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Part I Development of Nucleophilic Acylation Catalysts Part II Chiral Brønsted Acid Catalyzed Enantioselective Alcoholysis

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Part I Development of Nucleophilic Acylation Catalysts
Part II Chiral Brønsted Acid Catalyzed Enantioselective Alcoholysis

By

Guojian Lu

A dissertation presented to the
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requirements for the degree
of Doctor of Philosophy

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ABSTRACT OF THE DISSERTATION

Part I Development of Nucleophilic Acylation Catalysts

Part II Chiral Brønsted Acid Catalyzed Enantioselective Alcoholysis

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Chiral bicyclic amidines and isothioureas developed in our group have been showed as a new type of nucleophilic acyl transfer catalysts. Based on the previous achievement in our group, several aza-analogues and a 5,7-menbered ring bicyclic analogue of THTP were prepared. Its synthesis proved to be more laborious than that of the THTP analogue derivative, and the enantioselectivity was substantially lower.

Based on the previous discovery in our group that 1,2,4-triazole anion, as an active acyl transfer catalyst, can promote aminolysis and transesterification of moderately activated or even unactivated esters, a systematic study of pyrazole derivatives in this

transformation was demonstrated. Two types of derivatives with equal or better activity than pyrazole itself were identified.

Based on our achievement in the Dynamic Kinetic Resolution (DKR) of azlactones via acyl transfer catalysis, a new method of DKR of azlactones catalyzed by chiral Brønsted acid was developed, high enantioselectivity (85-92% ee) were obtained for the aryl-substituted azlactones. It was the first time that chiral Brønsted acid catalysis was applied to the enantioselective acylation reaction. The application of this new method was also applied to the kinetic resolution of oxazinones, modest enantioselectivity was obtained ($s \leq 9$).

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ABBREVIATIONS AND SYMBOLS USED IN THE DISSERTATION

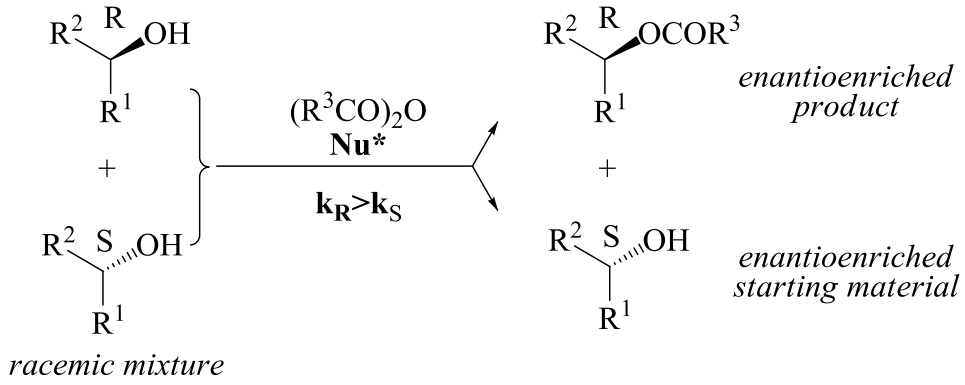
ABCs	Amidine-based catalysts
BINOL	1,1´-bi-2-naphthol
BTM	benzotetramisole
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-Dimethylaminopyridine
DHIP	2,3-dihydroimidazo[1,2-α]pyridine
DKR	dynamic kinetic resolution
ee	enantiomeric excess
HBTM	homobenzotetramisole
HTM	homotetramisole
KR	kinetic resolution
PPY	4-pyrrodinopyridine
TADDOL	α,α,α´,α´-Tetraaryl-1,3-dioxolan-4,5-dimethanol
TBD	Triazabicyclodecene
TFA	Trifluoroacetic acid
THTP	2,3,6,7-tetrahydro-5H-thiazolo[3,2-a]pyrimidine

Chapter 1 Synthesis and exploration of THTP analogues for acylation of alcohol

1.1 Nucleophilic acyl transfer catalysis

Acylation is a fundamental organic reaction which an acyl group is added to alcohols, amines, or other nucleophiles. Catalytic enantioselective acylation has attracted a great deal of interest from organic chemists in recent years[1]. Kinetic resolution[2] of secondary alcohols is one of the most important transformations in this category. (Figure 1.1)

Figure 1.1 KR of alcohols



Its practical significance lies in the fact that many enantiopure alcohols are important pharmaceutical drugs or intermediates. Most of the enantioselective acylation catalysts described to date[3] belong to the class of nucleophilic, or Lewis base catalysts[4]. Some of the best catalysts developed by other groups are shown in Figure 1.2.[5] They are believed to operate via the acyl transfer mechanism outlined in general form in Figure 1.3. Most of the catalysts illustrated above and many of their analogues incorporate in their structures several well-known achiral acyl transfer catalysts, such as the DMAP (**1.6)**[6], PPY (**1.7)**[7], *N*-methylimidazole (NMI) (**1.8)**[8], tributylphosphine (**1.9)**[9] and *N*-Heterocyclic carbene (NHC) (**1.10).**[10] (Figure 1.4)

Figure 1.2 Chiral nucleophilic catalysts developed by other groups

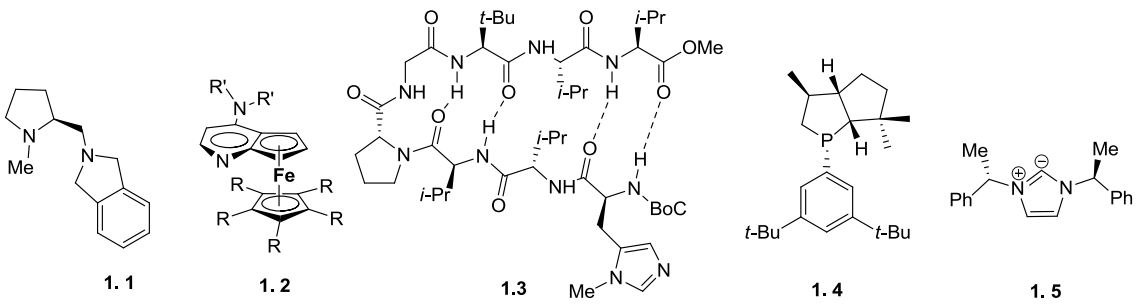


Figure 1.3 Acyl transfer catalysis

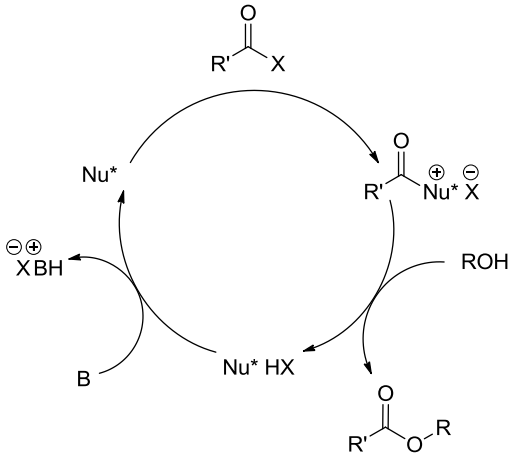
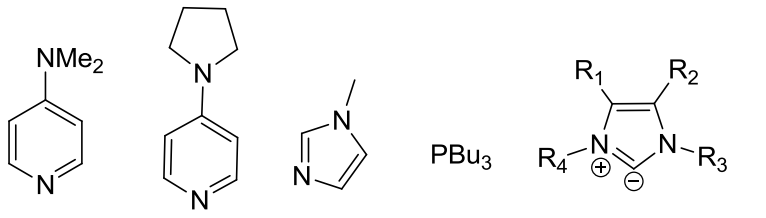


Figure 1.4 Achiral nucleophilic catalysts in acyl transfer reaction

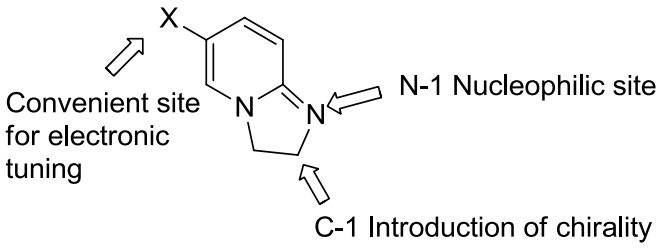


Chiral DMAP- and imidazole-based catalyst designs are the most popular because of their significant catalytic activities. However, due to the planar structures of DMAP and imidazole, the introduction of chiral environment to those core structures is a challenging problem.

1.2 The amidine-based catalysts developed in the Birman group

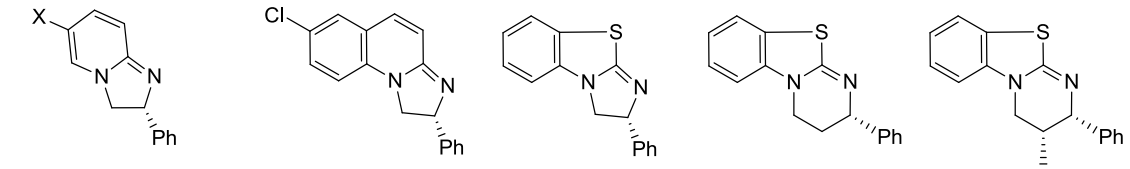
In 2003, our group developed a conceptually new approach to designing enantioselective acyl transfer catalysts[11]. Instead of inventing new ways to incorporate chirality into the structures of known acylation catalysts, Birman and coworkers decided to look for a new type of achiral catalyst, which would be easy to make chiral. A known heterocyclic compound, DHIP looked especially promising (Figure 1.5).

Figure 1.5 Structure of DHIP



In contrast to DMAP or imidazole, the carbon atom next to the nucleophilic nitrogen (N1) is tetrahedral, and therefore easily transformed into a chiral center. The electronic properties of this system can be tuned by introducing an electron-withdrawing or -donating group X on the pyridine ring at C6.

Figure 1.6 Several generations of amidine-based catalyst developed in our group



After demonstrating that the parent compound is catalytically active, our group went on to develop several generations of chiral catalysts illustrated in Figure 1.6. As can be seen from their structures, both the aromatic part and the imidazoline ring have

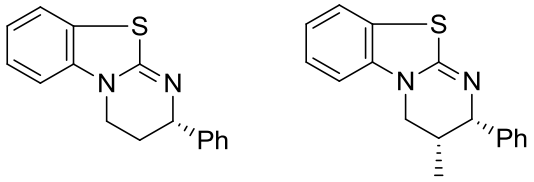
undergone modifications. The only part of the catalyst design that has remained constant is the amidine moiety itself, which is why these catalysts are now known as Amidine-based catalysts, or ABCs.

ABCs have been successfully applied to many enantioselective reactions both by our group and others. These include: KR of secondary alcohols[12a, b, c, d] and desymmetrization of diols via O-acylation;[12e] KR of lactams via *N*-acylation;[12f, g] conventional and Dynamic KR of several types of acyl donors via alcoholysis,[12h, i, j] Steglich rearrangement (C-acylation);[12k, l] [2+2] and [2+4] cycloadditions of ketenes,[12m, n, o] and epoxide opening.[12p]

1.3 Objectives of this study

During the studies outlined above, it became apparent that each structural subtype of ABCs displays its own unique character and reaction scope. Therefore, it was of great interest to explore new variations of the core structure. With this in mind, we decided to focus on modifying THTP, an active achiral catalyst, which ultimately served as the core of such catalysts as HBTM and HBTM-2. (Figure 1.7) Two types modifications have been undertaken, as discussed below.

Figure 1.7 Structure of HBTM and HBTM-2

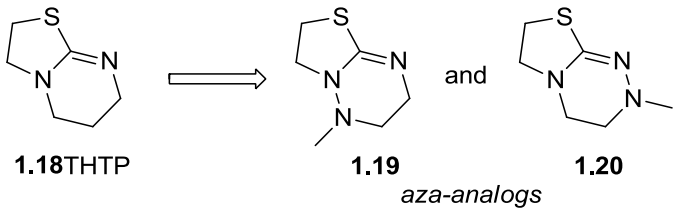


(*S*)-HBTM **1.16** (*S*)-HBTM-2 **1.17**

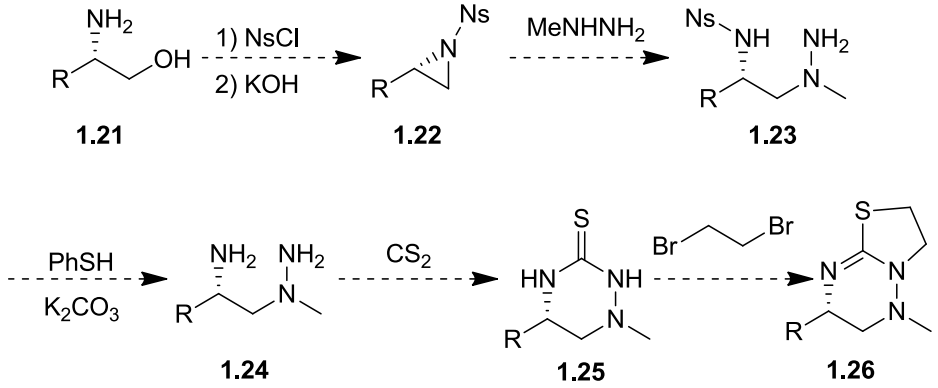
Aza-analogues of THTP. Specifically, we wanted to explore the effects of replacing one of the carbon atoms in the 6-membered ring with a tertiary amine. Our motivation was twofold: first, we sought to examine the effect of this substitution on the catalytic

activity (due to the so-called alpha-effect)[13](Figure 1.8) and second, develop a synthetic route to chiral analogues of aza-THTP starting with commercially available chiral 1,2-aminoalcohols. (Scheme 1.1)

Figure 1.8 Design of aza-analogues derivatives



Scheme 1.1 Synthetic route to the chiral analogues of aza-THTP



Ring-expanded analogues of THTP. Earlier studies in our group had established that the catalytic activities of both bicyclic amidines and isothioureas are critically dependent on the sizes of both rings. Thus, DBN and its sulfur analogue THTP are highly active, while similar compounds with a 6- or 7-membered ring A or 5-membered ring B are virtually inactive.[14] (Figure 1.9)

Figure 1.9 Structure of bicyclic amidines and isothioureas

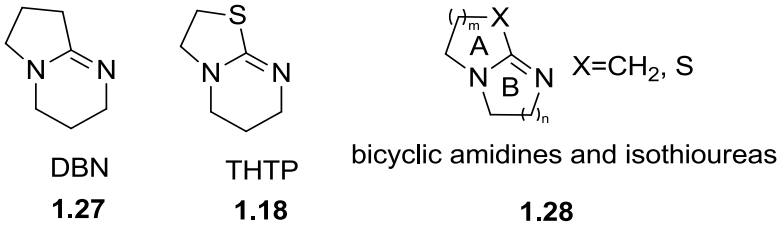
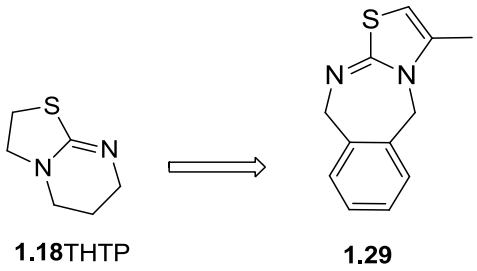


Figure 1.10 The 5, 7-membered ring bicyclic analogue



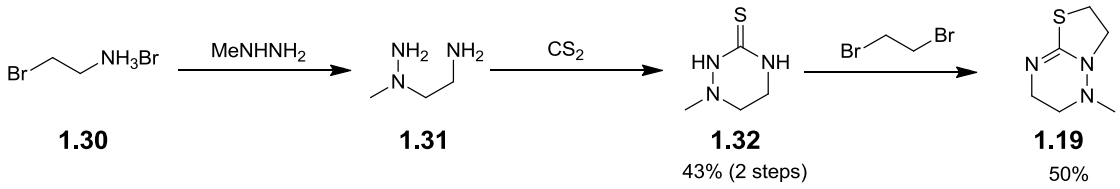
One potentially interesting variation that had remained unexplored was to expand ring B to 7-membered. (Figure 1.10) If successful, such a structure could give rise to a new generation of chiral catalysts that might interact with substrates in a fashion different from the existing ABCs.

1.4 Preparation of achiral aza-analogues of THTP

Fortunately for us, the synthesis of several achiral aza-analogues of THTP had been described in the literature[15] long before anyone was interested in their catalytic activities. We employed their synthesis with some slight modification to the experimental procedure. Aza-THTP **(1.19)** was prepared as follows. Treatment of 2-bromoethylamine hydrobromide with methylhydrazine gave compound **1.31** via selective alkylation of the substituted nitrogen[15b]. Without further purification, the resulting crude aminohydrazine **(1.31)** was heated with CS_2 directly to provide 1-methyl-1,2,4-triazinane-3-thione **(1.32)** in 43% overall yield. Its cycloalkylation with 1,2-dibromoethane proceeded

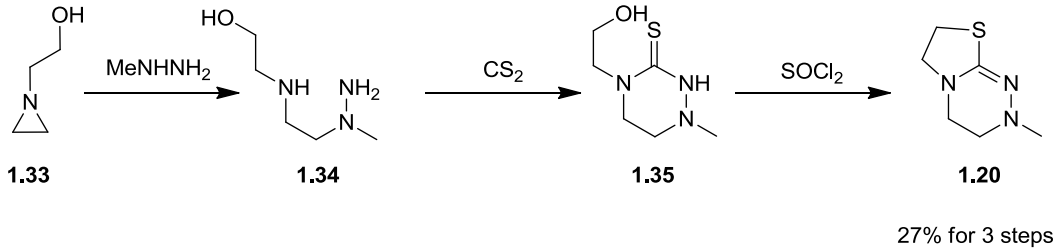
regioselectively at the hydrazine nitrogen, consistent with the literature report. (Scheme 1.2)

Scheme 1.2 Synthesis of compound **1.19**



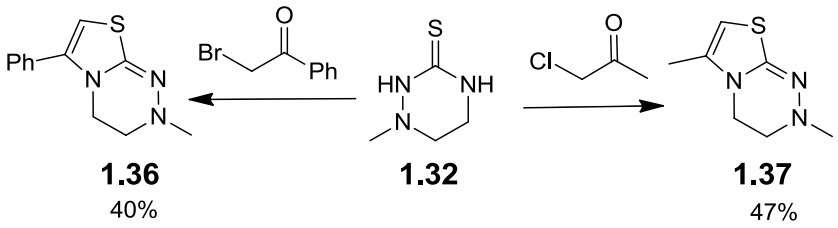
The regioisomer of **1.19** was prepared via a different synthetic route. (Scheme 1.3) 2-(aziridin-1-yl)ethanol **(1.33)** underwent nucleophilic ring opening with methylhydrazine to give compound **1.34.** Treatment with CS_2 gave compound **1.35,** which was cyclized with $SOCl_2$ to give the desired compound **1.20**. The structure of **1.20** follows unambiguously from the synthetic route. Its comparison with **1.19** also confirmed the identity of the latter.

Scheme 1.3 Synthesis of compound **1.20**



In contrast to the cycloalkylation used to prepare **1.19**, treatment of **1.32** with chloroacetone and 2-bromoacetophenone produced the opposite regioselectivity, again in accord with the original study. The difference is explained in terms of kinetic vs. thermodynamic control in the final cyclization step. Thus, compounds **1.36** and compound **1.37**. These analogs are structurally analogous to **1.20**. (Scheme 1.4)

Scheme 1.4 Synthesis of compound **1.36** and compound **1.37**

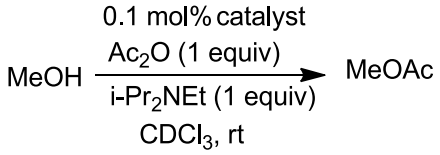


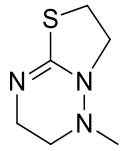
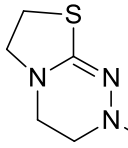
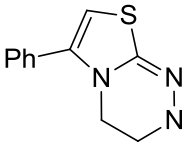
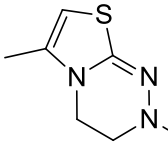
1.36 40% **1.32** **1.37** 47%

1.5 Catalytic activities of THTP analogues for acylation of methanol

Having prepared several aza-analogues of THTP, we evaluated their catalytic activities using the standard acylation of methanol test. The results are shown in Table 1.1. Compound **1.19** displayed the same activity as THTP (entries 2 and 3). In sharp contrast, its isomer **1.20** is virtually inactive. Modest catalytic activity was detected in the case of compounds **1.36** and **1.37**, presumably due to the aromaticity of the thiazole ring, which enhances the nucleophilicity of the amidine nitrogen. Overall, the results of this preliminary study were encouraging enough to proceed with the synthesis of a chiral analogue of **1.19**.

Table 1.1 Catalytic activities of THTP analogues for acylation of methanol



entry	Catalyst	Catalyst loading (mol %)	$t_{1/2}$
1	none	0	18 h[a]
2	THTP	0.1	25 min[a]
3	 **1.19**	0.1	25min
4	 **1.20**	5	10h
5	 **1.36**	0.1 5	15h 2.5h
6	 **1.37**	0.1 5	13h 45min

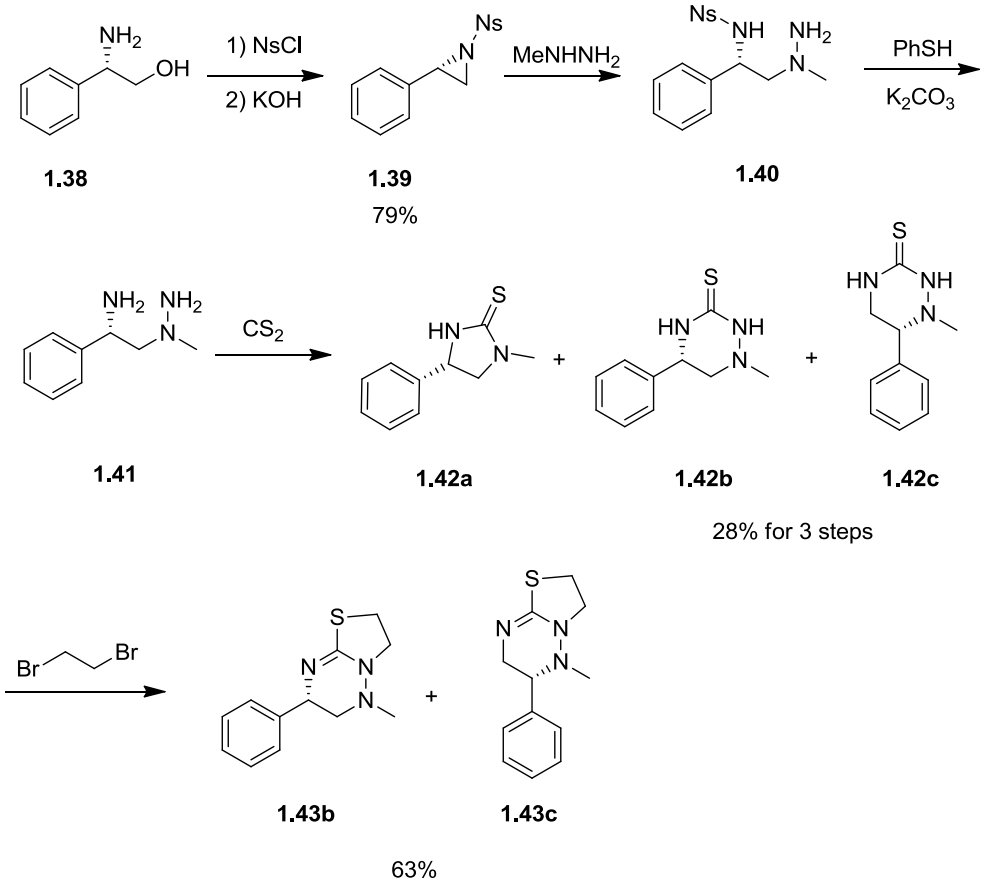
[a]Data from previous study[14]

1.6 Preparation of the chiral version of aza-analogues catalyst

Previous studies in our group on designing chiral ABCs indicated that the most suitable substituent for the C2 position is the phenyl group. Accordingly, we decided to prepare the 2-phenyl analogue of **1.19** starting with (*R*)-phenylglycinol using the

synthetic route shown in Scheme 1.5. Following a literature precedent, the amino alcohol was treated with 2 equivalents of p-$NO_2C_6H_4SO_2Cl$ (NsCl) and base to effect both protection of the amino group and cyclization to the activated *N*-sulfonylaziridine **(1.39)**. Upon treating **1.39** with methylhydrazine, an inseparable mixture was obtained, containing predominantly the products arising from the attack of the methylated nitrogen at either side of the aziridine ring[16].

Scheme 1.5 Synthesis of chiral aza-analogues of THTP



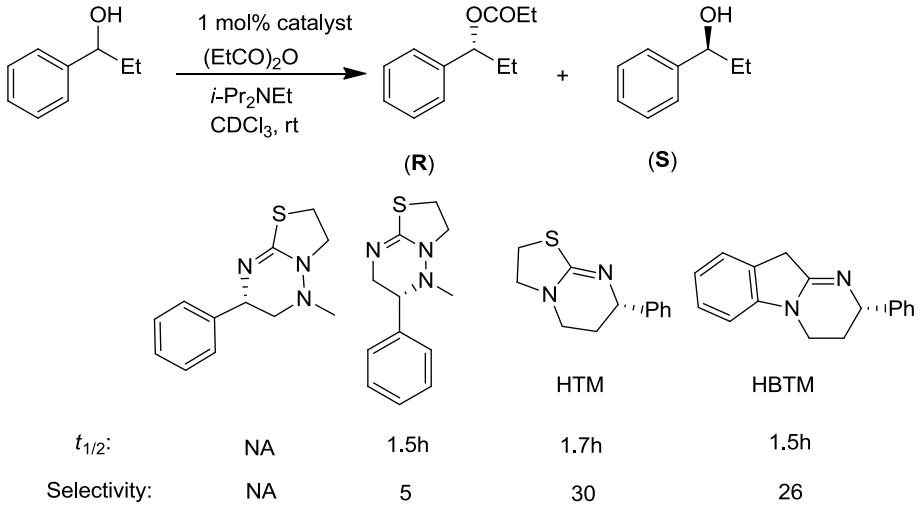
After removing the nosyl group with PhSH, the crude mixture was treated with CS_2 to give 3 compounds: the desired **(1.42b)**, its isomer **(1.42c)**, and imidazolidine-thione **(1.42a)**. The mixture of **1.42b** and **1.42c** was heated with 1,2-dibromoethane to afford **1.43b** and **1.43c** in about 1:1 ratio, which were separated by column chromatography.

(Scheme 1.5) The identity of each of these isomers was confirmed by ^{1}HNMR, ^{13}CNMR, HMQC and NOE. (See appendix)

1.7 Enantioelectivity for the Kinetic resolution of secondary alcohol

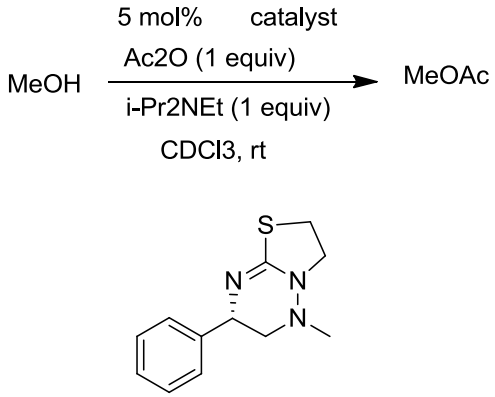
Compound **1.43b** and **1.43c** were tested for the kinetic resolution of 1-phenylpropanol. To our surprise, compound **1.43b** displayed no catalytic activity (0% conversion after 7h, at 1 mol% catalyst loading). The catalytic activity of its isomer **1.43c** was much better (similar to that of HTM and HBTM), which is consistent with lack of substitution at C2. Although the selectivity factor was low, even this result is remarkable, considering that the chiral center is on the β position relative to the nucleophilic nitrogen.

Figure 1.11 Stereoselectivity of chiral aza-analogues



The lack of catalytic activity of catalyst **1.43b** was surprising, considering its close similarity with HTM. To confirm this result, 5% catalyst loading was used to catalyze the acetylation of methanol. (Figure 1.12) The $t_{1/2}$ is about 5h, which indicates that the catalytic activity is indeed very low. The reason for this behavior is not clear at present.

Figure 1.12 Catalytic activity test of compound **1.43b** in acylation of methanol

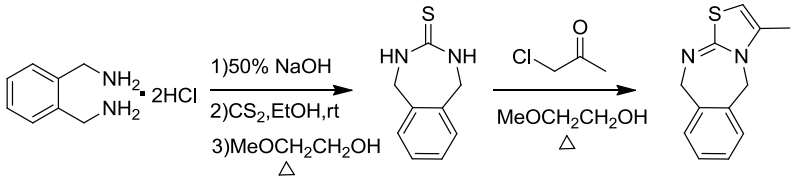


1.8 Synthesis of a 7-membered ring analogue of THTP

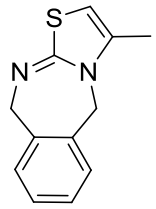
To explore the catalytic activity of a seven-membered ring analogue of THTP, I synthesized known compound **1.29** according to a slightly modified procedure from literature[17]. (Scheme 1.6)

Its activity in the MeOH-Ac_2O test turned out to be lower than that of THTP itself, but still fairly good. In fact, compound **1.29** was comparable to DBN and far more active than any other bicyclic amidines and isothioureas tested in our previous studies ($t_{1/2} \geq 3.5$ h at 5 mol% catalyst loading).

Scheme 1.6 Synthesis of compound **1.29**



1.44 **1.45** **1.29**

Entry	Catalyst	Catalyst loading (mol%)	$t_{1/2}$
1	 **1.29**	0.1 1	5h 30min
2	THTP	0.1	25 min[a]
3	DBN	1	40 min[a]

[a]Data from previous study [13]

1.9 Conclusions

In this chapter, several aza-analogues and a seven-membered ring analogue of THTP were prepared and their catalytic activities were investigated. Only one of the achiral aza-THTPs proved to be highly active. However, for reasons that are not clear at present, its 2-phenyl derivative **1.43b** lacks catalytic activity. At the same time, the 3-phenyl isomer **1.43c** is not only catalytically active, but also shows some enantioselectivity, despite the fact that the phenyl group is relatively far from the reactive site. Even if aza-THTPs do not find any applications in catalyst design in the future, this result suggests that ABCs with a chiral center at the β-position merit further study. The first results obtained with the 7-membered THTP analogue are also encouraging enough to warrant further exploration.

1.10 References

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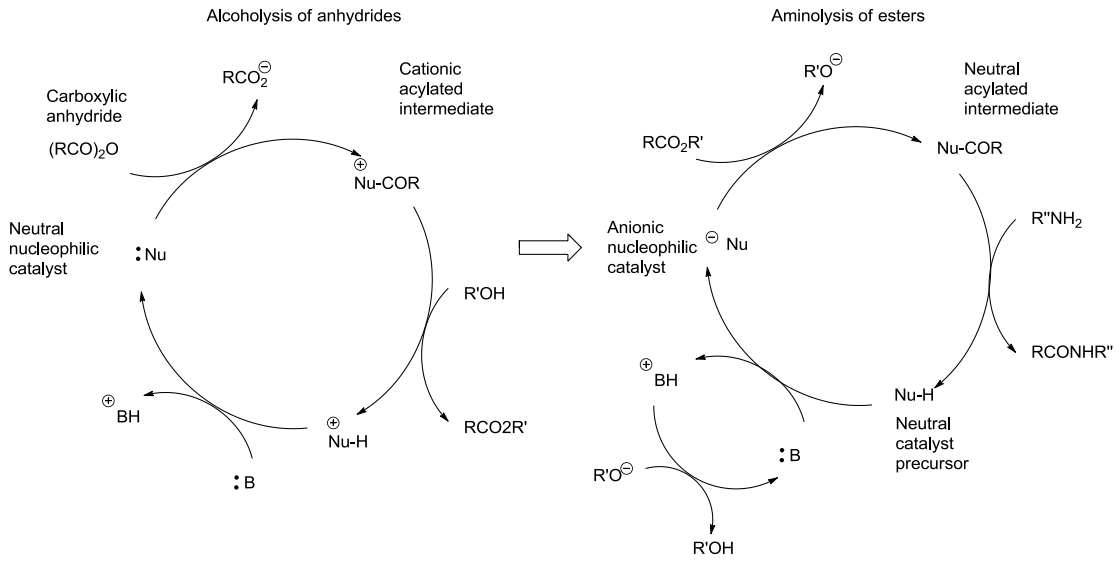
Chapter 2 Development of azoles derivatives as anionic acyl transfer catalysts

2.1 Introduction to anionic nucleophilic catalysis

The majority of acyl transfer catalysts used in organic synthesis are neutral organic molecules. Examples of achiral catalysts of this type are illustrated in Figure 1.4, and chiral ones can be found in Figure 1.2, Chapter 1. Their utility and wide popularity ultimately depends on their ability to react with acyl donors and transform them into activated intermediates, which will in turn transfer the acyl group to nucleophilic substrates.

Figure 2.1 Comparison of neutral nucleophilic and anionic nucleophilic catalysis

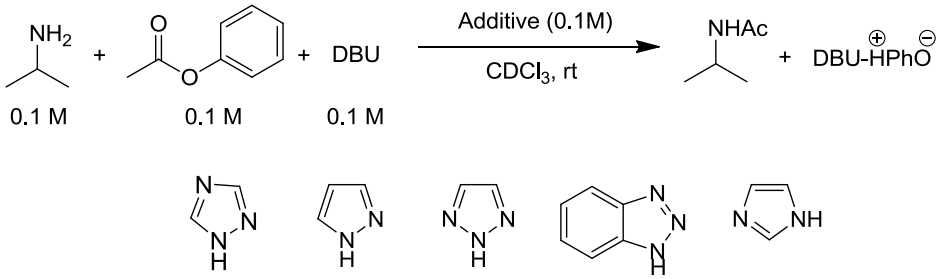


During the development of our neutral amidine-based acyl transfer catalysts, we became interested in developing a new method for the catalytic, enantioselective acylation of amines using easily available achiral acyl donors.[1] Anhydrides and acyl chlorides are unsuitable for this purpose, because they usually react with amines directly,

without any catalysis. On the other hand, carboxylic esters would be more attractive, because their background reaction with amines is extremely slow under ambient conditions. However, the neutral catalysts reported previously in the literature, which have been successfully applied to acylation reaction using carboxylic anhydrides or acyl chloride as the acyl donors, can only activate highly acivated carboxylic esters. To address this limitation, our group developed a new concept: anionic nucleophilic catalysis, illustrated in Figure 2.1.

A priori, anionic nucleophiles are expected to be more nucleophilic than their neutral counterparts, and therefore better able to attack the ester group. With this in mind, one of my labmates, Xing Yang, examined a number of protic nucleophiles for their ability to activate phenyl acetate for the acylation of isopropylamine in the presence of stoichiometric amounts of DBU (pK_a of protonated DBU is 13.28 predicted by SciFinder).[2] Among the many classes of nucleophiles tested, 1,2,4-triazole proved to be by far the most active. On the other hand, several other azoles, which are only slightly structurally different, displayed much lower activities. (Figure 2.3)

Figure 2.2 Activities of azoles compounds for aminolysis of esters



	2.1	**2.2**	**2.3**	**2.4**	**2.5**
pk_a	10.18	14.00	8.70	8.38	13.89
$t_{1/2}$	8min	2.2h	40min	4.3h	9h

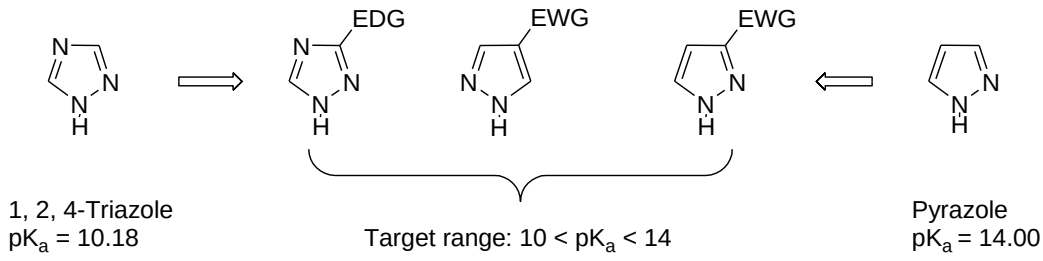
This effect was attributed to the difference in their electronic properties: less electron deficient, and therefore less acidic, azoles would not form high concentrations of the reactive anionic species in the presence of DBU, while too electron-deficient azoles would easily ionize, but their anions would be too unreactive.

After some optimization studies, Xing demonstrated that, at 5-20 mol% loading, 1,2,4-triazole anion serves as an effective acyl transfer catalyst in both aminolysis and transesterification of isopropenyl acetate and even completely unactivated esters, which require only substoichiometric amounts of DBU. Furthermore, he showed that the protonated counterion is not important: sodium and tetrabutylammonium salts of 1,2,4-triazole are even more catalytically active than the DBU-triazole mixture, when used in appropriate solvents. Overall, 1,2,4-triazole was judged to be a good candidate for our future studies on chiral anionic nucleophilic catalyst design.

2.2 Objectives of this study

Upon completion of Xing's study, we became interested in developing chiral 1,2,4-triazole derivatives for enantioselective acylation of amines, which was our original goal. We quickly realized that introduction of an effective chiral directing group into the triazole molecule was not going to be a trivial matter. Therefore, we thought to broaden our knowledge of the factors influencing the catalytic activity.

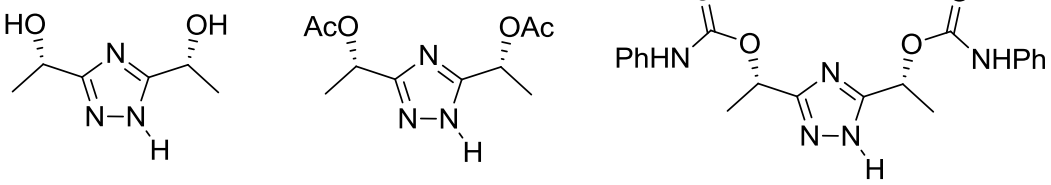
Figure 2.3 Electronic effects on the azole ring



First of all, we wanted to know exactly what range of pK_a values would be compatible with good catalytic activity. To close the gap between 1,2,4-triazole itself (pK_a 10.2) and pyrazole (pK_a 14.0), we planned to explore 1,2,4-triazole derivatives with electron-donating substituents and pyrazole derivatives with electron-withdrawing groups. (Figure 2.3)

Second, we wished to study the effect of steric hindrance. Xing had already prepared a series of C2-symmetrical chiral triazoles **2.6, 2.7, 2.8** (Figure 2.4) and found their catalytic activities to be fairly low.[3] Therefore, we wished to explore other substitution patterns that might allow us to design more effective chiral catalysts. Third, we needed to determine what types of cations can be used in conjunction with azole anions, in addition to those briefly tested by Xing in his preliminary study.

Figure 2.4 C2-symmetrical chiral triazoles



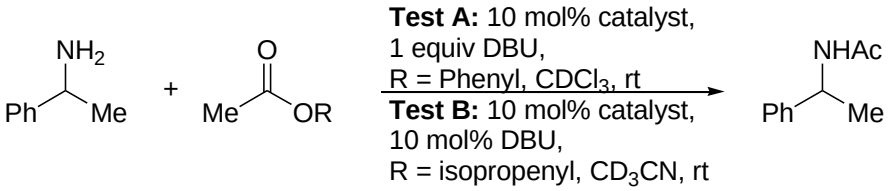
2.6 **2.7** **2.8**

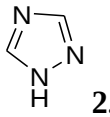
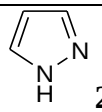
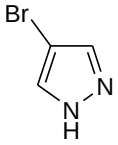
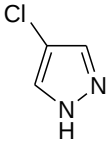
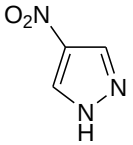
2.3 Structure-activity relationship of azole derivatives

2.3.1 The electronic effects of pyrazole derivatives on β position

Conveniently, several pyrazole derivatives with electron-withdrawing groups on the β position, such as 4-bromopyrazole **(2.9)**, 4-chloropyrazole **(2.10)** and 4-nitropyrazole **(2.11)**, are commercially available or can be easily synthesized. (Table 2.1)

Table 2.1 Electronic effects on β position of pyrazole ring



entry	catalyst	Predicted pK_a[a]	$t_{1/2}$ (h) Test A	$t_{1/2}$ (h) Test B
1	 **2.1**	10.18	2	2
2	 **2.2**	14.00	14	ND
3	 **2.9**	12.71	1	2.5
4	 **2.10**	12.71	1	ND
5	 **2.11**	9.63	6	20

[a] pK_a predicted by SciFinder

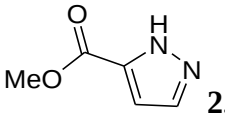
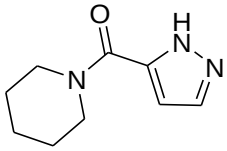
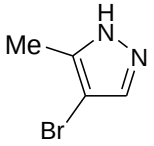
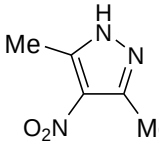
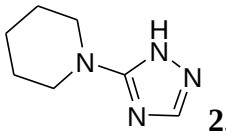
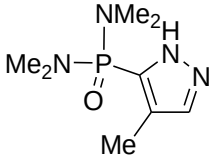
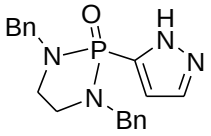
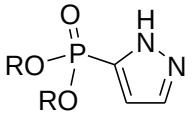
Catalytic activity was tested first using phenyl acetate in $CDCl_3$ according to the standard procedure developed previously by Xing. Later, the most promising catalysts were re-examined using isopropenyl acetate in CD_3CN, so that the accumulation of phenolate anion does not complicate the course of the reaction.[2] It was interesting to find that 4-bromopyrazole **(2.9)** and 4-chloropyrazole **(2.10)** displayed significant higher catalytic activity than did pyrazole itself and even a little higher than 1,2,4-triazole, as we expected based on their predicted pK_a values (both have pK_a=12.71). By contrast, the catalytic activity of 4-nitropyrazole **(2.11)** (pK_a=9.63) was lower than that of 1,2,4-

triazole, although was still higher than that of pyrazole. This result was also consistent with our prediction.

2.3.2 The electronic effects on α position of pyrazole ring

Substituents on the β position of pyrazole discussed above allowed us to evaluate the electronic effects without any complications from steric hindrance. Now we wanted to examine the influence of electron-withdrawing groups on the α-position of pyrazole, where steric and other effects would also play a role. Methyl 3-pyrazolecarboxylate **(2.12)** with pK_a=11.04 displayed by far the greatest catalytic activity in Test A and was equal to triazole in Test B (Table 2.2, entry 1). The corresponding amide which was prepared via a self-catalyzed aminolysis[2] (Scheme 2.4) was less reactive (entry 2). Even lower activity was found in disubstituted pyrazole **2.14** with pK_a 13.27 (entry 3). In all these cases, the acetylation was presumed to occur on the nitrogen distal to the α-substituent, to avoid the steric interaction. Trisubstituted pyrazole **2.15** with a pK_a well within "the optimal range" was very unreactive, as might be expected from the steric hindrance of both nitrogens. Surprisingly, triazole derivative **2.16** with an electron-donating substituent Proved to be a poor catalyst despite the promising pK_a.

Table 2.2 Electronic effects on α position of pyrazole ring

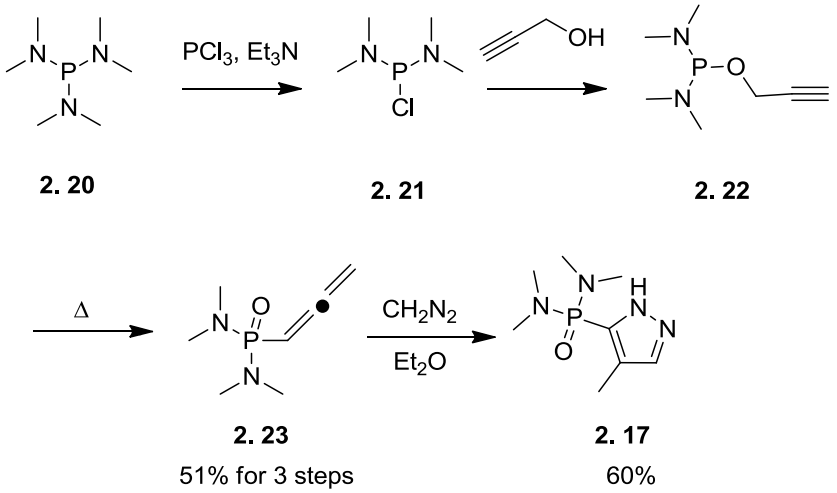
entry	catalyst	Predicted pK_a	$t_{1/2}$ (h) Test A	$t_{1/2}$ (h) Test B
1	 **2.12**	11.04	0.5	2
2	 **2.13**	12.98	3	2.5
3	 **2.14**	13.27	6	18
4	 **2.15**	10.75	96	ND
5	 **2.16**	11.9	9	ND
4	 **2.17**	NA[a]	12	ND
5	 **2.18**	NA[a]	6	ND
6	 R = L-Menthyl **2.19**	9.60[b]	2.5	3

[a] pK_a is not known [b] pK_a from a diethyl ester analogue

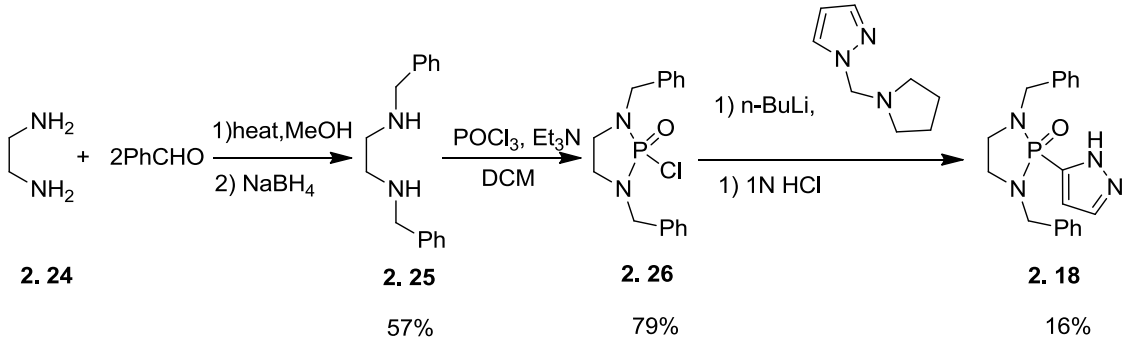
With these results in hand, we began to think more specifically about introducing chiral groups into the pyrazole core structure. At least for now, we decided to focus on the α-substitution. We reasoned that if a chiral group were to be attached via an ester or amide linkage, it would probably be too far from the distal nitrogen where the reaction is

supposed to take place. It occurred to us that phosphonate esters or phosphonamides might be more promising, both in terms of electronic properties (stronger than their carbonyl counterparts) and spatial configuration. A conceptual precedent for this idea can be found in the use of chiral phosphoramides as both catalyst and chiral auxiliaries in asymmetric transformations.[4] Three phosphorus compounds were synthesized as illustrated in Schemes 2.1-2.3[5, 6, 7, 8] and tested. Most interestingly, bis-(L-menthyl) pyrazolephosphonate **2.19** displayed catalytic activity only slightly lower than triazole.

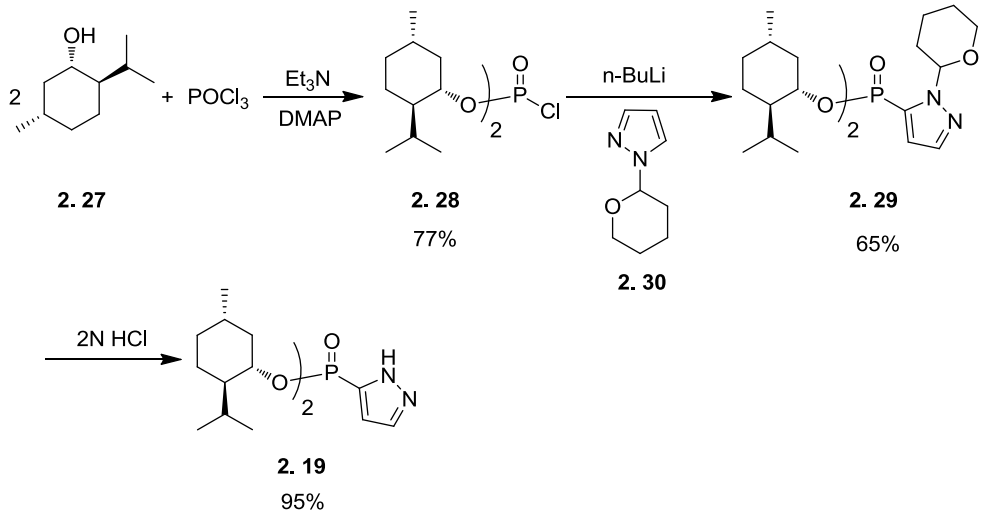
Scheme 2.1 Synthesis of compound **2.17**



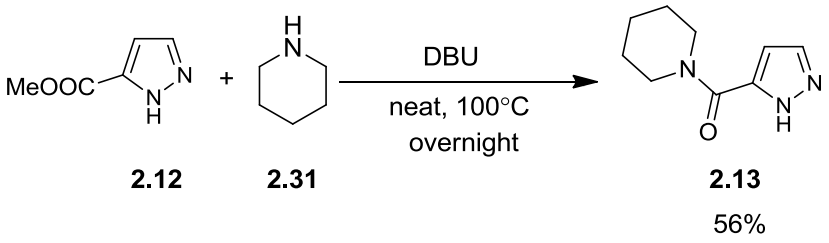
Scheme 2.2 Synthesis of compound **2.18**



Scheme 2.3 Synthesis of compound **2.19**



Scheme 2.4 Preparation of compound **2.13** via self-catalyzed aminolysis

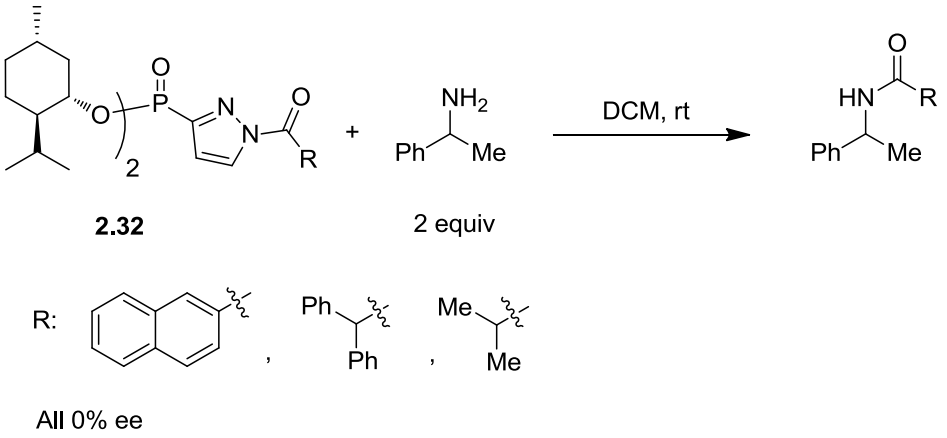


2.4 Enantioselectivity test of menthyl phosphonate pyrazole derivative

Due to its good activity and ease of preparation, the bis-menthyl phosphonate **2.19** was deemed to be an especially promising lead for developing enantioselective catalysts. Even though the chiral menthyl groups were not expected to provide good enantiodiscrimination, we decided to test the efficacy of this scaffold anyway. No ee was observed when **2.19** was used as a catalyst in the acetylation of α-phenethylamine with isopropenyl acetate. Three *N*-acylated derivatives of **2.19** were preformed and used as

stoichiometric acylating agents. Still, no enantioselectivity was observed. (Scheme 2.5) Due to time constraints, further study of pyrazole-based anionic catalysts was put on hold.

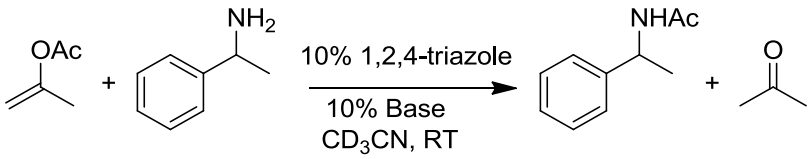
Scheme 2.5 Enantioselectivies of menthyl phosphonate pyrazole derivative

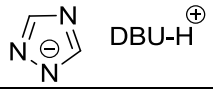
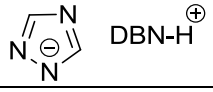
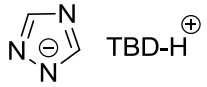
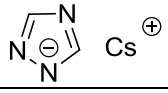
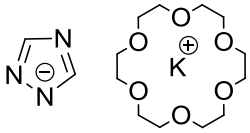


2.5 Variation of Counterions

In the studies described above, as well as Xing's original study, DBU has used routinely to deprotonate azoles in situ, simply out of convenience. We already knew, however, that it was not optimal for catalytic activity. Therefore, we decided to examine several other salts of 1,2,4-triazole that might ultimately prove to be more attractive as catalysts for reactions that do not produce acidic byproducts. Conditions of Test B, which generate only acetone as byproduct were chosen for their comparison.

Table 2.3 Catalytic activities of 1,2,4-triazole under different bases



Entry	Catalyst	$t_{1/2}$ (h) Test B
1		2
2		2.5
3		1.5
4		2.5
5		0.5

DBN (pK_a=13.42) TBD (pK_a=14.47)

Relatively minor differences were found between DBU and other commonly used strong bases: amidine DBN and guanidine TBD (Table 2.3, entries 1-3). More interestingly, cesium salt of triazole demonstrated comparable activity despite the fact that it was only partially soluble in acetonitrile (entry 4). Finally, the most rewarding result was obtained in the case of potassium salt of 1, 2, 4-triazole complexed with 18-Crown-6 (entry 5). This salt is a stable, not very hygroscopic solid easily soluble in organic solvents, which should make it a convenient catalyst. Its high activity suggests that crown ether-chelated alkaline metal cations might be superior to DBU for enantioselective catalysis where low catalyst loadings are especially important.

2.6 Conclusions

In this chapter, we have demonstrated that many pyrazole derivatives are comparable to 1,2,4-triazole in terms of catalytic activity. Furthermore, compared to triazole, pyrazole offers more opportunities for structural variation and therefore might have more potential for the development of chiral anionic catalysts. Although enantioselective acylation of amines with pyrazolephosphonate ester derivatives could not be demonstrated in the preliminary tests, the synthetic route to such compounds has been established. This should permit a more systematic study in the future. In addition, we have established that preformed alkaline metal salts of azole anions might provide an attractive alternative to their DBU salts.

2.7 References

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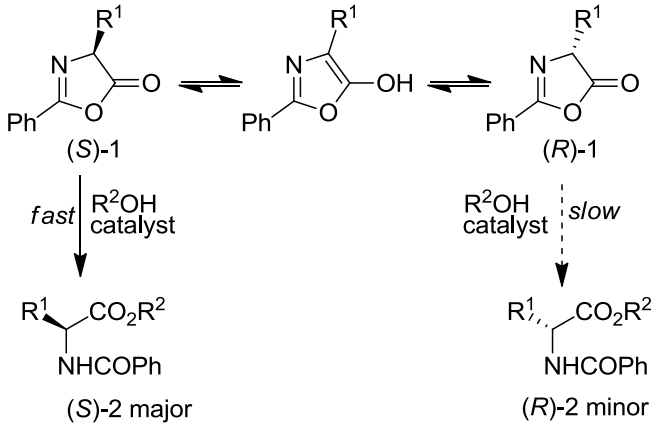
Chapter 3 Chiral Brønsted acid catalyzed enantioselective alcoholysis

3.1 Introduction

3.1.1 Chemistry of azlactones

Azlactones, or oxazolones, are an interesting class of heterocyclic compounds usually prepared via cyclodehydration of *N*-acylated α-amino acids. Their synthetic chemistry, including many enantioselective transformations, is remarkably rich and diverse. Since a comprehensive discussion of the different modes of reactivity displayed by azlactones is beyond the scope of this chapter, the reader is hereby referred to a recently published review.[1] We will focus our attention on only one aspect of their chemistry: enantioselective alcoholysis. In essence, azlactones may be thought of as cyclic anhydrides of as α-acylamino acids. Therefore, they are expected to react as acyl donors towards nucleophiles, such as alcohols or amines, producing esters or amides of the parent amino acid derivatives.

Figure 3.1 Mechanism of DKR of azlactones



One especially interesting feature of chiral azlactones bearing one substituent at C4 is the extreme ease with which they racemize in solution. This property is due to the fact

that the enol form of azlactones is an aromatic oxazole derivative, which makes the C4 proton unusually acidic (pK_a ca. 9).[2] Because of this rapid in situ racemization of azlactones, their enantioselective alcoholysis is accompanied by dynamic kinetic resolution (DKR) (Figure 3.1).[3]

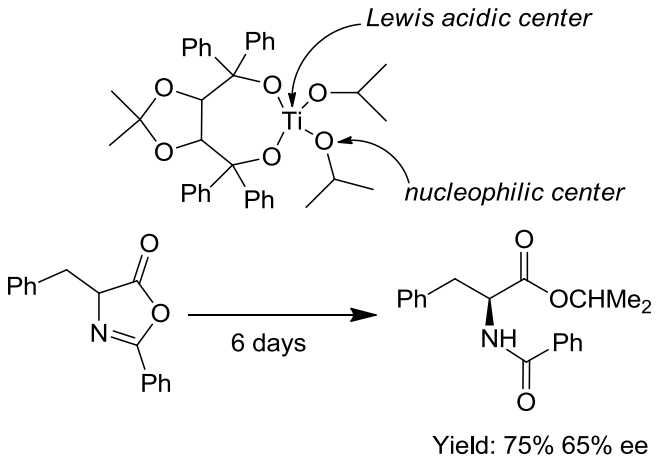
As shown in Figure 3.1, the two enantiomers of azlactone are in equilibrium with each other through the achiral enol intermediate. If one of the enantiomers undergoes alcoholysis faster than the other one (under asymmetric catalysis), then the equilibrium will be continuously drained in its direction. If the racemization is much faster than the alcoholysis of the slow-reacting enantiomer, then the entire racemic starting material will be transformed into one enantiomer of the product. This process is known as dynamic kinetic resolution (DKR). Compared to the conventional kinetic resolution (KR), which simply converts the two enantiomers of the starting material into two different compounds, DKR is inherently more efficient: while KR can achieve at most 50% yield of either enantiomeric product, DKR can produce up to 100% theoretical yield.

Due to the practical importance of enantioenriched α-amino acid derivatives, catalytic DKR of azlactones has received considerable attention from the synthetic community. Enzymatic methods were originally developed[4] years ago and continued to be optimized over the years. Somewhat later, approaches utilizing low-molecular weight catalysts began to appear. These nonenzymatic methods are reviewed in some detail in the next section, because they are directly relevant to the subject of my study described in this chapter.

3.1.2 Lewis acid-promoted DKR of azlactones

Seebach et al.[5] reported titanium TADDOLate as a stoichiometric reagent for the asymmetric ring opening of azlactones. Up to 65% ee were obtained in this study. As shown in Figure 3.2, titanium serves as a Lewis acidic center to activate the carbonyl oxygen of the azlactone substrate, while the isopropoxide group attacks the carbonyl carbon to provide enantioenriched ester as the product.

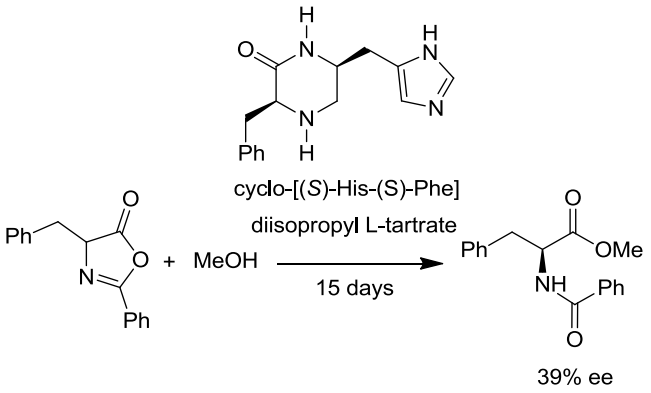
Figure 3.2 DKR of azlactones promoted by Lewis acids



3.1.3 DKR of azlactones catalyzed via hydrogen bonding catalysis.

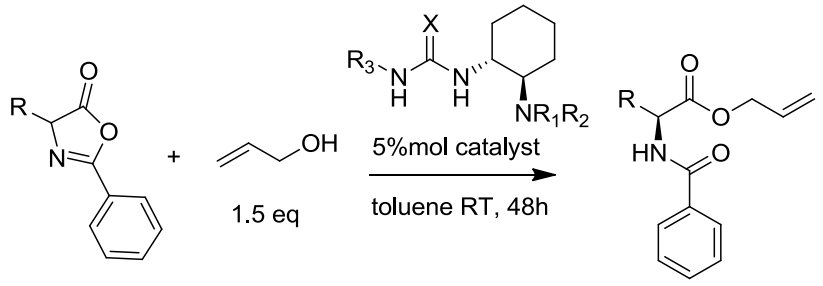
In 1999, Hua[6] achieved catalytic DKR of azlactones using a combination of a chiral diketopiperazine, *cyclo*-[(*S*)-His-(*S*)-Phe], with diisopropyl L-tartrate. The latter was presumed to activate the substrate via hydrogen bonding. However, only 39% ee was obtained. (Figure 3.3)

Figure 3.3 DKR of azlactones catalyzed via hydrogen bonding



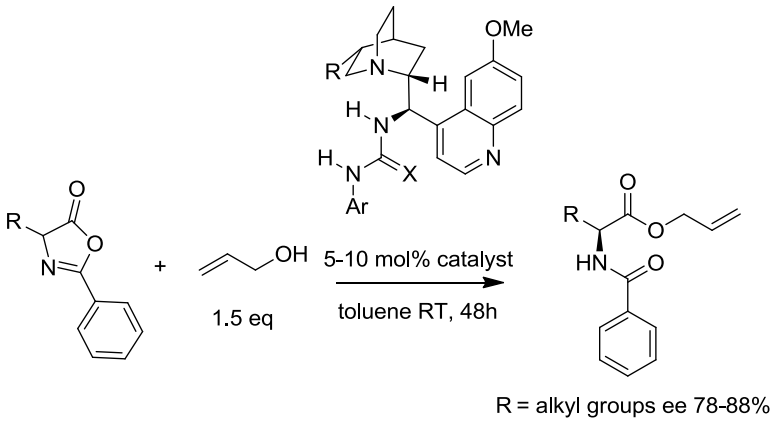
Much better results were achieved several years later using chiral thiourea-based bifunctional catalysts. Berkessel *et al.*[7] obtained moderate to good enantioselectivities (72-85% ee) for most of the substrates examined. The highest enantioselectivity (91% ee) was observed for the bulkiest *t*-Bu-substituted substrate. Unfortunately, the yield in this case was rather low (16%). (Figure 3.4)

Figure 3.4 DKR of azlactones catalyzed by chiral thiourea catalysts



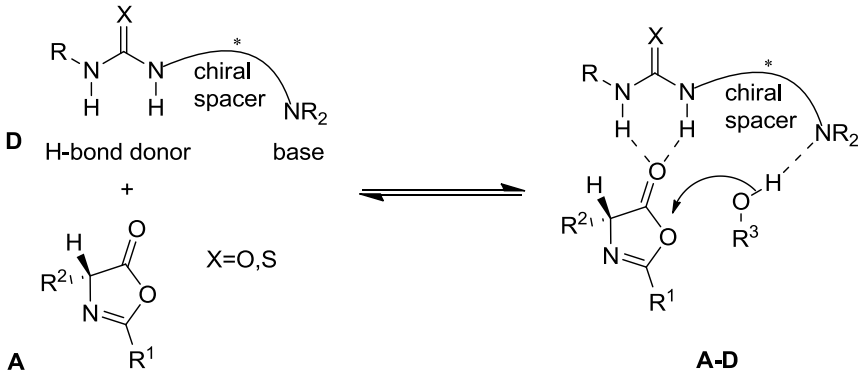
Shortly thereafter, Connon et al.[8] reported the DKR of azlactones catalyzed by the quinine-derived thiourea bifunctional catalysts. Moderate enantioselectivities (78-88% ee) were obtained for the alkyl-substituted azlactones. (Figure 3.5)

Figure 3.5 DKR of azlactones catalyzed by quinine-derived thiourea derivatives



According to Berkessel, the thiourea moiety is believed to activate the carbonyl group by double hydrogen bonding with the oxygen while the basic amine serves as a hydrogen bond acceptor towards the alcohol and thus directs the nucleophilic addition from the less hinder face of the substrate (Figure 3.6).

Figure 3.6 Mechanism of bifunctional chiral thiourea activation



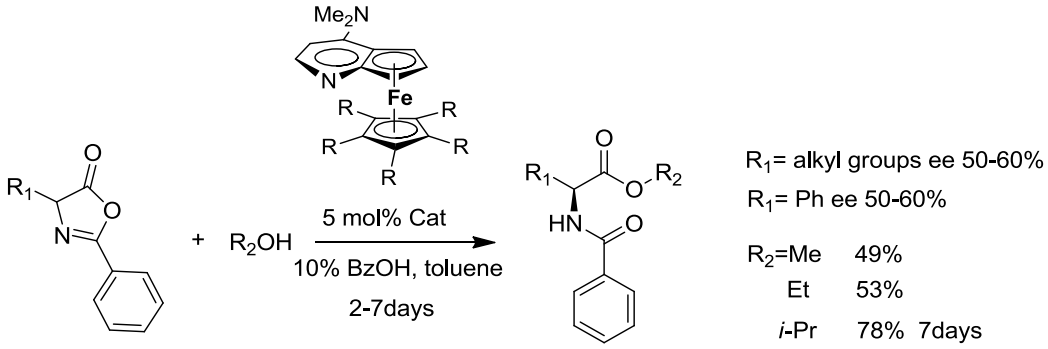
3.1.4 DKR of azlactones via acyl transfer catalysis

Promising levels of enantioselectivity (up to 78%ee) were achieved by Fu and co-workers in 1998 using their planar chiral DMAP derivatives as the acyl transfer catalyst.[9] Interestingly, they reported in their paper that addition of benzoic acid as a co-catalyst

was required, presumably to activate the azlactone. Moderate enantioselectivities were observed (50-60% ee) when using methanol for alcoholysis.

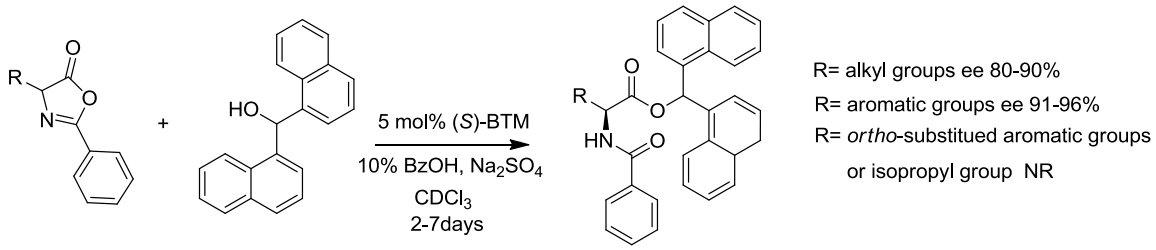
Higher enantioselectivity (78% ee) was obtained using isopropanol as the nucleophile, but the reaction rate was extremely slow (7 days). (Figure 3.7)

Figure 3.7 DKR of azlactones catalyzed by chiral DMAP derivatives



Higher enantioselectivities were obtained recently in our group by using our chiral isothiourea catalyst, (*S*)-BTM in combination with benzoic acid.[10] Use of di-(1-naphthyl) methanol was required to achieve high enantioselectivity. Alkyl-substituted azlactones produced ee's in the 80-90% range; while the corresponding aryl derivatives gave 76-96% ee's. However, some limitations of this methodology were also uncovered. Thus, substrates with an *ortho*-substituted aryl or isopropyl group at C4 failed to react. (Figure 3.8)

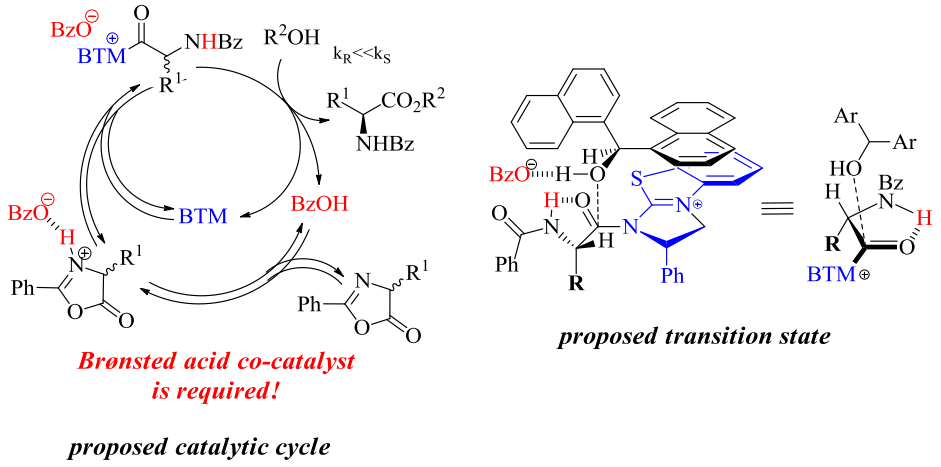
Figure 3.8 DKR of azlactones catalyzed by BTM



The mechanism of acyl transfer catalysis is somewhat more complicated than those discussed above. As shown in Figure 3.9, three steps are involved in its catalytic cycle proposed for the BTM-catalyzed DKR developed in our group. In the first step, the substrate is activated by protonation with benzoic acid. The ring opening by the nucleophilic catalyst occurs in the second step to form an acylated intermediate, which transfers the acyl group to the alcohol in the third step.

The first two steps are presumed to be easily reversible. The enantioselectivity is determined by the third step and depends on the alcohol employed. We have proposed that in the transition state, there is a hydrogen bond between the benzamide group and the reacting carbonyl group which fixes its conformation. The R group on the substrate is positioned next to the C2-phenyl group on the catalyst, which is probably why bulky substituents, such as isopropyl or *ortho*-substituted aryl groups, are not tolerated.

Figure 3.9 DKR of azlactones catalyzed by acyl transfer catalysts



3.2 The purpose of this project

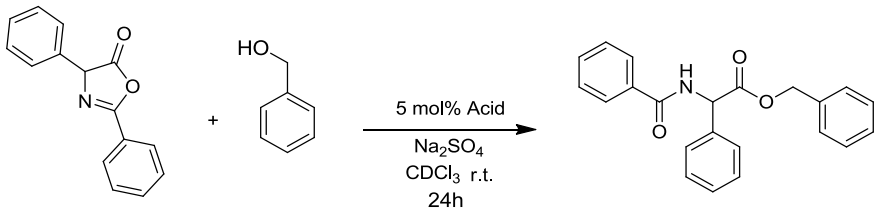
In the course of our recent studies described above, we first became aware that the presence of a proton source is necessary to activate azlactones towards nucleophilic

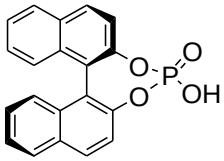
attack. However, no appreciable reaction was observed when benzoic acid was used by itself, in the absence of BTM. We hypothesized, nevertheless, that a sufficiently strong Brønsted acid might be able to activate azlactones enough to promote their *direct* alcoholysis without the intermediacy of a nucleophilic catalyst. A chiral Brønsted acid could then be used to effect DKR of azlactones via a mechanistically different alternative method. We were especially hopeful that BINOL phosphoric acids pioneered some years ago by Akiyama and Terada[11] would be competent in this reaction. Interestingly, there had been no prior reports of their use to promote enantioselective acylations of any sort, even though they have been successfully applied to a variety of other types of asymmetric transformations.[12]

3.3 DKR of azlactone catalyzed by stronger Brønsted acid

To test this, idea, we reacted 2,5-diphenylazlactone *(±)*-**1a** with benzyl alcohol in the presence of (*R*)-BINOL phosphoric acid (pK_a=1) which is more acidic than benzoic acid (pK_a=4.2). The reaction went smoothly to give the expected ester, albeit in essentially racemic form (2% ee). (Table 3.1). In order to support this result and demonstrate how strong an acid needs to be to promote direct alcoholysis of azlactones, several achiral acids were tested in this reaction. As already mentioned, benzoic acid (pK_a=4.2) is too weak to promote the reaction. However, the stronger trifluoroacetic acid (pK_a=-0.25) resulted in 40% conversion after 24h and methanesulfonic acid (pK_a=-2.6) provided 100% conversion.

Table 3.1 Alcoholysis of azlactones catalyzed by other acids

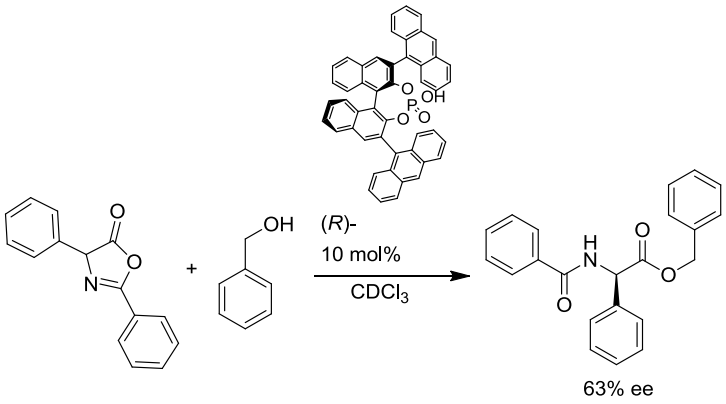


Entry	Acid	pK_a	Time, h	% conversion
1		1[a]	16	100
2	PhCOOH	4.2[b]	24	0
3	TFA	-0.25[b]	24	40
4	MsOH	-2.6[b]	24	100

[a] pK_a from reference [12d] [b] pK_a form Evans pK_a table

Encouraged by this result, we catalyzed the same reaction with 3,3'- bis-(9-anthryl) BINOL phosphoric acid. (Figure 3.10) The resulting 63% ee of the product indicated that we were moving in a promising direction.

Figure 3.10 Reaction catalyzed by substituted chiral phosphoric acid

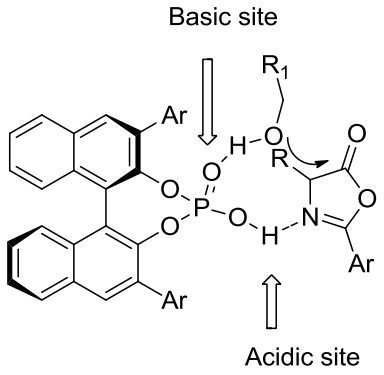


3.4 Proposed mechanism of chiral phosphoric acid catalysis

At this point, we proposed the mechanism illustrated in Figure 3.11. As mentioned in the literature[12b], chiral phosphoric acid is believed to serve as a bifunctional catalyst in

many cases. We surmised that the acid protonated the substrate on the nitrogen thus forming a close ion pair inside the chiral cavity formed by the anthracene groups; The phosphate anion in turn formed a hydrogen bond to the alcohol facilitating its attack on the azlactone carbonyl.

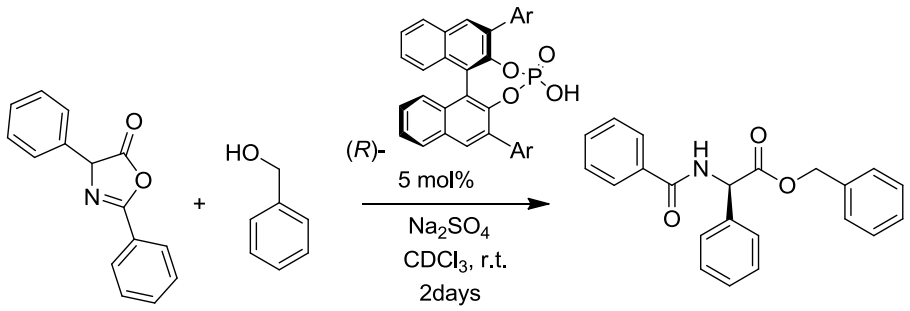
Figure 3.11 Phosphoric acid served as a bifunctional catalyst



3.5 Catalyst optimization

We began optimizing the new reaction by testing several additional 3, 3'-disubstituted derivatives of BINOL phosphoric acids (Table 3.2). None of them was as good as the initially chosen catalyst [3,3'- bis-(9-anthryl) BINOL phosphoric acid] however. Thus, we selected it for further studies.

Table 3.2 Optimization of the catalysts

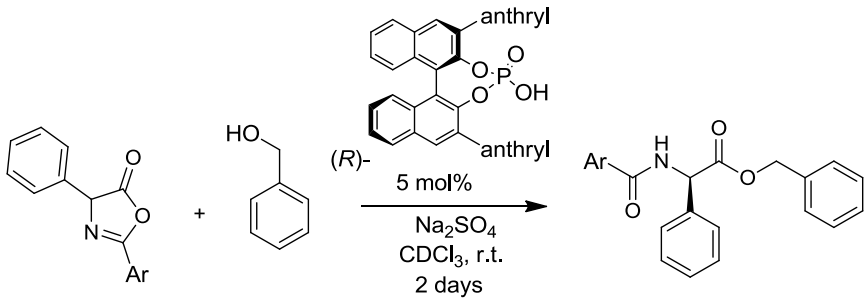


Entry	Ar	Con (%)	ee (%)
1	H	60	2
2	Ph(*S*)	96	-9
3	9-anthryl	91	63
4	9-phenanthryl	71	34
5	3,5-$(CF_3)C_6H_3$	65	25
6	$SiPh_3$	32	48
7	2,4,6-$(i\text{-}Pr)_3C_6H_2$	39	34
8	9-phenyl-anthryl	67	25

3.6 Substrates variation: C2 substitution effects

Since the C2 substituent on azlactones forms a removable part of the product, it was important to optimize it early on. It seemed that the influence of *para*-substituents on the C2 phenyl on the enantioselectivity was limited (Table 3.3, entries1-3). However, the 3,5-dimethoxyl-phenyl group lead to a substantial improvement (entry 4). Interestingly, in a recent study by Terada, the same C2 substituent also proved to be optimal in a different type of asymmetric transformation of azlactones catalyzed by chiral Brønsted acids.[13]

Table 3.3 Substrates variation



entry	Substrates (Ar)	Con (%)	ee (%)
1	4-ClC_6H_4	84	61
2	Ph	91	63
3	4-$MeOC_6H_4$	91	66
4	3,5- $MeOC_6H_4$	72	77

3.7 Optimization of reaction conditions

3.7.1 Solvent effects

Table 3.4 Solvent effects

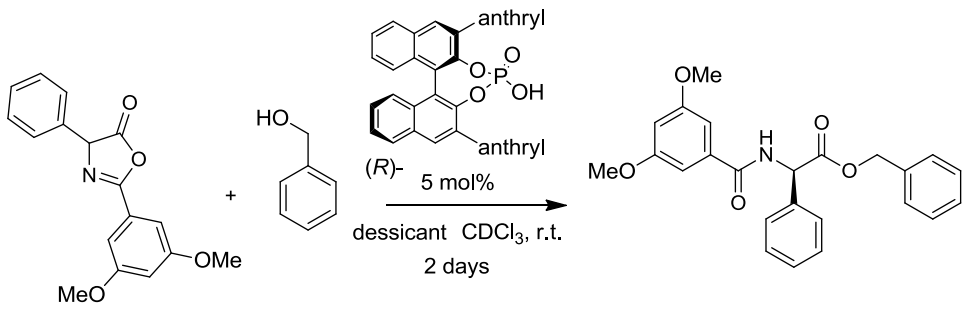
entry	Solvent	ee (%)
1	$CDCl_3$	77
2	CH_2Cl_2	74
3	Benzene	54
4	toluene	56
5	Et_2O	Substrate not soluble
6	THF	- (conversion is 35%)
7	EtOAc	- (conversion is 32%)

Several solvents were tried for this reaction. (Table 3.4) $CDCl_3$ initially chosen to facilitate NMR studies was, in fact, optimal (entry 1). The solubility of substrate was low in Et_2O (entry 5), and the conversions were very low in both THF and EtOAc (entries 6-7).

3.7.2 Use of desiccants

As described in the literature[9], azlactone is sensitive to moisture. As shown in Figure 3.12, a small amount of water decreased both of the reaction rate and enantioselectivity. Thus, addition of a drying agent was thought to be necessary.

Figure 3.12 Variation of desiccants



	+0.2ul H_2O	without Na_2SO_4	Na_2SO_4	$MgSO_4$	4A MS
ee	68%	74%	77%	78%	—
Conversion	41%	59%	72%	81%	22%

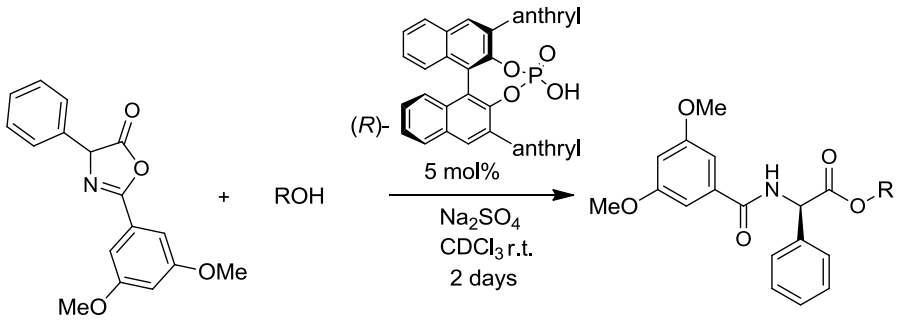
The reaction rate was very slow using 4Å MS. The addition of Na_2SO_4 helped increase slightly both of the reaction rate and enantioselectivity. $MgSO_4$ is better than Na_2SO_4, but due to the acidity of $MgSO_4$, Na_2SO_4 was eventually adopted for use as the drying agent in this reaction.

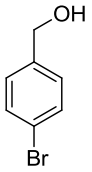
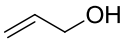
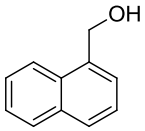
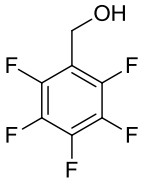
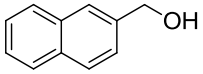
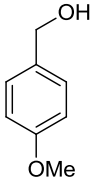
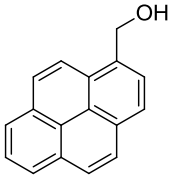
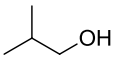
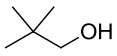
3.8 Variation of alcohols

Further study of alcohol effects indicated that the enantioselectivity of benzyl alcohol is slightly better than that of methanol, isopropanol and allyl alcohol (Figure 3.13). It seemed that the steric repulsion or π-π interaction between the benzyl alcohol and the substrate or catalyst may play a role, as we expected. Thus, several substituted benzyl alcohols were investigated in this reaction. One of these, 4-bromobenzyl alcohol was found to increase both the reaction rate and enantioselectivity. Several polycyclic benzylic alcohols were tested next. Experimental results showed that 1-naphthyl-, 2-naphthyl- and 1-pyrenyl-methanol all lead to significant improvement in both reaction rate and enantioselectivity, compared to monocyclic benzyl alcohols.

As a control experiment, two saturated bulky primary alcohols, were tested. The enantioselectivities were comparable to some benzylic alcohols and higher than in the case of methanol and isopropanol. Still, they were substantially lower than those observed with polycyclic benzylic alcohols. These results implied that both steric bulky at the β-position and π-π interactions might be important for the enantioselectivity. Ultimately, 1-naphthyl-methanol was chosen as the optimal alcohol for the rest of our studies.

Figure 3.13 Variation of alcohols



alcohols	conversion	ee	alcohols	conversion	ee
MeOH	76%	68%		95%	81%
i-PrOH	53%	71%			
	71%	75%		90%	91%
$PhCH_2OH$	72%	77%			
	65%	78%		94%	86%
	86%	76%		100%	90%
				80%	78%
				82%	81%

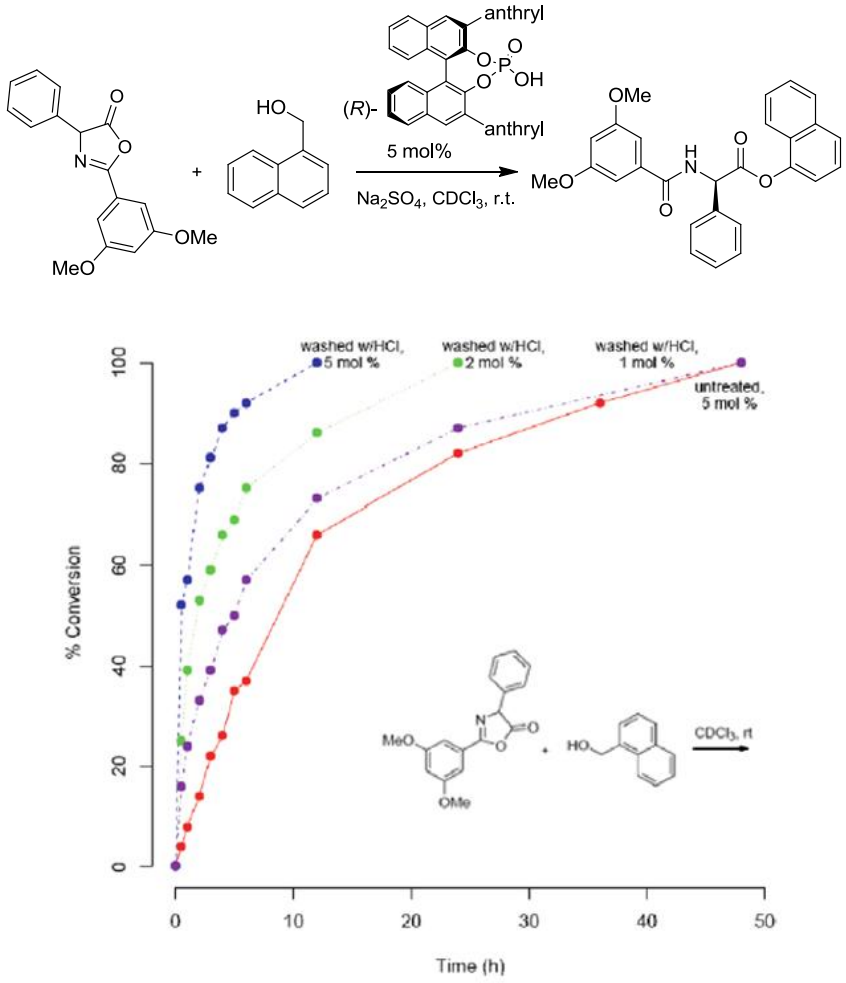
3.9 Reaction rate with catalysts treated and untreated by HCl

During the optimization process, it was interesting to find that the reaction rate was much faster with the catalyst washed by HCl than that purified by column chromatography (Silica gel, using CH_2Cl_2: Methanol=100:2 as the eluent). As shown in

Figure 3.14, the reaction was almost complete in 6 h with 5 mol% of the acid-washed catalyst, but took almost 2 days with the chromatographed catalyst.

We were interested in finding why the catalyst's activity depended so much on the method of preparation. However, almost at the same time, a paper published by Ishihara *et al.*[14] answered this question.

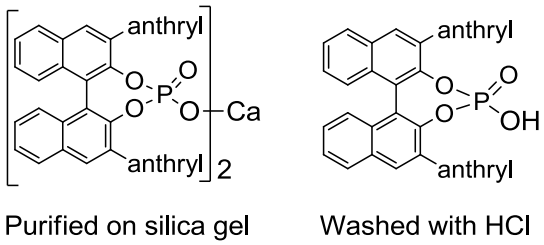
Figure 3.14 Influence of acid treatment on catalyst's activity



They mentioned that the catalyst purified by silica gel may contain calcium phosphorate salt which "may trigger unexpected excellent result" or decrease the reaction rate. Further study demonstrated that the catalyst purified by silica gel had similar catalytic activity and enantioselectivity with the calcium phosphorate. However, the

catalyst washed with HCl solution increased the reaction rate and decreased or even reversed the enantioselectivity. (Figure 3.15) The structure of calcium phosphorate salt was also confirmed by FAB-HRMS analysis.

Figure 3.15 Catalyst purified by silica gel



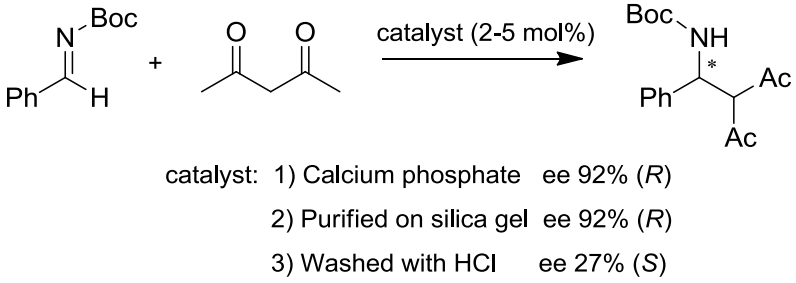
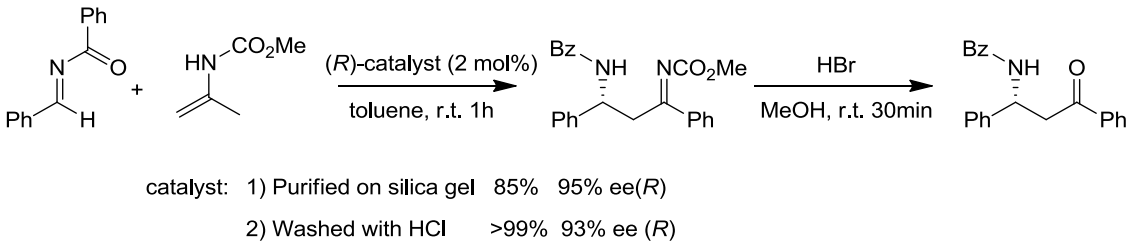


Figure 3.16 Terada's result



Recently, Terada[15] and co-workers reinvestigated their reactions published before with the catalyst washed by HCl and purified by silica gel. They agreed with Ishihara's results and pointed out that the differences between the acid-washed and chromatographed catalysts depend on the type of reaction. In Figure 3.16, they presented an example that the enantioselectivities of both catalysts were the same.

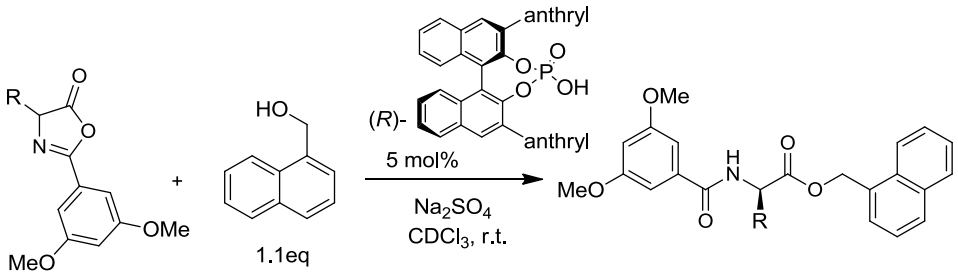
The phenomenon that the acid-washed catalysts increased the reaction rate was also observed by several other groups.[16]

Thus, it became clear to us that the catalyst we had used until now was calcium phosphorate, not the free phosphoric acid. However, the most important thing was not the catalytic activity, but enantioselectivity. We worried that the latter might drop dramatically using the catalyst washed with HCl solution. Fortunately, experimental results showed that enantioselectivity decreased only slightly (from 91% to 89%) with the acid-washed catalyst, while the reaction rate increased dramatically. Thus, the active catalyst was adopted for the rest of this study.

3.10 Substrate scope

After optimization of the reaction conditions, a series of representative substrates were investigated. As shown in Table 3.5, for the 4-phenyl substituted substrate, 89% ee value was obtained (entry 2). Low temperature (-20ºC) decreased the reaction rate, but didn't affect the enantioselectivity (entry 3).

Table 3.5 Substrate scope



Entry	Substrates (R)	Time (h)	Yield (%)	ee (%)
1	Ph	48	90	91 *
2	Ph	6	89	89
3	Ph	20	87	89 (-20°C)
4	4-ClC_6H_4	12	88	85
5	4-$MeOC_6H_4$	12	86	88
6	3-$MeOC_6H_4$	12	82	92
7	2-naphthyl	12	86	85
8	2-ClC_6H_4	24	88	91
9	2-$MeOC_6H_3$	24	86	89
10	1-naphthyl	24	86	91
11	Me	12	88	-8
12	Me	48	88	39*
13	*i*-Pr	12	84	50
14	Me	12	85	59**
15	*i*-Pr	12	83	29**

*****Using the chromatographed catalyst ** Using acid-washed (*R*)-TRIPS

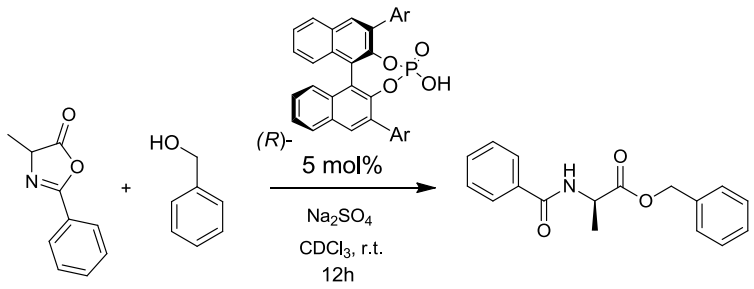
The new method is also applicable to other 4-aryl-azlactones cases (entries 4-10), for which 85~92% ee values were obtained. Substrates bearing an *ortho*-substitued aryl group on C4 reacted successfully, but required a longer reaction time (24h). By contrast, they failed to react in the presence of the chromatographed catalyst (see above) (entries 8-

10). It is also worth mentioning that the previously developed BTM-catalyzed method was ineffective for the same types of substrates.

It was interesting to find that opposite enantioselectivity (−8% ee) was observed for the 4-methyl-azlactone when it was catalyzed by the acid-washed catalyst (entry 11). However, when the chromatographed catalyst was used, +39% ee was obtained (entry 12). This observation was consistent with what had been mentioned in Ishihara's paper. For a more bulky alkyl-substituted substrate, 4-isopropyl-azlactone, 50% ee was obtained when it was catalyzed by the acid-washed catalyst (entry 13), but no reaction happened when using the catalyst purified on silica gel.

Still, the enantioselectivities in the case of alkyl-substituted azlactones were much lower than for the aryl-substituted ones. In an effort to find a better alternative, another widely used catalyst, (*R*)-TRIPS (also washed with HCl solution), was used on these substrates. An encouraging result (59% ee) was obtained for the 4-methyl-azlactone (entry 14). However, the enantioselectivity remained low (29% ee) in the case of 4-isopropyl-azlactone (entry 15). Testing several additional catalysts in the DKR of 4-methyl-azlactone with benzyl alcohol (Table 3.6) did not lead to any further improvement relative to the use of TRIPS in $CDCl_3$.

Table 3.6 Catalysts optimization of alkyl substrates

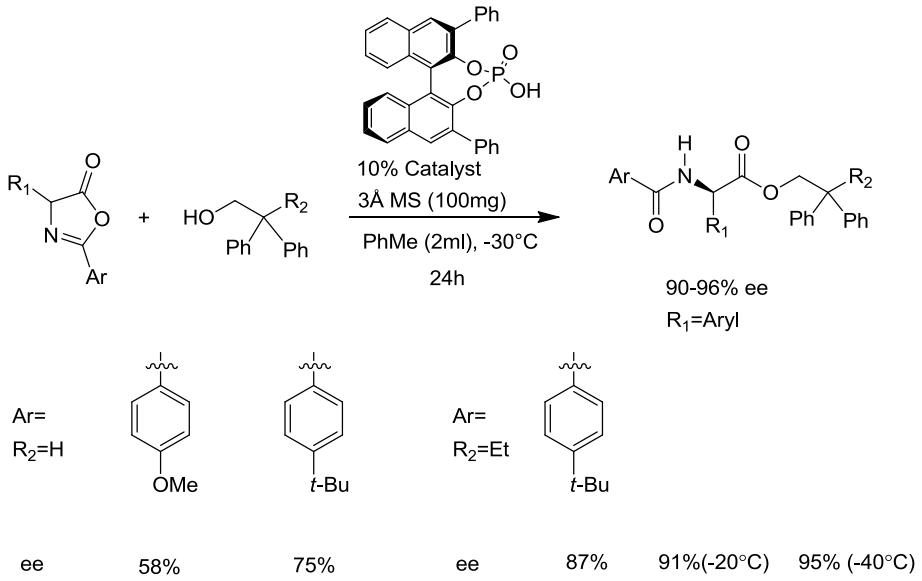


Entry	Catalyst	ee (%)
1	Vapol	6
2	9-anthracenyl	2 (7 in toluene)
3	9-phenanthryl	3
4	3,5-$(CF_3)C_6H_3$	4
5	$SiPh_3$	31
6	2,4,6-$(i\text{-}Pr)_3C_6H_2$	44 (24 in toluene)
7	10-phenyl-anthryl	9

3.11 A similar approach to the DKR of azlactones reported in the literature

Several months after our paper was published, another research group published a paper in *Synlett* using a similar method for the DKR of azlactones.[17] (Figure 3.17) They put a *para-t*-butylphenyl group on the C2 position of the substrates and used a rather elaborate bulky alcohol as the nucleophile to obtain 90-96% ee values for the 4-aryl-azlactones. Comparing their results with ours, we were happy to conclude that our protocol is more convenient and economical.

Figure 3.17 A similar approach to DKR of azlactones

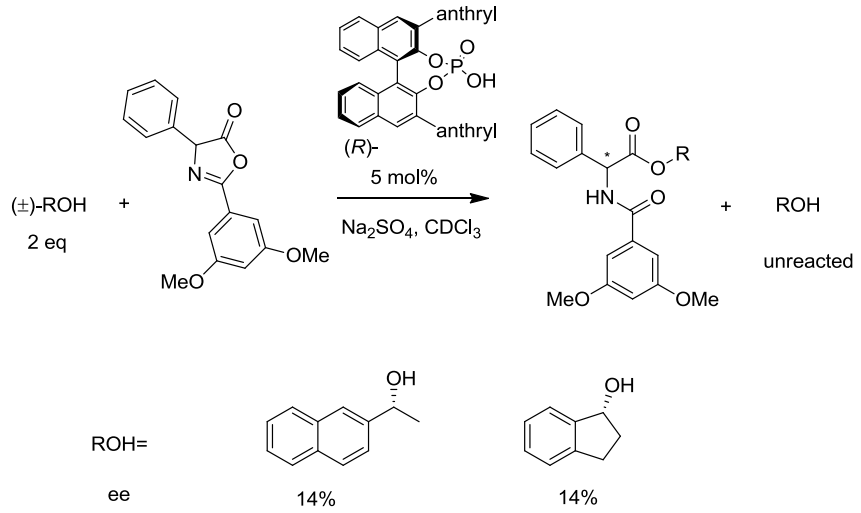


3.12 Acylation of racemic alcohols

With the achievement in the DKR of azlactones shown above, we wanted to explore a new idea: can a chiral secondary alcohol undergo enantioselective acylation under Brønsted acid catalysis?

As shown in Figure 3.18, (±)-4-phenyl-azlactone was subjected to alcoholysis with 2 eq of (±)-1-naphthalenemethanol. . After 3 days (catalyst purified on silica gel was used), the reaction was complete. Analysis of the unreacted alcohol showed that only 14% ee was obtained. An analogous experiment was performed using (±)-1-indanol (7 days) again producing 14% ee in the unreacted alcohol. The ester products formed in both cases as inseparable mixtures of diastereomers and were not analyzed further. Although only low ee's were obtained in these two cases, further systematic studies may lead to the identification of more successful substrates and conditions.

Figure 3.18 Acylation of racemic alcohols

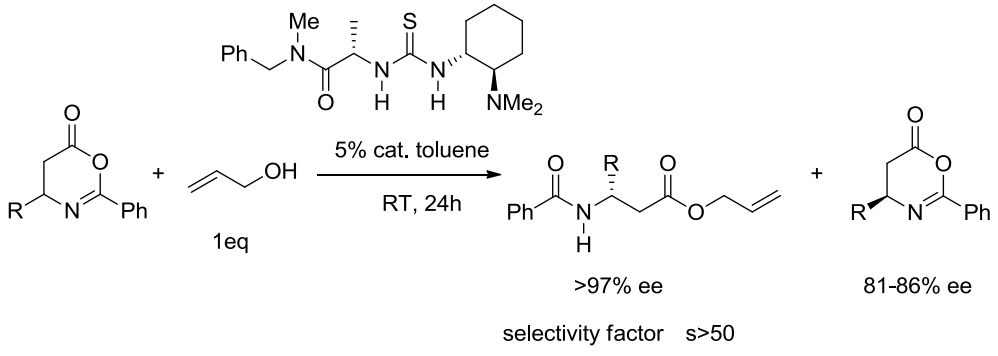


3.13 Brønsted acid catalyzed kinetic resolution of oxazinones

Encouraged by the high enatioselectivities achieved in the DKR of azlactones, we sought to test the application of our new method to the Kinetic Resolution of oxazinones, the six-membered ring analogues of azlactones.

Kinetic Resolution of oxazinones had already been reported by Berkessel *et al.*[18] Using their chiral thiourea as the catalyst, they obtained excellent selectivity factors. (Figure 3.19)

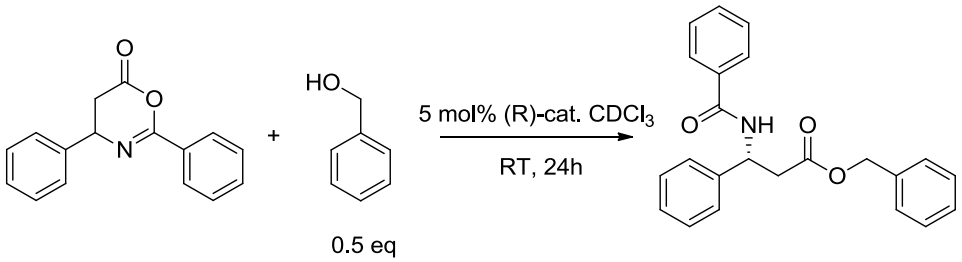
Figure 3.19 Kinetic resolution of oxazinones reported by Berkessel's group



3.13.1 Initial study

In the initial study, racemic 2,4-diphenyloxazinone was subjected to alcoholysis with 0.5 eq of benzyl alcohol in the presence of all available chiral phosphoric acids. As shown in Table 3.7, the reaction rate was lower than that of azlactone. Several catalysts showed similar and low enantioselectivities (s=~3) in this reaction (entries 2, 4, 6, 7).

Table 3.7 Kinetic Resolution of oxazinones

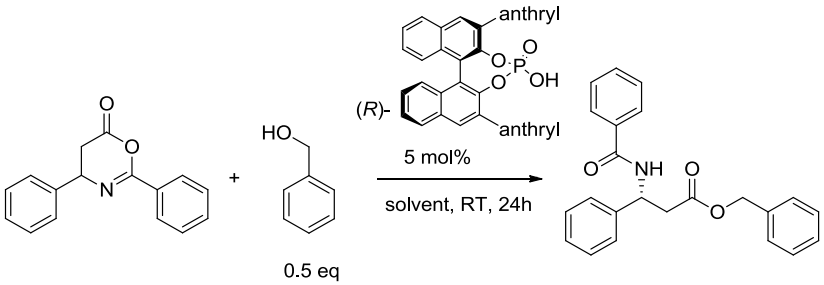


Entry	Catalyst	Ee of S.M.(%)	Ee of ester (%)	s	Con. (%)
1	3,5-$(CF_3)C_6H_3$	3	11	1.3	21
2	9-phenanthryl	21	41	2.9	34
3	$SiPh_3$	4	1	1.0	80
4	2,4,6-$(i\text{-}Pr)_3C_6H_2$	23	38	2.8	38
5	Ph	5	6	1.2	45
6	9-anthracenyl	30	41	3.2	42
7	9-phenyl-anthryl	30	38	2.9	44

3.13.2 Optimization of solvents

Because 9-antracenyl substituted BINOL phosphoric acid was available in large amount in our lab, it was used to optimize the reaction condition in the following study. As shown in Table 3.8, some improvement was achieved by carrying out the reaction in toluene or, even better, in a 1:3 $CDCl_3$-toluene mixture.

Table 3.8 Solvent effects

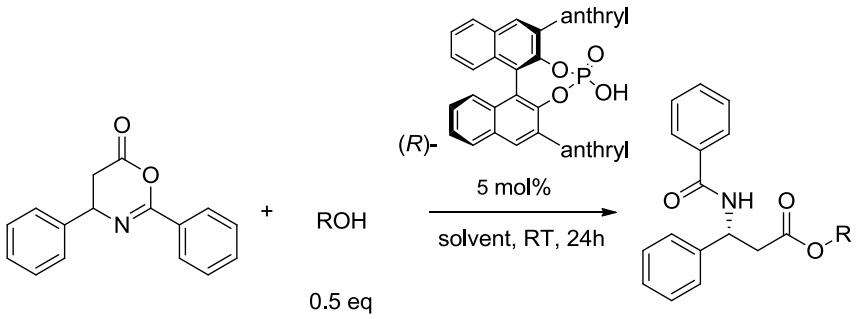


Entry	solvent	Ee of S.M. (%)	Ee of ester (%)	s	Conversion (%)
1	CD_3Cl	30	41	3.2	42
2	toluene	39	52	4.6	43
3	CD_3Cl/toluene=1/3	47	54	5.2	47

3.13.3 Alcohol effects

In the next step, several alcohols were tried in this reaction. As shown in Table 3.9, a small alcohol, methanol seems to be better than benzyl alcohol (entries 1-2). The secondary alcohol, isopropanol is much better than methanol under the same conditions (entries 4 and 2). An additional experiment showed that methanol achieves higher enanitoselectivity (s=9.2) in a mixture solvent (CD_3Cl/toluene=1/3) at 0ºC (entry 3).

Table 3.9 Alcohol effects

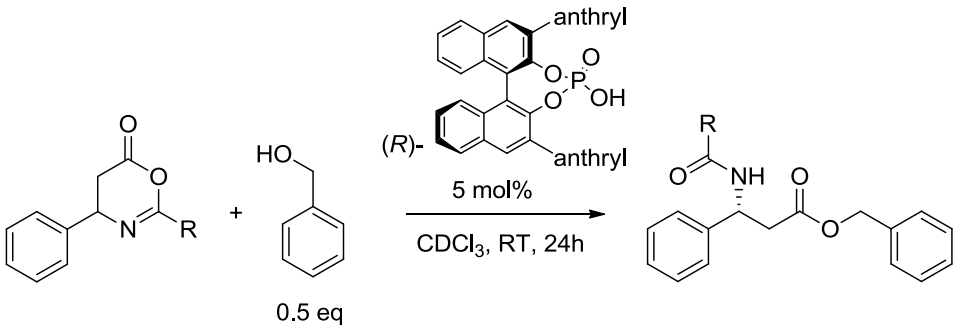


Entry	Alcohol	solvent	Ee of S.M. (%)	Ee of ester (%)	s	Conversion (%)
1	BnOH	toluene	39	52	4.6	43
2	MeOH	toluene	61	58	6.7	51
3	MeOH	$CDCl_3$/toluene=1/3 (0ºC,48h)	40	72	9.2	36
4	*i*-PrOH	toluene	60	67	9.2	47

3.13.4 Optimization of C2 substituent on the substrate

At the same time, the substitution effects on the substrates were also investigated. As shown in Table 3.10, replacement of the C2 phenyl group with 3,5-dimethoxyphenyl made no difference (entries1-2). However, some improvement was observed with *p*-chlorophenyl (entry 3). At this point, seeing that variation of several structural parameters and reaction conditions produces at best incremental increases in enantioselectivity, we decided to put this study on hold

Table 3.10 C2 substituent effects



Entry	R=	Ee of S.M. (%)	Ee of ester (%)	s	Conversion (%)
1	Ph	30	41	3.2	42
2	3,5-$(MeO)_2$Ph	27	41	3.1	40
3	4-ClPh	47	54	5.3	47

3.14 Conclusions

Chiral Brønsted acid catalysis has been applied to enantioselective acylation reactions for the first time. Its application to the Dynamic Kinetic Resolution of has been especially fruitful producing high yields and 85~92% ee values for the aryl-sbustituted-azlactones. Kinetic resolution of oxazinones under similar conditions was only modestly successful, giving a maximum selectivity factor of 9. Very low enantioselectivities were also obtained in a preliminary study on the KR of alcohols. However, these results still give us hope that new enantioselective acylation processes amenable to chiral Brønsted acid catalysis will be found in the future.

3.15 References

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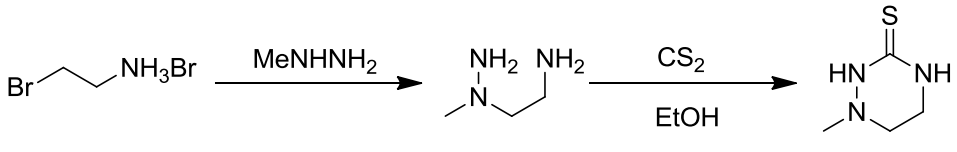
Chapter 4 Experimental

4.1 General.

Solvents used for chromatography were ACS or HPLC grade, as appropriate. Reactions were followed by thin layer chromatography (TLC) and by ^{1}HNMR. EM Science 60F silica gel plates were used for TLC analyses. Flash column chromatography was performed over ICN Ecochrom silica gel (32-63 mm). HPLC analyses were performed on a Shimadzu LC system using Chiralcel OD-H, Chiralpak AD and Chiralpak AD-H analytical chiral stationary phase columns (4.6x250 mm, Chiral Technologies, Inc.). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Mercury 300 MHz Varian spectrometer. The chemical shifts are reported as the values (ppm) relative to TMS using residual $CHCl_3$ peak (7.26 ppm) as the reference. High-Resolution mass spectral analyses were performed at Washington University MS Center on a Kratos MS-50TA spectrometer using Electro Spray Ionization (ESI) method. Melting points were measured on a Mel-Temp II capillary melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer Spectrum Bx FTIR spectrophotometer using potassium bromide plates.

4.2 Synthesis and exploration of THTP analogue for acyl transfer catalysis

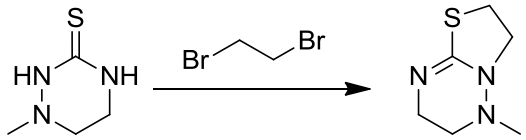
4.2.1 Preparation of THTP analogues



1. 30 1. 31 1. 32

To a solution of Bromoethylamine hydrobromide (2.05 g, 10mmol) in 10ml MeOH, was added a solution of methylhydrazine (2.11 ml, 40 mmol) at room temperature, the mixture was stirred at reflux for 7h, then cooled to room temperature, kept overnight. A solution of MeONa (1.35 g, 25 mmol) in 10 ml MeOH was added, stirred for 3h at room temperature. The mixture was concentrated to about 5ml, filtered to remove off the precipitate. The filtrate was concentrated to give a colorless liquid which was put to the next step without purification. To this liquid, was added 7ml of 50% EtOH solution and 1.5ml of CS_2 at room temperature. The mixture was stirred at refluxed overnight, cooled to room temperature. 2ml of conc. HCl was added, and kept at room temperature for overnight, a precipitate was formed, filtered to give a pale yellow powder which was washed with acetone to give 0.568g pale yellow powder, yield 43%.

^{1}HNMR (300 MHz, DMSO-d_6): δ 9.34(s, 1H), 8.10(s, 1H), 3.21-3.16(m, 2H), 2.85(t, *J*=6Hz, 2H), 2.46(s, 3H); **^{13}CNMR** (75 MHz, DMSO-d_6): δ 172.72, 47.93, 44.94, 36.07; **MS:** HR-ESI calculated for $C_4H_9N_3SH$ ($M+H^+$) m/z: 132.0590, found m/z: 132.0589;



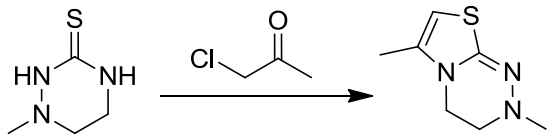
1. 32 **1. 19**

The mixture of compound **1.32** (262 mg, 2 mmol), 1,2-dibromoethane (0.15 ml, 1.8 mmol) and Na_2CO_3(0.636 g, 6 mmol) in 30ml of MeOH was stirred at reflux overnight, TLC showed that there was still a little amount of compound 1. Additional 1,2-dibromoethane (0.15 ml, 1.8 mmol) was added, continued to stir for 3h, TLC showed that the reaction was completed. The solvent was removed off to give a brown liquid which was dissolved in CH_2Cl_2, the organic phase was washed with sat. $NaHCO_3$ solution,

water and brine, then dried by Na_2SO_4. The crude product was purified by column chromatography (Neutral Al_2O_3, EtOAc) to give 155mg brown liquid, yield 50%.

^{1}HNMR (300 MHz, $CDCl_3$): δ 3.35(t, *J*=6Hz, 2H), 3.37(t, *J*=6Hz, 2H), 3.01(t, *J*=6Hz, 2H), 2.74(t, *J*=6Hz, 2H), 2.48(s, 3H); **^{13}CNMR** (75MHz, $CDCl_3$): δ 158.54, 53.10, 47.77, 44.19, 40.17, 24.17; **IR:** 3399.2, 2947.1, 2860.2, 1608.5; **MS:** HR-ESI calculated for $C_6H_{11}N_3SH$ ($M+H^+$) m/z:158.0746, found m/z:158.0745;

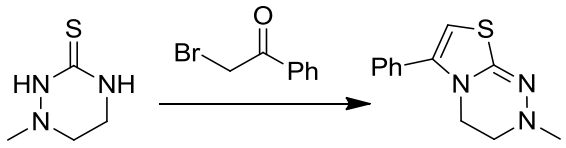
HMBC, HMQC, NOE: (See appendix)



1.32 **1.37**

The mixture of compound **1.32** (131 mg, 1 mmol), Na_2CO_3 (0.318 g, 3 mmol) and chloro acetone (96 ul, 1.2 mmol) in 20ml of EtOH was stirred at reflux overnight. The solvent was removed off to give a brown liquid which was dissolved in CH_2Cl_2. The organic phase was washed with sat. $NaHCO_3$, water and brine, dried by Na_2SO_4, purified by column chromatography (Neutral Al_2O_3, EtOAc) to give 80mg brown liquid, yield 47%.

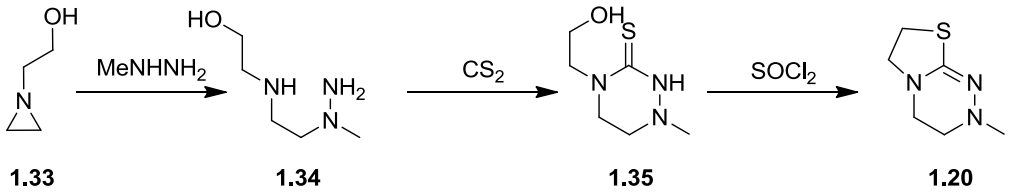
^{1}HNMR (300 MHz, $CDCl_3$): δ 5.26(s, 1H), 3.75(t, *J*=4.5Hz, 2H), 2.74(t, *J*=4.5Hz, 2H), 2.66(s, 3H); **^{13}CNMR** (75MHz, $CDCl_3$): δ 151.95, 134.15, 91.77, 48.12, 47.44, 43.99, 13.61; **IR:** 2930.39, 1726.7, 1262.3, 749.2; **MS:** HR-ESI calculated for $C_7H_{11}N_3SH$($M+H^+$) m/z:170.0746, found m/z: 170.0745;



1.32 **1.36**

The mixture of compound **1.32** (50 mg, 0.38 mmol) and bromo phenyl acetone(76 mg, 0.38 mmol) in 2 ml of EtOH was stirred at reflux overnight, the solvent was removed off to give a brown liquid which was dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$, water and brine, dried by Na_2SO_4, purified by column chromatography (Neutral Al_2O_3, EtOAc) to give 35 mg brown liquid, yield 40%.

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.38-7.30(m, 5H), 5.65(s, 1H), 3.73(t, *J*=6Hz, 2H), 2.75(s, 3H), 2.67(t, *J*=6Hz, 2H); **^{13}CNMR** (75MHz, $CDCl_3$): δ 152.30, 140.32, 130.70, 129.24, 129.01, 128.06; 95.77, 48.28, 47.48, 47.21; **IR:** 2953.1, 1605.6, 1358.6, 765.9; **MS:** HR-ESI calculated for $C_{12}H_{13}N_3SH$ ($M+H^+$) m/z: 232.0908, found m/z: 232.0902;



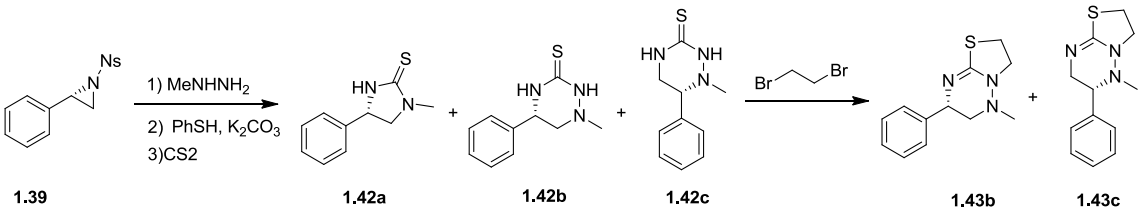
1.33 **1.34** **1.35** **1.20**

The mixture of 2-(aziridin-1-yl)ethanol (0.4 ml, 5 mmol), methylhydrazine (2.1 ml, 40 mmol) and 50 mg NH_4Cl was stirred at reflux overnight, the solvent and excess methylhydrazine were removed by rotavapor to give a colorless residue. To this residue, were added 20 ml CH_2Cl_2 and 2ml CS_2, the mixture was stirred at reflux overnight. The solvent and excess CS_2 were removed by rotavapor to give a brown liquid, 20 ml CH_2Cl_2 was added, the solution was washed with sat. $NaHCO_3$, water and brine, dried by Na_2SO_4, purified by column chromatography (Neutral Al_2O_3, EtOAc) to give 210 mg brown liquid, yield 27% for three steps.

^{1}HNMR (300 MHz, $CDCl_3$): δ 3.40(t, *J*=7.5Hz, 2H); 3.32(t, *J*=6Hz, 2H); 3.06(t, *J*=6Hz, 2H); 2.64(t, *J*=6Hz, 2H); 2.59(s, 3H); **^{13}CNMR** (75 MHz, $CDCl_3$): 150.27, 53.90, 48.95,

47.24, 46.43, 27.60; **IR:** 3390.4, 2949.1, 2858.7, 1613.3; **MS:** HR-ESI calculated for $C_6H_{11}N_3SH$ ($M+H^+$) m/z: 158.0746, found m/z: 158.0745;

HMBC, HMQC, NOE: (See appendix)



To a solution of Compound **1.39** (2.099 g, 6.0 mmol) in 30 ml THF, was added a solution of $MeNHNH_2$ (1.10 ml, 21 mmol) at 0°C, the mixture was warmed up to room temperature and stirred overnight, TLC showed that the reaction was completed. The solvent was removed off to give a brown residue. To this residue, was added 30ml CH_3CN, PhSH (1.0 ml, 10 mmol) and K_2CO_3 (1.60 g, 11.6 mmol), the mixture was kept stirring at 50°C for 3h or until TLC showed that the reaction was completed. The mixture was filtered, the filtrate was concentrated to give a brown residue. To this residue, was added 20 ml 50% EtOH and 10 ml of CS_2. The mixture was stirred at reflux overnight, the solvent and excess CS_2 was removed to give a residue, 20 ml of CH_2Cl_2 was added, the organic layer was washed with water, dried by Na_2SO_4, concentrated to give a crude product which was purified by column chromatography (Silica gel, EtOAc: Hexane=1:2) to give 400 mg brown solid which was a mixture of compound **1.42b** and **1.42c**, yield 28% for three steps.

To a mixture of **1.42b** and **1.42c** (27 mg, 0.13 mmol) in 3 ml EtOH, was added a solution of 1, 2-dibromoethane (22 µl, 0.26 mmol) and Na_2CO_3 (165 mg, 1.56 mmol), the mixture was stirred at reflux overnight, TLC showed that the reaction was completed. The solvent was removed to give a residue which was purified by column

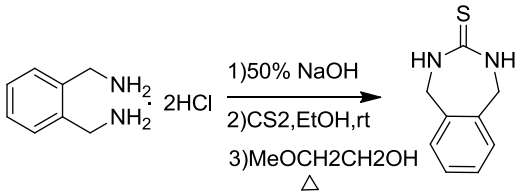
chromatography (Silica gel, EtOAc: Methanol=4:1) to give 9mg of compound **1.43b** and 10mg of compound **1.43c** respectively, yield 63%.

Characterization of compound 1.43b:

^{1}HNMR (600 MHz, $CDCl_3$): δ 7.30-7.19 (m, 5H), 4.45-4.43(m, 1H), 3.86-3.83(m, 1H), 3.64-3.59(m, 1H), 3.30-3.25(m, 1H), 3.07-3.00(m, 2H), 2.65(s, 3H), 2.60-2.56(m, 1H); **^{13}CNMR** (150MHz, $CDCl_3$): δ 159.79, 139.56, 128.58, 127.49, 127.01, 55.83, 52.96, 51.15, 44.64, 24.83; **IR**: 2922.1, 1604.2, 1580.5, 700.9; **MS:** HR-ESI calculated for $C_{12}H_{16}N_3SH$ ($M+H^+$) m/z: 234.1065, found m/z: 234.1060; **HMBC, HMQC, NOE:** (See appendix)

Characterization of compound 1.43c:

^{1}HNMR (600 MHz, $CDCl_3$): δ 7.33-7.18 (m, 5H), 3.94-3.90(m, 2H), 3.73-3.69(m, 1H), 3.66-3.63(m, 1H), 3.35-3.31(m, 1H), 3.06-3.02(m, 1H), 2.89-2.86(m, 1H), 2.52(s, 3H); **^{13}CNMR** (150 MHz, $CDCl_3$): δ 158.71, 138.32, 128.40, 127.98, 127.52, 59.21, 52.72, 42.58, 41.85, 24.21; **IR**: 2919.1, 2341.6, 1726.8, 1612.5, 739.91; **MS:** HR-ESI calculated for $C_{12}H_{16}N_3SH$ ($M+H^+$) m/z: 234.1065, found m/z: 234.1059; **HMBC, HMQC, NOE:** (See appendix)



1.44 **1.45**

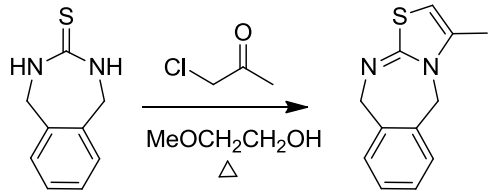
Compound **1.44** (2.09 g, 10 mmol) was dissolved in 10 ml H_2O, 5 ml of 50% NaOH solution was added, then the mixture was extracted with CH_2Cl_2, dried by Na_2SO_4, concentrated to give a brown liquid. To this liquid was added 20 ml EtOH and CS_2 (1.20 ml, 20 mmol). The mixture was stirred at room temperature overnight, the solvent was

removed to give a sticky solid. To this solid, was added 20 ml $MeOCH_2CH_2OH$. The mixture was stirred at reflux for 3h, cooled to room temperature, filtered to give 1.20 g white solid, yield 67%.

^{1}HNMR (300 MHz, DMSO-d_6): δ 8.13(s, 2H), 7.30-7.21(m, 4H), 4.34(d, *J*=6Hz, 4H);

^{13}CNMR (75 0MHz, DMSO-d_6): δ 179.44, 138.54, 128.77, 128.03, 46.11;

MS: HR-ESI calculated for $C_9H_{10}N_2SH$ ($M+H^+$) m/z: 179.0643, found m/z: 179.0639;



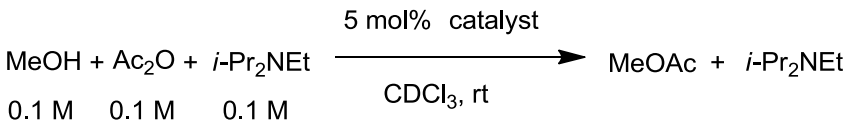
1.45 **1.29**

The mixture of compound **1.45** (89 mg, 0.5 mmol) and chloroacetone(48 μl, 0.6 mmol) in 5 ml $MeOCH_2CH_2OH$ was stirred at reflux for 3h. Then the mixture was cooled, the solvent was removed to give a brown liquid which was dissolved in CH_2Cl_2, the solution was washed with sat. $NaHCO_3$ solution, dried by Na_2SO_4, purified by column chromatography (Neutral Al_2O_3, EtOAc) to give 88 mg pale yellow solid, yield 81%.

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.34-7.17(m, 4H), 5.30(s, 1H), 4.89(s, 2H), 4.75(s, 2H), 2.05(s, 3H); **^{13}CNMR** (300MHz, $CDCl_3$): δ 161.63, 140.81, 134.60, 134.04, 129.22, 128.34, 127.94, 127.56, 93.41, 51.52, 48.16, 15.94;

MS: HR-ESI calculated for $C_{12}H_{12}N_2SH$ ($M+H^+$) m/z: 217.0799, found m/z: 217.0794;

4.2.2 Catalytic activities of THTP analogues for acylation of methanol



*Stock solution **A***: 0.25 M Ac_2O (24 µl, 0.25 mmol) in 1.0 ml $CDCl_3$.

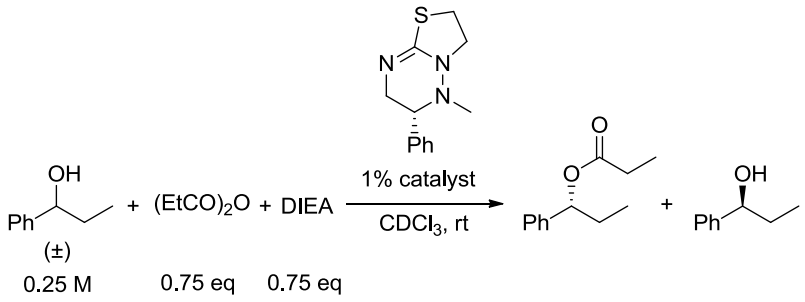
*Stock solution **B***: 0.25 M MeOH (10 µl, 0.25 mmol) and 0.25 M DIEA (44 µl, 0.25 mmol) in 1.0 ml $CDCl_3$.

*Stock solution **catalyst* (1.20)**: ***catalyst* (1.20)** (64 mg, 0.407 mmol) was dissolved in 8.14 ml $CDCl_3$ to make catalyst solution **(1)** (0.05 M). To 0.50 ml of catalyst solution **(1)**, was added 0.50 ml of $CDCl_3$ to make the *Stock solution **catalyst* (1.20)** (0.025 M).

The test was carried out by mixing 0.40 mL aliquots of *stock solutions **A***, *Stock solution **B*** and 0.20 ml of *Stock solution **catalyst* (1.20)** at room temperature and monitoring reaction progress by ^1H NMR. The time required to reach 50% conversion of MeOH into MeOAc was recorded as $t_{1/2}$ in Table **1.1**.

*Stock solution **catalyst* (1.36)** and ***catalyst* (1.37)** were prepared and tested according to the similar procedure. ***Catalysts* (1.19)** and **(1.29)** with different catalyst loading was tested according to the similar procedure.

4.2.3 Kinetic resolution of secondary alcohol catalyzed by chiral aza-analogues of THTP



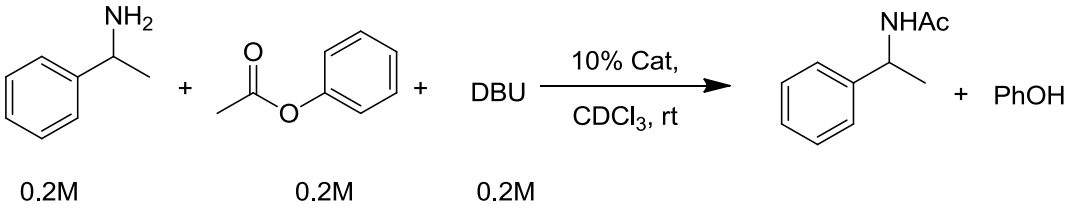
*Stock solution **catalyst***: To catalyst **1.43c** (13 mg, 0.056 mmol), was added 2.24 ml $CDCl_3$ to make *catalyst solution **A*** (0.025 M). To 0.20 ml of *catalyst solution **A***, was added 1.80 ml $CDCl_3$ to make 2.0 ml of *catalyst solution **B*** (0.0025 M).

To this 2.0 ml of *catalyst solution* ***B*** was added (±)-1-Phenylpropanol (68 µl, 0.5 mmol), propionic anhydride (48 µl, 0.375 mmol) and *i*-Pr_2Net (65 µl, 0.375 mmol) at room temperature. The reaction was monitored by ^{1}HNMR at room temperature by comparing integration values of peaks at δ 4.6 ppm and δ 5.7 ppm and stopped by pouring the contents into a vial with MeOH upon reaching conversion of 45-50%. The workup and HPLC analysis followed the standard procedure.

Time	#	ee_E %	ee_A %	C_{HPLC} %	s	C_{AVG} %	s_{AVG}
1.5h	1	55	46	45	5.4	46	5.5
	2	56	48	46	5.6		

4.3 Development of azoles derivatives for acyl transfer catalysis

4.3.1 General procedure for catalytic activity of catalysts

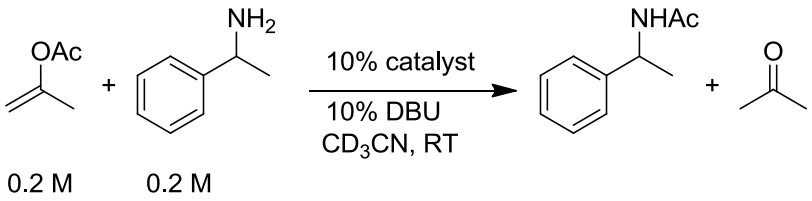


Stock solution ***A***: 0.4 M of phenyl acetate (253 µl, 2 mmol) and 0.4 M of α-phenethylamine (256 µl, 2 mmol) in 5.0 ml of $CDCl_3$.

Stock solution ***catalyst***: 0.04M of catalyst (0.2mmol) in 5.0ml of $CDCl_3$.

The test was carried out by mixing 0.50 ml aliquots of *stock solutions* ***A*** and ***catalyst*** at room temperature and monitoring reaction progress by ^{1}HNMR. The time required to reach 50% conversion of α-phenethylamine into *N*-α-phenethylacetamide was recorded as $t_{1/2}$.

4.3.2 Catalytic activities study by using isopropenyl acetate as acyl donor

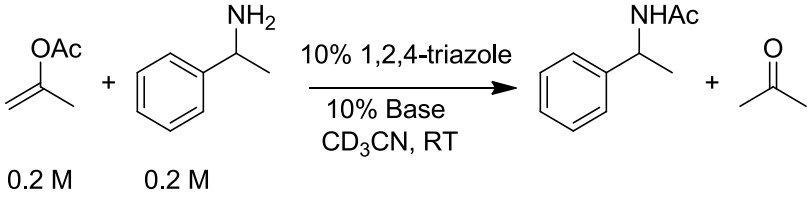


Stock solution ***catalyst***: 0.40 M of 1,2,4-triazole (55 mg, 0.80 mmol) and 0.40 M DBU (0.80 mmol, 120 µl) in 2 ml $CDCl_3$.

Stock solution of other ***catalysts*** can be prepared according to the similar procedure.

To 1ml of CD_3CN, were added isopropenyl acetate (22 µl, 0.20 mmol), α-phenethylamine (26 µl, 0.20 mmol) and 50 µl *Stock solution* ***catalyst***. Conversion of α-phenethylamine into N-phenethylacetamide was monitored by ^{1}HNMR until it reached its 50%.

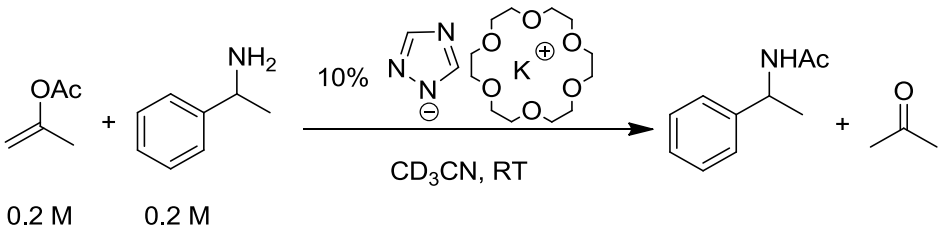
4.3.3 Catalytic activities of 1,2,4-triazole under different bases



Stock solution ***catalyst***: 0.40 M of 1,2,4-triazole (55 mg, 0.80 mmol) and 0.40 M of base (120 µl of DBU, or 99 µl of DBN or 111 mg of TBD) in 2 ml $CDCl_3$.

Catalytic activity test was carried out with the same procedure as that in **4.3.2**.

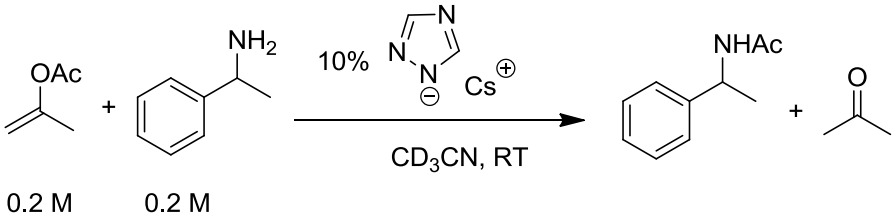
4.3.4 Catalytic activity of potassium 18-6-crown ether triazolide



Stock solution ***catalyst***: 0.40 M of potassium 18-6-crown ether triazolide (15 mg, 0.04 mmol) in 100 µl $CDCl_3$.

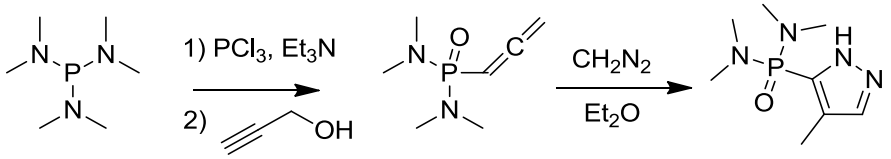
Catalytic activity test was carried out with the same procedure as that in **4.3.2**.

4.3.5 Catalytic activity of Cesium triazolide



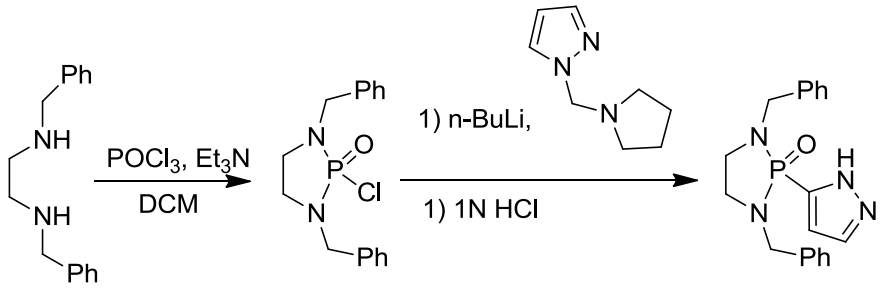
To 1ml of CD_3CN, were added isopropenyl acetate (22 µl, 0.20 mmol), α-phenethylamine (26 µl, 0.20 mmol) and Cesium triazolide (4 mg, 0.02 mmol) at room temperature. Conversion of α-phenethylamine into N-phenethylacetamide was monitored by ^{1}HNMR until it reached its 50%.

4.3.6 Preparation of Phosphoramide and phosphorate pyrazole derivatives



To a solution of PCl_3 (0.88 ml, 10 mmol) protected with Ar, was added a solution of HMPT (3.64 ml, 20 mmol) at 0ºC, the mixture was kept stirring for 2h. 30 ml of toluene was added, a solution of propargyl alcohol (1.75 ml, 30 mmol) and Et_3N (4.20 ml, 30 mmol) was added at 0ºC. The mixture was warmed up to room temperature, stirred at room temperature for 2h, then was stirred at 50 ºC for 1h, filtered to remove the precipitate. The filtrate was concentrated, purified by column chromatography (silica gel EtOAc:MeOH=10:1) to give 2.88 g pale yellow to colorless liquid which was put to the next step immediately. To a solution of this Allene phosphoramide **2.23** (0.23 g, 1.36 mmol) in 8 ml Et_2O was added a solution of CH_2N_2 (2.04 mmol) solution at 0ºC. The mixture was kept at 0ºC for 6 days, NMR showed that the conversion was about 60%. The solution was concentrated to give sticky crude product which was purified by column chromatography (silica gel EtOAc:MeOH=5:1) to give 50 mg of white solid.

^{1}HNMR (600 MHz, $CDCl_3$): δ 7.46(s, 1H), 2.67(s, 6H), 2.64(s, 6H), 2.20(s, 3H); **^{13}CNMR** (150MHz, $CDCl_3$): δ 138.56, 131.79, 120.84, 35.88, 9.52; **IR:** 2930, 2359, 1296, 1169, 982, 743; **MS:** HR-ESI calculated for $C_8H_{17}N_4OPH$ ($M+H^+$) m/z: 217.1218, found m/z: 217.1216; **HMBC, HMQC:** (See appendix)



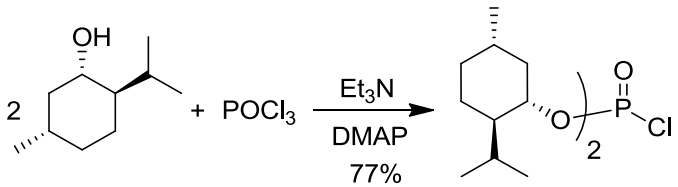
2.25 **2.26** **2.18**

To a solution of diamine **2.25** (1.808 g, 7.5 mmol) in 20 ml CH_2Cl_2, was added a solution of $POCl_3$ dropwise at 0ºC, the mixture was warmed up to room temperature, kept

stirring overnight, filtered. The filtrated was concentrated to give a residue which was dissolved in Et_2O, filtered again. The filtrate was concentrated to give a pale yellow liquid as the crude product, then the crude product was purified by column chromatography (silica gel Hexane:EtOAc=3:1) to give 1.908 g colorless liquid as the product which was put the next step immediately, yield 79%.

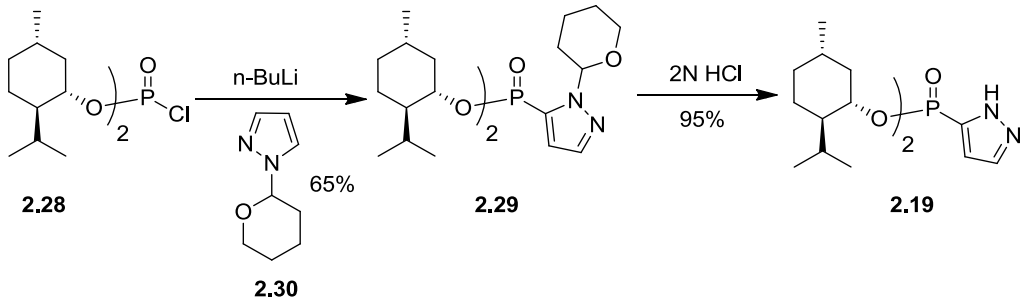
To a solution of 1-(pyrrolidin-1-ylmethyl)-1H-pyrazole (0.302 g, 2 mmol) in 10 ml anhydride THF, was added a solution of n-BuLi (0.96 ml, 2.4 mmol) at -78 ºC, then the mixture was stirred for 1h, a solution of phosphoramide chloride compound **2.26** (0.641 g, 2 mmol) in 5 ml THF was added at -78 ºC. The mixture was warmed up to room temperature, kept stirring overnight. Then the reaction was quenched with H_2O, extracted with ethyl acetate, washed with water and brine, dried by Na_2SO_4, concentrated to give a yellow sticky liquid as the crude product which was purified by column chromatography(Silica gel EtOAc:Methanol=10:1 to give 116 mg white powder as the product, yield 16%.

^{1}HNMR (600 MHz, $CDCl_3$): δ 8.13(s, 1H), 7.21-7.10(m, 10H), 6.79(s, 1H), 4.16-3.81(m, 4H), 3.29-3.05(m, 4H); **^{13}CNMR** (150 MHz, $CDCl_3$): δ 154.28, 140.12, 139.80, 138.83, 131.23, 131.08, 130.71, 130.35, 130.04, 115.45, 51.75, 51.25, 47.40, 46.64; **IR:** 2857, 1495, 1454, 1214, 1150, 728; **MS:** HR-ESI calculated for $C_{19}H_{21}N_4OPH$ ($M+H^+$) m/z: 353.1531, found m/z: 353.1526;



2.27 **2.28**

To a mixture of menthol (3.018 g, 19.3 mmol), Et_3N (3.23 ml, 23.2 mmol) and DMAP (0.236g, 1.93 mmol) in 30 ml CH_2Cl_2, was added a solution of $POCl_3$ (0.89 ml, 9.7 mmol) at 0 ºC, the mixture was warmed up to room temperature, kept stirring overnight. The mixture was washed with water and brine, dried by Na_2SO_4, concentrated to give a brown liquid as the crude product which was purified by column chromatography (Silica gel, EtOAc:Hexane=1:10) to give 2.942 g colorless liquid as the product, yield 77%. This compound was put to the next step immediately.

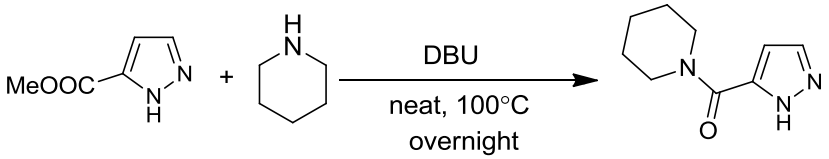


To a solution of compound **2.30** (152 mg, 1 mmol) in 5 ml THF, was added a solution of n-BuLi at -78 ºC, the mixture was kept stirring at -78 ºC for 2.5h. A solution of compound **2.28** (0.393 g, 1 mmol) in 5 ml THF was added. The mixture was warmed up to room temperature, kept stirring overnight. The reaction was quenched with water, the mixture was extracted with ethyl acetate, the organic phase was washed with water and brine, dried by Na_2SO_4, concentrated to give a brown liquid as the crude product which was purified by column chromatography(Silica gel EtOAc:Hexane=1:10) to give 0.33 g colorless liquid, yield 65%.

To a solution of compound **2.29** (0.240 g, 0.472 mmol) in 5 ml MeOH, was added 2N HCl solution drop by drop to adjust the pH=2, the mixture was kept stirring for 2h, TLC indicated that the reaction was completed, a solution of sat. $NaHCO_3$ was added to adjust the pH=7, then the solvent was removed off to give a residue. 20 ml of ethyl acetate was

added, the solution was washed with water and brine, dried by Na_2SO_4, concentrated to give 0.176 g white powder as the product, yield 95%.

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.94(s, 1H), 6.65(s, 1H), 4.38-4.27(m, 1H), 4.17-4.06(m, 1H), 2.36(d, *J*=12Hz, 1H), 2.30(m, 1H), 2.05(d, *J*=12Hz, 1H), 1.91-1.86(m, 1H), 1.66-1.54(m, 4H), 1.40-0.72(m, 25H), 0.40(d, *J*=6Hz, 3H); **^{13}CNMR** (75MHz, $CDCl_3$): δ 110.3, 78.5, 78.0, 48.8, 43.7, 43.0, 34.3, 31.7, 25.6, 22.1, 21.1, 16.0, 15.5; **IR:** 2954, 1726, 1456, 1231, 991; **MS:** HR-ESI calculated for $C_{23}H_{41}N_2O_3PNa$ ($M+Na^+$) m/z: 447.2752, found m/z: 447.2749; **HMBC, HMQC:** (See appendix)



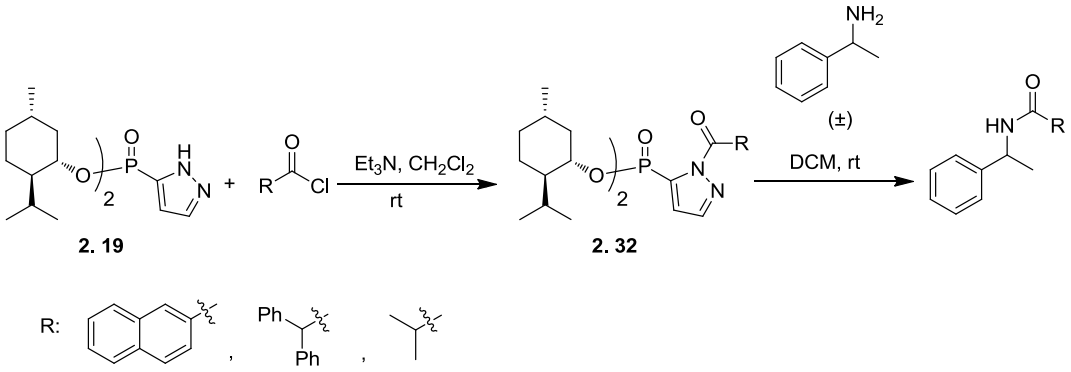
2.12 **2.31** **2.13**

56%

A mixture of compound 2.21 (189 mg, 1.5 mmol) and 2.31 (180 µl, 1.8 mmol) was heated at 100°C overnight. The product was purified by column chromatography (EtOAc: Hexane=2:1) to give 150 mg white powder as the product, yield 56%

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.56(s, 1H), 3.37(s, 4H), 1.65(s, 6H); **^{13}CNMR** (75MHz, $CDCl_3$): δ 106.8, 48.4, 43.9, 26.8, 25.9, 24.8; **IR:** 3205, 1601, 1507, 1214; **MS:** HR-ESI calculated for $C_9H_{13}N_3OH$ ($M+H^+$) m/z: 180.1131, found m/z: 180.1153;

4.3.7 Enantioselectivies of menthyl phosphorate pyrazole derivative



The mixture of compound **2.19** (176 mg, 0.41 mmol), 2-Naphthoyl chloride (79 mg, 0.41 mmol) and Et_3N (69 µl, 0.5 mmol) in 5 ml CH_2Cl_2 was stirred at room temperature overnight, TLC indicated that the reaction was completed. The solvent was removed to give a residue. To this residue was added Et_2O, the mixture was filtered to removed off the triethylammonium hydrochloride salt. The filtrate was concentrated to give 0.246 g white powder.

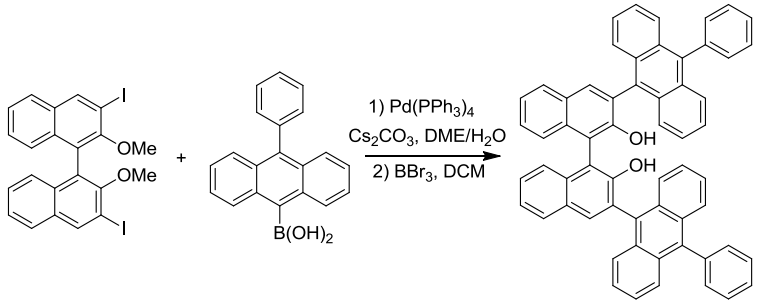
To a solution of compound **2.32** in 5 ml CH_2Cl_2, was added a solution of α-phenethylamine (159 µl, 1.23 mmol) at room temperature. The mixture was stirred for 1h, TLC showed that the reaction was completed. The mixture was concentrate to give a residue which was purified by column chromatography (Silica gel, EtOAc:Hexane=1:4) to give a white solid as the product. HPLC analysis showed that 0% ee was obtained.

The similar procedure was applied to the reactions using 2,2-Diphenylacetyl chloride and Isobutanoyl chloride as the acylating agents.

4.4 Chiral Brønsted Acid Catalyzed Dynamic Kinetic Resolution of Azlactones

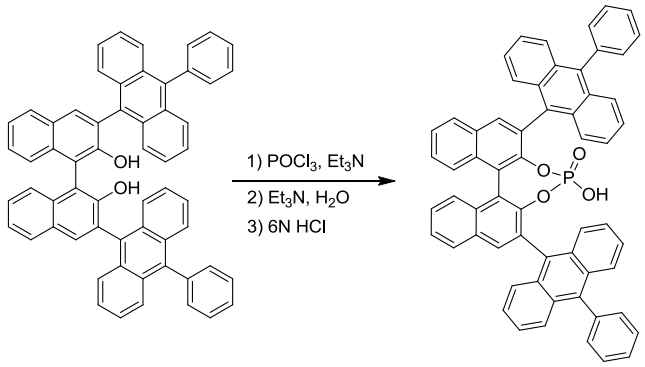
4.4.1 Synthesis of new catalyst

(*R*)-3,3'-bis-(9-phenylanthracen-10-yl)-2,2'-dihydroxy-1,1'-binapthyl.



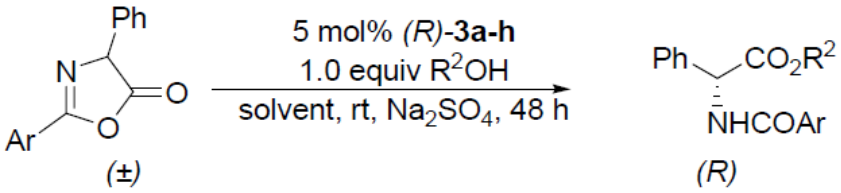
To a mixture of *(R)*-3,3'-diiodo-2,2'-dimethoxy-1,1'-binapthyl[1a] (297 mg, 0.53 mmol), 9-phenylanthracen-10-ylboronic acid[3] (650 mg, 2.18 mmol), $Pd(PPh_3)_4$ (66 mg, 0.053 mmol) and Cs_2CO_3 (1.04 g, 3.18 mmol) was added 32 mL of degassed aqueous 1,2-dimethoxyethane (DME/H_2O=3/1) under argon. Then the mixture was stirred under reflux for 24 h, cooled to roomtemperature, extracted with CH_2Cl_2, filtered through Celite, washed with saturated aqueousNH_4Cl solution, water, and brine, dried with Na_2SO_4 and concentrated on a rotary evaporator. The resulting crude intermediate was dissolved in 20 mL of CH_2Cl_2 and treated at 0 ºC with BBr_3 (0.35 mL, 3.71 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. It was then quenched with water, washed with saturated aqueous $NaHCO_3$, water, and brine, dried by Na_2SO_4, and rotary evaporated. Column chromatography (Hexane/EtOAc = 20:1) gave 0.35 g of beige powder (83% yield). **^{1}HNMR** (300 MHz, CDCl3):δ 8.10 (s, 2H), 7.98-7.92 (m, 4H), 7.78-7.71 (m, 6H), 7.65-7.37 (m, 20H), 7.34-7.23 (m, 4H) ; **^{13}CNMR** (75 MHz, CDCl3): δ 151.34, 139.07, 138.59, 134.21, 133.47, 131.48, 131.06, 130.77,130.72, 130.36, 130.31, 129.62, 128.76, 128.67, 127.82, 127.72, 127.68, 127.63, 127.52, 126.50, 126.43, 126.12, 125.49, 125.19, 124.56, 113.77; **IR** (KBr, cm-**1**) 3529, 3059, 1497, 1438, 1379,1259, 1208, 1091, 1025, 912, 770, 747, 702,611. **MS:** HR-ESI calculated for C60H38O2 [M+Na]:813.2764, found: 813.2763. **[**α**]D** = +69.7° (*c* 0.4, CH_2Cl_2)

***(R)*-3,3'-bis-(9-phenylanthracen-10-yl)-1,1'-binapthyl-2,2'-diyl-phosphoric acid.**



To a solution of the BINOL derivative prepared above (100 mg, 0.126 mmol) in 15 mL of CH_2Cl_2 stirring at 0 ºC was added Et_3N (88 µl, 0.630 mmol), followed by $POCl_3$ (18 µl, 0.190 mmol), and the mixture was allowed to warm to room temperature and stirred overnight, whereupon the reaction was complete by TLC. The mixture was treated with 2 mL of Et_3N and 10 mL of H_2O stirred for one more day and acidified with 6N HCl to adjust the pH to 2. After stirring for 2h, the mixture was washed with H2O and brine, dried by Na2SO4, and rotary evaporated. Column chromatography (CH_2Cl_2/MeOH=100:1 to 100:2) yielded 85 mg of the product as pale orange powder (79% yield). **^{1}HNMR** (300 MHz, CDCl3): δ 7.97 (s, 2H), 7.90 (d, *J*=7.8 Hz, 2H), 7.82 (d, *J*=8.4 Hz, 2H), 7.71 (d, *J*=8.1 Hz, 2H), 7.56-7.18 (m, 20H), 7.07-7.05 (m, 4H), 6.75-6.70 (m, 2H), 6.47-6.44 (m, 2H); **^{13}CNMR** (75 MHz, CDCl3): δ 148.19, 138.98, 137.60, 133.51, 133.24, 132.83, 131.56, 131.40, 130.53, 130.23, 129.68, 129.61, 128.75, 128.58, 127.80, 127.43, 127.17, 127.06, 126.51, 126.24, 126.14, 125.90, 125.30, 125.05, 124.60, 123.27; **IR** (KBr, cm-**1**) 3629, 3300, 3061, 2360, 1599, 1496, 1441, 1381, 1254, 1110, 1097, 911, 771, 744, 703. **MS:** HR-ESI calculated for C60H37O4P [M+Na]: 875.2322, found: 875.2322. **[**α**]D**= +119.1° (*c* 0.96, CH_2Cl_2)

4.4.2 Optimization of the DKR procedure



To a mixture of a freshly prepared azlactone substrate (0.10 mmol), an alcohol indicated (0.10 mmol) and *ca.* 50 mg of anhydrous sodium sulfate, was added a solution of a catalyst (0.005 mmol) in 1 mL of a solvent. The reaction mixture was stirred at room temperature for 2 days, while the reaction progress was monitored by ^{1}H NMR and/or TLC. After the reaction was complete, the mixture was applied directly to a silica gel column and eluted with hexane/CH_2Cl_2/EtOAc (50:15:15). Enantiomeric excess was determined by direct HPLC analysis of the ester product.

4.4.3 Comparison of untreated and activated forms of catalyst

Untreated catalyst. Catalyst was purified by chromatography (CH_2Cl_2/MeOH = 100:2). Solvent removal left yellow, compact residue, which was taken up in CH_2Cl_2, diluted with hexanes and evaporated again to dryness to produce flocculent, off-white powder.

Acid-washed catalyst. A solution of the purified catalyst in CH_2Cl_2 (see above) was shaken in a separatory funnel with 4M aqueous HCl, separated from the aqueous layer, dried over Na_2SO_4, diluted with hexane and evaporated to dryness.

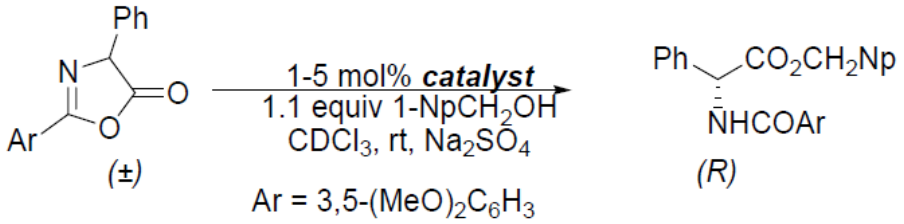


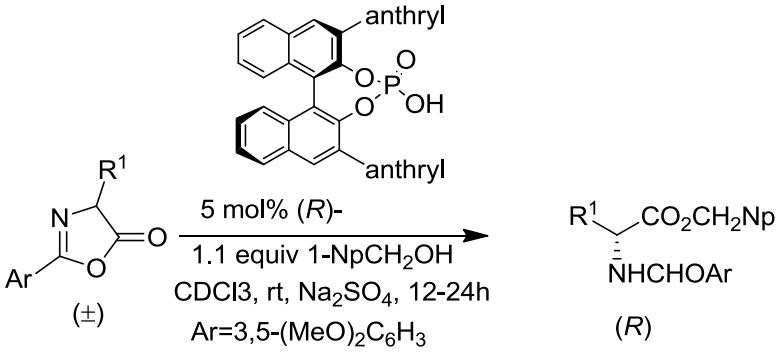
Table 1S.

Time (h)	Untreated catalyst, 5 mol%	Catalyst washed w/HCl, 5 mol%	Catalyst washed w/HCl, 2 mol%	Catalyst washed w/HCl, 1 mol%
0.5	4	52	25	16
1	8	57	39	24
2	14	75	53	33
3	22	81	59	39
4	26	87	66	47
5	35	90	69	50
6	37	92	75	57
12	66	100	86	73
24	82	-	100	87
36	92	-	-	-
48	100	-	-	100
%ee	90.3	89.0	88.6	88.0

Catalytic activity measurements. Stock solutions of both forms of catalyst in $CDCl_3$ (0.005 M) were prepared. These were added separately to identically prepared mixtures of azlactone (0.10 mmol), 1-naphthylmethanol (0.10 mmol), and Na_2SO_4. The solutions were transferred into NMR tubes and checked by ^1H NMR at time intervals indicated below, monitoring peaks at δ 5.5 ppm (singlet, starting material) and δ 5.8 ppm (doublet, product). The test was conducted analogously with lower catalyst loadings of acid-washed catalyst (using 0.002 M and 0.001 M stock solutions, respectively). In each case,

enantiomeric purity of the product was determined. The data shown in on the graph in Figure 2 are listed in Table 1S.

4.4.4 Optimized DKR procedure (Acid-washed catalyst)



To a mixture of a freshly prepared azlactone substrate (0.10 mmol), 1-naphthylmethanol (0.11 mmol), and *ca.* 50 mg of Na_2SO_4, was added a solution of catalyst (0.005 mmol, *washed w/HCl*) in 1 mL of $CHCl_3$. After 12-24 h, the mixture was applied directly to a silica gel column and eluted with hexane/CH_2Cl_2/EtOAc (10:3:3). Enantiomeric excess of the ester products was determined either directly by HPLC analysis or (for R_1 = *i*-Pr) after LAH reduction to the alcohol.

4.4.5 Absolute configuration of the products

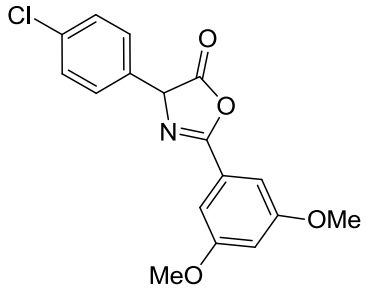
Absolute configuration of the major enantiomer was determined in the case of esters with R_1 =Ph, Me and *i*-Pr by HPLC comparison with authentic samples derived from commercially available amino acids. In the case of other e with R_1 = Aryl, the absolute configuration was assigned by analogy with R_1 = Ph.

4.4.6 Synthesis of azlactones

General procedure

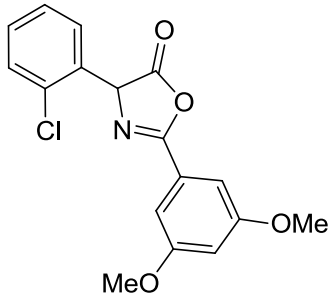
To a suspension of *N*-3, 5-dimethoxylbenzoyl amino acid (1 mmol) in 15 ml CH_2Cl_2, was added a solution of 1, 3-dicyclohexylcarbodiimide (0.206 g, 1 mmol) in 10 ml CH_2Cl_2 at 0℃, then warmed up to room temperature. The mixture was continued to stir at room temperature for about 2h, then filtered to remove the 1, 3-dicyclohexylurea. The filtrate was washed with sat. $NaHCO_3$ and brine, dried by Na_2SO_4 and concentrated to about 2 ml which was filter through Acrodisc. Then about 20 ml of hexane was added, kept in the freezer overnight, the mother liquid was removed and the azlactone was dried by vaccum.

All yields were unoptimized.



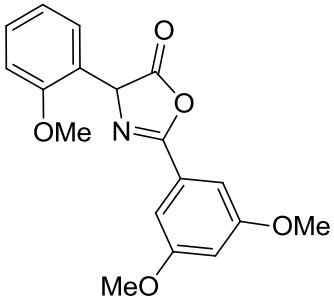
4-(4-chlorophenyl)-2-(3,5-dimethoxyphenyl)oxazol-5(4H)-one: 79% yield of pale powder.

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.40 (s, 4H), 7.23-7.22 (m, 2H), 6.71-6.70 (m, 1H), 5.50 (s, 1H), 3.86 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.96, 163.02, 161.31, 135.08, 132.06, 129.44, 128.42, 127.35, 106.38, 105.96, 67.72, 55.94; **IR**(thin film): 2938, 2359, 1829, 1651, 1596, 1206, 1158, 911; **MS**: HR-ESI calculated for $C_{17}H_{14}ClNO_4H$ ($M+H^+$) m/z: 332.0684 found: m/z: 332.0686.



4-(2-chlorophenyl)-2-(3,5-dimethoxyphenyl)oxazol-5(4H)-one: 90% yield of pale powder.

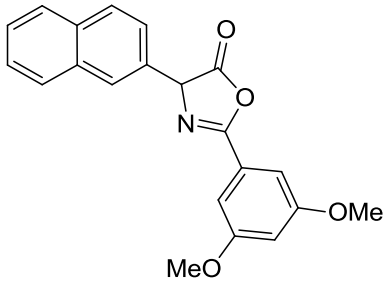
^{1}HNMR (300 MHz, $CDCl_3$): δ 7.49-7.46 (m, 1H), 7.37-7.22 (m, 5H), 6.70-6.68 (m, 1H), 5.88 (s, 1H), 3.85 (s, 6H); **^{13}CNMR** (75 MHz, $CDCl_3$): δ 175.35, 163.45, 161.28, 134.35, 131.64, 130.73, 130.61, 129.96, 127.65, 127.42, 106.46, 105.88, 67.40, 55.92; **IR**(thin film): 2937, 2359, 1831, 1648, 1594, 1205, 1158, 1039, 911; **MS**: HR-ESI calculated for $C_{17}H_{14}ClNO_4H$ ($M+H^+$) m/z: 332.0684 found: m/z: 332.0685.



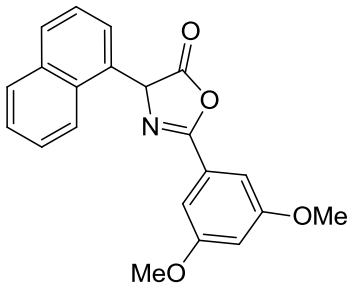
2-(3,5-dimethoxyphenyl)-4-(2-methoxyphenyl)oxazol-5(4H)-one: 92% yield of pale powder.

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.39-7.29 (m, 2H), 7.20-7.19 (m, 2H), 7.02-6.96 (m, 1H), 6.90 (d, *J*=8.1 Hz, 1H), 6.62-6.65 (m, 1H), 5.49 (s, 1H), 3.82 (s, 6H), 3.76 (s, 3H); **^{13}CNMR** (75 MHz, $CDCl_3$): δ 177.20, 162.56, 161.19, 157.77, 130.99, 127.97, 122.50, 121.38, 111.79, 106.09, 105.73, 66.83, 55.90; **IR**(thin film): 2937, 2359, 1829, 1650,

1595, 1157, 1040, 931; **MS**: HR-ESI calculated for $C_{18}H_{17}NO_5H$ ($M+H^+$) m/z: 328.1179, found: m/z: 328.1191.



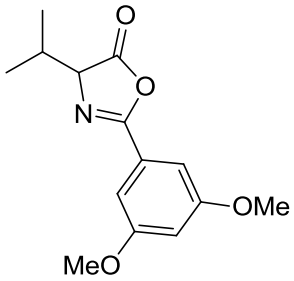
2-(3,5-dimethoxyphenyl)-4-(naphthalen-2-yl)oxazol-5(4H)-one: 69% yield of pale yellow powder. **^{1}HNMR** (300 MHz, $CDCl_3$): δ 7.91-7.84 (m, 4H), 7.56-7.50 (m, 3H), 7.28 (d, *J*=2.4 Hz, 2H), 6.72 (t, J=2.1 Hz, 1H), 5.69 (s, 1H), 3.87 (s, 6H); **^{13}CNMR** (75 MHz, $CDCl_3$): δ 176.33, 162.88, 161.31, 133.51, 130.93, 129.25, 128.32, 127.99, 126.82, 126.45, 124.43, 106.36, 105.98, 66.67, 55.95; **IR**(thin film): 2936, 2360, 1829, 1651, 1595, 1205, 1157, 1045, 909; **MS**: HR-ESI calculated for $C_{21}H_{17}NO_4H$ ($M+H^+$) m/z: 348.1230, found: m/z: 348.1232.



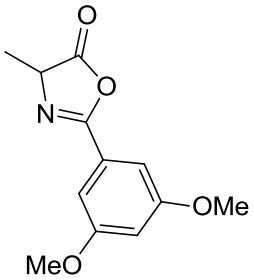
2-(3,5-dimethoxyphenyl)-4-(naphthalen-1-yl)oxazol-5(4H)-one: 59% yield of pale powder.

^{1}HNMR (300 MHz, $CDCl_3$): δ 8.18 (d, *J*=8.4 Hz, 1H), 7.94-7.88 (m, 2H), 7.68-7.55 (m, 2H), 7.49-7.40 (m, 2H), 7.28 (d, *J*=2.7 Hz, 2H), 6.72-6.70 (m, 1H), 6.28 (s, 1H), 3.86 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.04, 162.97, 161.30, 134.40, 131.27, 129.92,

129.66, 129.16, 127.62, 127.18, 126.47, 125.53, 125.16, 123.89, 106.37, 105.92, 66.29, 55.92; **IR**(thin film): 2938, 2359, 1826, 1651, 1595, 1205, 1158, 1036, 912; **MS**: HR-ESI calculated for $C_{21}H_{17}NO_4H$ ($M+H^+$) m/z: 348.1230, found: m/z: 348.1231.



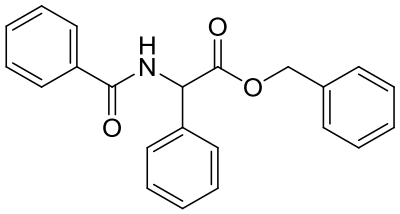
2-(3,5-dimethoxyphenyl)-4-isopropyloxazol-5(4H)-one: 78% yield of white powder recrystalized from hexane. **^{1}HNMR** (300 MHz, $CDCl_3$): δ 7.15-7.14 (m,2H), 6.65 (s, 1H), 4.28 (d, *J*=4.2 Hz, 1H), 3.84 (s, 6H), 2.41-2.35 (m, 1H), 1.14 (d, *J*=6.6 Hz, 3H), 1.02 (d, *J*=6.9 Hz, 3H); **^{13}CNMR** (75 MHz, $CDCl_3$): δ 177.93, 161.80, 161.19, 127.83, 105.88, 105.69, 71.02, 55.88, 31.49, 18.39, 17.80; **IR**(thin film): 2938, 2359, 1826, 1651, 1595, 1205, 1158, 1036, 912; **MS**: HR-ESI calculated for $C_{14}H_{17}NO_4H$ ($M+H^+$) m/z: 264.1230, found: m/z: 246.1232.



2-(3,5-dimethoxyphenyl)-4-methyloxazol-5(4H)-one: 64% yield of white powder. **^{1}HNMR** (300 MHz, $CDCl_3$): δ 7.12 (d, *J*=2.1 Hz, 2H), 6.65-6.64 (m, 1H), 4.45 (AB,1H), 3.83 (s, 6H), 1.59 (d, *J*=7.5 Hz, 3H); **^{13}CNMR** (75 MHz, $CDCl_3$): δ 179.09, 161.71, 161.19, 127.76, 105.99, 105.63, 61.35, 55.85, 17.10; **IR**(thin film): 2938, 2359, 1826,

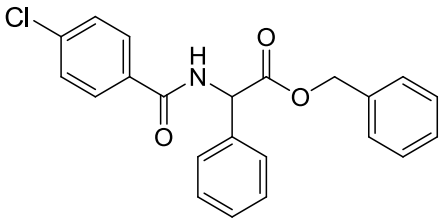
1651, 1595, 1205, 1158, 1036, 912; **MS**: HR-ESI calculated for $C_{12}H_{13}NO_4H$ ($M+H^+$) m/z: 236.0917, found: m/z: 236.0919.

4.4.7 Characterization data and HPLC properties of the products



benzyl 2-benzamido-2-phenylacetate:

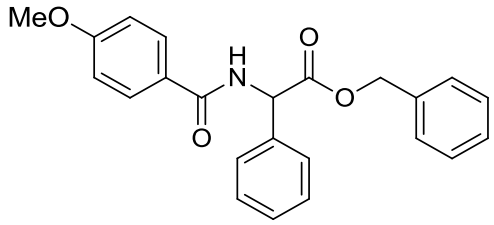
^{1}HNMR (300 MHz, $CDCl_3$): δ 7.74-7.71 (m, 2H), 7.44-7.10 (m, 13H), 5.75 (d, *J*=7.2 Hz, 1H), 5.13 (A of AB, J_{AB}=12.6 Hz, 1H), 5.09 (B of AB, J_{AB}=12.6 Hz, 1H); **^{13}CNMR** (75 MHz, $CDCl_3$): δ 171.13, 166.79, 136.75, 135.34, 133.88, 132.10, 129.23, 128.84, 128.77, 128.61, 128.18, 127.62, 127.41, 67.77, 57.17; **IR**(thin film): 3319, 3062, 1742, 1644, 1520, 1485, 1327, 1171, 696; **MS**: HR-ESI calculated for $C_{22}H_{19}NO_3H$ ($M+H^+$) m/z: 346.1445, found: m/z: 346.1438. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (R)-enantiomer: 27.1 min; (S)-enantiomer: 33.8 min.



benzyl 2-(4-chlorobenzamido)-2-phenylacetate:

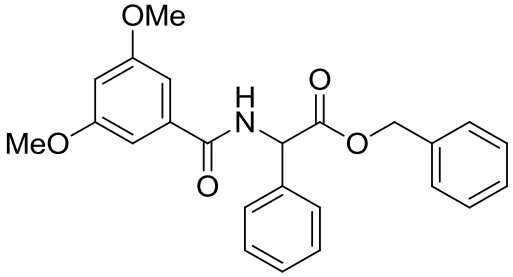
^{1}HNMR (300 MHz, $CDCl_3$): δ 7.77-7.74 (m, 2H), 7.42-7.28 (m, 9H), 7.23-7.19 (m, 2H), 7.13 (d, *J* = 6.6 Hz, 1H), 5.80 (d, *J* = 6.9 Hz, 1H), 5.19 (A of AB, J_{AB}=12 Hz, 1H), 5.17 (B of AB, J_{AB}=12 Hz, 1H); **^{13}CNMR** (75 MHz, $CDCl_3$): δ 171.02, 165.71, 138.40, 136.53, 135.23, 132.23, 129.26, 129.11, 128.90, 128.82, 128.77, 128.64, 128.17, 127.58, 100.08,

67.85, 67.20; **IR**(thin film): 3323, 3033, 2922, 1739, 1639, 1525, 1484, 1172, 696; **MS**: HR-ESI calculated for $C_{22}H_{18}ClNO_3H$ ($M+H^+$) m/z: 380.1048 found: m/z: 380.1035. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (R)-enantiomer: 8.8 min; (S)-enantiomer: 19.8 min.



benzyl 2-(4-methoxybenzamido)-2-phenylacetate

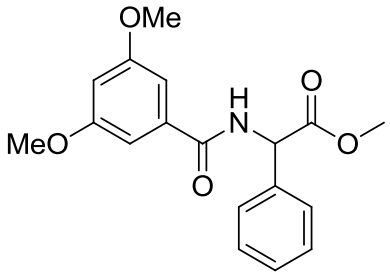
^{1}HNMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.7 Hz, 2H), 7.43-7.29 (m, 8H), 7.22-7.19 (m, 2H), 7.23-7.19 (m, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 6.6 Hz, 1H), 5.82 (d, *J* = 6.9 Hz, 1H), 5.22 (A of AB, J_{AB}=12 Hz, 1H), 5.18 (B of AB, J_{AB}=12 Hz, 1H), 3.84 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.25, 166.29, 162.72, 136.90, 135.36, 129.24, 129.18, 128.74, 128.57, 128.14, 127.59, 126.14, 114.02, 67.71, 57.11, 55.64; **IR** (KBr, cm^{-1}) 3317, 2922, 1741, 1641, 1606, 1496, 1254, 1175, 697; **MS**: HR-ESI calculated for $C_{23}H_{21}NO_4H$ ($M+H^+$) m/z: 376.1543, found m/z: 376.1536; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (R)-enantiomer: 11.9 min; (S)-enantiomer: 24.6 min.



benzyl 2-(3,5-dimethoxybenzamido)-2-phenylacetate

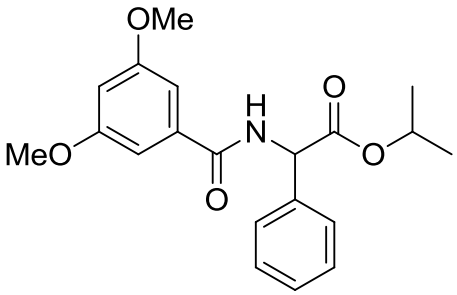
^{1}HNMR (300 MHz, $CDCl_3$): δ 7.43-7.26 (m, 8H), 7.23-7.16 (m,2H), 6.94-6.93 (m, 2H), 6.59-6.57 (m, 1H), 5.80 (d, *J* = 6.9 Hz, 1H), 5.22 (A of AB, J_{AB}=12 Hz, 1H), 5.18 (B of

AB, J_{AB}=12 Hz, 1H), 3.80 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.99, 166.65, 161.13, 136.63, 136.05,135.32, 129.21, 128.82, 128.76, 128.59,128.16, 127.61, 105.32, 104.23, 67.75, 57.24, 55.81; **IR** (KBr, cm^{-1}) 3315, 2923, 1743, 1648, 1594, 1521, 1205,1157,697; **MS**: HR-ESI calculated for $C_{24}H_{23}NO_5H$ ($M+H^+$) m/z: 406.1649, found m/z: 406.1643; **HPLC** (CHIRALCEL OD-H, IPA/hexane= 3/10, 1.0 mL/min): (S)-enantiomer: 18.9 min; (R)-enantiomer: 28.0 min.



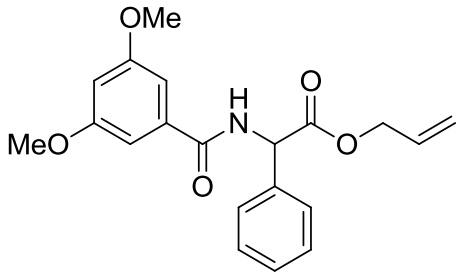
methyl 2-(3,5-dimethoxybenzamido)-2-phenylacetate

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.45-7.34 (m, 5H), 7.12 (d, J = 6.6 Hz, 1H), 6.94-6.93 (m, 2H), 6.59-6.57 (m, 1H), 5.74 (d, J = 6.9 Hz, 1H), 3.81 (s, 6H), 3.76 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.82, 166.82, 161.33,136.90, 136.22, 129.46, 129.06, 127.76, 105.52, 104.37, 57.31, 56.02, 53.33; **IR** (KBr, cm^{-1}) 3315, 2923, 1743, 1648, 1594, 1521, 1205, 1157, 697; **MS**: HR-ESI calculated for $C_{18}H_{19}NO_5H$ ($M+H^+$) m/z: 330.1336, found m/z: 330.1327; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 15.6 min; (R)-enantiomer: 18.1 min.



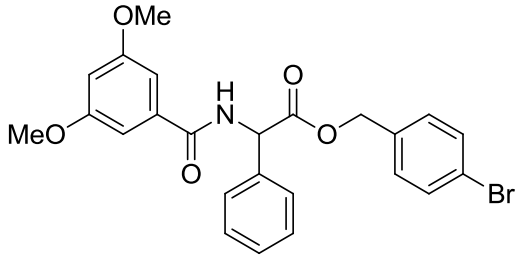
isopropyl 2-(3,5-dimethoxybenzamido)-2-phenylacetate

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.44-7.25 (m, 5H), 7.14 (d, *J* = 6.9 Hz, 1H), 6.94-6.93 (m, 2H), 6.59-6.57 (m, 1H), 5.69 (d, *J* = 6.6 Hz, 1H), 5.12-5.04 (m, 1H), 3.81 (s, 6H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.12 (d, *J*= 6.0 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.63, 166.55, 161.12, 137.03, 136.21, 129.11, 128.63, 127.43, 105.29, 104.15, 70.09, 57.20, 55.82, 21.94, 21.57; **IR** (KBr, cm^{-1}) 3319, 2922, 1737, 1651, 1594, 1520, 1456, 1354, 1206, 1157, 1105, 1064, 698; **MS**: HR-ESI calculated for $C_{20}H_{23}NO_5H$ ($M+H^+$) m/z: 358.1649, found m/z: 358.1636; **HPLC** (CHIRALCEL AS-H, IPA/hexane=2/10, 1.0 mL/min): (S)-enantiomer: 11.3min; (R)-enantiomer: 14.2 min.



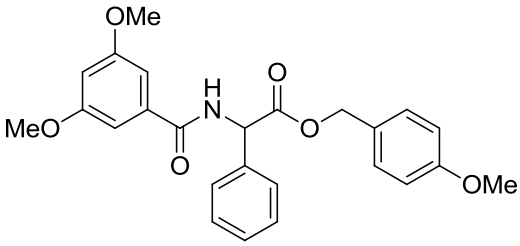
allyl 2-(3,5-dimethoxybenzamido)-2-phenylacetate

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.46-7.31 (m, 5H), 7.13 (d, *J* = 6.9 Hz, 1H), 6.94-6.93 (m, 2H), 6.59-6.57 (m, 1H), 5.91-5.79 (m, 1H), 5.76 (d, *J* = 6.9 Hz, 1H), 5.24-20 (m, 1H), 5.18-5.17 (m, 1H) 4.68-4.64 (m, 2H), 3.81 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.83, 166.62, 161.13, 136.69, 136.05, 131.47, 129.24, 128.85, 118.94, 105.31, 104.19, 66.54, 57.19, 55.81; **IR** (KBr, cm^{-1}) 3313, 2921, 1742, 1646, 1594, 1521, 1455, 1352, 1205, 1157, 1054, 699; **MS**: HR-ESI calculated for $C_{20}H_{21}NO_5H$ ($M+H^+$) m/z: 356.1492, found m/z: 356.1483; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (R)-enantiomer: 31.8 min; (S)-enantiomer: 58.8 min.



4-bromobenzyl 2-(3,5-dimethoxybenzamido)-2-phenylacetate

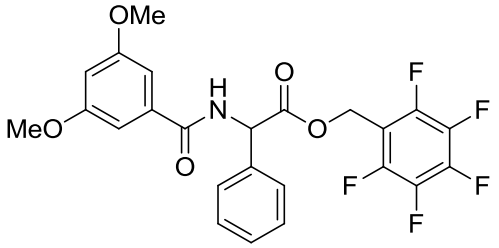
^{1}HNMR (300 MHz, $CDCl_3$): δ 7.43-7.33 (m, 7H), 7.11-7.04 (m, 3H), 6.93-6.92 (m, 2H), 6.59-6.58 (m, 1H), 5.76 (d, *J* = 6.9 Hz, 1H), 5.13 (s, 2H), 3.80 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.88, 166.70, 161.14, 136.40, 135.94, 134.36, 131.91, 129.76, 129.29, 128.96, 127.61, 122.64, 105.32,104.20, 66.86, 57.27, 55.82; **IR** (KBr, cm^{-1}) 3315, 2922, 1744, 1652, 1594, 1519, 1455, 1352, 1205, 1157, 1069, 698; **MS**: HR-ESI calculated for $C_{24}H_{22}BrNO_5H$ ($M+H^+$) m/z: 484.0754, found m/z: 484.0735; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 24.4 min; (R)-enantiomer: 41.7 min.



4-methoxybenzyl 2-(3,5-dimethoxybenzamido)-2-phenylacetate

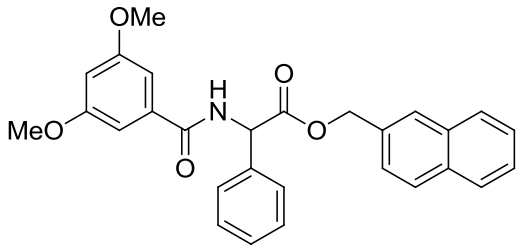
^{1}HNMR (300 MHz, $CDCl_3$): δ 7.40-7.32 (m, 4H), 7.19-7.12 (m, 3H), 6.85-6.82 (m, 2H), 6.59-6.57 (m, 1H), 5.17 (A of AB, J_{AB}=12 Hz, 1H), 5.10 (B of AB, J_{AB}=12 Hz, 1H), 3.81 (s, 6H), 3.79 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.23, 166.59, 161.13, 159.97, 136.71, 136.09, 130.13, 129.17, 128.76, 127.56, 114.14, 105.30,104.20, 67.71, 57.19, 55.80, 55.48; **IR** (KBr, cm^{-1}) 3316, 2918, 2849, 1739, 1653, 1593, 1514, 1456, 1352,

1248, 1205, 1157, 1064, 1032, 822, 699; **MS**: HR-ESI calculated for $C_{25}H_{25}NO_6H$ ($M+H^+$) m/z: 436.1755, found m/z: 436.1769; **HPLC** (CHIRALCEL OD-H, IPA/hexane=2/10, 1.0 mL/min): (S)-enantiomer: 27.4 min; (R)-enantiomer: 36.4 min.



perfluorobenzyl 2-(3,5-dimethoxybenzamido)-2-phenylacetate

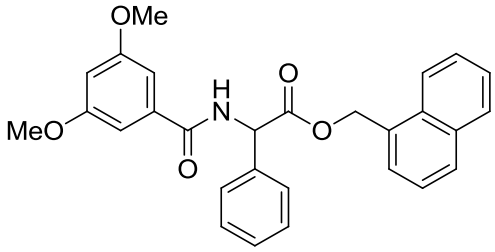
^{1}HNMR (300 MHz, $CDCl_3$): δ 7.38-7.33 (m, 5H), 6.97 (d, *J* = 6.6 Hz, 1H), 6.92-6.91 (m, 2H), 6.59-6.58 (m, 1H), 5.73 (d, *J* = 6.9 Hz, 1H), 5.28 (s, 2H), 3.81 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.50, 166.75, 161.15, 135.84, 135.80, 129.29, 129.08, 127.48, 105.31, 104.22, 57.16, 55.81, 54.72; **IR** (KBr, cm^{-1}) 3316, 2921, 1751, 1657, 1594, 1523, 1508, 1456, 1353, 1206, 1157, 1061, 941, 698; **MS**: HR-ESI calculated for $C_{24}H_{18}F_5NO_5H$ ($M+H^+$) m/z: 496.1178, found m/z: 496.1172; **HPLC** (CHIRALCEL AD-H, IPA/hexan=2/10, 1.0 mL/min): (S)-enantiomer: 15.3 min; (R)-enantiomer: 31.3 min.



naphthalen-2-ylmethyl 2-(3,5-dimethoxybenzamido)-2-phenylacetate

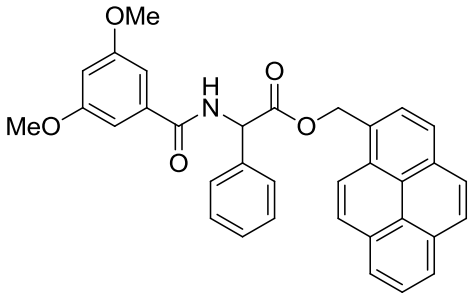
^{1}HNMR (300 MHz, $CDCl_3$): δ 7.83-7.72 (m, 3H), 7.62 (s, 1H), 7.51-7.42 (m, 4H), 7.36-7.34 (m, 3H), 7.31-7.28 (m, 1H), 7.15 (d, *J* = 6.6 Hz, 1H), 6.95-6.94 (m, 2H), 6.59-6.58 (m, 1H), 5.83 (d, *J* = 6.9 Hz, 1H), 5.34 (s, 2H), 3.80 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.00, 166.66, 161.14, 136.65, 136.05, 133.33, 133.30, 132.77, 129.26, 128.88, 128.59,

128.21, 127.90, 127.64, 127.16, 126.54, 125.54, 105.30, 104.23, 67.80, 57.30, 55.82; **IR** (KBr, cm^{-1}) 3318, 2920, 1741, 1652, 1594, 1510, 1455, 1353, 1205, 1156, 1064, 698; **MS**: HR-ESI calculated for $C_{28}H_{25}NO_5H$ ($M+H^+$) m/z: 456.1805, found m/z: 456.1816; **HPLC** (CHIRALCEL OD-H, IPA/hexane=4/10, 1.0 mL/min): (S)-enantiomer: 30.1 min; (R)-enantiomer: 42.3 min.



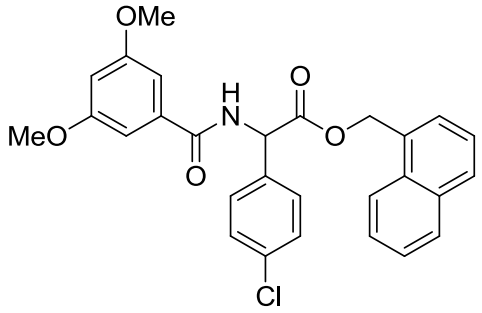
naphthalen-1-ylmethyl 2-(3,5-dimethoxybenzamido)-2-phenylacetate

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.87-7.82 (m, 2H), 7.77-7.74 (m, 1H), 7.51-7.37 (m, 6H), 7.32-7.28 (m, 3H), 7.2 (d, *J* = 6.9 Hz, 1H), 6.95-6.93 (m, 2H), 6.59-6.58 (m, 1H), 5.79 (d, *J* = 6.9 Hz, 1H), 5.64 (s, 2H), 3.78 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.04, 166.68, 161.13, 136.52, 136.05, 133.88, 131.67, 130.72, 129.76, 129.18128.85, 128.80, 127.68, 127.58, 126.82, 126.19, 125.36,123.63, 105.33, 104.24, 66.46, 57.34, 55.82; **IR** (KBr, cm^{-1}) 3327, 2920, 1740, 1651, 1594, 1512, 1456, 1353, 1263, 1205, 1156, 1063, 1049, 792, 776; **MS**: HR-ESI calculated for $C_{28}H_{25}NO_5H$ ($M+H^+$) m/z: 456.1805, found m/z: 456.1814; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 24.8 min; (R)-enantiomer: 46.1 min.



pyren-1-ylmethyl 2-(3,5-dimethoxybenzamido)-2-phenylacetate

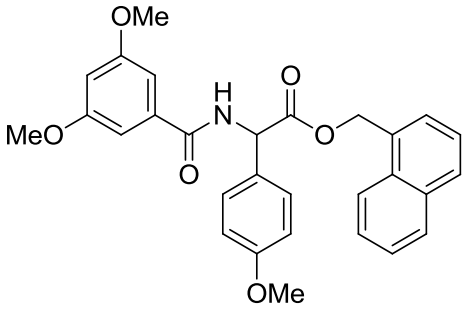
^{1}HNMR (300 MHz, $CDCl_3$): δ 8.21-8.19 (m, 2H), 8.11-8.00 (m, 6H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.39-7.36 (m, 3H), 7.26-7.24 (m, 2H), 7.13 (d, *J* = 6.9 Hz, 1H), 6.92-6.91 (m, 2H), 6.57-6.55 (m, 1H), 5.89 (s, 2H), 5.81 (d, *J* = 6.9 Hz, 1H), 3.76 (s, 6H); **^{13}C NMR** (75 MHz,$CDCl_3$): δ 171.06, 166.66, 161.10, 136.49, 136.04, 132. 11, 131.38, 130.86, 129.73, 129.17, 128.78, 128.45,128.17, 128.02, 127.84, 127.54, 126.32, 125.77, 125.74,125.02, 125.76, 124.70, 122.90, 195.29, 104.20, 66.68, 57.39, 55.79; **IR** (KBr, cm^{-1}) 3329, 2922, 1734, 1639, 1593, 1520, 1455, 1352, 1260, 1205, 1156, 1064, 844, 750; **MS**: HR-ESI calculated for $C_{34}H_{27}NO_5Na$ ($M+Na^+$) m/z: 552.1781, found m/z: 552.1805; **HPLC** (CHIRALCEL OD-H, IPA/hexane=4/10, 1.0 mL/min): (S)-enantiomer: 22.8 min; (R)-enantiomer: 40.7 min.



naphthalen-1-ylmethyl 2-(4-chlorophenyl)-2-(3,5-dimethoxybenzamido)acetate

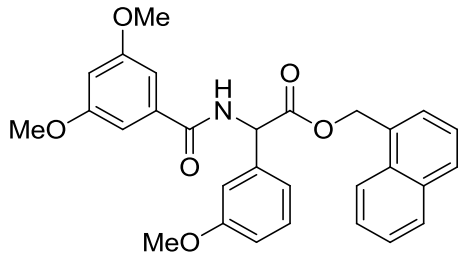
^{1}HNMR (300 MHz, $CDCl_3$): δ 7.87-7.83 (m, 2H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.52-7.47 (m, 4H), 7.43-7.37 (m, 5H), 7.28-7.18 (m, 5H), 6.91 (d, *J* = 2.4 Hz, 2H), 6.59-6.57 (m, 1H), 5.72 (d, *J* = 6.6 Hz, 1H), 5.65 (A of AB, J_{AB}=12 Hz, 1H), 5.62 (B of AB, J_{AB}=12 Hz, 1H)), 3.79 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.64, 166.56, 161.16, 135.80, 135.17, 134.67, 133.89, 131.63, 130.43, 129.95,129.24, 128.89, 128.82, 127.99, 126.85, 126.26, 125.30,123.49, 105.29, 104.29, 66.77, 56.67, 55.81; **IR** (KBr, cm^{-1}) 3299, 2923, 1740, 1644, 1594, 1513, 1492, 1352, 1205, 1157, 1091, 1064, 794, 775; **MS**: HR-ESI

calculated for $C_{28}H_{24}ClNO_5H$ ($M+H^+$) m/z: 490.1416, found m/z: 490.1410; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 35.6 min; (R)-enantiomer: 47.9 min.



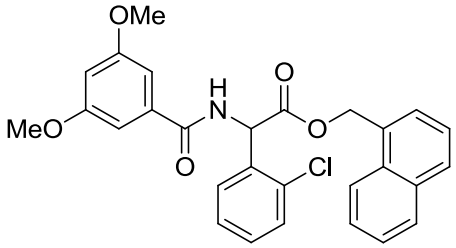
naphthalen-1-ylmethyl 2-(3,5-dimethoxybenzamido)-2-(4-methoxyphenyl)acetate

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.86-7.82 (m, 2H), 7.77-7.74 (m, 1H), 7.51-7.38 (m, 4H), 7.30-7.26 (m, 2H), 7.07 (d, *J* = 6.6 Hz, 1H), 6.91 (d, *J* = 2.1 Hz, 2H), 6.82-6.77 (m, 2H), 6.57 (t, *J* = 2.1Hz, 1H), 5.70 (d, *J* = 6.9 Hz, 1H), 5.63 (s, 2H), 3.79 (s, 6H), 3.77 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 192.25, 171.22, 166.62, 161.11, 159.97, 136.11, 133.87, 131.68, 130.77, 129.73, 128.79, 128.59, 127.71, 126.77, 126.15, 125.35, 123.68,114.54, 105.28, 104.20, 66.38, 56.77, 55.51; **IR** (KBr, cm^{-1}) 3316, 2924, 1741, 1653, 1594, 1512, 1458, 1353, 1249, 1205, 1177, 1157, 1063, 797; **MS**: HR-ESI calculated for $C_{29}H_{27}NO_6H$ ($M+H^+$) m/z: 486.1911, found m/z: 486.1934; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 35.0 min; (R)-enantiomer: 49.9 min.



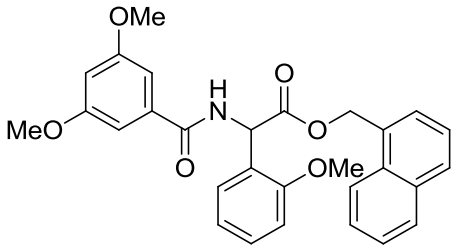
naphthalen-1-ylmethyl 2-(3,5-dimethoxybenzamido)-2-(3-methoxyphenyl)acetate

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.87-7.82 (m, 2H), 7.77-7.75 (m, 1H), 7.51-7.38 (m, 4H), 7.26-7.18 (m, 1H), 7.11 (d, *J* = 6.6 Hz, 1H), 6.97-6.81 (m, 5H), 6.59-6.58 (m, 1H), 5.75 (d, *J* = 7.2 Hz, 1H), 5.64 (s, 2H), 3.80 (s, 6H), 3.66 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.90, 166.66, 161.13, 160.17, 137.88, 136.04, 133.88, 131.68, 130.72, 130.20, 129.78, 128.83, 127.78, 126.84, 126.19, 125.35, 123.64, 119.69, 114.63, 112.96, 105.31, 104.24, 66.49, 57.26, 55.40; **IR** (KBr, cm^{-1}) 3313, 2923, 1741, 1651, 1595, 1513, 1456, 1353, 1263, 1205, 1156, 1063, 1049, 792, 776; **MS**: HR-ESI calculated for $C_{29}H_{27}NO_6H$ ($M+H^+$) m/z: 486.1911, found m/z: 486.1910; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 26.5 min; (R)-enantiomer: 47.0 min.



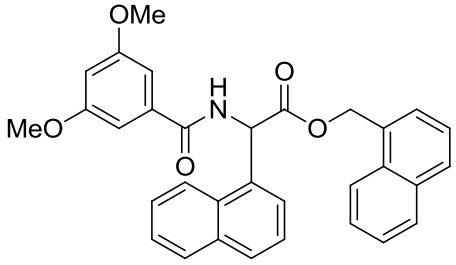
naphthalen-1-ylmethyl 2-(2-chlorophenyl)-2-(3,5-dimethoxybenzamido)acetate

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.85-7.76 (m, 3H), 7.49-7.36 (m, 5H), 7.32-7.13 (m, 4H), 6.92-6.91 (m, 2H), 6.58-6.56 (m, 1H), 6.11 (d, *J* = 7.2 Hz, 1H), 5.66 (s, 2H), 3.78 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.33, 166.59, 161.11, 135.94, 134.83, 133.83, 133.78, 131.63, 130.70, 130.67, 130.36, 129.92, 129.69, 128.80, 127.63, 127.44, 126.72, 126.11, 125.30, 123.57, 105.32, 104.27, 66.64, 57.79, 55.67; **IR** (KBr, cm^{-1}) 3315, 2924, 1743, 1651, 1594, 1512, 1456, 1352, 1205, 1157, 1063, 797, 754, 735; **MS**: HR-ESI calculated for $C_{28}H_{24}ClNO_5H$ ($M+H^+$) m/z: 490.1416, found m/z: 490.1410; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 32.6 min; (R)-enantiomer: 79.1 min.



naphthalen-1-ylmethyl 2-(3,5-dimethoxybenzamido)-2-(2-methoxyphenyl)acetate

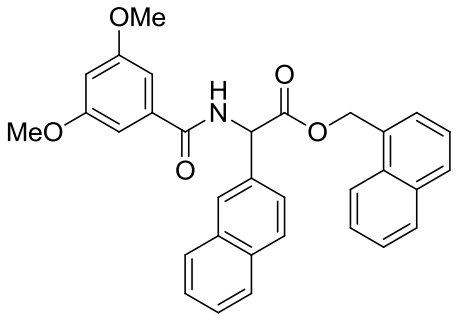
^{1}HNMR (300 MHz, $CDCl_3$): δ 7.82 (t, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.49-7.32 (m, 5H), 7.27-7.20 (m, 2H), 6.95-6.88 (m, 3H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.56-6.55 (m, 1H), 5.96 (d, *J* = 8.1 Hz, 1H), 5.67 (A of AB, J_{AB}=12 Hz, 1H), 5.57 (B of AB, J_{AB}=12 Hz, 1H), 3.78 (s, 6H), 3.30 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.04,166.73, 161.03, 157,10, 136.61, 133.84, 131.76, 131.34, 131.12, 129.96, 129.40, 128.68, 127.72, 126.66, 126.03, 125.50,125.36, 123.81, 121.18, 111.03, 105.34, 103.94, 66.04, 55.76, 55.13, 54.49; **IR** (KBr, cm^{-1}) 3353, 2922, 1743, 1659, 1594, 1512, 1495, 1461, 1351, 1252, 1205, 1147, 1063, 755; **MS**: HR-ESI calculated for $C_{29}H_{27}NO_6H$ ($M+H^+$) m/z: 486.1911, found m/z: 486.1895; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 26.9 min; (R)-enantiomer: 38.8 min.



naphthalen-1-ylmethyl 2-(3,5-dimethoxybenzamido)-2-(naphthalen-1-yl)acetate

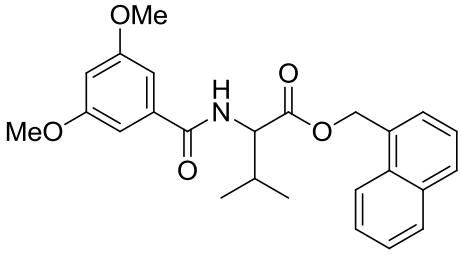
^{1}HNMR (300 MHz, $CDCl_3$): δ 8.16-8.13 (m, 1H), 7.86-7.78 (m, 3H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.49-7.24 (m, 8H), 7.05 (d, *J* = 7.5 Hz, 2H), 6.90-6.89 (m, 2H), 6.56-6.52 (m, 2H), 5.66 (s, 2H), 3.76 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.53,166.92, 161.09, 135.96,

134.31, 133.79, 132.41, 131.60, 131.30, 130.72, 129.71, 129.65, 129.10, 128.72, 127.75, 127.25, 126.67, 126.35, 126.07, 125.37, 125.27, 123.58, 123.44, 105.33, 104.27, 66.41, 55.80, 54.50; **IR** (KBr, cm^{-1}) 3312, 2922, 1740, 1653, 1594, 1511, 1457, 1349, 1205, 1194, 1156, 1063, 792, 776; **MS**: HR-ESI calculated for $C_{32}H_{27}NO_5H$ ($M+H^+$) m/z: 506.1962, found m/z: 506.1941; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 22.9 min; (R)-enantiomer: 66.6 min.



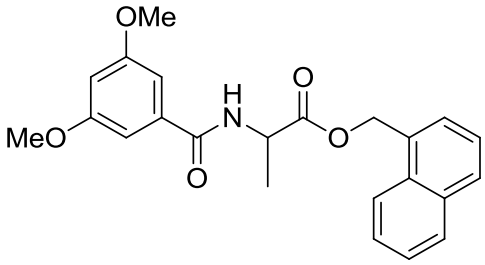
naphthalen-1-ylmethyl 2-(3,5-dimethoxybenzamido)-2-(naphthalen-2-yl)acetate

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.82-7.74 (m, 5H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.51-7.34 (m, 6H), 7.27-6.95 (m, 2H), 6.95-6.94 (m, 1H), 6.59-6.58 (m, 1H), 5.96 (d, *J* = 6.6 Hz, 1H), 5.64 (s, 2H), 3.79 (s, 6H); **^{13}C NMR** (75 MHz,$CDCl_3$): δ 170.05, 166.70, 161.14, 136.04, 133.88, 133.84, 133.47, 133.44, 131.65, 130.64, 129.81, 129.10,128.77, 128.33, 127.87, 126.93, 126.73, 126.68, 126.63, 126.14, 125.30, 124.98, 123.55, 105.33, 104.29, 66.61, 57.43, 55.80; **IR** (KBr, cm^{-1}) 3313, 2923, 1741, 1654, 1595, 1511, 1458, 1351, 1205, 1157, 1064, 793,776; **MS**: HR-ESI calculated for $C_{32}H_{27}NO_5H$ ($M+H^+$) m/z: 506.1962, found m/z: 506.1939; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 27.1 min; (R)-enantiomer: 50.7 min.



naphthalen-1-ylmethyl 2-(3,5-dimethoxybenzamido)-3-methylbutanoate

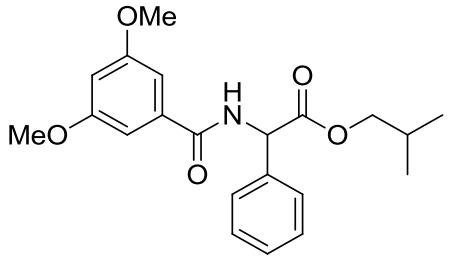
^{1}HNMR (300 MHz, $CDCl_3$): δ 8.03-7.99 (m, 1H), 7.91-7.86 (m, 2H), 7.58-7.43 (m, 4H), 6.90 (d, J = 2.1 Hz, 2H), 6.60-6.58 (m, 2H), 5.71 (A of AB, J_{AB}=12 Hz, 1H), 5.61 (B of AB, J_{AB}=12 Hz, 1H), 4.82 (dd, J_1 = 8.7 Hz, J_2 = 4.5 Hz, 1H), 3.80 (s, 6H), 2.32-2.17 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.18, 167.40, 161.13, 136.64, 133.95, 131.80, 130.99, 129.84, 128.99, 128.11, 126.94, 126.27, 125.45, 123.65, 105.23, 103.96, 65.73, 57.76, 55.79, 31.84, 19.27, 17.91; **IR** (KBr, cm^{-1}) 3328, 2961, 2924, 1736, 1654, 1594, 1525, 1458, 1355, 1205, 1156, 1064, 794, 777; **MS**: HR-ESI calculated for $C_{25}H_{27}NO_5H$ ($M+H^+$) m/z: 422.1962, found m/z: 422.1960; **HPLC** (for alcohol obtained by LAH reduction) (CHIRALCEL AS-H, IPA/hexane=1/10, 1.0 mL/min): (S)-enantiomer: 13.2 min; (R)-enantiomer: 26.7 min.



naphthalen-1-ylmethyl 2-(3,5-dimethoxybenzamido)propanoate

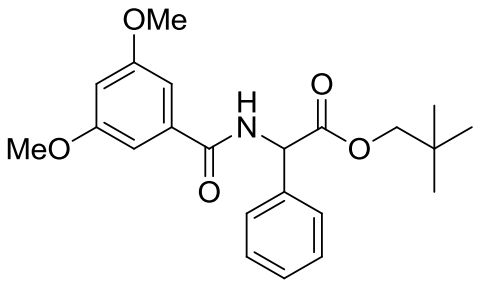
^{1}HNMR (300 MHz, $CDCl_3$): δ 8.01-7.98 (m, 1H), 7.91-7.86 (m, 2H), 7.57-7.43 (m, 4H), 6.90 (d, J = 2.4 Hz, 2H), 6.73 (d, J = 6.9 Hz, 1H), 6.58-6.57 (m, 1H), 5.70 (A of AB, J_{AB}=15 Hz, 1H), 5.64 (B of AB, J_{AB}=15 Hz, 1H), 4.87-4.77 (m, 1H), 3.80 (s, 6H), 1.48 (d,

J = 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.20, 166.92, 161.11, 136.36, 133.98, 131.79, 130.98, 129.84, 129.00, 127.91, 126.97, 126.28, 125.45, 123.62, 105.16, 104.17, 66.00, 55.79, 48.99, 18.76; **IR** (KBr, cm^{-1}) 3319, 2925, 1741, 1645, 1594, 1532, 1456, 1354, 1205, 1156, 1063, 776; **MS**: HR-ESI calculated for $C_{23}H_{37}NO_5H$ ($M+H^+$) m/z: 394.1649, found m/z: 394.1640;**HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 33.4 min; (R)-enantiomer: 38.6 min.



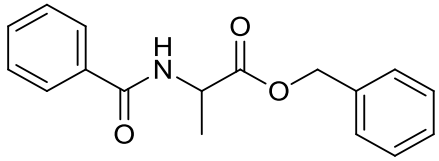
isobutyl 2-(3,5-dimethoxybenzamido)-2-phenylacetate

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.45-7.42 (m, 2H), 7.39-7.29 (m, 3H), 7.19 (d, *J* = 6.6 Hz, 1H), 6.95-6.94 (m, 2H), 6.59-6.57 (m, 1H), 5.74 (d, *J* = 6.9 Hz, 1H), 3.96-3.93 (m, 2H), 3.81 (s, 6H), 1.98-1.80 (m, 1H), 0.82 (dd, J_1 = 6.6 Hz, J_2 = 1.5 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.20, 166.59, 161.13, 137.01, 136.13, 129.14, 128.72, 127.47, 105.30, 104.18, 72.12, 57.20, 55.80, 27.88, 19.04; **IR** (KBr, cm^{-1}) 3316, 2961, 1741, 1651, 1595, 1522, 1456, 1353, 1206, 1157, 1065, 699; **MS**: HR-ESI calculated for $C_{21}H_{25}NO_5H$ ($M+H^+$) m/z: 372.1805, found m/z: 372.1808; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 21.3 min; (R)-enantiomer: 34.6 min.



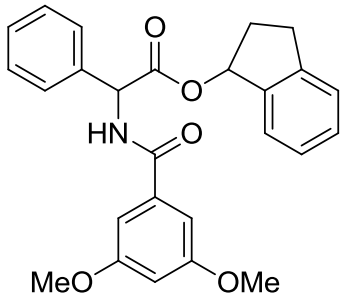
neopentyl 2-(3,5-dimethoxybenzamido)-2-phenylacetate

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.46-7.43 (m, 2H), 7.39-7.31 (m, 3H), 7.21 (d, *J* = 6.9 Hz, 1H), 6.96-6.95 (m, 2H), 6.59-6.58 (m, 1H), 5.75 (d, *J* = 6.9 Hz, 1H), 3.93-3.78 (m, 8H), 0.82 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.20, 166.58, 161.14, 137.09, 136.15, 129.12, 128.71, 127.43, 105.30, 104.18, 75.27, 57.25, 55.82, 31.72, 26.41; **IR** (KBr, cm^{-1}) 3318, 2958, 1741, 1648, 1594, 1522, 1205, 1157, 698; **MS**: HR-ESI calculated for $C_{22}H_{27}NO_5H$ ($M+H^+$) m/z: 386.1962, found m/z: 386.1968; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 15.6 min; (R)-enantiomer: 39.9 min.

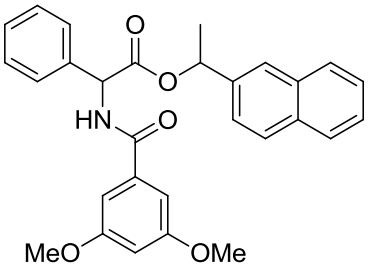


^{1}HNMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* =7.2 Hz, 2H), 7.01 (d, *J* = 6.9 Hz, 1H), 5.21 (A of AB, J_{AB}=12 Hz, 1H), 5.17 (B of AB, J_{AB}=12 Hz, 1H), 4.88-4.79 (m, 1H), 1.51(d, *J* =7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.29, 167.18,

135.59, 134.14, 131.91, 128.86, 128.75, 128.67, 128.34, 127.33, 67.43, 48.86, 18.66; **IR** (KBr, cm^{-1}) 3331, 1738, 1650, 1520, 909, 732; **MS**: HR-ESI calculated for $C_{17}H_{16}NO_3H$ ($M+H^+$) m/z: 284.1281, found m/z: 284.1279; **HPLC** (CHIRALCEL OD-H, IPA/hexane=1/10, 1.0 mL/min): (R)-enantiomer: 15.4 min; (S)-enantiomer: 17.7 min.

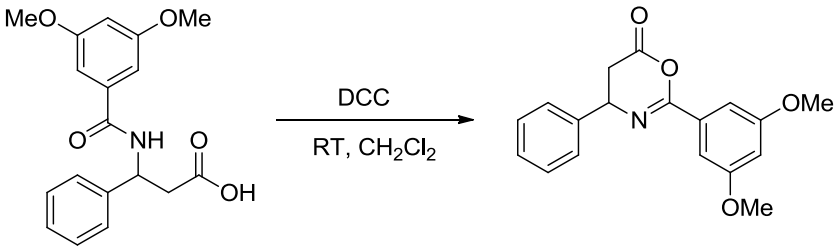


IR (KBr, cm^{-1}) 3367, 1736, 1655, 1594, 1206, 1157; **MS**: HR-ESI calculated for $C_{26}H_{25}NO_5H$ ($M+H^+$) m/z: 432.1806, found m/z: 432.1807;



IR (KBr, cm^{-1}) 3330, 1740, 1655, 1595, 1517, 1355, 1206, 1157, 1063; **MS**: HR-ESI calculated for $C_{29}H_{27}NO_5H$ ($M+H^+$) m/z: 470.1962, found m/z: 470.1961;

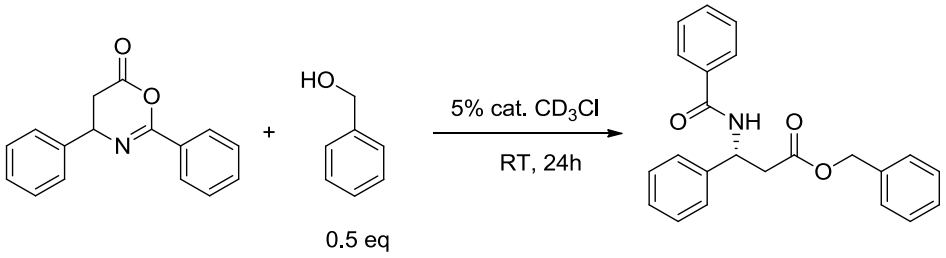
4.4.8 General procedure to prepare oxazinones



The mixture of N-protected β-amino acid (329mg, 1mmol) and DCC (206mg, 1mmol) in 10ml CH_2Cl_2 was stirred at room temperature for 3h, filtered to remove the precipitate. The filtrate was concentrate and purified by column chromatography (Silica gel, EtOAc:Hexane=1:5) to give 150mg white powder as the product.

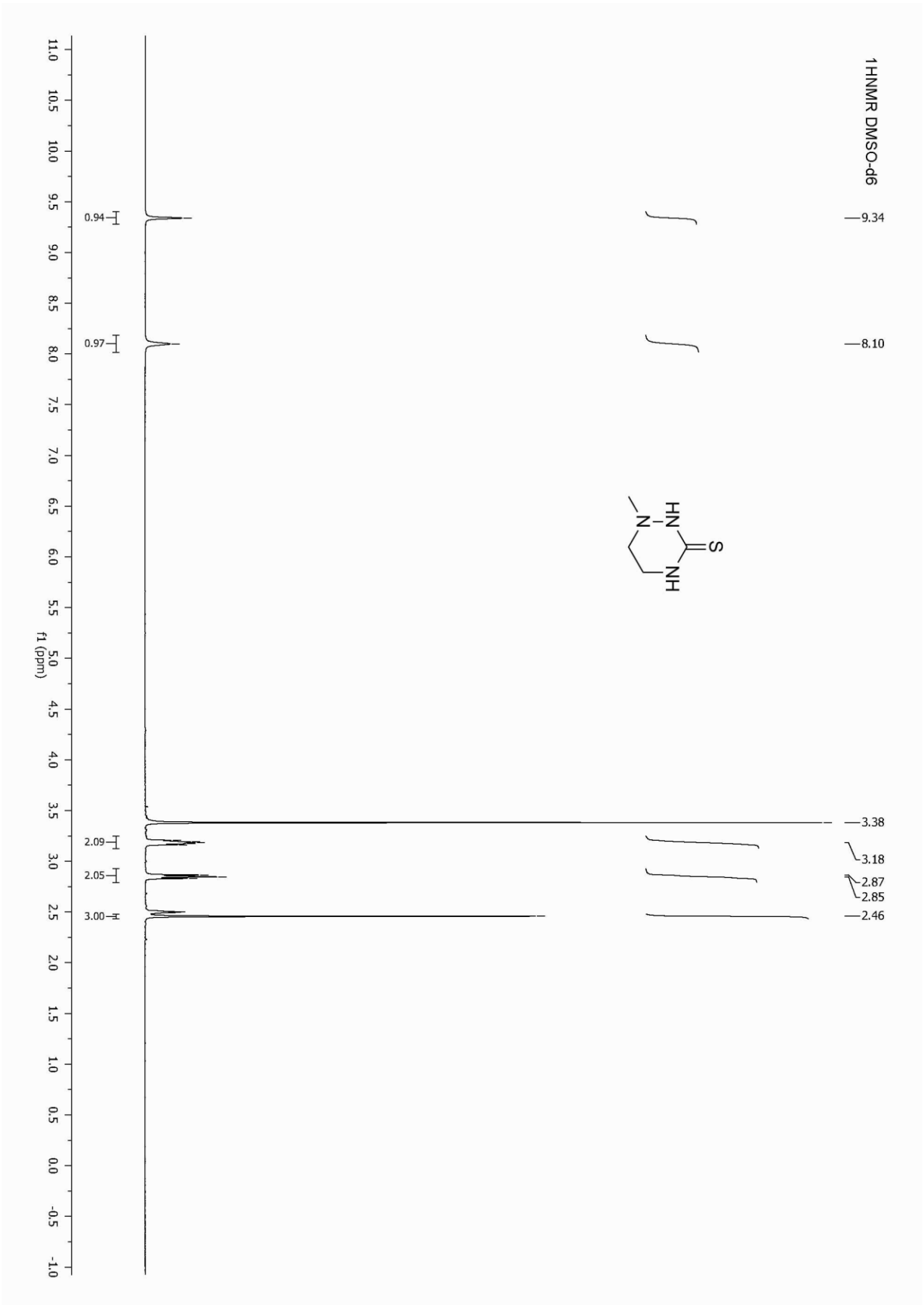
^{1}HNMR (300 MHz, $CDCl_3$): δ 7.34-7.24 (m, 5H), 7.20-7.19 (m, 2H), 6.56 (t, J = 2.29 Hz, 1H), 4.99 (X of ABX, 1H), 3.77 (s, 6H), 2.99 (A of ABX, J_{AB}=15Hz, J_{AX}=27Hz, 1H), 2.97 (B of ABX, J_{AB}=18Hz, J_{BX}=30Hz, 1H);; **^{13}C NMR** (75 MHz, $CDCl_3$): 166.08, 161.39, 154.08, 141.02, 132.76, 129.54, 128.53, 126.84, 106.21, 105.51, 57.19, 56.23, 36.79; **IR** (KBr, cm^{-1}) 1788, 1670, 1596, 1454, 1205, 1156, 1062, 1030; **MS**: HR-ESI calculated for $C_{18}H_{17}NO_4H$ ($M+H^+$) m/z: 312.1230, found m/z: 312.1233;

4.4.9 General procedure for kinetic resolution of oxazinones



The mixture of oxazinone (25mg, 0.1mmol), benzyl alcohol (5.2 µl, 0.05mmol) and 0.005mmol catalyst in 1ml $CDCl_3$ was stirred at room temperature. The reaction was monitored by ^{1}HNMR until the conversion reached 45-50%. The mixture was purified by column chromatography (Silica gel, EtOAc:Hexane=1:5) to give the unreacted oxazinone and (EtOAc:CH_2Cl_2:Hexane=3: 3:10) to give the product.

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.72-7.69 (m, 2H), 7.46-7.12 (m, 14H), 5.62-5.55(m, 1H), 5.02 (A of AB, J_{AB}=12 Hz, 1H), 4.99 (B of AB, J_{AB}=12 Hz, 1H), 2.97 (A of ABX, J_{AB}=15Hz, J_{AX}=27Hz, 1H), 2.95 (B of ABX, J_{AB}=15Hz, J_{BX}=30Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) :δ 171.58, 166.68, 140.57, 135.49, 134.35, 131.85, 128.99, 128.82, 128.61, 128.50, 127.88, 127.24, 126.45, 66.98, 50.03, 40.17; **IR** (KBr, cm^{-1}) 3311, 1733, 1637, 1537; **MS**: HR-ESI calculated for $C_{23}H_{21}NO_3H$ ($M+H^+$) m/z: 360.1594, found m/z: 360.1600; **HPLC** (CHIRALCEL OD-H, IPA/hexane=2/10, 1.0 mL/min): (R)-enantiomer: 11.6 min; (S)-enantiomer: 18.5 min.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2.05
3.00
9.34
8.10
3.38
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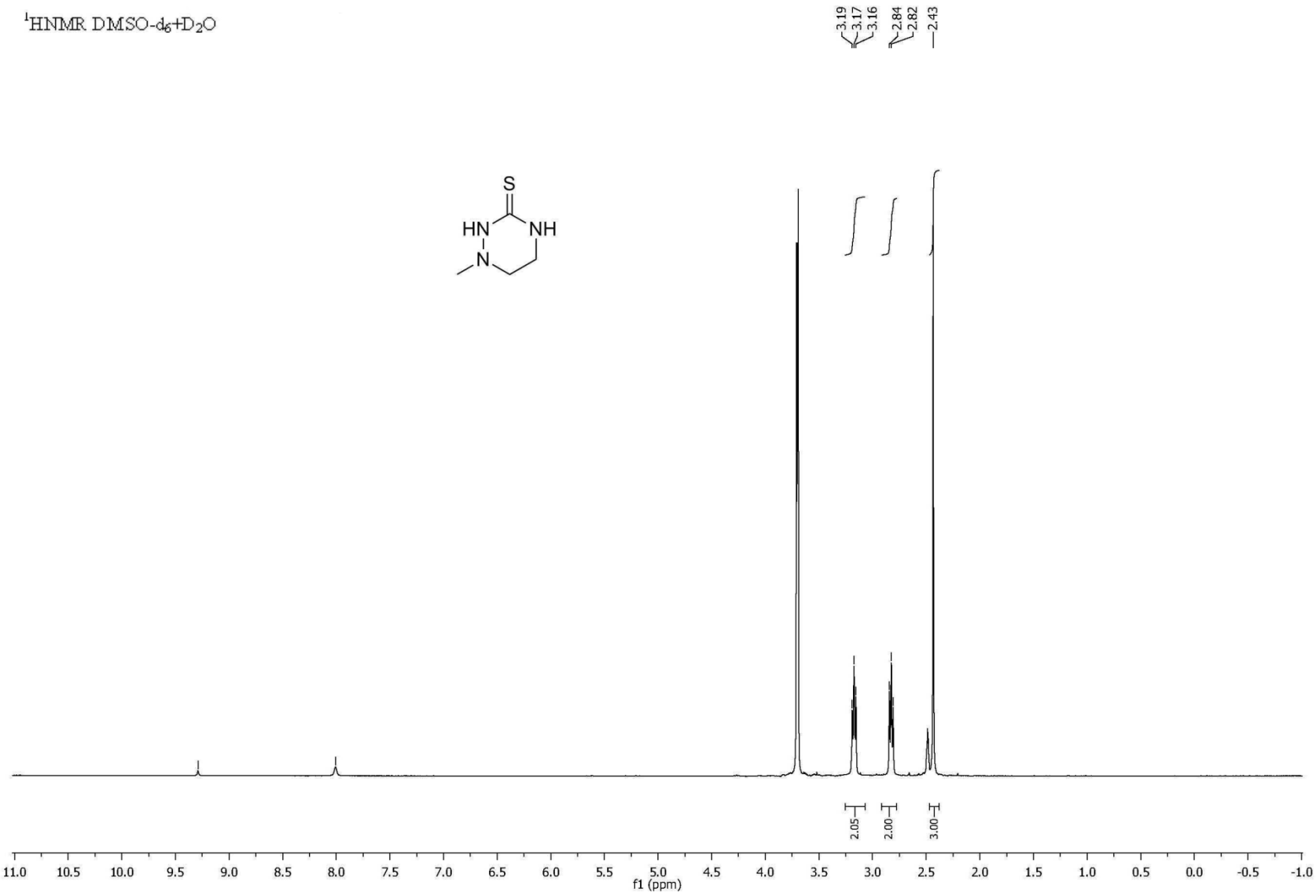
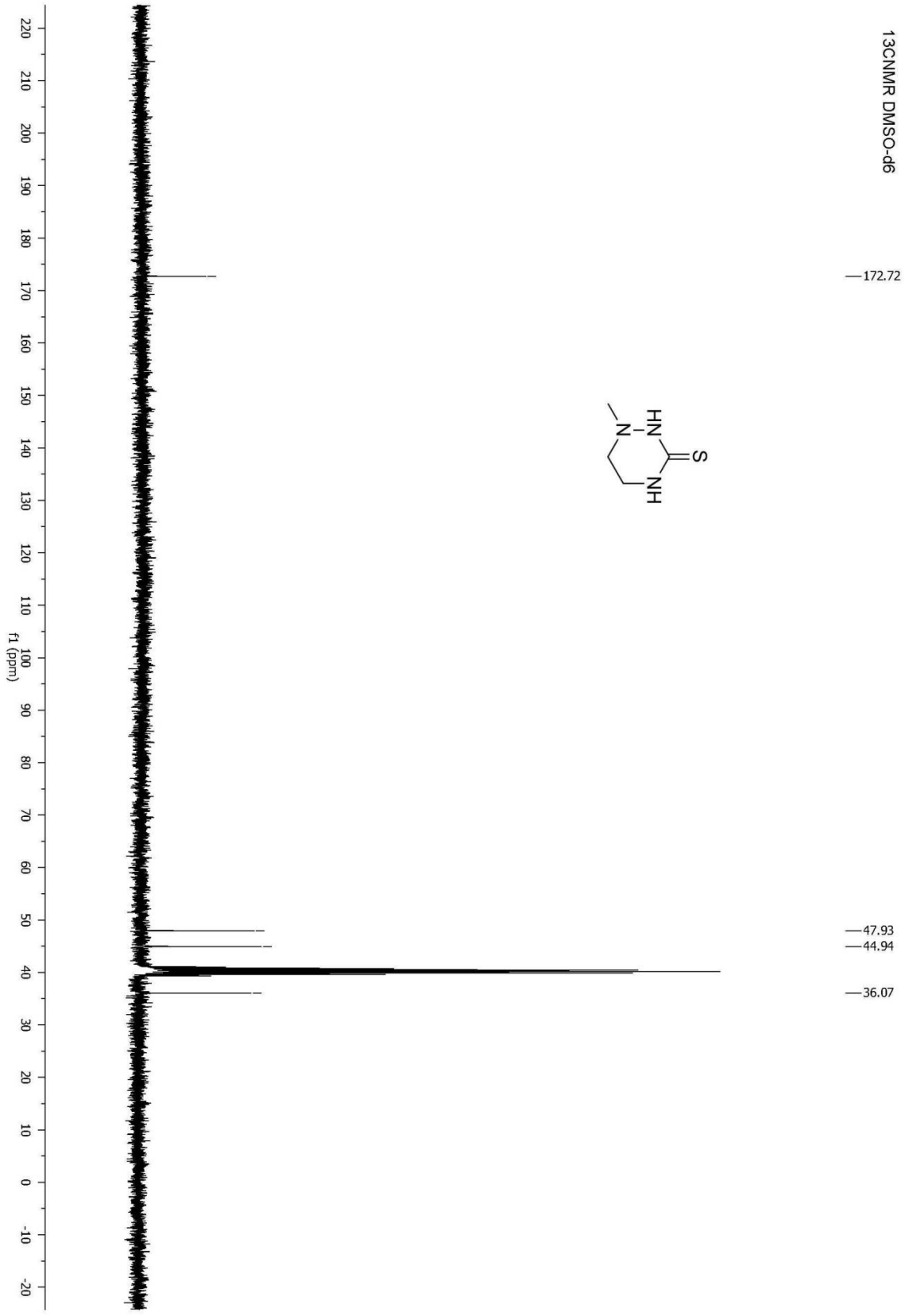
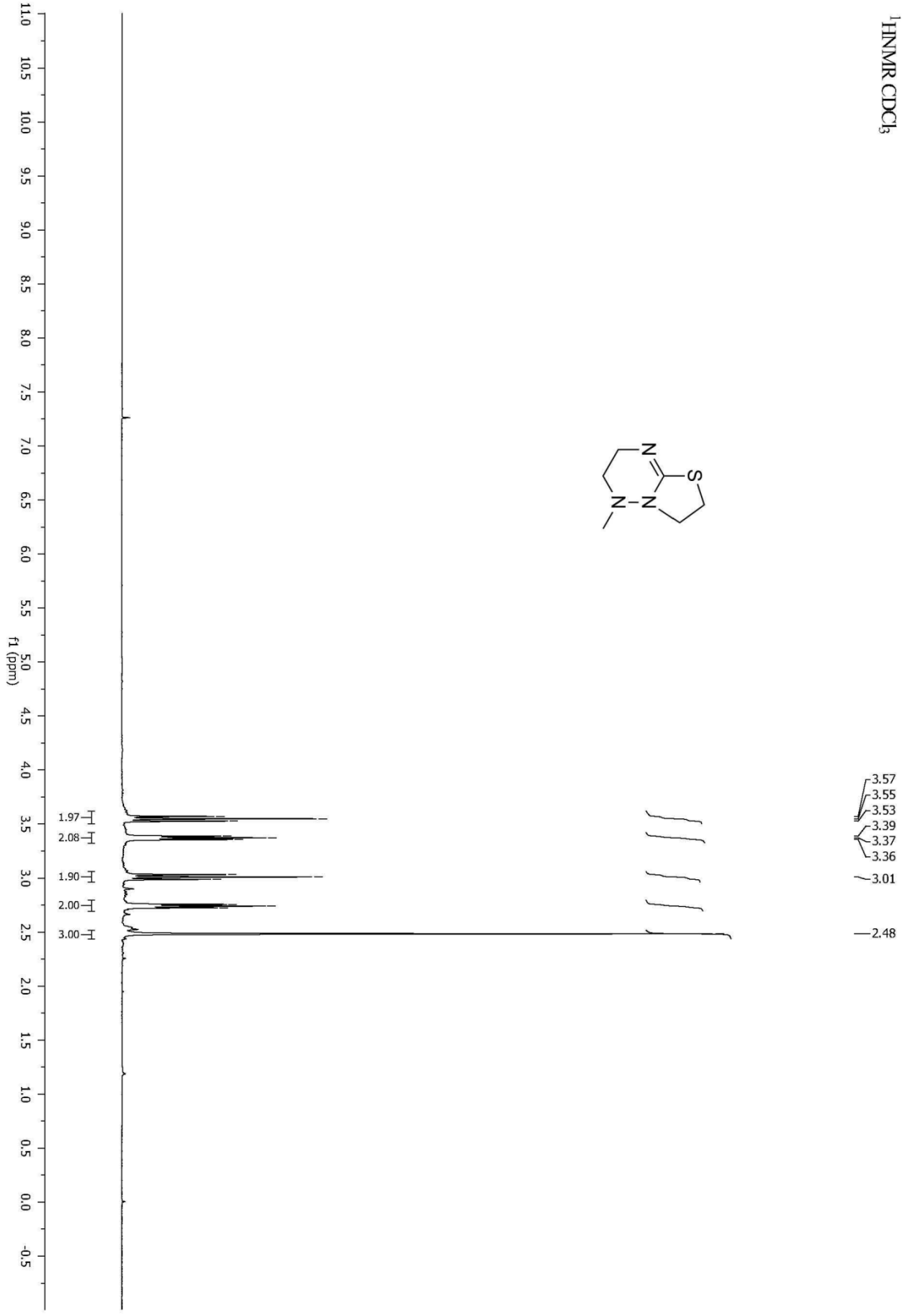
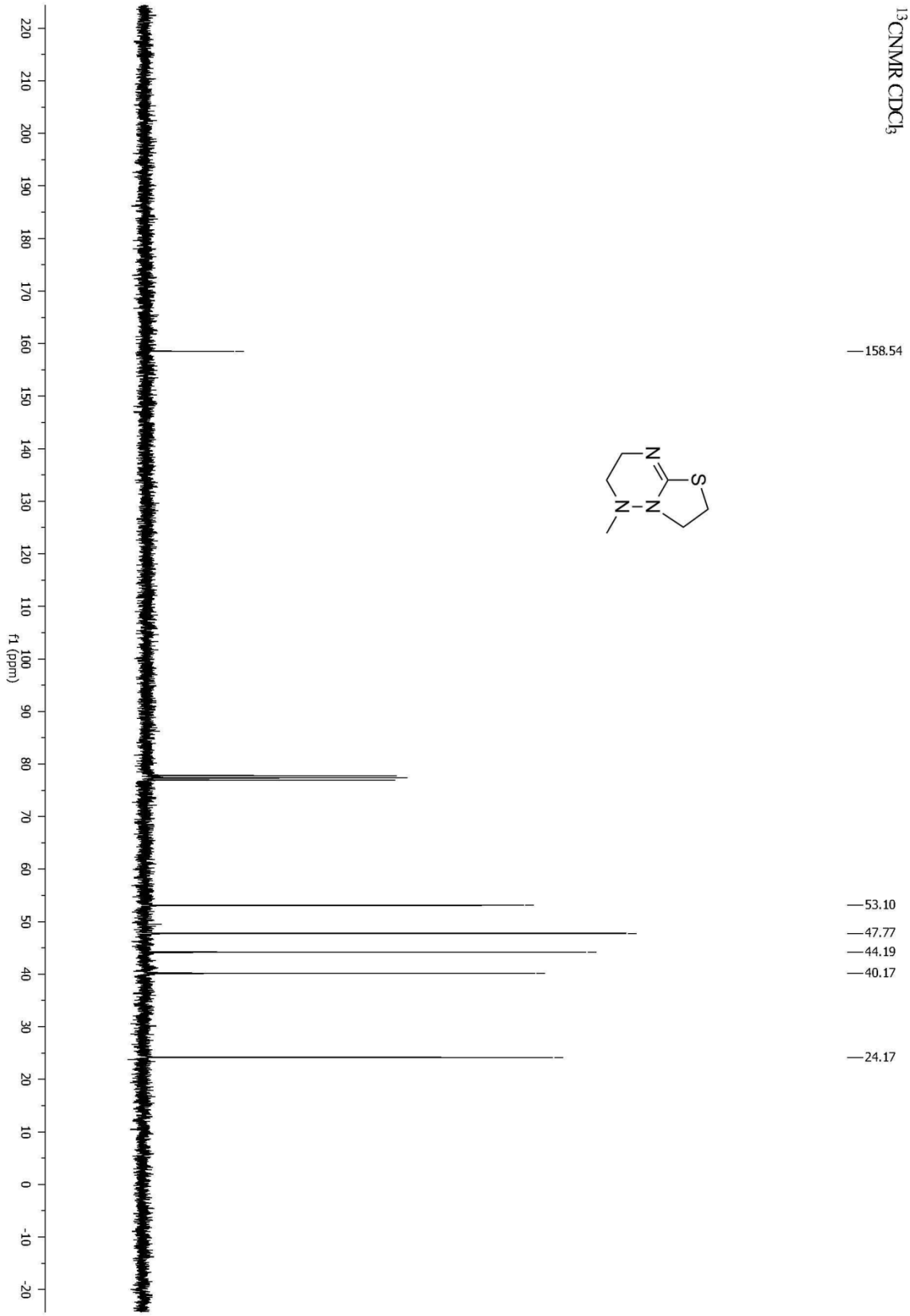
2.87
2.85
2.46
N
NH
NH
S

^{1}HNMR DMSO-d_6+D_2O

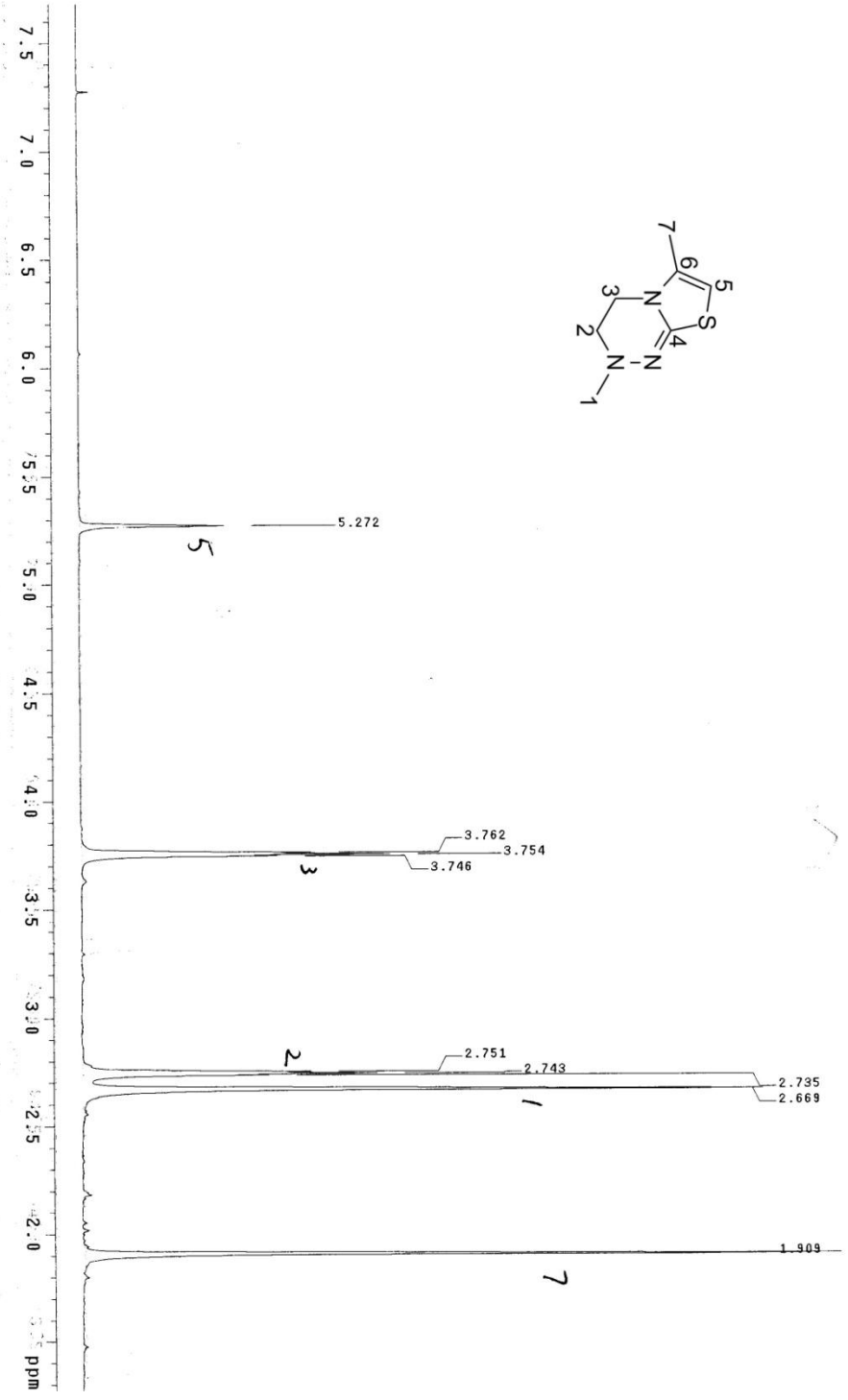


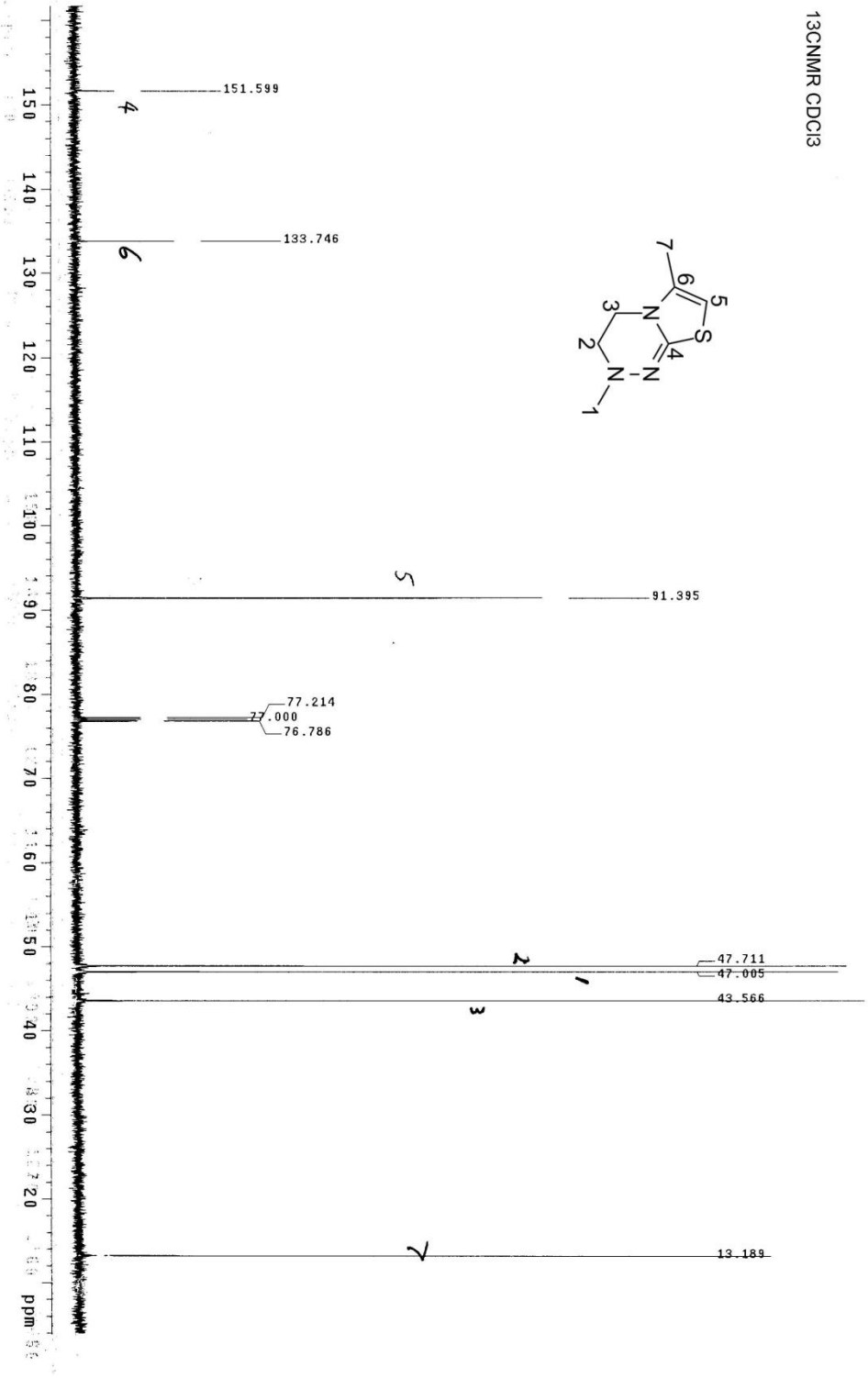

13CNMR DMSO-d6
172.72
47.93
44.94
36.07
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
HN
N
NH
S

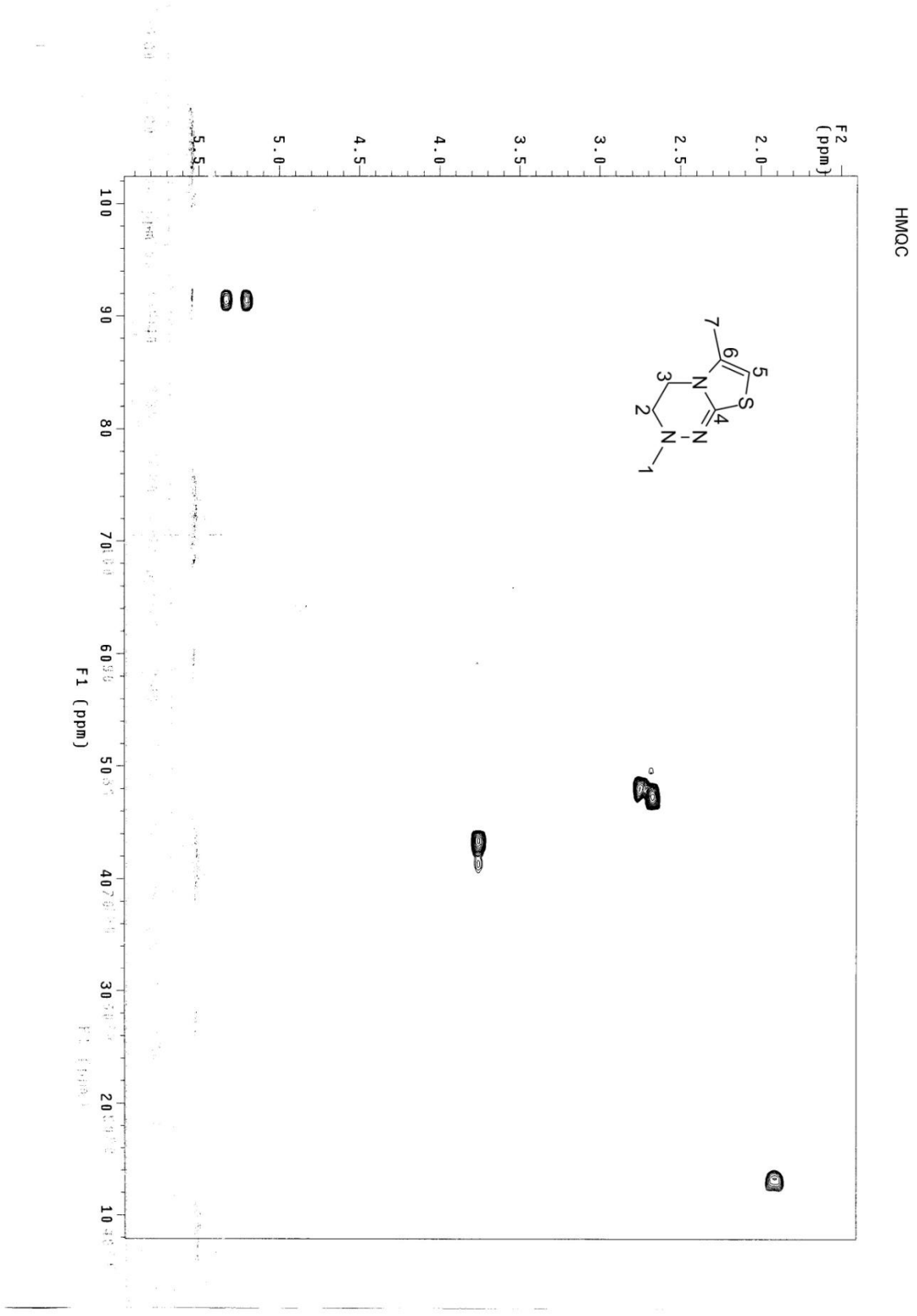

^{1}HNMR $CDCl_3$
f1 (ppm)
1.97
2.08
1.90
2.00
3.00
3.57
3.55
3.53
3.39
3.37
3.36
3.01
2.48


^{13}CNMR CDCl$_3$
158.54
53.10
47.77
44.19
40.17
24.17
f1 (ppm)

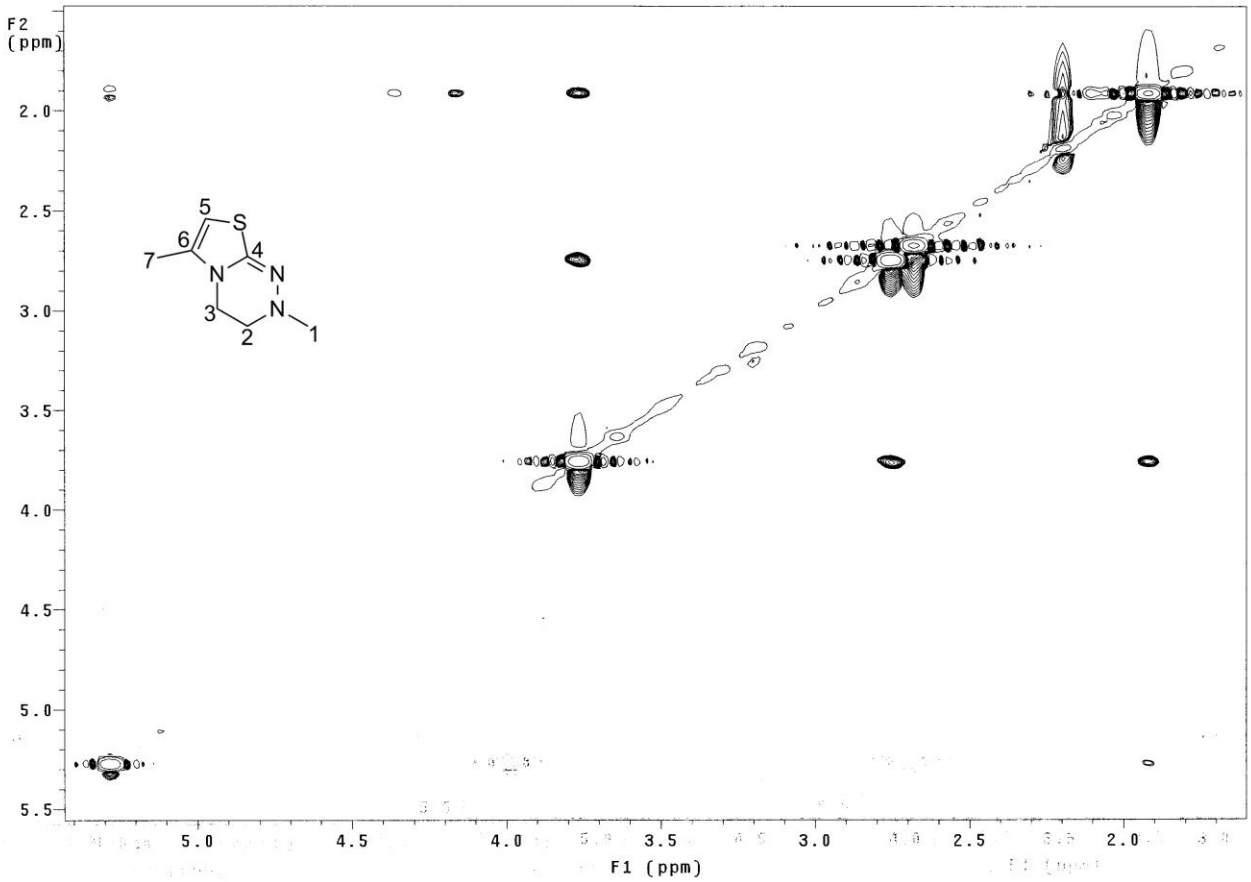
1HNMR CDCl3

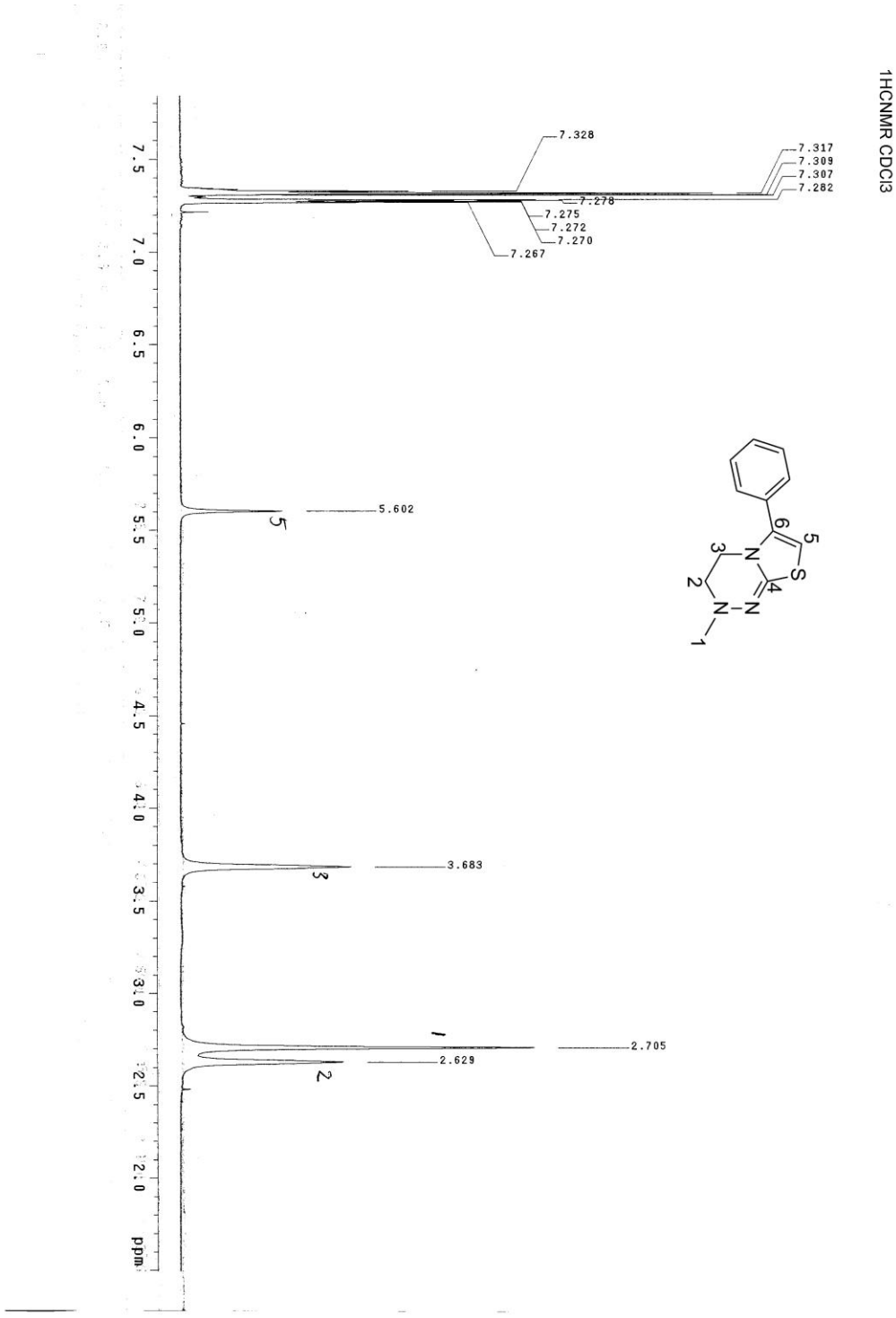


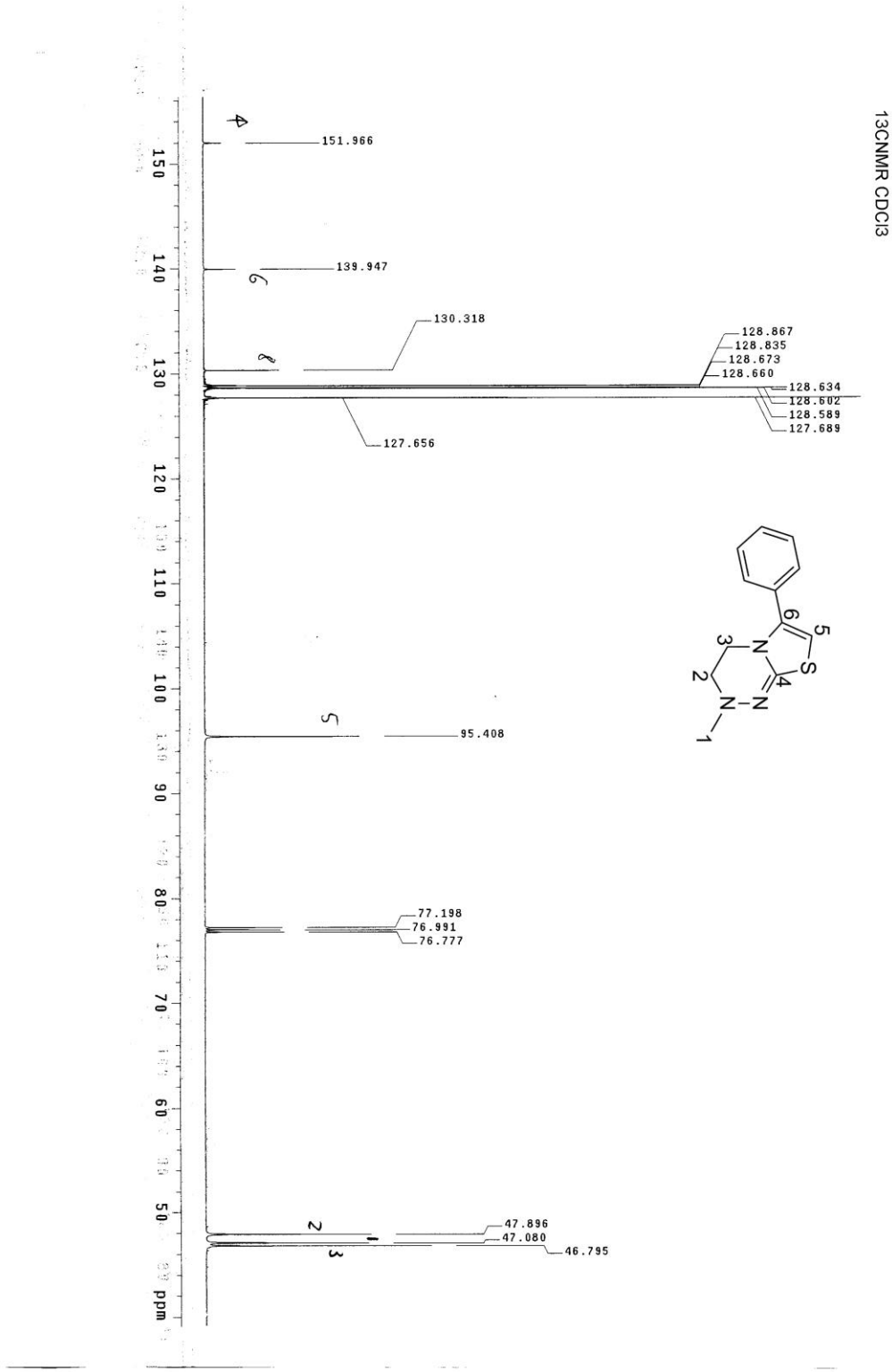

13CNMR CDCl3
151.599
133.746
91.395
77.214
77.000
76.786
47.711
47.005
43.566
13.189
ppm

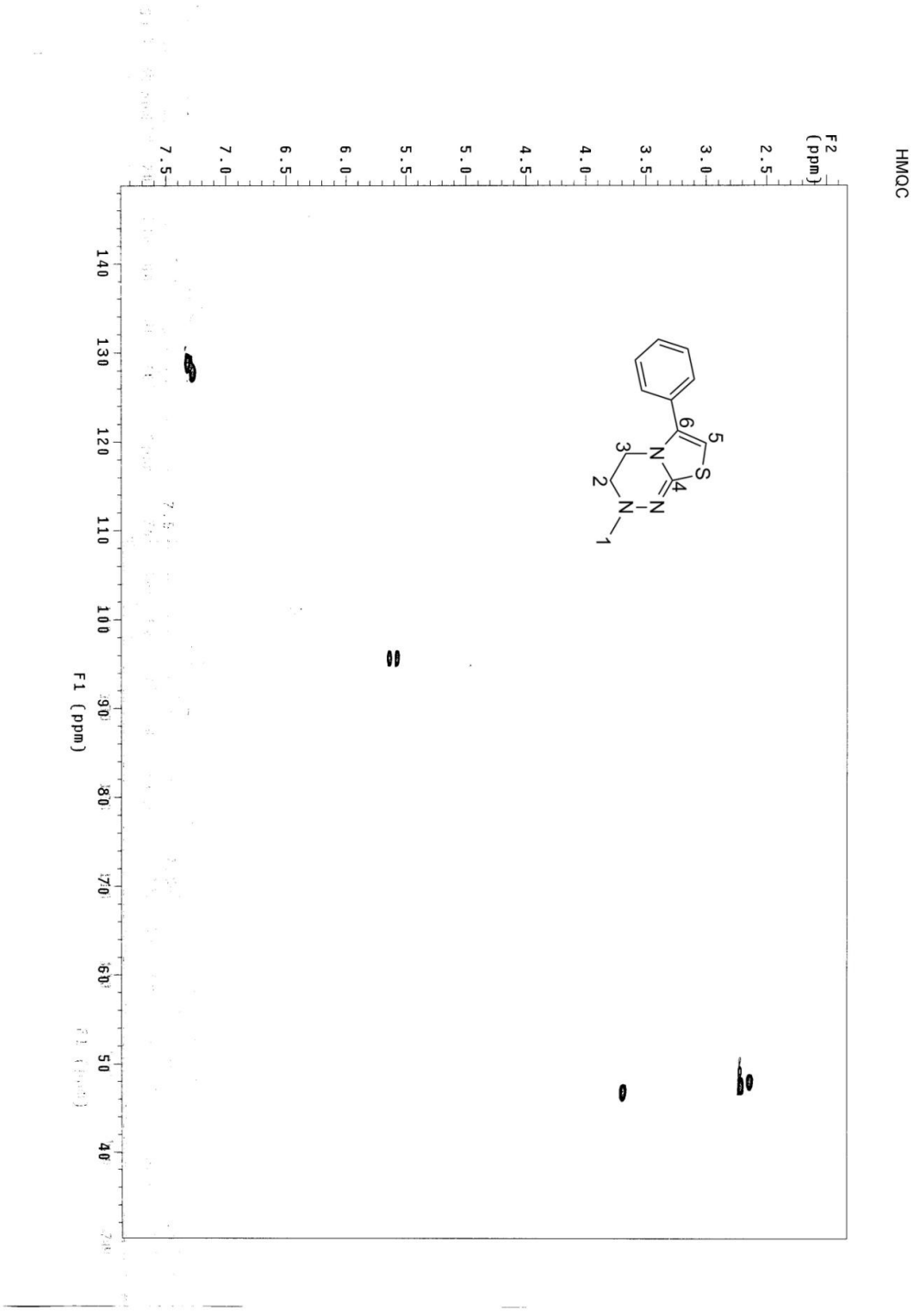

HMQC
F2 (ppm)
F1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
100
90
80
70
60
50
40
30
20
10
7
6
5
S
4
3
N
2
N
N
1

NOE

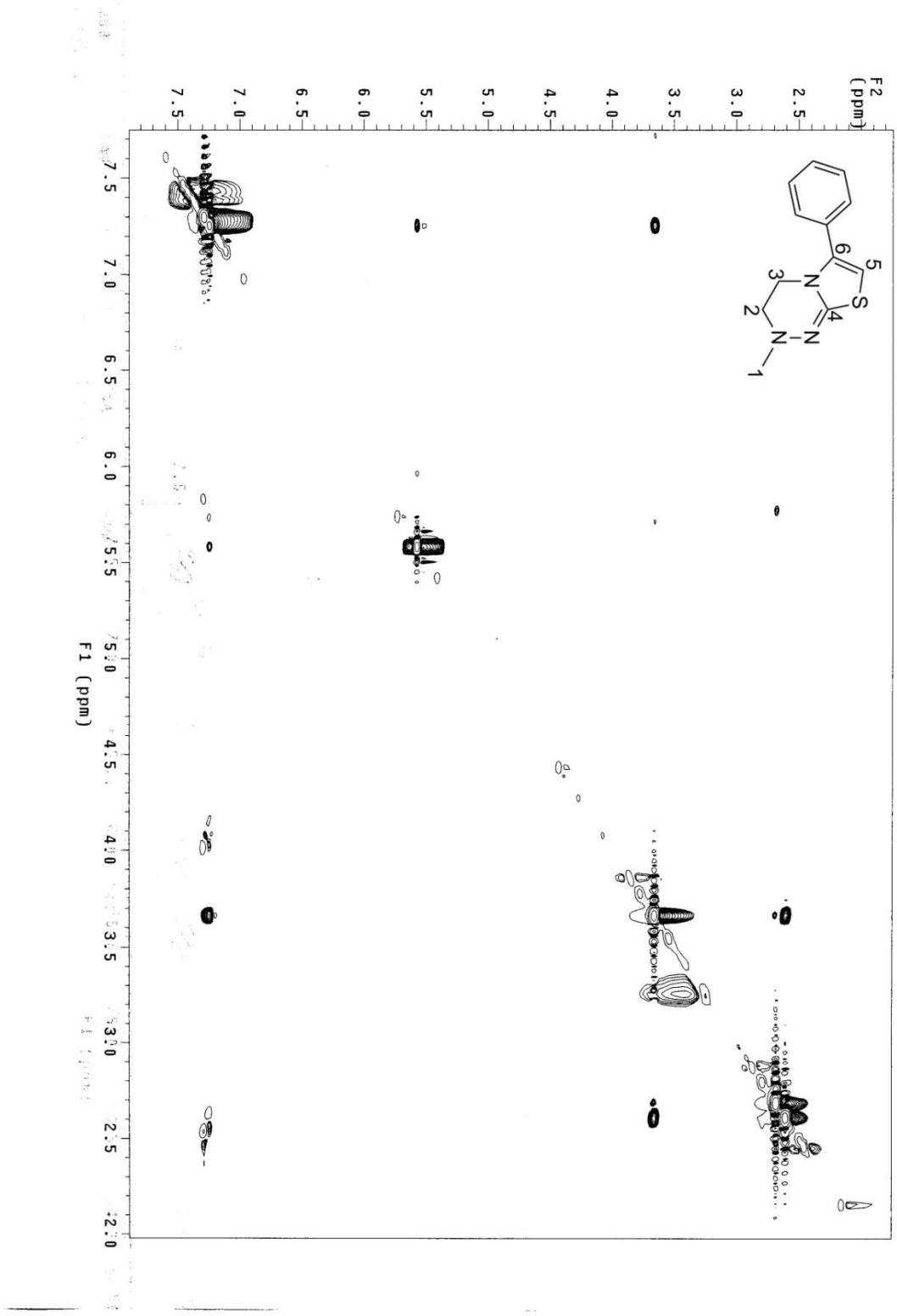

NOE
F2 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5
S
6
4
7
N
N
3
N
2
1
5.0
4.5
4.0
3.5
3.0
2.5
2.0
F1 (ppm)


1HCNMR CDCl3
7.328
7.317
7.309
7.307
7.282
7.278
7.275
7.272
7.270
7.267
5.602
3.683
2.705
2.629
ppm

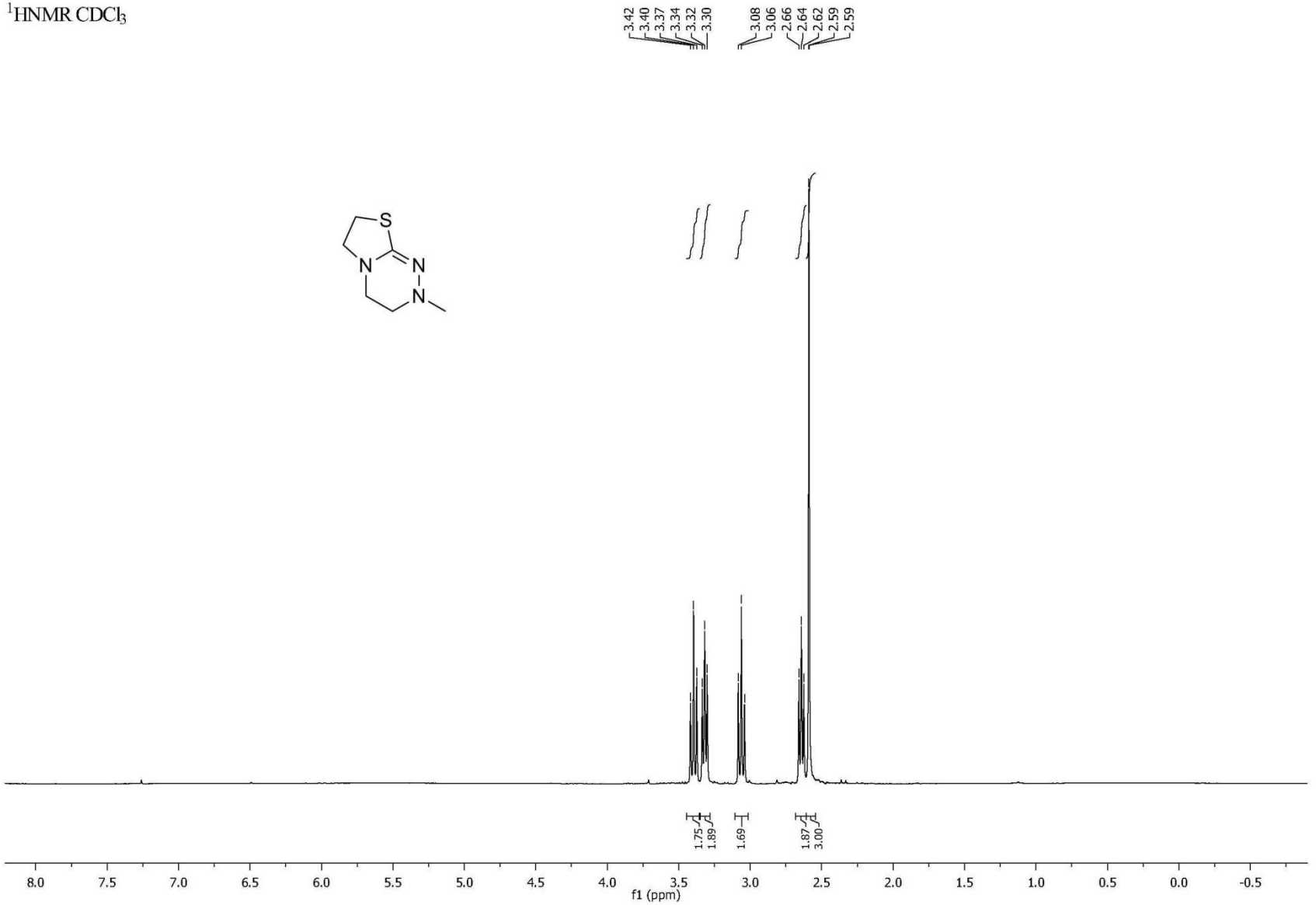

13CNMR CDCl3
151.966
139.947
130.318
128.867
128.835
128.673
128.660
128.634
128.602
128.589
127.689
127.656
95.408
77.198
76.991
76.777
47.896
47.080
46.795
ppm

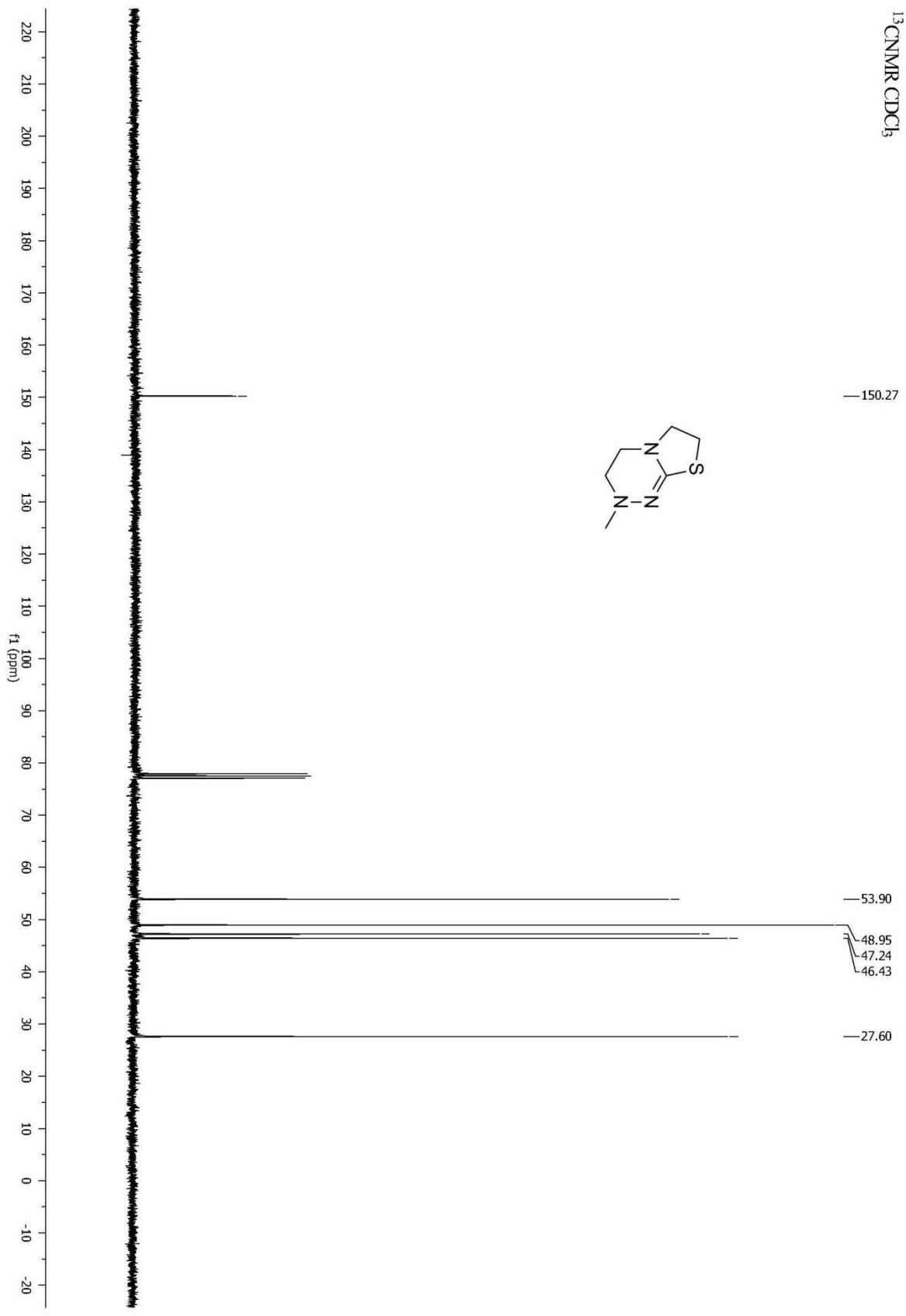

HMQC
F2 (ppm)
F1 (ppm)
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
40
50
60
70
80
90
100
110
120
130
140
N
S
N
N
1
2
3
4
5
6

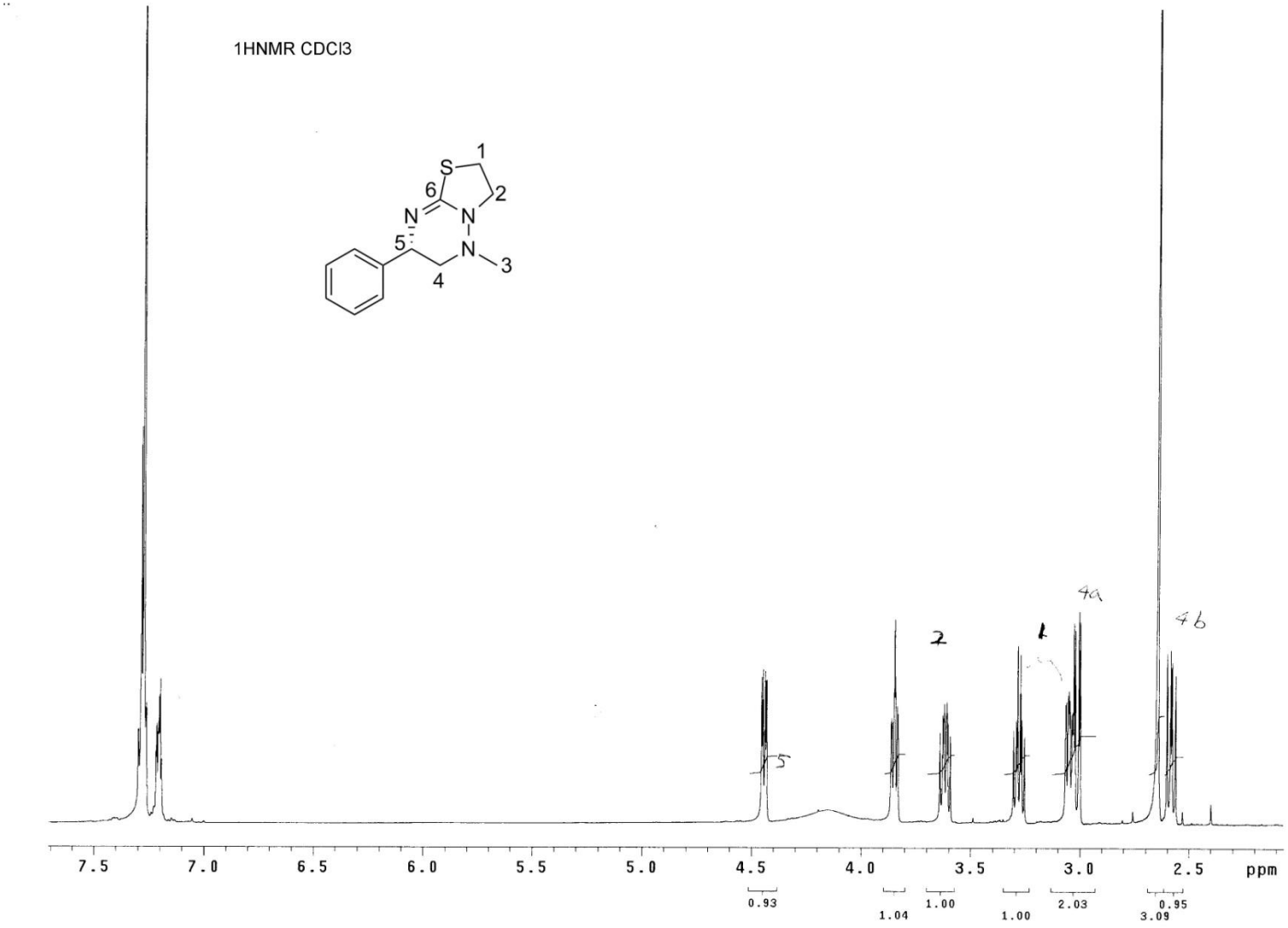
NOE



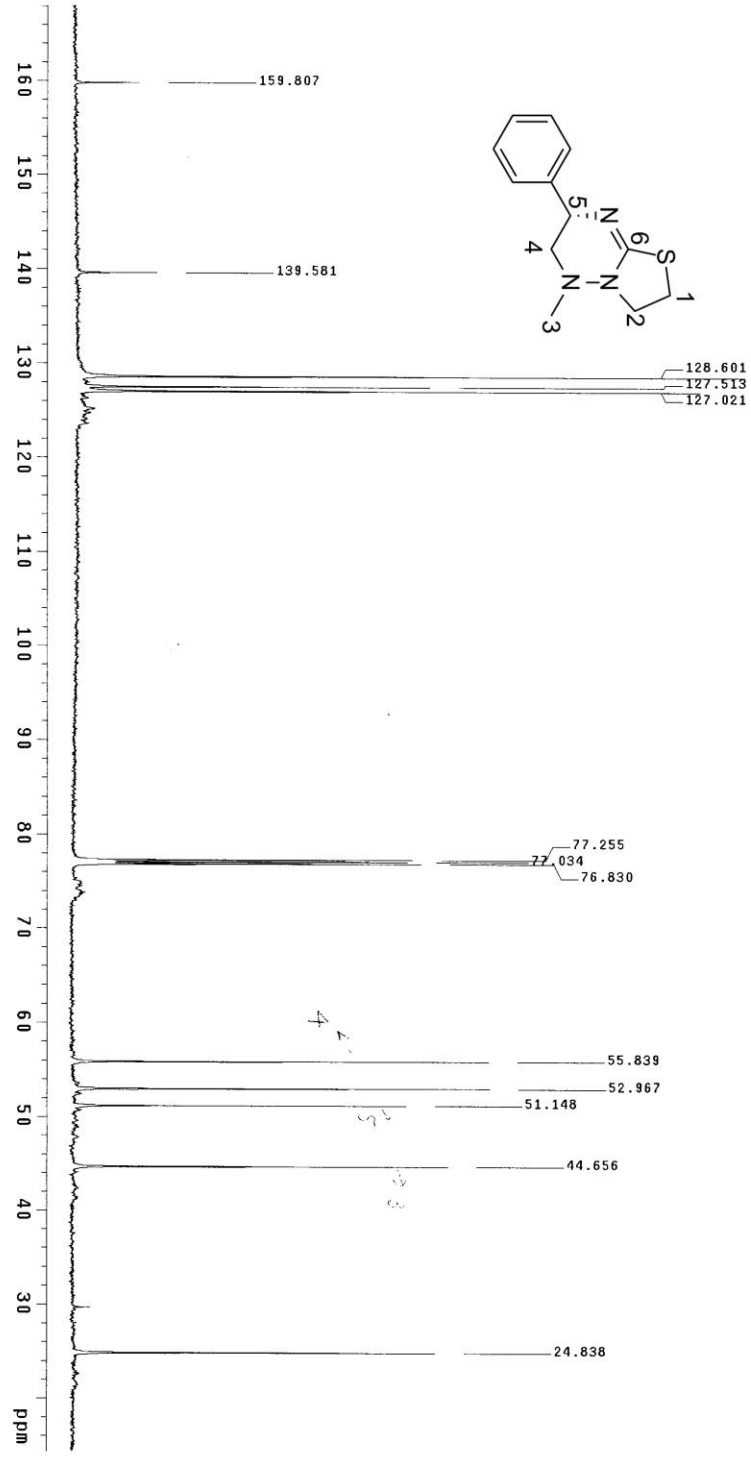
^{1}HNMR $CDCl_3$

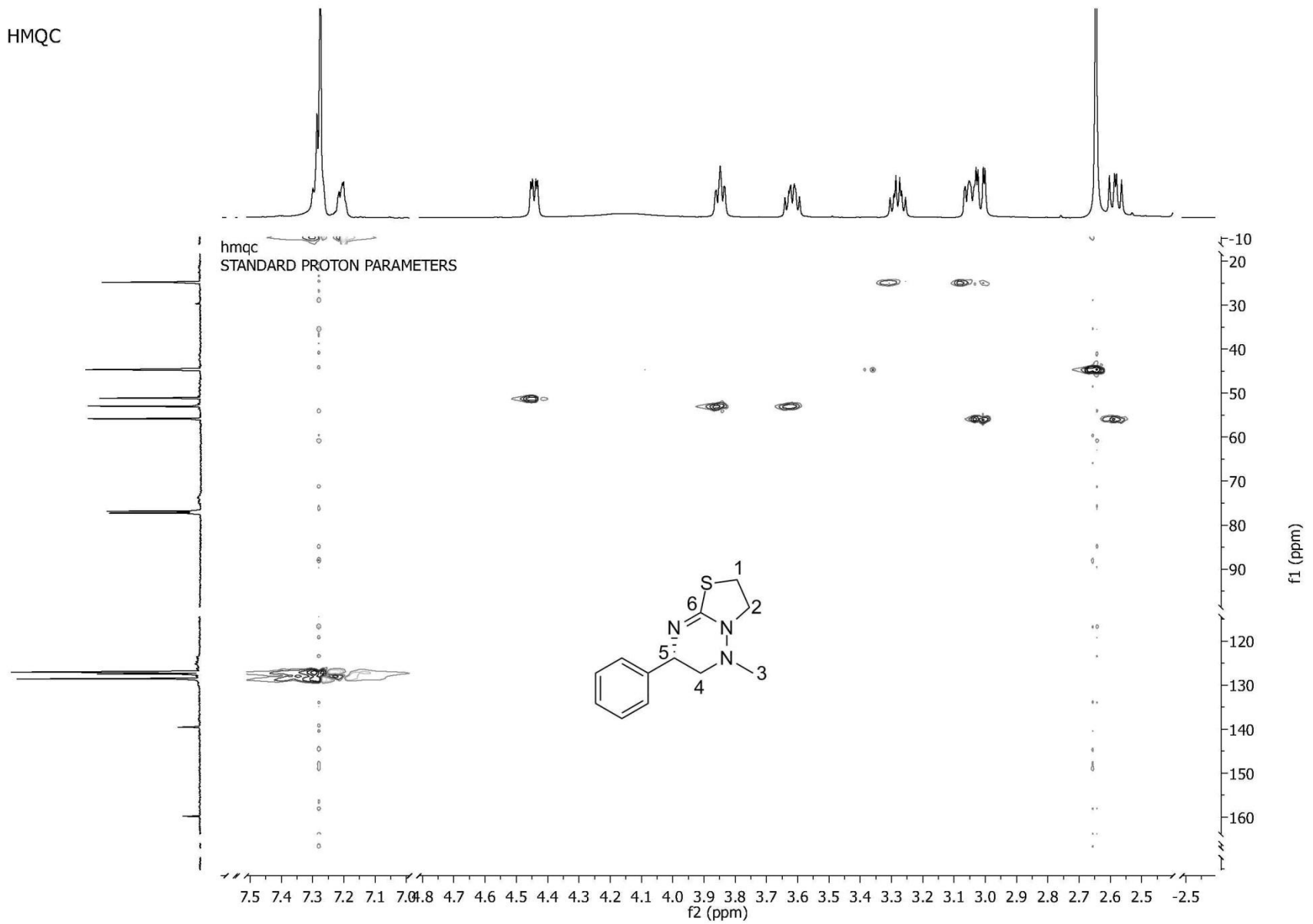

3.42
3.40
3.37
3.34
3.32
3.30
3.08
3.06
2.66
2.64
2.62
2.59
2.59
S
N
N
N
1.75
1.89
1.69
1.87
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


^{13}CNMR CDCl$_3$
150.27
53.90
48.95
47.24
46.43
27.60
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
N
S
N
N

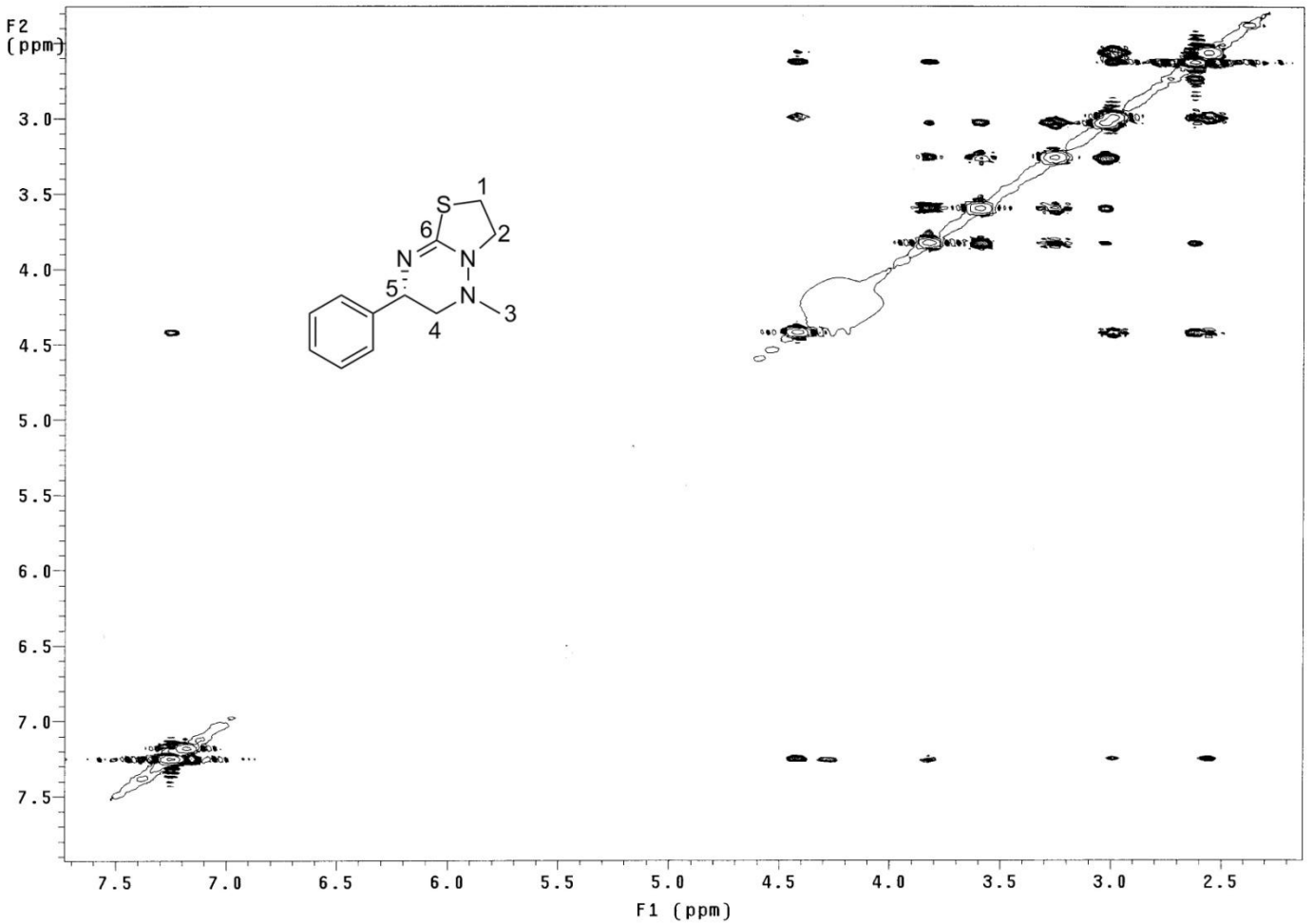

1HNMR CDCl3
S
1
2
6
N
N
5
N
3
4
4a
2
1
4b
5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
0.93
1.04
1.00
1.00
2.03
0.95
3.09

13CNMR CDCl3

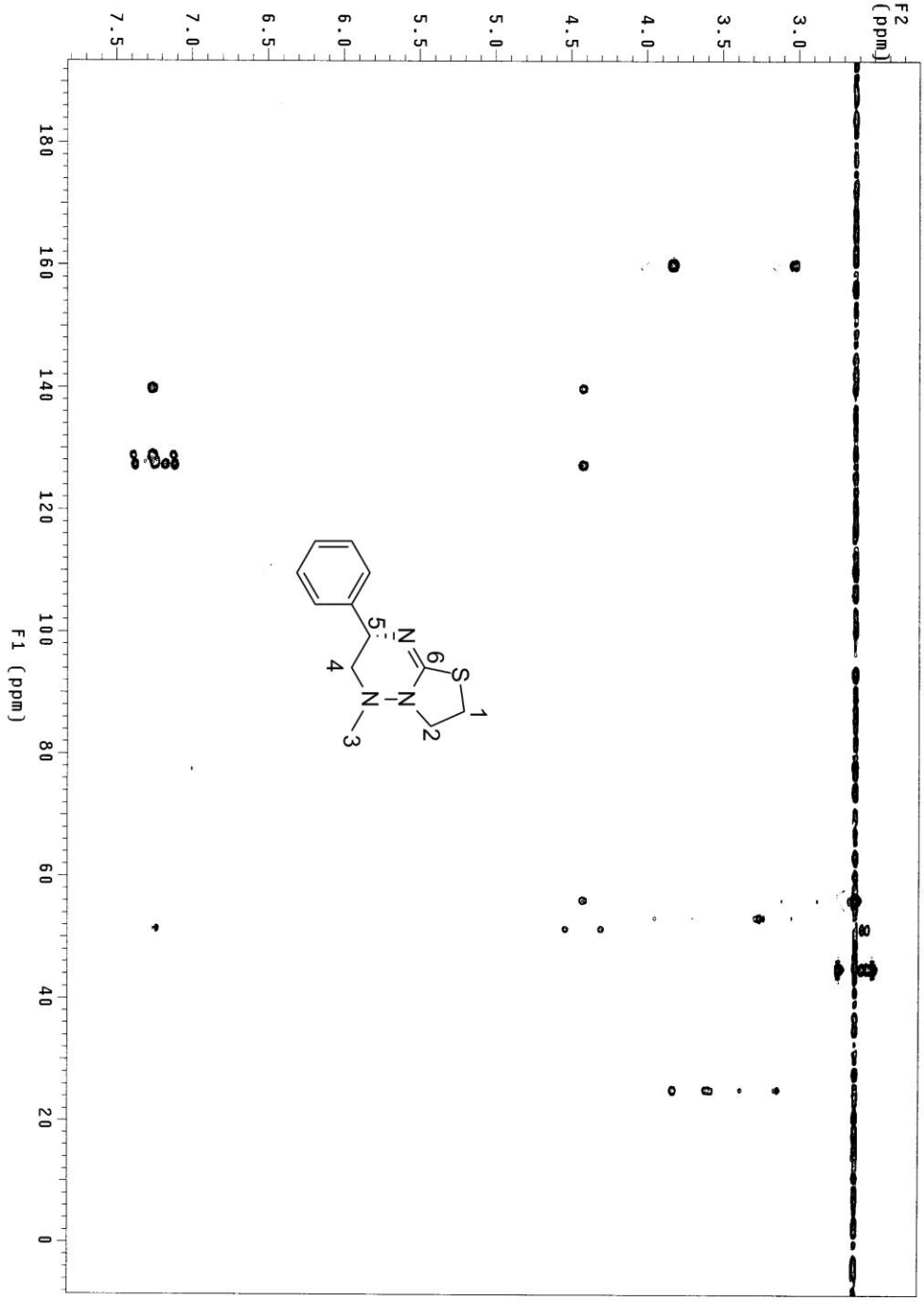



HMQC
hmqc
STANDARD PROTON PARAMETERS
f2 (ppm)
f1 (ppm)

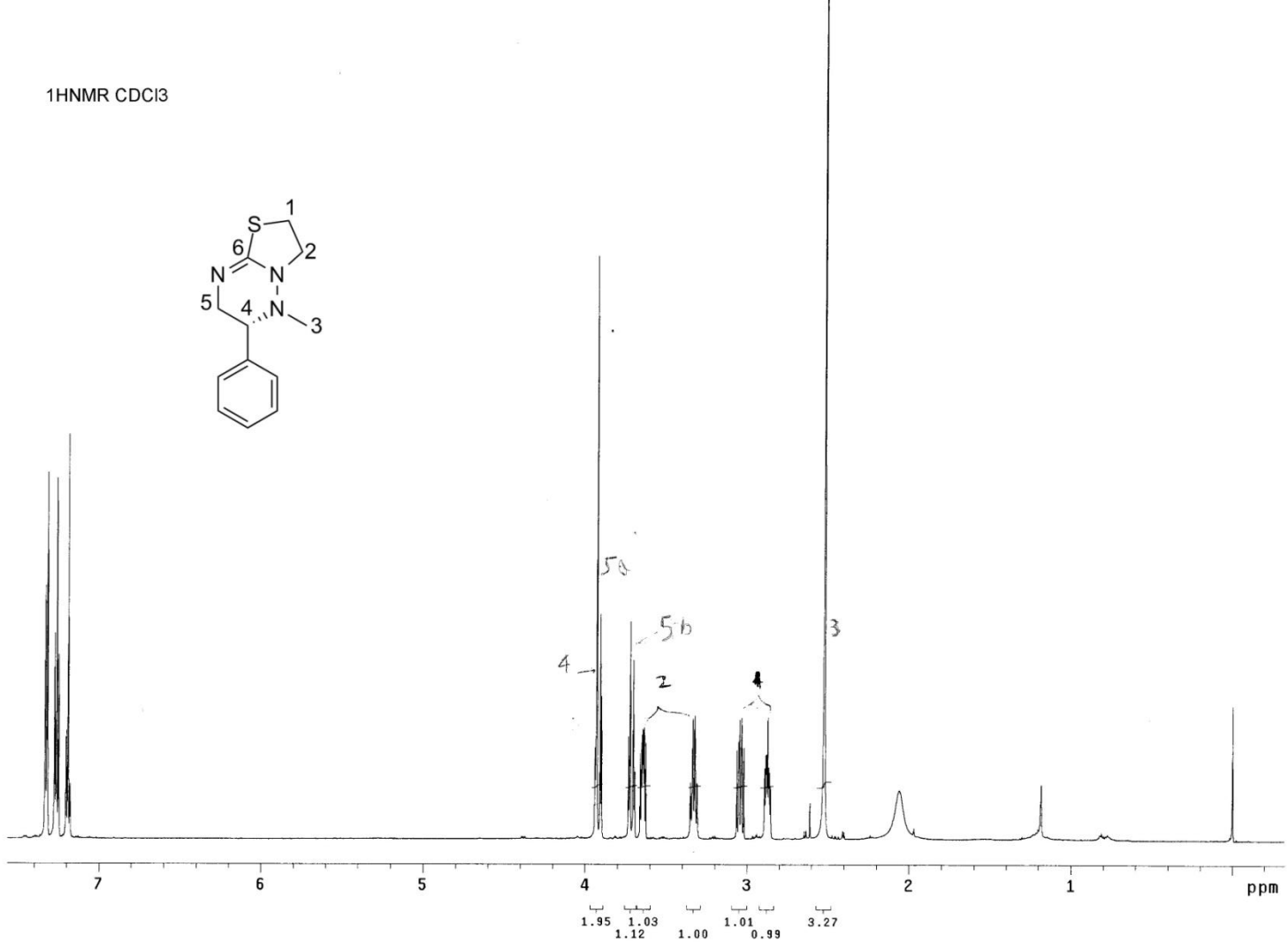
NOE

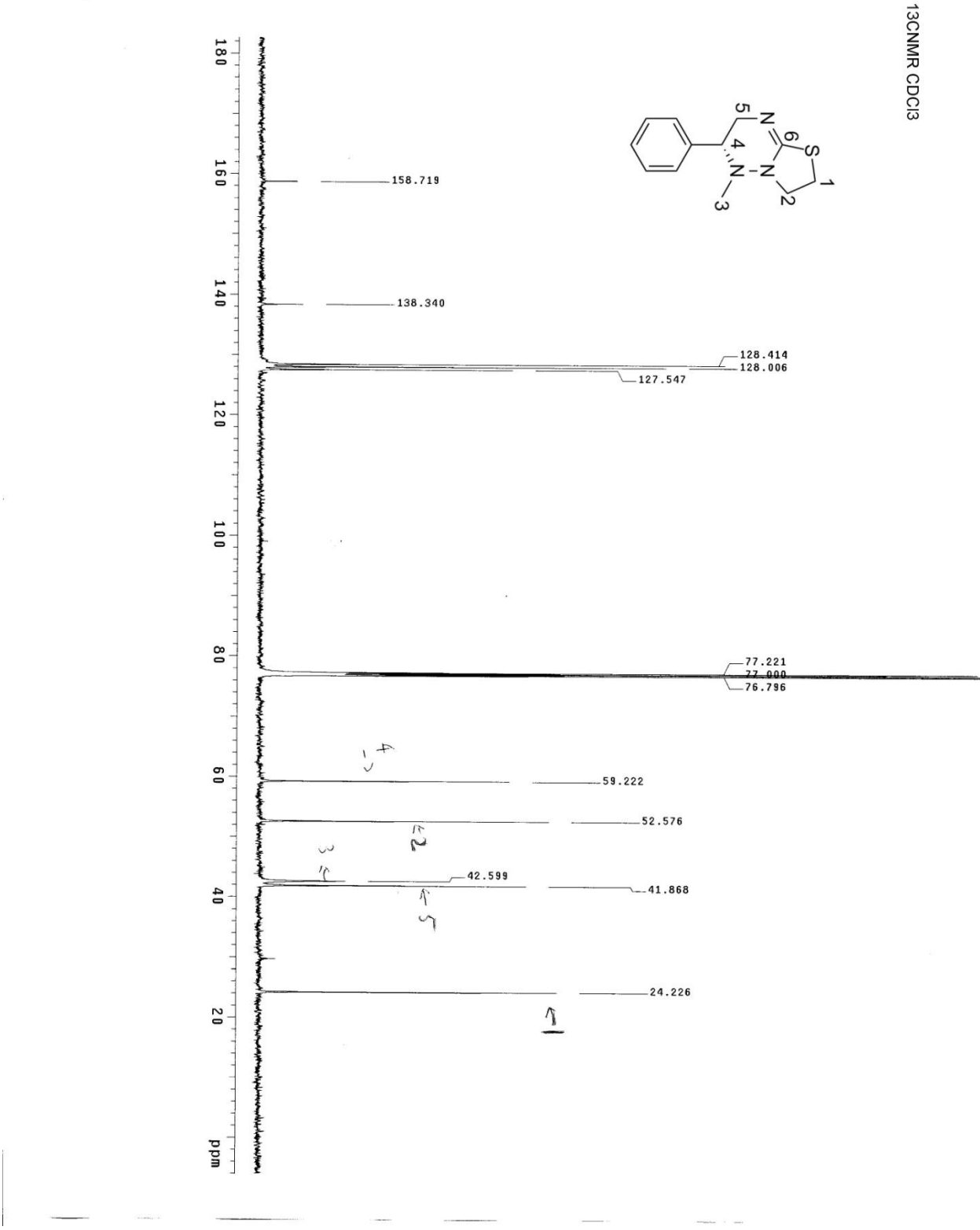

F2 (ppm)
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
S
1
2
3
4
5
6
N
N
N
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
F1 (ppm)

HMBC

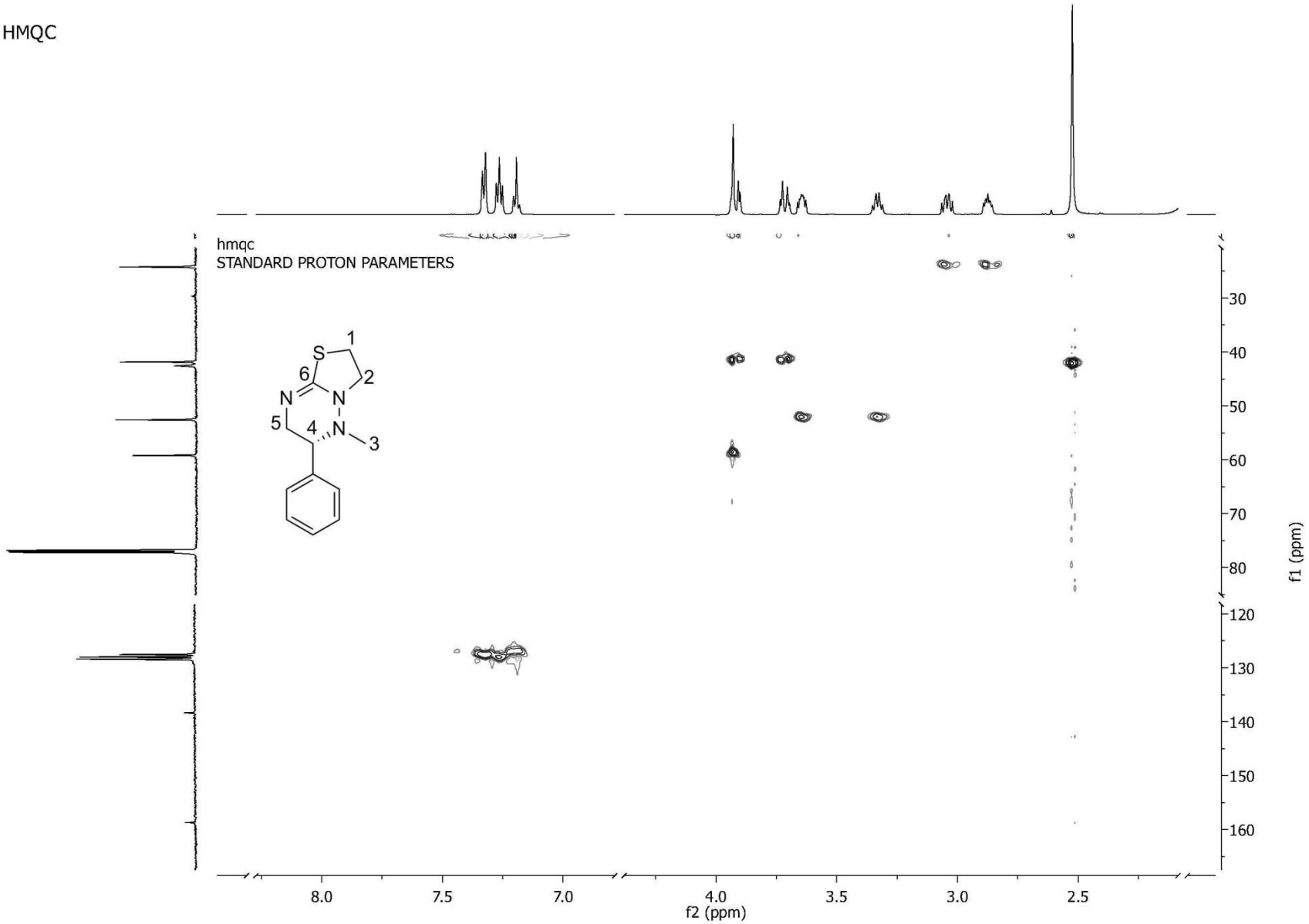


1HNMR CDCl3

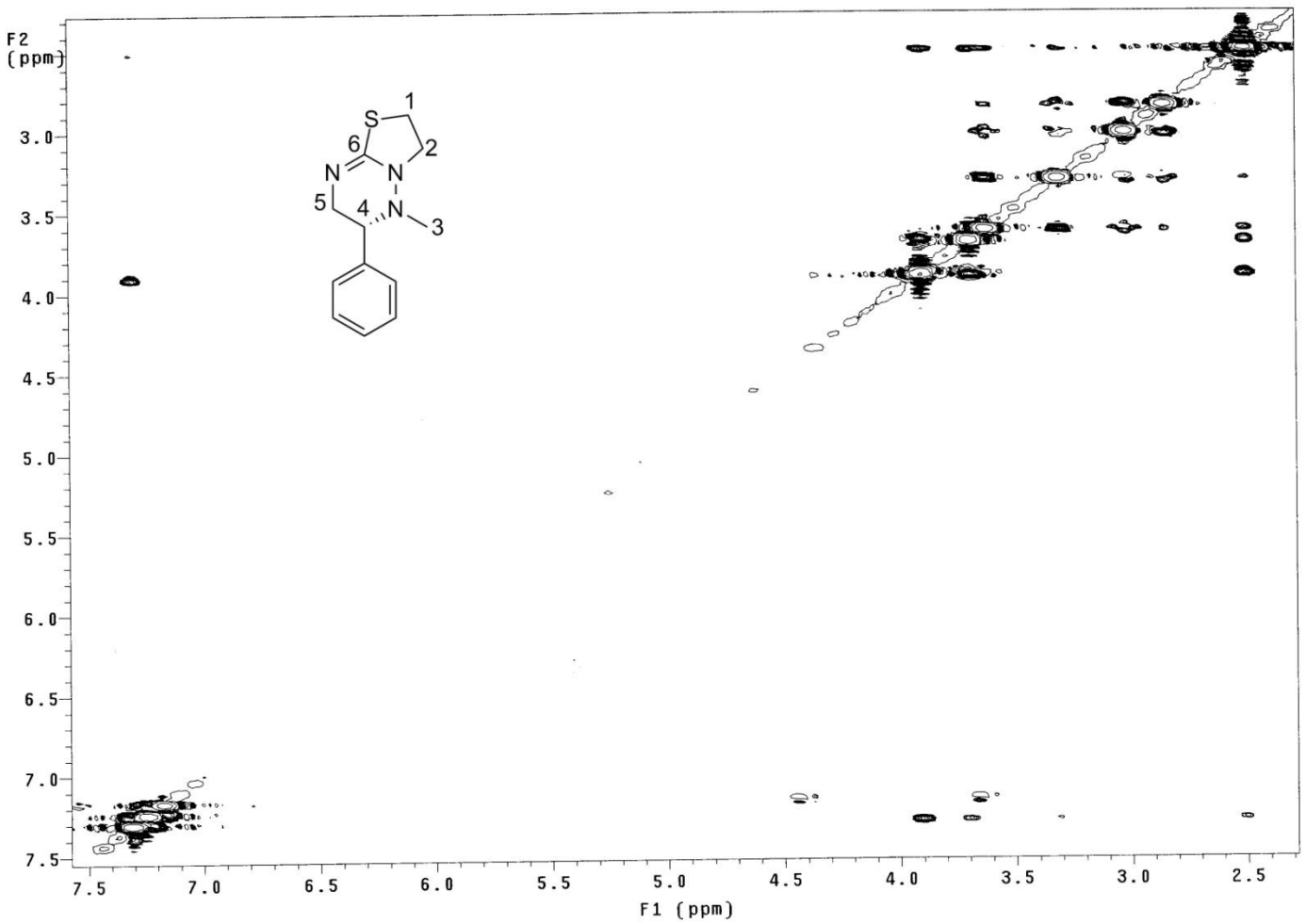



13CNMR CDCl3
158.719
138.340
128.414
128.006
127.547
77.221
77.000
76.796
59.222
52.576
42.599
41.868
24.226
ppm

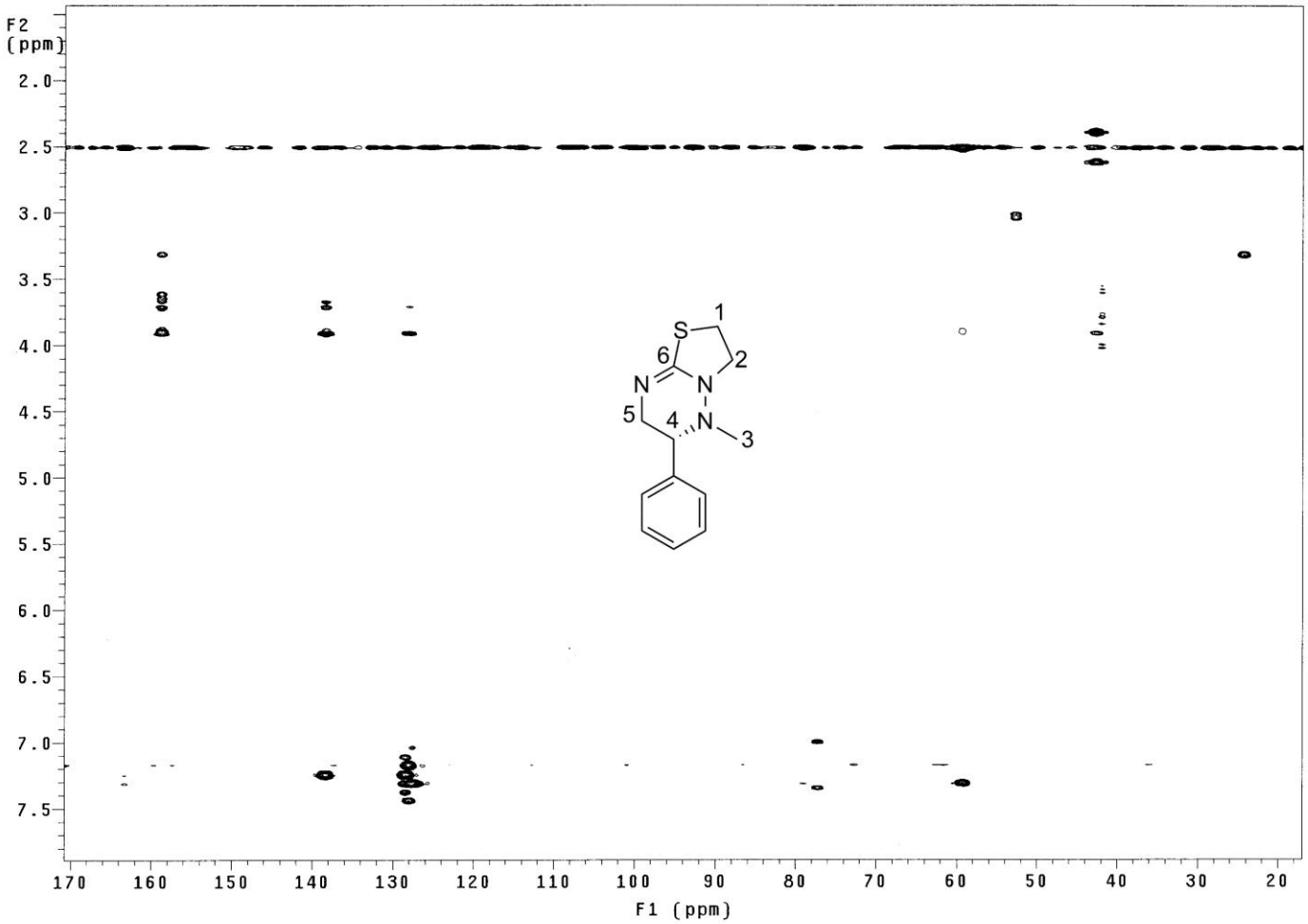
HMQC

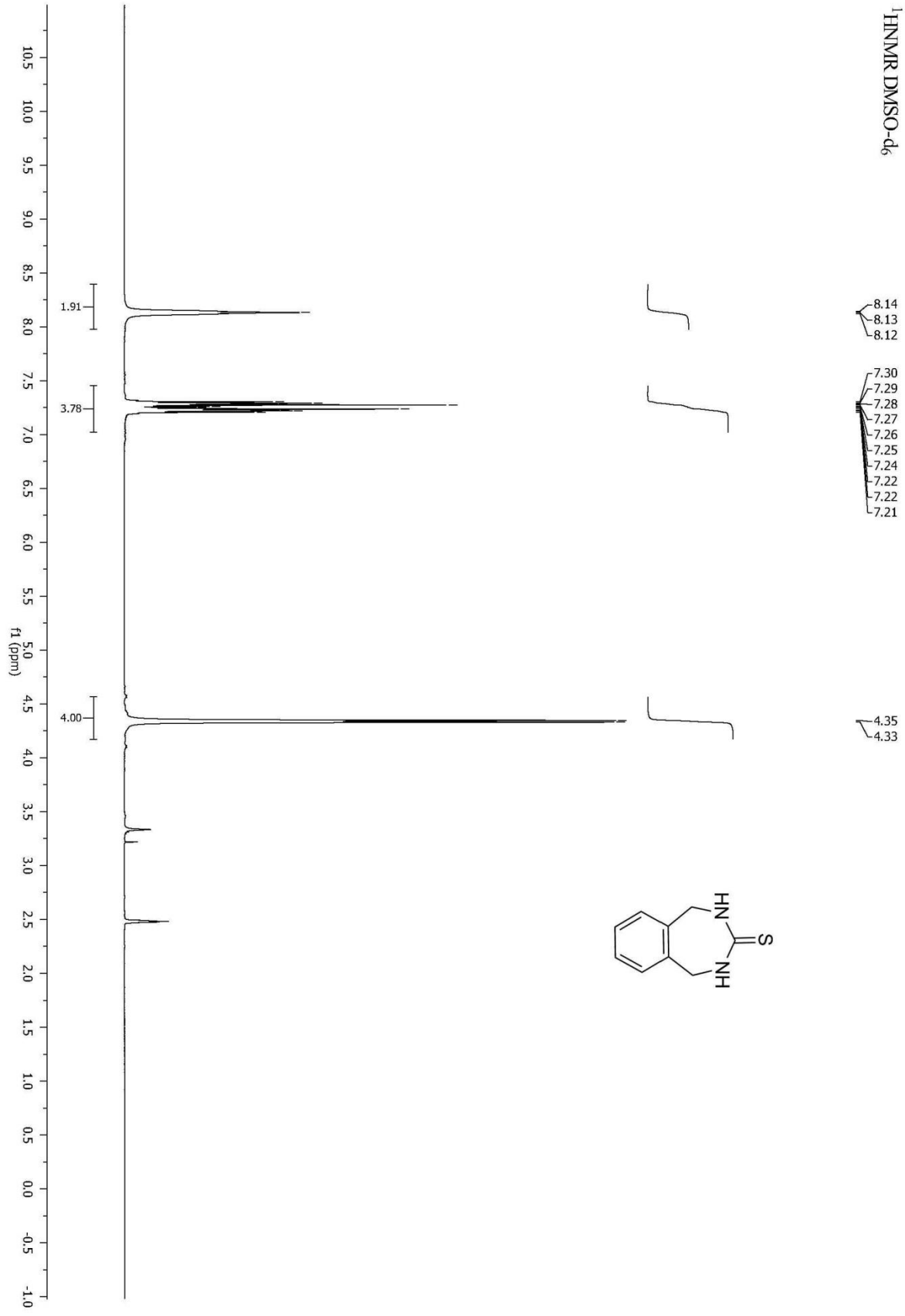

hmqc
STANDARD PROTON PARAMETERS
S
N
N
N
1
2
3
4
5
6
8.0
7.5
7.0
4.0
3.5
3.0
2.5
f2 (ppm)
30
40
50
60
70
80
120
130
140
150
160
f1 (ppm)

NOE

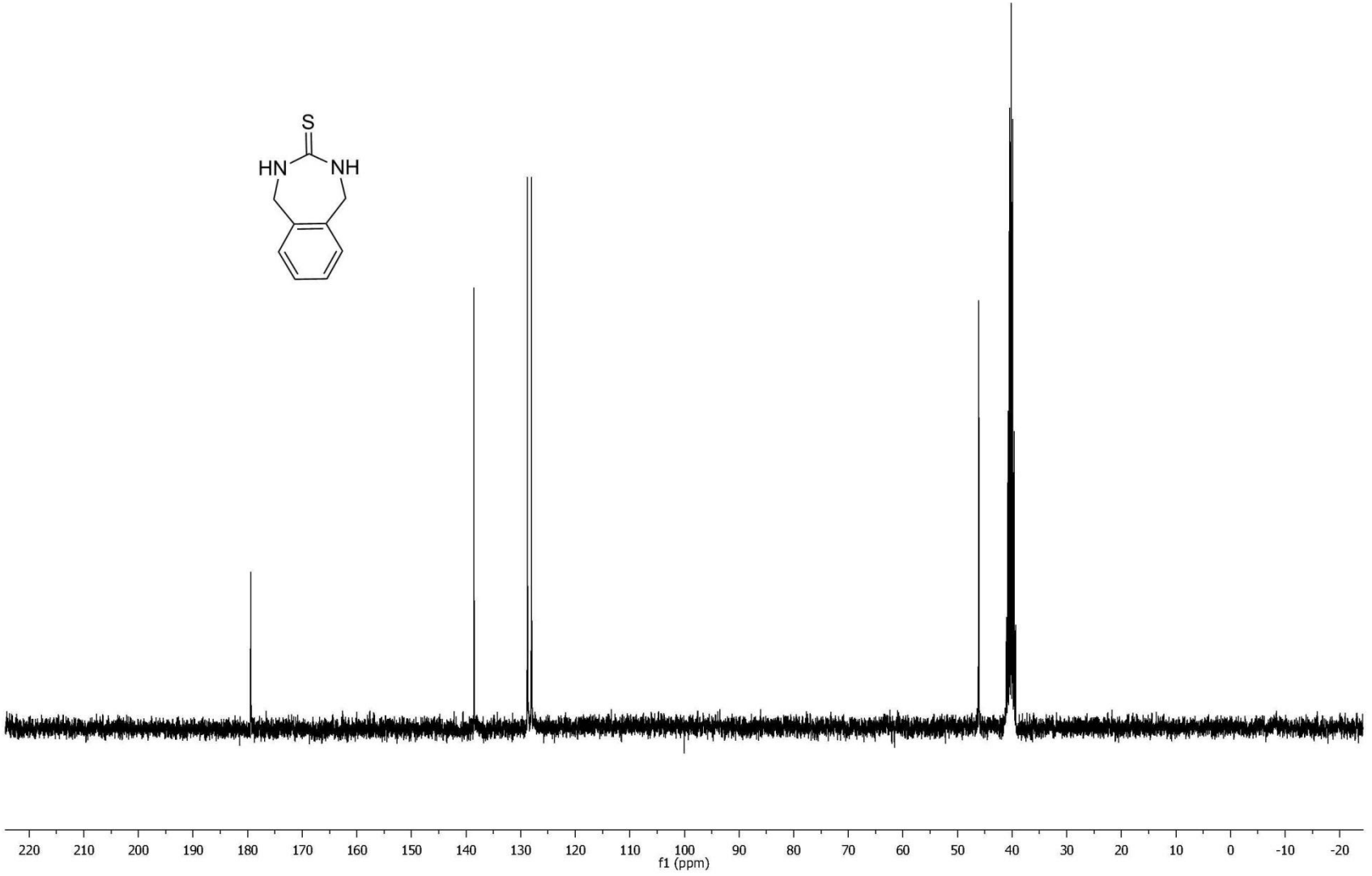

F2 (ppm)
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
S
1
2
6
N
N
5
4
N
3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
F1 (ppm)

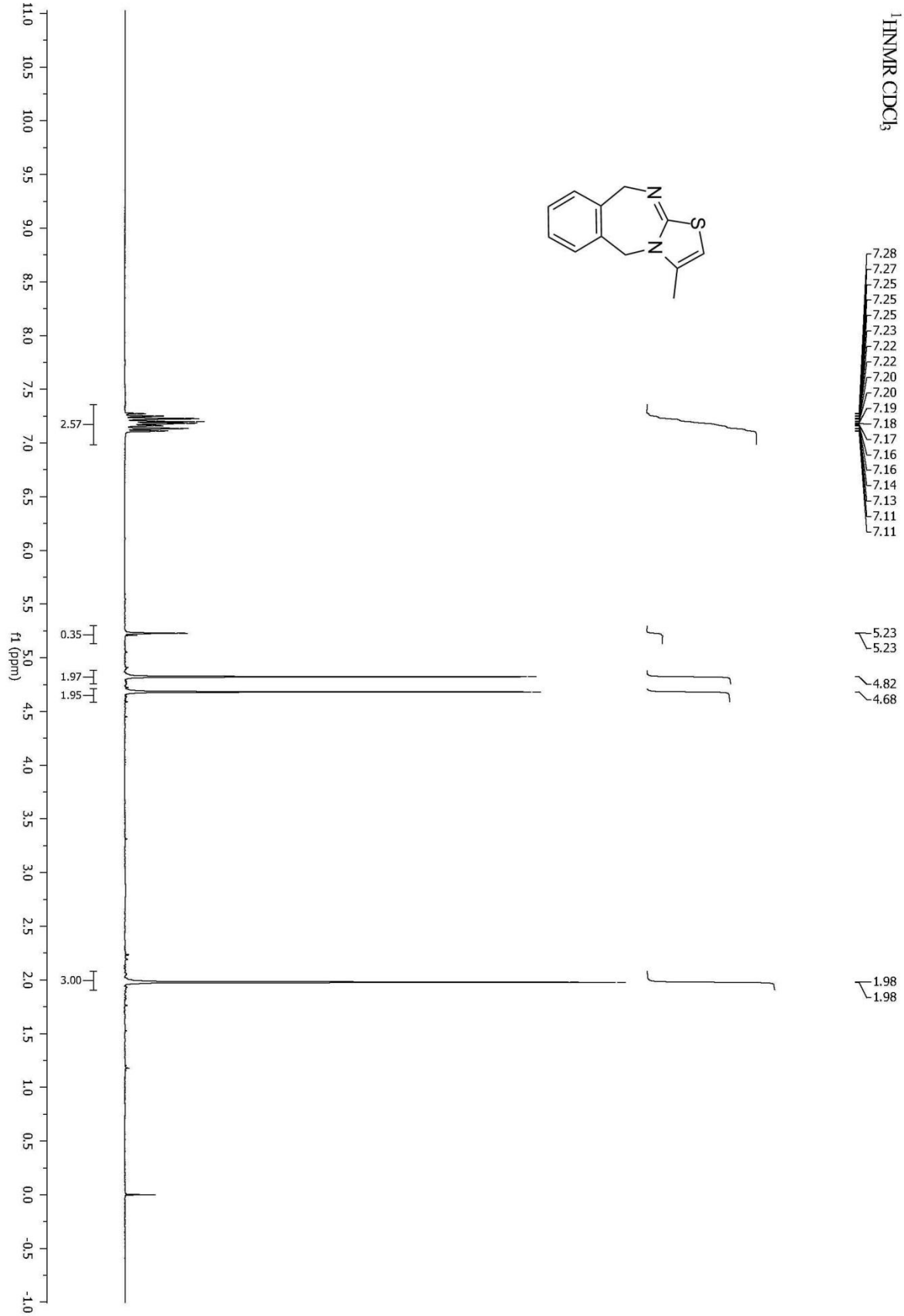
HMBC

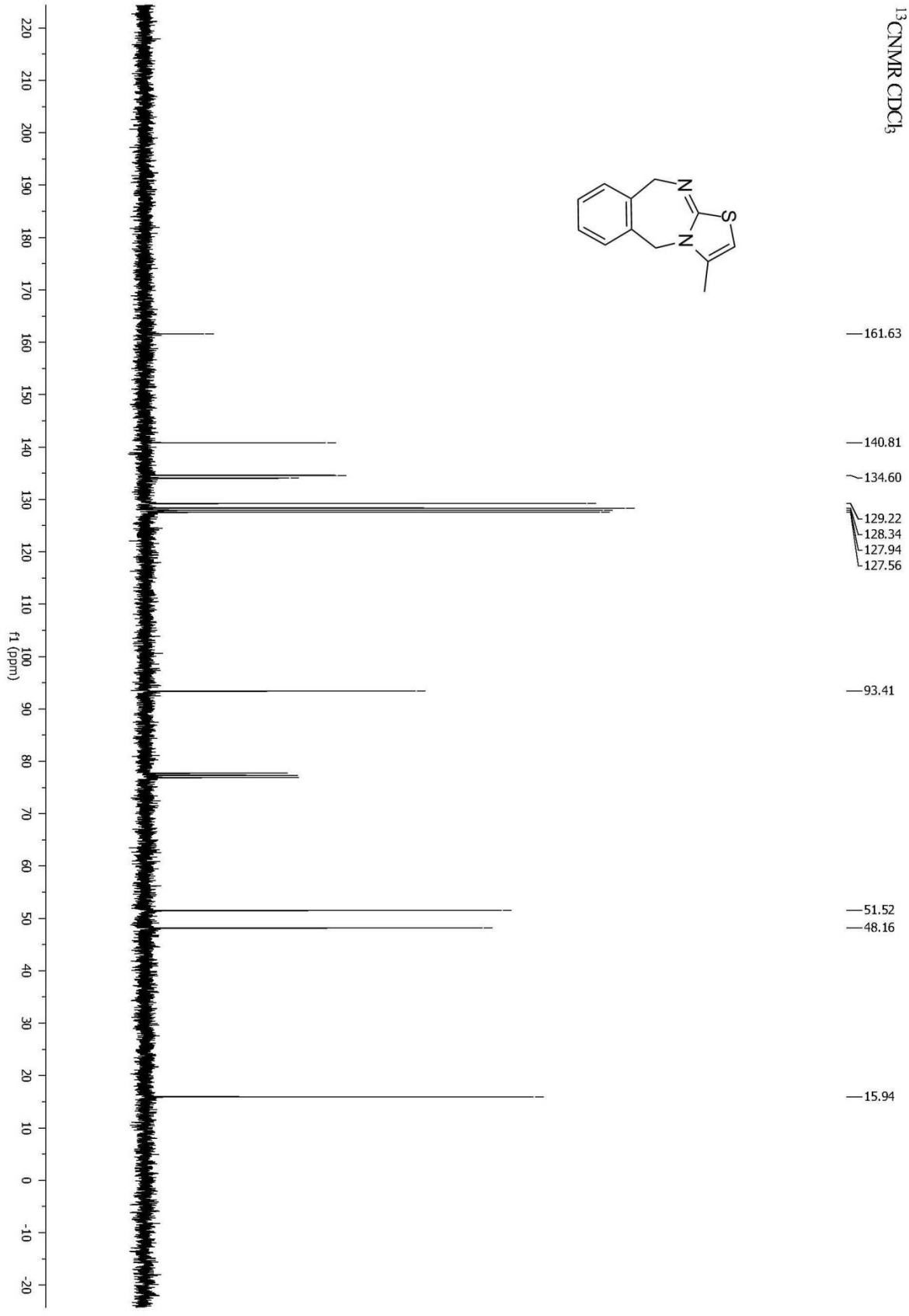

F2
(ppm)
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
F1 (ppm)
S
1
2
6
N
N
5
4
N
3

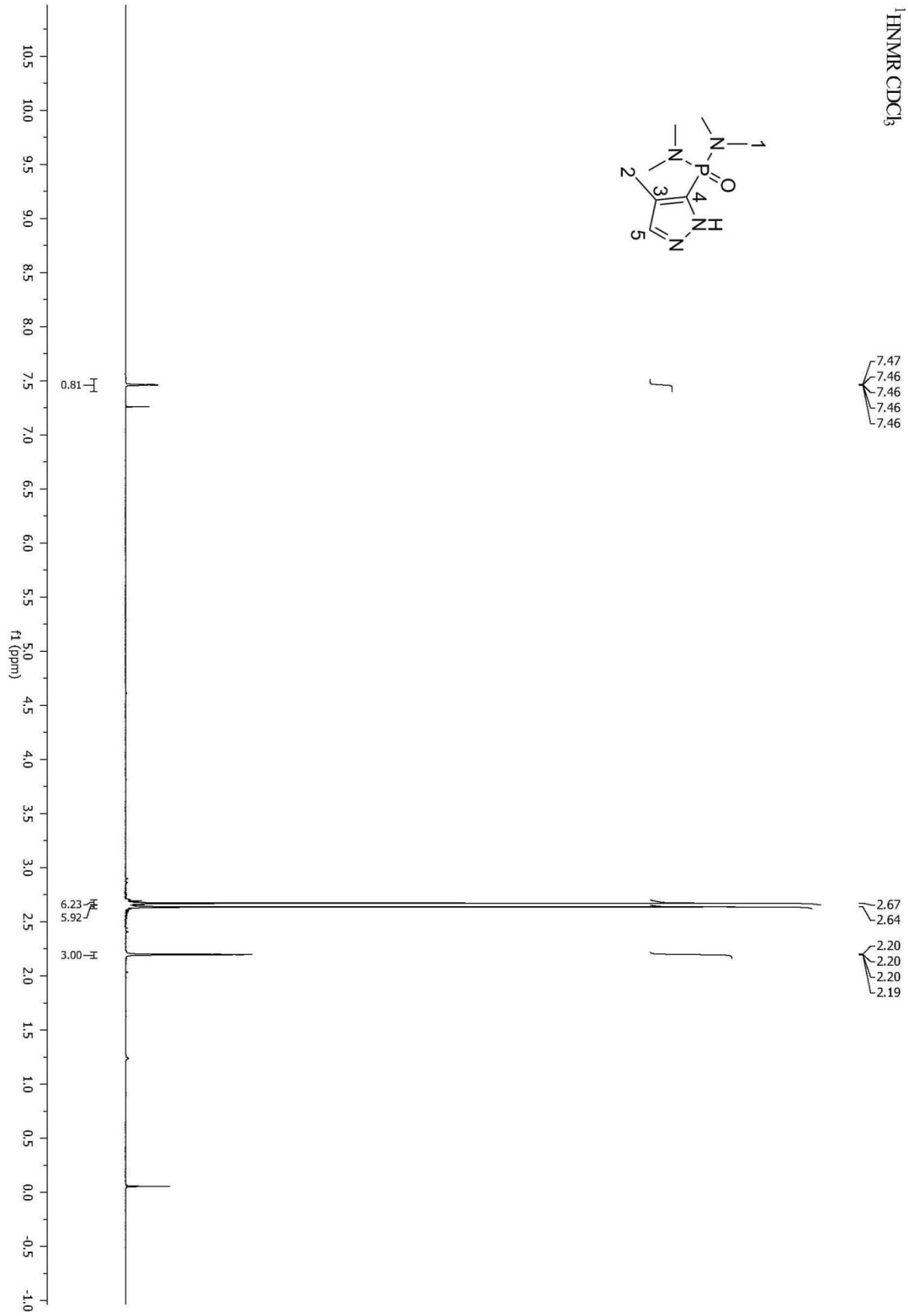

^{1}HNMR DMSO-d_6
8.14
8.13
8.12
7.30
7.29
7.28
7.27
7.26
7.25
7.24
7.22
7.22
7.21
4.35
4.33
1.91
3.78
4.00
f1 (ppm)
HN
NH
S

^{13}CNMR DMSO-d_6

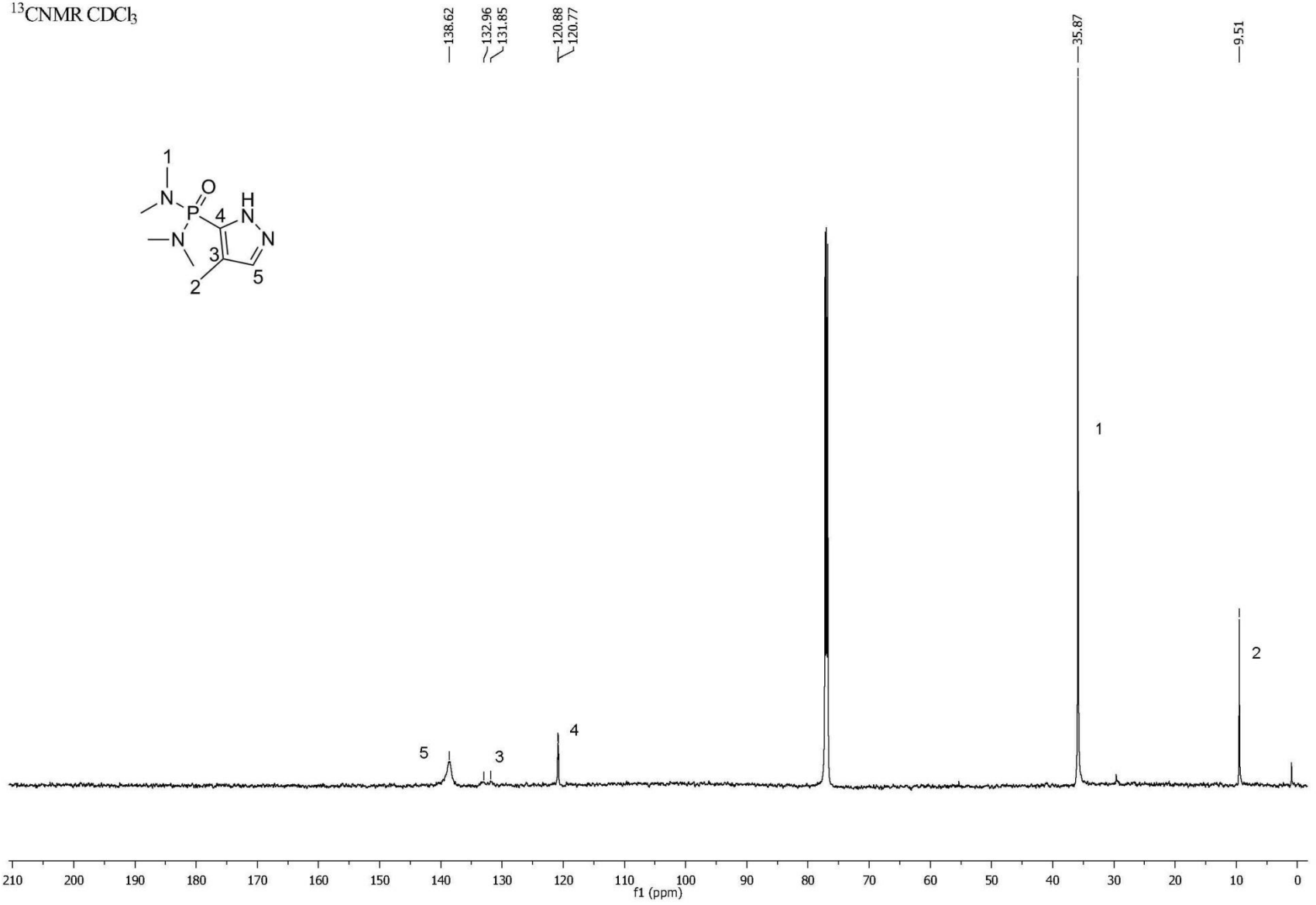


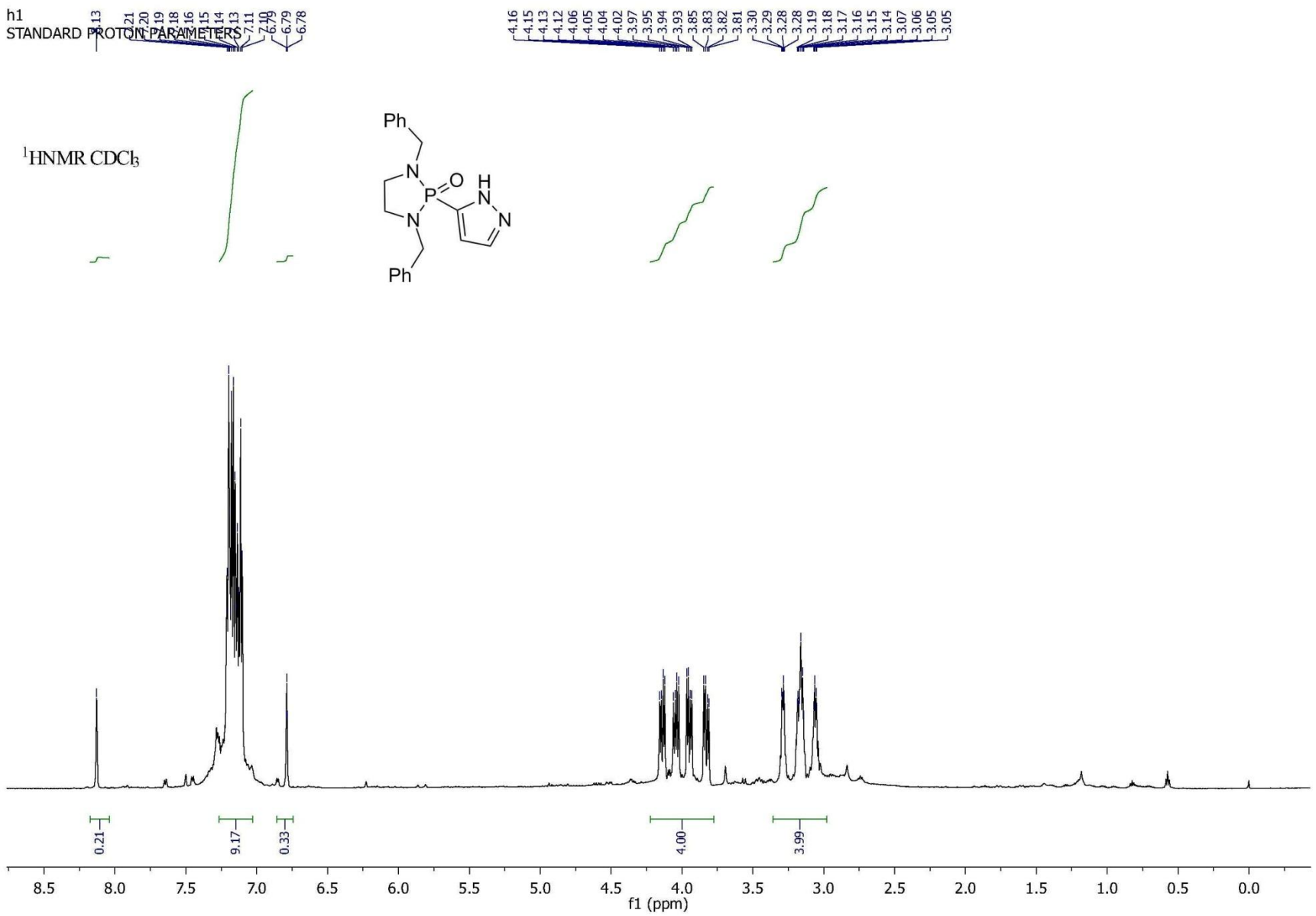

^{1}HNMR $CDCl_3$
f1 (ppm)
2.57
0.35
1.97
1.95
3.00
7.28
7.27
7.25
7.25
7.25
7.23
7.22
7.22
7.20
7.20
7.19
7.18
7.17
7.16
7.16
7.14
7.13
7.11
7.11
5.23
5.23
4.82
4.68
1.98
1.98

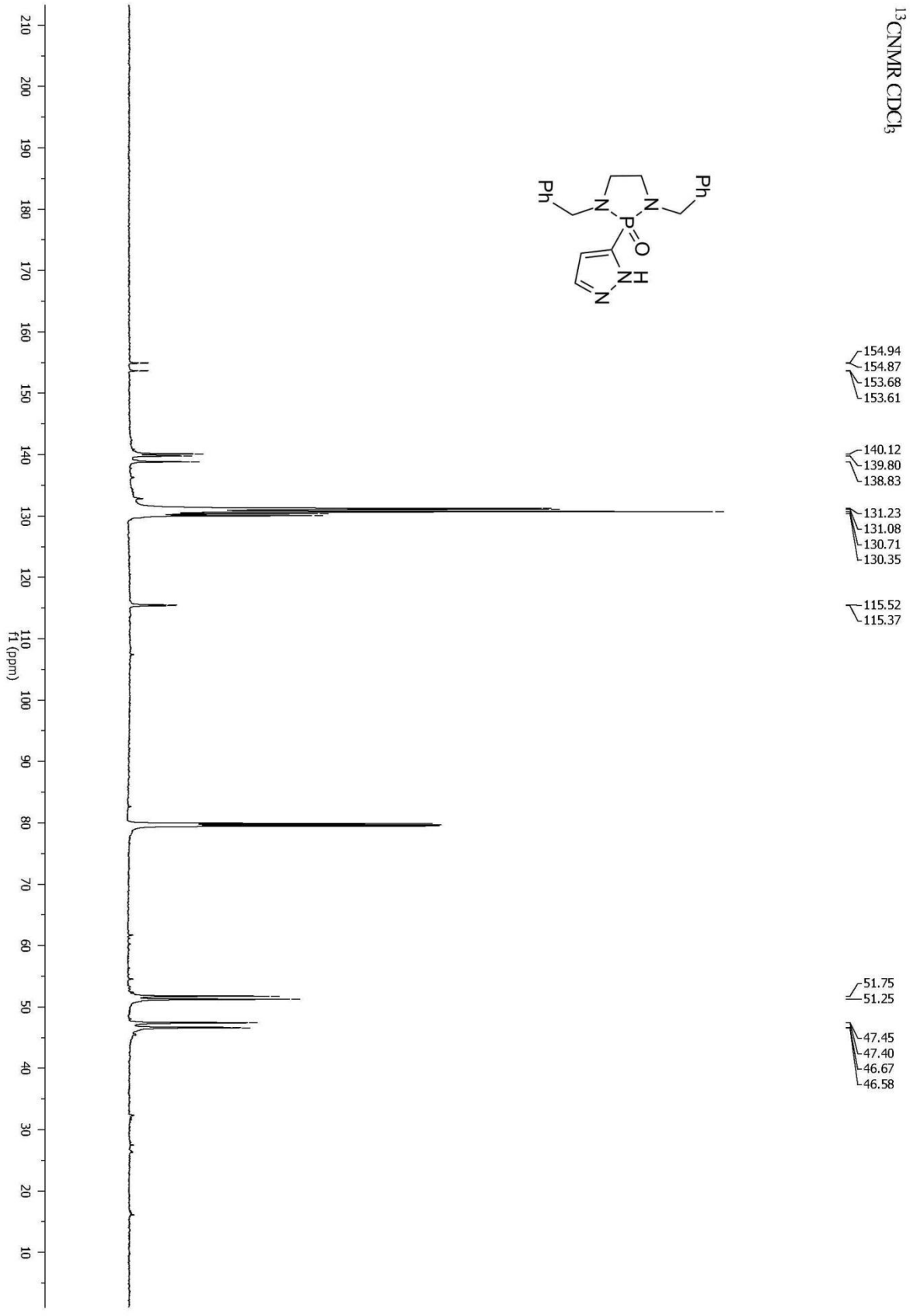

^{13}CNMR CDCl$_3$
N
S
N
161.63
140.81
134.60
129.22
128.34
127.94
127.56
93.41
51.52
48.16
15.94
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

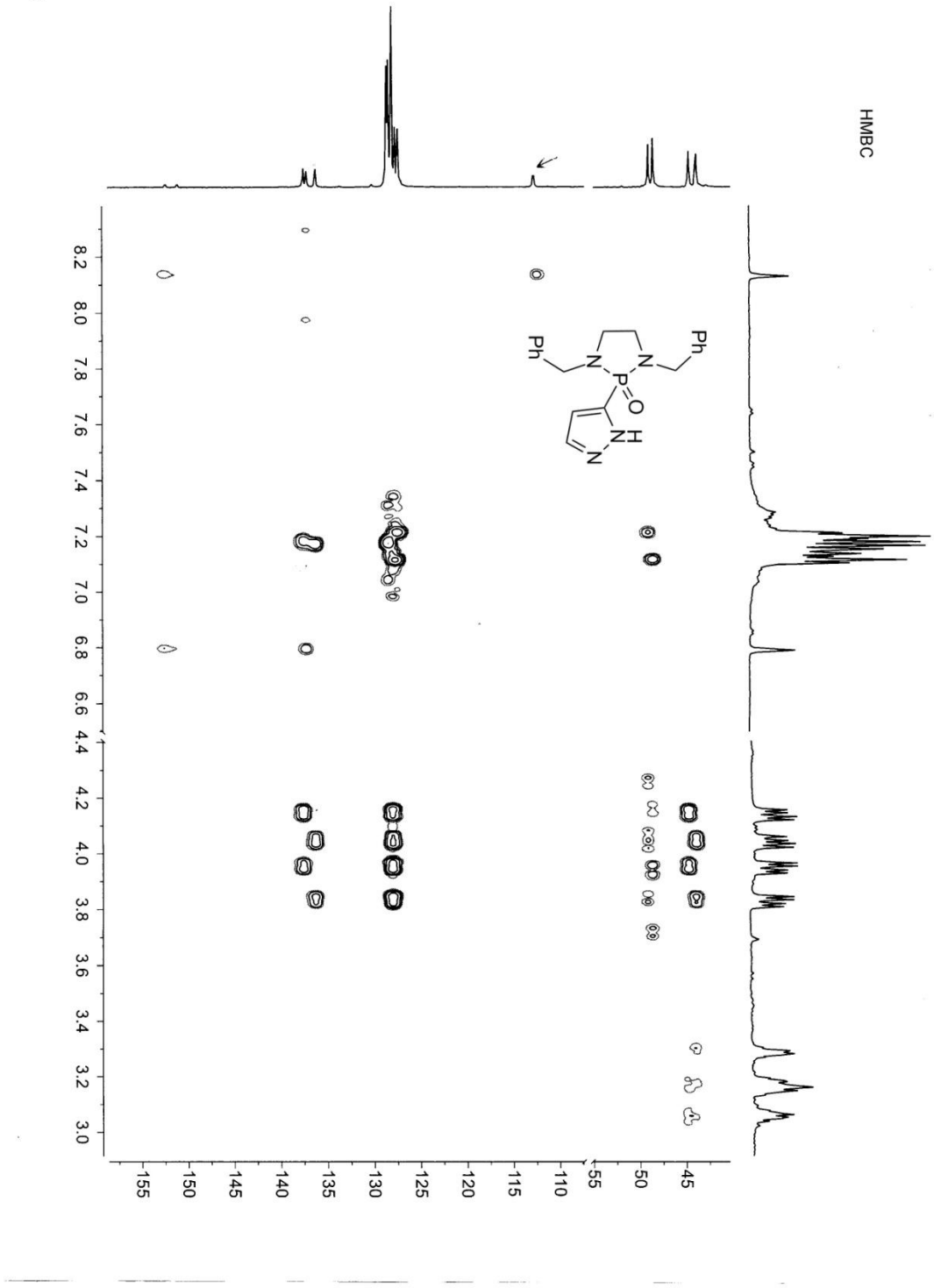

^{1}HNMR $CDCl_3$
7.47
7.46
7.46
7.46
7.46
2.67
2.64
2.20
2.20
2.20
2.19
0.81
6.23
5.92
3.00
f1 (ppm)

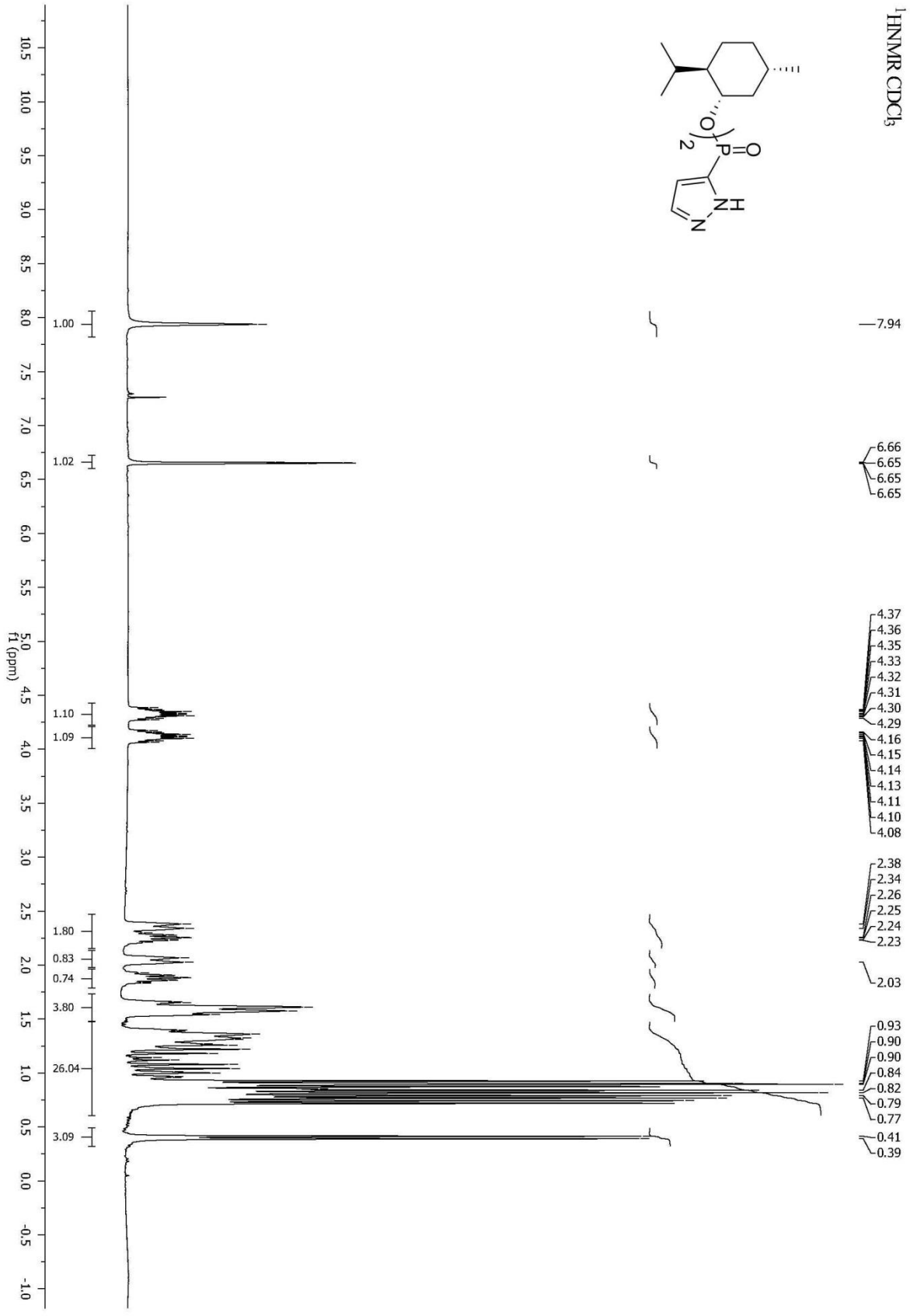
^{13}CNMR $CDCl_3$

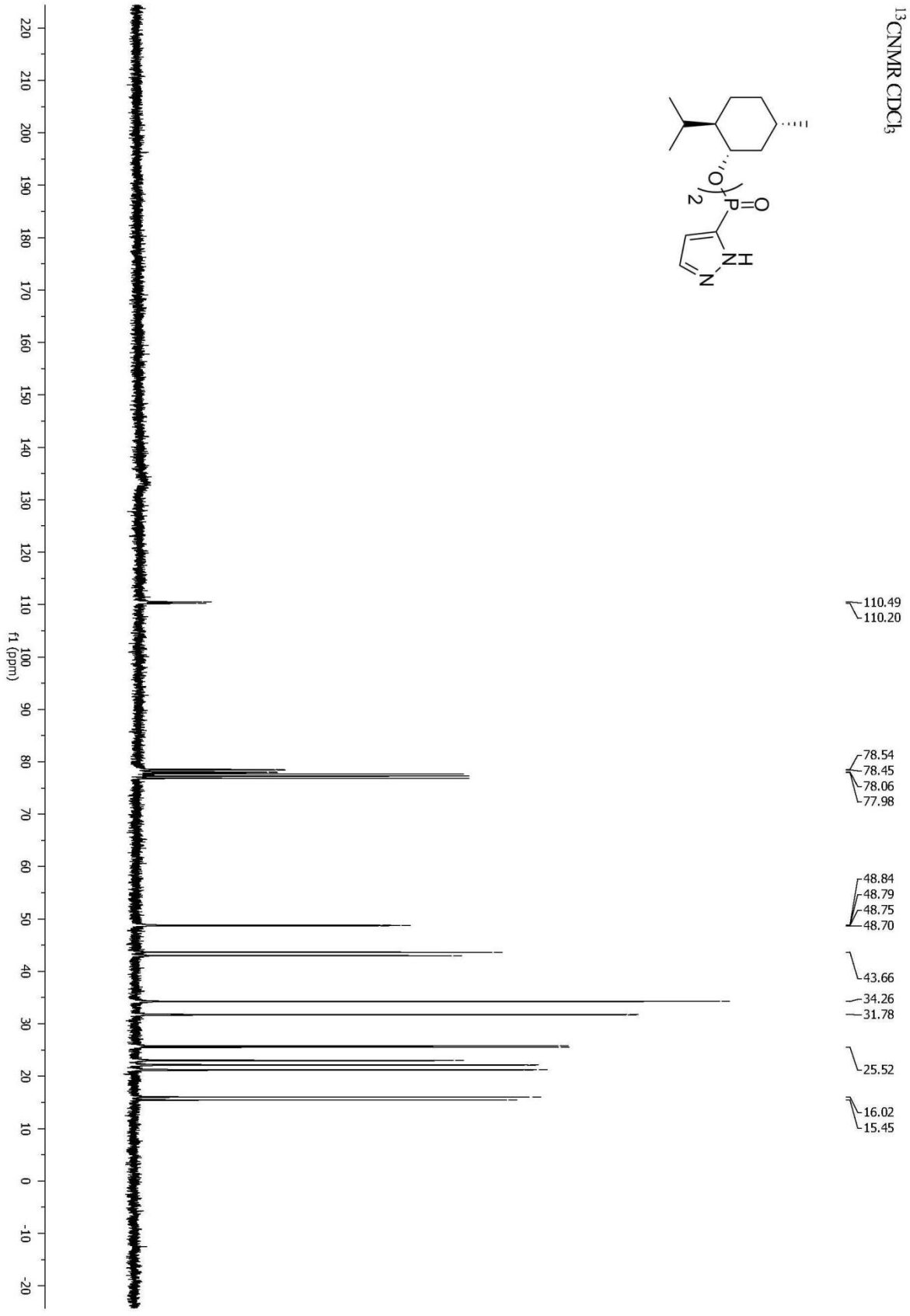


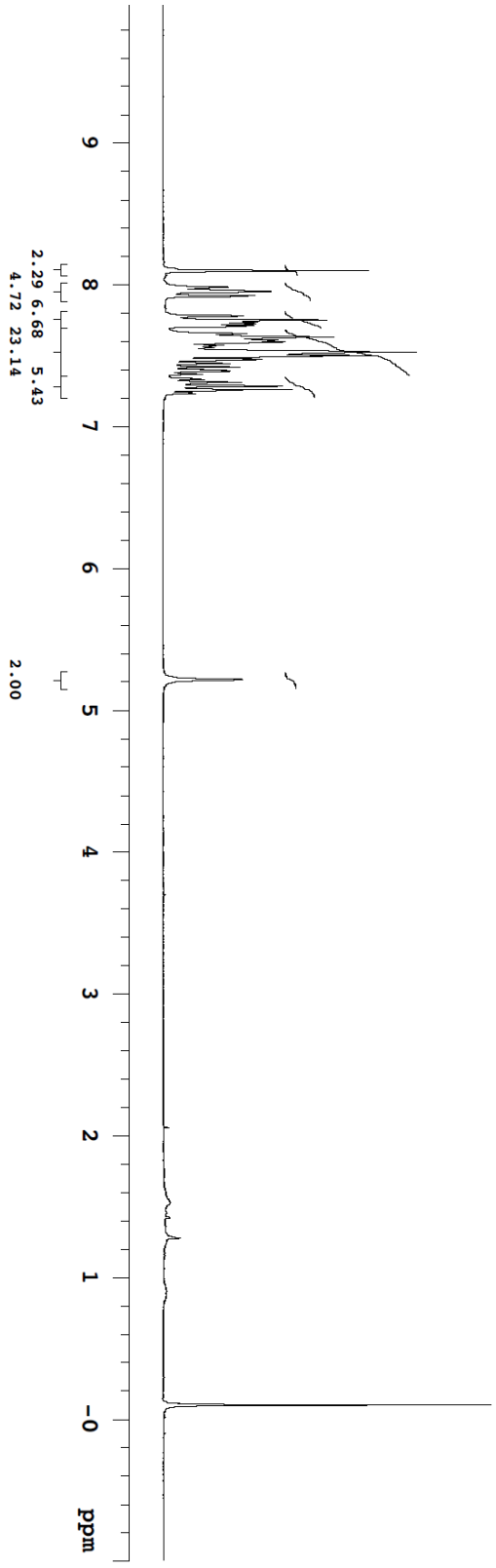

h1
STANDARD PROTON PARAMETERS
8.13
7.21
7.20
7.19
7.18
7.16
7.15
7.14
7.13
7.11
7.10
6.79
6.79
6.78
4.16
4.15
4.13
4.12
4.06
4.05
4.04
4.02
3.97
3.95
3.94
3.93
3.85
3.83
3.82
3.81
3.30
3.29
3.28
3.28
3.19
3.18
3.17
3.16
3.15
3.14
3.07
3.06
3.05
3.05
1HNMR CDCl3
Ph
N
P
O
H
N
N
N
Ph
0.21
9.17
0.33
4.00
3.99
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

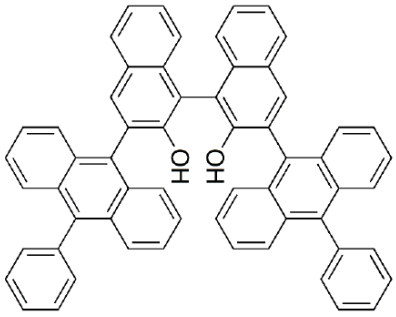

^{13}CNMR CDCl$_3$
Ph
Ph
N
N
P
O
N
H
N
154.94
154.87
153.68
153.61
140.12
139.80
138.83
131.23
131.08
130.71
130.35
115.52
115.37
51.75
51.25
47.45
47.40
46.67
46.58
f1 (ppm)

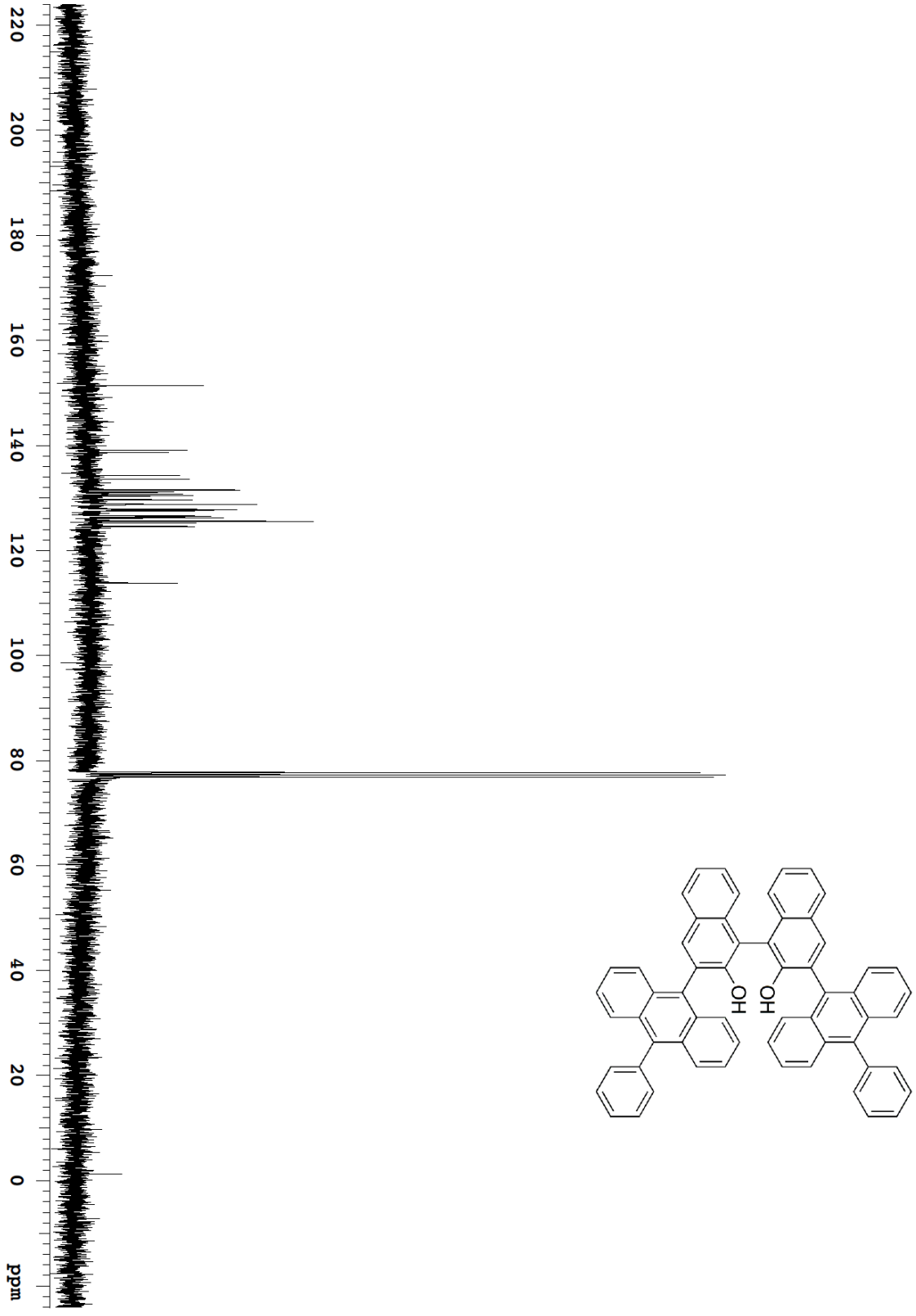

HMBC
Ph
Ph
N
N
P
O
N
H
N
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
155
150
145
140
135
130
125
120
115
110
55
50
45

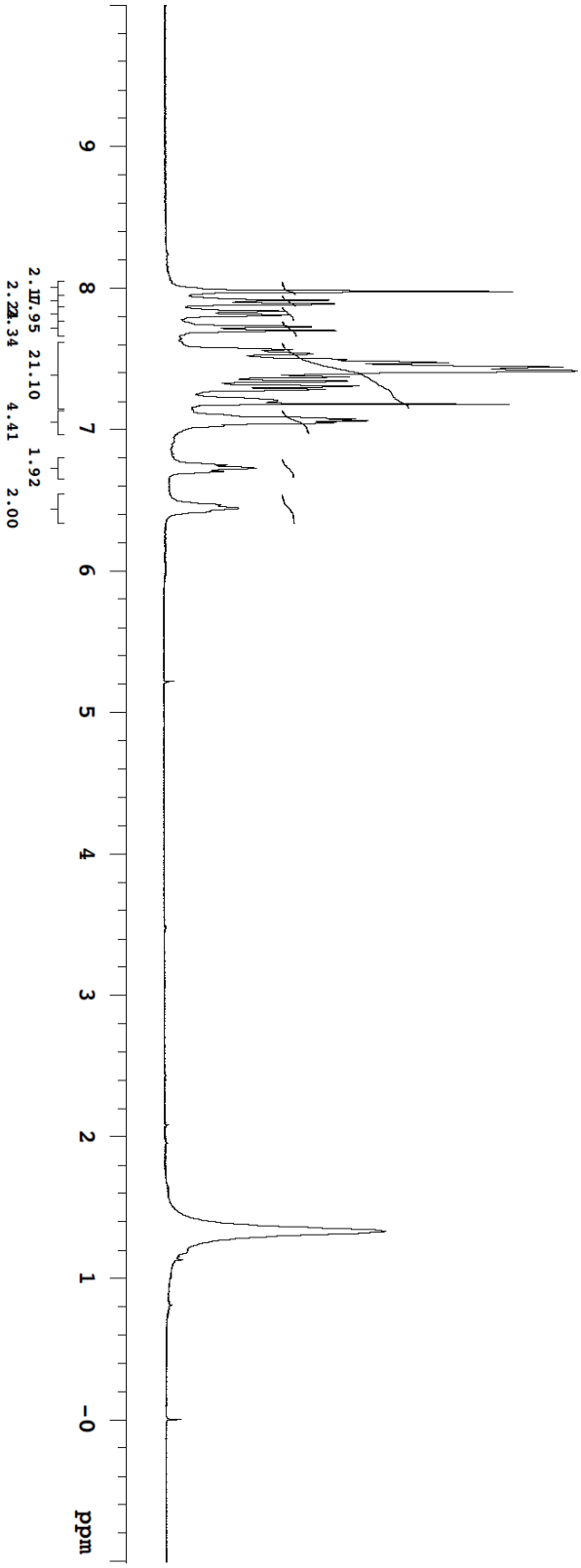

^{1}HNMR CDCl$_3$
f1 (ppm)
1.00
1.02
1.10
1.09
1.80
0.83
0.74
3.80
26.04
3.09
7.94
6.66
6.65
6.65
6.65
4.37
4.36
4.35
4.33
4.32
4.31
4.30
4.29
4.16
4.15
4.14
4.13
4.11
4.10
4.08
2.38
2.34
2.26
2.25
2.24
2.23
2.03
0.93
0.90
0.90
0.84
0.82
0.79
0.77
0.41
0.39

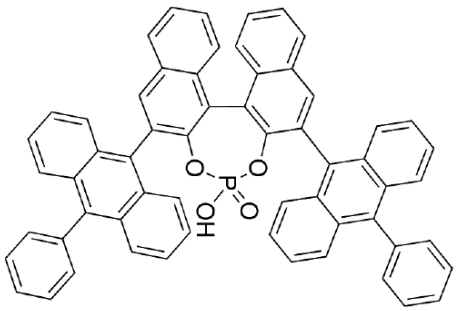

^{13}CNMR CDCl$_3$
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
110.49
110.20
78.54
78.45
78.06
77.98
48.84
48.79
48.75
48.70
43.66
34.26
31.78
25.52
16.02
15.45

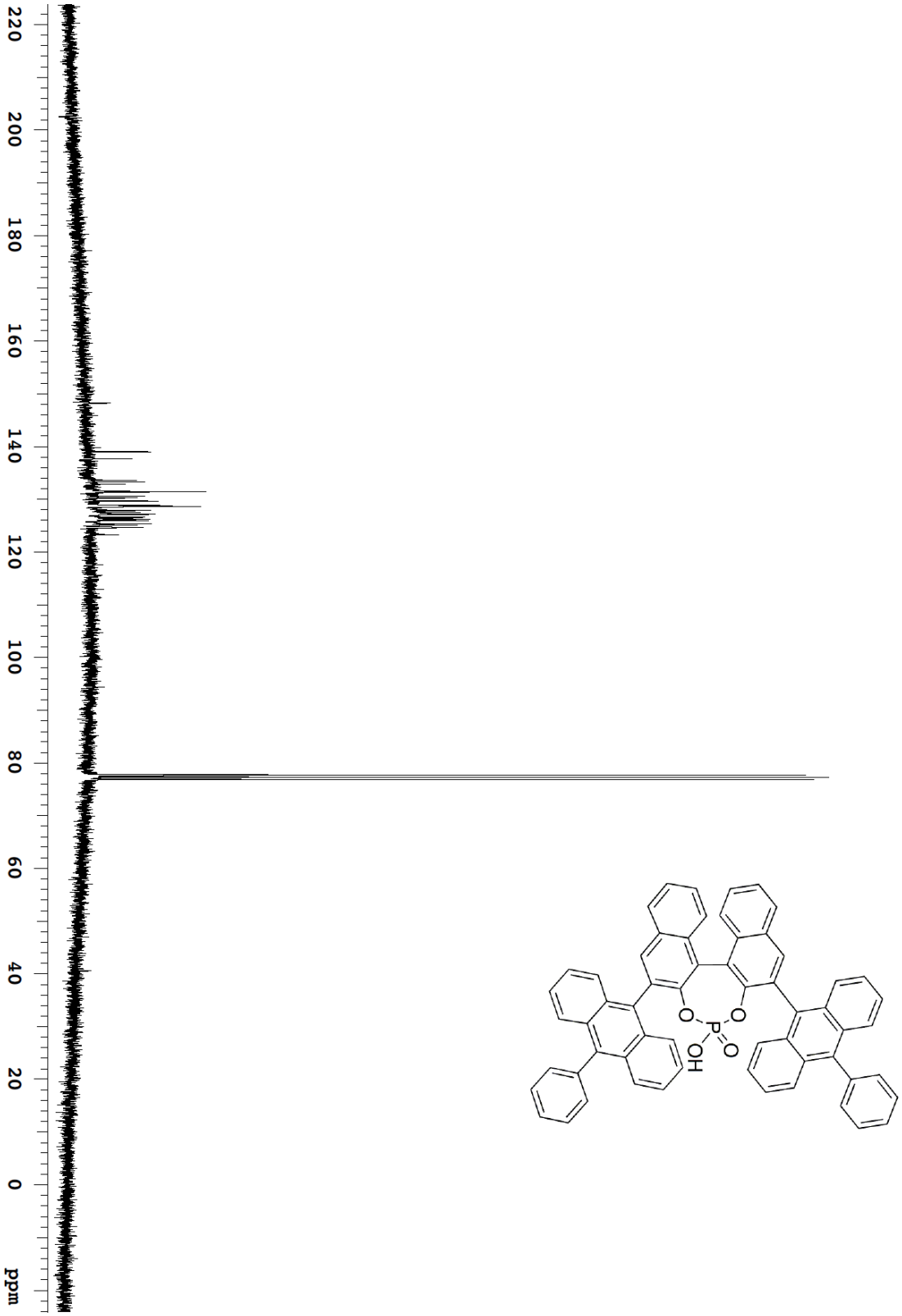

9
8
7
6
5
4
3
2
1
0
ppm
2.29 6.68 5.43
4.72 23.14
2.00

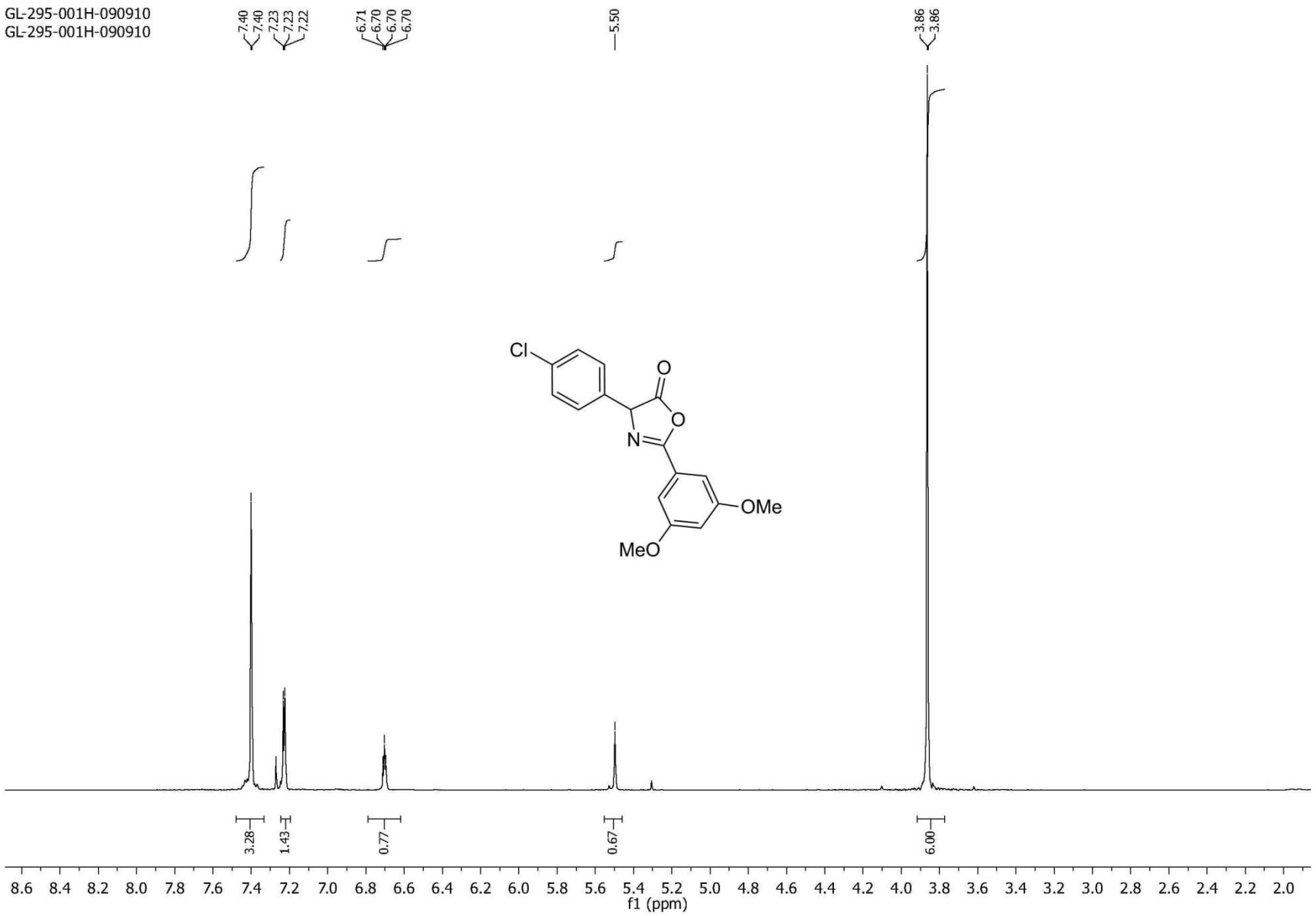

OH
HO

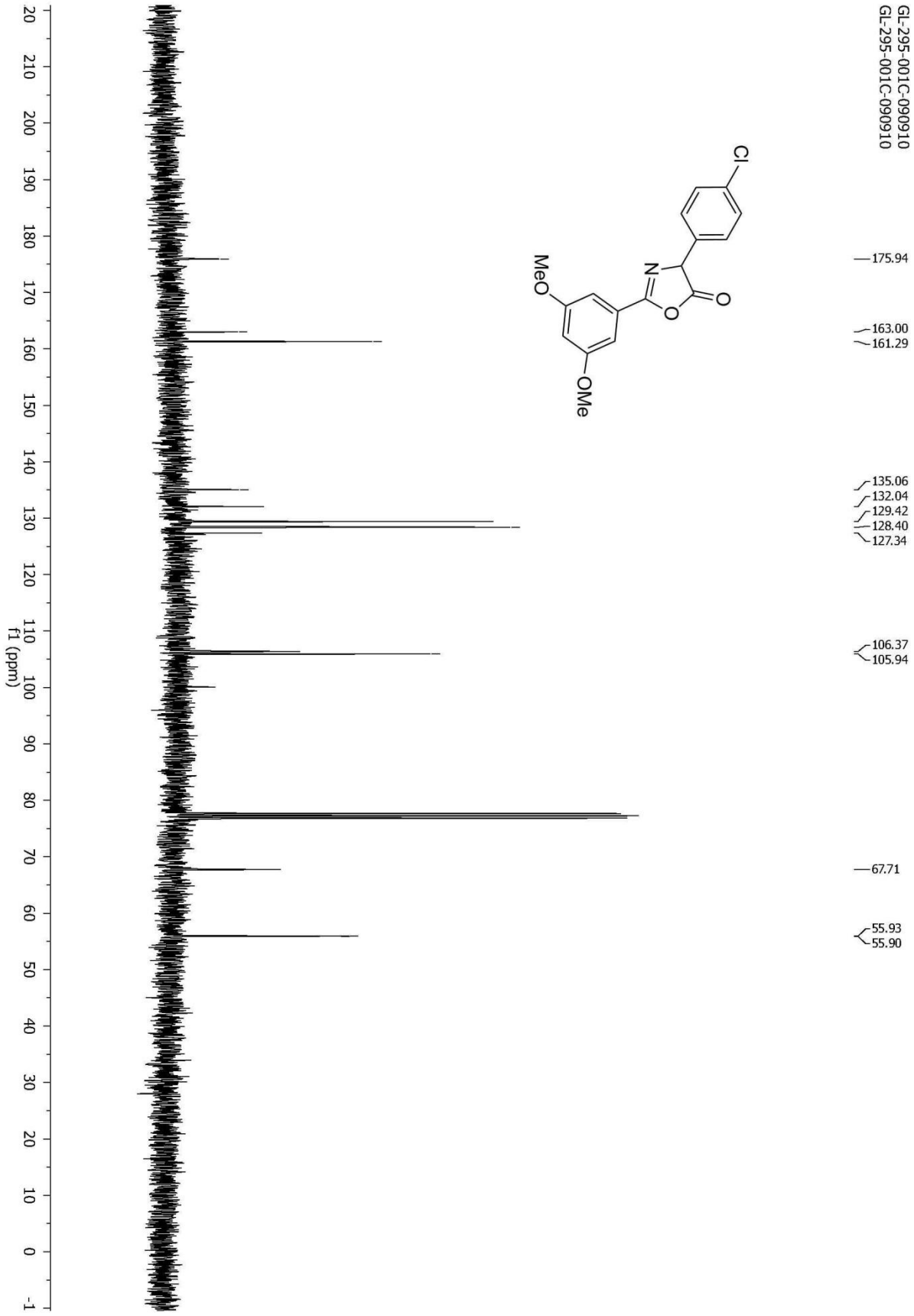

220
200
180
160
140
120
100
80
60
40
20
0
ppm
OH
HO


9
8
7
6
5
4
3
2
1
0
ppm
2.17
7.95
21.10
1.92
2.22
4.34
4.41
2.00

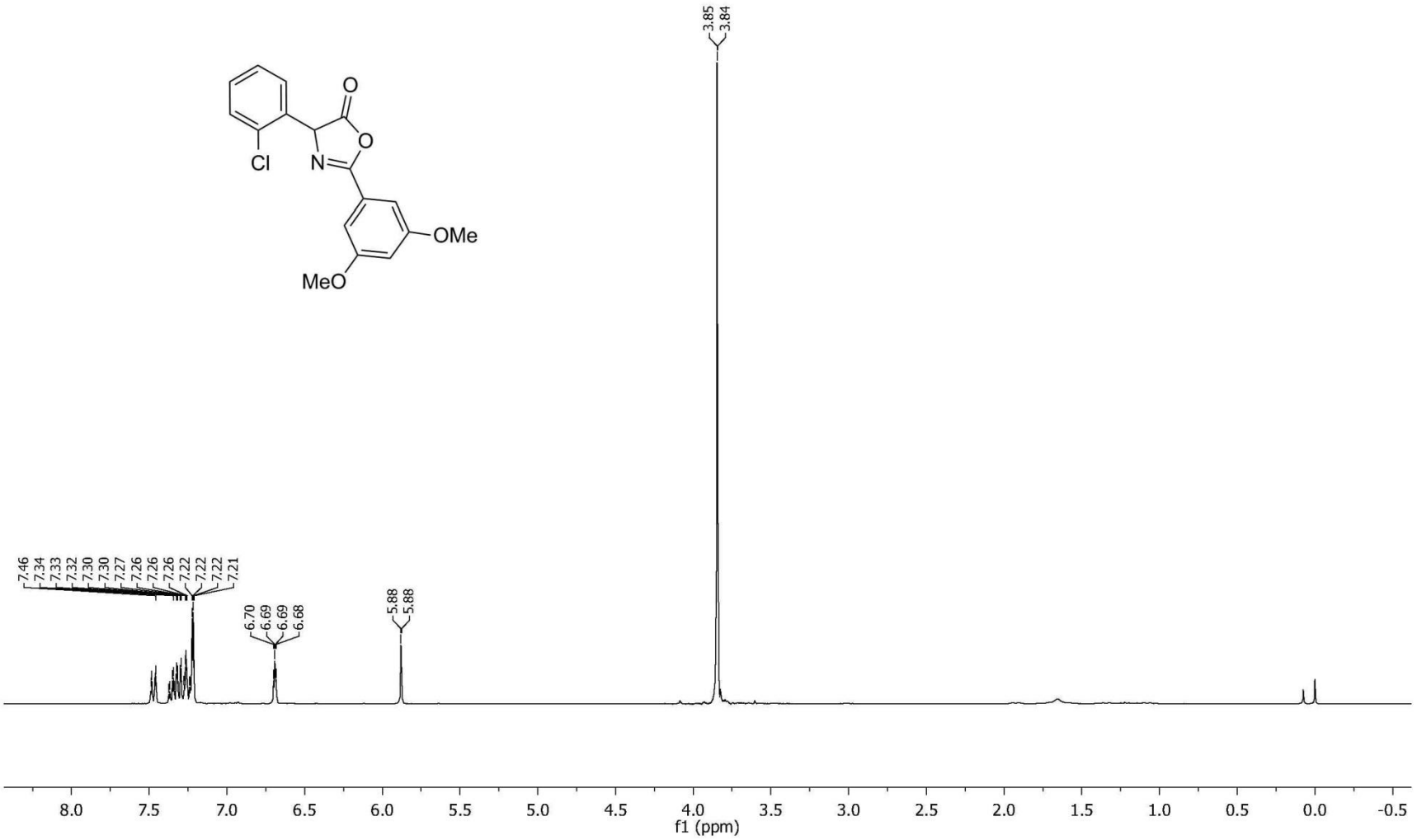

O
O
P
O
OH

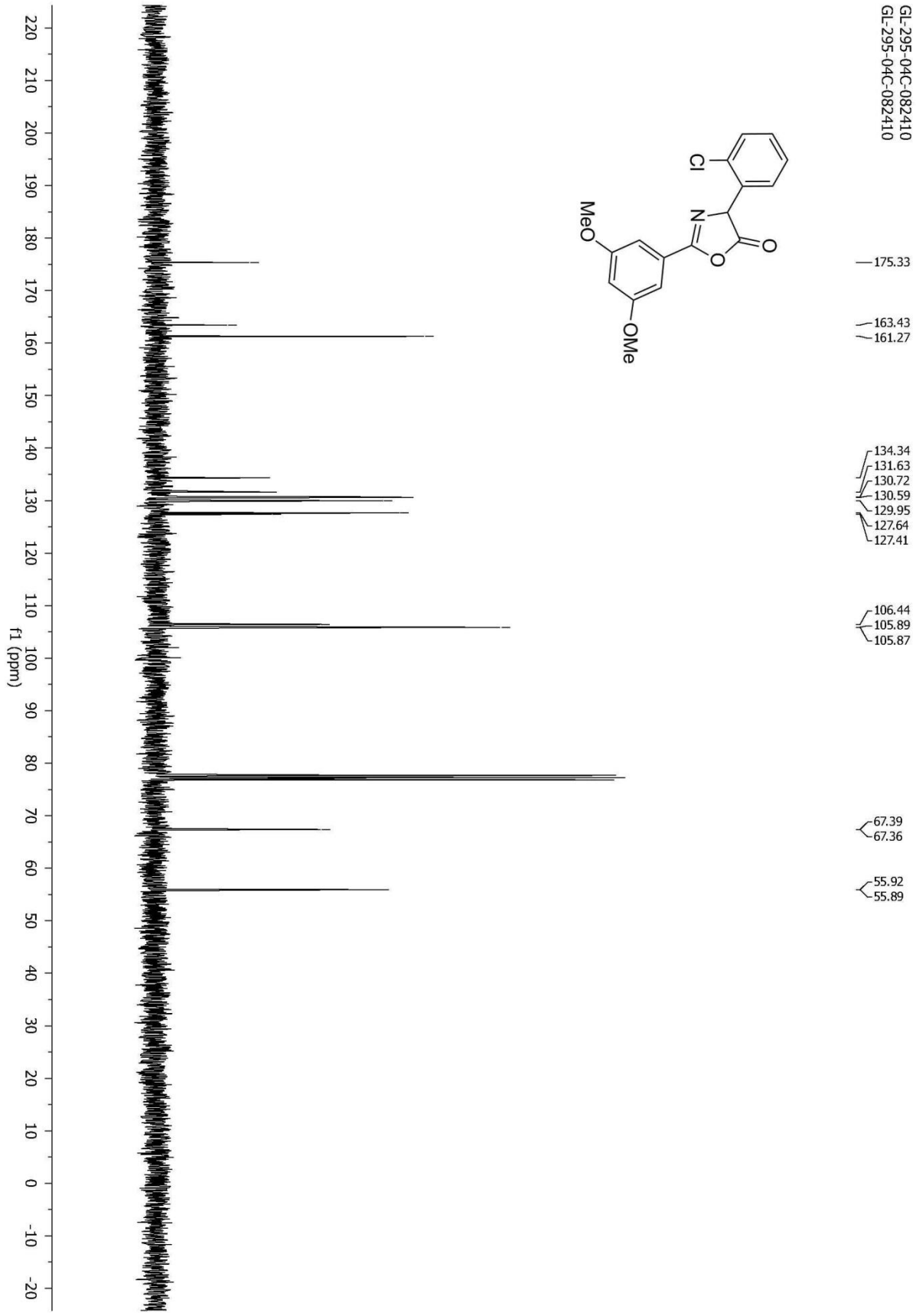

220
200
180
160
140
120
100
80
60
40
20
0
ppm
O
P
O
O
HO

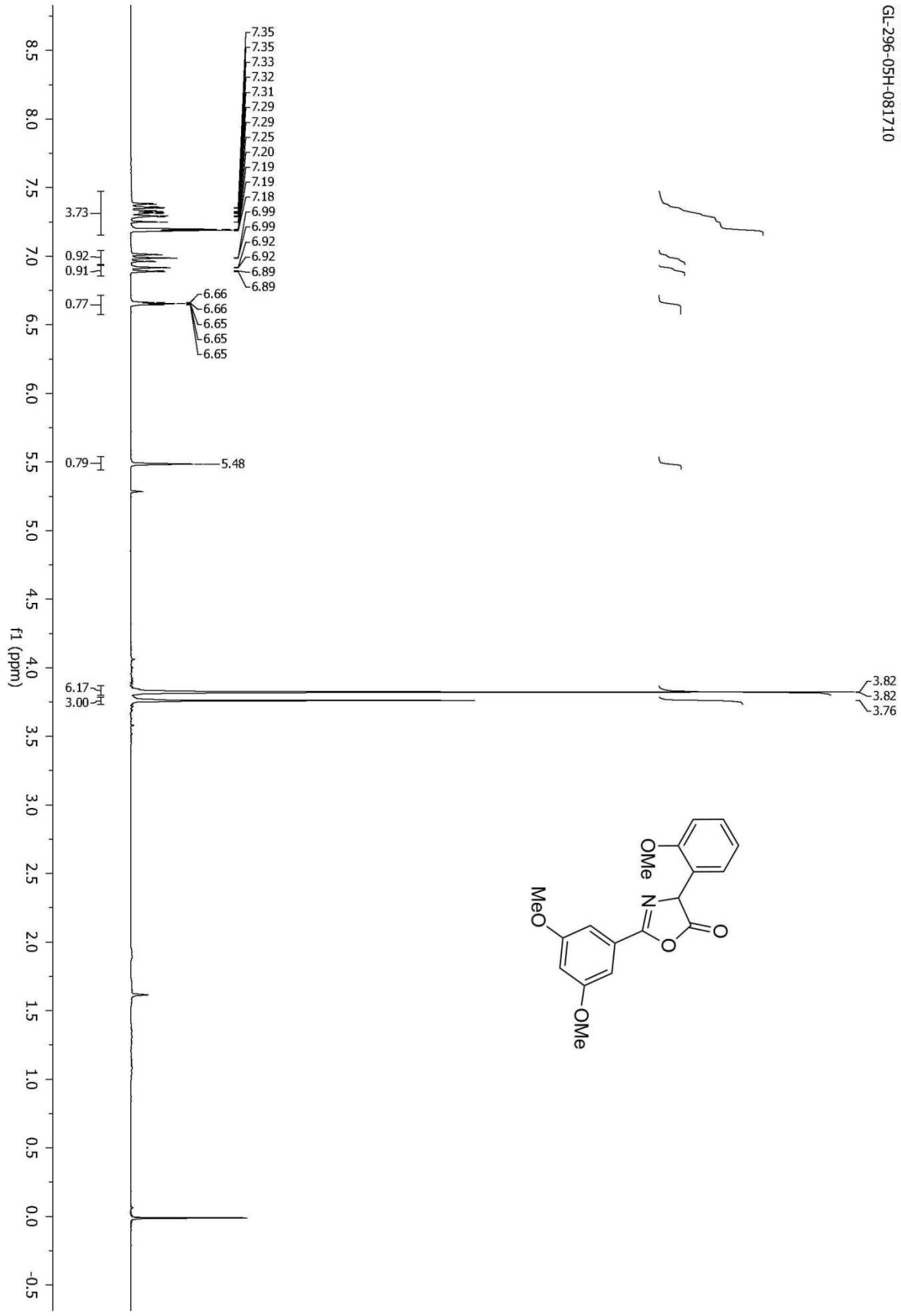

GL-295-001H-090910
GL-295-001H-090910
7.40
7.40
7.23
7.23
7.22
6.71
6.70
6.70
6.70
5.50
3.86
3.86
Cl
O
O
N
OMe
MeO
3.28
1.43
0.77
0.67
6.00
8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0
f1 (ppm)

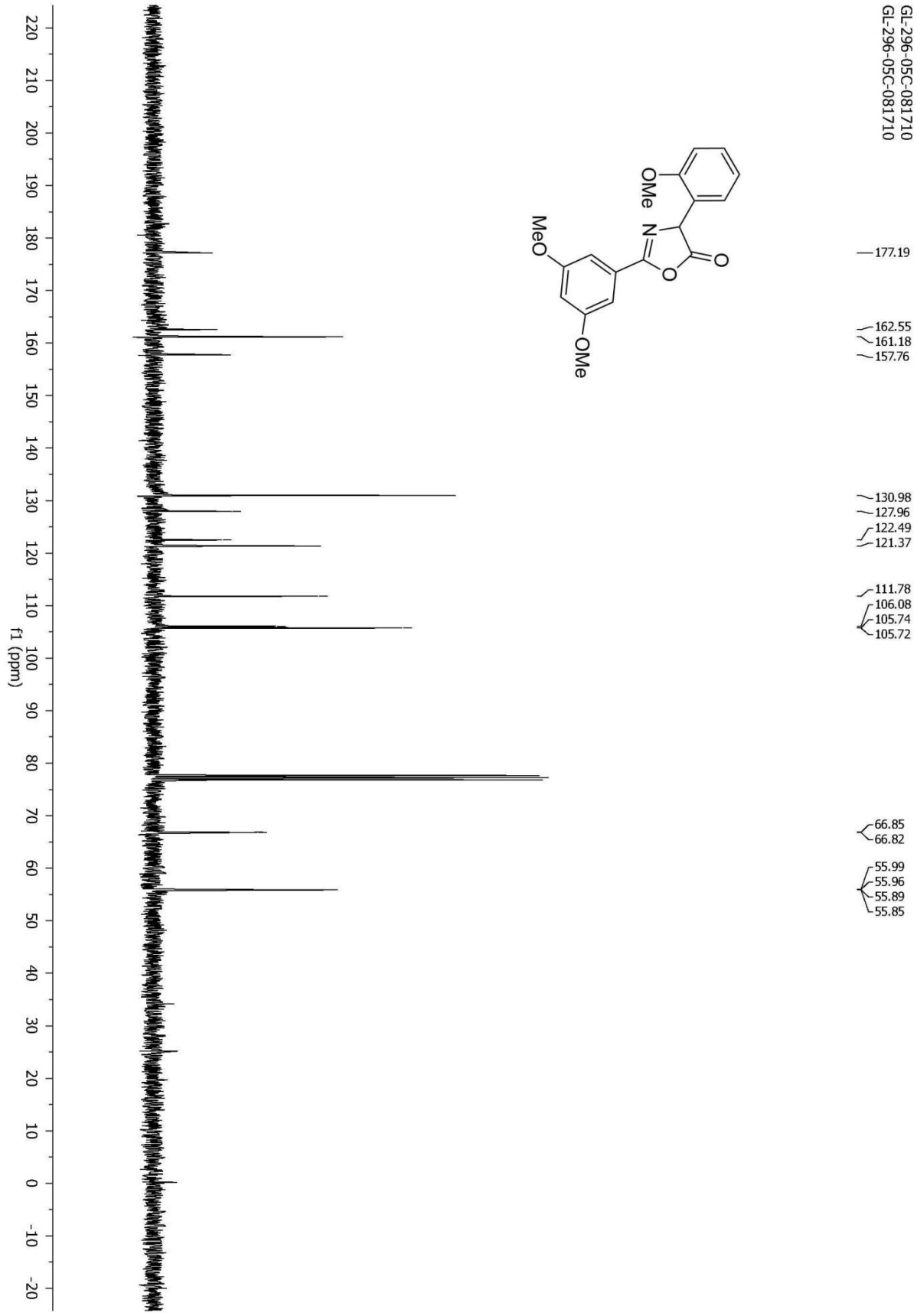

GL-295-001C-090910
GL-295-001C-090910
175.94
163.00
161.29
135.06
132.04
129.42
128.40
127.34
106.37
105.94
67.71
55.93
55.90
Cl
MeO
OMe
N
O
O
f1 (ppm)

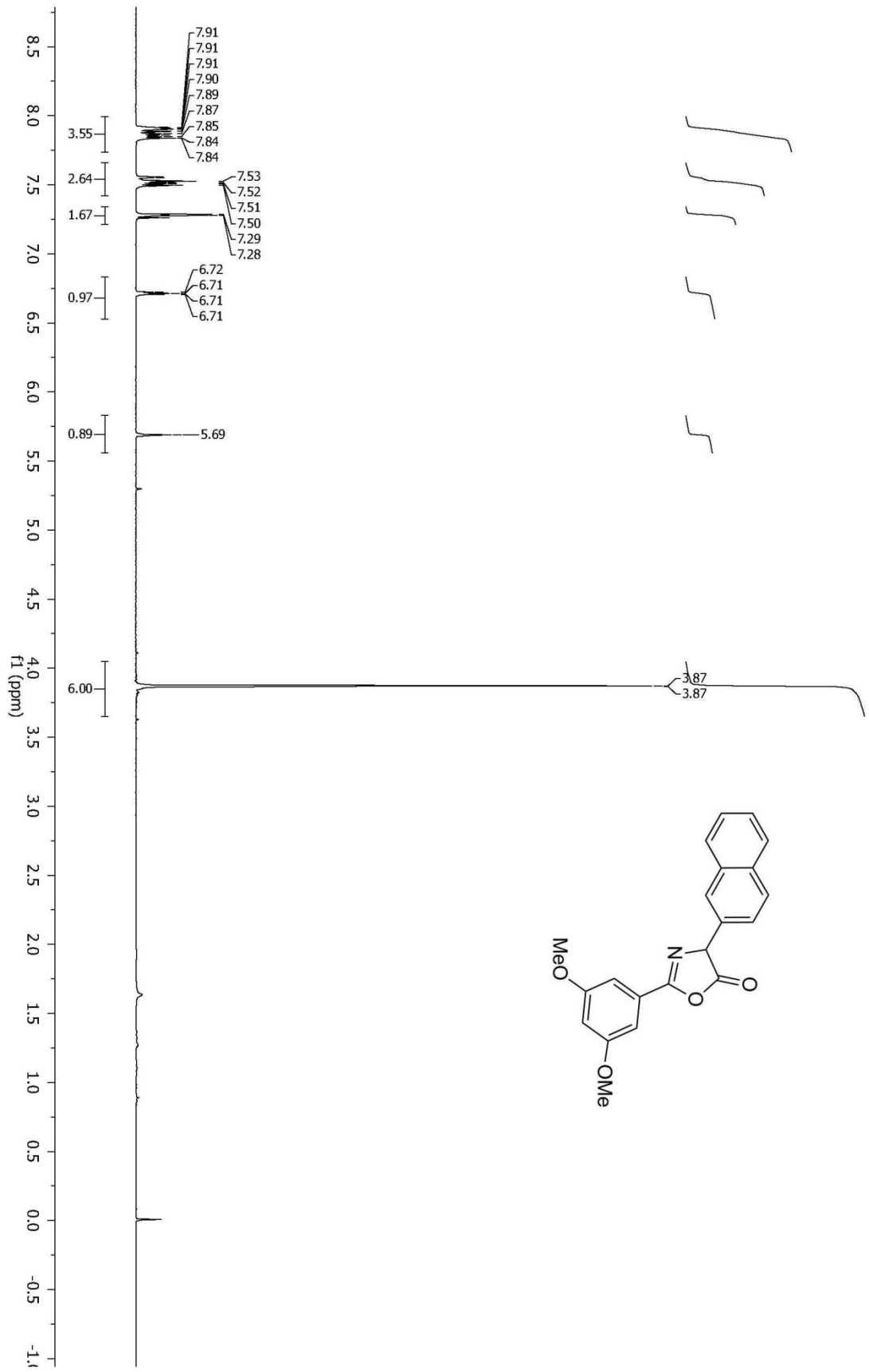
GL-295-04H-082410
GL-295-04H-082410

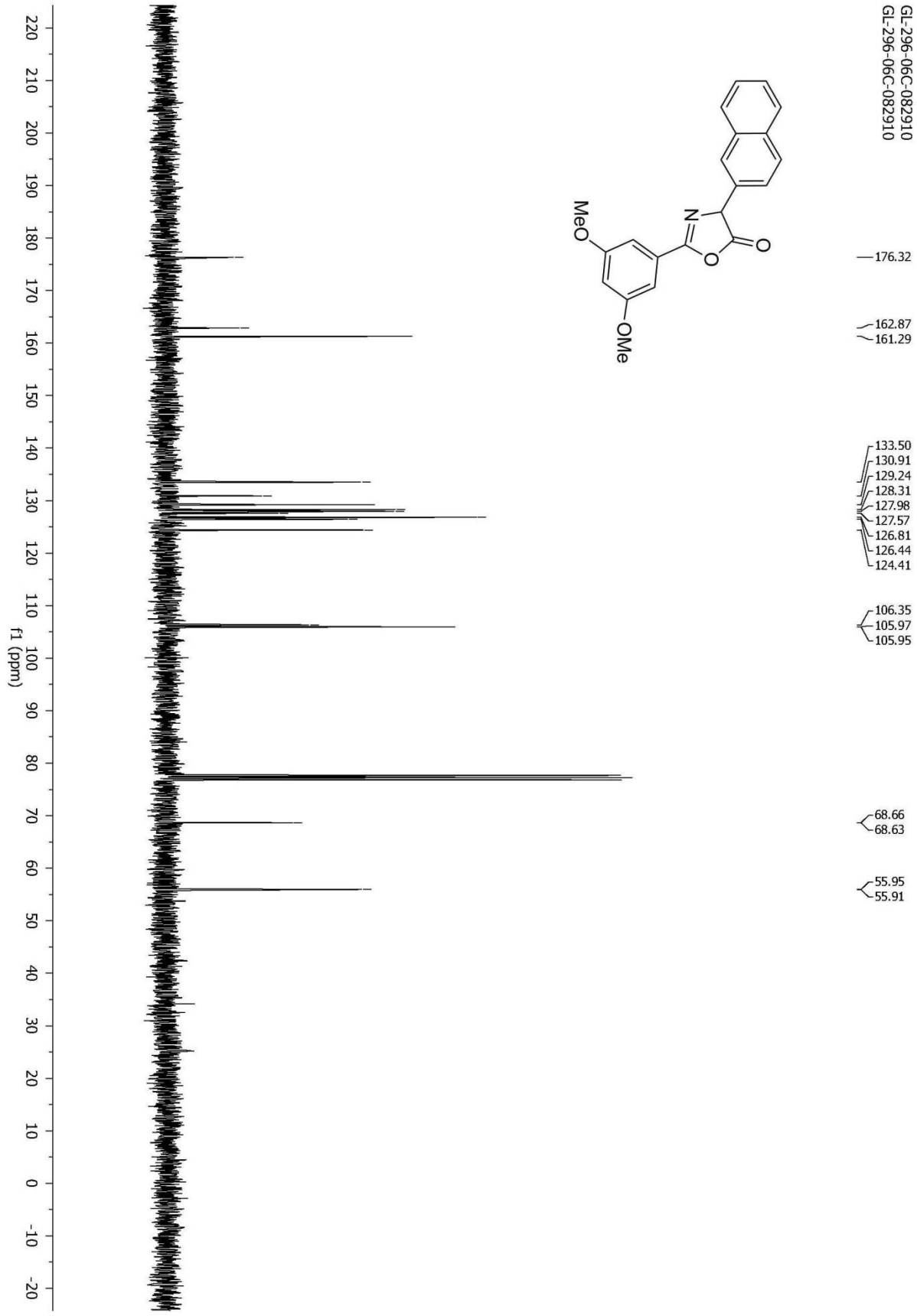



GL-295-04C-082410
GL-295-04C-082410
Cl
N
O
O
MeO
OMe
175.33
163.43
161.27
134.34
131.63
130.72
130.59
129.95
127.64
127.41
106.44
105.89
105.87
67.39
67.36
55.92
55.89
f1 (ppm)

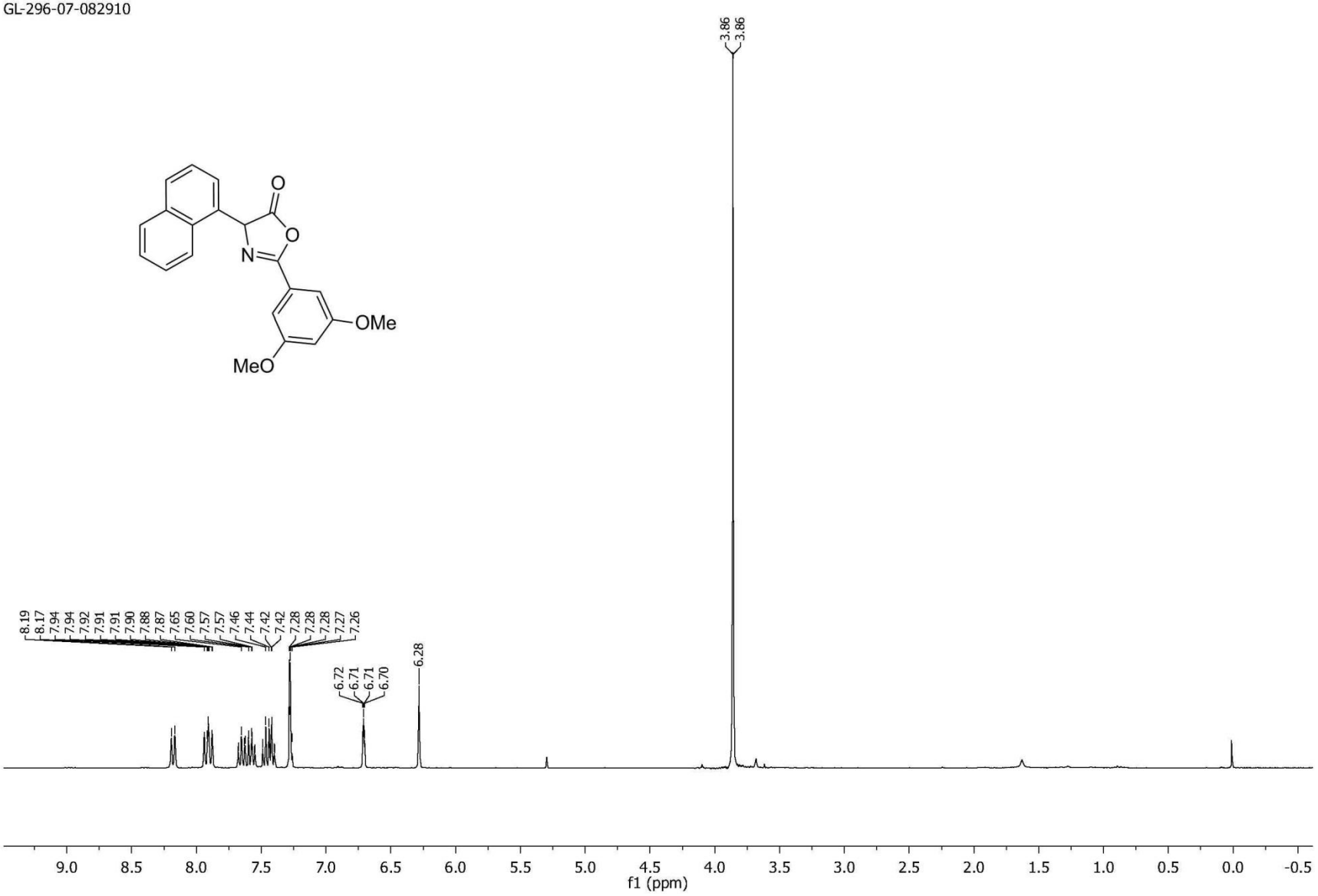

GL-296-05H-081710
GL-296-05H-081710
7.35
7.35
7.33
7.32
7.31
7.29
7.29
7.25
7.20
7.19
7.19
7.18
6.99
6.99
6.92
6.92
6.89
6.89
6.66
6.66
6.65
6.65
6.65
5.48
3.82
3.82
3.76
3.73
0.92
0.91
0.77
0.79
6.17
3.00
f1 (ppm)
OMe
N
O
O
MeO
OMe

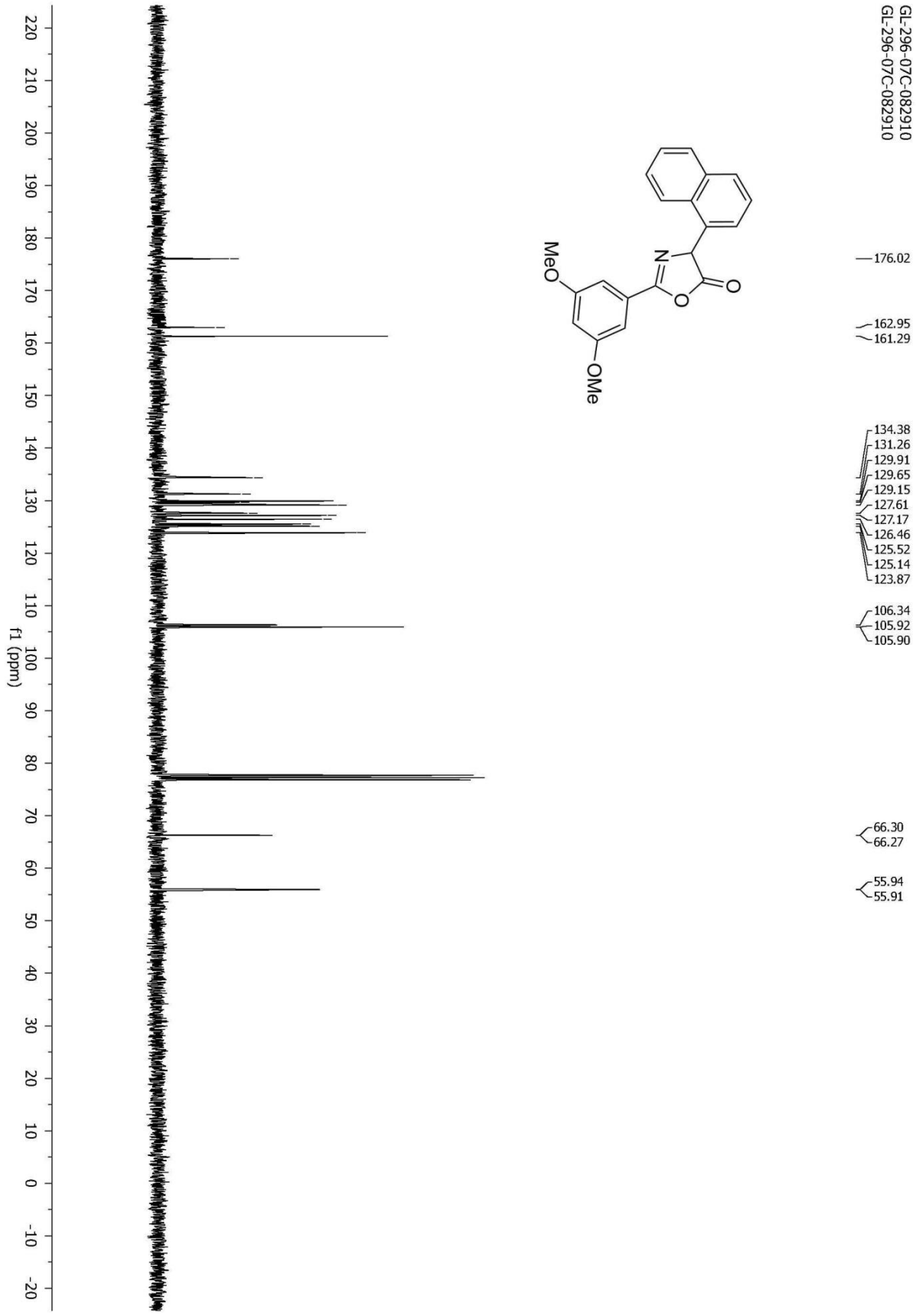

GL-296-05C-081710
GL-296-05C-081710
OMe
N
O
O
MeO
OMe
177.19
162.55
161.18
157.76
130.98
127.96
122.49
121.37
111.78
106.08
105.74
105.72
66.85
66.82
55.99
55.96
55.89
55.85
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

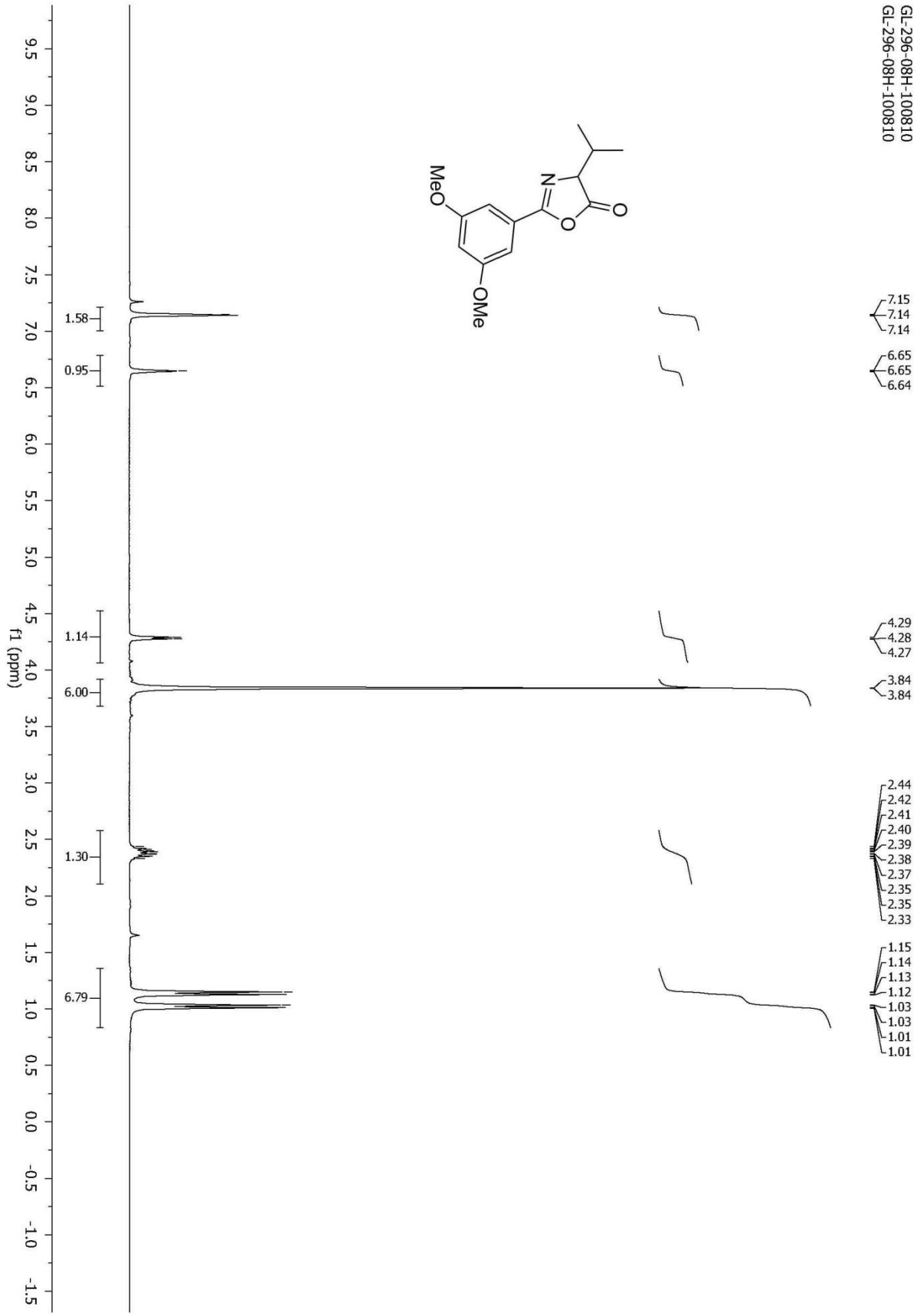

GL-296-06H-082910
GL-296-06-082910
7.91
7.91
7.91
7.90
7.89
7.87
7.85
7.84
7.84
7.53
7.52
7.51
7.50
7.29
7.28
6.72
6.71
6.71
6.71
5.69
3.87
3.87
3.55
2.64
1.67
0.97
0.89
6.00
MeO
OMe
N
O
O
f1 (ppm)

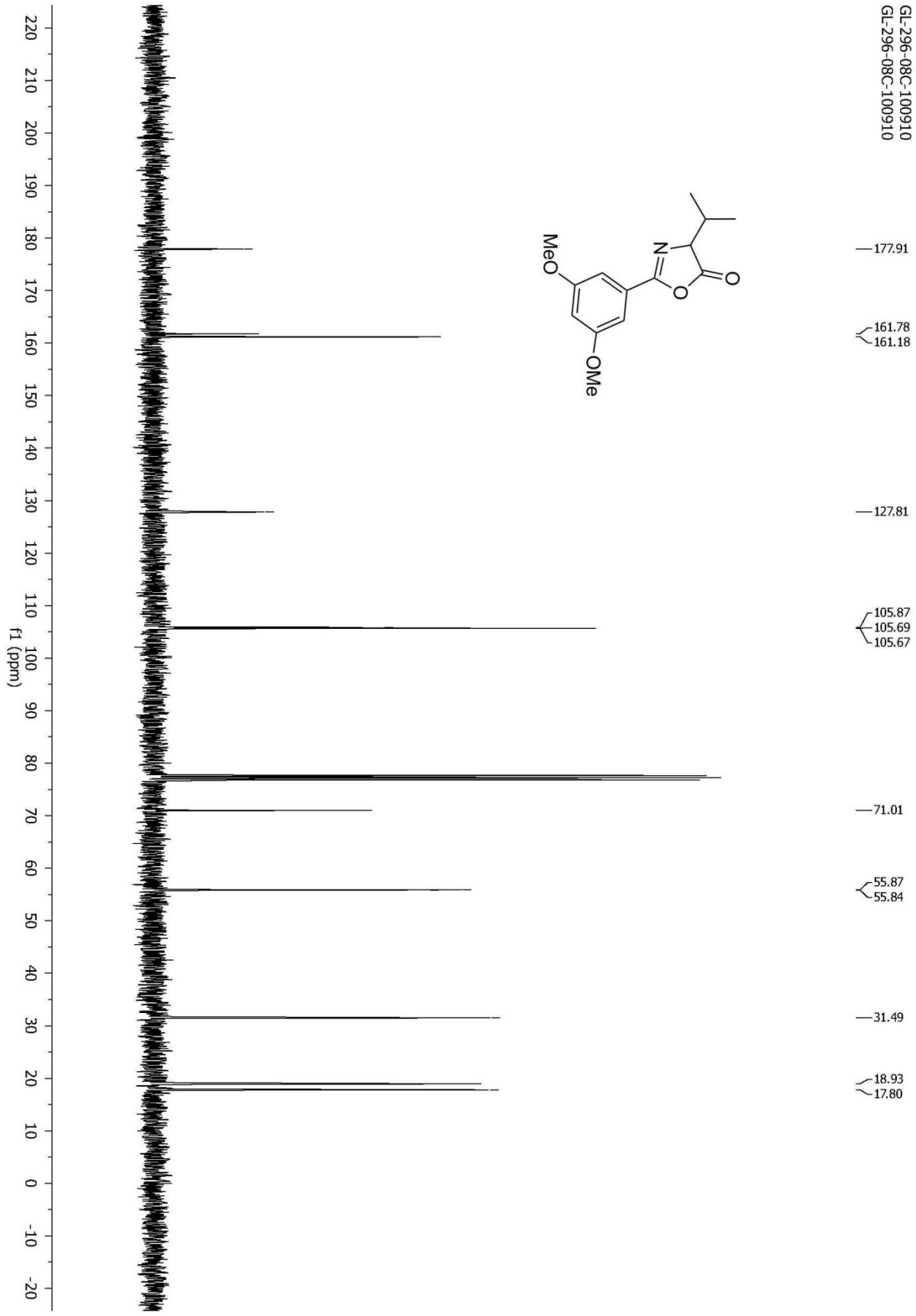

GL-296-06C-082910
GL-296-06C-082910
MeO
OMe
N
O
O
176.32
162.87
161.29
133.50
130.91
129.24
128.31
127.98
127.57
126.81
126.44
124.41
106.35
105.97
105.95
68.66
68.63
55.95
55.91
f1 (ppm)

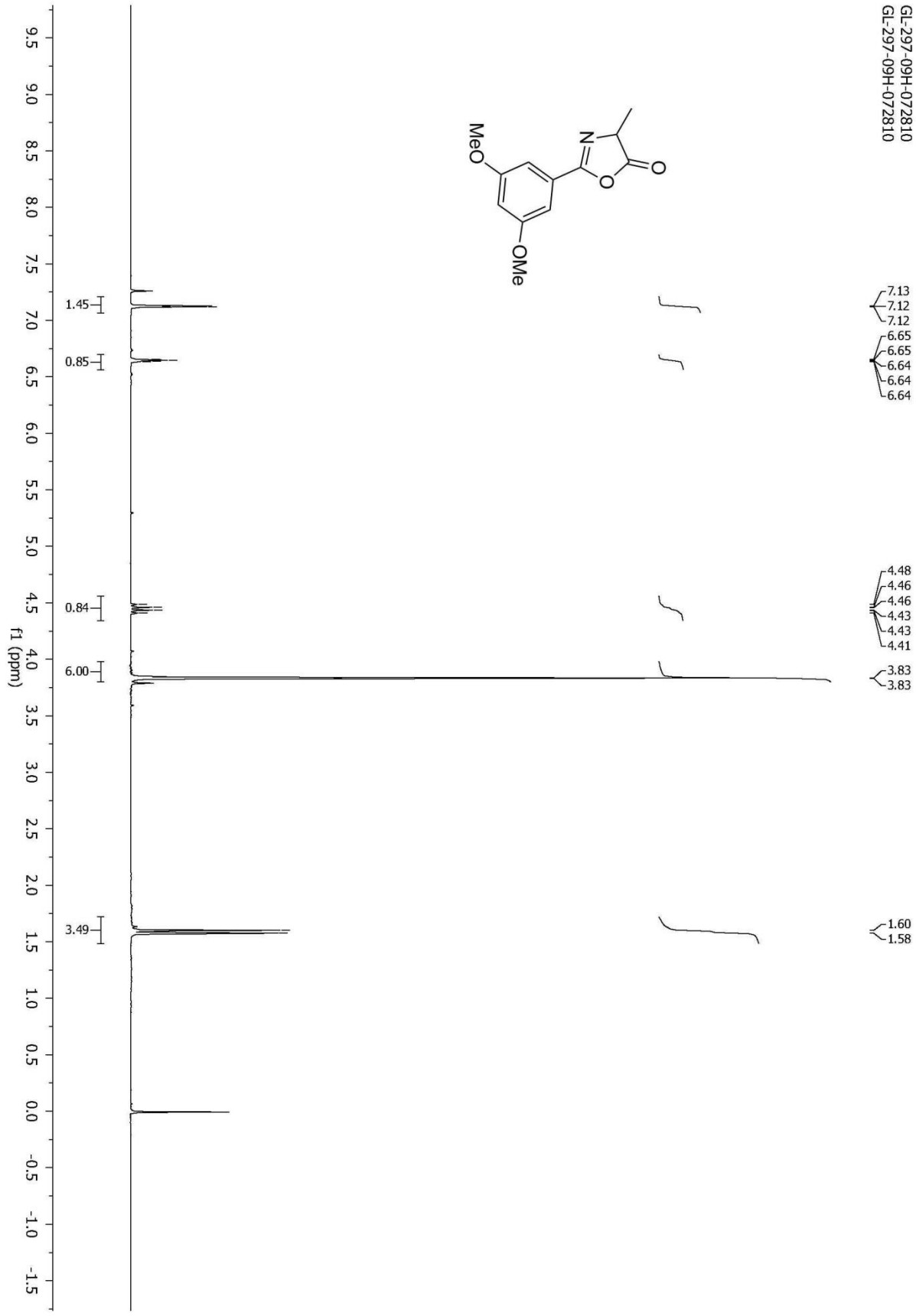
GL-296-07H-082910
GL-296-07-082910

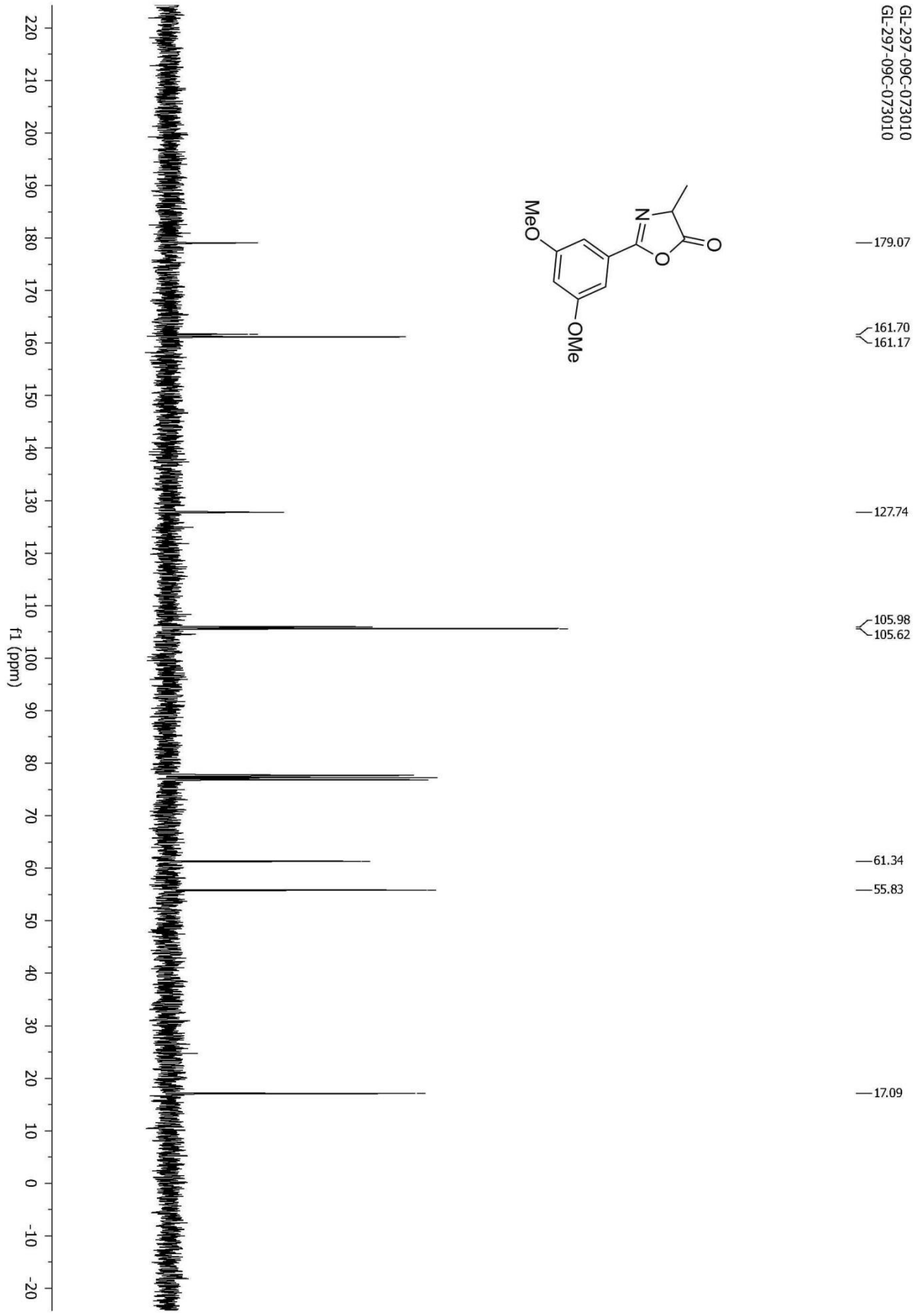


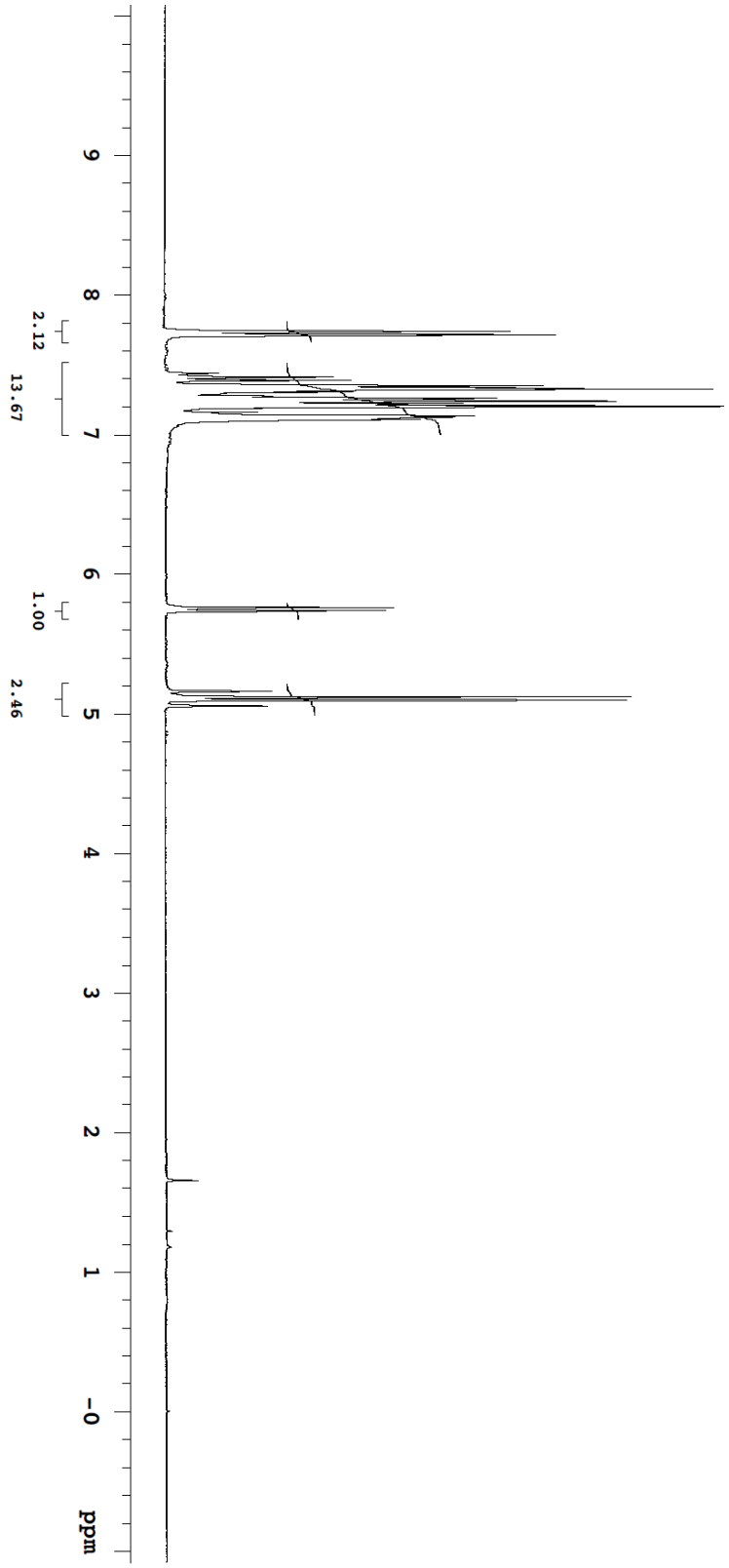

GL-296-07C-082910
GL-296-07C-082910
MeO
OMe
N
O
O
176.02
162.95
161.29
134.38
131.26
129.91
129.65
129.15
127.61
127.17
126.46
125.52
125.14
123.87
106.34
105.92
105.90
66.30
66.27
55.94
55.91
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

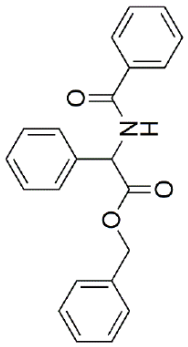

GL-296-08H-100810
GL-296-08H-100810
MeO
OMe
N
O
O
1.58
0.95
1.14
6.00
1.30
6.79
f1 (ppm)
7.15
7.14
7.14
6.65
6.65
6.64
4.29
4.28
4.27
3.84
3.84
2.44
2.42
2.41
2.40
2.39
2.38
2.37
2.35
2.35
2.33
1.15
1.14
1.13
1.12
1.03
1.03
1.01
1.01

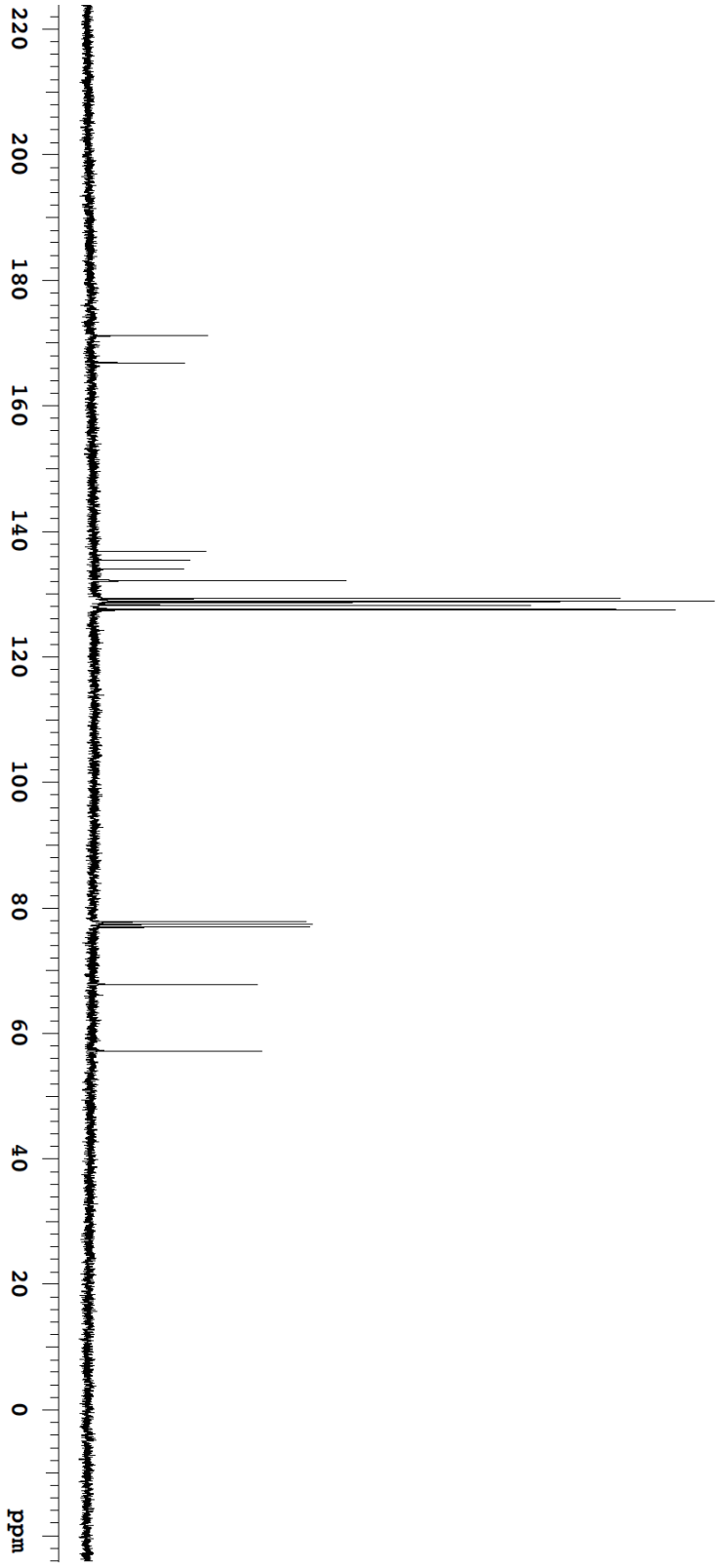

GL-296-08C-100910
GL-296-08C-100910
MeO
OMe
N
O
O
O
177.91
161.78
161.18
127.81
105.87
105.69
105.67
71.01
55.87
55.84
31.49
18.93
17.80
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

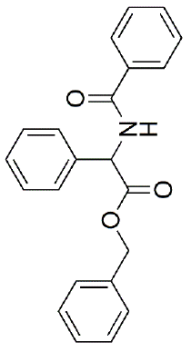

GL-297-09H-072810
GL-297-09H-072810
MeO
OMe
N
O
O
7.13
7.12
7.12
6.65
6.65
6.64
6.64
6.64
4.48
4.46
4.46
4.43
4.43
4.41
3.83
3.83
1.60
1.58
1.45
0.85
0.84
6.00
3.49
f1 (ppm)

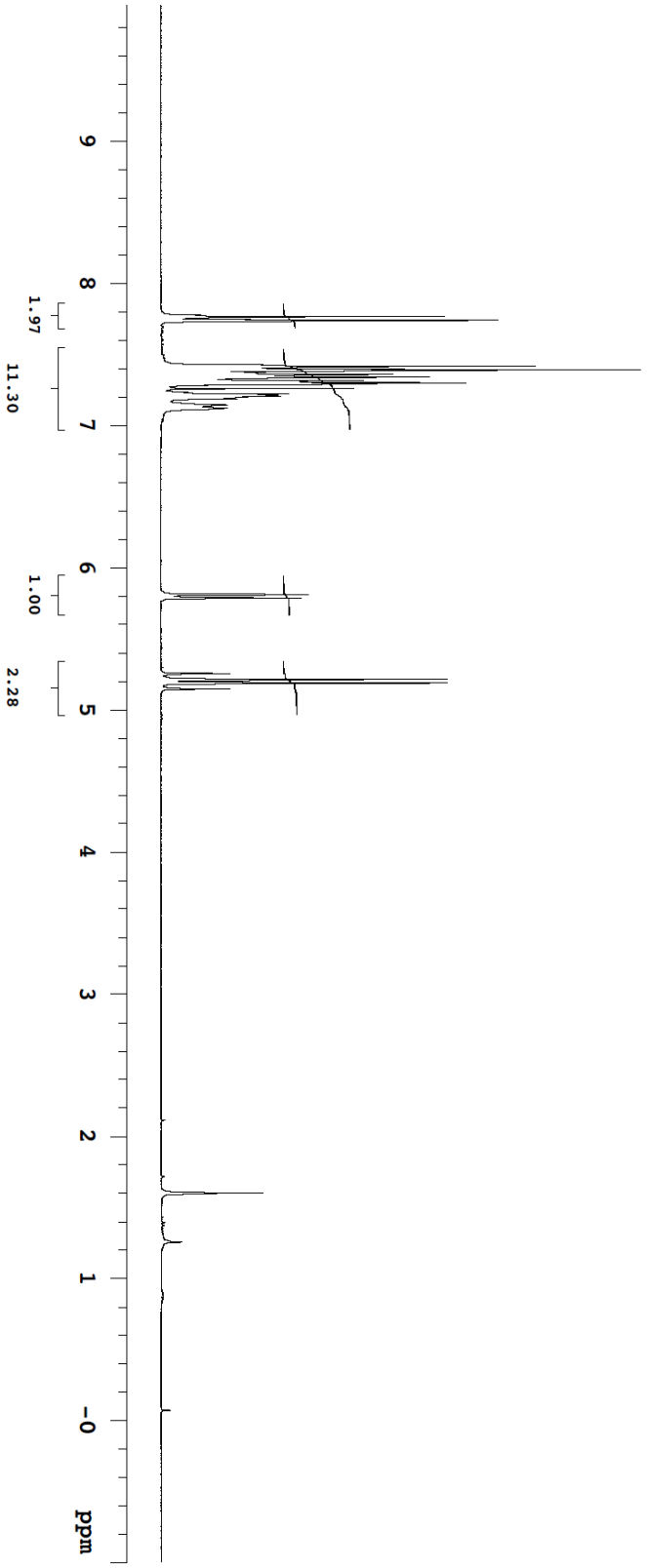

GL-297-09C-073010
GL-297-09C-073010
MeO
OMe
N
O
O
179.07
161.70
161.17
127.74
105.98
105.62
61.34
55.83
17.09
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

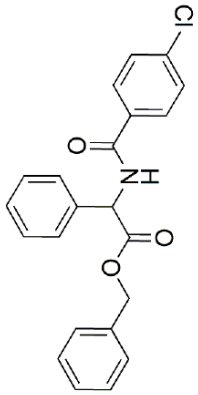

9
8
7
6
5
4
3
2
1
-0
ppm
2.12
13.67
1.00
2.46

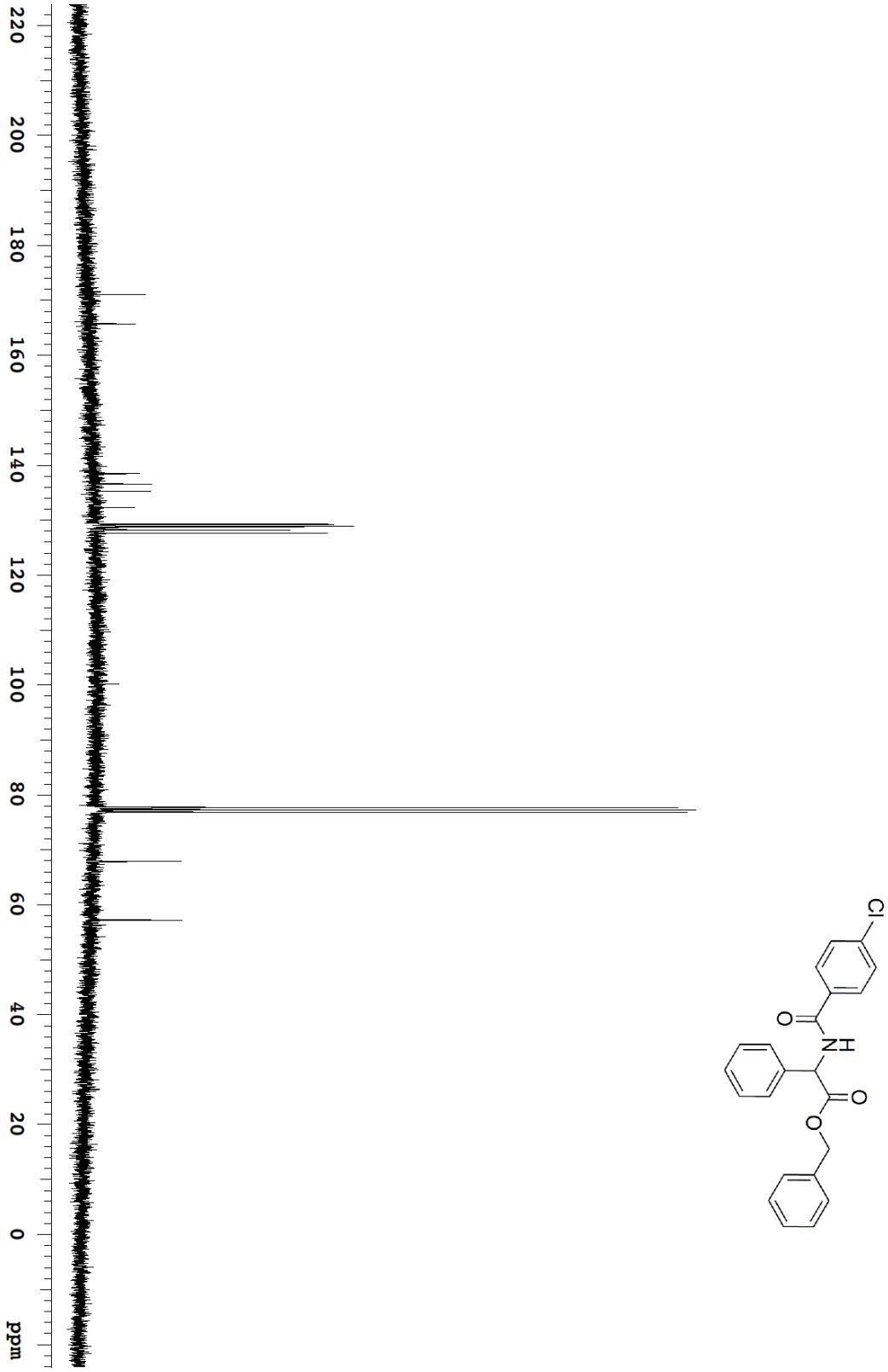

O
N
H
O
O

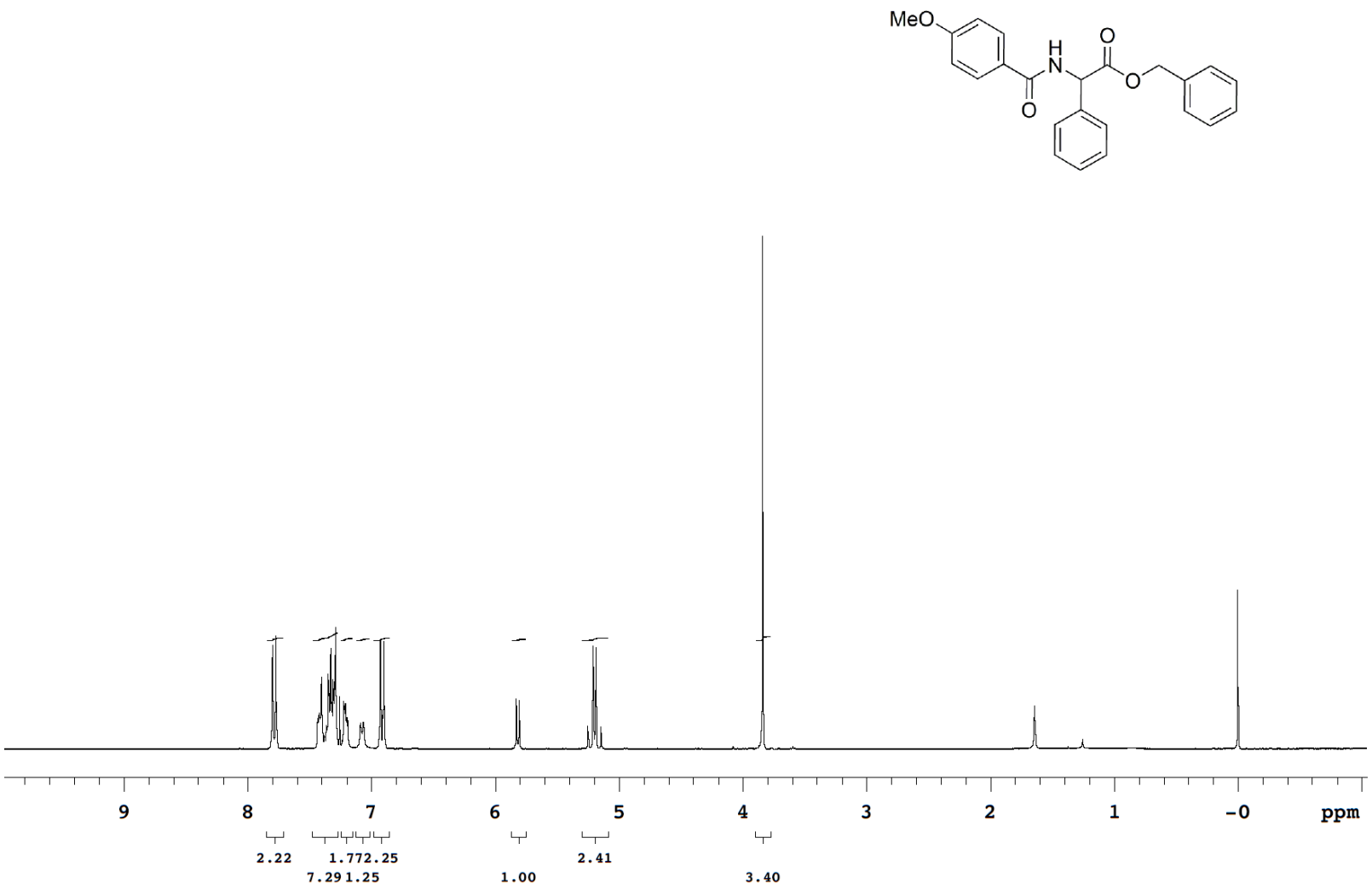

220
200
180
160
140
120
100
80
60
40
20
0
ppm

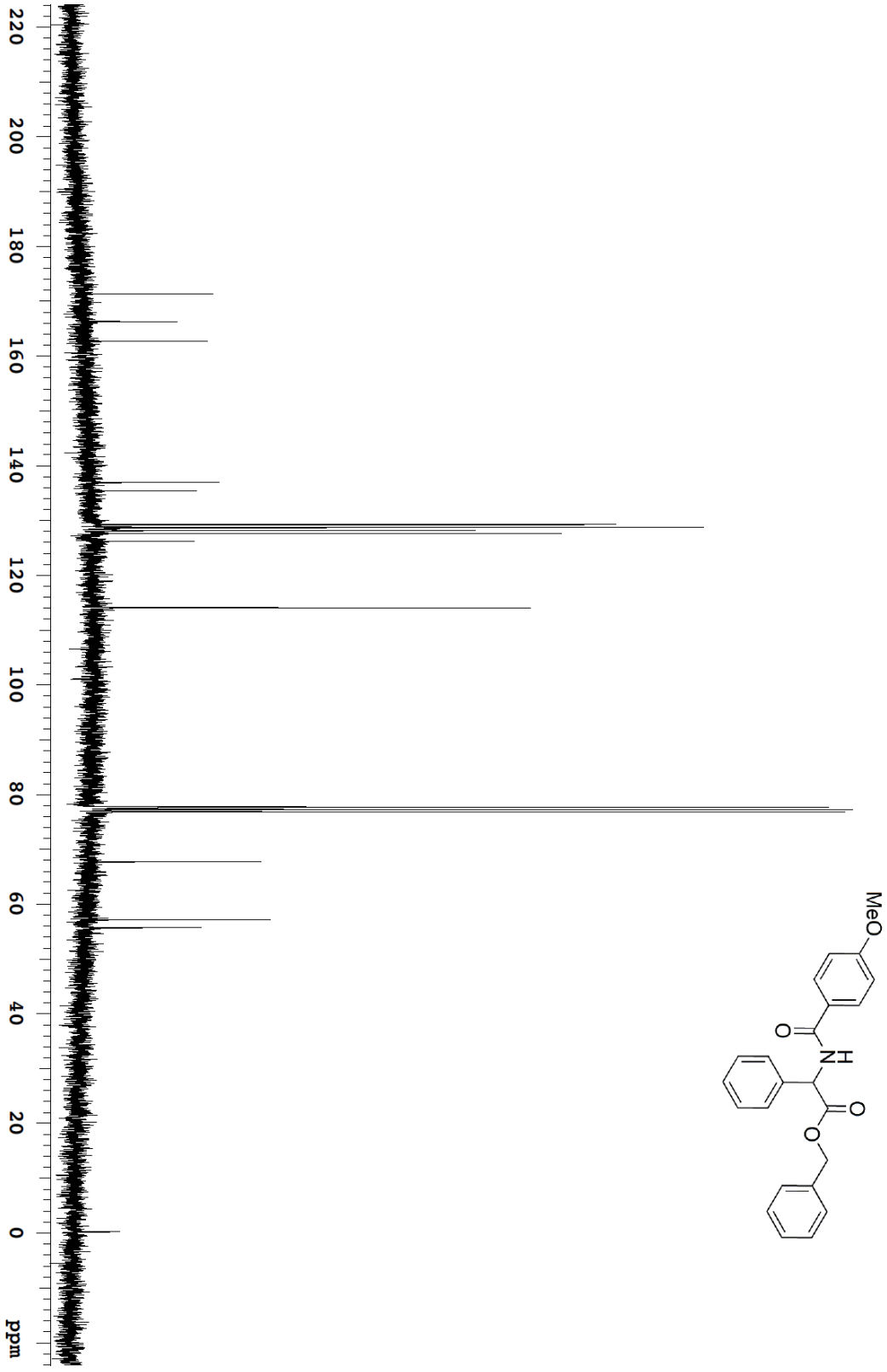

O
N
H
O
O

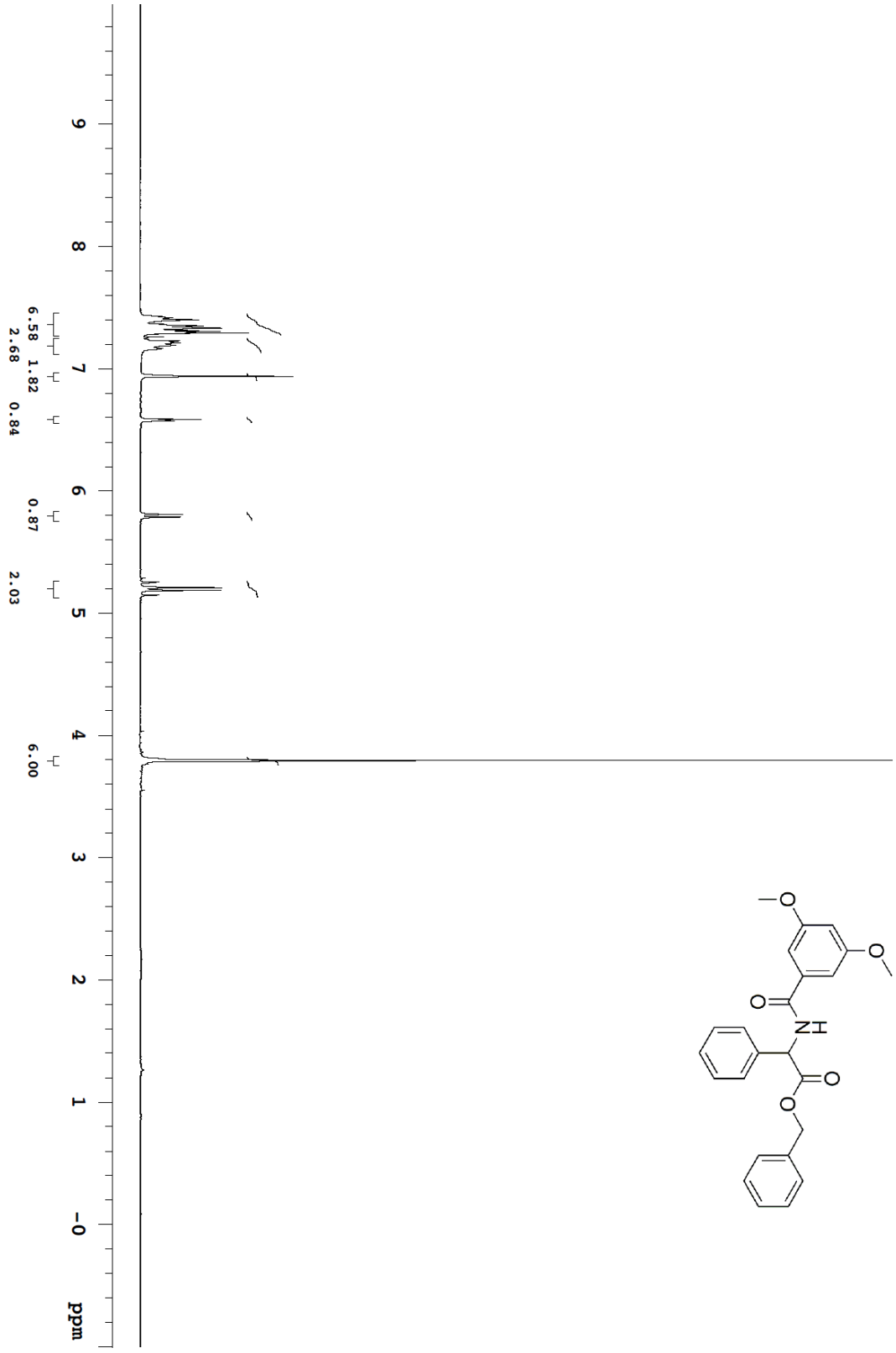

9
8
7
6
5
4
3
2
1
0
ppm
1.97
11.30
1.00
2.28

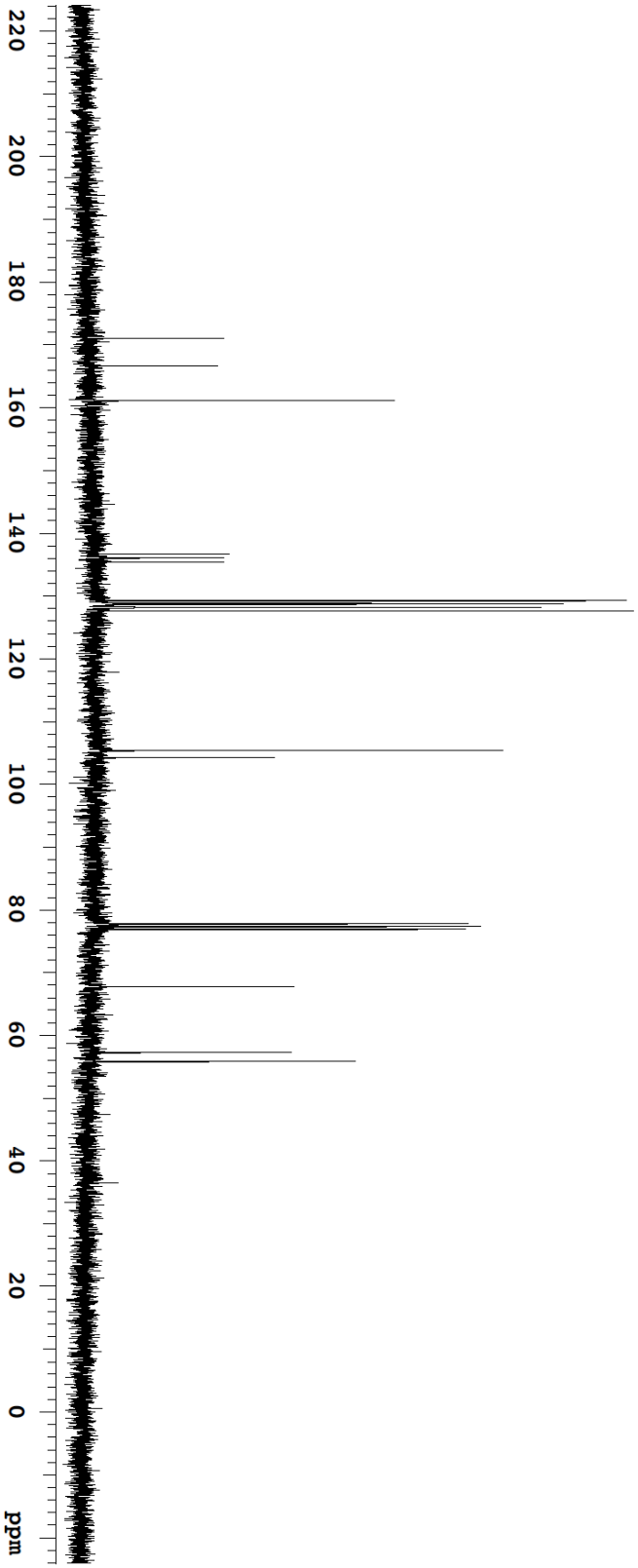

Cl
O
N
H
O
O

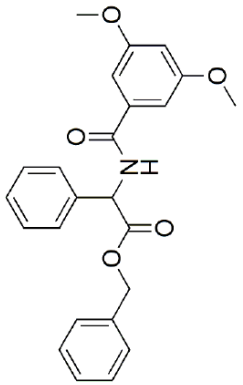

220
200
180
160
140
120
100
80
60
40
20
0
ppm
Cl
O
NH
O
O

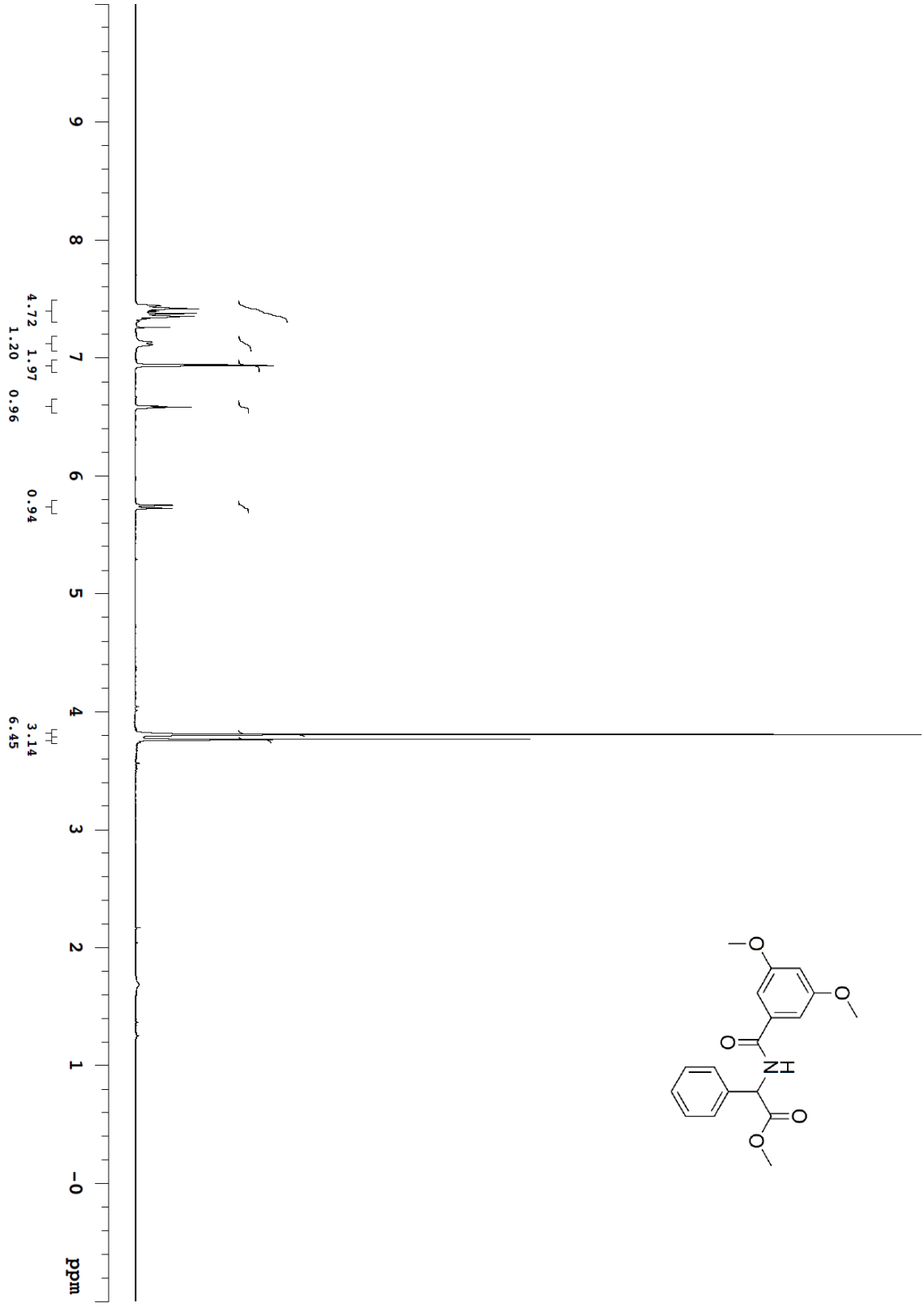

MeO
H
N
O
O
O
9
8
7
6
5
4
3
2
1
-0
ppm
2.22
7.29
1.77
1.25
2.25
1.00
2.41
3.40

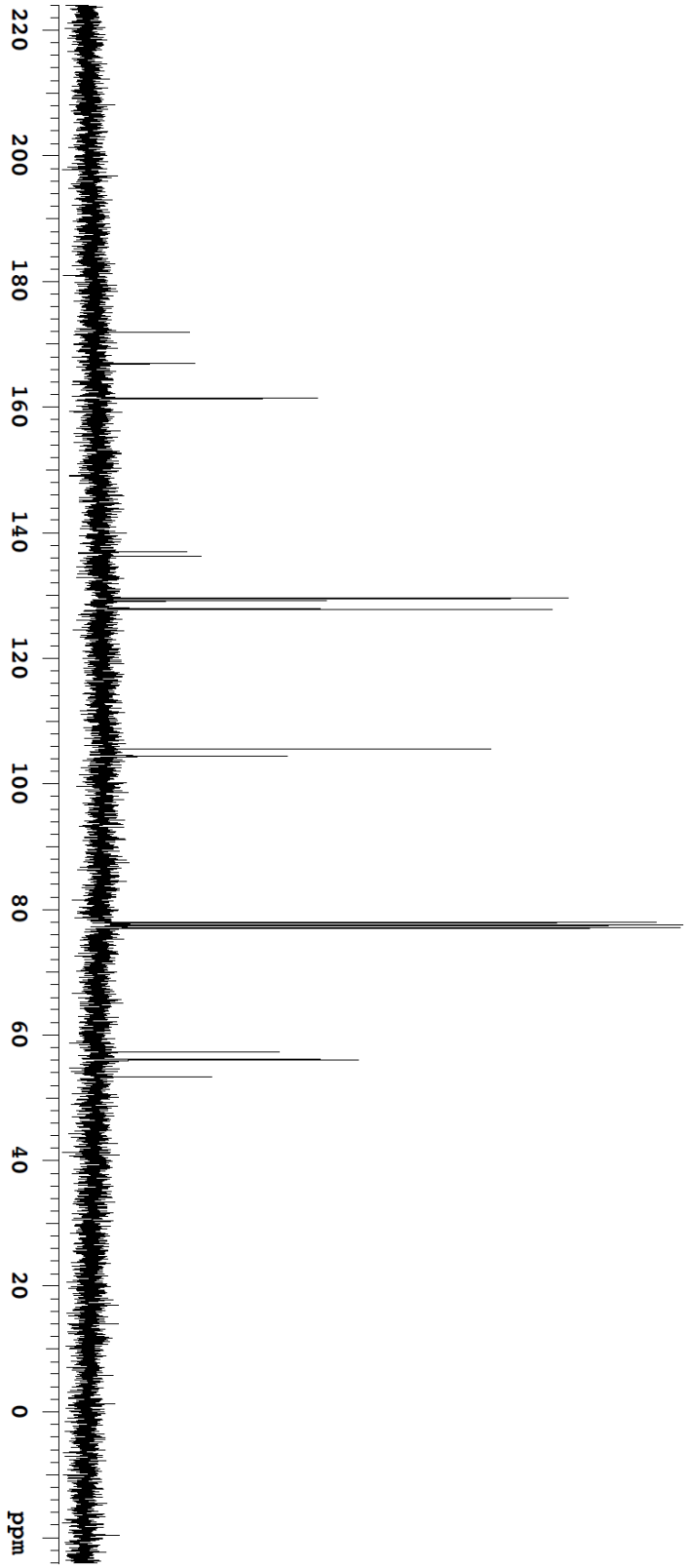

220
200
180
160
140
120
100
80
60
40
20
0
ppm
MeO
O
NH
O
O

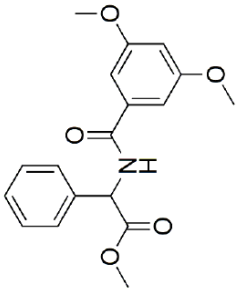

9
8
7
6
5
4
3
2
1
-0
ppm
6.58
1.82
2.68
0.84
0.87
2.03
6.00
O
O
O
NH
O
O

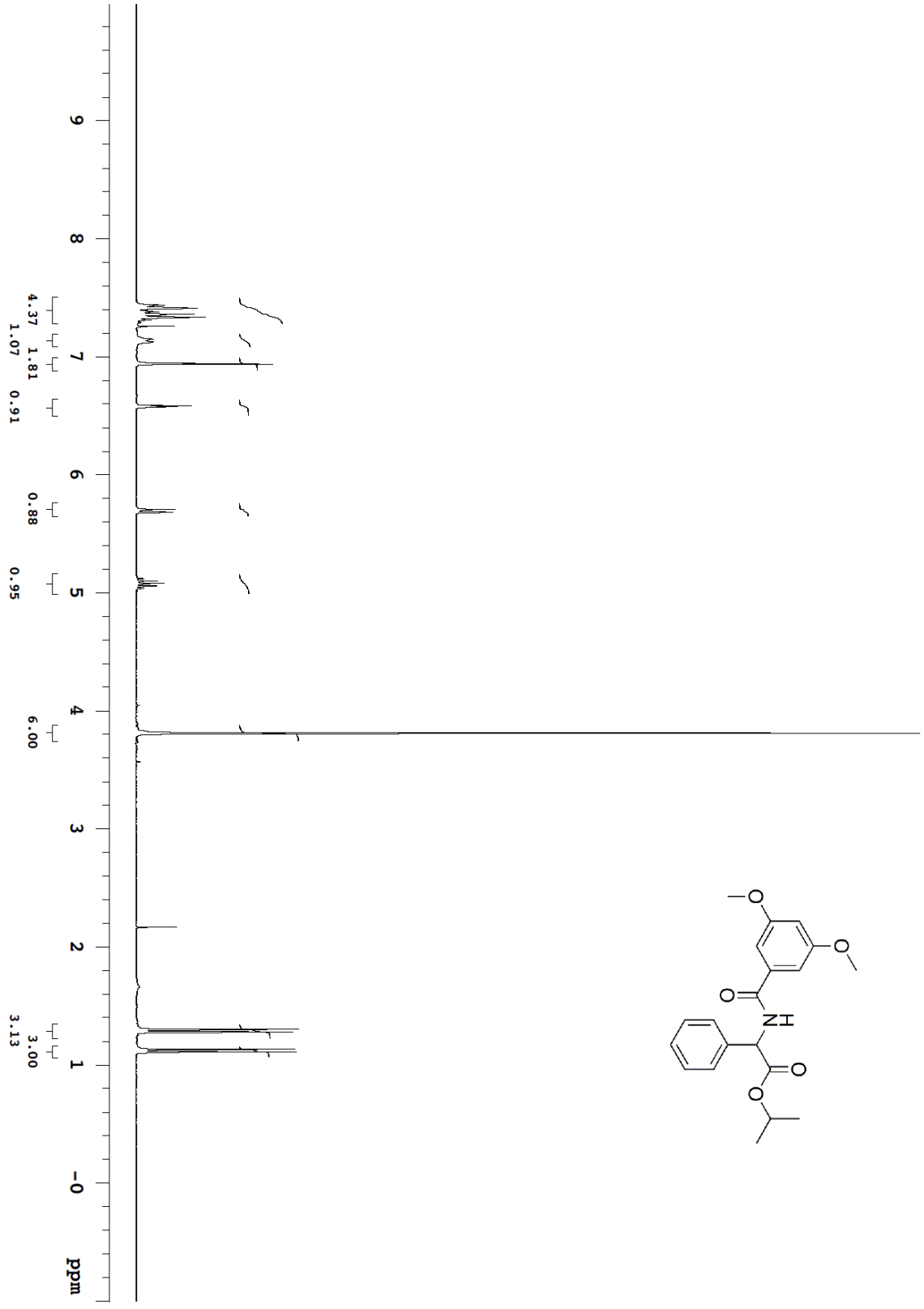

220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
O
O
NH
O
O


9
8
7
6
5
4
3
2
1
-0
ppm
4.72
1.97
1.20
0.96
0.94
3.14
6.45
O
O
O
N
H
O
O


220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
O
O
NH
O
O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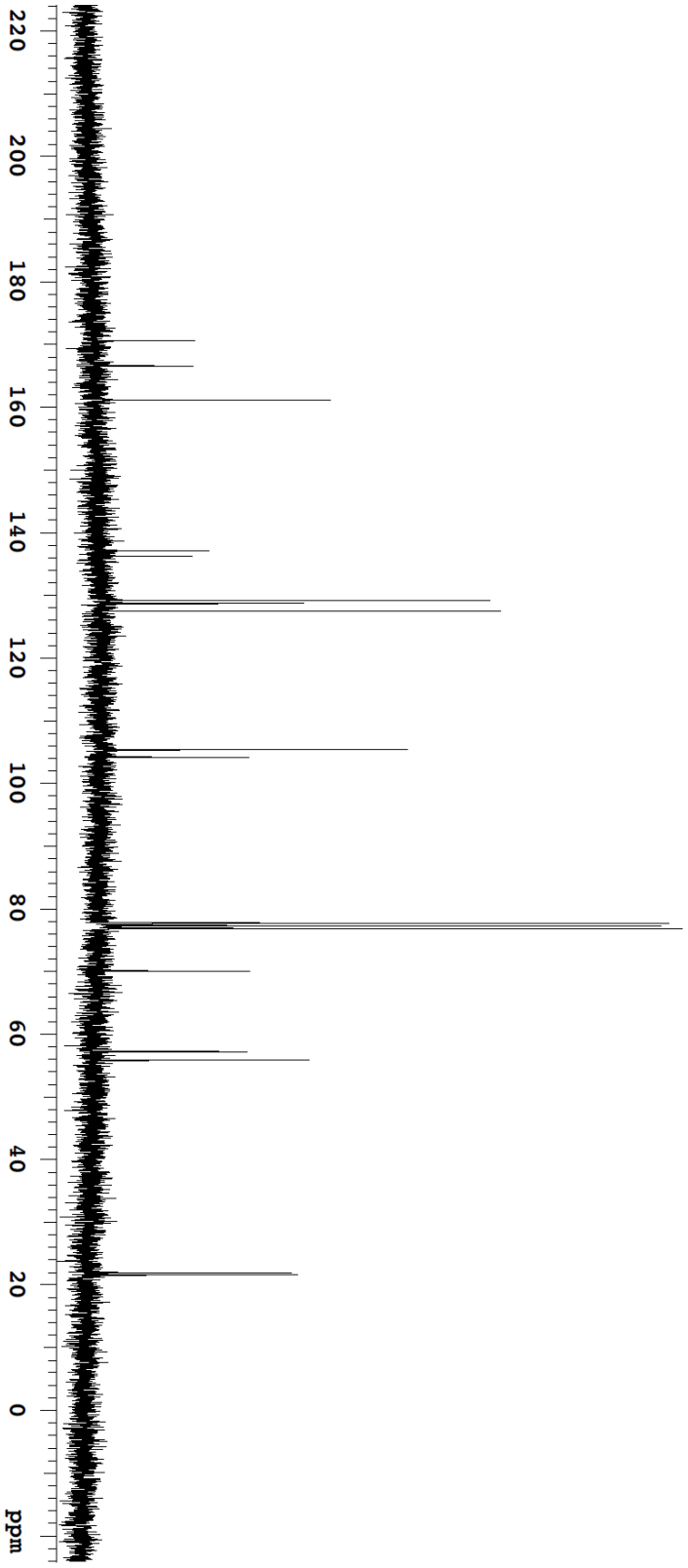
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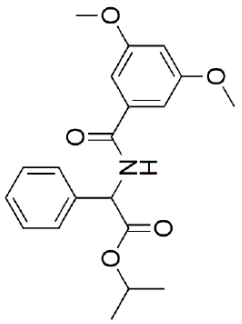
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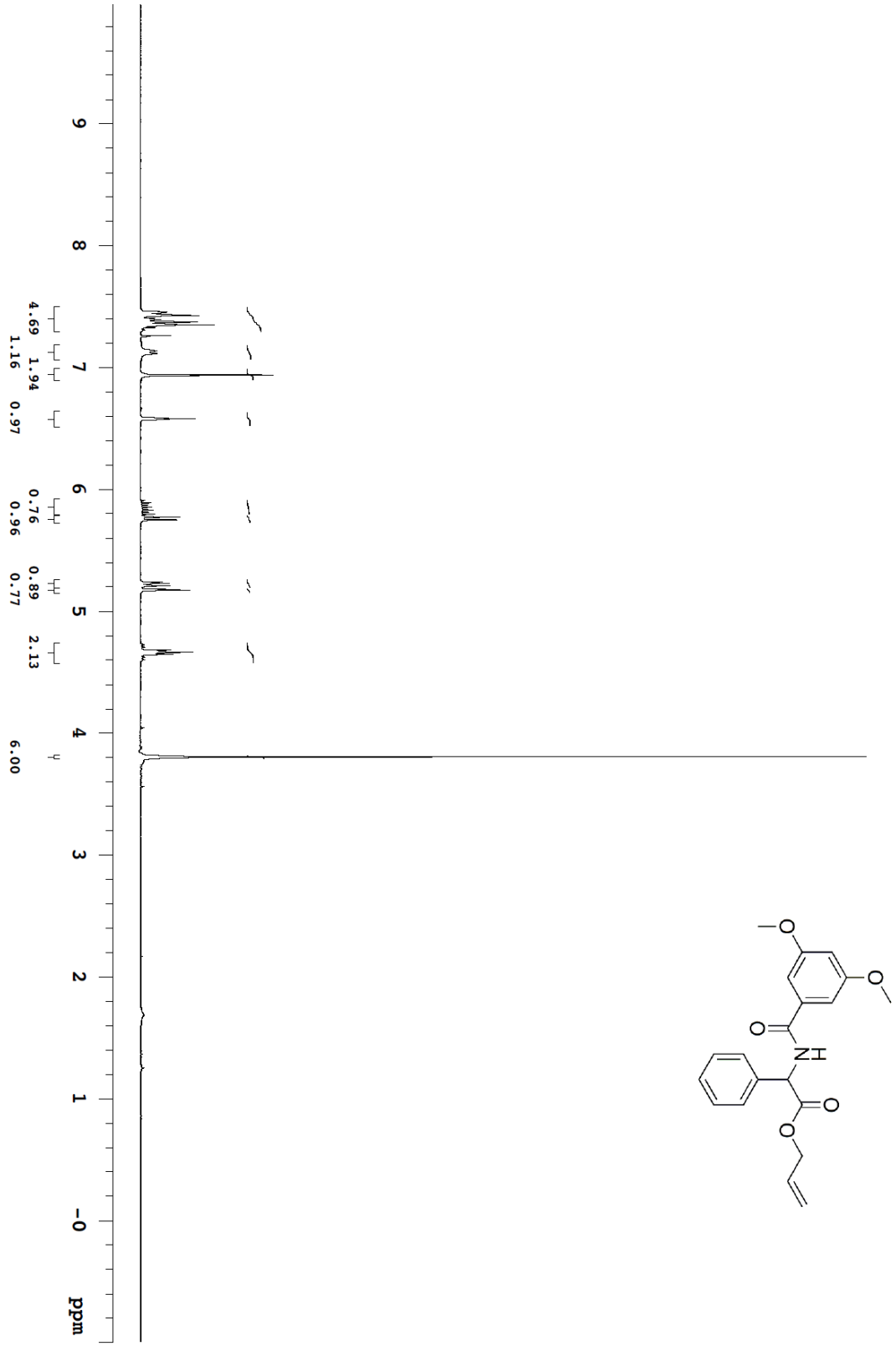
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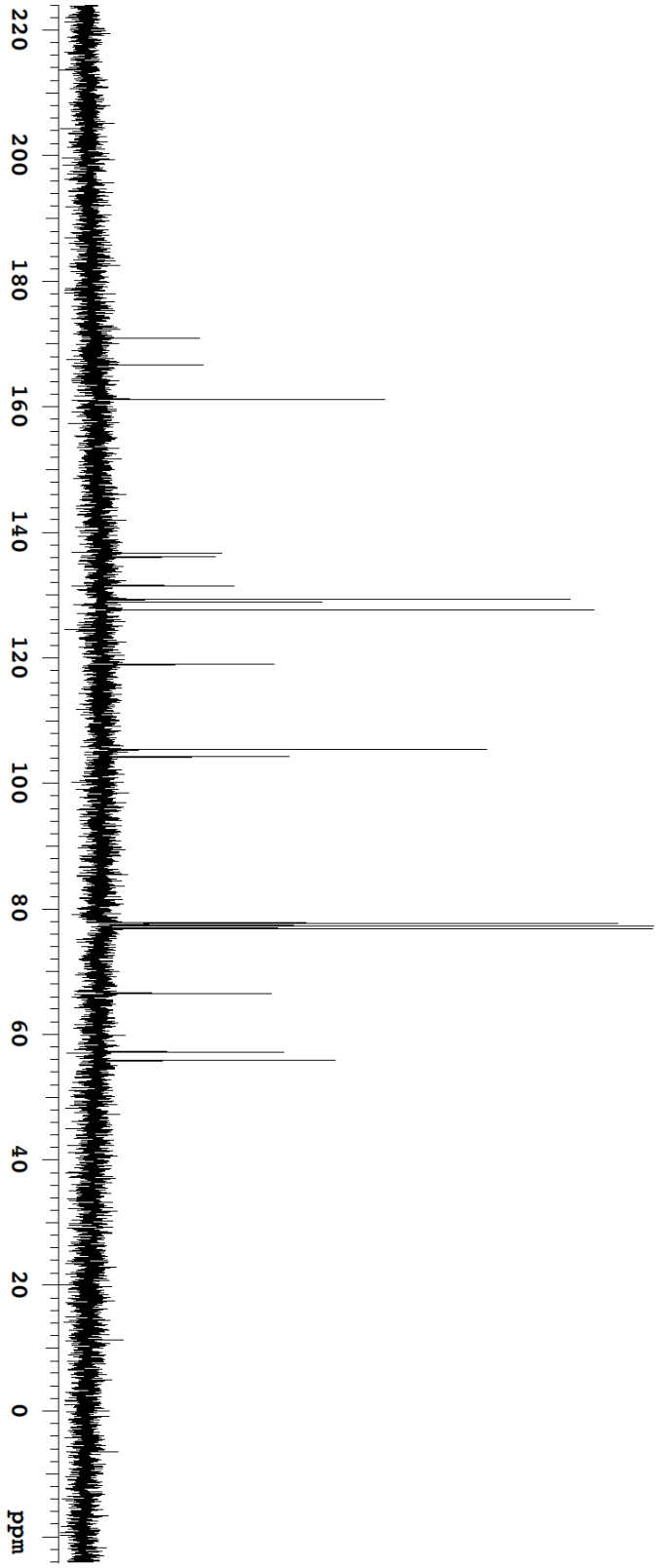
O
O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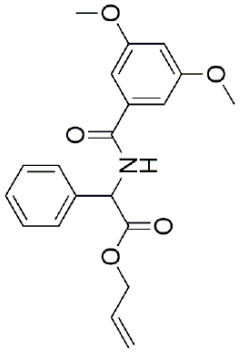
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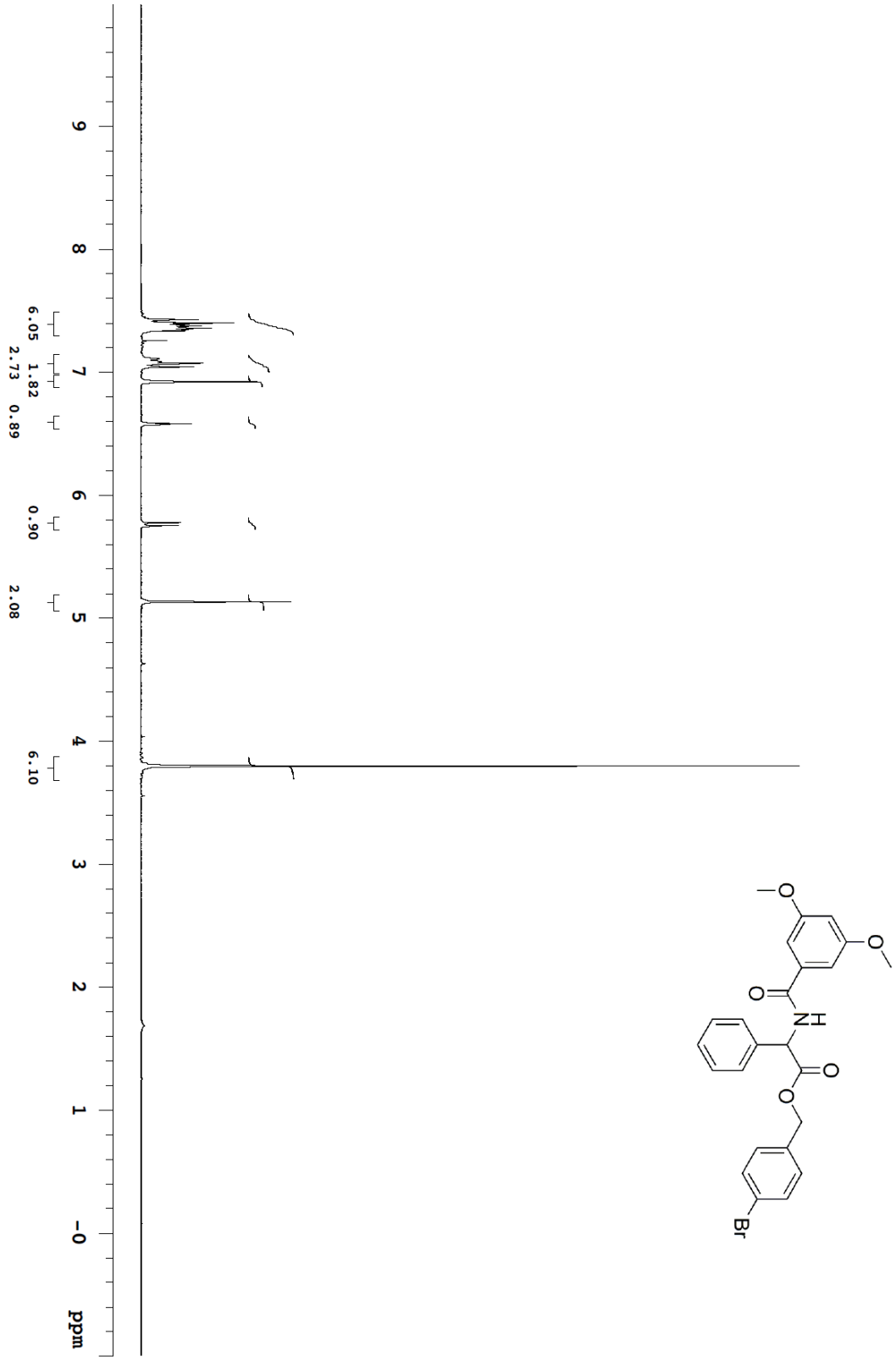
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2.08
6.10
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NH
O
O
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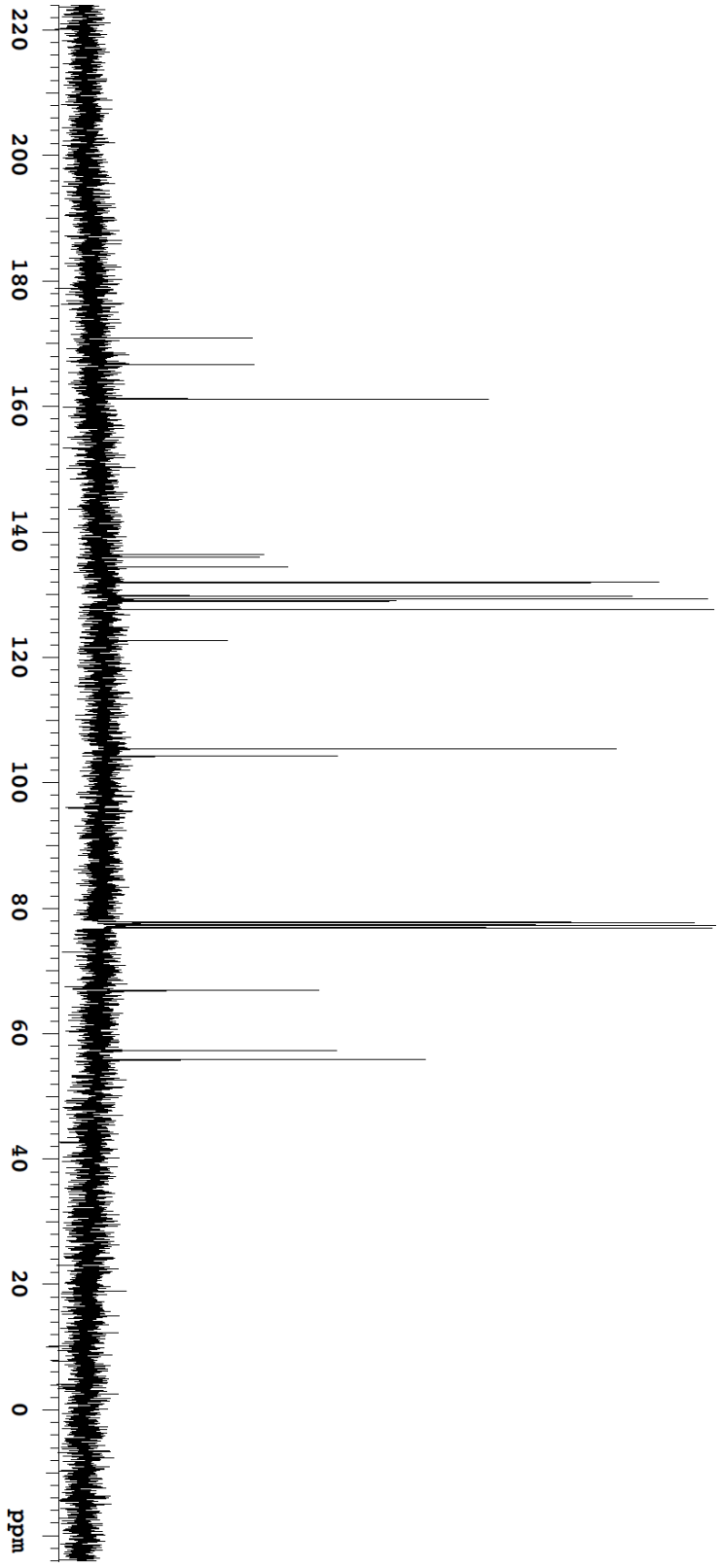
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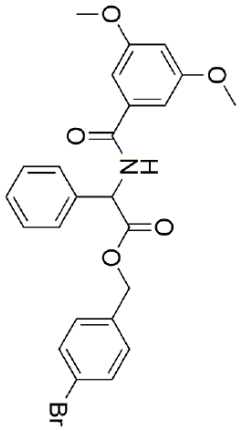
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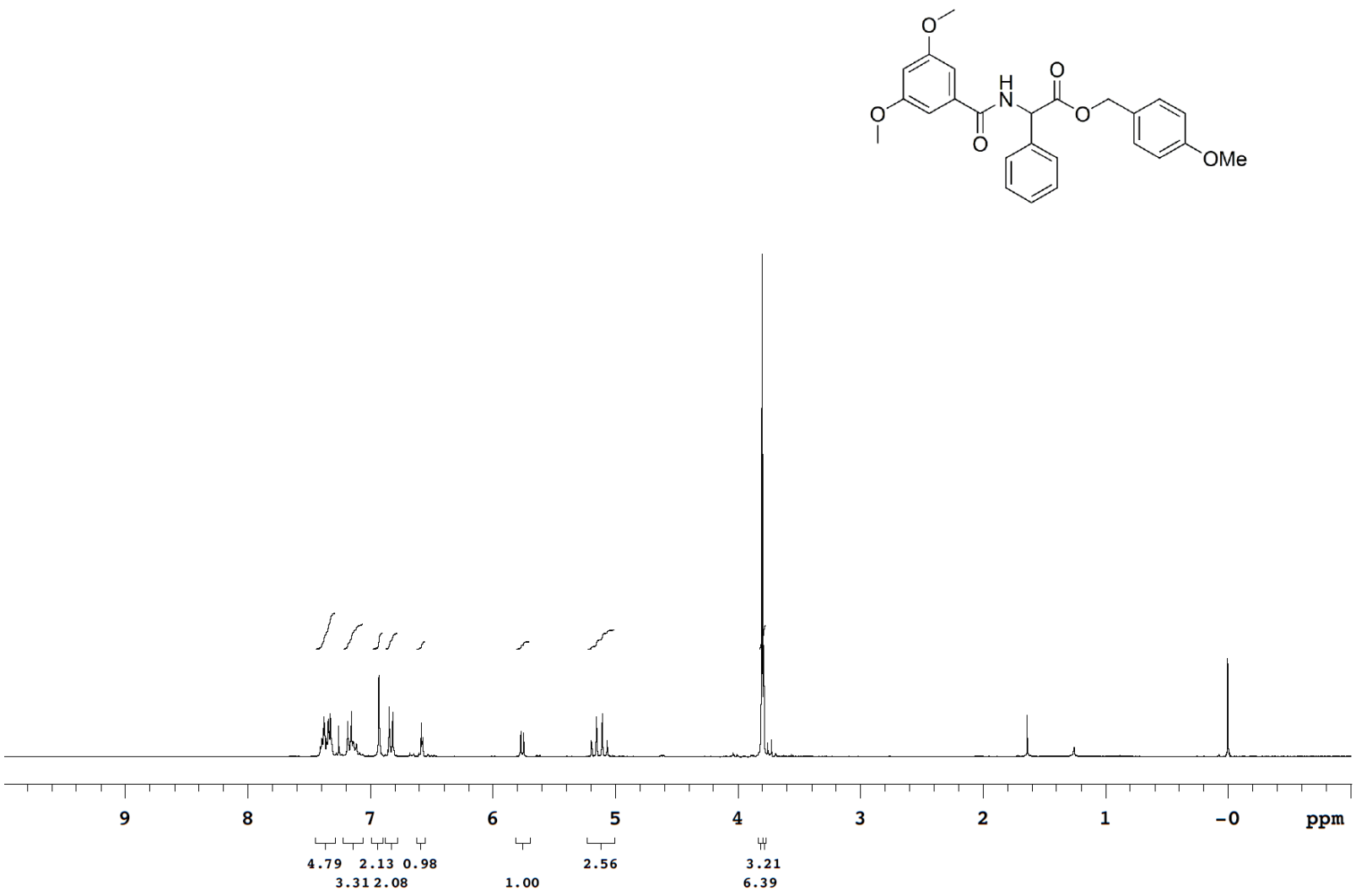
O
O
Br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O
O
O
OMe
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7
6
5
4
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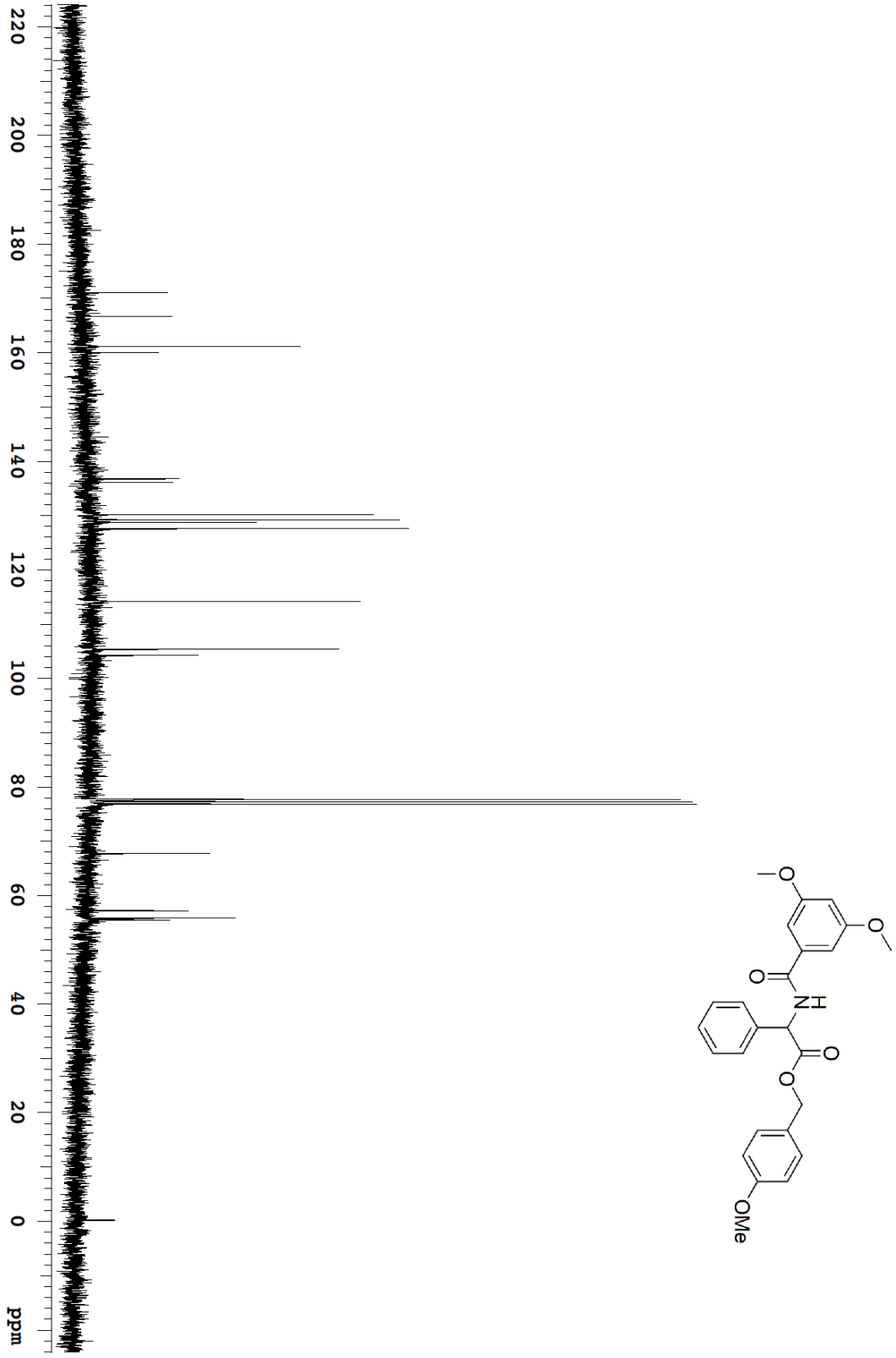
2.08
1.00
2.56
3.21
6.39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ppm
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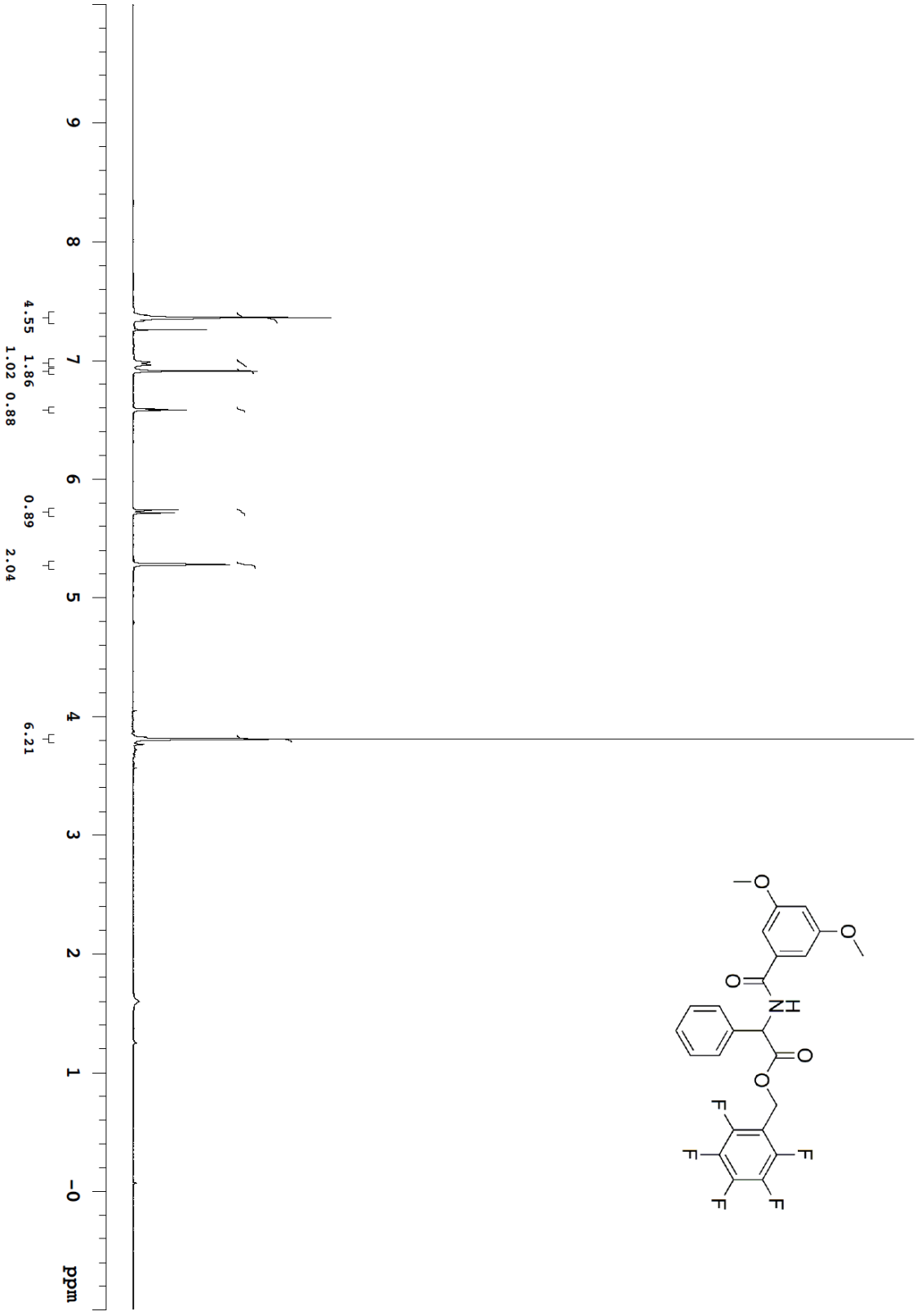
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5
4
3
2
1
-0
ppm
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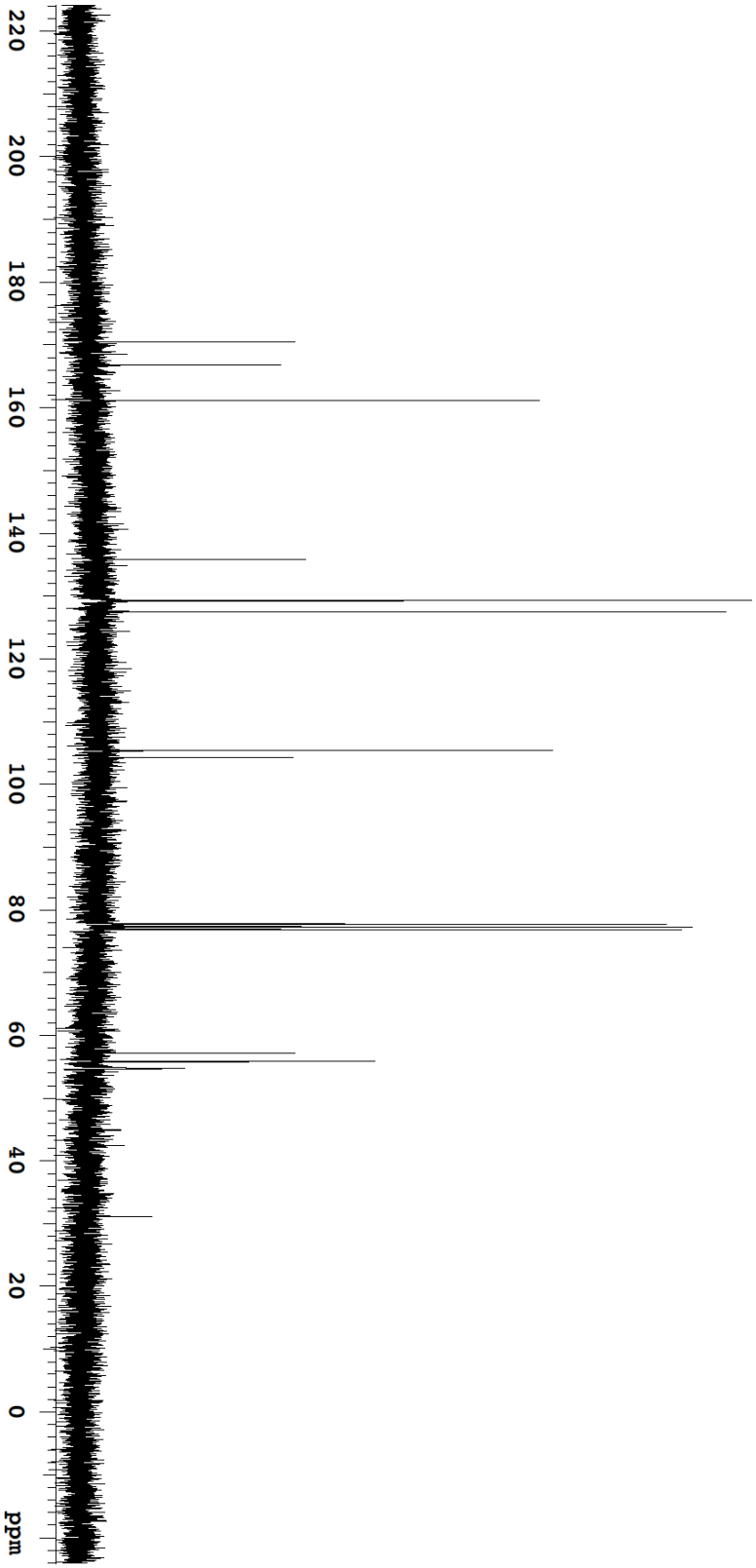
0.88
0.89
2.04
6.21
O
O
O
N
H
O
O
F
F
F
F
F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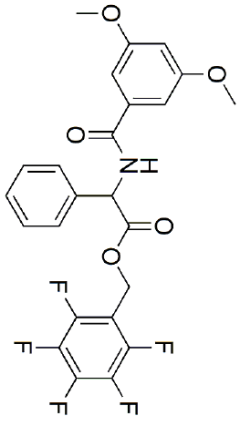
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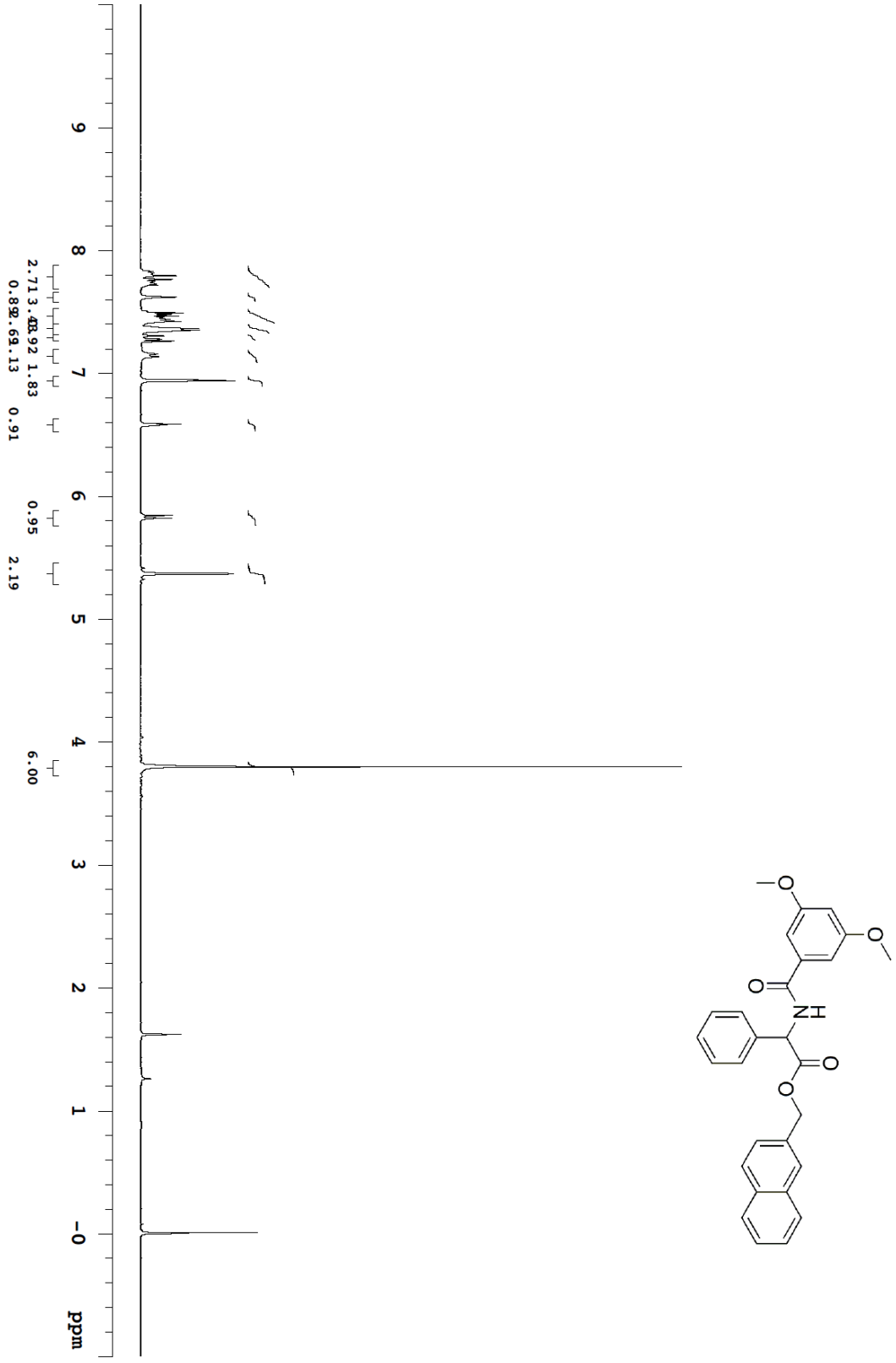
O
H
N
O
O
F
F
F
F
F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0.95
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6.00
0.89
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1.13
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O
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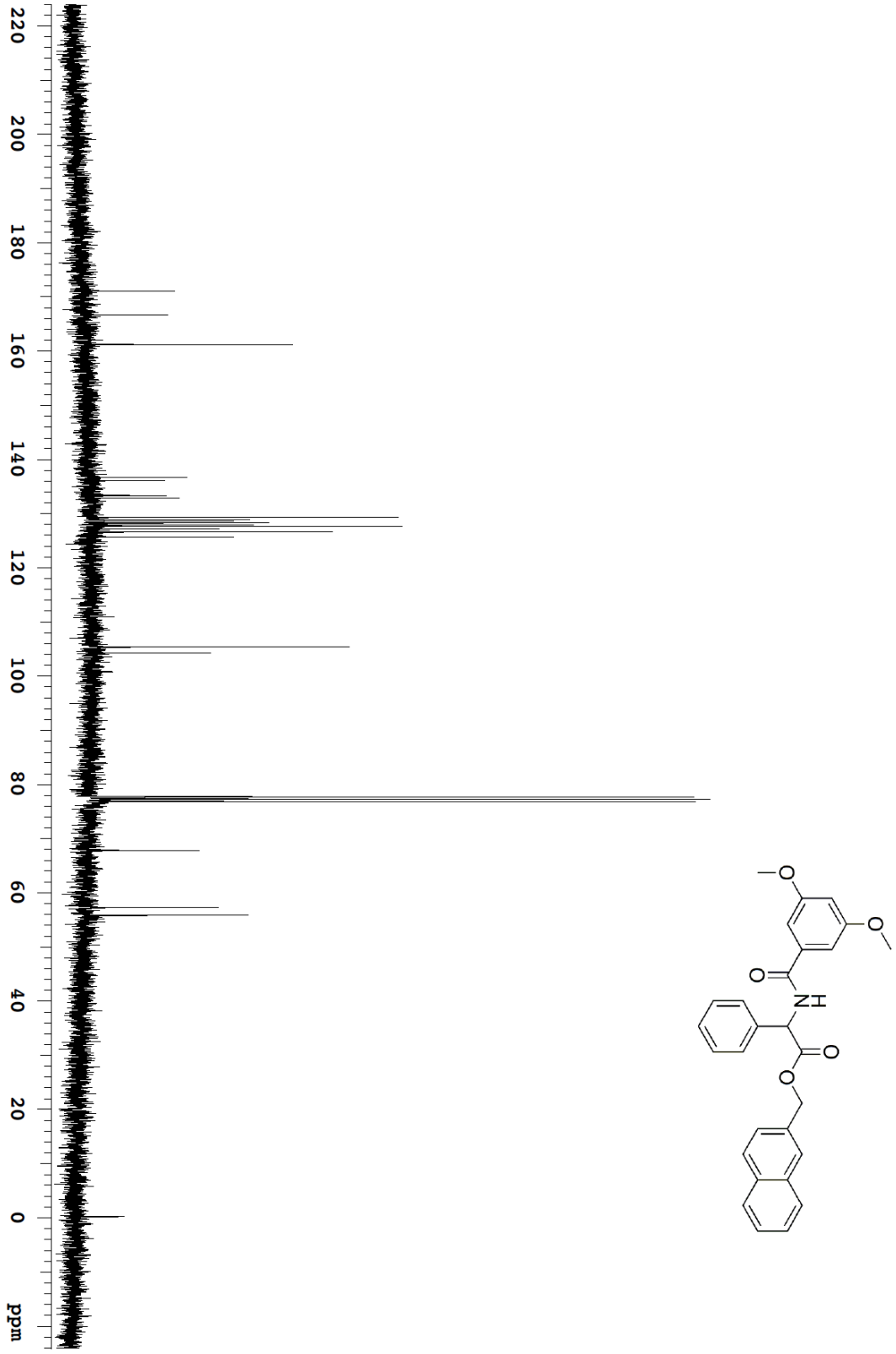
O
O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100
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60
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ppm
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O
NH
O
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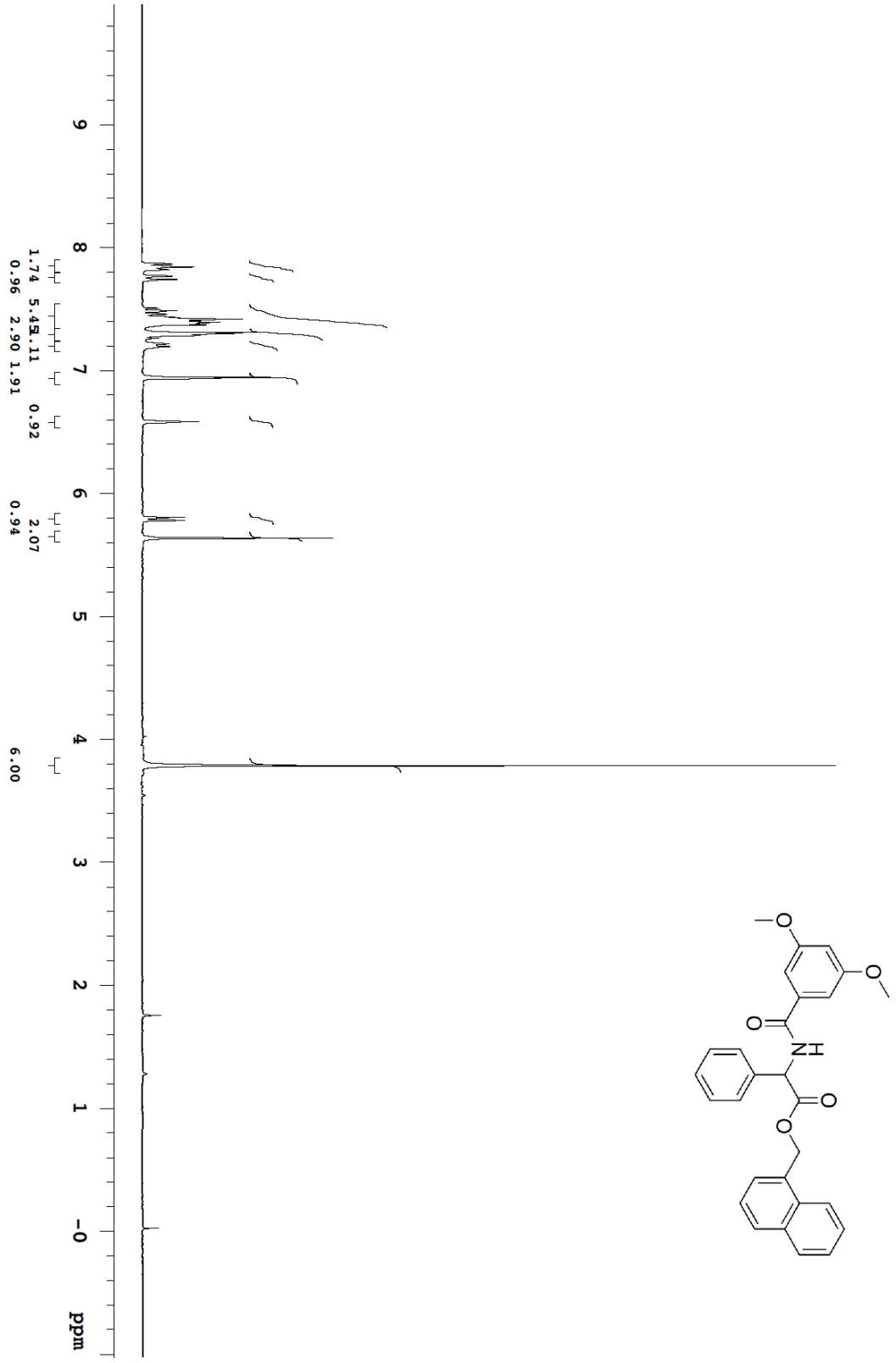
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3
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1
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ppm
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1.91
2.07
0.94
6.00
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O
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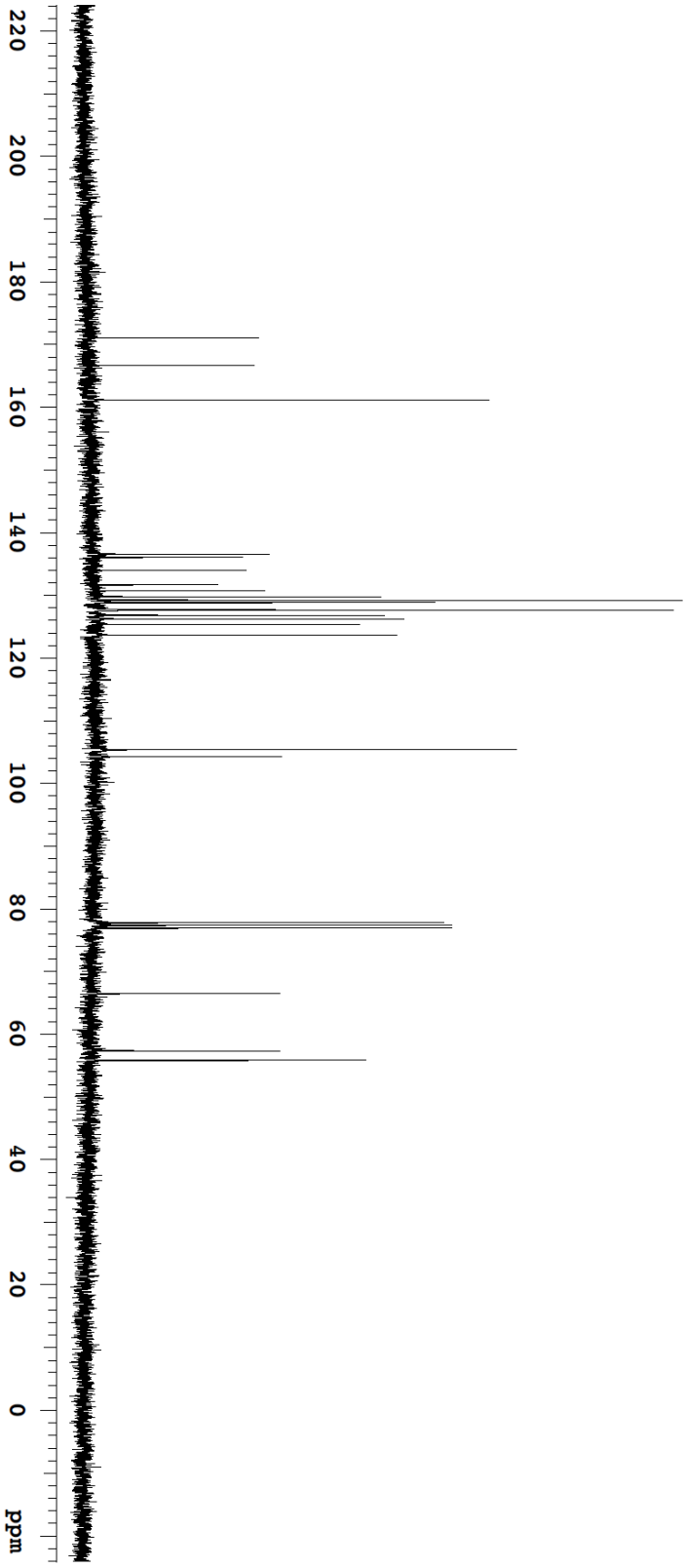
O
O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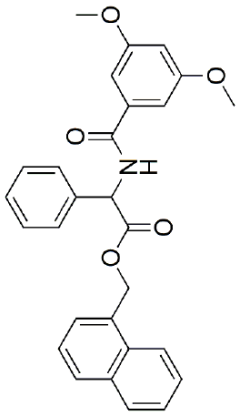
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O
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O
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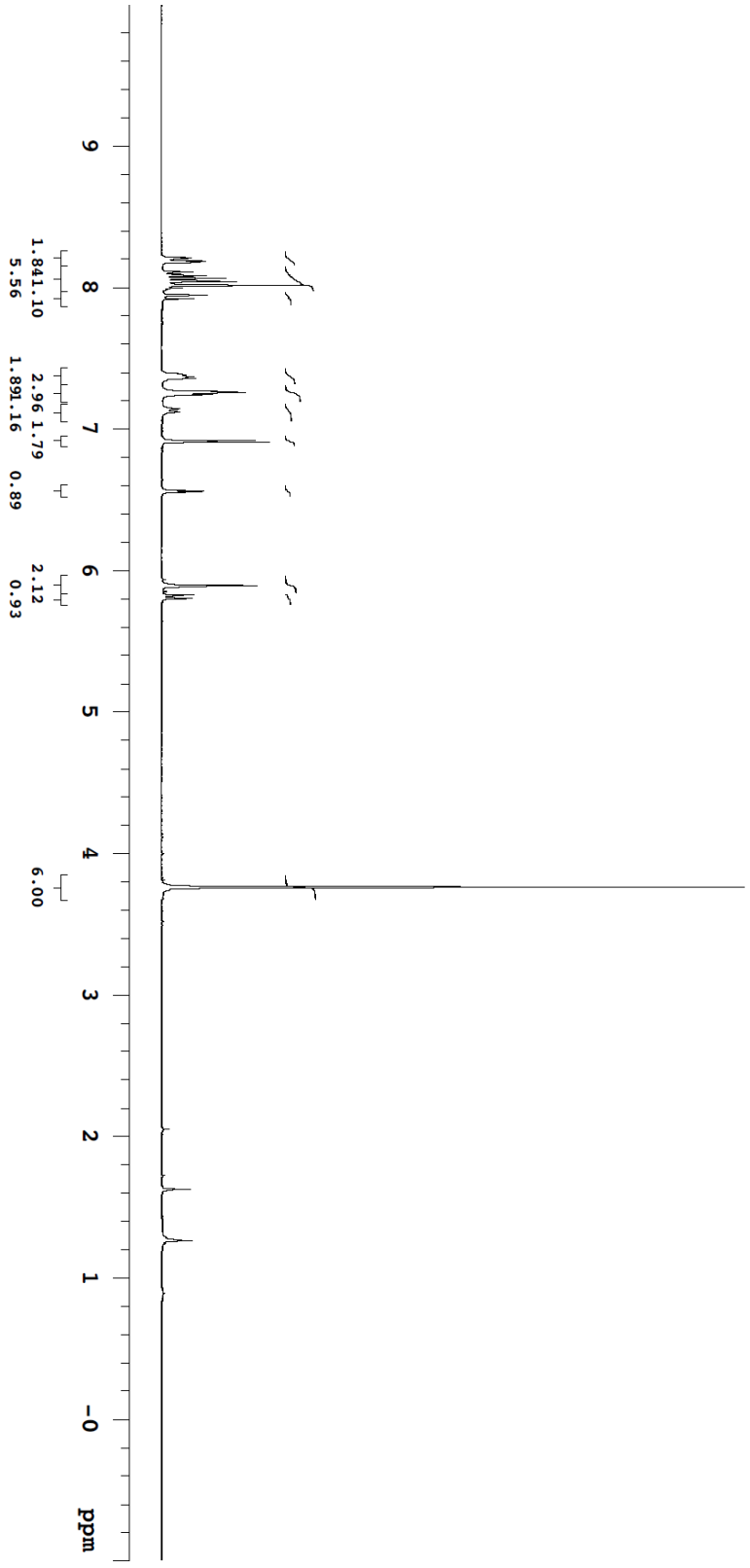
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4
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1.89 1.16
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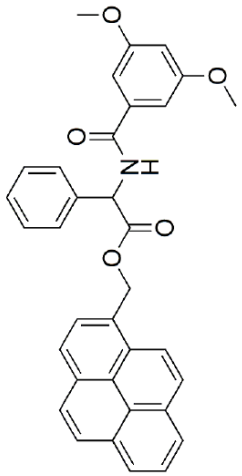
0.89
2.12
0.93
6.00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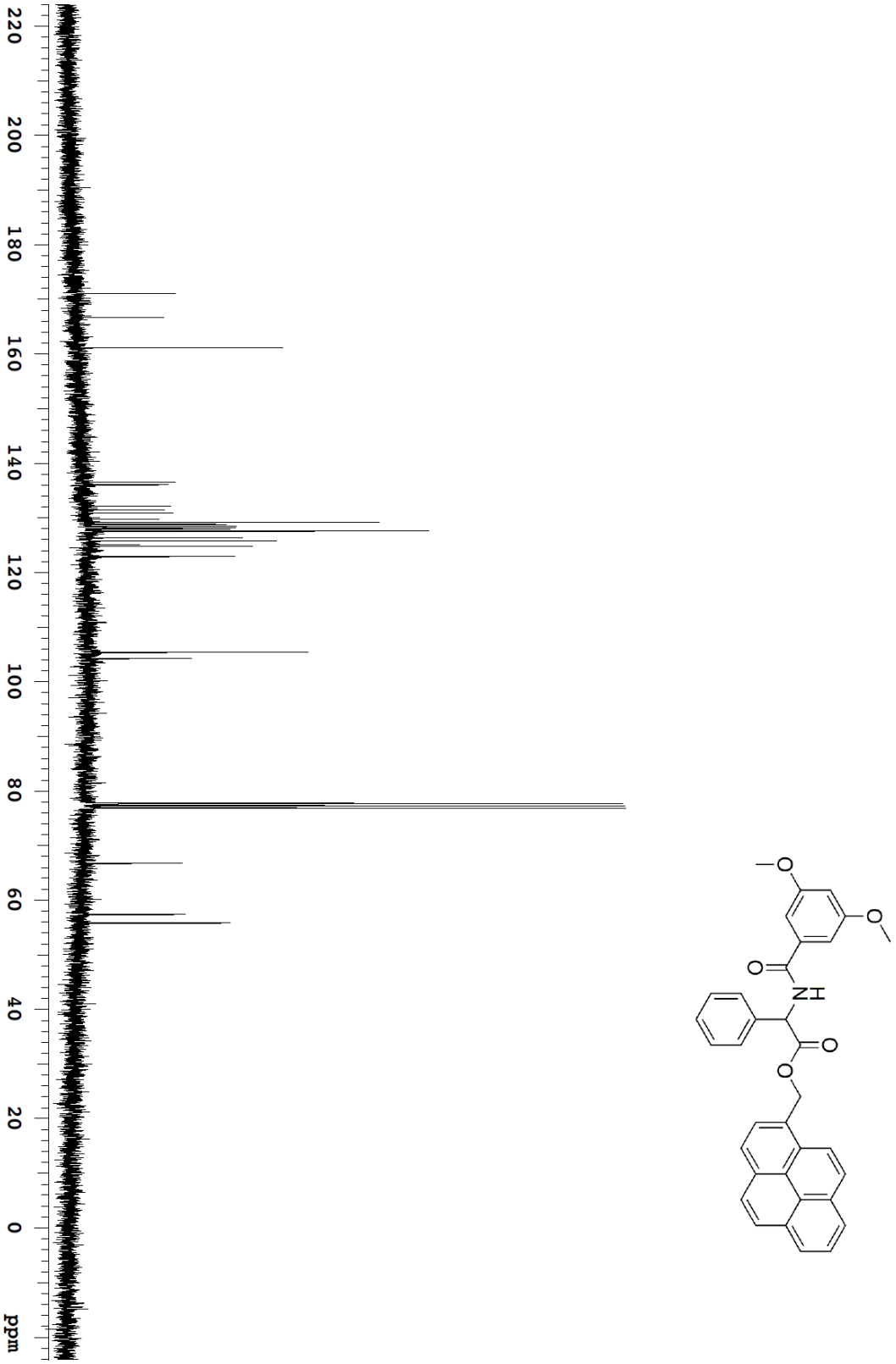
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60
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ppm
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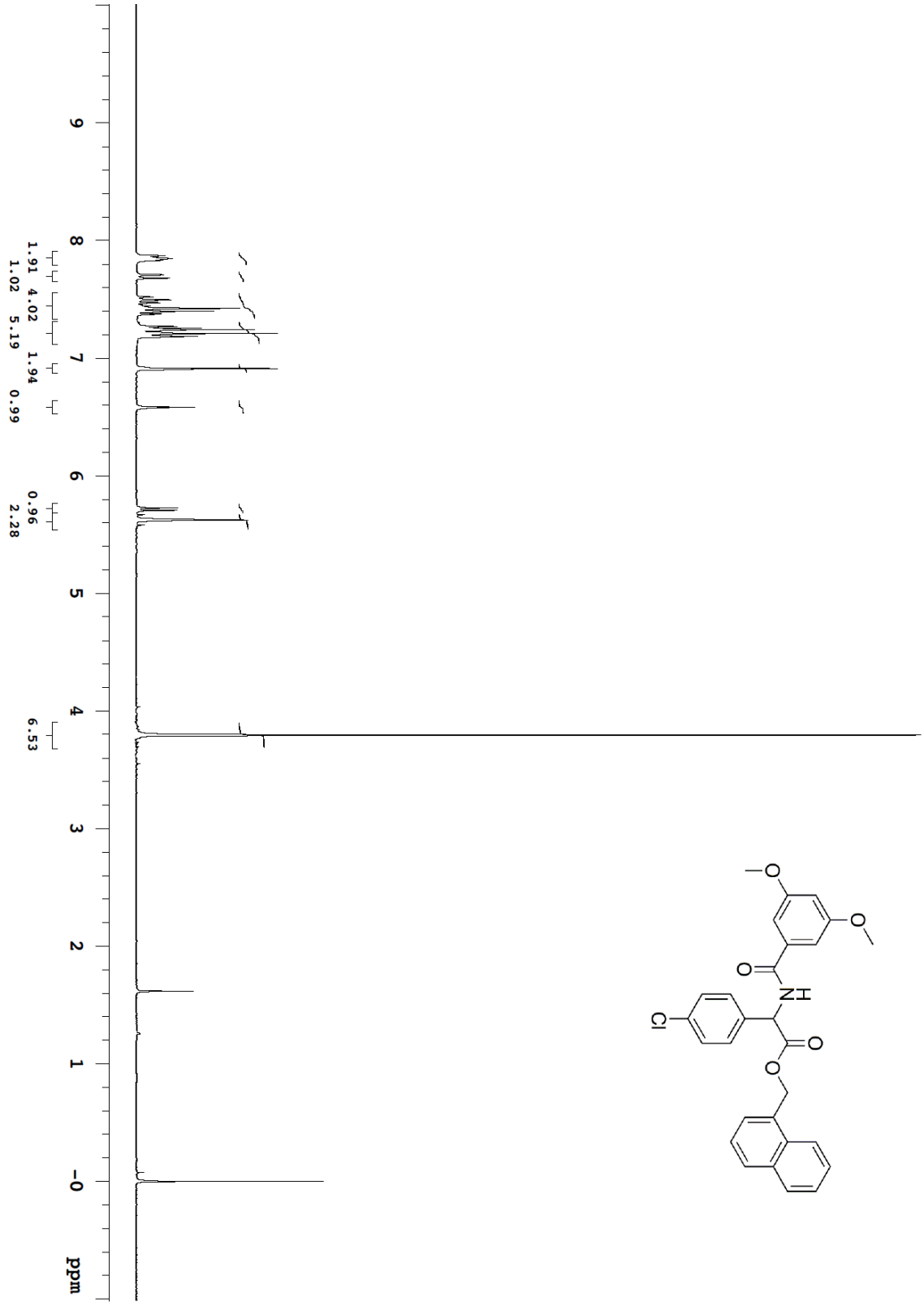
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5
4
3
2
1
0
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1.02 5.19 0.99
0.96
2.28
6.53
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O
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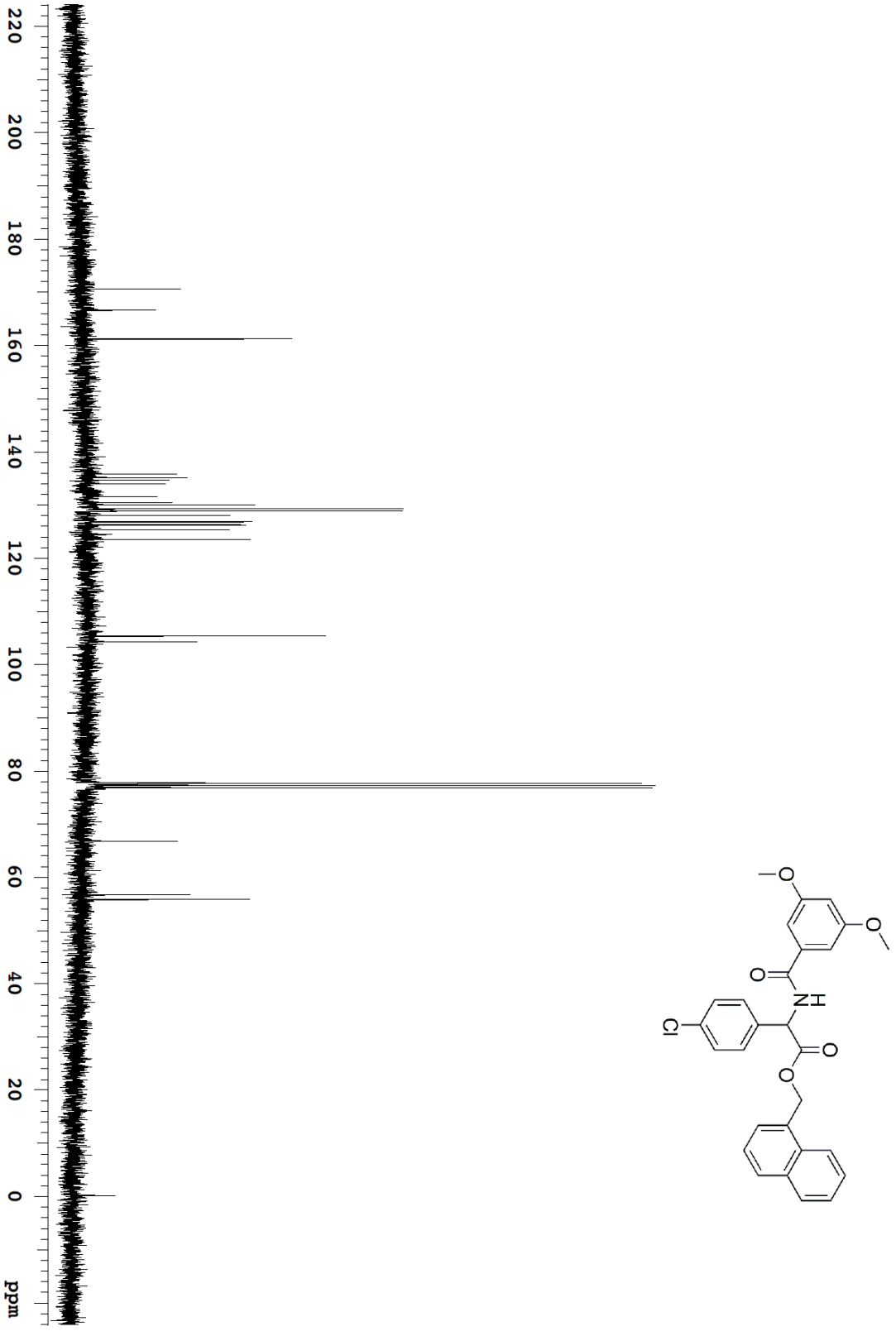
Cl
O
O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120
100
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60
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20
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ppm
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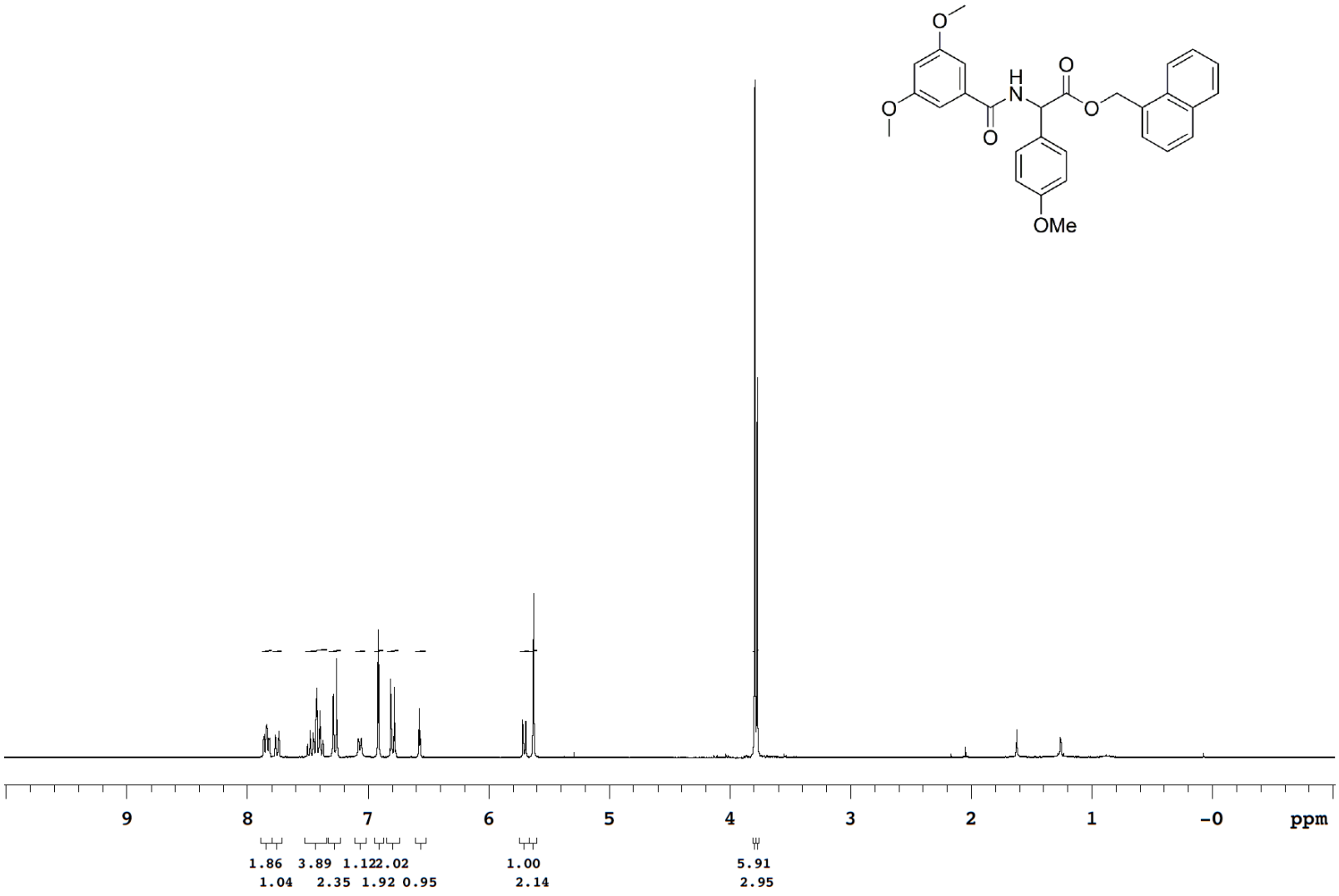
O
NH
Cl
O
O


O
O
H
N
O
O
O
OMe
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8
7
6
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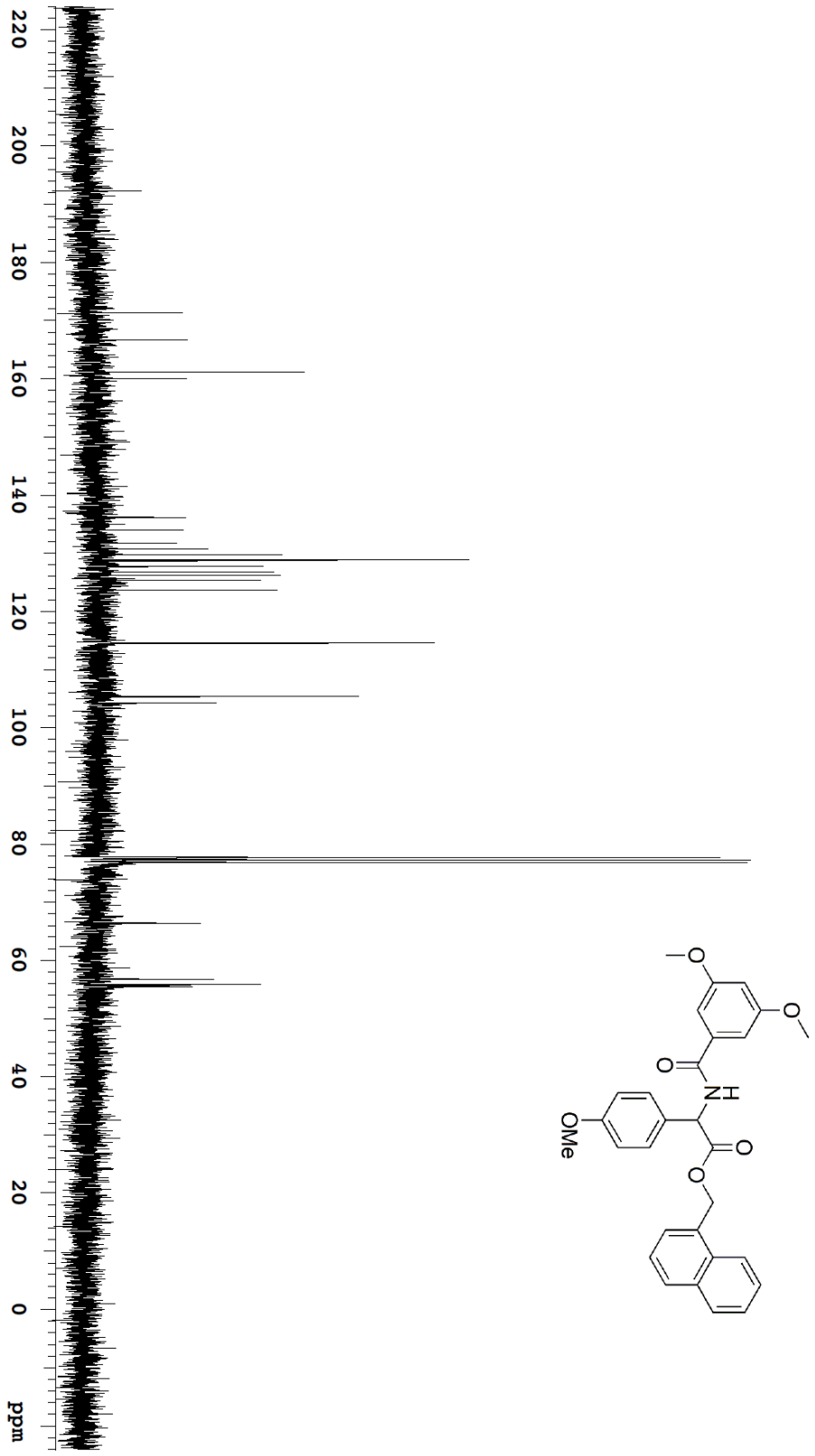
1.04 2.35 1.92 0.95 2.14 2.95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40
20
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O
O
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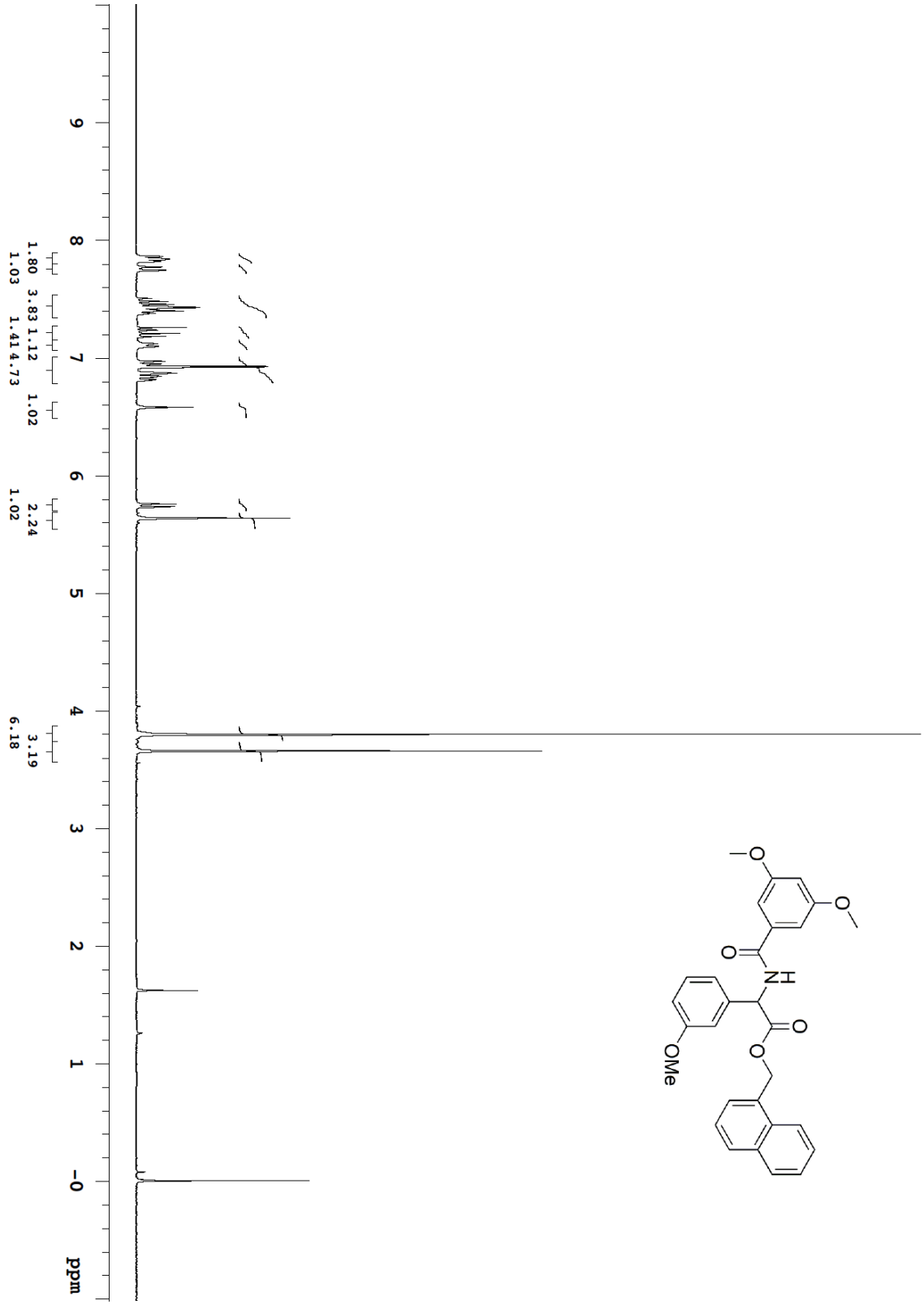
H
O
O
OMe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4
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1.02 2.24
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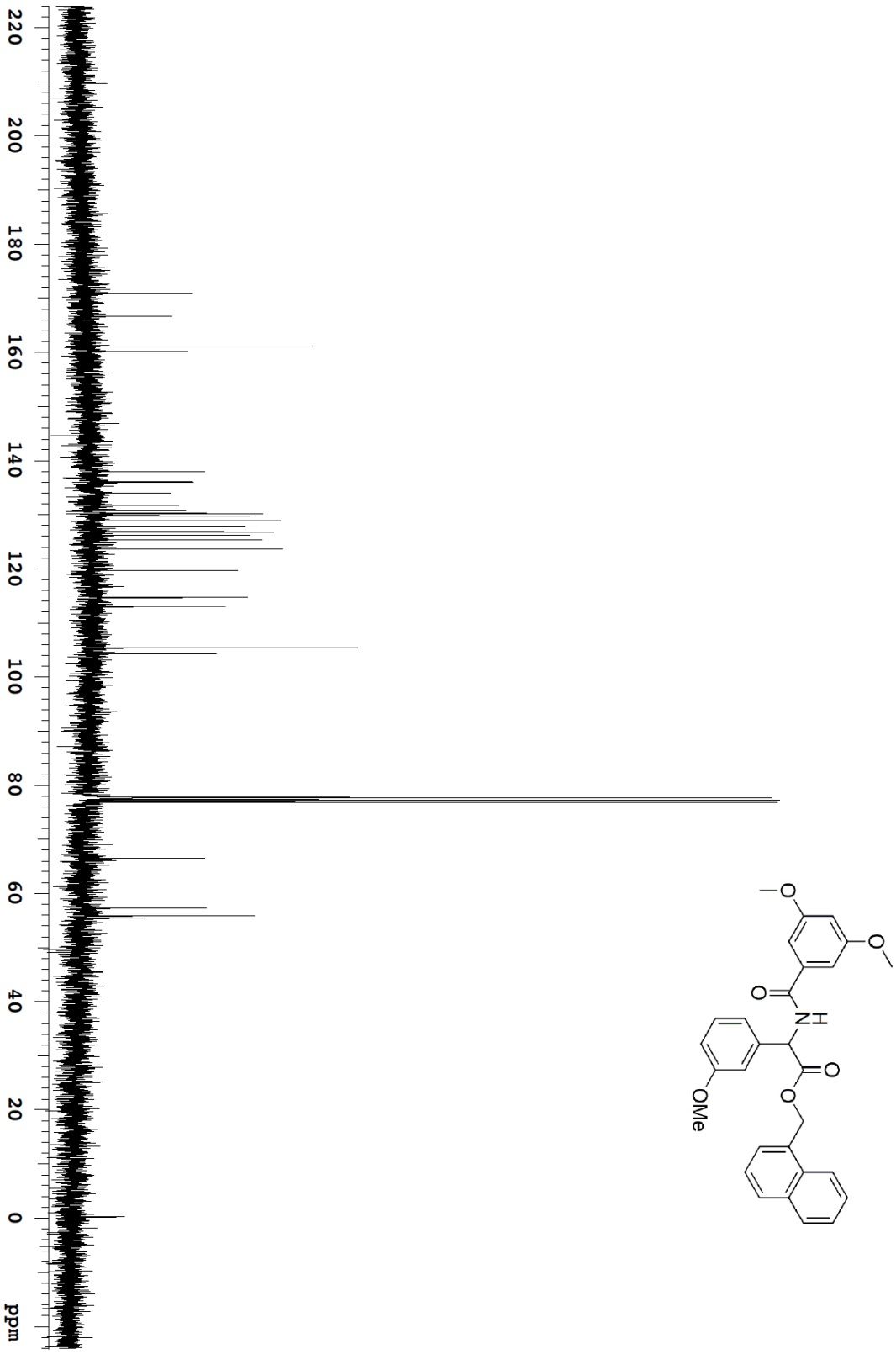
N
H
O
O
OMe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120
100
80
60
40
20
0
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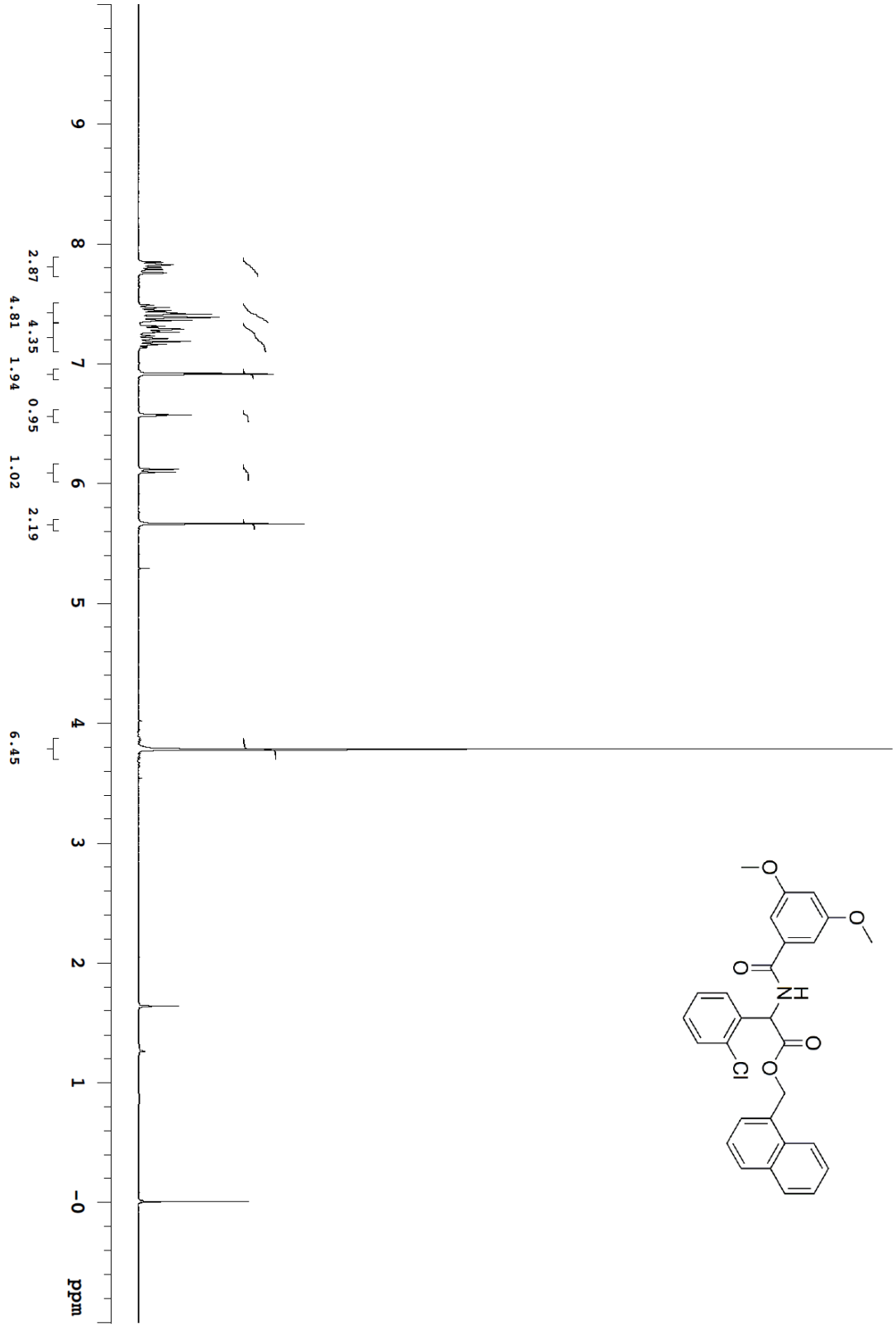
O
O
N
H
O
O
OMe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1.02
2.19
6.45
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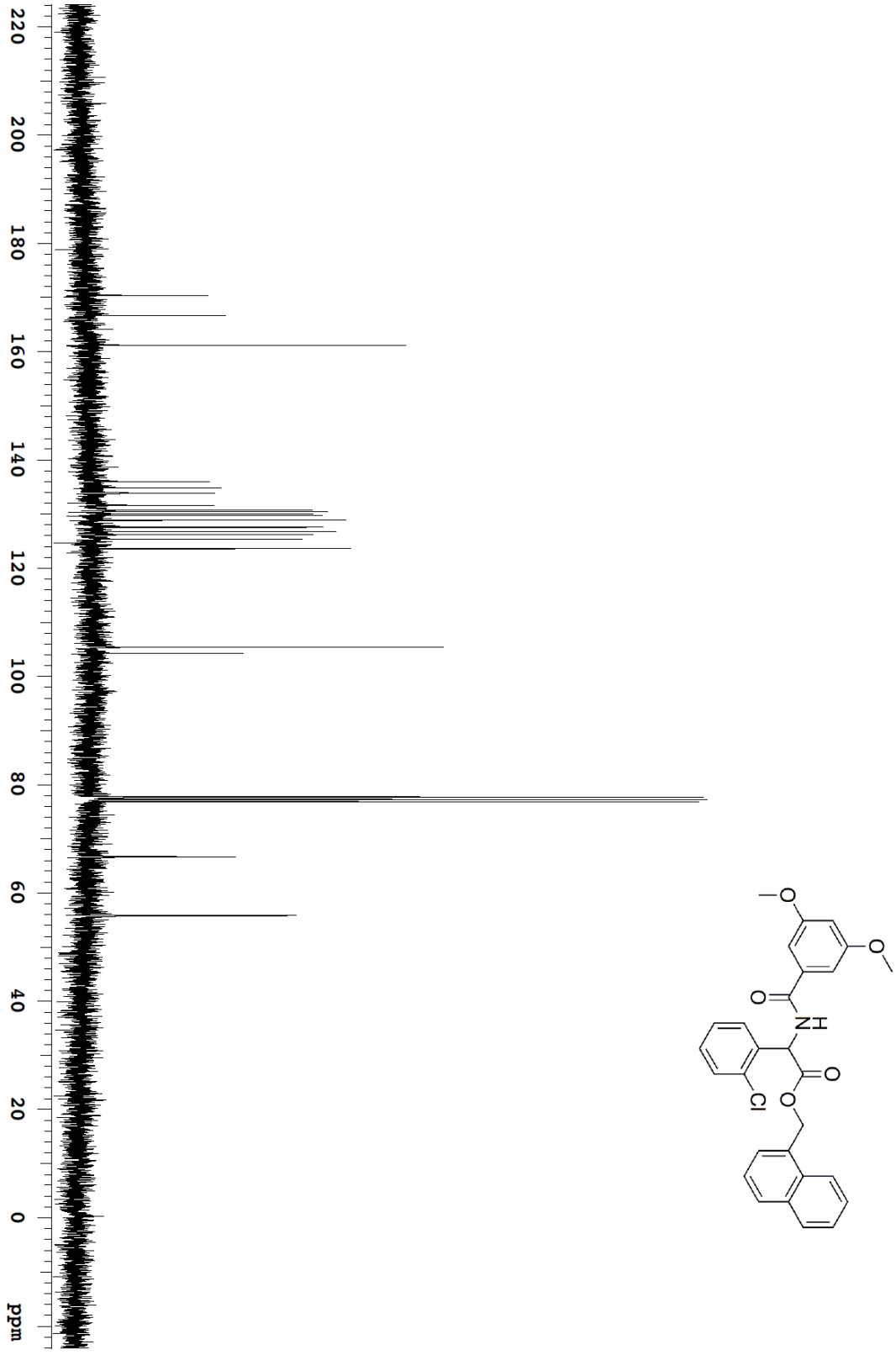
NH
O
O
Cl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ppm
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NH
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O
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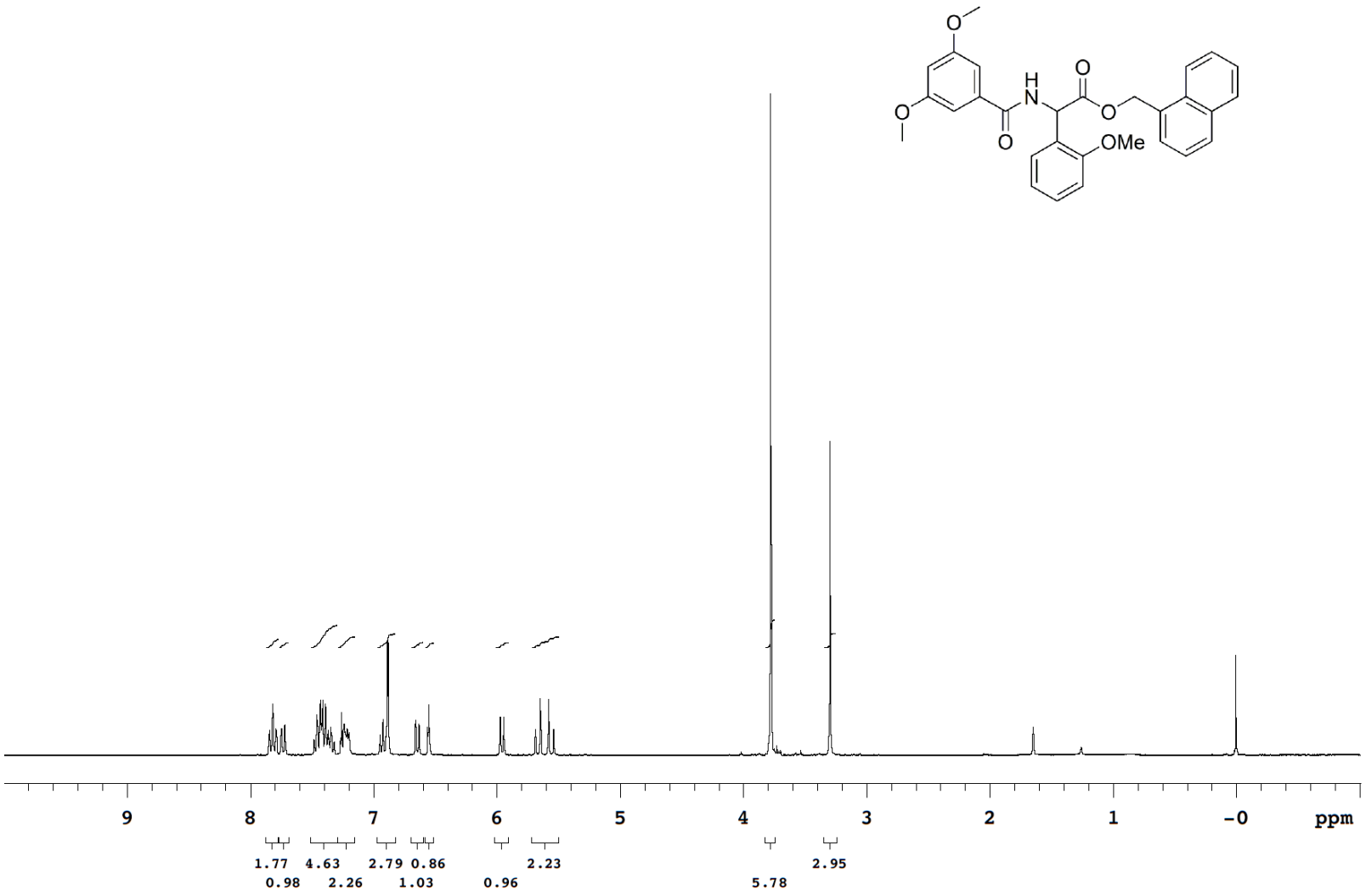
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O
O
O
O
OMe
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6
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4
3
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1
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1.03
0.96
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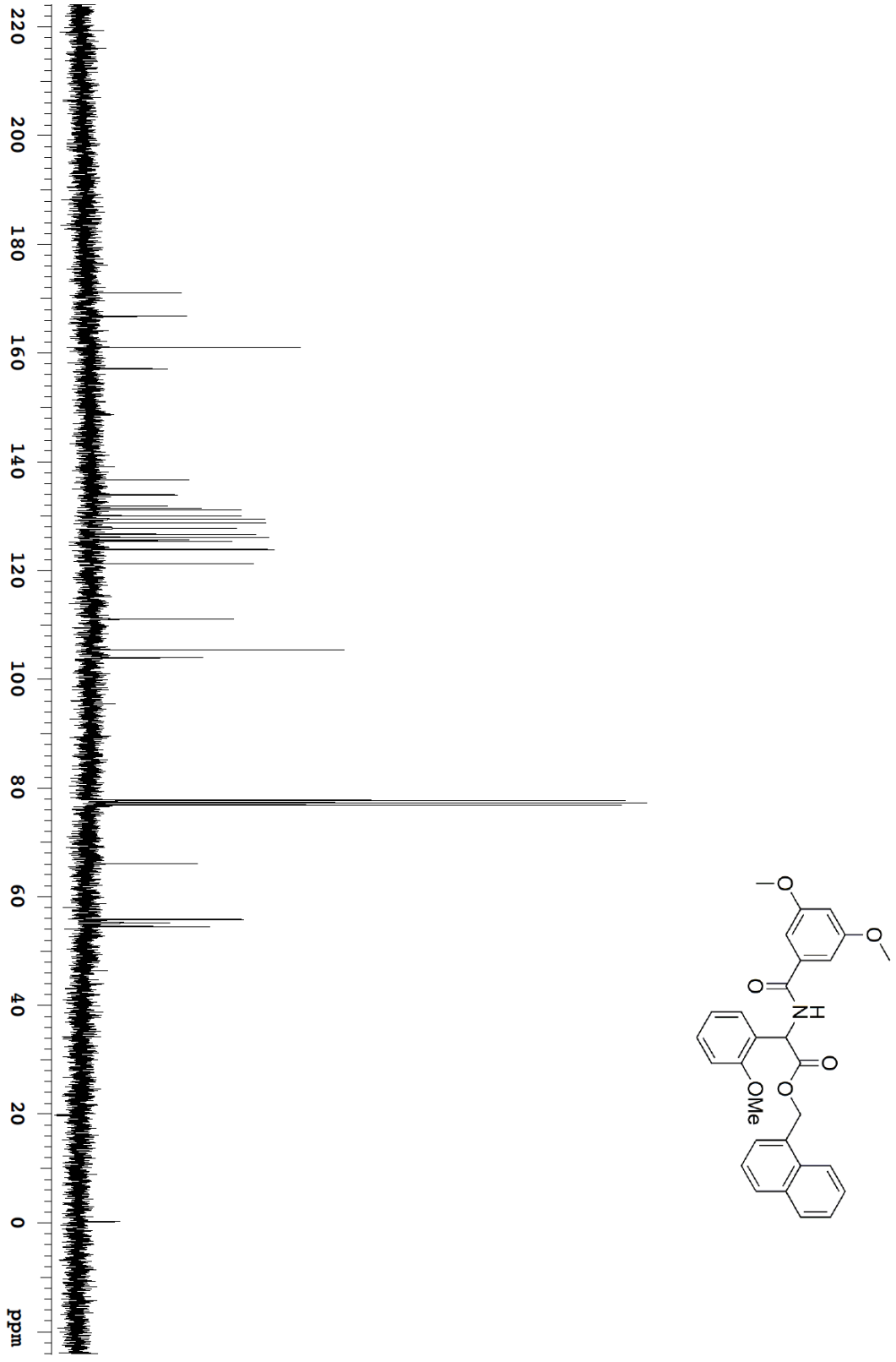
5.78
2.95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60
40
20
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ppm
O
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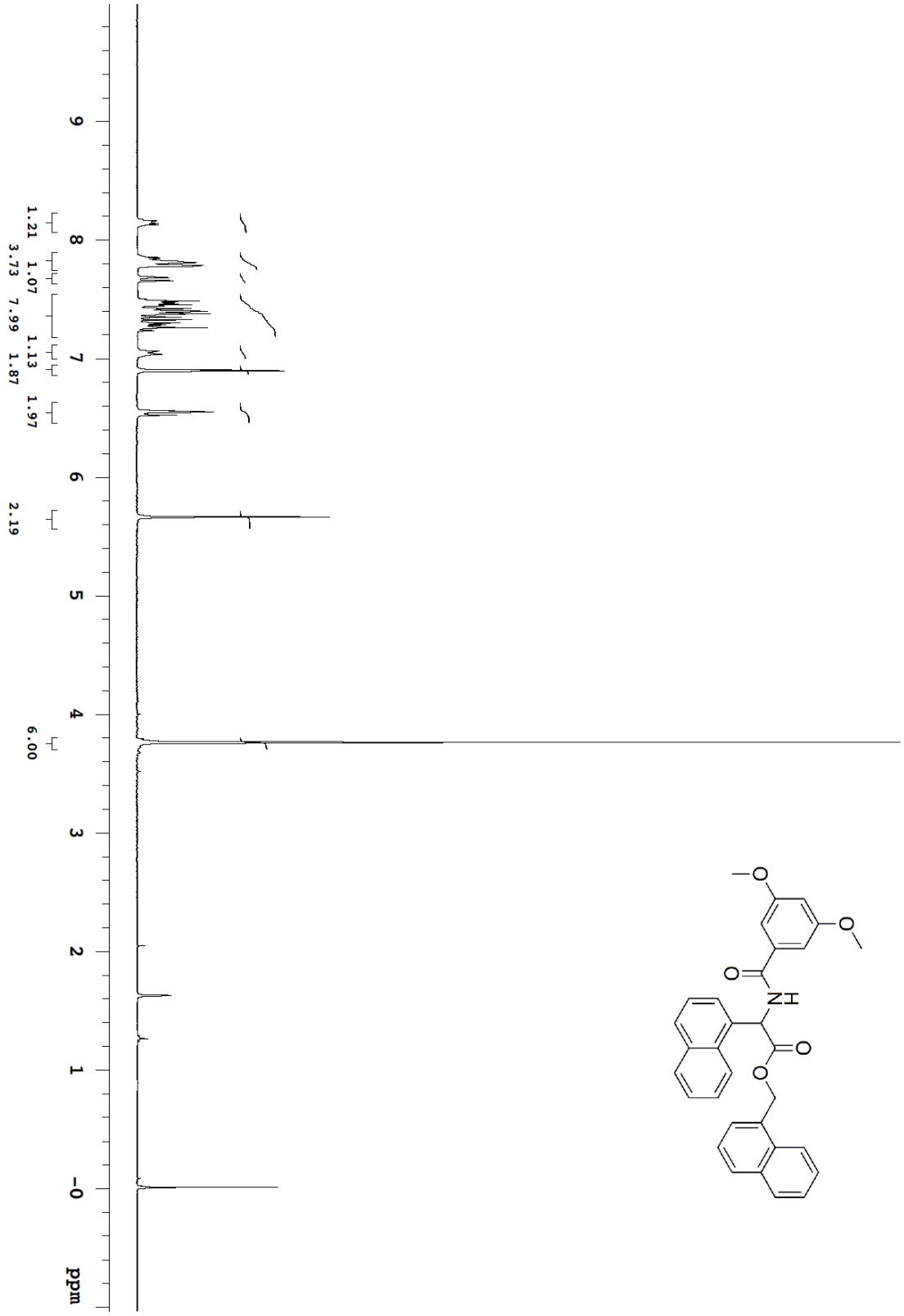
O
NH
O
O
OMe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6
5
4
3
2
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-0
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3.73
7.99
1.87
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6.00
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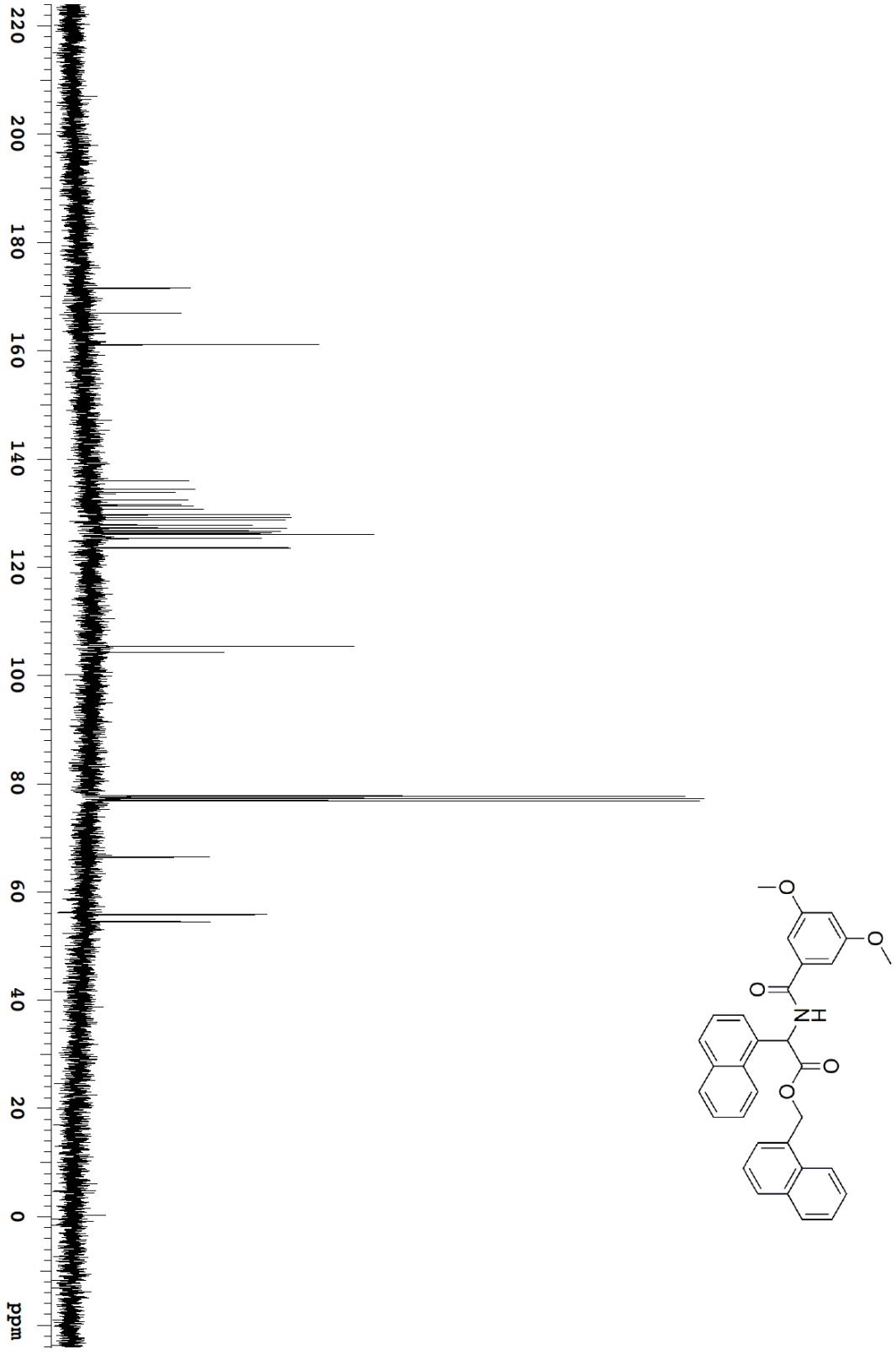
O
NH
O
O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ppm
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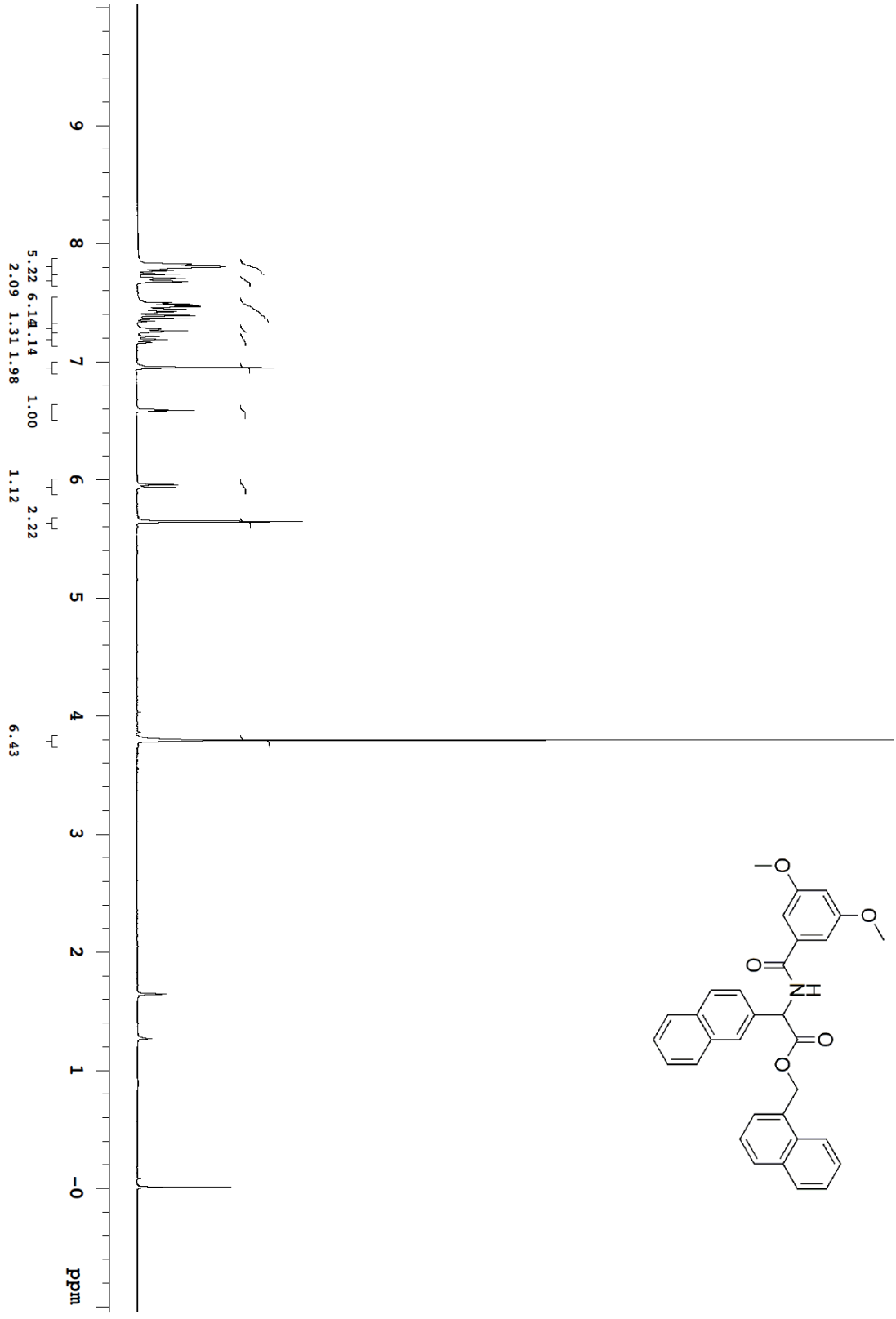
O
NH
O
O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4
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2
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0
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2.09 1.31 1.98
1.00
1.12
2.22
6.43
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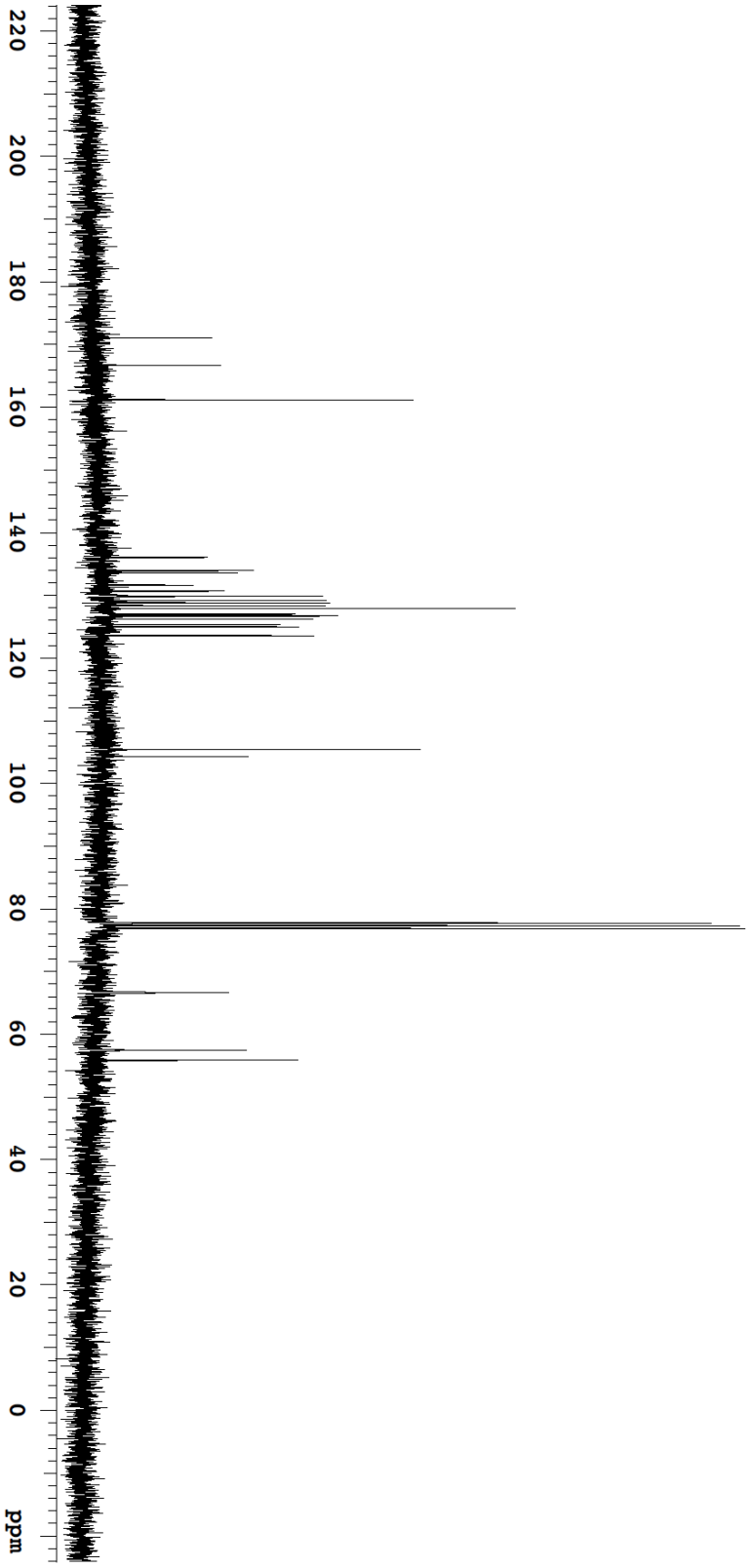
O
NH
O
O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200
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120
100
80
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40
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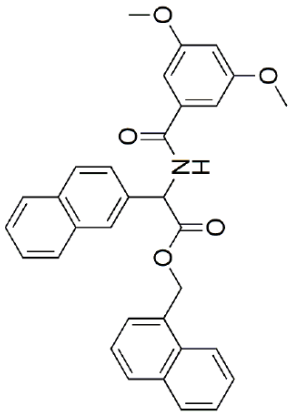
0
ppm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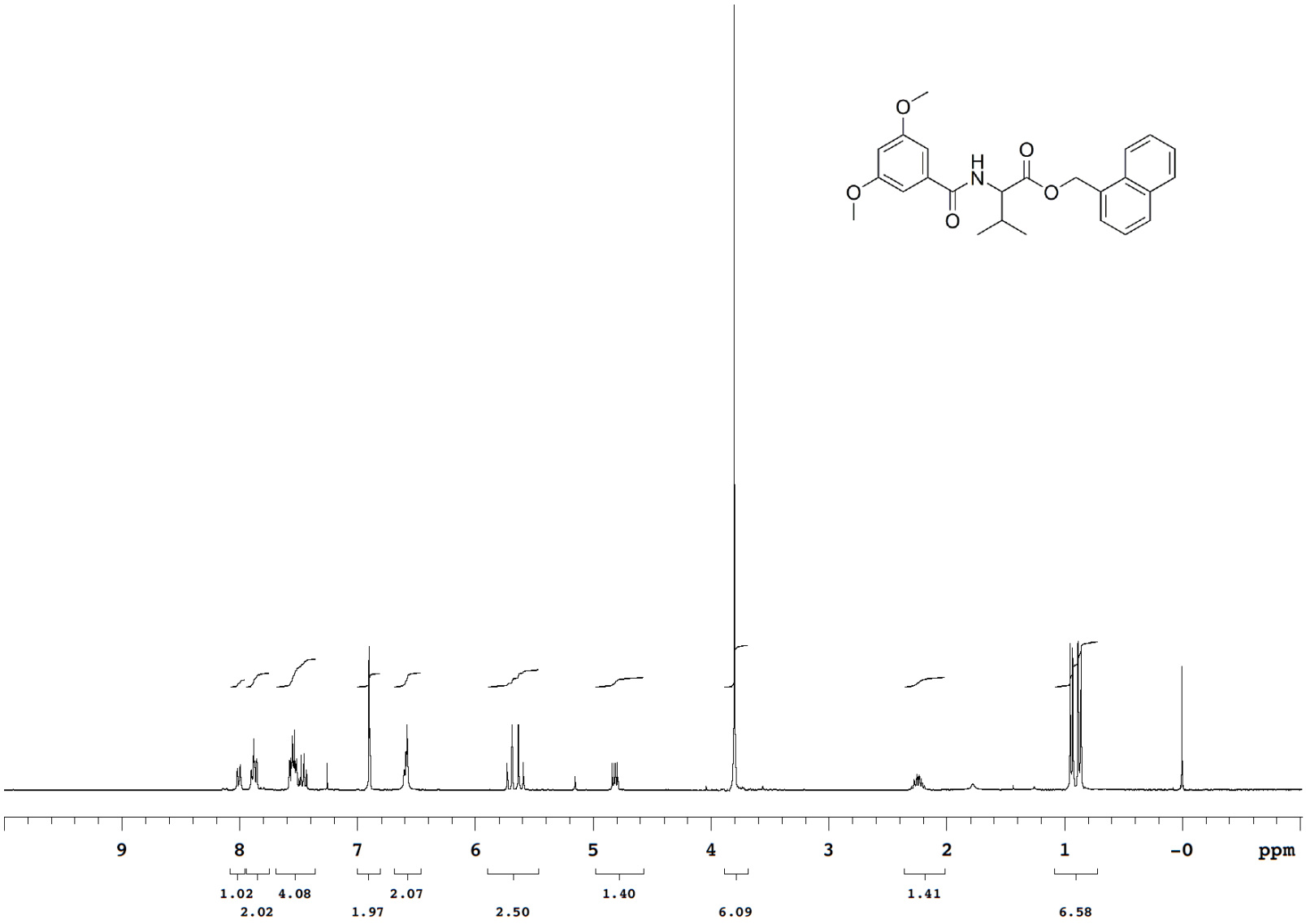
O
O


O
O
H
N
O
O
O
9
8
7
6
5
4
3
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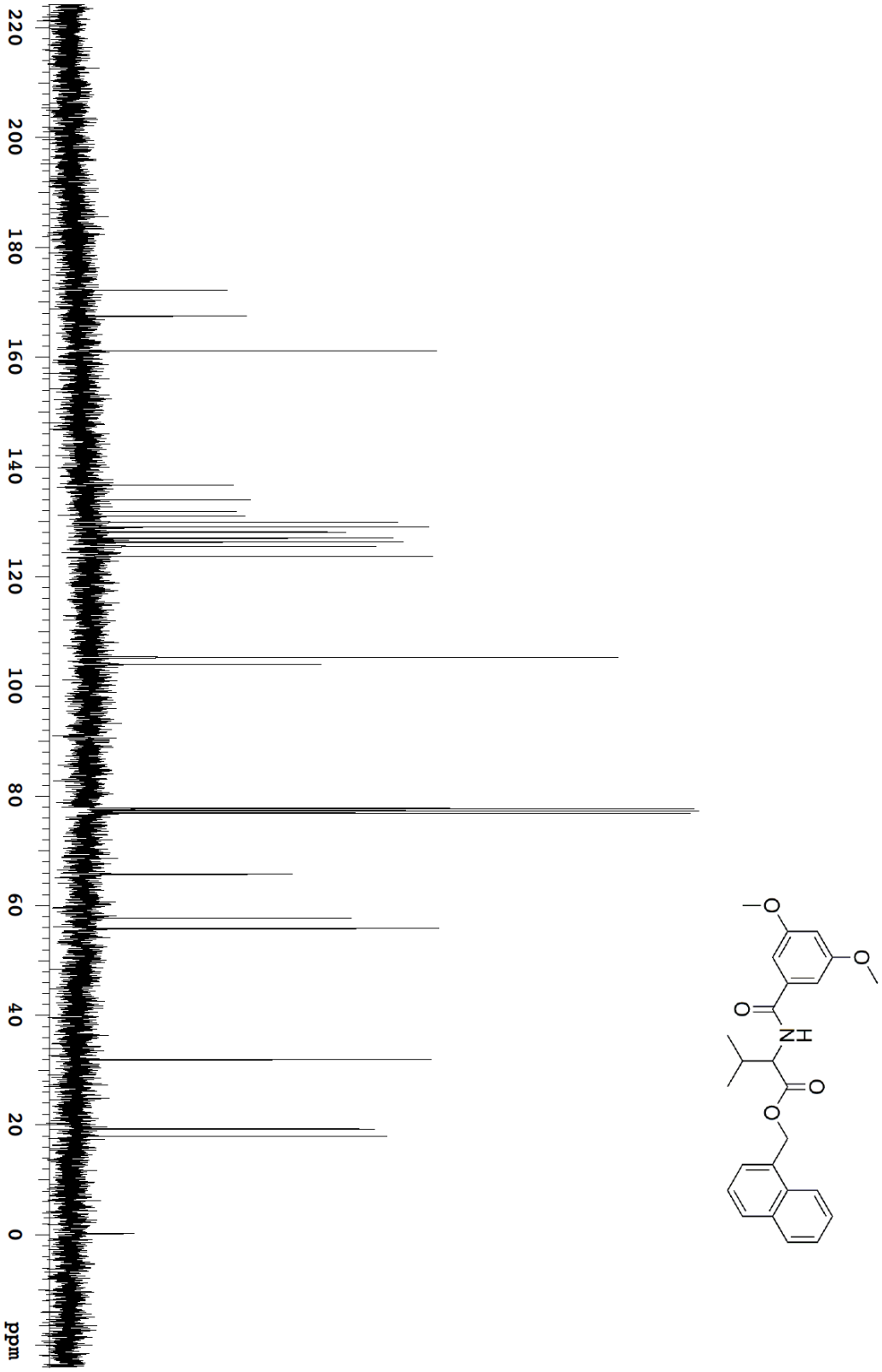
4.08
2.07
1.40
1.41
2.02
1.97
2.50
6.09
6.58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140
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100
80
60
40
20
0
ppm
O
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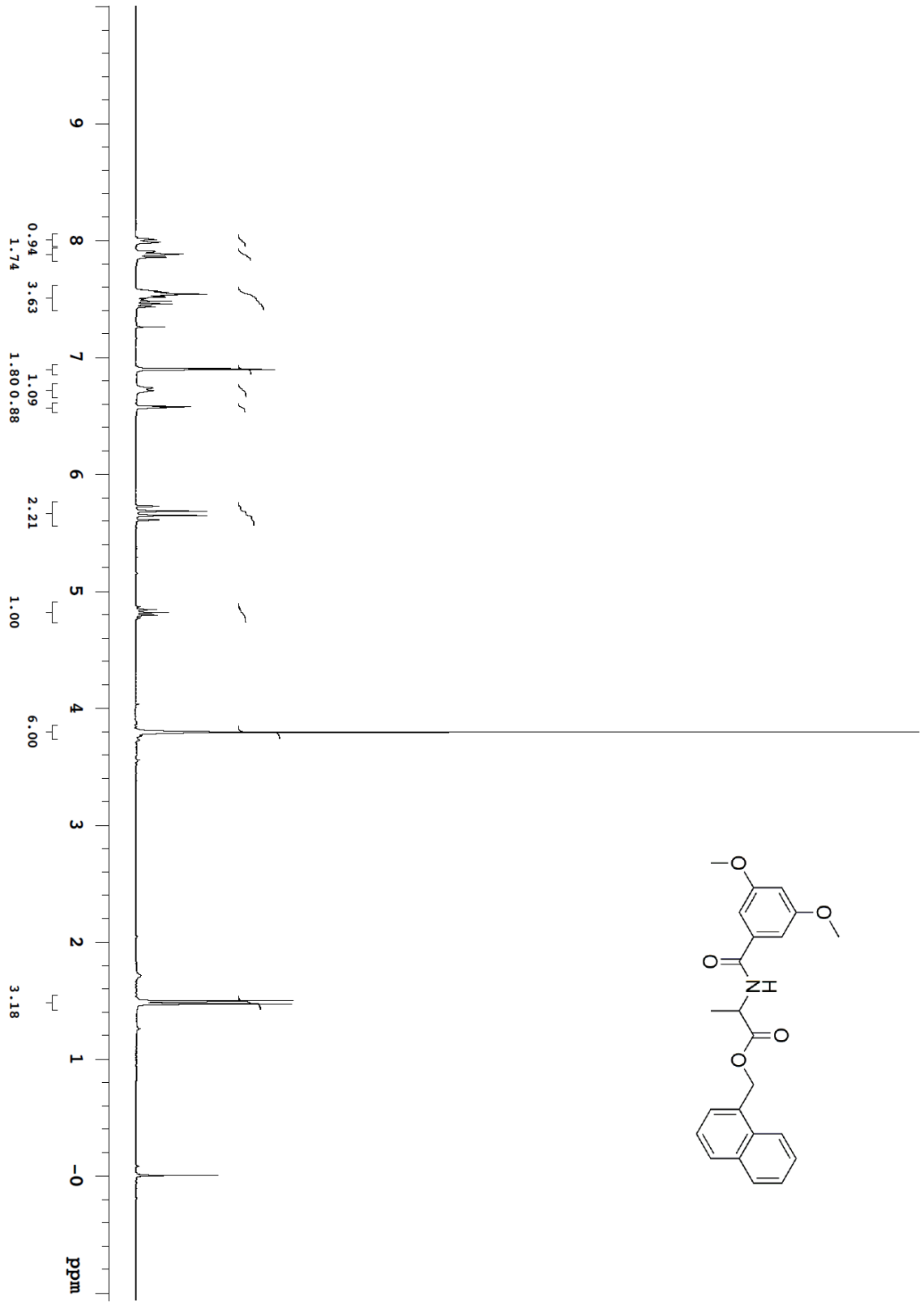
O
NH
O
O


9
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6
5
4
3
2
1
0
ppm
0.94
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1.80
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0.88
2.21
1.00
6.00
3.18
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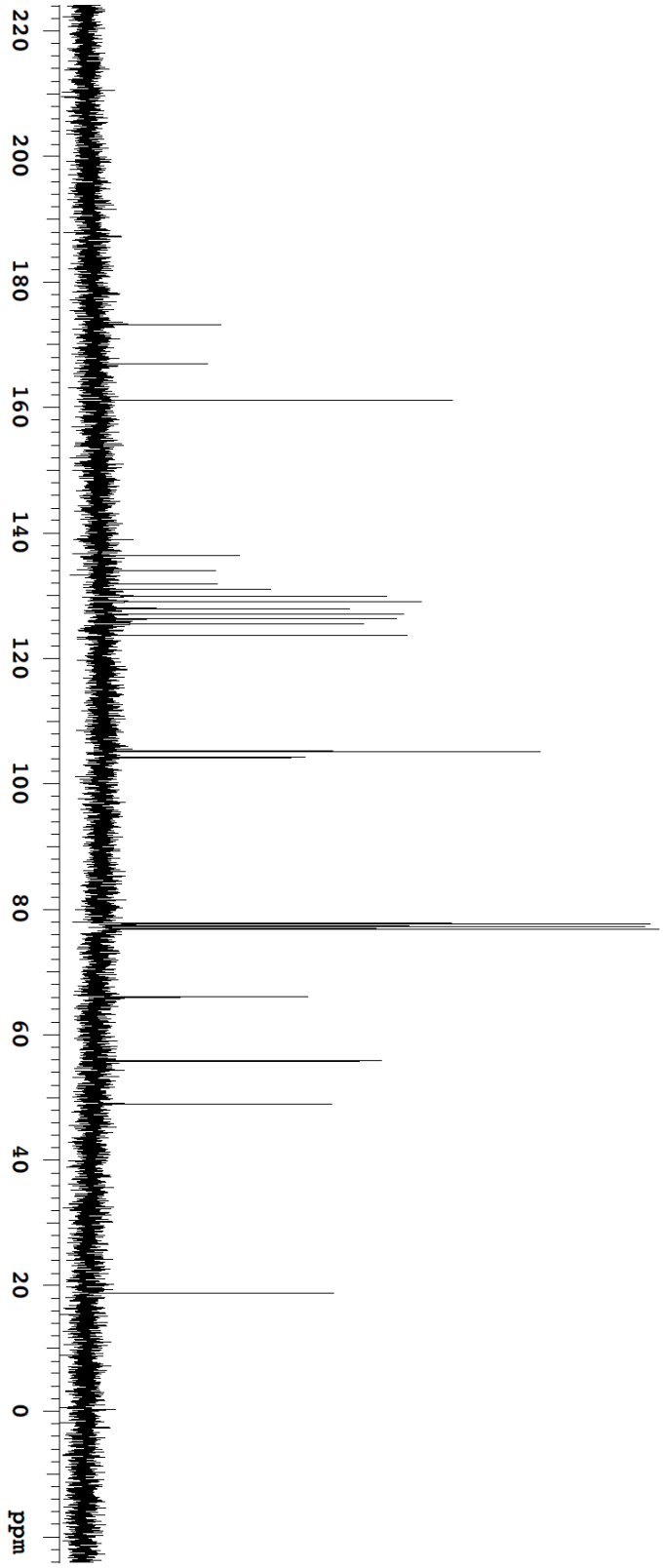
O
O
O
O


220
200
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140
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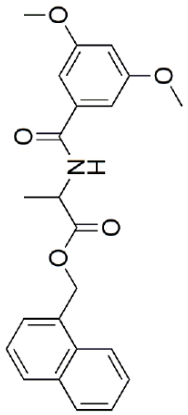
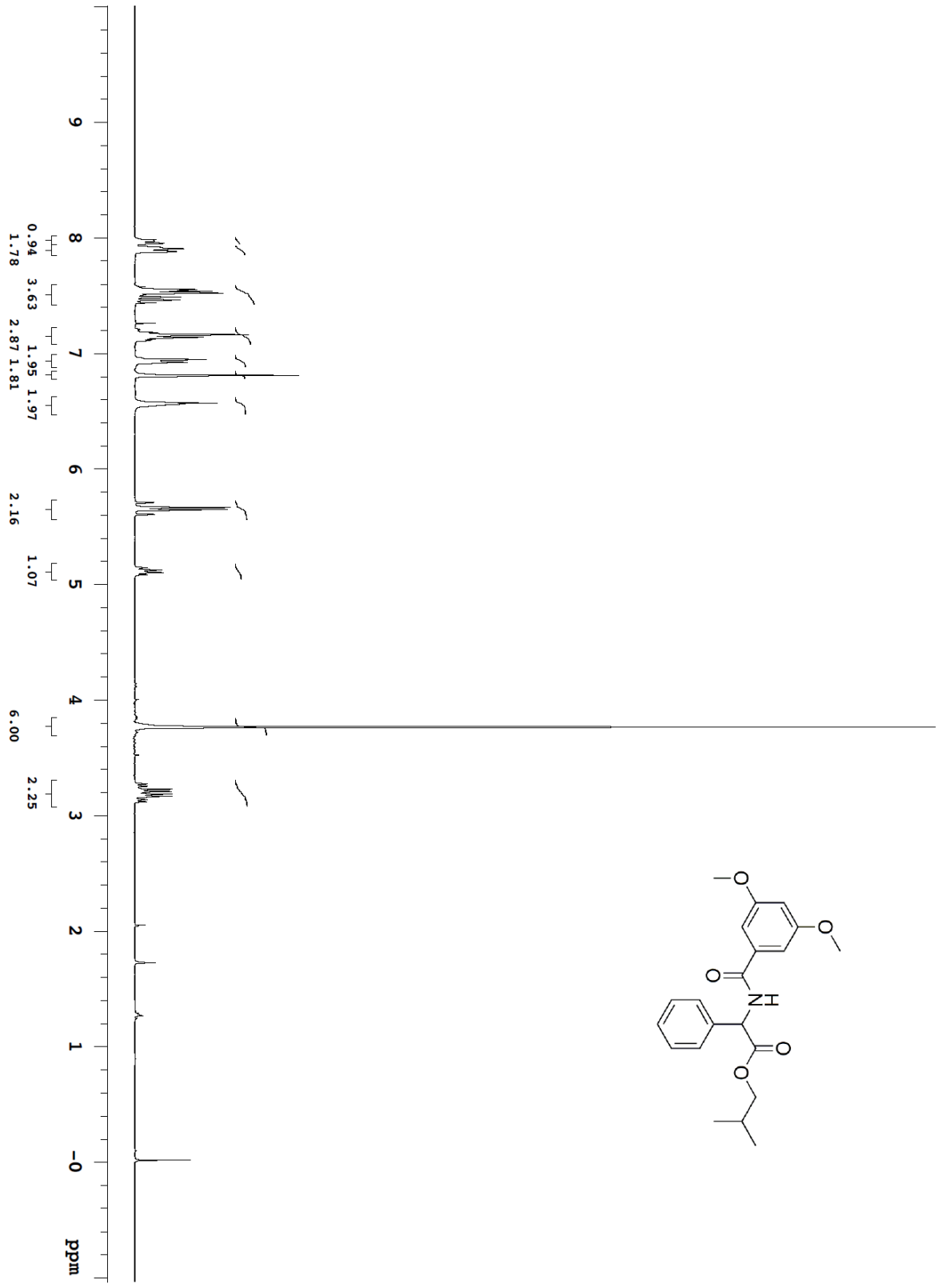
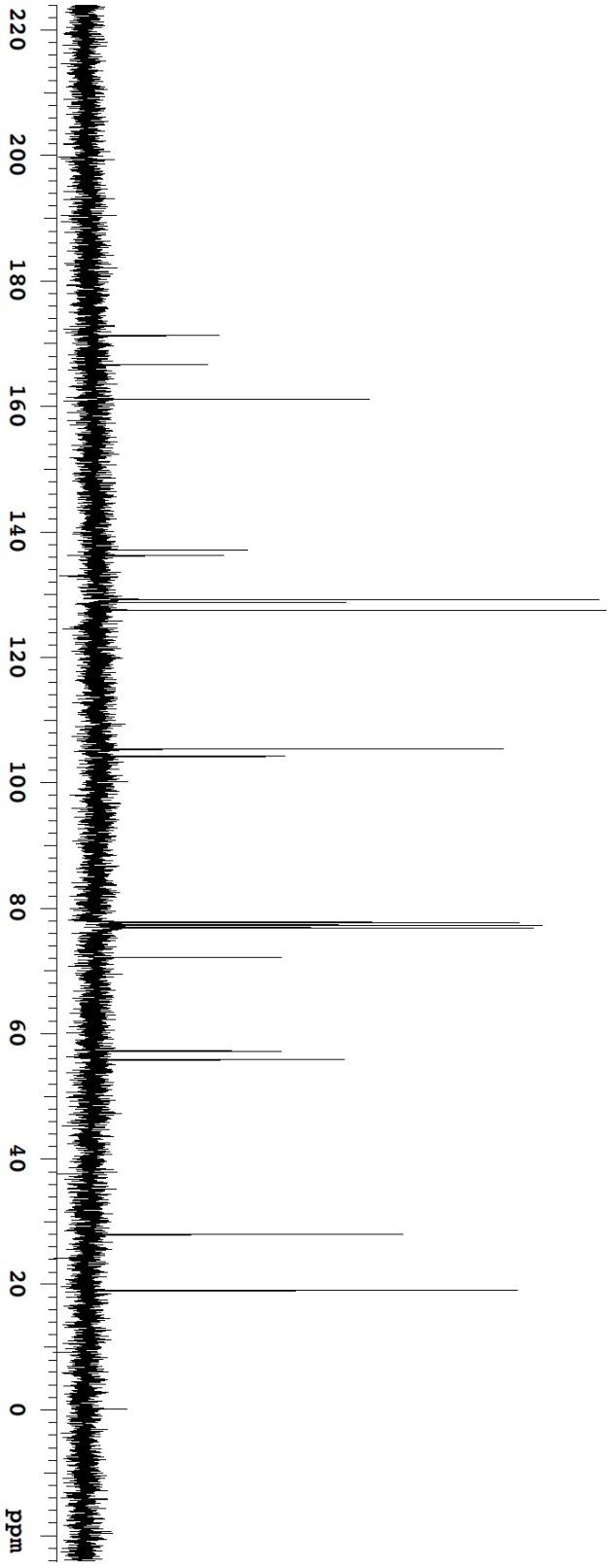
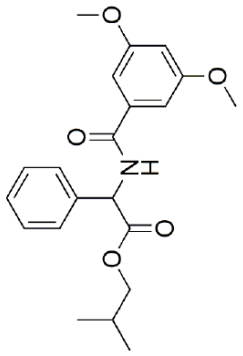
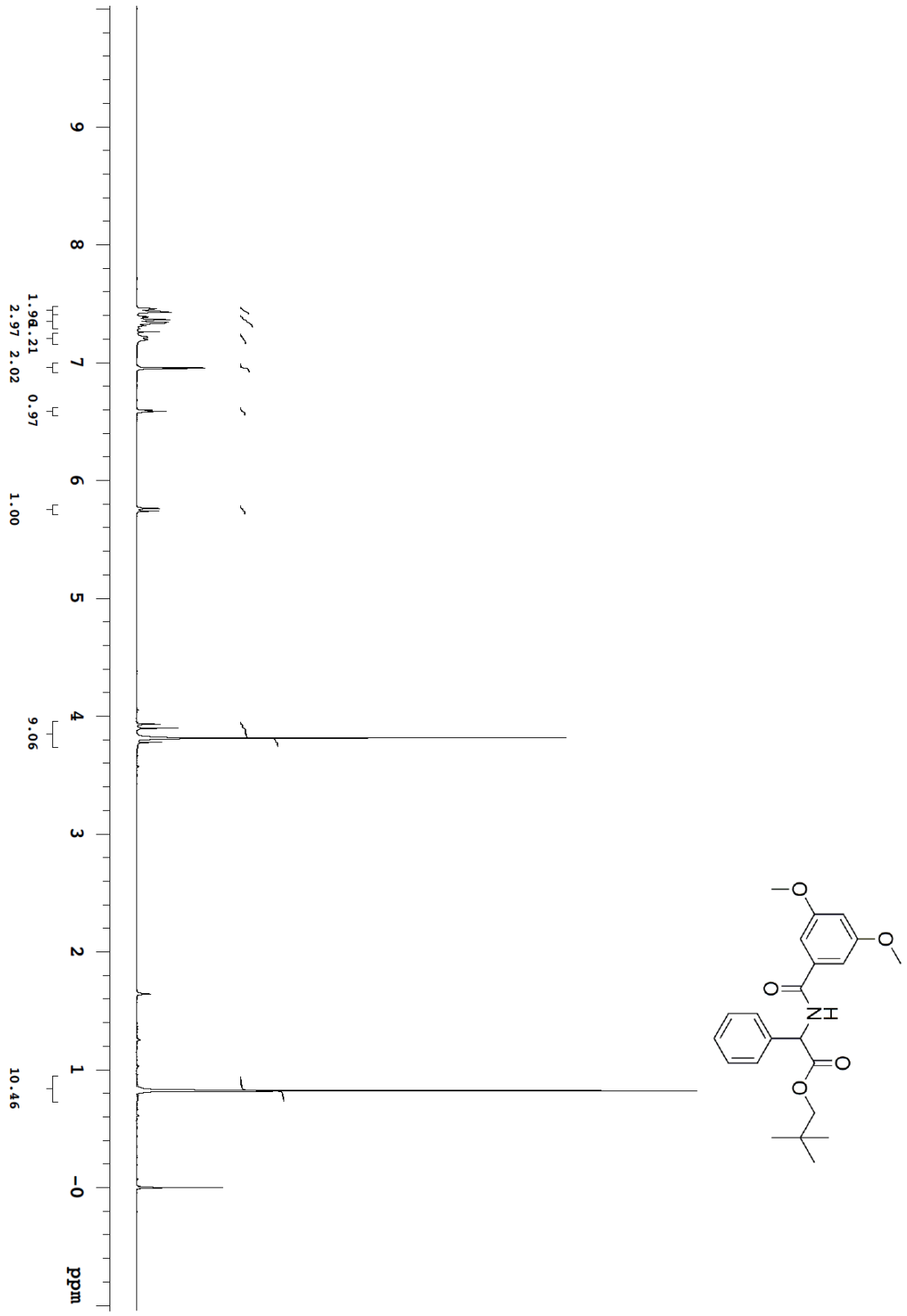
100
80
60
40
20
0
ppm

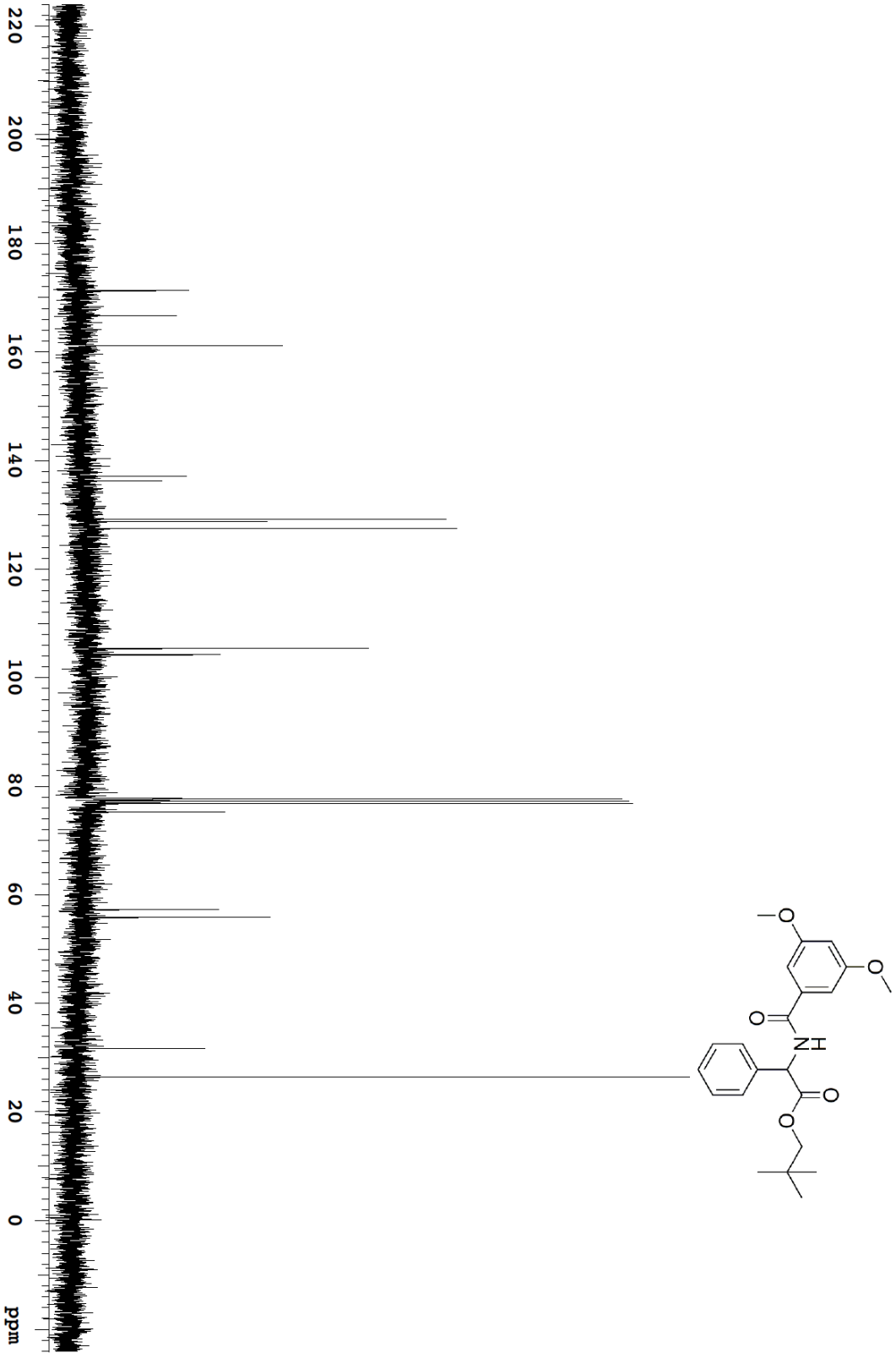

O
O
O
NH
O
O

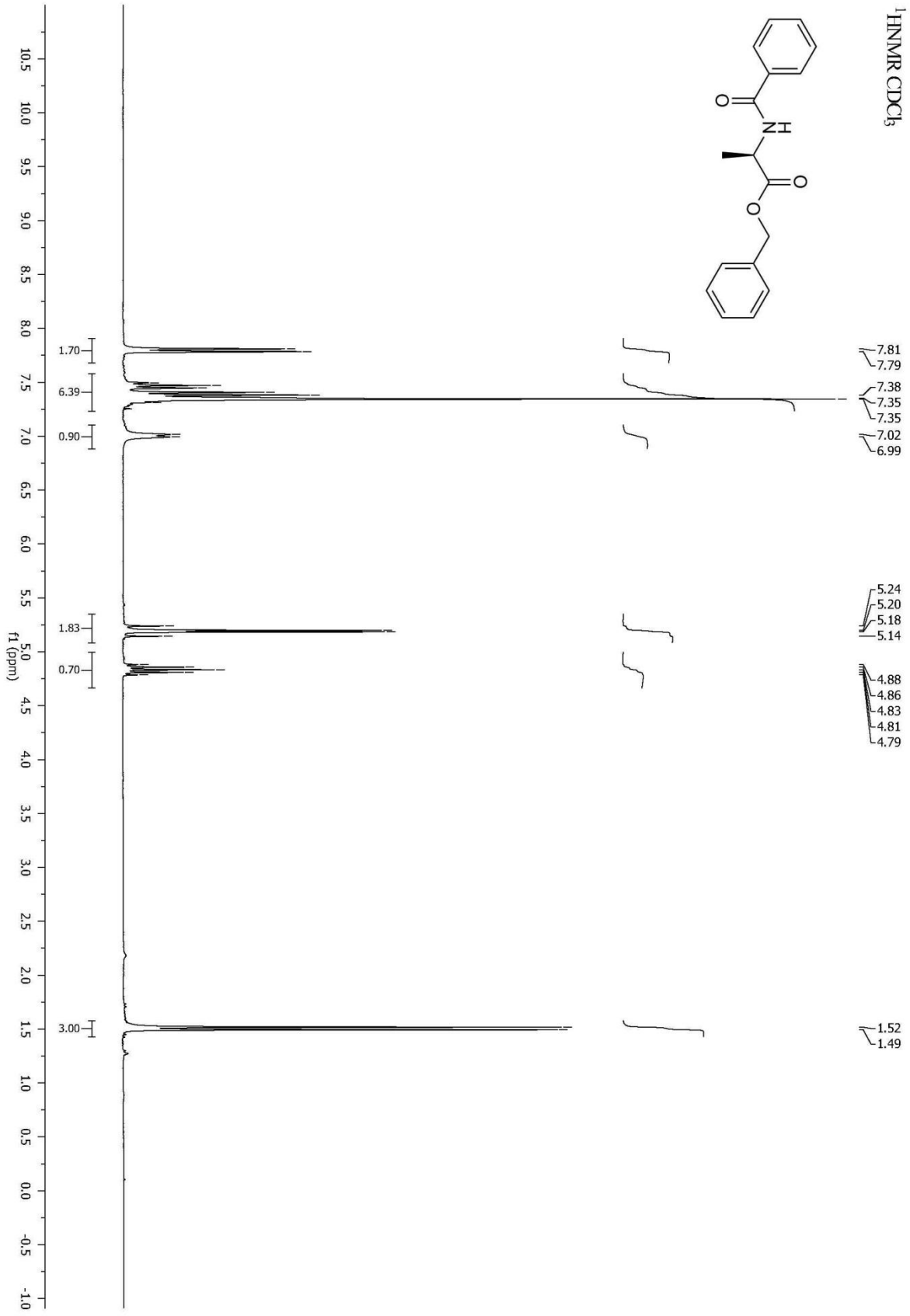

9
8
7
6
5
4
3
2
1
0
ppm
0.94
3.63
1.95
1.97
1.78
2.87
1.81
2.16
1.07
6.00
2.25
O
O
O
NH
O
O

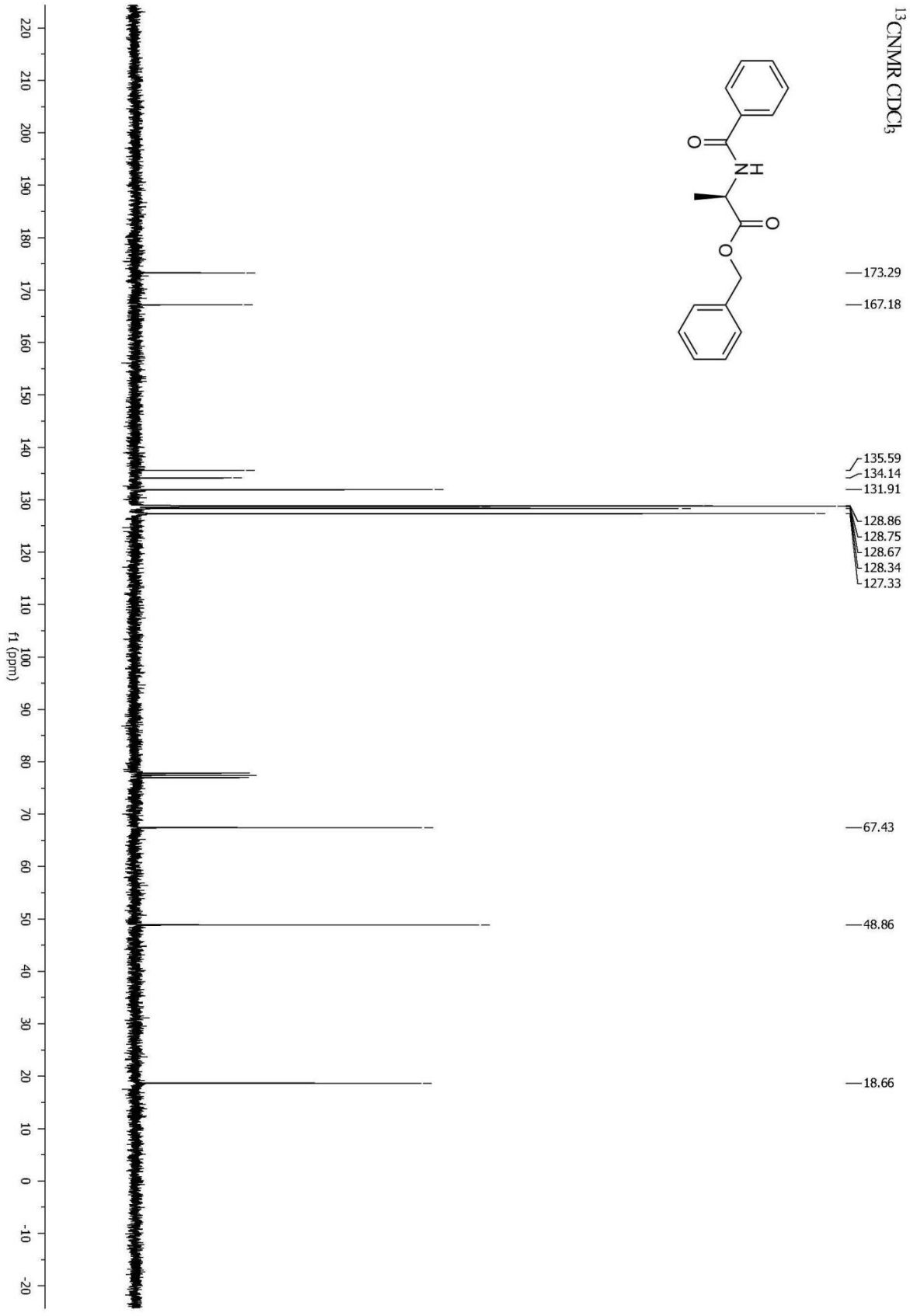

220
200
180
160
140
120
100
80
60
40
20
0
ppm

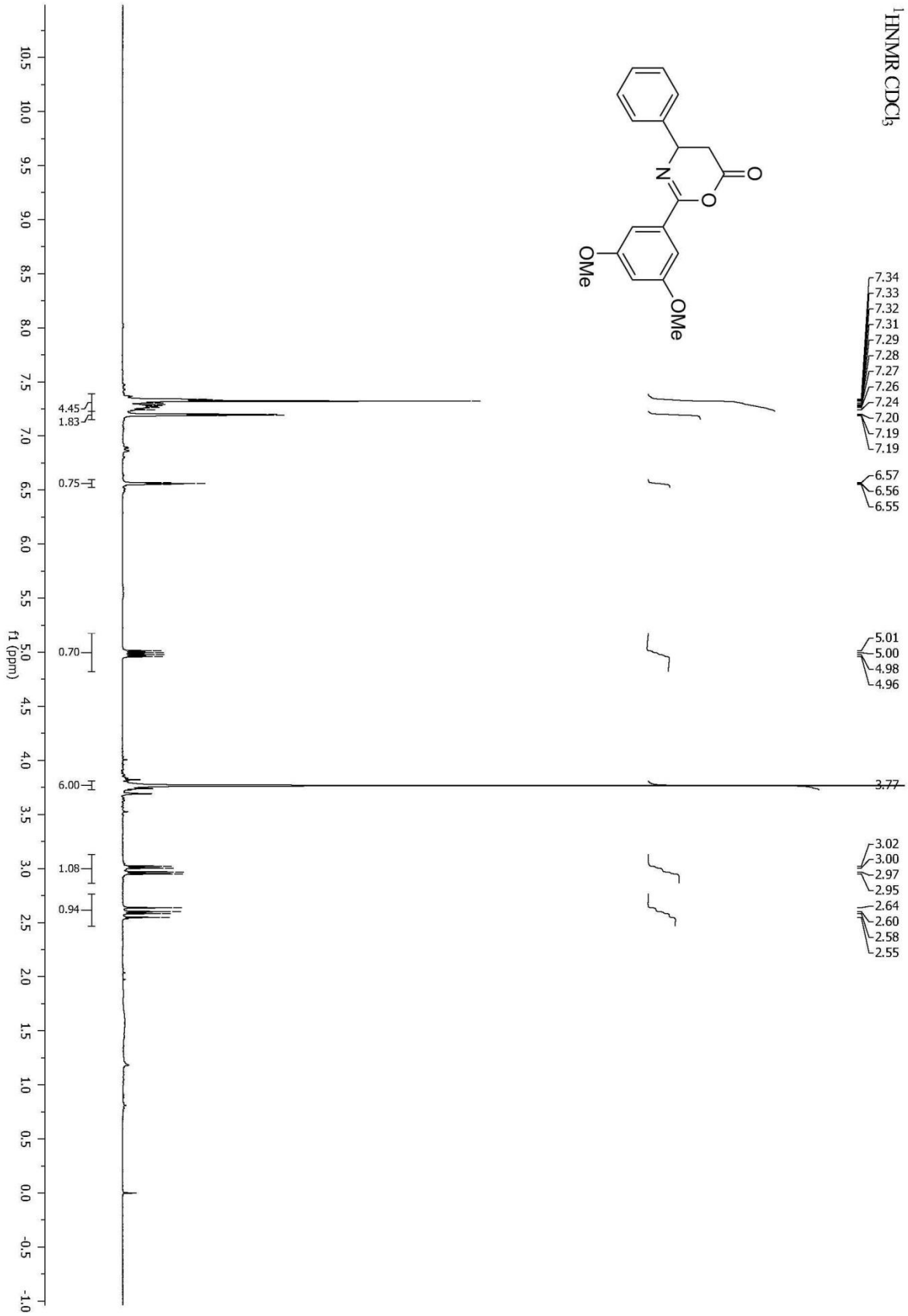

O
O
O
NH
O
O

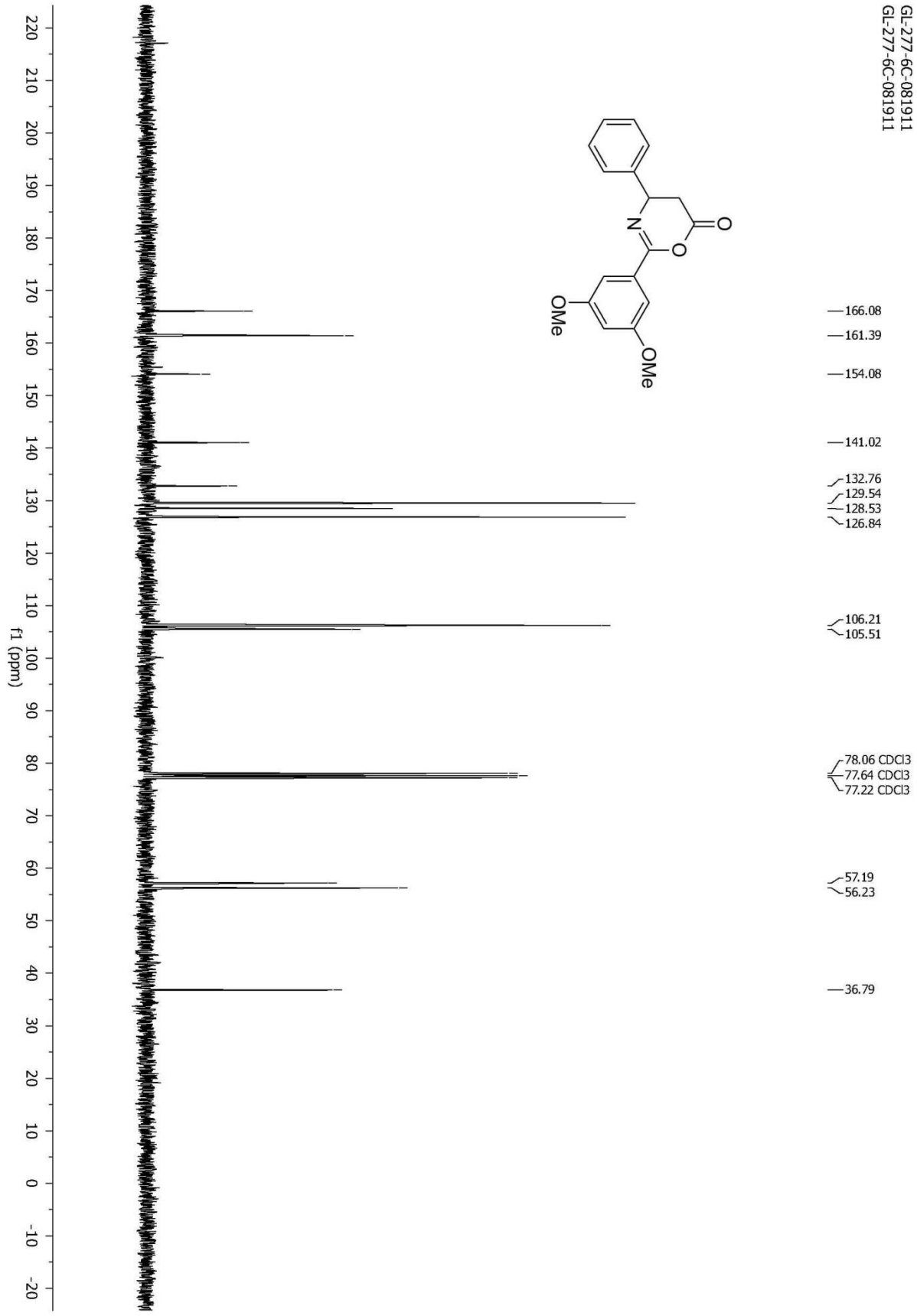

9
8
7
6
5
4
3
2
1
0
ppm
1.98
4.21
2.97
2.02
0.97
1.00
9.06
10.46
O
O
O
NH
O
O

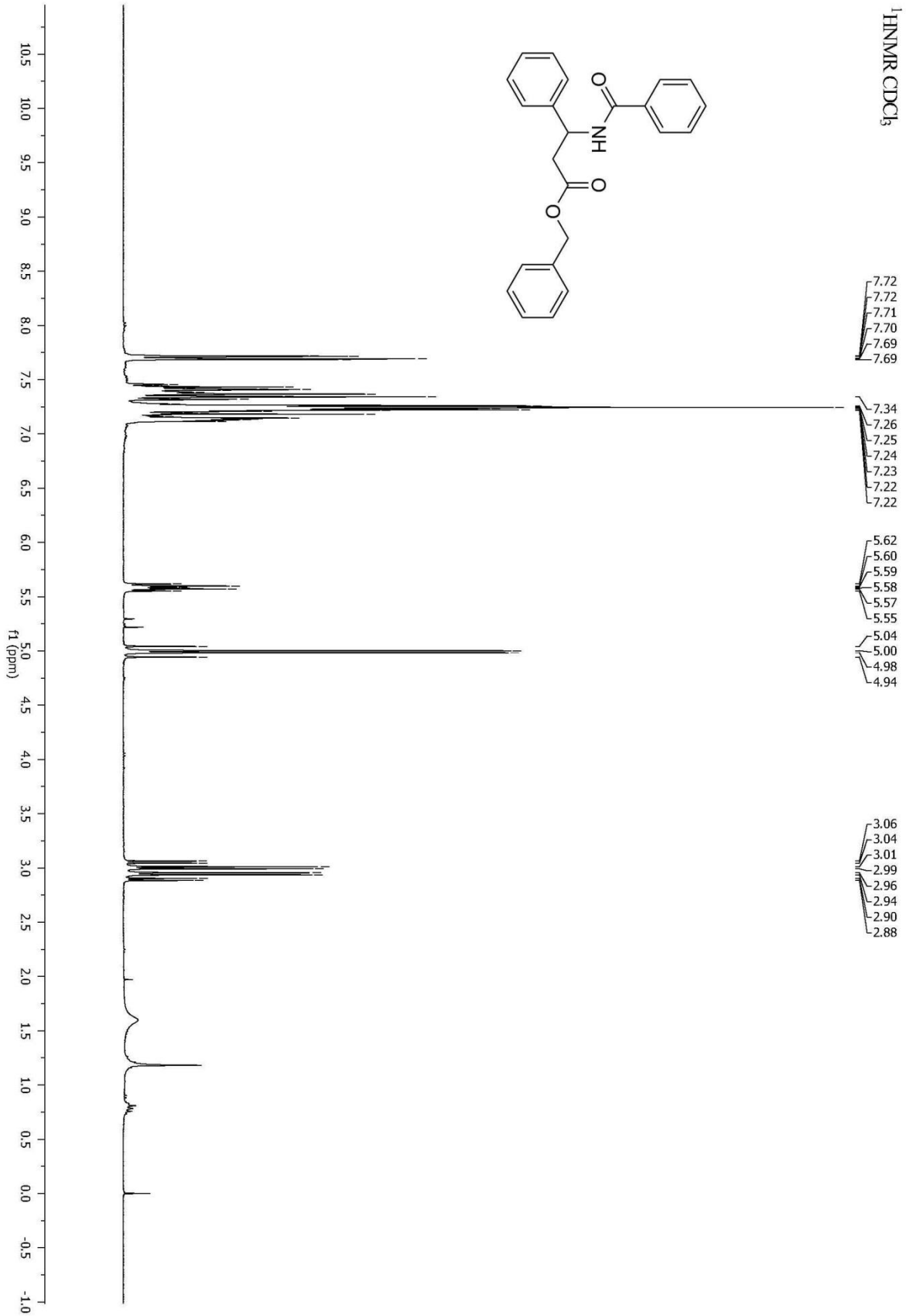

220
200
180
160
140
120
100
80
60
40
20
0
ppm
O
O
O
NH
O
O

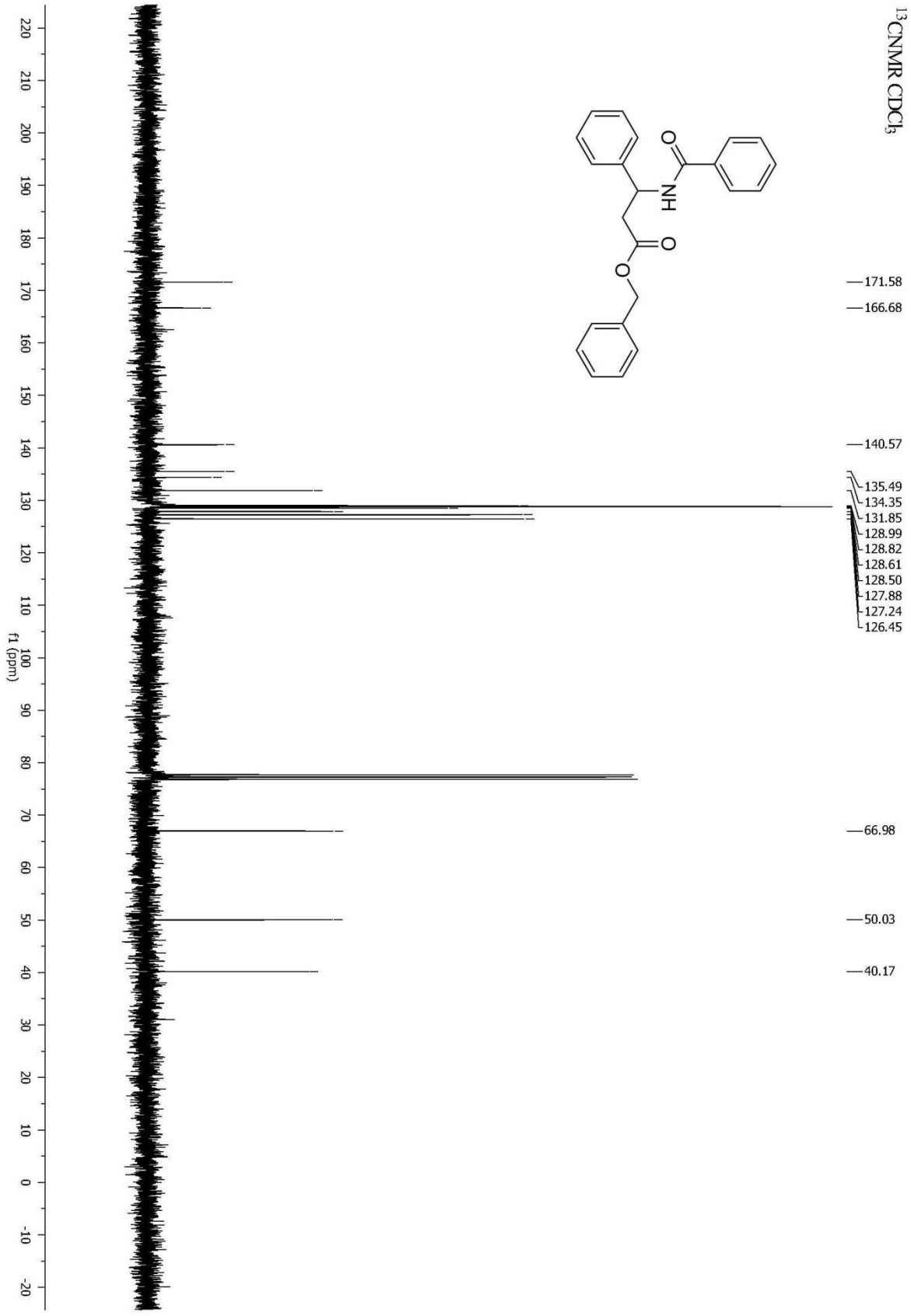

^{1}HNMR CDCl$_3$
1.70
6.39
0.90
1.83
0.70
3.00
7.81
7.79
7.38
7.35
7.35
7.02
6.99
5.24
5.20
5.18
5.14
4.88
4.86
4.83
4.81
4.79
1.52
1.49
f1 (ppm)

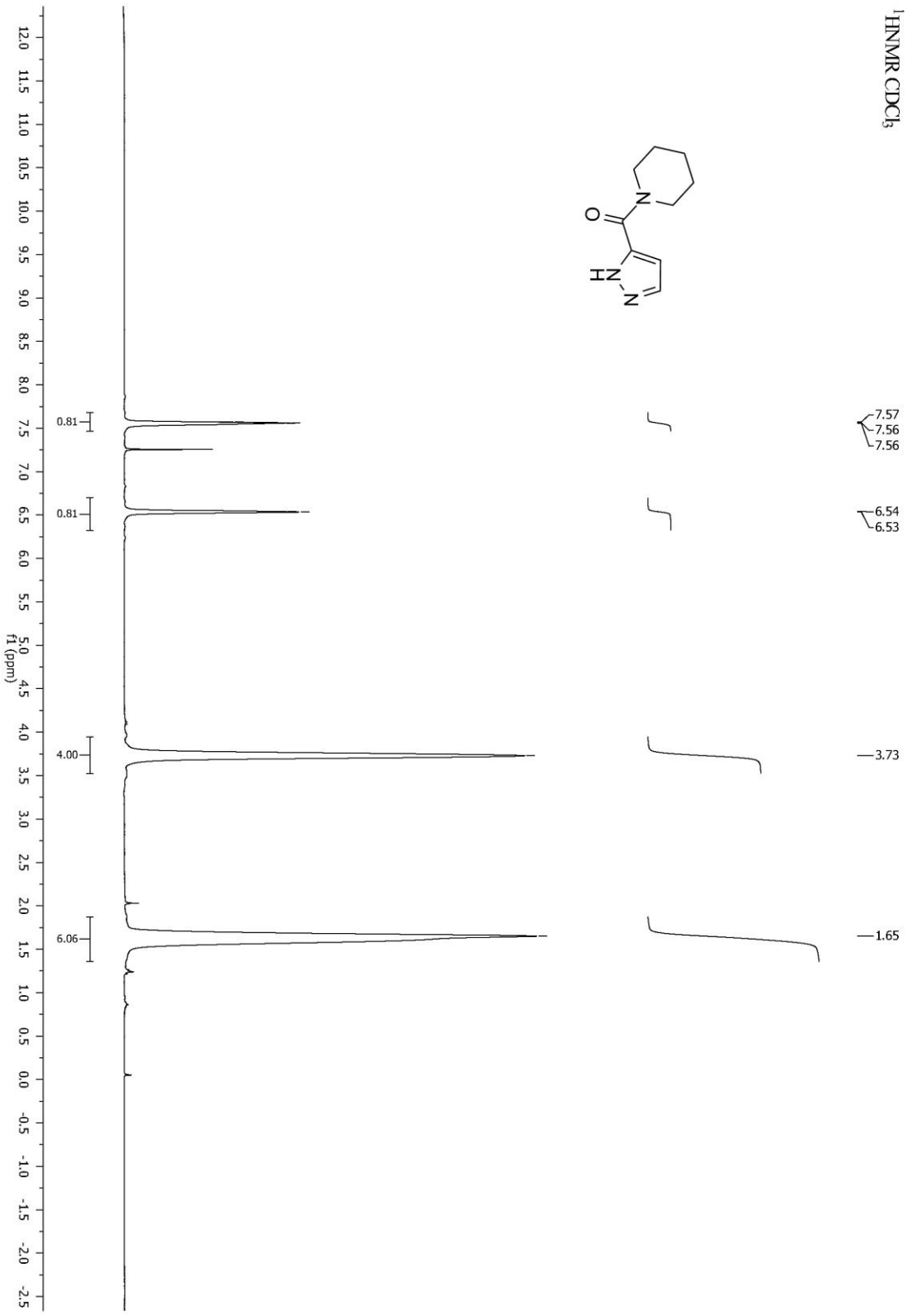

^{13}CNMR CDCl$_3$
173.29
167.18
135.59
134.14
131.91
128.86
128.75
128.67
128.34
127.33
67.43
48.86
18.66
f1 (ppm)

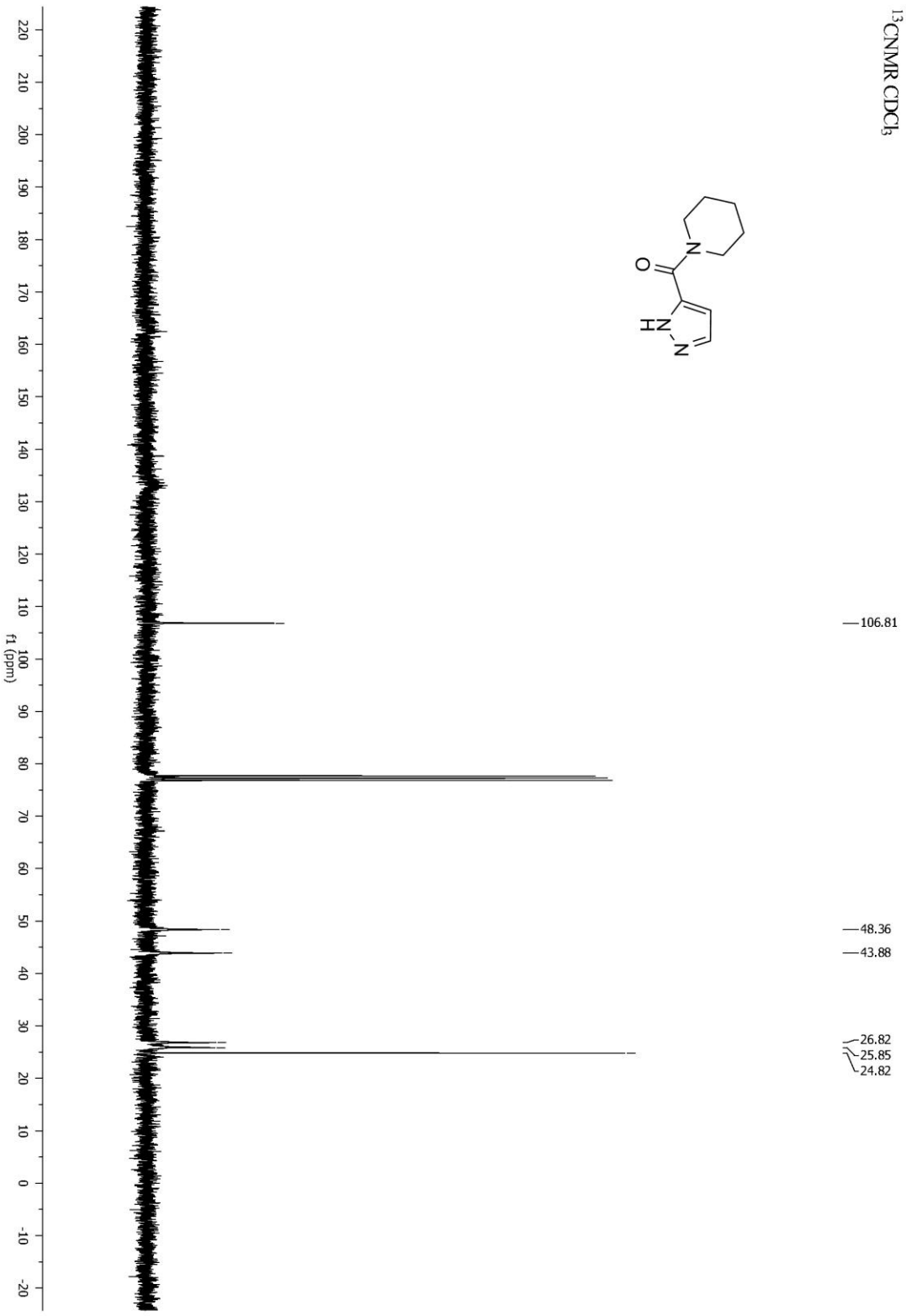

^{1}HNMR CDCl$_3$
OMe
OMe
O
N
O
O
7.34
7.33
7.32
7.31
7.29
7.28
7.27
7.26
7.24
7.20
7.19
7.19
6.57
6.56
6.55
5.01
5.00
4.98
4.96
3.77
3.02
3.00
2.97
2.95
2.64
2.60
2.58
2.55
4.45
1.83
0.75
0.70
6.00
1.08
0.94
f1 (ppm)


GL-277-6C-081911
GL-277-6C-081911
166.08
161.39
154.08
141.02
132.76
129.54
128.53
126.84
106.21
105.51
78.06 CDCl3
77.64 CDCl3
77.22 CDCl3
57.19
56.23
36.79
OMe
OMe
N
O
O
f1 (ppm)


^{1}HNMR CDCl$_3$
7.72
7.72
7.71
7.70
7.69
7.69
7.34
7.26
7.25
7.24
7.23
7.22
7.22
5.62
5.60
5.59
5.58
5.57
5.55
5.04
5.00
4.98
4.94
3.06
3.04
3.01
2.99
2.96
2.94
2.90
2.88
f1 (ppm)


^{13}CNMR CDCl$_3$
171.58
166.68
140.57
135.49
134.35
131.85
128.99
128.82
128.61
128.50
127.88
127.24
126.45
66.98
50.03
40.17
f1 (ppm)


^{1}HNMR CDCl$_3$
7.57
7.56
7.56
6.54
6.53
3.73
1.65
0.81
0.81
4.00
6.06
f1 (ppm)


^{13}CNMR CDCl$_3$
106.81
48.36
43.88
26.82
25.85
24.82
f1 (ppm)