DEVELOPMENT OF REDOX–NEUTRAL REACTION CASCADES

by

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Professor Daniel Seidel

And approved by

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ABSTRACT OF THE DISSERTATION

Development of Redox–Neutral Reaction Cascades

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Dissertation Director:

Professor Daniel Seidel

In Chapter I, I give a general introduction to redox–neutral reaction cascades. In Chapter II, a Lewis acid catalyzed formation of tetrahydroquinolines via an intramolecular rodox process is described. Gadolinium triflate was proven to be a superior catalyst for this transformation. More importantly, a catalytic enantioselective intramolecular redox reaction was successfully achieved by the use of magnesium triflate in combination of a DBFox ligand. In Chapter III, a novel transformation between *o*-aminobenzaldehyde and secondary cyclic amines is described. This novel transformation leads to synthetically useful cyclic aminal skeletons. Two natural products, deoxyvasicinone and rutaecarpine, were synthesized directly from the oxidation of the aminal skeletons. In addition, a one-pot procedure for the synthesis of cyclic aminals promoted by Brønsted acids is also described, starting from *o*-aminobenzaldehydes and primary amines. In Chapter IV, non-conventional functionalizations of azomethine ylides are described. Azomethine ylides are proven to be protonated by suitable proton sources, which results in the corresponding iminium ions. Nucleophiles can attack these iminium ions, leading to synthetically useful skeletons.

ACKNOWLEDGEMENTS

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Finally, I would like to thank the financial support from Rutgers University and NSF that funded parts of the research discussed in this dissertation.

DEDICATION

To my family.

Table of Contents

List of Figures

List of Schemes

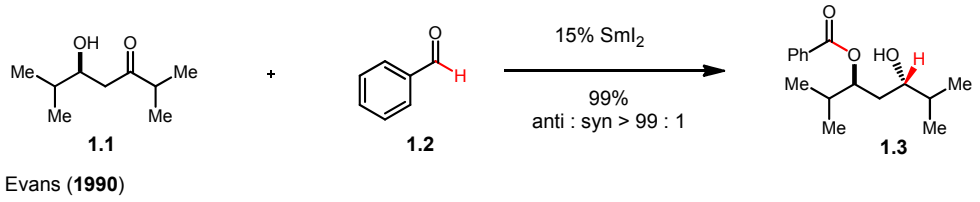
List of Tables

Chapter I Introduction

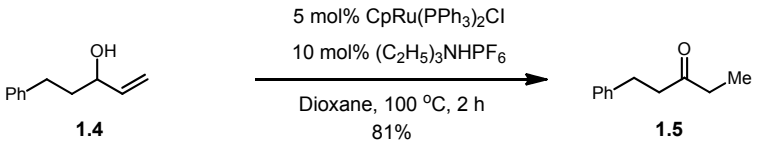
1.1 Background

One main goal of organic synthesis is to develop synthetic methods that allow for the construction of target molecules with as little effort as possible. Redox–neutral processes are powerful tools for this purpose; they address both atom and step economy.[1] Redox–neutral processes can both introduce molecular complexity quickly and shorten synthetic routes dramatically by avoiding reduction and oxidation steps. For example, Evans and Trost have individually reported exciting advances in this field (Scheme 1.1).[2] The use of redox–neutral processes is a very powerful tool for the total synthesis of complex molecules.[1,3]

Scheme 1.1 **Examples of Redox–Neutral Processes**



Evans (**1990**)



Trost (**1993**)

Carbon-hydrogen bonds, most of which are hard to cleave due to their high bond dissociation energy (e.g. $BDE_{C–H\ (methane)}$ = 105 kcal/mol), are the most common bonds found in organic molecules. Carbon-halogen bonds, which have relatively low bond dissociation energy (e.g. $BDE_{C–Cl\ (chloromethane)}$ = 77 kcal/mol, $BDE_{C–Br\ (bromomethane)}$ = 66

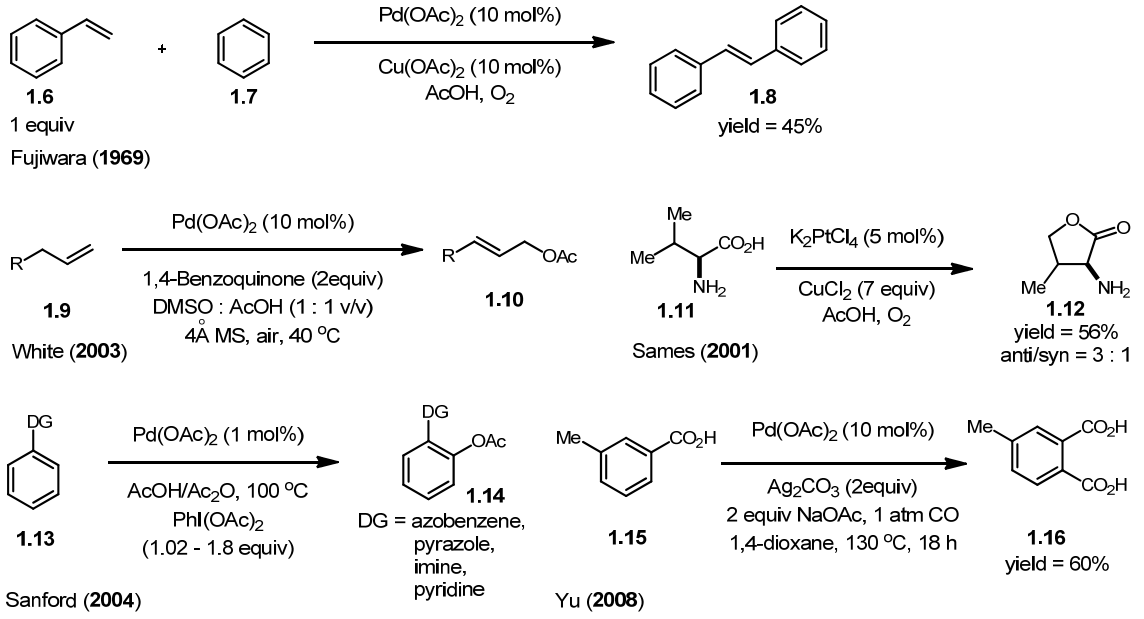
kcal/mol, $BDE_{C–I\ (iodomethane)}$ = 53 kcal/mol), are widely used in organic synthesis.[4] For example, transition metal catalyzed cross-coupling reactions that form carbon-carbon, carbon-nitrogen, carbon-oxygen, and carbon-sulfur bonds by the use of organohalides are explored extensively and often applied in industrial syntheses. The preparation of halogenated precursors, however, lowers the synthetic efficiency. Additionally, because of the ubiquitous presence of carbon-hydrogen bonds, the direct transformation of relatively unreactive carbon-hydrogen bonds into carbon-carbon bonds or carbon-heteroatom bonds has now become one of the most attractive research subjects in synthetic organic chemistry. Therefore, redox–neutral reaction cascades that involve C–H functionalization exhibit great advantages and potential towards the highly efficient syntheses of complex molecules.

1.2 C–H Bond Insertion by Transition Metals

Transition metal complexes that activate carbon-hydrogen bonds have been studied extensively.[5] Transition metals first insert into the carbon-hydrogen bonds to form carbon-metal bonds, which can be later transformed into carbon-carbon or carbon-heteroatom bonds (Scheme 1.2). In 1969, Fujiwara reported a palladium (II) acetate catalyzed aromatic substitution of olefins, in which an electrophilic aromatic substitution was involved in the C–H functionalization (Scheme 1.2).[5a] Another important type of metal-catalyzed C–H functionalization involves a chelating-directed cyclometalation. For example, in 2001, Sames disclosed a platinum-catalyzed lactone formation via the direct C–H functionalization of amino acids (Scheme 1.2).[5i] In 2004, Sanford disclosed the chelating-directed oxidative C–H functionalization in which the directing group could be pyridine, azobenzene, an imine or pyrazole (Scheme 1.2).[5j] Yu subsequently

developed a C–H functionalization directed by carboxylic acid derivatives (Scheme 1.2).[5l] Another notable development in 2004 occurred when White published a palladium (II) acetate catalyzed synthesis of allylic acetates via the C–H oxidation of monosubstituted olefins, with 1,4-dibenzophenone as the oxidant (Scheme 1.2).[5k] These important examples set the stage for futher development of C–H functionalization. In most cases, oxidants were required to complete the catalytic cycle.

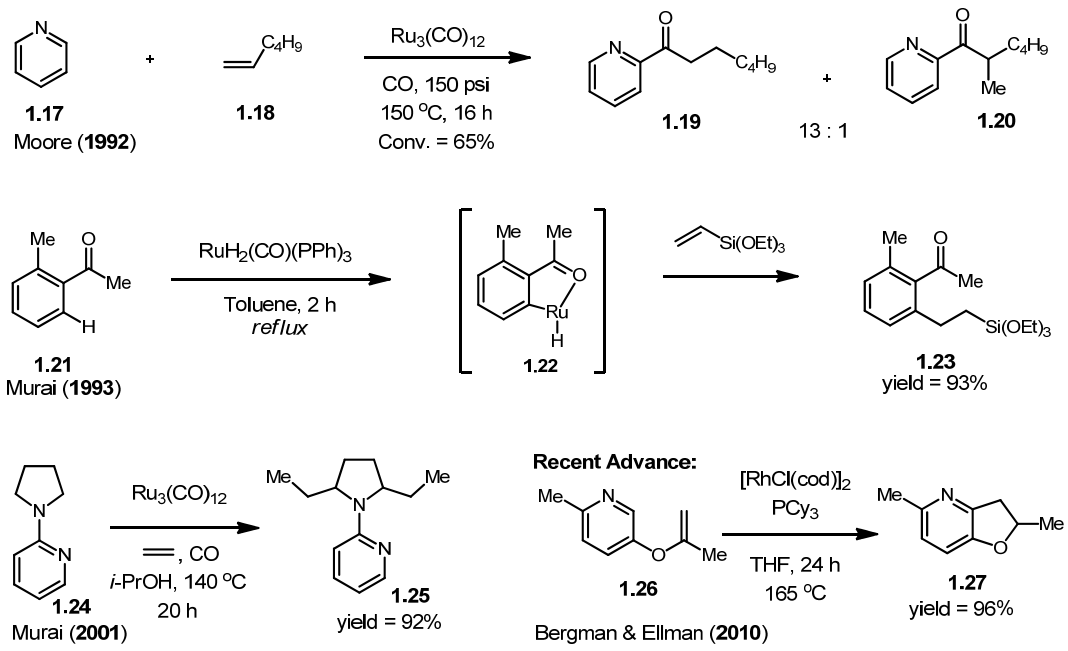
Scheme 1.2 **Transition Metal Insertion into C–H Bonds**



There are a number of notable examples of metal-catalyzed C–H functionalizations which are redox–neutral processes and do not require oxidants. For example, in 1992, Moore reported a ruthenium-catalyzed three-component coupling reaction of pyridine, olefin, and carbon monoxide which led to the formation of the corresponding *α*-acylpyridines (Scheme 1.3).[5e] In 1993, Murai disclosed the efficient and selective addition of aromatic C–H bonds to olefins (Scheme 1.3).[5f] In light of this

pioneering research, numerous studies have focused on this type of chemistry. For example, in 2001, Murai reported a ruthenium-catalyzed coupling reaction of a sp^3 C–H bond α to a nitrogen atom in an alkylamine with olefins, in which a pyridine moiety was required as a directing group (Scheme 1.3).[5g] Very recently, Bergman and Ellman reported an intramolecular version of this type of C–H bond functionalization, aimed at the synthesis of multicyclic pyridine derivatives (Scheme 1.3).[5n] This type of redox–neutral C–H bond functionalization demonstrates great advantages in synthetic organic chemistry. In most cases, however, directing groups in the substrates are required.

Scheme 1.3 **Transition Metal Insertion into C–H Bonds (Redox–Neutral)**

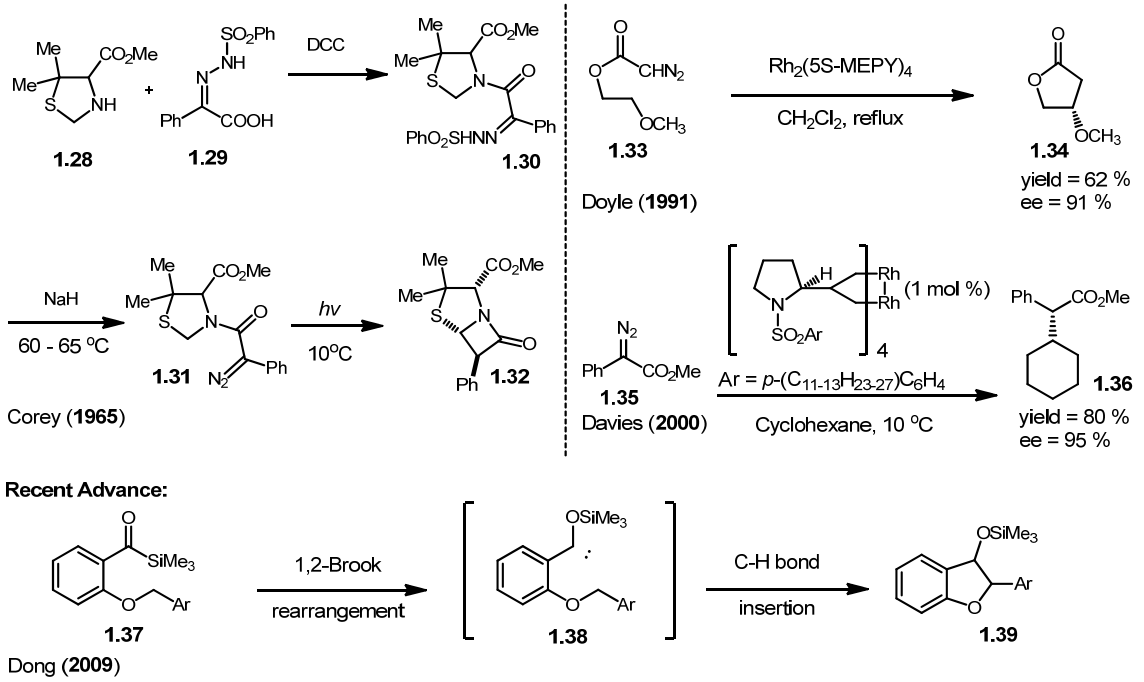


1.3 C–H Functionalization via Carbene Insertion

Alternatively, intramolecular carbene insertion provides an efficient and straightforward approach to functionalize unreactive C–H bonds.[6] For example, in 1965, Corey and co-workers established a new synthetic route towards the core of the

penicillins, which is outlined in Scheme 1.4.[6a] In his work, he documented the construction of the penicillanic acid system in three steps via an intramolecular carbene insertion, that starts from the readily available thiazolidine. In recent years, additional examples have been reported with respect to this type of annulation via carbene insertion. Notably, enantioselective intra- or intermolecular carbene insertion have been developed successfully, in particular from the labs of Doyle and Davies (Scheme 1.4).[6b-e] Recently, Dong reported that siloxycarbenes derived from acylsilanes can undergo Brook rearrangement/carbene insertion cascades under microwave irradiation (Scheme 1.4).[6f]

Scheme 1.4 **Examples of Carbene Insertions**

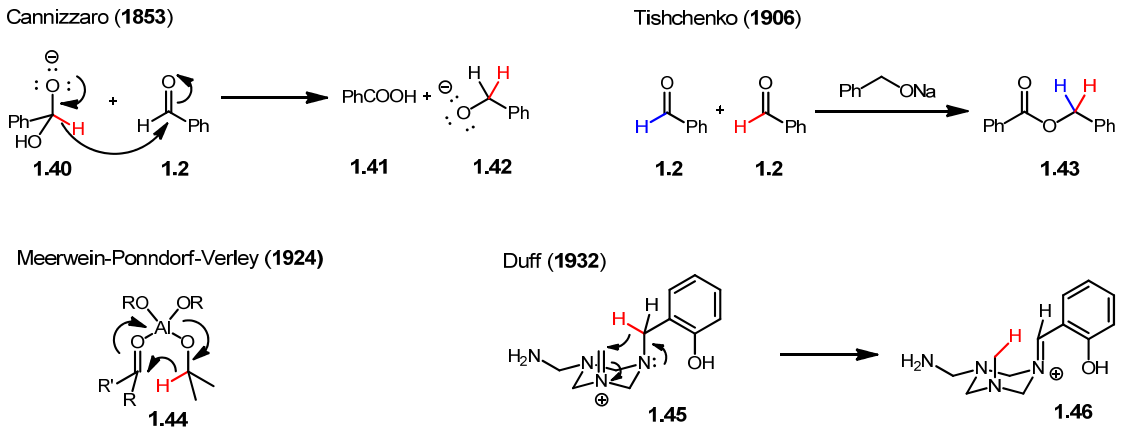


1.4 C–H Functionalization Involving a Hydride Shift

1.4.1 Organic Molecules as Hydride Donors

Apart from the aforementioned approaches, hydride shift reactions provide another important complementary approach to the functionalization of carbon-hydrogen bonds.[7] Numerous classical organic reactions that are documented in the literature involve a hydride shift process. For instance, the Cannizaro, Tishchenko, Meerwein-Ponndorf-Verley, and Duff reactions, which are important tools for the introduction of new functional groups in organic synthesis, involve inter- or intramolecular hydride transfer mechanisms (Scheme 1.5).

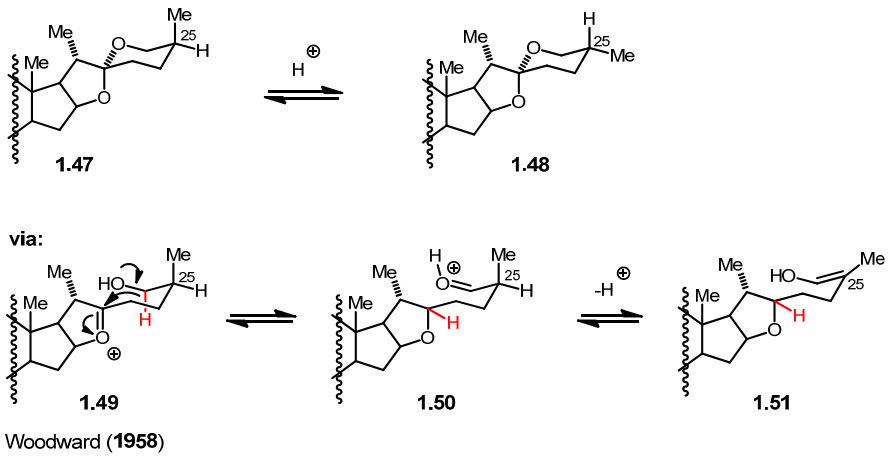
Scheme 1.5 **Organic Molecules as Hydride Donors**



1.4.2 Early Examples of Reaction Cascades Initiated by Hydride Shifts

In 1958, Woodward disclosed the isomerization of steroidal sapogenins at C-25 under acidic conditions (Scheme 1.6), which was believed to proceed by a redox mechanism that involved a reversible 1,5-hydride transfer between the oxonium intermediates **1.49** and **1.50**.[8] The oxonium intermediate **1.50** was deprotonated to form the enol intermediate **1.51**, leading to the isomerization of **1.47** at C-25. Woodward's pioneering study set a very important milestone in the research of reaction cascades initiated by hydride shifts.

Scheme 1.6 **Acid Catalyzed Interconversion of Sapogenins**



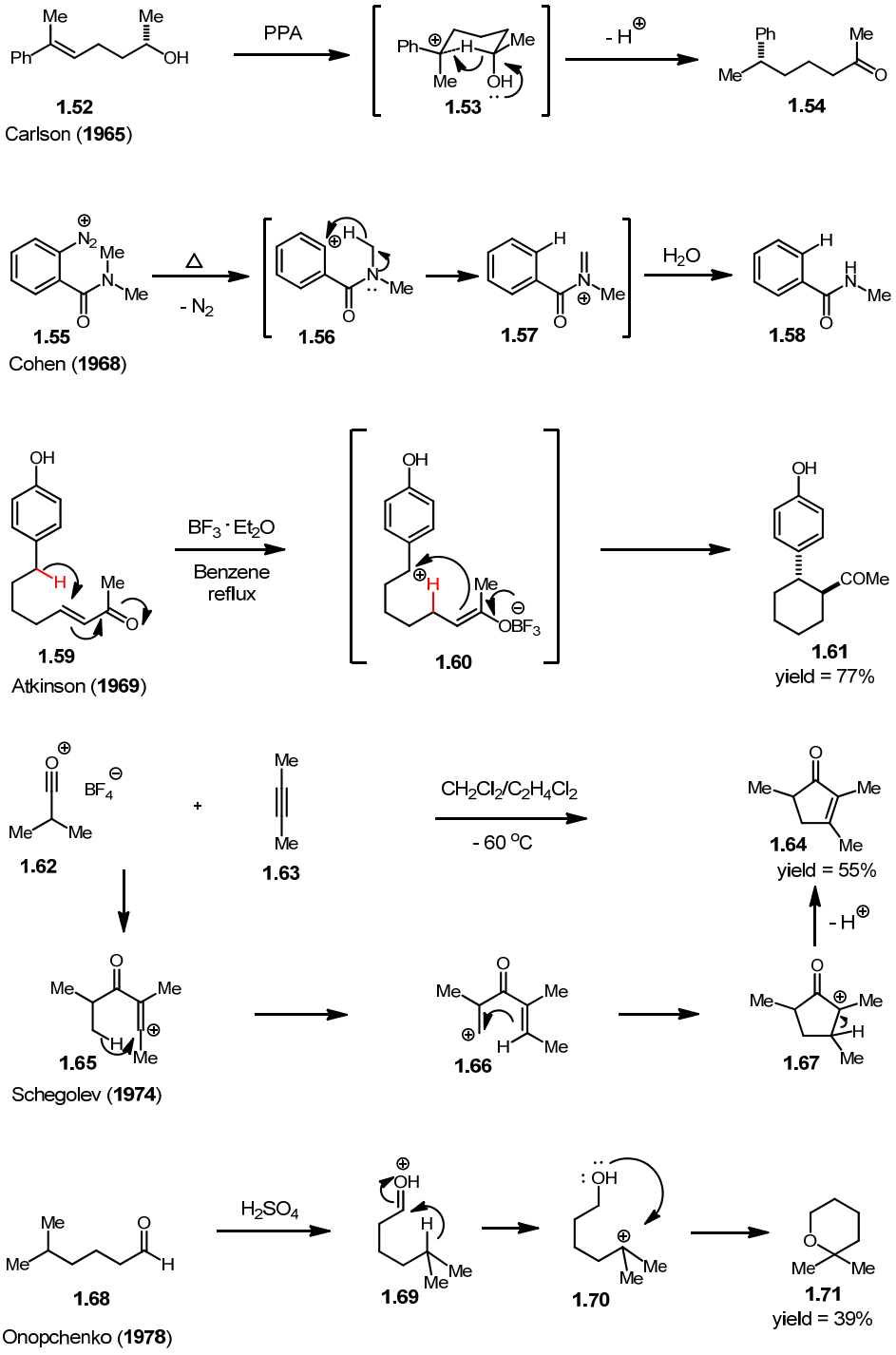
Woodward (**1958**)

Other early examples of reaction cascades initiated by 1,5-hydride shifts were reported in the following years, and are outlined in Scheme 1.7. For example, in 1965, Carlson disclosed the transformation of γ-hydroxy olefins to the corresponding saturated ketones, catalyzed by polyphosphoric acid. This reaction was believed to proceed by a 1,5-hydride shift process on carbocation intermediate **1.53** (Scheme 1.7).[9a] In 1968, Cohen reported that the decomposition of aromatic diazonium salts resulted in carbocation **1.56**, which initiated an intramolecular 1,5-hydride shift, leading to the intermediate **1.57**. The resulting intermediate **1.43** was hydrolyzed to form the final product **1.58** (Scheme 1.7).[9b]

Notably, in 1969, Atkinson disclosed an interesting hydride shift initiated annulation, in which a benzylic hydride in an acyclic molecule **1.59** could be transferred to an α,β-unsaturated ketone via a 1,5-hydride shift to form the charge separated intermediate **1.60**. The following ring closure occurred, leading to the cyclic ring system **1.61** (Scheme 1.7).[10a] Remarkably, vinyl cation intermediates **1.62** derived from the

acylation of acetylenes could produce the 2,3,5-trimethylcyclopentenone **1.64** via a 1,5-hydride shift/ring-closure process.[10b] Furthermore, when 5-methylhexanal **1.68** was

Scheme 1.7 **Early Examples of Reaction Cascades Initiated by Hydride Shifts**

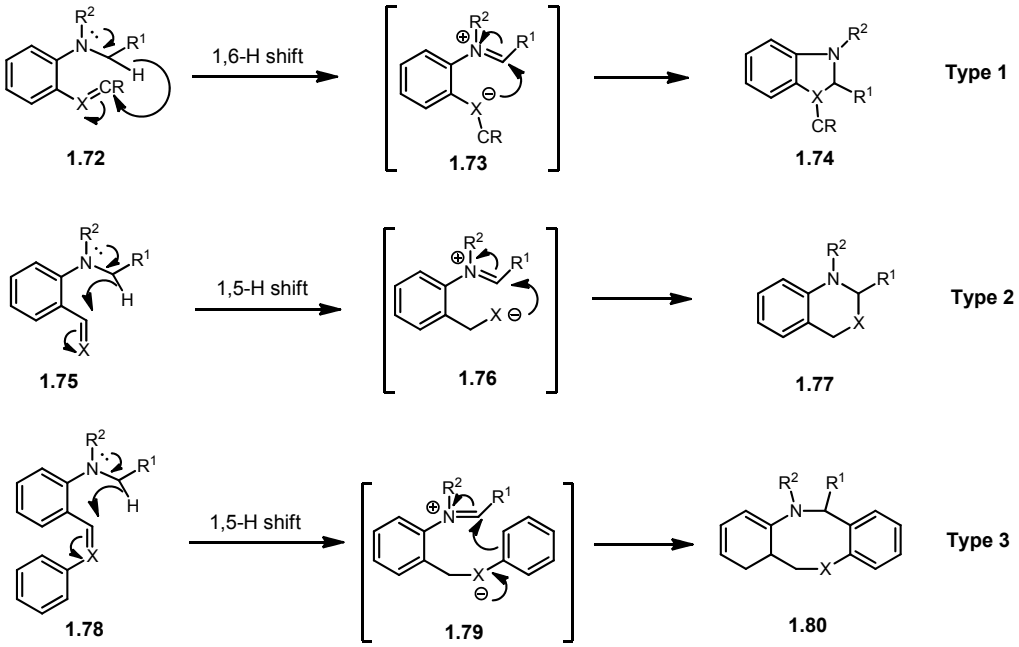


activated with an excess of 96% sulfuric acid, it underwent a 1,5-hydride shift/ring-closure process to give 2,2-dimethyltetrahydropyran **1.71** with a yield of 39%, as disclosed in 1978 by Schulz.[10c]

These examples represent excellent applications of the redox–neutral concept in organic synthesis, and demonstrate a great potential for the efficient construction of cyclic systems. In light of these precedents, especially Woodward's pioneering study, increasing examples of reaction cascades initiated by hydride transfers have been reported in recent years.

1.4.3 *Tert*-Amino Effect

Scheme 1.8 ***Tert*-Amino Effect Involving Hydride Shift/Cyclization Cascades**



The *tert*-amino effect, the most important redox–neutral reaction cascade related to the research presented in this dissertation, will be introduced in this section.[11] In 1972,

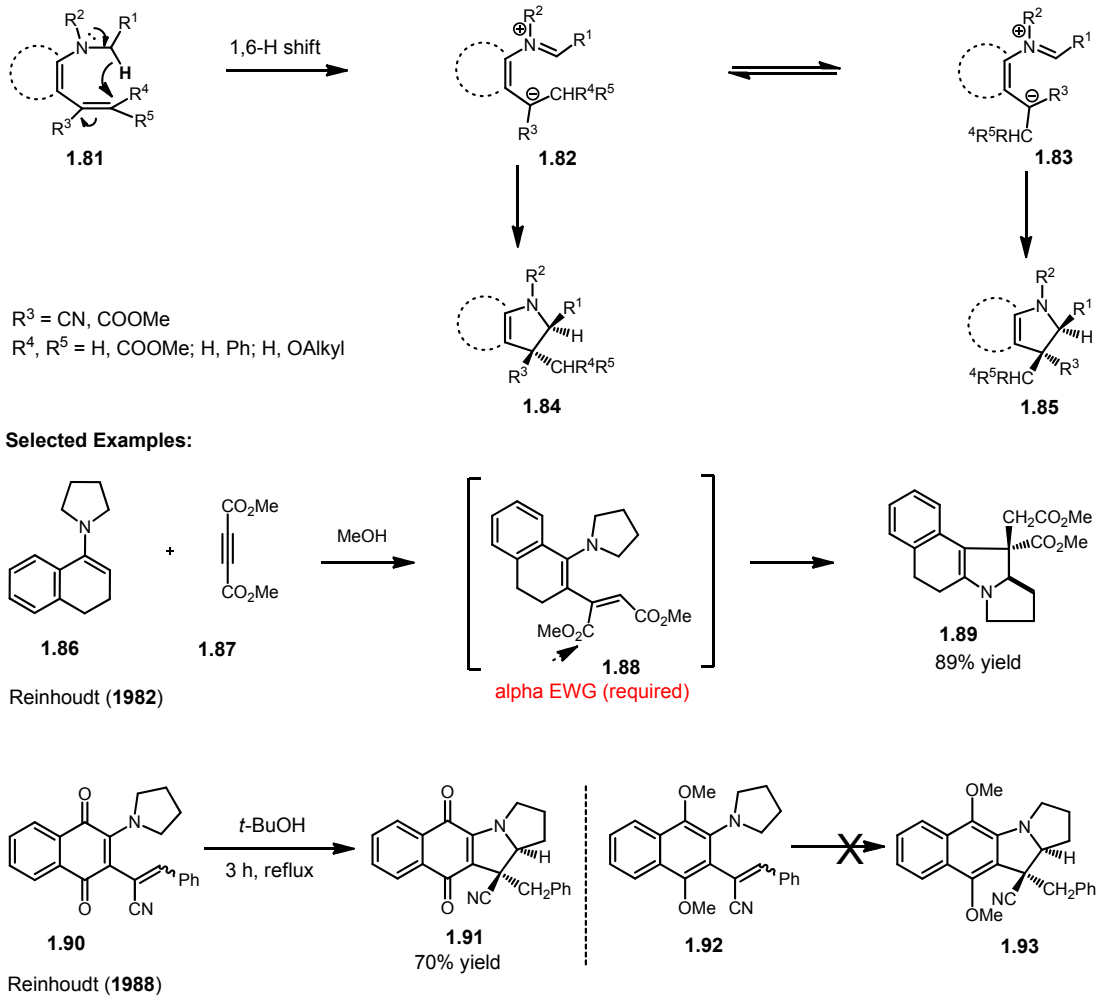
Meth-Cohn and Suschitzky first introduced the term *tert*-amino effect.[11a] It refers to a cyclization reaction of *ortho*-substituted tertiary anilines. Typically, the reactions involve a 1,5- or 1,6-hydride shift from the α position of a tertiary amino group to the *ortho*-substituent, which results in a zwitterionic intermediate. The zwitterionic intermediate then cyclizes to form the heterocyclic system (Scheme 1.8). In 1895, Pinnow reported the first example of the *tert*-amino effect.[12] Studies of the *tert*-amino effect are well established and have been divided into five types depending on the size of the ring formed and the mechanism of the key step.[11b, 11c] Here, we will discuss three types of *tert*-amino effects whose mechanisms involve a hydride shift (Scheme 1.8).

1.4.3.1 Type 1 *tert*-Amino Effect

The first type of the *tert*-amino effect involves five-membered ring formation, in which an antarafacial 1,6-hydride shift occurs from the α position of the tertiary amine to the *ortho*-substituent, leading to the 1,5-dipolar species **1.73**. Then, the 1,5-dipolar species readily undergoes a cyclization reaction to form the heterocyclic system **1.74** (Scheme 1.8).[11, 13] In 1981, Verboom and Reinhoudt reported an important example of the type 1 *tert*-amino effect reaction starting from the pyrrolidine enamine of α-tetralone **1.86** and dimethyl acetylenedicarboxylate **1.87**, which are known to produce [2+2] cycloadducts followed by a ring-opening that leads to aminodiene **1.88** (Scheme 1.9).[13a] The electron-withdrawing group (R^3 in Scheme 1.9) at the α position is essential for the 1,6-hydride shift because it can stabilize the resulting anionic center of the dipolar intermediate. Electron-deficient systems such as benzoquinones **1.90** enhance the formation of the dipolar intermediate, whereas hydroquinones such as **1.92** do not (Scheme 1.9).[14] Typically, pyrrolidine enamines are more reactive than piperidine

enamines, and morpholine enamines are the least reactive.[13e] Lewis-acid catalyzed examples of this reaction are rare.[15] Notably, Viehe extended the reaction to a broad class of simple acyclic enamines that require relatively mild reaction conditions.[16] The type 1 reaction of the *tert*-amino effect is a very useful tool for the construction of the pyrrolizidine skeleton.

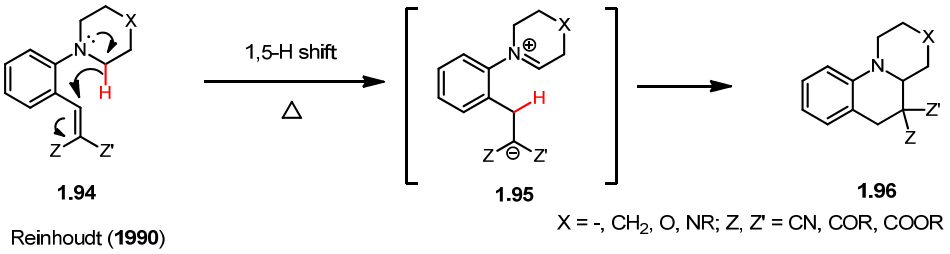
Scheme 1.9 **Type 1 *tert*-Amino Effect**



1.4.3.2 Type 2 *tert*-Amino Effect

The second type of the *tert*-amino effect involves six-membered ring formation, in which a suprafacial 1,5-hydride shift (or a sigmatropic hydrogen transfer) occurs from the α position of the tertiary amine to the *ortho*-substituent, leading to the 1,6-dipolar species **1.95**. Then, the 1,6-dipolar species readily undergoes a cyclization reaction to form the heterocyclic system **1.96** (Scheme 1.10). In 1984, Verboom and Reinhoudt first

Scheme 1.10 **Type 2 *tert*-Amino Effect**

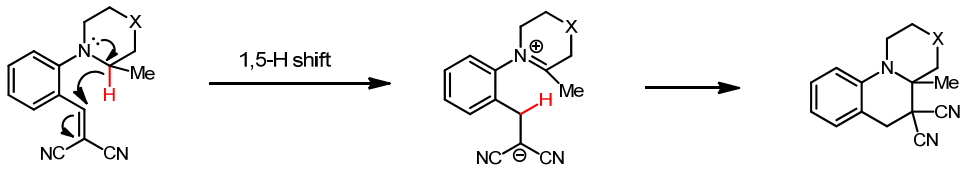


reported such a mechanistically distinct type of the *tert*-amino effect when two electron withdrawing groups are at the β position of the vinyl moiety.[17] After their discovery, variants of this type of reactions have been reported.[11,18] Most of these types of reactions are conducted under thermal conditions, and Lewis acid activated examples are rare.[19] In general, the pyrrolidine moieties react much faster than do piperidine moieties, and morpholine moieties exhibit the lowest reactivity. No example of this type of reaction

has been observed with only one electron-withdrawing group at the *β* position of the *ortho* vinyl moiety until Joris' work in 2008, in which a single nitro group acted as the hydride acceptor moiety.[18j] This result prompted our investigation of the *tert*-amino effect that utilizes the activation of Lewis acids. The rate determining step of this redox–neutral process was proven to be an irreversible 1,5-hydride shift by Verboom and Reinhoudt.[20] In some examples, the benzene ring has been replaced by different heterocycles,[21] and one of the acceptors (Z in Scheme 1.10) can also be a heterocycle.[22]

Notably, Verboom and Reinhoudt demonstrated two interesting aspects of the type 2 *tert*-amino effect. First, they showed that this type of hydride shift/cyclization process occurs regioselectively (Scheme 1.11).[23] Tertiary amino moieties that contain an *α* substituent like a methyl or an ethyl group can render the hydride from the tertiary carbon exclusively, which leads to a more stabilized dipolar intermediate. The product containing a quaternary bridgehead carbon is formed selectively in the cyclization step.

Scheme 1.11 **Regioselectivity of the *tert*-Amino Effect**



1.99
Reinhoudt (**1989**)

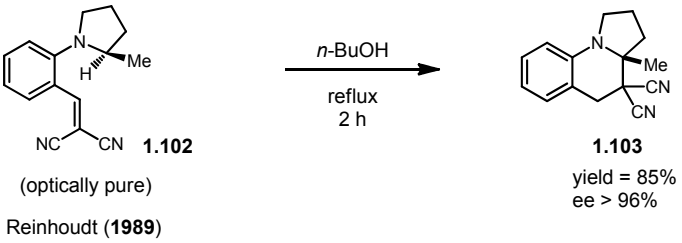
1.100

1.101
X = -, CH_2

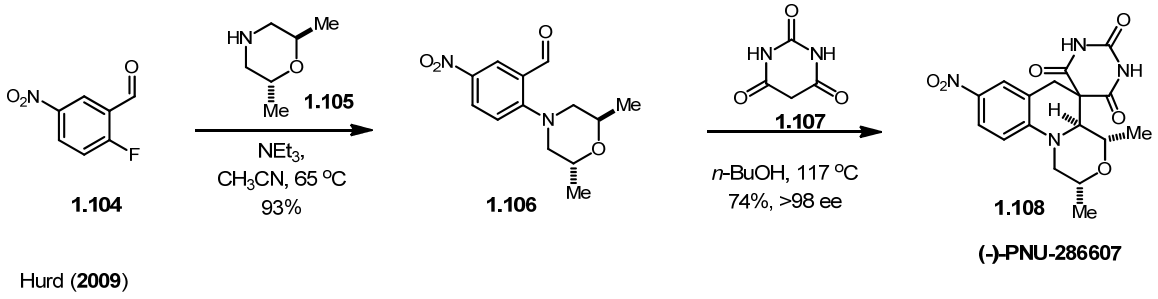
Amazingly, this reaction not only takes place regioselectively but also stereospecifically. In 1987, Verboom and Reinhoudt documented the self-reproduction of chirality in the type 2 *tert*-amino effect reaction (Scheme 1.12).[24] Starting with the enantiopure *ortho*-vinyl tertiary aniline **1.102** containing an *α* substituent such as a

methyl group, the reaction proceeds via a 1,5-hydride shift under thermal reaction conditions. Although the chiral center of **1.102** is lost temporarily after the hydride transfer, the 1,5-hydride shift proceeds through an enantioselective process that results in a chiral helical dipolar intermediate. Thus, the chiral information of the original compound is preserved in the helical dipolar intermediate. The resulting carbanion of the dipolar intermediate attacks the iminium ion exclusively on the same side from which the migrating hydrogen is transferred, which leads to an optically pure product.

Scheme 1.12 **Self-Reproduction of Chirality in the *tert*-Amino Effect**



Scheme 1.13 **Recent Application of the *tert*-Amino Effect in Organic Synthesis**

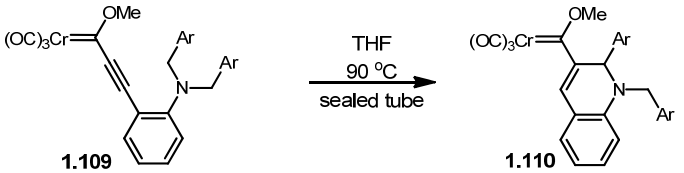


Recently, Hurd disclosed the synthesis of (-)-PNU-286607 via an asymmetric cyclization of alkylidene barbiturates starting with an enantiopure morpholine species **1.105** (Scheme 1.13).[25] This work is an excellent example of the application of the *tert*-

amino effect in the synthesis of biologically active compounds, involving the epimerization of one of the chiral carbon centers on the morpholine moiety.

In addition to *ortho*-vinyl moieties as hydride acceptors, Barluenga showed successfully in 2008 that *ortho*-alkynyl tertiary anilines could undergo such a redox–neutral process (Scheme 1.14).[26] Although the substrates are limited to alkynyl Fischer carbene complexes, considering recent advances in transition metal activated alkynes as hydride acceptors in redox–neutral reaction cascades,[31] it is reasonable to predict that *ortho*-alkynyl anilines will become a hot topic in this field.

Scheme 1.14 **Alkynyls as Hydride Acceptors**



1.109 **1.110**

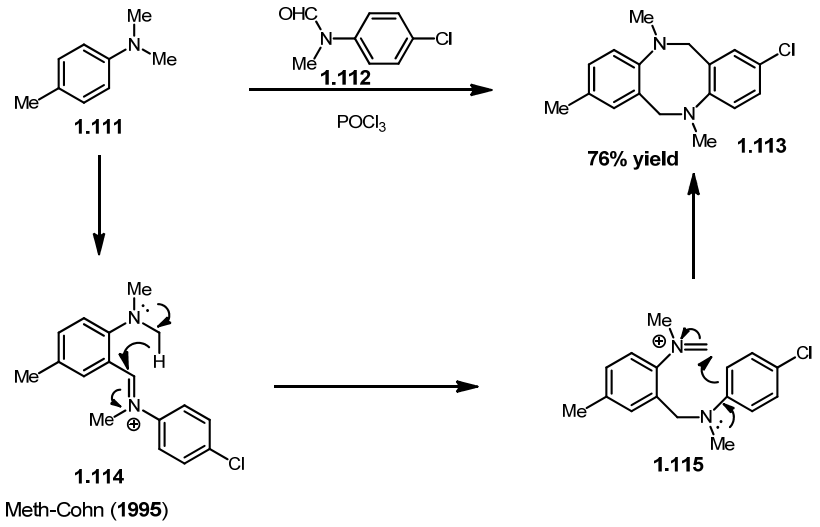
Barluenga (**2008**)

1.4.3.3 Type 3 *tert*-Amino Effect

The type 3 *tert*-amino effect refers to *tert*-amino effect reactions that involve the construction of ring systems of size greater than six. The mechanism of the type 3 *tert*-amino effect is similar to that of the type 2 *tert*-amino effect; both involve a 1,5-hydride shift. In 1995, Meth-Cohn reported the reaction of *p*-substituted *tert*-anilines with N-formyl-N-substituted arylamides, using $POCl_3$, to form the novel diazocine product **1.113** (Scheme 1.15).[27a] The reaction is believed to involve a Vilsmeier formylation *ortho* to the tertiary amino group followed by a 1,5-hydride shift. The resulting iminium ion **1.115** is then attacked by the aromatic ring. Not many examples of this type of reaction have

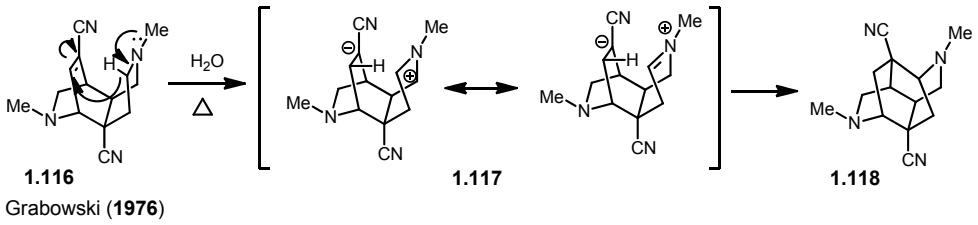
been reported, and the extension of this chemistry is currently being actively investigated.[27]

Scheme 1.15 **Type 3 *tert*-Amino Effect**

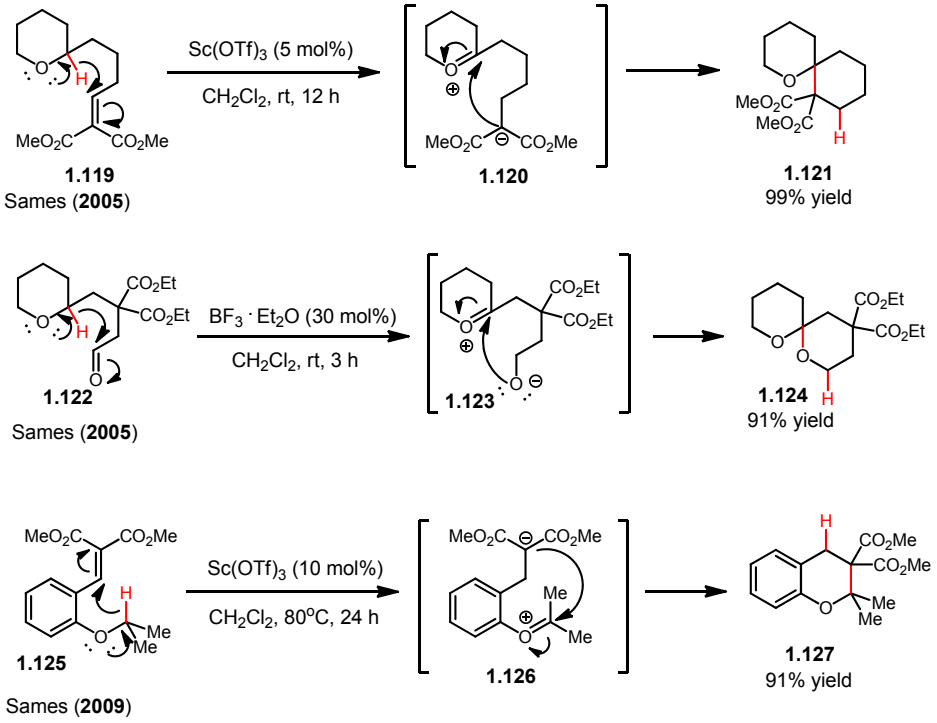


To date, only conjugated systems of tertiary amines can undergo this process, and no successful examples of unconjugated systems have been reported for the *tert*-amino effect except the work of Grabowski in 1976 (Scheme 1.16).[28] In his work, the rigid geometry of the starting material is vital, because it keeps the hydride and the acceptor in close proximity.

Scheme 1.16 ***tert*-Amino Effect in Unconjugated Systems**



Scheme 1.17 **C–H Functionalization of Ethers**



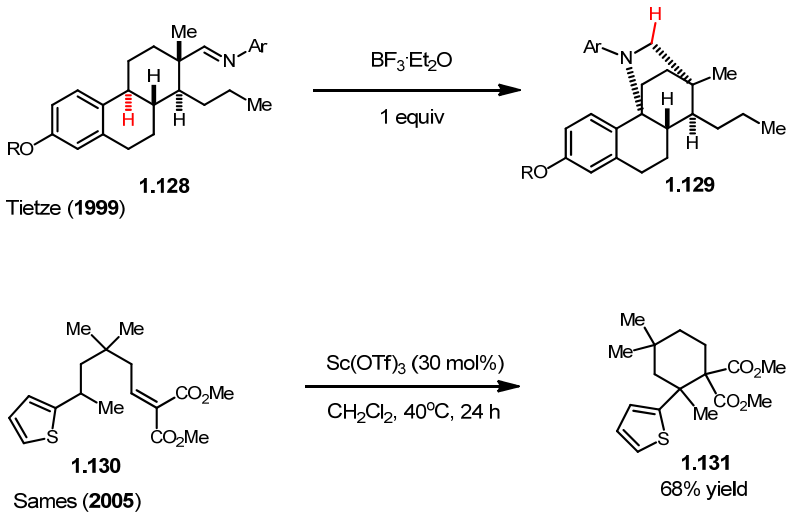
1.4.4 Redox Annulation Involving C–H Functionalization of the *α* Position of Ethers

In light of investigations of the aforementioned isomerization of steroidal sapogenins, the redox functionalization of the C–H bond *α* to an ether oxygen has been further explored in recent years by the Sames group (Scheme 1.17).[29] In his work, ethers are always tethered to electron-deficient alkenes. Upon activation with catalytic amounts of Lewis acids, the alkene moieties are capable of abstracting the hydride *α* to the ether oxygen. Next, a dipolar intermediate is formed that contains a relatively stabilized anion and oxonium moiety. The following cyclization leads to a new C–C bond, which provides facile access to spiro or bicylic heterocycles.

1.4.5 Redox Annulation Involving C–H Functionalization of the Benzylic Hydride

Although Atkinson has successfully demonstrated a cyclization reaction that involves a benzylic hydride transfer process, further studies of benzylic C–H bond functionalization via a 1,5-hydride shift/cyclization redox process are rare.[10a, 30, 31a-d] For example, in 1999, Tietze reported the 1,5-shift of a benzylic hydride to an iminium ion on the steroid skeleton **1.128** followed by ring closure to form the bridged steroid alkaloid **1.129** in good yields (Scheme 1.18).[30a] Recently, Sames also showed that Lewis acid activated alkylidene malonates **1.130** could trigger such a hydride shift initiated reaction cascade (Scheme 1.18).[29a]

Scheme 1.18 **C–H Functionalization of the Benzylic Hydride**

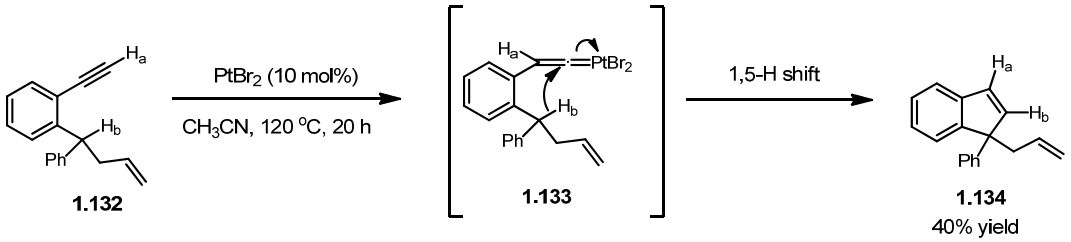


1.4.6 Alkynes as Hydride Acceptors

Although electron-deficient olefins are widely used as hydride acceptors to initiate redox annulations that involve hydride shifts, alkynes that are activated by a transition metal provide another option for the hydride acceptor. In 2006, Yamamoto

reported the first example of this type of reaction (Scheme 1.19), followed by an extensive exploration by Chatani, Sames, He, Urabe, and Gagosz over the course of two years.[31] Transition metals like platinum, gold or ruthenium react with the alkyne to form a metal-vinylidene intermediate such as **1.133**. The activated alkyne **1.133** will readily undergo a 1,5-hydride shift followed by a cyclization sequence to form **1.134**.

Scheme 1.19 **Alkynes as Electron-Deficient Moieties**



Yamamoto (**2006**)

These discoveries significantly extended the substrate scope for this type of transformation because the hydride acceptor moiety is a simple alkyne, unlike olefins which require electron-deficient groups for further activation. More exciting discoveries in this field are anticipated.

1.5 Objectives

The redox–neutral reaction cascade involving C–H functionalization has emerged as a powerful tactic in organic synthesis as it enables quick access to molecular complexity via unconventional bond forming reactions. Although a number of examples have been presented regarding the redox annulation process that involves C–H bond functionalization, many challenges remain in this field. For example, little effort has been focused on the use of Lewis acids to accelerate the *tert*-amino effect. No precedent has been reported in the field of catalytic enantioselective redox processes via C–H

functionalization. Greater effort in pursuing the broad synthetic applicability of intramolecular redox–neutral reactions is necessary, and advances in the field should be of significance in complex molecular synthesis.

In the research presented in this dissertation, the main objectives are to develop novel redox–neutral reaction cascades that involve C–H bond functionalization, to apply these new methodologies in natural product synthesis, and to explore the catalytic enantioselective intramolecular annulations via a hydride shift. We hope that our discoveries in this field can address some unsolved problems and provide useful information for further studies. Chapter II will introduce the development of Lewis acid catalyzed polycyclic tetrahydroquinoline formation and the first catalytic enantioselective redox process via C–H functionalization. Chapter III will discuss the novel redox–neutral synthesis of ring-fused aminals that involves a hydride shift and its application to the synthesis of natural products. Chapter IV will focus on the non-traditional functionalization of azomethine ylides, another attractive redox–neutral process.

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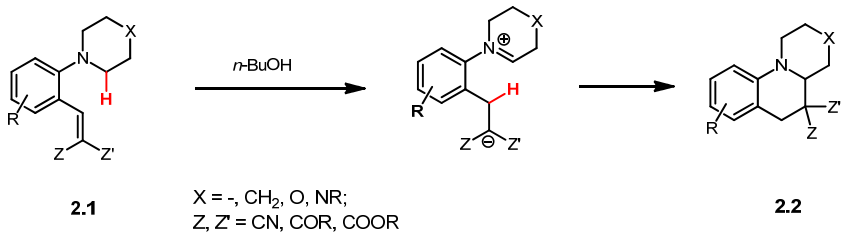
Chapter II Lewis Acid Catalyzed Formation of Tetrahydroquinolines via an Intramolecular Redox Process & Catalytic Enantioselective Intramolecular Redox Reactions

2.1 Background

Tetrahydroquinolines, which display a diverse array of biological activities, have attracted considerable attention in the synthetic community.[1] The Povarov reaction[2] and various reductions of quinolines[3] are the common methods used in the synthesis of tetrahydroquinolines. The functionalization of relatively unreactive C–H bonds via intramolecular hydride shift/cyclization processes provides intriguing opportunities for the rapid generation of molecular complexity. The type 2 *tert*-amino effect provides such an approach to polycyclic tetrahydroquinolines, which are not readily available by other means (Scheme 2.1). Polycyclic tetrahydroquinolines **2.2** are readily obtained under thermal conditions via the rearrangement of tertiary anilines **2.1** that bear an appropriate electron deficient vinyl substituent in the *ortho* position. In this process, the C–H bond α to the tertiary amine nitrogen transfers as a hydride to the electron deficient vinyl moiety, giving rise to a dipolar intermediate. Subsequent C–C bond formation produces tetrahydroquinolines **2.2**.[4] This transformation has been of limited synthetic utility since harsh reaction conditions are typically required. Whereas microwave acceleration of thermal rearrangements have been reported,[5] surprisingly little effort has been focused on the catalytic activation of substrates by Lewis acids. Lewis acids such as zinc chloride or boron trifluoride-diethyl ether have been reported in stoichiometric amounts, with heating still being required to induce the rearrangement.[6] In this chapter we introduce an efficient Lewis acid catalyzed approach that readily proceeds at room temperature, and

which can significantly enhance the applicability of this rearrangement. Moreover, a catalytic enantioselective variant of this process, which has never been achieved before, will be discussed.

Scheme 2.1 **Tetrahydroquinoline Synthesis via Redox–neutral C–H Bond Functionalization**

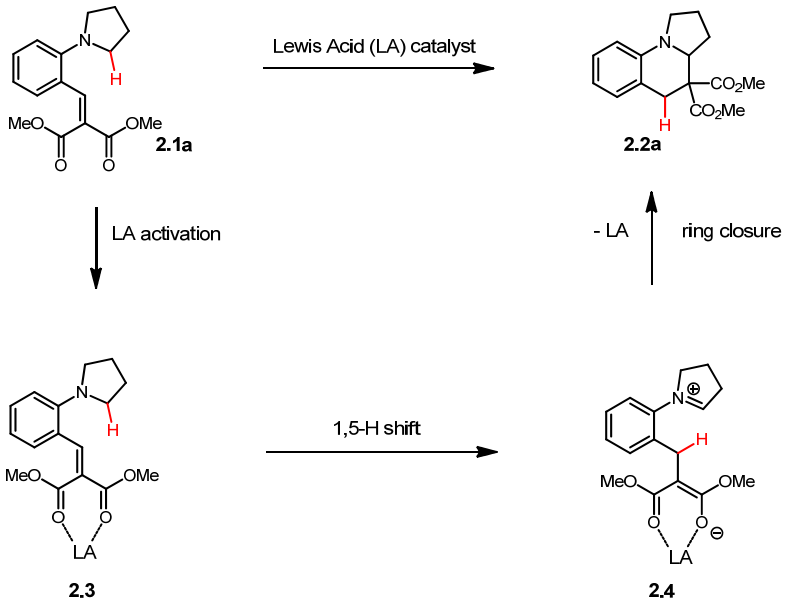


2.2 Lewis Acid Catalyzed Formation of Tetrahydroquinolines

2.2.1 General Consideration

Intramolecular redox functionalizations of C–H bonds have been reported via activation by a catalytic amount of Lewis acids.[7] As part of a program to develop intramolecular redox reactions of broad synthetic applicability,[8] we decided to investigate the rearrangement of **2.1a** to **2.2a** with the activation of catalytic amounts of Lewis acids (Scheme 2.2).[9] Alkylidene malonates, typical hydride acceptor moieties in the type 2 *tert*-amino effect, are susceptible to activation by a Lewis acid catalyst capable of chelating to the malonate subunit. It is anticipated that this chelating interaction will increase the hydride acceptor capability of the *ortho* vinyl moiety, which will trigger the transformation under mild conditions. The zwitterionic intermediate **2.4** resulting from the 1,5-hydride shift is expected to undergo cyclization to form **2.2a**.

Scheme 2.2 **Proposed Lewis Acid Catalyzed Process**

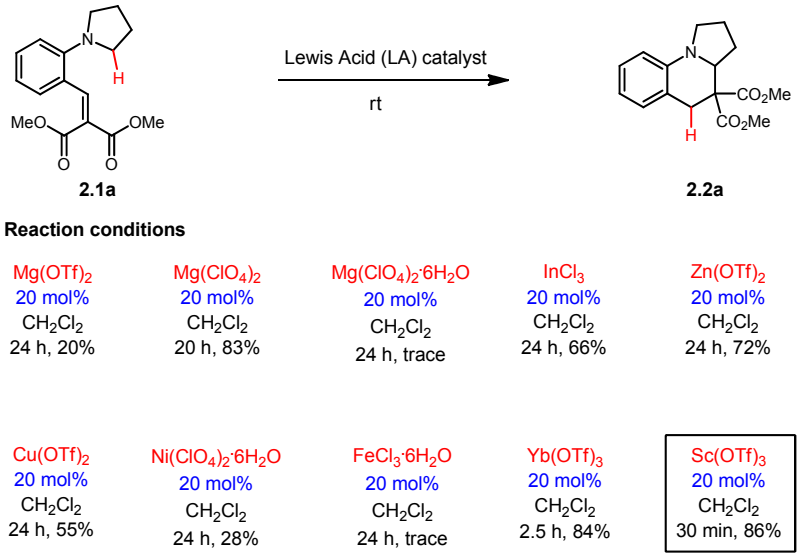


2.2.2 Reaction Conditions Optimization

First, catalytic amounts of various Lewis acids were investigated for the rearrangement of **2.1a** to **2.2a** at room temperature (Figure 2.1). Magnesium triflate (20 mol%) gave rise to 20% yield of **2.2a** after 24 hours at room temperature with dichloromethane as the solvent. Notably, good yields were achieved with magnesium perchlorate as the catalyst, while magnesium perchlorate hexahydrate exhibited significantly lower reactivity and only trace amounts of the product were detected. Several main group and transition metal salts such as indium (III) chloride, zinc (II) triflate, copper (II) triflate, and nickel (II) perchlorate hexahydrate also catalyzed this rearrangement, but provided no improvement of yield or reactivity. Iron (III) chloride failed to activate **2.1a**. Ytterbium triflate readily catalyzed this transformation more efficiently, which provided 84% yield of **2.2a** after 2.5 hours. Pleasingly, a rapid

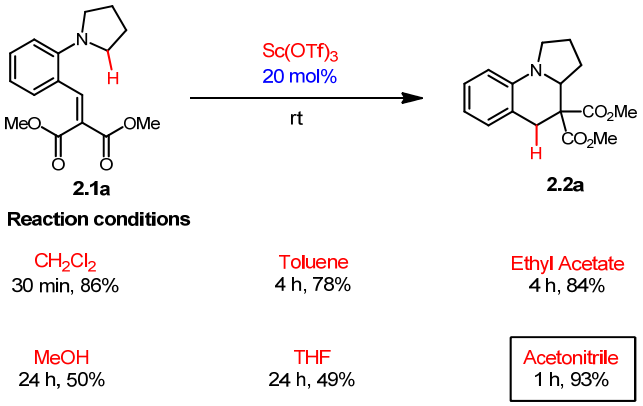
generation of **2.2a** was achieved in the presence of catalytic amounts of scandium (III) triflate after 30 minutes with 86% yield.

Figure 2.1 **Reactions Catalyzed with Various Lewis Acids**



Subsequently, a number of solvents such as toluene, ethyl acetate, tetrahydrofuran, methanol, and acetonitrile were evaluated for this transformation in the presence of 20 mol% of scandium triflate as the catalyst (Figure 2.2). A good yield was also obtained when the reaction was conducted in ethyl acetate. Significantly reduced yields were

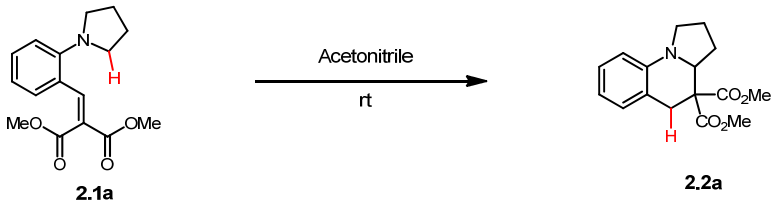
Figure 2.2 **Reactions Catalyzed by $Sc(OTf)_3$ in Different Solvents**



observed in the cases of toluene, methanol, and tetrahydrofuran. Gratifyingly, acetonitrile was found to be superior to other solvents with regard to yield, although slightly longer reaction times were required when compared to dichloromethane.

Next, efforts were made to further optimize the reaction conditions, with respect to catalyst and molarity. The use of 10 mol% of scandium triflate required 4 hours to complete the transformation of **2.1a** in acetonitrile, whereas 5 mol% of scandium triflate required up to 22 hours to complete the transformation with a reduced yield. A 0.1 M concentration was found to provide the best result in terms of reaction rate and yield. Other rare-earth metals such as lanthanide triflate and gadolinium triflate were also evaluated as catalysts. Ultimately, gadolinium triflate showed a remarkable rate acceleration when compared to scandium triflate even with as low as 5 mol% of catalyst loading. Therefore, gadolinium triflate was selected as the optimal catalyst for this study. The use of 0.1 M concentration was established to be the optimal condition for this transformation in the presence of 5 mol% of gadolinium triflate as the catalyst.

Figure 2.3 **Further Optimization of Reaction Conditions**



2.1a **2.2a**

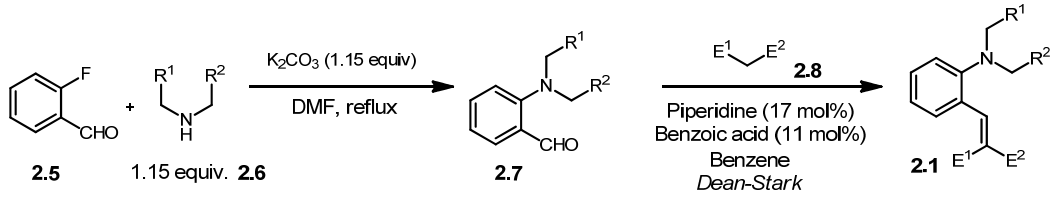
Reaction conditions

$Sc(OTf)_3$ 10 mol% 4 h, 93% 0.1 M	$Sc(OTf)_3$ 5 mol% 22 h, 83% 0.1 M	$Sc(OTf)_3$ 10 mol% 24 h, 91% 0.25 M	$Sc(OTf)_3$ 10 mol% 24 h, 89% 0.5 M	$Sc(OTf)_3$ 10 mol% 24 h, 89% 1.0 M
$La(OTf)_3$ 10 mol% 45 min, 86% 0.1 M	$Gd(OTf)_3$ 10 mol% 15 min, 93% 0.1 M	$Gd(OTf)_3$ 5 mol% 15 min, 90% 0.1 M	$Gd(OTf)_3$ 10 mol% 50 min, 75% 0.1 M *(run in CH_2Cl_2)*	

2.2.3 Substrate Scope Regarding the Hydride Acceptor Moieties

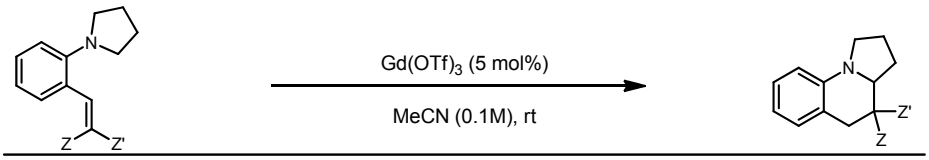
A variety of alkylidenemalonates were readily prepared according to the general routes, which are shown in Figure 2.4.

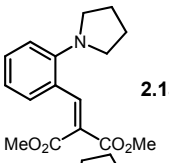
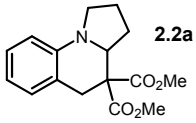
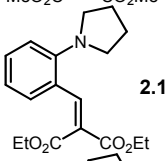
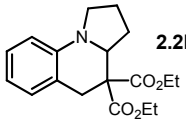
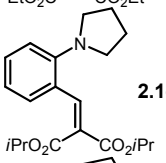
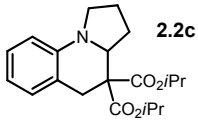
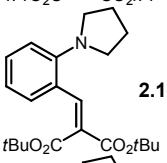
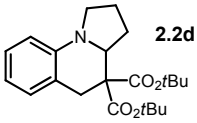
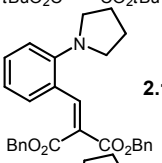
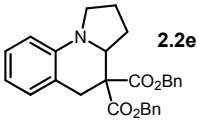
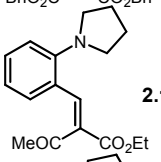
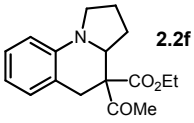
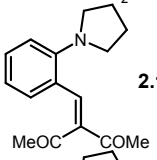
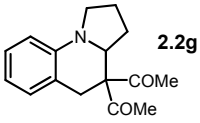
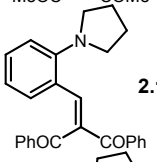
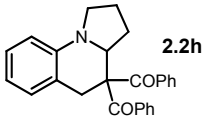
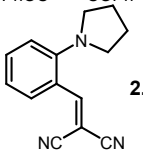
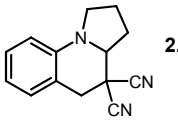
Figure 2.4 **Preparation of Alkylidenemalonates**



The scope of the reaction with regard to the acceptor moieties is summarized in Table 2.1. Different malonate esters readily participated in this reaction, giving rise to products in good yields after relatively short reaction times (Table 2.1, entries 1-4). An exception is the benzyl ester **2.1e**, which rearranged to product **2.2e** in lower yield, and required a longer reaction time (Table 2.1, entry 5). The *β*-ketoester derived starting material **2.1f** (*E*/*Z* ratio = 53:47) rearranged to the corresponding product **2.2f**, which was isolated as a mixture of diastereomers (Table 2.1, entry 6). Diketones **2.1g** and **2.1h** also rearranged efficiently to products **2.2g** and **2.2h**, respectively (Table 2.1, entries 7 and 8). These substrates required slightly longer reaction times when compared to the corresponding malonate compounds. As anticipated, due to the limited propensity of the dinitrile substrate **2.1i** to engage in chelating interactions with the Lewis acids, no rearrangement of this compound was observed after 24 hours under normal conditions (Table 2.1, entry 9). Further heating of the reaction mixture at 40 °C for an additional 24 hours gave only trace amounts of product **2.2i**.

Table 2.1 **Evaluation of Different Acceptor Groups**[a]



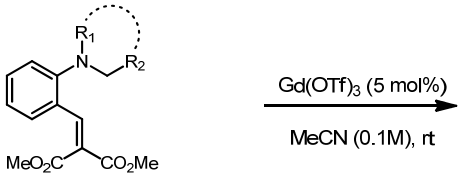
entry	starting material	product	time	yield (%)
1	 **2.1a**	 **2.2a**	15 min	90
2	 **2.1b**	 **2.2b**	15 min	82
3	 **2.1c**	 **2.2c**	10 min	87
4	 **2.1d**	 **2.2d**	30 min	70
5	 **2.1e**	 **2.2e**	2 h	57
6	 **2.1f**	 **2.2f**	5 min	55 64 : 36 dr
7	 **2.1g**	 **2.2g**	3 h	76
8	 **2.1h**	 **2.2h**	3 h	92
9	 **2.1i**	 **2.2i**	24 h	NR

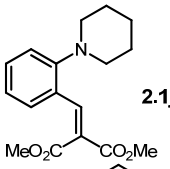
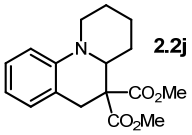
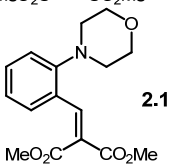
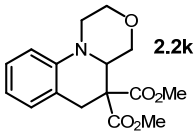
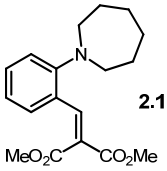
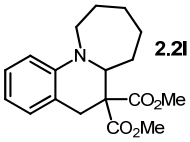
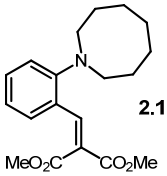
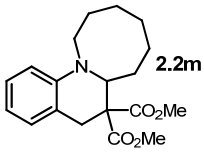
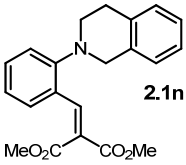
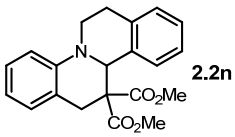
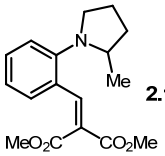
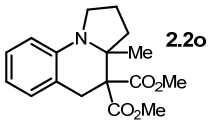
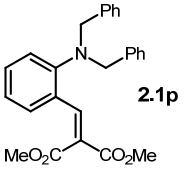
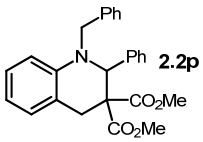
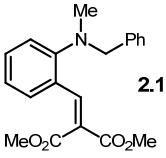
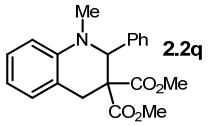
[a] Reaction were performed on a 1 mmol scale and were run to full conversion.

2.2.4 Substrate Scope with Regard to Different Amine Donors

The scope of this rearrangement was explored further by evaluating a number of different amine donors (Table 2.2). The piperidine derived compound **2.1j** required a longer reaction time compared to the pyrrolidine compound **2.1a** (Table 2.2, entry 1). The related morpholine compound **2.1k** did not efficiently rearrange at room temperature, but full consumption of **2.1k** occurred at 40 °C, with product **2.2k** being isolated in 78% yield (Table 2.2, entry 2). The corresponding seven- and eight-membered amine starting materials **2.1l** and **2.1m** rearranged readily to the corresponding products (Table 2.2, entries 3 and 4). The relative rates of this transformation with regard to the amine moieties was observed to be azocane > pyrrolidine > azepane > piperidine > morpholine. Presumably due to enhanced the hydride donor capabilities of benzylic C–H bonds, the tetrahydroisoquinoline **2.1n** rapidly rearranged to **2.2n** upon exposure to gadolinium triflate (Table 2.2, entry 5). The 2-methylpyrrolidine derived starting material **2.1o** gave rise to a single regioisomer **2.2o** upon rearrangement (Table 2.2, entry 6). This finding likely reflects the increased hydride donor capability of a tertiary over a secondary C–H bond. Starting materials that incorporate noncyclic amines also rearranged to the expected products (Table 2.2, entries 7 and 8). Although structurally closely related, **2.1p** required heating at 40 °C for 24 hours to reach full conversion to form **2.2p**, while **2.1q** completely rearranged into **2.2q** after 2 hours at room temperature. This significant rate difference is likely due to unfavorable steric interactions in the course of the reaction. Only a single regioisomer of **2.2q** was isolated, which can be attributed to the superior hydride donor capability of benzylic over primary C–H bonds.

Table 2.2 **Evaluation of Different Amine Donor Groups**



entry	starting material	product	time	yield (%)
1	 **2.1j**	 **2.2j**	3h	91
2[a]	 **2.1k**	 **2.2k**	12 h	78
3	 **2.1l**	 **2.2l**	20 min	82
4	 **2.1m**	 **2.2m**	5 min	81
5	 **2.1n**	 **2.2n**	5 min	87
6	 **2.1o**	 **2.2o**	5 min	82
7[a]	 **2.1p**	 **2.2p**	24 h	70
8	 **2.1q**	 **2.2q**	2 h	94

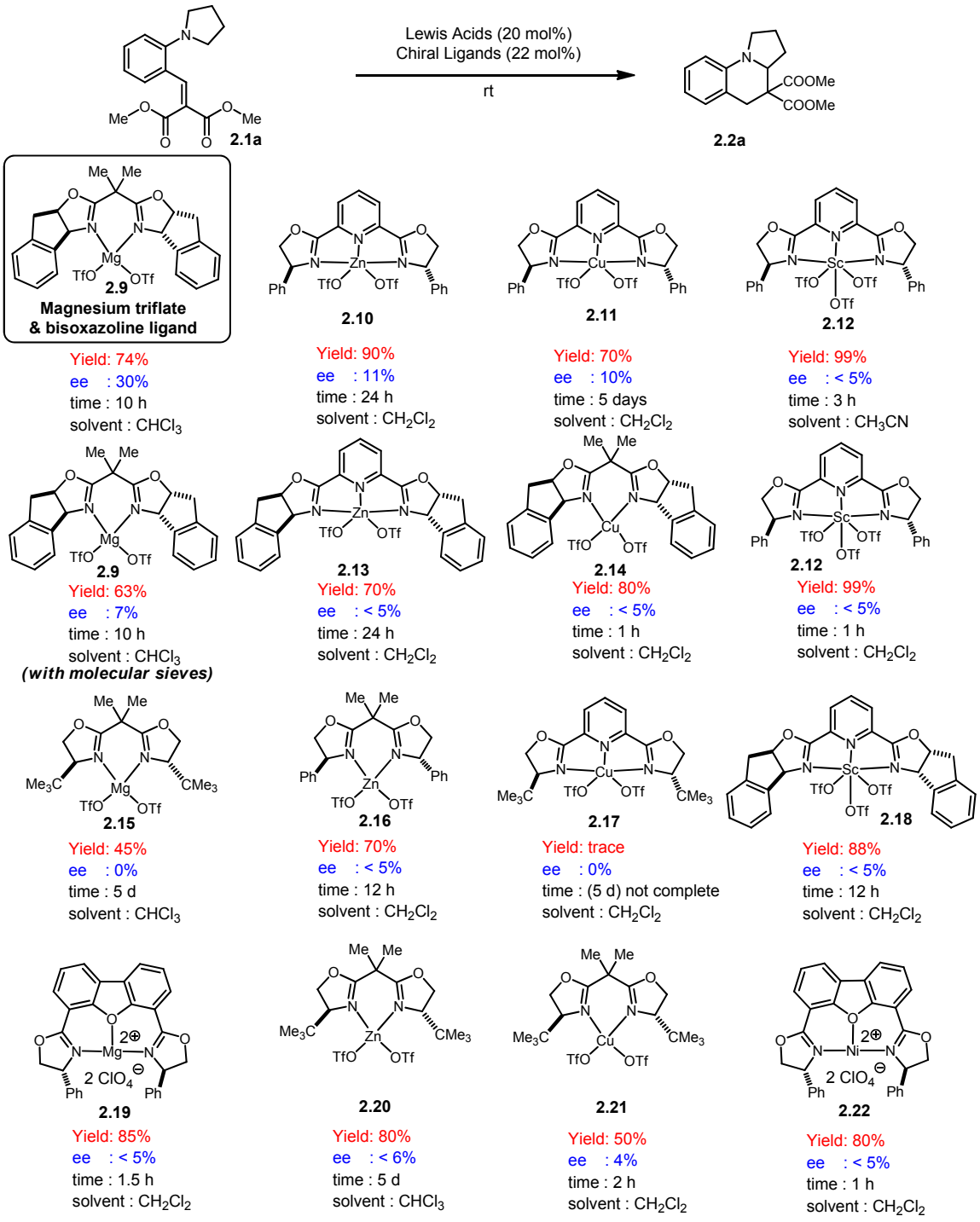
[a] Reaction was performed at 40 °C.

2.3 Enantioselective Process with Substrates Bearing an Alkylidene Malonate Moiety

So far we have successfully demonstrated that intramolecular redox–neutral C–H bond functionalizations can be significantly accelerated by Lewis acid catalysis, providing efficient access to polycyclic tetrahydroquinolines under very mild conditions. By using chiral ligands capable of chelating to Lewis acids, the C–H bond functionalization can be made enantioselective. Therefore, a number of chiral transition metal complexes were evaluated (Figure 2.5). Notably, chiral magnesium bisoxazoline ligand catalyst **2.9** was effective in catalyzing the rearrangement of **2.1a** to **2.2a** (Figure 2.5).[10] In this instance, product **2.2a** was isolated in 74% yield and 30% ee, illustrating for the first time that such a reaction is amendable to enantioselective catalysis. Reduced enantioselectivity (7% ee) was obtained with molecular sieves as an additive. No significant enantioenrichment in product **2.2a** was observed with other magnesium-chiral ligands catalyst complexes.

A variety of other chiral Lewis acids were tested as catalysts in this transformation in an attempt to improve the enantioselectivity (Figure 2.5). Zinc (II) triflate was investigated, which offered at most 11% ee in combination with different chiral ligands. No improvement was observed when copper (II) triflate was used as the Lewis acid. Scandium (III) triflate in combination with different enantiopure PyBox ligands gave rise to racemic products exclusively. No enantioselectivity was also observed with chiral ligand complexes of nickel (II) perchlorate.

Figure 2.5 **Attempts towards an Enantioselective Process**



In order to explore the enantioselective process with regard to different hydride acceptor moieties, diisopropyl malonate **2.1c** was evaluated (Figure 2.6). Although the chiral magnesium bisoxazoline catalyst **2.9** still provided the best results, the enantioselectivity was lower than that obtained for substrate **2.1a** with dimethyl malonate as the acceptor moiety.

Figure 2.6 **Evaluation of the Enantioselective Process with 2.1c**

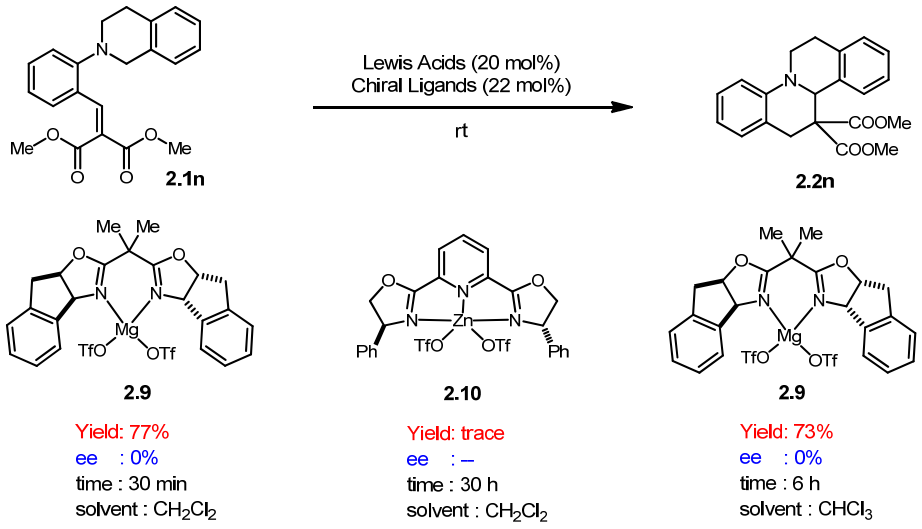
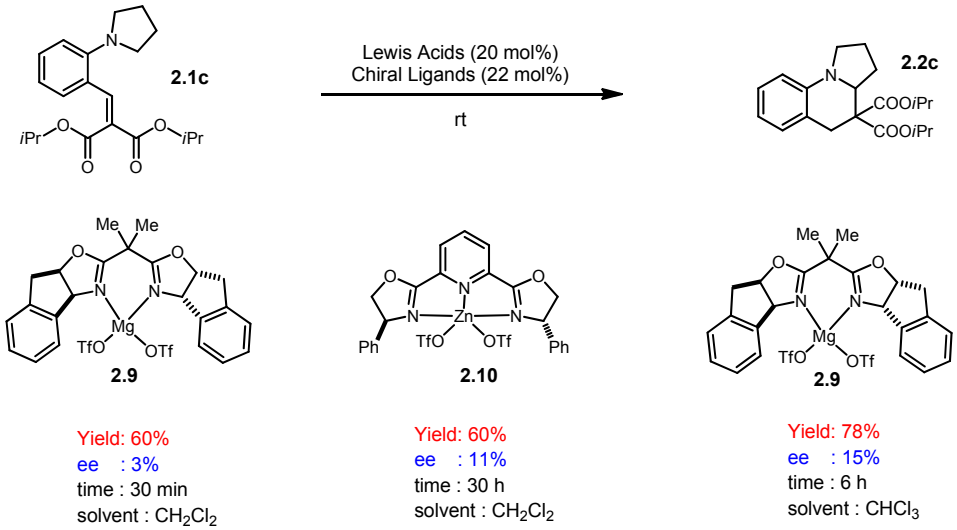


Figure 2.7 **Evaluation of the Enantioselective Process with 2.1n**



In another attempt to improve the efficiency of this process, the substrate **2.1n** with tetrahydroisoquinoline as the amine moiety was evaluated. However, only racemic products were obtained in all cases (Figure 2.7).

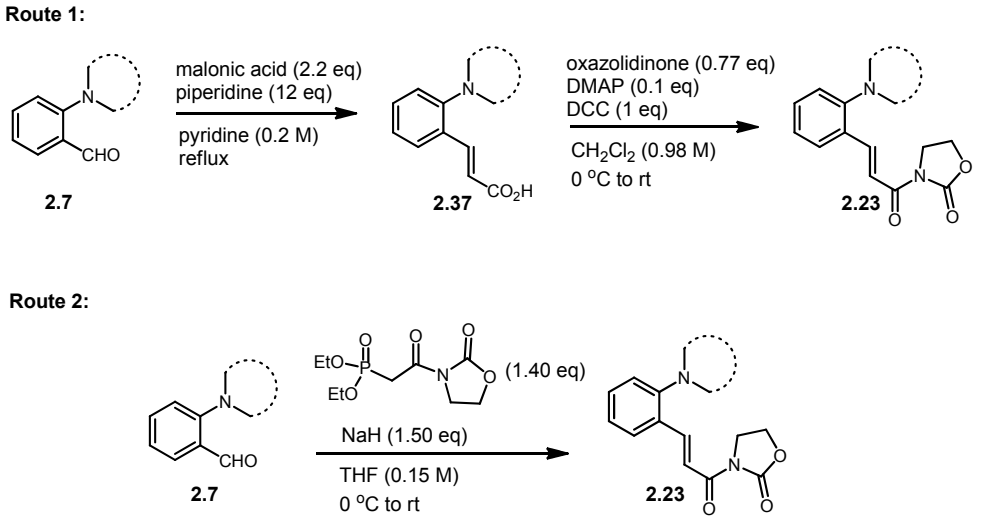
Interestingly, the product **2.2a** with 30% ee was racemized in the presence of 5 mol% of gadolinium triflate in acetonitrile at room temperature with stirring for 24 hours. This phenomenon clearly shows the reversibility of the Mannich portion of the rearrangement.

2.4 Enantioselective Process with Substrates Bearing an Acyl Oxazolidinone Moiety

2.4.1 General Consideration

So far, we have successfully demonstrated that Lewis acids such as gadolinium triflate or scandium triflate can efficiently catalyze the transformation of compounds **2.1** (Z, Z′ = COR, COOR) to **2.2** under very mild conditions. Unfortunately, attempts to develop a catalytic enantioselective variant of this reaction have been met with limited

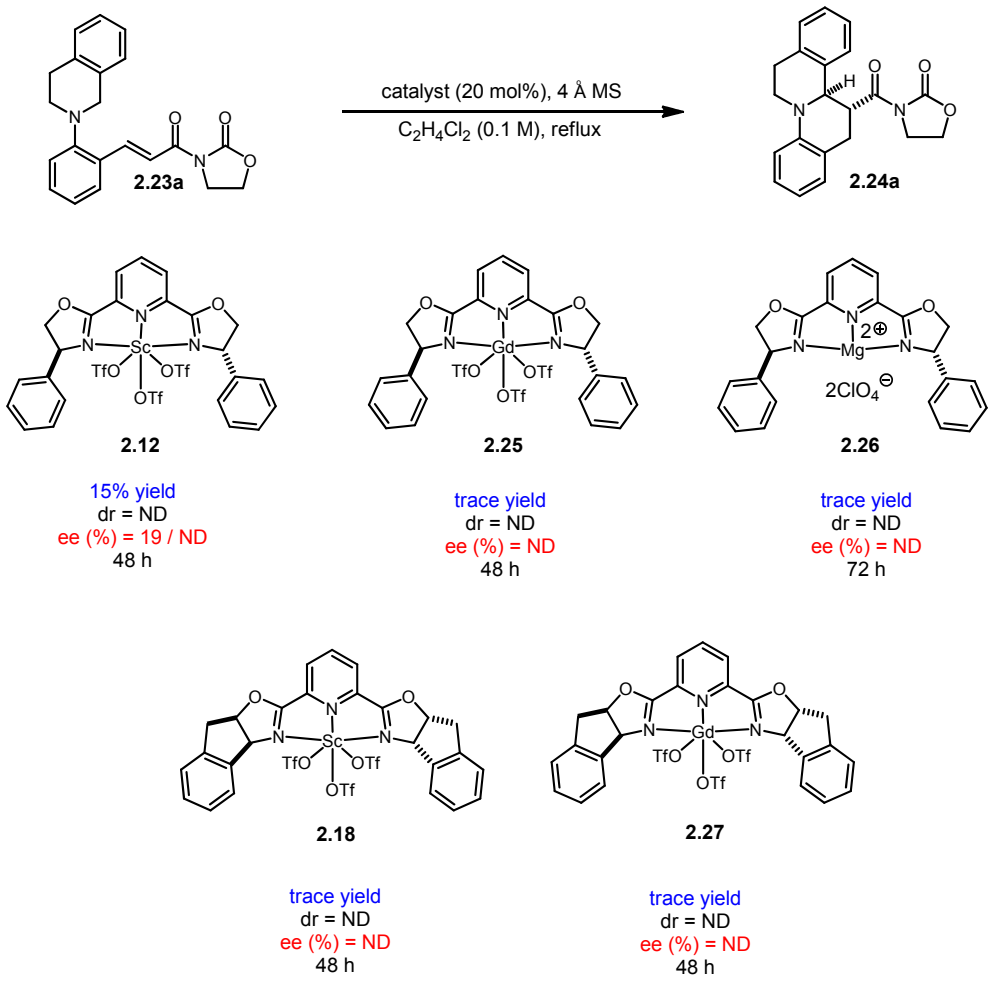
Scheme 2.3 **Synthesis of 2.23**



success. However, we speculated that the limitation requiring the presence of two activating groups for the thermally promoted rearrangements of compounds **2.1** could be overcome by Lewis acid catalysis.[11] Therefore, we decided to investigate a substrate bearing an acyl oxazolidinone (e.g., **2.23a**), which is known to be capable of chelating to a chiral metal complexes, as an alternative hydride acceptor moiety.[12] Two routes were successfully developed to synthesize the acyl oxazolidinone substrates, which are outlined in Scheme 2.3.

2.4.2 Reaction Conditions Optimization

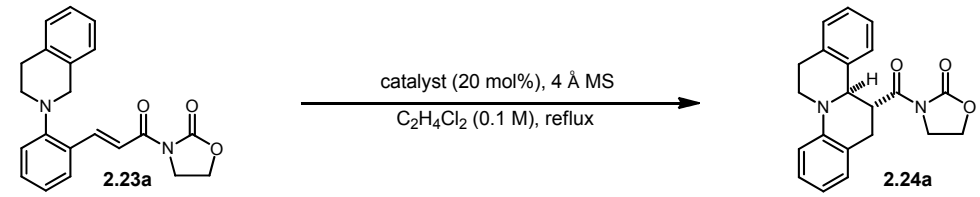
Figure 2.8 **Investigations of Substrates Bearing an Acyl Oxazolidinone**



Scandium or gadolinium triflate, which exhibited excellent reactivity towards the transformation of **2.1a** to **2.2a**, was initially used to promote the rearrangement of **2.23a** to **2.24a**. However, scandium or gadolinium triflate in combination with chiral ligands only gave rise to disappointing results (Figure 2.8). Extremely slow transformations were observed. Only trace amounts of product **2.24a** in low enantioselectivity was observed in one instance (Figure 2.8).

Much to our satisfaction, the use of nickel perchlorate in combination with Ph-DBFox[13] led to the formation of **2.24a** in good diastero- and enantioselectivity and further optimization was undertaken to obtain the best condition (Figure 2.9). In the absence of molecular sieves, slightly reduced selectivities were observed. Inferior results were obtained upon the use of nickel tetrafluoroborate or nickel hexafluoroantimonate. Whereas zinc perchlorate catalyzed the reaction less efficiently, magnesium salts in combination with Ph-DBFox led to excellent conversions. The best result was obtained with magnesium triflate. While the diastereoselectivity in this case was slightly lower than in the nickel perchlorate catalyzed process, the overall yield and enantioselectivity was improved. The use of Bn-DBFox or *i*Pr-DBFox in combination with various nickel or magnesium salts resulted in no further improvement. It is important to note that 1,2-dichloroethane is uniquely effective as a solvent. No transformation of **2.23a** was observed when reactions were performed in other solvents such as toluene, trifluorotoluene, chloroform, dichloromethane or acetonitrile (all at reflux temperature). When the reaction was performed at temperatures lower than 84 °C (reflux), no or very sluggish product formation was observed.

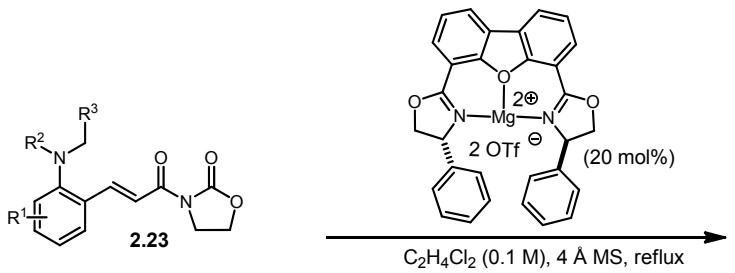
Figure 2.9 **Further Investigations to Achieve High Enantioselectivity**

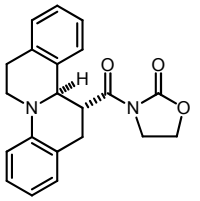


2.23a → **2.24a**

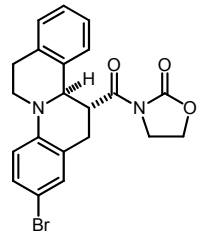
2.22	**2.22**	**2.28**
68% yield dr = 89 : 11 ee (%) = 90 / 85 12 h	70% yield dr = 83 : 17 ee (%) = 89 / 81 12 h ***without molecular sieves***	68% yield dr = 88 : 12 ee (%) = 83 / 85 48 h
2.29	**2.30**	**2.19**
28% yield dr = ND ee (%) = 71 / ND 72 h	30% yield dr = ND ee (%) = 58 / ND 72 h	89% yield dr = 75 : 25 ee (%) = 87 / 91 12 h
2.31	**2.32**	**2.33**
75% yield dr = 81 : 19 ee (%) = 77 / 77 12 h	88% yield dr = 74 :26 ee (%) = 94 / 85 30 h	29% yield dr = ND ee (%) = 54 / ND 48 h
2.34	**2.35**	**2.36**
18% yield dr = ND ee (%) = 44 / ND 48 h	80% yield dr = 81 : 19 ee (%) = 75 / 73 12 h	35% yield dr = ND ee (%) = 45 / ND 72 h

Figure 2.10 **Scope of the Reaction**[a,b]

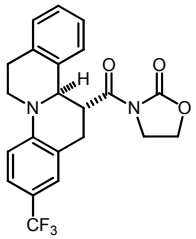




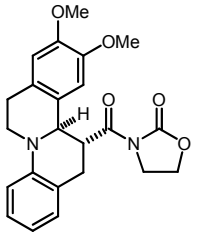
2.24a (88% yield)
dr = 75 : 25
ee (%) = 93 / 86
30 h



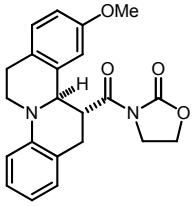
2.24b (80% yield)
dr = 69 : 31
ee (%) = 89 / 87
24 h



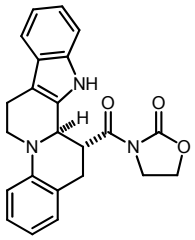
2.24c (94% yield)[b]
dr = 60 : 40
ee (%) = 88 / 89
24 h



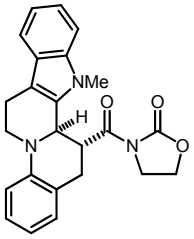
2.24d (86% yield)
dr = 84 : 16
ee (%) = 92 / ND
36 h



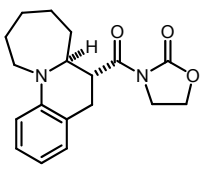
2.24e (84% yield)
dr = 90 : 10
ee (%) = 93 / ND
18 h



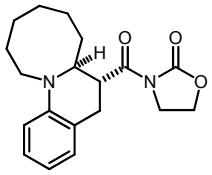
2.24f (80% yield)
dr = 75 : 25
ee (%) = 82 / 98
24 h



2.24g (75% yield)
dr = 60 : 40
ee (%) = 90 / 92
22 h



2.24h (83% yield)
dr = 70 : 30
ee (%) = 75 / 71
60 h



2.24i (97% yield)
dr = 50 : 50
ee (%) = 70 / 60
7 h

[a] Reactions were performed on a 0.3 mmol scale. The ee's were determined by HPLC analysis, dr's by ^{1}H-NMR. [b] $Ni(ClO4)_2{\cdot}6H2O$ was used instead of $Mg(OTf)_2$.

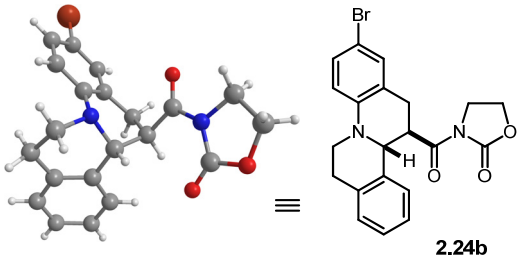
2.4.3 Substrate Scope

Under the optimized conditions, the scope of the reaction was explored (Figure 2.10). Various substitution patterns on the basic substrate framework were well tolerated (products **2.24a**–**e**). Electron deficient substituents like bromo or trifluoromethyl on the conjugated benzene ring increased the reactivity slightly since they increase the capability of the hydride acceptor moiety. The tetrahydroisoquinoline moiety with a methoxy substituent, which served as a better hydride donor, led to better diastereoselectivity and reactivity. Starting materials derived from *β*-carboline and *N*-Me-*β*-carboline underwent the rearrangement successfully, which gave rise to products **2.24f** and **2.24g** in good yields and high levels of stereoselectivity. Products **2.24h** and **2.24i** which incorporate seven or eight membered azacycles were formed in good yields but with reduced levels of enantio- and diastereoselectivity.

2.4.4 Mechanistic Insights

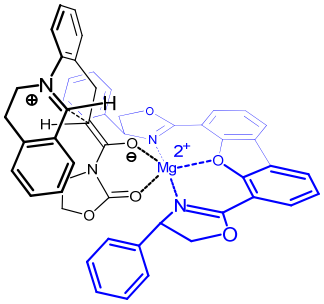
The absolute configurations of products **2.24b** and **2.24e** were determined by X-ray crystallographic analysis. Figure 2.11 shows proposed transition states that account for the formation of the major product enantiomer and minor product enantiomer. Formation of the opposite enantiomer would suffer from severe interactions between the substrate and the phenyl residue of the ligand, a fact that helps to explain the observed high levels of enantioselectivity at this relatively high reaction temperature. The proposed trigonal bipyramidal coordination geometry for the magnesium DBFox complex has previously been suggested by Kanemasa et al.[12d]

Figure 2.11 **Absolute Configuration and Proposed Transition States**

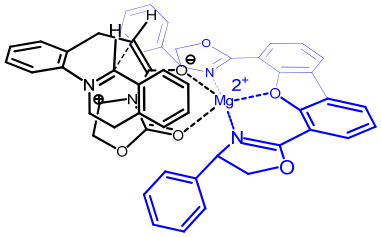


2.24b

Absolute configuration of 2.24b (X-ray).



Proposed transition state **A**
Z-enolate leading to major product **2.24a**
trigonal bipyramidal geometry

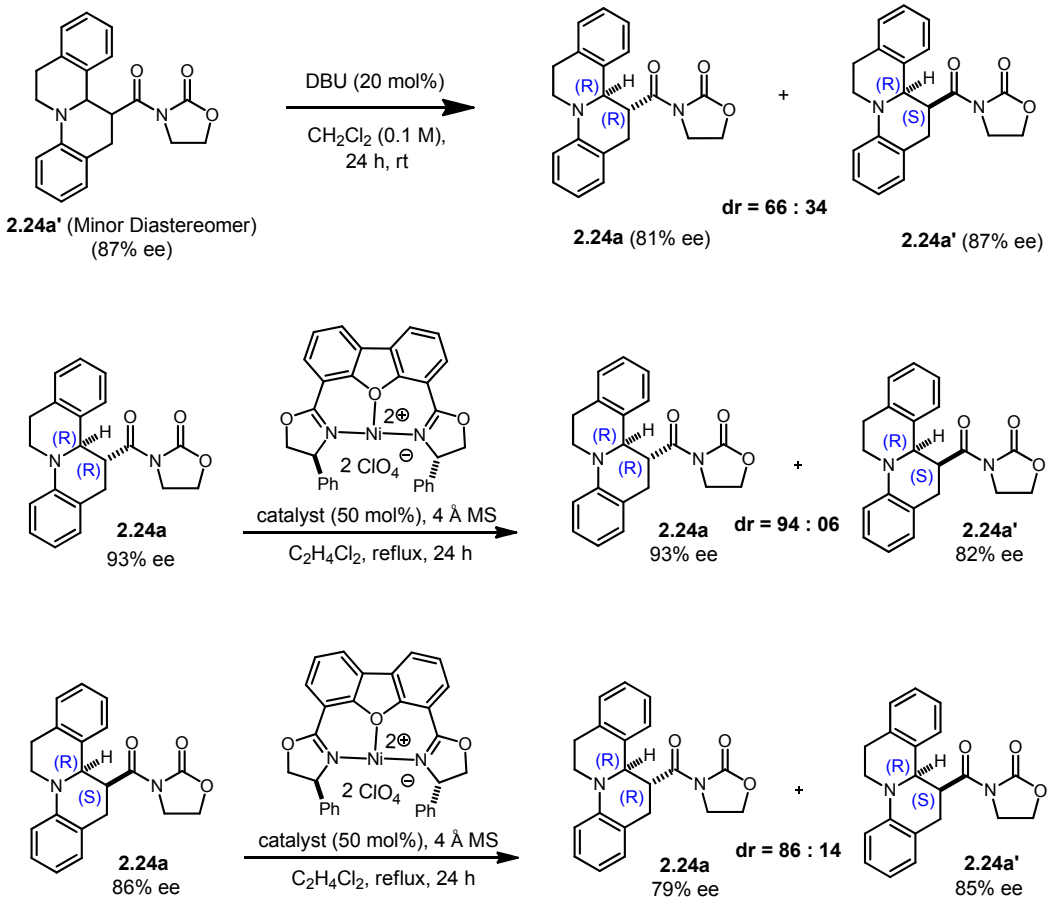


Proposed transition state **B**
E-enolate leading to minor product **2.24a'**
trigonal bipyramidal geometry

The two proposed transition states are consistent with the formation of either diastereomer. The *Z*-enolate is believed to be involved in the formation of the major diastereomer **2.24a**, whereas the minor diastereomer **2.24a'** can be derived from the corresponding *E*-enolate (Figure 2.11).

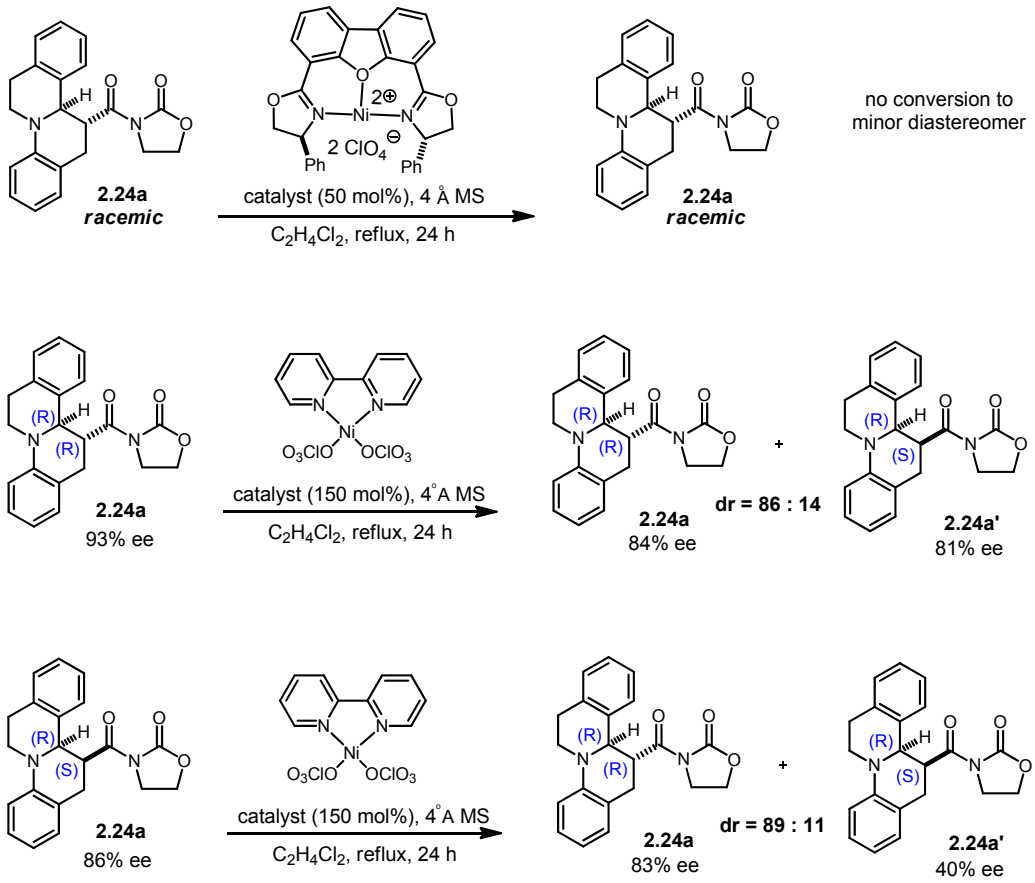
The absolute configuration of the minor diastereomer **2.24a′** was determined as outlined in Figure 2.12. Upon exposure to DBU, partial equilibration to the major diastereomer **2.24a** with slight erosion of enantioselectivity was observed. As revealed by HPLC correlation, compound **2.24a** was recovered as the same enantiomer (*R*,*R*) that is formed in the catalytic reaction. This establishes the absolute configuration of **2.24a'** as shown.

Figure 2.12 **Interconversion between 2.24a and 2.24a'**



We further explored the possibility of an interconversion between **2.24a** and **2.24a'** under the reaction conditions (Figure 2.12). Due to its higher reactivity, we have opted to use the nickel catalyst for this study. As outlined in Figure 2.13, exposure of either diastereomer to the reaction conditions leads to the formation of a mixture of diastereomers (the different ratios suggest that a thermodynamic equilibrium had not been reached after 24 hours). Epimerization of the stereogenic center attached to the acyl oxazolidinone could occur through an enolization process similar to that seen for DBU. In addition, given the slight erosion in enantioselectivity, a retro-Mannich/Mannich mechanism might be operative.

Figure 2.13 **Equilibration/Reversibility Experiments**



Furthermore, as shown in Figure 2.13, no enantioselectivity and no conversion to the minor diastereomer were observed when the racemic product **2.24a** was refluxed in dichloroethane for 24 hours in the presence of 50 mol% of nickel perchlorate and enantiopure Ph-DBFOX. The product **2.24a** with 93% ee was exposed to 150 mol% of nickel perchlorate and an achiral ligand (2,2-bipyridine), resulting in slightly lower ee value and both diastereomers (Figure 2.13). Similarly, the exposure of the minor diastereomer **2.24a'** with 86% ee to the achiral metal complex gave rise to both diastereomers with lower ee values, especially the resulting minor diastereomer, which was recovered with only 40% ee (Figure 2.13). This significant erosion of

enantioselectivity again suggested that a retro-Mannich/Mannich mechanism would be more likely to occur here.

2.5 Conclusion

In summary, we have demonstrated that intramolecular redox–neutral C–H bond functionalizations can be significantly accelerated by gadolinium triflate, providing a rapid generation of polycyclic tetrahydroquinolines under very mild conditions. More importantly, we have described the first example of a catalytic enantioselective hydride shift/ring closure reaction cascade by applying acyl oxazolidinone as an alternative hydride acceptor moiety under the catalysis of a magnesium-(-)Ph-DBFOX complex. Ring-fused tetrahydroquinolines are obtained in good yields with high levels of enantioselectivity. Recently, Kim disclosed an enantioselective organocatalytic approach for this type of transformation.[14] It is anticipated that this study will set the stage for a variety of other catalytic enantioselective processes involving hydride shift triggered reaction cascades.

Experimental Section

General Information: Starting materials, reagents and solvents were purchased from commercial sources and were used as received. Reactions were run under an atmosphere of nitrogen unless mentioned otherwise. Purification of the reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light or permanganate stain followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz instrument and chemical shifts are reported in parts per million (ppm) downfield from TMS, using residual $CDCl_3$ (7.26 ppm) or DMSO-d_6 (2.49 ppm) as an internal standard. Data are reported as follows: chemical shift, multiplicity (app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex; br = broad), coupling constant(s) in Hz and integration. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz and VNMRS-400 MHZ instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm; DMSO-d_6 at 39.7 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. Optical rotations were recorded on Perkin-Elmer 343 polarimeter at 589 nm and 293 K. HPLC analyses were carried out on an Agilent 1100 series HPLC with auto sampler and a multiple wavelength detector.

General procedure for the preparation of aminobenzaldehyde:

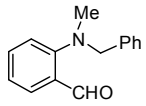
To a solution of 2-fluorobenzaldehyde (2.48 g, 20 mmol) and potassium carbonate (3.18 g, 23 mmol) in DMF (20 mL) was added the amine (23 mmol). The resulting reaction mixture was heated under reflux until complete consumption of 2-fluorobenzaldehyde as judged by TLC analysis. The reaction mixture was subsequently allowed to cool to room temperature, diluted with water (100 mL), and extracted with ethyl acetate (3 x 75 mL). The combined organic layers were washed with a saturated NH_4C1 solution (3 x 75 mL) and subsequently dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by column chromatography.

2-(azocan-1-yl)benzaldehyde (2.7m): The title compound was prepared according to the general procedure (3 h) and isolated as a liquid in 65% yield. (R_f = 0.50 in 80% CH_2Cl_2/Hex); IR (film) 2924, 2849, 1681, 1594, 1483, 1449, 1374, 1274, 1186, 1160, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.23 (d, *J* = 4.6Hz, 1H), 7.68 (d, *J* = 7.7Hz, 1H), 7.49 – 7.26 (m, 1H), 7.07 (d, *J* = 8.4Hz, 1H), 6.86 (t, *J* = 7.4Hz, 1H), 3.48 – 3.19 (comp, 4H), 1.87 – 1.46 (comp, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) 191.3, 155.8, 134.6, 130.6, 127.7, 119.9, 119.5, 55.5, 27.8, 27.4, 25.2; Chemical Formula: $C_{14}H_{19}NO$, *m/z* (ESIMS) 218.6 $[M + H]^+$.

2-(dibenzylamino)benzaldehyde (2.7p): The title compound was prepared according to the general procedure (12 h) and isolated as a liquid in 25% yield (R_f = 0.61 in 80% CH_2Cl_2/Hex); IR (film) 3062, 3028, 2938, 2840, 2733, 1686, 1595, 1494, 1481, 1452, 1384, 1365, 1276, 1254, 1189, 1161, 1028, 833, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.57 (s, 1H), 7.91 – 7.81 (m, 1H), 7.51 – 7.41 (m, 1H), 7.39 –

7.24 (comp, 6H), 7.20 (d, *J* = 7.7Hz, 4H), 7.09 (dt, *J* = 9.7, 20.3Hz, 2H), 4.30 (s, 4H).; ^{13}C NMR (125 MHz, $CDCl_3$) 191.31, 154.42, 137.12,134.44, 129.83, 129.57, 128.64, 128.43, 127.44, 122.89, 122.40, 58.70; Chemical Formula: $C_{21}H_{19}NO$, *m/z* (ESIMS) 324.7 $[M + Na]^+$.

2-(benzyl)methyl)amino)benzaldehyde (2.7q): The title compound was prepared according to the general procedure (4 h) and isolated as a liquid in 75% yield (R_f = 0.42 in 15% EtOAc/Hex); IR (film) 2843, 1684, 1596, 1483, 1452, 1276, 1190, 945, 832, 763, 734, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 10.42 (s, 1H), 7.84 (dd, *J* = 1.7, 7.7, 1H), 7.49 (ddd, *J* = 1.8, 7.2, 8.3, 1H), 7.41 – 7.22 (comp, 5H), 7.20 – 7.01 (comp, 2H), 4.35 (s, 2H), 2.83 (s, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) 191.14, 155.57, 137.30, 134.57, 130.07, 128.45, 128.25, 128.02, 127.34, 121.54, 119.41, 62.26, 42.24.; Chemical Formula: $C_{15}H_{15}NO$, *m/z* (ESIMS) 258.1 $[M + Na]^+$.



General procedure for the preparation of alkylidenemalonates:

A mixture of aminobenzaldehyde (20 mmol), malonate (21 mmol), piperidine (3.4 mmol) and benzoic acid (2.2 mmol) in benzene (21 ml) was refluxed using Dean-Stark trap and monitored by TLC. After completion of the reaction, benzene was evaporated off and the reaction mixture was dissolved in ethyl acetate. Then, the organic solution was washed sequentially with water (20 ml), 5% aqueous HCl (2 x 20 ml), saturated aqueous sodium bicarbonate (2 x 20 ml), brine (20 ml) and dried over magnesium sulfate. After filtration, the solvent was evaporated and crude reaction mixture was purified by either by triturating with methanol or by column chromatography.

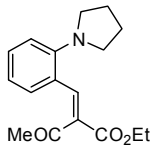
diethyl 2-(2-(pyrrolidin-1-yl)benzylidene)malonate (2.1b): The reaction was carried out according to the general procedure (12 h). The product was obtained as a yellow liquid in 90% yield. (R_f = 0.49 in 20% EtOAc/Hex); IR (film) 2979, 2873, 2834, 1732, 1620, 1597, 1481, 1451, 1373, 1349, 1257, 1207, 1163, 1096, 1066, 1025, 955, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.99 (d, J = 6.1, 1H), 7.28 – 7.17 (comp, 2H), 6.81 (d, J = 8.2, 1H), 6.75 (app t, J = 7.5, 1H), 4.29 (q, J = 7.1, 2H), 4.27 – 4.21 (m, 2H), 3.40 – 3.21 (m, 4H), 2.01 – 1.85 (m, 4H), 1.42 – 1.29 (m, 3H), 1.20 (app q, J = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 166.68, 164.70, 150.07, 144.73, 130.55, 129.68, 123.58, 122.71, 118.40, 114.41, 61.28, 61.25, 52.26, 25.62, 14.17, 13.87; Chemical Formula: $C_{18}H_{23}NO_4$, *m/z* (ESIMS) 656.9 $[2M + Na]^+$.

diisopropyl 2-(2-(pyrrolidin-1-yl)benzylidene)malonate (2.1c): The reaction was carried out according to the general procedure (24 h). The product was obtained as a yellow solid in 94% yield. (R_f = 0.40 in 15% EtOAc/Hex); mp: 90 – 91 °C; IR (KBr) 2980, 2932, 2967, 2935, 1728, 1709, 1612, 1599, 1495, 1484, 1467, 1452, 1375, 1357, 1275, 1210, 1193, 1108, 1096, 1063, 929, 911, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.91 (s, 1H), 7.27 (d, *J* = 7.7, 1H), 7.18 (t, *J* = 7.7, 1H), 6.77 (d, *J* = 8.3, 1H), 6.72 (t, *J* = 7.5, 1H), 5.20 – 5.08 (comp, 2H), 3.27 (t, *J* = 6.3, 4H), 1.90 (app dd, *J* = 5.0, 7.7, 4H), 1.29 (d, *J* = 6.3, 6H), 1.21 (d, *J* = 6.3, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.98, 163.97, 149.80, 143.57, 130.27, 129.52, 124.35, 122.67, 118.20, 114.29, 68.54, 68.50, 52.03, 25.38, 21.63, 21.30.; Chemical Formula: $C_{20}H_{27}NO_4$, *m/z* (ESIMS) 346.2 $[M + H]^+$.

di-*tert*-butyl 2-(2-(pyrrolidin-1-yl)benzylidene)malonate (2.1d): The reaction was carried out according to the general procedure (12 h). The product was obtained as a yellow liquid in 95% yield. (R_f = 0.47 in 15% EtOAc/Hex); IR (film) 2976, 2873, 1712, 1622, 1597, 1481, 1451, 1392, 1367, 1272, 1158, 1096, 1067, 1031, 849, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.78 (s, 1H), 7.32 (d, *J* = 7.7, 1H), 7.23 – 7.16 (m, 1H), 6.79 (d, *J* = 8.3, 1H), 6.74 (app t, *J* = 7.4, 1H), 3.28 (t, *J* = 6.6, 4H), 1.96 – 1.87 (m, 4H), 1.54 (s, 9H), 1.50 – 1.43 (s, 9H).; ^{13}C NMR (125 MHz, $CDCl_3$) 165.97, 163.95, 149.76, 142.35, 130.07, 129.82, 126.85, 123.13, 118.16, 114.27, 81.64, 81.41, 52.04, 28.11, 27.88, 27.82, 27.78, 25.54.; Chemical Formula: $C_{22}H_{31}NO_4$, *m/z* (ESIMS) 374.2 $[M + H]^+$.

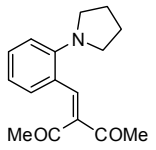
dibenzyl 2-(2-(pyrrolidin-1-yl)benzylidene)malonate (2.1e): The reaction was carried out according to the general procedure (12h). The product was obtained as a yellow liquid in 95% yield. (R_f = 0.48 in 20% EtOAc/Hex); IR (film) 3064, 3032, 2955, 2872, 1732, 1597, 1496, 1486, 1453, 1378, 1354, 1256, 1191, 1096, 1062, 1028, 955, 911, 749, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.06 (s, 1H), 7.41 – 7.29 (comp, 5H), 7.29 – 7.11 (comp, 8H), 6.79 (d, J = 8.3, 1H), 6.63 (t, J = 7.5, 1H), 5.27 (s, 2H), 5.19 (s, 2H), 3.26 (t, J = 6.5, 4H), 1.94 – 1.80 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 166.59, 164.63, 150.36, 146.24, 135.98, 135.46, 130.98, 129.93, 128.74, 128.66, 128.62, 128.38, 128.36, 128.12, 123.12, 122.78, 118.78, 114.74, 67.38, 67.08, 52.53, 25.81; Chemical Formula: $C_{28}H_{27}NO_4$, *m/z* (ESIMS) 464.2 $[M + Na]^+$.

(*E*)-ethyl 3-oxo-2-(2-(pyrrolidin-1-yl)benzylidene)butanoate (2.1f): The reaction was



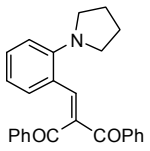
carried out according to the general procedure (2 h). The product was obtained as a yellow liquid in 91% yield. dr = 53 : 47, determined by integration of one set of ^{1}H-NMR signals (δminor 1.31 ppm, δmajor 1.17 ppm). (R_f = 0.31 in 15% EtOAc/Hex); IR (film) 2974, 1715, 1663, 1596, 1480, 1450, 1250, 1193, 1061, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereoisomer) 7.83 (d, *J* = 6.9, 1H), 7.24 – 7.21 (comp, 2H), 6.74 (app dd, *J* = 7.8, 15.6, 2H), 4.22 (dd, *J* = 7.2, 14.3, 2H), 3.28 – 3.25 (m, 4H), 2.39 (s, 3H), 1.93 (app d, *J* = 6.6, 4H), 1.17 (t, *J* = 7.1, 3H). ; ^{13}C NMR of diastereomeric mixture (125 MHz, $CDCl_3$) 202.31, 194.94, 167.80, 165.04, 150.15, 149.94, 143.87, 143.08, 131.87, 130.84, 130.73, 130.70, 130.49, 129.60, 122.92, 122.39, 118.67, 118.56,114.71, 114.52, 61.19, 61.16, 52.33, 52.08, 30.85, 26.86, 25.54, 25.52, 14.14, 13.79; Chemical Formula: $C_{17}H_{21}NO_3$, *m/z* (ESIMS) 288.1 $[M + H]^+$.

3-(2-(pyrrolidin-1-yl)benzylidene)penatane-2,4-dione (2.1g): The reaction was carried



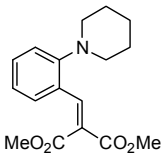
out according to the general procedure (1 h). The product was obtained as a yellow liquid in 95% yield. (R_f = 0.23 in 15% EtOAc/Hex); IR (film) 2968, 2871, 1709, 1683, 1657, 1595, 1479, 1450, 1354, 1281, 1239, 1163, 971, 753 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.84 (s, 1H), 7.29 – 7.23 (m, 1H), 7.10 (dd, *J* = 1.5, 7.7, 1H), 6.86 (dd, *J* = 0.7, 8.3, 1H), 6.81 – 6.75 (m, 1H), 3.30 (dd, *J* = 5.4, 7.8, 4H), 2.39 (s, 3H), 2.26 (s, 3H), 2.02 – 1.91 (m, 4H).; ^{13}C NMR (125 MHz, $CDCl_3$) 204.63, 196.37, 150.06, 142.40, 139.78, 131.29, 130.69, 122.65, 119.08, 114.99, 52.27, 31.15, 27.15, 25.54; Chemical Formula: $C_{16}H_{19}NO_2$, *m/z* (ESIMS) 258.3 $[M + H]^+$.

1,3-diphenyl-2-(2-(pyrrolidin-1-yl)benzylidene)propane-1,3-dione (2.1h): The



reaction was carried out according to the general procedure (6 h). The product was obtained as a yellow solid in 92% yield. (R_f = 0.25 in 15% EtOAc/Hex); mp: 134 – 136 °C; IR (KBr) 2974, 2945, 1671, 1627, 1594, 1477, 1446, 1368, 1342, 1284, 1230, 1210, 1175, 875, 761, 725, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.93 – 7.88 (comp, 2H), 7.87 – 7.82 (comp, 2H), 7.78 (s, 1H), 7.54 (ddd, *J* = 1.3, 2.5, 8.7, 1H), 7.50 – 7.42 (comp, 3H), 7.36 (dd, *J* = 4.8, 10.7, 2H), 7.17 (dd, *J* = 1.3, 7.7, 1H), 7.14 – 7.08 (m, 1H), 6.71 – 6.62 (m, 2H), 3.20 (t, *J* = 6.5, 4H), 2.01 – 1.75 (app t, *J*= *6.5*, 4H)..; ^{13}C NMR (125 MHz, $CDCl_3$) 196.27, 195.28, 150.15, 145.96, 137.74, 136.96, 136.63, 133.18, 132.32, 130.75, 130.68, 129.39, 129.08, 128.50, 128.40, 123.12, 118.81, 114.81, 52.08, 25.44.; Chemical Formula: $C_{26}H_{23}NO_2$, *m/z* (ESIMS) 404.1 $[M + Na]^+$.

dimethyl 2-(2-(piperidin-1-yl)benzylidene)malonate (2.1j): The reaction was carried



out according to the general procedure (12 h). The product was obtained as a yellow solid in 85% yield. (R_f = 0.48 in 20% EtOAc/Hex); mp: 78 – 80 °C; IR (film) 2936, 2862, 2792, 1735, 1621, 1598, 1485, 1450, 1435, 1379, 1358, 1290, 1258, 1214, 1101, 1069, 763 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.11 (s, 1H), 7.34 (dd, J = 4.6, 12.8, 2H), 7.01 (d, J = 7.9, 1H), 6.96 (t, J = 7.5, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 2.97 – 2.84 (m, 4H), 1.80 – 1.66 (m, 4H), 1.65 – 1.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 167.27, 164.96, 154.16, 142.45, 131.16, 128.78, 127.33, 124.08, 121.89, 118.43, 54.33, 52.43, 52.40, 26.38, 24.20; Chemical Formula: $C_{17}H_{21}NO_4$, *m/z* (ESIMS) 628.9 $[M + H]^+$.

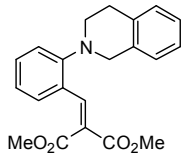
dimethyl 2-(2-morpholinobenzylidene)malonate (2.1k): The reaction was carried out according to the general procedure (4 h). The product was obtained as a yellow liquid in 98% yield. (R_f = 0.11 in 20% EtOAc/Hex); IR (film) 3037, 2954, 2885, 2852, 1716, 1624, 1597, 1485, 1448, 1362, 1332, 1266, 1165, 1117, 1069, 1042, 936, 920, 765, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.10 (s, 1H), 7.42 – 7.30 (m, 2H), 7.02 (app t, J = 8.1, 2H), 3.95 – 3.81 (comp, 7H), 3.80 – 3.72 (m, 3H), 3.05 – 2.90 (m, 4H)**;** ^{13}C NMR (125 MHz, $CDCl_3$) 166.92, 164.64, 152.46, 141.89, 131.29, 129.00, 127.46, 125.01, 122.84, 118.25, 67.09, 53.06, 52.50, 52.42; Chemical Formula: $C_{16}H_{19}NO_5$, *m/z* (ESIMS) 306.1 $[M + H]^+$.

dimethyl 2-(2-(azepan-1-yl)benzylidene)malonate (2.1l): The reaction was carried out according to the general procedure (1.5 h). The product was obtained as a yellow liquid in 95% yield. (R_f = 0.49 in 20% EtOAc/Hex); IR (film) 2929, 2854, 1735, 1620, 1595, 1486, 1448, 1361, 1259, 1215, 1163, 1104, 1069, 762 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$) 8.09 (s, 1H), 7.28 (app t, J = 7.8, 2H), 7.06 (app t, J = 10.0, 1H), 6.89 (app t, J = 7.5, 1H), 3.85 (s, 3H), 3.76 (d, J = 4.1, 3H), 3.27 – 3.12 (comp, 4H), 1.86 – 1.66 (comp, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) 167.20, 164.83, 155.06, 144.04, 130.75, 128.93, 126.64, 123.51, 120.84, 118.96, 56.06, 52.34, 52.31, 29.20, 27.04; Chemical Formula: $C_{18}H_{23}NO_4$, *m/z* (ESIMS) 657.0 $[2M + Na]^+$.

dimethyl 2-(2-(azocan-1-yl)benzylidene)malonate (2.1m): The reaction was carried out according to the general procedure (3 h). The product was obtained as a yellow liquid in 95% yield. (R_f = 0.37 in 15% EtOAc/Hex); IR (film) 2924, 2847, 1735, 1617, 1595, 1462, 1435, 1257, 1211, 1069, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.18 (s, 1H), 7.33 – 7.24 (comp, 2H), 7.14 (d, *J* = 8.2, 1H),

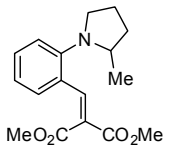
6.89 (app t, *J* = 7.5, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.35 – 3.09 (m, 4H), 1.72 (comp, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) 167.22, 164.84, 154.48, 144.31, 130.96, 129.13, 127.16, 123.64, 121.06, 119.85, 55.21, 52.37, 28.13, 27.58, 25.01.; Chemical Formula: $C_{19}H_{25}NO_4$, *m/z* (ESIMS) 332.2 $[M + H]^+$.

dimethyl 2-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzylidene)malonate (2.1n): The



reaction was carried out according to the general procedure (1 h). The product was obtained as a yellow liquid in 86% yield. (R_f = 0.48 in 20% EtOAc/Hex); IR (film) 3060, 3024, 2951, 2839, 1735, 1622, 1598, 1488, 1455, 1433, 1380, 1358, 1259, 1215, 1165, 1102, 1069, 936, 757 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.13 (s, 1H), 7.38 (dd, *J* = 4.5, 11.3, 2H), 7.23 – 7.18 (comp, 3H), 7.17 – 7.10 (comp, 2H), 7.03 (app t, *J* = 7.5, 1H), 4.30 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.29 (t, *J* = 5.8, 2H), 3.03 (t, *J* = 5.7, 2H).**;** ^{13}C NMR (125 MHz, $CDCl_3$) 167.00, 166.80, 164.68, 152.34, 142.30, 134.40, 134.28, 131.06, 129.00, 128.93, 127.23, 126.30, 125.84, 124.71, 122.19, 118.24, 53.11, 52.74, 52.42, 52.39, 52.36.; Chemical Formula: $C_{21}H_{21}NO_4$, *m/z* (ESIMS) 231.1 $[M + H]^+$.

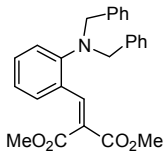
dimethyl 2-(2-(2-methylpyrrolidin-1-yl)benzylidene)malonate (2.1o): The reaction



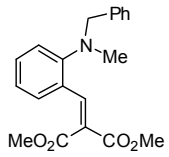
was carried out according to the general procedure (4 h). The product was obtained as a yellow liquid in 95% yield. (R_f = 0.28 in 15% EtOAc/Hex); IR (film) 2953, 1735, 1620, 1596, 1474, 1352, 1260, 1214, 1057, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.97 (s, 1H), 7.31 – 7.21 (comp, 2H), 6.90 (d, *J* = 8.1, 1H), 6.82 (app t, *J* = 7.5, 1H), 3.85 (d, *J* = 4.4, 3H), 3.81 – 3.73 (comp, 4H), 3.63 – 3.54 (m, 1H), 3.08 (app td, *J* = 2.7, 8.9, 1H), 2.25 – 2.13 (m, 1H), 1.89 (ddd, *J* = 7.2, 9.6, 11.7, 1H), 1.83 – 1.70 (m, 1H), 1.64 (app dq, *J* = 8.0, 11.9, 1H), 1.10 (d, *J* = 6.0,

3H).; ^{13}C NMR (125 MHz, $CDCl_3$) 167.28, 165.17, 149.85, 144.68, 130.56, 129.19, 125.23, 122.92, 119.52, 116.41, 55.50, 55.33, 52.42, 52.37, 34.25, 24.50, 19.09; Chemical Formula: $C_{17}H_{21}NO_4$, *m/z* (ESIMS) 304.2 $[M + H]^+$.

dimethyl 2-(2-(dibenzylamino)benzylidene)malonate (2.1p): The reaction was carried out according to the general procedure (1.5 h). The product was obtained as a yellow liquid in 95% yield. (R_f = 0.25 in 15% EtOAc/Hex); IR (film) 3035, 2958, 2831, 1734, 1623, 1595, 1489, 1452, 1435, 1363, 1262, 1214, 109, 764, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.47 (s, 1H), 7.44 – 7.39 (m, 1H), 7.32 (dd, *J* = 4.8, 9.8, 4H), 7.29 – 7.22 (comp, 7H), 7.02 (t, *J* = 7.5, 1H), 6.93 (d, *J* = 8.1, 1H), 4.22 (s, 4H), 3.87 (s, 3H), 3.80 (s, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) 166.82, 164.53, 150.66, 142.95, 137.31, 130.45, 128.86, 128.52, 128.43, 128.23, 127.04, 125.24, 122.63, 121.58, 57.20, 52.34, 52.21.; Chemical Formula: $C_{26}H_{25}NO_4$, *m/z* (ESIMS) 438.2 $[M + Na]^+$.



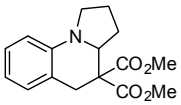
dimethyl 2-(2-(benzyl(methyl)amino)benzylidene)malonate (2.1q): The reaction was carried out according to the general procedure (1.5 h). The product was obtained as a yellow solid in 96% yield. (R_f = 0.40 in 20% EtOAc/Hex); mp: 93 – 95 °C; IR (film) 3060, 3019, 2949, 2844, 2792, 1727, 1618, 1596, 1487, 1436, 1364, 1298, 1266, 1071, 947, 768, 737, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.25 (s, 1H), 7.39 – 7.21 (comp, 7H), 7.09 – 6.93 (comp, 2H), 4.14 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 167.01, 164.68, 152.87, 143.03, 137.69, 130.92, 129.02, 128.35, 128.27, 127.45, 127.17, 124.78, 122.09, 119.23, 61.95, 52.38, 52.36, 40.61; Chemical Formula: $C_{20}H_{21}NO_4$, *m/z* (ESIMS) 340.3 $[M + H]^+$.



General procedure for the hydride shift reaction of alkylidenemalonates with Gadolinium triflate:

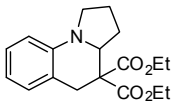
To a stirred solution of alkylidenemalonate (1 mmol) in 10 mL of CH_3CN was added Gadolinium triflate (0.05 mmol) and was stirred at room temperature. The reaction was monitored by TLC. After the completion of the reaction, the solvent was evaporated off. The crude product was dissolved in dichloromethane (20 ml), washed with 25 ml of 1M NaOH. The aqueous layer was extracted with dichloromethane (20 ml x 3). The combined organic layers were washed with brine (25 ml) and dried with sodium sulfate. The solvent was evaporated off and the crude product was purified by column chromatography.

dimethyl 1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4,4(5H)-dicarboxylate (2.2a):



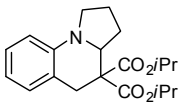
The reaction was carried out according to the general procedure (15 min). The product was obtained as a white solid in 90% yield. (R_f = 0.30 in 15% EtOAc/Hex); mp: 85 – 86 °C; IR (KBr) 2952, 2844, 1753, 1731, 1606, 1506, 1460, 1436, 1292, 1266, 1244, 1209, 1162, 1103, 1062, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.10 (app t, *J* = 7.7, 1H), 7.03 (d, *J* = 7.4, 1H), 6.62 (app t, *J* = 7.4, 1H), 6.48 (d, *J* = 8.1, 1H), 3.85 – 3.76 (comp, 4H), 3.59 (d, *J* = 0.9, 3H), 3.44 – 3.23 (comp, 4H), 2.52 – 2.40 (m, 1H), 2.23 – 2.04 (comp, 2H), 2.03 – 1.90 (m, 1H).; ^{13}C NMR (125 MHz, $CDCl_3$) 171.35, 168.94, 143.70, 128.37, 127.43, 118.56, 115.88, 110.84, 62.02, 53.13, 52.55, 52.01, 47.30, 36.79, 27.77, 23.40; Chemical Formula: $C_{16}H_{19}NO_4$, *m/z* (ESIMS) 290.1 $[M + H]^+$.

diethyl 1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4,4(5H)-dicarboxylate (2.2b): The



reaction was carried out according to the general procedure (15 mins). The product was obtained as a oil in 82% yield. (R_f = 0.19 in 50% CH_2Cl_2/Hex); IR (film) cm^{-1} 3060, 2979, 2897, 2833, 1731, 1605, 1504, 1461, 1366, 1355, 1339, 1296, 1266, 1237, 1161, 1099, 1058, 1042, 745 ^{1}H NMR (500 MHz, $CDCl_3$) 7.08 (app t, J = 7.7, 1H), 7.02 (d, J = 7.4, 1H), 6.60 (app td, J = 0.9, 7.4, 1H), 6.46 (d, J = 8.0, 1H), 4.33 – 4.20 (comp, 2H), 4.12 – 3.95 (comp, 2H), 3.79 (dd, J = 6.9, 9.0, 1H), 3.33 (app ddt, J = 10.0, 25.1, 32.2, 5H), 2.50 (app dtd, J = 8.7, 10.3, 12.3, 1H), 2.24 – 1.87 (comp, 3H), 1.31 (dd, J = 5.1, 9.2, 3H), 1.06 (dd, J = 5.0, 9.2, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 170.96, 168.48, 143.88, 128.44, 127.41, 118.80, 115.82, 110.78, 62.24, 61.38, 60.66, 53.10, 47.43, 37.00, 27.84, 23.54, 14.02, 13.78; Chemical Formula: $C_{18}H_{23}NO_4$, *m/z* (ESIMS) 318.2 $[M + H]^+$.

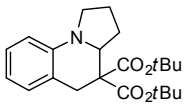
diisopropyl 1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4,4(5H)-dicarboxylate (2.2c):



The reaction was carried out according to the general procedure (10min). The product was obtained as a yellow solid in 87% yield. (R_f = 0.31 in 50% CH_2Cl_2/Hex); mp: 82 – 86 °C; IR (film) 2979, 29332, 2868, 2833, 1727, 1605, 1505, 1461, 1385, 1374, 1357, 1266, 1243, 1201, 1182, 1162, 1109, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.07 (app t, J = 7.7, 1H), 7.00 (d, J = 7.4, 1H), 6.57 (app t, J = 7.1, 1H), 6.45 (d, J = 8.0, 1H), 5.13 (hept, J = 6.3, 1H), 4.88 (hept, J = 6.2, 1H), 3.78 (dd, J = 6.7, 9.2, 1H), 3.40 (app td, J = 2.7, 8.5, 1H), 3.26 (ddd, J = 15.7, 21.9, 22.4, 3H), 2.59 – 2.42 (m, 1H), 2.19 – 2.03 (comp, 2H), 2.02 – 1.86 (m, 1H), 1.28 (dd, J = 1.6, 6.2, 6H), 1.11 (d, J = 6.3, 3H), 0.99 (d, J = 6.2, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 170.62, 167.99, 143.90, 128.50, 127.48, 118.71, 115.66, 110.66, 69.00, 68.01, 62.42, 52.64, 47.53, 37.20, 27.79,

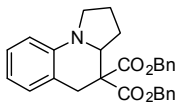
23.69, 21.60, 21.56, 21.42, 21.31; Chemical Formula: $C_{20}H_{27}NO_4$, *m/z* (ESIMS) 713.1 $[2M + Na]^+$.

di-*tert*-butyl 1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4,4(5H)-dicarboxylate (2.2d):



The reaction was carried out according to the general procedure (0.5 h). The product was obtained as a white solid in 70% yield. (R_f = 0.60 in 15% EtOAc/Hex); mp: 64 – 65 °C; IR (KBr) 2975, 1724, 1638, 1605, 1504, 1477, 1460, 1392, 1368, 1277, 1250, 1158, 849, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.07 (app t, *J* = 7.7, 1H), 7.01 (d, *J* = 7.3, 1H), 6.57 (app t, *J* = 7.3, 1H), 6.43 (d, *J* = 8.1, 1H), 3.74 (dd, *J* = 6.9, 9.0, 1H), 3.39 (app td, *J* = 2.7, 8.4, 1H), 3.25 (dd, *J* = 8.9, 15.7, 2H), 3.13 (d, *J* = 15.5, 1H), 2.53 (app dt, *J* = 10.3, 20.5, 1H), 2.21 – 2.04 (comp, 2H), 2.02 – 1.89 (m, 1H), 1.51 (s, 9H), 1.24 (s, 9H).; ^{13}C NMR (125 MHz, $CDCl_3$) 170.47, 167.75, 144.04, 128.44, 127.32, 119.25, 115.52, 110.46, 81.75, 80.84, 62.51, 53.77, 47.48, 37.47, 27.91, 27.82, 27.63, 23.76; Chemical Formula: $C_{22}H_{31}NO_4$, *m/z* (ESIMS) 396.1 $[M + Na]^+$.

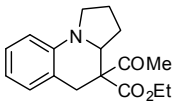
dibenzyl 1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4,4(5H)-dicarboxylate (2.2e):



The reaction was carried out according to the general procedure B (2 h). The product was obtained as colorless oil in 57% yield. (R_f = 0.70 in 50% CH_2Cl_2/Hex); IR (film) 3064, 3033, 2958, 2848, 1732, 1605, 1577, 1500, 1459, 1372, 1356, 1339, 1325, 1265, 1227, 1161, 1120, 1099, 1055, 1041, 990, 909, 745, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.41 – 7.28 (comp, 5H), 7.27 – 7.18 (comp, 3H), 7.10 (app t, J = 7.7, 1H), 7.01 (ddd, J = 2.9, 4.9, 7.2, 3H), 6.61 (app td, J = 0.9, 7.4, 1H), 6.45 (d, J = 8.0, 1H), 5.20 (s, 2H), 5.03 (d, J = 12.4, 1H), 4.95 (d, J = 12.5, 1H), 3.81 (dd, J = 6.9, 8.9, 1H), 3.44 (d, J = 15.9, 1H), 3.31 (app dt, J = 9.7, 22.9, 2H), 3.20 (dd, J = 8.3, 15.8, 1H), 2.50 – 2.36 (m, 1H), 2.14 – 2.02 (m, 1H), 2.01 – 1.80 (comp, 2H); ^{13}C NMR

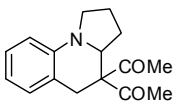
(125 MHz, $CDCl_3$) 170.73, 168.38, 143.88, 135.50, 135.39, 128.59, 128.57, 128.34, 128.32, 128.04, 127.92, 127.83, 127.54, 118.77, 116.06, 111.05, 67.21, 66.64, 62.29, 53.57, 47.35, 36.95, 27.83, 23.44; Chemical Formula: $C_{28}H_{27}NO_4$, *m/z* (ESIMS) 464.3 $[M + Na]^+$.

ethyl 4-acetyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline-4-carboxylate (2.2f):



The reaction was carried out according to the general procedure (5min). The product was obtained as a pink solid in 55% yield as a diastereomer (dr = 36 : 64), determined by integration of one set of ^{1}H-NMR signals (δminor 1.31 ppm, δmajor 1.17 ppm) in 55% yield. (R_f = 0.21 in 50% CH_2Cl_2/Hex); IR (film) 2977, 2864, 1738, 1712, 1604, 1577, 1505, 1478, 1460, 1355, 1337, 1297, 1260, 1203, 1161, 1101, 1042, 745, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.10 (dd, J = 8.5, 16.7, 1H), 7.05 – 7.00 (comp, 1H), 6.65 – 6.57 (comp, 1H), 6.46 (d, J = 8.0, 1H), 4.14 – 4.00 (comp, 2H), 3.70 (dd, J = 6.7, 9.1, 1H), 3.44 – 3.23 (comp, 3H), 3.10 (d, J = 15.5, 1H), 2.43 – 2.24 (comp, 4H), 2.20 – 1.87 (comp, 3H), 1.07 (app t, J = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 204.74, 203.51, 171.56, 169.77, 143.94, 143.74, 128.39, 128.36, 127.86, 127.33, 118.95, 117.59, 115.78, 115.76, 110.98, 110.71, 62.34, 61.86, 61.36, 60.81, 59.07, 57.10, 47.33, 47.01, 36.42, 36.05, 28.04, 27.68, 27.64, 27.56, 23.52, 23.46, 13.98, 13.74; Chemical Formula: $C_{17}H_{21}NO_3$, *m/z* (ESIMS) 288.2 $[M + H]^+$.

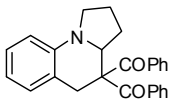
1,1'-(1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline-4,4-diyl)diethanone (2.2g): The



reaction was carried out according to the general procedure (3 h). The product was obtained as an oil in 76% yield. (R_f = 0.31 in 15% EtOAc/Hex); IR (film) 2083, 1715, 1689, 1643, 1604, 1503, 1442, 1352, 1184 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.12 (app t, *J* = 7.7, 1H), 7.08 (d, *J* = 7.4, 1H), 6.65 (app t, *J* =

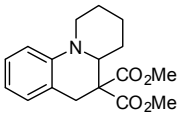
7.4, 1H), 6.49 (d, *J* = 8.1, 1H), 3.64 (app dt, *J* = 7.7, 15.2, 1H), 3.36 – 3.23 (comp, 3H), 3.15 (d, *J* = 16.5, 1H), 2.27 – 2.16 (comp, 4H), 2.06 – 1.88 (comp, 6H).; ^{13}C NMR (125 MHz, $CDCl_3$) 207.51, 205.57, 144.06, 128.57, 127.86, 118.09, 116.24, 111.25, 63.81, 61.19, 46.77, 34.52, 29.09, 27.56, 27.43, 23.11.; Chemical Formula: $C_{16}H_{19}NO_2$, *m/z* (ESIMS) 258.2 $[M + H]^+$.

(1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline-4,4-diyl)bis(phenylmethanone)



(2.2h): The reaction was carried out according to the general procedure (3 h). The product was obtained as yellow oil in 92% yield. (R_f = 0.44 in 15% EtOAc/Hex); IR (film) 3064, 2961, 2848, 1680, 1658, 1604, 1578, 1504, 1460, 1446, 1353, 1337, 1297, 1230, 1203, 1180, 1160, 941, 909, 732, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.94 – 7.89 (comp, 2H), 7.67 – 7.62 (comp, 2H), 7.52 – 7.46 (m, 1H), 7.44 – 7.34 (comp, 3H), 7.27 (t, *J* = 7.5, 2H), 7.11 (t, *J* = 7.7, 1H), 6.81 (d, *J* = 7.3, 1H), 6.61 – 6.50 (comp, 2H), 3.96 (dd, *J* = 6.3, 9.7, 1H), 3.49 (app q, *J* = 16.0, 2H), 3.42 – 3.33 (comp, 2H), 2.19 (app dq, *J* = 9.9, 14.0, 1H), 1.99 (app dt, *J* = 6.1, 10.9, 1H), 1.93 – 1.83 (comp, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 198.80, 197.52, 144.68, 138.01, 137.05, 132.85, 132.26, 129.21, 128.84, 128.56, 128.23, 128.16, 127.51, 119.51, 116.35, 111.21, 64.38, 63.26, 47.45, 38.73, 28.78, 23.77.; Chemical Formula: $C_{26}H_{23}NO_2$, *m/z* (ESIMS) 404.2 $[M + Na]^+$.

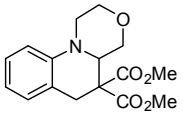
dimethyl 2,3,4,4a-tetrahydro-1*H*-pyrido[1,2-a]quinoline-5,5(6*H*)-dicarboxylate (2.2j):



The reaction was carried out according to the general procedure (3 h). The product was obtained as an oil in 91% yield. (R_f = 0.76 in 50% CH_2Cl_2/Hex); IR (film) 3072, 2996, 2927, 2855, 1735, 1602, 1502, 1456, 1352, 1209, 1144, 1025, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.09 (app t, J = 7.9, 1H), 7.05 (d, J =

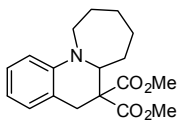
7.2, 1H), 6.75 (d, J = 8.3, 1H), 6.66 (app t, J = 7.3, 1H), 4.07 – 3.97 (comp, 2H), 3.76 (s, 3H), 3.62 (s, 3H), 3.38 (d, J = 15.8, 1H), 3.17 (d, J = 16.0, 1H), 3.09 – 2.97 (m, 1H), 1.90 (d, J = 13.1, 1H), 1.81 – 1.56 (comp, 2H), 1.55 – 1.41 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 169.64, 169.34, 143.54, 128.83, 127.39, 120.47, 116.91, 112.09, 59.75, 56.79, 52.62, 52.45, 48.43, 29.79, 25.74, 25.23, 22.47; Chemical Formula: $C_{17}H_{21}NO_4$, *m/z* (ESIMS) 628.9 $[M + H]^+$.

dimethyl 1,2,4,4a-tetrahydro-[1,4]oxazino[4,3-a]quinoline-5,5(6H)-dicarboxylate



(2.2k): The reaction was carried out according to the general procedure (12 h, 40°C). The product was obtained as a solid in 78% yield. (R_f = 0.25 in 20% EtOAc/Hex); mp: 104 – 106 °C; IR (film) 2954, 2854, 1736, 1604, 1496, 1436, 1339, 1256, 1224, 1175, 1123, 1068, 1036, 955, 753, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.16 – 7.09 (m, 1H), 7.03 (d, J = 6.9, 1H), 6.79 – 6.71 (comp, 2H), 3.99 – 3.80 (comp, 3H), 3.77 – 3.62 (comp, 9H), 3.18 (ddd, J = 8.8, 12.3, 20.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 169.80, 168.81, 144.50, 128.66, 127.69, 121.69, 118.67, 112.66, 67.51, 65.97, 58.54, 55.47, 52.94, 52.63, 48.07, 33.33; Chemical Formula: $C_{16}H_{19}NO_5$, m/z (ESIMS) 632.8 $[2M + Na]^+$.

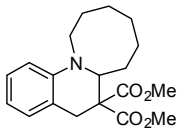
dimethyl 6a,7,8,9,10,11-hexahydroazepino[1,2-a]quinoline-6,6(5*H*)-dicarboxylate



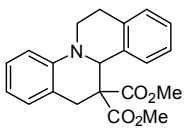
(2.2l): The reaction was carried out according to the general procedure (20 min). The product was obtained as a white solid in 82% yield. (R_f = 0.23 in 50% CH_2Cl_2/Hex); mp: 111 – 114 °C; IR (film) 2949, 2855, 1739, 1603, 1497, 1457, 1435, 1341, 1236, 1162, 1139, 1070, 1030, 999, 749 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.06 (app t, J = 7.2, 2H), 6.65 – 6.53 (comp, 2H), 4.15 (d, J = 7.8, 1H), 3.97 – 3.85 (m, 1H), 3.78 (d, J = 1.4, 3H), 3.63 (d, J = 1.4, 3H), 3.43 (d, J = 17.0, 1H), 3.31 (d, J

= 17.0, 1H), 3.26 – 3.17 (m, 1H), 2.12 – 1.99 (m, 1H), 1.75 – 1.37 (comp, 7H).; ^{13}C NMR (125 MHz, $CDCl_3$) 169.65, 169.47, 142.36, 128.98, 127.28, 116.90, 115.30, 109.72, 60.26, 55.37, 52.53, 49.69, 30.59, 28.47, 27.22, 25.98, 25.61, 25.45; Chemical Formula: $C_{18}H_{23}NO_4$, *m/z* (ESIMS) 318.1 $[M + H]^+$.

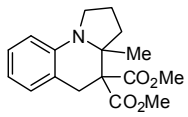
dimethyl 7,8,9,10,11,12-hexahydro-5*H*-azocino[1,2-a]quinoline-6,6(6a*H*)-dicarboxylate (2.2m): The reaction was carried out according to the general procedure (5 min). The product was obtained as an oil in 81% yield. (R_f = 0.34 in 15% EtOAc/Hex); IR (film) 3023, 2924, 2849, 1733, 1603, 1574, 1500, 1450, 1434, 1350, 1236, 1148, 1061, 1020, 947, 908, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.07 (dd, *J* = 8.1, 17.4, 2H), 6.69 – 6.57 (comp, 2H), 4.19 (dd, *J* = 3.9, 9.8, 1H), 3.88 – 3.73 (comp, 4H), 3.62 (s, 3H), 3.44 – 3.24 (comp, 3H), 1.95 – 1.29 (comp, 10H).; ^{13}C NMR (125 MHz, $CDCl_3$) 170.15, 169.75, 142.81, 129.28, 127.34, 117.87, 115.77, 111.56, 60.38, 55.79, 54.44, 52.84, 52.65, 30.65, 28.57, 27.67, 27.63, 27.38, 25.96.; Chemical Formula: $C_{19}H_{25}NO_4$, *m/z* (ESIMS) 332.2 $[M + H]^+$.



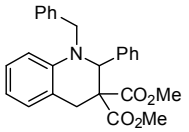
dimethyl 11b,13-dihydro-6*H*-isoquinolino[2,1-a]quinoline-12,12(7*H*)-dicarboxylate (2.2n): The reaction was carried out according to the general procedure (5 min). The product was obtained as a yellow solid in 87% yield. (R_f = 0.30 in 60% CH_2Cl_2/Hex); mp: 124 – 127 °C; IR (KBr) 3048, 3019, 2951, 2827, 1735, 1602, 1494, 1456, 1433, 1382, 1356, 1250, 1070, 960, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.23 – 7.10 (comp, 6H), 6.82 (d, J = 8.1, 1H), 6.78 (app t, J = 7.4, 1H), 5.09 (s, 1H), 3.98 – 3.91 (m, 1H), 3.76 – 3.69 (comp, 4H), 3.66 (d, J = 11.9, 3H), 3.57 (d, J = 16.5, 1H), 3.34 – 3.18 (comp, 2H), 2.82 – 2.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 170.74, 169.56, 145.27, 136.81, 134.83, 128.79, 128.52, 126.88, 126.79, 125.83, 125.60, 121.38,



118.08, 112.01, 61.23, 59.39, 52.79, 52.41, 43.75, 34.04, 28.08; Chemical Formula: $C_{21}H_{21}NO_4$, *m/z* (ESIMS) 352.2 $[M + H]^+$.



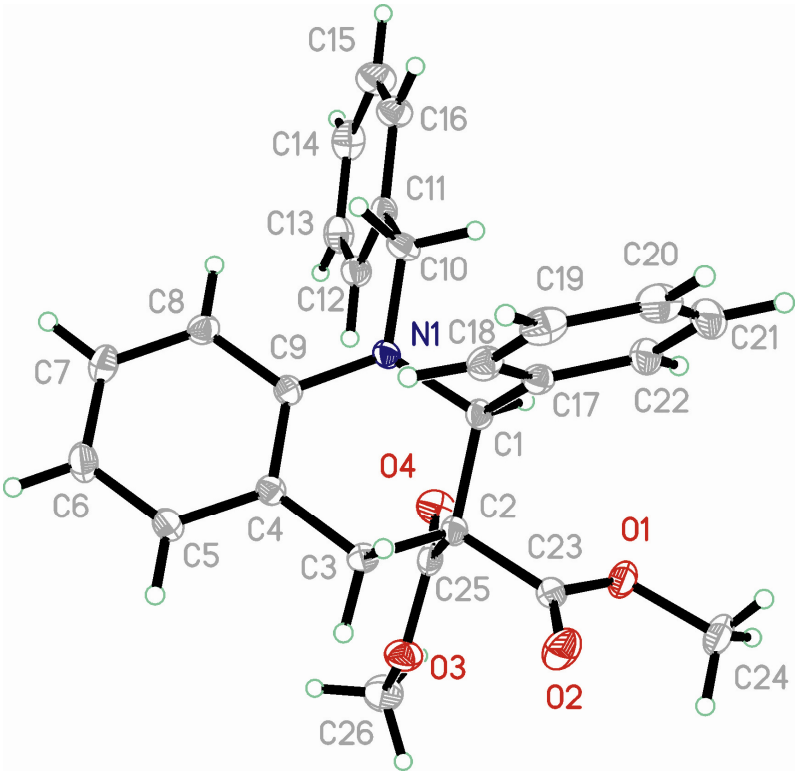
dimethyl 3a-methyl-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4,4(5*H*)-dicarboxylate (2.2o): The reaction was carried out according to the general procedure (5 min). The product was obtained as a liquid in 82% yield. (R_f = 0.37 in 15% EtOAc/Hex; IR (film) 2950, 2132, 1732, 1646, 1606, 1499, 1459, 1359, 1272, 1237, 1161, 1060, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.12 (app t, *J* = 7.7, 1H), 7.06 (d, *J* = 7.3, 1H), 6.61 (td, *J* = 1.0, 7.3, 1H), 6.52 (d, *J* = 7.9, 1H), 3.86 – 3.77 (comp, 3H), 3.69 – 3.60 (m, 1H), 3.59 – 3.51 (comp, 4H), 3.39 – 3.30 (m, 1H), 3.21 (d, *J* = 17.2, 1H), 2.65 (app td, *J* = 8.8, 12.0, 1H), 2.21 – 2.04 (comp, 2H), 1.95 (ddd, *J* = 1.5, 7.3, 12.4, 1H), 1.07 (s, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) 171.01, 169.11, 142.81, 128.58, 127.52, 116.52, 115.14, 111.51, 62.52, 56.15, 52.33, 52.09, 47.74, 35.76, 32.65, 24.19, 22.21.; Chemical Formula: $C_{17}H_{21}NO_4$, *m/z* (ESIMS) 304.2 $[M + H]^+$.



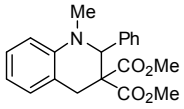
dimethyl 1-benzyl-2-phenyl-1,2-dihydroquinoline-3,3(4*H*)-dicarboxylate (2.2p): The reaction was carried out according to the general procedure (24 h, 40 °C). The product was obtained as a white solid in 70% yield. (R_f = 0.25 in 15% EtOAc/Hex); mp: 149 – 151 °C; IR (KBr) 2941, 2365, 1760, 1719, 1605, 1498, 1453, 1265, 1229, 1203, 1179, 1170, 1057, 955, 748, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.38 – 7.28 (comp, 7H), 7.25 (ddd, *J* = 3.8, 7.5, 15.0, 1H), 7.20 (app dt, *J* = 3.8, 7.6, 2H), 7.13 (d, *J* = 7.4, 1H), 7.07 (t, *J* = 7.8, 1H), 6.71 (t, *J* = 7.3, 1H), 6.57 (d, *J* = 8.2, 1H), 5.36 (d, *J* = 1.5, 1H), 4.53 (d, *J* = 17.2, 1H), 4.37 (d, *J* = 17.3, 1H), 3.69 (s, 3H), 3.60 (s, 3H), 3.50 – 3.34 (comp, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 169.57, 168.65, 144.30, 139.74, 138.42, 129.16, 128.35, 128.31, 128.22, 128.00, 127.95, 126.76, 126.70,

117.75, 116.55, 111.02, 64.71, 57.47, 55.00, 52.91, 52.50, 28.59.; Chemical Formula: $C_{26}H_{25}NO_4$, *m/z* (ESIMS) 416.2 $[M + H]^+$.

Product **2.2p** was further characterized by X–ray crystallography:



Dimethyl 1-methyl-2-phenyl-1,2-dihydroquinoline-3,3(4*H*)-dicarboxylate (2.2q): The



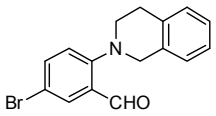
reaction was carried out according to the general procedure (2 h). The product was obtained as a white solid in 94% yield. (R_f = 0.74 in CH_2Cl_2); mp: 126 – 129 °C; IR (film) 3054, 3031, 2952, 2827, 2792, 1740, 1605, 1506, 1453, 1433, 1342, 1292, 1261, 1233, 1176, 1147, 1060, 1001, 748, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.27 (dd, J = 5.9, 9.3, 3H), 7.23 – 7.13 (comp, 3H), 7.08 (d, J = 7.1, 1H), 6.71 – 6.59 (comp, 2H), 5.17 (d, J = 1.1, 1H), 3.62 (s, 6H), 3.37 – 3.21 (comp, 2H),

2.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 169.63, 168.74, 144.13, 139.50, 128.75, 128.20, 128.08, 128.01, 127.50, 117.12, 115.71, 109.25, 65.58, 57.00, 52.78, 52.36, 37.42, 28.62; Chemical Formula: $C_{20}H_{21}NO_4$, *m/z* (ESIMS) 700.8 $[2M + Na]^+$.

Procedure for the catalytic enantioselective 1,5-hydride shift reaction:

To a flask containing $Mg(OTf)_2$ (22 mg, 69 mmol, 0.2 equiv.), (1*S*,2*R*)-dimethyl-inda-box[5] (27 mg, 76 mmol, 0.22 equiv.) was added 3.5 ml of anhydrous $CHCl_3$ and the mixture was stirred for 2 h. To the reaction mixture was added (100 mg, 0.346 mmol) malonate (**2.1a**). The reaction mixture was stirred at room temperature until the complete consumption of malonate (**2.1a**) as judged by TLC analysis. After completion of the reaction (12 h), the reaction mixture was adsorbed onto silica gel and purified by column chromatography using EtOAc/hexanes (1:9) as eluent to afford analytically pure **2.2a** as a white solid in 74% yield. The IR, Mass, ^{1}H and ^{13}C data were exactly matched with the racemic compound (**2.2a**). $[\alpha]_D$ –32.5° (c 1.0, $CHCl_3$, 31% *ee*); Chiral HPLC condition: Daicel Chiralpak OJ-H, hexanes/*i*-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R=15.5 min (major) and t_R=17.1 min.

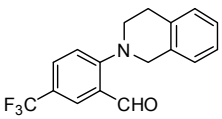
5-bromo-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzaldehyde (2.7b): The title compound



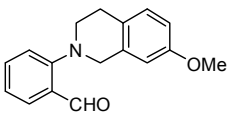
was prepared according to the general procedure (12 h) and isolated as a yellow liquid in 60% yield. (R_f = 0.40 in 10% EtOAc/Hex); IR (film) 3061, 3015, 2922, 2833, 1682, 1586, 1474, 1388, 1224, 1180, 1112, 936, 881, 818, 741, 671 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.24 (s, 1H), 7.94 (app d, *J* = 2.5 Hz, 1H), 7.65 – 7.55 (m, 1H), 7.24 – 7.17 (comp, 3H), 7.09 (app dd, *J* = 7.7, 5.1 Hz, 2H), 4.31 (s, 2H), 3.44 (t, *J* = 5.9 Hz, 2H), 3.12 (t, *J* = 5.9 Hz, 2H).;^{13}C NMR (125 MHz, $CDCl_3$) 189.82,

153.95, 137.37, 133.97, 133.59, 132.44, 129.84, 128.97, 126.72, 126.29, 126.20, 121.00, 115.30, 54.69, 53.50, 28.84; Chemical Formula: $C_{16}H_{14}BrNO$, *m/z* (ESIMS) 316.2 (^{81}Br) $[M - H]^+$, 314.2 (^{79}Br) $[M - H]^+$

2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-5-(trifluoromethyl)benzaldehyde (2.7c): The title compound was prepared according to the general procedure (12 h) and isolated as a yellow liquid in 72% yield (R_f = 0.35 in 10% EtOAc/Hex); IR (film) 2930, 2838, 1690, 1615, 1570, 1505, 1464, 1429, 1381, 1332, 1276, 1262, 1237, 1164, 1118, 1079, 1051, 1019, 934, 911, 827, 742, 665, 645, 628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10 23 (s, 1H), 8.09 (app d, *J* = 2.0 Hz, 1H), 7.77 – 7.67 (m, 1H), 7.31 – 7.18 (comp, 4H), 7.13 (app dd, *J* = 5.0, 3.3 Hz, 1H), 4.43 (s, 2H), 3.57 (t, *J* = 5.8 Hz, 2H), 3.09 (t, *J* = 5.8 Hz, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 189.51, 156.43, 133.94, 133.22, 131.10, 128.89, 128.31, 128.26 ($q_{C–F}$, *J* = 3.8 Hz), 126.89, 126.83, 126.31, 126.26, 123.12 ($q_{C–F}$, *J* = 33.5 Hz) , 118.50, 53.98, 53.07, 28.74; Chemical Formula: $C_{17}H_{14}F_3NO$, *m/z* (ESIMS) 304.3 $[M - H]^+$.

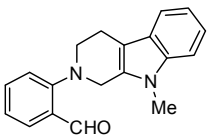


2-(7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)benzaldehyde (2.7e): The title compound was prepared according to the general procedure (13 h) and isolated as a yellow liquid in 50% yield. (R_f = 0.35 in 10% EtOAc/Hex); IR (film) 2925, 2834, 1682, 1612, 1594, 1504, 1483, 1453, 1432, 1375, 1320, 1277, 1251, 1233, 1214, 1190, 1159, 1120, 1038, 935, 829, 766.cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.33 (s, 1H), 7.85 (app dd, *J* = 7.7, 1.6 Hz, 1H), 7.58 – 7.47 (m, 1H), 7.17 (app d, *J* = 8.2 Hz, 1H), 7.10 (app dt, *J* = 11.1, 7.1 Hz, 2H), 6.86 – 6.76 (m, 1H), 6.65 (app d, *J* = 2.5 Hz, 1H), 4.30 (s, 2H), 3.81 (s, 3H), 3.44 (t, *J* = 5.8 Hz, 2H), 2.97 (t, *J* = 5.8 Hz, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 191.25, 157.86, 155.05, 135.02, 134.76,



129.88, 129.81, 128.54, 126.21, 122.17, 119.02, 112.86, 110.97, 55.25, 54.83, 53.72, 28.03; Chemical Formula: $C_{17}H_{17}NO_2$, *m/z* (ESIMS) 268.2 $[M + H]^+$.

2-(9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)benzaldehyde (2.7g): The

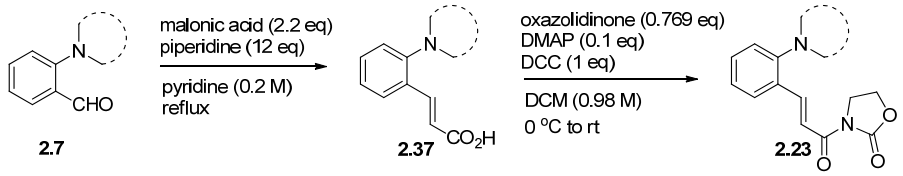


title compound was prepared according to the general procedure (10 h) and isolated as a yellow solid in 64% yield. (R_f = 0.66 in 50% EtOAc/Hex); mp: 115 – 116 °C ; IR (KBr) 3056, 2979, 2923, 2882, 2837, 2097, 1680, 1589, 1463, 1384, 1349, 1279, 1221, 1190, 1039, 984, 920, 827, 752, 636 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.43 (s, 1H), 7.93 (app d, *J* = 7.6 Hz, 1H), 7.59 (app dd, *J* = 12.0, 7.9 Hz, 2H), 7.35 (app d, *J* = 8.1 Hz, 1H), 7.28 (app dd, *J* = 12.7, 7.6 Hz, 2H), 7.19 (app dd, *J* = 15.4, 7.8 Hz, 2H), 4.40 (s, 2H), 3.65 (s, 3H), 3.61 – 3.53 (comp, 2H), 3.02 (app d, *J* = 4.3 Hz, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 191.08, 154.96, 136.97, 134.66, 132.34, 129.76, 128.60, 126.43, 122.23, 121.08, 119.21, 118.98, 117.90, 108.65, 107.70, 53.91, 48.53, 29.06, 21.54; Chemical Formula: $C_{19}H_{18}N_2O$, *m/z* (ESIMS) 289.3 $[M – H]^+$.

General procedure for the preparation of substrates:

Two different routes were followed for the preparation of substrates.

Route I:

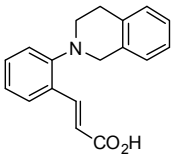


General procedure for the preparation of 2.37:

To a stirred solution of aminobenzaldehyde **2.7** (2 mmol), piperidine (24 mmol) and pyridine (12 ml) was added malonic acid (4.4 mmol) and the reaction mixture was heated

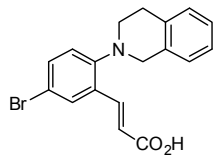
under reflux for 6 h. After completion of the reaction, the volatiles were removed and the residue was dissolved in ethyl acetate. This solution was washed sequentially with water (2 x 20 ml) and brine (20 ml), dried over sodium sulfate and filtered. The solvent was evaporated off and the crude yellow solid was purified by silica gel column chromatography (40% EtOAc in hexanes).

(*E*)-3-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)acrylic acid (2.37a): The title



compound was prepared according to the general procedure and isolated as a yellow solid in 88% yield (R_f = 0.36 in 40% EtOAc/Hex); mp: 120 – 122 °C; IR (KBr) 3440, 2802, 2369, 2328, 2096, 1633, 1491, 1486, 1454, 1442, 1379, 1294, 1258, 1193, 943, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.25 (d, *J* = 16.1 Hz, 1H), 7.63 (app dd, *J* = 7.7, 1.1 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.22 (app dd, *J* = 6.8, 4.1 Hz, 3H), 7.17 (app d, *J* = 7.8 Hz, 1H), 7.15 – 7.09 (comp, 2H), 6.48 (d, *J* = 16.1 Hz, 1H), 4.28 (s, 2H), 3.30 (t, *J* = 5.7 Hz, 2H), 3.08 (t, *J* = 5.7 Hz, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 172.93, 152.44, 144.56, 134.46, 134.40, 131.19, 129.00, 128.21, 128.20, 126.31 (x 2) 125.85, 122.74, 119.01, 116.88, 53.69, 52.60, 29.15.; Chemical Formula: $C_{18}H_{17}NO_2$, *m/z* (ESIMS) 280.3 $[M + H]^+$.

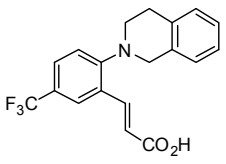
(*E*)-3-(5-bromo-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)acrylic acid (2.37b): The



title compound was prepared according to the general procedure and isolated as a yellow solid in 95% yield. (R_f = 0.20 in 70% EtOAc/Hex); mp: 182 – 183 °C; IR (KBr) 3421, 3072, 3015, 2923, 2847, 2599, 1687, 1624, 1476, 1417, 1379, 1316, 1212, 1111, 936, 874, 811, 748, 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.09 (d, *J* = 16.1 Hz, 1H), 7.69 (app d, *J* = 2.4 Hz, 1H), 7.46 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.24 – 7.15 (comp, 3H), 7.09 (app dd, *J* = 4.4, 2.8 Hz, 1H), 7.01 (app d, *J* =

8.7 Hz, 1H), 6.42 (d, *J* = 16.1 Hz, 1H), 4.22 (s, 2H), 3.25 (t, *J* = 5.7 Hz, 2H), 3.03 (t, *J* = 5.7 Hz, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 172.10, 151.34, 143.14, 134.23, 134.07, 133.75, 130.81, 130.16, 129.06, 126.50, 126.32, 126.02, 120.82, 117.97, 115.57,53.54, 52.46, 28.98; Chemical Formula: $C_{18}H_{16}BrNO_2$, *m/z* (ESIMS) 358.1 (^{81}Br) $[M - H]^+$, 356.1(^{79}Br) $[M - H]^+$.

(*E*)-3-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-5-(trifluoromethyl)phenyl)acrylic acid



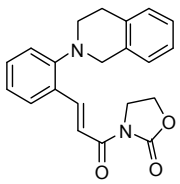
(2.37c): The title compound was prepared according to the general procedure and isolated as a yellow solid in 94% yield (R_f = 0.36 in 40% EtOAc/Hex); mp: 162 – 164 °C; IR (KBr) 3582, 3431, 2904, 2361, 2324, 1692, 1612, 1499, 1413, 1379, 1333, 1285, 1269, 1166, 1107, 1080, 947, 869, 749, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.10 (d, *J* = 16.1 Hz, 1H), 7.80 (app s, 1H), 7.60 (app d, *J* = 8.5 Hz, 1H), 7.25 – 7.16 (comp, 4H), 7.15 – 7.11 (m, 1H), 6.50 (d, *J* = 16.1 Hz, 1H), 4.31 (s, 2H), 3.36 (t, *J* = 5.7 Hz, 2H), 3.06 (t, *J* = 5.7 Hz, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 172.18, 154.73, 143.53, 134.15, 133.71, 129.10, 127.73 (q, *J* = 3.4 Hz), 126.64, 126.36, 126.15, 125.54 ($q_{C–F}$, *J* = 3.7 Hz), 124.28 ($q_{C–F}$, *J* = 32.9 Hz), 124.15, 123.05, 118.78, 118.22, 53.13, 52.32, 28.95; Chemical Formula: $C_{19}H_{16}F_3NO_2$, *m/z* (ESIMS) 348.3 $[M + H]^+$.

General procedure for DCC coupling:

To a suspension of oxazolidin-2-one (1.13 mmol), DMAP (0.15 mmol), and acid **2.37** (1.47 mmol) in dichloromethane (1.5 ml) at 0 ^{o}C was added DCC (1.47 mmol) in one portion. After 15 min the reaction mixture was allowed to warm up to room temperature and stirring was continued for 12 h. The dicyclohexylurea precipitate was filtered off and

washed with dichloromethane (10 ml). The filtrate was washed with brine (10 ml), dried over sodium sulfate, filtered and concentrated at reduced pressure to furnish the crude product, which was purified by silica gel chromatography (40% EtOAc in hexanes).

(*E*)-3-(3-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)acryloyl)oxazolidin-2-one

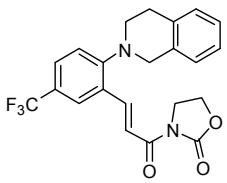


(2.23a): The title compound was prepared according to the general procedure and isolated as a yellow solid in 60% yield (R_f = 0.42 in 40% EtOAc/Hex); mp: 116 – 118 °C; IR (KBr) 2929, 2745, 2173, 2092, 1771, 1666, 1643, 1485, 1458, 1384, 1351, 1278, 1218, 1127, 1035, 935, 767 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.30 (d, *J* = 15.8 Hz, 1H), 7.87 (d, *J* = 15.8 Hz, 1H), 7.71 (app d, *J* = 7.6 Hz, 1H), 7.37 (app t, *J* = 7.5 Hz, 1H), 7.17 (app t, *J* = 6.9 Hz, 3H), 7.13 (app d, *J* = 8.1 Hz, 1H), 7.08 (app t, *J* = 7.6 Hz, 2H), 4.44 (t, *J* = 8.0 Hz, 2H), 4.25 (s, 2H), 4.13 (t, *J* = 8.0 Hz, 2H), 3.28 (t, *J* = 5.7 Hz, 2H), 3.06 (t, *J* = 5.7 Hz, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 165.68, 153.66, 152.70, 143.82, 134.59, 134.54, 131.21, 128.99, 128.73, 128.49, 126.32, 126.29, 125.83, 122.77, 119.00, 116.09, 62.04, 53.77, 52.60, 42.81, 29.24; Chemical Formula: $C_{21}H_{20}N_2O_3$, *m/z* (ESIMS) 347.3 $[M - H]^+$.

(*E*)-3-(3-(5-bromo-2-(3,4-dihydroisoquinolin-2(1*H*)-l)phenyl)acryloyl)oxazolidin-2-one (2.23b): The title compound was prepared according to the general procedure and isolated as a yellow solid in 60% yield. (R_f = 0.28 in 40% EtOAc/Hex); mp: 66 – 68 °C; IR (KBr) 3072, 3023, 2966, 2919, 2819, 1775, 1678, 1612, 1478, 1348, 1213, 1109, 1035, 937, 856, 813, 748, 701, 659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.16 (d, *J* = 15.8 Hz, 1H), 7.89 – 7.74 (comp, 2H), 7.44 (app d, *J* = 8.6 Hz, 1H), 7.17 (app d, *J* = 4.8 Hz, 3H), 7.08 (app d, *J* = 5.1 Hz, 1H), 6.99 (app d, *J* = 8.6 Hz, 1H), 4.44 (t, *J* = 7.9 Hz, 2H), 4.21 (s, 2H), 4.11 (t, *J* = 7.9 Hz, 2H),

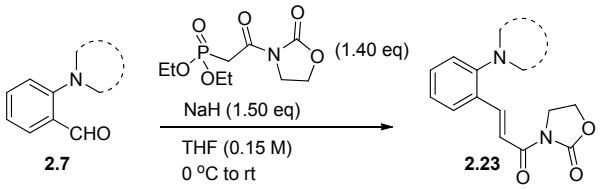
3.23 (app d, J = 5.2 Hz, 2H), 3.03 (app s, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 165.24, 153.56, 151.48, 142.18, 134.27, 134.10, 133.67, 130.83, 130.55, 128.96, 126.37, 126.25, 125.89, 120.67, 117.15, 115.51, 62.07, 53.56, 52.39, 42.73, 29.04; Chemical Formula: $C_{21}H_{19}BrN_2O_3$, *m/z* (ESIMS) 427.3 (^{81}Br) $[M - H]^+$, 426.2 (^{79}Br) $[M]^+$, 425.4 (^{79}Br) $[M - H]^+$.

(*E*)-3-(3-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-5-trifluoromethyl)phenyl)acryloyl)



oxazolidin-2-one (2.23c): The title compound was prepared according to the general procedure and isolated as a yellow solid in 59% yield (R_f = 0.42 in 40% EtOAc/Hex); mp: 166 – 168 °C; IR (KBr) 2913, 2819, 2365, 2140, 1774, 1683, 1658, 1622, 1499, 1385, 1355, 1330, 1282, 1269, 1220, 1108, 1035, 865, 816, 718, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.16 (d, J = 15.8 Hz, 1H), 7.95 – 7.84 (comp, 2H), 7.58 (dd, J = 8.5, 1.8 Hz, 1H), 7.24 – 7.14 (comp, 4H), 7.14 – 7.08 (m, 1H), 4.45 (app dd, J = 9.7, 6.4 Hz, 2H), 4.31 (s, 2H), 4.13 (app dd, J = 15.1, 7.4 Hz, 2H), 3.34 (t, J = 5.8 Hz, 2H), 3.06 (t, J = 5.8 Hz, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 165.26, 154.86, 153.57, 142.60, 134.21, 133.75, 129.01, 128.23, 127.60 ($q_{C–F}$, J = 3.7 Hz), 126.29, 126.03, 125.67 ($q_{C–F}$, J = 3.7 Hz), 125.19, 124.28, 124.15 ($q_{C–F}$, J = 32.9 Hz), 118.63, 117.37, 62.10, 53.12, 52.23, 42.74, 29.01.; Chemical Formula: $C_{22}H_{19}F_3N_2O_3$, *m/z* (ESIMS) 439.2 $[M + Na]^+$.

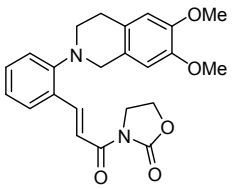
Route II:



General procedure:

To a suspension of NaH (3 mmol, 60 wt.%) in THF (6 ml) at 0 °C was added a solution of diethyl-2-oxo-2-(2-oxooxazolidin-3-yl)ethylphosphonate (2.80 mmol) in THF (1 ml) and the reaction mixture was stirred at rt for 30 min. A solution of aminobenzaldehyde **2.7** (2 mmol) in THF (3 ml) was then added dropwise to the reaction mixture and stirring at rt was continued until complete consumption of aldehyde as judged by TLC. The reaction mixture was subsequently quenched with water and extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (40% EtOAc in hexanes).

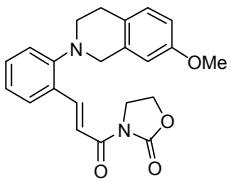
(*E*)-3-(3-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)acryloyl)oxazoli-



din-2-one (2.23d): The title compound was prepared according to the general procedure (24 h) and isolated as a yellow solid in 63% yield. (R_f = 0.20 in 50% EtOAc/Hex); mp: 120 – 122 °C; IR (KBr) 3084, 3060, 2986, 2913, 2831, 1772, 1675, 1611, 1518, 1484, 1452, 1352, 1256, 1224, 1114, 1035, 756, 733, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 15.9 Hz, 1H), 7.86 (d, *J* = 15.9 Hz, 1H), 7.69 (app dd, *J* = 7.7, 1.4 Hz, 1H), 7.40 – 7.30 (m, 1H), 7.14 – 7.02 (comp, 2H), 6.62 (app d, *J* = 2.7 Hz, 2H), 4.46 – 4.38 (comp, 2H), 4.17 (s, 2H), 4.11 (app

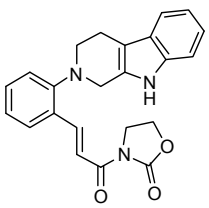
dd, *J* = 9.8, 6.3 Hz, 2H), 3.86 (comp, 6H), 3.25 (t, *J* = 5.5 Hz, 2H), 2.94 (t, *J* = 5.5 Hz, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 165.64, 153.61, 152.63, 147.52, 147.30, 143.79, 131.13, 128.56, 128.41, 126.45, 126.36, 122.62, 118.94, 115.95, 111.63, 109.12, 62.00, 55.91, 55.85, 53.23, 52.61, 42.75, 28.66.; Chemical Formula: $C_{23}H_{24}N_2O_5$, *m/z* (ESIMS) 407.4 $[M - H]^+$.

(*E*)-3-(3-(2-(7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)acryloyl)oxazolidin-



2-one (2.23e): The title compound was prepared according to the general procedure (36 h) and isolated as a yellow solid in 70% yield. A minor amount of an unidentified impurity (< 3%, estimated) could not be removed and the compound was used as is in the next step. (R_f = 0.22 in 40% EtOAc/Hex); mp: 70 – 72 °C; IR (KBr) 3096, 3060, 2919, 2832, 1773, 1675, 1607, 1495, 1352, 1217, 1109, 1034, 934, 858, 757, 702, 582 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 15.8 Hz, 1H), 7.86 (d, *J* = 15.8 Hz, 1H), 7.70 (app dd, *J* = 7.7, 1.3 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.09 (comp, 3H), 6.76 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.63 (app d, *J* = 2.5 Hz, 1H), 4.45 (t, *J* = 8.0 Hz, 2H), 4.22 (s, 2H), 4.14 (t, *J* = 8.0 Hz, 2H), 3.79 (s, 3H), 3.26 (t, *J* = 5.8 Hz, 2H), 2.96 (t, *J* = 5.8 Hz, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 165.69, 157.74, 153.66, 152.63, 143.88, 135.62, 131.19, 129.89, 128.72, 128.51, 126.69, 122.75, 119.08, 116.07, 112.60, 111.06, 62.05, 55.30, 53.92, 52.81, 42.82, 28.29.; Chemical Formula: $C_{22}H_{22}N_2O_4$, *m/z* (ESIMS) 401.2 $[M + Na]^+$.

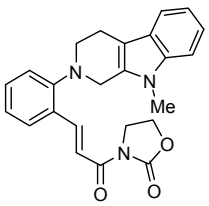
(*E*)-3-(3-(2-(3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)phenyl)acryloyl)oxazolidin-



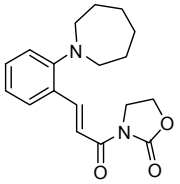
2-one (2.23f): The title compound was prepared according to the general procedure (36 h) and isolated as a yellow solid in 65% yield.

(R_f = 0.36 in 50% EtOAc/Hex); mp: 175 – 177 °C; IR (KBr) 3348, 3092, 2920, 2843, 1777, 1662, 1598, 1450, 1357, 1213, 1116, 1039, 749, 700, 587 cm^{-1}; ^1H NMR (500 MHz, DMSO) 10.84 (s, 1H), 8.08 (d, *J* = 15.9 Hz, 1H), 7.81 (d, *J* = 15.9 Hz, 1H), 7.63 (app d, *J* = 7.7 Hz, 1H), 7.43 (app dt, *J* = 7.9, 3.8 Hz, 2H), 7.32 (app d, *J* = 8.1 Hz, 1H), 7.25 (app d, *J* = 8.1 Hz, 1H), 7.14 (app t, *J* = 7.5 Hz, 1H), 7.04 (app t, *J* = 7.5 Hz, 1H), 6.97 (app t, *J* = 7.5 Hz, 1H), 4.40 (t, *J* = 7.9 Hz, 2H), 4.26 (s, 2H), 4.00 (t, *J* = 7.9 Hz, 2H), 3.29 – 3.25 (comp, 2H), 2.83 (t, *J* = 5.7 Hz, 2H).; ^{13}C NMR (125 MHz, DMSO) 164.78, 153.79, 152.27, 141.38, 135.90, 132.34, 131.30, 127.93, 127.57, 126.64, 122.86, 120.57, 119.53, 118.43, 117.43, 116.54, 111.00, 106.76, 62.44, 52.67, 48.40, 42.70, 21.64.; Chemical Formula: $C_{23}H_{21}N_3O_3$, *m/z* (ESIMS) 387.4 $[M]^+$.

(*E*)-3-(3-(2-(9-methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)phenyl)acryloyl)oxazolidin-2-one (2.23g): The title compound was prepared according to the general procedure (36 h) and isolated as a yellow solid in 70% yield. (R_f = 0.43 in 50% EtOAc/Hex); mp: 96 – 98 °C; IR (KBr) 2950, 2916, 1772, 1672, 1607, 1475, 1351, 1216, 1112, 1038, 921, 863, 750, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.34 (d, *J* = 15.8 Hz, 1H), 7.91 (d, *J* = 15.8 Hz, 1H), 7.74 (app d, *J* = 7.7 Hz, 1H), 7.54 (app d, *J* = 7.7 Hz, 1H), 7.37 (app t, *J* = 7.6 Hz, 1H), 7.31 (app d, *J* = 8.1 Hz, 1H), 7.22 (app t, *J* = 7.6 Hz, 1H), 7.19 – 7.08 (comp, 3H), 4.38 (comp, 2H), 4.31 (s, 2H), 4.08 (comp, 2H), 3.64 (s, 3H), 3.36 (t, *J* = 5.4 Hz, 2H), 2.97 (app s, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) 165.50, 153.61, 152.46, 143.54, 137.00, 132.98, 131.06, 128.83, 128.39, 126.65, 122.85, 120.92, 119.27, 118.90, 118.02, 116.17, 108.63, 108.03, 61.97, 52.89, 47.74, 42.69, 29.19, 21.80.; Chemical Formula: $C_{24}H_{23}N_3O_3$, *m/z* (ESIMS) 424.2 $[M + Na]^+$.

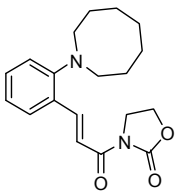


(*E*)-3-(3-(2-(azepan-1-yl)phenyl)acryloyl)oxazolidin-2-one (2.23h): The title



compound was prepared according to the general procedure (48 h) and isolated as a yellow liquid in 40% yield. (R_f = 0.50 in CH_2Cl_2); IR (film) 2925, 2854, 1774, 1676, 1609, 1594, 1483, 1448, 1386, 1351, 1220, 1161, 1107, 1035, 971, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.32 (d, *J* = 15.8 Hz, 1H), 7.79 (d, *J* = 15.8 Hz, 1H), 7.63 (app dd, *J* = 7.7, 1.5 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.12 – 7.07 (m, 1H), 6.97 (app t, *J* = 7.5 Hz, 1H), 4.51 – 4.41 (m, 2H), 4.15 (app dd, *J* = 9.7, 6.4 Hz, 2H), 3.27 – 3.14 (comp, 4H), 1.88 – 1.70 (comp, 8H).; ^{13}C NMR (125 MHz, $CDCl_3$) 165.79, 155.57, 153.63, 145.36, 130.93, 128.47, 128.28, 121.52, 119.98, 114.93, 61.99, 56.41, 42.81, 29.14, 27.17; Chemical Formula: $C_{18}H_{22}N_2O_3$, *m/z* (ESIMS) 629.4 $[2M + H]^+$.

(*E*)-3-(3-(2-(azocan-1-yl)phenyl)acryloyl)oxazolidin-2-one (2.23i): The title compound



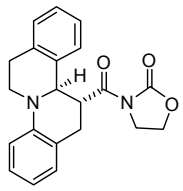
was prepared according to the general procedure (48 h) and isolated as a yellow liquid in 50% yield (R_f =0.42 in 40% EtOAc/Hex); IR (film) 2920, 2851, 2361, 2348, 1773, 1677, 1609, 1481, 1447, 1386, 1351, 1268, 1217, 1109, 1035, 997, 912, 862, 753, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.41 (d, *J* = 15.8 Hz, 1H), 7.77 (d, *J* = 15.8 Hz, 1H), 7.63 (app d, *J* = 7.8 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.15 (app d, *J* = 8.3 Hz, 1H), 6.97 (app dd, *J* = 11.1, 3.8 Hz, 1H), 4.46 – 4.38 (t, *J* = 7.9 Hz, 2H), 4.12 (t, *J* = 7.9 Hz, 2H), 3.20 (comp, 4H), 1.82 – 1.64 (comp, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.59, 155.07, 153.57, 145.28, 131.00, 128.96, 128.33, 121.79, 121.01, 115.00, 61.93, 55.22, 42.74, 28.16, 27.45, 25.16; Chemical Formula: $C_{19}H_{24}N_2O_3$, *m/z* (ESIMS) 329.3 $[M + H]^+$, 657.5 $[2M – H]^+$.

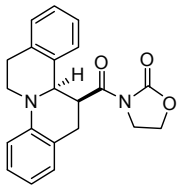
General procedure for the catalytic enantioselective 1,5-hydride shift reaction:

A mixture of (*S*,*S*)-DBFOX/Ph (0.066 mmol, 0.22 equiv) and $Mg(OTf)_2$ (0.06 mmol, 0.20 equiv) in dichloroethane (3 ml) was stirred at rt for 4 h. Subsequently, starting material **2.23** (0.3 mmol) and 4Å molecular sieves (0.15 g) were added to the reaction mixture and it was stirred at rt for 30 min. Stirring was then continued under reflux until complete consumption of starting material as judged by TLC analysis. After completion, the molecular sieves were removed by filtration through celite. The crude reaction mixture was concentrated under reduced pressure and was purified by silica gel chromatography (40% EtOAc in hexanes) to afford analytically pure trans and cis diastereoisomers.

Racemic compounds were prepared by using 2,2' bipyridine as ligand and $Ni(ClO_4)_2 \cdot 6H_2O$ as metal salt.

The absolute configuration of **2.24b** was established by X-ray crystallography and the remaining compounds are assigned by analogy.

3-((11bR, 12R)-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl)oxazolidin-2-one (2.24a, major diastereomer): 
Following the general procedure (30 h) the title compound was obtained as an off-white solid in 85% yield (combined yield, dr: 75:25). mp: 78 – 80 °C; (R_f = 0.38 in 40% EtOAc/Hex); $[\alpha]_D^{20}$ + 39.1 (c 1.0, $CHCl_3$, 93% *ee*); IR (KBr) 3448, 3051, 3011, 2967, 2937, 2894, 1621, 1585, 1550, 1483, 1455, 1379, 1265, 1211, 1179, 1090, 1052, 1027, 916, 810, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (ddd, *J* = 10.9, 3.7, 1.8 Hz, 1H), 7.13 (app dd, *J* = 8.9, 4.3 Hz, 3H), 7.10 (app d, *J* = 7.6 Hz, 2H), 6.93 (app d, *J* = 8.2 Hz, 1H), 6.79 (app dd, *J* = 10.5, 4.2 Hz, 1H), 4.60 – 4.51 (comp, 2H), 4.29 – 4.20 (m, 1H), 4.08 – 4.00 (m, 1H), 3.89 (comp, 3H), 3.51 – 3.42 (m, 1H), 3.39 – 3.29 (m, 1H), 3.21 – 3.12 (m, 1H), 2.98 – 2.90 (m, 1H), 2.84 (app dt, *J* = 15.9, 4.4 Hz, 1H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.14, 152.87, 145.99, 136.31, 135.28, 129.03, 128.73, 127.00, 126.84, 126.02, 125.33, 123.50, 118.80, 116.17, 61.70, 59.99, 46.94, 42.69, 40.57, 29.49, 28.17; Chemical Formula: $C_{21}H_{20}N_2O_3$, *m/z* (ESIMS) 349.2 $[M + H]^+$; HPLC: Daicel Chiralcel AD-H, hexanes/*i*-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R=20.7 min and t_R=28.5 min (major).

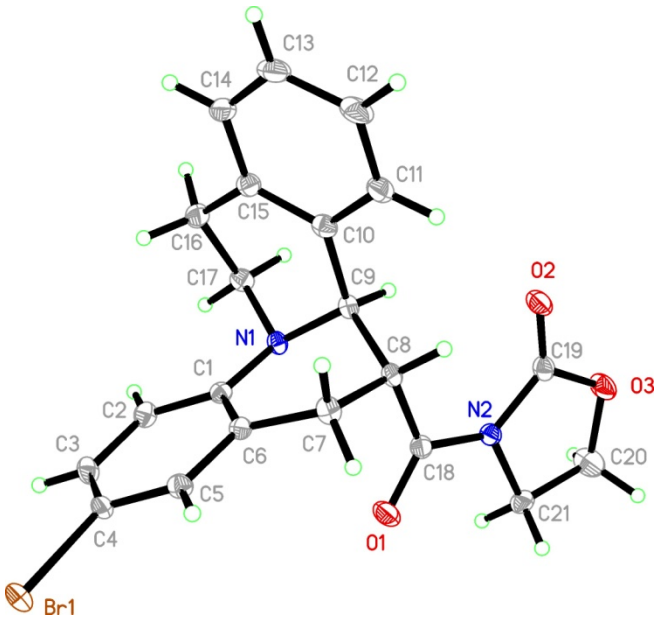
3-((11bR, 12S)-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl)oxazolidin-2-one (2.24a', minor diasteromer): 
The title compound was isolated as a yellowish solid. mp: 80 – 82 °C; (R_f = 0.46 in 40% EtOAc/Hex); $[\alpha]_D^{20}$ + 133.4 (c 0.5, $CHCl_3$, 86% *ee*); IR (KBr) 3448, 3051, 3011, 2967, 2937, 2894, 1621, 1585, 1550, 1483, 1455, 1379, 1265, 1211, 1179, 1090, 1052, 1027, 916, 810, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (app d, *J* = 7.4 Hz, 1H), 7.23 – 7.10 (comp, 4H), 7.03 (app d, *J* = 7.1 Hz, 1H), 6.83 (app d, *J* = 8.2 Hz,

1H), 6.70 (app t, *J* = 7.3 Hz, 1H), 5.02 – 4.93 (m, 1H), 4.73 (d, *J* = 3.7 Hz, 1H), 4.22 – 4.17 (m, 1H), 4.08 – 4.02 (m, 1H), 3.96 (dd, *J* = 17.1, 8.2 Hz, 1H), 3.73 (app dt, *J* = 10.7, 8.6 Hz, 1H), 3.52 (ddd, *J* = 10.7, 9.3, 5.6 Hz, 1H), 3.40 (dd, *J* = 17.1, 8.2 Hz, 1H), 3.22 – 3.04 (comp, 3H), 2.77 (app d, *J* = 12.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.95, 153.25, 146.16, 136.01, 135.49, 128.87, 128.24, 127.06, 126.31, 126.13, 126.10, 120.74, 117.08, 111.07, 61.81, 58.25, 42.69, 42.65, 42.18, 29.89, 29.19; Chemical Formula: $C_{21}H_{20}N_2O_3$, *m/z* (ESIMS) 349.2 $[M + H]^+$; HPLC: Daicel Chiralcel OD-H, hexanes/*i*-PrOH=95/05, Flow rate = 1 mL/min, UV = 254 nm, t_R=76.7 min (major) and t_R=86.9 min.

3-((11bR, 12R)-2-bromo-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl)oxazolidin-2-one (2.24b, major diasteromer): Following the general procedure (24 h) the title compound was obtained as a pale yellow solid in 80% yield (combined yield, dr: 69:31). mp: 180 – 181 °C; (R_f = 0.23 in 40% EtOAc/Hex); $[\alpha]_D^{20}$ + 32.4 (c 0.5, $CHCl_3$, 89% *ee*); IR (KBr) 3448, 3051, 3011, 2967, 2937, 2894, 1775, 1695, 1484, 1386, 1283, 1212, 1112, 1037, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.07 (comp, 6H), 6.77 (app d, *J* = 8.7 Hz, 1H), 4.56 (comp, 2H), 4.28 (app td, *J* = 9.0, 6.1 Hz, 1H), 4.10 (app dd, *J* = 16.9, 8.7 Hz, 1H), 3.96 (app dd, *J* = 18.2, 9.8 Hz, 1H), 3.91 – 3.83 (comp, 2H), 3.47 – 3.38 (m, 1H), 3.24 (dd, *J* = 16.5, 7.9 Hz, 1H), 3.15 (ddd, *J* = 15.4, 10.0, 5.0 Hz, 1H), 2.88 (dd, *J* = 16.5, 4.8 Hz, 1H), 2.78 (app dt, *J* = 15.9, 3.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.68, 152.96, 144.70, 136.13, 135.10, 131.40, 129.63, 128.81, 127.15, 125.78, 125.68, 125.52, 117.11, 110.55, 61.83, 59.60, 46.87, 42.70, 40.25, 28.69, 27.63; Chemical Formula: $C_{21}H_{19}BrN_2O_3$, *m/z* (ESIMS) 427.2 (^{81}Br) $[M – H]^+$, 426.4 (^{79}Br) $[M]^+$, 425.3

(^{79}Br) $[M - H]^+$; HPLC: Daicel Chiralcel AD-H, hexanes/*i*-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R=31.6 min and t_R=34.3 min (major).

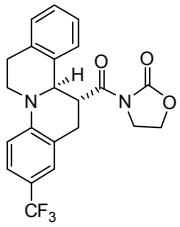
The absolute configuration was assigned by X-ray crystallography



3-((11bR, 12S)-2-bromo-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl)oxazolidin-2-one (2.24b', minor diasteromer): The title compound was isolated as a yellowish solid. mp: 130 – 131 °C; (R_f = 0.30 in 40% EtOAc/Hex); $[\alpha]_D^{20}$ + 95.6 (c 1.0, $CHCl_3$, 87% *ee*); IR (KBr) 3420, 3051, 2982, 2908, 2843, 1778, 1694, 1589, 1484, 1387, 1224, 1115, 1029, 916, 810, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (app s, 1H), 7.15 – 7.07 (comp, 3H), 7.07 – 7.03 (comp, 2H), 6.60 (app d, *J* = 8.8 Hz, 1H), 4.88 (ddd, *J* = 7.4, 3.8, 2.6 Hz, 1H), 4.65 (d, *J* = 3.8 Hz, 1H), 4.16 (app td, *J* = 9.0, 5.6 Hz, 1H), 3.97 – 3.87 (comp, 2H), 3.74 – 3.65 (m, 1H), 3.47 (ddd, *J* = 11.0, 9.1, 5.6 Hz, 1H), 3.28 (dd, *J* = 17.1, 7.6 Hz, 1H), 3.11 (app td, *J* = 11.7, 2.8 Hz, 1H), 3.05 – 2.91 (comp, 2H), 2.68 (app dt, *J* =

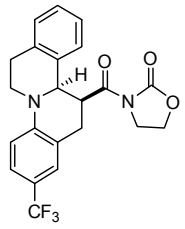
15.3, 2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.69, 152.96, 144.70, 136.13, 135.10, 131.40, 129.63, 128.81, 127.15, 125.78, 125.68, 125.52, 117.11, 110.55, 61.83, 59.60, 46.87, 42.70, 40.25, 28.69, 27.63; Chemical Formula: $C_{21}H_{19}BrN_2O_3$, *m/z* (ESIMS) 427.2 (^{81}Br) $[M - H]^+$, 426.4 (^{79}Br) $[M]^+$, 425.3 (^{79}Br) $[M - H]^+$; HPLC: Daicel Chiralcel AD-H, hexanes/*i*-PrOH=95/05, Flow rate = 1 mL/min, UV = 254 nm, t_R=46.1 min and t_R=48.2 min (major).

3-((11bR, 12R)-2-(trifluoromethyl)-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl)-oxazolidin-2-one (2.24c, major diasteromer):



Following the general procedure (24 h) except the metal salt $Ni(ClO_4)_2$•$6H_2O$ was used instead of $Mg(OTf)_2$, the title compound was obtained as a light yellow solid in 91% yield (combined yield, dr: 60:40). mp: 82 – 84 °C; (R_f = 0.39 in 40% EtOAc/Hex); $[\alpha]_D^{20}$ + 34.4 (c 1.0, $CHCl_3$, 88% *ee*); IR (KBr) 3448, 3051, 3011, 2967, 2937, 2894, 1621, 1585, 1550, 1483, 1455, 1379, 1265, 1211, 1179, 1090, 1052, 1027, 916, 810, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.22 (app d, *J* = 8.4 Hz, 1H), 7.15 – 7.03 (comp, 4H), 6.80 (app d, *J* = 8.6 Hz, 1H), 4.60 (d, *J* = 6.1 Hz, 1H), 4.50 (ddd, *J* = 8.3, 6.1, 5.3 Hz, 1H), 4.27 – 4.18 (m, 1H), 4.06 (app dt, *J* = 16.4, 8.2 Hz, 1H), 3.94 – 3.85 (comp, 2H), 3.83 – 3.76 (m, 1H), 3.42 – 3.34 (m, 1H), 3.18 (dd, *J* = 16.3, 8.3 Hz, 1H), 3.10 (ddd, *J* = 16.0, 11.0, 5.1 Hz, 1H), 2.87 (dd, *J* = 16.3, 5.1 Hz, 1H), 2.70 (app dt, *J* = 15.8, 3.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.48, 153.02, 147.86, 136.38, 135.17, 128.73, 127.28, 126.18, 125.96, 125.54, 124.15 ($q_{C–F}$, *J* = 3.7 Hz), 123.49, 122.49, 119.32 ($q_{C–F}$, *J* = 32.4 Hz), 113.49, 61.87, 59.23, 46.36, 42.70, 40.57, 28.88, 27.73; Chemical Formula:

$C_{22}H_{19}F_3N_2O_3$, *m/z* (ESIMS) 413.3 (^{18}F) $[M]^+$; HPLC: Daicel Chiralcel AD-H, hexanes/*i*-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R=16.7 min and t_R=24.4 min (major).



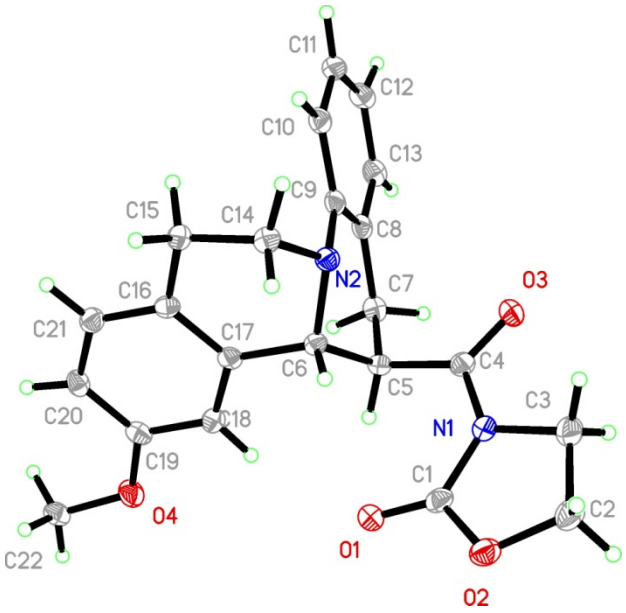
3-((11bR, 12S)-2-(trifluoromethyl)-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl)-oxazolidin-2-one (2.24c', minor diastereomer): The title compound was isolated as a yellowish solid. mp: 80 – 82 °C; (R_f = 0.51 in 40% EtOAc/Hex); $[\alpha]_D^{20}$ + 148.2 (c 1.0, $CHCl_3$, 89% *ee*); IR (KBr) 3448, 3051, 3011, 2967, 2937, 2894, 1621, 1585, 1550, 1483, 1455, 1379, 1265, 1211, 1179, 1090, 1052, 1027, 916, 810, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (app d, *J* = 8.8 Hz, 1H), 7.19 (app t, *J* = 5.3 Hz, 1H), 7.14 (app d, *J* = 7.2 Hz, 2H), 7.11 (app d, *J* = 8.6 Hz, 1H), 7.07 (app t, *J* = 7.8 Hz, 1H), 6.73 (app d, *J* = 8.7 Hz, 1H), 4.93 (ddd, *J* = 6.3, 3.7, 2.3 Hz, 1H), 4.76 (d, *J* = 3.7 Hz, 1H), 4.16 (app td, *J* = 9.0, 5.9 Hz, 1H), 4.05 – 3.99 (m, 1H), 3.99 – 3.92 (m, 1H), 3.65 (ddd, *J* = 11.0, 9.2, 7.8 Hz, 1H), 3.47 (ddd, *J* = 11.0, 9.2, 5.9 Hz, 1H), 3.33 (dd, *J* = 17.0, 7.2 Hz, 1H), 3.24 – 3.14 (m, 1H), 3.07 – 2.96 (comp, 2H), 2.69 (app d, *J* = 15.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.24, 153.25, 148.10, 135.92, 135.06, 128.40, 126.61, 126.44, 126.05, 125.93 ($q_{C–F}$, *J* = 3.8 Hz), 124.66 ($q_{C–F}$, *J* = 3.9 Hz), 124.64, 119.61, 117.98 ($q_{C–F}$, *J* = 32.7 Hz), 110.10, 61.88, 57.91, 42.90, 42.61, 41.14, 30.26, 28.99.; Chemical Formula: C22H19F3N2O3, *m/z* (ESIMS) 413.3 (^{18}F) $[M]^+$; HPLC: Daicel Chiralcel OD-H, hexanes/*i*-PrOH=95/05, Flow rate = 1 mL/min, UV = 254 nm, t_R=63.5 min and t_R=72.7 min (major).

3-((11bR, 12R)-9,10-dimethoxy-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl)-oxazolidin-2-one (2.24d): Following the general procedure (36 h) the title compound was obtained as a light yellow solid in 86% yield (combined yield, dr: 84:16). mp: 125 – 128 °C; (R_f = 0.25 in 60% EtOAc/Hex); $[\alpha]_D^{20}$ + 49.8 (c 1.0, $CHCl_3$, 92% *ee*); IR (film) 3056, 2998, 2958, 2913, 2831, 1773, 1703, 1602, 1514, 1494, 1456, 1386, 1326, 1256, 1205, 1129, 1104, 1040, 756, 734, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.05 (comp, 2H), 6.93 (app d, *J* = 8.2 Hz, 1H), 6.78 (app dd, *J* = 10.6, 4.1 Hz, 1H), 6.65 (app d, *J* = 19.8 Hz, 2H), 4.53 (ddd, *J* = 9.0, 7.0, 5.1 Hz, 1H), 4.46 (d, *J* = 7.0 Hz, 1H), 4.26 (app td, *J* = 9.0, 6.0 Hz, 1H), 4.09 (app dt, *J* = 8.8, 7.7 Hz, 1H), 3.96 (ddd, *J* = 10.9, 9.3, 7.6 Hz, 1H), 3.91 – 3.76 (comp, 8H), 3.47 – 3.37 (m, 1H), 3.31 (dd, *J* = 16.4, 9.0 Hz, 1H), 3.06 (ddd, *J* = 14.3, 9.1, 4.8 Hz, 1H), 2.91 (dd, *J* = 16.4, 4.9 Hz, 1H), 2.73 (app dt, *J* = 15.7, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.41, 152.94, 147.89, 146.81, 146.06, 129.06, 128.59, 126.85, 126.78, 123.54, 118.90, 116.56, 111.40, 109.59, 61.73, 59.74, 56.14, 55.76, 47.17, 42.79, 40.46, 29.57, 27.71; Chemical Formula: $C_{23}H_{24}N_2O_5$, *m/z* (ESIMS) 407.4 $[M - H]^+$; HPLC: Daicel Chiralcel AD-H, hexanes/*i*-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R=52.6 min (major) and t_R=90.1 min.

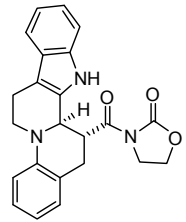
3-((11bR, 12R)-10-methoxy-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl)-oxazolidin-2-one (2.24e): Following the general procedure (18 h) the title compound was obtained as a light yellow solid in 84% yield (combined yield, dr: 90:10). mp: 81 – 82 °C; (R_f = 0.20 in 40% EtOAc/Hex); $[\alpha]_D^{20}$ + 68.3 (c 1.0, $CHCl_3$, 93% *ee*); IR (KBr) 3444, 3101, 3060, 3002, 2933, 2831, 1770, 1699, 1606, 1490, 1380, 1285, 1213, 1115, 1039,

995, 853, 812, 758, 703, 637 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.13 (app dd, *J* = 11.3, 4.1 Hz, 1H), 7.09 (app d, *J* = 7.4 Hz, 1H), 7.05 (app d, *J* = 8.2 Hz, 1H), 6.92 (app d, *J* = 8.2 Hz, 1H), 6.81 – 6.73 (comp, 2H), 6.69 (app d, *J* = 2.6 Hz, 1H), 4.59 – 4.50 (comp, 2H), 4.29 (app td, *J* = 9.0, 5.7 Hz, 1H), 4.09 (app dd, *J* = 16.8, 8.9 Hz, 1H), 3.97 (ddd, *J* = 10.9, 9.2, 7.9 Hz, 1H), 3.89 (app ddd, *J* = 11.5, 9.4, 5.1 Hz, 2H), 3.77 (s, 3H), 3.42 (ddd, *J* = 12.5, 9.5, 4.3 Hz, 1H), 3.37 – 3.27 (m, 1H), 3.12 – 3.02 (m, 1H), 2.99 – 2.90 (m, 1H), 2.76 (app dt, *J* = 15.7, 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.11, 157.53, 152.94, 145.82, 136.42, 129.58, 128.96, 128.33, 126.81, 123.48, 118.73, 116.00, 112.56, 111.51, 61.79, 59.97, 55.34, 47.16, 42.76, 40.58, 29.27, 27.12; Chemical Formula: $C_{22}H_{22}N_2O_4$, *m/z* (ESIMS) 378.2 $[M]^+$; HPLC: Daicel Chiralcel AD-H, hexanes/*i*-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R=34.1 min (major) and t_R=44.3 min.

The absolute configuration was assigned by X-ray crystallography.



3-((11bR, 12R)-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl)

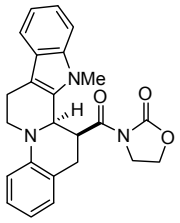


oxazolidin-2-one (2.24f, major diastereomer): Following the general procedure (24 h) the title compound was obtained as a red solid in 80% yield (combined yield, dr: 75:25). mp: 139 – 141 °C; (R_f = 0.33 in 50% EtOAc/Hex); $[\alpha]_D^{20}$ + 38.3 (c 0.06, $CHCl_3$, 82% *ee*); IR (KBr) 3383, 3064, 2918, 2835, 1771, 1690, 1601, 1486, 1460, 1387, 1215, 1115, 1039, 909, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.50 (app d, *J* = 7.8 Hz, 1H), 7.30 (app d, *J* = 8.1 Hz, 1H), 7.17 (app td, *J* = 7.6, 1.2 Hz, 2H), 7.09 (app ddd, *J* = 14.4, 8.4, 3.7 Hz, 3H), 6.84 (app td, *J* = 7.4, 0.9 Hz, 1H), 4.77 (d, *J* = 8.4 Hz, 1H), 4.45 – 4.31 (comp, 3H), 4.15 – 4.02 (comp, 2H), 3.80 (ddd, *J* = 12.7, 6.2, 5.0 Hz, 1H), 3.51 (app dt, *J* = 12.8, 5.5 Hz, 1H), 3.18 (dd, *J* = 15.9, 5.5 Hz, 1H), 3.04 (dd, *J* = 15.9, 9.8 Hz, 1H), 2.96 – 2.90 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.21, 152.90, 146.63, 135.99, 132.78, 128.94, 127.13, 126.72, 124.01, 121.91, 120.04, 119.44, 118.53, 118.34, 110.87, 110.52, 61.98, 54.85, 48.16, 42.77, 40.92, 31.05, 21.44; Chemical Formula: $C_{23}H_{21}N_3O_3$, *m/z* (ESIMS) 386.0 $[M - H]^+$; HPLC: Daicel Chiralcel AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=36.6 min (major) and t_R=46.6 min.

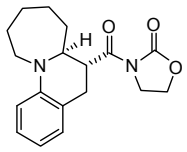
3-((11bR, 12S)-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl) oxazolidin-2-one (2.24f', minor diastereomer): The title compound was obtained as a reddish yellow solid. mp: 193 – 195 °C; (R_f = 0.43 in 50% EtOAc/Hex); $[\alpha]_D^{20}$ + 36.0 (c 0.125, $CHCl_3$, 98% *ee*); IR (KBr) 3384, 2920, 2850, 1792, 1671, 1607, 1464, 1394, 1328, 1274, 1208, 1124, 1045, 964, 820, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.40 (app d, *J* = 7.8 Hz, 1H), 7.34 (app d, *J* = 8.1 Hz, 1H), 7.17 – 7.08 (comp, 3H), 7.07 – 7.02 (m, 1H), 6.89 (app d, *J* = 7.4 Hz, 1H), 6.71 – 6.64 (m, 1H), 5.05 (app s, 1H), 4.70 (ddd, *J* = 11.9, 4.4, 2.9 Hz, 1H), 4.40 (app ddd, *J* = 16.2, 11.1, 6.1 Hz, 2H), 4.31 (app td, *J* = 9.0, 6.6 Hz, 1H), 4.08

(app qdd, *J* = 11.0, 9.2, 6.9 Hz, 2H), 3.43 (ddd, *J* = 14.2, 12.2, 4.3 Hz, 1H), 3.14 (dd, *J* = 15.5, 12.1 Hz, 1H), 3.01 (app dddd, *J* = 14.9, 12.1, 5.3, 2.5 Hz, 1H), 2.94 – 2.87 (m, 1H), 2.62 (dd, *J* = 15.5, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.70, 152.82, 144.26, 135.55, 132.64, 129.38, 127.28, 126.94, 122.70, 121.73, 119.17, 118.44, 117.98, 114.76, 111.24, 111.18, 61.99, 55.59, 47.54, 42.99, 41.05, 27.96, 18.42.; Chemical Formula: $C_{23}H_{21}N_3O_3$, *m/z* (ESIMS) 386.2 $[M - H]^+$; HPLC: Daicel Chiralcel AD-H, hexanes/*i*-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, t_R=39.8 min and t_R=50.3 min (major).

3-((11bR, 12R)-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl)oxazolidin-2-one (2.24g, major diastereomer): Following the general procedure (22 h) the title compound was obtained as a light yellow solid in 72% yield (combined yield, dr: 60:40). mp: 92 – 94 °C; (R_f = 0.40 in 50% EtOAc/Hex); $[\alpha]_D^{20}$ + 20.3 (c 1.0, $CHCl_3$, 90% *ee*); IR (KBr) 3421, 3047, 2913, 2846, 1774, 1697, 1602, 1468, 1382, 1211, 1112, 1037, 908, 841, 744, 635 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (app d, *J* = 7.8 Hz, 1H), 7.18 (app d, *J* = 1.1 Hz, 1H), 7.15 – 7.06 (comp, 2H), 7.02 (app dd, *J* = 10.4, 4.2 Hz, 3H), 6.79 (app t, *J* = 7.4 Hz, 1H), 4.68 (app dt, *J* = 13.7, 6.1 Hz, 2H), 4.19 – 4.09 (m, 1H), 3.91 – 3.85 (comp, 2H), 3.83 – 3.75 (comp, 2H), 3.57 (s, 3H), 3.47 – 3.39 (m, 1H), 3.23 (dd, *J* = 16.3, 7.8 Hz, 1H), 2.98 – 2.91 (m, 1H), 2.88 (dd, *J* = 16.3, 4.7 Hz, 1H), 2.80 (app dt, *J* = 15.4, 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.77, 153.08, 146.78, 138.38, 133.91, 129.11, 126.87, 126.80, 125.12, 121.79, 120.54, 119.34, 119.10, 118.56, 110.80, 108.95, 61.86, 56.38, 48.46, 43.14, 39.80, 31.20, 29.21, 20.62; Chemical Formula: $C_{24}H_{23}N_3O_3$, *m/z* (ESIMS) 424.2 $[M + Na]^+$; HPLC: Daicel Chiralcel AD-H, hexanes/*i*-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=17.9 min and t_R=22.8 min (major).

3-((11bR, 12S)-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl)oxazolidin-2-one (2.24g', minor diastereomer): 

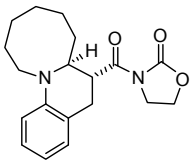
The title compound was obtained as a yellowish solid. mp: 109 – 111 °C; (R_f = 0.53 in 50% EtOAc/Hex); $[\alpha]_D^{20}$ + 164.3 (c 1.0, $CHCl_3$, 92% *ee*); IR (KBr) 3406, 3064, 2916, 2835, 1772, 1670, 1605, 1470, 1351, 1233, 1111, 1038, 923, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (app d, *J* = 7.8 Hz, 1H), 7.35 (app d, *J* = 8.2 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.18 – 7.10 (comp, 3H), 6.87 (app d, *J* = 8.2 Hz, 1H), 6.78 (app t, *J* = 7.4 Hz, 1H), 5.01 (app dd, *J* = 7.0, 2.9 Hz, 1H), 4.79 – 4.73 (m, 1H), 4.08 – 4.01 (m, 1H), 3.89 (app td, *J* = 8.7, 3.3 Hz, 1H), 3.71 (s, 3H), 3.66 (dd, *J* = 16.3, 5.9 Hz, 1H), 3.38 – 3.29 (comp, 2H), 3.19 (comp, 2H), 2.98 – 2.86 (comp, 2H), 2.82 – 2.74 (m, 1H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.33, 153.37, 147.08, 138.16, 132.74, 129.10, 126.71, 125.71, 121.97, 121.77, 119.45, 117.96, 117.83, 112.42, 110.14, 109.47, 61.66, 54.51, 43.43, 43.03, 41.17, 30.19, 28.82, 21.61; Chemical Formula: $C_{24}H_{23}N_3O_3$, *m/z* (ESIMS) 424.2 $[M + Na]^+$; HPLC: Daicel Chiralcel AD-H, hexanes/*i*-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R=22.9 min and t_R=30.8 min (major).

3-((11bR, 12R)-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl)oxazolidin-2-one (2.24h, mixture of diastereomer): 

Following the general procedure (60 h) the title compound was obtained as a light yellow solid in 83% yield (dr: 70:30). mp: 51 – 53 °C; (R_f = 0.23 in 20% EtOAc/Hex); $[\alpha]_D^{20}$ + 30.6 (c 1.0, $CHCl_3$, 75% *ee*, 71% *ee*); IR (KBr) 2926, 2855, 1774, 1698, 1601, 1501, 1476, 1455, 1386, 1362, 1326, 1309, 1269, 1208, 1109, 1039, 744, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (app dt , *J* = 24.1, 7.8 Hz, 4H),

6.58 (app dd, *J* = 9.5, 6.1 Hz, 4H), 4.41 (app ddd, *J* = 21.0, 12.3, 4.8 Hz, 4H), 4.13 – 4.04 (m, 1H), 4.03 – 3.88 (comp, 5H), 3.87 – 3.79 (comp, 2H), 3.72 – 3.64 (m, 1H), 3.37 (dd, *J* = 16.6, 13.6 Hz, 1H), 3.17 (app tdd, *J* = 15.2, 10.9, 5.1 Hz, 2H), 3.06 (app dd, *J* = 16.6, 6.0 Hz, 1H), 2.98 (dd, *J* = 16.6, 3.9 Hz, 1H), 2.69 (app dd, *J* = 16.6, 4.7 Hz, 1H), 2.13 – 1.98 (comp, 2H), 1.93 – 1.83 (m, 1H), 1.70 – 1.51 (comp, 10H), 1.51 – 1.32 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.81, 173.45, 153.39, 152.97, 143.80, 143.06, 129.31, 128.57, 127.30, 127.09, 118.99, 118.18, 115.40, 115.02, 110.22, 109.78, 76.68, 62.03, 62.00, 59.59, 58.33, 49.64, 49.43, 42.85, 42.73, 40.52, 35.01, 30.40, 27.18, 26.77, 26.55, 26.53, 25.85, 25.79, 25.46, 25.04.; Chemical Formula: $C_{18}H_{22}N_2O_3$, *m/z* (ESIMS) 315.3 $[M + H]^+$; HPLC: Daicel Chiralcel OD-H, hexanes/*i*-PrOH=95/05, Flow rate = 1 mL/min, UV = 254 nm, t_R=60.9 min (major), t_R=68.4 min; and t_R=91.4 min, t_R=96.7 min (major).

3-((11bR, 12R)-7,11b,12,13-tetrahydro-6*H*-isoquinolino[2,1-*a*]quinoline-12-carbonyl)oxazolidin-2-one (2.24i, mixture of diastereomer):



Following the general procedure (7 h) the title compound was obtained as a light yellow solid in 97% yield (dr: 1:1). mp: 58 – 60 °C; (R_f = 0.36 in 40% EtOAc/Hex); $[\alpha]_D^{20}$ + 46.5 (c 1.0, $CHCl_3$, 70% *ee*, 60% *ee*); IR (KBr) 2924, 2852, 2077, 1773, 1691, 1601, 1573, 1499, 1478, 1450, 1386, 1325, 1308, 1263, 1217, 1108, 1040, 969, 941, 744, 70, 665, 645 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 – 7.03 (comp, 3H), 7.00 (app d, *J* = 7.2 Hz, 1H), 6.68 (app d, *J* = 8.2 Hz, 1H), 6.65 – 6.55 (comp, 3H), 4.45 – 4.38 (comp, 2H), 4.34 (app dd, *J* = 16.6, 8.4 Hz, 2H), 4.07 (app dd, *J* = 18.2, 9.3 Hz, 1H), 4.04 – 3.98 (m, 1H), 3.98 – 3.82 (comp, 6H), 3.82 – 3.75 (m, 1H), 3.70 (app d, *J* = 8.8 Hz, 1H), 3.39 – 3.26 (comp, 2H), 3.19 (app dd, *J* = 18.2, 7.1 Hz, 1H), 3.09 (dd, *J* = 16.7, 6.4 Hz, 1H), 2.96 (app d, *J* = 16.7 Hz, 1H), 2.67 (dd, *J* = 16.7, 3.8 Hz, 1H), 1.99 –

1.83 (comp, 2H), 1.83 – 1.58 (comp, 11H), 1.59 – 1.36 (comp, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.55 (x 2) , 153.30, 153.01, 143.89, 143.36, 129.37, 128.57, 127.09, 126.97, 119.16, 118.99, 115.30, 115.28, 111.75, 111.08, 61.98, 61.96, 59.16, 58.26, 53.73, 52.93, 42.76, 42.60, 40.57, 40.36, 33.39, 28.63, 27.58, 27.33, 27.31, 27.30, 27.16, 26.53, 26.36, 26.13, 25.49, 24.87.; Chemical Formula: $C_{19}H_{24}N_2O_3$, *m/z* (ESIMS) 329.3 $[M + H]^+$; HPLC: Daicel Chiralcel OD-H, hexanes/*i*-PrOH=95/05, Flow rate = 1 mL/min, UV = 254 nm, t_R=39.6 min, t_R=50.2 min (major); and t_R=68.2 min, t_R=80.0 min (major).

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14. Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 11847.

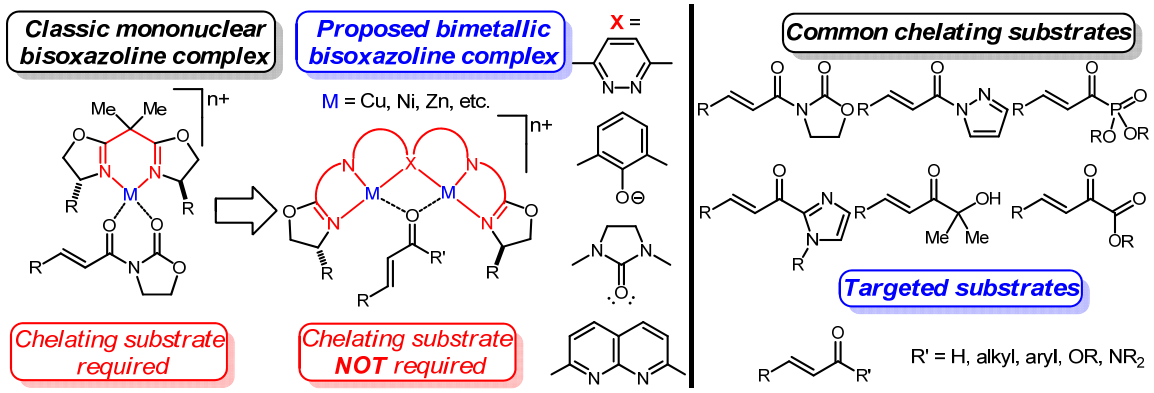
Chapter III Redox–Neutral Synthesis of Cyclic Aminals

3.1 Aminal Formation Derived from *o*-Aminobenzaldehyde and Cyclic Amines

3.1.1 Background

Our projects related to aminal formations initially arose from a serendipitous discovery during the course of another project. Due to our interest in developing new concepts for asymmetric catalysis using transition metals, we attempted to design chiral bimetallic ligands (Figure 3.1). Most of the chiral ligands that are currently used form mononuclear metal complexes. For instance, chiral bisoxazoline ligands play an important role in asymmetric Lewis acid catalysis. These ligands bind to Lewis acids via bidentate chelation, which results in chiral Lewis acid complexes.[1] Substrates are then activated by chelating to these chiral complexes, therefore leading to enantioselectivity for the reaction. Although these mononuclear metal complexes are used widely in asymmetric catalysis, they require chelatable substrates, which generally require extra

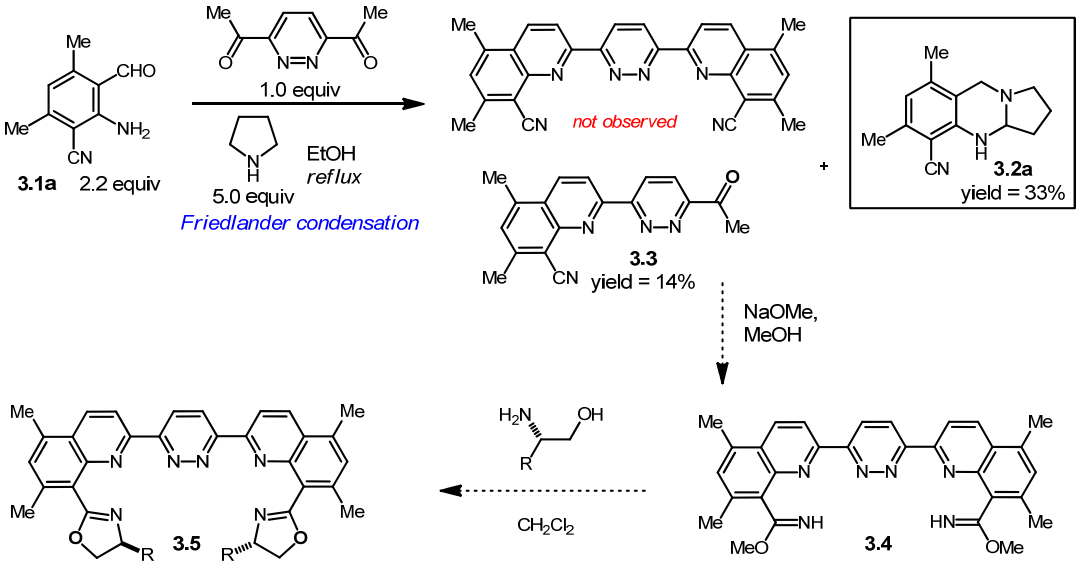
Figure 3.1 **Proposed Bimetallic Ligands**



synthetic steps, thus lowering atom economy and synthetic efficiency. Our aim was to develop binuclear metal complexes that can overcome these limitations of monometallic complexes.[2]

In order to obtain binuclear metal complexes, we started with a hexa-dentate chiral ligand with a pyridazine bridge. The proposed synthetic route is outlined in Scheme 3.1. However, the Friedländer condensation for the reaction between **3.1a** and 3,6-diacetyl-pyridazine did not proceed as expected.[3] Instead, the mono-substituted product **3.3** was obtained in 14% yield. Surprisingly, a novel ring-fused aminal **3.2a** was also formed by the condensation of **3.1a** and pyrrolidine under thermal conditions. An insoluble precipitate was observed, however, its insolubility prevented any characterization. We presumed that this precipitate corresponded to the desired product. Although pyrrolidine is frequently used as the base promoter in Friedländer condensation

Scheme 3.1 **Proposed Synthetic Routes and an Unexpected Aminal Product**



between *o*-aminobenzaldehydes and ketones,[3,4] to the best of our knowledge, aminals such as **3.2** have not been reported previously as side products of the Friedländer condensation. Using three equivalents of pyrrolidine, the *o*-aminobenzaldehyde **3.1a** was consumed completely, and the aminal product **3.2a** was obtained in 95% yield.

3.1.2 A New Transformation between Cyclic Amines and *o*-Aminobenzaldehydes

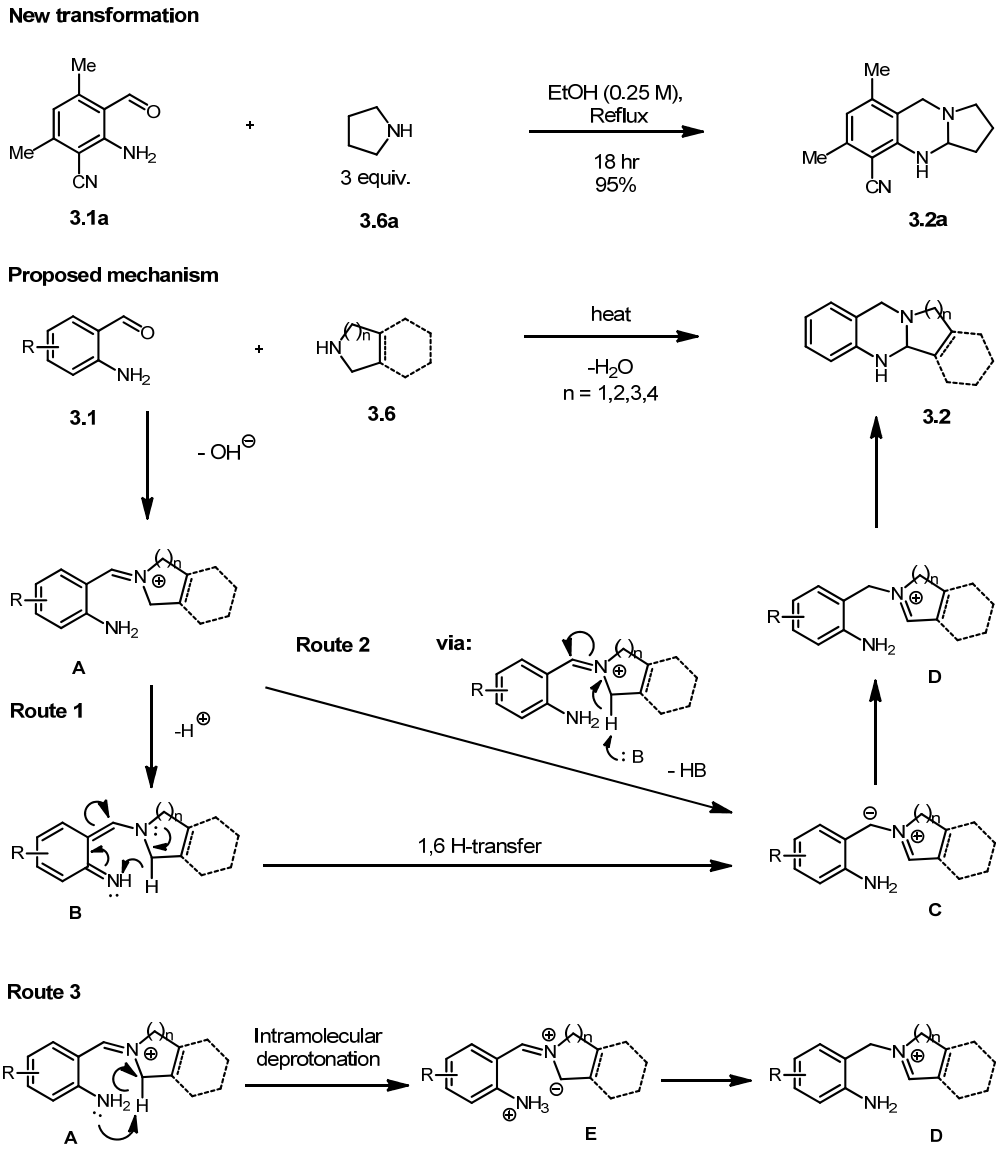
In this redox–neutral condensation reaction, a C–H bond α to a ring nitrogen is replaced by a C–N bond, concomitant with the formation of a new ring system.[5,6] This thermally promoted reaction between an *o*-aminobenzaldehyde and a cyclic amine results in the formation of a ring-fused aminal and thus provides convenient access to this structural motif (Scheme 3.2).[7] This new transformation represents the direct functionalization of nitrogen heterocycles, which offers an attractive entry to important molecular targets that might otherwise require lengthy synthetic procedures.[8]

Based on this transformation, we proposed a mechanistic hypothesis for this aminal formation involving the loss of a proton from the intermediate iminium ion **A** upon rearrangement of the adjacent π-system. The resulting quinoidal intermediate **B** is envisioned to undergo a 1,6-hydrogen transfer to form a dipolar intermediate **C** (Scheme 3.2, route 1).[9,10]

However, because it was reported that dipolar intermediates could be generated from tetrahydroisoquinoline and aldehydes,[11] route 2 cannot be ruled out (Scheme 3.2). In this pathway, intermediate **A** could be deprotonated by excess pyrrolidine, resulting in the direct formation of the dipolar intermediate intermediate **C**.

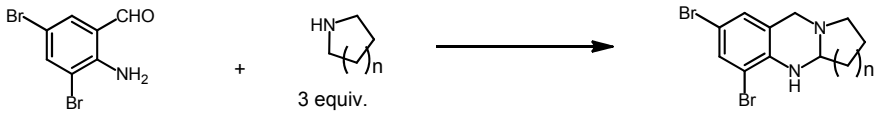
In addition, transient dipoles have previously been generated by the condensation of cyclic amines with α-dicarbonyl compounds, followed by trapping through intra or intermolecular dipolar cycloadditions.[12] This evidence suggests that tertiary amine moiety of the intermediate **A** can possibly be deprotonated by the neighboring amine moiety intramolecularly, leading to the dipolar intermediate **E** (Scheme 3.2, route 3).

Scheme 3.2 **New Transformation and Proposed Mechanism**



Presumably, the dipolar intermediate **C** is protonated to form the intermediate iminium ion **D**. Then, the amino group of the intermediate **D** attacks the neighboring iminium ion moiety, which ultimately leads to the final product **3.2** (Scheme 3.2).

Table 3.1 **Optimization of the Reaction Conditions**[a]



entry	amine	solvent	temperature (°C)	additive	time (h)	yield (%)
1	Piperidine	EtOH	78	--	48	6
2	Piperidine	DMF	153	--	24	NR
3	Piperidine	Toluene	110	--	24	6
4[b]	Piperidine	Piperidine	120	--	48	NR
5	Piperidine	THF	66	--	12	NR
6	Piperidine	MeCN	82	--	18	NR
7	Piperidine	*i*PrOH	83	--	22	13
8	Piperidine	EtOH	78	TFA (30 mol%)	24	6
9	Piperidine	EtOH	78	NaOMe (30 mol%)	24	NR
10[b]	Piperidine	EtOH	120	--	48	35
11[b]	Piperidine	EtOH	140	--	48	61
12[b]	Piperidine	*i*PrOH	140	--	48	65
13[b]	Piperidine	Toluene	140	--	48	53
14	Piperidine	Toluene	110	--	24	17
15	Pyrrolidine	EtOH	78	--	24	80

[a] Reactions were run on a 0.35 mmol scale in ethanol solution (0.25 M) at reflux. [b] The reaction was run in a sealed tube.

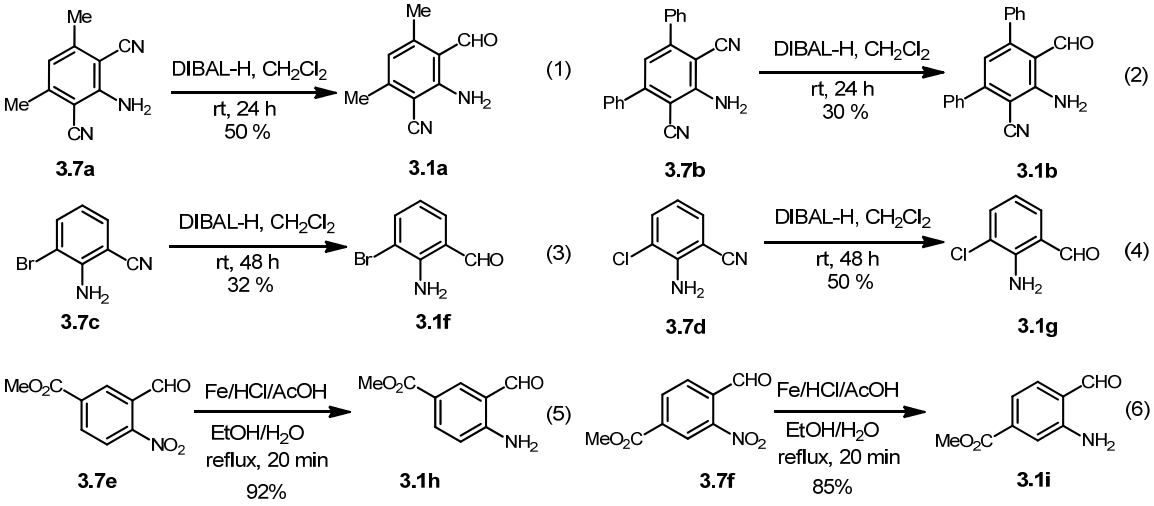
3.1.3 Optimization of the Reaction Conditions

In light of this intriguing discovery, efforts were hence undertaken to optimize the reaction conditions, which are outlined in Table 3.1. We started to evaluate the reaction conditions with piperidine as the amine component because it demonstrated a reduced reactivity in comparison to pyrrolidine and provided only 6% yield of the corresponding product **3.8** when the reaction was conducted under the original conditions (Table 3.1, entry 1). When morpholine was used as the amine component, none of the corresponding aminal product was detected. Alcoholic solvents proved to be better than other solvents such as toluene, DMF, THF, acetonitrile or piperidine (Table 3.1, entries 1-7). When trifluoroacetic acid was used as an additive, no improvement of the reaction was observed (Table 3.1, entry 8). The use of sodium methoxide as an external base completely shut down the reaction (Table 3.1, entry 9), which indicates that the iminium ion formation is vital to trigger this transformation. A significant improvement was achieved by conducting the reaction in a sealed tube at a higher temperature. While 35% of the expected product was isolated at 120 °C in a sealed tube in ethanol (Table 3.1, entry 10), 61% yield was obtained at a higher temperature (140 °C) (Table 3.1, entry 11). The yield was slightly improved when isopropanol was used as the solvent (Table 3.1, entry 12), whereas toluene led to a reduced yield (Table 3.1, entries 13 and 14). In summary, we found that the transformation between *o*-aminobenzaldehydes and secondary amines was favored by alcoholic solvents and could be promoted further by using a sealed tube.

3.1.4 Substrate Scope for the Novel Transformation

Using the optimized conditions, we further investigated the scope of this intriguing transformation. First, a number of previously unreported *o*-aminobenzaldehydes were prepared. The *o*-aminobenzaldehydes **3.1a** and **3.1b** were obtained readily by DIBAL-H reduction of the corresponding dinitrile anilines **3.7a** and **3.7b** (Figure 3.2, eqs 1 and 2). Similarly, the halogenated *o*-aminobenzaldehydes **3.1f** and **3.1g** were synthesized via DIBAL-H reduction of the corresponding *o*-nitrile-aniline precursors **3.7c** and **3.7d** (Figure 3.1, eqs 3 and eq 4). Good yields were achieved for the preparation of *o*-aminobenzaldehydes **3.1h** and **3.1i**, which were obtained from the corresponding *o*-nitrobenzaldehydes by iron reduction under acidic conditions.

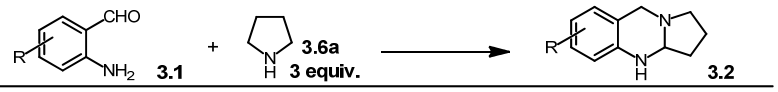
Figure 3.2 **Preparation of *o*-Aminobenzaldehydes**

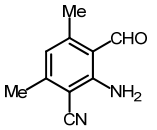
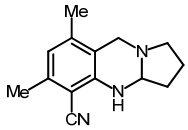
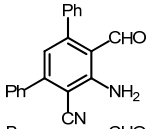
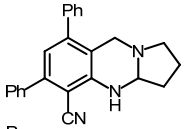
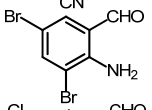
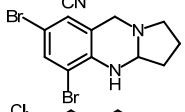
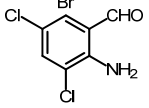
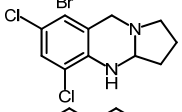
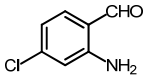
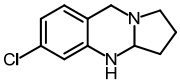
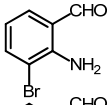
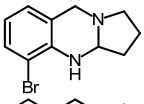
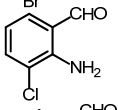
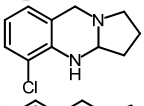
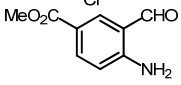
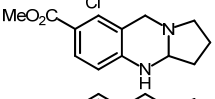
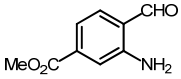
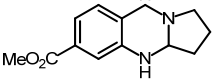
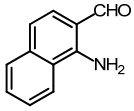
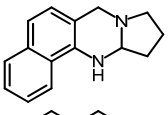
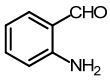
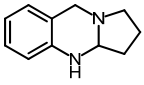
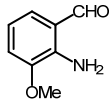
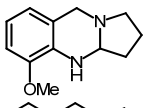
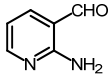
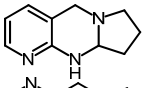
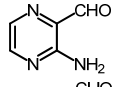
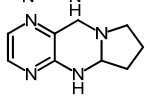
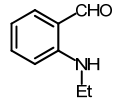
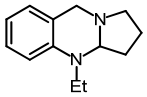


Using the newly synthesized *o*-aminobenzaldehydes, the scope of this reaction was evaluated and is summarized in Table 3.2. A range of aminoaldehydes was allowed to react with three equivalents of pyrrolidine in an ethanol solution under reflux. *o*-Aminobenzaldehydes with different functional groups and electronic properties proved to

be suitable substrates, providing products in good yields. The two *o*-aminobenzaldehydes (**3.1a** and **3.1b**) that were prepared as precursors for bimetallic ligands exhibited excellent reactivity (Table 3.2, entries 1 and 2). Halogen substituted *o*-aminobenzaldehydes (**3.1c** and **3.1d**) also provided good yields of the corresponding aminal products (Table 3.2, entries 3 and 4). However, the yield for the *o*-aminobenzaldehyde **3.1e**, which contains a chloro substituent at the *para* position of the carbonyl group, was significantly diminished (Table 3.2, entry 5). On the other hand, good reactivities and yields were obtained when the halogen substituents were *ortho* to the amino group (Table 3.2, entries 6 and 7). When aminobenzaldehydes containing methyl ester substituents (**3.1h** and **3.1i**) were explored under the original reaction conditions, a partial transesterification occurred in an ethanol solution (Table 3.2, entries 8 and 9). Therefore, in these two cases, the reaction was run in a sealed tube in methanol at 100 °C. The aminonaphthaldehyde **3.1j** provided a 58% yield of **3.2j** after 48 hours (Table 3.2, entry 10). The unsubstituted aminobenzaldehyde **3.1k** gave a 73% yield of the corresponding aminal **3.2k**, although 72 hours were required to complete the reaction (Table 3.2, entry 11). In the case of the electron-rich *o*-aminobenzaldehyde **3.1l**, which exhibited low reactivity, the transformation was conducted in a sealed tube in ethanol at 140 °C (Table 3.2, entry 12). Heterocyclic aminobenzaldehydes such as **3.1m** and **3.1n** provided ring-fused aminals in excellent yields (Table 3.2, entries 13 and 14). A substituent on the nitrogen atom of the aminoaldehyde was also well tolerated (Table 3.2, entry 15). In general, electron-poor aminobenzaldehydes were particularly reactive (Table 3.2, entries 3, 4, 6, 7, 13 and 14), whereas more electron-rich substrates (Table

Table 3.2 **Variation of the Aminoaldehyde Component**[a]



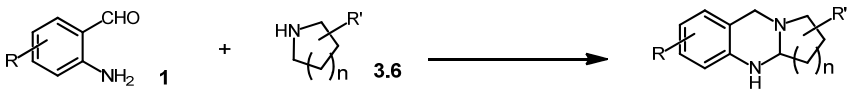
entry	aminoaldehyde		product		time (h)	yield(%)
1		**3.1a**		**3.2a**	18	95
2		**3.1b**		**3.2b**	12	92
3		**3.1c**		**3.2c**	23	92
4		**3.1d**		**3.2d**	12	84
5		**3.1e**		**3.2e**	72	57
6		**3.1f**		**3.2f**	36	83
7		**3.1g**		**3.2g**	18	76
8		**3.1h**		**3.2h**	24	76
9		**3.1i**		**3.2i**	24	60
10		**3.1j**		**3.2j**	48	58
11		**3.1k**		**3.2k**	72	73
12		**3.1l**		**3.2l**	48	81
13		**3.1m**		**3.2m**	36	94
14		**3.1n**		**3.2n**	13	91
15		**3.1o**		**3.2o**	80	84

[a] Reactions were run on a 1 mmol scale in ethanol solution (0.25 M) at reflux.

3.2, entries 11 and 12) provided products in good yields albeit with extended reaction times.

Next, a variety of *o*-aminoaldehydes were allowed to react with various secondary cyclic amines, and the results are summarized in Table 3.3. Piperidine demonstrated a reduced reactivity under normal reaction conditions; this required that the reaction be performed in isopropanol at 140 °C in a sealed tube. This condition provided the expected product **3.8** in a 67% yield (Table 3.3, entry 1). The analogous seven-membered aza-heterocycle azepane **3.6c** exhibited a better reactivity, which provided the aminal **3.9** in a yield of 77% in a sealed tube (Table 3.3, entry 2). The eight-membered aza-heterocycle azocane **3.6d** gave the expected product in 60% yield under reflux (Table 3.3, entry 3). In this new type of transformation, the reactivity of these cyclic amines decreased in the following order: pyrrolidine > azocane > azepane > piperidine > morpholine. Amines containing benzylic hydrogen atoms α to the ring nitrogen were particularly effective substrates (Table 3.3, entries 4–6). However, the scope of the amine components appeared to be limited to heterocyclic secondary amines. Furthermore, not all of the cyclic amines underwent this transformation. For example, neither indoline nor isoindoline gave rise to the corresponding cyclic aminal (Table 3.3, entries 7 and 8). No reaction was observed with either methylbenzyl amine or dibenzyl amine (Table 3.3, entries 9 and 10). Trace amounts of the expected product were detected when morpholine was allowed to react with **3.1c** in ethanol at 140 °C in a sealed tube. *o*-Aminoacetophenone was also evaluated as a substrate, but no transformation was detected.

Table 3.3 **Variation of the Amine Component**[a]



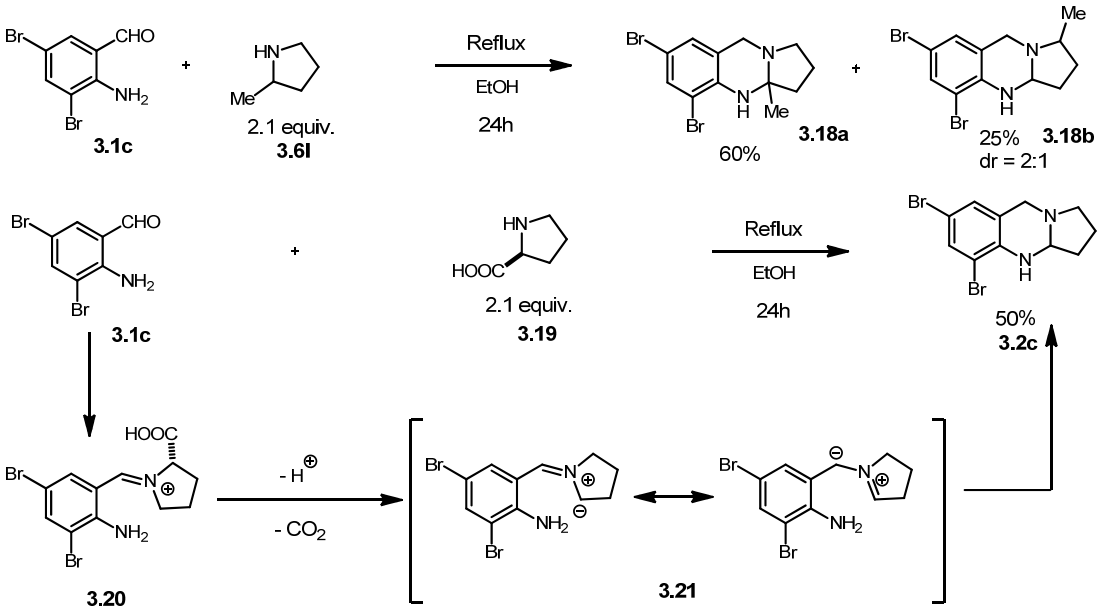
entry	amino-aldehyde	amine (equiv)	product	time (h)	yield (%)
1[b]	**3.1c**	(3) **3.6b**	**3.8**	48	67
2[c]	**3.1c**	(3) **3.6c**	**3.9**	24	77
3	**3.1a**	(3) **3.6d**	**3.10**	48	60
4	**3.1k**	(3) **3.6e**	**3.11**	72	95
5	**3.1k**	(2.1) **3.6f**	**3.12**	72	66
6	**3.1h**	(2) **3.6g**	**3.13**	48	80
7[c]	**3.1c**	(3) **3.6h**	**3.14**	48	NR[d]
8[c]	**3.1c**	(3) **3.6i**	**3.15**	48	ND[e]
9[c]	**3.1c**	(3) **3.6j**	**3.16**	48	NR[d]
10[c]	**3.1c**	(3) **3.6k**	**3.17**	48	NR[d]

[a] Reactions were run on a 1 mmol scale in ethanol solution (0.25 M) at reflux. [b] The reaction was run in a sealed tube in isopropanol solution at 140 °C. [c] The reaction was run in a sealed tube in ethanol solution at 140 °C. [d] No reaction. [e] No desired product formation.

3.1.5 Mechanistic Insights

In order to investigate the regioselectivity of this transformation, 2-methyl-pyrrolidine was evaluated as the amine moiety (Figure 3.3). The reaction of 2-methyl-pyrrolidine with *o*-aminobenzaldehyde **3.1c** provided a mixture of regioisomers. The more substituted regioisomer was the major product of this reaction, and the minor regioisomer was obtained as a 2:1 mixture of diastereomers. This latter observation

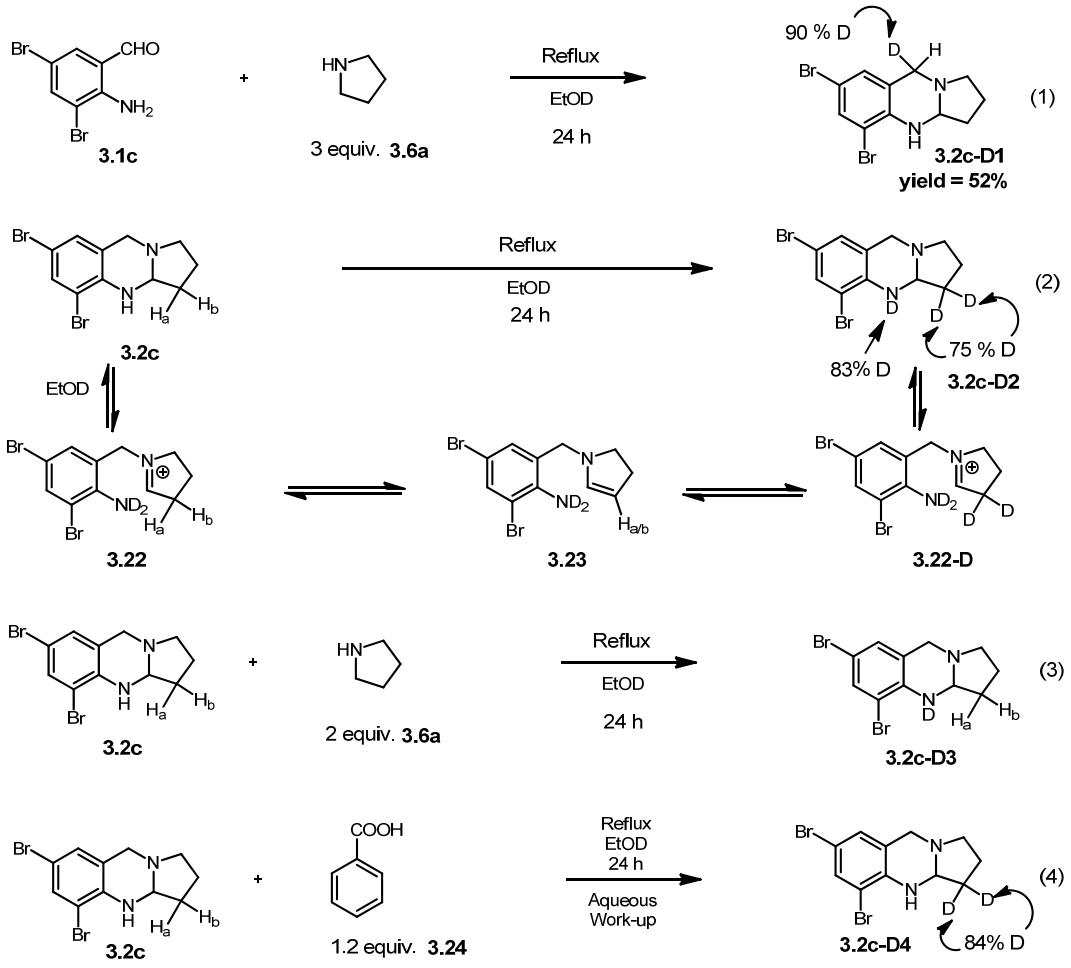
Figure 3.3 **Mechanistic Insights**



combined with the notably increased reactivity of benzylic amines suggests that a 1,6-hydride shift may have occurred.[10] Further mechanistic insights are provided by the observation that the reaction of aminobenzaldehyde **3.1c** with proline gave the same product as the corresponding reaction with pyrrolidine under identical conditions (Figure 3.3). It is well established that reactions of aldehydes with proline and other *N*-alkylated amino acids form 1,3-dipolar intermediates upon decarboxylation.[13] This finding is

consistent with the notion that 1,3-dipoles are likely intermediates in this reaction. However, this type of 1,3-dipole functionalization is unusual,[14] and it indicates an unconventional functionalization of azomethine ylides in the final step of the reaction cascade.

Figure 3.4 **Deuterium Labeling Experiments**



In order to investigate the mechanism, ethanol-OD was adopted as the solvent. A deuterium incorporation of approximately 90% was detected for the benzylic hydrogen in the aminal product by NMR analysis, which shows that the hydride at the α position of

pyrrolidine was not incorporated in the benzylic position of the product. Therefore, a 1,3-hydride shift was unlikely to have occurred in this reaction.

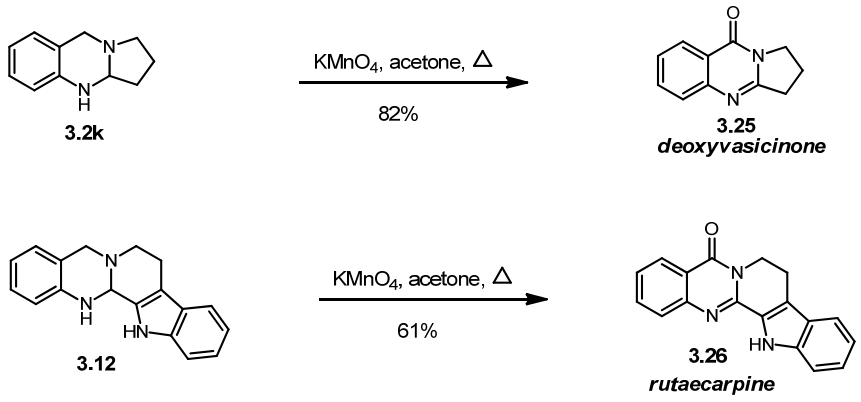
In order to establish the reversibility of the transformation, the aminal product **3.2c** was heated under reflux in ethanol-OD for 24 hours. In this case, the benzylic hydrogens of **3.2c** remained undeuterated. Instead, H_a and H_b were significantly exchanged with deuterium by 75% (Figure 3.4, eq. 2), which can be explained by the reversibility of the cyclization. The cyclic aminal underwent a ring-opening reaction, which resulted in the corresponding iminium ion intermediate **3.22**. Deprotonation of the iminium ion led to the enamine intermediate **3.23**, which could further abstract the deuterium from ethanol-OD to form the iminium ion, followed by another cyclization reaction. This interesting result suggests that the further functionalization of the aminal product is possible due to the availability of the enamine intermediate **3.23**. Furthermore, in the absence of pyrrolidine, this phenomenon clearly shows that the final ring-closure step is reversible, but that the functionalization of the 1,3-dipole is irreversible.

However, since no deuterium incorporation was detected for either H_a or H_b in the aminal formation reaction (Figure 3.4, eq. 1), we needed to examine the possibility that pyrrolidine could inhibit their deuteration (Figure 3.4, eq. 3). Interestingly, no deuterium exchange occurred for either the benzylic hydrogen or H_a/H_b in the presence of 2 equivalents of pyrrolidine. This observation suggests that the cyclization step is irreversible under the present reaction conditions in the presence of excess amounts of pyrrolidine. Furthermore, 1.2 equivalents of benzoic acid assisted in the ring-opening of aminal **3.2c**, followed by the exchange of deuterium (Figure 3.4, eq. 4). In this case, there is no deuterium incorporation in the secondary amine due to the aqueous work-up.

3.1.6 Application of Aminals in the Synthesis of Natural Products

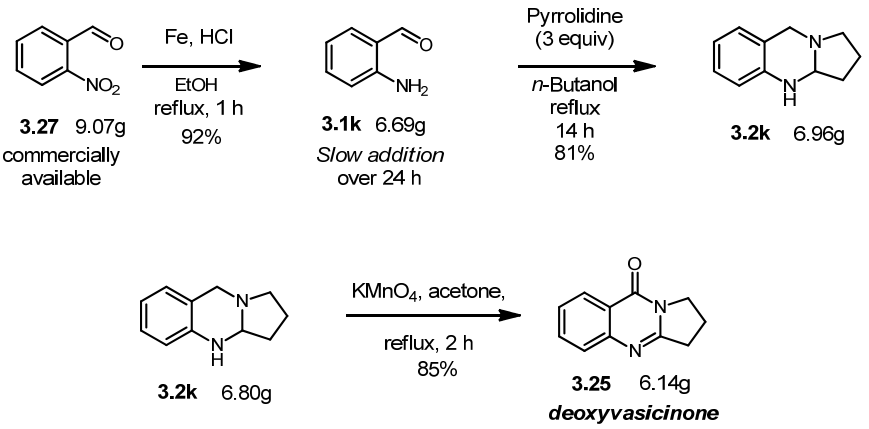
Aminals are found in a number of natural products.[15] In addition, aminals with the general structure **3.2** represent reduced versions of quinazolinone alkaloids. These alkaloids have attracted significant attention in the synthetic community due to their diverse array of biological activities.[16,17] Selective oxidation of ring fused aminals provides a rapid access to this structural motif (Figure 3.5). With one additional step, two steps from commercially available materials, deoxyvasicinone[18] and rutaecarpine[19] were obtained in 82% and 61% yields, respectively.

Figure 3.5 **Natural Product Syntheses**



In order to synthesize these versatile building blocks on a large scale, efforts were made to optimize the synthetic procedures. While the aminal formation between **3.1k** and pyrrolidine did not achieve good yields on a large scale under the original reaction conditions, *n*-butanol was found to provide more efficient access to this ring fused aminal under reflux with good yields. A syringe pump was used to add the *o*-aminobenzaldehyde slowly, which further improved the yield, as a high concentration of *o*-aminobenzaldehyde leads to self-condensation.[20]

Figure 3.6 **Large Scale Synthesis of Deoxyvasicinone**



3.1.7 Summary

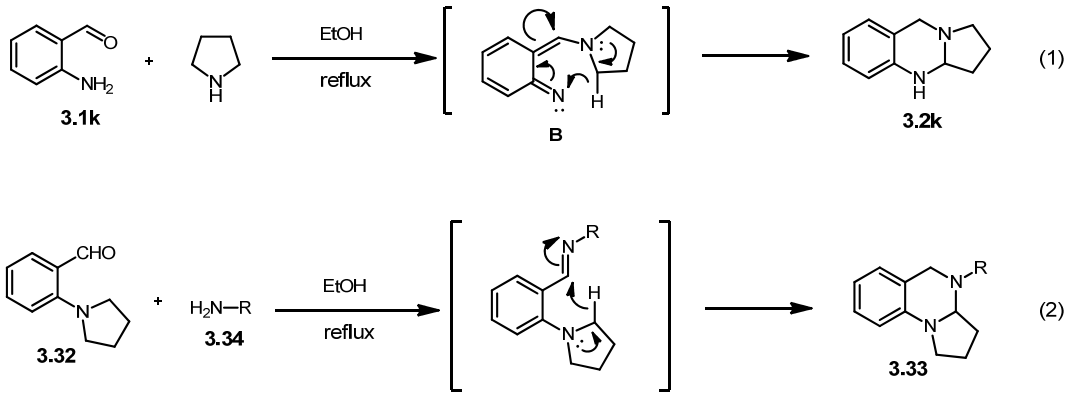
Thus far, we have demonstrated a novel redox–neutral reaction cascade that involves the functionalization of a relatively unreactive C–H bond. In this transformation a C–H bond *α* to the tertiary ring nitrogen of cyclic amines is functionalized to form a C–N bond, which results in a ring-fused aminal. This novel transformation demonstrates fast access to synthetic useful aminal skeletons starting from readily available substrates. Further studies will be required to delineate the mechanism of this transformation. Azomethine ylides are likely intermediates in this reaction, however, at present, there is no direct evidence that would favor a 1,6-hydride shift/ring-closure process over an intra- or intermolecular deprotonation mechanism. In addition, the efficient synthesis of deoxyvasicinone and rutaecarpine demonstrated the great potential of this redox–neutral chemistry. Subsequently, Dang and Bai reported a similar transformation of *o*-aminobenzaldehyde **4.21** with different amino acids (Figure 4.2, eq 6).[21a]

3.2 Brønsted Acid Promoted Redox Aminal Formation

3.2.1 Background

We have just discussed a novel process for cyclic aminal synthesis, in which a hydride is presumably transferred to the neighboring nitrogen atom of the imine moiety of the intermediate **B** (Figure 3.7, eq 1).[21b] In order to further expand the substrate scope with respect to the hydride acceptor moiety, we started to investigate different imine moieties. Because the imine moiety is well-known to be more electrophilic at the carbon atom, we decided to explore the transformation of intermediate **E** derived from *o*-aminobenzaldehyde **3.32** and primary amine **3.34** (Figure 3.7, eq 2). In this transformation, another type of cyclic aminal **3.33** could be synthesized via a similar hydride shift initiated reaction cascade.

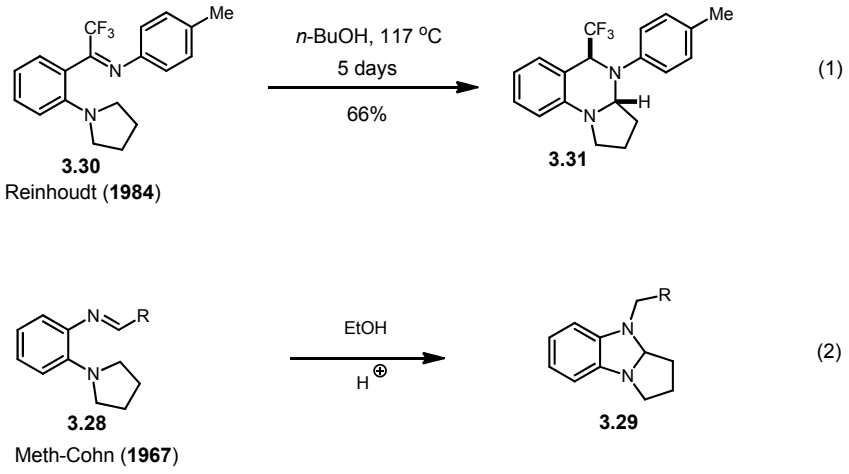
Figure 3.7 **Another Type of Aminal Formation**



In 1984, Reinhoudt showed that the transformation of imine **3.28** to aminal **3.29** was initiated by a 1,5-hydride shift. This is the first example of the type 2 *tert*-amino effect involving a C–N bond formation (Figure 3.8, eq 1).[22] Five days of reaction time is necessary for the complete transformation of **3.28** in *n*-butanol under reflux, giving

product **3.29** in 66% yield as a single diastereomer. Harsh reaction conditions and limited substrate scope are drawbacks of this reaction. No further efforts were made to extend the reaction scope and improve the reaction conditions for this important type of *tert*-amino effect involving a C–N bond formation.

Figure 3.8 **Aminal Formations in the *tert*-Amino Effect**



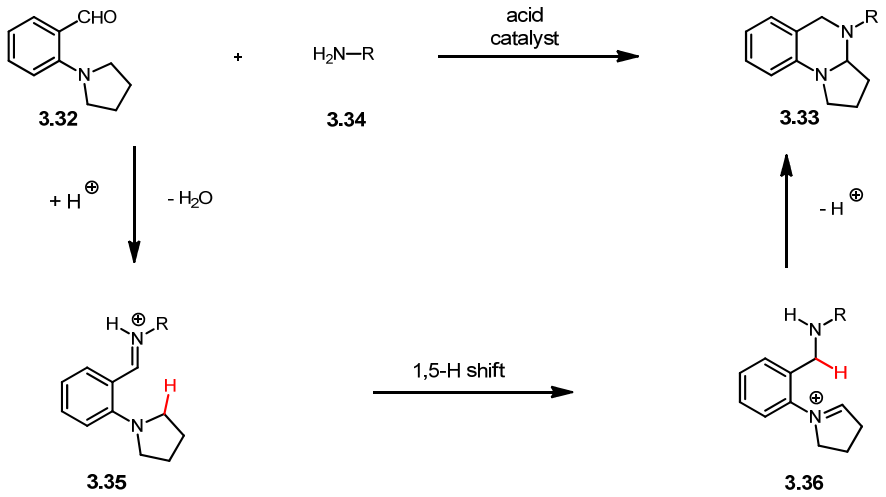
Furthermore, α-functionalization of tertiary amines is involved in a number of aminal forming reactions (Figure 3.8, eq 2). The acid-catalyzed reaction outlined in eq 2 is an early example of the type 1 *tert*-amino effect and is known to occur in the presence of an acid, often at room temperature.[23] The initial products **3.29**, which are known to be unstable, readily undergo oxidation to yield the corresponding benzimidazolium salts.[23]

Recently, the *tert*-amino effect reactions have received increased interest. However, relatively few attempts have been successful in developing catalytic approaches.[24] In order to expand the scope and synthetic utility of these intriguing transformations, it is highly desirable to employ efficient catalysts that can provide milder reaction conditions as well as shorter reaction times. Hence, we introduce an

intramolecular redox–neutral synthesis of polycyclic aminals from *o*-aminobenzaldehydes and primary amines in a simple one-pot procedure promoted by Brønsted acids.

We speculated that this transformation could be readily realized as a one-pot acid-catalyzed procedure because we could produce the imine *in situ*, with no isolation required (Scheme 3.3). Thus, the reaction of *ortho*-(*tert*)-aminobenzaldehydes such as **3.32** with primary amines can possibly provide direct access to the potentially useful heterocyclic skeleton **3.33**.[5a,7]

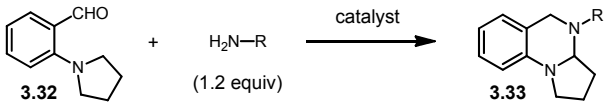
Scheme 3.3 **Proposed Brønsted Acid-Promoted Process**



3.2.2 Evaluation of Potential Catalysts

Brønsted and Lewis acids were evaluated as catalysts for the reaction between *o*-aminobenzaldehyde **3.32** and aniline (Table 3.4, entries 1-14). No formation of **3.33a** was observed when the reaction was performed in ethanol in the absence of acids. Interestingly, addition of trifluoroacetic acid (20 mol%) to the reaction mixture at room

Table 3.4 **Evaluation of Potential Catalysts**



Entry	R	Temp.[°C]	Catalyst (equiv)	Solvent	Time [h]	Yield [%]
1	Ph	rt	CF_3COOH (0.2)	EtOH	48	38
2	Ph	reflux	CF_3COOH (0.2)	EtOH	12	66
3	Ph	reflux	CF_3COOH (0.2)	MeCN	5	57
4	Ph	reflux	CF_3COOH (0.2)	THF	12	38
5	Ph	reflux	CF_3COOH (0.2)	CH_2Cl_2	36	30
6	Ph	reflux	CF_3COOH (0.2)	PhH	7	60
7	Ph	reflux	CF_3COOH (1.2)	EtOH	12	53
8	Ph	reflux	CF_3SO_3H (0.2)	EtOH	3	71
9	Ph	reflux	4-Me-$C_6H_4SO_3H$ (0.2)	EtOH	12	53
10	Ph	reflux	2,4-$(NO_2)_2$-$C_6H_3SO_3H$ (0.2)	EtOH	12	66
11	Ph	reflux	CH_3COOH (0.2)	EtOH	24	50
12	Ph	reflux	HCl (1.2)	EtOH	12	71
13	Ph	reflux	$Zn(OTf)_2$ (0.1)	EtOH	12	52
14	Ph	reflux	$Yb(OTf)_3$ (0.1)	EtOH	12	45
15	Bn	rt	CF_3COOH (0.2)	EtOH	24	NR
16	Bn	reflux	CF_3COOH (0.2)	EtOH	24	54
17	Bn	reflux	CF_3COOH (0.2)	MeCN	24	57
18	Bn	reflux	CF_3COOH (0.2)	THF	24	NR
19	Bn	reflux	$MeSO_3H$ (0.2)	EtOH	24	53
20	Ph	reflux	4-Me-$C_6H_4SO_3H$ (0.2)	EtOH	24	48
21	Bn	reflux	CF_3COOH (1.2)	EtOH	12	75
22	Bn	reflux	H_3PO_4 (0.2)	EtOH	24	NR
23	Bn	reflux	CH_3COOH (0.2)	EtOH	24	31
24	Bn	reflux	CF_3SO_3H (0.2)	EtOH	24	60
25	Bn	reflux	HCl (1.2)	EtOH	12	47
26	Bn	reflux	$Zn(OTf)_2$ (0.1)	EtOH	24	53
27	Bn	reflux	$Yb(OTf)_3$ (0.1)	EtOH	24	53

temperature led to the formation of **3.33a**, but the reaction remained incomplete even after 48 hours (Table 3.4, entry 1). Under the same conditions but at reflux temperature, the reaction was complete after 12 h and **3.33a** was isolated in 66% yield (Table 3.4, entry 2). Different solvents like THF, benzene, dichloromethane and acetonitrile were

evaluated (Table 3.4, entries 3-6). Acetonitrile and benzene could enhance the rate of the reaction but the yield was lower (Table 3.4, entries 3 and 6). When dichloromethane and THF were used as solvents, the reaction was sluggish (Table 3.4, entries 4 and 5). Ethanol proved to be the best solvent among those evaluated. Addition of excess trifluoroacetic acid (Table 3.4, entry 7) did not lead to a shortened reaction time but instead resulted in a reduced yield of product **3.33a**. Strong acids like *p*-TSA, 2,4-dinitrobenzenesulfonic acid and hydrochloric acid rendered good reactivities and yields (Table 3.4 entries 9, 10 and 12). Weak acids like acetic acid led to an incomplete reaction (Table 3.4, entry 11). Other acids listed as viable catalysts, including Lewis acids such as zinc (II) triflate and ytterbium (III) triflate (Table 3.4, entries 13 and 14). Ultimately, triflic acid (20 mol%) was identified as the optimal catalyst with **3.33a** being isolated in 71% yield (Table 3.4, entry 8).

A different reactivity pattern was observed for the reaction of *o*-aminobenzaldehyde **3.32** with benzylamine (Table 3.4, entries 15-27). No reaction was observed in the absence or presence of trifluoroacetic acid (20 mol%) at room temperature (Table 3.4, entry 15). Performing the reaction in the presence of trifluoroacetic acid (20 mol%) under reflux conditions led to a full conversion with the formation of **3.33b** in 54% yield (Table 3.4, entry16). Ethanol was proven to be the optimal solvent among those tested (Table 3.4, entries 16-18). Then, a number of Brønsted and Lewis acids were evaluated for the reaction of **3.32** with benzylamine. The reaction did not go to a full conversion when methanesulfonic acid, *p*-TSA or acetic acid were used as catalysts (Table 3.4, entries 19, 20 and 23). No reaction occurred in the case of phosphoric acid (Table 3.4, entry 22). Good reactivity was observed with the

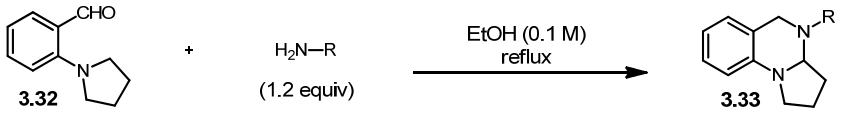
addition of triflic acid (20 mol%) or hydrochloric acid (120 mol%) (Table 3.4, entries 24 and 25). Remarkably, with 10 mol% zinc triflate or ytterbium triflate catalyst loading, the reaction went to completion after 24 hours under reflux and gave 53% yields in both cases (Table 3.4, entries 26 and 27). Ultimately, the maximum yield for **3.33b** (75%) was obtained when excess trifluoroacetic acid (1.2 equivalent) was used (Table 3.4, entry 21).

Presumably, the actual acid catalyst is an ammonium salt in cases where less than one equivalent of acid is used to facilitate the transformation. Of course, the nature of the counteranion is expected to have a drastic, if nonobvious role, as complex counterion effects are well-documented in the context of iminium catalysis.[25]

3.2.3 Substrate Scope for the Brønsted Acid-Promoted Process

The scope of the reaction of aminobenzaldehyde **3.32** with different aromatic amines was subsequently evaluated (Table 3.5, entries 1-9). Electronically diverse anilines with various substitution patterns provided a facile access to products **3.33** in moderate to good yields. The reaction rate for *p*-ethylaniline was significantly slower than aniline (Table 3.5, entries 1 and 2). Meanwhile, methoxy substituent at the *para* position of aniline enhanced the reaction rate, giving the product in 57% yield after 30 minutes (Table 3.5, entry 4). Bulky substituents on both *ortho* positions of the aniline moiety were readily accommodated (Table 3.5, entry 3). The reaction of **3.32** with 4-cyanoaniline showed excellent reactivity, which proceeded readily at room temperature to provide the corresponding product **3.33f** in 50% yield (Table 3.5, entry 5). *p*-Bromoaniline also exhibited good reactivity (Table 3.5, entry 6). However, a longer reaction time was required for the full conversion of *o*-fluoroaniline (Table 3.5, entry 7).

Table 3.5 **Variation of the Amine Component**[a]

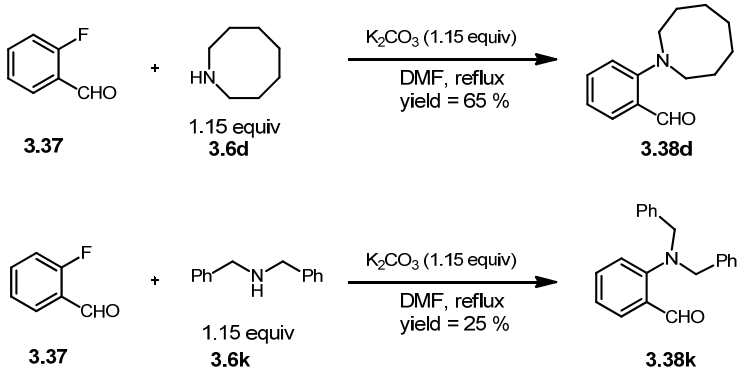


entry	method	product	time (h)	yield(%)
1	A	**3.33a**	3	71
2	A	**3.33c**	12	67
3	A	**3.33d**	5	71
4	A	**3.33e**	0.5	57
5	C	**3.33f**	15	50
6	A	**3.33g**	1.5	65
7	A	**3.33h**	6	50
8	A	**3.33i**	24	35
9	A	**3.33j**	48	36
10	B	**3.33b**	24	75
11	B	**3.33k**	15	70
12	B	**3.33l**	24	65
13	B	**3.33m**	24	66

[a] Method A: CF_3SO_3H (0.2 equiv), reflux. Method B: CF_3COOH (1.2 equiv), reflux. Method C: CF_3SO_3H (0.2 equiv), room temperature.

The use of heterocyclic amines such as 2-aminopyridine or aminopyrimidine (Table 3.5, entries 8 and 9) gave rise to products **3.33i** and **3.33j** in lower yields, presumably due to the availability of multiple protonation sites that might interfere with the catalytic process. Aliphatic amines were also evaluated in the reaction with *o*-aminobenzaldehyde **3.32**. It gave products **3.33** in good yields in all cases (Table 3.5, entries 10-13), using reaction conditions previously optimized for benzylamine. No significant differences of reactivity and yields were observed among these aliphatic amines. Generally, electron deficient anilines demonstrated higher reactivity than electron rich anilines, which was reasonable because the hydride shift step was the rate determining step and the iminium ions derived from electron deficient anilines were better hydride acceptors.

Figure 3.9 **Preparation of *o*-Aminobenzaldehydes**

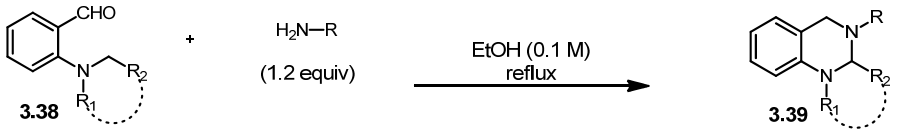


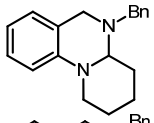
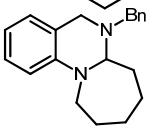
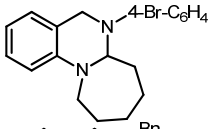
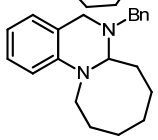
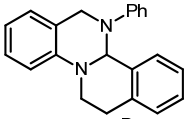
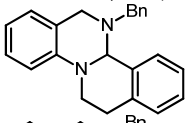
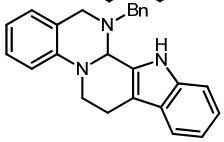
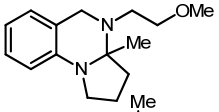
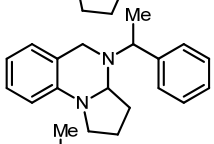
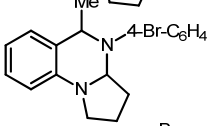
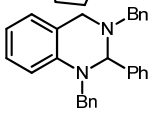
A range of *o*-aminobenzaldehydes were prepared to evaluate the scope of the reaction. The required starting materials were readily obtained from 2-fluorobenzaldehyde and the corresponding secondary amines.[26] Previously unreported *o*-aminobenzaldehydes such as **3.37d** and **3.37k** were prepared following the similar procedure via the SN_{Ar} reaction between the corresponding secondary amines and 2-

fluorobenzaldehyde in the presence of potassium carbonate under reflux in DMF (Figure 3.9).

The scope of the reaction with respect to the aminobenzaldehyde component is summarized in Table 3.6. A number of structurally diverse *o*-aminobenzaldehydes gave rise to products **3.39** upon reaction with primary amines in the presence of acid. The aminobenzaldehyde with a piperidine moiety showed poor reactivity and moderate yield (Table 3.6, entry 1). In contrast, azepane and azocane derivatives exhibited great reactivity and excellent yields (Table 3.6, entries 2-4). *o*-Aminobenzaldehydes derived from cyclic amines bearing benzylic α C–H bonds were particularly reactive (Table 3.6, entries 5-7), presumably due to the increased hydride donor capabilities of these substrates. The reactivity of the secondary amines turned out to be tetrahydroisoquinoline > azocane > azepane > pyrrolidine > piperidine. Compound **3.39h** was isolated as a single regioisomer resulting from the functionalization at the more substituted position (Table 3.6, entry 8). This finding likely reflects the increased hydride donor capability of a tertiary over a secondary C–H bond. Reaction of **3.32** with α-methylbenzylamine gave rise to products **3.39i** as a 59:41 mixture of diastereomers (Table 3.6, entry 9). Similarly, reaction of 2-pyrrolidinyl acetophenone with 4-bromoaniline resulted in the formation of **3.39j** as a 66:34 mixture of diastereomers (Table 3.6, entry 10), illustrating that aminoacetophenones are also viable substrates in this transformation. The low isolated yield of product **3.39k** is likely a reflection of product instability rather than reactivity of the starting material (Table 3.6, entry 11) as a full conversion of the aminobenzaldehyde was observed.

Table 3.6 **Variation of the Aminoaldehyde Component**[a]

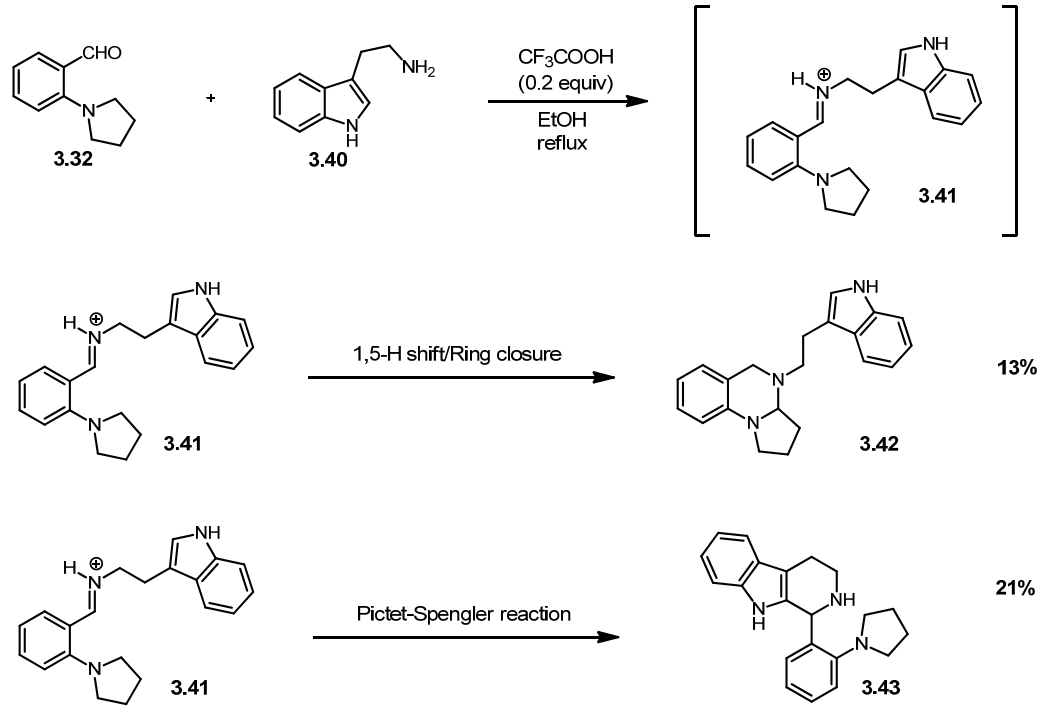


entry	method	product		time (h)	yield(%)
1	B		**3.39a**	24	65
2	B		**3.39b**	2	82
3	B		**3.39c**	1.5	90
4	C		**3.39d**	1.5	85
5	B		**3.39e**	12	99
6	B		**3.39f**	0.5	64
7	B		**3.39g**	1	74
8	B		**3.39h**	1	60
9	B		**3.39i**[b]	15	52
10	A		**3.39j**[c]	3	65
11	B		**3.39k**	12	27

[a] Method A: CF_3SO_3H (0.2 equiv), reflux. Method B: CF_3COOH (1.2 equiv), reflux. Method C: CF_3SO_3H (0.2 equiv), room temperature. [b] dr = 59 : 41. [c] dr = 66 :34.

The reaction of **3.32** with tryptamine was investigated in order to compare the title reaction to a potentially competing Pictet-Spengler pathway, which shared a common iminium ion intermediate **3.41** (Figure 3.10).[23g] Interestingly, a mixture of both products was obtained with the product **3.43**, resulting from the Pictet-Spengler pathway, being the predominantly formed species. Although the overall yields of this non-optimized process were low, the findings demonstrated the relative ease with which acid-catalyzed hydride shift reactions could occur.

Figure 3.10 **Competing Reaction Pathways**



3.2.4 Summary

We have shown that reactions involving the type 2 *tert*-amino effect can be accelerated by Brønsted acids. Since only one example of the synthesis of these aminal skeletons had been reported involving a 1,5-hydride shift/ring closure process, the present

method provides facile access to extensive classes of novel ring-fused aminals. Subsequent to our report, Akiyama disclosed a similar redox–neutral process for the synthesis of this type of aminal promoted by TsOH.[27]

3.3 Conclusion

Two intriguing transformations were documented in this chapter. In both cases, polycyclic quinazolinone scaffolds, which have attracted significant attention due to their diverse array of biological activities, were synthesized via the replacement of the original unreactive C–H bond α to the tertiary amine with a C–N bond. In particular, the facile synthesis of deoxyvasicinone and rutaecarpine demonstrates the great applicability of the redox–neutral process.

In general, both of these reactions consist of the following three steps. (1) The condensation of *o*-aminobenzaldehydes and amines renders intermediates *in situ* that contain a conjugated imine and a tertiary amine moiety. (2) The conjugated intermediate readily undergoes an imine-iminium exchange via a 1,6- or 1,5-hydride shift process to form a dipolar intermediate under thermal conditions and/or Brønsted acid activation. (3) The dipolar intermediate undergoes ring closure, which leads to a polycyclic ring system. Numerous examples have been documented concerning C–C bond formation in this type of *tert*-amino effect. However, only one example has been reported with respect to the C–N bond formation in this type of reaction involving a six-membered ring formation. In this sense, our research has expanded the scope of the *tert*-amino effect.

Experimental Section

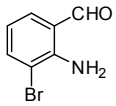
General Information: Starting materials, reagents and solvents were purchased from commercial sources and were used as received with the exception of pyrrolidine, piperidine, and hexamethyleneimine which were distilled prior to use. Unless mentioned otherwise, reactions were run under an atmosphere of nitrogen. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light and permanganate stain, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; integration; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer.

2-amino-3-cyano-4,6-diphenylbenzaldehyde (3.1b): To a solution of 2,6-dicyano-3,5-diphenylaniline (0.6 g, 2.03 mmol) in 5 mL of anhydrous dichloromethane at 0 °C, was slowly added 3.04 mL of DIBAL-H (3.04 mmol, 1 M solution in toluene). The reaction mixture was allowed to warm up to room temperature and was stirred for an additional 24 h. The reaction mixture was diluted with ether and cooled to 0°C. Water (0.12 mL) was added slowly, followed by careful addition of 15% aqueous NaOH (0.12 mL). Subsequently, water (0.3 mL) was added slowly and the reaction mixture was stirred rapidly at room temperature for 15 minutes. Anhydrous magnesium sulfate was then added, it was stirred for 15 minutes and the salts were removed by filtration. The volatile components were removed under reduced pressure and the crude product was purified by column chromatography to give the title compound 0.182 g as a solid in 30% yield. (R_f = 0.17 in 40% CH_2Cl_2/Hex); mp: 220–222 °C; IR (KBr) 3474, 3316, 2923, 2877, 2209, 1650, 1593, 1570, 1499, 1400, 1296, 1226, 779, 763, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.86 (s, 1H), 7.63–7.59 (m, 2H), 7.53–7.44 (comp, 6H), 7.42–7.37 (m, 2H), 6.75 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 193.4, 153.3, 153.2, 151.5, 138.0, 137.6, 130.0, 129.8, 129.1, 129.0, 128.8, 128.7, 120.1, 116.6, 115.1, 96.1; Chemical Formula: $C_{20}H_{14}N_2O$, *m/z* (ESIMS) 299.2 $[M + H]^+$.

2-amino-3-cyano-4,6-dimethylbenzaldehyde (3.1a): Starting from 2,6-dicyano-3,5-dimethylaniline, the reaction was carried out in analogy to the preparation of **1b**. After purification by column chromatography, the title compound was obtained as a solid in 50% yield. (R_f = 0.33 in CH_2Cl_2); mp: 175–181 °C; IR (KBr) 3440, 3321, 2208, 1658, 1651, 1607, 1585, 1548, 1505, 1441, 1405, 1375, 1309, 1225, 868, 592 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.29 (s, 1H), 7.11 (br s, 2H), 6.39 (s, 1H),

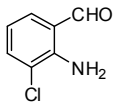
2.57 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 191.2, 152.5, 150.2, 148.3, 120.8, 115.8, 114.5, 96.9, 21.3, 19.3; Chemical Formula: $C_{10}H_{10}N_2O$, *m/z* (ESIMS) 175.2 $[M + H]^+$.

2-amino-3-bromobenzaldehyde (3.1f): Starting from 2-amino-3-bromobenzonitrile, the



reaction was carried out in analogy to the preparation of **1b**. After purification by column chromatography, the title compound was obtained as an oil in 32% yield. (R_f = 0.19 in 20% CH_2Cl_2/Hex); IR (KBr) 3467, 3350, 2851, 2765, 1666, 1609, 1578, 1538, 1446, 1409, 1307, 1198, 1139, 1061, 882, 763, 726, 669 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 9.80 (s, 1H), 7.59 (dd, 1H, *J* = 1.5 Hz, *J* = 7.7 Hz), 7.45 (dd, 1H, *J* = 1.5 Hz, *J* = 7.7 Hz), 6.69 (br s, 2H), 6.64 (app t, 1H, *J* = 7.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 193.1, 146.8, 137.9, 135.2, 119.5, 116.7, 110.0 ; Chemical Formula: C_7H_6BrNO, *m/z* (ESIMS) 200.1 (^{79}Br) $[M + 1]^+$, 202.1 (^{81}Br) $[M + 1]^+$.

2-amino-3-chlorobenzaldehyde (3.1g): Starting from 2-amino-3-chlorobenzonitrile, the

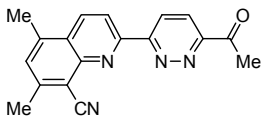


reaction was carried out in analogy to the preparation of **1b**. After purification by column chromatography, the title compound was obtained as a solid in 50% yield. (R_f = 0.34 in 30% CH_2Cl_2/Hex); mp: 30–31 °C; IR (KBr) 3480, 3359, 2860, 2774, 1681, 1612, 1581, 1546, 1465, 1450, 1408, 1327, 1196, 1146, 1075, 884, 765, 726, 677 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 9.85 (s, 1H), 7.42 (app ddd, 2H, *J* = 1.5 Hz, *J* = 5.6 Hz, *J* = 7.4 Hz), 6.70 (app t, 1H, *J* = 7.8 Hz), 6.62 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 193.1, 146.8, 137.9, 135.2, 119.5, 116.8, 110.0; Chemical Formula: C_7H_6ClNO, *m/z* (ESIMS) 156.6 $[M + H]^+$.

methyl 4-amino-3-formyl benzoate (3.1h): Methyl 3-formyl-4-nitro benzoate (0.5 g, 2.39 mmol), iron powder (1.02 g, 18.35 mmol), and conc. HCl (2 drops), were added to a mixture of EtOH, HOAc and H_2O (2:2:1, 25 mL). The resulting suspension was heated at reflux for 15 min and then stirred at 25 °C for 30 min. Subsequently, it was filtered, diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The organic layer was washed with saturated $NaHCO_3$ (2 x 100 mL) and H_2O (2 x 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound 0.390 g as a solid in 91% yield. (R_f = 0.41 in 20% EtOAc/Hex); mp: 122–124 °C; IR (KBr) 3451, 3334, 3200, 2961, 2803, 2728, 1683, 1613, 1549, 1485, 1444, 1391, 1368, 1275, 1164, 983, 901, 825, 767, 703, 592 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.88 (s, 1H), 8.22 (d, 1H, J = 2.0 Hz), 7.93 (dd, 1H, J = 2.0 Hz, J = 8.7 Hz), 6.64 (d, 1H, J = 8.7 Hz), 6.56 (br s, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 193.9, 166.4, 153.2, 138.9, 136.1, 118.4, 118.1, 116.0, 52.1; Chemical Formula: $C_9H_9NO_3$, *m/z* (ESIMS) 180.4 $[M + H]^+$.

methyl 3-amino-4-formyl benzoate (3.1i): Starting with methyl 3-nitro-4-formyl benzoate, the reaction was carried out in analogy to the preparation of **1h**. After purification by column chromatography, the title compound was obtained as a solid in 70% yield. (R_f = 0.48 in 20% EtOAc/Hex); mp: 119–121 °C; IR (KBr) 3463, 3360, 3066, 2961, 2827, 2745, 1712, 1666, 1626, 1598, 1545, 1492, 1435, 1310, 1262, 1186, 995, 812, 759, 522 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.94 (s, 1H), 7.55 (d, 1H, J = 8.4 Hz), 7.36–7.32 (comp, 2H), 6.22 (br s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 194.2, 166.6, 149.6, 135.9, 135.7, 121.1, 117.8, 116.8, 52.7; Chemical Formula: $C_9H_9NO_3$, *m/z* (ESIMS) 180.2 $[M + H]^+$.

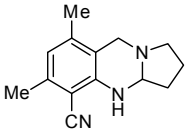
2-(6-acetylpyridazin-3-yl)-5,7-dimethylquinoline-8-carbonitrile (3.3): To a stirred solution of aminoaldehyde (0.26 mmol) and 3,6-diacetyl-pyridazine (0.12 mmol) in 1.2 mL of EtOH was added the secondary amine (0.6 mmol), followed by heating at reflux. The reaction mixture was monitored by TLC. After 3 hours, the reaction was complete. The solvent was evaporated off and the crude product was purified by column chromatography. The title compound was obtained as a solid in 14% yield. (R_f = 0.45 in 50% EtOAc/Hex); mp: 67–71 °C; IR (KBr) 3078, 2955, 2926, 2862, 2214, 1701, 1601, 1572, 1450, 1362, 1343, 1257, 1228, 1195, 1135, 1076, 1012 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.15 (d, J = 8.7 Hz, 1H), 8.99 (d, J = 8.8 Hz, 1H), 8.56 (d, J = 8.8 Hz, 1H), 8.32 (d, J = 8.7 Hz, 1H), 7.40 (s, 1H), 2.98 (s, 3H), 2.80 (s, 3H), 2.78 (s, J = 3.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 198.36, 159.62, 156.01, 153.75, 148.01, 147.17, 140.16, 134.43, 130.54, 126.71, 126.58, 125.91, 119.73, 116.72, 111.10, 26.48, 21.61, 19.24; Chemical Formula: $C_{18}H_{14}N_4O$, *m/z* (ESIMS) 303.3 $[M + H]^+$.



General Procedure for the Reaction between Aminoaldehyde and Amines:

To a stirred solution of aminoaldehyde (1 mmol) in 4 mL of EtOH was added the secondary amine (3 mmol), followed by heating at reflux. The reaction mixture was monitored by TLC. After the completion of the reaction, the solvent was evaporated off and the crude product was purified by column chromatography.

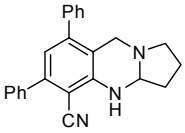
6,8-dimethyl-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-5-carbonitrile (3.2a)



The reaction was carried out according to the general procedure (18 h). The product was obtained as a white solid in 95% yield. (R_f = 0.47 in 2% MeOH/EtOAc); mp: 138–140 °C; IR (KBr) 3363, 2942, 2922, 2842, 2209, 1598,

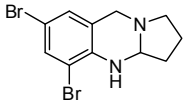
1580, 1508, 1477, 1460, 1333, 1291, 1267, 1190, 1123, 1103 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.38 (s, 1H), 4.53 (br s, 1H), 4.33 (dd, 1H, J = 3.0 Hz, J = 5.0 Hz), 3.87 (app d, 2H, J = 3.8 Hz), 2.88 (app dt, 1H, J = 6.5 Hz, J = 8.8 Hz), 2.81 (app dt, 1H, J = 4.8 Hz, J = 8.8 Hz), 2.36 (s, 3H), 2.14–2.27 (m, 1H), 2.14 (s, 3H), 1.89–2.07 (comp, 2H), 1.72–1.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 145.9, 140.7, 139.5, 120.3, 117.2, 114.3, 93.9, 70.1, 50.1, 47.0, 32.0, 21.2, 20.3, 18.9; Chemical Formula: $C_{14}H_{17}N_3$, *m/z* (ESIMS) 228.1 $[M + H]^+$.

6,8-diphenyl-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-5-carbonitrile (3.2b)



The reaction was carried out according to the general procedure (12 h). The product was obtained as a white solid in 92% yield. (R_f = 0.28 in 40% EtOAc/Hex); mp: 154–158 °C; IR (KBr) 3333, 3055, 3026, 2957, 2908, 2831, 2211, 1735, 1586, 1509, 1460, 1441, 1429, 1379, 1336, 1309, 1279, 1189, 1134, 1008, 776, 765, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.58–7.54 (m, 2H), 7.47–7.36 (comp, 6H), 7.32–7.29 (m, 2H), 6.66 (s, 1H), 4.89 (br s, 1H), 4.52 (dd, 1H, J = 2.7 Hz, J = 5.1 Hz), 4.07 (d, 1H, J = 16.4 Hz), 3.74 (d, 1H, J = 16.4 Hz), 2.84–2.77 (m, 1H), 2.73 (app dt, 1H, J = 4.8 Hz, J = 8.8 Hz), 2.26–2.15 (m, 1H), 2.08–1.88 (comp, 2H), 1.82–1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 146.9, 145.7, 143.6, 139.6, 138.8, 128.52, 128.50, 128.47, 128.40, 128.37, 127.9, 119.6, 117.7, 114.5, 92.8, 70.8, 49.4, 47.9, 32.4, 21.4; Chemical Formula: $C_{24}H_{21}N_3$, *m/z* (ESIMS) 352.2 $[M + H]^+$

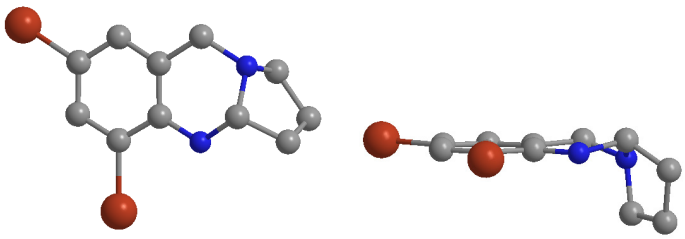
5,7-dibromo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline (**3.2c**) The reaction was



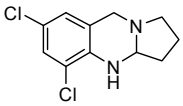
carried out according to the general procedure (23 h). The product was obtained as a white solid in 92% yield. (R_f = 0.19 in 40% EtOAc/Hex); mp: 122–124 °C; IR (KBr) 3403, 3052, 2971, 2938, 2907, 2839, 1768, 1692, 1575, 1438,

1349, 1258, 1119, 980, 927, 861, 747, 722, 637 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$) 7.37 (app d, 1H, J = 1.7 Hz), 6.99 (app d, 1H, J = 0.9 Hz), 4.37 (ddd, 1H, J = 5.2 Hz, J = 2.8 Hz, J = 0.8 Hz), 4.23 (br s, 1H), 4.09 (d, 1H, J = 16.2 Hz), 3.78 (d, 1H, J = 16.2 Hz), 2.82–2.75 (comp, 2H), 2.20–2.11 (m, 1H), 2.04–1.87 (comp, 2H), 1.73 (dddd, 1H, J = 2.8 Hz, J = 4.2 Hz, J = 9.9 Hz, J = 12.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 139.6, 132.5, 129.2, 121.7, 109.0, 108.3, 71.3, 49.9, 49.6, 32.7, 21.7; Chemical Formula: $C_{11}H_{12}Br_2N_2$, *m/z* (ESIMS) 335.1 (^{81}Br) $[M + H]^+$, 333.0 $[M + H]^+$, 331.1 (^{79}Br) $[M + H]^+$.

Product **3.2c** was further characterized by X-ray crystallography:



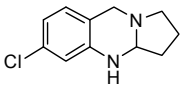
5,7-dichloro-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline (3.2d) The reaction was



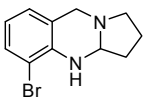
carried out according to the general procedure (12 h). The product was obtained as a white solid in 84% yield. (R_f = 0.33 in 40% EtOAc/Hex); mp: 72–75 °C; IR (KBr) 3415, 3039, 2973, 2907, 2841, 1597, 1491, 1454, 1436, 1349, 1259, 1185, 1120, 981 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.12 (app d, 1H, J = 2.2 Hz), 6.85 (app d, 1H, J = 1.2 Hz), 4.42–4.35 (m, 1H), 4.22 (br s, 1H), 4.11 (d, 1H, J = 16.2 Hz), 3.83 (d, 1H, J = 16.2 Hz), 2.91–2.75 (comp, 2H), 2.19 (app ddt, 1H, J = 5.3 Hz, J = 8.6 Hz, J = 12.6 Hz), 2.12–1.89 (m, 2H), 1.76 (dddd, 1H, J = 2.9 Hz, J = 4.3 Hz, J =

9.9 Hz, J = 12.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 138.2, 127.0, 125.8, 121.3, 121.1, 118.5, 71.1, 49.9, 49.6, 32.5, 21.6; Chemical Formula: $C_{11}H_{12}Cl_2N_2$, *m/z* (ESIMS) 243.2 $[M]^+$.

6-chloro-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline (3.2e) The reaction was carried out according to the general procedure (72 h). The product was obtained as a white solid in 57% yield. (R_f = 0.22 in 40% EtOAc/Hex); mp: 83–84 °C; IR (KBr) 3213, 2970, 2941, 2827, 2793, 1858, 1603, 1579, 1491, 1382, 1351, 1249, 1143, 1083, 1001, 914, 848, 829, 600 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 6.84 (d, 1H, J = 8.0 Hz), 6.63 (dd, 1H, J = 2.0 Hz, J = 8.0 Hz), 6.49 (d, 1H, J = 2.0 Hz), 4.22 (dd, 1H, J = 3.8 Hz, J = 5.1 Hz), 4.01 (d, 1H, J = 15.8 Hz), 3.90–3.74 (comp, 2H), 2.94 (app dt, 1H, J = 5.9 Hz, J = 8.9 Hz), 2.72 (app dt, 1H, J = 5.1 Hz, J = 8.8 Hz), 2.13 (app tdd, 1H, J = 5.6 Hz, J = 10.9 Hz, J = 12.4 Hz), 2.05–1.87 (comp, 2H), 1.69–1.61 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 144.3, 132.6, 128.5, 117.9, 117.4, 114.3, 71.1, 50.2, 49.9, 32.2, 21.5; Chemical Formula: $C_{11}H_{13}ClN_2$, *m/z* (ESIMS) 209.1 $[M + H]^+$.

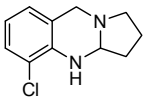


5-bromo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline (3.2f) The reaction was carried out according to the general procedure (36 h). The product was obtained as an oil in 83% yield. (R_f = 0.30 in 40% EtOAc/Hex); IR (film) 3398, 2970, 2838, 1600, 1485, 1443, 1346, 1379, 1292, 1265, 1146, 1118, 1069, 756, 721, 619 cm^{-1} ^{1}H NMR (500 MHz, $CDCl_3$) 7.26 (app d, 1H, J = 7.9 Hz), 6.87 (app d, 1H, J = 7.4 Hz), 6.52 (app t, 1H, J = 7.7 Hz), 4.36–4.31 (m, 1H), 4.25 (br s, 1H), 4.09 (d, 1H, J = 15.9 Hz), 3.83 (d, 1H, J = 15.9 Hz), 2.88 (app dt, 1H, J = 6.4 Hz, J = 8.9 Hz), 2.75 (app dt, 1H, J = 4.8 Hz, J = 8.7 Hz), 2.16 (ddd, 1H, J = 5.6 Hz, J = 11.2 Hz, J = 17.4 Hz), 2.01 (dddd, 1H, J = 5.4 Hz, J = 9.9 Hz, J = 14.8 Hz, J = 15.4 Hz), 1.96–1.87 (m, 1H),



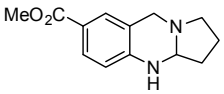
1.78–1.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 140.3, 130.4, 126.4, 120.3, 117.9, 108.9, 71.2, 50.0, 49.9, 32.4, 21.5; Chemical Formula: $C_{11}H_{13}BrN_2$, *m/z* (ESIMS) 255.2 (^{81}Br) $[M + H]^+$, 253.3 (^{79}Br) $[M + H]^+$.

5-chloro-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline (3.2g) The reaction was



carried out according to the general procedure (18 h). The product was obtained as an oil in 76% yield. (R_f = 0.44 in 2% MeOH/EtOAc); IR (film) 3407, 2971, 2840, 1602, 1488, 1379, 1346, 1295, 1265, 1179, 1142, 1119, 1070, 758, 723 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.11 (app d, 1H, *J* = 7.9 Hz), 6.86 (app d, 1H, *J* = 7.4 Hz), 6.59 (app t, 1H, *J* = 7.7 Hz), 4.37–4.33 (m, 1H), 4.26 (br s, 1H), 4.12 (d, 1H, *J* = 16.0 Hz), 3.88 (d, 1H, *J* = 16.0 Hz), 2.92 (app dt, 1H, *J* = 6.3 Hz, *J* = 8.8 Hz), 2.78 (app dt, 1H, *J* = 4.9 Hz, *J* = 8.8 Hz), 2.19 (app dtd, 1H, *J* = 5.6 Hz, *J* = 11.0 Hz, *J* = 16.4 Hz), 2.04 (app ddt, 1H, *J* = 5.4 Hz, *J* = 10.1 Hz, *J* = 15.1 Hz), 1.98–1.89 (m, 1H), 1.79–1.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 139.3, 127.3, 125.7, 120.1, 118.4, 117.4, 71.1, 50.0, 49.9, 32.4, 21.5; Chemical Formula: $C_{11}H_{13}ClN_2$, *m/z* (ESIMS) 209.1 $[M + H]^+$.

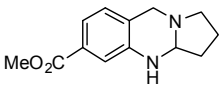
methyl 1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-7-carboxylate (3.2h) To a



stirred solution of methyl 4-amino-3-formyl benzoate (1 mmol) in 4 mL of methanol was added pyrrolidine (3 mmol). The mixture was heated at 100°C in a sealed tube for 24 h. Following solvent removal and purification of the crude product by column chromatography, the product was obtained as a white solid in 76% yield. (R_f = 0.43 in 5% MeOH/EtOAc); mp: 118–120 °C; IR (KBr) 3375, 2942, 2874, 2804, 1685, 1608, 1513, 1436, 1381, 1363, 1321, 1293, 1237, 1198, 1142, 1111, 1096, 1002, 989, 908, 832, 768, 443 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.66 (dd, 1H, *J* = 1.9 Hz, *J* = 8.4 Hz), 7.62 (app s, 1H), 6.40 (app d, 1H, *J* = 8.4 Hz), 4.38 (dd, 1H, *J* = 2.8

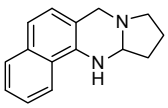
Hz, J = 5.1 Hz), 4.31 (br s, 1H), 4.10 (d, 1H, J = 16.0 Hz), 3.83 (d, 1H, J = 16.0 Hz), 3.81 (s, 3H), 2.82 (app dt, 1H, J = 6.6 Hz, J = 8.9 Hz), 2.76 (app dt, 1H, J = 4.9 Hz, J = 8.8 Hz), 2.15–2.07 (m, 1H), 2.01–1.85 (comp, 2H), 1.64 (dddd, 1H, J = 2.9 Hz, J = 4.3 Hz, J = 9.8 Hz, J = 12.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 167.6, 147.5, 129.7, 129.6, 118.6, 117.2, 113.1, 70.9, 51.7, 49.8, 49.5, 32.5, 21.7; Chemical Formula: $C_{13}H_{16}N_2O_2$, *m/z* (ESIMS) 233.1 $[M + H]^+$.

methyl 1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline-6-carboxylate (3.2i) To a



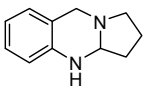
stirred solution of methyl 3-amino-4-formyl benzoate (1 mmol) in 4 mL of methanol was added pyrrolidine (3 mmol). The mixture was heated at 100°C in a sealed tube for 24 h. Following solvent removal and purification of the crude product by column chromatography, the product was obtained as a white solid in 60% yield. (R_f = 0.43 in 5% MeOH/EtOAc); mp: 119–120 °C; IR (KBr) 3400, 2970, 2942, 2842, 1713, 1614, 1581, 1499, 1479, 1459, 1439, 1342, 1312, 1289, 1278, 1230, 1216, 1101, 1018, 854, 755, 440 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.32 (dd, 1H, J = 1.6 Hz, J = 7.8 Hz), 7.18 (app d, 1H, J = 1.6 Hz), 6.97 (app d, 1H, J = 7.8 Hz), 4.21 (dd, 1H, J = 4.0 Hz, J = 5.1 Hz), 4.06 (d, 1H, J = 16.3 Hz), 3.96–3.87 (comp, 2H), 3.86 (s, 3H), 2.94 (app dt, 1H, J = 5.8 Hz, J = 8.8 Hz), 2.71 (app dt, 1H, J = 5.3 Hz, J = 8.8 Hz), 2.13 (ddd, 1H, J = 5.6 Hz, J = 11.0 Hz, J = 18.0 Hz), 2.04–1.85 (comp, 2H), 1.66 (app tdd, 1H, J = 4.2 Hz, J = 10.2 Hz, J = 12.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 167.6, 143.3, 129.3, 127.5, 124.5, 119.2, 115.8, 71.3, 52.1, 50.6, 50.4, 32.2, 21,5; Chemical Formula: $C_{13}H_{16}N_2O_2$, *m/z* (ESIMS) 233.2 $[M + H]^+$.

7,9,10,11,11a,12-hexahydrobenzo[h]pyrrolo[2,1-b]quinazoline (3.2j) The reaction was



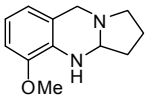
carried out according to the general procedure (48 h). The product was obtained as a white solid in 58% yield. (R_f = 0.27 in 5% MeOH/EtOAc); mp: 130–133 °C; IR (KBr) 3227, 3062, 2977, 2956, 2915, 2856, 1576, 1520, 1487, 1407, 1363, 1340, 1325, 1304, 1260, 1120, 1093, 775, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.82–7.75 (comp, 2H), 7.47–7.40 (comp, 2H), 7.30 (d, 1H, *J* = 8.3 Hz), 7.11 (d, 1H, *J* = 8.3 Hz), 4.19–4.11 (comp, 3H), 4.06 (d, 1H, *J* = 15.6 Hz), 3.14 (app dt, 1H, *J* = 5.1 Hz, *J* = 8.8 Hz), 2.69 (app dt, 1H, *J* = 6.1 Hz, *J* = 8.8 Hz), 2.30 (app dtd, 1H, *J* = 5.5 Hz, *J* = 10.8 Hz, *J* = 16.1 Hz), 2.12–2.03 (m, 1H), 2.02–1.92 (m, 1H), 1.88–1.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 137.6, 133.3, 128.6, 126.0, 125.5, 125.2, 124.3, 120.0, 118.9, 115.2, 72.4, 51.9, 50.9, 31.9, 21.3; Chemical Formula: $C_{15}H_{16}N_2$, *m/z* (ESIMS) 225.1 $[M + H]^+$.

1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline (3.2k) The reaction was carried out



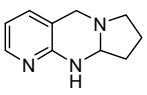
according to the general procedure (72 h). The product was obtained as a white solid in 73% yield. (R_f = 0.25 in 5% MeOH/EtOAc); mp: 63–64 °C [lit. 69-70 °C]; IR (KBr) 3246, 2966, 2826, 1608, 1585, 1478, 1383, 1255, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.02 (app t, 1H *J* = 7.6 Hz), 6.95 (app d, 1H *J* = 7.4 Hz), 6.70 (app dt, 1H, *J* = 0.9 Hz, *J* = 7.4 Hz), 6.54 (d, 1H, *J* = 7.9 Hz), 4.17–4.13 (m, 1H), 4.04 (d, 1H, *J* = 15.6 Hz), 3.90 (d, 1H, *J* = 15.6 Hz), 3.67 (br s, 1H), 3.03 (app dt, 1H, *J* = 5.5 Hz, *J* = 8.8 Hz), 2.68 (app dt, 1H, *J* = 5.5 Hz, *J* = 8.8 Hz), 2.18–2.09 (m, 1H), 1.97–2.07 (m, 1H), 1.96–1.87 (m, 1H), 1.66 (app tdd, 1H, *J* = 4.4 Hz, *J* = 10.2 Hz *J* = 12.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$)142.9, 127.2, 127.0, 119.4, 118.1, 114.9, 71.2, 50.5, 50.3, 31.8, 21.1; Chemical Formula: $C_{11}H_{14}N_2$, *m/z* (ESIMS) 175.1 $[M + H]^+$.

5-methoxy-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline (3.2l) To a stirred



solution of methyl 3-amino-4-formyl benzoate (0.151 g, 1 mmol) in 4 mL of ethanol was added pyrrolidine (0.25 ml, 3 mmol). The mixture was heated at 140°C in a sealed tube for 48 h. Following solvent removal and purification of the crude product by column chromatography, the product 0.165 g was obtained as a pale yellow solid in 81% yield. (R_f = 0.20 in 70% EtOAc/Hex); mp: 84–86 °C; IR (KBr) 3398, 3031, 2970, 2934, 2909, 2851, 1609, 1587, 1496, 1478, 1457, 1354, 1313, 1247, 1184, 1139, 1119, 1082, 1037, 1008, 980, 898, 762, 728, 686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.67–6.59 (comp, 3H), 4.21 (dd, 1H, *J* = 4.0 Hz, *J* = 4.9 Hz), 4.12–4.06 (comp, 2H), 3.90 (d, 1H, *J* = 15.8 Hz), 3.83 (s, 3H), 3.01 (app dt, 1H, *J* = 5.9 Hz, *J* = 8.8 Hz), 2.72 (app dt, 1H, *J* = 5.1 Hz, *J* = 8.8 Hz), 2.14 (app tdd, 1H, *J* = 5.5 Hz, *J* = 10.9 Hz, *J* = 12.2 Hz), 2.03 (dddd, 1H, *J* = 5.4 Hz, *J* = 9.0 Hz, *J* = 10.7 Hz, *J* = 14.8 Hz), 1.91 (app dddt, 1H, *J* = 4.6 Hz, *J* = 5.8 Hz, *J* = 8.8 Hz, *J* = 10.6 Hz), 1.78–1.71 (m, 1H)**;** ^{13}C NMR (125 MHz, $CDCl_3$) 146.3, 132.7, 119.4, 119.1, 116.8, 107.8, 70.7, 55.4, 50.3, 50.0, 32.0, 21.3; Chemical Formula: $C_{12}H_{16}N_2O$, *m/z* (ESIMS) 205.1 $[M + H]^+$.

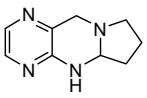
5,7,8,9,9a,10-hexahydropyrido[2,3-d]pyrrolo[1,2-a]pyrimidine (3.2m) The reaction



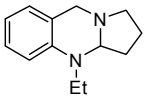
was carried out according to the general procedure (36 h). The product was obtained as a white solid in 94% yield. (R_f = 0.28 in 30% MeOH/EtOAc); mp: 123–126 °C; IR (KBr) 3225, 3093, 2912, 2842, 1584, 1523, 1458, 1444, 1357, 1339, 1303, 1268, 1179, 1120, 1092, 762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.91 (app d, 1H, *J* = 5.0 Hz), 7.17 (dd, 1H, *J* = 0.6 Hz, *J* = 7.2 Hz), 6.55 (dd, 1H, *J* = 5.0 Hz, *J* = 7.2 Hz), 4.85 (br s, 1H), 4.56 (dd, 1H, *J* = 2.3 Hz, *J* = 5.0 Hz), 4.13 (d, 1H, *J* = 16.2 Hz), 3.81 (d, 1H, *J* = 16.2 Hz) 2.79–2.87 (comp, 2H), 2.16 (dddd, 1H, *J* = 5.0 Hz, *J* = 6.4 Hz, *J* = 11.1 Hz, *J* = 12.5 Hz), 1.90–1.99 (comp, 2H), 1.73 (dddd, 1H, *J* = 2.3 Hz, *J* = 4.1 Hz, *J* = 9.8

Hz, J = 12.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 154.8, 146.7, 134.9, 113.5, 113.3, 71.2, 49.7, 48.9, 32.8, 21.8; Chemical Formula: $C_{10}H_{13}N_3$, *m/z* (ESIMS) 176.1 $[M + H]^+$.

5,5a,6,7,8,10-hexahydropyrrolo[2,1-b]pteridine (3.2n) The reaction was carried out according to the general procedure (13 h). The product was obtained as a white solid in 91% yield. (R_f = 0.30 in 30% MeOH/EtOAc); mp: 92–95 °C; IR (KBr) 3227, 3116, 2978, 2917, 2840, 1579, 1557, 1487, 1455, 1442, 1335, 1311, 1263, 1187, 1144, 1110, 1093, 1005, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.81 (d, 1H, J = 2.7 Hz), 7.77 (d, 1H, J = 2.7 Hz), 4.88 (s, 1H), 4.62 (dd, 1H, J = 2.2 Hz, J = 5.0 Hz), 4.20 (d, 1H, J = 17.2 Hz), 3.96 (d, 1H, J = 17.2 Hz), 2.94 (app dt, 1H, J = 4.5 Hz, J = 9.0 Hz), 2.83 (app dt, 1H, J = 6.8 Hz, J = 9.0 Hz), 2.19 (app ddt, 1H, J = 5.2 Hz, J = 6.3 Hz, J = 11.4 Hz), 2.10–1.92 (comp, 2H), 1.80–1.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 151.0, 140.6, 137.3, 132,9, 70.7, 51.2, 49.8, 32.3, 21.6; Chemical Formula: $C_9H_{12}N_4$, *m/z* (ESIMS) 177.1 $[M + H]^+$.

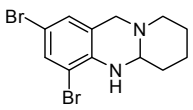


4-ethyl-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline (3.2o) The reaction was carried out according to the general procedure (80 h). The product was obtained as an oil in 84% yield. (R_f = 0.26 in 30% EtOAc/Hex); IR (film) 3354, 2969, 2876, 2842, 2786, 1650, 1605, 1494, 1457, 1373, 1325, 1255, 1168, 1134, 1045, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.11 (app t, 1H, J = 7.5 Hz), 6.94 (app d, 1H, J = 7.0 Hz), 6.71 (app d, 1H, J = 8.2 Hz), 6.67 (app t, 1H, J = 7.3 Hz), 3.87–3.92 (comp, 2H), 3.82 (d, 1H, J = 14.5 Hz), 3.46 (app qd, 1H, J = 7.1 Hz, J = 14.4 Hz), 3.14–3.24 (comp, 2H), 2.56 (ddd, 1H, J = 5.0 Hz, J = 7.8 Hz, J = 8.9 Hz), 2.08–2.16 (m, 1H), 1.82–2.03 (comp, 3H), 1.17 (t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$)



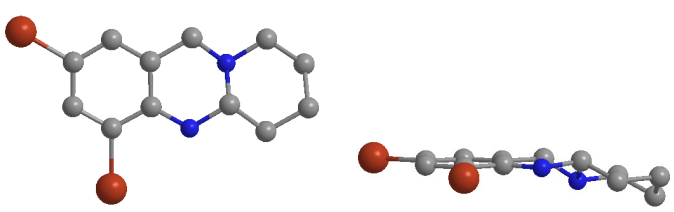
144.6, 127.5, 127.1, 121.2, 116.8, 112.1, 76.7, 52.5, 51.8, 41.7, 30.7, 20.7, 12.5; Chemical Formula: $C_{13}H_{18}N_2$, *m/z* (ESIMS) 203.1 $[M + H]^+$.

2,4-dibromo-5a,6,7,8,9,11-hexahydro-5H-pyrido[2,1-b]quinazoline (3.8) To a stirred



solution of 2-amino-3,5-dibromobenzaldehyde (1 mmol) in 4 mL of isopropanol was added piperidine (3 mmol). The mixture was heated at 140°C in a sealed tube for 48 h. Subsequent to solvent removal, the crude product was purified by column chromatography to give the product as a white solid in 67% yield. (R_f = 0.28 in 30% EtOAc/Hex); mp: 89–92 °C; IR (KBr) 3405, 2936, 2853, 2771, 1596, 1561, 1486, 1442, 1370, 1351, 1294, 1272, 1190, 1119, 856, 713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.36 (app d, 1H, *J* = 2.1 Hz), 6.96 (app d, 1H, *J* = 1.4 Hz), 4.22 (s, 1H), 3.79 (br s, 1H), 3.72–3.59 (comp, 2H), 2.96–2.88 (m, 1H), 2.25–2.15 (m, 1H), 1.95–1.87 (m, 1H), 1.76 (app tt, 1H, *J* = 4.9 Hz, *J* = 10.1 Hz), 1.71–1.64 (comp, 2H), 1.63–1.54 (m, 1H), 1.50–1.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 139.1, 132.5, 128.7, 122.3, 108.5, 108.3, 70.2, 56.0, 51.5, 31.9, 25.6. 21.3; Chemical Formula: $C_{12}H_{14}Br_2N_2$, *m/z* (ESIMS) 349.1 (^{81}Br) $[M + H]^+$, 347.0 $[M + H]^+$, 345.0 (^{79}Br) $[M + H]^+$.

Product **3.8** was further characterized by X-ray crystallography:

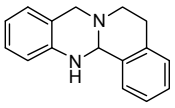


2,4-dibromo-5,5a,6,7,8,9,10,12-octahydroazepino[2,1-b]quinazoline (3.9) To a stirred solution of 2-amino-3,5-dibromobenzaldehyde (1 mmol) in 4 mL of isopropanol was added hexamethyleneimine (3 mmol). The mixture was heated at 140°C in a sealed tube for 24 h. Subsequent to solvent removal, the crude product was purified by column chromatography to give the product as an oil in 77% yield. (R_f = 0.56 in 30% EtOAc/Hex); IR (film) 3400, 2924, 2850, 1724, 1593, 1479, 1357, 1318, 1279, 1235, 1136, 1001, 949, 857, 738, 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.37 (app d, 1H, *J* = 2.1 Hz), 6.95 (app d, 1H, *J* = 1.0 Hz), 4.23 (app t, 1H, *J* = 5.2 Hz), 4.20 (br s, 1H), 4.07 (d, 1H, *J* = 15.6 Hz), 3.67 (d, 1H, *J* = 15.6 Hz), 2.86–2.79 (m, 1H), 2.46 (app td, 1H, *J* = 4.1 Hz, *J* = 9.4 Hz), 2.14–2.06 (m, 1H), 1.83–1.74 (m, 1H), 1.74–1.58 (comp, 5H), 1.57-1.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 140.1, 132.4, 128.6, 123.3, 108.7, 108.2, 72.0, 57.6, 50.1, 35.5, 29.4, 29.2, 22.0; Chemical Formula: $C_{13}H_{16}Br_2N_2$, *m/z* (ESIMS) 363.1 (^{81}Br) $[M + H]^+$, 361.1 $[M + H]^+$, 359.2 (^{79}Br) $[M + H]^+$.

1,3-dimethyl-5a,6,7,8,9,10,11,13-octahydro-5H-azocino[2,1-b]quinazoline-4-carbonitrile (3.10) The reaction was carried out according to the general procedure (48 h). The product was obtained as a white solid in 60% yield. (R_f = 0.72 in 30% EtOAc/Hex); mp: 288–292 °C; IR (KBr) 3332, 2918, 2853, 2214, 1598, 1580, 1507, 1483, 1471, 1446, 1334, 1298, 1267, 1133, 1113, 1104, 1026, 888, 825 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.33 (s, 1H), 4.52 (br s, 1H), 4.27 (dd, 1H, *J* = 4.3 Hz, *J* = 9.5 Hz), 3.93 (d, 1H, *J* = 16.3 Hz), 3.70 (d, 1H, *J* = 16.3 Hz), 2.90 (ddd, 1H, *J* = 3.5 Hz, *J* = 10.8 Hz, *J* = 14.5 Hz), 2.35 (s, 3H), 2.30 (app td, 1H, *J* = 4.6 Hz, *J* = 14.8 Hz), 2.11 (s, 3H), 1.96–1.86 (m, 1H), 1.83 (dddd, 1H, *J* = 2.7 Hz, *J* = 4.5 Hz, *J* =

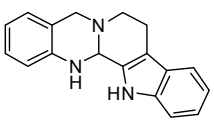
7.2 Hz, *J* = 14.3 Hz), 1.79–1.50 (m, 7H), 1.46 (app dtd, 1H, *J* = 3.8 Hz, *J* = 7.7 Hz, *J* = 15.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 147.2, 140.7, 139.7, 120.0, 117.7, 116.1, 93.4, 70.9, 54.1, 47.2, 31.4, 29.7, 26.7, 25.2, 24.4, 20.6, 19.1; Chemical Formula: $C_{17}H_{23}N_3$, *m/z* (ESIMS) 270.1 $[M + H]^+$.

6,8,13,13a-tetrahydro-5H-isoquinolino[1,2-b]quinazoline (3.11) The reaction was



carried out according to the general procedure (48 h). The product was obtained as an oil in 95% yield. (R_f = 0.33 in 30% EtOAc/Hex); IR (film) 3387, 3024, 2916, 2837, 2791, 2740, 1725, 1606, 1583, 1487, 1424, 1339, 1305, 1249, 1112, 1044, 1021, 936, 749 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.36 (app dd, 1H, *J* = 1.7 Hz, *J* = 7.2 Hz), 7.30–7.23 (comp, 2H), 7.20 (app dd, 1H, *J* = 1.2 Hz, *J* = 7.2 Hz), 7.07 (app t, 1H, *J* = 7.6 Hz), 7.01 (app d, 1H, *J* = 7.5 Hz), 6.77 (app dt, 1H, *J* = 1.1 Hz, *J* = 7.4 Hz), 6.58 (d, 1H, *J* = 8.0 Hz), 5.16 (d, 1H, *J* = 3.2 Hz), 4.35 (d, 1H, *J* = 15.8 Hz), 3.87 (d, 1H, *J* = 15.8 Hz), 3.86 (br s, 1H), 3.21 (ddd, 1H, *J* = 4.8 Hz, *J* = 8.3 Hz, *J* = 11.4 Hz), 3.06 (ddd, 1H, *J* = 5.7 Hz, *J* = 8.3 Hz, *J* = 14.0 Hz), 2.98 (app td, 1H, *J* = 4.8 Hz, *J* = 16.4 Hz), 2.72 (app td, 1H, *J* = 5.3 Hz, *J* = 10.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 142.3, 135.8, 134.9, 129.3, 128.1, 127.5, 127.3, 126.5, 126.4, 119.8, 118.7, 115.6, 69.7, 56.0, 45.5, 29.4; Chemical Formula: $C_{16}H_{16}N_2$, *m/z* (ESIMS) 237.1 $[M + H]^+$.

5,7,8,13,13b,14-hexahydroindolo[2',3':3,4]pyrido[2,1-b]quinazoline (3.12) The



reaction was carried out according to the general procedure (72 h). The product was obtained as an oil in 66% yield. (R_f = 0.25 in 40% EtOAc/Hex); IR (film) 3395, 3204, 3053, 2912, 2844, 2807, 1608, 1588, 1494, 1469, 1454, 1343, 1325, 1306, 1265, 1164, 1112, 741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.53 (s, 1H), 7.51 (app d, 1H, *J* = 7.8 Hz), 7.30–7.09 (comp, 4H), 7.05 (app d, 1H, *J* = 7.5 Hz),

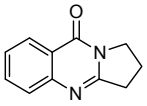
6.92 (app dt, 1H, *J* = 1.1 Hz, *J* = 7.5 Hz), 6.80 (app d, 1H, *J* = 7.9 Hz), 4.72 (s, 1H), 4.01–3.90 (comp, 2H), 3.26 (app td, 1H, *J* = 4.7 Hz, *J* = 11.4 Hz), 3.00–2.79 (comp, 2H), 2.76 (ddd, 1H, *J* = 4.7 Hz, *J* = 8.7 Hz, *J* = 11.5 Hz), 1.73 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 141.6, 136.5, 131.8, 127.7, 127.6, 126.9. 123.9, 122.4, 121.3, 119.9, 119.4, 118.9, 111.4, 110.4, 68.5, 55.7, 49.1, 21.7; Chemical Formula: $C_{18}H_{17}N_3$, *m/z* (ESIMS) 276.2 $[M + H]^+$.

methyl 7,9,14,14a-tetrahydrobenzo[4,5]isoquinolino[1,2-b]quinazoline-11-carboxylate (3.13) The reaction was carried out according to the general procedure (48 h). The product was obtained as a white solid in 80% yield. (R_f = 0.32 in 20% EtOAc/Hex); mp: 176–179 °C; IR (KBr) 3338, 3043, 2944, 2839, 1694, 1608, 1512, 1433, 1333, 1294, 1249, 1187, 1125, 1012, 780, 767 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.86 (app d, 1H, *J* = 8.3 Hz), 7.77–7.70 (comp, 3H), 7.51–7.43 (comp, 2H), 7.40 (app d, 1H, *J* = 6.9 Hz), 7.28 (app d, 1H, *J* = 7.2 Hz), 6.40 (app d, 1H, *J* = 8.3 Hz), 5.75 (s, 1H), 4.68 (d, 1H, *J* = 16.5 Hz), 4.37–4.31 (comp, 2H), 3.99 (d, 1H, *J* = 16.5 Hz), 3.94 (d, 1H, *J* = 14.7 Hz), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 167.5, 146.6, 133.6, 133.0, 132.9, 129.9, 129.8, 128.8, 126.6, 126.4, 126.3, 125.7, 123.2, 123.1, 119.5, 117.1, 113.2, 69.3, 54.6, 51.9, 49.3; Chemical Formula: $C_{21}H_{18}N_2O_2$, *m/z* (ESIMS) 331.1 $[M + H]^+$.

5,7-dibromo-3a-methyl-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline (3.18) The reaction was carried out according to the general procedure (24 h). Product **3.18a** was obtained as an oil in 60% yield. Additionally, **3.18b** was obtained as an oil in 25% yield (2:1 mixture of diastereomers). For **3.18a**: (R_f = 0.22 in 30% EtOAc/Hex); IR (film) 3400, 2970, 2848, 1644, 1591, 1478, 1448, 1374, 1322,

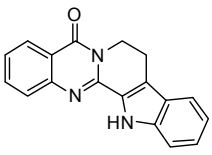
1290, 1208, 1196, 1152, 1125, 1032, 857, 745, 711, 547 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$) 7.40 (app d, 1H, *J* = 1.7 Hz), 7.03 (app d, 1H, *J* = 1.0 Hz), 4.22 (br s, 1H), 4.18 (d, 1H, *J* = 17.1 Hz), 3.70 (d, 1H, *J* = 17.1 Hz), 3.00 (ddd, 1H, *J* = 5.2 Hz, *J* = 7.2 Hz, *J* = 8.8 Hz), 2.59 (app q, 1H, *J* = 8.5 Hz), 2.03–1.95 (m, 1H), 1.93–1.81 (comp, 3H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 138.7, 132.5, 129.3, 120.0, 108.7, 107.5, 74.4, 51.0, 45.6, 40.0, 26.2, 20.0; Chemical Formula: $C_{12}H_{14}Br_2N_2$, *m/z* (ESIMS) 349.0 (^{81}Br) $[M + H]^+$, 347.0 $[M + H]^+$, 345.0 (^{79}Br) $[M + H]^+$.

Deoxyvasicinone (3.25): To a solution of **3.2k** (0.042 g, 0.24 mmol) in acetone (2.4 mL),



$KMnO_4$ (2.5eq. 0.603 mmol) was added. The reaction mixture was heated at reflux for 80 min, allowed to cool to room temperature and filtered. The filtrate was concentrated and purified by column chromatography to give the product as a white solid in 82% yield. (R_f = 0.34 in 2% MeOH/EtOAc); mp: 99–102 °C [lit. 105-107 °C]; IR (KBr) 1666, 1622, 1560, 1466, 1425, 1385, 1337, 1322, 772, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.25 (app d, 1H, *J* = 7.9 Hz), 7.70 (app t, 1H, *J* = 7.6 Hz), 7.62 (app d, 1H, *J* = 8.1 Hz), 7.42 (app t, 1H, *J* = 7.5 Hz), 4.18 (t, 2H, *J* = 7.2 Hz), 3.16 (t, 2H, *J* = 7.9 Hz), 2.22-2.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 161.1, 159.6, 149.3, 134.3, 126.9, 126.5, 126.4, 120.6, 46.6, 32.7, 19.7; Chemical Formula: $C_{11}H_{10}N_2O$, *m/z* (ESIMS) 187.3 $[M + H]^+$.

Rutaecarpine (3.26): To a solution of **3.12** (0.048g, 0.174mmol) in acetone (1.75 mL),



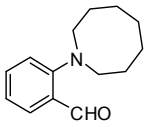
$KMnO_4$ (2.5eq. 0.436 mmol) was added. The reaction mixture was heated at reflux for 2 h, cooled to room temperature and filtered. The filtrate was concentrated and purified by column chromatography to give the product as a white solid in 61% yield. (R_f = 0.28 in dichloromethane); mp: 256–

260 °C [lit. 256–258 °C]; IR (KBr) 3342, 1669, 1600, 1577, 1559, 1541, 1522, 1507, 1458 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.44 (br s, 1H), 8.33 (app dd, 1H, *J* = 1.2 Hz, *J* = 7.9 Hz), 7.71 (app ddd, 1H, *J* = 1.5 Hz, *J* = 7.0 Hz, *J* = 8.4 Hz), 7.65 (app dd, 2H, *J* = 4.4 Hz, *J* = 13.1 Hz), 7.46–7.29 (comp, 3H), 7.21–7.15 (m, 1H), 4.59 (t, 2H, *J* = 6.9 Hz), 3.24 (t, 2H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 161.8, 147.8, 145.2, 138.5, 134.6, 127.5, 127.4, 126.9, 126.4, 125.9, 125.8, 121.4, 120.9, 120.3, 118.6, 112.3, 41.4, 19.9; Chemical Formula: $C_{18}H_{13}N_3O$, *m/z* (ESIMS) 288.4 $[M + H]^+$.

General procedure for the preparation of aminoaldehyde (22):

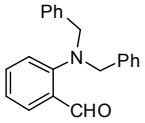
To a solution of 2-fluorobenzaldehyde (2.48 g, 20 mmol) and potassium carbonate (3.18 g, 23 mmol) in DMF (20 mL) was added the amine (23 mmol). The resulting reaction mixture was heated under reflux until complete consumption of 2-fluorobenzaldehyde, as judged by TLC analysis. The reaction mixture was subsequently allowed to cool to room temperature, diluted with water (100 mL), and extracted with ethyl acetate (3 x 75 mL). The combined organic layers were washed with a saturated NH_4C1 solution (3 x 75 mL) and subsequently dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by column chromatography.

2-(azocan-1-yl)benzaldehyde (3.38d): The title compound was prepared according to the general procedure and isolated as a liquid in 65% yield. (R_f = 0.50 in 80% CH_2Cl_2/Hex); IR (film) 2924, 2849, 1681, 1594, 1483, 1449, 1374, 1274, 1186, 1160, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.23 (app d, *J* = 4.6 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.49 – 7.26 (m, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.86 (app t, *J* = 7.4 Hz, 1H), 3.48 – 3.19 (comp, 4H), 1.87 – 1.46 (comp, 10H); ^{13}C NMR (125 MHz,



$CDCl_3$) 191.3, 155.8, 134.6, 130.6, 127.7, 119.9, 119.5, 55.5, 27.8, 27.4, 25.2; Chemical Formula: $C_{14}H_{19}NO$, *m/z* (ESIMS) 218.6 $[M + H]^+$.

2-(dibenzylamino)benzaldehyde (3.38k): The title compound was prepared according to the general procedure and isolated as a liquid in 25% yield (R_f = 0.61 in 80% CH_2Cl_2/Hex); IR (film) 3062, 3028, 2938, 2840, 2733, 1686, 1595, 1494, 1481, 1452, 1384, 1365, 1276, 1254, 1189, 1161, 1028, 833, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.57 (s, 1H), 7.91 – 7.81 (m, 1H), 7.51 – 7.41 (m, 1H), 7.39 – 7.24 (m, 6H), 7.20 (d, *J* = 7.7 Hz, 4H), 7.09 (app dt, *J* = 9.7, 20.3Hz, 2H), 4.30 (s, 4H).; ^{13}C NMR (125 MHz, $CDCl_3$) 191.31, 154.42, 137.12,134.44, 129.83, 129.57, 128.64, 128.43, 127.44, 122.89, 122.40, 58.70; Chemical Formula: $C_{21}H_{19}NO$, *m/z* (ESIMS) 324.7 $[M + Na]^+$.



General procedure A for the reaction between aminoaldehydes and amines:

To a stirred solution of aminoaldehyde (1 mmol) in 10 mL of EtOH was added the primary amine (1.2 mmol) and triflic acid (0.2 mmol), followed by heating at reflux. The reaction mixture was monitored by TLC. After the completion of the reaction, 0.3 ml of triethylamine was added. Then the solvent was evaporated off and the crude product was dissolved in ethyl acetate (20 ml) and washed with 25 ml of 1M NaOH. The aqueous layer was extracted with ethyl acetate (20 ml x 3). The combined organic layers were washed with brine (25 ml) and dried with sodium sulfate. The solvent was evaporated off and the crude product was purified by column chromatography.

General procedure B for the reaction between aminoaldehydes and amines:

To a stirred solution of aminoaldehyde (1 mmol) in 10 mL of EtOH was added the primary amine (1.2 mmol) and trifluoroacetic acid (1.2 mmol), followed by heating at reflux. The reaction mixture was monitored by TLC. After the completion of the reaction, 1.0 ml of triethylamine was added. Then the solvent was evaporated off and the crude product was dissolved in ethyl acetate (20 ml) and washed with 25 ml of 1M NaOH. The aqueous layer was extracted with ethyl acetate (20 ml x 3). The combined organic layers were washed with brine (25 ml) and dried with sodium sulfate. The solvent was evaporated off and the crude product was purified by column chromatography.

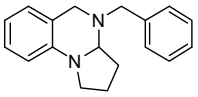
General procedure C for the reaction between aminoaldehydes and amines:

To a stirred solution of aminoaldehyde (1 mmol) in 10 mL of EtOH was added the primary amine (1.2 mmol) and triflic acid (0.2 mmol), followed by stirring at room temperature. The reaction mixture was monitored by TLC. After the completion of the reaction, 0.3 ml of triethylamine was added. Then the solvent was evaporated off and the crude product was dissolved in ethyl acetate (20 ml) and washed with 25 ml of 1M NaOH. The aqueous layer was extracted with ethyl acetate (20 ml x 3). The combined organic layers were washed with brine (25 ml) and dried with sodium sulfate. The solvent was evaporated off and the crude product was purified by column chromatography.

4-phenyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.33a): The reaction was carried out according to the general procedure A (3 h). The product was obtained as a white solid in 71% yield. (R_f = 0.34 in 8% EtOAc/Hex); mp: 82 – 84 °C; IR (KBr) 3031, 2970, 2937, 2835, 1606, 1596, 1510, 1494, 1477, 1461, 1398,

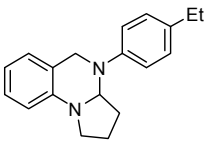
1363, 1323, 1308, 1256, 1207, 1193, 774, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.32 (app tt, *J* = 2.0, 3.9 Hz, 2H), 7.22 – 7.10 (m, 4H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.69 – 6.63 (m, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 4.65 (dd, *J* = 5.3, 8.3 Hz, 1H), 4.40 (d, *J* = 14.9 Hz, 1H), 4.12 (d, *J* = 14.9 Hz, 1H), 3.47 (app td, *J* = 3.1, 8.7 Hz, 1H), 3.39 (dd, *J* = 8.6, 16.2 Hz, 1H), 2.14 – 1.85 (comp, 3H), 1.80 – 1.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.25, 143.45, 128.92, 127.75, 125.90, 125.15, 124.72, 120.83, 116.15, 111.32, 76.66, 57.29, 47.06, 31.94, 22.24; Chemical Formula: $C_{17}H_{18}N_2$, *m/z* (ESIMS) 251.2 $[M + H]^+$.

4-benzyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.33b): The reaction was



carried out according to the general procedure B (24 h). The product was obtained as a colorless oil in 75% yield. (R_f = 0.24 in 2% EtOAc/ CH_2Cl_2); IR (film) 3066, 3025, 2968, 2834, 1606, 1578, 1509, 1483, 1462, 1395, 1369, 1321, 1304, 1160, 1130, 741, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.45 – 7.26 (comp, 5H), 7.11 (app t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.2 Hz, 1H), 6.59 (app td, *J* = 0.9, 7.4 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 4.17 (dd, *J* = 5.3, 8.3 Hz, 1H), 3.95 (d, *J* = 13.1 Hz, 1H), 3.69 (d, *J* = 14.8 Hz, 1H), 3.57 (d, *J* = 14.8 Hz, 1H), 3.50 – 3.30 (comp, 3H), 2.35 – 2.25 (m, 1H), 2.19 – 2.09 (m, 1H), 2.07 – 1.86 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 143.20, 138.26, 129.00, 128.25, 127.61, 127.05, 126.40, 119.37, 115.72, 110.34, 78.43, 56.50, 54.43, 46.61, 31.77, 22.38; Chemical Formula: $C_{18}H_{20}N_2$, *m/z* (ESIMS) 265.2 $[M + H]^+$.

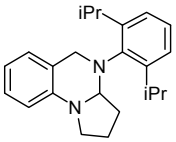
4-(4-ethylphenyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.33c): The



reaction was carried out according to the general procedure A (12 h). The product was obtained as a white solid in 67% yield. (R_f = 0.34 in 15% Ether/Hex); mp: 67 – 69 °C; IR (KBr) 2959, 2851, 1605, 1509, 1457, 1359, 1345,

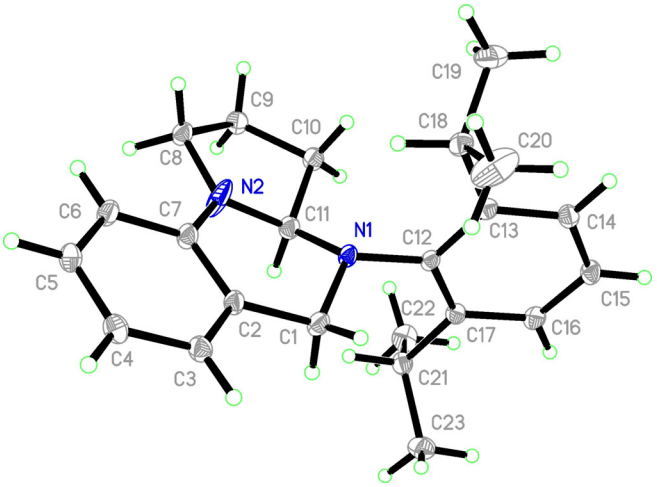
1194, 1178, 1104, 840, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.20 – 7.07 (comp, 5H), 6.96 (d, *J* = 7.3 Hz, 1H), 6.65 (app t, *J* = 7.4 Hz, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 4.63 (dd, *J* = 5.3, 8.2 Hz, 1H), 4.38 (d, *J* = 14.9 Hz, 1H), 4.09 (d, *J* = 14.9 Hz, 1H), 3.53 – 3.34 (comp, 2H), 2.64 (app q, *J* = 7.6 Hz, 2H), 2.11 – 1.84 (comp, 3H), 1.74 (app tt, *J* = 8.2, 11.1 Hz, 1H), 1.32 – 1.19 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 147.96, 143.58, 140.91, 128.41, 127.82, 126.05, 125.30, 121.03, 116.18, 111.40, 76.86, 57.59, 47.24, 32.11, 28.38, 22.39, 15.60; Chemical Formula: $C_{19}H_{22}N_2$, *m/z* (ESIMS) 279.5 $[M + H]^+$.

4-(2,6-diisopropylphenyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.33d):

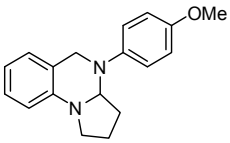


The reaction was carried out according to the general procedure A (5h). The product was obtained as a white solid in 71% yield. (R_f = 0.30 in 20% CH_2Cl_2/Hex); mp: 186 – 189 °C; IR (KBr) 3049, 3021, 2926, 2863, 2778, 1604, 1578, 1477, 1445, 1395, 1386, 1363, 1319, 1300, 1259, 1249, 1189, 1157, 1048, 763 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.25 (dd, *J* = 5.2, 10.0 Hz, 1H), 7.21 – 7.09 (comp, 3H), 6.97 (d, *J* = 7.3 Hz, 1H), 6.70 (app t, *J* = 7.3 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 4.96 (dd, *J* = 5.6, 7.9 Hz, 1H), 4.64 (d, *J* = 15.3 Hz, 1H), 3.98 (d, *J* = 15.3 Hz, 1H), 3.73 (app dt, *J* = 6.9, 13.9 Hz, 1H), 3.57 – 3.35 (comp, 2H), 3.11 (app dt, *J* = 6.8, 13.6 Hz, 1H), 2.09 – 1.85 (comp, 2H), 1.84 – 1.73 (m, 1H), 1.50 (app dt, *J* = 8.4, 12.1 Hz, 1H), 1.28 (dd, *J* = 3.3, 6.8 Hz, 6H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.48, 149.30, 144.26, 141.92, 127.10, 127.00, 125.79, 124.36, 123.73, 121.78, 116.31, 112.71, 74.60, 53.95, 47.52, 31.26, 28.84, 27.26, 25.49, 25.29, 24.30, 23.56, 22.54; Chemical Formula: $C_{23}H_{30}N_2$, *m/z* (ESIMS) 335.2 $[M + H]^+$

Product **3.33d** was further characterized by X–ray crystallography:

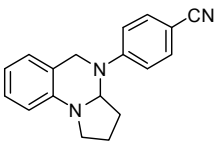


4-(4-methoxyphenyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.33e): The



reaction was carried out according to the general procedure A (0.5 h). The product was obtained as a yellow solid in 57% yield. (R_f = 0.65 in CH_2Cl_2); mp: 73 – 75 °C; IR (KBr) 3040, 2931, 2833, 1606, 1579, 1509, 1482, 1461, 1392, 1362, 1322, 1288, 1244, 1204, 1180, 1134, 1121, 1104, 1037, 1016, 992, 835, 816, 772, 744, 713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.17 – 7.09 (comp, 3H), 6.96 (d, *J* = 7.3 Hz, 1H), 6.89 – 6.83 (comp, 2H), 6.64 (app tt, *J* = 1.9, 3.8 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 4.58 (dd, *J* = 4.9, 8.2 Hz, 1H), 4.38 (d, *J* = 14.9 Hz, 1H), 4.02 (d, *J* = 14.9 Hz, 1H), 3.80 (s, 3H), 3.47 (app td, *J* = 2.8, 8.6 Hz, 1H), 3.42 – 3.32 (m, 1H), 2.02 – 1.83 (comp, 3H), 1.76 – 1.61 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 157.07, 143.37, 143.05, 127.71, 126.73, 125.98, 120.80, 115.97, 114.13, 111.19, 77.20, 57.55, 55.37, 47.09, 31.91, 22.26; Chemical Formula: $C_{18}H_{20}N_2O$, *m/z* (ESIMS) 281.2 $[M]^+$.

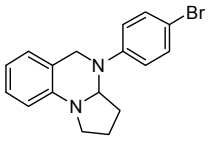
4-(1,2,3,3a-tetrahydropyrrolo[1,2-a]quinazolin-4(5H)-yl)benzonitrile (3.33f): The



reaction was carried out according to the general procedure C (15 h).

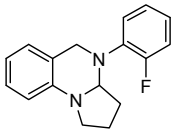
The product was obtained as a white solid in 50% yield. (R_f = 0.51 in CH_2Cl_2); mp: 116 – 118 °C; IR (KBr) 3048, 2949, 2838, 2213, 1602, 1513, 1461, 1383, 1175, 820, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.58 – 7.50 (comp, 2H), 7.20 (app t, *J* = 7.7 Hz, 1H), 7.08 – 6.98 (comp, 3H), 6.77 (app t, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 4.59 (dd, *J* = 5.5, 8.3 Hz, 1H), 4.46 (d, *J* = 14.8 Hz, 1H), 4.29 (d, *J* = 14.8 Hz, 1H), 3.52 – 3.40 (m, 1H), 3.34 (app td, *J* = 5.3, 8.9 Hz, 1H), 2.43 – 2.30 (m, 1H), 2.14 – 1.91 (comp, 2H), 1.78 (app dq, *J* = 8.9, 12.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 152.83, 144.24, 133.05,128.18, 125.62, 122.11, 120.09, 119.58, 118.03, 112.21, 103.39, 75.00, 52.60, 46.15, 31.23, 21.49; Chemical Formula: $C_{18}H_{17}N_3$, *m/z* (ESIMS) 276.2 $[M + H]^+$.

4-(4-bromophenyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.33g): The



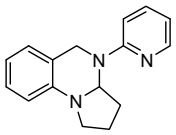
reaction was carried out according to the general procedure A (1.5 h). The product was obtained as a white solid in 65% yield. (R_f = 0.27 in 50% CH_2Cl_2/Hex); mp: 97 – 99 °C; IR (KBr) 2967, 2831, 1604, 1578, 1508, 1496, 1483, 1461, 1394, 1362, 1322, 1290, 1254, 1233, 1206, 1175, 1130, 1101, 1070, 1036, 1007, 992, 842, 823, 805, 744, 716, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.45 – 7.38 (comp, 2H), 7.15 (app t, *J* = 7.5 Hz, 1H), 7.07 – 7.00 (comp, 2H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.67 (app td, *J* = 0.9, 7.4 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 4.62 (dd, *J* = 5.3, 8.3 Hz, 1H), 4.38 (d, *J* = 15.0 Hz, 1H), 4.09 (d, *J* = 15.0 Hz, 1H), 3.51 – 3.31 (comp, 2H), 2.14 – 1.85 (comp, 3H), 1.70 (app ddt, *J* = 8.3, 10.8, 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 149.14, 143.43, 131.94, 127.87, 126.82, 125.88, 120.43, 117.69, 116.36, 111.39, 76.44, 56.97, 46.95, 31.66, 22.16; Chemical Formula: $C_{17}H_{17}BrN_2$, *m/z* (ESIMS) 329.2 $[M + H]^+$.

4-(2-fluorophenyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.33h): The



reaction was carried out according to the general procedure A (6 h). The product was obtained as a white solid in 50% yield. (R_f = 0.37 in 10% Ether/Hex); mp: 80 – 82 °C; IR (KBr) 3064, 3047, 3023, 2978, 2962, 2937, 2847, 2790, 1604, 1576, 1497, 1483, 1461, 1366, 1327, 1262, 1222, 1196, 1172, 1033, 772, 746 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$) 7.22 – 7.02 (comp, 5H), 6.96 (d, *J* = 7.3 Hz, 1H), 6.67 (app t, *J* = 7.4 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 4.92 – 4.76 (m, 1H), 4.52 (d, *J* = 15.2 Hz, 1H), 4.13 (d, *J* = 15.2 Hz, 1H), 3.55 – 3.31 (comp, 2H), 2.12 (ddd, *J* = 2.6, 7.6, 12.4 Hz, 1H), 2.05 – 1.86 (comp, 2H), 1.69 (ddd, *J* = 8.5, 11.0, 19.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 160.05, 158.08, 143.62, 136.92, 136.84, 127.68, 127.04, 127.02, 126.17, 126.10, 125.85, 124.39, 124.36, 120.38, 116.25, 116.18, 116.02, 111.54, 75.80, 55.89, 46.88, 30.80, 22.18; Chemical Formula: $C_{17}H_{17}FN_2$, *m/z* (ESIMS) 267.3 $[M - H]^+$.

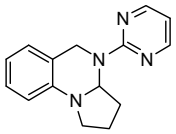
4-(pyridin-2-yl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.33i): The reaction



was carried out according to the general procedure A (24 h). The product was obtained as a yellow liquid in 35% yield. (R_f = 0.46 in 2% EtOAc/ CH_2Cl_2); IR (film) 3043, 2967, 2815, 1591, 1561, 1497, 1479, 1460, 1436, 1379, 1320, 1213, 1158, 1047, 977, 768, 749 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$) 8.31 – 8.22 (m, 1H), 7.51 (ddd, *J* = 2.0, 7.2, 8.5Hz, 1H), 7.24 – 7.16 (m, 1H), 7.11 (d, *J* = 7.3 Hz, 1H), 6.85 – 6.64 (comp, 4H), 4.85 (d, *J* = 14.7 Hz, 1H), 4.72 (dd, *J* = 5.4, 8.6 Hz, 1H), 4.33 (d, *J* = 14.7 Hz, 1H), 3.49 (app td, *J* = 5.7, 8.7 Hz, 1H), 3.33 (app td, *J* = 5.7, 9.0 Hz, 1H), 2.64 (app tdd, *J* = 3.1, 5.4, 12.1 Hz, 1H), 2.15 – 1.93 (comp, 2H), 1.81 (ddd, *J* = 9.2, 12.2, 18.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 159.35, 147.79, 144.83, 137.09, 127.84,

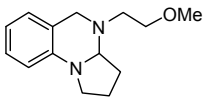
125.61, 123.57, 117.93, 114.74, 112.31, 111.43, 73.83, 48.63, 46.04, 31.33, 21.29; Chemical Formula: $C_{16}H_{17}N_3$, *m/z* (ESIMS) 250.3 $[M - H]^+$.

4-(pyrimidin-2-yl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.33j): The



reaction was carried out according to the general procedure A (48 h). The product was obtained as a white solid in 36% yield. (R_f = 0.17 in 5% EtOAc/ CH_2Cl_2); mp: 105 – 107 °C; IR (film) 3024, 2960, 2825, 1585, 1547, 1486, 1459, 1371, 1350, 1316, 1280, 1227, 1175, 1156, 797, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.34 (d, *J* = 4.7 Hz, 2H), 7.22 (app t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 6.82 (dd, *J* = 4.2, 10.7 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.52 (t, *J* = 4.7 Hz, 1H), 5.47 (d, *J* = 14.8 Hz, 1H), 4.79 (dd, *J* = 5.4, 8.9 Hz, 1H), 4.22 (d, *J* = 14.8 Hz, 1H), 3.53 (app td, *J* = 4.0, 9.3 Hz, 1H), 3.23 (app td, *J* = 7.1, 9.3 Hz, 1H), 2.86 – 2.63 (m, 1H), 2.23 – 1.90 (comp, 2H), 1.89 – 1.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 160.71, 157.41, 145.78, 127.99, 125.72, 125.49, 119.02, 112.91, 110.12, 72.84, 45.20, 43.35, 30.57, 20.49; Chemical Formula: $C_{15}H_{16}N_4$, *m/z* (ESIMS) 253.2 $[M + H]^+$.

4-(2-methoxyethyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.33k): The



reaction was carried out according to the general procedure B (15 h). The product was obtained as a liquid in 70% yield. (R_f = 0.27 in 60% EtOAc/Hex); IR (film) 2969, 2874, 1666, 1607, 1581, 1509, 1483, 1462, 1392, 1369, 1307, 1196, 1159, 1119, 960, 742, 716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.08 (app t, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 7.3 Hz, 1H), 6.59 (app t, *J* = 7.4 Hz, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 4.14 (dd, *J* = 5.5, 8.5 Hz, 1H), 3.94 (d, *J* = 14.9 Hz, 1H), 3.80 (d, *J* = 14.9 Hz, 1H), 3.65 – 3.53 (comp, 2H), 3.43 – 3.35 (comp, 3H), 3.32 (dd, *J* = 8.8, 16.1 Hz, 1H), 2.83 (app dt, *J* = 5.9, 13.3 Hz, 1H), 2.55 (app dt, *J* = 5.9, 13.2 Hz, 1H), 2.21 (ddd, *J* = 1.9, 7.2,

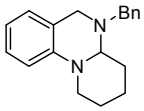
12.3 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.99 – 1.75 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 143.17, 127.60, 126.44, 118.96, 115.64, 110.27, 78.06, 70.98, 58.84, 55.37, 50.59, 46.43, 31.20, 22.24.; Chemical Formula: $C_{14}H_{20}N_2O$, *m/z* (ESIMS) 233.4 $[M + H]^+$.

4-butyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.33l): The reaction was carried out according to the general procedure B (24 h). The product was obtained as a colorless oil in 65% yield. (R_f = 0.20 in 5% EtOAc/ CH_2Cl_2); IR (film) 2955, 2931, 2869, 2755, 1607, 1510, 1483, 1463, 1396, 1369, 1351, 1320, 1307, 1160, 1138, 741, 715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.09 (app t, *J* = 7.7 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.61 (app td, *J* = 0.8, 7.4 Hz, 1H), 6.43 (d, *J* = 7.9 Hz, 1H), 4.06 – 3.87 (comp, 2H), 3.56 (d, *J* = 14.5 Hz, 1H), 3.40 (app td, *J* = 2.3, 8.7 Hz, 1H), 3.34 (app dt, *J* = 8.1, 16.2 Hz, 1H), 2.71 (ddd, *J* = 7.0, 8.9, 12.2 Hz, 1H), 2.23 (app tdd, *J* = 3.9, 7.7, 8.9 Hz, 2H), 2.14 – 2.02 (m, 1H), 1.94 (app qdd, *J* = 5.5, 7.9, 8.7 Hz, 1H), 1.80 (app tt, *J* = 8.3, 11.7 Hz, 1H), 1.68 – 1.53 (comp, 2H), 1.49 – 1.30 (comp, 2H), 0.97 (app t, *J* = 7.4 Hz, 3H)**;** ^{13}C NMR (125 MHz, $CDCl_3$) 143.07, 127.51, 126.24, 119.46, 115.53, 110.20, 78.42, 54.45, 52.02, 46.40, 31.70, 29.38, 22.25, 20.71, 13.94; Chemical Formula: $C_{11}H_{13}N_2$, *m/z* (ESIMS) 231.1 $[M + H]^+$.

4-cyclopentyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.33m): The reaction was carried out according to the general procedure B (24 h). The product was obtained as an oil in 66% yield. (R_f = 0.26 in 10% EtOAc/ CH_2Cl_2); IR (film) 3043, 2957, 2866, 1607, 1510, 1482, 1462, 1394, 1362, 1323, 1305, 1161, 1133, 739 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.06 (app t, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 7.3 Hz, 1H), 6.56 (app td, *J* = 0.8, 7.4 Hz, 1H), 6.39 (d, *J* = 7.9 Hz, 1H), 4.08 (dd, *J* = 4.8, 9.1 Hz, 1H), 3.81 (d, *J* = 14.2 Hz, 1H), 3.71 (d, *J* = 14.2 Hz, 1H), 3.44 (app p, *J* = 8.0 Hz, 1H),

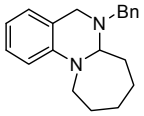
3.40 – 3.26 (comp, 2H), 2.24 (app dt, *J* = 5.7, 11.4 Hz, 1H), 2.14 – 2.02 (m, 1H), 2.00 – 1.78 (comp, 3H), 1.77 – 1.46 (comp, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) 143.04, 127.49, 126.14, 120.11, 115.42, 110.05, 77.55, 60.89, 47.89, 46.24, 32.24, 29.99, 24.61, 23.94, 23.17, 22.36; Chemical Formula: $C_{16}H_{22}N_2$, *m/z* (ESIMS) 243.2 $[M + H]^+$.

5-benzyl-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinazoline (3.39a): The reaction



was carried out according to the general procedure B (24 h). The product was obtained as a colorless oil in 65% yield. (R_f = 0.21 in 2% EtOAc/ CH_2Cl_2); IR (film) 3060, 3019, 2936, 2853, 1601, 1493, 1453, 1441, 1341, 1236, 1125, 1007, 747, 731, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.34 (app dt, *J* = 7.3, 12.7 Hz, 4H), 7.26 (dd, *J* = 5.5, 8.5 Hz, 1H), 7.15 (dd, *J* = 4.1, 11.4 Hz, 1H), 6.87 (app t, *J* = 9.0 Hz, 2H), 6.68 (app t, *J* = 7.3 Hz, 1H), 4.09 – 3.97 (comp, 2H), 3.90 (dd, *J* = 3.5, 10.2 Hz, 1H), 3.83 (d, *J* = 13.5 Hz, 1H), 3.71 (dd, *J* = 11.6, 15.0 Hz, 2H), 2.90 – 2.74 (m, 1H), 1.97 – 1.84 (m, 1H), 1.82 – 1.69 (comp, 2H), 1.62 – 1.48 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 144.54, 139.46, 128.91, 128.23, 127.54, 127.51, 126.88, 120.60, 117.05, 112.25, 75.37, 56.05, 49.27, 47.63, 29.19, 24.87, 23.59; Chemical Formula: $C_{19}H_{22}N_2$, *m/z* (ESIMS) 279.2 $[M + H]^+$.

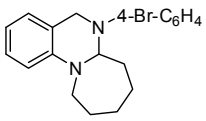
6-benzyl-5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinazoline (3.39b): The reaction



was carried out according to the general procedure B (2 h). The product was obtained as an oil in 82% yield. (R_f = 0.33 in 10% EtOAc/Hex); IR (film) 3061, 3025, 2926, 2854, 1602, 1574, 1503, 1468, 1454, 1364, 1348, 1327, 1314, 1292, 1275, 1171, 1120, 1104, 1069, 1055, 910, 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.34 (app t, *J* = 6.1 Hz, 4H), 7.31 – 7.25 (m, 1H), 7.14 (app t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.62 (dd, *J* = 4.1, 7.7 Hz, 2H), 4.35 (d, *J* = 16.8 Hz, 1H), 3.95 – 3.83 (comp,

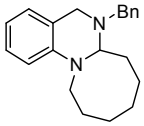
2H), 3.69 – 3.63 (comp, 2H), 3.59 (d, *J* = 16.8 Hz, 1H), 3.09 – 2.99 (m, 1H), 2.11 (ddd, *J* = 5.5, 10.8, 21.2 Hz, 1H), 1.96 – 1.77 (comp, 2H), 1.70 – 1.51 (comp, 3H), 1.50 – 1.30 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 142.65, 139.07, 129.09, 128.22, 127.53, 127.28, 126.95, 116.56, 114.92, 108.93, 76.32, 57.95, 47.59, 46.86, 35.65, 26.23, 26.21, 24.82; Chemical Formula: $C_{20}H_{24}N_2$, *m/z* (ESIMS) 293.2 $[M + H]^+$.

6-(4-bromophenyl)-5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinazoline (3.39c):



The reaction was carried out according to the general procedure A (1.5 h). The product was obtained as a white solid in 90% yield. (R_f = 0.5 in 50% CH_2Cl_2/Hex); mp: 105 – 108 °C; IR (KBr) 3064, 2933, 2910, 2852, 1605, 1584, 1511, 1493, 1482, 1471, 1459, 1380, 1365, 1350, 1297, 1263, 1236, 1214, 1171, 1152, 1115, 1058, 1009, 968, 812, 739, 735, 711 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.36 – 7.29 (comp, 2H), 7.11 (app t, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.86 – 6.79 (comp, 2H), 6.69 – 6.58 (comp, 2H), 4.82 (dd, *J* = 4.3, 9.9 Hz, 1H), 4.57 (d, *J* = 16.2 Hz, 1H), 4.34 (d, *J* = 16.2 Hz, 1H), 3.89 (ddd, *J* = 3.3, 6.3, 15.0 Hz, 1H), 3.31 – 3.16 (m, 1H), 2.25 – 2.09 (m, 1H), 2.01 – 1.82 (comp, 2H), 1.69 (app tdt, *J* = 6.9, 13.6, 19.2 Hz, 3H), 1.60 – 1.45 (m, 1H), 1.44 – 1.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 148.73, 142.34, 131.82, 127.79, 126.41, 118.89, 117.31, 115.69, 111.90, 110.05, 74.85, 47.02, 46.25, 32.95, 26.30, 25.90, 24.63; Chemical Formula: $C_{13}H_{17}N_2$, *m/z* (ESIMS) 357.3 $[M + 1]^+$.

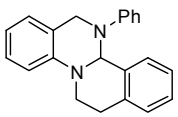
6-benzyl-6,6a,7,8,9,10,11,12-octahydro-5H-azocino[1,2-a]quinazoline (3.39d): The



reaction was carried out according to the general procedure B (1.5 h). The product was obtained as an oil in 85% yield. (R_f = 0.38 in 10% EtOAc/Hex);

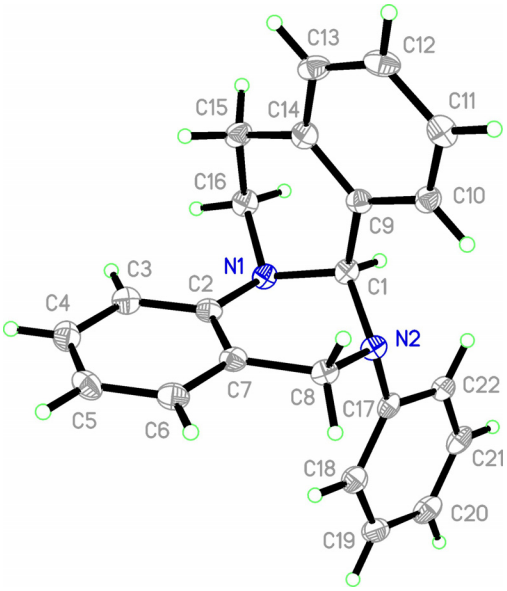
IR (film) 3061, 3026, 2921, 2849, 1602, 1574, 1500, 1463, 1452, 1365, 1346, 1323, 1293, 1218, 1176, 1151, 1103, 1071, 1027, 1016, 995, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.40 – 7.34 (comp, 4H), 7.33 – 7.28 (m, 1H), 7.19 (dd, *J* = 4.2, 11.3 Hz, 1H), 6.95 (d, *J* = 7.2 Hz, 1H), 6.67 (dd, *J* = 5.0, 12.2 Hz, 2H), 4.34 (d, *J* = 16.8 Hz, 1H), 3.95 (app dt, *J* = 4.4, 15.0 Hz, 1H), 3.89 – 3.85 (m, 1H), 3.58 (comp, 3H), 3.19 – 3.08 (m, 1H), 2.02 – 1.58 (comp, 7H), 1.54 – 1.30 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 142.46, 139.00, 128.95, 128.20, 127.42, 127.36, 126.92, 116.78, 115.21, 110.06, 78.18, 57.44, 52.35, 47.71, 35.00, 28.26, 27.78, 26.92, 26.77; Chemical Formula: $C_{21}H_{26}N_2$, *m/z* (ESIMS) 307.2 $[M + H]^+$.

5-phenyl-5,6,12,13-tetrahydro-4bH-isoquinolino[2,1-a]quinazoline (3.39e): The

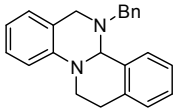


reaction was carried out according to the general procedure C (12 h) at rt. The product was obtained as a white solid in 99% yield. (R_f = 0.58 in 10% EtOAc/Hex); mp: 139 – 141 °C; IR (KBr) 3059, 3032, 2963, 2911, 1599, 1581, 1492, 1470, 1450, 1427, 1362, 1342, 1288, 1253, 1221, 1200, 1137, 1061, 1035, 985, 972, 948, 873, 770, 757, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.63 (d, *J* = 7.4 Hz, 1H), 7.34 – 6.85 (comp, 11H), 6.70 (app t, *J* = 7.3 Hz, 1H), 6.07 (s, 1H), 4.40 (app dd, *J* = 16.6, 40.2 Hz, 2H), 4.28 (dd, *J* = 4.8, 14.5 Hz, 1H), 3.51 (ddd, *J* = 4.1, 12.7, 14.4 Hz, 1H), 3.23 – 3.10 (m, 1H), 2.58 (dd, *J* = 3.7, 16.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.73, 143.75, 137.29, 136.52, 129.15, 128.86, 127.55, 127.44, 126.80, 126.28, 125.87, 122.06, 120.65, 118.43, 117.99, 113.55, 73.75, 46.50, 45.22, 24.91; Chemical Formula: $C_{22}H_{20}N_2$, *m/z* (ESIMS) 313.2 $[M + H]^+$.

Product **3.39e** was further characterized by X–ray crystallography:

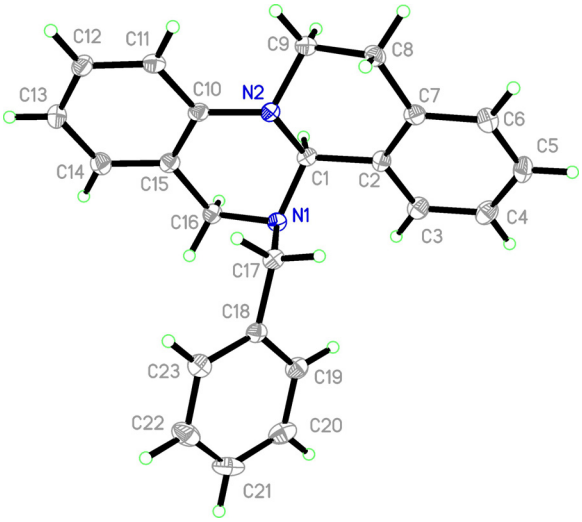


5-benzyl-5,6,12,13-tetrahydro-4bH-isoquinolino[2,1-a]quinazoline (3.39f): The

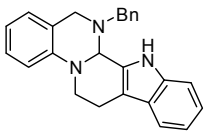


reaction was carried out according to the general procedure B (0.5 h). The product was obtained as a white solid in 64% yield. (R_f = 0.30 in 60% CH_2Cl_2/Hex); IR (film) 3061, 3026, 2895, 2848, 1602, 1576, 1493, 1455, 1382, 1346, 1326, 1291, 1264, 1221, 1145, 1109, 996, 932 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.82 (d, *J* = 7.7 Hz, 1H), 7.47 – 7.23 (comp, 6H), 7.18 (dd, *J* = 7.6, 18.1 Hz, 2H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 7.3 Hz, 1H), 6.71 (app t, *J* = 7.3 Hz, 1H), 5.34 (s, 1H), 4.20 (dd, *J* = 4.1, 12.7 Hz, 1H), 3.90 (app t, *J* = 15.2 Hz, 2H), 3.76 (app s, 2H), 3.28 (app td, *J* = 3.4, 12.6 Hz, 1H), 3.21 – 3.06 (m, 1H), 2.69 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 144.63, 139.81, 136.74, 136.40, 128.71, 128.38, 128.19, 127.73, 127.39, 127.13, 126.83, 126.75, 126.63, 121.01, 117.76, 112.21, 74.80, 53.37, 49.10, 43.57, 27.37; Chemical Formula: $C_{23}H_{22}N_2$, *m/z* (ESIMS) 327.2 $[M + H]^+$.

Product **3.39f** was further characterized by X–ray crystallography:

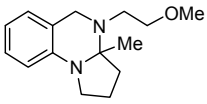


1-benzyl-1,2,8,9,14,14b-hexahydroindolo[2',3':3,4]pyrido[1,2-a]quinazoline (3.39g):



The reaction was carried out according to the general procedure B (1 h). The product was obtained as a solid in 74% yield. (R_f = 0.24 in 10% EtOAc/Hex); mp: 86 – 90 °C; IR (film) 3421, 3058, 3028, 2902, 2844, 1602, 1576, 1490, 1453, 1391, 1337, 1315, 1291, 1265, 1240, 1217, 1139, 1103, 980, 957, 943 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.29 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.39 (app dt, *J* = 6.7, 7.2 Hz, 5H), 7.31 (app t, *J* = 7.1 Hz, 1H), 7.21 (app t, *J* = 7.3 Hz, 2H), 7.12 (app t, *J* = 7.5 Hz, 2H), 6.85 (d, *J* = 7.2 Hz, 1H), 6.74 (app t, *J* = 7.3 Hz, 1H), 5.50 (s, 1H), 4.38 (dd, *J* = 4.4, 13.6 Hz, 1H), 4.00 – 3.74 (comp, 4H), 3.33 (ddd, *J* = 4.0, 11.8, 13.6 Hz, 1H), 3.12 – 2.98 (m, 1H), 2.72 (d, *J* = 15.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 144.43, 139.14, 135.88, 132.72, 128.78, 128.33, 127.67, 127.58, 127.19, 127.09, 122.02, 120.50, 119.41, 118.38, 118.14, 113.20, 111.76, 111.14, 72.22, 54.30, 48.75, 44.97, 19.62; Chemical Formula: $C_{25}H_{23}N_3$, *m/z* (ESIMS) 364.4 $[M - H]^+$.

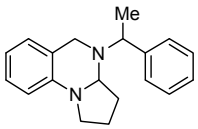
4-(2-methoxyethyl)-3a-methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline



(3.39h): The reaction was carried out according to the general

procedure B (1 h). The product was obtained as an oil in 60% yield. (R_f = 0.25 in 30% EtOAc/CH_2Cl_2); IR (film) 2967, 2927, 2876, 2830, 2770, 1606, 1580, 1508, 1484, 1461, 1308, 1180, 1142, 1119, 1092, 998, 743, 715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.08 (app t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.3 Hz, 1H), 6.61 (app t, *J* = 7.3 Hz, 1H), 6.45 (d, *J* = 8.0 Hz, 1H), 3.96 (d, *J* = 15.3 Hz, 1H), 3.77 (d, *J* = 15.3 Hz, 1H), 3.56 (app t, *J* = 6.3 Hz, 2H), 3.52 – 3.43 (m, 1H), 3.43 – 3.32 (comp, 4H), 2.91 (app dt, *J* = 6.7, 13.2 Hz, 1H), 2.51 – 2.36 (m, 1H), 2.14 – 1.83 (comp, 4H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 141.99, 127.40, 126.29, 118.97, 115.44, 111.54, 77.57, 72.14, 58.90, 51.88, 50.61, 46.55, 39.40, 21.62, 15.73; Chemical Formula: $C_{15}H_{22}N_2O$, *m/z* (ESIMS) 247.3 $[M + H]^+$.

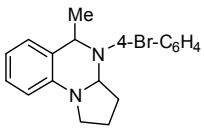
4-(1-phenylethyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.39i): The



reaction was carried out according to the general procedure B (15 h). The product was obtained as a mixture of diastereomers in 52% yield, dr = 59 : 41 determined by integration of one set of ^1H-NMR signals (δmajor 1.49 – 1.45 ppm, δminor 1.67 – 1.62 ppm). (R_f = 0.28 in 1% EtOAc/ CH_2Cl_2); IR (film) 3026, 2970, 2936, 2875, 2828, 1606, 1581, 1509, 1483, 1460, 1395, 1373, 1321, 1304, 1159, 1132, 1106, 741, 714, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (major diastereomer) 7.54 (d, *J* = 7.7 Hz, 2H), 7.45 – 7.25 (comp, 4H), 6.83 (d, *J* = 7.3 Hz, 1H), 6.58 (app t, *J* = 7.4 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 4.38 (comp, 1H), 4.32 (dd, *J* = 4.7, 9.1 Hz, 1H), 3.76 (d, *J* = 14.2 Hz, 1H), 3.50 – 3.35 (comp, 3H), 2.32 (app dt, *J* = 5.7, 11.3 Hz, 1H), 2.23 – 1.83 (comp, 3H), 1.46 (app t, *J* = 12.1 Hz, 3H); ^{13}C NMR of the diastereomeric mixture (125 MHz, $CDCl_3$) 143.2, 143.1, 142.8, 138.9, 128.2, 128.0, 127.9, 127.7, 127.4, 127.3, 127.2, 126.6, 126.0, 125.9, 120.8, 120.2, 115.3(6), 115.3(3), 110.3, 110.0, 76.2, 76.0, 57.5, 56.3, 47.7, 46.5, 46.4, 32.4, 32.2, 22.3, 22.2, 19.1, 9.8; Chemical Formula: $C_{19}H_{22}N_2$, *m/z*

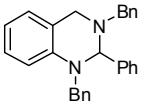
(ESIMS) 279.1 $[M + H]^+$.

4-(4-bromophenyl)-5-methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline



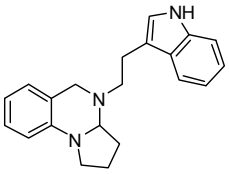
(3.39j): The reaction was carried out according to the general procedure A (3 h). The product was obtained as a mixture of diastereomers in 65% yield dr = 66 : 34, determined by integration of one set of ^{1}H-NMR signals (δmajor 1.43 – 1.38 ppm, δminor 1.31 – 1.27 ppm). (R_f = 0.21 in 10% EtOAc/Hex); IR (film) 3064, 3035, 2969, 2921, 2864, 2839, 2676, 2602, 1604, 1503, 1486, 1461, 1358, 1327, 1239, 1192, 1066, 1043, 1007, 837, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)(major diastereomer) 7.42 – 7.33 (comp, 2H), 7.22 – 7.15 (m, 1H), 7.02 (dd, *J* = 1.1, 7.5 Hz, 1H), 6.96 – 6.91 (comp, 2H), 6.70 (app t, *J* = 7.4 Hz, 1H), 6.57 (app t, *J* = 8.3 Hz, 1H), 4.93 (dd, *J* = 5.4, 8.6 Hz, 1H), 4.36 (q, *J* = 6.9 Hz, 1H), 3.50 – 3.33 (comp, 2H), 2.29 – 2.19 (m, 1H), 2.06 – 1.75 (comp, 2H), 1.71 – 1.58 (m, 1H), 1.41 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR of the diastereomers (125 MHz, $CDCl_3$) 148.0, 147.4, 143.3, 142.9, 132.0, 131.5, 128.3, 128.0, 127.6, 127.5, 126.4, 126.0, 125.5, 124.6, 118.4, 116.9, 116.7, 115.8, 111.2, 111.0, 77.0(3), 68.8, 59.9, 58.3, 46.6(2), 46.5(9), 32.2, 31.0, 22.0, 21.6, 21.4, 19.8; Chemical Formula: $C_{12}H_{15}N_2$, *m/z* (ESIMS) 343.2 $[M + H]^+$.

1,3-dibenzyl-2-phenyl-1,2,3,4-tetrahydroquinazoline (3.39k): The reaction was carried out according to the general procedure B (12 h). The product was obtained as a white solid in 27% yield. (R_f = 0.23 in 5% EtOAc/Hex); mp: 118 – 120 °C; IR (film) 3083, 3060, 3027, 2920, 2844, 1651, 1602, 1575, 1499, 1464, 1451, 1403, 1339, 1323, 1277, 1199, 1146, 1104, 1027, 951, 769, 742, 698, 645 cm^{-1}; ^{1}H NMR (500



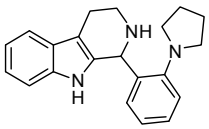
MHz, $CDCl_3$) 7.41 – 7.21 (comp, 15H), 7.14 (app t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.67 (app t, *J* = 7.3 Hz, 1H), 5.10 (s, 1H), 4.75 (d, *J* = 17.0 Hz, 1H), 4.13 (d, *J* = 17.0 Hz, 1H), 3.90 (comp, 3H), 3.45 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 143.81, 141.11, 139.02, 138.97, 128.95, 128.58, 128.33, 128.26, 127.79, 127.64, 127.39, 127.25, 127.05, 127.04, 126.79, 118.26, 116.06, 109.61, 78.05, 57.94, 51.77, 46.97; Chemical Formula: $C_{28}H_{26}N_2$, *m/z* (ESIMS) 391.4 $[M + H]^+$.

4-(2-(1H-indol-3-yl)ethyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline (3.42):



The reaction was carried out according to the general procedure B (12 h). The product was obtained as a white solid in 13% yield. (R_f = 0.31 in 50% EtOAc/Hex); mp: 75 – 78 °C; IR (film) 3409, 3043, 2968, 2856, 1660, 1606, 1572, 1509, 1482, 1458, 1368, 1269, 1228, 1152, 1129, 1101, 1047, 1000, 960, 925 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.03 (s, 1H), 7.74 – 7.50 (m, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.23 – 7.16 (m, 1H), 7.16 – 7.07 (comp, 2H), 7.01 (dd, *J* = 4.7, 20.9 Hz, 2H), 6.62 (app t, *J* = 7.4 Hz, 1H), 6.44 (d, *J* = 8.0 Hz, 1H), 4.13 (d, *J* = 14.5 Hz, 1H), 4.06 (dd, *J* = 5.3, 8.5 Hz, 1H), 3.75 (d, *J* = 14.5 Hz, 1H), 3.47 – 3.38 (m, 1H), 3.33 (dd, *J* = 8.8, 16.0 Hz, 1H), 3.22 – 3.00 (comp, 3H), 2.70 – 2.55 (m, 1H), 2.23 (app dt, *J* = 6.1, 11.9 Hz, 1H), 2.15 – 2.02 (m, 1H), 2.01 – 1.79 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 143.18, 136.24, 127.75, 127.42, 126.46, 121.98, 121.58, 119.41, 119.28, 118.74, 115.77, 114.28, 111.13, 110.43, 78.37, 54.68, 52.98, 46.55, 31.77, 23.58, 22.39; Chemical Formula: $C_{21}H_{23}N_3$, *m/z* (ESIMS) 318.2 $[M + H]^+$.

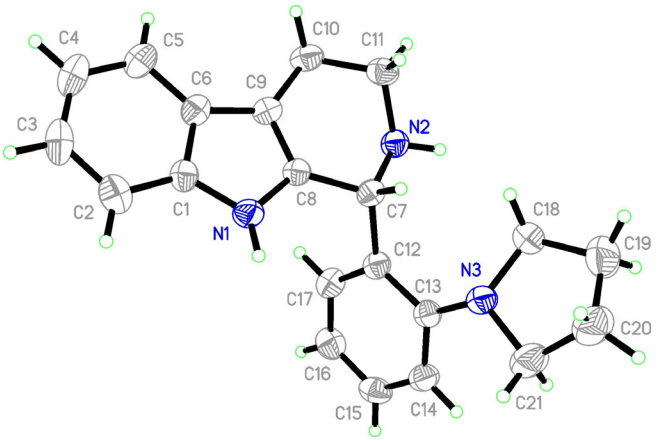
1-(2-(pyrrolidin-1-yl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3.43): The



reaction was carried out according to the general procedure B (12 h).

The product was obtained as a yellow solid in 21% yield. (R_f = 0.20 in 10% MeOH/EtOAc); mp: 184 – 186 °C; IR (film) 3397, 3054, 2936, 2840, 1666, 1596, 1484, 1448, 1351, 1308, 1264, 1188, 1138, 1096, 1006, 954, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.73 (s, 1H), 7.53 (dd, *J* = 2.4, 6.4 Hz, 1H), 7.25 – 7.17 (comp, 2H), 7.15 – 7.07 (comp, 4H), 6.90 (app td, *J* = 1.1, 7.5 Hz, 1H), 5.64 (s, 1H), 3.44 – 3.37 (m, 1H), 3.34 – 3.27 (comp, 2H), 3.26 – 3.19 (comp, 2H), 3.17 – 3.10 (m, 1H), 2.96 – 2.79 (comp, 2H), 2.05 (s, 1H), 2.00 – 1.90 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 149.48, 135.74, 135.70, 134.25, 129.74, 128.47, 127.46, 122.09, 121.40, 119.20, 118.44, 118.03, 110.73, 109.99, 53.15, 52.94, 43.09, 24.81, 22.70; Chemical Formula: $C_{21}H_{23}N_3$, *m/z* (ESIMS) 318.2 $[M + H]^+$.

Product **3.43** was further characterized by X–ray crystallography:



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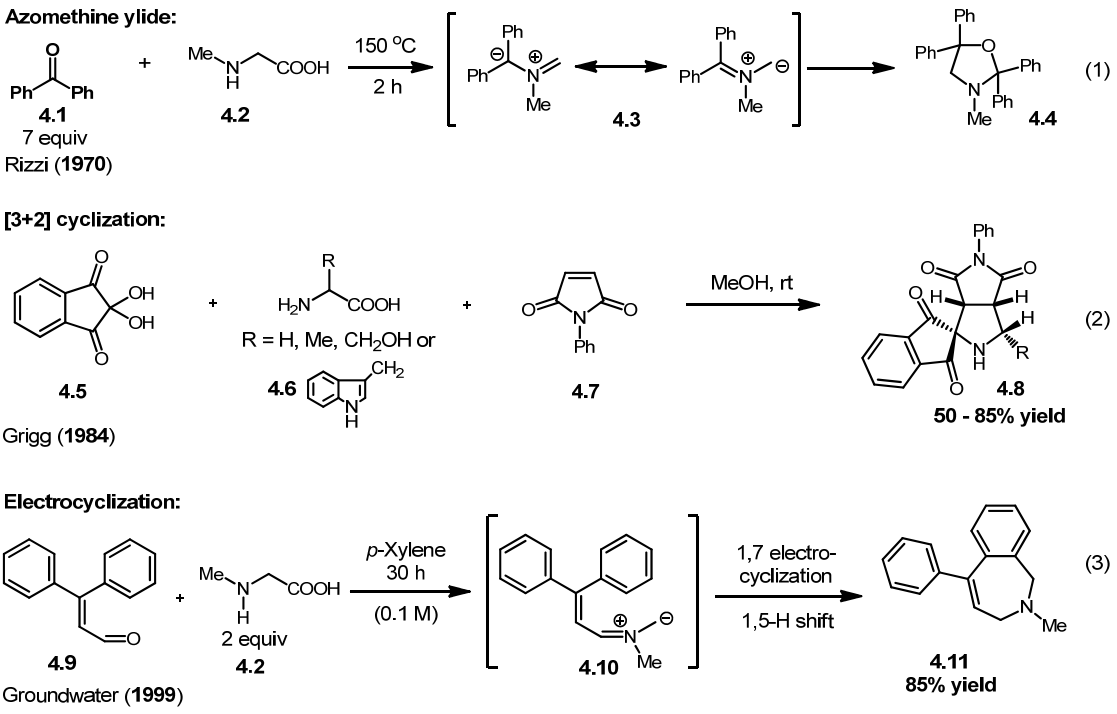
Chapter IV Non-Conventional Functionalization of Azomethine Ylides

4.1 Background

In 1862, Strecker first reported decarboxylative reactions of α-amino acids with carbonyl compounds in what is now known as the Strecker degradation.[1] Then, in 1970, Rizzi first disclosed the intermediacy of azomethine ylides **4.3** in the decarboxylative condensation of an amino acid **4.2** with benzophenone **4.1** (Figure 4.1, eq. 1).[2] In the 1980's, Grigg provided detailed insights into the mechanism of this type of dipole

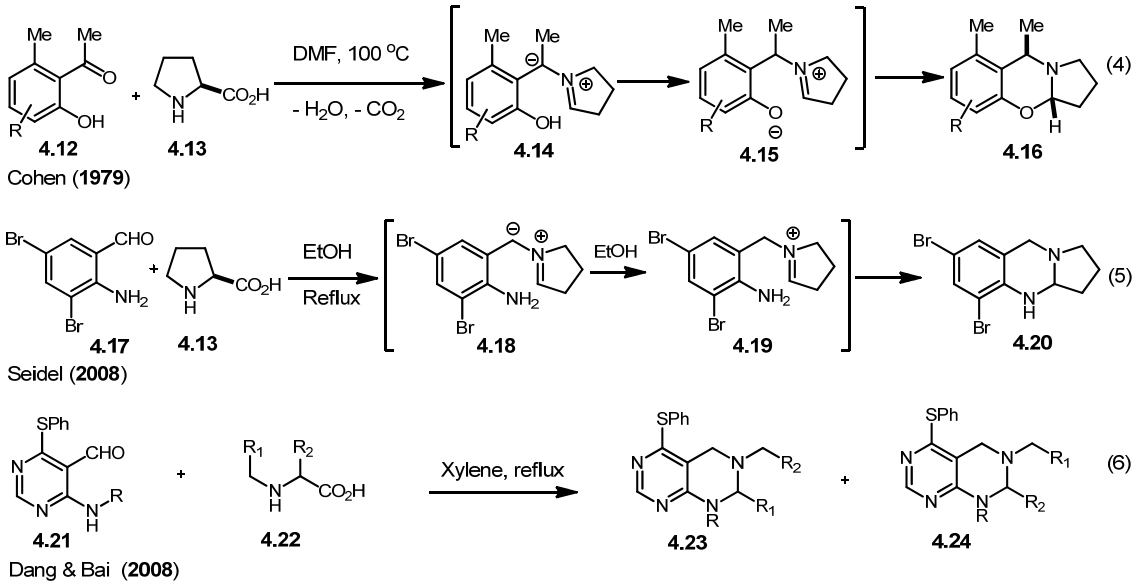
Figure 4.1 **Azomethine Ylides**



formation (Figure 4.1, eq. 2).[3] Inter- and intramolecular [3+2] cycloadditions of azomethine ylides, which provide some of the best routes to pyrrolidine skeletons, have been widely studied.[4] While the most prevalent reaction of azomethine ylides is the [3+2]

cycloaddition, 1,5- and 1,7-electrocyclizations of azomethine ylides are also well established (Figure 4.1, eq. 3).[5]

Figure 4.2 **Non-Conventional Functionalizations of Azomethine Ylides**



Both [3+2] cycloadditions and 1,5- or 1,7-electrocyclizations of azomethine ylides proceed through a pericyclic pathway. In contrast, non-pericyclic reactions are rarely reported with these dipolar species. In 1979, Cohen disclosed a novel annulation reaction between proline and 2-hydroxy-6-methylacetophenones **4.12** under thermal reaction conditions (Figure 4.2, eq 4).[6] The azomethine ylide **4.14**, derived from a decarboxylative condensation, can abstract the proton from the neighboring hydroxyl group. The resulting iminium ion intermediate **4.15** cyclizes to form a polycyclic ring system **4.16** via a C–O bond formation. However, the substrate scope is quite limited to acetophenones bearing an *ortho* methyl substituent **4.12** (Figure 4.2, eq 4). This intriguing result demonstrates a new type of functionalization for azomethine ylides,

which exhibits great potential for the rapid generation of molecular complexity. However, little attention has been focused on this research area so far.

As discussed in chapter 3, we have discovered the ring-fused aminal formation between *o*-aminobenzaldehyde **4.17** and proline (Figure 4.2, eq 5).[7] It is well known that azomethine ylides can be generated by the decarboxylative condensation of proline and aldehydes. The azomethine ylide **4.18** derived from this decarboxylative condensation is protonated to form the corresponding iminium ion **4.19**. The reactive intermediate **4.19** is next attacked by the neighboring amino group to form a C–N bond, leading to the formation of the new ring system **4.20**. Subsequently, Dang and Bai reported a similar transformation of *o*-aminobenzaldehyde **4.21** with different amino acids (Figure 4.2, eq 6).[8]

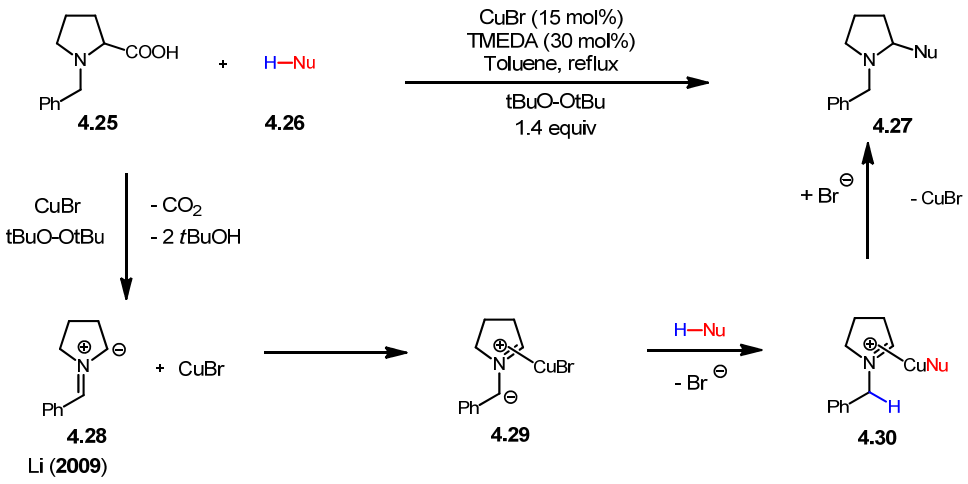
In light of the aforementioned work, we decided to explore this type of non-conventional functionalization of azomethine ylides. Examples of this type have been reported, involving C–O or C–N bond formation in the ring closure step. However, there was still no precedent of this type of annulation involving C–C bond formation. The transformation is thought to proceed via a protonation of the azomethine ylide by a pronucleophile (e.g. OH, NH_2), resulting in the formation of a tethered iminium ion pair that ultimately cyclizes to form a novel heterocycle. We envisioned that other types of pronucleophiles bearing relatively active protons might also be capable of this type of transformation. For instance, nucleophilic moieties, such as indoles and naphthols, contain a relatively acidic proton. These pronucleophiles are proposed as suitable reagents for the protonation of azomethine ylides to form the corresponding iminium ion

intermediates. Subsequently, the nucleophilic site of indoles or naphthols will attack the iminium ion to form a new C–C bond.

4.2 Decarboxylative Three-Component Couplings of α-Amino Acids

4.2.1 General Consideration

Figure 4.3 **Intermolecular Functionalization of Azomethine Ylides**

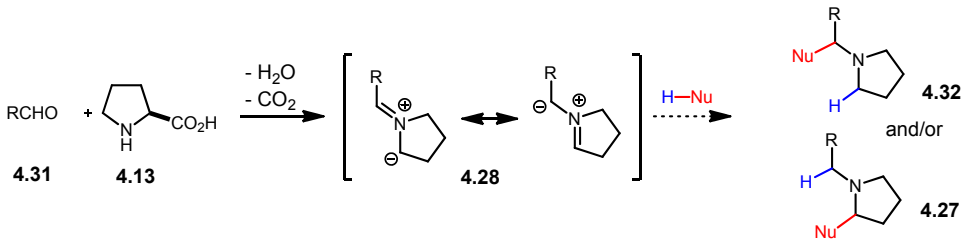


Concurrently, Li's group showed N-benzyl amino acids **4.25** could be functionalized with various nucleophiles in the presence of superstoichiometric amounts of oxidant under the catalysis of metal salts, which led to synthetically useful products (Figure 4.3).[9] N-benzylated amino acids **4.25** were preformed and then oxidized by a peroxide to form an azomethine ylide **4.28**. A metal catalyst was proposed to bind to the azomethine ylide resulting in an intermediate **4.29** prior to the functionalization of nucleophiles (Figure 4.3).

Given our interest in developing redox–neutral processes and due to the growing appreciation for a redox economy, we were excited to come up with an idea of using *in*

situ generated azomethine ylides **4.28** in related reactions with what would constitute nontraditional dipolarophiles (Figure 4.4).

Figure 4.4 **Proposed Three-Component Coupling of the α-Amino Acid**

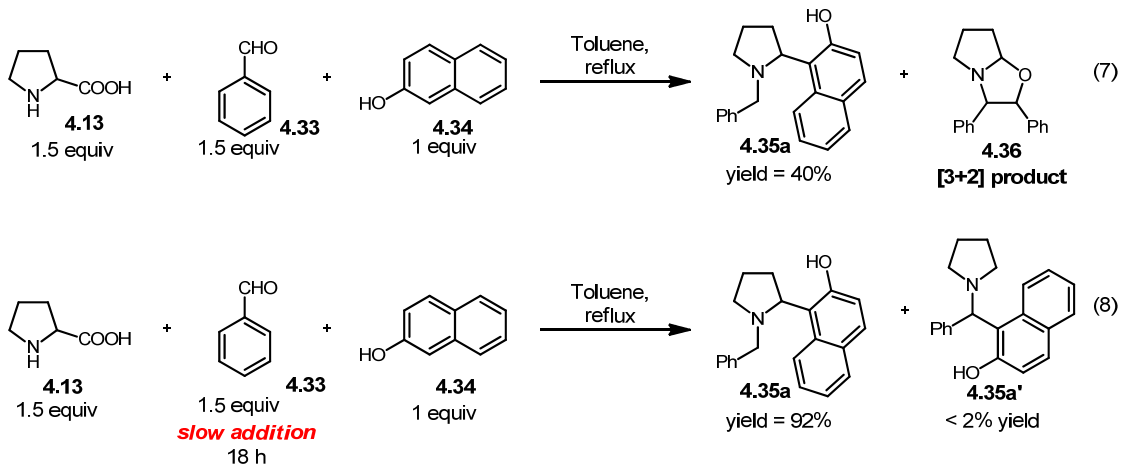


4.2.2 Non-Tranditional Functionalization of Azomethine Ylides with Naphthols and Indoles

First, the reaction between proline, benzaldehyde and 2-naphthol was investigated (Figure 4.5, eq 7). In this reaction, one would anticipate that 2-naphthol would react with the *in situ* generated azomethine ylide **4.28**. Pleasingly, the expected product **4.35a** was obtained in 40% yield upon simple heating of a mixture of the three components in toluene under reflux. Significant quantities of the known product **4.36**, derived from the [3+2] cycloaddition of the azomethine ylide and excess benzaldehyde, were detected by ^{1}H NMR analysis of the crude reaction mixture. In order to suppress the formation of the cycloaddition product **4.36**, benzaldehyde was delivered slowly into a mixture of proline and *β*-naphthol at reflux via syringe pump over 18 hours. Gratifyingly, no cycloaddition product was observed and the desired product **4.35a** was isolated in excellent yield (92%) (Figure 4.5, eq 8). ^{1}H NMR analysis of the crude reaction mixture indicated the presence of trace amounts of the regioisomeric product (< 2%). The distribution between **4.35a**

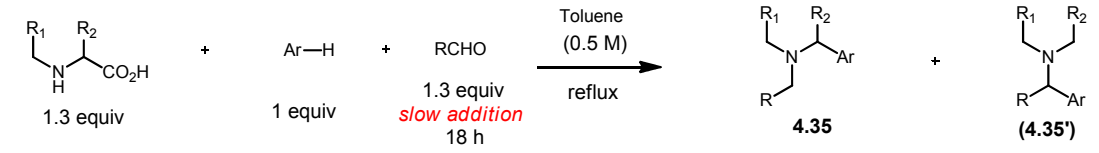
and **4.35a′** shows that the azomethine ylide prefers to abstract the proton from the benzylic position resulting in an iminium ion in the pyrrolidine ring in this case.

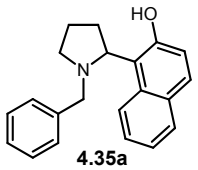
Figure 4.5 **Enhancement Due to Slow Addition**



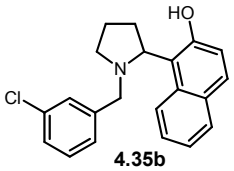
A number of *in situ* generated azomethine ylides were allowed to react with naphthols (Scheme 4.1). Aromatic aldehydes, bearing electron deficient substituents, readily underwent a three-component decarboxylative coupling reaction with proline and *β*-naphthol in good yields and excellent regioselectivity (Scheme 4.1, **4.35b-d)**. In contrast, significantly reduced regioselectivity was observed when an electron donating substituent was present in the aromatic aldehyde (Scheme 4.1, **4.35e** and **4.35f**). This is consistent with the fact that the electron distribution of the 1,3-dipoles can be changed by substituents of the azomethine ylides. Not only the aromatic aldehydes underwent this facile three-component coupling reaction, but also aliphatic aldehydes, which gave rise to the expected products in moderate yields (Scheme 4.1, **4.35g** and **4.35h**). Different naphthol derivatives were allowed to react with proline and benzaldehyde, which led to good yields and regioselectivity (Scheme 4.1, **4.35i-k**). So far, coupling reactions strongly preferred to occur on the pyrrolidine ring instead of the benzylic position.

Scheme 4.1 **Reactions of Azomethine Ylides with Naphthols**

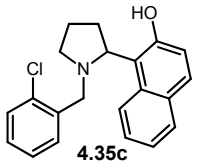




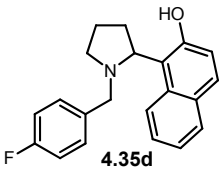
4.35a
91% (2%)



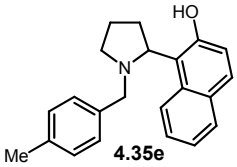
4.35b
85% (2%)



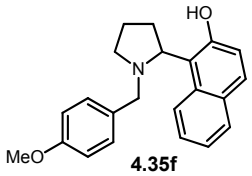
4.35c
74% (3%)



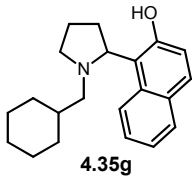
4.35d
79% (4%)



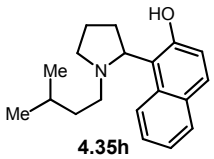
4.35e
66% (11%)



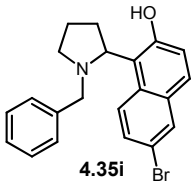
4.35f
63% (18%)



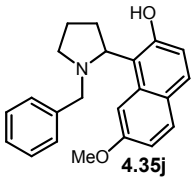
4.35g
61% (nd)



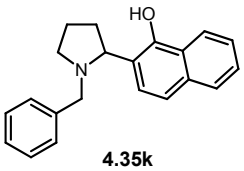
4.35h
41% (nd)



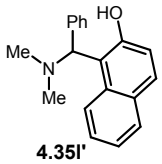
4.35i
82% (4%)



4.35j
87% (4%)

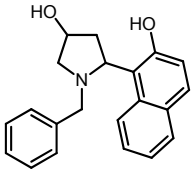


4.35k
52% (nd)

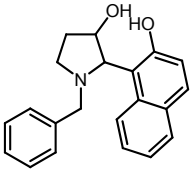


4.35l'
31%

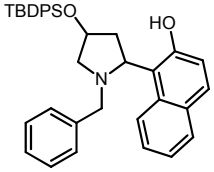
Products that were not obtained:



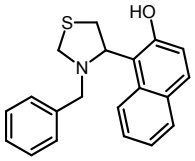
4.35m (or 4.35m')
NR



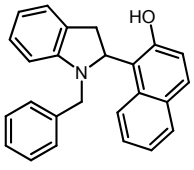
4.35n (or 4.35n')
NR



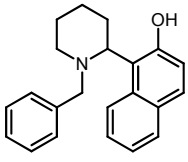
4.35o (or 4.35o')
NR



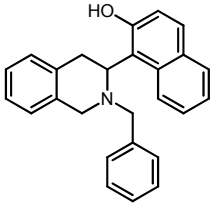
4.35p (or 4.35p')
NR



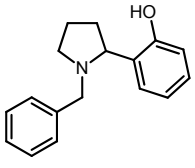
4.35q (or 4.35q')
NR



4.35r (or 4.35r')
NR



4.35s (or 4.35s')
NR

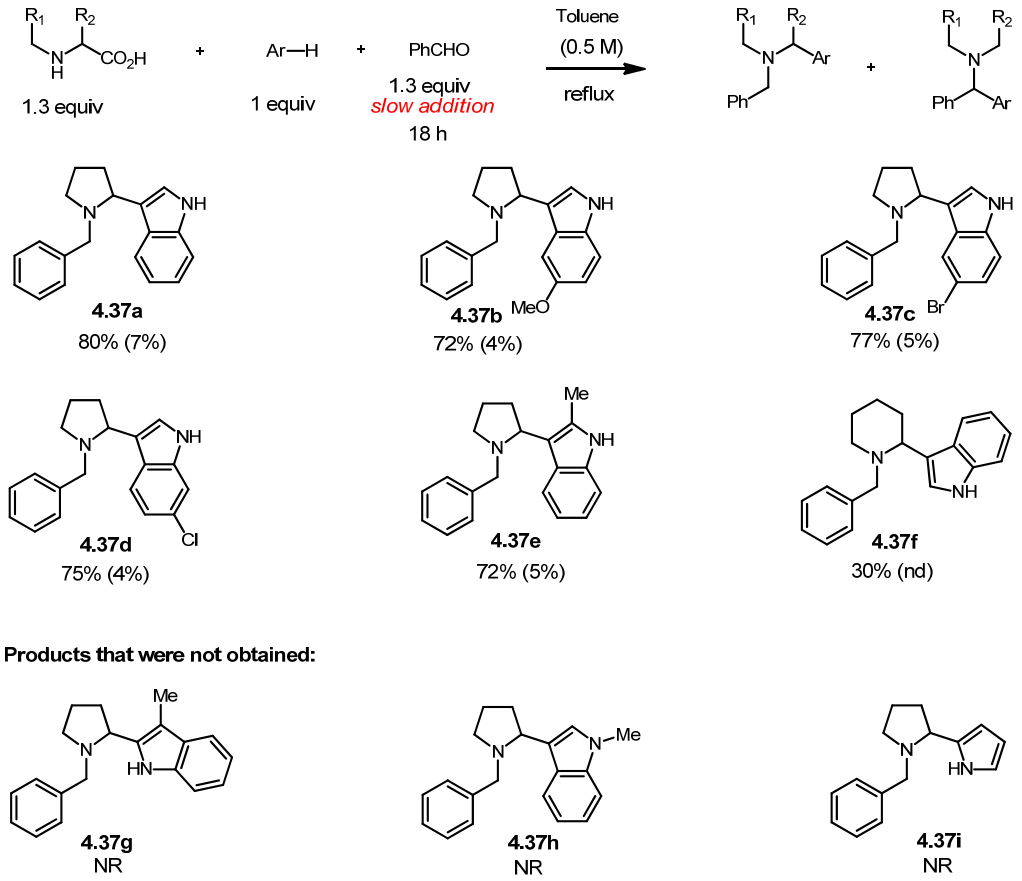


4.35t (or 4.35t')
NR

Notably, this trend reversed completely when sarcosine was investigated (Scheme 4.1, **4.35l′**). This again indicates the substituent effect for the protonation of azomethine ylides.

However, when other types of α-amino acids were investigated, no expected products were observed (Scheme 4.1, **4.35m-s**). The formation of N-benzylpyrrole was detected in cases of **4.35m-o**. The use of phenol as the dipolarophile led to a complicated reaction mixture, which is probably due to multiple nucleophilic sites of phenol.

Scheme 4.2 **Reactions of Azomethine Ylides with Indoles**



Indoles, another class of nucleophilic dipolarophiles, readily underwent the three-component decarboxylative coupling reaction, which is summarized in Scheme 4.2. A

variety of indoles exhibited good reactivity and selectivity (Scheme 4.2, **4.37a-e**). The azomethine ylide derived from pipecolic acid gave rise to 30% yield of the expected product **4.37f** upon the functionalization of indole.

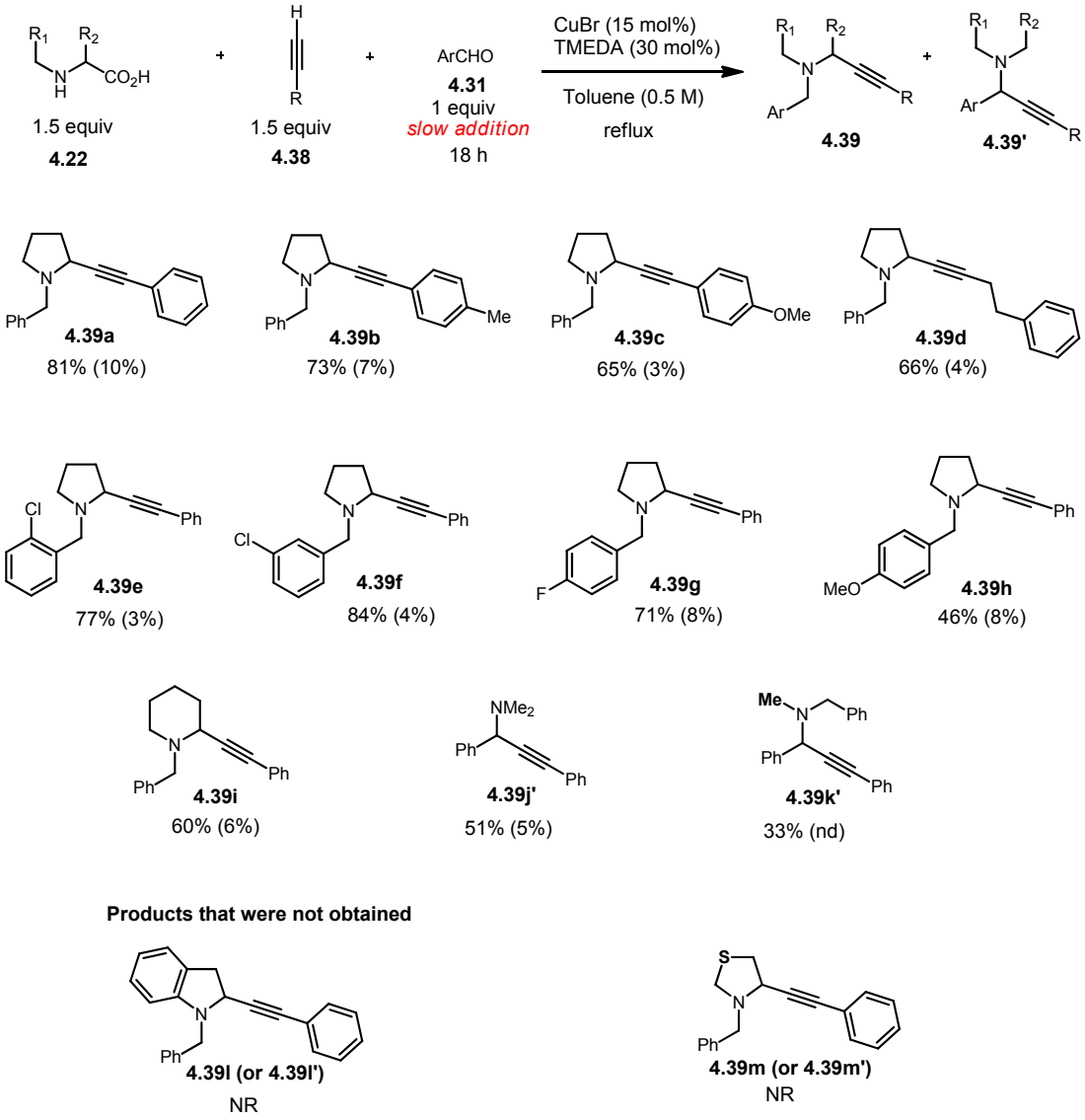
However, 3-methylindole failed to transform these azomethine ylides probably due to the relatively weaker nucleophilicity (Scheme 4.2, **4.37g**). As expected, no desired product was obtained when the azomethine ylide derived from benzaldehyde and proline was treated with N-methylindole, even though it is generally considered a stronger nucleophile than unsubstituted indole (Scheme 4.2, **4.37h**).[10] This result indicates that a relatively active proton is vital for the transformation to proceed and no bond formation will occur without the protonated azomethine ylide. When pyrrole was used as the dipolarophile, a complicated reaction mixture was obtained and no expected product **4.37i** was observed.

4.2.3 Non-Traditional Functionalization of Azomethine Ylides with Alkynes

Terminal alkynes readily engaged in this transformation as nucleophilic dipolarophiles. Catalytic amounts of copper (I) bromide and tetramethyl ethylenediamine (TMEDA) were required for the activation of alkynes. The resulting copper acetylides functioned as the active nucleophilic dipolarophiles in this case. Similar to indoles and naphthols, no oxidant or preformed N-alkyl amino acid derivatives are necessary. Phenylacetylene readily participated in the coupling reaction with the azomethine ylide to generate the desired product **4.39a** in 81% yield (Scheme 4.3, **4.39a**), concomitant with the corresponding constitutional isomer **4.39a′**. A variety of alkynes examined under the reaction conditions all led to decent yields and good regioselectivity (Scheme 4.3, **4.39a-**

d). Again, azomethine ylides generated from aldehydes with electron deficient substituents exhibited excellent regioselectivity (Scheme 4.3, **4.39e-g**), while the

Scheme 4.3 **Reactions of Azomethine Ylides with Alkynes**



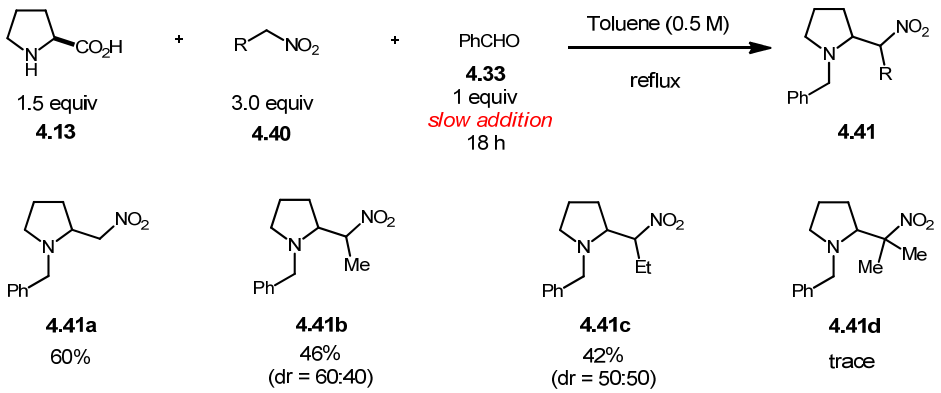
regioisomeric product was significantly increased in the case of *p*-anisaldehyde (Scheme 4.3, **4.39h**). In the case of pipecolic acid, 60% yield of the desired product was obtained with good regioselectivity. The constitutional isomer **4.39j′** was isolated as the major

product when sarcosine was used for the reaction, and exclusive formation of **4.39k′** was detected when N-benzylglycine was used for the reaction. When other types of α-amino acids were investigated, no expected products were observed (Scheme 4.1, **4.39l** and **4.39m**). Concurrently, Li's group reported a similar three-component coupling reaction of alkynes.[11]

4.2.4 Non-Traditional Functionalization of Azomethine Ylides with Nitroalkanes

Nitroalkanes were also evaluated in this process with azomethine ylides, as summarized in Scheme 4.4. Nitromethane gave rise to a 60% yield of the expected product **4.41a** and no regioisomeric product **4.41a′** was detected. Nitroethane and 1-nitropropane led to desired products (**4.41b** and **4.41c**) as a mixture of diastereomers in lower yields. The reduced yield might be due to the increased steric hindrance, since only trace amounts of the decarboxylative coupling product **4.41d** was obtained in the case of 2-nitropropane.

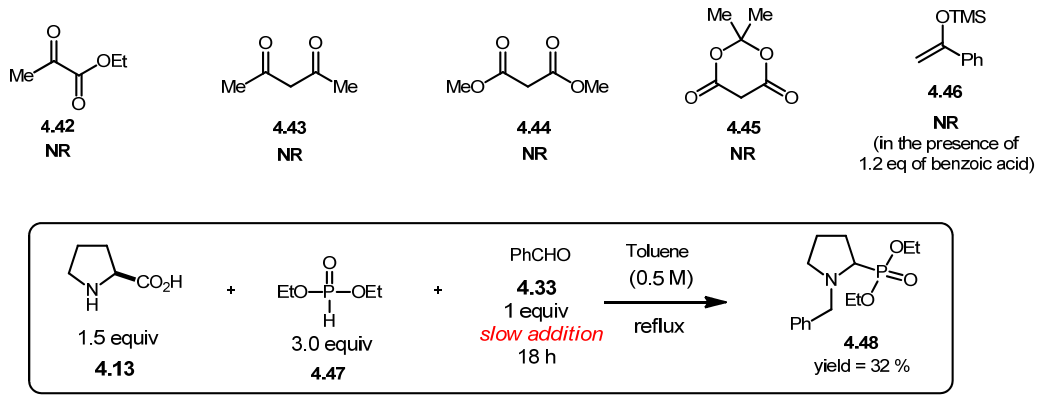
Scheme 4.4 **Reactions of Azomethine Ylides with Nitroalkanes**



4.2.5 Non-Traditional Functionalization of Azomethine Ylides with Other Types of Nucleophiles

A variety of nucleophiles were investigated in this coupling reaction with the azomethine ylide derived from proline and benzaldehyde under thermal conditions (Scheme 4.5). Unfortunately, no expected product was observed in all cases with the exception of diethyl phosphite **4.47**, which provided the desired product **4.48** in 32% yield.

Scheme 4.5 **Reactions of Azomethine Ylides with Other Types of Nucleophiles**

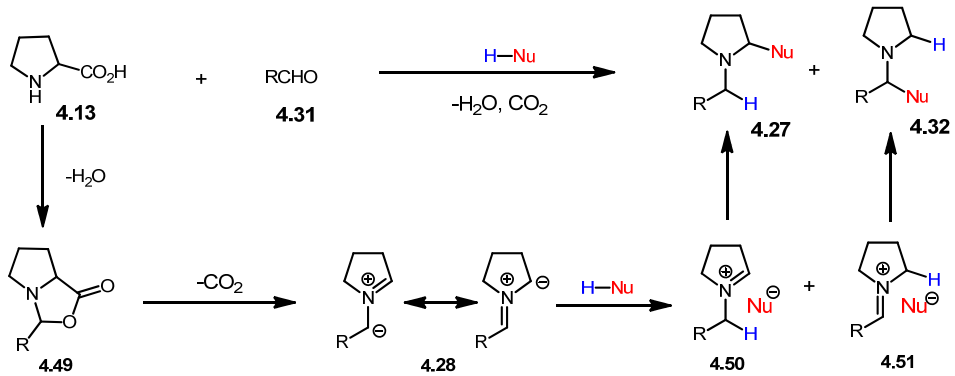


4.2.6 Mechanistic Insights

A proposed mechanism for the three-component decarboxylative coupling reaction is outlined in Figure 4.6. First, oxazolidin-5-one **4.49** is formed upon the condensation between proline and an aldehyde. Oxazolidin-5-one **4.49** will then readily undergo a decarboxylative reaction to render the azomethine ylide **4.28** under thermal conditions. The resulting azomethine ylide **4.28** is not expected to participate in the nucleophilic addition directly. Instead, the protonation of the dipolar intermediate **4.28** by the relatively acidic proton in the pronucleophile (H–Nu) occurs to generate the ion

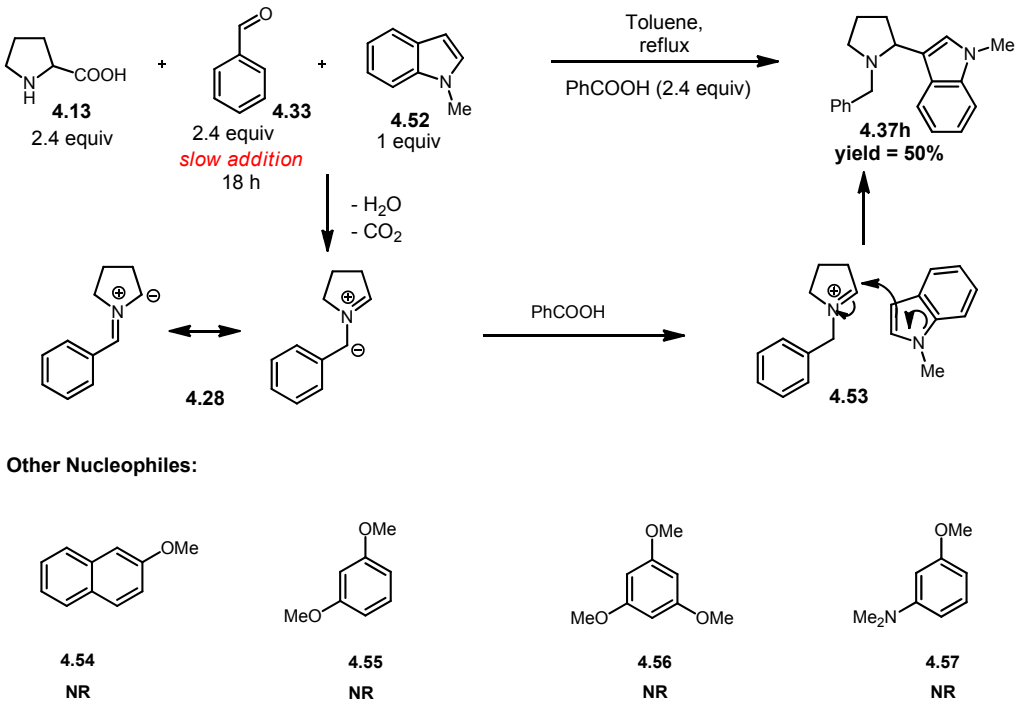
pairs **4.50** and **4.51**. This leads to the nucleophilic addition rendering the coupling products **4.50** and **4.51**. A concerted mechanism between the azomethine ylide and the nucleophile, which would lead to the formation of the final product directly, cannot be ruled out. The formation of two isomers can be readily explained by this proposed mechanism, since the charge distribution in the azomethine ylide intermediate **4.28** is one of the most important factors in determining the regioselectivity of this reaction. The more electron deficient character of the substituent yields a higher partial negative charge located at the benzylic position. Subsequently, the benzylic position with the electron withdrawing group is more likely to abstract a proton, which results in an intermediate **4.50** with an iminium ion in the pyrrolidine ring. This ultimately leads to the formation of pyrrolidines **4.27** with substituents on the ring. In contrast, electron rich character appears to reduce the tendency for the protonation at the benzylic position. The high regioselectivity for products bearing *m*-chloro-phenyl or *o*-chloro-phenyl and reduced regioselectivity for products bearing *p*-MeO-phenyl or *p*-Me-phenyl in all cases can now be well explained by this electronic effect of the azomethine ylide.

Figure 4.6 **Proposed Mechanism**



As we discussed previously, N-methylindole does not participate in this intermolecular transformation, since there is no suitable proton source in the system.

Figure 4.7 **Benzoic Acid as the Acid Promoter**



However, if the protonation of the azomethine ylide is required prior to nucleophilic addition, the scope of nucleophiles for this reaction could be extended greatly by addition of an external proton source. This might help to convert the azomethine ylide intermediate **4.28** to the corresponding iminium ion **4.53**. A variety of acids were evaluated in order to facilitate the formation of **4.37h**. Notably, benzoic acid turned out to be a suitable external proton source, which gave rise to the formation **4.37h** in 50% isolated yield (Figure 4.7). Reactions that were conducted in the presence of other stronger acids like *p*-TSA or trifluoroacetic acid led to the formation of the bis-indole byproduct. When the coupling reactions were investigated in the presence of benzoic

acid with other nucleophiles which did not contain a relatively acidic proton, no expected products were observed (Figure 4.7, **4.54-4.57**).

4.2.7 Summary

In summary, an intermolecular nucleophilic functionalization for azomethine ylides has been successfully demonstrated by our research team. Azomethine ylides can be protonated with suitable external proton sources to form the corresponding iminium ions. The iminium ion intermediate will readily react in Friedel-Crafts type alkylations, Mannich reactions, and alkynylations with different nucleophiles. Widespread application of this type of transformation is anticipated since it provides rapid generation of molecular complexity from readily available proline.

4.3 Azomethine Ylides Annulations

4.3.1 Decarboxylative Annulations of Azomethine Ylides

We have successfully introduced a nontraditional intermolecular functionalization of azomethine ylides by nucleophiles in a protic environment. Another challenge is the intramolecular version of this type of functionalization involving C–C bond formation (Figure 4.8). This type of intramolecular functionalization of azomethine ylides could be of great synthetic utility, since some natural products such as harmicine,[12] crispine A, [13] and epiquinamide[14] could possibly be directly synthesized through this pathway (Figure 4.9). In order to investigate this idea, we synthesized the indole-aldehyde substrate **4.61**, which could produce the azomethine ylide **4.62** upon treatment with amino acids. The desired product **4.63** would be formed by the functionalization of the indole moiety (Figure 4.8).

Figure 4.8 **A New Type of Annulation Involving the Non-Conventional Functionalization of Azomethine Ylides**

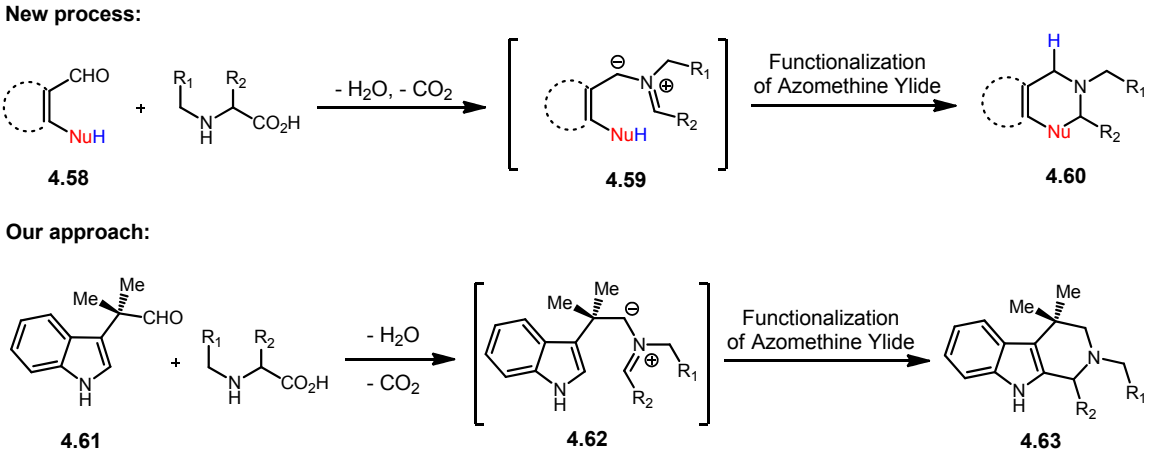
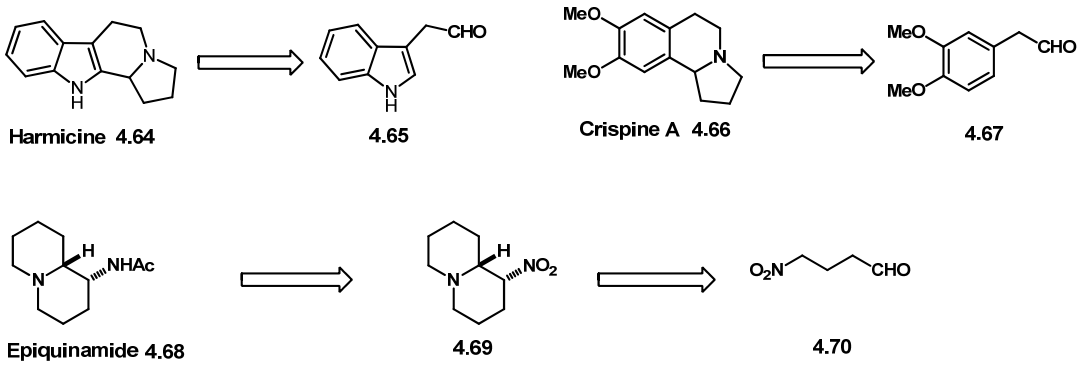


Figure 4.9 **Proposed Natural Products Syntheses**



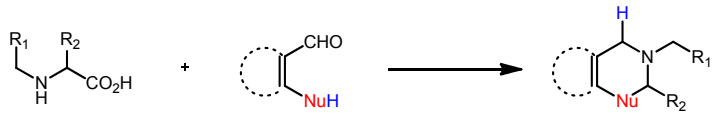
Gratifyingly, the desired annulation product **4.71** was obtained in 75% yield, when proline and indole-aldehyde **4.61** were reacted together directly in toluene under reflux. A slightly improved yield (80%) was achieved when indole-aldehyde **4.61** was added slowly into the reaction mixture over 18 hours under reflux (Table 4.1, entry 1). Since the azomethine ylide derived from indole-aldehyde **4.61** is not conjugated with the indole moiety, this type of transformation significantly enhances the synthetic utility of azomethine ylides. In addition, other amino acids readily react with indole-aldehyde **4.61**

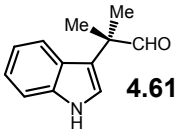
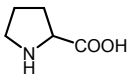
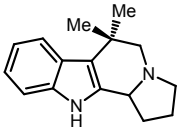
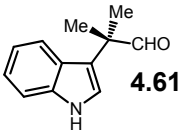
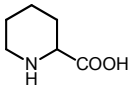
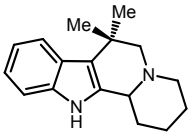
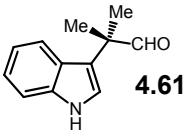
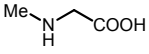
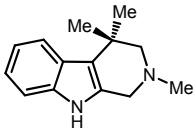
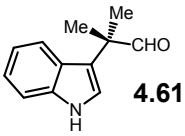
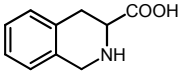
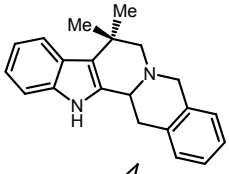
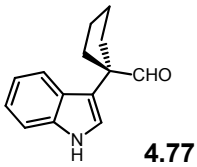
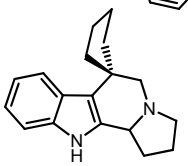
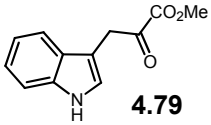
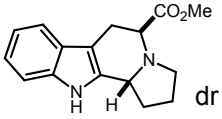
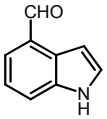
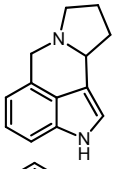
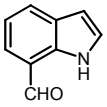
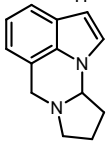
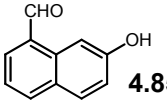
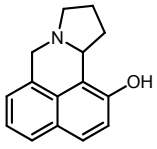
through this type of annulation. Pipecolic acid provided an excellent yield (90%), although it exhibited lower reactivity, requiring an additional 24 hours to completely consume indole-aldehyde **4.61** (Table 4.1, entry 2). Sarcosine, an acyclic secondary amino acid, did not undergo the transformation with indole-aldehyde **4.61** in toluene under reflux. When higher temperatures were applied by refluxing in xylenes, the decarboxylative annulations occurred. In this case, 12 equivalents of amino acid were required to ensure the completion of the reaction between scarcosine and indole-aldehyde **4.61** (Table 4.1, entry 3). This could be explained by the decomposition of sarcosine, which led to dimethyl amine and carbon dioxide upon the treatment of indole-aldehyde **4.61**. In the case of amino acid **4.75**, no annulation reaction was detected with indole-aldehyde **4.61** refluxing in toluene or xylenes. Microwave irradiation was applied to assist this transformation, which gave rise to 52% yield of the expected product **4.76**, as well as the formation of the corresponding regioisomeric product **4.92** in 25% yield (Table 4.1, entry 4). The presence of both of the regioisomeric products suggested that the isomerization of either the azomethine ylide or the iminium ion intermediate occurred prior to the ring closure. Indole-aldehyde **4.77** bearing a spiro-5-membered ring showed good reactivity in the reaction with proline, which produced the expected product **4.78** in 79% yield in toluene (Table 4.1, entry 5). Notably, the α-ketoester **4.79**, an enolizable substrate, readily reacted with proline to yield the expected product **4.80** as a mixture of diastereomers (Table 4.1, entry 6).

At this point, we have successfully demonstrated that non-conjugated indole-aldehydes are suitable substrates for this unprecedented type of process. Subsequently, we evaluated conjugated aldehydes in this process. 4-Formylindole **4.81** was added

slowly to a reaction mixture of proline in *n*-butanol under reflux, which gave rise to 63% yield of the expected product **4.82** after 18 hours (Table 4.1, entry 7). Another analogue, 7-formylindole **4.83**, also readily underwent this transformation resulting in an aminal product **4.84** after 30 minutes under microwave irradiation (Table 4.1, entry 8). Furthermore, 2-naphthol could also readily participate in this reaction as a nucleophilic moiety. 8-Formyl-2-naphthol **4.85** showed great reactivity when treated with proline, which produced 91% yield of the desired product **4.86** after 30 minutes under thermal conditions in toluene (Table 4.1, entry 9). These three examples indicate that conjugated π-systems can readily undergo this type of decarboxylative annulation. Moreover, these examples are distinctly different from conventional electrocyclization reactions, because the azomethine ylide intermediates cannot attain a fully conjugated pericyclic reaction pathway. Therefore, the mechanism of these examples with conjugated π-systems is likely to be similar to non-conjugated π-systems.

Table 4.1 **Scope of the Decarboxylative Annulations**[a]



entry	aldehyde	amino acid (equiv)	product		time[b] [h]	yield (%)
1	 **4.61**	 **4.13** (1.5)		**4.71**	18+2	80
2	 **4.61**	 **4.62** (1.5)		**4.73**	18+24	90
3	 **4.61**	 **4.2** (12)		**4.74**	20	61
4[c]	 **4.61**	 **4.75** (2)		**4.76**	20 min	52
5	 **4.77**	**4.13** (1.5)		**4.78**	18+2	79
6	 **4.79**	**4.13** (2)		**4.80** dr = 75:25	1.75	52
7	 **4.81**	**4.13** (3)		**4.82**	18+2	63
8[d]	 **4.83**	**4.13** (2)		**4.84**	30 min	61
9	 **4.85**	**4.13** (1.5)		**4.86**	30 min	91

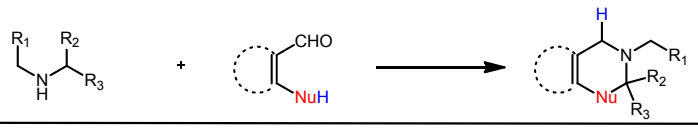
[a] Reactions were performed under reflux in PhMe (entries 2,5,9), in xylenes (entries 3,4,6,8) or in *n*-BuOH (entry 7). [b] Slow addition time + additional reaction time (entries 2,5,7) or reaction time (other entries). [c] under microwave irradiation at 250 °C. [d] under microwave irradiation at 200 °C.

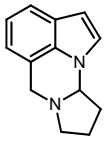
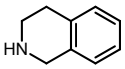
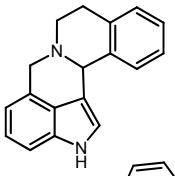
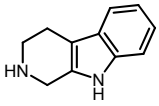
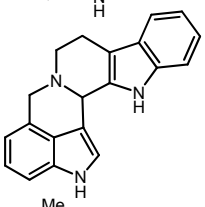
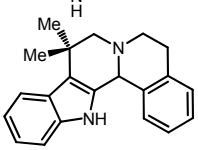
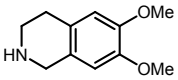
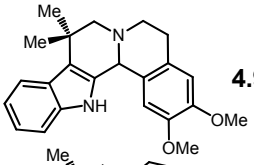
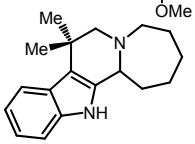
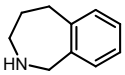
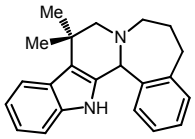
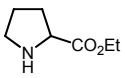
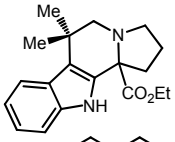
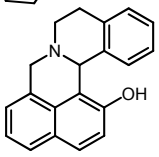
4.3.2 Non-Decarboxylative Annulations of Azomethine Ylides

Apart from the decarboxylative iminium ion pathway, azomethine ylides can be obtained through the deprotonation of an iminium ion intermediate.[15] This suggests that non-conventional functionalizations of azomethine ylides can be achieved using simple secondary amines or amino acid esters.

Hence, we first investigated the reaction of pyrrolidine with 7-formylindole **4.83**. Notably, it provided the expected cyclic aminal product **4.84** in 81% yield in *n*-butanol (Table 4.2, entry 1). More reactive secondary amines such as tetrahydroisoquinoline **4.98** and *β*-carboline **4.90** readily participated in the reaction with 4-formylindole **4.81**, resulting in clean reactions and moderate yields of the desired products (Table 4.2, entries 2 and 3). In addition to the conjugated π-systems, the non-conjugated indole-aldehyde **4.61** was also explored, which exhibited poor reactivity with amines under thermal conditions, even with more reactive amines like tetrahydroisoquinoline. Pleasingly, microwave irradiation successfully enhanced the reaction between indole-aldehyde **4.61** and tetrahydroisoquinoline (Table 4.2, entry 4). Other tetrahydroisoquinoline analogues readily gave rise to the corresponding polycyclic systems under microwave irradiation (Table 4.2, entries 5 and 7). Indole-aldehyde **4.61** could also participate in the reaction with azepane **4.95**, an aliphatic cyclic amine, giving 43% yield of the expected product **4.96** (Table 4.2, entry 6). The azomethine ylide derived from an amino ester **4.99** and the indole-aldehyde **4.61** underwent the facile annulation to provide the expected product **4.100** bearing a quaternary carbon center exclusively after 20 minutes under microwave irradiation (Table 4.2, entry 8). Furthermore, naphthol-aldehyde **4.85** showed excellent

Table 4.2 **Scope of the Non-Decarboxylative Annulations**[a]



entry	aldehyde	amine (equiv)	product		time[b] [h]	yield (%)
1	**4.83**	 **4.87** (3)		**4.84**	18+1	81
2	**4.81**	 **4.88** (3)		**4.89**	18+2	78
3	**4.81**	 **4.90** (2)		**4.91**	18+2	54
4[c]	**4.61**	**4.88** (3)		**4.92**	20 min	64
5[d]	**4.61**	 **4.93** (3)		**4.94**	20 min	61
6[c]	**4.61**	 **4.95** (10)		**4.96**	5	43
7[c]	**4.61**	 **4.97** (5)		**4.98**	1	54
8[c]	**4.61**	 **4.99** (3)		**4.100**	20 min	73
9	**4.85**	**4.88** (3)		**4.101**	30 min	81

[a] Reactions were performed under reflux in *n*-BuOH (entries 1,2,3,6), in xylenes (entries 4,5,7,8) or PhMe (entry 9). [b] Slow addition time + additional reaction time (entries 1-3) or reaction time (remaining entries). [c] under microwave irradiation at 250 °C. [d] under microwave irradiation at 200 °C.

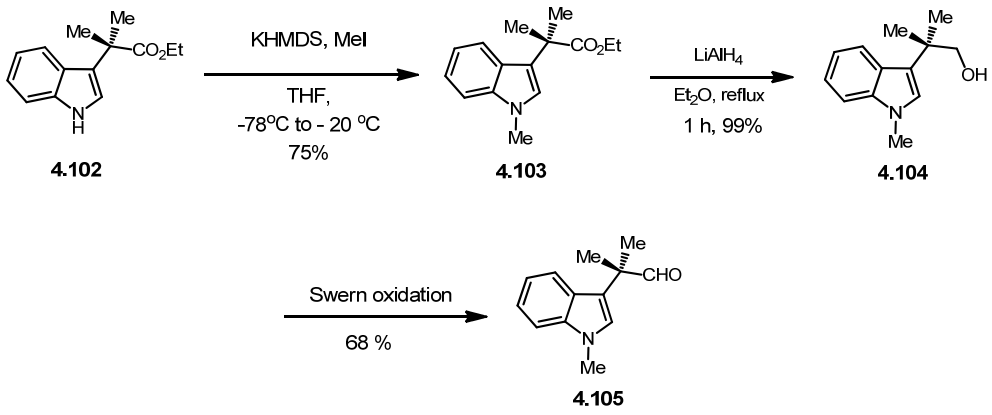
reactivity when treated with tetrahydroisoquinoline, which gave the corresponding product **4.101** in 81% yield after 30 minutes in toluene under reflux (Table 4.2, entry 9).

Although amines and an amino ester proved to be suitable partners for this non-conventional functionalization of azomethine ylides, the substrate scope was still more limited than that of amino acids. For instance, aliphatic amines demonstrated poor reactivity. This might be due to the difficulty of the formation of azomethine ylide by the deprotonation of the iminium ion. No reaction occurred when homoproline ethyl ester was applied in the reaction with indole-aldehyde **4.61** under microwave irradiation.

4.3.3 Mechanistic Insight

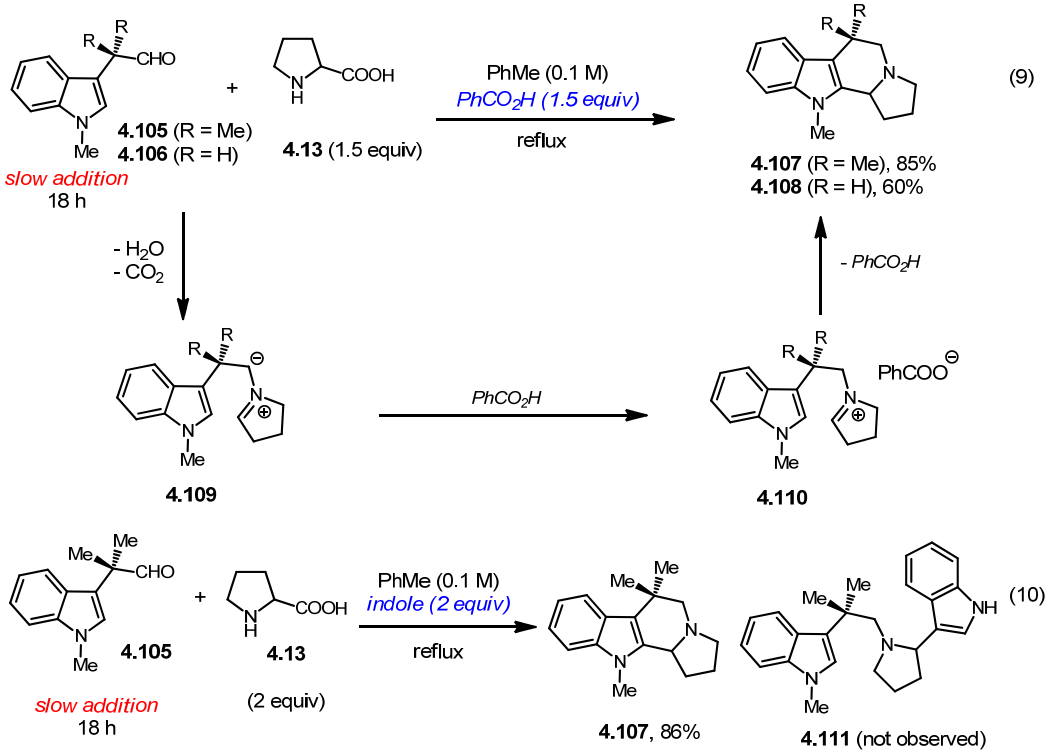
In order to establish the necessity of the acidic proton in the nucleophile partner, the indole moieties were methylated in both non-enolizable substrate **4.105** and enolizable substrate **4.106**. The synthesis of the previously unknown compound **4.105** is shown in Figure 4.11.

Figure 4.10 **Synthesis of 4.105**



As expected, no reaction was detected between proline and either **4.105** or **4.106**. However, these reactions proceeded smoothly to produce product **4.107** in the presence of 1.5 equivalents of benzoic acid, which is believed to protonate the azomethine ylide to form the corresponding iminium ion **4.110** (Figure 4.5, eq 1). Similarly, when **4.106** was added slowly into a solution of proline in toluene under reflux conditions, the expected product **4.108** was isolated in 60% yield in the presence of benzoic acid. These findings demonstrate that the direct nucleophilic addition is not feasible on the azomethine ylide and that the acidic proton is vital for the reaction to proceed. This pathway transforms an azomethine ylide to the corresponding iminium ion for a nucleophilic attack.

Figure 4.11 **Mechanistic Insights**



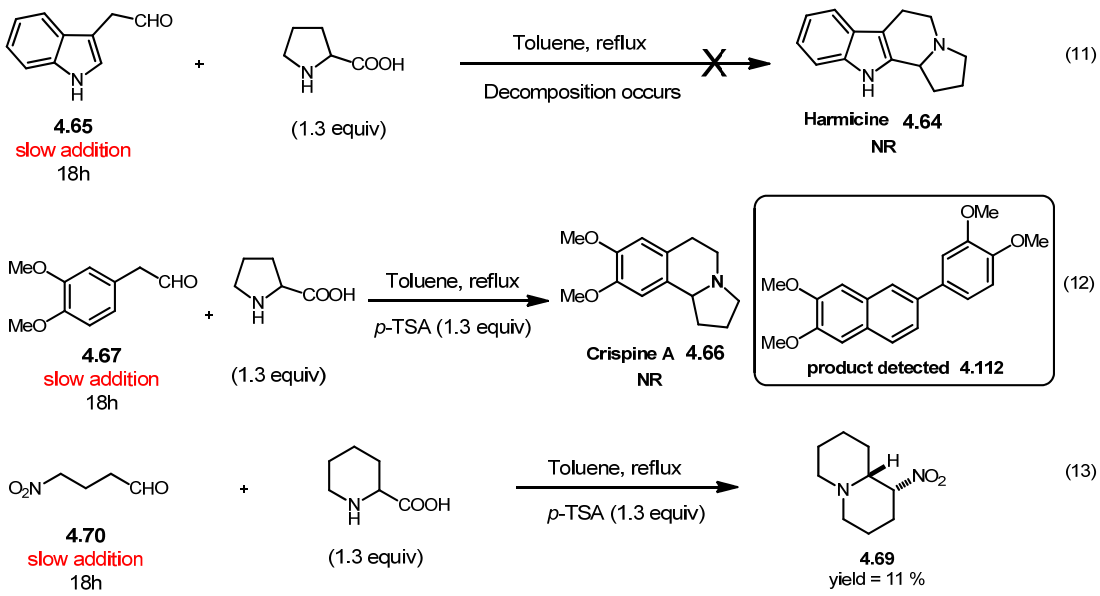
We next attempted to investigate the competition reaction between inter- and intramolecular pathways. Proline was allowed to react with **4.105** in the presence of

excess amounts of indole under reflux. Presumably, indole acted as the external proton source enabling the formation of the iminium ion with the depronated indole as the counteranion. The resulting ion pair might go through two pathways, via either an intra- or intermolecular pathway, to produce **4.107** or **4.111**. Interestingly, only **4.107** was obtained in 86% yield and no product from the intermolecular pathway was detected (Figure 4.11, eq 10).

4.3.4 Attempted Natural Product Syntheses

Preliminary attempts were made to synthesize natural products such as harmicine, crispine A, and epiquinamide following the proposed synthetic routes (Figure 4.12). Due to the instability of the precursor **4.65**, the reaction did not proceed as expected and failed to produce harmicine (Figure 4.12, eq 11). Since no reaction was observed for the

Figure 4.12 **Attempted Natural Product Syntheses**



reaction of **4.67** with proline in the presence of benzoic acid, the stronger acid *p*-TSA was evaluated. However, this led to a known dimerization product derived from **4.67** (Figure 4.12, eq 12).[16] Although difficulties were met in the preparation of harmicine and crispine A, the desired product **4.69** was successfully isolated in the reaction of 4-nitrobutanal with homoproline (Figure 4.12, eq 13). Efforts are still required to improve the yield of this reaction. Because **4.69** has been reported as a precursor in the preparation of epiquinamide,[17] this route could possibly provide synthetically useful access to epiquinamide and its analogues.

4.3.5 Summary

A new type of 1,6-annulation of the azomethine ylide has been developed by our group. The rapid generation of a variety of polycyclic ring systems, especially the analogues of harmicine, demonstrates the great utility of this type of azomethine ylide transformation. Other kinds of nucleophiles are anticipated to functionalize azomethine ylides similarly, which could lead to the widespread use of this method in the synthesis of alkaloids and related biologically active compounds.

4.4 Conclusion

We successfully demonstrated both intra- and intermolecular non-conventional functionalizations of azomethine ylides. It is believed that the azomethine ylide can be readily protonated to form the corresponding iminium ion, which is not readily available by other means and is of great synthetic utility. It is anticipated that our research will set the stage for the functionalization of 1,3-dipoles.

Experimental Sections

General Information: Reagents and solvents were purchased from commercial sources and were used as received. Toluene was freshly distilled from sodium under nitrogen prior to use. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light and permanganate stain, followed by heating. A CEM Discover-S microwave was used for reactions conducted under microwave irradiation. If so mentioned, a silicon carbide passive heating element (diameter: 10 mm, length: 18 mm) was used for efficient microwave absorption. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz and VNMRS-400 instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2SO$ at 2.50 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex; br = broad; integration; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm, $(CD_3)_2SO$ at 39.5 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer or on a Finnigan 2001 Fourier Transform Ion Cyclotron Resonance Mass Spectrometer.

General Procedure A:

Amino aicds (1.2 mmol) and nucleophile (1.0 mmol) were mixed in 2 mL of toluene in a round bottom flask equipped with a condensor. The flask was put into a pre-heated oil bath (130 ^{o}C). The aldehyde (1.2 mmol, 4.8M aldehyde solution in toluene) was delivered over 18 hours via syringe pump. After 18 hours, the reaction mixture was cooled to room temperature. Solvent was removed under reduced pressure. The residue was purified by flash column chromatography.

General Procedure B:

Amino aicds (1.3 mmol) and nucleophile (3.0 mmol) were mixed in 2 mL of toluene in a round bottom flask equipped with a condensor. The flask was put into a pre-heated oil bath (130 ^{o}C). The aldehyde (1.0 mmol, 4.0M aldehyde solution in toluene) was delivered over 18 hours via syringe pump. After 18 hours, the reaction mixture was cooled to room temperature. Solvent was removed under reduced pressure. The residue was purified by flash column chromatography.

General Procedure C:

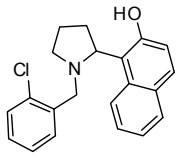
To a solution of *N*,*N*,*N*',*N*'-tetramethylethylenediamine **(**0.3mmol) in toluene was added CuBr (0.15 mmol, 15 mol%). The mixture was stirred for 10 min under nitrogen at room temperature. Amino aicds (1.5 mmol), nucleophile (1.5 mmol) were added. The flask was put into a pre-heated oil bath (130 ^{o}C). The aldehyde (1.0 mmol, 4.0M aldehyde solution in Toluene) was delivered over 18 hours via syringe pump. After 18 hours, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through a short pad of silica gel eluting with ethyl acetate. Solvent was removed under

reduced pressure. The residue was purified by flash column chromatography.

General Procedure D:

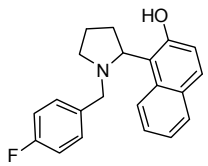
Amino aicds (2.4 mmol), benzoic acid (2.4 mmol) and nucleophile (1.0 mmol) were mixed in 10mL of toluene in a round bottom flask equipped with a condensor. The flask was put into a pre-heated oil bath (130 ^{o}C). The aldehyde (2.4 mmol, 4.8M aldehyde solution in Toluene) was delivered over 18 hours via syringe pump. After 18 hours, the reaction mixture was cooled to room temperature. The reaction mixture was basified with 20 mL 1M NaOH solution, extracted with CH_2Cl_2 (2 x 20 mL). Combine organic layers, washed with 30 mL brine and dried with sodium sulfate. Solvent was removed under reduced pressure. The residue was purified by flash column chromatography.

1-(1-(2-chlorobenzyl)pyrrolidin-2-yl)naphthalen-2-ol (4.35c): Title compound was



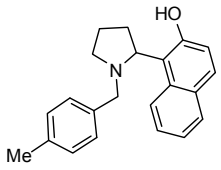
prepared according to the general procedure A as a yellow oil in 74% yield. (R_f = 0.37 in 10% EtOAc/Hex); IR (film) 3061, 2968, 2874, 1621, 1598, 1521, 1467, 1414, 1360, 1314, 1270, 1239, 1140, 1094, 1051, 1041, 950, 816, 746 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 12.97 (br s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.84 (app d, J = 8.1 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.52 (app ddd, J = 10.9, 9.1, 4.3 Hz, 2H), 7.43 – 7.33 (comp, 2H), 7.32 – 7.13 (comp, 3H), 4.61 (app t, J = 8.1 Hz, 1H), 4.06 (d, J = 13.6 Hz, 1H), 3.81 (d, J = 13.6 Hz, 1H), 3.40 – 3.27 (m, 1H), 2.66 – 2.32 (comp, 2H), 2.32 – 1.95 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 155.45, 134.59, 134.03, 132.72, 131.04, 129.39, 129.00, 128.79, 128.53, 128.40, 126.91, 126.28, 122.29, 120.82, 119.62, 114.72, 65.00, 54.47, 52.55, 31.45, 22.78; Chemical Formula: $C_{21}H_{20}ClNO$, *m/z* (ESIMS) 338.3 $[M + H]^+$.

1-(1-(4-fluorobenzyl)pyrrolidin-2-yl)naphthalen-2-ol (4.35d): Title compound was



prepared according to the general procedure A as a white solid in 79% yield. (R_f = 0.28 in 10% EtOAc/Hex); mp: 120-122 °C; IR (film) 3055, 2956, 2816, 1621, 1600, 1509, 1467, 1415, 1360, 1271, 1239, 1223, 1159, 1091, 951, 857, 818, 769, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 13.15 (br s, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.83 (app t, J = 7.3 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.41 – 7.28 (comp, 3H), 7.25 (app t, J = 6.5 Hz, 1H), 7.07 (app dd, J = 12.0, 5.3 Hz, 2H), 4.47 (app t, J = 8.2 Hz, 1H), 4.08 (d, J = 12.8 Hz, 1H), 3.27 – 3.13 (comp, 2H), 2.55 – 2.33 (comp, 2H), 2.09 – 1.90 (comp, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) 162.13 ($d_{C–F}$, J = 245.9 Hz), 155.39, 132.75, 132.73, 130.92 ($d_{C–F}$, J = 8.1 Hz), 129.02, 128.82, 128.40, 126.30, 122.31, 120.80, 119.67, 115.19 ($d_{C–F}$, J = 21.3 Hz), 114.57, 64.74, 57.54, 52.26, 31.48, 22.49; Chemical Formula: $C_{21}H_{20}FNO$, *m/z* (ESIMS) 322.3 $[M + H]^+$.

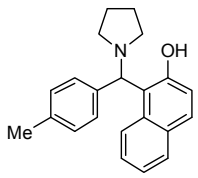
1-(1-(4-methylbenzyl)pyrrolidin-2-yl)naphthalen-2-ol (4.35e) The reaction was carried



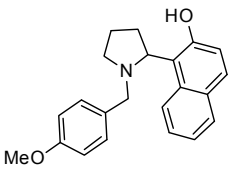
out according to the general procedure A. The product was obtained as a yellow oil in 66% yield and 10% of the regiochemical isomer. (R_f = 0.30 in 10% EtOAc/Hex); IR (film) 3048, 3019, 2954, 2923, 2872, 1621, 1599, 1519, 1467, 1415, 1359, 1271, 1240, 1094, 816, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 13.39 (br s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.87 (app d, J = 8.1 Hz, 1H), 7.80 (d, J = 8.7 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.40 (app dd, J = 7.9, 7.0 Hz, 1H), 7.32 – 7.28 (comp, 3H), 7.23 (d, J = 7.9 Hz, 2H), 4.52 (app, t, J = 8.2 Hz, 1H), 4.15 (d, J = 12.7 Hz, 1H), 3.33 – 3.18 (comp, 2H), 2.58 – 2.39 (comp, 5H), 2.10 – 1.92 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 155.56, 137.00, 133.83, 132.78, 129.28, 129.03, 128.91, 128.78,

128.36, 126.22, 122.21, 120.84, 119.74, 114.72, 64.66, 57.94, 52.19, 31.56, 22.52, 21.01; Chemical Formula: $C_{22}H_{23}NO$, *m/z* (ESIMS) 318.3 $[M + H]^+$

1-(pyrrolidin-1-yl(p-tolyl)methyl)naphthalen-2-ol (4.35e') (R_f = 0.20 in 10% EtOAc/Hex); IR (film) 3049, 3023, 2969, 2874, 1621, 1599, 1581, 1514, 1483, 1467, 1452, 1414, 1380, 1350, 1328, 1312, 1267, 1237, 1157, 1139, 1125, 1113, 952, 890, 843, 817, 742, 629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 13.91 (br s, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.72 – 7.68 (m, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.53 – 7.46 (comp, 2H), 7.37 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.22 (ddd, J = 8.0, 6.8, 1.0 Hz, 1H), 7.18 – 7.12 (m, 1H), 7.07 (app t, J = 7.2 Hz, 2H), 5.11 (s, 1H), 3.20 (br s, 1H), 2.66 (br s, 1H), 2.50 – 2.05 (comp, 5H), 1.99 – 1.71 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 155.70, 138.48, 137.47, 132.08, 129.35, 129.34, 128.85, 128.80, 128.47, 126.27, 122.26, 121.19, 119.96, 116.89, 70.65, 53.48 (br), 23.55, 20.95; Chemical Formula: $C_{22}H_{23}NO$, *m/z* (ESIMS) 318.1 $[M + H]^+$.

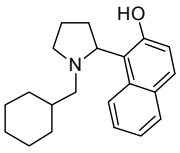


1-(1-(4-methoxybenzyl)pyrrolidin-2-yl)naphthalen-2-ol (4.35f) The reaction was carried out according to the general procedure A. The product was obtained as a yellow oil in 68% yield and 28% of the regiochemical isomer. (R_f = 0.15 in 10% EtOAc/Hex); IR (film) 3043, 2955, 2834, 1621, 1599, 1583, 1513, 1467, 1416, 1359, 1316, 1303, 1270, 1246, 1177, 1093, 1034, 950, 818, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 13.23 (br s, 1H), 7.90 (app t, J = 6.9 Hz, 1H), 7.83 (app t, J = 7.4 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.36 (app dt, J = 12.5, 6.3 Hz, 1H), 7.26 (app dt, J = 13.6, 8.9 Hz, 3H), 6.92 (d, J = 8.6 Hz, 2H), 4.48 (app t, J = 8.1 Hz, 1H), 4.09 (d, J = 12.7 Hz, 1H), 3.83 (s, 3H), 3.28 – 3.14 (comp, 2H), 2.56 – 2.37 (comp, 2H), 2.07 – 1.88 (comp, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$)



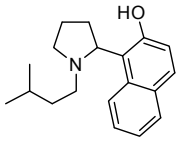
158.91, 155.54, 132.75, 130.55, 128.95, 128.91, 128.78, 128.36, 126.23, 122.22, 120.85, 119.73, 114.75, 113.70, 64.54, 57.53, 55.09, 52.12, 31.61, 22.53; Chemical Formula: $C_{22}H_{23}NO_2$, *m/z* (ESIMS) 334.2 $[M + H]^+$.

1-(1-(cyclohexylmethyl)pyrrolidin-2-yl)naphthalen-2-ol (4.35g) Title compound was



prepared according to the general procedure A as a colorless oil in 61% yield. (R_f = 0.33 in 10% EtOAc/Hex); IR (film) 3054, 2923, 2850, 2810, 2669, 1621, 1599, 1583, 1520, 1468, 1451, 1415, 1365, 1342, 1320, 1271, 1240, 1161, 1140, 1078, 947, 816, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 13.23 (br s, 1H), 7.87 (app t, J = 12.9 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.72 (app t, J = 10.0 Hz, 1H), 7.47 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.32 (app dd, J = 7.9, 7.0 Hz, 1H), 7.18 (app t, J = 14.3 Hz, 1H), 4.31 (app t, J = 8.6 Hz, 1H), 3.55 – 3.40 (m, 1H), 2.62 (app t, J = 11.3 Hz, 1H), 2.48 – 2.37 (m, 1H), 2.33 (dd, J = 18.4, 9.1 Hz, 1H), 2.17 – 1.90 (comp, 5H), 1.84 (app dd, J = 17.4, 14.0 Hz, 1H), 1.75 – 1.55 (comp, 4H), 1.36 – 1.11 (comp, 3H), 1.06 – 0.80 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 155.51, 132.75, 128.73, 128.69, 128.23, 126.11, 122.07, 120.78, 119.67, 114.99, 66.29, 61.88, 52.42, 36.53, 31.86, 31.49, 30.85, 26.40, 26.02, 25.78, 22.90; Chemical Formula: $C_{21}H_{27}NO$, *m/z* (ESIMS) 310.3 $[M + H]^+$.

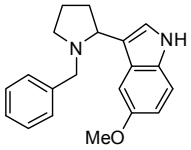
1-(1-isopentylpyrrolidin-2-yl)naphthalen-2-ol (**4.35h**) Title compound was prepared



according to the general procedure A as a colorless oil in 41% yield. (R_f = 0.25 in 10% EtOAc/Hex); IR (film) 3054, 2954, 2869, 1621, 1599, 1582, 1520, 1468, 1416, 1367, 1344, 1317, 1271, 1240, 1161, 1140, 1083, 956, 816, 745 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$) 13.70 (br s, 1H), 7.86 – 7.75 (comp, 2H), 7.73 – 7.66 (m, 1H), 7.50 – 7.41 (m, 1H), 7.31 (app dt, J = 14.4, 3.7 Hz, 1H), 7.17 – 7.08 (m, 1H), 4.37 (app t, J = 8.5 Hz, 1H), 3.55 – 3.46 (m, 1H), 2.93 – 2.82 (m, 1H), 2.50 – 2.35 (comp,

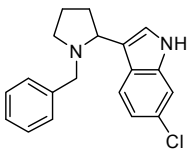
2H), 2.28 (ddd, J = 11.9, 10.1, 4.8 Hz, 1H), 2.13 – 1.87 (comp, 3H), 1.67 – 1.40 (comp, 3H), 0.87 (app dt, J = 18.2, 9.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 155.88, 132.69, 128.75, 128.70, 128.21, 126.12, 122.08, 120.86, 119.85, 115.02, 65.86, 53.24, 52.61, 37.26, 32.00, 26.38, 23.09, 22.94, 22.15; Chemical Formula: $C_{19}H_{25}NO$, *m/z* (ESIMS) 284.3 $[M + H]^+$

3-(1-benzylpyrrolidin-2-yl)-5-methoxy-1H-indole (4.37b) Title compound was



prepared according to the general procedure A as a yellow oil in 72% yield. (R_f = 0.14 in 30% EtOAc/Hex); IR (film) 3417, 3054, 3025, 2942, 2827, 2785, 1583, 1483, 1453, 1438, 1287, 1252, 1212, 1171, 1106, 1071, 1028, 925, 796, 735, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.20 (br s, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.37 (app dt, J = 14.8, 7.6 Hz, 4H), 7.30 (app t, J = 6.1 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 2.2 Hz, 1H), 6.98 (dd, J = 8.8, 2.4 Hz, 1H), 4.13 (d, J = 13.1 Hz, 1H), 3.99 (s, 3H), 3.76 (app t, J = 8.3 Hz, 1H), 3.23 (app dd, J = 12.4, 4.6 Hz, 1H), 3.17 (d, J = 13.1 Hz, 1H), 2.35 – 2.25 (comp, 2H), 2.21 – 1.83 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 153.47, 140.00, 131.95, 128.75, 127.94, 126.97, 126.47, 122.92, 117.32, 112.00, 111.80, 102.04, 62.27, 58.22, 55.92, 53.31, 32.77, 22.12; Chemical Formula: $C_{20}H_{22}N_2O$, *m/z* (ESIMS) 307.1 $[M + H]^+$.

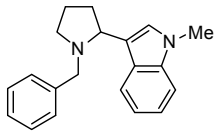
3-(1-benzylpyrrolidin-2-yl)-6-chloro-1H-indole (4.37d) Title compound was prepared



according to the general procedure A as a yellow oil in 75% yield. (R_f = 0.25 in 30% EtOAc/Hex); mp: 61-64 °C; IR (film) 3422, 3060, 3025, 2964, 2874, 2792, 1618, 1494, 1452, 1372, 1333, 1227, 1093, 1073, 1061, 905, 846, 804, 737, 700 cm^{-1} ^{1}H NMR (500 MHz, $CDCl_3$) 8.02 (br s, 1H), 7.84 (app t, J = 12.6 Hz, 1H), 7.36 (app t, J = 4.7 Hz, 1H), 7.30 – 7.16 (comp, 6H), 7.11 (app dt, J = 19.9, 10.0 Hz, 1H),

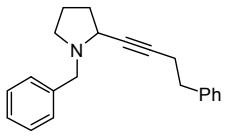
3.96 (d, J = 13.0 Hz, 1H), 3.65 (app t, J = 8.2 Hz, 1H), 3.12 (app dd, J = 12.2, 4.9 Hz, 1H), 3.04 (d, J = 13.0 Hz, 1H), 2.25 – 2.14 (comp, 2H), 2.08 – 1.88 (comp, 2H), 1.82 (app dtd, J = 12.4, 8.8, 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 139.85, 137.12, 128.72, 128.03, 127.79, 126.58, 125.10, 122.69, 121.09, 119.81, 118.15, 111.05, 62.18, 58.32, 53.39, 32.89, 22.19; Chemical Formula: $C_{19}H_{19}ClN_2$, *m/z* (ESIMS) 311.3 $[M + H]^+$.

3-(1-benzylpyrrolidin-2-yl)-1-methyl-1H-indole (4.37h) Title compound was prepared



according to the general procedure D as a yellow oil in 50% yield. (R_f = 0.34 in 30% EtOAc/Hex); IR (film) 3058, 3026, 2961, 2873, 2782, 1613, 1549, 1493, 1472, 1452, 1373, 1346, 1325, 1241, 1194, 1155, 1130, 1106, 1072, 738, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.96 (app dd, J = 7.9, 0.8 Hz, 1H), 7.39 – 7.22 (comp, 7H), 7.19 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 7.13 (s, 1H), 4.08 (d, J = 13.1 Hz, 1H), 3.80 (s, 3H), 3.72 (app t, J = 8.3 Hz, 1H), 3.21 – 3.14 (m, 1H), 3.10 (d, J = 13.1 Hz, 1H), 2.32 – 2.18 (comp, 2H), 2.15 – 1.93 (comp, 2H), 1.92 – 1.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 140.22, 137.48, 128.71, 127.94, 127.09, 126.69, 126.42, 121.46, 120.20, 118.57, 116.52, 109.16, 62.26, 58.40, 53.44, 33.26, 32.62, 22.19; Chemical Formula: $C_{20}H_{22}N_2$, *m/z* (ESIMS) 291.2 $[M + H]^+$.

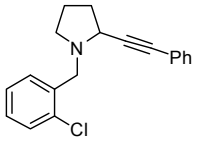
1-benzyl-2-(4-phenylbut-1-yn-1-yl)pyrrolidine **(4.39d)** Title compound was prepared



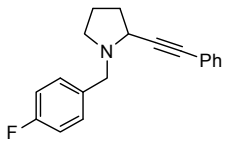
according to the general procedure C as a yellow oil in 65% yield. (R_f = 0.28 in 10% EtOAc/Hex); IR (film) 3084, 3061, 3026, 2948, 2875, 2804, 1940, 1876, 1800, 1603, 1494, 1453, 1372, 1354, 1321, 1217, 1182, 1144, 1108, 1074, 1028, 910, 745, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.62 – 7.02 (comp, 10H), 4.01 (d, J = 12.9 Hz, 1H), 3.50 (d, J = 12.9 Hz, 1H), 3.35 (app td, J = 5.4, 2.6 Hz, 1H), 2.92 (app t, J = 7.5 Hz, 2H), 2.80 – 2.68 (m, 1H), 2.62 (app td, J = 7.4, 1.9 Hz, 2H),

2.53 – 2.36 (m, 1H), 2.17 – 2.04 (m, 1H), 2.01 – 1.70 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 140.64, 138.70, 129.06, 128.38, 128.20, 127.99, 126.71, 126.10, 83.99, 79.88, 56.93, 54.04, 51.21, 35.25, 31.60, 21.76, 20.83; Chemical Formula: $C_{21}H_{23}N$, *m/z* (ESIMS) 290.3 $[M + H]^+$.

1-(2-chlorobenzyl)-2-(phenylethynyl)pyrrolidine (4.39e) Title compound was prepared according to the general procedure C as a yellow oil in 77% yield. (R_f = 0.29 in 10% EtOAc/Hex); IR (film) 3054, 2956, 2876, 2805, 1597, 1571, 1489, 1470, 1442, 1371, 1355, 1320, 1254, 1216, 1133, 1110, 1069, 1050, 1037, 754, 691 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.63 – 7.57 (m, 1H), 7.52 (app dt, J = 5.1, 3.7 Hz, 2H), 7.41 (app d, J = 7.9 Hz, 1H), 7.38 – 7.31 (comp, 3H), 7.28 (app dd, J = 10.8, 4.2 Hz, 1H), 7.21 (tt, J = 15.6, 7.8 Hz, 1H), 4.21 (d, J = 14.0 Hz, 1H), 3.90 (d, J = 14.0 Hz, 1H), 3.76 (dd, J = 7.3, 5.2 Hz, 1H), 2.93 (app td, J = 8.8, 5.2 Hz, 1H), 2.64 (app td, J = 8.8, 6.2 Hz, 1H), 2.25 (app ddt, J = 13.5, 10.2, 6.9 Hz, 1H), 2.11 (app ddt, J = 12.2, 10.0, 4.9 Hz, 1H), 2.05 – 1.93 (m, 1H), 1.93 – 1.77 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 136.60, 134.03, 131.61, 130.69, 129.28, 128.10, 127.93, 127.80, 126.46, 123.28, 88.77, 84.78, 54.78, 53.83, 51.66, 31.62, 22.14; Chemical Formula: $C_{19}H_{18}ClN$, *m/z* (ESIMS) 296.2 $[M + H]^+$.

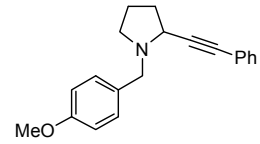


1-(4-fluorobenzyl)-2-(phenylethynyl)pyrrolidine (4.39g) Title compound was prepared according to the general procedure C as a yellow oil in 71% yield. (R_f = 0.24 in 10% EtOAc/Hex); IR (film) 3049, 2958, 2876, 2809, 1952, 1887, 1601, 1508, 1489, 1442, 1370, 1320, 1292, 1221, 1154, 1113, 1091, 1015, 826, 756, 691, 526 cm^{-1}; ^{1}H NMR of the major regioisomer (500 MHz, $CDCl_3$) 7.71 – 6.94 (comp, 9H), 4.06 (d, J = 12.9 Hz, 1H), 3.69 – 3.52 (comp, 2H), 2.82 (ddd, J = 14.1,

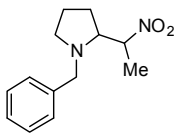


11.5, 5.2 Hz, 1H), 2.62 – 2.51 (m, 1H), 2.28 – 2.14 (m, 1H), 2.08 (app ddt, J = 12.3, 9.9, 4.8 Hz, 1H), 2.02 – 1.76 (comp, 2H); ^{13}C NMR of regioisomers (125 MHz, $CDCl_3$) 163.35, 163.10, 160.91, 160.67, 135.38, 135.35, 134.55, 134.51, 131.70, 131.63, 130.58, 130.50, 129.74, 129.66, 128.21, 128.17, 128.09, 127.89, 123.27, 123.01, 115.03, 114.98, 114.82, 114.77, 88.53, 87.09, 86.30, 84.98, 58.22, 56.33, 54.28, 51.41, 50.04, 31.58, 23.44, 21.98; Chemical Formula: $C_{19}H_{18}FN$, *m/z* (ESIMS) 280.4 $[M + H]^+$.

1-(4-methoxybenzyl)-2-(phenylethynyl)pyrrolidine (4.39h) Title compound was prepared according to the general procedure C as a yellow oil in 46% yield. (R_f = 0.12 in 10% EtOAc/Hex); IR (film) 2953, 2909, 2876, 2832, 2808, 2062, 1946, 1876, 1611, 1585, 1511, 1489, 1462, 1442, 1371, 1355, 1320, 1300, 1246, 1178, 1102, 1070, 1036, 821, 756, 691, 552, 520 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.52 – 7.44 (m, 2H), 7.39 – 7.27 (comp, 5H), 6.93 – 6.84 (m, 2H), 4.01 (app t, J = 10.5 Hz, 1H), 3.80 (s, 3H), 3.64 – 3.54 (comp, 2H), 2.78 (app tt, J = 18.7, 9.4 Hz, 1H), 2.55 (app td, J = 8.8, 6.0 Hz, 1H), 2.25 – 2.11 (m, 1H), 2.11 – 1.72 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 158.57, 131.64, 130.76, 130.28, 128.15, 127.83, 123.37, 113.49, 88.78, 84.86, 56.39, 55.14, 54.16, 51.35, 31.56, 21.94; Chemical Formula: $C_{20}H_{21}NO$, *m/z* (ESIMS) 292.3 $[M + H]^+$.

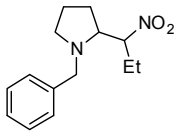


1-benzyl-2-(1-nitroethyl)pyrrolidine (4.41b) The reaction was carried out according to the general procedure B. The product was obtained as a mixture of diastereomers in 46% yield, dr = 57 : 43 determined by integration of one set of 1H-NMR signals (δmajor 4.55 – 4.40 ppm, δminor 4.76 – 4.62 ppm). (R_f = 0.25 in 10% EtOAc/Hex); IR (film) 3083, 3054, 3027, 2968, 2876, 2800, 1539, 1494, 1453, 1390, 1354, 1324, 1300, 1211, 1124, 1072, 1028, 868, 744, 701 cm^{-1}; ^{1}H NMR



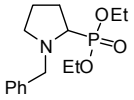
(500 MHz, $CDCl_3$) (major diastereomer) 7.49 – 7.17 (comp, 5H), 4.49 (app p, J = 6.6 Hz, 1H), 3.90 (d, J = 13.0 Hz, 1H), 3.53 (d, J = 13.0 Hz, 1H), 3.37 – 3.28 (m, 1H), 3.00 – 2.83 (m, 1H), 2.40 – 2.20 (m, 1H), 1.99 – 1.62 (comp, 4H), 1.54 – 1.48 (comp, 3H); ^{13}C NMR of the diastereomers (125 MHz, $CDCl_3$) 139.26, 139.14, 128.58, 128.56, 128.25, 128.22, 126.99, 126.99, 85.75, 84.79, 66.49, 66.31, 60.20, 59.84, 54.33, 54.32, 26.85, 26.72, 24.04, 23.14, 15.77, 14.10; Chemical Formula: $C_{13}H_{18}N_2O_2$, *m/z* (ESIMS) 235.2 $[M + H]^+$.

1-benzyl-2-(1-nitropropyl)pyrrolidine (4.39c) The reaction was carried out according



to the general procedure B. The product was obtained as a mixture of diastereomers in 42% yield, dr = 50 : 50 determined by integration of one set of 1H-NMR signals (δmajor 4.62 – 4.54 ppm, δminor 4.32 – 4.25 ppm). (R_f = 0.31 in 10% EtOAc/Hex); IR (film) 3089, 3060, 3027, 2971, 2878, 2799, 1541, 1494, 1454, 1375, 1354, 1332, 1297, 1255, 1210, 1120, 1074, 1028, 806, 745, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (major diastereomer) 7.52 – 7.06 (comp, 10H), 4.57 (ddd, J = 10.5, 5.8, 3.7 Hz, 1H), 4.28 (ddd, J = 11.1, 7.2, 2.8 Hz, 1H), 4.15 (d, J = 13.0 Hz, 1H), 3.90 (d, J = 13.0 Hz, 1H), 3.53 (app t, J = 10.6 Hz, 1H), 3.39 (app t, J = 11.8 Hz, 1H), 3.29 (ddd, J = 9.0, 7.2, 3.5 Hz, 1H), 3.03 – 2.85 (comp, 3H), 2.42 – 2.31 (m, 1H), 2.23 (app tt, J = 17.3, 8.6 Hz, 1H), 2.14 – 1.61 (comp, 12H), 0.99 (comp, 6H); ^{13}C NMR of the diastereomers (125 MHz, $CDCl_3$) 139.40, 139.03, 128.59, 128.56, 128.17, 126.94, 126.88, 94.05, 91.61, 66.10, 65.73, 60.66, 59.56, 54.14, 54.01, 27.66, 26.21, 24.12, 24.00, 22.97, 22.61, 10.71, 10.60; Chemical Formula: $C_{14}H_{20}N_2O_2$, *m/z* (ESIMS) 249.3 $[M + H]^+$.

1-benzyl-2-(1-nitropropyl)pyrrolidine (4.48) The reaction was carried out according to



the general procedure B. The product was obtained as a colorless oil in 32% yield. (R_f = 0.40 in 10% EtOAc/Hex); IR (film) 3465, 3092, 3056, 3011, 2978, 2795, 2716, 1688, 1495, 1453, 1390, 1374, 1293, 1230, 1163, 1054, 963, 746, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 77.64 – 6.97 (comp, 5H), 4.41 (d, J = 13.0 Hz, 1H), 4.34 – 3.99 (comp, 4H), 3.42 (d, J = 13.0 Hz, 1H), 3.07 – 2.83 (comp, 2H), 2.34 – 1.95 (comp, 3H), 1.89 – 1.62 (comp, 2H), 1.56 – 1.04 (comp, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 139.6, 129.1, 128.3, 127.0, 62.9 (d, J = 6.9 Hz), 62.0 (d, J = 7.3 Hz), 60.4 (d, J = 2.6 Hz), 59.7 (d, J = 174.1 Hz), 54.5 (d, J = 15.1 Hz), 27.2 (d, J = 2.1 Hz), 24.6 (d, J = 5.9 Hz), 16.89 (d, J = 5.6 Hz), 16.81 (d, J = 5.6 Hz); Chemical Formula: $C_{15}H_{24}NO_3P$, *m/z* (ESIMS) 298.0 [M + H]$^+$.

Ethyl 2-methyl-2-(1-methyl-1H-indol-3-yl)propanoate (4.103): THF (28.8 mL) was added to a flame-dried 200-mL round-bottom flask equipped with a septum and a nitrogen inlet. The flask was cooled to –78 ºC, followed by addition of KHMDS (6.5 mL, 0.5 M in toluene, 2.4 mmol). A solution of ethyl 2-(1H-indol-3-yl)-2-methylpropanoate (0.5g, 2.16 mmol) in 5 mL THF was added via syringe. The resulting mixture was then warmed to 0 °C and stirred for 2 hours before re-cooling to –78 ºC. Methyl iodide (0.41 mL, 6.5 mmol) was then added. The mixture was allowed to warm to 0 °C and stirred for 3 hours. The reaction mixture was then placed in a freezer (–20 ºC) for 24 hours. The reaction was quenched by addition of water (10 mL) and then extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried with sodium sulfate. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a white solid in 75% yield. (R_f = 0.33 in 10%

EtOAc/hexanes); mp: 74–75 °C; IR (KBr) 3415, 3121, 3059, 2989, 2975, 2933, 2873, 1718, 1485, 1476, 1458, 1444, 1426, 1394, 1382, 1373, 1361, 1339, 1330, 1300, 1261, 1231, 1178, 1154, 1131, 1108, 1097, 1058, 1023, 995, 826, 769, 744, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (app d, *J* = 8.1 Hz, 1H), 7.29 (app d, *J* = 8.2 Hz, 1H), 7.24–7.19 (m, 1H), 7.11–7.06 (m, 1H), 6.94 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 1.69 (s, 6H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 137.5, 126.1, 125.3, 121.4, 120.5, 119.3, 118.8, 109.3, 60.7, 42.0, 32.7, 26.3, 14.2; Chemical Formula: $C_{15}H_{19}NO_2$, *m/z* (ESIMS) 246.1 $[M + H]^+$.

2-Methyl-2-(1-methyl-1H-indol-3-yl)propan-1-ol (4.1064): Compound **4.103** (0.43 g, 1.75 mmol), dissolved in ether (10 mL), was added dropwise over 30 minutes to a stirred suspension of lithium aluminum hydride (0.76 g, 20 mmol) in ether (10 mL). The resulting mixture was then heated under reflux for 1 hour. The reaction mixture was allowed to cool to room temperature and excess of lithium aluminum hydride was carefully quenched with ice-water (100 mL). The organic layer was separated and the aqueous layer was extracted further with ether (5 x 50 mL). The combined organic layers were dried with sodium sulfate and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a colorless oil in 99% yield. (R_f = 0.30 in 30% EtOAc/hexanes); IR (film) 3386, 3047, 2961, 2871, 1613, 1543, 1484, 1464, 1423, 1374, 1360, 1327, 1241, 1151, 1107, 1040, 765, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (app dd, *J* = 8.1, 0.8 Hz, 1H), 7.33 (app d, *J* = 8.2 Hz, 1H), 7.25 (ddd, *J* = 8.2, 5.4, 1.0 Hz, 1H), 7.15–7.09 (m, 1H), 6.91 (app d, *J* = 3.4 Hz, 1H), 3.80 (d, *J* = 2.4 Hz, 2H), 3.77 (s, 3H), 1.47 (s, 6H), 1.31 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 127.0, 126.0,

121.4, 120.9, 119.4, 118.6, 109.5, 71.5, 37.6, 32.6, 25.4; Chemical Formula: $C_{13}H_{17}NO$, *m/z* (ESIMS) 204.1 $[M + H]^+$.

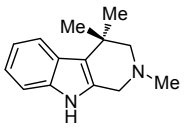
2-Methyl-2-(1-methyl-1H-indol-3-yl)propanal (4.105): Dichloromethane (4.3 mL) was added to a flame-dried 25-mL round-bottom flask equipped with a septum and a nitrogen inlet. The flask was cooled to –78 ºC and oxalyl chloride (0.20 mL, 2.4 mmol) was added. DMSO (0.32 mL, 4.5 mmol) was then added dropwise and the mixture was allowed to stir at –78 ºC for 10 minutes. Subsequently, **4.104** (0.35 g, 1.7 mmol), dissolved in 4 mL of dichloromethane, was added dropwise at –78 ºC. After stirring for 15 minutes, triethylamine (1.25 mL, 9.0 mmol) was added dropwise and the mixture was allowed to stir for another 15 minutes at –78 ºC. The flask was then transferred into an ice bath and stirred for 10 minutes. The reaction mixture was poured into ice-cold 1 M HCl solution (15 mL), extracted with dichloromethane (3 x 10 mL), washed with pH 7.4 buffer (10 mL) and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a pink solid in 68% yield. (R_f = 0.30 in 10% EtOAc/hexanes); mp: 59–60 °C; IR (KBr) 3409, 3120, 3051, 2986, 2966, 2925, 2807, 2708, 1713, 1676, 1537, 1485, 1463, 1419, 1389, 1379, 1359, 1329, 1253, 1232, 1135, 1108, 1015, 980, 908, 842, 828 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.56 (app d, *J* = 8.1 Hz, 1H), 7.32 (app d, *J* = 8.3 Hz, 1H), 7.26–7.21 (m, 1H), 7.13–7.06 (m, 1H), 6.96 (s, 1H), 3.79 (s, 3H), 1.55 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 137.6, 126.6, 126.2, 121.9, 120.2, 119.3, 115.1, 109.5, 46.5, 32.8, 21.9; Chemical Formula: $C_{13}H_{15}NO$, *m/z* (ESIMS) 202.2 $[M + H]^+$.

6,6-Dimethyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (4.71): Toluene (5 mL) was added to a round-bottom flask containing L-proline (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed into a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **4.61** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature. The residue was purified by flash column chromatography. The title compound was obtained as a yellow solid in 80% yield. (R_f = 0.28 in 25% MeOH/EtOAc); mp: 44–47 °C; IR (film) 3398, 3187, 3053, 2956, 2874, 1656, 1620, 1459, 1386, 1361, 1331, 1287, 1264, 1218, 1149, 1093, 1060, 738, 765, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.68 (app dd, *J* = 13.0, 5.3 Hz, 1H), 7.34–7.28 (m, 1H), 7.16–7.03 (comp, 2H), 3.62 (dd, *J* = 9.5, 6.9 Hz, 1H), 3.08 (ddd, *J* = 10.1, 8.3, 3.2 Hz, 1H), 2.87 (d, *J* = 11.3 Hz, 1H), 2.81 (app dd, *J* = 18.2, 8.3 Hz, 1H), 2.51 (d, *J* = 11.3 Hz, 1H), 2.20–2.08 (m, 1H), 2.01 (app qdd, *J* = 14.6, 9.1, 6.4 Hz, 1H), 1.86–1.67 (comp, 2H), 1.49 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 133.9, 125.9, 120.9, 119.7, 119.1, 116.3, 111.1, 63.2, 59.3, 53.4, 33.7, 28.7, 28.3, 27.8, 22.8; Chemical Formula: $C_{16}H_{20}N_2$, *m/z* (ESIMS) 241.2 $[M + H]^+$.

7,7-Dimethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (4.73): Toluene (5 mL) was added to a round-bottom flask containing DL-pipecolic acid

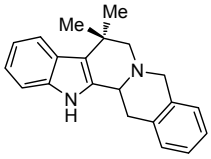
(0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **4.61** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 24 hours. The reaction mixture was then allowed to cool to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a yellow solid in 90% yield. (R_f = 0.35 in 30% EtOAc/hexanes); mp: 46–48 °C; IR (film) 3414, 3261, 3053, 2935, 2857, 2796, 2750, 1618, 1459, 1442, 1391, 1373, 1357, 1321, 1307, 1283, 1265, 1205, 1127, 1110, 1082, 1050, 764, 738 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73–7.62 (comp, 2H), 7.31 (app d, *J* = 7.9 Hz, 1H), 7.19–7.08 (comp, 2H), 3.13 (dd, *J* = 10.8, 2.5 Hz, 1H), 2.96 (app d, *J* = 11.1 Hz, 1H), 2.59 (d, *J* = 11.2 Hz, 1H), 2.46 (d, *J* = 11.2 Hz, 1H), 2.40–2.30 (m, 1H), 2.03 (app dd, *J* = 16.4, 13.5 Hz, 1H), 1.93 (app d, *J* = 12.3 Hz, 1H), 1.82–1.67 (comp, 2H), 1.62–1.40 (comp, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 134.5, 126.1, 120.7, 119.7, 119.0, 116.7, 110.9, 68.8, 60.4, 55.8, 32.8, 30.1, 28.4, 27.0, 25.8, 24.5; Chemical Formula: $C_{17}H_{22}N_2$, *m/z* (ESIMS) 255.2 $[M + H]^+$.

2,4,4-Trimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (4.74): Sarcosine (6.0 mmol) and **4.61** (0.5 mmol) along with 10 mL of xylenes were placed in a round-bottom flask equipped with a reflux condenser containing a nitrogen inlet. The flask was placed in a pre-heated oil bath (170 °C). After 20 hours, the reaction mixture was allowed to cool to room temperature. Following removal of the solvent, the residue was purified by flash column chromatography. The title compound



was obtained as a white solid in 61% yield. (R_f = 0.31 in 70% EtOAc/hexanes); mp: 174–176 °C; IR (KBr) 3140, 3103, 3060, 2925, 2851, 2796, 2752, 1453, 1397, 1384, 1360, 1330, 1299, 1263, 1238, 1179, 1103, 1031, 881, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.64 (app t, *J* = 8.4 Hz, 1H), 7.22 (app dd, *J* = 11.7, 4.5 Hz, 1H), 7.13–7.04 (comp, 2H), 3.38 (s, 2H), 2.45 (s, 2H), 2.44 (s, 3H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 130.8, 125.8, 120.9, 119.6, 119.0, 116.6, 111.1, 68.9, 52.8, 46.1, 33.1, 27.8; Chemical Formula: $C_{14}H_{18}N_2$, *m/z* (ESIMS) 215.1 $[M + H]^+$.

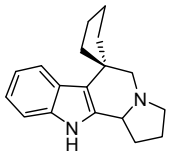
8,8-Dimethyl-5,7,8,13,13b,14-hexahydroindolo[2',3':3,4]pyrido[1,2-b]isoquinoline



(4.76): (*S*)-(-)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid (1.0 mmol) and **4.61** (0.5 mmol) along with 10 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was sealed and irradiated for 20 minutes (250 °C, 160 psi). The reaction mixture was then allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a light orange-colored solid in 52% yield and **4.92** was obtained as a light yellow solid in 25% yield. (R_f = 0.36 in 15% EtOAc/hexanes); mp: 58–61 °C; IR (KBr) 3405, 3049, 2952, 2923, 2862, 2797, 2738, 1491, 1458, 1374, 1356, 1340, 1320, 1309, 1263, 1146, 1107, 1085, 742, 686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (br s, 1H), 7.71 (app d, *J* = 7.8 Hz, 1H), 7.36 (app dd, *J* = 8.0, 0.6 Hz, 1H), 7.24–7.07 (comp, 6H), 4.06 (d, *J* = 14.9 Hz, 1H), 3.74 (d, *J* = 14.9 Hz, 1H), 3.64 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.19 (dd, *J* = 15.5, 3.6 Hz, 1H), 3.06–2.97 (m, 1H), 2.82 (d, *J* = 11.2 Hz, 1H), 2.58 (d, *J* = 11.2 Hz, 1H), 1.52 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 134.9, 133.5, 133.3, 128.7, 126.5, 126.3, 126.1, 125.9, 121.2, 119.9, 119.3, 117.4,

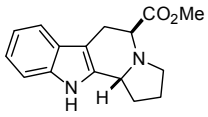
111.0, 67.4, 57.7, 56.5, 34.9, 32.7, 28.4, 26.9; Chemical Formula: $C_{21}H_{22}N_2$, *m/z* (ESIMS) 303.2 $[M + H]^+$.

1',2',3',5',11',11b'-Hexahydrospiro[cyclopentane-1,6'-indolizino[8,7-b]indole] (4.78):



Toluene (5 mL) was added to a round-bottom flask containing L-proline (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **4.77** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a light brown solid in 79% yield. (R_f = 0.20 in 20% MeOH/EtOAc); mp: 60–62 °C; IR (film) 3396, 3142, 3053, 2952, 2869, 1453, 1332, 1263, 1181, 1061, 1013, 738, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 7.61 (app t, *J* = 10.1 Hz, 1H), 7.28 (app t, *J* = 7.6 Hz, 1H), 7.15–7.03 (comp, 2H), 3.68 (dd, *J* = 8.9, 7.5 Hz, 1H), 3.12–3.01 (m, 1H), 2.94 (d, *J* = 11.5 Hz, 1H), 2.87–2.76 (m, 1H), 2.57 (d, *J* = 11.5 Hz, 1H), 2.30–2.06 (comp, 3H), 2.04–1.89 (comp, 3H), 1.87–1.71 (comp, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 134.6, 125.4, 120.9, 119.2, 119.1, 115.4, 111.2, 61.1, 59.0, 53.2, 44.0, 38.0, 38.0, 28.6, 25.9, 25.8, 23.0; Chemical Formula: $C_{18}H_{22}N_2$, *m/z* (ESIMS) 267.2 $[M + H]^+$.

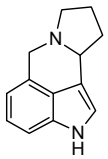
Methyl 2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole-5-carboxylate (4.80): L-



Proline (1.0 mmol) and **4.79** (0.5 mmol) along with 10 mL of xylenes

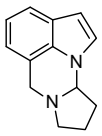
were placed in a round-bottom flask equipped with a reflux condenser containing a nitrogen inlet. The flask was placed in a pre-heated oil bath (170 °C). After 1.75 hours, the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a mixture of diastereomers in 52% yield, dr = 70:30 as determined by integration of one set of ^{1}H-NMR signals (δ_{major} 3.66 ppm, δ_{minor} 3.84 ppm). The relative configuration of the major diastereomer was determined by NOSY. (R_f = 0.15 in EtOAc); IR (film) 3395, 3055, 2951, 2874, 1735, 1621, 1451, 1360, 1328, 1305, 1267, 1206, 1177, 1141, 1107, 1010, 908, 736, 702, 644 cm^{-1}; ^{1}H NMR of the major diastereomer (500 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 7.53–7.46 (m, 1H), 7.34–7.28 (m, 1H), 7.19–7.07 (comp, 2H), 4.75–4.66 (m, 1H), 4.13 (app t, *J* = 4.2 Hz, 1H), 3.66 (s, 3H), 3.22–3.17 (comp, 2H), 3.01–2.93 (m, 1H), 2.85 (app dd, *J* = 16.1, 8.1 Hz, 1H), 2.44–2.30 (m, 1H), 2.04–1.70 (comp, 3H); ^{13}C NMR of diastereomers (125 MHz, $CDCl_3$) δ 173.2, 172.8, 136.2, 136.0, 135.1, 134.7, 127.2, 127.1, 121.8, 121.6, 119.7, 119.4, 118.1, 110.8, 110.7, 107.3, 105.2, 58.7, 58.1, 57.5, 52.8, 52.3, 52.1, 50.3, 44.3, 30.2, 28.8, 23.1(4), 23.1(3), 19.7, 19.0; Chemical Formula: $C_{16}H_{18}N_2O_2$, *m/z* (ESIMS) 271.2 $[M + H]^+$.

2,6,8,9,10,10a-Hexahydrodipyrrolo[1,2-b:4',3',2'-de]isoquinoline (4.82): *n*-Butanol (5 mL) was added to a round-bottom flask containing L-proline (1.5 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (140 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **4.81** (0.5 mmol) in *n*-butanol (4.5 mL) was added slowly by syringe pump over 18 hours.



Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a pale pink solid in 63% yield. (R_f = 0.19 in 50% MeOH/EtOAc); mp: 185–188 °C; IR (KBr) 3407, 3143, 3088, 3054, 3000, 2967, 2933, 2868, 2811, 2738, 1602, 1457, 1444, 1367, 1340, 1311, 1248, 1228, 1150, 1105, 1026, 977, 925, 871, 817, 757, 741 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.78 (br s, 1H), 7.17 (app d, *J* = 8.1 Hz, 1H), 7.09–6.97 (comp, 2H), 6.78 (app d, *J* = 7.0 Hz, 1H), 4.17 (d, *J* = 15.2 Hz, 1H), 4.11–3.93 (comp, 2H), 2.85 (app d, *J* = 3.4 Hz, 1H), 2.74 (app d, *J* = 6.8 Hz, 1H), 2.34–2.20 (m, 1H), 1.96–1.70 (comp, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 134.2, 127.6, 125.5, 122.7, 118.56, 114.6, 113.0, 110.0, 59.8, 51.1, 51.0, 29.6, 22.4; Chemical Formula: $C_{13}H_{14}N_2$, *m/z* (ESIMS) 199.2 $[M + H]^+$.

8,9,10,10a-Tetrahydro-6H-dipyrrolo[2,1-b:3',2',1'-ij]quinazoline (4.84): L-Proline

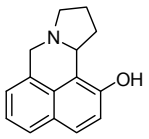


(1.0 mmol) and **4.83** (0.5 mmol) along with 5 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 30 minutes (200 °C, 110 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a white solid in 61% yield. (R_f = 0.33 in 30% EtOAc/hexanes); mp: 84–86 °C; IR (KBr) 3072, 2930, 2840, 1480, 1450, 1361, 1341, 1275, 1195, 1112, 1075, 775, 726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (app t, *J* = 10.3 Hz, 1H), 7.12 (d, *J* = 3.1 Hz, 1H), 7.10–7.04 (m, 1H), 6.92 (app dd, *J* = 17.8, 7.1 Hz, 1H), 6.51 (d, *J* = 3.1 Hz, 1H), 5.39 (app dt, *J* = 19.9, 10.0 Hz, 1H), 4.53 (d, *J* = 16.5 Hz, 1H), 4.14 (d, *J* = 16.5, 1H),

3.10 (app td, J = 9.0, 3.9 Hz, 1H), 2.67 (app td, J = 9.2, 7.3 Hz, 1H), 2.52–2.31 (comp, 2H), 2.14–1.96 (m, 1H), 1.90–1.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.8, 126.0, 122.9, 119.8, 118.6, 118.4, 117.3, 101.1, 73.2, 49.4, 46.8, 30.4, 21.6; Chemical Formula: $C_{13}H_{14}N_2$, *m/z* (ESIMS) 199.1 $[M + H]^+$.

Alternate preparation of 4.84: *n*-Butanol (5 mL) was added to a round-bottom flask containing pyrrolidine (1.5 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed into a pre-heated oil bath (140 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **4.83** (0.5 mmol) in *n*-butanol (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a white solid in 81% yield.

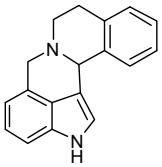
1-Benzyl-2-(4-phenylbut-1-yn-1-yl)pyrrolidine9,10,11,11a-tetrahydro-7H-benzo-



[de]pyrrolo[2,1-a]isoquinolin-1-ol (4.86): L-Proline (0.75 mmol) and **4.85** (0.5 mmol) along with 10 mL of toluene were added to a round-bottom flask equipped with a reflux condenser. The flask was placed in a pre-heated oil bath (130 °C). After 30 minutes, the reaction mixture was allowed to cool to room temperature. Following removal of the solvent under vacuo, the residue was purified by flash column chromatography. The title compound was obtained as a white solid in 91% yield. (R_f = 0.30 in 25% MeOH/EtOAc); mp: 176–177 °C; IR (KBr) 3048, 2955, 2877, 2807, 1625, 1587, 1508, 1434, 1381, 1358, 1320, 1308, 1267, 1128, 1112, 1103, 971, 963,

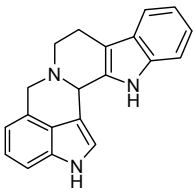
941, 911, 878, 823, 758, 629, 562 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 9.49 (br s, 1H), 7.71–7.48 (comp, 2H), 7.24–7.03 (comp, 3H), 4.06 (d, *J* = 14.3 Hz, 1H), 3.75–3.58 (comp, 2H), 3.13–2.97 (m, 1H), 2.63–2.51 (comp, 2H), 1.95–1.63 (comp, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 150.3, 132.4, 129.4, 127.3, 126.8, 125.7, 122.0, 122.0, 118.3, 117.8, 60.8, 52.9, 52.7, 29.5, 21.6; Chemical Formula: $C_{15}H_{15}NO$, *m/z* (ESIMS) 226.3 $[M + H]^+$.

6,8,9,13b-Tetrahydro-2H-isoquinolino[2,1-b]pyrrolo[4,3,2-de]isoquinoline (4.89): *n*-



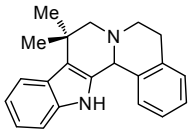
Butanol (5 mL) was added to a round-bottom flask containing tetrahydroisoquinoline (1.5 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (140 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **4.81** (0.5 mmol) in *n*-butanol (4.5 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a white solid in 78% yield. (R_f = 0.34 in 40% EtOAc/hexanes); mp: 194–197 °C; IR (KBr) 3416, 3136, 3082, 3032, 3000, 2924, 2852, 2791, 2735, 1737, 1614, 1494, 1442, 1381, 1371, 1354, 1298, 1383, 1237, 1153, 1124, 1098, 1064, 1047, 1028, 941, 925, 797, 766, 748, 739, 713, 703, 635, 597, 581, 521 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.64 (br s, 1H), 7.43 (app d, *J* = 7.5 Hz, 1H), 7.24 (app t, *J* = 7.3 Hz, 1H), 7.15 (app dt, *J* = 14.8, 7.1 Hz, 3H), 7.01 (app t, *J* = 7.5 Hz, 1H), 6.78–6.68 (comp, 2H), 5.32 (s, 1H), 4.33 (d, *J* = 15.8 Hz, 1H), 3.95 (d, *J* = 15.8 Hz, 1H), 2.99–2.86 (m, 1H),

2.76–2.59 (comp, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 137.4, 133.6, 133.5, 128.9, 127.8, 126.8, 126.0, 125.5, 124.4, 122.0, 119.7, 113.4, 113.2, 109.0, 57.3, 54.9, 46.0, 29.1; Chemical Formula: $C_{18}H_{16}N_2$, *m/z* (ESIMS) 261.2 $[M + H]^+$.

4,6,7,12,12b,14-Hexahydroindolo[2',3':3,4]pyrido[1,2-b]pyrrolo[4,3,2-de]isoquinoline (4.91): 

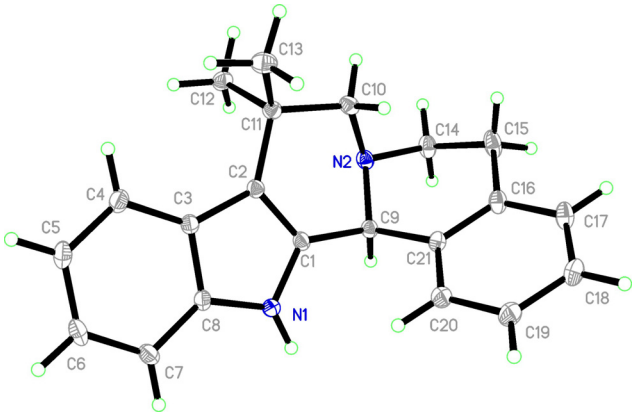
n-Butanol (5 mL) was added to a round-bottom flask containing **4.90** (1.0 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (140 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **4.81** (0.5 mmol) in *n*-butanol (4.5 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was.then allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a yellow solid in 54% yield. (R_f = 0.30 in 60% EtOAc/hexanes); mp: 226–231 °C; IR (KBr) 3448, 3085, 3050, 2956, 2931, 2882, 2845, 2818, 1617, 1457, 1328, 1307, 1254, 1232, 1113 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.94 (br s, 1H), 10.75 (br s, 1H), 7.41–7.35 (comp, 2H), 7.25 (s, 1H), 7.15 (app d, *J* = 8.1 Hz, 1H), 7.07–7.00 (comp, 2H), 6.96 (app t, *J* = 7.4 Hz, 1H), 6.76 (app d, *J* = 7.0 Hz, 1H), 5.27 (s, 1H), 4.18 (d, *J* = 15.3 Hz, 1H), 4.06 (d, *J* = 15.3 Hz, 1H), 3.02 (app dd, *J* = 11.3, 5.6 Hz, 1H), 2.92 (app dt, *J* = 11.7, 5.9 Hz, 1H), 2.80–2.70 (comp, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 136.2, 134.8, 133.1, 128.6, 126.6, 124.8, 122.0, 120.4, 118.9, 118.3, 117.5, 113.2, 111.4, 111.2, 108.9, 105.9, 54.5, 54.1, 49.2, 21.3; Chemical Formula: $C_{20}H_{17}N_3$, *m/z* (ESIMS) 300.2 $[M + H]^+$.

9,9-Dimethyl-5,6,8,9,14,14b-hexahydroindolo[2',3':3,4]pyrido[2,1-a]isoquinoline



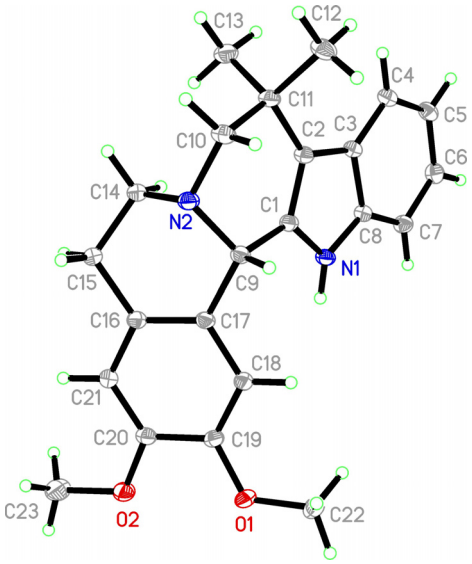
(4.92): Tetrahydroisoquinoline (1.5 mmol) and **4.61** (0.5 mmol) along with 5 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 20 minutes (250 °C, 140 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a light yellow solid in 64% yield. (R_f = 0.21 in 30% EtOAc/hexanes); mp: 148–151 °C; IR (KBr) 3140, 3101, 3059, 2925, 2864, 2847, 1457, 1332, 1302, 1262, 1190, 1101, 1075, 970, 908, 880, 742, 662 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.68 (app d, *J* = 7.8 Hz, 1H), 7.39 (app d, *J* = 7.4 Hz, 1H), 7.32–7.22 (comp, 3H), 7.19 (app d, *J* = 7.3 Hz, 1H), 7.15–7.06 (comp, 2H), 5.22 (s, 1H), 3.27–3.14 (comp, 2H), 3.10–3.03 (comp, 2H), 2.97–2.83 (comp, 2H), 1.53 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 134.9, 134.8, 132.2, 129.8, 127.0, 126.6, 126.4, 126.2, 121.1, 120.0, 119.2, 115.7, 111.1, 64.7, 57.2, 48.0, 32.2, 29.3, 28.7, 28.2; Chemical Formula: $C_{21}H_{22}N_2$, *m/z* (ESIMS) 303.2 $[M + H]^+$.

The title compound was further characterized by X-ray crystallography:

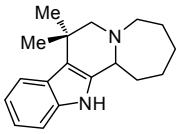


2,3-Dimethoxy-9,9-dimethyl-5,6,8,9,14,14b-hexahydroindolo[2',3':3,4]pyrido[2,1-a]isoquinoline (4.94): 4.93 (1.5 mmol) and **4.61** (0.5 mmol) along with 5 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 20 minutes (200 °C, 45 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a white solid in 61% yield. (R_f = 0.31 in 50% EtOAc/hexanes); mp: 188–190 °C; IR (KBr) 3379, 2998, 2969, 2954, 2920, 2903, 2861, 2831, 1612, 1519, 1455, 1444, 1374, 1355, 1339, 1327, 1296, 1279, 1259, 1238, 1226, 1212, 1197, 1141, 1102, 1064, 1036, 1012, 871, 845, 180, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.69 (app d, J = 7.6 Hz, 1H), 7.32 (app d, J = 7.7 Hz, 1H), 7.18–7.05 (comp, 2H), 6.88 (s, 1H), 6.67 (s, 1H), 5.11 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.23 (ddd, J = 12.6, 7.8, 5.1 Hz, 1H), 3.19–3.12 (m, 1H), 3.11–3.01 (comp, 2H), 2.89–2.73 (comp, 2H), 1.53 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 147.5, 136.0, 132.5, 126.9, 126.5, 126.4, 121.0, 120.0, 119.12, 115.6, 112.3, 111.2, 110.1, 64.3, 56.7, 56.3, 55.8, 47.9, 32.1, 29.4, 28.6, 27.5; Chemical Formula: $C_{23}H_{26}N_2O_2$, *m/z* (ESIMS) 363.2 $[M + H]^+$.

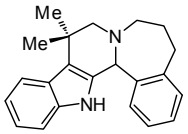
The title compound was further characterized by X-ray crystallography:



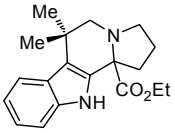
8,8-Dimethyl-2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-b]indole



(4.96): Azepane (5.0 mmol) and **4.61** (0.5 mmol) along with 2 mL of *n*-butanol were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 5 hours (200 °C, 45 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a yellow oil in 43% yield. (R_f = 0.33 in EtOAc); IR (film) 3404, 3247, 3053, 2926, 2857, 1459, 1376, 1356, 1325, 1274, 1129, 1114, 1082, 1015, 762, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.59 (comp, 2H), 7.32–7.24 (m, 1H), 7.15–7.03 (comp, 2H), 3.74 (dd, *J* = 8.6, 3.4 Hz, 1H), 2.94–2.83 (comp, 2H), 2.70 (d, *J* = 11.5 Hz, 1H), 2.60 (d, *J* = 11.5 Hz, 1H), 2.05–1.95 (m, 1H), 1.92–1.54 (comp, 7H), 1.46 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 135.9, 126.0, 120.8, 119.8, 118.9, 117.0, 110.8, 66.8, 60.3, 56.8, 33.8, 33.0, 27.7, 27.41, 27.37, 27.0, 25.6; Chemical Formula: $C_{18}H_{24}N_2$, *m/z* (ESIMS) 269.2 $[M + H]^+$.

10,10-Dimethyl-6,7,9,10,15,15b-hexahydro-5H-benzo[3',4']azepino[1',2':1,2]pyrido [3,4-b]indole (4.98): 

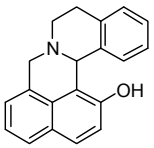
4.97 (2.5 mmol) and **4.61** (0.5 mmol) along with 2 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 1 hour (250 °C, 140 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a thick yellow oil in 54% yield. (R_f = 0.20 in 10% EtOAc/hexanes); IR (film) 3400, 3174, 3056, 2927, 2859, 1458, 1376, 1355, 1327, 1266, 1113, 1079, 740, 635 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (app d, *J* = 7.7 Hz, 1H), 7.61 (br s, 1H), 7.28 (app d, *J* = 7.8 Hz, 1H), 7.20–7.09 (comp, 4H), 7.08–7.03 (m, 1H), 6.52 (app d, *J* = 7.5 Hz, 1H), 5.30 (s, 1H), 3.33–3.22 (m, 1H), 3.04–2.94 (m, 1H), 2.92–2.82 (m, 1H), 2.66–2.57 (m, 1H), 2.50 (d, *J* = 11.6 Hz, 1H), 2.36 (d, *J* = 11.6 Hz, 1H), 2.09–2.01 (m, 1H), 1.96–1.81 (m, 1H), 1.50 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 136.4, 132.3, 128.9, 128.4, 127.5, 126.1, 125.7, 121.2, 120.0, 119.5, 119.1, 111.0, 63.8, 58.7, 33.1, 32.7, 29.7, 27.5(1), 27.4(8), 25.7; Chemical Formula: $C_{22}H_{24}N_2$, *m/z* (ESIMS) 317.3 $[M + H]^+$.

Ethyl 6,6-dimethyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole-11b-carboxylate (4.100): 

4.99 (1.5 mmol) and **4.61** (0.5 mmol) along with 5 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 20 minutes (250 °C, 114 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a thick yellow oil in 74%

yield. (R_f = 0.40 in 10% MeOH/EtOAc); IR (film) 3388, 3055, 2956, 1715, 1617, 1457, 1385, 1364, 1320, 1297, 1262, 1101, 1023, 857, 765, 738, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.71 (app t, *J* = 10.3 Hz, 1H), 7.36 (app d, *J* = 8.1 Hz, 1H), 7.21–7.14 (m, 1H), 7.10 (app t, *J* = 7.3 Hz, 1H), 4.31–4.12 (comp, 2H), 3.33 (ddd, *J* = 9.5, 7.3, 5.3 Hz, 1H), 3.21 (app dt, *J* = 9.5, 7.1 Hz, 1H), 3.13 (d, *J* = 13.2 Hz, 1H), 3.00 (d, *J* = 13.2 Hz, 1H), 2.64 (ddd, *J* = 12.5, 7.9, 4.5 Hz, 1H), 2.30–2.15 (m, 1H), 1.94–1.79 (comp, 2H), 1.54 (s, 3H), 1.43 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 136.5, 131.7, 125.5, 121.6, 120.3, 119.1, 118.0, 111.1, 67.3, 61.6, 59.9, 53.1, 37.4, 32.6, 28.5, 28.4, 23.8, 14.2; Chemical Formula: $C_{19}H_{24}N_2O_2$, *m/z* (ESIMS) 313.2 $[M + H]^+$.

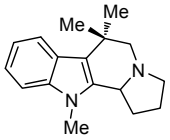
5,6,8,14b-Tetrahydrobenzo[de]isoquinolino[1,2-a]isoquinolin-14-ol (4.101):



Tetrahydroisoquinoline (1.5 mmol), **4.85** (0.5 mmol) and 10 mL of toluene were added to a round-bottom flask equipped with a condenser containing a nitrogen inlet. The flask was placed in a pre-heated oil bath (130 °C). After 30 minutes, the reaction mixture was allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a white solid in 81% yield. (R_f = 0.27 in 60% EtOAc/hexanes); mp: 224–227 °C; IR (KBr) 3056, 2939, 2821, 1629, 1589, 1514, 1484, 1452, 1436, 1374, 1316, 1277, 1121, 1040, 954,881, 820, 763, 744 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 9.81 (br s, 1H), 7.71 (app d, *J* = 8.9 Hz, 1H), 7.60 (app d, *J* = 8.1 Hz, 1H), 7.26 (app d, *J* = 8.9 Hz, 1H), 7.18–7.13 (m, 1H), 7.12–7.05 (comp, 3H), 6.96 (app t, *J* = 7.0 Hz, 1H), 6.74 (app d, *J* = 7.7 Hz, 1H), 5.51 (s, 1H), 4.00 (d, *J* = 14.7 Hz, 1H), 3.79 (d, *J* = 14.7 Hz, 1H), 3.65–3.53 (m, 1H), 3.40–3.34 (m, 1H), 3.24–3.13 (m, 1H),

2.69 (app dd, J = 17.7, 6.2 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 150.3, 135.1, 133.9, 132.3, 128.8, 128.4, 128.4, 127.6, 127.5, 126.2, 125.8, 125.5, 122.2, 121.9, 117.9, 117.6, 55.5, 49.6, 47.8, 22.2; Chemical Formula: $C_{20}H_{17}NO$, *m/z* (ESIMS) 288.3 $[M + H]^+$.

6,6,11-Trimethyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (4.107):

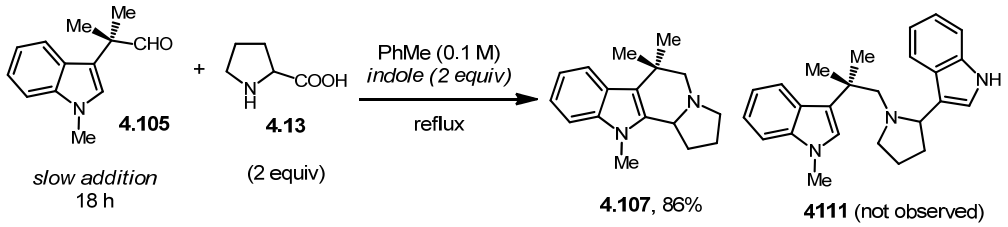


Toluene (5 mL) was added to a round-bottom flask containing L-proline (0.75 mmol) and benzoic acid (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **4.105** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature, neutralized with 10 mL of 1 M NaOH aqueous solution and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as yellow oil in 85% yield. (R_f = 0.28 in 5% MeOH/EtOAc); IR (film) 3416, 3045, 2953, 2870, 2789, 1667, 1468, 1417, 1383, 1359, 1328, 1316, 1291, 1265, 1224, 1196, 1161, 1101, 1083, 1061, 1018, 762, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (app d, J = 7.9 Hz, 1H), 7.30 (app d, J = 8.2 Hz, 1H), 7.19 (app dd, J = 11.2, 4.0 Hz, 1H), 7.11 (app td, J = 7.5, 0.9 Hz, 1H), 3.87–3.77 (m, 1H), 3.66 (s, 3H), 3.11 (ddd, J = 11.0, 8.3, 2.7 Hz, 1H), 3.02–2.94 (m, 1H), 2.79 (d, J = 11.0 Hz, 1H), 2.48 (d, J = 11.0 Hz, 1H), 2.34–2.24 (m, 1H), 2.18–2.06 (m, 1H), 1.99–1.77 (comp, 2H), 1.51 (s, 3H), 1.49 (s, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 137.3, 136.1, 125.3, 120.4, 119.8, 118.6, 115.5, 108.9, 62.7, 58.5, 54.1, 33.6, 30.0, 29.2, 27.9, 27.7, 23.2; Chemical Formula: $C_{17}H_{22}N_2$, *m/z* (ESIMS) 255.2 $[M + H]^+$.

11-Methyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (4.108): Toluene (5 mL) was added to a round-bottom flask containing L-proline (0.75 mmol) and benzoic acid (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **4.106** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. Then the reaction mixture was cooled to room temperature, neutralized with 10 mL of 1 M NaOH aqueous solution and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with sodium sulfate and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as yellow oil in 60% yield. (R_f = 0.25 in 30% MeOH/EtOAc); IR (film) 3397, 3049, 2934, 2842, 1660, 1614, 1470, 1376, 1352, 1321, 1283, 1244, 1188, 1157, 1129, 1086, 1011 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (app dd, *J* = 7.8, 0.7 Hz, 1H), 7.29 (app dd, *J* = 8.2, 0.7 Hz, 1H), 7.23–7.18 (m, 1H), 7.14–7.09 (m, 1H), 4.30–4.22 (m, 1H), 3.66 (s, 3H), 3.29–3.20 (m, 1H), 3.06–2.89 (comp, 4H), 2.78–2.68 (m, 1H), 2.50–2.39 (m, 1H), 2.01–1.90 (comp, 2H), 1.90–1.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 137.0, 126.6, 120.8, 118.8, 118.0, 108.6, 106.6, 56.2, 50.9, 46.4, 30.3, 30.1, 23.7, 18.7; Chemical Formula: $C_{15}H_{18}N_2$, *m/z* (ESIMS) 227.2 $[M + H]^+$.

Reaction between indole, 4.65 and L-proline:



Toluene (5 mL) was added to a round-bottom flask containing L-proline (1.0 mmol) and indole (1.0 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed into a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **4.105** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. Then the reaction mixture was allowed to cool to room temperature and the residue was purified by flash column chromatography. Compound **4.107** was obtained as yellow oil in 86% yield.

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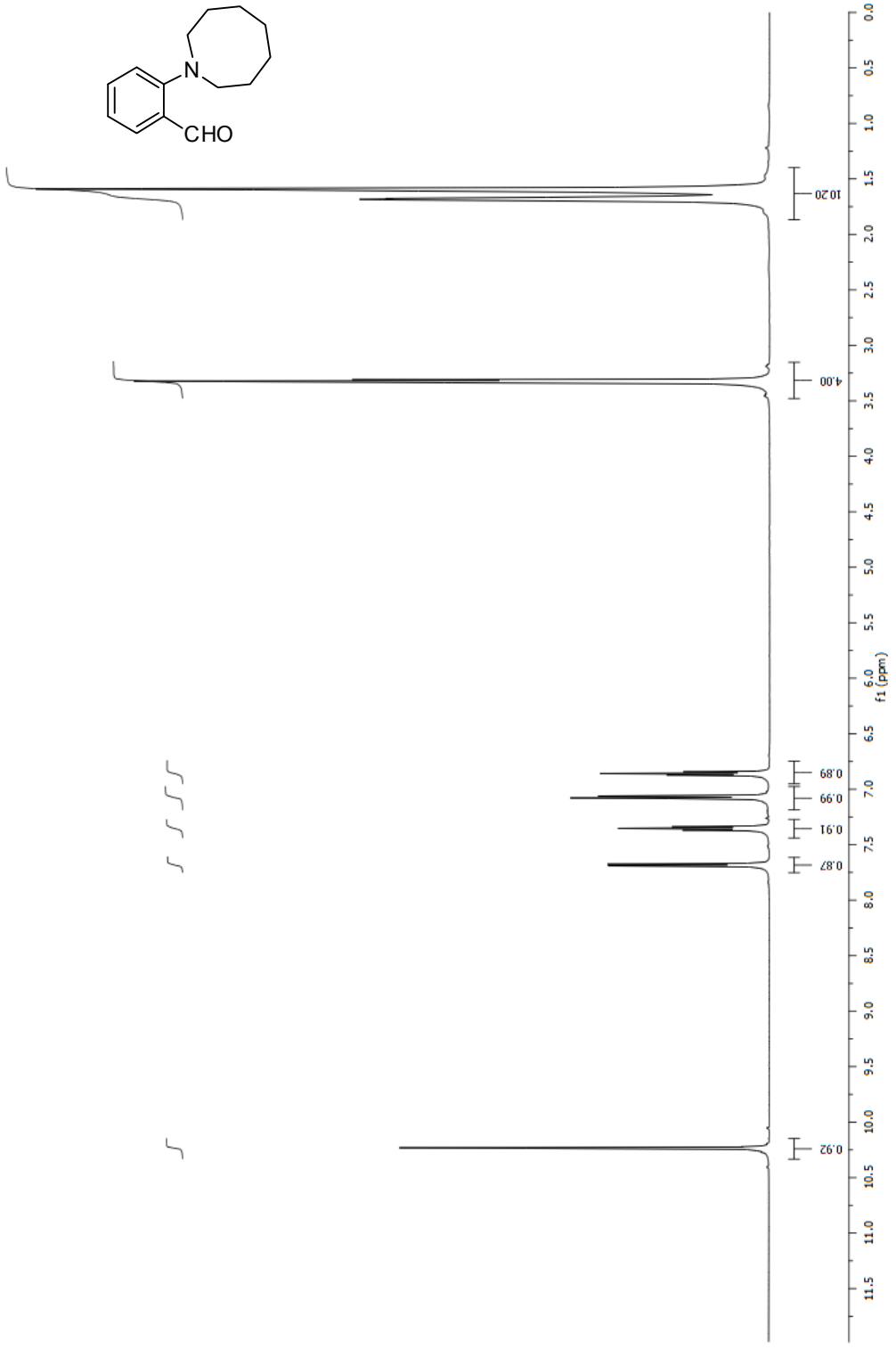
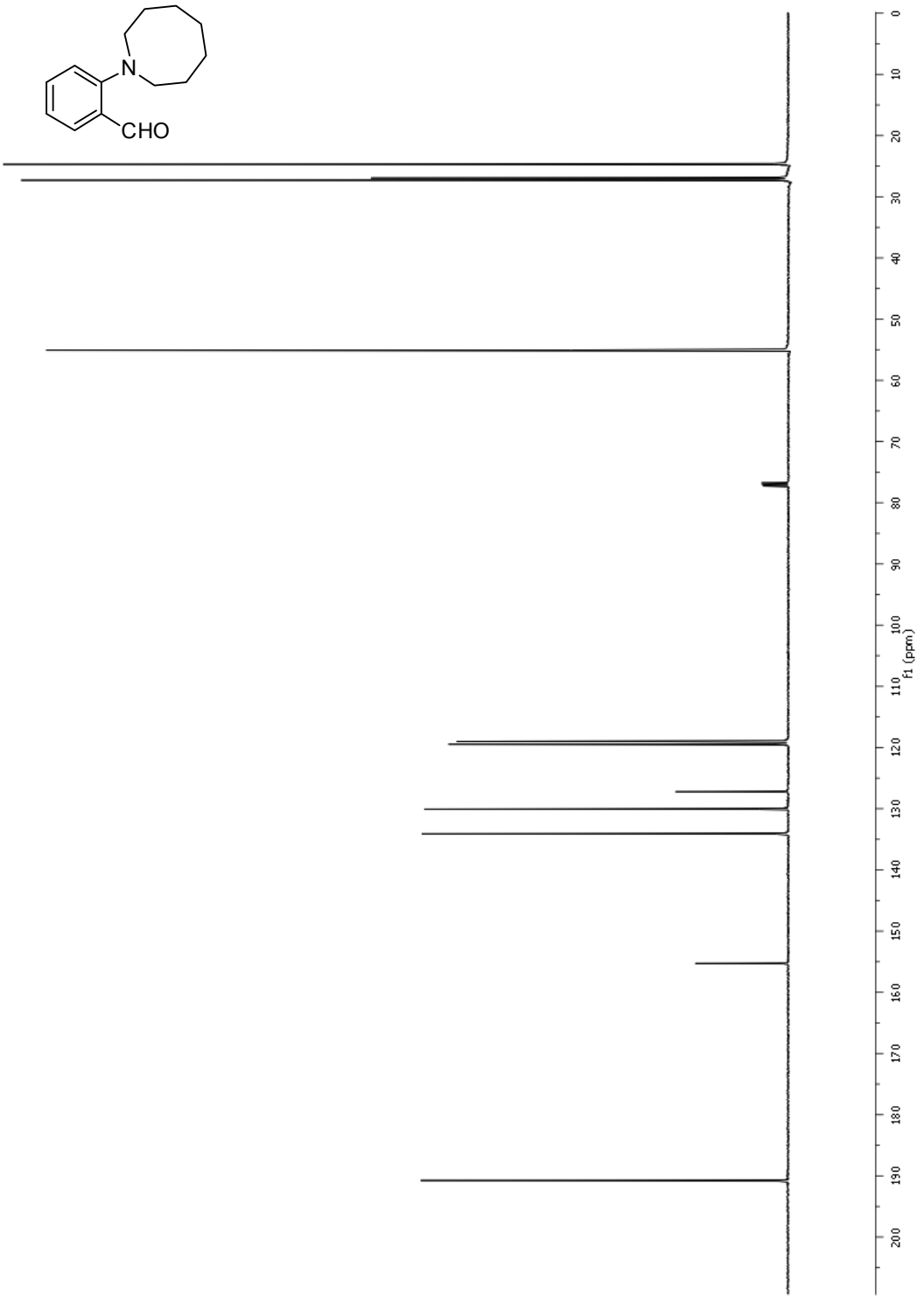
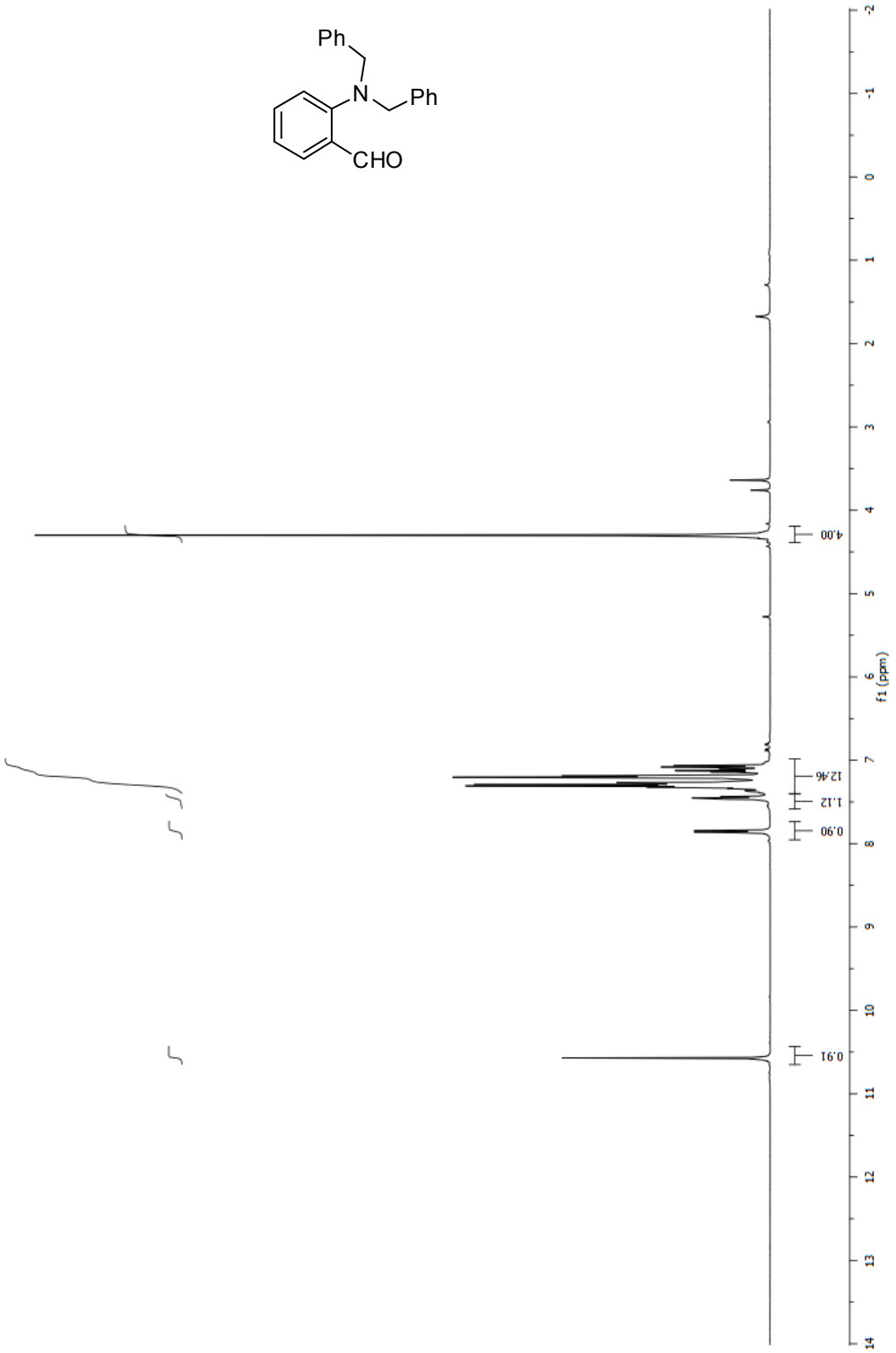
Spectra Section

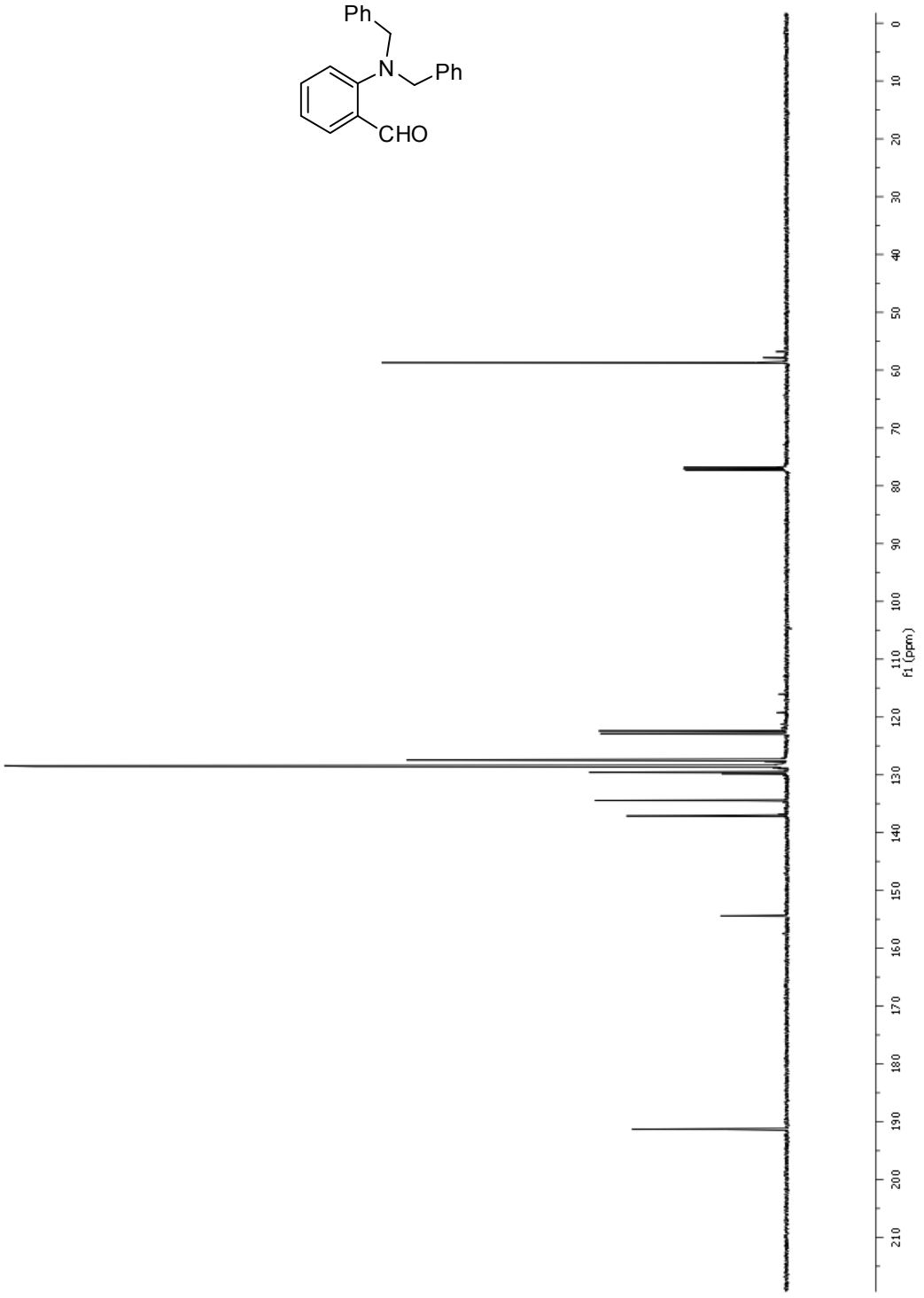
^{1}H–NMR and ^{13}C–NMR of **2.7m**:



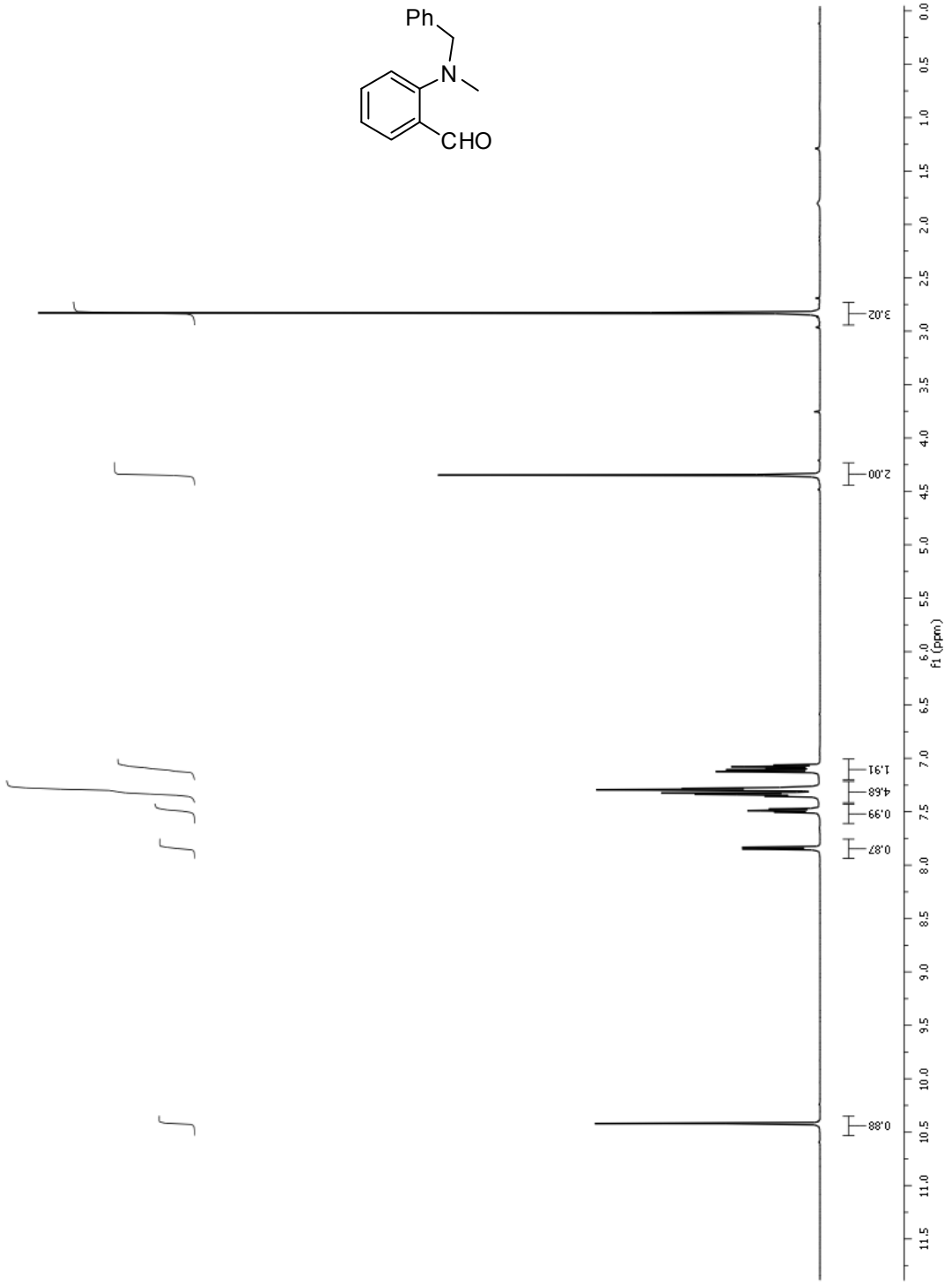

N
CHO
f1 (ppm)

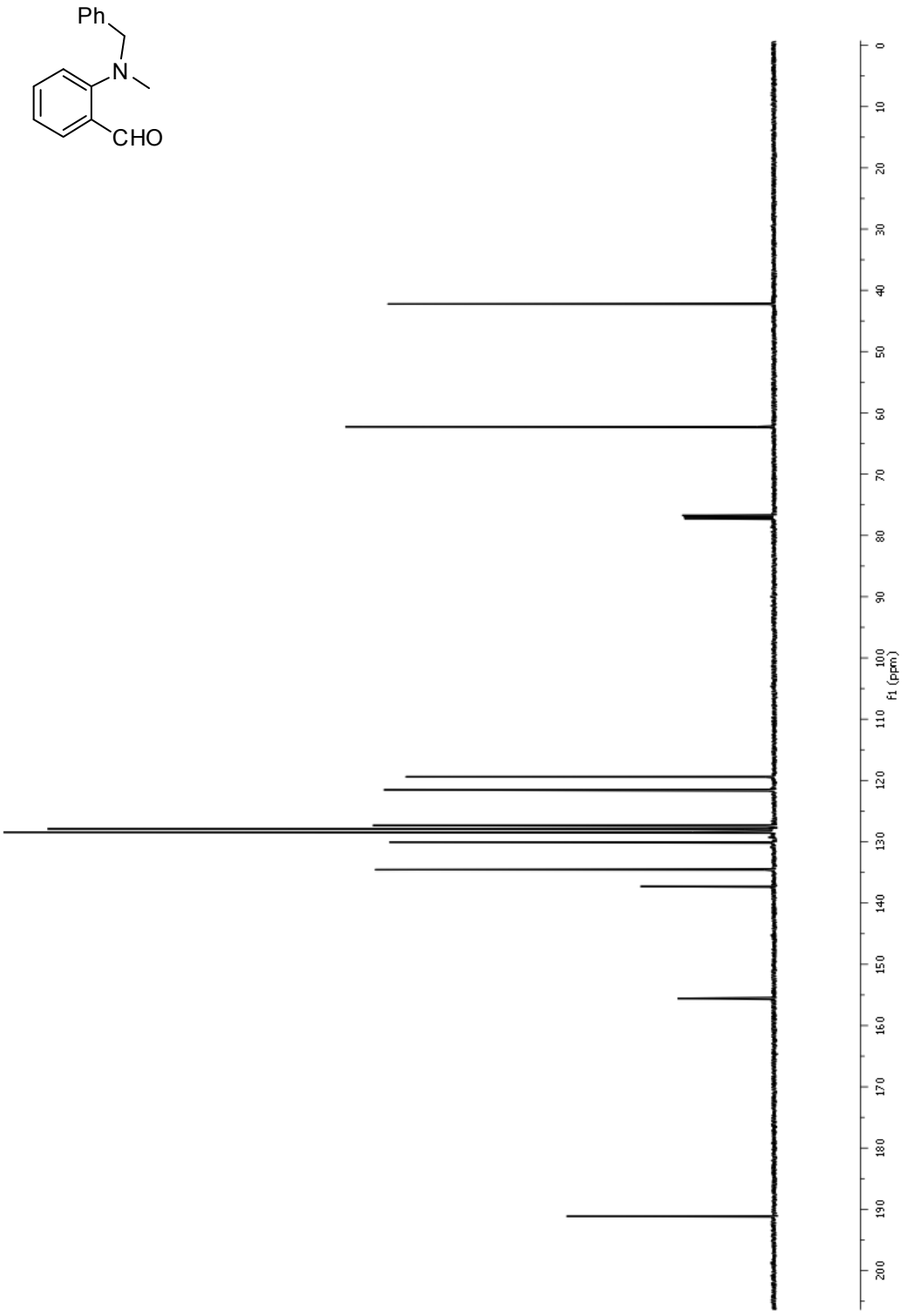
^{1}H–NMR and ^{13}C–NMR of **2.7p**:



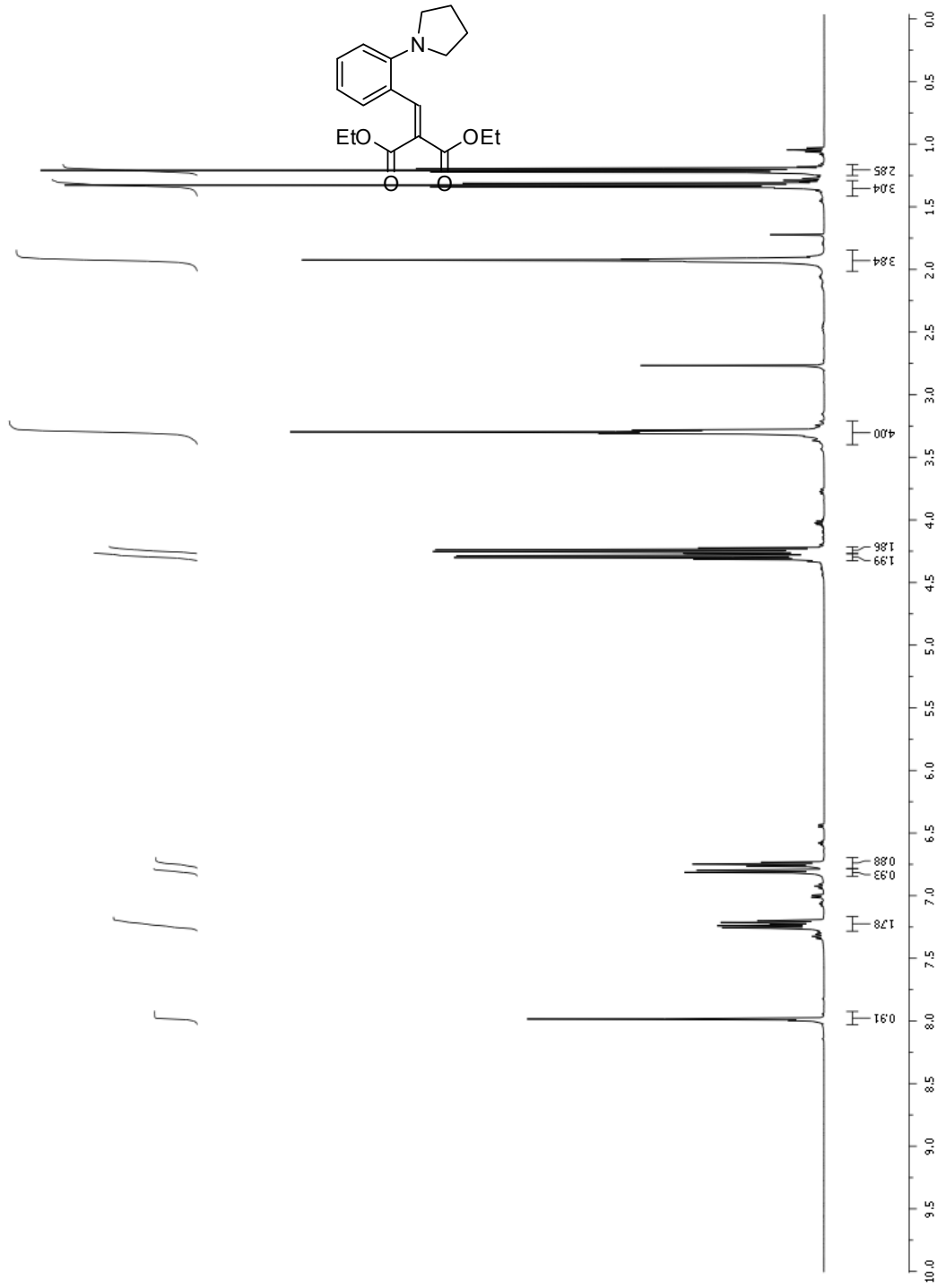

Ph
N
Ph
CHO
f1 (ppm)

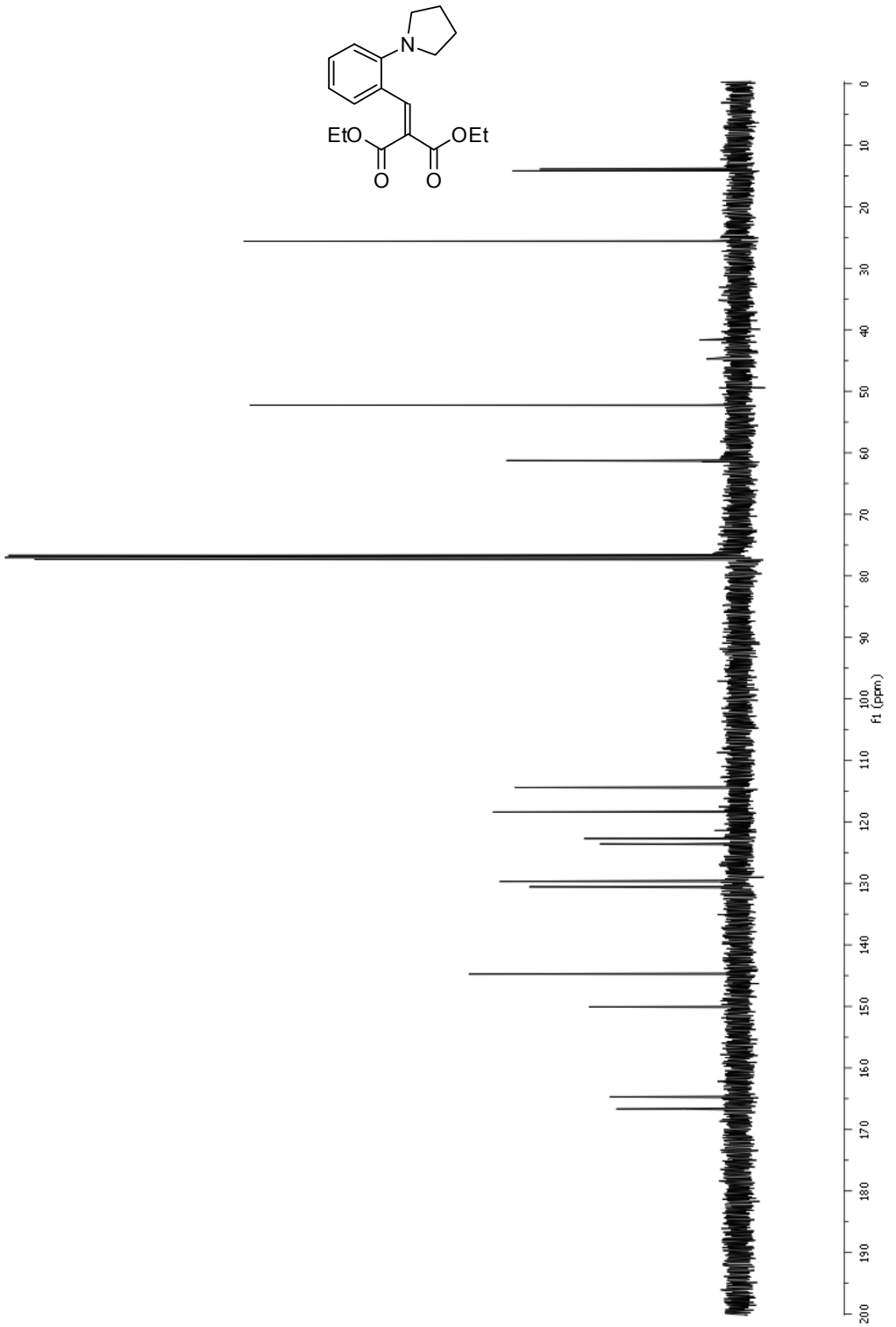
^{1}H–NMR and ^{13}C–NMR of **2.7q**:



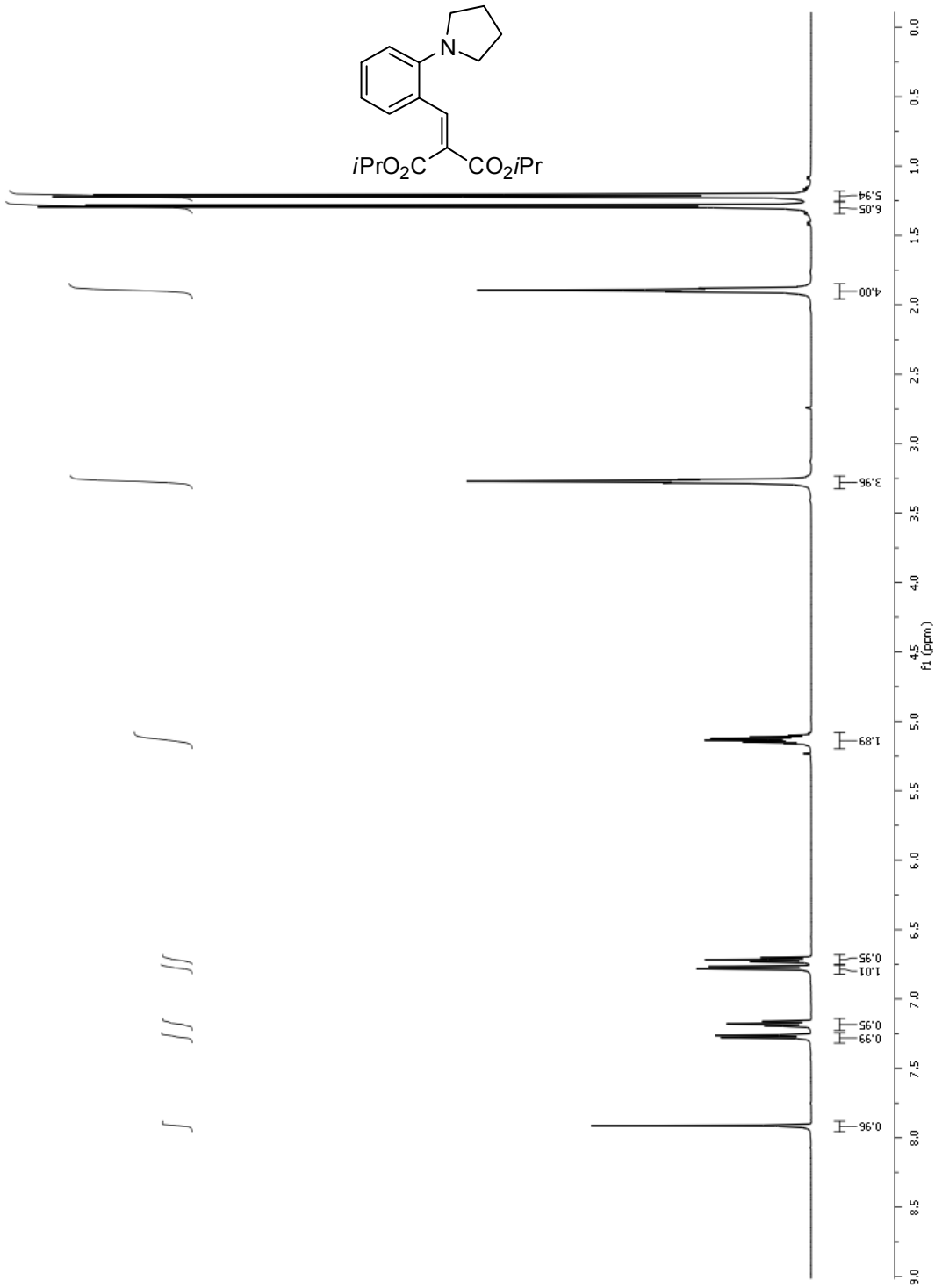

Ph
N
CHO
f1 (ppm)

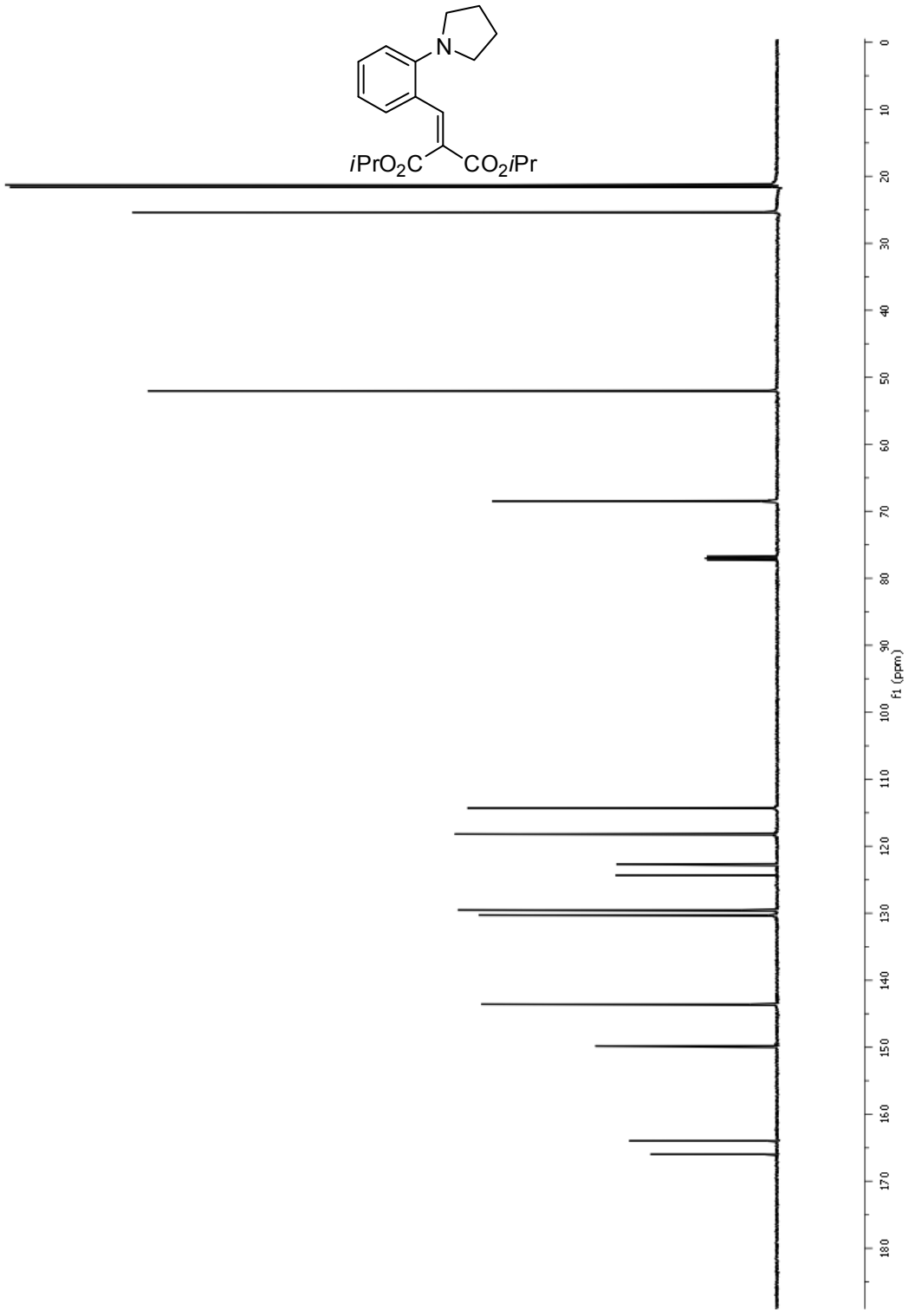
^{1}H–NMR and ^{13}C–NMR of **2.1b**:



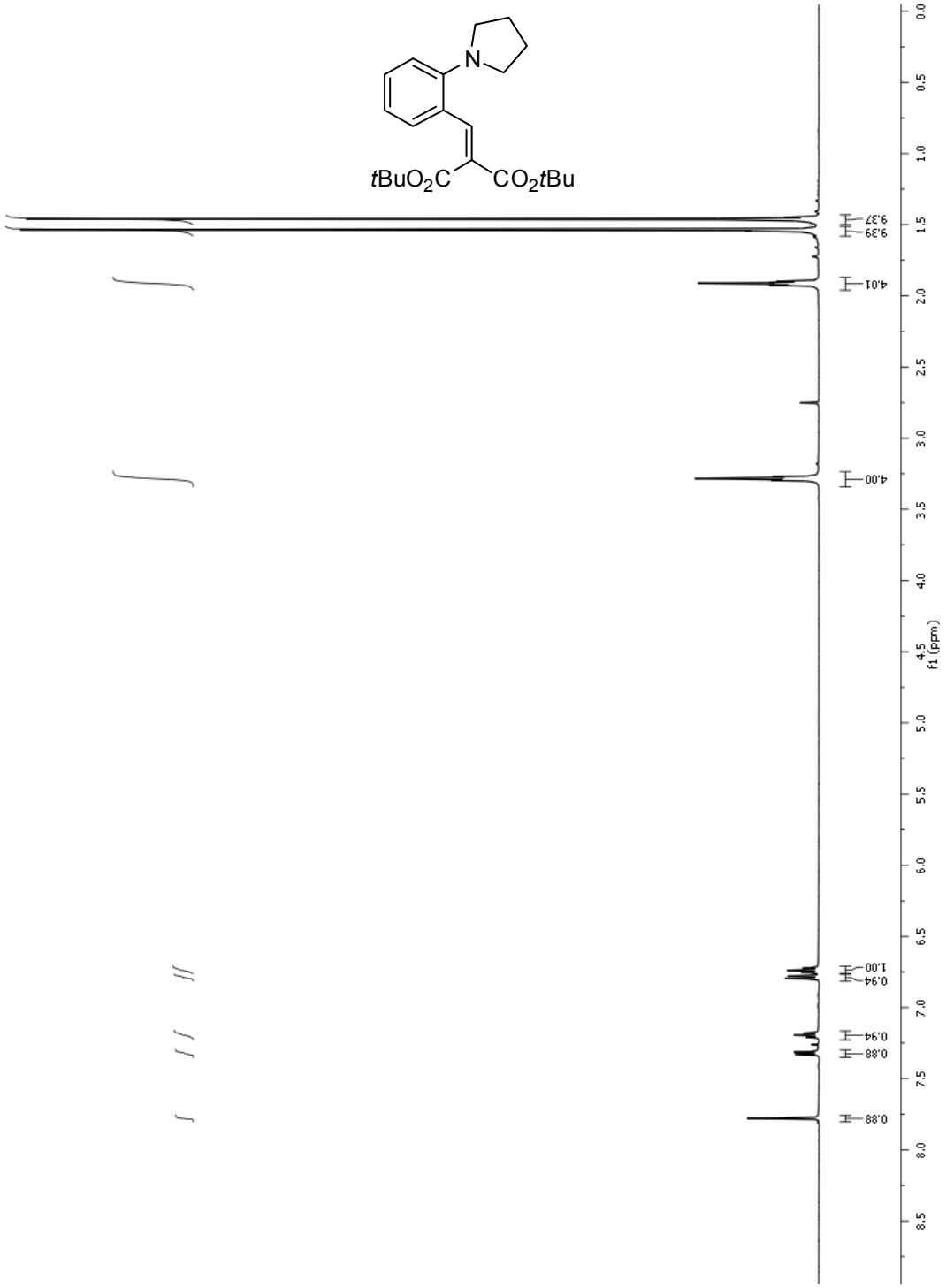

N
EtO
OEt
O
O
F1 (ppm)

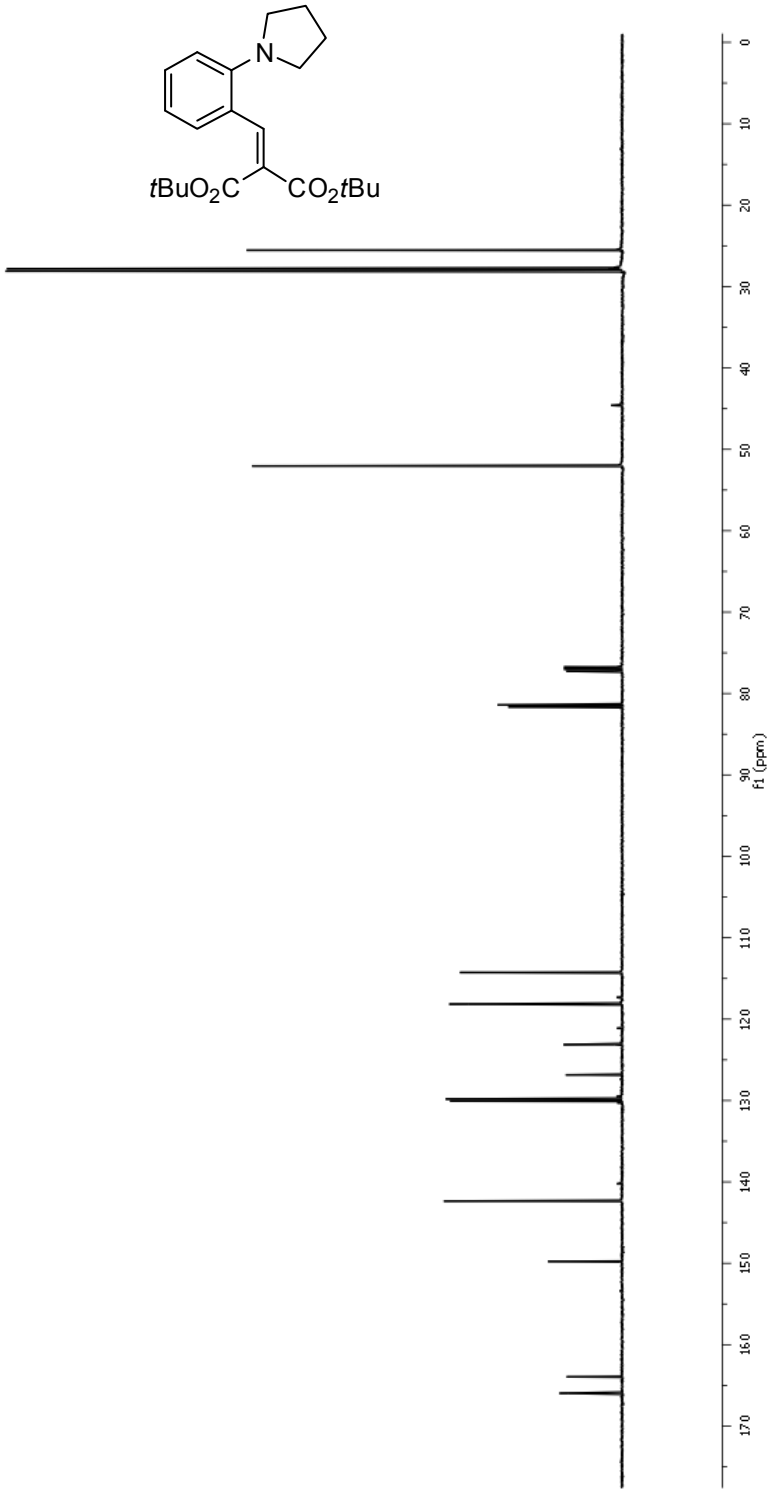
^{1}H–NMR and ^{13}C–NMR of **2.1c**:



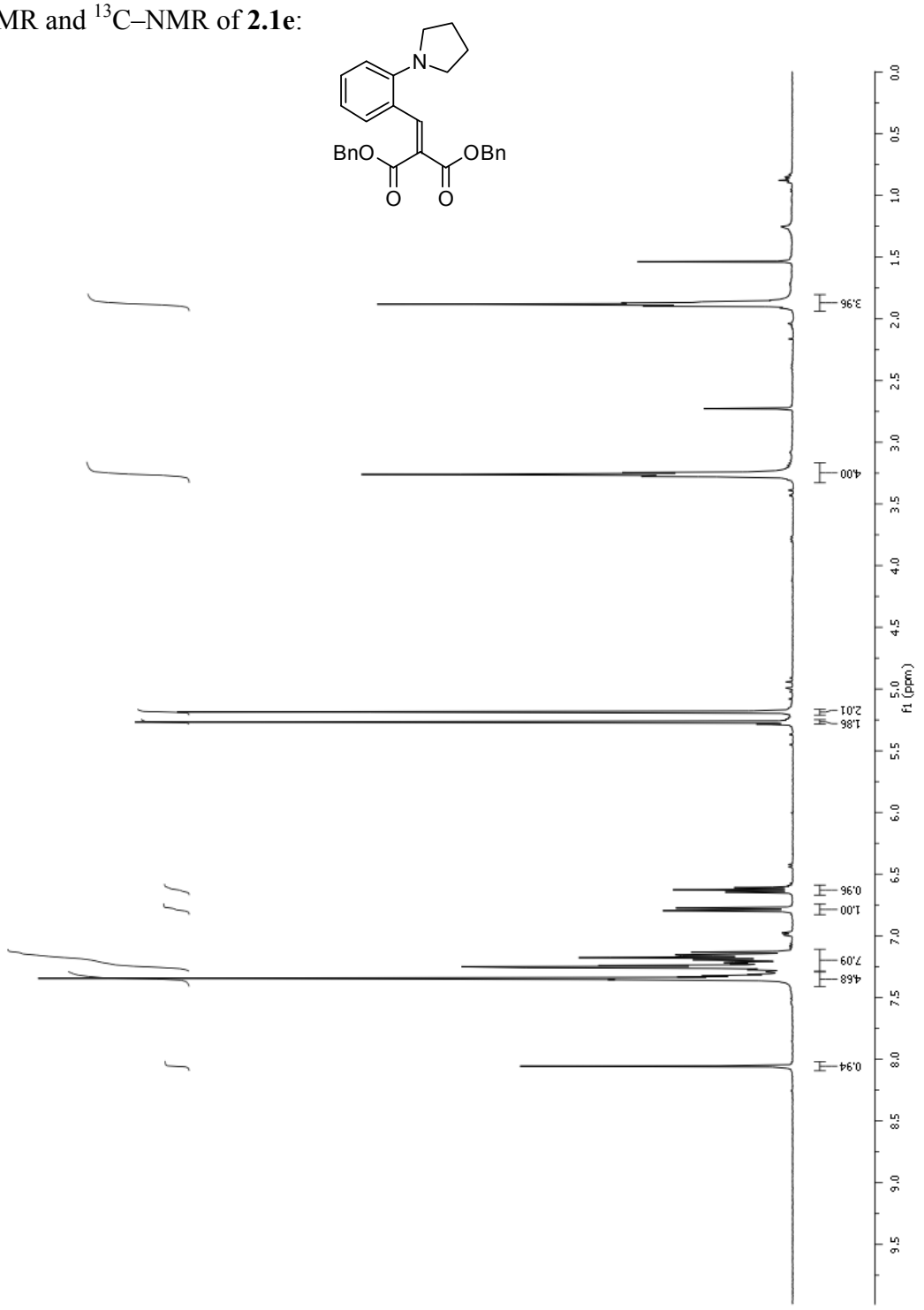

N
iPrO2C
CO2iPr
F1 (ppm)

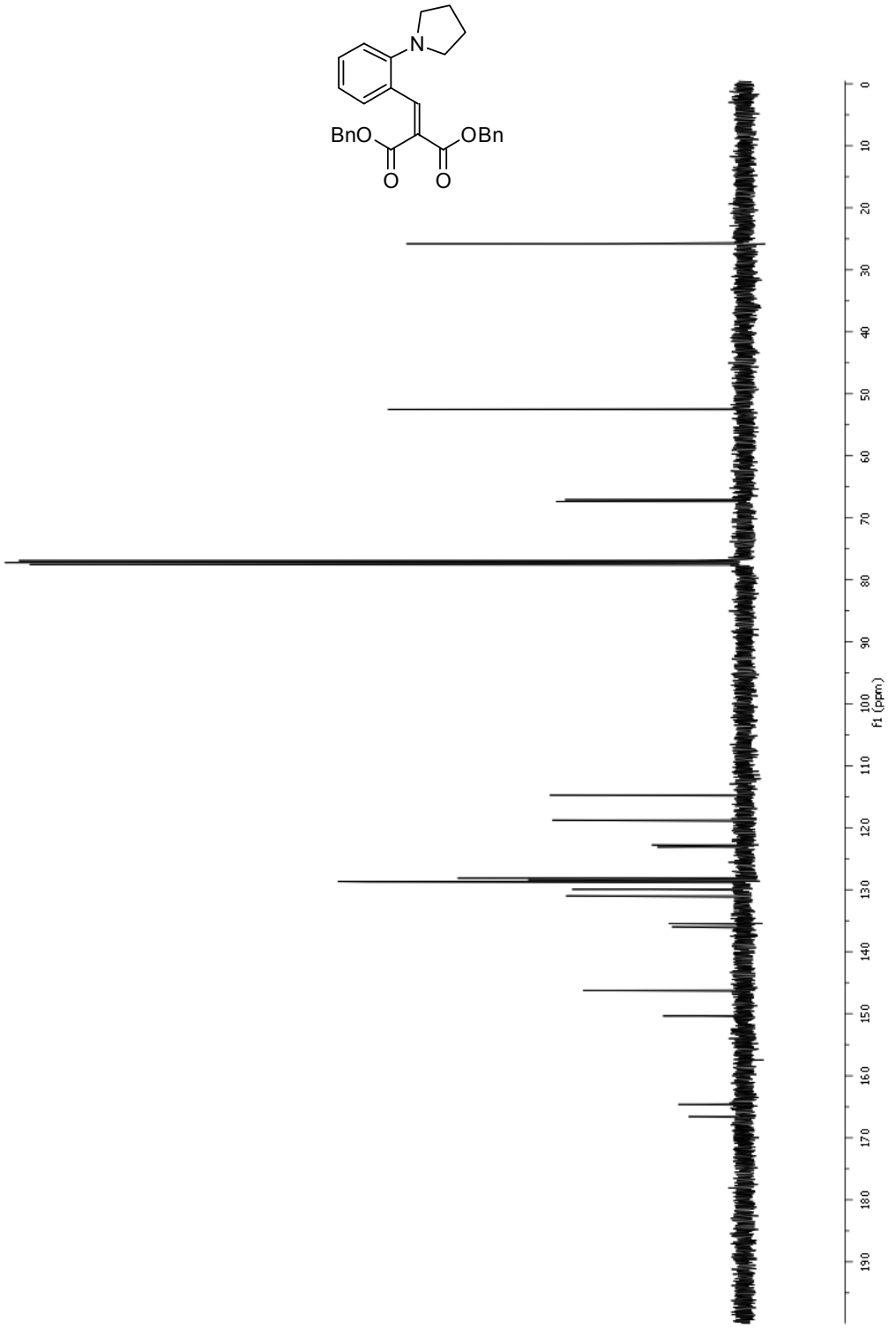
^{1}H–NMR and ^{13}C–NMR of **2.1d**:



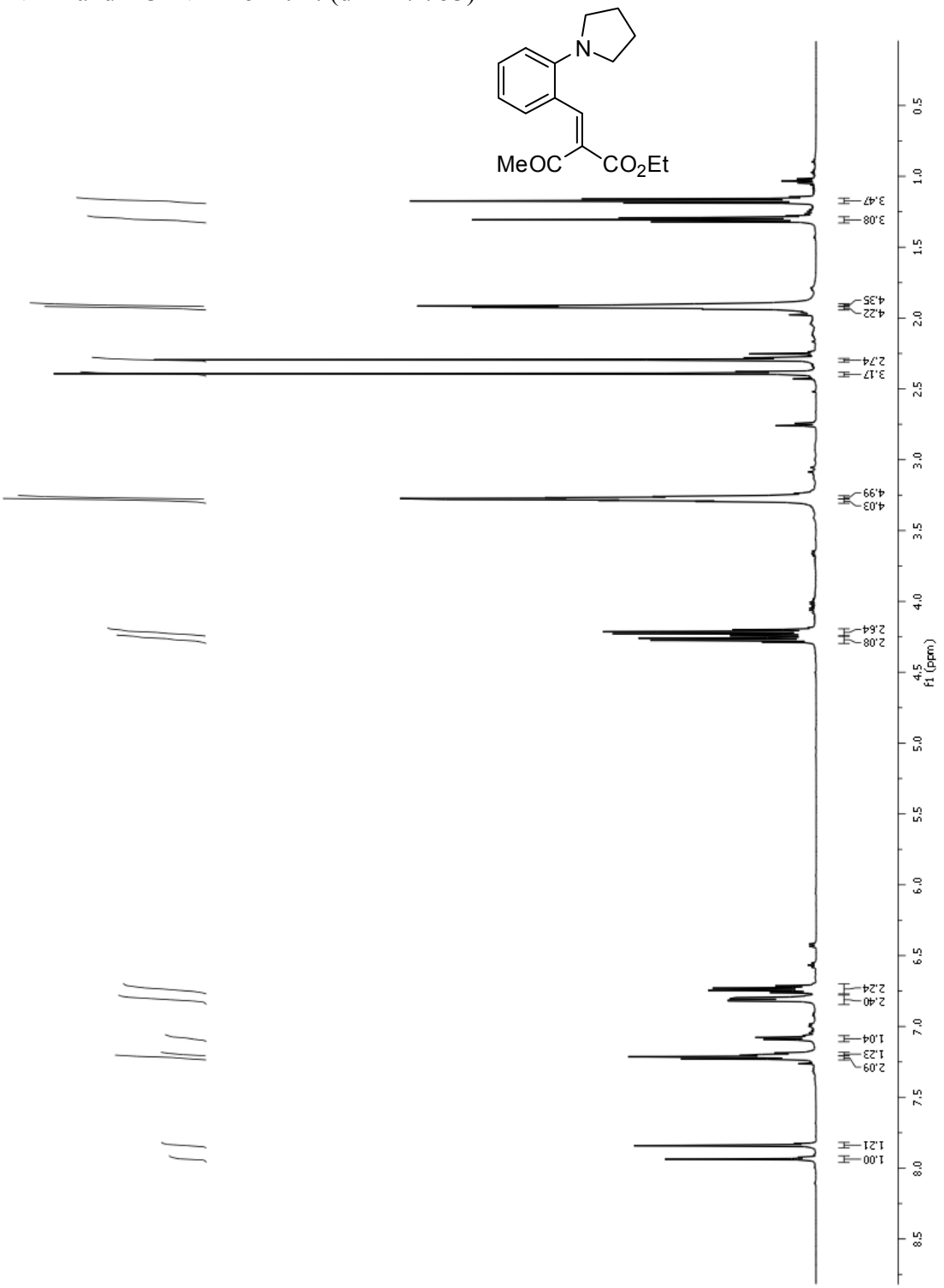

N
tBuO2C
CO2tBu
f1 (ppm)

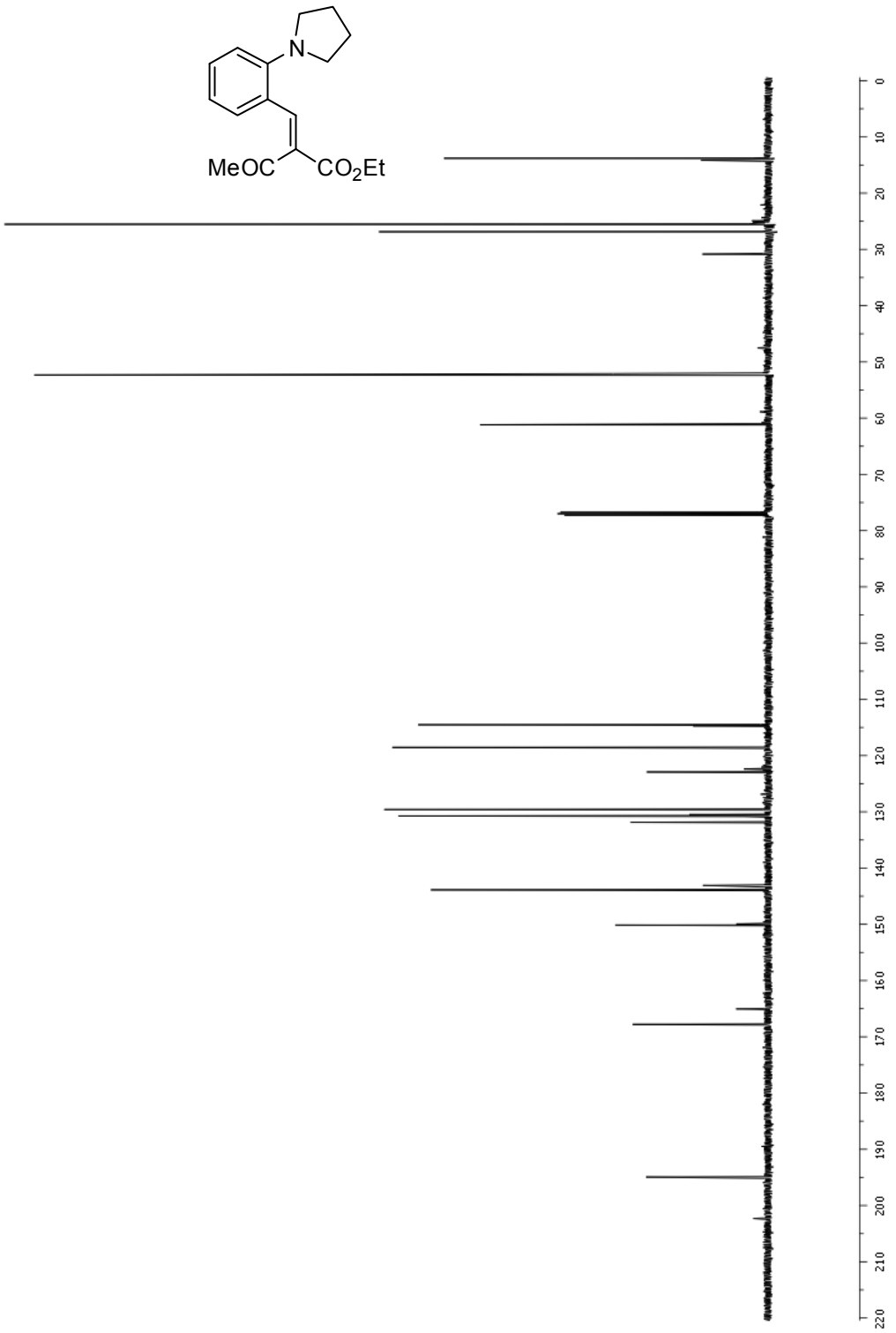
^{1}H–NMR and ^{13}C–NMR of **2.1e**:



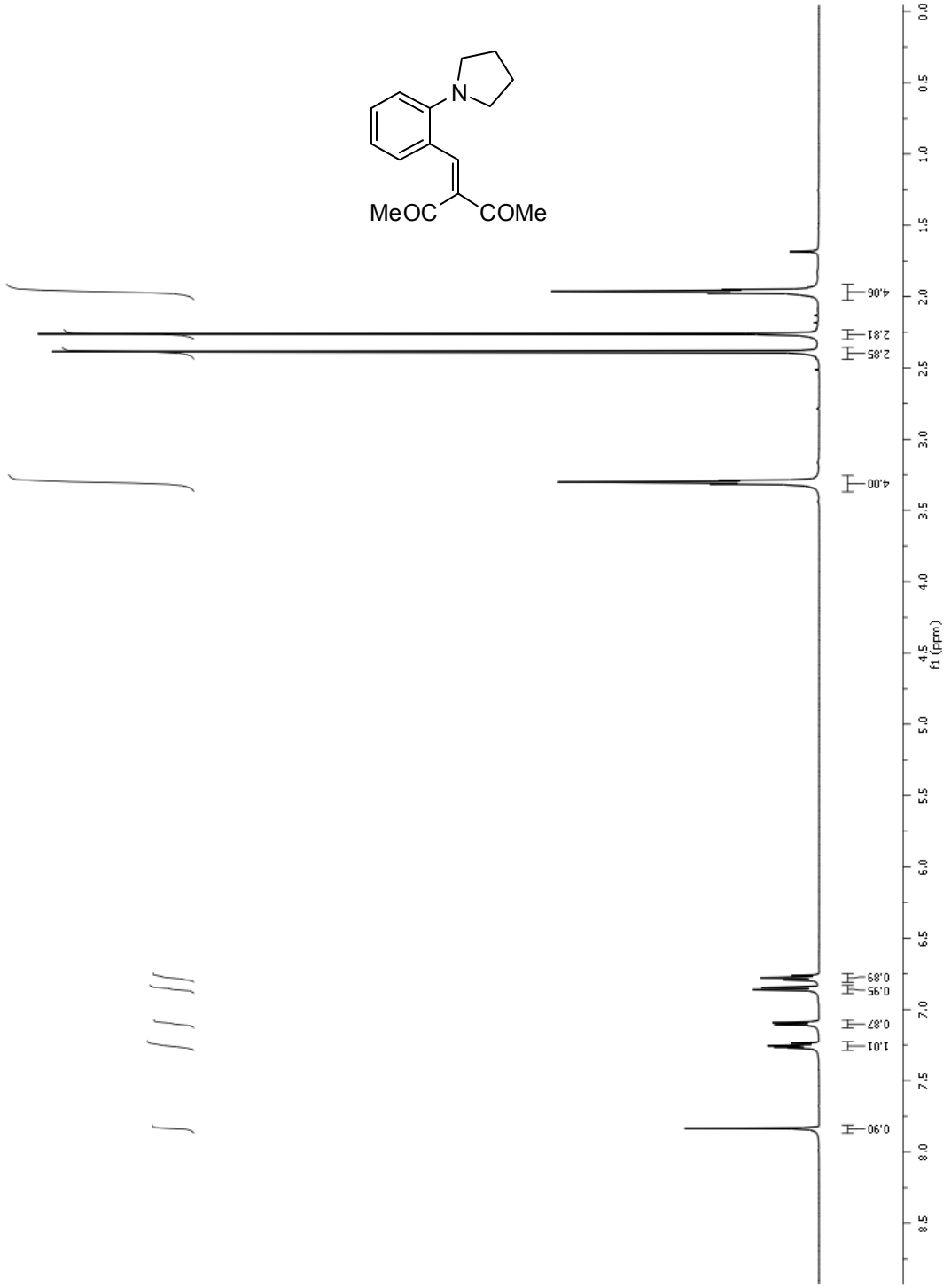

N
BnO
OBn
O
O
F1 (ppm)

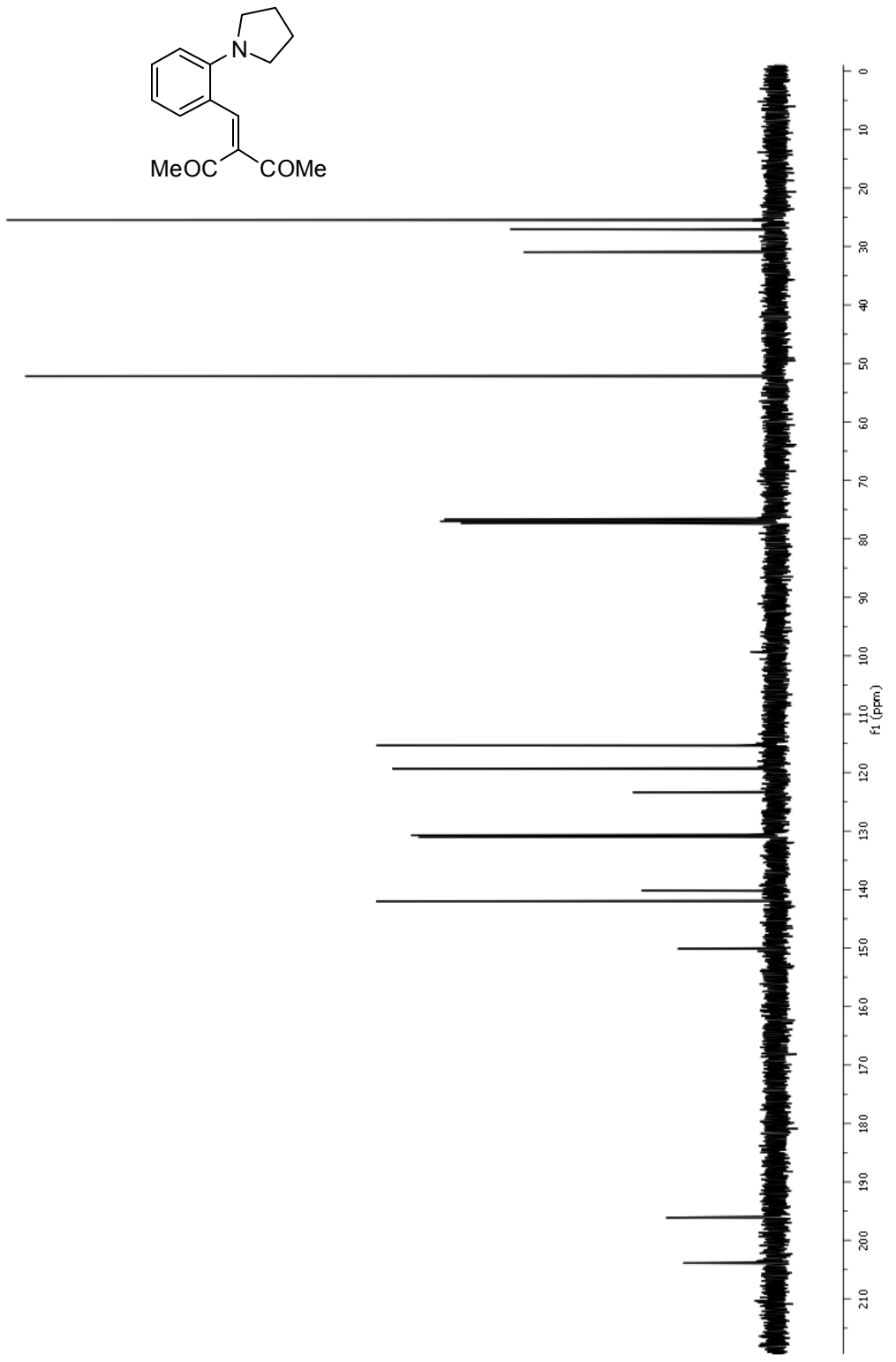
^{1}H–NMR and ^{13}C–NMR of **2.1f**: (dr = 47 : 53)



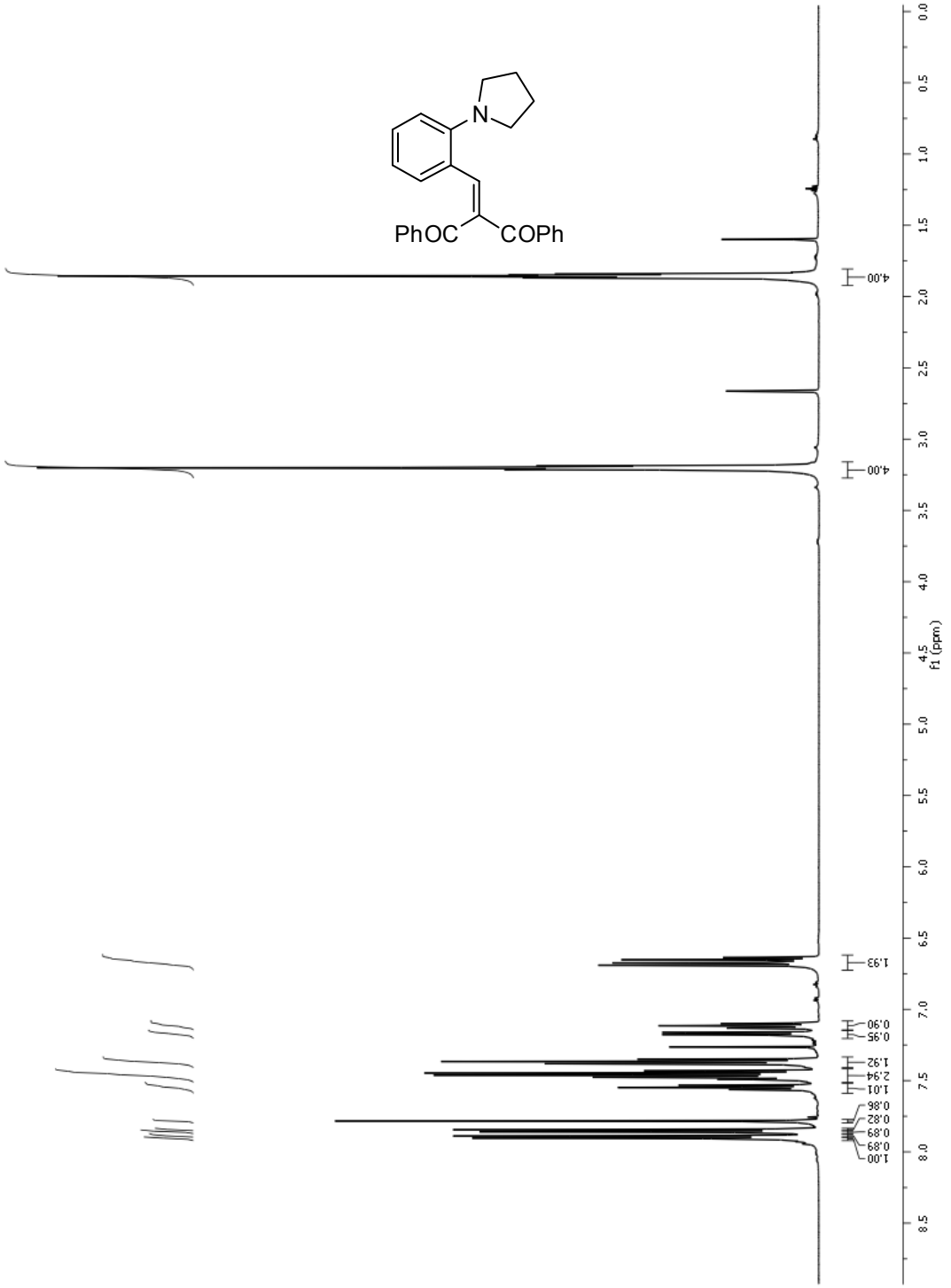

N
MeOC
CO2Et
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

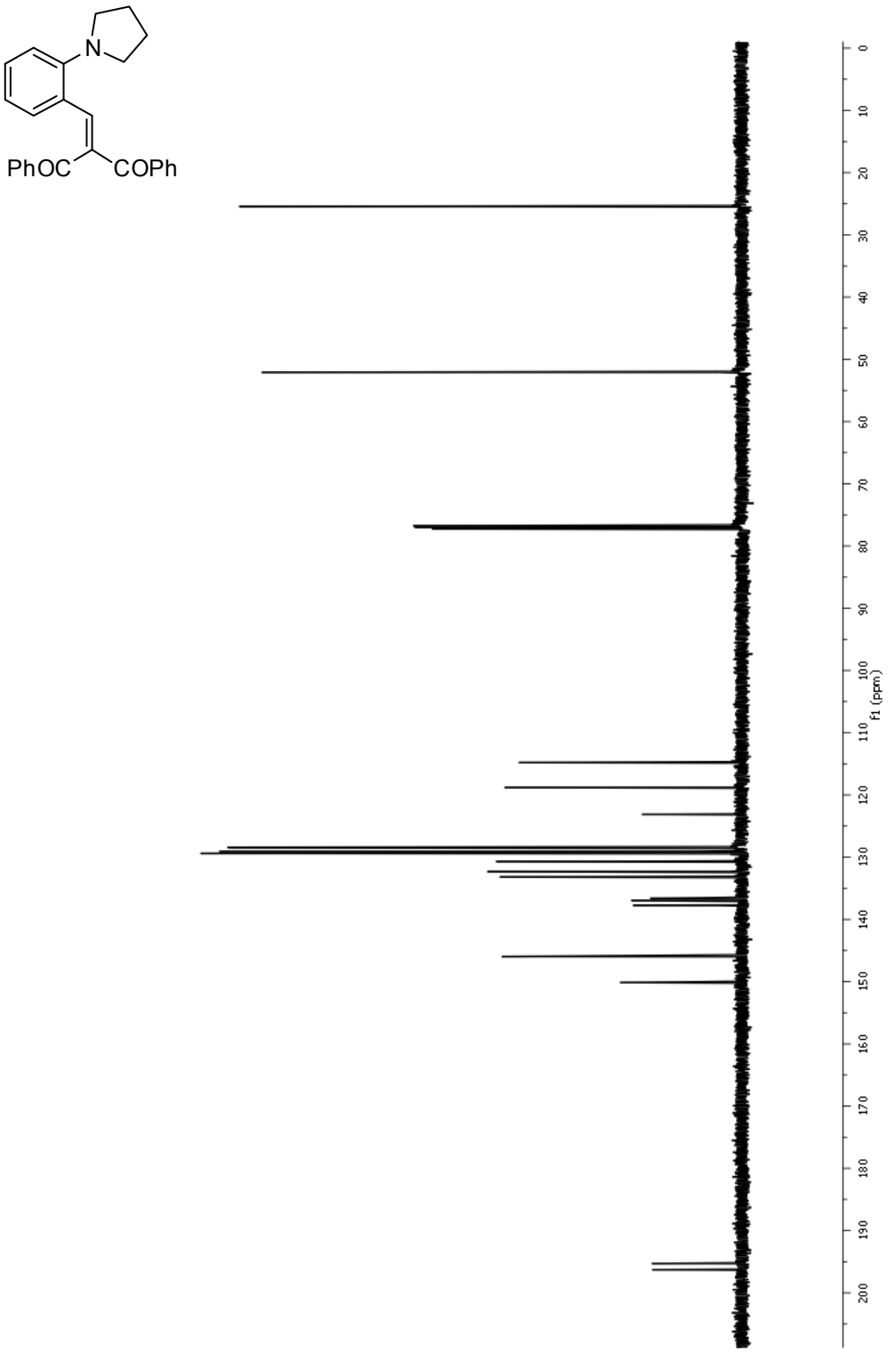
^{1}H–NMR and ^{13}C–NMR of **2.1g**:



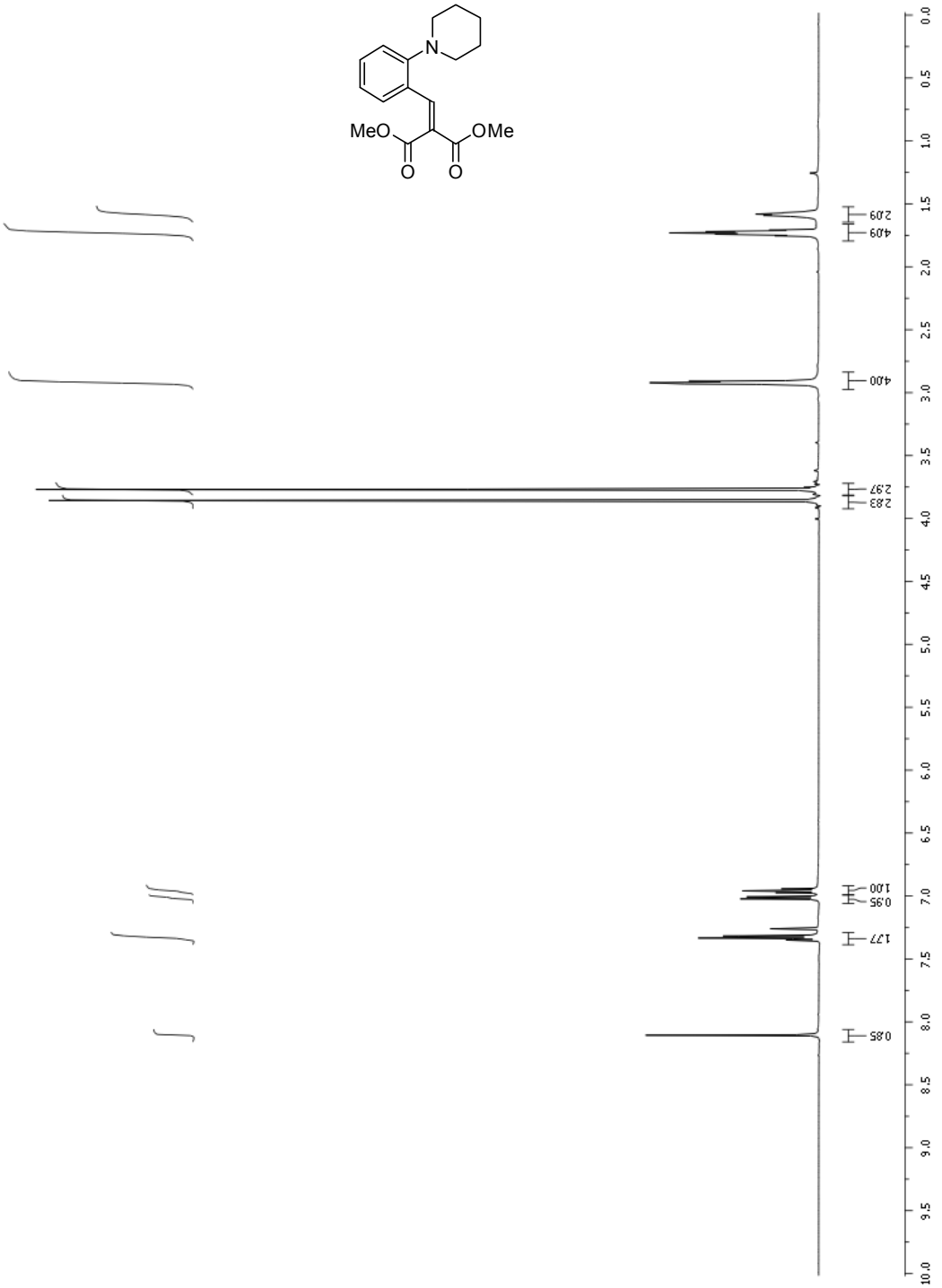

N
MeOC
COMe
f1 (ppm)

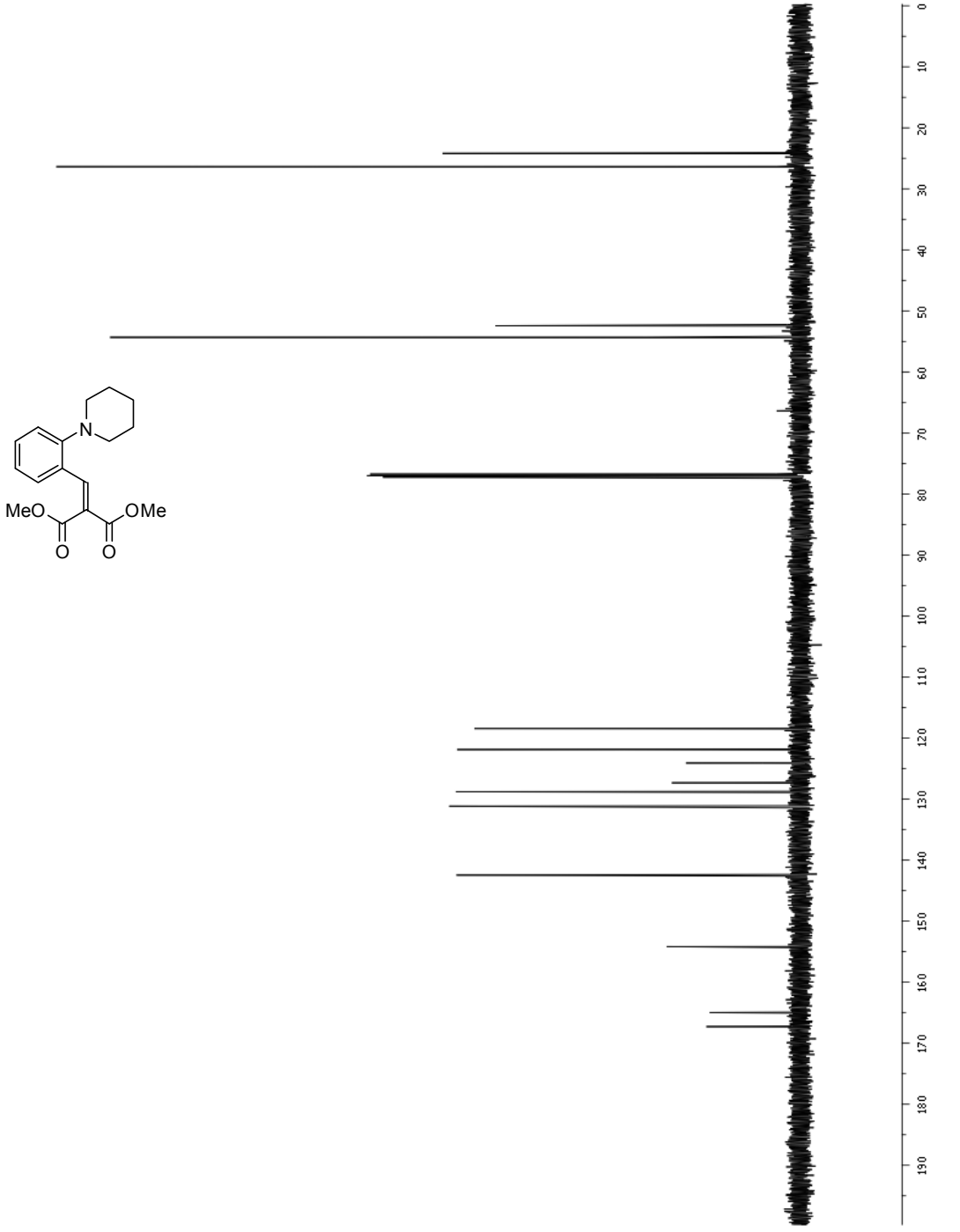
^{1}H–NMR and ^{13}C–NMR of **2.1h**:



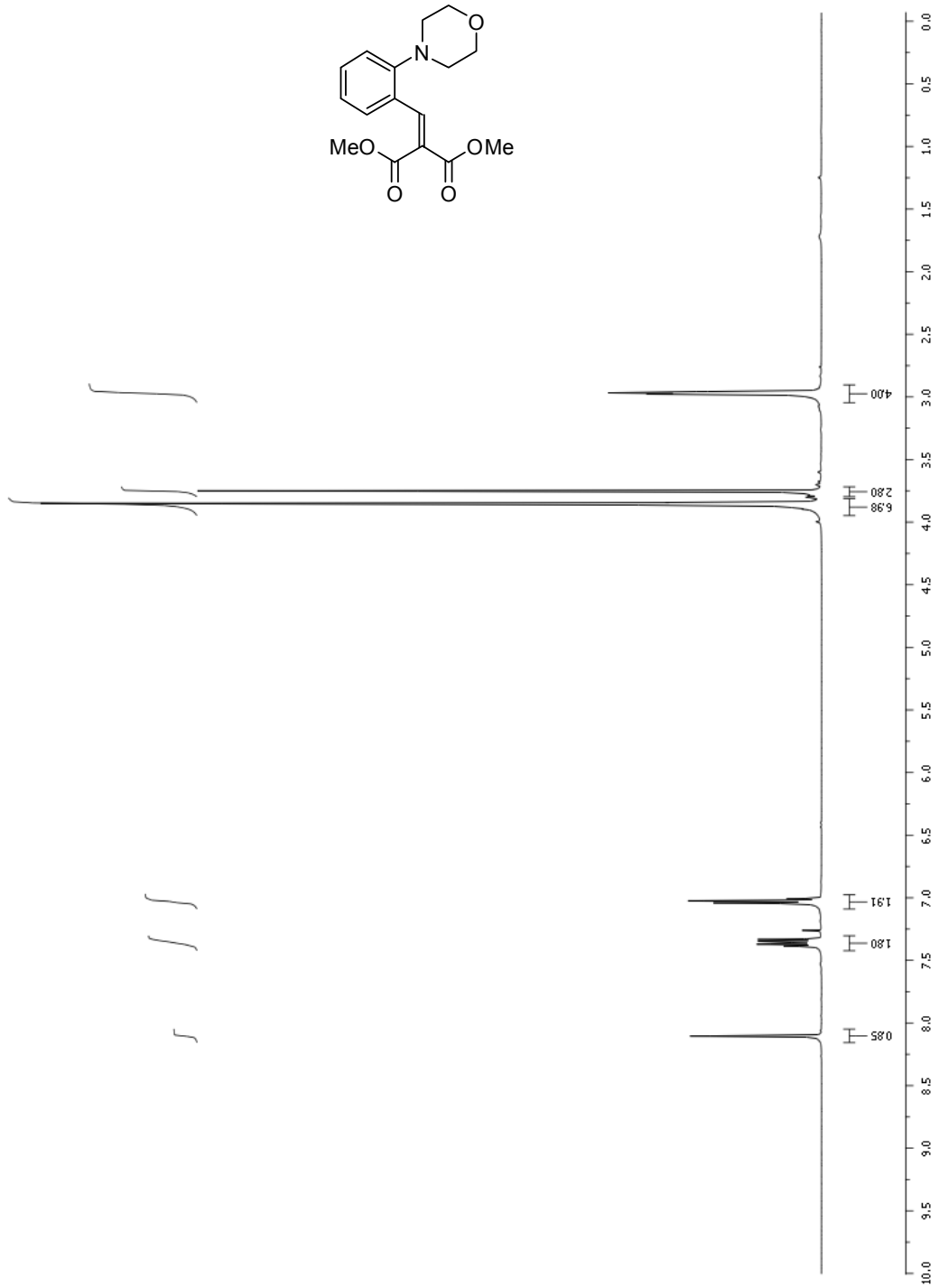

N
PhOC
COPh
f1 (ppm)

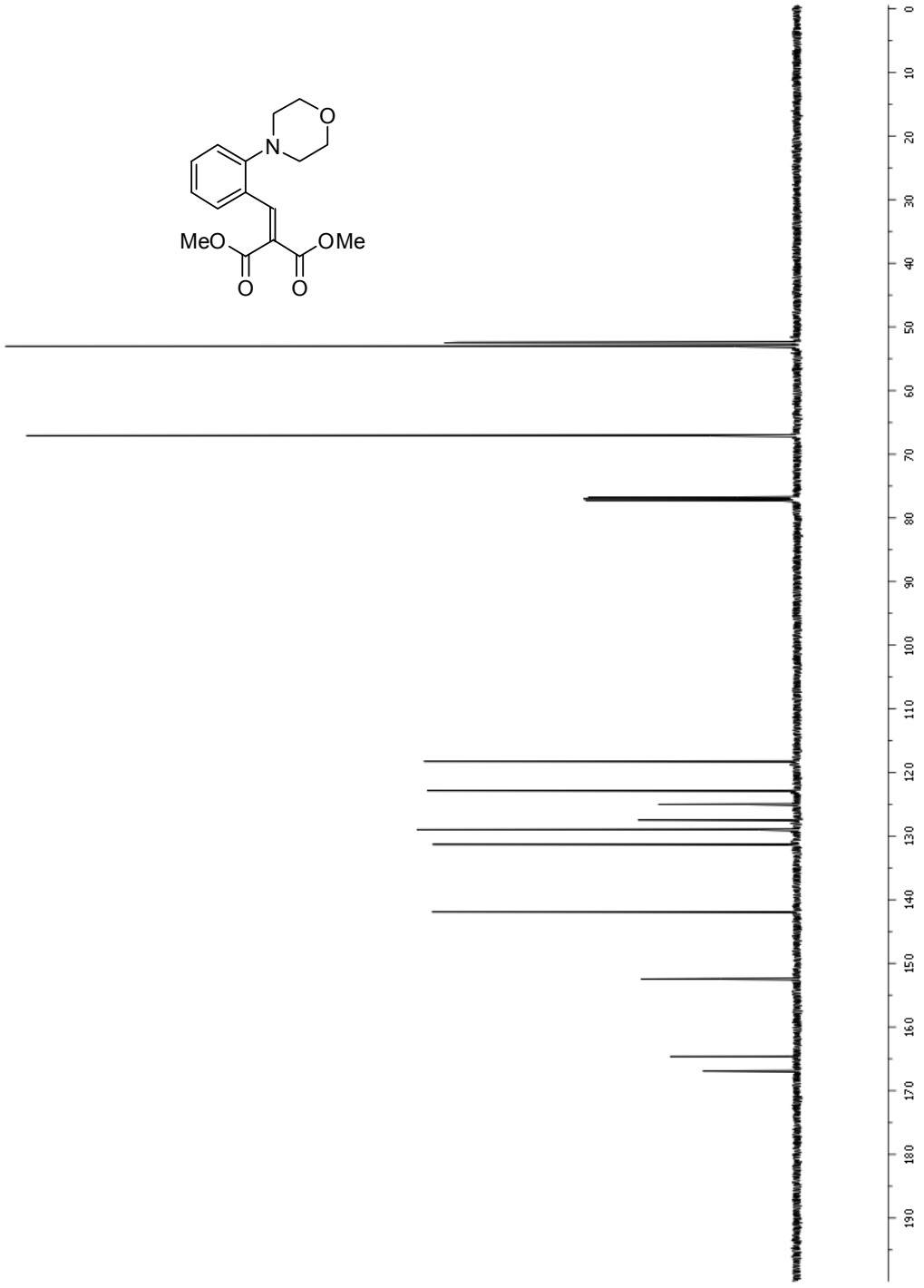
^{1}H–NMR and ^{13}C–NMR of **2.1j**:



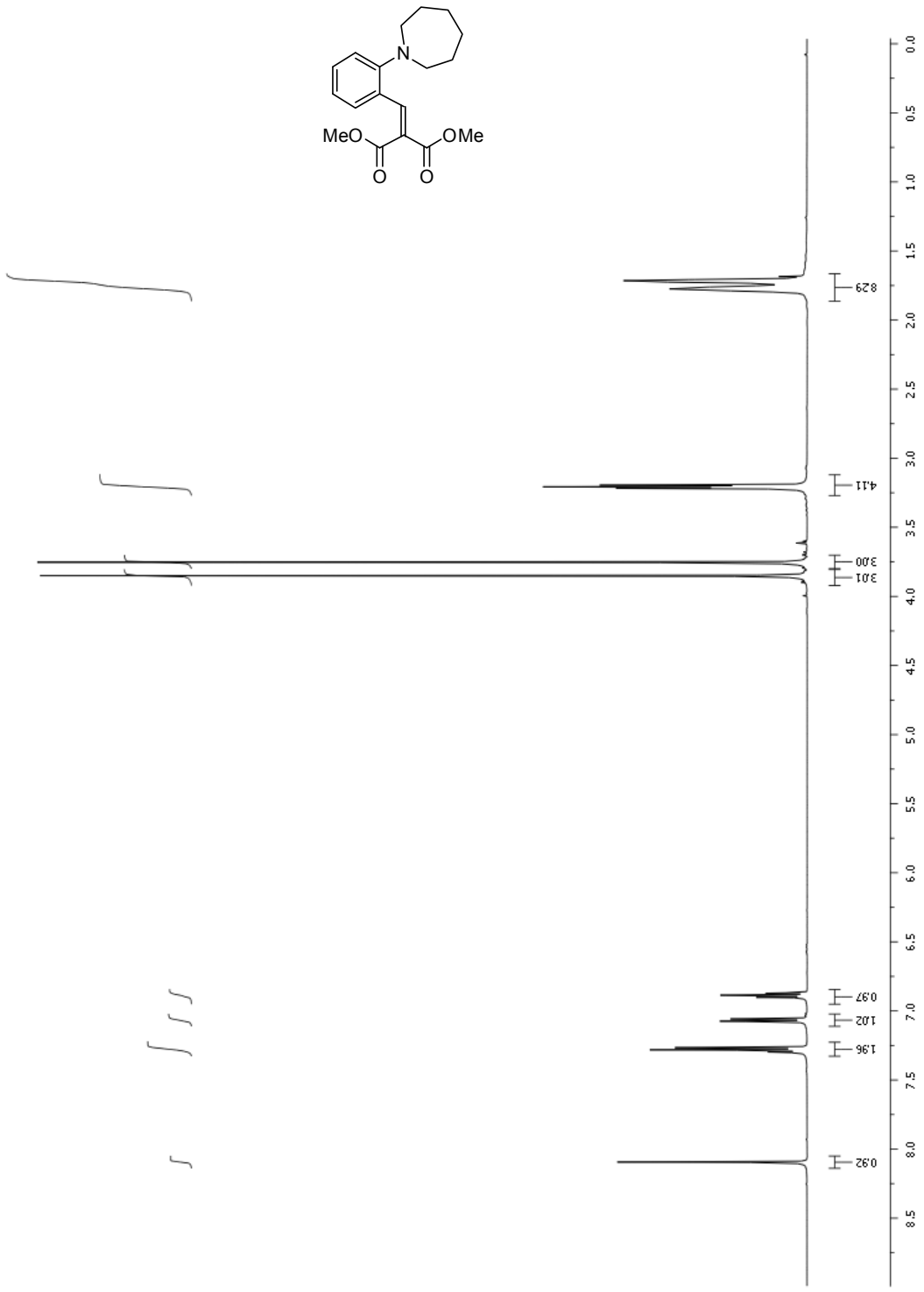

N
MeO
OMe
O
O
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

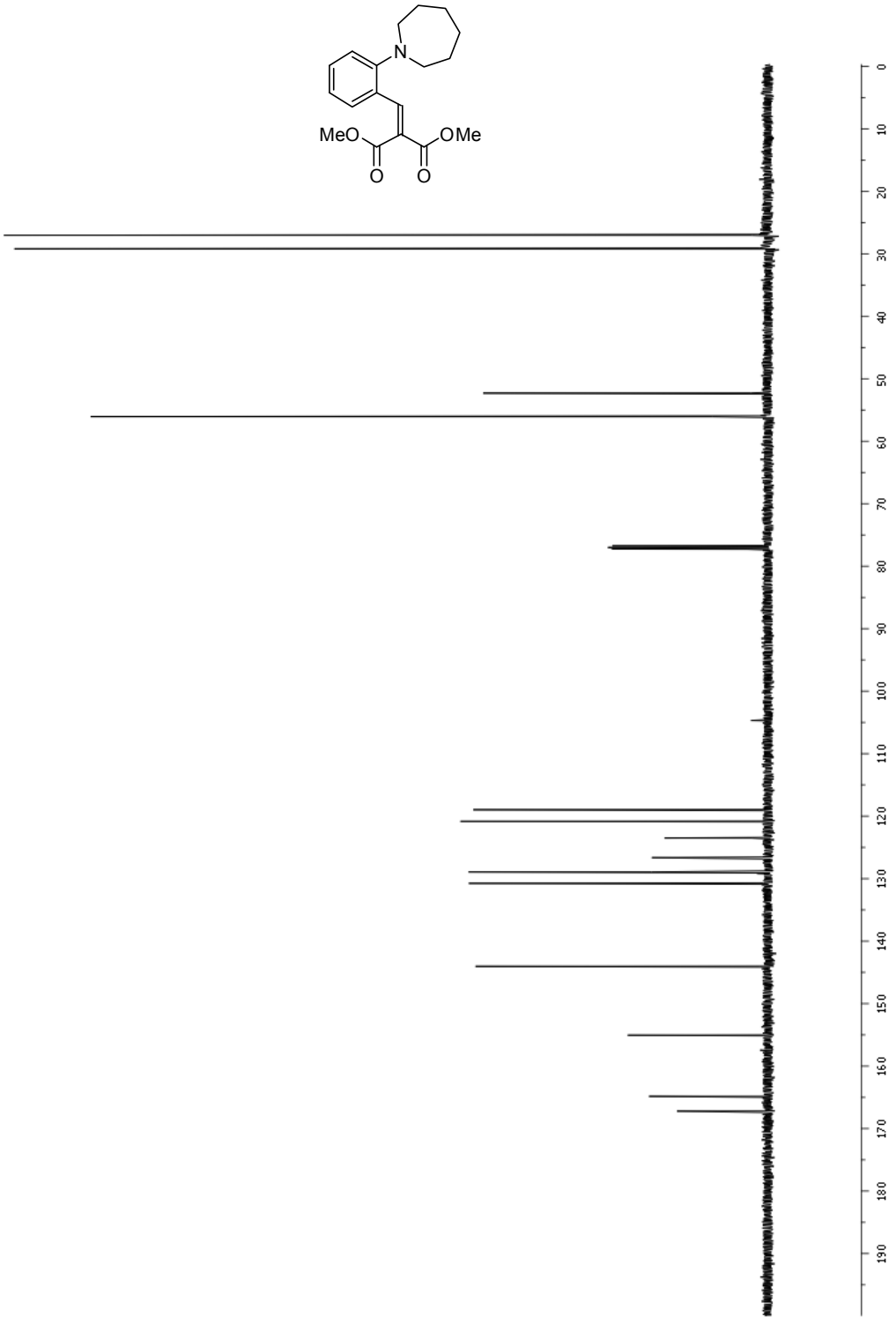
^{1}H–NMR and ^{13}C–NMR of **2.1k**:



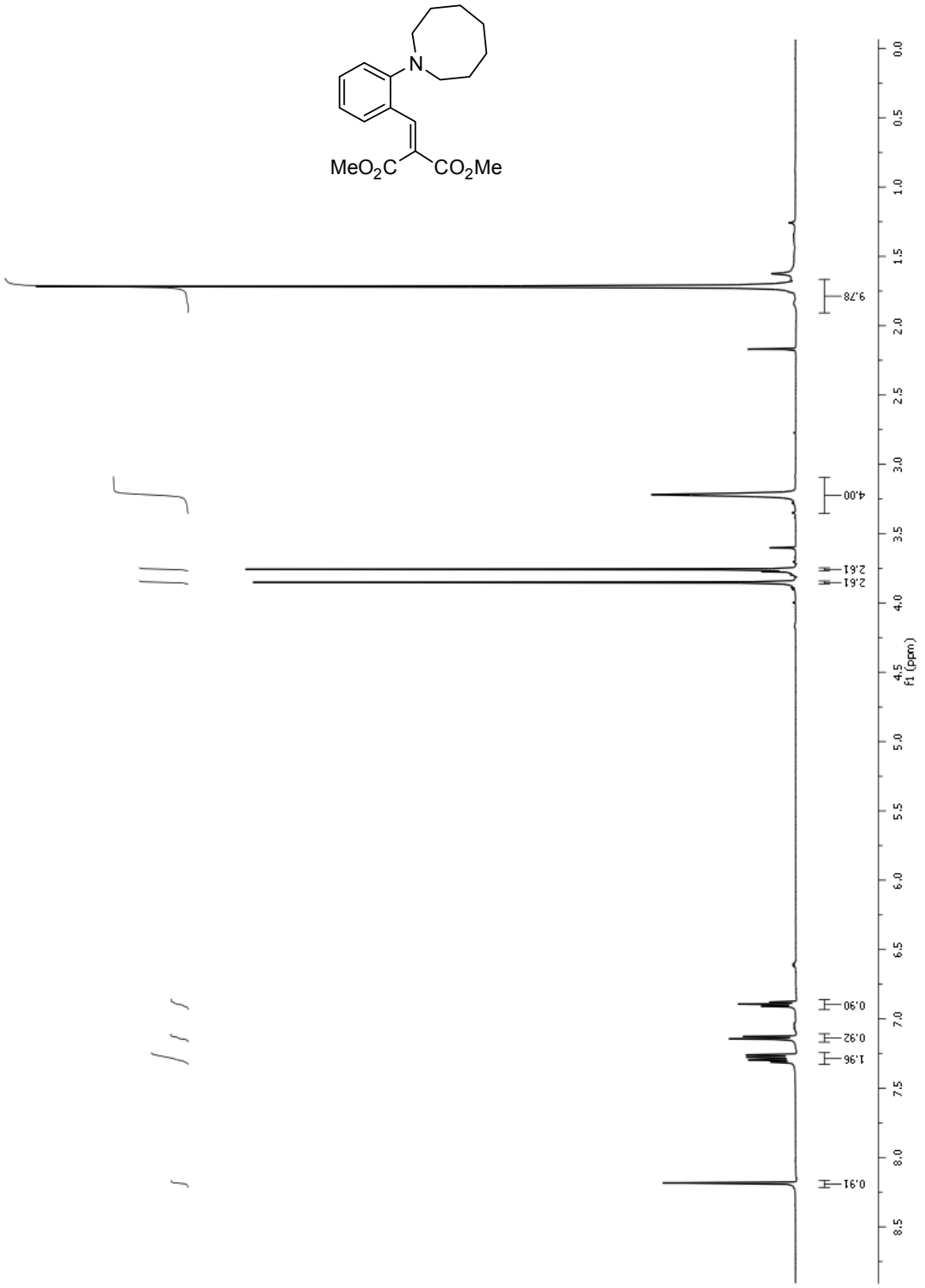

O
N
MeO
OMe
O
O

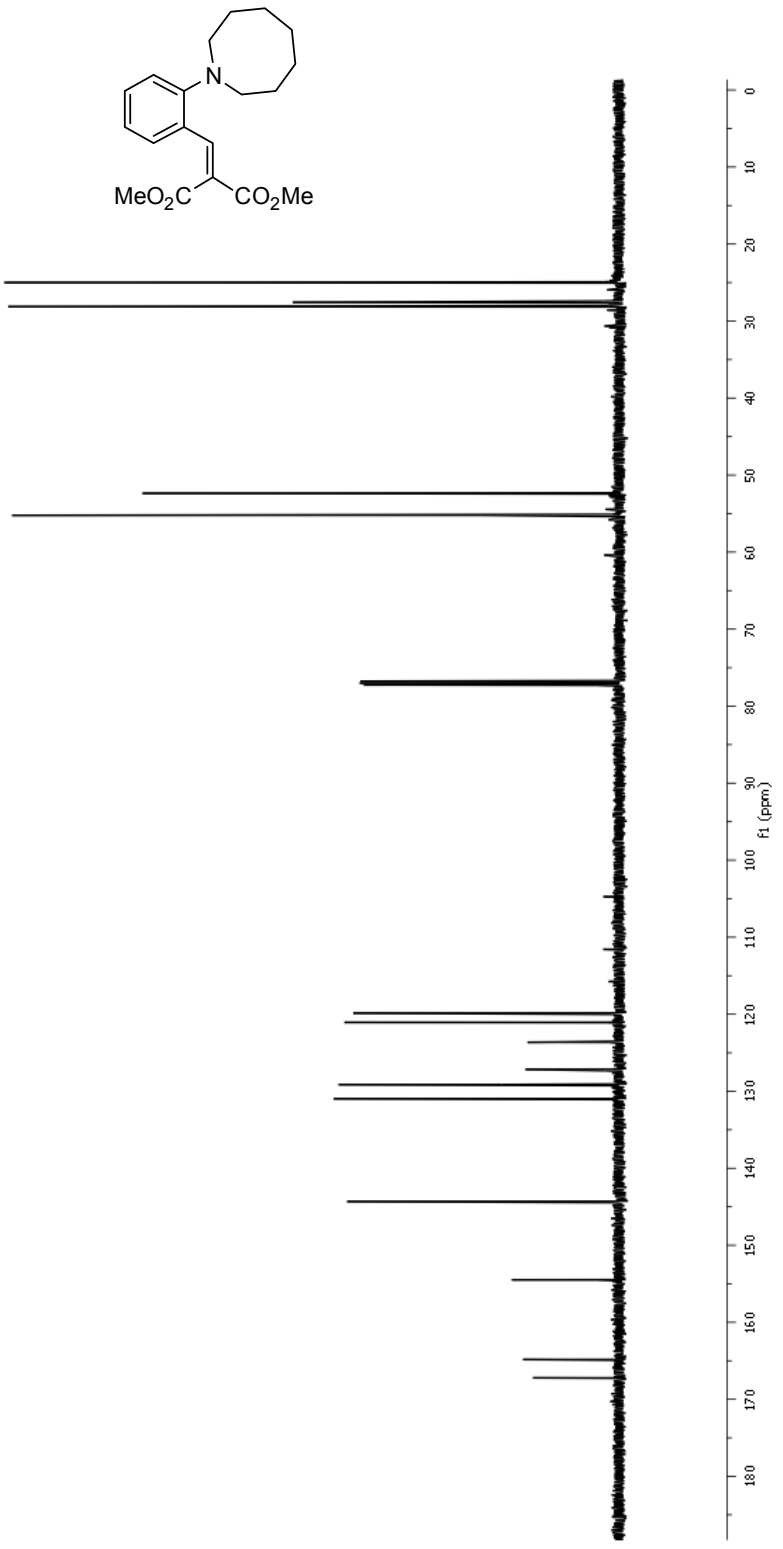
^{1}H–NMR and ^{13}C–NMR of **2.1l**:



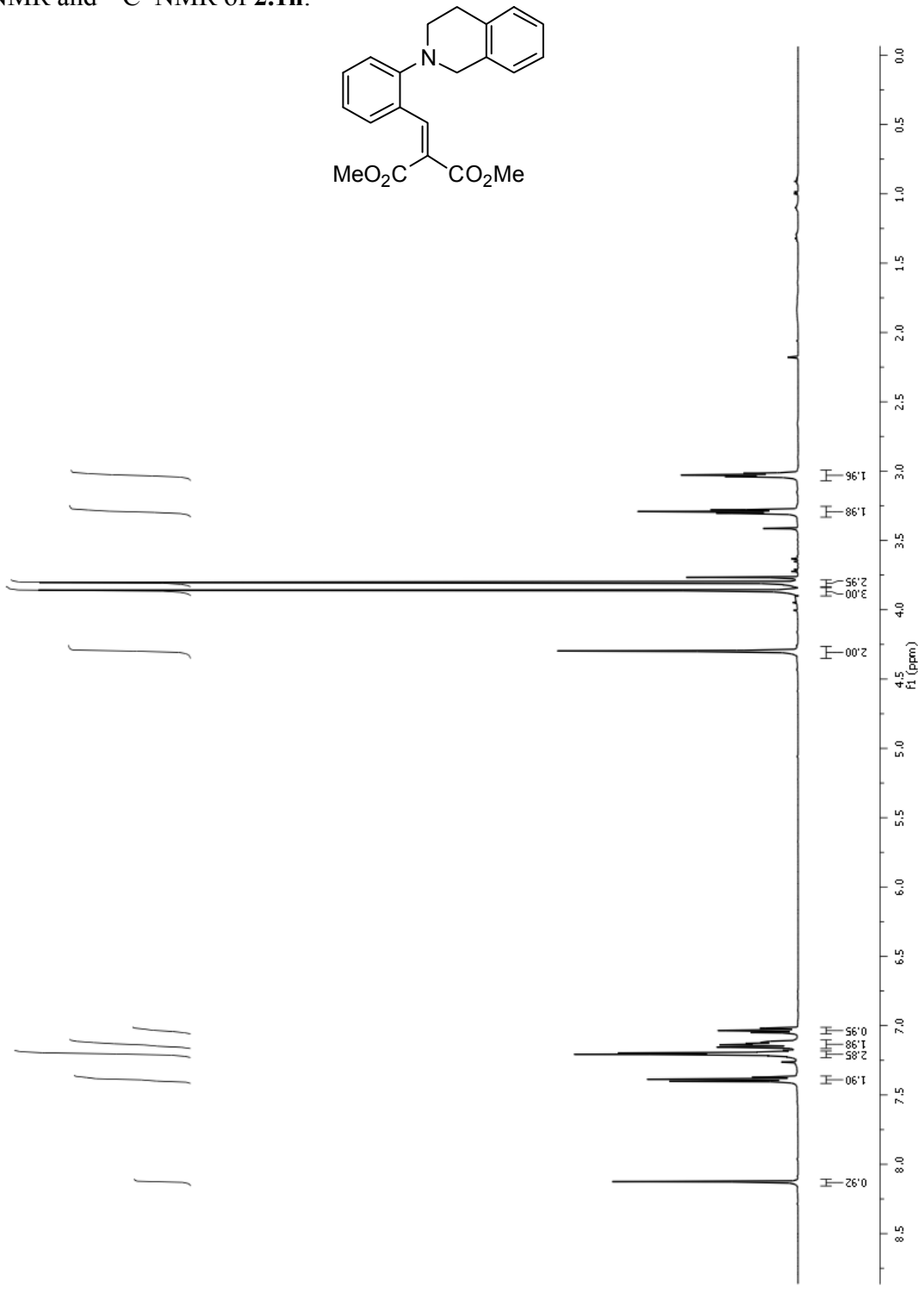

N
MeO
OMe
O
O
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

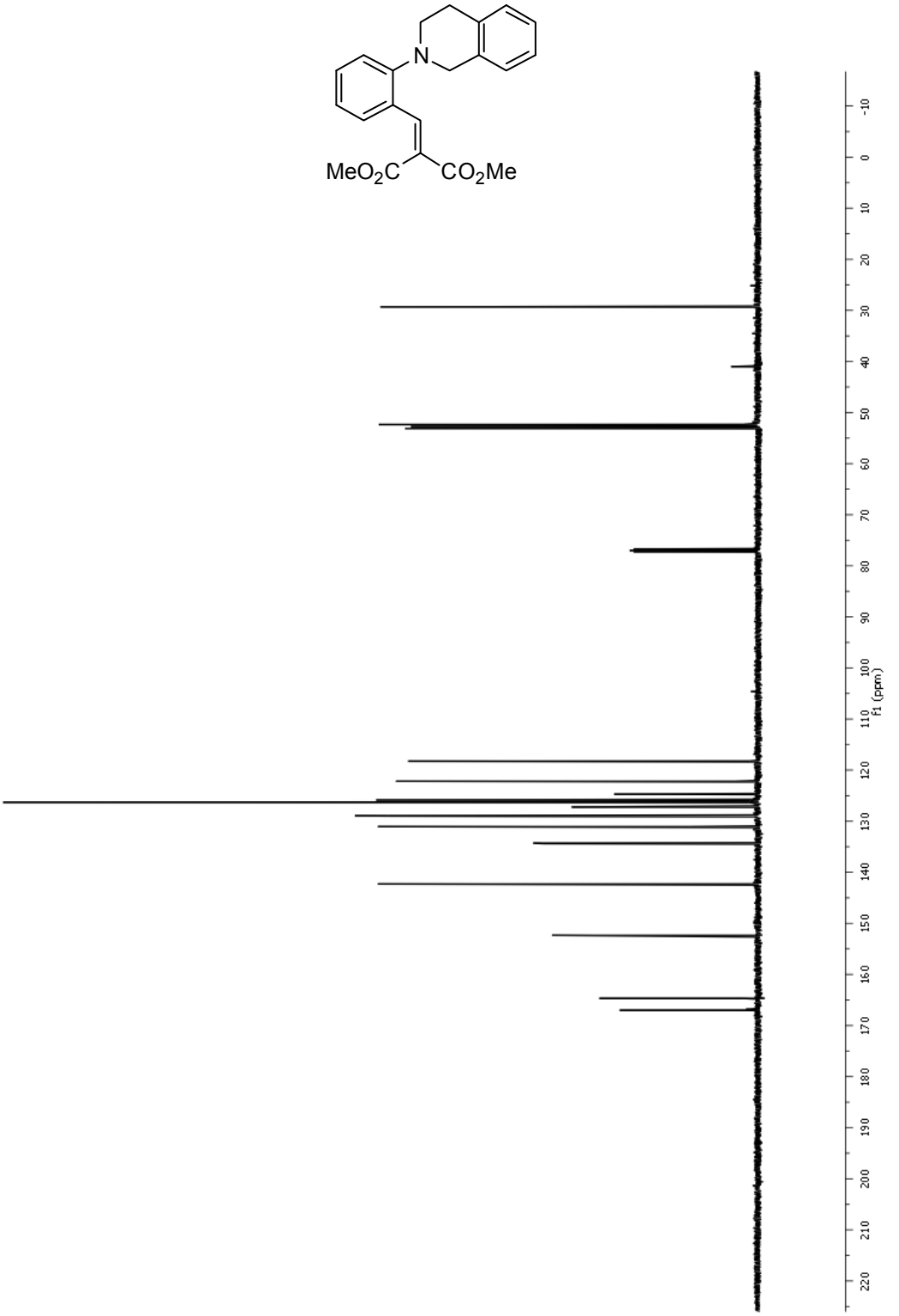
^{1}H–NMR and ^{13}C–NMR of **2.1m**:



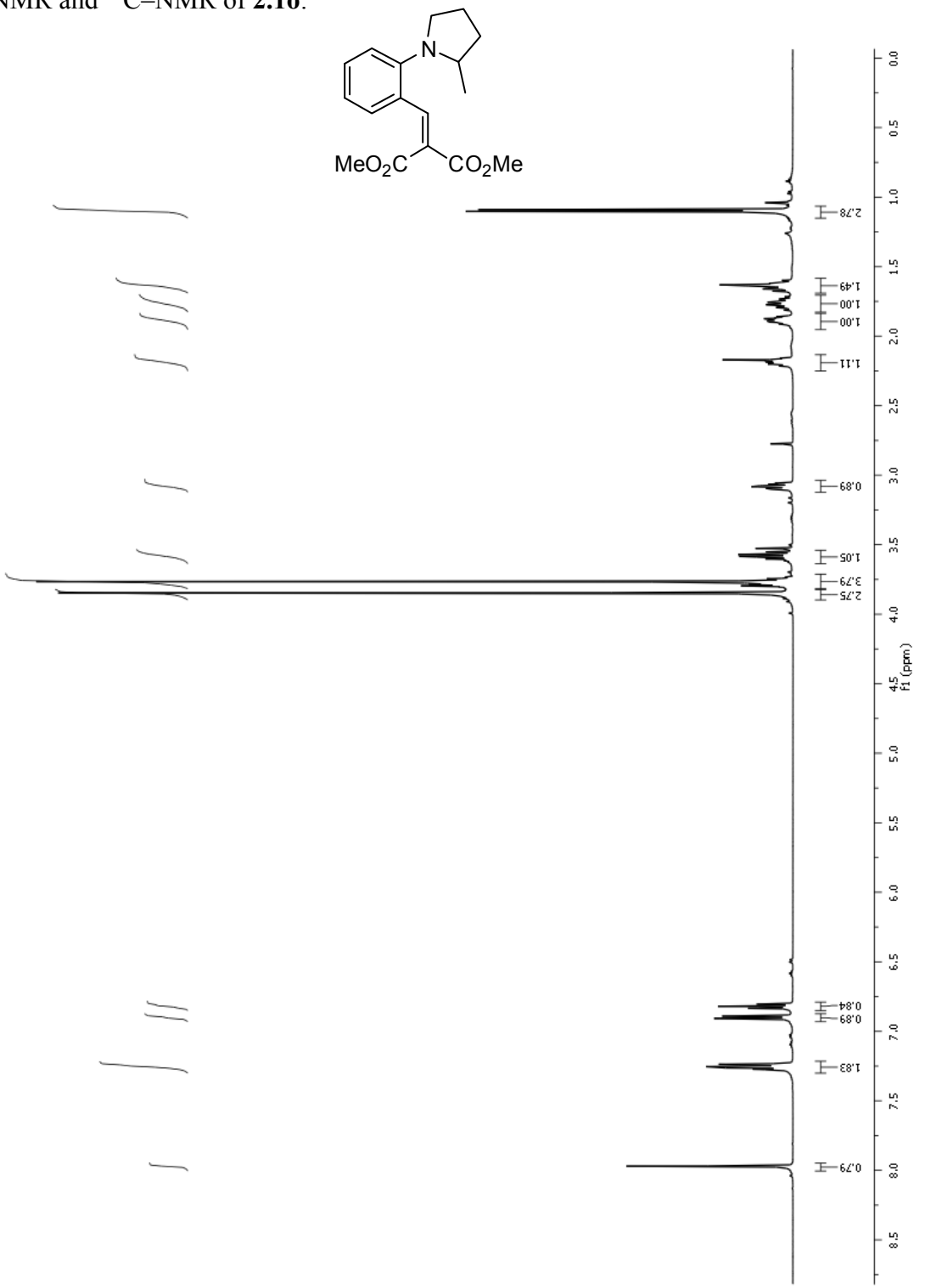

N
MeO2C
CO2Me
f1 (ppm)

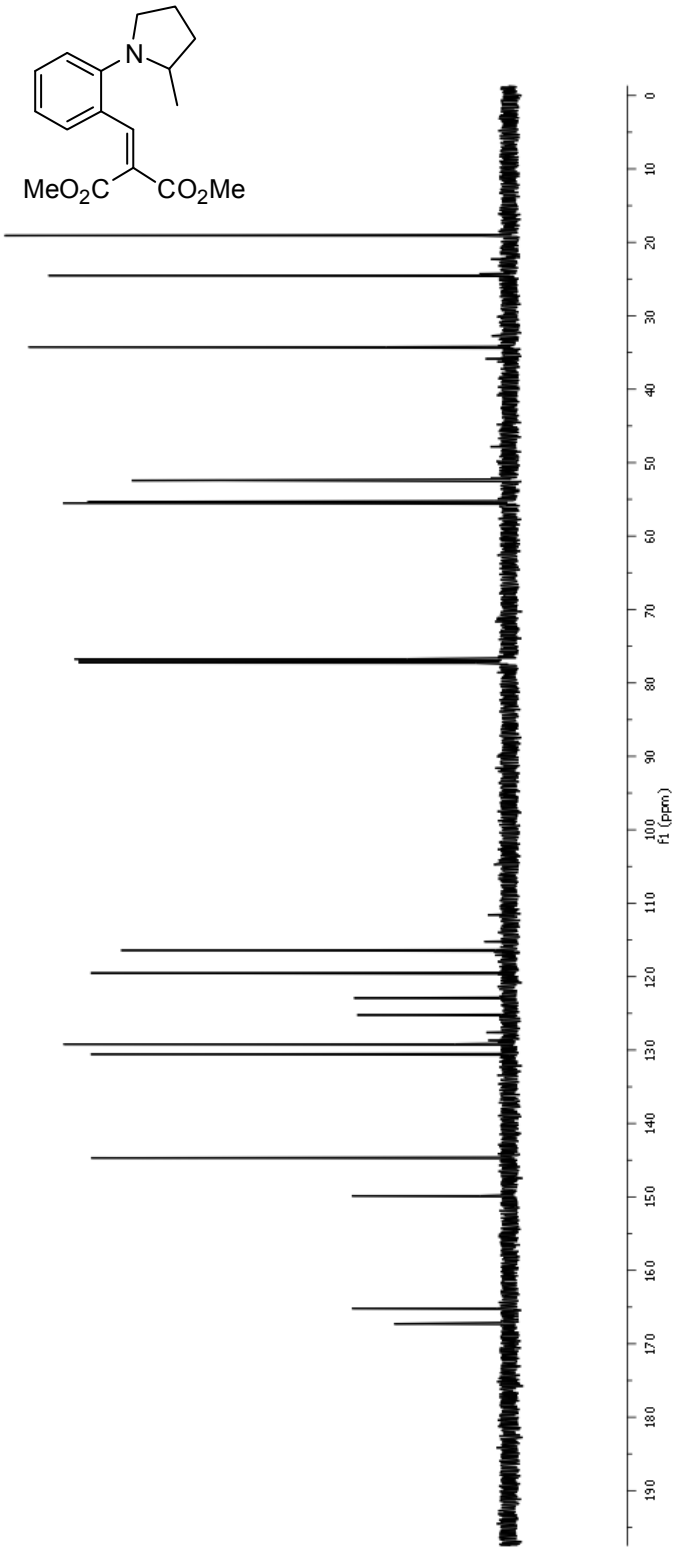
^{1}H–NMR and ^{13}C–NMR of **2.1n**:



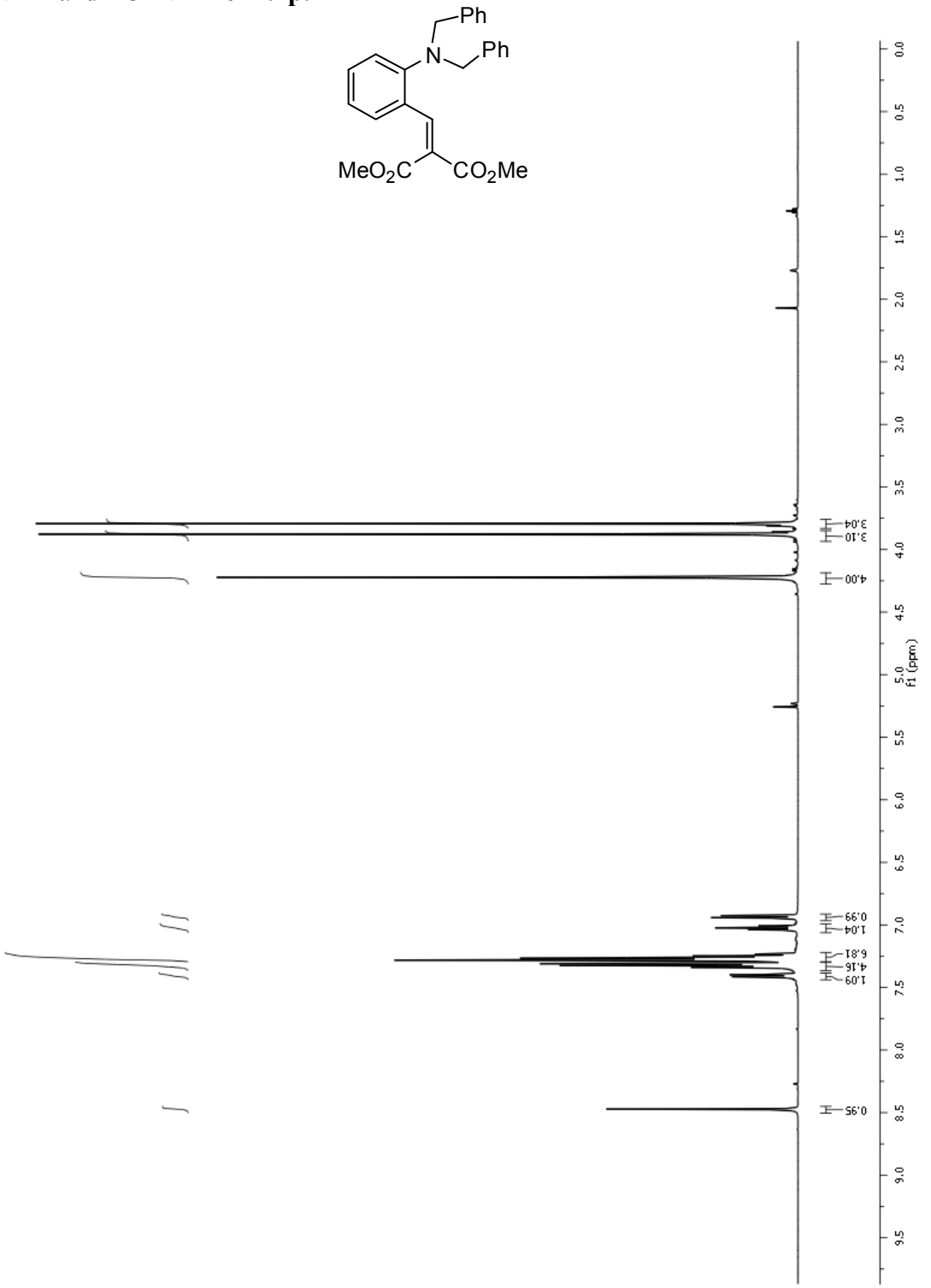

N
MeO2C
CO2Me
f1 (ppm)

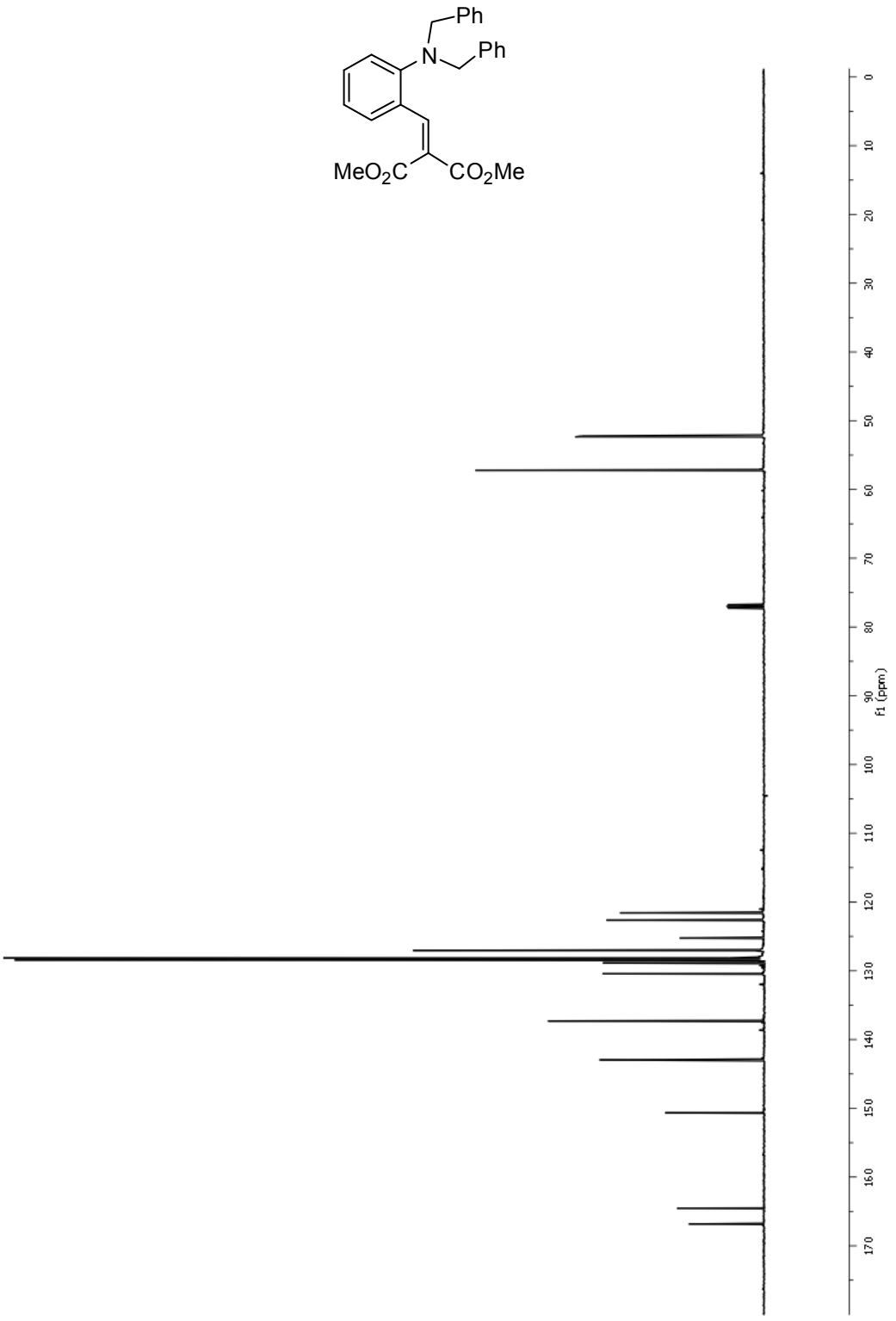
^{1}H–NMR and ^{13}C–NMR of **2.1o**:



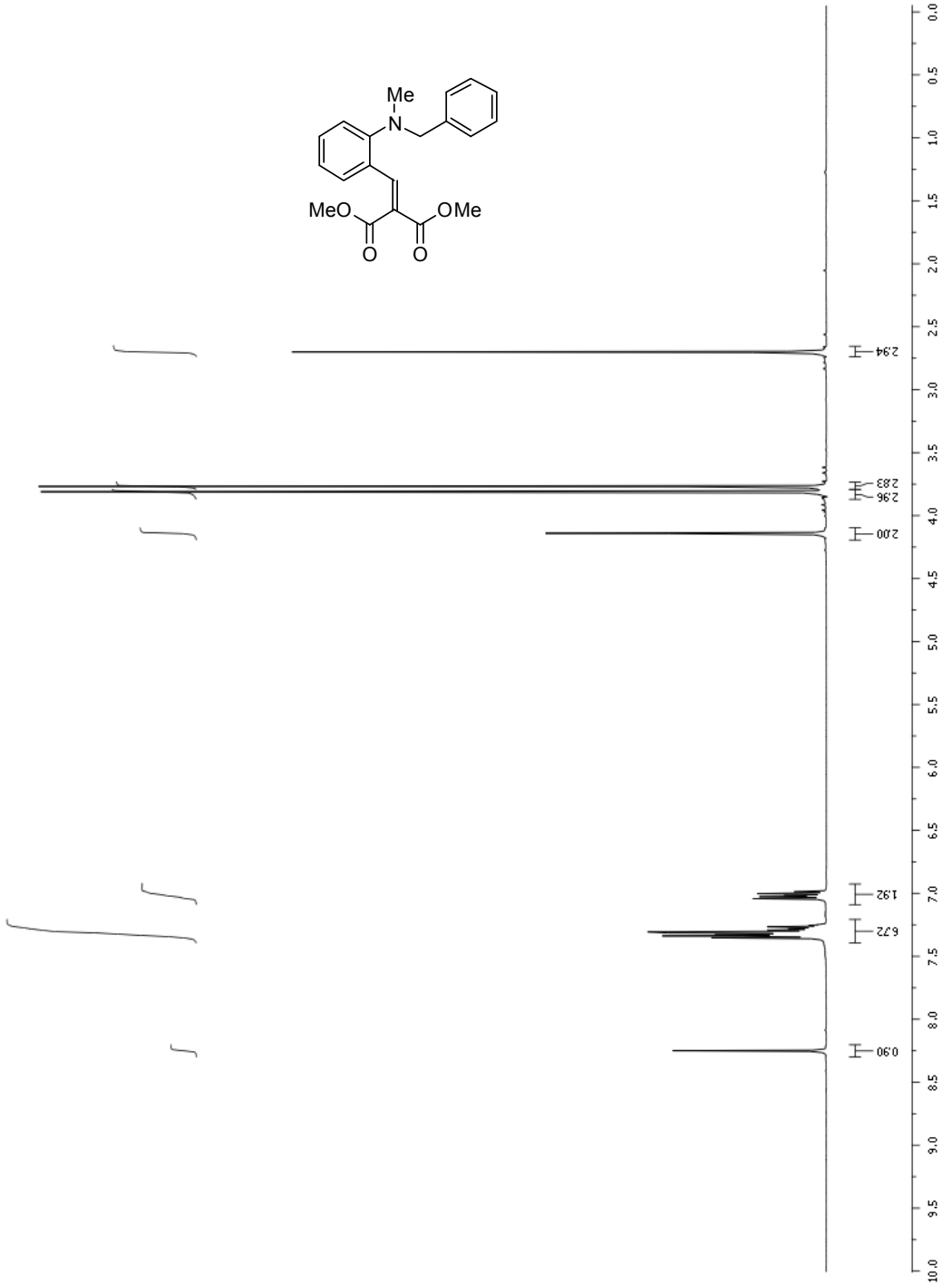

N
MeO2C
CO2Me
f1 (ppm)

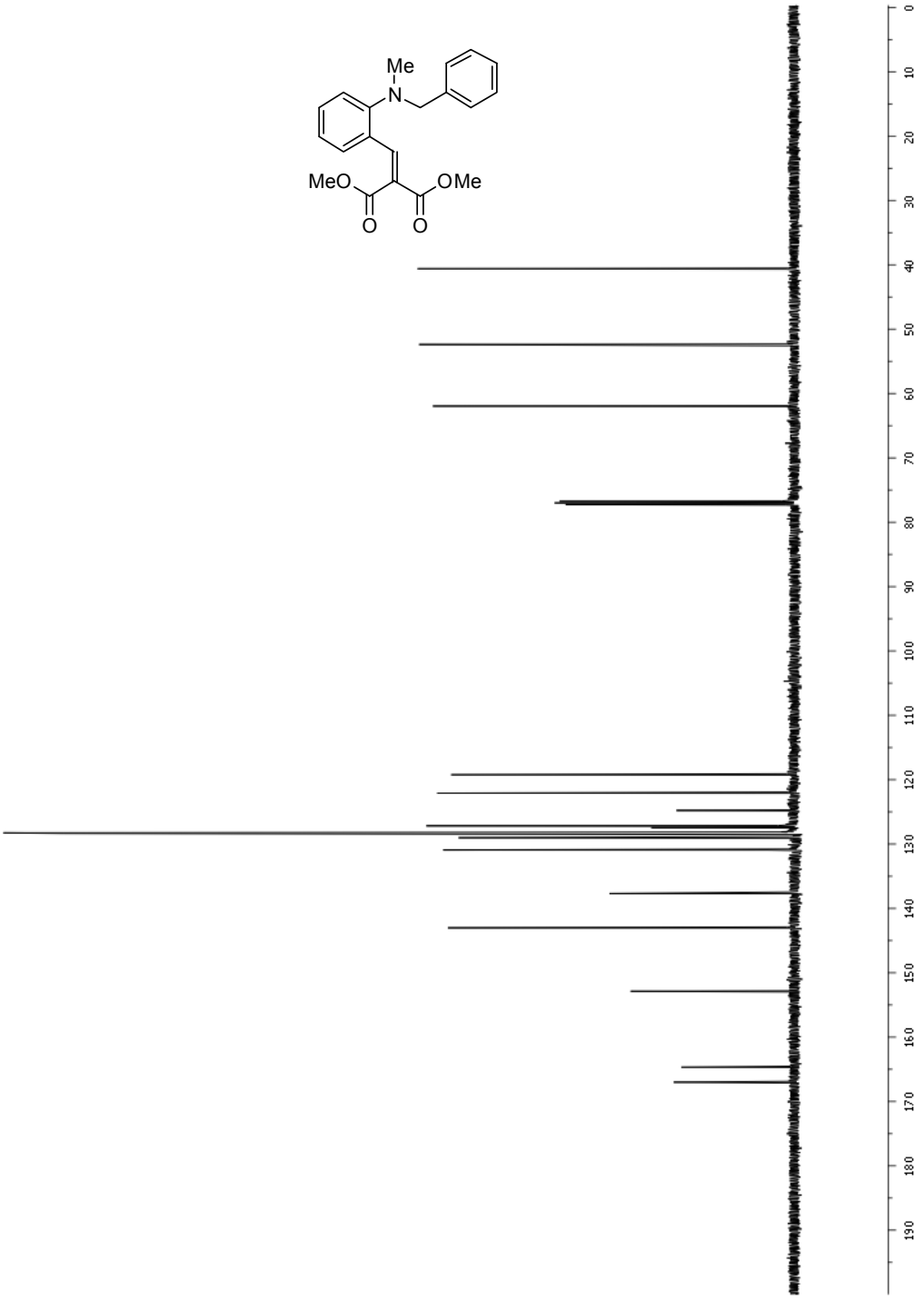
^{1}H–NMR and ^{13}C–NMR of **2.1p**:



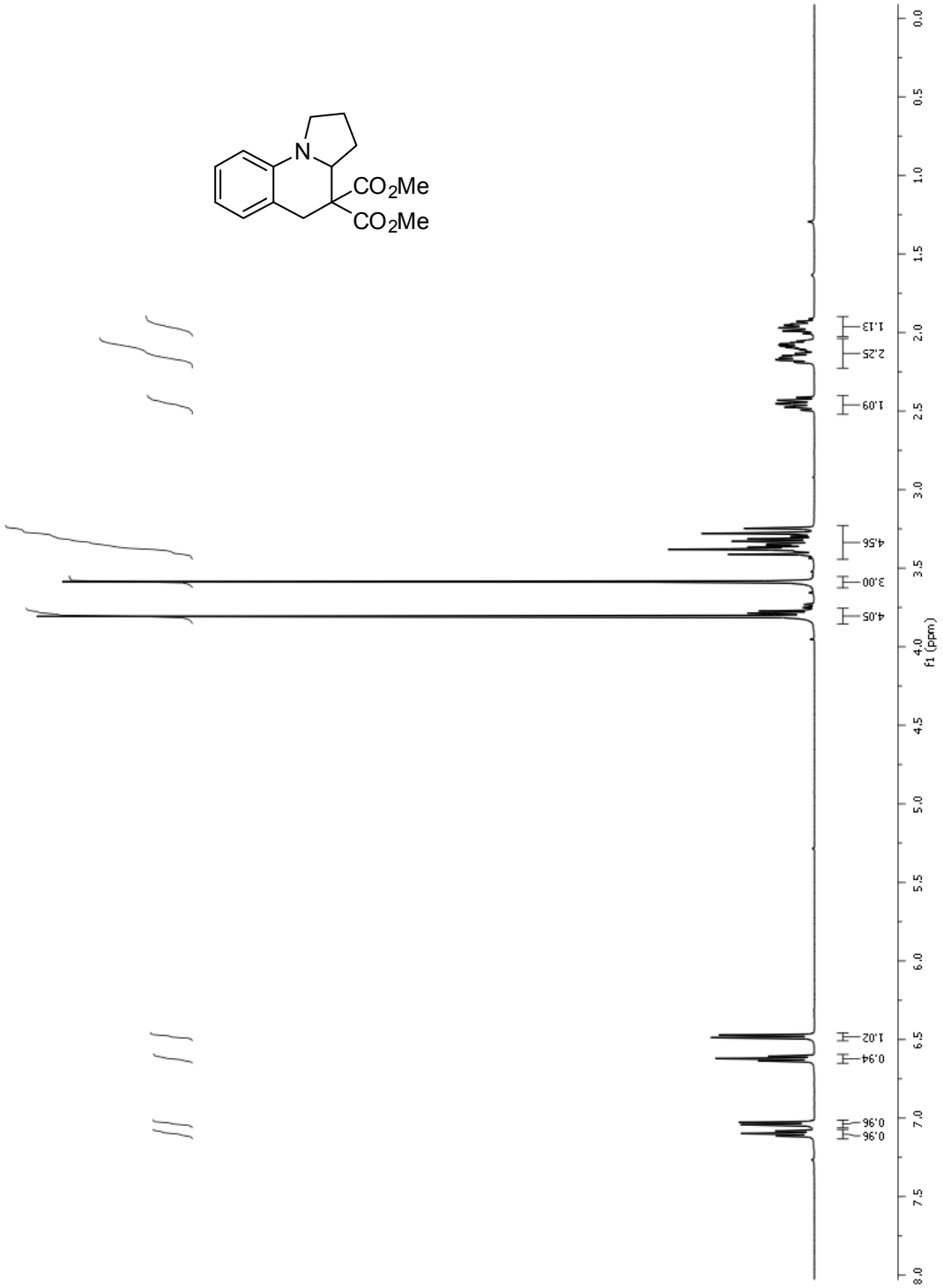

Ph
N
Ph
MeO2C
CO2Me
f1 (ppm)

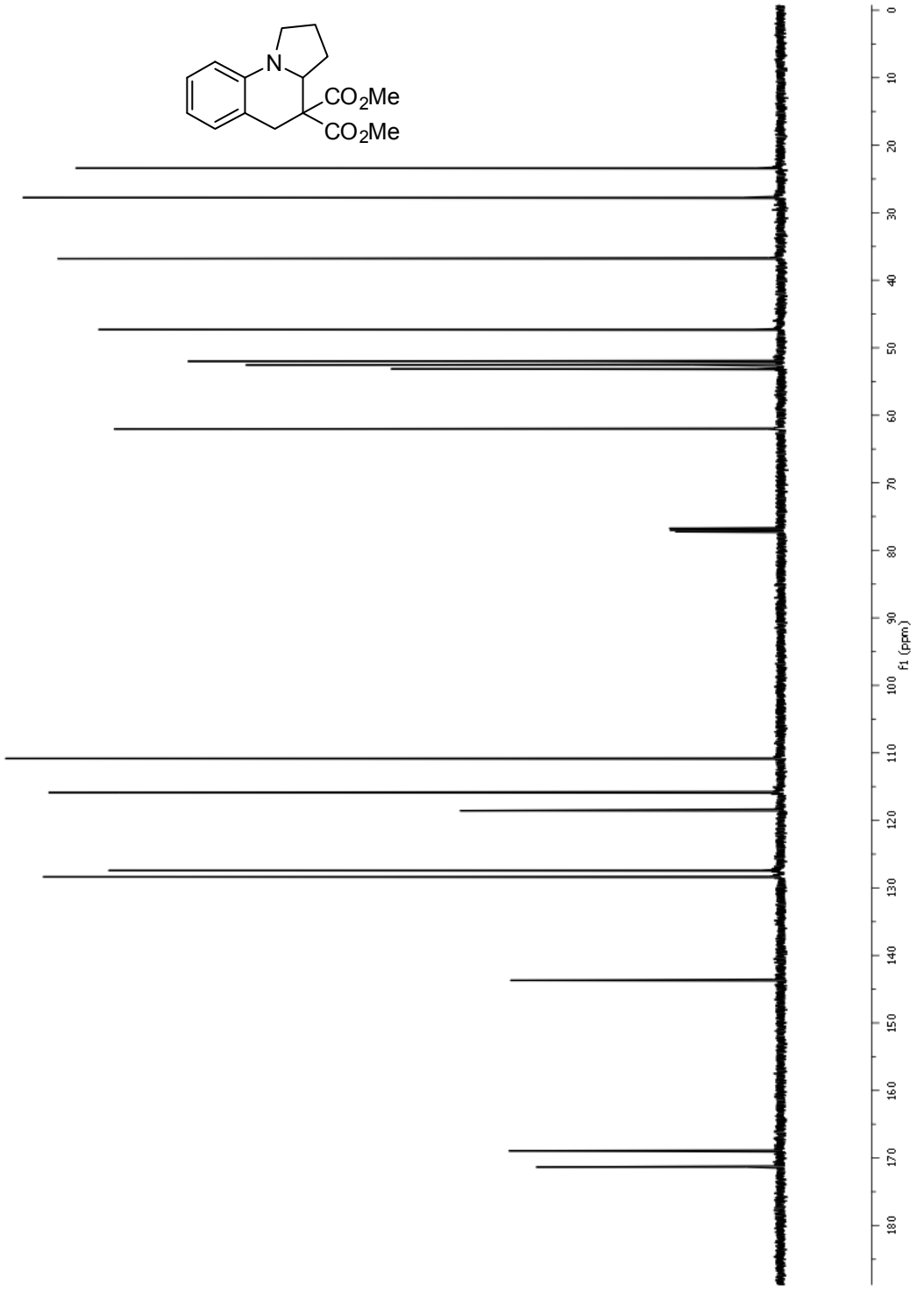
^{1}H–NMR and ^{13}C–NMR of **2.1q**:



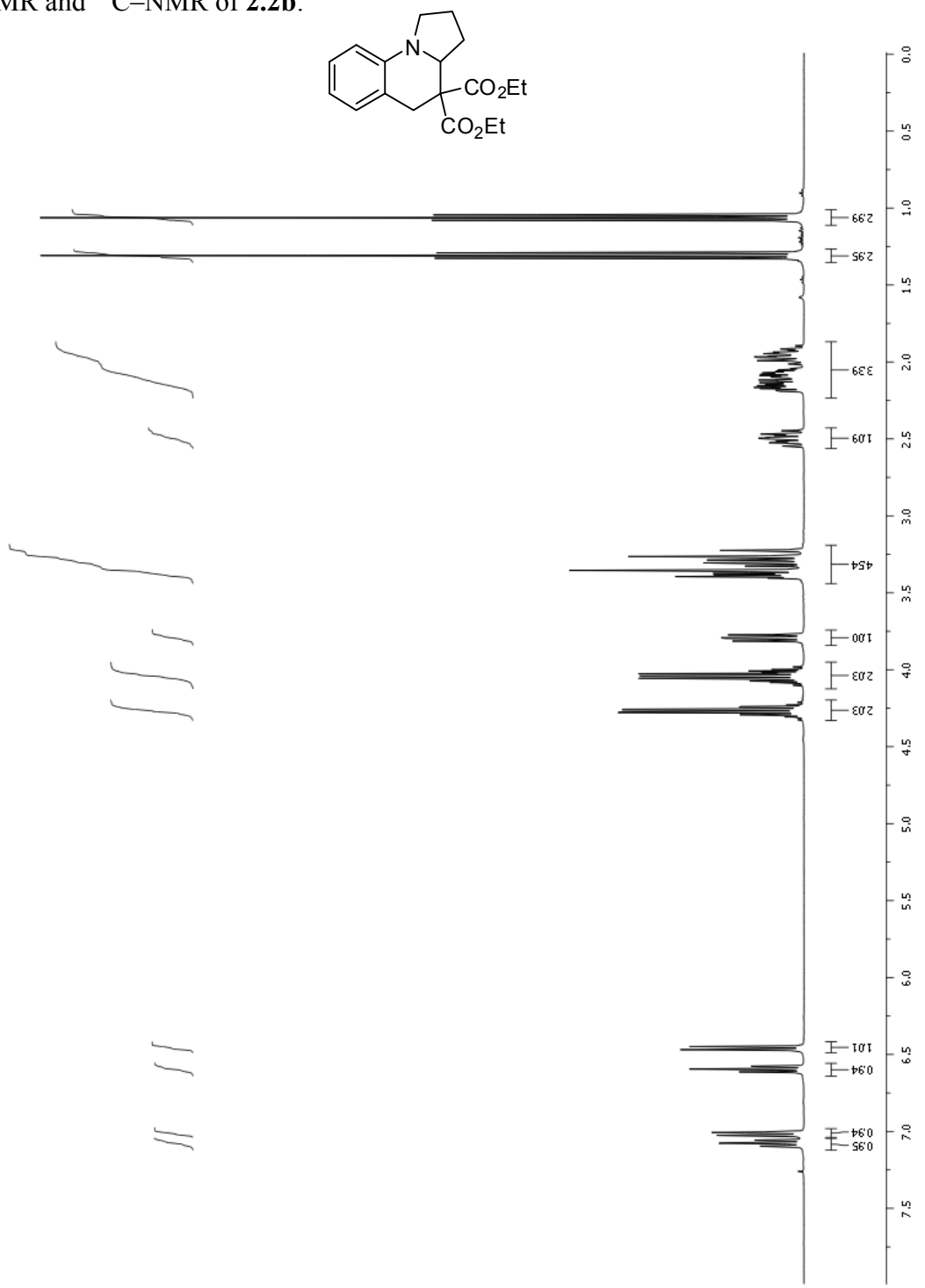

Me
N
MeO
OMe
O
O

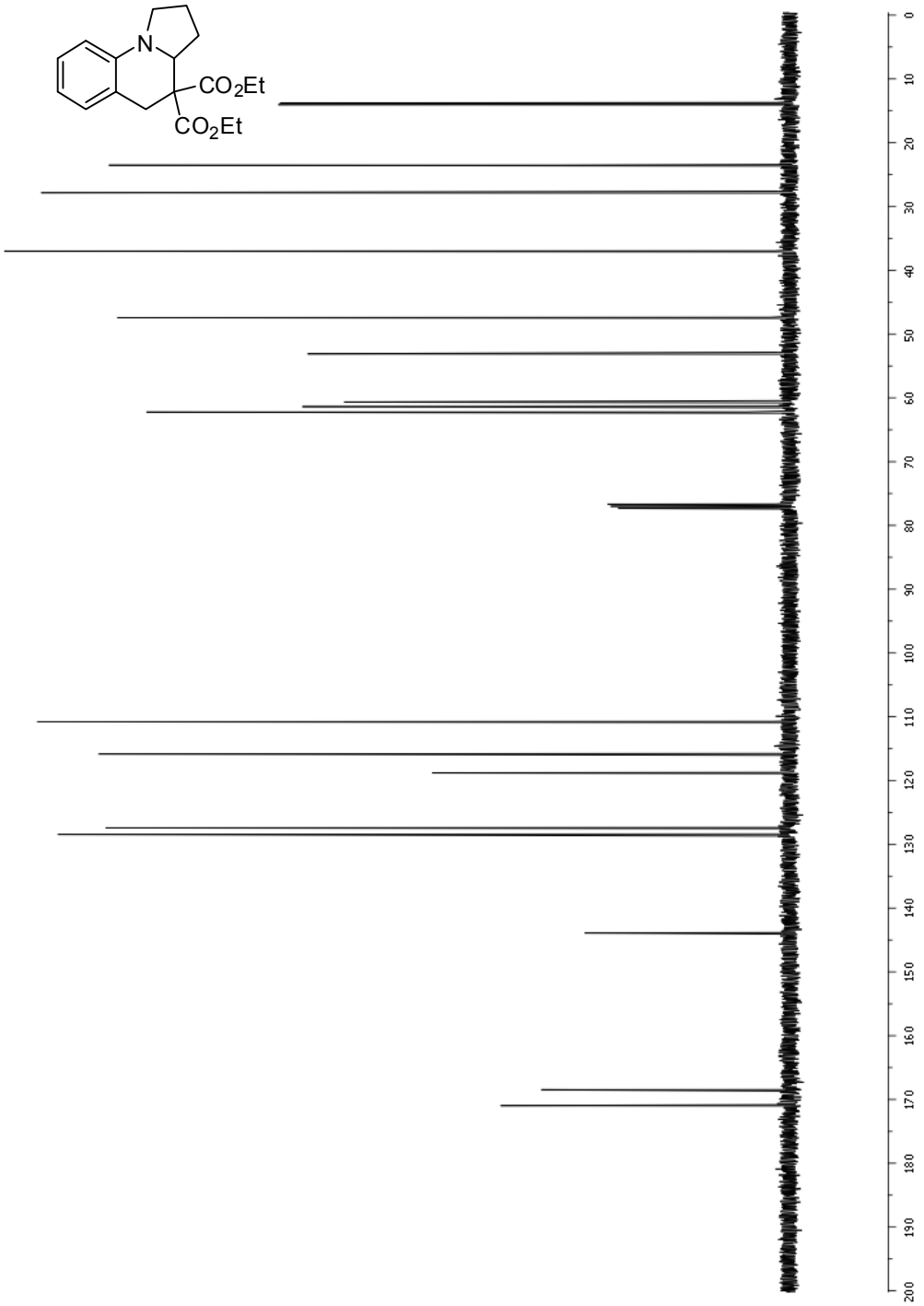
^{1}H–NMR and ^{13}C–NMR of **2.2a**:



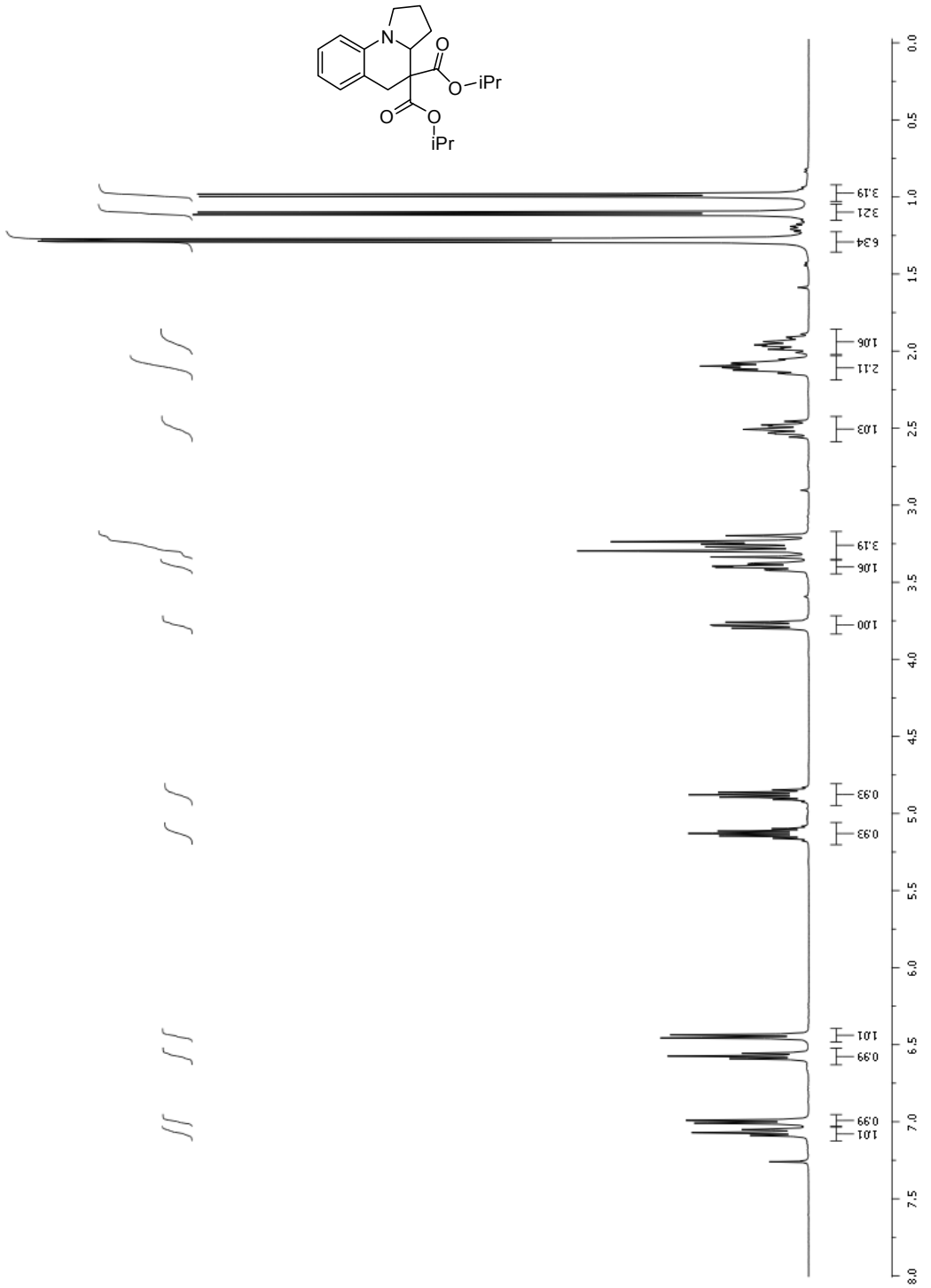

N
CO2Me
CO2Me
f1 (ppm)

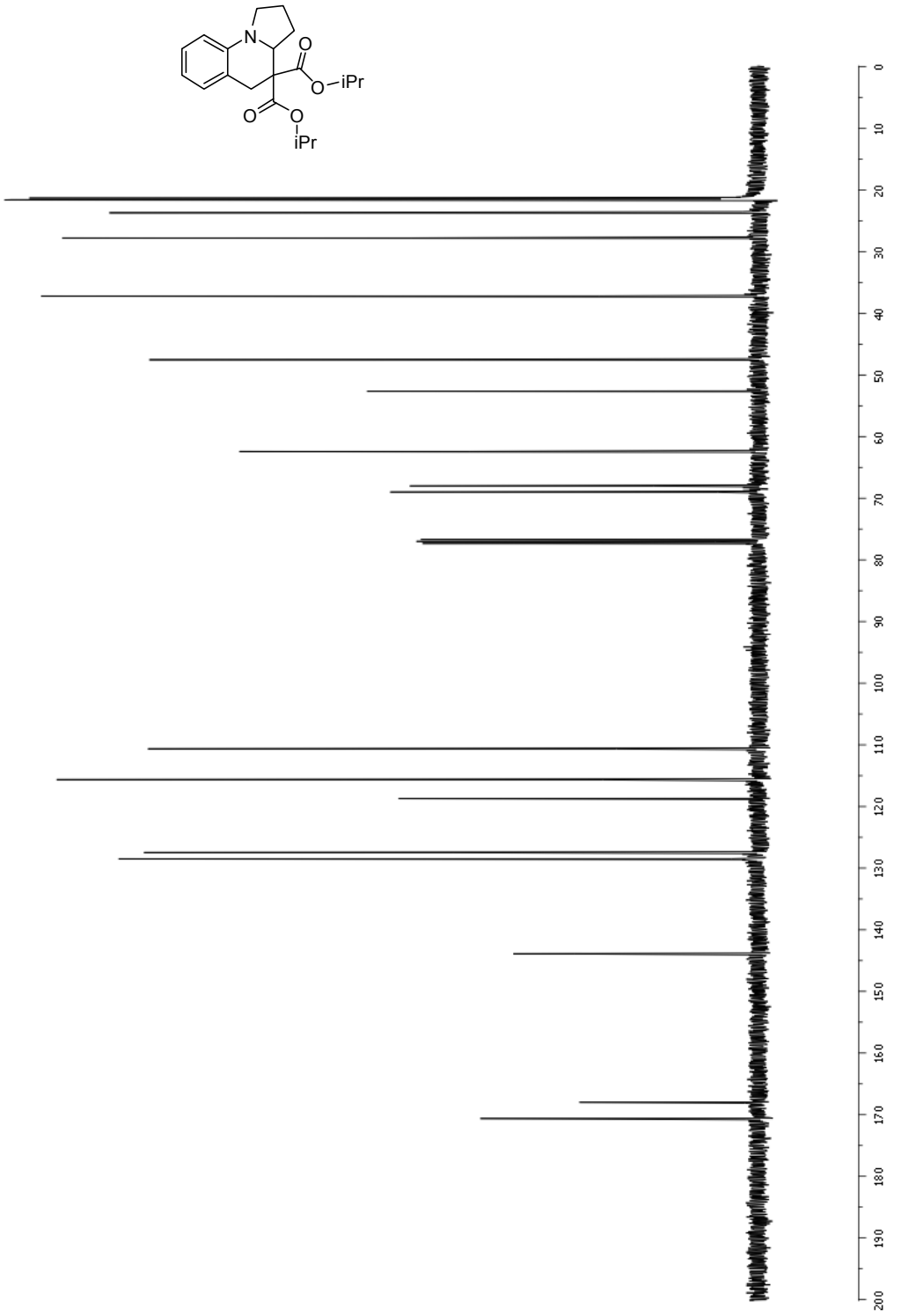
^{1}H–NMR and ^{13}C–NMR of **2.2b**:



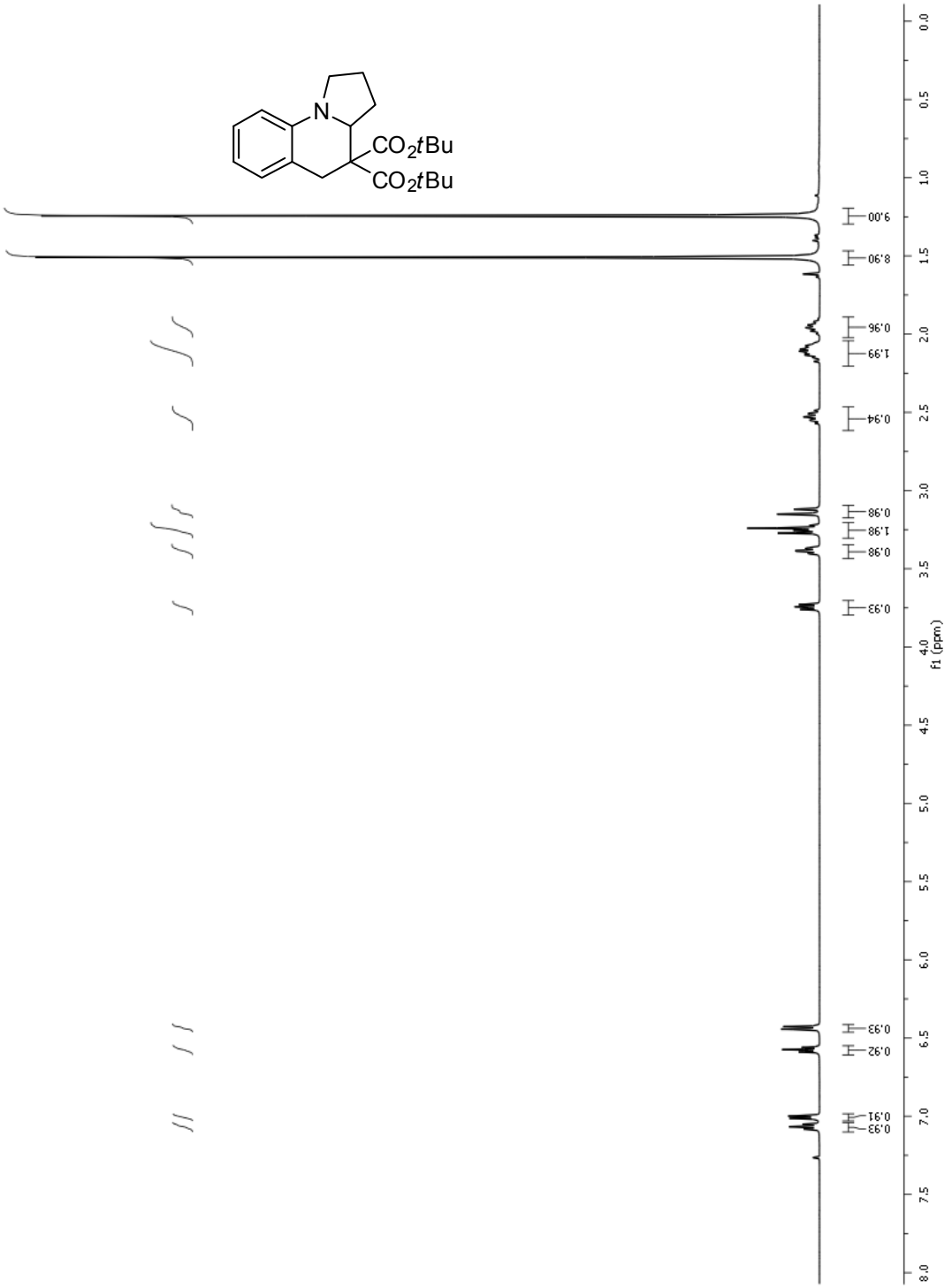

N
CO2Et
CO2Et

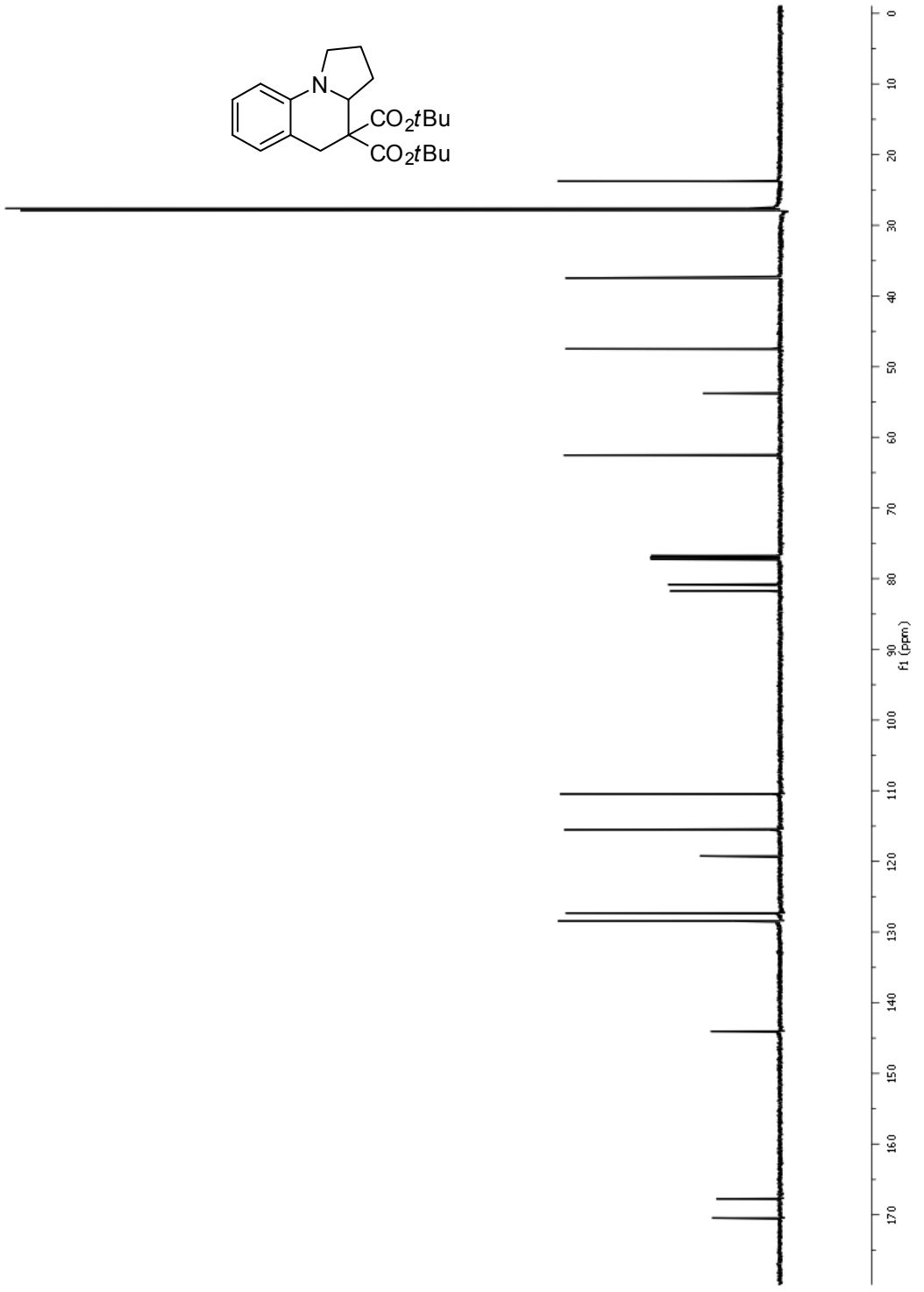
^{1}H–NMR and ^{13}C–NMR of **2.2c**:



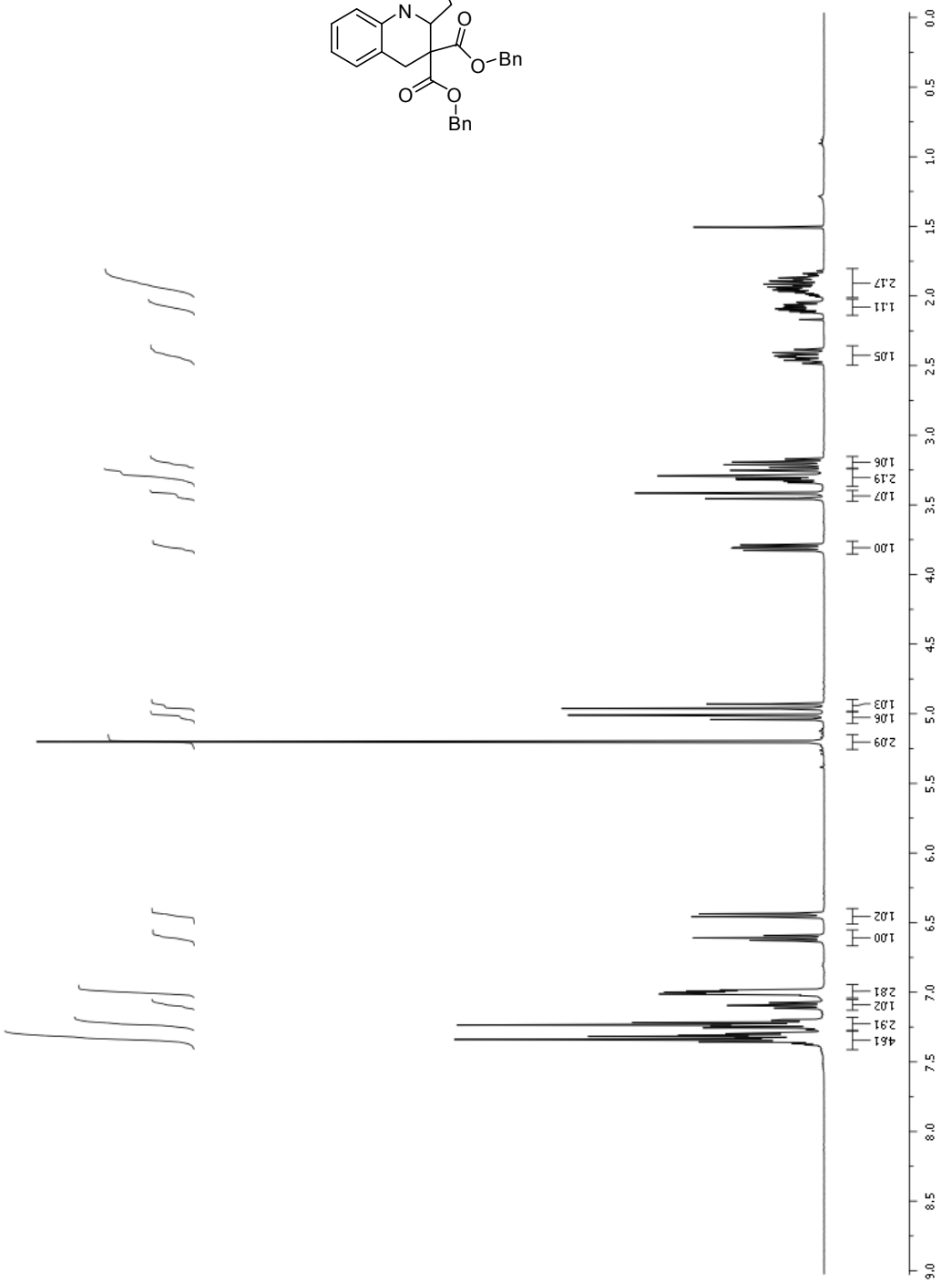

N
O
O
iPr
O
O
iPr
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

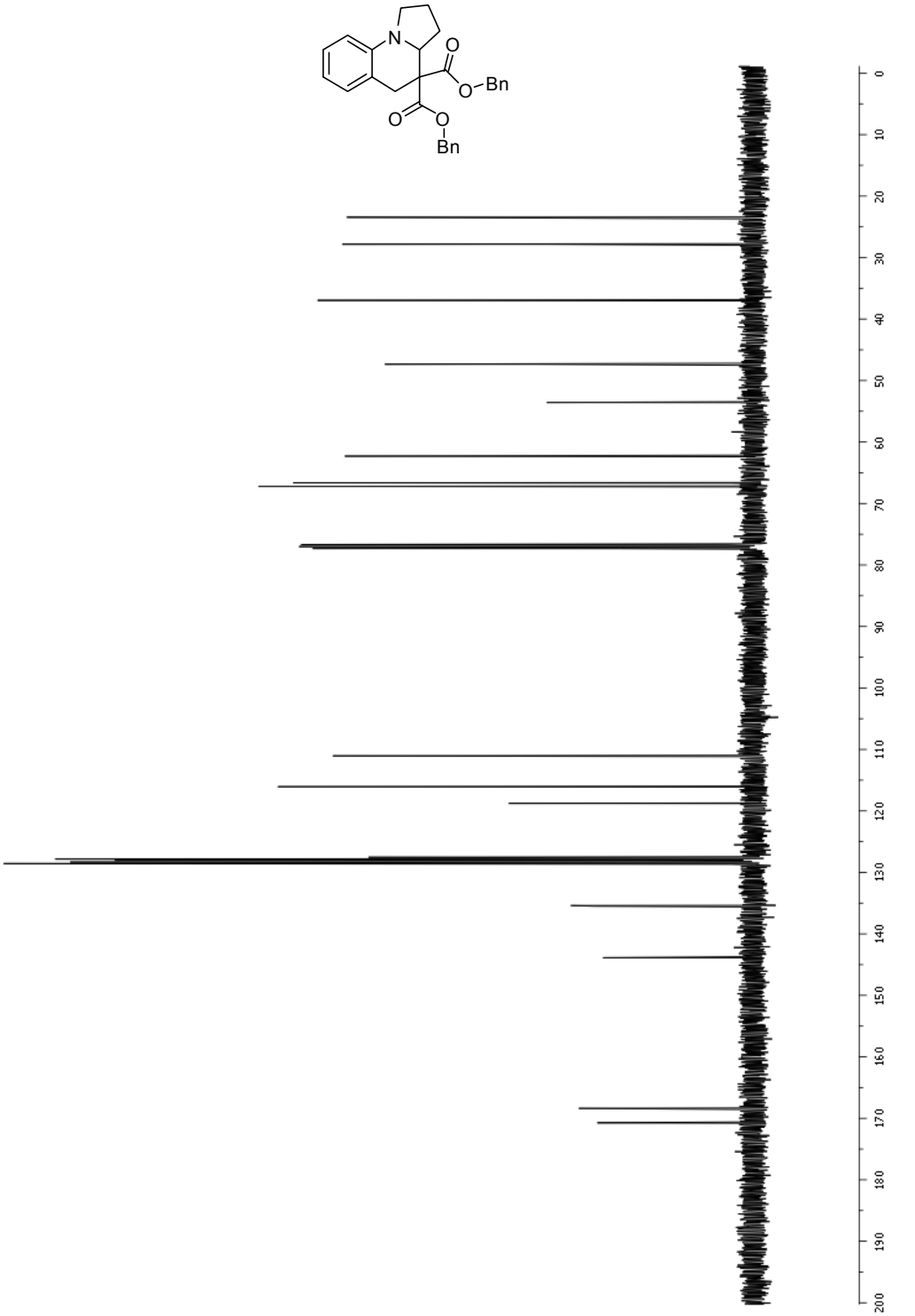
^{1}H–NMR and ^{13}C–NMR of **2.2d**:



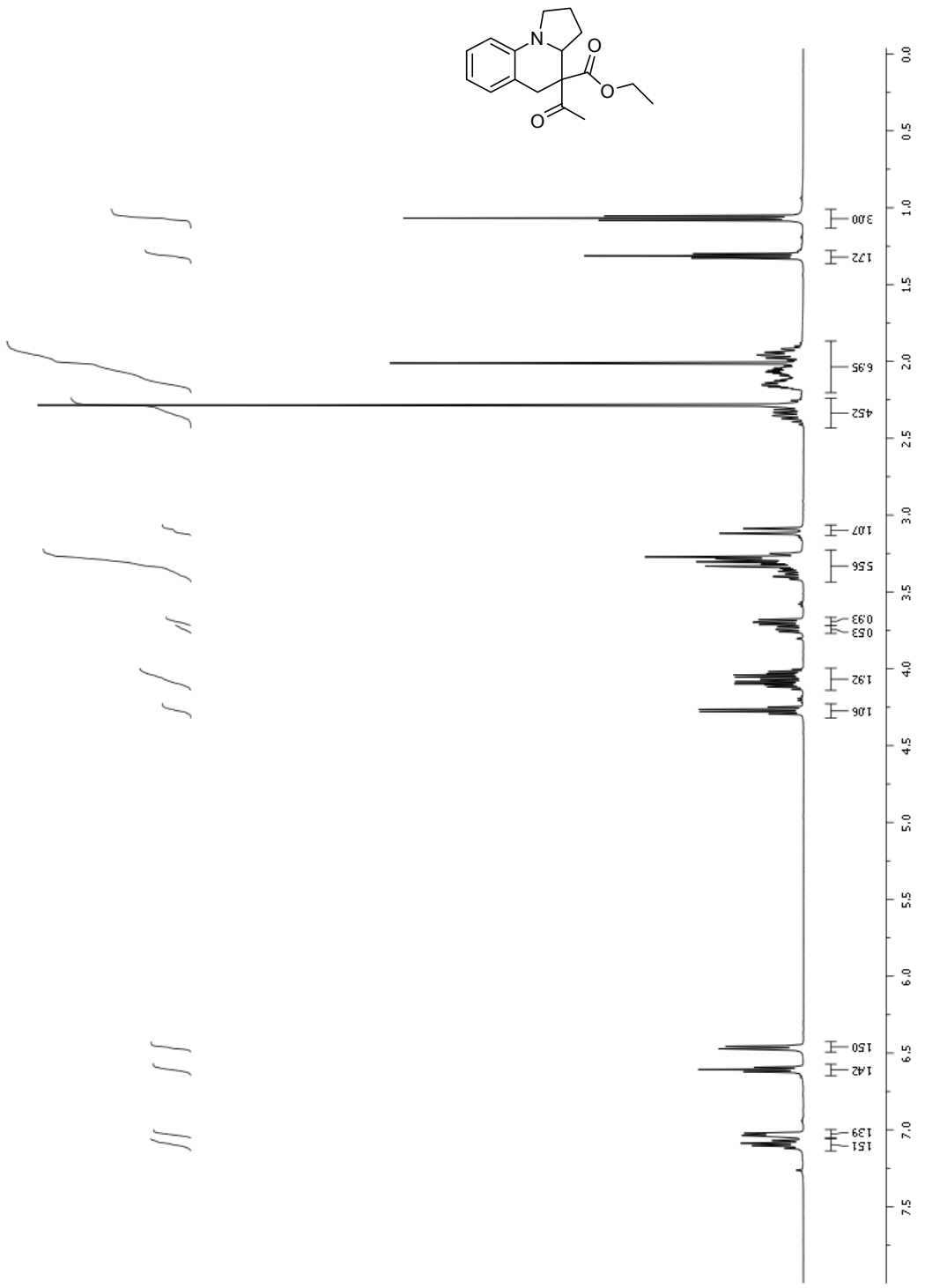

N
CO2tBu
CO2tBu
f1 (ppm)

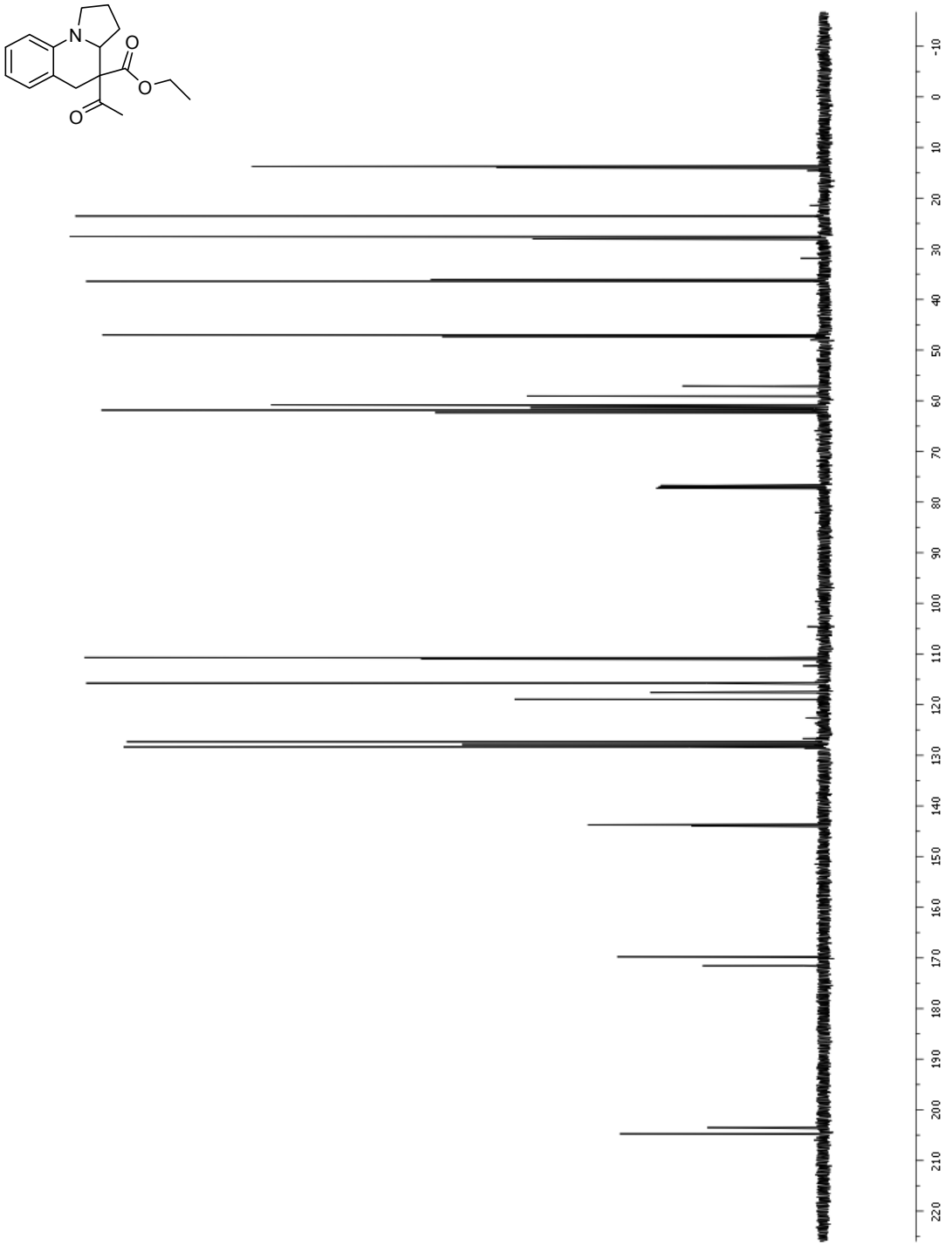
^{1}H–NMR and ^{13}C–NMR of **2.2e**:



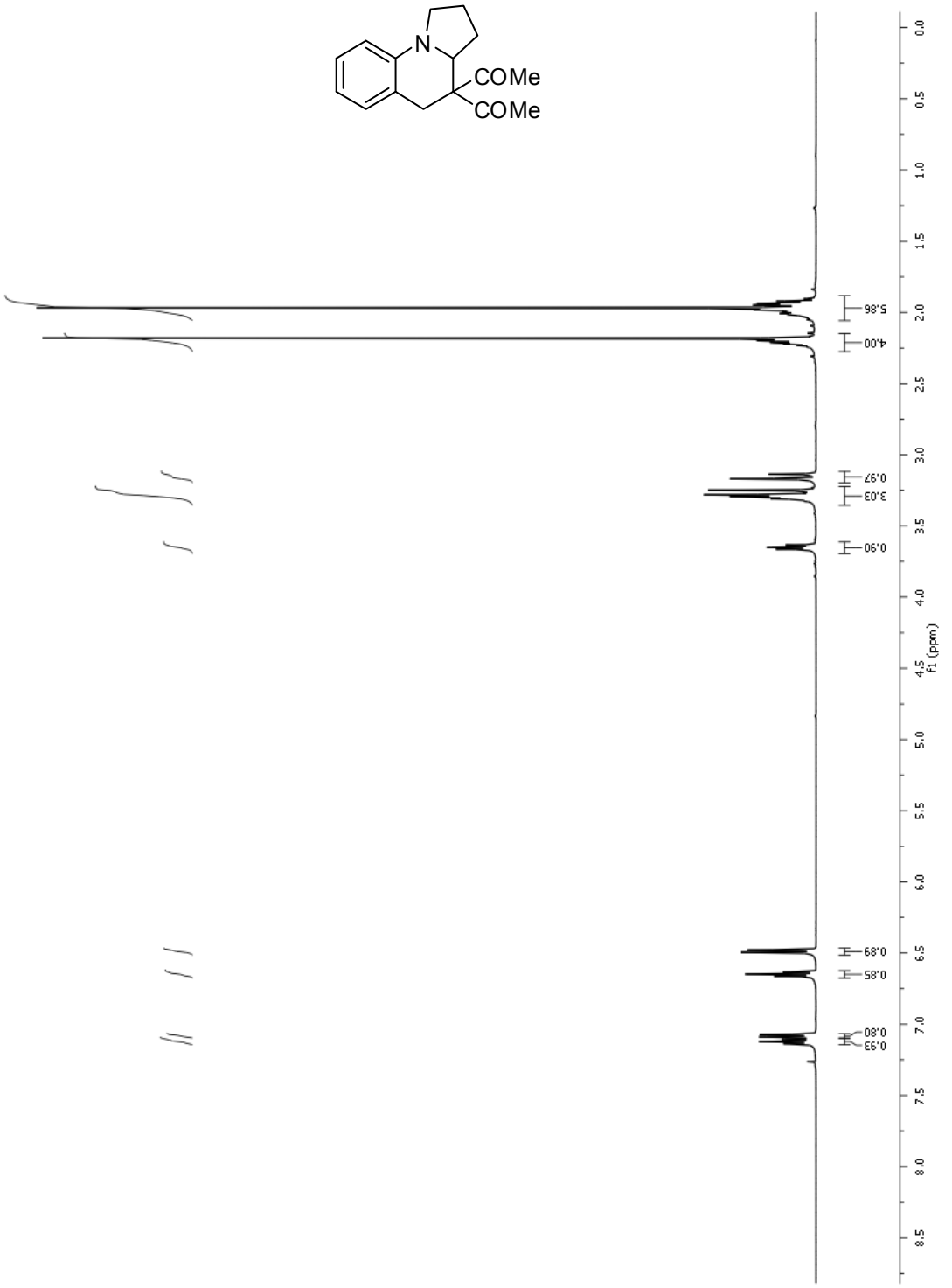

N
O
O
Bn
O
O
Bn
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

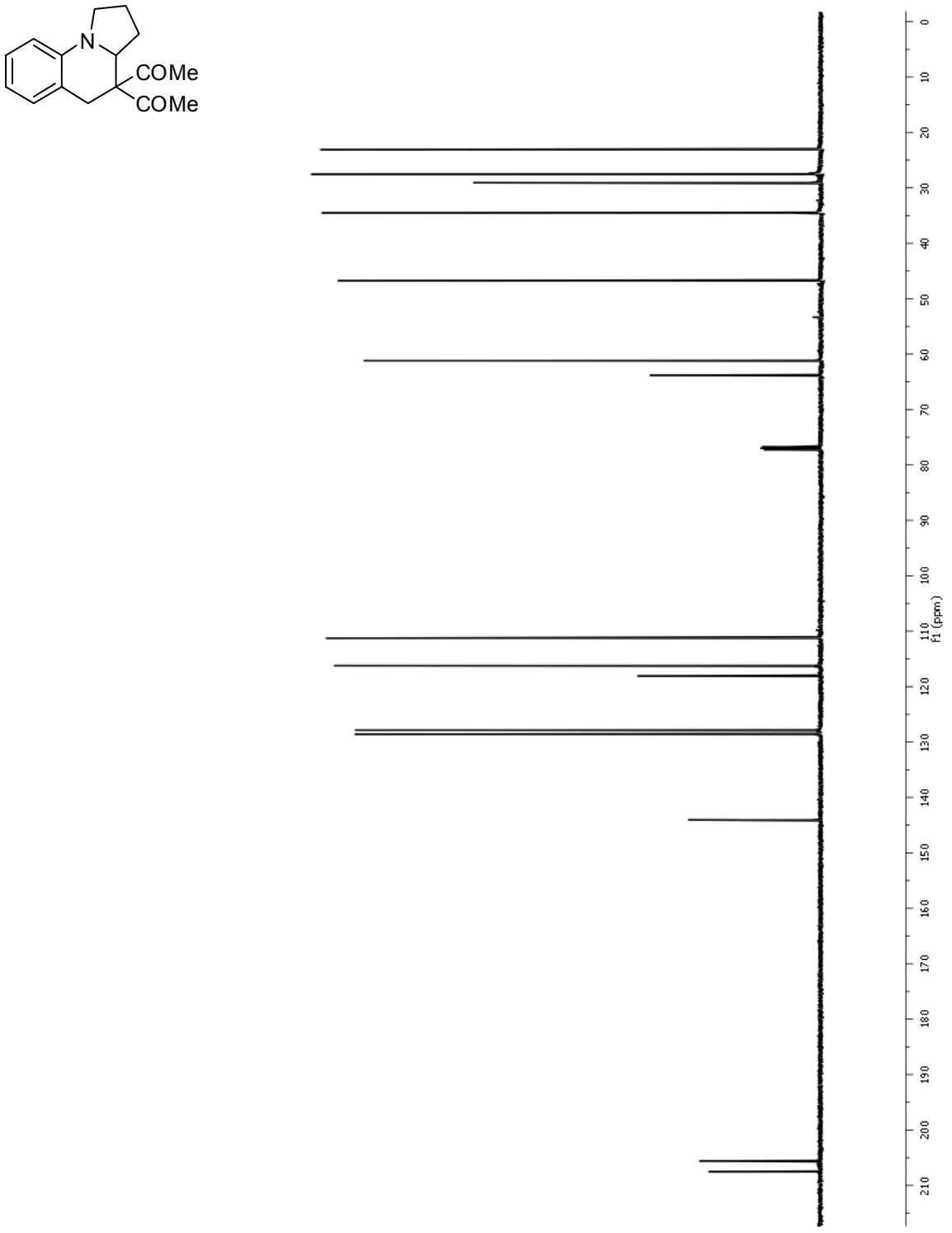
^{1}H–NMR and ^{13}C–NMR of **2.2f**: (dr = 36 : 64)



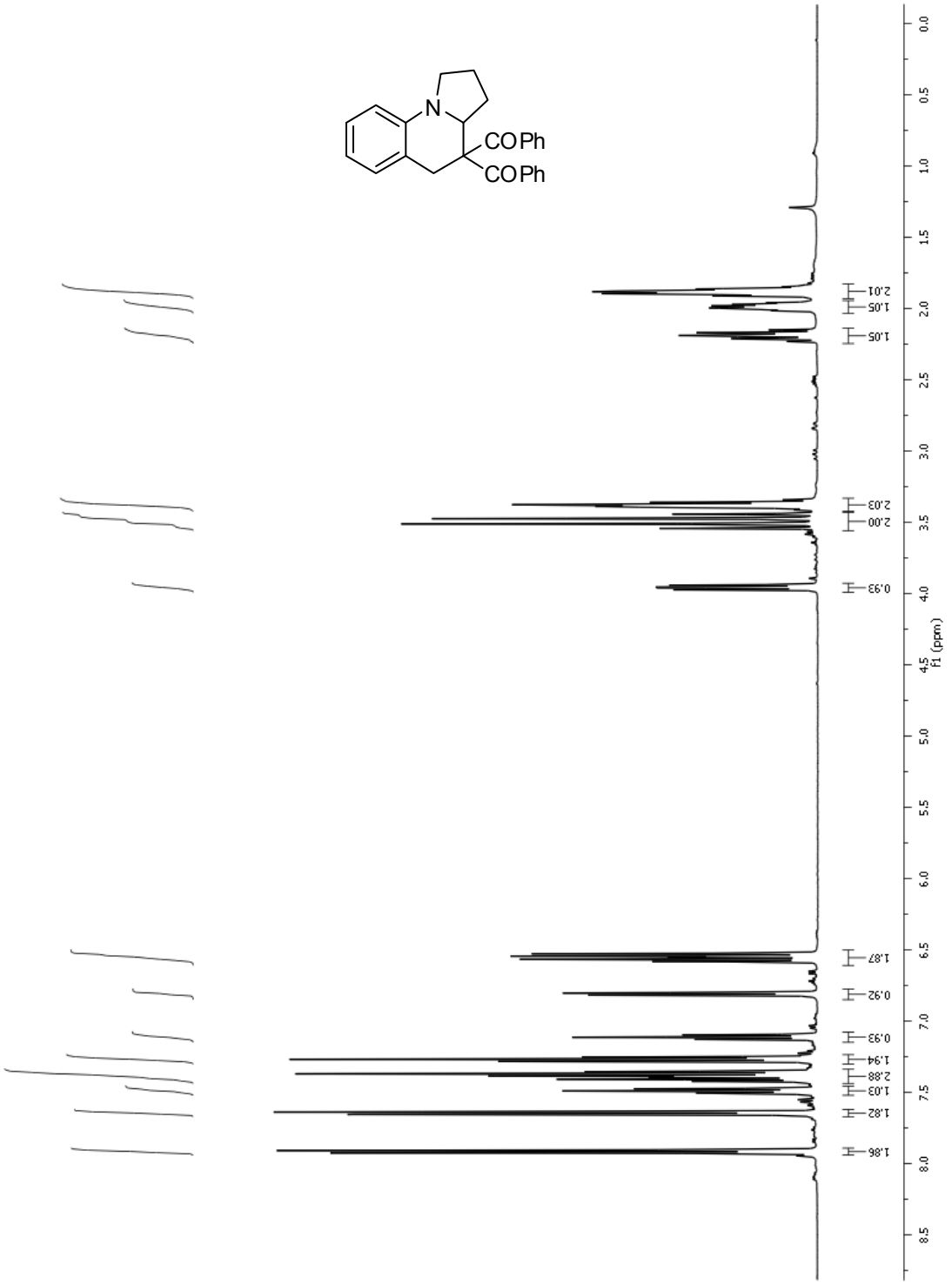

N
O
O
O
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220

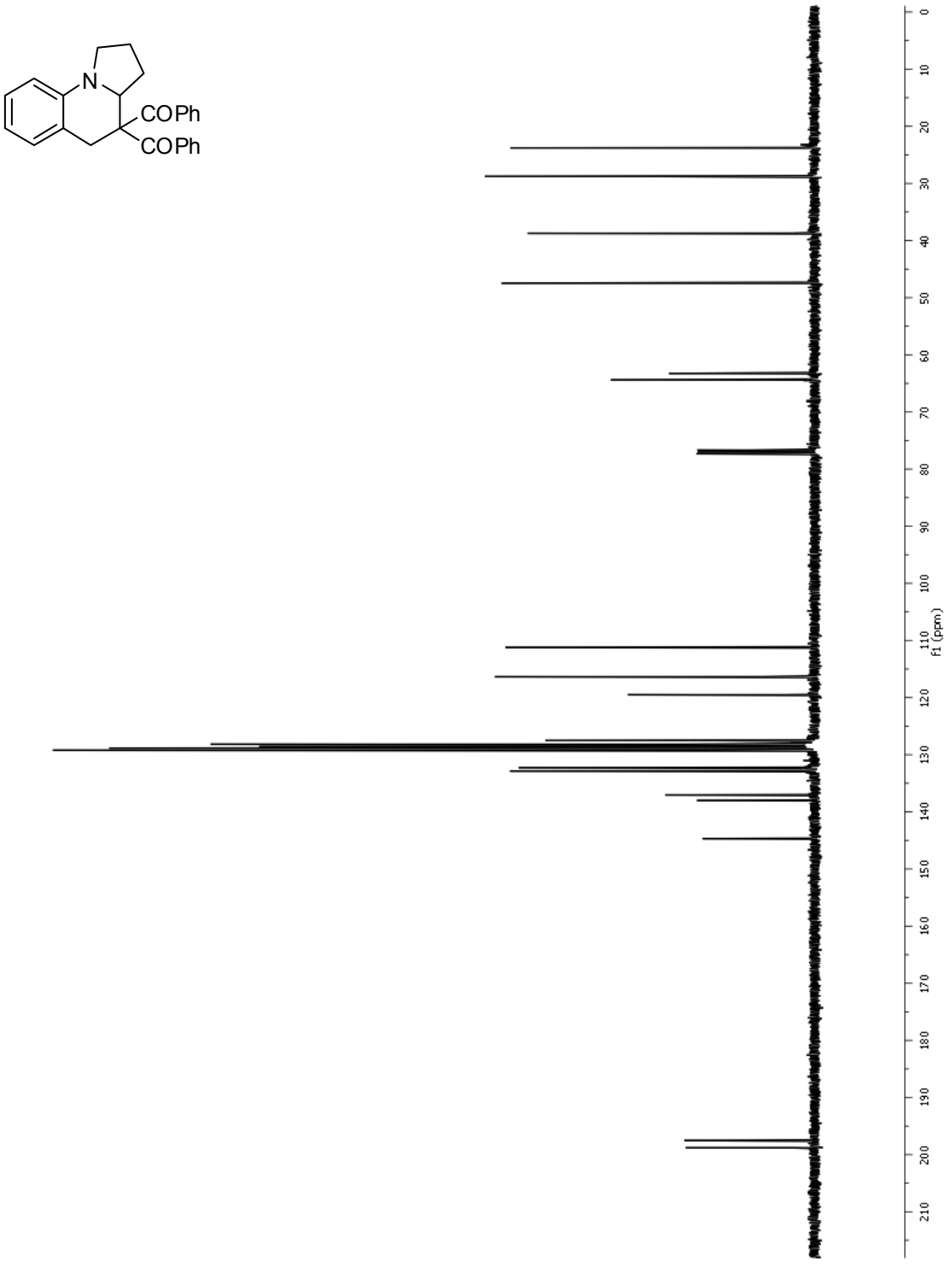
^{1}H–NMR and ^{13}C–NMR of **2.2g**:



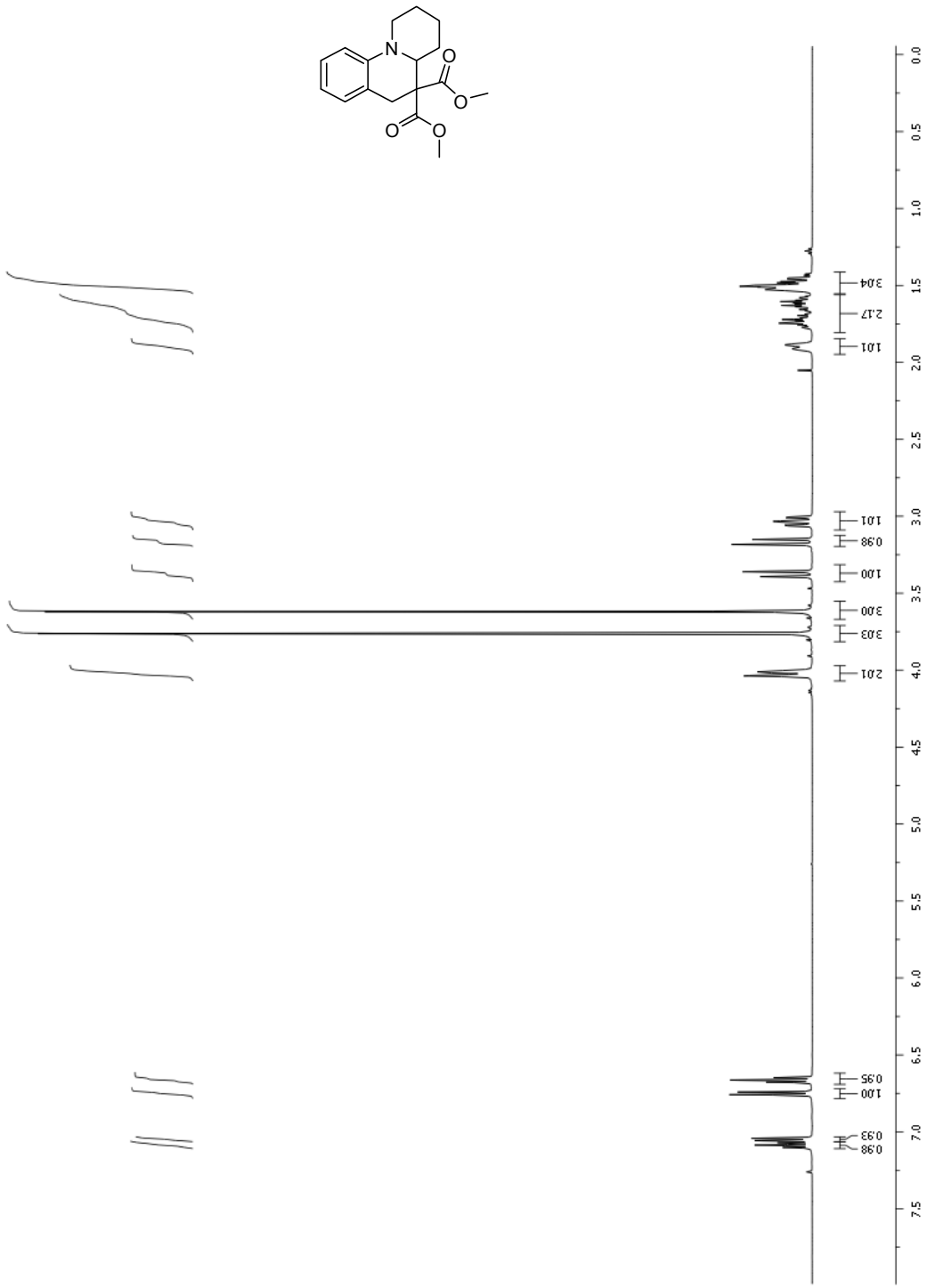

N
COMe
COMe
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

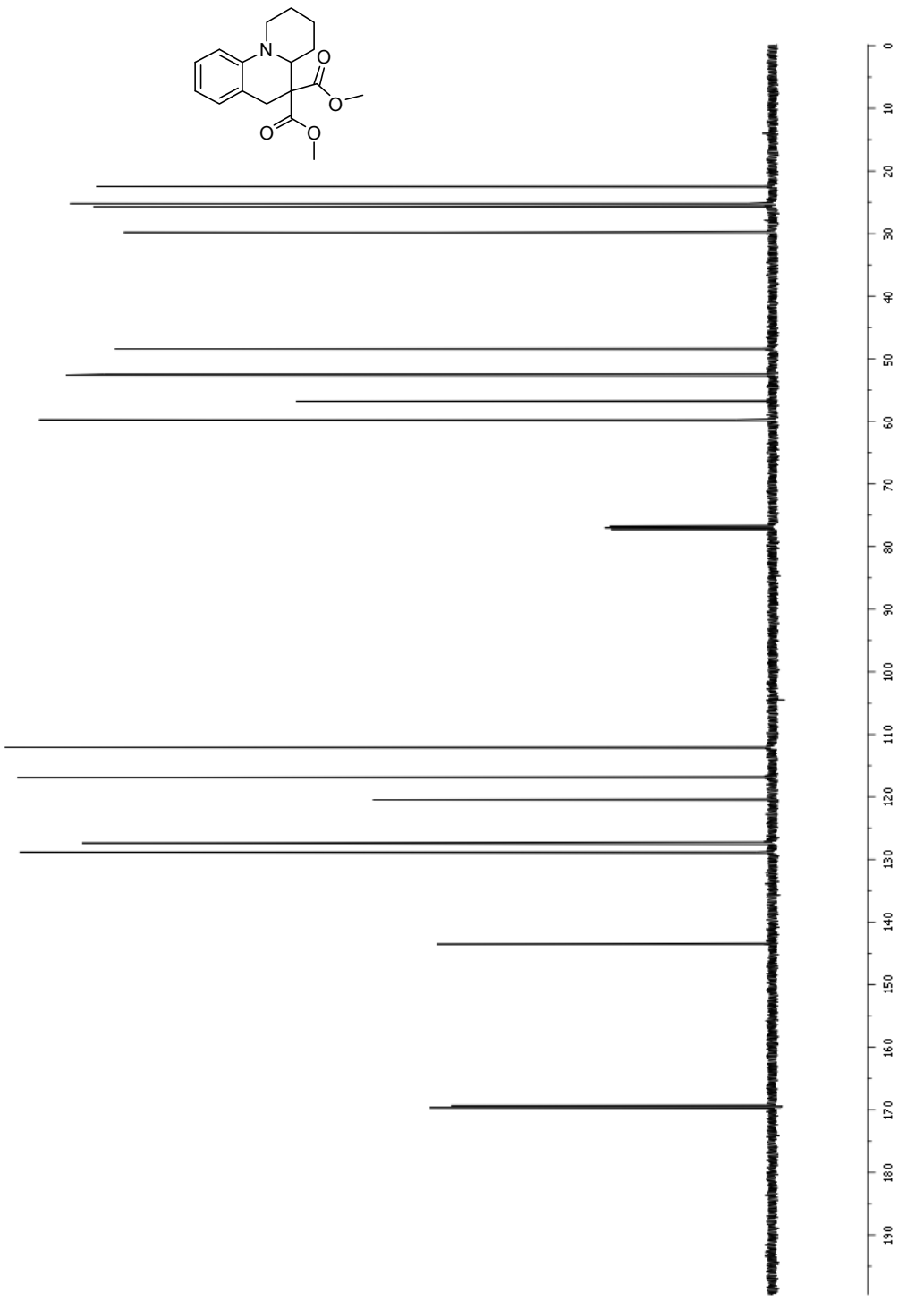
^{1}H–NMR and ^{13}C–NMR of **2.2h**:



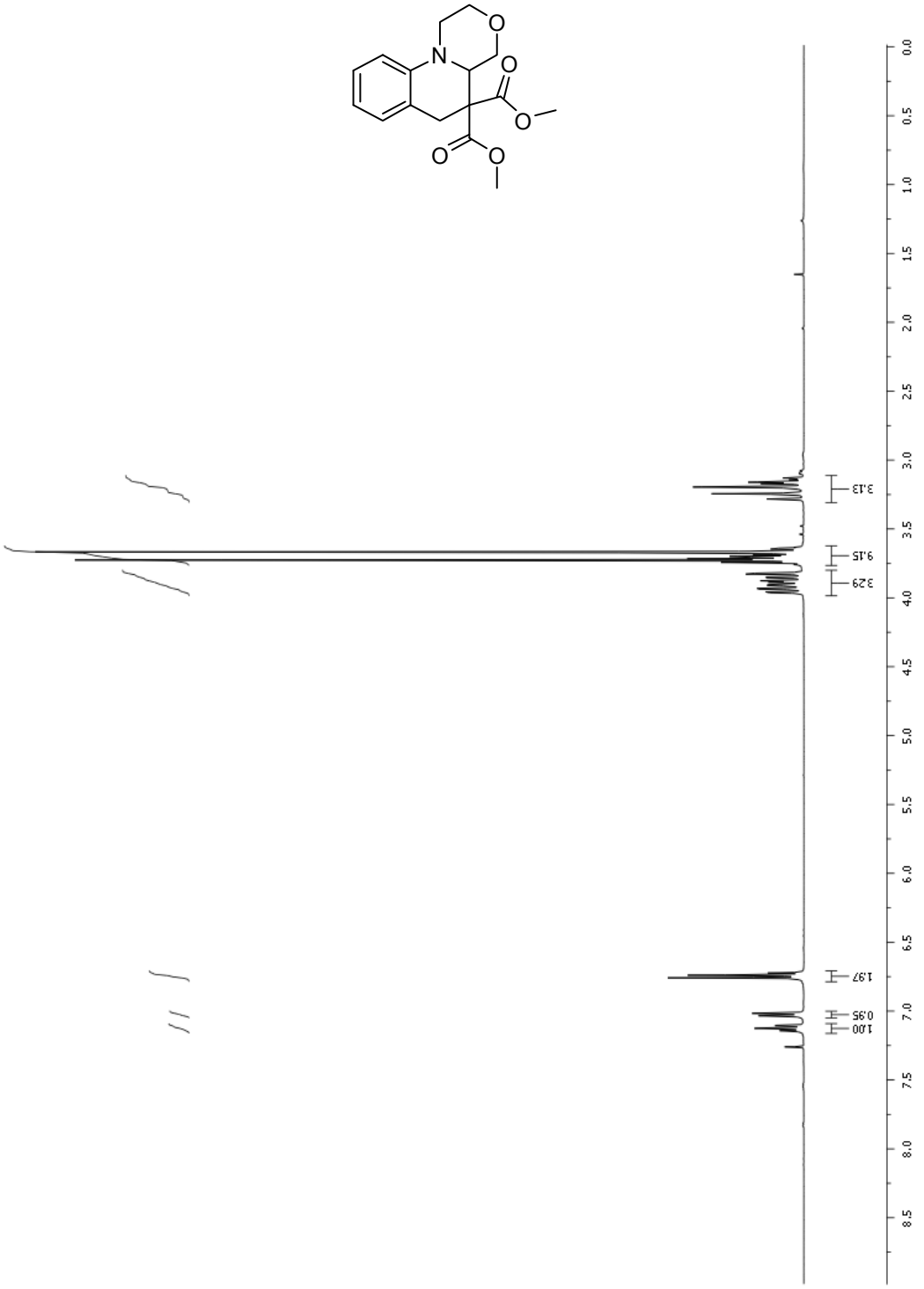

N
COPh
COPh
F1 (ppm)

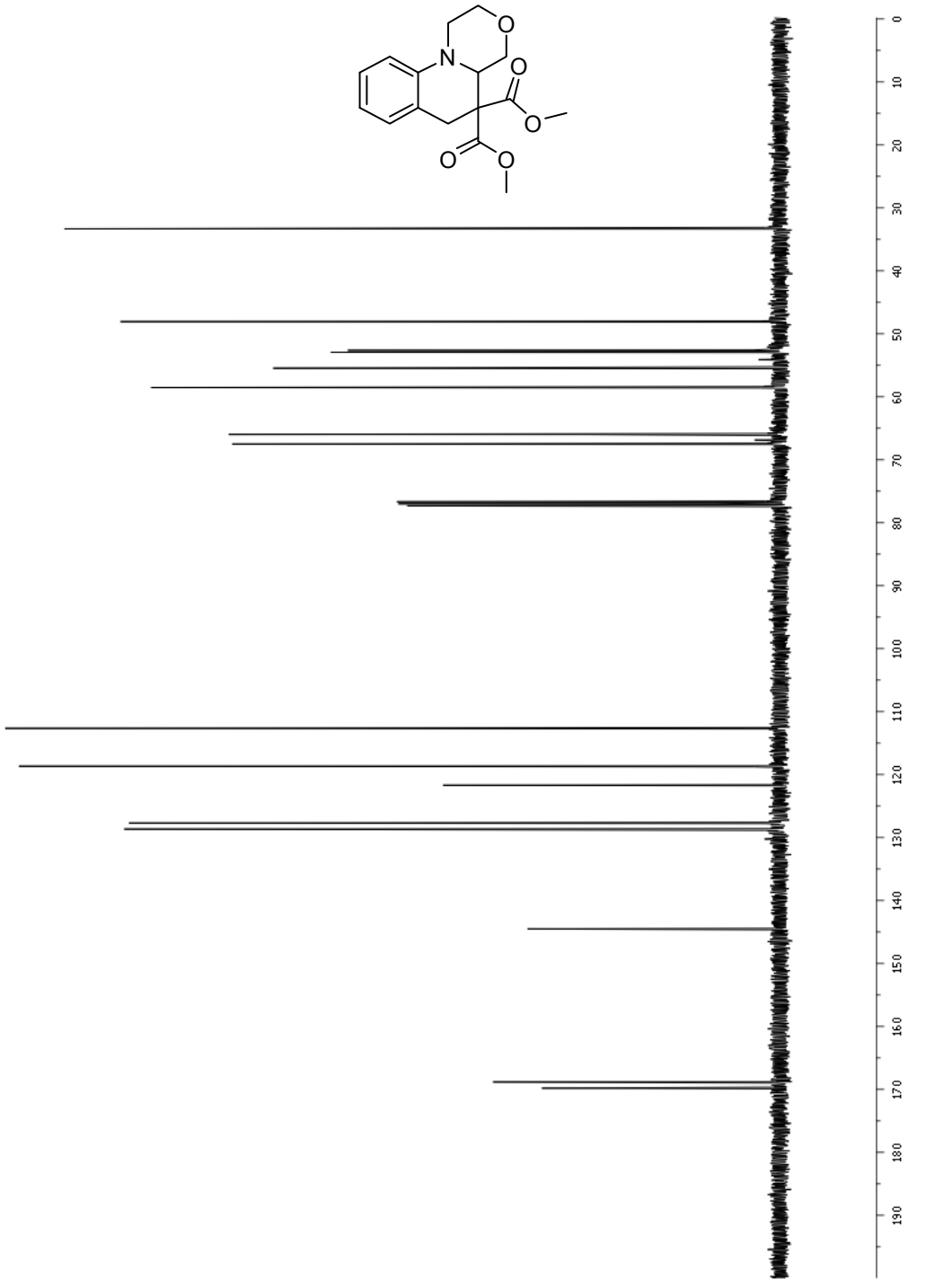
^{1}H–NMR and ^{13}C–NMR of **2.2j**:



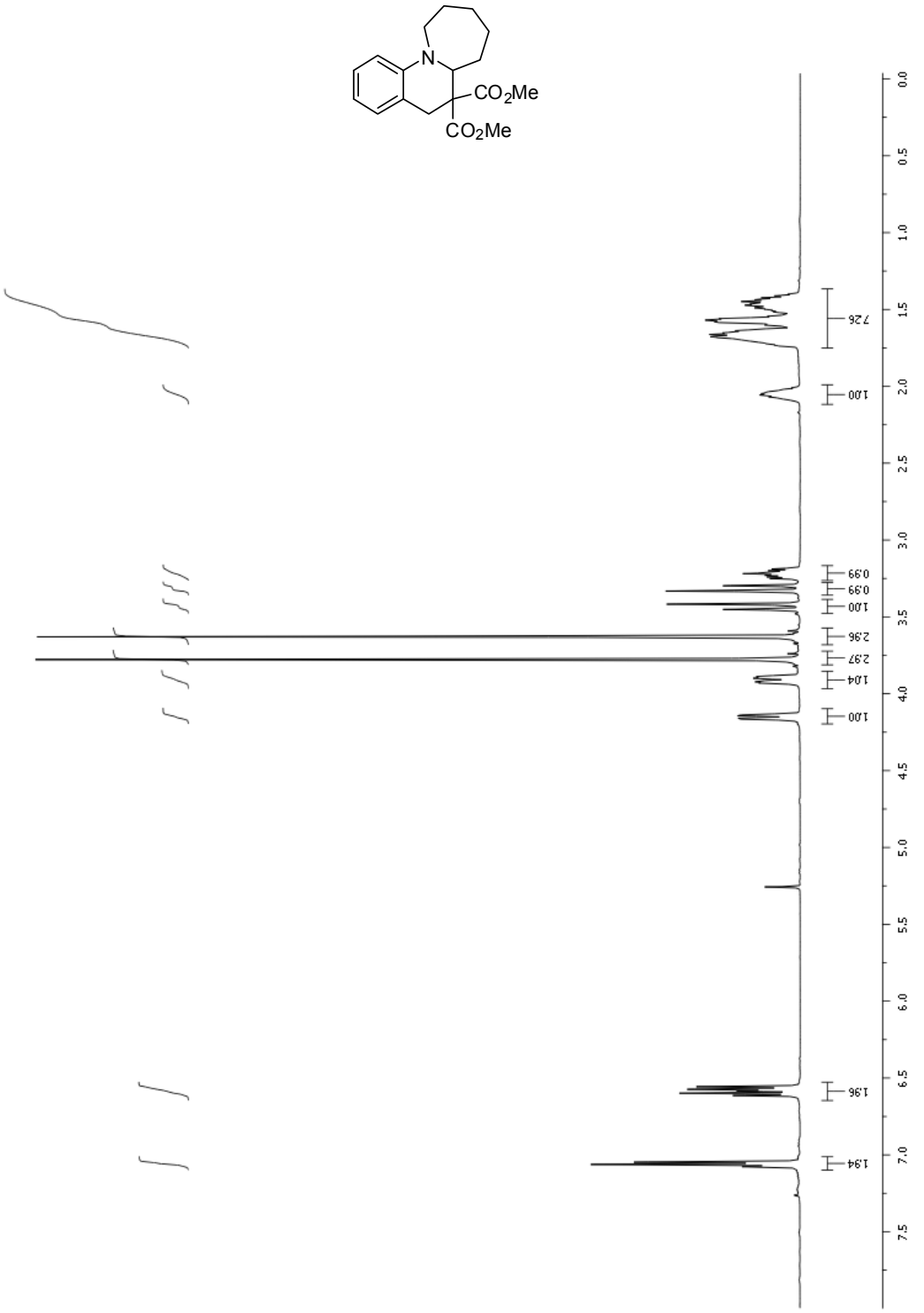

N
O
O
O
O
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

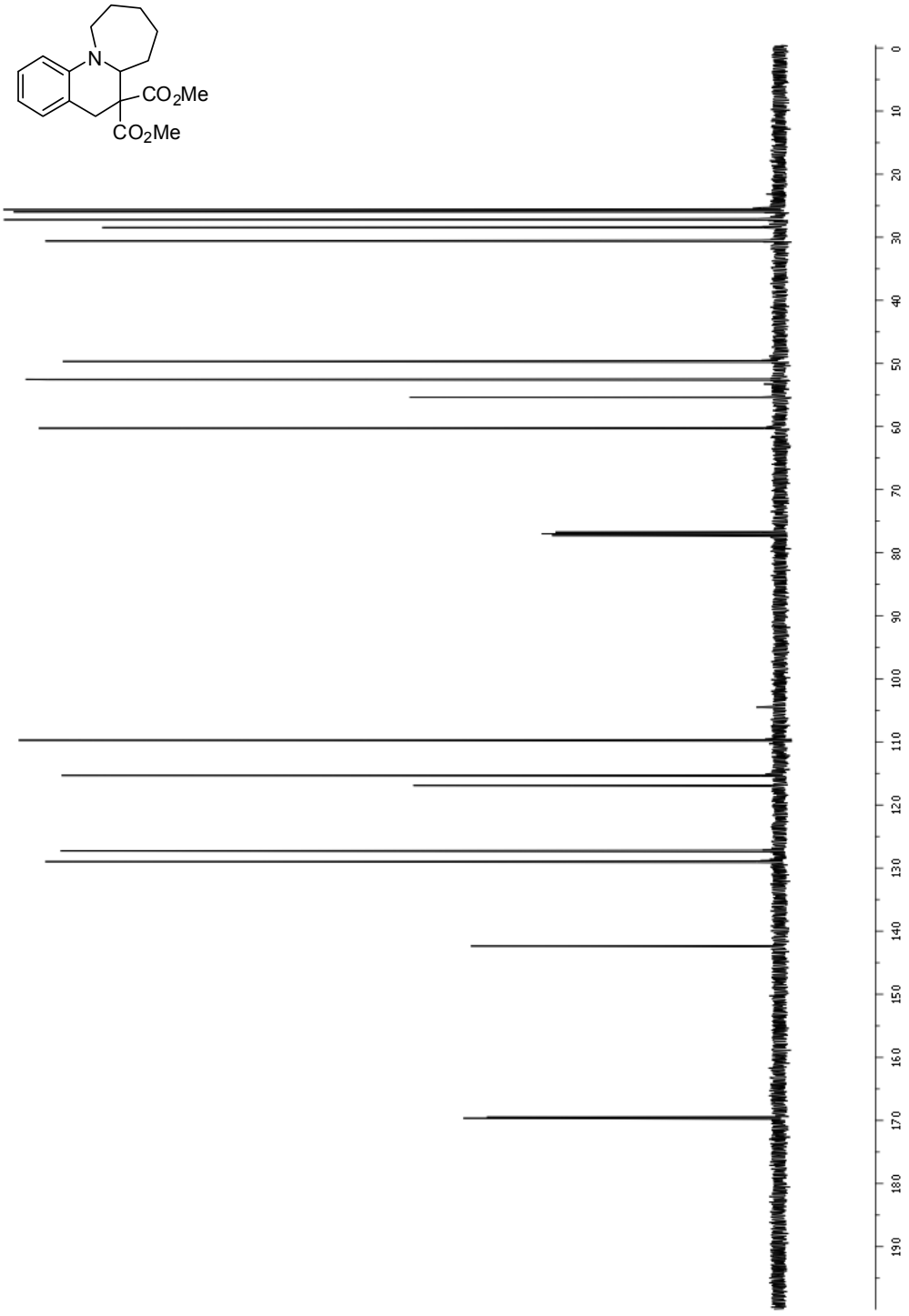
^{1}H–NMR and ^{13}C–NMR of **2.2k**:



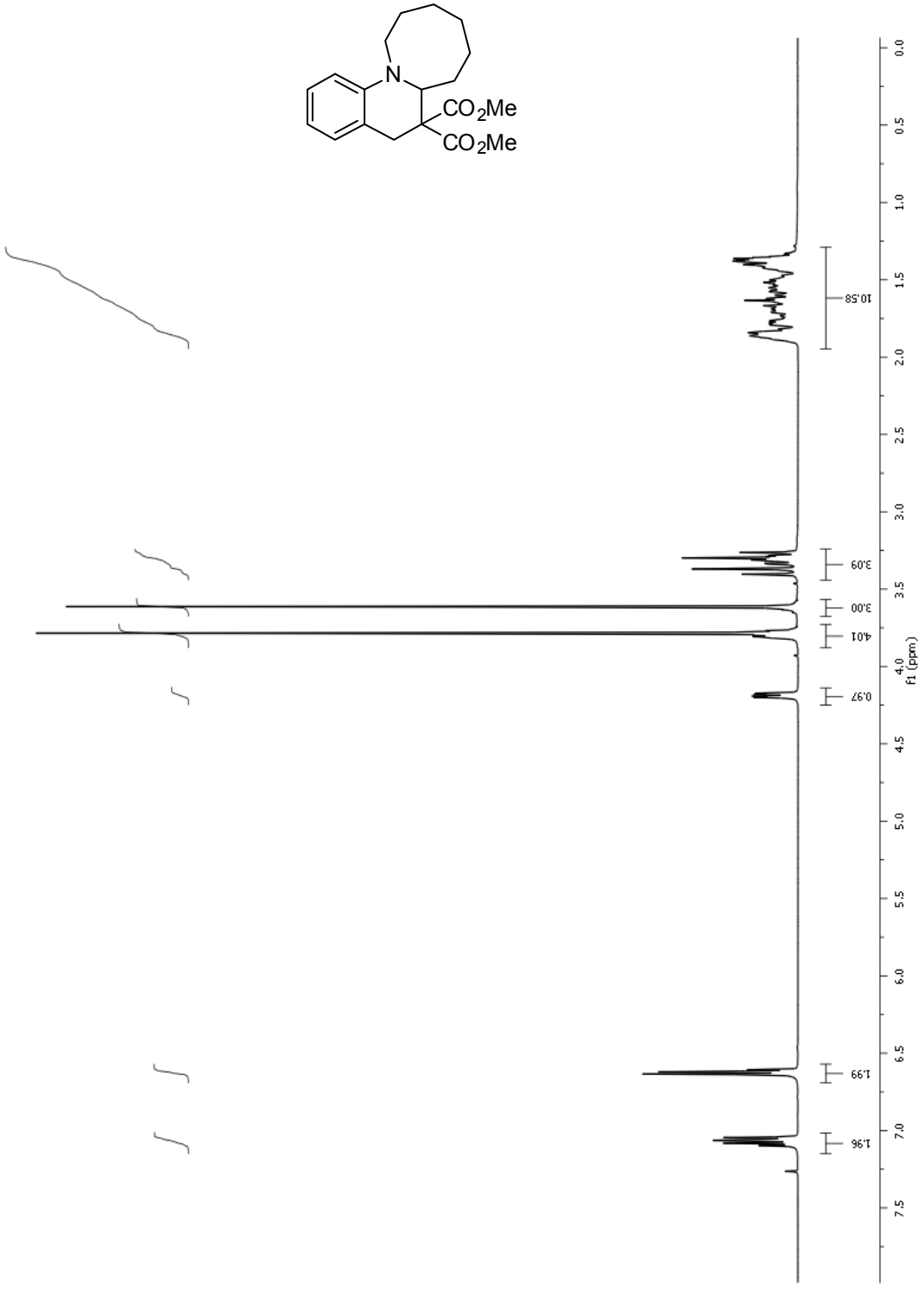

N
O
O
O
O
O
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

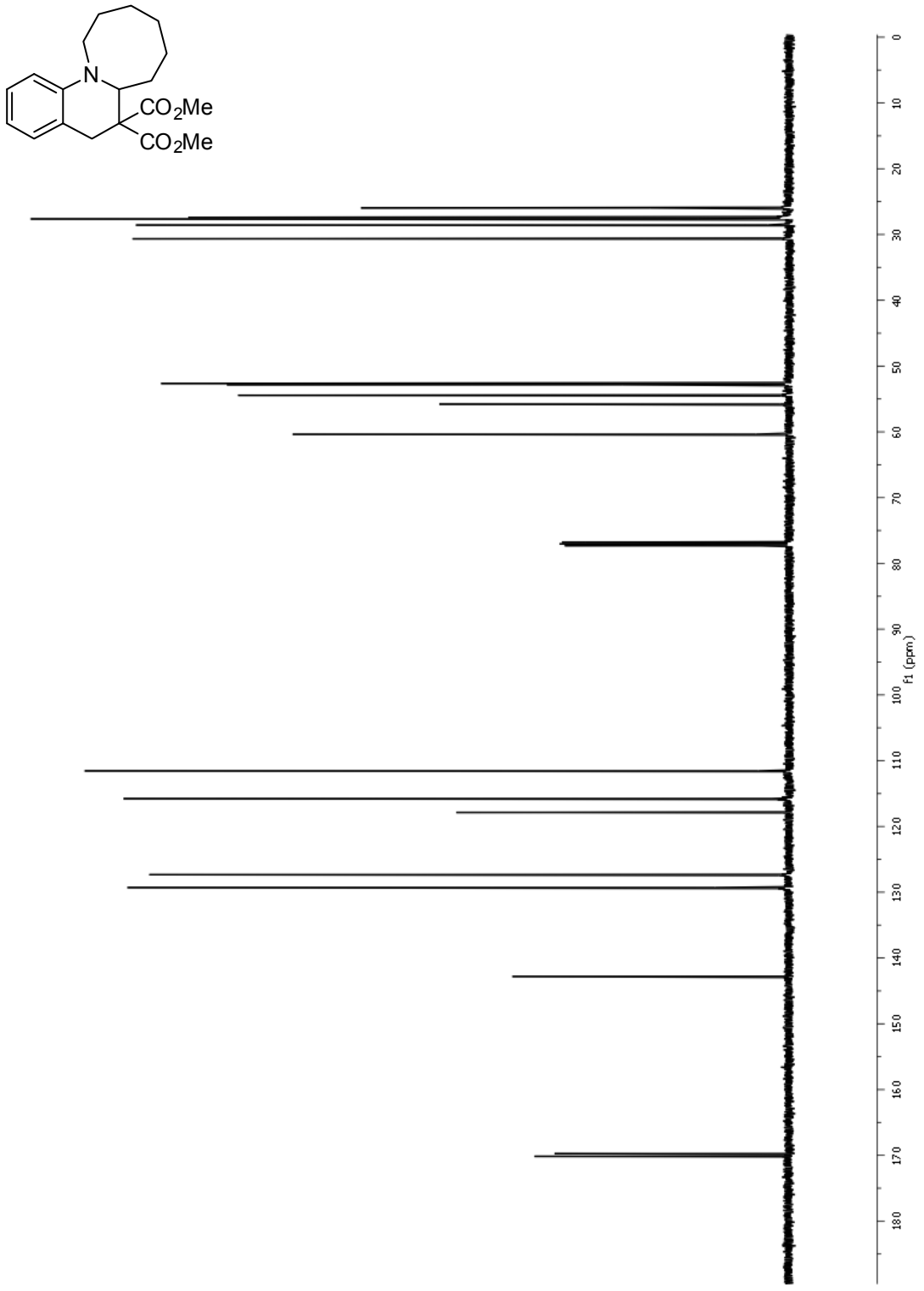
^{1}H–NMR and ^{13}C–NMR of **2.2l**:



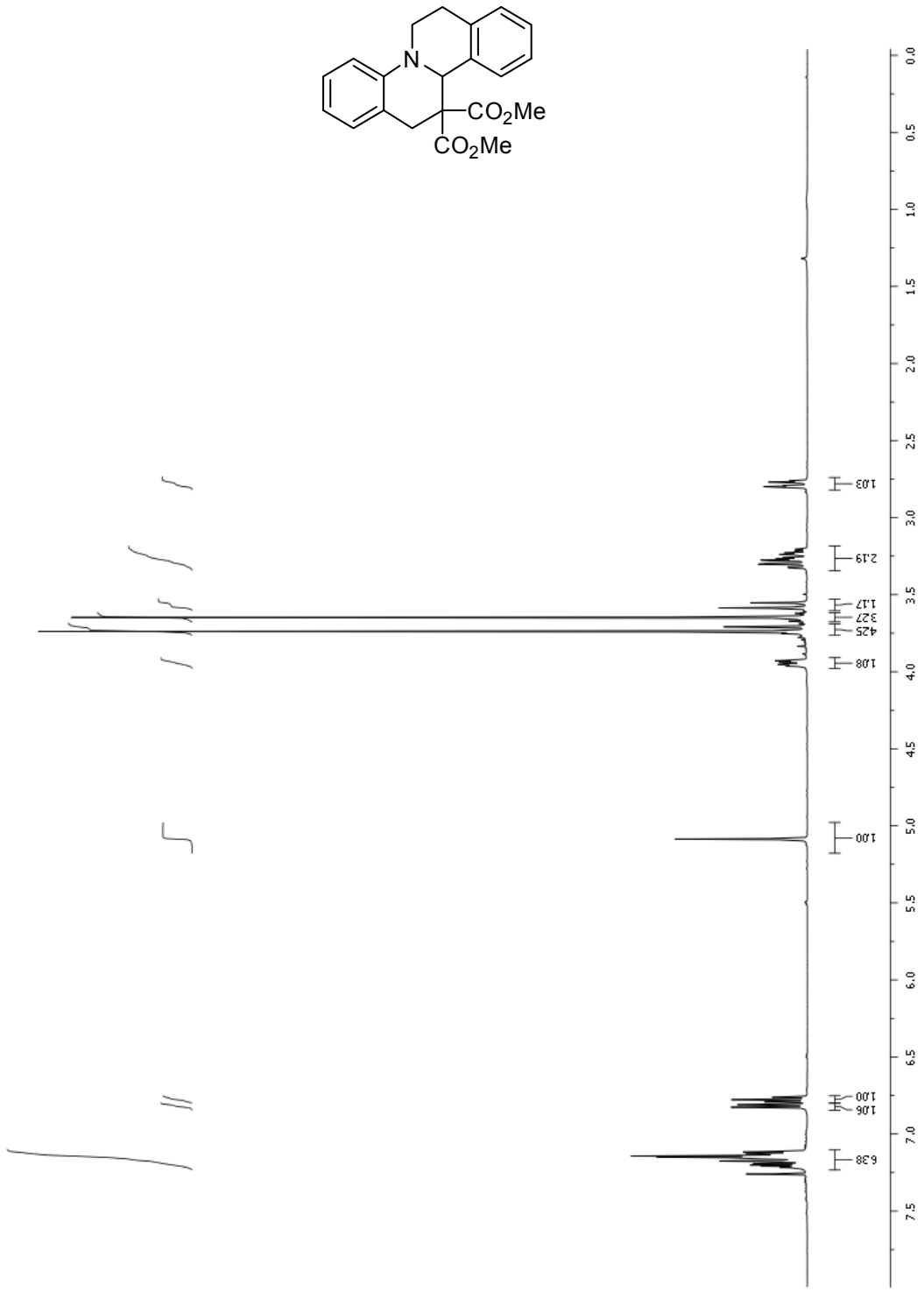

N
CO2Me
CO2Me

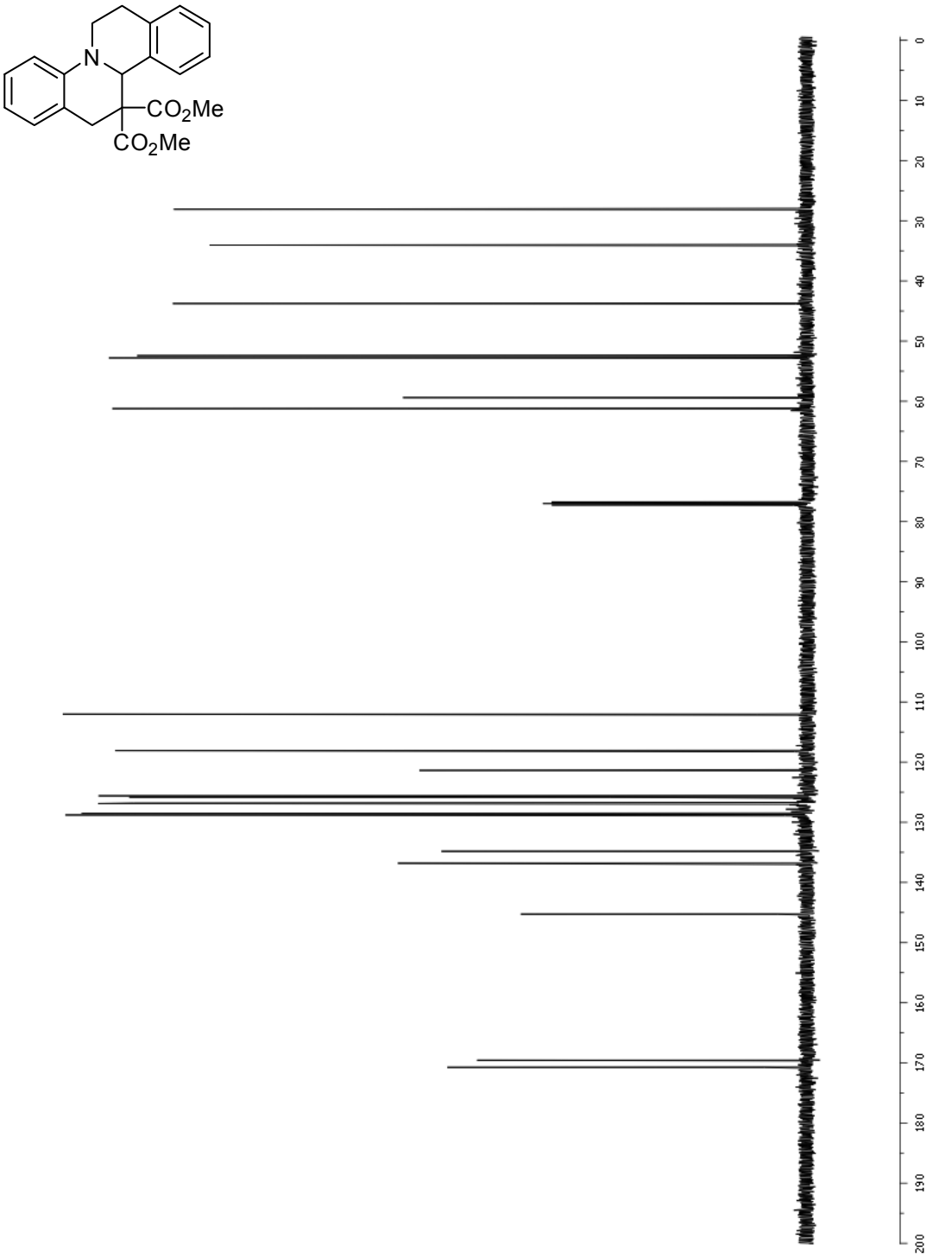
^{1}H–NMR and ^{13}C–NMR of **2.2m**:



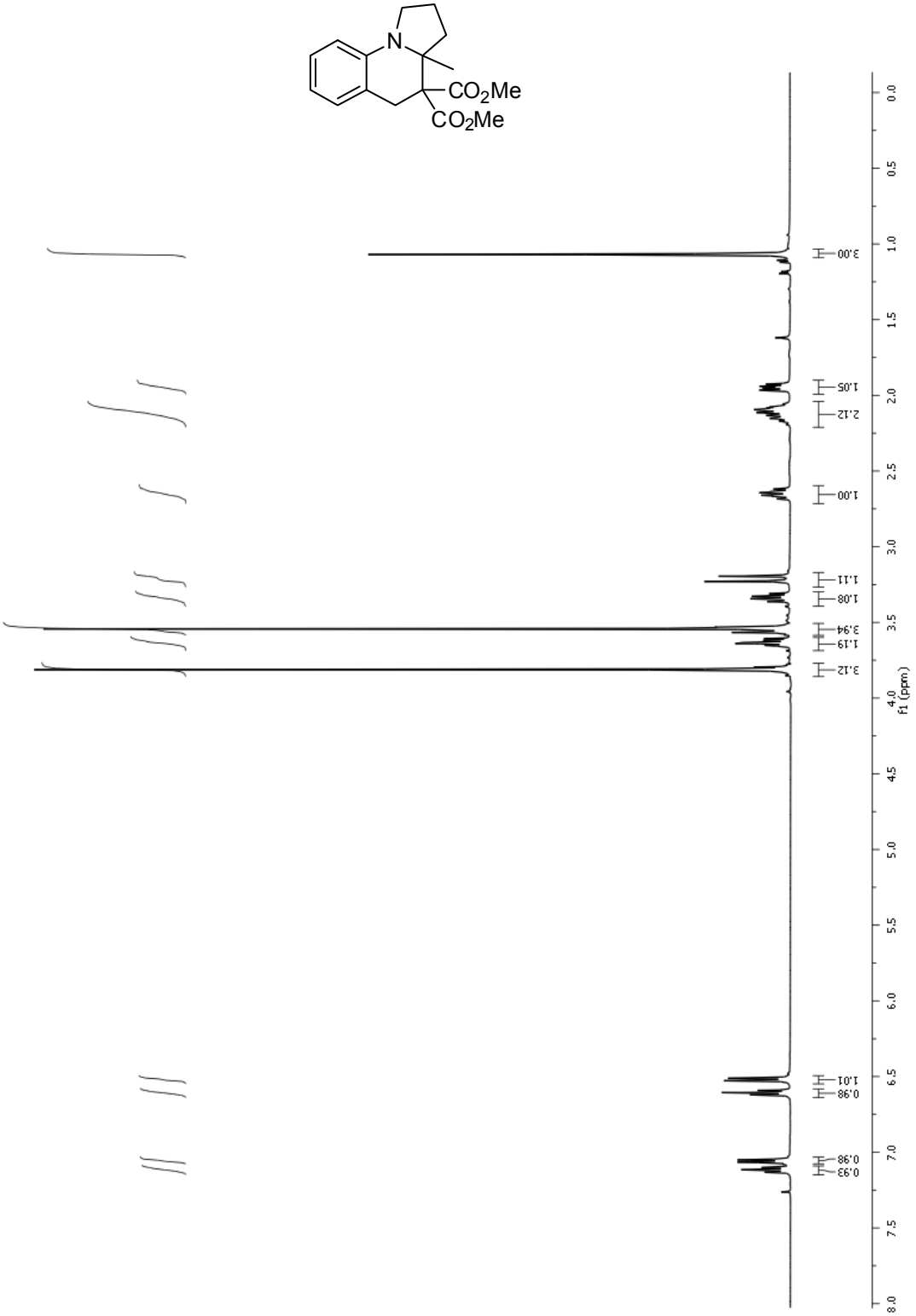

N
CO2Me
CO2Me
f1 (ppm)

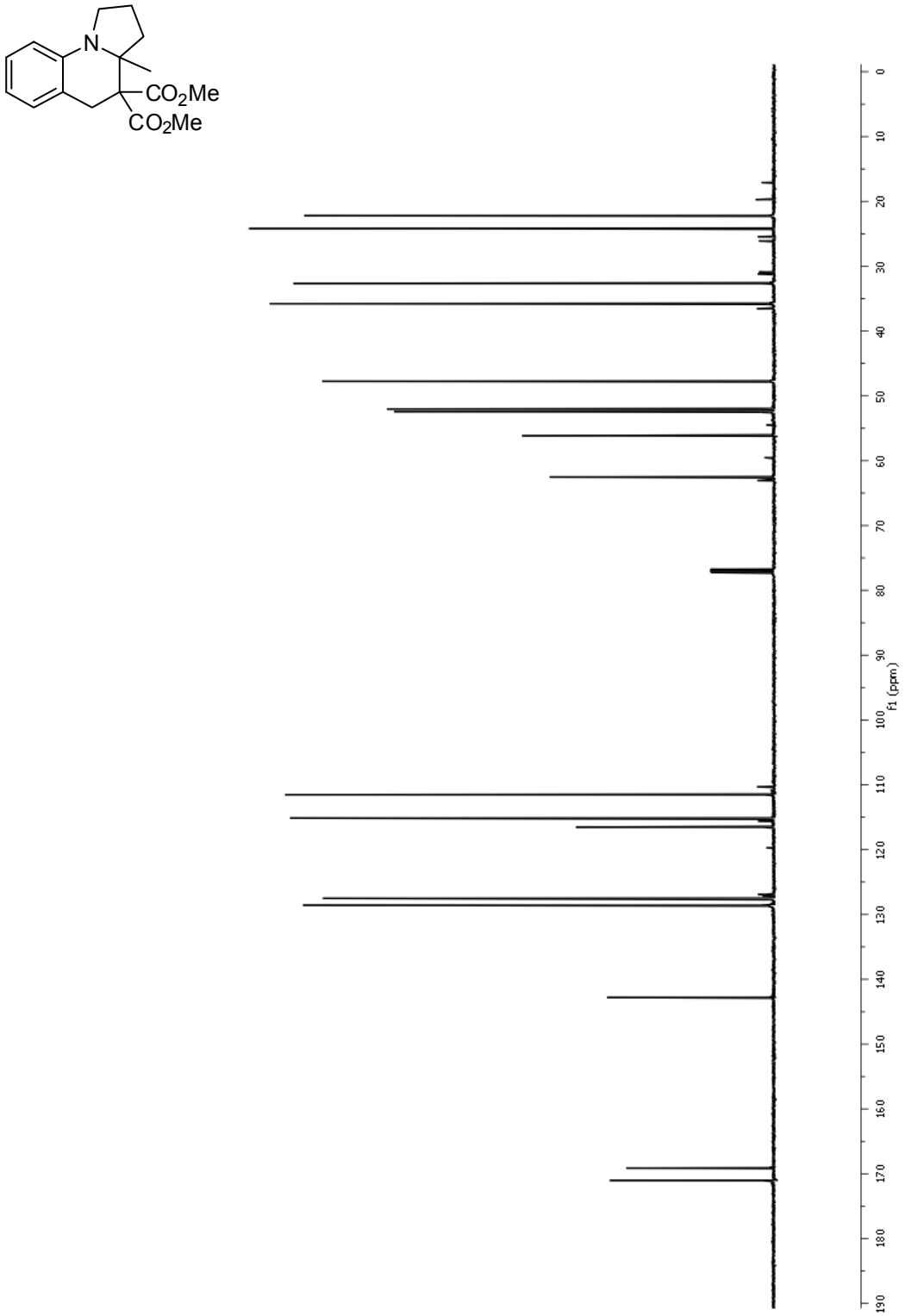
^{1}H–NMR and ^{13}C–NMR of **2.2n**:



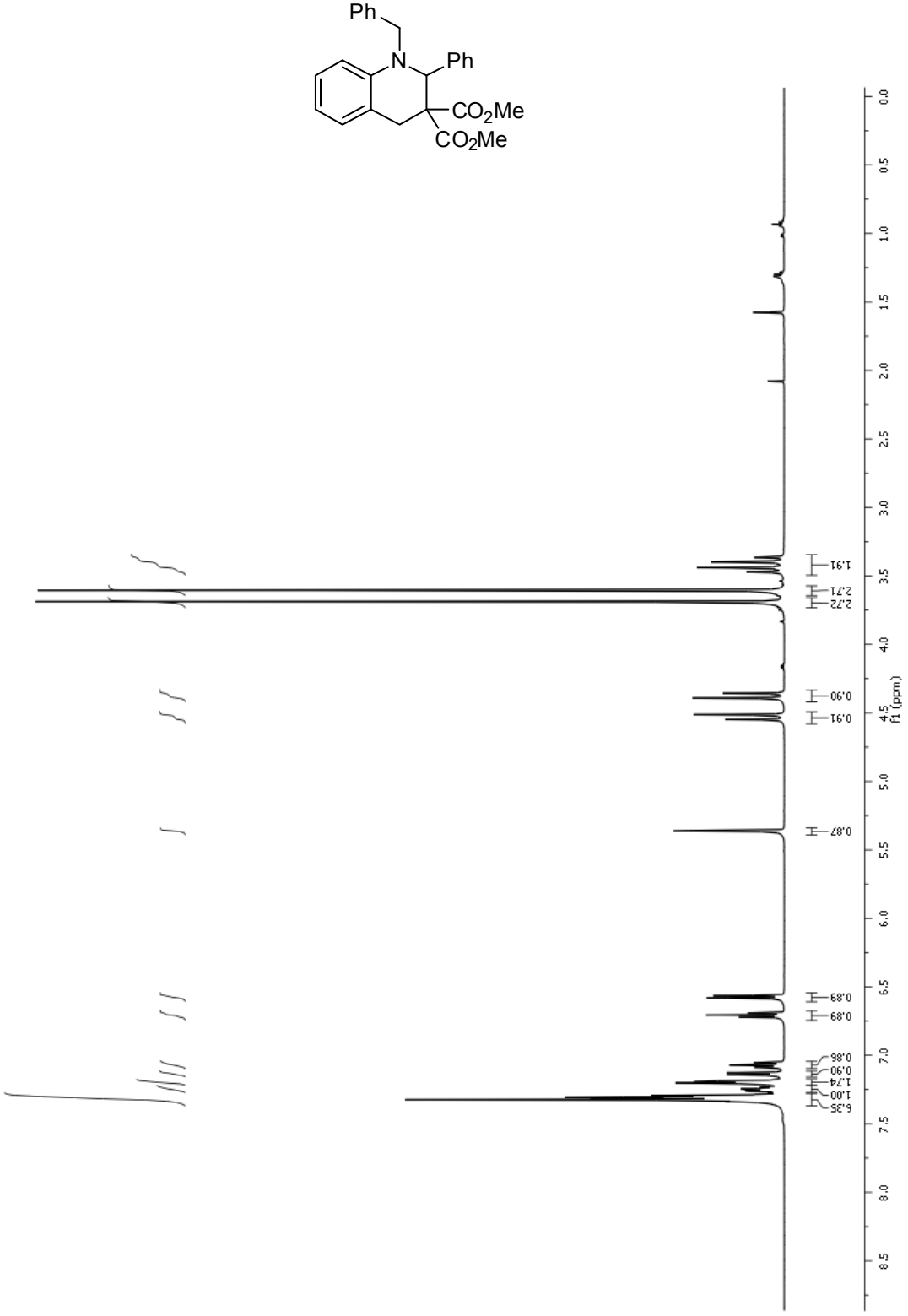

N
CO2Me
CO2Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

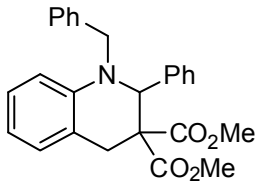
^{1}H–NMR and ^{13}C–NMR of **2.2o**:

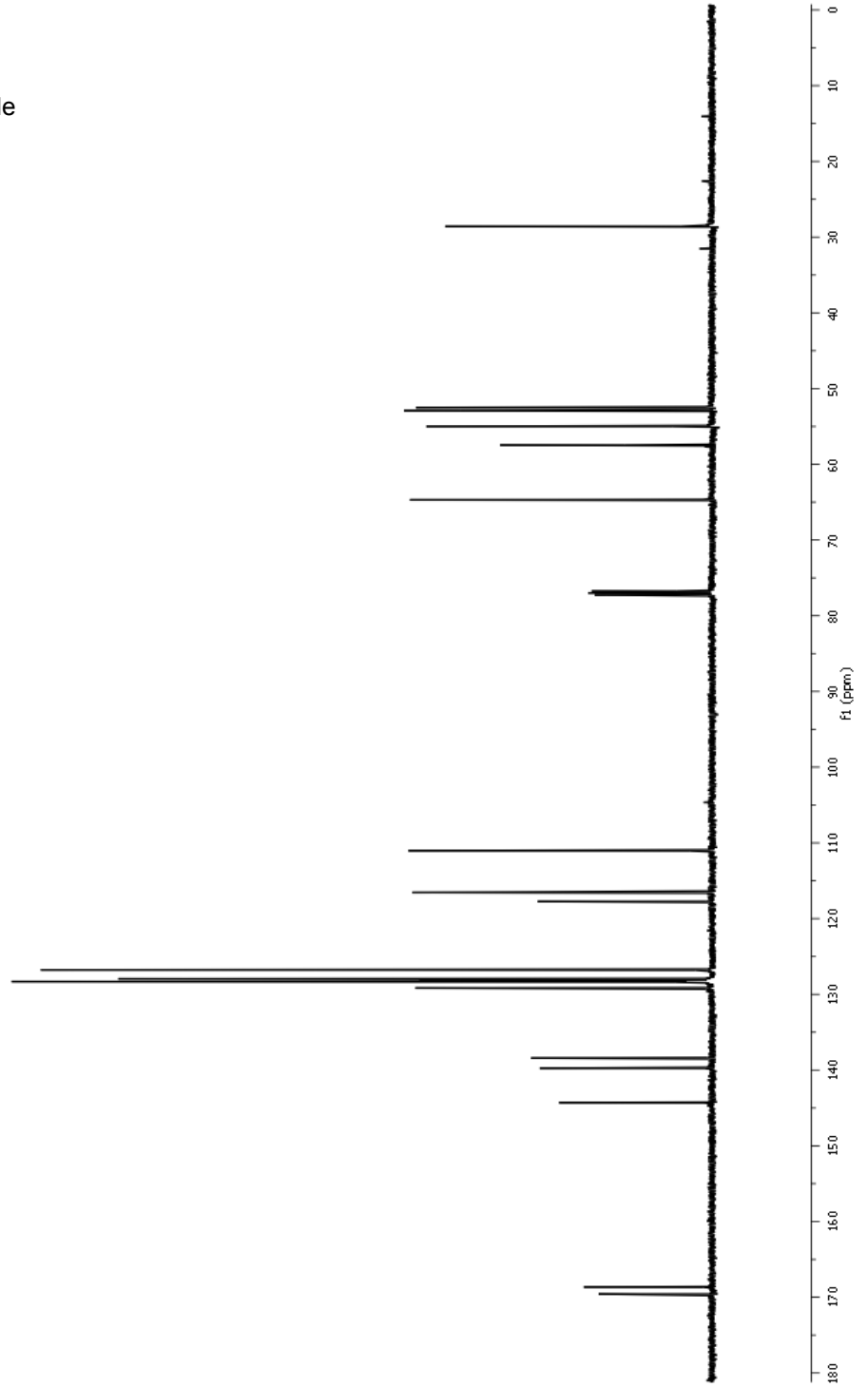



N
CO2Me
CO2Me
f1 (ppm)

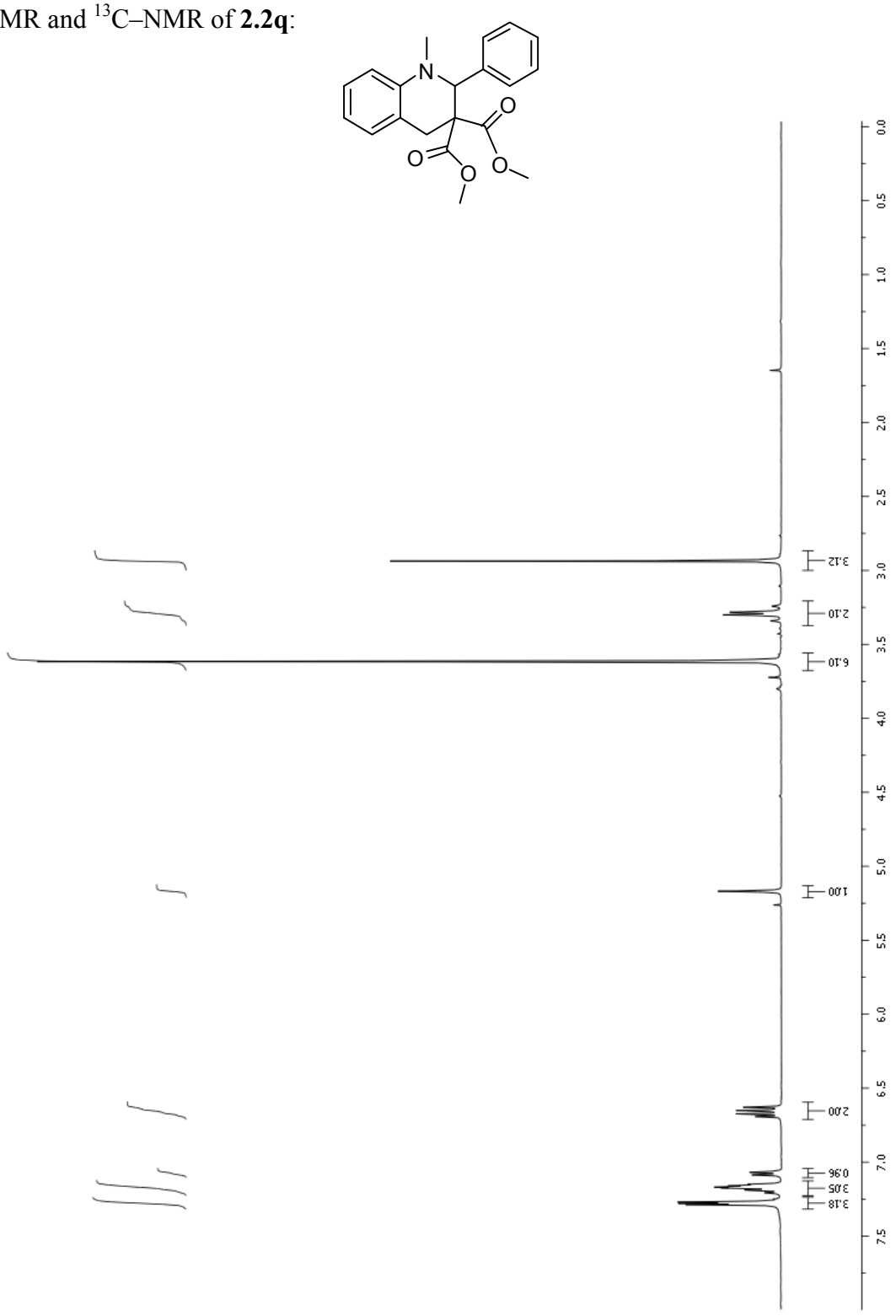
^{1}H–NMR and ^{13}C–NMR of **2.2p**:

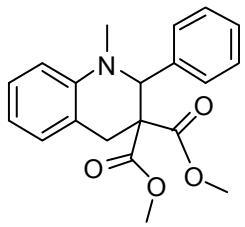



Ph
N
Ph
CO2Me
CO2Me


f1 (ppm)

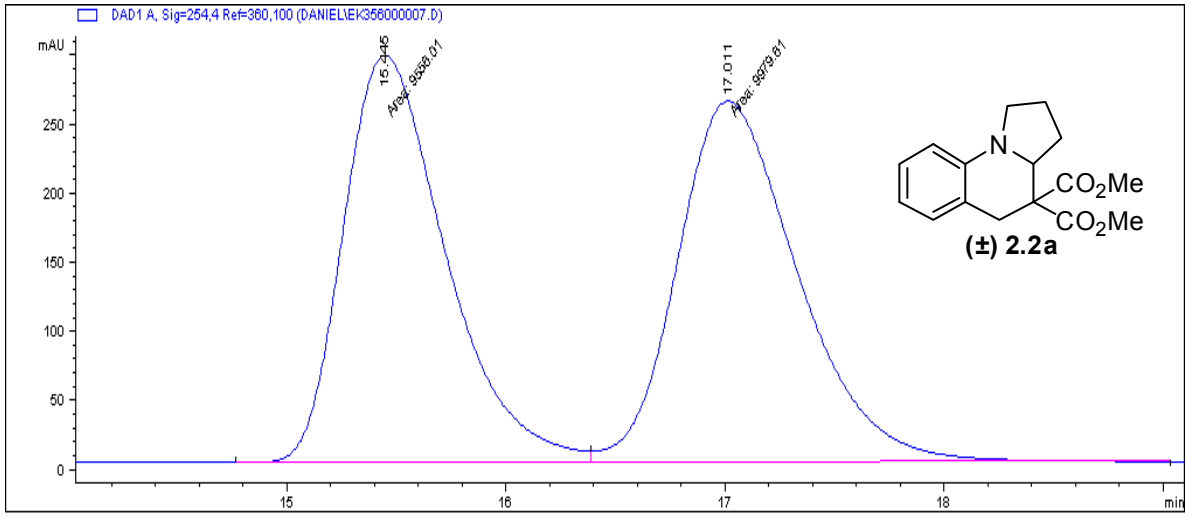
^{1}H–NMR and ^{13}C–NMR of **2.2q**:

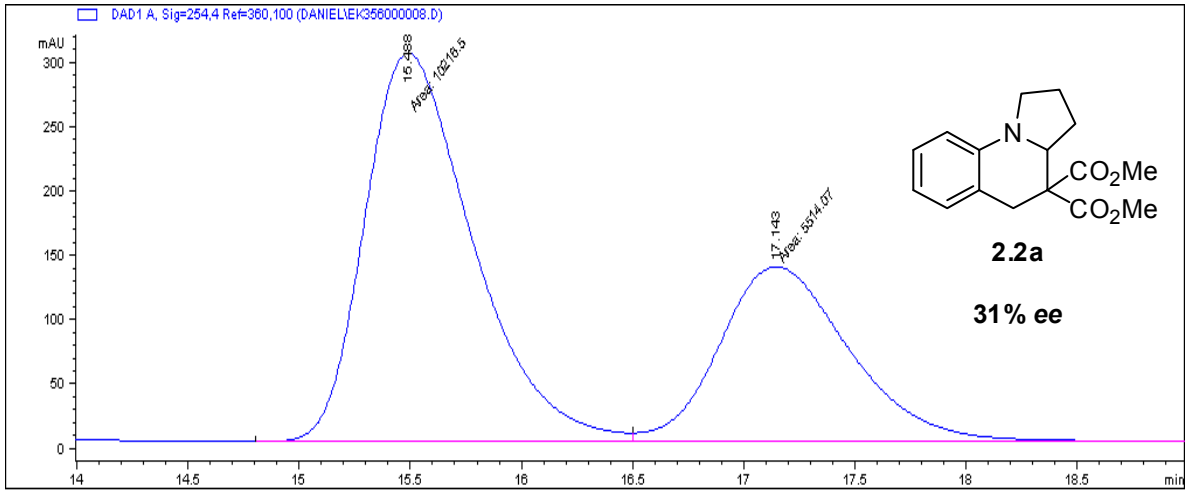



N
O
O
O
O

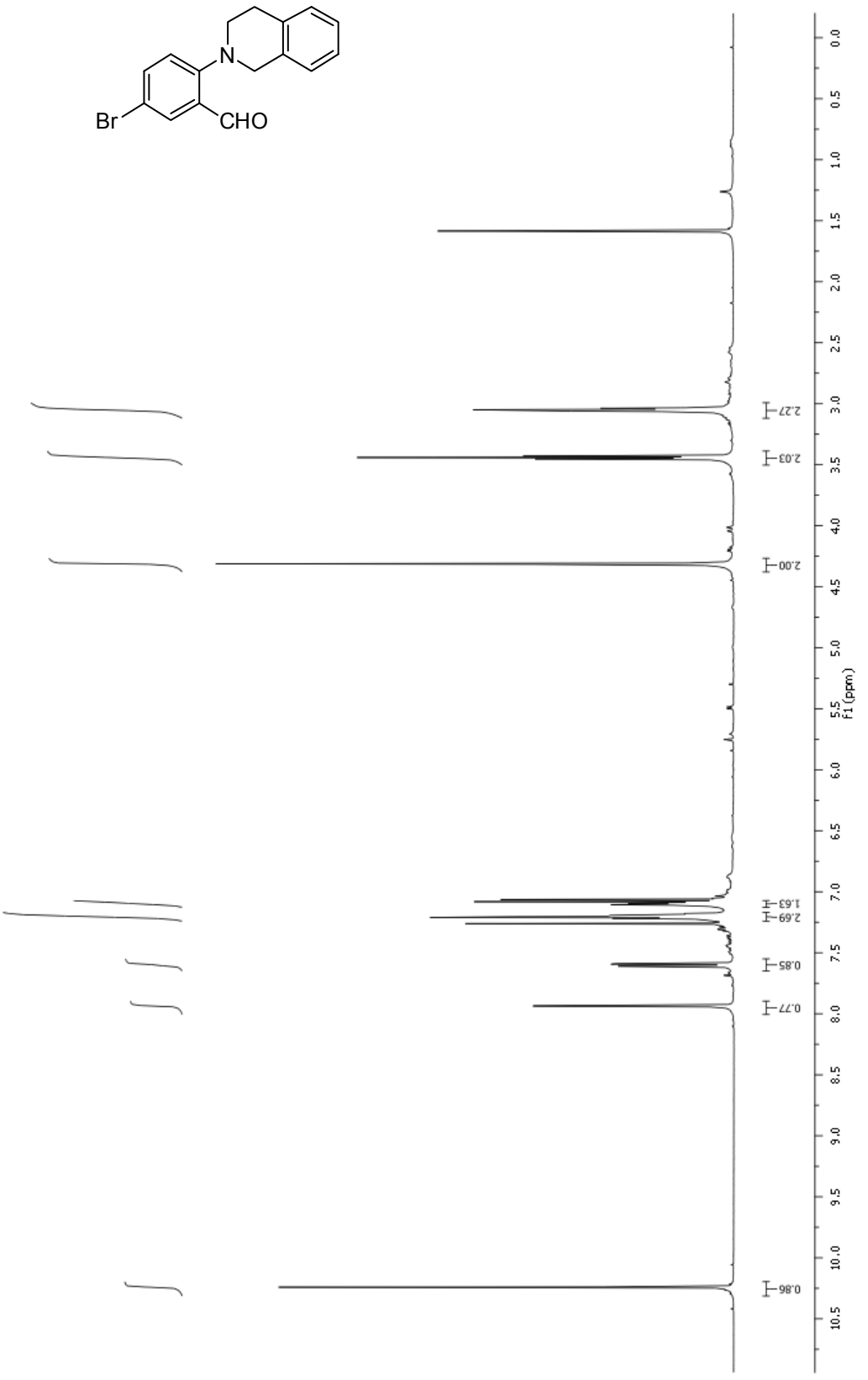
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

HPLC profile of **2.2a**

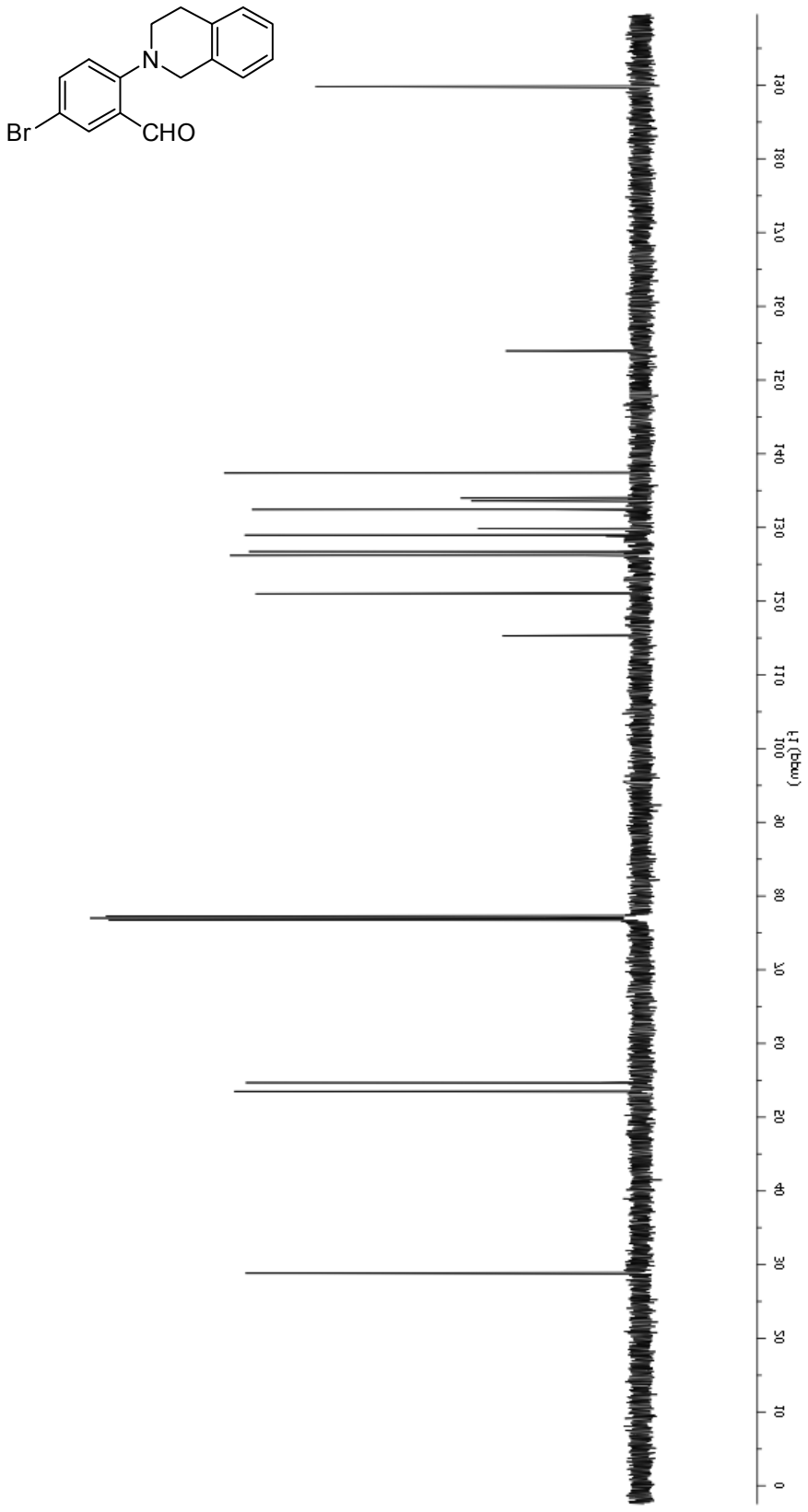




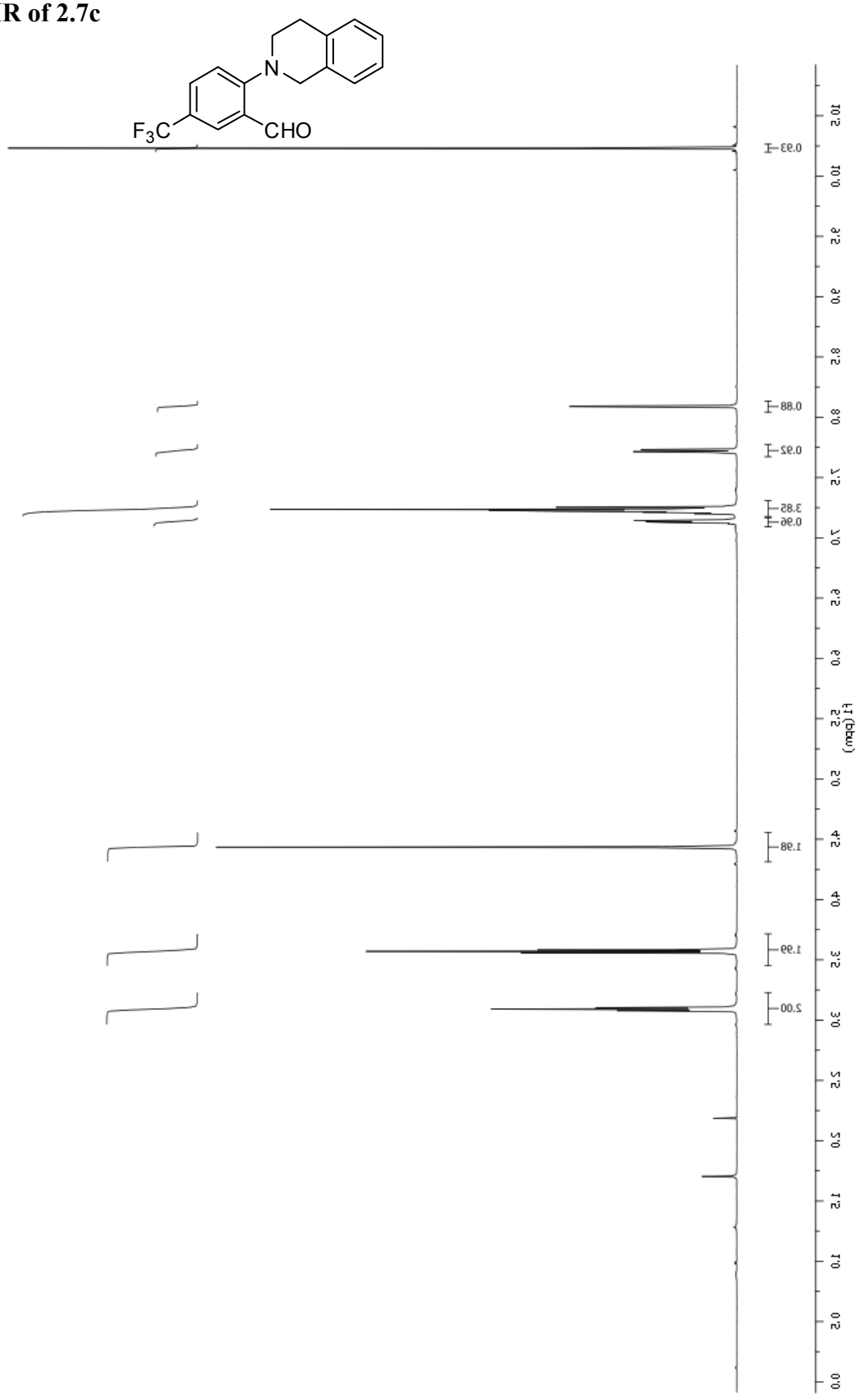
^{1}H NMR of 2.7b



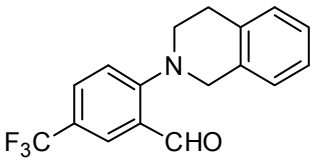
^{13}C NMR of 2.7b



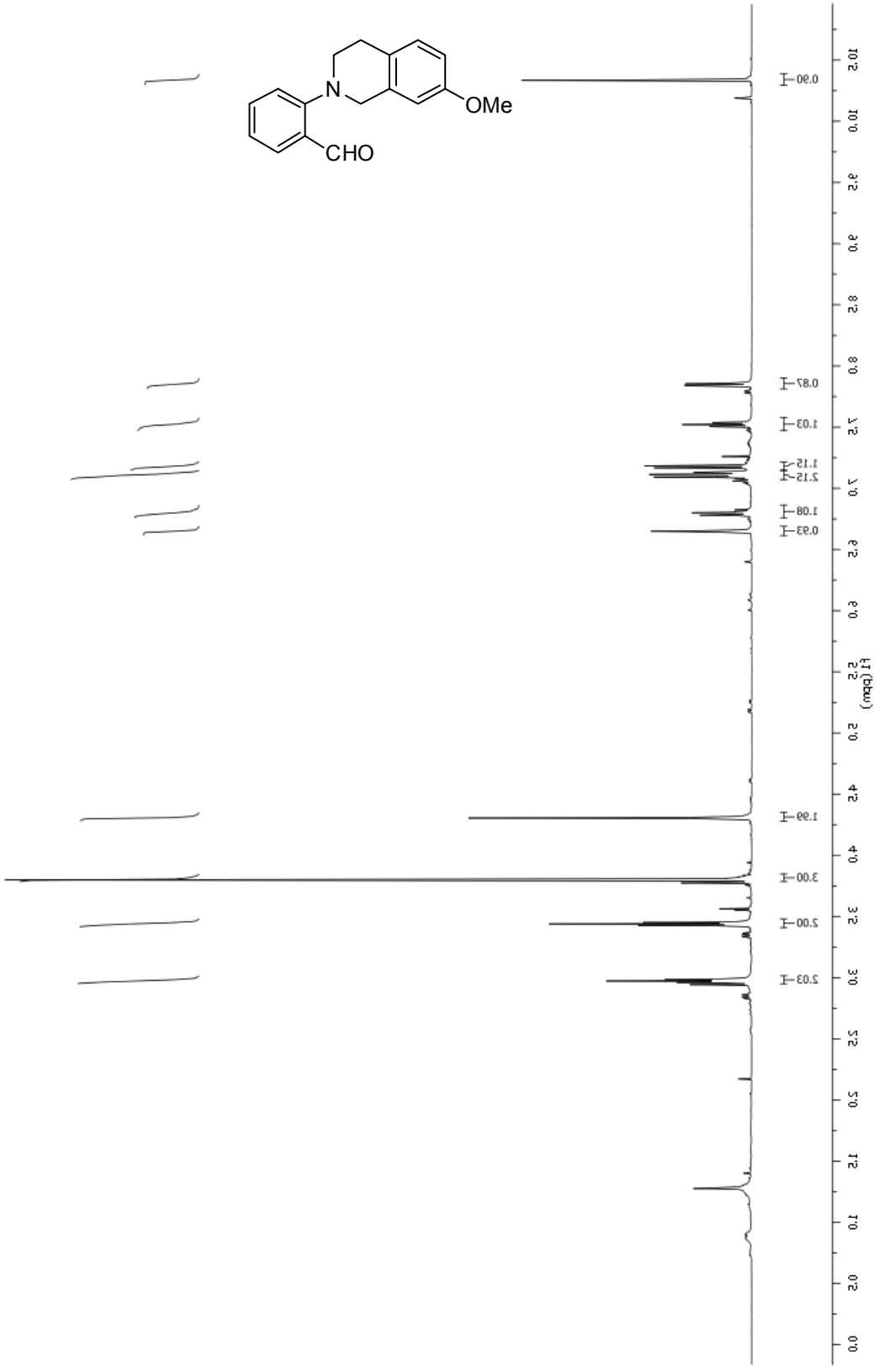
^{1}H NMR of 2.7c



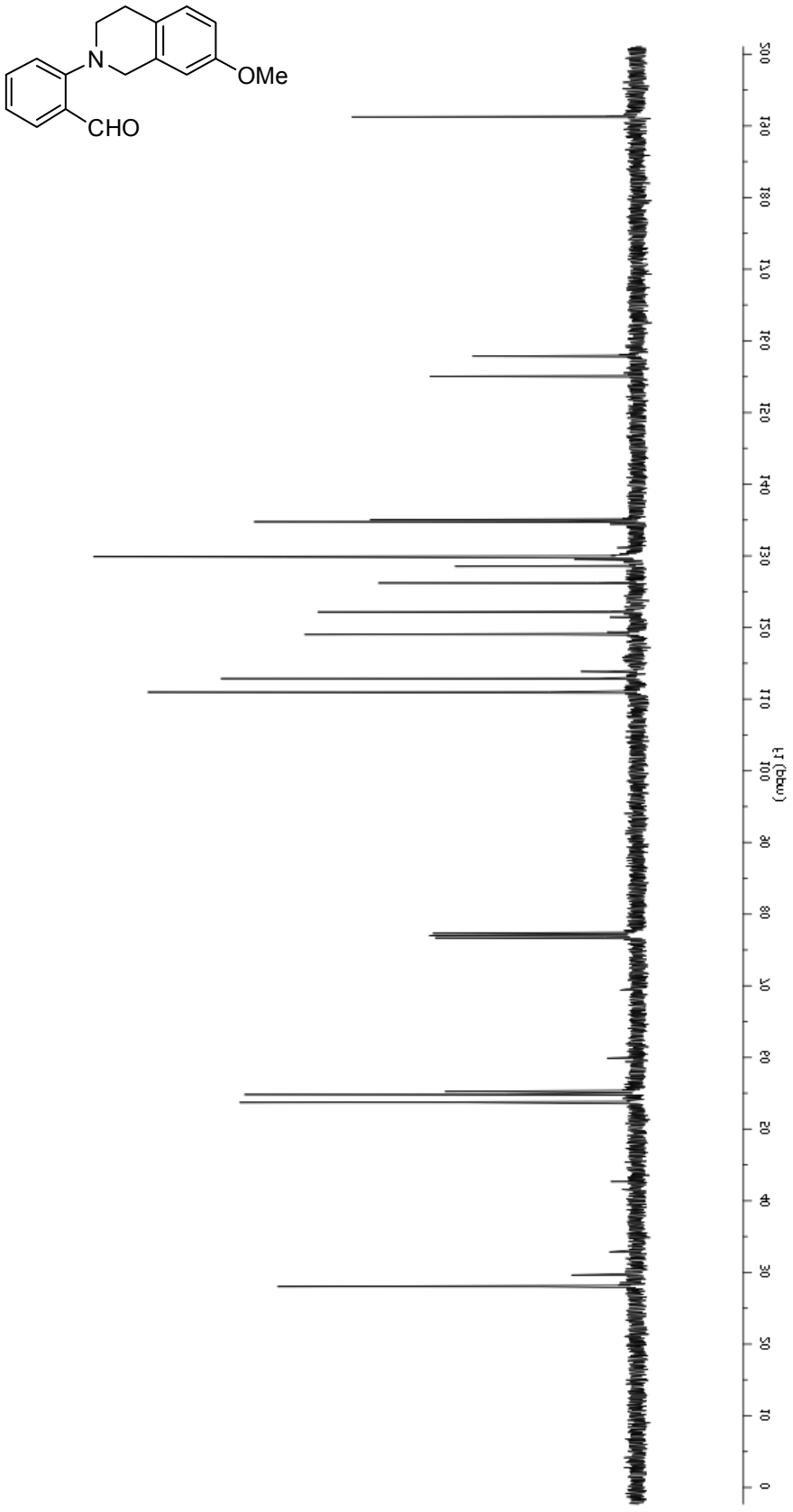
^{13}C NMR of 2.7c



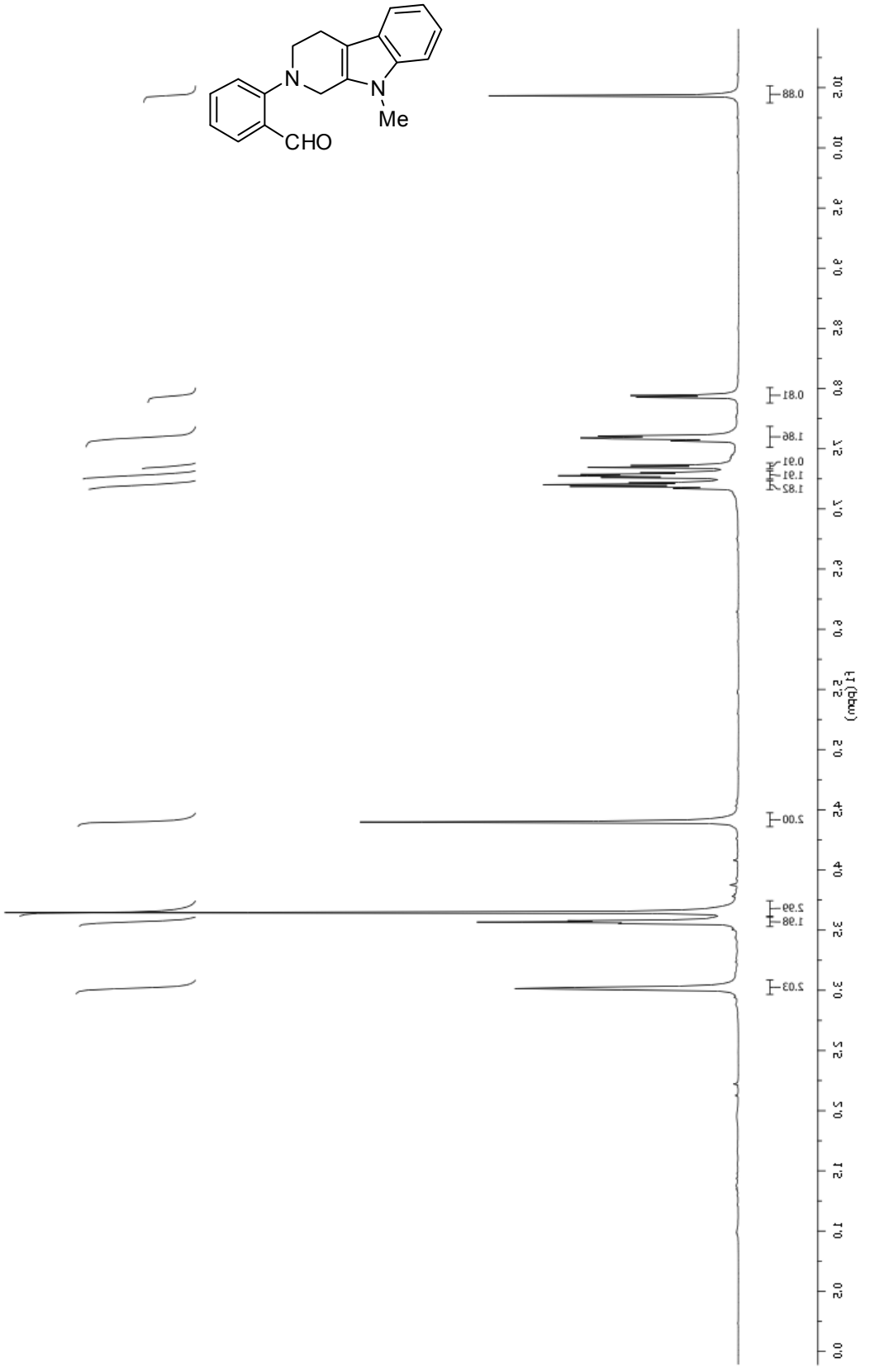
^{1}H NMR of 2.7e



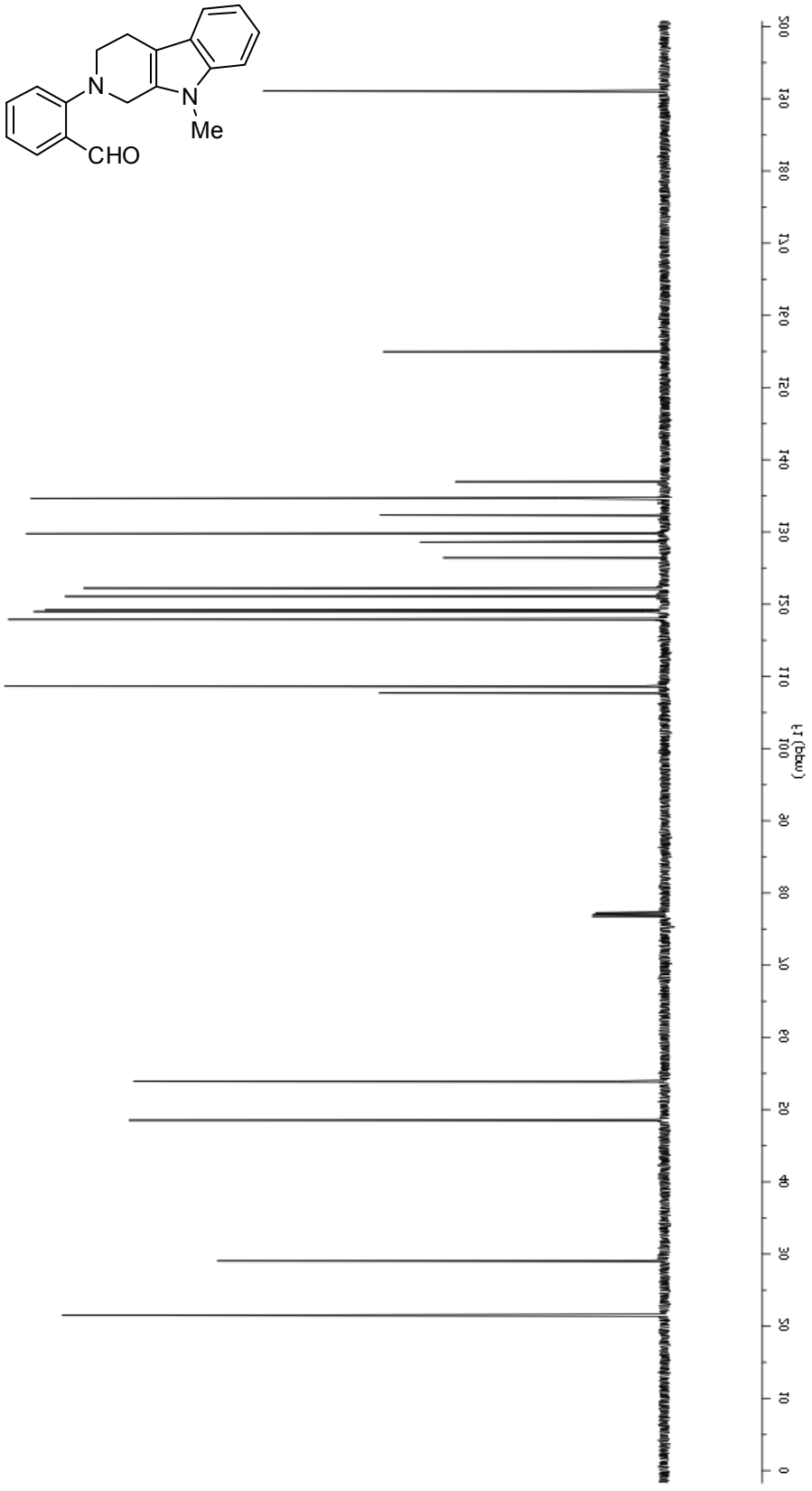
^{13}C NMR of 2.7e



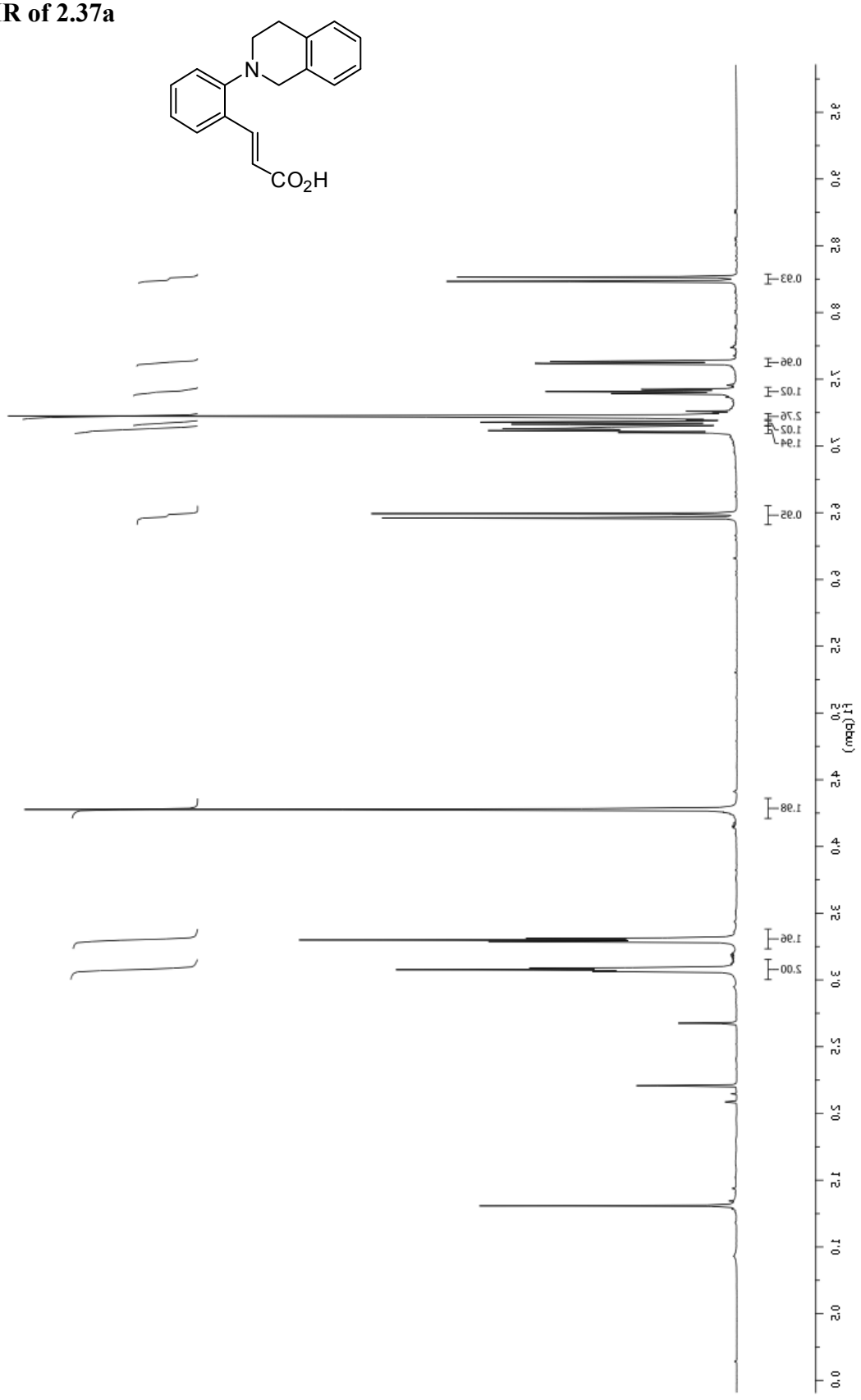
^{1}H NMR of 2.7g



^{13}C NMR of 2.7g



^{1}H NMR of 2.37a



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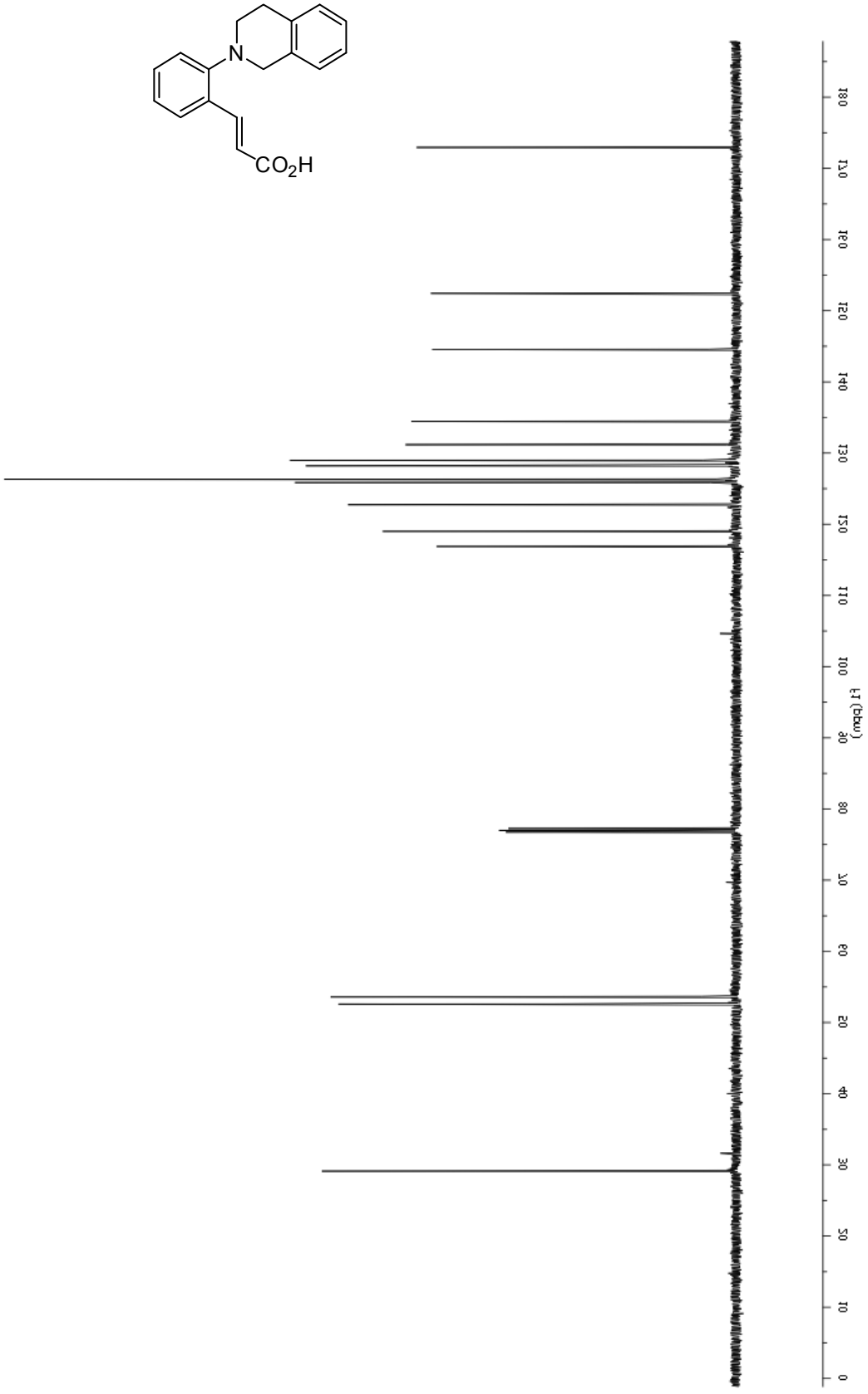

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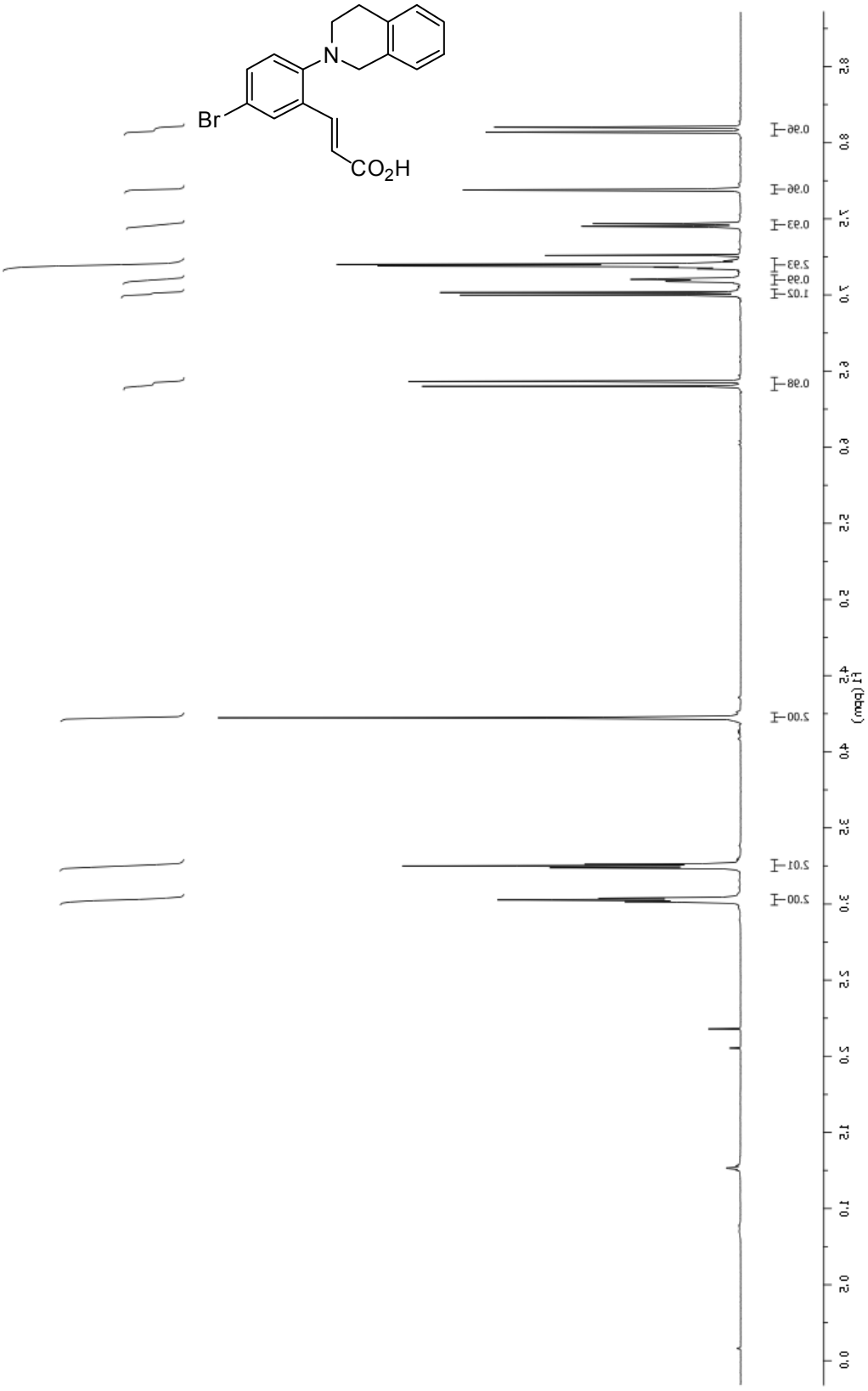

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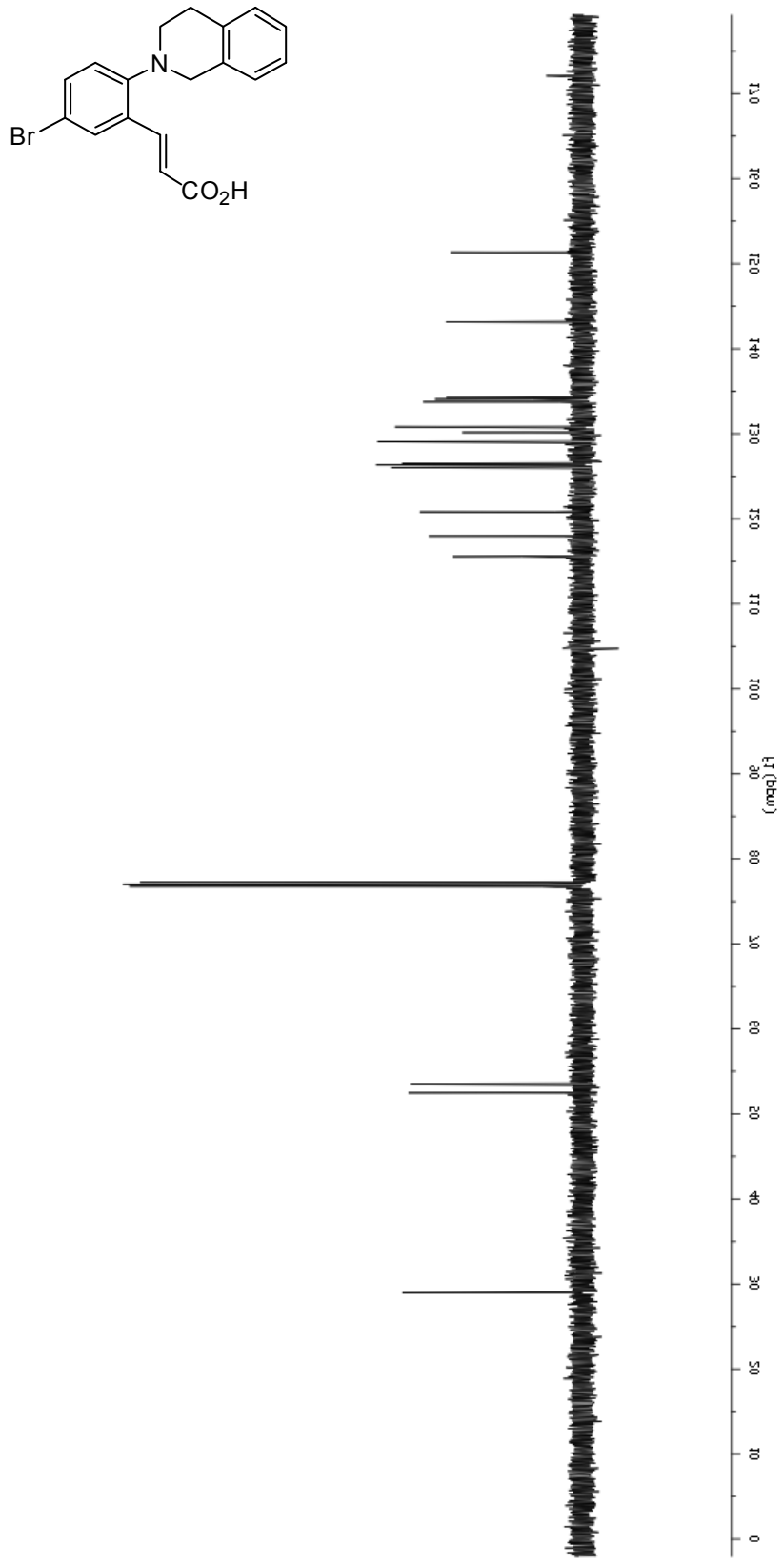

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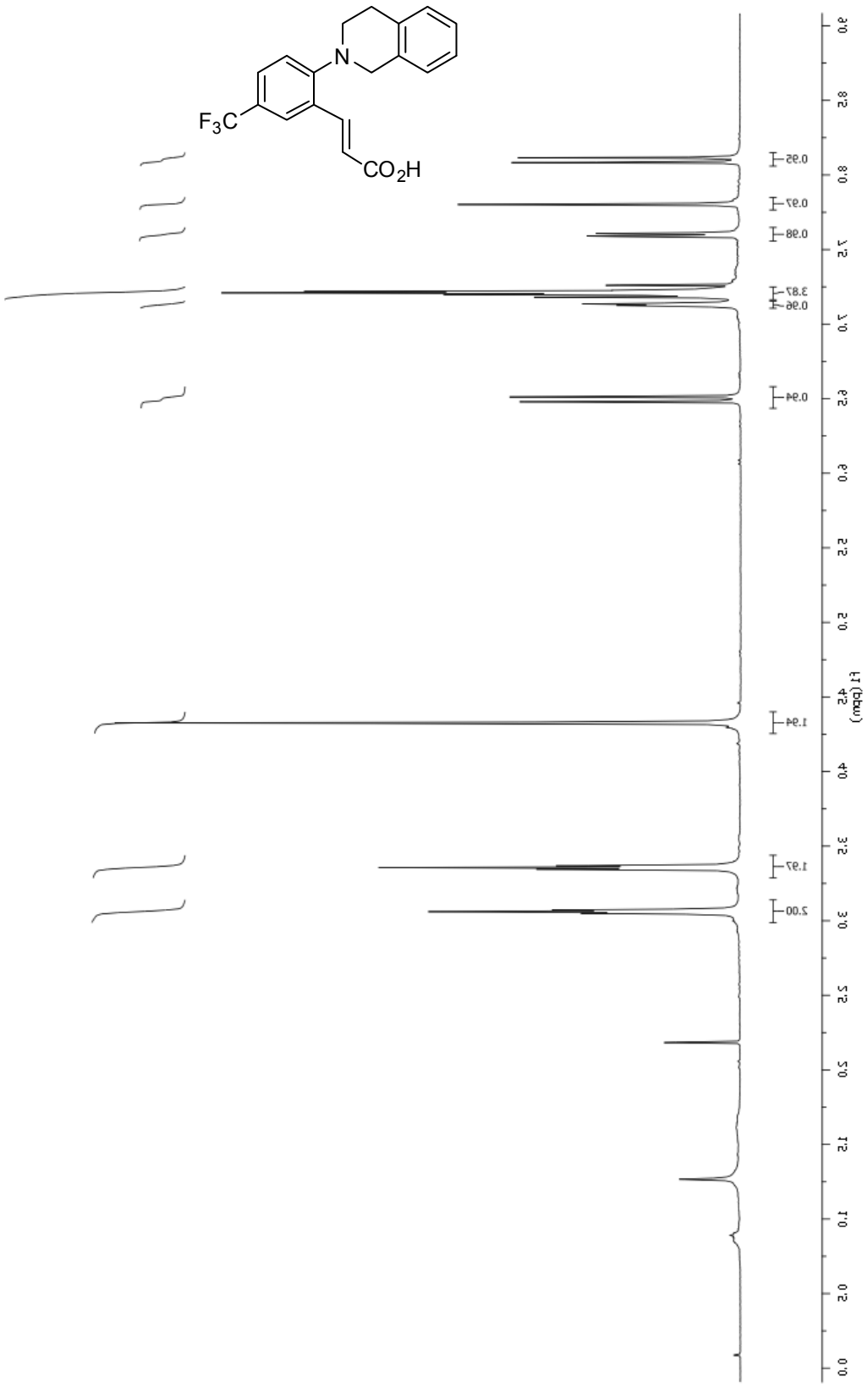

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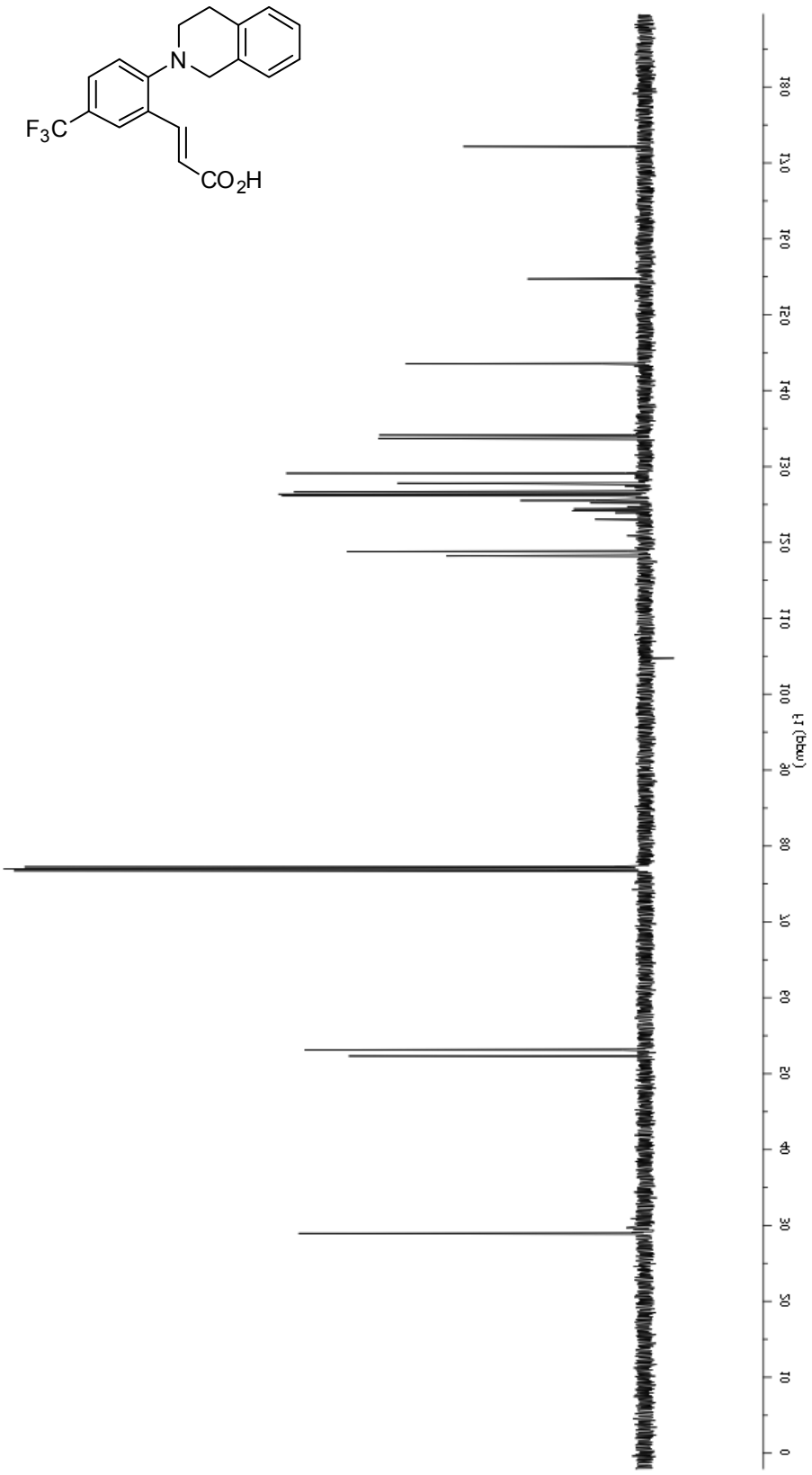
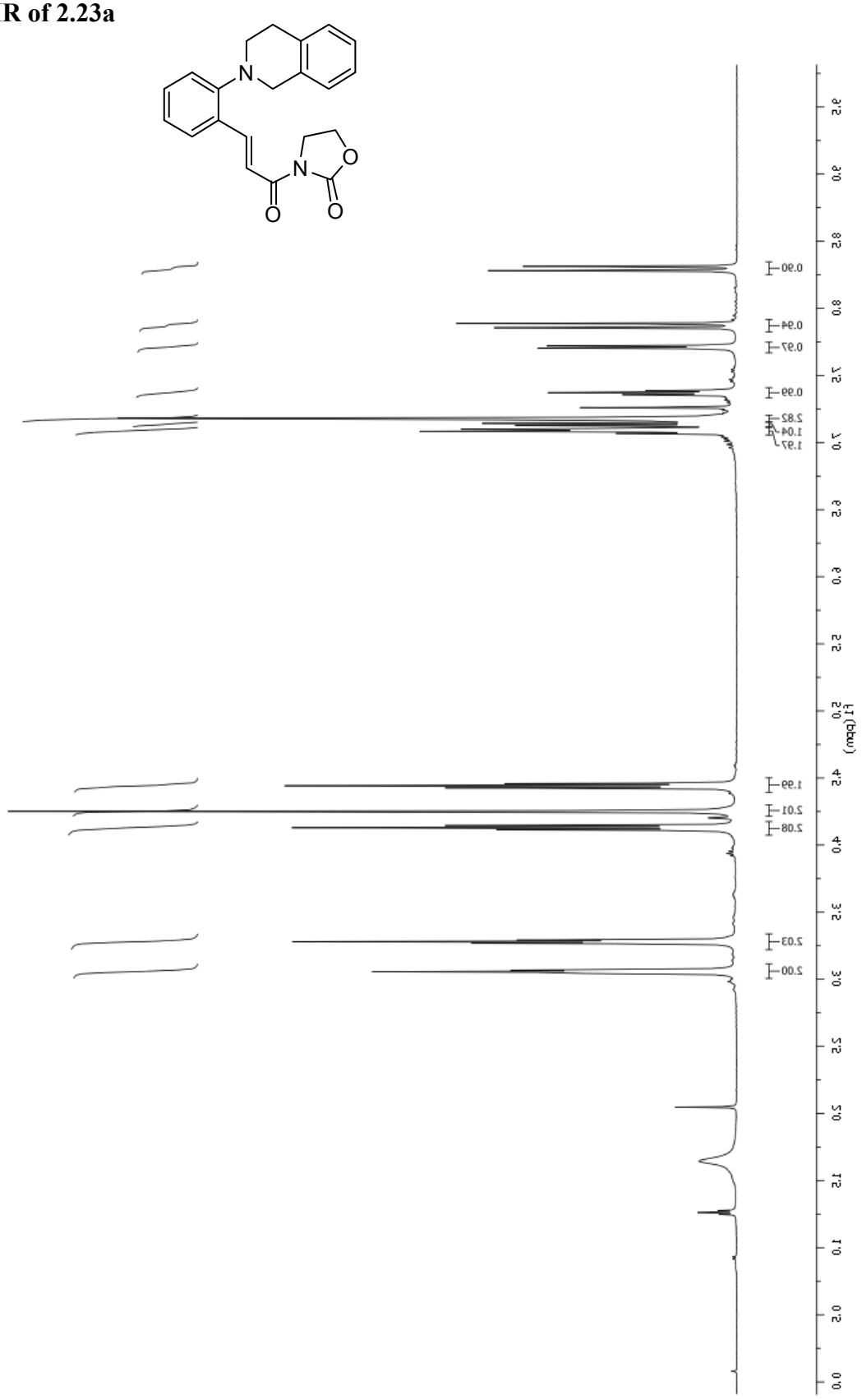


^{1}H NMR of 2.23a



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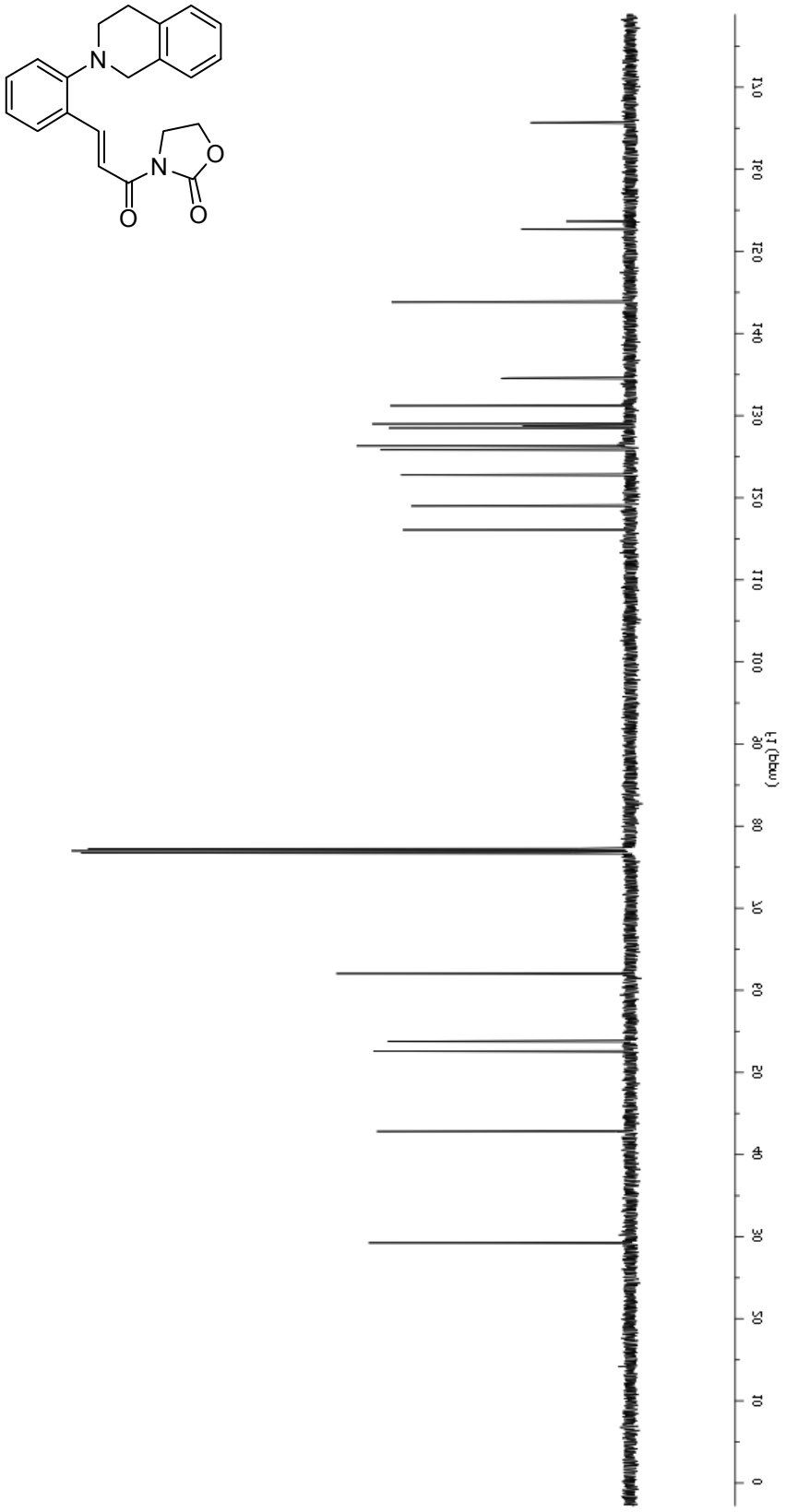

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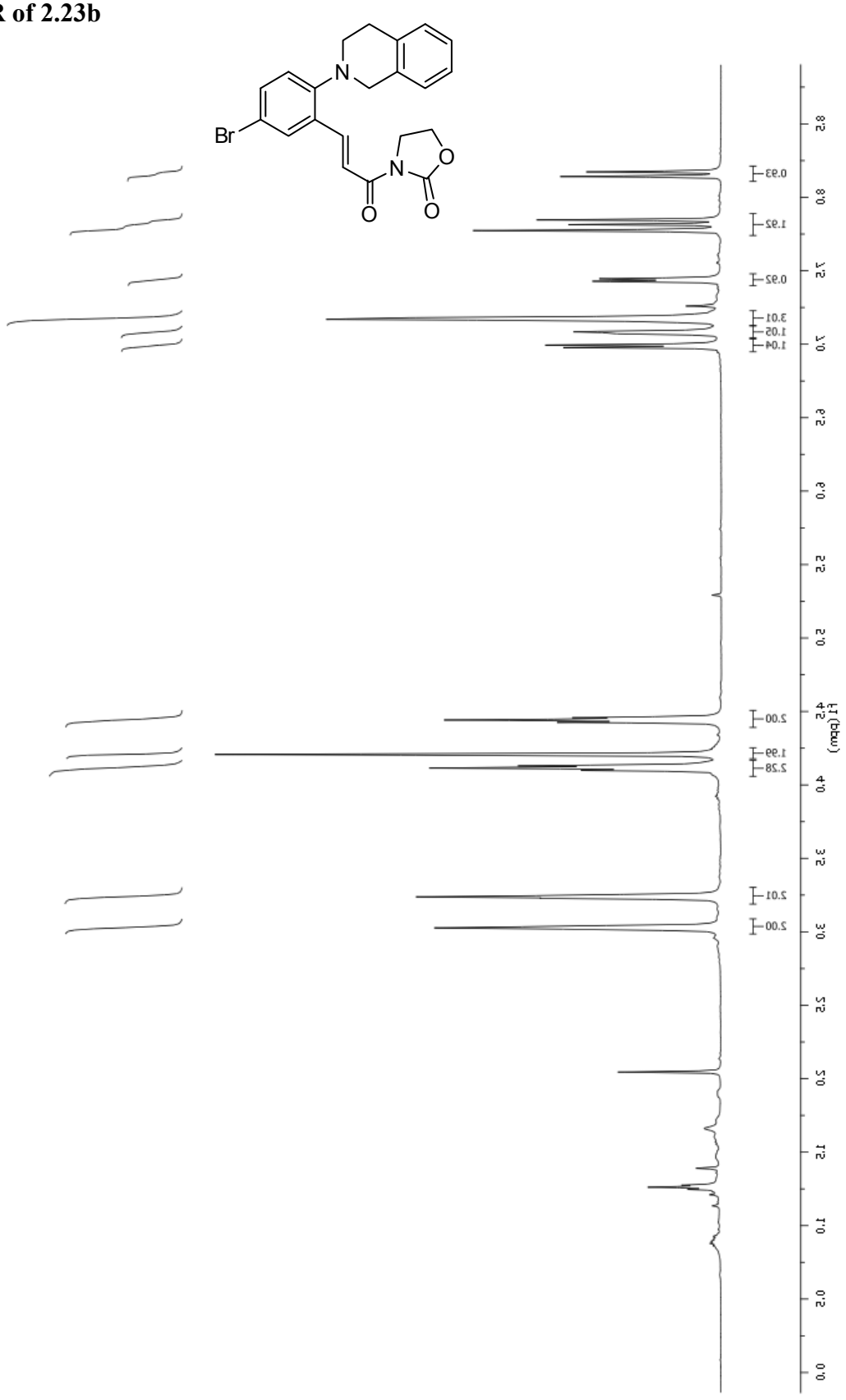

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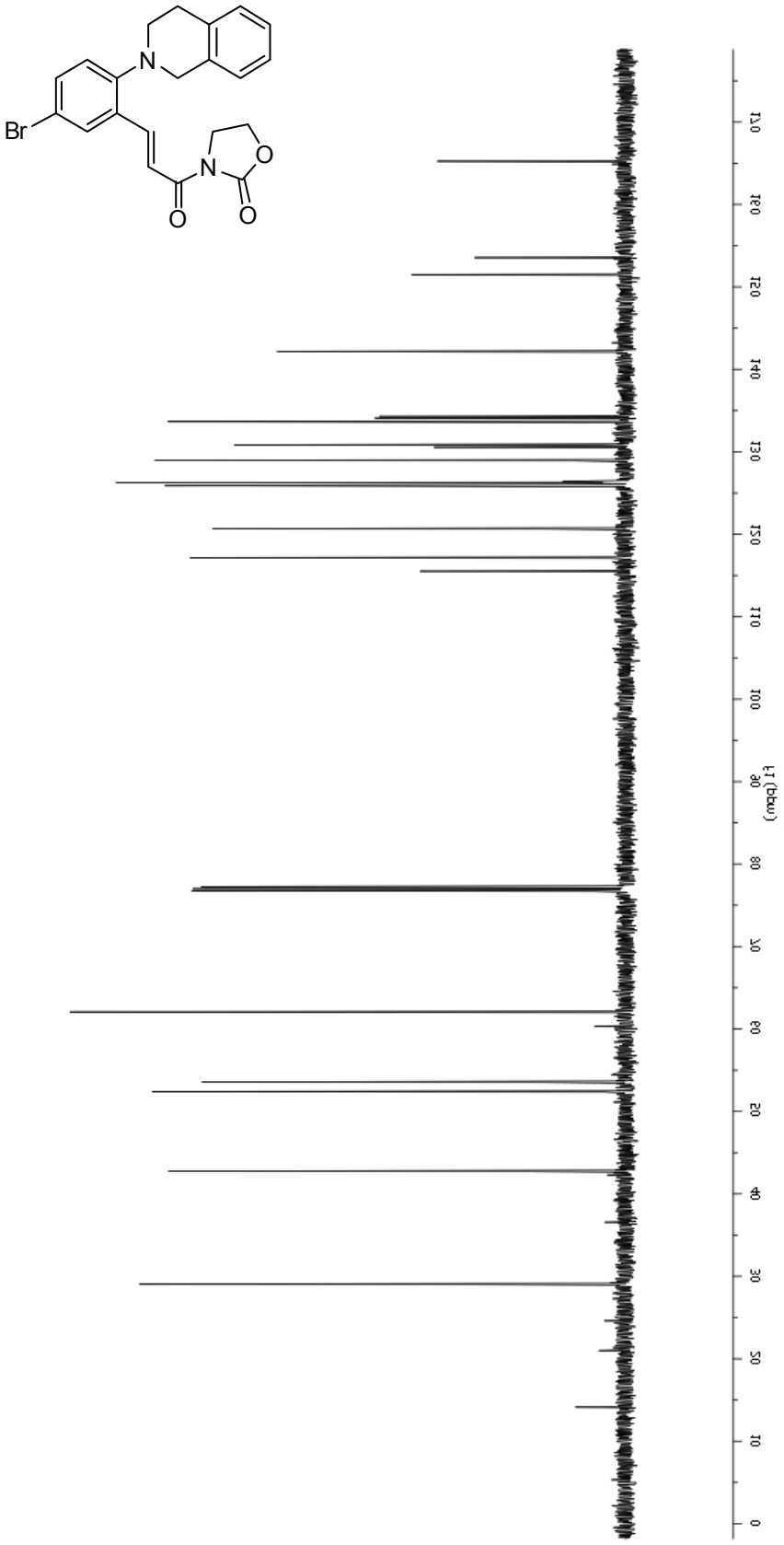

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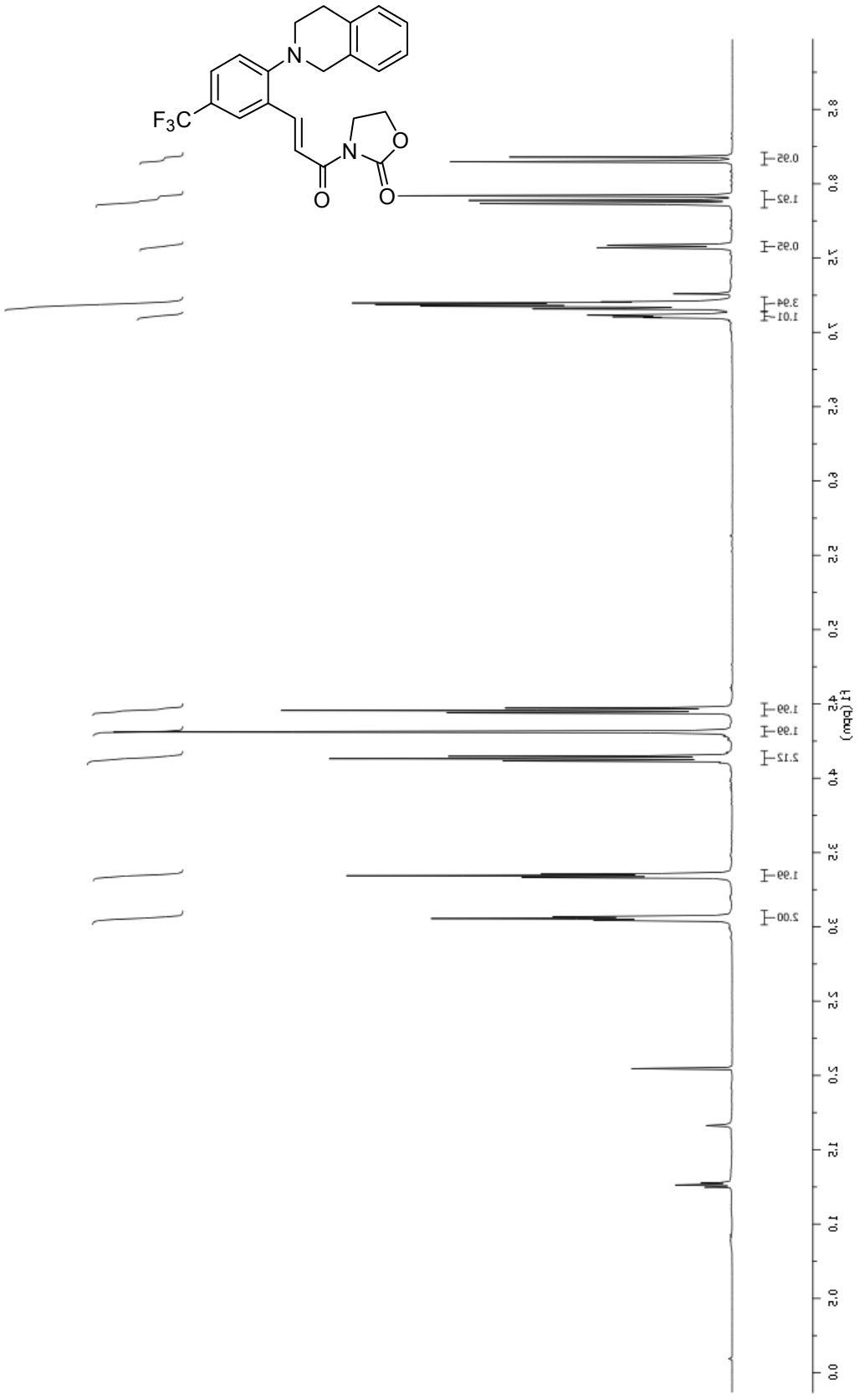
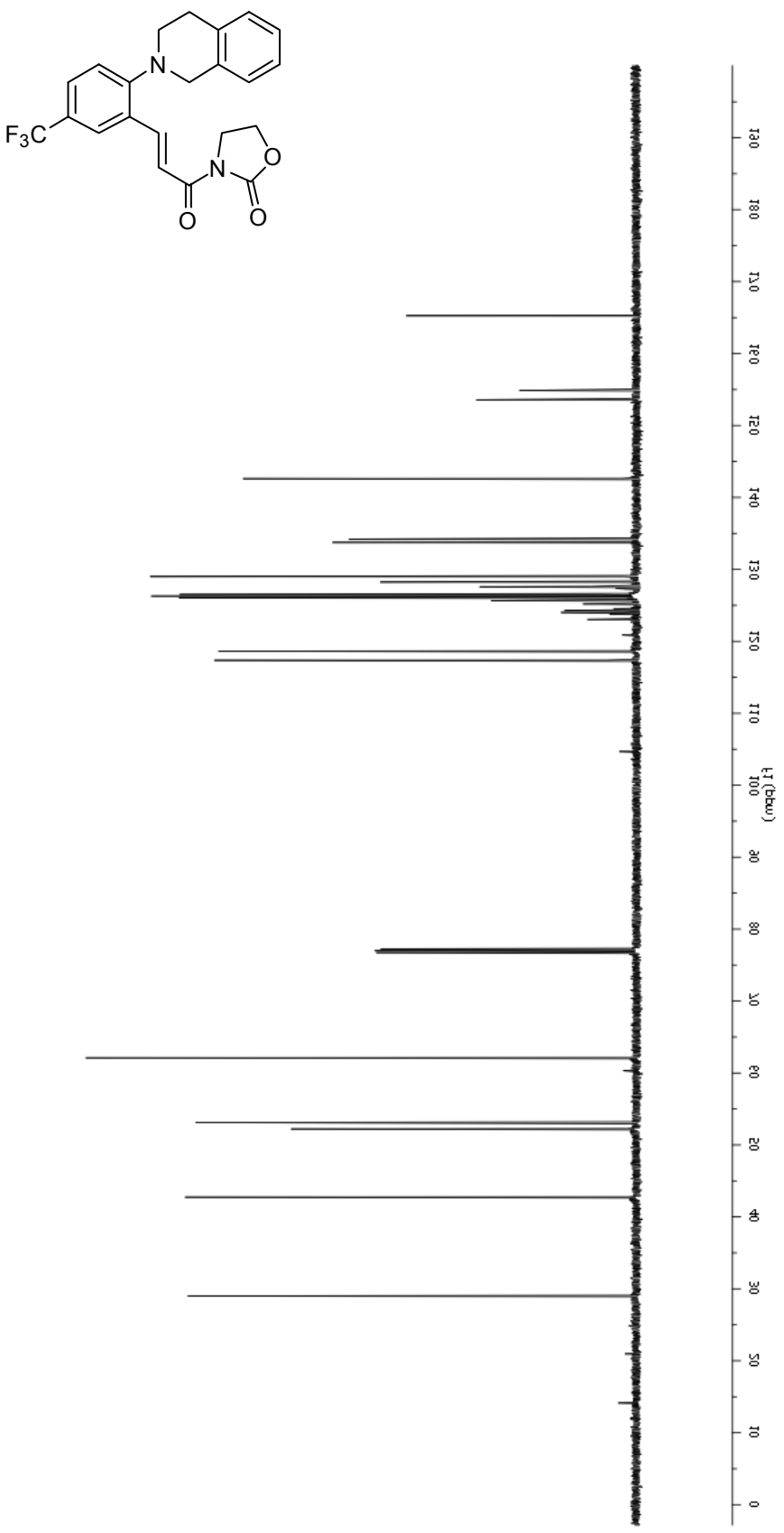
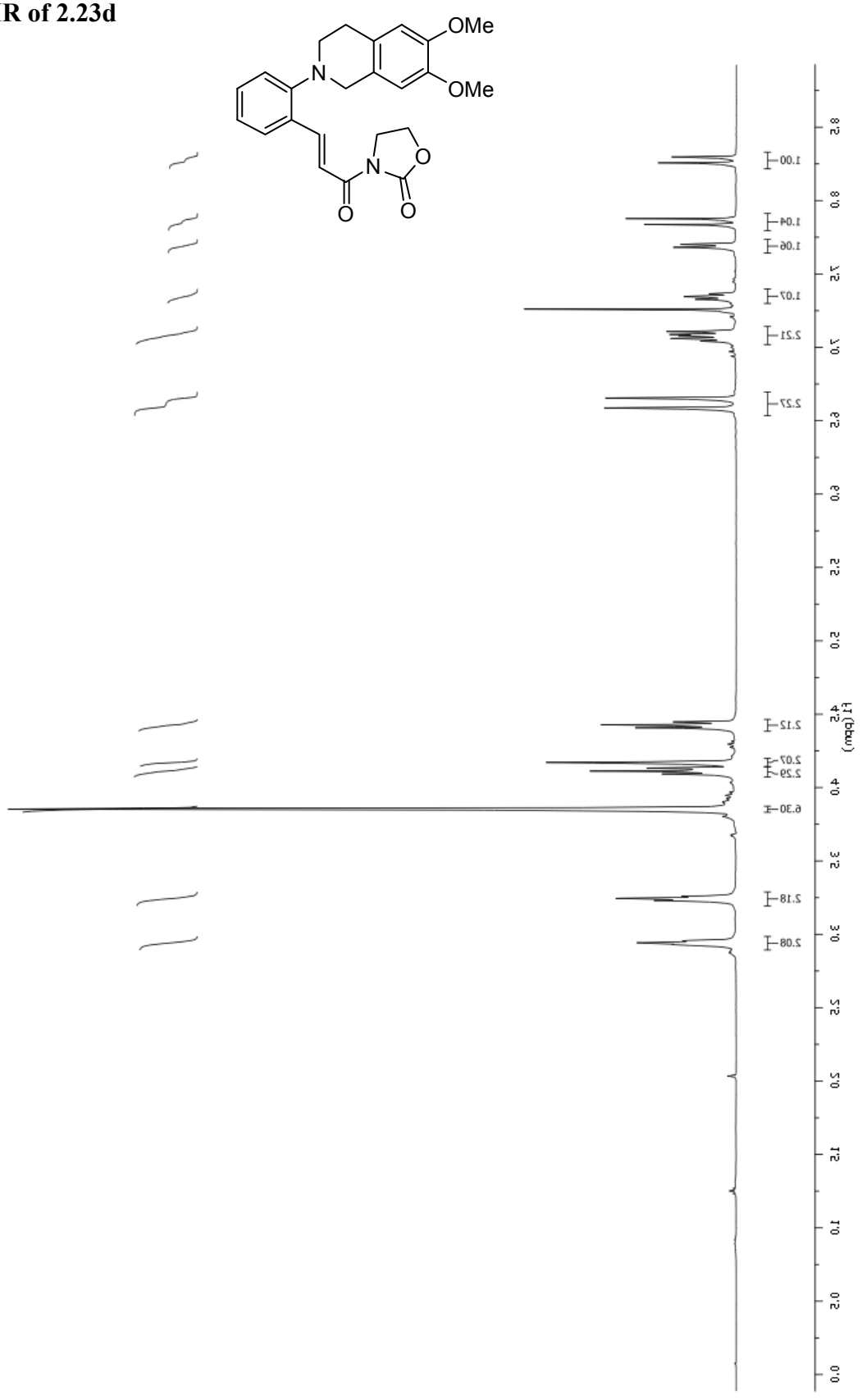


^{13}C NMR of 2.23c



^{1}H NMR of 2.23d



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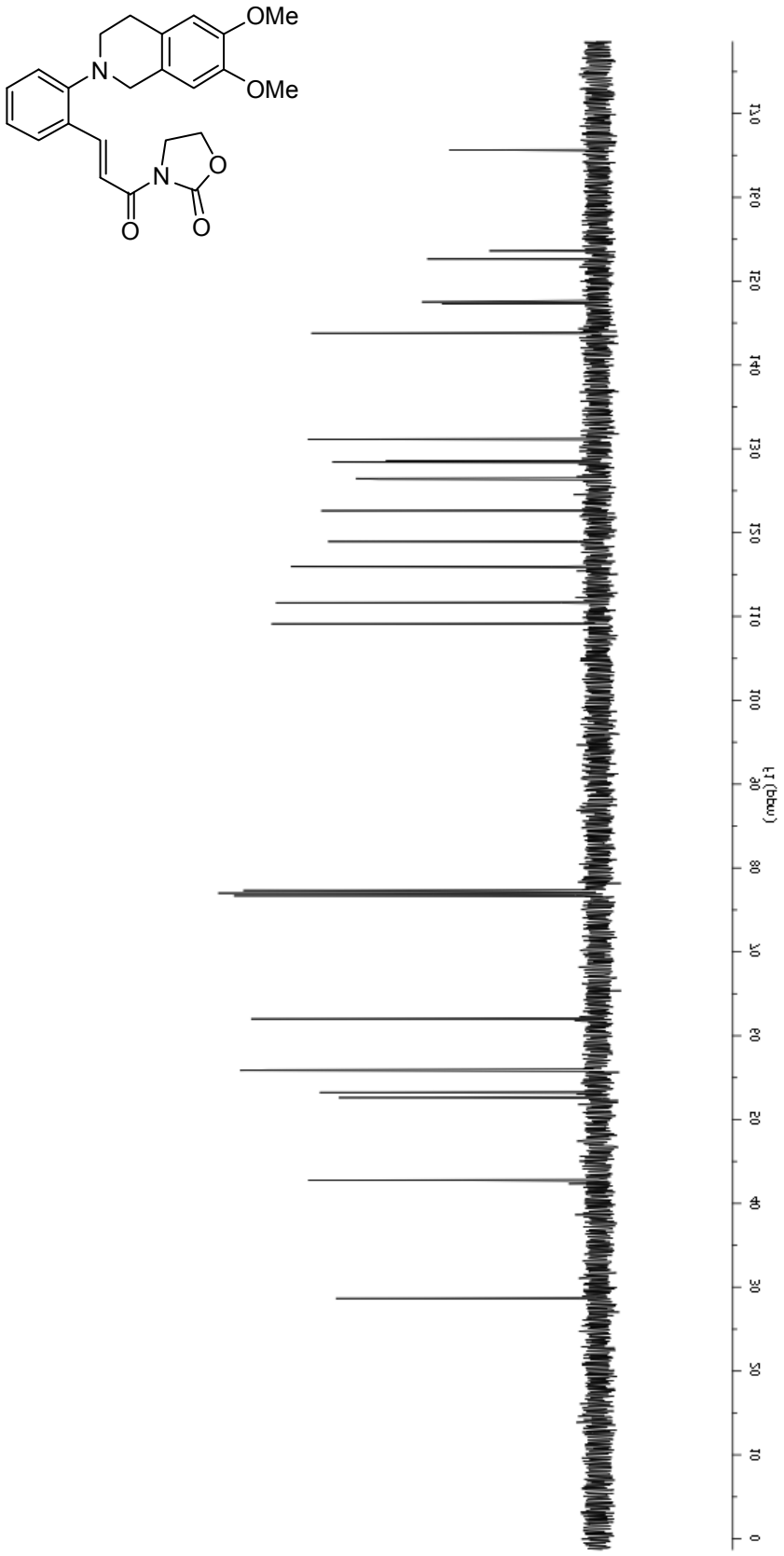

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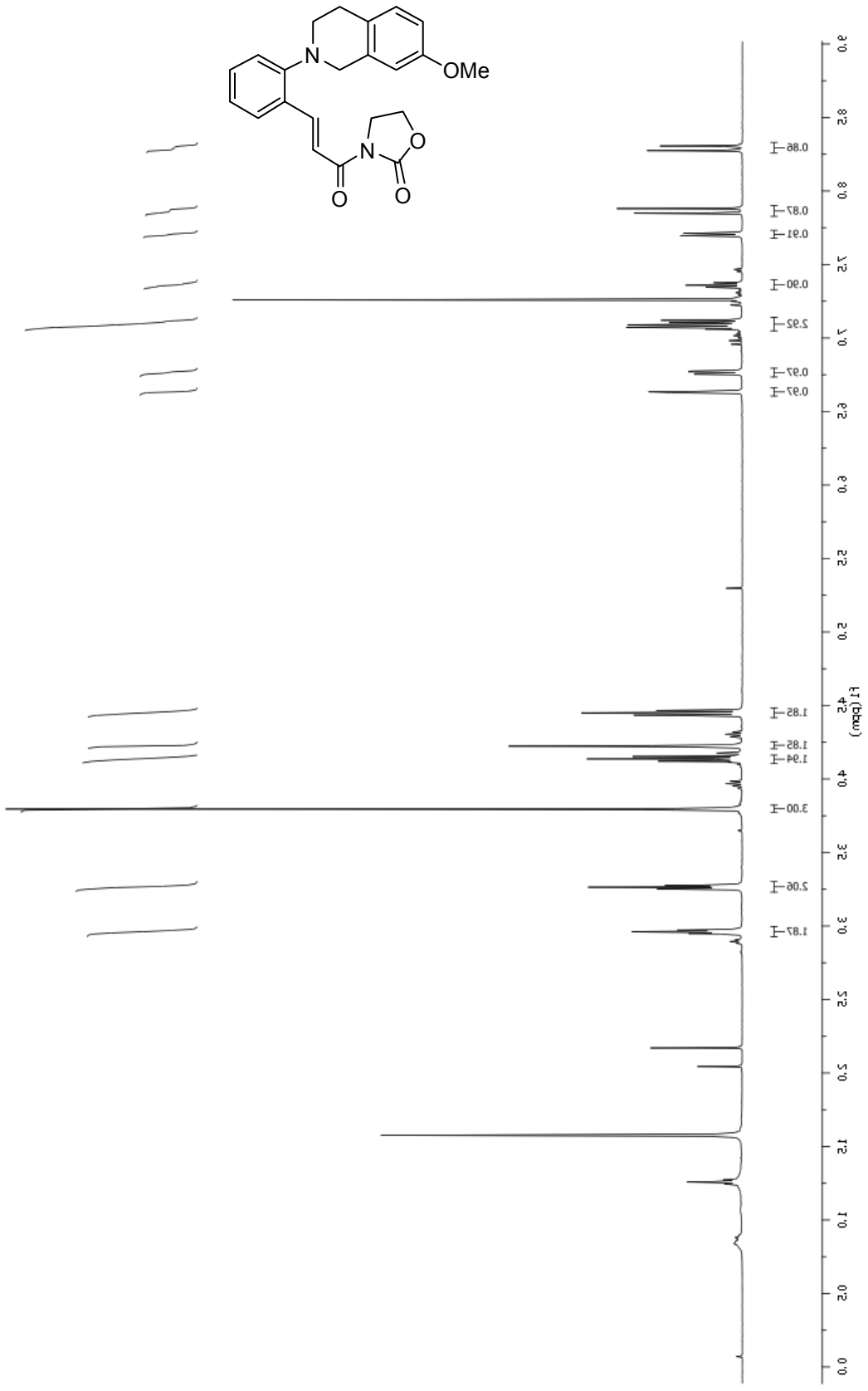

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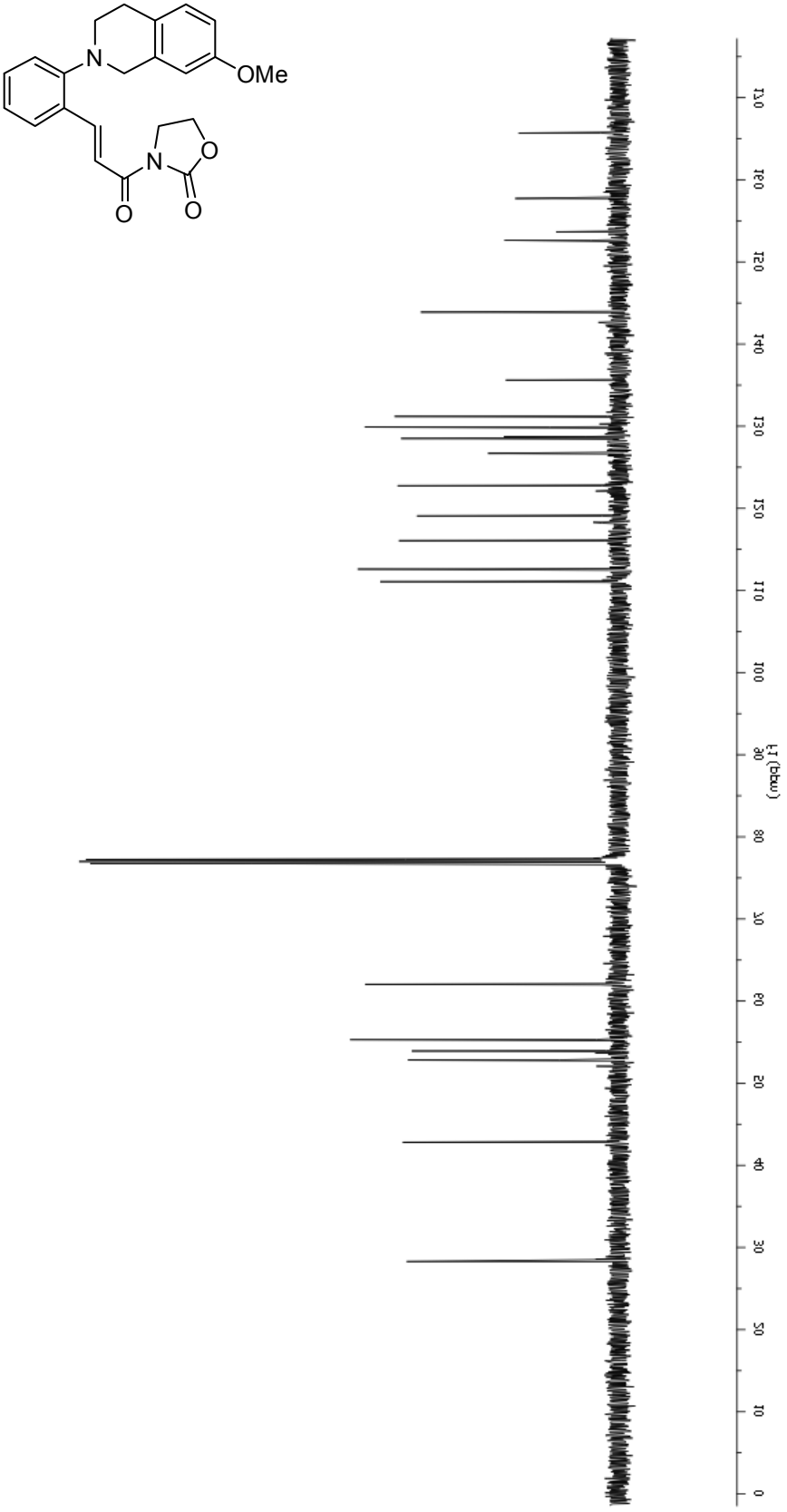

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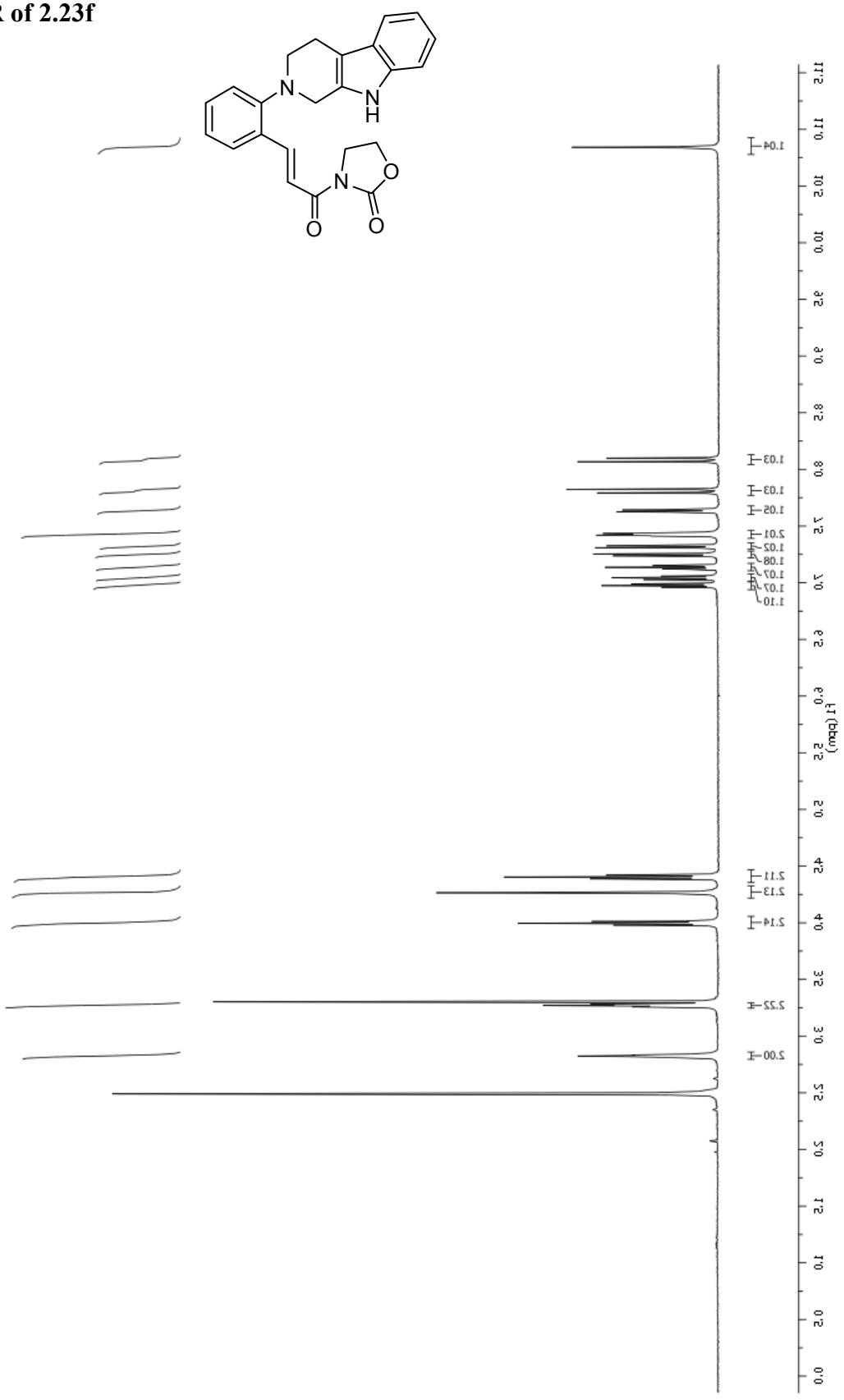

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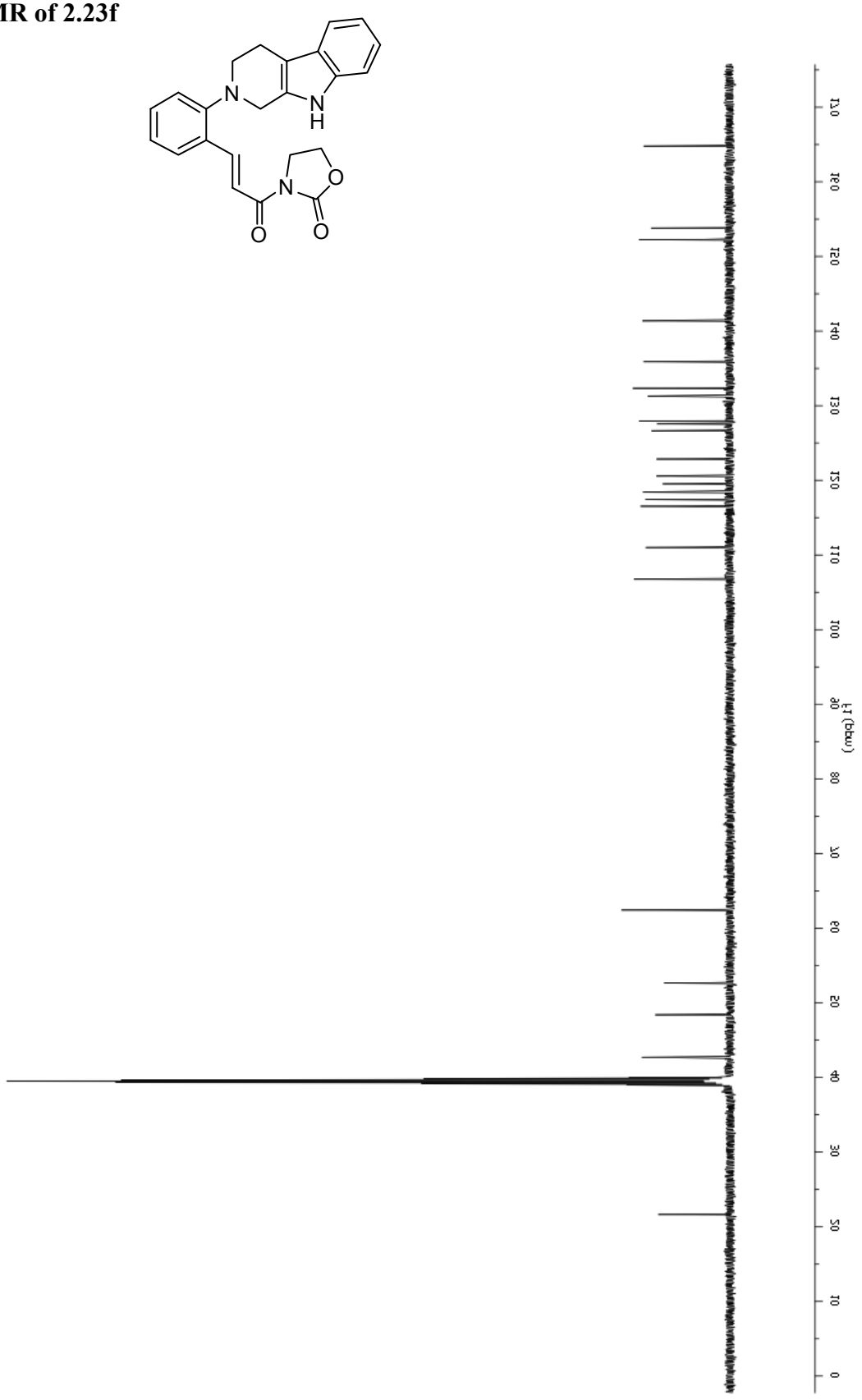
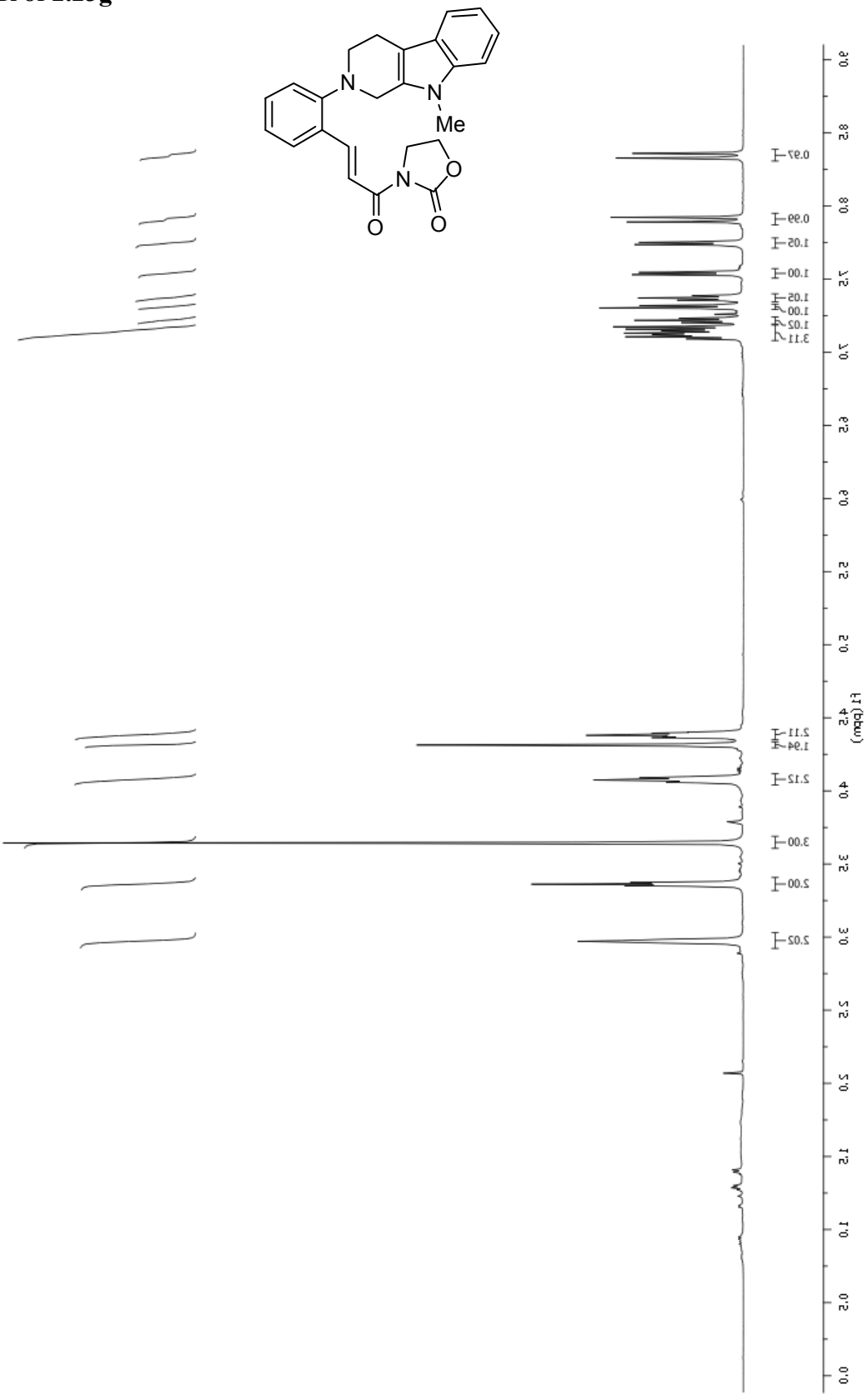


^{1}H NMR of 2.23g



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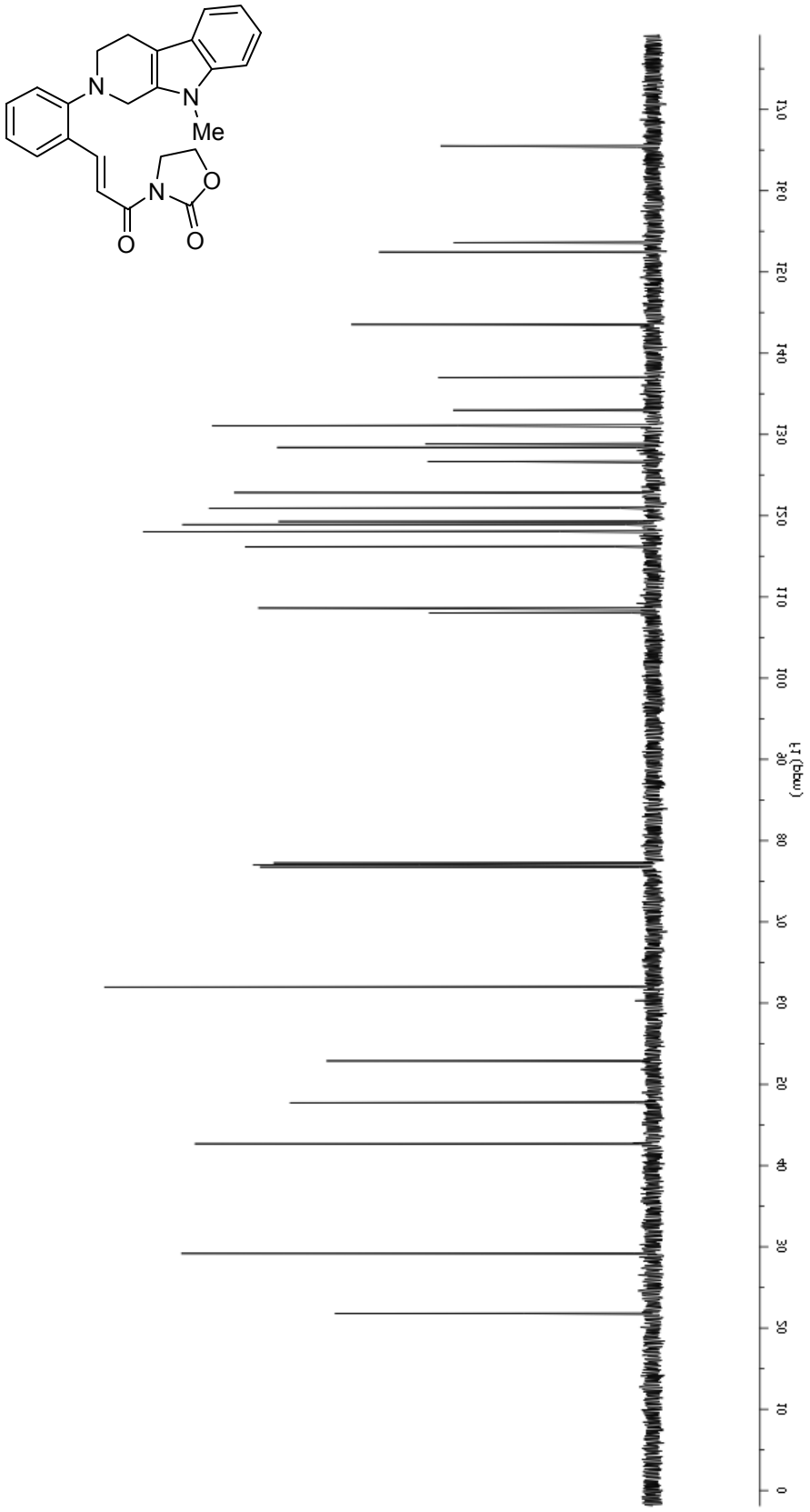

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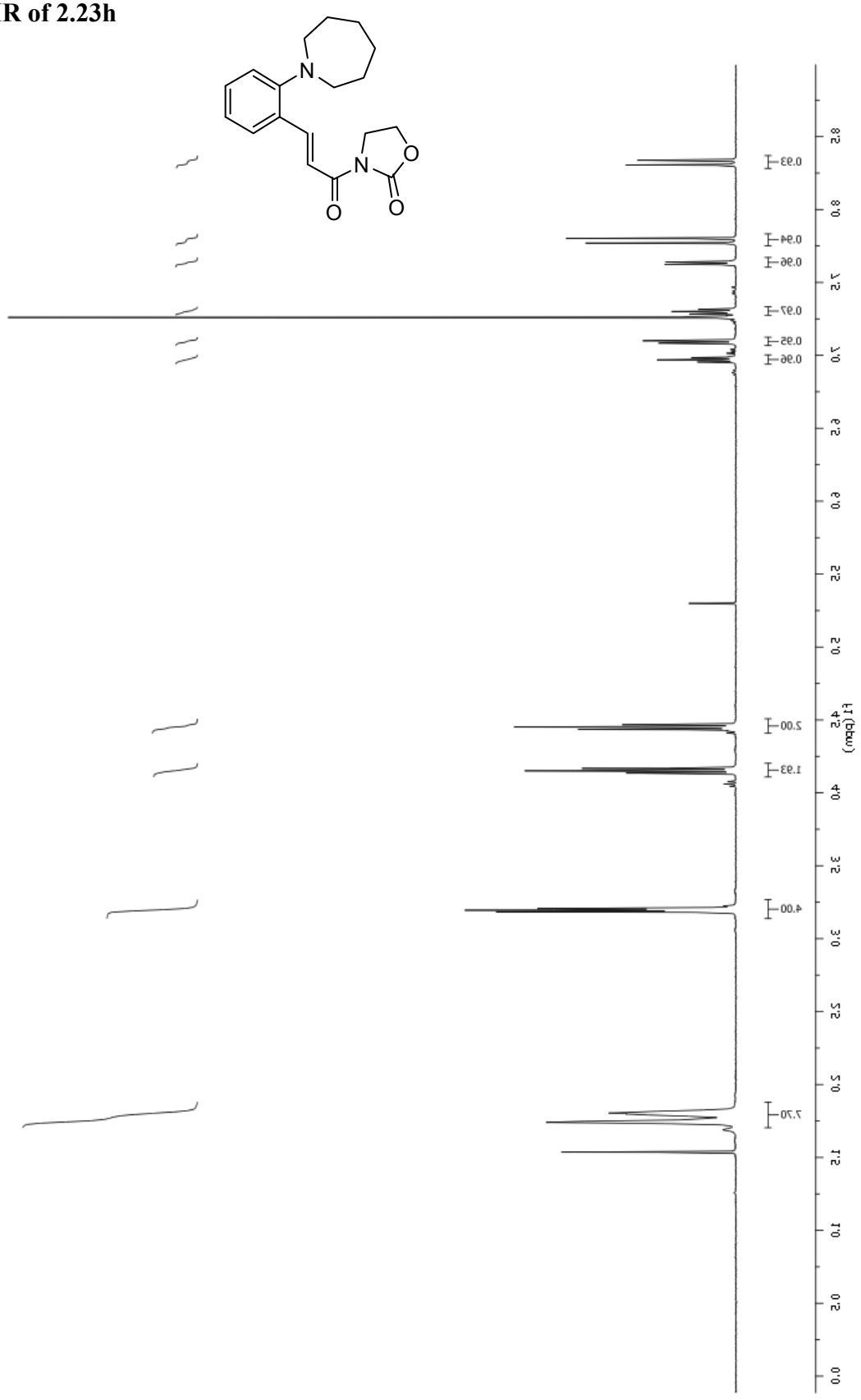

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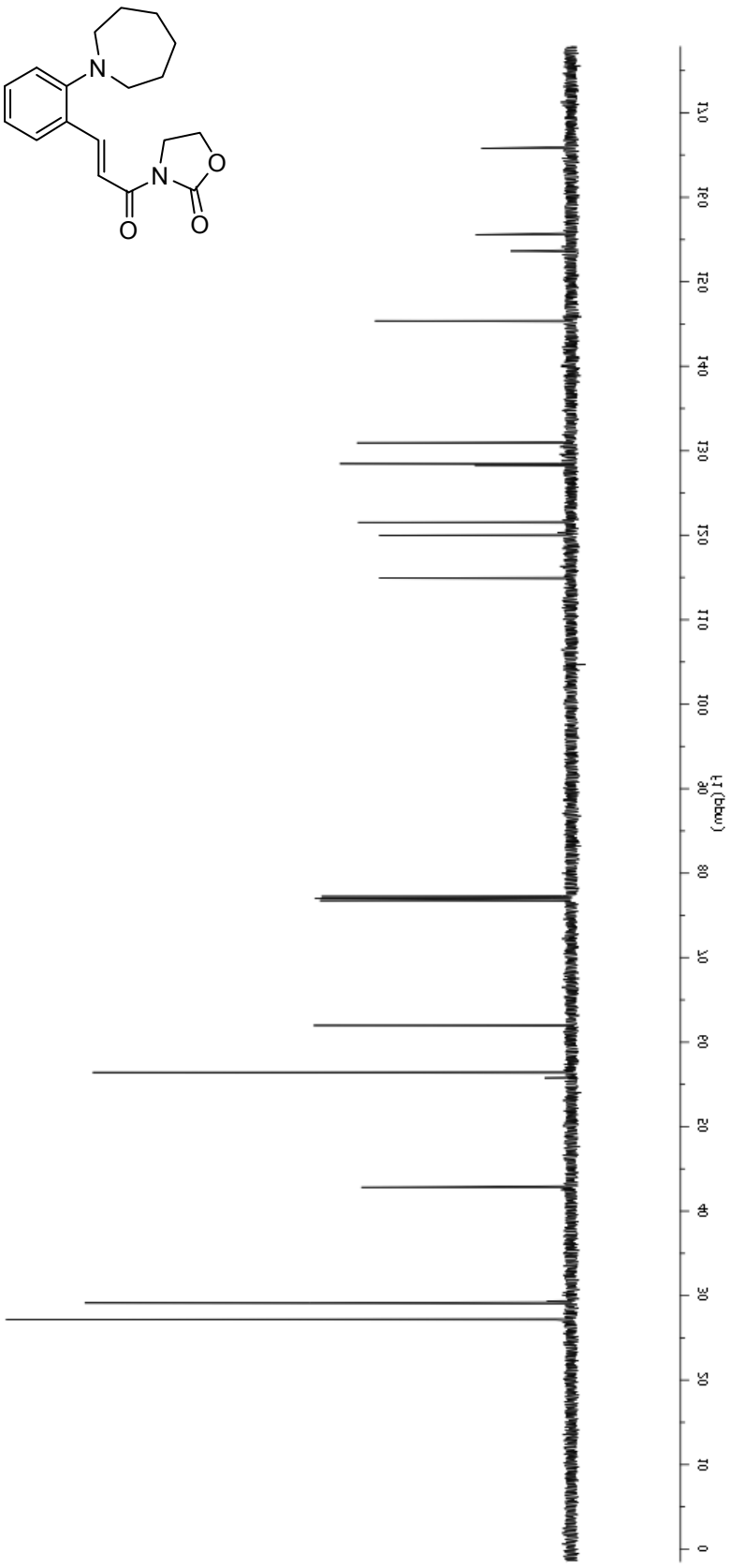
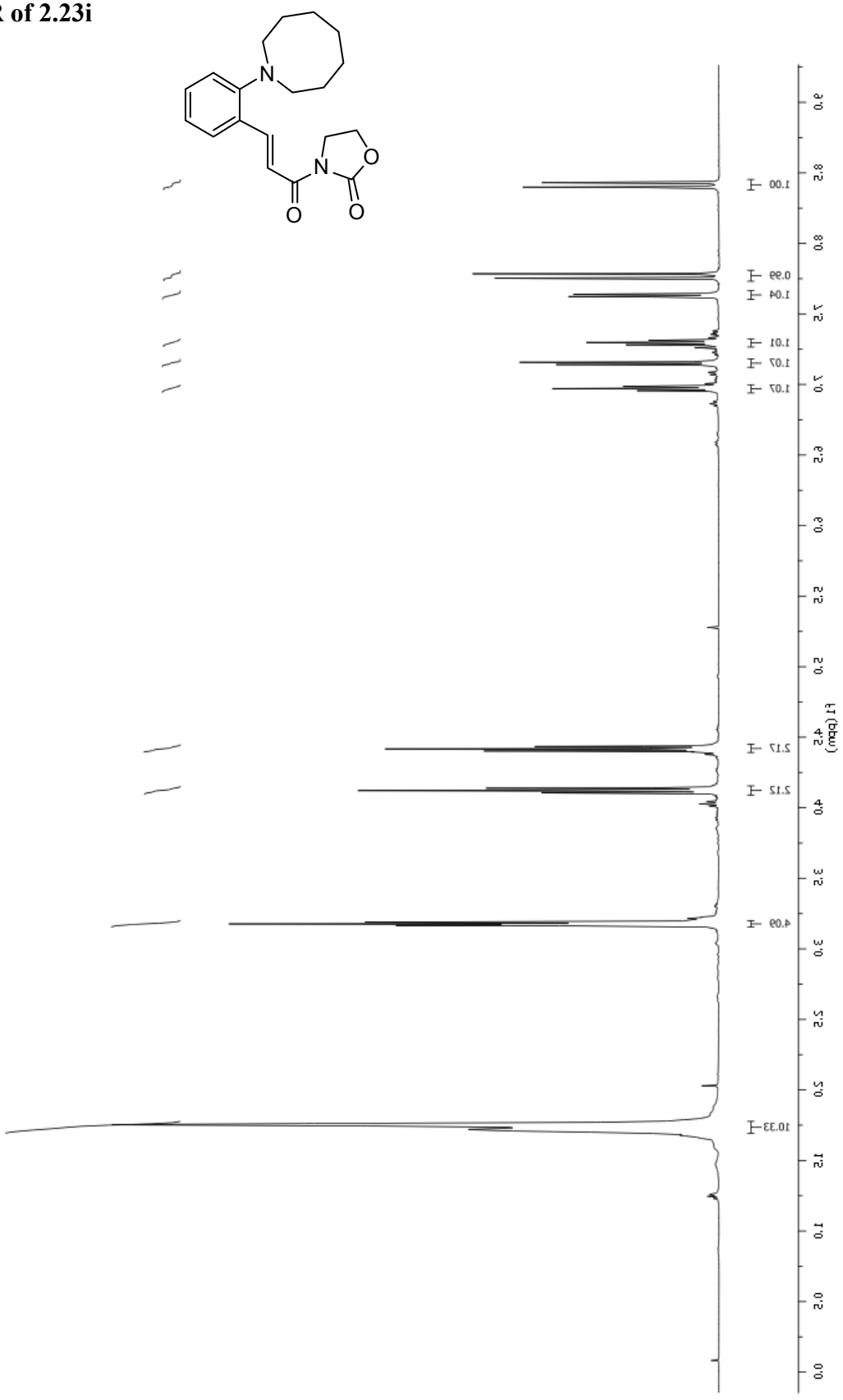


^{1}H NMR of 2.23i



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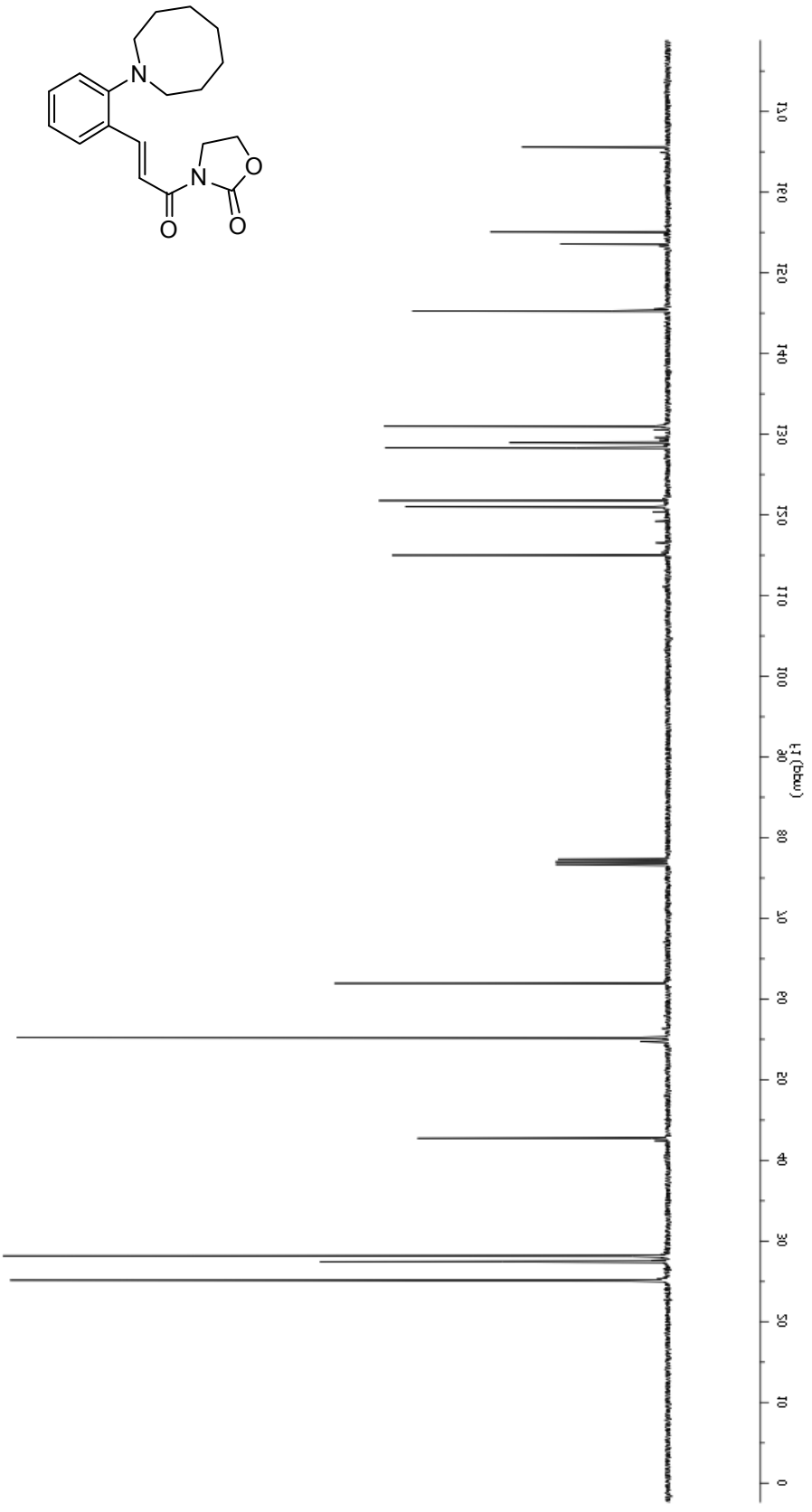
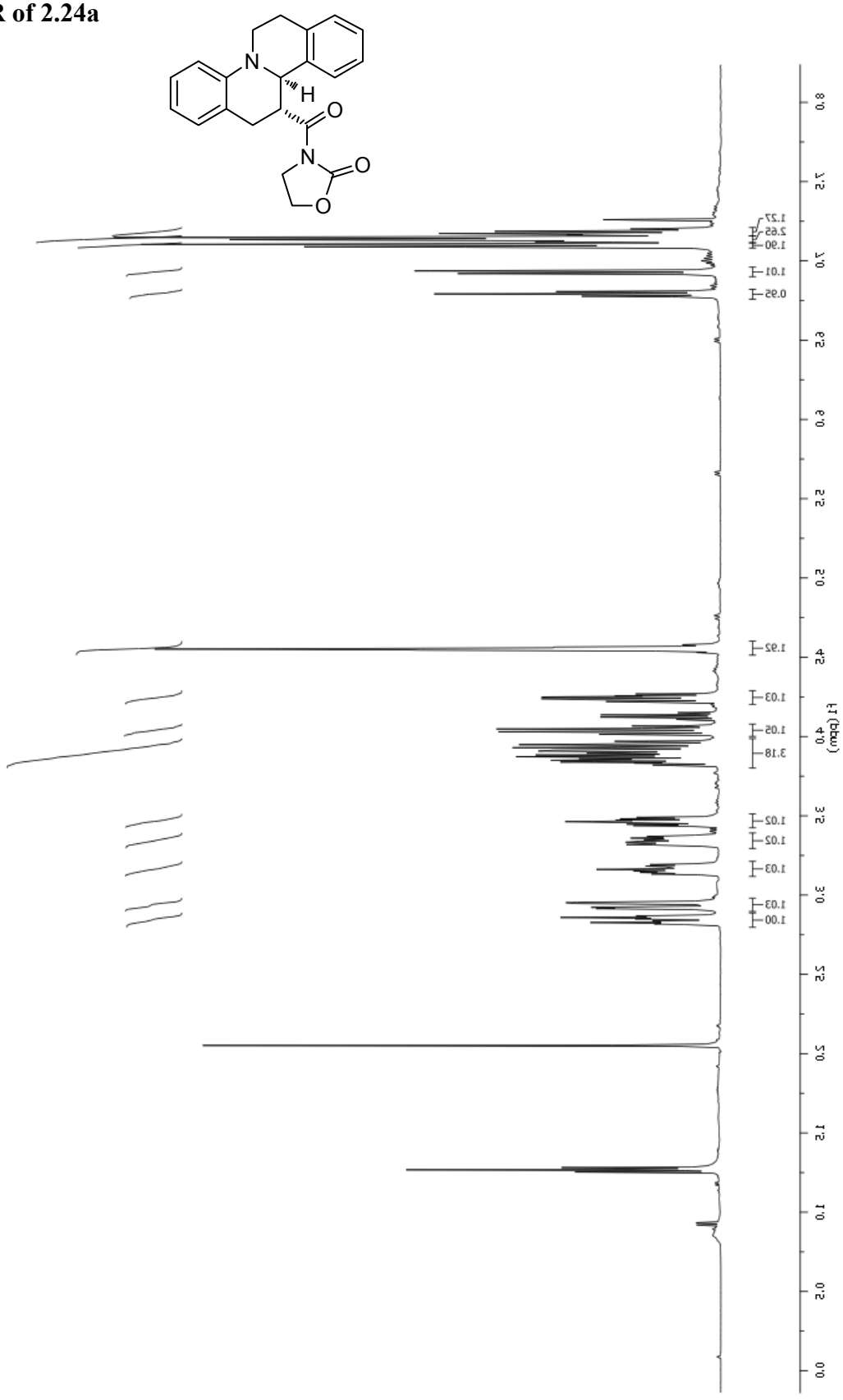


^{1}H NMR of 2.24a



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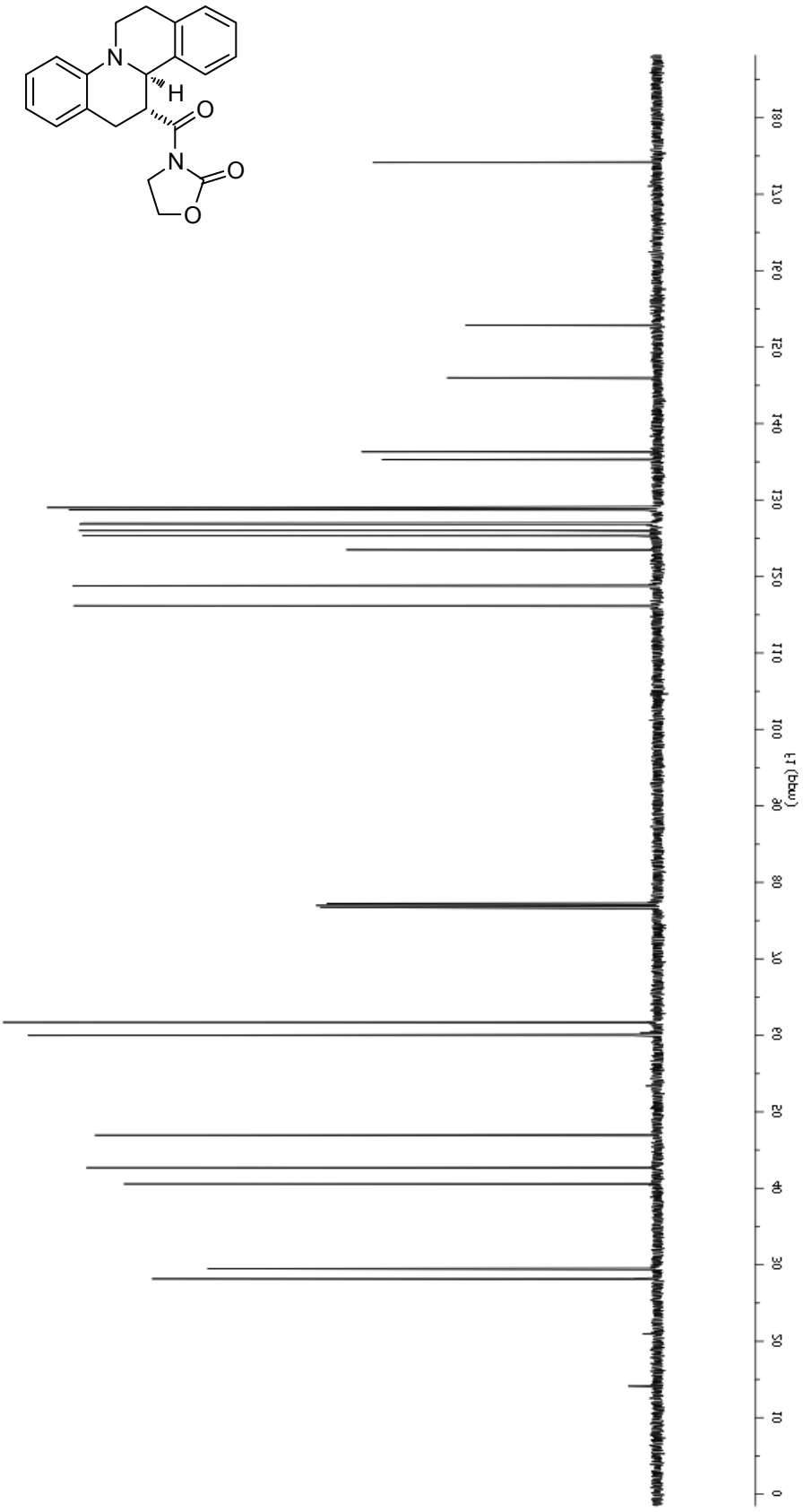

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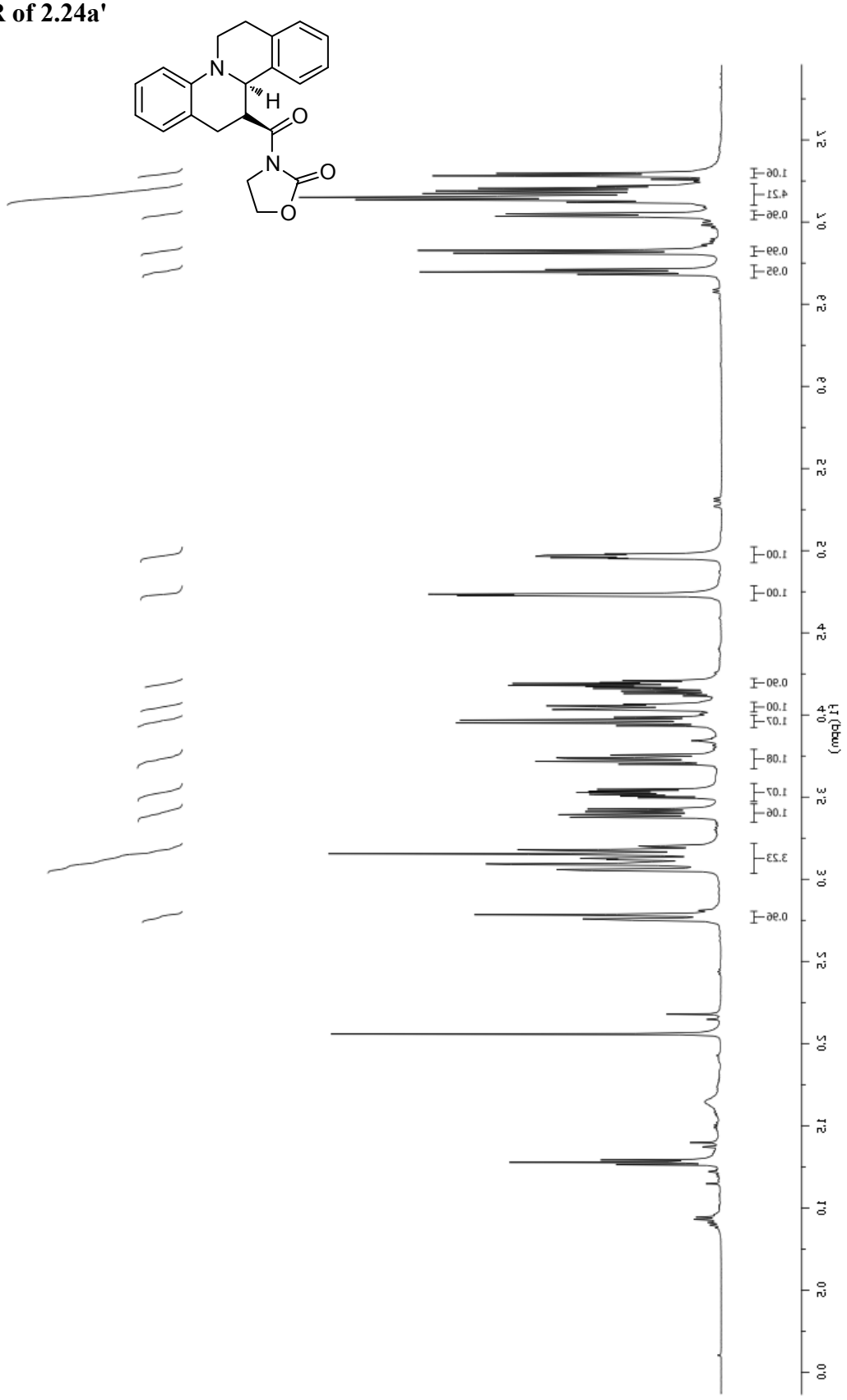

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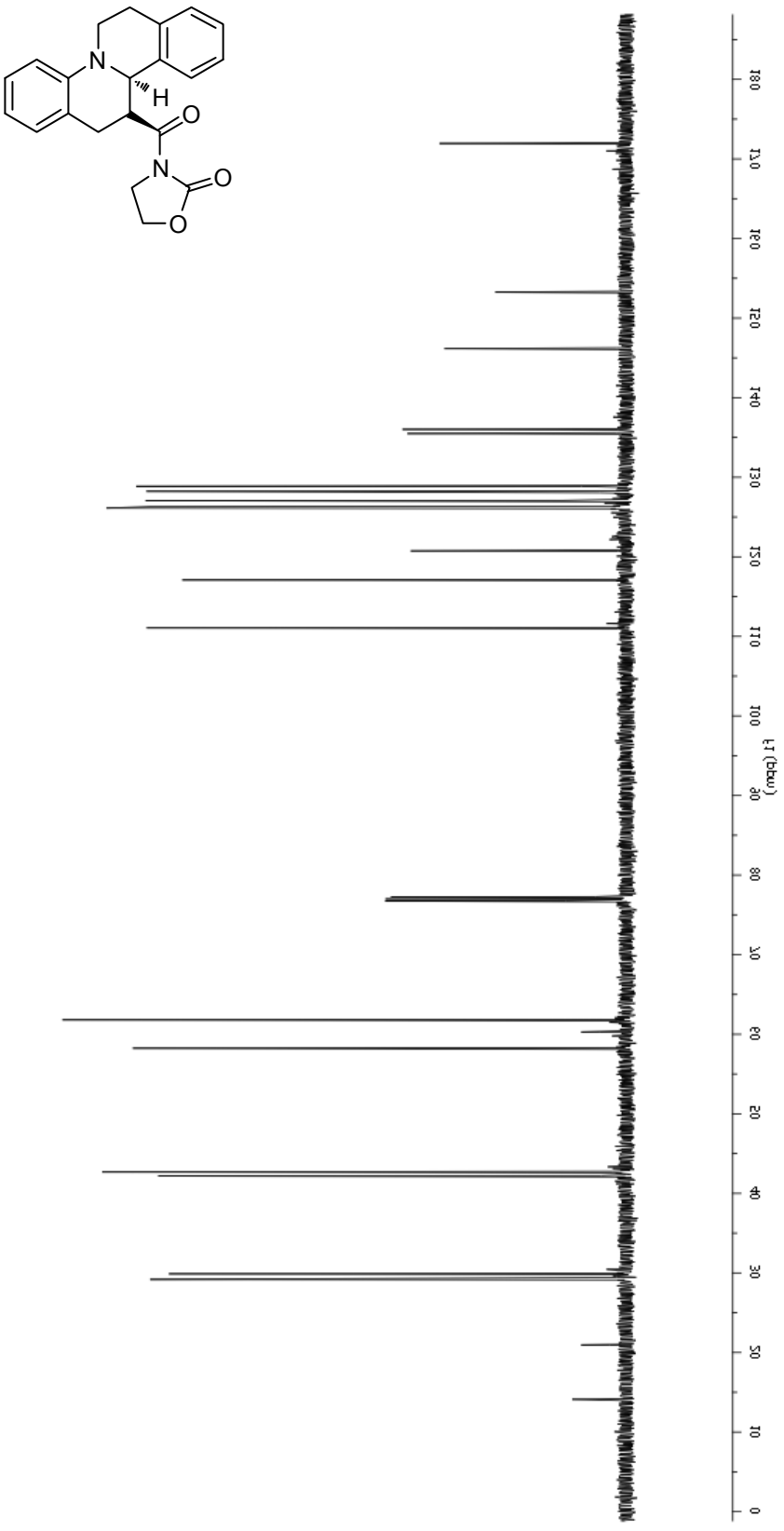

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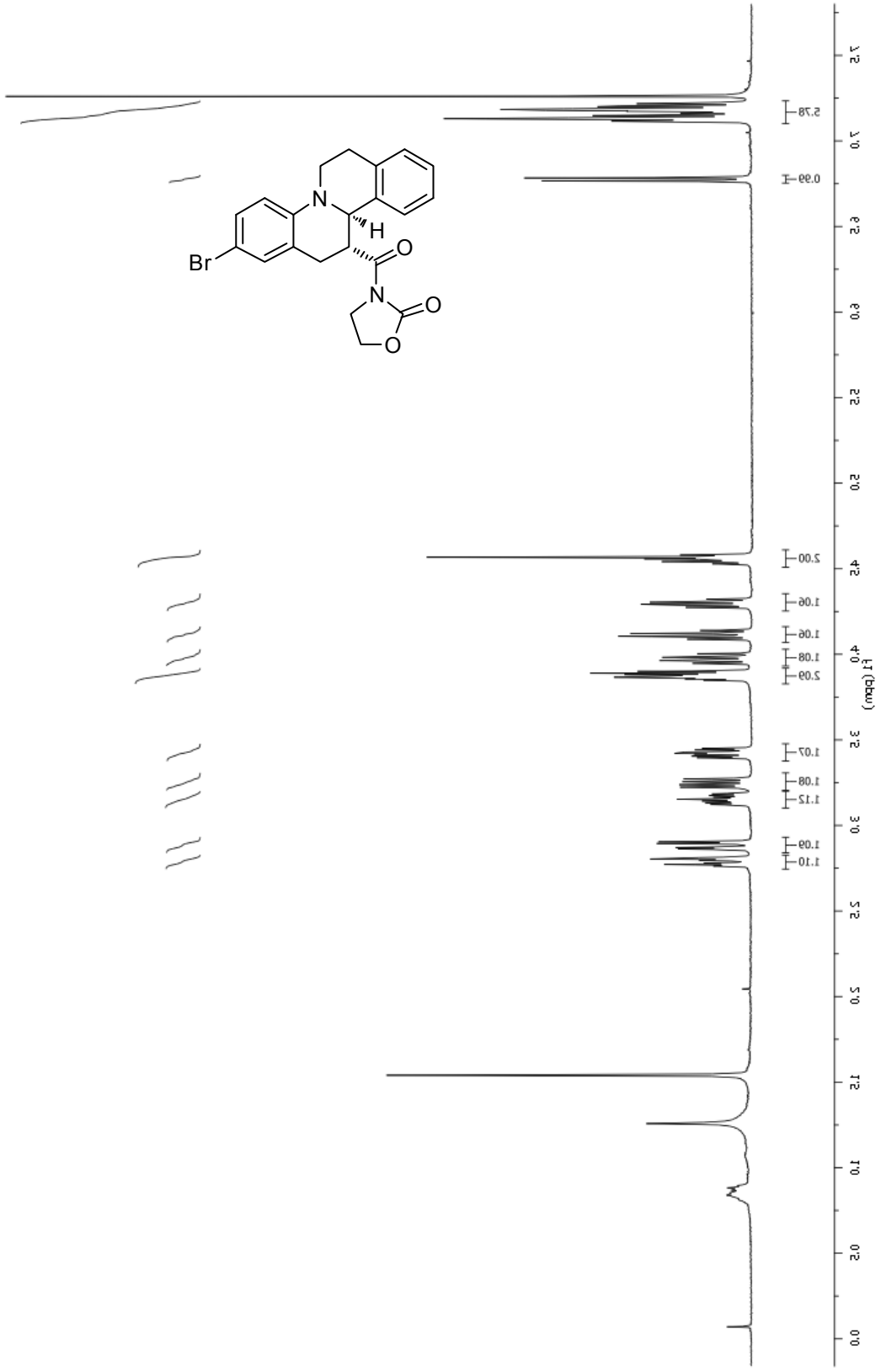

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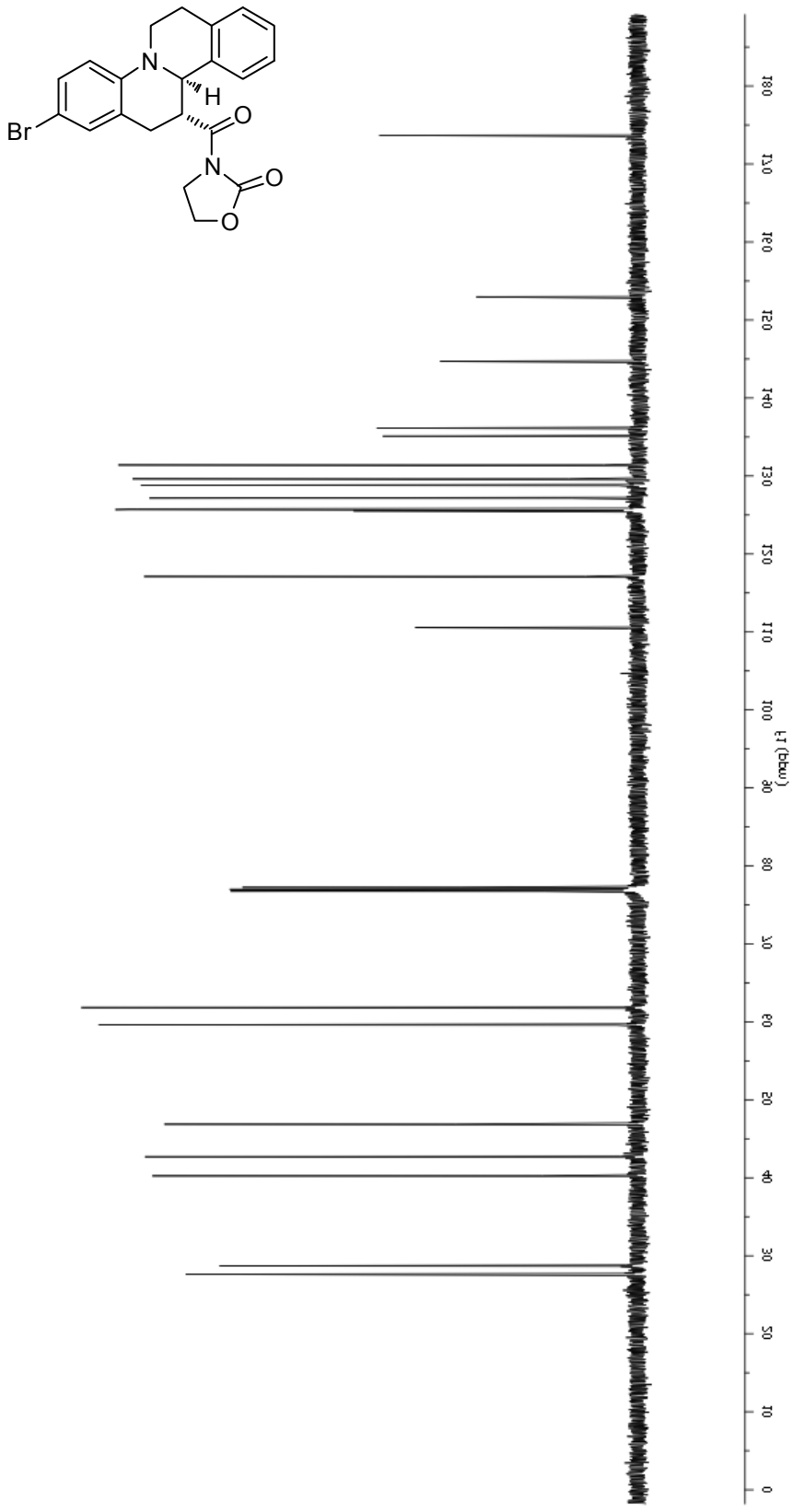
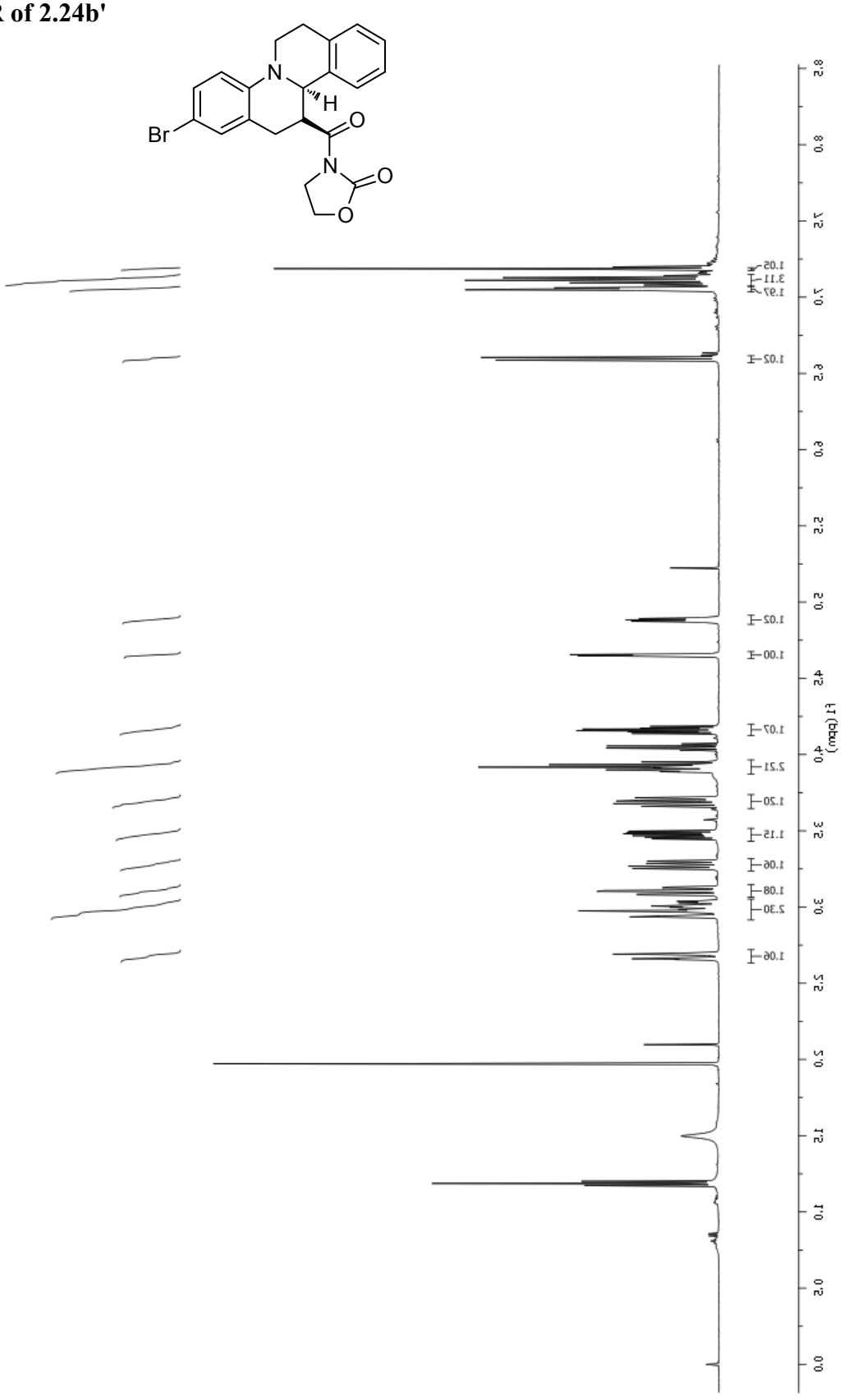


^{1}H NMR of 2.24b'



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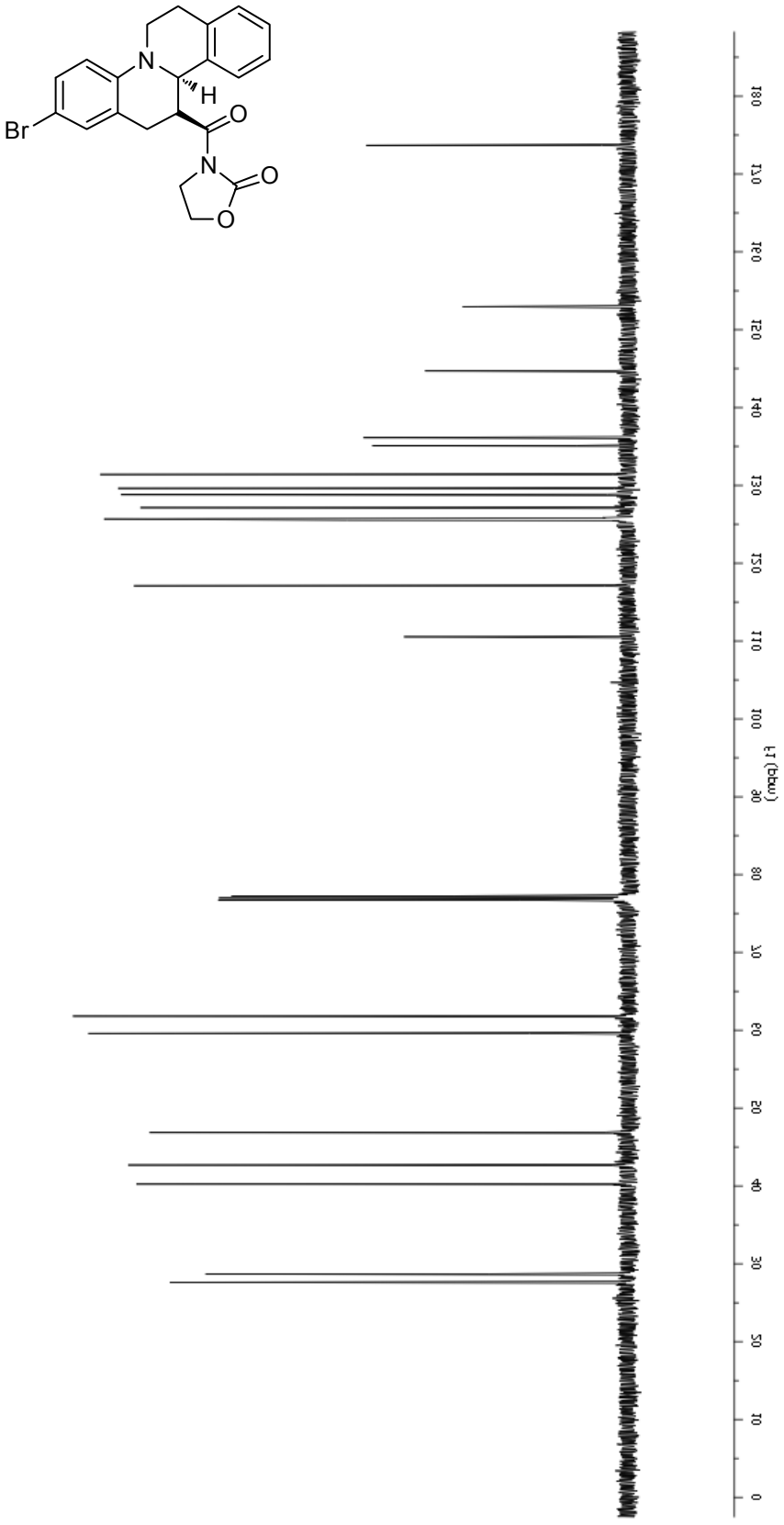

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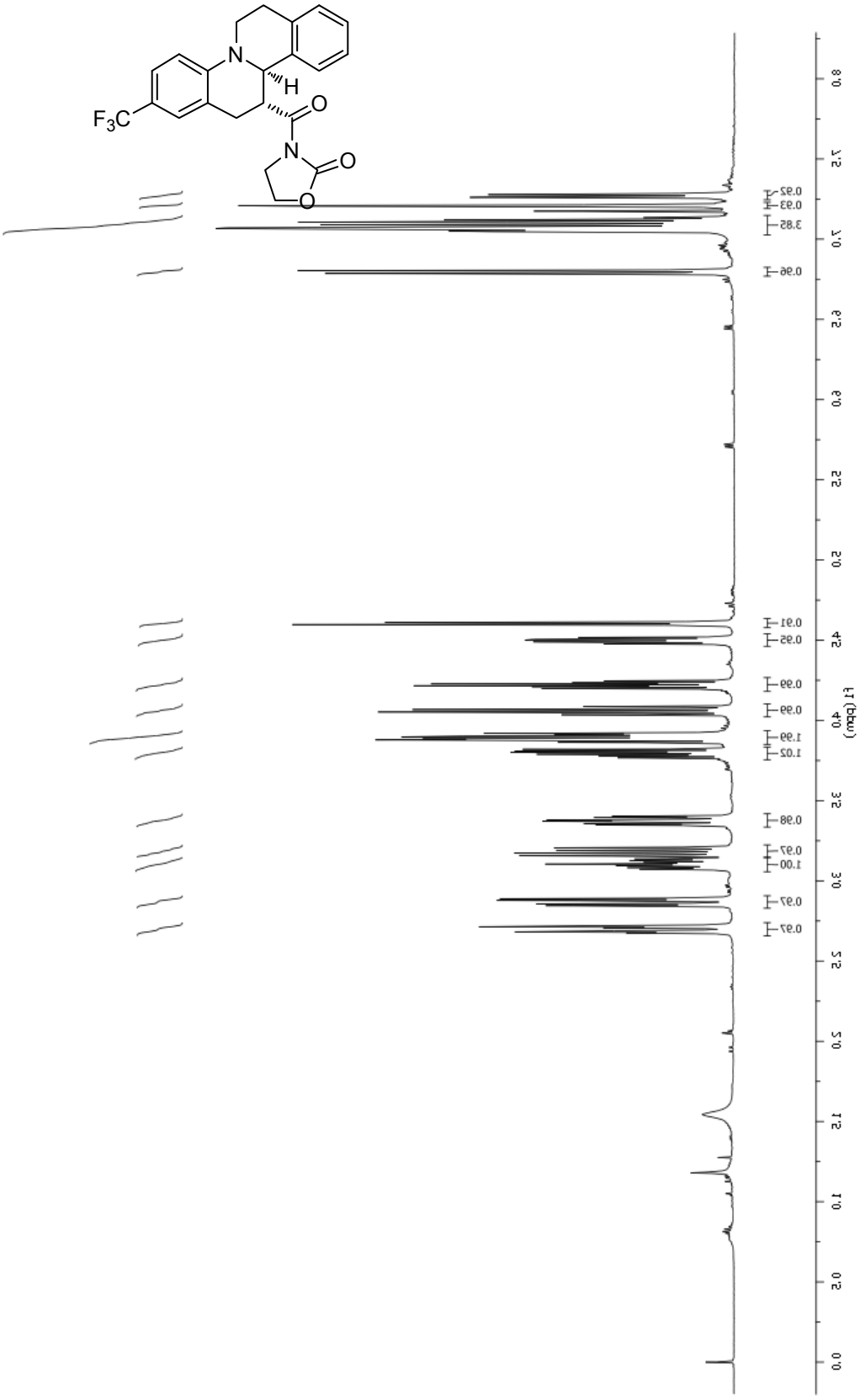

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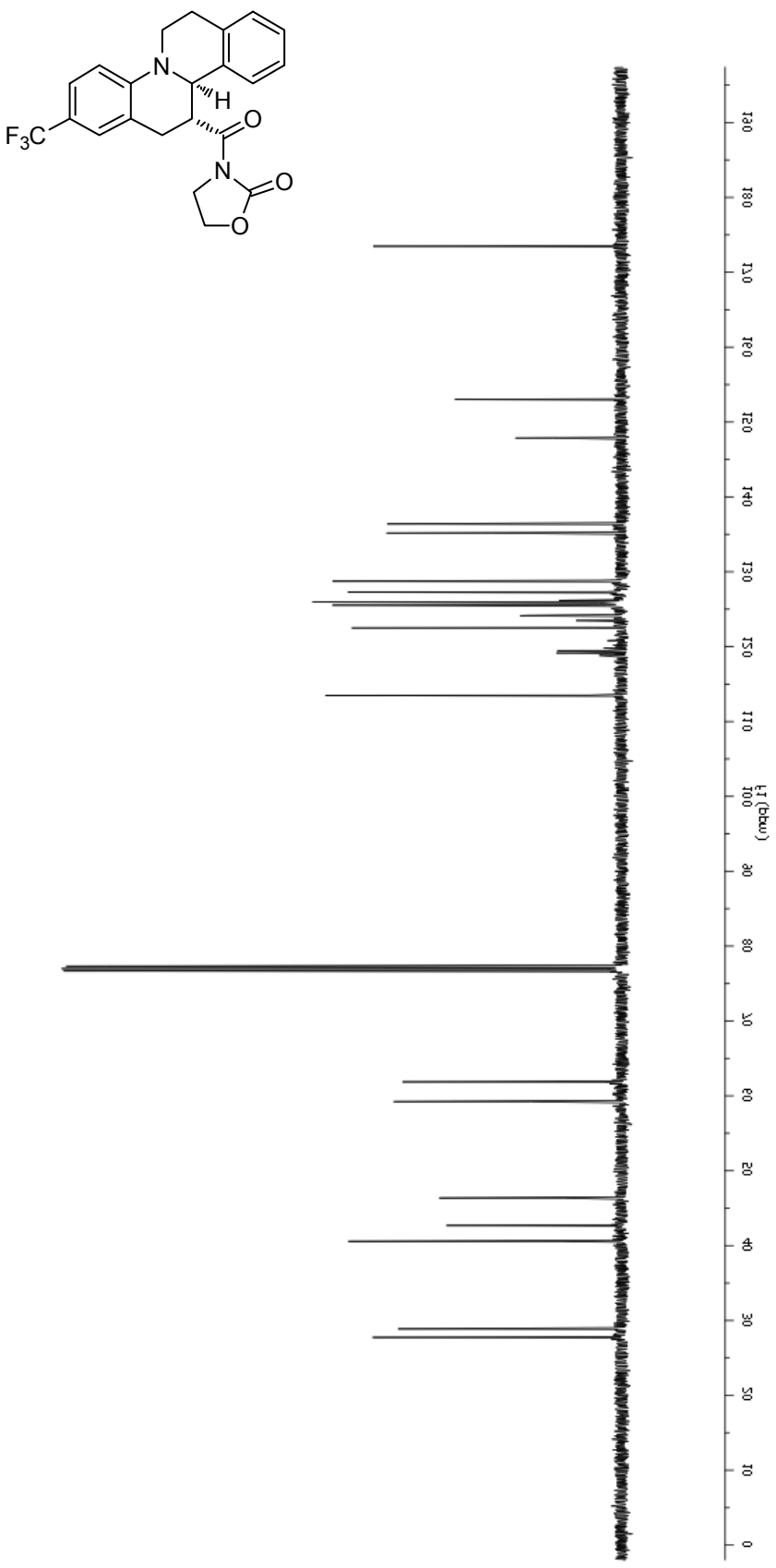

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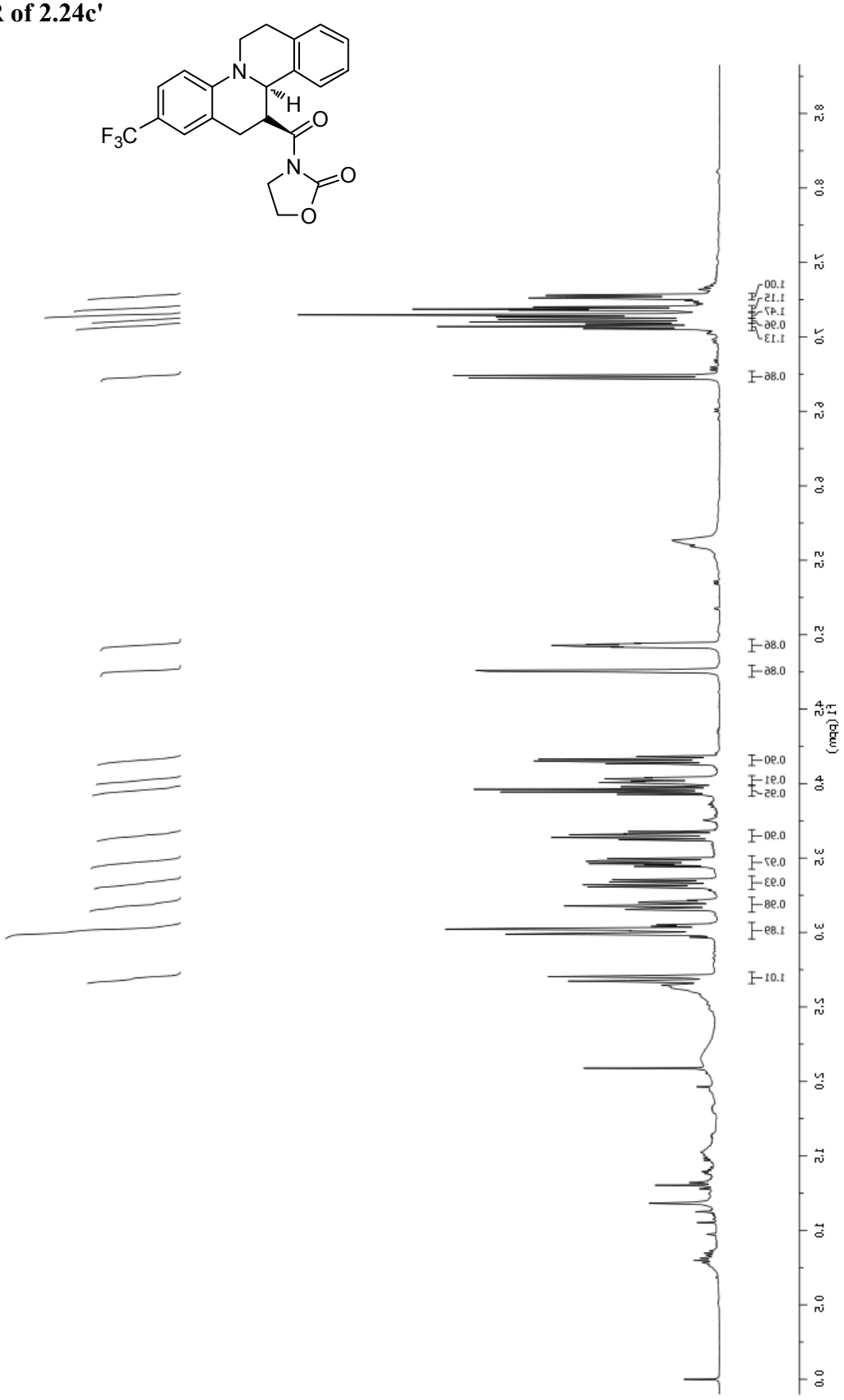

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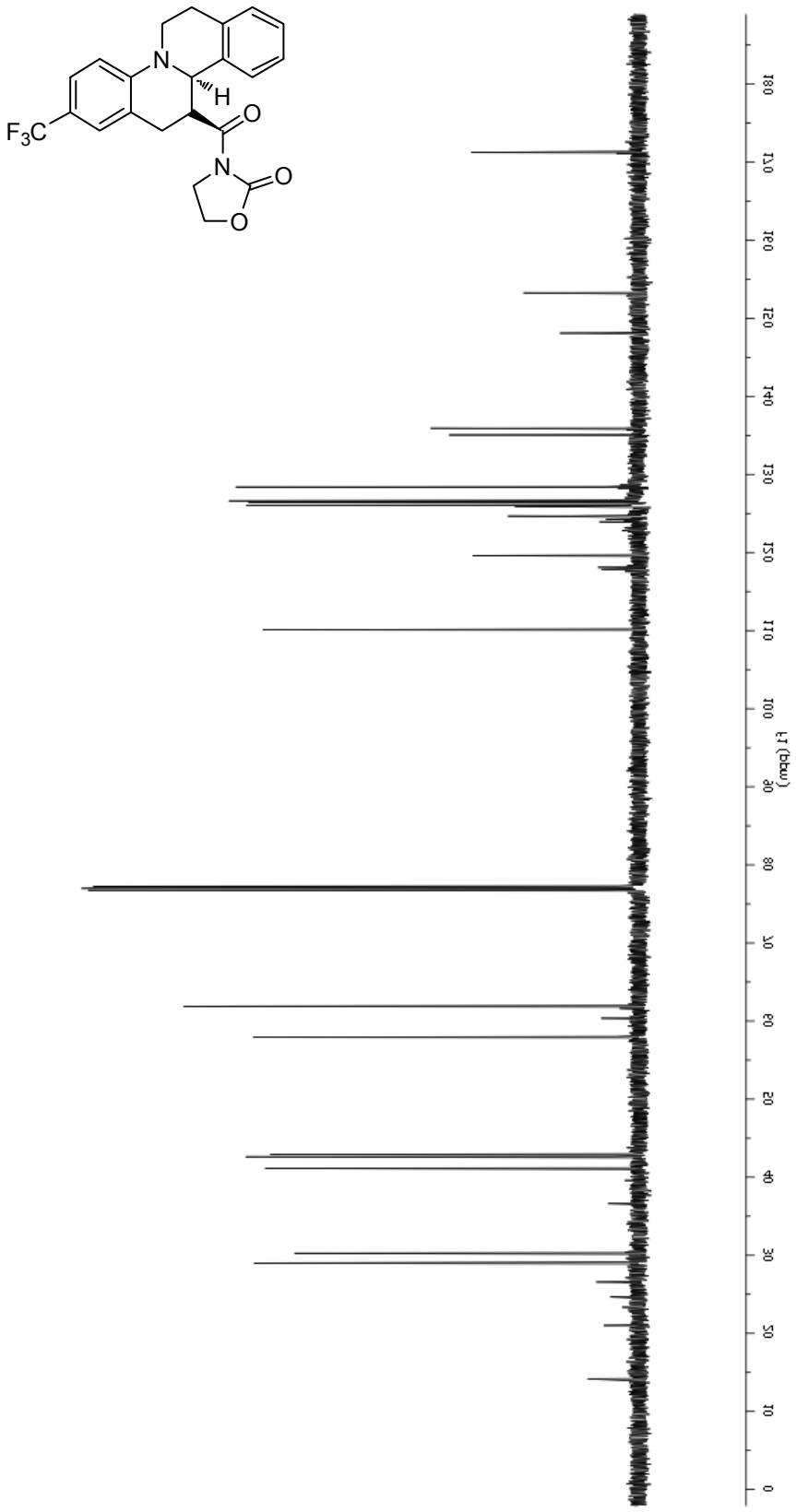

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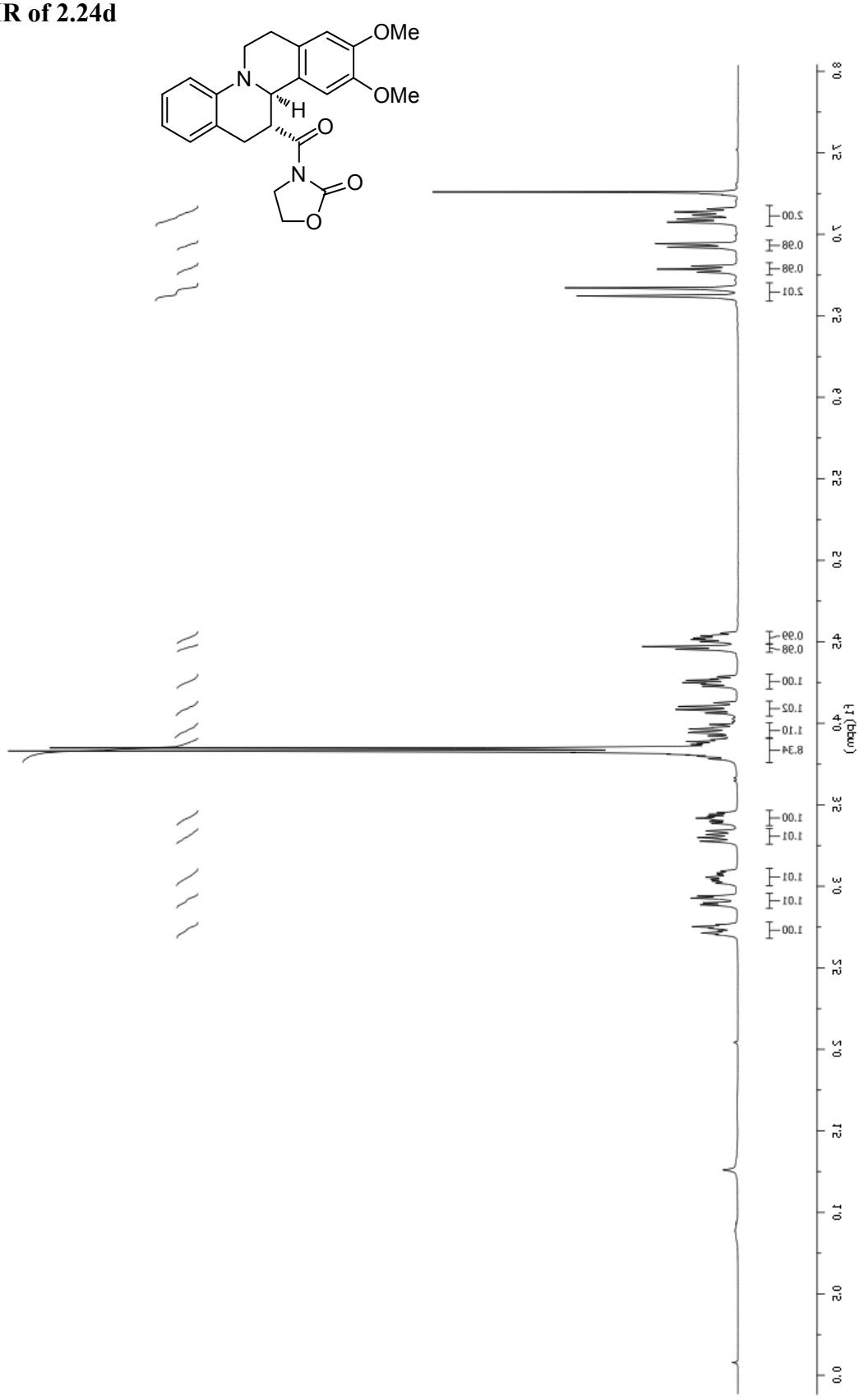

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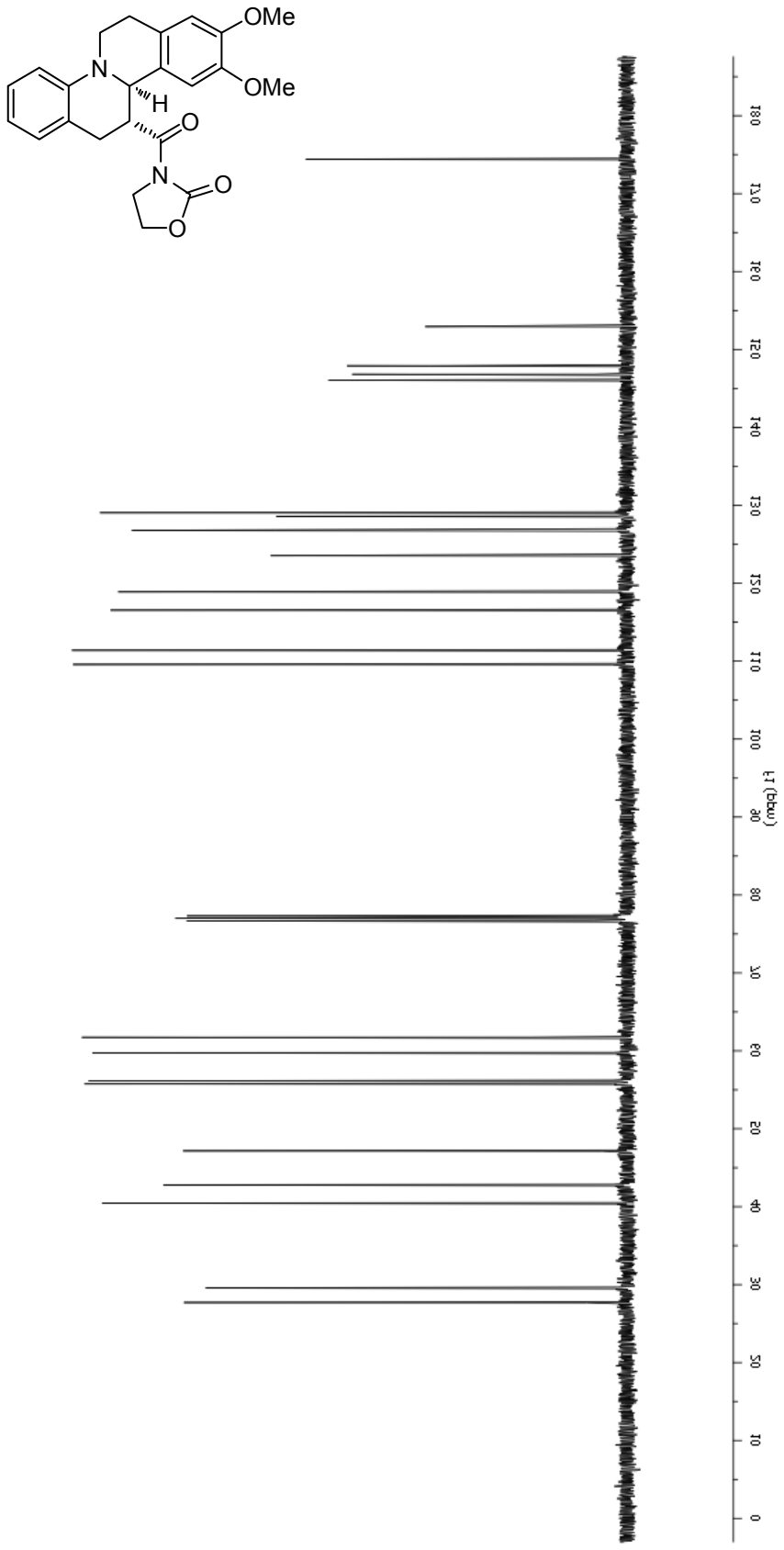

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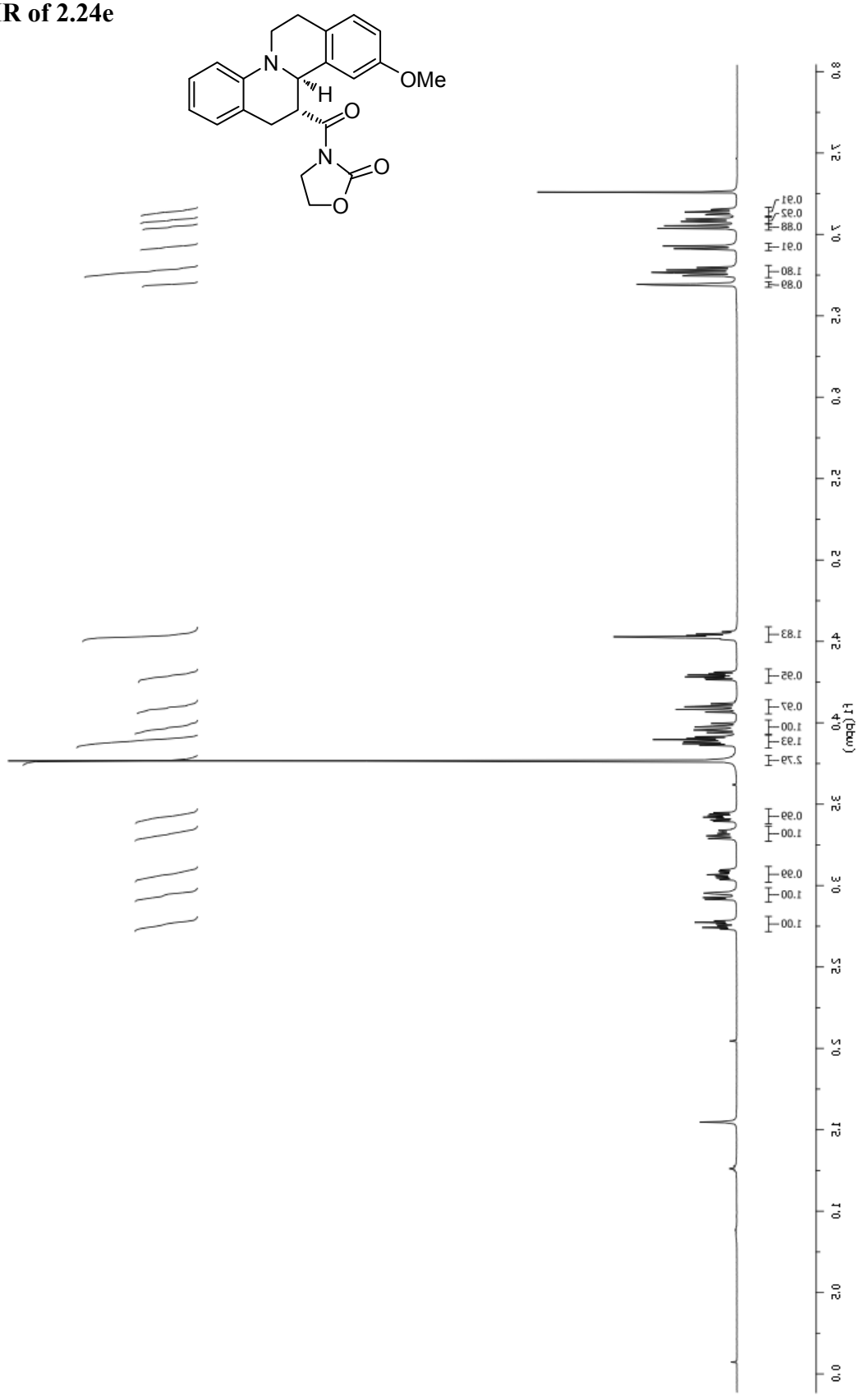

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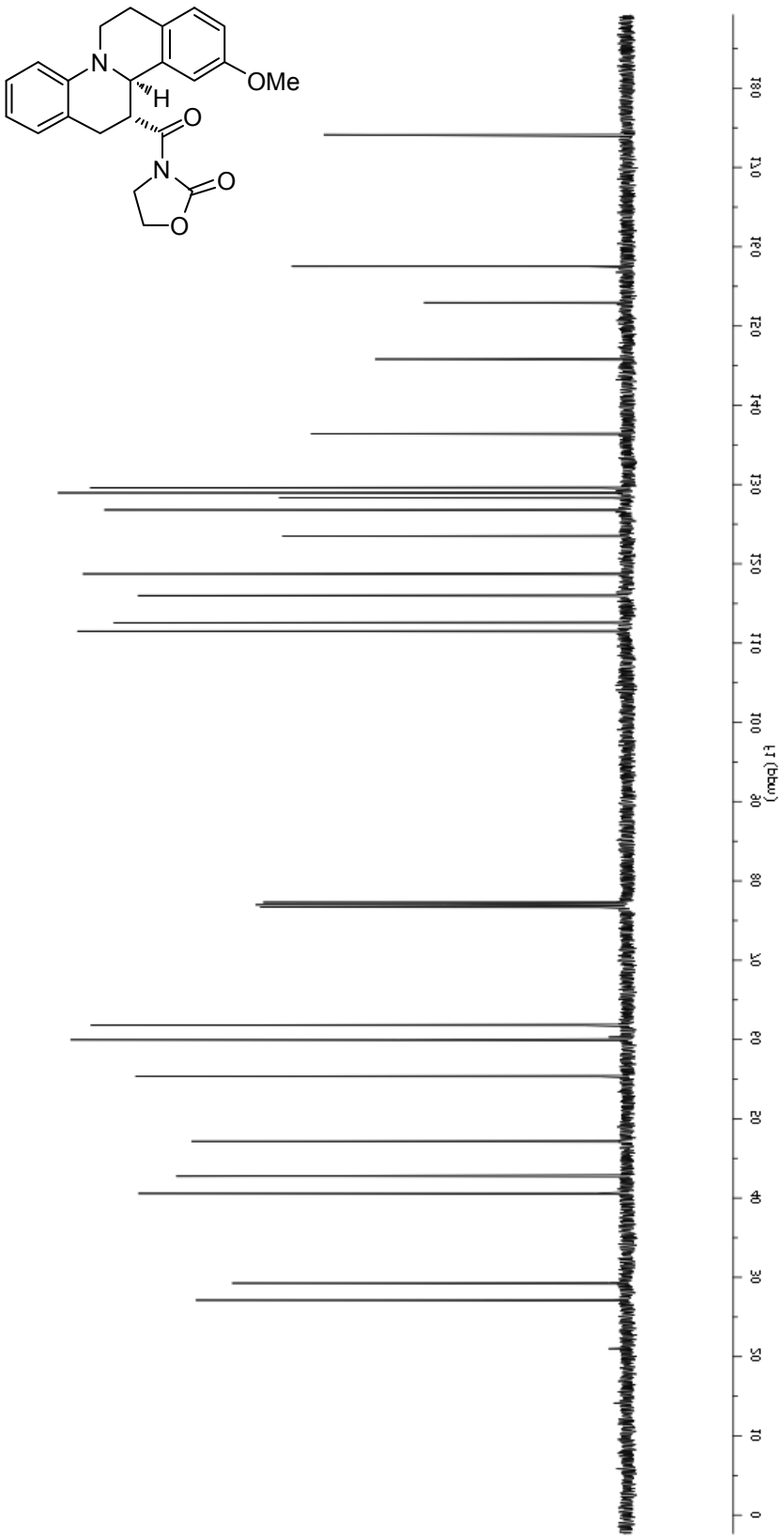

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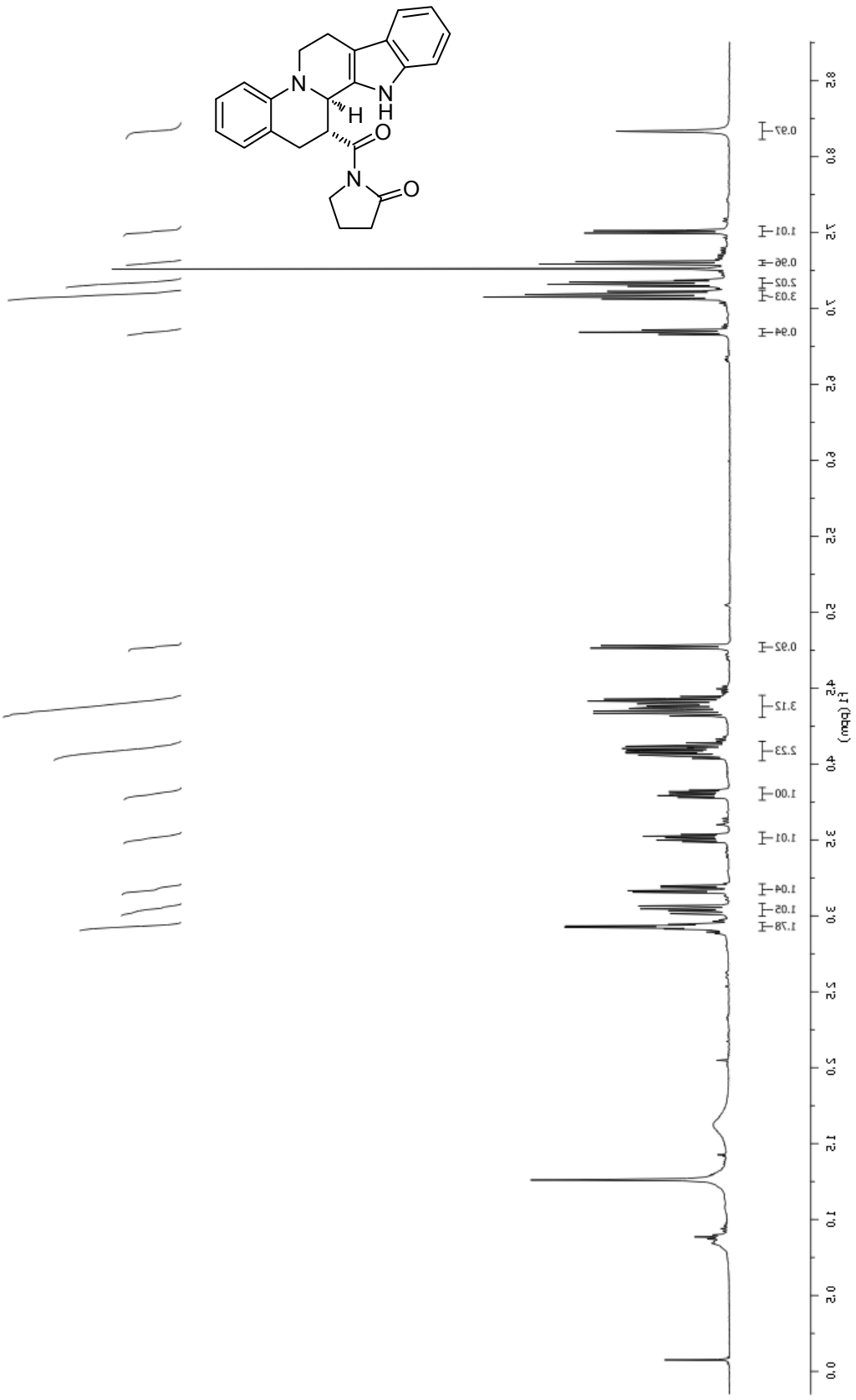

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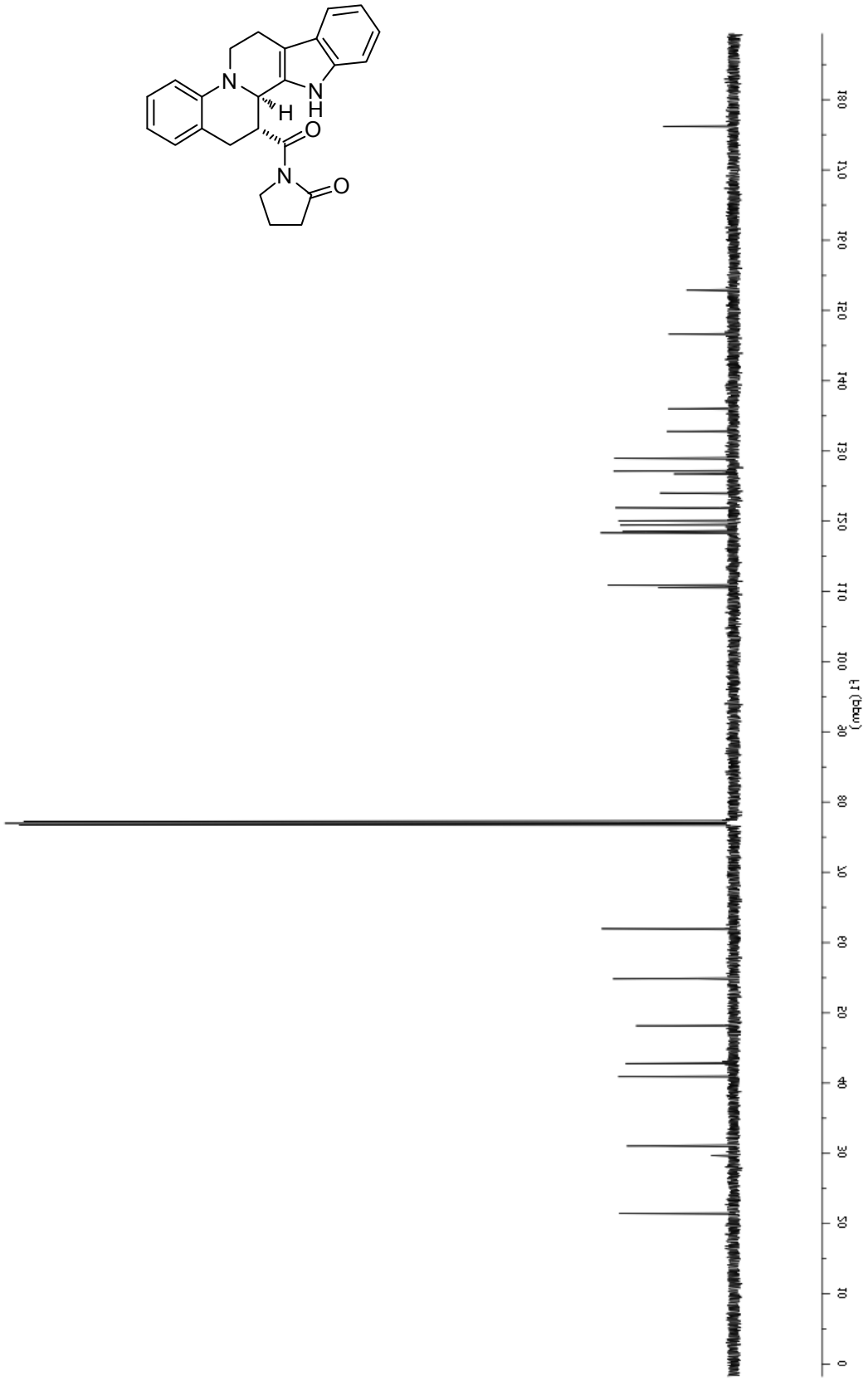

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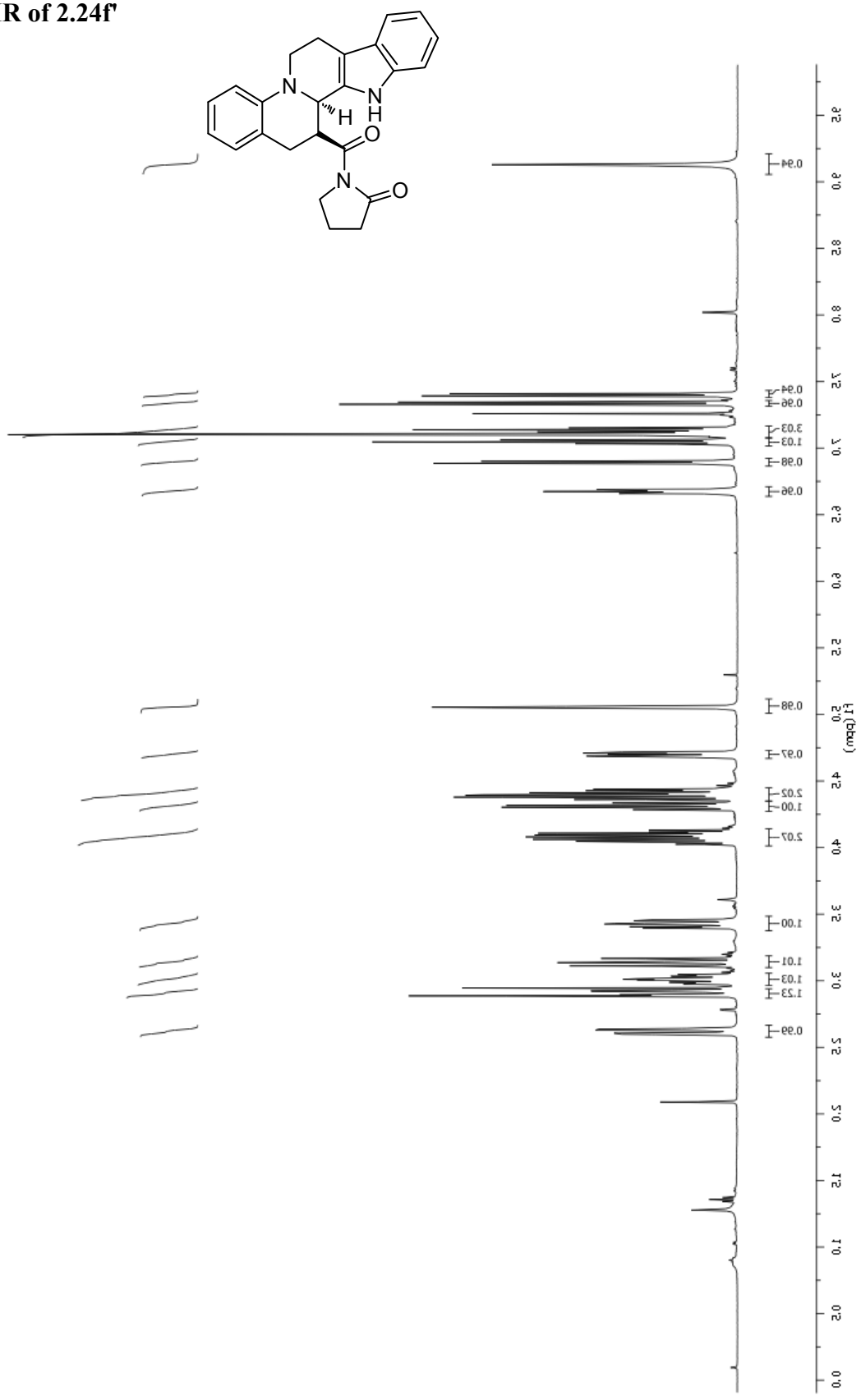

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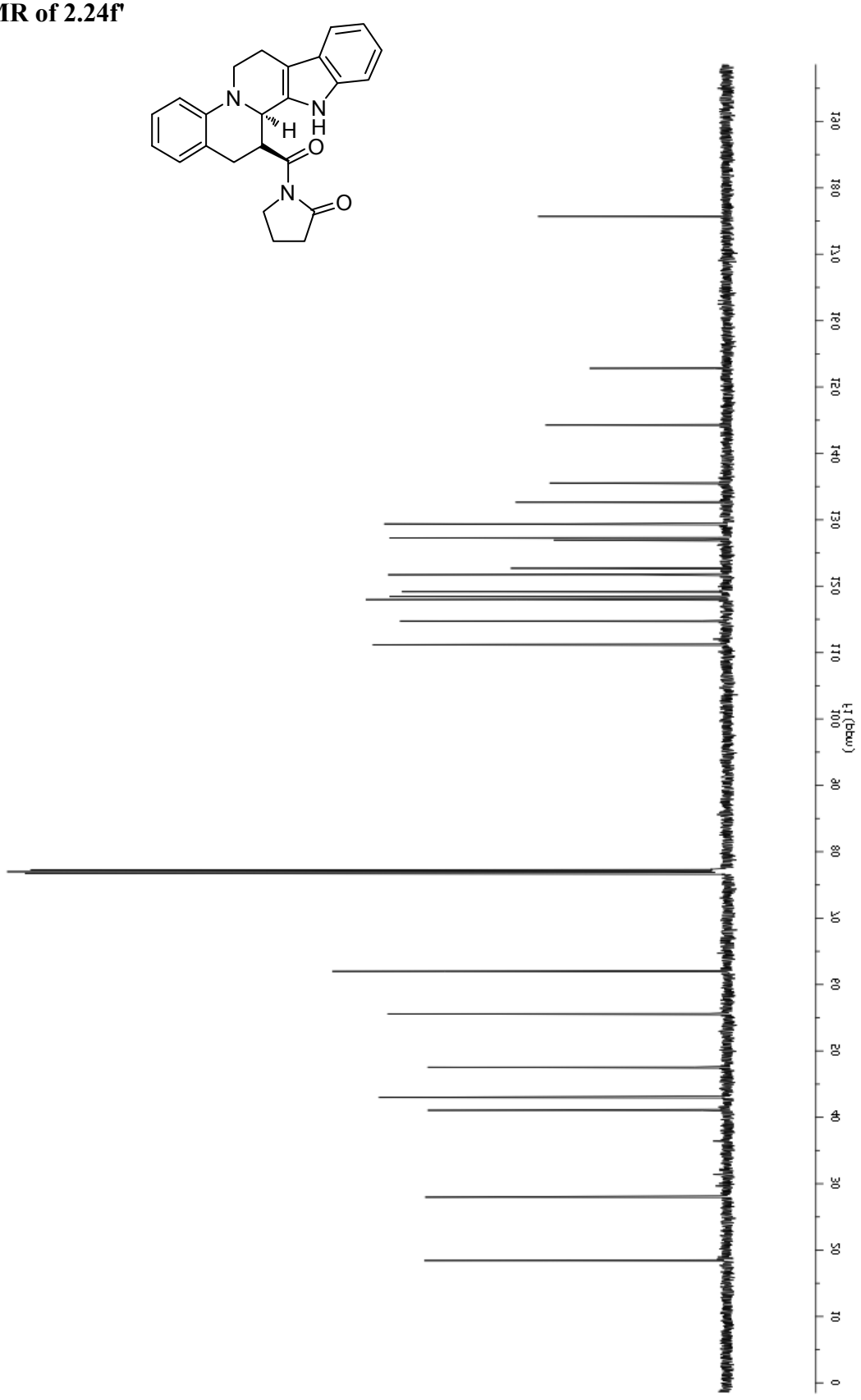

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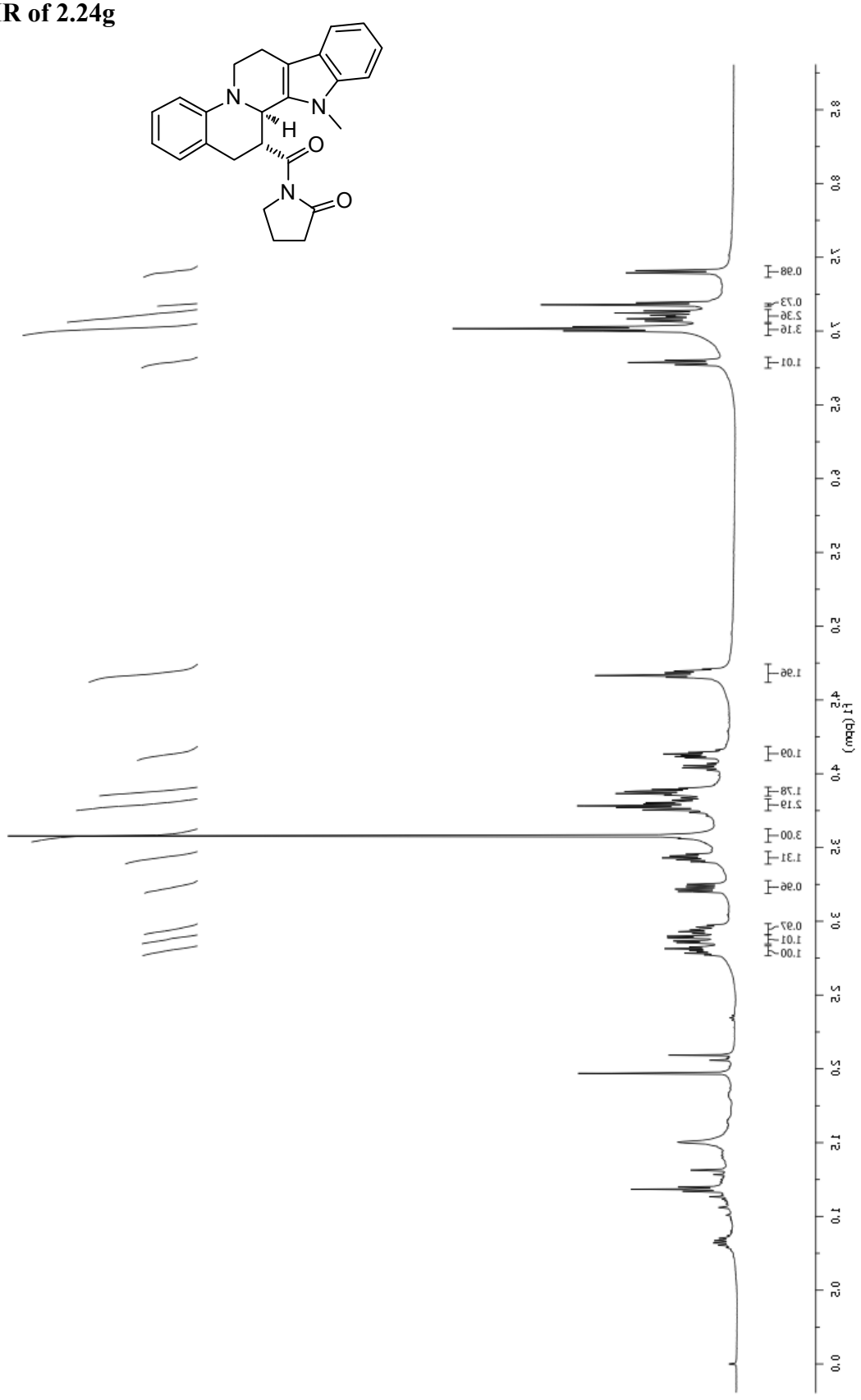

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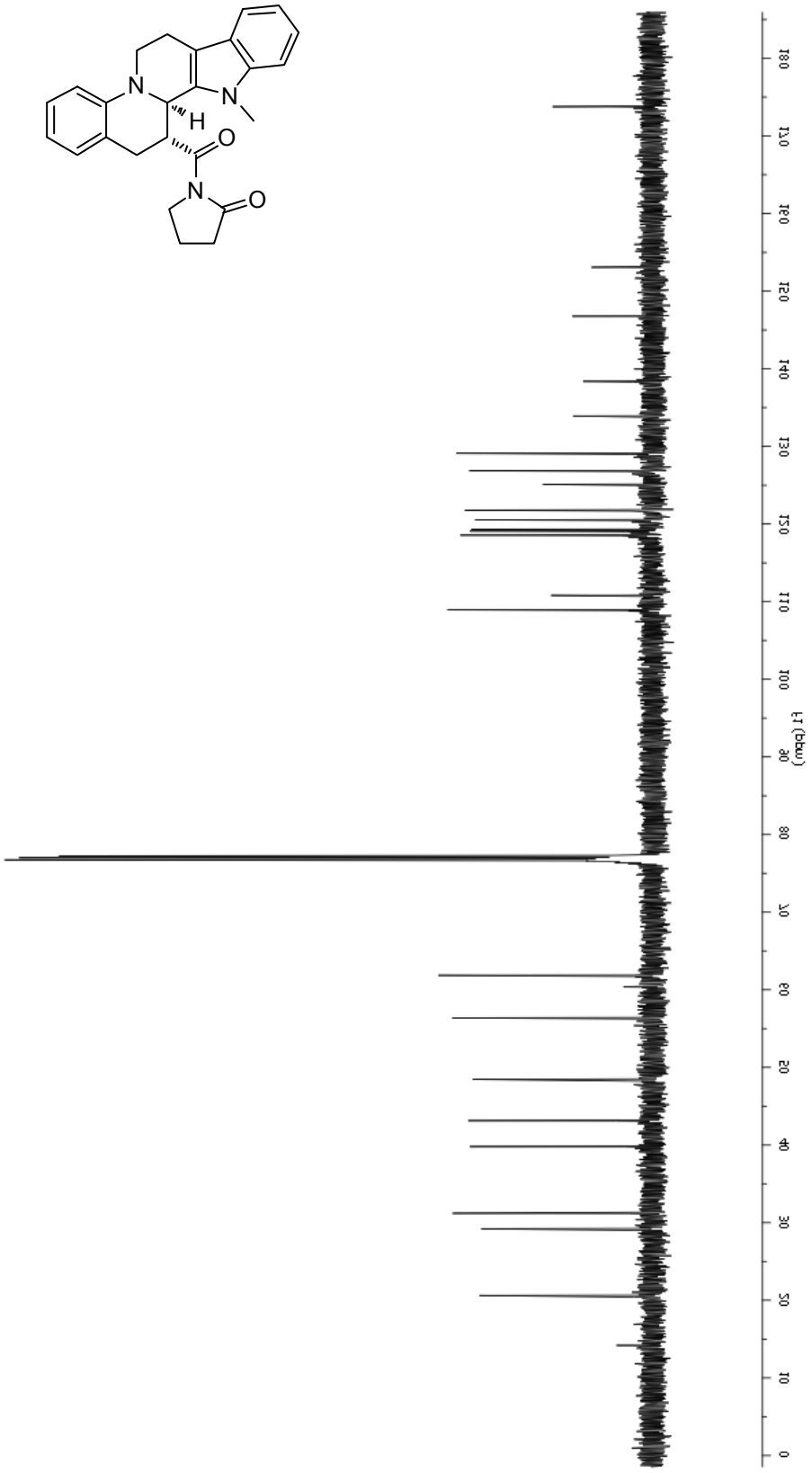

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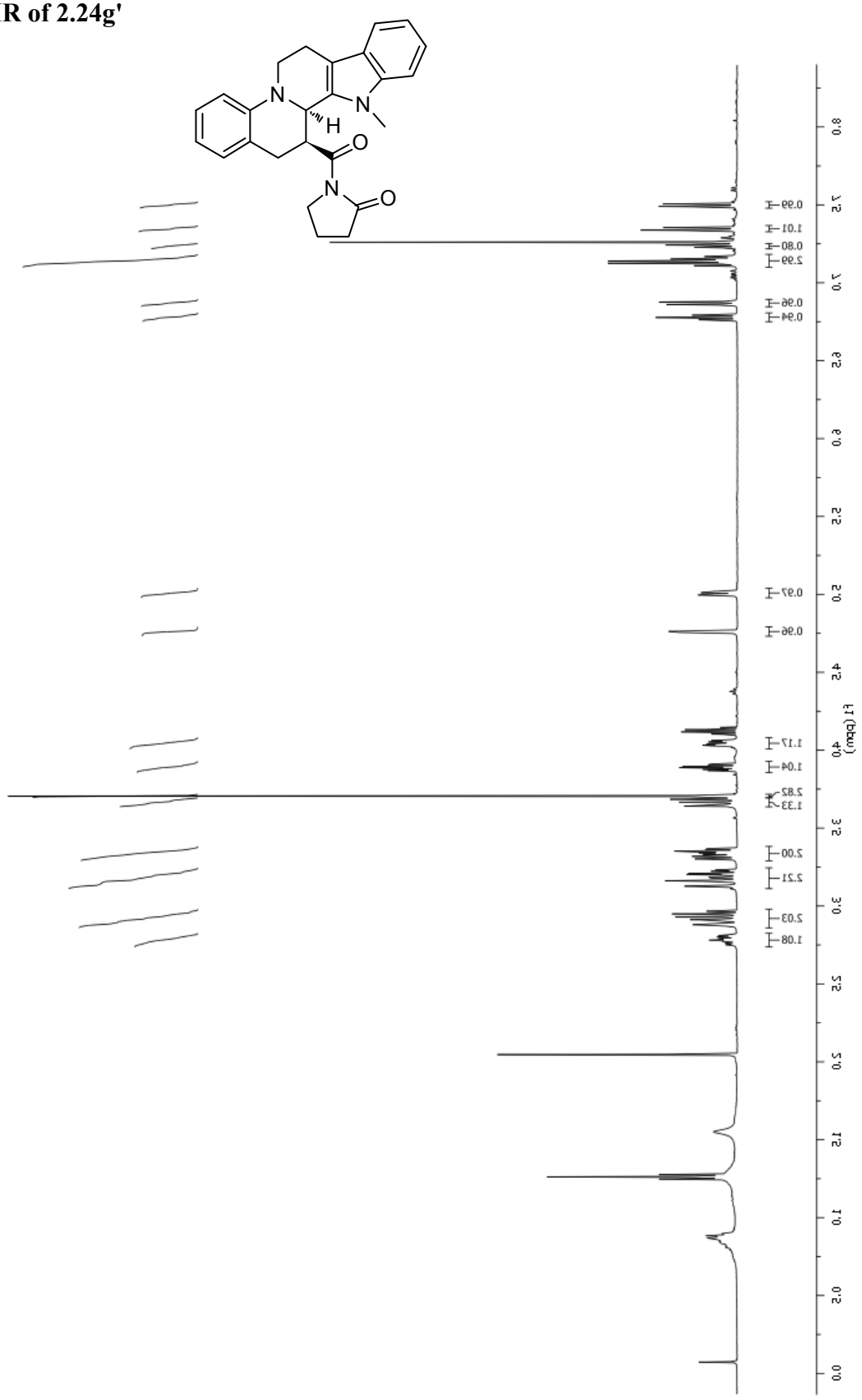
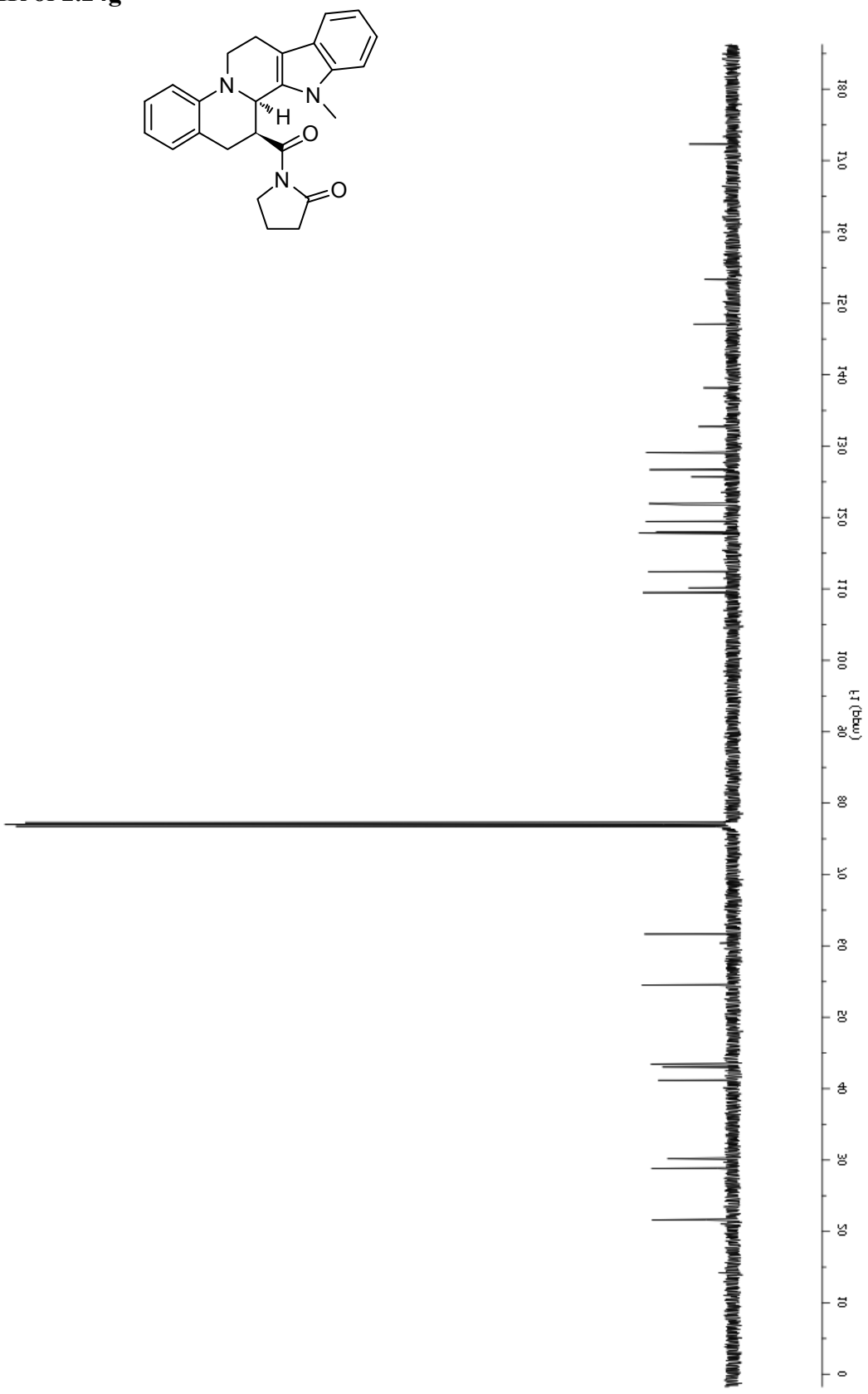
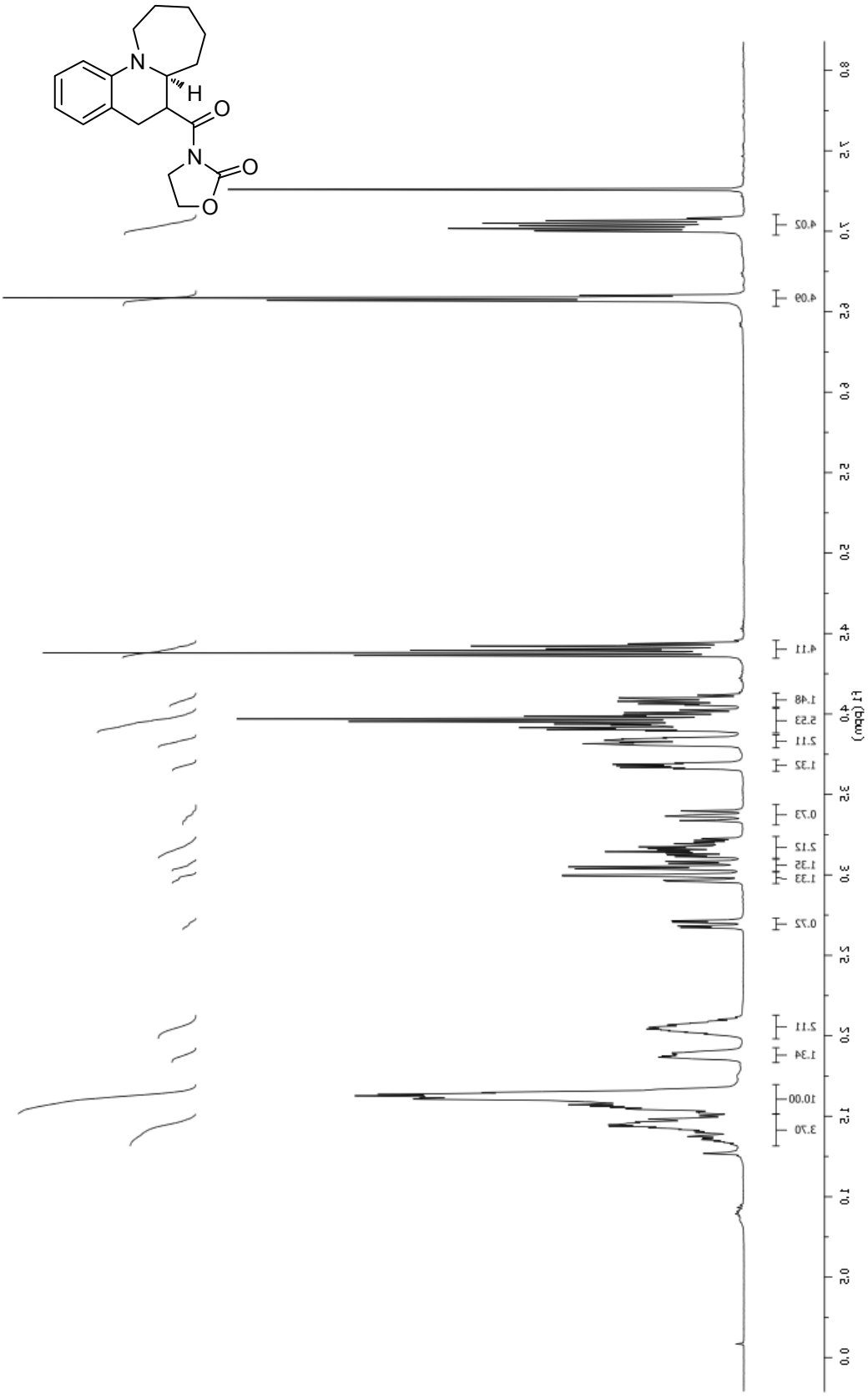


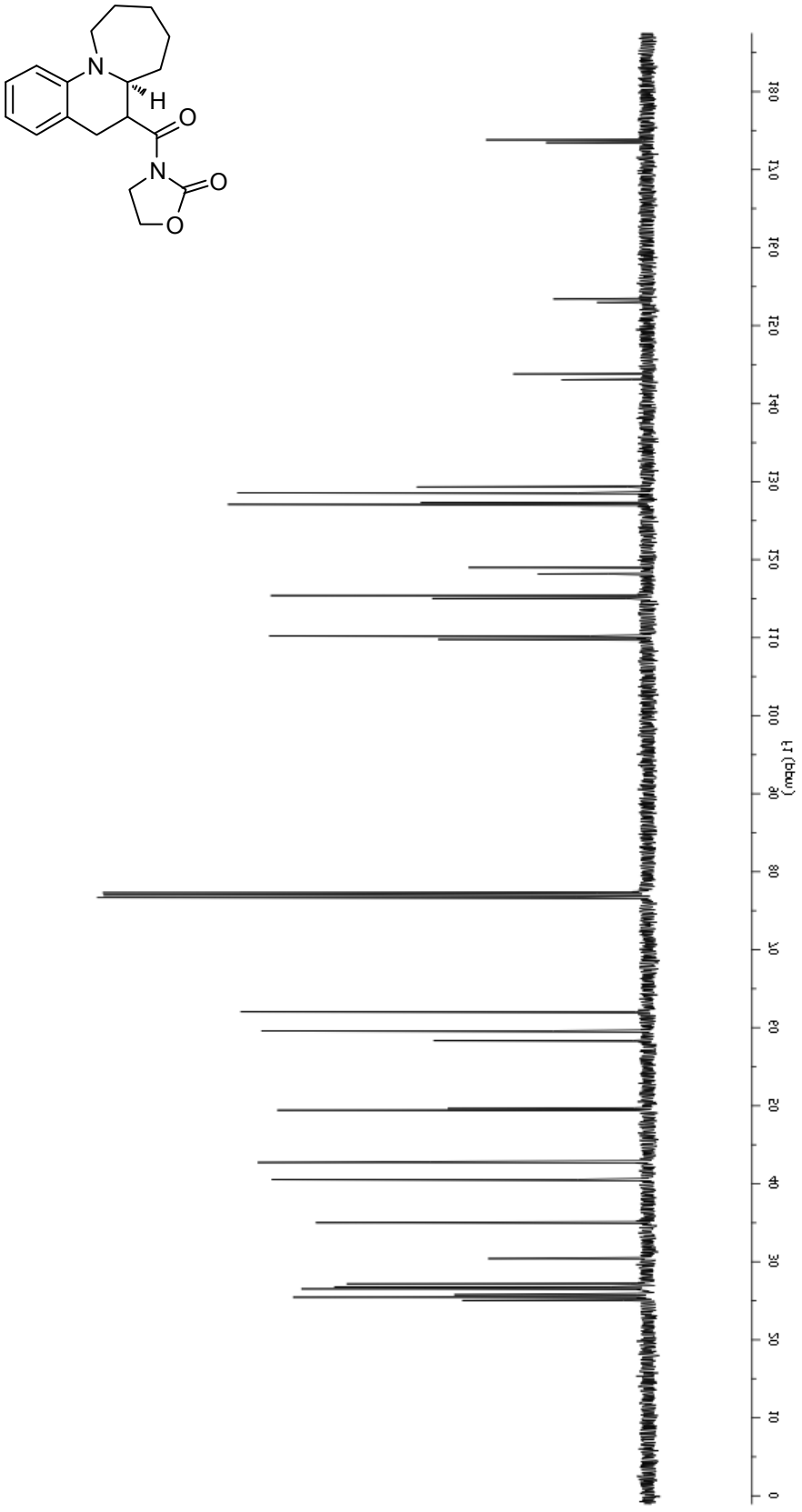
^{13}C NMR of 2.24g'



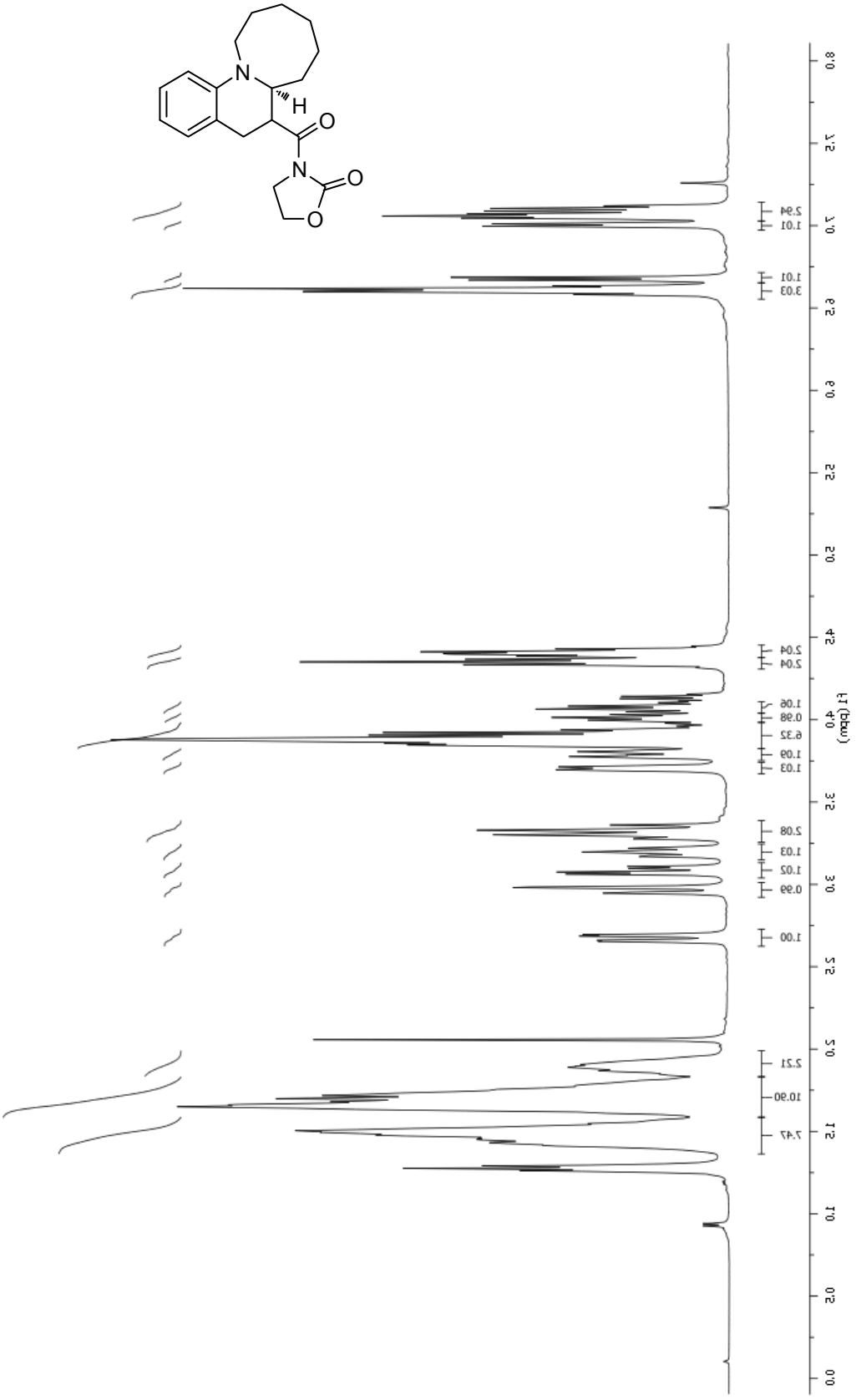
^{1}H NMR of 2.24h



^{13}C NMR of 2.24h



^{1}H NMR of 2.24i



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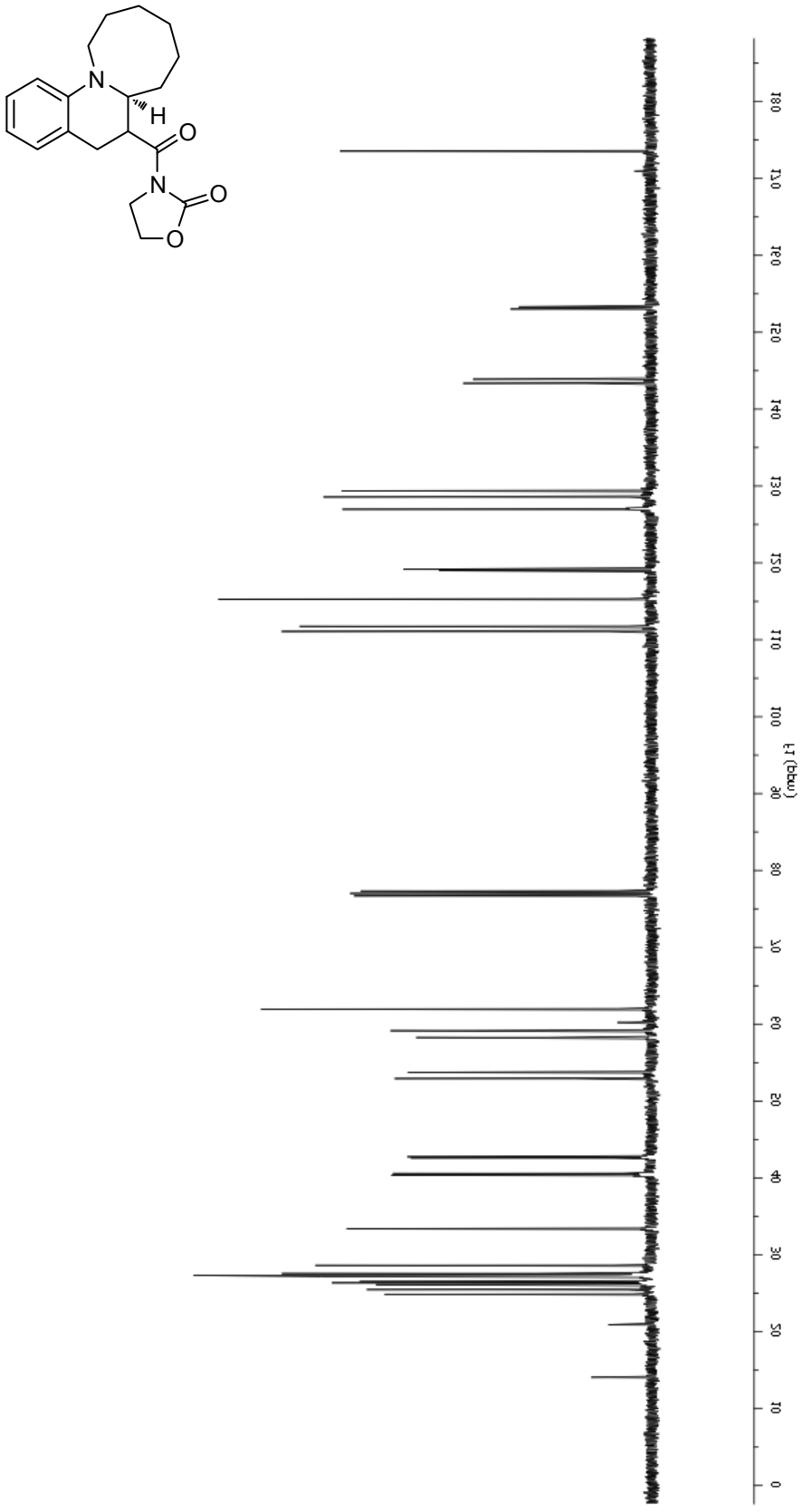
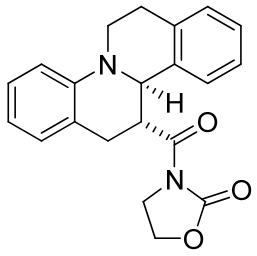
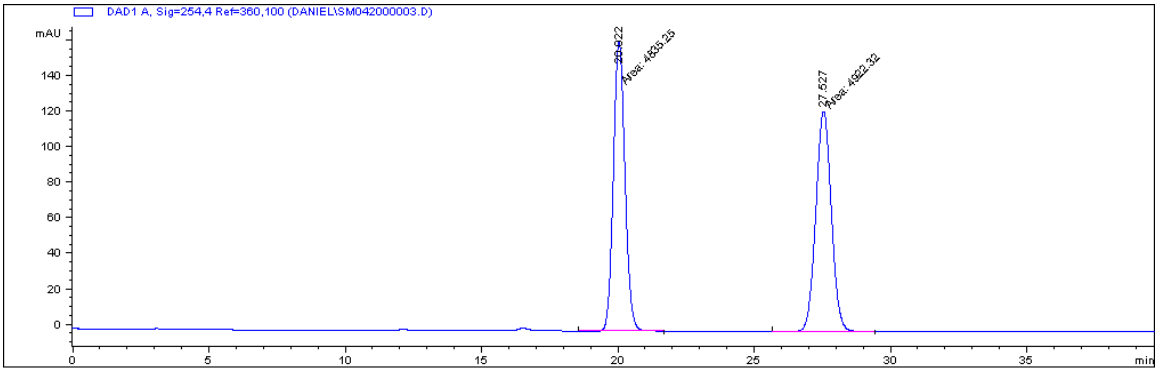
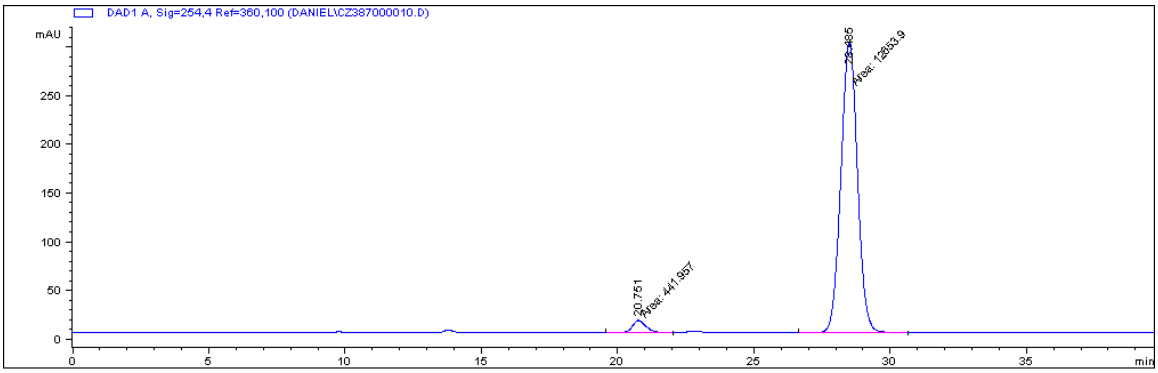


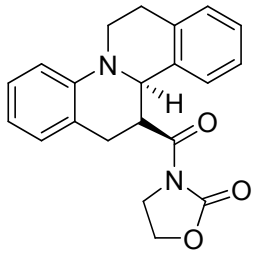
HPLC Profile of 2.24a

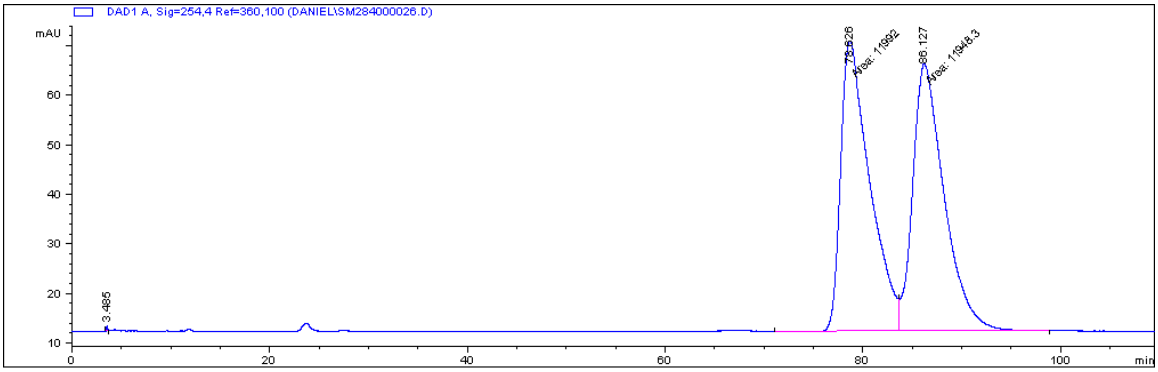


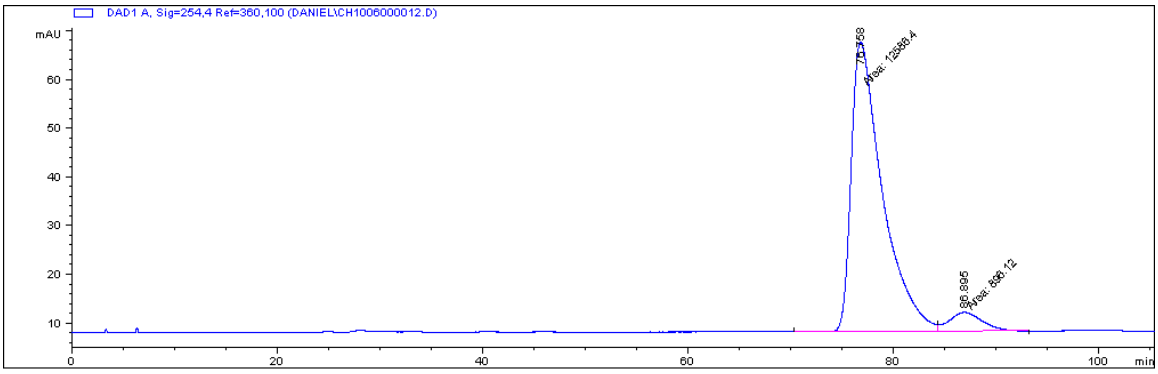




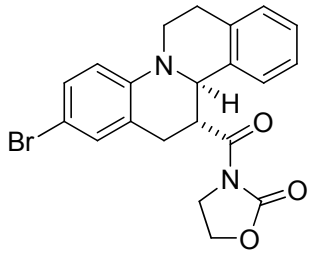
HPLC Profile of 2.24a'

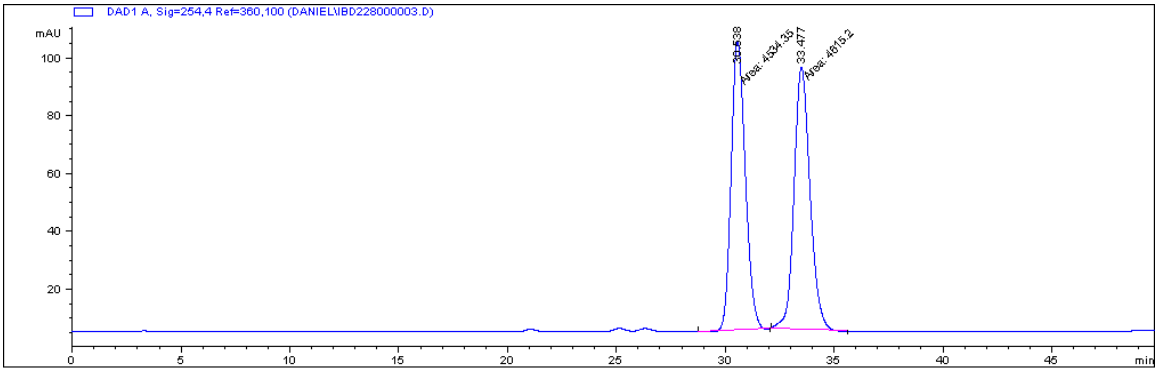


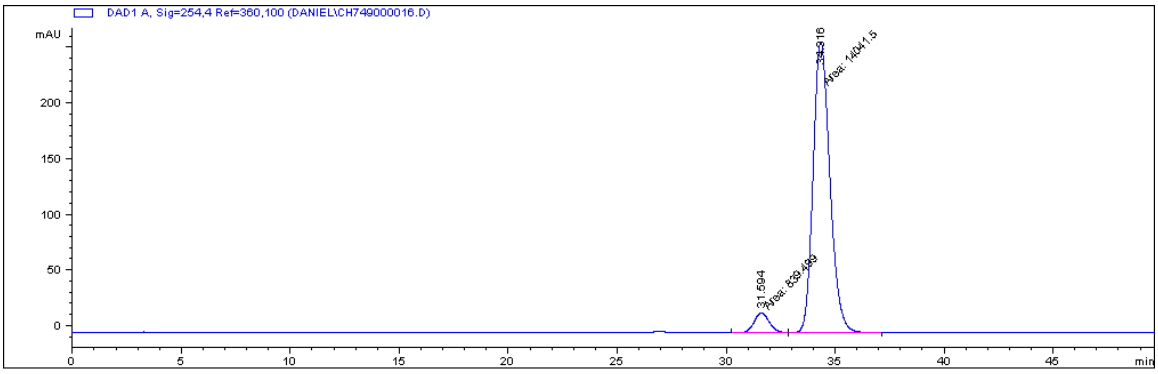




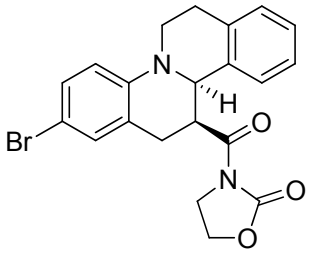
HPLC Profile of 2.24b

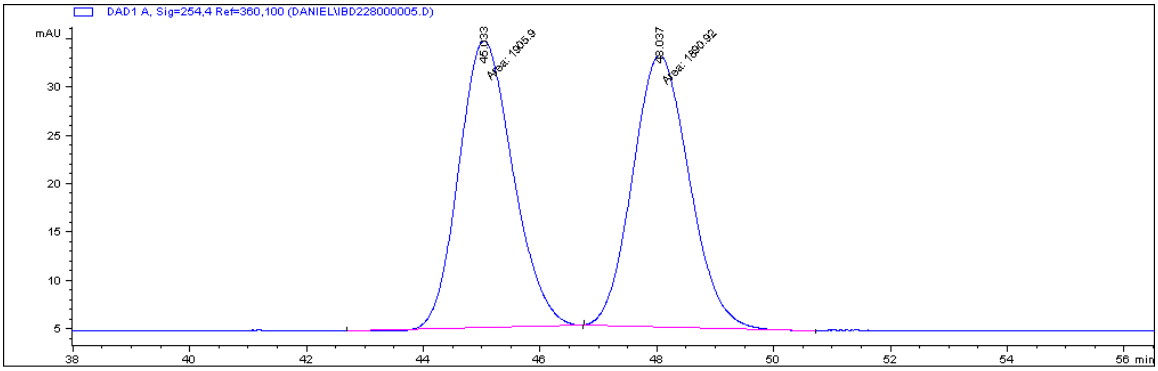


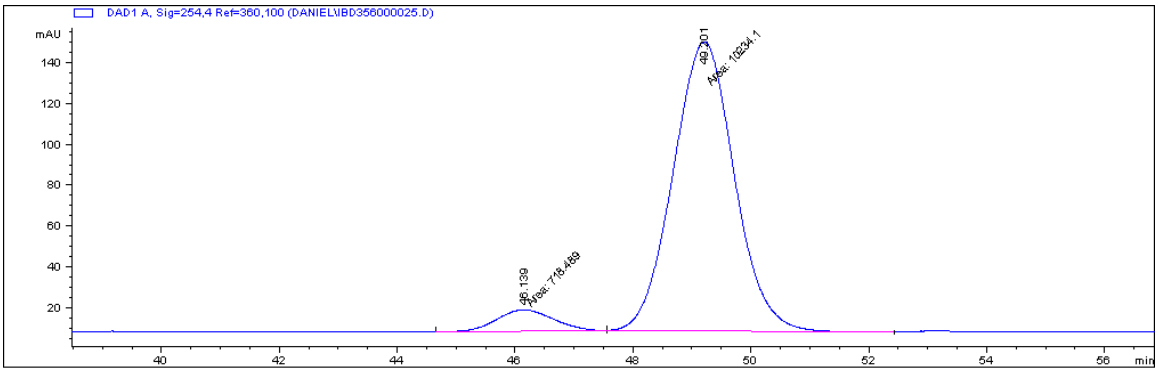




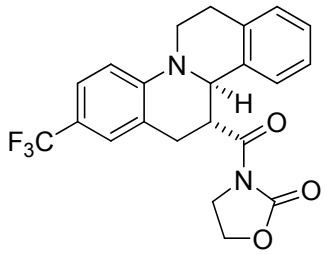
HPLC Profile of 2.24b'

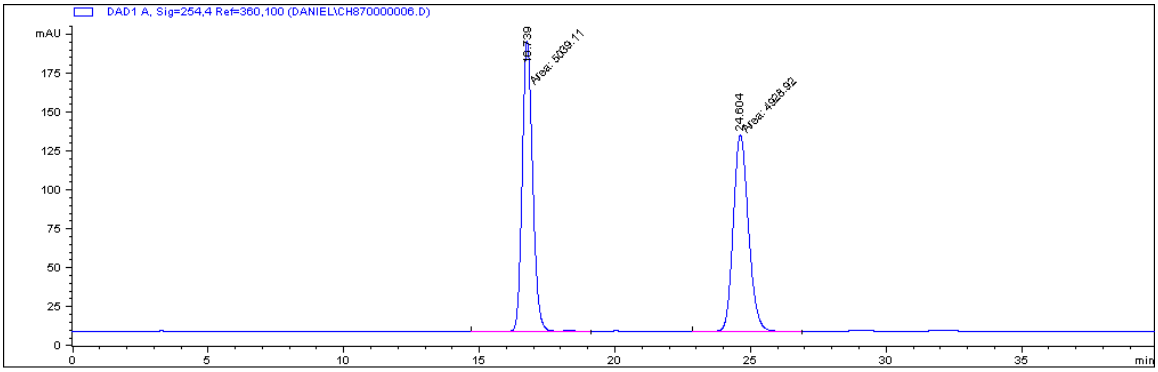


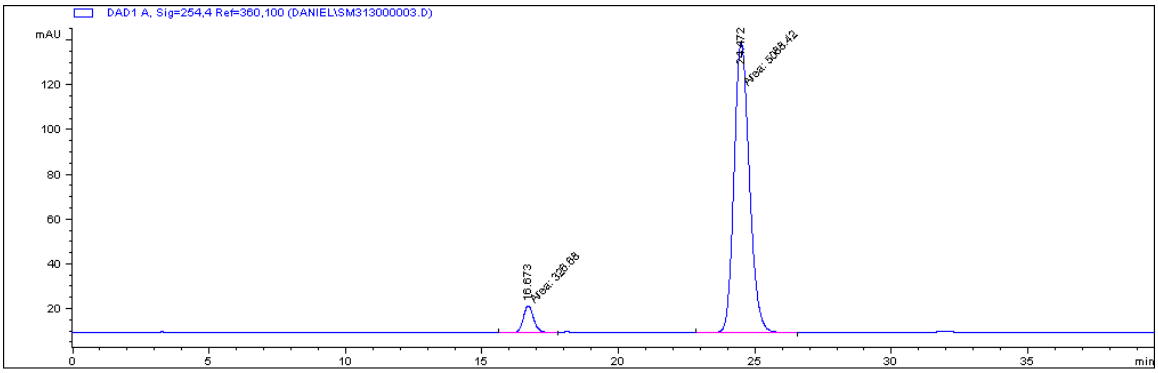




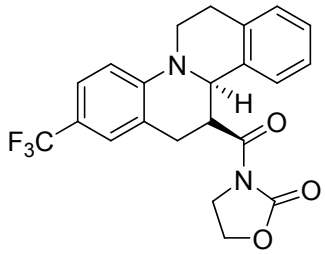
HPLC Profile of 2.24c

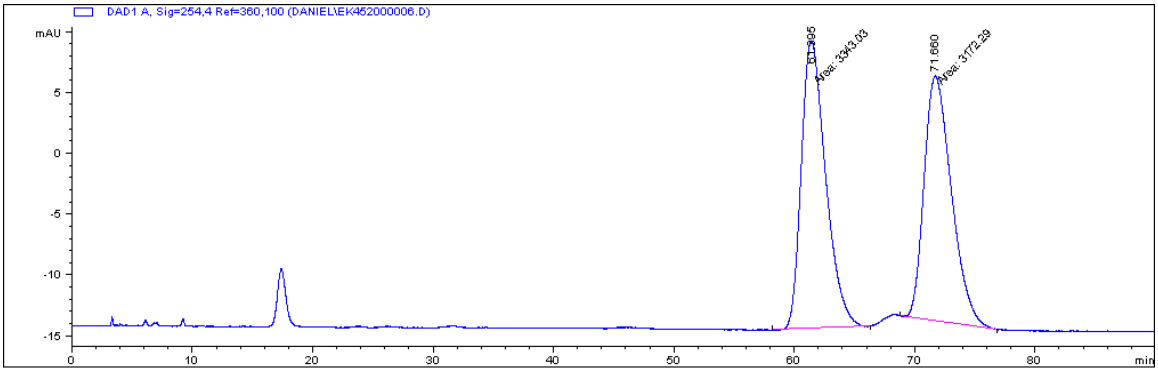


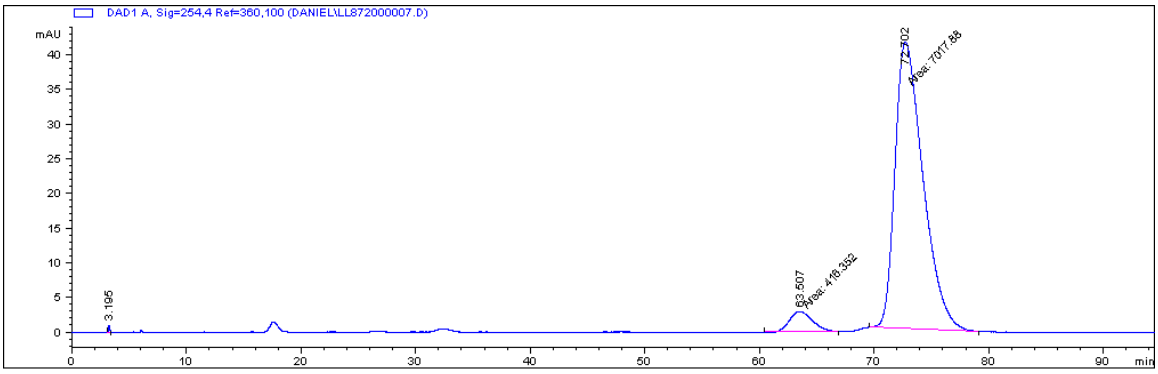




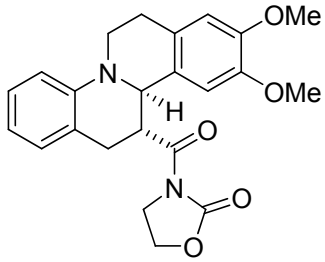
HPLC Profile of 2.24c'

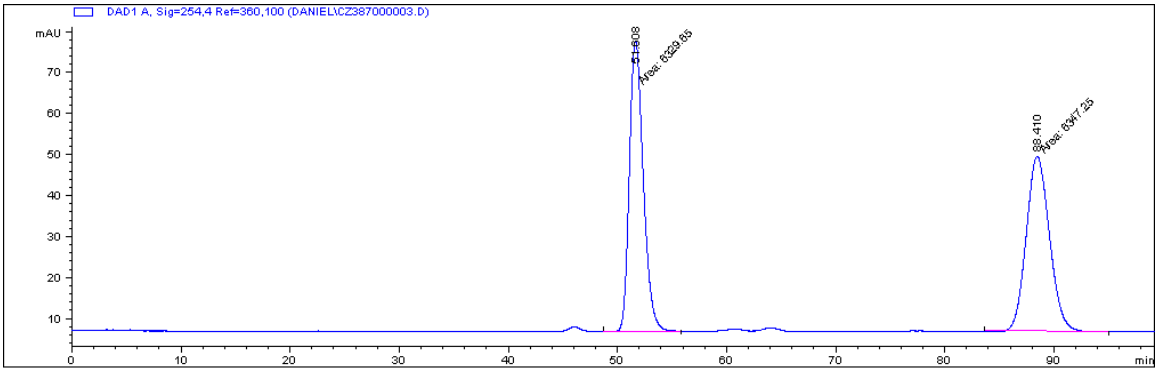


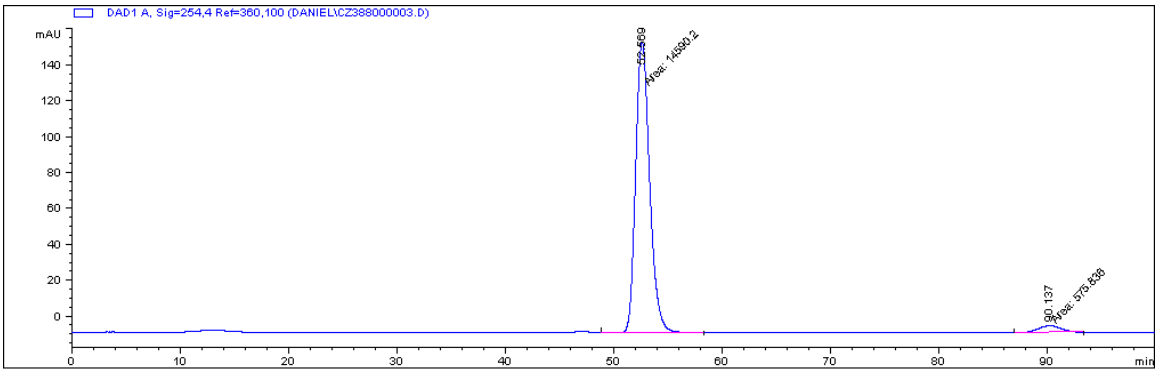




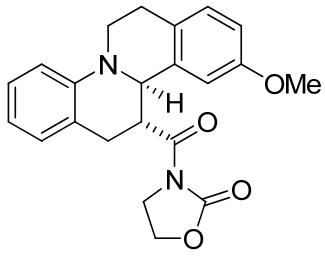
HPLC Profile of 2.24d

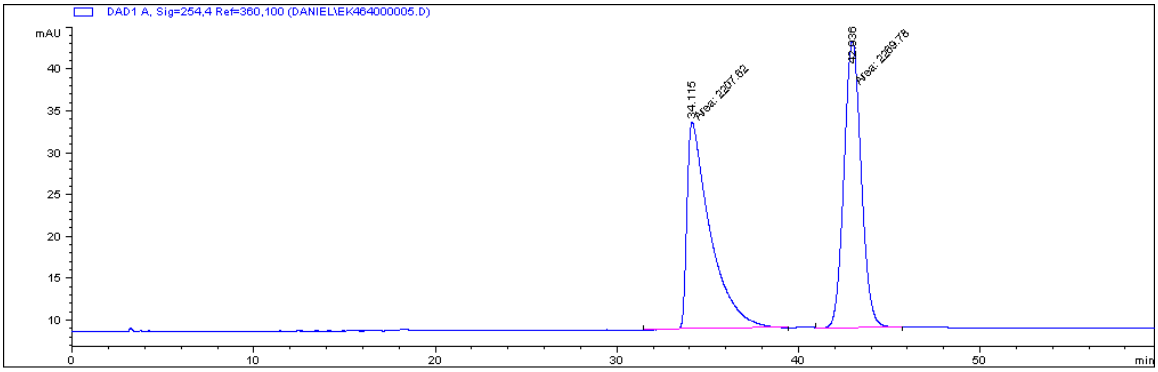


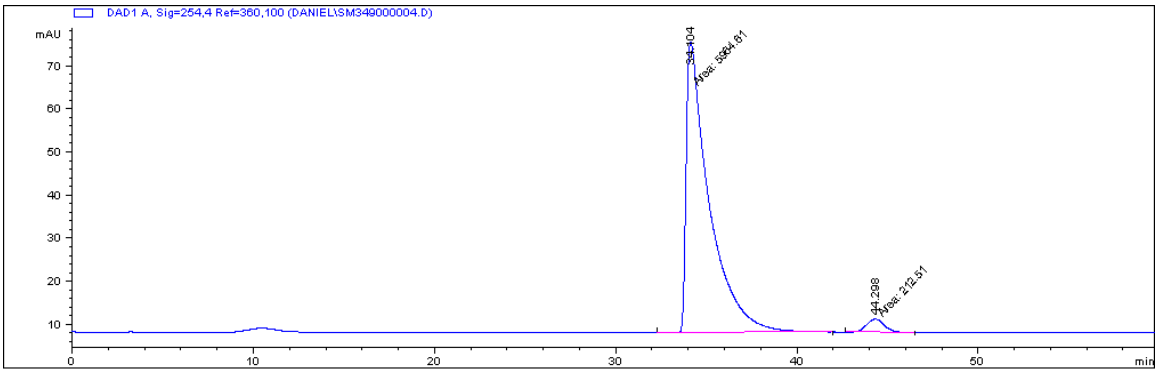




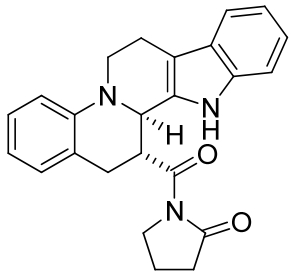
HPLC Profile of 2.24e

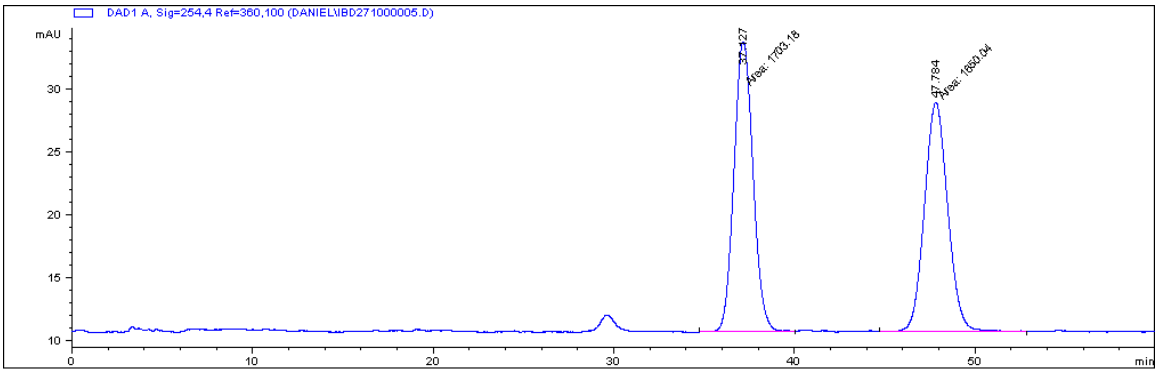


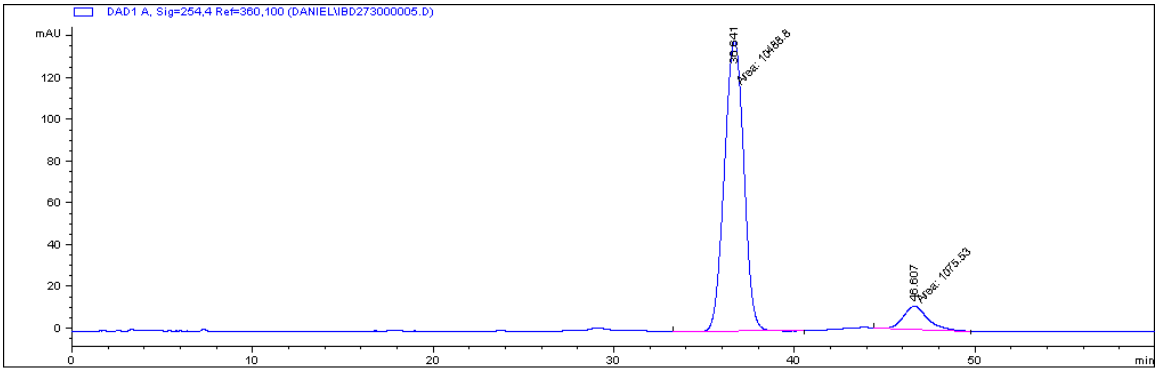




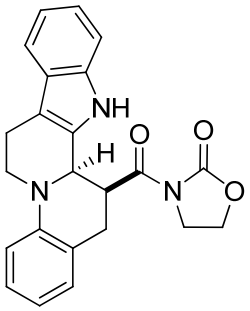
HPLC Profile of 2.24f

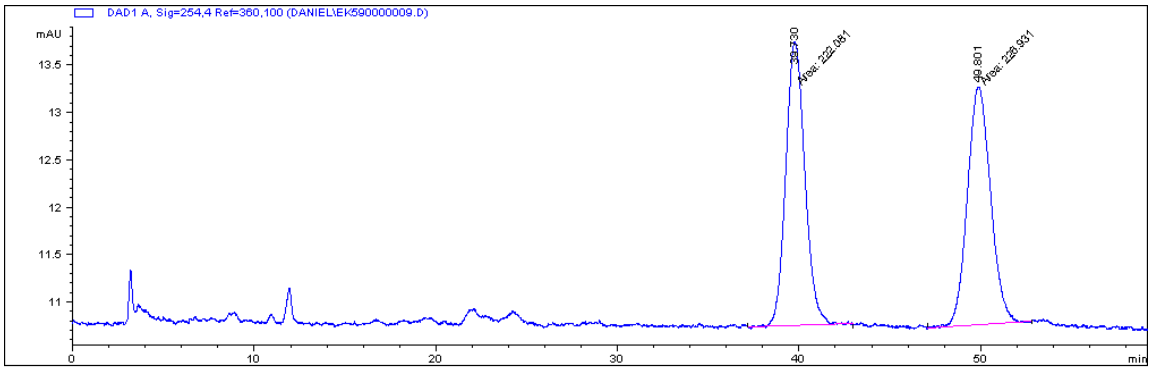


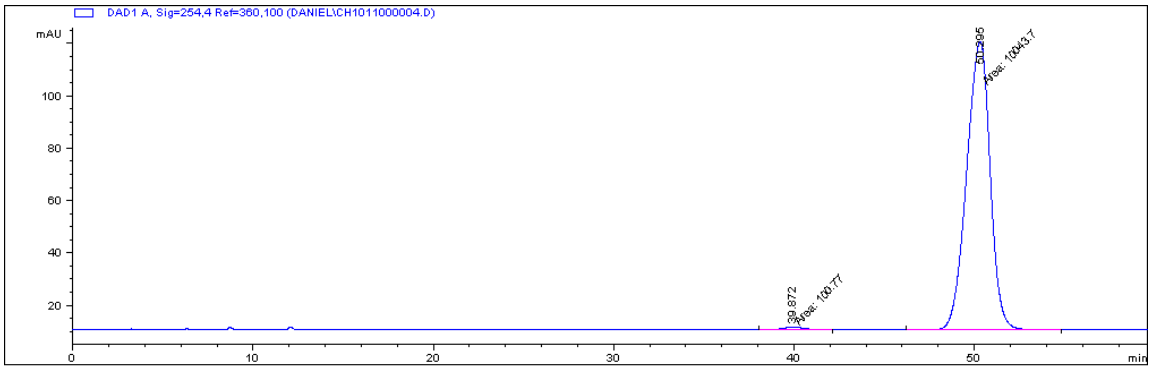




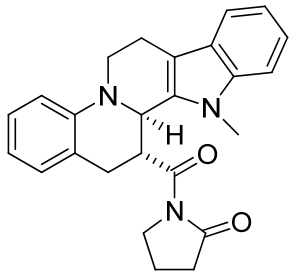
HPLC Profile of 2.24f'

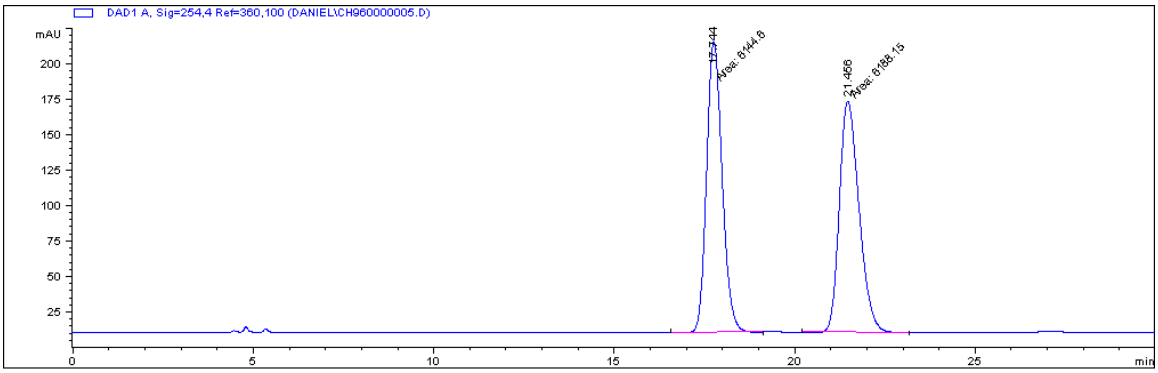


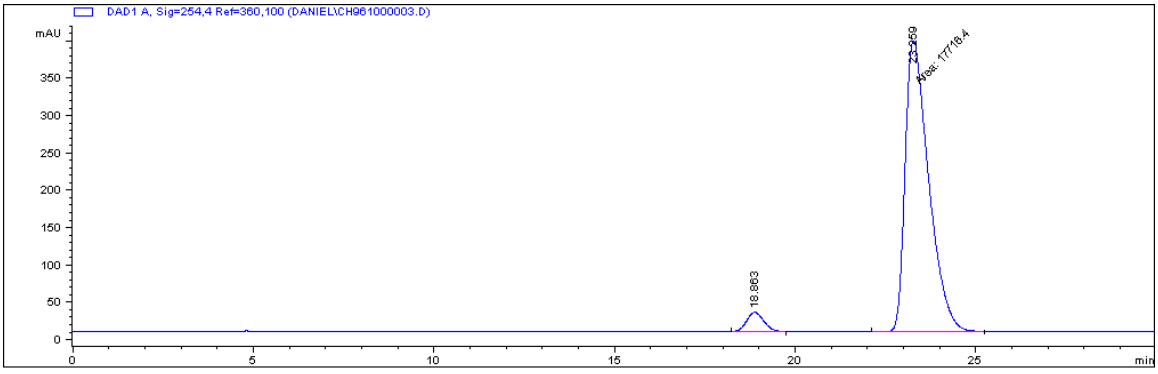




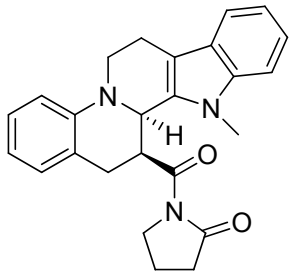
HPLC Profile of 2.24g

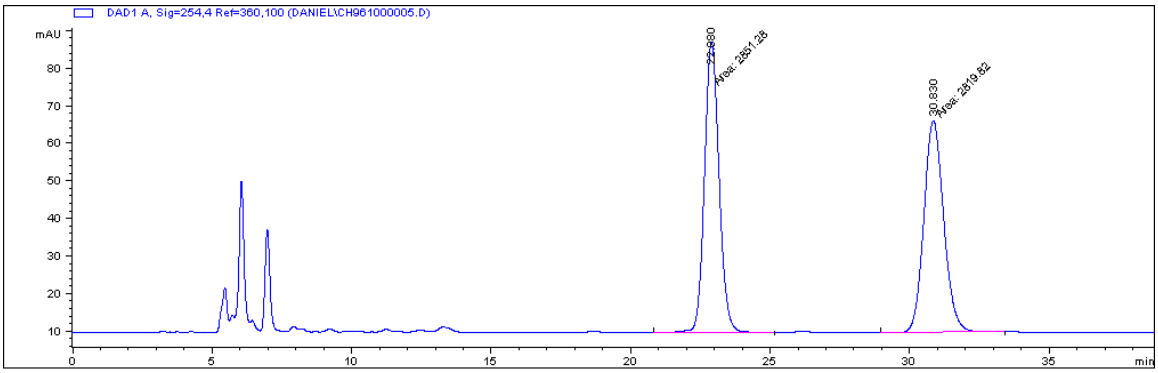


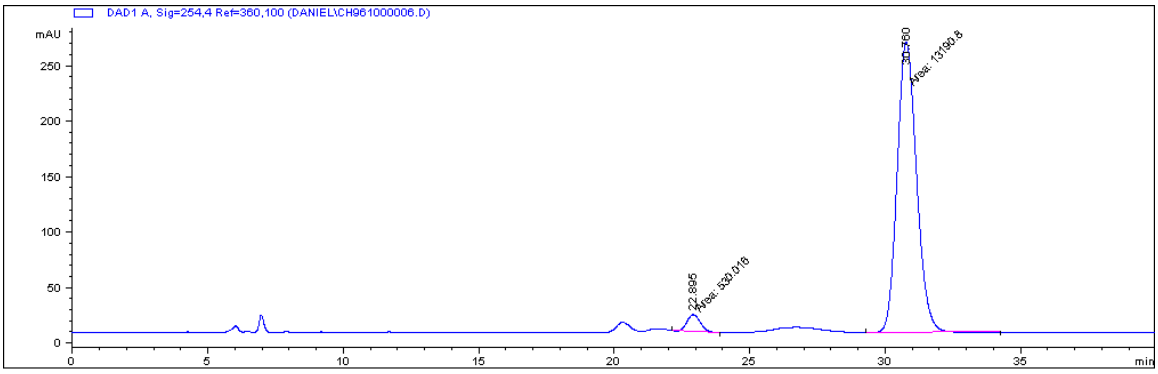




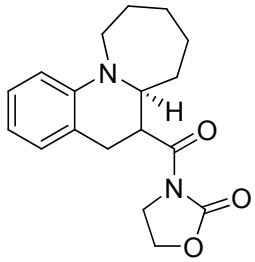
HPLC Profile of 2.24g'

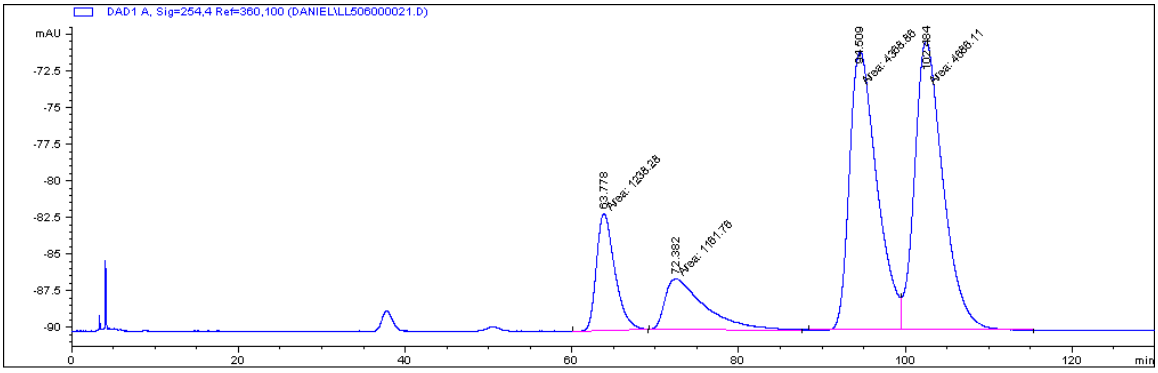


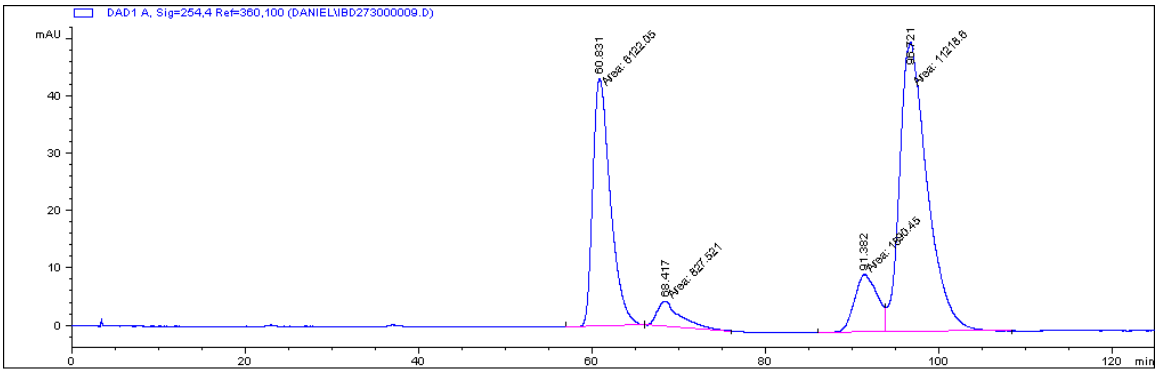




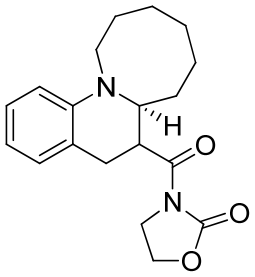
HPLC Profile of 2.24h

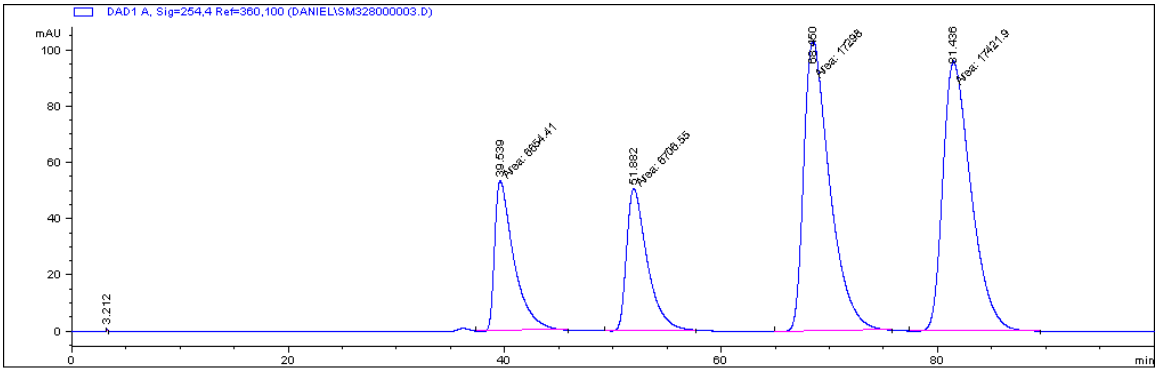


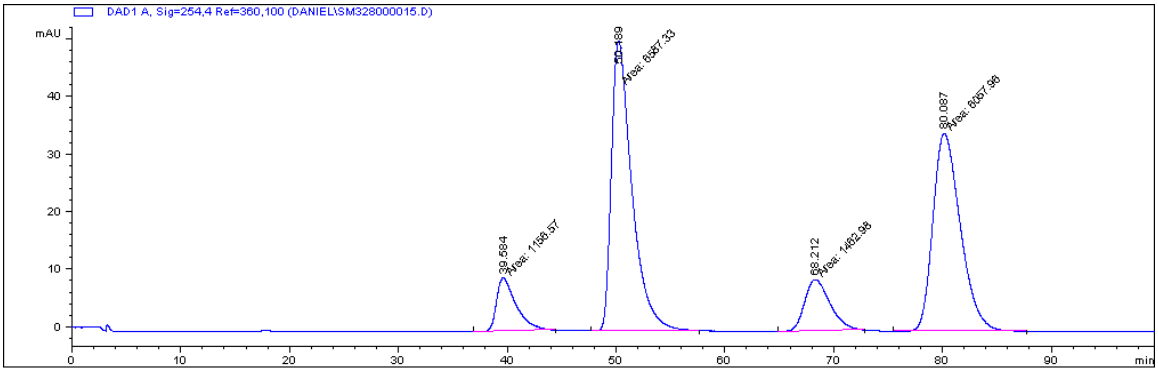




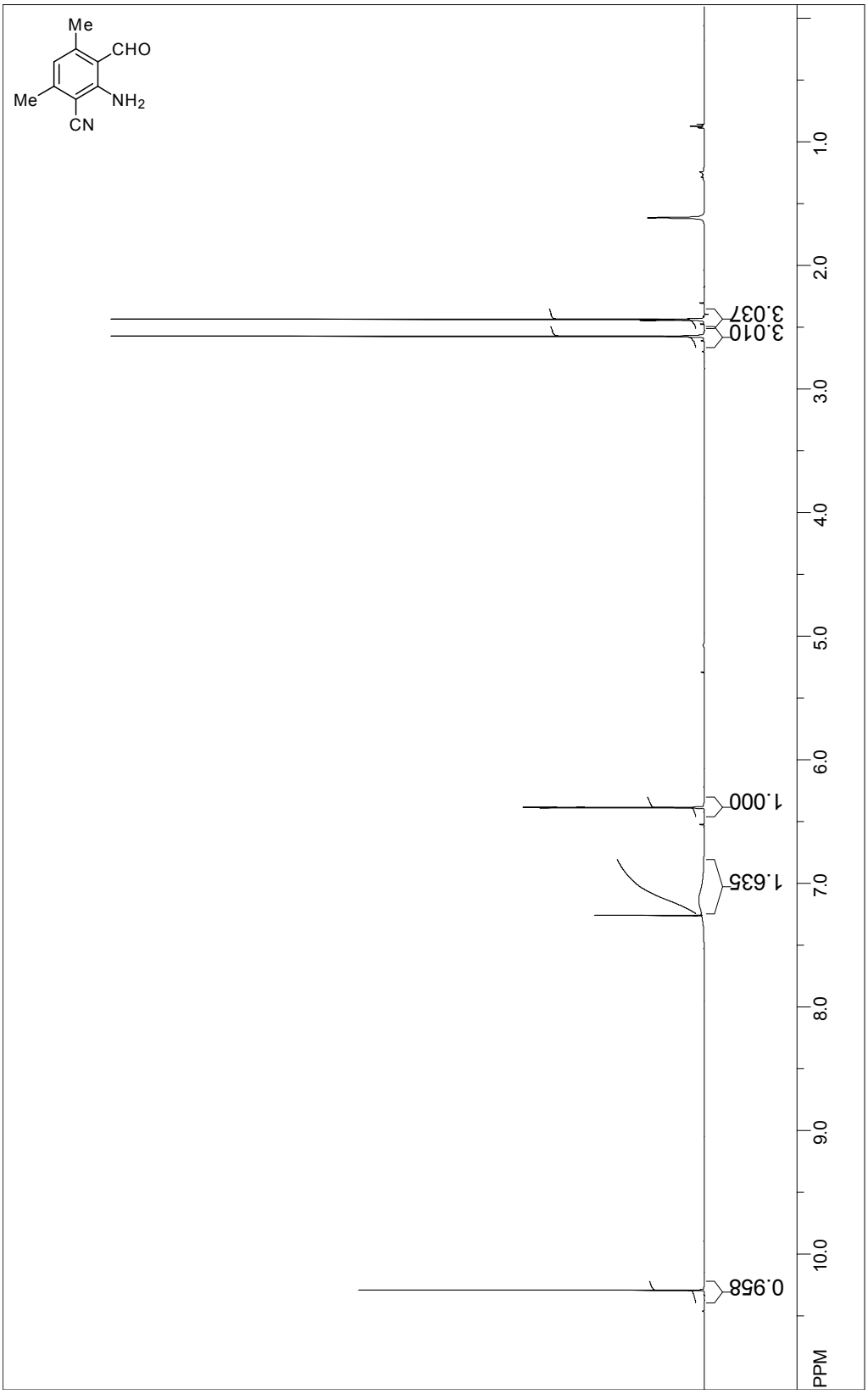
HPLC Profile of 2.24i

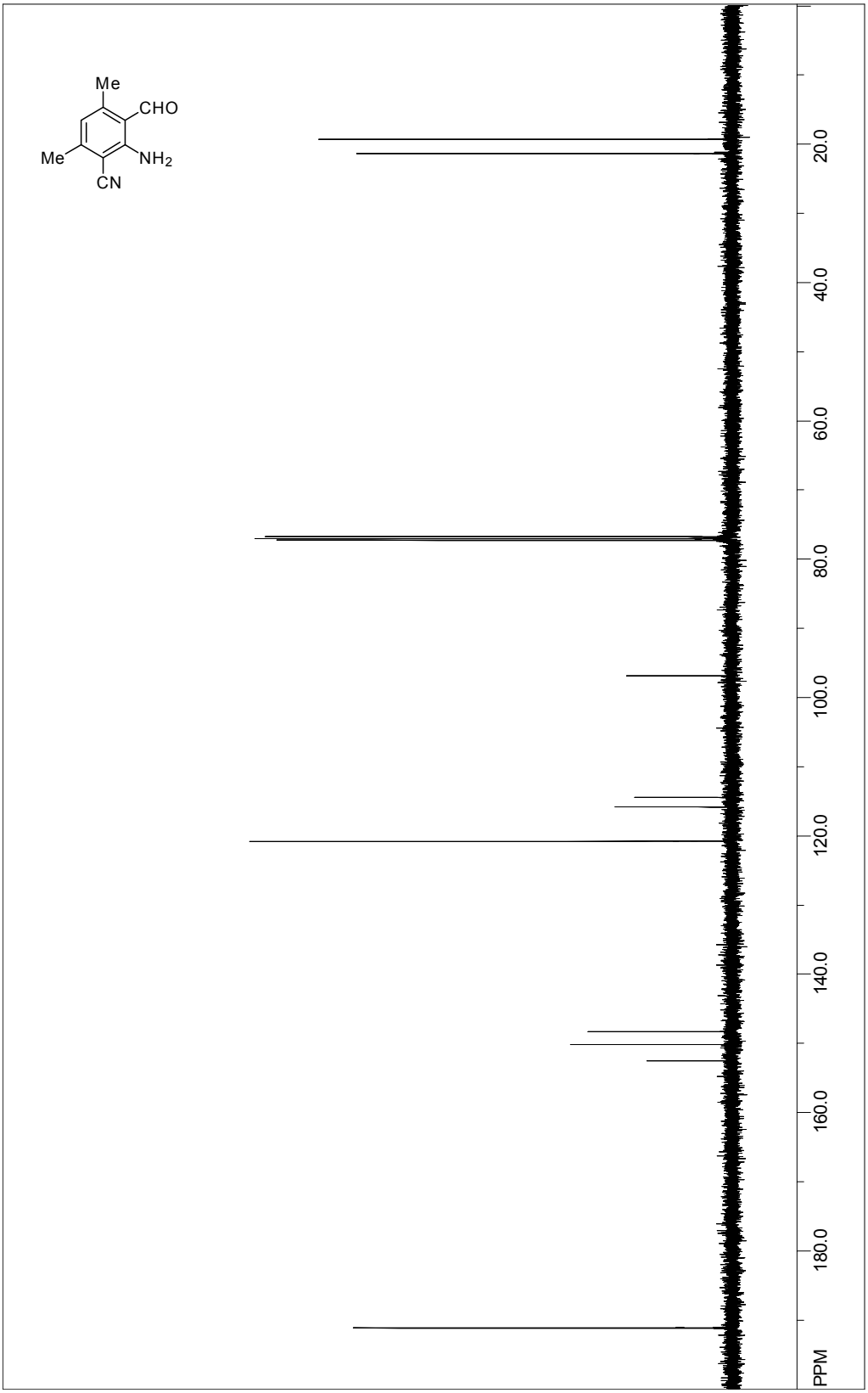




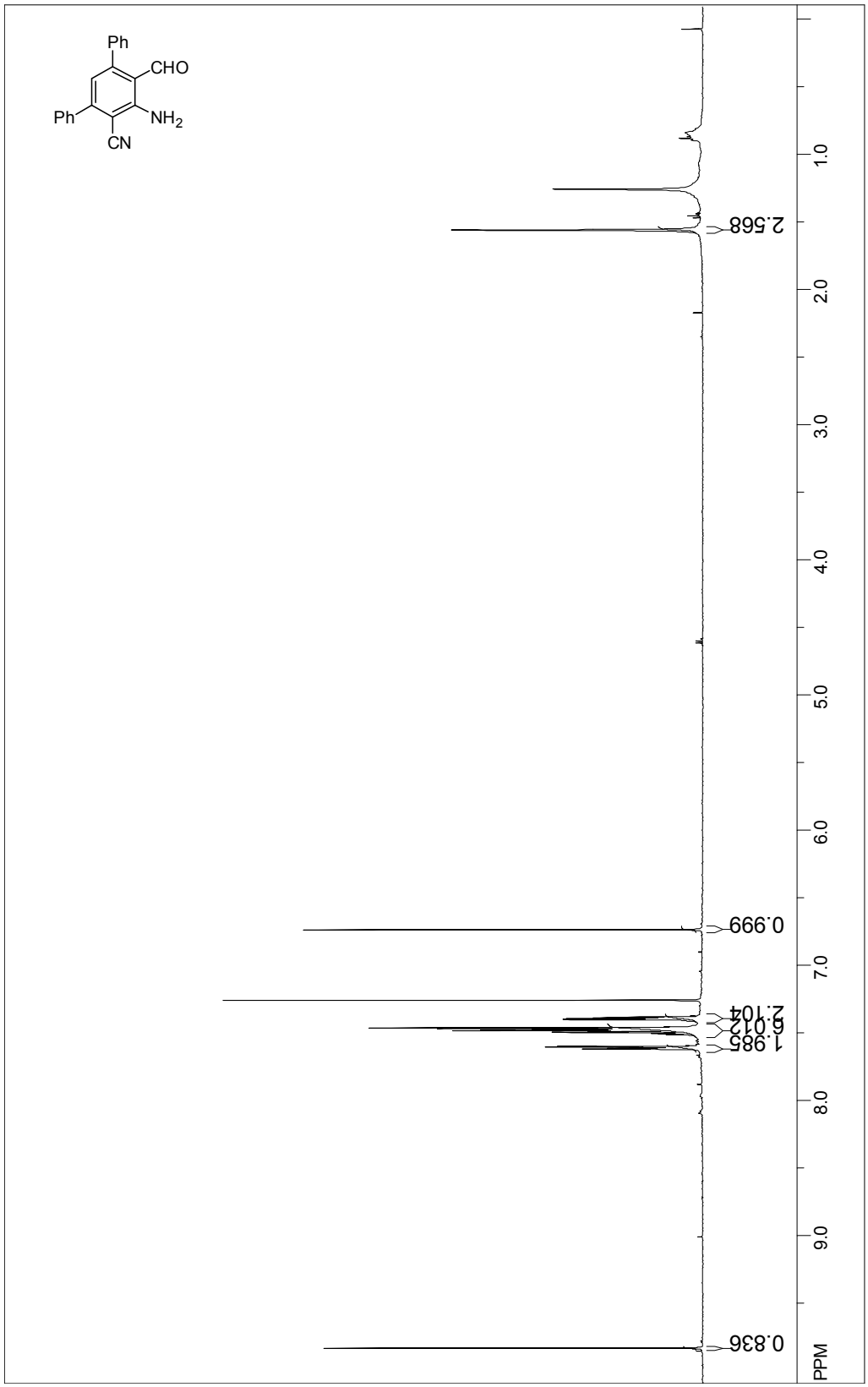


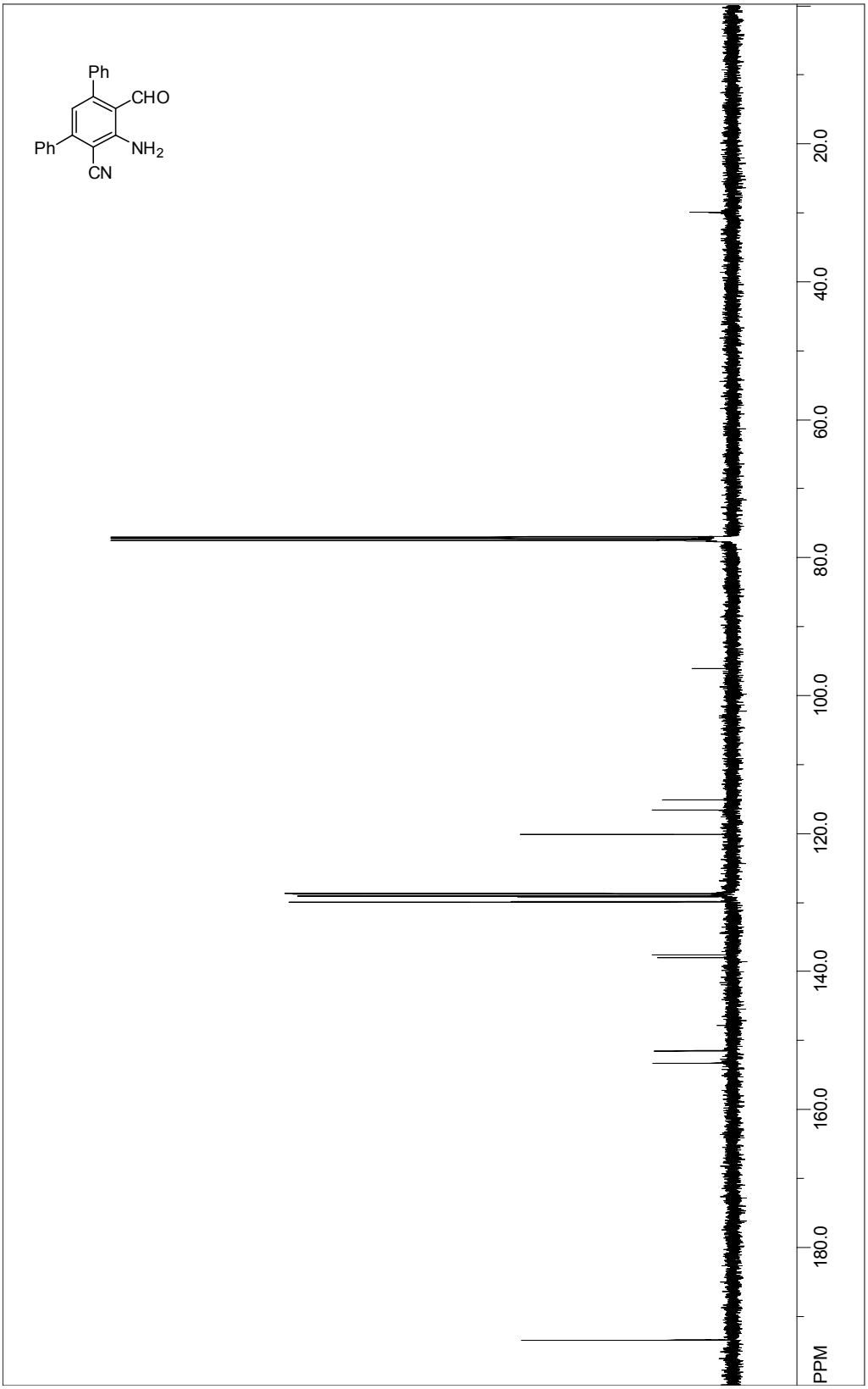
^{1}H-NMR and ^{13}C-NMR of **3.1a**:



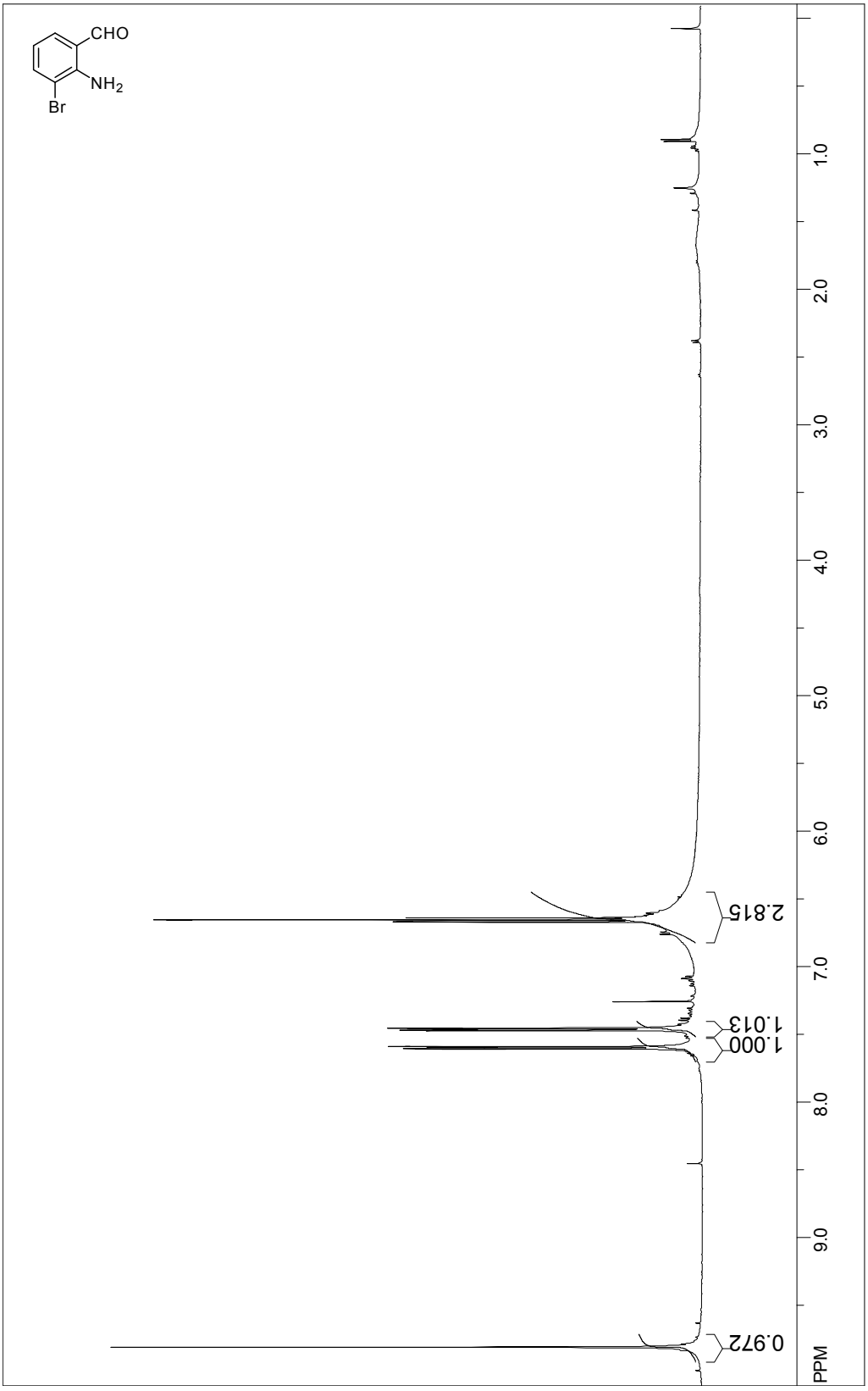

Me
CHO
Me
NH2
CN
20.0
40.0
60.0
80.0
100.0
120.0
140.0
160.0
180.0
PPM

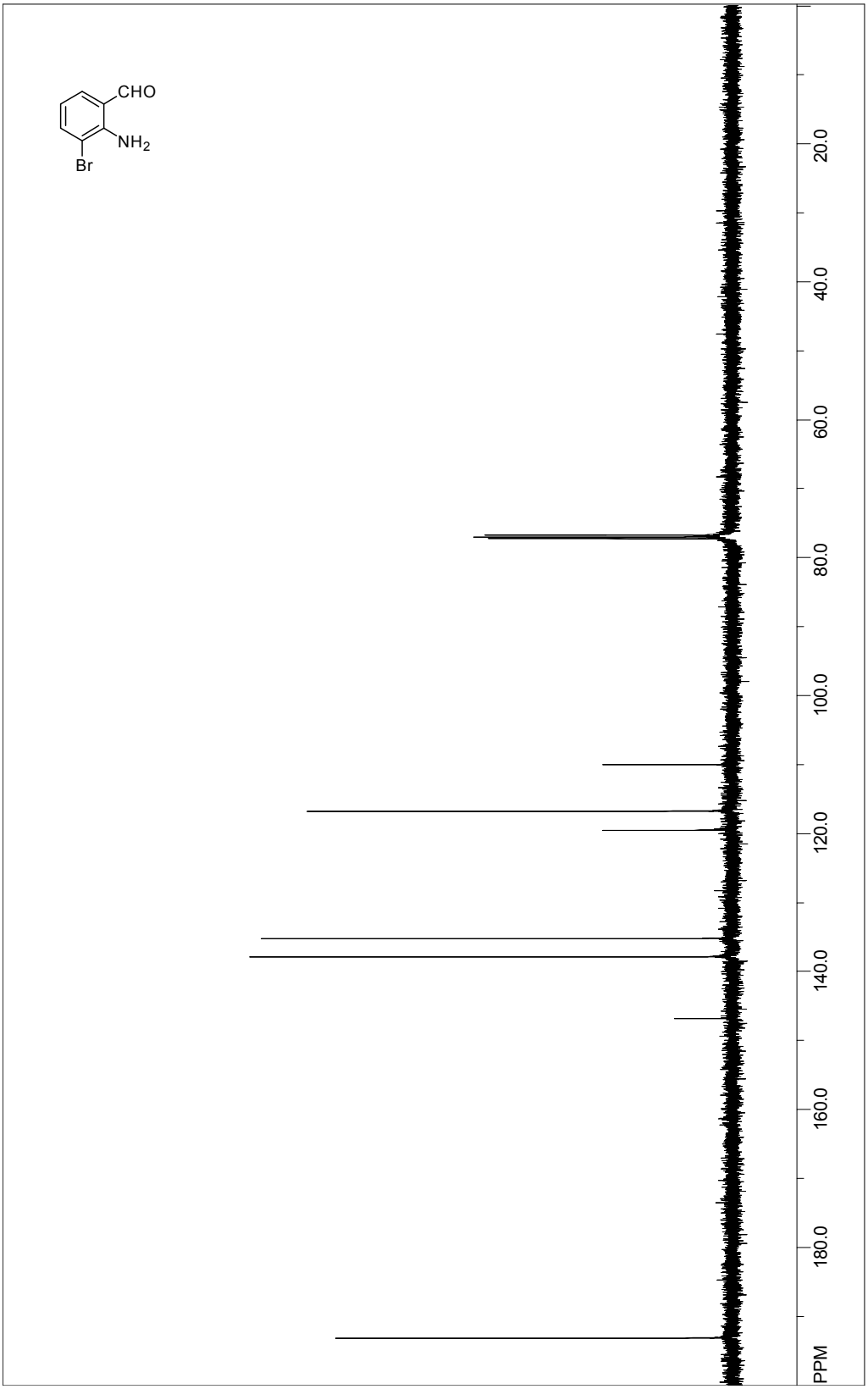
^{1}H-NMR and ^{13}C-NMR of **3.1b**:



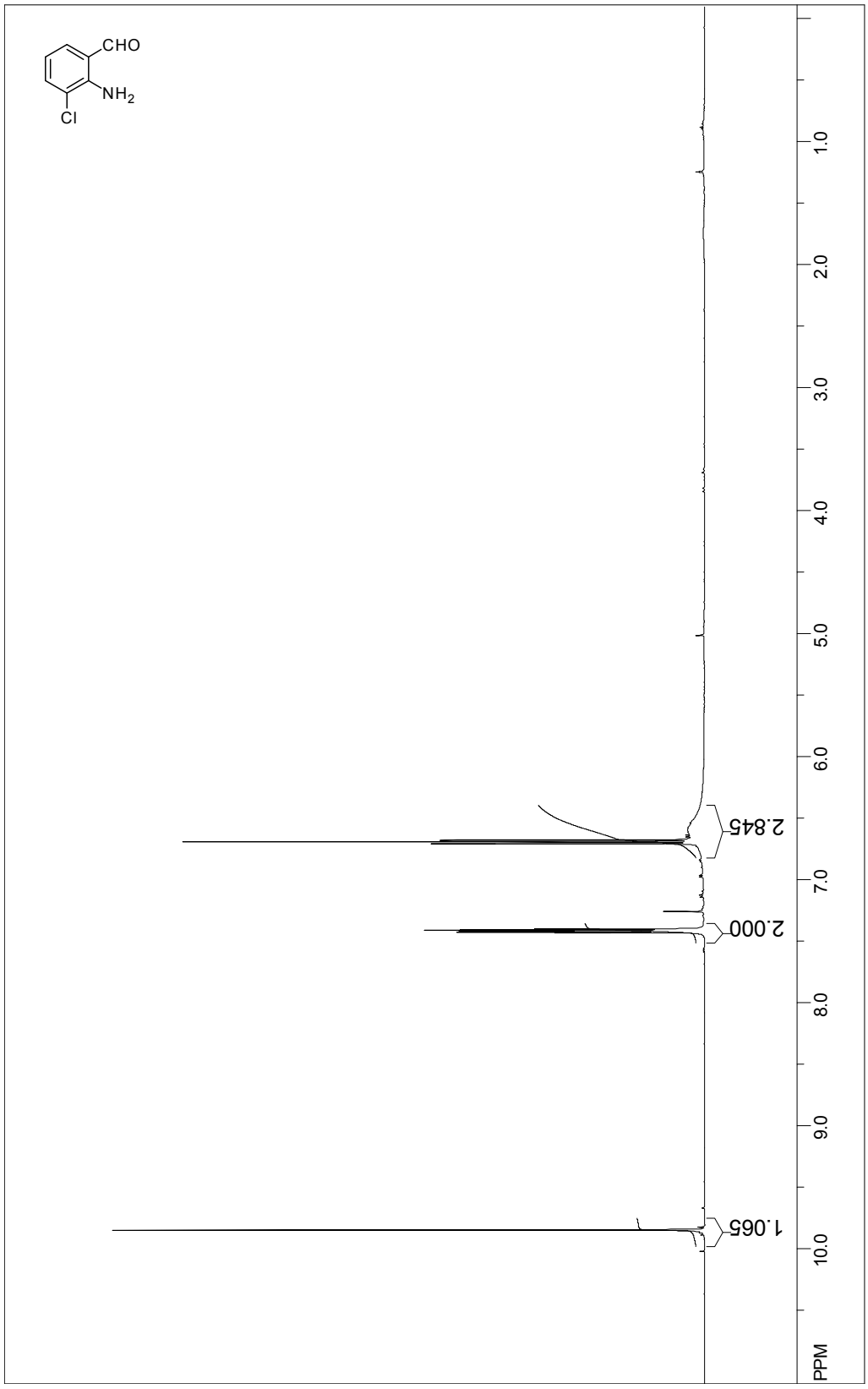

Ph
CHO
Ph
NH2
CN
20.0
40.0
60.0
80.0
100.0
120.0
140.0
160.0
180.0
PPM

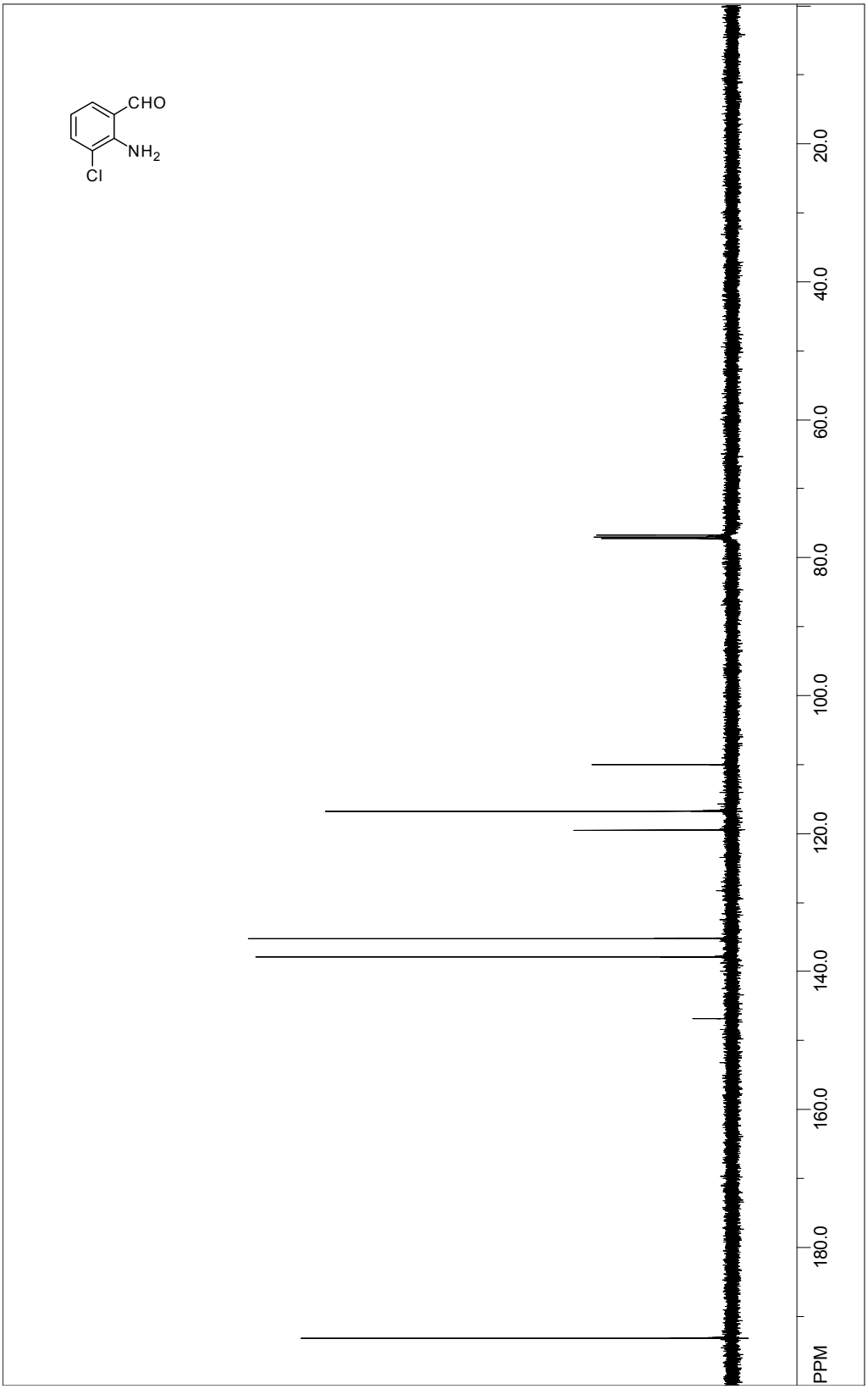
^{1}H-NMR and ^{13}C-NMR of 2-amino-3-bromobenzaldehyde **3.1f**:



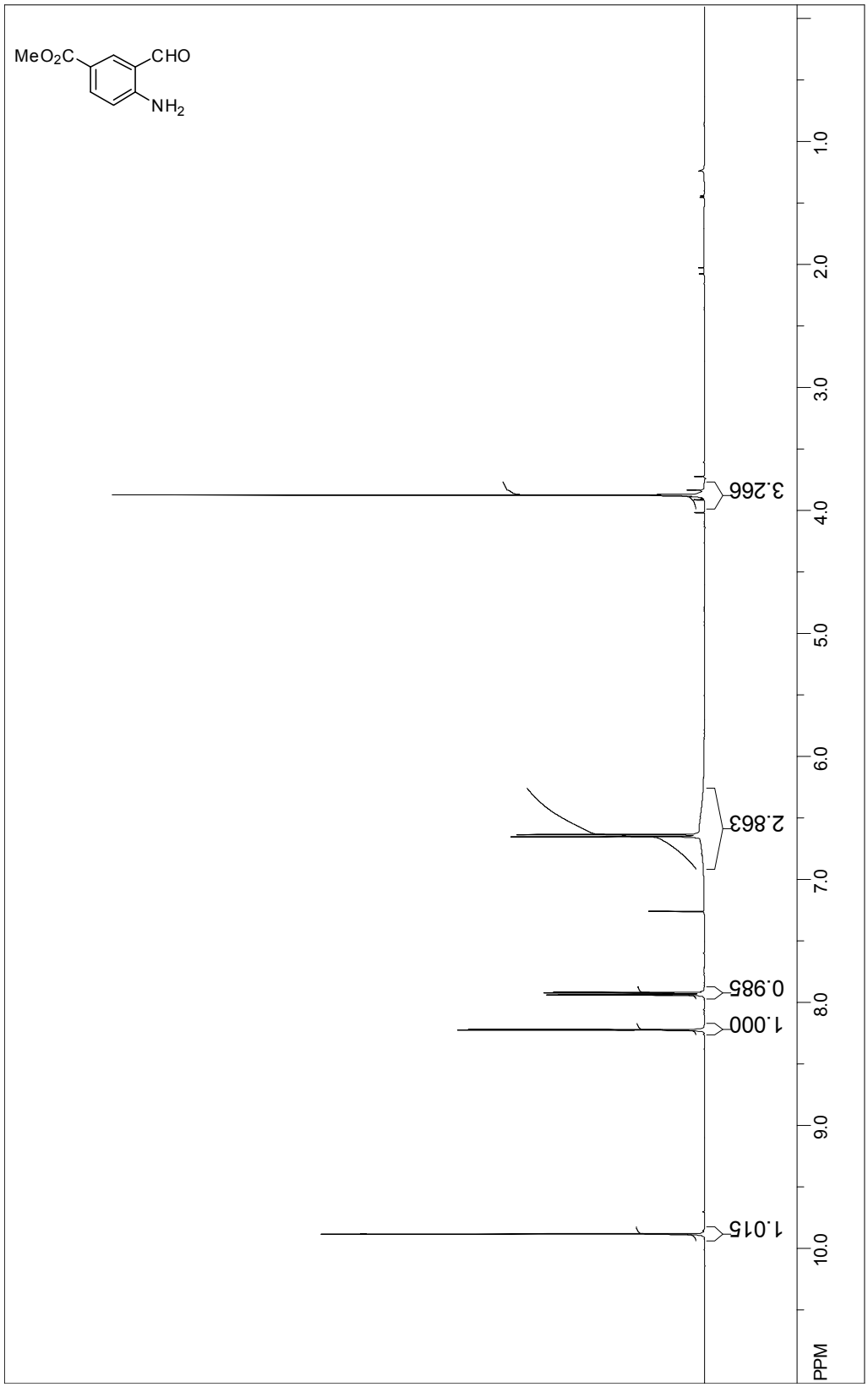

CHO
NH2
Br
20.0
40.0
60.0
80.0
100.0
120.0
140.0
160.0
180.0
PPM

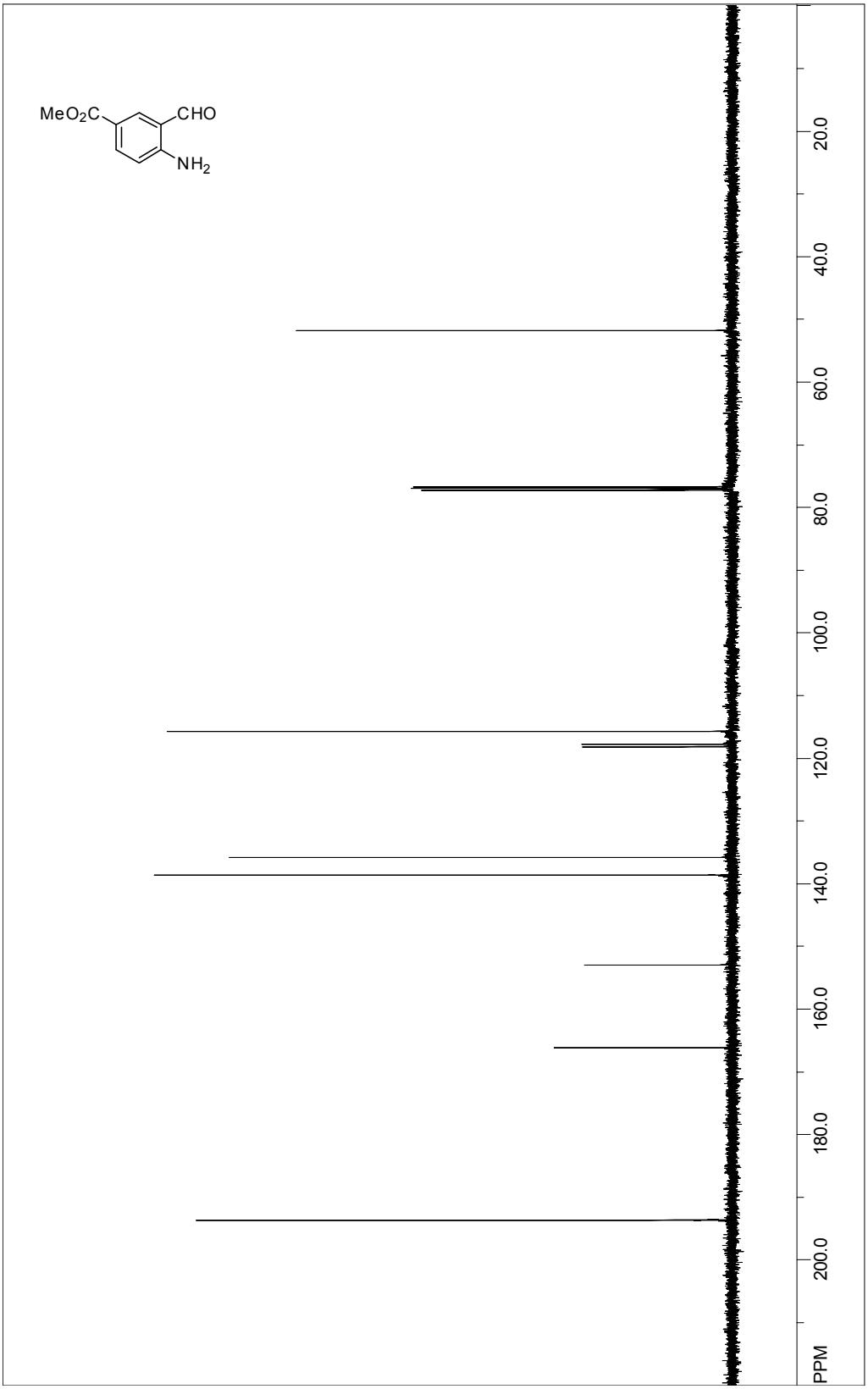
^{1}H-NMR and ^{13}C-NMR of 2-amino-3-chlorobenzaldehyde **3.1g**:



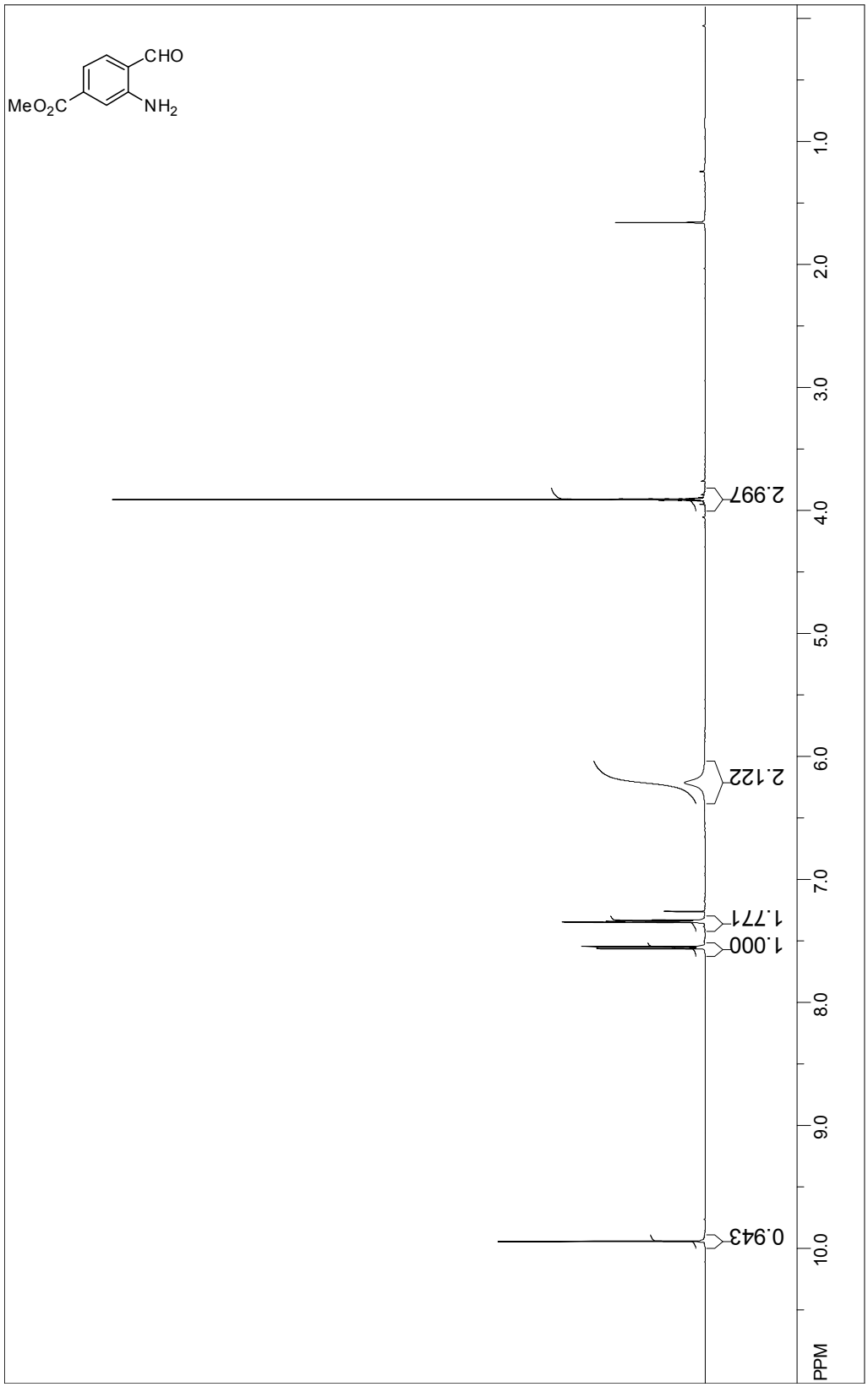

CHO
NH2
Cl
20.0
40.0
60.0
80.0
100.0
120.0
140.0
160.0
180.0
PPM

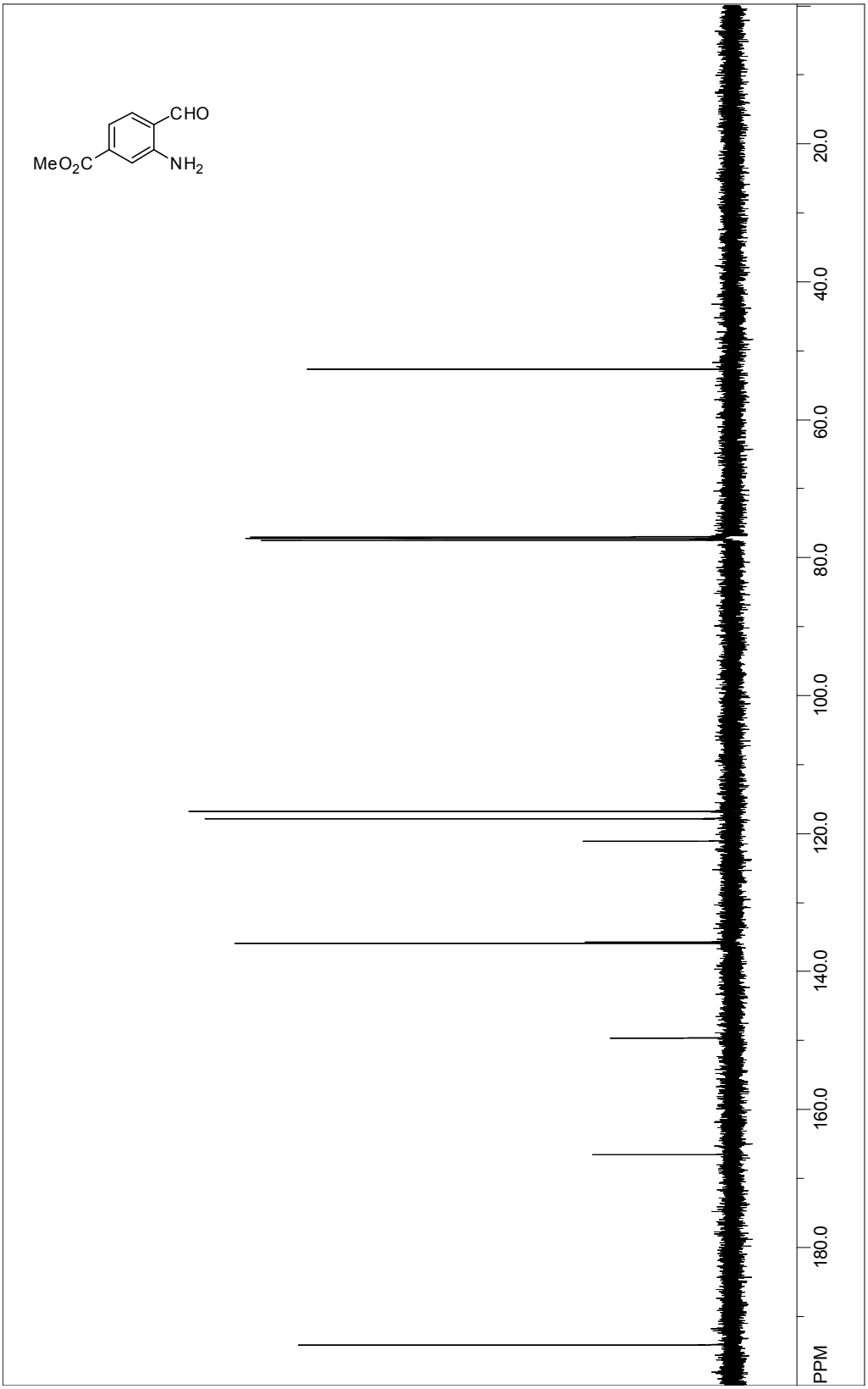
^{1}H-NMR and ^{13}C-NMR of methyl 4-amino-3-formylbenzoate **3.1h**:



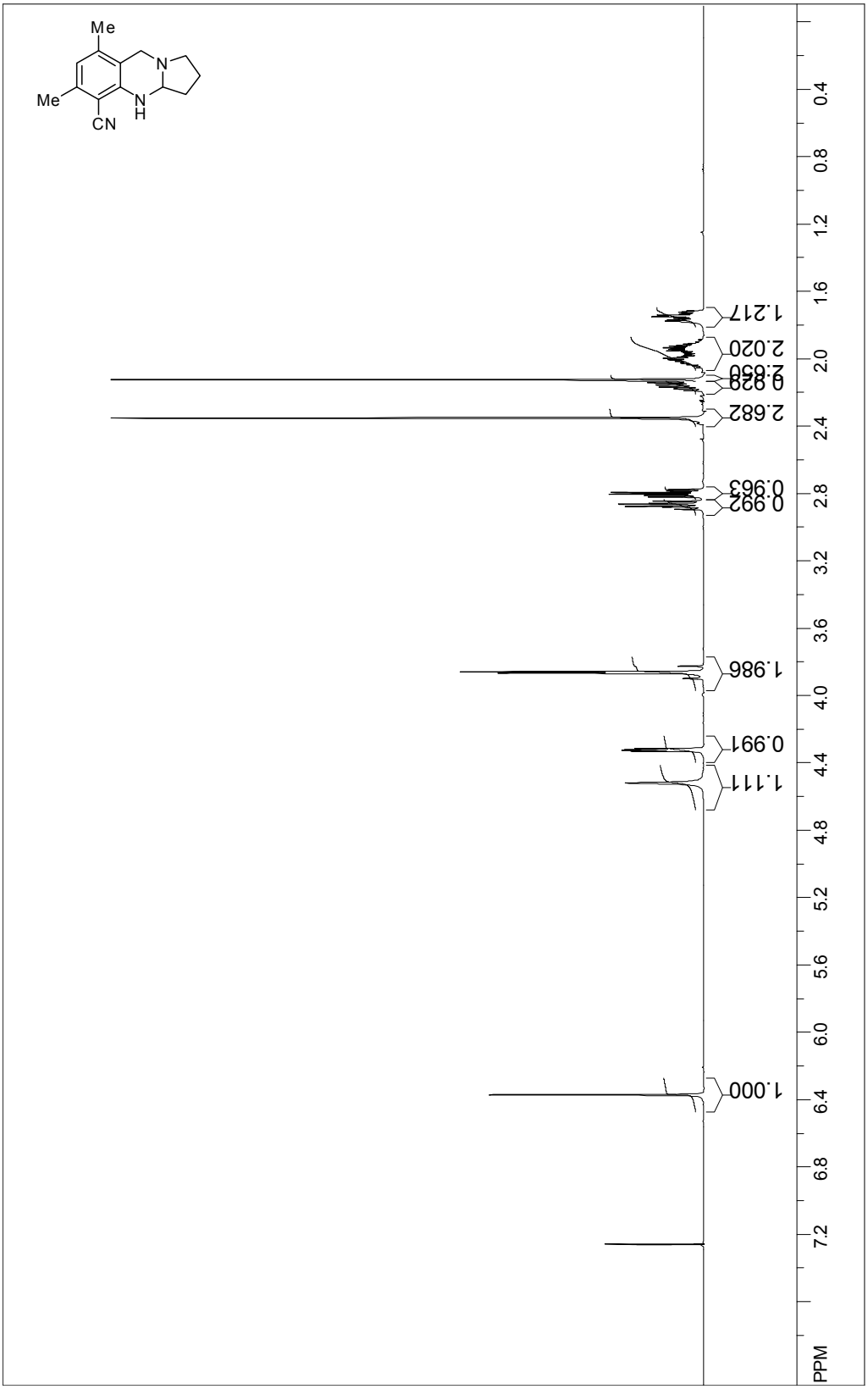

MeO2C
CHO
NH2
20.0
40.0
60.0
80.0
100.0
120.0
140.0
160.0
180.0
200.0
PPM

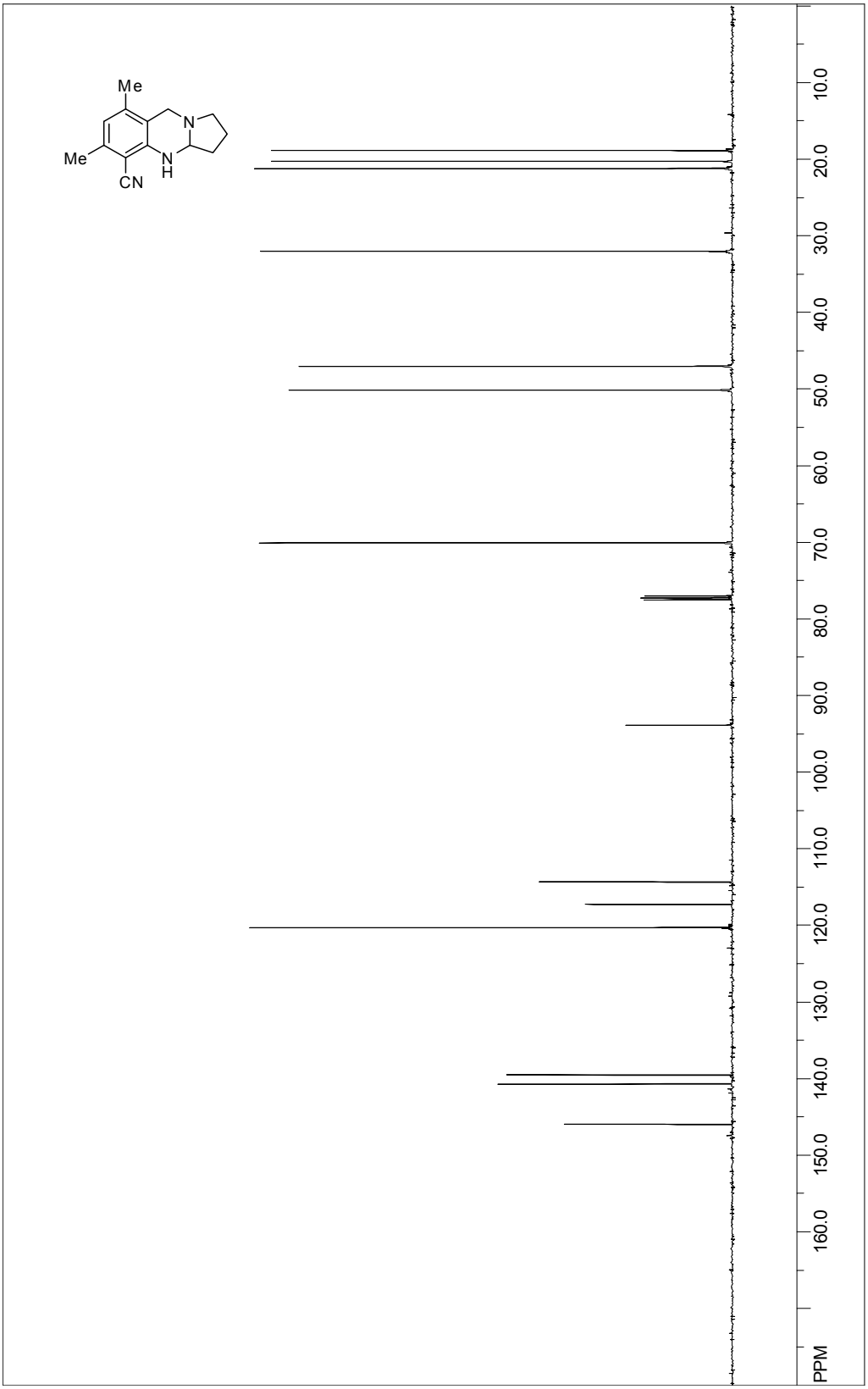
^{1}H-NMR and ^{13}C-NMR of methyl methyl 3-amino-4-formylbenzoate **3.1i**:



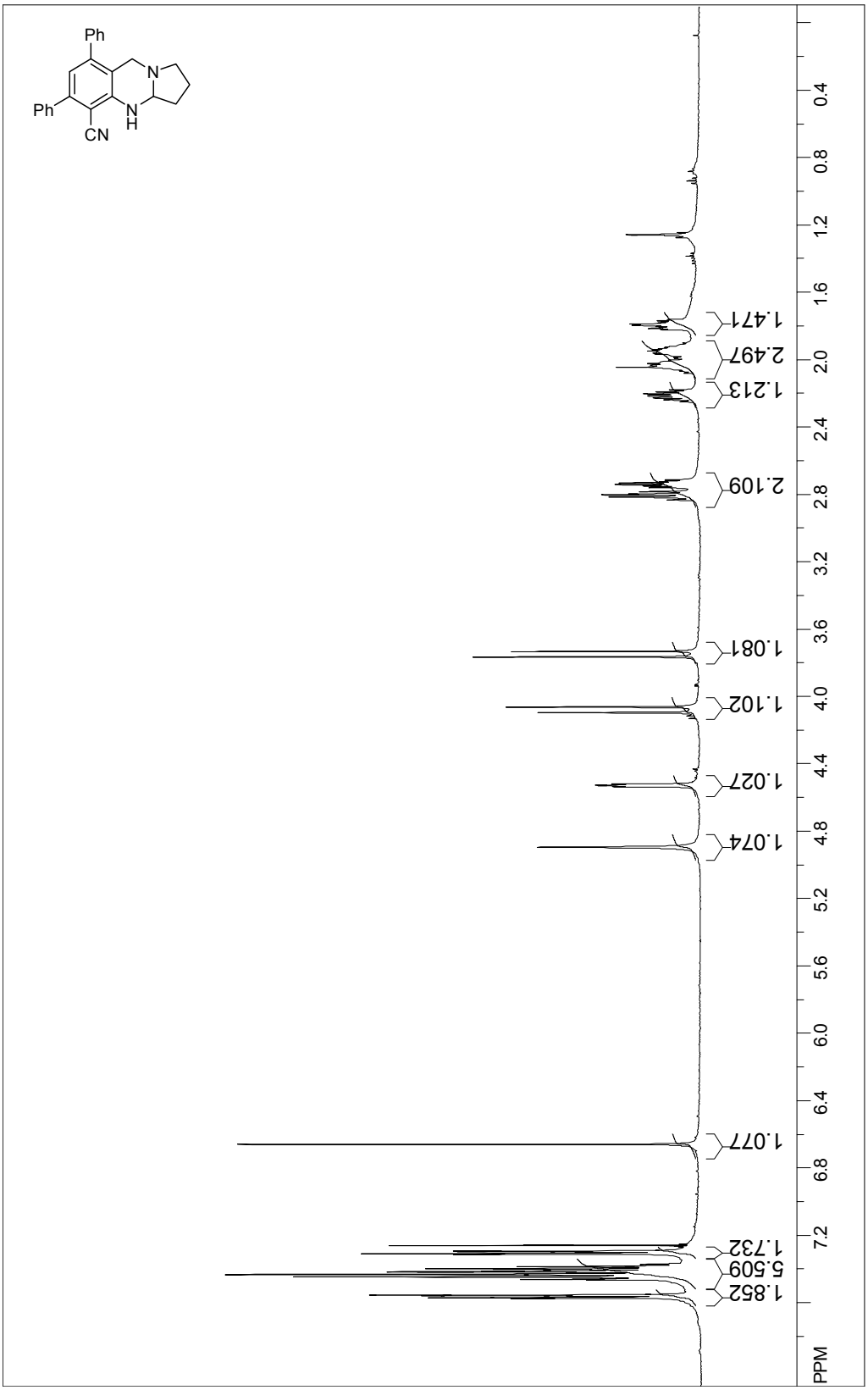

CHO
MeO2C
NH2
20.0
40.0
60.0
80.0
100.0
120.0
140.0
160.0
180.0
PPM

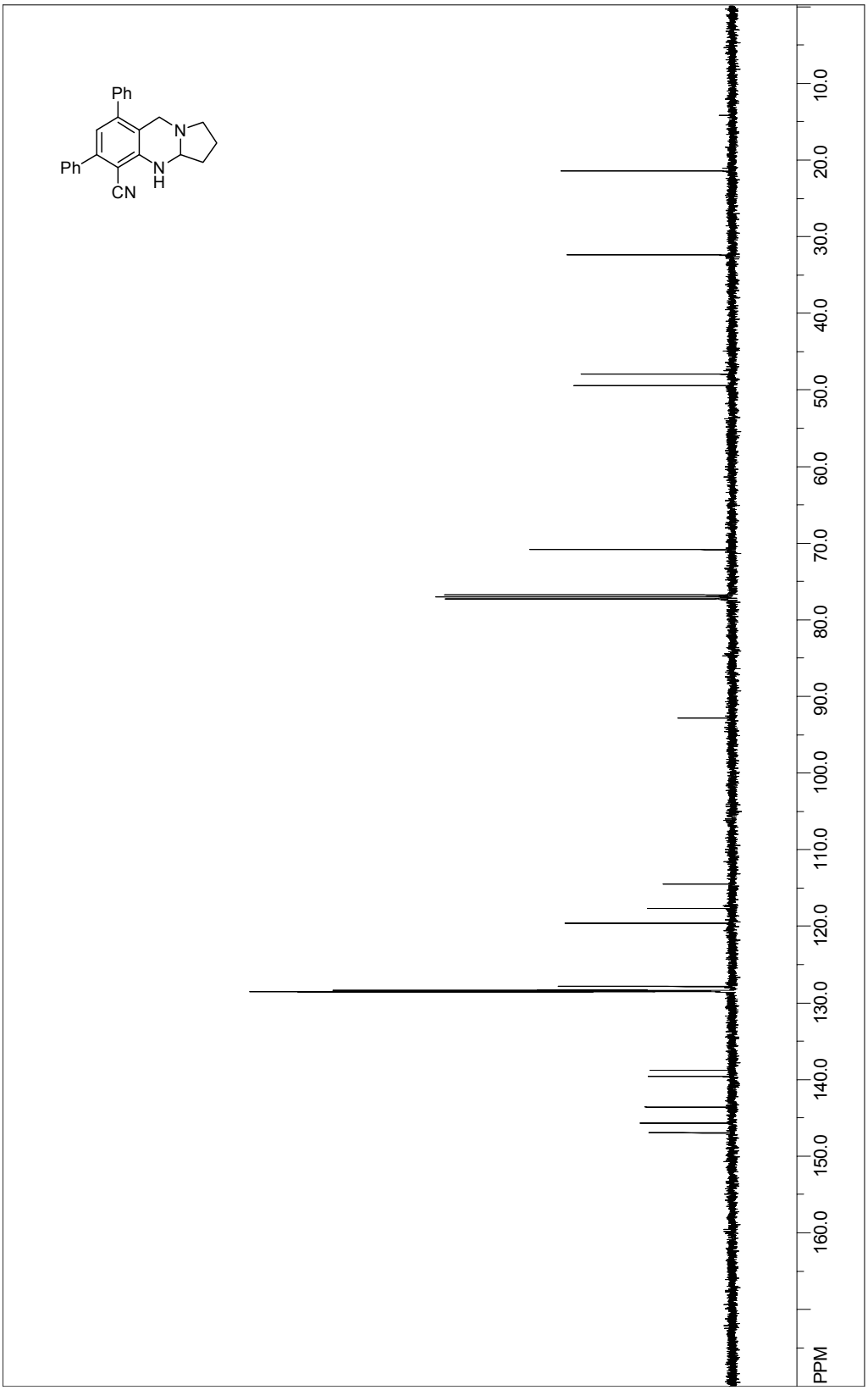
^{1}H-NMR and ^{13}C-NMR of **3.2a**:



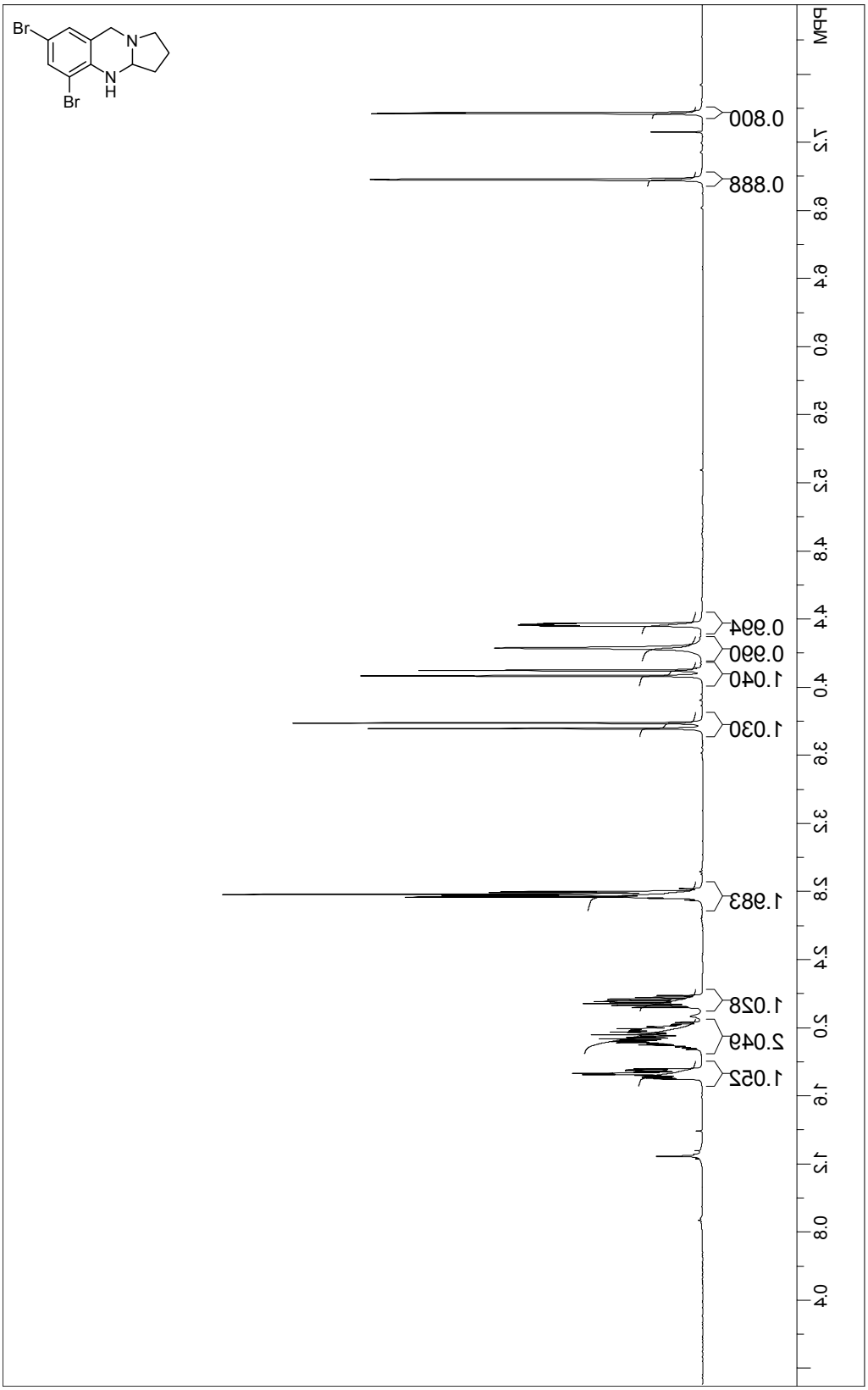

Me
Me
N
N
H
CN
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

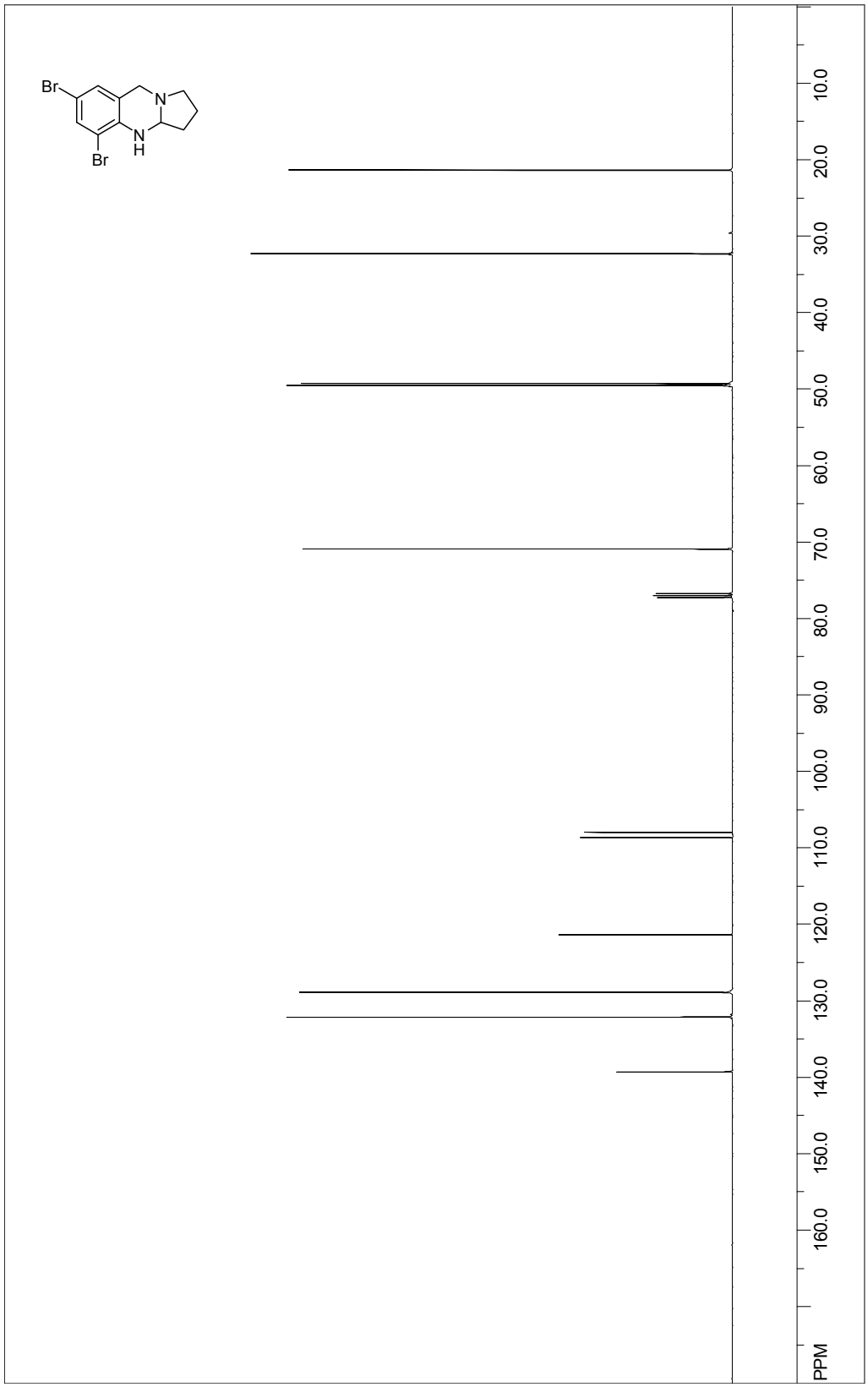
^{1}H-NMR and ^{13}C-NMR of **3.2b**:



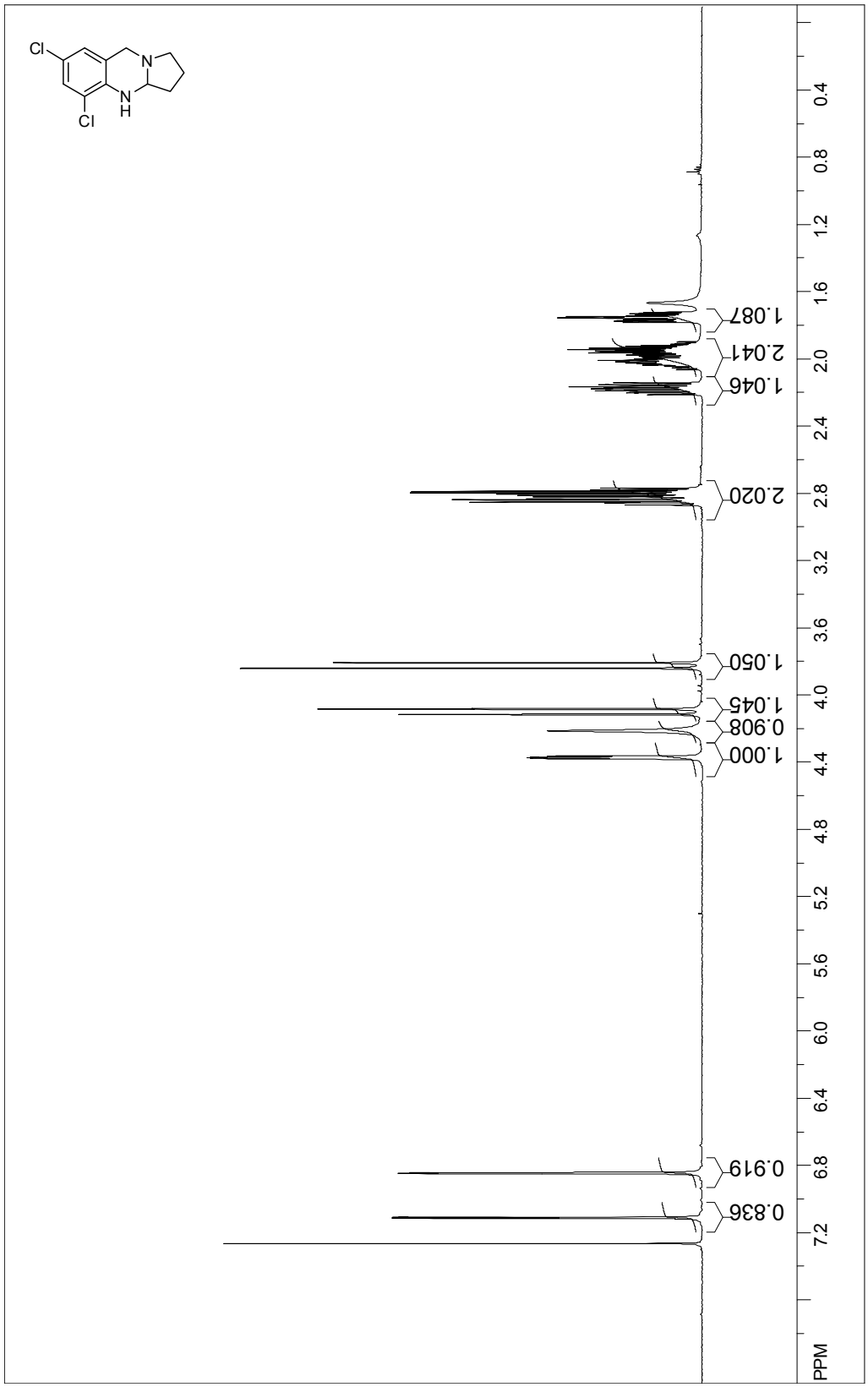

Ph
Ph
N
H
CN
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

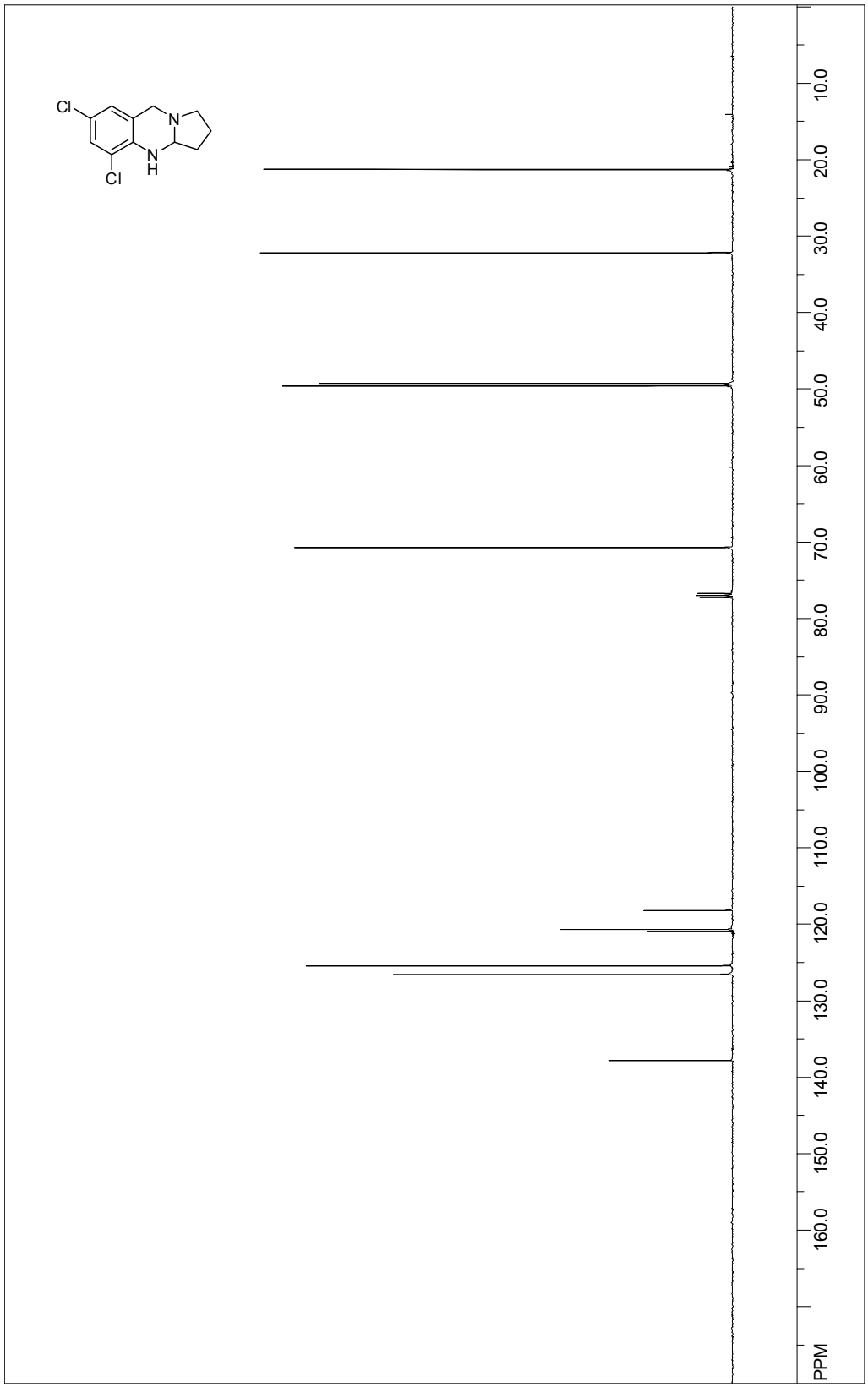
^{1}H-NMR and ^{13}C-NMR of **3.2c**:



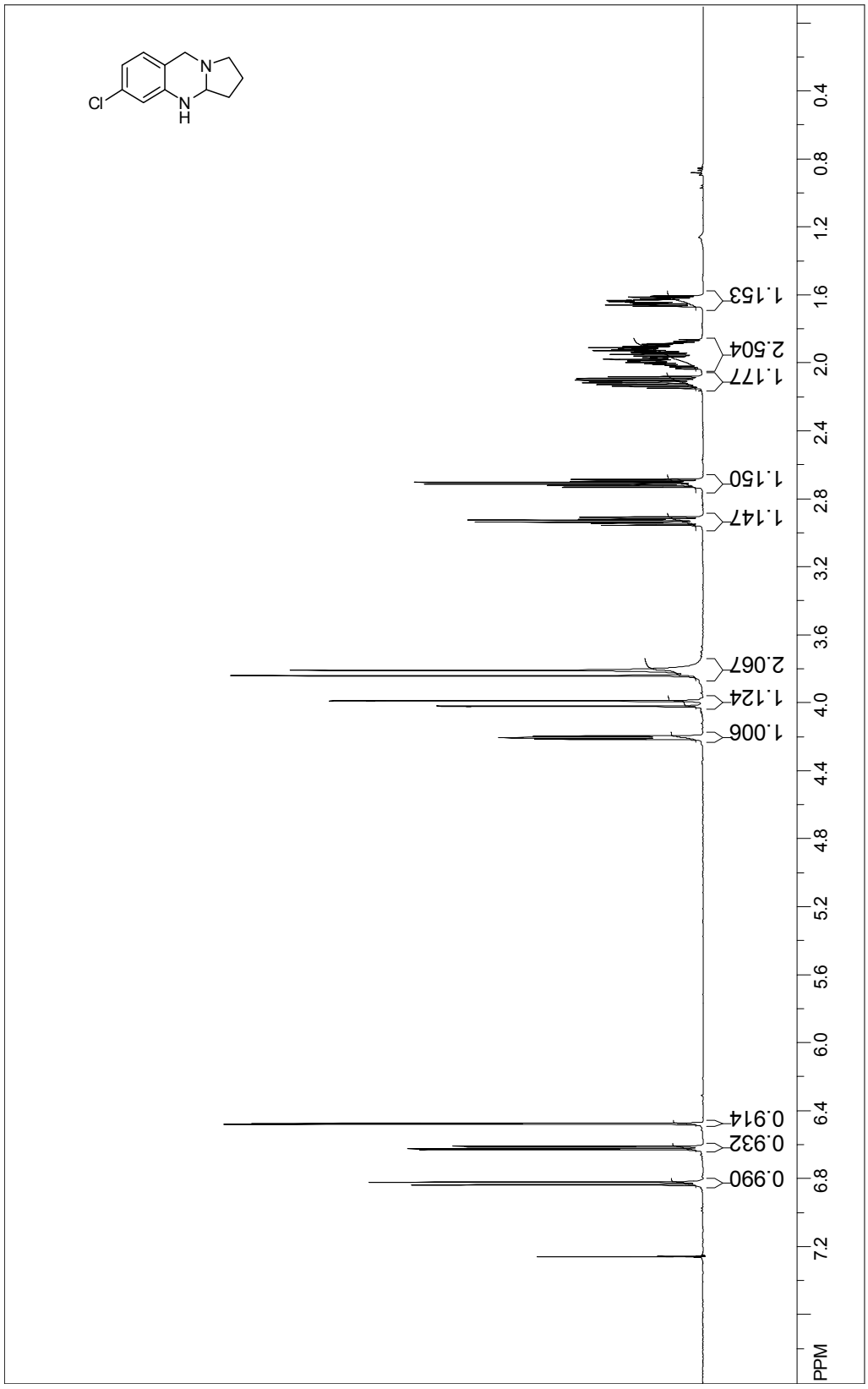

Br
N
N
H
Br
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

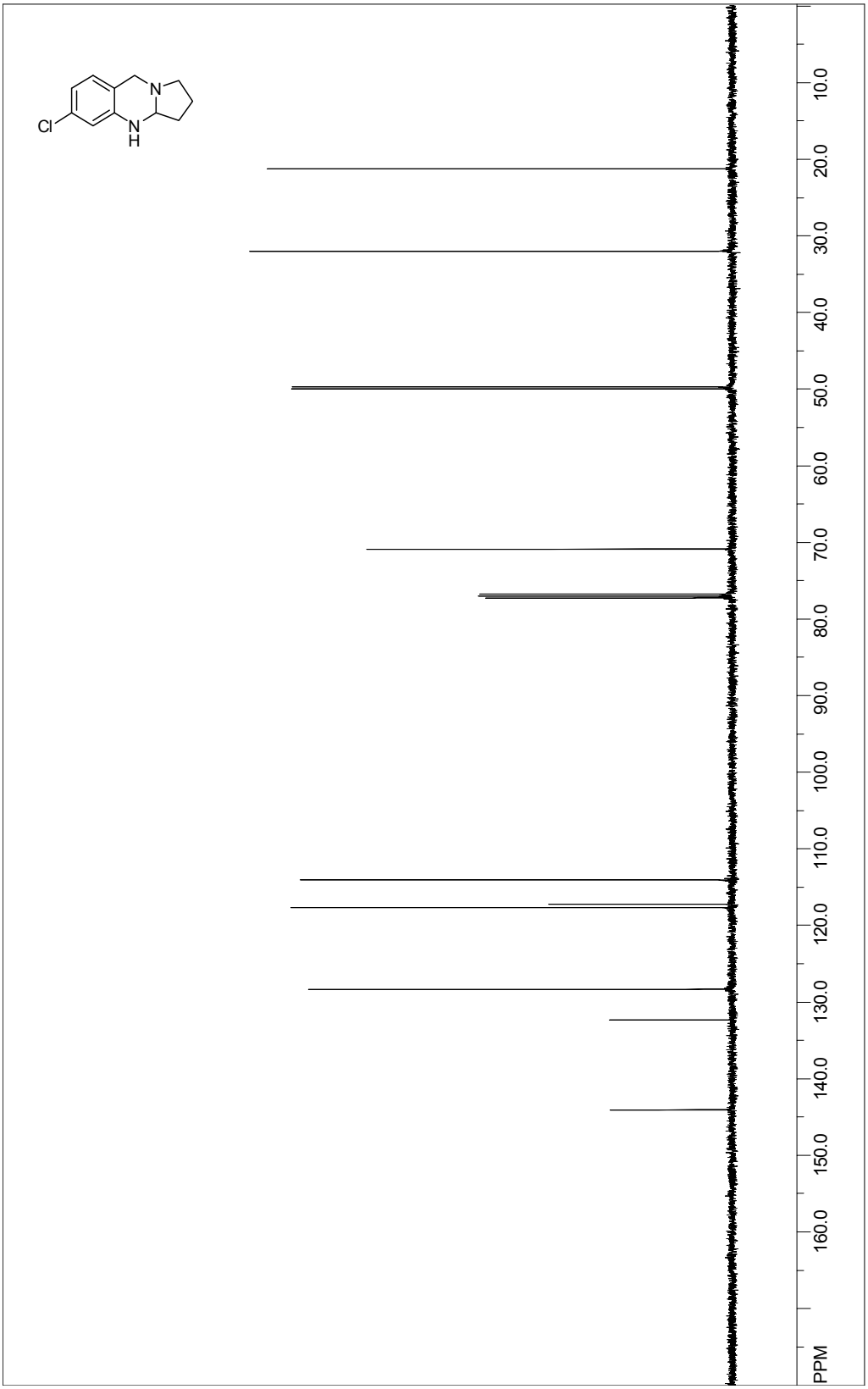
^{1}H-NMR and ^{13}C-NMR of **3.2d**:



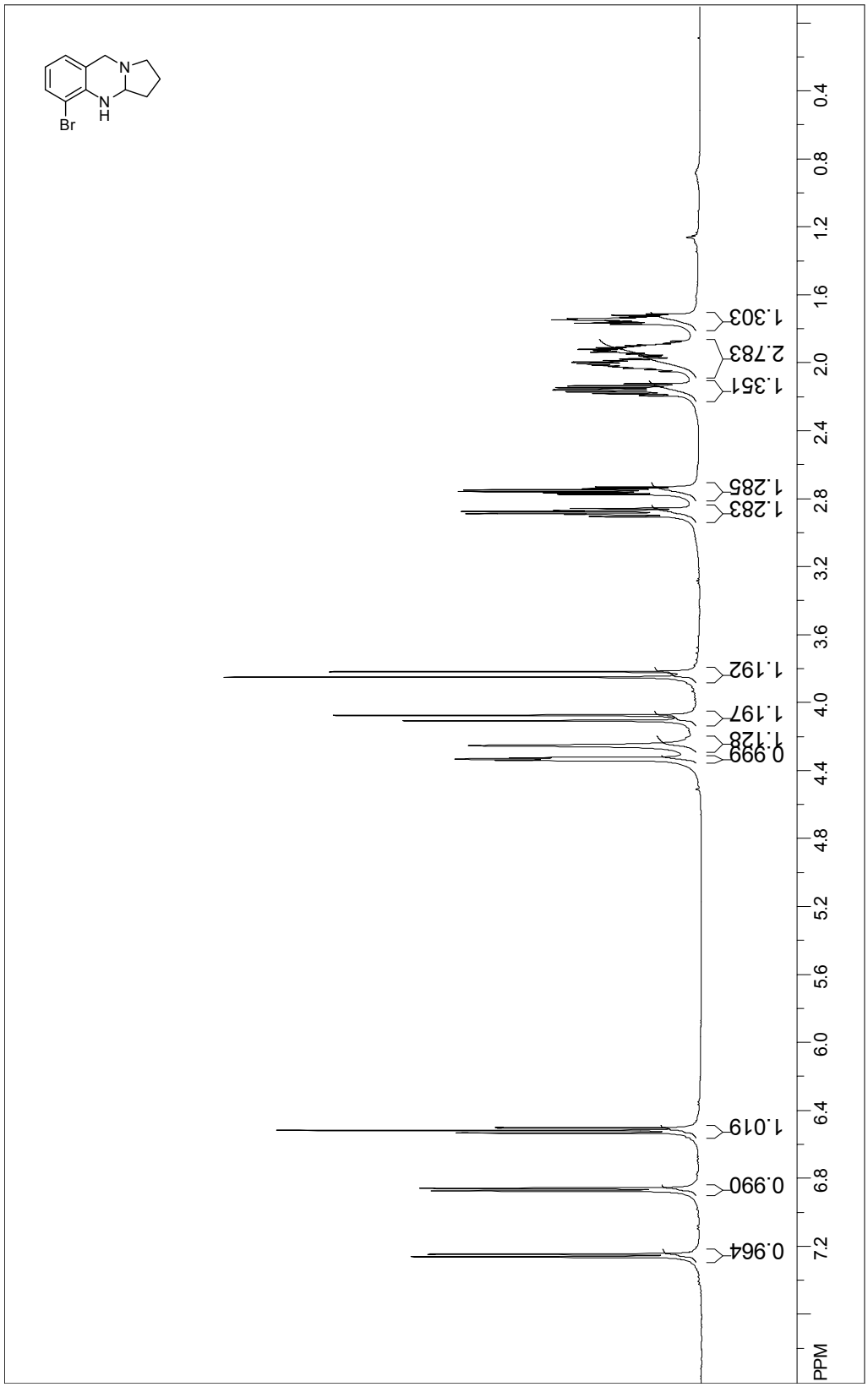

Cl
N
N
H
Cl
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

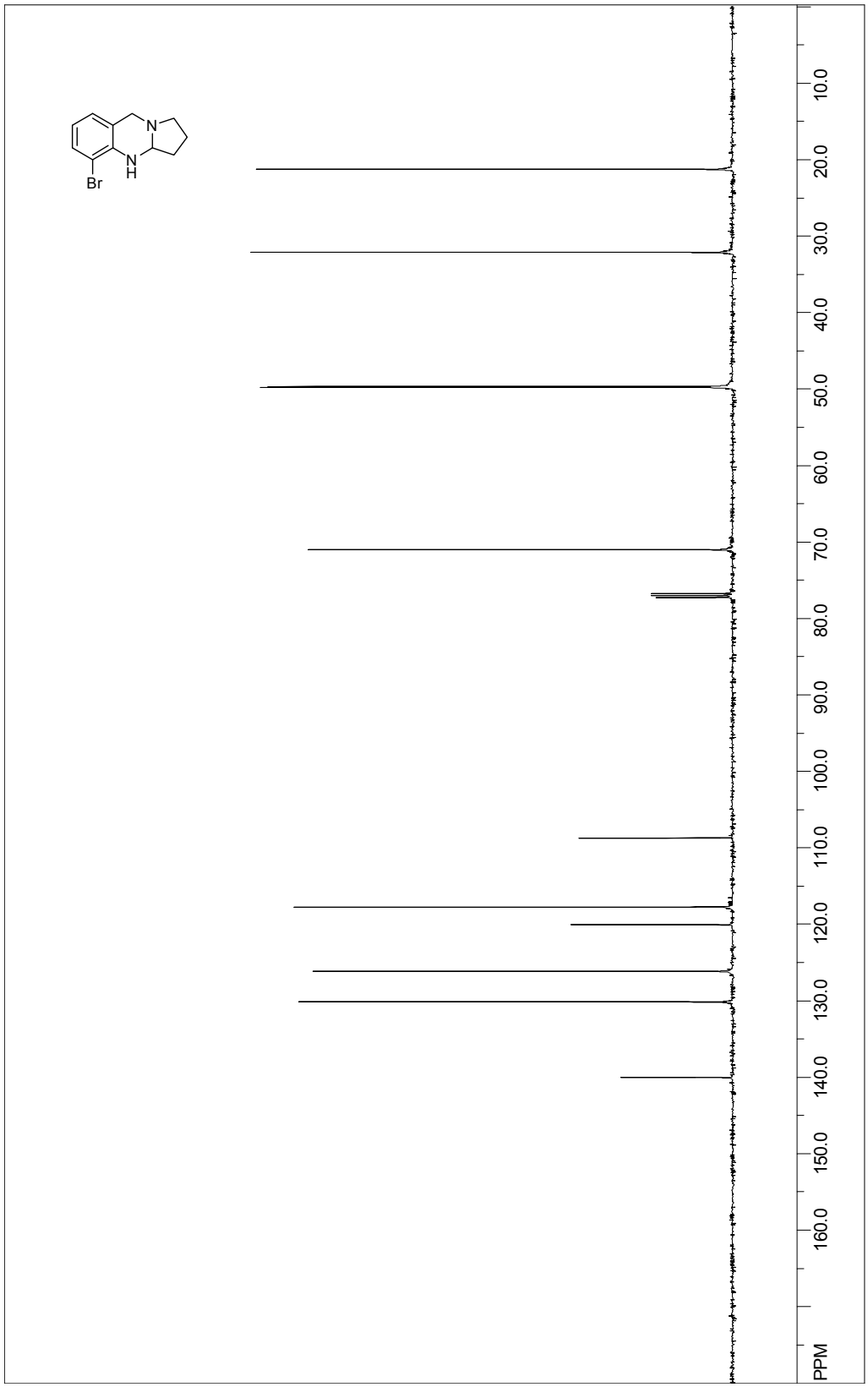
^{1}H-NMR and ^{13}C-NMR of **3.2e**:



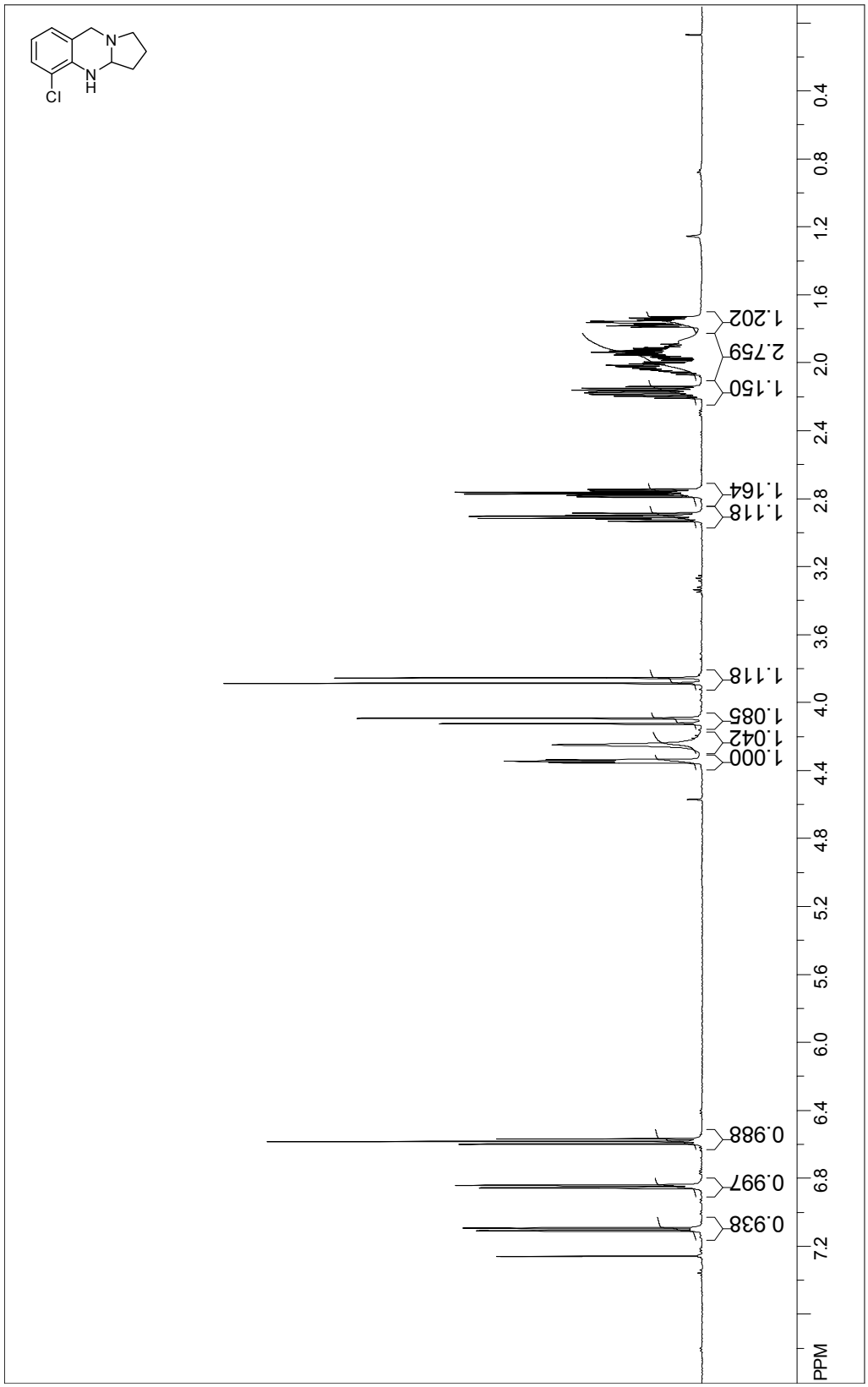

Cl
N
H
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

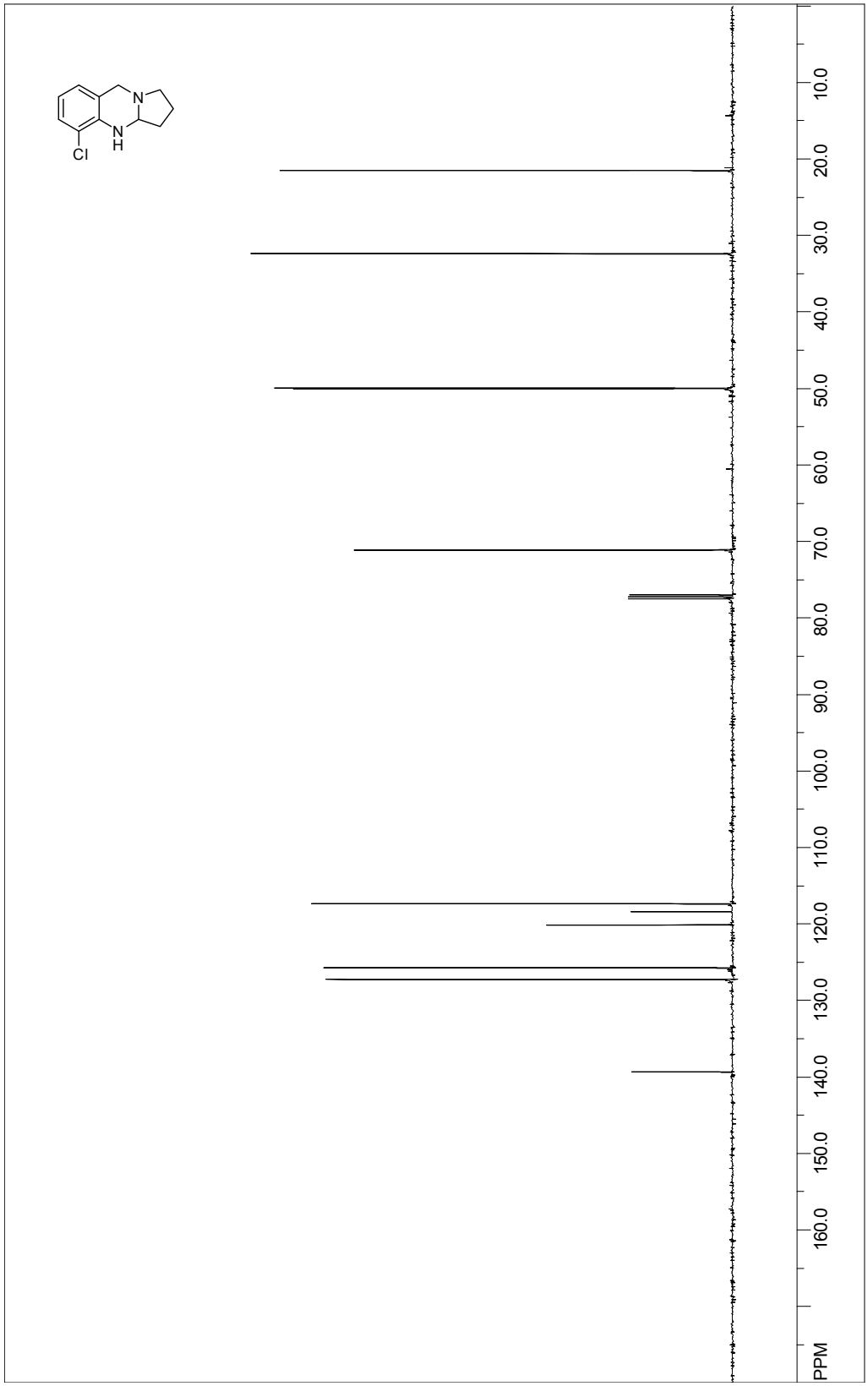
^{1}H-NMR and ^{13}C-NMR of **3.2f**:



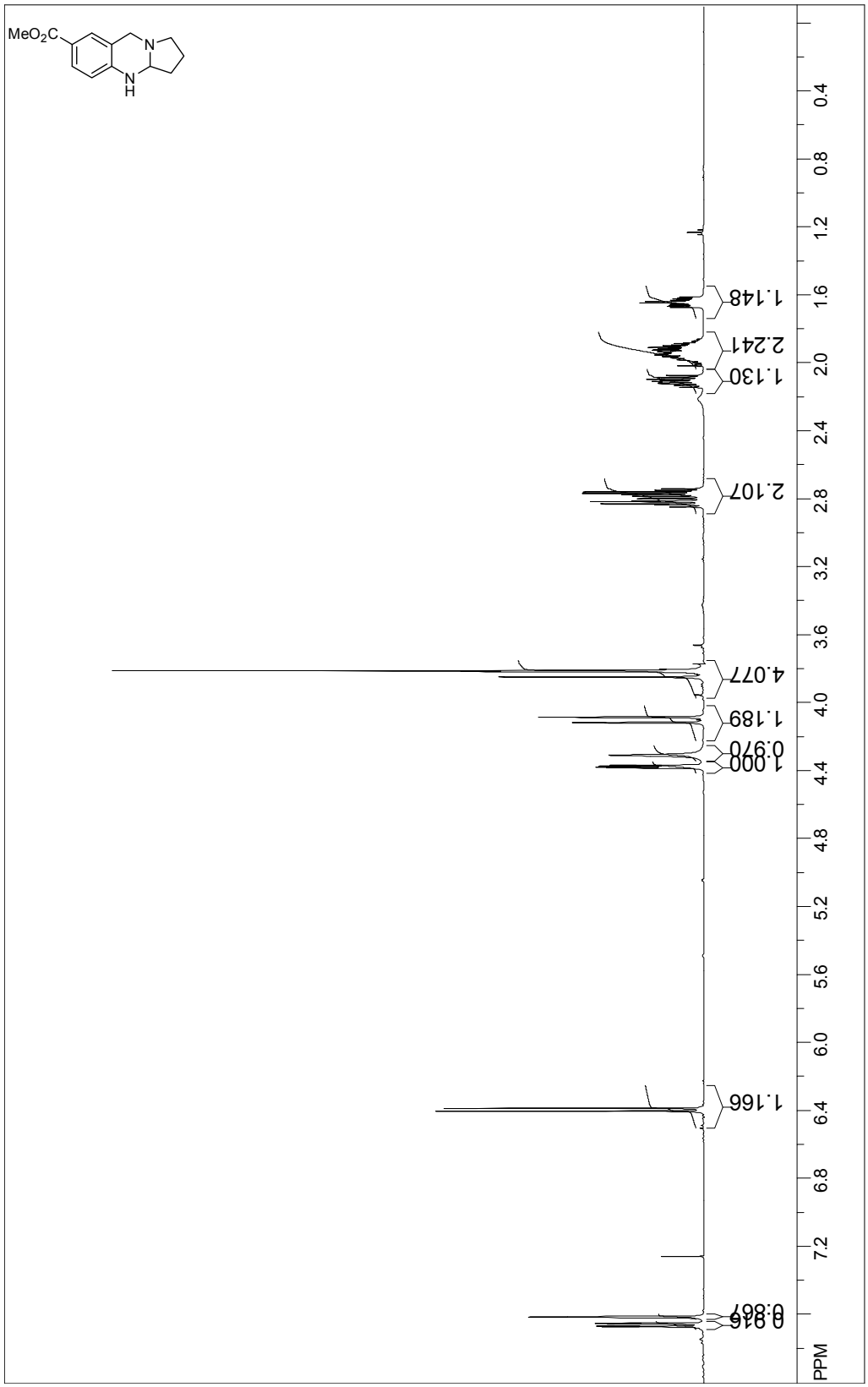

Br
N
H
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

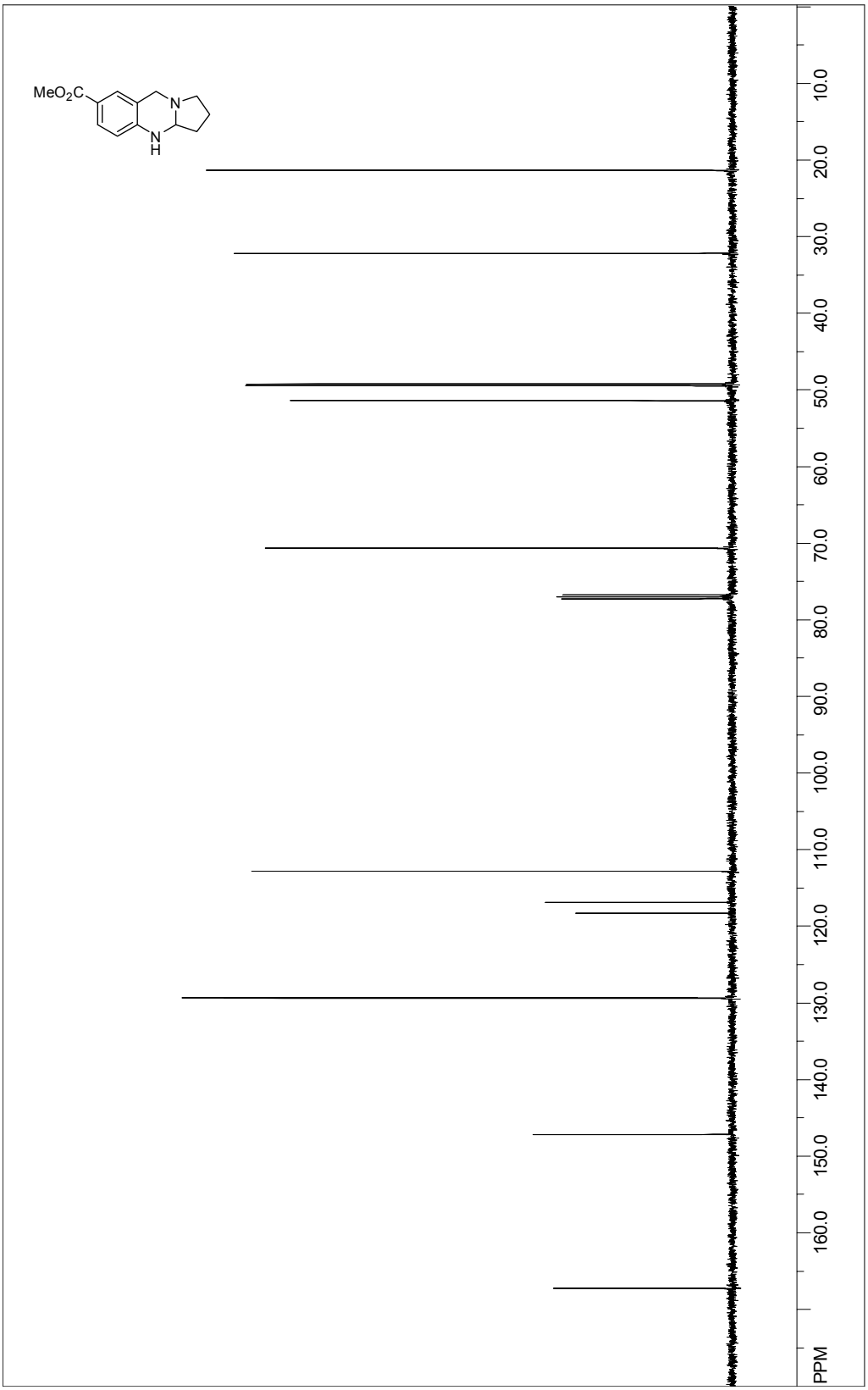
^{1}H-NMR and ^{13}C-NMR of **3.2g**:



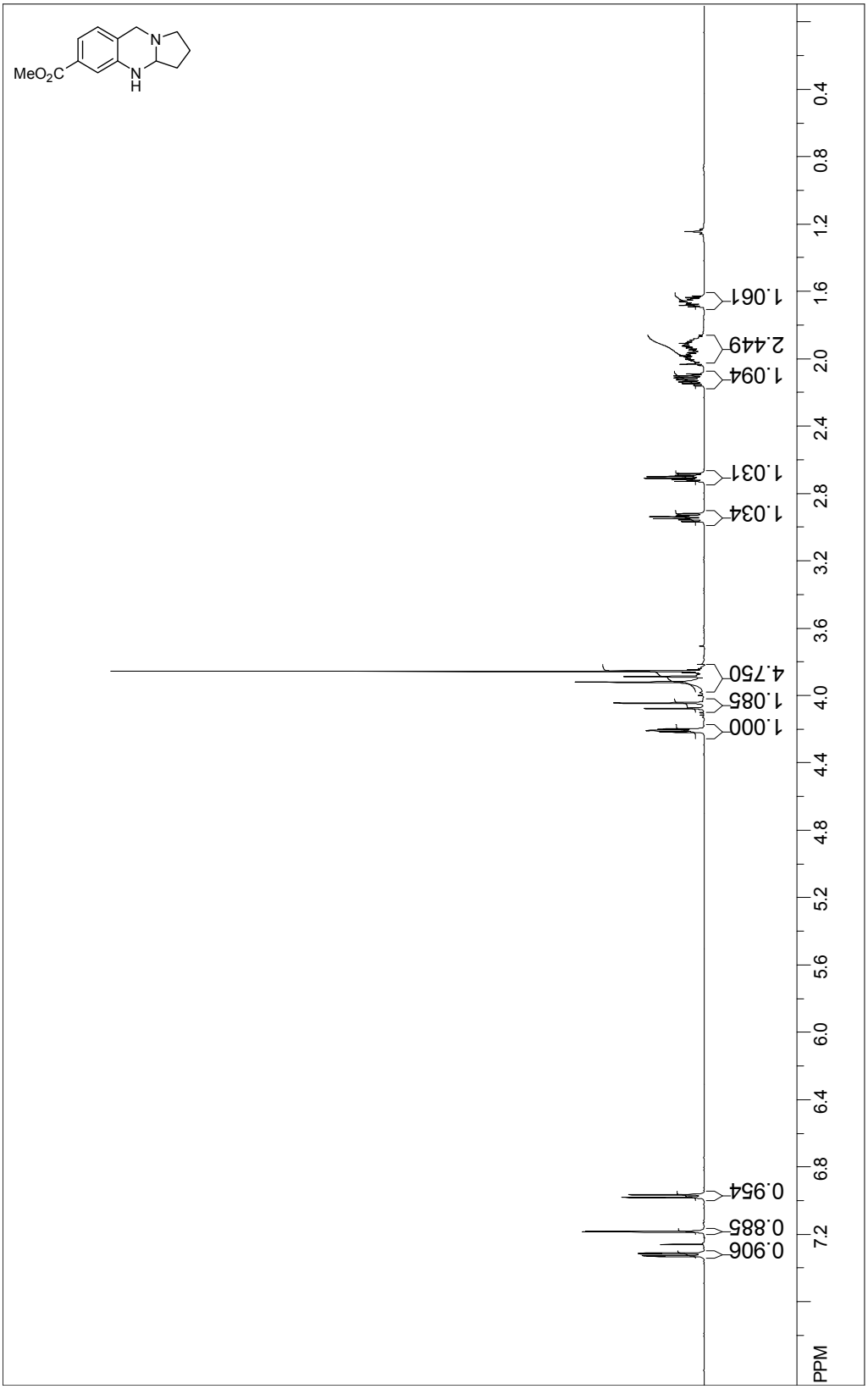

N
N
H
Cl
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

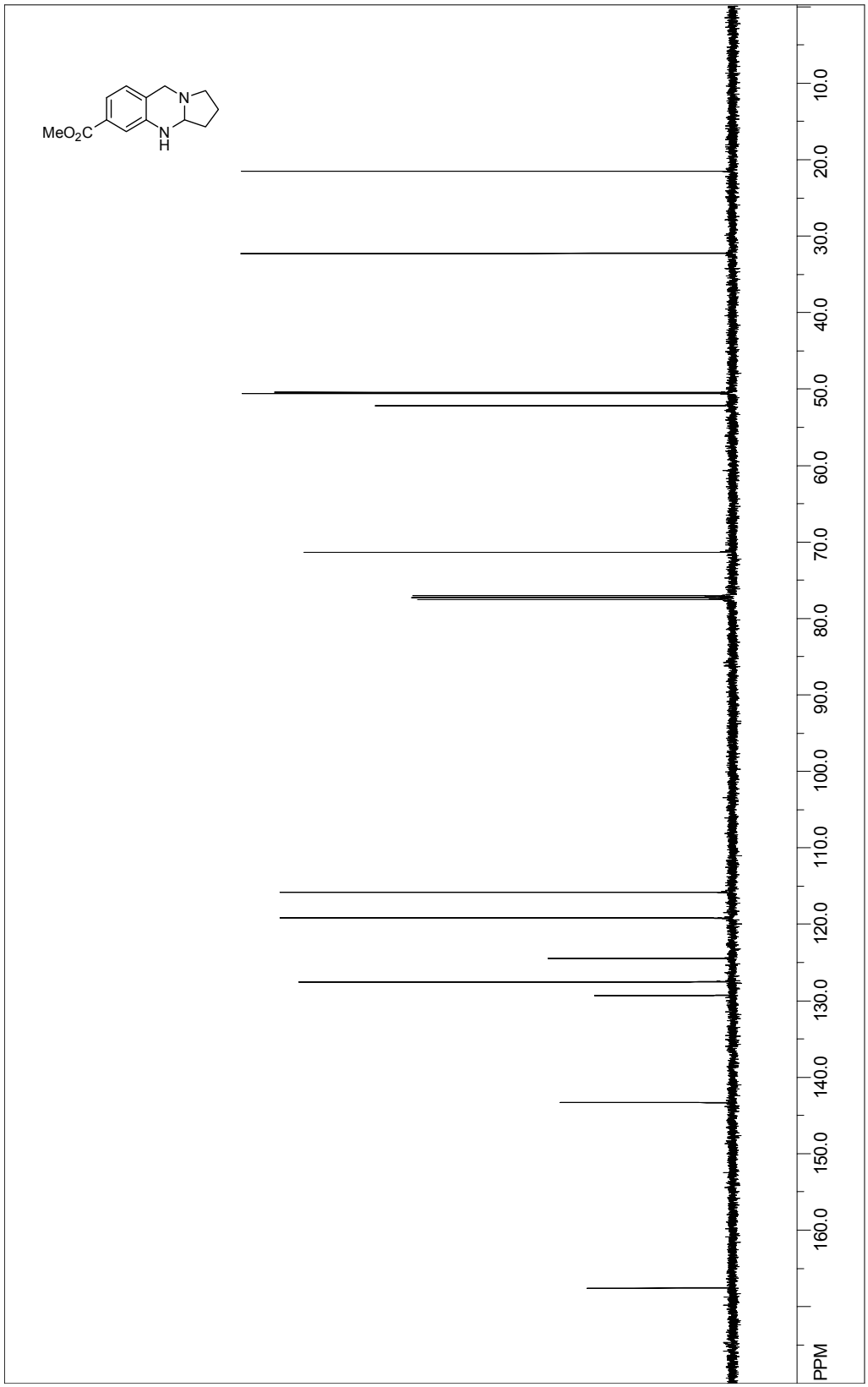
^{1}H-NMR and ^{13}C-NMR of **3.2h**:



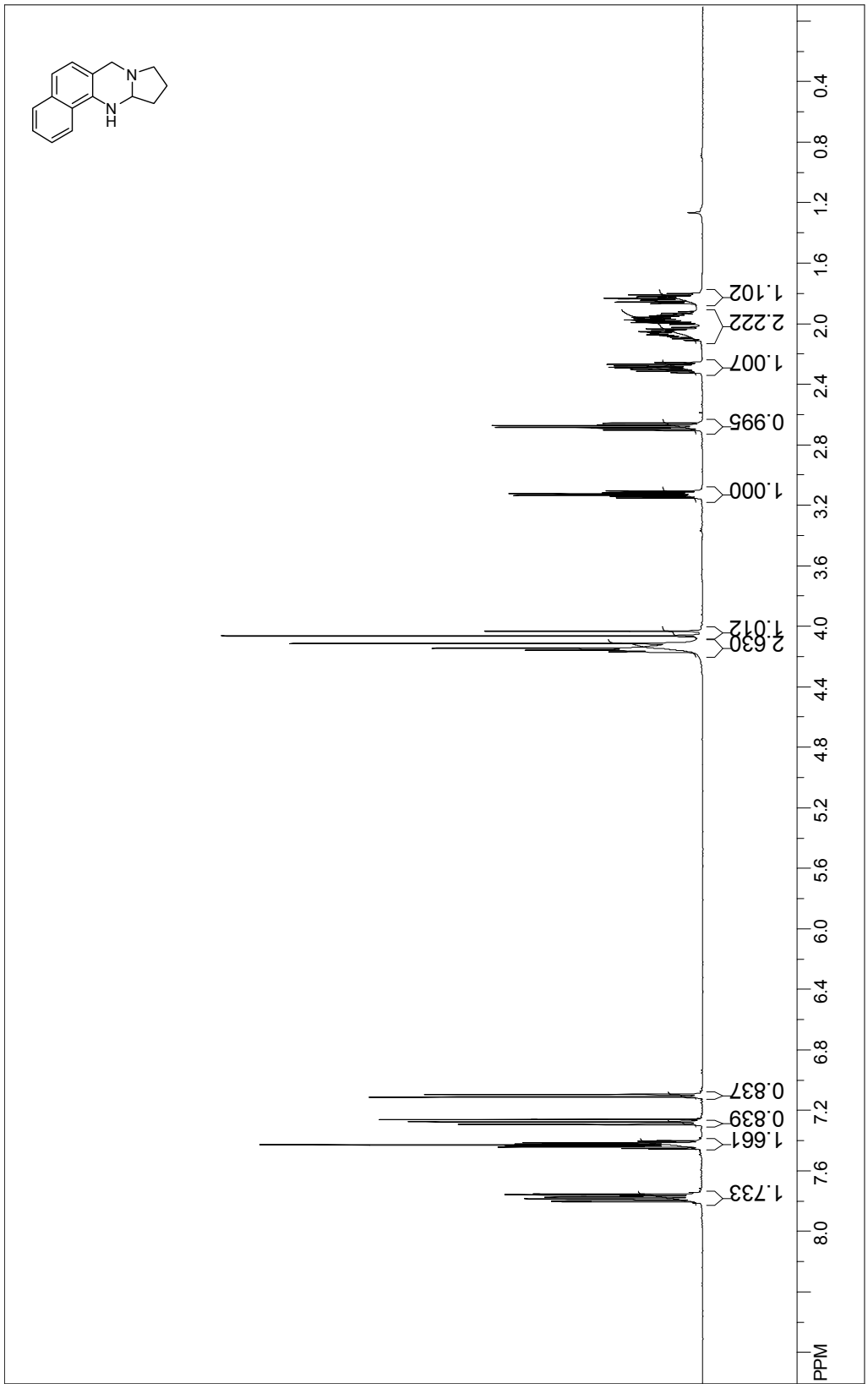

MeO2C
N
N
H
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

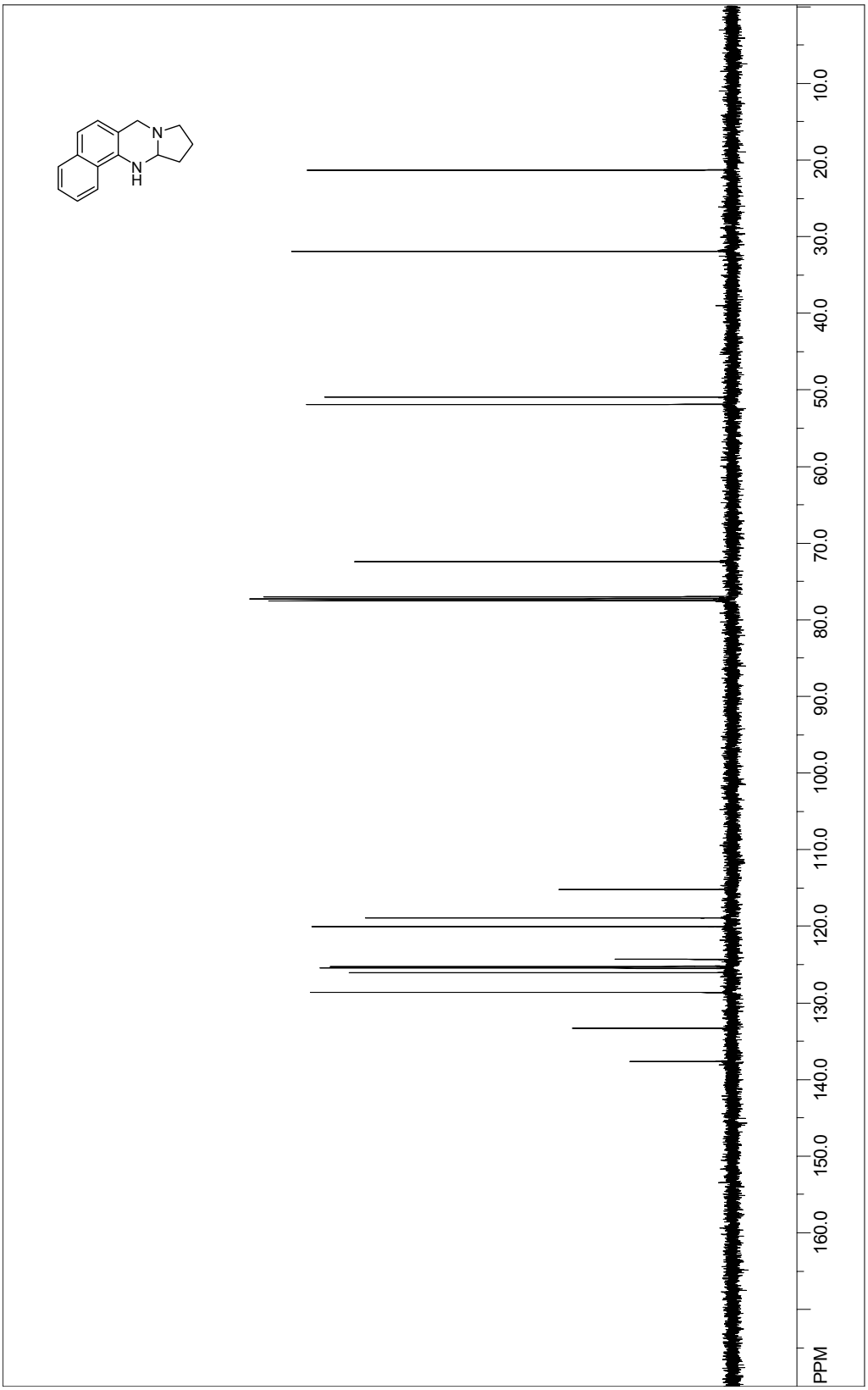
^{1}H-NMR and ^{13}C-NMR of **3.2i**:



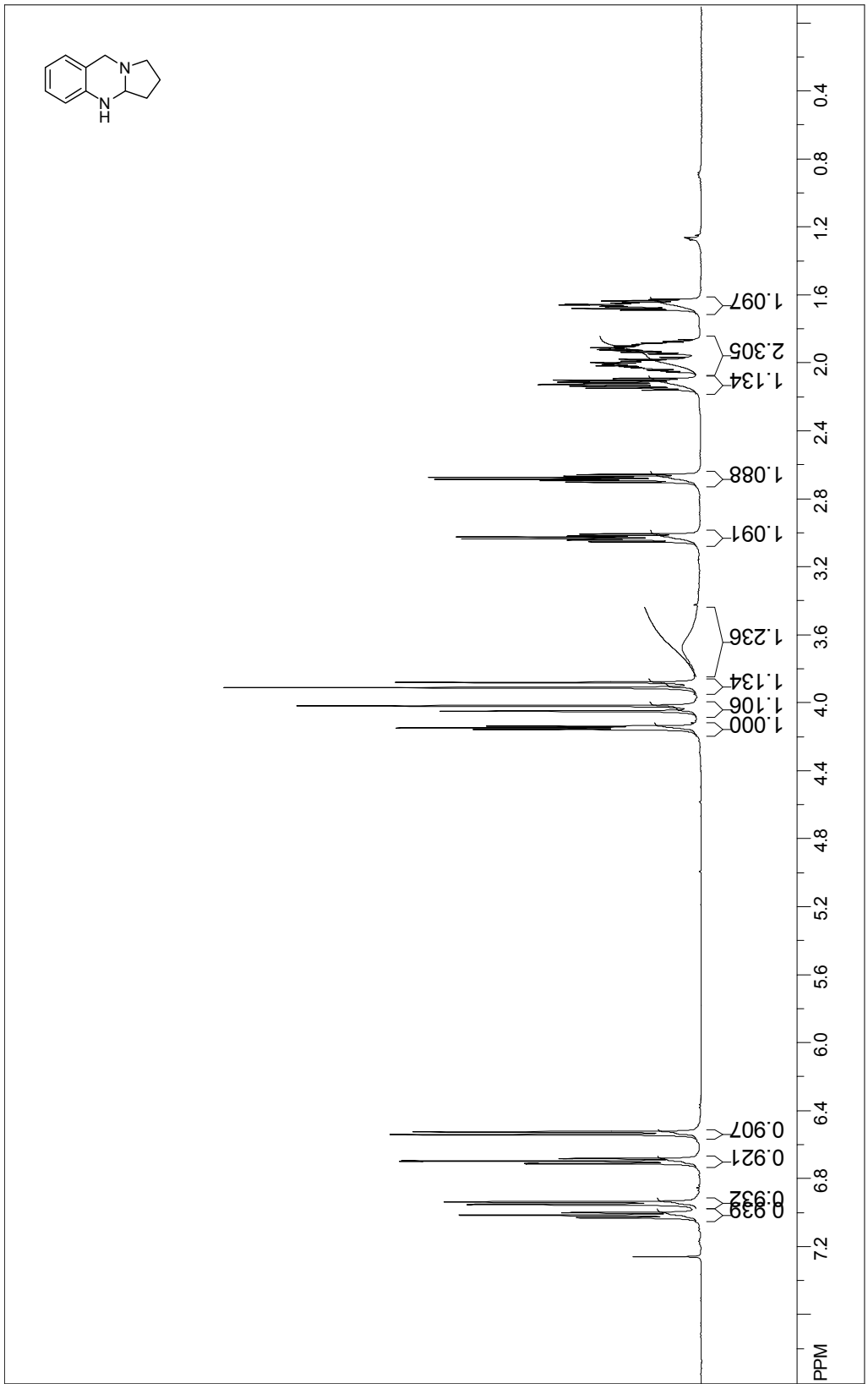

MeO2C
N
H
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

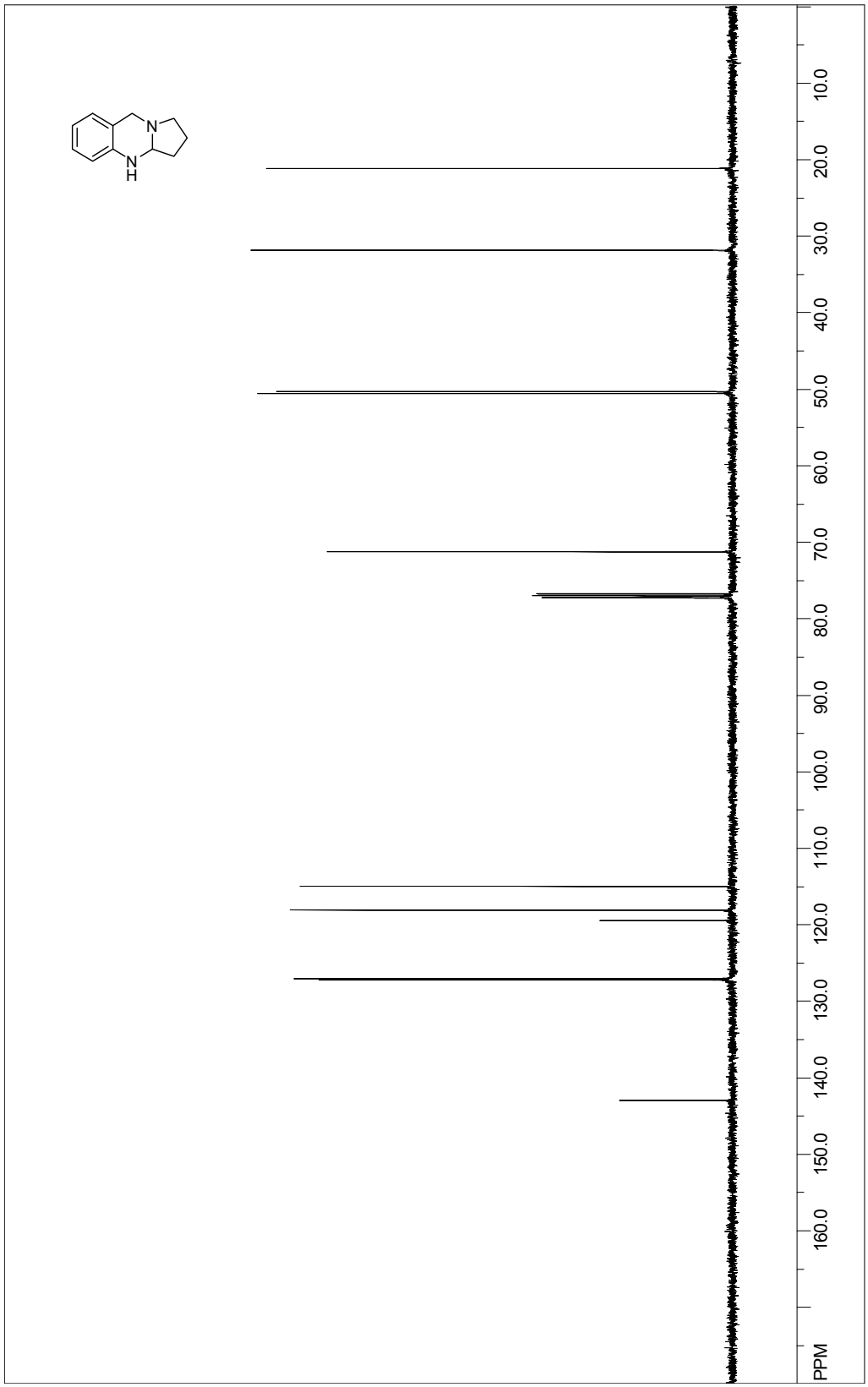
^{1}H-NMR and ^{13}C-NMR of **3.2j**:



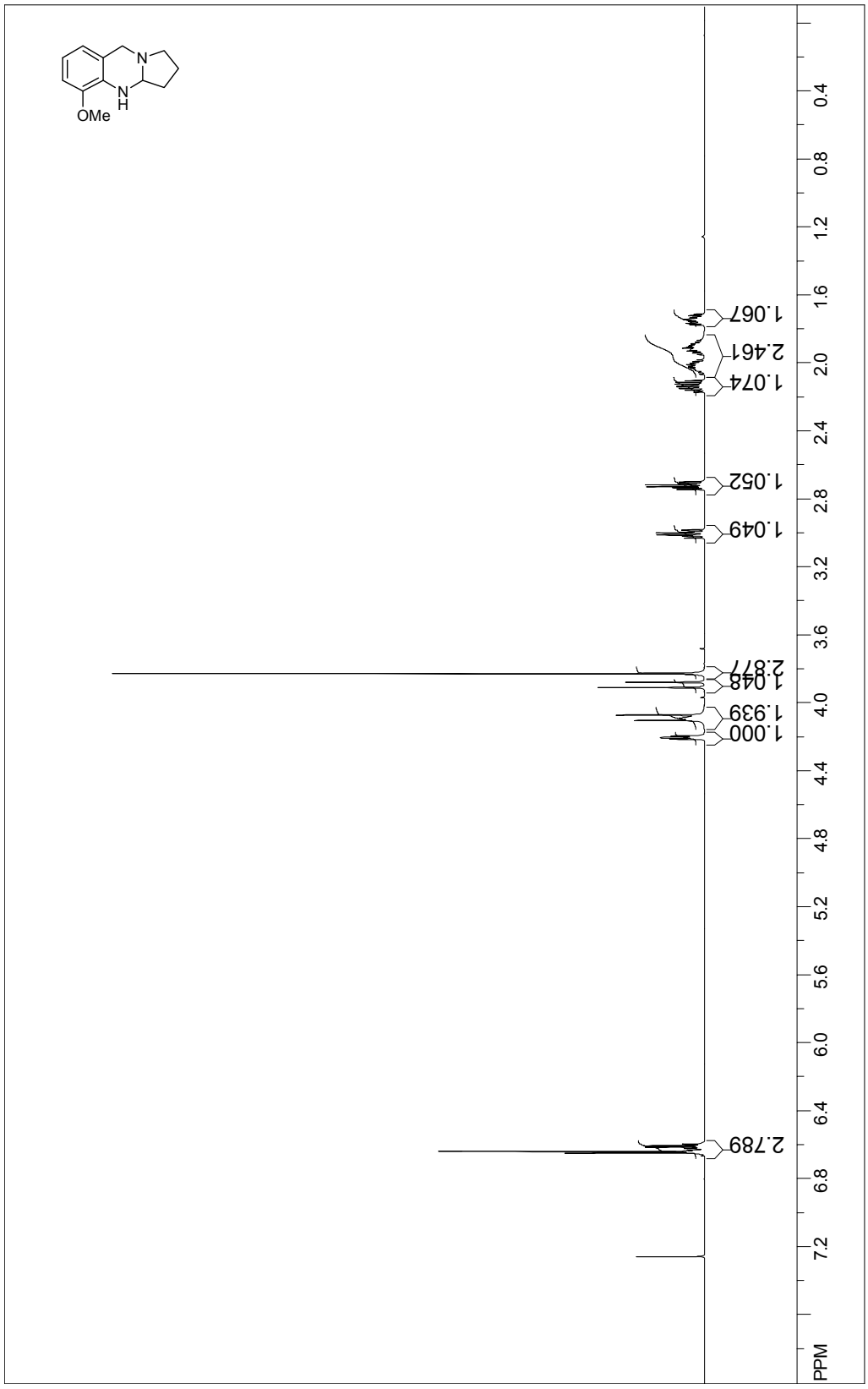

N
H
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

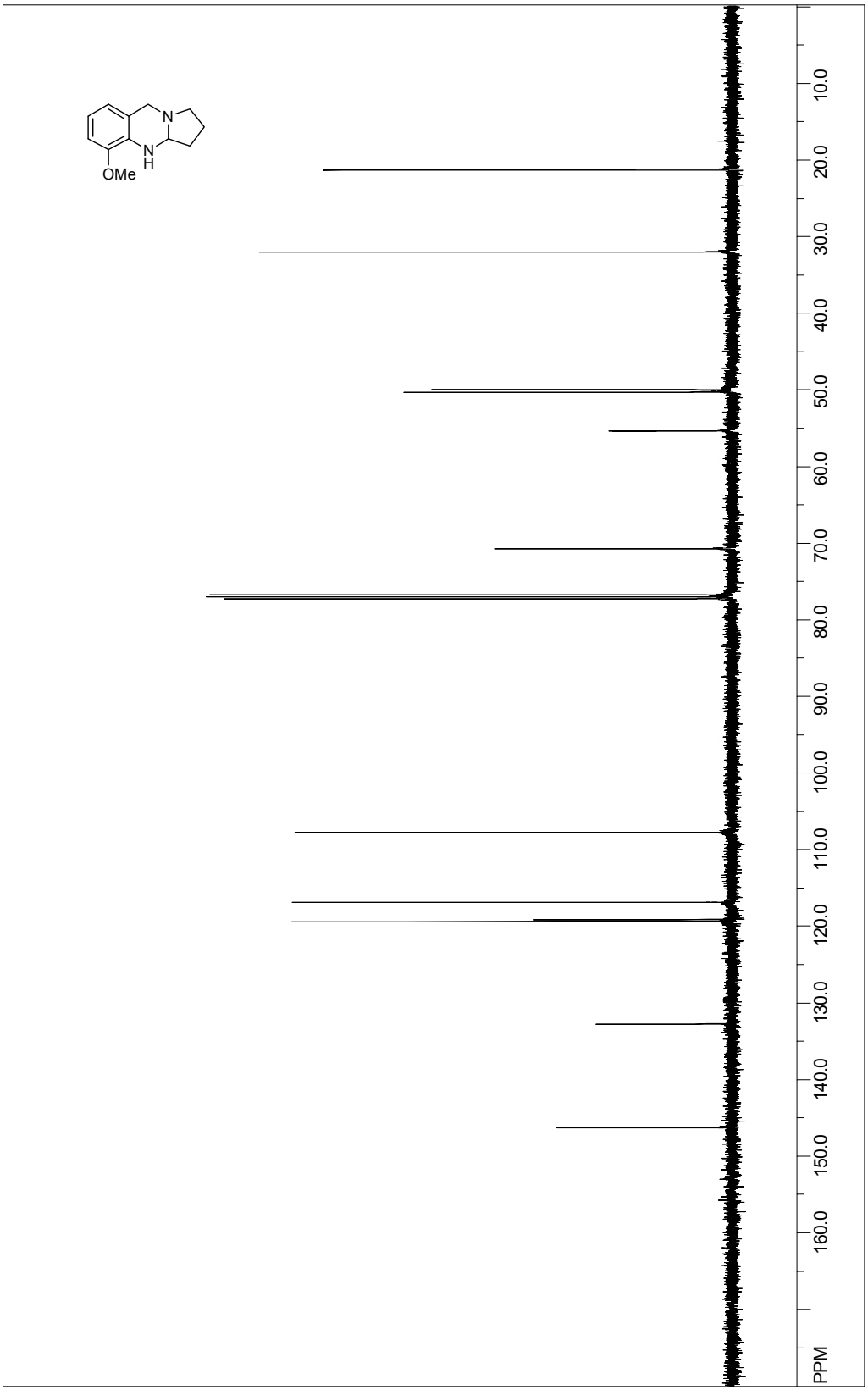
^{1}H-NMR and ^{13}C-NMR of **3.2k**:



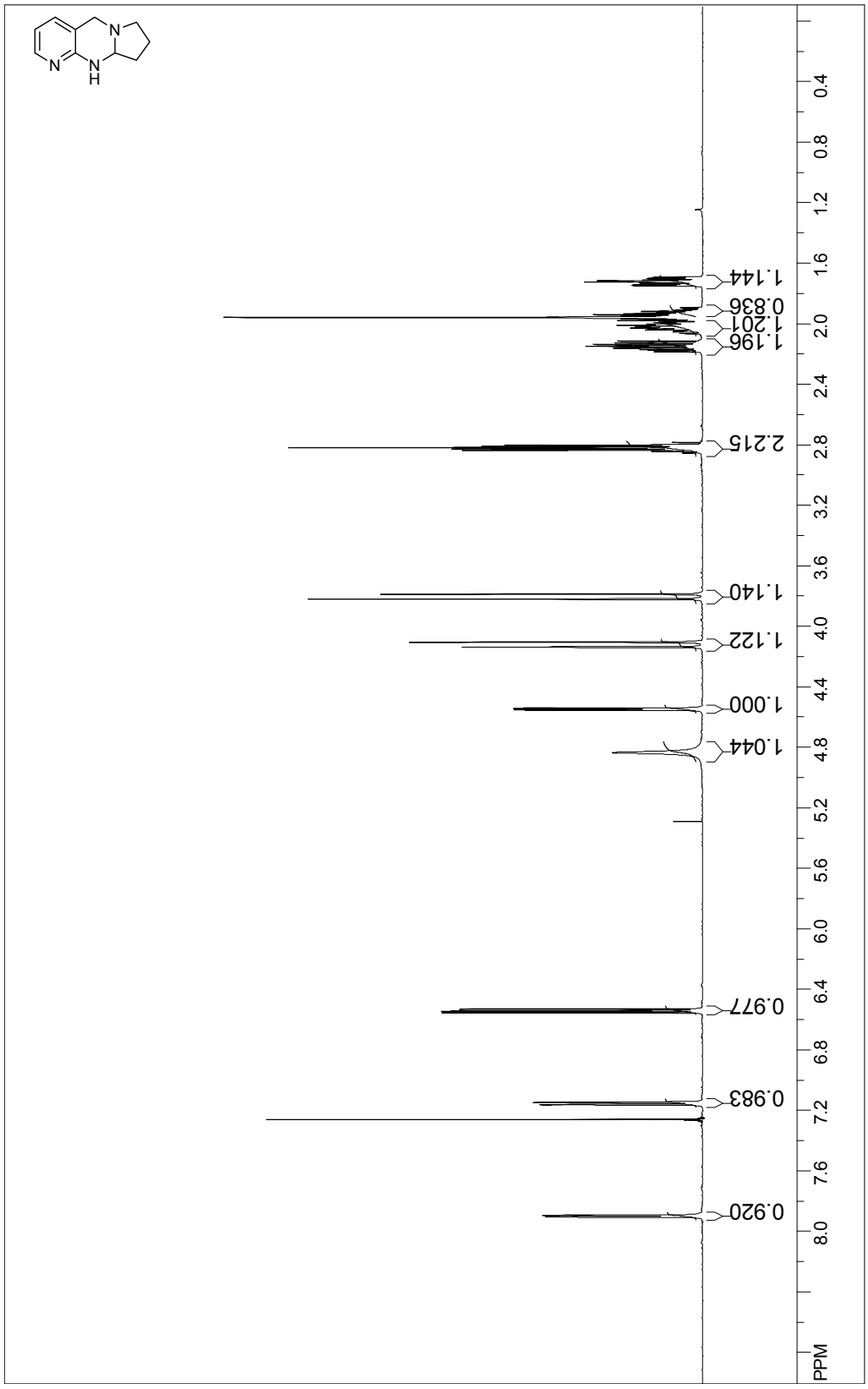

N
N
H
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

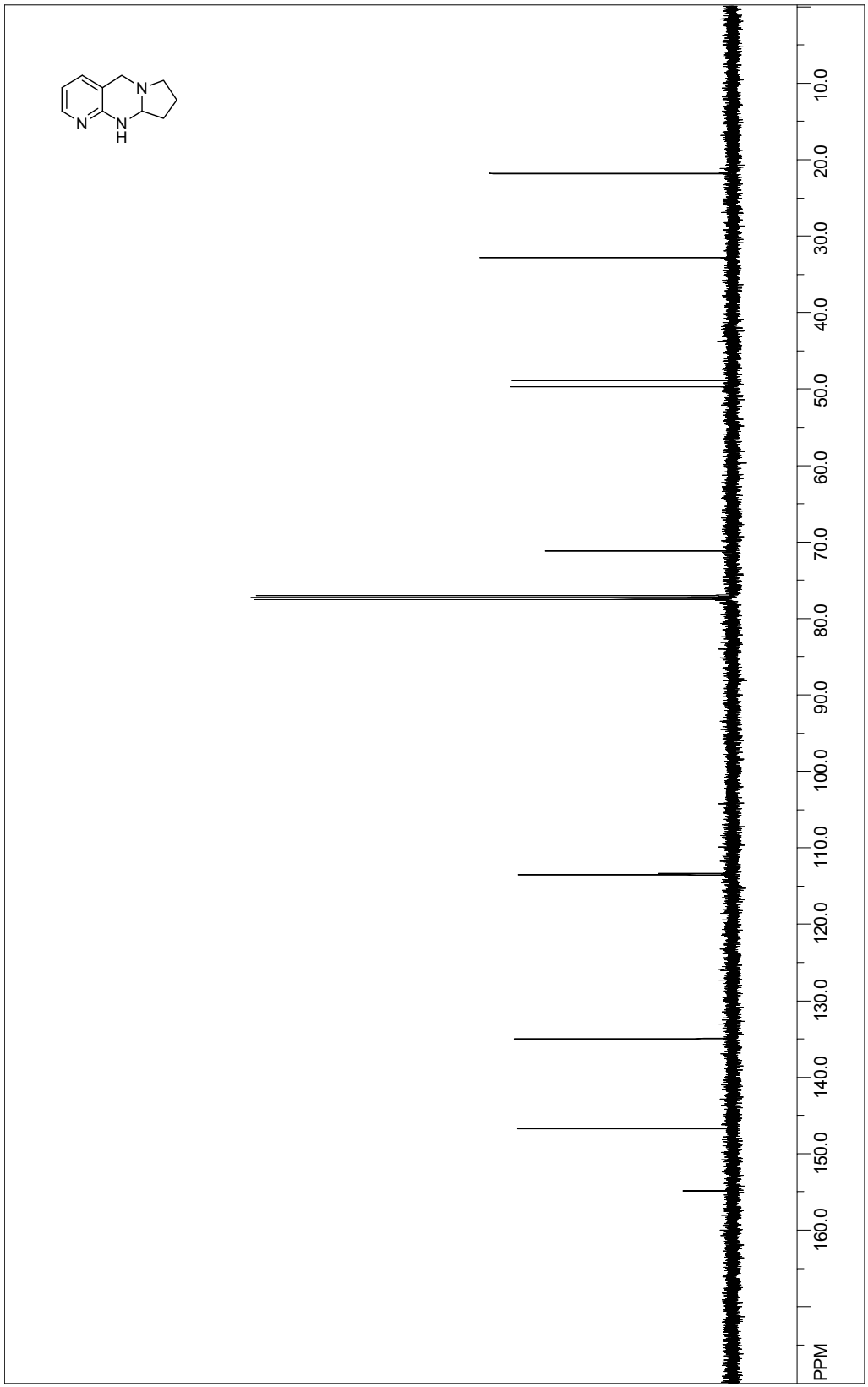
^{1}H-NMR and ^{13}C-NMR of **3.2l**:



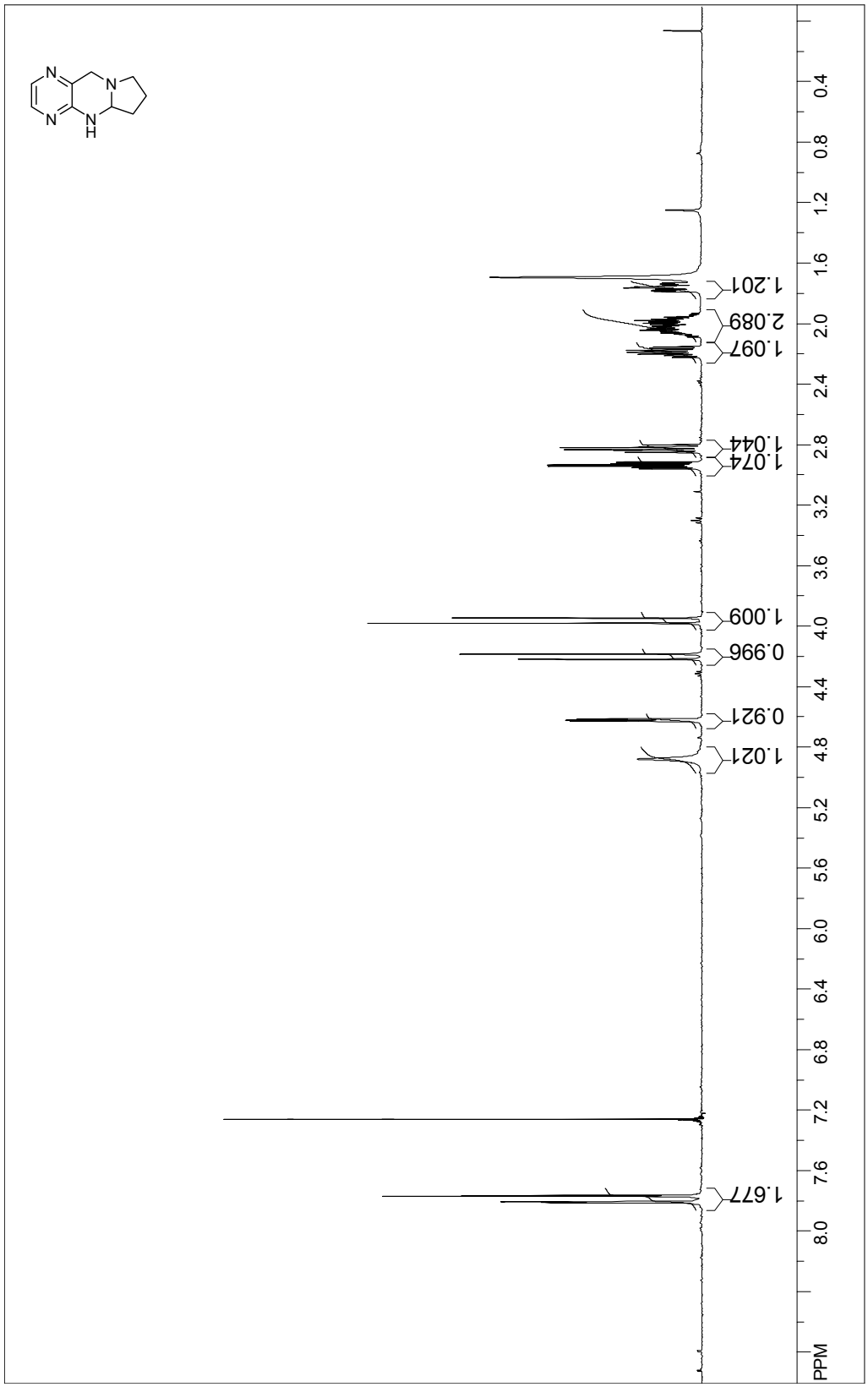

N
H
OMe
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

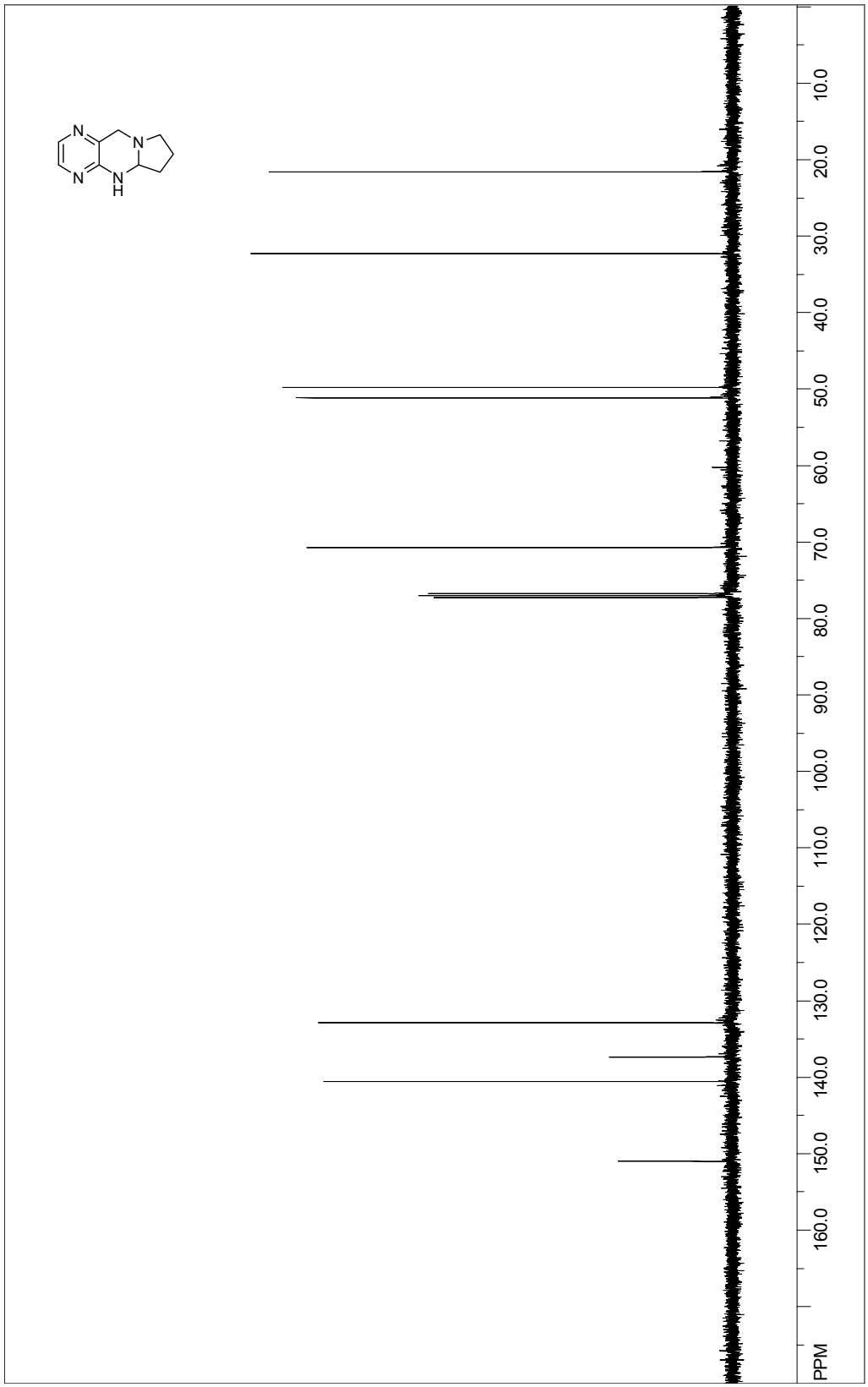
^{1}H-NMR and ^{13}C-NMR of **3.2m**:



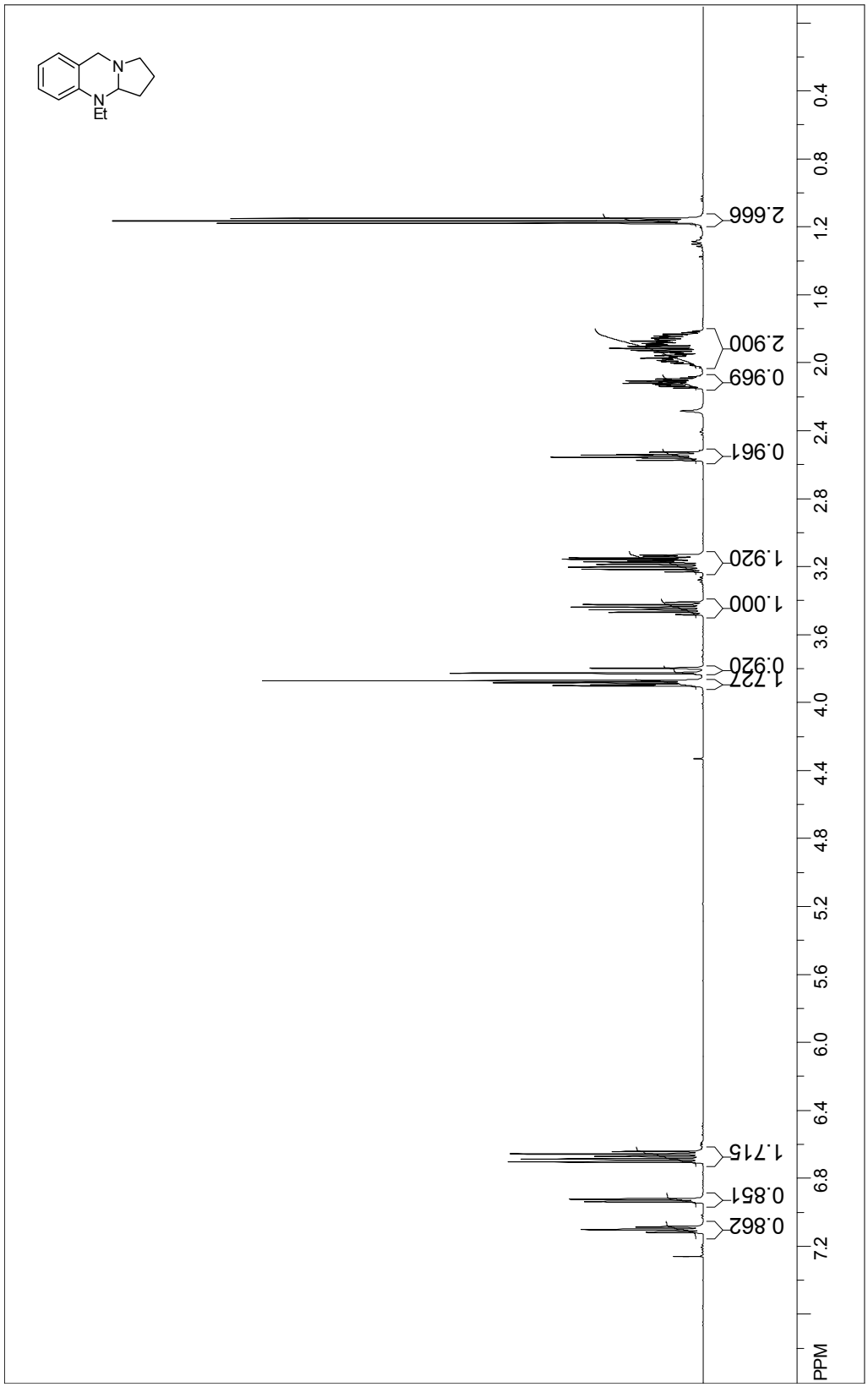

N
N
H
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

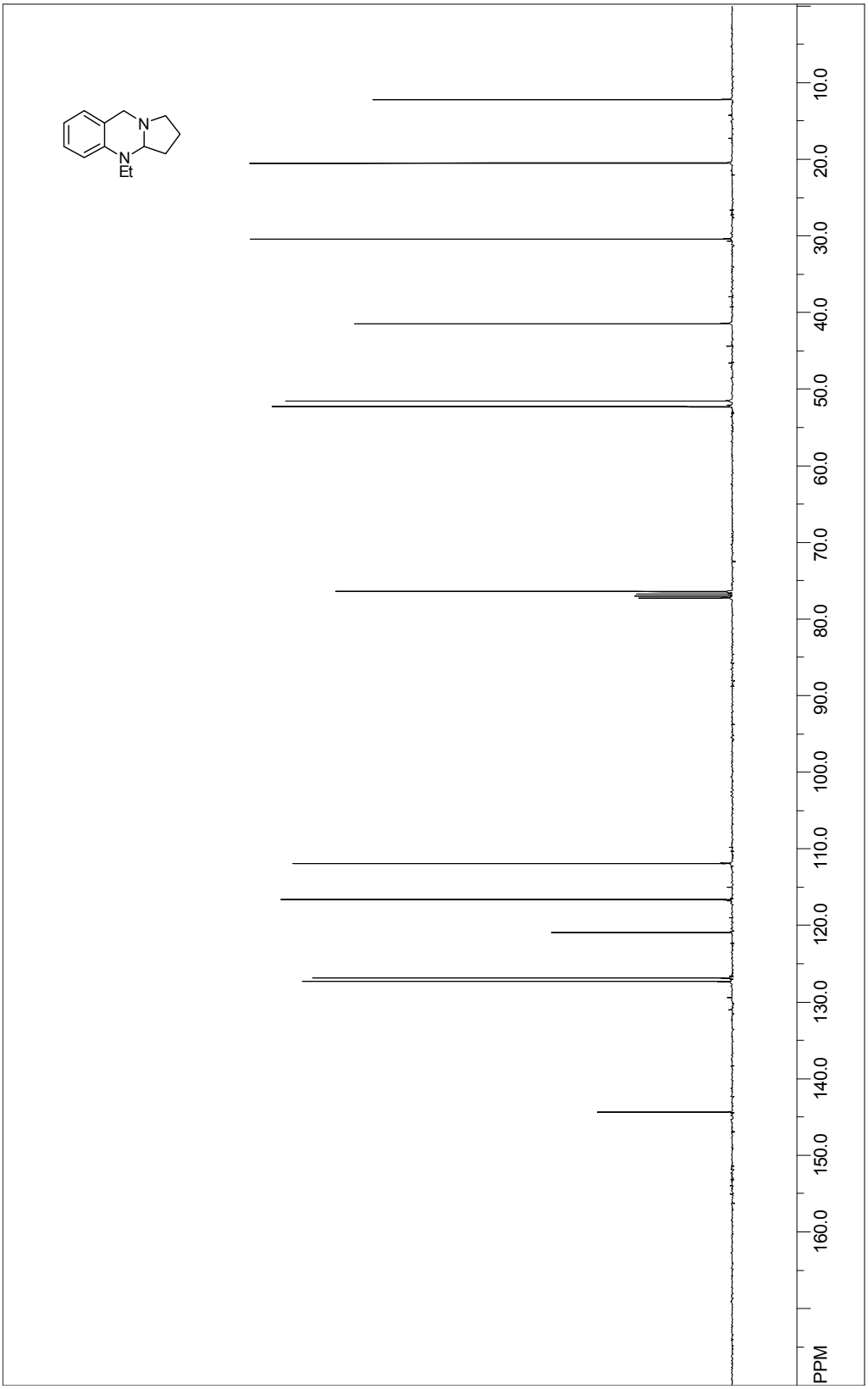
^{1}H-NMR and ^{13}C-NMR of **3.2n**:



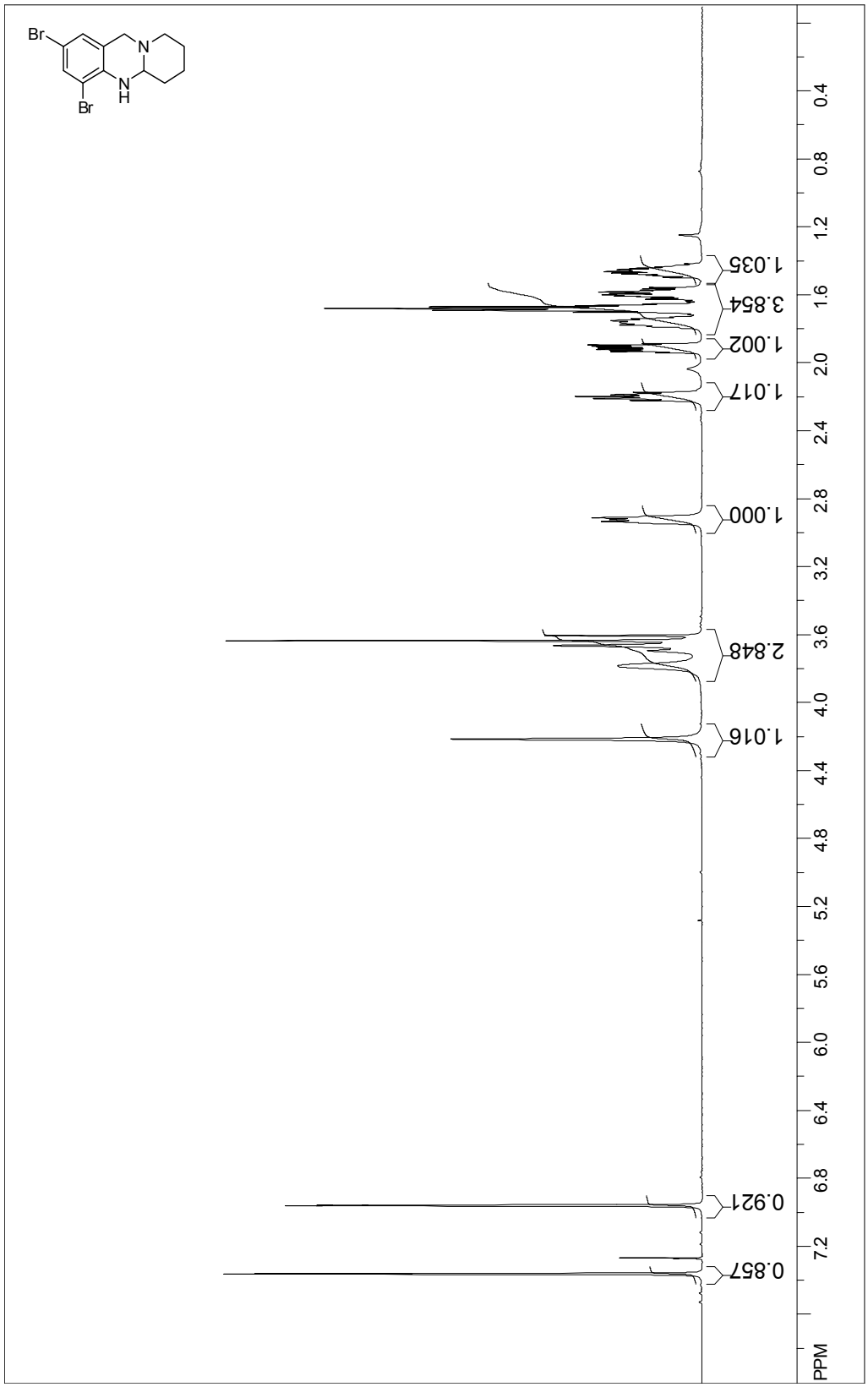

N
N
N
N
H
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

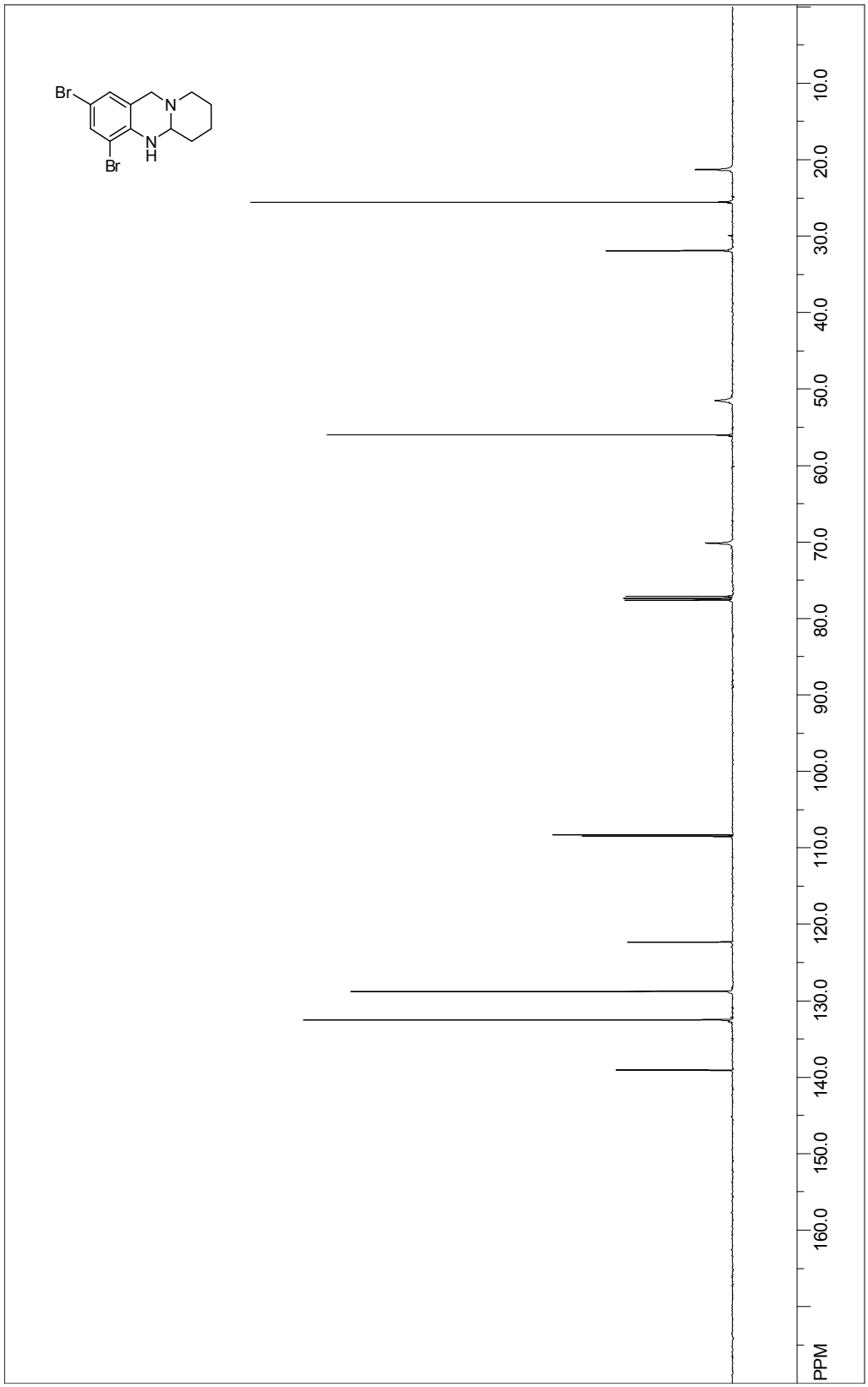
^{1}H-NMR and ^{13}C-NMR of **3.2o**:



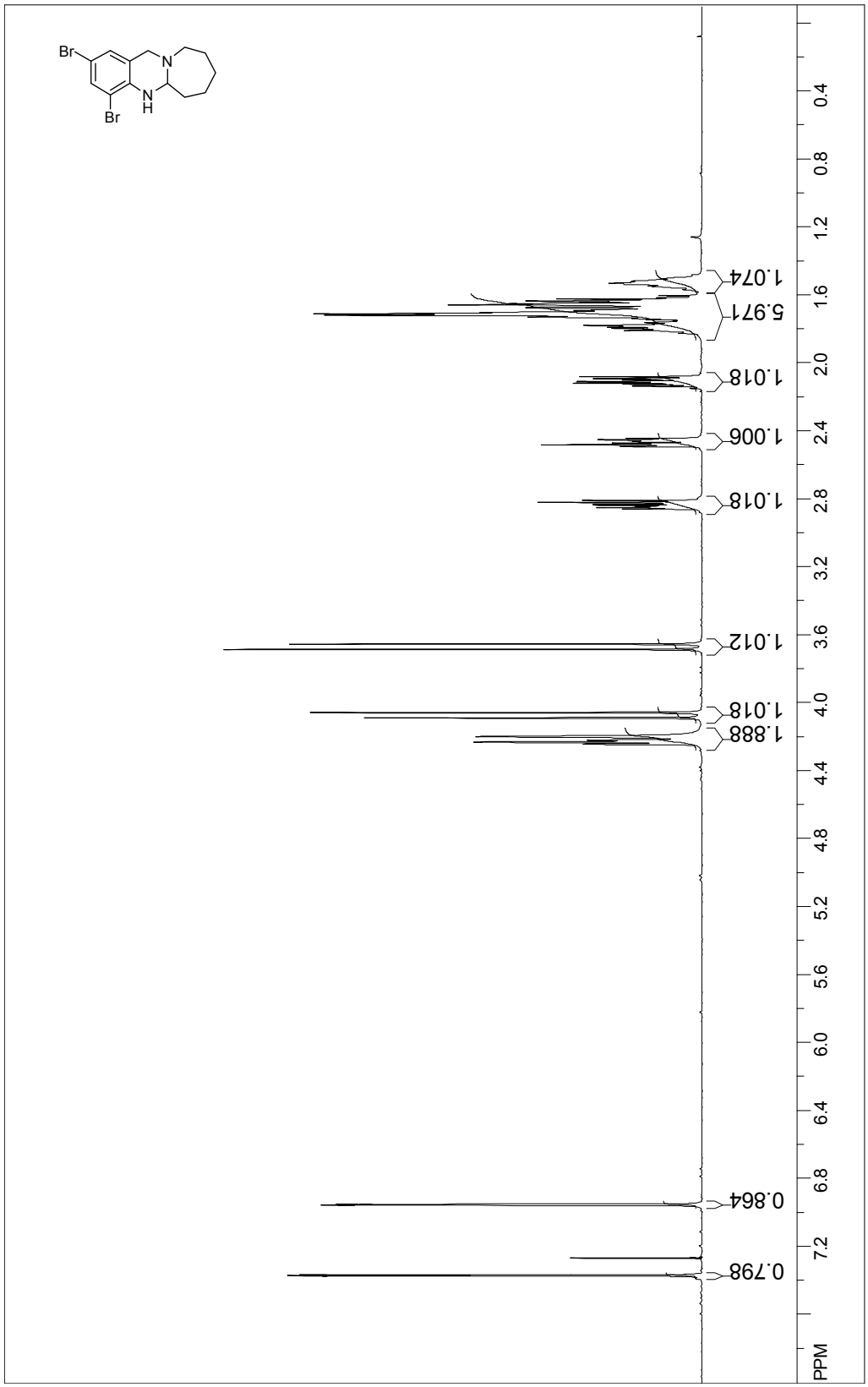

N
N
Et
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

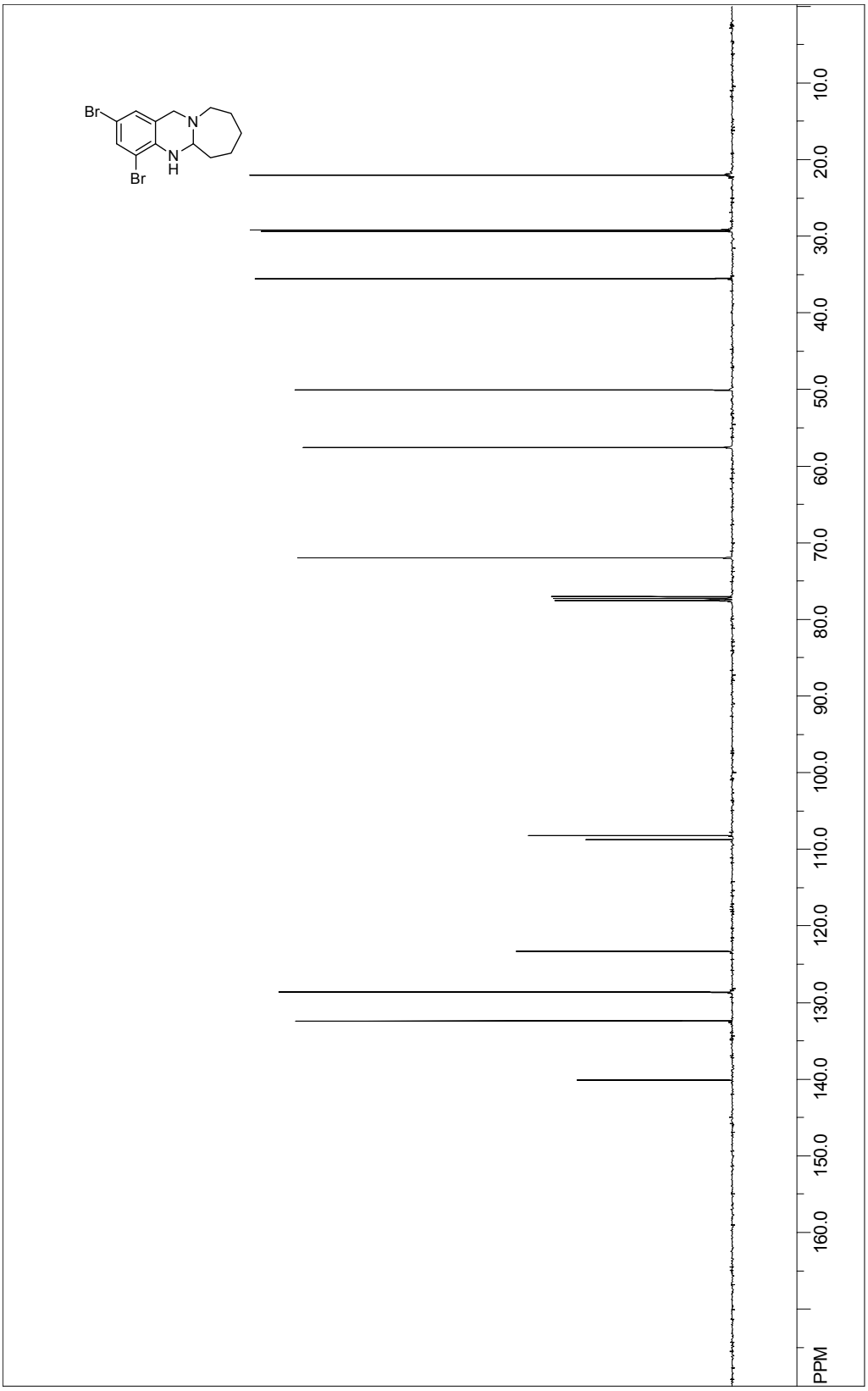
^{1}H-NMR and ^{13}C-NMR of **3.8**:



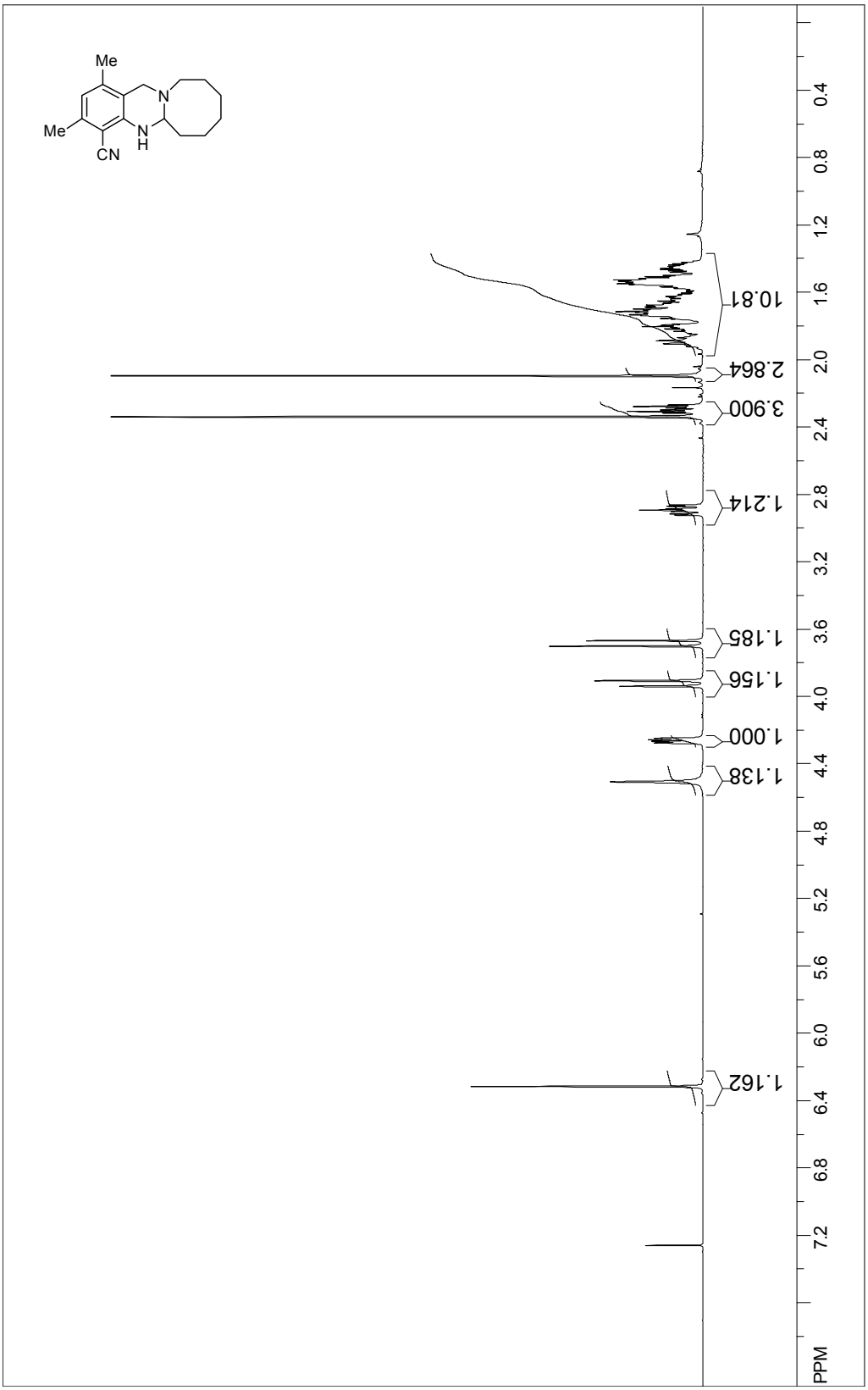

Br
N
N
H
Br
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

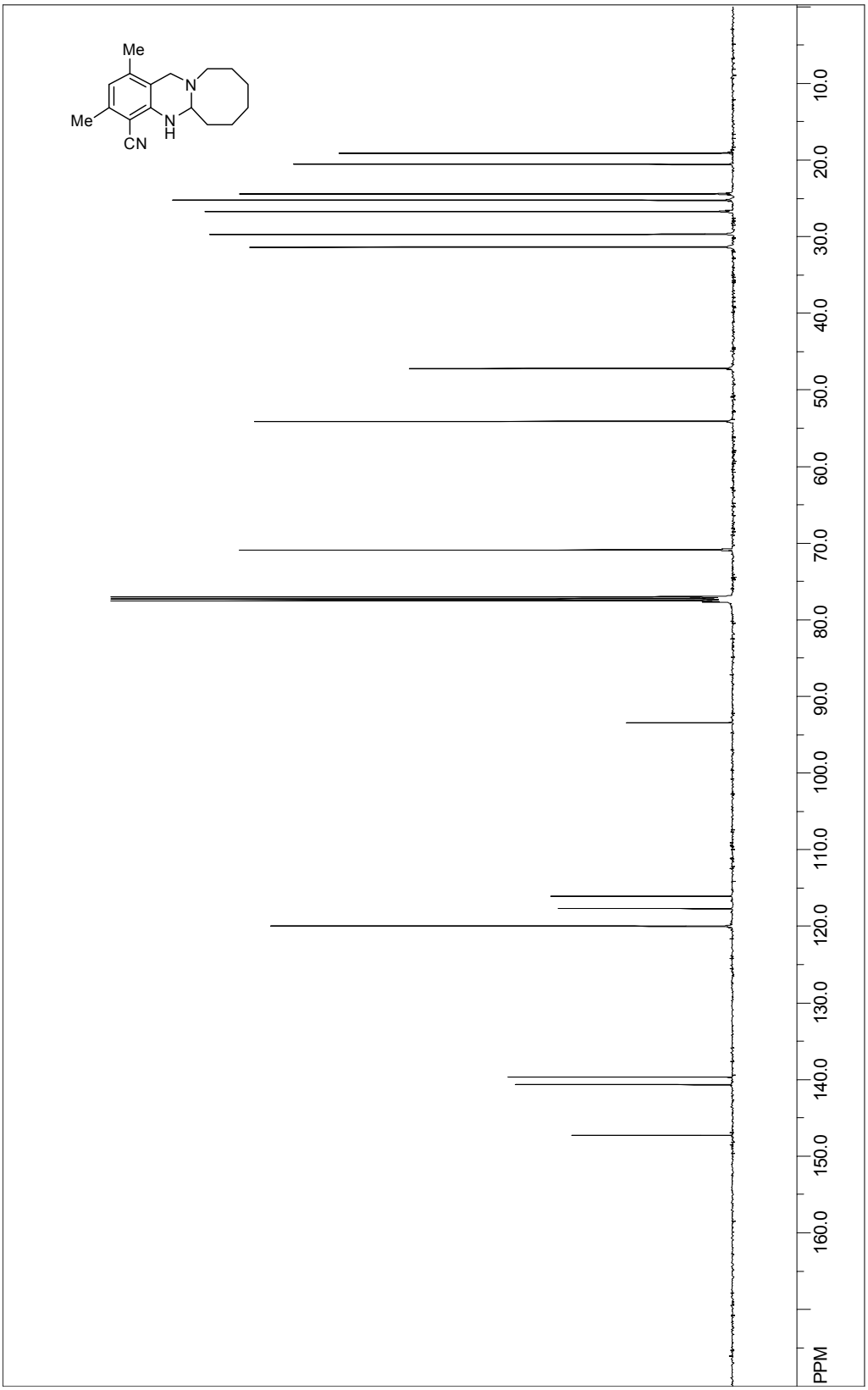
^{1}H-NMR and ^{13}C-NMR of **3.9**:



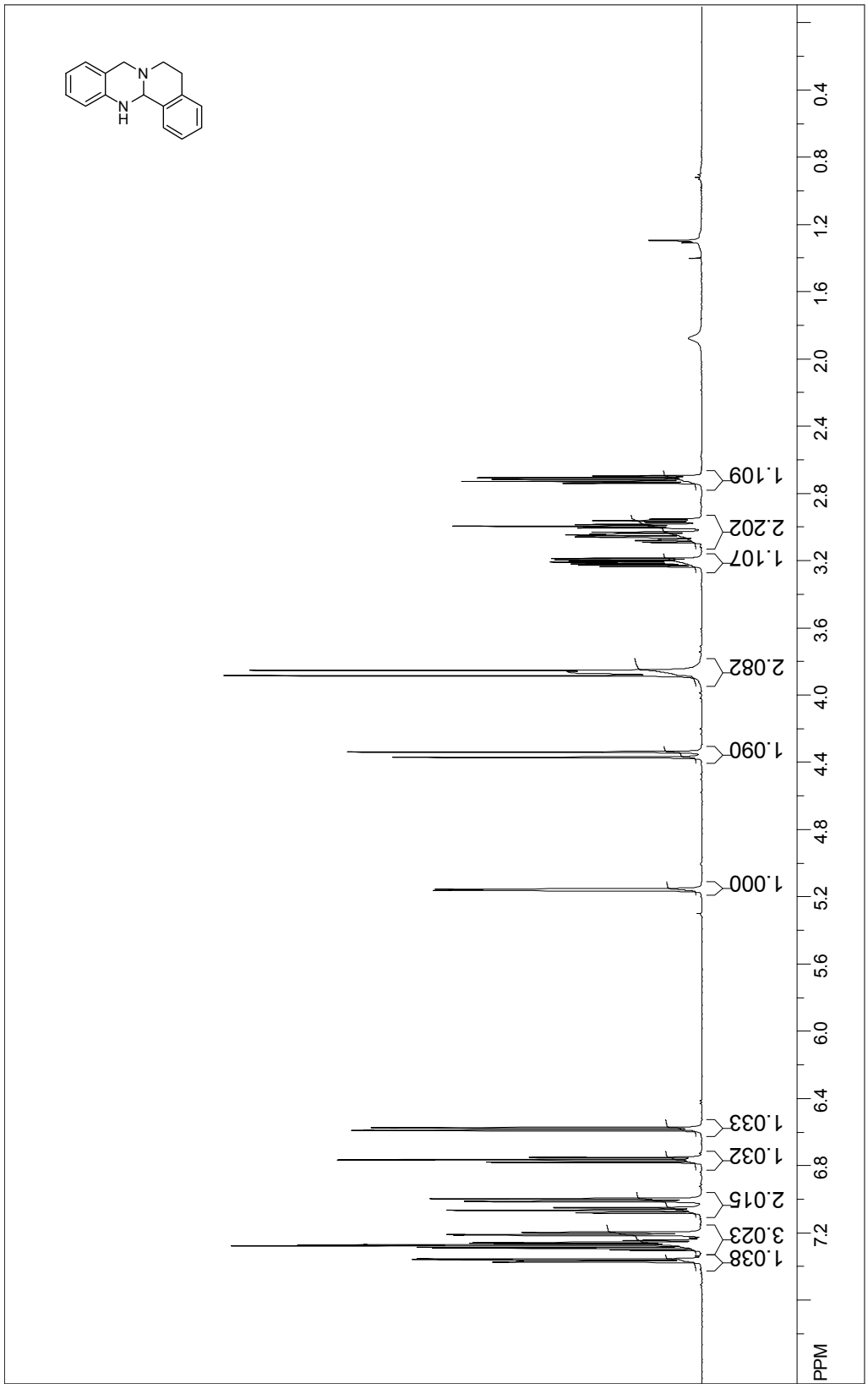

Br
N
N
H
Br
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

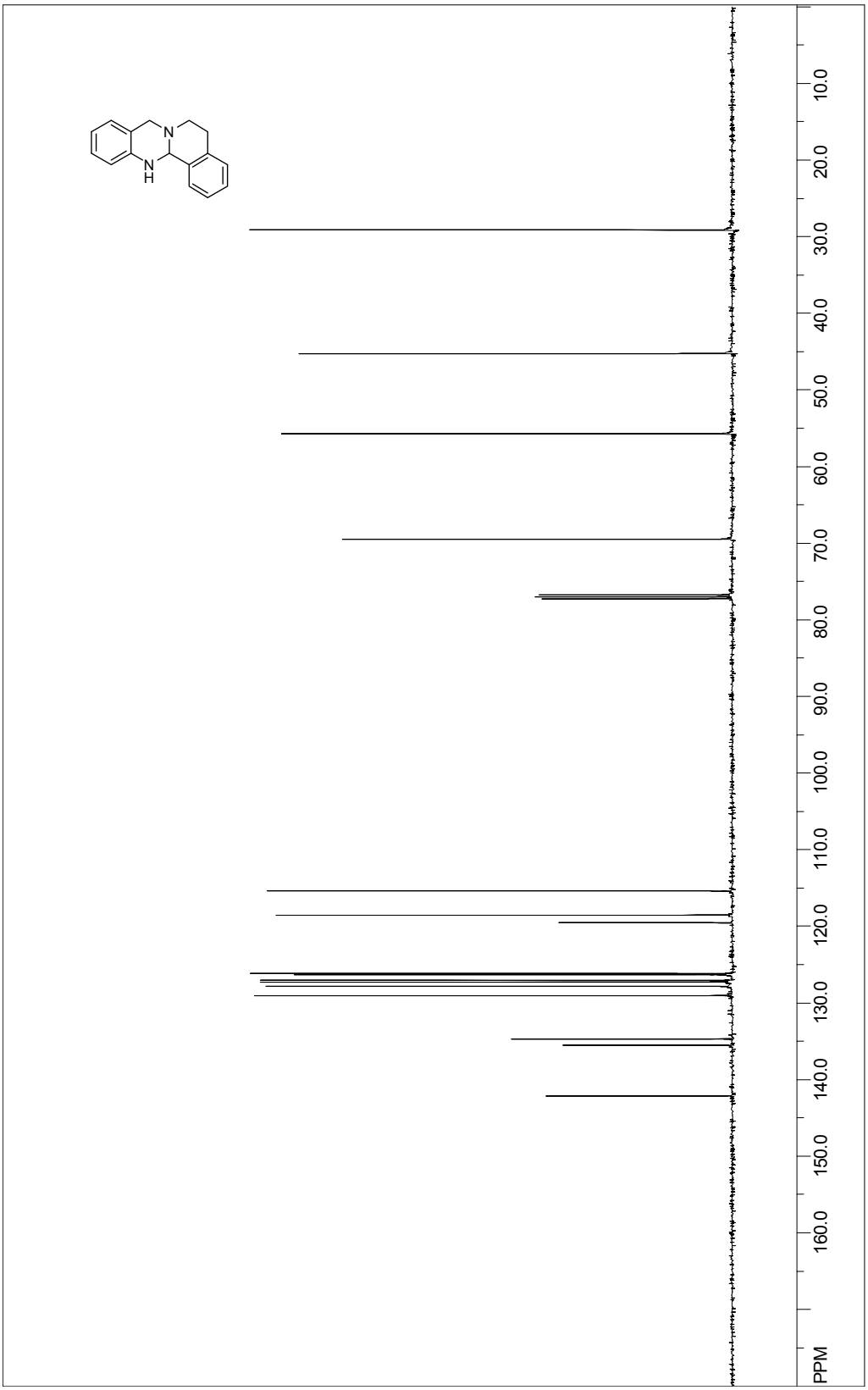
^{1}H-NMR and ^{13}C-NMR of **3.10**:



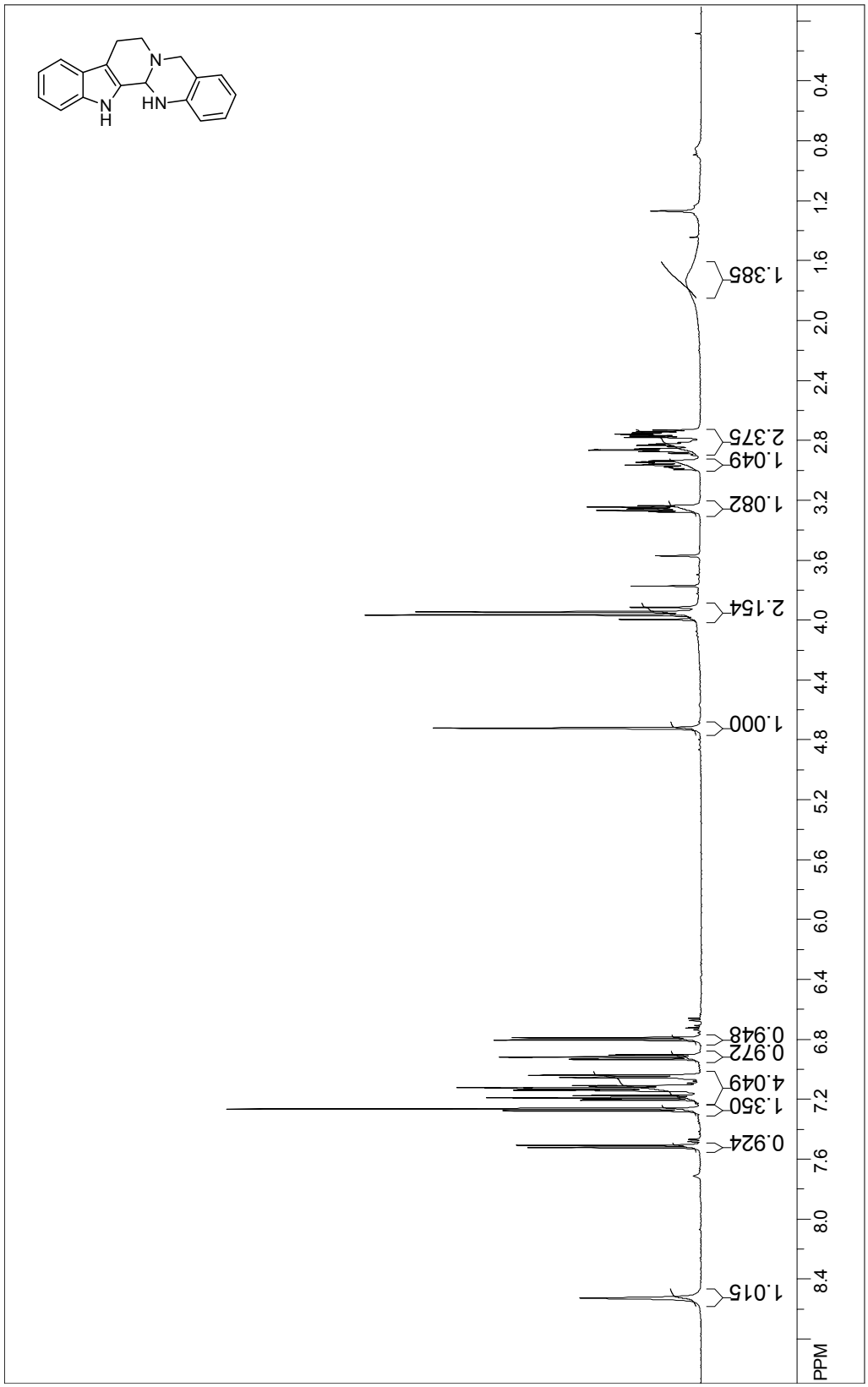

Me
Me
N
N
H
CN
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

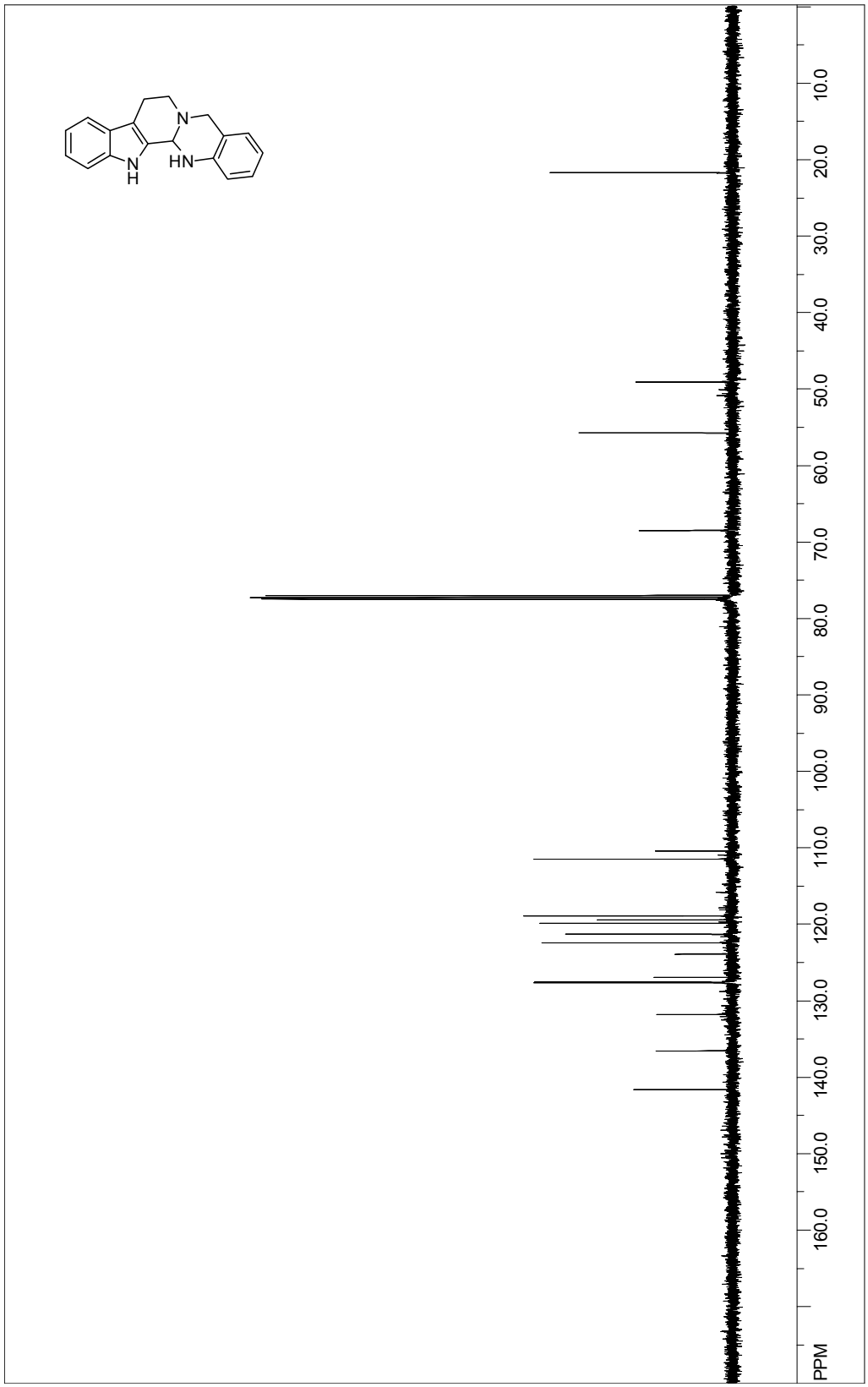
^{1}H-NMR and ^{13}C-NMR of **3.11**:



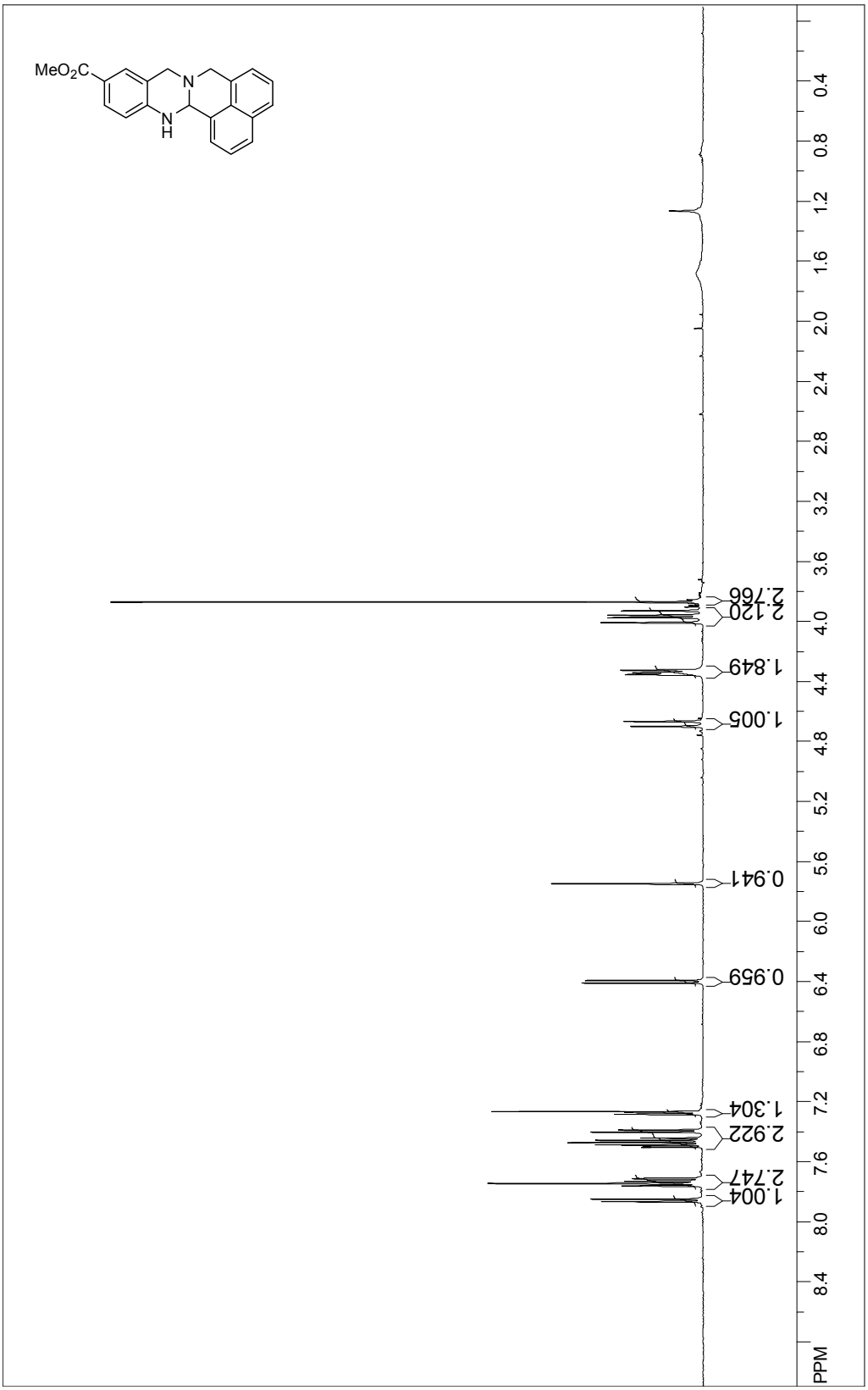

N
H
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

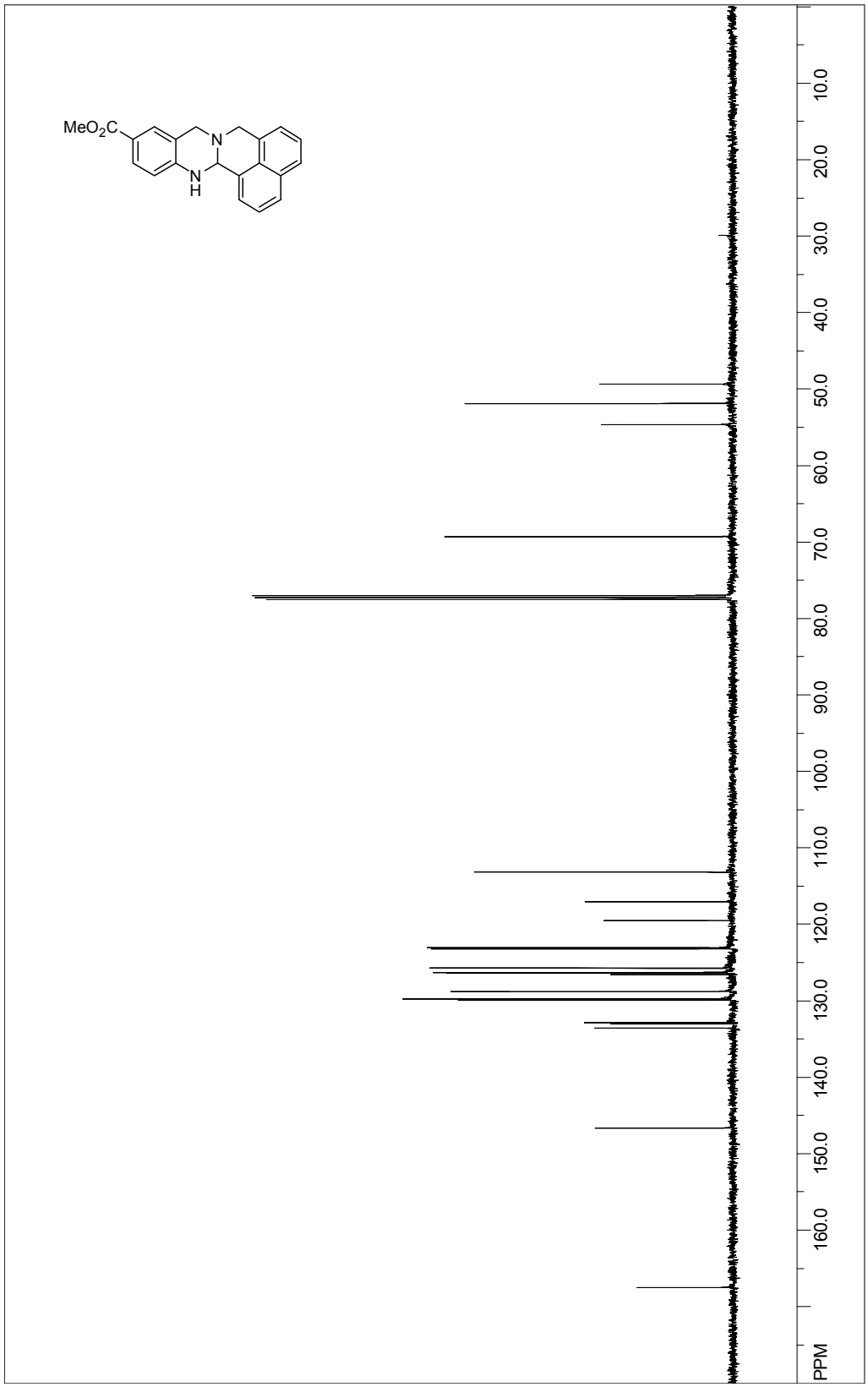
^{1}H-NMR and ^{13}C-NMR of **3.12**:



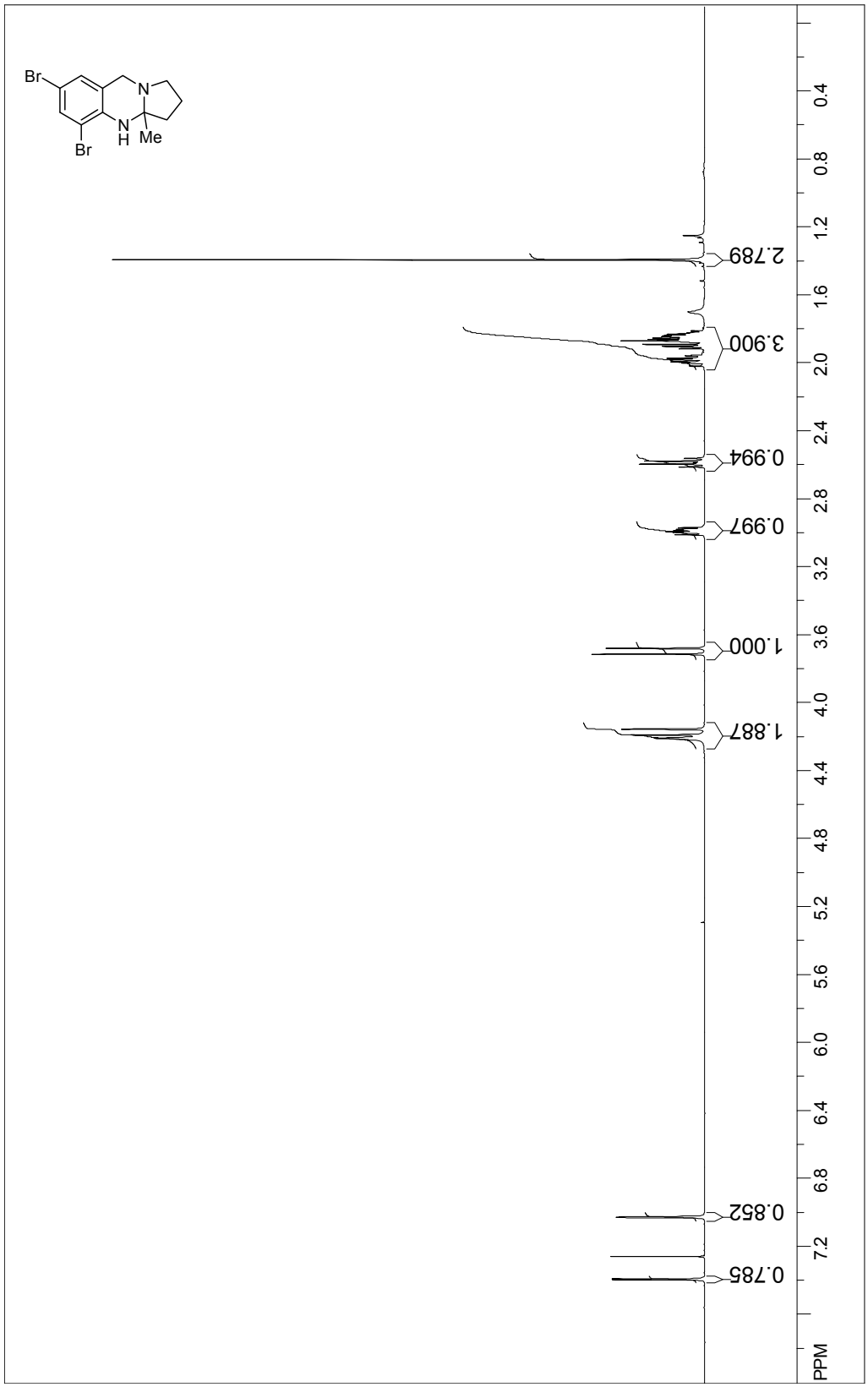

N
HN
H
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

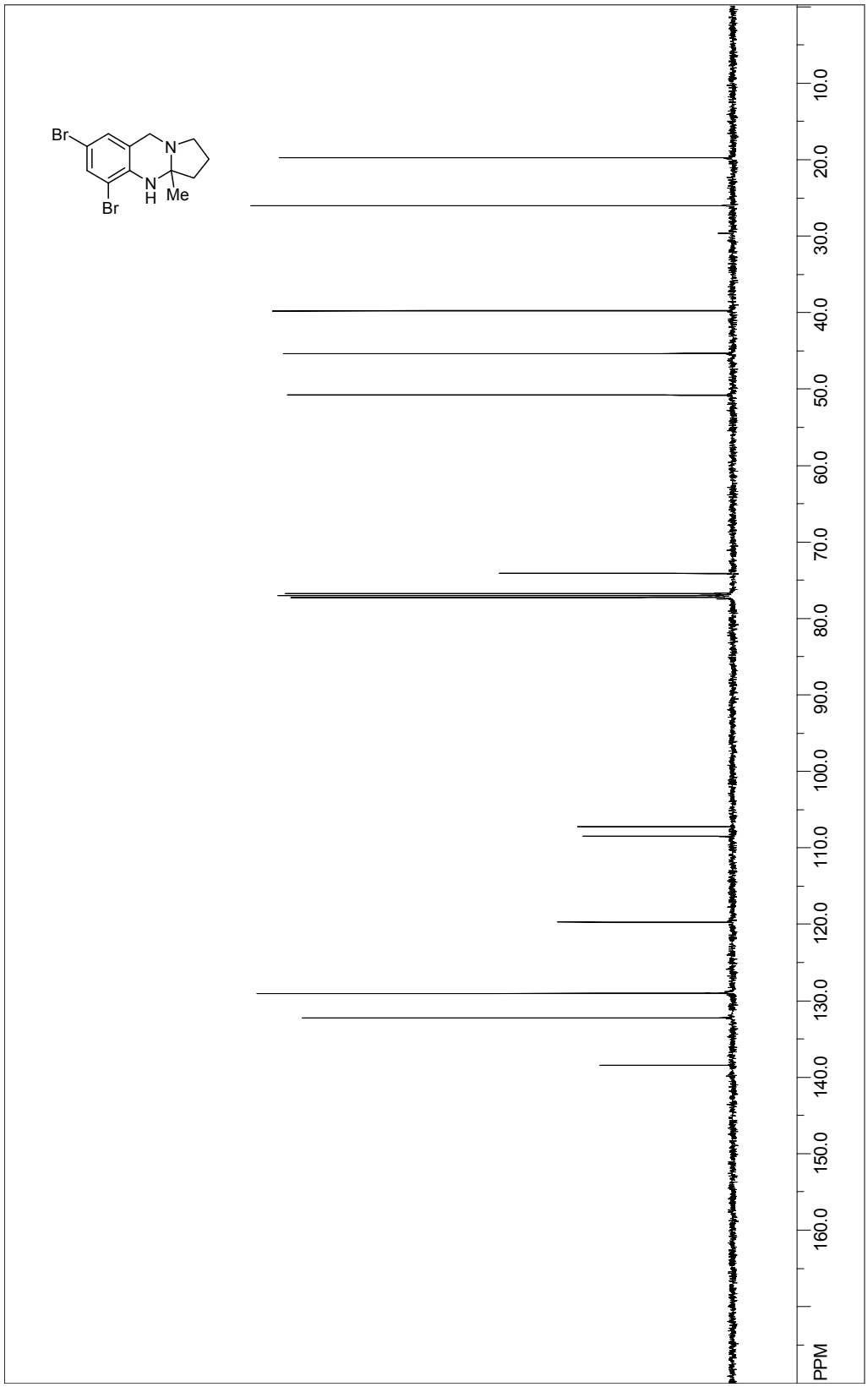
^{1}H-NMR and ^{13}C-NMR of **3.13**:



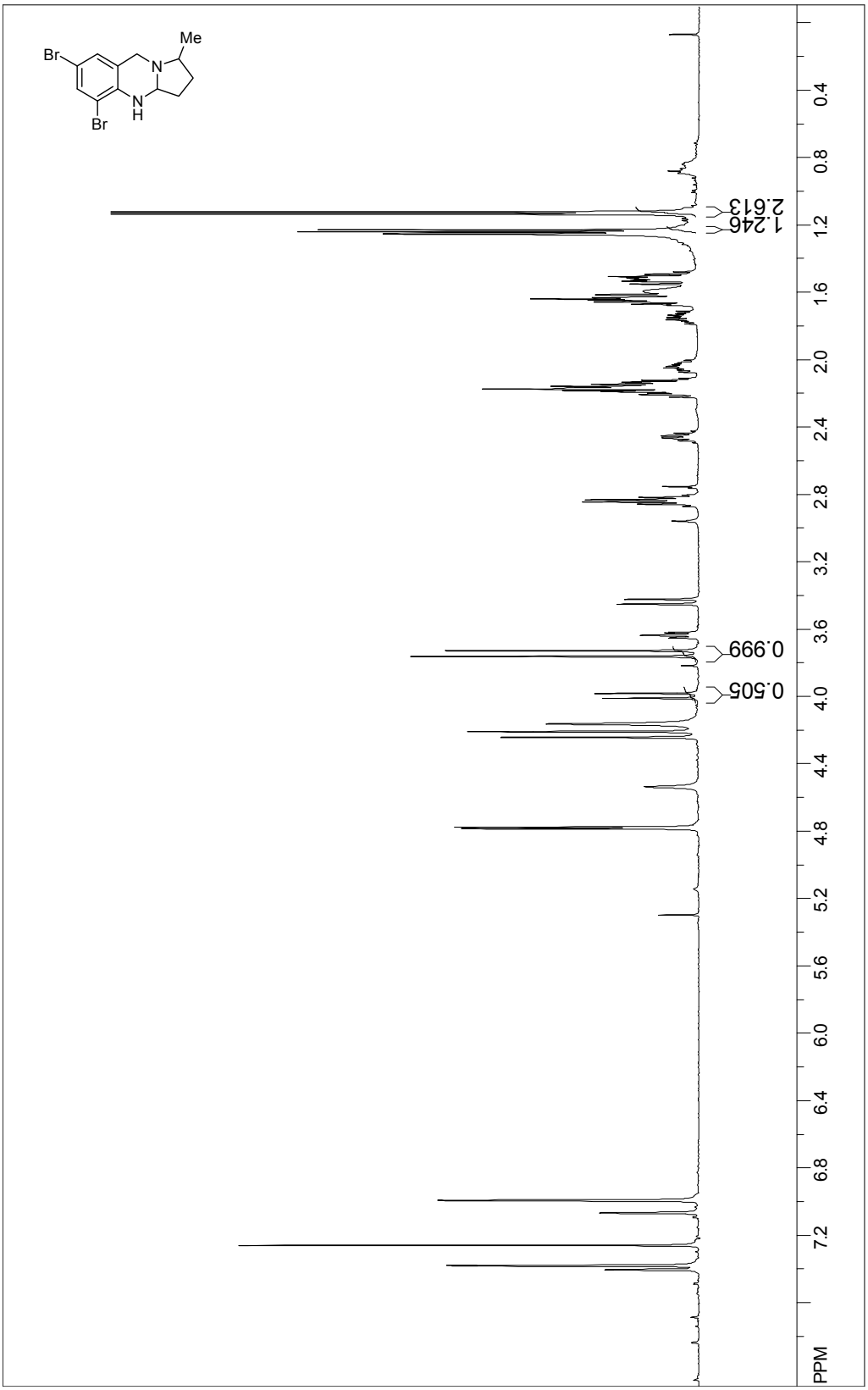

MeO2C
N
N
H
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

^{1}H-NMR and ^{13}C-NMR of **3.18a**:

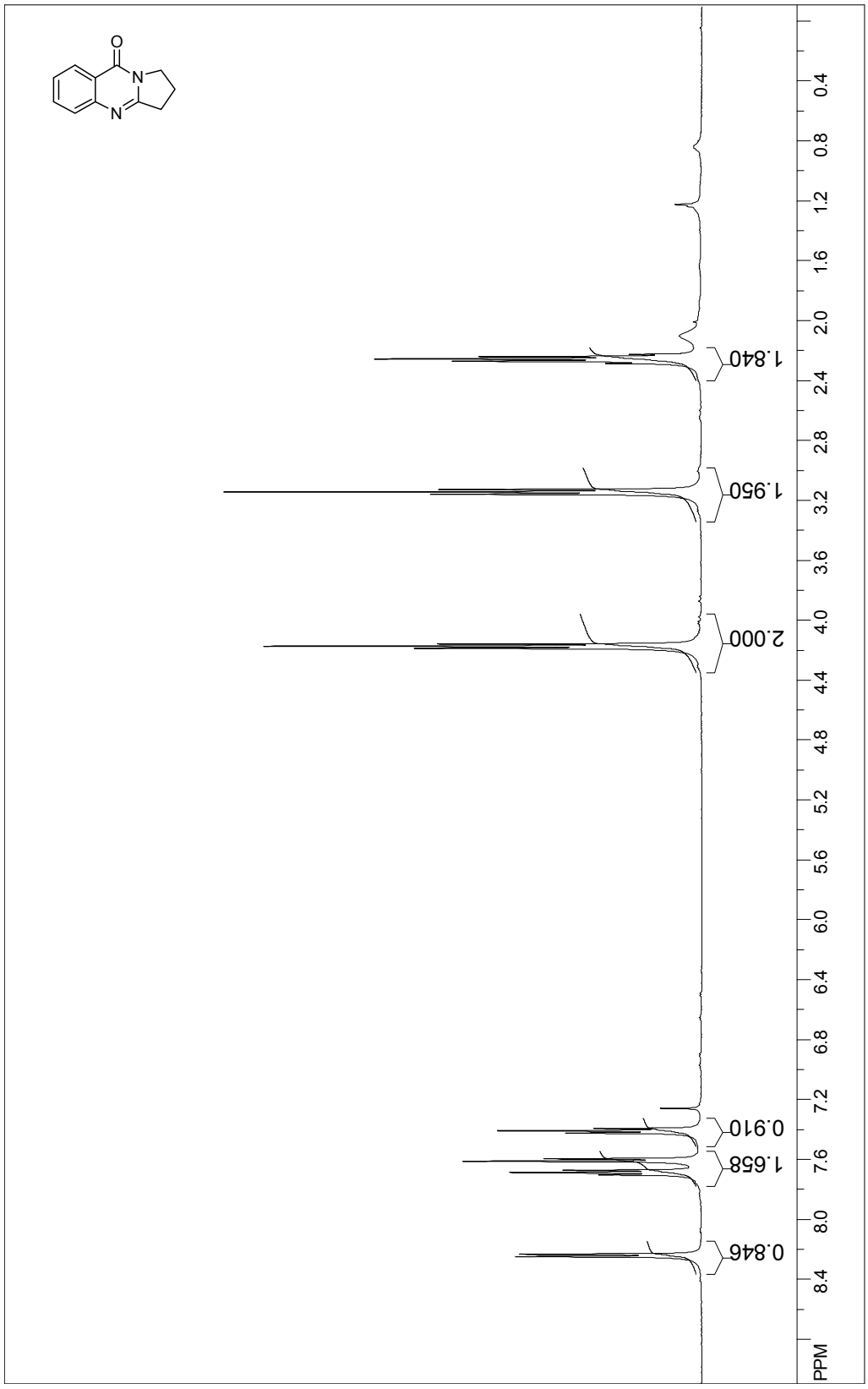


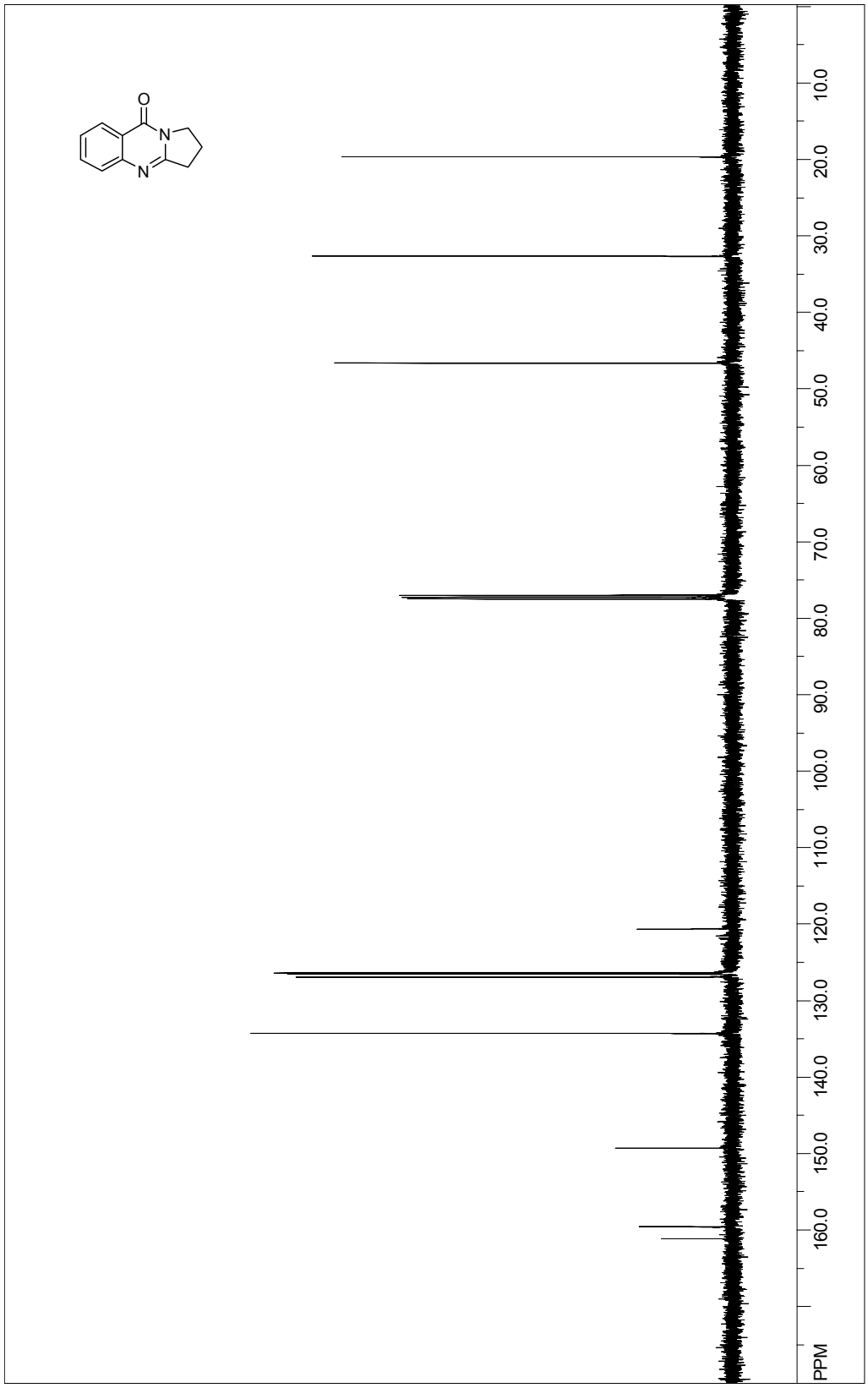

Br
N
N
H
Me
Br
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

^{1}H-NMR of the mixture of **3.18b**:

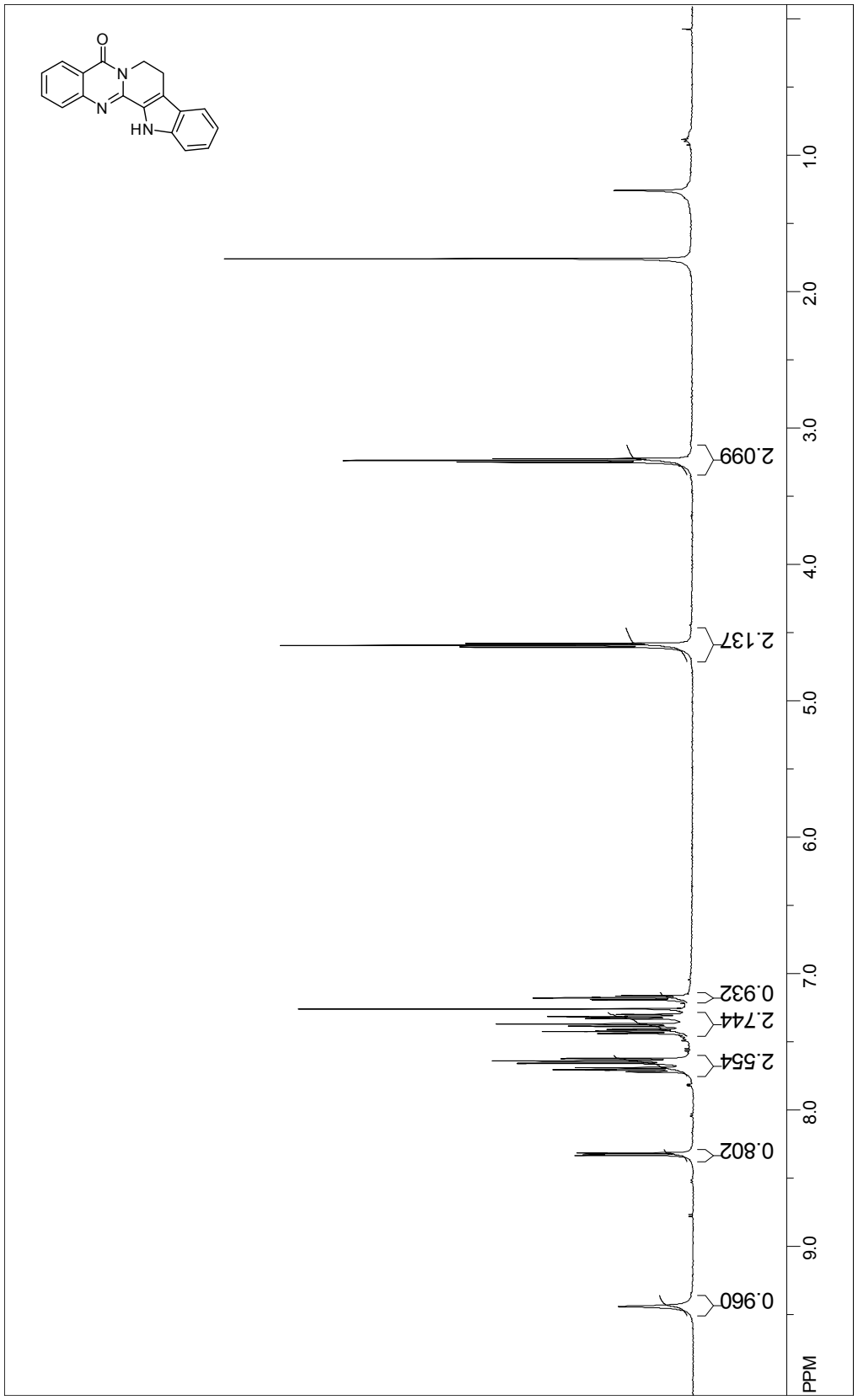


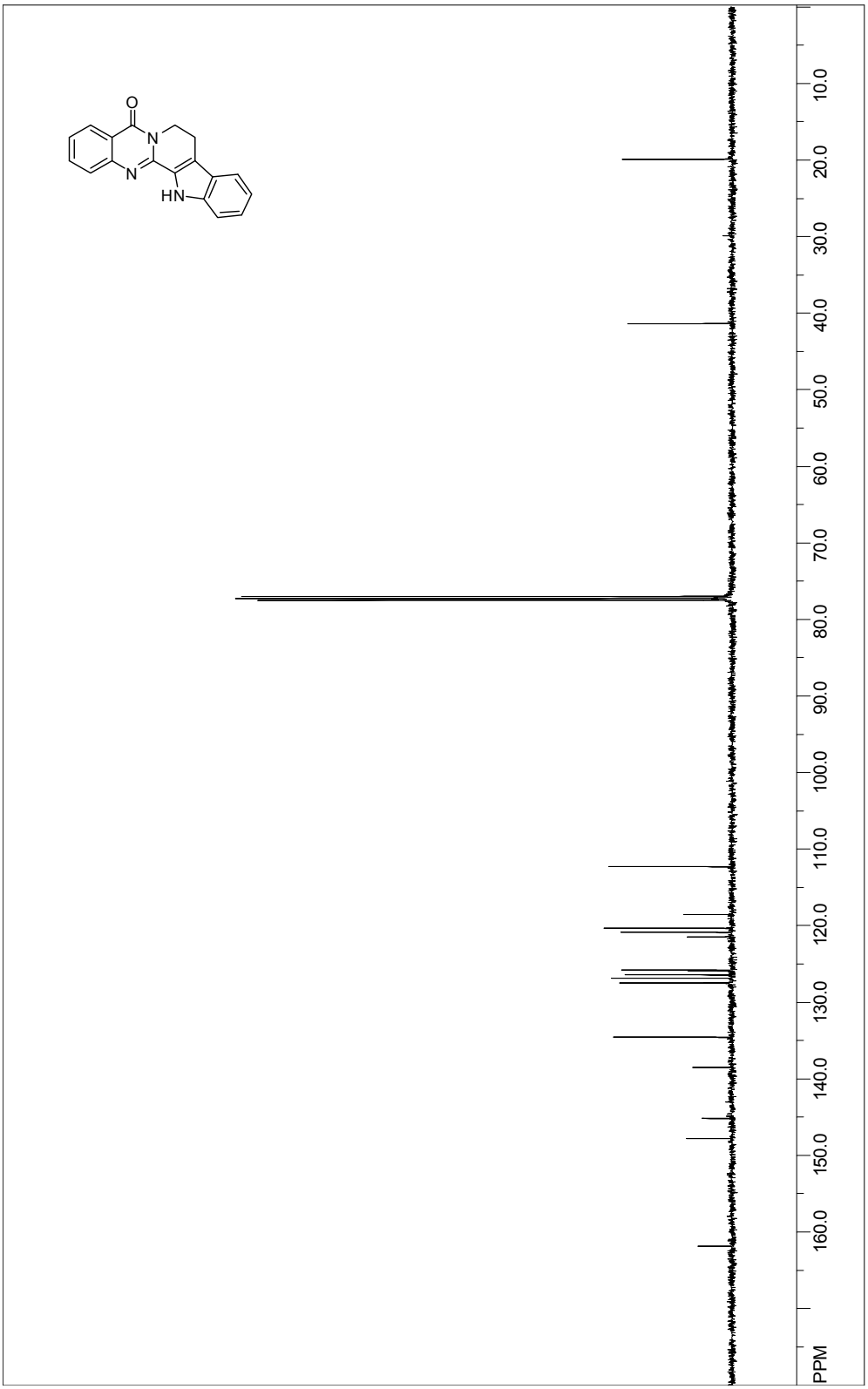
^{1}H-NMR and ^{13}C-NMR of Deoxyvasicinone:



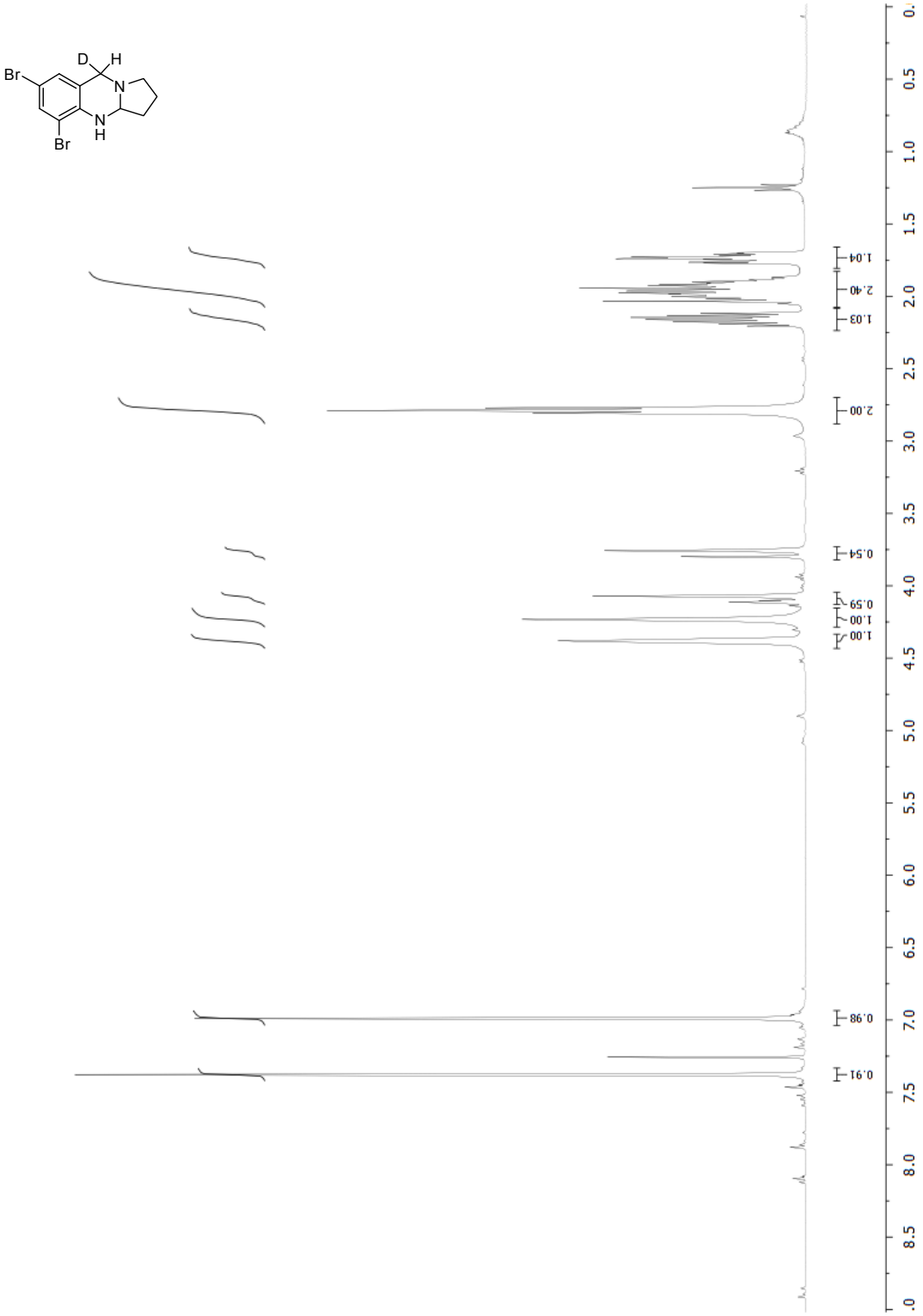

O
N
N
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

^{1}H-NMR and ^{13}C-NMR of Rutaecarpine:

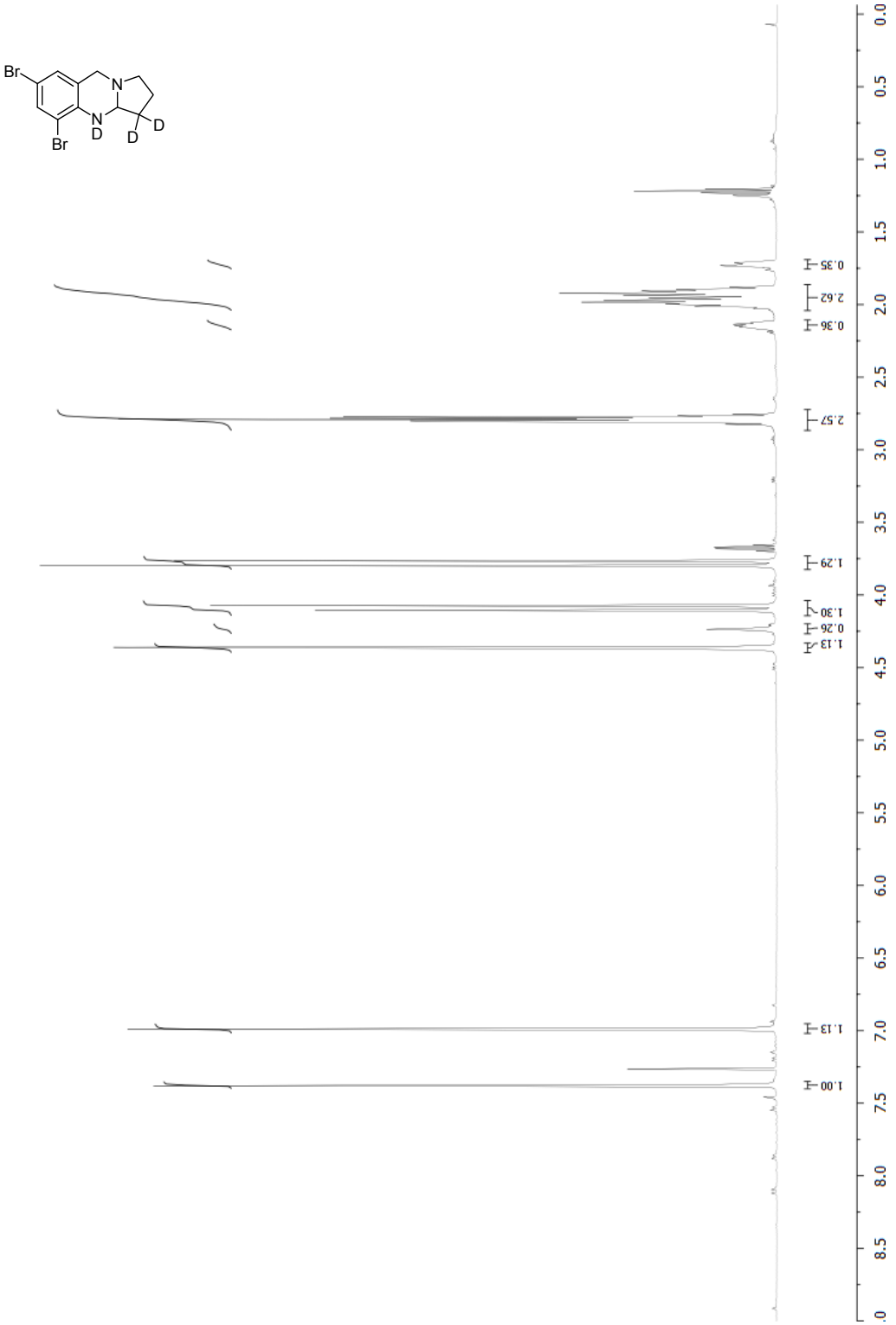



O
N
N
HN
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
PPM

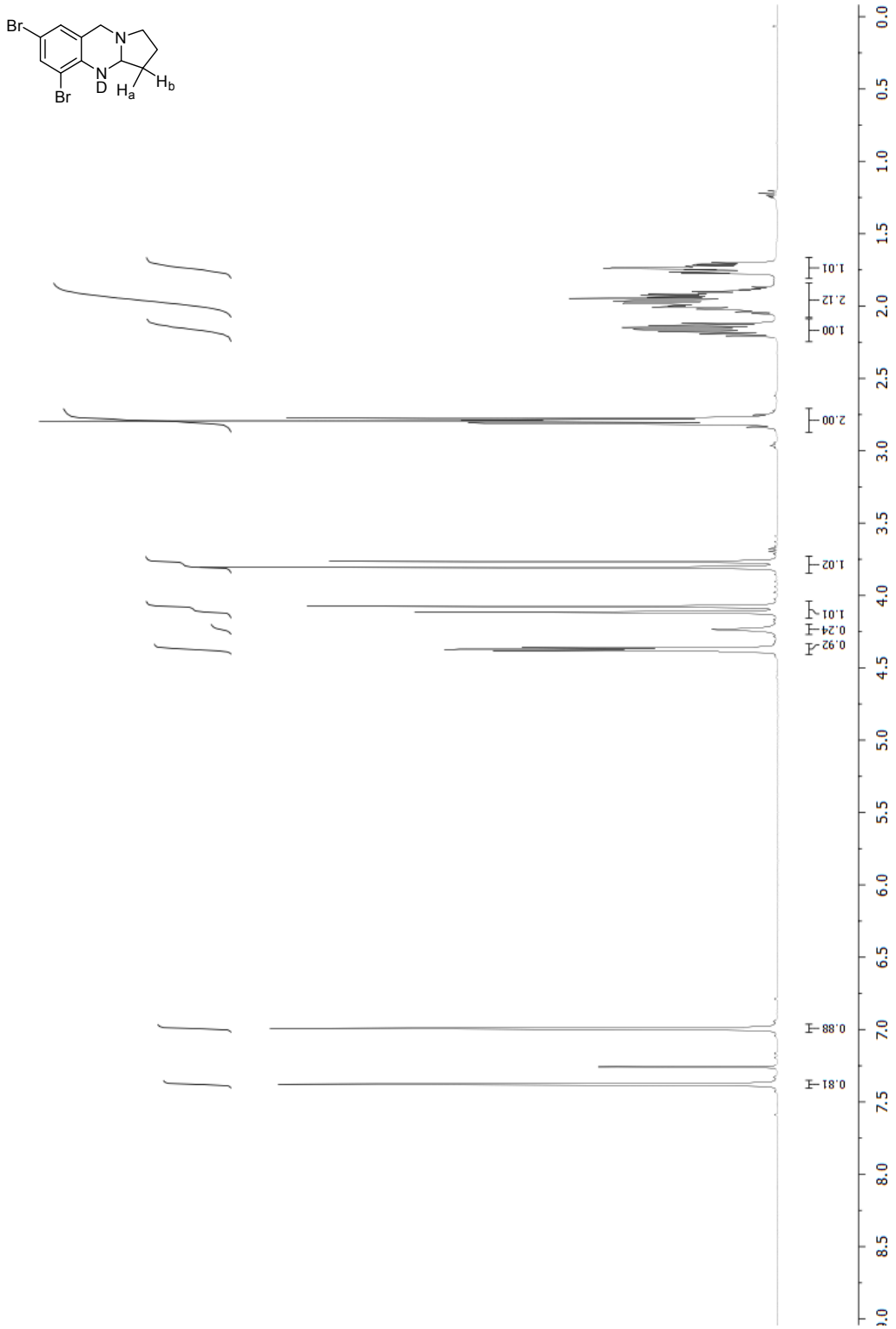
^{1}H-NMR of **3.2c-D1**



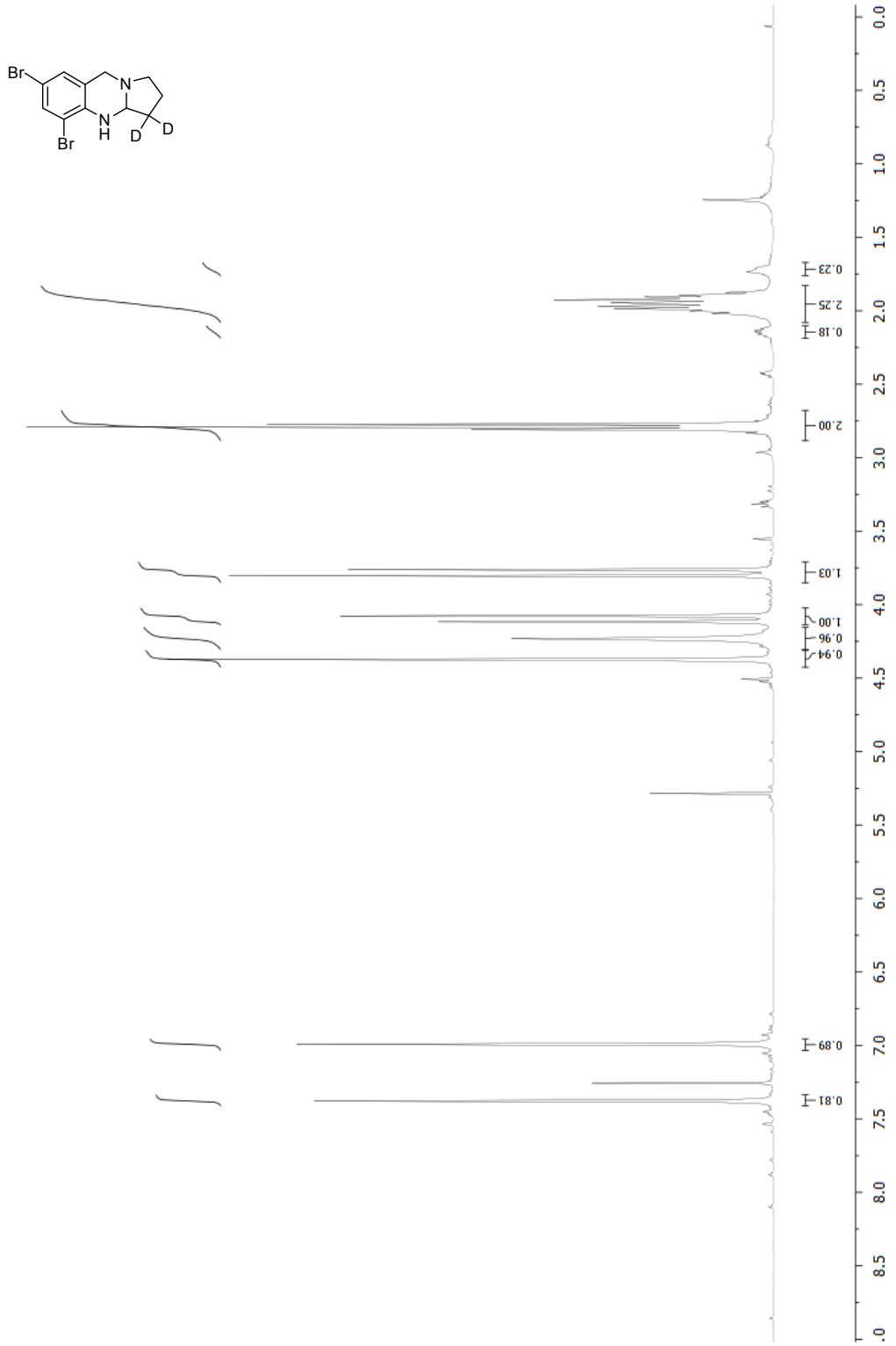
^{1}H-NMR of **3.2c-D2**



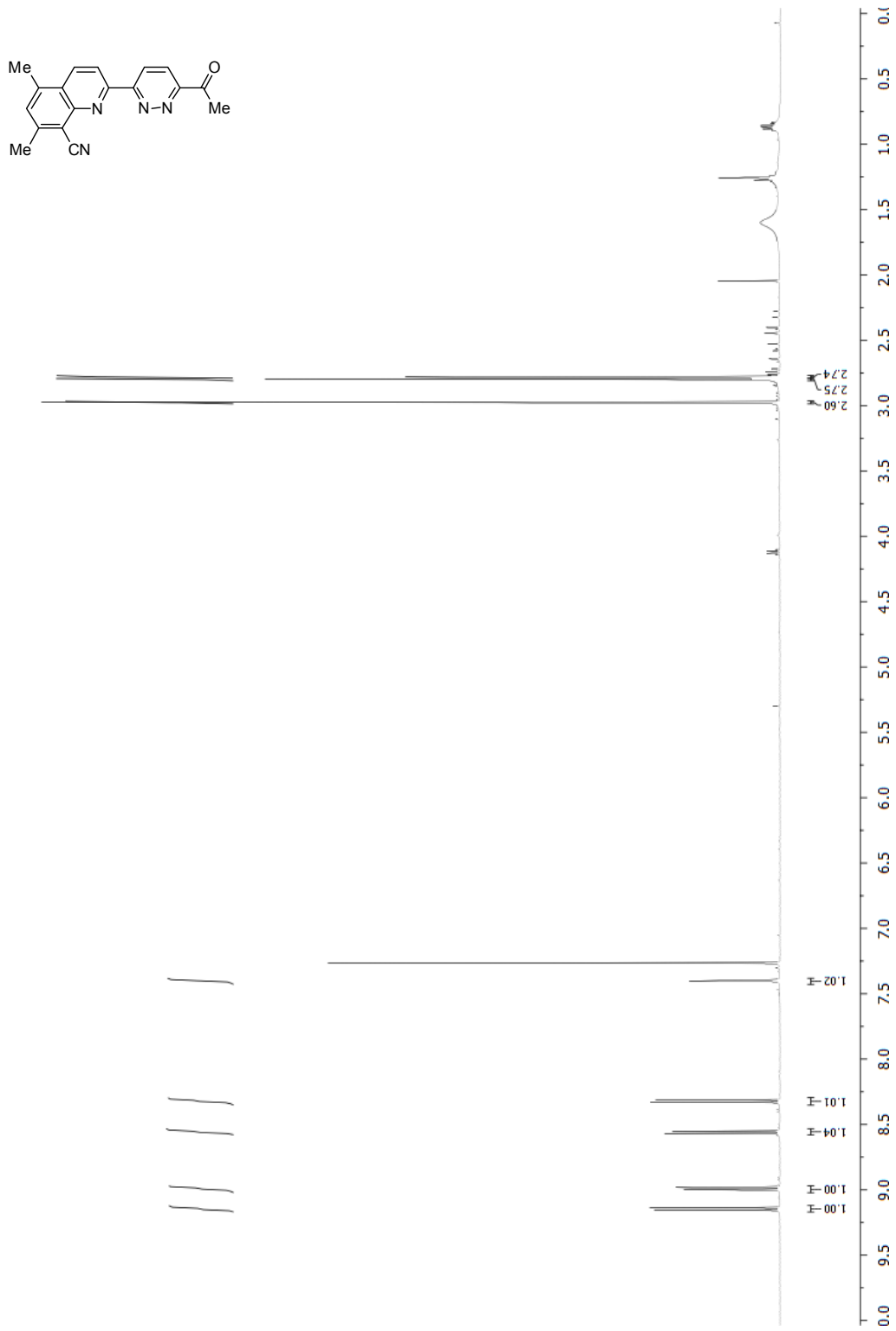
^{1}H-NMR of **3.2c-D3**

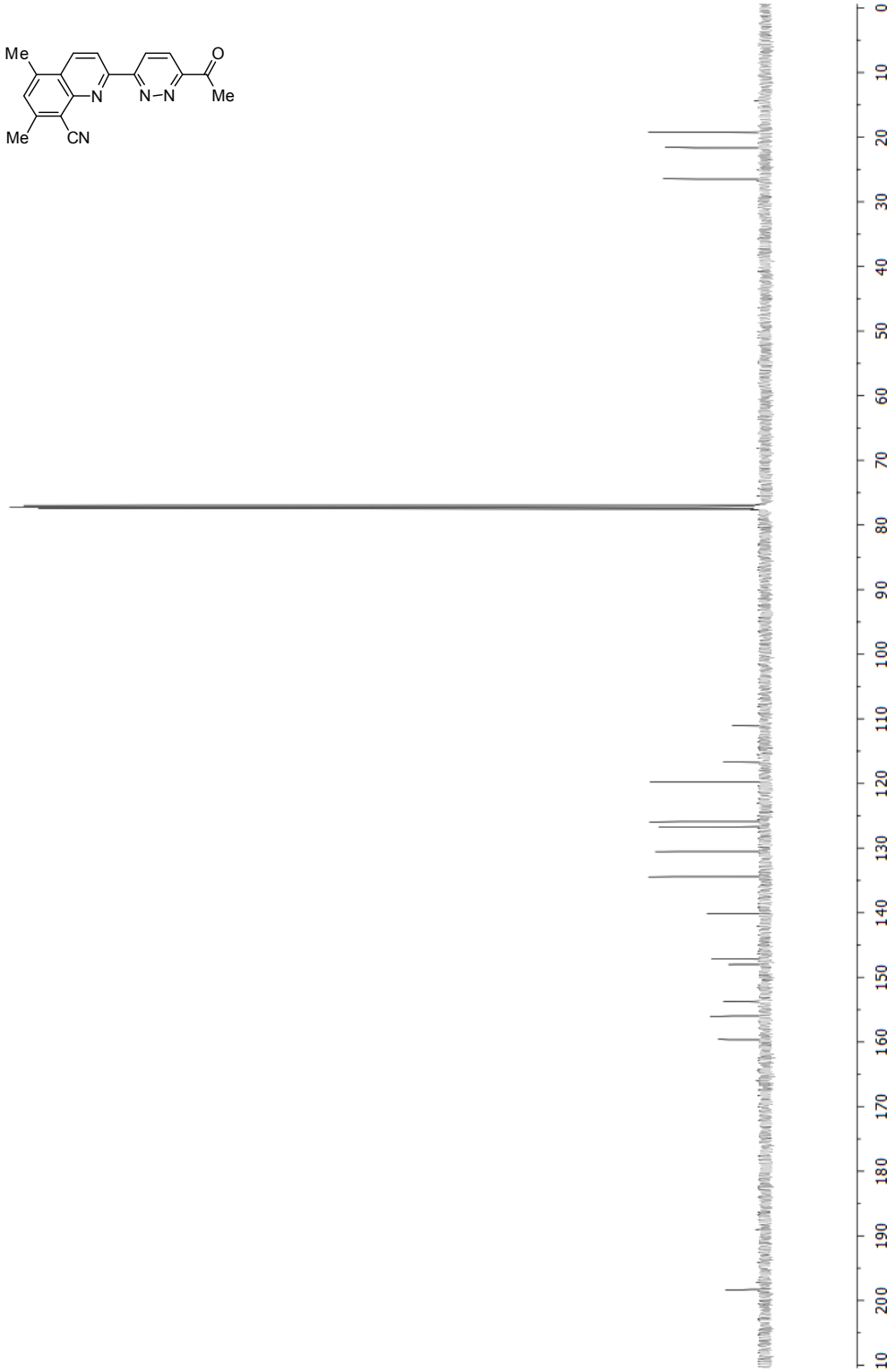


^{1}H-NMR of **3.2c-D4**

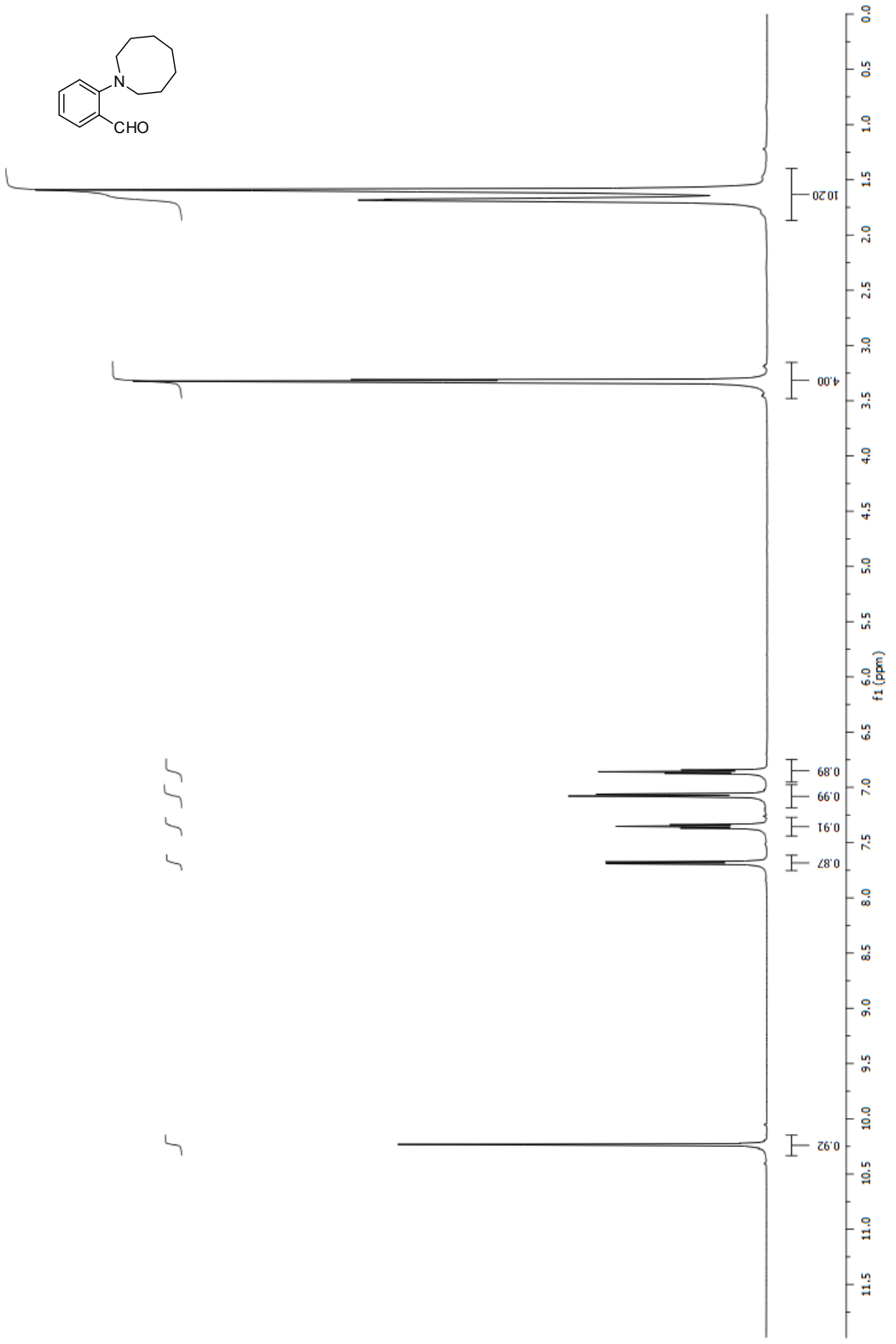


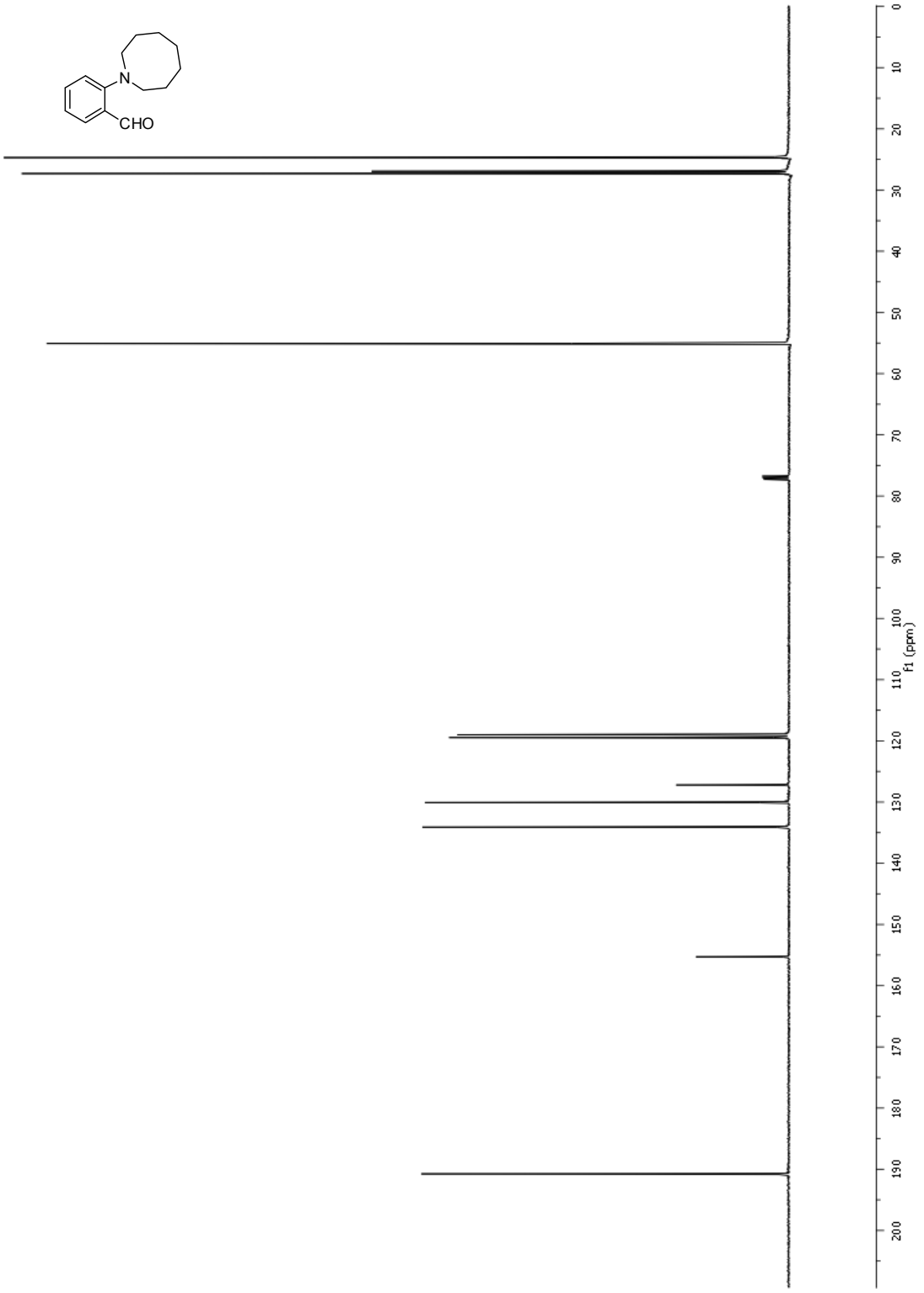
^{1}H–NMR and ^{13}C–NMR of **3.3**:



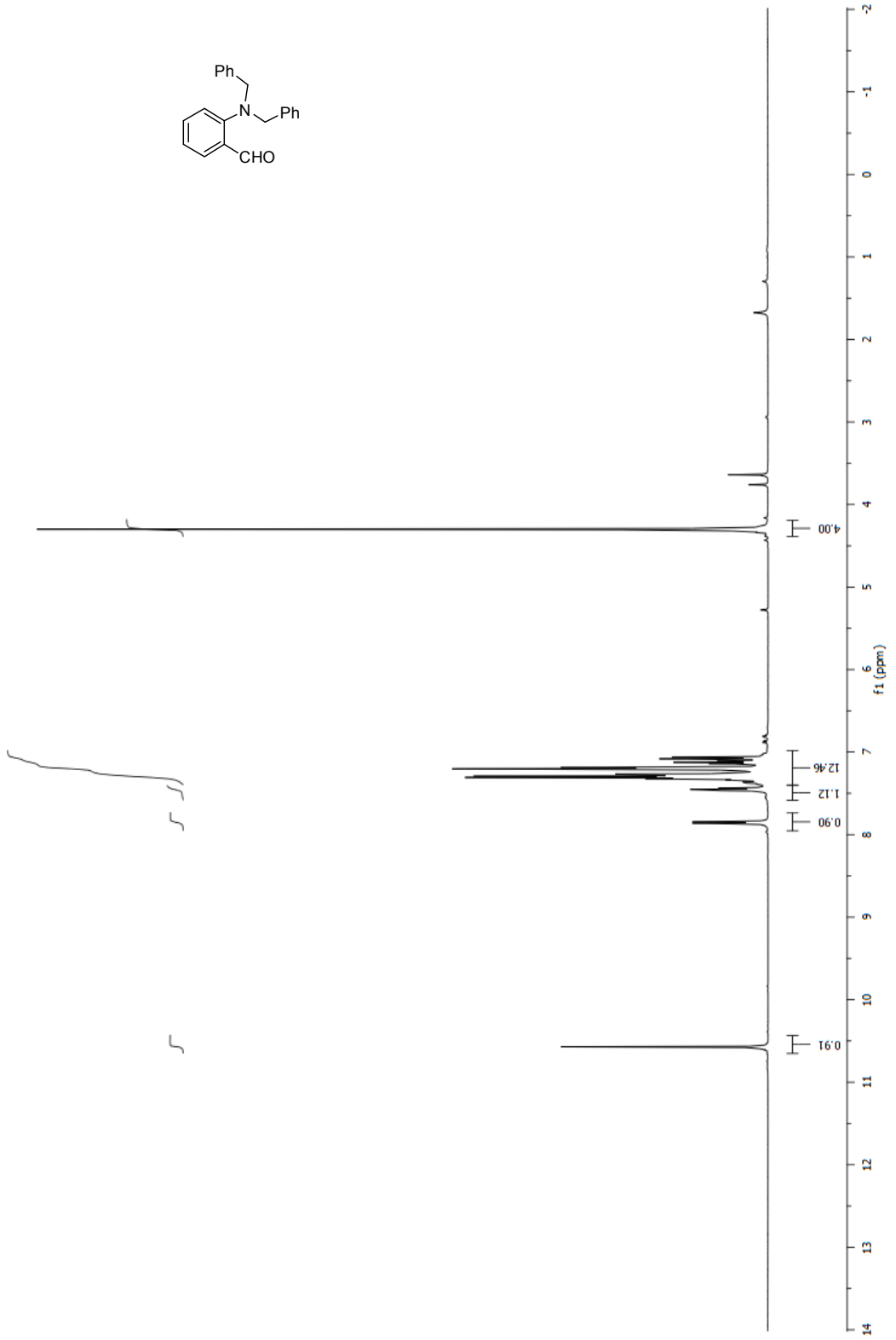

Me
O
N
N–N
Me
Me
CN
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
10

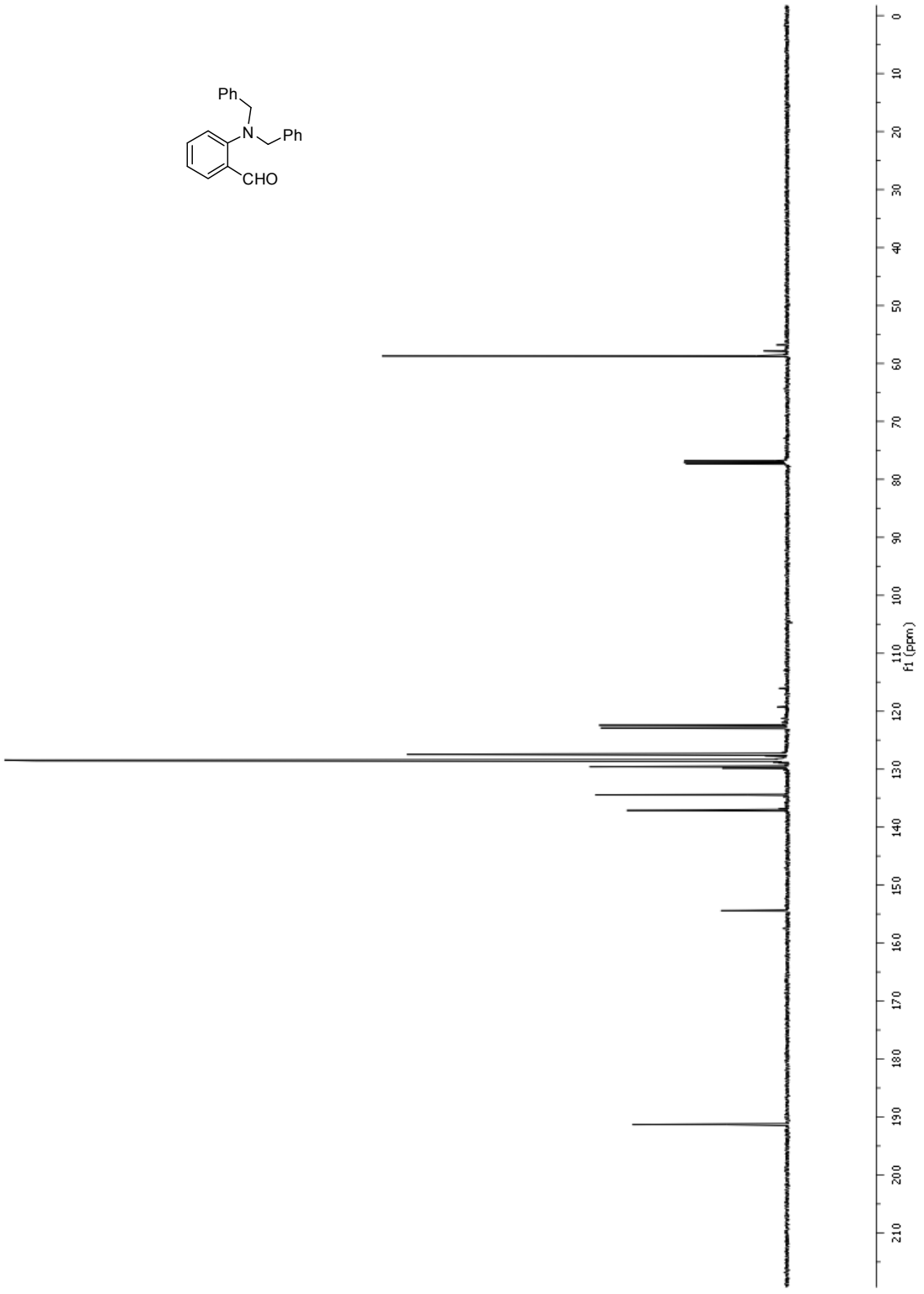
^{1}H–NMR and ^{13}C–NMR of **3.32d**:



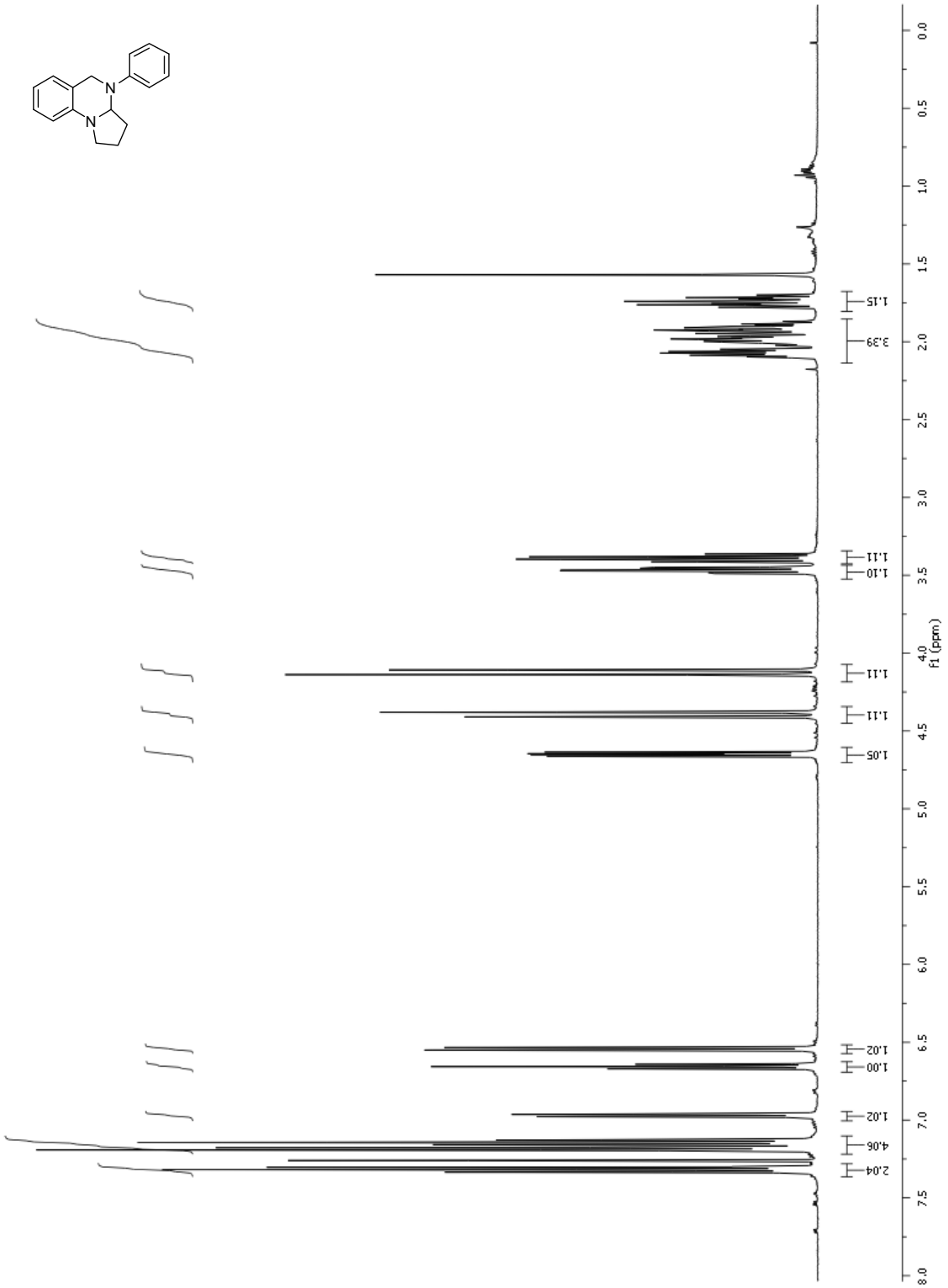

N
CHO
f1 (ppm)

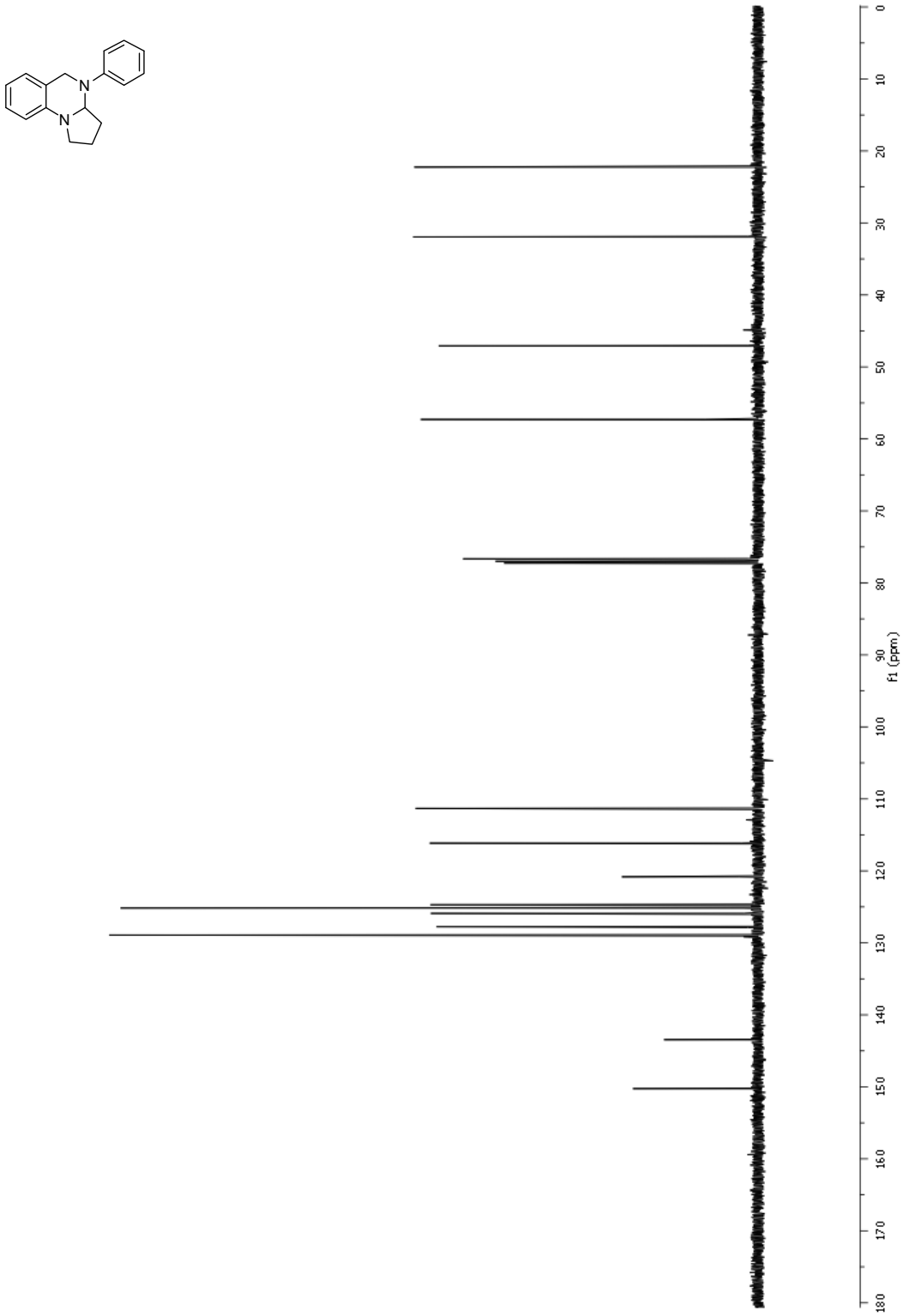
^{1}H–NMR and ^{13}C–NMR of **3.32k**:



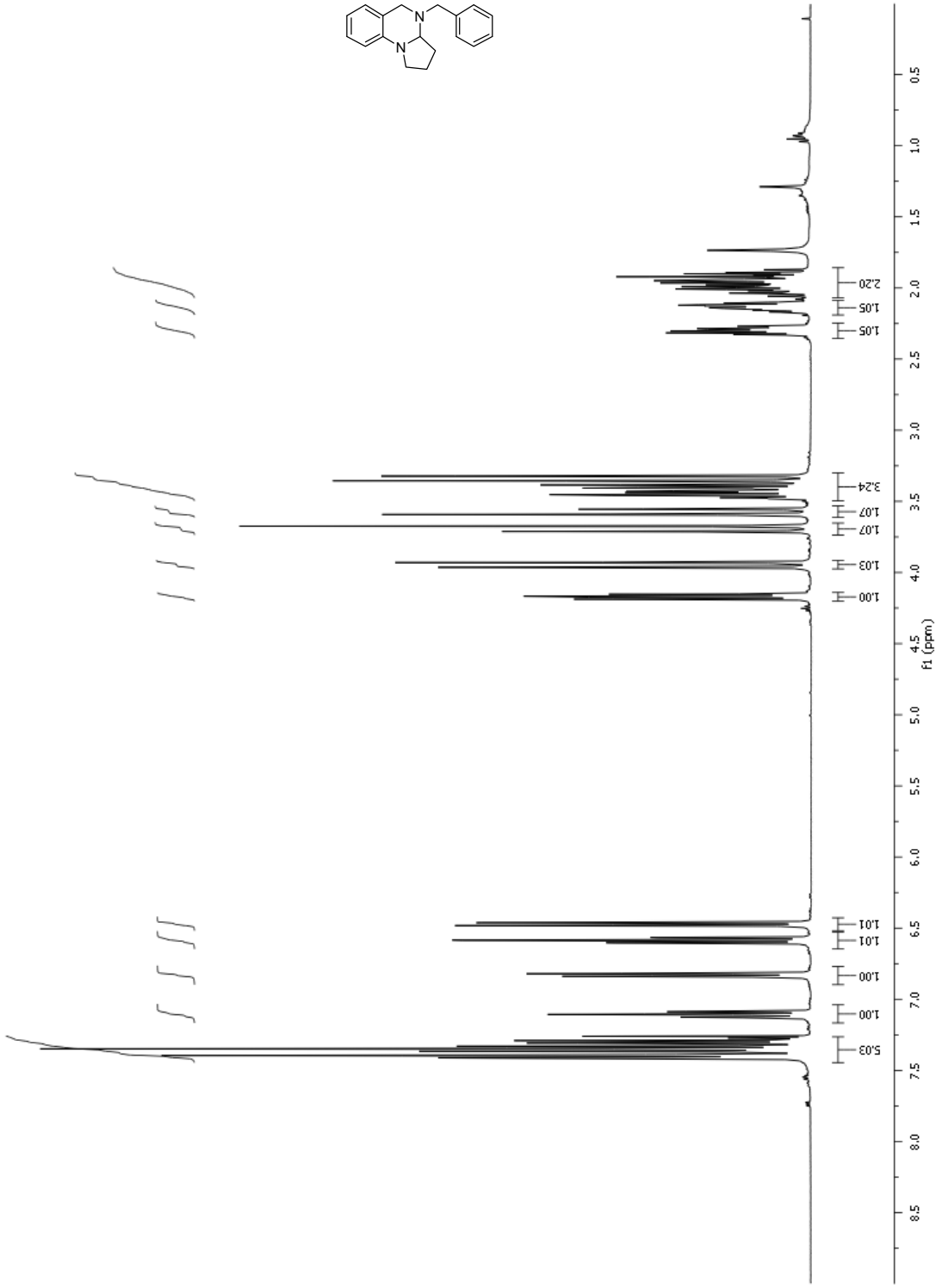

Ph
N
Ph
CHO
f1 (ppm)

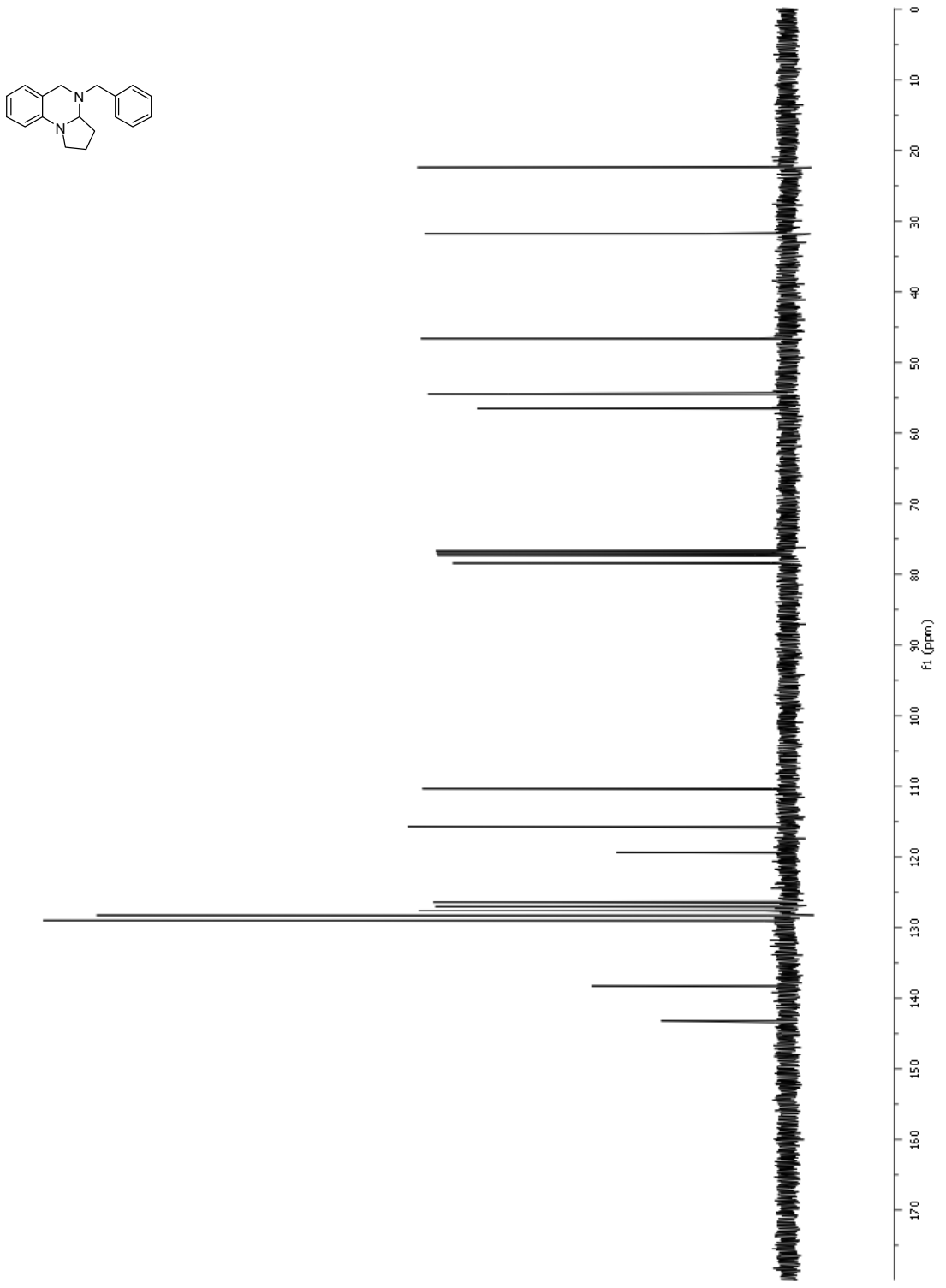
^{1}H–NMR and ^{13}C–NMR of **3.33a**:



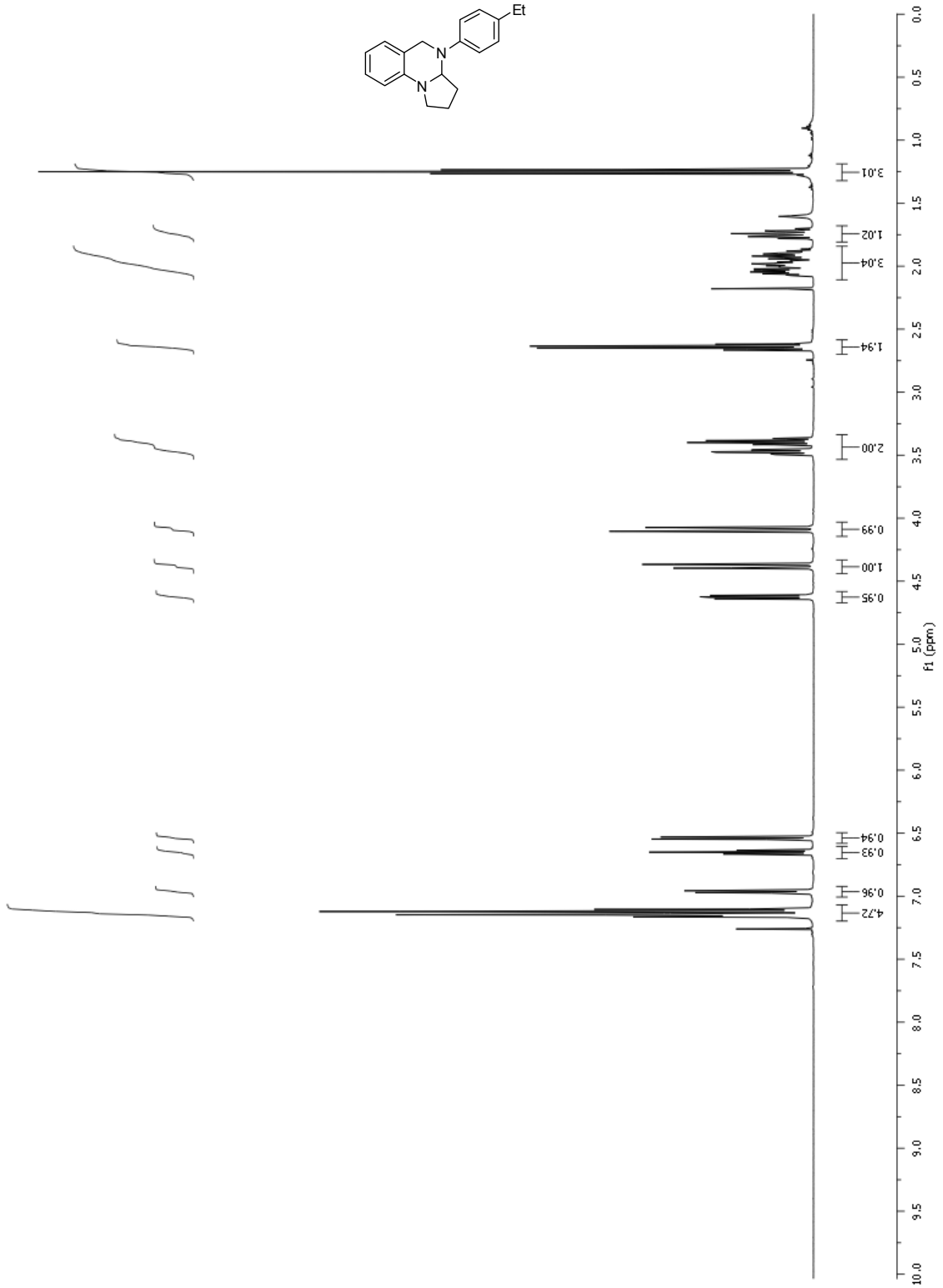

N
N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

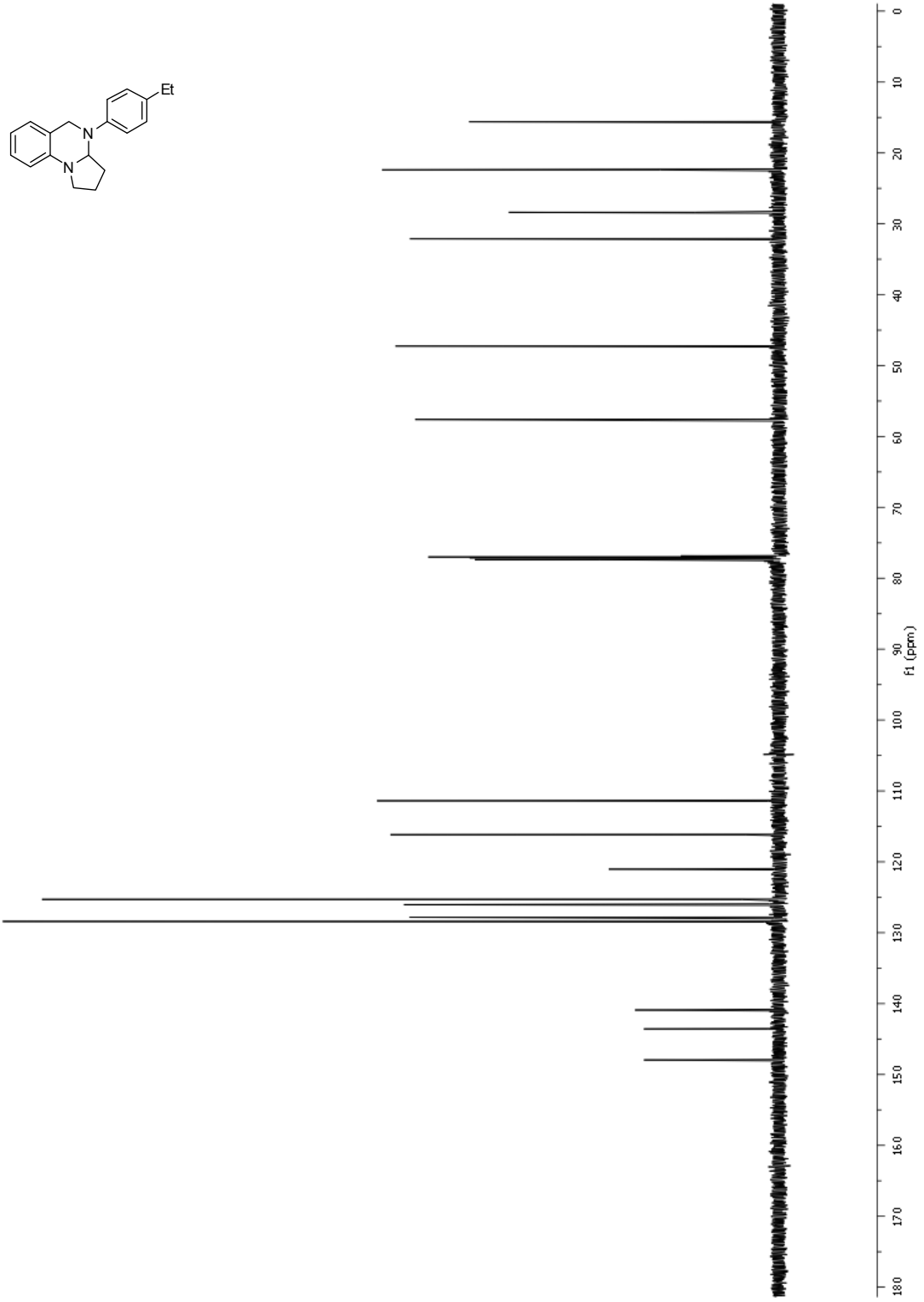
^{1}H–NMR and ^{13}C–NMR of **3.33b**:



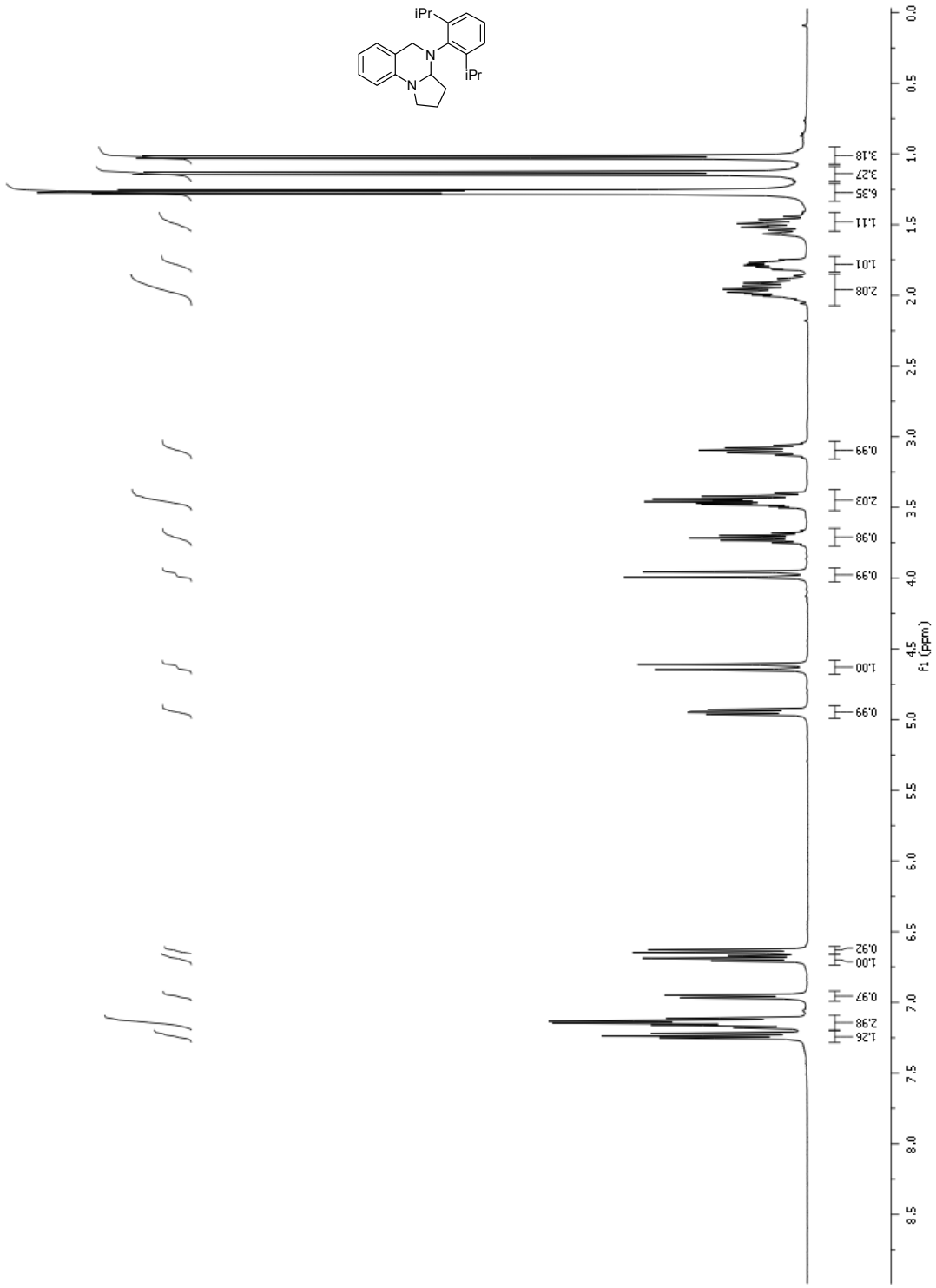

N
N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

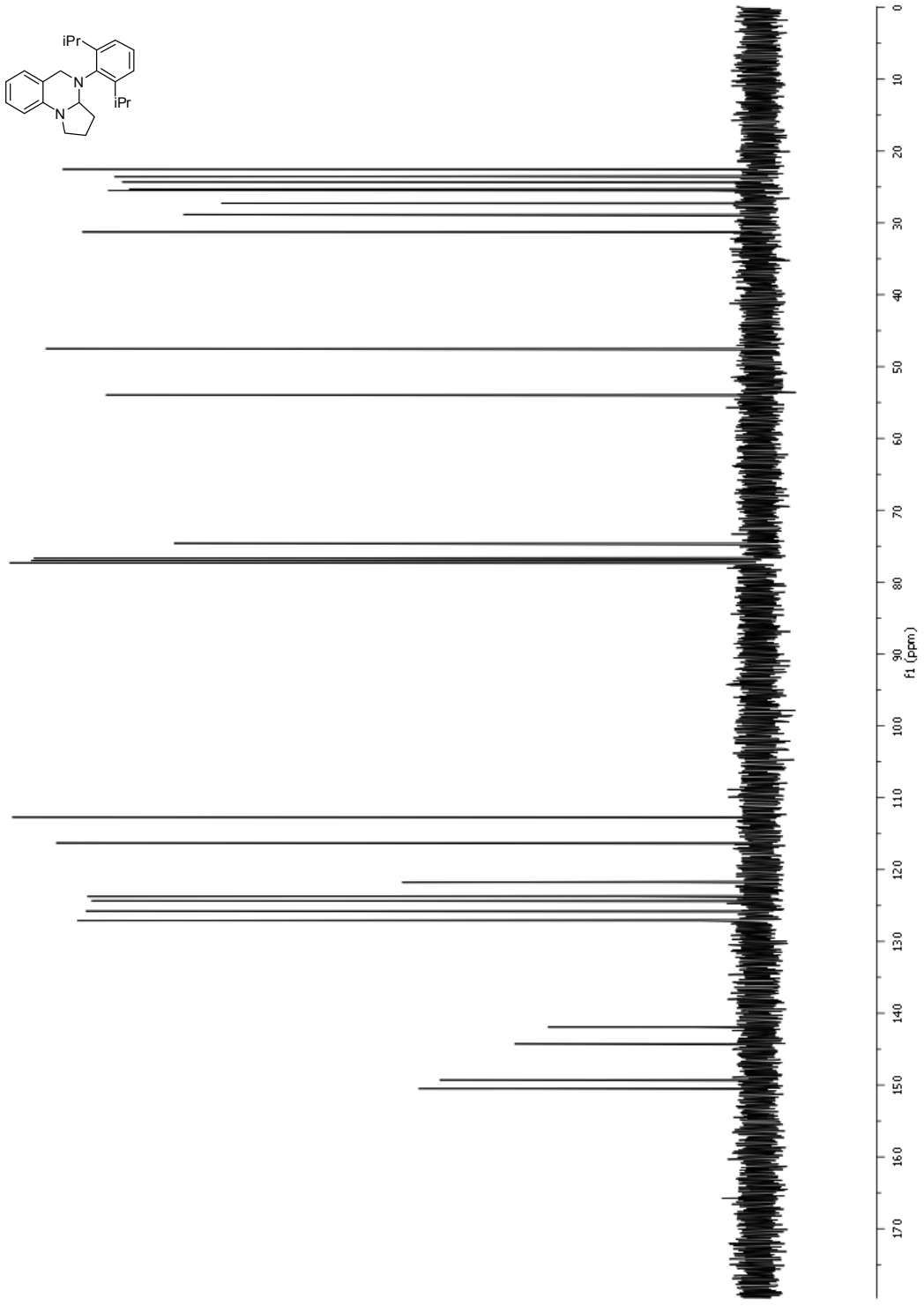
^{1}H–NMR and ^{13}C–NMR of **3.33c**:



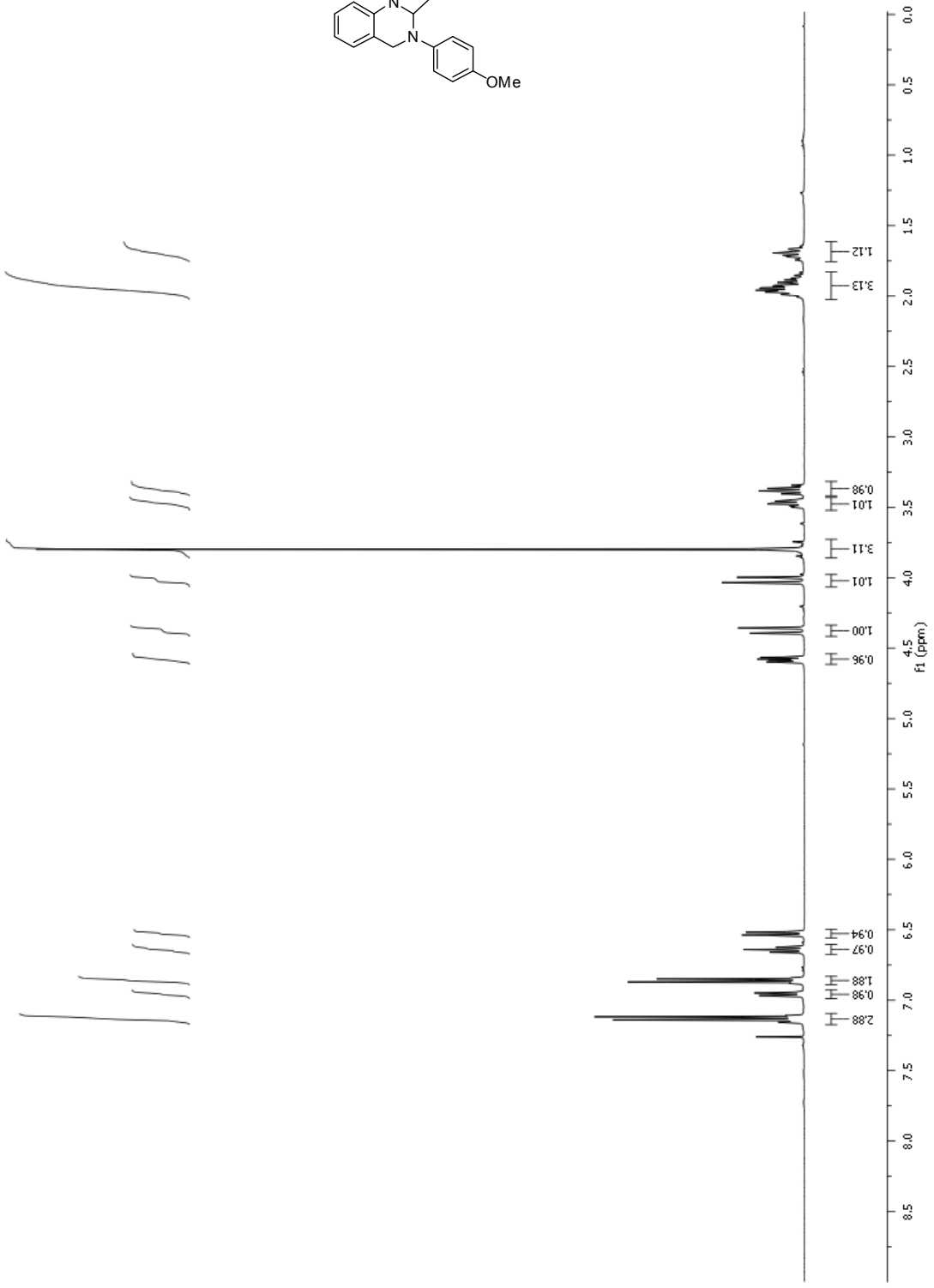

Et
N
N
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

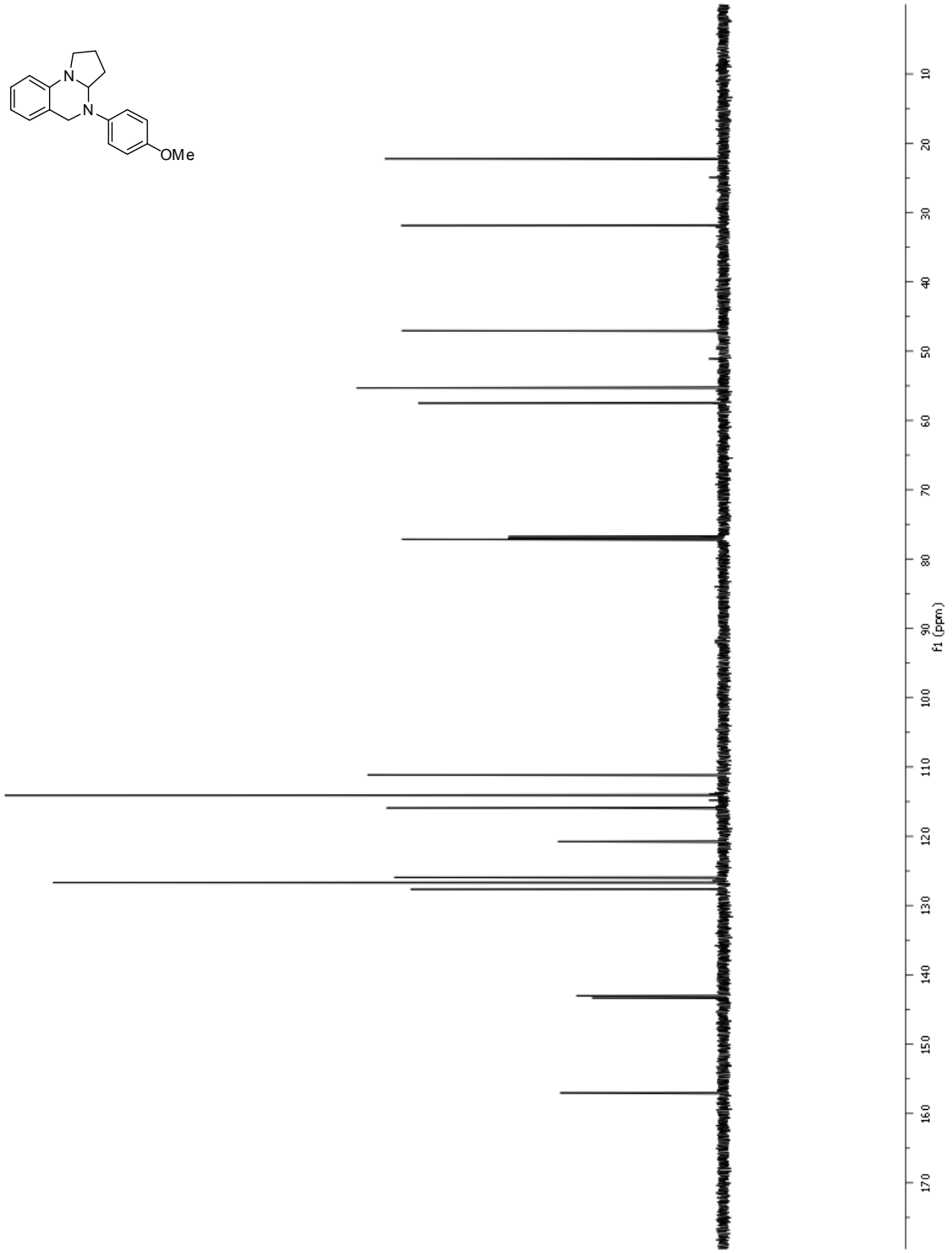
^{1}H–NMR and ^{13}C–NMR of **3.33d**:



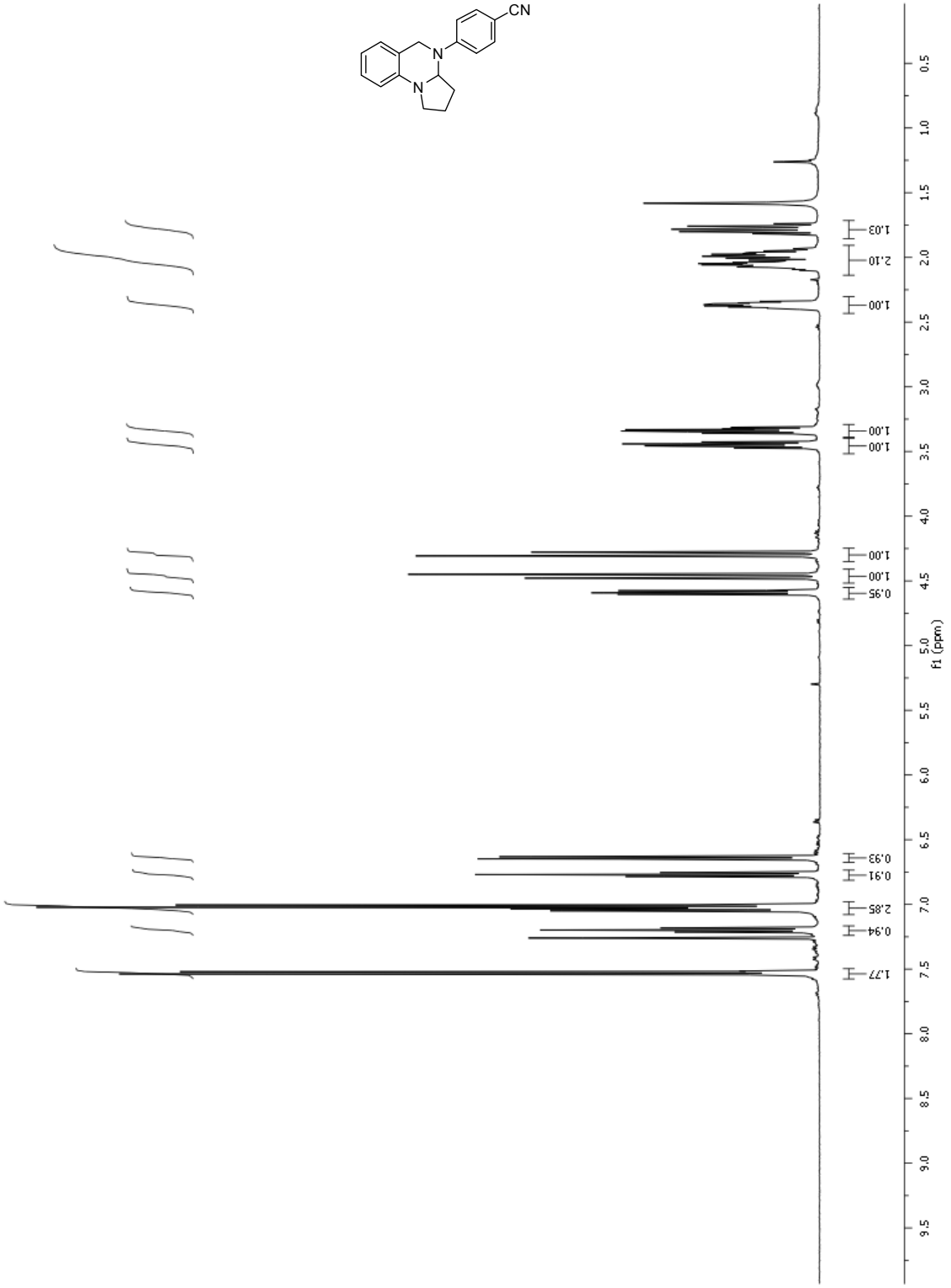

iPr
iPr
N
N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

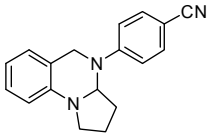
^{1}H–NMR and ^{13}C–NMR of **3.33e**:

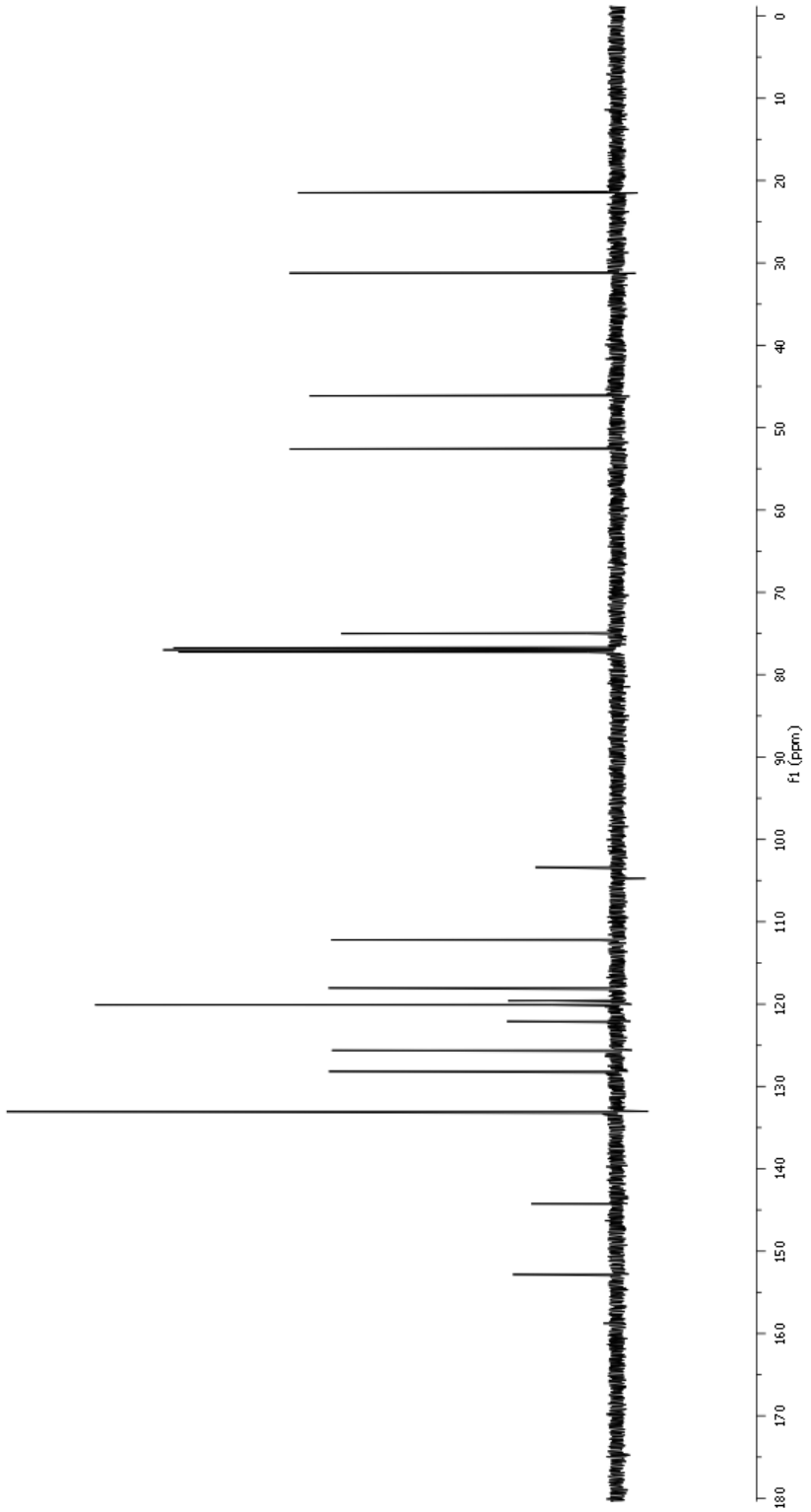



N
N
OMe
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

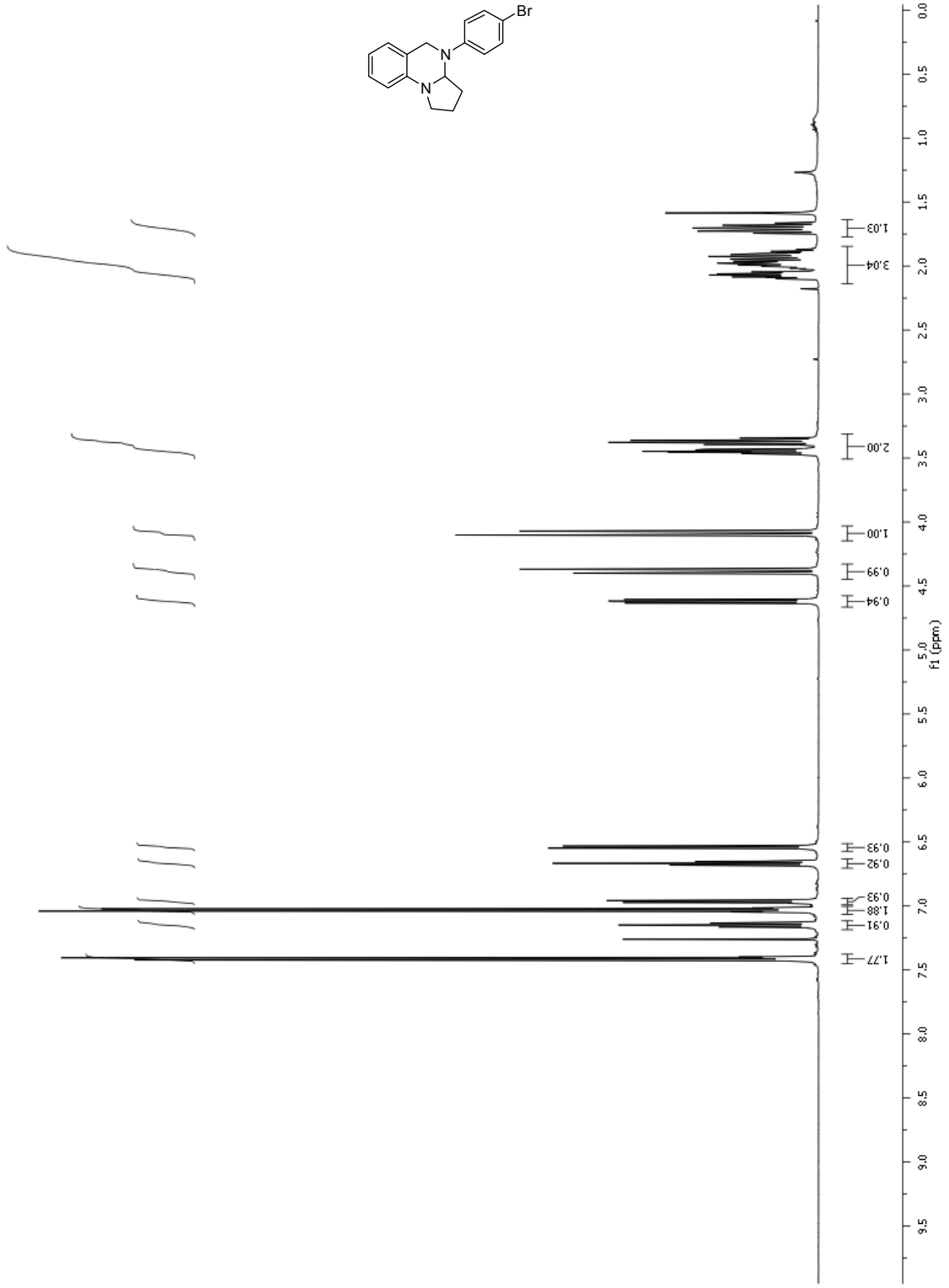
^{1}H–NMR and ^{13}C–NMR of **3.33f**:

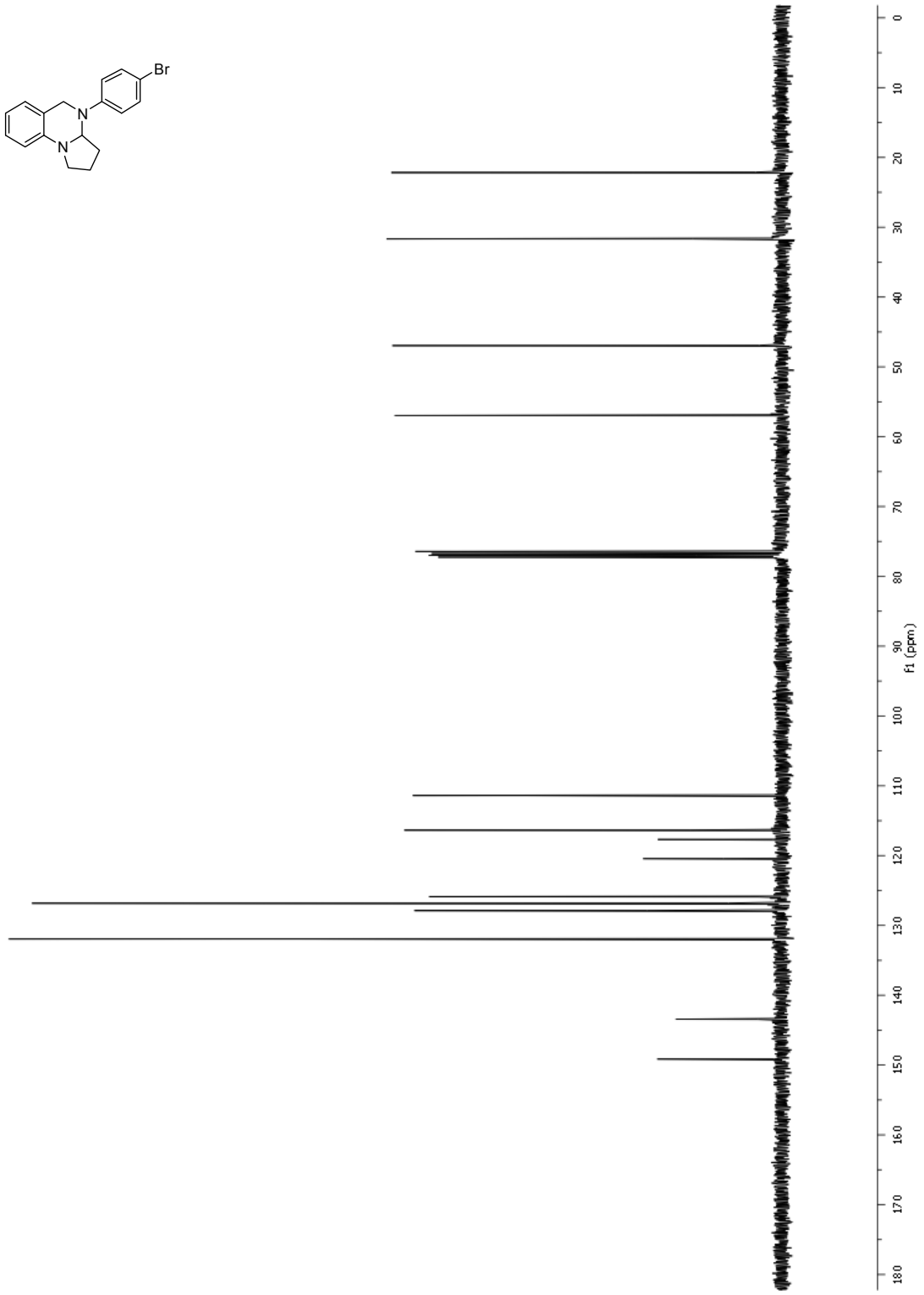



CN
N
N

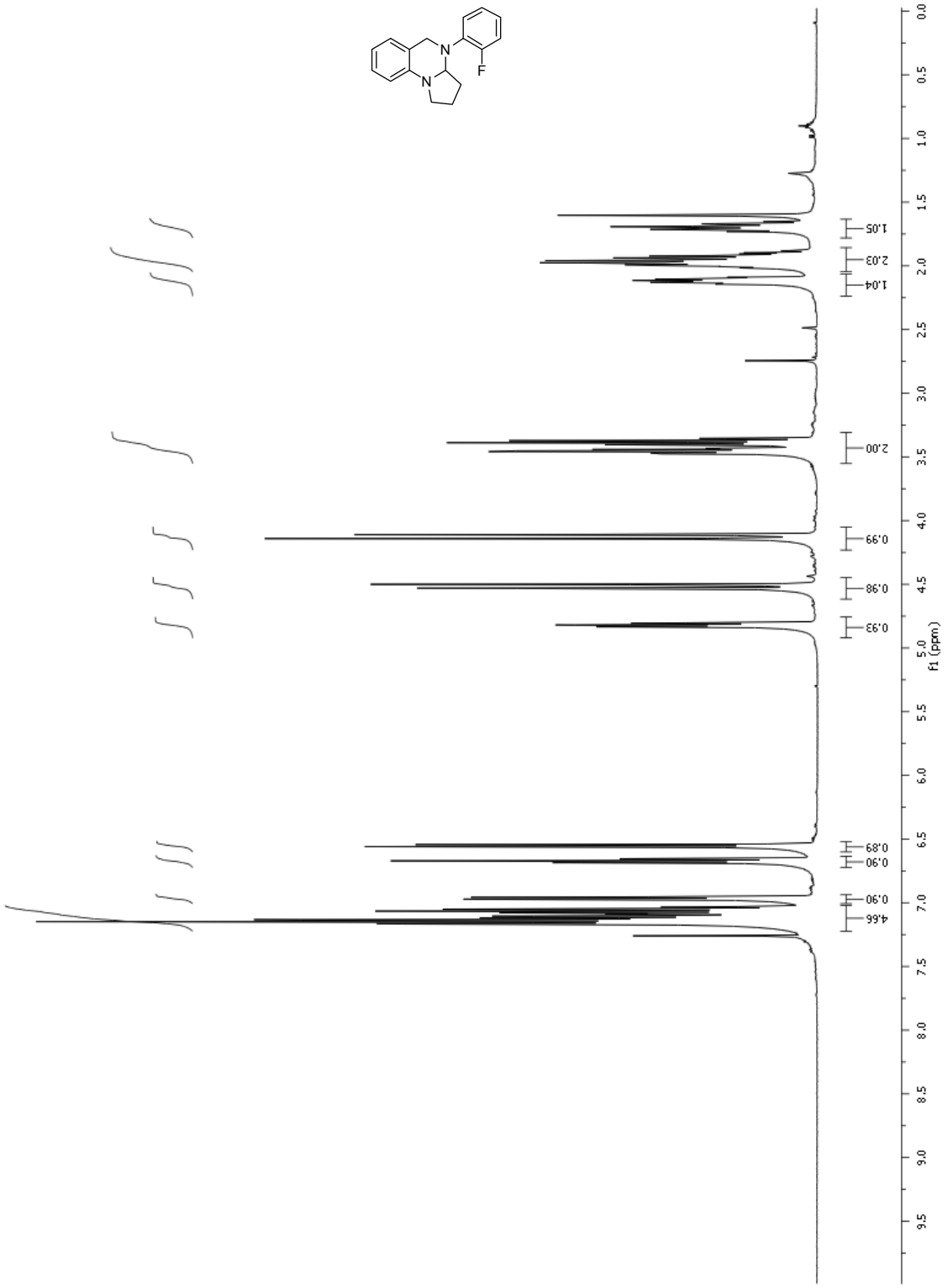

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

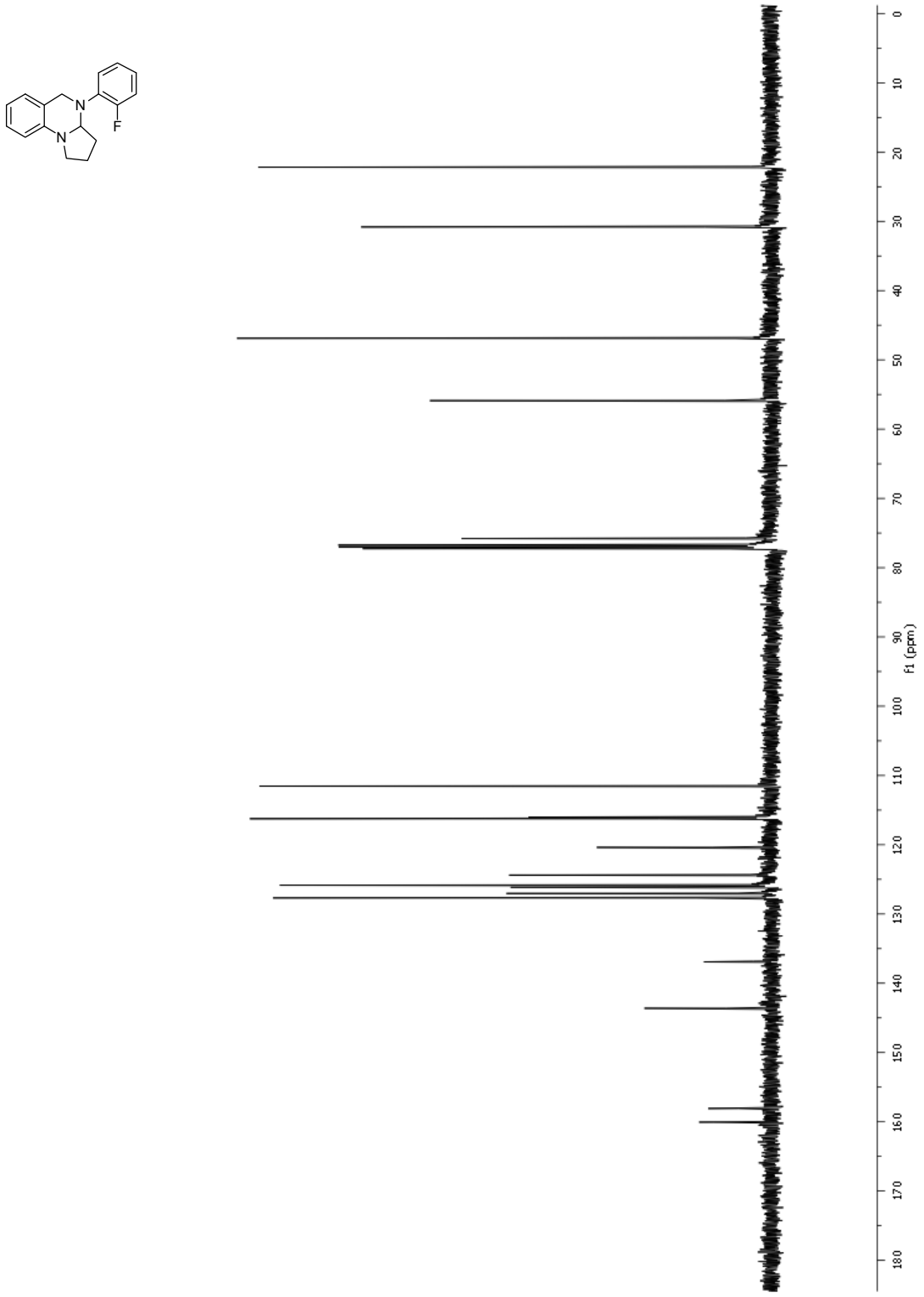
^{1}H–NMR and ^{13}C–NMR of **3.33g**:



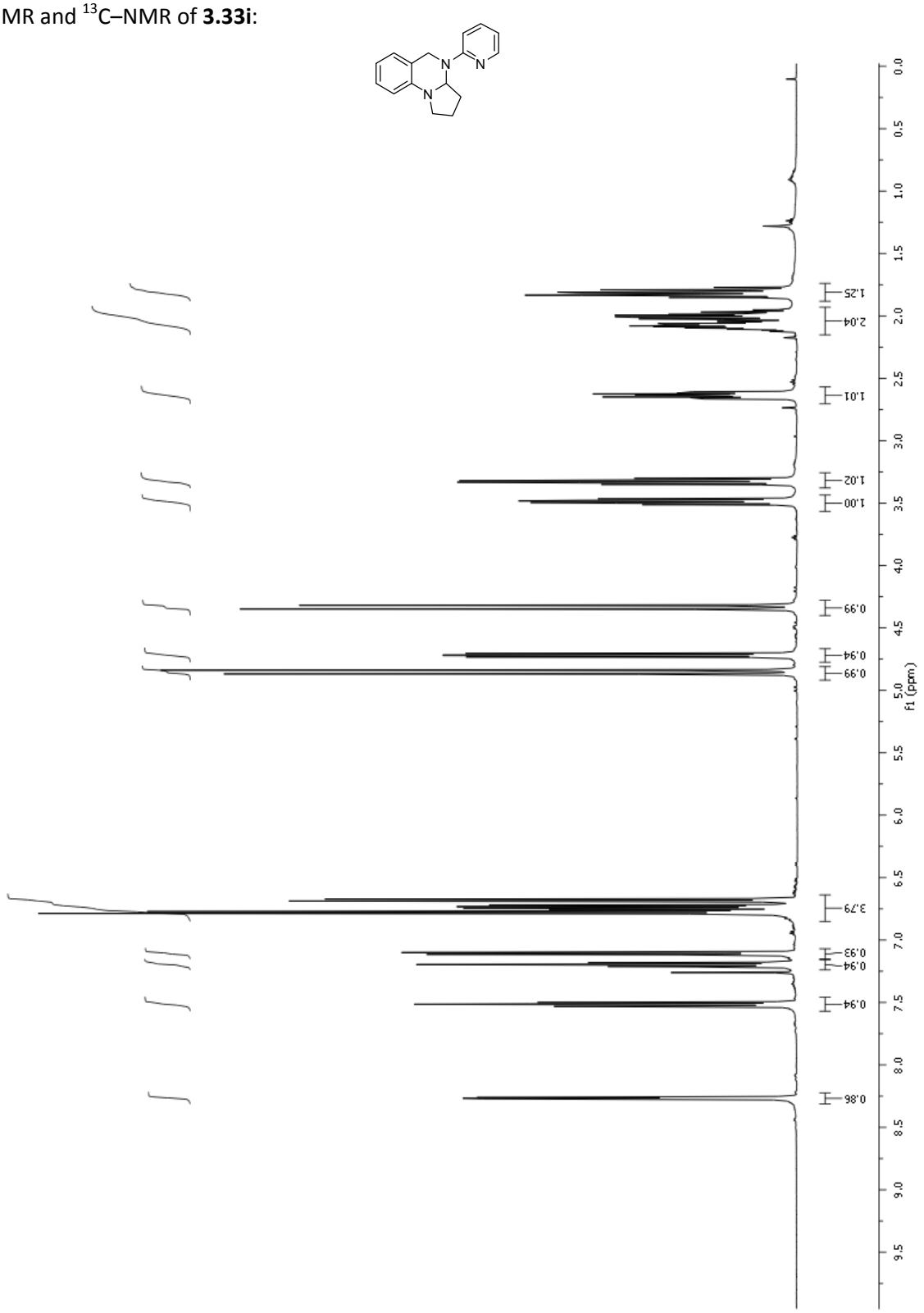

Br
N
N
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

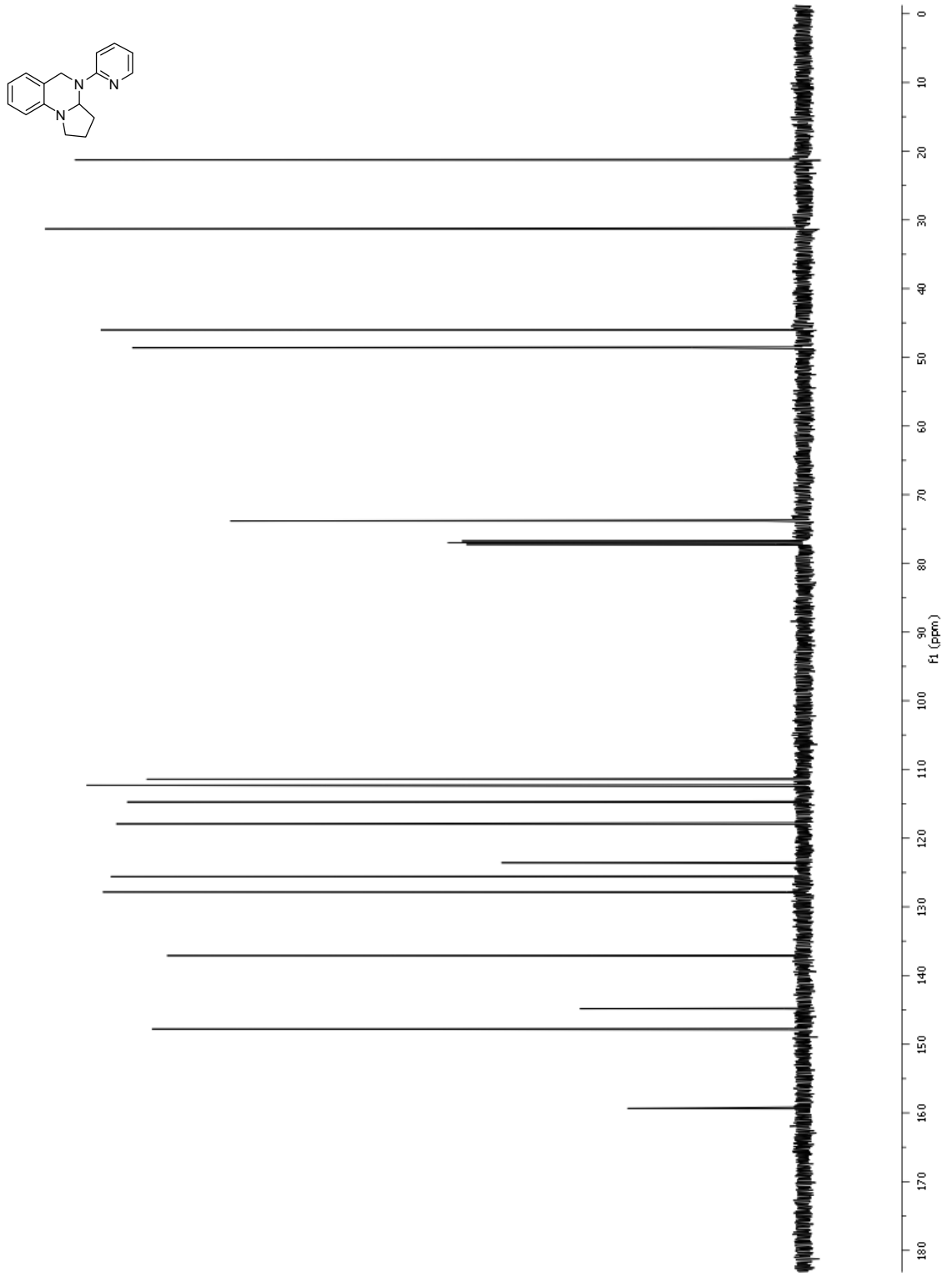
^{1}H–NMR and ^{13}C–NMR of **3.33h**:



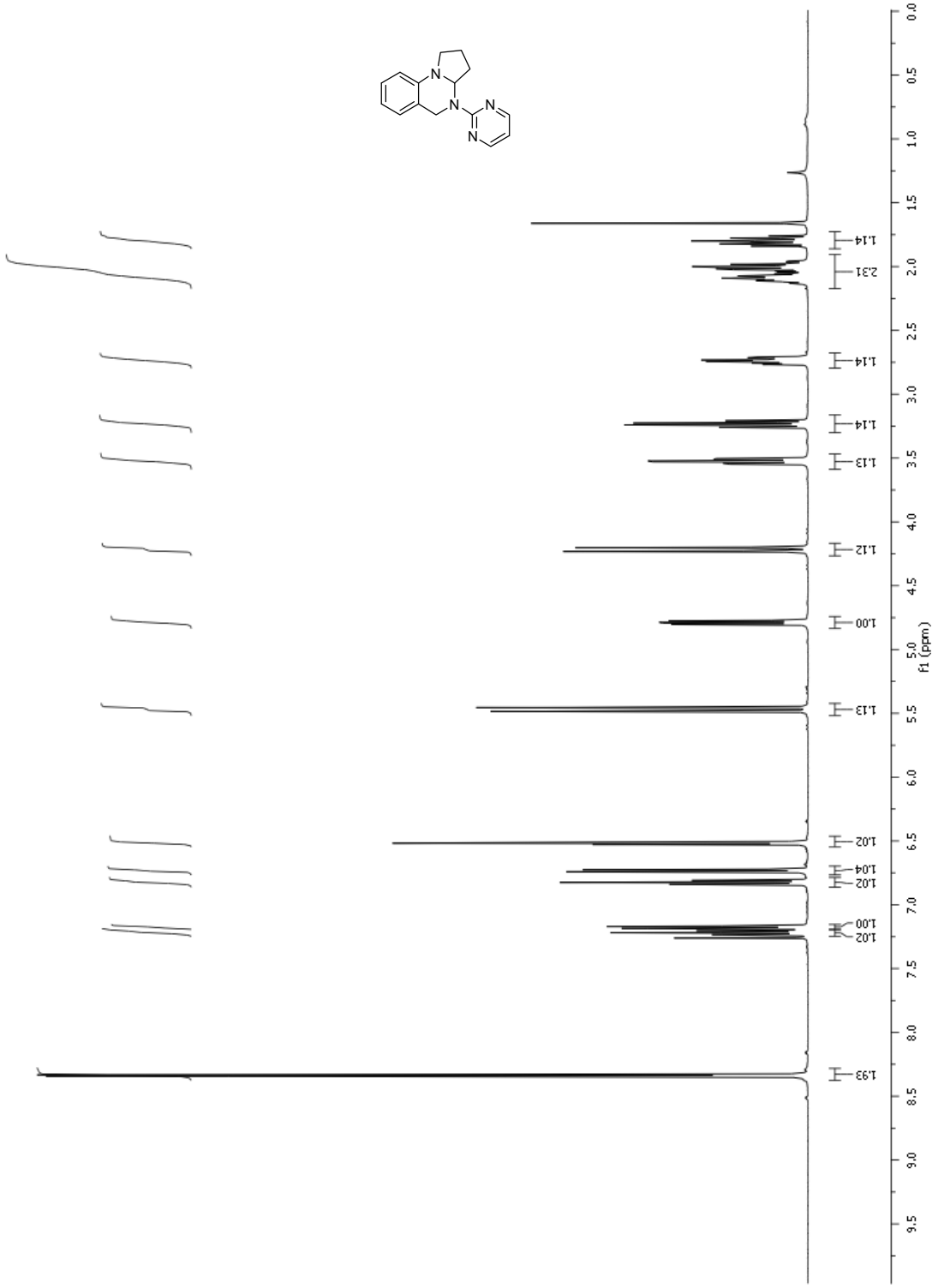

N
N
F
f1 (ppm)

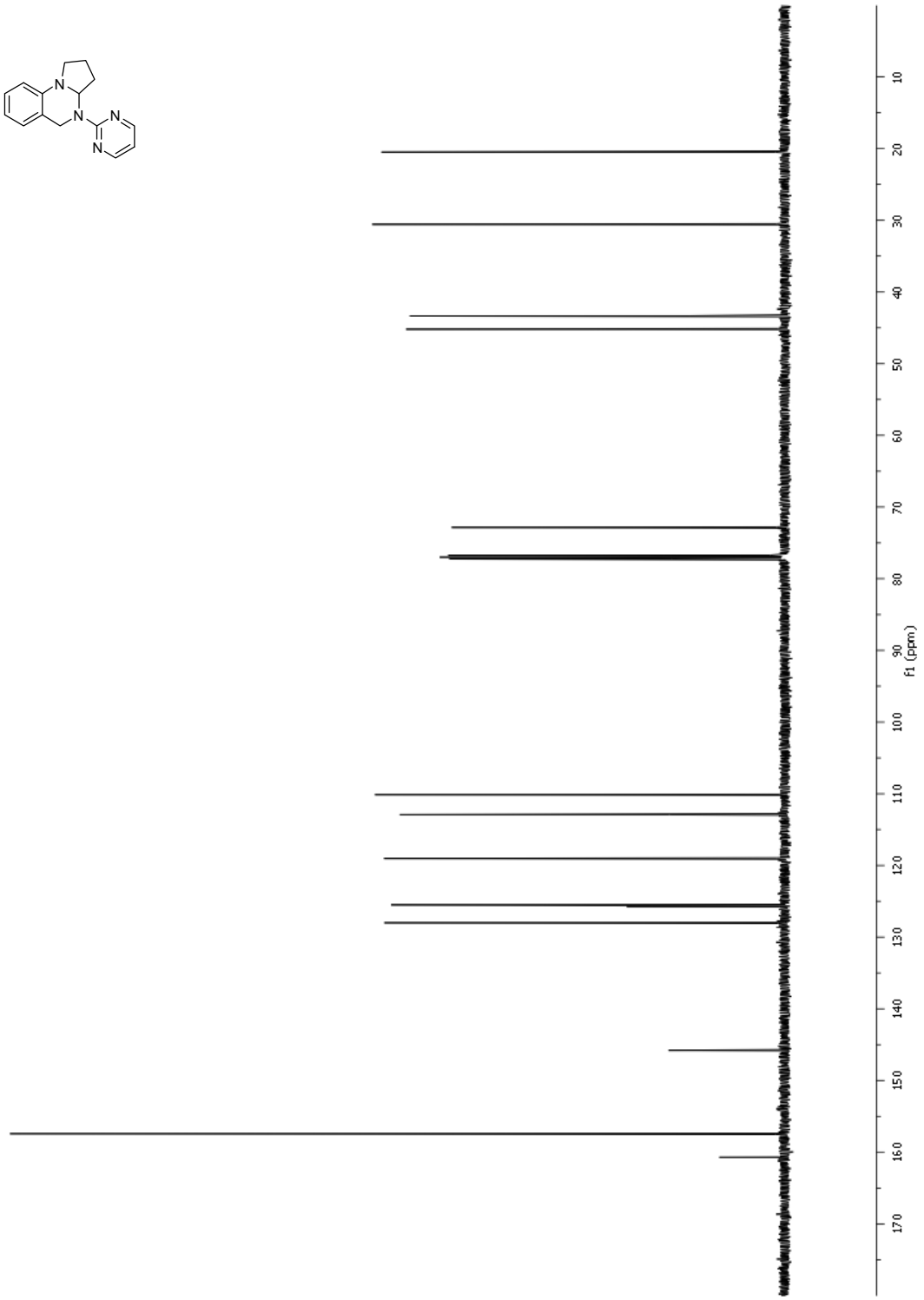
^{1}H–NMR and ^{13}C–NMR of **3.33i**:



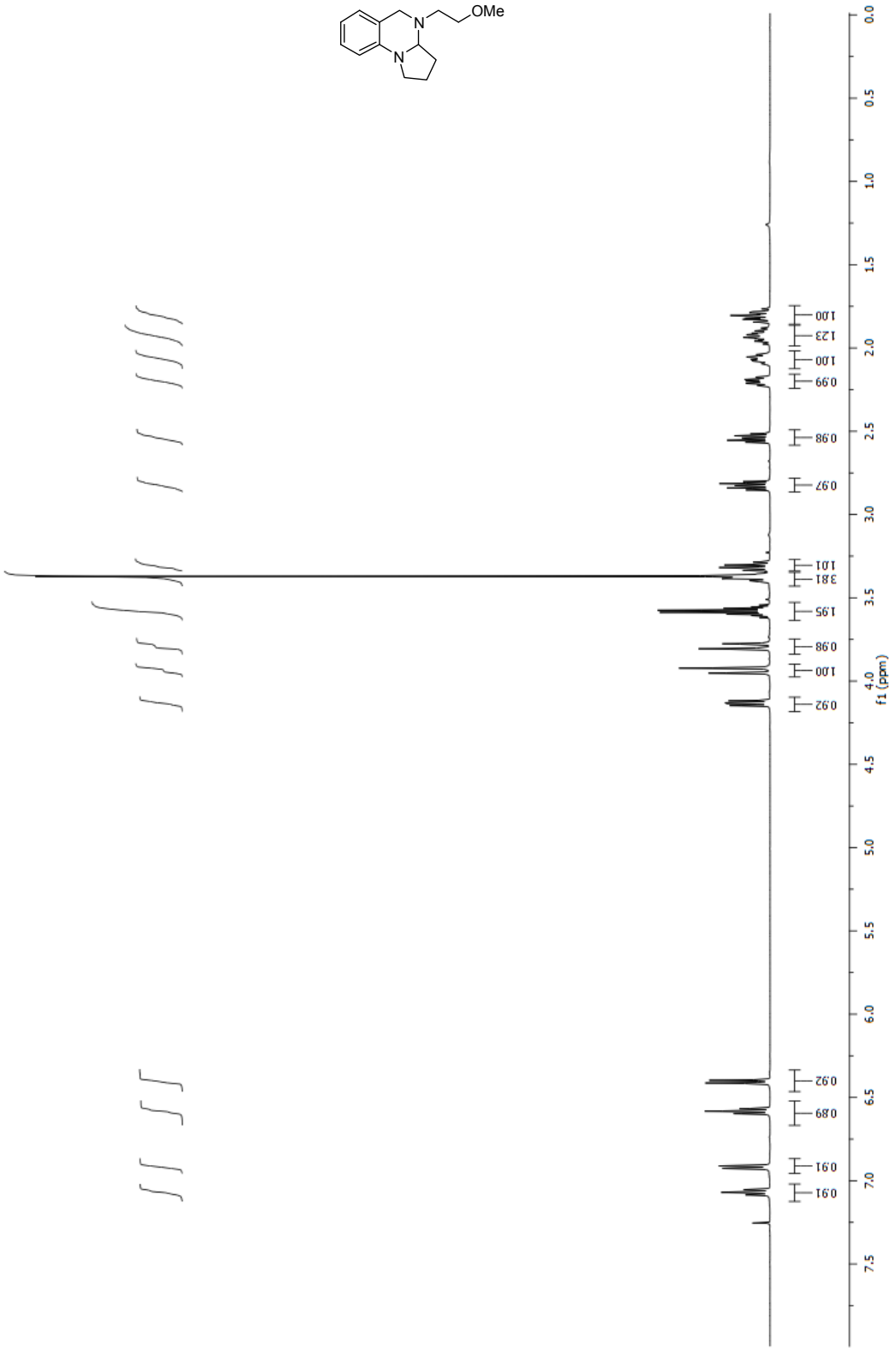

N
N
N
0
10
20
30
40
50
60
70
80
90
f1 (ppm)
100
110
120
130
140
150
160
170
180

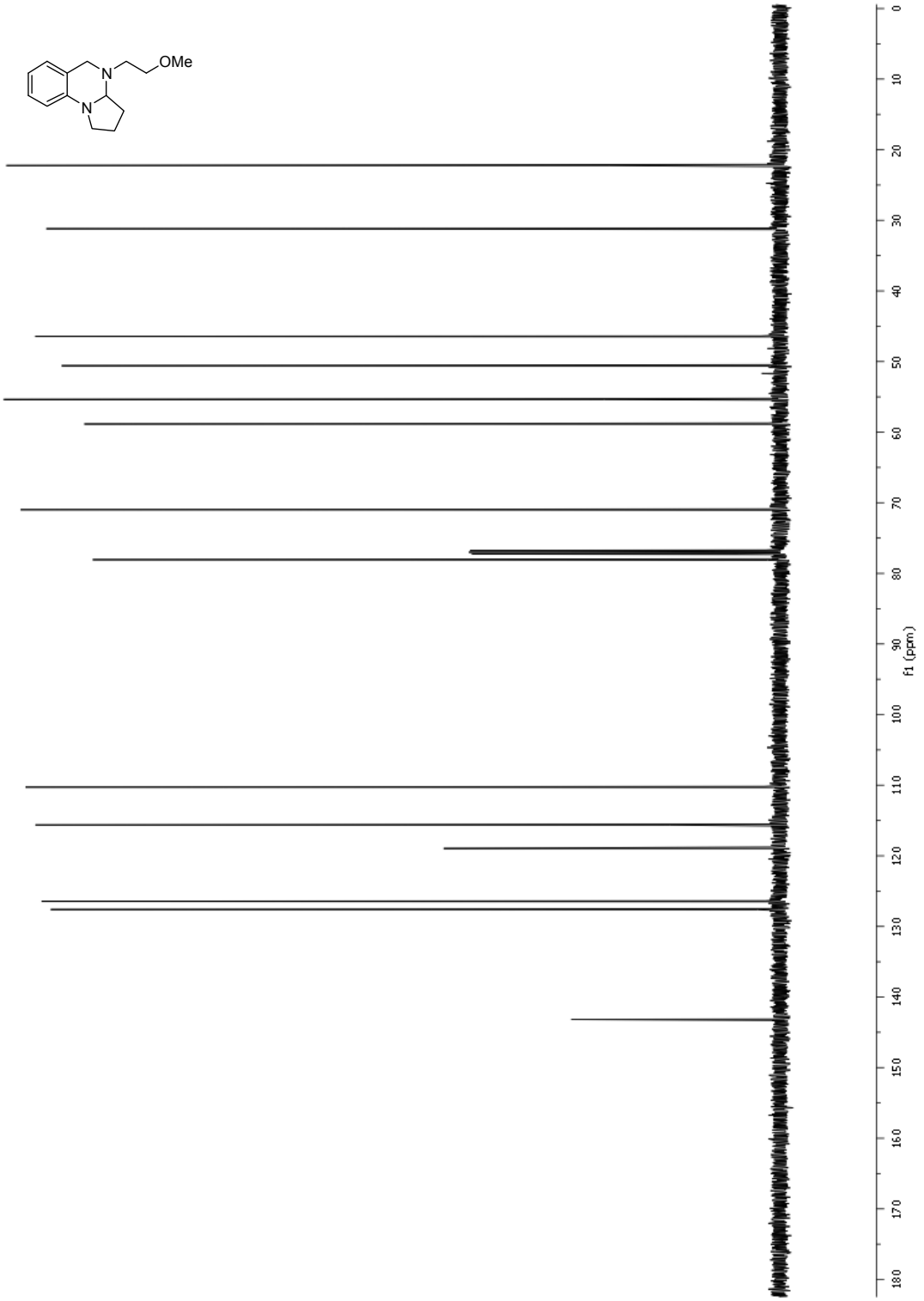
^{1}H–NMR and ^{13}C–NMR of **3.33j**:



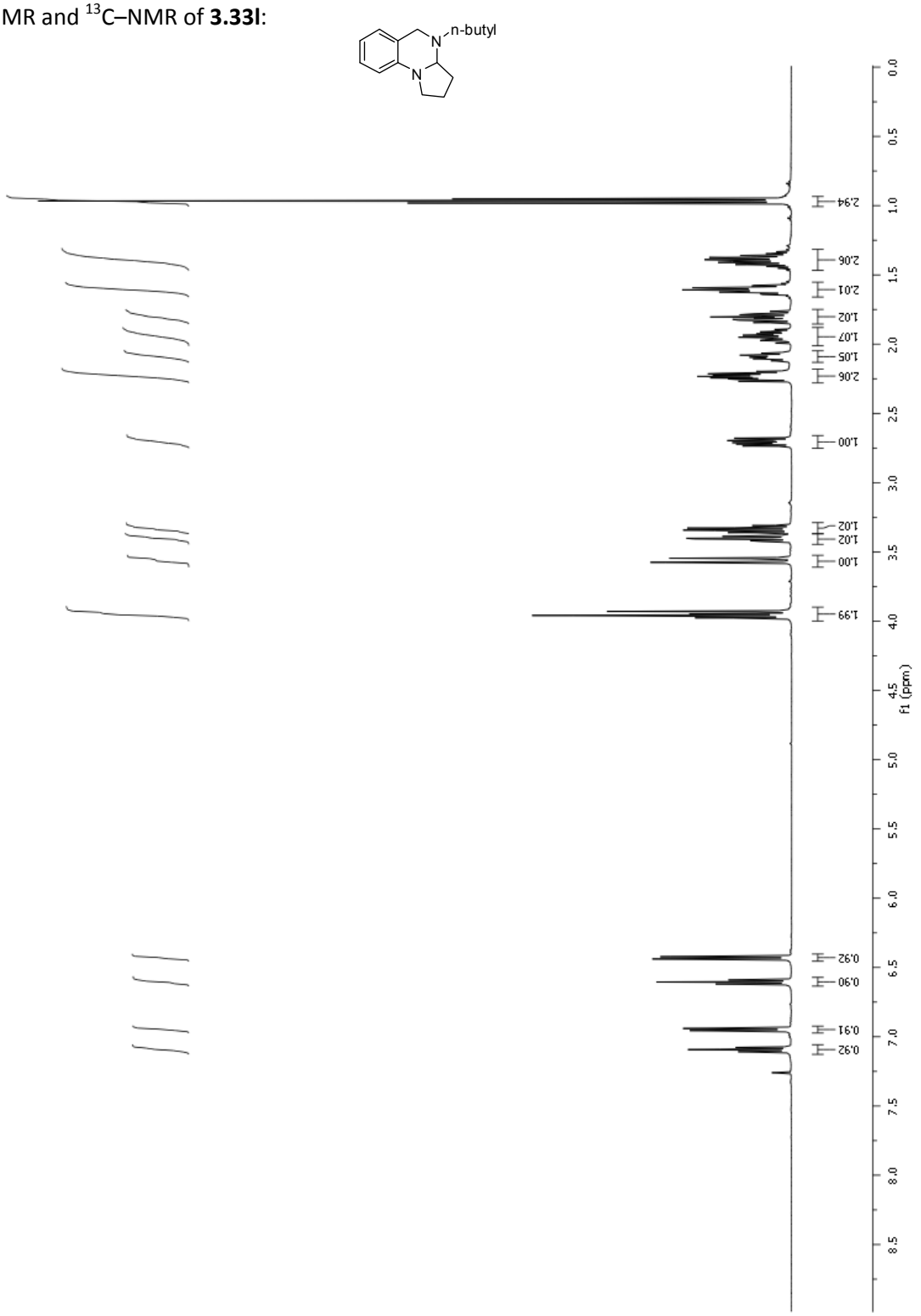

N
N
N
N
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
F1 (ppm)

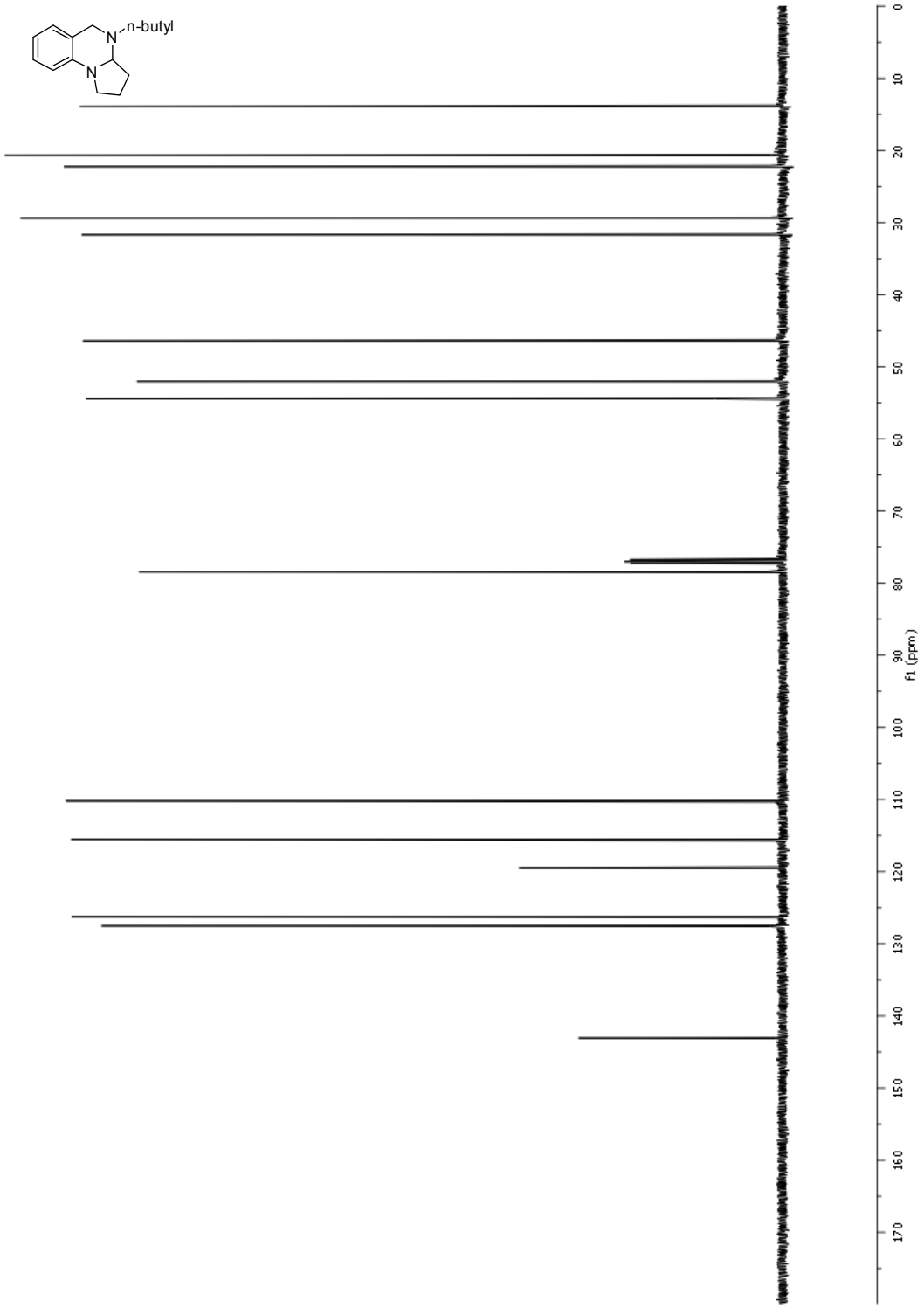
^{1}H–NMR and ^{13}C–NMR of **3.33k**:



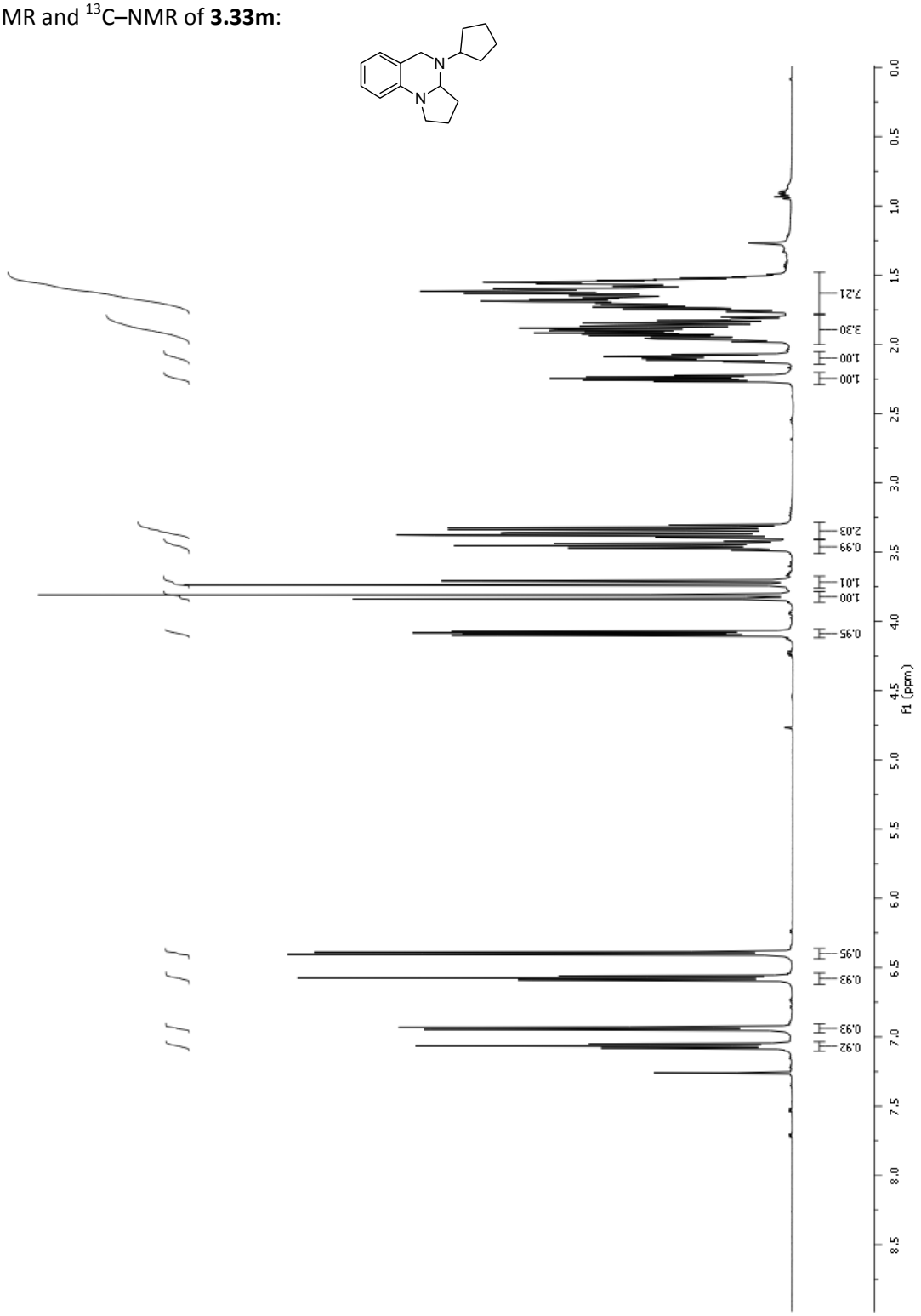

OMe
N
N
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

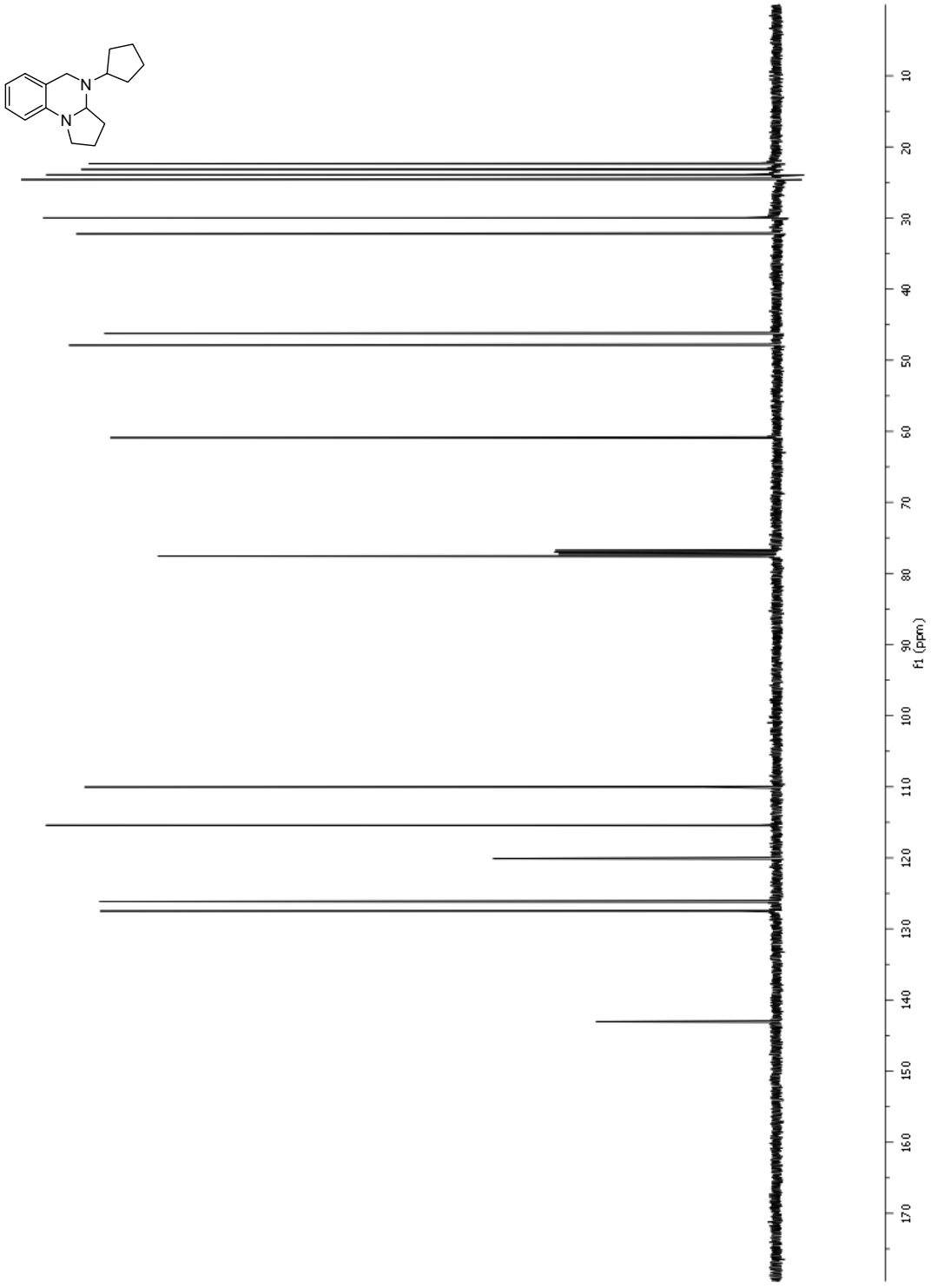
^{1}H–NMR and ^{13}C–NMR of **3.33l**:



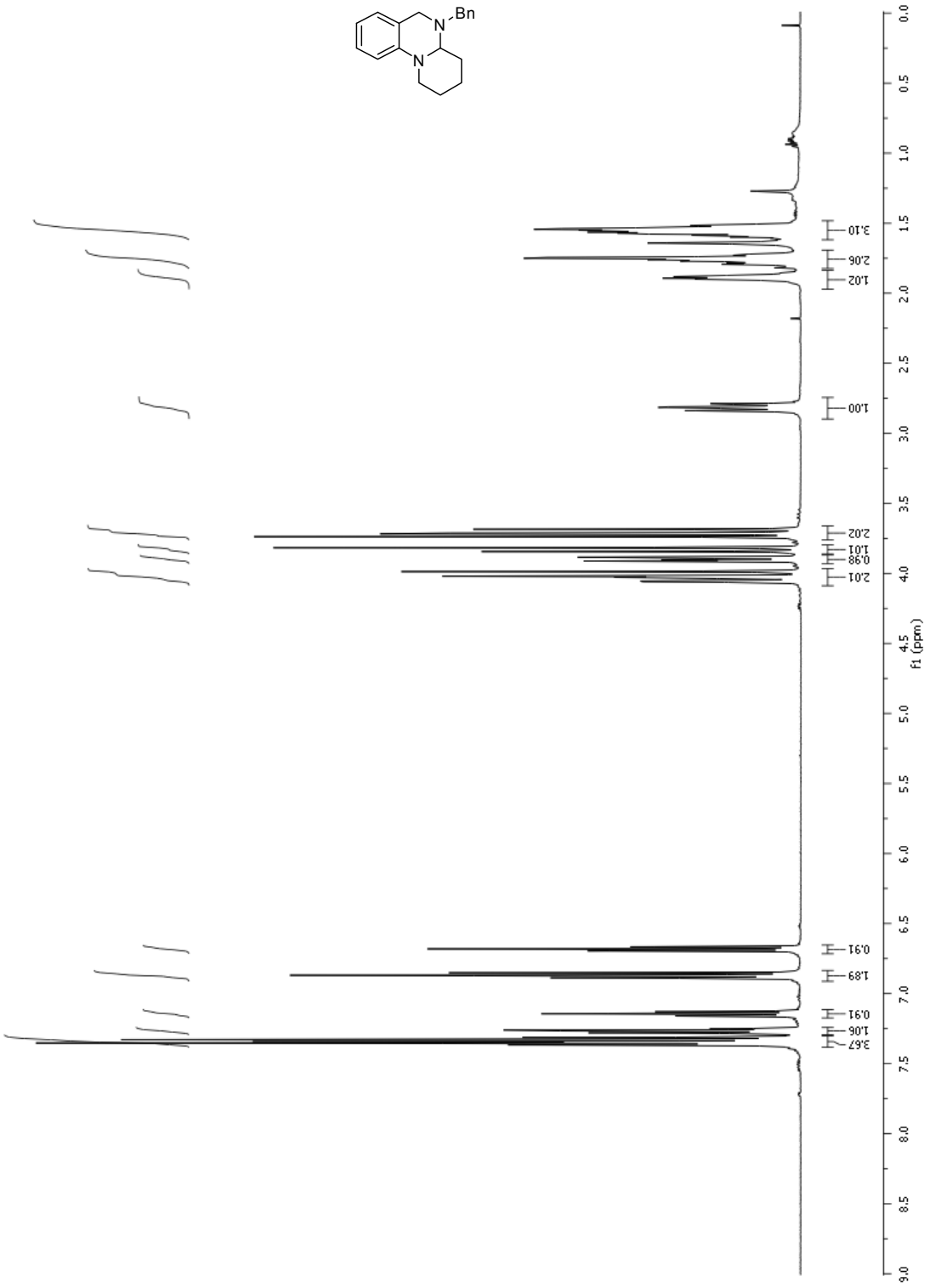

n-butyl
N
N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

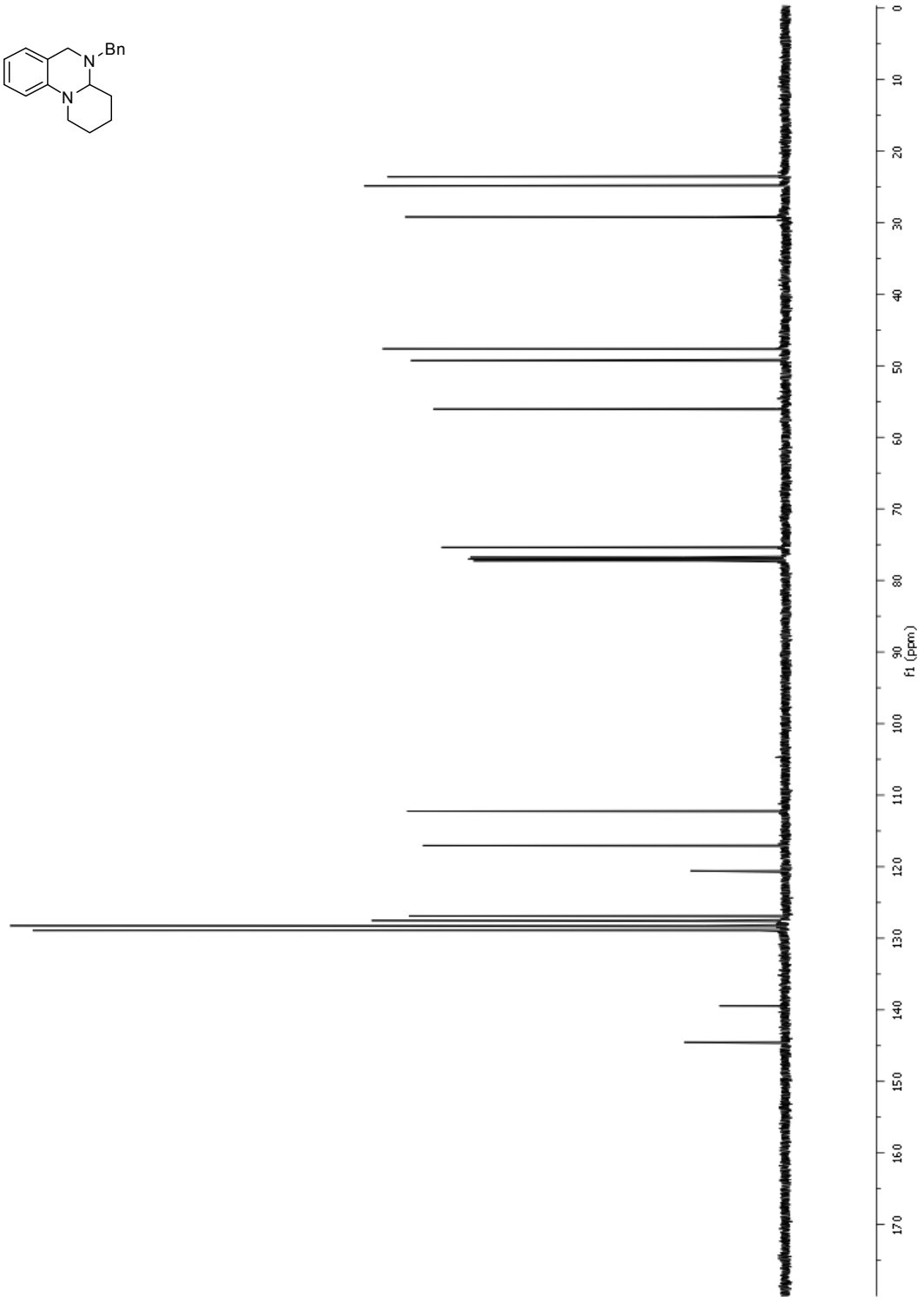
^{1}H–NMR and ^{13}C–NMR of **3.33m**:



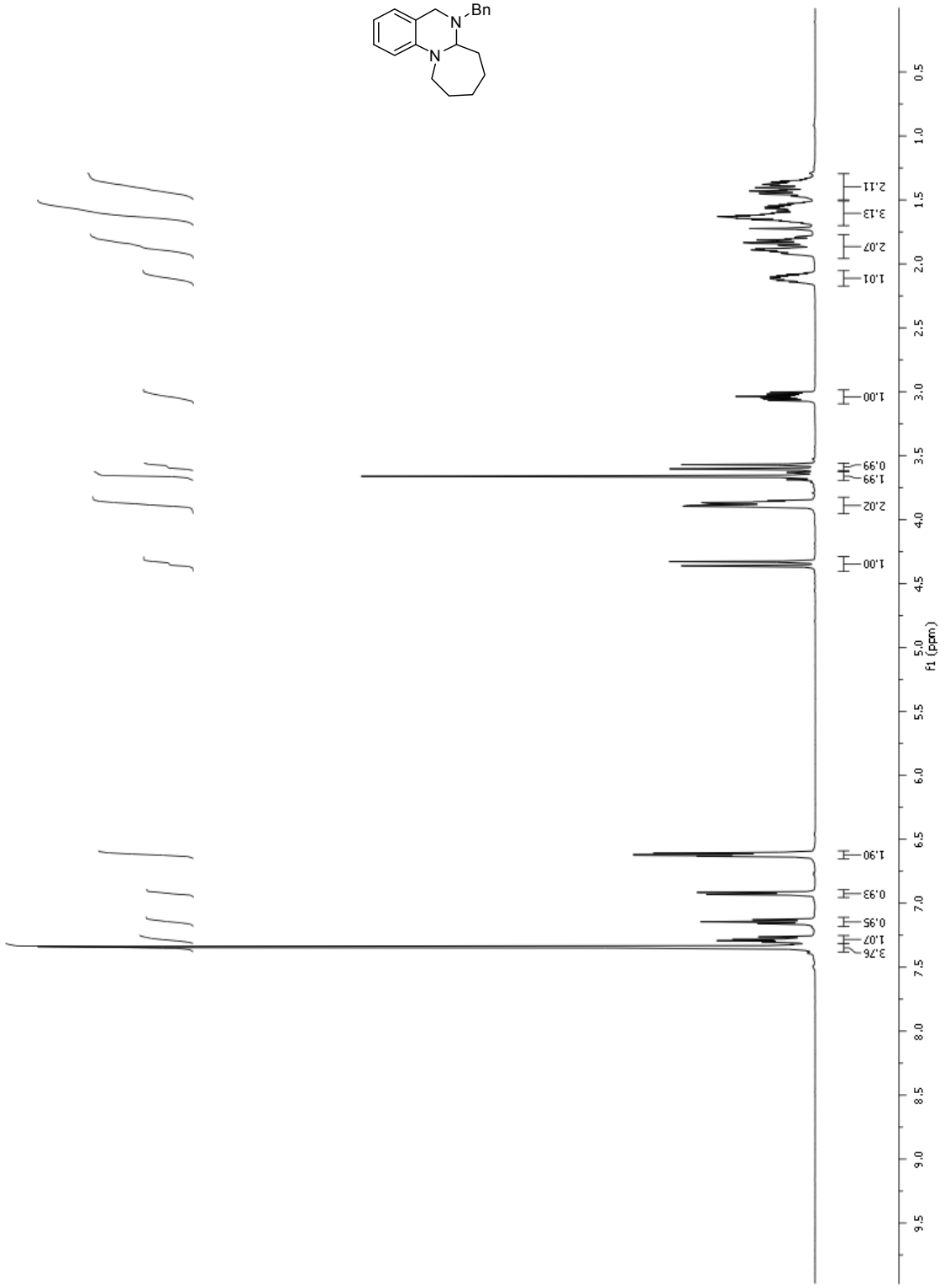

N
N
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

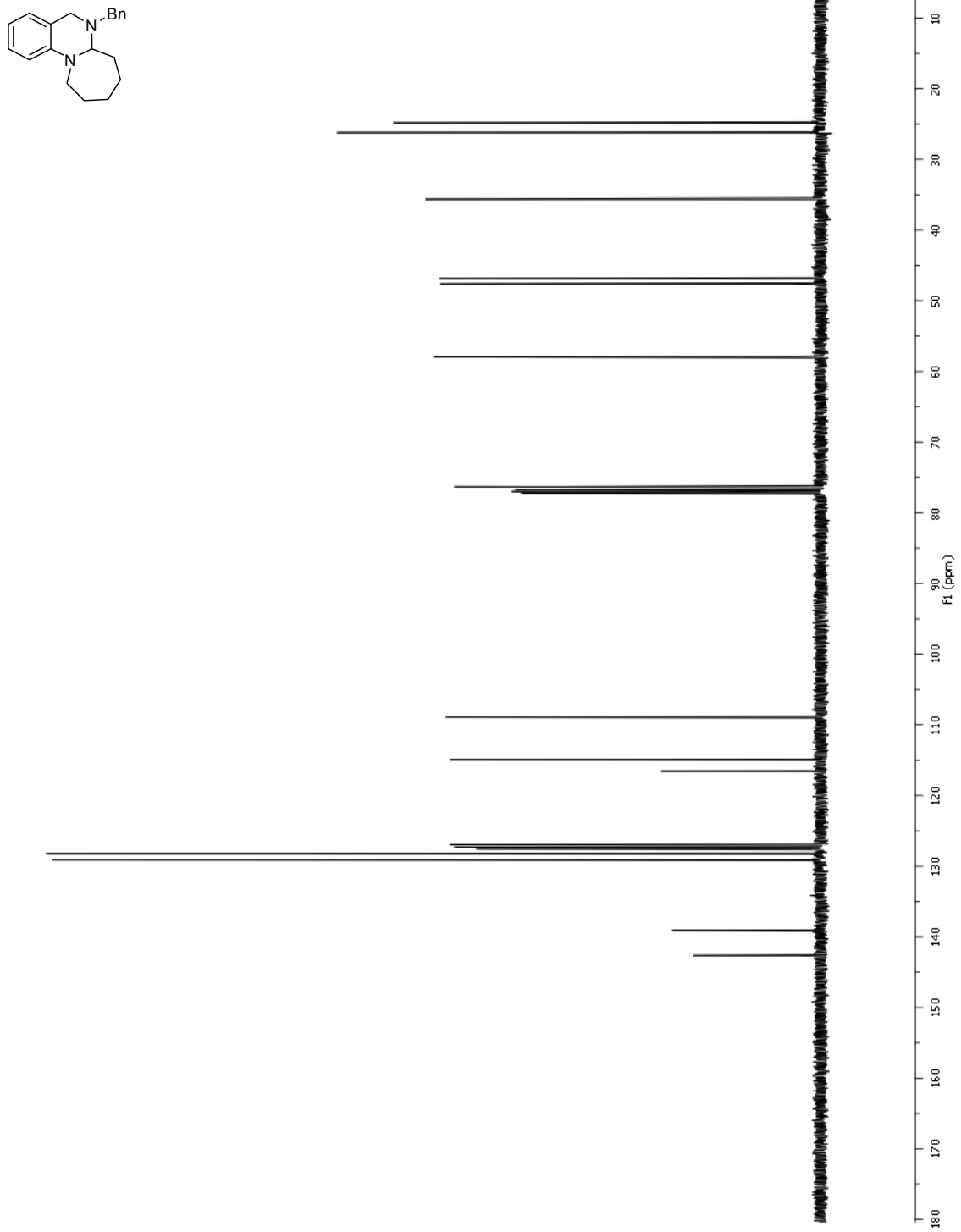
^{1}H–NMR and ^{13}C–NMR of **3.39a**:



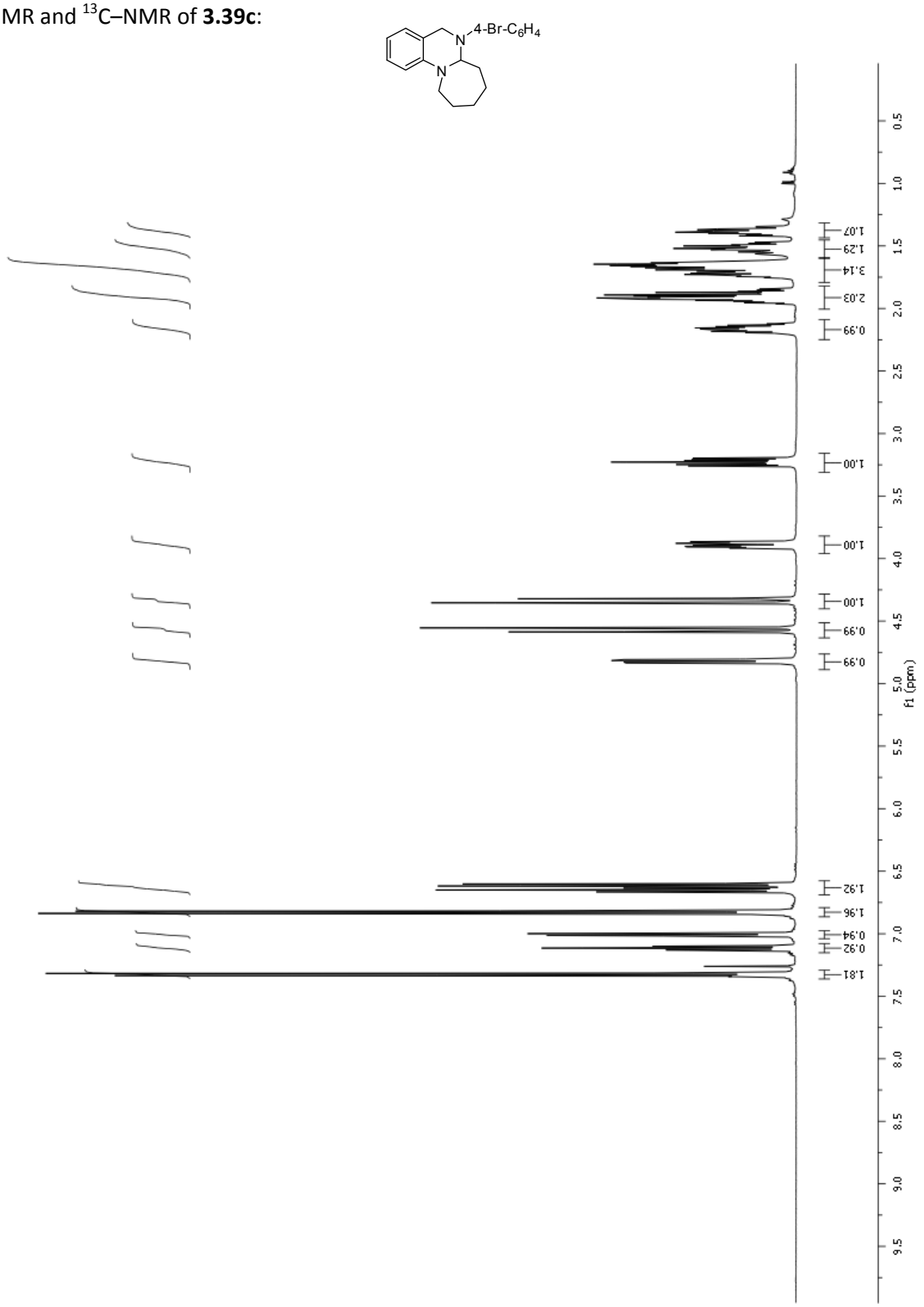

Bn
N
N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
F1 (ppm)

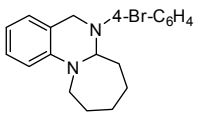
^{1}H–NMR and ^{13}C–NMR of **3.39b**:




N
Bn
N
f1 (ppm)

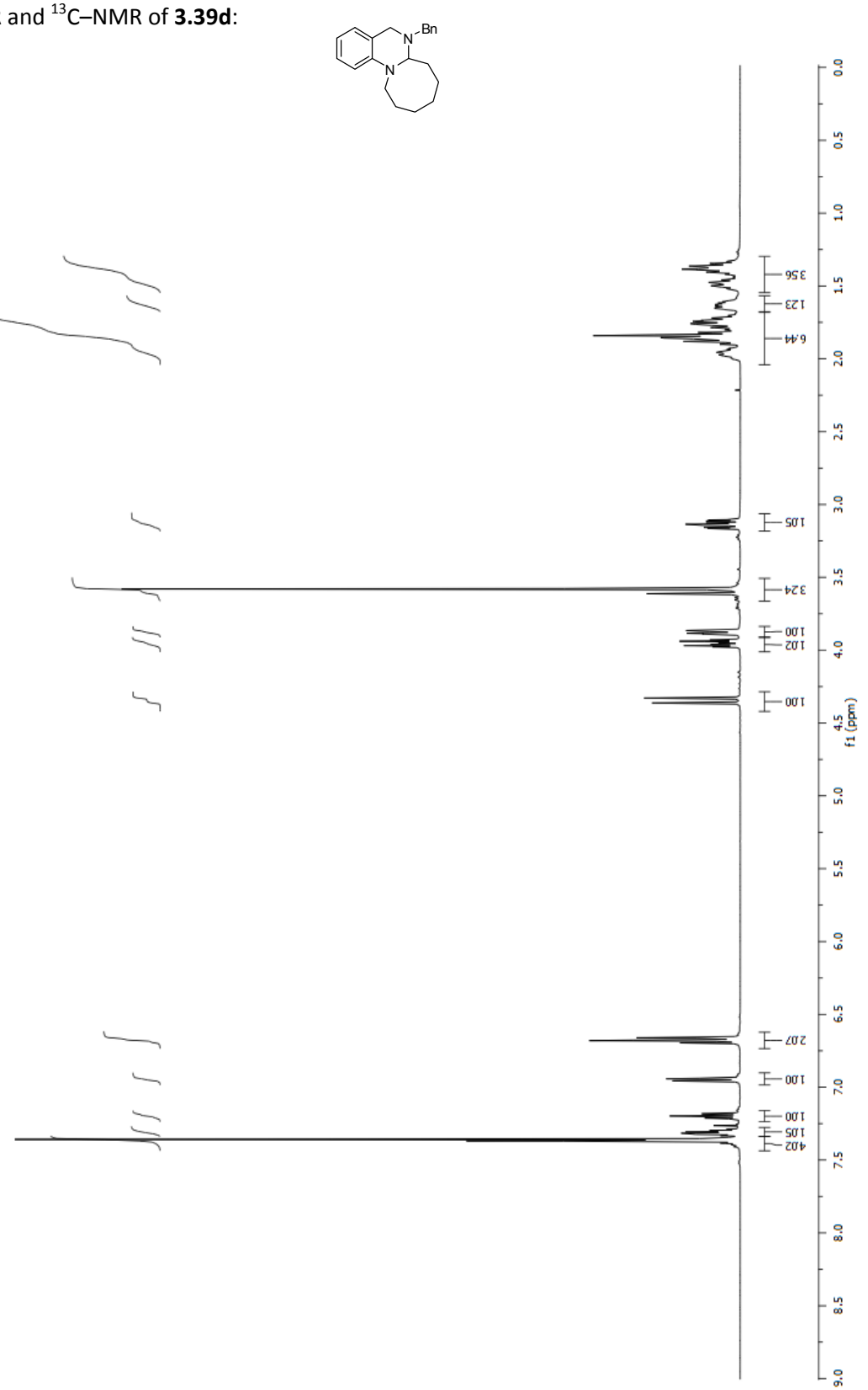
^{1}H–NMR and ^{13}C–NMR of **3.39c**:

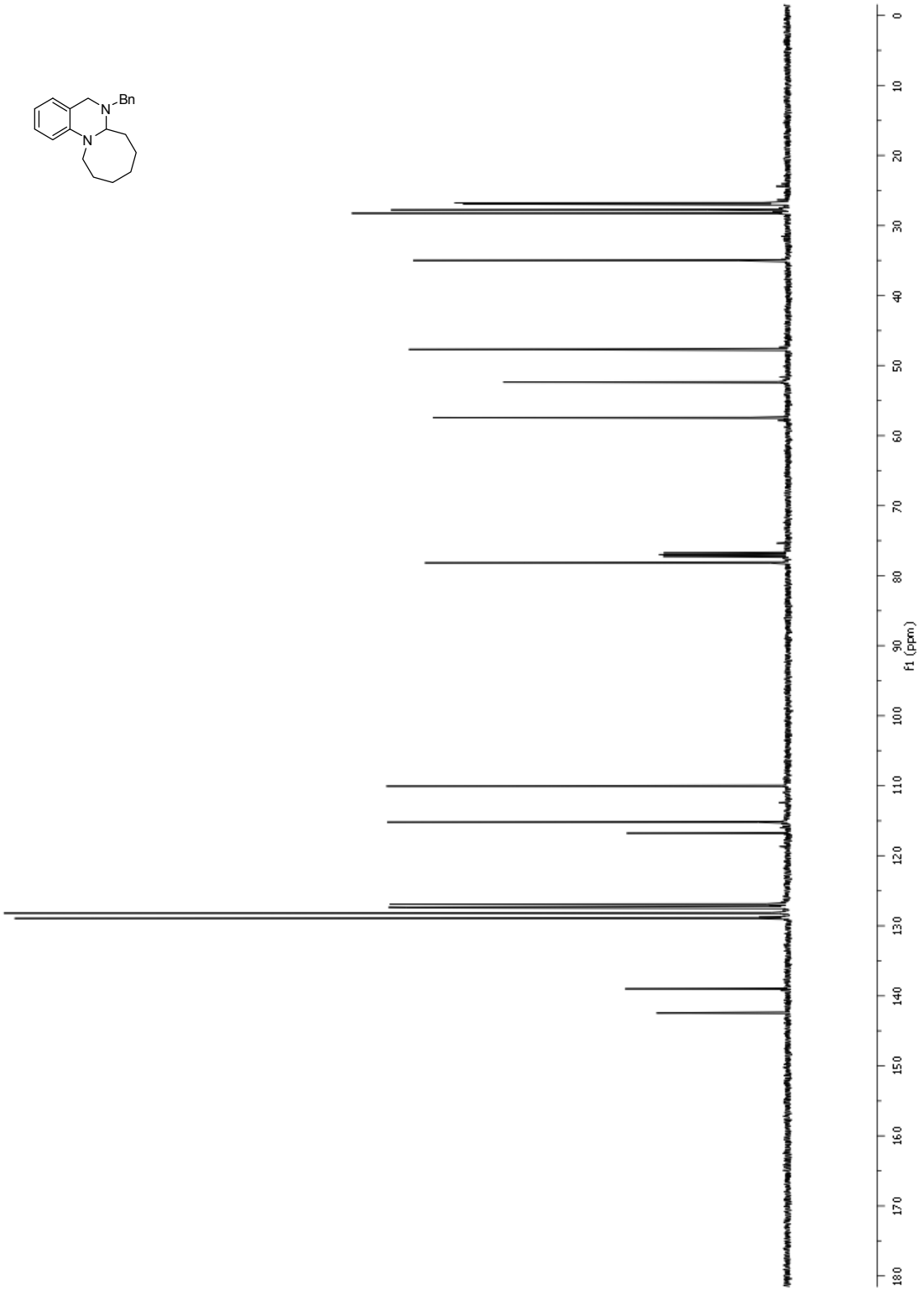



4-Br-C6H4
N
N

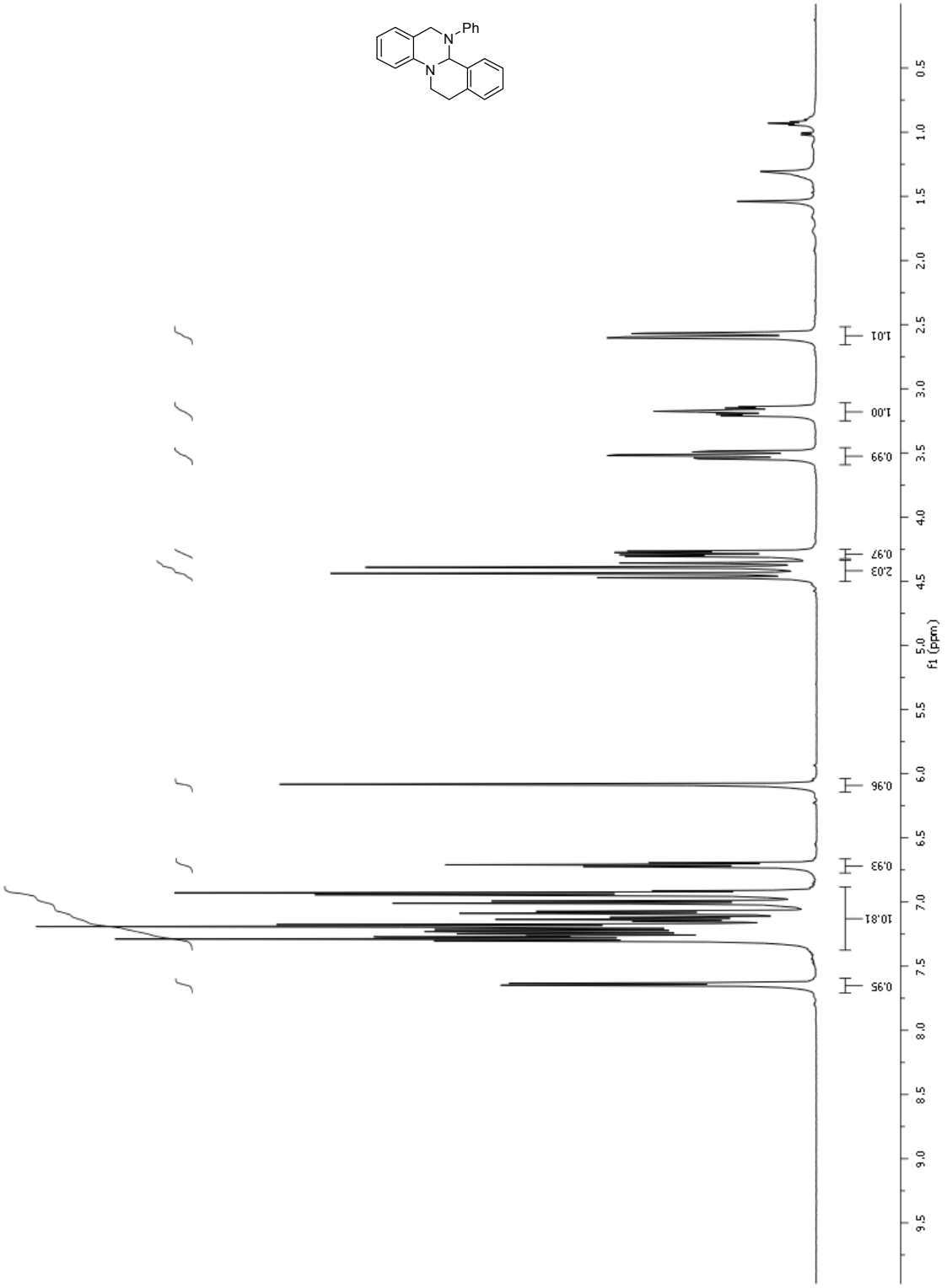
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

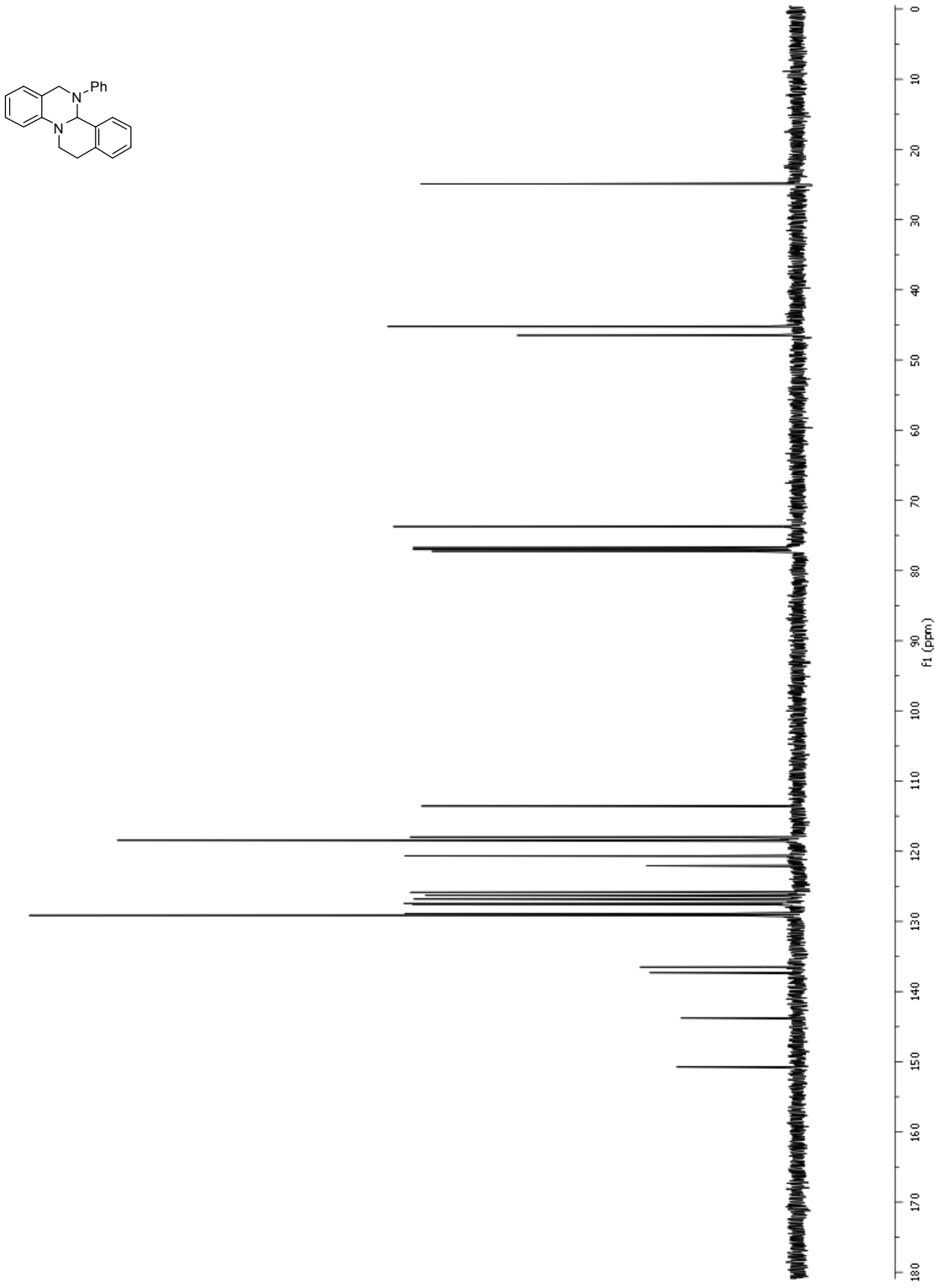
^{1}H–NMR and ^{13}C–NMR of **3.39d**:



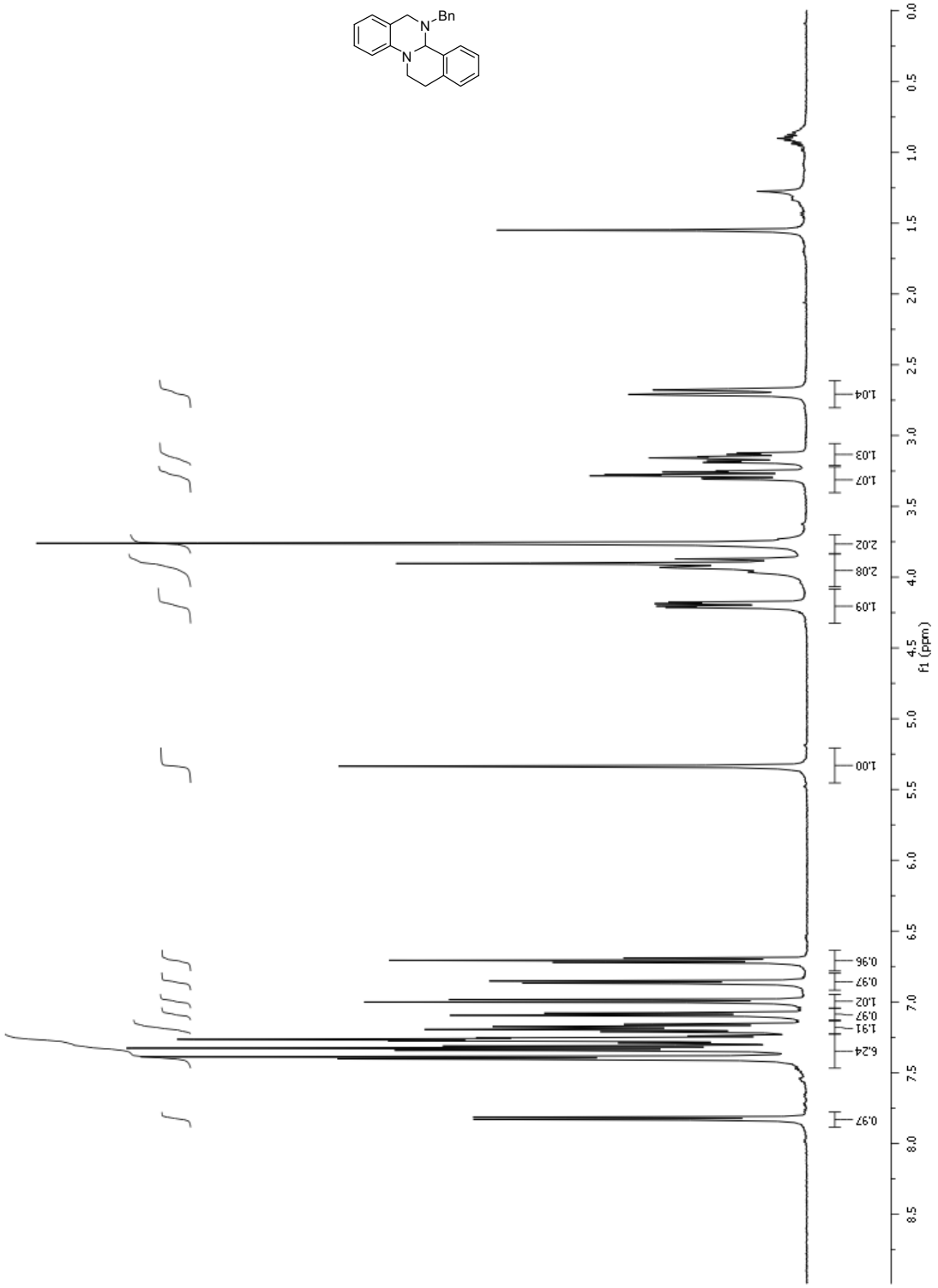

N
Bn
N
f1 (ppm)

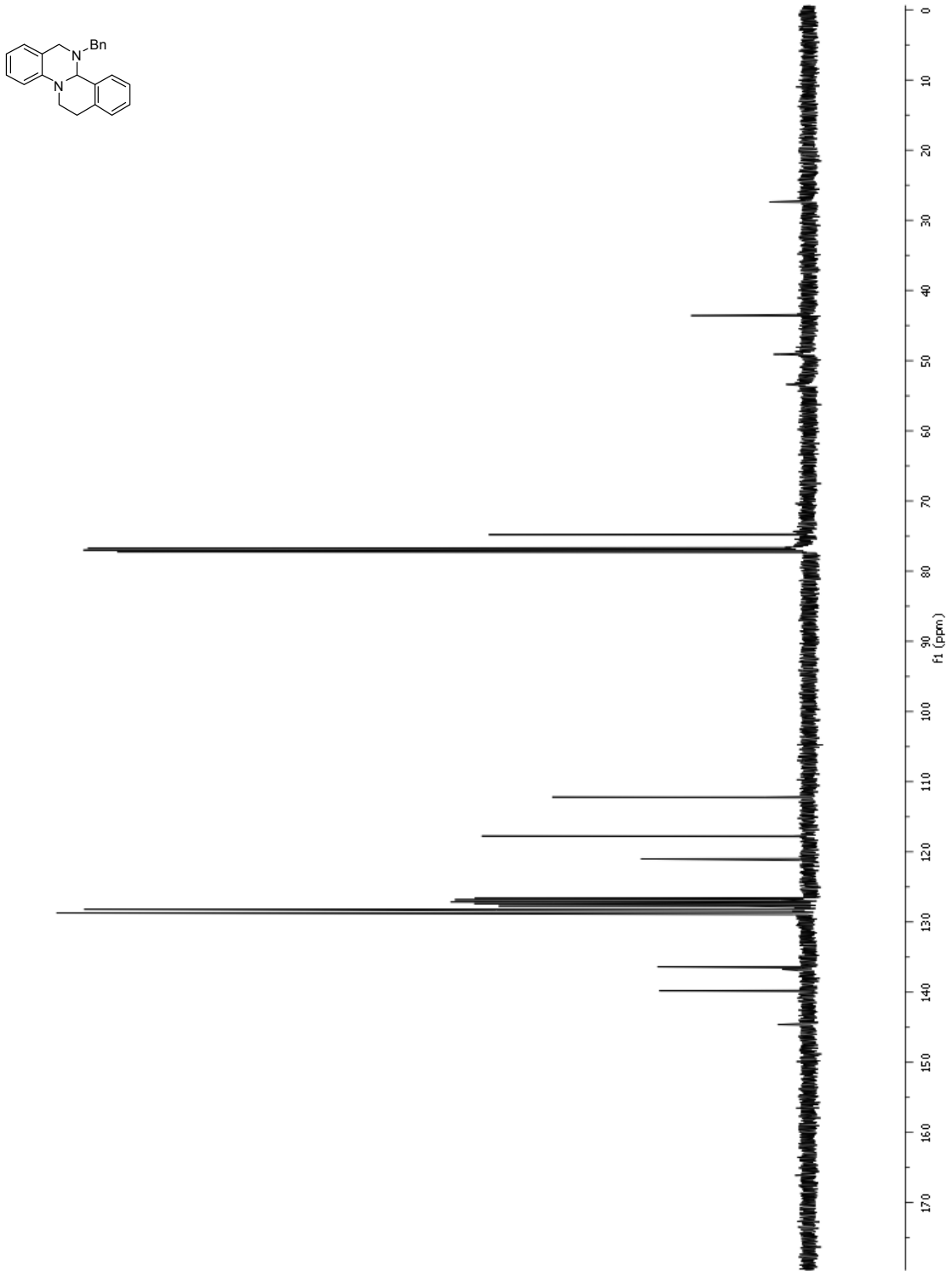
^{1}H–NMR and ^{13}C–NMR of **3.39e**:



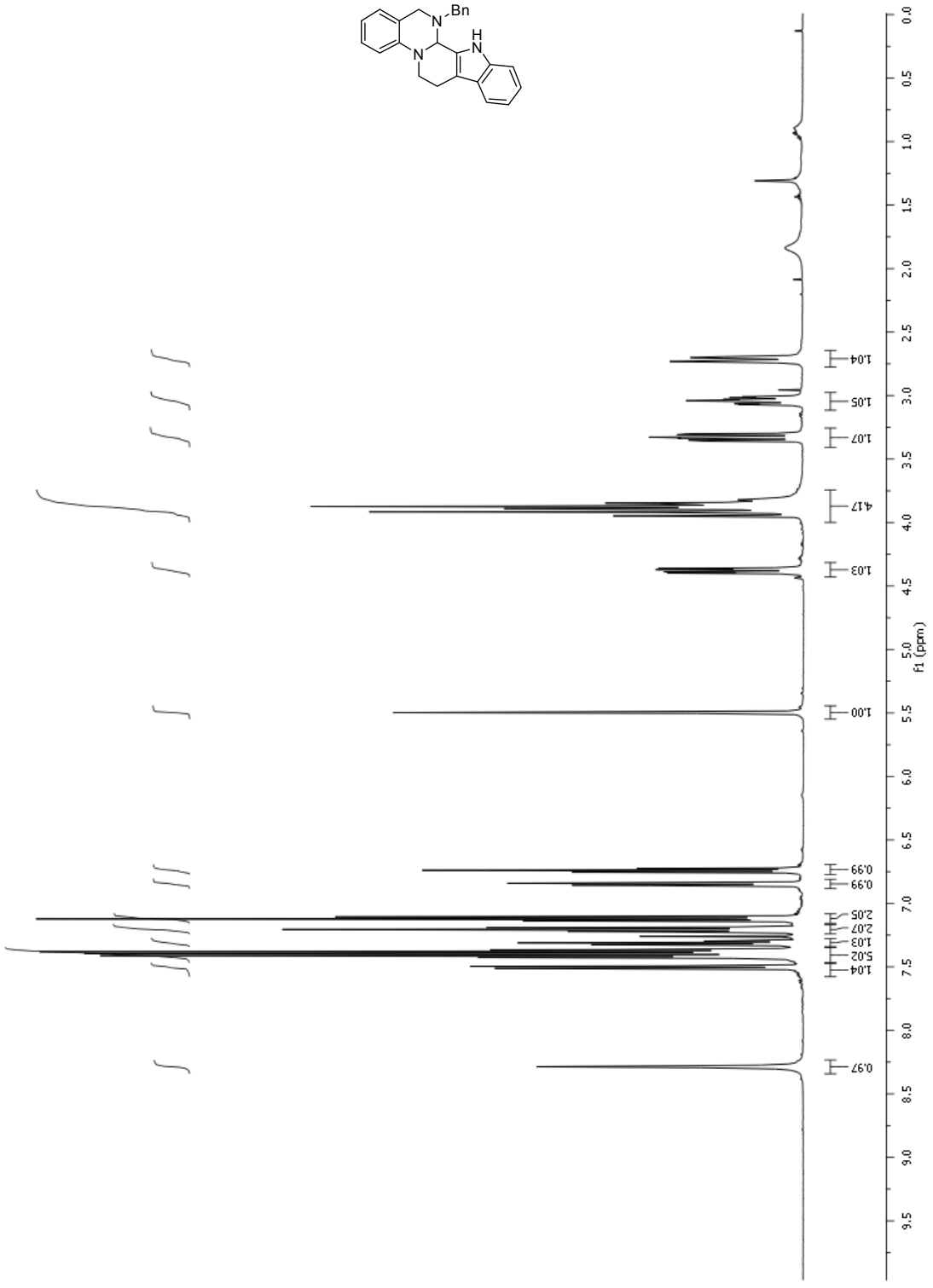

Ph
N
N
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

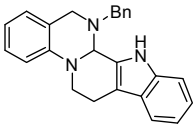
^{1}H–NMR and ^{13}C–NMR of **3.39f**:




Bn
N
N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

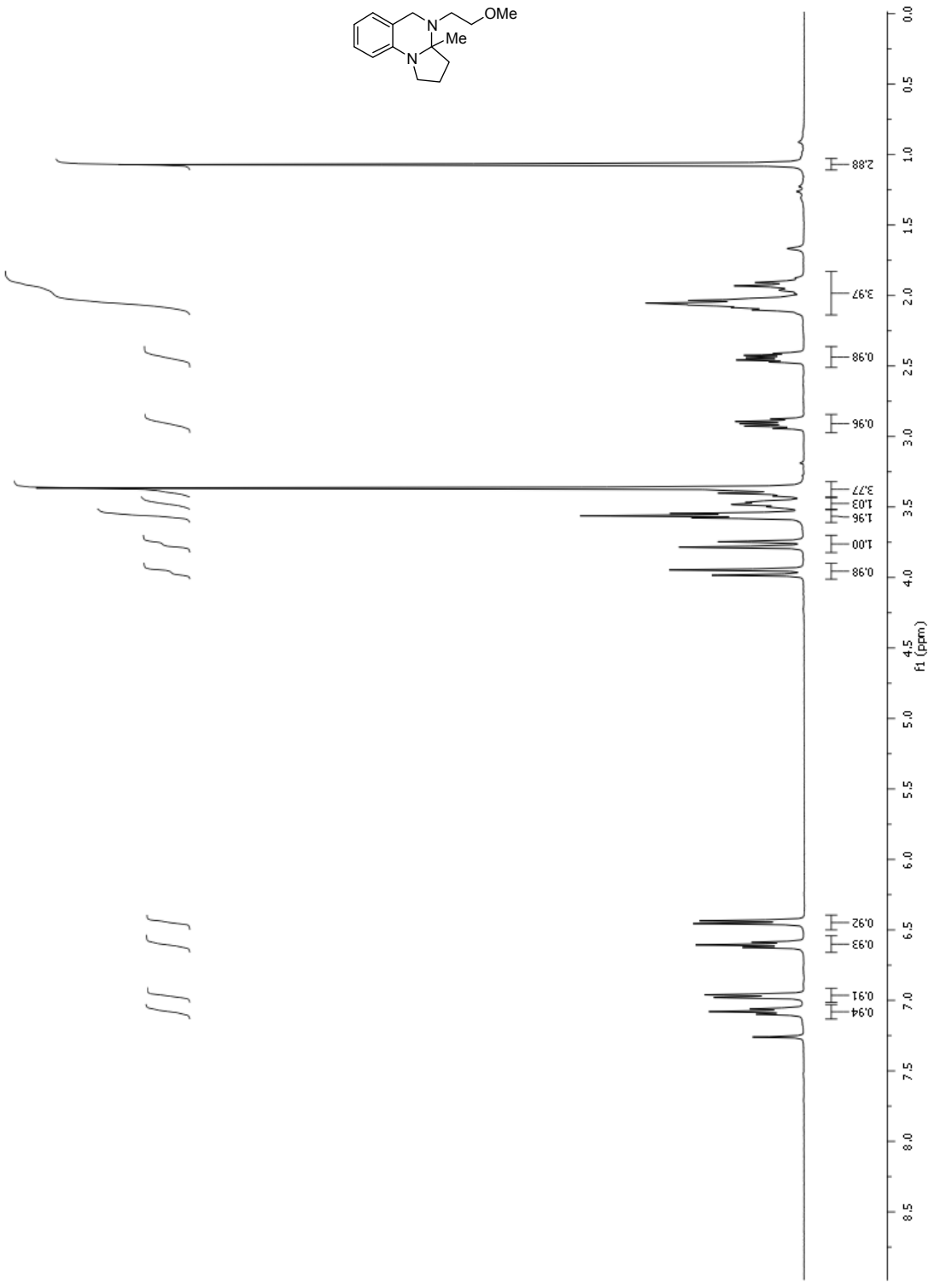
^{1}H–NMR and ^{13}C–NMR of **3.39g**:

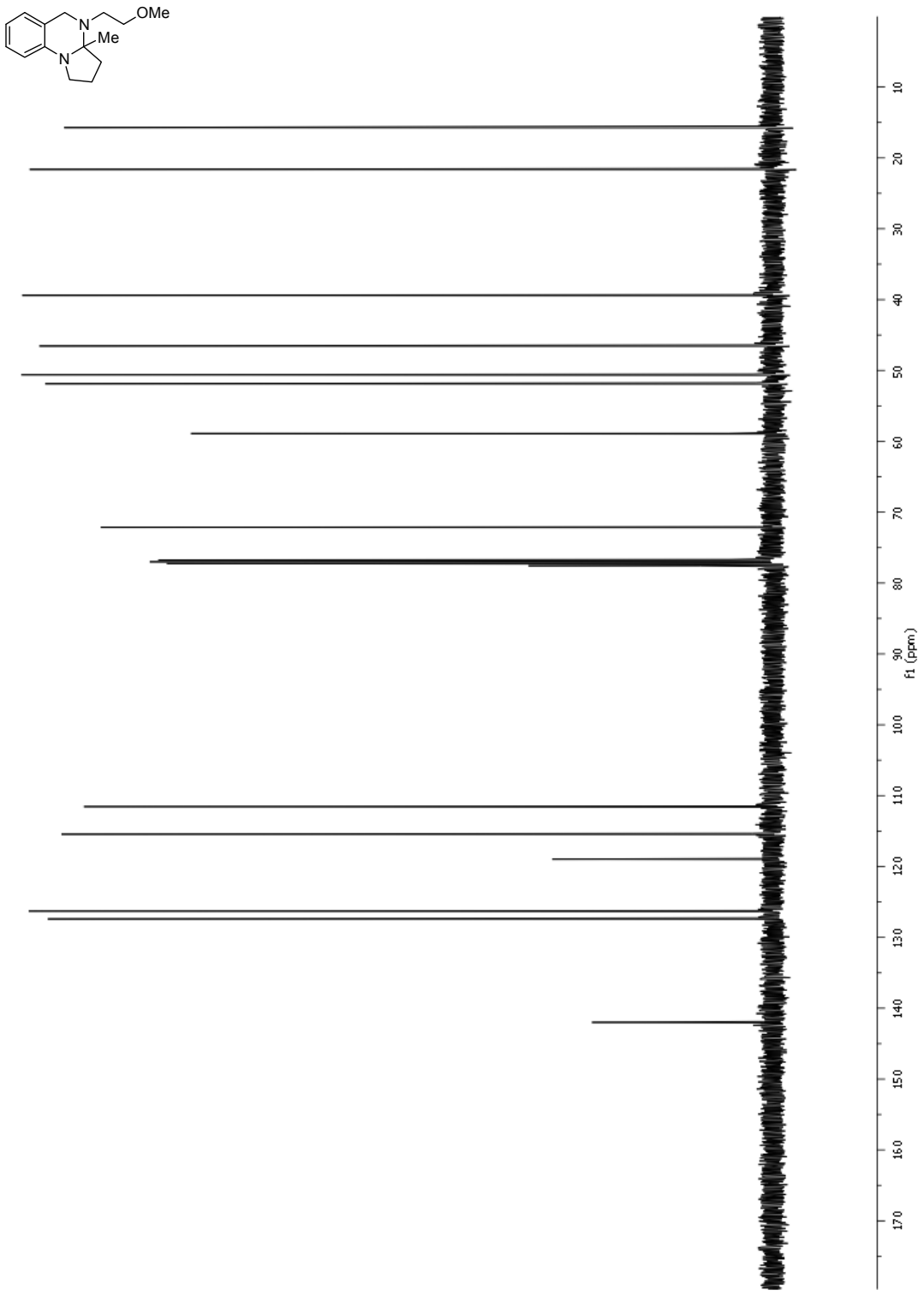



Bn
N
H
N
N

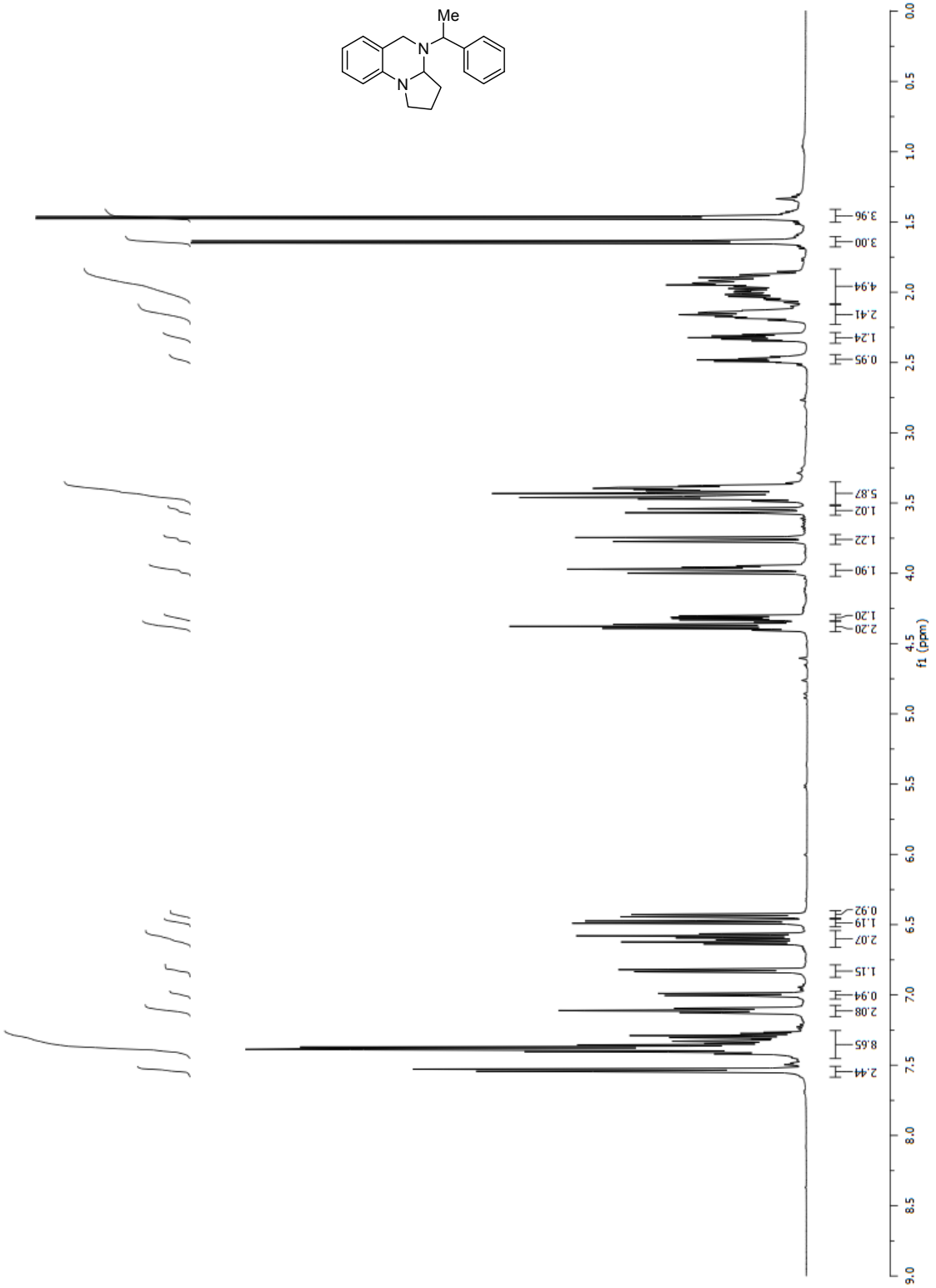
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
F1 (ppm)

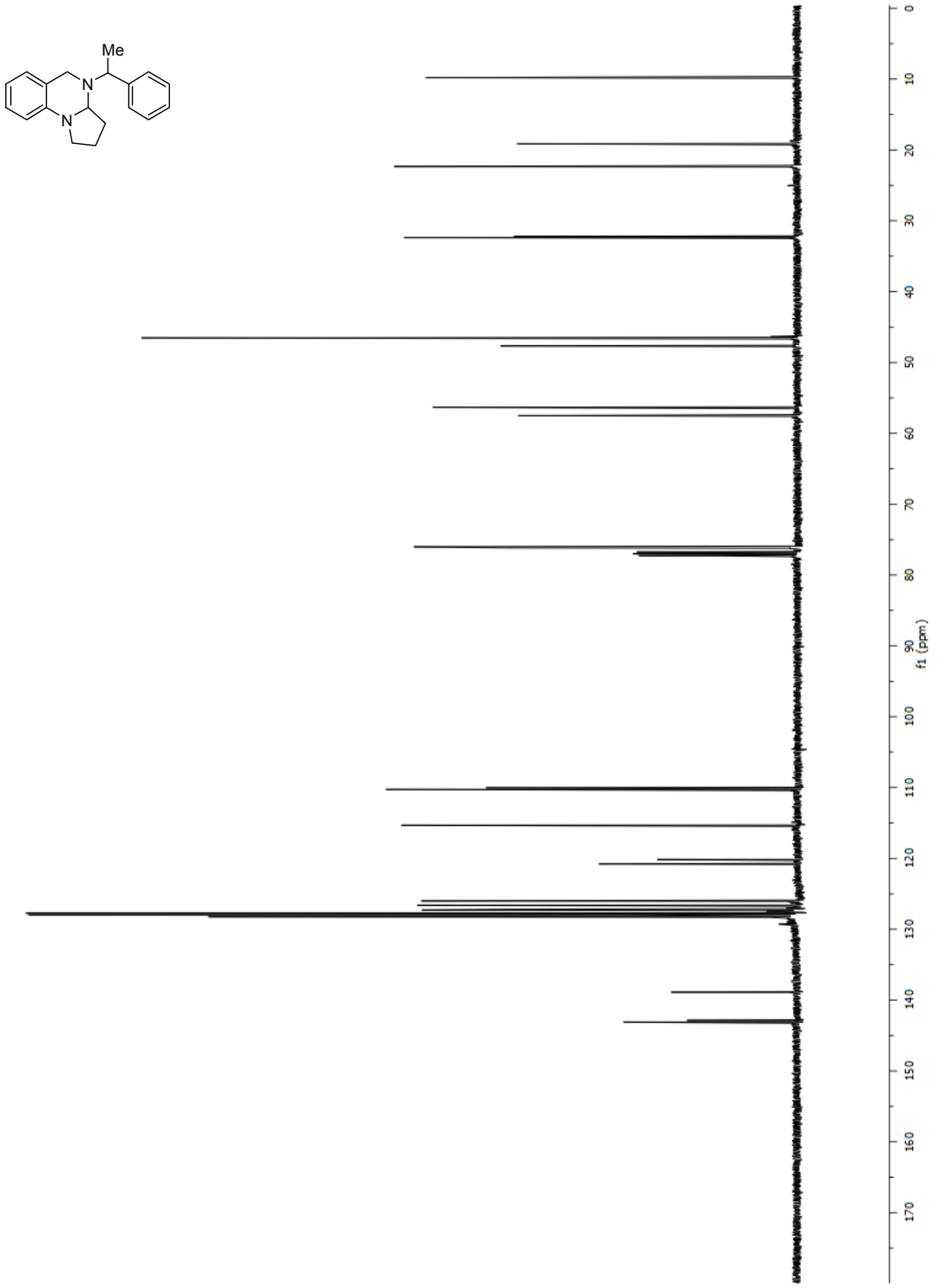
^{1}H–NMR and ^{13}C–NMR of **3.39h**:



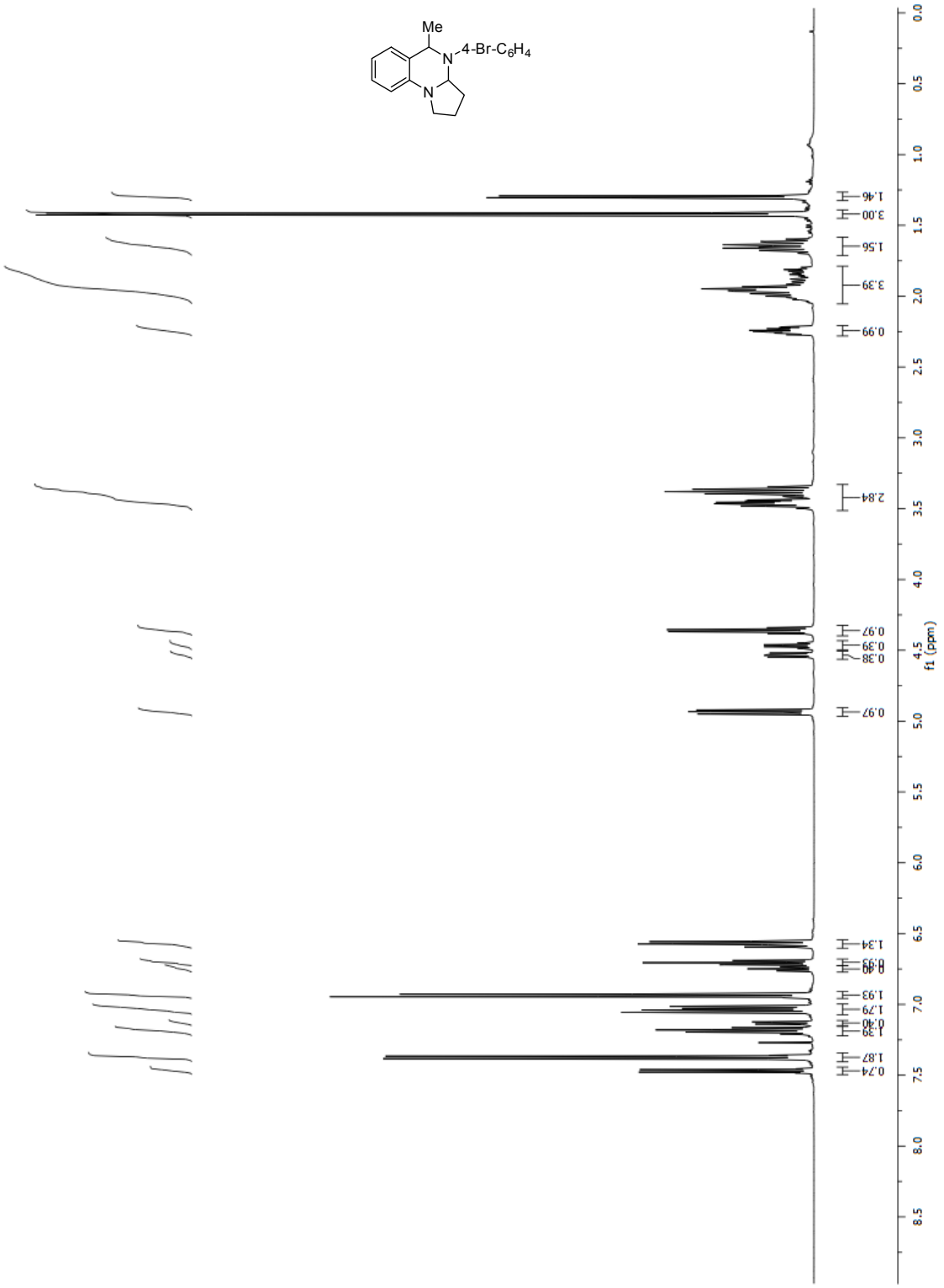

OMe
N
Me
N
F1 (ppm)

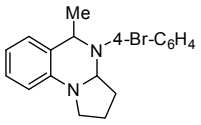
^{1}H–NMR and ^{13}C–NMR of **3.39i** (dr = 59 : 41):




Me
N
N
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

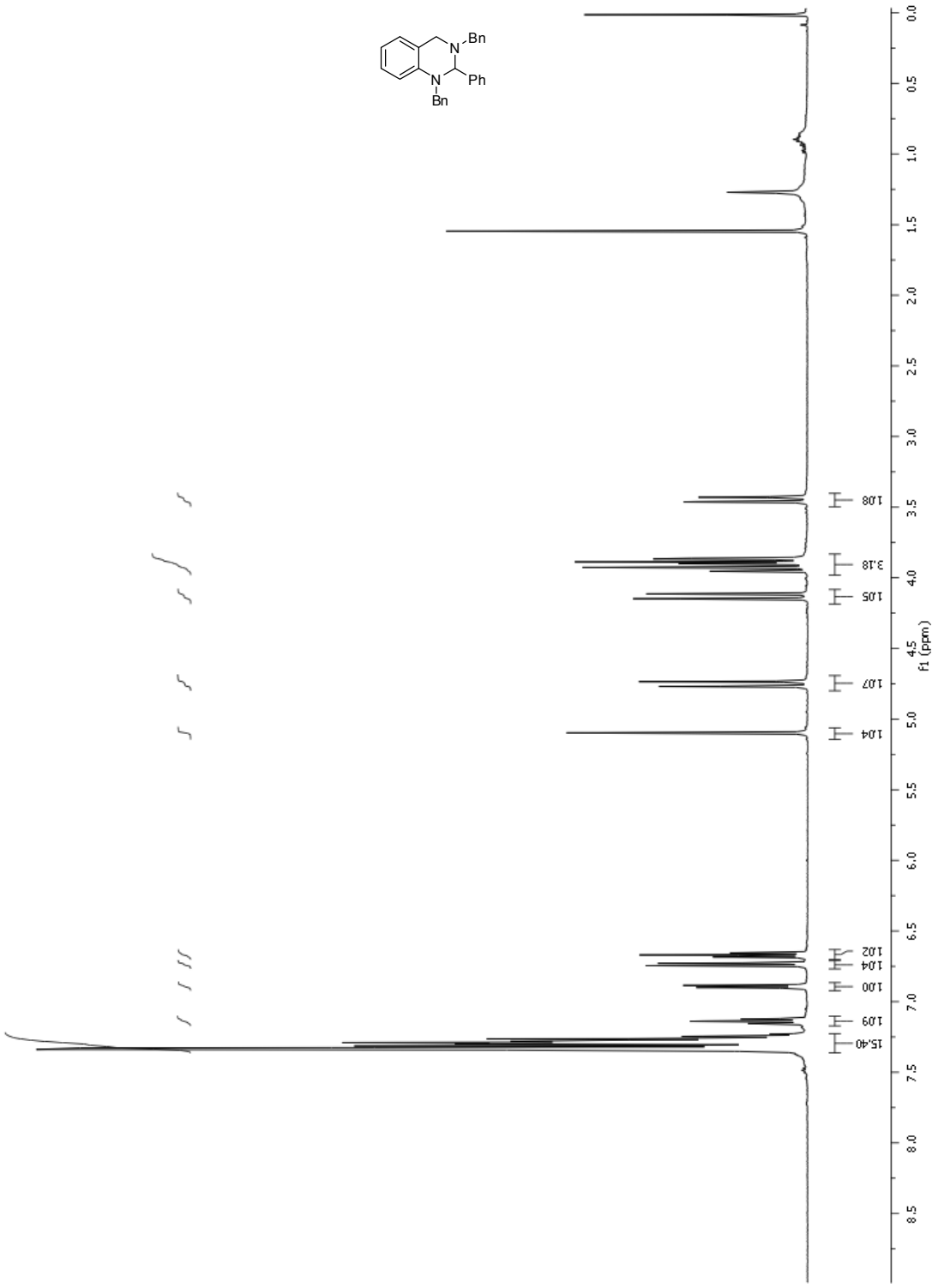
^{1}H–NMR and ^{13}C–NMR of **3.39j** (dr = 66 : 34):

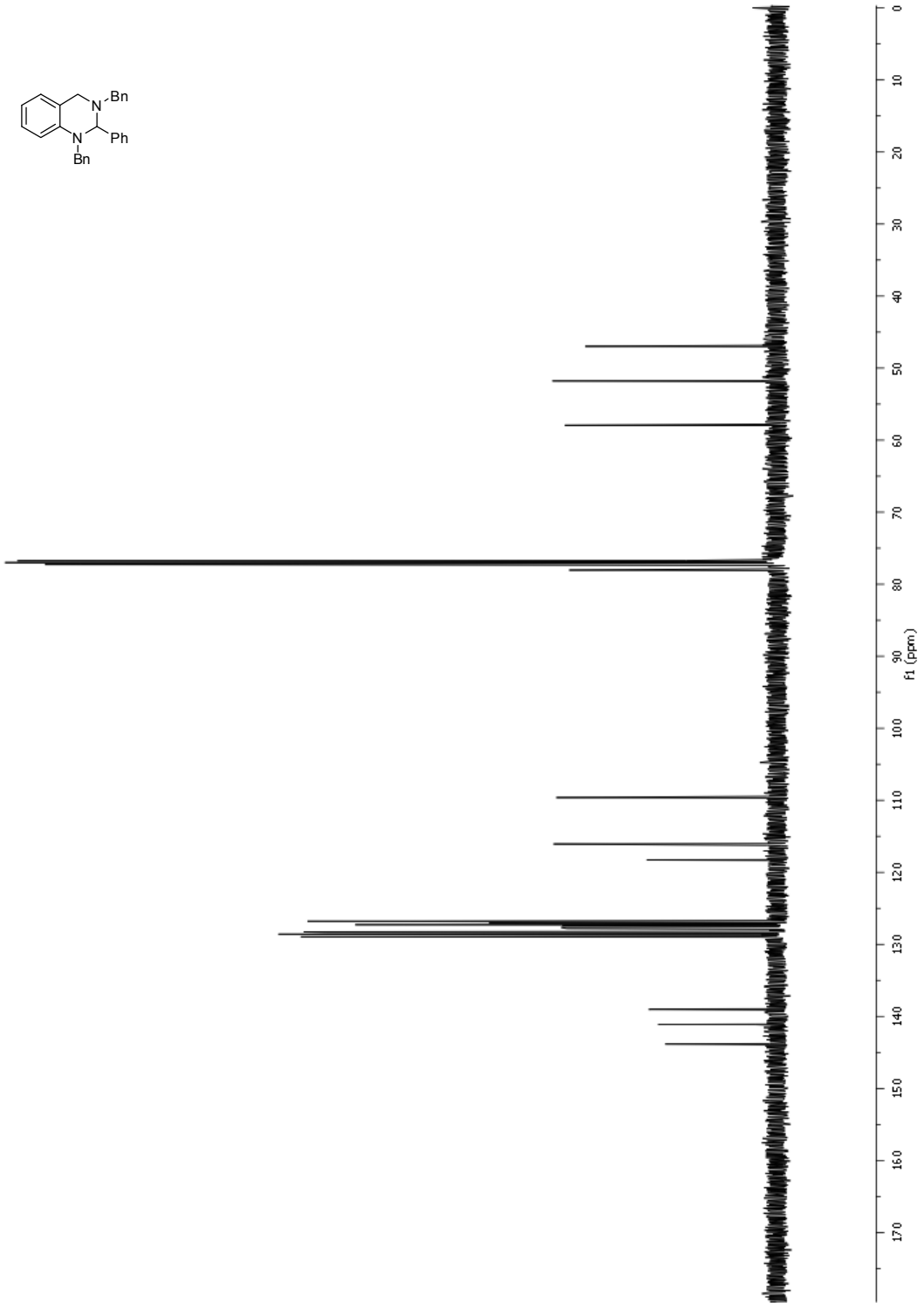



Me
4-Br-C6H4
N
N

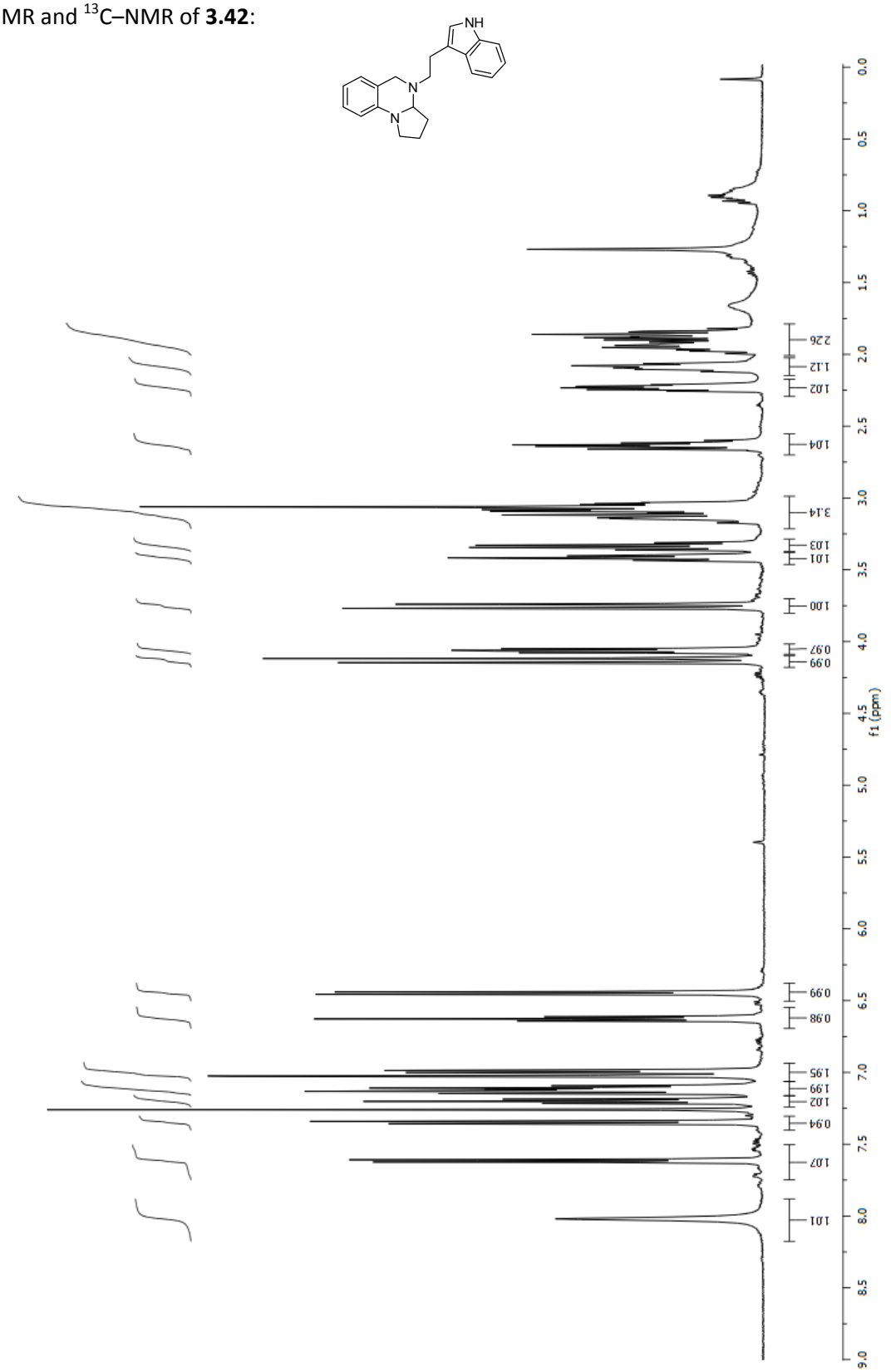
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

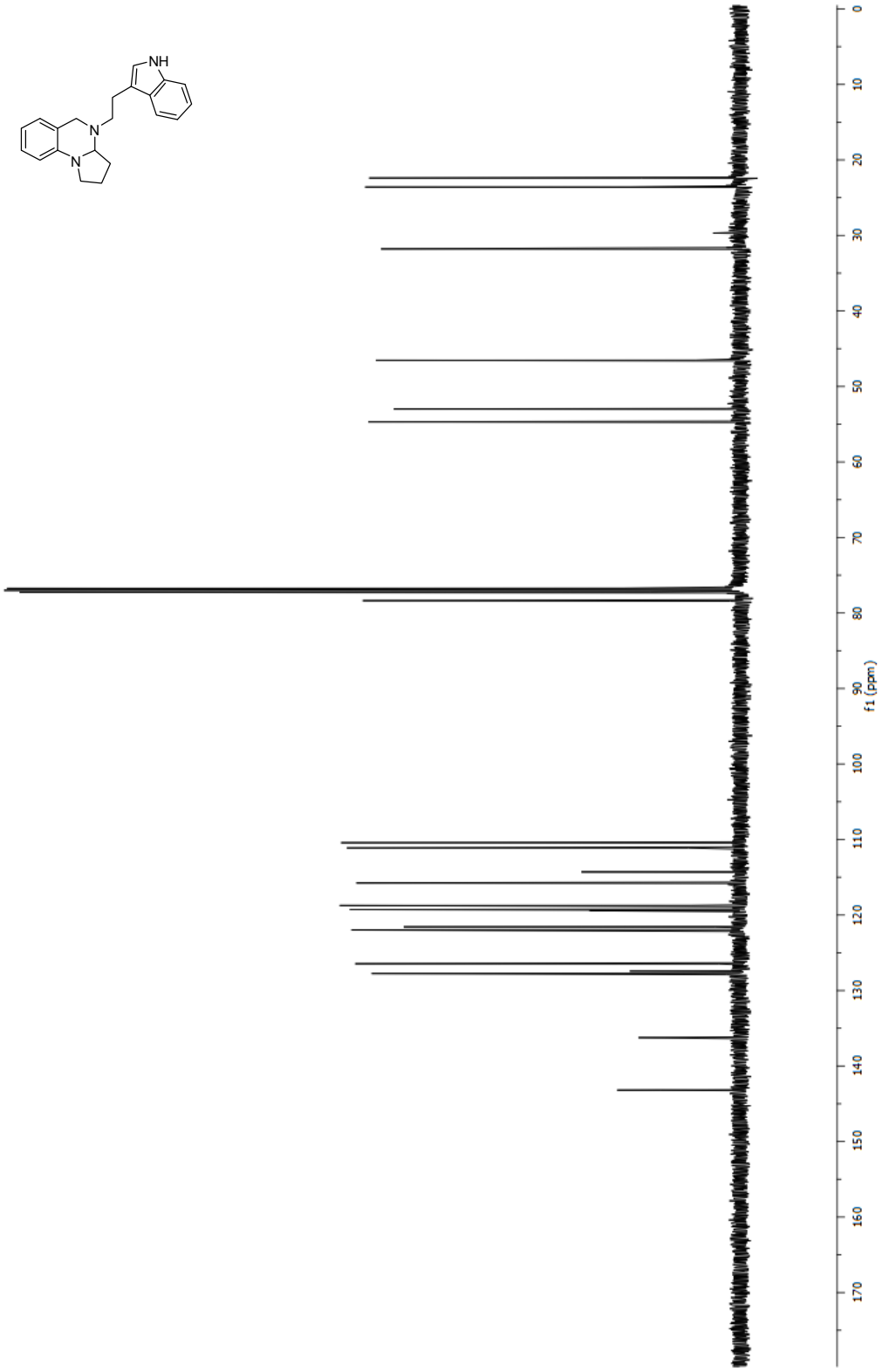
^{1}H–NMR and ^{13}C–NMR of **3.39k** (TMS containing $CDCl_3$ was used):



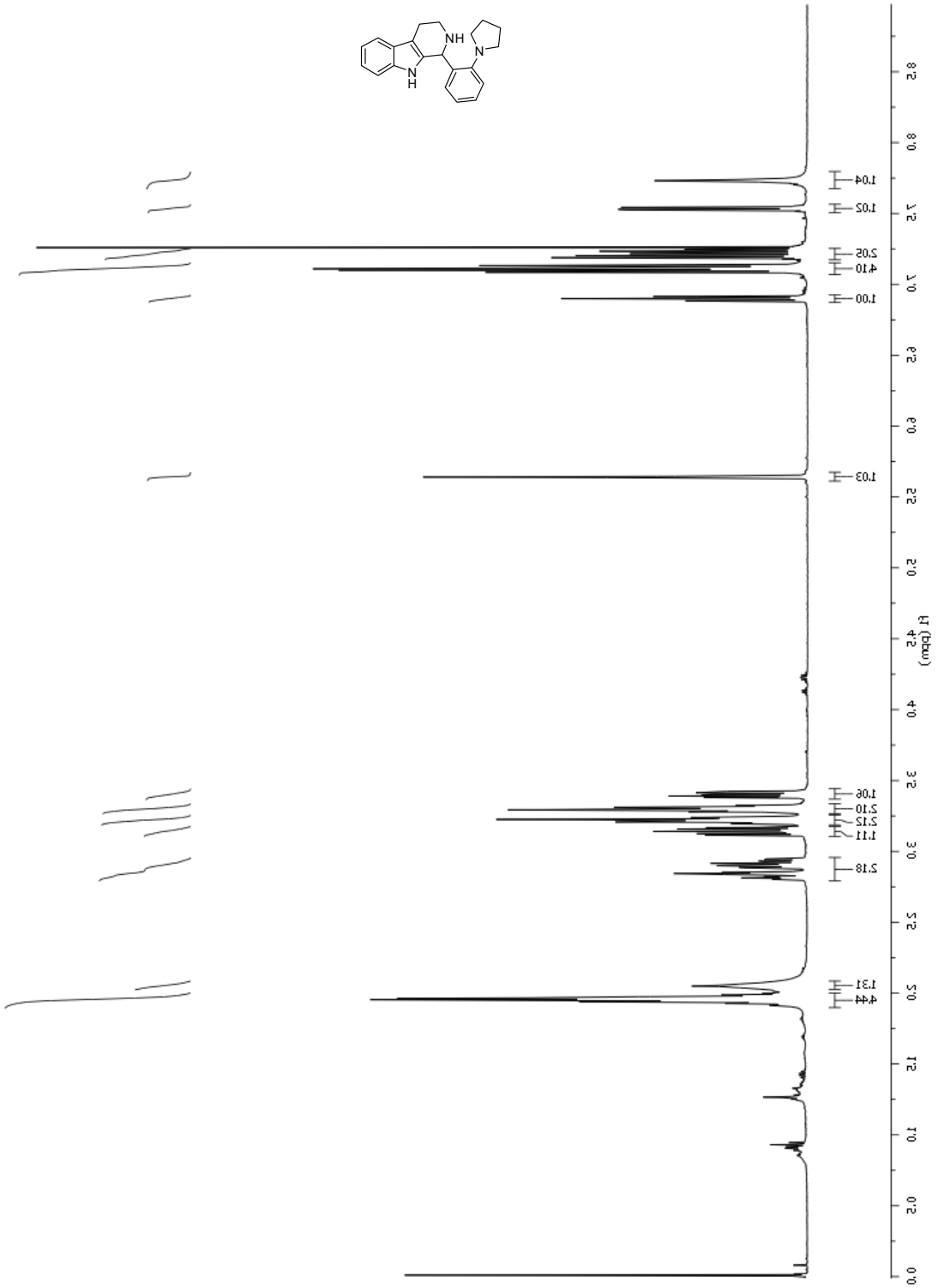

Bn
N
Ph
N
Bn
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
F1 (ppm)

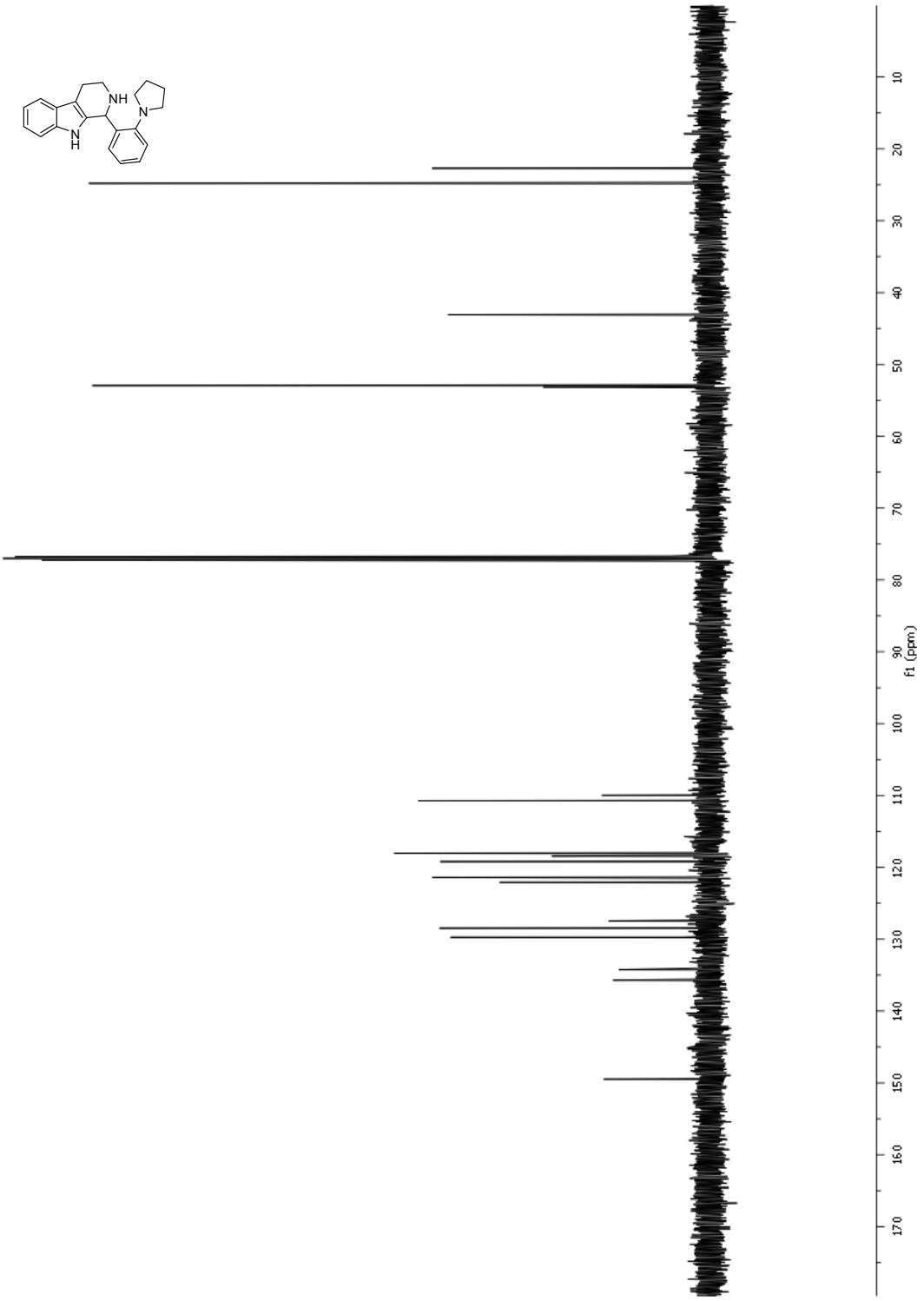
^{1}H–NMR and ^{13}C–NMR of **3.42**:

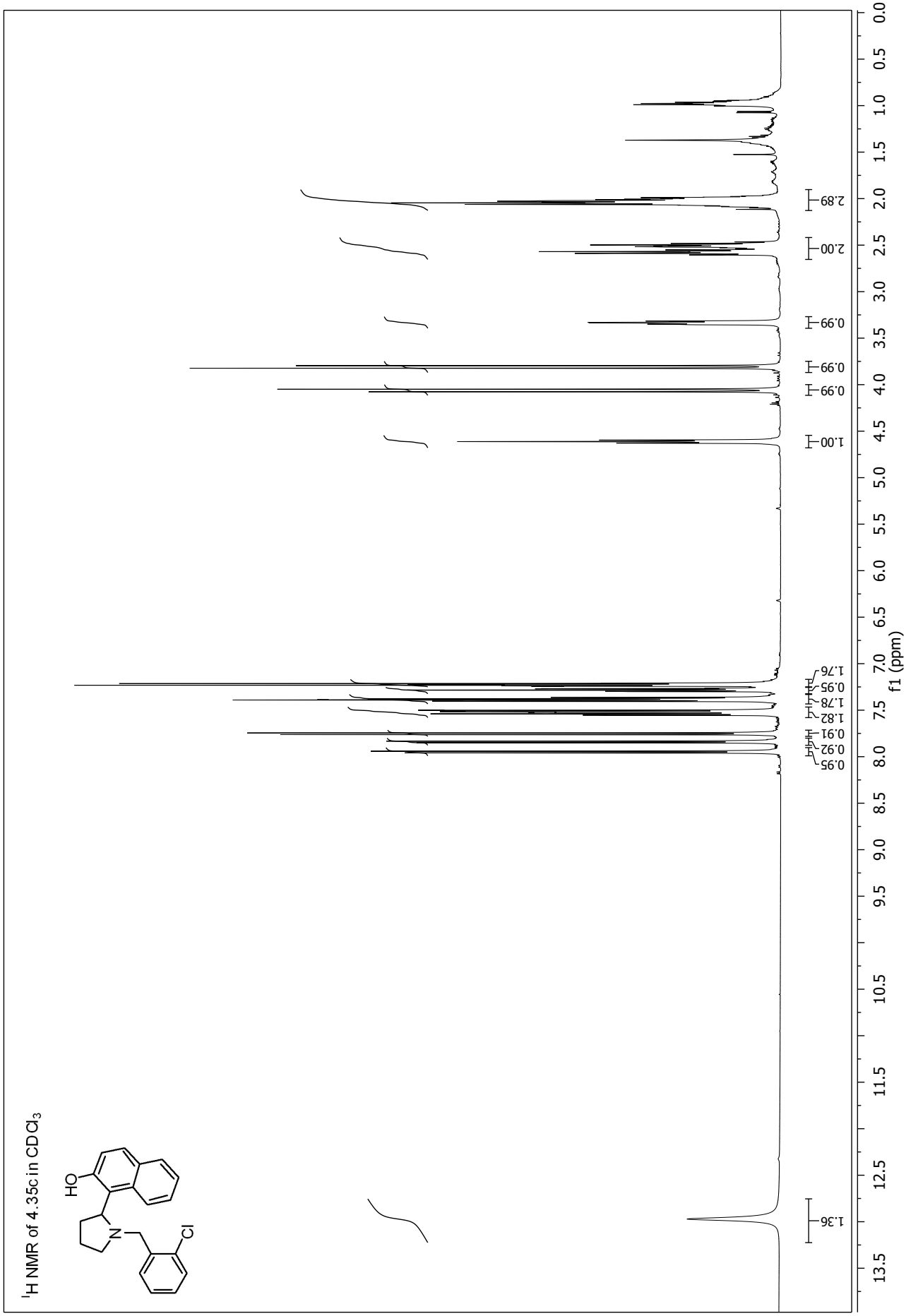


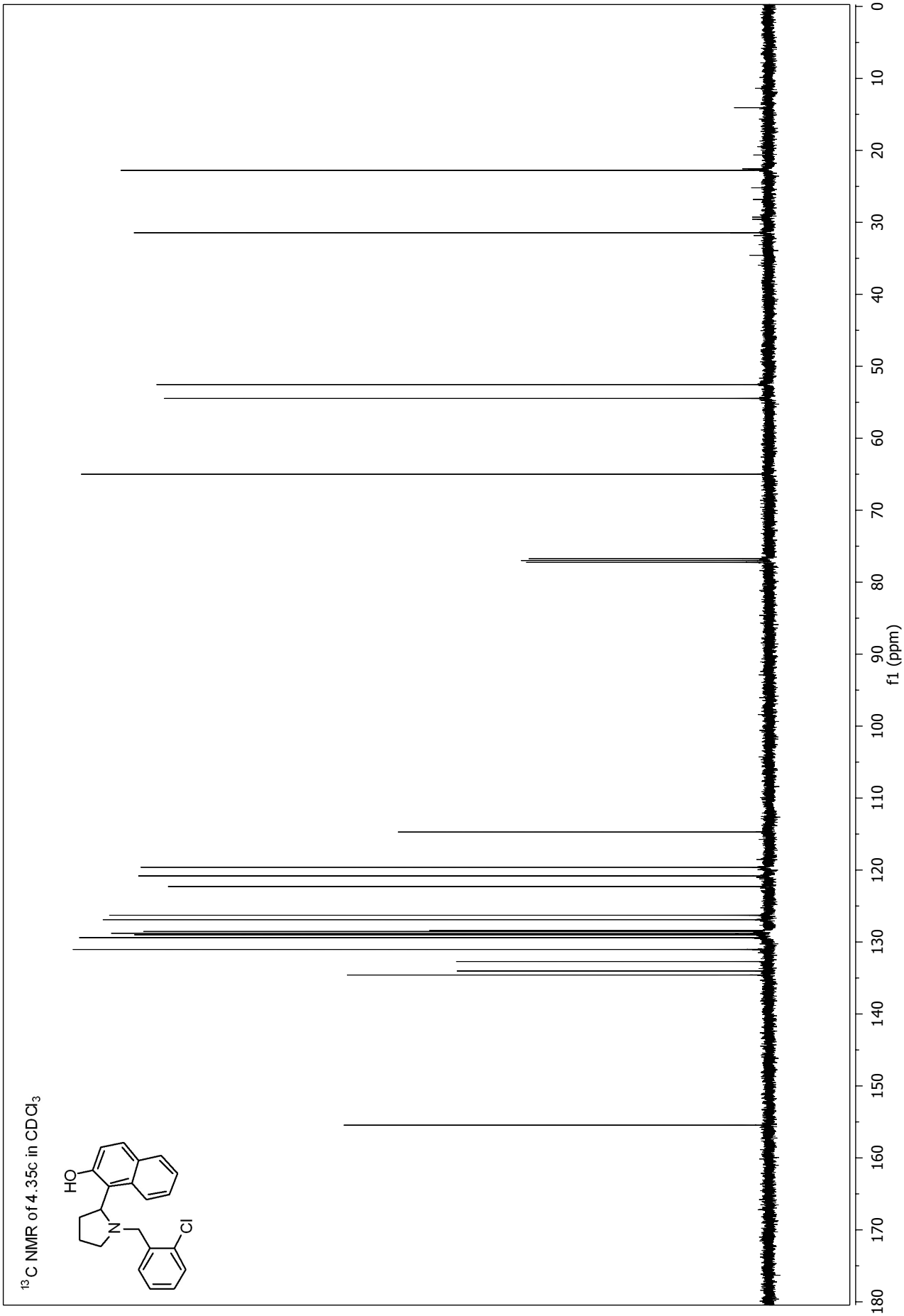

NH
N
N
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

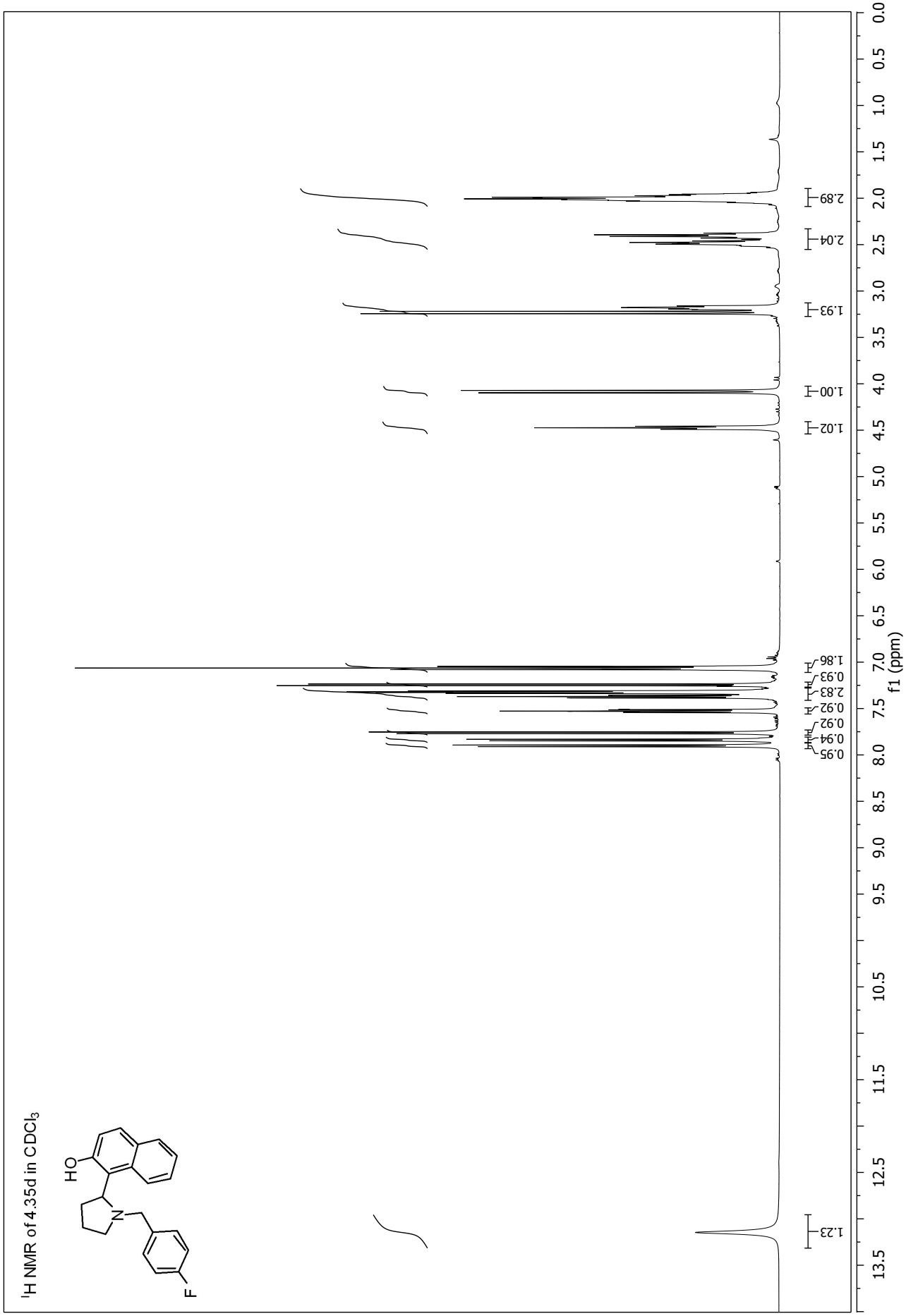
^{1}H–NMR and ^{13}C–NMR of **3.43** (TMS containing $CDCl_3$ was used):

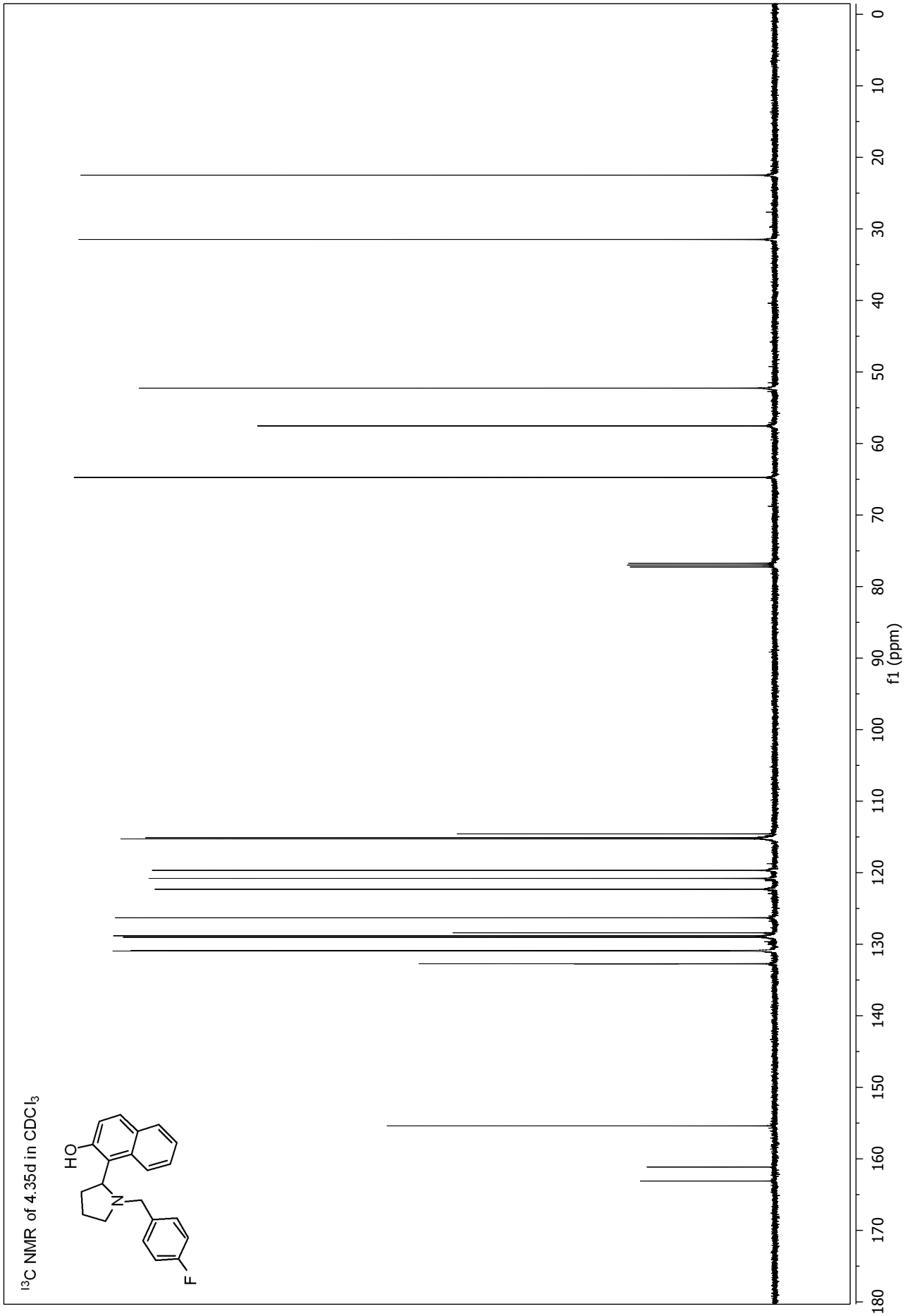


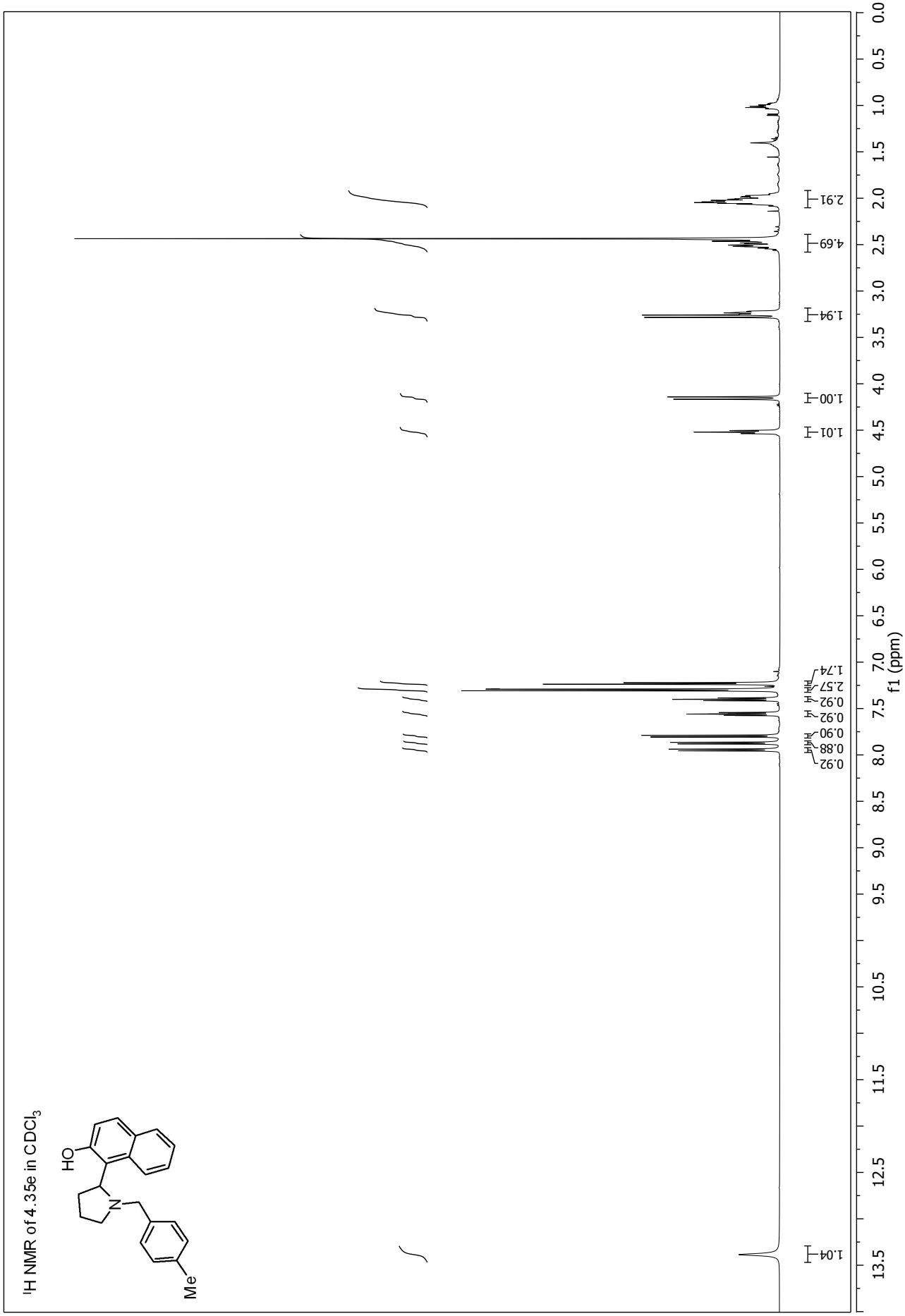

NH
N
H
N
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
F1 (ppm)

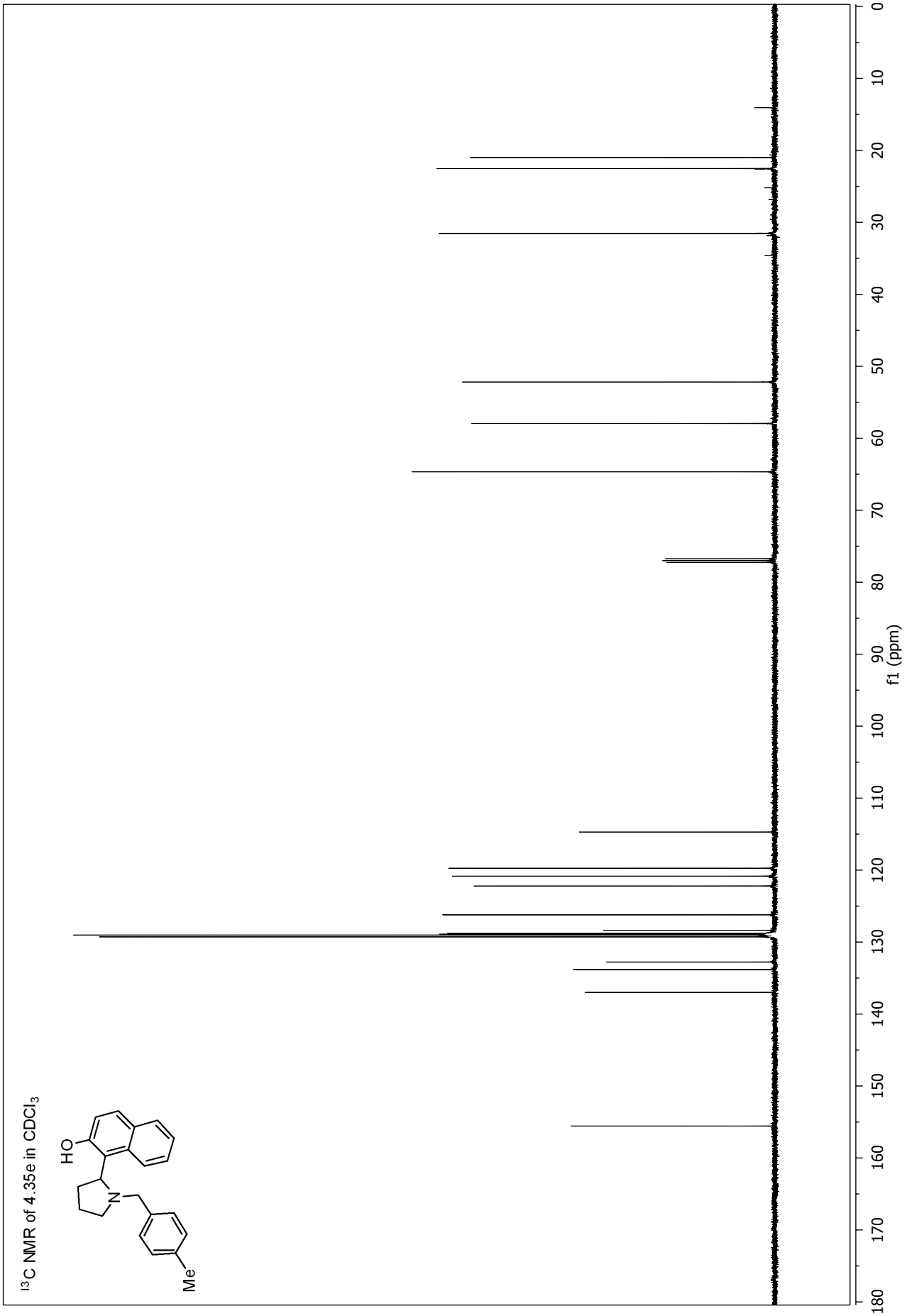

^{1}H NMR of 4.35c in $CDCl_3$
HO
N
Cl
1.36
2.89
2.00
0.99
0.99
0.99
1.00
0.95
0.92
0.91
1.82
1.78
0.95
1.76
f1 (ppm)

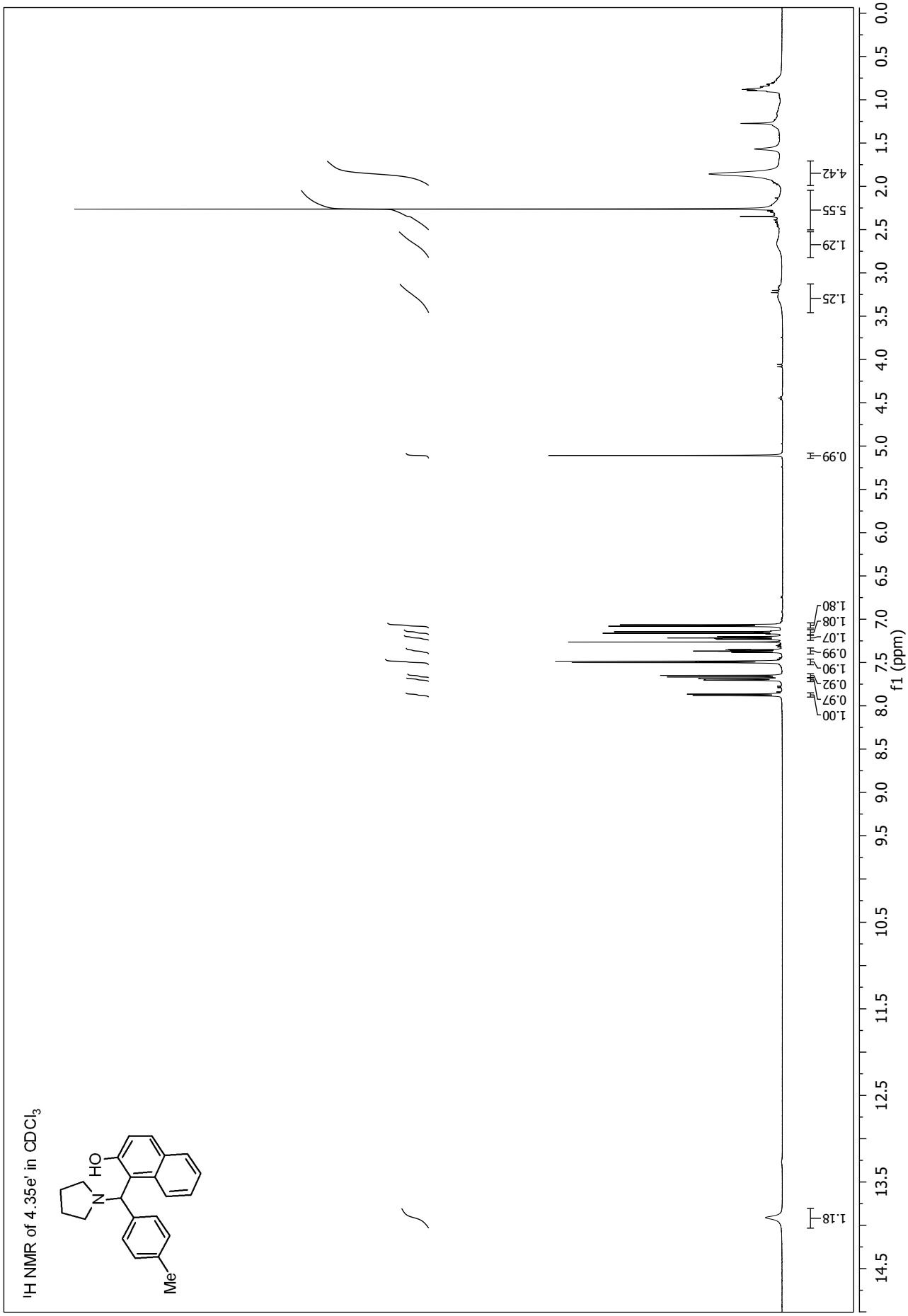

^{13}C NMR of 4.35c in $CDCl_3$
HO
N
Cl
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

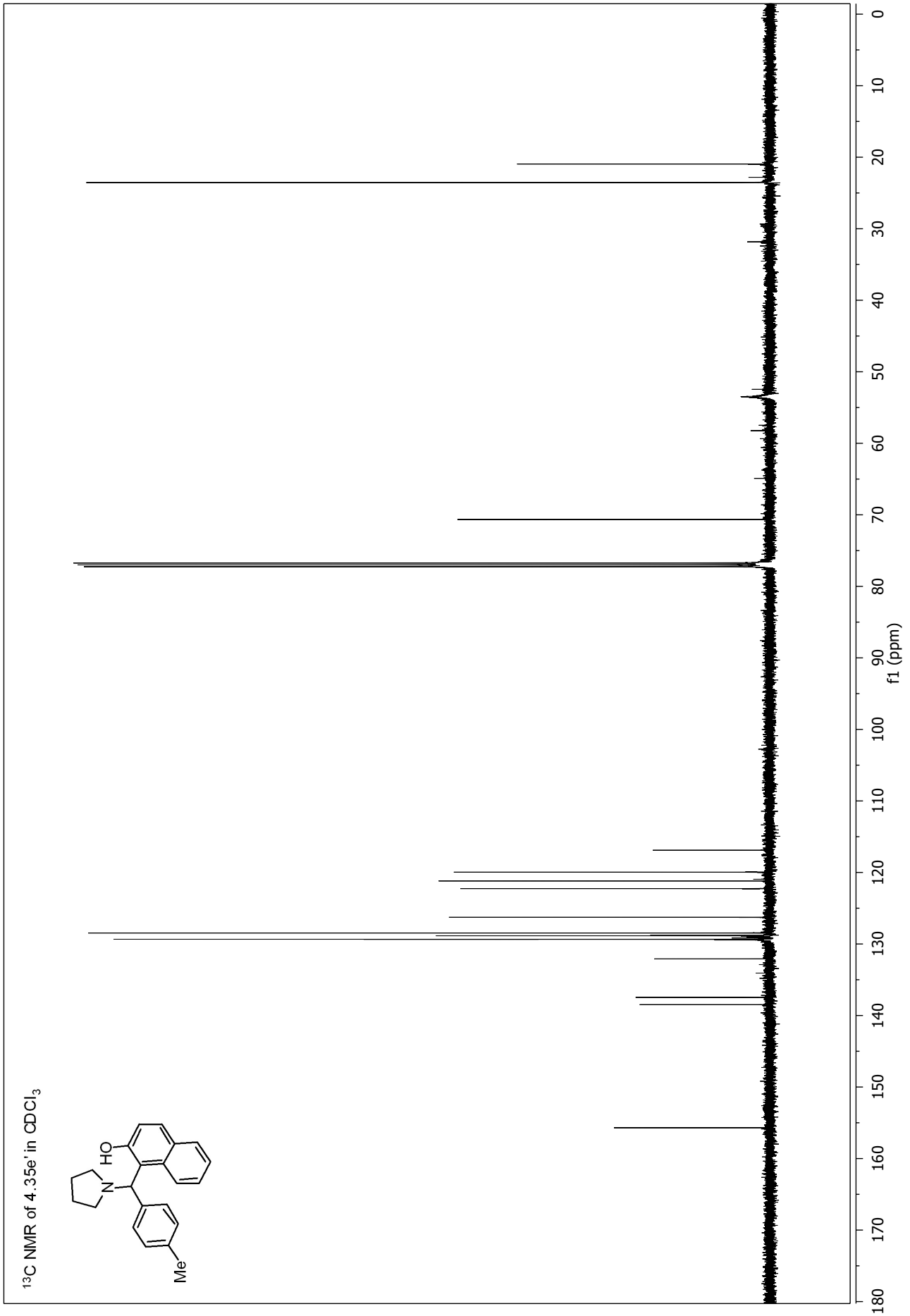

^{1}H NMR of 4.35d in $CDCl_3$
HO
N
F
1.23
0.95
0.94
0.92
0.92
2.83
0.93
1.86
1.02
1.00
1.93
2.04
2.89
f1 (ppm)

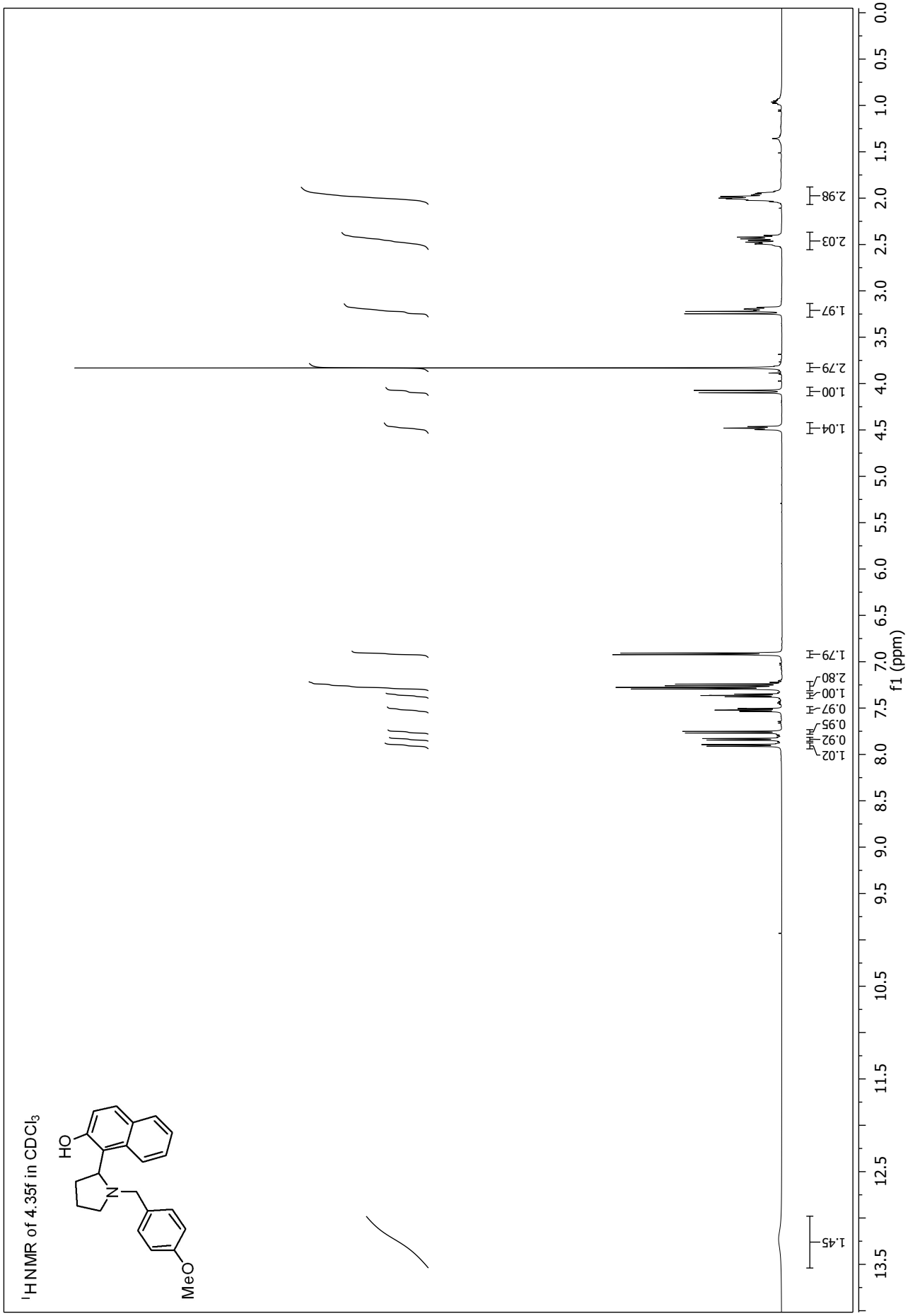

^{13}C NMR of 4.35d in $CDCl_3$
HO
N
F
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

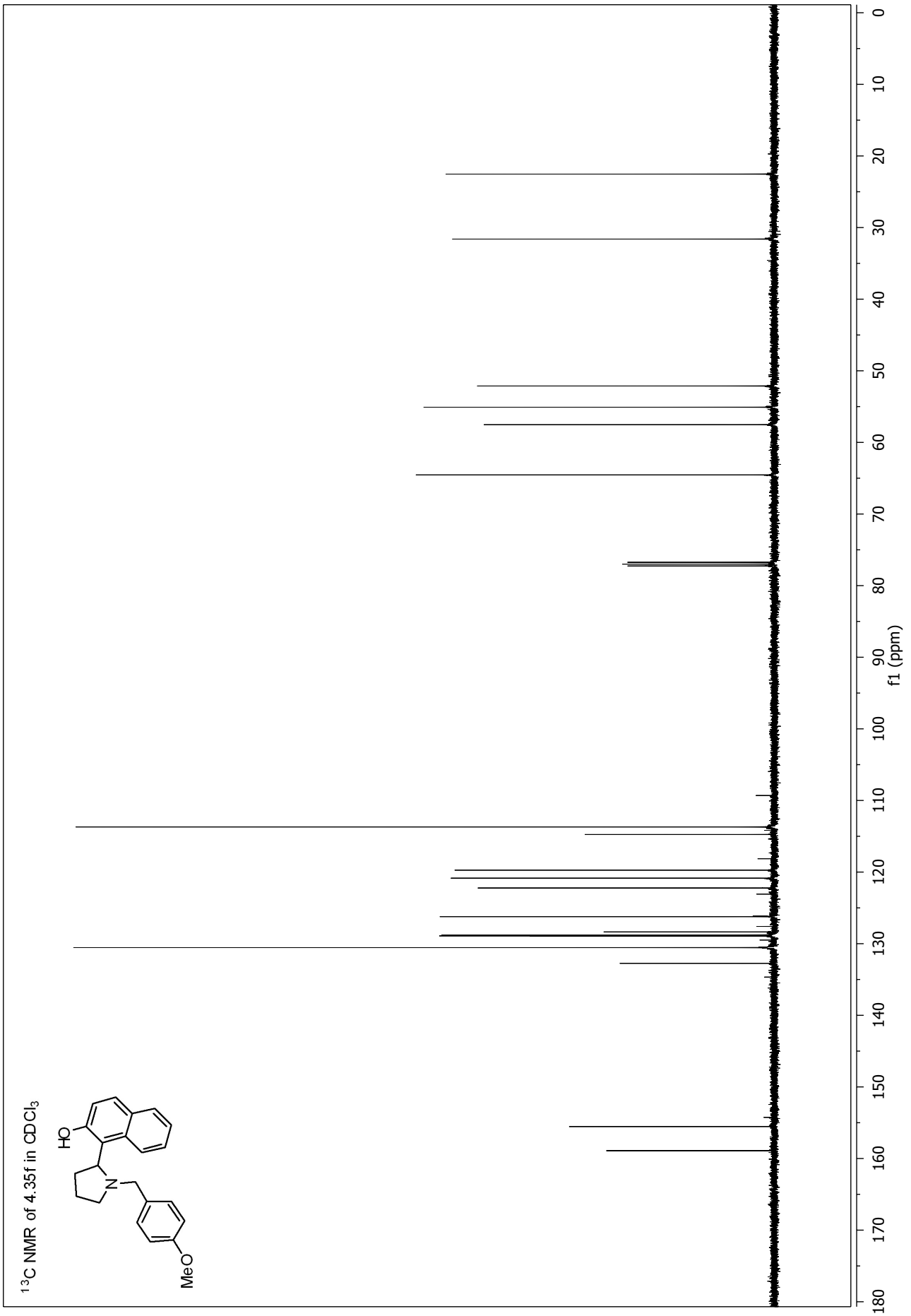

^{1}H NMR of 4.35e in $CDCl_3$
HO
N
Me
1.04
0.92
0.88
0.90
0.92
2.57
0.92
1.74
1.01
1.00
1.94
4.69
2.91
f1 (ppm)

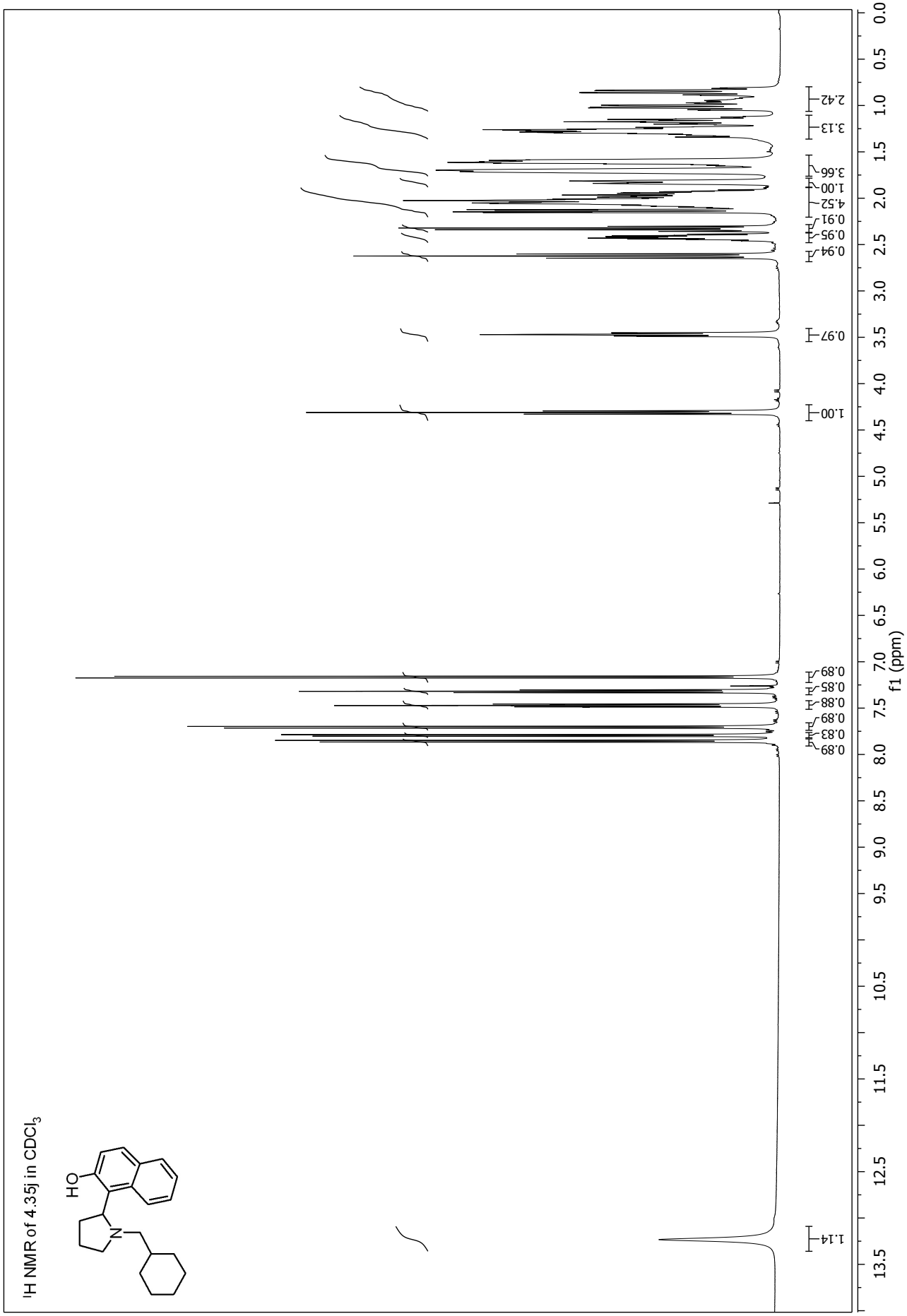

^{13}C NMR of 4.35e in $CDCl_3$
HO
N
Me
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

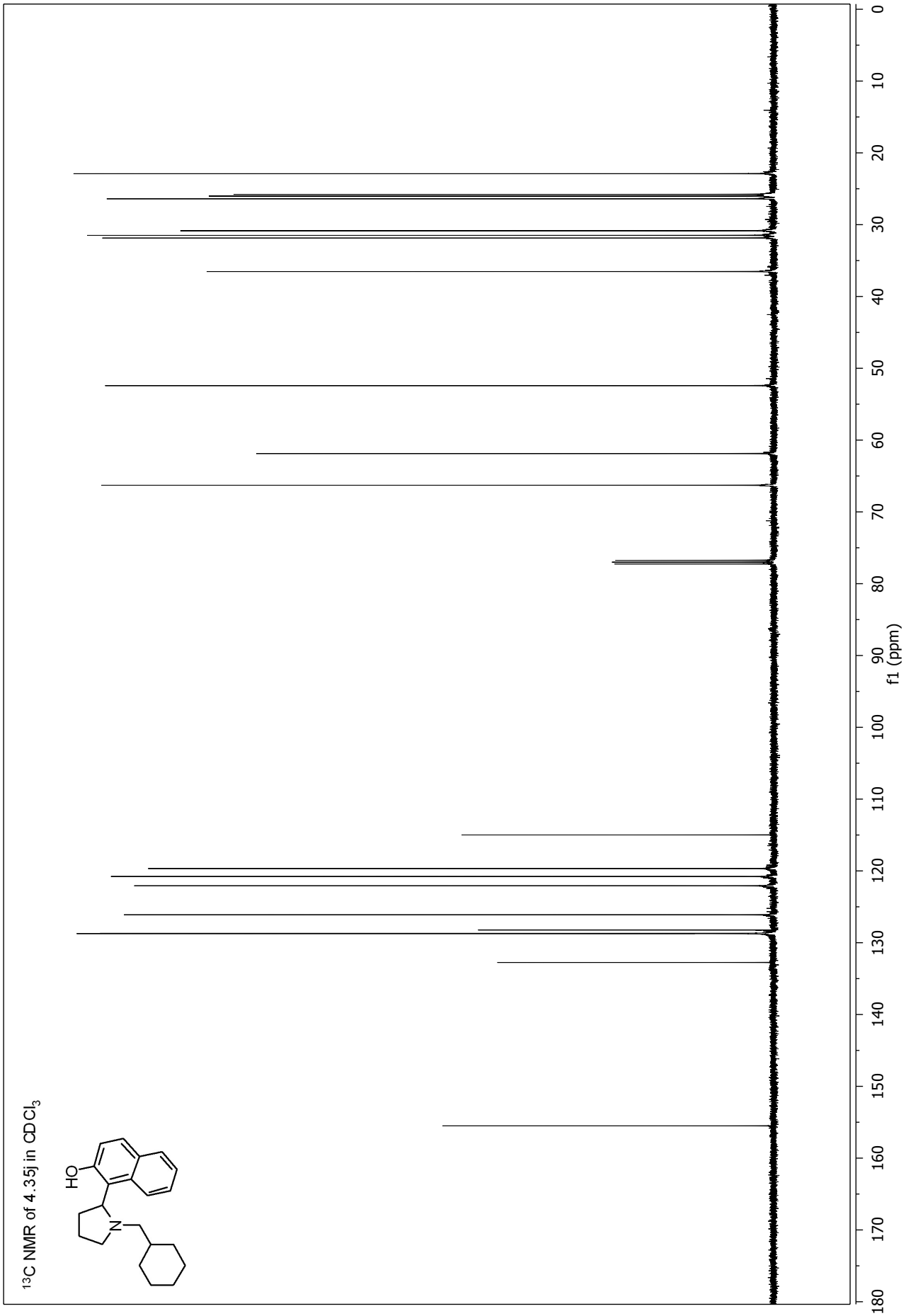

^{1}H NMR of 4.35e' in $CDCl_3$
HO
N
Me
4.42
5.55
1.29
1.25
0.99
1.80
1.08
1.07
0.99
1.90
0.92
0.97
1.00
1.18
f1 (ppm)

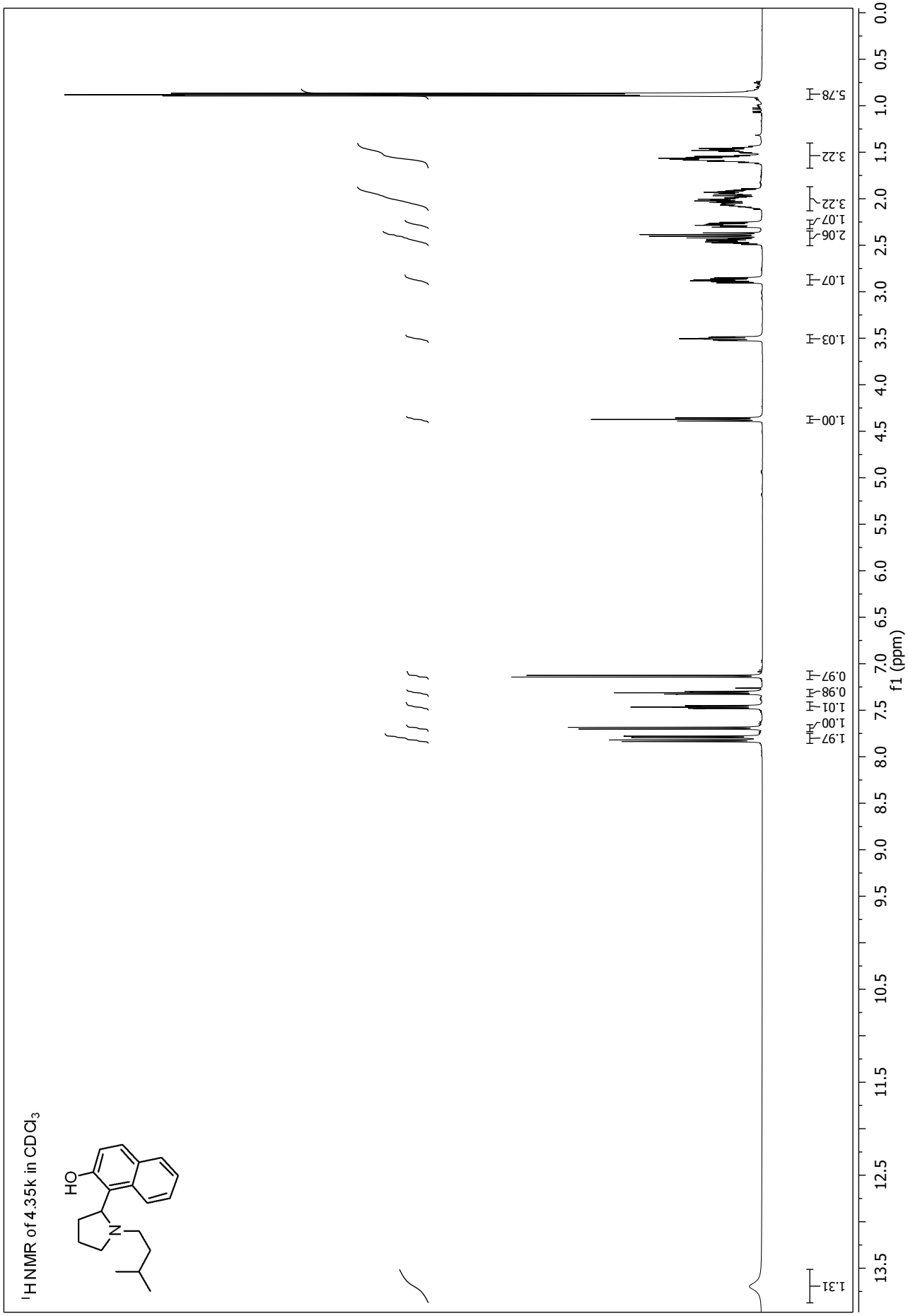

^{13}C NMR of 4.35e' in CDCl$_3$
HO
N
Me
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

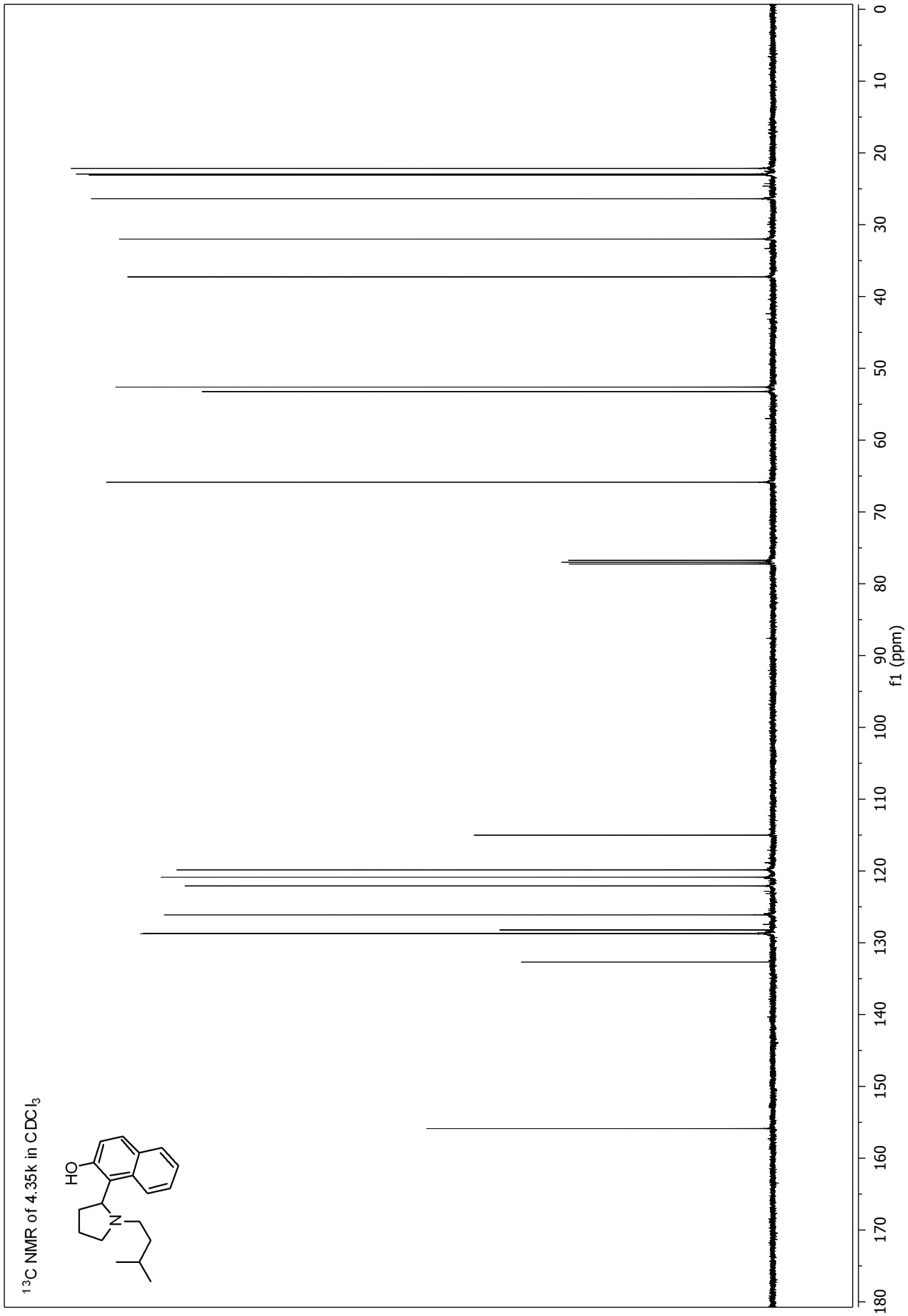

^{1}H NMR of 4.35f in $CDCl_3$
HO
N
MeO
1.45
1.02
0.92
0.95
0.97
1.00
2.80
1.79
1.04
1.00
2.79
1.97
2.03
2.98
f1 (ppm)

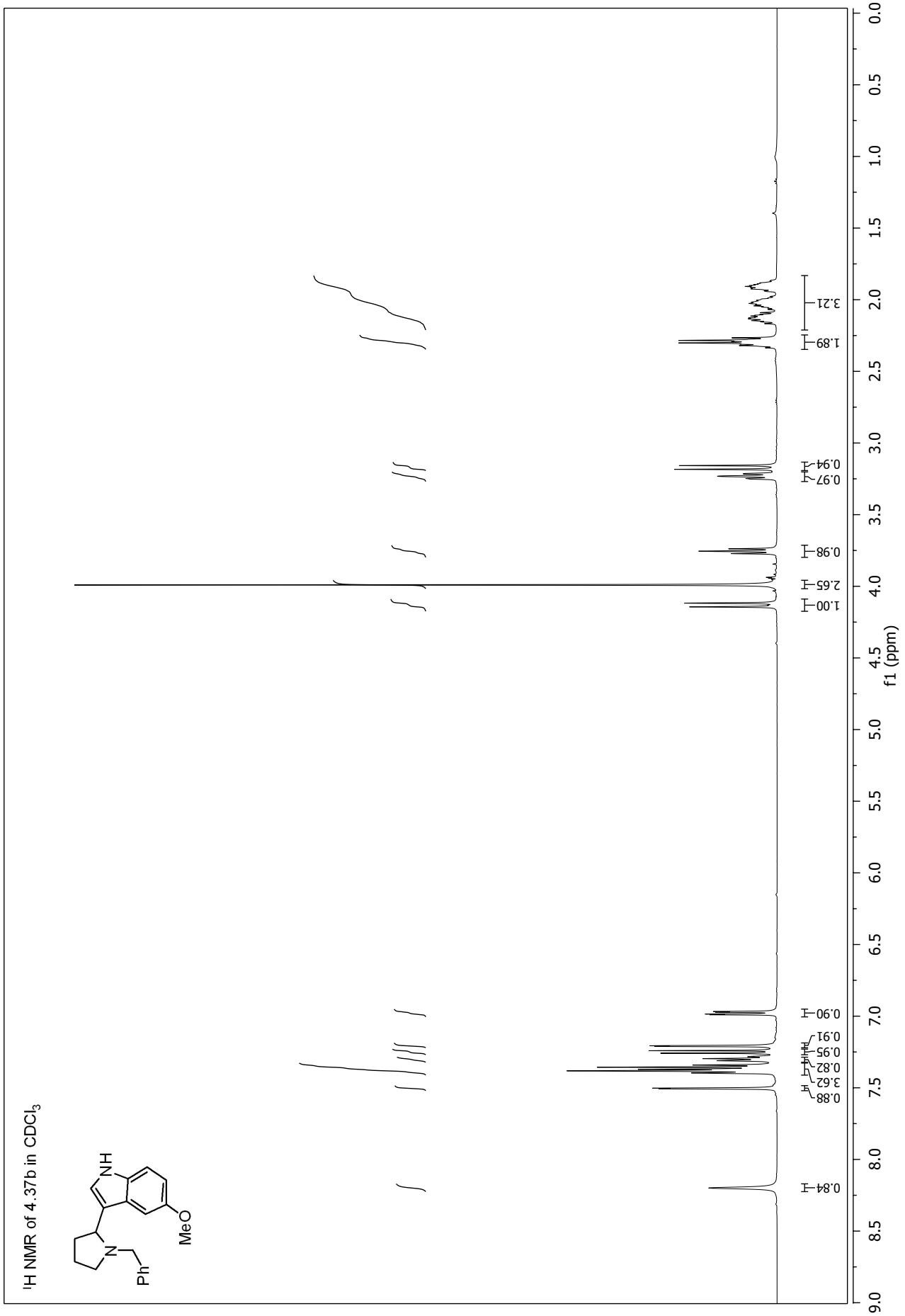

^{13}C NMR of 4.35f in $CDCl_3$
HO
N
MeO
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

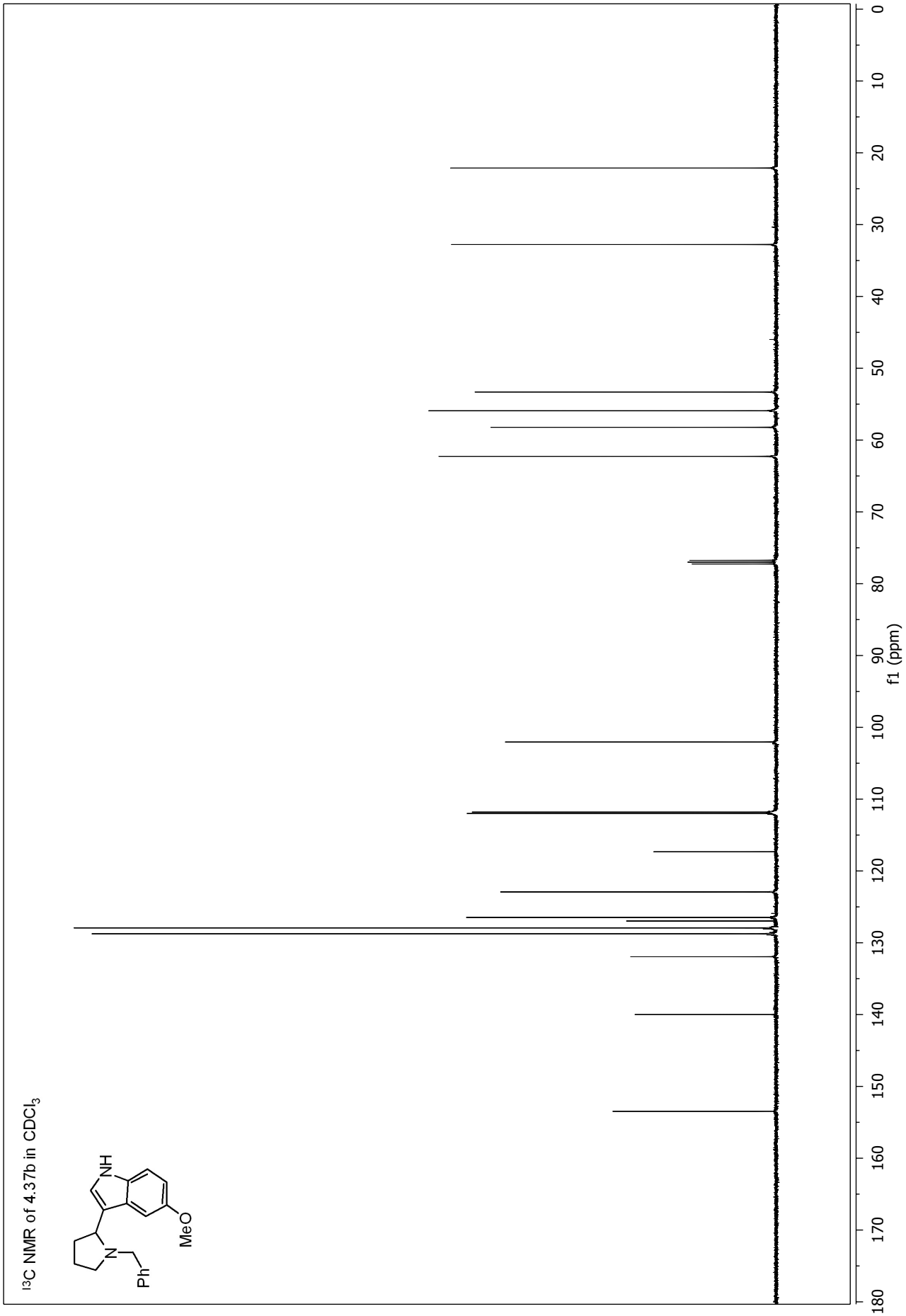

^{1}H NMR of 4.35j in $CDCl_3$
HO
N
1.14
0.89
0.83
0.89
0.88
0.85
0.89
1.00
0.97
0.94
0.95
0.91
4.52
1.00
3.66
3.13
2.42
f1 (ppm)

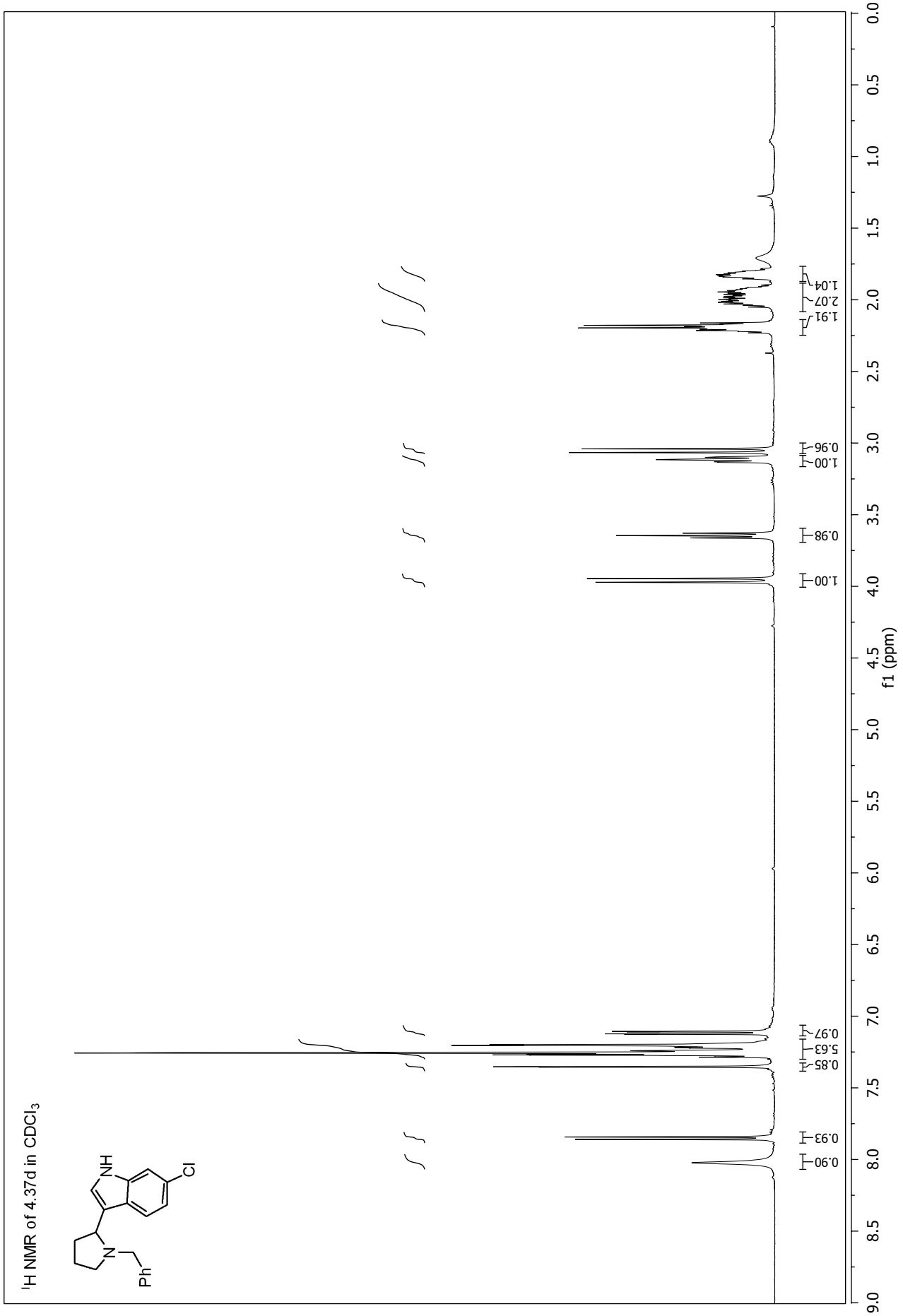

^{13}C NMR of 4.35j in $CDCl_3$
HO
N
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

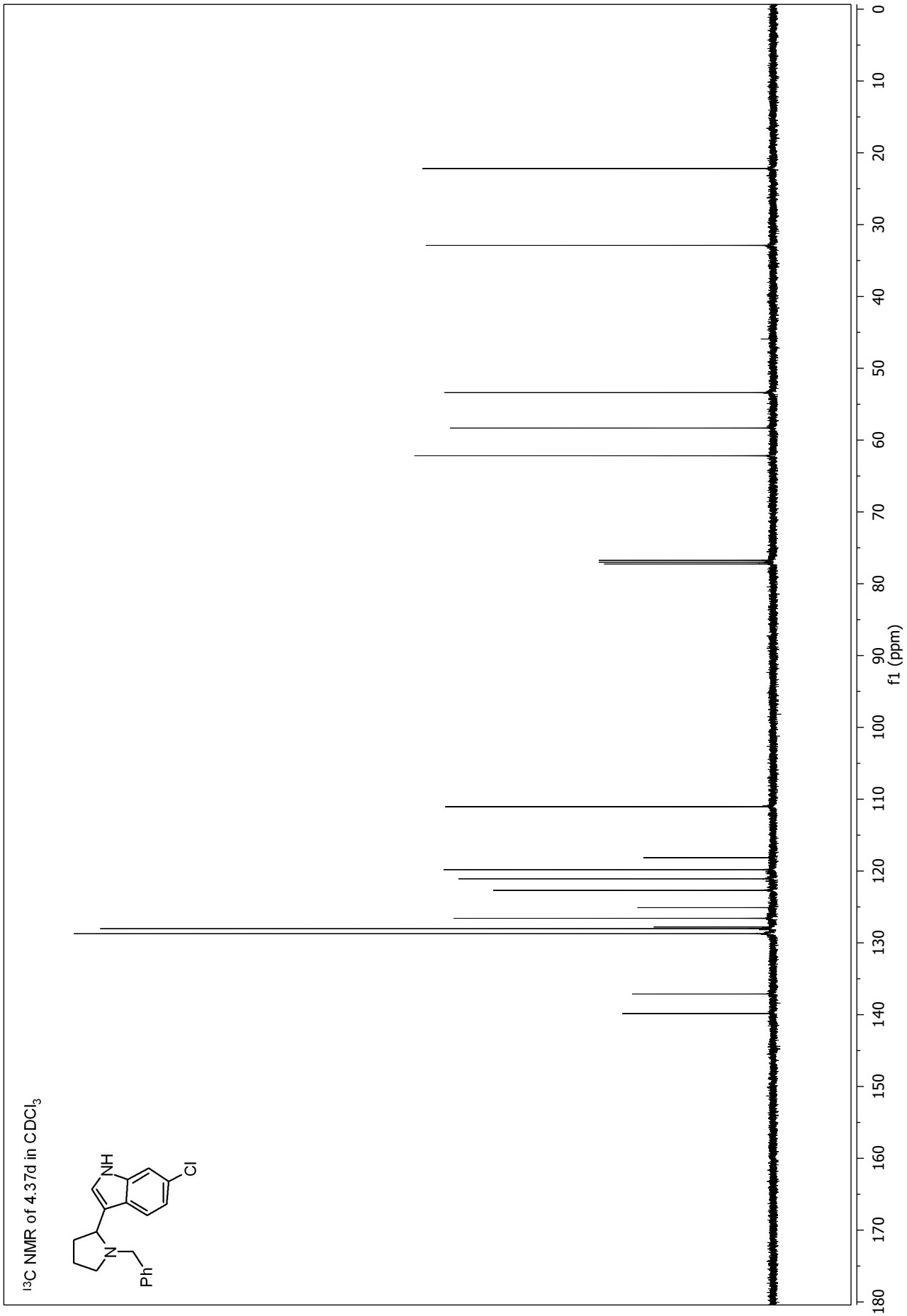

^{1}H NMR of 4.35k in $CDCl_3$
HO
N
5.78
3.22
3.22
1.07
2.06
1.07
1.03
1.00
0.97
0.98
1.01
1.00
1.97
1.31
f1 (ppm)

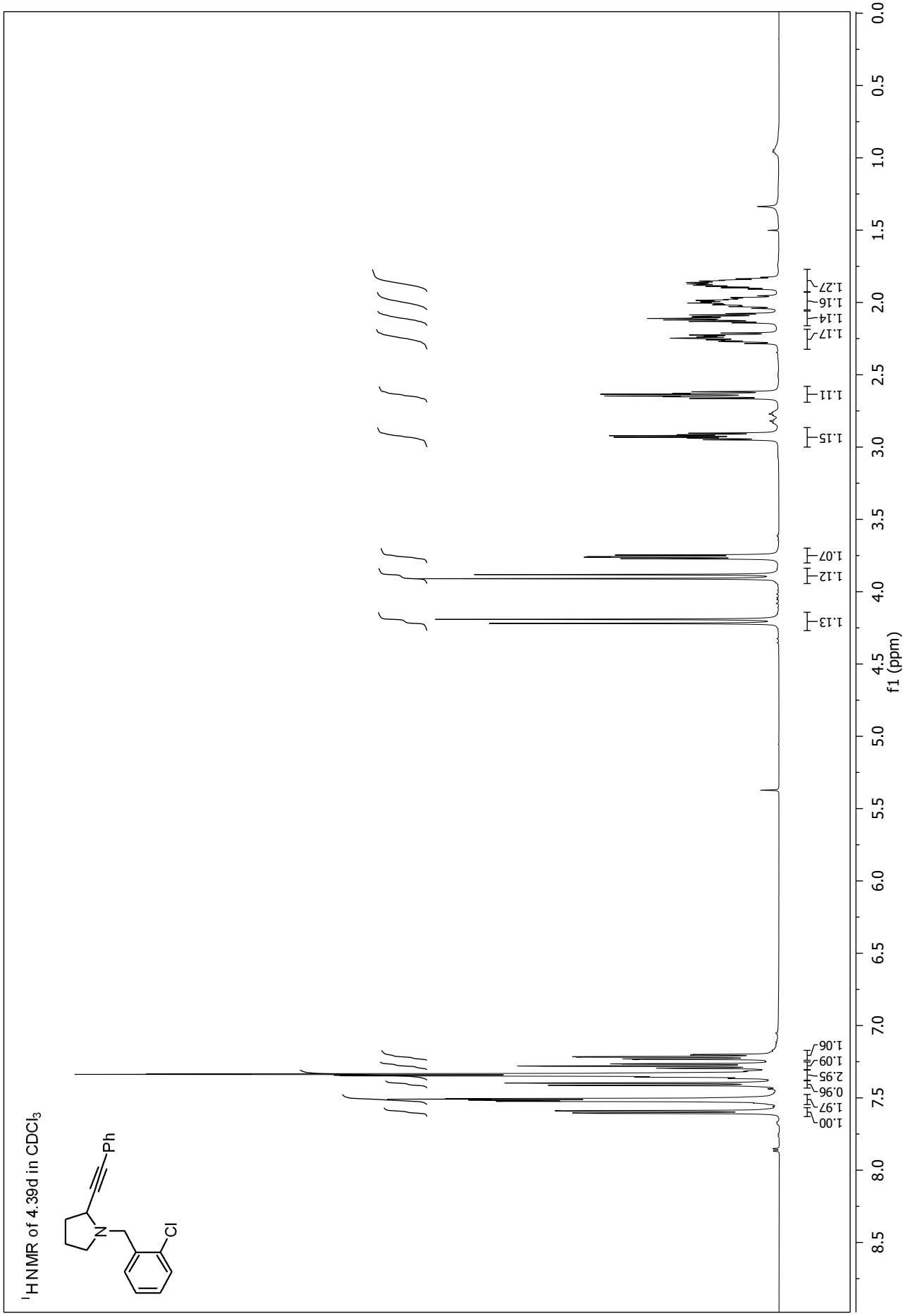

^{13}C NMR of 4.35k in $CDCl_3$
HO
N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

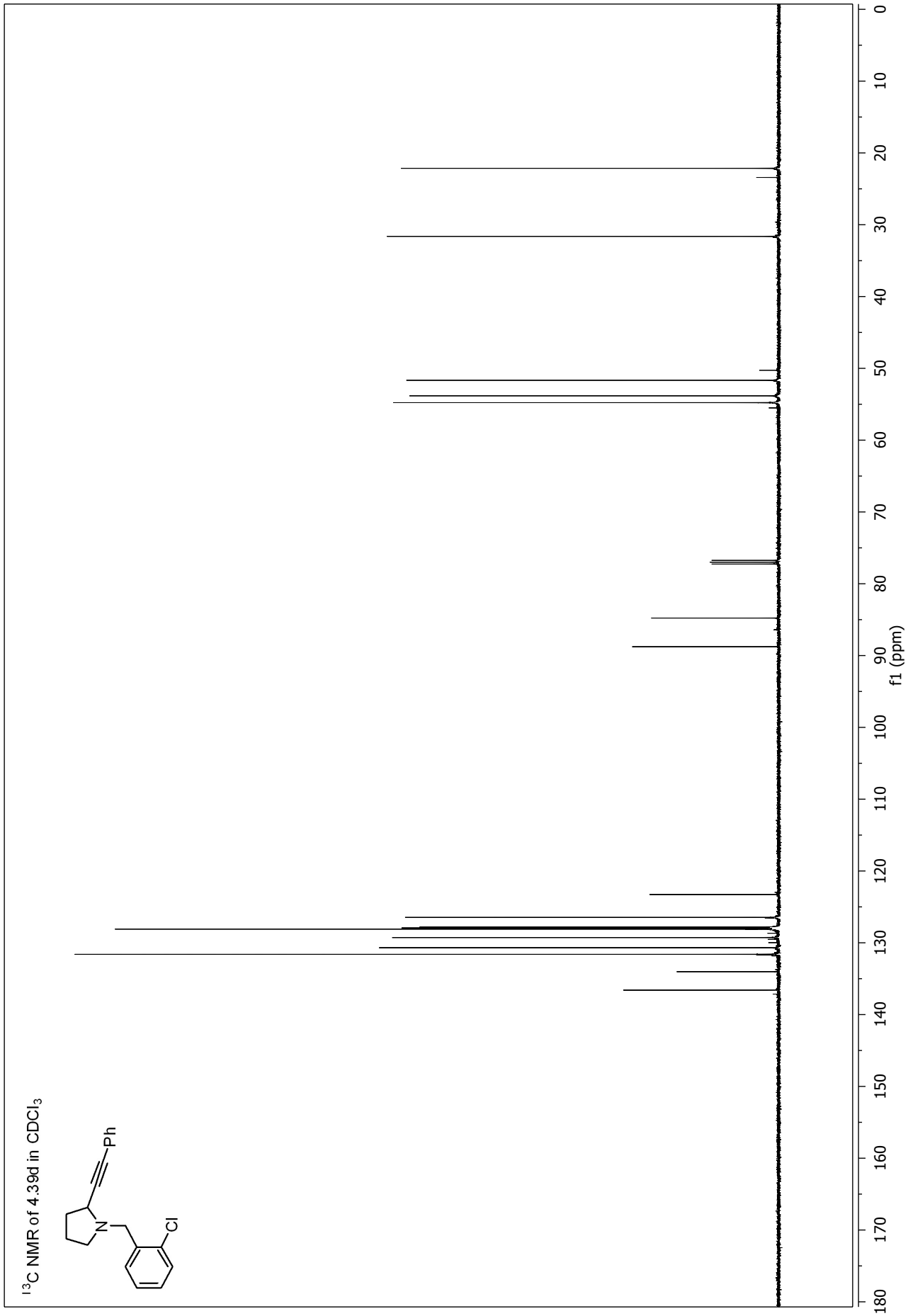

^{1}H NMR of 4.37b in $CDCl_3$
NH
MeO
N
Ph
0.84
0.88
3.62
0.82
0.95
0.91
0.90
1.00
2.65
0.98
0.94
0.97
1.89
3.21
f1 (ppm)

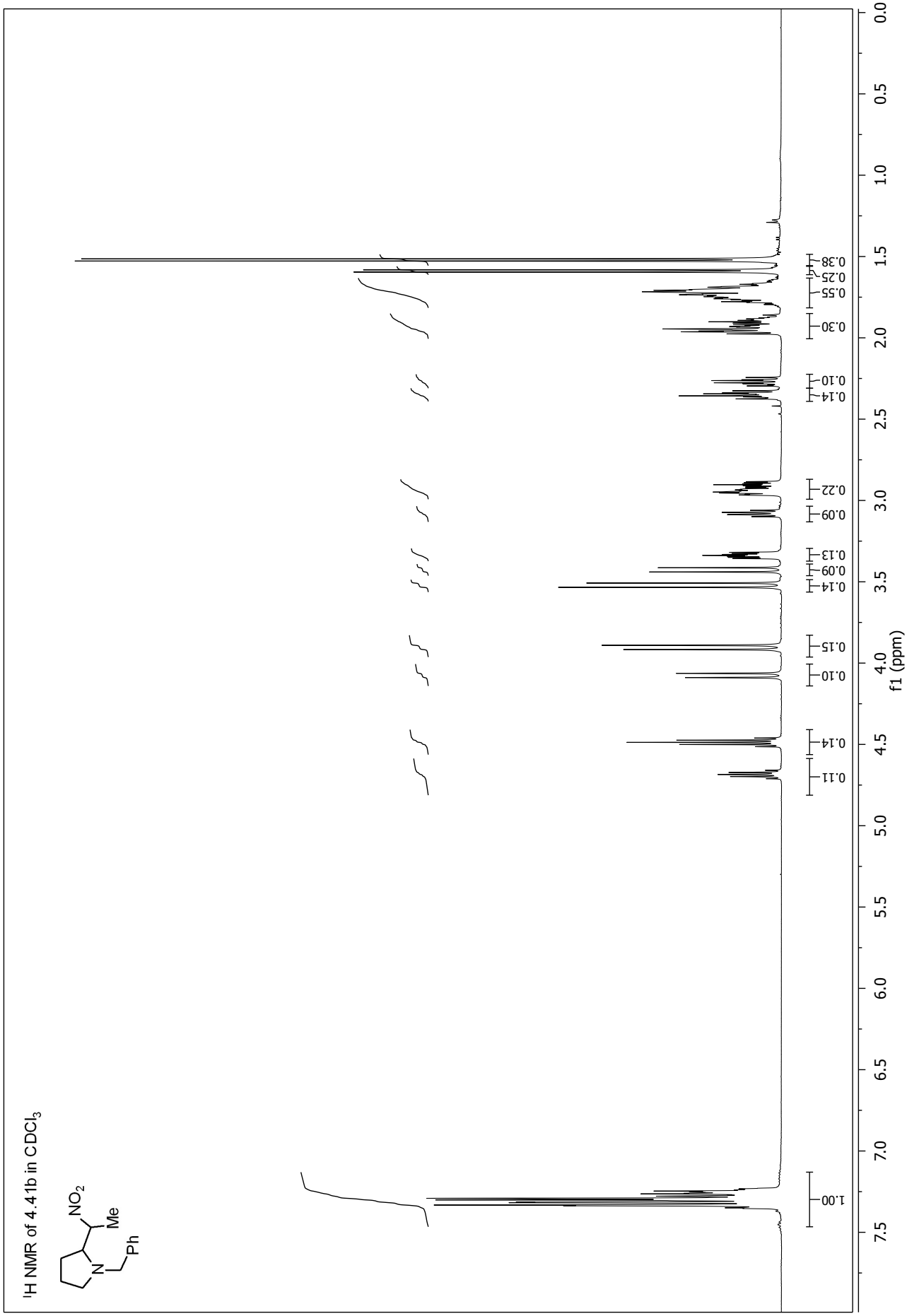

^{13}C NMR of 4.37b in $CDCl_3$
NH
MeO
N
Ph
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

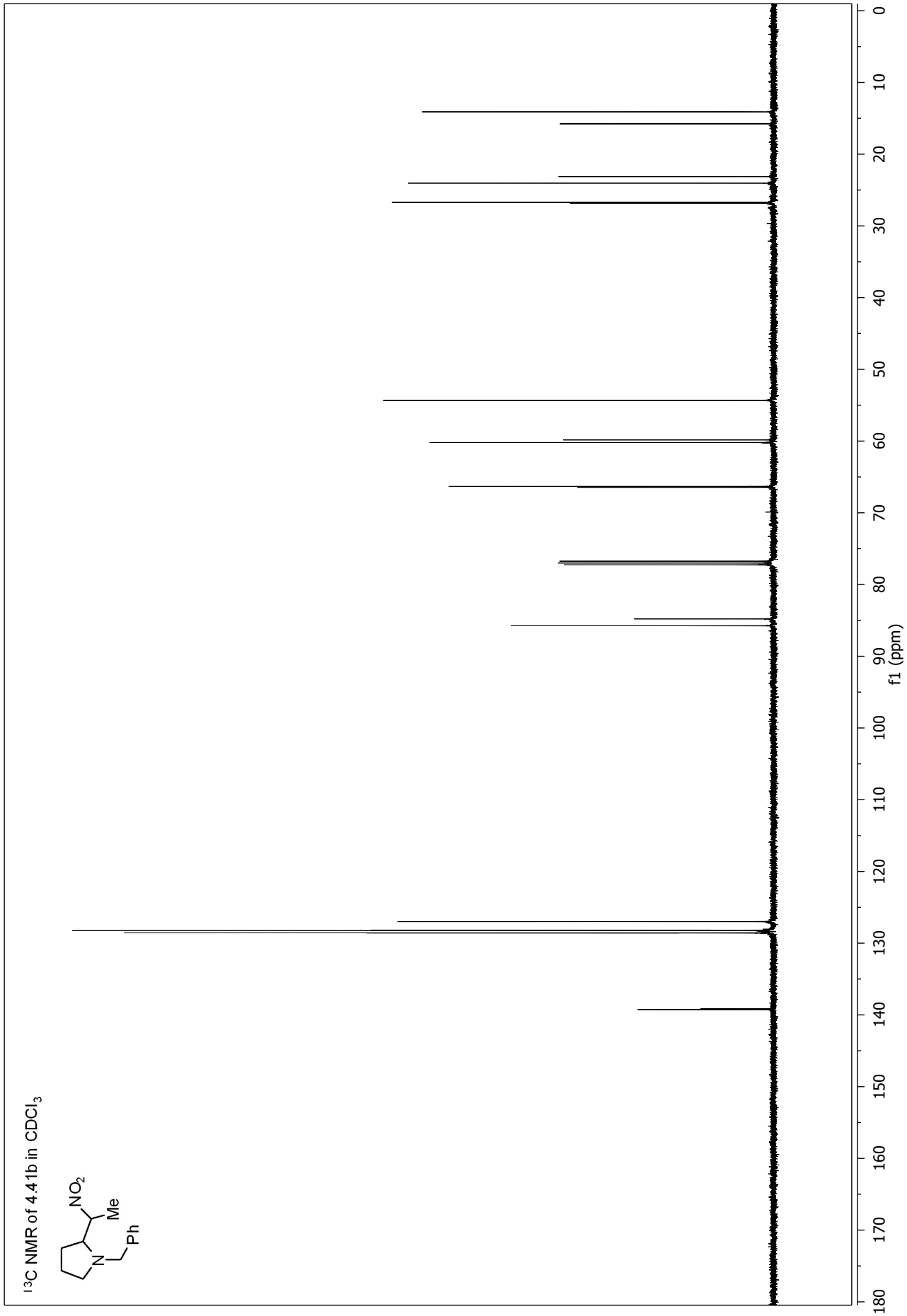

^{1}H NMR of 4.37d in $CDCl_3$
NH
Cl
N
Ph
0.90
0.93
0.85
5.63
0.97
1.00
0.98
1.00
0.96
1.00
1.91
2.07
1.04
f1 (ppm)

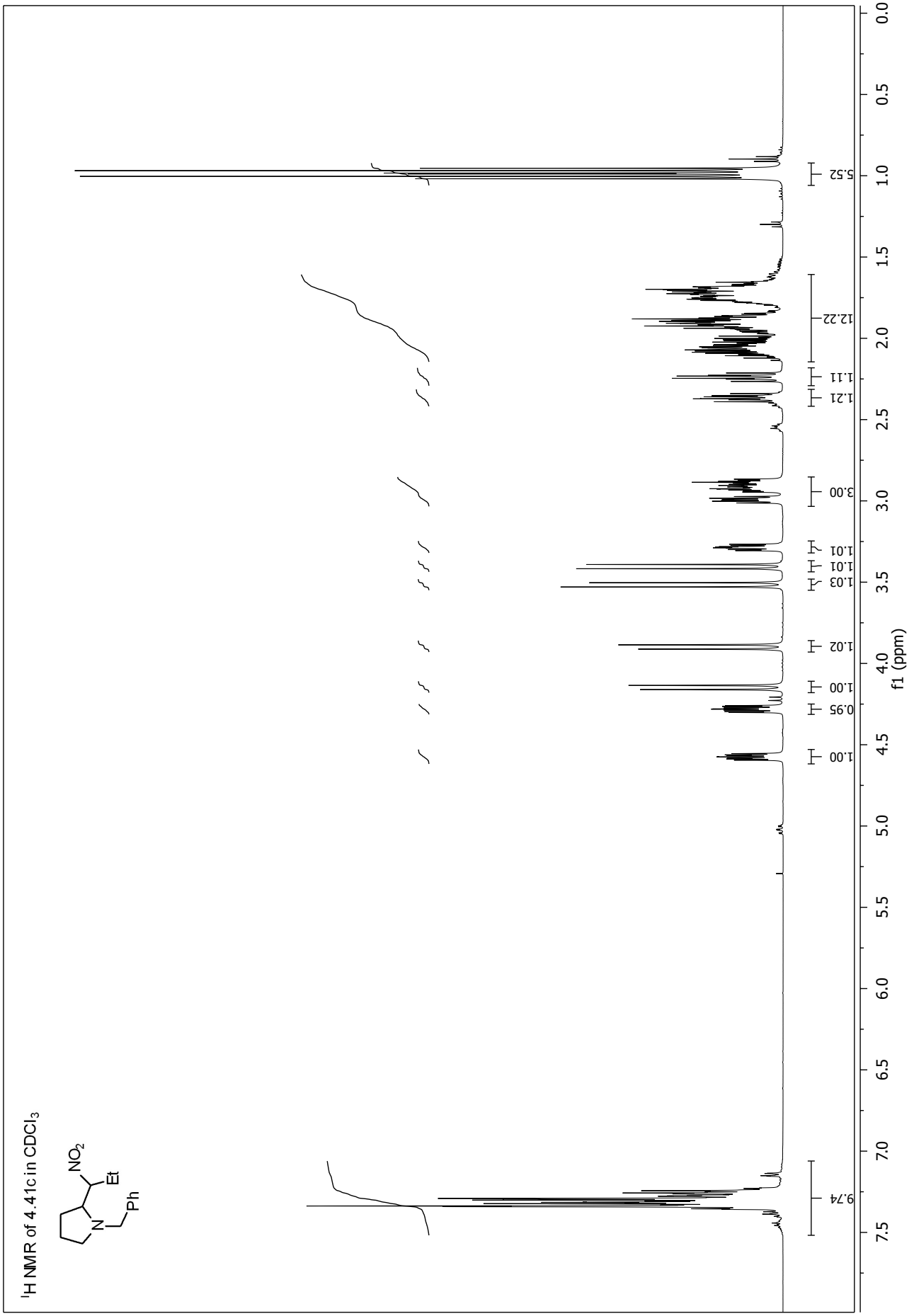

^{13}C NMR of 4.37d in $CDCl_3$
NH
Cl
N
Ph
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

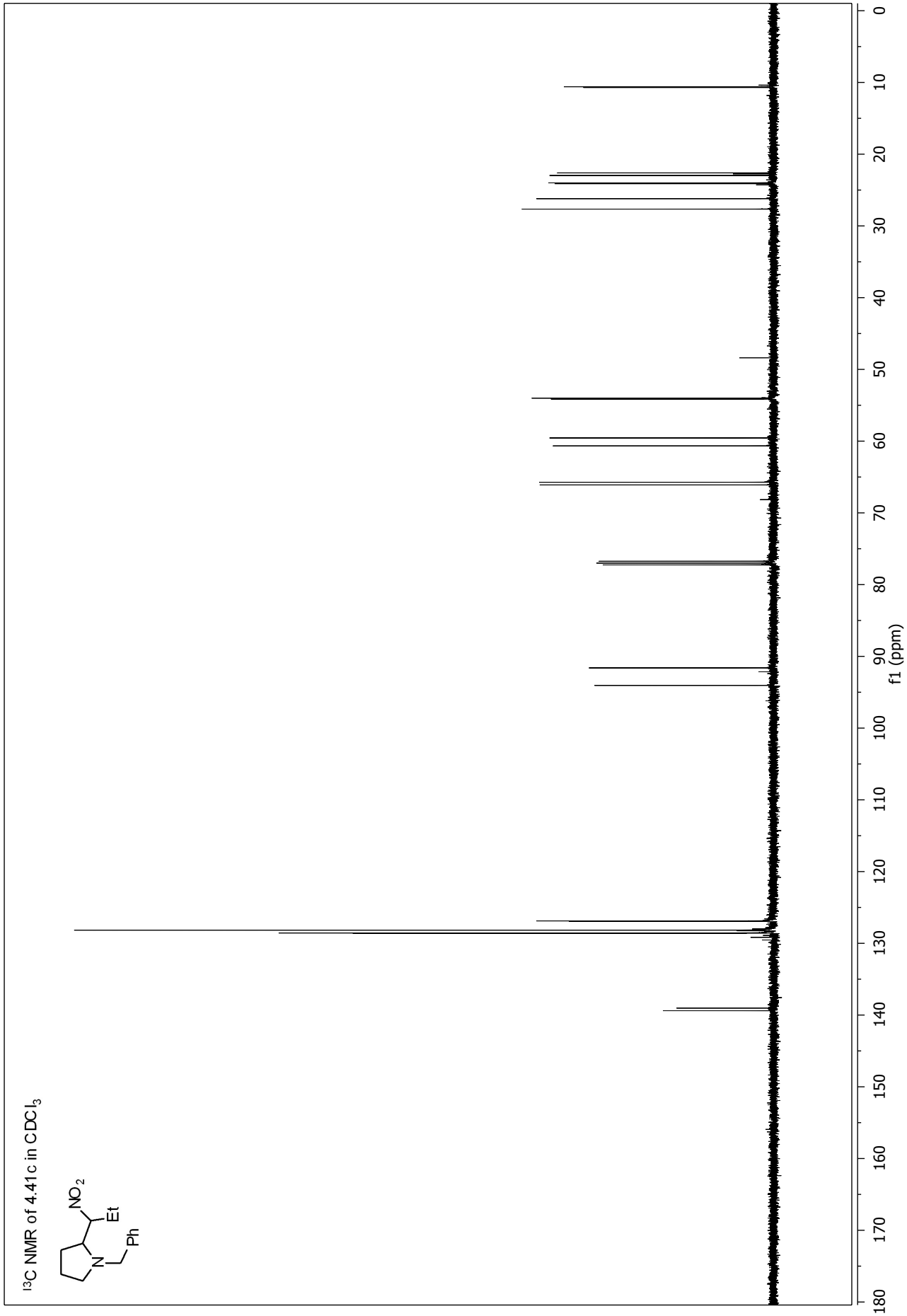

^{1}H NMR of 4.39d in $CDCl_3$
Ph
N
Cl
1.00
1.97
0.96
2.95
1.09
1.06
1.13
1.12
1.07
1.15
1.11
1.17
1.14
1.16
1.27
f1 (ppm)

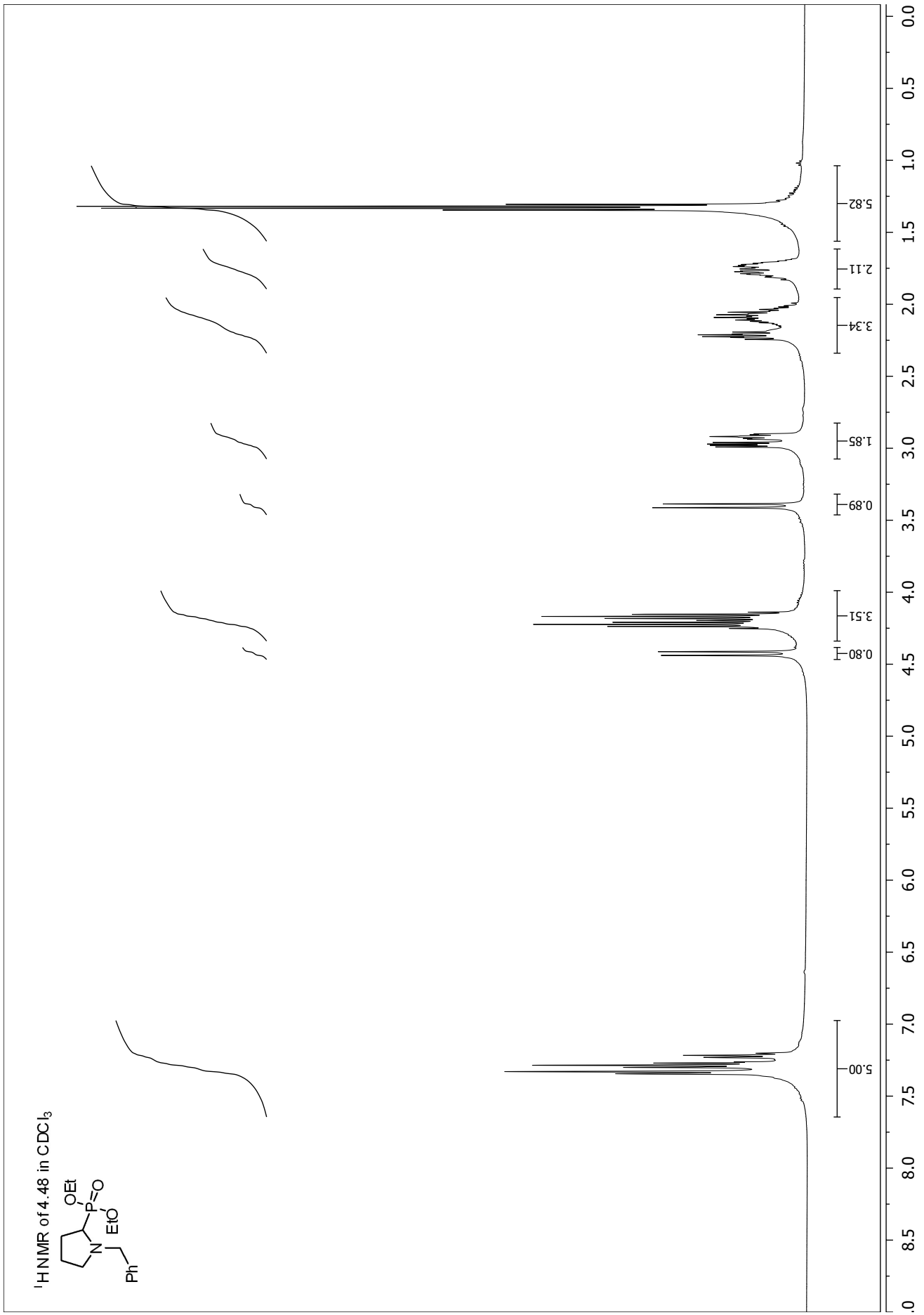

^{13}C NMR of 4.39d in $CDCl_3$
Ph
N
Cl
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

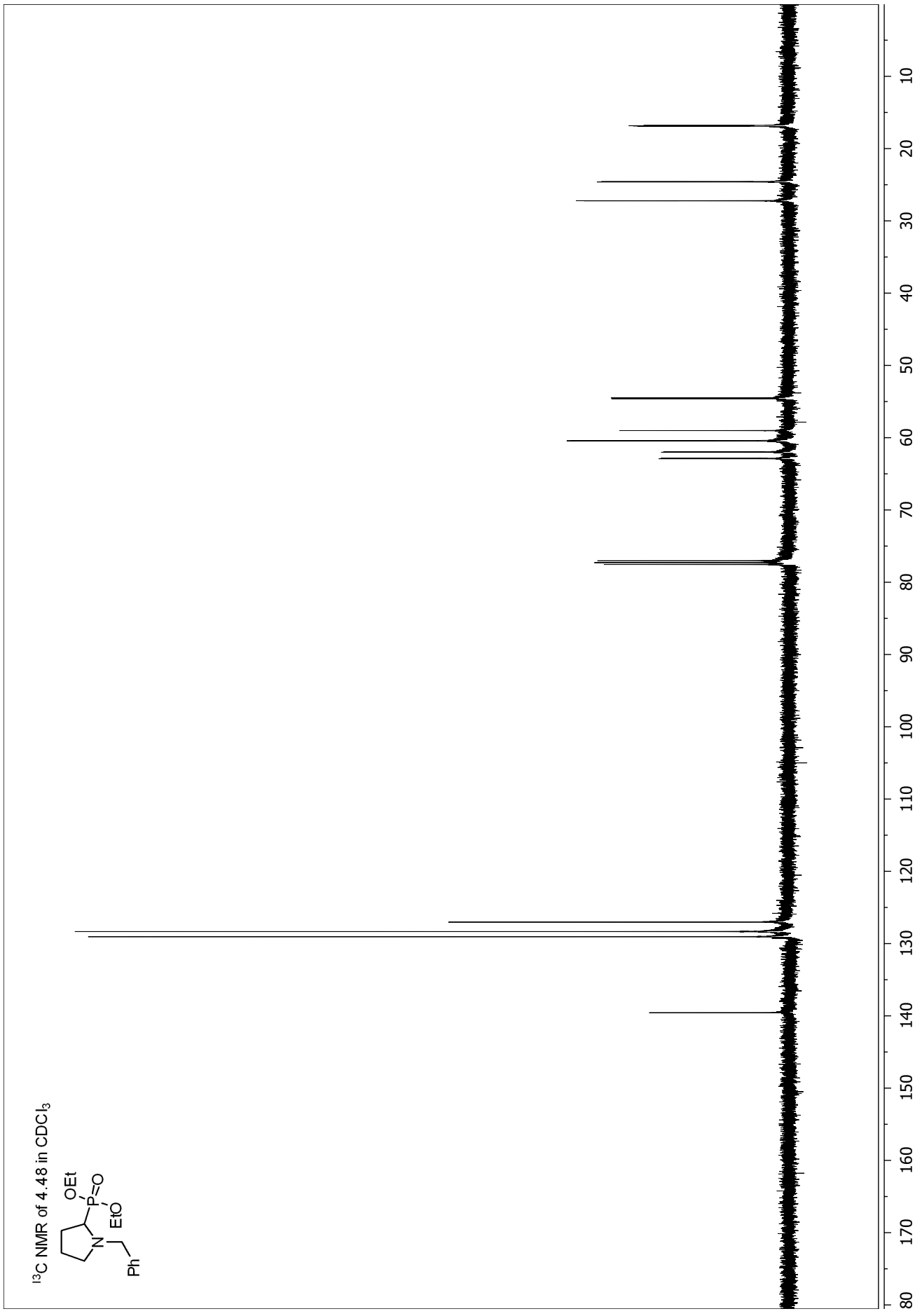

^{1}H NMR of 4.41b in $CDCl_3$
NO_2
Me
Ph
N
1.00
0.11
0.14
0.10
0.15
0.14
0.09
0.13
0.09
0.22
0.14
0.10
0.30
0.55
0.25
0.38
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

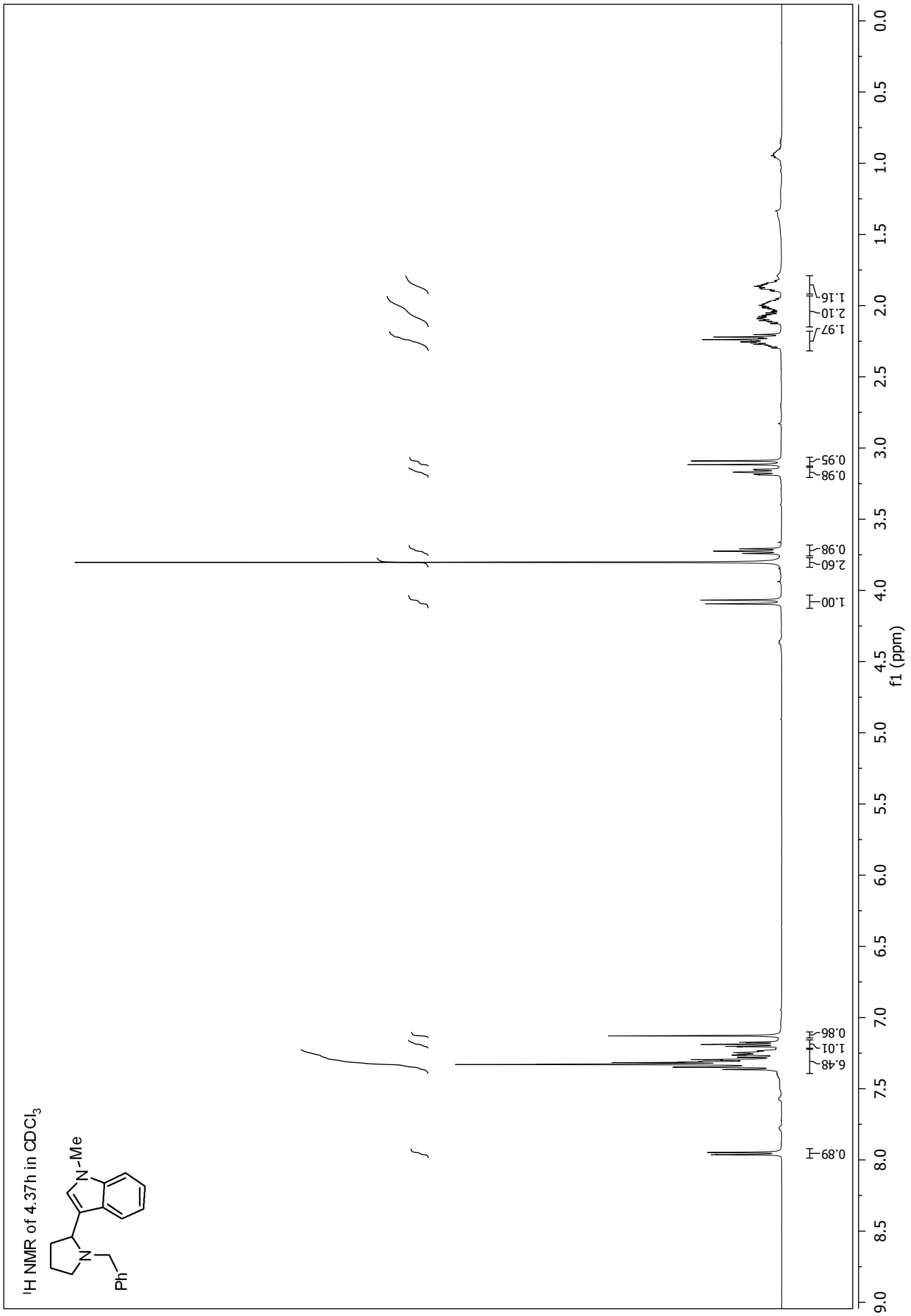

^{13}C NMR of 4.41b in $CDCl_3$
NO_2
Me
Ph
N
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

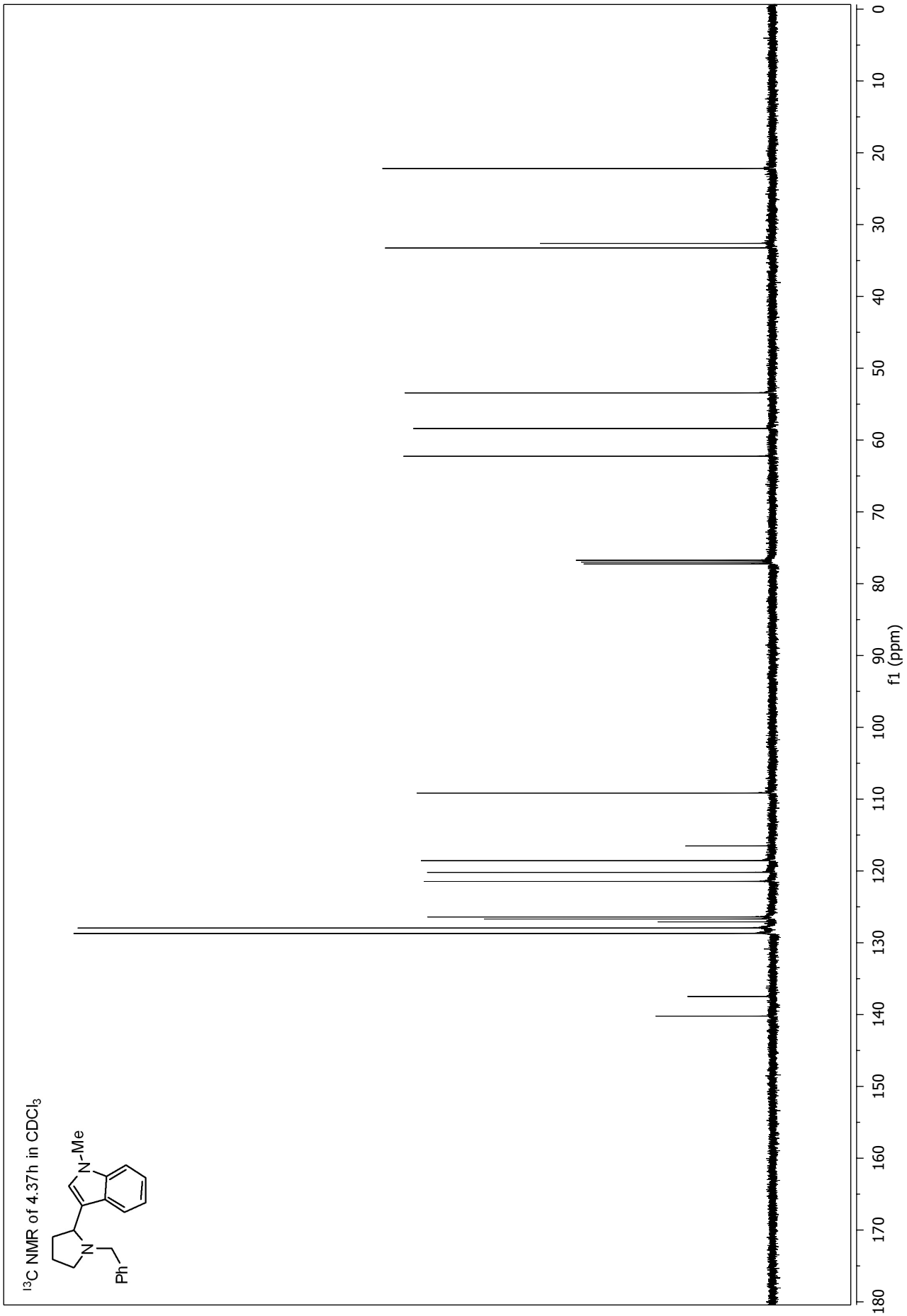

^{1}H NMR of 4.41c in $CDCl_3$
NO_2
Et
Ph
N
9.74
0.95
1.00
1.00
1.02
1.03
1.01
1.01
3.00
1.21
1.11
12.22
5.52
f1 (ppm)


^{13}C NMR of 4.41c in $CDCl_3$
NO_2
Et
N
Ph
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

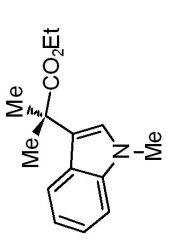

^{1}H NMR of 4.48 in $CDCl_3$
OEt
P=O
EtO
N
Ph
5.82
2.11
3.34
1.85
0.89
3.51
0.80
5.00
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5


^{13}C NMR of 4.48 in $CDCl_3$
OEt
P=O
EtO
N
Ph
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

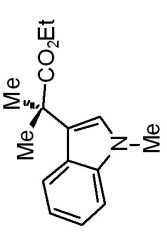

^{1}H NMR of 4.37h in $CDCl_3$
N-Me
N
N
Ph
0.89
6.48
1.01
0.86
2.60
0.98
1.00
0.98
0.95
1.97
2.10
1.16
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
f1 (ppm)


^{13}C NMR of 4.37h in $CDCl_3$
N-Me
N
N
Ph
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

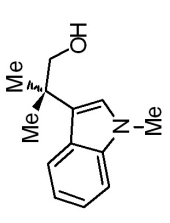
^{1}H NMR of **4.103** in $CDCl_3$



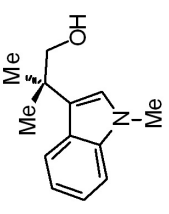
^{13}C NMR of **4.103** in $CDCl_3$



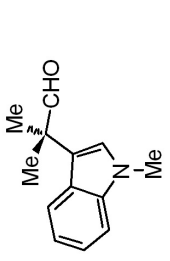
^{1}H NMR of **4.104** in $CDCl_3$



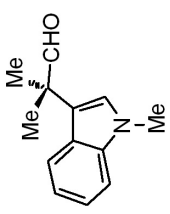
^{13}C NMR of **4.104** in $CDCl_3$



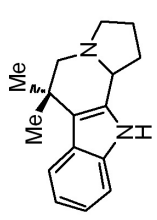
^{1}H NMR of **4.105** in $CDCl_3$



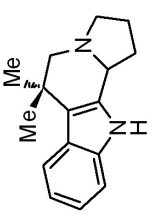
^{13}C NMR of **4.105** in $CDCl_3$



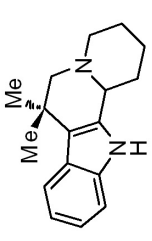
^{1}H NMR of **4.71** in $CDCl_3$



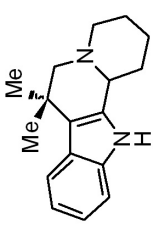
^{13}C NMR of **4.71** in $CDCl_3$



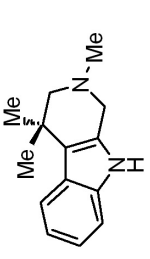
^{1}H NMR of **4.73** in $CDCl_3$



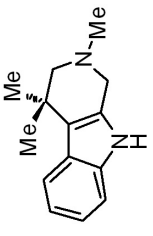
^{13}C NMR of **4.73** in $CDCl_3$



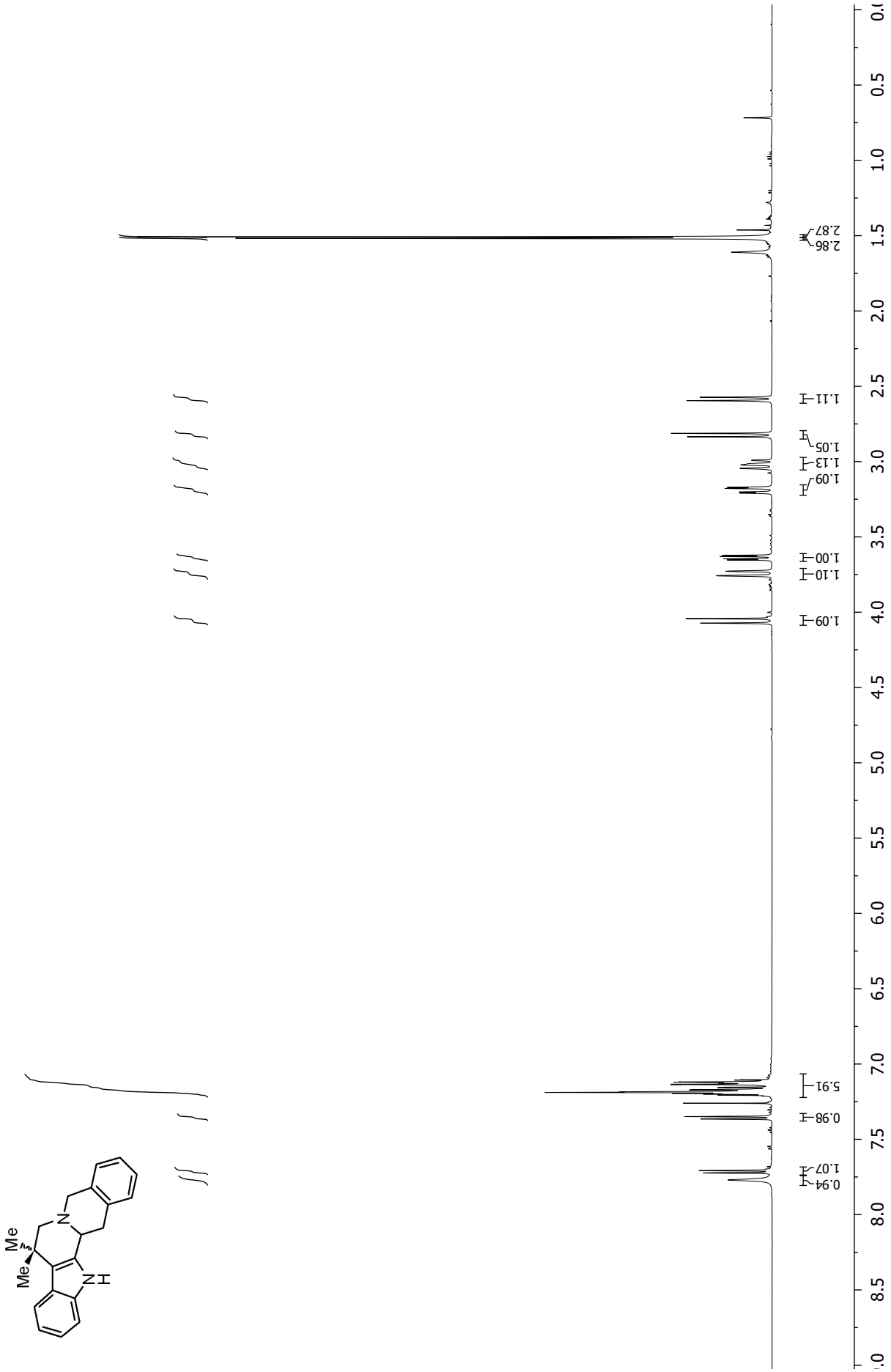
^{1}H NMR of **4.74** in $CDCl_3$



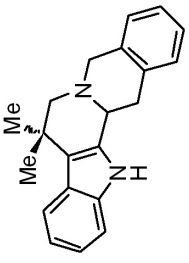
^{13}C NMR of **4.74** in $CDCl_3$



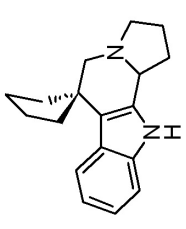
^{1}H NMR of **4.76** in $CDCl_3$



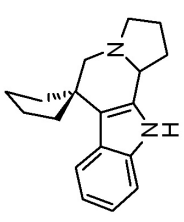
^{13}C NMR of **4.76** in $CDCl_3$



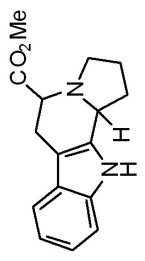
^{1}H NMR of **4.78** in $CDCl_3$



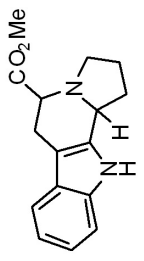
^{13}C NMR of **4.78** in $CDCl_3$



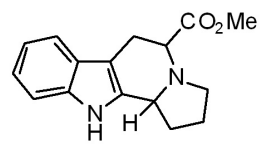
^{1}H NMR of **4.80** in $CDCl_3$



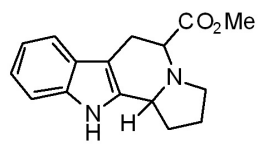
^{13}C NMR of **4.80** in $CDCl_3$



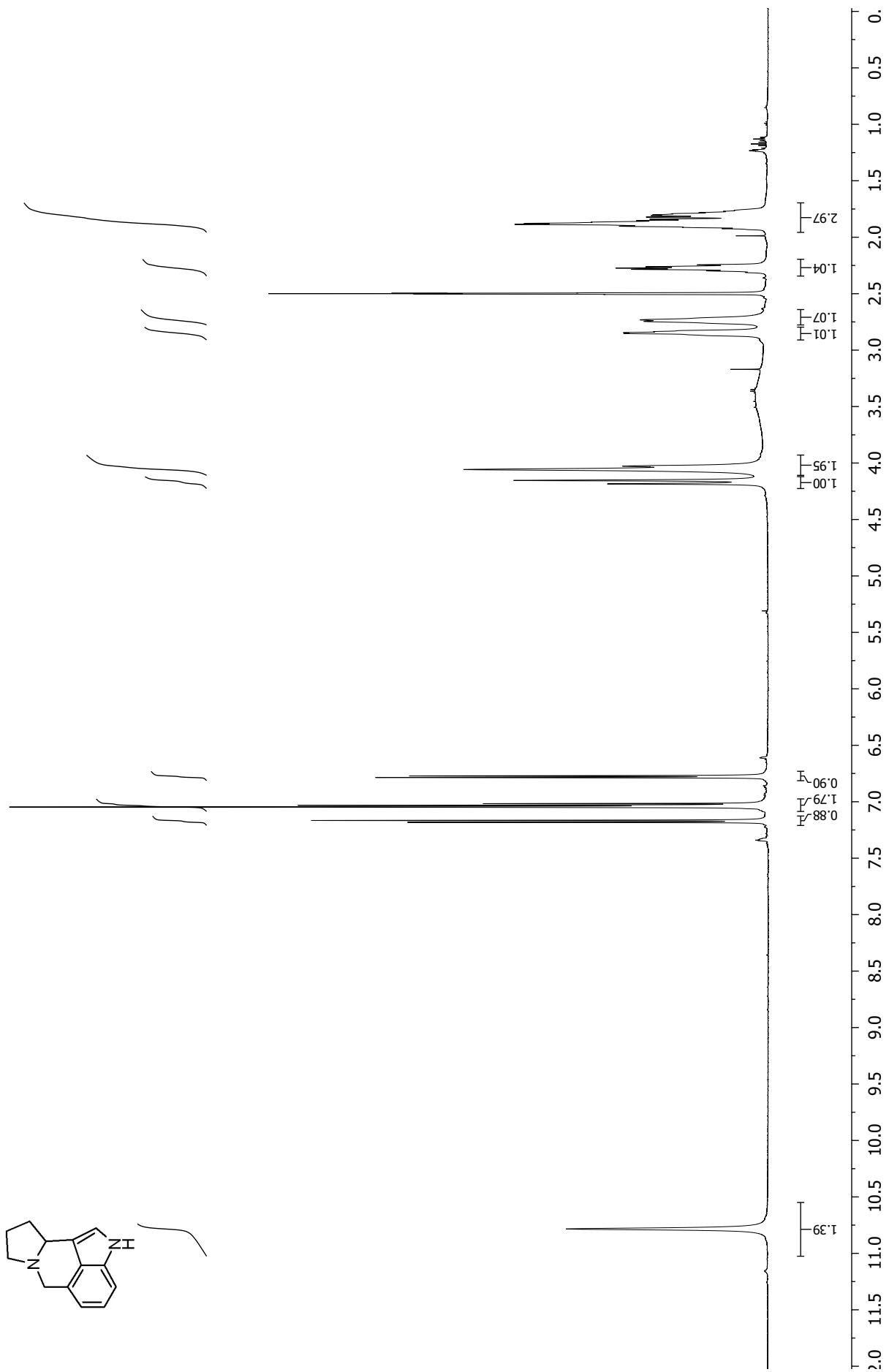
Nosy of **4.80** in $CDCl_3$



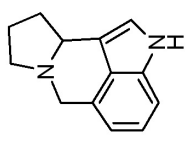
Nosy of **4.80** in $CDCl_3$



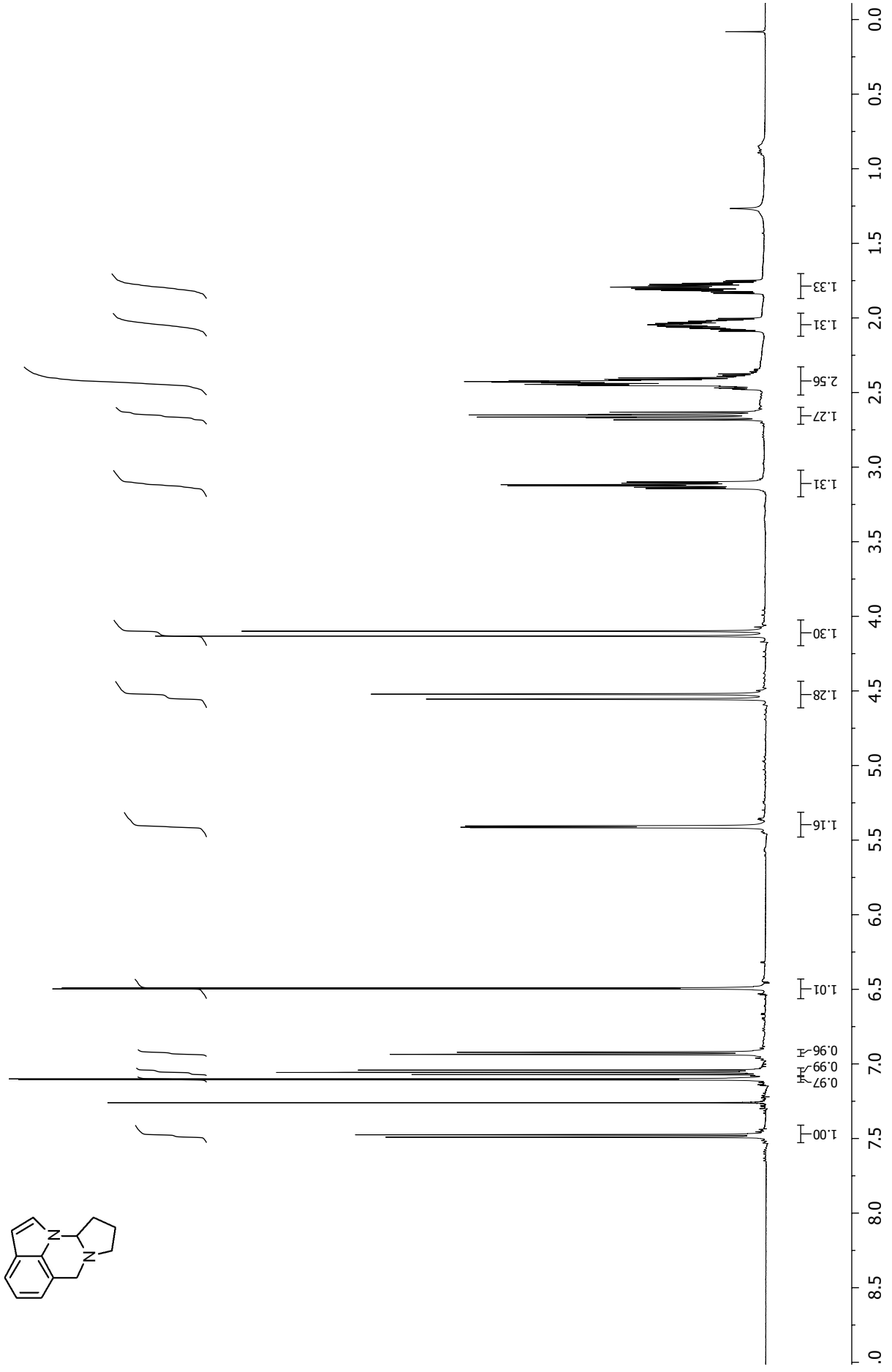
^{1}H NMR of **4.82** in DMSO-d_6



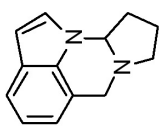
^{13}C NMR of **4.82** in DMSO-d_6

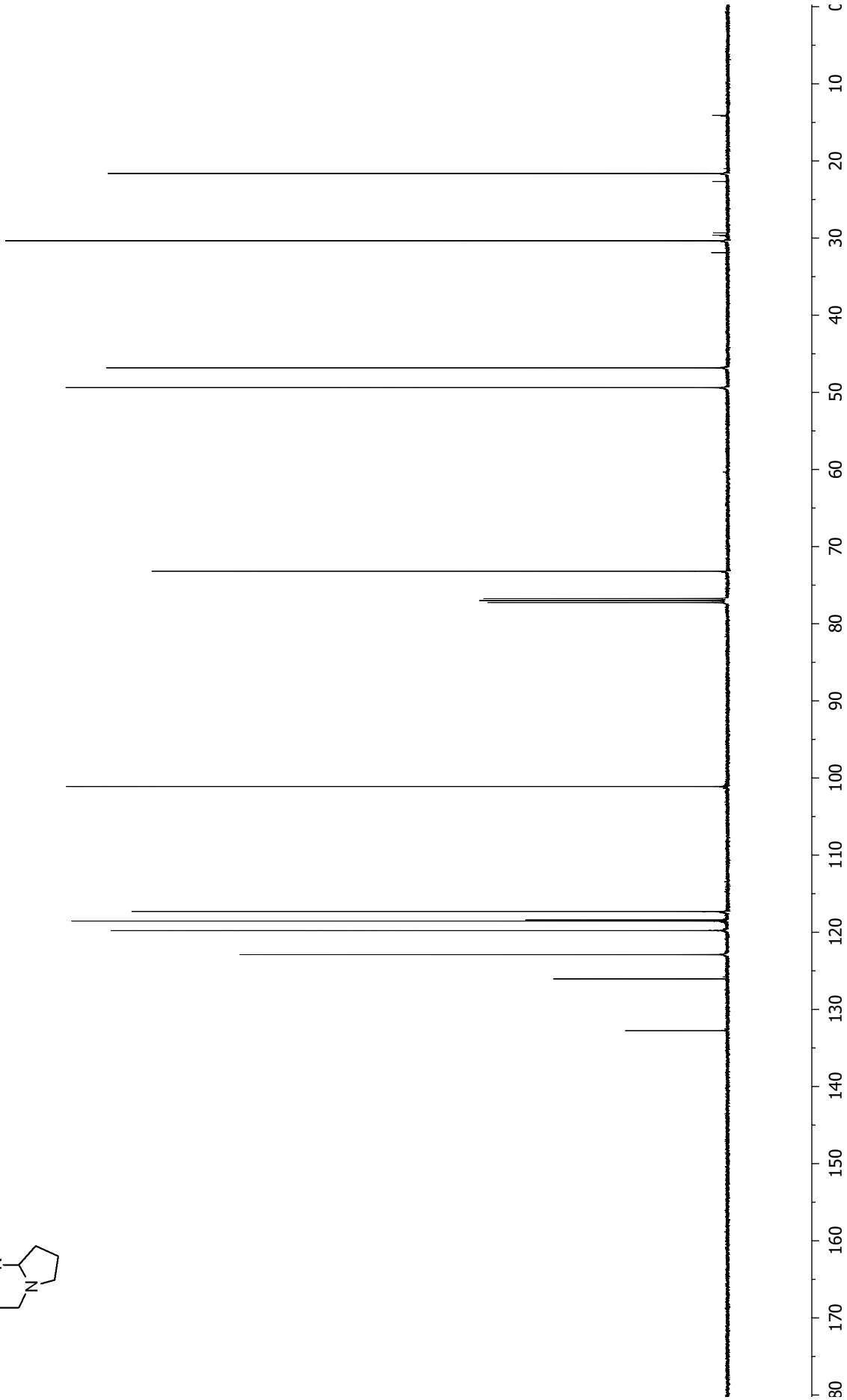


^{1}H NMR of **4.84** in $CDCl_3$

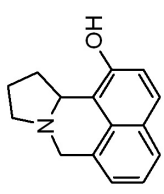


^{13}C NMR of **4.84** in $CDCl_3$

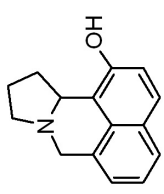




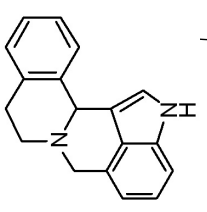
^{1}H NMR of **4.86** in DMSO-d_6



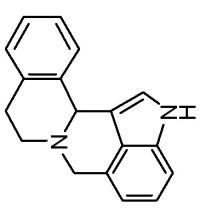
^{13}C NMR of **4.86** in DMSO-d_6



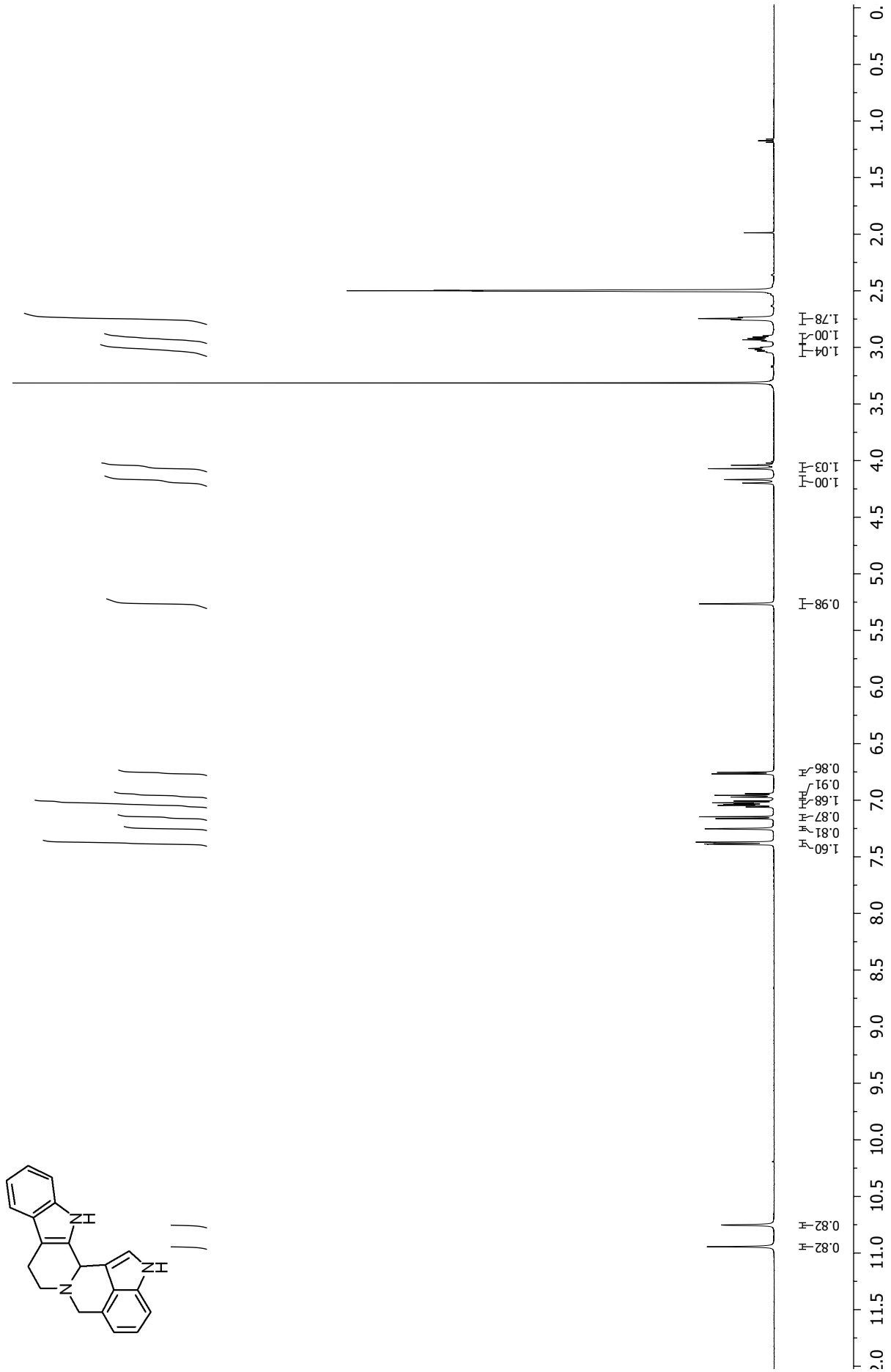
^{1}H NMR of **4.89** in DMSO-d_6



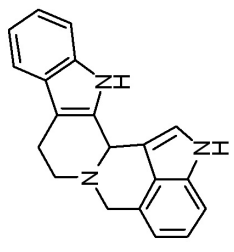
^{13}C NMR of **4.89** in DMSO-d_6



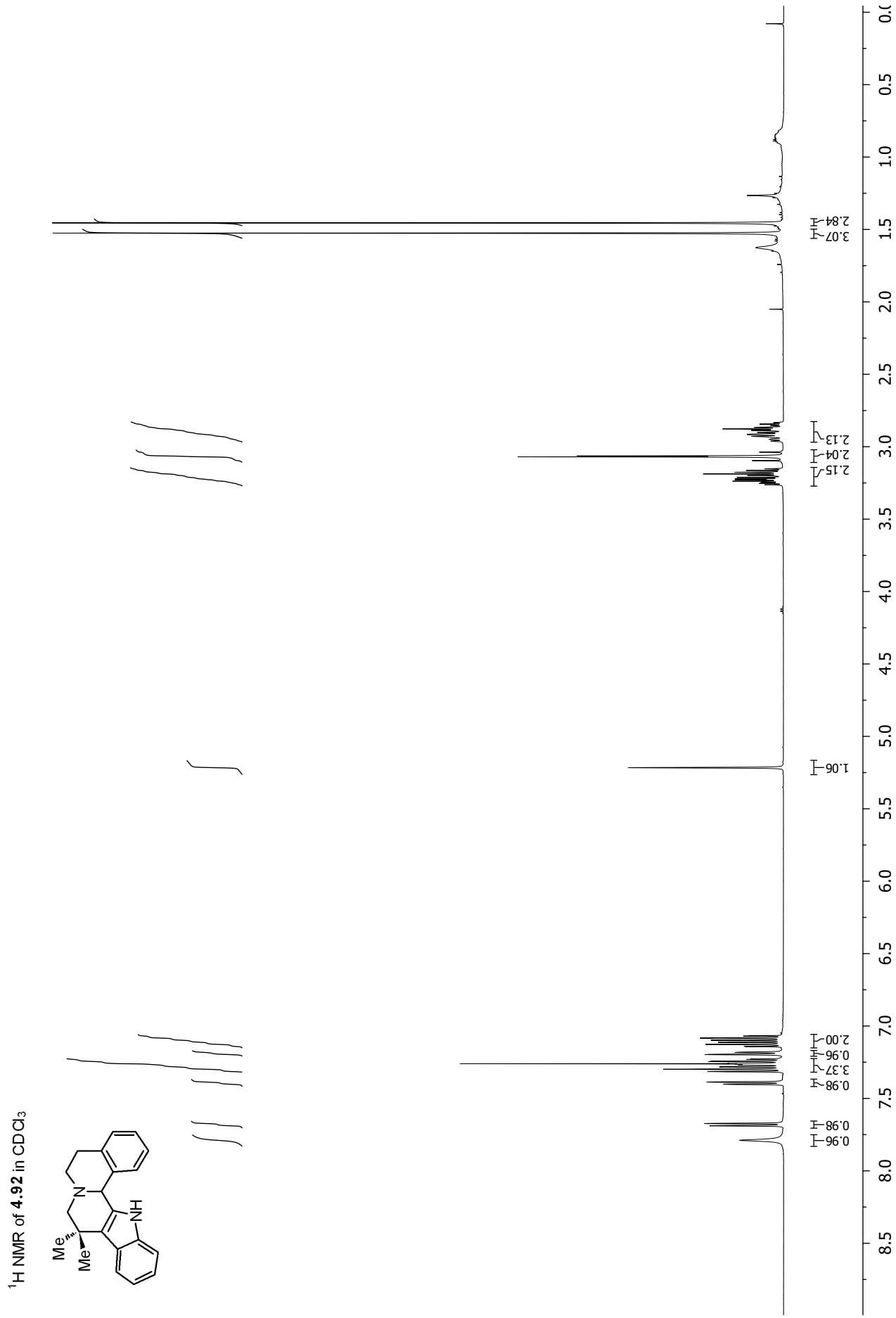
^{1}H NMR of **4.91** in DMSO-d_6



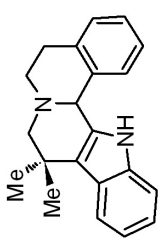
^{13}C NMR of **4.91** in DMSO-d_6



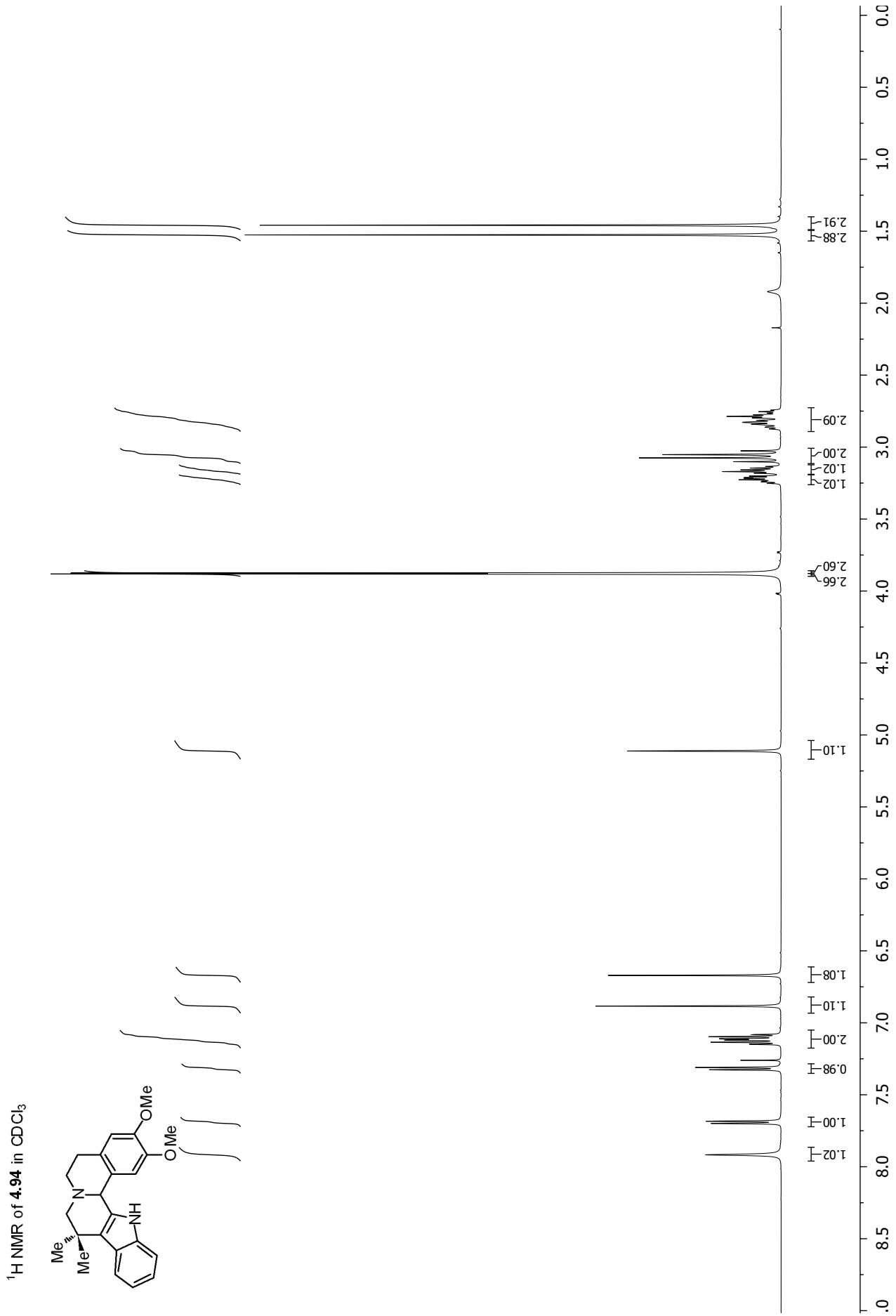
^{1}H NMR of **4.92** in $CDCl_3$



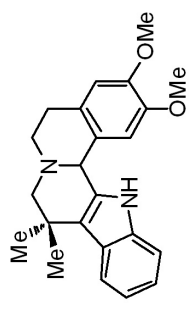
^{13}C NMR of **4.92** in $CDCl_3$



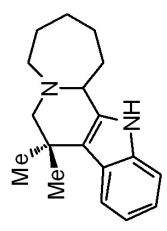
^{1}H NMR of **4.94** in $CDCl_3$



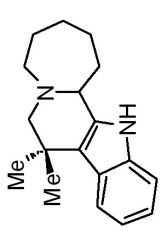
^{13}C NMR of **4.94** in $CDCl_3$



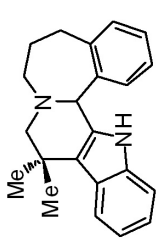
^{1}H NMR of **4.96** in $CDCl_3$



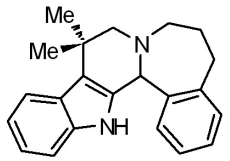
^{13}C NMR of **4.96** in $CDCl_3$



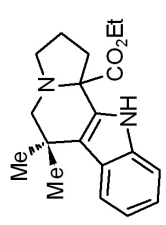
^{1}H NMR of **4.98** in $CDCl_3$



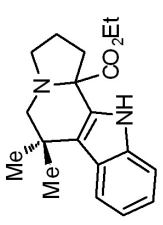
^{13}C NMR of **4.98** in $CDCl_3$



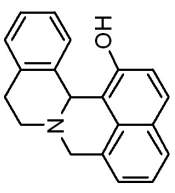
^{1}H NMR of **4.100** in $CDCl_3$



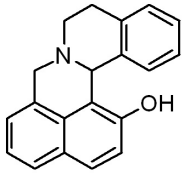
^{13}C NMR of **4.100** in $CDCl_3$



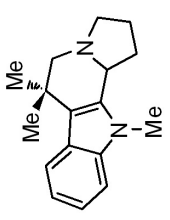
^{1}H NMR of **4.101** in DMSO-d_6



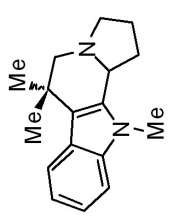
^{13}C NMR of **4.101** in DMSO-d_6



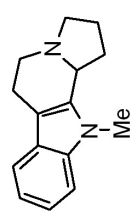
^{1}H NMR of **4.107** in $CDCl_3$



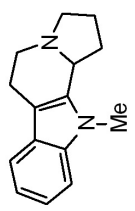
^{13}C NMR of **4.107** in $CDCl_3$



^{1}H NMR of **4.108** in $CDCl_3$



^{13}C NMR of **4.108** in $CDCl_3$



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2005 -- present ***Ph.D.***, Organic Chemistry
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Advisor: Professor Qing-xiang Guo

AWARDS

- 2009-2010 “Reid graduate fellowship award”, Rutgers University, New Jersey
- 2008-2009 “Excellence in Research Award”, Rutgers University, New Jersey
- 2007-2008 "Damle Award" for research excellence, Rutgers University, New Jersey
- 2001-2005 Outstanding Student Scholarship, University of Science and Technology of China

PUBLICATIONS

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