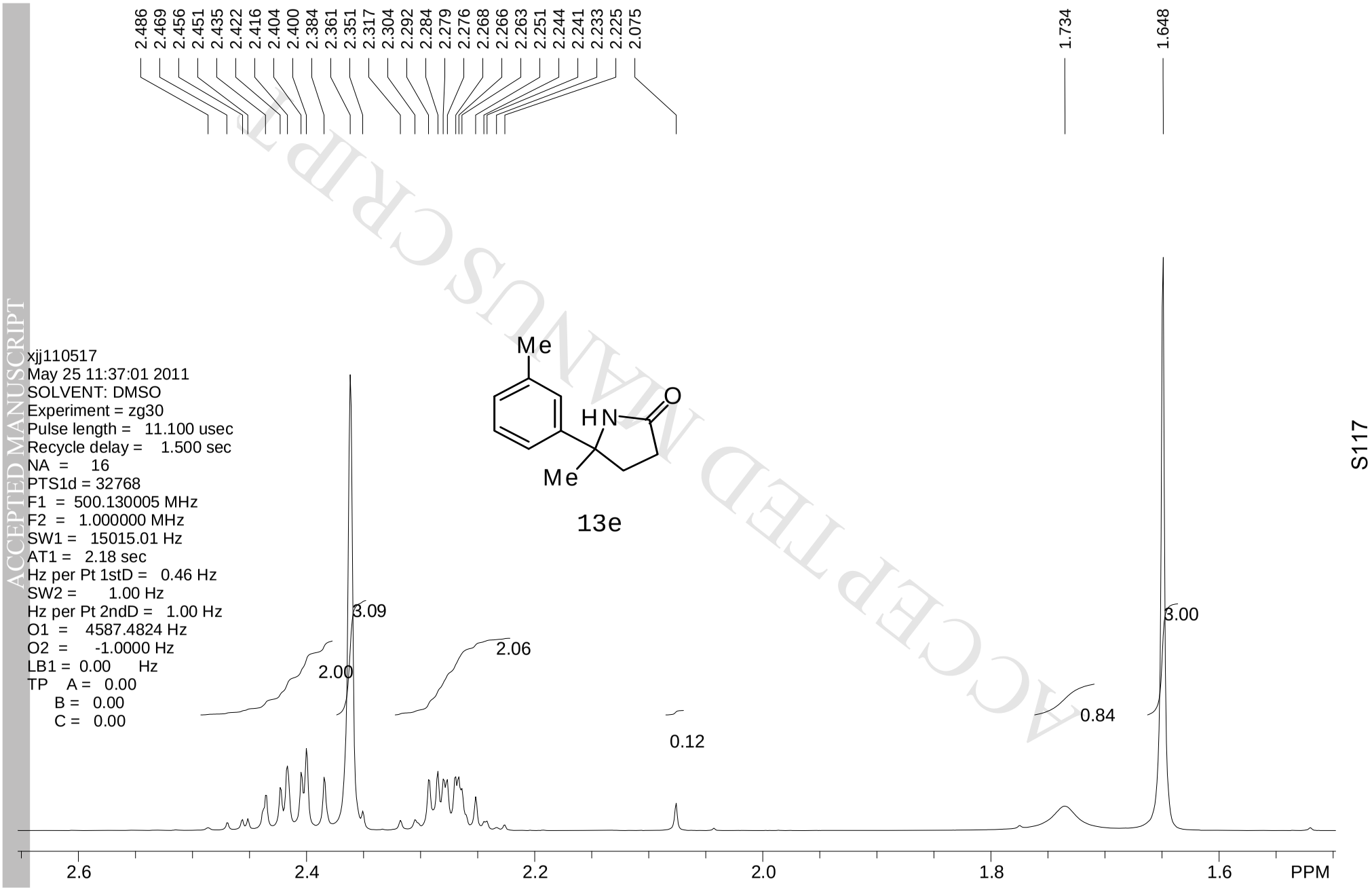

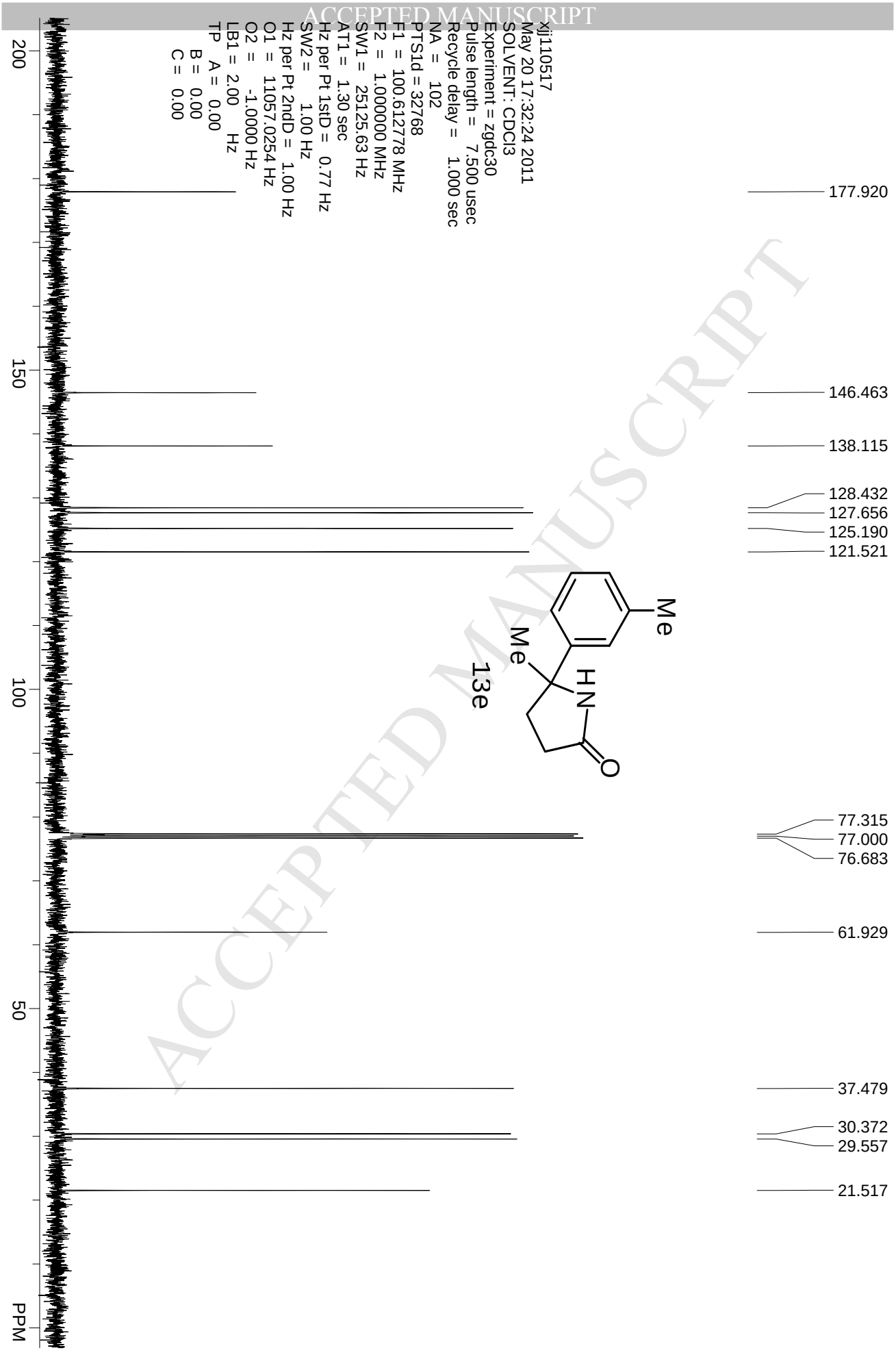

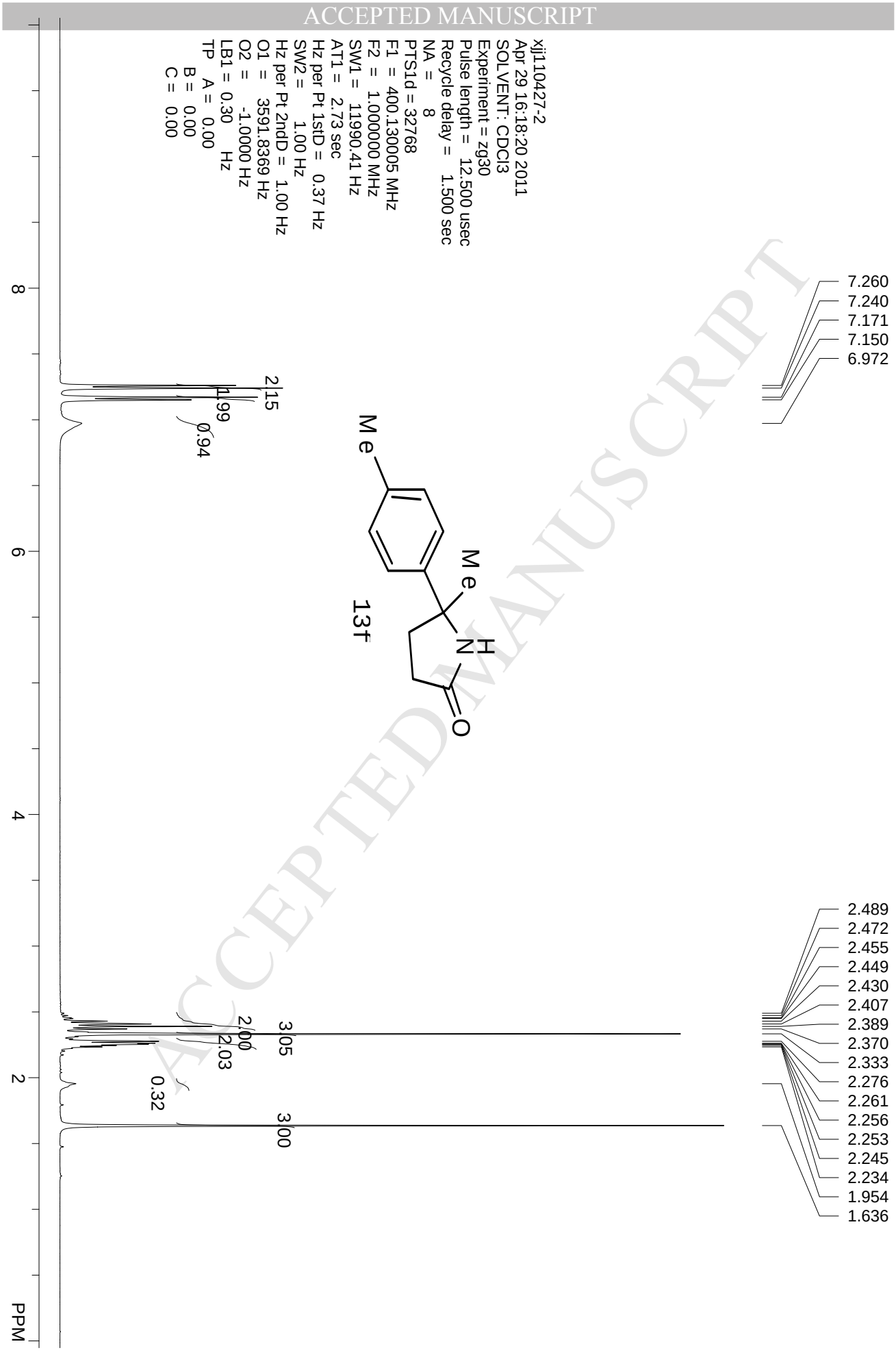

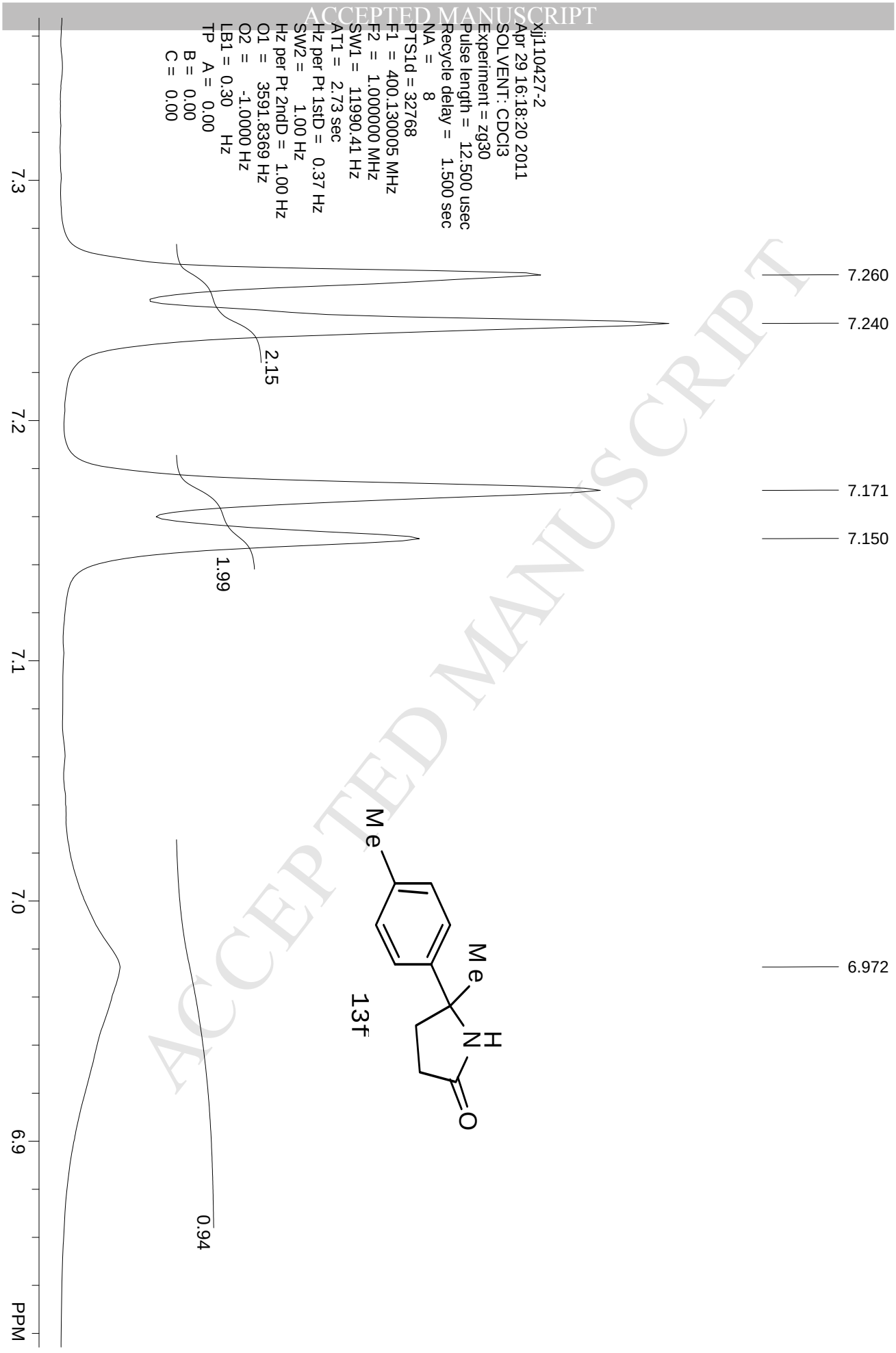

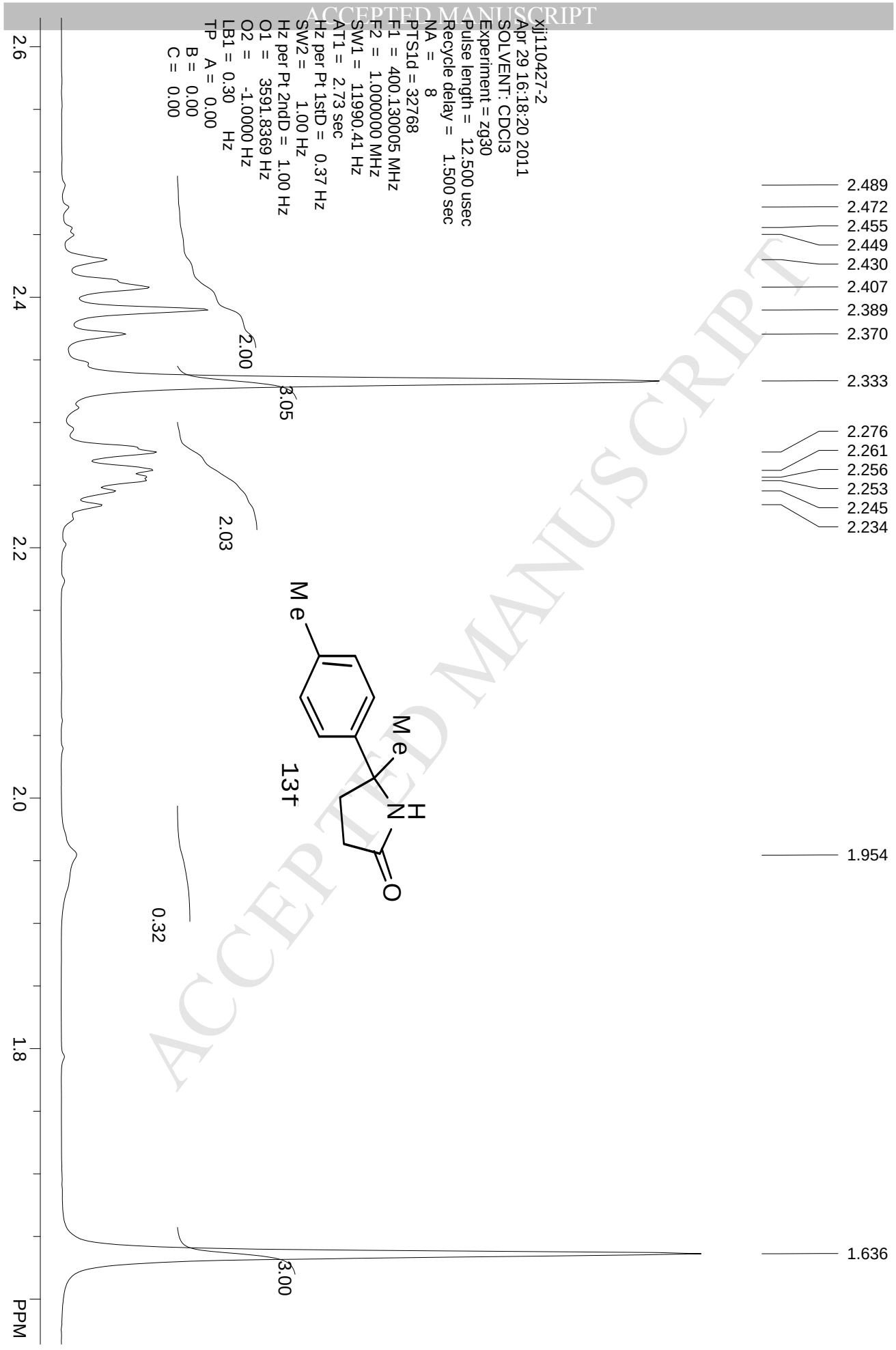

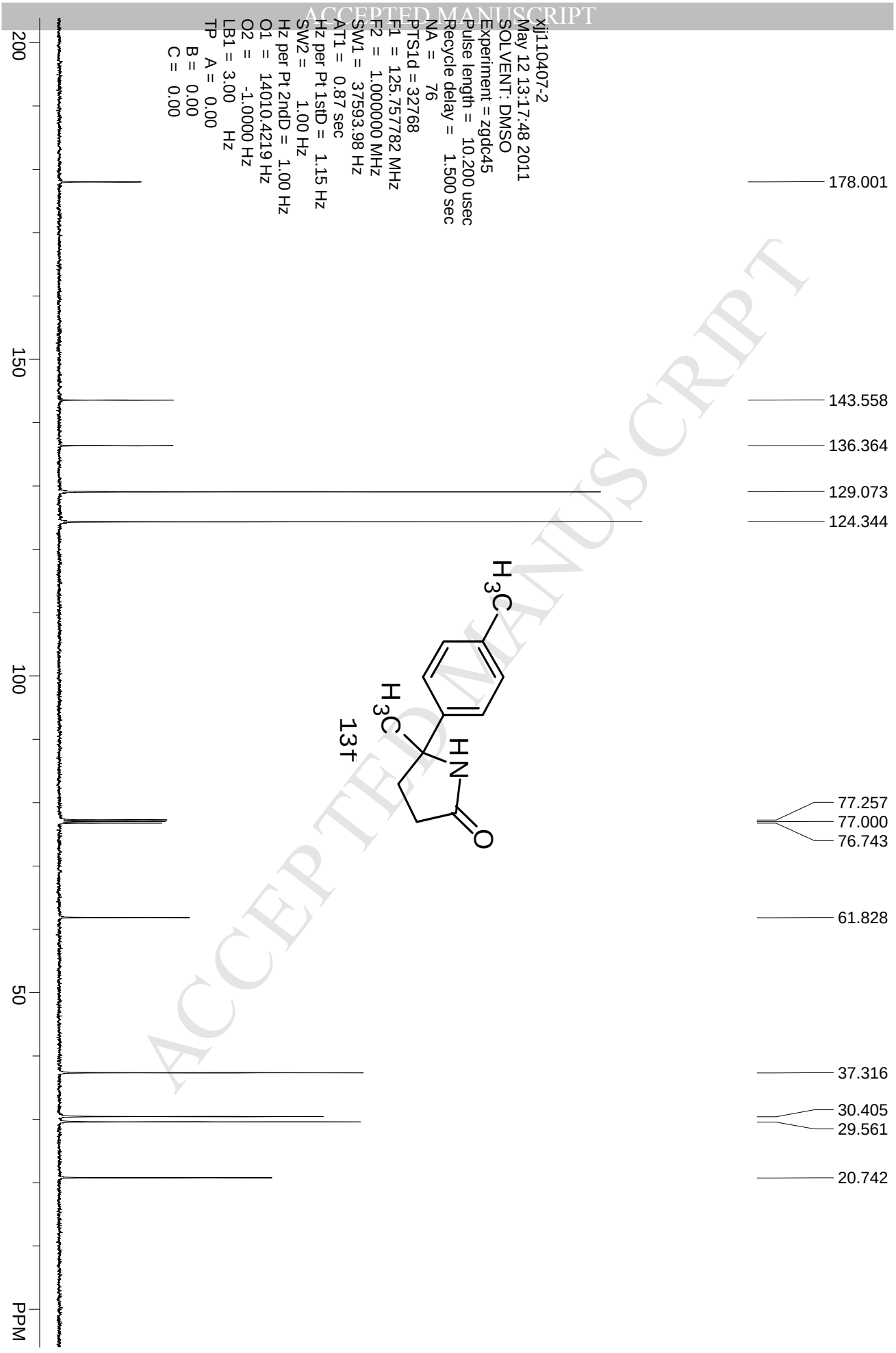

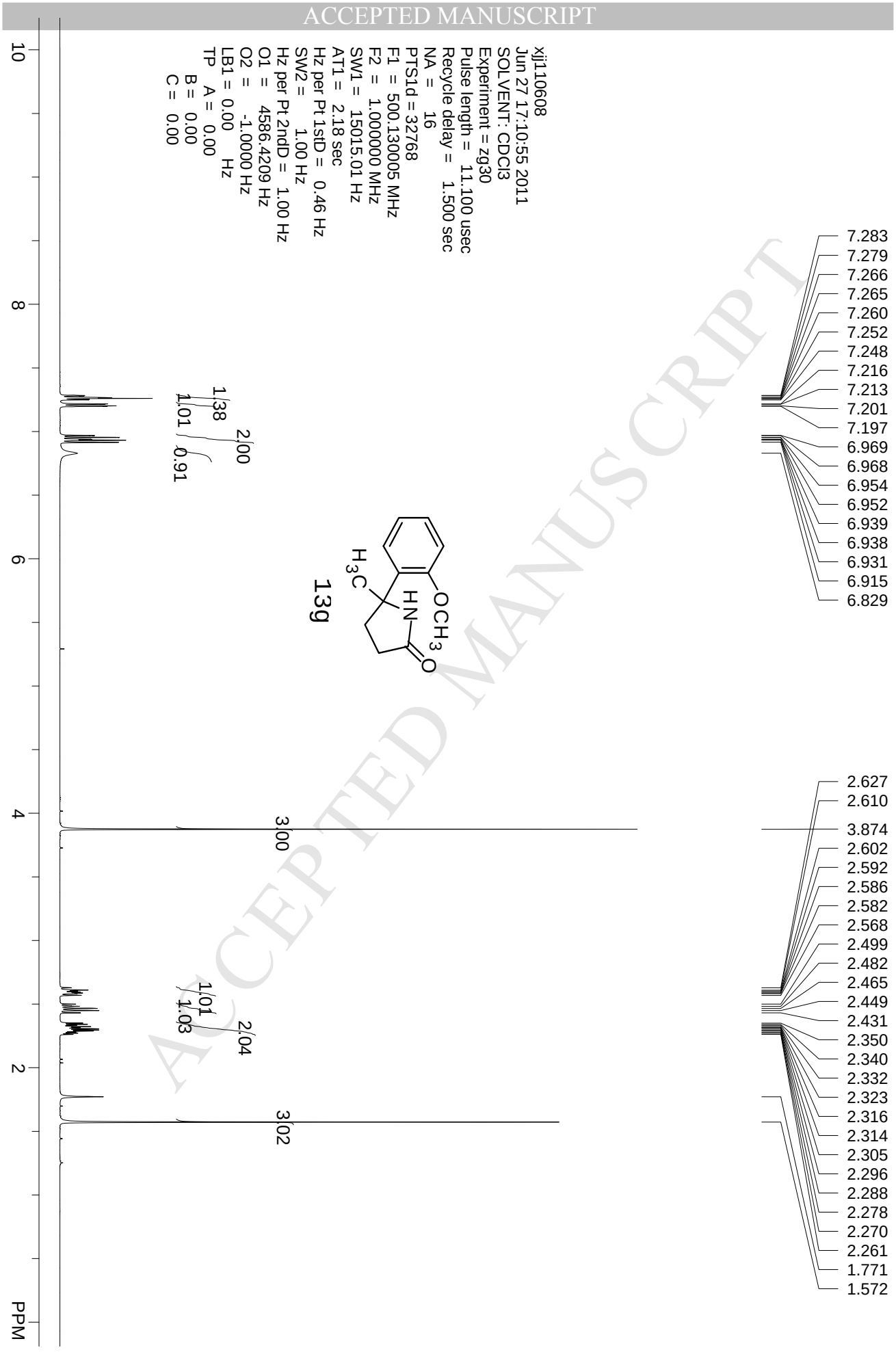

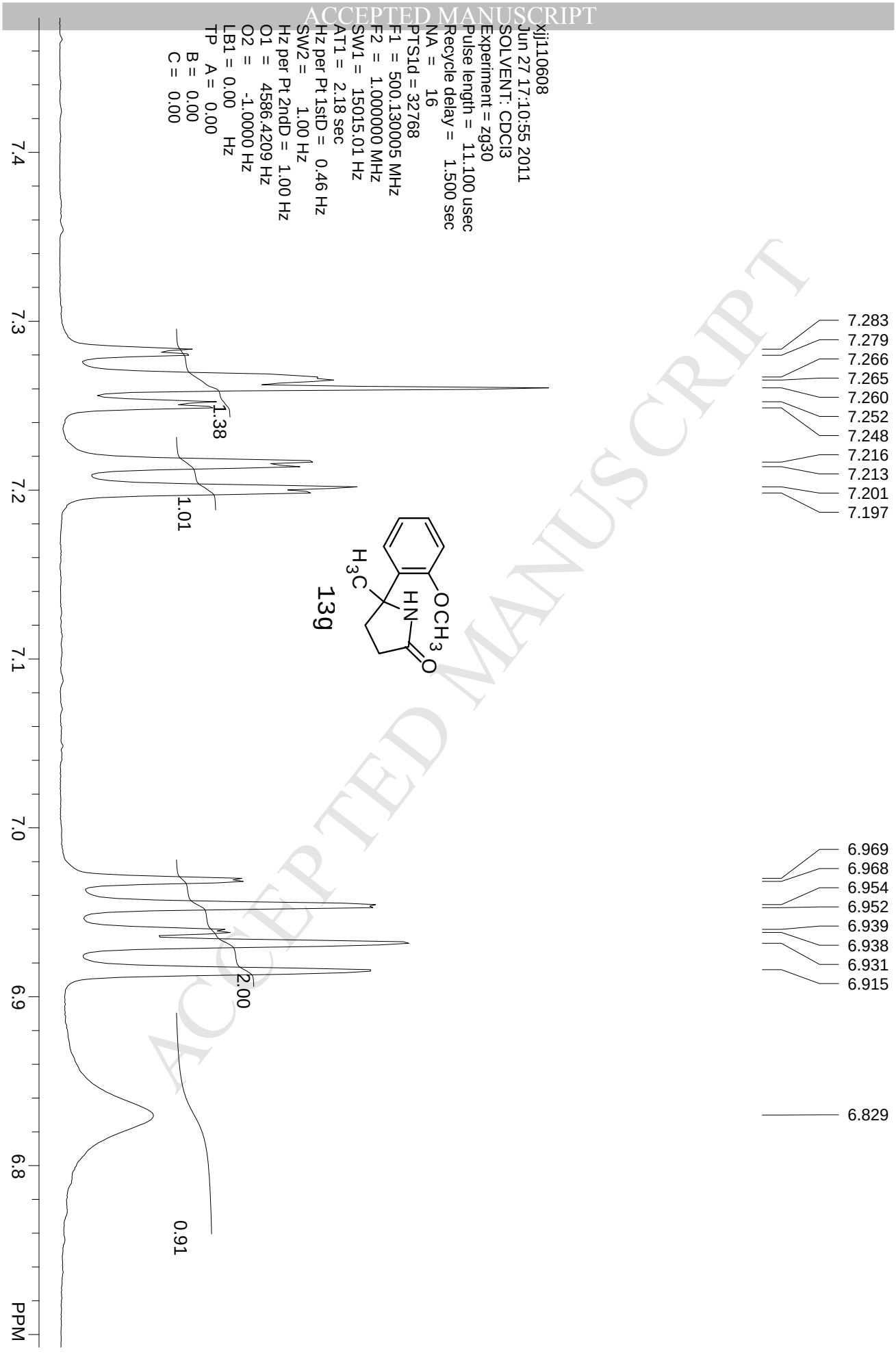

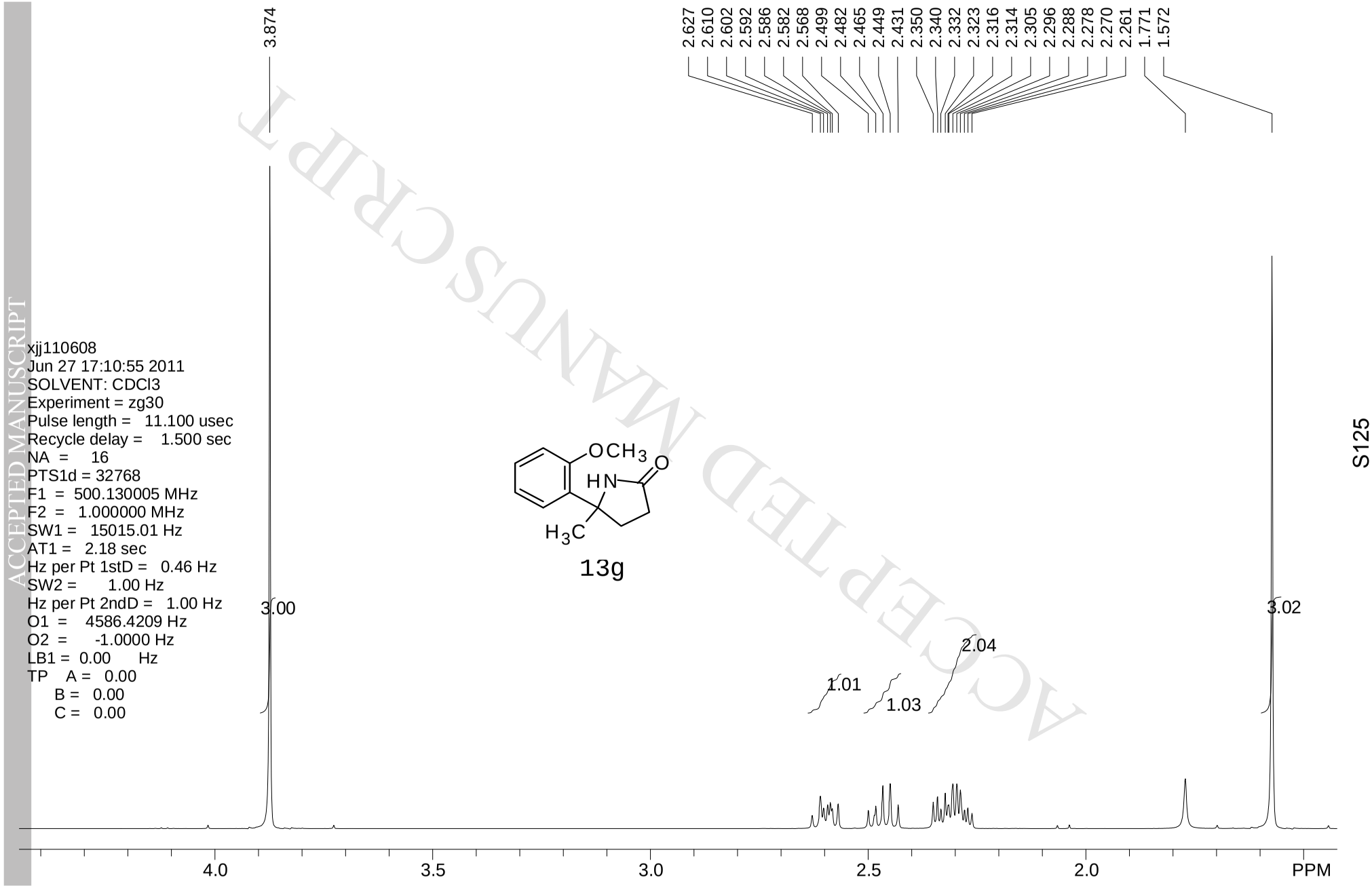

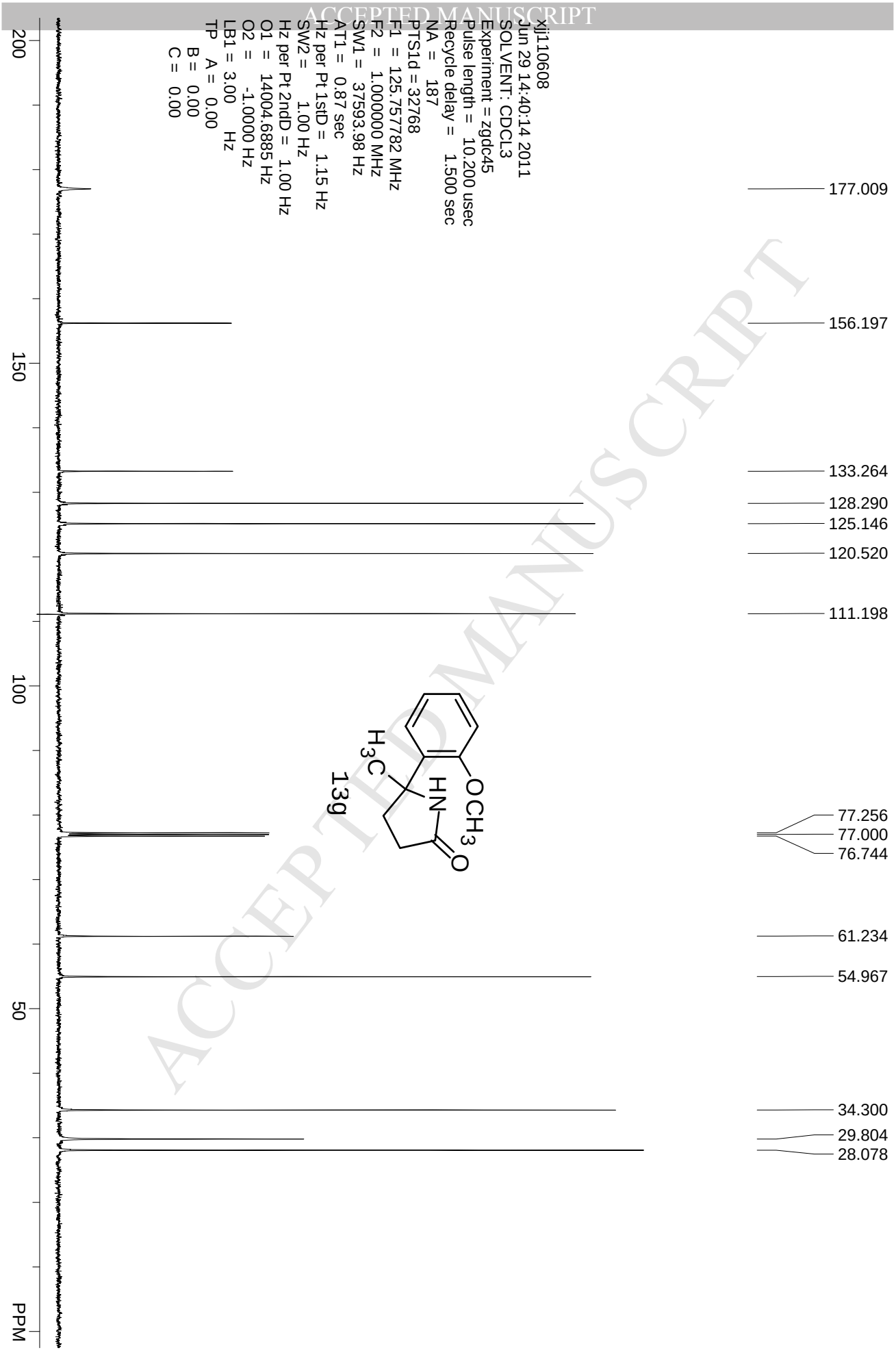

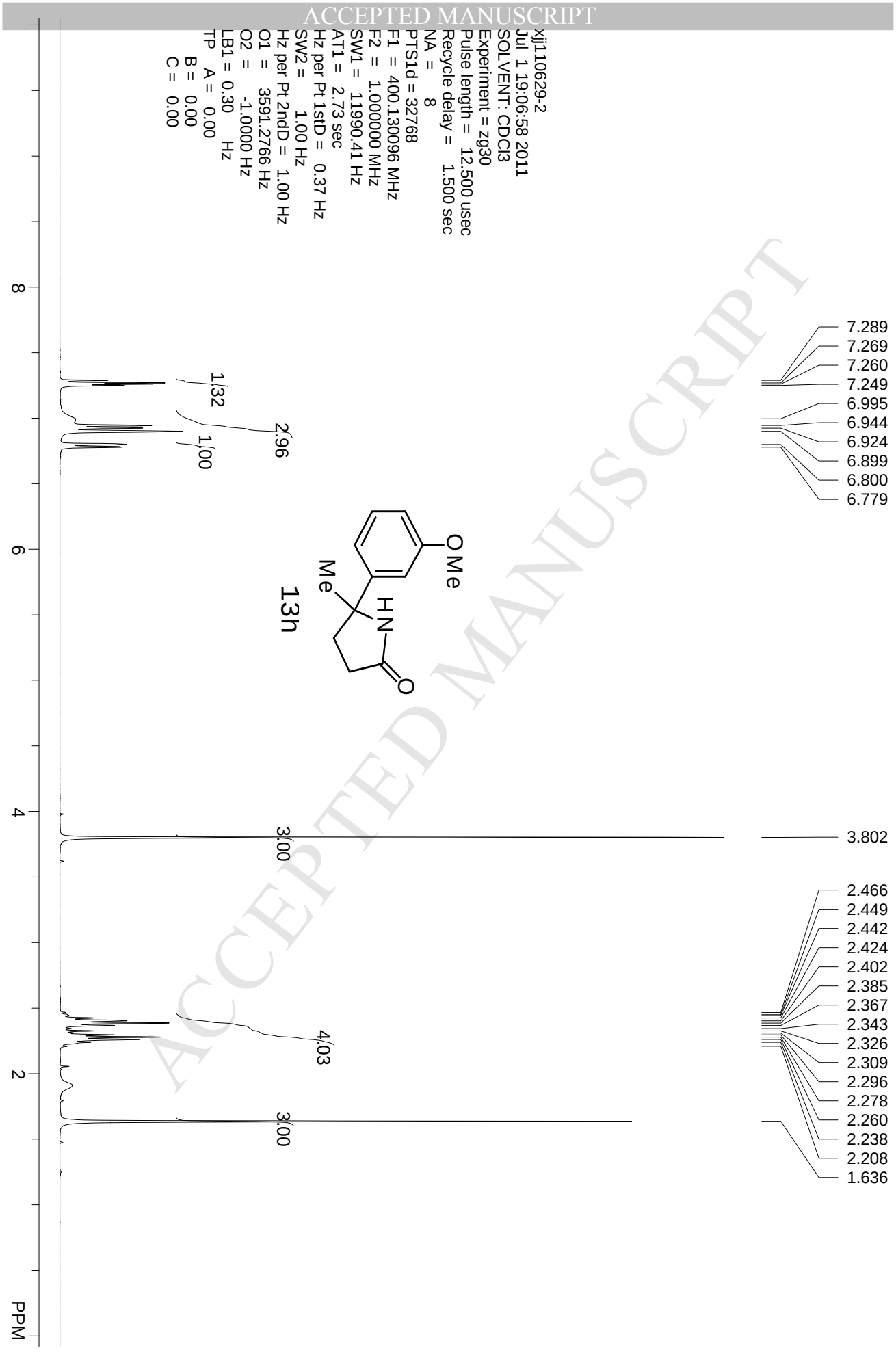

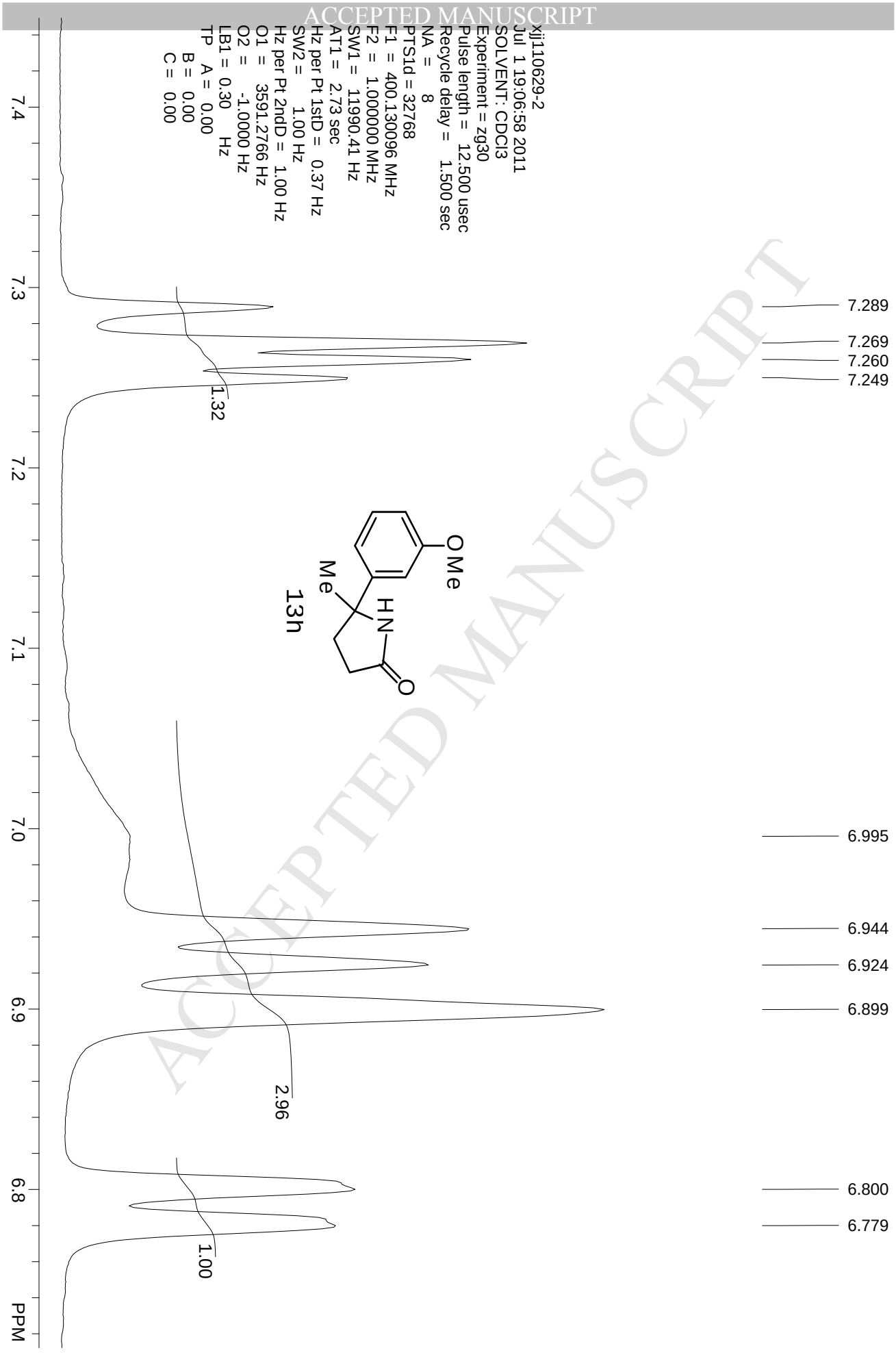

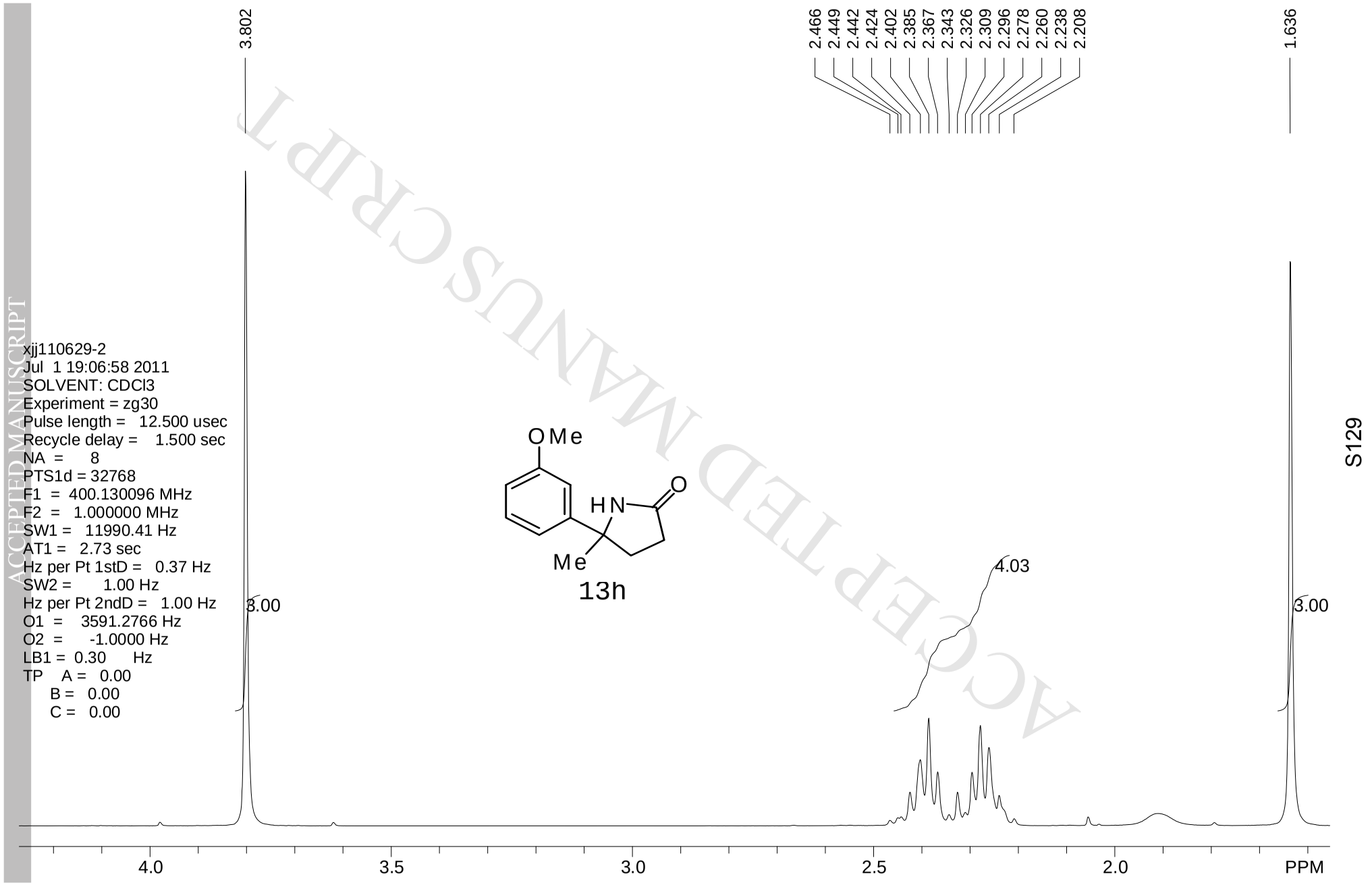

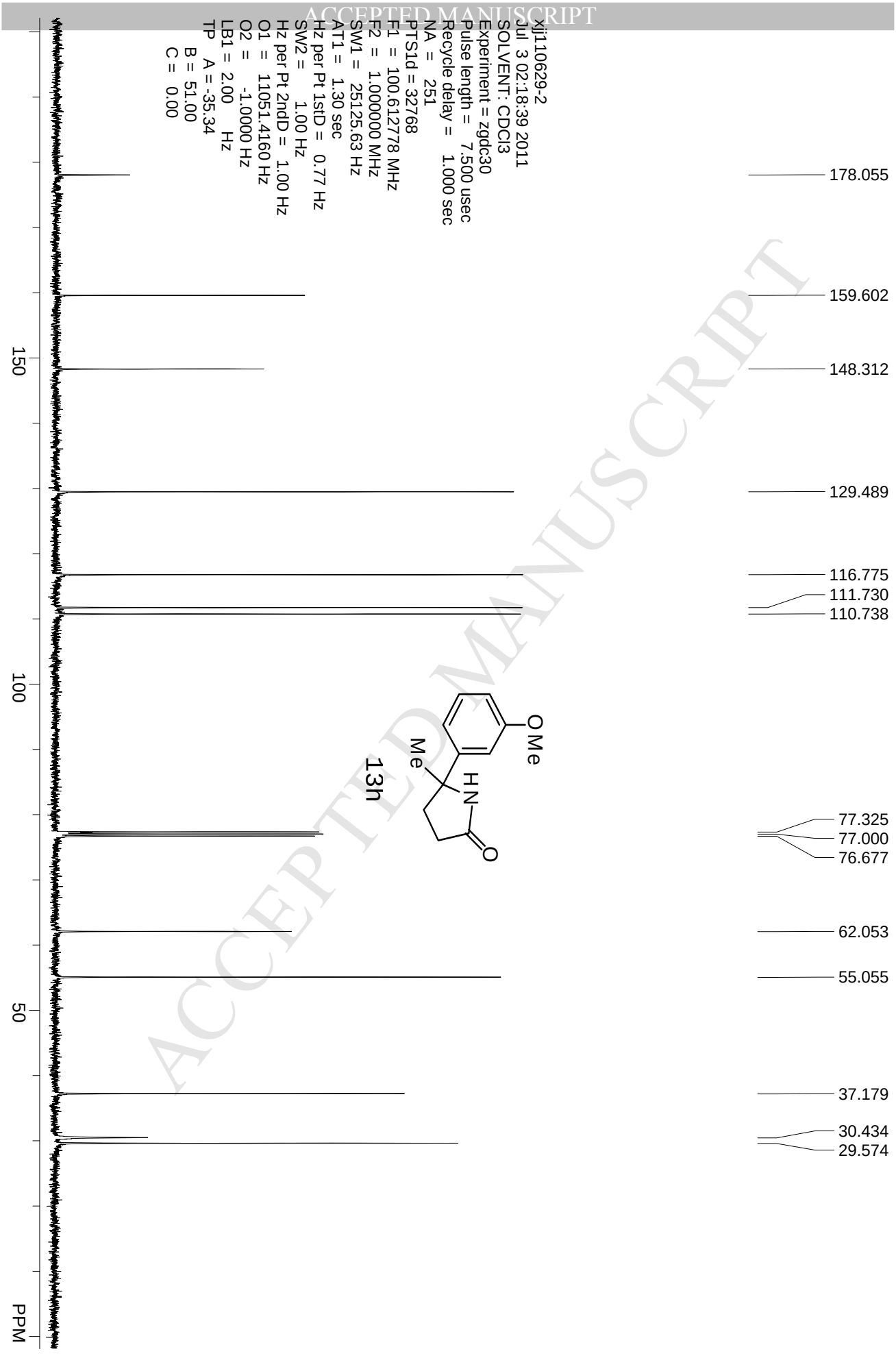

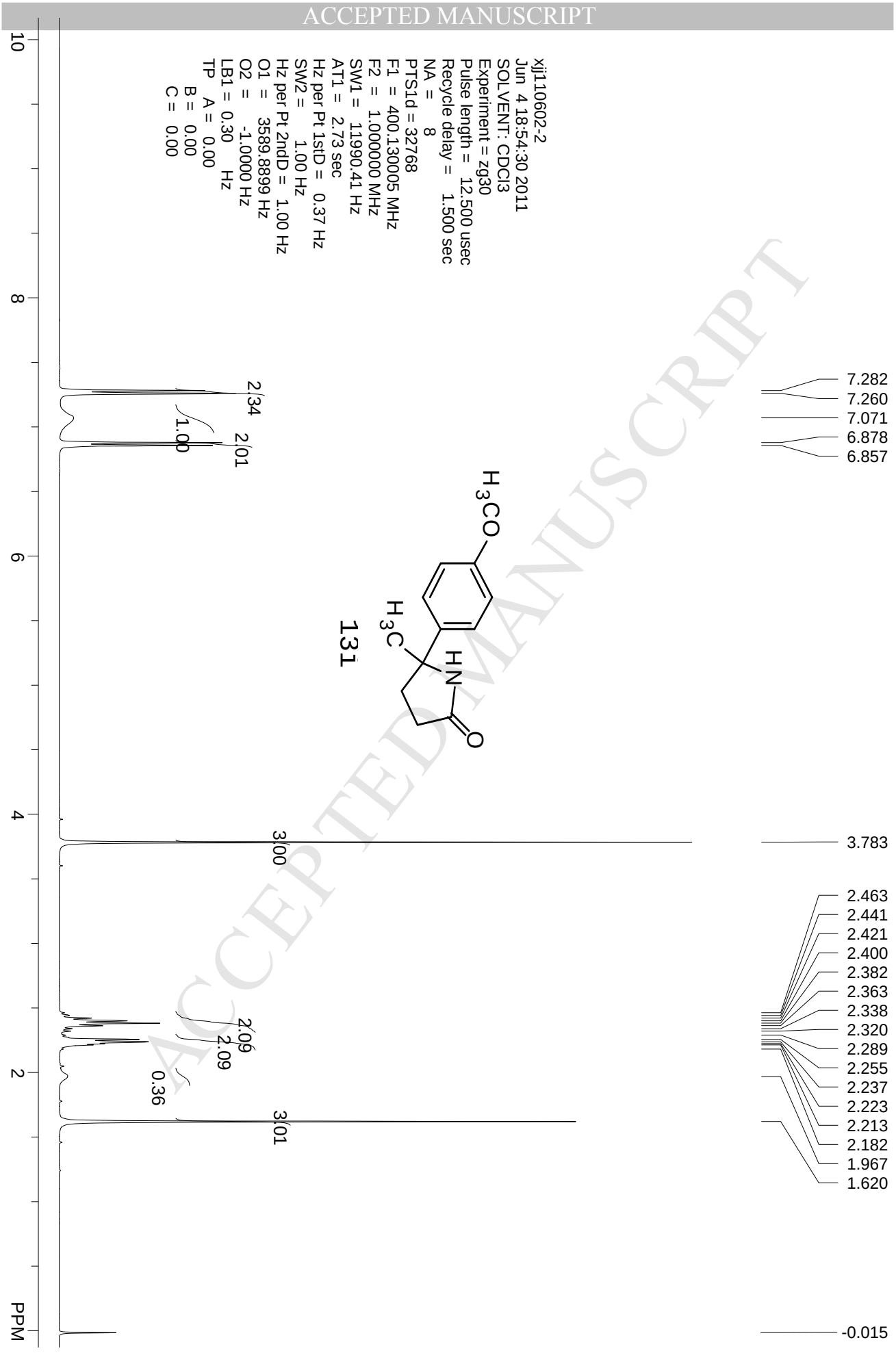

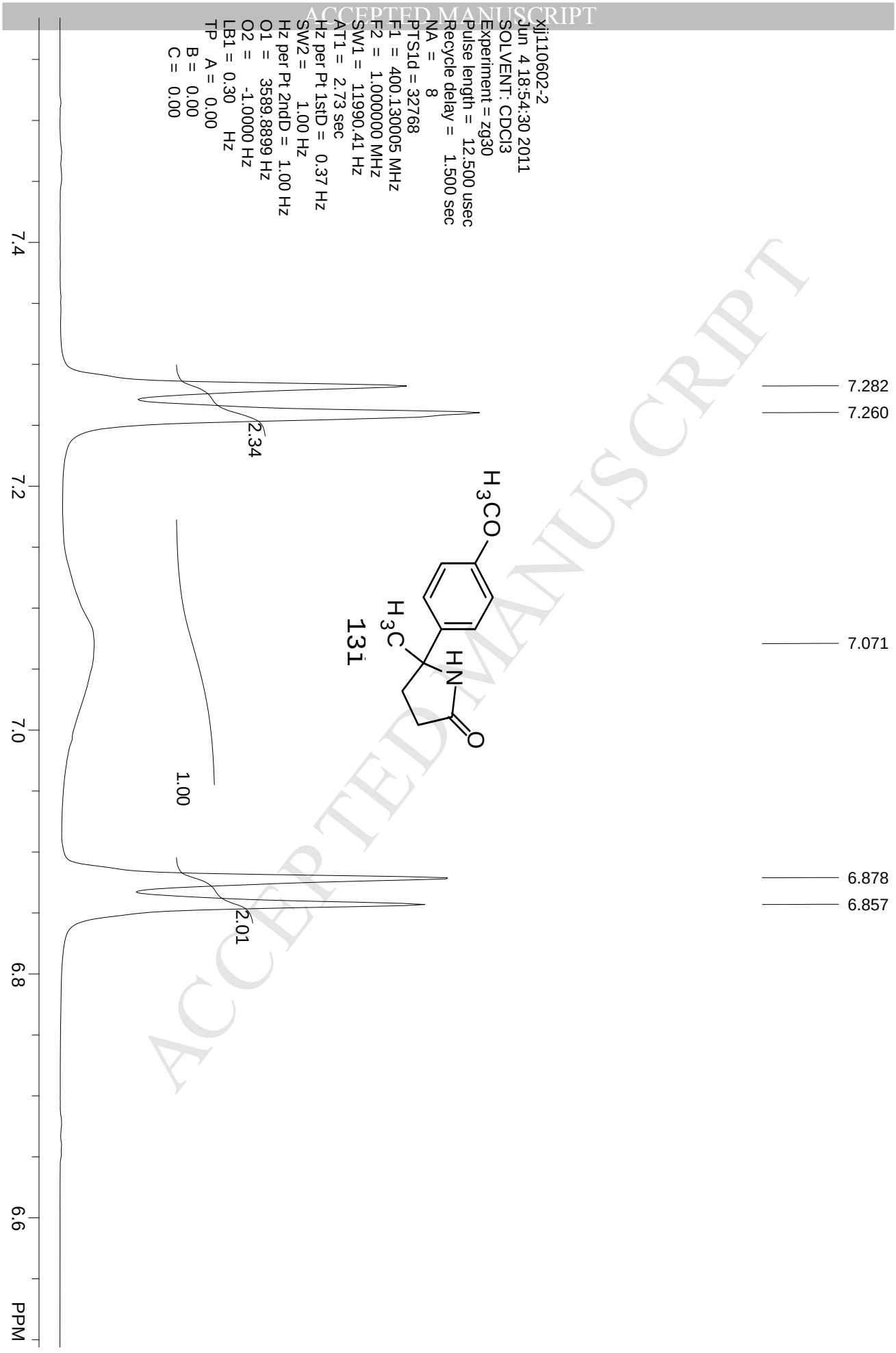

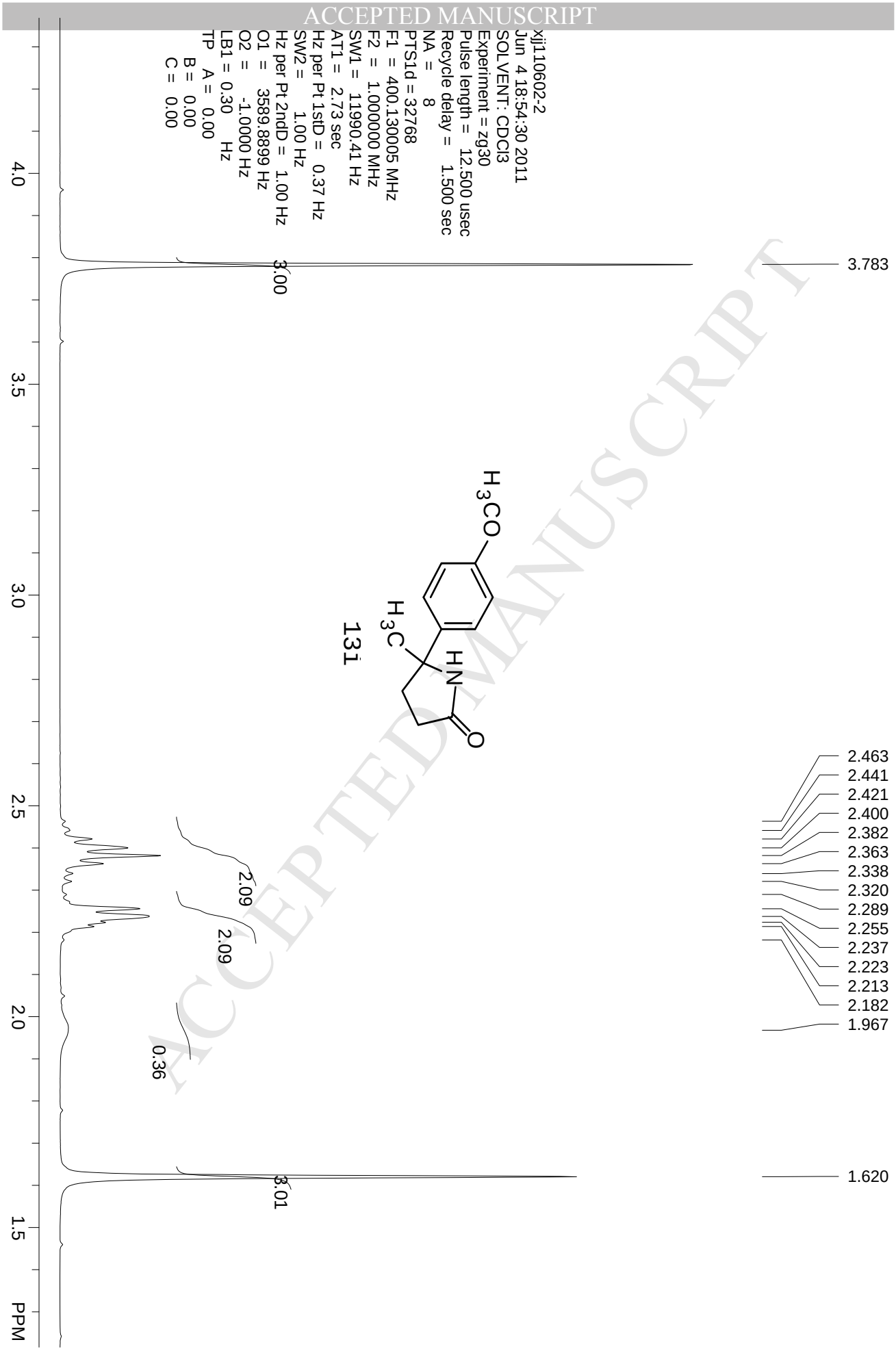


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