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Kinetic Resolution of N-Acyl-b-Lactams, b-Lactams, and N-Acyl-Thiolactams using Amidine-Based Catalysts

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by

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

LIST OF ABBREVIATIONS

1. ABC – Amidine Based Catalyst
2. *ee* – Enantiomeric excess
3. *C*, conv – Conversion
4. ***s*** – Selectivity factor
5. BTM – Benzotetramisole
6. HBTM – Homobenzotetramisole
7. Cl-PIQ - 7-chloro-2-pheny1-2,3-dihydroimidazo[1,2-a]quinoline
8. *k* – Reaction rate
9. KR – Kinetic Resolution
10. $CDCl_3$ – Deuterated chloroform
11. CH_2Cl_2 – Methylene chloride
12. THF – Tetrahydrofuran
13. CH_3CN – Acetonitrile
14. MeOH – Methanol
15. BnOH, $PhCH_2OH$ – Benzyl alcohol
16. Na_2SO_4 – Sodium sulfate
17. OBu-*t* – Boc, *tert*-butyl carbamate
18. PMP – *p*-Methoxyphenyl
19. *i*Pr – Isopropyl
20. Et – Ethyl
21. Ph - Phenyl
22. $PhCO_2H$ – Benzoic acid
23. $LiBF_4$ – Lithium tetrafluoroborate
24. *i*-Pr_2NEt – diisopropylethylamine

25. (*i*-PrCO)$_2$O – Isobutyric anhydride

26. LA – Lewis Acid

27. TS – Transition State

28. Eq. – Equation

29. SM – Starting Material

30. PR – Product

31. H^+ - Hydrogen cation (proton)

32. DMAP – 4-Dimethylaminopyridine

33. NHC – N-Heterocyclic carbene

34. equiv – Equivalent

35. mL – milliliter

36. mg – milligram

37. g – gram

38. µL – microliter

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To my parents, my son, and my husband

ABSTRACT OF THE DISSERTATION

Kinetic Resolution of N-Acyl-β-Lactams, β-Lactams, and N-Acyl-Thiolactams Using Amidine-Based Catalysts

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In the context of enantioselective nucleophilic acyl substitution, there are 3 types of processes depending where chirality is present: **Type I**, where the nucleophile (alcohol or amine) gets resolved, **Type II**, where chirality resides in the leaving group, and **Type III**, where a chiral acyl donor is attained in enantioenriched form. All these transformations can be used to physically separate enantiomers from a racemate in the presence of an asymmetric acylation catalyst and thus can be termed as "kinetic resolutions" or KR. Considerable progress has been done in the **Type I** transformation, where chiral alcohols, thiols, and amines are achieved with great selectivities via asymmetric enzymatic and non-enzymatic acylation. KR of chiral acyl donors (**Type III**) has also been accomplished using both enzymatic and non-enzymatic modes of catalysis. However, **Type II** process has only been reported enzymatically.

Since 2003 our group has developed 4 consecutive generations of amidine-based catalysts (ABCs) that have engaged in a variety of enantioselective acylation transformations, mostly

Type I (KR of various alcohols and lactams (and thiolactams) via asymmetric acylation) and **Type III** (enantioselective alcoholysis of α-substituted acids and azlactones) processes.

As a contribution and an extension to enantioselective, catalytic, nucleophilic acyl substitution study with ABCs, my work has left a mark in all three types of processes discussed above. An unprecedented KR of N-acyl-β-lactams via enantioselective alcoholysis (**Type III)** has been achieved with great results. The established protocol leads to preparation of β-amino acids derivatives in enantioenriched form. Equally unique in this transformation is the mode of action of ABCs, where for the first time the nucleophilic attack of our catalysts on chiral acyl donors was in itself highly enantioselective – a phenomenon in contrast to usual behavior of ABCs in previously studied processes in our lab. Similarly novel, or at least conceptually, was the accomplishment of the first asymmetric *de-acylation* (**Type II**) process reported to date using non-enzymatic acyl transfer catalyst in the form of asymmetric alcoholysis of N-acyl-thiolactams. The KR poses an alternate route to obtaining enantioenriched thiazolidin-2-thiones and oxazolidine-2-thiones. And last but not least, the first enantioselective N-acylation of β-lactams (a **Type I** process) has been obtained with acceptable to good selectivities. This method complements the enantioselective alcoholysis of N-acyl-β-lactams, since it achieves unscathed enantioenriched β-lactams.

Chapter I

Introduction to Nucleophilic Acyl Substitution. Fundamentals and Terminology.

1.1 Types of enantioselective nucleophilic acyl substitution in kinetic resolution

Enantioselective acyl substitution reactions may be classified according to the location of the stereogenic centers: 1) in the nucleophile Y (**Type I**); 2) in the leaving group X (**Type II**); or 3) in the acyl group (**Type III**) (**Figure 1.1-1**).

Figure 1.1-1: Three ways to induce chirality in asymmetric nucleophilic acyl substitution

These three types of processes can be exemplified by using formation and hydrolysis of esters as shown in **Figures 1.1-2** and **1.1-3**. In **Type I** process (**Figures 1.1-2**, left) an achiral acyl donor acylates one of the enantiomers of a racemic alcohol forming an ester, while the other enantiomer remains mostly unreacted. In **Type II** transformation, the reverse happens (**Figures 1.1-2**, right): one of the enantiomers of a racemic ester is hydrolyzed selectively. **Type I** and **II** processes will produce the same mixture of the enantioenriched alcohol and ester, if their enantioselectivities are opposite. Both enantioselective esterification of a chiral acid and the complementary hydrolysis of the corresponding ester belong to **Type III** process.

[i] Of course, additional possibilities may arise from various combinations of individual types of processes. For example, enantioselective hydrolysis of a racemic lactone may be viewed as a "mixed" **Type II**-**Type III** process

Figure 1.1-2: Examples of **Type I** and **II** processes

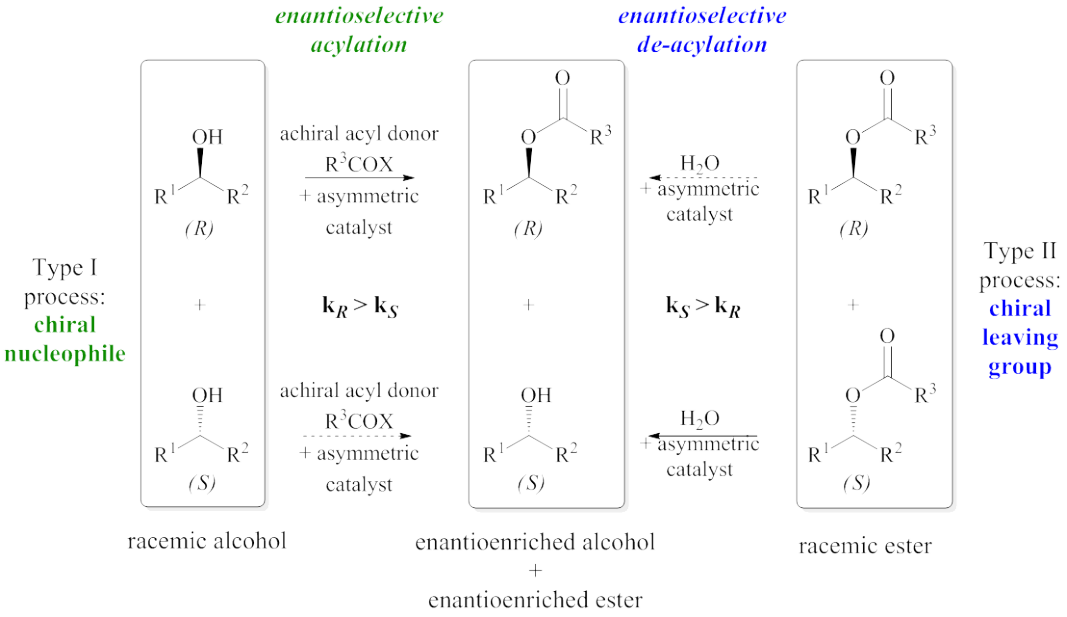


Figure 1.1-3: Examples of **Type III** process

All of the aforementioned transformations can be used to achieve physical separation of a racemic mixture into individual enantiomers and, thus, can be termed “kinetic resolutions” or

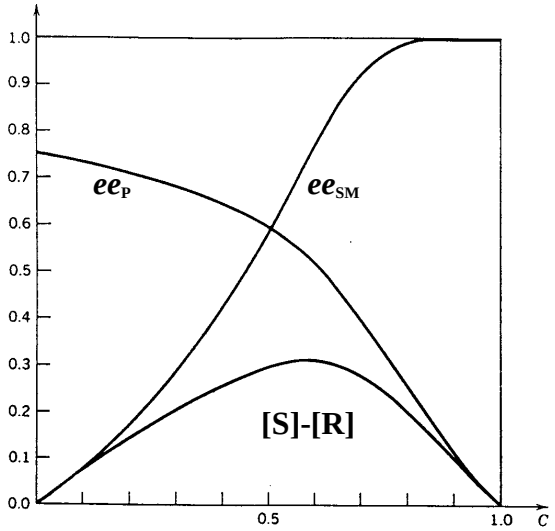
KR[1]. By IUPAC definition, "KR is the achievement of partial or complete resolution by virtue of unequal rates of a reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, solvent, etc.)". All three types of enantioselective nucleophilic acyl substitutions discussed above have been successfully carried out using enzymes[2]. Considerable progress has also been made in the development of non-enzymatic asymmetric acylation catalysts. They have accomplished considerable success especially in the KR of alcohols and, to a lesser extent, amines and thiols (**Type I**).[3] However, until recently, there have been no reports of these catalysts working in the "reverse" to achieve enantioselective *deacylation* (**Type II**). The first non-enzymatic example of such a transformation can be found in Chapter IV of this thesis. Several examples of Type III process (enantioselective alcoholysis of activated chiral acyl donors) have also been achieved using non-enzymatic catalysts.[4]

The efficiency of KR is often described by selectivity factor (**s**), which is the ratio of relative rate constants of the two enantiomers ($s = k_{fast}/k_{slow}$) (**Scheme 1.1-1**).[5] S-value remains unchanged throughout the progress of a reaction unlike enantiomeric excess (*ee*), which changes in the course of KR.

Many common asymmetric catalysts that have been effective in catalyzing acylation reactions are just chiral versions of simpler achiral catalysts, such as 4-dialkylaminopyridines (i.e. DMAP)[6], N-alkylimidazoles (i.e NMI)[7], phosphines (i.e. tributylphosphine)[8], N-heterocyclic carbenes (NHC)[9] (**Figure 1.1-4**). They are believed to operate through a similar catalytic cycle via an acyl transfer mechanism. In the step I, the nucleophilic catalyst :Nu in the presence of an acyl donor RCOX would form a reactive intermediate (usually a zwitterionic

salt), which gets attacked by a sufficiently nucleophilic substrate Y-H in step II, forming product RCOY and releasing the catalyst :Nu for subsequent reuse.

Scheme 1.1-1: Determination of selectivity factor (s) in KR



Calculated for s = 7

$$(\pm)\text{-Starting Material (SM)} \xrightarrow[k_R > k_S]{} (R)\text{-Product}\ (ee_P) + (S)\text{-SM}\ (ee_{SM})$$

Enatiomeric Excess: $\dfrac{[\text{Major}] - [\text{Minor}]}{[\text{Major}] + [\text{Minor}]}$

Conversion: $C = \dfrac{ee_{SM}}{ee_{SM} + ee_P}$

Selectivity factor: $s = \dfrac{k_{fast}}{k_{slow}} = \dfrac{\ln[(1-C)(1-ee_{SM})]}{\ln[(1-C)(1+ee_{SM})]}$

Figure 1.1-4: Common achiral acylation catalysts and catalytic cycle

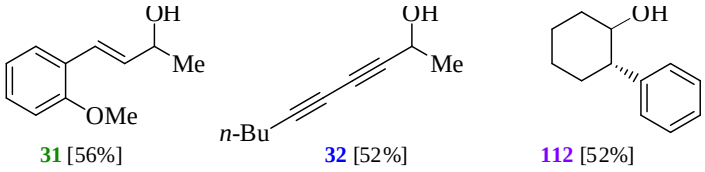
1.2 Acyl trasfer catalysts designed in our group and their application in Types I-III processes

From 2003 till 2009, our group designed and synthesized four consecutive generations of amidine-based catalysts (ABCs) **I-1** through **I-4** that operate via an enantioselective acyl transfer mechanism[10] (**Figure 1.2-1**). Their advantages are simple design, ease of preparation, versatility, and high enantioselectivity.

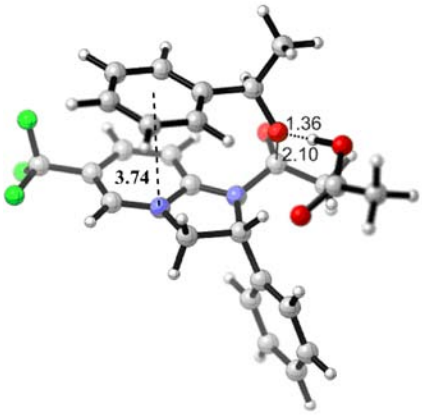
Figure 1.2-1: Amidine-Based Catalysts developed in our group

Prior to the studies described in this thesis, ABCs demonstrated their efficacy in **Type I** KR of various secondary alcohols (benzylic, allylic, propargylic, cyclic)[11], displaying good to excellent selectivity factors (**Scheme 1.2-1**, s-value in bold color corresponding to the catalyst used in the study, % conversion in [brackets]). Based on experimental results later confirmed by computational studies of transition state (TS) models in KR of benzylic alcohols, the catalysts' mode of action has been described by π-cation interactions between the nucleophilic substrate and the N-acylated catalyst[12]. Later, ABCs were used to resolve oxazolidinones, with a similar mechanism to the one of alcohols (**Scheme 1.2-2**).[13]

Scheme 1.2-1: KR of 2º alcohols using ABCs and TS model with CF_3-PIP



31 [56%] **32** [52%] **112** [52%]



Scheme 1.2-2: KR of oxazolidiones using ABCs

ABCs have also proved to be successful in less explored **Type III** transformation with KR of acyl donors – a study pioneered by Xing Yang in our group. One could envision mechanistic similarities between the KR of alcohols and acyl donors, yet in the latter both acyl

activation and alcoholysis steps in the catalytic cycle could result in enantiodiscrimination (**Scheme 1.2-3**).

Scheme 1.2-3: KR of alcohols (**Type I** process) vs KR of acyl donors (**Type III** process)

Xing demonstrated that HBTM can resolve various α-substituted carboxylic acids with good enantioselectivities[14] (**Scheme 1.2-4, A**). Furthermore, Xing was able to accomplish the dynamic kinetic resolution (DKR) of α-arylthio- and α-alkylthio-alkanoic acids with great *ee*s and yields[15] (**Scheme 1.2-4, B**). Unlike conventional KR, DKR is based on a rapid *in situ* equilibration between fast- and slow-reacting enantiomers. Hence, it is a more efficient process since it can generate up 100% yield of only one enantioenriched product. In both cases (KR and DKR), Xing noticed that enantioselectivity was strongly dependent on the nature of alcohol used. The need to use the bulky di(1-naphthyl)methanol indicated that the second step in the catalytic cycle determined enantiodifferentiation, analogously to previously studied acylation of alcohols and oxazolidinones (**Figure 1.2-2**). Experimental results, later confirmed by computational studies[16], suggested the origin of enantioselectivity stemmed from cation-π interaction between the bulky alcohol and acylated HBTM and that the alcohol attack was according to the polar Felkin-Ahn model[17]. Another example of **Type III** process accomplished by Xing in

collaboration with Guojian Lu was the DKR of azlactones.[18] This work served as a point of reference for the subsequent studies discussed in Chapter II and, hence, will be described in more detail later.

Scheme 1.2-4: KR (and DKR) of α-substituted carboxylic acids using HBTM

Figure 1.2-2: Proposed catalytic cycle and TS model in the KR (or DKR) of α-substituted acids

In the following chapters of this thesis, I will be describing my contribution in the enantioselective nucleophilic acyl substitution field, apart from what has been discussed above. I was fortunate to have had my work leave a mark in all **Types I-III** processes using ABCs developed in our group.

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Chapter II

Kinetic Resolution of N-Acyl-β-Lactams via Enantioselective Alcoholysis using Amidine-based Catalysts

2.1 Introduction

Due to their specific biological properties, β-amino acids and their derivatives have been known and used in various applications[1]. There are many approaches to their preparation in enantiopure form, one of which is through ring opening of enantioenriched β-lactams or β-lactam derivatives[2]. Despite the breakthroughs in the asymmetric synthesis of the latter, the β-lactam substrate scope often remained limited[3]. Hence, the enzymatic hydrolysis of their racemates[4] still remains a viable method for preparing enantiopure β-amino acids[5] (**Scheme 2.1-1**). Despite their high efficacy, enzymes have serious shortcomings, such as availability only in one enantiomeric form, narrow substrate or reaction scope, and/or, at times, high cost.

Scheme 2.1-1: Enzymatic approaches to KR of β-lactams

Although non-enzymatic kinetic resolution (KR) of β-lactam racemates would be an attractive method to obtain enantioenriched β-amino acids, to the best of our knowledge, it has

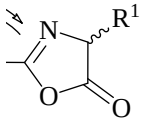
not been reported until our work in this area[6,7]. Hence, in this chapter, I will be describing the first enantioselective alcoholysis of β-lactam derivatives and my efforts to elucidate the mechanism of this process using ABCs **I-2** through **I-4**.

In the investigation of KR of various chiral acyl donors[8], Xing Yang in collaboration with Guojian Lu has developed a protocol for DKR of azlactones[9] (**Scheme 2.1-2**) to obtain enantioenriched α-amino acids. They have noticed that changing the amount of benzoic acid relative to the catalyst did not have a significant effect on the reaction rate or enantioselectivity, although in its absence the reaction did not seem to proceed at all. Such activation with Brønsted acid in combination with an enantioselective acyl transfer catalyst has been previously reported by others.[10] Apart from that, the catalytic cycle and catalyst's mode of action in this process seemed to be consistent with ABCs previous behavior (**Figure 2.1-1**)[8, 11, 12]. The success of the DKR of azlactones with BTM led me to investigate other classes of chiral acyl donors that could use a combination of ABC with a Brønsted acid and that would generate enantioenriched products of practical use.

Scheme 2.1-2: DKR of azlactones

Figure 2.1-2: Proposed catalytic cycle and origin of enantioselectivity in DKR of azlactones

Brønsted acid co-catalyst is required!



2.2 Experimental design and findings

Initially we turned our attention to oxazinones, the ring-expanded homologues of azlactones, which would lead to enantioenriched β-amino acid derivatives. The KR of oxazinones has been previously achieved by Berkessel *et al* using a bifunctional thiourea catalyst with impressive selectivities[13]. When 4-phenyl oxazinone **II-1** was subjected to KR with di(1-naphthyl)methanol in the presence of our catalytic system it did react, however, the selectivity was disappointingly low (**Table 2.2-1**, entry 1). Interestingly, when less hindered alcohols were used, the results were approximately the same (entries 2,3).

Table 2.2-1: KR of oxazinone (±)-**II-1**: Alcohol screening[a]

Entry	R	Conversion (%)	s
1	$(1\text{-Np})_2CH$ (**II-2a**)	56	3.9
2	$PhCH_2$ (**II-2b**)	51	2.9
3	Me (**II-2c**)	48	3.3

Reaction conditions: 0.1 mmol (±)-**II-1**, 0.05 mmol ROH, *(S)*-BTM (10 mmol%), $PhCO_2H$ (10 mmol%), in $CDCl_3$, rt. [a] Results averaged from duplicate runs

This suggested that the mechanism of this transformation might be entirely different from what was observed in the DKR of azlactones, where enantioselectivity depended critically on the alcohol used. The absence of such dependence in the case of oxazinones indicated to us that enantioselectivity might arise in the first step in the catalytic cycle. Witnessing a new phenomenon, we were excited about its prospects despite initial disappointing results. Therefore, we decided to try the KR of N-acyl-β-lactam **II-3a**, the constitutional isomer of **II-1** (**Figure 2.2-1**). Since **II-3a** would produce the same reactive intermediate **II-4** upon ring-opening as **II-1**, we reasoned that the N-acyl-β-lactam could potentially undergo KR in similar fashion to **II-1** in the presence of BTM, but hopefully with better enantioselectivity.

Figure 2.2-1: Proposed catalytic cycle for oxazinone **II-1** and N-acyl-β-lactam **II-3a**

Gratifyingly, when I tried the KR conditions with di(1-naphthyl)methanol on N-bezoyl-4-phenyl-β-lactam **II-3a**, the selectivity significantly improved (**Table 2.2-2**, entry 1). Furthermore, again, switching to less hindered alcohols gave essentially the same results with this substrate (entries 2,3), suggesting a similar mechanism as in the case of oxazinone **II-1** (**Figure 2.2-1**). This observation seemed to indicate that the enantioselectivity–determining step is *irreversible* and that N-acyl-β-lactams are more suitable substrates for appreciable induction of asymmetry during the nucleophilic attack of our catalyst than oxazinones.

Table 2.2-2: KR of N-acyl-β-lactam (±)-**II-3a**: Alcohol screening[a]

Entry[a]	R	Time (hrs)	Conversion (%)	s
1	$(1\text{-Np})_2CH$ (**II-2a'''**)	68	51	21
2	$PhCH_2$ (**II-2a''**)	68	52	19
3	Me (**II-2a'**)	24	52	21

General conditions: 0.1 mmol (±)-**II-3a**, 0.5 mmol ROH, 10 mol% *(S)*-BTM, 10 mol% $PhCO_2H$, in $CDCl_3$, rt.
[a] Results averaged from duplicate runs

As part of the optimization study, I briefly investigated whether a Lewis acid (LA) could also be applied to the catalytic alcoholysis of N-acyl-β-lactam **II-3a** with comparable mode of action to benzoic acid. It was a challenge, however, to find common Lewis acids that would dissolve in chloroform and, hence, to run accurate and reproducible experiments (I could not

make stock solutions and working with very small amounts of Lewis acids could have led to experimental errors). When $LiBF_4$ was tried in the KR of **II-3a** with benzyl alcohol, despite its poor solubility, it did give similar selectivity and reaction times to the case of benzoic acid (**Scheme 2.2-1**).

Scheme 2.2-1: KR of N-acyl-β-lactam (±)-**II-3a** in presence of a Lewis Acid

Mindful of the fact that LAs could potentially catalyze alcoholysis of the substrates by themselves, a qualitative background test with several Lewis acids varying in potency was performed (**Table 2.2-3**). These results indicate that some LAs, $Sc(OTf)_3$ and $Cu(OTf)_2$, do indeed catalyze the alcoholysis of N-acyl-β-lactams. This observation could provide some ideas for future new designs of asymmetric catalysts including the corresponding metals. Since LAs did not offer any apparent advantages compared to benzoic acid, we continued to use the latter in our optimization study.

Table 2.2-3: Lewis acid background reaction check for N-acyl-β-lactam (±)-**II-3a**

Entry	Lewis Acid (10 mol%)	Solubility of LA in $CDCl_3$	Time	Background reaction
1	LiCl	Not soluble	40 hrs	no
2	$Mg(ClO_4)_2$	Not soluble	40 hrs	no
4	$Sc(OTf)_3$	Not soluble	17 hrs	Only ester product observed
6	$Cu(OTf)_2$	Not soluble	17 hrs	Only ester product observed
7	$Zn(OTf)_2$	Not soluble	40 hrs	no
8	$ZnBr_2$	Not soluble	40 hrs	no

Reaction conditions: 0.1 mmol (±)-**II-3a** and 0.1 mmol BnOH in $CDCl_3$, 0.01 mmol Lewis Acid, rt.

We then proceeded to test our other most potent ABCs, HBTM **I-4a** and Cl-PIQ **I-2** (**Table 2.2-4**). Although the alcoholysis occurred in both cases, the KR proved to be less enantioselective than in the one of BTM *ent*-**I-3** (Entries 3,4 vs 2). As expected, no reaction happened in the absence of catalyst (entry 1).

Table 2.2-4: KR of N-acyl-β-lactam (±)-**II-3a**: Catalyst screening[a]

Entry[a]	Catalyst	Time (days)	Conversion (%)	s
1	none	1	NR[b]	ND[c]
2	*(S)*-BTM *ent*-**I-3**	1	60	18
3	*(S)*-HBTM **I-4a**	3	62	12^{-1}

4	*(R)*-Cl-PIQ **I-2**	7	42	2.5^{-1}

General conditions: 0.1 mmol (±)-**II-3a**, 0.075 mmol ROH, catalyst (10 mol%), $PhCO_2H$ (10 mol%), in $CDCl_3$, rt. [a] Results averaged from duplicate runs. [b] Determined by H^1 NMR. [c] No reaction. [d] Not determined

The variation of acyl group on the β-lactam nitrogen was explored next (**Table 2.2-5**). Both *N*-Boc **II-3b** and *N*-isobutyryl **II-3c** derivatives were unreactive (entries 2,3). Introducing an electron-withdrawing group to the benzoyl substituent proved to affect both the rate and the enantioselectivity in this process. 4-Chlorobenzoyl derivative underwent KR with an appreciable enhancement of selectivity factor with similar rate compared to the benzoyl compound (entry 4). When reaction was run at 0 °C, the enantioselectivity did improve notably, but the rate was much too slow to be considered practical (entry 5). However, 4-Nitrobenzoyl group demonstrated, as expected, the acceleration in methanolysis rate led to a diminished enantioselectivity (entry 6). The selectivity factor did not improve when the temperature of the reaction was lowered to 0 ºC (entry 7). 3,5-Dinotrobenzoyl substrate **II-3f** underwent ring-opening even faster, but with considerably lower selectivity factor (entry 8).

Table 2.2-5: KR of N-acyl-β-lactam (±)-**II-3a**: N-acyl group screening[a]

Entry[a]	R	Time	Conversion (%)	s
1	Ph	24 hrs	60	18
2	OBu-*t* (**II-3b**)	7 days	NR	ND
3	Me_2CH (**II-3c**)	7 days	NR	ND

4	*p*-ClC_6H_4 (**II-3d**)	20 hrs	53	26
5[b]	*p*-ClC_6H_4 (**II-3d**)	7 days	51	37
6	*p*-$NO_2C_6H_4$ (**II-3e**)	5 hrs	53	20
7[b]	*p*-$NO_2C_6H_4$ (**II-3e**)	36 hrs	50	20
8	3,5-$(NO_2)_2C_6H_4$ (**II-3f**)	1 hrs	72	2.6

General conditions: 0.1 mmol (±)-**II-3**, 0.05 mmol MeOH, 10 mol% *(S)*-BTM, 10 mol% $PhCO_2H$, in $CDCl_3$, rt.
[a] Results based on duplicate runs [b] Reaction conducted at 0 ºC.

Due to the limited solubility of N-benzoyl-β-lactams, the solvent screening was a relatively short process (Table **2.2-6**). The substrate **II-3d** dissolved best in chloroform and methylene chloride, the latter leading to a lower selectivity factor (entry 2 vs 1). Toluene gave comparable enantioselectivity to chloroform, albeit at a more sluggish rate (entry 3). Additionally, it was a poor medium for a smooth KR as the starting material precipitated out within minutes from the beginning of reaction despite a decrease in concentration, affecting the accuracy of results. Although the substrate displayed better solubility in acetonitrile than toluene, the selectivity suffered significantly (entry 4). Tetrahydrofuran seemed to be an unsuitable solvent for this system altogether, as the reaction was very slow and led to undesired side products that complicated the purification and analysis process (entry 5).

Table 2.2-6: KR of N-acyl-β-lactam (±)-**II-3d**: Solvent screening[a]

Entry[a]	Solvent	Time (days)	Conversion (%)	s
1	$CDCl_3$	1.5	47	28
2	CD_2Cl_2	3.5	55	20.5
3	d^8-toluene	7	38	29
4	CD_3CN	3.5	54	12
5	d^8-THF	7	20[b]	ND

General conditions: 0.1 mmol (±)-**II-3d**, 0.075 mmol MeOH, 10 mol% *(R)*-BTM, 10 mol% $PhCO_2H$, in solvent, rt. [a] Results based on duplicate runs [b] Determined by H^1 NMR

Once the optimization process was completed, we began to investigate the substrate scope (**Table 2.2-7**). Surprisingly, having R^3 changed from phenyl to 1-napthyl improved enantioselectivity only slightly (entry 2 vs 1), while isopropyl substituent gave an unexpectedly impressive selectivity factor of 78 (entry 3). To our delight, once cis-ring-fused N-acyl-β-lactams from **II-7** to **II-12** were subjected to the same KR conditions, the results were even more exciting, enantioselectivities ranging from 111 to 211 (entries 4-9). Unfortunately, when we switched to trans-disubstituted monocyclic substrate **II-13**, it failed to react completely over the course of one week (entry 10).

Table 2.2-7: KR of N-acyl-β-lactams: Substrate scope[a]

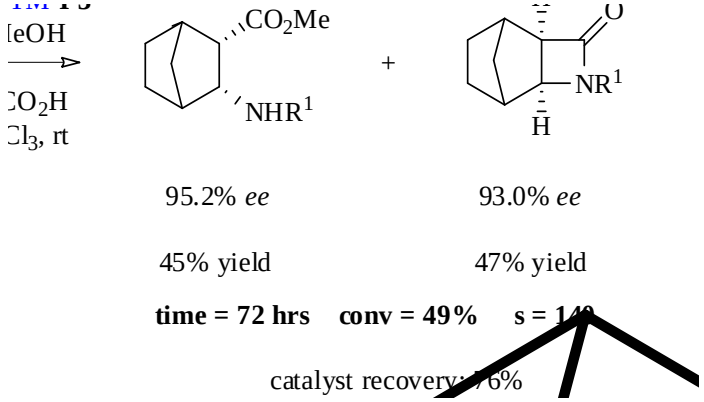
Entry	Substrate[a,b]	Time	ee_{PR} (%)	ee_{SM} (%)	Conv (%)	s
1	**II-3d**	20 h	79	90	53	26
2	**II-5**	22 h	78	95	55	30
3	**II-6**	3 d	93	84	47	78
4	**II-7**	56 h	96	92	49	166
5	**II-8**	24 h	89	99.8	53	111
6	**II-9**	4 d	97	81	45	196
7	**II-10**	7 d	98	59	38	211
8	**II-11**	66 h	95	95	50	156

9	**II-12**	32 h	96	82	46	124
10	**II-13**	7 d	ND	ND	NR	ND

General conditions: 0.1 mmol (±)-substrate, 0.075 mmol MeOH, 10 mol% *(S)*-BTM, 10 mol% $PhCO_2H$, in $CDCl_3$, rt. [a] Results based on duplicate runs. [b]The absolute configuration of the fast reacting enantiomer shown.

To demonstrate the practical utility of this process, the KR of substrate **II-11** on a 1-gram scale was performed, giving similar results to the small scale KR of the same substrate, with excellent yields of enantioenriched species and a 76% catalyst recovery (**Scheme 2.2-2**).

Scheme 2.2-2: Preparative-scale KR of N-acyl-β-lactam (±)-**II-11**



To explain the origin of enantioselectivity, we initially envisioned that the catalyst would prefer a facial attack on β-lactam carbonyl with the N-benzoyl group away from the catalyst's phenyl substituent at C-2 to avoid steric interactions with the ring hydrogens (**Figure 2.2-2**).

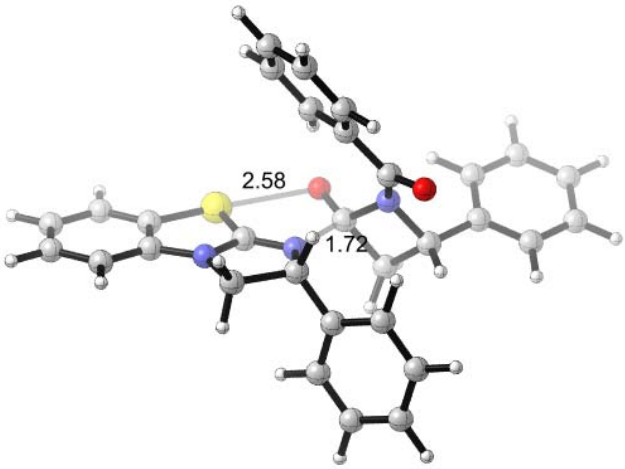
Figure 2.2-2: Initial proposed model for enantiodiscrimination in KR of N-acyl-β-lactams

The proposed model also explained the increase in enantioselectivity with cis-ring-fused substrates and lack of reaction with trans-substituted N-acyl-β-lactams. Having R^2 and R^3 groups cis to each other would only enhance the blockage on the face they are pointing towards, while trans substitution would hinder the catalyst attack from either face. The model excluded the acid, since it was unclear to us at that time what role it played.

Subsequent preliminary computational studies on **II-3a**, however, demonstrated that our initially proposed model was too simplistic, even if it accounted for the available experimental results (**Figure 2.2-3**). The transition states were built with Xing Yang's help introducing two important interactions, not taken in consideration in our initial proposed model for enantiodifferentiation: 1) the π-cation interaction between the benzothiazolium moiety and phenyl in the aroyl group of N-acyl-β-lactam and 2) the S-O interaction, where the amide

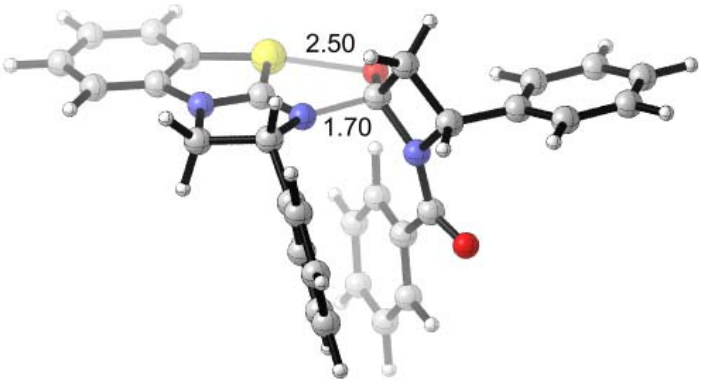
carbonyl from the β-lactam core lies in the same plane as the catalyst and is directed toward its benzothiazolium part (**Figure 2.2-3**). Throughout this study, the method used was Gaussian, DFT B3LYP/3-21G(d). According to these preliminary calculations, the fast-reacting enantiomer (in **TS-*(S)*-BTM-*(R)*-II-3a**) was favored energetically by 4.5 kcal/mol over the slow-reacting enantiomer (**TS-*(S)*-BTM-*(S)*-II-3a**), presumably due to taking advantage of the π-cation stacking. The S-O interaction stays prevalent in both TSs (~2.5 Å). That said, please note that these studies are crude and might provide only qualitative clues to the substrate chiral recognition in this KR. Additional research needs to be performed to explore all possible TSs before we can confirm that the proposed draft models do indeed represent the global minima. Those have not yet been carried out due to limited time and demand of expertise in computational chemistry and software.

Figure 2.2-3: Preliminary computational studies of TSs of fast- and slow-reacting enantiomers of **II-3a**



TS-*(S)*-BTM-*(R)*-II-3a

$\Delta\Delta G^{\ddagger}$= 0.0 kcal/mol



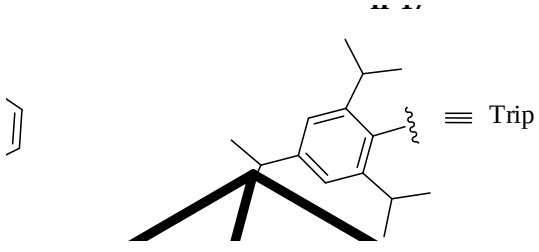
TS-*(S)*-BTM-*(S)*-II-3a

$\Delta\Delta G^{\ddagger}$= 4.5 kcal/mol

2.3 An extension to the study on other modes of catalysis and the role of the Brønsted acid in the KR of N-acyl-β-lactams

After examining enantioselective alcoholysis of N-acyl-β-lactams promoted by ABCs[14], we were curious whether other known types of asymmetric catalysts might also be effective in this process. Keeping in mind that chiral thioureas were highly successful in the alcoholysis of azlactones[15] and oxazinones[13a], we tested the catalysts **II-14** through **II-16** available in our lab. Among these only **II-15** proved to be catalytically active in the KR of **II-11**. However, the enantioselectivity was low (**Table 3.2-1**, entry 2). Switching the solvent to toluene or acetonitrile did not change the outcome (entries 3, 4). Chiral phosphoric acid-based catalyst **II-17** previously identified in our lab by Guojian Lu as an efficient catalyst in the DKR of azlactones[16], also turned out to be completely ineffective (entry 5).

Table 2.3-1: KR of N-acyl-β-lactam (±)-**II-11**: Screening of other catalysts[a]



Entry[a]	Catalyst	Time (days)	ee_{PR} (%)	ee_{SM} (%)	Conv (%)	s
1	**II-14**	4	ND	ND	NR	ND
2	**II-15**	4	51	25	34	4
3[b]	**II-15**	4	44	39	47	4
4[c]	**II-15**	4	13	6	30	1.4
5	**II-16**	4	ND	ND	<10	ND
6	**II-17**	7	ND	ND	NR	ND

General conditions: 0.05 mmol (±)-**II-11**, 0.025 mmol MeOH, 10 mol% catalyst, in $CDCl_3$, rt, unless otherwise specified. [a] Results averaged from duplicate runs. [b] Reaction conducted in toluene. [c] Reaction conducted in acetonitrile

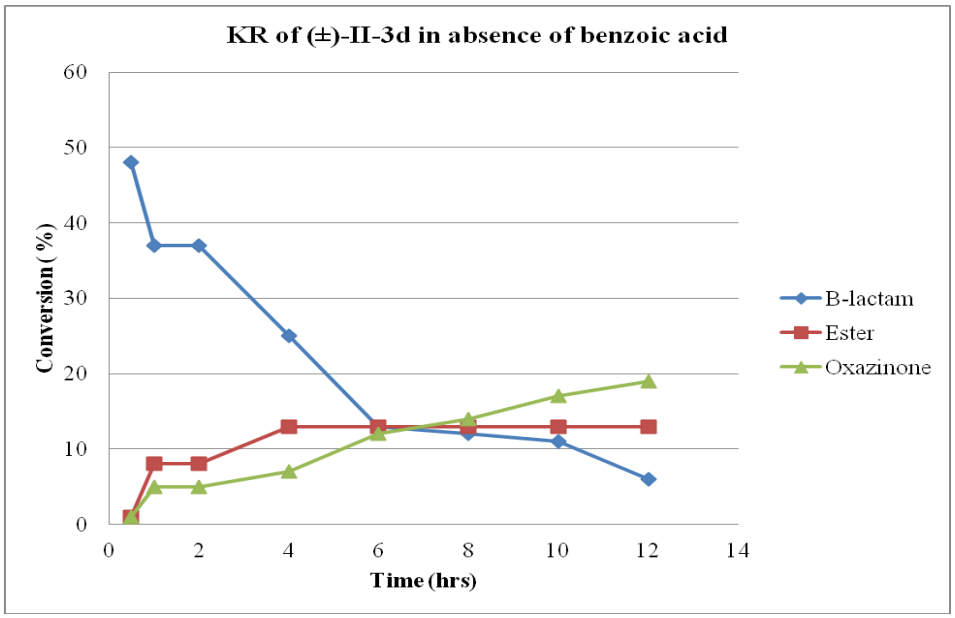
We soon shifted our attention to the investigation of the role of acid (benzoic acid in this case) in the KR of N-acyl-β-lactam. Initially we thought that Brønsted acid (or Lewis acid) was paramount to the KR of N-acyl-β-lactams, as in the case of the DKR of azlactones, where the reaction would not proceed at all in its absence. However, when benzoic acid was omitted from our standard alcoholysis protocol, the ring-opening did occur, albeit with a reduced selectivity (**Scheme 2.3-1**). We also noticed the formation of a side product by H^1 NMR that was not observed previously in the presence of $PhCO_2H$. The initial attempt to collect it and analyze it after purification failed, as it would decompose on silica gel. We came to suspect, however, that the mysterious side product might be the isomeric oxazinone **II-1a**. That indeed was the case when compound **II-1a** was synthesized according to a modified procedure established by Berkessel *et al*[13]. The unique sets of doublet of doublets at 5.04, 3.04, and 2.64 ppm of **II-1a** matched very closely the ones of previously reported **II-1** (5.07, 3.06, and 2.68 ppm).

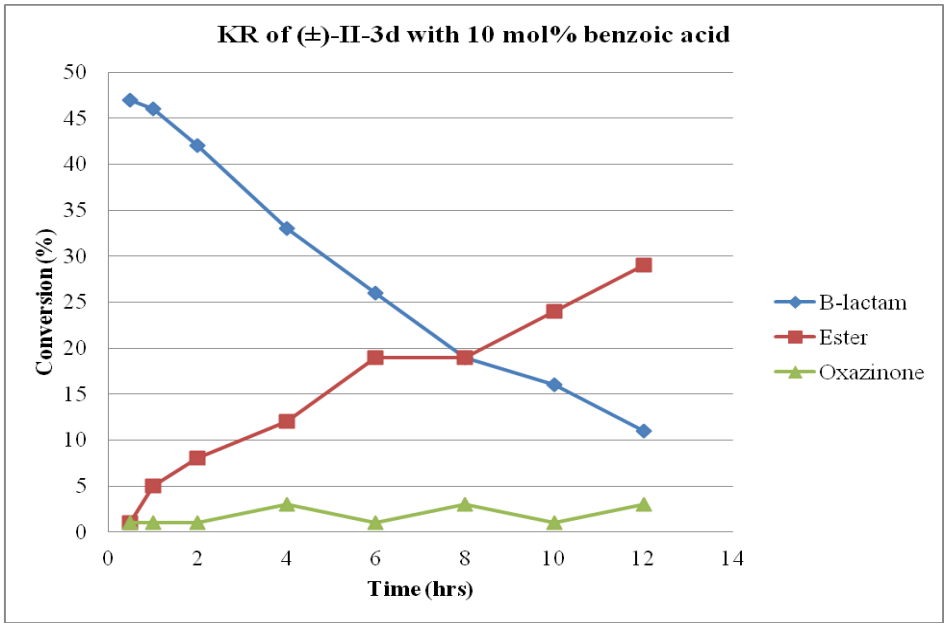
Scheme 2.3-1: KR of N-acyl-β-lactam (±)-**II-3d** in the absence of benzoic acid

We initially reasoned that the formation of an oxazinone, which KR was not as effective as in the case of N-acyl-β-lactams under our protocol, might be the culprit of lower ester enantioselectivity when acid was not added. For that to be true we needed to demonstrate that the oxazinone **II-1a** formed was not enantioenriched. To measure the *ee* and monitor the formation of oxazinone over time, KR of N-acyl-β-lactam **II-3d** was run in the presence and absence of benzoic acid and analyzed by H^1 NMR using 2,6-methoxytoluene as an internal standard (**Scheme 2.3-2**). In the absence of acid, we noticed that initially ester and oxazinone were forming at approximately the same rate, but at around the 4^{th} hour the ester stopped forming while the N-acyl-β-lactam continued to get consumed, leading to more oxazinone in solution. Furthermore, after careful purification and analysis, the oxazinone **II-1a**'s *ee* was comparable to that of unreacted starting material and ester. This process was a case where we formed 3 enantioenriched species and we no longer could discuss enantioselectivity in terms of conversion and selectivity factor as we did in Chapter I, 1.1. We used an alternative equation, also devised by Kagan[16], to calculate the selectivity factor to account only for the product formed: $s = \ln[1-C(1+ee_{PR})]/\ln[1-C(1-ee_{PR})]$, where C (% conv) was determined by ^1H NMR. On the other hand,

in the presence of acid, oxazinone **II-1a** was barely detectable by H^1 NMR, which explained why it has not been noticed before.

Scheme 2.3-2: KR of N-acyl-β-lactam (±)-**II-3d** in the presence and absence of acid





All these findings were puzzling to us, because although we had more details on the acid's mechanistic role, we could not explain why the *ee*s were lower in the absence of acid. The opening of the oxazinone under this catalytic system would produce product ester equally or very similarly enantioenriched as the one produced by opening the fast-reacting N-acyl-β-lactam enantiomer. That said, it is noteworthy to mention a 10% discrepancy between the percentage of N-acyl-β-lactam used and the percentage sum of products formed, which may be due to inaccuracy in weighing of reagents and/or analyzing ^{1}H NMR spectra.

To get more insights on the mechanism of this transformation, a series of reactions were performed by tweaking the catalytic system (**Table 2.3-2**). As expected, no reaction happened in the absence of catalyst within 24 hours, with or without benzoic acid (entries 5, 4). We were wondering if increasing the amount of acid in the presence of our catalyst would further improve the selectivity factor, and that did not seem to be the case when amount of benzoic acid was changed to 20 mol% or 50 mol% (entries 2, 3). Eliminating the possibility that this process might

be base catalyzed, BTM **I-3** was substituted with 1 equivalent of 2,6-collidine and only 15% conversion after 48 hours was observed (however, no ester peaks were visible after 24 hours).

Table 2.3-2: KR of N-acyl-β-lactam (±)-**II-3d**: Testing the catalytic system

Entry	Additives	Time	ee_{ester}	$ee_{\beta\text{-lac}}$	ee_{ox}	Conv (%)	s
1[a, b]	10 mol% *(R)*-BTM + 20 mol% $PhCO_2H$	24 hrs	82.8	82.9	ND	50	27
3[b,c]	10 mol% *(R)*-BTM + 50 mol% $PhCO_2H$	24 hrs	81.0	89.6	ND	52.5	29
4	none	24 hrs	ND	ND	ND	NR[d]	NA
5[e]	10 mol% $PhCO_2H$	24 hrs	ND	ND	ND	NR[d]	NA
6[f]	1 equiv 2,4,6-collidine	48 hrs	ND	ND	ND	15[d]	NA

Reaction conditions: 0.1 mmol (±)-**II-3d**, 0.075 mmol MeOH, 0.75 mL $CDCl_3$, rt, unless otherwise specified. [a] 0.1 mmol (±)-**II-3d**, 0.075 mmol MeOH, 10 mol% *(R)*-BTM, 0.1 mmol 2,6-methoxytoluene, 20 mol% $PhCO_2H$, in$CDCl_3$, rt. [b] Results based on a single run. [c] 0.1 mmol (±)-**II-3d**, 0.075 mmol MeOH, 10 mol% *(R)*-BTM, 0.1 mmol 2,6-methoxytoluene, 50 mol% $PhCO_2H$, in$CDCl_3$. [d] Determined by H^1 NMR. [e] 0.1 mmol (±)-**II-3d**, 0.075 mmol MeOH, 0.1 mmol $PhCO_2H$, 0.75 mL $CDCl_3$, rt. [f] 0.1 mmol (±)-**II-3d**, 0.075 mmol MeOH, 0.1 mmol 2,4,6-collidine, in $CDCl_3$, rt.

With no methanol in the reaction medium, we could technically achieve the KR of N-acyl-β-lactams to obtain enantioenriched oxazinones (**Scheme 2.3-3**). This in itself could be an interesting study to be investigated alone. Again the presence of Brønsted acid made a difference in the selectivity factor and reaction times. Albeit the reaction occurred at a slower rate, the acid seemed to contribute somehow towards higher enantioselectivity (s = 45 vs 35).

Scheme 2.3-3: KR of N-acyl-β-lactam (±)-**II-3d** in the absence of methanol

Interestingly, when the KR of oxazinone **II-1a** was investigated in the presence and absence of acid, it was not a discrepancy in selectivities that became visible, but in rates (**Scheme 2.3-4**). Using benzoic acid, the KR happened three times faster compared to KR in the absence of acid. This could suggest that the acid not only hindered the formation of oxazinone but also sped up its alcoholysis (in case any oxazinone did form) so it would not linger in the reaction mixture as much as it did when no acid was there.

Scheme 2.3-4: KR of oxazinone (±)-**II-1a** in absence and presence of acid

Based on all these findings we proposed the mechanism of acid's role in the process of asymmetric alcoholysis of N-acyl-β-lactams described in **Figure 2.3-1**.

Figure 2.3-1: Proposed mechanism of acid's role in alcoholysis of N-acyl-β-lactam **II-3d**

In the set of conditions ***a*** (BTM **I-3**, $PhCO_2H$, MeOH), the nucleophilic attack of BTM **I-3** would generate reactive intermediate **II-18a** (benzoate counterion omitted for clarity). Experimental results did suggest oxazinone **II-1a** formation, but we have reason to believe that the direction of equilibrium would be more towards the intermediate **II-18a**, since the amide moiety is not as nucleophilic in protonated form for subsequent cycloaddition. Even when oxazinone **II-1a** forms, it would be in activated form, which would become more susceptible to ring opening back to intermediate **II-18a**. It could also be that the rate of methanolysis was faster than that of forming the oxazinone **II-1a**. In the set of conditions ***b*** (BTM **I-3**, MeOH), the attack

of the catalyst would form the zwitterion **II-18b**, which possesses a nucleophilic amide moiety that could lead to the cyclized **I-1a** more readily than in the case of protonated intermediate **II-18a**. Having witnessed experimentally a build-up of oxazinone **I-1a** in this case and a reduction in ester product **II-2d'** formation might suggest a difference in rates of methanolysis and oxazinone **II-1a** formation. This scheme might hypothesize more on the mechanism of acid's mode of action, but it does not explain how its addition helps/leads to a more enantioselective process. Showing an equilibrium between zwitterionic intermediate **II-18b** and oxazinone **I-1a** contradicts our initial statement that in the case of KR of oxazinone the first step in the catalytic cycle would be irreversible. At this point, it would be more cautious to say that the first step is just the enantioselectivity determining step in the case of KR of oxazinones, since no apparent improvement in selectivity was observed when bulkier alcohols were added instead of methanol. However, in the case of alcoholysis of N-acyl-β-lactams, the likelihood of reversibility in the first step in the catalytic cycle (attack of catalyst on the chiral acyl donor) is minimal, due to energetically disfavored formation of a strained 4-membered lactam ring under those set of mild conditions.

As a result, this project was more complex and time-consuming than envisioned and additional tools, such as computational and more careful kinetic studies, are needed to untangle it - an investigation that prevails in the group's future plans.

2.4 Substrate synthesis

Despite that racemic β-lactams have been mentioned in numerous studies, their synthesis to achieve a wide scope of substrates with decent yields was not a trivial matter. Hence, it is

noteworthy to discuss the methods that were used in making them and some of the challenges we have encountered while doing so.

Racemic β-lactams can be obtained via three main approaches (**Figure 2.4-1**): 1) [2+2] reaction of olefins with clorosulfonyl isocyanate (CSI)[4a,b,e] (**Eq. 1**); 2) Enolate-imine cyclocondensation[18] (**Eq. 2**); 3) Staudinger reaction ([2+2] reaction of ketenes generated *in situ* and imines) followed by CAN deprotection (**Eq. 3**).

From all these methods, the one depicted in **Eq. 1** was the most efficient, when conditions were previously reported for particular cases or established by trial and error in our lab. Substrates **II-19**, **III-4** (see Chapter III), and all the *cis*-ring-fused β-lactams were generated by this method. However, the [2+2] cycloaddition of each substrate depended on different and special conditions: temperature (from 0 ºC to reflux at 80 ºC), reaction time (from 2 hours to 3 days), solvent (neat, diethyl ether, methylene chloride, toluene). If one parameter was changed for optimization purposes, it raised the risk of obtaining little to no product at all. Hence, it was impossible to operate under one general procedure. Due to their similarity in structures, it was puzzling to us why their synthesis was so particular to each case. The enolate-imine cyclocondesation (**Eq. 2)** was an equally important route to obtaining the substrates (especially the ones used in Chapter III) we could not otherwise make using the one discussed in **Eq. 1**. The method, however, was not efficient and produced low yields of desired product with numerable undesired ones, making the purification process painful. Even though, at times, I had to repeat the procedure more than once just to obtain enough material for further processing, it was gratifying to have generated products not previously achieved under any other method. I did, however, fail to make the methyl- and *o*-methylphenyl-substituted β-lactams using this route.

Figure 2.4-1: Methods for β-lactam synthesis

To extend the study on other substrates with practical utility, I intended to synthesize **II-20**, **II-21**, and **II-22** under method described in **Eq. 3**, having the starting materials readily available in our lab**.** In the case of **II-20**, the Staudinger reaction failed, despite trying two different protocols using the same starting materials[19]. In the cases of substrates **II-21**[6c,d,20] and **II-22**[21], the Staudinger reaction itself occurred as previously described in the literature (with up

to 40% yield). The unreported deprotection with CAN of **II-22** PMP-protected derivative was troublesome and, despite all efforts taken, I was not successful at obtaining the desired product **II-22.** The substrate **II-21** was relevant to taxol synthesis[6] and the reported CAN oxidation of its PMP-protected derivative did lead to **II-21**, although in disappointing yield overall. However, benzoylation of **II-21** generated two compounds in 1:3 ratio. The one in least amount seemed to be the desired product. Unfortunately, I did not have enough material to be tested in the subsequent KR and had to repeat the whole synthesis again to obtain more substrate **II-21**. Due to unexpected difficulties encountered in the preparation of other substrates, this study of substrate scope was postponed, and we moved on to other pending projects that were seeking immediate attention.

2.5 Conclusion

The asymmetric alcoholysis of N-acyl-β-lactams with BTM has proven to be an effective method of obtaining enantioenriched β-amino acids. This transformation demonstrates for the first time that the nucleophilic attack of ABC on chiral acyl donors can in itself be highly enantioselective – a phenomenon in high contrast to the usual behavior of these catalysts. Cis ring-fused substrates display higher enantioselectivity. The plausible origin of enantioselectivity has been discussed/debated. Brønsted acid was necessary for higher enantioselectivity, but was not paramount to the occurrence of the KR. The mechanistic role of the acid in this transformation remains yet unclear and will be subject to further investigation in our group, along with extension of this mechanism to other classes of substrates.

2.6 References

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Chapter III

Kinetic Resolution of β-Lactams via Enantioselective N-Acylation using Amidine-based Catalysts

3.1 Introduction

β-Lactams have had a well-known application in pharmaceuticals (e.g. antibiotics[1] and cholesterol lowering drugs[2]) and have been serving as versatile intermediates in the preparation of other classes of organic compounds (e.g. amino acids derivatives, nylon-3 polymers, etc.)[3]. Despite successfully accomplishing the asymmetric alcoholysis of N-acyl-β-lactams[4] in our lab, the method does not generate enantioenriched β-lactams, since deprotection of the N-acyl-β-lactam would cause ring opening. Asymmetric synthesis of β-lactams[5] has been achieved by a number of groups, from which most promising results were attained by Fu *et al* using chiral DMAP-based catalyst[6], Bode *et al* using NHC-based catalyst[7], and Lectka *et al* using cinchona alkaloid derivative benzoylquinine[8]. However, in all those cases the substrate scope remained limited. Therefore, enzymatic kinetic resolution (KR)[9] of their racemates, achieved via β-lactam ring opening[10] or O-acylation of N-hydroxymethyl derivatives[11], continues to be a viable approach to enantioenriched β-lactams (**Scheme 2.1-1**, Chapter II 2.1). When β-lactams are available in racemic form, their nonenzymatic, catalytic KR can be accomplished directly via enantioselective N-acylation – a protocol that had not been established before.

In 2006, our group became successful at resolving chiral oxazolidinones via asymmetric N-acylation using ABCs.[12] Before our work in this area, there were no reports of KR of any lactams via enantioselective N-acylation. Having racemic β-lactams available from KR of N-acyl-β-

lactams, we wondered whether they were suitable substrates for asymmetric N-acylation and, hence, suitable nucleophiles for **Type I** process using our most efficient ABCs **I-2** through **I-4**.

3.2 Experimental design and findings

While working on the KR of N-acyl-β-lactams, I also tried the enantioselective acylation of (±)-4-phenyl-β-lactam **III-1** under the set of conditions established in our group in the successful catalytic, asymmetric N-acylation of oxazolidinones[12] (**Table 3.2-1**). Disappointingly, BTM *ent*-**I-3** proved to be inept in this process as no reaction happened after 24 hours (entry 1). HBTM **I-4a** did not show much superiority to *ent*-**I-3** with only 10% conversion after 48 hours, despite its higher catalytic activity to previously developed catalysts in our lab (entry 2). Those results did not come as too surprising, since we thought that the pK_a of the amide moiety would be too high to allow acylation. Just when we were about to give up on the project, my labmate, Xing Yang, tried the acylation with Cl-PIQ **I-2** and, to our delight, it gave promising results (entry 3).

Table 3.2-1: KR of β-lactam (±)-**III-1**: Catalyst screening

Entry	Catalyst	Time (hrs)	Conv (%)	s
1	*(S)*-BTM *ent*-**I-3**	24	NR	ND
2	*(S)*-HBTM **I-4a**	48	~10	ND
3	*(S)*-Cl-PIQ *ent*-**I-2**	24	33	10

General conditions: 0.1 M (±)-**III-1**, 0.1 M $(i\text{-PrCO})_2O$, 0.1 M $i\text{-Pr}_2\text{NEt}$, 0.01 M catalyst in $CDCl_3$.

Encouraged by this finding and acquired experience in synthesizing many of the requisite substrates in the course of my earlier study (Chapter II), Xing and I started a collaboration. Xing continued with the optimization studies by varying the anhydride and the solvent (**Table 3.2-2**) and I began synthesizing additional substrates according to established procedures (see **Figure 2.4-1**, Chapter II, 2.4) to be investigated after optimization was complete. The bulk of isobutyric anhydride proved to be crucial for notable selectivity (entry 1), since acetic and propionic anhydrides generated little to no enantioselectivity (entry 2 and 3). Methylene chloride and tetrahydrofuran produced lower selectivities compared to chloroform (entries 4,5 vs. 1). Switching to *tert*-amyl alcohol led to improved results both enantioselectivity and rate wise, despite a reduction in substrate concentration due to limited solubility (entry 6). Lowering the temperature to 0 °C enhanced the selectivity factor appreciably and the rate was still acceptable (entry 7). Lowering the catalyst or acylating agent/base loading only prolonged the rate of reaction and was considered impractical (entries 8, 9). Using 2-methyl-3-butyn-2-ol at room temperature led to similar results to *tert*-amyl alcohol (entry 10); however, due to its higher freezing point (+3 vs -12 °C) lowering the temperature to 0 ° would not be a viable route to increase enantioselectivity in this case. Therefore, *tert*-amyl alcohol became the solvent of choice.

Table 3.2-2: KR of β-lactam (±)-**III-1:** Acyl donor and solvent screening

Entry	R	Solvent	Temp (°C)	Time (hrs)	Conv (%)	s
1	*i*-Pr (**III-2a**)	$CDCl_3$	23	24	33	10
2	Me (**III-2b**)	$CDCl_3$	23	4	35	1.0
3	Et (**III-2c**)	$CDCl_3$	23	10	35	1.8
4	*i*-Pr (**III-2a**)	CD_2Cl_2	23	24	21	5.5
5	*i*-Pr (**III-2a**)	THF	23	24	22	6.6
6[a]	*i*-Pr (**III-2a**)	$EtMe_2COH$	23	10	45	16
7[a]	*i*-Pr (**III-2a**)	$EtMe_2COH$	0	24	47	20
8[b]	*i*-Pr (**III-2a**)	$EtMe_2COH$	0	48	33	19
9[c]	*i*-Pr (**III-2a**)	$EtMe_2COH$	0	24	35	21
10[a]	*i*-Pr (**III-2a**)	$HC{\equiv}CMe_2COH$	23	10	41	16

General conditions: 0.1 M (±)-**III-1**, 0.2 M $(i\text{-PrCO})_2O$, 0.2 M $i\text{-Pr}_2NEt$, 0.01 M *(S)*-Cl-PIQ, unless otherwise specified. [a] 0.05 M (±)-**III-1**, 0.1 M $(i\text{-PrCO})_2O$, 0.1 M $i\text{-Pr}_2NEt$, 0.005 M *(S)*-Cl-PIQ (10 mol%). [b] 0.05 M (±)-**III-1**, 0.1 M $(i\text{-PrCO})_2O$, 0.1 M $i\text{-Pr}_2NEt$, 0.0025 M *(S)*-Cl-PIQ (5 mol%). [c] 0.05 M (±)-**III-1**, 0.05 M $(i\text{-PrCO})_2O$, 0.05 M $i\text{-Pr}_2NEt$, 0.005 M *(S)*-Cl-PIQ (10 mol%).

With optimization conditions and most starting materials in place, Xing and I worked on the substrate scope together (**Table 3.2-3**). We explored a range of substrates bearing aryl, heteroaryl, and alkyl groups at C-4. Counterintuitively, both *p*-chloro- and *p*-methoxy-phenyl substituted substrates **III-3** and **III-4** gave higher selectivity compared to their phenyl-substituted analogue **III-1** (entries 2,3 vs 1). The 2-naphthyl group led to the best results in this study (entry 6). Having chlorine in the *ortho* position on the ring hindered the KR, as both rate and s-value diminished considerably (entry 4). The heteroaryl-substituted substrate **III-8** underwent N-acylation, albeit with lower enantioselectivity (entry 7). Additional alkyl groups at C-3 were tolerated, although both reaction times and selectivity factors were negatively affected (entries 8,

9). All of the substrates discussed above were limited to bearing aryl (or heteroaryl) groups, as we expected that cation-π interactions with the catalyst would be crucial for the reaction to occur. In accord with this prediction, when the non-aryl substrate **III-12** was subjected to the same conditions, it failed to react altogether (entry 11).

Table 3.2-3: KR of β-lactams: Substrate scope

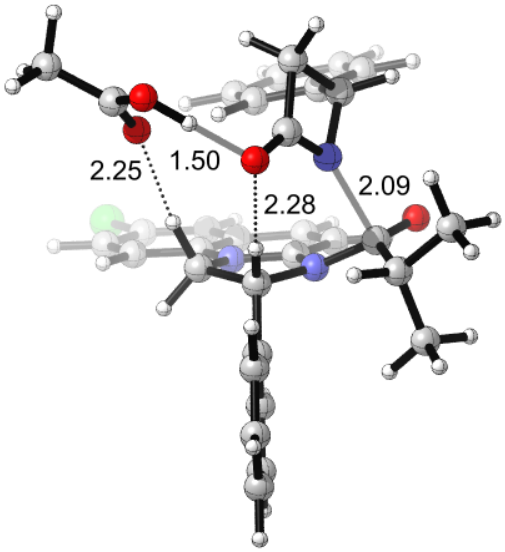
Entry	Substrate[a,b]	Time (hrs)	ee_{PR} (%)	ee_{SM} (%)	Conv (%)	s
1	**III-1**	24	84	62.5	43	22
2	**III-3**	30	79	94	54	30
3	**III-4**	30	90	66	42	38
4	**III-5**	30	48	8	14	3
5[c]	**III-6**	72	83	57	41	19
6		30	85	97	53	54

	III-7					
7	**III-8**	30	65	95	59	17
8[c]	**III-9**	72	82	44	38	16
9[c]	**III-10**	72	81	28	26	13
10	**III-11**	30	78	56	42	14
11[d]	**III-12**	34	ND	ND	NR	ND

General conditions: 0.05 M (±)-substrate, 0.1 M (*i*-PrCO)$_2$O, 0.1 M *i*-Pr$_2$NEt, 0.01 M *(S)*-Cl-PIQ, *tert*-amyl alcohol, 0 ºC, unless otherwise specified. [a] Absolute configuration of the fast reacting enantiomer is shown [b] Results based on duplicate runs. [c] 0.05 M (±)-substrate, 0.2 M (*i*-PrCO)$_2$O, 0.2 M *i*-Pr$_2$NEt, 0.01 M *(S)*-Cl-PIQ (10 mol%). [d] Reaction performed in $CDCl_3$ at rt 0.05 M (±)-substrate, 0.1 M (*i*-PrCO)$_2$O, 0.1 M *i*-Pr$_2$NEt, 0.0025 M *(S)*-Cl-PIQ (5 mol%).

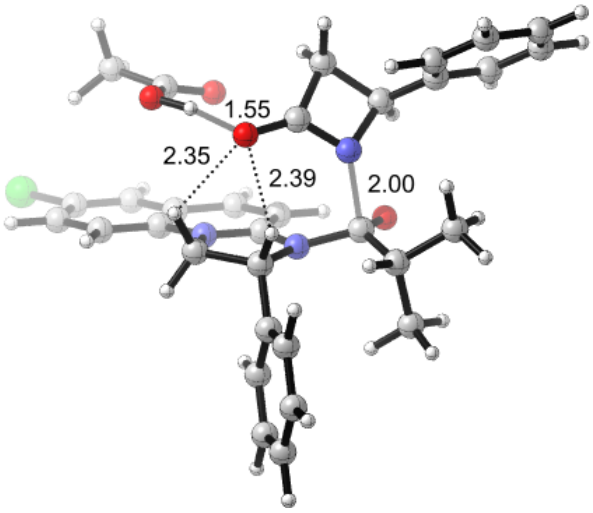
The absolute configuration of **III-1** and of the indene-derived substrate **III-11** was consistent with the results previously obtained with oxazolidinones and alcohols. Thus, we hypothesized that the TS for the catalytic N-acylation of β-lactams should be qualitatively similar to our previously proposed model for alcohols[13] (Figure 1.1-1, Chapter I, 1.1). Indeed, a computational study later carried out by Xing[14,15] produced TS structures **TS-*(R)*-Cl-PIQ-*(R)*-III-1** and **TS-*(R)*-Cl-PIQ-*(S)*-III-1**, which were in accordance with our predictions (**Figure 3.2-1**).

Figure 3.2-1: Transition states for fast- and slow-reacting enantiomers of β-lactam **III-1**



TS-*(R)*-Cl-PIQ-*(R)*-III-1

$\Delta\Delta G^{\ddagger}$= 0.0 kcal/mol



TS-*(R)*-Cl-PIQ-*(S)*-III-1

$\Delta\Delta G^{\ddagger}$= 3.4 kcal/mol

3.3 Conclusions

We have achieved the first non-enzymatic asymmetric KR of β-lactams via N-acylation using Cl-PIQ *ent*-**I-2**. The method requires the presence of aryl and heteroaryl substituted β-lactams – a trend of ABCs consistent with other studied classes of compounds in our group (i.e. alcohols, oxazolidinones)[16]. Our experimental observations and computational studies point to the involvement of cation-π interactions between the fast-reacting enantiomer and catalyst, in analogy with alcohols and oxazolidinones.

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Chapter IV

Kinetic Resolution of N-Acyl-Thiolactams via Catalytic Enantioselective Deacylation

4.1 Introduction

Oxazoldine-2-thiones and thiazolidine-2-thiones thiolactams have had a wide application in organic synthesis as chiral auxiliaries,[1] intermediates,[2] and chiral reagents in resolution of other compounds.[3] Some oxazoldine-2-thiones can be actually found in the structure of natural products that display biological activity.[4] Asymmetric synthesis of above mentioned thiolactams is usually achieved from the reaction of their corresponding chiral β-amino alcohols with carbon disulfide,[5] although β-amino thiols have also been used in synthesis of thiazolidine-2-thiones.[6] However, when the corresponding β-amino alcohols are not available in enantiopure form, the kinetic resolution[7] (KR) of racemic thiolactams via asymmetric acyl transfer catalysis can serve as a practical protocol for obtaining them in enantioenriched form.

In Chapter I, 1.1, we mentioned that that **Type I** and **II** processes are often complimentary and can be catalyzed by a single enzyme (**Figure 1.1-2**). So far, we have only witnessed considerable progress in Type I transformation using various acyl transfer asymmetric catalysts.[8] However, to the best of our knowledge, the *asymmetric deacylation* (**Type II** process) of any classes of compounds using acylation catalysts has not been reported yet.[9] In 1999, Yan *et al* reported a reverse action of achiral acyl-transfer catalyst DMAP in *deacylation* of N-acyl-oxazolidine-2-thione via alcoholysis,[10] followed by Wu *et al* with the same transformation of N-acyl-thiazolidine-2-thione.[11] Of course, both these processes were not enantioselective. Thus, this chapter describes the first instances of *asymmetric deacylation* using ABCs, providing also an

alternative method to obtaining enantioenriched oxazolidine-2-thiones and thiazolidione-2-thiones via alcoholysis of their corresponding racemic N-acyl-derivatives.

While working on the asymmetric acylation of lactams and thiolactams,[12] Xing Yang subjected (±)-4-phenylthiozoline-2-thione **IV-1** to standard acylating KR conditions[13] with BTM **I-3**, which also included the quenching of excess anhydride with methanol when reaction reached 50% conversion by H^1 NMR. His initial results are shown in **Scheme 4.1-1**. However, if the quenched mixture stayed too long in the presence of methanol, then the conversion (and selectivity) dropped significantly, which was not in agreement with the one observed by H^1 NMR. We hypothesized that this could be a case where BTM **I-3** participated also in the asymmetric deacylation (reverse reaction) of the enantioenriched N-acyl-thiozolidine-2-thione **IV-2a**, especially since we were aware that such a transformation has been previously reported with DMAP. These observations gave me the opportunity to step into this project and investigate the reverse process in more detail.

Scheme 4.1-1: KR of thiazolodin-2-thione (±)-**IV-1** via enantioselective N-acylation

4.2 Experimental design and findings

To test this presupposition, I preliminarily subjected crude racemic N-acyl-thiazolidine-2-thione **IV-2a**, which was contaminated with traces of isobutyric acid, to methanolysis in the presence of

BTM **I-3**. And to our surprise, the selectivity factor improved significantly (s = 88 vs 30), albeit at a slower rate (**Scheme 4.2-1**).

Scheme 4.2-1: Preliminary enantioselective deacylation of (±)-**IV-2a**

Encouraged by these data, **IV-2a** was purified and the optimization process was initiated (**Table 4.2-1**). Interestingly, once the pure **IV-2a** was subjected to the KR conditions with MeOH and *(R)*-BTM **I-3** the reaction was sluggish and led to diminished enantioselectivity (entry 2). We quickly realized that the traces of isobutyric acid were adventitious in the initial trial, and that the acid served as a co-catalyst. Introducing benzoic acid made the protocol more reproducible (entry 3). As expected, in the absence of a catalytic system, the background reaction was insignificant (entry 1). Testing other most effective catalysts from our group, Cl-PIQ **I-2** and HBTM **I-4a**, led to disappointing results (entries 4, 5). Making sure that the nature of the alcohol in the deacylation did not play a role in the chiral recognition of **IV-2a**, methanol was exchanged for its more sterically hindered analogues, benzyl alcohol and di(1-naphthyl)methanol (entries 6, 7). They delivered comparable results to methanol and, therefore, we continued with the optimization using the latter.

Table 4.2-1: KR of N-acyl-thiazolidine-2-thione (±)-**4-5a**: Catalyst and Alcohol screening[a]

Entry	Catalyst	ROH	Time	Conv (%)	s
1	none	MeOH	7 days	<10[a]	ND[c]
2	*(R)*-BTM	MeOH	4 days	55	26
3	*(R)*-BTM + 10 mol% $PhCO_2H$	MeOH	24 hrs	48	78
4	*(S)*-HBTM + 10 mol% $PhCO_2H$	MeOH	7 days	<10[b]	ND[c]
5	*(R)*-Cl-PIQ + 10 mol% $PhCO_2H$	MeOH	7 days	37	6.7
6	*(R)*-BTM + 10 mol% $PhCO_2H$	$PhCH_2OH$	24 hrs	49	81
7	*(R)*-BTM + 10 mol% $PhCO_2H$	$(1\text{-Np})_2CHOH$	24 hrs	50	84

General conditions: 0.05 mmol (±)-**IV-2a**, 0.075 mmol ROH, 0.01 mmol catalyst, 0.75 mL $CDCl_3$, rt, unless otherwise specified. [a] Results averaged from duplicate runs. [b]Determined by H^1 NMR. [c] not determined

Using **I-3** as the catalyst of choice, we continued the optimization by varying the N-acyl group, then the solvent (**Table 4.2-2**). The bulkiness of the isopropyl group was crucial for increased enantioselectivity (entry 1), since N-propionyl-derivative delivered only a selectivity factor of 15, although at a much faster rate (entry 2). Switching the N-acyl group to benzoyl stalled the reaction considerably (entry 3). Among solvents examined, methylene chloride and tetrahydrofuran were inferior to chloroform, as they gave diminished results (entries 4, 6), while

toluene was a bit superior to chloroform (entry 5). For convenience while monitoring the reaction by NMR we used the latter for the rest of this study.

Table 4.2-2: KR of N-acyl-thiazolidine-2-thione (±)-**IV-2**: Solvent Screening[a]

Entry[a]	R	Solvent	Time	Conv (%)	s
1	*i*-Pr (**IV-2a**)	$CDCl_3$	24 hrs	48	78
2	Et (**IV-2b**)	$CDCl_3$	12 hrs	57	15
3	Ph (**IV-2c**)	$CDCl_3$	7 days	<10[b]	ND
4	*i*-Pr (**IV-2a**)	CD_2Cl_2	24 hrs	49	41
5	*i*-Pr (**IV-2a**)	toluene	24 hrs	47	86
6	*i*-Pr (**IV-2a**)	diethyl ether	7 days	42	3.9

General conditions: 0.05 mmol (±)-**IV-2**, 0.075 mmol MeOH, 0.01 mmol *(R)*-BTM, 0.75 mL solvent, rt. [a] Results based on duplicate runs. [b] Determined by H^1 NMR.

With the optimization process complete, we continued with investigation of substrate scope in the case of N-isobutyryl-thiazolidine-2-thiones (**Table 4.2-3**). The phenyl-substituted derivatives with electron-donating group (EDG) on the phenyl ring gave the best selectivities in this study, 90 with *p*-methoxy- and 108 with *o*-methoxy (entries 2, 3). Having an electron-withdrawing group (EWG) on the phenyl ring led to significantly diminished enantioselectivities (entries 4, 5). An interesting observation was that in both those cases, with EDG and EWG, *ortho* substituents gave notably higher results compared to the *para* ones. Switching **R** to 1- and 2-

naphthyl, as well as with thienyl group, was no match in efficiency to the phenyl one in **IV-2a**, which was surprising considering that same groups displayed higher selectivities in the N-acylation KR of analogous classes of compounds. Both substrates **IV-10** and **IV-11** underwent the KR, albeit with diminished results. However, they do play a more symbolic role since they are not aryl-substituted, but still contain extended π-systems. Any other attempt to expand the applicability of this method to other non-aryl substrates or other extended π-systems failed, as **IV-12** did not react at all in the course of one week, and **IV-13** gave insignificant selectivity. We had higher expectations for the indane-fused substrate **IV-14**, but its KR produced a disappointing **s-**value of 2.3. This was in contrast to the results in the N-acylation with Cl-PIQ **I-2** of indane-fused oxazolidin-2-one and β-lactam, which gave selectivities 36 and 14, respectively. To confirm that these results were not related to the nature of the deacylation process itself, the forward reaction of **4-18** (**Scheme 4.2-2**) was set up using previously set conditions for N-acylation of analogous compounds using Cl-PIQ **4-1** and BTM **4-2**[12]. Unfortunately, the results did not improve in either case.

Table 4.2-3: KR of N-isobutyryl-thiazolidine-2-thiones: Substrate scope[a]

Entry	Substrate[a]	Time (days)	ee_{PR} (%)	ee_{SM} (%)	Conv (%)	s
1	**IV-2a**	1	93	84	48	78
2	**IV-3**	1	93.5	89	49	90
3	**IV-4**	1	95	84	47	108
4	**IV-5**	0.6	76.5	90	54	23
5	**IV-6**	1	86	86	50	36
6	**IV-7**	5	74.5	99	48	30
7	**IV-8**	2	85	78	57	37
8	**IV-9**	1.5	87	71	45	32

9	**IV-10**	1	88	77	47	37
10	**IV-11**	0.6	75	73	49	15
12	**IV-12**	7	ND	ND	NR[b]	ND
12	**IV-13**	7	15.5	6	27	1.4
13	**IV-14**	7	32	16	33	2.3

General conditions: 0.05 mmol (±)-substrate, 0.075 mmol MeOH, 10 mol% $PhCO_2H$, 10 mol% *(R)*-BTM, in $CDCl_3$, rt. [a] Results averaged from at least duplicate runs [a] Results averaged from duplicate runs [b] NR = no reaction

Scheme 4.2-1: Enantioselective N-acylation of thiolactam (±)-**IV-15**

With study on N-isobutyryl-thiazolidine-2-thiones coming to an end, the investigation of KR of analogous N-isobutyryl-oxazolidin-2-thiones was only to begin (**Table 4.2-4**). Using the same study of optimized conditions established with N-isobutyryl-thiazolidine-2-thiones, a substrate scope started with KR of the N-isobutyryl-4-phenyl-oxazolidine-2-thione **IV-16** (entry 1). The de-acylation of **IV-16** gave what would be generally considered good selectivity factor of 57, although lower than in the case of the analogous thiazolidine-2-thione derivative **IV-2a** (s = 78) and than in the KR via N-acylation of corresponding oxazolidine-2-thione (s = 82). Additionally, the reaction time was longer than in the case of **IV-2a**. Despite the fact that the rest of the substrates gave increasingly sluggish rates and diminished enantioselectivities compared to the phenyl-substituted one, they had not been resolved before in our study of asymmetric N-acylation and, hence, their KR represented practical merit based on their overall good selectivities in the range of 13 to 59, with the exception of **IV-21**. By analogy, we thought that an EDG on the phenyl substituent would positively affect the results and an EWG would impede them. However, the data were random and did not follow any particular trend (entries 2-5). The ester-derivative **IV-21** underwent methanolysis slowly and with only a 2.6 s-value (entry 6). Surprisingly at first, in the case of **IV-21** we observed that the apparent enantioselectivity plummeted with time (entry 6 vs. 7).

Table 4.2-4: Asymmetric deacylation of N-isobutyryl-oxazolidin-2-thiones

Entry	Substrate[a]	Time (days)	ee_{PR} (%)	ee_{SM} (%)	Conv (%)	s
1	**IV-16**	2	94	53	36	57
2	**IV-17**	4	92	83	47	59
3	**IV-18**	6	92	40	30	38
4	**IV-19**	3	64	86	57	13
5	**IV-20**	3	88	67	43	32
6	**IV-21**	4	31	35	53	2.6
7	**IV-21**	1	71	29	29	7.9

General conditions: 0.05 mmol (±)-substrate, 0.075 mmol MeOH, 0.01 mmol *(R)*-BTM, 10 mol% $PhCO_2H$, 0.75 mL $CDCl_3$, rt. [a] Results averaged from at least duplicate runs

Hypothesizing that there might be a slow N-acyl exchange between deacylated product *(R)*-**IV-22** and *(S)*-**IV-21** under the reaction conditions and, since the forward KR was accomplished faster, the N-acylation of **4-25** was performed and monitored over time by taking and analyzing aliquots by HPLC (**Table 4.2-5**). Our premises have been confirmed by experimental evidence, as indeed just 1.5 hours after which reaction reached 52% conversion and **s** of 17, the *ee*s of both *(R)*-**IV-21** and *(S)*-**IV-22** deteriorated significantly to give a 7.5 selectivity factor. The process reached almost complete racemization after 48 hours.

Table 4.2-5: Enantioselective acylation of thiolactam (±)-**IV-22**

Entry[a]	Time (hrs)	*ee%* of *(R)*-**IV-21**	*ee%* of *(S)*-**IV-22**	Conv (%)	s
1	0.5	75	82	52	17
2	1	57	62	48	7.5
3	3	39	47	54	3.5
4	8	33	36	52	2.8
5	48	3.0	3.8	56	1.1

General conditions: 0.05 mmol (±)-**IV-22**, 0.05 mmol *i*-Pr_2NEt, 0.05 mmol $(i\text{-}Pr_2CO)_2O$, 0.0025 mmol *(R)*-BTM, 0.5 mL $CDCl_3$, rt. [a] Results averaged from duplicate runs

To find the culprit in this N-acyl exchange, a control experiment was set up in which roughly equimolar amounts of enantioenriched *(R)*-**IV-21** and *(S)*-**IV-22** were mixed with 10 mol% of *(R)*-BTM **I-3** in one vial and in separate vials with alternating additives that could be present

under the regular reaction condition (Hunig's base, isobutyric acid) (**Table 4.2-6**). Unexpectedly, the results indicated that BTM **I-3** was responsible for the N-acyl exchange, in the presence (entry 3) or absence (entry 2) of benzoic acid, as the *ee*s deteriorated significantly after 24 hours. Other additives did not seem to have contributed to the racemization process (entries 4, 5).

Table 4.2-6: Racemization of **IV-21** and **IV-22**

Entry	Additive(s)	% *ee* after 24 hrs	
		(R)-**IV-21**	*(S)*-**IV-22**
1	none	81	77
2	10 mol% *(R)*-BTM **I-3**	18	14
3	10 mol% *(R)*-BTM **I-3** + 10 mol% $PhCO_2H$	20	11
4	50 mol% *i*-Pr_2NEt	81	74
5	10 mol% *i*-$PrCO_2H$	82	75

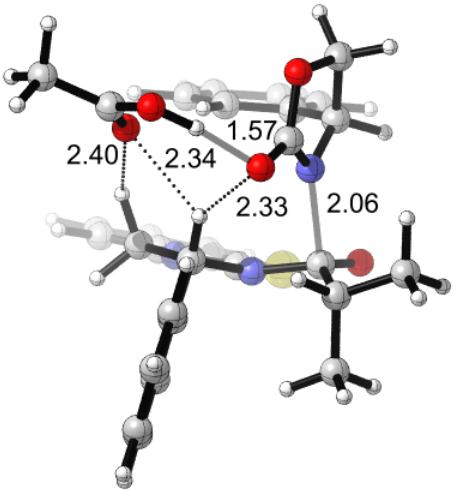
General conditions: 0.1 M *(R)*-**IV-21**, 0.1 M *(S)*-**IV-22**, additive(s), in $CDCl_3$, rt.

There is a chance that this exchange might have happened to some extent in the case of other substrates in this study, especially when the reaction times were long. Therefore, the experimentally shown selectivity factors could be lower than their "actual" ones.

In proposing the origin of enantioselectivity, experimental data suggest that de-acylation of N-acyl-thiolactams most probably goes through the same TSs as the "forward" (N-acylation) reaction of the corresponding thiolactams. Thus, the chiral recognition of the former can be described by analogy by TSs obtained in computational studies of N-acylation of 4-phenyloxazolidinone **IV-26**, performed by Xing Yang (**Figure 4.2-1**).[12] The fast-reacting diastereomer **TS-*(R)*-BTM-*(S)*-IV-26** is favored by 3.1 kal/mol due to π-cation interaction

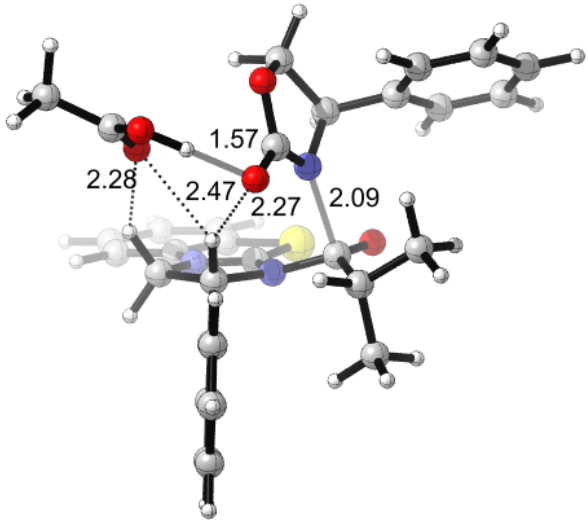
between tziazolium moiety of the catalyst and the phenyl ring of the substrate, analogous to enantioselective acylation of alcohols.

Figure 4.2-1: TSs of BTM-catalyzed N-acylation of oxazolidinone **IV-26**



TS-*(R)*-BTM-*(S)*-IV-26

$\Delta\Delta G^{\ddagger}$ = 0.0 kcal/mol



TS-*(R)*-BTM-*(R)*-IV-26

$\Delta\Delta G^{\ddagger}$ = 3.1 kcal/mol

4.3 Conclusion

We have demonstrated for the first time a catalytic asymmetric deacylation promoted by an acyl transfer catalyst. The asymmetric methanolysis of N-acyl-thiazolidine- and oxazolidine-2-thiones has been successfully accomplished with better enantioselectivities in the former case than the latter. The KR of N-acyl-thiazolidine-2-thiones produced better selectivity factors than in the forward N-acylation reaction of their deacylated derivatives and, hence, can be viewed as an alternative method for their enantioselective synthesis. There has been some evidence in one

investigated substrate case (although it could also be applicable to other substrates) of N-acyl exchange between enantioenriched products over prolonged time, promoted by the catalyst from the reaction mixture.

4.4 References

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Chapter V
Experimental Part

5.1 General

All reagents and solvents were obtained commercially and used as received. Solvents used for HPLC were HPLC grade and for other purposes ACS grade. HPLC Analyses were performed on a Shimadzu LC system using Chiracel OD-H, Chiralpak AD and AD-H analytical chiral stationary phase columns (4.6x250 mm, Chiral Technologies, Inc.). Flash column chromatography was performed over ICN Echochrom silica gel (32-63μm). ^{1}H and ^{13}C NMR spectra were recorded on a Unity 300 MHz Varian spectrometer. High-resolution mass spectral analyses were performed at Washington Univerity MS Center on a Kratos MS-40TA spectrometer using Electro Spray Ionization (ESI) method. Infrared spectra were obtained from a Perkin-Elmer Spectrum Bx FTIR spectrophotometer using potassium bromide plates. Melting points were measured on a Mel-Temp II capillary melting point aparatus. The signs of optical rotation were determined in $CHCl_3$ on a Rudolph Autopol III polarimeter.

Catalysts BTM, Cl-PIQ, and HBTM were prepared as previously described.[1]

Selectivity factors and % conversions were calculated using Kagan's equations[2]: conversion **C** = $ee_{SM}/(ee_{SM}+ee_{PR})100\%$ and selectivity factor **s** = $\ln[(1—C)(1—ee_{SM})]/\ln[(1—C)(1+ee_{SM})]$, unless otherwise specified.

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5.2 KR OF N-ACYL-B-LACTAMS VIA ENANTIOSELECTIVE ALCOHOLYSIS USING AMIDINE-BASED CATALYSTS

5.2.1 General

Refer to Chapter II for notation of compounds. **Note:** Recrystallization of BTM from Et_2O/hexanes[1] is recommended to ensure reproducible performance. Oxazinones **II-1** and **II-1a** were prepared via a modification of a published procedure[2] using DCC to effect the cyclization step. Racemic *N*-(p-nitrobenzoyl)- and *N*-(3,5-dinitrobenzoyl)-4-phenyl-azetidin-2-ones (see Table 5.2.2-3) were prepared via deprotonation of (±)-4-phenyl-azetidin-2-one with *n*-butyllithium and acylation with the corresponding acyl chloride.[3] All substrates **II-3** through **II-13** were prepared via DMAP-catalyzed acylation of the corresponding racemic β-lactams.[4] The precursors to substrates **II-3** and **II-7** through **II-12** were obtained via cycloaddition of the corresponding alkenes with chlorosulfonyl isocyanate.[5] The precursors to substrates **II-5** and **2-II-6** were synthesized from the corresponding aldehydes via condensation of their *N*-(trimethylsilyl)imines with *tert*-butyl acetate Li enolate, according to a general procedure.[6] The precursor to substrate **II-13** was synthesized via dilithiation and alkylation of (±)-4-phenyl-azetidin-2-one, as previously described.[7] The substrates **II-20**, **II-21**, **II-22** were attempted to be synthesized by Staudinger reaction, followed by deprotection with CAN, using previously reported procedures[8,9,10].

5.2.2 Kinetic Resolution experiments

5.2.2.1 Optimization studies

General procedure. To a solution of a racemic substrate (0.10 mmol) in 0.25 mL of $CDCl_3$ was added 0.25 mL of a stock solution of 0.040 M *(S)*-BTM (0.010 mmol) and 0.040 M benzoic acid

(0.010 mmol) in $CDCl_3$ followed by 0.25 mL of a 0.30 M solution of methanol in $CDCl_3$ (0.075 mmol). The reaction mixture was stirred magnetically at rt. Its progress was checked periodically by withdrawing aliquots, diluting them with $CDCl_3$ and analyzing by ^1H NMR. Upon reaching approximately 50% conversion, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, concentrated, and separated by flash chromatography (silica gel, CH_2Cl_2, then CH_2Cl_2/EtOAc). Enantiomeric enrichment of the ester product and the unreacted starting material was determined by chiral stationary phase HPLC (for HPLC conditions, see individual compounds in Characterization Data and HPLC Propersties section 5.2.7). Each experiment was performed at least in duplicate, unless otherwise specified. The results compiled in following Tables in 5.2 section were obtained using variations of this basic protocol, as indicated.

Table 5.2.2.1-1: KR of Oxazinone (±)-**II-1**: Survey of alcohols[a]

entry	**Alcohol**	**#**	**ee_{PR}** %	**ee_{SM}** %	**C_{HPLC}** %	**s**	**C_{AVG}** %	**s_{AVG}**
1	1-Np_2CHOH	1	35.3	30.82	46.61	2.77	51	2.9
		2	33.62	42.04	55.56	2.86		
2	$PhCH_2OH$	1	39.9	60.36	60.2	4.4	56	3.9
		2	40.82	45.18	52.53	3.62		
3	MeOH	1	34.48	31.84	48.01	2.75	48	3.3
		2	44.68	39.9	47.17	3.27		

[a]) See General Procedure, except the substrate was dissolved in 0.5 mL of $CDCl_3$ and 0.05 mmol of the alcohol indicated was used.

Table 5.2.2.1-2: KR of *N*-benzoyl-β-Lactam (±)-**II-3a**: Survey of alcohols and catalysts[a]

entry	alcohol	catalyst	time	#	ee_{PR} %	ee_{SM} %	C_{HPLC} %	s	C_{AVG} %	s_{AVG}
1	1-Np_2CHOH	*(S)*-BTM	68 h	1	78.40	84.96	52.01	22.11	51	21
				2	79.32	78.64	49.78	20.55		
2	$PhCH_2OH$	*(S)*-BTM	68 h	1	72.01	88.70	55.36	17.5	52	19
				2	80.44	75.88	48.54	20.92		
3	$PhCH_2OH$	*(S)*-BTM	48 h	1	73.00	90.28	55.21	19.24	55	19[b]
				2	72.68	90.58	55.56	18.41		
4	MeOH	*(S)*-BTM	68 h	1	66.70	96.14	59.04	18.94	60	18
				2	60.94	97.66	61.58	17.13		
5	$PhCH_2OH$	*(R)*-Cl-PIQ	7 d	1	31.88	21.36	40.12	2.36	42	2.5[c]
				2	33.74	26.40	43.90	2.57		
6	MeOH	*(S)*-HBTM	3 d	1	56.84	90.48	61.42	10.73	62	12[c]
				2	55.94	96.02	63.19	12.94		

[a]) See General Procedure, except the substrate was dissolved in 0.5 mL of $CDCl_3$ and 0.05 mmol of the alcohol indicated was used. [b]) **II-3a** was dissolved in 0.5 mL of $CDCl_3$, followed by 0.25 mL of 0.04 M BTM (0.01 mmol), 0.25 mL of 0.2 M of $PhCH_2OH$ (0.05 mmol) in $CDCl_3$, 2 mg $LiBF_4$ (0.02 mmol) [c]) The absolute configuration of the product was inverted, in accord with that of the catalyst.

Table 5.2.2.1-3: KR of *N*-acyl-β-Lactams (±)-**II-3**: Survey of *N*-Acyl groups

entry	R^1	time	#	ee_{PR} %	ee_{SM} %	C_{HPLC} %	s	C_{AVG} %	s_{AVG}
1	*t*-BuO (**II-3b**)	7 d	1	ND	ND	ND	ND	ND	ND
			2	ND	ND	ND	ND		
2	*i*-Pr (**II-3c**)	7 d	1	ND	ND	ND	ND	ND	ND
			2	ND	ND	ND	ND		
3	4-ClC_6H_4 (**II-3d**)	20 h	1	79.66	88.78	52.71	25.89	53	26
			2	78.92	90.70	53.47	26.26		
4	4-$NO_2C_6H_4$ (**II-3e**)	5 h	1	75.34	87.80	53.82	20.2	53	20
			2	76.46	83.88	52.31	19.52		
5[a]	4-$NO_2C_6H_4$ (**II-3e**)	36 h	1	79.34	78.42	49.71	20.49	50	20
			2	78.46	76.64	49.41	18.98		
6	3,5-$(NO_2)_2C_6H_4$ (**III-3f**)	1 h	1	20.46	52.68	72.03	2.38	72	2.6
			2	23.76	60.14	71.68	2.76		

[a]) The reaction was conducted at 0 °C.

Table 5.2.2.1-4: KR of *N*-acyl-β-Lactam (±)-**II-3d**: Survey of solvents[a]

entry	solvent	time d	#	ee_{PR} %	ee_{SM} %	C_{HPLC} %	s	C_{AVG} %	s_{AVG}
1	CD_2Cl_2	3.5	1	74.72	89.30	54.44	20.40	55	20.5
			2	73.38	91.76	55.56	20.66		
2[b]	d^8-toluene	7	1	90.26	43.50	32.52	29.96	38	29
			2	86.82	66.48	43.37	28.23		
3[c]	CD_3CN	3.5	1	79.66	88.78	52.71	25.89	53	26
			2	78.92	90.70	53.47	26.26		
4	d^8-tetrahydrofuran	7	1	75.34	87.80	53.82	20.2	53	20
			2	76.46	83.88	52.31	19.52		

[a]) See General Procedure, except reaction was run in solvent of choice instead of $CDCl_3$. [b]) **II-3d** precipitated out of solution almost immediately after reaction was started.

Table 5.2.2.1-5: KR of *N*-acyl-β-Lactams: Substrate scope[a]

entry	substrate	time	#	ee_{PR} %	ee_{SM} %	C_{HPLC} %	s	C_{AVG} %	s_{AVG}
1		22 h	1	78.96	94.82	54.56	30.76	55	30
			2	77.88	94.24	54.75	28.25		
2		3 d	1	93.74	84.42	47	83.07	47	78
			2	93.06	83.46	47.28	73.12		

3	56 h	1	96.0	89.9	48.36	151.2	49	166
		2	96.21	93.38	49.25	180.1		
4	24 h	1	87.82	99.82	53.20	105.68	53	111
		2	87.56	99.62	53.24	91.80		
		3	89.72	99.80	52.66	125.10		
		4	89.24	99.84	52.80	122.89		
5	4 d	1	96.84	80.42	45.37	154.79	45	196
		2	97.88	81.6	45.46	237.39		
6	7 d	1	97.84	59.19	37.69	167.48	38	211
		2	98.58	58.94	37.42	255.06		
7	66 h	1	95.34	94.22	49.70	150.97	50	156
		2	95.36	95.52	50.04	161.73		
8	32 h	1	95.76	83.66	46.69	122.68	46	124
		2	99.16	80.02	45.52	125.94		
9	7 d	1	ND	ND	ND	ND	ND	ND
		2	ND	ND	ND	ND		

[a]) See General Procedure.

5.2.2.2 Assignment of the absolute configuration

(a) The absolute configuration of the ester derived from substrate **II-3a** in the presence of *(S)*-BTM was determined to be *(R)* on the basis of HPLC comparison with an enantioenriched sample of the same compound synthesized by acylation of authentic *(+)-(R)*-ester **A**.[11]

(b) The unreacted substrate **II-8** was determined to have the *(1S, 2S)* absolute configuration on the basis of HPLC comparison with an enantioenriched sample of the same compound synthesized by acylation of authentic (−)-*(1R, 2R)-β*-lactam **B**.[12]

The absolute configurations of all other enantioenriched products were assigned by analogy with these two cases.

5.2.2.3 Preparative-scale KR of N-acyl-β-lactam (±)-II-11

A 50 mL round-bottom flask was charged with the racemic substrate **II-11** (1.00 g, 3.62 mmol), Na_2SO_4 (~0.4 g), *(R)*-BTM (90.6 mg, 0.362 mmol), benzoic acid (45.2 mg, 0.362 mmol) and 27 ml of dry $CHCl_3$. Once the reactants dissolved, methanol (108 µL, 2.71 mmol) was added at once. The reaction progress was monitored by ^{1}H NMR analysis of small aliquots of the reaction mixture. After 72 h, upon reaching ~50% conversion by ^{1}H NMR, the reaction mixture was worked up with water. The organic phase was rotary evaporated and the crude residue was purified by flash chromatography on silica gel. The unreacted *N*-acyl-β-lactam (92.96% *ee*, 0.473 g, 47% yield) and then the ester (95.23% *ee*, 0.491 g, 45% yield) were eluted with pure CH_2Cl_2. Further elution with 5% isopropanol and 1% triethylamine in CH_2Cl_2 was used to recover the

catalyst (0.083 g, 76% recovery). Conversion and s were calculated using Kagan's equation to be 49% and 140, respectively.

5.2.2.4 Other modes of catalysis in KR of N-acyl-β-lactam (±)-II-11

General Procedure: To a solution of a racemic substrate **II-11** (0.05 mmol) in 0.25 mL of $CDCl_3$ was added 0.25 mL of a stock solution of 0.040 M catalyst (0.010 mmol) and 0.15 M MeOH (0.0375 mmol) in $CDCl_3$. See catalyst structures and notations in Chapter II, 2.3. The reaction mixture was stirred magnetically at rt. Its progress was checked periodically by withdrawing aliquots, diluting with $CDCl_3$, and analyzing by ^1H NMR. Upon reaching approximately 50% conversion, the reaction mixture was diluted with CH_2Cl_2 and separated by flash chromatography (silica gel, CH_2Cl_2, then CH_2Cl_2/EtOAc). Enantiomeric enrichment of the ester product and the unreacted starting material was determined by chiral stationary phase HPLC. Each experiment was performed at least in duplicate.

Table 5.2.2.4-1: Other modes of catalysis in KR of N-acyl-β-lactam (±)-**II-11**

entry	Catalyst	#	ee_{PR} %	ee_{SM} %	C_{HPLC} %	s	C_{AVG} %	s_{AVG}
1	**II-14**	1	ND	ND	ND	ND	NR[a]	ND
		2	ND	ND	ND	ND		
2	**II-15**	1	62.20	20.54	24.82	5.23	47	4.2
		2	40.32	30.30	42.91	3.12		

3	**II-16**	1	48.64	40.22	45.26	4.22	47	3.7[b]
		2	39.34	37.80	49.00	3.26		
4	**II-16**	1	14.82	3.34	18.39	1.39	30	1.4[c]
		2	10.88	7.96	42.25	1.34		
5	**II-17**	1	ND	ND	ND	ND	<10[a]	ND
		2	ND	ND	ND	ND		
6	**II-18**	1	ND	ND	ND	ND	NR[a]	ND
		2	ND	ND	ND	ND		

[a]) Determined by ^{1}H NMR. [b]) General procedure was used, except toluene was used instead of $CDCl_3$. [c]) General procedure was used, except acetonitrile was used instead of $CDCl_3$.

5.2.2.5 Study of acid role in KR of N-acyl-β-lactams

Entries from Table 5.2.2.5-1, 5.2.2.5-2, 5.2.2.5-3, 5.2.2.5-4 will generally follow one of these 4 procedures, unless otherwise specified.

Procedure A: To 0.05 mmol of substrate and Na_2SO_4 was added 0.2 mL of 0.025 M stock solution of *(R)*-BTM (10 mol%) in $CDCl_3$, followed by 0.175 mL of stock solution of 0.21 M of methanol (0.0375 mmol) in $CDCl_3$. Sample runs were analyzed and processed as described in any other procedure from above.

Procedure B: To 0.05 mmol of substrate was added 0.1 mL of 0.05 M stock solution of *(R)*-BTM (10 mol%) in $CDCl_3$ and 0.1 mL of 0.05 M benzoic acid (10 mol%) in $CDCl_3$, followed by 0.175 mL of stock solution of 0.21 M of MeOH (0.0375 mmol) in $CDCl_3$. Sample runs were analyzed and processed as described in any other procedure from above.

The following stock solutions have been made for **Procedures C** and **D**: 1) Stock Solution A: 114.24 g, 8 mmol of **2-7d** and 60.8 mg, 8 mmol of 2,6-methoxy-toluene (8 mmol) were dissolved in 1.6 mL $CDCl_3$. 2) Stock Solution B: 10 mg, 0.8 mmol of *(R)*-BTM and 12 mL of methanol were dissolved in 0.8 mL of $CDCl_3$. 2) Stock Solution C: 2.5 mg, 0.4 mmol of benzoic acid was dissolved in 0.3 mL of $CDCl_3$.

Procedure C: To Vials #1 and #2 0.2 mL of Stock Solution A, 0.2 mL of Stock Solution B, 75 μL $CDCl_3$, and Na_2SO_4 were added. To Vial #3 was added double the amounts of solutions added in Vial #1, 2. Aliquots were removed exclusively from Vial #3 for ^1H NMR analysis. After 14 hours, the reaction mixture from vial #1, 2 were diluted with CH_2Cl_2 and separated by flash chromatography (silica gel, CH_2Cl_2, then CH_2Cl_2/EtOAc). Enantiomeric enrichment of the products and the unreacted starting material was determined by chiral stationary phase HPLC.

Procedure D: To Vials #1 and #2 0.2 mL of Stock Solution A, 0.2 mL of Stock Solution B, 75 μL Stock Solution C, and Na_2SO_4 were added. To Vial #3 was added double the amounts of solutions added in Vial #1, 2. Aliquots were removed exclusively from Vial #3 for ^1H NMR analysis. After 22 hours, the reaction mixtures from vial #1, 2 were diluted with CH_2Cl_2 and separated by flash chromatography (silica gel, CH_2Cl_2, then CH_2Cl_2/EtOAc). Enantiomeric enrichment of the products and the unreacted starting material was determined by chiral stationary phase HPLC.

Table 5.2.2.5-1: Testing the catalytic system in the KR of N-acyl-β-lactam (±)-**II-3d**

entry	Additive	Time h	#	ee_{ester} %	$ee_{\beta\text{-lac}}$ %	ee_{ox}	C_{HPLC} %	s
			1	66.82	92.96	ND[b]	58.03	16.52
1[a]	*(R)*-BTM	24	2	68.06	93.19	87.52	NA	NA
			3	64.98	93.46	87.60	NA	NA
2[b]	*(R)*-BTM + $PhCO_2H$	24	1	82.79	82.86	ND	50.02	27.30
3[d]	*(R)*-BTM + $PhCO_2H$	24	1	81.04	89.60	ND	52.51	28.68
4[e]	none	24	1	ND	ND	ND	NR[f]	ND
5[g]	2,4,6-collidine	48	1	ND	ND	ND	15[f]	ND

[a]) Procedure A was followed [b]) Decomposed on column. [c]) Procedure B was followed, except 0.05 mmol of 2,6-methoxytoluene was also added and 0.1 mL of 0.1 M benzoic acid was used instead of 0.05 M. [d]) Procedure B was followed, except 0.05 mmol of 2,6-methoxytoluene was added also and 0.1 mL of 0.25M of benzoic acid was used instead 0.05 M. [e]) to 0.05 mmol **II-3d** was added 0.375 mL of 0.1 M solution of methanol in $CDCl_3$ [g]) To 0.05 mmol of **II-3d** was added 0.05 mmol of 2,4,6-collidine and 0.375 mL of 0.1 M solution of methanol in $CDCl_3$ [f]) Determined by ^1H NMR

Table 5.2.2.5-2: KR of N-acyl-β-lactam (±)-**II-3d** to obtain enantiopure oxazinone (±)-**II-1a**

entry	Catalyst/ Additive	Time h	#	$ee_{\beta\text{-lac}}$ %	ee_{ox} %	C_{HPLC} %	s
1[a]	none	24	1	55.00	90.50	37.80	34.82
2[b]	10 mol% $PhCO_2H$	24	1	36.68	93.84	28.10	45.06

[a]) Procedure A was followed, except **II-3d** was dissolved in 0.175 mL $CDCl_3$ and no methanol was added. [b]) Procedure B was followed, except **II-3d** was dissolved in 0.175 mL $CDCl_3$ and no methanol was added.

Table 5.2.2.5-3: KR of oxazinone (±)-**II-1a** in presence and absence of acid

entry	Additive	#	ee_{PR} %	ee_{SM} %	C_{HPLC} %	s	C_{AVG} %	s_{AVG}
1	none	1	45.52	39.84	46.67	3.87	48	3.8
		2	43.50	41.14	48.61	3.72		
2	10 mol% $PhCO_2H$	1	36.38	44.26	54.89	3.21	53	3.0
		2	34.54	48.04	51.88	2.89		

[a]) Procedure A was followed. [b]) Procedure B was followed.

Table 5.2.2.5-4: Monitoring formation of products in KR of N-acyl-β-lactam (±)-**II-3d** in presence and absence of acid

entry	Additive	#	ee_{ester} %	$ee_{\beta\text{-lac}}$ %	ee_{ox}	C_{HPLC} %	s	C_{AVG} %	s_{AVG}
1[a]	none	1	75.62	63.02	65.80	$C_{ox}=19$[b] $C_{ester}=13$[b]	$s_{ox}=6$[c] $s_{ester}=8$[c]	NA	NA
		2	77.84	65.86	ND[d]	NA	NA		
2[e]	10 mol% $PhCO_2H$	1	83.02	86.82	ND[d]	51.12	30.20	51.5	29
		2	81.32	88.10	ND[d]	52.00	28.01		

	Time	**without $PhCO_2H$[a]**			**With 10 mol% $PhCO_2OH$[c]**		
Entry		β-lactam used (%)	Ester formed (%)	Oxazinone formed (%)	β-lactam used (%)	Ester formed (%)	Oxazinone formed (%)
1	0.5 hrs	<2	<1	<1	3	$\underline{<}$ 1	< 1
2	1 hrs	14	8	5	4	5	< 1
3	2 hrs	14	8	5	8	8	< 1
4	4 hrs	25	13	7	17	12	< 3
5	6 hrs	37	13	12	24	19	< 1
6	8 hrs	38	13	14	31	19	< 3
7	10 hrs	39	13	17	34	24	< 1
8	12 hrs	44	13	19	39	29	< 1

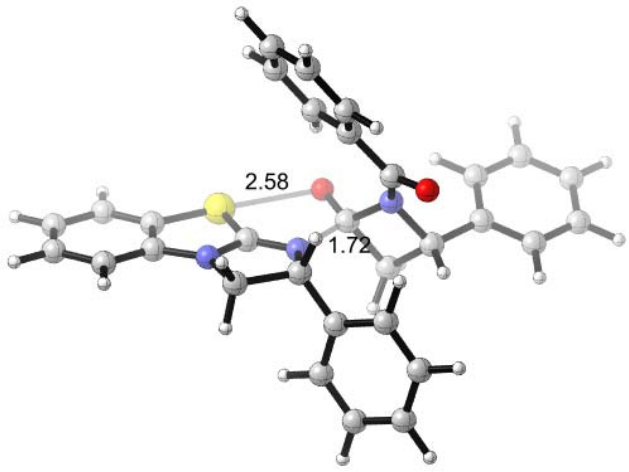
[a]) Procedure C was followed. [b]) % Conv was determined by ^{1}H NMR. [c]) S-value was calculated using Kagan's alternative equation: s = ln[1-C(1+eePR)]/ln[1-C(1-eePR)] [d]) Not enough material for analysis. [e]) Procedure D was followed.

5.2.3 Preliminary Computational Studies on KR of N-acyl-β-lactams

The proposed transition states for fast and slow reacting enantiomers were located under DFT B3LYP/3-21G(d) level calculations. The TSs were constructed under the following assumptions:

A. BTM attacks the acyl carbonyl from the less hindered face of the substrate.

B. The acyl carbonyl is nearly coplanar with the benzothiazolium moiety and points towards the sulfur atom (S-O interaction).



TS-*(S)*-BTM-*(R)*-II-3a

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 nectivity
Symbolic Z-matrix:
 Charge =  0 Multiplicity = 1
 N                    -0.6049    0.50576  -0.3496
 C                    -1.82114   0.19323  -0.71113
 N                    -2.80354   0.75481   0.05797
 S                    -2.4269   -0.81966  -1.98744
 C                    -4.10514   0.47792  -0.35991
 C                    -4.09098  -0.36289  -1.495
 C                    -5.28298  -0.76787  -2.08149
 H                    -5.27839  -1.41508  -2.95059
 C                    -5.30591   0.91803   0.18974
 H                    -5.31407   1.56166   1.06031
 C                    -6.5003    0.50795  -0.40887
 H                    -7.44323   0.84193   0.00648
 C                    -6.4919   -0.32529  -1.5324
 H                    -7.42744  -0.6322   -1.98324
 C                    -2.20928   1.58173   1.13792
 H                    -2.43895   2.63882   0.98396
 H                    -2.56457   1.25456   2.1172
 C                    -0.65843   1.29446   0.95494
 H                    -0.31151   0.62411   1.74264
 C                     0.66136  -0.34422  -1.14111
 O                     0.11142  -1.26282  -1.83162
 N                     1.6482   -0.59811   0.03525
 C                     1.68025   0.73451  -1.65486
 H                     2.05578   0.483    -2.64617
 H                     1.29902   1.75283  -1.60664
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C	2.66554	0.36804	-0.48961
C	1.57086	-0.96999	1.35338
O	2.32396	-0.45677	2.21895
C	0.52824	-1.97413	1.74051
C	-0.24531	-2.69708	0.8219
C	0.37402	-2.19919	3.11598
C	-1.18117	-3.62185	1.29259
H	-0.12738	-2.52325	-0.24406
C	-0.55797	-3.12344	3.57822
H	1.01285	-1.64191	3.79009
C	-1.34088	-3.83673	2.66383
H	-1.78167	-4.18105	0.58397
H	-0.67153	-3.29598	4.64247
H	-2.0655	-4.56106	3.01921
C	0.19369	2.5461	0.93349
C	1.31486	2.63003	1.77012
C	-0.11927	3.61891	0.0867
C	2.09448	3.79051	1.77802
H	1.61144	1.76695	2.35861
C	0.66286	4.77346	0.095
H	-0.96792	3.54817	-0.58606
C	1.76677	4.86443	0.94905
H	2.96084	3.84826	2.42651
H	0.41592	5.59829	-0.56317
H	2.37192	5.76346	0.95809
H	2.86224	1.18206	0.20678
C	3.9397	-0.30824	-0.9405
C	5.18216	0.29909	-0.73455
C	3.88239	-1.53925	-1.61083
C	6.35401	-0.30596	-1.19684
H	5.23351	1.24519	-0.2055
C	5.05084	-2.143	-2.07221
H	2.91638	-2.00771	-1.76347
C	6.2908	-1.52825	-1.86727
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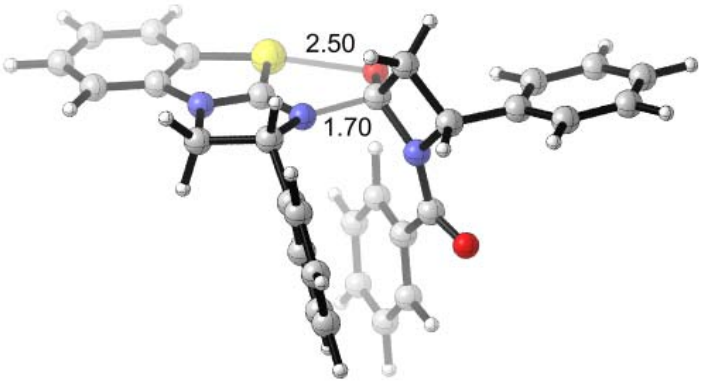
H	4.99745	-3.09462	-2.58904
H	7.19853	-2.00149	-2.22404



TS-*(S)*-BTM-*(S)*-II-3a

```
E(RB3LYP) = -1899.07750226 a.u.
# opt=(calcfc,ts,noeigen,maxstep=5) freq=noraman b3lyp/3-21g* geom=con
 nectivity
Symbolic Z-matrix:
 Charge =  0 Multiplicity = 1
 N                     0.78822  -0.024    -0.91228
 C                     1.97146  -0.5391   -0.6707
 N                     3.01782   0.26119  -1.0347
 S                     2.45671  -2.07136  -0.01481
 C                     4.28266  -0.26507  -0.76681
 C                     4.16787  -1.55174  -0.19816
 C                     5.30791  -2.2698    0.1408
 H                     5.22777  -3.25868   0.57678
 C                     5.52869   0.31156  -0.99566
 H                     5.61222   1.29991  -1.42983
 C                     6.66944  -0.41716  -0.64901
 H                     7.64746   0.01639  -0.81829
 C                     6.56287  -1.69412  -0.08706
 H                     7.45836  -2.24327   0.17625
 C                     2.51795   1.55854  -1.5509
 H                     2.69173   2.35277  -0.8201
 H                     2.97973   1.80837  -2.50793
 C                     0.96371   1.26825  -1.69532
 H                     0.72338   1.05371  -2.74196
 C                    -0.52706  -1.07904  -0.68813
 O                    -0.04417  -2.12661  -0.11553
 N                    -1.64114  -0.23477  -0.08281
 C                    -1.35326  -1.05903  -2.03366
 H                    -0.8949   -0.49516  -2.8465
 H                    -1.61614  -2.06656  -2.35248
 C                    -2.51364  -0.30368  -1.29265
 H                    -2.76323   0.682    -1.68939
 C                    -3.74596  -1.15843  -1.08506
 C                    -4.99545  -0.7528   -1.56023
 C                    -3.62654  -2.39913  -0.43858
 C                    -6.11492  -1.57494  -1.40476
 H                    -5.09587   0.21349  -2.04338
 C                    -4.74304  -3.21825  -0.28313
 H                    -2.65412  -2.70684  -0.06666
 C                    -5.99083  -2.80984  -0.76701
 H                    -7.08056  -1.24779  -1.77366
 H                    -4.64352  -4.17451   0.21811
 H                    -6.8582   -3.44811  -0.64216
 C                    -2.02876   0.42247   1.06534
 O                    -3.06181   1.12173   1.05351
 C                    -1.18697   0.31185   2.30149
 C                    -0.20396  -0.66325   2.50818
 C                    -1.47662   1.23648   3.31566
 C                     0.50414  -0.68169   3.71351
 H                    -0.0245   -1.40887   1.73877
 C                    -0.76473   1.21797   4.51099
 H                    -2.27751   1.94278   3.13416
 C                     0.23474   0.2585    4.71039
 H                     1.26141  -1.44067   3.87623
 H                    -0.99078   1.93717   5.29026
```

H	0.78891	0.23738	5.64236
C	0.12749	2.42615	-1.20291
C	-0.48406	3.27869	-2.12937
C	0.01165	2.69565	0.16529
C	-1.1975	4.39773	-1.6933
H	-0.40612	3.06718	-3.19132
C	-0.71324	3.80381	0.59941
H	0.44176	2.01349	0.8878
C	-1.31221	4.66161	-0.32771
H	-1.66983	5.05207	-2.41654
H	-0.82401	3.98461	1.6615
H	-1.87829	5.51997	0.01392

5.2.4 Characterization data and HPLC properties.

Note: *Melting points and spectral data were determined using racemic samples. The absolute configuration, where indicated, corresponds to the major enantiomer produced using (S)-BTM.*

Known compound.[1] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.15 (m, 2H), 7.55-7.26 (m, 8H), 5.07 (dd, J_1= 11 Hz, J_2= 5 Hz, 1H), 3.06 (dd, J_1= 16 Hz, J_2= 5 Hz, 1H), 2.68 (dd, J_1= 16 Hz, J_2= 11 Hz, 1H); **HPLC** (CHIRALCEL OD-H, hexane/isopropanol 10:1, 1 mL/min): 11.1 min (minor); 12.3 min (major).

White solid; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.04 (d, J= 8.5 Hz, 2H), 7.43-7.25 (m, 7H), 5.02 (dd, J_1= 11.4 Hz, J_2= 5.0 Hz, 1H), 3.04 (dd, J_1= 16.1 Hz, J_2= 5.0 Hz, 1H), 2.64 (dd, J_1= 16.1 Hz, J_2= 11.4 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.25, 152.85, 140.41, 138.35, 129.24, 128.98, 128.84, 128.77, 127.99, 126.22, 56.57, 36.09; **IR** (KBr, cm^{-1}): 1792, 1672, 1603, 1585, 1492, 1449, 1274, 1198, 1135; **MS**: HR-ESI calculated for $[(C_{16}H_{12}ClNO_2)+H]^+$: 286.0557, found: 286.0638; **HPLC** (CHIRALCEL AD-H, hexane/isopropanol 100:1, 1 mL/min): 31.2 min (major); 36.8 min (minor).

Known compound.[3,4b] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.02 (d, J=6 Hz, 2H), 7.63-7.57 (m, 1H), 7.51-7.31 (m, 7 H), 5.30 (dd, J_1= 6 Hz, J_2= 3 Hz, 1H), 3.53 (dd, J_1= 15 Hz, J_2= 6 Hz, 1H), 3.10(dd, J_1= 15 Hz, J_2= 3 Hz, 1H); **HPLC** (CHIRALPAK AD, hexane/isopropanol 100:1, 1 mL/min): 52.5 min (minor); 82.2 min (major).

White solid; **mp**: 204-206 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.35 (s,1H), 7.90-7.75 (m, 6H), 7.66 (d, *J*= 7.1, 2H), 7.56-7.26 (m, 14H), 7.2 (d, *J*= 7.1 Hz, 1H), 7.05 (d, *J*= 7.1 Hz, 1H), 5.70 (m, 1H), 3.26 (dd, J_1= 15.9 Hz, J_2= 5.0 Hz, 1H), 3.12 (dd, J_1= 15.9 Hz, J_2= 5.0 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.2, 166.7, 140.5, 134.5, 134.3, 134.2, 134.1, 134.0, 131.8, 131.1, 129.4, 129.2, 129.1, 129.0, 128.8, 127.9, 127.2, 127.1, 126.5, 126.2, 126.1, 126.0, 125.9, 125.5, 123.3, 71.8, 49.8, 40.0; **IR** (KBr, cm^{-1}): 3312, 3060, 1735, 1638, 1532, 1511; **MS**: HR-ESI calculated for $[2(C_{37}H_{29}NO_3)+H]^+$: 1071.4368, found: 1071.4410; **HPLC** (CHIRALCEL OD-H, hexane/isopropanol 4:1, 1 mL/min): 11.1 min (minor); 14.6 min (major); sign of rotation: (+).

White solid; **mp:** 138-141 ºC; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.80 (d, *J*= 8.3 Hz, 2H), 7.51-7.19 (m, 13H), 5.70-5.63 (m, 1H); 5.10 (d, *J*= 12.1 Hz, 1H), 5.04 (d, *J*= 12.1 Hz, 1H), 3.11 (dd, J_1 = 15.7 Hz, J_2 = 5.5 Hz, 1H), 3.00 (J_1 = 15.7 Hz, J_2 = 5.5 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.6, 166.7, 140.6, 135.5, 134.4, 131.9, 129.0, 128.8, 128.6, 128.5, 127.9, 127.3, 126.5, 66.9, 50.0, 40.2; **IR** (KBr, cm^{-1}): 3435 (br), 2094 (br), 1732, 1637, 1530, 1489; **MS**: HR-ESI calculated for $[(C_{23}H_{21}NO_3)+H]^+$: 360.1594, found: 360.1586; **HPLC** (CHIRALCEL OD-H, hexane/isopropanol 4:1, 1 mL/min): 9.4 min (minor); 14.3 min (major).

Known compound.[13] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.84 (d, *J*=7 Hz, 2H), 7.54-7.26 (m, 8H), 5.64 (m, 1H), 3.64 (s, 3H), 3.10-2.93 (m, 2H); **HPLC** (CHIRALCEL OD-H, hexane/isopropanol 10:1, 1 mL/min): 7.3 min (minor); 9.7 min (major).

Known compound.[4a] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36 (m, 5H), 4.93 (dd, J_1= 6 Hz, J_2= 3 Hz, 1H), 3.44 (dd, J_1= 15 Hz, J_2= 3 Hz, 1H), 2.92 (dd, J_1= 16 Hz, J_2= 3 Hz, 1H), 1.38 (s, 9H).

White solid; **mp**: 95-97 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 5.02 (dd, J_1 = 9.9 Hz, J_2 = 3.3 Hz, 1H), 3.53 (dd, J_1=16.2, J_2= 6.6 Hz, 1H), 3.41 (m, 1H), 2.97 (dd, J_1= 16.2 Hz, J_2= 3.3 Hz, 1H), 1.25 (d, *J*=7.1 Hz, 3H), 1.17 (d, *J*=7.1Hz, 3H); **^{13}C NMR** (75 MHz, CDCl3): δ 175.1, 165.1, 138.3, 129.2, 128.6, 125.9, 52.2, 45.5, 35.1, 19.1, 17.8; **IR** (KBr,

cm^{-1}): 2973, 1775, 1697, 1285, 1253; **MS**: HR-ESI calculated for $[(C_{13}H_{15}NO_2)+H]^+$: 218.1176, found: 218.1175.

White solid; **mp**: 117-120 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.99 (d, *J*=9.1 Hz, 2H), 7.47-7.30 (m, 7H), 5.29 (dd, J_1= 6.9 Hz, J_2= 3.8 Hz, 1H), 3.58 (dd, J_1= 16.2 Hz, J_2= 6.9 Hz), 3.14 (dd, J_1= 16.2 Hz, J_2= 3.6 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.9, 164.4, 140.1, 138.3, 131.7, 130.5, 129.2, 128.9, 128.8, 126.3, 52.1, 44.7; **IR** (KBr, cm^{-1}): 3436 (br), 1790, 1674, 1310; **MS**: HR-ESI calculated for $[(C_{16}H_{12}ClNO_2)+H]^+$: 286.0629, found: 286.0628; **HPLC** (CHIRALCEL OD-H, hexane/isopropanol 4:1, 1 mL/min): 12.2 min (major); 16.4 min (minor); sign of rotation: (−).

White solid; **mp**: 124-129 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.79 (d, *J*= 8.8 Hz, 2H), 7.59 (d (br), *J*= 8.0 Hz, 1H), 7.42 (d, *J*= 8.8 Hz, 1H), 7.34-7.29 (m, 5H), 5.60 (m, X from ABX pattern, 1H), 3.64 (s, 1H), 3.07-2.91 (dd, AB from ABX pattern, J_1= 16.0 Hz, J_2= 5.5 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.4, 165.7, 140.6, 138.1, 132.8, 129.1, 129.0, 128.7, 127.9, 126.4, 52.2, 50.1, 39.7; **IR** (KBr, cm^{-1}): 3435 (br), 2100 (br), 1636; **MS**: HR-ESI calculated for $[C_{17}H_{16}ClNO_3+H]^+$: 318.0891, found: 318.0890; **HPLC** (CHIRALCEL OD-H, hexane/isopropanol 4:1, 1 mL/min): 11.1 min (major); 12.6 min (minor); sign of rotation: (−).

White solid; **mp**:138-140 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.34 (d, *J*= 8.8 Hz, 2H), 8.17 (d, *J*= 8.8 Hz, 1H), 7.44-7.36 (m, 5H), 5.32 (dd, J_1= 6.9 Hz, J_2= 3.8 Hz, 1H), 3.64 (dd, J_1= 16.5 Hz, J_2= 6.9 Hz, 1H), 3.21 (dd, J_1= 16.5 Hz, J_2= 3.8 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.5, 161.7, 148.5, 137.1, 135.5, 130.1, 129.4, 129.3, 126.5, 122.7, 53.0, 45.3; **IR** (KBr, cm^{-1}): 3435 (br), 2099 (br), 1793, 1675, 1524, 1311; **MS**: HR-ESI calculated for $[(C_{16}H_{12}N_2O_4)+Na]^+$: 319.0695, found: 319.0712; **HPLC** (CHIRALPAK AS-H, hexane/isopropanol 4:1, 0.8 mL/min): 21.6 min (major); 31.1 min (minor); sign of rotation: (−).

White solid; **mp**:136-138 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.30 (d, *J*= 8.5 Hz, 2H), 8.01 (d, *J* = 9.1 Hz, 2 H), 7.81(d (br), *J*= 8.3 Hz, 1H), 7.37-7.27 (m, 5H), 5.61 (m, X from ABX pattern, 1H), 3.67 (s, 3H), 3.01 (AB from ABX pattern, J_1= 16.0 Hz, J_2= 5.5 Hz,

2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.5, 164.7, 149.9, 140.2, 139.9, 129.1, 128.5, 128.2, 126.4, 124.1, 52.3, 50.4, 39.5; **IR** (KBr, cm^{-1}): 3435 (broad), 2092 (broad), 1643, 1525, 1345; **MS**: HR-ESI calculated for $[(C_{16}H_{14}N_2O_5)+H]^+$: 329.1132, found: 329.1126; **HPLC** (CHIRALCEL OD-H, hexane/isopropanol 4:1, 0.8 mL/min): 31.9 min (major); 58.3 min (minor); sign of rotation: (−).

White solid; **mp**: 157-159 °C; **^{1}H NMR** (300 MHz, $CDCl_3$):, δ 9.26 (app. t, J = 2.1 Hz, 1H); 9.17 (app. d, J = 2.2 Hz, 2H), 7.45-7.38 (m, 5H), 5.37 (dd, J_1= 6.6 Hz, J_2= 3.9 Hz, 1H), 3.72 (dd, J_1= 16.8 Hz, J_2= 6.6 Hz, 1H), 3.32 (dd, J_1= 16.8 Hz, J_2= 3.9 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.4, 164.1, 150.6, 137.8, 137.6, 131.2, 129.3, 128.9, 126.3, 123.5, 52.6, 45.1; **IR** (KBr, cm^{-1}): 3435 (broad), 2100 (broad), 1797, 1630, 1542, 1345, 1311; **MS**: HR-ESI calculated for $[(C_{16}H_{11}N_3O_6)+Na]^+$: 364.0546, found: 364.0554; **HPLC** (CHIRALPAK AS-H, hexane/isopropanol 4:1, 0.8 mL/min): 40.2 min (major); 59.9 min (minor).

White solid; **mp**: 184-188 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.18 (t, J= 1.9 Hz, 1H), 8.99 (d, J= 1.9 Hz, 2H), 8.03 (d (br), J= 8.0 Hz, 1H), 7.83-7.30 (m, 5H), 5.62 (m, X from ABX pattern, 1H), 3.69 (s, 3H), 3.11-2.97 (dd, AB from ABX pattern, J_1= 16.0 Hz, J_2=5.5 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.4, 162.2, 148.9, 139.8, 137.9, 129.2, 128.4, 127.5, 126.4, 121.4, 52.5, 50.9, 39.3; **IR** (KBr, cm^{-1}): 3434 (broad), 2092 (broad), 1642, 1540, 1344; **MS**: HR-ESI calculated for $[(C_{17}H_{15}N_3O7)+Na]^+$: 396.0802, found: 396.0793; **HPLC** (CHIRALPAK AS-H, hexane/isopropanol 4:1, 1 mL/min): 23.6 min (major); 35.8 min (minor).

White solid; **mp**: 181-183 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.1 (d, J= 8.3 Hz, 2H), 7.94-7.82 (m, 3H), 7.61-7.41 (m, 6H), 6.01 (dd, J_1= 6.3 Hz, J_2= 4.1 Hz, 1H), 3.78 (dd, J_1= 16.2 Hz, J_2= 6.6 Hz, 1H), 3.04 (dd, J_1= 16.2 Hz, J_2= 4.0 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.4, 164.3, 140.3, 134.1, 133.6, 131.9, 130.5, 130.3, 129.4, 128.96, 128.91, 126.9, 126.4, 125.6, 122.6, 121.6, 49.9, 44.9; **IR** (KBr, cm^{-1}): 3434 (br), 2092 (br), 1792, 1644; **MS**: HR-ESI calculated for $[(C_{20}H_{14}ClNO_2)+H]^+$: 336.0786, found: 336.0785; **HPLC** (CHIRALPAK AS-H, hexane/isopropanol 20:1, 1 mL/min): 23.6 min (minor); 31.8 min (major); sign of rotation: (−).

Clear colorless semi-solid; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.12 (d, *J*= 8.5 Hz, 2H), 7.89-7.71 (m, 4H), 7.59-7.34 (m, 6H), 6.37 (m, X of ABX pattern, 1H), 3.61 (s, 3H), 3.11 (m, AB of ABX pattern, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.2, 165.6, 138.1, 135.9, 134.2, 132.7, 130.9, 129.2, 129.0, 128.9, 128.7, 127.1, 126.2, 125.4, 123.1, 123.0, 52.2, 46.7, 39.1; **IR** (KBr, cm^{-1}): 3298 (br), 1737, 1635, 1595, 1539, 1486; **MS**: HR-ESI calculated for $[(C_{21}H_{18}ClNO_3)+Na]^+$: 368.1048, found: 368.1056; **HPLC** (CHIRALCEL OD-H, hexane/isopropanol 4:1, 1 mL/min): 8.9 min (major); 15.2 min (minor); sign of rotation: (−).

Clear colorless oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.88 (d, *J*= 8.5 Hz, 2H), 7.44 (d, *J*= 8.5 Hz, 2H), 4.20 (m, 1H), 3.00 (dd, J_1= 16.5 Hz, J_2= 6.6 Hz, 1H), 2.82 (dd, J_1= 16.5 Hz, J_2= 2.8 Hz, 1H), 2.37 (m, 1H), 1.00 (d, *J*= 6.6 Hz, 3H), 0.96 (d, *J*= 6.6 Hz, 3H) ; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.8, 164.8, 139.8, 131.5, 130.9, 128.7, 54.9, 37.5, 29.5, 19.0, 15.9; **IR** (KBr, cm^{-1}): 3565, 2963, 2874, 1793.2, 1674, 1592, 1572, 1488, 1466, 1313; **MS**: HR-ESI calculated for $[(C_{13}H_{14}ClNO_2)+Na]^+$: 274.0605, found: 274.0599. **HPLC:** Converted into Me ester by treatment with MeONa/MeOH and analyzed as described below.

White solid; **mp**: 105-108 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.72 (d, *J*= 8.5 Hz, 2H), 7.39 (d, *J*= 8.5 Hz, 2H), 6.94 (d (br), *J*= 9.1 Hz, 1H), 4.21 (m, 1H), 3.69 (s, 3H), 2.70 (diastereotopic dd, 2H), 1.94 (m, 1H), 0.98 (diastereotopic doublets, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.2, 165.9, 137.9, 133.3, 129.0, 128.6, 52.2, 52.1, 36.1, 31.9, 19.7, 19.5; **IR** (KBr, cm^{-1}): 3349, 2950, 2872, 1740, 1638, 1546, 1489; **MS**: HR-ESI calculated for $[(C_{14}H_{18}ClNO_3)+H]^+$: 284.1047, found: 284.1052; **HPLC** (CHIRALCEL OD-H, hexane/isopropanol 10:1, 1 mL/min): 6.6 min (minor); 8.4 min (major); sign of rotation: (−).

Clear, colorless oil; **^{1}H NMR** (300 MHz, $CDCl_3$ δ 7.81 (d, *J*= 8.3 Hz, 2H), 7.30 (d, *J*= 8.5 Hz, 2H), 4.46 (app. t, *J*= 5.0 Hz, 1H), 3.40 (app dd, J_1= 8.0 Hz, J_2= 4.7 Hz, 1H), 2.22 (app dd, J_1= 13.8 Hz, J_2= 5.2 Hz, 1H), 1.99 (app dd, J_1= 12.4 Hz, J_2= 5.0 Hz, 1H), 1.83-1.72 (m, 1H), 1.66-1.35 (m, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.8, 164.8, 139.3, 131.3, 130.9, 128.5, 56.7, 52.9, 29.2, 26.2, 23.0; **IR** (KBr, cm^{-1}): 3548, 2963, 2871, 1784, 1700,

1592, 1489, 1402, 1317; **MS**: HR-ESI calculated for $[(C_{13}H_{12}ClNO_2)+Na]^+$: 272.0449, found: 272.0449; **HPLC** (CHIRALPAK AD, hexane/isopropanol 100:1, 1 mL/min): 19.8 min (minor); 27.2 min (major); sign of rotation: (−).

White solid; **mp**: 95-98 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.70 (d, *J*= 8.8 Hz, 2H), 7.40 (d, *J*= 7.6 Hz, 2H), 7.00 (d (br), *J*= 7.4 Hz, 1H), 4.65 (app. quintet, J_1= 7.4 Hz, 1H), 3.67 (s, 3H), 3.08 (app. dd, J_1= 14.8 Hz, J_2= 7.7 Hz, 1H), 2.13-1.99 (m, 3H), 1.91-1.63 (m, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.8, 165.9, 137.9, 133.1, 129.0, 128.6, 52.7, 52.2, 46.3, 32.5, 28.9, 22.6; **IR** (KBr, cm^{-1}): 3339, 2944, 1722, 1641, 1541, 1488, 1325; **MS**: HR-ESI calculated for $[(C_{14}H_{16}ClNO_3)+H]^+$: 282.0891, found: 282.0898; **HPLC** (CHIRALPAK AS-H, hexane/isopropanol 10:1, 1 mL/min): 16.8 min (minor); 31.4 min (major); sing of rotation: (−).

White solid; **mp**: 124-128 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.92 (d, *J*=7.7 Hz, 2H), 7.80 (d, *J*= 7.1 Hz, 1H), 7.33 (m, 5H), 5.63 (d, *J*= 5.5 Hz, 1H), 4.03 (m, 1H), 3.44 (app. d, *J*= 17.6 Hz, 1H), 3.21 (dd, J_1= 17.6 Hz, J_2= 10.7 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.1, 164.9, 143.9, 139.6, 138.9, 131.4, 130.5, 129.9, 128.7, 128.4, 127.6, 126.0, 61.0, 50.7, 31.4; **IR** (KBr, cm^{-1}): 3434, 1788, 1667, 1320, 1309, 1276; **MS**: HR-ESI calculated for $[(C_{17}H_{12}ClNO_2)+Na]^+$: 320.0447, found: 320.0449; **HPLC** (CHIRALCEL OD-H, hexane/isopropanol 100:1, 1 mL/min): 22.5 min (major); 28.2 min (minor); sign of rotation: (+).

White solid; **mp**: 145-148 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.72 (d, *J*= 8.8 Hz, 2H), 7.41 (d, *J*= 11.0 Hz, 2H), 7.35 (app d, *J*= 5.5 Hz, 1H), 7.29-7.20 (m, 3H), 6.95 (d (br), *J*= 9.1 Hz, 1H), 6.01 (app t, *J*= 8.53 Hz, 1H), 3.74-3.67 (m, 1H), 3.65 (s, 3H), 3.41 (dd, J_1= 16.2 Hz, J_2= 5.8 Hz, 1H), 3.23 (dd, J_1= 16.2 Hz, J_2= 8.5 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.3, 166.1, 141.4, 141.1, 138.1, 132.8, 129.1, 128.9, 128.7, 127.7, 125.0, 124.7, 55.7, 52.3, 47.9, 34.8; **IR** (KBr, cm^{-1}): 3435, 2100, 1726, 1643, 1528; **MS**: HR-ESI calculated for $[(C_{18}H_{16}ClNO_3)+H]^+$: 330.0891, found: 330.0893; **HPLC** (CHIRALCEL OD-H, hexane/isopropanol 100:1, 1 mL/min): 71.8 min (minor); 81.0 min (major); sign of rotation: (+).

Clear, colorless oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.90 (d, *J*= 8.5 Hz, 2H), 7.41 (d, *J*= 8.8 Hz, 2H), 4.39 (m, 1H), 3.33 (m, 1H), 2.16-2.08 (m, 1H), 1.97-1.75 (m, 3H), 1.68-1.50 (m, 4H); **^{13}C NMR** (75 MHz,

$CDCl_3$): δ 172.6, 169.9, 143.9, 135.7, 135.3, 133.0, 53.8, 50.2, 27.9, 24.4, 23.8, 21.7; **IR** (KBr, cm^{-1}): 3547, 2943, 2867, 1785, 1668, 1591, 1325, 1296, 1284; **MS**: HR-ESI calculated for $[(C_{14}H_{14}ClNO_2)+Na]^+$: 286.0605, found: 286.0600; **HPLC** (CHIRALPAK AS-H, hexane/isopropanol 100:1, 0.8 mL/min): 17.2 min (minor); 20.4 min (major); sign of rotation: (−).

White solid; **mp**: 116-118 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.70 (d, *J*= 8.5 Hz, 2H), 7.41 (d, *J*= 8.5 Hz, 2H), 7.30 (d (br), *J*= 8.8 Hz, 1H), 4.34-4.25 (m, 1H), 3.72 (s, 3H), 2.91 (app. q, *J*= 4.3 Hz, 1H), 2.21-2.15 (m, 1H), 1.82-1.44 (m, 6H), 1.31-1.22 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.2, 165.4, 137.8, 133.3, 128.9, 128.6, 52.0, 48.7, 44.5, 29.6, 27.7, 24.6, 22.6; **IR** (KBr, cm^{-1}): 3319, 2936, 2859, 1731, 1639, 1527, 1484; **MS**: HR-ESI calculated for $[(C_{15}H_{18}ClNO_3)+H]^+$: 296.1081, found: 296.1051; **HPLC** (CHIRALPAK AS-H, hexane/isopropanol 20:1, 1 mL/min): 25.1 min (minor); 32.1 min (major); sign of rotation: (−).

Clear, colorless crystals; **mp**: 61-66 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.84 (d, *J*= 8.5 Hz, 2H), 7.38 (d, *J*= 8.5 Hz, 2H), 5.93-5.88 (m, 1H), 5.82-5.76 (m, 1H), 4.54 (app. t, *J*= 5.2 Hz, 1H), 3.45 (app t, *J*= 7.0 Hz, 1H), 2.87 (app. dd, J_1= 17.9 Hz, J_2= 6.6 Hz, 1H), 2.57-2.49 (app dd, 1H), 2.24-2.17 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.9, 165.3, 139.6, 131.4, 130.9, 128.6, 126.2, 125.6, 49.7, 46.2, 24.6, 21.6; **IR** (KBr, cm^{-1}): 3567, 3040, 2842, 1787, 1670, 1319; **MS**: HR-ESI calculated for $[(C_{14}H_{12}ClNO_2)+Na]^+$: 284.0435, found: 284.0441; **HPLC** (CHIRALPAK AS-H, hexane/isopropanol 50:1, 1 mL/min): 12.1 min (minor); 15.1 min (major); sign of rotation: (−).

White solid; **mp**: 126-128 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.70 (d, *J*= 8.5 Hz, 2H), 7.40 (d, *J*= 8.5 Hz, 2H), 7.04 (d (br), *J*= 9.1 Hz, 1H), 5.68 (m, 2H), 4.65 (m, 1H), 3.72 (s, 3H), 2.94 (m, J_1= 9.6 Hz, J_2= 5.8 Hz, 1H), 2.68-2.59 (m, 1H), 2.48-2.38 (m, 2H), 2.33-2.23 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.6, 165.9, 137.9, 133.2, 129.0, 128.6, 125.2, 125.1, 52.3, 45.7, 42.1, 30.0, 26.4; **IR** (KBr, cm^{-1}): 3332, 3028, 2948, 1732, 1635, 1534, 1486; **MS**: HR-ESI calculated for $[(C_{15}H_{16}ClNO_3)+H]^+$: 294.0891, found: 294.0897; **HPLC** (CHIRALPAK AS-H, hexane/isopropanol 5:1, 1 mL/min): 12.7 min (minor); 21.8 min (major); sign of rotation: (+).

White solid; **mp**:106-108 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.90 (d, *J*=8.8 Hz, 2H), 7.42 (d, *J*= 8.8 Hz, 2H), 4.01 (app. d, *J*=4.7 Hz, 1H), 3.06 (app. d, *J*= 4.7 Hz, 1H), 2.89 (app. d, *J*= 3.3 Hz, 1H), 2.57 (app. d, *J*= 2.5 Hz, 1H), 1.74-1.58 (m, 3H), 1.35 (app d, *J*= 11.3 Hz, 1H), 1.2 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.5, 164.9, 139.5, 131.3, 130.8, 128.6, 55.92, 55.89, 55.4, 37.6, 35.3, 31.6, 27.4, 24.8; **IR** (KBr, cm^{-1}): 3546, 2963, 2874, 1782, 1669, 1593, 1401, 1323; **MS**: HR-ESI calculated for $[(C_{15}H_{14}ClNO_2)+Na]^+$: 298.0605, found: 298.0605; **HPLC** (CHIRALPAK AD, hexane/isopropanol 100:1, 1 mL/min): 23.7 min (minor); 37.5 min (major); sign of rotation: (+).

White solid; **mp**: 101-105 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.58 (d, *J*= 8.5 Hz, 2H), 7.42 (d (br), *J*= 8.5 Hz, 1H), 7.25 (d, *J*= 8.5 Hz, 2H), 4.26 (app. t, *J*= 8.5 Hz, 1H), 3.51 (s, 3H), 2.69 (app d, *J*= 8.5 Hz, 1H), 2.36 (app s, 1H), 2.16 (app d, *J*= 3.0 Hz, 1H), 1.84 (app d, *J*= 10.7 Hz, 1H), 1.47 (m, 2H), 1.30-1.17 (m, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.9, 165.3, 137.6, 133.1, 128.9, 128.5, 54.7, 51.9, 51.3, 42.8, 41.6, 34.9, 29.0, 26.5; **IR** (KBr, cm^{-1}): 3314, 2958, 2874, 1730, 1646, 1595, 1532, 1484; **MS**: HR-ESI calculated for $[(C_{16}H_{18}ClNO_3)+H]^+$: 308.1048, found: 308.1052; **HPLC** (CHIRALPAK AD, hexane/isopropanol 20:1, 0.8 mL/min): 26.21 min (major); 45.7 min (minor); sign of rotation: (+).

White solid; **mp**: 106-109 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.93 (d, *J*= 8.5 Hz, 2H), 7.43 (d, *J*= 8.5 Hz, 2H), 6.32 (m, 1H), 6.23 (m, 1H), 4.07 (app. d, *J*= 4.7 Hz, 2H), 3.45 (app s, 1H), 3.10 (m, 2H), 1.76-1.61 (m, 2H); **^{13}CNMR** (75MHz, CDCl3): δ 165.6, 165.2, 139.7, 138.6, 136.6, 131.4, 130.6, 128.7, 55.6, 54.9, 43.5, 41.2, 40.5; **IR** (KBr, cm^{-1}): 2985, 2360, 1787, 1669, 1592, 1489, 1401, 1320, 1282; **MS**: HR-ESI calculated for $[(C_{15}H_{12}ClNO_2)+Na]^+$: 296.0449, found: 296.0447; **HPLC** (CHIRALPAK AD, hexane/isopropanol 100:1, 1 mL/min): 19.0 min (major); 23.3 min (minor); sign of rotation: (+).

White solid; **mp**: 128-131 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.72 (d, *J*= 8.5 Hz, 2H), 7.64 (d (br), *J*= 8.8 Hz, 1H), 7.41 (d, *J*= 8.3 Hz, 2H), 6.30 (m, 1H), 6.25 (m, 1H), 4.31 (app. t, *J*= 8.5 Hz, 1H), 3.69 (s, 3H), 3.03 (app s, 1H), 2.87 (app s, 1H), 2.71 (app. d, *J*= 8.3 Hz, 1H), 2.02 (app d, *J*= 9.7 Hz), 1.61 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.9, 165.6, 138.3, 137.9, 137.7, 133.0, 129.1, 128.5, 53.4, 51.5, 48.9, 47.2, 45.5, 44.4; **IR** (KBr, cm^{-1}): 3434 (br), 2092 (br), 1644, 1533, 1484; **MS**: HR-ESI calculated for $[(C_{16}H_{16}ClNO_3)+H]^+$: 306.0891, found:

306.0890; **HPLC** (CHIRALPAK AS-H, hexane/isopropanol 4:1, 0.8 mL/min): 9.6 min (minor); 19.3 min (major); sign of rotation: (−).

Clear, faint yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.01 (d, *J*= 8.3 Hz, 2H), 7.47-7.30 (m, 7H), 4.94 (d, *J*= 3.6 Hz, 1H), 3.23 (m, 1H), 1.99-1.77 (m, 2H), 1.54-1.28 (m, 4H), 0.94 (t, *J*= 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.8, 165.1, 140.0, 138.4, 131.7, 130.6, 129.2, 128.8, 128.6, 126.1, 59.2, 58.1, 29.3, 28.6, 22.7, 14.0; **IR** (KBr, cm^{-1}): 3553 (broad), 3089, 3065, 3032, 2957, 2930, 2859, 1790, 1670, 1592, 1573, 1489, 1458, 1401, 1298 (broad); **MS**: HR-ESI calculated for $[(C_{20}H_{20}ClNO_2)+H]^+$: 342.1255, found: 342.1252.

5.2.5 References

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5.3 KR OF β-LACTAMS VIA ENANTIOSELECTIVE N-ACYLATION USING AMIDINE-BASED CATALYSTS

5.3.1 General

See Chapter III for substrate notation/numbering. Racemic β-lactams **III-1**, **III-3**, **III-10**, and **III-12** were obtained via cycloaddition of chlorosulfonyl isocyanate with the corresponding olefins.[1] Substrate **III-9** was prepared via alkylation of (±)-**III-1** as previously described.[2] All other substrates were synthesized from the corresponding aldehydes via condensation of their N-(trimethylsilyl)imines with *tert*-butyl acetate Li enolate, according to a general procedure.[3]

5.3.2 Kinetic resolution experiments

General Procedure: A racemic β-lactam (0.10 mmol) and *(S)*-Cl-PIQ **(**2.8 mg, 0.010 mmol) were stirred in 2 mL of *tert*-amyl alcohol at rt for *ca.* 10 min until most of the solids dissolved. Then, *i*-Pr_2NEt (34 μL, 0.20 mmol) was added, the solution was cooled to 0 ^oC and stirred for 5 min, and treated with isobutyric anhydride (34 μL, 0.20 mmol). After stirring at 0 ^oC for 24-72 h, the reaction mixture was quenched by addition of methanol (100 μL) and the solvent removed under vacuum. After determining the % conversion in the crude residue by ^1H NMR, it was separated by flash chromatography (hexanes/EtOAc 1:1 in all cases, except substrates **III-9** and **III-10** requiring 2:1 ratio). The enantiomeric enrichment of the N-acylated product and the recoved β-lactam were analyzed by HPLC. The calculated value for conversion was in agreement with that estimated by ^1H NMR. The results are provided from duplicate runs, unless otherwise specified and are summarized in Table 5.3.2-2.

Optimization Study Procedure: Optimization studies were conducted in a similar fashion using General Procedure, except 0.025 mmol (3.6 mg) of 4-phenyl-azetidin-2-one **III-1**. The conditions and results of these experiments are summarized in Table 5.3.2-1. Reaction mixtures were analyzed HPLC, by removing aliquots, diluting them with CH_2Cl_2 and hexane, and injecting directly into the HPLC line.

Preparative Scale Resolution Procedure: Racemic 4-(*p*-chlorophenyl)-azetidin-2-one **III-3** (545 mg, 3.00 mmol), *(R)*-Cl-PIQ (84 mg, 0.30 mmol), and N,N′-diisopropylethylamine (1.0 mL, 6.0 mmol) were dissolved in 60 mL of *tert*-amyl alcohol. After cooling the reaction mixture to 0 °C, isobutyric anhydride (1.0 mL, 6.0 mmol) was added and the stirring continued for 30 h at the same temperature, whereupon the reaction was quenched with 3 mL of methanol. After rotary evaporation of the solvent, the crude mixture was applied directly to a silica gel column and eluted first with dichloromethane, then 1:1 hexane/ethyl acetate mixture and finally isopropanol with 5% triethylamine until the bright-yellow catalyst was eluted (55 mg, 65% recovery). The *(R)*-enantiomer of the N-acylated product was isolated with 74.4% ee (438 mg, *ca.* 98% pure, 57% yield); the *(S)*-enantiomer of the starting material was recovered with 97.9% ee (234 mg, *ca.* 98% pure, 42% yield). According to Kagan's equation, the reaction proceeded to 56.8% conversion with 29.8 selectivity factor (*cf.* Table 5.3.2-2, entry 2).

Table 5.3.2-1: KR of β-lactams: Optimization study

Entry[g]	catalyst	solvent	temp, °C	time, h	ee_{PR} %	ee_{SM} %	C_{HPLC} %	s
1	*(R)*-BTM	$CDCl_3$	23	24	ND	ND	0[a]	ND
2	*(S)*-HBTM	$CDCl_3$	23	48	ND	ND	~10[a]	ND
3	*(R)*-Cl-PIQ	$CDCl_3$	23	24	75.2	36.4	33	10
4[b]	*(R)*-Cl-PIQ	$CDCl_3$	23	4.0	1.88	0	35[a]	1.0
5[c]	*(R)*-Cl-PIQ	$CDCl_3$	23	10	22.6	12.2	35	1.8
6	*(R)*-Cl-PIQ	CD_2Cl_2	23	24	64.7	17.4	21	5.5
7	*(R)*-Cl-PIQ	THF	23	24	68.9	19.7	22	6.6
8[d]	*(R)*-Cl-PIQ	$EtMe_2COH$	23	10	78.4	65.3	45	16
9[d]	*(R)*-Cl-PIQ	$EtMe_2COH$	0	24	80.8	73.1	47	20
10[e]	*(R)*-Cl-PIQ	$EtMe_2COH$	0	48	85.6	42.7	33	19
11[f]	*(R)*-Cl-PIQ	$EtMe_2COH$	0	24	86.2	46.3	35	21
12[d]	*(R)*-Cl-PIQ	$HC{\equiv}CMe_2COH$	23	10	80.3	55.9	41	16

See Optimization Study Procedure: 0.1 M (±)-**III-1**, 0.1 M $(i\text{-PrCO})_2O$, 0.1 M $i\text{-Pr}_2NEt$, 0.01 M (10 mol%) catalyst, unless specified otherwise. [a]) Conversion was determined by ^1H NMR. [b]) $(MeCO)_2O$ was used instead of $(i\text{-PrCO})_2O$. [c]) $(EtCO)_2O$ was used instead of $(i\text{-PrCO})_2O$. [d]) 0.05 M (±)-**III-1** and 0.005 M (10 mol%) *(R)*-Cl-PIQ was used. [e]) 0.05 M (±)-**III-1** and 0.0025 M (5 mol%) *(R)*-Cl-PIQ were used. [f]) 0.05 M (±)-**III-1**, 0.05 M $(i\text{-PrCO})_2O$, 0.05 M $i\text{-Pr}_2NEt$, and 0.005 M (10 mol%) *(R)*-Cl-PIQ, were used. [g]) Results based on single runs.

Table 5.3.2-2: KR of β-lactams: Substrate scope

entry	substrate	time	#	ee_{PR} %	ee_{SM} %	C_{HPLC} %	s	C_{AVG} %	s_{AVG}
1	**III-1**	24	1	84.1	62.0	42.4	21.8	43	22
			2	83.5	63.4	43.1	21.3		
2	**III-3**	30	1	78.5	94.6	54.6	29.7	54	30
			2	80.4	93.2	53.6	31.2		
3	**III-4**	30	1	89.8	69.0	43.4	38.5	42	38
			2	90.1	63.1	41.2	36.8		
4	**III-5**	30	1	46.0	8.62	15.8	2.94	14	3.1
			2	50.0	7.28	12.7	3.22		
5[b]	**III-6**	72	1	83.1	54.2	39.6	18.5	41	19
			2	82.8	59.9	42.0	19.4		
6	**III-7**	30	1	85.9	97.3	53.1	56.0	53	54
			2	84.7	97.5	53.5	52.3		
7	**III-8**	30	1	65.3	94.7	59.2	16.7	59	17
			2	65.0	94.9	59.4	16.6		
8[b]	**III-9**	72	1	81.2	47.2	36.8	15.3	38	16
			2	82.2	51.7	38.6	17.0		

9[b,d]		72	1	79.6	25.6	24.3	11.3	26	13
			2	82.4	31.2	27.5	14.1		
	III-10								
			1	78.8	54.4	40.9	14.4		
10		30						42	14
			2	77.5	57.9	42.8	14.1		
	III-11								
			1	ND	ND	0[e]	ND		
11[c]		24						0[e]	ND
			2	ND	ND	0[e]	ND		
	III-12								

See General Procedure: 0.05 M racemic substrate, 0.1 M (i-PrCO)$_2$O, 0.1 M i-Pr$_2$NEt, 0.01 M (10 mol%) *(R)*-Cl-PIQ, *tert*-amyl alcohol, 0 °C, unless specified otherwise. The data reported are averages of duplicate runs. [a]) Absolute configuration of the fast reacting enantiomer is shown.[b]) 0.2 M (4 equiv) of (i-PrCO)$_2$O and i-Pr$_2$NEt were used. [c]) reaction performed in $CDCl_3$ at rt. [d]) Absolute stereochemistry notation is inverted in this case according to CIP nomenclature rules. [e]) determined by ^{1}H NMR.

5.3.3 Characterization data and HPLC properties

Note: *Absolute configuration was established on the basis of prior literature reports in the case of substrates **III-1** and **III-11**. In all other cases, it was assigned by analogy.*

Previously reported.[4] **^{1}H NMR** (400 MHz, CDCl3) δ 2.85 (dd, J_1= 15.0 Hz, J_2= 0.9 Hz, 1H), 3.42 (ddd, J_1= 15.0 Hz, J_2= 5.1 Hz, J_3= 1.8 Hz, 1H), 4.71 (dd, J_1 = 5.1 Hz, J_2= 2.3 Hz, 1H), 6.59 (bs, 1H), 7.10-7.60 (m, 5H); **HPLC** (CHIRALCEL AD-H, isopropanol/hexane 1:50, 0.8 mL/min): 35.8 min (minor), 39.4 min (major).

Previously reported.[5] **HPLC** (CHIRALCEL AD-H, isopropanol/hexane 1:50, 1 mL/min): 18.3 min; 26.4 min.

White solid. **mp.** 82-83 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.41-7.29(m, 5H), 5.02 (dd, J_1 = 6.6 Hz, J_2 = 3.3 Hz, 1H), 3.49 (dd, J_1 = 16.2 Hz, J_2 = 6.3 Hz, 1H), 2.96 (dd, J_1 = 16.5 Hz, J_2 = 3.3 Hz, 1H), 2.82-2.74 (m, 2H), 1.16 (t, J = 7.2Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ. 171.8, 165.4, 138.1, 129.2, 128.7, 126.1, 52.4, 45.6, 30.4, 8.1; **IR** (KBr, cm^{-1}) 3032, 2980, 1787, 1704, 1374, 1282, 698; **MS**: HR-ESI calculated for $[C_{12}H_{13}NO_2+H]^+$: 204.1019, found: 204.1028. **HPLC** (CHIRALCEL AD-H, isopropanol/hexane 1:50, 1 mL/min): 15.6 min (minor), 20.3 min (major).

White solid; **mp**: 95-97 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 5.02 (dd, J_1 = 9.9 Hz, J_2 = 3.3 Hz, 1H), 3.53 (dd, J_1=16.5, J_2= 6.6 Hz, 1H), 3.41 (septet, J = 6.9 Hz, 1H), 2.97 (dd, J_1= 16.2 Hz, J_2= 3.3 Hz, 1H), 1.25 (d, J=7.1 Hz, 3H), 1.17 (d, J=7.1Hz, 3H); **^{13}C NMR** (75 MHz, CDCl3): δ 175.1, 165.1, 138.3, 129.2, 128.6, 125.9, 52.2, 45.5, 35.1, 19.1, 17.8; . **IR** (KBr, cm^{-1}): 2973, 1775, 1697, 1285, 1253; **MS**: HR-ESI calculated for $[(C_{13}H_{15}NO_2)+H]^+$: 218.1176, found: 218.1175. **HPLC** (CHIRALCEL AD-H, isopropanol/hexane 1:50, 0.8 mL/min): 11.3 min (minor), 13.4 min (major).

Previously reported.[6] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26-7.36 (m, 4H), 6.30 (s, br, 1H), 4.70-4.72 (dd, J_1= 2.4 Hz; J_2= 5.2 Hz, 1H), 3.45 (1H, ddd, J_1= 14.9 Hz, J_2= 5.3 Hz, J_3 = 2.6 Hz, 1H), 2.84 (dd, J_1= 14.9 Hz, J_2 = 1.8 Hz, 1H); **HPLC:** Converted into its corresponding N-isobutyryl derivative and analyzed as described below.

White solid; **mp**: 80-81 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.34 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.7 Hz, 2H), 4.98 (dd, J_1 = 6.6 Hz, J_2 = 3.3 Hz, 1H), 3.49 (dd, J_1 = 16.5 Hz, J_2 = 6.3 Hz, 1H), 3.30-3.21 (m, 1H), 2.91 (dd, J_1 = 16.5 Hz, J_2 = 3.3 Hz, 1H), 1.22 (d, J = 6.9 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ. 175.2, 164.7, 136.8, 134.5, 129.4, 127.4, 51.6, 45.4, 35.2, 19.1, 17.7; **IR** (KBr, cm^{-1}) 2975, 1788, 1703, 1277, 1089; **MS**: HR-ESI calculated for $[C_{13}H_{14}ClNO_2+H]^+$: 252.0786, found: 252.0788; **HPLC** (CHIRALCEL AD-H, isopropanol/hexane 1:50, 1.0 mL/min): 11.5min (minor), 20.9 min (major).

Previously reported.[7] **^{1}H NMR** (200 MHz CDCl3): δ 7.28 (m, 2H), 6.89 (m, 2H), 6.29 (bs, 1H), 4.67 (dd, J_1= 5.3 Hz, J_2= 2.6 Hz, 1H), 3.40 (ddd, J_1= 14.9 Hz, J_2= 5.3 Hz, J_3= 2.4 Hz, 1H), 2.83 (ddd, J_1= 14.9 Hz, J_2= 2.6 Hz,

J_3= 0.8 Hz, 1H); **HPLC:** Converted into its corresponding N-isobutyryl derivative and analyzed as described below.

Colorless oil.**^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.24 (d, *J* = 9.0 Hz, 2H), 6.89 (m, *J* = 8.7 Hz 2H), 4.96 (dd, J_1 = 6.6 Hz, J_2 = 3.3 Hz, 1H), 3.80 (s, 3H), 3.45 (dd, J_1 = 16.5 Hz, J_2 = 6.3 Hz, 1H), 3.30-3.20 (m, 1H), 2.93 (dd, J_1 = 16.5 Hz, J_2 = 3.3 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.2, 165.3, 159.9, 130.2, 127.3, 114.6, 55.5, 51.9, 45.4, 35.1, 19.1, 17.8; **IR** (KBr, cm^{-1}) 2972, 1783, 1700, 1515, 1279, 1248; **MS**: HR-ESI calculated for $[C_{14}H_{17}NO_3+H]$: 248.1281, found: 248.1285; **HPLC** (CHIRALCEL AD-H, isopropanol/hexane 1:50, 1.0 mL/min): 18.7min (minor), 23.0 min (major).

Previously reported.[6] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26-7.47 (m, 4H), 6.33 (s, br, 1H), 5.06 (dd, J_1= 5.4 Hz, J_2= 2.6 Hz, 1H), 3.52-3.58 (ddd, J_1= 8.3 Hz, J_2= 5.4 Hz, J_3= 2.9 Hz, 1H), 2.83 (dd, J_1= 14.9 Hz, J_2 = 2.6 Hz, 1H); **HPLC** (CHIRALCEL AD-H, isopropanol/hexane 1/20, 1 mL/min): 15.7 min (minor), 20.5 min (major).

Yellowish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.40-7.36 (m, 1H), 7.28-7.23 (m, 2H), 7.15-7.10 (m, 1H), 5.35 (dd, J_1 = 6.3 Hz, J_2 = 3.6 Hz, 1H), 3.60 (dd, J_1 = 16.2 Hz, J_2 = 6.3 Hz, 1H), 3.39-3.29 (m, 1H), 2.85 (dd, J_1 = 16.5 Hz, J_2 = 3.3 Hz, 1H), 1.32 (d, *J* = 6.9 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.4, 164.7, 135.6, 132.6, 130.1, 129.4, 127.4, 125.9, 50.2, 44.9, 35.2, 19.4, 17.7; **IR** (KBr, cm^{-1}) 2974, 1790, 1704, 1273, 755; **MS**: HR-ESI calculated for $[C_{13}H_{14}ClNO_2+H]^+$: 252.0786, found: 252.0789; **HPLC** (CHIRALCEL AD-H, IPA:Hexane 1:50, 1 mL/min): 10.7 min (major), 12.7 min (minor).

Previously reported without characterization.[8] White solid, **mp**: 153-155 °C. **^{1}H NMR** (300 MHz, DMSO): δ 8.62 (br, 1H), 7.95-7.84 (m, 3H), 7.59-7.49 (m, 4H), 5.29 (dd, J_1 = 4.8 Hz, J_2 = 2.4 Hz, 1H), 3.63 (ddd, J_1 = 14.4 Hz, J_2 = 4.8 Hz, J_3 = 2.4 Hz, 1H), 2.58 (dd, J_1 = 14.4 Hz, J_2 = 2.4 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO): δ 167.6, 137.9, 133.8, 130.4, 129.3, 128.3, 127.1, 126.7, 126.1, 123.7, 122.3, 47.5, 47.2; **IR** (KBr, cm^{-1}) 3246, 1753, 800, 777; **MS**: HR-ESI calculated for $[C_{13}H_{11}NO+H]$: 198.0913, found: 198.0913; **HPLC** (CHIRALCEL OD-H, isopropanol/hexane 1:4, 1.0 mL/min): 14.6 min (minor), 26.0 min (major).

White solid, **mp**: 110-112 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.92-7.80 (m, 3H), 7.58-7.43 (m, 3H), 7.25 (d, J = 6.9 Hz, 1H), 5.75 (dd, J_1 = 6.6 Hz, J_2 = 3.6 Hz, 1H), 3.73 (dd, J_1 = 16.2 Hz, J_2 = 6.6 Hz, 1H), 3.47-3.39 (m, 1H), 2.89 (dd, J_1 = 16.2 Hz, J_2 = 3.6 Hz, 1H), 1.41 (d, J = 6.9 Hz, 3H) 1.24 (d, J = 6.9 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.6, 165.0, 134.0, 133.5, 130.2, 129.4, 128.7, 126.8, 126.2, 125.6, 122.5, 121.5, 50.1, 45.7, 35.4, 19.6, 17.7; **IR** (KBr, cm^{-1}) 3052, 2973, 1785, 1701, 1275, 776; **MS**: HR-ESI calculated for [$C_{17}H_{17}NO_2$+H]: 268.1332, found: 268.1338; **HPLC** (CHIRALCEL AD-H, isopropanol/hexane 1:20, 1.0 mL/min): 12.4 min (major), 16.4 min (minor).

White crystals; **mp**: 154-155 °C. **^{1}H NMR** (300 MHz, DMSO): δ 8.50 (br, 1H), 7.94-7.87 (m, 4H), 7.54-7.47 (m, 3H), 4.80 (dd, J_1 = 5.4 Hz, J_2 = 2.4 Hz, 1H), 3.42 (ddd, J_1 = 14.7 Hz, J_2 = 5.4 Hz, J_3 = 2.4 Hz, 1H), 2.58 (dd, J_1 = 14.7 Hz, J_2 = 1.8 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO): δ 167.8, 139.8, 133.5, 133.2, 129.0, 128.4, 128.3, 127.1, 126.7, 125.0, 124.5, 49.5, 47.8; **IR** (KBr, cm^{-1}) 3247, 3053, 2955, 1742, 1357, 1181, 821; **MS**: HR-ESI calculated for [$C_{13}H_{11}NO$+H]: 198.0913, found: 198.0924; **HPLC:** Converted into its corresponding N-isobutyryl derivative and analyzed as described below.

White solid; **mp**: 112-113 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.88-7.78 (m, 4H), 7.52-7.46 (m, 2H), 7.39 (dd, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 1H), 5.18 (dd, J_1 = 6.3 Hz, J_2 = 3.3 Hz, 1H), 3.55 (dd, J_1 = 16.5 Hz, J_2 = 6.3 Hz, 1H), 3.61-3.27 (m, 1H), 3.04 (dd, J_1 = 16.5 Hz, J_2 = 3.3 Hz, 1H), 1.26 (d, J = 6.9 Hz, 3H) 1.18 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.2, 165.1, 135.5, 133.5, 133.5, 129.3, 128.2, 128.0, 126.8, 126.6, 125.7, 122.9, 52.4, 45.5, 35.2, 19.1, 17.8; **IR** (KBr, cm^{-1}) 3054, 2973, 1786, 1702, 1386, 1280, 747; **MS**: HR-ESI calculated for [$C_{17}H_{17}NO_2$+H]: 268.1332, found: 268.1334; **HPLC** (CHIRALCEL AD-H, isopropanol/hexane 1:20, 1.0 mL/min): 9.4 min (minor), 14.3 min (major).

Yellow solid; **mp**: 72-74 °C. **^{1}H NMR** (300 MHz, DMSO): δ 8.50 (br, 1H), 7.47 (dd, J_1 = 5.4 Hz, J_2 = 1.2 Hz, 1H), 7.09 (d, J = 3.3 Hz, 1H), 6.99 (dd, J_1 = 4.8 Hz, J_2 = 3.6 Hz, 1H), 4.90 (dd, J_1 = 5.4 Hz, J_2 = 2.4 Hz, 1H), 3.36 (ddd, J_1 = 14.7 Hz, J_2 = 5.1 Hz, J_3 = 2.1 Hz, 1H), 2.76 (dd, J_1 = 14.7 Hz, J_2 = 1.8 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO): δ 167.6, 146.6, 127.8, 125.9, 125.6, 46.7, 45.5;

MS: HR-ESI calculated for $[C_7H_7NOS+H]^+$: 154.0321, found: 154.0322; **HPLC** (CHIRALCEL OD-H, isopropanol/hexane 1:10, 1.0 mL/min): 15.3 min (minor); 16.8 min (major).

Colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.27 (dd, J_1 = 5.4 Hz, J_2 = 1.5 Hz, 1H), 7.11 (m, 1H), 6.98 (dd, J_1 = 5.4 Hz, J_2 = 3.6 Hz, 1H), 5.29 (dd, J_1 = 6.6 Hz, J_2 = 3.3 Hz, 1H), 3.53 (dd, J_1 = 16.5 Hz, J_2 = 6.3 Hz, 1H), 3.26-3.17(m, 1H), 3.13 (dd, J_1 = 16.5 Hz, J_2 = 3.3 Hz, 1H), 1.20 (d, J = 6.9 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.1, 164.5, 141.4, 127.3, 126.5, 125.7, 48.2, 45.8, 35.2, 19.1, 17.7; **IR** (KBr, cm^{-1}) 2974, 1788, 1702, 1276, 704; **MS**: HR-ESI calculated for $[C_{11}H_{13}NO_2S+H]^+$: 224.074, found: 224.0745; **HPLC** (CHIRALCEL AD-H, isopropanol/hexane 1:100, 1.0 mL/min): 15.1 min (minor), 18.2 min (major).

Previously reported.[2] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.30 (s, 5H), 7.0 (s, br, 1H), 4.25 (d, J = 2.0 Hz, 1H), 2.95 (dt, J_1= 7.0 Hz, J_2 = 2.0 Hz, lH), 0.8-2.1 (m, 9H); **HPLC** (CHIRALCEL AD-H, IPA:Hexane 1:50, 1.0 mL/min): 20.2 min (minor); 23.3 min (major).

Colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.39-7.24 (m, 5H), 4.65 (d, J = 3.3 Hz, 1H), 3.33-3.24 (m, 1H), 3.09-3.03 (m, 1H), 1.96-1.73 (m, 2H), 1.50-1.27 (m, 4H) 1.24 (d, J = 6.9 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.2, 168.3, 138.1, 128.9, 128.2, 125.5, 59.0, 58.9, 35.0, 29.1, 28.4, 22.4, 18.9, 17.5, 13.8; **IR** (KBr, cm^{-1}) 2931, 1784, 1704, 1273, 696; **MS**: HR-ESI calculated for $[C_{17}H_{23}NO_2+H]^+$: 274.1802, found: 274.1805; **HPLC** (CHIRALCEL AD-H, isopropanol/hexane 1:50, 1.0 mL/min): 6.1 min (minor), 7.1 min (major).

Previously reported.[9] **^{1}H NMR** (270 MHz, CDCl3): δ 7.84 (m, 3H), 7.72 (s, 1H), 7.47-7.53 (m, 2H), 7.31-7.34 (m, 1H), 6.36 (br s,1H), 4.66 (s, 1H), 1.53 (s, 3H), 0.79 (s, 3H); **HPLC** (CHIRALCEL AD-H, isopropanol/ hexane 1:50, 1 mL/min): 35.0 min (major), 39.8 min (minor) (stereochemical notation inverted according to CIP nomenclature rules).

White solid; **mp**: 101-102 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.86-7.78 (m, 3H), 7.55 (s, 1H), 7.52-7.44 (m, 2H), 7.20 (dd, J_1 = 5.4 Hz, J_2 = 1.5 Hz, 1H), 4.96 (s, 1H), 3.45-3.36 (m, 1H), 1.55 (s, 3H), 1.39 (d, J

= 6.9 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.84 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.9, 171.9, 133.4, 133.3, 133.0, 128.7, 128.1, 128.0, 126.7, 126.4, 125.1, 123.8, 64.8, 55.1, 35.5, 23.4, 19.6, 18.2, 17.8; **IR** (KBr, cm^{-1}) 2971, 1785, 1705, 1386, 1280; **MS**: HR-ESI calculated for $[C_{19}H_{21}NO_2+H]$: 296.1645, found: 296.1647; **HPLC** (CHIRALCEL AD-H, isopropanol/hexane 1:50, 1 mL/min): 12.5 min (minor), 18.7 min (major) *(stereochemical notation inverted according to CIP nomenclature rules).*

Previously reported.[10] **^{1}H NMR** (400 MHz, $CDCl_3$): δ)7.21–7.34 (m, 4H), 6.23 (br s, 1H), 5.03 (d, *J*= 4.2 Hz, 1H), 4.03 (d, *J*= 10.5 Hz, 1H), 3.35 (d, *J*= 17.3 Hz, 1H), 3.07 (dd, J_1= 17.5 Hz, J_2= 10.5 Hz, 1H); **HPLC** (CHIRALCEL OD-H, IPA:Hexane 1:20, 1.0 mL/min): 19.0 min (minor), 29.1min (major).

Colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.2 Hz, 1H), 7.35-7.22 (m, 3H), 5.43 (d, *J* = 5.1 Hz, 1H), 4.04-3.97 (m, 1H), 3.41-3.03 (m, 3H), 1.17 (d, *J* = 6.9 Hz, 3H) 1.03 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.2, 168.0, 143.7, 138.7, 129.7, 128.2, 127.5, 125.9, 60.7, 51.5, 34.9, 31.0, 18.7, 18.1; **IR** (KBr, cm^{-1}) 2974, 1784, 1698, 1293, 761; **MS**: HR-ESI calculated for $[C_{14}H_{15}NO_2+H]^+$: 230.1176, found: 230.1179; **HPLC** (CHIRALCEL AD-H, isopropanol/hexane 1:100, 1.0 mL/min): 8.1 min (major); 10.0 min (minor).

5.3.4 References

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5.4 KR OF N-ACYL-THIOLACTAMS VIA ENANTIOSELECTIVE DE-ACYLATION USING AMIDINE-BASED CATALYSTS

5.4.1 General

See Chapter IV for substrate notation/numbering. Racemic thazolidine-2-thiones and oxazolidine-2-thiones were prepared according to previously described procedures. [1,2] Their N-acylated derivatives were prepared via DMAP-catalyzed acylation with anhydrides as previously reported.[3]

5.4.2 Kinetic Resolution experiments

5.4.2.1 Optimization studies

General procedure. To a solution of a racemic substrate (0.05 mmol) in 0.2 mL of $CDCl_3$ was added 0.2 mL of a stock solution of 0.025 M (*R*)-BTM (0.005 mmol) and 0.025 M benzoic acid (0.005 mmol) in $CDCl_3$ followed by 0.1 mL of a stock solution of 0.375 M methanol (0.0375 mmol) in $CDCl_3$. The reaction mixture was stirred magnetically at rt. Its progress was checked periodically by withdrawing aliquots, diluting them with $CDCl_3$ and analyzing by ^1H NMR. Upon reaching approximately 50% conversion, the reaction mixture was directly loaded on column and purified by flash chromatography (CH_2Cl_2, then CH_2Cl_2/EtOAc). Enantiomeric enrichment of the deacylated product and the unreacted starting material was determined by chiral stationary phase HPLC (for HPLC conditions, see Characterization and HPLC Properties, 5.3.3). Each experiment in Section 5.4.2 was performed at least in duplicate.

Table 5.4.2.1-1: KR of N-acyl thiolactams (±)-**IV-2** using BTM: Optimization study[a]

entry	Catalyst	R	time, d	#	ee_{PR} %	ee_{SM} %	C_{HPLC} %	s	C_{AVG} %	s_{AVG}
1[b]	none	*i*-Pr	7	-	ND	ND	ND	ND	<10[k]	ND
2[c]	BTM	*i*-Pr	4	1	76.56	90.98	54.30	23.42	55	26
				2	76.00	96.48	55.94	28.90		
3	*(R)*-BTM + $PhCO_2H$	*i*-Pr	1	1	93.28	84.67	47.58	77.58	47	78
				2	93.24	85.16	47.74	77.94		
				3	93.62	82.08	46.72	77.63		
				4	93.78	82.74	46.87	80.75		
4[d]	*(R)*-BTM + $PhCO_2H$	*i*-Pr	1	1	93.08	89.56	48.77	84.98	49	81
				2	92.80	87.44	48.51	77.02		

5[e]	*(R)*-BTM + $PhCO_2H$	*i*-Pr	1	1	91.62	94.34	50.73	82.40	50	84
				2	95.54	92.06	49.87	85.03		
6	*(R)*-BTM + $PhCO_2H$	Et	1	1	67.30	91.70	57.67	16.02	57	15
				2	67.58	88.02	56.57	14.59		
7	*(R)*-BTM + $PhCO_2H$	Ph	7	-	ND	ND	ND	ND	<10[k]	ND
8[f]	*(R)*-Cl-PIQ + $PhCO_2H$	*i*-Pr	7	1	63.86	36.26	36.22	6.42	37	6.7
				2	65.28	40.98	38.57	7.06		
9[g]	*(S)*-HBTM + $PhCO_2H$	*i*-Pr	3	1	61.56	53.40	46.45	7.06	47	7.0
				2	60.86	54.12	47.07	6.95		
10[h]	*(R)*-BTM + $PhCO_2H$	*i*-Pr	1	1	86.50	82.56	48.83	35.43	49	41
				2	89.12	83.90	48.49	45.94		
11[i]	*(R)*-BTM + $PhCO_2H$	*i*-Pr	1	1	93.04	85.82	47.98	76.75	47	86
				2	94.84	81.22	46.13	95.09		
12[j]	*(R)*-BTM + $PhCO_2H$	*i*-Pr	2	1	30.28	22.10	42.19	2.29	42	3.9
				2	57.64	40.24	41.11	5.46		

[a]) See General Procedure, unless otherwise specified. [b]) To 0.05 mmol **IV-2** in 0.4 mL $CDCl_3$, 0.1 mL stock solution of 0.375 M methanol in $CDCl_3$ was added. [c]) To 0.05 mmol **IV-2** in 0.2 mL $CDCl_3$, was added 0.2 mL of a stock solution of 0.025 M (*R*)-BTM (0.005 mmol) in $CDCl_3$, followed by 0.1 mL of a stock solution of 0.375 M methanol (0.0375 mmol) in $CDCl_3$.[d]) 0.0375 mmol $PhCH_2OH$ was used instead of methanol. [e]) 0.75 equiv $(1\text{-Naphthyl})_2CHOH$ was used instead of methanol. [f]) 10 mol% of *(R)*-Cl-PIQ was used instead of *(R)*-BTM. [g]) 10 mol% *(S)*-HBTM was used instead of *(R)*-BTM. [h]) $CD_2Cl_2$was used instead of $CDCl_3$. [i]) Toluene was used instead of $CDCl_3$. [j]) Diethyl ether was used instead of $CDCl_3$. [k]) Estimated by ^1H NMR.

Table 5.4.2.1-2: Deacylation of N-isobutyryl-thiazolidine-2-thiones: Substrate scope[a]

entry	R^1	time	#	ee_{PR} %	ee_{SM} %	C_{HPLC} %	s	C_{AVG} %	s_{AVG}
1	*p*-$MeOC_6H_4$	1 d	1	93.96	88.40	48.48	94.91	49	90
			2	93.08	89.50	49.02	84.83		
2	*o*-$MeOC_6H_4$	1 d	1	95.56	83.98	46.78	117.31	47	108
			2	94.82	83.42	46.80	108.12		
			3	94.74	83.76	46.92	98.08		
3	*p*-ClC_6H_4	16 hrs	1	75.28	91.42	54.84	22.31	54	23
			2	78.26	88.74	53.14	23.96		
4	*o*-ClC_6H_4	22 hrs	1	85.90	85.50	49.88	35.95	50	36
			2	86.10	85.68	49.88	36.66		
5	2-naphthyl	2 d	1	73.82	99.08	57.30	34.08	57	37
			2	75.92	99.30	56.67	39.52		
6	1-naphthyl	5 d	1	86.32	76.62	47.02	31.41	48	30
			2	84.62	79.78	48.53	29.17		
7	2-thienyl	1.5 d	1	87.52	72.70	45.38	32.64	45	32
			2	87.38	69.60	44.34	30.85		
8	*trans*-PhCH=CH	1 d	1	88.28	76.84	46.54	37.25	47	37
			2	88.22	77.88	46.89	37.69		
9	CO_2Me	15 hrs	1	74.56	71.17	48.84	14.43	49	15
			2	74.84	75.08	50.08	15.48		
10	*i*-Pr	7 d	1	ND	ND	0	ND	0	ND
			2	ND	ND	0	ND		
11	$PhCH_2$	7 d	1	14.92	6.02	28.75	1.43	27	1.4
			2	15.92	5.26	24.83	1.45		

12	7	1	29.68	15.02	33.60	2.12	33	2.3
		2	34.04	16.90	33.18	2.38		

[a]) See General Procedure.

Table 5.4.2.1-3: Deacylation of N-isobutyryl-oxazolidine-2-thiones: Substrate scope[a]

entry	**R[1]**	**time**	**#**	**ee**$_{PR}$ %	**ee**$_{SM}$ %	**C**$_{HPLC}$ %	**s**	**C**$_{AVG}$ %	**s**$_{AVG}$
1	Ph	2 d	1	94.18	53.20	36.10	56.85	36	57
			2	94.18	52.12	35.63	56.17		
2	*p*-$MeOC_6H_4$	4 d	1	91.46	83.38	47.69	58.74	47	59
			2	91.62	82.10	47.26	58.41		
3	*o*-$MeOC_6H_4$	6 d	1	93.70	34.92	27.15	43.26	30	38
			2	90.76	45.02	33.16	32.17		
4	*p*-ClC_6H_4	3 d	1	67.54	86.08	56.03	13.92	57	13
			2	61.62	86.84	58.49	11.44		
5	*o*-ClC_6H_4	3 d	1	88.94	63.12	41.51	32.64	43	32
			2	87.14	70.34	44.67	30.55		
6	CO_2Me	4 d	1	33.10	35.60	51.82	2.75	53	2.6
			2	28.66	35.30	55.19	2.47		
7	CO_2Me	1 d	1	68.38	31.76	31.72	7.23	29	7.9
			2	71.90	34.26	32.27	8.51		

3	72.72	26.12	26.43	8.15
4	71.84	22.80	24.09	7.61

[a]) See General Procedure.

5.4.2.2 Enantioselective N-acylation of thiolactam (±)-IV-15

The previously published standard procedure was followed.[4] Racemic thiazolidinethione **IV-15** (10.4 mg, 0.050 mmol) was dissolved almost completely in 0.4 mL of $CDCl_3$ with gentle heating. The solution was allowed to cool to ambient temperature and stirred magnetically. A 0.1 mL stock solution of 0.375M N,N-Diisopropylethylamine, 0.05 M (0.005 mmol, 10 mol%) of the specified catalyst was added, followed by isobutyric anhydride (6 μL, 5.6 mg, 0.0375 mmol). After stirring for several minutes, the solution became hazy. After the specified period of time, the reaction mixture was diluted with a small amount of methylene chloride, applied directly to a silica gel column, eluted, and analyzed as described above. The results are summarized in Table 4S below.

Table 5.4.2.2-1: Enantioselective N-acylation of thiolactam **(±)-IV-15**

entry	**catalyst**	**time**	**#**	**ee_{PR}** %	**ee_{SM}** %	**C_{HPLC}** %	**s**	**C_{AVG}** %	**s_{AVG}**
1	*(R)*-BTM	2 h	1	53.16	19.46	26.80	3.94	26	3.8
			2	50.68	17.00	25.12	3.60		

2	*(R)*-Cl-PIQ	24 h	1	19.96	1.62	7.51	1.52	12	1.6
			2	21.20	4.20	16.54	1.60		

5.4.2.3 Enantioselective N-acylation of thiolactam (±)-IV-22.

Racemic oxazolidinethione **IV-22** (8.1 mg, 0.050 mmol) was dissolved in 0.3 mL of $CDCl_3$. The solution was stirred magnetically and treated sequentially with a 0.1 mL of stock solution of 0.25 M N,N-diisopropylethylamine (0.025 mmol) and 0.02 M *(R)*-BTM (0.002 mmol, 4 mol%), and 0.1 mL stock solution of 0.25 M isobutyric anhydride (0.025 mmol). After the specified period of time, an aliquot of the reaction mixture was diluted with 1:1 hexane/methylene chloride and injected directly into HPLC (ODH, hexane/isopropanol 85:15, 1mL/min). The results are summarized in Table 5S below.

Table 5.4.2.3-1: Enantioselective N-acylation of thiolactam (±)-**IV-22** over time

entry	**time**	**#**	**ee_{PR}** %	**ee_{SM}** %	**C_{HPLC}** %	**s**	**C_{AVG}** %	**s_{AVG}**
1	0.5 h	1	74.68	81.84	52.29	17.22	50	16
		2	76.22	68.18	47.22	14.98		
2	1 h	1	62.30	57.24	47.88	7.54	48	7.2
		2	60.28	54.24	47.36	6.83		
3	3 h	1	39.42	46.52	54.13	3.54	54	4.1
		2	47.56	53.72	53.04	4.68		
4	8 h	1	33.12	35.74	51.90	2.75	50	2.7

		2	33.16	31.30	48.56	2.65		
5	48 h	-	-2.98	3.80	56.05	1.10	-	-

5.4.2.4 N-Acyl exchange experiments

Five vials were each charged with partially enantioenriched samples of *(R)*-**IV-21** (0.037 mmol, 82.06 % *ee*), *(S)*-**IV-22** (0.037 mmol, 77.72 % *ee*) and 0.27 mL $CDCl_3$. Vial # 1 was charged with an additional 0.1 mL $CDCl_3$ and left as a blank, Vial #2 was treated with 0.1 mL 0.037 M solution of *(R)*-BTM (0.92 mg, 0.0037mmol, 10 mol%) in $CDCl_3$, Vial #3 with 0.1 mL 0.037M solution of *(R)*-BTM (0.92 mg, 0.0037 mmol, 10 mol%) and benzoic acid (0.46 mg, 0.0037 mmol, 10 mol%) in $CDCl_3$,Vial #4 with 0.1 mL 0.185 M solution of N,N-diisopropylethylamine (3.21 μL, 0.0185 mmol, 0.5 equiv) in $CDCl_3$, and Vial #5 with 0.1 mL 0.037M solution of isobutyric acid (0.34 μL, 0.0037 mmol, 10 mol%) in $CDCl_3$. All vials were left stirring at rt for 24 h and analyzed by injecting directly into HPLC (OD-H, 85:15 hexane/isopropanol). The results are listed in Table 6S below.

Table 5.4.2.4-1: Acyl exchange experiment

entry	**additive**	*(R)*-**IV-21** %ee	*(S)*-**IV-22** %ee
1	none	81.32	76.90
2	10 mol% *(R)*-BTM **2**	17.94	13.58
3	10 mol% *(R)*-BTM + BzOH	19.56	10.60

4	50 mol% *i*-Pr_2NEt	81.16	74.44
5	10 mol% *i*-$PrCO_2H$	81.64	75.31

5.4.3 Characterization and HPLC properties

Note: *Melting points and spectral data were determined using racemic samples. Signs of optical rotation are reported only in those cases when >0.01° absolute rotation was recorded. The HPLC data refer to samples obtained in kinetic resolutions using (R)-BTM.*

Previously reported.[2] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.60 (br s, 1H), 7.50–7.40 (m, 5H), 5.35–5.25 (m, 1H), 3.85 (dd, J_1 = 11.2 Hz, J_2 = 8.0 Hz, 1H), 3.51 (dd, J_1 = 11.2 Hz, J_2 = 8.3 Hz, 1H).

Previously reported.[2] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.40–7.30 (m, 5H), 6.24 (dd, J_1=8.2 Hz, J_2=1.6 Hz, 1H), 3.93 (dd, J_1=11.3 Hz, J_2=8.2 Hz. 1H), 3.38 (dq, J_1=18.1 Hz, J_2=7.3 Hz, 1H), 3.20 (dq, J_1=18.1 Hz, J_2=7.3 Hz, 1H), 3.07 (dd, J_1=11.3 Hz, J_2=1.6 Hz, 1H), 1.13 (t, *J*=7.3 Hz, 3H); **HPLC** (OD-H, hexane/isopropanol 95:5): 25.8 min (major); 27.8 min (minor).

Previously reported.[4] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.41-7.26 (m, 5H), 6.15 (dd, *J1* = 8.1 Hz, *J2* = 2.4 Hz, 1H), 4.52-4.43 (m, 1H), 3.88 (m, 1H), 3.09 (dd, *J1* = 8.4 Hz, *J2* = 2.4 Hz, 1H), 1.21-1.12 (m, 6H).

Yellow solid; **mp**: 159-161 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.77 (d, 2H, *J*= 8.2 Hz), 7.54-7.35 (m, 8H), 5.94 (app. t, *J*= 7.9, 2H), 3.84 (dd, J_1=11.4 Hz, J_2=7.3 Hz, 2H), 3.56 (dd, J_1=11.4 Hz, J_2=8.2 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 202.1, 171.3, 137.8, 133.8, 133.0, 129.7, 129.1, 128.8, 128.4, 126.3, 71.7, 38.1; **IR** (KBr, cm^{-1}): 3061, 3031, 1699, 1598, 1494, 1449, 1366, 1335, 1316, 1288, 1268; **MS**: HR-ESI calculated for $[(C_{16}H_{13}NOS_2)+H]^+$: 300.0503, found: 300.0511.

White solid; **mp:** 115-118 ºC; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.87 (s, broad, 1H), 7.29 (d, *J*= 8.8 Hz, 2H), 6.92 (d, *J*= 8.5 Hz, 2H), 5.27 (app. t, *J*= 8.2 Hz, 1H), 3.79 (s, 3H), 3.78 (dd, J_1= 11.1 Hz; J_2= 7.9 Hz, 1H), 3.47 (dd, J_1= 11.1 Hz, J_2= 8.5 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 160.2, 129.7, 127.6, 114.6, 67.1, 55.4, 41.6; **IR** (KBr, cm^{-1}): 3136, 3001, 2956, 2934, 2835, 1611, 1586, 1514, 1478, 1303, 1250; **MS**: HR-ESI calculated for $[(C_{10}H_{11}NOS_2)+H]^+$: 226.0355, found: 226.0357; **HPLC** (OD-H, hexane/isopropanol 4:1): 16.2 min (minor); 25.1 min (major); (+) sign of rotation.

Yellow crystals; **mp:** 109-111 ºC; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.26 (d, *J*= 8.8 Hz, 2H), 6.87 (d, *J*= 8.5 Hz, 2H), 6.08 (dd, J_1= 7.9 Hz, J_2=2 .6 Hz, 1H), 4.42 (m, 1H), 3.83 (dd, J_1= 11.1 Hz, J_2= 7.9 Hz, 1H), 3.80 (s, 3H), 3.06 (dd, J_1= 11.4 Hz, J_2= 2.9 Hz, 1H), 1.15 (d, *J*= 6.7 Hz, 3H), 1.09 (d, *J*= 6.7 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 201.9, 179.0, 159.6, 131.2, 129.9, 114.3, 70.1, 55.3, 36.7, 34.3, 19.3, 19.2; **IR** (KBr, cm^{-1}): 2967, 2929, 1699, 1611, 1513, 1464, 1314, 1303, 1250; **MS**: HR-ESI calculated for $[(C_{14}H_{17}NO_2S_2)+H]^+$: 296.0773, found: 296.0768; **HPLC** (OD-H, hexane/isopropanol 9:1): 10.5 min (minor); 13.9 min (major); (−) sign of rotation.

Off-white solid; **mp**: 142-145 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.64 (s, broad, 1H), 7.31 (m, 2H), 6.96 (m, 2H), 5.65 (app. t, *J*= 7.6 Hz, 1H), 3.93 (dd, J_1= 11.1 Hz; J_2= 8.1 Hz, 1 H), 3.84 (s, 3H), 3.46 (dd, J_1= 11.1 Hz, J_2= 7.6 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 201.8, 156.1, 129.9, 126.0, 120.9, 110.7, 61.7, 55.5, 39.8; **IR** (KBr, cm^{-1}): 3133 (br), 2937, 1601, 1491, 1461, 1289, 1245; **MS**: HR-ESI calculated for $[(C_{10}H_{11}NOS_2)+H]^+$: 226.0355, found: 226.0343; **HPLC** (AD-H, hexane/isopropanol 9:1): 9.6 min (minor); 12.9 (major); (+) sign of rotation.

Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.29 (m, 1H), 7.10 (d, *J*= 7.0 Hz, 1H), 6.93 (m, 2H), 6.44 (app. d, *J*= 7.9 Hz, 1H), 4.51 (m, 1H), 3.81 (s, 3H), 3.80 (dd, J_1= 11.1 Hz, J_2= 7.9 Hz, 1H), 3.05 (dd, J_1= 11.1 Hz, J_2= 1.5 Hz, 1H), 1.20 (distereotpic doublets, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 203.3, 178.6, 155.6, 129.4, 126.5, 125.1, 120.6, 110.8, 66.0, 55.5, 35.7, 33.9, 19.6, 19.1; **IR** (KBr, cm^{-1}): 3425 (br), 2969, 2918, 1702, 1492, 1462; **MS**: HR-ESI calculated for $[(C_{14}H_{17}NO_2S_2)+H]^+$: 296.0773, found: 296.0771; **HPLC** (OD-H, hexane/isopropanol 9:1): 6.6 min (major); 7.7 min (minor); (−) sign of rotation.

White solid; **mp:** 127-130 ºC; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.13 (s, broad, 1H), 7.33 (m, 4H), 5.29 (app. t, J= 7.9 Hz, 1H), 3.85 (dd, J_1= 11.1 Hz, J_2= 8.2 Hz, 1H), 3.43 (dd, J_1= 11.1 Hz, J_2= 8.2 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 201.5, 136.5, 135.0, 129.5, 127.6, 66.7, 41.4; **IR** (KBr, cm^{-1}): 3134 (br), 2940, 1491, 1411, 1288, 1263; **MS**: HR-ESI calculated for $[(C_9H_8ClNS_2)+H]^+$: 229.9859, found: 229.9861; **HPLC** (OD-H, hexane/isopropanol 4:1): 12.9 min (minor); 22.8 min (major); (+) sign of rotation.

Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36-7.25 (m, 4H), 6.11 (dd, J_1=7.9 Hz, J_2=1.8 Hz, 1H), 4.45 (m, J= 6.7 Hz, 1H), 3.88 (dd, J_1= 11.1 Hz, J_2= 3.9 Hz, 1H), 3.04 (dd, J_1= 11.4 Hz, J_2= 2.3 Hz, 1H), 1.17 (d, J= 6.7 Hz, 3H), 1.13 (d, J= 6.7 Hz Hz, 3H); **^{13}C NMR** (75 MHz, CDCl3): δ 202.7, 178.5, 136.1, 131.5, 130.3, 129.5, 127.3, 125.7, 67.8, 35.2, 33.9, 19.6, 18.9. **IR** (KBr, cm^{-1}): 3281 (br), 2974, 2933, 2870, 1701, 1492, 1466, 1348, 1309, 1257, 1230; **MS**: HR-ESI calculated for $[(C_{13}H_{14}ClNOS_2)+H]^+$: 300.0278, found: 300.0280; **HPLC** (OD-H, hexane/isopropanol 95:5): 15.47 min (minor); 17.01 min (major); (−) sign of rotation.

White solid; **mp**:144-147 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.40 (s, broad, 1H), 7.69 (m, 1H), 7.45-7.23 (m, 3H), 5.68 (dd, J_1= 8.5 Hz, J_2= 5.9 Hz, 1H), 4.04 (dd, J_1= 11.4 Hz, J_2= 8.5 Hz, 1H), 3.35 (dd, J_1= 11.4 Hz, J_2= 6.2 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 202.4, 135.6, 131.9, 130.2, 130.1, 127.7, 126.9, 63.6, 40.1; **IR** (KBr, cm^{-1}): 3359, 3143, 3058, 2937, 1613, 1474, 1436, 1296, 1262; **MS**: HR-ESI calculated for $[(C_9H_8ClNS_2)+H]^+$: 229.9859, found: 229.9850; **HPLC** (OD-H, hexane/isopropanol 4:1): 9.4 min (minor); 18.9 min (major); (+) sign of rotation.

Yellow solid; **mp**: 67-70 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35 (m, 1H), 7.22-7.15 (m, 3H), 6.40 (dd, J_1= 8.2 Hz, J_2= 1.5 Hz, 1H), 4.44 (m, 1H), 3.85 (dd, J_1= 11.4 Hz, J_2= 8.2 Hz, 1H), 3.00 (dd, J_1= 11.4 Hz, J_2= 1.5 Hz, 1H), 1.14 (distereotopic doublets, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 201.6, 178.9, 137.7, 134.3, 129.2, 126.9, 69.7, 36.3, 34.1, 19.4, 19.1; **IR** (KBr, cm^{-1}): 3380, 3288, 3064, 2974, 2933, 2871, 1704, 1593, 1574, 1467, 1443, 1382, 1352, 1307, 1229; **MS**: HR-ESI calculated for $[(C_{13}H_{14}ClNOS_2)+H]^+$: 300.0278, found: 300.0273; **HPLC** (AD-H, hexane/isopropanol 100:1, 0.8 mL/min): 7.3 min (major); 9.0 min (minor); (−) sign of rotation.

White solid; **mp**: 196-197 °C (dec); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.85 (m, 3H), 7.50 (m, 4H), 7.28 (s, broad, 1H), 6.03 (app. t, *J*= 7.7 Hz, 1H), 4.07 (dd, J_1= 11.1 Hz, J_2= 8.4 Hz, 1H), 3.53 (dd, J_1= 11.1 Hz, J_2= 6.8 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 202.3, 134.2, 133.2, 129.7, 129.5, 127.2, 126.3, 125.5, 123.5, 121.8, 63.8, 40.8; **IR** (KBr, cm^{-1}): 3134 (br), 2922, 2852, 2357, 2339, 1470, 1301, 1260; **MS**: HR-ESI calculated for $[(C_{13}H_{11}NS_2)+H]^+$: 246.0406, found: 246.0395; **HPLC** (AD-H, hexane/isopropanol 95:5): 21.8 min (minor); 28.1 min (major), (+) sign of rotation.

Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.93-7.81 (m, 3H), 7.61-7.43 (m, 3H), 7.26 (m, 1H), 6.53 (dd, J_1= 8.8 Hz, J_2= 3.5 Hz, 1H), 4.94 (app. t, *J*= 8.8 Hz, 1H), 4.73 (m,1H), 4.39 (dd, J_1= 8.8 Hz, J_2= 3.5 Hz, 1H), 1.24 (distereotopic doublets, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 185.7, 178.0, 134.2, 133.8, 129.6, 129.4, 129.2, 127.0, 126.2, 125.5, 121.8, 58.9, 32.9, 19.4, 18.9; **IR** (KBr, cm^{-1}): 3453 (br), 2971, 2919, 2340, 2358, 1703, 1366, 1318; **MS**: HR-ESI calculated for $[(C_{17}H_{17}NOS_2)+H]^+$: 316.0817, found: 316.0824; **HPLC** (OD-H, hexane/isopropanol 9:1,): 19.5 min (minor); 27.2 min (major); (−) sign of rotation.

White solid; **mp**: −(dec); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.88 (m, 4H), 7.56-7.47 (m, 3H), 7.45 (s, broad, 1H), 5.48 (app. t, *J*= 8.2 Hz, 1H), 3.92 (dd, J_1= 11.1 Hz, J_2= 7.9 Hz, 1H), 3.61 (dd, J_1= 11.4 Hz, J_2= 8.5 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ201.9, 135.2, 133.5, 133.2, 129.6, 128.1, 127.9, 127.0, 126.9, 125.6, 123.3, 67.5, 41.6, 29.7; **IR** (KBr, cm^{-1}): 3440 (br), 2919, 2850, 1659 (br); **MS**: HR-ESI calculated for $[(C_{13}H_{11}NS_2)+H]^+$: 246.0406, found: 246.0393; **HPLC** (OD-H, hexane/isopropanol 4:1): 34.2 min (minor); 39.2 min (major); (+) sign of rotation.

Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.83 (m, 3H), 7.47 (m, 2H), 6.31 (dd, J_1= 8.2 Hz, J_2= 2.3 Hz, 1H), 4.52 (m, 1H), 3.92 (dd, J_1= 11.1 Hz, J_2= 8.5 Hz, 1H), 3.17 (dd, J_1= 11.1 Hz, J_2= 2.0 Hz, 1H), 1.19 (d, *J*= 6.7 Hz, 3H), 1.14 (d, *J*= 6.7 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 201.9, 178.9, 136.5, 133.1, 129.1, 128.2, 127.7, 126.6, 126.5, 124.7, 123.3, 70.6, 36.4,

34.2, 19.3, 19.2; **IR** (KBr, cm^{-1}): 3455 (br), 2967, 2341, 1698, 1334; **MS**: HR-ESI calculated for $[(C_{17}H_{17}NOS_2)+H]^+$: 316.0824, found: 316.0818; **HPLC** (AD-H, hexane/isopropanol 100:1): 14.6 min (minor); 24.0 min (major); (−) sign of rotation.

White solid; **mp**: 140-144 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.34 (d, *J*=5.0 Hz, 1H), 7.12 (d, *J*= 2.9 Hz, 1H), 7.01 (m, 1H), 5.58 (app. t, *J*= 7.9 Hz, 1H), 3.87 (dd, J_1= 11.1 Hz, J_2= 7.6 Hz, 1H), 3.62 (dd, J_1= 11.1 Hz, J_2= 8.2 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ200.9, 140.3, 127.3, 126.5, 126.2, 62.7, 41.8 ; **IR** (KBr, cm^{-1}): 3444 (br), 2085 (br), 1636, 1484; **MS**: HR-ESI calculated for $[(C_7H_7NS_3)+H]^+$: 201.9811, found: 201.9813. **HPLC:** (OD-H, hexane/isopropanol 4:1): 13.4 min (minor); 18.6 min (major); (+) sign of rotation.

Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25 (d, *J*= 6.2 Hz, 1H), 7.16 (d, *J*= 3.5 Hz, 1H), 6.96 (m, 1H), 6.51 (dd, J_1= 7.5 Hz, J_2= 1.3 Hz, 1H), 4.40 (m, 1H), 3.88 (dd, J_1= 11.4 Hz, J_2= 7.5 Hz, 1H), 3.24 (dd, J_1= 11.4 Hz, J_2= 1.8 Hz, 1H), 1.18 (d, *J*= 7.0 Hz, 3H), 1.12 (d, *J*= 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 200.4, 178.6, 140.7, 126.6, 126.4, 125.4, 65.9, 36.4, 33.9, 19.3, 19.1; **IR** (KBr, cm^{-1}): 3455 (br), 2970, 2917, 2341, 1697, 1329, 1299; **MS**: HR-ESI calculated for $[(C_{11}H_{13}NOS_3)+H]^+$: 272.0232, found: 272.0230; **HPLC** (OD-H, hexane/isopropanol 9:1): 13.2 min; (major); 14.3 min (minor); (−) sign of rotation.

White solid; **mp**: 154-157 °C; **^{1}H NMR** (300 MHz, $CDCl_3$□□ δ 7.42 (m, 5H), 6.69 (d, *J*= 15.8 Hz, 1H), 6.25 (dd, J_1= 15.5 Hz, J_2=7.9 Hz, 1H), 4.94 (app.q, *J*= 7.9 Hz, 1H), 3.72 (dd, J_1= 11.1 Hz, J_2= 7.9 Hz, 1H), 3.43 (dd, J_1= 11.1 Hz, J_2= 7.9 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ201.4, 134.5, 133.7, 130.2, 128.8, 128.7, 128.5, 126.8, 124.3, 66.0, 39.3; **IR** (KBr, cm^{-1}): 3105, 2672, 2565, 1686, 1492, 1454, 1427, 1326, 12923072; **MS**: HR-ESI calculated for $[(C_{11}H_{11}NS_2)+H]^+$: 222.0402, found: 222.0406; **HPLC** (OD-H, hexane/isopropanol 4:1): 20.1 min (major); 30.6 min (minor); (+)sign of rotation.

Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ7.41 -7.24 (m, 5H), 6.71 (d, *J*=15.8 Hz, 1H), 6.37 (dd, J_1= 15.8 Hz, J_2= 7.3 Hz, 1H), 5.81 (app t, *J*= 8.2 Hz, 1H), 4.44 (m, 1H), 3.72 (dd, J_1= 11.4 Hz, J_2= 7.6 Hz, 1H), 3.03 (dd, J_1= 11.4 Hz, J_2= 1.8 Hz, 1H), 1.20 (distereotopic doublets, 6H); **^{13}C NMR** (75

MHz, $CDCl_3$): δ 200.9, 178.9, 135.6, 134.0, 128.7, 128.4, 126.8, 123.7, 68.9, 347.6, 34.0, 19.4, 19.2; **IR** (KBr, cm^{-1}): 3285 (br), 2973, 2932, 1698, 1494, 1466, 1448, 1392, 1327, 1313, 1250; **MS**: HR-ESI calculated for $[(C_{15}H_{17}NOS_2)+H]^+$: 292.0824, found: 292.0819; **HPLC** (OD-H, hexane/isopropanol 9:1): 10.8 min (minor); 17.5 min (major); (−) sign of rotation.

Previously reported.[5] **^{1}H NMR** (90 MHz, $CDCl_3$): δ 7.8-8.3 (br, 1H), 4.85 (app. t, *J* = 7.5 Hz, 1H), 3.90 (s, 3 H), 3.85 (d, 2 H, *J* = 7.5 Hz, 2H); **HPLC** (OD-H, hexane/isopropanol 4:1): 14.6 min (minor); 17.6 min (major).

Yellow solid; **mp**: 97-100 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.60 (m, 1H), 4.46 (m, 1H), 3.78 (s, 3H), 3.65 (m, 1H), 3.34 (m, 1H), 1.18 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 200.0, 179.1, 168.9, 67.7, 53.3, 33.8, 30.8, 19.2, 18.9; **IR** (KBr, cm^{-1}): 3439 (br), 2918, 1753, 1702, 1355, 1314; **MS**: HR-ESI calculated for $[(C_9H_{13}NO_3S_2)+H]^+$: 248.0415, found: 248.0411; **HPLC** (AD-H, hexane/isopropanol 99:1): 14.9 min (minor); 18.4 min (major); (−) sign of rotation.

Previously reported.[1] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.05 (br s, 1H), 4.11 (m, lH), 3.53(dd, J_1 =11.0 Hz, J_2 = 8.2 Hz, 1H), 3.32 (dd, J_1 =11.0 Hz, J_2 = 8.2 Hz, 1H), 2.01 (m, lH), 1.03 (d, *J* = 8.5 Hz, 3H), 1.00 (d, *J* = 7.2 Hz, 3H).

Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.14 (m (app. t), 1H), 4.49 (m, 1H), 3.48 (dd, J_1= 11.4 Hz, J_2= 7.9 Hz, 1H), 2.66 (dd, J_1= 11.4 Hz, J_2= 1.5 Hz, 1H), 2.33 (m, 1H), 1.23 (d, *J*= 6.7 Hz, 3H), 1.16 (d, *J*= 6.7 Hz, 3H), 1.05 (d, *J*= 6.7 Hz, 3H), 0.96 (d, *J*= 6.7 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 202.5, 178.8, 71.9, 33.3, 30.7, 30.3, 19.9, 19.2, 19.0, 17.7; **IR** (KBr, cm^{-1}): 3288, 3159, 2966, 2933, 2873, 1810, 1740, 1698, 1467, 1353, 1277, 1254; **MS**: HR-ESI calculated for $[(C_{10}H_{17}NOS_2)+H]^+$: 232.0824, found: 232.0827.

Previously reported.[2] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45 (br s, 1H), 7.40–7.26 (m, 3H), 7.23–7.17 (m, 2H), 4.52–4.40 (m, 1H), 3.60 (dd, J_1= 11.2 Hz, J_2= 7.7 Hz, 1H), 3.33 (dd, J_1= 11.2 Hz, J_2= 6.8 Hz, 1H), 3.03 (dd, J_1= 13.6 Hz, J_2= 7.6 Hz, 1H), 2.98 (dd, J_1= 13.6 Hz, J_2= 6.7 Hz, 1H): **HPLC** (OD-H, hexane/isopropanol 4:1): 11.5 min (major); 14.0 min (minor).

Yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.31 (m, 5H), 5.31 (m, 1H), 4.47 (m, 1H), 3.36 (dd, J_1= 7.3 Hz, J_2= 6.4 Hz, 1H), 3.22 (dd, J_1= 13.2 Hz, J_2= 3.8 Hz, 1H), 3.03 (dd, J_1= 12.9 Hz, J_2= 10.3 Hz, 1H), 2.87 (app. d, J= 12.3 Hz, 1H), 1.21 (distereotopic doublets, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 201.1, 179.0, 136.6, 129.5, 128.9, 127.2, 69.2, 36.8, 33.6, 31.9, 19.7, 19.1; **IR** (KBr, cm^{-1}): 3278 (br), 3146 (br), 3026, 2973, 2932, 2871, 1698, 1495, 1467, 1342, 1259; **MS**: HR-ESI calculated for $[(C_{14}H_{17}NOS_2)+H]^+$: 280.0824, found: 280.0827; **HPLC** (OD-H, hexane/isopropanol 95:5): 9.9 min (minor); 11.4 min (major).

Previously reported.[6] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.69-8.49 (bs, 1H), 7.34 (m, 4H), 5.61 (d, J = 8.3 Hz, 1H), 4.80 (ddd, J_1 = 8.3 Hz, J_2 = 7.6 Hz, J_3=3.3 Hz, 1H), 3.50 (dd, J_1 = 17.1 Hz, J_2=7.6 Hz, 1H), 3.28 (dd, J_1 = 17.1 Hz, J_2 = 3.3 Hz, 1H); **HPLC** (OD-H, hexane/isopropanol 4:1): 12.9 min (minor); 23.1 min (major).

Yellow solid; **mp**: 100-102 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.31 (m, 4H), 6.54 (d, J= 7.0 Hz, 2H), 4.54 (m, 2H), 3.38 (dd, J_1= 17.0 Hz, J_2= 6.4 Hz, 1H), 3.15 (app. d, J= 17.0 Hz, 1H), 1.26 (distereotopic doublets, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 200.9, 179.9, 139.2, 138.9, 129.4, 128.1, 125.9, 125.1, 76.2, 46.8, 36.4, 33.6, 19.5, 19.4; **IR** (KBr, cm^{-1}): 2972, 2932, 2870, 1695, 1460, 1382, 1346, 1250; **MS**: HR-ESI calculated for $[(C_{14}H_{15}NOS_2)+H]^+$: 278.0668, found: 278.0663; **HPLC** (AD-H, hexane/isopropanol 95:5): 6.5 min (major); 8.4 min (minor).

Previously reported.[1] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.30 (br s**,** 1H), 7.28-7.41 (m, 5H), 5.14 (dd, J_1 = 9.2 Hz, J_2 = 6.9 Hz, 1H), 4.98 (t, J = 9.0 Hz, 1H), 4.45 (dd, J_1 = 8.8 Hz, J_2 = 6.9 Hz, 1H); **HPLC** (OD-H, hexane/isopropanol 10:1): 30.0 min (minor); 52.0 min (major); (+) sign of rotation.

Previously reported.[4] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.41-7.25 (m, 5H), 5.69 (dd, J_1 = 9.0 Hz, J_2 =3.9 Hz, 1H), 4.78 (t, J = 9.0 Hz, 1H), 4.66-4.57 (m, 1H), 4.41 (dd, J_1 = 9.0 Hz, J_2 = 3.9 Hz, 1H), 1.17 (d, J = 6.9Hz, 3H), 1.12 (d, J = 6.9Hz, 3H); **HPLC** (OD-H, hexane/isopropanol 20:1): 16.1 min (major); 22.0 min (minor).

Yellow solid; **mp**: 94-97 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.53 (s, broad, 1H), 7.15 (d, *J*= 8.5 Hz, 2H), 6.83 (d, *J*= 8.8 Hz, 2H), 5.03 (dd, J_1= 9.0 Hz, J_2= 7.3 Hz, 1H), 4.86 (app. t, *J*= 9.1 Hz, 1H), 4.32 (dd, J_1= 8.8 Hz, J_2= 6.7 Hz, 1H), 3.72 (s, 3H); **^{13}CNMR** (75MHz, CDCl3): δ 189.4, 159.9, 129.9, 127.6, 114.6, 76.9, 59.7, 55.4; **IR** (KBr, cm^{-1}): 3272 (br), 2932, 2958, 1657, 1611, 1513, 1250; **MS**: HR-ESI calculated for $[(C_{10}H_{11}NO_2S)+H]^+$: 210.0579, found: 210.0583; **HPLC** (OD-H, hexane/isopropanol 4:1): 15.2 min (minor); 24.0 min (major); (+) sign of rotation.

White solid; **mp**: 100-103 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.20 (d, *J*=8.5 Hz, 2H), 6.87 (d, *J*=8.5 Hz, 2 H), 5.62 (dd, J_1= 8.5 Hz, J_2= 3.8 Hz, 1H), 4.73 (app. t, *J*= 8.8 Hz, 1H), 4.57 (m, 1H), 4.38 (dd, J_1= 9.1 Hz, J_2=4.1 Hz, 1H), 3.76 (s, 3H), 1.14 (d, *J*= 6.7 Hz, 3H), 1.07 (d, *J*= 6.7 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ185.2, 178.1, 159.8, 130.5, 127.5, 114.5, 73.8, 61.9, 55.3, 32.9, 19.1, 18.5; **IR** (KBr, cm^{-1}): 2973, 2934, 2873, 2836, 1706, 1612, 1586, 1515, 1466, 1365; **MS**: HR-ESI calculated for $[(C_{14}H_{17}NO_3S)+H]^+$: 280.0999, found: 280.1002; **HPLC** (OD-H, hexane/isopropanol 95:5): 23.9 min (minor); 27.1 min (major); (−) sign of rotation.

Colorless oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.44 (s, broad, 1H), 7.30 (m, 2H), 6.97 (m, 1H), 6.88 (d, *J*= 8.2 Hz, 1H), 5.38 (dd, J_1=9.4 Hz, J_2=6.7 Hz, 1H), 4.99 (dd, J_1= 9.4 Hz, J_2= 9.1 Hz, 1H), 4.43 (dd, J_1= 9.1 Hz, J_2= 6.7 Hz, 1H), 3.82 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 190.1, 156.3, 129.9, 126.1, 125.8, 120.9, 110.6, 76.6, 55.5, 55.4; **IR** (KBr, cm^{-1}): 3180 (br), 2965, 1590, 1493, 1462, 1246 ; **MS**: HR-ESI calculated for $[(C_{10}H_{11}NO_2S)+H]^+$: 210.0580, found: 210.0583; **HPLC** (AD-H, hexane/isopropanol 95:5): 19.0 min (minor); 31.1 min (major); (+) sign of rotation.

White solid; **mp**: 97-99 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.29 (m, 1H), 7.05 (m, 1H), 6.93 (m, 2H), 5.93 (dd, J_1= 9.1 Hz, J_2= 3.8 Hz, 1H), 4.70 (m, 2H), 4.33 (dd, J_1= 9.1 Hz, J_2= 4.4 Hz, 1H), 3.85 (s, 3H), 1.18 (distereotopic doublets, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 186.0, 178.0, 156.3, 129.8, 126.5, 126.0, 120.8, 110.9, 73.0, 58.6, 55.5, 32.7, 19.3, 18.6; **IR** (KBr, cm^{-1}): 3404 (br), 2970, 2920, 2849, 2341, 2360, 1704, 1603, 1493, 1464, 1336, 1297; **MS**: HR-ESI calculated for $[(C_{14}H_{17}NO_3S)+H]^+$: 280.0998, found: 280.1002; **HPLC** (OD-H, hexane/isopropanol 95:5): 13.9 min (major); 16.1 min (minor); (−) sign of rotation.

White powder; **mp**: 147-149 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.12 (s, broad, 1H), 7.39 (d, *J*= 8.5 Hz, 2H), 7.26 (d, *J*= 8.2 Hz, 2H), 5.12 (dd, J_1= 9.1 Hz, J_2= 6.7 Hz, 1H), 4.99 (app.t, *J*= 9.1 Hz, 1H), 4.43 (dd, J_1= 8.5 Hz, J_2= 6.7 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 189.9, 136.4, 135.2, 129.6, 127.6, 59.6; **IR** (KBr, cm^{-1}): 3190 (br), 1654, 1492, 1417, 1262; **MS**: HR-ESI calculated for $[(C_9H_8ClNOS)+H]^+$: 214.0085, found: 214.0088; **HPLC** (OD-H, hexane/isopropanol 4:1): 12.8 min (minor); 24.7 min (major); (+) sign of rotation.

Colorless oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35 (d, *J*=8.5 Hz, 2H), 7.23 (d, *J*= 8.5 Hz, 2H), 5.66 (dd, J_1= 8.8 Hz, J_2= 3.8 Hz, 1H), 4.78 (app. t, *J*= 8.8 Hz, 1H), 4.59 (m, 1H), 4.38 (dd, J_1= 8.5 Hz, J_2= 3.8 Hz, 1H), 1.18 (d, *J*= 6.7 Hz, 3H), 1.12 (d, *J*= 6.7 Hz, 3H); **^{13}C NMR** (75 MHz, CDCl3): δ 184.9, 178.1, 137.1, 134.8, 129.4, 127.4, 73.3, 61.7, 32.8, 19.1, 18.6; **IR** (KBr, cm^{-1}): 3411 (br), 2973, 2920, 1706, 1494, 1467, 1347, 1332, 1293; **MS**: HR-ESI calculated for $[(C_{13}H_{14}ClNO_2S)+H]^+$: 284.0503, found: 284.0507; **HPLC** (OD-H, hexane/isopropanol 9:1): 18.7 min (major); 23.7 min (minor); (−) sign of rotation.

White solid; **mp**: 95-97 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.63 (s, broad, 1H), 7.45-7.26 (m, 4H), 5.53 (m, 1H), 5.10 (app. t, *J*= 9.1 Hz, 1H), 4.42 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 190.3, 135.8, 131.9, 130.1, 130.0, 127.8, 126.4, 76.6, 57.2; **IR** (KBr, cm^{-1}): 3242 (br), 2923, 1654, 1596, 1507, 1475, 1438, 1260; **MS**: HR-ESI calculated for $[(C_9H_8ClNOS)+H]^+$: 214.0084, found: 214.0088; **HPLC** (AD-H, hexane/isopropanol 97:3): 25.4 min (minor); 28.9 min (major); (+) sign of rotation.

White solid; **mp**:124-126 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.42 (m, 1H), 7.28 (m, 2H), 7.09 (m, 1H), 6.09 (dd, J_1= 8.8 Hz, J_2= 3.5 Hz, 1H), 4.82 (app. t, *J*= 8.5 Hz, 1H), 4.67 (m, 1H), 4.35 (dd, J_1= 10.0 Hz, J_2= 4.1 Hz, 1H), 1.23 (distereotopic doublets, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 185.5, 177.9, 135.8, 131.9, 130.3, 129.8, 127.6, 125.4, 72.9, 59.6, 32.7, 19.2, 18.8; **IR** (KBr, cm^{-1}): 3530 (br), 2871, 2922, 2851, 1467, 1445, 1365, 1327, 1298; **MS**: HR-ESI calculated for $[(C_{13}H_{14}ClNO_2S)+H]^+$: 284.0506, found: 284.0507; **HPLC** (AD-H, hexane/isopropanol 100:1): 10.2 min (major); 15.2 min (minor); (−) sign of rotation.

Previously reported.[5] **^{1}H NMR** (90 MHz, $CDCl_3$): δ 8.98 (br, 1 H), 5.01 (m,

3 H); 3.96 (s, 3 H); **HPLC** (OD-H, hexane/isopropanol 7:3): 10.4 min (minor); 15.2 min (major).

Clear and colorless oil; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.16 (dd, J_1=9.4 Hz, J_2=4.4 Hz, 1H), 4.62 (m, 2H), 4.48 (dd, J_1= 9.4 Hz, J_2= 4.4 Hz, 1H), 3.79 (s, 3H), 1.25 (d, J= 6.7 Hz, 3H), 1.20 (d, J= 6.7 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 184.1, 178.5, 168.4, 68.4, 59.8, 53.3, 32.5, 18.9, 18.7; **IR** (KBr, cm^{-1}): 3490 (br), 2917, 1752, 1704, 1467, 1437, 1345, 1294; **MS**: HR-ESI calculated for $[(C_9H_{13}NO_4S)+H]^+$: 232.0638, found: 232.0636; **HPLC** (OD-H, hexane/isopropanol 4:1): 13.4 min (major); 19.6 min (minor); (−) sign of rotation.

5.4.5 References

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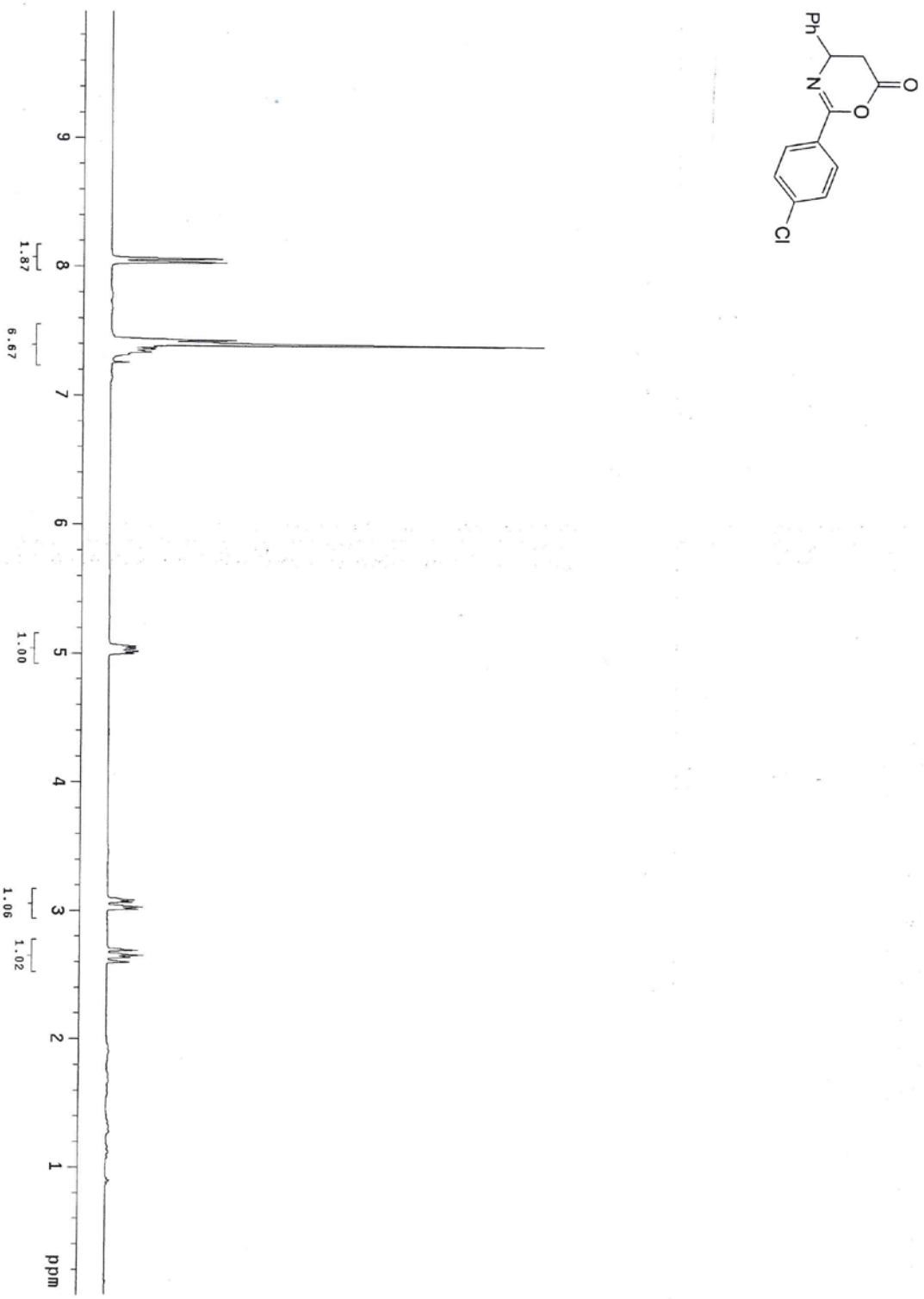
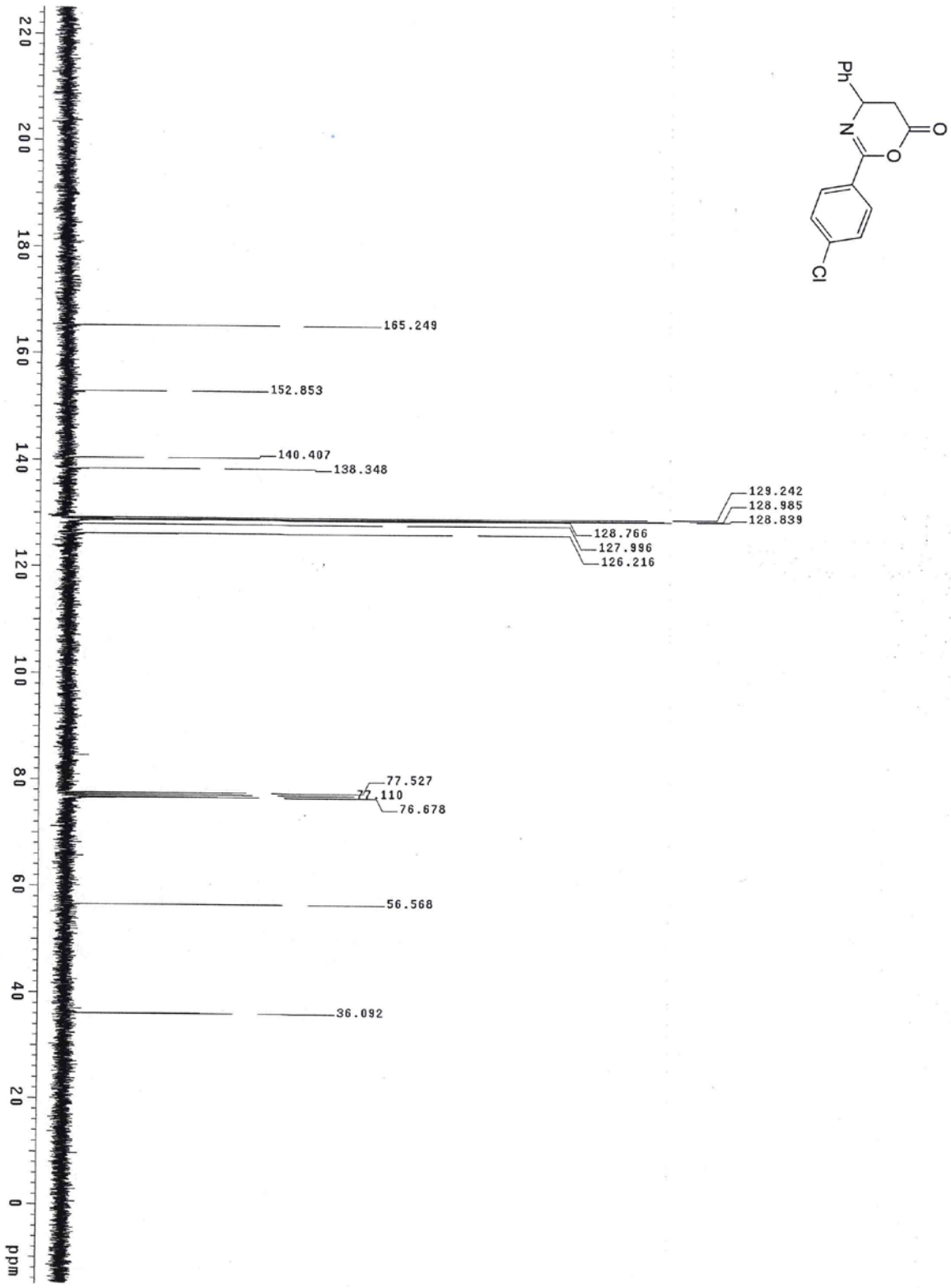
APPENDIX

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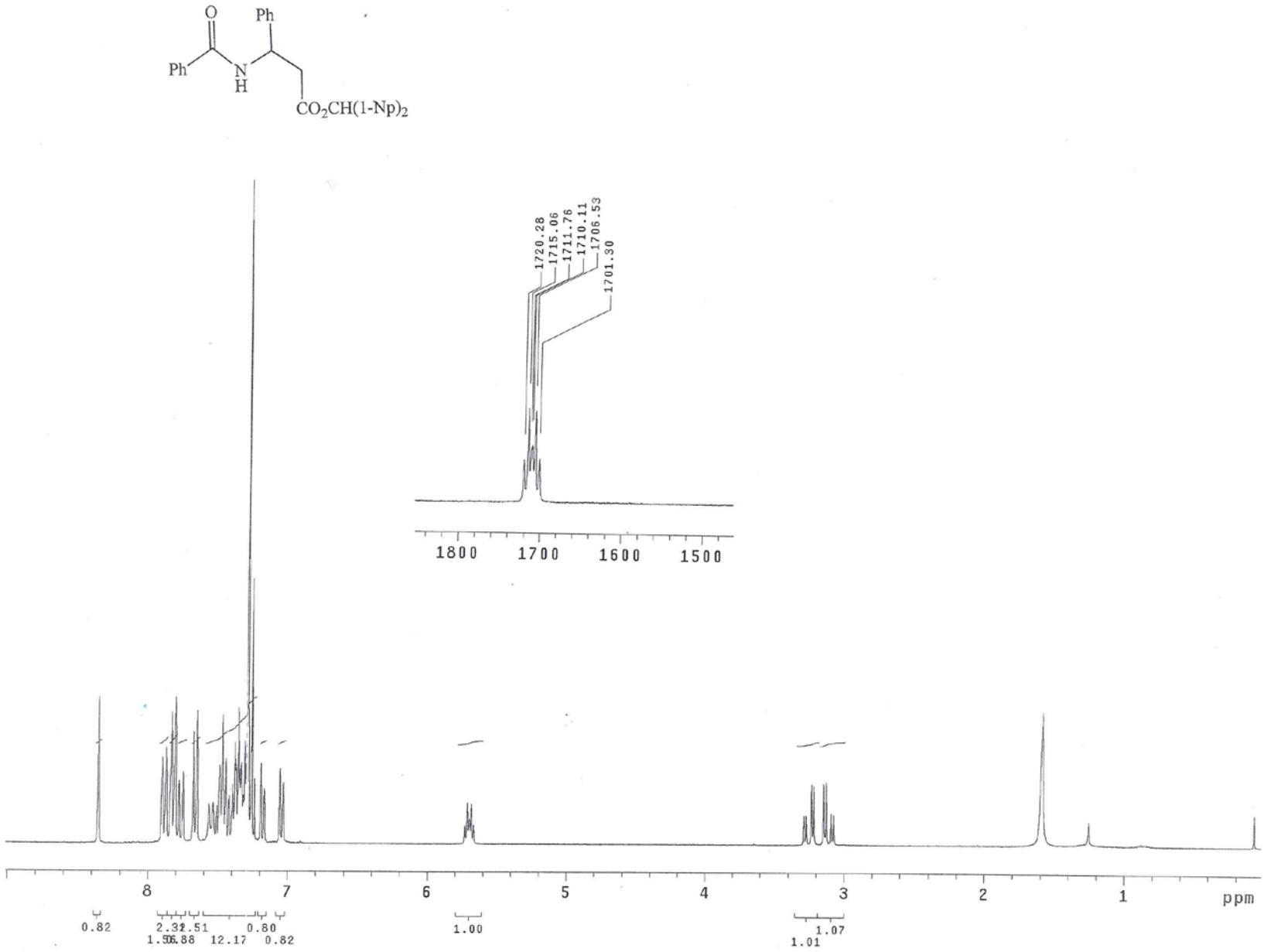
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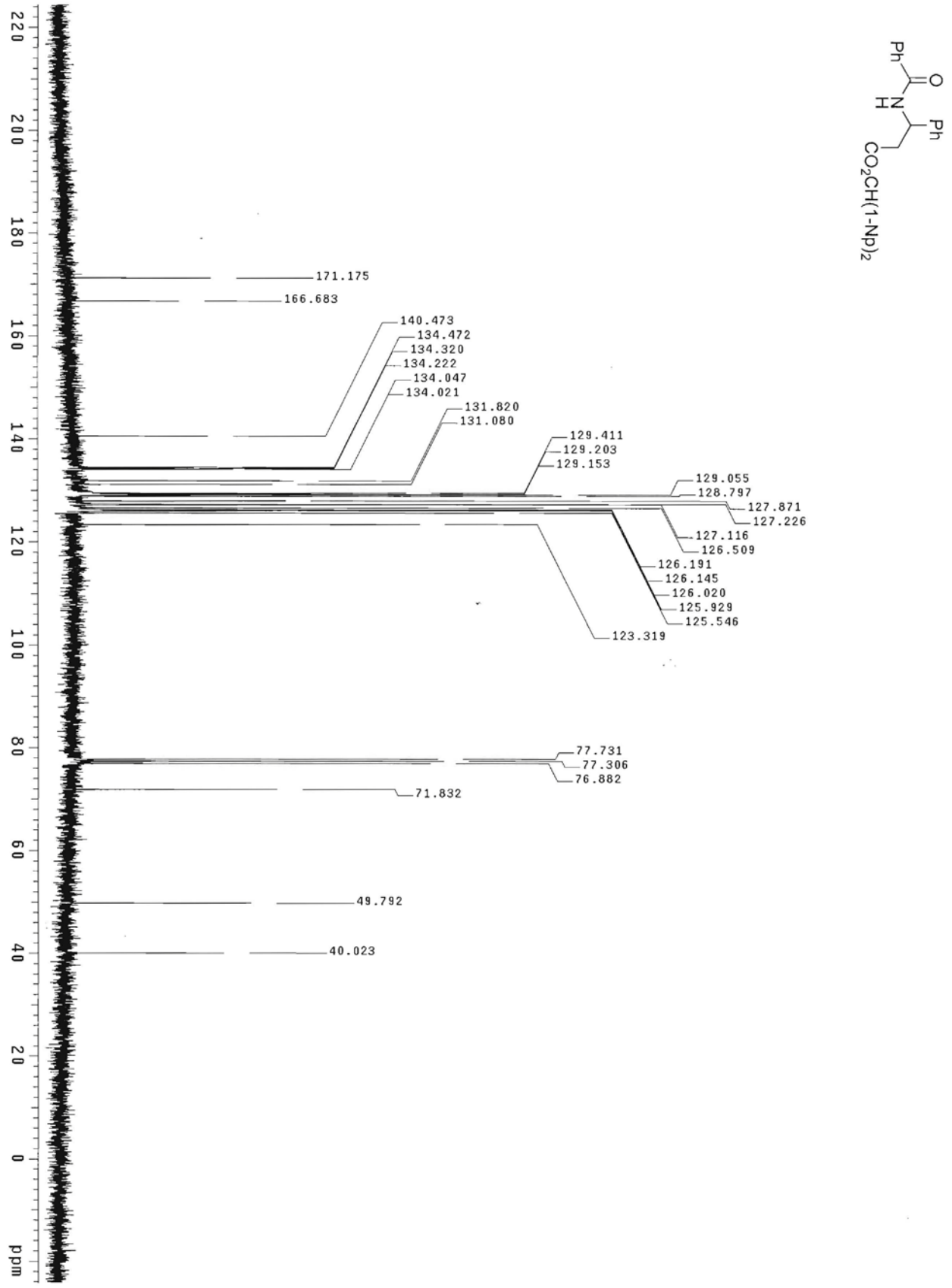
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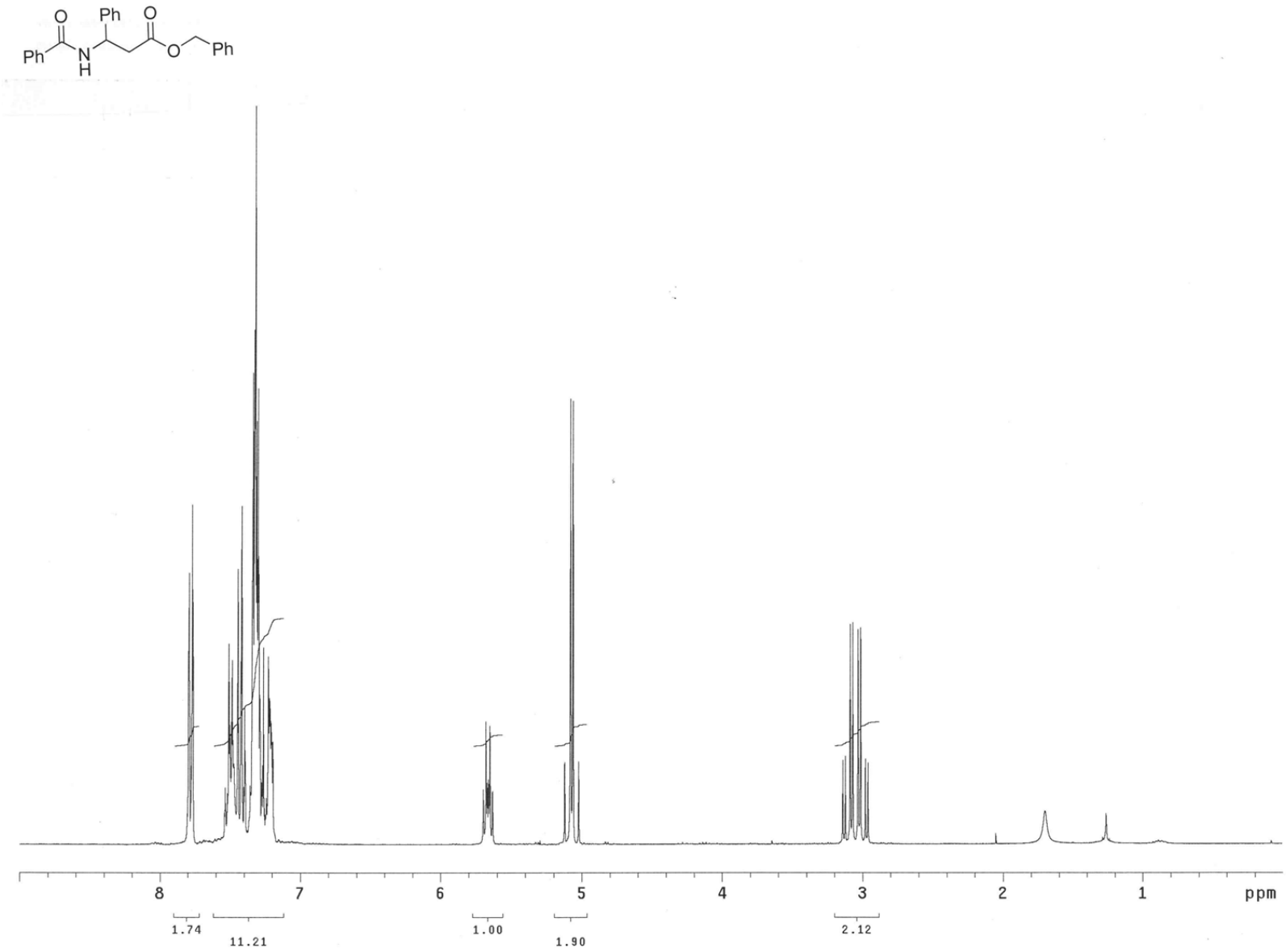
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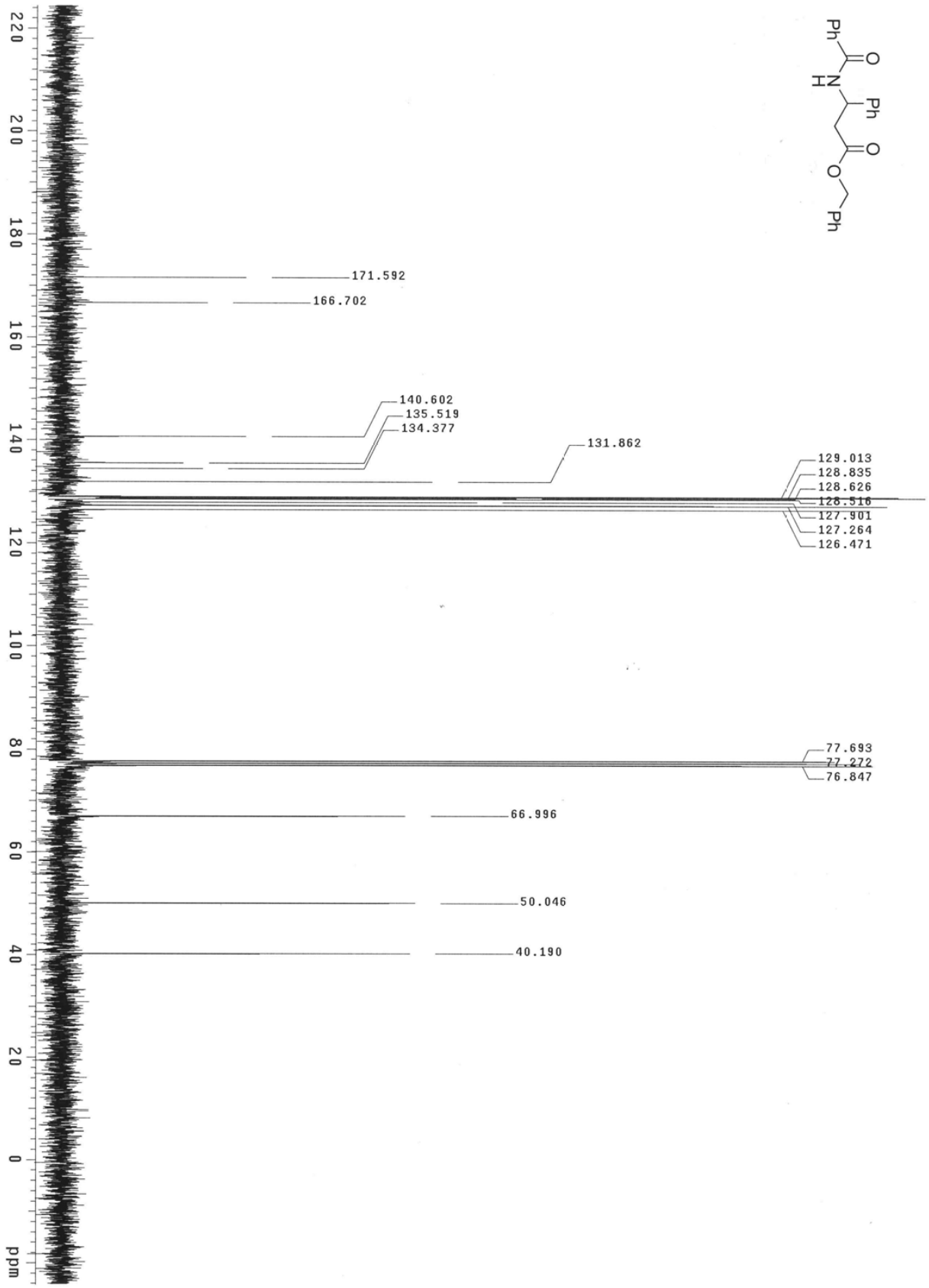
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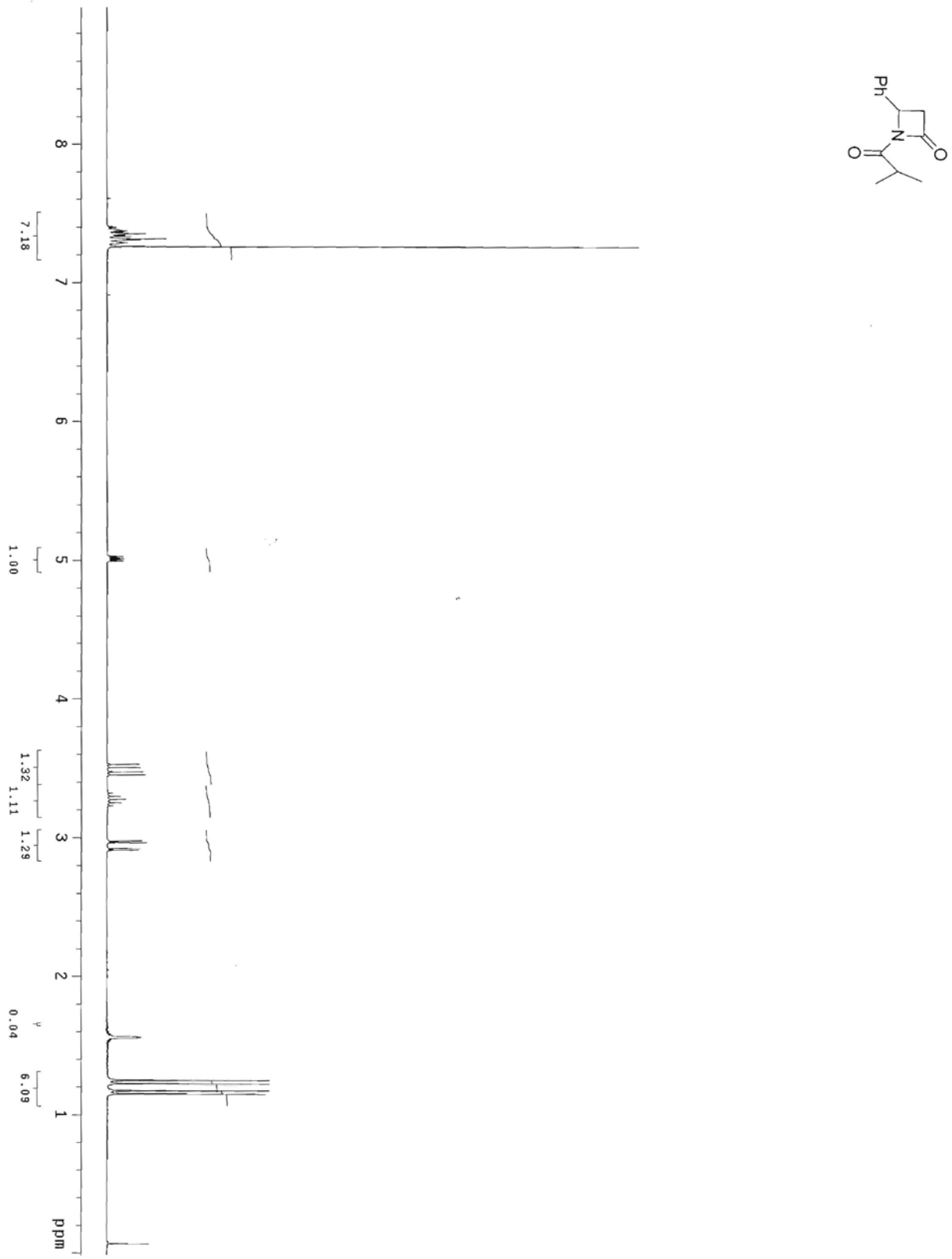
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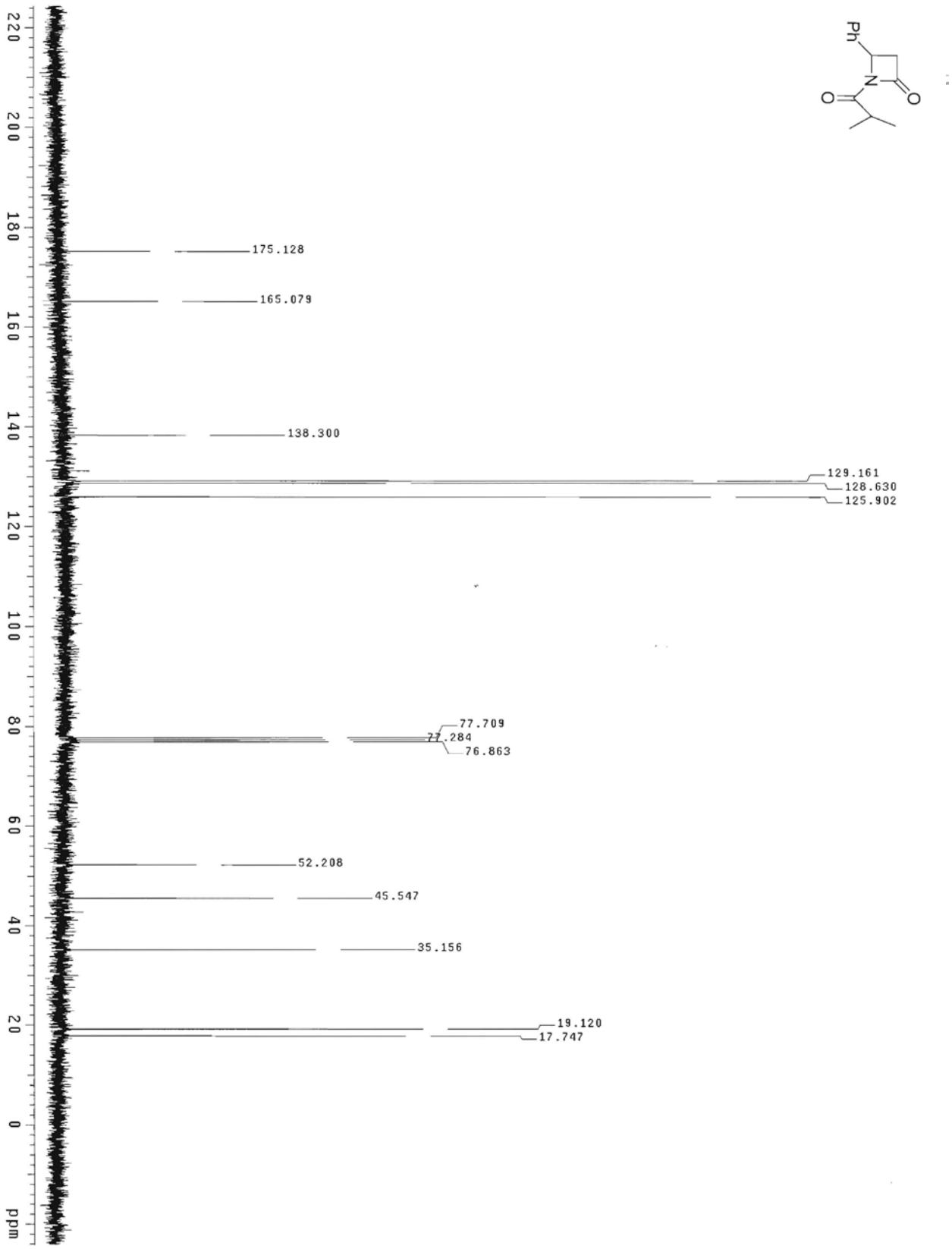
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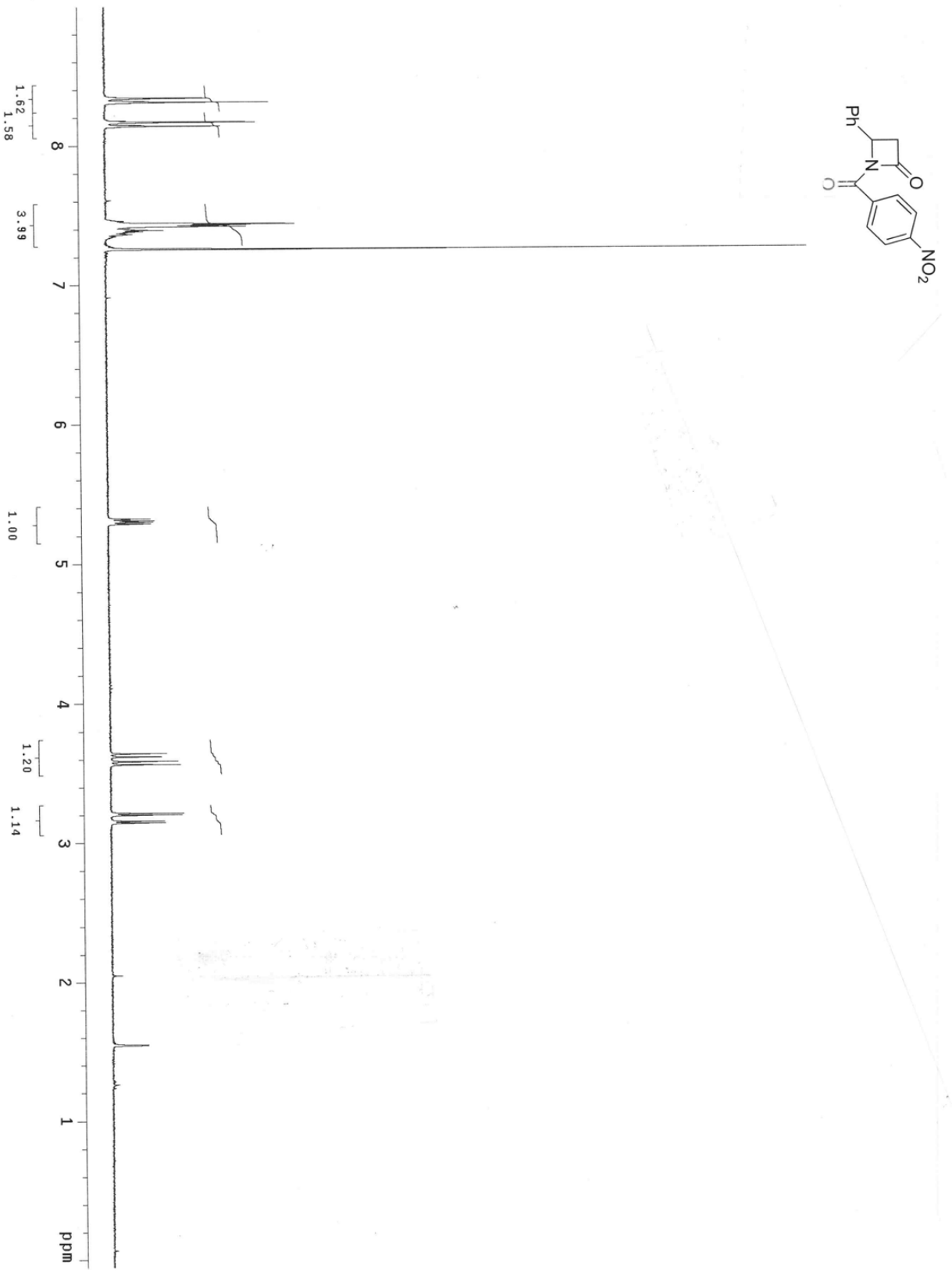
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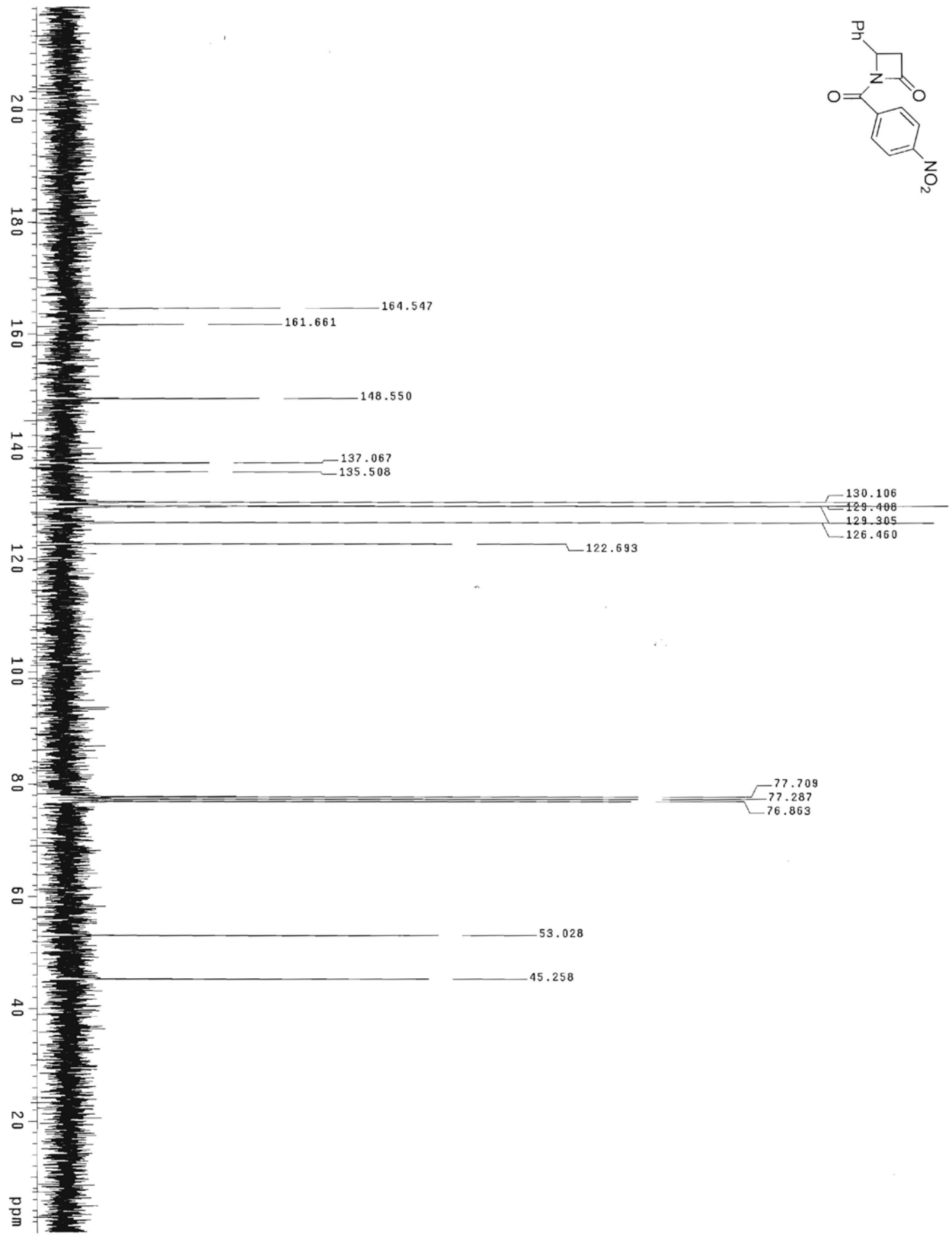
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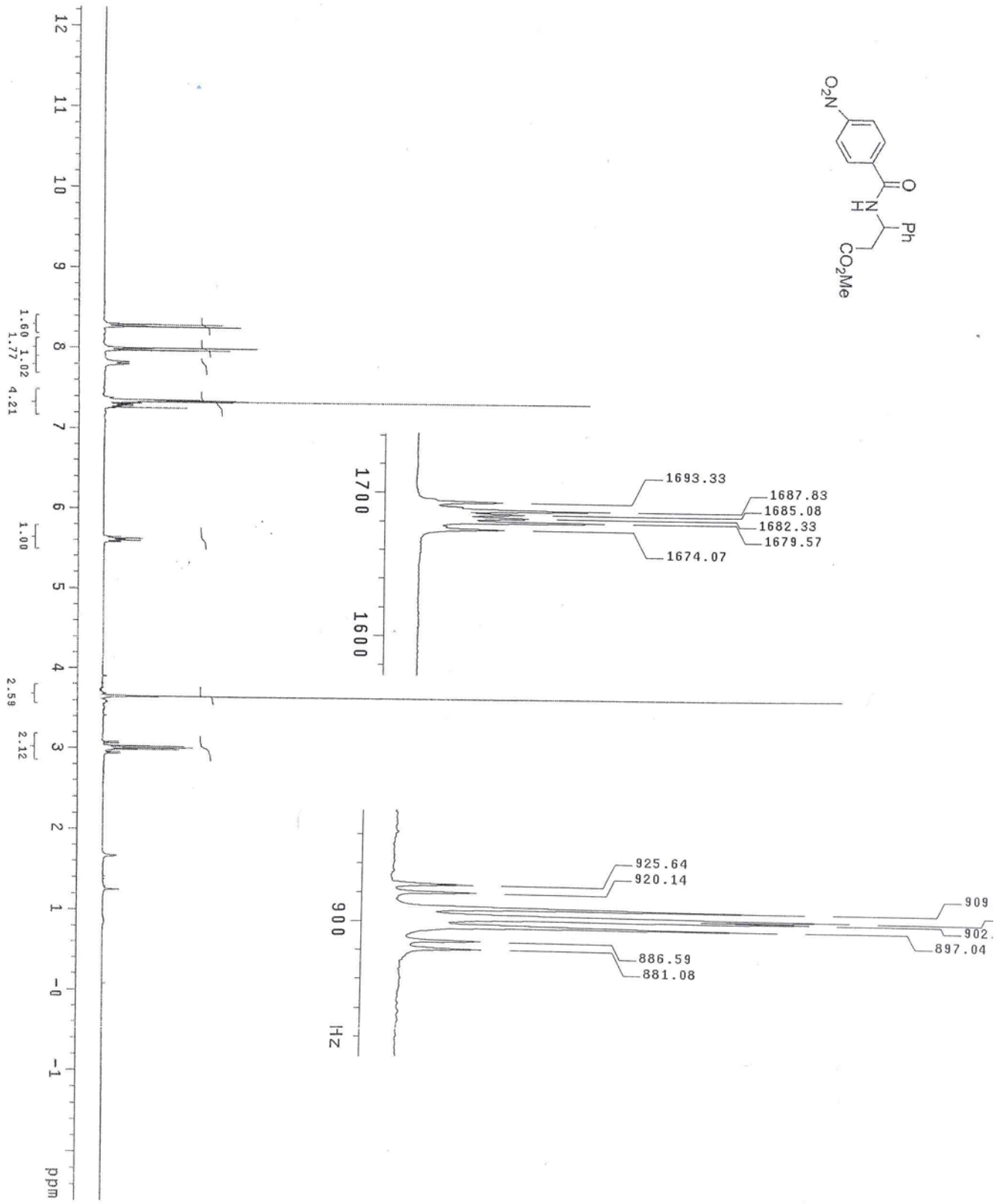
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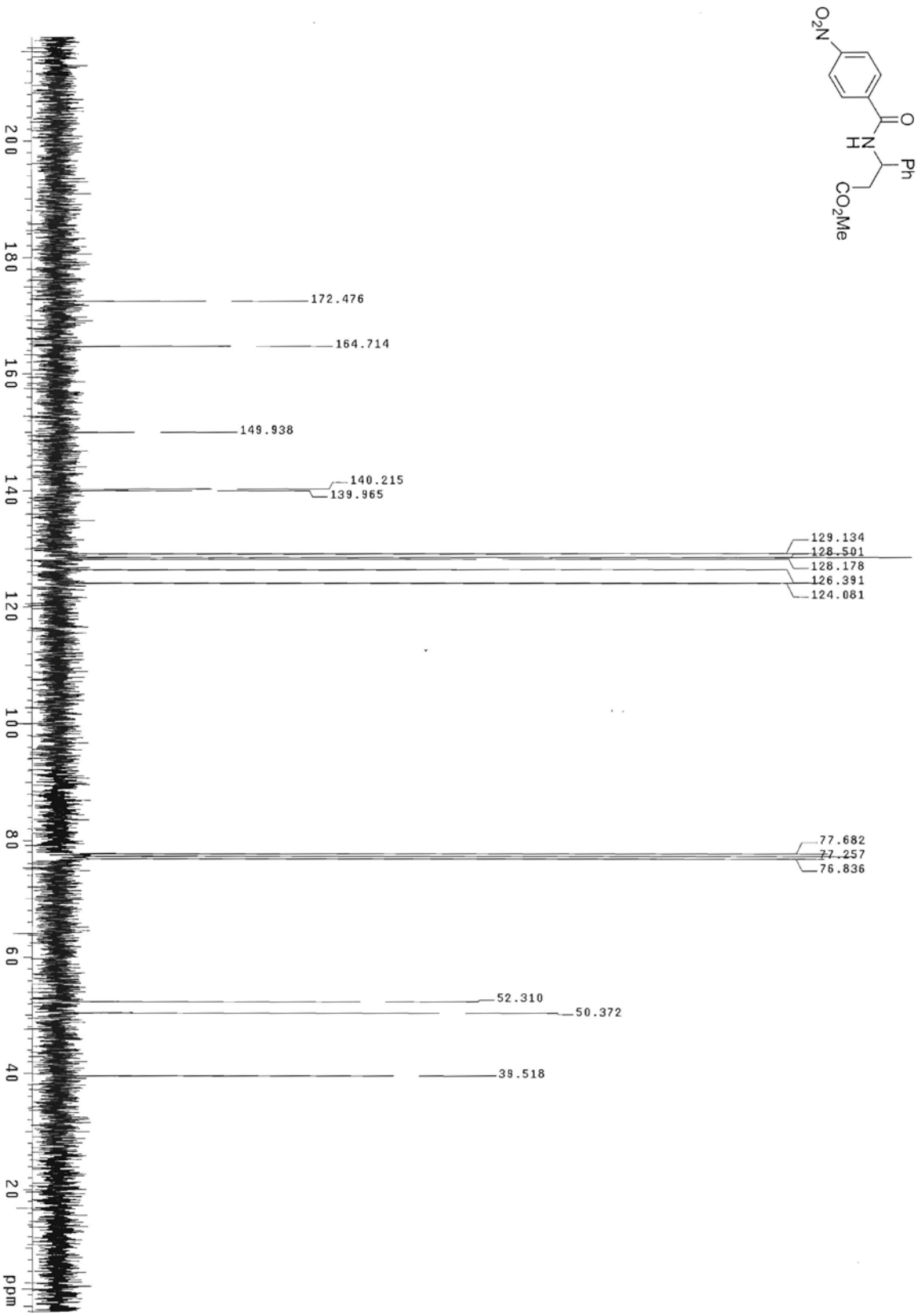
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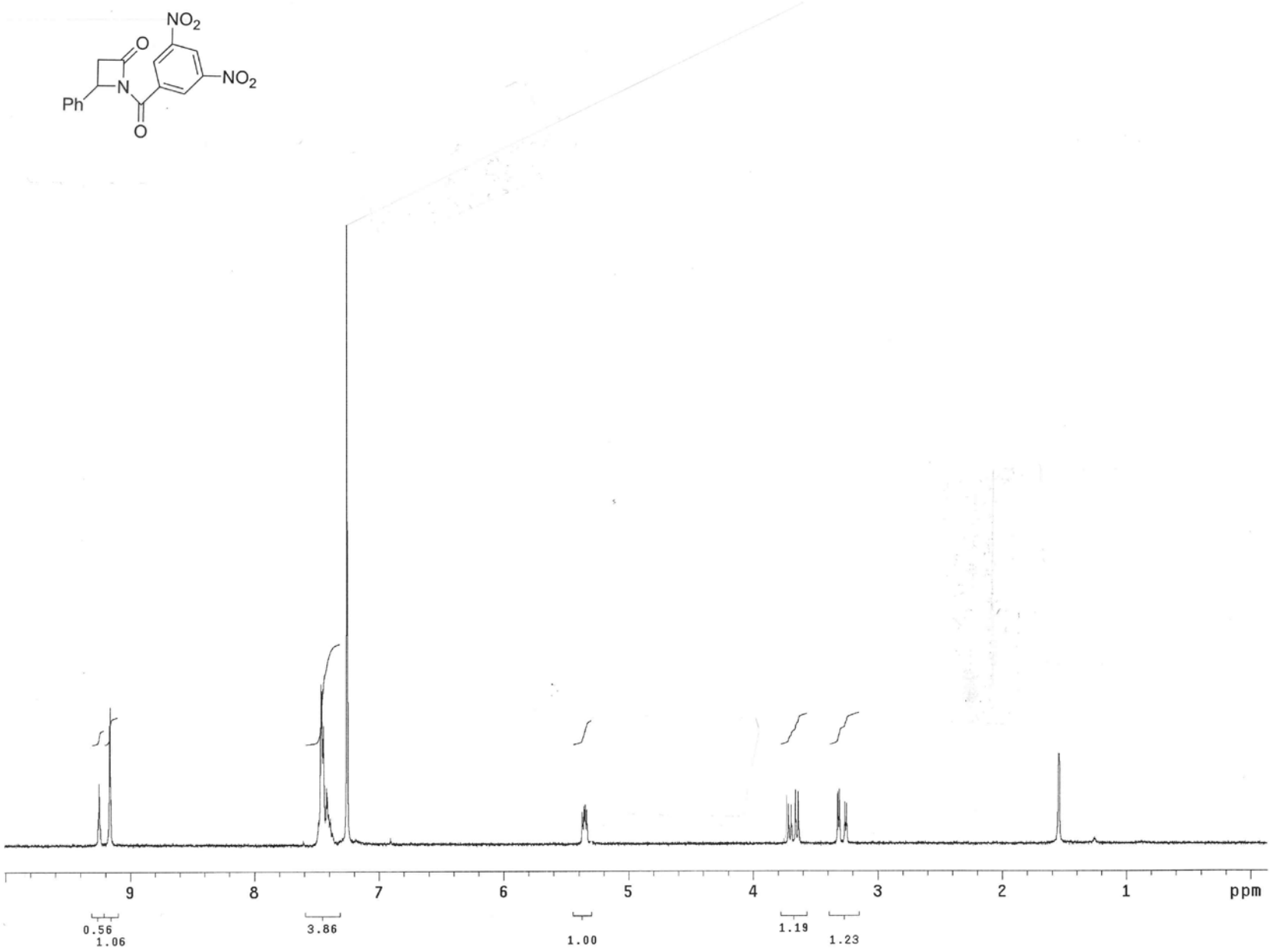
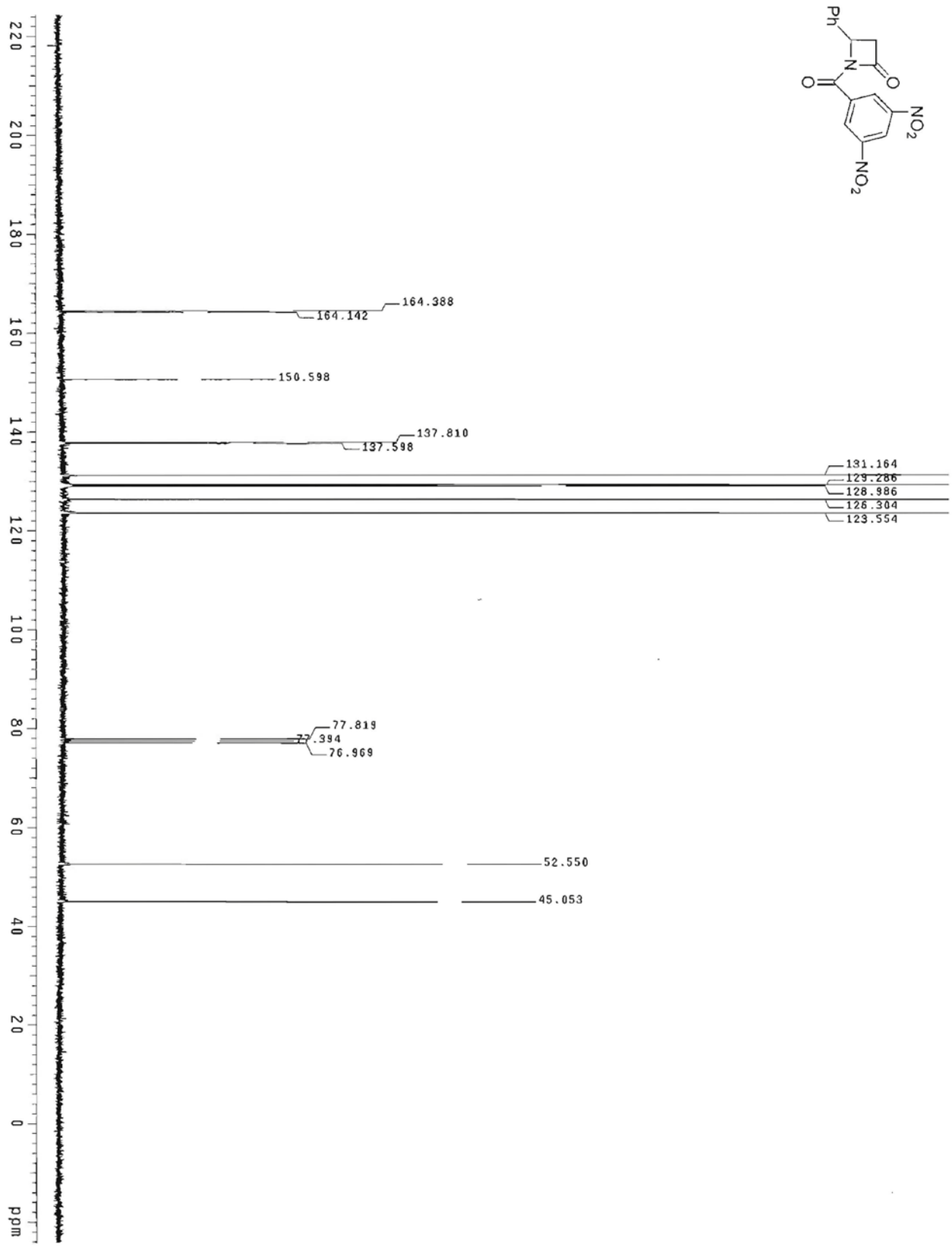
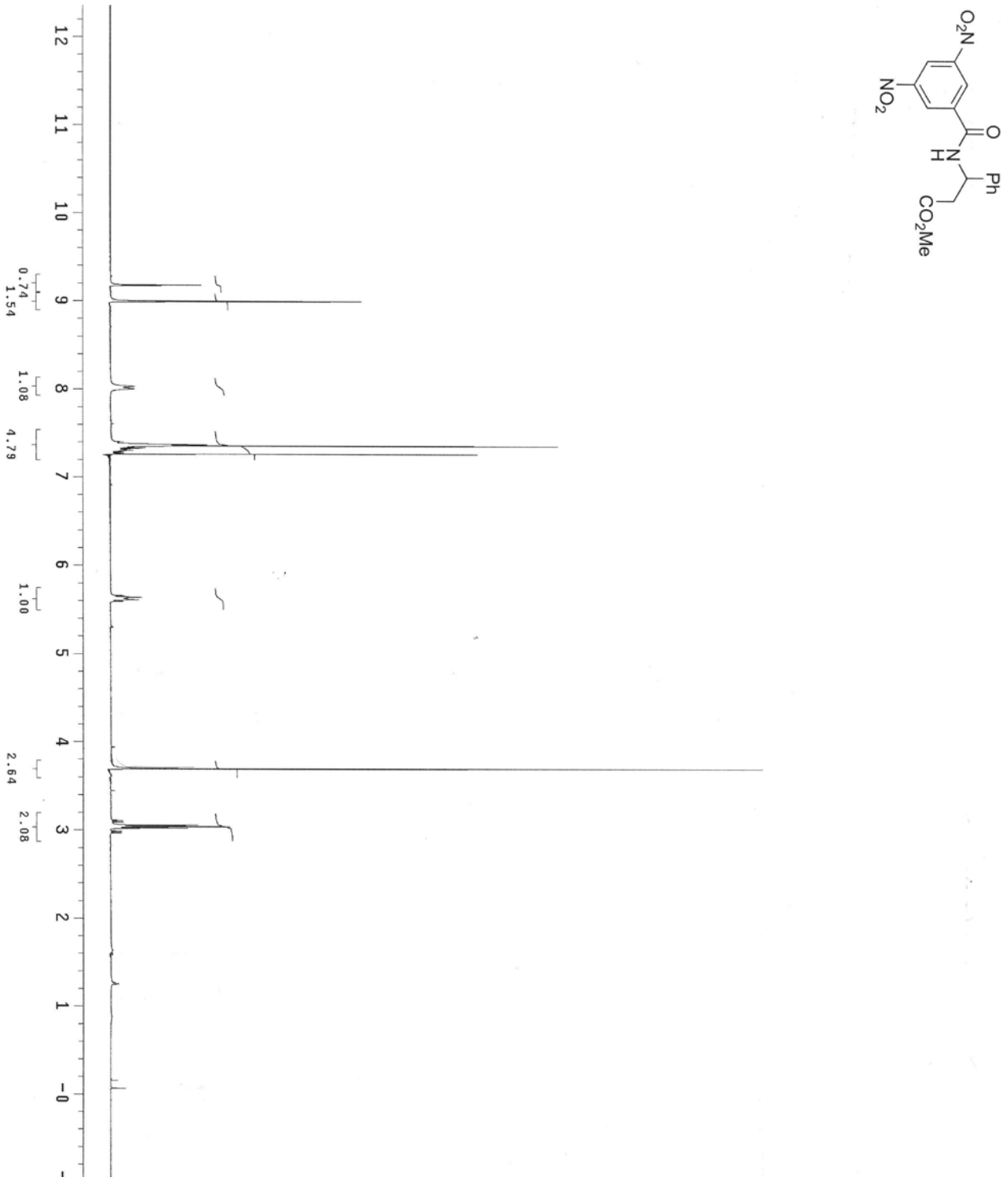
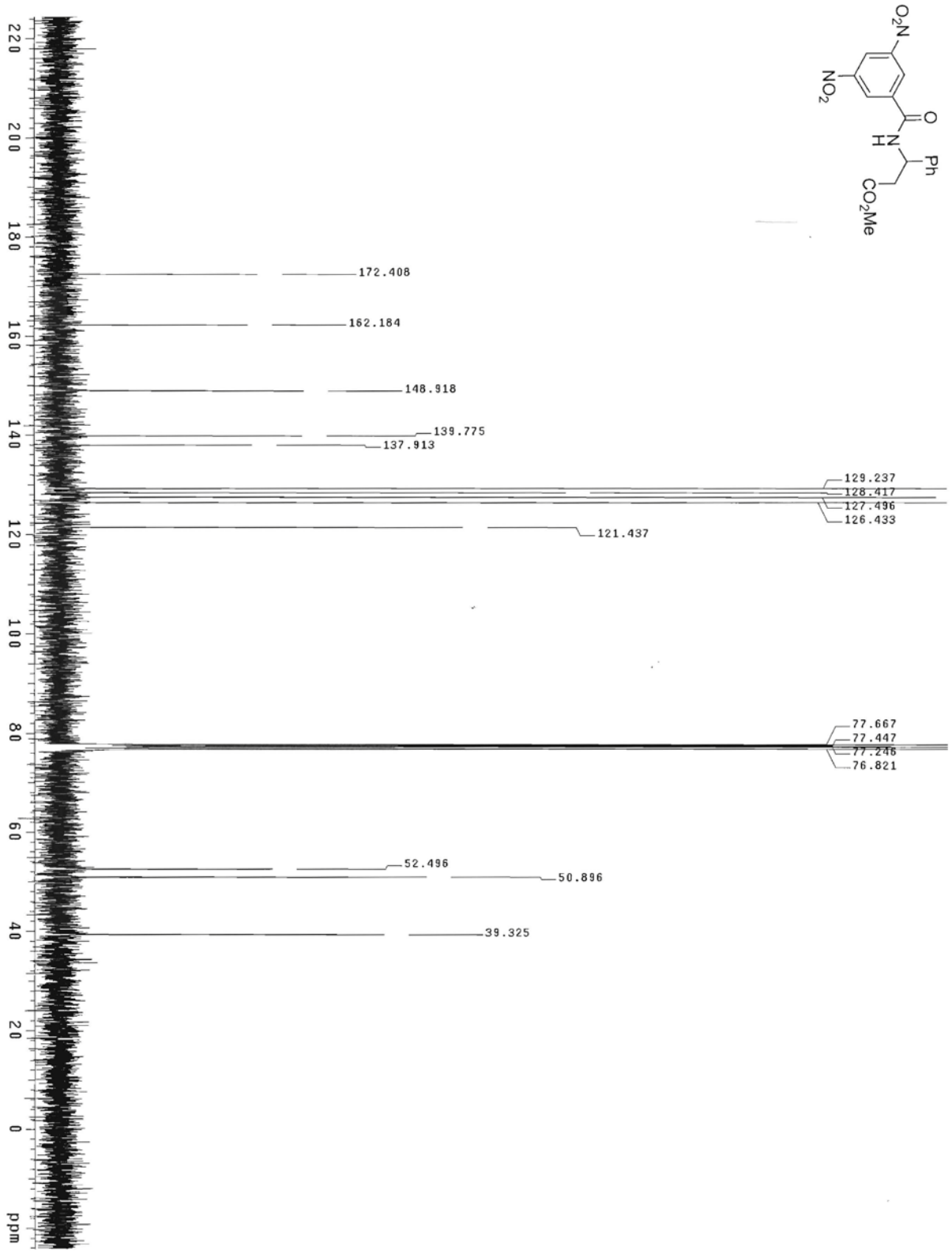
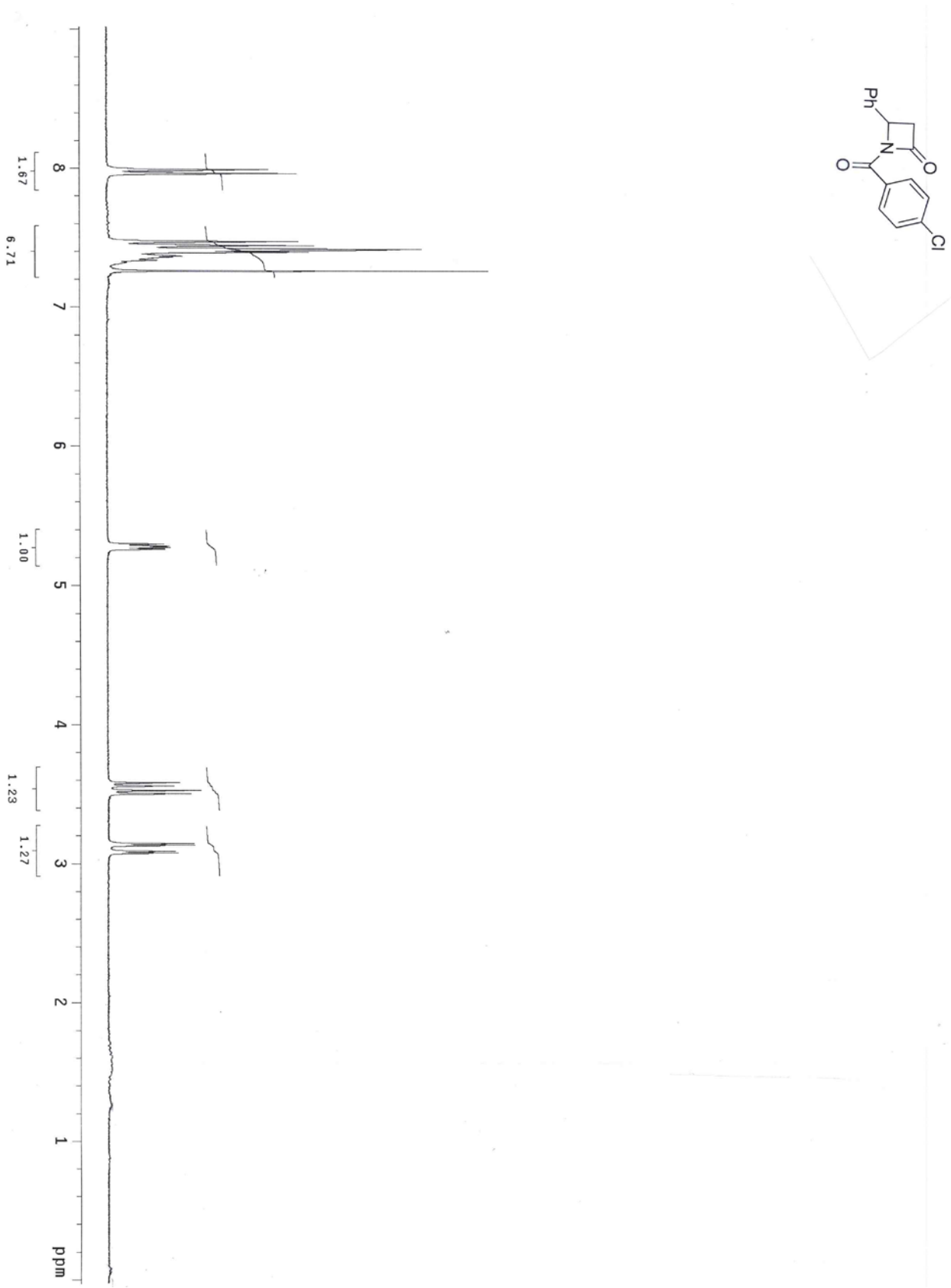
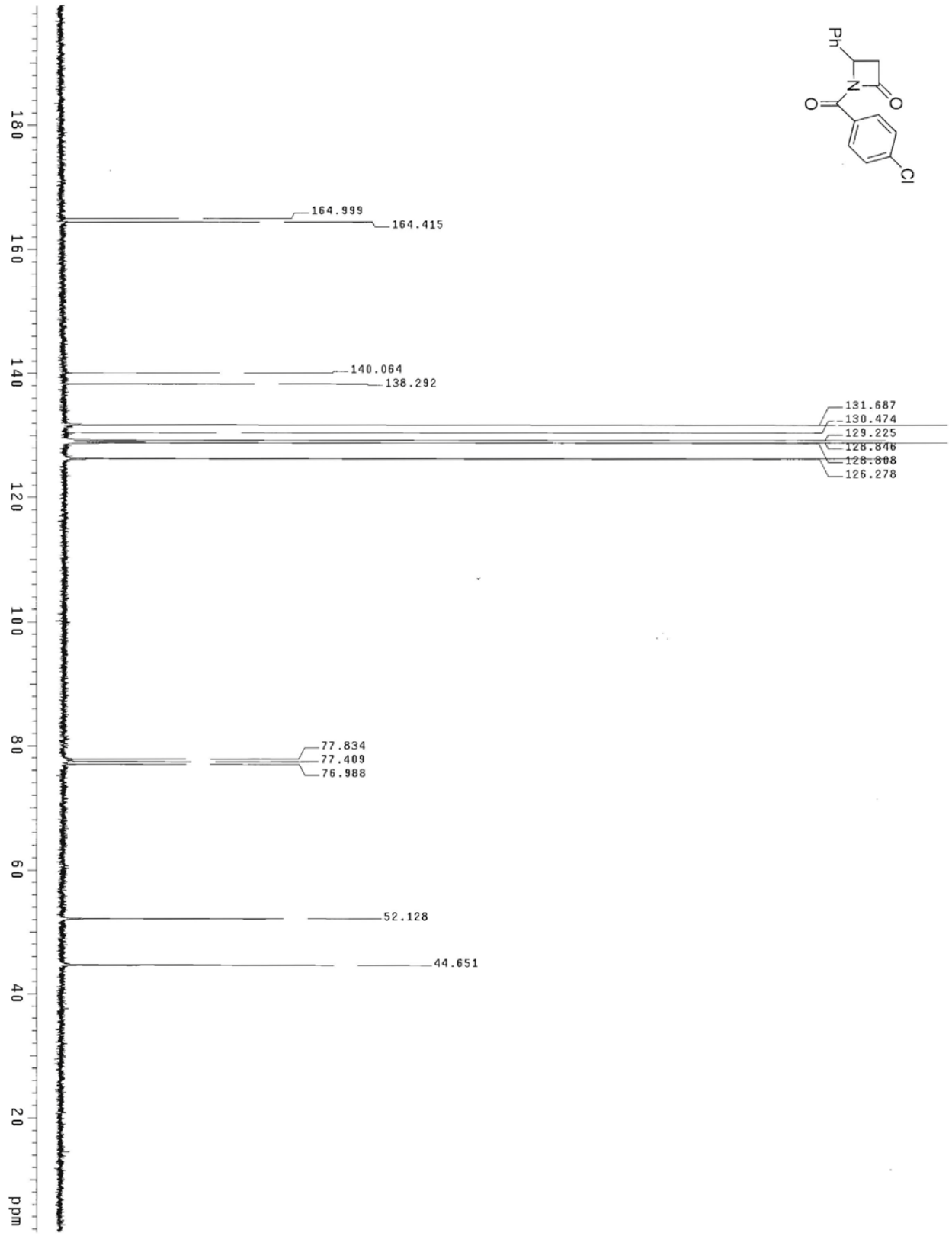

NO2
NO2
O
N
Ph
O
9
8
7
6
5
4
3
2
1
ppm
0.56
1.06
3.86
1.00
1.19
1.23

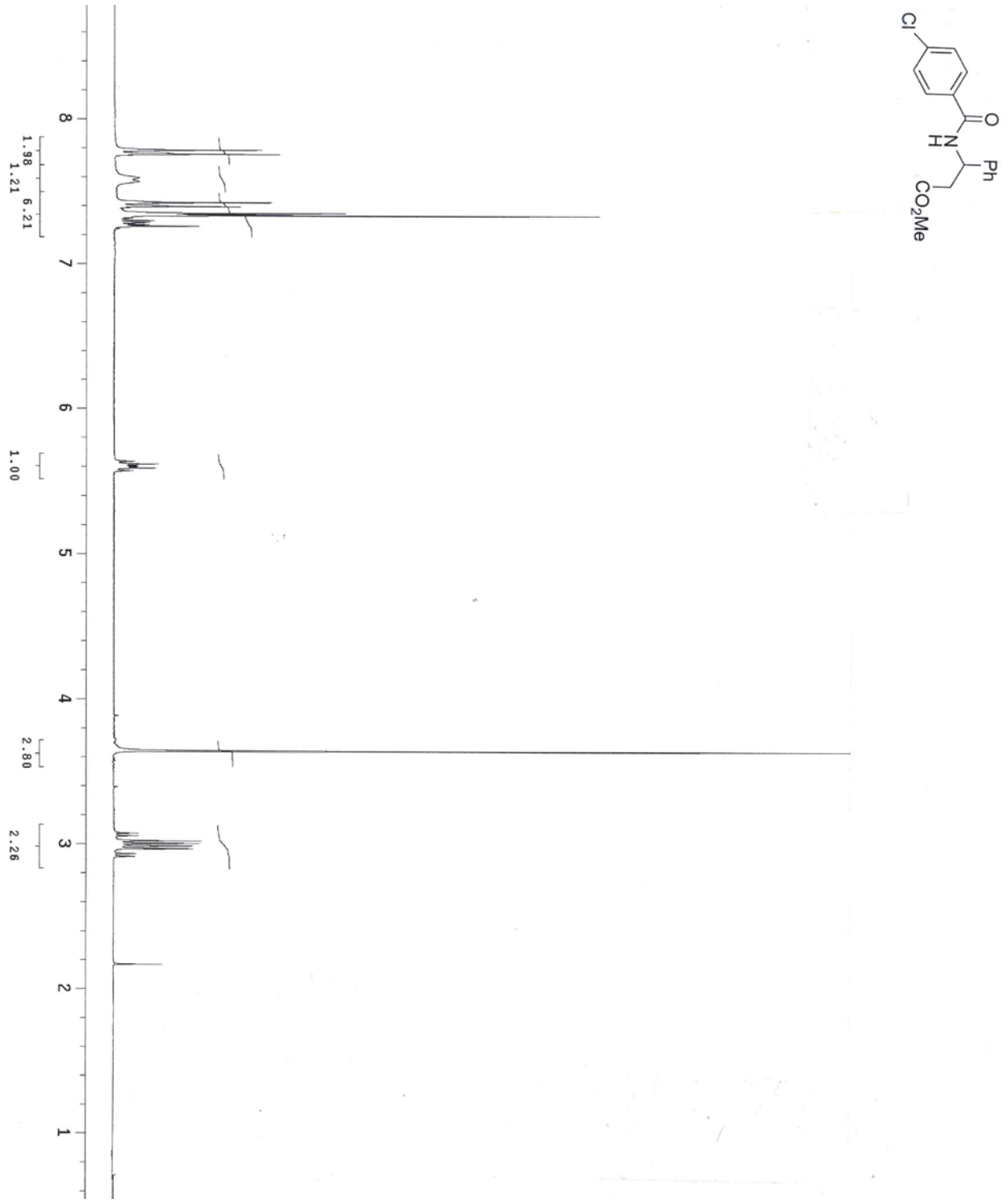

Ph
N
O
O
NO2
NO2
164.388
164.142
150.598
137.810
137.598
131.164
129.286
128.986
126.304
123.554
77.819
77.394
76.969
52.550
45.053
220
200
180
160
140
120
100
80
60
40
20
0
ppm

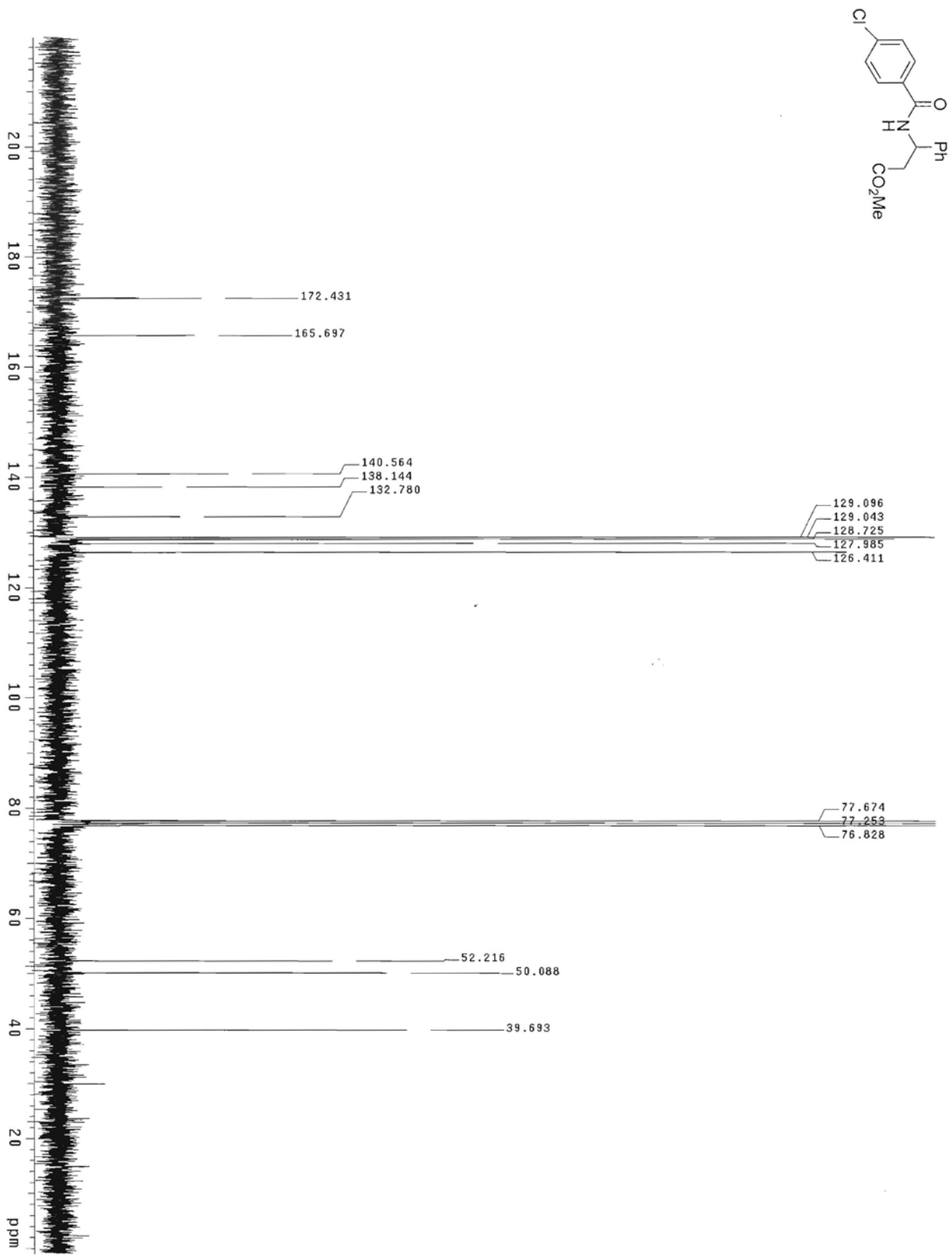

O2N
NO2
O
N
H
Ph
CO2Me
12
11
10
9
8
7
6
5
4
3
2
1
-0
0.74
1.54
1.08
4.79
1.00
2.64
2.08

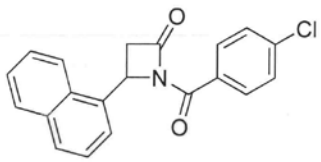

172.408
162.184
148.918
139.775
137.913
129.237
128.417
127.496
126.433
121.437
77.667
77.447
77.246
76.821
52.496
50.896
39.325
ppm

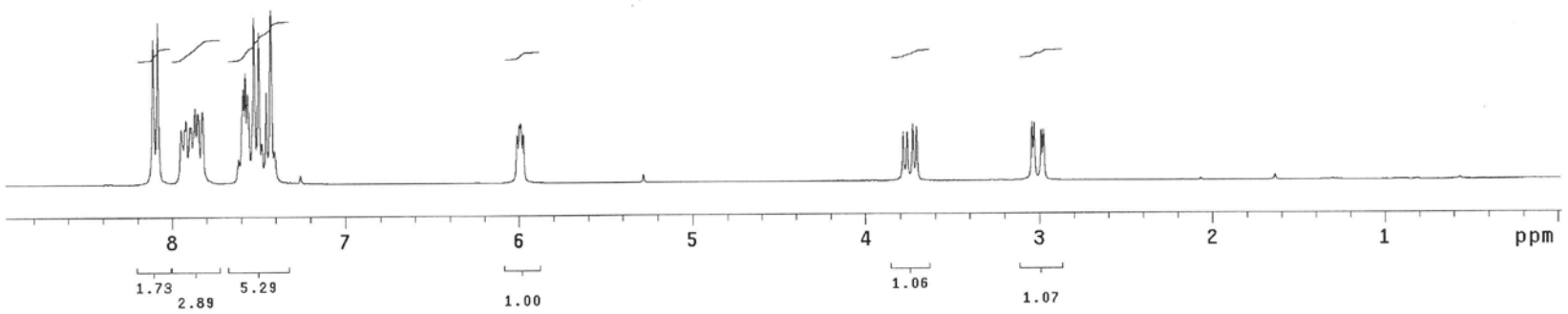

Ph
N
O
O
Cl
8
7
6
5
4
3
2
1
ppm
1.67
6.71
1.00
1.23
1.27

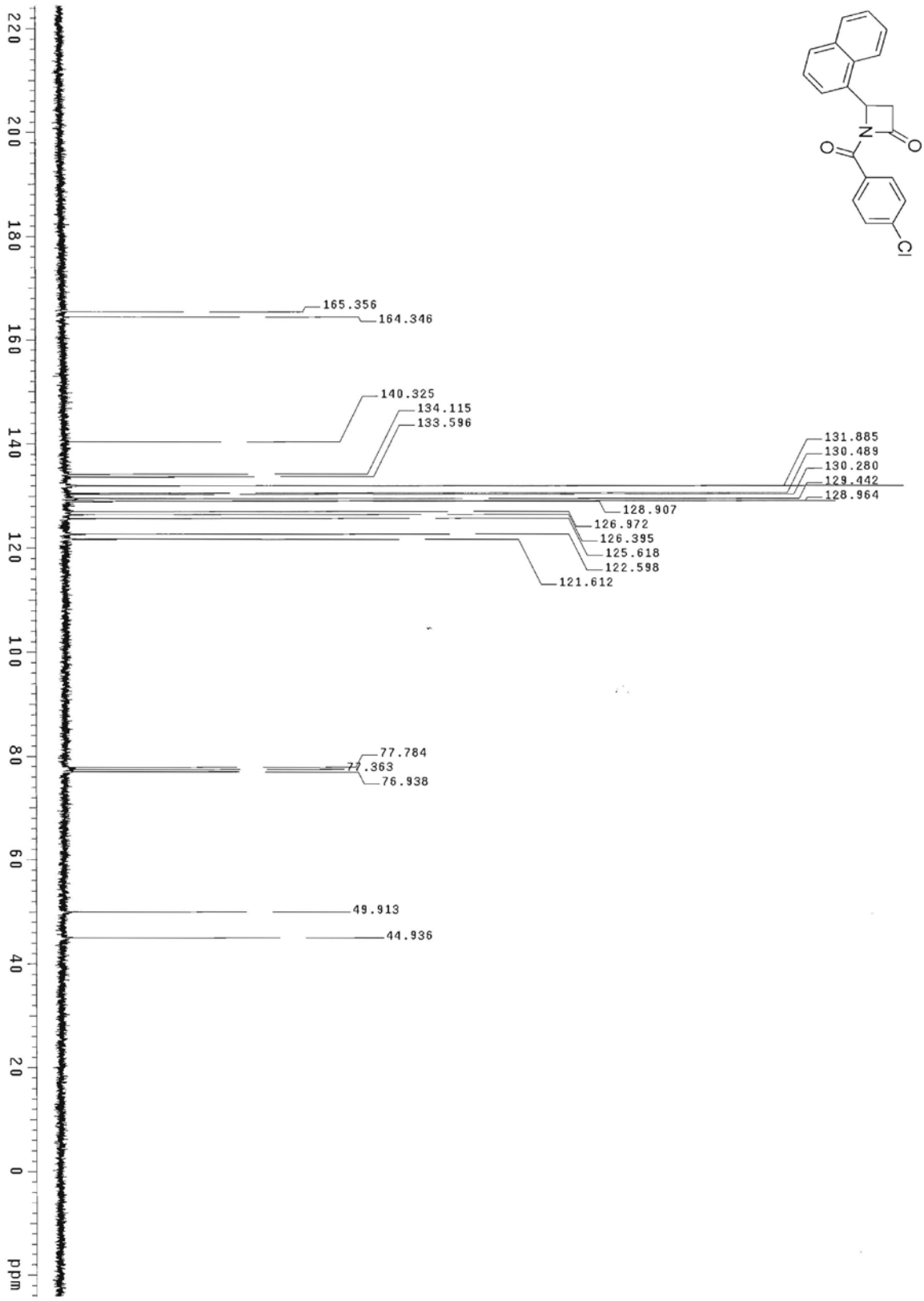

Ph
N
O
O
O
Cl
164.999
164.415
140.064
138.292
131.687
130.474
129.225
128.846
128.808
126.278
77.834
77.409
76.988
52.128
44.651
180
160
140
120
100
80
60
40
20
ppm

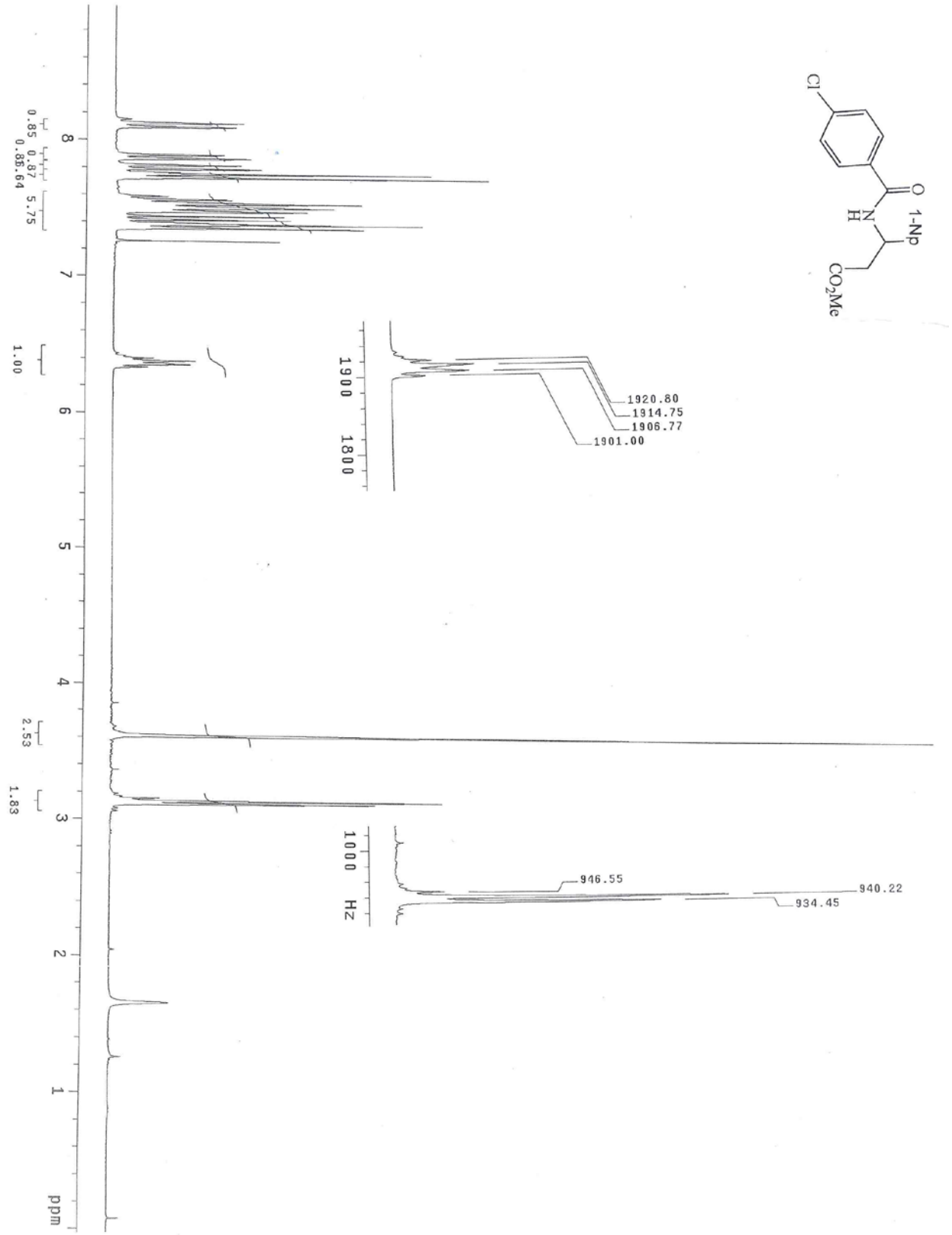

Cl
O
N
H
Ph
CO2Me
8
7
6
5
4
3
2
1
1.98
1.21
6.21
1.00
2.80
2.26

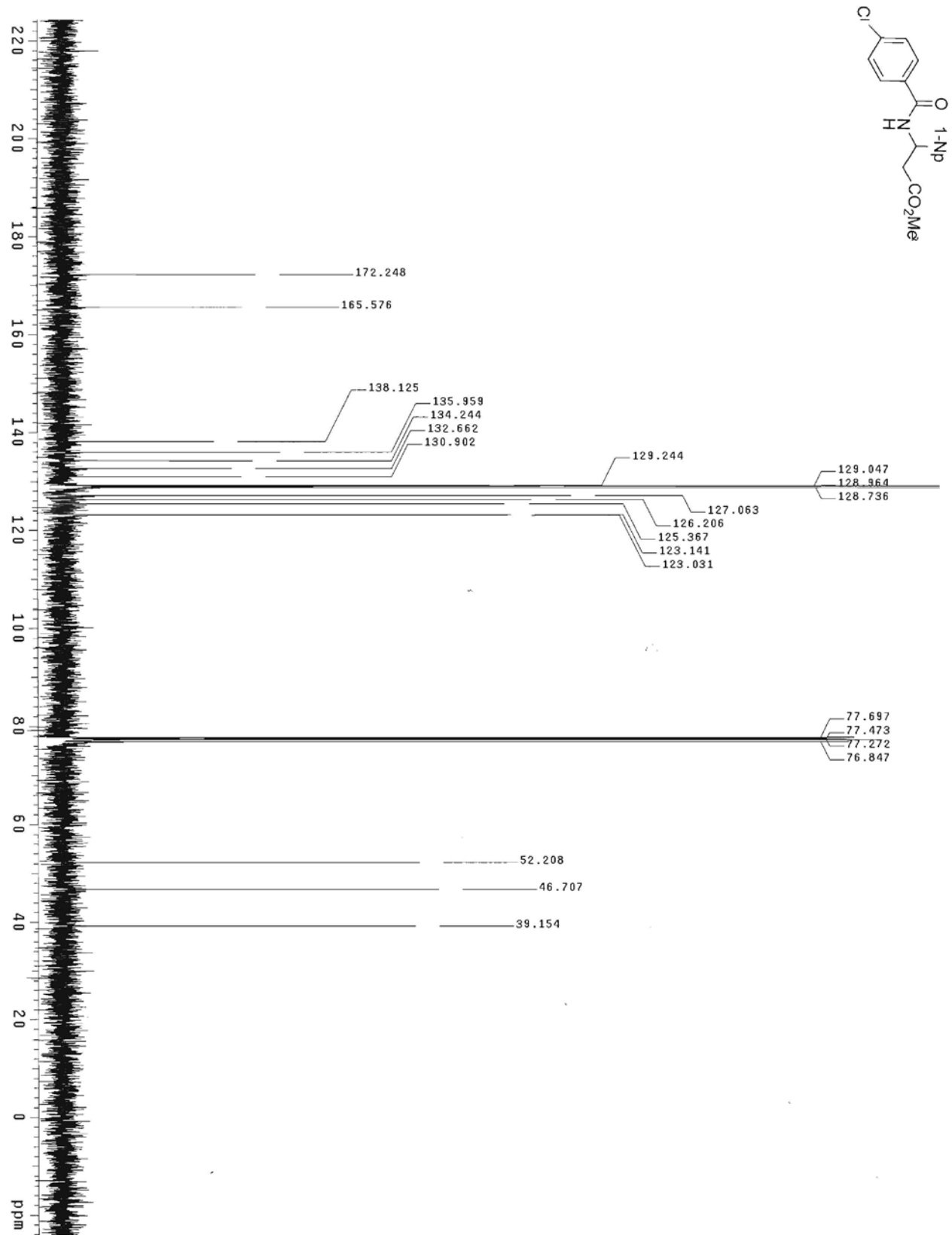

Cl
O
N
H
Ph
CO2Me
172.431
165.697
140.564
138.144
132.780
129.096
129.043
128.725
127.985
126.411
77.674
77.253
76.828
52.216
50.088
39.693
200
180
160
140
120
100
80
60
40
20
ppm

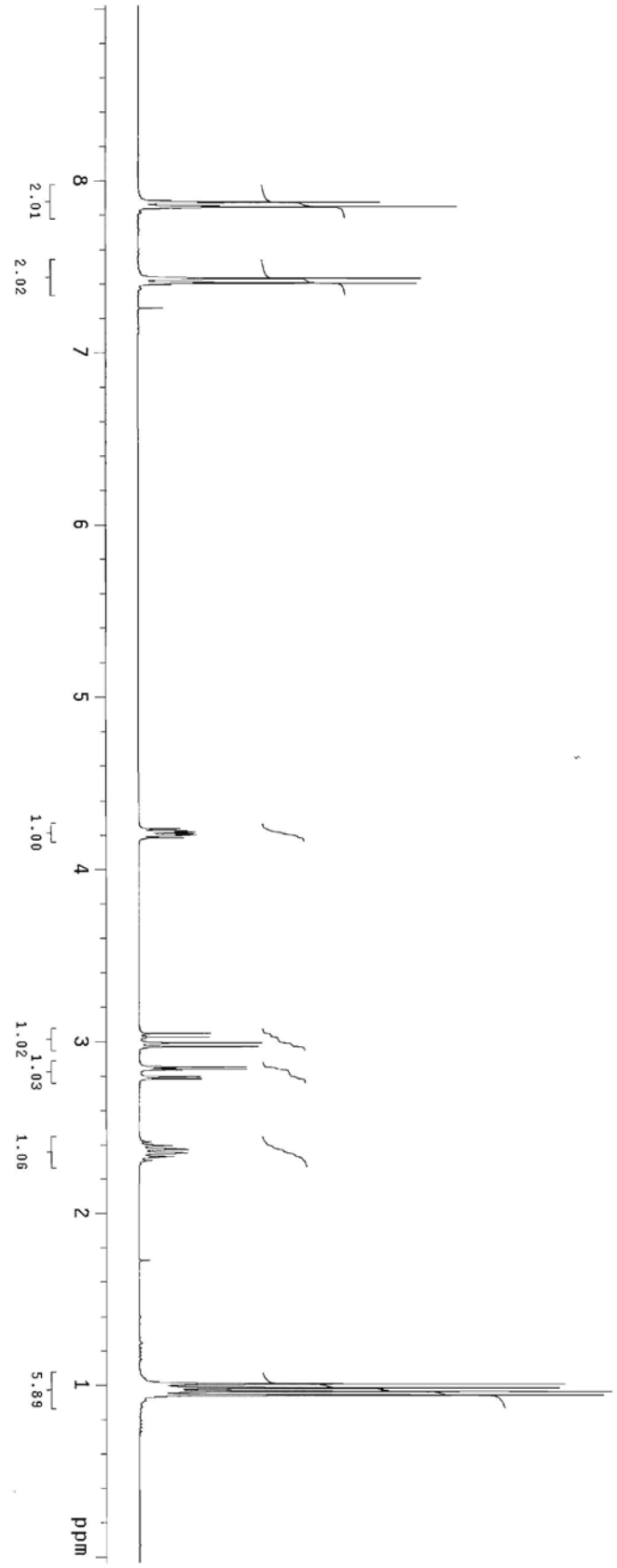

O
Cl
N
O

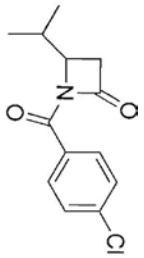

8
7
6
5
4
3
2
1
ppm
1.73
2.89
5.29
1.00
1.06
1.07

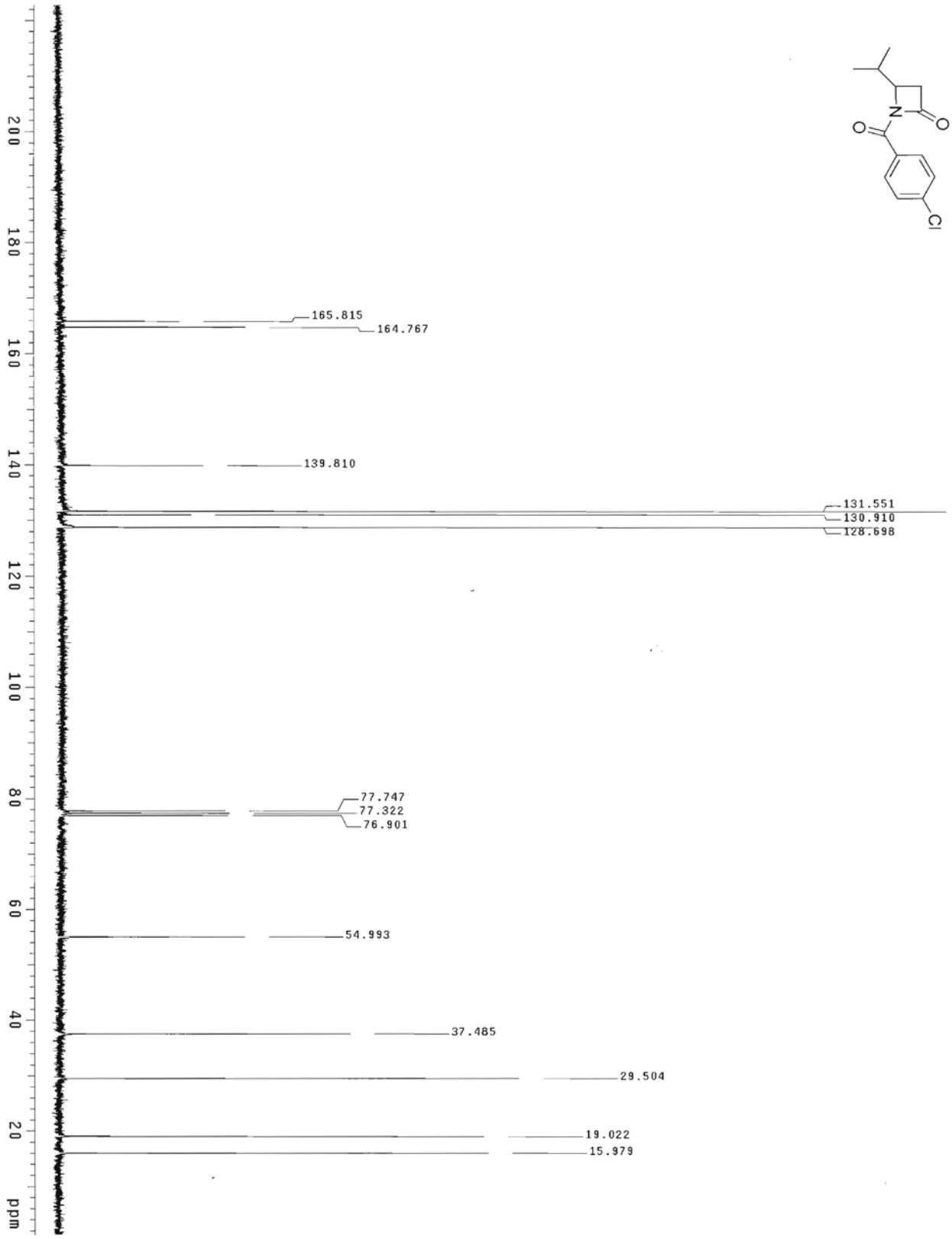

220
200
180
160
140
120
100
80
60
40
20
0
ppm
165.356
164.346
140.325
134.115
133.596
131.885
130.489
130.280
129.442
128.964
128.907
126.972
126.395
125.618
122.598
121.612
77.784
77.363
76.938
49.913
44.936
N
O
O
Cl

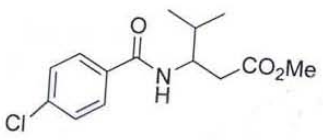

Cl
O
1-Np
N
H
CO2Me
1920.80
1914.75
1906.77
1901.00
1900
1800
946.55
940.22
934.45
1000
Hz
0.85
0.87
5.75
0.88.64
1.00
2.53
1.83
8
7
6
5
4
3
2
1
ppm

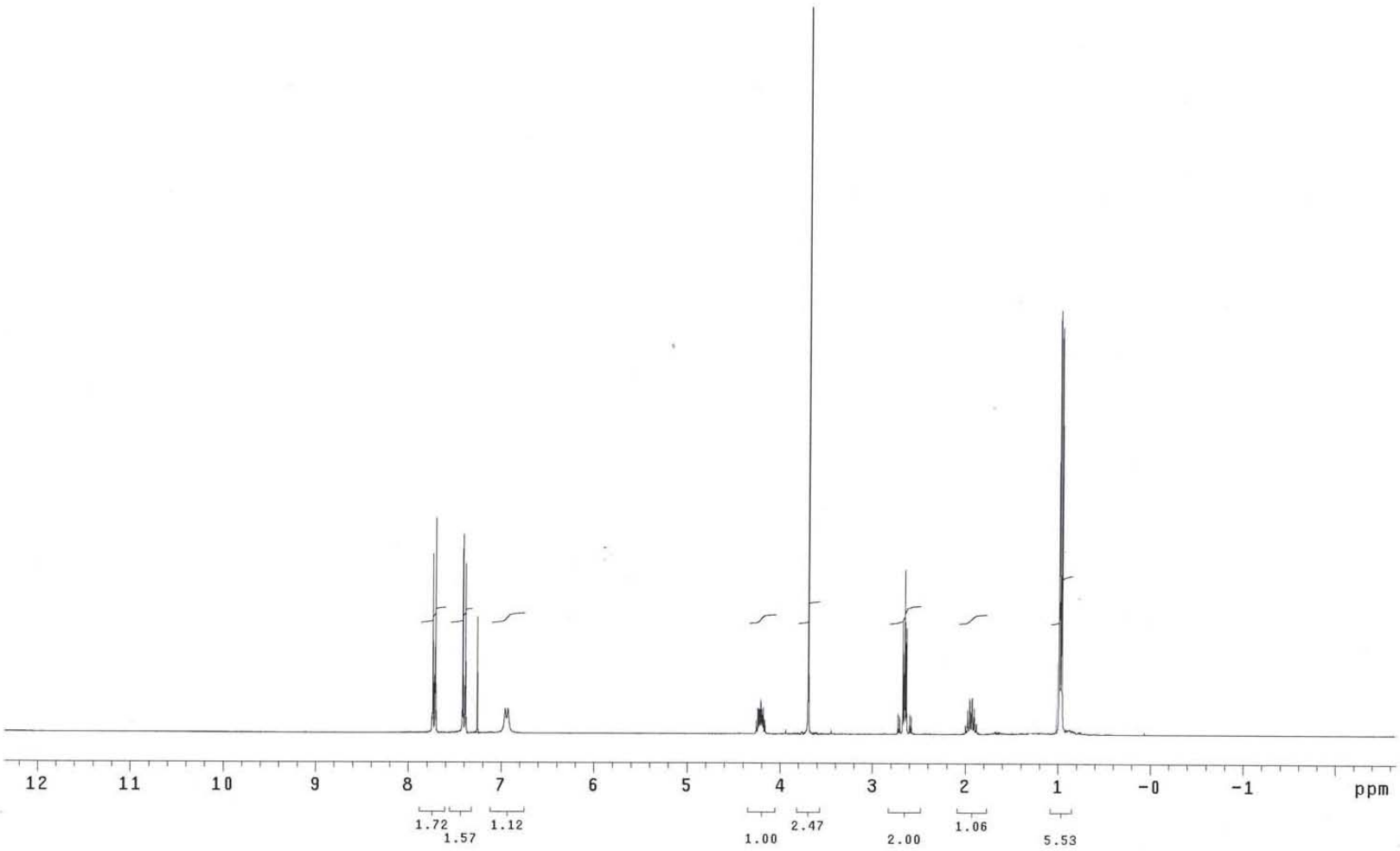

Cl
O
N
H
1-Np
CO2Me
172.248
165.576
138.125
135.959
134.244
132.662
130.902
129.244
129.047
128.964
128.736
127.063
126.206
125.367
123.141
123.031
77.697
77.473
77.272
76.847
52.208
46.707
39.154
220
200
180
160
140
120
100
80
60
40
20
0
ppm

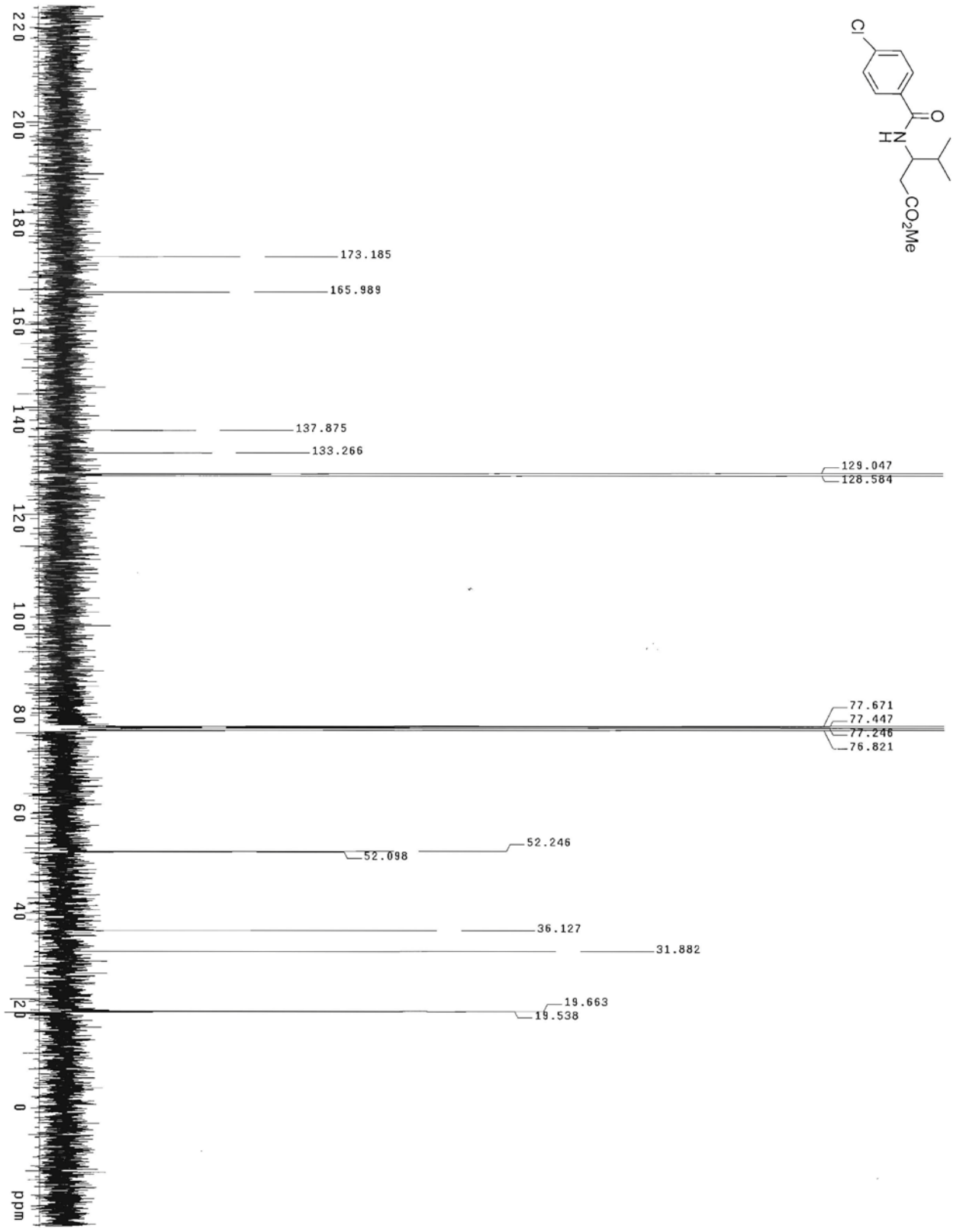

8
7
6
5
4
3
2
1
ppm
2.01
2.02
1.00
1.02
1.03
1.06
5.89

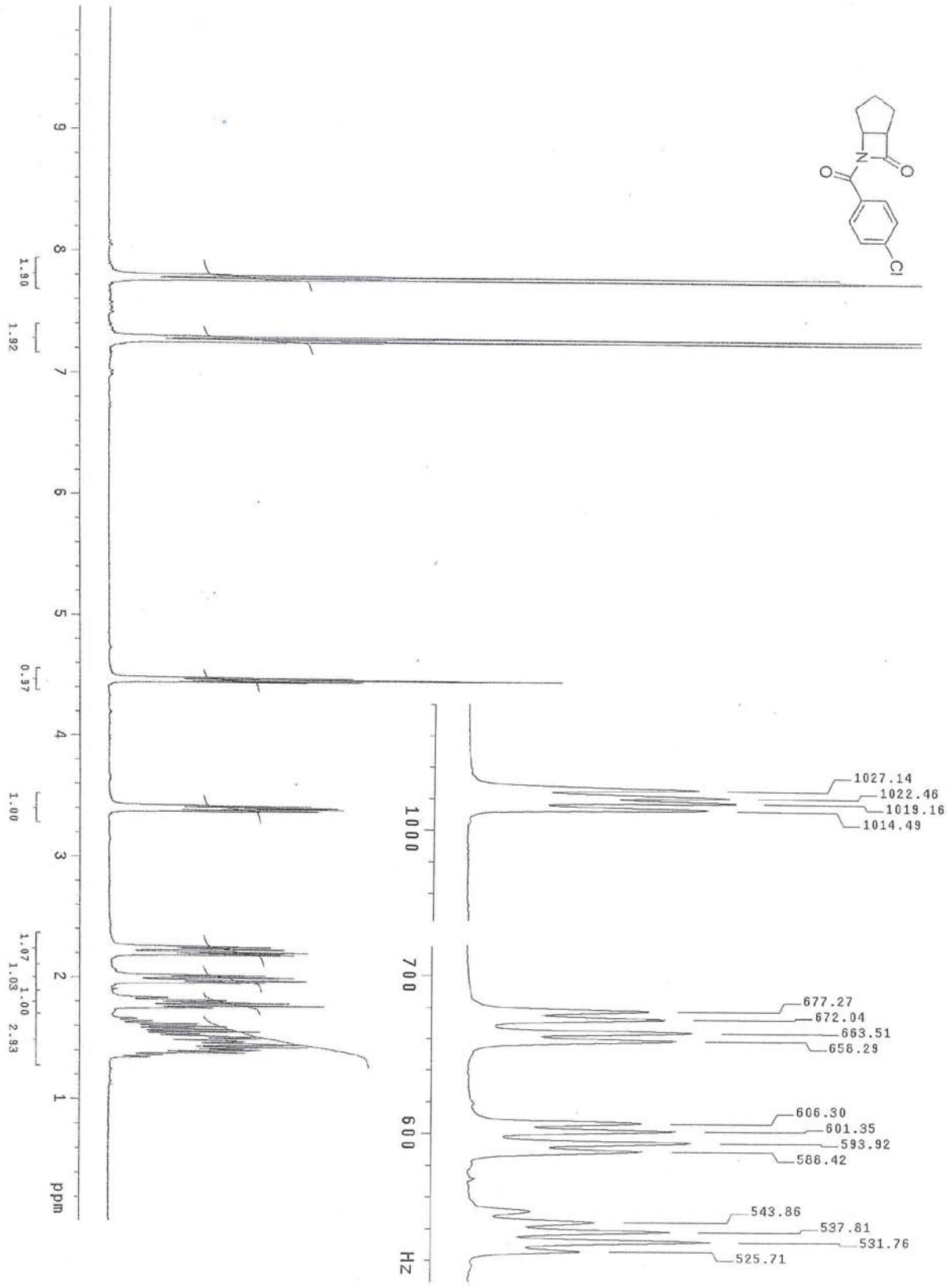

N
O
O
Cl

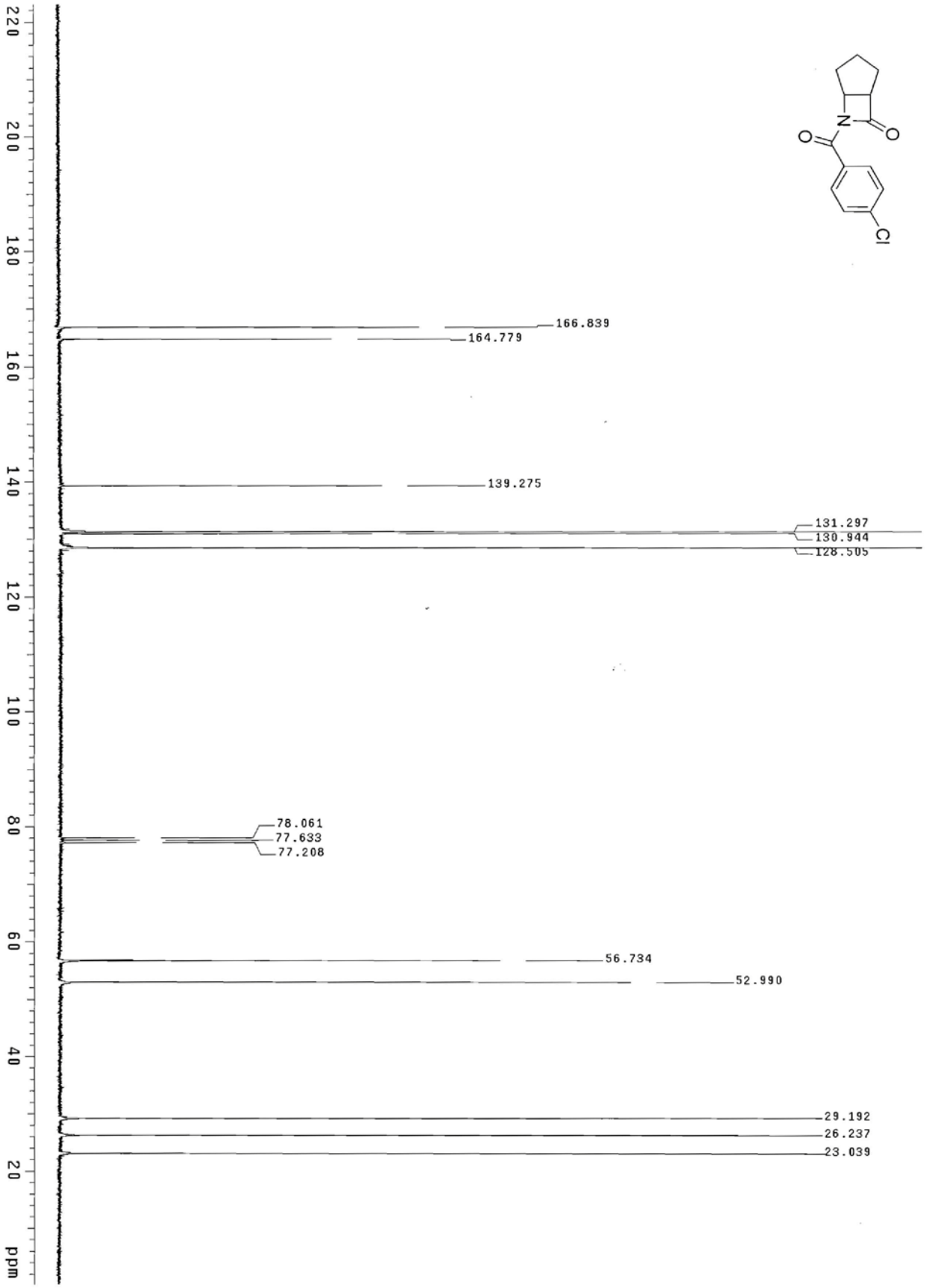

165.815
164.767
139.810
131.551
130.910
128.698
77.747
77.322
76.901
54.993
37.485
29.504
19.022
15.979
ppm

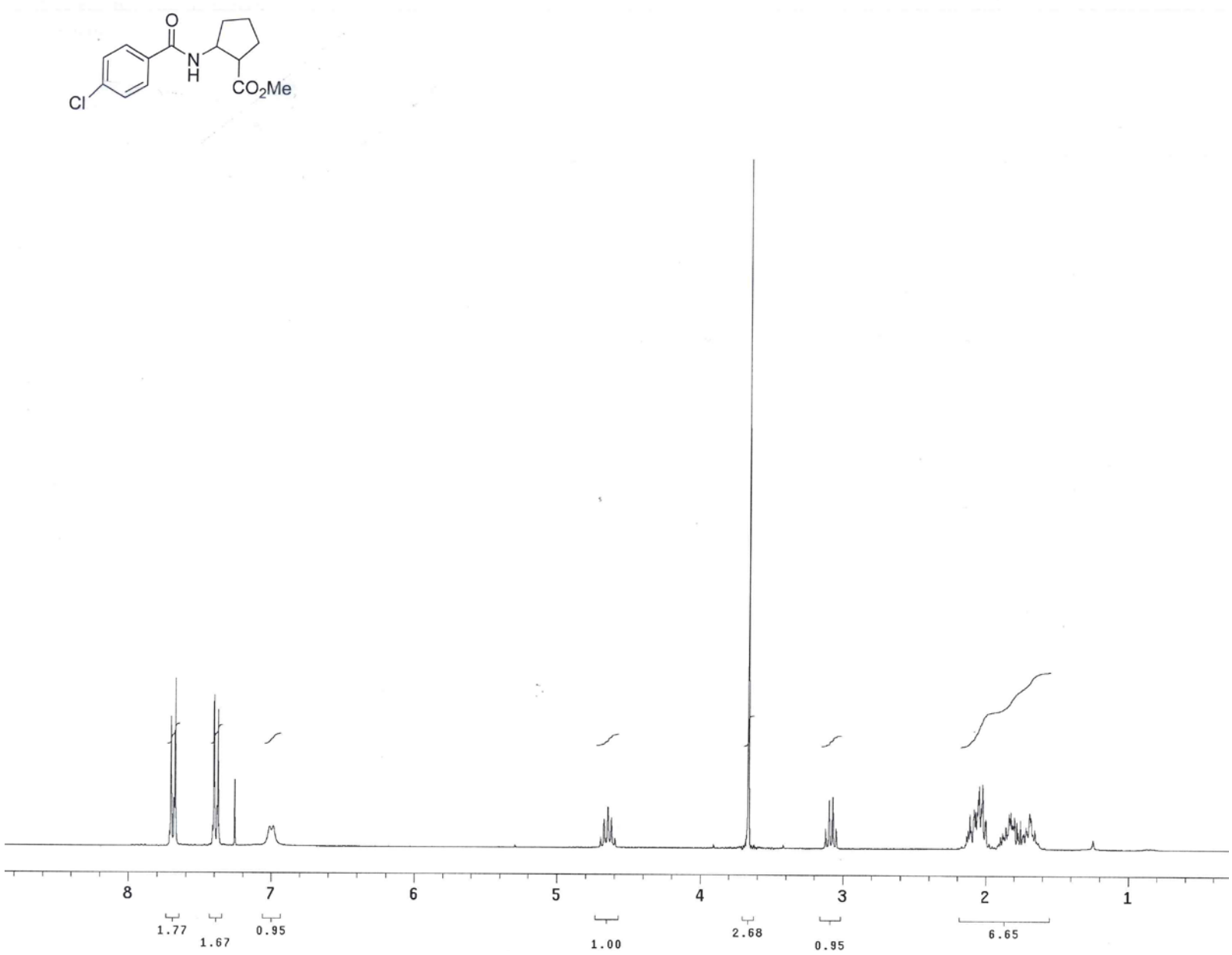

O
N
H
CO2Me
Cl

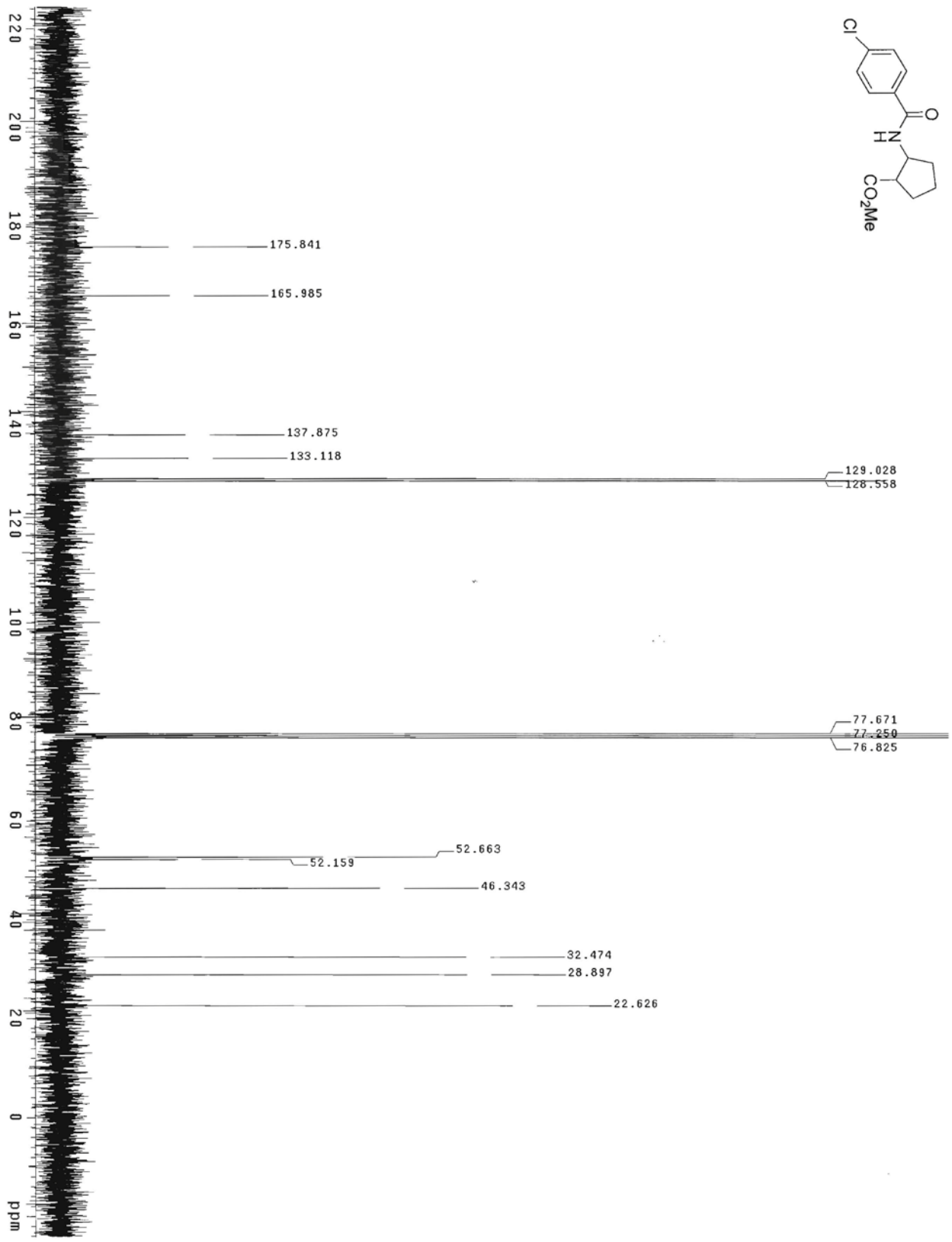

12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
1.72
1.57
1.12
1.00
2.47
2.00
1.06
5.53

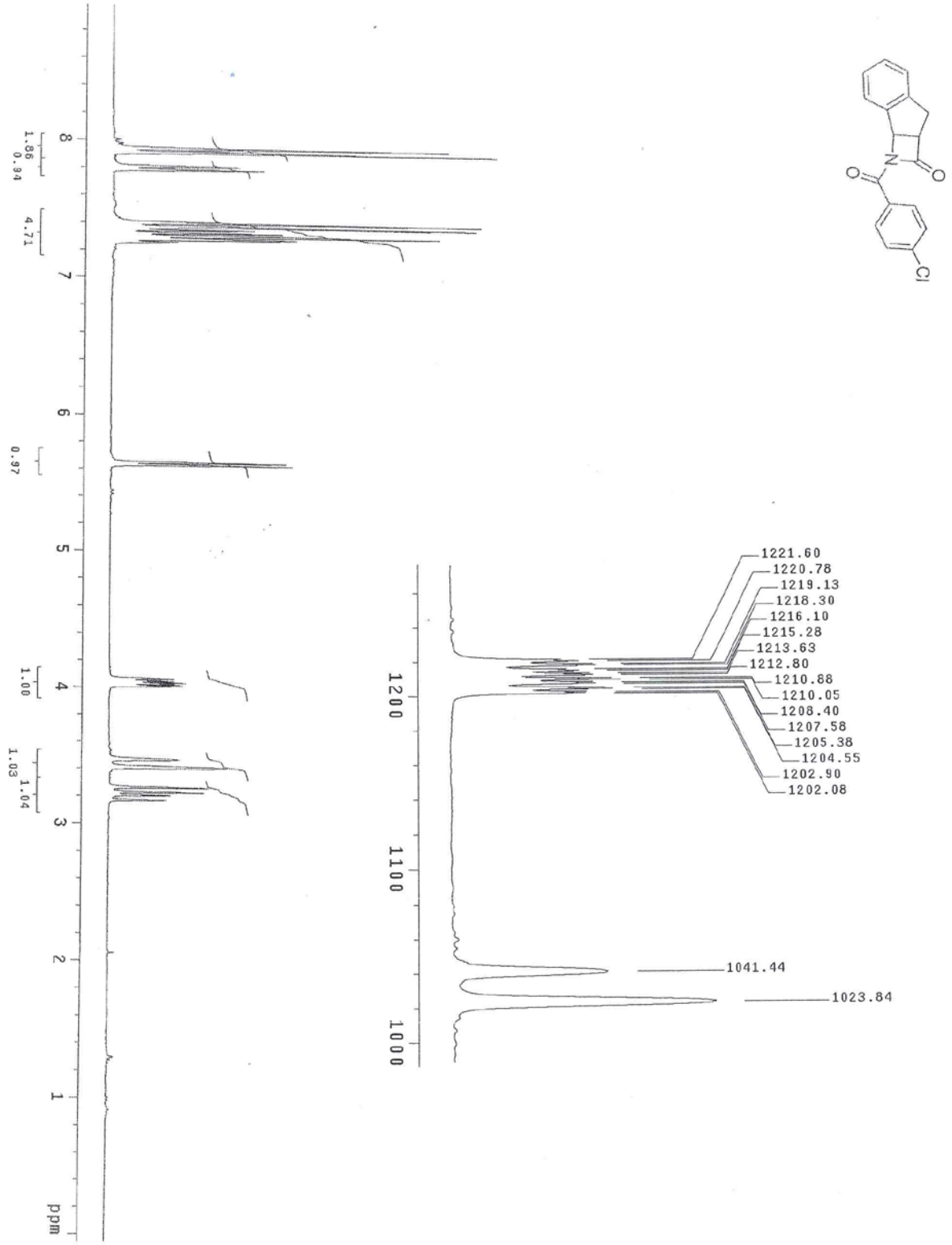

Cl
O
N
H
CO2Me
173.185
165.989
137.875
133.266
129.047
128.584
77.671
77.447
77.246
76.821
52.246
52.098
36.127
31.882
19.663
19.538
220
200
180
160
140
120
100
80
60
40
20
0
ppm

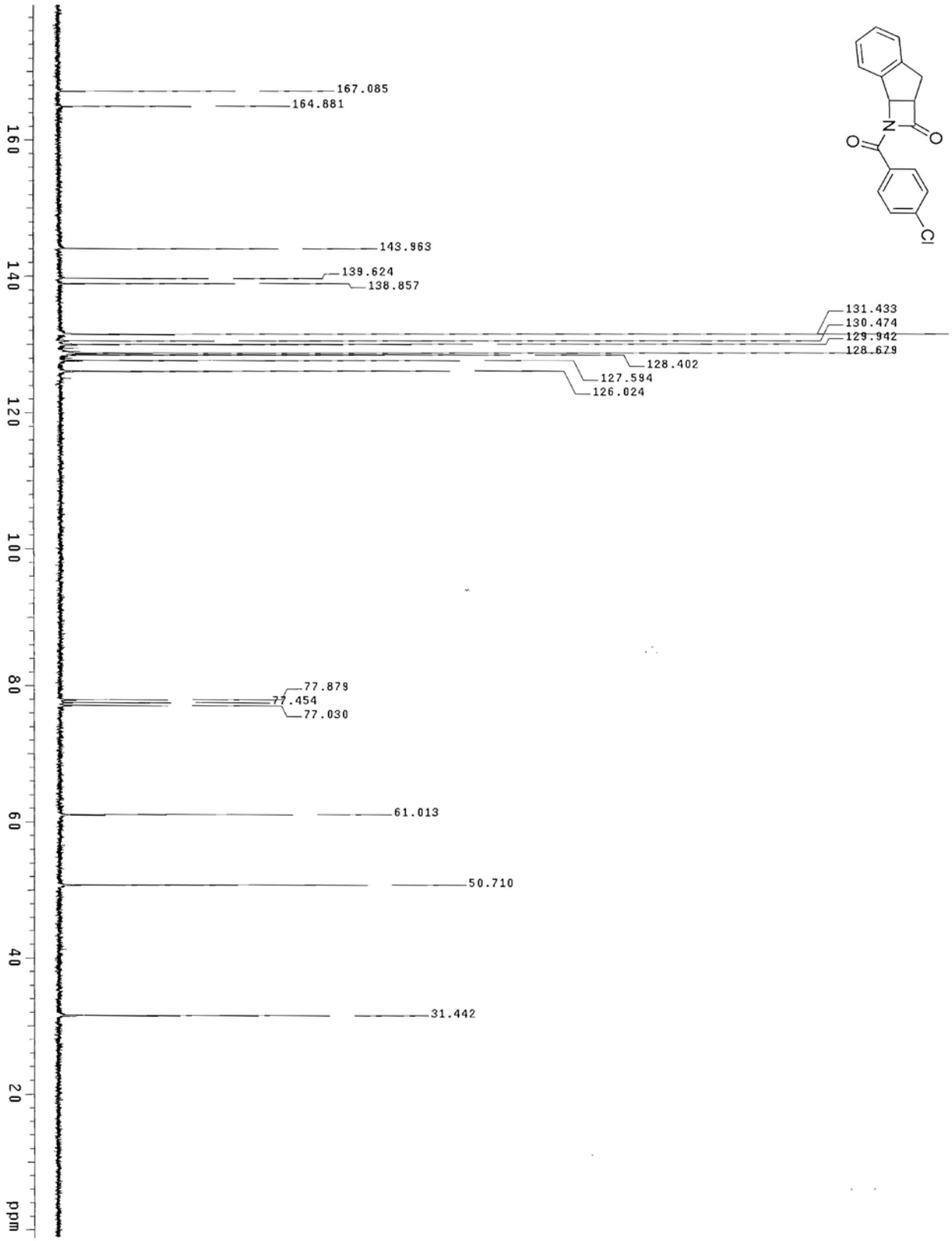

1.90
1.92
0.97
1.00
1.07
1.03
1.00
2.93
ppm
1000
700
600
Hz
1027.14
1022.46
1019.16
1014.49
677.27
672.04
663.51
658.29
606.30
601.35
593.92
588.42
543.86
537.81
531.76
525.71
Cl

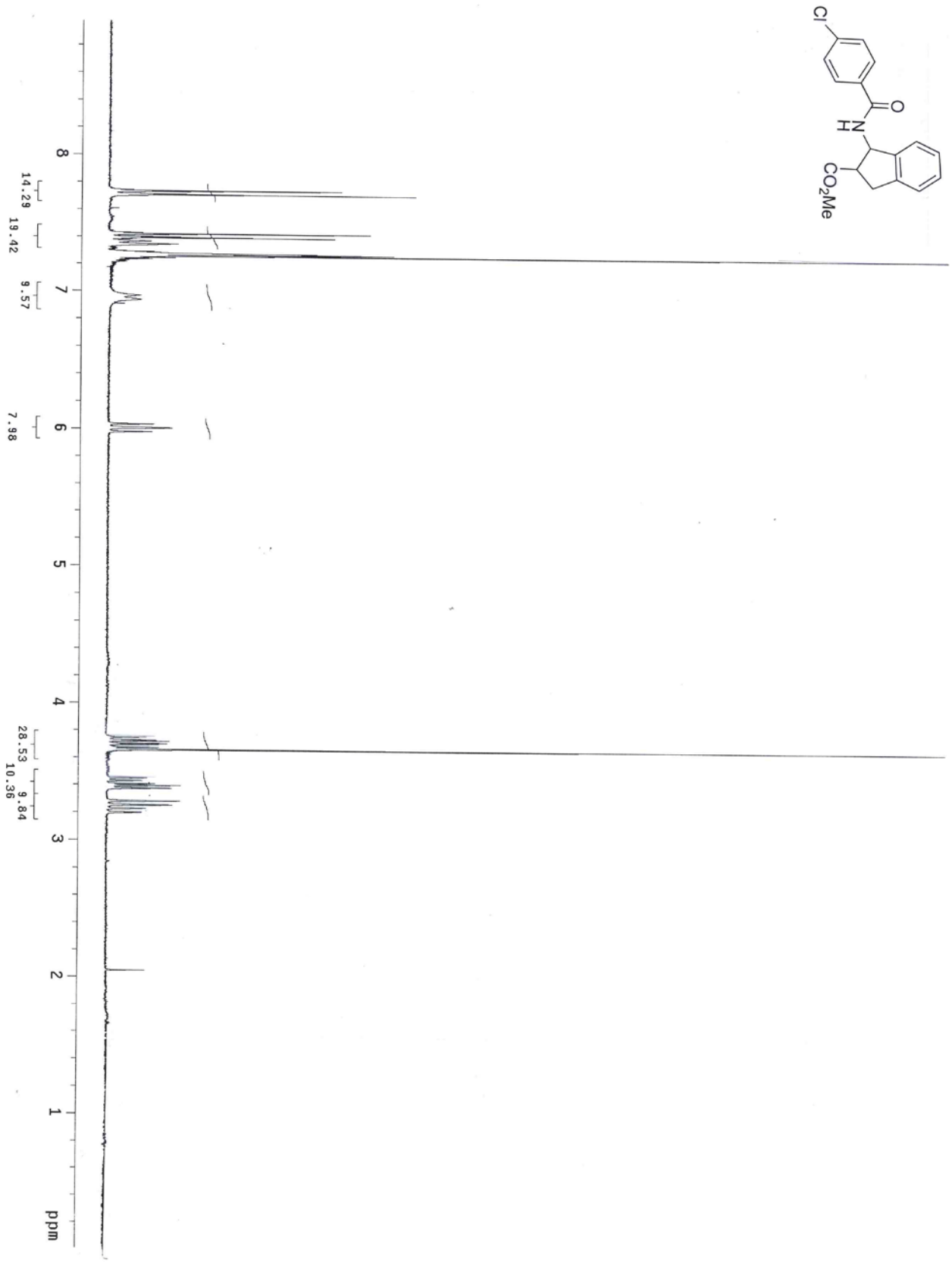

220
200
180
160
140
120
100
80
60
40
20
ppm
166.839
164.779
139.275
131.297
130.944
128.505
78.061
77.633
77.208
56.734
52.990
29.192
26.237
23.039
N
O
O
Cl

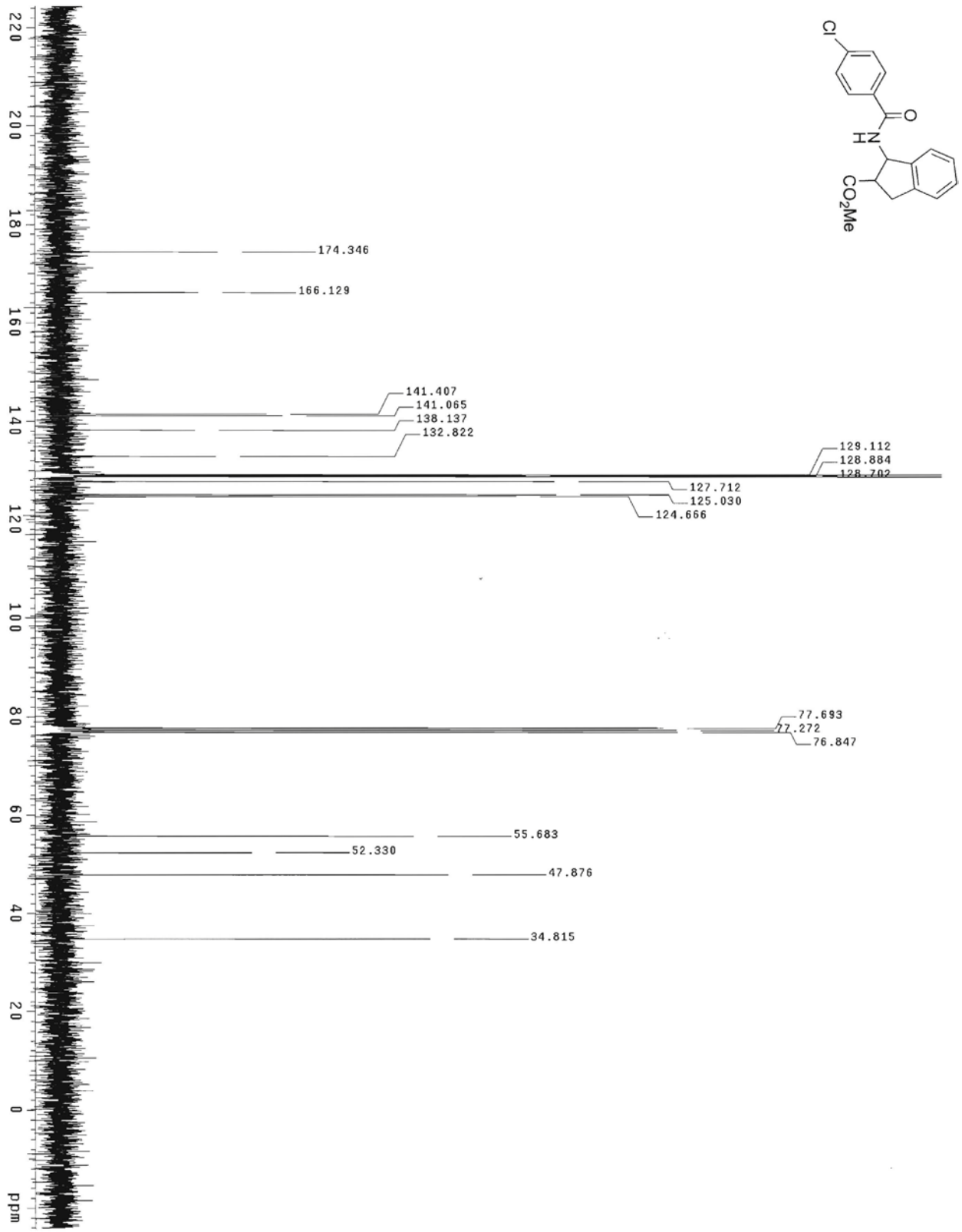

O
N
H
Cl
CO2Me
8
7
6
5
4
3
2
1
1.77
1.67
0.95
1.00
2.68
0.95
6.65

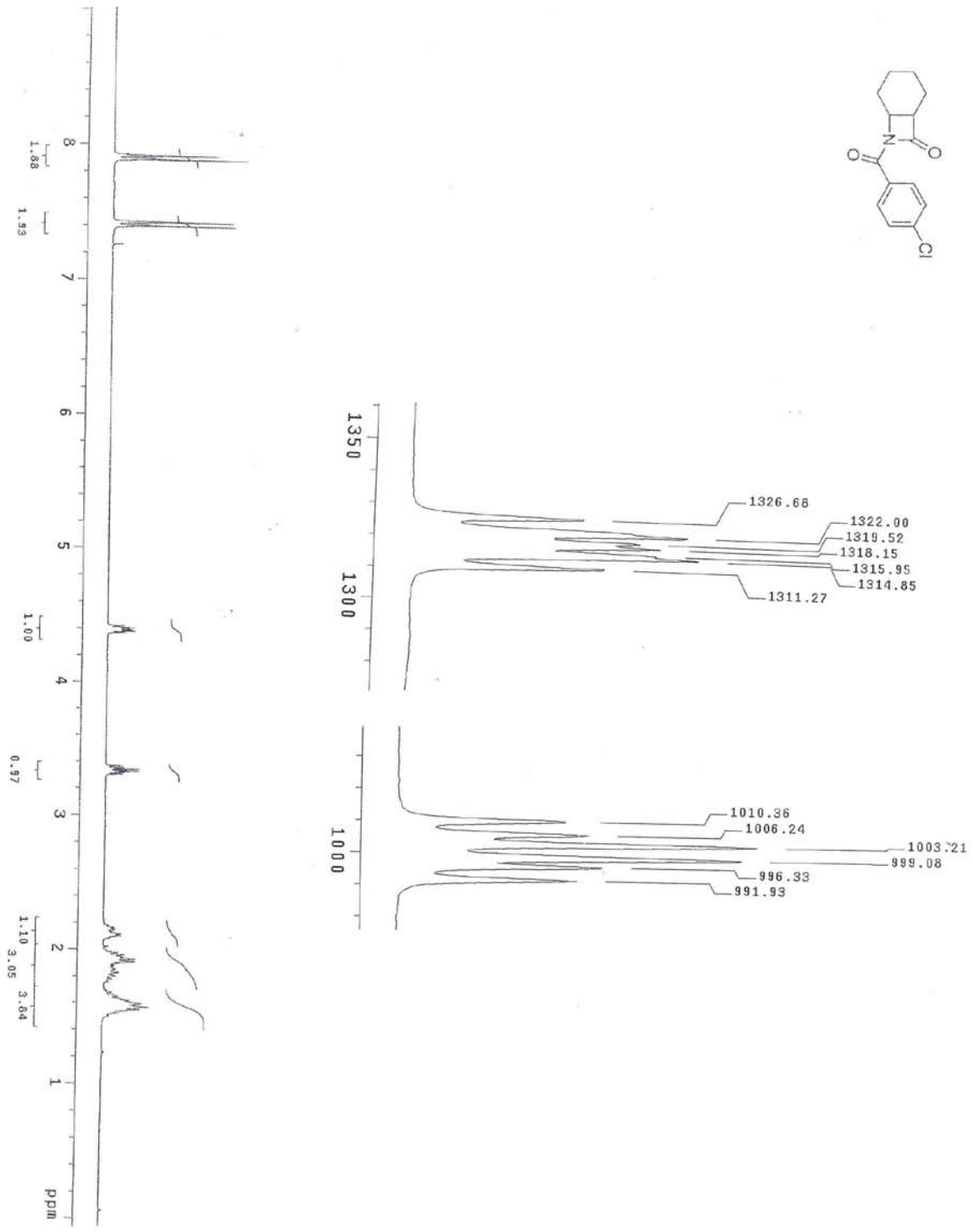

175.841
165.985
137.875
133.118
129.028
128.558
77.671
77.250
76.825
52.663
52.159
46.343
32.474
28.897
22.626
ppm

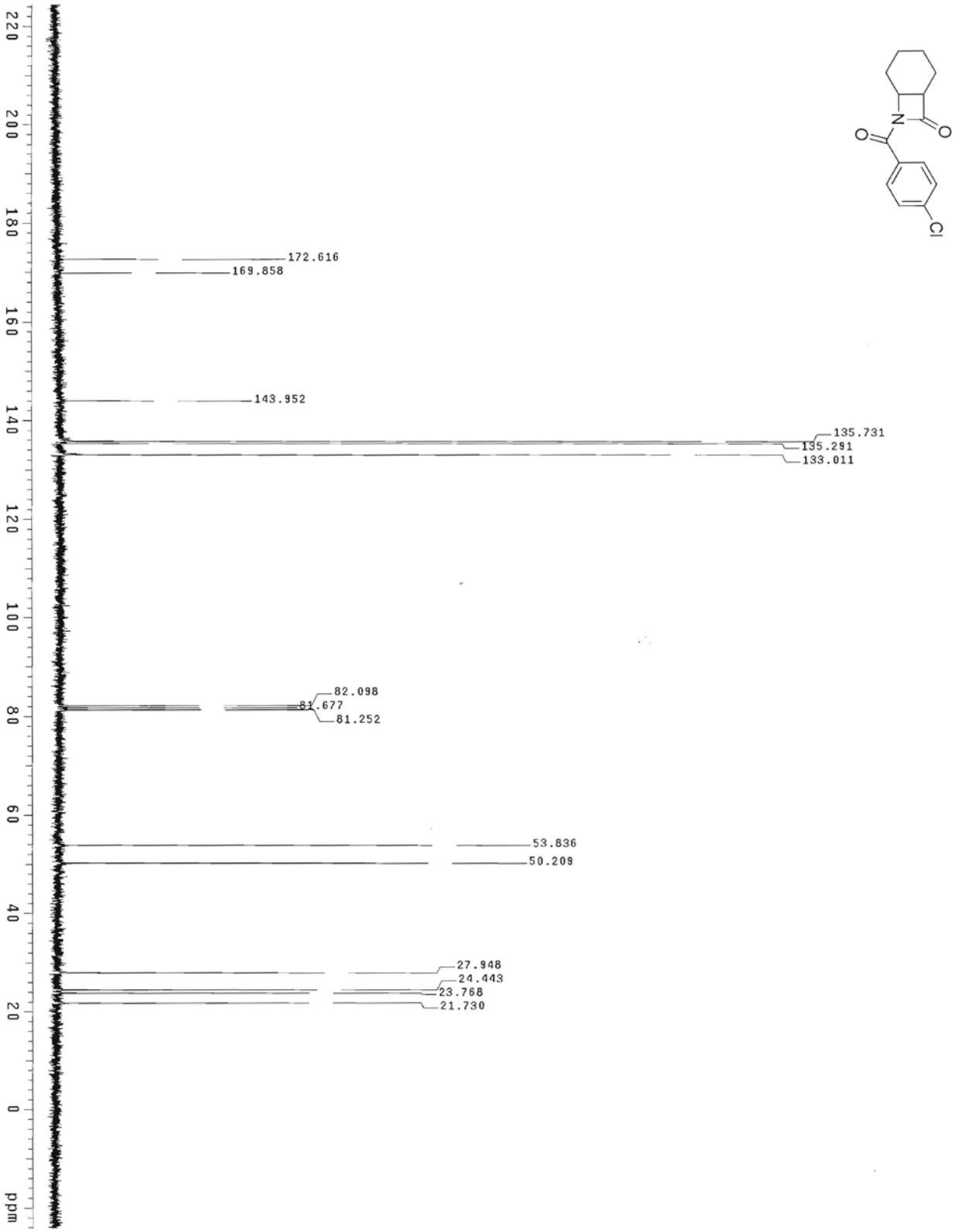

1.86
0.94
4.71
0.97
1.00
1.03
1.04
8
7
6
5
4
3
2
1
ppm
1221.60
1220.78
1219.13
1218.30
1216.10
1215.28
1213.63
1212.80
1210.88
1210.05
1208.40
1207.58
1205.38
1204.55
1202.90
1202.08
1200
1100
1000
1041.44
1023.84
N
O
O
Cl

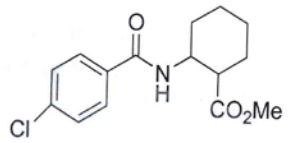

167.085
164.881
143.963
139.624
138.857
131.433
130.474
129.942
128.679
128.402
127.594
126.024
77.879
77.454
77.030
61.013
50.710
31.442
160
140
120
100
80
60
40
20
ppm
O
N
O
Cl

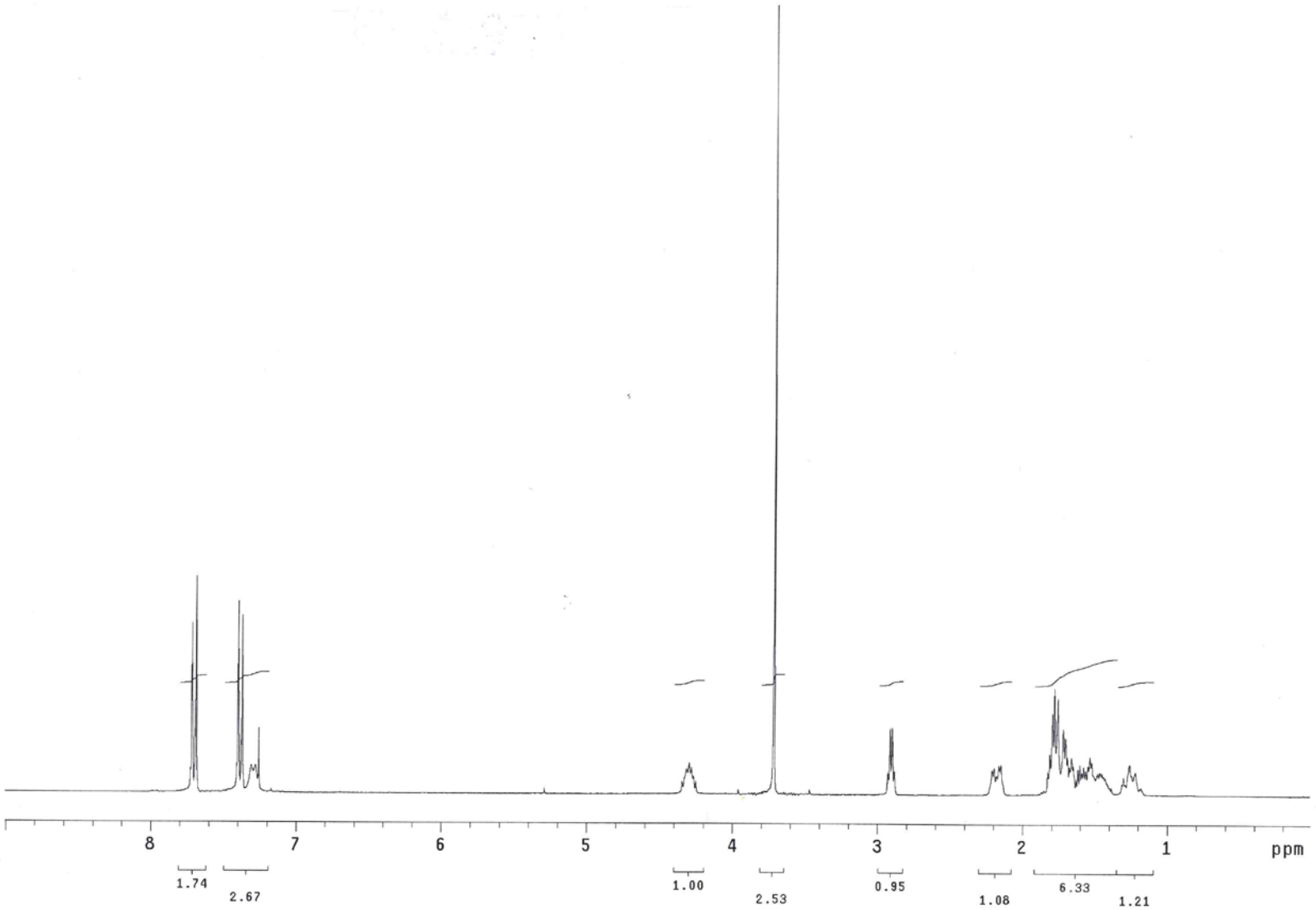

Cl
O
N
H
CO2Me
8
7
6
5
4
3
2
1
ppm
14.29
19.42
9.57
7.98
28.53
9.84
10.36

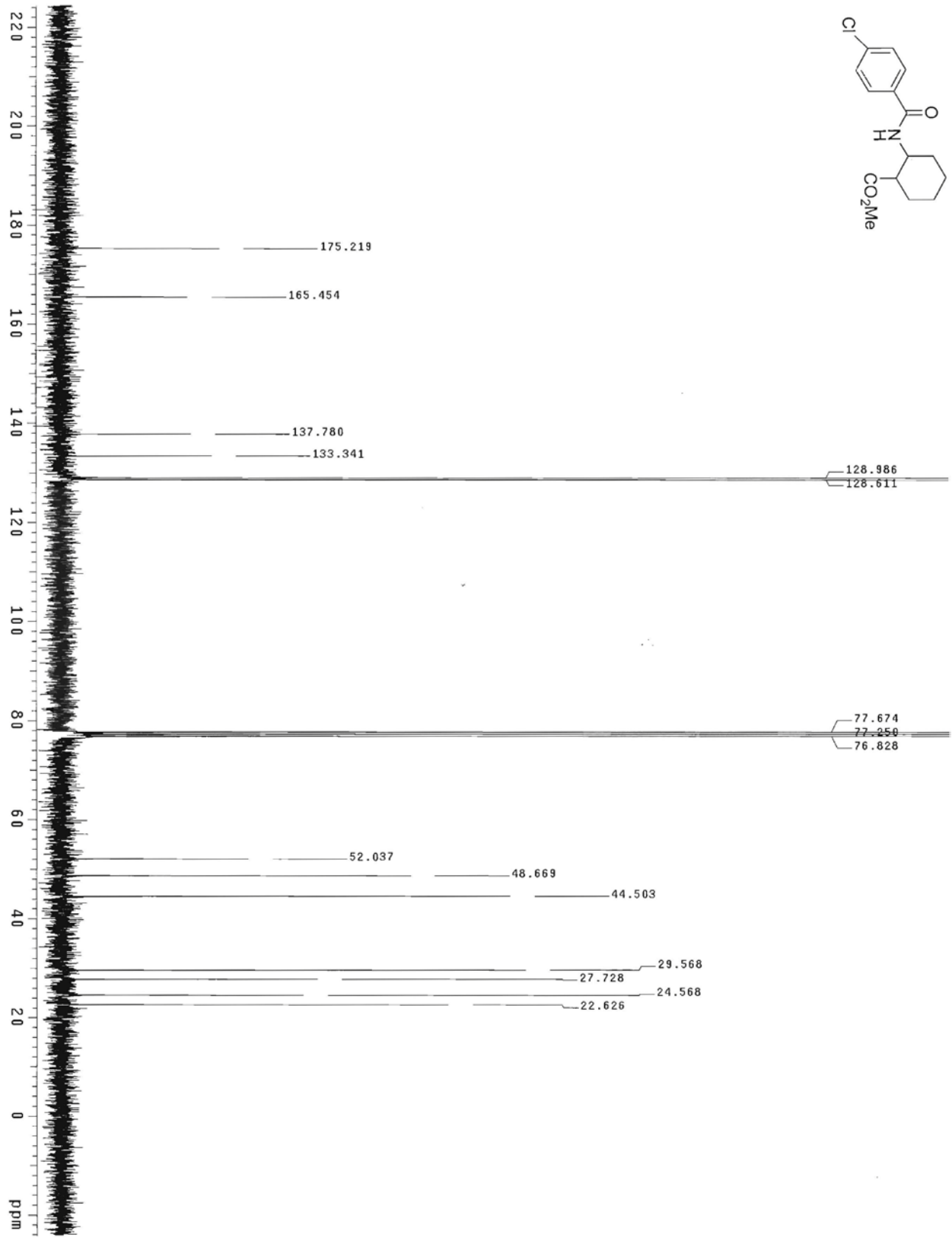

Cl
O
N
H
CO2Me
174.346
166.129
141.407
141.065
138.137
132.822
129.112
128.884
128.702
127.712
125.030
124.666
77.693
77.272
76.847
55.683
52.330
47.876
34.815
220
200
180
160
140
120
100
80
60
40
20
0
ppm

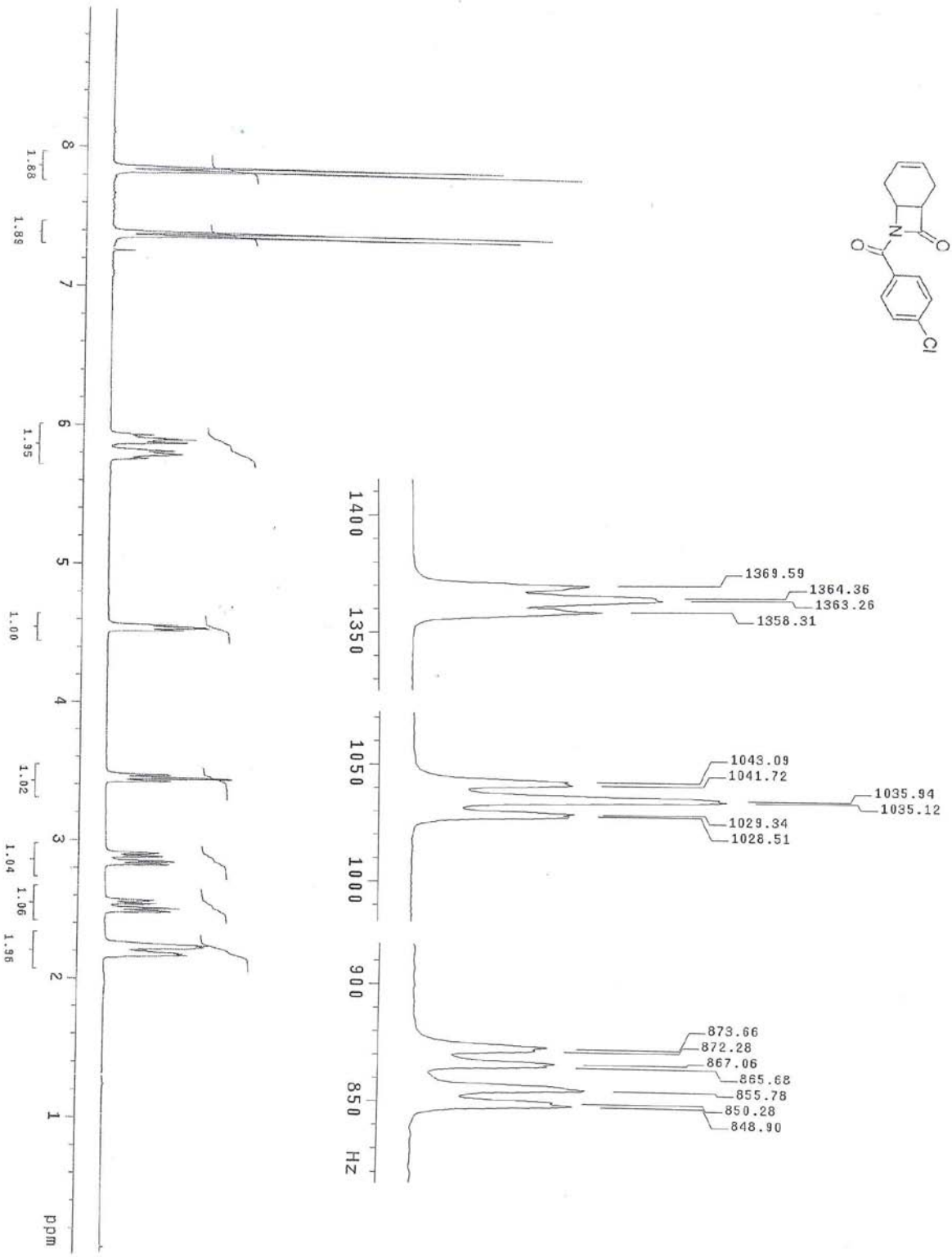

1.88
1.93
1.00
0.97
1.10
3.05
3.04
ppm
1350
1300
1000
1326.68
1322.00
1319.52
1318.15
1315.95
1314.85
1311.27
1010.36
1006.24
1003.21
999.08
996.33
991.93
O
N
O
Cl

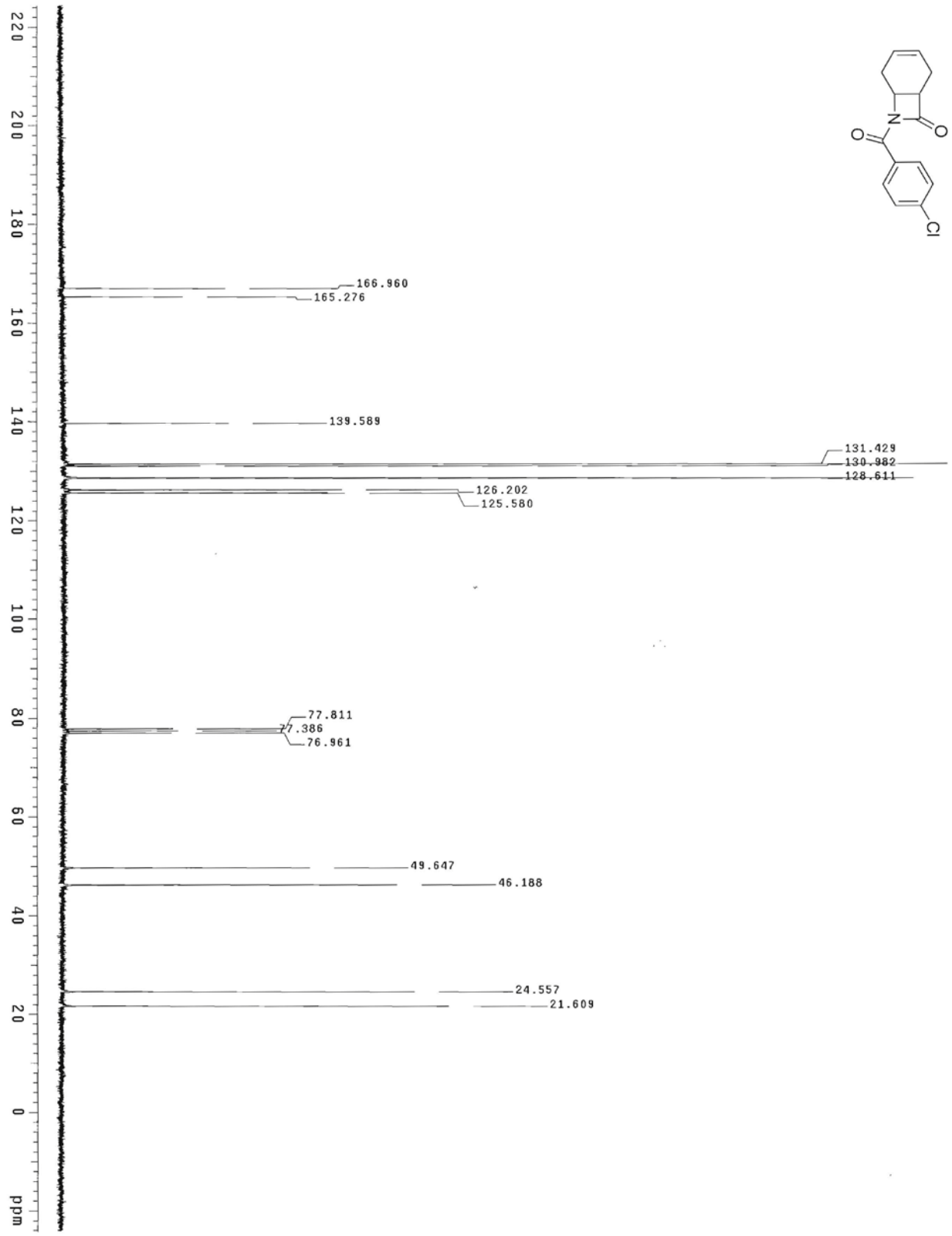

220
200
180
160
140
120
100
80
60
40
20
0
ppm
172.616
169.858
143.952
135.731
135.291
133.011
82.098
81.677
81.252
53.836
50.209
27.948
24.443
23.768
21.730
N
O
O
O
Cl

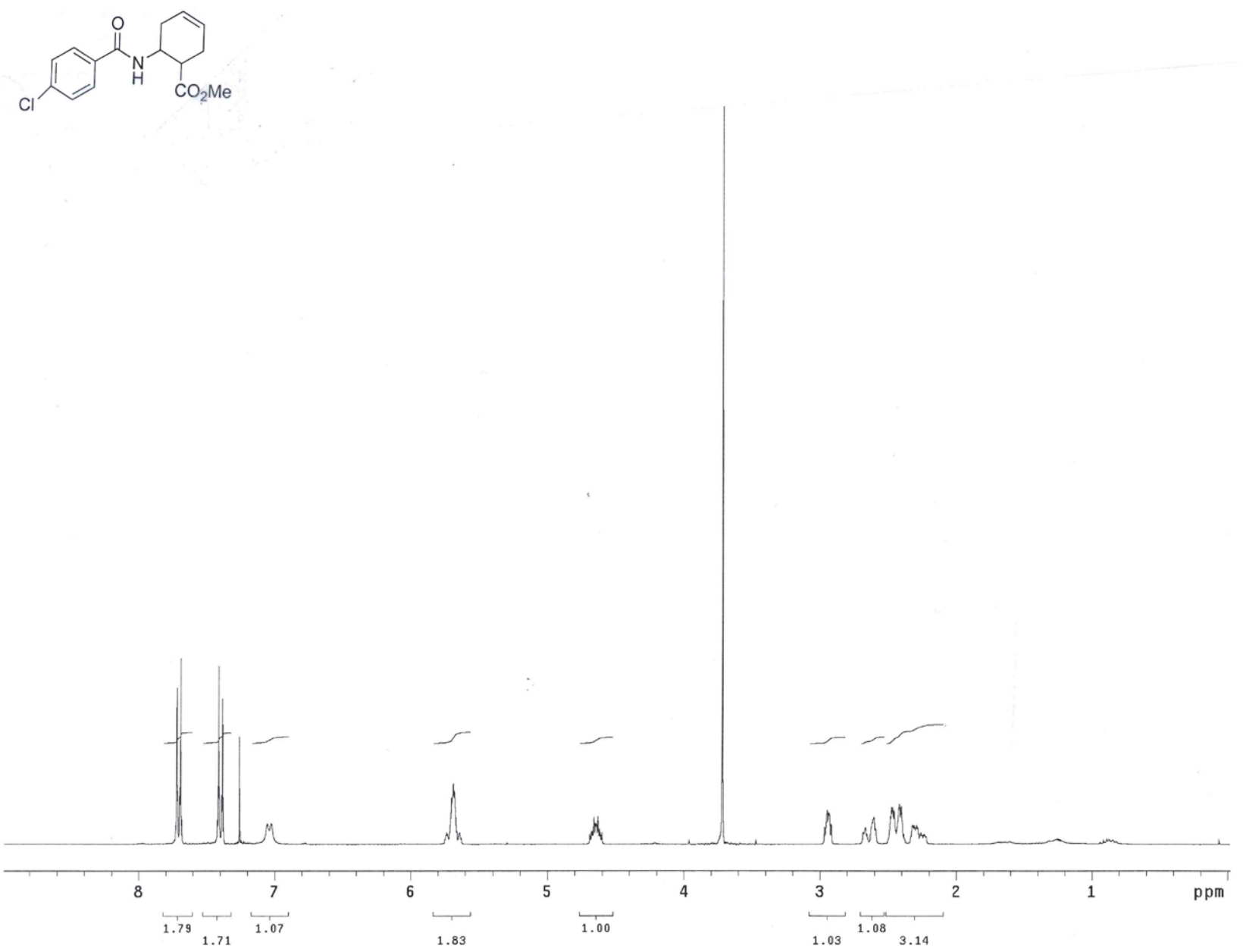

O
N
H
Cl
CO2Me

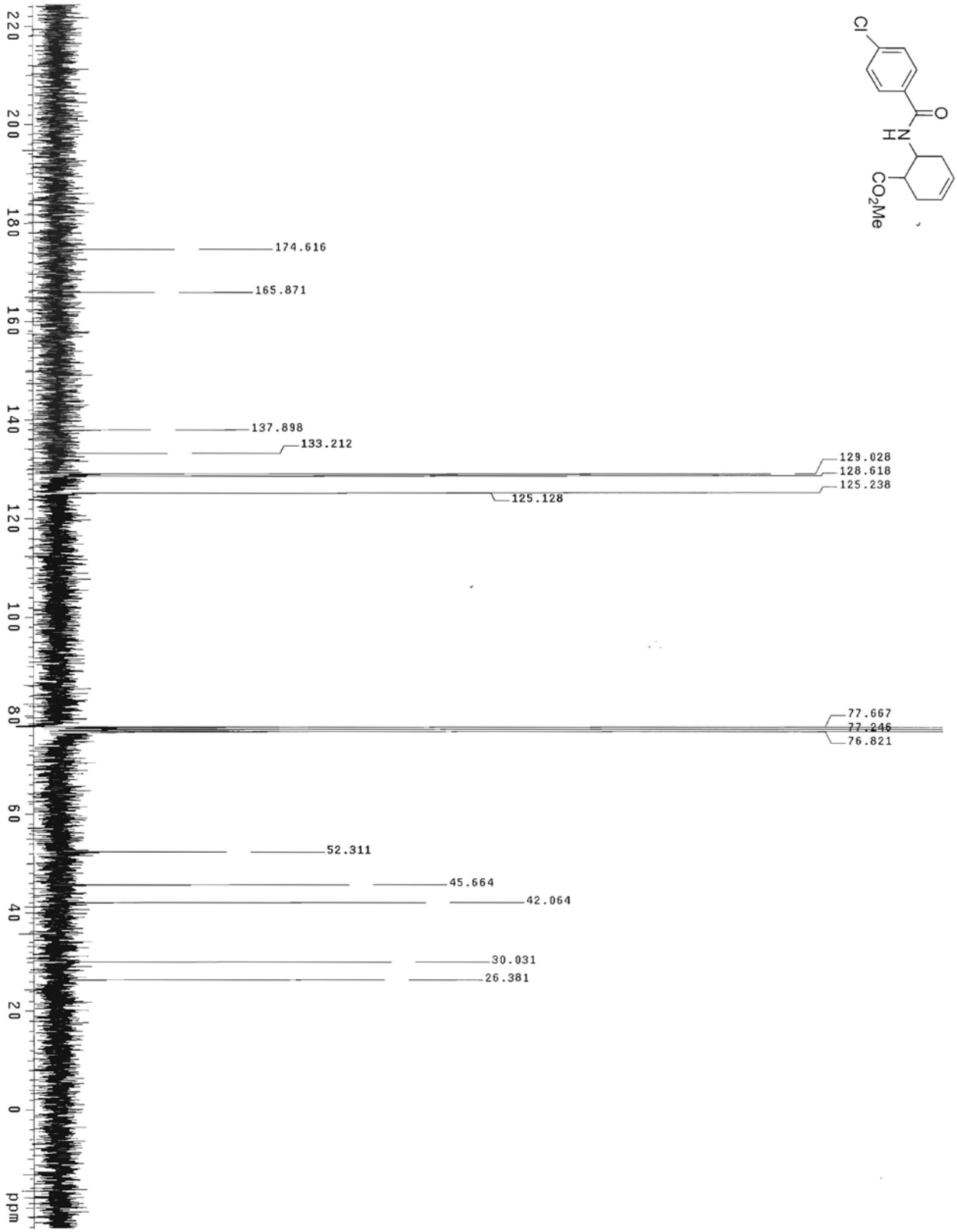

8
7
6
5
4
3
2
1
ppm
1.74
2.67
1.00
2.53
0.95
1.08
6.33
1.21

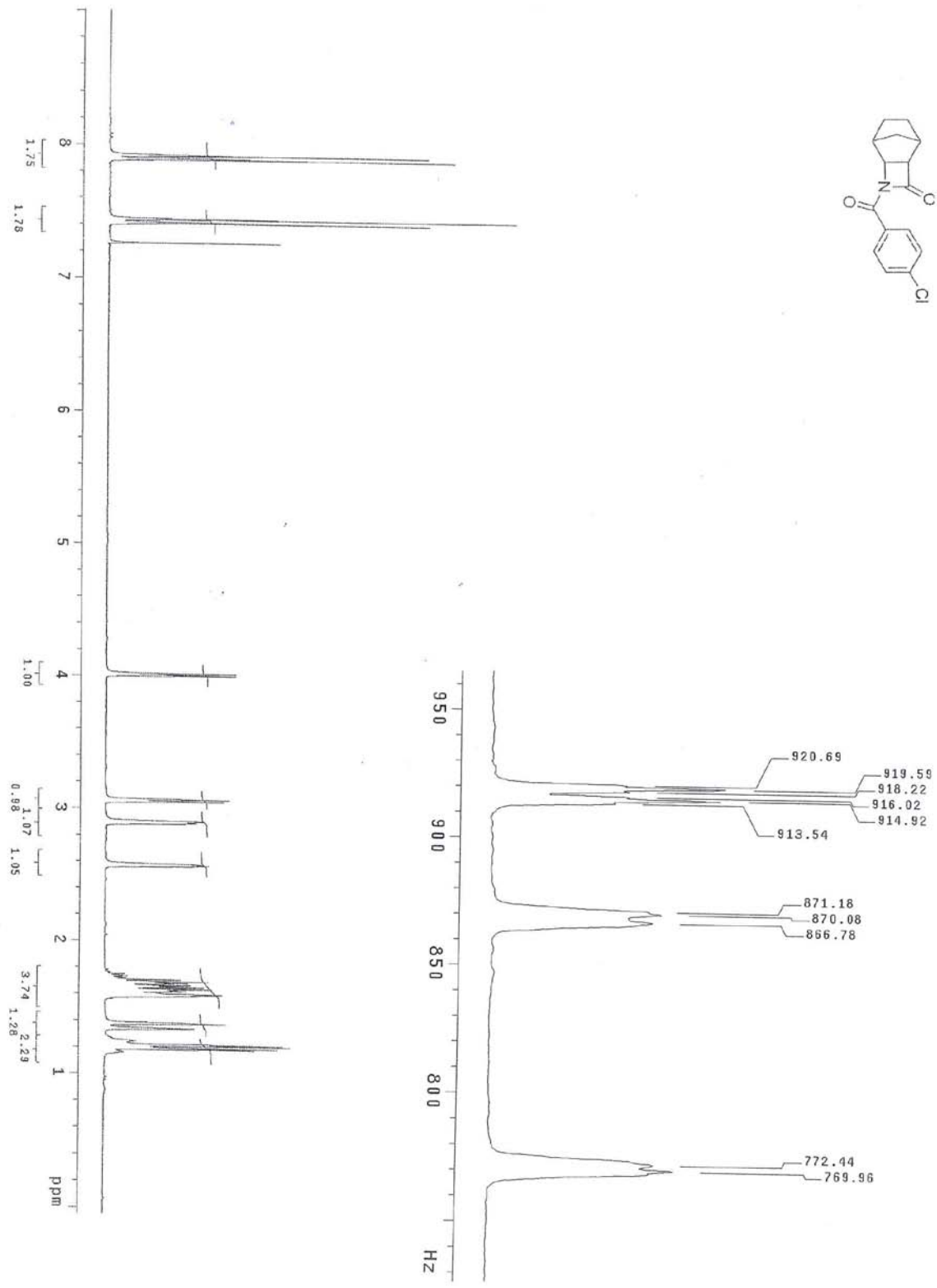

175.219
165.454
137.780
133.341
128.986
128.611
77.674
77.250
76.828
52.037
48.669
44.503
29.568
27.728
24.568
22.626
ppm
Cl
O
N
H
CO2Me

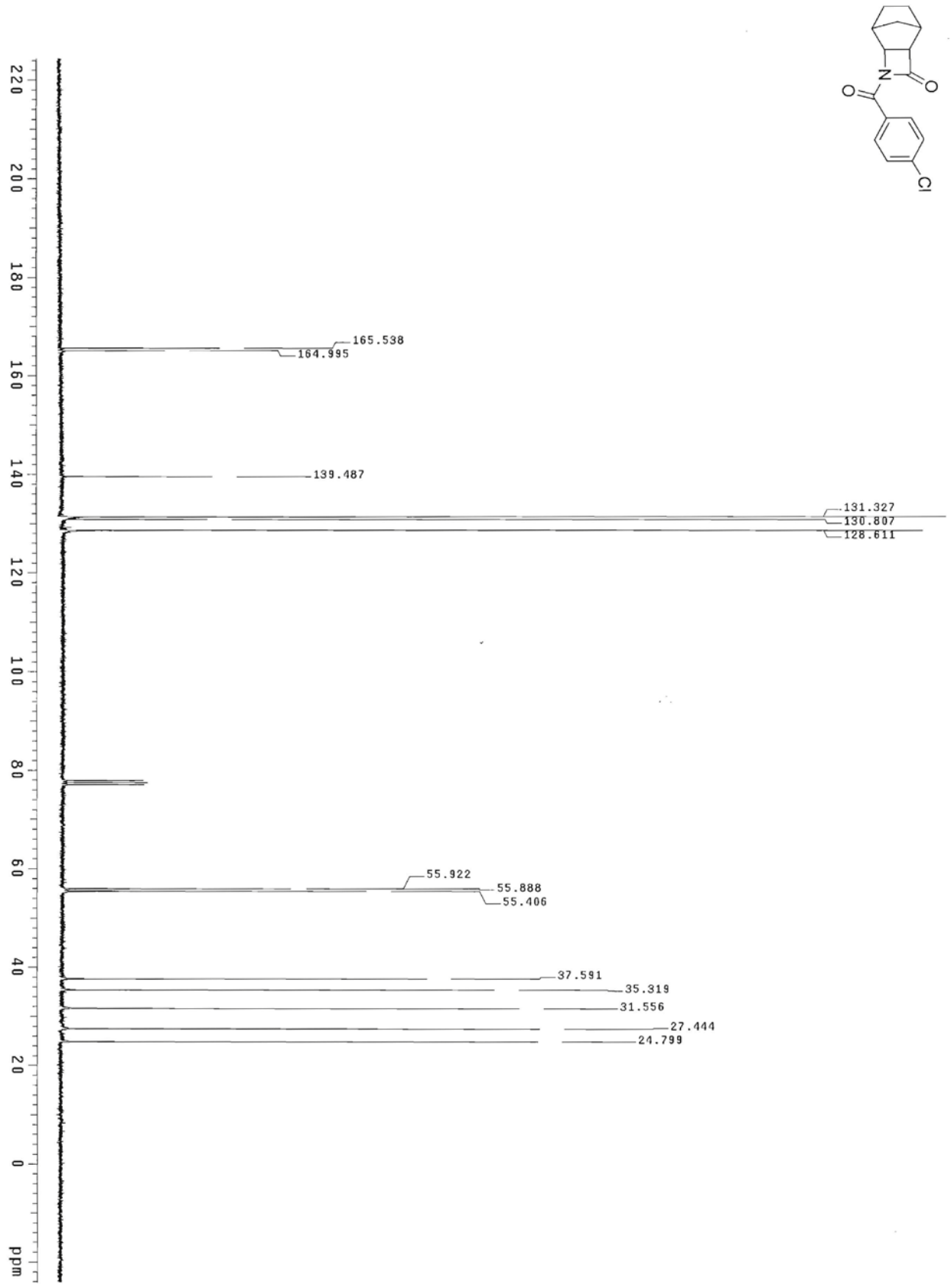

1.88
1.89
1.95
1.00
1.02
1.04
1.06
1.96
8
7
6
5
4
3
2
1
ppm
1400
1350
1050
1000
900
850
Hz
1369.59
1364.36
1363.26
1358.31
1043.09
1041.72
1035.94
1035.12
1029.34
1028.51
873.66
872.28
867.06
865.68
855.78
850.28
848.90
O
N
O
O
Cl

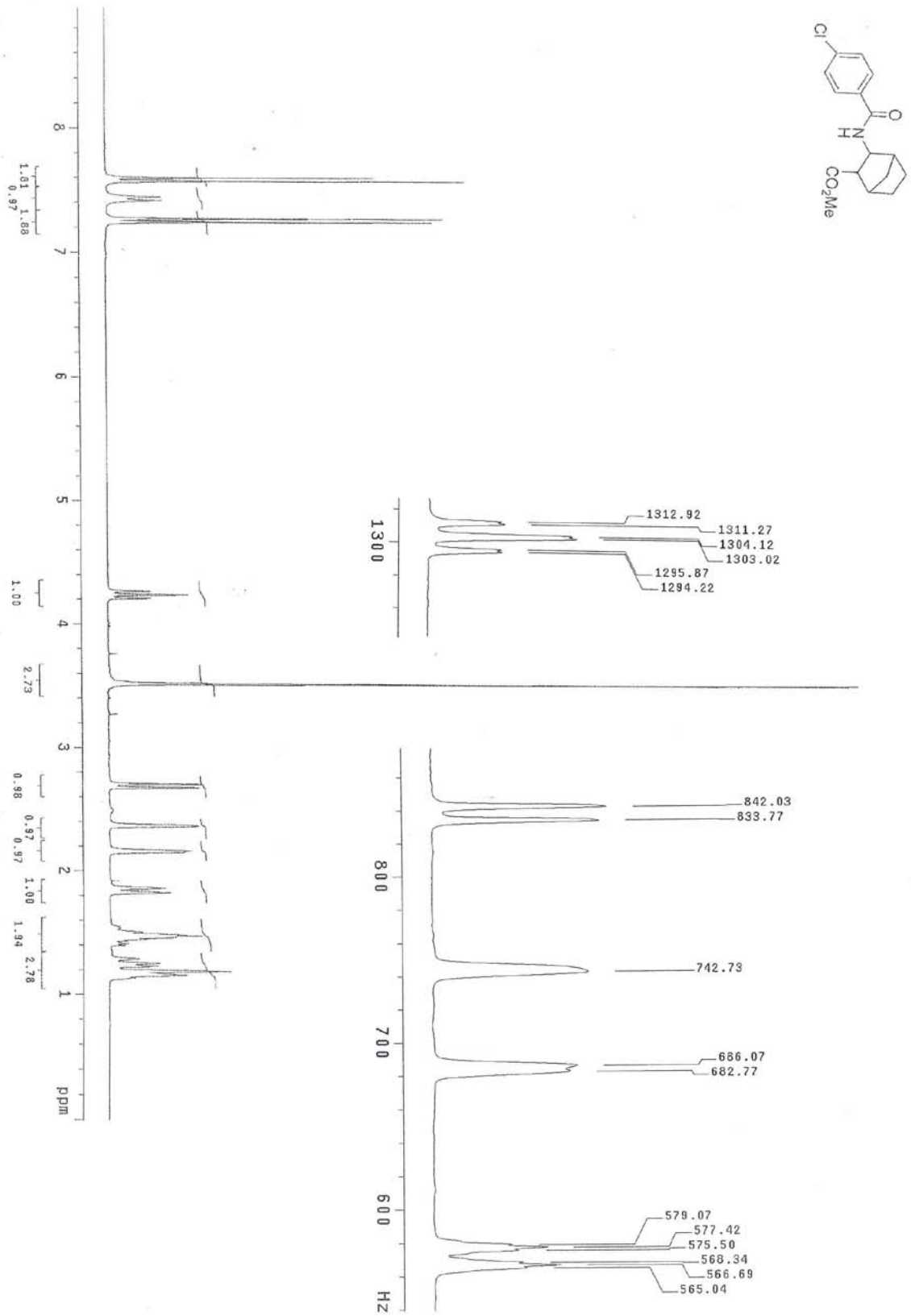

166.960
165.276
139.589
131.429
130.982
128.611
126.202
125.580
77.811
77.386
76.961
49.647
46.188
24.557
21.609
ppm
O
N
O
Cl

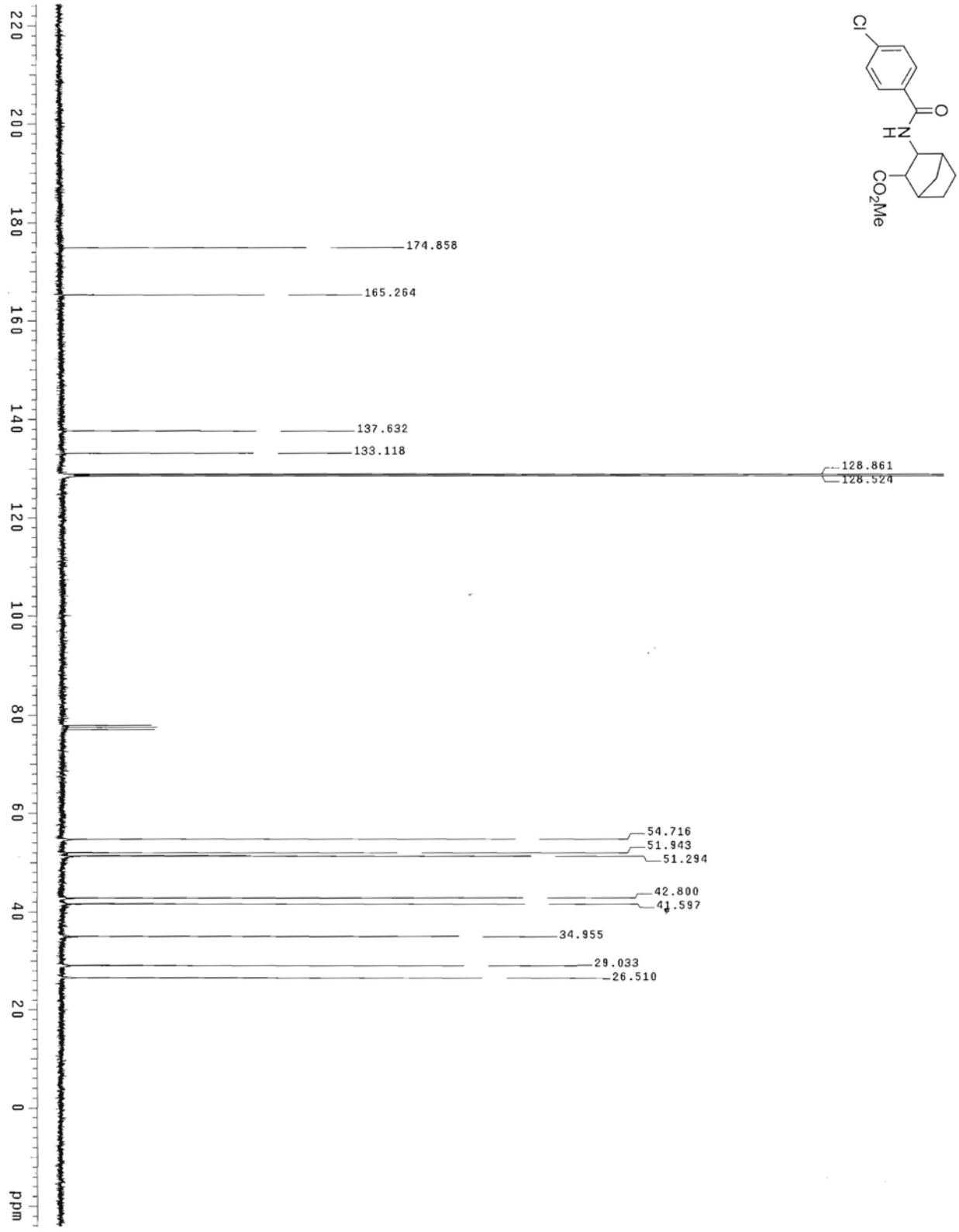

O
N
H
Cl
CO2Me
8
7
6
5
4
3
2
1
ppm
1.79
1.71
1.07
1.83
1.00
1.03
1.08
3.14

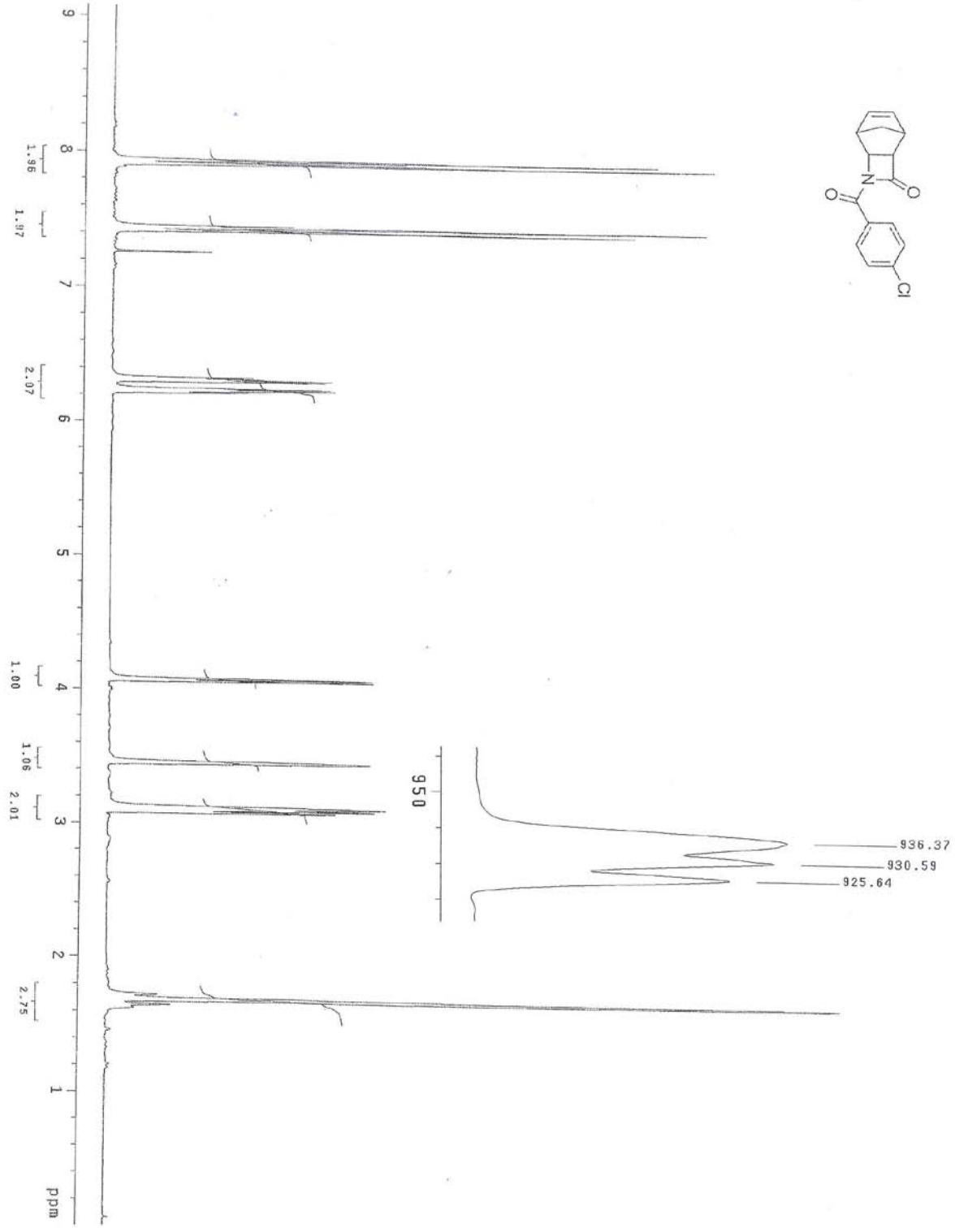

Cl
O
N
H
CO2Me
174.616
165.871
137.898
133.212
129.028
128.618
125.238
125.128
77.667
77.246
76.821
52.311
45.664
42.064
30.031
26.381
220
200
180
160
140
120
100
80
60
40
20
0
ppm

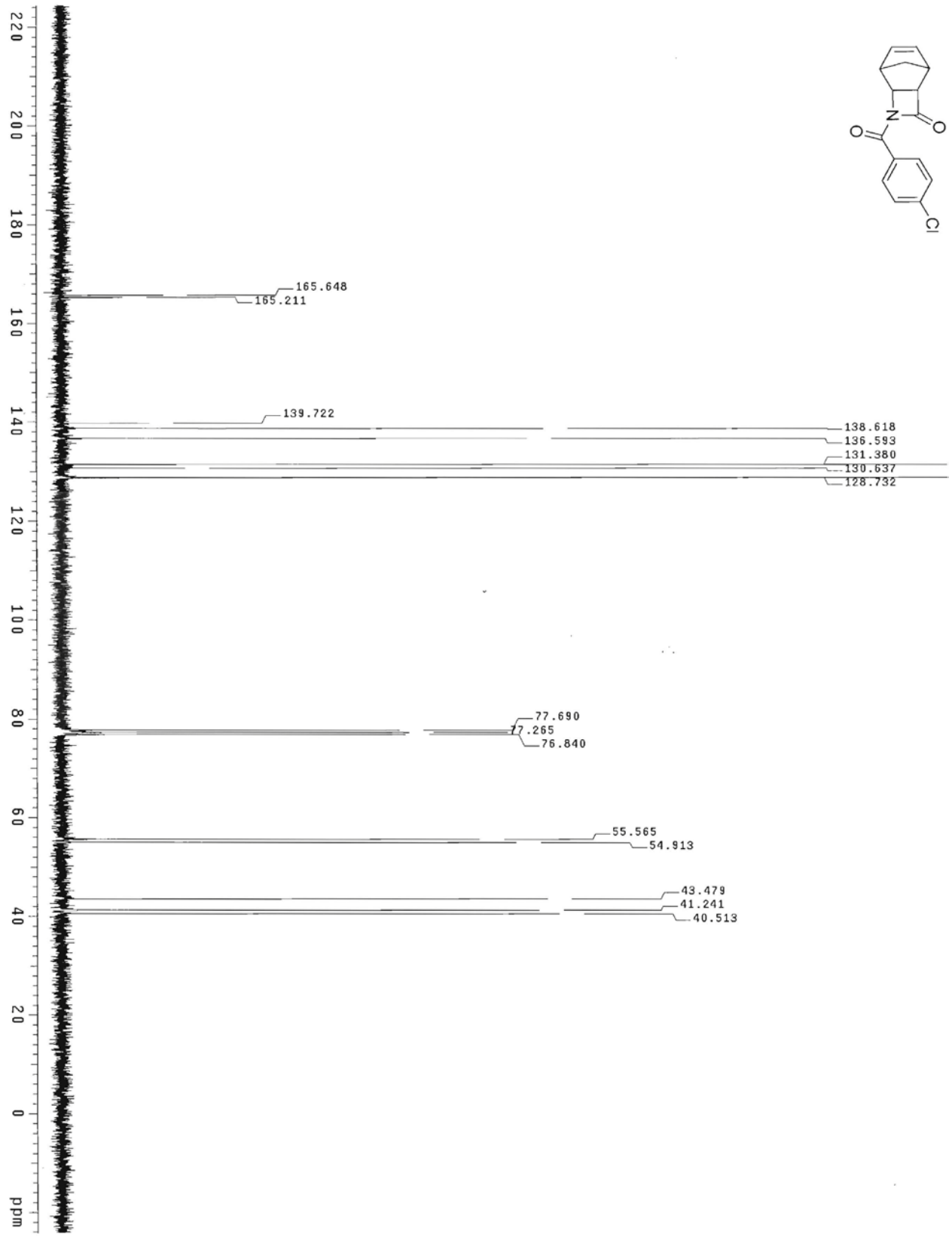

8
7
6
5
4
3
2
1
ppm
1.75
1.78
1.00
0.98
1.07
1.05
3.74
1.28
2.29
950
900
850
800
Hz
920.69
919.59
918.22
916.02
914.92
913.54
871.18
870.08
866.78
772.44
769.96
O
N
O
Cl

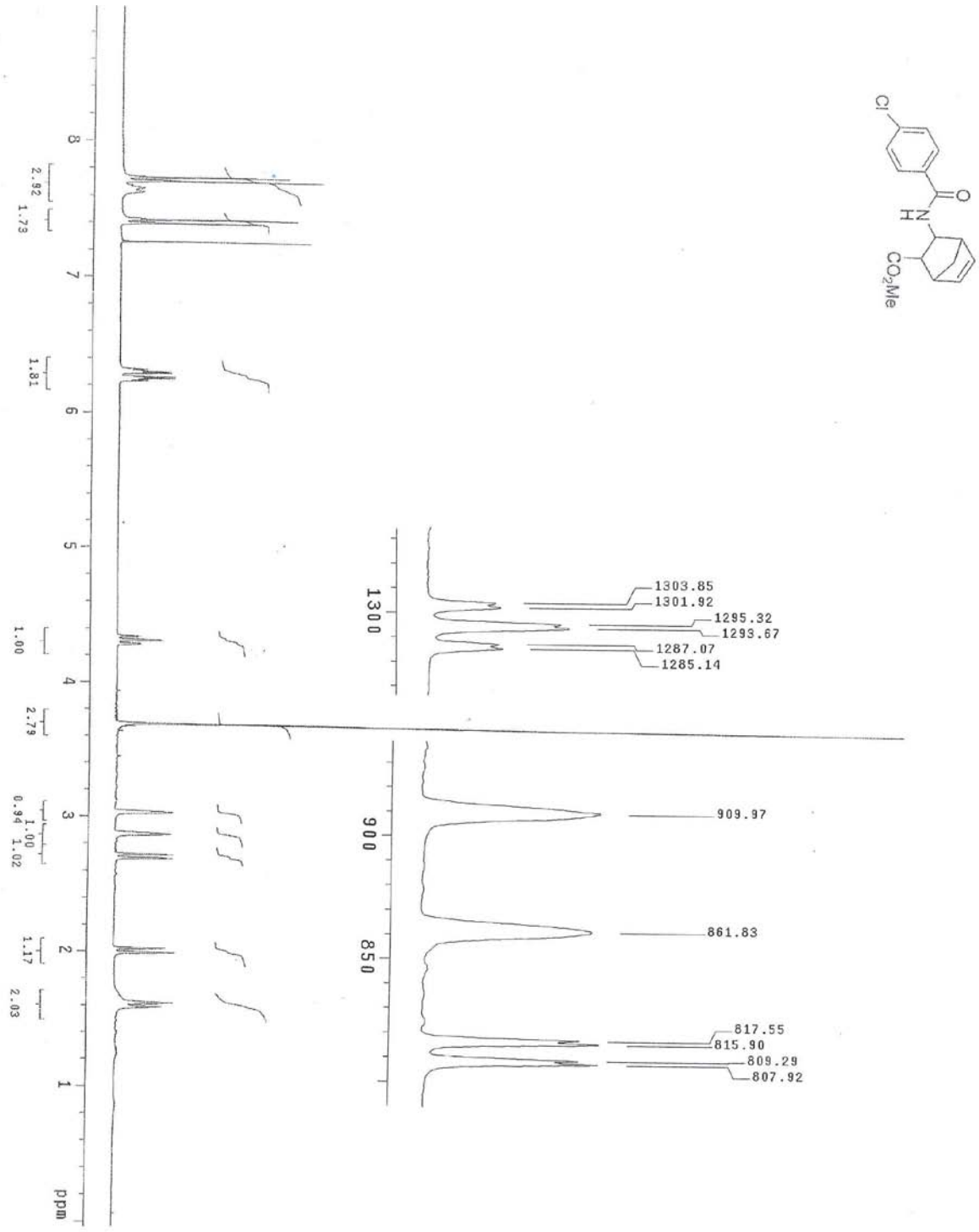

220
200
180
160
140
120
100
80
60
40
20
0
ppm
165.538
164.995
139.487
131.327
130.807
128.611
55.922
55.888
55.406
37.591
35.319
31.556
27.444
24.799
N
O
O
O
Cl

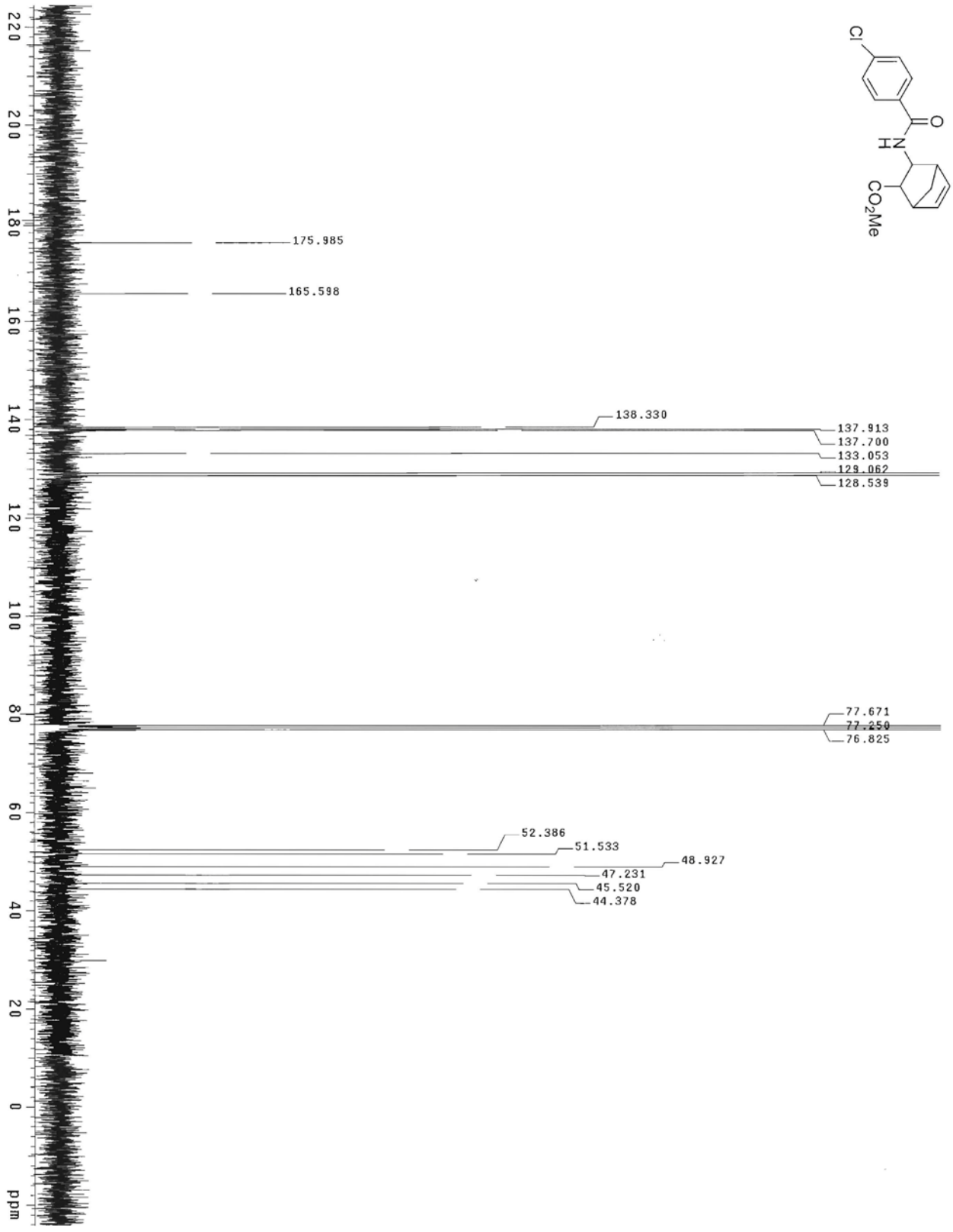

Cl
O
N
H
CO2Me
1312.92
1311.27
1304.12
1303.02
1295.87
1294.22
842.03
833.77
742.73
686.07
682.77
579.07
577.42
575.50
568.34
566.69
565.04
1300
800
700
600
Hz
ppm

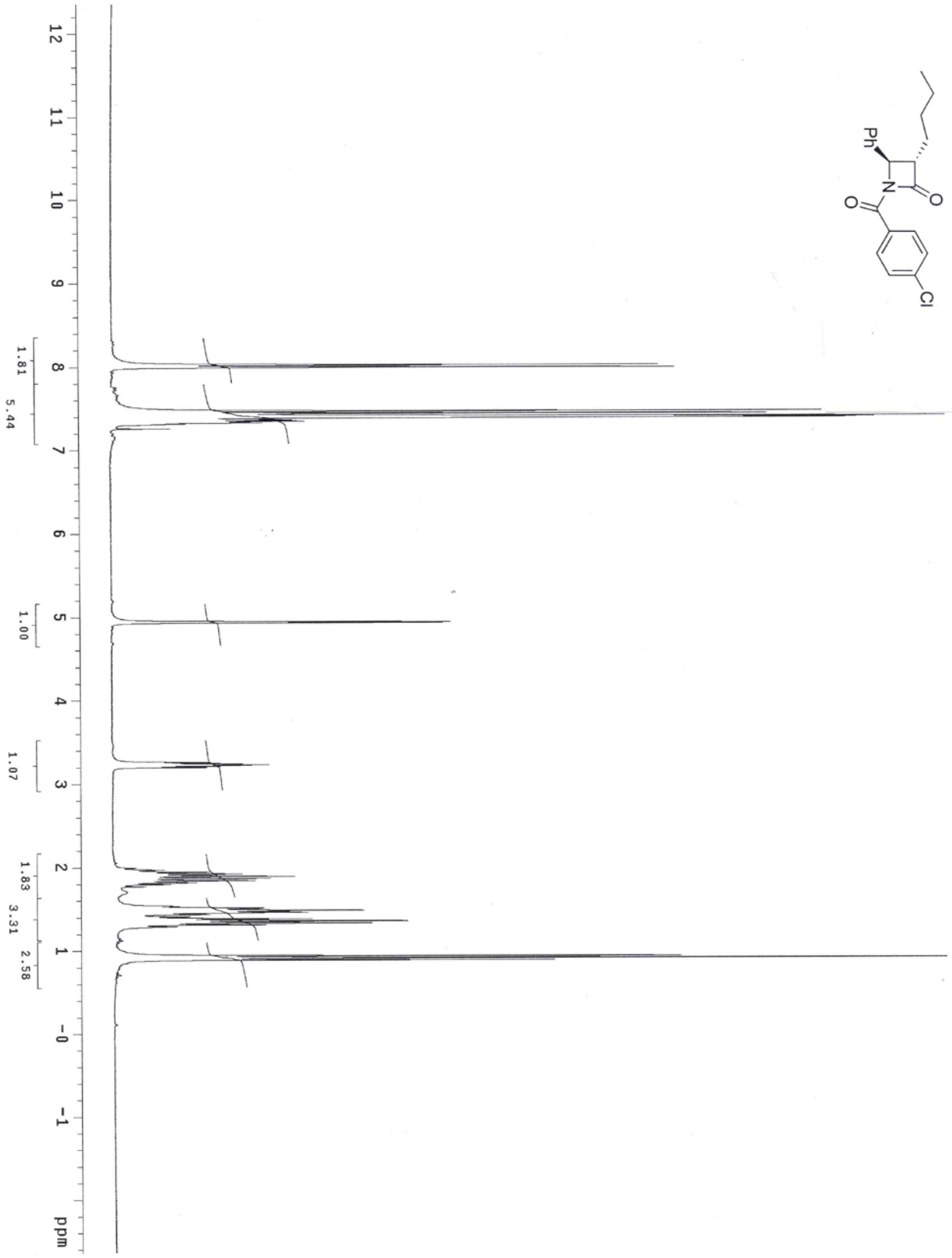

174.858
165.264
137.632
133.118
128.861
128.524
54.716
51.943
51.294
42.800
41.597
34.955
29.033
26.510
220
200
180
160
140
120
100
80
60
40
20
0
ppm
Cl
O
N
H
CO2Me

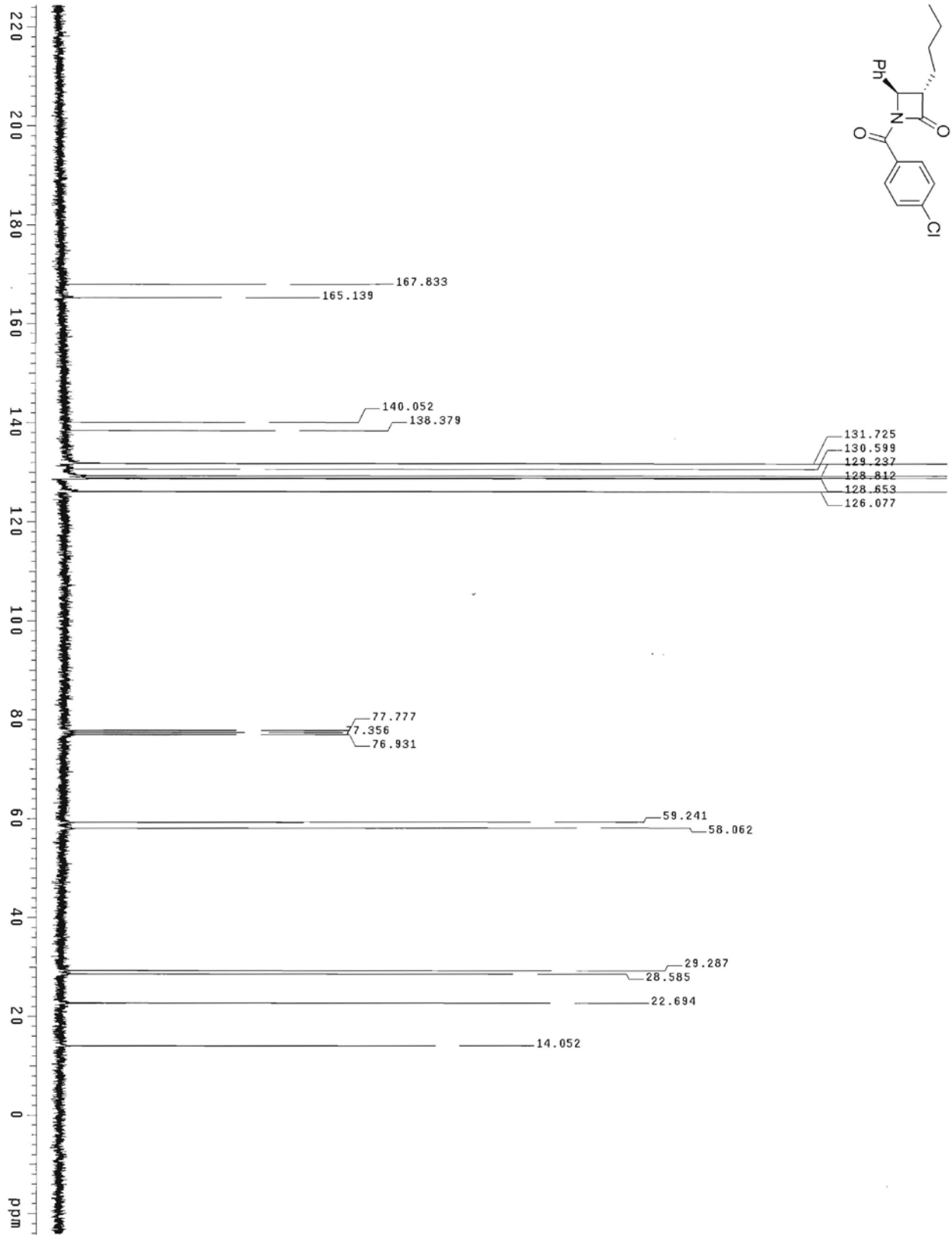

9
8
7
6
5
4
3
2
1
ppm
1.96
1.97
2.07
1.00
1.06
2.01
2.75
950
936.37
930.59
925.64
O
N
O
Cl

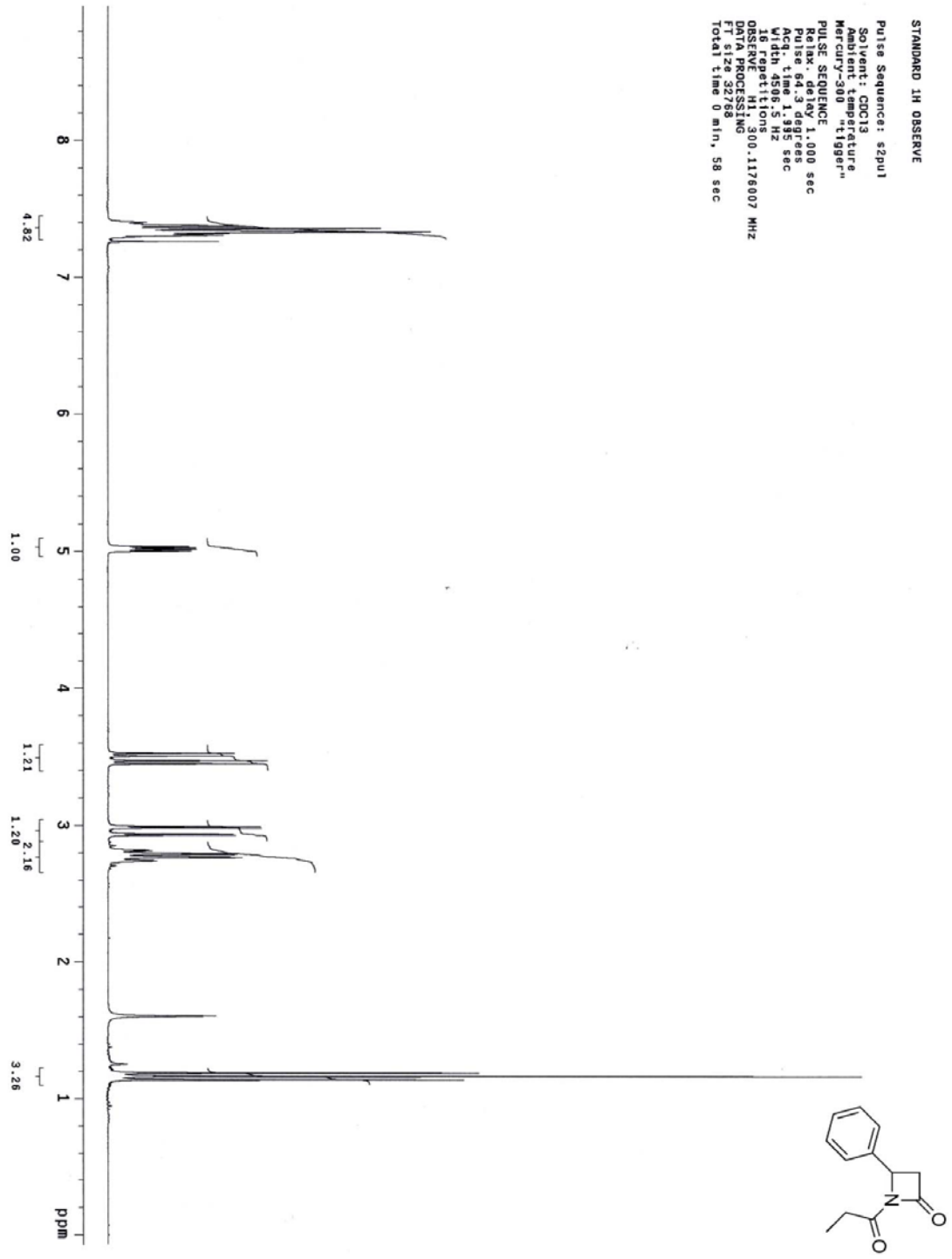

165.648
165.211
139.722
138.618
136.593
131.380
130.637
128.732
77.690
77.265
76.840
55.565
54.913
43.479
41.241
40.513
ppm

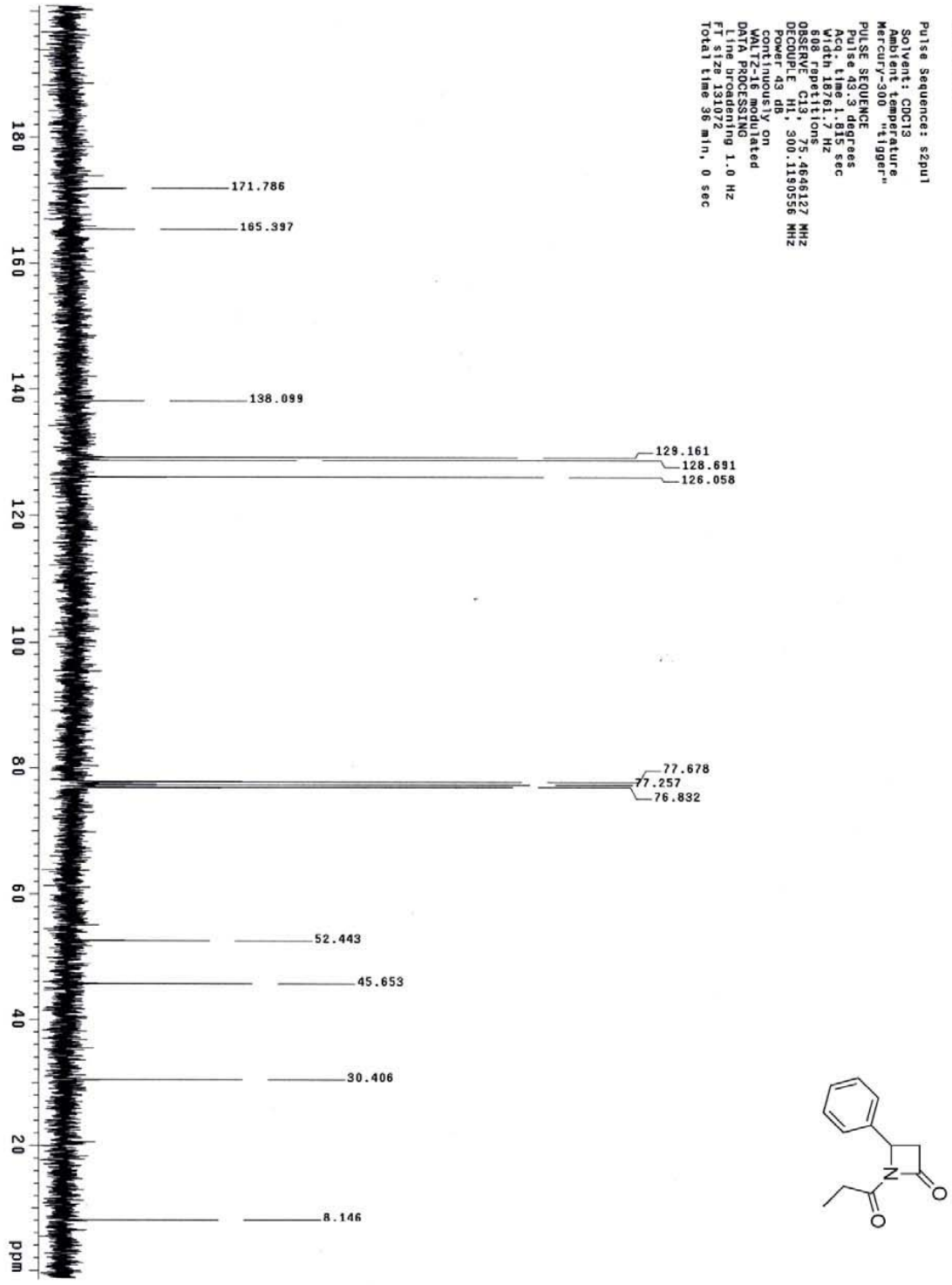

Cl
O
H
N
CO2Me
1303.85
1301.92
1295.32
1293.67
1287.07
1285.14
909.97
861.83
817.55
815.90
809.29
807.92
1300
900
850
ppm

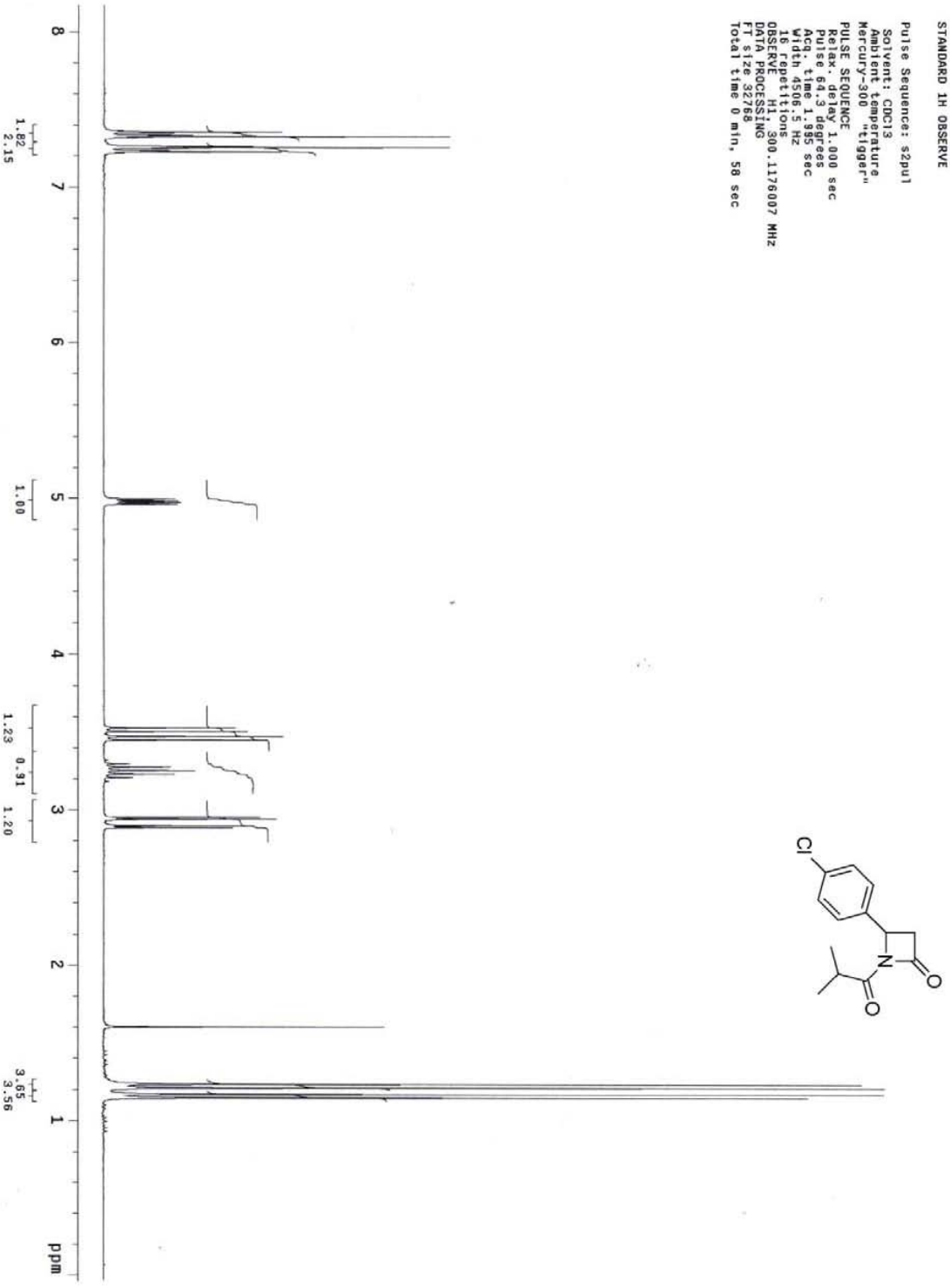

175.985
165.598
138.330
137.913
137.700
133.053
129.062
128.539
77.671
77.250
76.825
52.386
51.533
48.927
47.231
45.520
44.378
Cl
O
N
H
CO2Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm

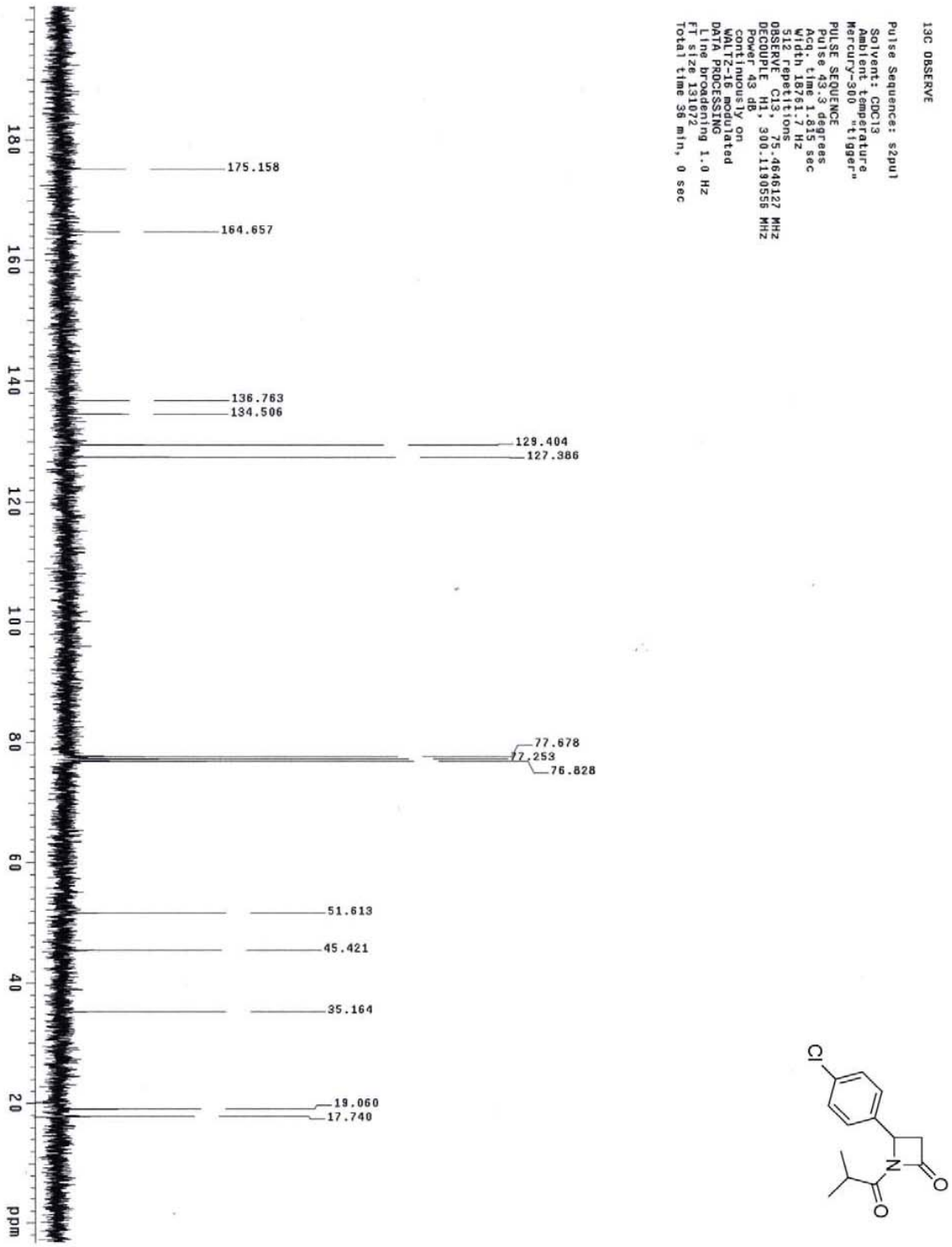

Ph
N
O
O
Cl
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
1.81
5.44
1.00
1.07
1.83
3.31
2.58

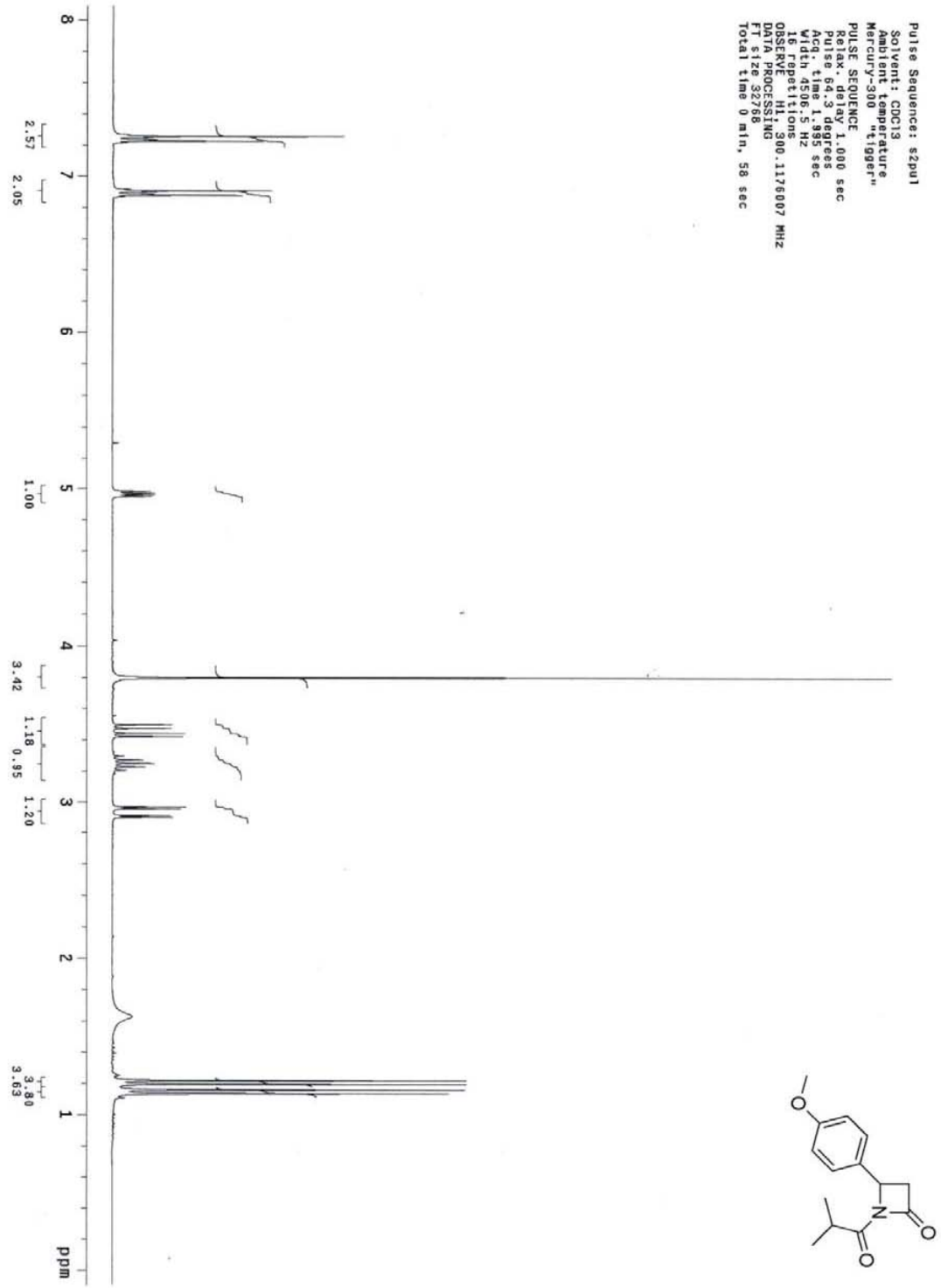

Ph
N
O
O
Cl
167.833
165.139
140.052
138.379
131.725
130.599
129.237
128.812
128.653
126.077
77.777
77.356
76.931
59.241
58.062
29.287
28.585
22.694
14.052
220
200
180
160
140
120
100
80
60
40
20
0
ppm

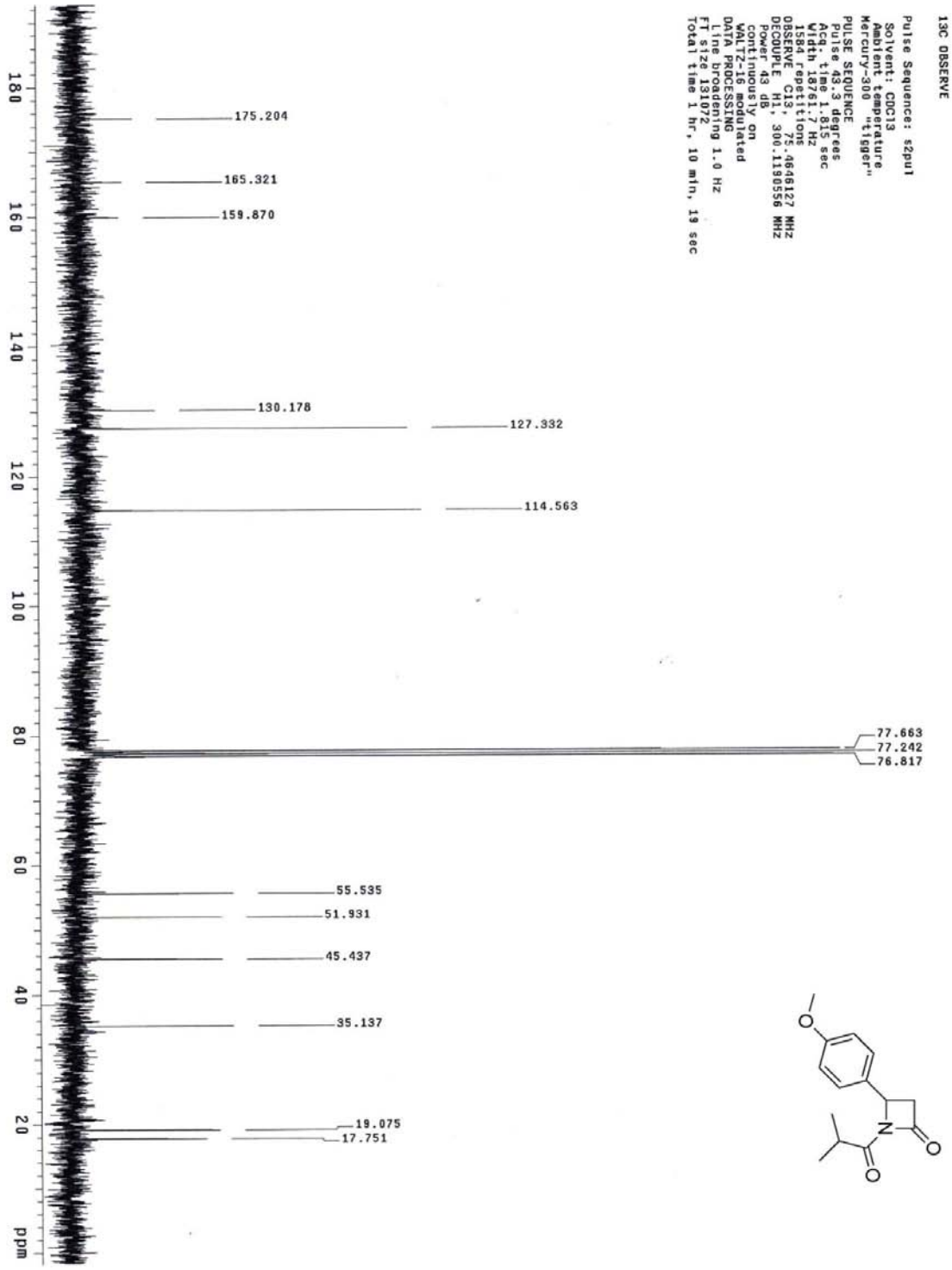

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tiger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec
4.82
1.00
1.21
1.20
2.16
3.26
8
7
6
5
4
3
2
1
ppm
N
O
O

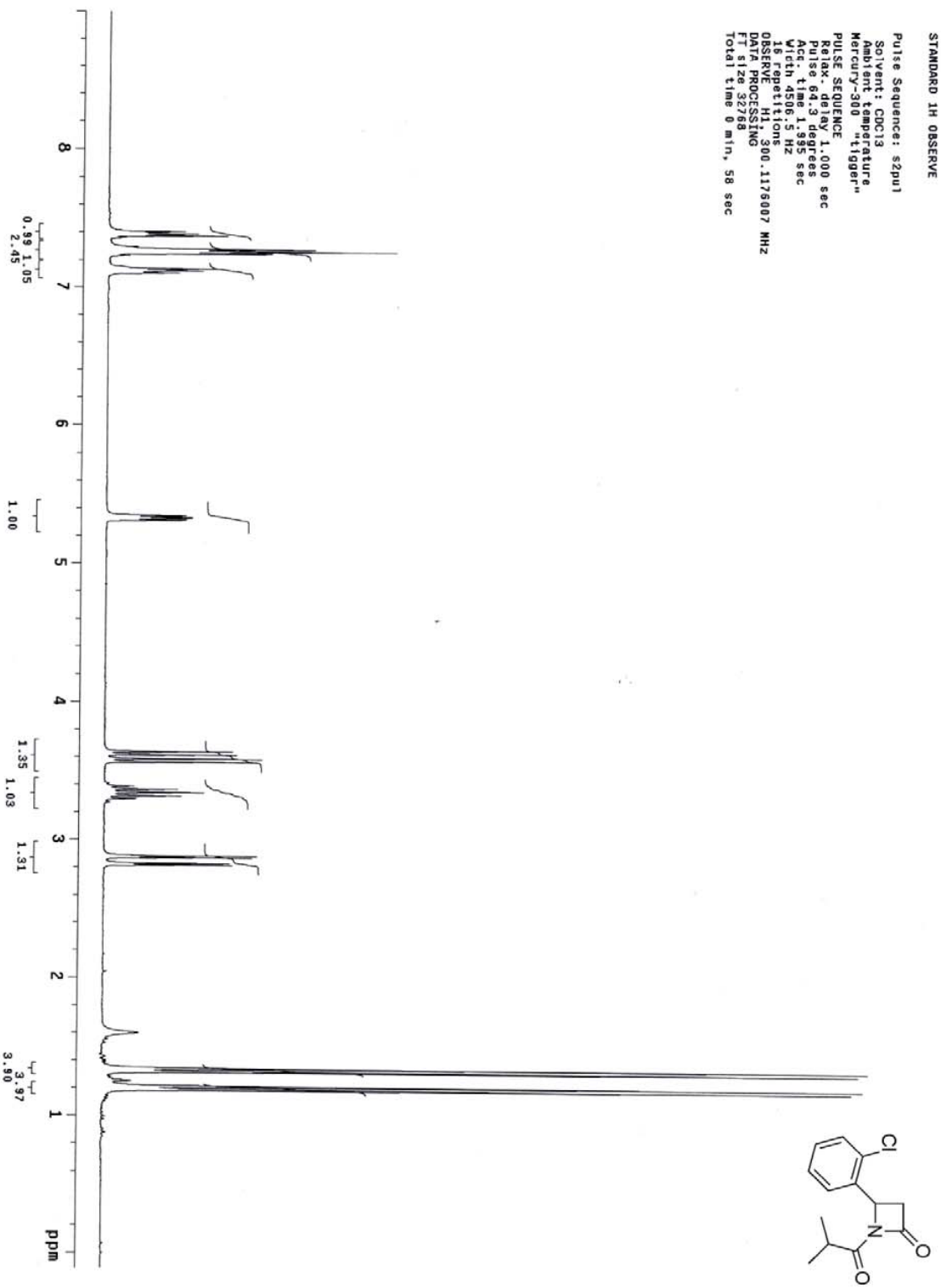

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Pulse 43.3 degrees
Acq. time 1.915 sec
Width 18761.7 Hz
68 repetitions
OBSERVE C13, 75.4646127 MHz
DECOUPLE H1, 300.1190556 MHz
Power 43 dB
continuously on
WALTZ16 modulated
DATA PROCESSING
FT size 131072
Line broadening 1.0 Hz
Total time 36 min, 0 sec
171.786
165.397
138.099
129.161
128.691
126.058
77.678
77.257
76.832
52.443
45.653
30.406
8.146
ppm
180
160
140
120
100
80
60
40
20
N
O
O

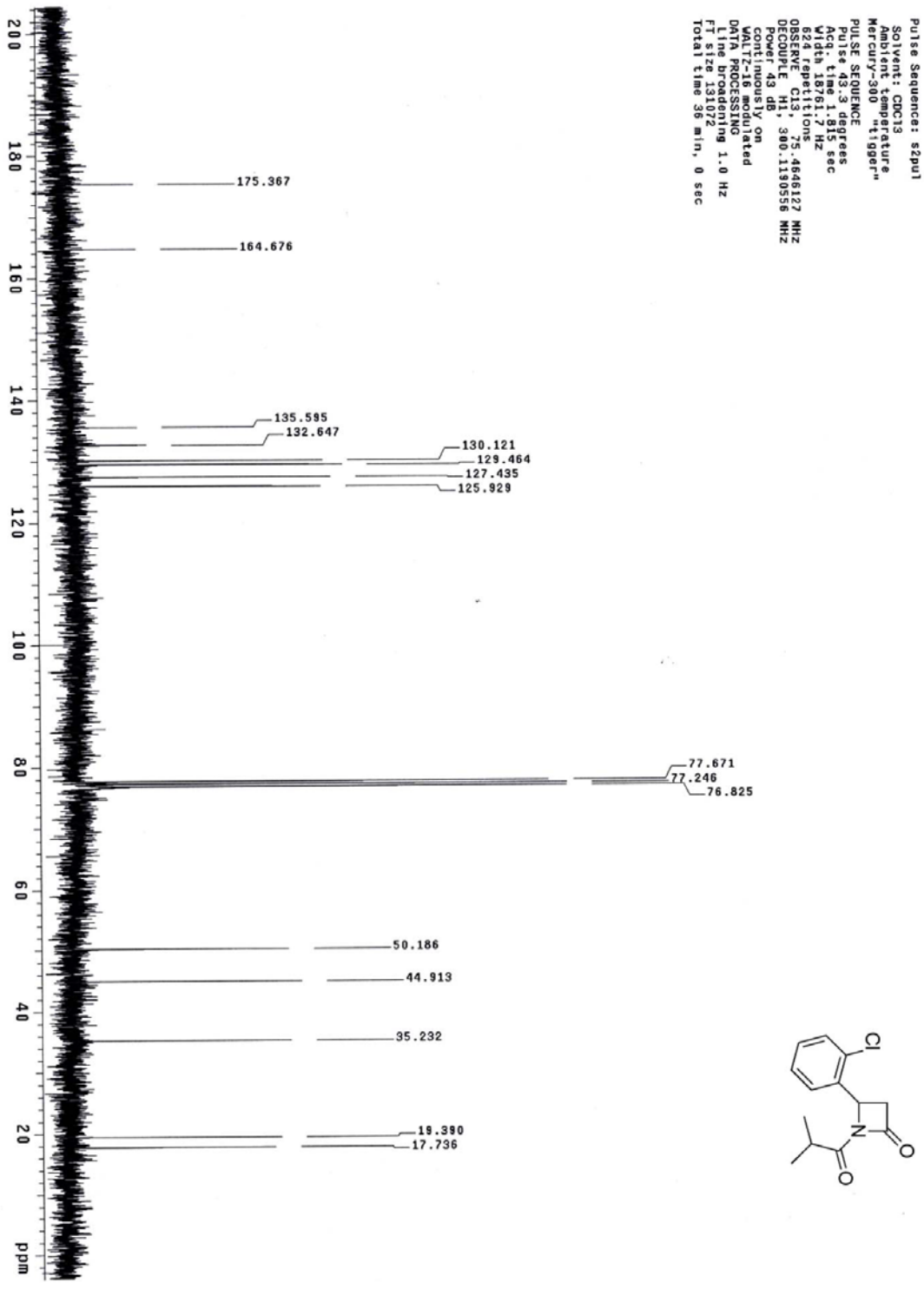

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.985 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec
Cl
O
N
O
1.82
2.15
1.00
1.23
0.91
1.20
3.65
3.56
8
7
6
5
4
3
2
1
ppm


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Pulse 63.3 degrees
Acq. time 1.885 sec
Width 18761.7 Hz
512 repetitions
OBSERVE C13, 75.4646127 MHz
DECOUPLE H1, 300.1190556 MHz
Power 63 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 36 min, 0 sec
175.158
164.657
136.763
134.506
129.404
127.386
77.678
77.253
76.828
51.613
45.421
35.164
19.060
17.740
ppm
Cl
N
O
O


STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE 1.000 sec
Relax. delay
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec
2.57
2.05
1.00
3.42
1.18
0.95
1.20
3.80
3.63
8
7
6
5
4
3
2
1
ppm
O
N
O
O


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Pulse 43.3 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1584 repetitions
OBSERVE C13, 75.4648127 MHz
DECOUPLE H1, 300.1190550 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 10 min, 19 sec
175.204
165.321
159.870
130.178
127.332
114.563
77.663
77.242
76.817
55.535
51.931
45.437
35.137
19.075
17.751
ppm
O
N
O
O

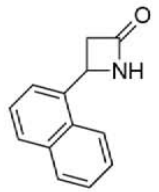

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec
0.99 1.05
2.45
1.00
1.35
1.03
1.31
3.97
3.90
ppm
Cl
N
O
O

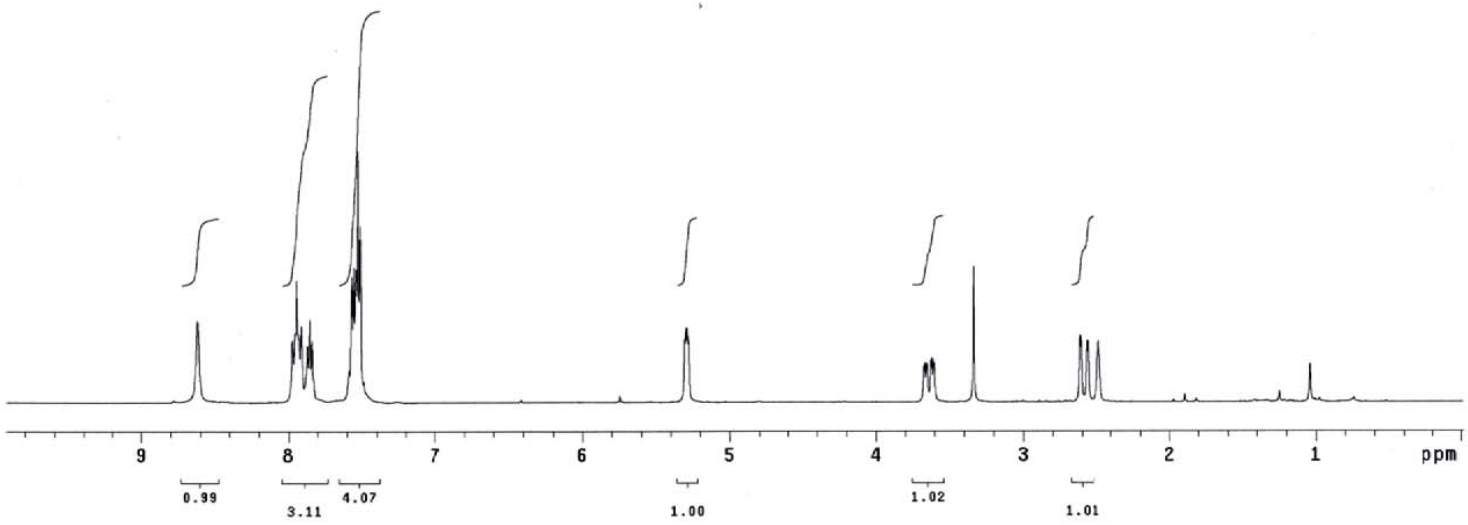

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Pulse 43.3 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
624 repetitions
OBSERVE C13, 75.4646127 MHz
DECOUPLE H1, 300.1190556 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 36 min, 0 sec
175.367
164.676
135.595
132.647
130.121
129.464
127.435
125.929
77.671
77.246
76.825
50.186
44.913
35.232
19.390
17.736
ppm
Cl
N
O
O

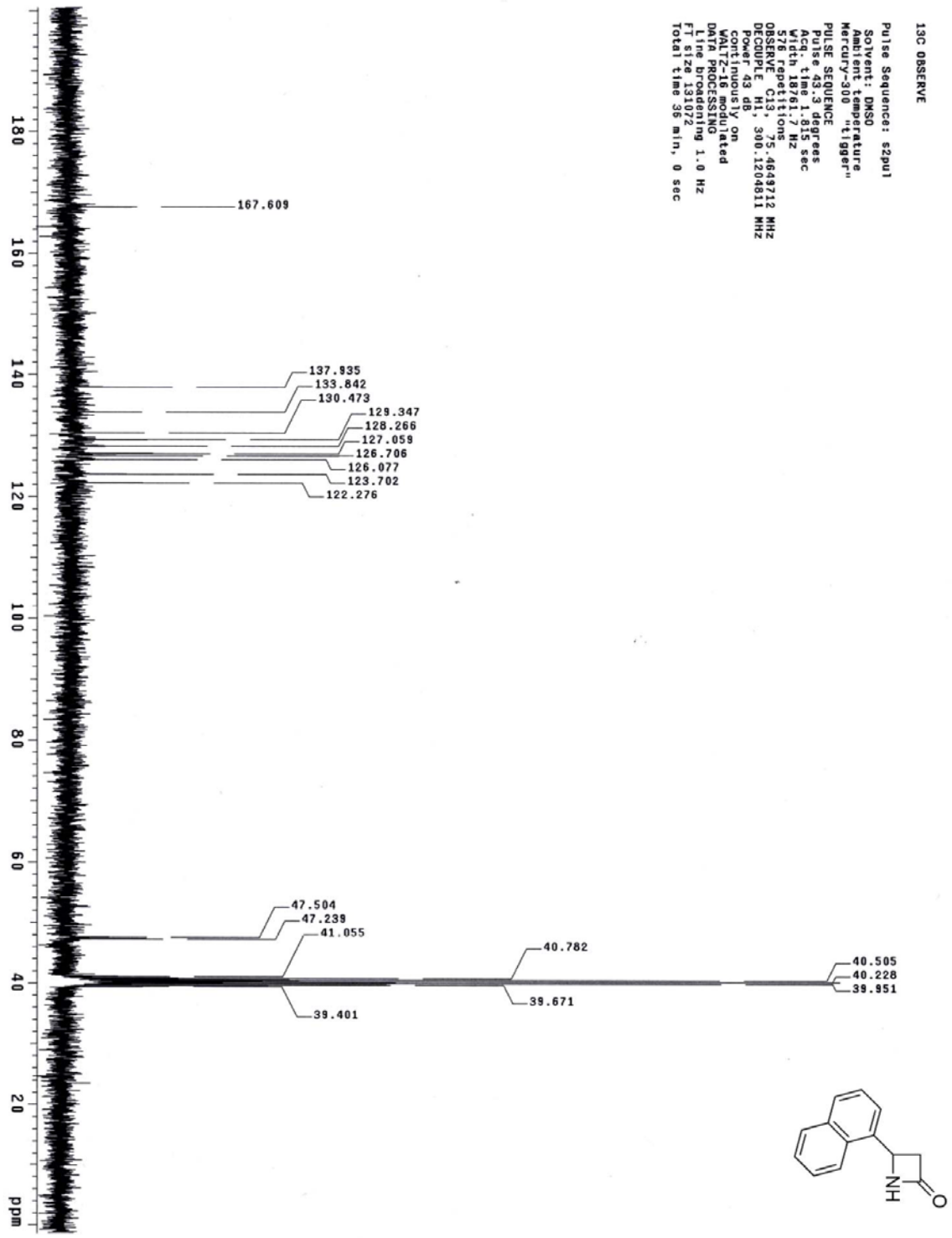
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
Mercury-300 "tigger"

PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1190263 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec

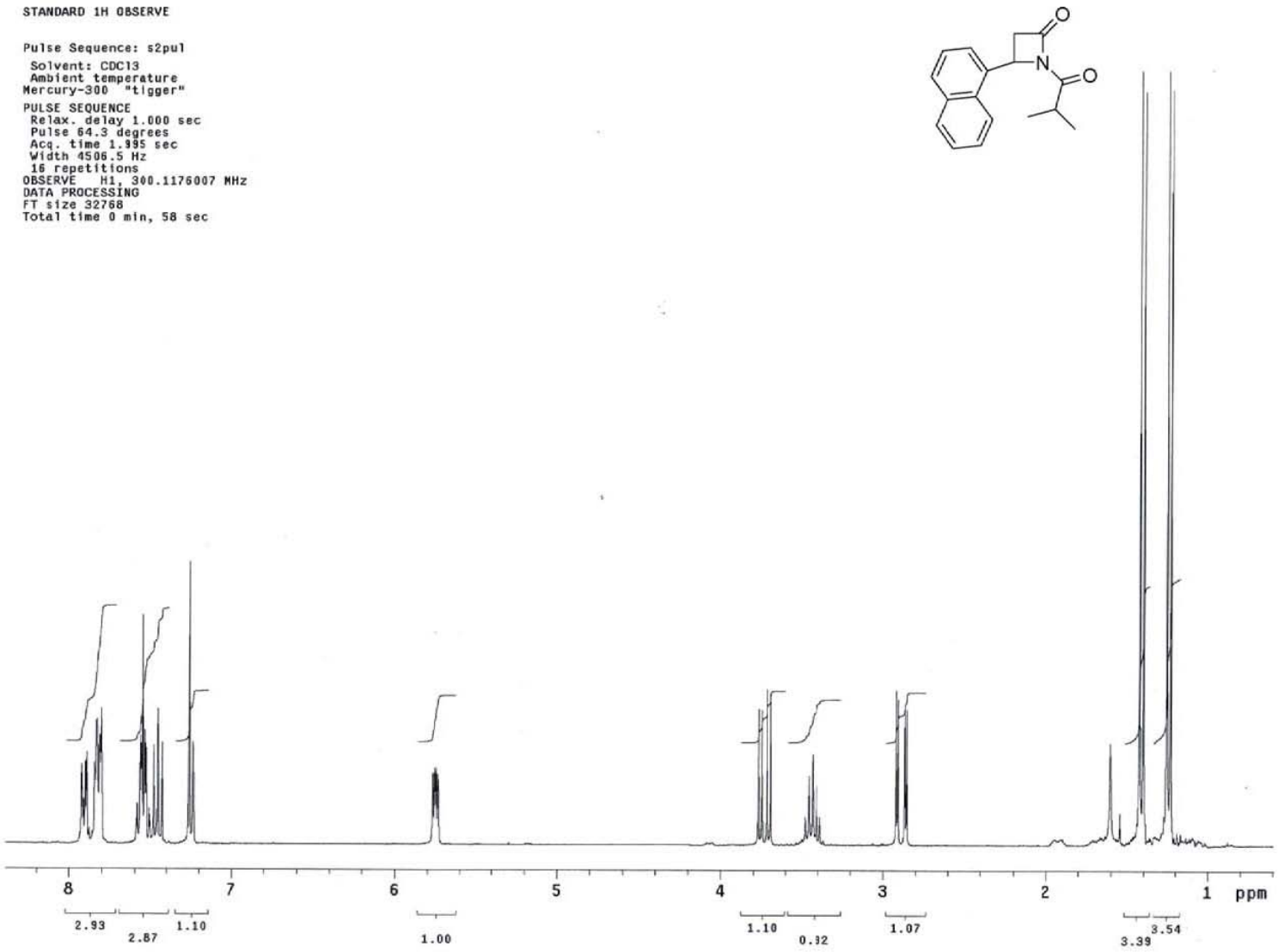


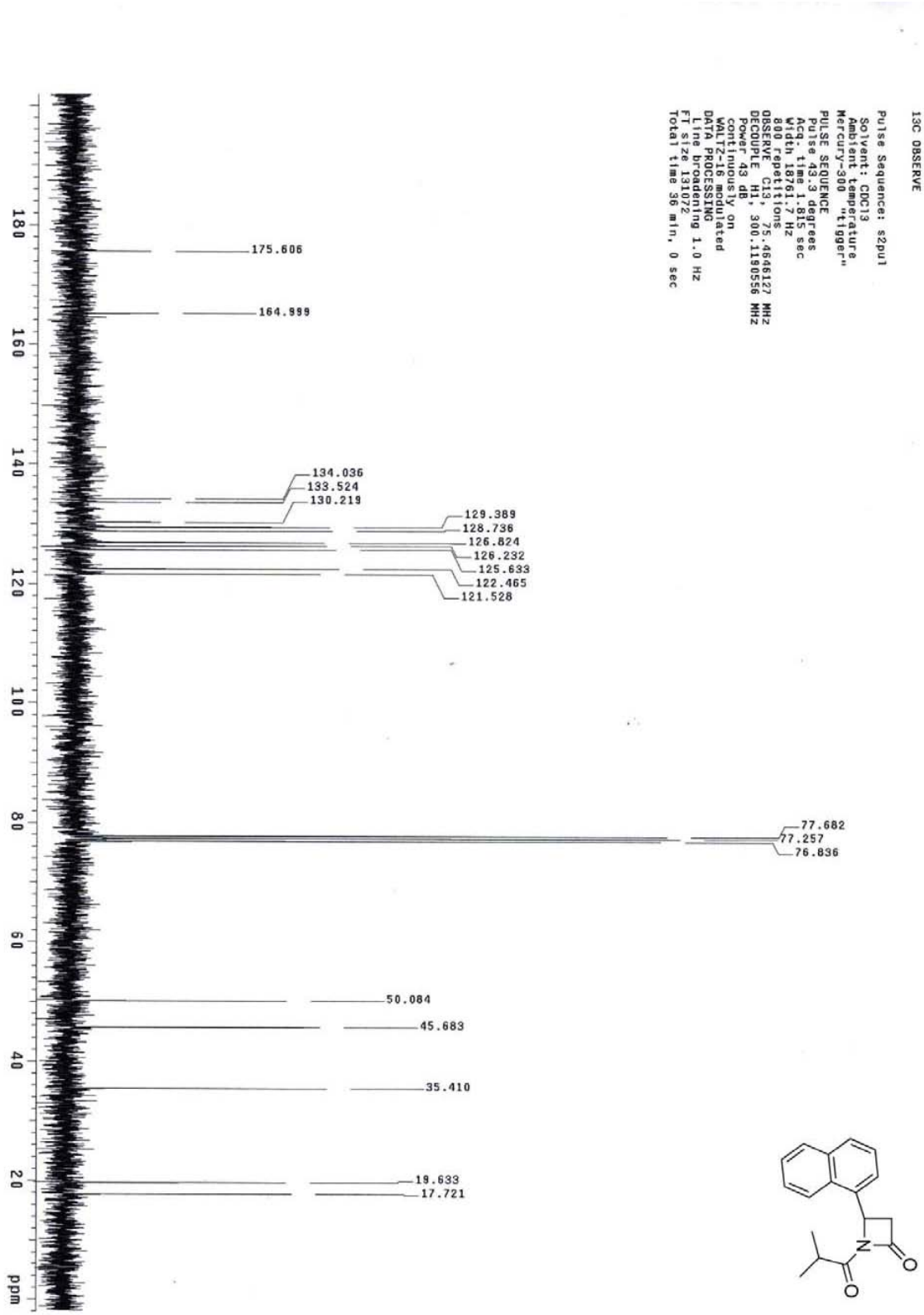



13C OBSERVE
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Pulse 43.3 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
576 repetitions
OBSERVE C13, 75.4649712 MHz
DECOUPLE H1, 300.1204811 MHz
Power 43 dB
continuously on
WALTZ16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 36 min, 0 sec
167.609
137.935
133.842
130.473
129.347
128.266
127.059
126.706
126.077
123.702
122.276
47.504
47.239
41.055
40.782
40.505
40.228
39.951
39.671
39.401
ppm
NH
O

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec

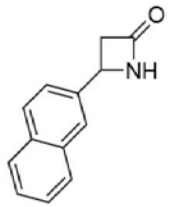


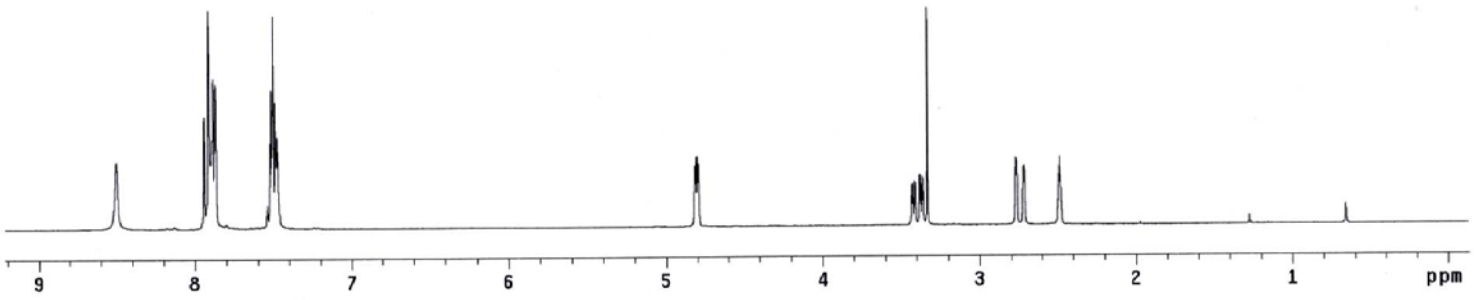

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Pulse 43.3 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
800 repetitions
OBSERVE C13, 75.4646127 MHz
DECOUPLE H1, 300.1190556 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 36 min, 0 sec
175.606
164.999
134.036
133.524
130.219
129.389
128.736
126.824
126.232
125.633
122.465
121.528
77.682
77.257
76.836
50.084
45.683
35.410
19.633
17.721
180
160
140
120
100
80
60
40
20
ppm
N
O
O

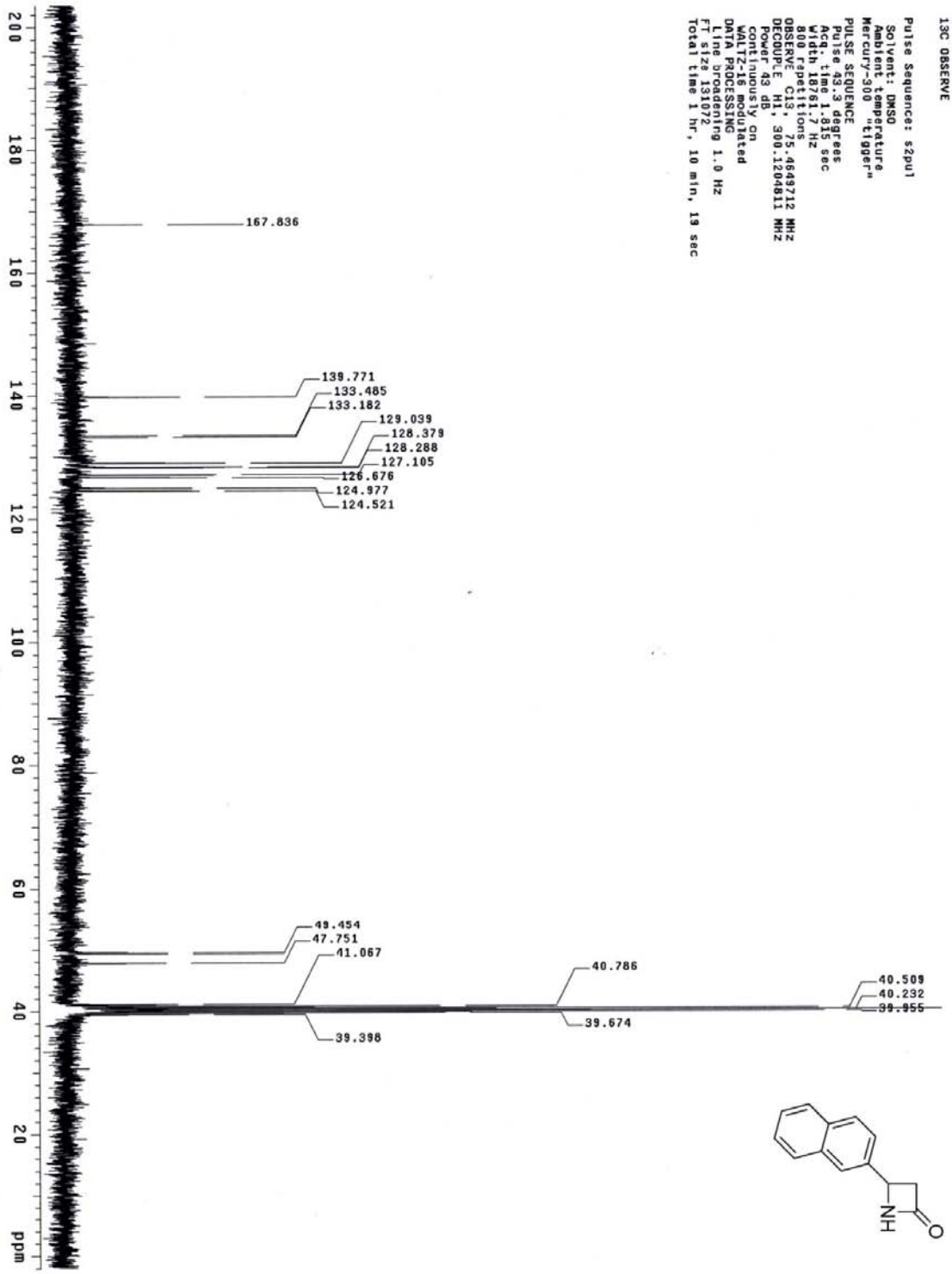
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
Mercury-300 "tigger"

PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1190263 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec



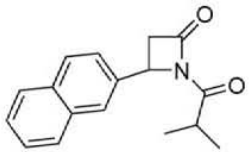


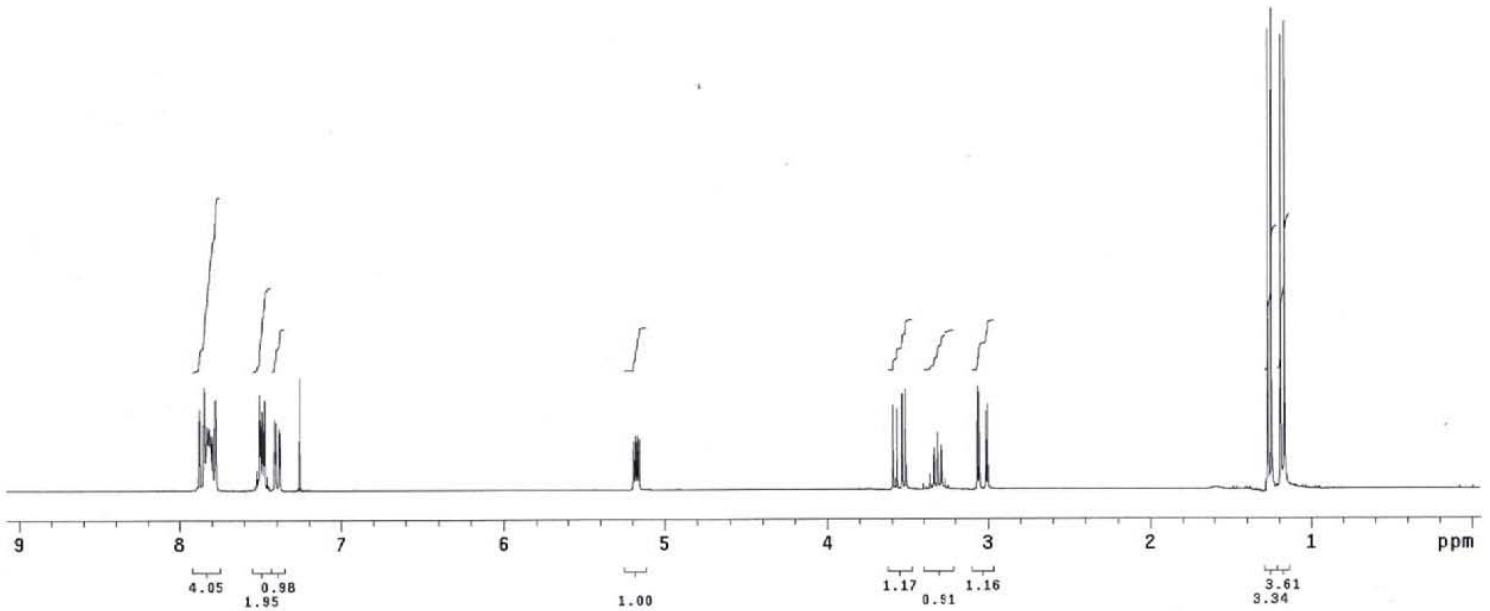

13C OBSERVE
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Pulse 43.3 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
800 repetitions
OBSERVE C13, 75.4649712 MHz
DECOUPLE H1, 300.1204811 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 10 min, 19 sec
167.836
139.771
133.485
133.182
129.039
128.379
128.288
127.105
126.676
124.977
124.521
49.454
47.751
41.067
40.786
40.509
40.232
39.955
39.674
39.398
NH
O
200
180
160
140
120
100
80
60
40
20
ppm

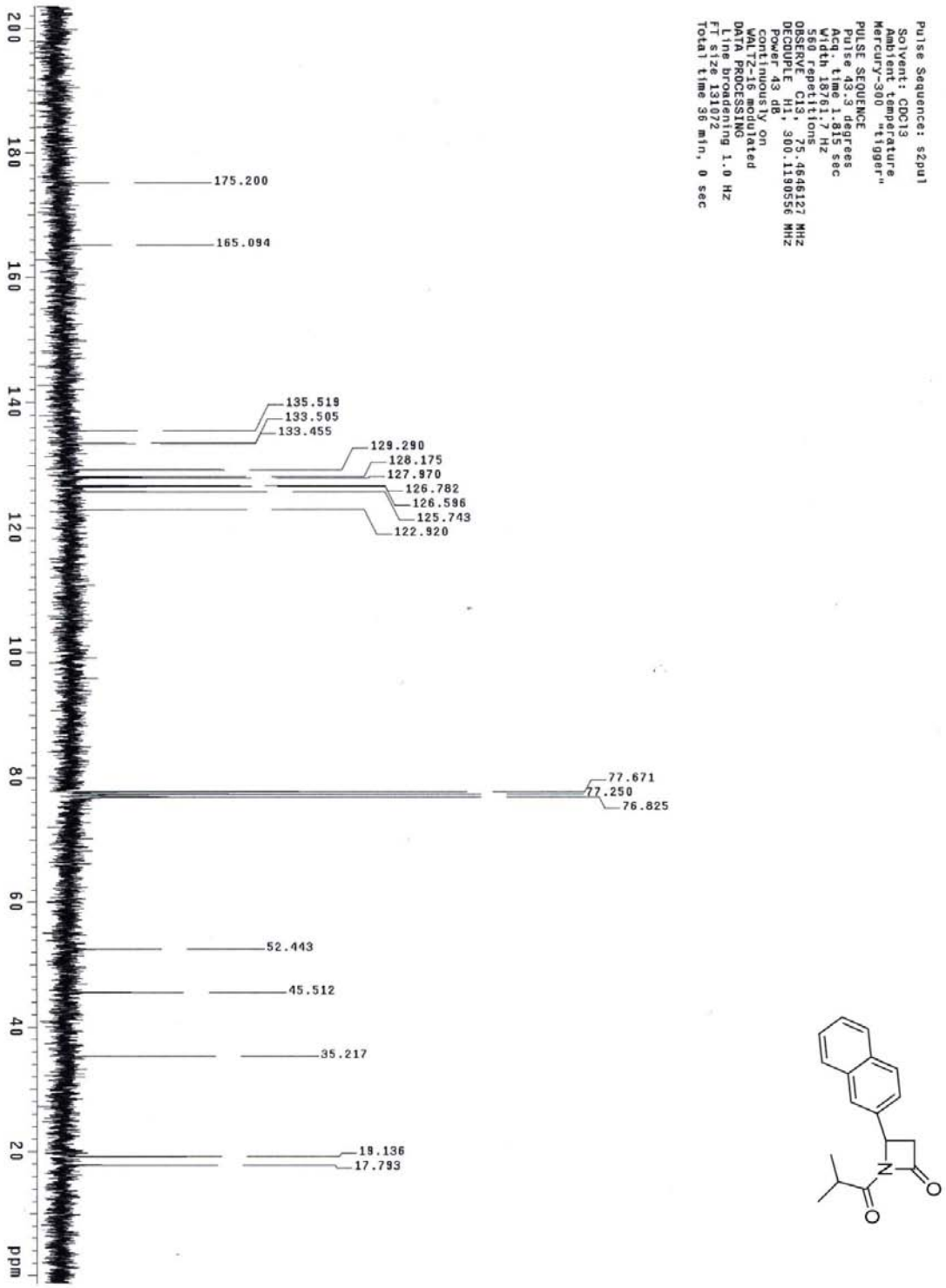
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"

PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec



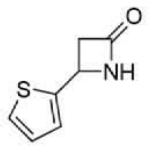


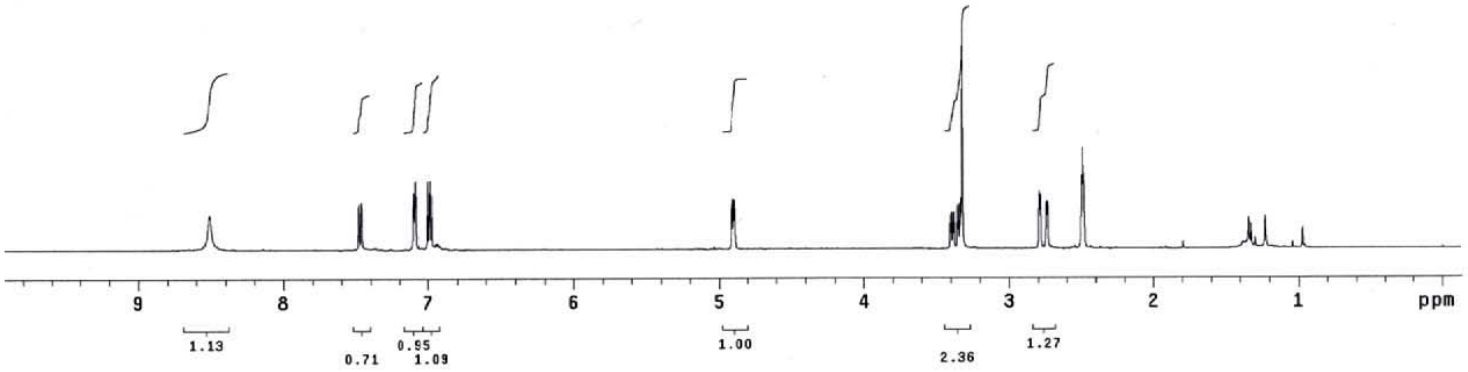

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Pulse 43.3 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
560 repetitions
OBSERVE C13, 75.4646127 MHz
DECOUPLE H1, 300.1190556 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 36 min, 0 sec
175.200
165.094
135.518
133.505
133.455
129.290
128.175
127.870
126.782
126.596
125.743
122.920
77.671
77.250
76.825
52.443
45.512
35.217
19.136
17.793
200
180
160
140
120
100
80
60
40
20
ppm
N
O
O

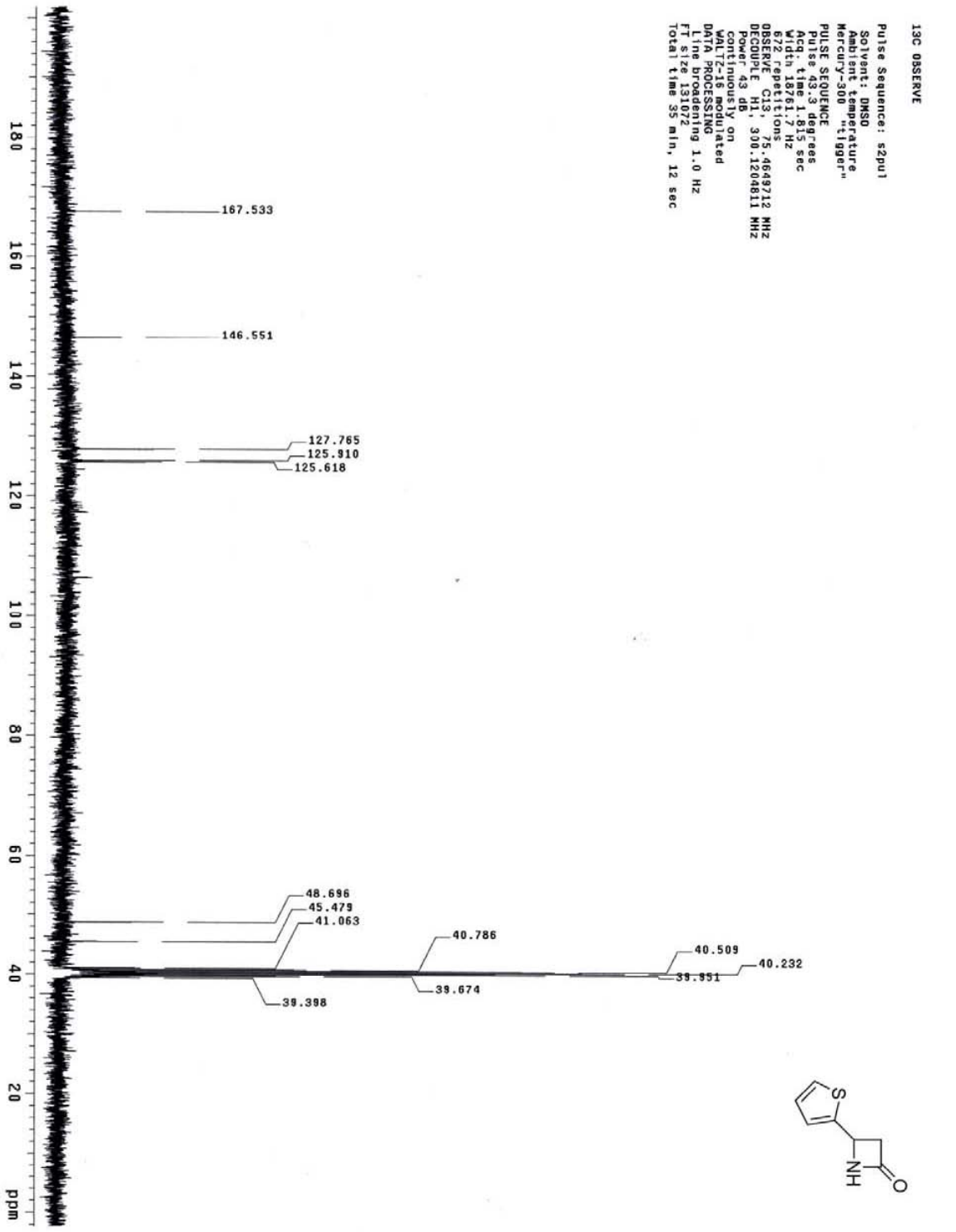
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
Mercury-300 "tigger"

PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1190263 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec

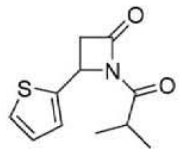


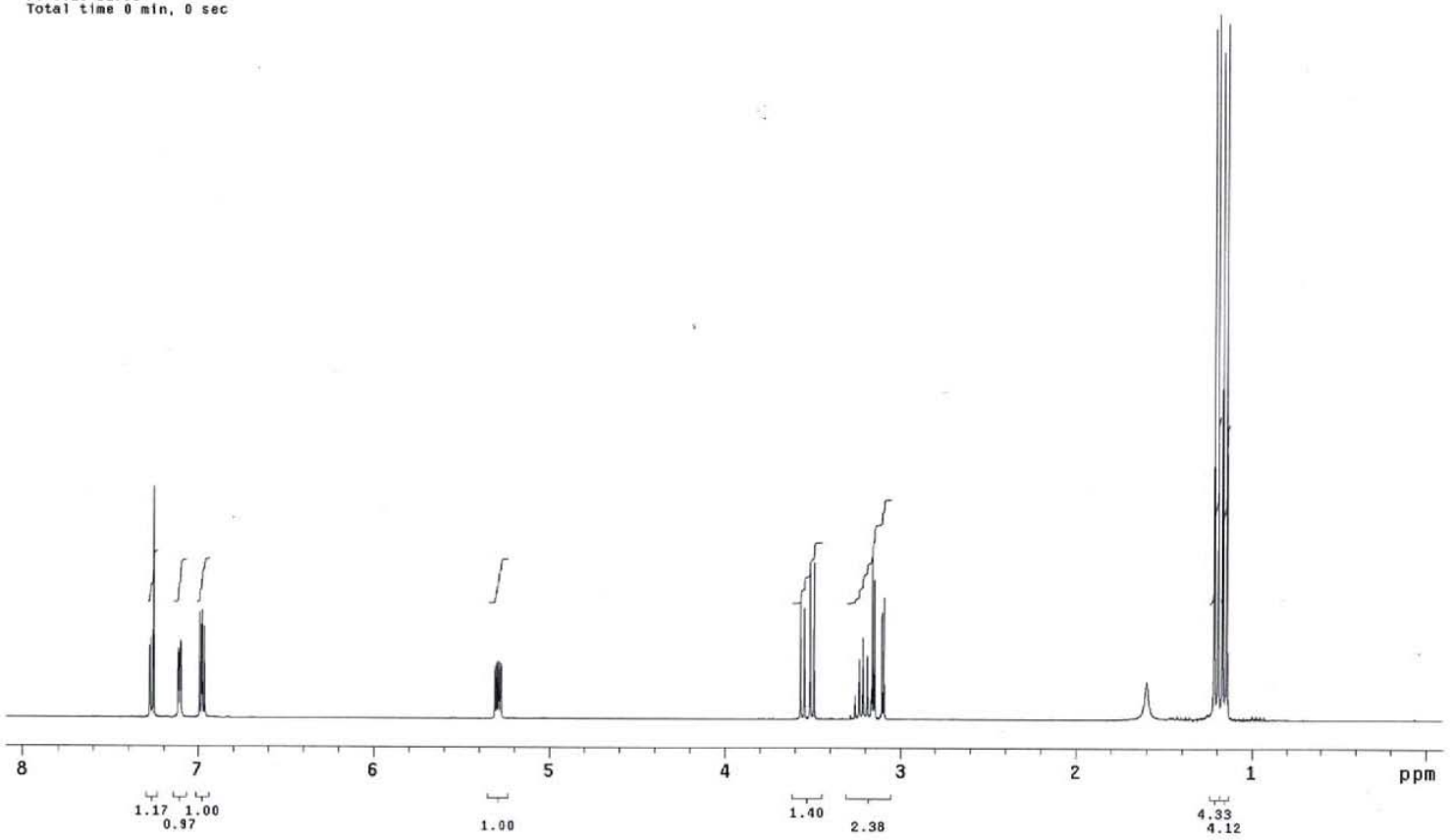


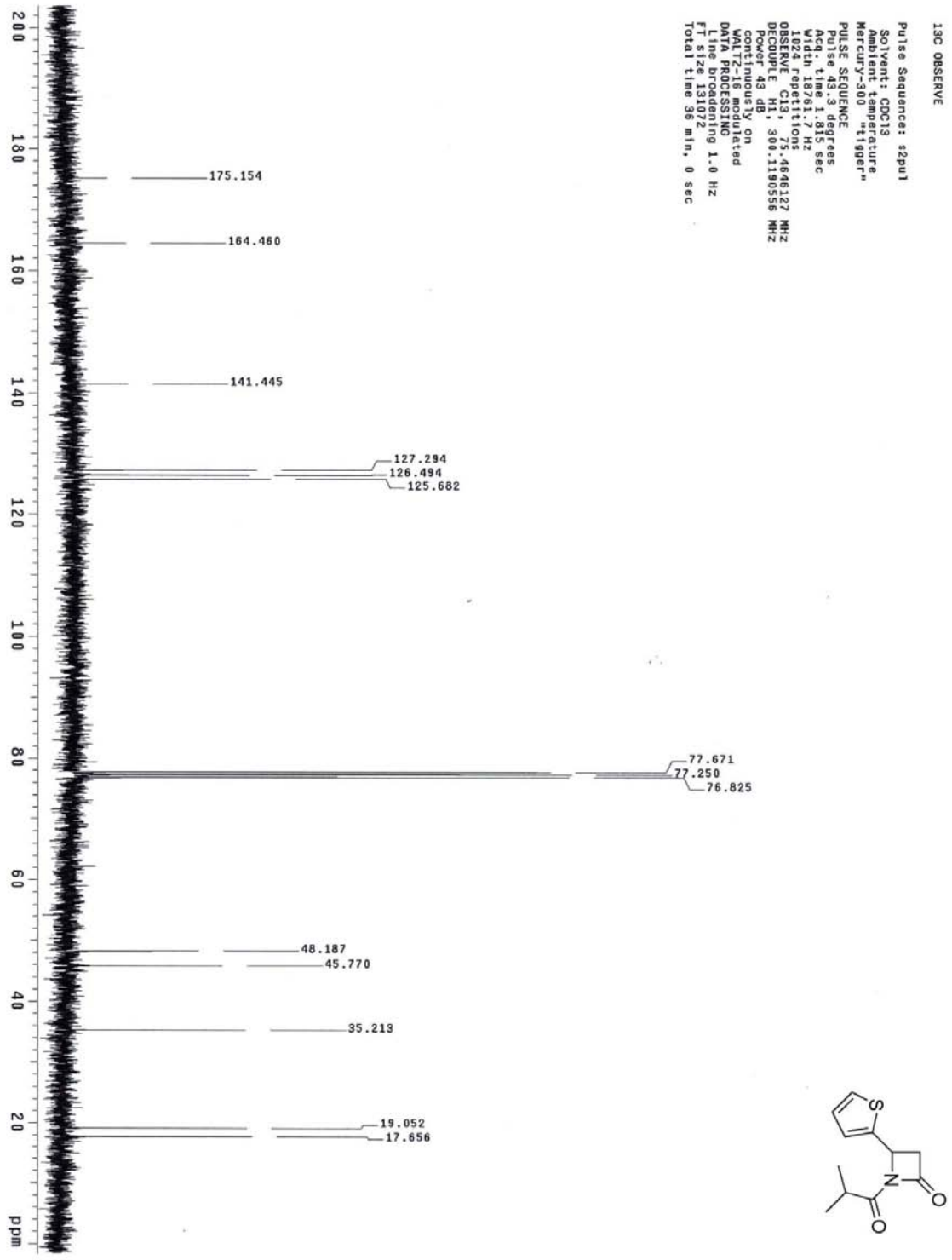

13C OBSERVE
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Pulse 43.3 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
672 repetitions
OBSERVE C13, 75.4649712 MHz
DECOUPLE H1, 300.1204811 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 35 min, 12 sec
167.533
146.551
127.765
125.910
125.618
48.696
45.479
41.063
40.786
40.509
40.232
39.951
39.674
39.398
180
160
140
120
100
80
60
40
20
ppm
S
NH
O

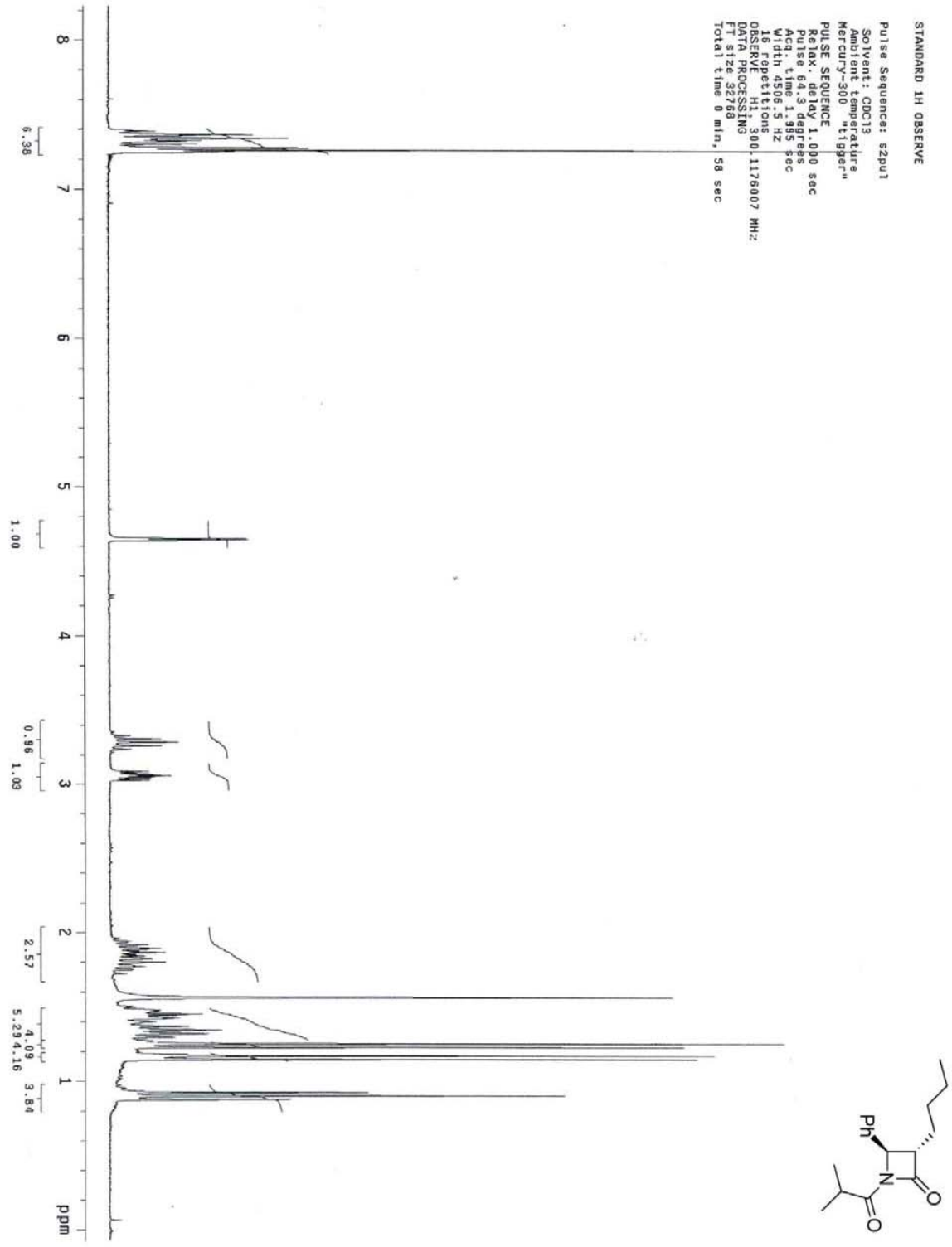
STANDARD 1H OBSERVE

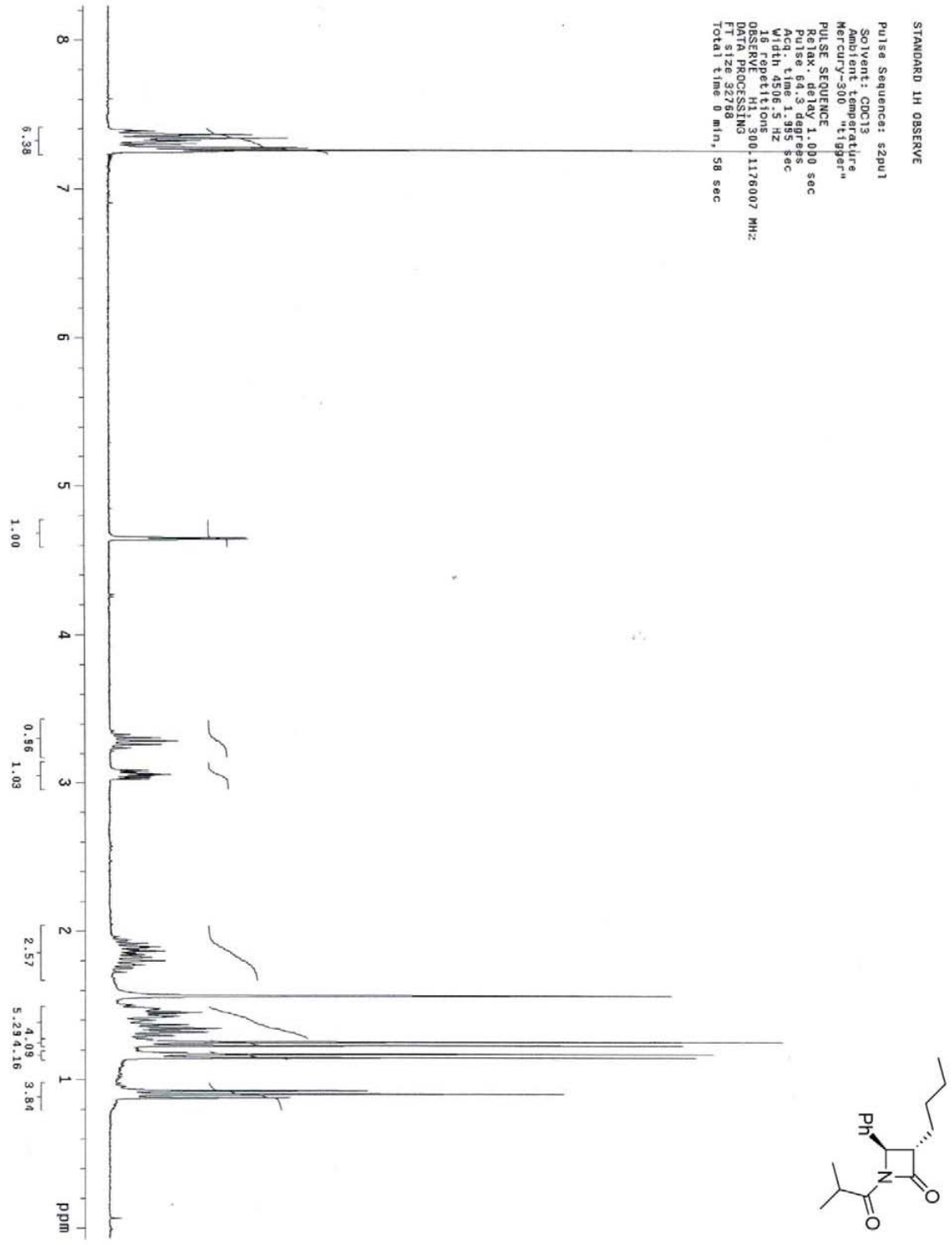
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec

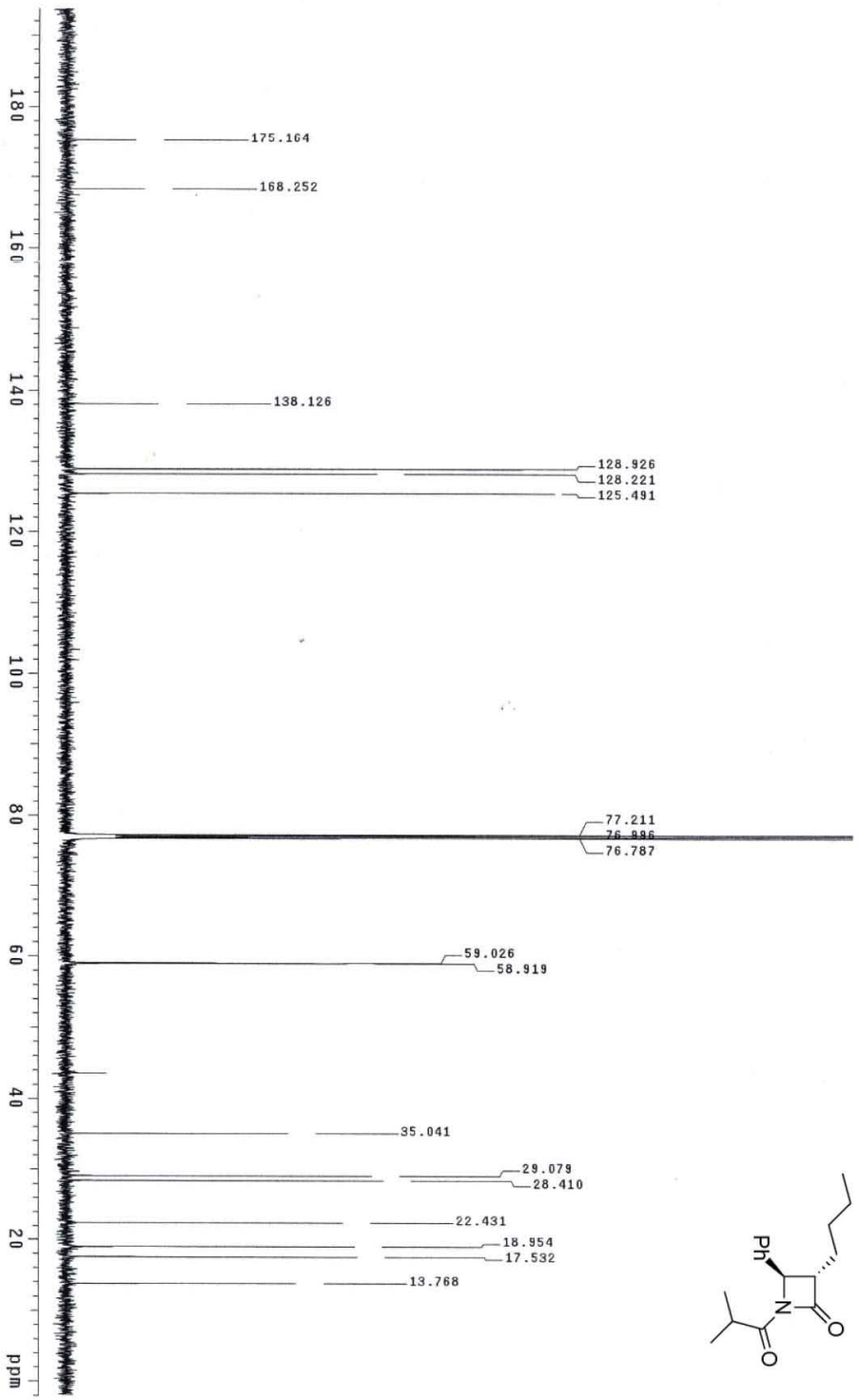


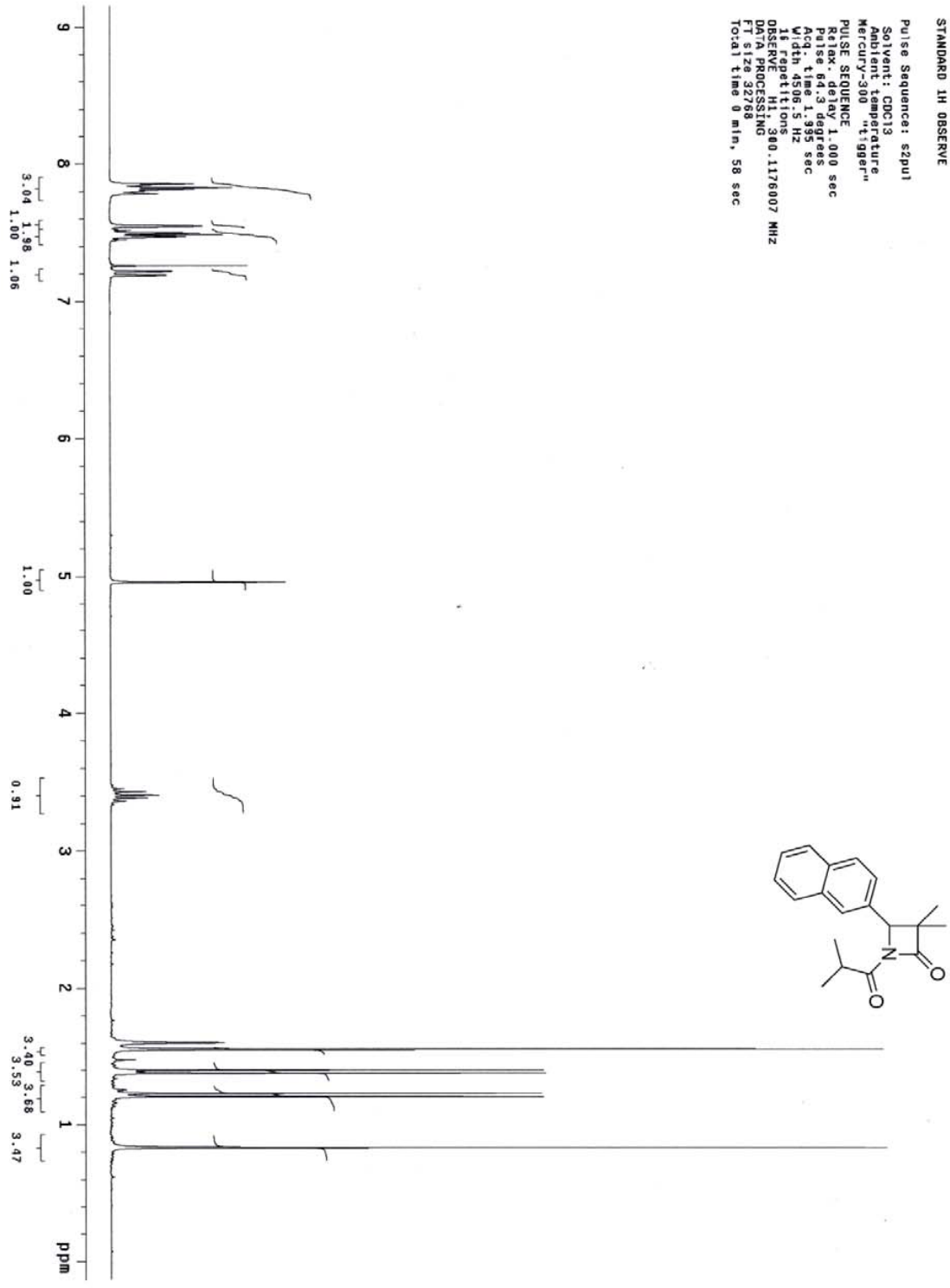


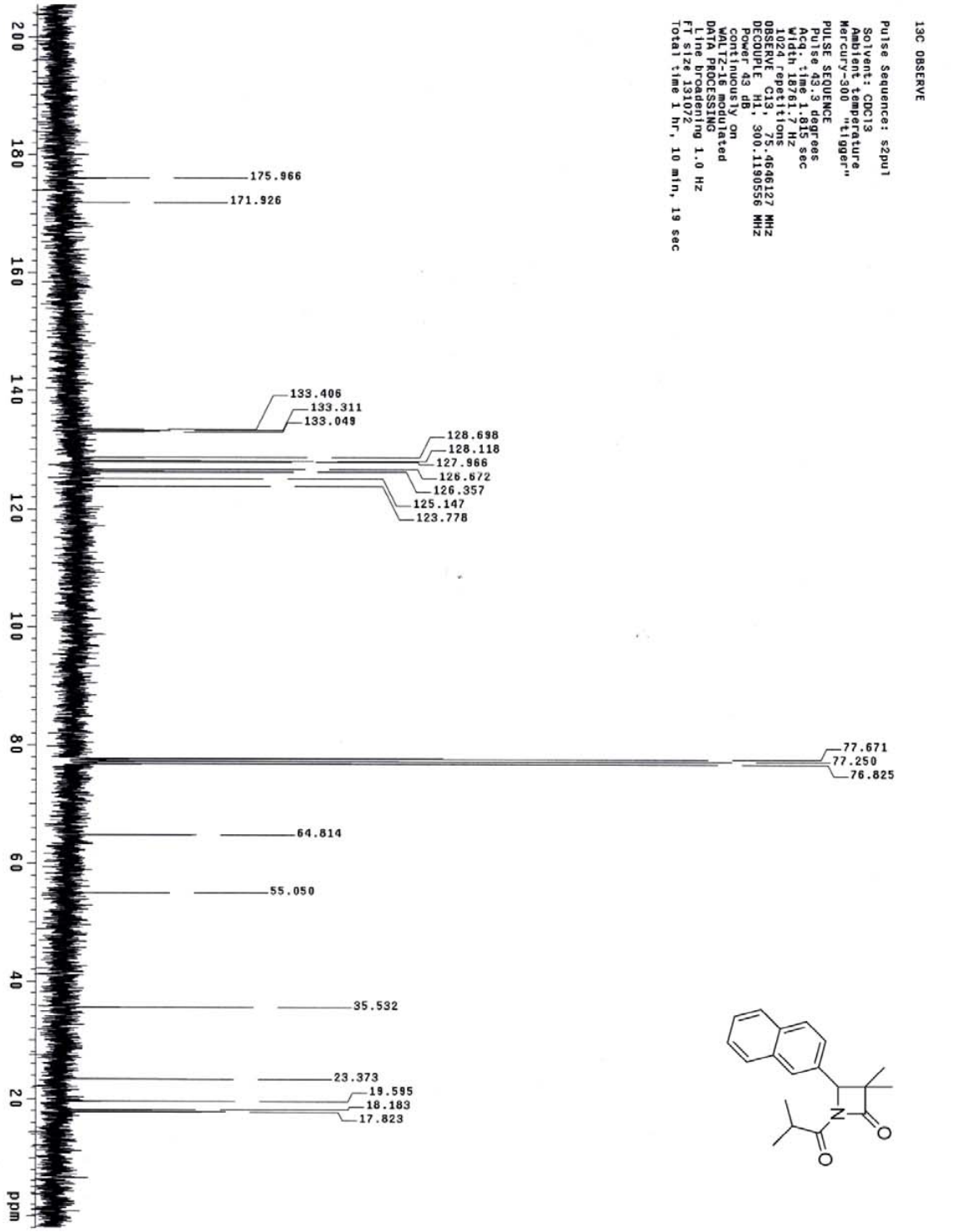

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Pulse 43.3 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1024 repetitions
OBSERVE C13, 75.4646127 MHz
DECOUPLE H1, 300.1190556 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 36 min, 0 sec
175.154
164.460
141.445
127.294
126.494
125.682
77.671
77.250
76.825
48.187
45.770
35.213
19.052
17.656
200
180
160
140
120
100
80
60
40
20
ppm
S
N
O
O

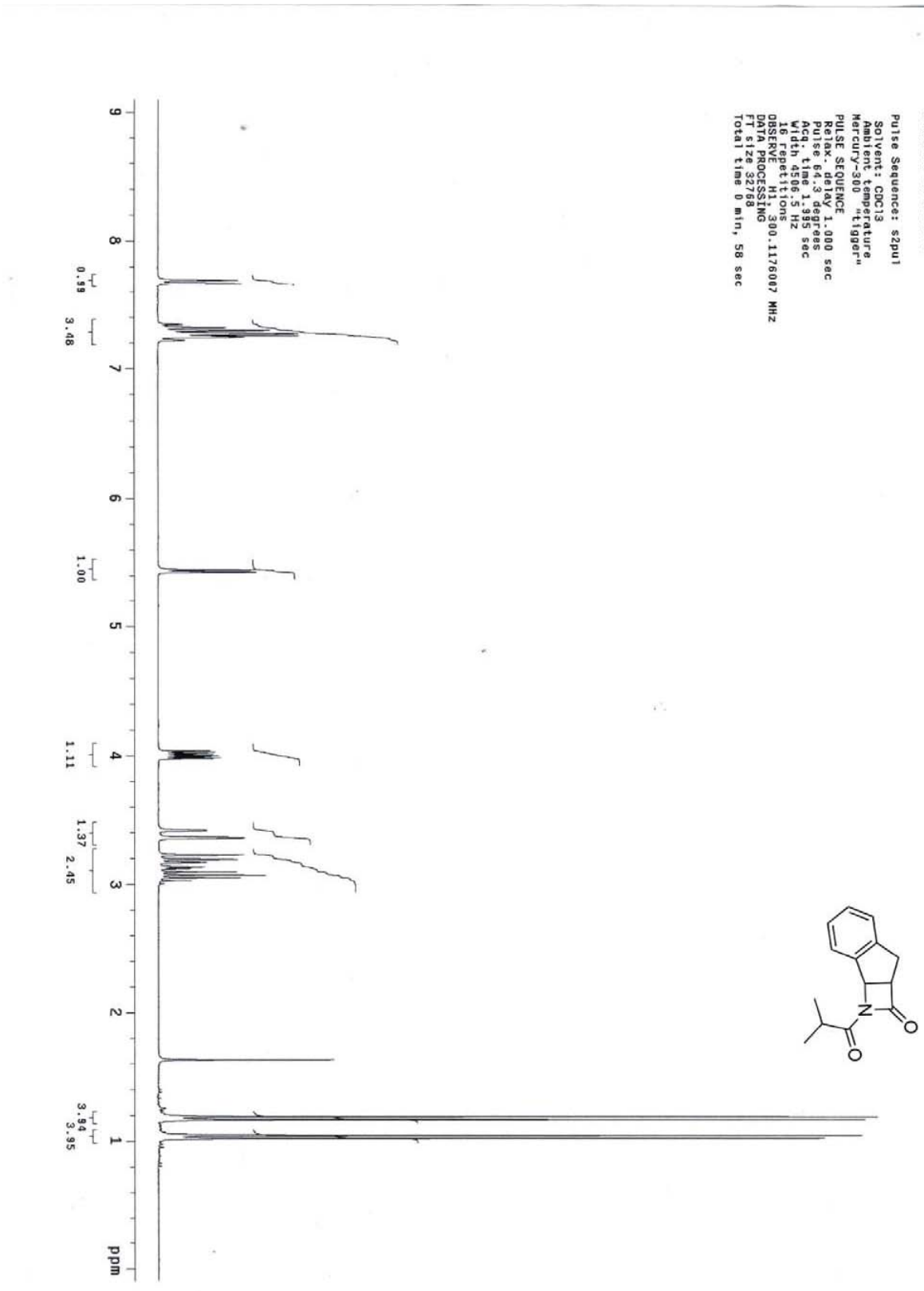

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec
8
7
6
5
4
3
2
1
ppm
6.38
1.00
0.96
1.03
2.57
4.09
5.29
4.16
3.84
Ph
N
O
O

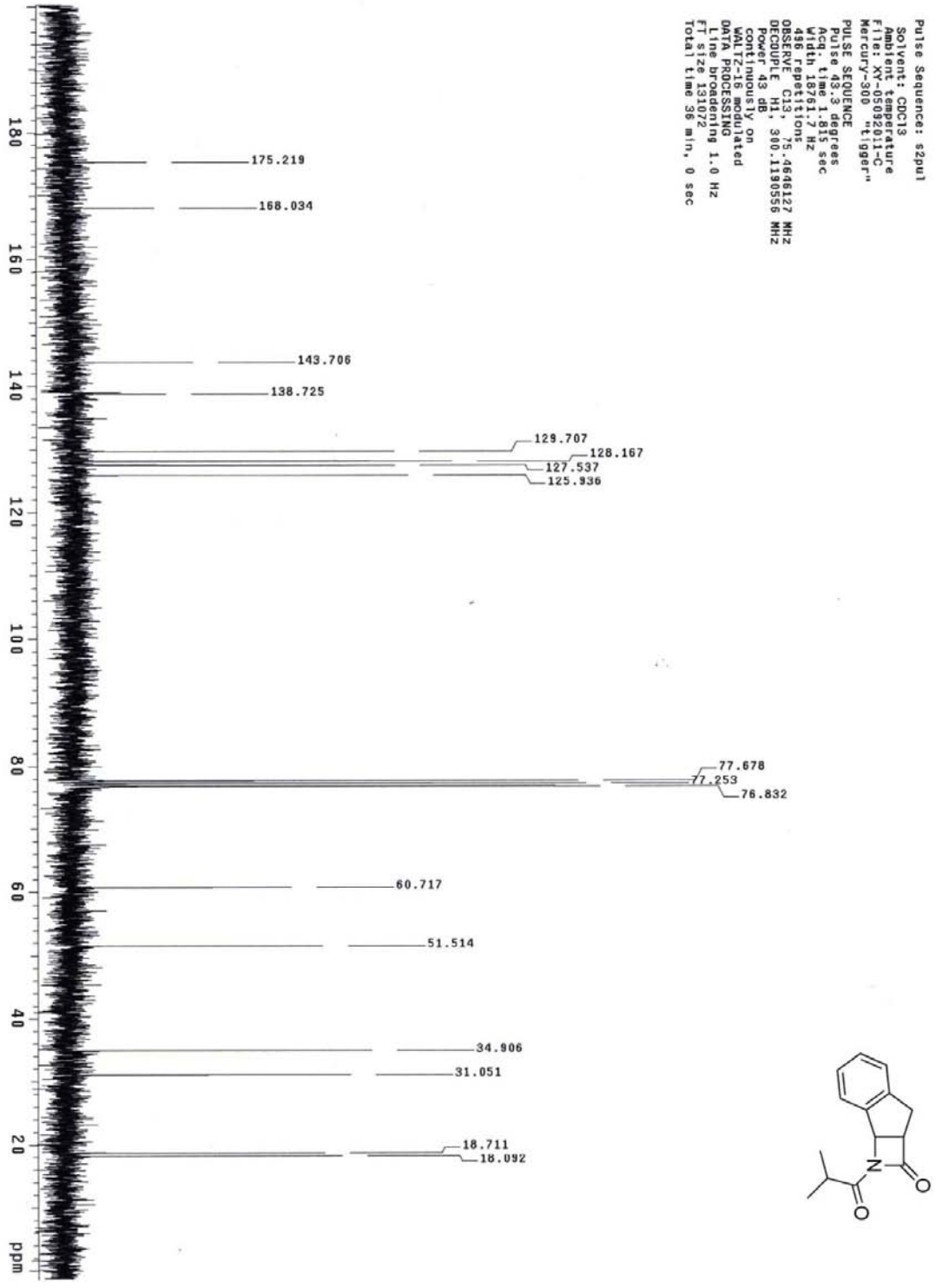

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec
8
7
6
5
4
3
2
1
ppm
6.38
1.00
0.96
1.03
2.57
4.09
5.29
4.16
3.84
Ph
N
O
O

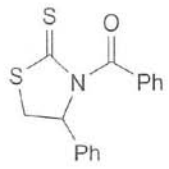

175.164
168.252
138.126
128.926
128.221
125.491
77.211
76.896
76.787
59.026
58.919
35.041
29.079
28.410
22.431
18.954
17.532
13.768
ppm
180
160
140
120
100
80
60
40
20
Ph
N
O
O

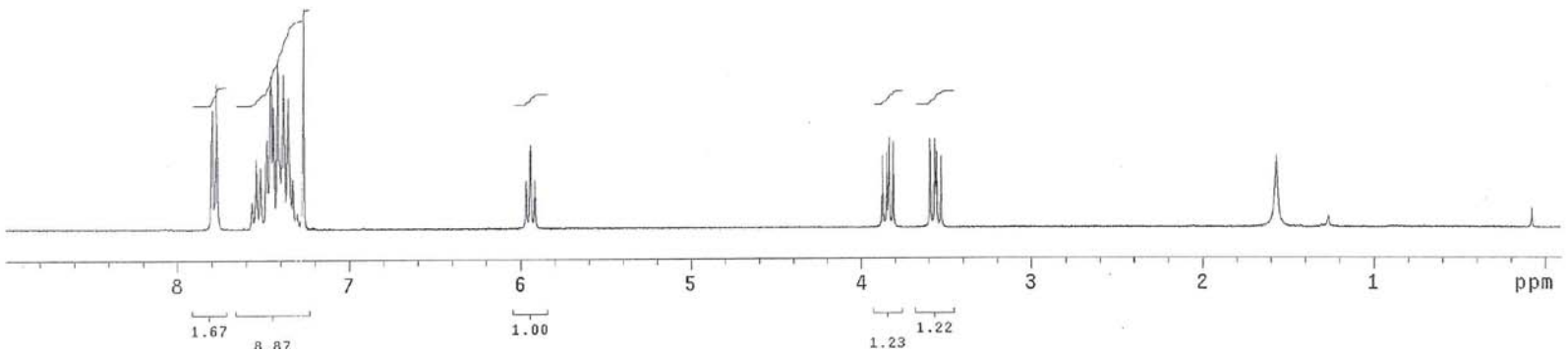

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tfgger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec
N
O
O
9
8
7
6
5
4
3
2
1
ppm
3.04
1.98
1.00
1.06
1.00
0.91
3.40
3.68
3.53
3.47

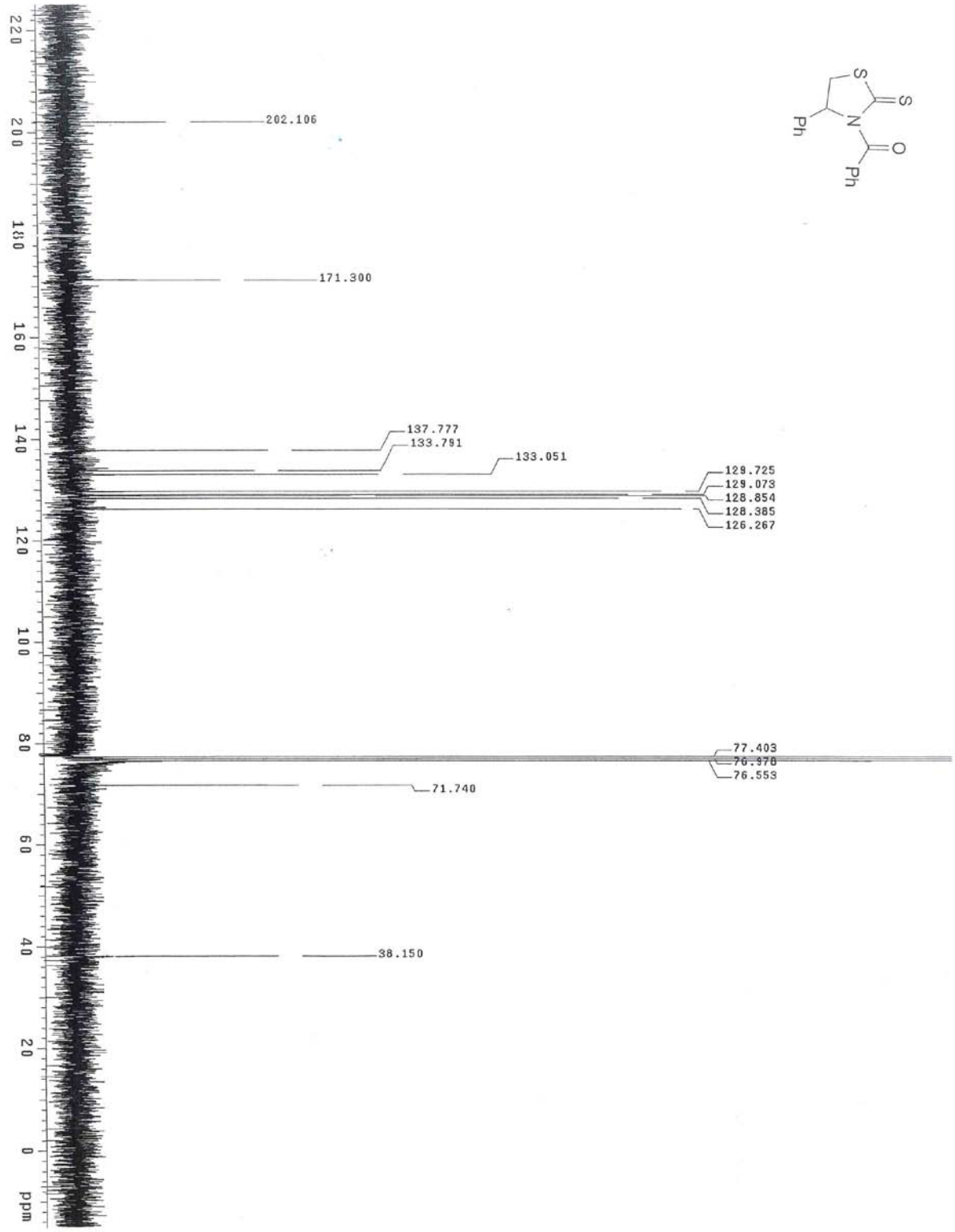

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Pulse 43.3 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1024 repetitions
OBSERVE C13, 75.4646127 MHz
DECOUPLE H1, 300.1190556 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 10 min, 19 sec
175.966
171.926
133.406
133.311
133.049
128.698
128.118
127.966
126.672
126.357
125.147
123.778
77.671
77.250
76.825
64.814
55.050
35.532
23.373
19.595
18.183
17.823
ppm
N
O
O

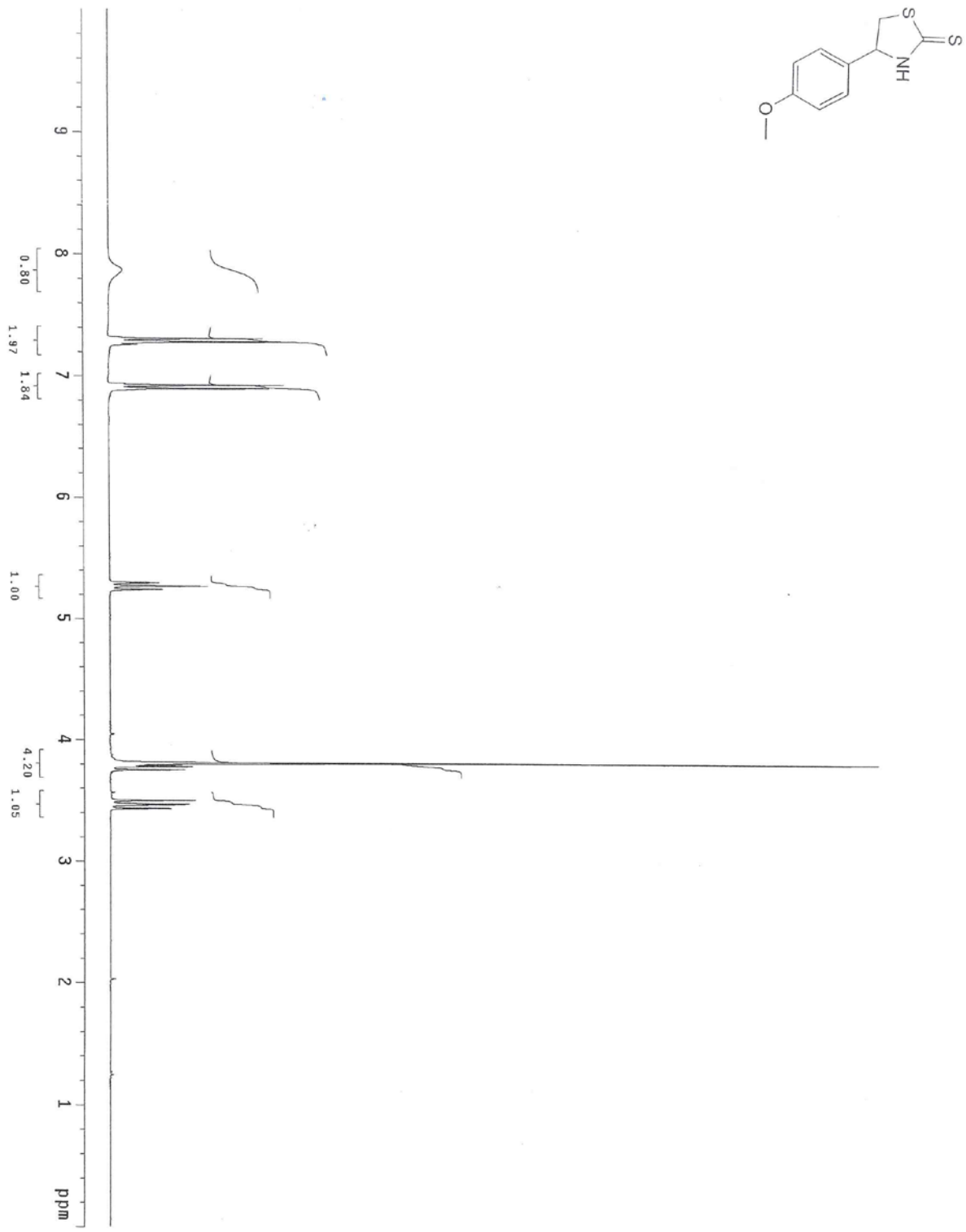

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec
0.99
3.48
1.00
1.11
1.37
2.45
3.94
3.95
ppm
O
N
O

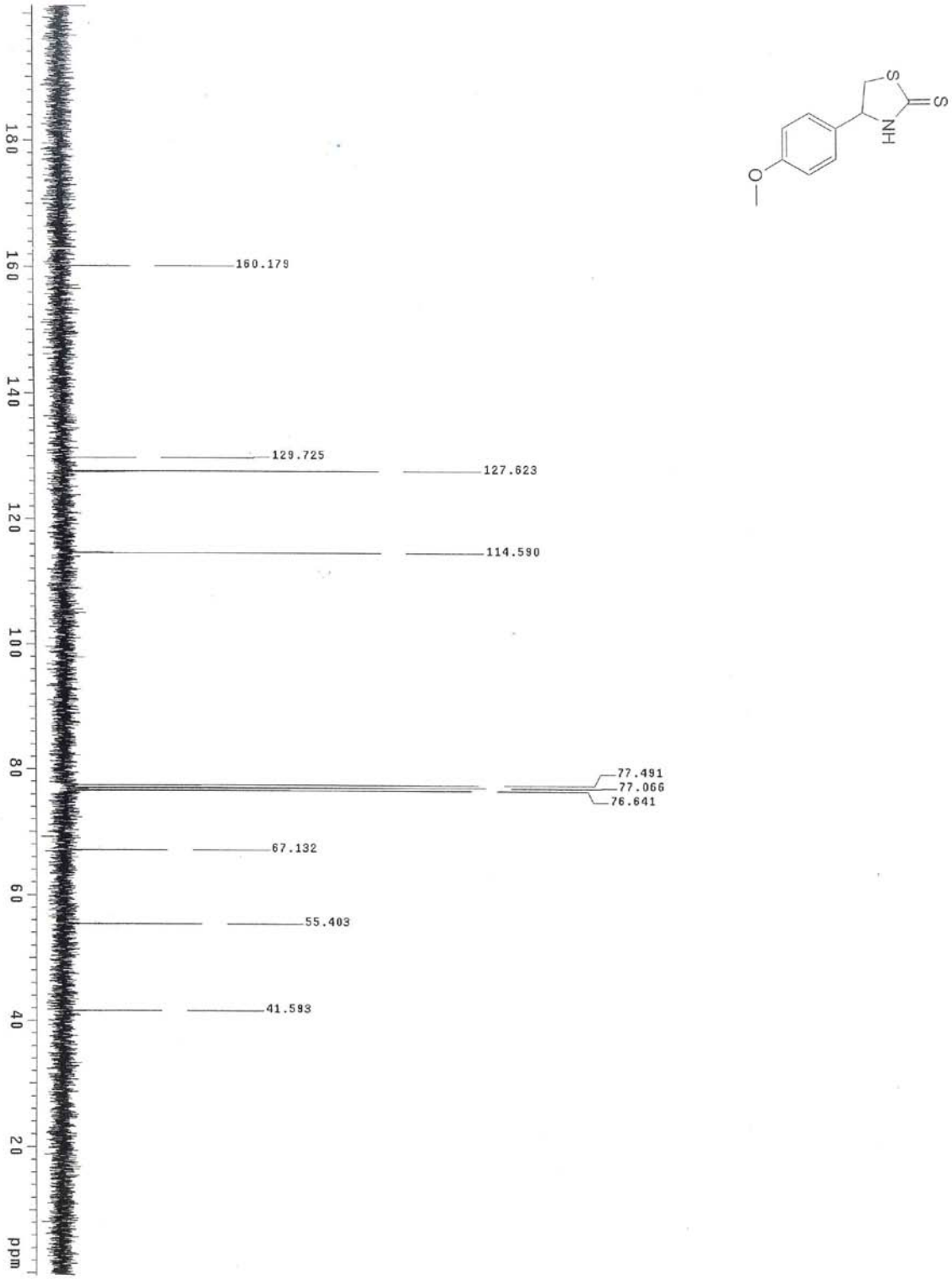

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: XY-05092011-C
Mercury-300 "tiger"
PULSE SEQUENCE
Pulse 43.3 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
496 repetitions
OBSERVE C13, 75.4646127 MHz
DECOUPLE H1, 300.1190536 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 36 min, 0 sec
175.219
168.034
143.706
138.725
129.707
128.167
127.537
125.936
77.678
77.253
76.832
60.717
51.514
34.906
31.051
18.711
18.092
ppm
N
O
O

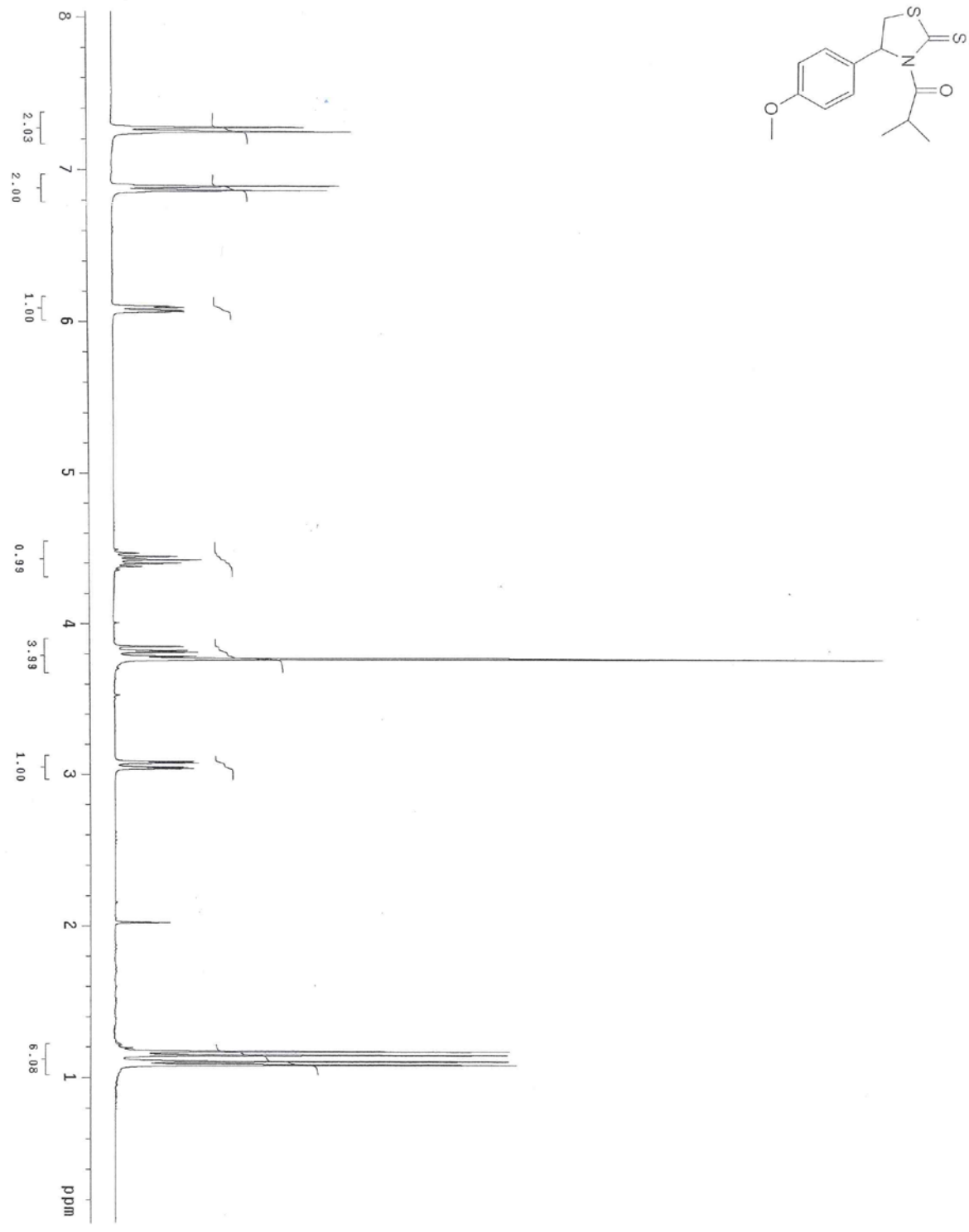

S
O
S
N
Ph
Ph

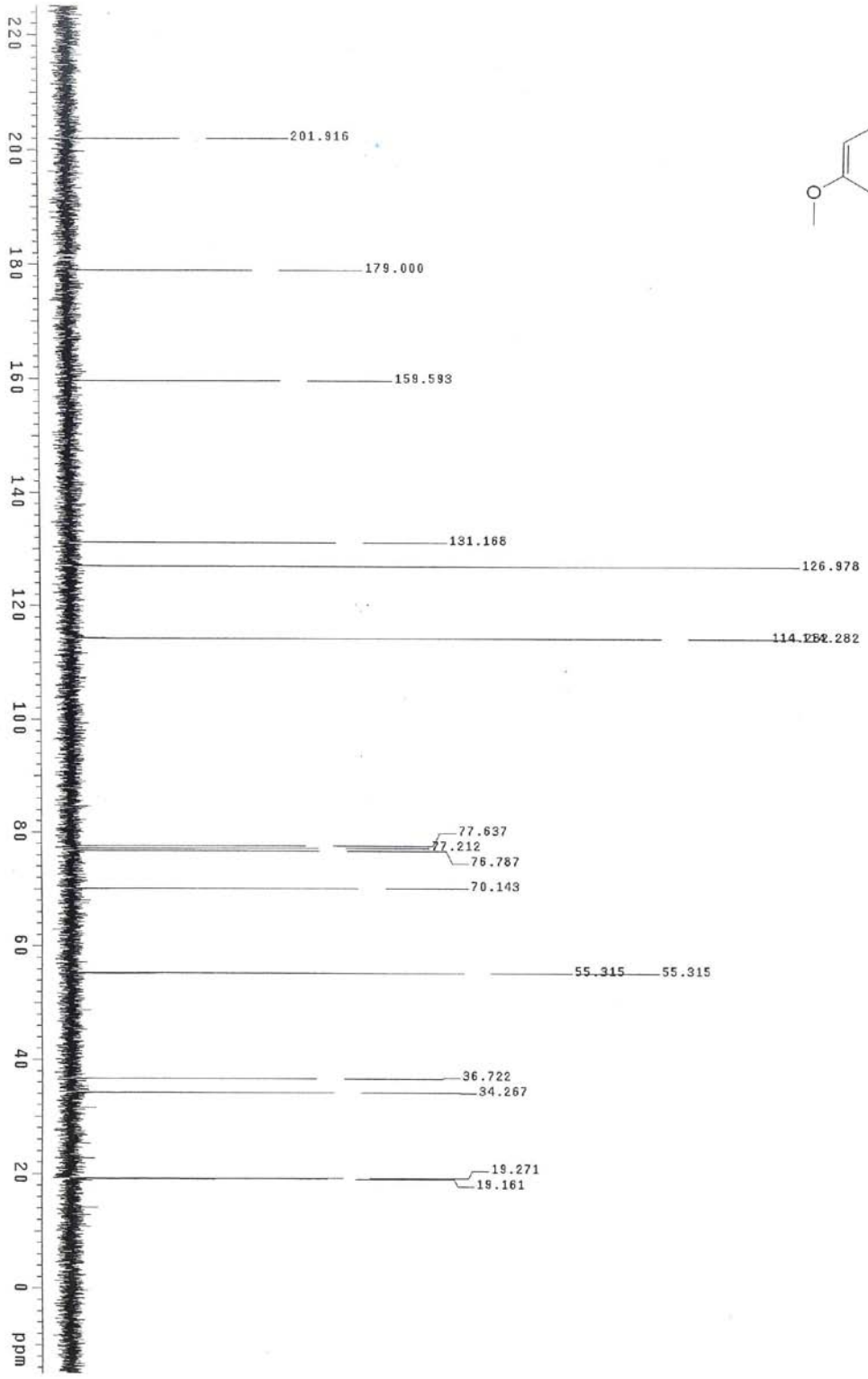

8
7
6
5
4
3
2
1
ppm
1.67
8.87
1.00
1.23
1.22

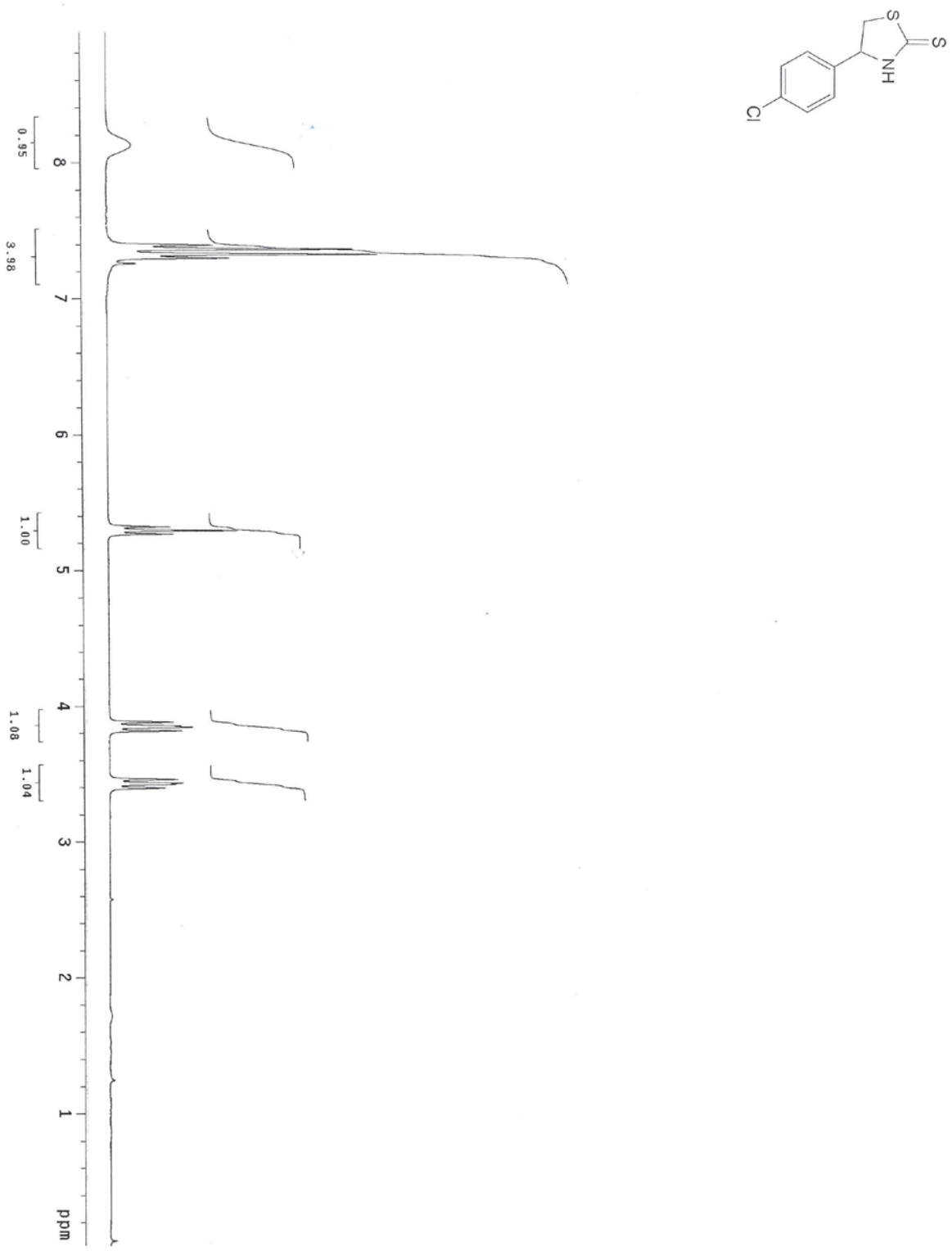

202.106
171.300
137.777
133.791
133.051
129.725
129.073
128.854
128.385
126.267
77.403
76.978
76.553
71.740
38.150
Ph
Ph
ppm

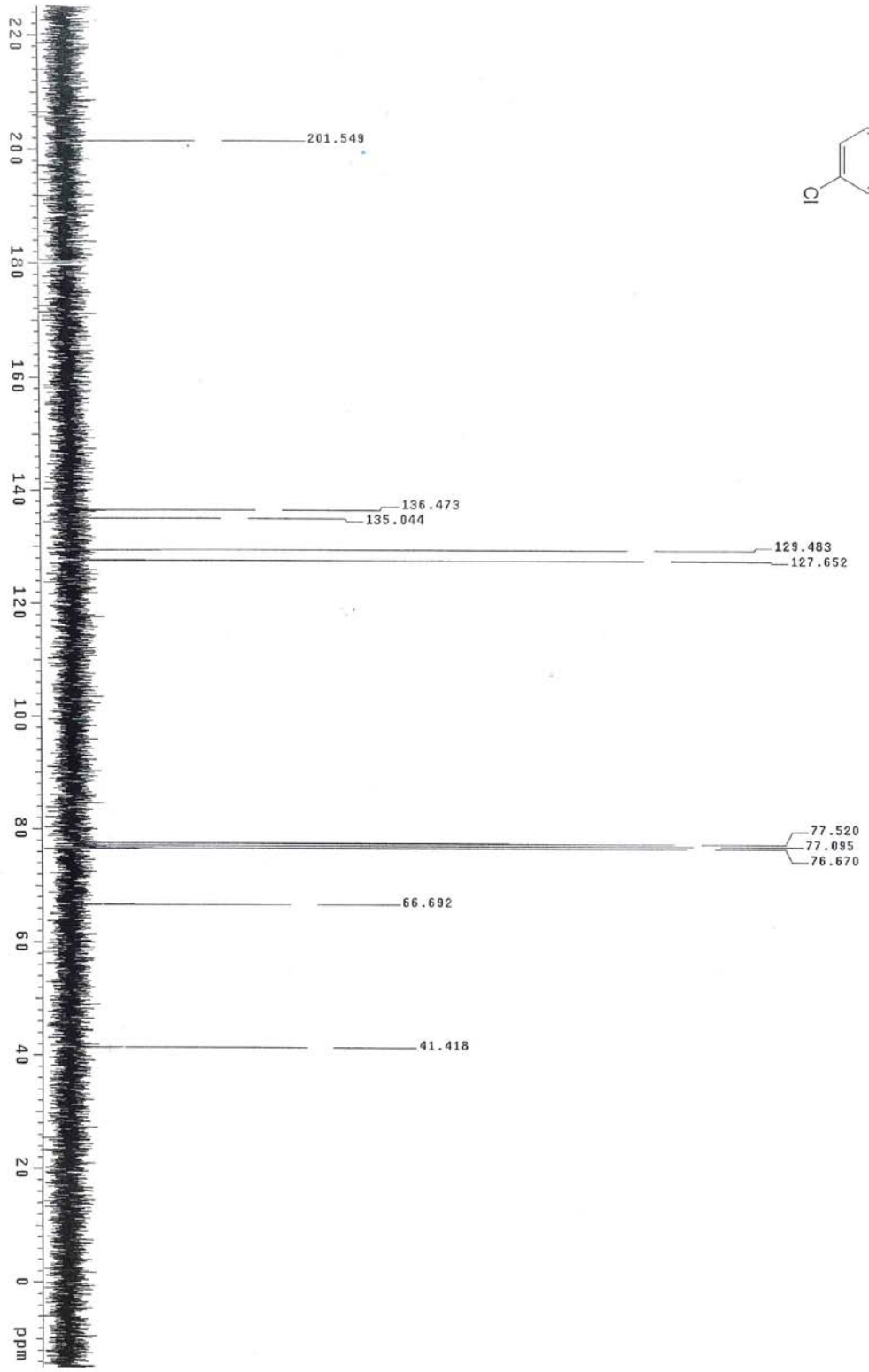

S
S
NH
O
9
8
7
6
5
4
3
2
1
ppm
0.80
1.97
1.84
1.00
4.20
1.05

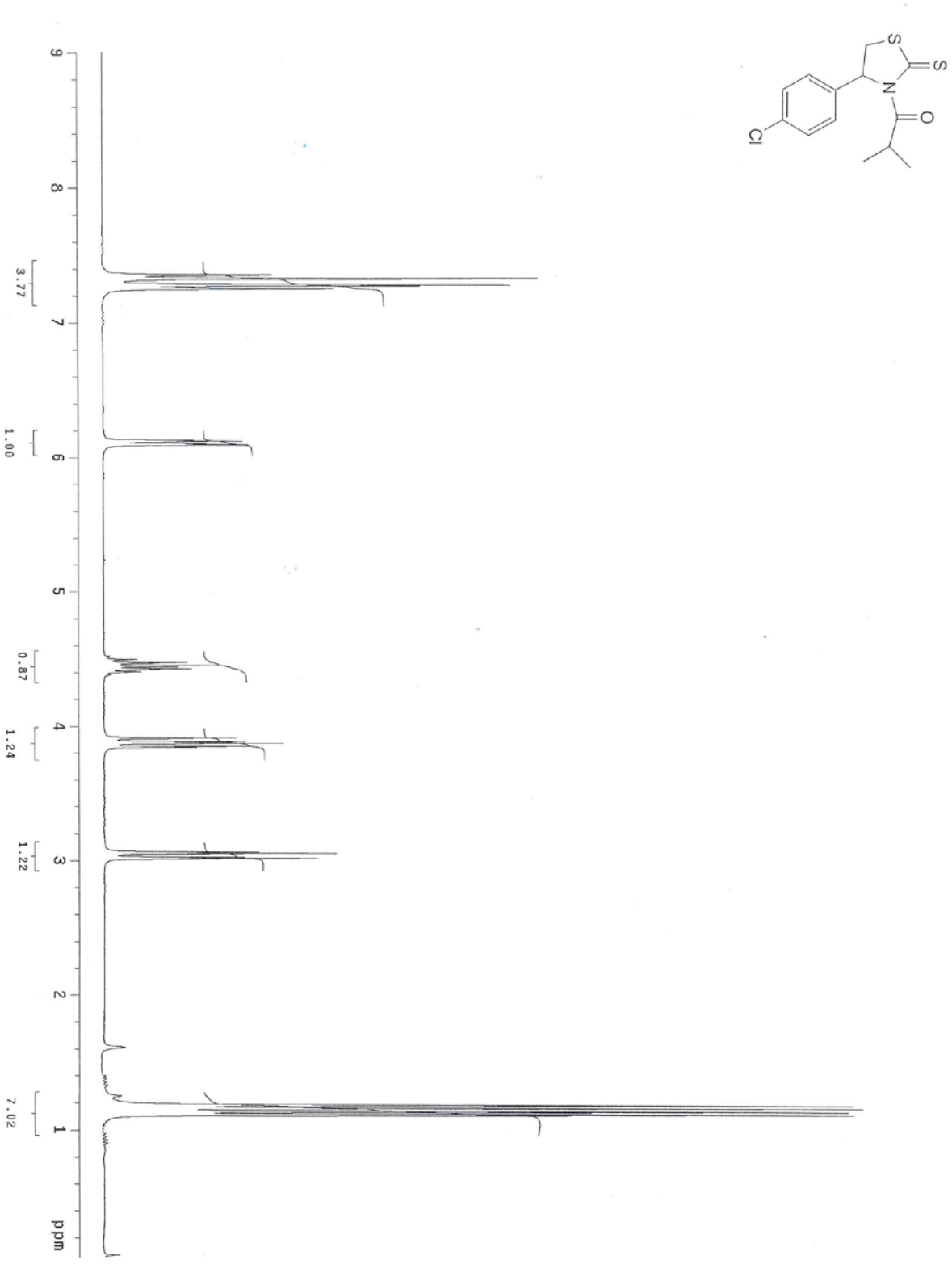

160.179
129.725
127.623
114.590
77.491
77.066
76.641
67.132
55.403
41.593
ppm

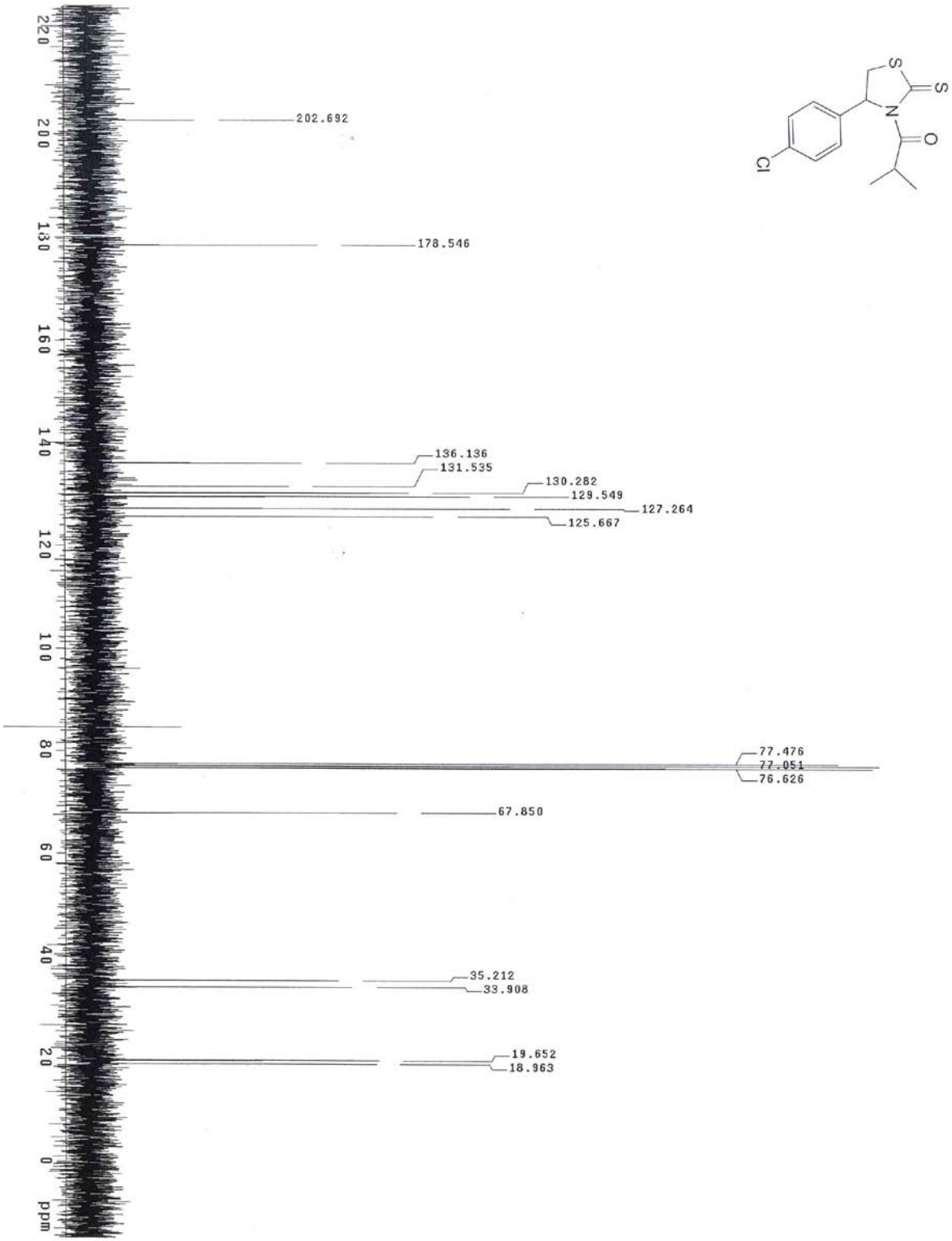

S
S
N
O
O
8
7
6
5
4
3
2
1
ppm
2.03
2.00
1.00
0.99
3.99
1.00
6.08

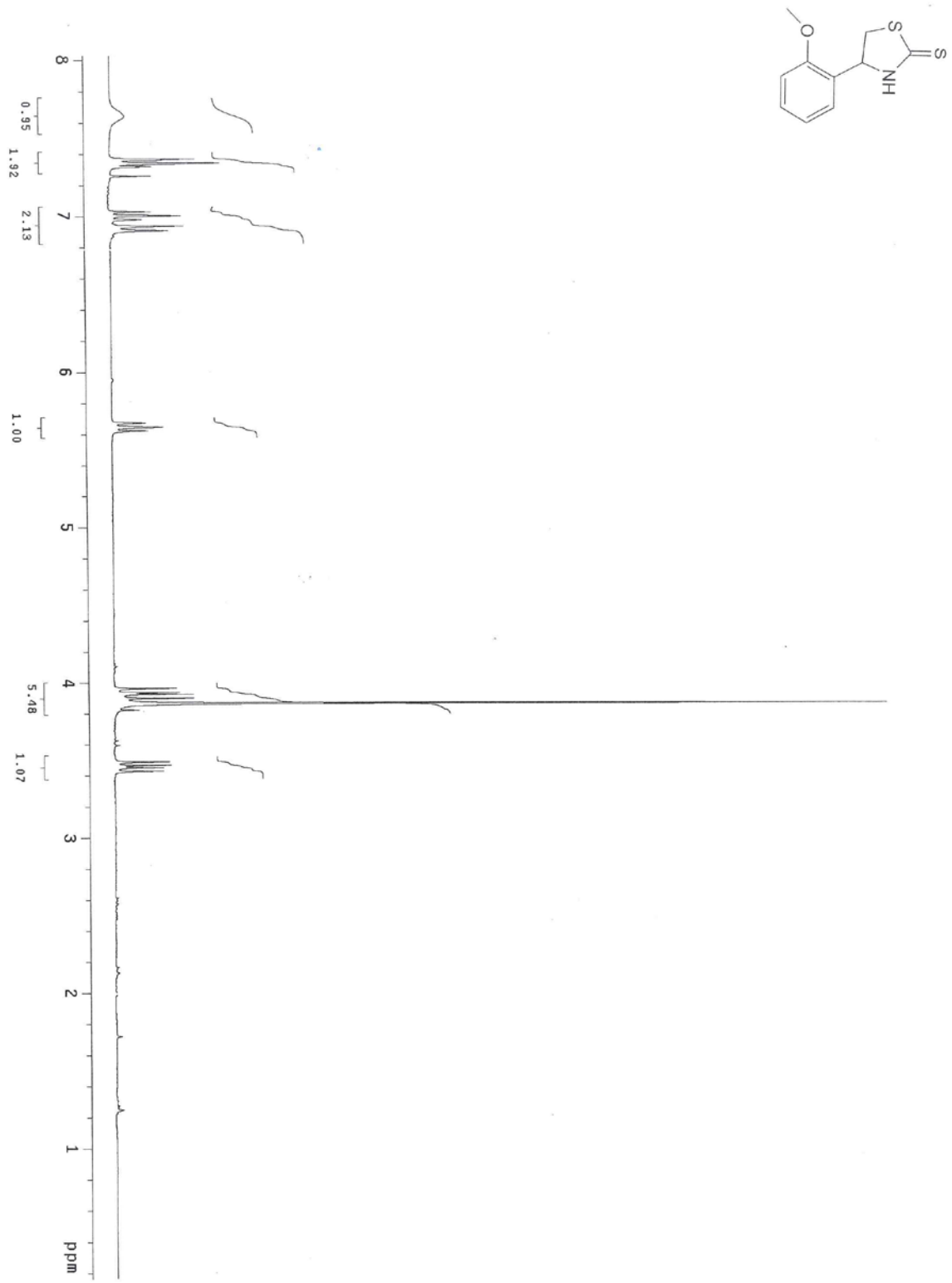

201.916
179.000
159.593
131.168
126.978
114.282
77.637
77.212
76.787
70.143
55.315
55.315
36.722
34.267
19.271
19.161
220
200
180
160
140
120
100
80
60
40
20
0
ppm
S
S
N
O
O

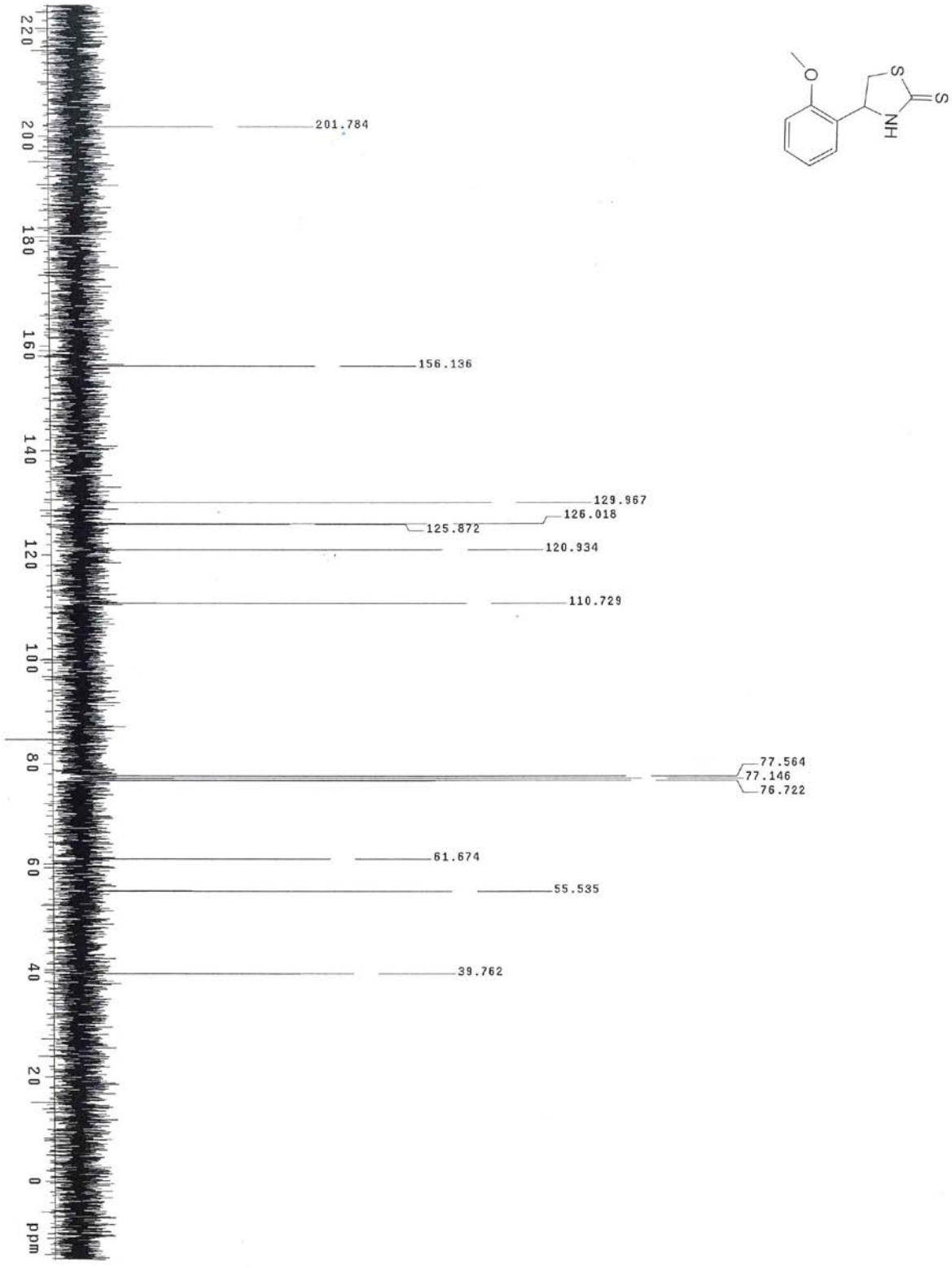

S
S
NH
Cl
0.95
3.98
1.00
1.08
1.04
8
7
6
5
4
3
2
1
ppm

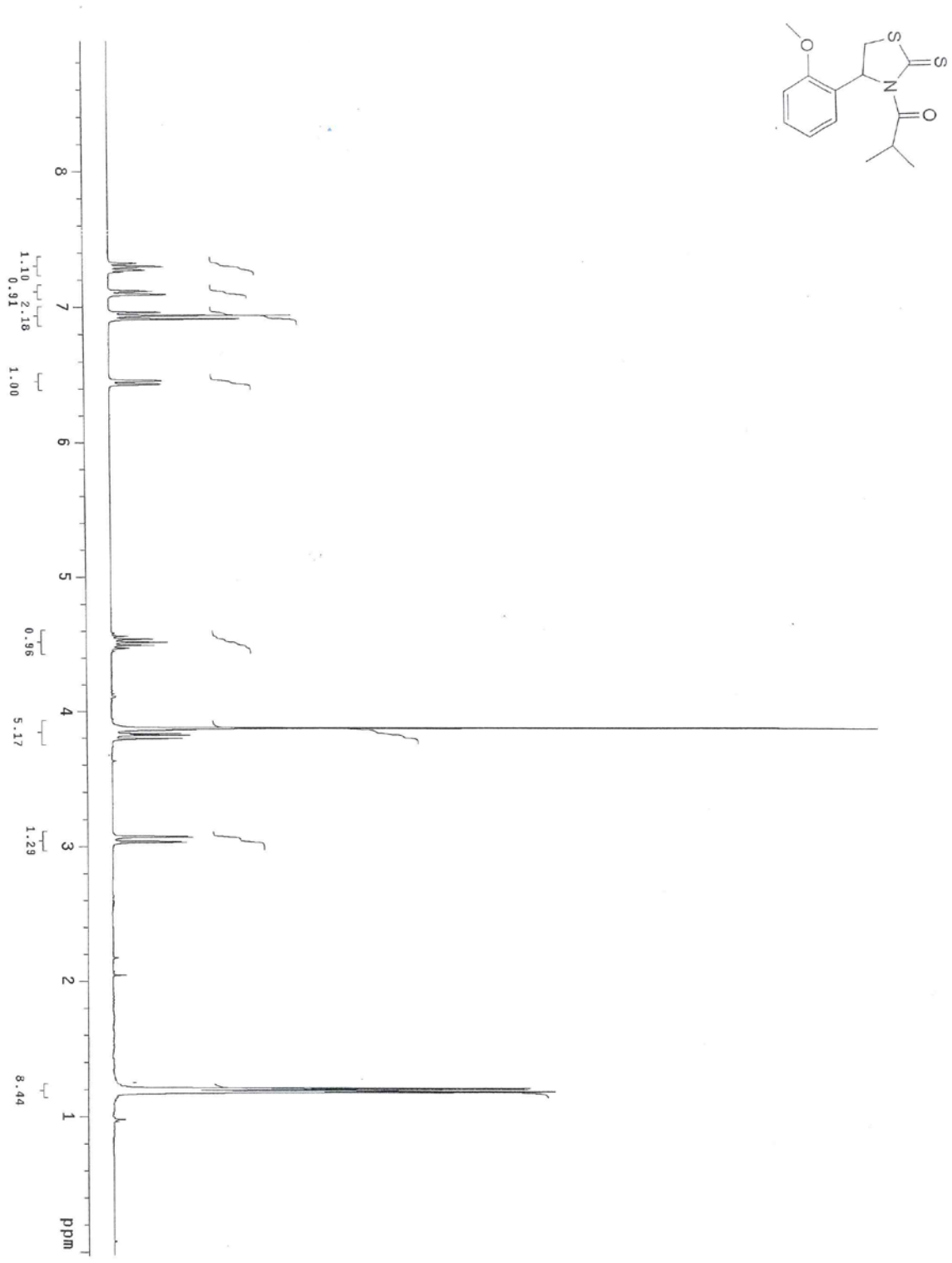

201.549
136.473
135.044
129.483
127.652
77.520
77.095
76.670
66.692
41.418
220
200
180
160
140
120
100
80
60
40
20
0
ppm
S
S
NH
Cl

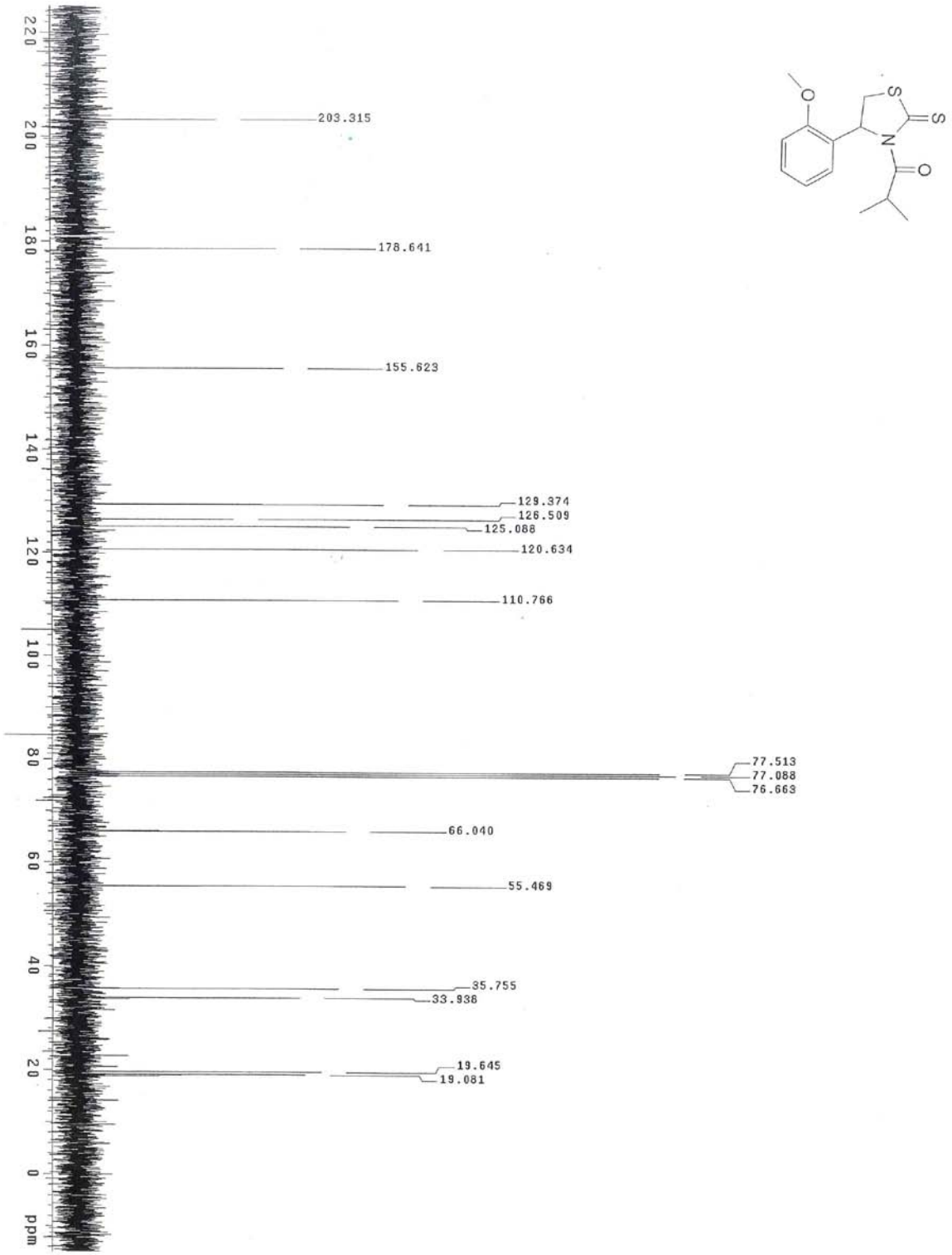

S
S
N
O
Cl
9
8
7
6
5
4
3
2
1
ppm
3.77
1.00
0.87
1.24
1.22
7.02

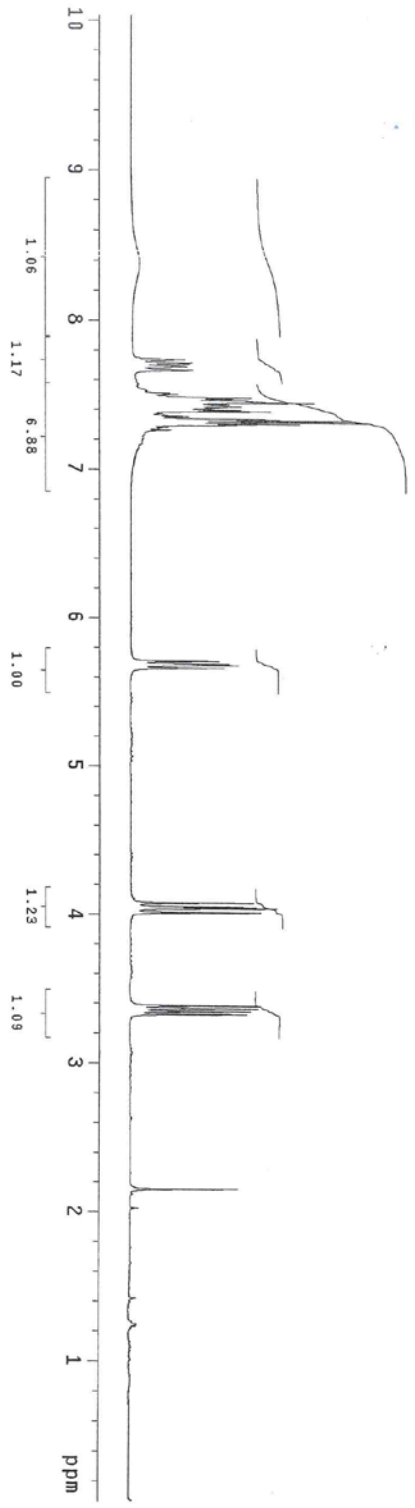

220
200
180
160
140
120
100
80
60
40
20
0
ppm
202.692
178.546
136.136
131.535
130.282
129.549
127.264
125.667
77.476
77.051
76.626
67.850
35.212
33.908
19.652
18.963
S
S
N
O
Cl

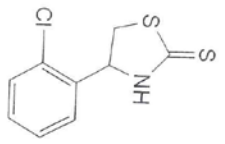

O
S
S
NH
8
7
6
5
4
3
2
1
ppm
0.95
1.92
2.13
1.00
5.48
1.07

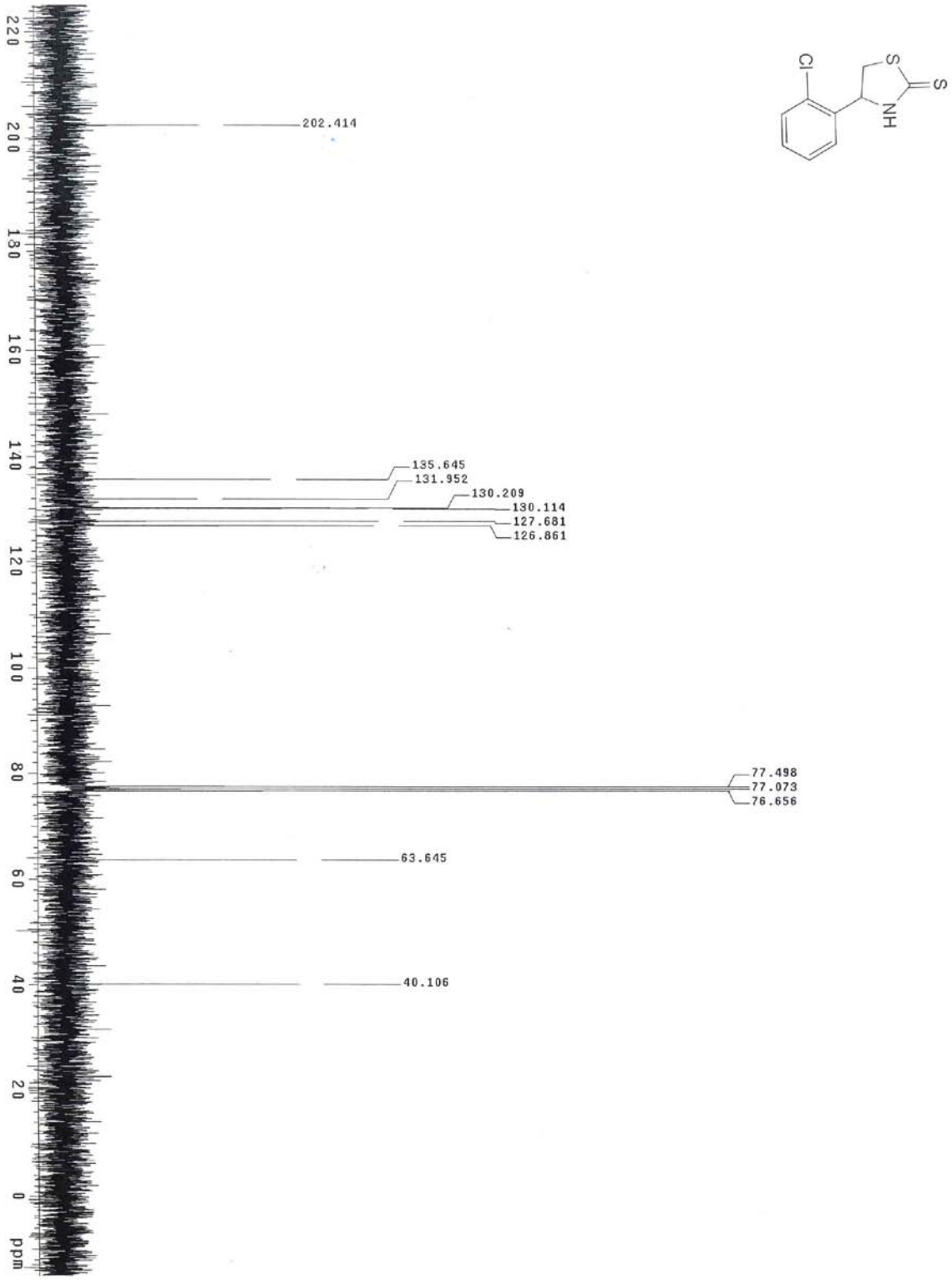

201.784
156.136
129.967
126.018
125.872
120.934
110.729
77.564
77.146
76.722
61.674
55.535
39.762
ppm


O
S
S
N
O
8
7
6
5
4
3
2
1
ppm
1.10
2.18
0.91
1.00
0.96
5.17
1.29
8.44


203.315
178.641
155.623
129.374
126.509
125.088
120.634
110.766
77.513
77.088
76.663
66.040
55.469
35.755
33.938
19.645
19.081
220
200
180
160
140
120
100
80
60
40
20
0
ppm
O
S
S
N
O


10
9
8
7
6
5
4
3
2
1
ppm
1.06
1.17
6.88
1.00
1.23
1.09


Cl
S
S
NH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131.952
130.209
130.114
127.681
126.861
77.498
77.073
76.656
63.645
40.106
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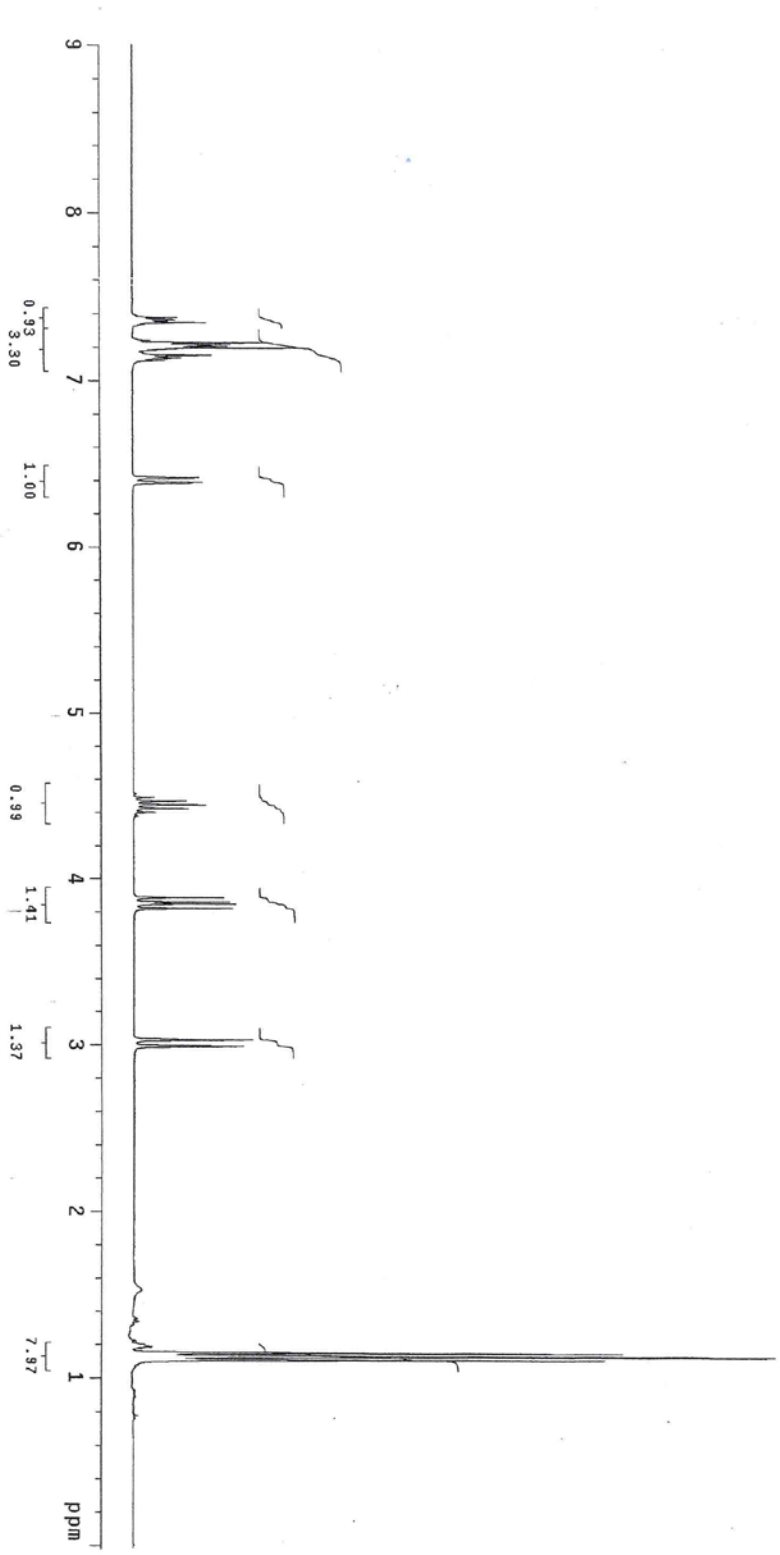
200
180
160
140
120
100
80
60
40
20
0
ppm
Cl
S
S
NH


9
8
7
6
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4
3
2
1
ppm
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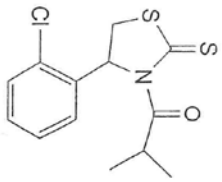
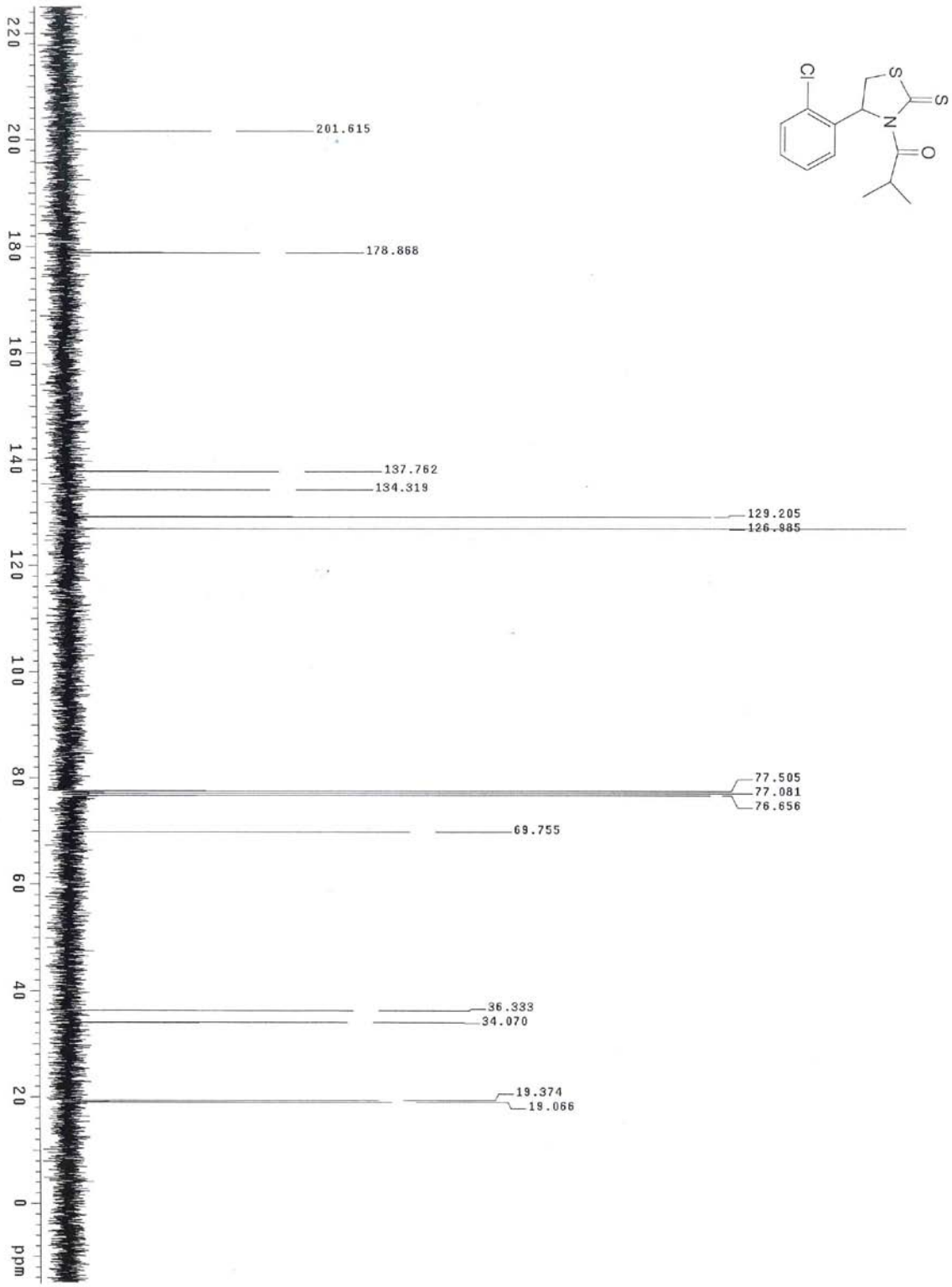
3.30
1.00
0.99
1.41
1.37
7.97


Cl
S
S
N
O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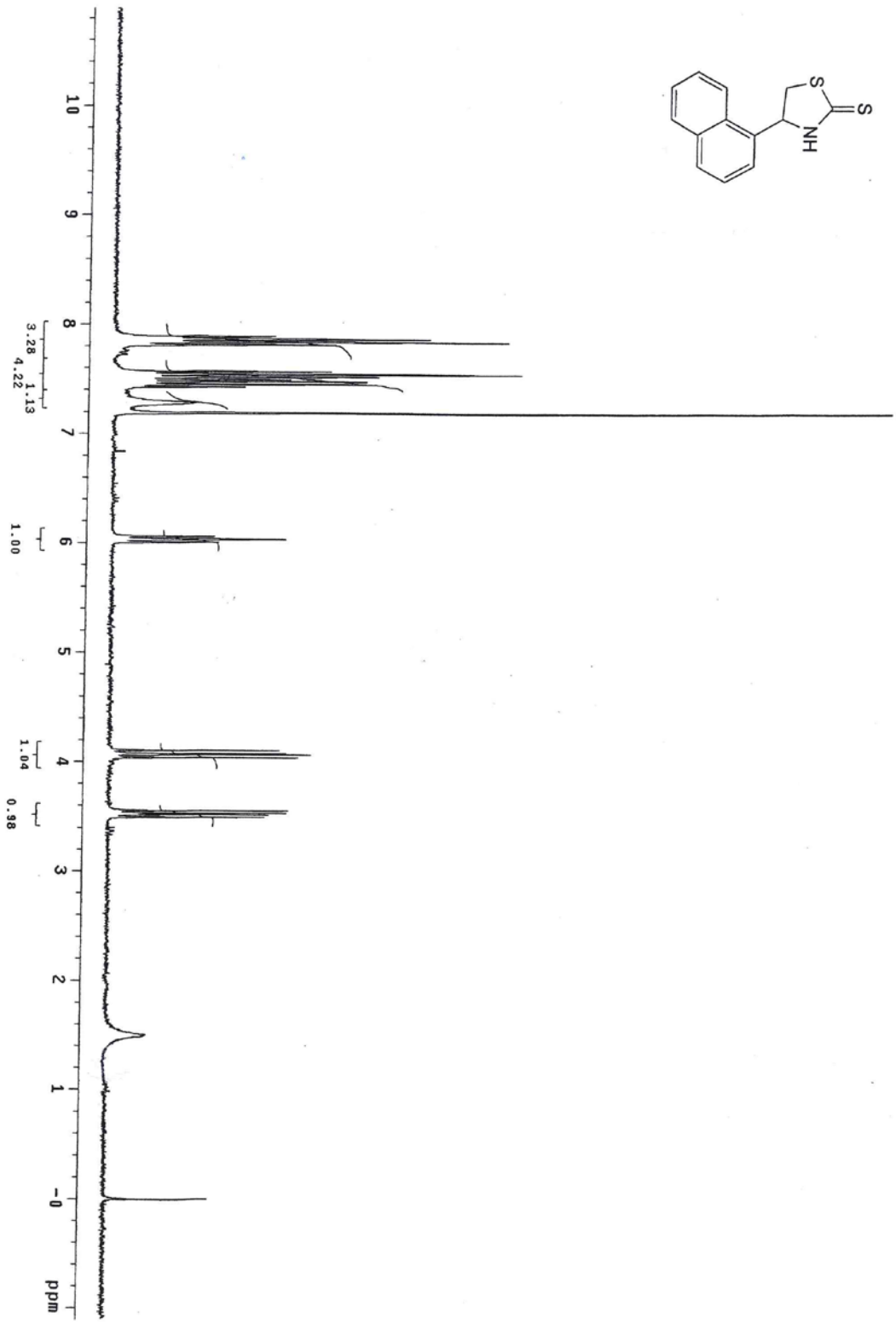
178.868
137.762
134.319
129.205
126.985
77.505
77.081
76.656
69.755
36.333
34.070
19.374
19.066
ppm


S
S
NH
10
9
8
7
6
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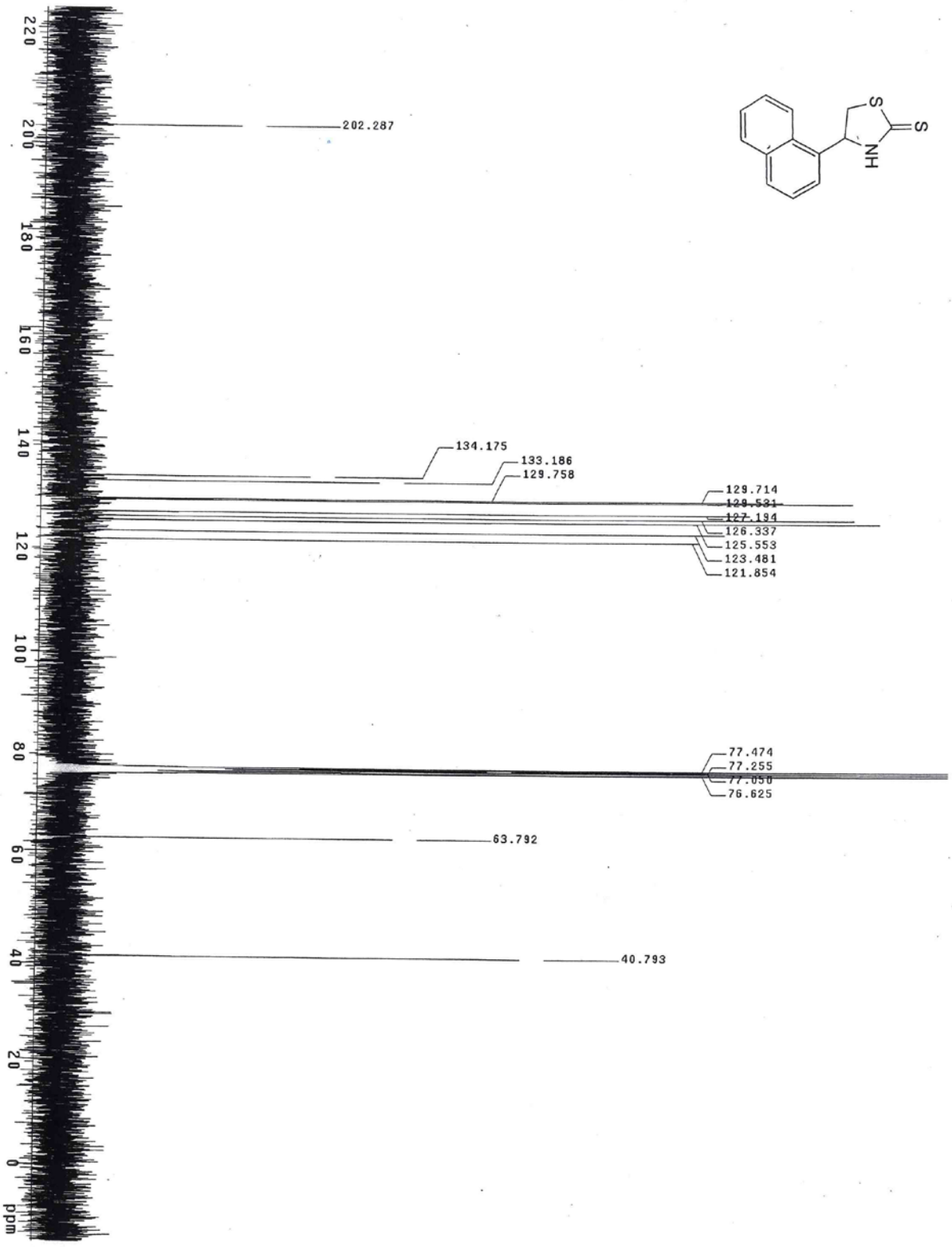
4
3
2
1
-0
ppm
3.28
1.13
4.22
1.00
1.04
0.98


202.287
134.175
133.186
129.758
129.714
128.531
127.194
126.337
125.553
123.481
121.854
77.474
77.255
77.050
76.625
63.792
40.793
S
S
NH
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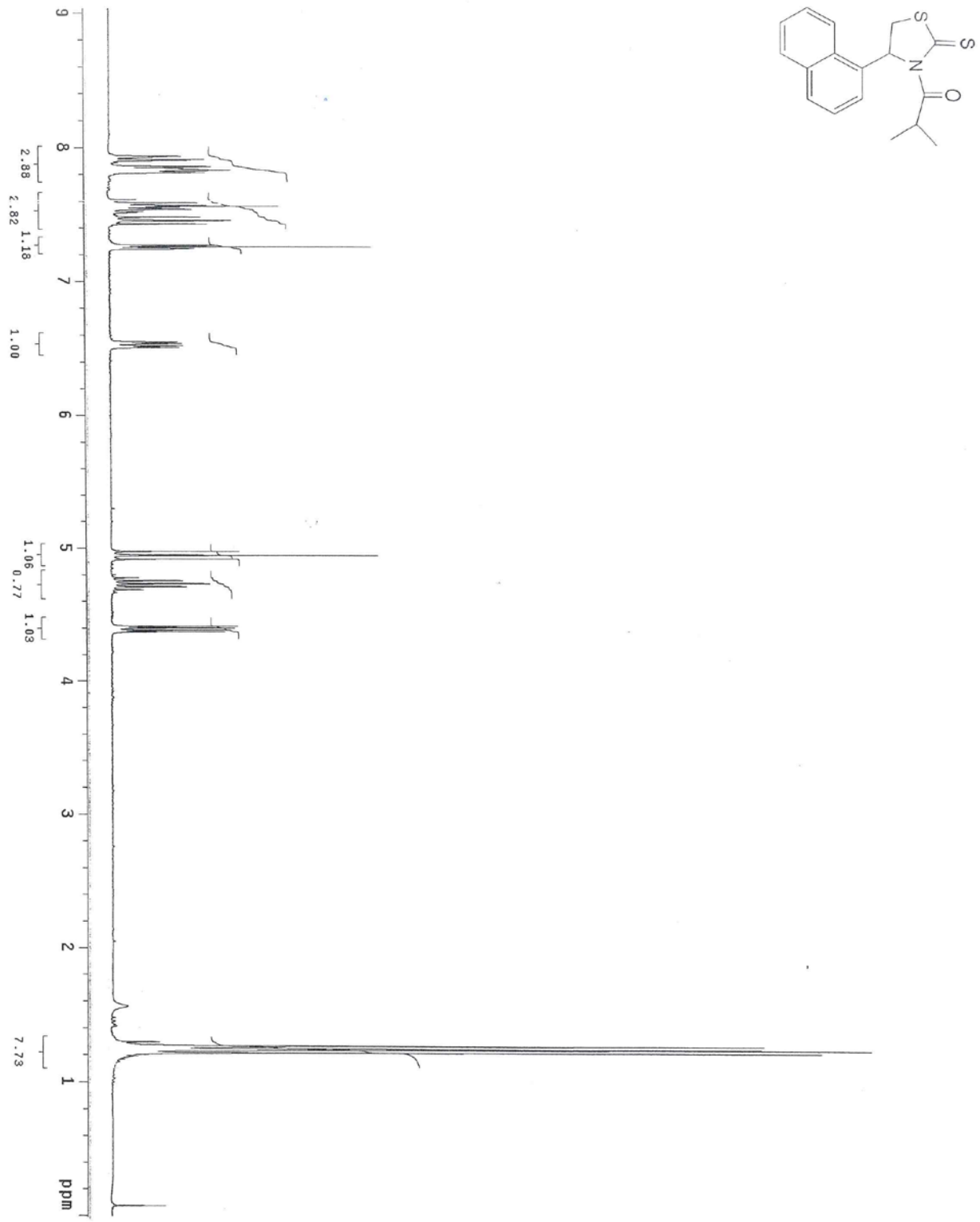
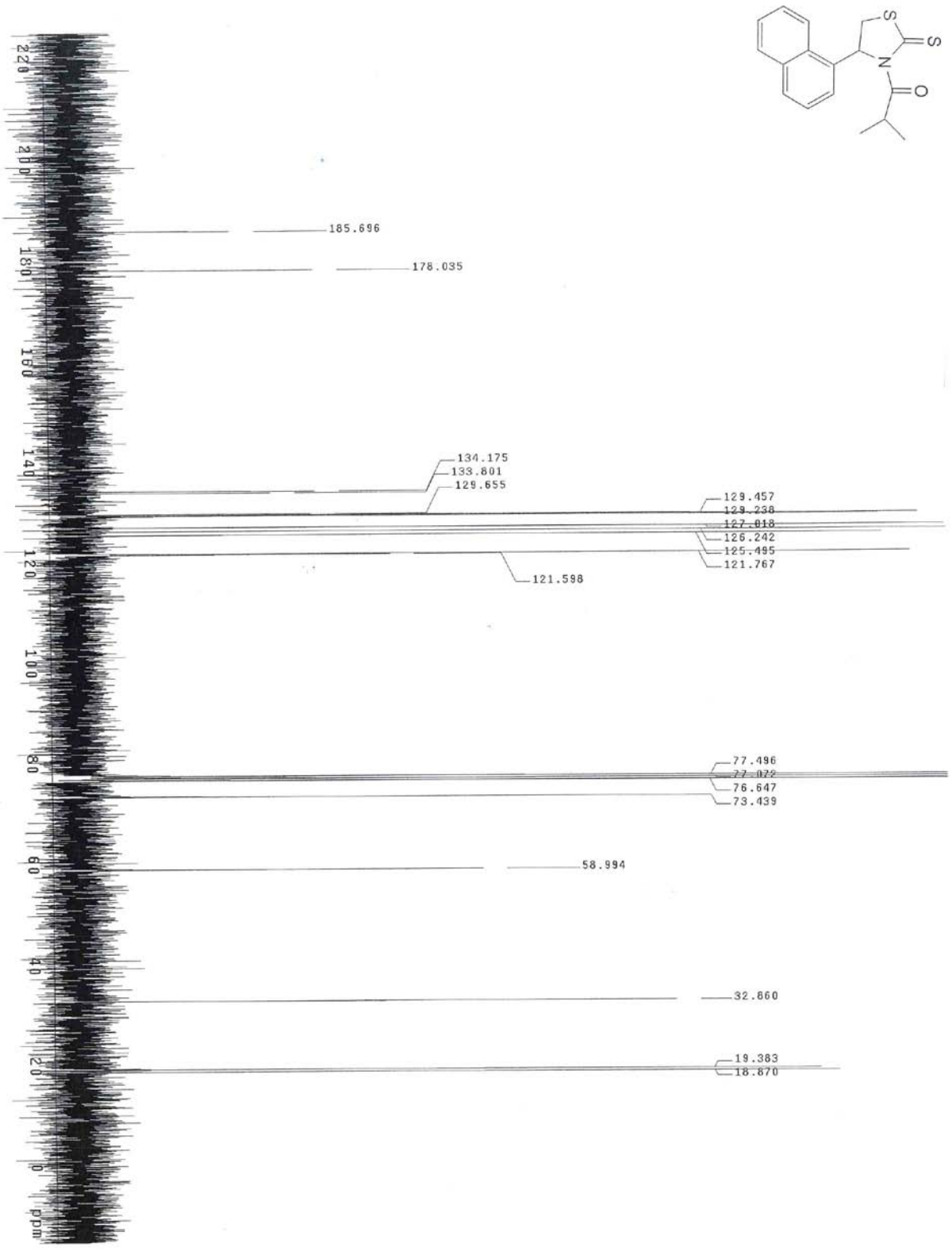
200
180
160
140
120
100
80
60
40
20
0
ppm


S
S
N
O
9
8
7
6
5
4
3
2
1
ppm
2.88
2.82
1.18
1.00
1.06
0.77
1.03
7.73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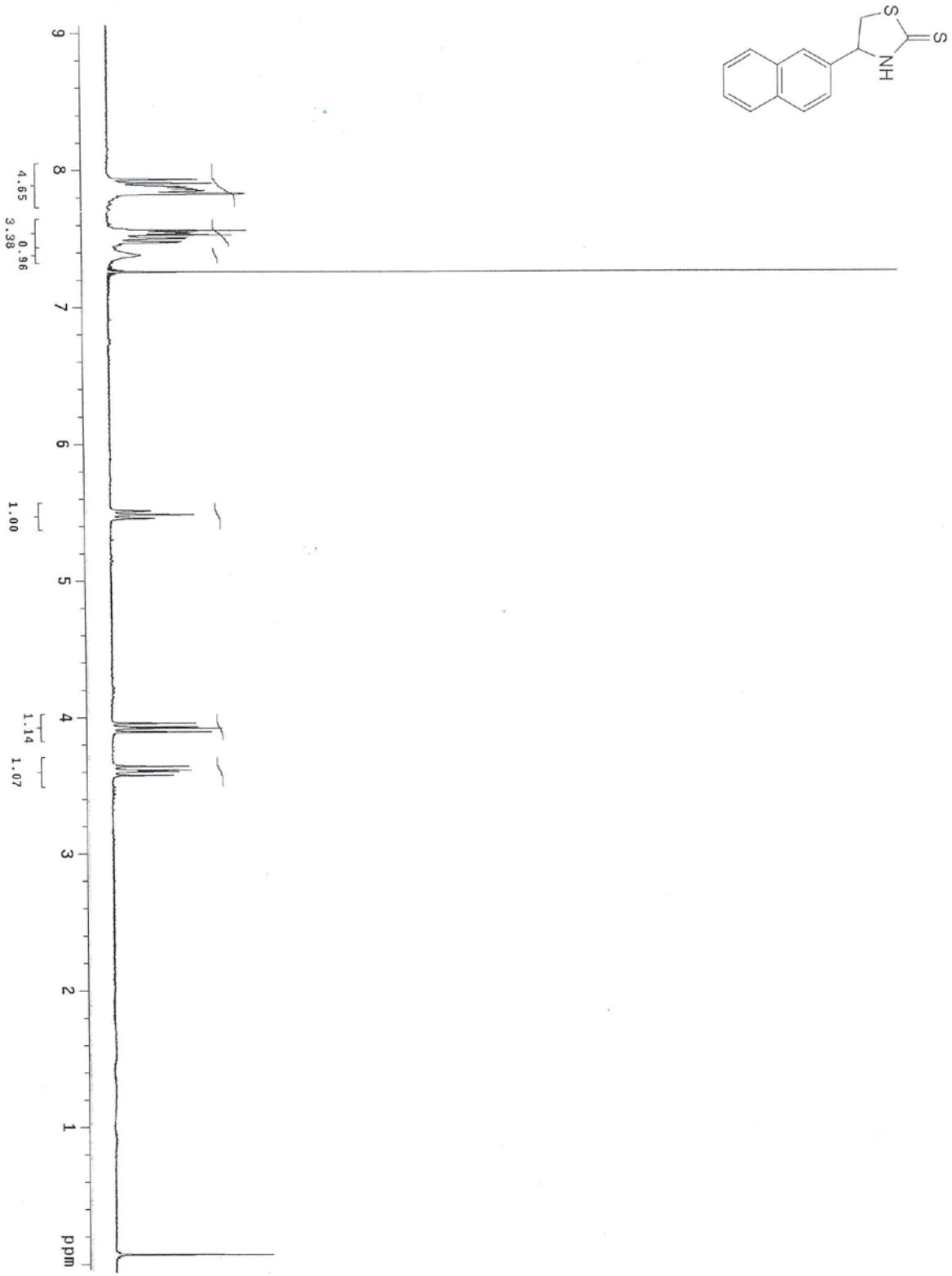
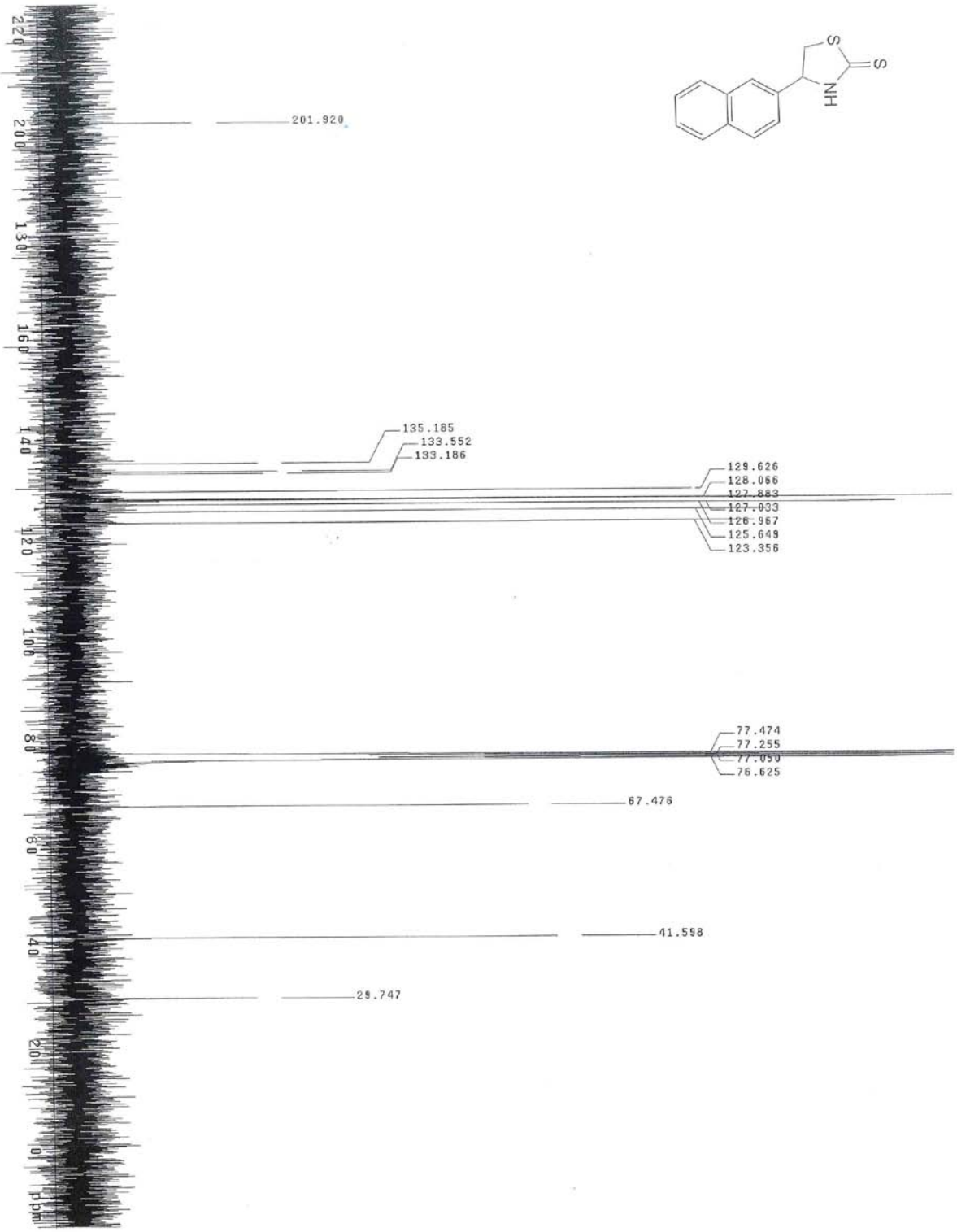
178.035
134.175
133.801
129.655
129.457
128.238
127.818
126.242
125.495
121.767
121.598
77.496
77.072
76.647
73.439
58.994
32.860
19.383
18.870
ppm


S
S
NH
9
8
7
6
5
4
3
2
1
ppm
4.65
3.38
0.96
1.00
1.14
1.07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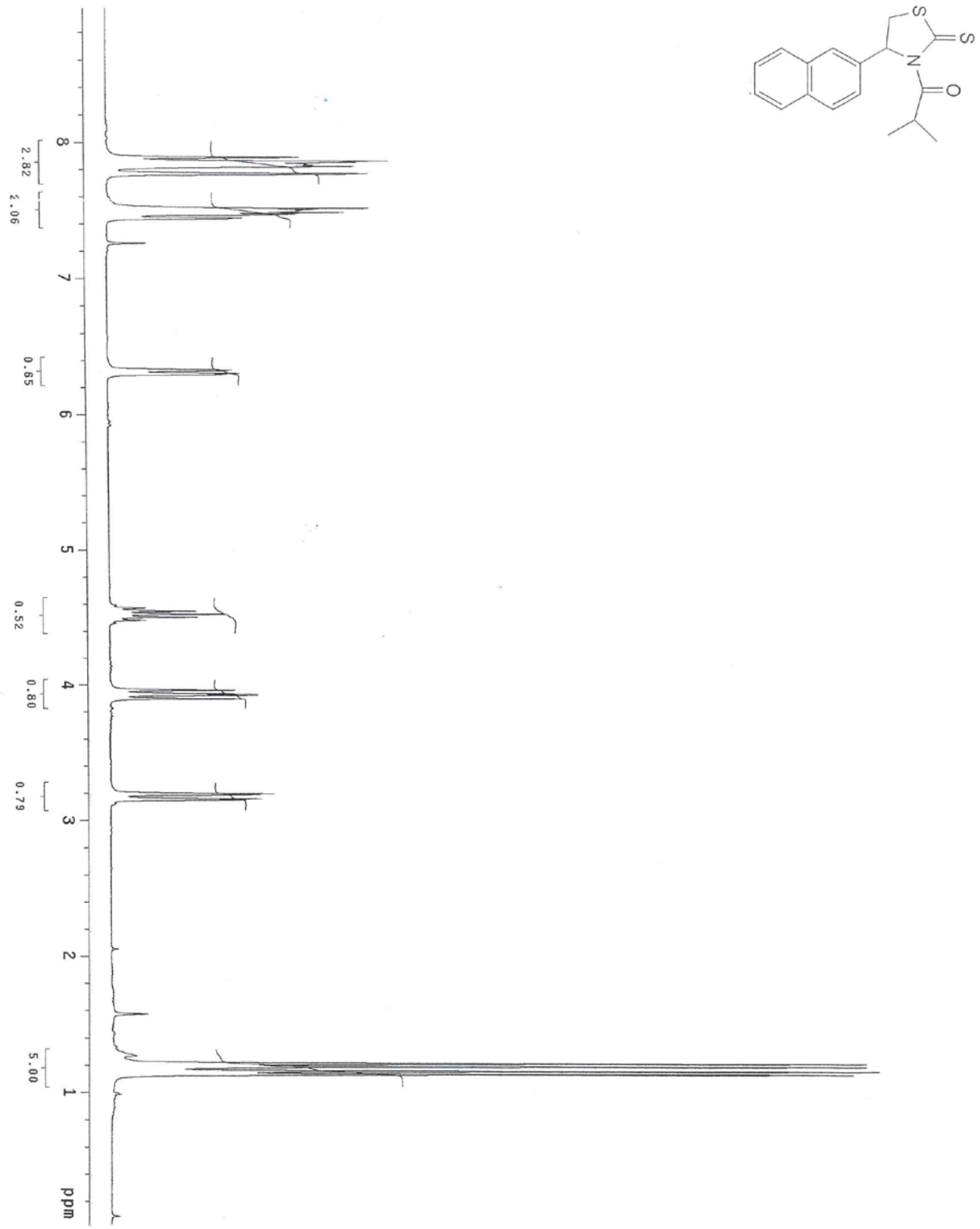
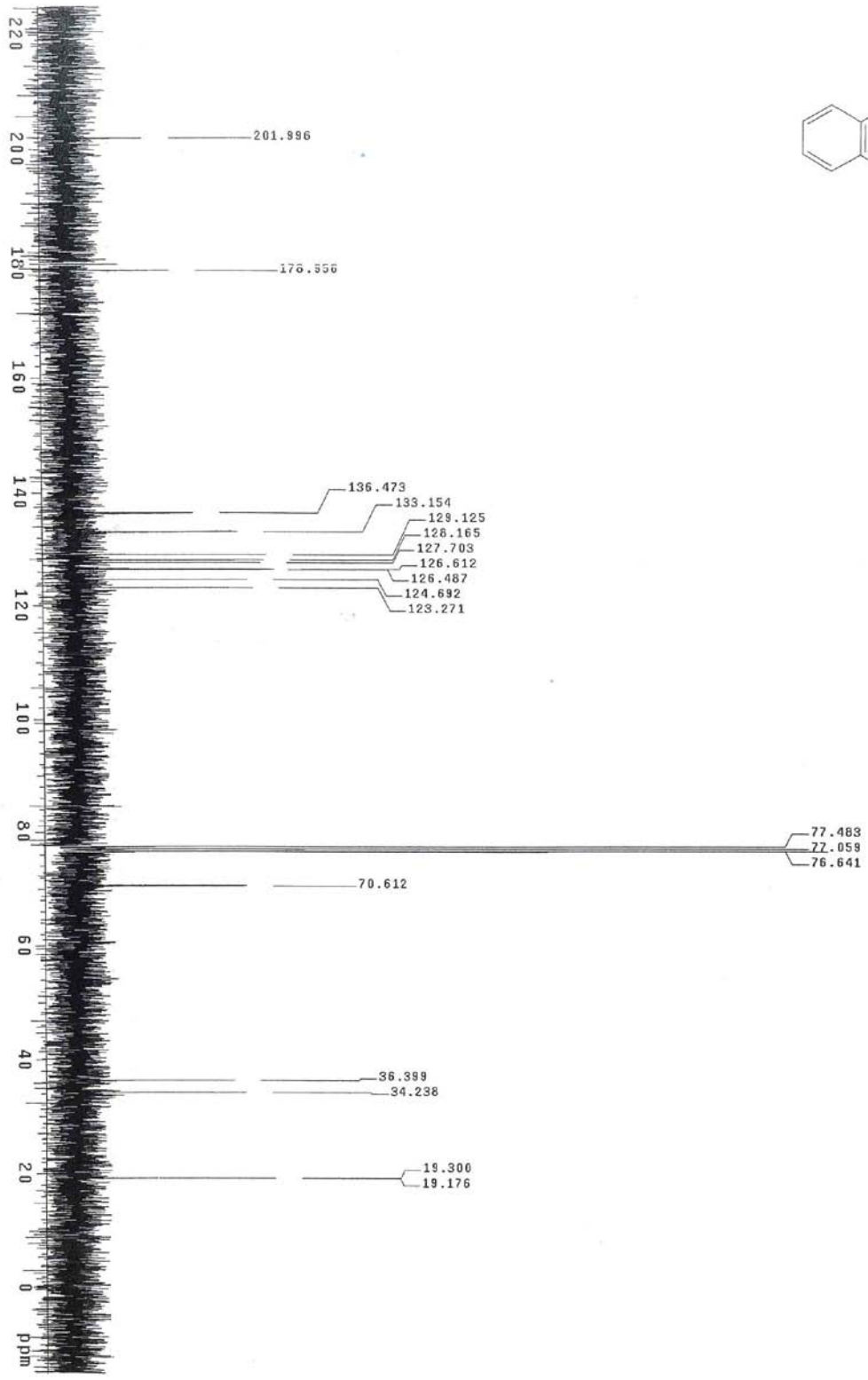
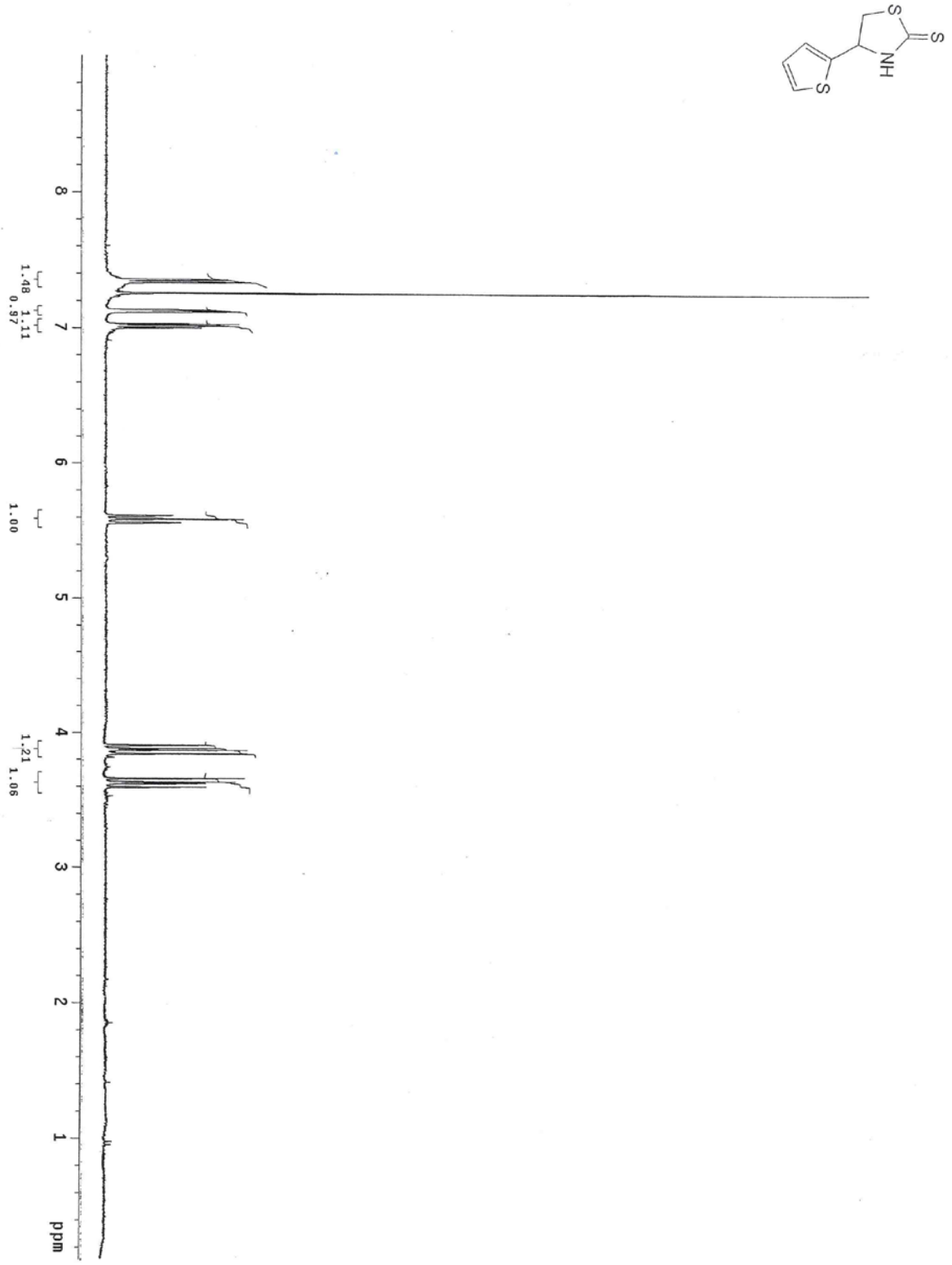
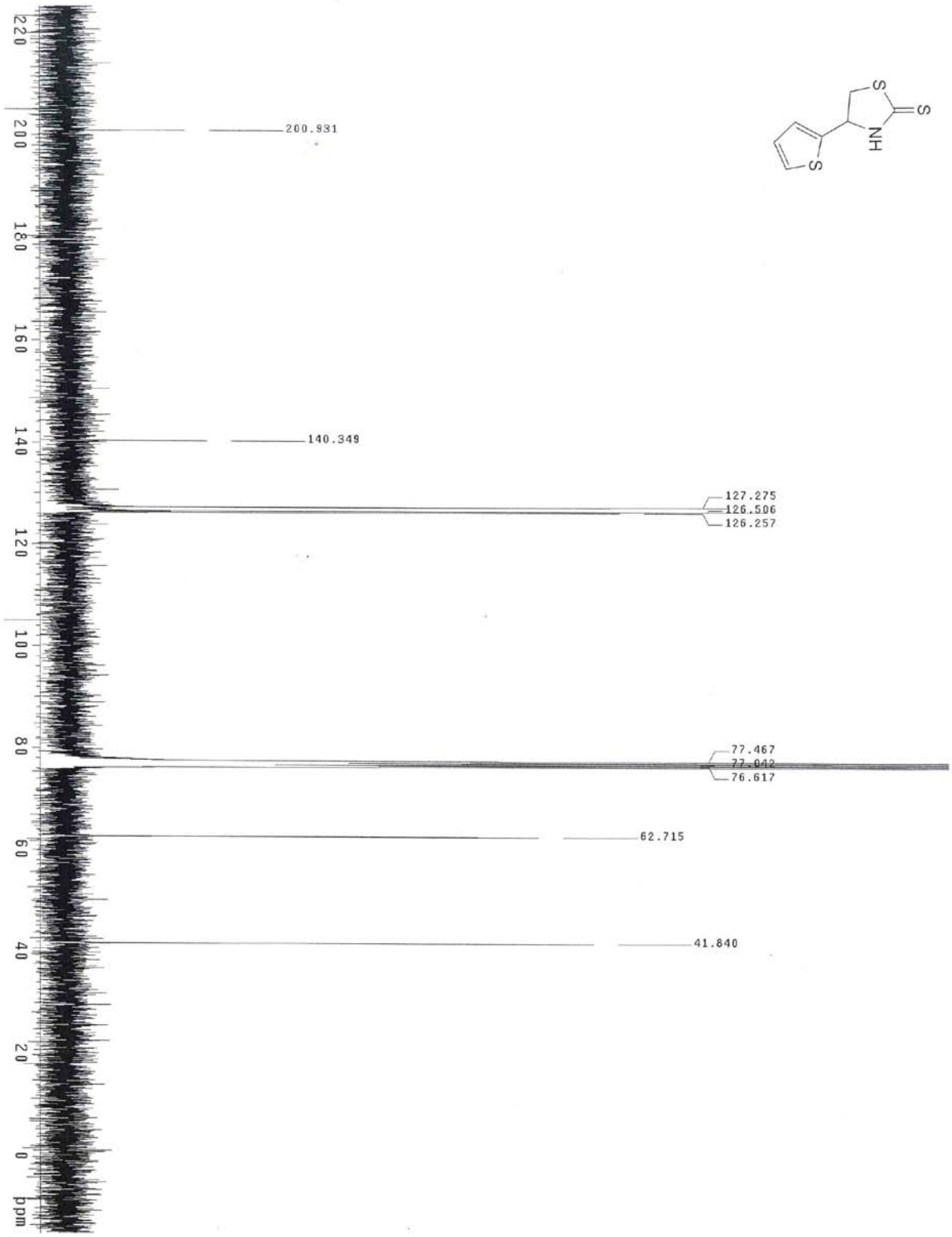
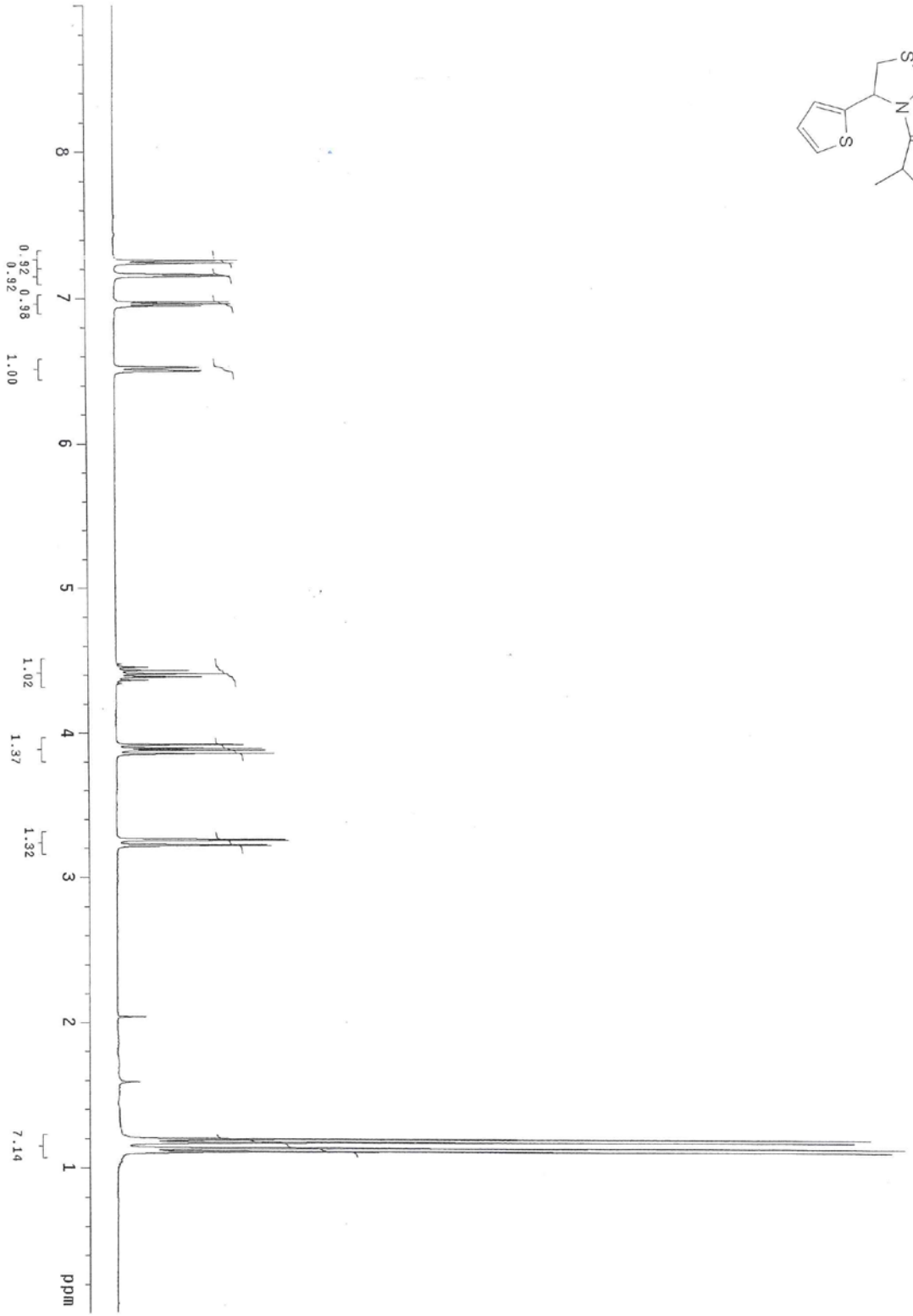
135.185
133.552
133.186
129.626
128.056
127.883
127.033
126.967
125.649
123.356
77.474
77.255
77.050
76.625
67.476
41.598
29.747
S
S
NH

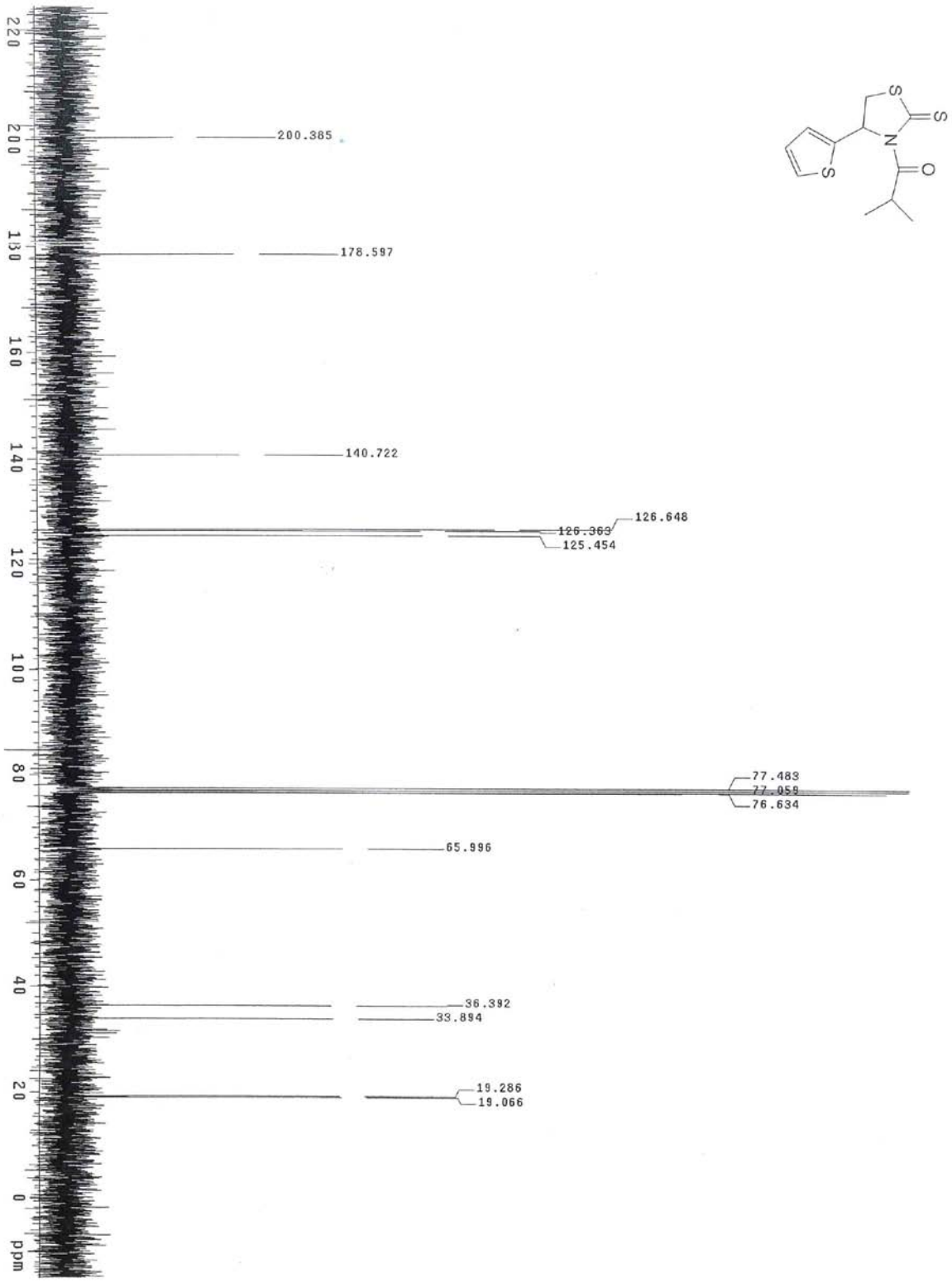

S
S
N
O
8
7
6
5
4
3
2
1
ppm
2.82
2.06
0.65
0.52
0.80
0.79
5.00


201.996
178.356
136.473
133.154
129.125
128.165
127.703
126.612
126.487
124.692
123.271
77.483
77.059
76.641
70.612
36.399
34.238
19.300
19.176
ppm


S
S
NH
S
8
7
6
5
4
3
2
1
ppm
1.48
1.11
0.97
1.00
1.21
1.06


200.931
140.349
127.275
126.506
126.257
77.467
77.042
76.617
62.715
41.840
220
200
180
160
140
120
100
80
60
40
20
0
ppm
S
S
NH
S


8
7
6
5
4
3
2
1
ppm
0.92
0.92
0.98
1.00
1.02
1.37
1.32
7.14
S
S
N
O
S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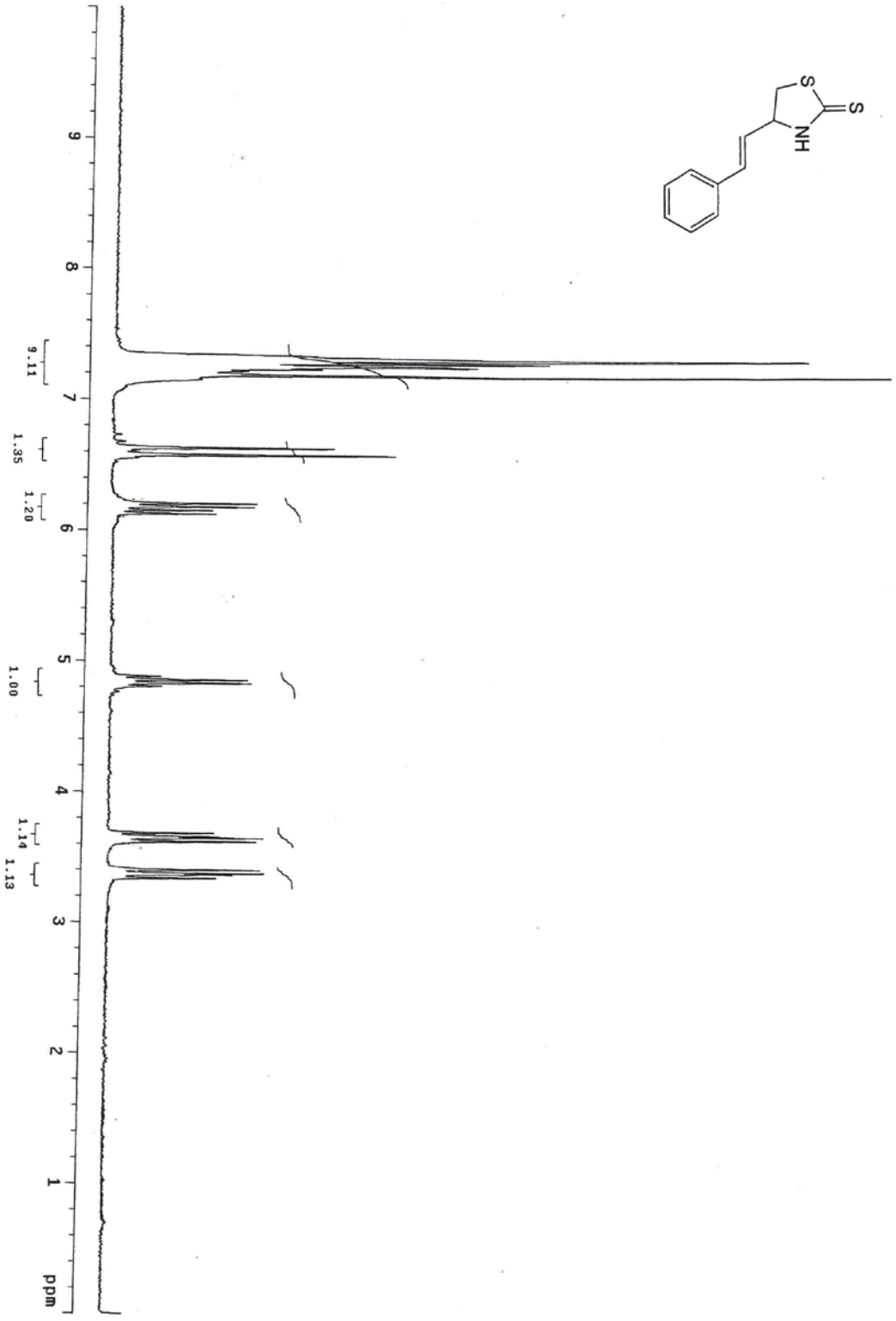
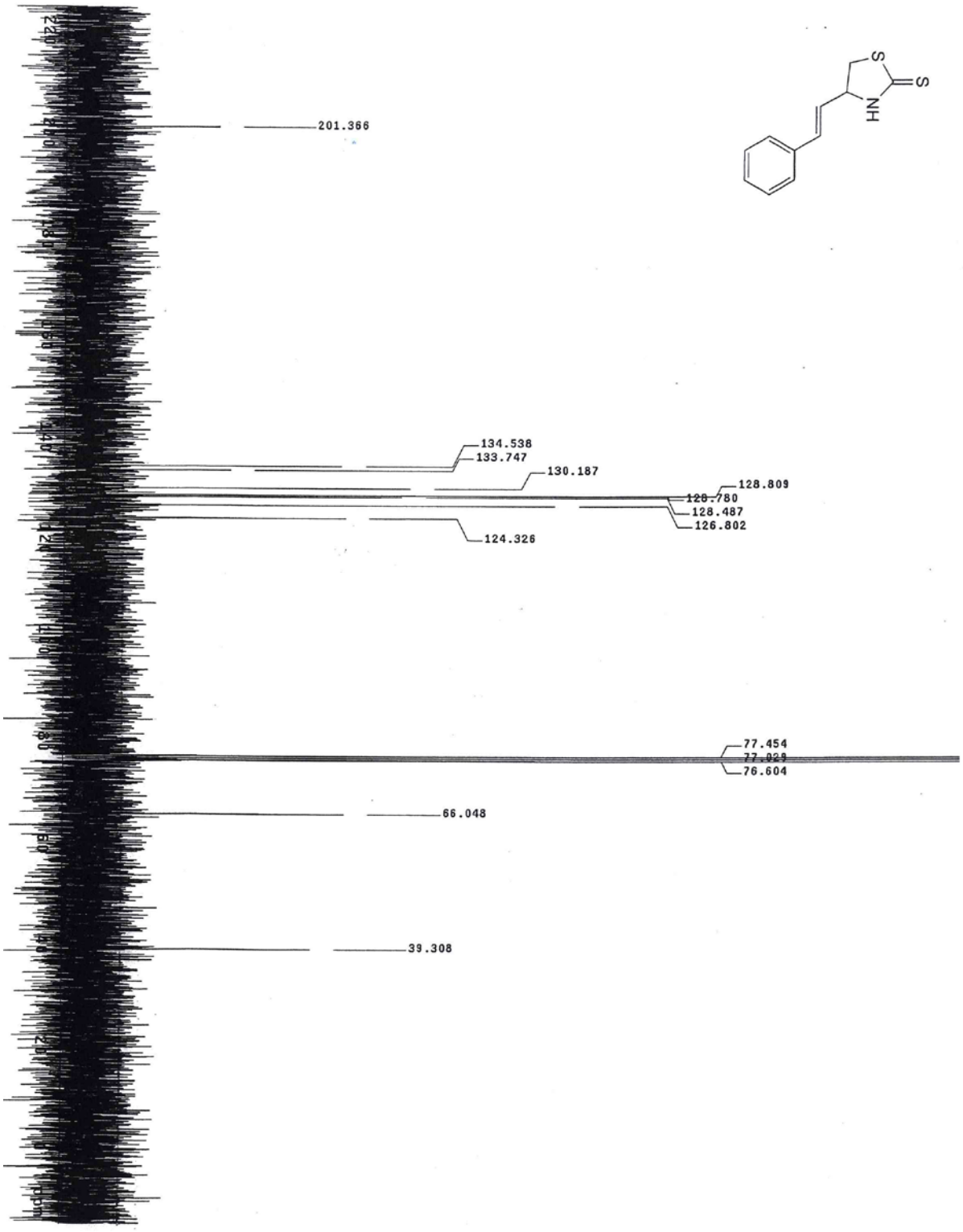
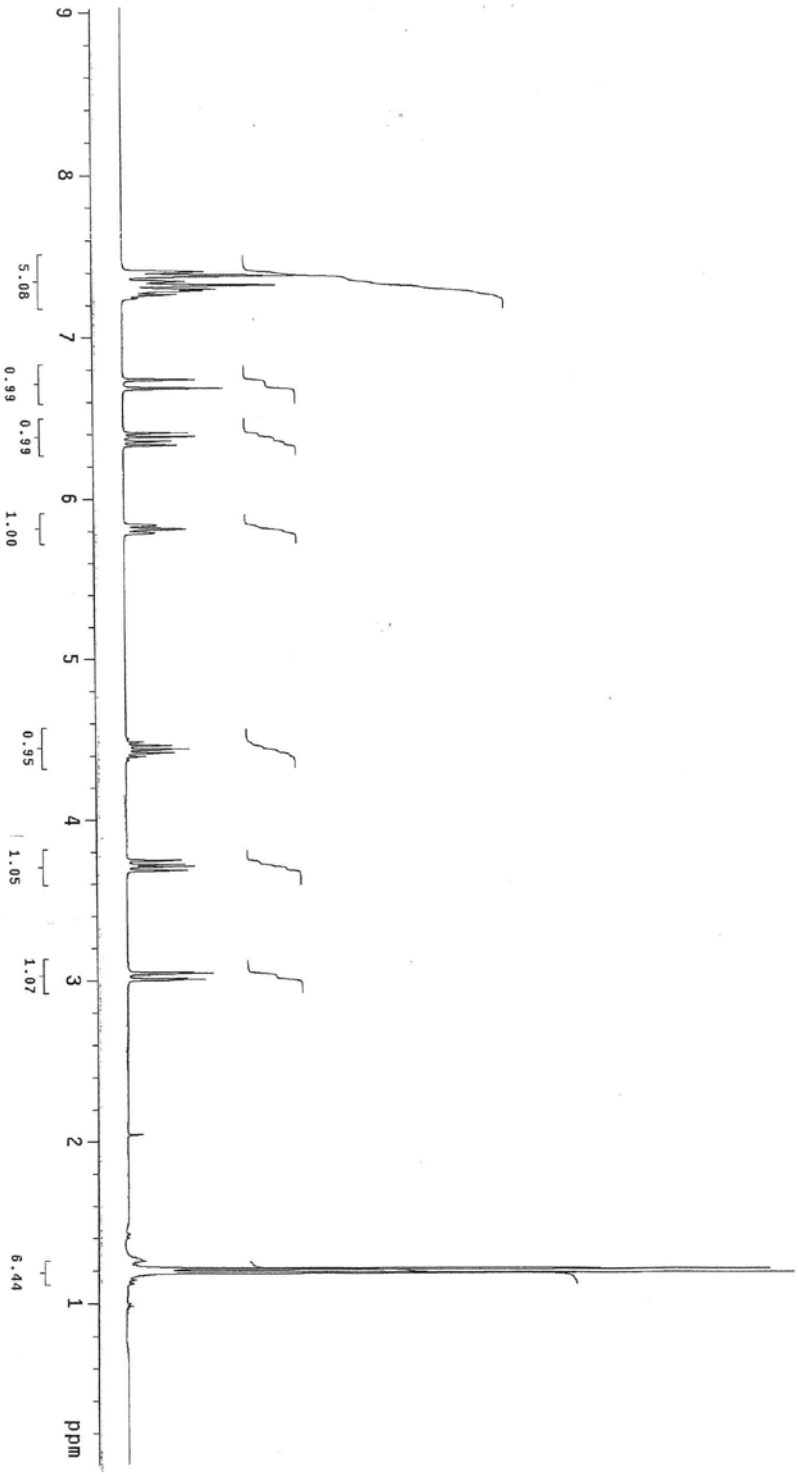
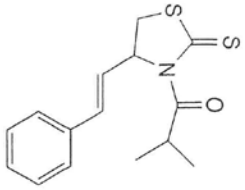
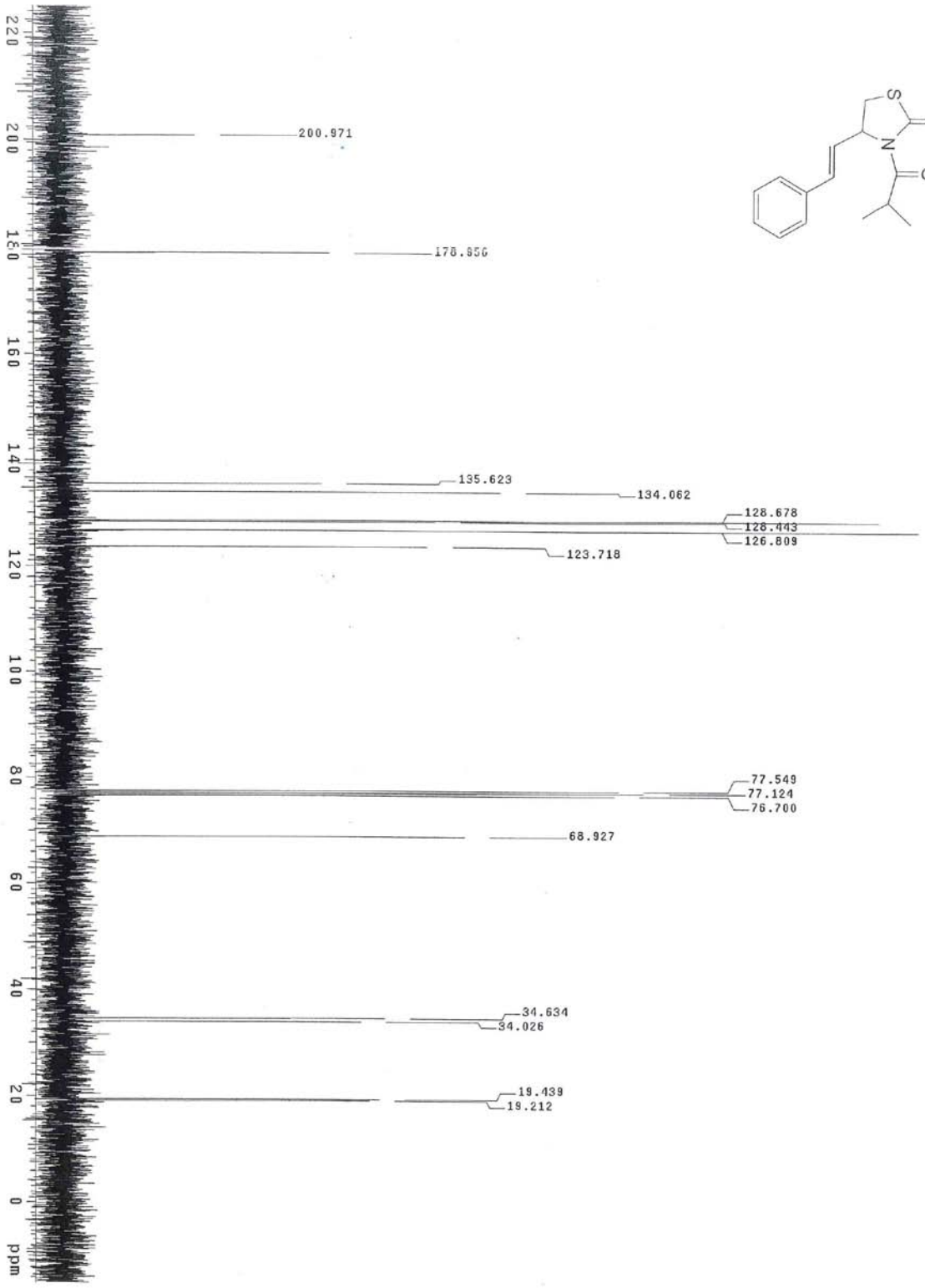
140.722
126.648
126.363
125.454
77.483
77.059
76.634
65.996
36.392
33.894
19.286
19.066
ppm


S
S
NH
9
8
7
6
5
4
3
2
1
ppm
9.11
1.35
1.20
1.00
1.14
1.13


201.366
134.538
133.747
130.187
128.809
128.780
128.487
126.802
124.326
77.454
77.029
76.604
66.048
39.308
S
S
HN


9
8
7
6
5
4
3
2
1
ppm
5.08
0.99
0.99
1.00
0.95
1.05
1.07
6.44


S
S
N
O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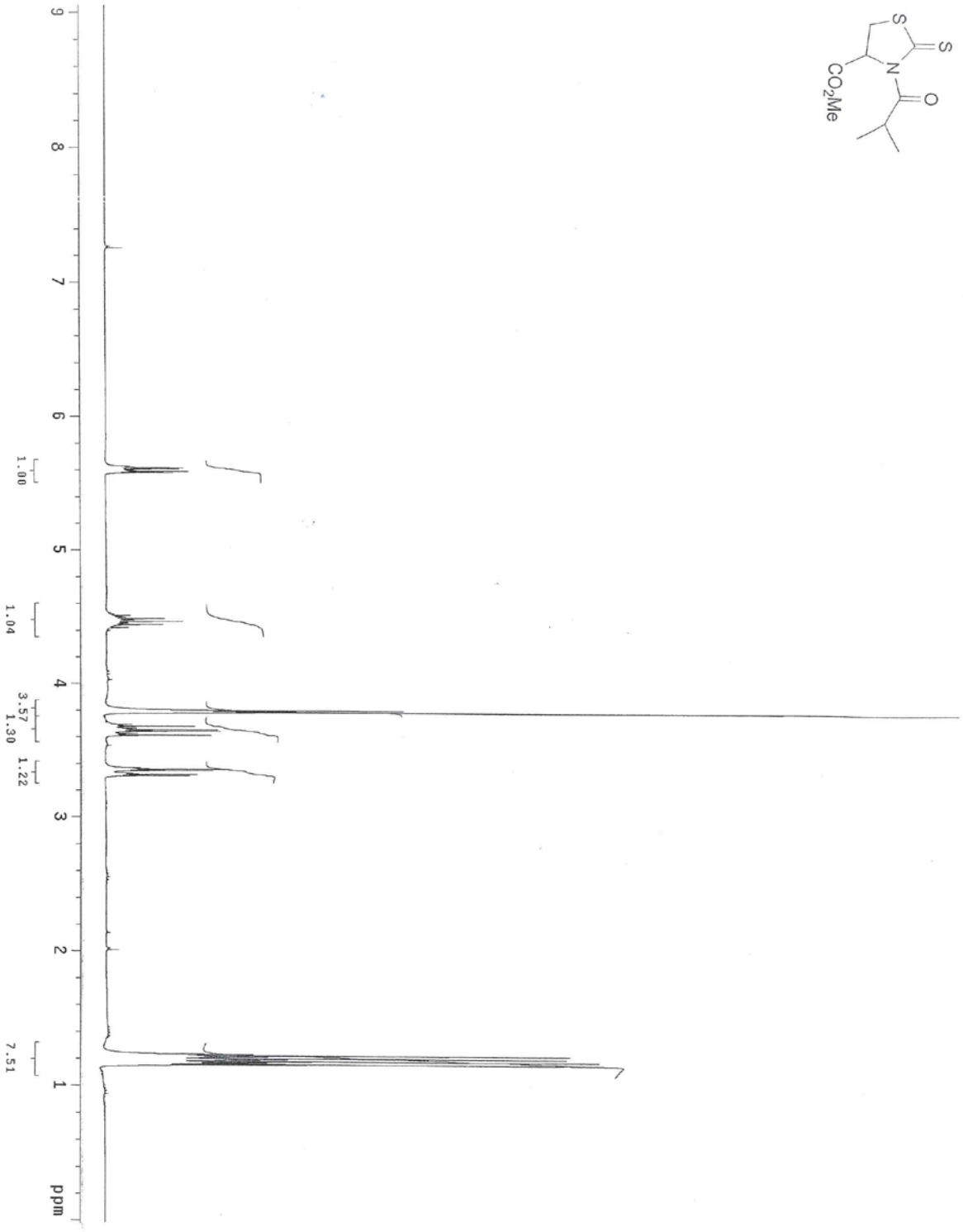
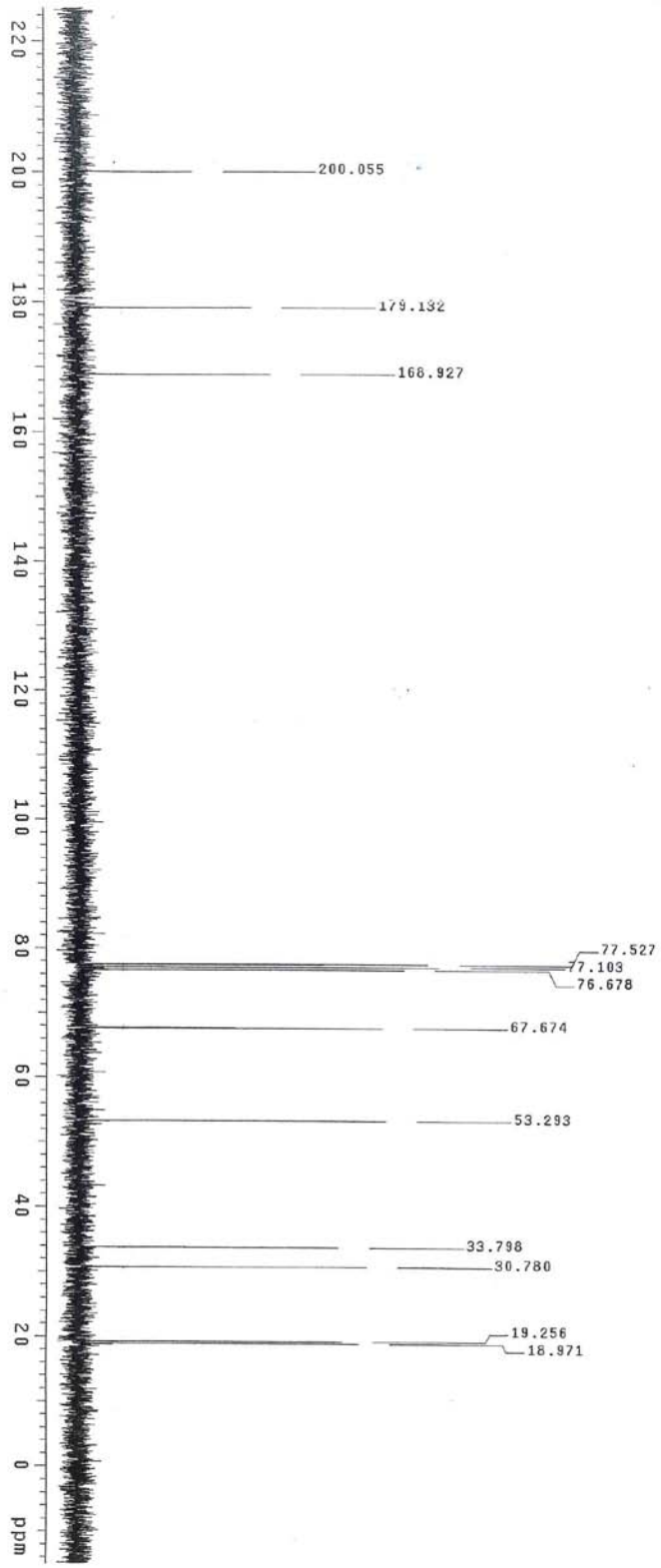
134.062
128.678
128.443
126.809
123.718
77.549
77.124
76.700
68.927
34.634
34.026
19.439
19.212
S
S
N
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm


S
S
N
O
CO2Me
9
8
7
6
5
4
3
2
1
ppm
1.00
1.04
3.57
1.30
1.22
7.51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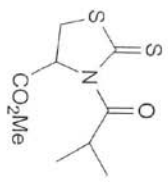
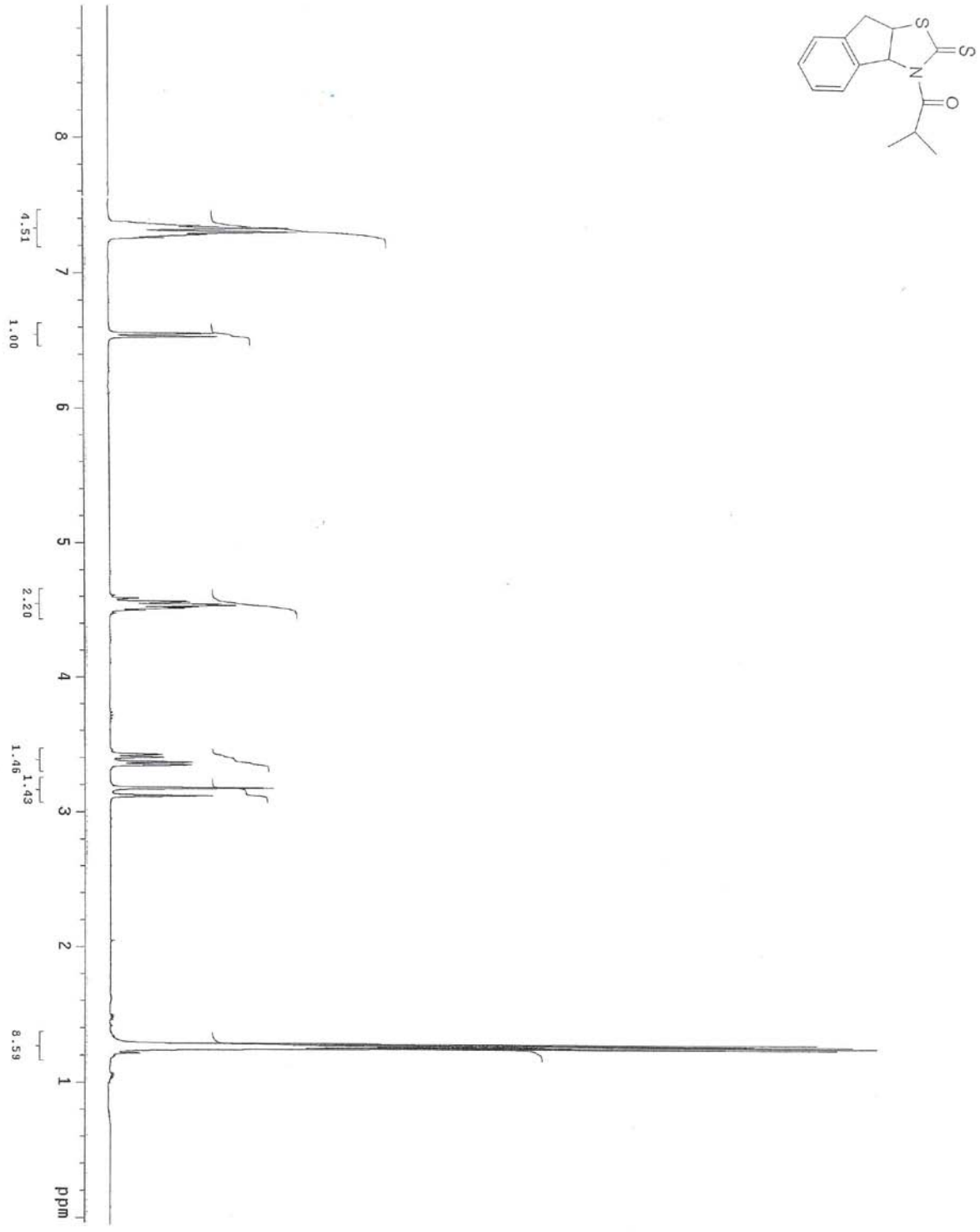
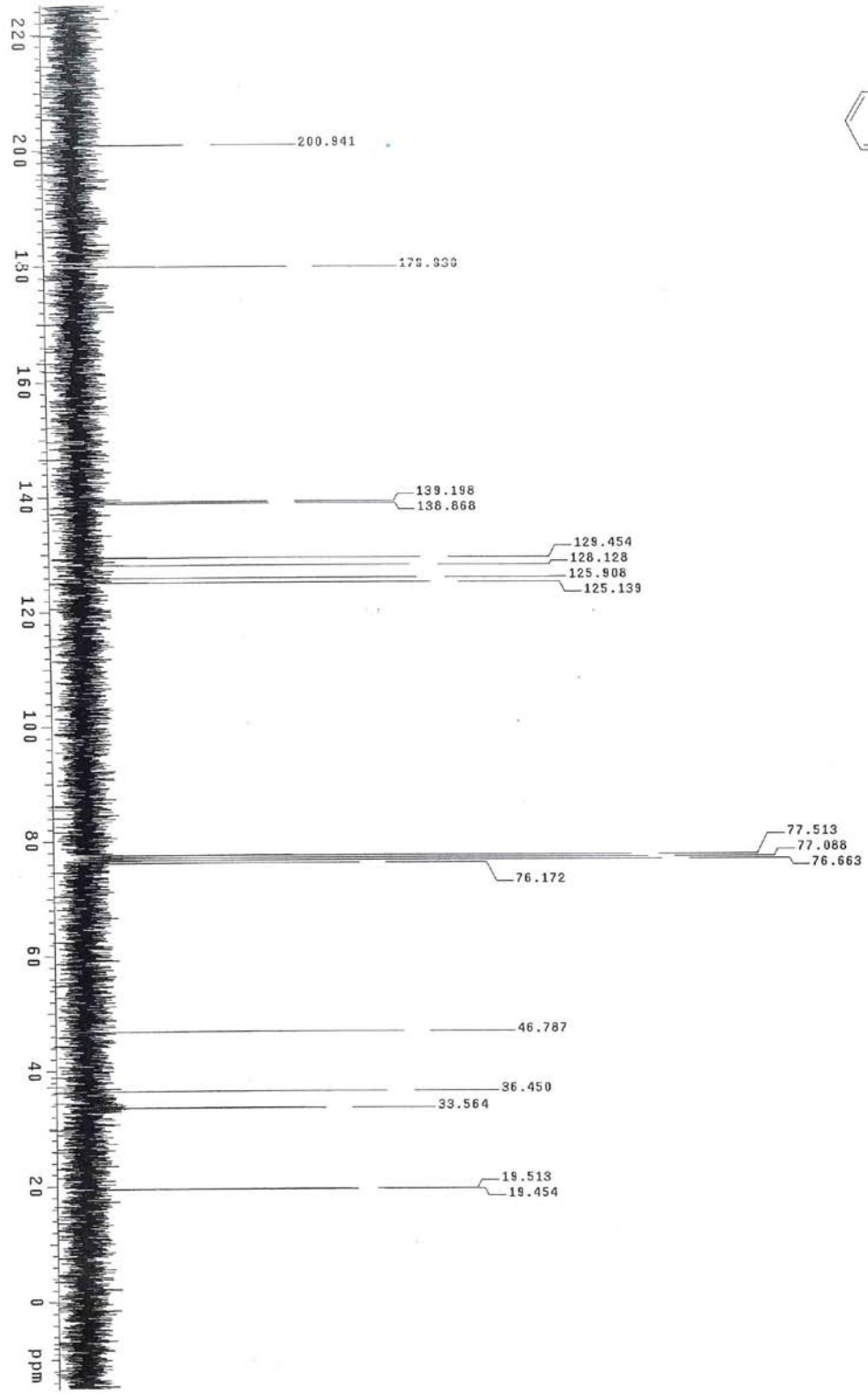
179.132
168.927
77.527
77.103
76.678
67.674
53.293
33.798
30.780
19.256
18.971
220
200
180
160
140
120
100
80
60
40
20
0
ppm


S
S
N
O
CO2Me


S
S
N
O
8
7
6
5
4
3
2
1
ppm
4.51
1.00
2.20
1.46
1.43
8.59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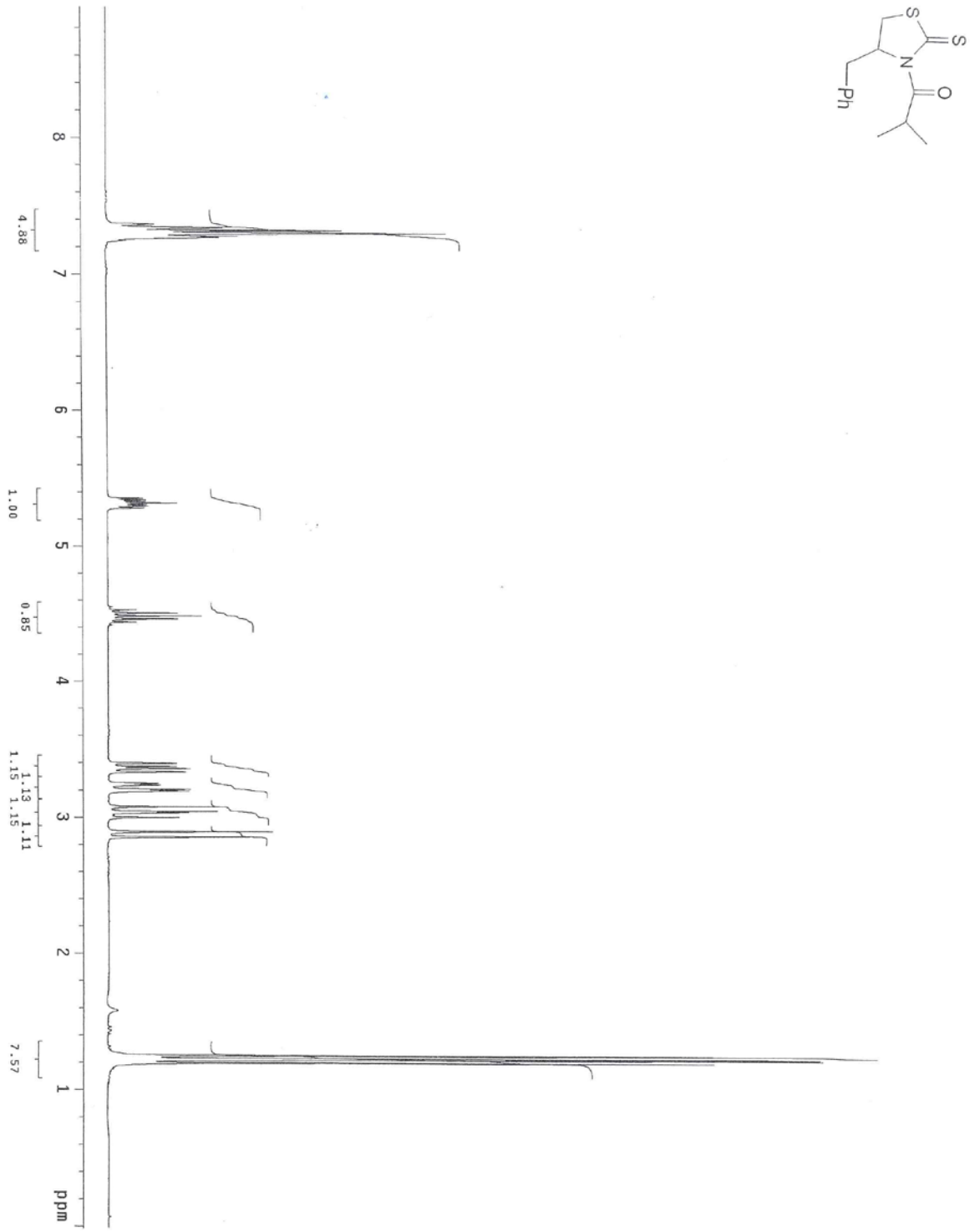
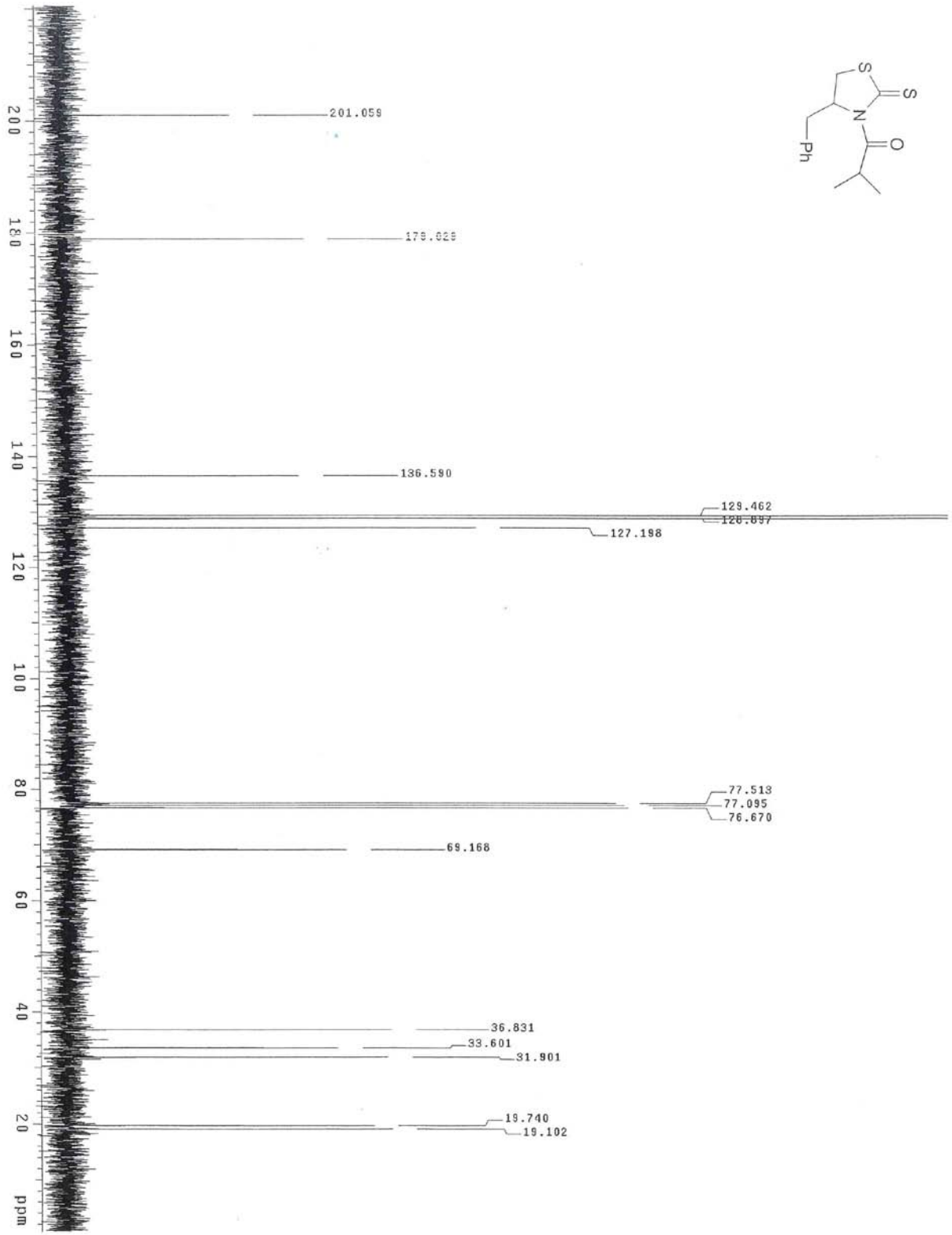
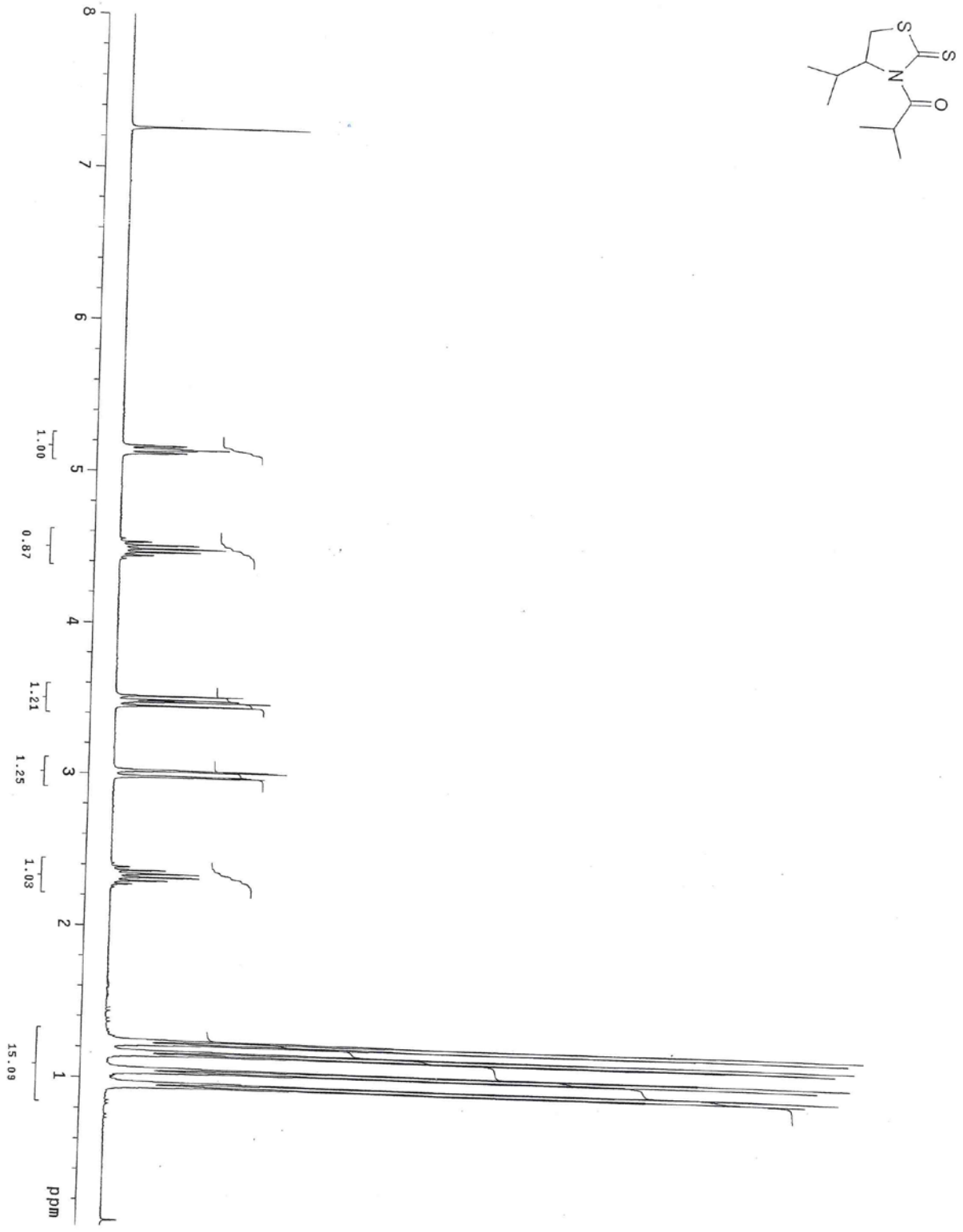
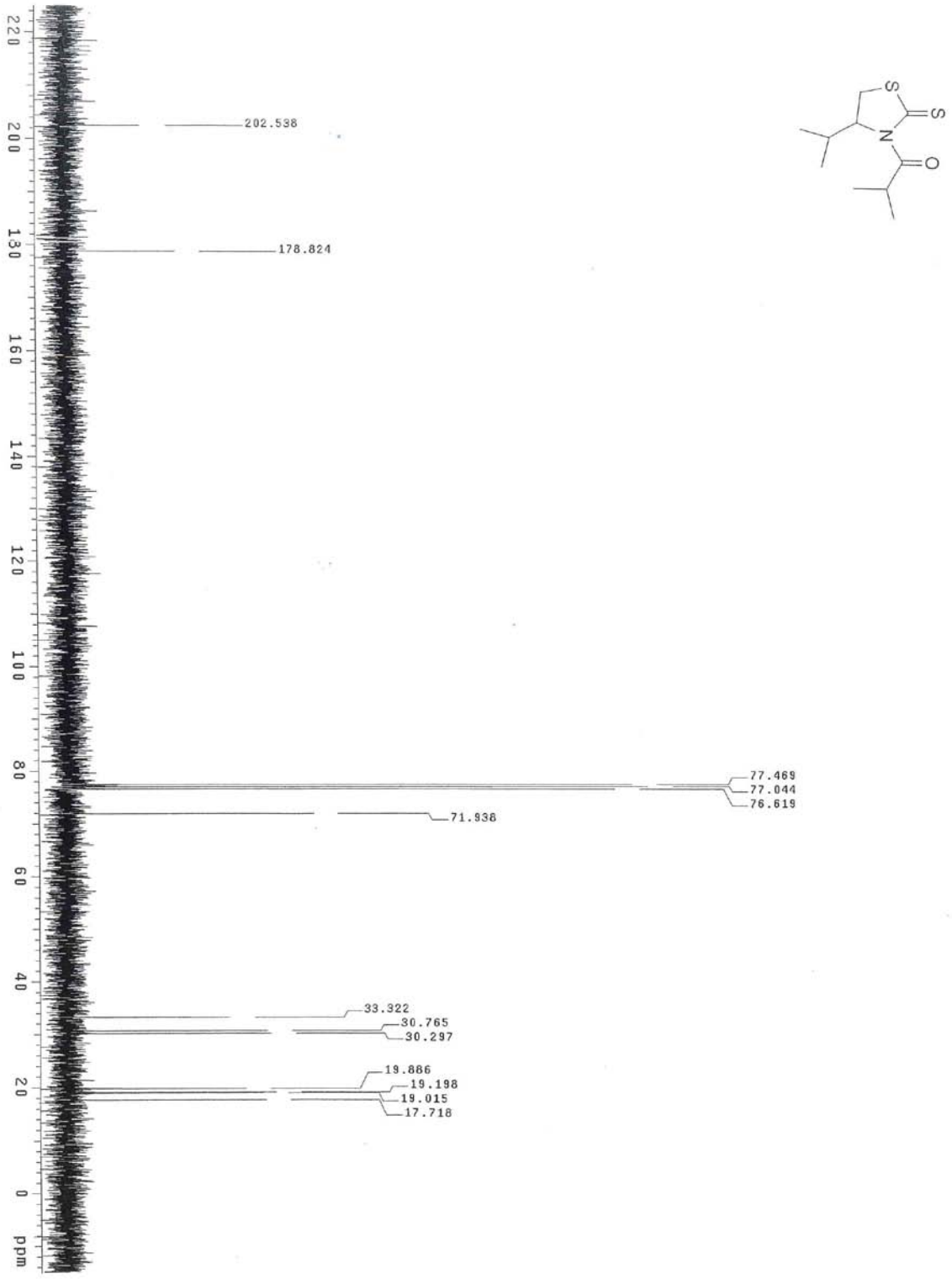
139.198
138.868
129.454
128.128
125.908
125.139
77.513
77.088
76.663
76.172
46.787
36.450
33.564
19.513
19.454
220
200
180
160
140
120
100
80
60
40
20
0
ppm
S
S
N
O


S
S
N
O
Ph
8
7
6
5
4
3
2
1
ppm
4.88
1.00
0.85
1.13
1.15
1.11
1.15
7.57


201.059
179.029
136.590
129.462
128.697
127.198
77.518
77.095
76.670
69.168
36.831
33.601
31.901
19.740
19.102
200
180
160
140
120
100
80
60
40
20
ppm
S
S
N
O
Ph


S
S
N
O
8
7
6
5
4
3
2
1
ppm
1.00
0.87
1.21
1.25
1.03
15.09


202.538
178.824
77.469
77.044
76.619
71.938
33.322
30.765
30.297
19.886
19.198
19.015
17.718
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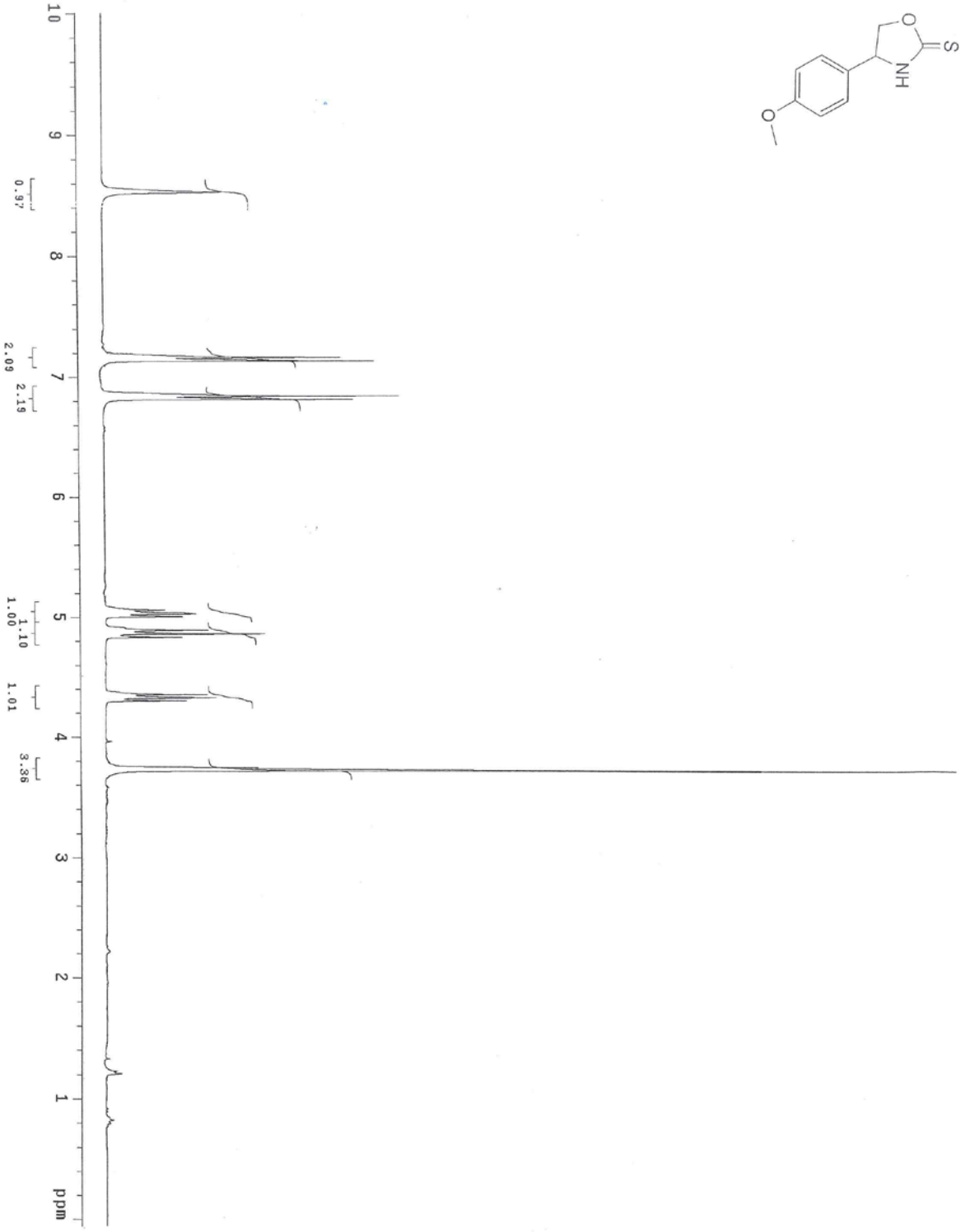
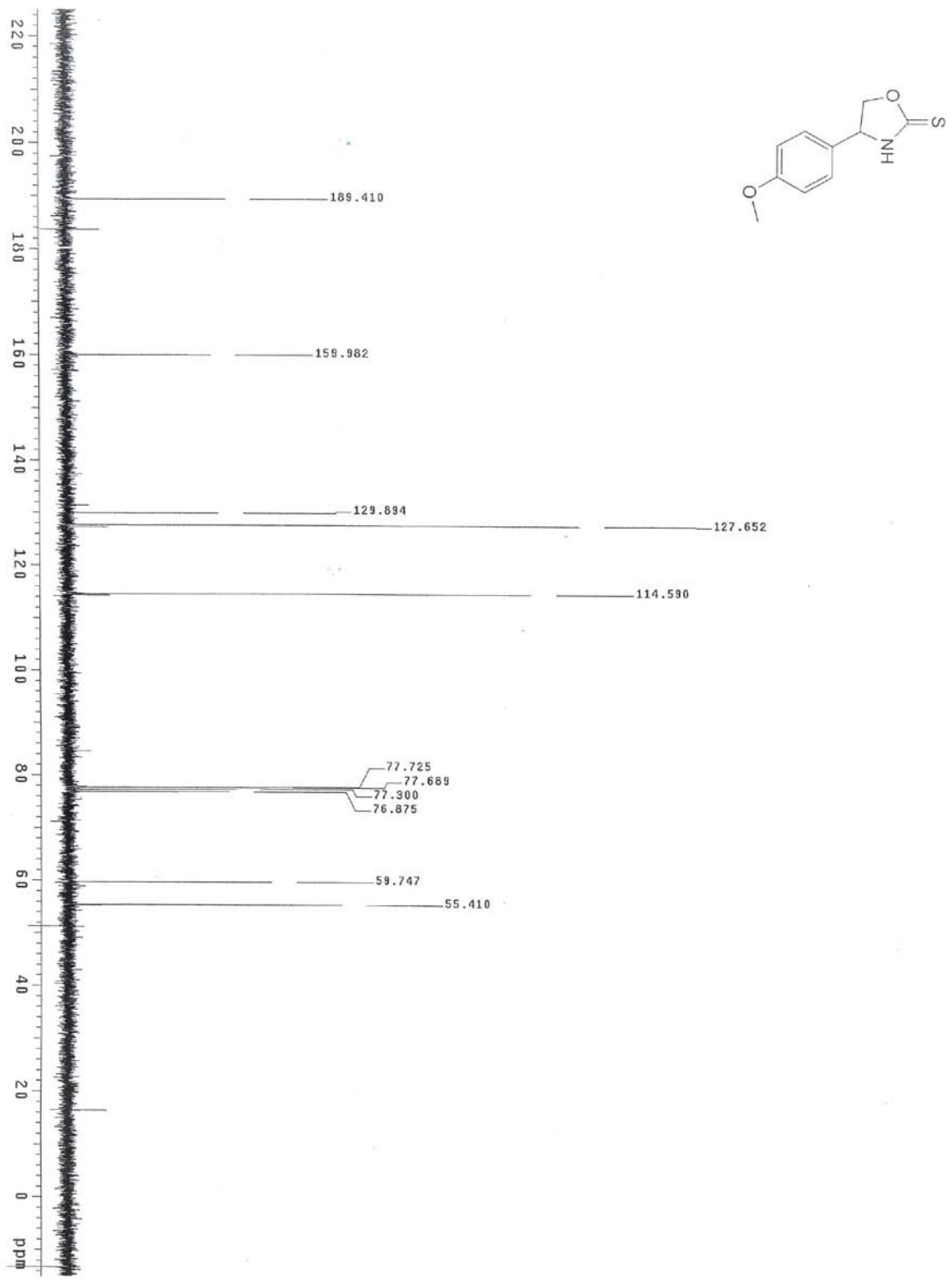
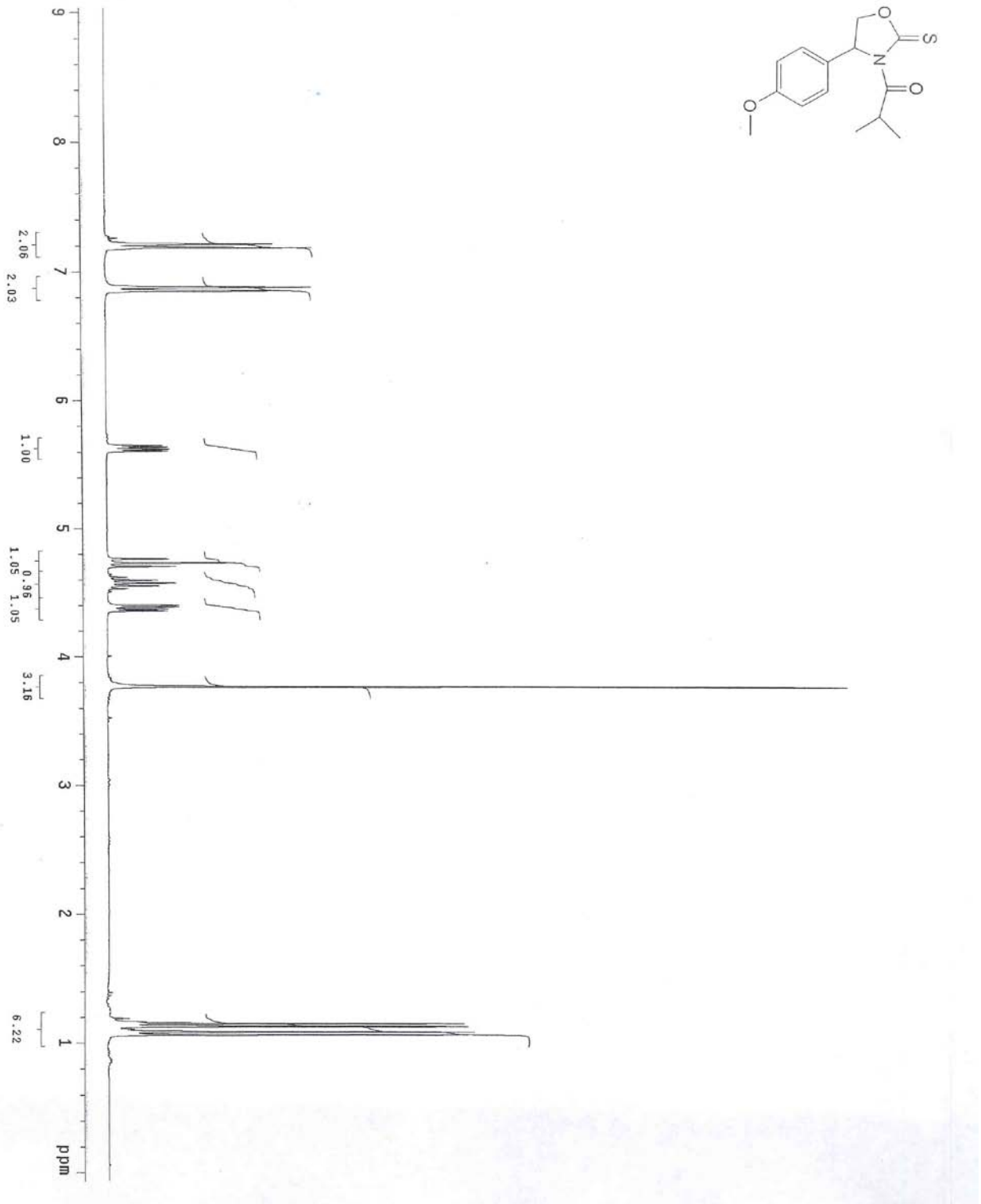
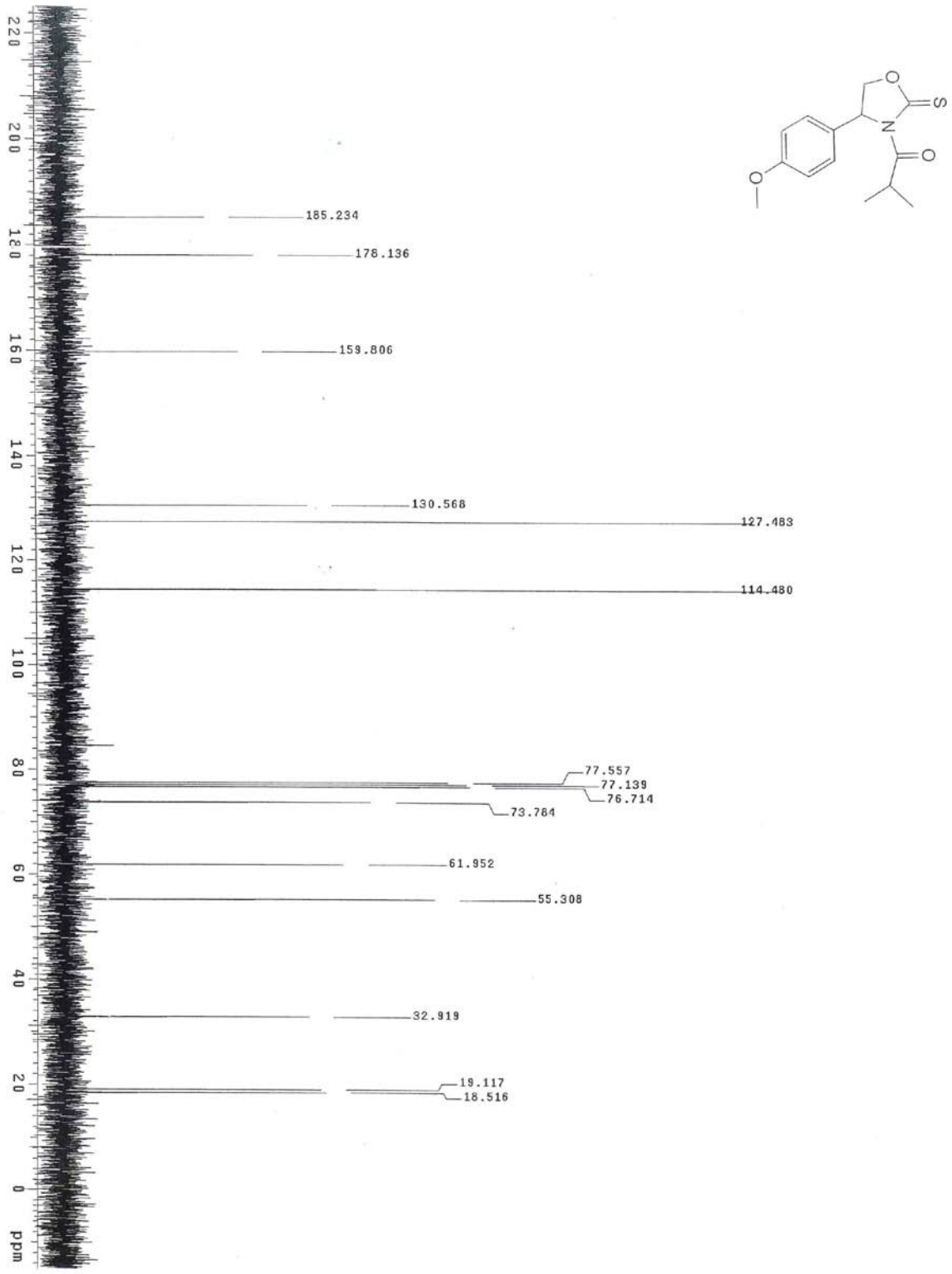
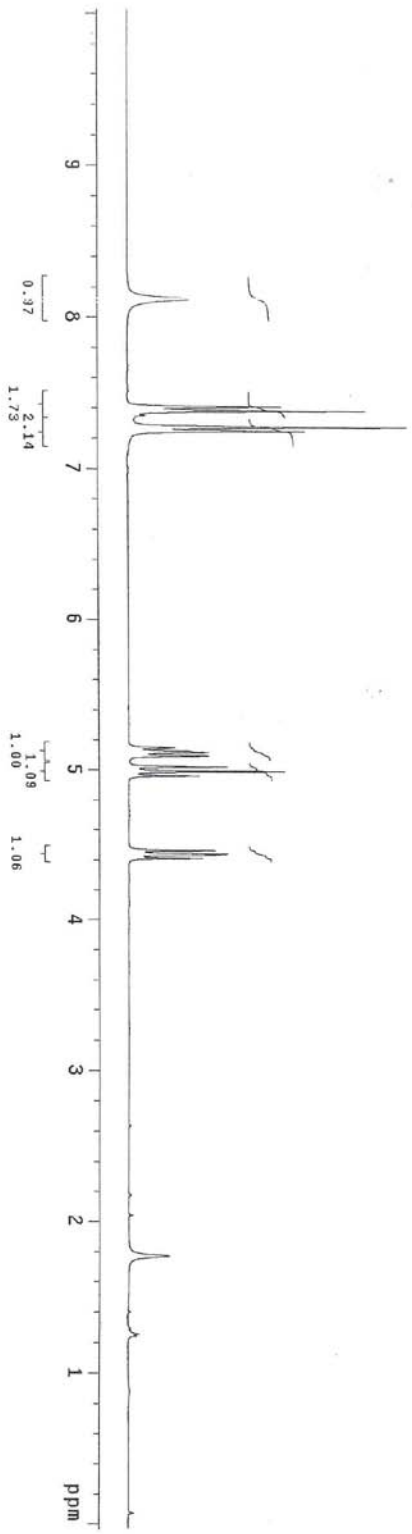
200
180
160
140
120
100
80
60
40
20
0
ppm
S
S
N
O

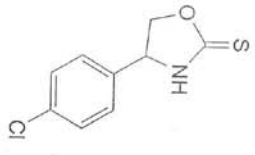

10
9
8
7
6
5
4
3
2
1
ppm
0.97
2.09
2.19
1.00
1.10
1.01
3.36
O
S
NH
O

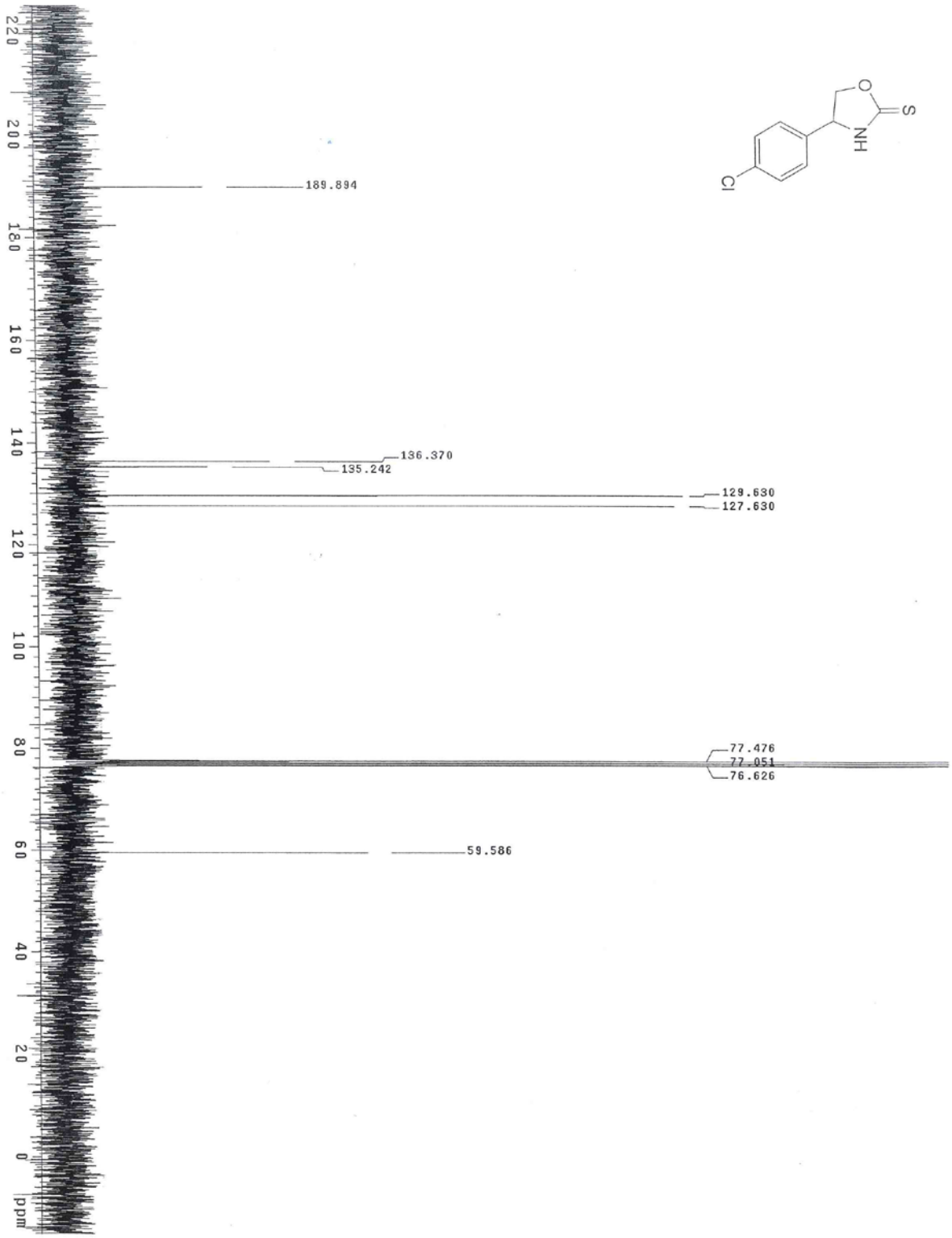

189.410
159.982
129.894
127.652
114.590
77.725
77.689
77.300
76.875
59.747
55.410
220
200
180
160
140
120
100
80
60
40
20
0
ppm
O
S
NH
O

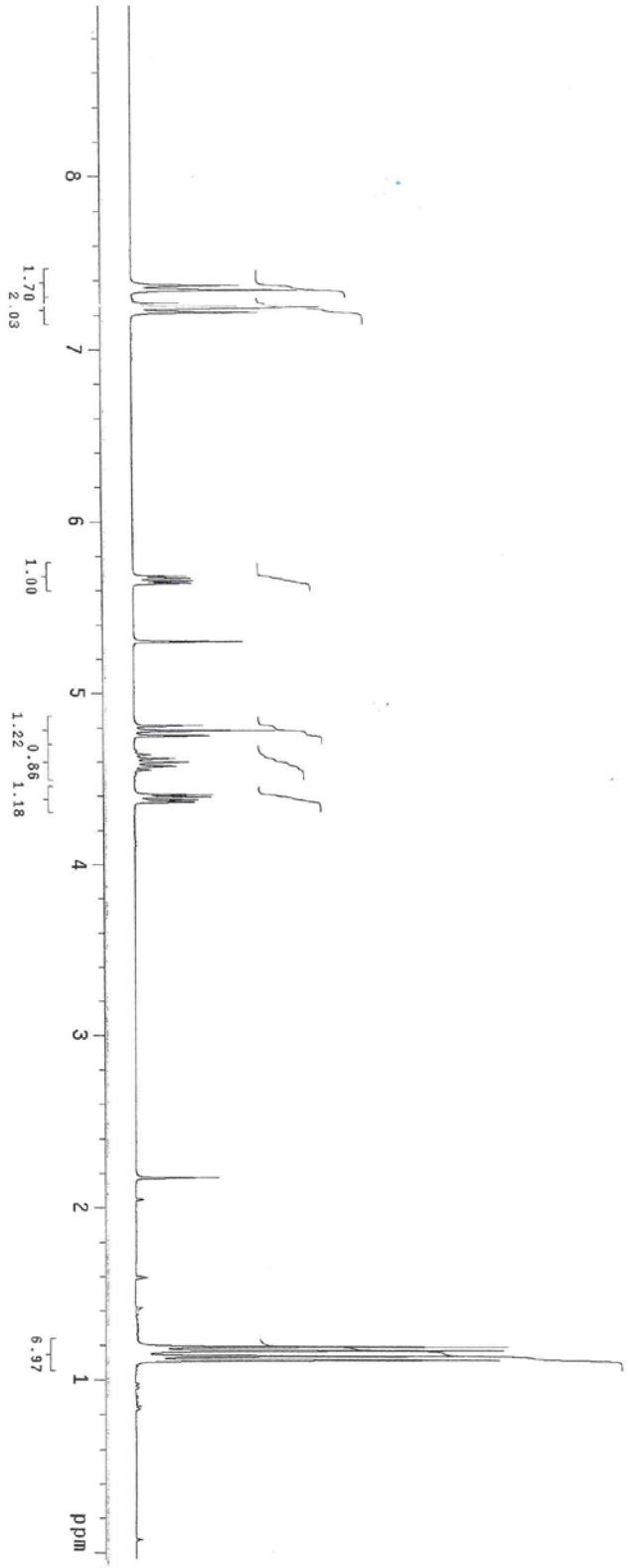

9
8
7
6
5
4
3
2
1
ppm
2.06
2.03
1.00
0.96
1.05
1.05
3.16
6.22
O
S
N
O
O

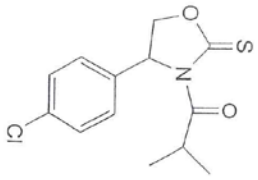

185.234
178.136
159.806
130.568
127.483
114.480
77.557
77.139
76.714
73.784
61.952
55.308
32.919
19.117
18.516
ppm

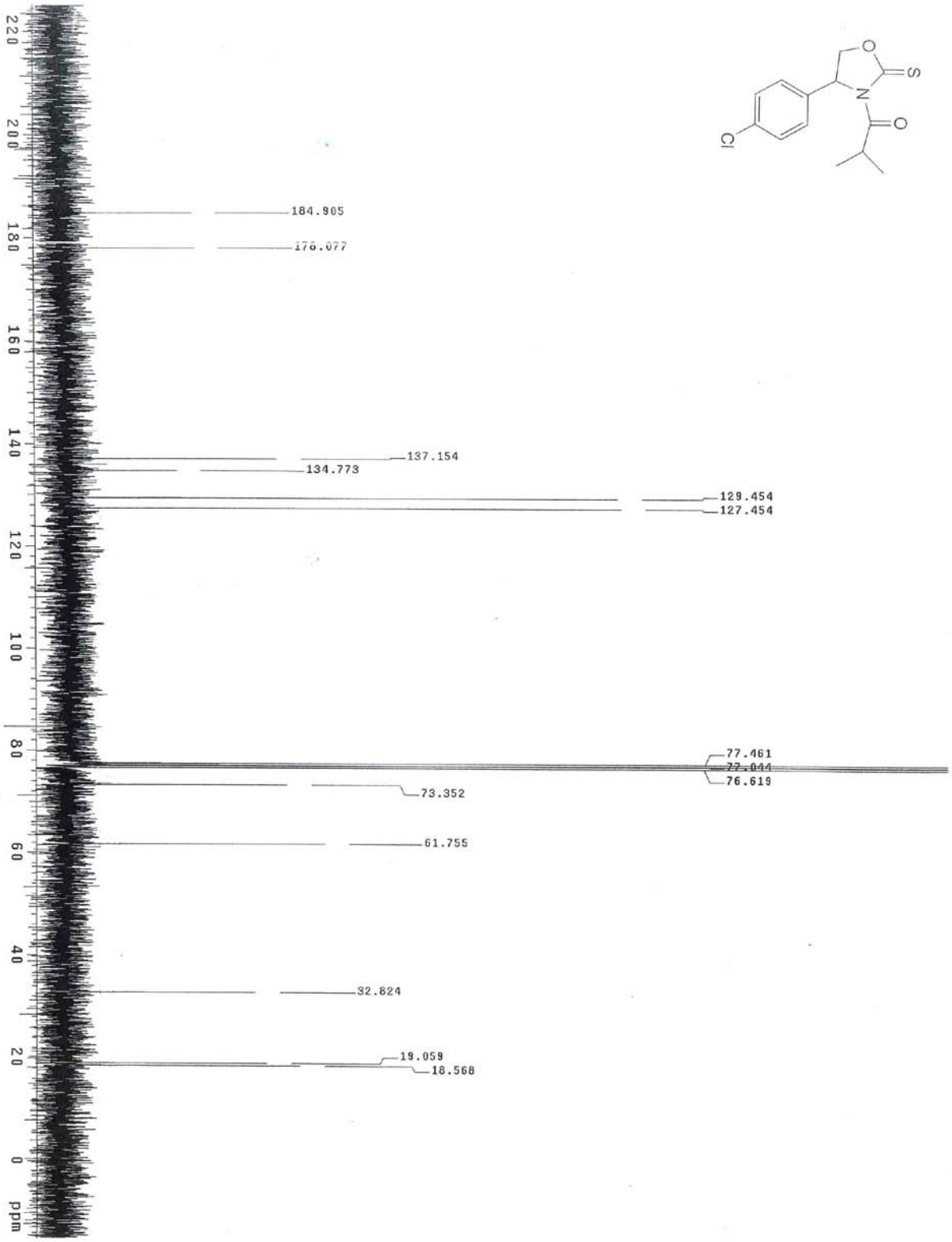

9
8
7
6
5
4
3
2
1
ppm
0.97
2.14
1.73
1.09
1.00
1.06

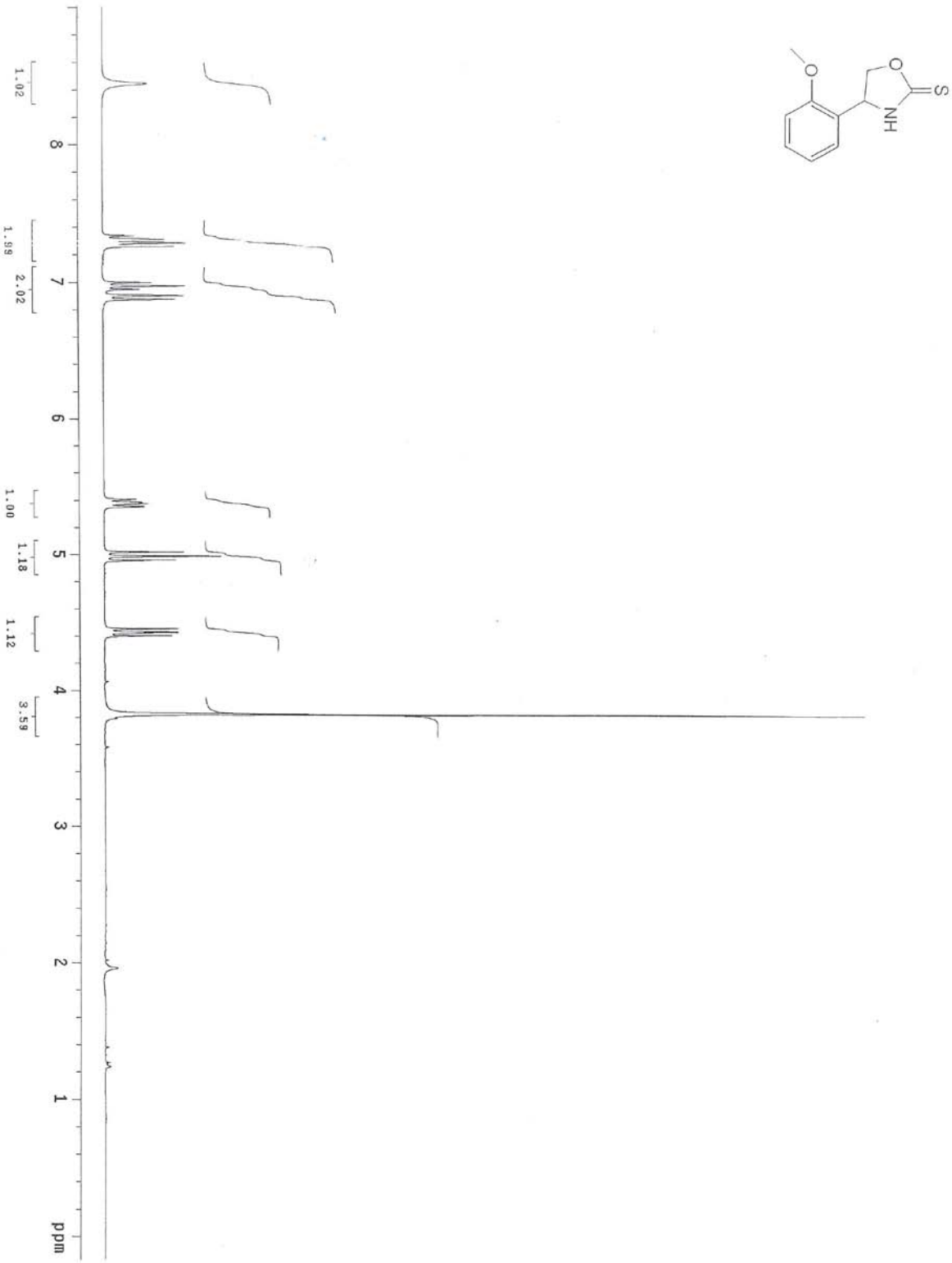

O
S
NH
Cl

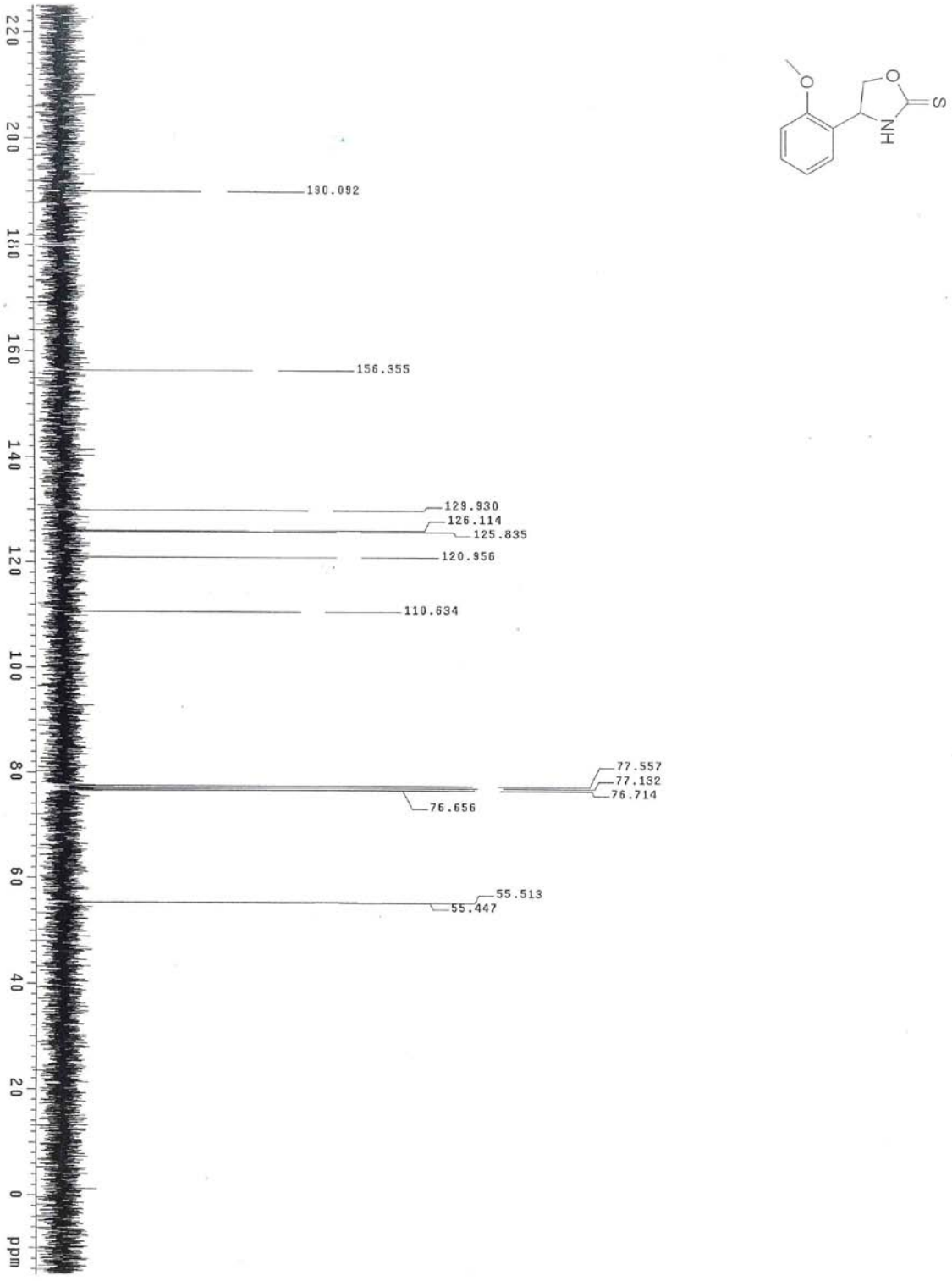

189.894
136.370
135.242
129.630
127.630
77.476
77.051
76.626
59.586
220
200
180
160
140
120
100
80
60
40
20
0
ppm
O
S
NH
Cl

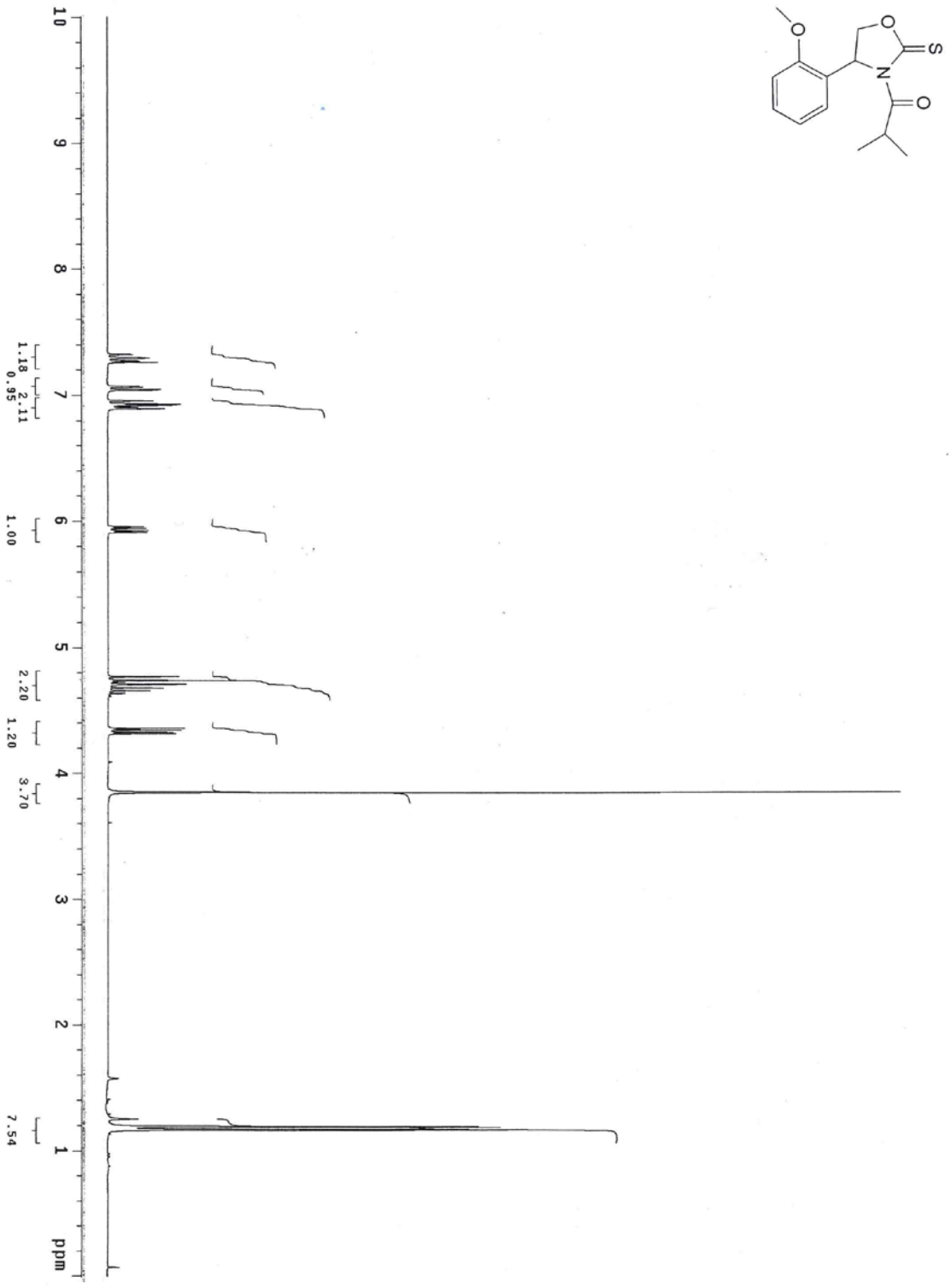

8
7
6
5
4
3
2
1
ppm
1.70
2.03
1.00
0.86
1.22
1.18
6.97

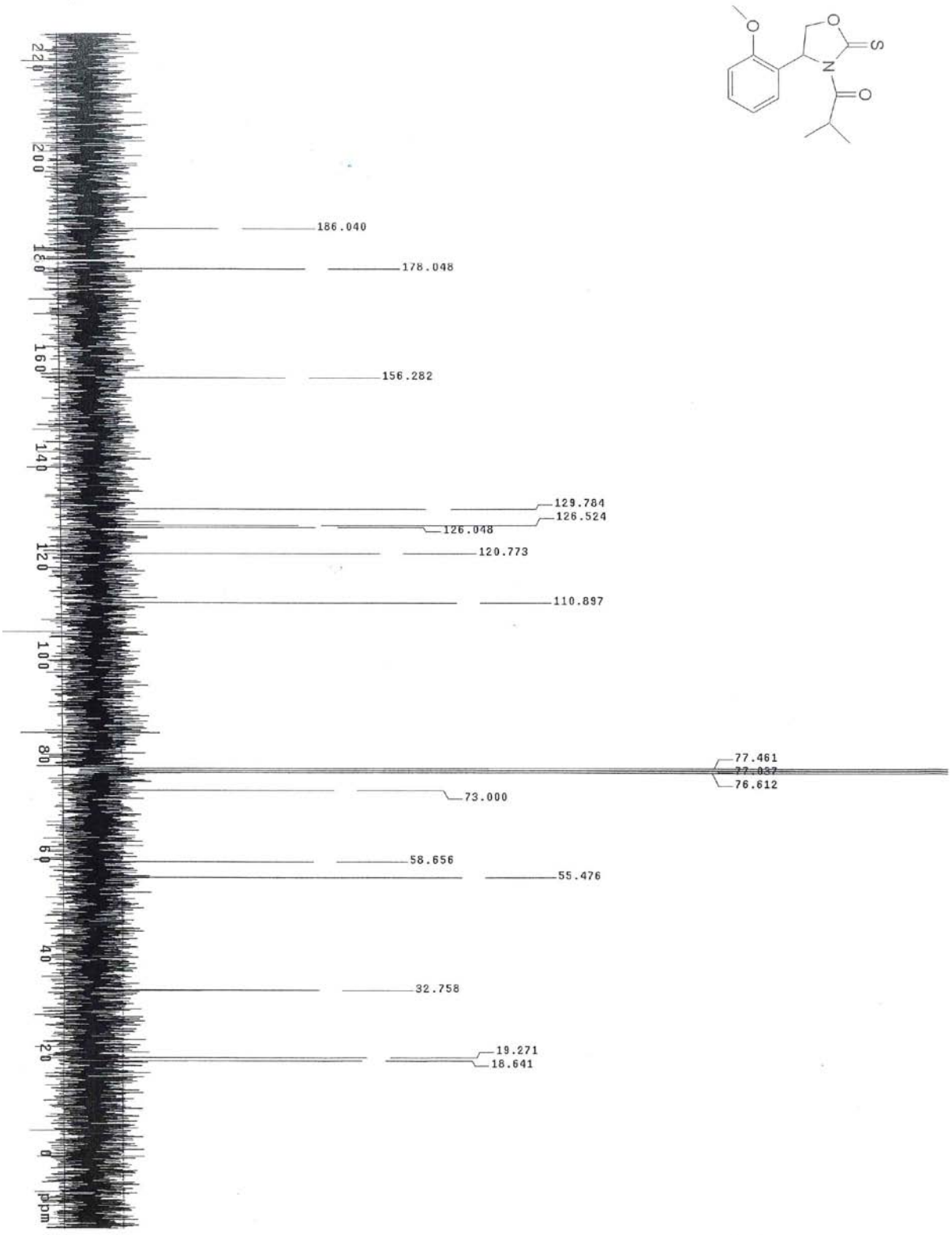

O
S
N
O
Cl

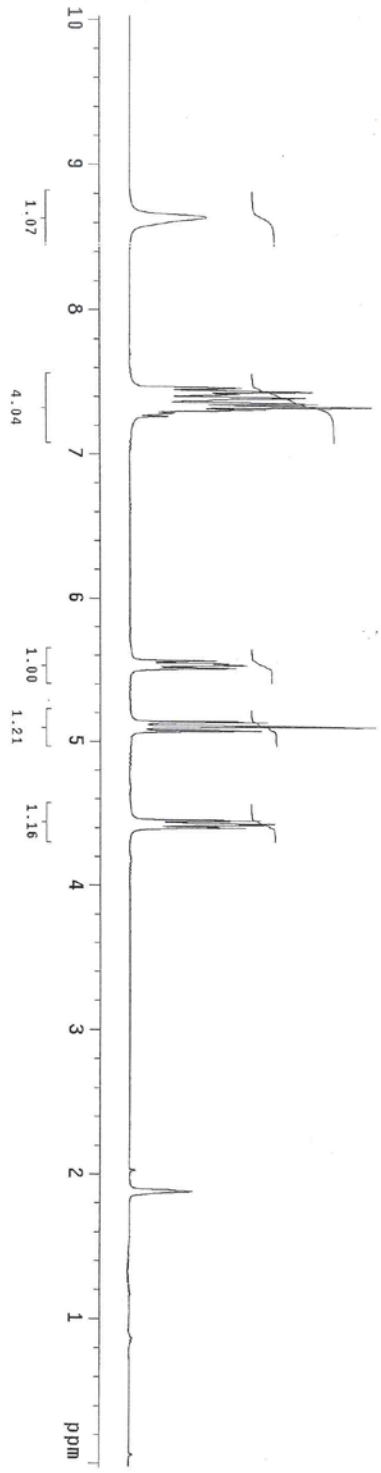

184.905
176.077
137.154
134.773
129.454
127.454
77.461
77.044
76.619
73.352
61.755
32.824
19.059
18.568
ppm

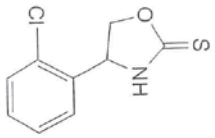

O
O
S
NH
1.02
1.99
2.02
1.00
1.18
1.12
3.59
8
7
6
5
4
3
2
1
ppm

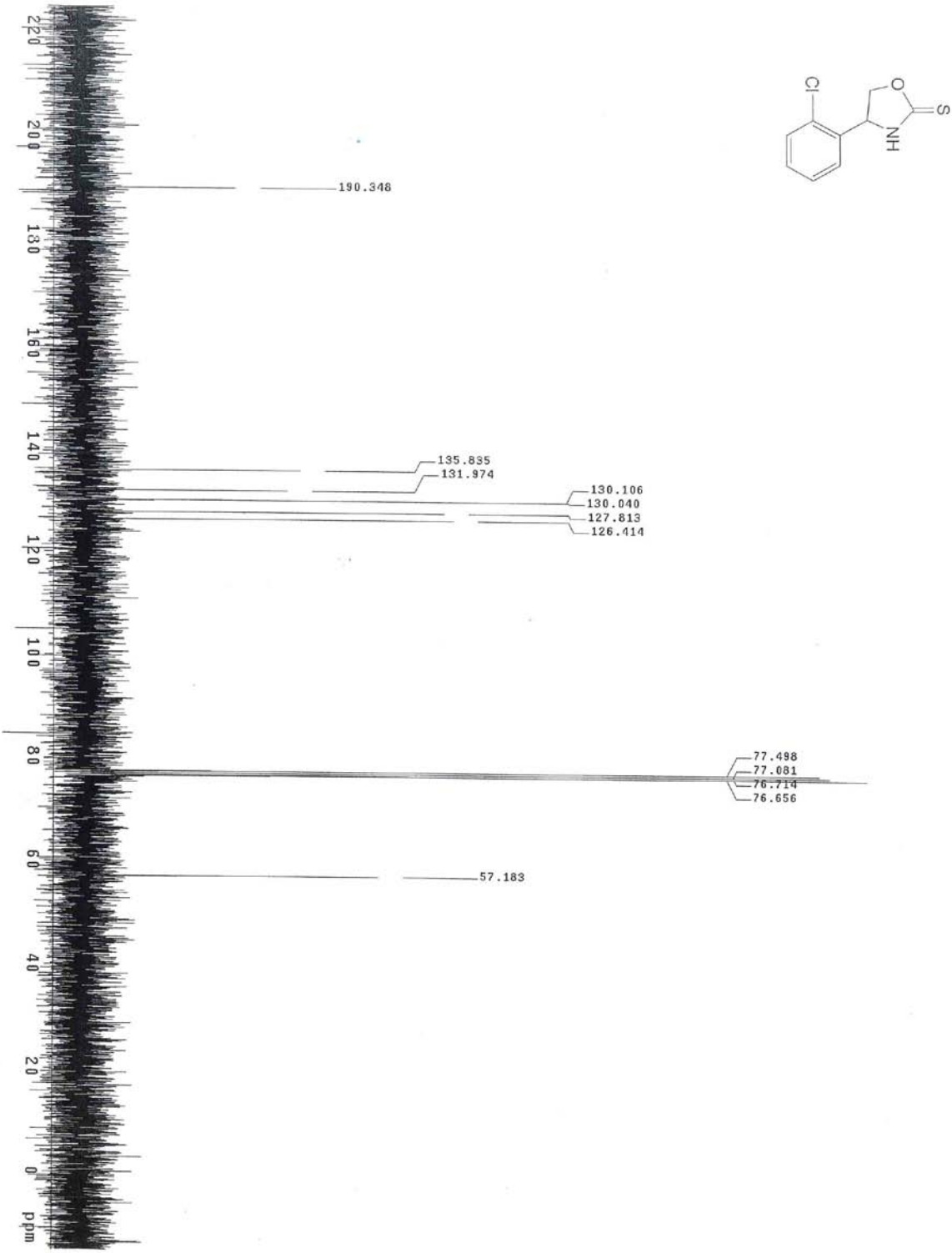

190.092
156.355
129.930
126.114
125.835
120.956
110.634
77.557
77.132
76.714
76.656
55.513
55.447
ppm

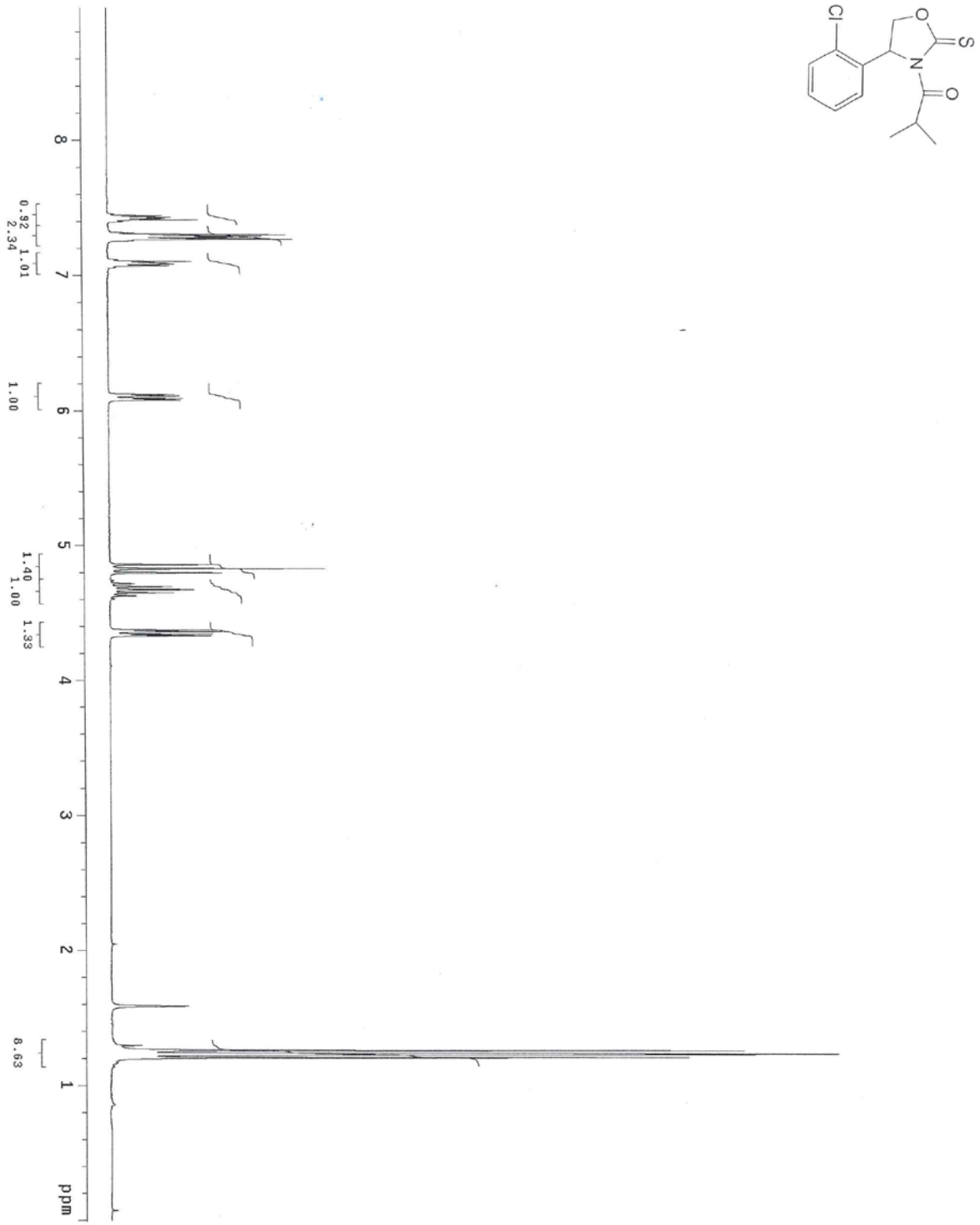

O
O
S
N
O
10
9
8
7
6
5
4
3
2
1
ppm
1.18
2.11
0.95
1.00
2.20
1.20
3.70
7.54

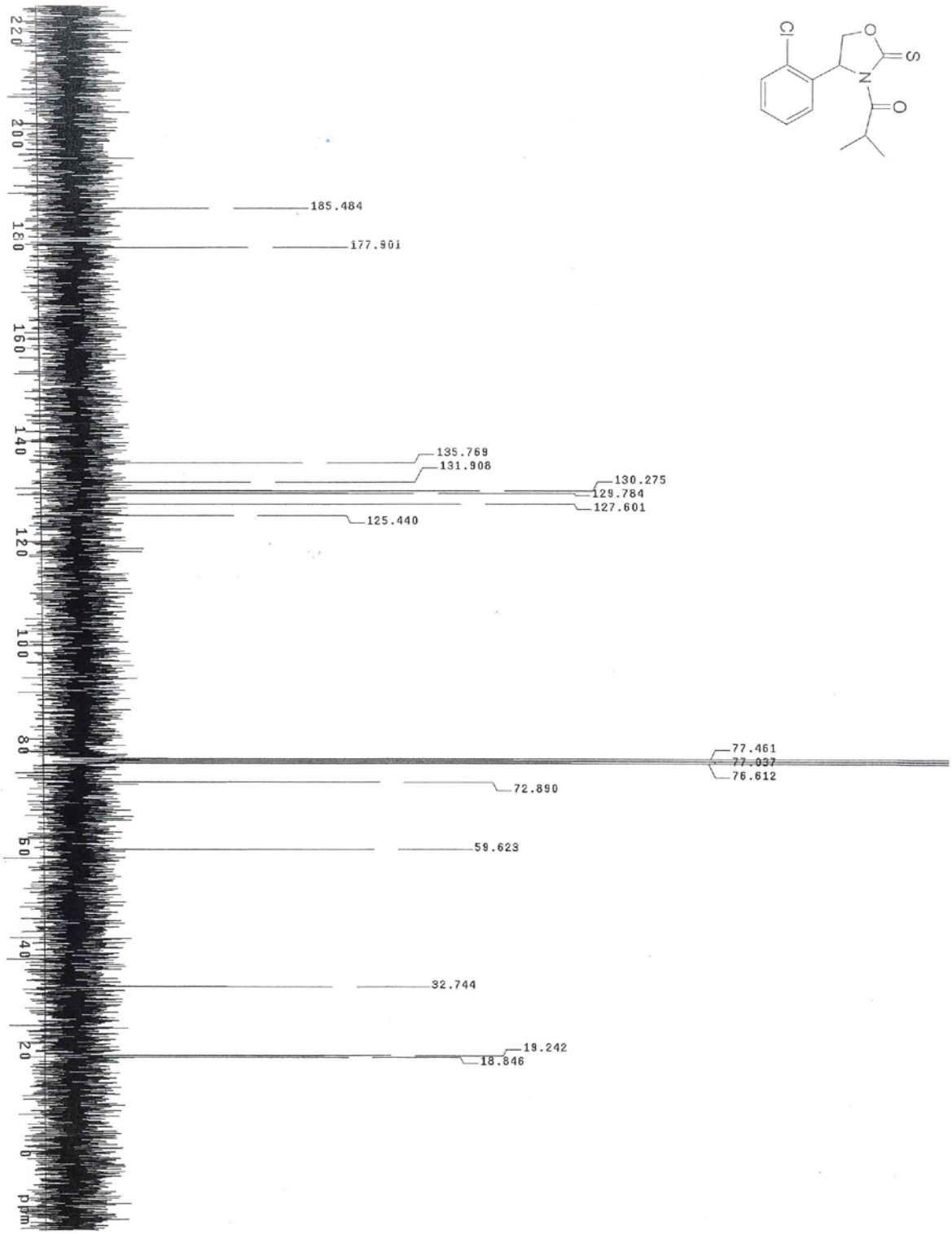

O
O
S
N
O
186.040
178.048
156.282
129.784
126.524
126.048
120.773
110.897
77.461
77.037
76.612
73.000
58.656
55.476
32.758
19.271
18.641
ppm

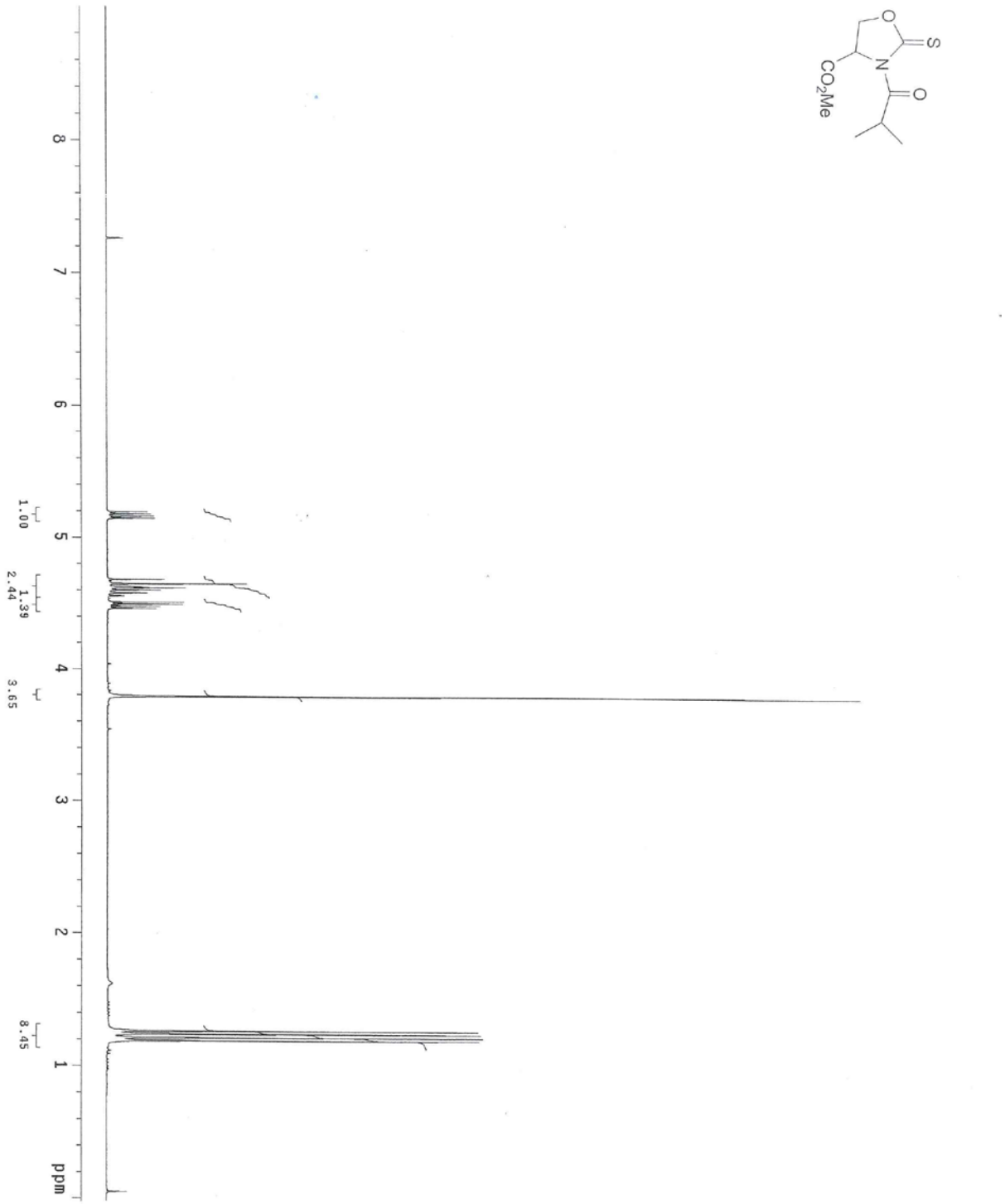

10
9
8
7
6
5
4
3
2
1
ppm
1.07
4.04
1.00
1.21
1.16

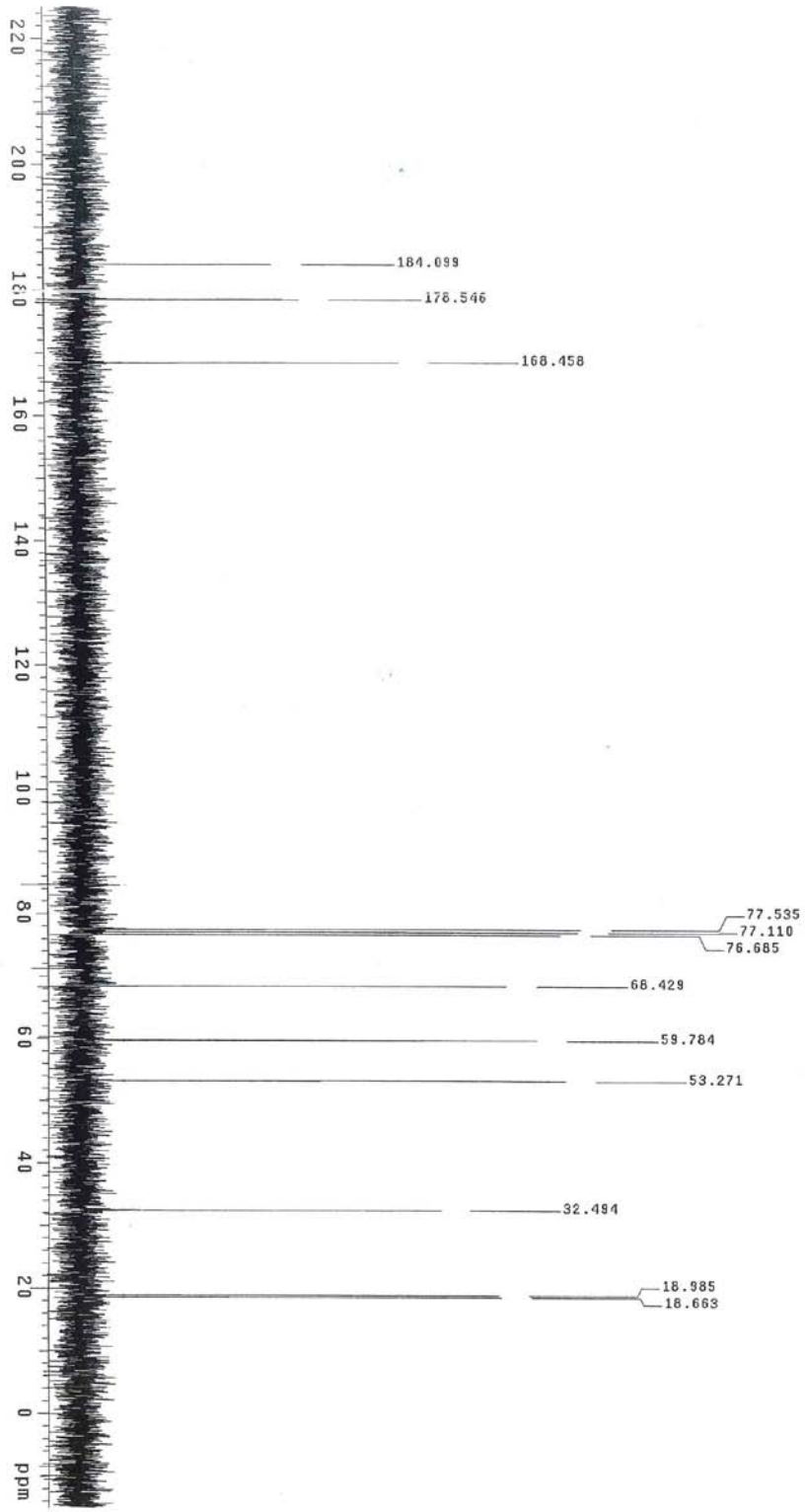

Cl
O
S
NH

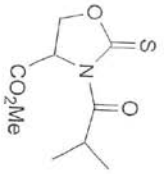

190.348
135.835
131.974
130.106
130.040
127.813
126.414
77.498
77.081
76.714
76.656
57.183
Cl
O
S
NH
ppm


Cl
O
S
N
O
8
7
6
5
4
3
2
1
ppm
0.92
1.01
2.34
1.00
1.40
1.00
1.33
8.63


185.484
177.901
135.769
131.908
130.275
129.784
127.601
125.440
77.461
77.037
76.612
72.890
59.623
32.744
19.242
18.846
ppm


S
O
N
O
CO2Me
8
7
6
5
4
3
2
1
ppm
1.00
2.44
1.39
3.65
8.45


184.099
178.546
168.458
77.535
77.110
76.685
68.429
59.784
53.271
32.494
18.985
18.663
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
S
N
O
CO2Me