ONE-POT, BENZYLIC AMINATION REACTIONS OF AZINE *N*-OXIDES

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By

Menekşe Liman

June, 2017

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We certify that I have read this thesis and that in my opinion it is fully adequate, in scope and in quality, as a thesis of the degree of Master of Science.

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Zeynel Seferoğlu

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Director of the Graduate School

ABSTRACT

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Menekşe Liman

M.S. in Department of Chemistry

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June, 2017

Nitrogen-containing aromatic heterocycles, found in many biologically active natural products and pharmaceutical drugs, constitute a highly important class of compounds in organic chemistry. In this context, areas such as the discoveries of new synthetic methods for both the synthesis and derivatization of nitrogen-containing heterocyclic compounds as well as for the introduction of nitrogen to a compound attract significant attention in the areas of organic and pharmaceutical chemistry. In this study, we have developed a new one-pot synthetic method for the benzylic amination of azine-*N*-oxides containing a methyl group at the 2-position. Following the optimization studies, the substrate scope of the developed reaction has been investigated in detail. The reaction tolerates quinoline and isoquinoline *N*-oxides with electron donating and withdrawing substituents as the electrophilic reaction partner as well as a broad range of nucleophilic primary, secondary and aromatic amines.

Keywords: Heterocyclic compounds, Azine *N*-Oxides, Benzylic amination

ÖZET

AZİN *N*-OKSİT BİLEŞİKLERİNİN BENZİLİK AMİNASYONU

Menekşe Liman

Kimya Bölümü, Yüksek Lisans

Tez Danışmanı: Yunus Emre Türkmen

Haziran, 2017

Azot içeren aromatik heteosiklik bileşiklere hem biyolojik açıdan aktif doğal ürünlerin hem de ilaçların yapısında sıklıkla rastlanmaktadır. Bu kapsamda, azot içeren heterosiklik bileşiklerin sentezlenmesini, türevlendirilmesini ve bileşiğe yeni azot eklenmesini sağlayacak yeni sentetik yöntemlerin bulunması organik ve ilaç kimyasında oldukça önem taşımaktadır. Bu çalışmada, 2 pozisyonunda metil grubu içeren azin *N*-oksitlerin benzilik pozisyondan tek basamakta aminasyonunu sağlayacak yeni bir sentez yöntemi geliştirilmiştir. Optimizasyon çalışmalarının ardından, geliştirilen yöntem ile substrat kapsamı detaylı bir şekilde incelenmiştir. Belirlenen bu kimyasal tepkime, yapısında elektron verici ve çekici gruplar içeren kinolin ve isokinolin *N*-oksit türevleri ile nükleofilik birincil, ikincil ve aromatik aminler arasında başarılı bir şekilde uygulanabilmektedir.

Anahtar Kelimeler: Heterosiklik bileşikler, Azin *N*-oksit, Benzilik aminasyon

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Dedicated to my beloved mother and father..

LIST OF ABBREVIATIONS

EtOAc	Ethyl Acetate
FTIR	Fourier Transform Infra-Red
HRMS	High Resolution Mass Spectrometry
***i*Pr$_2$EtN**	*N*,*N*-Diisopropylethylamine (Hünig's Base)
m-CPBA	*m*-Chloroperbenzoic acid
MeCN	Acetonitrile
MeOH	Methanol
MsCl	Methanesulfonyl chloride
Ms$_2$O	Methanesulfonic anhydride
NMR	Nuclear Magnetic Resonance
PyBroP	Bromotripyrrolidinophosphonium hexafluorophosphate
TLC	Thin Layer Chromatography
Tf$_2$O	Trifluoromethanesulfonic anhydride
TsCl	*p*-Toluenesulfonyl chloride
Ts$_2$O	*p*-Toluenesulfonic anhydride
UV	Ultraviolet

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CHAPTER 1

INTRODUCTION

1.1 Heterocyclic Chemistry and Heterocyclic Compounds

Heterocyclic chemistry is one of the important branches of organic chemistry. In 1800's, the era of heterocyclic chemistry began with the acceleration of development in organic chemistry.[1] For more than a century, a large section of organic chemistry has been shaped by the evolution of heterocyclic chemistry. By definition, the synthesis, properties and various applications of heterocyclic compounds are the main subjects covered by heterocyclic chemistry. Broadly, heterocyclic compounds, in other words heterocycles, are defined as any class of organic chemical compounds characterized by the fact that some or all of the atoms in their molecules are joined in rings containing at least one atom of an element other than carbon.[2] Although there are many examples for the incorporation of different elements as heteroatoms on the ring system, the most commonly observed heteroatoms in heterocycles are nitrogen, oxygen and sulfur. Some of the widely used heterocycles are given in Figure 1.

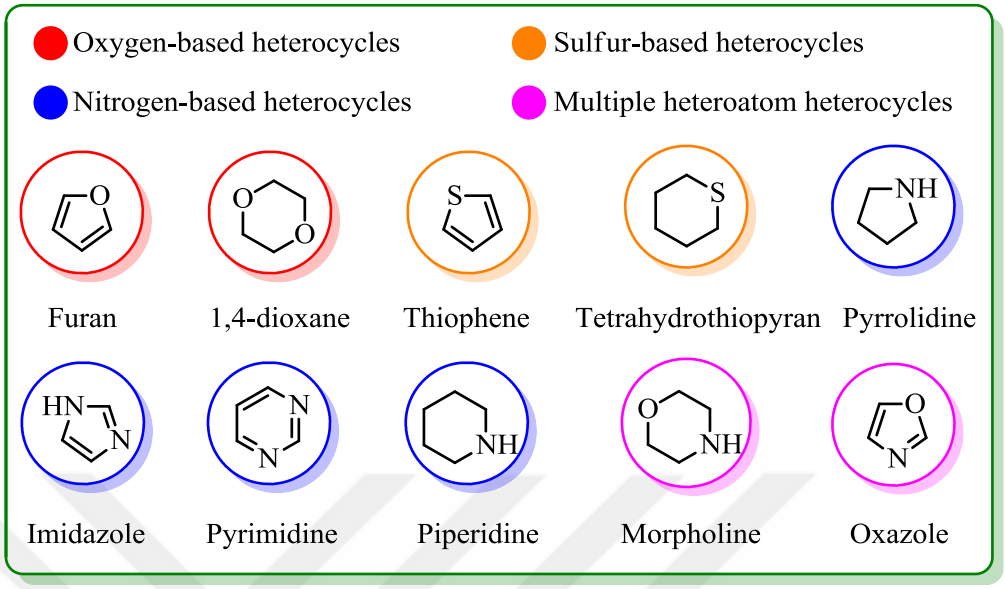


Figure 1. Some of the widely used heterocycles in organic chemistry

Heterocyclic organic structures can be encountered both in natural and non-natural products. In nature, such heterocycles are among the key structures for biological systems. For instance, some vitamins such as thiamin (vitamin B_1), riboflavin (vitamin B_2), nicotinamide (vitamin B_3), pyridoxal (vitamin B_6) and ascorbic acid (vitamin C), hormones, hemoglobin, enzymes and proteins which are essential to human life and biological processes are composed of heterocyclic structures. Besides, the building blocks of nucleic acids and three of amino acids- Proline, Tryptophan and Histidine- are heterocyclic compounds (Figure 2).[3]

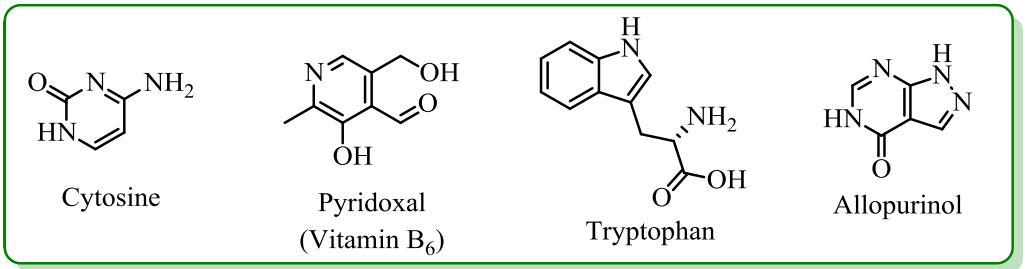


Figure 2. Heterocycles in biological systems

1.1.1 General Applications of Heterocyclic Compounds

Synthetic heterocyclic compounds can be designed for a broad range of applications. They can be used as agrochemicals or veterinary products, in material science as dyestuff or fluorescent sensors. These compounds can also act as organic conductors and organic light-emitting diodes[4] (OLEDs)[5] (Figure 3)[6,7]. Moreover, medicinal chemists benefit extensively from heterocycles to develop new drugs against diseases. These heterocycles are preferred to be utilized in a diverse array of applications due to their ring stabilization, structural tunability and high degree of diversity. It is also possible to derivatize or manipulate heterocycles easily by the addition of functional groups either as substituents or as part of the ring itself.[3] Due to the fact that such heterocycles are important compounds both biologically and industrially, not surprisingly, development of new synthetic methodologies to obtain different heterocyclic compounds has gained importance.

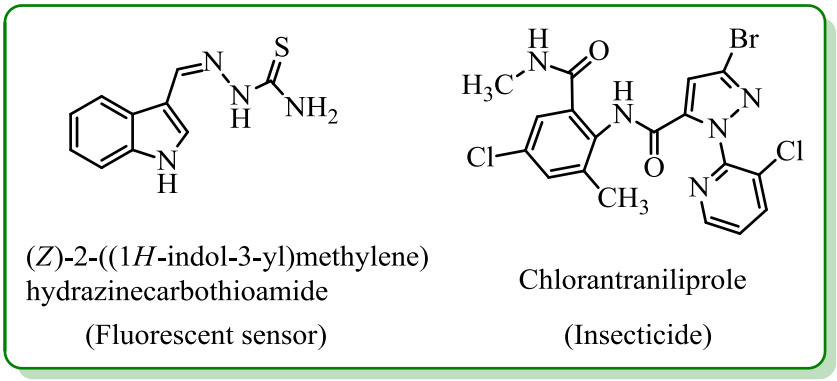


Figure 3. Heterocycles in different applications

1.2 Nitrogen-containing Heterocyclic Compounds in Drug Discovery

Heterocyclic organic compounds are mostly used in pharmaceutical and medicinal chemistry. These heterocycles play a crucial role on drug chemistry, especially for the

synthesis of new medicinal drugs. The main reason of this preference is the rich activity of heterocycles in biological systems.

According to a study, among 25-top selling pharmaceuticals in 2014, 12 of them contain heterocyclic domains within their structures. Four of these drugs are shown in Figure 4. Another result of this study indicates that almost all of these pharmaceuticals containing heterocyclic structure have also at least one nitrogen atom.[8]

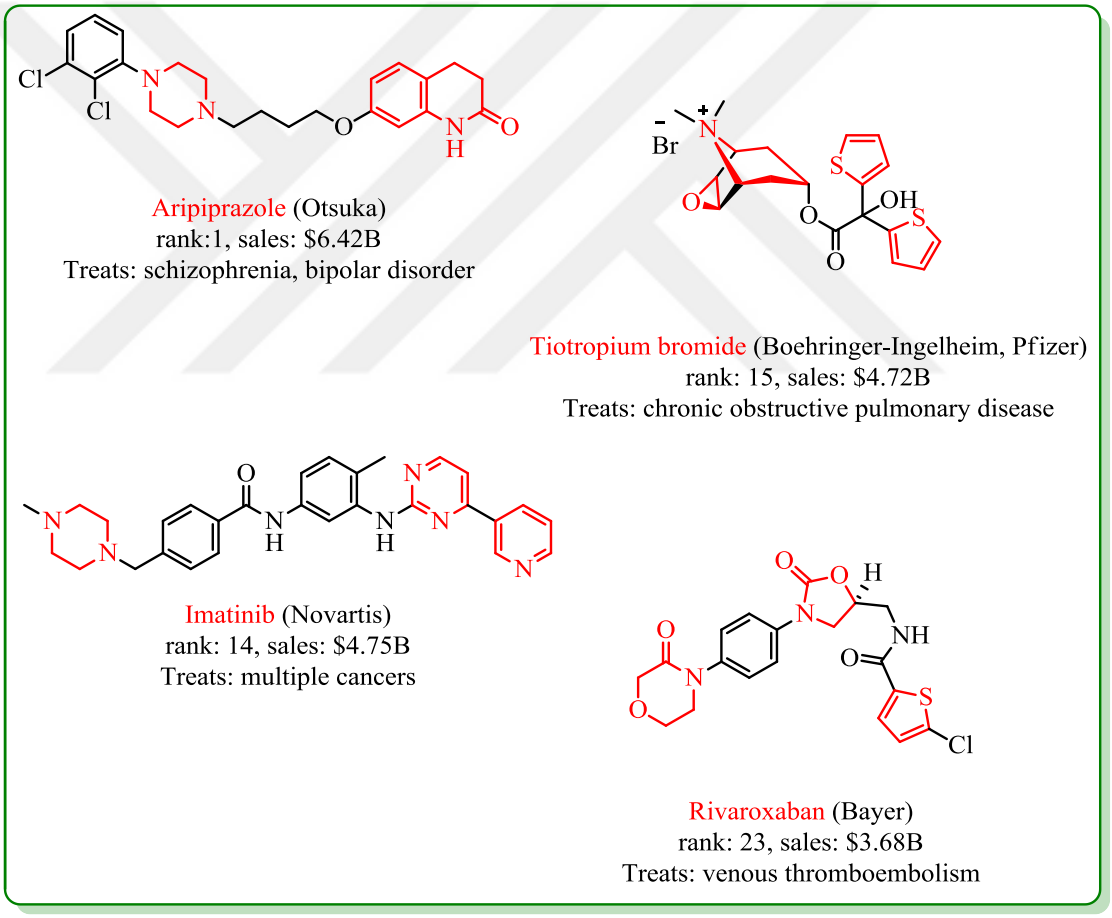


Figure 4. Four of top-selling pharmaceutical drugs (in 2014) containing heterocyclic domains

There is also another survey about the top selling 200 pharmaceutical drugs in the USA. This study reveals that 92% of most selling 200 drugs contains at least one nitrogen

atom.[9] These studies do not only demonstrate the importance of heterocyclic compounds in medicinal chemistry, but they also highlight the beneficial effects of the presence of nitrogen atoms within heterocycles. In summary, it can be concluded that molecules with heterocycles containing nitrogen are important compounds in organic and pharmaceutical chemistry and they have a huge impact on the historical development of drugs.

For many years, nitrogen containing heterocycles have been used to synthesize drugs to combat diseases including fatal ones. These can be used as cholesterol reducing[10], anti-inflammatory, anti-fungal, anti-hypertensive, therapeutic agents as well as for cancer treatment.[5] Some of the examples of widely known drugs composed of nitrogenous heterocycles are given in Figure 5.

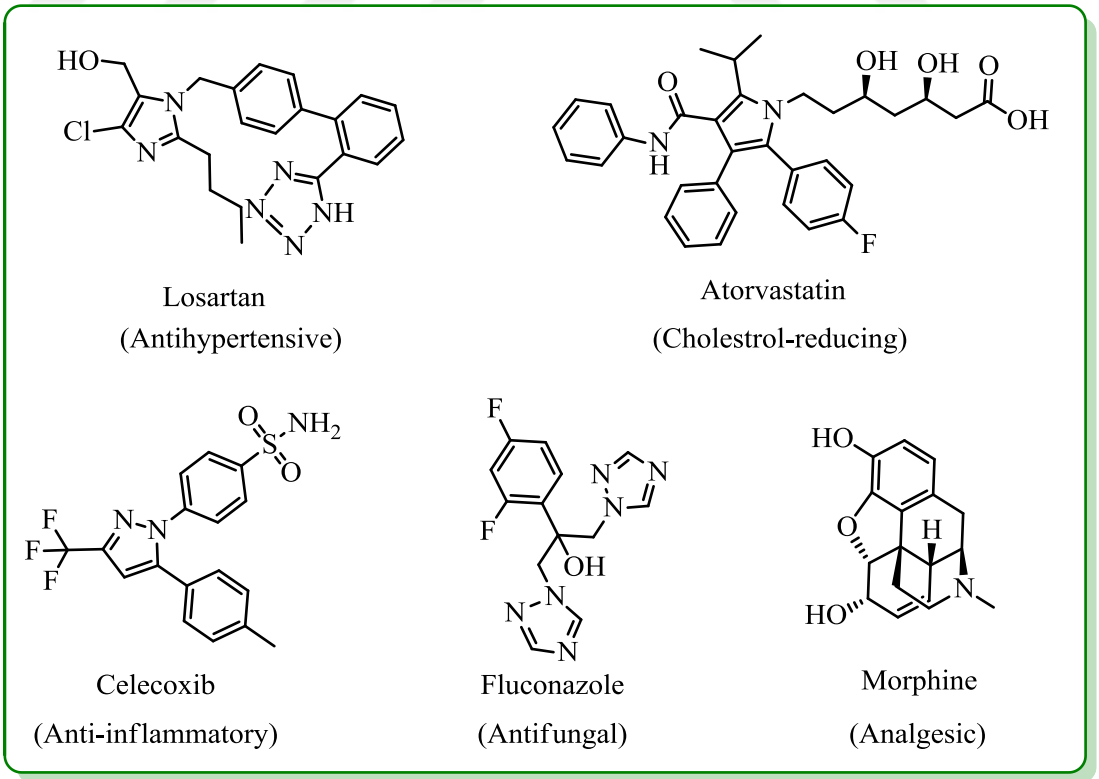


Figure 5. Pharmaceutical drugs composed of nitrogenous heterocycles

1.3 Use of Azine *N*-Oxides in Pharmaceutical Chemistry

Even though nitrogen containing heterocyclic compounds take enormous place among pharmaceuticals, having nitrogen on the ring system is not enough by itself to invent or develop new drugs. Some modifications on heterocycles may be required in line with the intended purpose to develop pharmaceutical drugs. By taking advantage of easy manipulation of heterocycles, various types of effective drugs with desired properties can be synthesized. One of the changes in the structure for nitrogen containing heterocycles can be *N*-oxidation. With *N*-oxidation, biologically active compounds and beneficial therapeutic agents can be obtained. Although heterocyclic *N*-oxides in chemistry have drawn attention for many years, they have started to dominate drug discovery recently. These heterocyclic *N*-oxides can be observed as either a part of a drug or can be used as synthetic intermediates during the development of drugs (Figure 6)[11].

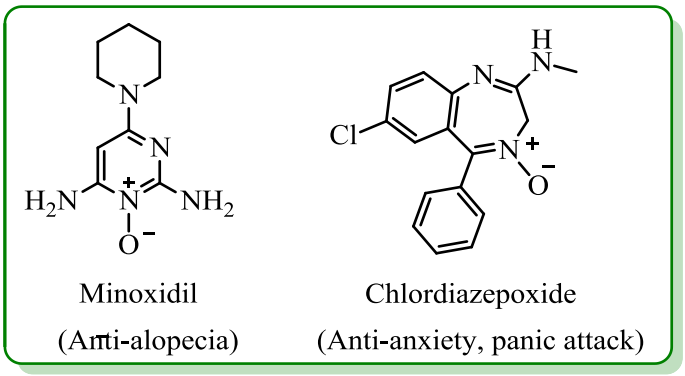


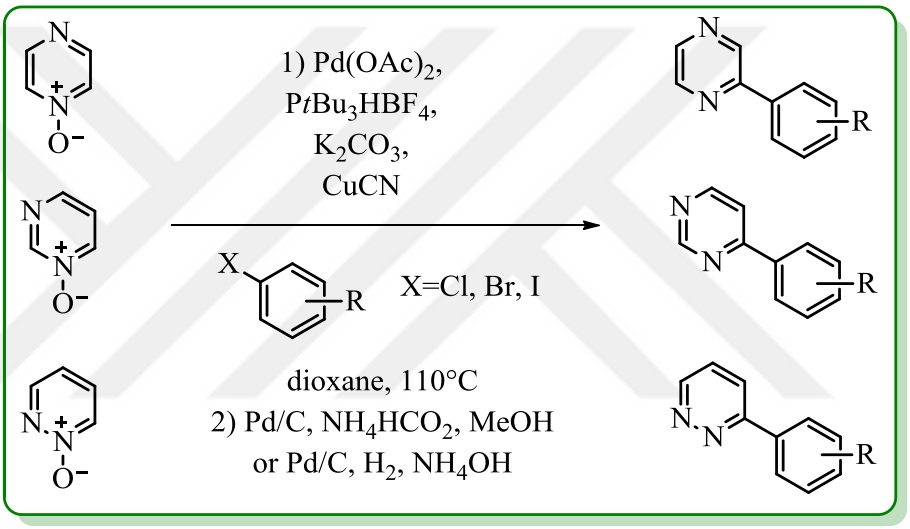
Figure 6. Heterocyclic *N*-oxides as pharmaceutical drugs

Heterocyclic *N*-oxides, especially azine *N*-oxides, are common building blocks of pharmaceuticals due to being bioactive compounds. For this reason, to find out new methodologies for modification, derivatization or functionalization of azine compounds

has been risen subject. Actually, there are various effective methods to functionalize nitrogen containing heterocycles.

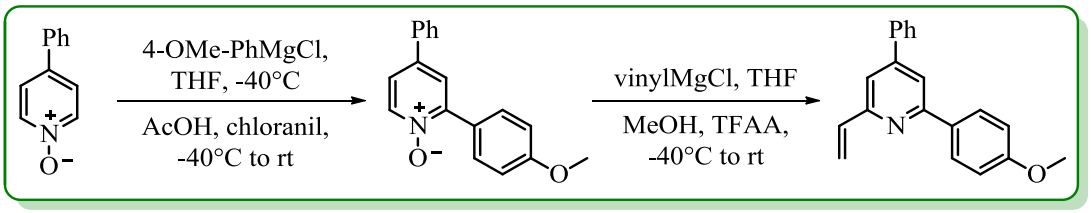
1.4 Methods for Derivatization of Azine Components

In heterocyclic chemistry, cross-coupling reactions are one of widely used methods for derivatization of azine components such as pyridine, quinoline or isoquinoline.[12,13,14]



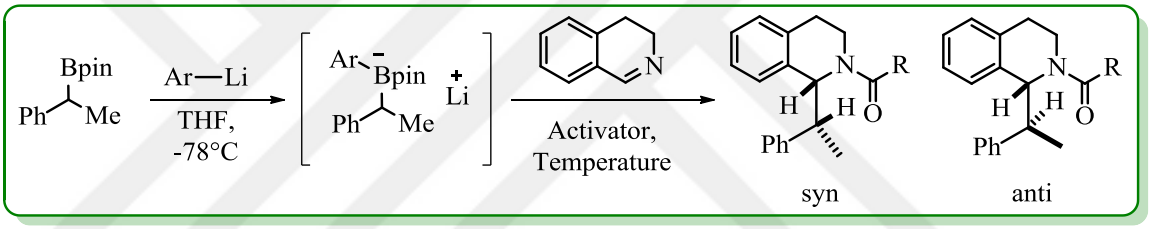
Scheme 1. Cross-coupling reactions for derivatization of azine *N*-oxide derivatives with aryl chlorides, bromides and iodides [15]

Pyridine and pyridine-like azine components have electrophilic characteristics due to their electron-deficient nature. Thus, they can react directly with aryl lithium reagents which are strong nucleophiles.[16] Similarly, aryl Grignard reagents can also react directly with azine *N*-oxides as nucleophilic addition reaction.[17] In a collaborative work between Almqvist research group and Acadia Pharmaceuticals Company reported in 2010, pyridine *N*-oxide derivatives were shown to react efficiently with aryl Grignard reagents to afford arylated pyridine products after treatment with trifluoroacetic anhydride (Scheme 2)[18].



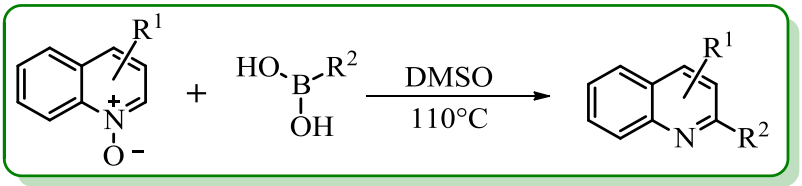
Scheme 2. Synthesis of substituted pyridines with Grignard reagents

In 2014, the studies of Aggarwal and co-workers showed that pre-activated pyridine and quinoline derivatives reacted with chiral boronate complexes in an enantio-spesific and diastereo-selective manner (Scheme 3) [19].



Scheme 3. Reaction of pre-activated quinoline derivatives with chiral boronate complexes

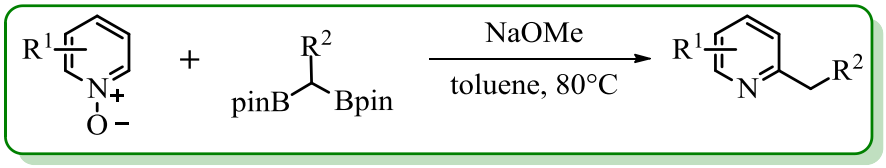
A work published in 2015 by Antonchick and co-workers indicates that quinoline *N*-oxide derivatives reacted directly with aryl boronic acid derivatives for arylation reactions without being activated and in the absence of metal catalyst (Scheme 4) [20].



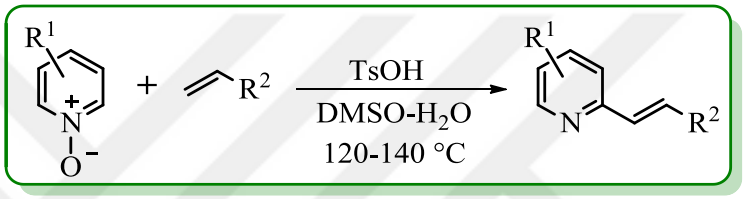
Scheme 4. Arylation reaction between quinoline *N*-oxide derivatives with aryl boronic acid

In addition to arylation reactions, alkylation and alkenylation reactions of pyridine *N*-oxide derivatives were investigated in recent studies by the Cho and Bower research

groups (Scheme 5 and 6).[21,22] Moreover, Janssen Research and Development Company reported highly efficient amination reactions of pyridine *N*-oxides.[23,24]

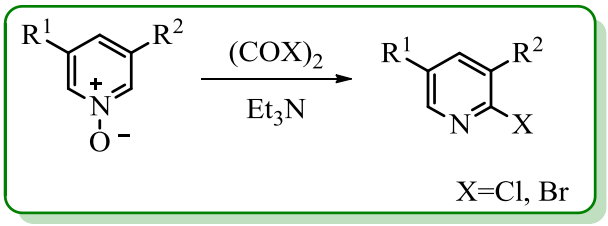


Scheme 5. Alkylation of pyridine *N*-oxide derivatives, pin=pinacol



Scheme 6. Alkenylation of pyridine *N*-oxide derivatives

Lastly, transformation of azine *N*-oxides to bromo- or chloro-azine derivatives via oxalyl bromide and oxalyl chloride, respectively, was conducted by the researchers of Amgen Biopharmaceutical Company in 2015 (Scheme 7).[25]



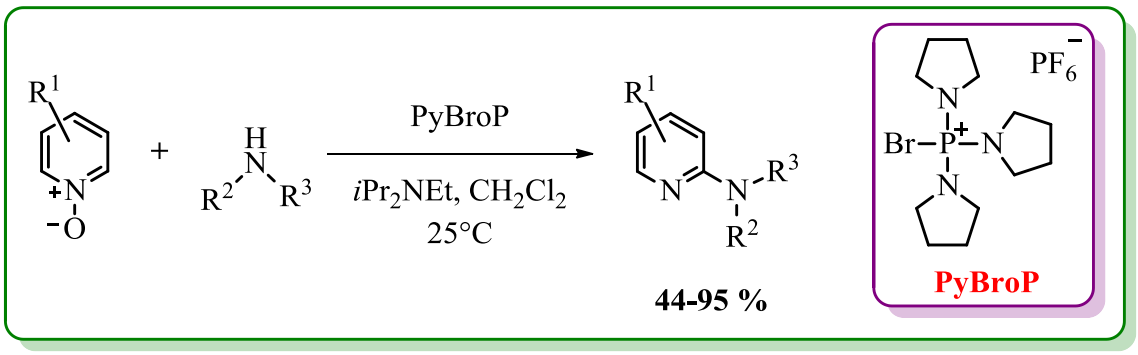
Scheme 7. Bromination or chlorination pyridine *N*-oxide derivatives

As it is seen in the above examples, most of the recent methods for the derivatization of azine *N*-oxides have been explored and developed by different pharmaceutical companies. This observation underscores the importance of such reactions for the derivatization of azine compounds in drug development and pharmaceutical industry.

1.5 PyBroP as Activating Agent

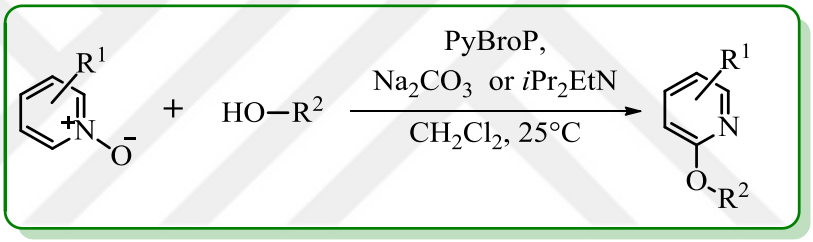
In addition to aforementioned studies, pyridine and pyridine-like azine compounds can be functionalized through the utilization of activating agents. In the absence of activating agents, reactions usually require harsh conditions that generally result in low functional group tolerance.[26,27] On the other hand, activated *N*-oxides can be prepared via activating agent and these pre-activated *N*-oxides can undergo reactions under milder conditions compared to non-activated *N*-oxides derivative.

In the light of this information, pyridine and pyridine-like azine components are needed to be strongly activated in order to react with many different nucleophiles under mild conditions. For this purpose, in an ongoing research program of Pfizer, one of the world's largest research-based pharmaceutical companies, PyBroP (Bromotripyrrolidinophosphonium hexafluorophosphate) was discovered to be highly successful to activate azine *N*-oxide compounds and utilized in a myriad of synthetically useful organic transformations (Scheme 8)[28].

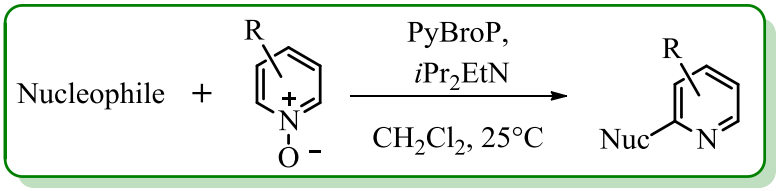


Scheme 8. Amination reaction of pyridine *N*-oxide derivatives by using PyBroP as activating agent

In these studies, azine *N*-oxide components were initially activated by PyBroP and then, reacted with 1° and 2° amines, silyl ketene acetals, phenol derivatives and various other nucleophiles so that functionalized. Azine products were obtained in a single step.[28,29,30,31] In addition, Londregan and co-workers reported in 2016 that activated azine *N*-oxides could undergo addition reactions with non-phenolic aliphatic alcohols that possess lower nucleophilicity (Scheme 9).[32,33] A general reaction scheme for the derivatization of azine components via nucleophilic addition reaction under mild conditions is given in Scheme 10.[29]

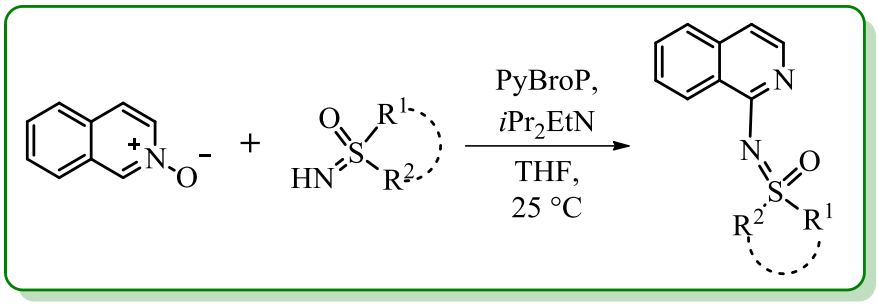


Scheme 9. Reaction between activated azine *N*-oxides and non-phenolic aliphatic alcohols



Scheme 10. Derivatization of azine *N*-oxides via nucleophilic addition reactions

Another study in which PyBroP was used as an activating agent was published in 2016 by Singh and co-workers.[34] In this study, sulfoximine components were used as nucleophile and *N*-azine sulfoximine products were obtained in high yields (Scheme 11).



Scheme 11. Nucleophilic addition reactions of azine *N*-oxides using sulfoximine components

As a result of these investigations using PyBroP, functionalization of heterocyclic compounds with various nucleophiles can be achieved under mild conditions, which is a noteworthy development because carbon-heteroatom bonds can be formed under metal free conditions.[34] Hence, environmentally friendly and metal-free reaction conditions for derivatization of heterocycles have been developed. This type of reaction conditions has been widely preferred among organic and pharmaceutical chemists due to the atom-economical nature of these methods.

1.5.1 Other Activating Agents

In order to activate azine *N*-oxide derivatives, activating agents containing sulfonyl or anhydride groups can be also used instead of PyBroP. For instance, TsCl, MsCl, Ts_2O, Ms_2O and Tf_2O are among the commonly used activating agents (Figure 7).

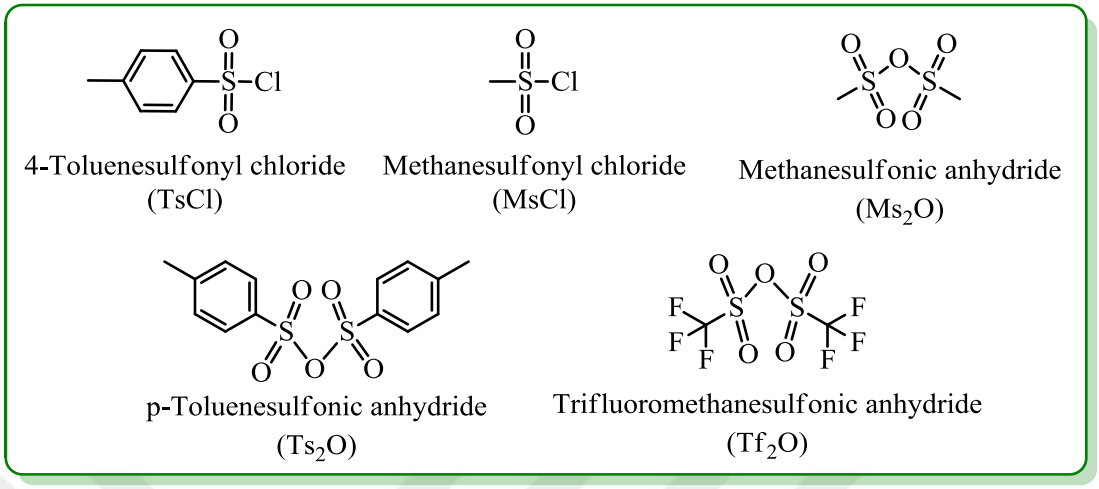
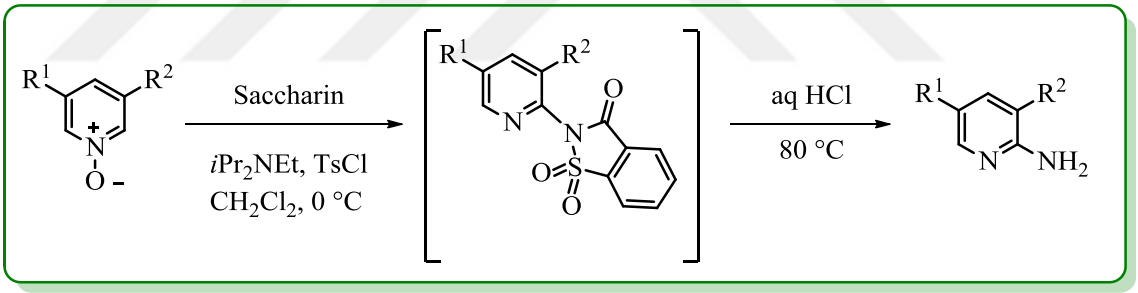


Figure 7. Various activating agents

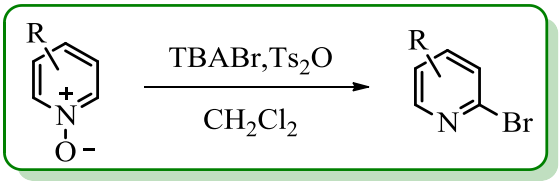
A study by Amgen Biopharmaceutical Company shows that azine *N*-oxides activated by TsCl can react with saccharine as the nucleophile and then, amino pyridine derivatives can be obtained in high yields after acidic hydrolysis (Scheme 12)[35].



Scheme 12. Synthesis of amino pyridine derivatives by using TsCl as activating agents

Recently, there has been a growing interest among organic and pharmaceutical chemists in the transformation of azine *N*-oxides to bromo- or chloro-azine derivatives. However, traditional reagents used for this synthetic transformation such as $POCl_3$, $POBr_3$, $SOCl_2$, phosgene ($COCl_2$), etc. either work with poor regioselectivity and low yields or require harsh reaction conditions such as high temperature or excessive use of reagents. In a collaborative work between Bristol-Myers Squibb Pharmaceutical Company and Scripps Research Institute reported in 2013, azine *N*-oxides were shown to be transformed to

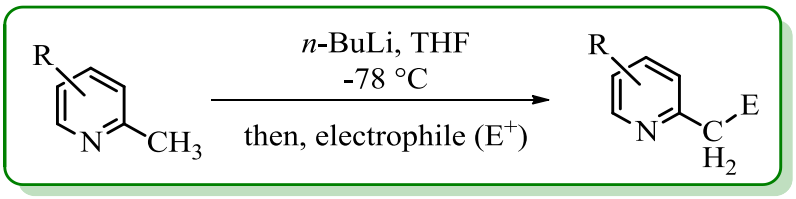
bromo-azine derivatives under mild conditions. Rather than PyBroP, Ts_2O was preferred in this work as the activating agent (Scheme 13)[36].



Scheme 13. Bromination of azine *N*-oxide derivatives by using Ts_2O as activating agent

1.6 Traditional Methods for Derivatization of 2-methyl Azine Components

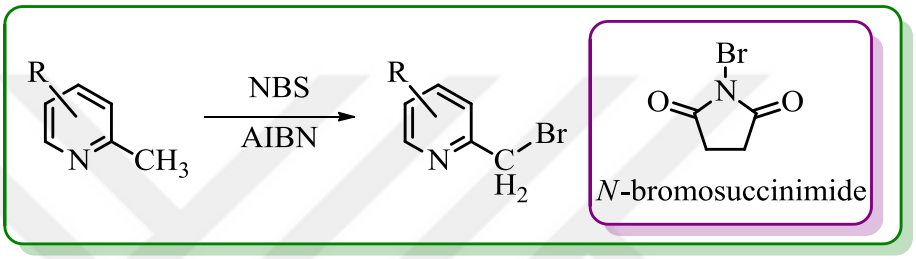
There exist a number of traditional methods for the derivatization of 2-methyl azine compounds. For instance, protons of the $-CH_3$ group in 2-methyl pyridine (2-picoline) and related compounds have weak acidic character and one of the protons can be abstracted using a strong base like *n*-BuLi. The picolinate anion formed this way has nucleophilic and basic character, and thus, it can react with an appropriate electrophile to yield a functionalized azine compound (Scheme 14).[37] The requirement of having cryogenic conditions and using air-sensitive and highly reactive bases can be considered as the drawbacks of this synthetic methodology.



Scheme 14. One of traditional methods for derivatization of 2-methyl azine *N*-oxide derivatives

Another method for the benzylic functionalization of azine compounds is radical bromination reaction using NBS. Although the synthesis of $Ar-CH_2Br$ compounds can

be achieved in a single step, mono-bromo product is difficult to be obtained in high yield due to the possibility of multiple halogenations. Usually, a mixture of mono-bromination and multiple-bromination products is obtained in these reactions (Scheme 15)[38]. On the other hand, NBS may not be used for reactions with complex molecules with other functional groups due to the high reactivity of this brominating agent.



Scheme 15. Benzylic bromination reaction using NBS

1.7 Synthesis via Rearrangement Reactions

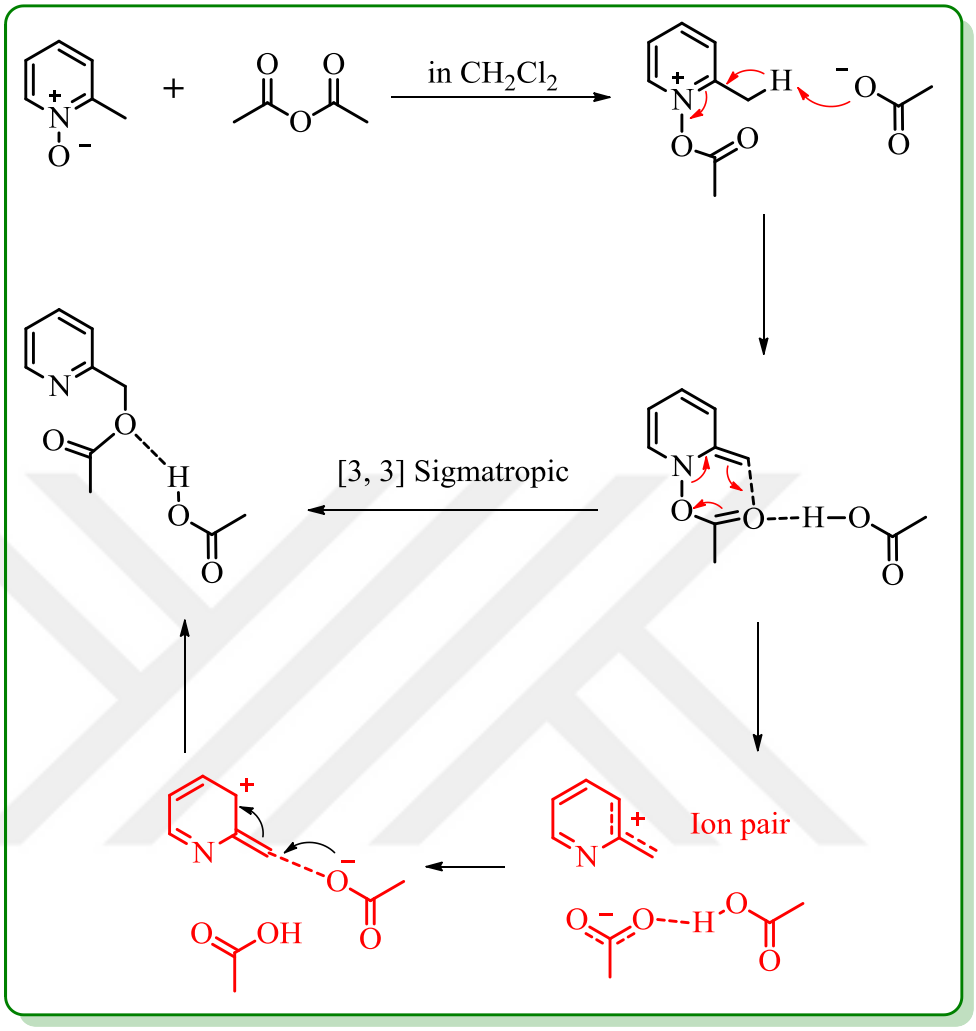
Functionalized or substituted pyridine or pyridine-like azine *N*-oxide derivatives can be achieved either by rearrangement of *N*-oxides or by rearrangement of an alternative heterocycle. The former is named as *Boekelheide Rearrangement* and the latter one is *Ciamician-Dennstedt Rearrangement*.

1.7.1 Boekelheide Rearrangement

Boekelheide rearrangement is a rearrangement reaction of 2-alkylpyridine *N*-oxide and related compounds. It is a frequently used method for functionalization of pyridine *N*-oxide derivatives from the carbon substituent at the C-2 position under relatively mild conditions.[39,40] Basically, pyridine *N*-oxide is reacted with acetic anhydride. The first step is oxygen acylation of N-O part in heterocycle. Then, a proton from the C-2

position of pyridine *N*-oxide is abstracted. Following this step, a concerted [3, 3]-sigmatropic shift can afford the rearranged azine product. Alternatively, a stepwise mechanism has also been proposed for the rearrangement step. As shown in Scheme 16, the leaving of the acetate (OAc^-) would give an ion pair which can give the rearrangement product upon recombination.[41]

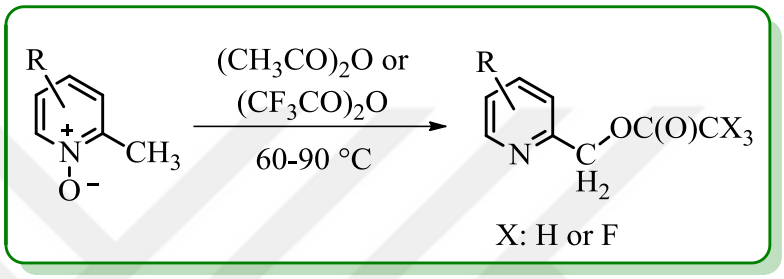
Although acetic anhydride is the most commonly used anhydride for the Boekelheide rearrangement, rearrangement can be also done by Ms_2O or Ts_2O. These sulfonyl based anhydrides can provide target products containing good leaving groups. Besides them, trifluoroacetic anhydride (TFAA), phenyl acetic anhydride or trichloroacetic anhydride can also be employed.[39]



Scheme 16. Mechanism of Boekelheide rearrangement

In the literature, there are some important examples of Boekelheide rearrangement for derivatization of 2-methyl azine *N*-oxides. When 2-methyl azine *N*-oxide compounds are heated with acetic anhydride or trifluoroacetic anhydride, 2-acetoxymethyl or 2-trifluoroacetoxymethyl azine derivatives can be obtained as products (Scheme 17).[42,43,44] Although these types of reactions are beneficial in organic chemistry, they have some drawbacks. Primarily, acetic anhydride is used as solvent in this reaction rather than a stoichiometric compound. Also, these types of reactions require high temperatures. Secondly and more importantly, 2-acetoxymethyl or 2-trifluoroacetoxymethyl azine

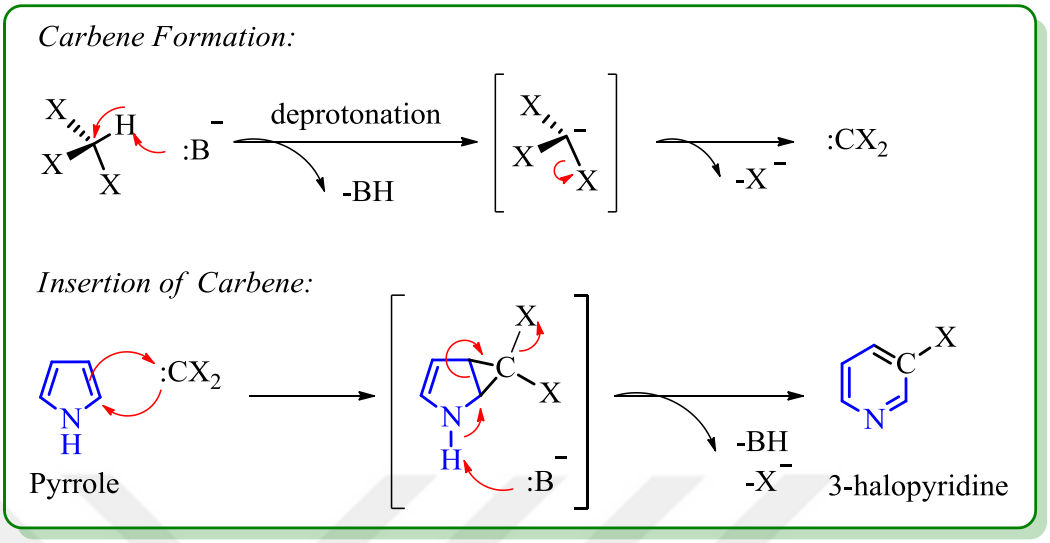
derivatives should be hydrolyzed in basic environment to get 2-hydroxymethyl derivatives. Then, these 2-hydroxymethyl derivatives are needed to be re-activated for derivatization with nucleophiles because they do not have enough electrophilic character. As seen, these reactions require at least two-three steps which decrease the atom economy of the whole sequence.



Scheme 17. Derivatization of azine *N*-oxide derivatives by using with acetic anhydride or trifluoroacetic anhydride

1.7.2 Ciamician-Dennstedt Rearrangement

Ciamician-Dennstedt rearrangement is a rearrangement for transformation of pyrroles to 3-halopyridines with dihalogen carbene in the presence of a strong base.[45,46,47,48] This method can also be extended to synthesize 3-halogen substituted quinoline derivatives from indoles. In the mechanism, dihalocarbene is initially formed via α-elimination. Then, formed dihalocarbene undergoes a cyclopropanation reaction with pyrrole resulting in an intermediate named as 6,6-dihalo-2-azabicyclo[3.1.0]hexane. Afterwards, ring expansion takes place to form 3-halogen substituted pyridine derivative (Scheme 18).[49] Ciamician-Dennstedt reaction is commonly used to synthesize calixarenes composed of pyrrole by making carbon bridge.[50]



Scheme 18. Mechanism of Ciamician-Dennstedt rearrangement

1.8 Cross-Coupling Reactions for Drug Synthesis

Within the last two decades, cross-coupling reactions have become widely used and predominant synthetic method in pharmaceutical chemistry due to the success of these reactions and their broad substrate scope. Heck reaction which is one of the most popular coupling reactions can be used for the synthesis of Taxol (anti-cancer drug) (Figure 8).[51] The strategic bond formation in morphine can be also done by Heck coupling.[52]

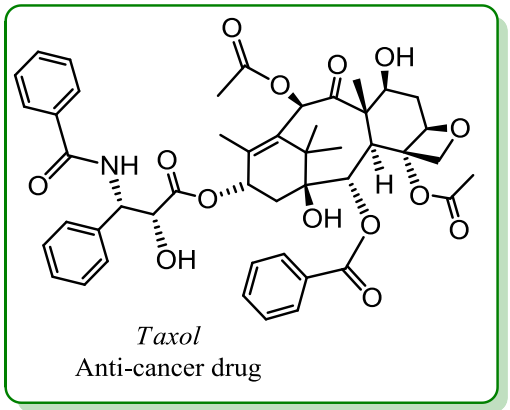
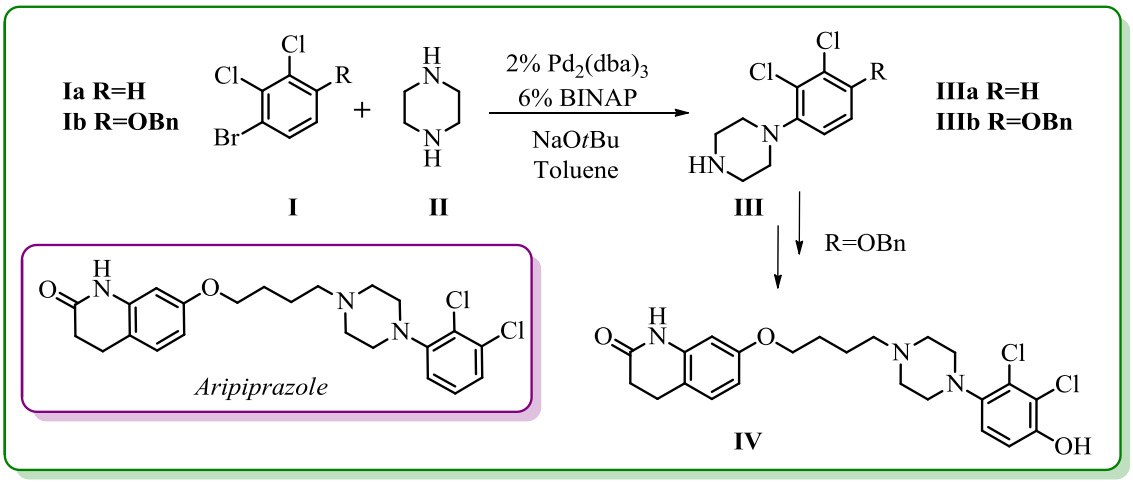


Figure 8. Taxol, as anti-cancer drug

As mentioned under the title of *Nitrogen containing Heterocyclic Compounds in Drug Discovery*, 12 top-selling drugs contain nitrogenous heterocycles. To emphasize the common usage of coupling reactions in drug syntheses, two of top-selling drugs are given as examples below, the synthesis of which were accomplished via Pd-catalyzed C-N coupling reactions.

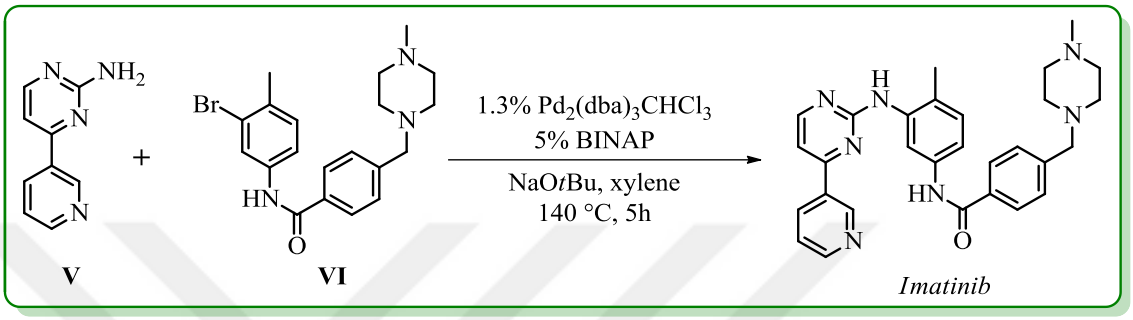
Aripiprazole, discovered by Otsuka Pharmaceutical, is ranked first among top-selling 25 pharmaceuticals. The synthesis of this medicine is carried out by a Pd-catalyzed amination reaction.[53] The reaction between aryl bromide (**I**) and piperazine (**II**) is performed by using $Pd_2(dba)_3$ as the Pd(0) source and BINAP as the ligand. Compound **IIIa** can give *Aripiprazole*, while **IIIb** should be converted to **IV** in 2 steps. Ultimately, Aripiprazole can be obtained via coupling reaction (Scheme 19).



Scheme 19. Synthesis of Aripiprazole by Pd-catalyzed amination reaction

Imatinib, developed by Novartis, was the 14th top-selling drug in the world in 2014. In a similar way, this can be also synthesized by taking advantage of a Pd catalyzed cross-coupling reaction.[53] First, aminopyrimidine (**V**) and aryl bromide (**VI**) are reacted in the

presence of Pd-BINAP catalyst to give the C-N coupling product. With the help of NaO*t*Bu, HBr byproduct can be quenched. With the final coupling reaction, *Imatinib* is synthesized (Scheme 20).



Scheme 20. Synthesis of Imatinib by Pd catalyzed cross-coupling reaction

Although cross-coupling reactions are commonly used methodologies for drug development, they can bear certain disadvantages. The origin of these drawbacks can be divided into two classes; geometrical and environmental. In 2009, a conceptually important article entitled "*Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success*" was published by Lovering. As stated in this article, cross-coupling reactions between two aryls have become the preferred method in drug discovery due to their robustness and reliability. However, this situation resulted in having libraries of "flat" compounds that are rich in sp^2 hybridized carbons rather than sp^3.[54] In fact, active sites of proteins have 3-dimensional structures and it is claimed that 2-dimensional small molecules cannot interact with 3-dimensional active sites of proteins well enough. Therefore, it is argued that clinical success may increase if molecules whose biological activity is to be tested should have more sp^3 hybridized carbons. As a result, the development of new synthetic methods for derivatization of

heterocyclic compounds with carbons having sp^3 hybridization is expected to attract more attention in the upcoming years.

Besides geometrical drawbacks of cross-coupling reactions, there are some environmental issues. For cross coupling reactions, toxic heavy metals, especially Pd, are used as catalysts. Even though these types of reactions provide target products in high yields, using transition metals usually requires harsh conditions such as high temperatures. In addition to this, toxic or hazardous solvents are often needed to obtain desired products. Moreover, in some cases, excess amount of starting material is used to get higher yields. To surmount these drawbacks, synthetic organic chemists have focused on developing new safer and environmentally milder synthetic methodologies.[55]

1.9 One-Pot Synthesis

Recently, one-pot synthesis of target products, which avoid tedious purification procedures of reaction intermediates, is considered as a better way in synthetic organic and process chemistry due to minimization of waste. As a general term, one-pot synthesis includes sequential transformations or formation of bonds in a single reaction vessel. Basically, multi-step reactions can utilize from one-pot synthesis. There are two main subclasses of one-pot synthesis which are domino and consecutive reactions, respectively.[56,57]

In domino reactions, more than one transformations or bond formations take place in one-pot under the same reaction conditions without addition of other components. Thus, each step occurs as a result of a transformation in the previous step. After all

transformations are followed, desired product is obtained in a single reaction vessel (Figure 9).[57]

Consecutive reaction is also composed of a sequence of individual steps. In a consecutive reaction, following the first transformation another component such as reagent, catalyst or mediator is added to the reaction environment causing that a new step takes place. Remarkably, each individual step can be carried at different temperature. After the sequence of these individual steps, target product can be obtained (Figure 9).[56]

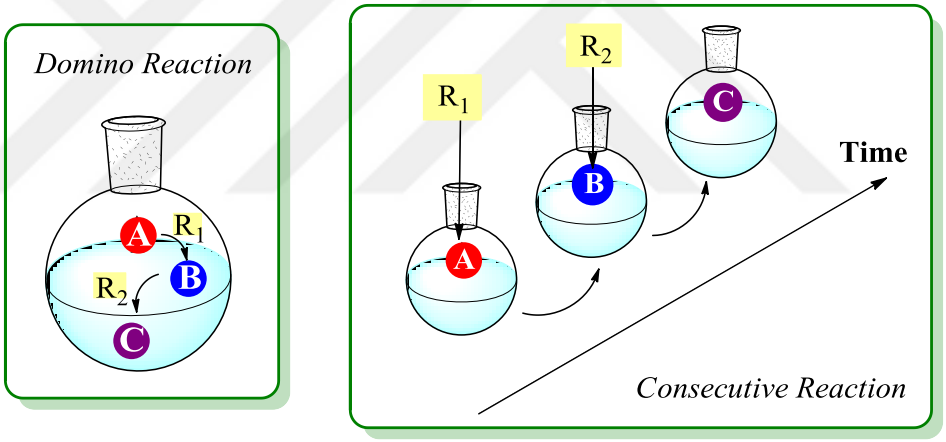
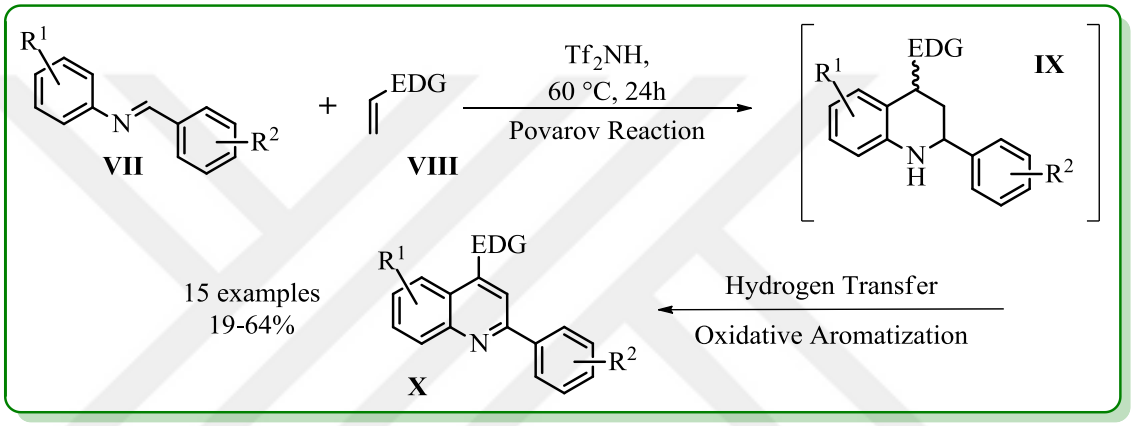


Figure 9. Visualization of domino and consecutive reactions

In this context, the important thing to take into consideration is to design a reaction method such that each reaction in the sequence has to be high yielding because the formation of by products or side-products can lower the overall yield of the final product. In this way, the amounts of such byproducts and side-products can be minimized and the target product can be obtained in high yield.

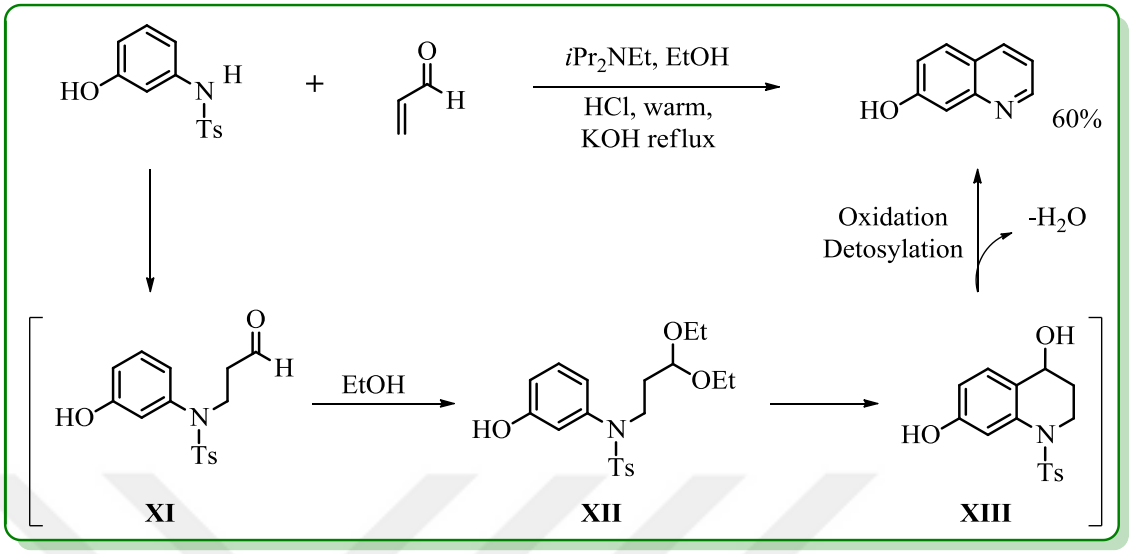
In the literature, there are many examples including synthesis of organic compounds or some hybrid materials via metal-free one-pot synthesis.[58] Shindoh and co-workers

developed a procedure to synthesize imidazopyrrolo-quinolines in one-pot by using triflic imide and triflic acid catalysts.[59] In the presence of Tf_2NH as Brønsted acid catalyst, **VII** is reacted with **VIII** at 60 °C in dichloromethane for 24 h. Then, transfer of hydrogen from **IX** to **VII** takes place. With the help of Tf_2NH, **IX** is oxidized and **X** is formed at the end of multi-steps (Scheme 21).



Scheme 21. Synthesis of imidazopyrrolo-quinolines in one-pot by using triflic imide and triflic acid catalysts

Another example that demonstrates the efficiency of one-pot synthesis is by Cameron and co-workers. 7-hyrdoxyquinoline was synthesized in one-pot procedure that operates in four steps. At the first stage, intermediate **XI** was formed upon an aza-Michael reaction, and stable acetal **XII** was obtained from conversion of intermediate **XI** by EtOH. After this transformation, Friedel-Craft reaction, dehydration, oxidation and detosylation reactions take place sequentially resulting in the formation of the target product, 7-hydroxyquinoline (Scheme 22).[58,60]



Scheme 22. Synthesis of 7-hydroxyquinoline in one-pot

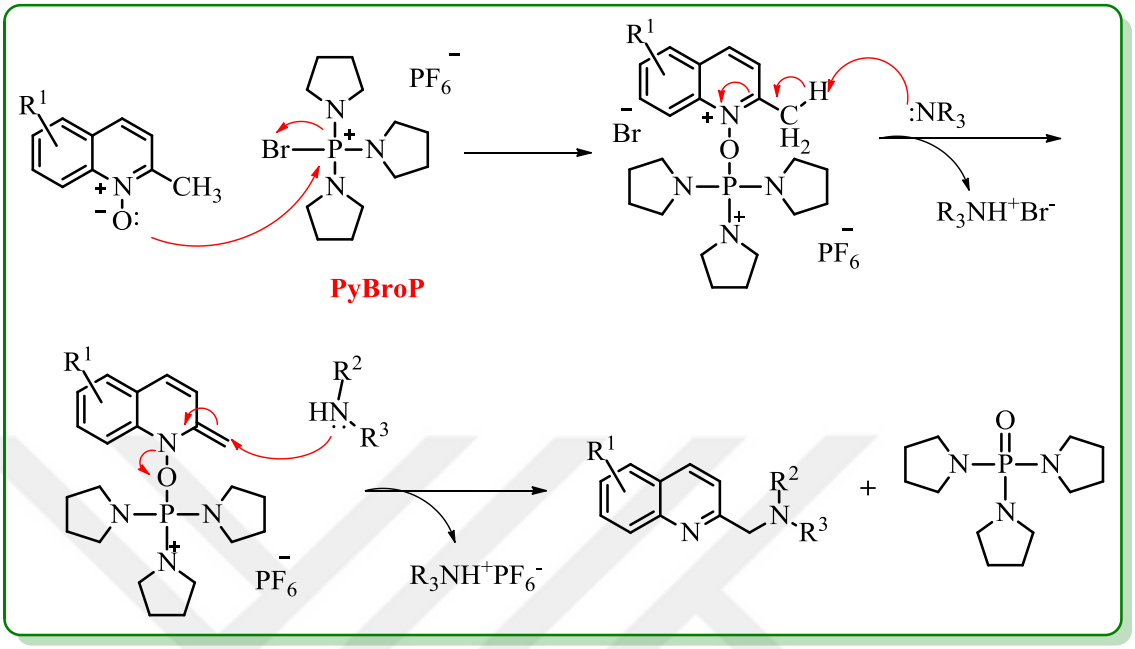
Compared to traditional methods, one-pot synthetic procedures constitute a more efficient approach to obtain desired products by reducing the number of intermediate steps. With the aid of one-pot strategy, costs of process, chemicals or equipment can be reduced, energy and labor can be saved and most importantly, reaction times can be shortened. In this way, more environmentally friendly, cleaner and safer methodologies can be developed by minimizing chemical waste. As a result of all these factors, drawbacks of traditional processes can be eliminated. Hence, complex target products can be synthesized more economically and ecologically via one-pot methods in a short period of time.[57,61]

1.10 The Aim of This Work

The aim of this work is to develop a new synthetic methodology for the benzylic amination reactions of 2-methyl azine *N*-oxide compounds under mild conditions. Given the importance of such heterocyclic compounds in medicinal and agricultural chemistry

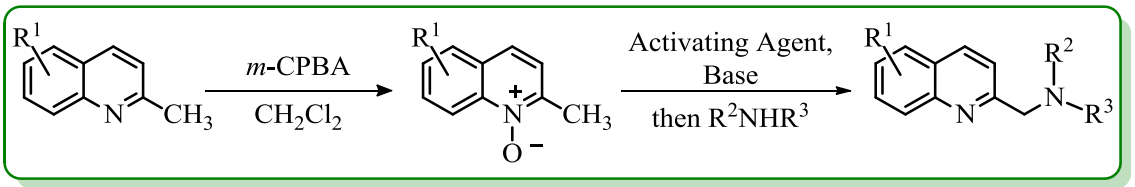
as well as in organometallic chemistry as nitrogen-based ligands, an operationally-simple and high-yielding method that works in a single step is expected to be of high utility to organic chemists. This designed synthetic transformation has several advantages compared to traditional methods. Firstly, this synthetic method supports the transformation from azine *N*-oxide to functionalized form in one-pot, which is economically and environmentally more favorable and feasible. Additionally, via umpolung strategy, this method can be applied to nucleophiles which cannot be used in other methods. It is expected that this developed strategy provide new opportunities for organic synthetic chemists, especially medicinal chemists.

The initially designed mechanism of the benzylic amination reaction is given in Scheme 23. PyBroP is given in this scheme as a representative activating agent. According to this design, first the activating agent is proposed to react with the azine *N*-oxide derivative and activate it via transforming it into a more electrophilic species. In addition, this activation would render the -CH_3 protons more acidic such that a moderately strong base would be able to deprotonate it. Afterwards, the nucleophilic attack of a primary or secondary amine is expected to give the desired benzylic amination product. This whole sequence has been designed to operate in a one-pot manner so that the product would be obtained in pure form after single purification.



Scheme 23. The initially designed mechanism of the benzylic amination reaction

As will be explained in detail in the Results & Discussions section, benzylic amination reactions of azine *N*-oxide derivatives have been investigated in this study and a new one-pot methodology has been developed. For this purpose, azine *N*-oxide compounds were initially synthesized according to a literature procedure (Scheme 24). Then, an in-depth optimization study was carried out screening a broad range of activating agents, bases, solvents and temperatures. After the successful determination of optimal reaction conditions, the substrate scope and functional group tolerance of the developed benzylic amination reaction has been examined.



Scheme 24. Two main sequential steps of this work

CHAPTER 2

RESULTS & DISCUSSION

2.1 Internal Standard Method

During the optimization studies, reaction yields were determined by the application of internal standard method via ^{1}H-NMR spectroscopy. This method is preferred among synthetic chemists because it is a faster method compared to column chromatography and there is no need for any individual experimental procedure for isolation or purification. Hence, time can be saved effectively which is crucial for tedious optimization studies. Without purification, yields after each reaction can be determined by comparing peak areas of target product and the internal standard in the NMR spectrum.[62]

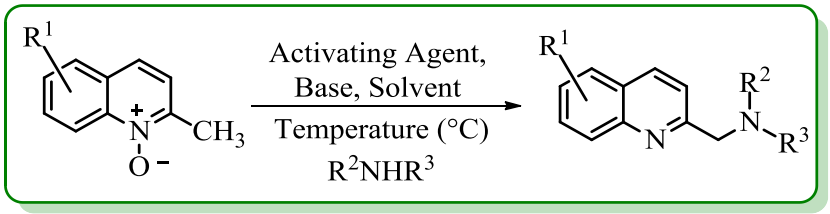
A typical procedure for the determination of reaction yield by internal standard method is as follows: At the end of test reaction given in Scheme 26, an aqueous work-up is carried out and after the removal of the organic solvent *in vacuo*, and 1,3,5-trimethoxybenzene as the internal standard whose amount is equal to the starting material **1** in terms of mmol was then added to the extracted crude mixture. The resulting mixture was completely dissolved in $CDCl_3$. It should be noted that for the ^{1}H-NMR measurement, relaxation delay (D1) parameter was set to 10 sec to ensure accurate integration values. At the end of the NMR measurement, the integral of singlet signal at 6.07 ppm that belongs to 1,3,5-trimethoxybenzene was adjusted as 3.00. Thus, the

integral of doublet signal at 8.10 ppm belonging to benzylic amination product **8** provides the determination of the NMR yield of the targeted product.

In order to check the accuracy and reproducibility of this applied internal standard method, purified product after amination reaction Compound **8** and 1,3,5-trimethoxybenzene were mixed in 1:1 ratio in mmol. After ^{1}H-NMR measurement, the integration of two determined signals (*6.07 ppm and 8.10 ppm)* satisfied the expected values. Thus, the accuracy and reproducibility of this method was confirmed.

2.2 Optimization of Benzylic Amination Reaction

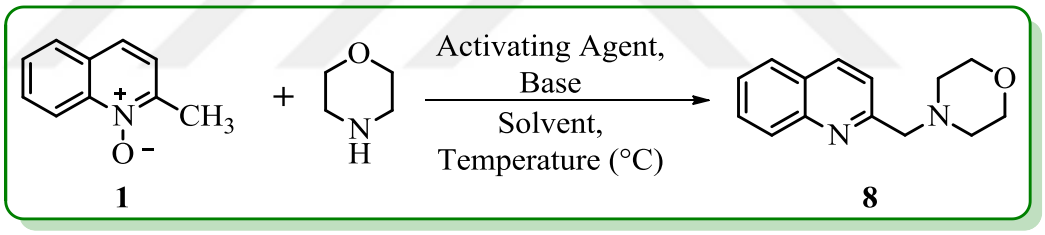
Initially, the benzylic amination reaction of quinaldine *N*-oxide with morpholine was optimized. In this context, parameters such as activating agent, base, solvent, and temperature were systematically investigated. Afterwards, parameters which resulted in the highest yield under the mildest and economically most feasible conditions were determined by using internal standard method via ^{1}H-NMR spectroscopy. At the end of optimization studies, a new synthetic methodology was developed. With this new methodology, azine *N*-oxide compounds including methyl group at the 2-position can be transformed to functionalized azine compounds via umpolung (polarity inversion) strategy in a single step. The targeted reaction for amination at benzylic position is given below (Scheme 25).



Scheme 25. The targeted reaction for amination at benzylic position

2.2.1 Investigation of Activating Agents

Among parameters that were investigated for optimized conditions, activating agents were considered first. Different types of commercially available activating agents were examined comprehensively. Within this concept, reaction between quinaldine *N*-oxide (**1**) and morpholine was chosen as the test reaction (Scheme 26). This reaction was expected to give Compound **8** as the product in case of success. Morpholine was chosen as nucleophile for two reasons. First, it is a common structural motif encountered in medicinal chemistry. Second, since the -CH_2 groups attached to nitrogen and oxygen atoms of morpholine have distinct chemical shifts, ^{1}H-NMR analysis of the targeted product Compound **8** would be facilitated.



1 **8**

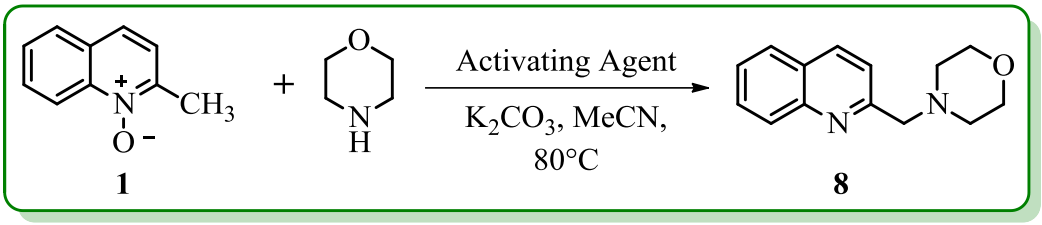
Scheme 26. The benzylic amination reaction of quinaldine *N*-oxide with morpholine as the test reaction for optimization

In accordance with this purpose, quinaldine *N*-oxide as the starting material of this test reaction was synthesized from commercially available quinaldine (2-methylquinoline) using *m*-CPBA. Initially, PyBroP was used as an activating agent in the test reaction (Scheme 27), while various types of solvents, different bases and temperature values from room temperature to 80°C were examined. Unfortunately, the formation of Compound **8** could not be observed in any of these experiments. In each trial, unreacted starting material quinaldine *N*-oxide (**1**) was recovered.

Since PyBroP was not a successful activating agent for benzylic amination reaction, other activating agents were systematically investigated (Table 1). Meanwhile, base, solvent and temperature were kept constant as K_2CO_3, MeCN and 80°C, respectively (Scheme 27). Similar to the case of PyBroP, no target product formation was observed when Ph_3PBr_2 was tested as activating agent (Table 1, Entry 2). This result is not unexpected when the structural similarity of Ph_3PBr_2 to PyBroP is considered. On the other hand, Compound **8** as the benzylic amination product was obtained in 81% yield when TsCl was used as activating agent (Entry 3). It was observed that reaction yield decreased to 71% with the use of MsCl rather than TsCl (Entry 4). When *N*-oxide compound reacts with TsCl or MsCl, chloride (Cl^-) anion is formed. In order to investigate the effect of the counter anion on reaction yield, Ts_2O and Ms_2O were also tested as activating agents in the optimization studies. When the reaction was tested using Ts_2O and Ms_2O, the amination product **8** was obtained in 70% and 67% yield, respectively (Entries 5 and 6). These results show us that, while still active, Ts_2O and Ms_2O have slightly lower performance compared to TsCl and MsCl. In addition to these experiments, Tf_2O, which is more electron deficient, was investigated but only 7% yield was achieved (Entry 7).

Although the reactions mentioned above were carried out under an inert atmosphere of nitrogen, to ensure the absence of unwanted water vapor or moisture, the test reaction was conducted using 4Å molecular sieves and TsCl was used as activating agent. The yield of this reaction was found to be 80% yield which means that the presence of molecular sieves did not provide additional advantage (Table 1, Entry 8). Consequently, TsCl was selected to be the activating agent for benzylic amination reaction because of

the fact that it gave the highest yield among the ones investigated. It is economically more feasible than others as well.



Scheme 27. The test reaction for screening of activating agents

Table 1. Screening of various activating agents

Entry [a]	Activating Agent	Yield (%)[b]
1	PyBroP	*No product formation*
2	Ph_3PBr_2	*No product formation*
3	TsCl	81
4	MsCl	71
5	Ts_2O	70
6	Ms_2O	67
7	Tf_2O	7
8	TsCl [c]	80

[a] In these experiments, 0.31 mmol of quinaldine *N*-oxide (1.0 equiv.), 0.37 mmol of activating agent (1.2 equiv.), 0.68 mmol of K_2CO_3 (2.2 equiv.), 0.47 mmol of morpholine (1.5 equiv.) and 2.0 ml of MeCN were used.

[b] Yields were determined by internal standard method via ^{1}H-NMR spectroscopy. 1,3,5-trimethoxybenzene was used as internal standard.

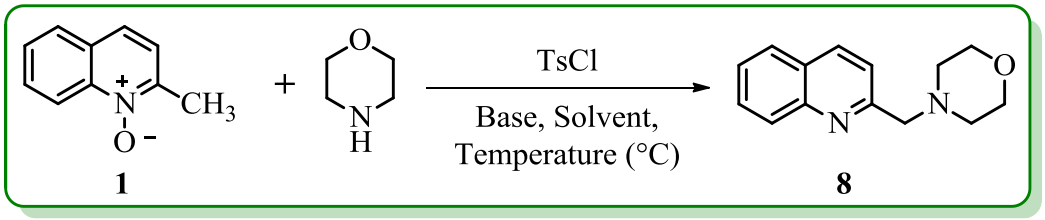
[c] In this experiment, activated 4Å molecular sieves were used.

2.2.2 Investigation of Base, Solvent and Temperature

After determining TsCl as the activating agent, base, solvent and temperature parameters were also investigated. First of all, different organic amine bases and inorganic bases were tested for the targeted reaction (Scheme 28). Among K_2CO_3, Na_2CO_3 and K_3PO_4 as the inorganic bases tested, K_2CO_3 gave the highest yield, 81% yield, when solvent and temperature were kept constant as MeCN and 80°C, respectively (Table 2, Entries 1-3). When CH_2Cl_2 was used as solvent rather than MeCN, reaction was carried out at 35°C. As compared to reaction in MeCN at 80°C, yield was observed to rise from 81% to 90% (Entry 4).

Following this successful outcome, TsCl and K_2CO_3 were kept constant and the effects of several solvents on the yield of targeted reaction were examined. THF, toluene, $PhCF_3$, 2-MeTHF and TBME were screened as reaction solvents, and all gave lower yields compared to CH_2Cl_2 (Table 2, Entries 5-10). Thus, CH_2Cl_2 was chosen as optimal solvent. With this choice, temperature was also determined as 35°C.

Finally, the effect of different bases on the yield was checked again with the determined conditions which are TsCl as activating agent, CH_2Cl_2 as solvent and 35°C as temperature. Among the organic amine bases, the yield of amination product using Et_3N was 60%, while Hünig's base and DBU performed poorly, <5% and 13% yield, respectively (Table 2, Entries 11-13). This way, it was decided that K_2CO_3 would be the preferred base for optimized conditions.



1 **8**

Scheme 28. The test reaction for screening of bases, solvents and temperatures

Table 2. Screening of bases, solvents and temperatures

Entry [a]	Base	Solvent	Temperature(ºC)	Yield(%)[b]
1	K_2CO_3	MeCN	80	81
2	Na_2CO_3	MeCN	80	61
3	K_3PO_4	MeCN	80	76
4 [c]	K_2CO_3	CH_2Cl_2	35	90
5	K_2CO_3	THF	35	64
6	K_2CO_3	Toluene	35	27
7	K_2CO_3	$PhCF_3$	35	62
8	K_2CO_3	$PhCF_3$	60	53
9	K_2CO_3	2-MeTHF	60	34
10	K_2CO_3	TBME	35	27
11	Et_3N	CH_2Cl_2	35	60
12	Hünig's Base	CH_2Cl_2	35	<5
13	DBU	CH_2Cl_2	35	13

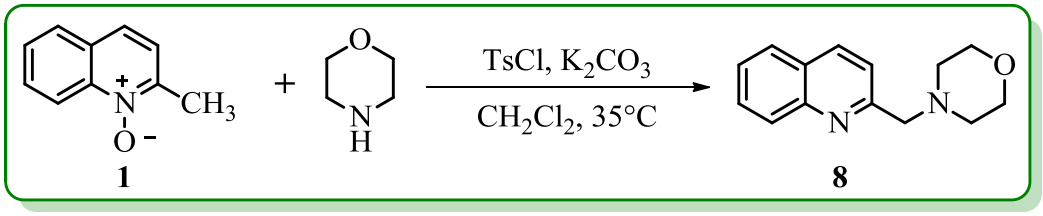
[a] In these experiments, 0.31 mmol of quinaldine *N*-oxide (1.0 equiv.), 0.37 mmol of activating agent (1.2 equiv.), 0.68 mmol of base (2.2 equiv.), 0.47 mmol of morpholine (1.5 equiv.) and 2.0 ml of solvent were used.

[b] Yields were determined by internal standard method via ^{1}H-NMR spectroscopy. 1,3,5-trimethoxybenzene was used as internal standard.

[c] In this experiment, 0.31 mmol of quinaldine *N*-oxide (1 equiv.), 0.43 mmol of activating agent (1.4 equiv.), 0.78 mmol of K_2CO_3 (2.5 equiv.), 0.62 mmol of morpholine (2.0 equiv.) and 2.0 ml of CH_2Cl_2 were used.

During these optimization studies, equivalents of reagents were also modified depending on which conditions gave the highest yield. At the end, optimized conditions with modified equivalents were determined as 0.31 mmol of quinaldine *N*-oxide (1.0 equivalent), 0.43 mmol of activating agent (1.4 equivalent), 0.78 mmol of K_2CO_3 (2.5 equivalent), 0.62 mmol of morpholine (2.0 equivalent) and 2.0 ml of CH_2Cl_2.

When the reaction was carried out under the optimized conditions, benzylic amination product **8** was obtained in pure form in 82% yield after column chromatography (Scheme 29). Detailed characterization of product was done by using various spectroscopic techniques such as ^{1}H-NMR and ^{13}C-NMR spectroscopy, FTIR and HRMS. The optimized conditions were used in the subsequent section in which the substrate scope of the reaction was examined.



Scheme 29. The optimized conditions for the benzylic amination reaction

2.3 Substrate Scope

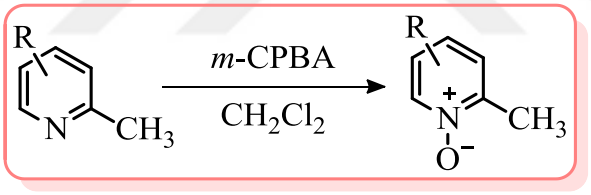
In this section, a detailed substrate scope research was undertaken for the benzylic amination reaction the optimized conditions of which were determined as described in the previous section. (Scheme 29) Both electrophilic azine *N*-oxide derivatives and different nucleophilic components of the reaction were studied.

2.3.1 Preparation of Azine *N*-Oxide Derivatives

In this part, morpholine was used as the nucleophilic component and various types of azine *N*-oxide derivatives were investigated. Initially, different azine *N*-oxides were synthesized from commercially available quinaldine derivatives having different substituents using *m*-chloroperbenzoic acid (*m*-CPBA) as the oxidizing agent (Scheme 30). The syntheses of these compounds were explained in detail in the experimental section and the yields provided are the reaction yields after purification by silica gel column chromatography. The characterization of all products have been performed by FTIR, ^{1}H- and ^{13}C-NMR spectroscopy and high-resolution mass spectrometry (HRMS).

As indicated in Figure 10, Compound **1** without any substituent was synthesized in 93% yield starting from the commercially available quinaldine (2-methylquinoline). Also, *N*-oxide derivatives having bromine or methoxy groups at the 6- position were obtained in high yields (95% and 92%, respectively). The importance of Compound **2** is that after the benzylic amination reaction, Ar-Br moiety of Compound **2** can be used as a functional handle to be utilized in Suzuki- Miyaura cross coupling reactions for further functionalization.[63] Besides, the aim of the synthesis of Compound **3** is to test whether the developed amination reaction would be successful with an electron-rich quinaldine *N*-oxide derivative as the methoxy substituent is an electron donating group. Moreover, azine *N*-oxide product of 4-chloroquinaldine was synthesized in 96% yield. There are two main reasons for the preparation of 4-chloroquinaldine *N*-oxide (**4**). First, chlorine, being an electron withdrawing substituent, is expected to render the aromatic *N*-oxide electron deficient, and this would allow us to test the success of our methodology with an electron deficient substrate. Second, the benzylic amination product of this substrate

would be capable of undergoing an S_NAr reaction with another nucleophile from the 4-position and therefore, would have the potential to get functionalized further. 1-methylisoquinoline *N*-oxide (**5**) was synthesized in 85% yield. The doubly Boc protected of 4-amino quinaldine was also converted successfully to its *N*-oxide, and Compound **6** was obtained in 81% yield. Given the importance of dimethylaminopyridine (DMAP) analogues in organic synthesis, the benzylic amination of Compound **6** can be converted to quinoline-based DMAP-type analogues after the deprotection of –Boc groups. Finally, Compound **7** was synthesized starting from 3-methylisoquinoline in 96 yield%. The investigation of Compound **5** and Compound **7** in the benzylic amination reactions would allow us to make a comparison in the reactivities of isoquinoline and quinoline substrates.



Scheme 30. The synthesis of different azine *N*-oxides

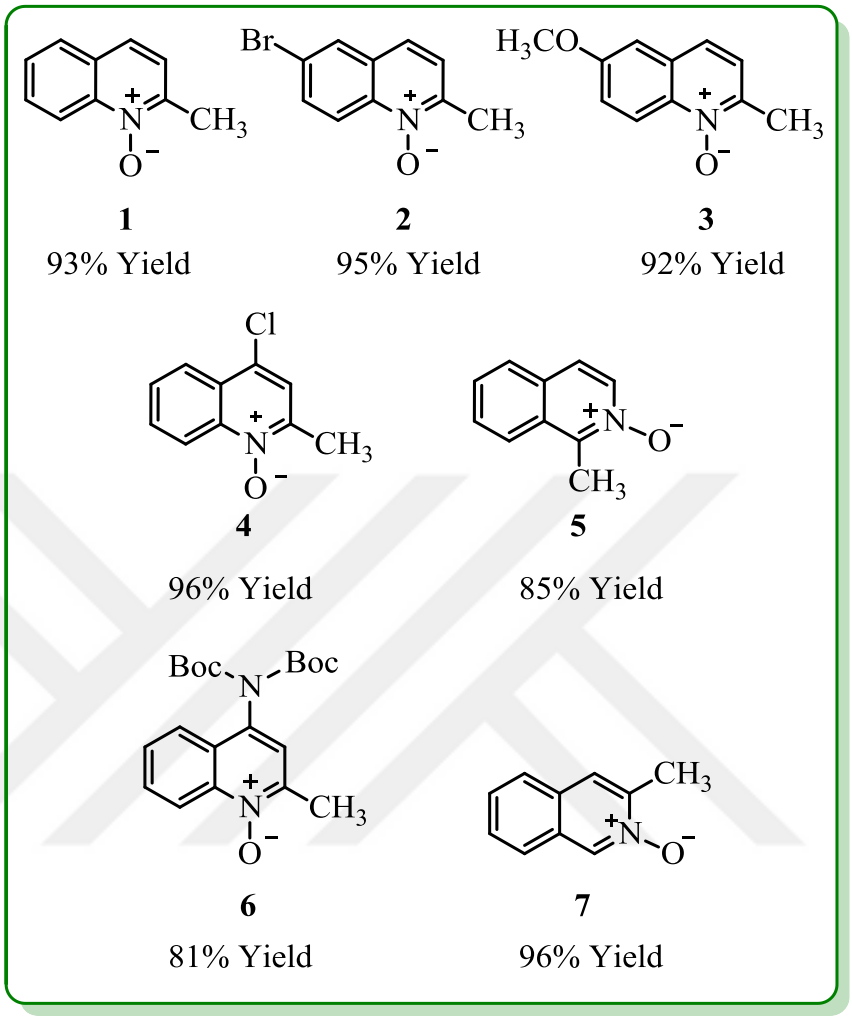


Figure 10. Synthesized azine *N*-oxides

In addition to these achievements, there was an unsuccessful attempt to prepare 8-chloroquinaldine *N*-oxide (**21**). Surprisingly, the treatment of the commercially available 8-chloroquinaldine with *m*-CPBA using the standard conditions did not provide the desired *N*-oxide product (**21**) (Figure 11). This unexpected result can be explained by the enhanced steric hindrance on the nitrogen imparted by the chlorine at the 8- position and $–CH_3$ group at the 2- position so that *m*-CPBA cannot approach the nitrogen for oxygen transfer.

Besides, to widen substrate scope for electrophilic components, 2-methyl pyridine *N*-oxide (picoline *N*-oxide) **22** (Figure 11) was purchased from Alfa Aesar and tested directly in the benzylic amination reaction.

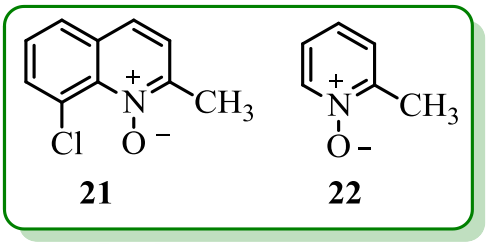
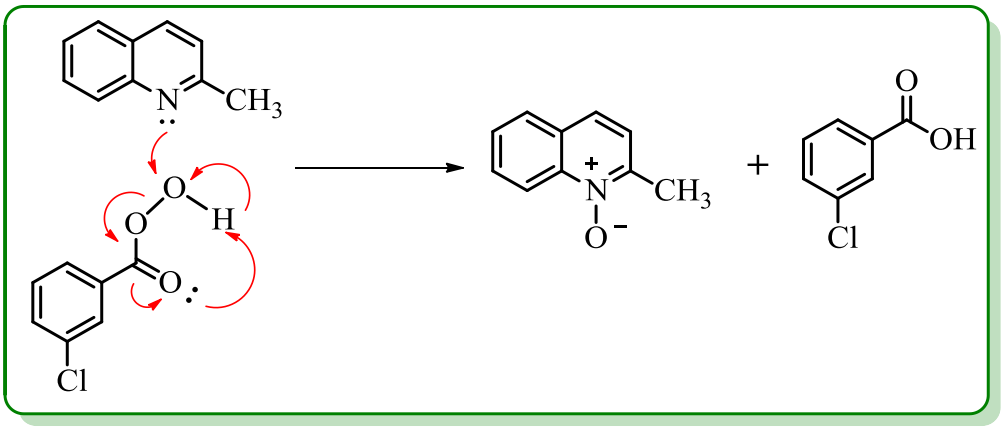


Figure 11. Chemical structures of 8-chloroquinaldine *N*-oxide (**21**) and 2-methyl pyridine *N*-oxide (**22**)

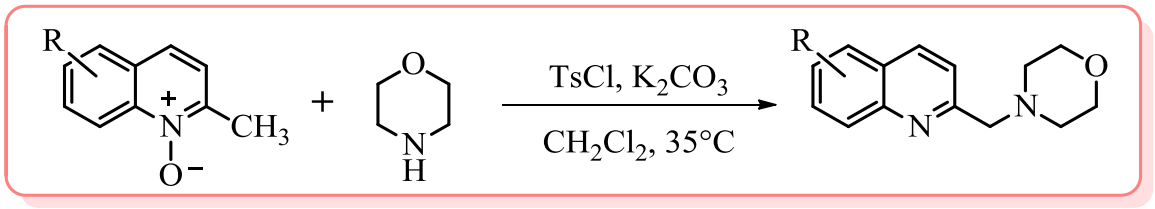
The reaction between azine derivatives and *m*-CPBA to give azine *N*-oxide products can be best described as an oxygen transfer reaction. A plausible mechanism for this oxidation reaction is shown below (Scheme 31). After the oxygen is transferred from *m*-CPBA to azine derivative, *m*-chlorobenzoic acid is formed as a stoichiometric byproduct.



Scheme 31. Oxidation reaction between azine *N* derivatives and *m*-CPBA

2.3.2 Screening of Azine *N*-Oxide Derivatives in the Benzylic Amination Reaction

After the synthesis of azine *N*-oxide derivatives to be used as reactants in the benzylic amination reactions, their reactions with morpholine were carried out under the optimized conditions (Scheme 32). The results obtained are given in Figure 12. Compound **8** was obtained as the product of the reaction between quinaldine *N*-oxide and morpholine in 82% isolated yield. For azine *N*-oxide derivatives having –Br and –OMe substituent at the 6-position, benzylic amination products Compound **9** and Compound **10** were obtained in 66% and 47%, respectively, after purification by column chromatography. As a result of these yield values, it can be argued that an electron donating group on quinoline ring such as methoxy group can slightly reduce the reaction yield. When chloro-substituted *N*-oxide derivative (**4**) was subjected to the reaction conditions, benzylic amination product Compound **11** was isolated in 69% yield. Moreover, isoquinoline-based *N*-oxide reactant (**5**) afforded the amination product Compound **12** in 53%. This result shows that the newly developed amination protocol has the potential to be extended beyond isoquinolines to other heterocyclic ring systems. Finally, when the doubly Boc-protected aminoquinoline *N*-oxide derivative (**6**) was reacted with morpholine, amination product (**13**) was isolated successfully, albeit in a slightly lower yield (40%).



Scheme 32. Benzylic amination reactions of different azine *N*-oxides with morpholine

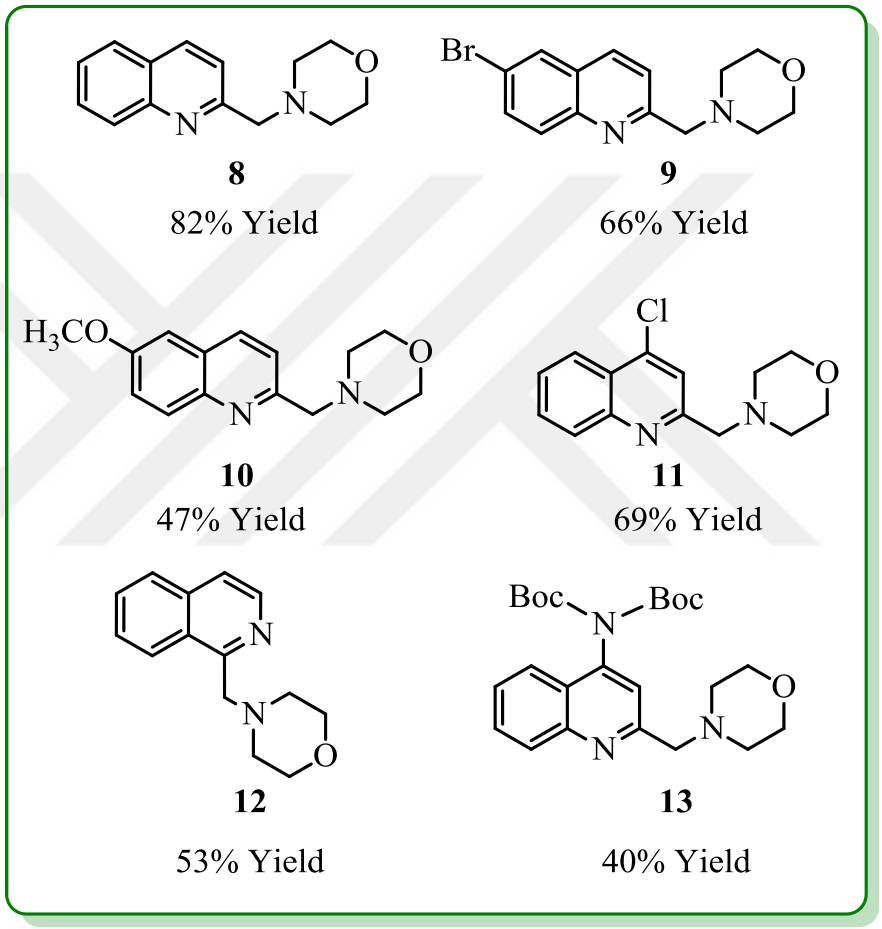
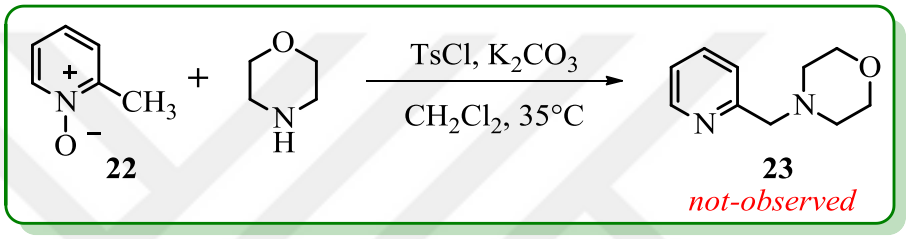


Figure 12. Products of different azine *N*-oxides after benzylic amination reactions with morpholine

As explained above, quinaldine *N*-oxide derivatives and 1-methylisoquinoline *N*-oxide gave successful results with newly developed benzylic amination reaction. However, when 3-methylisoquinoline *N*-oxide (**7**) was subjected to the same reaction conditions, no amination product was obtained. Afterwards, pyridine based *N*-oxide compounds were desired to be investigated within the substrate scope. For this purpose,

commercially available 2-methylpyridine *N*-oxide **22** (Scheme 33) was reacted with morpholine under optimized conditions. However, targeted product could not be obtained under the optimized conditions and starting *N*-oxide was recovered intact (Scheme 33). Although different solvents and temperatures were tested to overcome this issue, Compound **23** could not be formed. These results show the limitations of the current methodology.

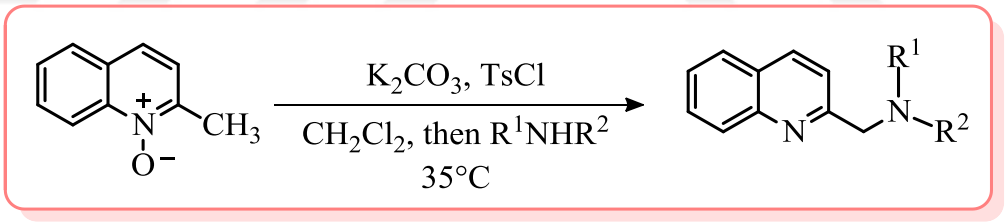


Scheme 33. Benzylic amination reaction of 2-methylpyridine *N*-oxide with morpholine

2.3.3 Screening of Nucleophilic Amines in the Benzylic Amination Reaction

In the previous section, different azine *N*-oxide derivatives were reacted with morpholine to investigate electrophilic components of the substrate scope. In this part, different nucleophilic components were investigated in depth. Firstly, quinaldine *N*-oxide was kept constant as the electrophilic component and amine-based nucleophiles were tested. Various amine bases were reacted with quinaldine *N*-oxide for benzylic amination under the optimized conditions (Scheme 34). The results obtained are given in Figure 13. In the first stage of this part, piperidine and *N*-Boc piperazine which have both 6- membered rings were investigated as nucleophilic amines in order to make a direct comparison with morpholine. Gratifyingly, the product of piperidine addition to quinaldine *N*-oxide (**14**) was obtained in pure form in 76% yield. *N*-Boc piperazine was synthesized starting from as described in a literature procedure.[64] Reaction of *N*-Boc

piperazine with quinaldine *N*-oxide using the standard reaction conditions gave amination product **17** in 72% yield. Imidazole was tested as a heteroaromatic nucleophile in the amination reaction. We were pleased to obtain the desired amination product **16** in 61% yield after purification. Other than these, pyrrolidine and diethyl amine which are also secondary amines were tested in benzylic amination reaction. The yields after column chromatography were determined as 62% (**15**) and 73% (**18**), respectively. While cyclohexyl amine, which is cyclic and a primary amine performed with 46% yield (**19**), benzylic amination product of α-methyl benzyl amine (**20**) was obtained in 64% yield. From these observations, it can be concluded that secondary amines are higher yielding substrates compared to primary amines due to their higher nucleophilicity.



Scheme 34. Benzylic amination reactions of quinaldine *N*-oxide with different amines

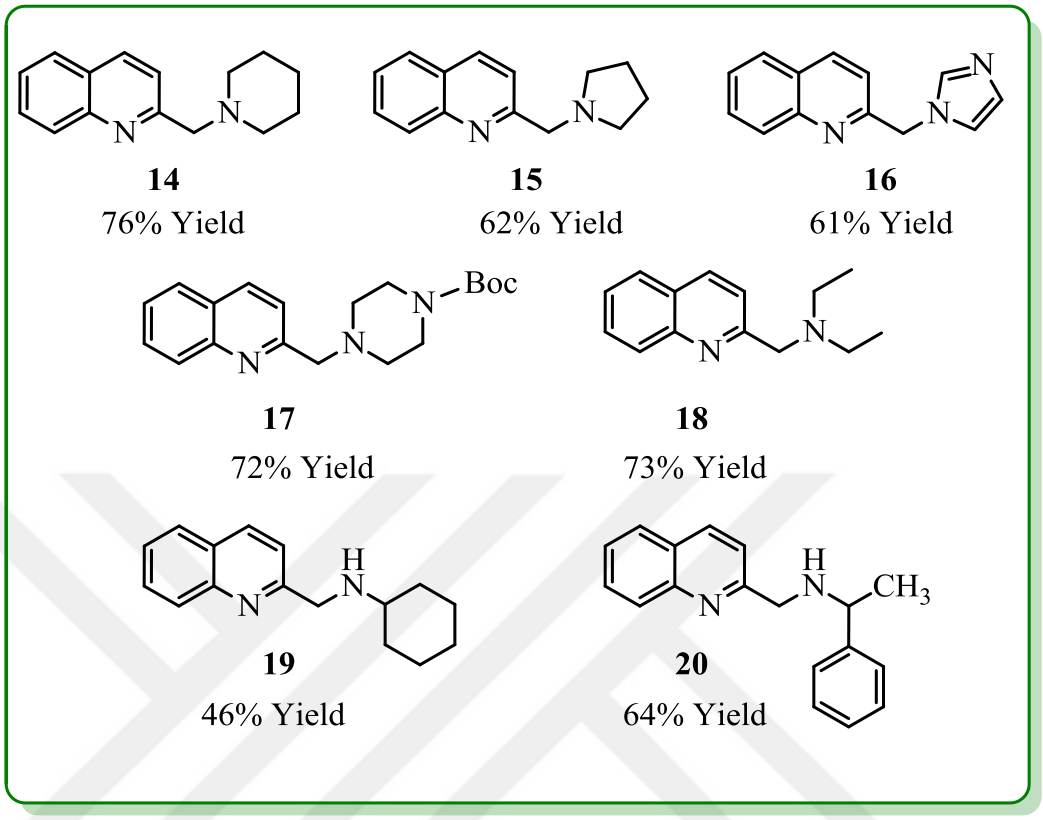
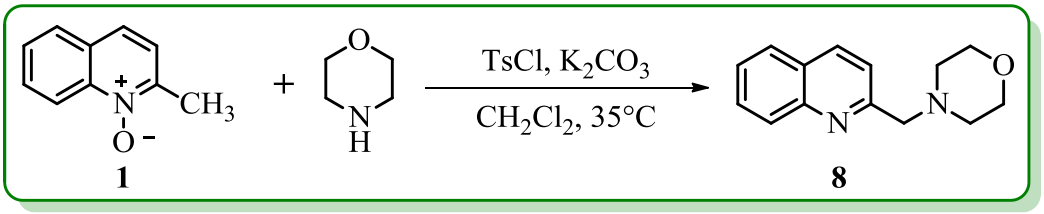


Figure 13. Products of quinaldine *N*-oxide after benzylic amination reactions with various amines

2.4 Scalability of Benzylic Amination Reaction

Within the last few years, special attention is given to the scalability of newly developed synthetic methodologies. Following the successful investigation of the substrate scope of the benzylic amination reaction, we next opted to investigate the scalability of this method. To this end, reaction scale was increased up to 10.0 mmol. Benzylic amination reaction between quinaldine *N*-oxide (1.59 g) and morpholine (1.80 ml) was carried out under the optimized conditions (Scheme 29).



Scheme 35. The optimized conditions for the benzylic amination reaction

After purification by column chromatography, amination product **8** was obtained in 64% yield (1.46 g). In order to ensure the reproducibility of this reaction at large scale, it was conducted a second time. Similarly, yield of the product was determined as 63% (1.44 g) after column chromatography. Even though the yield at large scale was lower (64%) as compared to yield at small scale (82%, 0.31 mmol scale), these results demonstrate that the newly developed method can be successfully applied in gram scale in a reproducible manner.

CHAPTER 3

EXPERIMENTAL

3.1 Experimental Details

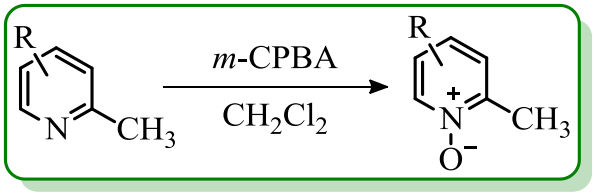
3.1.1 Methods and Materials

All the experiments in this work were conducted under nitrogen atmosphere with the use of Schlenk line. Glassware were dried in oven before the experiment. Chemicals for the experiments were purchased from Acros, Merck, TCI, Sigma-Aldrich, Alfa Aesar, and Carlo Erba and they used without further purification. Reactions were monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 Å F254. For TLC visualization, either KMnO4 solution or UV lamp (254 nm) was used. Purification was done by flash column chromatography using GemChem 40-63 μm silica gel. All organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure.

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker DPX 400 spectrometer in $CDCl_3$. For calibration of ^{1}H-NMR spectra, either the signal of internal standard which is tetramethylsilane (TMS) as 0 ppm or the signal of $CDCl_3$ as 7.26 ppm was used. The signal resulting from $CDCl_3$ was calibrated as 77.16 ppm for ^{13}C-NMR spectra. Chemical shifts (δ) were reported in parts per million (ppm) and the coupling constants (*J*) were in Hertz (Hz). Spin multiplicities were indicated as the following: s (singlet), d (doublet), t (triplet), m (multiplet), quint (quintet), dd (doublet of doublet), dt (doublet of triplet), and ddd (doublet of doublet of doublet). HRMS data were acquired on Agilent Technologies 6224 TOF LC/MS. For FTIR spectra, Bruker ATR spectrometer was used.

3.2 Synthesis of Azine *N*-Oxides

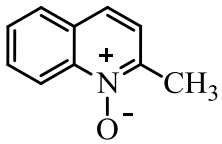
3.2.1 General Procedure I



Scheme 36. The synthesis of different azine *N*-oxides

Quinaldine (2-methylquinoline) or methylisoquinoline derivative (1.50 mmol) was dissolved in 10 ml of CH_2Cl_2. It was cooled down to 0°C and stirred for 15 minutes. Then, *m*-CPBA (1.65 mmol, 70-75% pure) was added as solid as carefully. The resulting solution was stirred for 22 hours at room temperature. After 22 hours, 10 ml of saturated $NaHCO_3$ solution was added to the reaction mixture and the aqueous solution was extracted three times with CH_2Cl_2. The combined organic phase was washed once with brine (15 ml). It was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the product was performed by flash column chromatography using silica gel.[65]

Compound 1



N-oxide derivative **1** was prepared according to General Procedure I using quinaldine (2.00 g, 14.0 mmol), *m*-CPBA (3.656 g, 15.4 mmol) and 100 ml of CH_2Cl_2. Purification by flash column chromatography (5% MeOH in EtOAc, 7.5% MeOH in EtOAc, 10%

MeOH in EtOAc and then 12.5% MeOH in EtOAc) gave pure *N*-oxide product **1** as a pale yellow solid (2.064 g, 93% yield).

$\boldsymbol{R_f}$ = 0.20 (MeOH: EtOAc, 1:19)

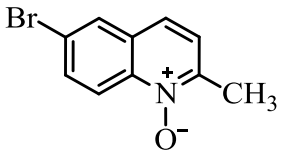
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.68 (1 H, d, *J* = 8.8 Hz), 7.70 (1 H, d, *J* = 8.1 Hz), 7.62 (1 H, ddd, *J* = 8.4, 7.0 and 1.4 Hz), 7.51 (1 H, d, *J* = 8.5 Hz), 7.46 (1 H, dt, *J* = 7.0 and 1.1 Hz), 7.16 (1 H, d, *J* = 8.5 Hz), 2.61 (3 H, s)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 145.5, 141.4, 130.0, 129.1, 127.9, 127.5, 124.8, 122.8, 119.3, 18.6

IR $\nu_{max.}$ (ATR, solid)/cm^{-1} 3064, 3045, 3001, 2986, 2953, 2919, 1565, 1512, 1554, 1425, 1333, 1271, 1240, 1214, 1202

HRMS (ESI) calculated $C_{10}H_{10}NO$ $[M+H]^+$ 160.0757, observed 160.0763

Compound 2



N-oxide derivative **2** was prepared according to General Procedure I using 6-bromoquinaldine (1.00 g, 4.5 mmol), *m*-CPBA (1.179 g, 4.95 mmol) and 50 ml of CH_2Cl_2. Purification by flash column chromatography (5% MeOH in EtOAc, then 7.5% MeOH in EtOAc) gave pure *N*-oxide product **2** as a pale yellow solid (1.023 g, 95% yield).

$\boldsymbol{R_f}$ = 0.23 (MeOH: EtOAc, 1:19)

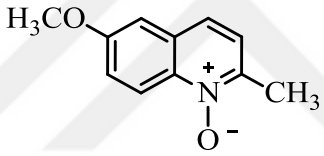
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.62 (1 H, d, *J* = 9.2 Hz), 7.96 (1 H, d, *J* = 2.0 Hz), 7.77 (1 H, dd, *J* = 9.3 and 2.1 Hz), 7.52 (1 H, d, *J* = 8.6 Hz), 7.31 (1 H, d, *J* = 8.6 Hz), 2.67 (3 H, s)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 146.2, 140.5, 133.6, 130.5, 130.1, 124.3, 123.7, 122.2, 121.7, 18.8

IR $\nu_{max.}$ (ATR, solid)/cm^{-1} 3057, 3034, 1557, 1504, 1446, 1324, 1303, 1238, 1144, 910, 885, 807

HRMS (ESI) calculated $C_{10}H_9BrNO$ $[M+H]^+$ 237.9862, observed 237.9869

Compound 3



N-oxide derivative **3** was prepared according to General Procedure I using 6-methoxyquinaldine (300 mg, 1.7 mmol), *m*-CPBA (452 mg, 1.9 mmol) and 19 ml of CH_2Cl_2. Purification by flash column chromatography (5% MeOH in EtOAc, 7.5% MeOH in EtOAc and then 10% MeOH in EtOAc) gave pure *N*-oxide product **3** as a pale yellow solid (302 mg, 92% yield).

$\boldsymbol{R_f}$ = 0.17 (MeOH: EtOAc, 1:19)

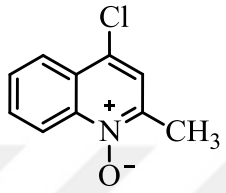
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.65 (1 H, d, *J* = 9.5 Hz), 7.49 (1 H, d, *J* = 8.5 Hz), 7.32 (1 H, dd, *J* = 9.5 and 2.7 Hz), 7.22 (1 H, d, *J* = 8.6 Hz), 7.04 (1 H, d, *J* = 2.7 Hz), 3.89 (3 H, s), 2.64 (3 H, s)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 158.8, 143.7, 137.4, 130.6, 124.2, 123.5, 122.3, 121.3, 106.0, 55.7, 18.5

IR $\nu_{max.}$ (ATR, solid)/cm^{-1} 3056, 2964, 2931, 1615, 1571, 1513, 1474, 1434, 1332, 1317, 1221, 1202, 1031, 1009

HRMS (ESI) calculated $C_{11}H_{12}NO_2$ $[M+H]^+$ 190.0863, observed 190.0863

Compound 4



N-oxide derivative **4** was prepared according to General Procedure I using 4-chloroquinaldine (266 mg, 1.5 mmol), *m*-CPBA (393 mg, 1.65 mmol) and 10 ml of CH_2Cl_2. Purification by flash column chromatography (5% MeOH in EtOAc, then 7.5% MeOH in EtOAc) gave pure *N*-oxide product **4** as a pale yellow solid (279 mg, 96% yield).

$\boldsymbol{R_f}$ = 0.21 (2% MeOH in EtOAc)

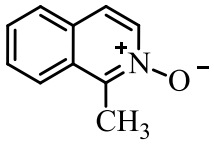
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.77 (1 H, d, *J* = 8.7 Hz), 8.14 (1 H, d, *J* = 8.4 Hz), 8.78 (1 H, t, *J* = 8.4 Hz), 7.67 (1 H, t, *J* = 8.2 Hz), 7.39 (1 H, s), 2.67 (3 H, s)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 145.7, 142.3, 131.1, 129.1, 128.6, 126.9, 125.1, 122.9, 120.2, 18.7

IR $\nu_{max.}$ (ATR, solid)/cm^{-1} 3033, 3021, 1584, 1561, 1505, 1331, 1267, 1229, 1138, 1101

HRMS (ESI) calculated $C_{10}H_9ClNO$ $[M+H]^+$ 194.0367, observed 194.0376

Compound 5



N-oxide derivative **5** was prepared according to General Procedure I using 1-methylisoquinoline (127 mg, 0.887 mmol), *m*-CPBA (232 mg, 0.976 mmol) and 10 ml of CH_2Cl_2. Purification by flash column chromatography (10% MeOH in EtOAc, 12.5% MeOH in EtOAc and then 15% MeOH in EtOAc) gave pure *N*-oxide product **5** as a pale yellow solid (119 mg, 85% yield).

$\boldsymbol{R_f}$ = 0.20 (MeOH: EtOAc, 1:19)

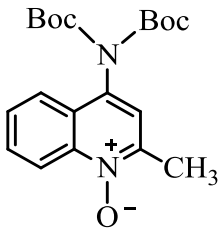
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.19 (1 H, d, *J* = 7.1 Hz), 7.91 (1 H, d, *J* = 8.5 Hz), 7.73 (1 H, d, *J* = 7.9 Hz), 7.61 (1 H, dt, *J* = 7.0 and 1.4 Hz), 7.54 (1 H, ddd, *J* = 8.1, 7.1 and 1.2 Hz), 7.50 (1 H, d, *J* = 7.2 Hz), 2.86 (3 H, s)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 145.7, 136.5, 129.1, 129.0, 128.8, 128.5, 127.4, 124.1, 121.9, 13.0

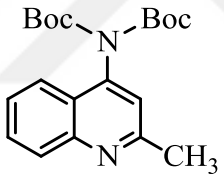
IR $\nu_{max.}$ (ATR, solid)/cm^{-1} 3046, 2923, 2852, 1601, 1557, 1503, 1394, 1325, 1270, 1212, 1145

HRMS (ESI) calculated $C_{10}H_{10}NO$ $[M+H]^+$ 160.0757, observed 160.0758

Compound 6



Before the synthesis of *N*-oxide derivative **6**, *tert*-butyl (2-methylquinolin-4-yl) carbamate was synthesized according to a procedure given in the literature.[66] To a solution of 4-amino-2-methylquinoline (1.00 g, 6.32 mmol) in THF (30 ml) was added $(Boc)_2O$ (2.759 g, 12.64 mmol), triethylamine (2.12 ml, 15.16 mmol) and DMAP (4-dimethylaminopyridine) (77 mg, 0.632 mmol). The reaction mixture was stirred at room temperature overnight then quenched with water (50 ml) and extracted with EtOAc (3x50 ml). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. Double protected 4-aminoquinaldine (**24**) (1.5861 g, 70% yield) was purified by silica gel column chromatography (1:2 EtOAc:Hexane).



24

N-oxide derivative **6** was prepared according to General Procedure I using double protected 4-aminoquinaldine **24** (400 mg, 1.12 mmol), *m*-CPBA (292 mg, 1.23 mmol) and 20 ml of CH_2Cl_2. Purification by flash column chromatography (only EtOAc) gave pure *N*-oxide product **6** as a yellow solid (338 mg, 81% yield).

$\boldsymbol{R_f}$ = 0.35 (1% MeOH in EtOAc)

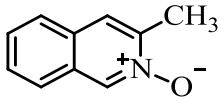
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.78 (1 H, dd, *J* = 8.9 and 0.8 Hz), 7.79-7.74 (2 H, m), 7.63 (1 H, ddd, *J*= 8.4, 6.8 and 1.2 Hz), 7.17 (1 H, s), 2.72 (3 H, s), 1.32 (18 H, s)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 150.8, 146.1, 142.3, 133.4, 130.6, 128.4, 126.9, 122.9, 122.7, 120.2, 84.0, 27.9, 19.0

IR $\nu_{max.}$ (ATR, solid)/cm^{-1} 3074, 2978, 2935, 1780, 1395, 1366, 1326, 1279, 1254, 1225, 1154, 1099, 961, 850, 777, 454

HRMS (ESI) calculated $C_{20}H_{27}N_2O_5$ $[M+H]^+$ 375.1914, observed 375.1911

Compound 7



N-oxide derivative **7** was prepared according to General Procedure I using 3-methylisoquinoline (300 mg, 2.1 mmol), *m*-CPBA (549 mg, 2.31 mmol) and 20 ml of CH_2Cl_2. Purification by flash column chromatography (10% MeOH in EtOAc, then 12.5% MeOH in EtOAc) gave pure *N*-oxide product **7** as a pale yellow solid (320 mg, 96% yield).

$\boldsymbol{R_f}$ = 0.10 (2% MeOH in EtOAc)

^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.68 (1 H, s), 7.54-7.48 (2 H, m), 7.45 (1 H, s), 7.37-7.35 (2 H, m), 2.49 (3 H, s)

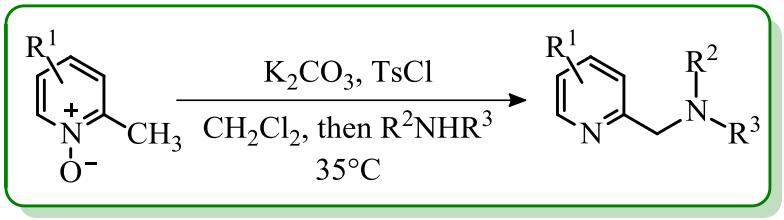
^{13}C NMR (100 MHz; $CDCl_3$) δ: 145.0, 135.4, 128.3, 127.9, 127.7, 127.5, 125.1, 123.7, 122.4, 17.0

IR $\nu_{max.}$ (ATR, solid)/cm^{-1} 3220, 3050, 2923, 2851, 1670, 1636, 1604, 1450, 1315, 1097, 891, 758, 679, 470, 434

HRMS (ESI) calculated $C_{10}H_{10}NO$ $[M+H]^+$ 160.0757, observed 160.0758

3.3 Benzylic Amination of Azine *N*-Oxide Derivatives

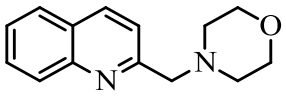
3.3.1 General Procedure II



Scheme 37. Benzylic amination reactions of different azine *N*-oxides with different nucleophiles

Azine *N*-oxide derivative (0.31 mmol) was dissolved in anhydrous CH_2Cl_2 (2.0 mL) at room temperature under nitrogen atmosphere. After the addition of K_2CO_3 (0.78 mmol), the reaction mixture was cooled down to 0 °C in an ice-water bath. After five minutes, TsCl (0.43 mmol) was added, and it was stirred for five more minutes at this temperature. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 5 hours. The nucleophilic amine (0.62 mmol) was then added, and the reaction mixture was stirred at 35 °C for 18 hours. After the mixture was cooled down to room temperature, water (4 mL) was added and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the product was performed with flash column chromatography using silica gel.

Compound 8



Amination product **8** was prepared according to General Procedure II using quinaldine *N*-oxide **1** (200 mg, 1.26 mmol), K_2CO_3 (428 mg, 3.1 mmol), TsCl (332 mg, 1.74

mmol), morpholine (224 µl, 2.52 mmol) and 8 ml of CH_2Cl_2. Purification by flash column chromatography (MeOH: EtOAc 1:19) gave pure product **8** as a yellow oil (234 mg, 82% yield).

This reaction was also performed in 10.0 mmol scale following General Procedure II using quinaldine *N*-oxide **1** (1.59 g, 10.0 mmol), K_2CO_3 (3.46 g, 25.0 mmol), TsCl (2.67 g, 14.0 mmol), morpholine (1.80 ml, 20.0 mmol) and 40 ml of CH_2Cl_2. Purification by flash column chromatography (MeOH: EtOAc 1:19) gave pure product **8** as a yellow oil (1.464 g, 64% yield).

$\boldsymbol{R_f}$ = 0.39 (MeOH: EtOAc, 1:19)

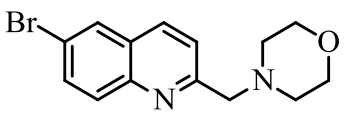
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.11 (1 H, d, *J* = 8.5 Hz), 8.07 (1 H, d, *J* = 8.5 Hz), 7.78 (1 H, d, *J* = 8.1 Hz), 7.68 (1 H, ddd, *J* = 8.4, 6.9 and 1.4 Hz), 7.62 (1 H, d, *J* = 8.4 Hz), 7.50 (1 H, ddd, *J* = 8.1, 7.0 and 1.0 Hz), 3.83 (2 H, s), 3.73 (4 H, t, *J* = 4.7 Hz), 2.55 (4 H, t, *J* = 4.6 Hz)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 159.2, 147.8, 136.5, 129.5, 129.2, 127.6, 127.5, 126.3, 121.2, 67.1, 65.7, 54.0

IR $\nu_{max.}$ (ATR, oil)/cm^{-1} 2957, 2852, 2808, 1618, 1599, 1503, 1453, 1425, 1349, 1327, 1265

HRMS (ESI) calculated $C_{14}H_{17}N_2O$ $[M+H]^+$ 229.1335, observed 229.1691

Compound 9



Amination product **9** was prepared according to General Procedure II using 6-bromoquinaldine *N*-oxide **2** (74 mg, 0.31 mmol), K_2CO_3 (107 mg, 0.78 mmol), TsCl (83 mg, 0.43 mmol), morpholine (56 µl, 0.62 mmol) and 2 ml of CH_2Cl_2. Purification by flash column chromatography (only EtOAc, then 2% MeOH in EtOAc) gave pure product **9** as a pale yellow solid (63 mg, 66% yield).

$\boldsymbol{R_f}$ = 0.34 (MeOH: EtOAc, 1:19)

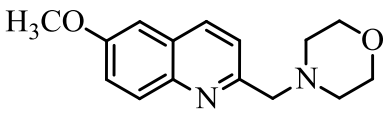
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.00 (1 H, d, *J* = 8.5 Hz), 7.93 (1 H, d, *J* = 2.0 Hz), 7.91 (1 H, d, *J* = 9.0 Hz), 7.73 (1 H, dd, *J* = 8.9 and 2.2 Hz), 7.63 (1 H, d, *J* = 8.5 Hz), 3.79 (2 H, s), 3.73 (4 H, t, 4.6 Hz), 2.53 (4 H, t, *J* = 4.6 Hz)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 159.8, 146.4, 135.5, 133.0, 131.0, 129.7, 128.6, 122.1, 120.1, 67.1, 65.6, 54.0

IR $\nu_{max.}$ (ATR, solid)/cm^{-1} 2961, 2849, 2813, 1593, 1484, 1452, 1346, 1286, 1262, 1111, 1068, 1011, 828

HRMS (ESI) calculated $C_{14}H_{16}BrN_2O$ $[M+H]^+$ 307.0441, observed 307.0454

Compound 10



Amination product **10** was prepared according to General Procedure II using 6-methoxyquinaldine *N*-oxide **3** (58.7 mg, 0.31 mmol), K_2CO_3 (107 mg, 0.78 mmol), TsCl (83 mg, 0.43 mmol), morpholine (56 µl, 0.62 mmol) and 2 ml of CH_2Cl_2. Purification by flash column chromatography (5% MeOH in EtOAc, then 7.5% MeOH in EtOAc) gave pure product **10** as a dark orange oil (37.4 mg, 47% yield).

$\boldsymbol{R_f}$ = 0.40 (MeOH: EtOAc, 1:19)

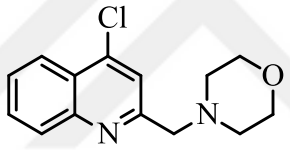
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.00 (1 H, d, *J* = 8.5 Hz), 7.96 (1 H, d, *J* = 9.2 Hz), 7.56 (1 H, d, *J* = 8.4 Hz), 7.34 (1 H, dd, *J* = 9.2 and 2.8 Hz), 7.05 (1 H, d, *J* = 2.8 Hz), 3.91 (3 H, s), 3.79 (2 H, s), 3.73 (4 H, t, 4.7 Hz), 2.54 (4 H, t, *J* = 4.6 Hz)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 157.7, 156.5, 143.9, 135.3, 130.6, 128.5, 122.1, 121.6, 105.3, 67.1, 65.6, 55.6, 54.0

IR $\nu_{max.}$ (ATR, oil)/cm^{-1} 2961, 2934, 2854, 2812, 1623, 1600, 1482, 1264, 1229, 1070

HRMS (ESI) calculated $C_{15}H_{19}N_2O_2$ $[M+H]^+$ 259.1441, observed 259.1443

Compound 11



Amination product **11** was prepared according to General Procedure II using 4-chloroquinaldine *N*-oxide **4** (60 mg, 0.31 mmol), K_2CO_3 (107 mg, 0.78 mmol), TsCl (83 mg, 0.43 mmol), morpholine (56 µl, 0.62 mmol) and 2 ml of CH_2Cl_2. Purification by flash column chromatography (2% MeOH in EtOAc) gave pure product **11** as a pale yellow solid (56 mg, 69% yield).

$\boldsymbol{R_f}$ = 0.50 (2% MeOH in EtOAc)

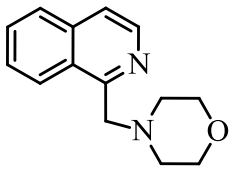
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.20 (1 H, d, *J* = 8.4 Hz), 8.07 (1 H, d, *J* = 8.5 Hz), 7.76-7.72 (2 H, m), 7.60 (1 H, t, *J* = 8.2 Hz), 3.79 (2 H, s), 3.75 (4 H, t, *J* = 4.6 Hz), 2.55 (4 H, t, *J* = 4.5 Hz)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 159.5, 148.6, 143.1, 130.5, 129.5, 127.3, 125.7, 124.1, 121.1, 67.1, 65.3, 54.0

IR $\nu_{max.}$ (ATR, solid)/cm^{-1} 2949, 2925, 2856, 1588, 1554, 1492, 1449, 1404, 1138

HRMS (ESI) calculated $C_{14}H_{16}ClN_2O$ $[M+H]^+$ 263.0946, observed 263.0947

Compound 12



Amination product **12** was prepared according to General Procedure II using 1-methylisoquinoline *N*-oxide **5** (49.4 mg, 0.31 mmol), K_2CO_3 (107 mg, 0.78 mmol), TsCl (83 mg, 0.43 mmol), morpholine (56 µl, 0.62 mmol) and 2 ml of CH_2Cl_2. Purification by flash column chromatography (MeOH: EtOAc 1:19) gave pure product **12** as a pale yellow oil (37.3 mg, 53% yield).

$\boldsymbol{R_f}$ = 0.30 (2% MeOH in EtOAc)

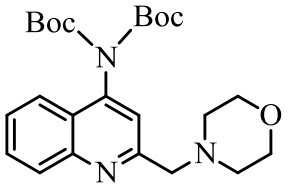
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.20 (1 H, d, *J* = 8.4 Hz), 8.07 (1 H, d, *J* = 8.5 Hz), 7.76-7.72 (2 H, m), 7.60 (1 H, t, *J* = 8.2 Hz), 3.79 (2 H, s), 3.75 (4 H, t, *J* = 4.6 Hz), 2.55 (4 H, t, *J* = 4.5 Hz)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 157.5, 141.7, 136.5, 130.1, 127.9, 127.2, 127.1, 126.3, 120.7, 67.1, 63.8, 54.0

IR $\nu_{max.}$ (ATR, oil)/cm^{-1} 3051, 2959, 2815, 1623, 1586, 1563, 1454, 1344, 1244, 1115, 1005

HRMS (ESI) calculated $C_{14}H_{17}N_2O$ $[M+H]^+$ 229.1335, observed 229.1340

Compound 13



In order to synthesize Compound **13**, General Procedure II was applied. Due to not completely consumption of Compound **6**, reaction mixture was stirred overnight without addition of morpholine. As 24 hours were completed, morpholine was added to reaction mixture and by heating up to 35°C, reaction was started. In this synthesis, double protected 4-amino quinaldine *N*-oxide (Compound **6**, 116 mg, 0.31 mmol), K_2CO_3 (107 mg, 0.78 mmol) TsCl (83 mg, 0.43 mmol) and morpholine (56 µl, 0.62 mmol) were dissolved in 2 ml of CH_2Cl_2. After purification by using only EtOAc, product **13** was obtained as dark yellowish oil (54.5 mg, 40% yield).

$\boldsymbol{R_f}$ = 0.5 (only EtOAc)

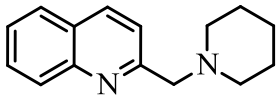
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.09 (1 H, ddd, *J* = 8.5, 0.9 and 0.5 Hz), 7.81 (1 H, ddd, *J* = 8.3, 1.4 and 0.5 Hz), 7.70 (1 H, ddd, *J* = 8.4, 6.8 and 1.6 Hz), 7.55 (1 H, ddd, *J* = 7.0, 5.8 and 1.2 Hz), 7.51 (1 H, s), 3.86 (2 H, s), 3.73 (4 H, t, *J* =4.6 Hz), 2.54 (4 H, t, *J* = 4.6 Hz), 1.29 (18 H, s)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 159.9, 150.9, 149.0, 144.9, 129.8, 129.6, 127.1, 125.2, 122.0, 120.3, 83.5, 67.1, 65.4, 53.9, 27.9

IR $\nu_{max.}$ (ATR, oil)/cm^{-1} 3003, 2980, 2934, 2861, 2803, 1736, 1698, 1619, 1452, 1363, 1337, 1271, 1241, 1159, 1112, 1075, 747, 701, 631

HRMS (ESI) calculated $C_{24}H_{34}N_3O_5$ $[M+H]^+$ 444.2493, observed 444.2478

Compound 14



Amination product **14** was prepared according to General Procedure II using quinaldine *N*-oxide **1** (50 mg, 0.31 mmol), K_2CO_3 (107 mg, 0.78 mmol), TsCl (83 mg, 0.43 mmol), piperidine (61 μl, 0.62 mmol) and 2 ml of CH_2Cl_2. Purification by flash column chromatography (only EtOAc, then 2% MeOH in EtOAc) gave pure product **14** as a yellow oil (54 mg, 76% yield).

$\boldsymbol{R_f}$ = 0.30 (MeOH: EtOAc, 1:19)

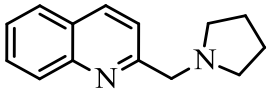
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.09 (1 H, d, *J* = 8.8 Hz), 8.06 (1 H, d, *J* = 8.5 Hz), 7.77 (1 H, dd, *J* = 8.1 and 1.1 Hz), 7.67 (1 H, ddd, *J* = 8.4, 6.9 and 1.4 Hz), 7.65 (1 H, d, *J* = 8.5 Hz), 7.48 (1 H, ddd, *J* = 8.0, 6.9 and 1.1 Hz), 3.79 (2 H, s), 2.47 (4 H, t, *J* = 4.8 Hz), 1.60 (4 H, quint, *J* = 5.6 Hz), 1.45 (2 H, app quint, *J* = 5.7 Hz)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 160.5, 147.8, 136.3, 129.3, 129.2, 127.6, 127.5, 126.1, 121.3, 66.2, 55.0, 26.2, 24.4

IR $\nu_{max.}$ (ATR, oil)/cm^{-1} 2931, 2852, 2799, 1599, 1502, 1424, 1298, 1153, 1111, 1038, 988, 828

HRMS (ESI) calculated $C_{15}H_{19}N_2$ $[M+H]^+$ 227.1543, observed 227.1545

Compound 15



Amination product **15** was prepared according to General Procedure II using quinaldine *N*-oxide **1** (50 mg, 0.31 mmol), K_2CO_3 (107 mg, 0.78 mmol), TsCl (83 mg, 0.43 mmol), pyrrolidine (52 µl, 0.62 mmol) and 2 ml of CH_2Cl_2. Purification by flash column chromatography (only EtOAc, 2% MeOH in EtOAc and then 5% MeOH in EtOAc) gave pure product **15** as a yellow oil (42 mg, 62% yield).

$\boldsymbol{R_f}$ = 0.18 (MeOH: $CHCl_3$, 1:19)

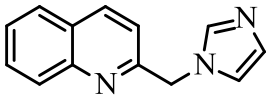
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.09 (2 H, app t, *J* = 9.6 Hz), 7.78 (1 H, d, *J* = 8.1 Hz), 7.67 (1 H, ddd, *J* = 8.4, 6.9 and 1.4 Hz), 7.60 (1 H, d, *J* = 8.4 Hz), 7.49 (1 H, ddd, *J* = 8.0, 7.0 and 1.1 Hz), 3.96 (2 H, s), 2.64-2.61 (4 H, m), 1.83-1.79 (4 H, m)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 160.3, 147.8, 136.4, 129.4, 129.3, 127.6, 127.5, 126.1, 121.2, 63.1, 54.5, 23.8

IR $\nu_{max.}$ (ATR, oil)/cm^{-1} 2959, 2788, 1599, 1502, 1424, 1347, 1313, 1120, 997, 951, 875, 827

HRMS (ESI) calculated $C_{14}H_{17}N_2$ $[M+H]^+$ 213.1386, observed 213.1396

Compound 16



Amination product **16** was prepared according to General Procedure II using quinaldine *N*-oxide **1** (50 mg, 0.31 mmol), K_2CO_3 (107 mg, 0.78 mmol), TsCl (83 mg, 0.43 mmol), imidazole (42.2 mg, 0.62 mmol) and 2 ml of CH_2Cl_2. Purification by flash column chromatography (10% MeOH in $CHCl_3$) gave pure product **16** as a light pink solid (40 mg, 61% yield).

$\boldsymbol{R_f}$ = 0.23 (5% MeOH in $CHCl_3$)

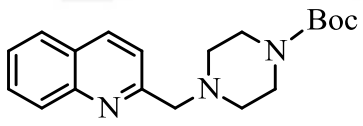
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.11 (1 H, d, *J* = 8.4 Hz), 8.05 (1 H, d, *J* = 8.5 Hz), 7.79 (1 H, dd, *J* = 8.2 and 1.0 Hz), 7.73 (1 H, ddd, *J* = 8.4, 7.0 and 1.5 Hz), 7.66 (1 H, s), 7.54 (1 H, ddd, *J* = 8.1,7.0 and 1.2 Hz), 7.12 (1 H, s), 7.04-7.00 (2 H, m), 5.40 (2 H, s)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 156.2, 147.7, 137.9, 137.7, 130.24, 130.15, 129.2, 127.7, 127.5, 127.0, 119.7, 118.7, 53.3

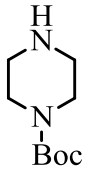
IR $\nu_{max.}$ (ATR, solid)/cm^{-1} 3111, 3093, 3043, 2959, 2923, 2851, 1596, 1566, 1504,1424, 1385, 1082, 818, 742, 660, 475.

HRMS (ESI) calculated $C_{13}H_{12}N_3$ $[M+H]^+$ 210.1026, observed 210.1027

Compound 17



Before the synthesis of the amination product **17**, *tert*-Butyl piperazine-1-carboxylate (*N*-Boc piperazine) **24** was synthesized according to a procedure given in the literature.[64] To the mixture of piperazine (2.00 g, 23.22 mmol), MeOH (20 ml) and triethylamine (4.85 ml, 34.77 mmol) was added Boc anhydride (2.027 g, 9.288 mmol) dropwise and stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure to remove methanol. Then, EtOAc (10 ml) was added to the reaction mixture and separated solid was filtered off. Filtrate was washed with water (3x2 ml), dried over Na_2SO_4 and concentrated under vacuum.



25

tert-butyl piperazine-1-carboxylate

Amination product **17** was prepared according to General Procedure II using quinaldine *N*-oxide **1** (50 mg, 0.31 mmol), K_2CO_3 (107 mg, 0.78 mmol), TsCl (83 mg, 0.43 mmol), *N*-Boc piperazine **25** (116 mg, 0.62 mmol) and 2 ml of CH_2Cl_2. Purification by flash column chromatography (2% MeOH in EtOAc) gave pure product **17** as a dark orange solid (73 mg, 72% yield).

$\boldsymbol{R_f}$ = 0.55 (MeOH: EtOAc, 1:19)

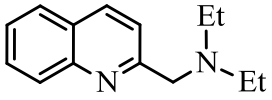
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.11 (1 H, d, *J* = 8.5 Hz), 8.06 (1 H, d, *J* = 8.6 Hz), 7.78 (1 H, dd, *J* = 8.2 and 1.1 Hz), 7.68 (1 H, ddd, *J* = 8.4, 7.0 and 1.4 Hz), 7.61 (1 H, d, *J* = 8.5 Hz), 7.50 (1 H, ddd, *J* = 8.0, 7.0 and 1.1 Hz), 3.84 (2 H, s), 3.45 (4 H, t, *J* = 5.0 Hz), 2.49 (4 H, t, *J* = 4.9 Hz), 1.44 (9 H, s)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 159.2, 154.9, 147.7, 136.6, 129.6, 129.1, 127.6, 127.5, 126.4, 121.2, 79.7, 65.2, 53.3, 43.5, 28.5

IR $\nu_{max.}$ (ATR, solid)/cm^{-1} 2977, 2864, 2810, 1677, 1600, 1502, 1407, 1366, 1236

HRMS (ESI) calculated $C_{19}H_{26}N_3O_2$ $[M+H]^+$ 328.2020, observed 328.2024

Compound 18



Amination product **18** was prepared according to General Procedure II using quinaldine *N*-oxide **1** (50 mg, 0.31 mmol), K_2CO_3 (107 mg, 0.78 mmol), TsCl (83 mg, 0.43 mmol), diethylamine (64 µl, 0.62 mmol) and 2 ml of CH_2Cl_2. Purification by flash column chromatography (only EtOAc, 5% MeOH in EtOAc and then 7.5% MeOH in EtOAc) gave pure product **18** as a brown oil (48.4 mg, 73% yield).

$\boldsymbol{R_f}$ = 0.46 (MeOH: EtOAc, 1:19)

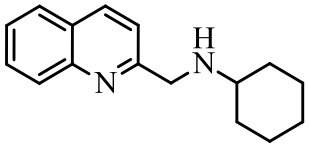
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.08 (1 H, d, *J* = 8.6 Hz), 8.05 (1 H, d, *J* = 8.5 Hz), 7.77 (1 H, dd, *J* = 8.1 and 0.9 Hz), 7.68 (1 H, d, *J* = 8.5 Hz), 7.66 (1 H, ddd, *J* = 8.4, 6.9 and 1.4 Hz), 7.48 (1 H, ddd, *J* = 8.0, 6.9 and 1.1 Hz), 3.89 (2 H, s), 2.62 (4 H, q, *J* = 7.2 Hz), 1.06 (6 H, t, *J* = 7.2 Hz)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 161.8, 147.7, 136.2, 129.3, 129.1, 127.6, 127.5, 126.0, 121.2, 60.6, 47.7, 12.1

IR $\nu_{max.}$ (ATR, oil)/cm^{-1} 2967, 2927, 1619, 1600, 1503, 1453, 1424, 1372, 1203, 1115, 1065

HRMS (ESI) calculated $C_{14}H_{19}N_2$ $[M+H]^+$ 215.1543, observed 215.1543

Compound 19



Amination product **19** was prepared according to General Procedure II using quinaldine *N*-oxide **1** (50 mg, 0.31 mmol), K_2CO_3 (107 mg, 0.78 mmol), TsCl (83 mg, 0.43 mmol), cyclohexyl amine (71 µl, 0.62 mmol) and 2 ml of CH_2Cl_2. Purification by flash column

chromatography (5% MeOH in EtOAc, 10% MeOH in EtOAc and then 12% MeOH in EtOAc) gave pure product **19** as a brown oil (34.9 mg, 46% yield).

$\boldsymbol{R_f}$ = 0.37 (MeOH: EtOAc, 1:9)

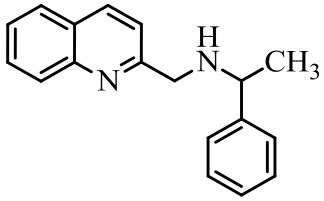
^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.08 (1 H, d, *J* = 8.6 Hz), 8.05 (1 H, d, *J* = 8.5 Hz), 7.77 (1 H, d, *J* = 8.1 Hz), 7.67 (1 H, ddd, *J* = 8.4, 6.9 and 1.4 Hz), 7.48 (1 H, ddd, *J* = 8.0, 7.0 and 1.0 Hz), 7.44 (1 H, d, *J* = 8.4 Hz), 4.12 (2 H, s), 2.58-2.52 (1 H, m), 2.17 (1 H, s), 1.99-1.96 (2 H, m), 1.76-1.73 (2 H, m), 1.31-1.14 (6 H, m)

^{13}C NMR (100 MHz; $CDCl_3$) δ: 160.9, 147.9, 136.4, 129.4, 129.1, 127.6, 127.4, 126.0, 120.8, 57.0, 53.2, 33.8, 26.3, 25.1

IR $\nu_{max.}$ (ATR, oil)/cm^{-1} 3043, 2924, 2851, 1618, 1599, 1504, 1448, 1425, 1263, 1113

HRMS (ESI) calculated $C_{16}H_{21}N_2$ $[M+H]^+$ 241.1699, observed 241.1702

Compound 20



Amination product **20** was prepared according to General Procedure II using quinaldine *N*-oxide **1** (50 mg, 0.31 mmol), K_2CO_3 (107 mg, 0.78 mmol), TsCl (83 mg, 0.43 mmol), α-methyl benzyl amine (80 µl, 0.62 mmol) and 2 ml of CH_2Cl_2. Purification by flash column chromatography (MeOH: EtOAc 1:19) gave pure product **20** as a yellow oil (52 mg, 64% yield).

$\boldsymbol{R_f}$ = 0.55 (MeOH: EtOAc, 1:19)

^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.06 (2 H, t, *J* = 8.0 Hz), 7.77 (1 H, d, *J* = 8.1 Hz), 7.68 (1 H, t, *J* = 7.7 Hz), 7.48 (1 H, , *J* = 8.0, 7.0 and 1.2 Hz), 7.44-7.40 (2 H, m), 7.36-7.31 (3 H, m), 7.27-7.23 (1 H, m) 3.95 (2 H, s), 3.94-3.88 (1 H, m), 1.45 (3 H, d, *J* = 6.6 Hz)

IR $\nu_{max.}$ (ATR, oil)/cm^{-1} 3661, 2966, 2925, 1600, 1564, 1504, 1451, 1425, 1264

HRMS (ESI) calculated $C_{18}H_{19}N_2$ $[M+H]^+$ 263.1397, observed 261.1381

CHAPTER 4

CONCLUSION

In this work, a new synthetic method for the derivatization of 2-methyl azine *N*-oxide compounds was developed. 2-methyl azine *N*-oxide derivatives could be functionalized efficiently at benzylic position via amination reactions with a one-pot operation in high yields. At the first stage of the work, optimization studies for the target reaction between quinaldine *N*-oxide and morpholine were carried out. Parameters of activating agent, base, solvent and temperature were investigated in detail, and optimization studies were finalized successfully. As a result of this part, TsCl, K_2CO_3, CH_2Cl_2 and 35°C were determined as the optimized conditions.

In the second part, various types of azine *N*-oxides, which are electrophilic components of the target reaction, were evaluated under the optimized conditions. For this purpose, quinoline and isoquinoline based azine *N*-oxides were synthesized in high yields using *m*-CPBA. These *N*-oxides gave the corresponding products satisfactorily after the benzylic amination reactions under the optimized conditions. After screening of azine *N*-oxide derivatives, several amines, which were nucleophiles for the target reaction, were investigated in detail and the targeted amination products were obtained in pure form successfully. All these results demonstrate that this newly developed synthetic method can be applied in a wide range of substrate scope. Besides, the reproducibility and scalability of the benzylic amination reaction were also verified. To sum up, a new one-pot strategy for transformation of 2-methyl azine *N*-oxide to functionalized form was developed.

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APPENDIX A

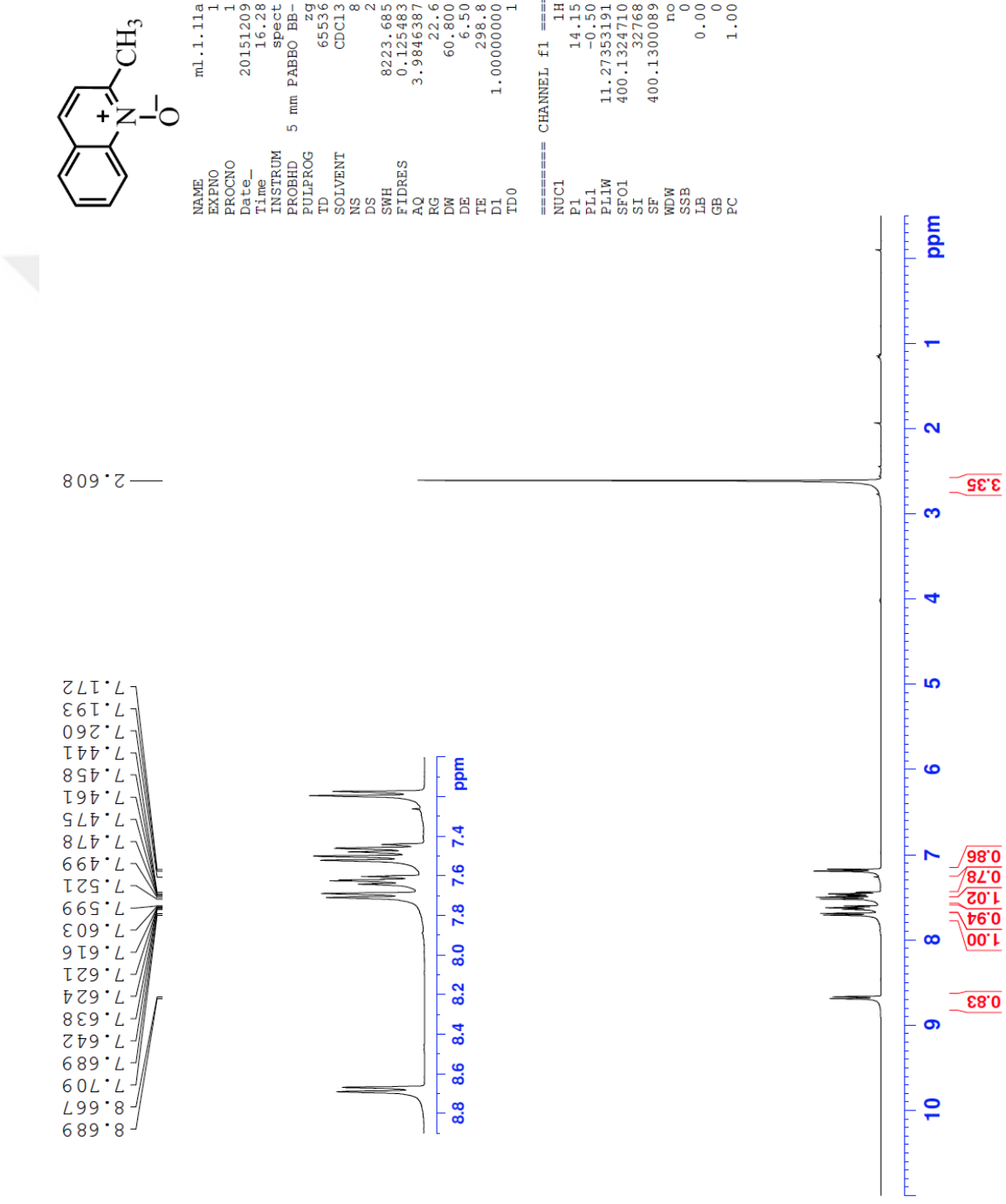

Figure 14. ^{1}H-NMR spectrum of Compound **1**

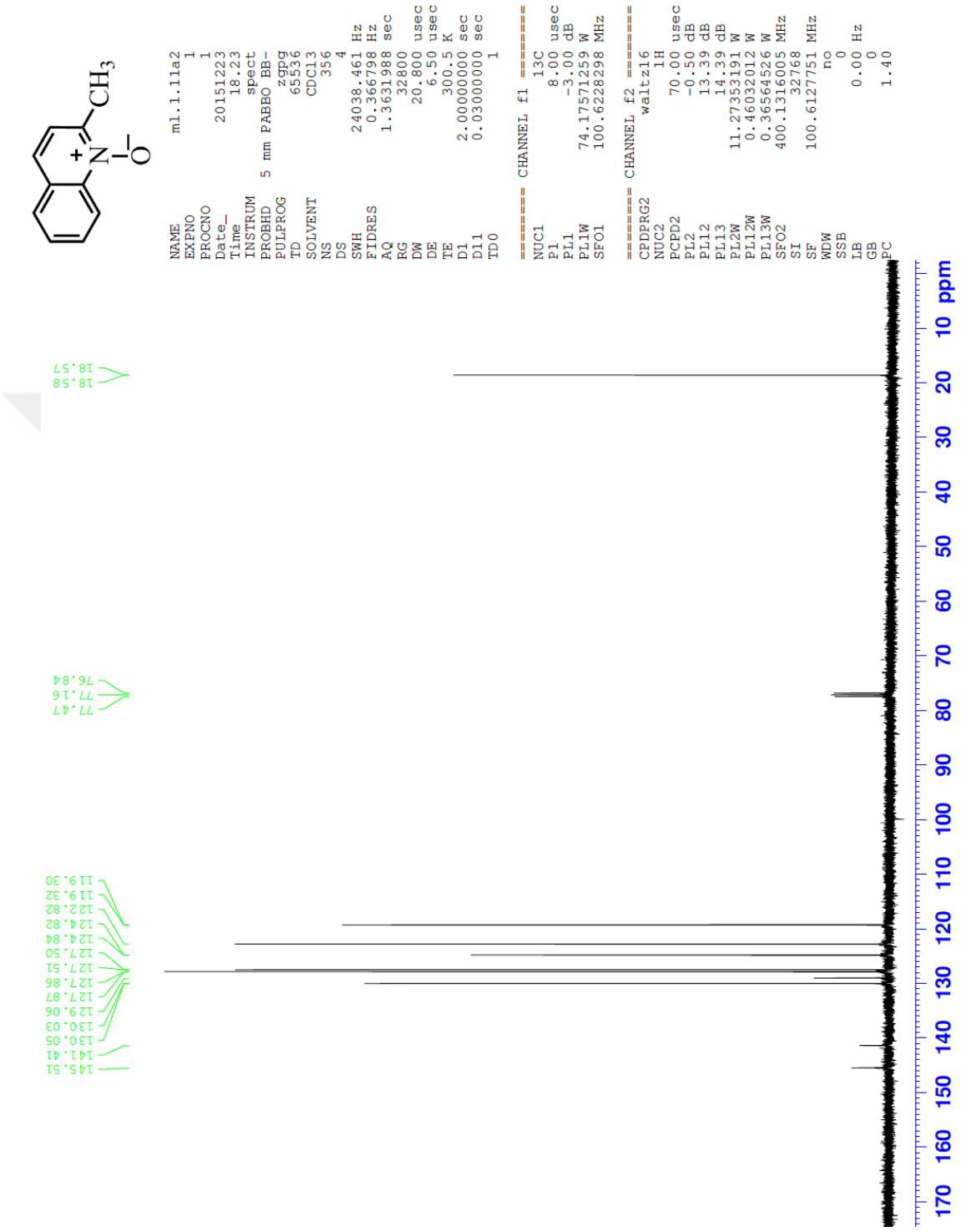

Figure 15. ^{13}C-NMR spectrum of Compound **1**

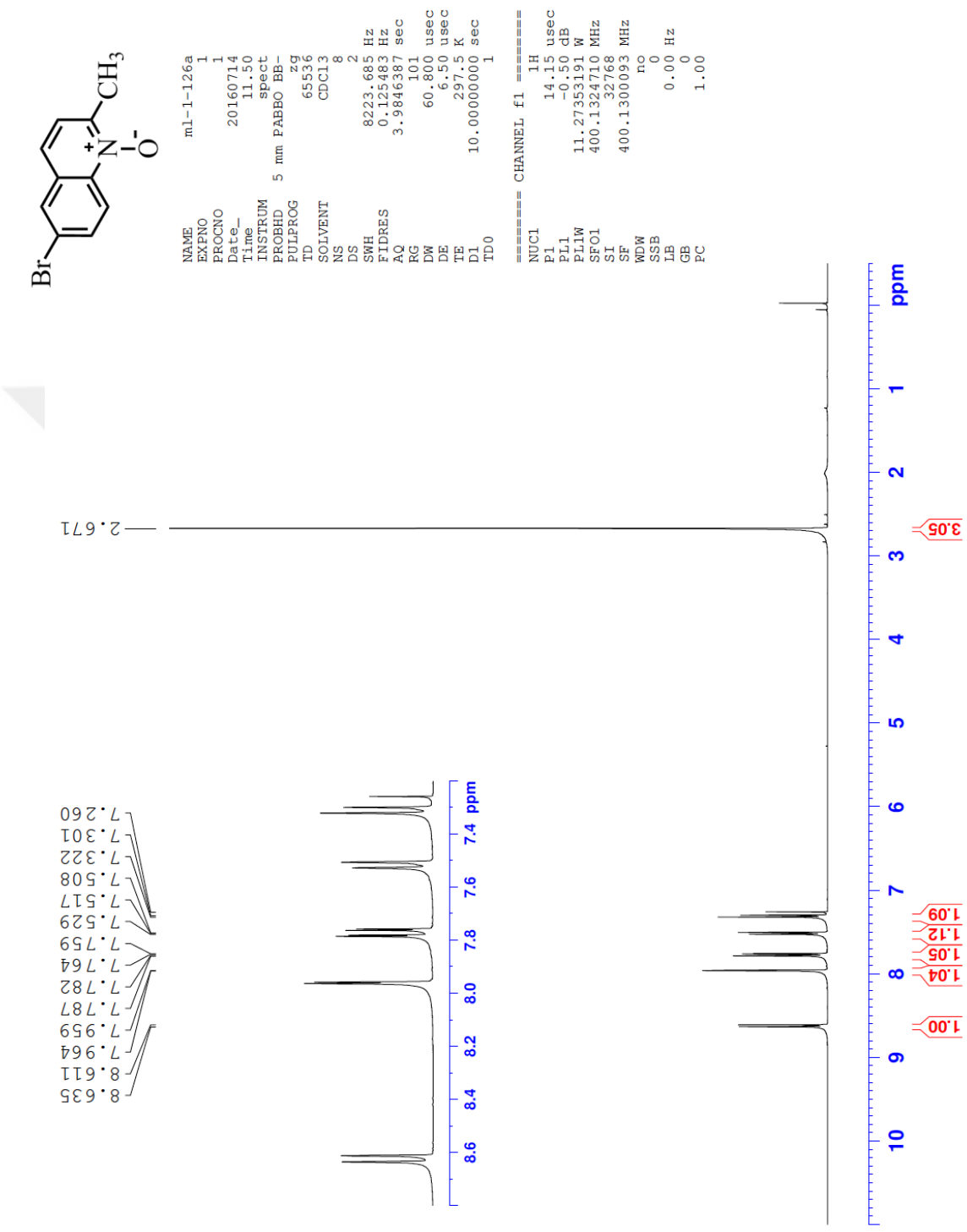

Figure 16. ^{1}H-NMR spectrum of Compound **2**

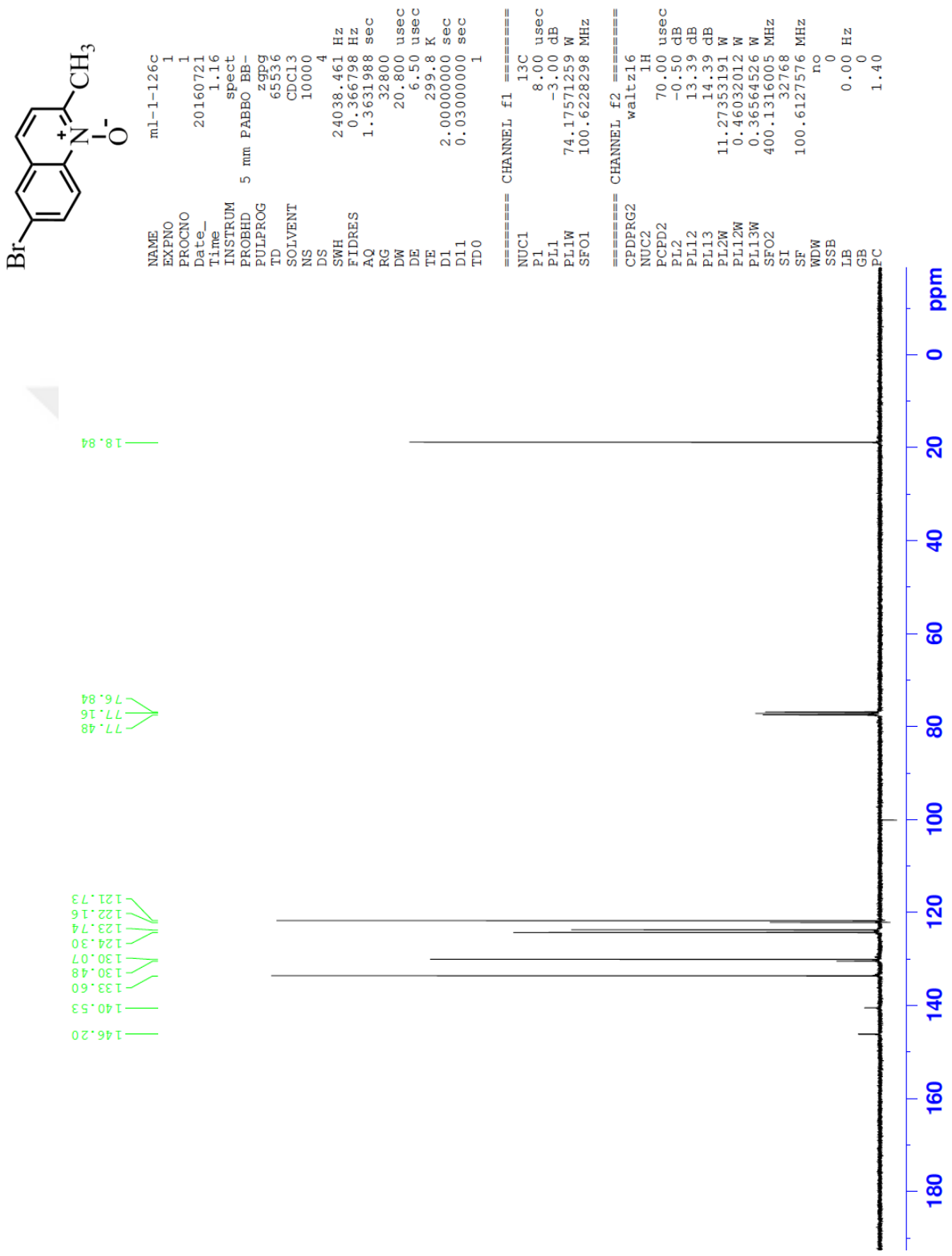

Figure 17. ^{13}C-NMR spectrum of Compound **2**

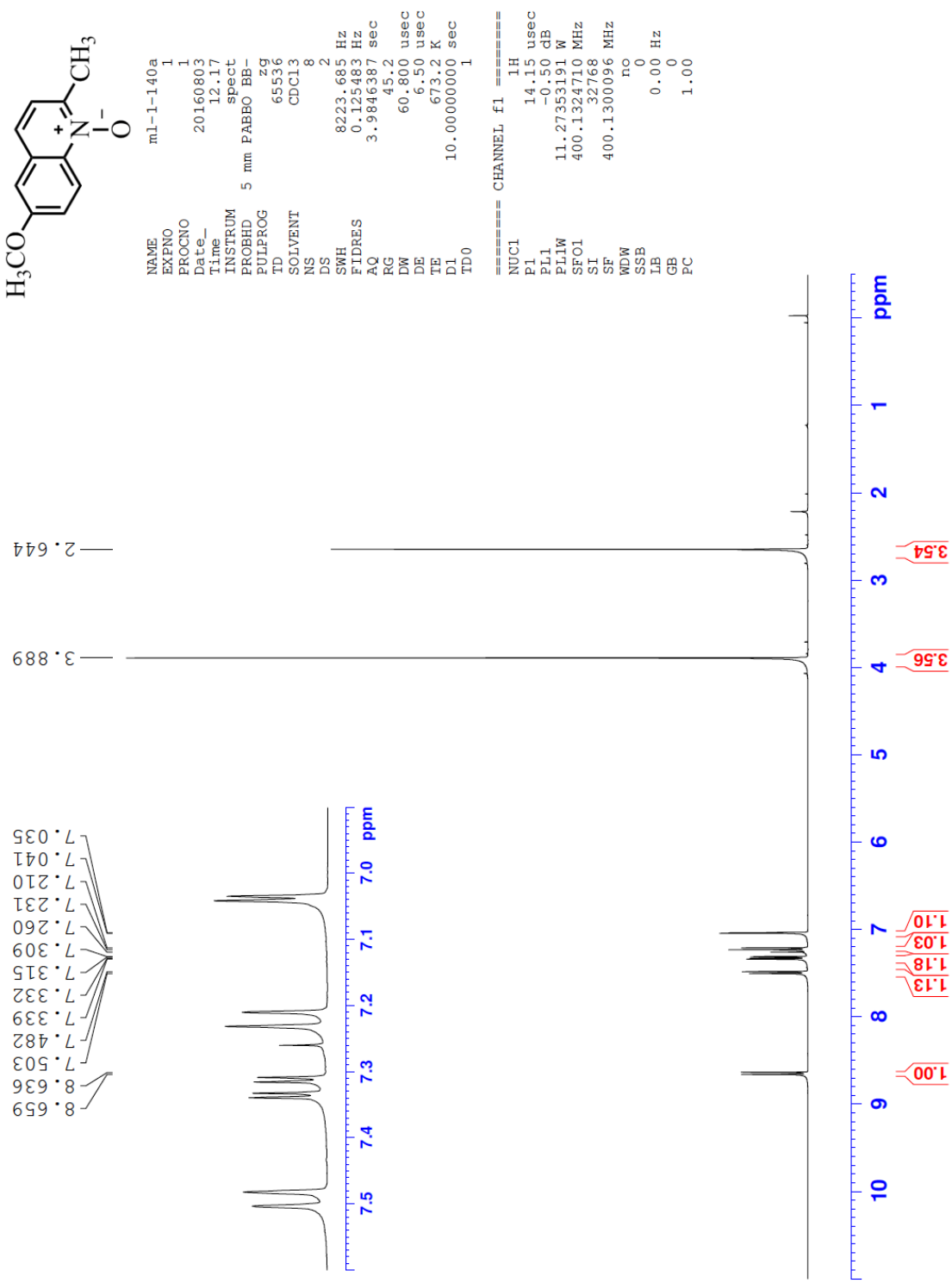

Figure 18. ^{1}H-NMR spectrum of Compound **3**

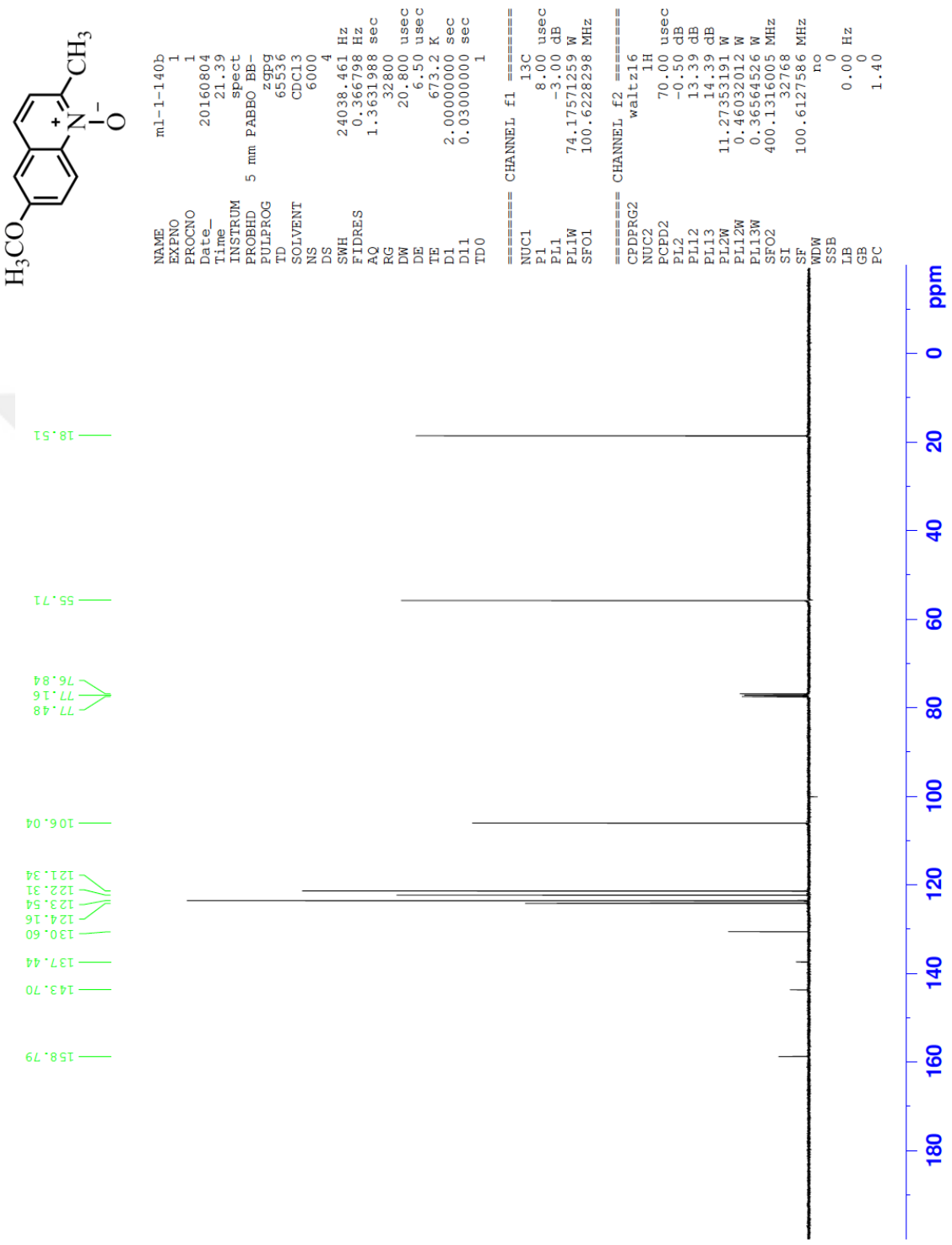

Figure 19. ^{13}C-NMR spectrum of Compound **3**

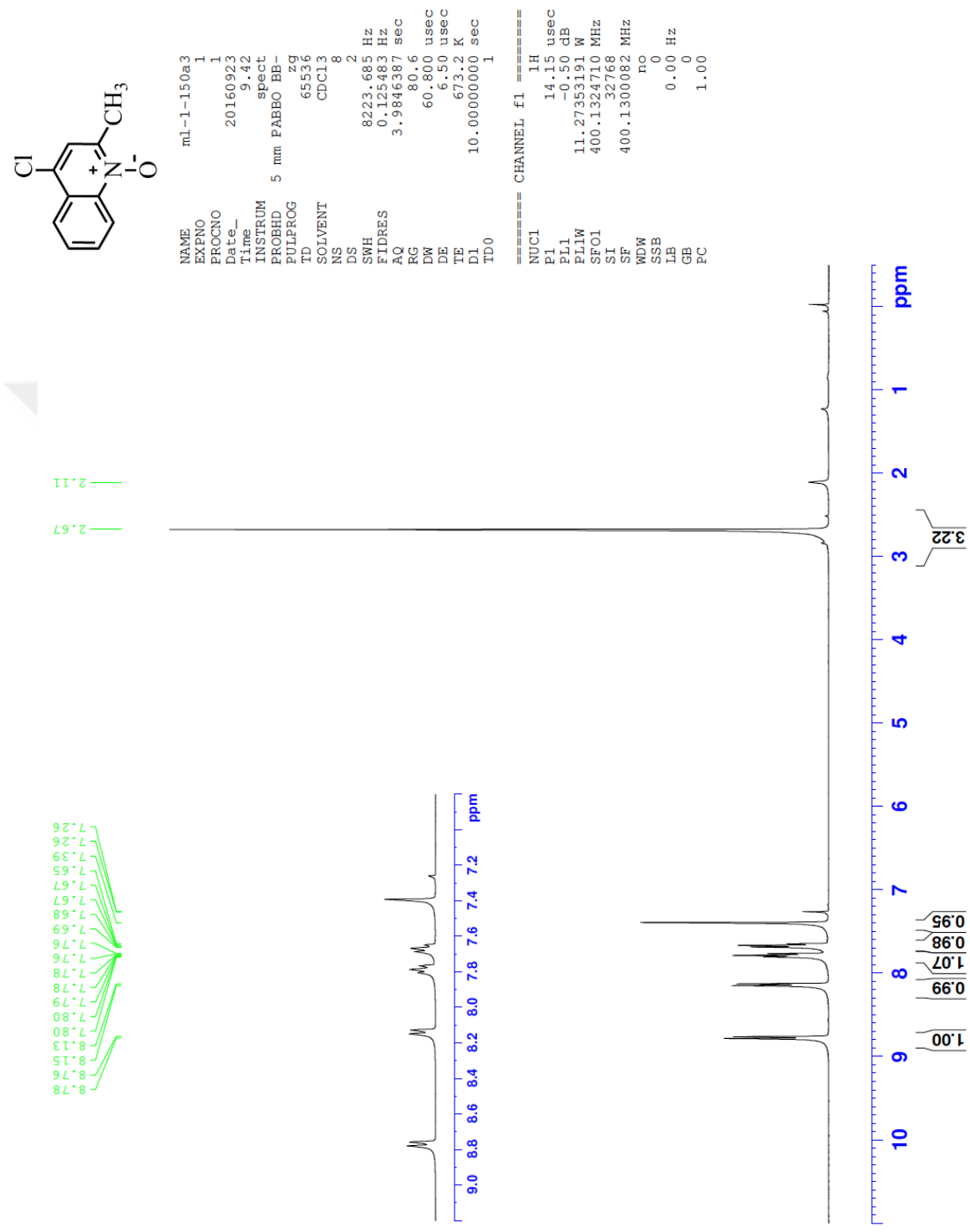

Figure 20. ^{1}H-NMR spectrum of Compound **4**

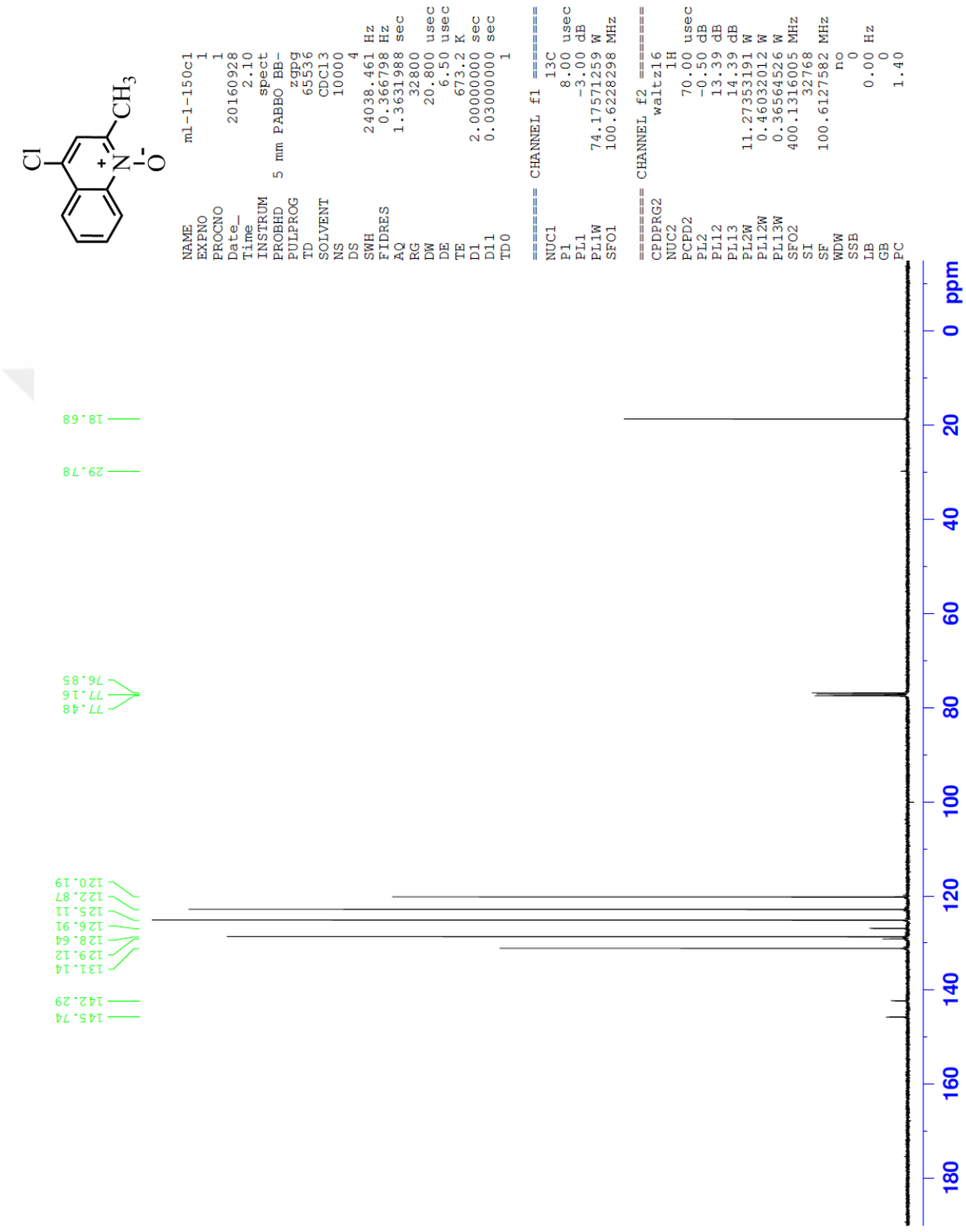

Figure 21. ^{13}C-NMR spectrum of Compound **4**

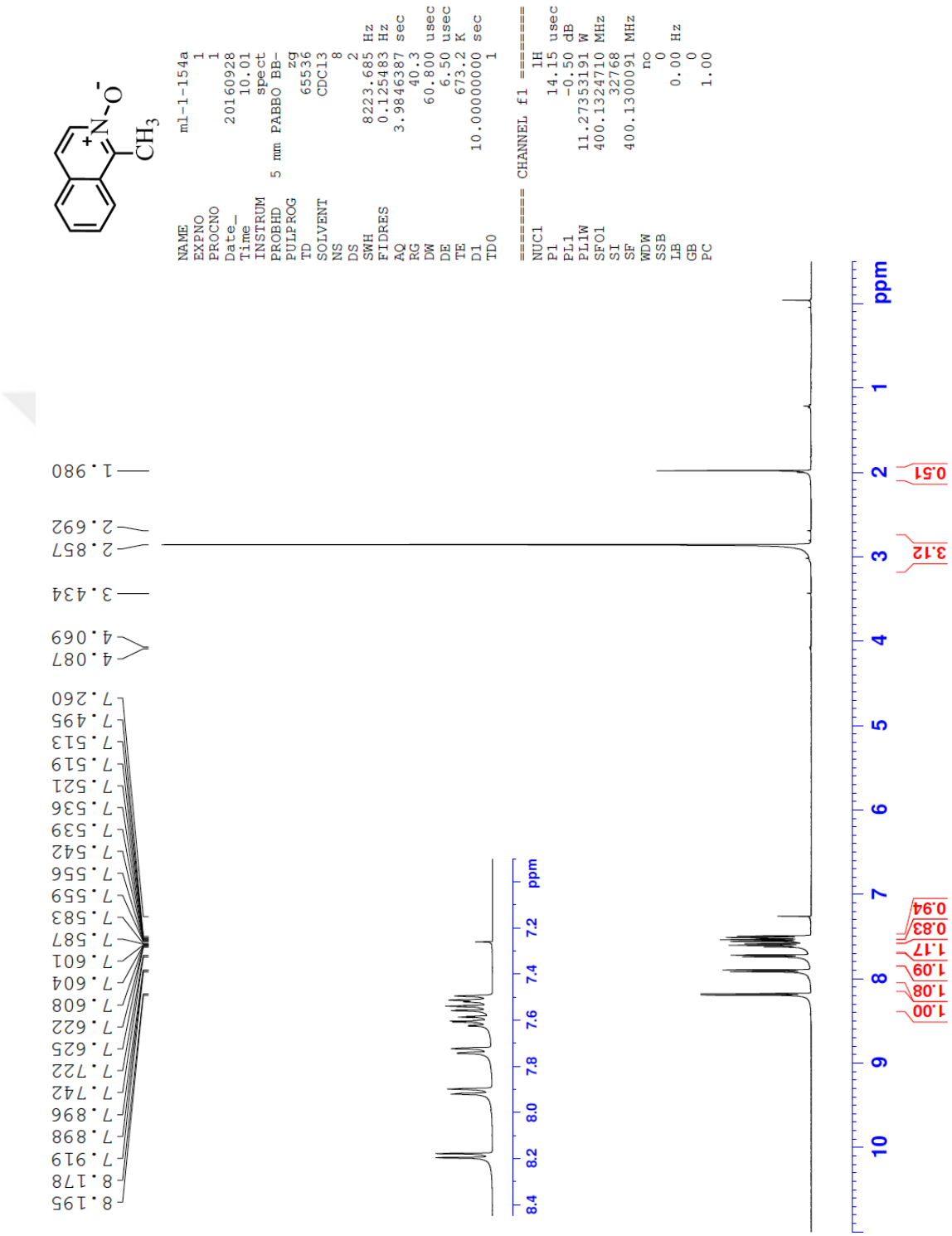

Figure 22. ^{1}H-NMR spectrum of Compound **5**

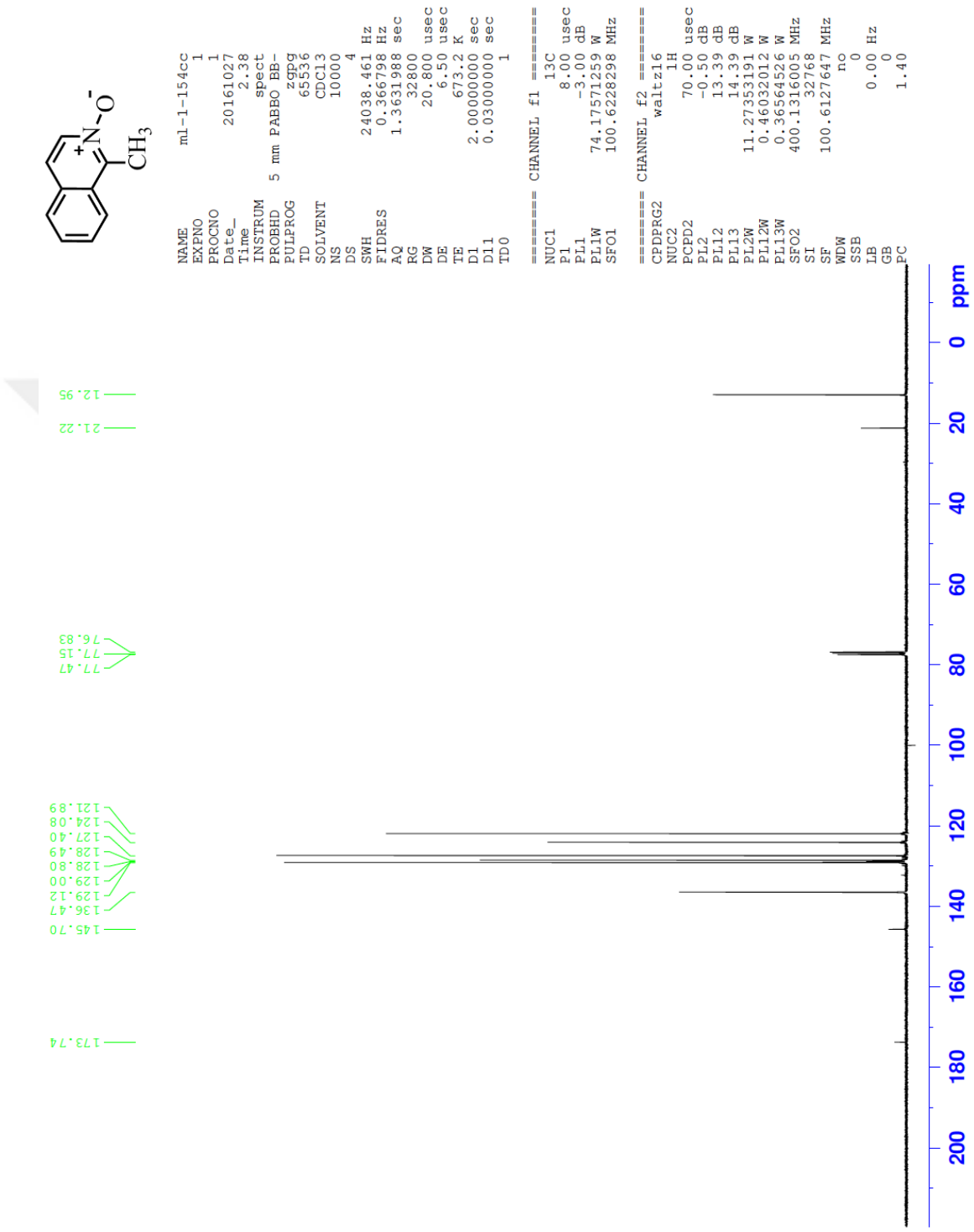

Figure 23. ^{13}C-NMR spectrum of Compound **5**

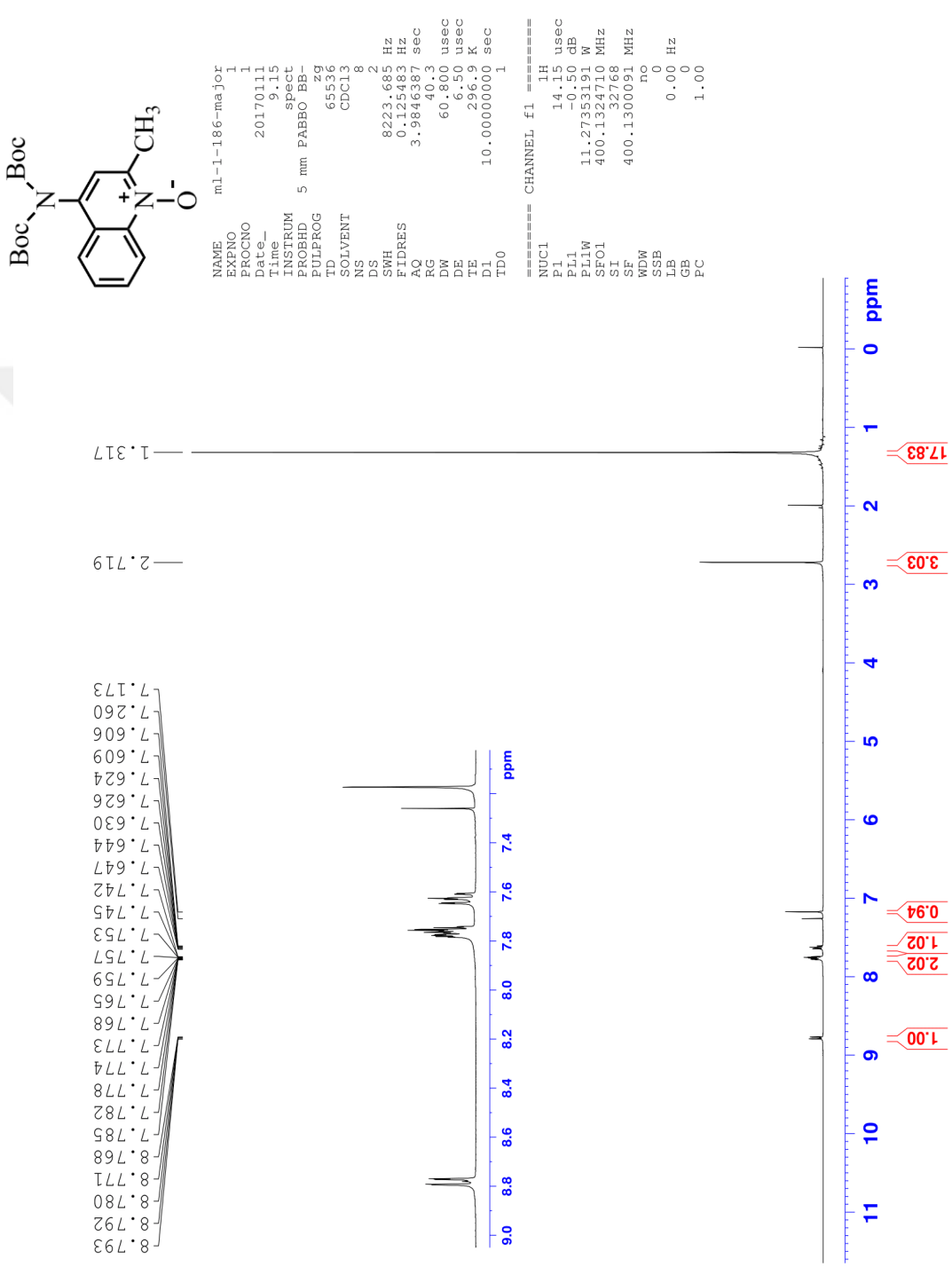

Figure 24. [1]H-NMR spectrum of Compound **6**

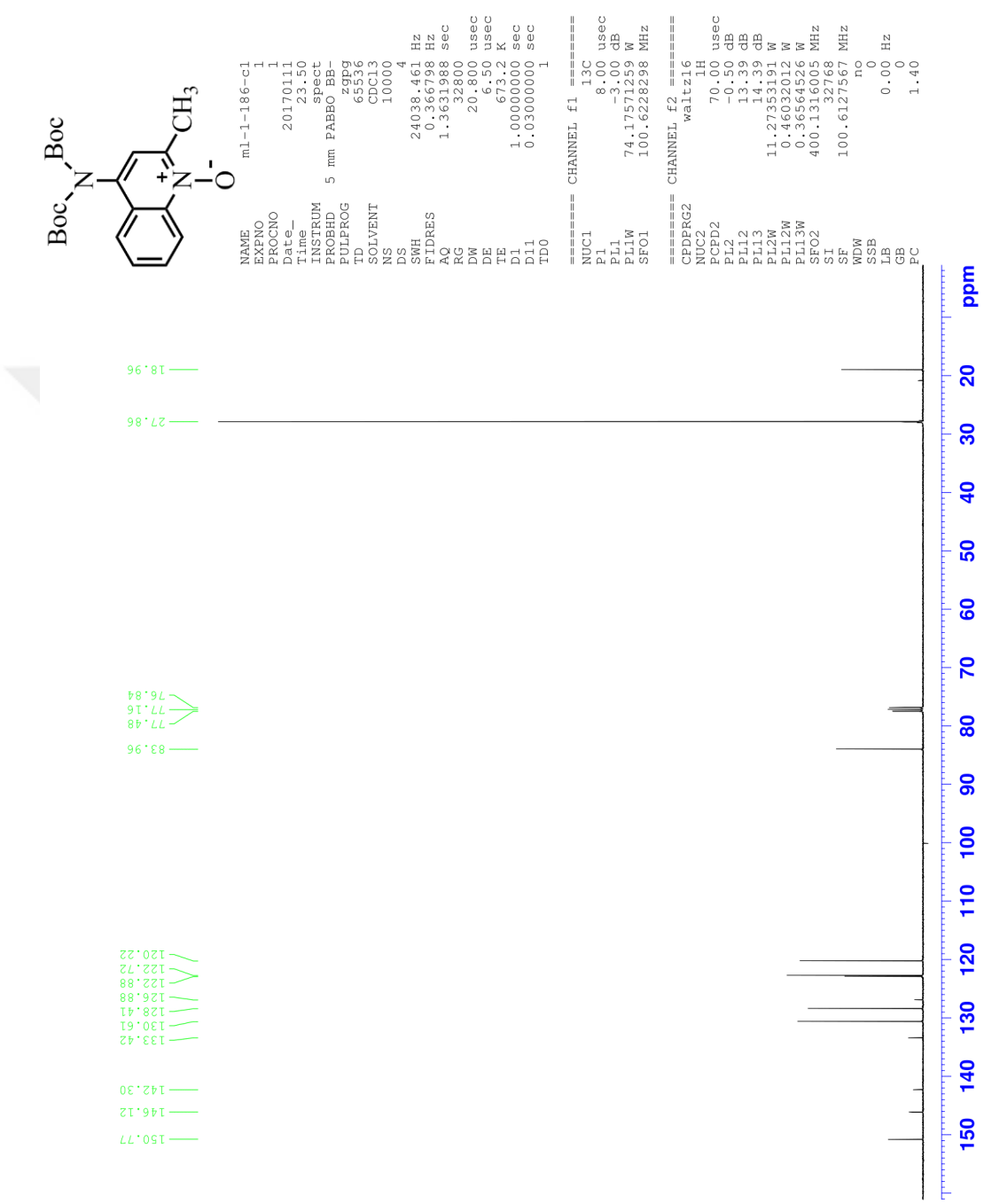

Figure 25. ^{13}C-NMR spectrum of Compound **6**

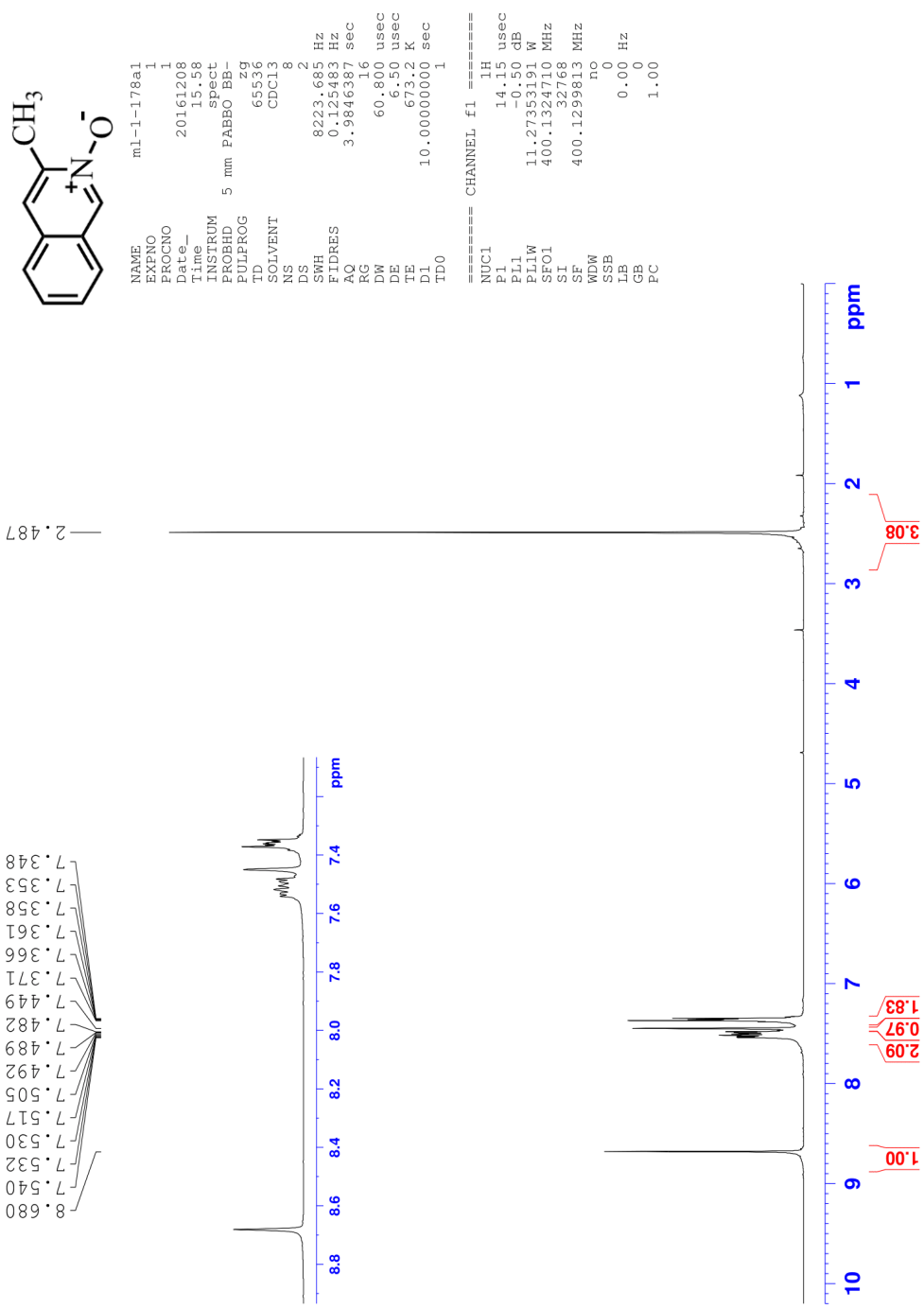

Figure 26. [1]H-NMR spectrum of Compound **7**

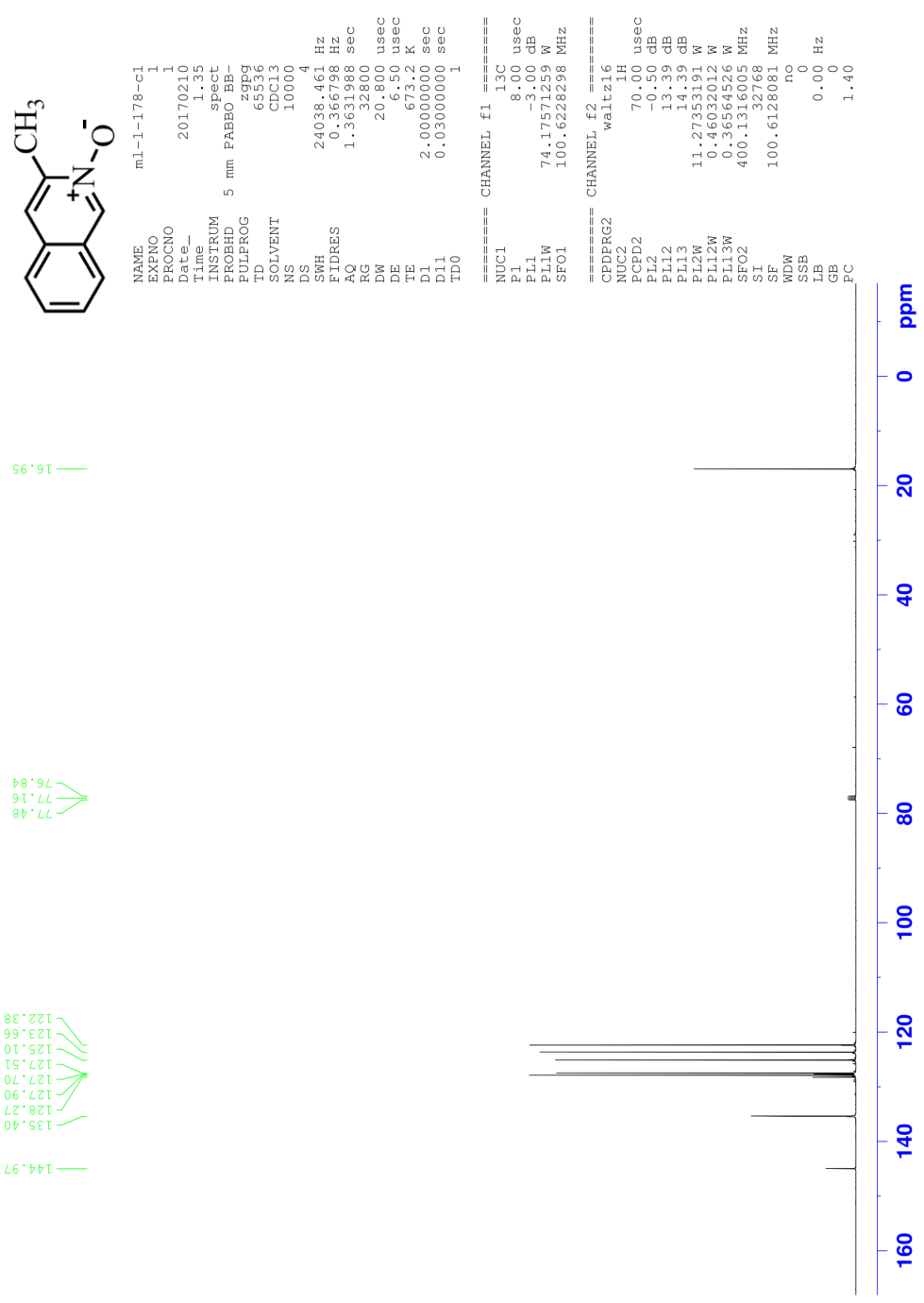

Figure 27. ^{13}C-NMR spectrum of Compound **7**

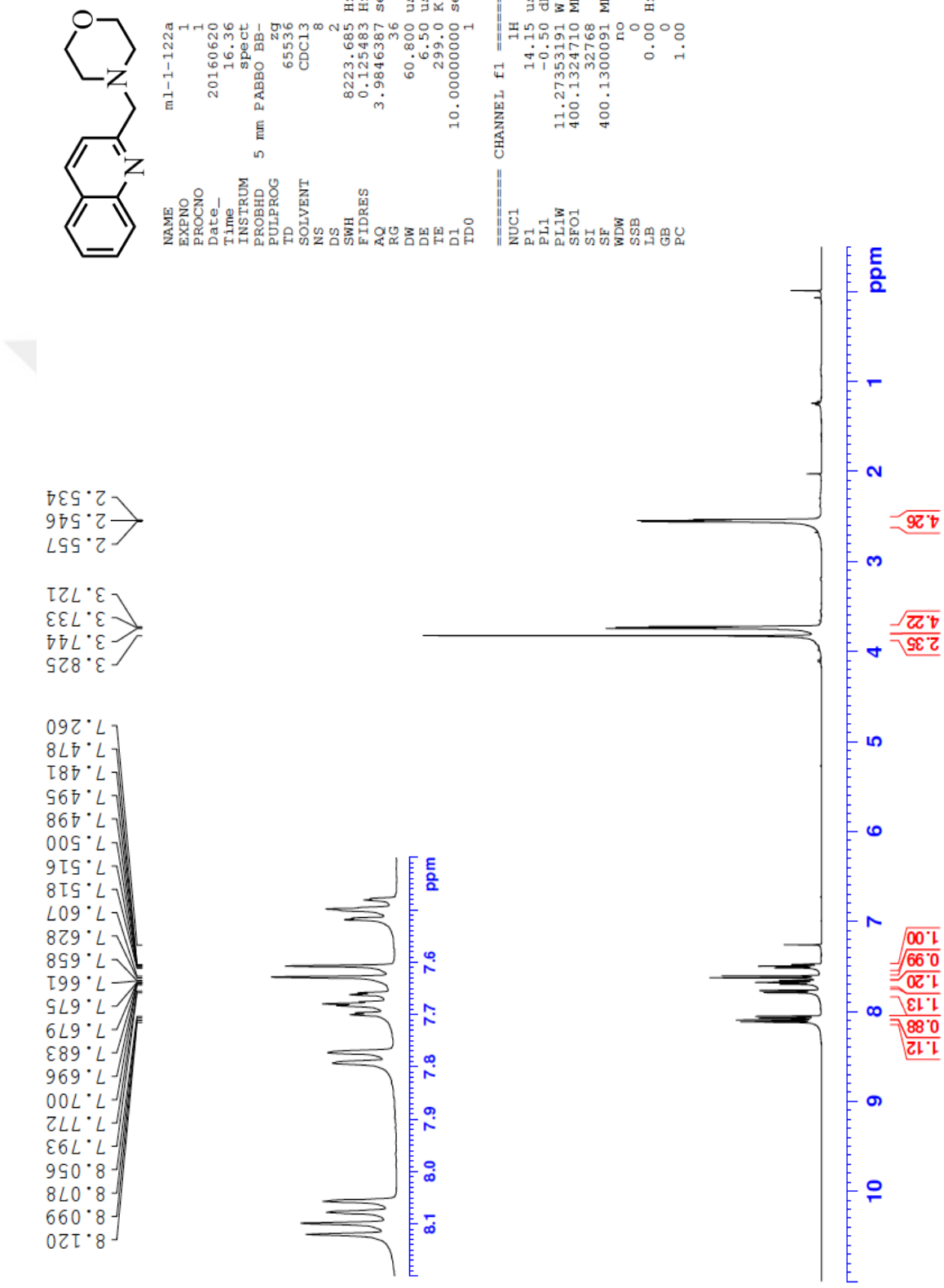

Figure 28. ^{1}H-NMR spectrum of Compound **8**

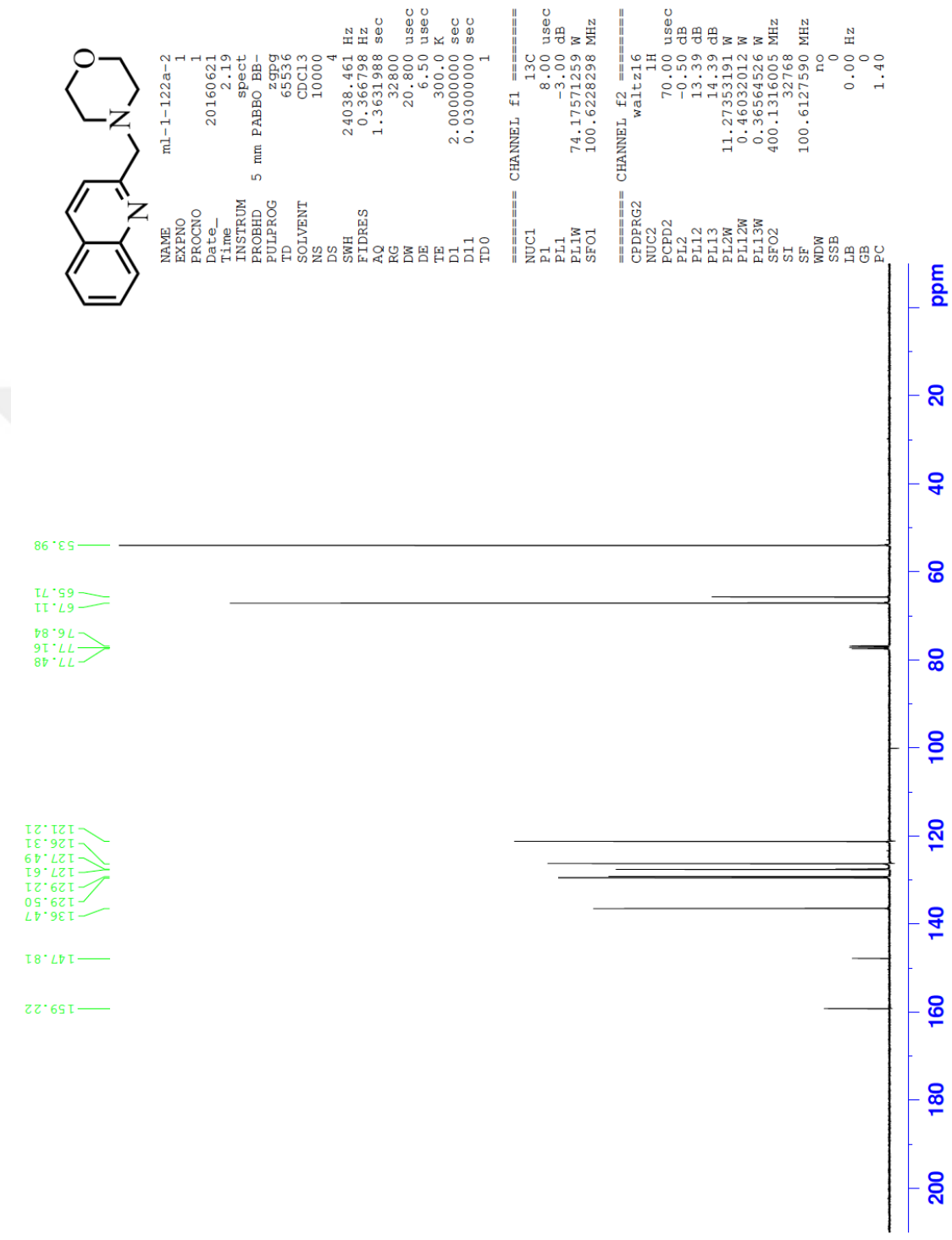

Figure 29. ^{13}C-NMR spectrum of Compound **8**

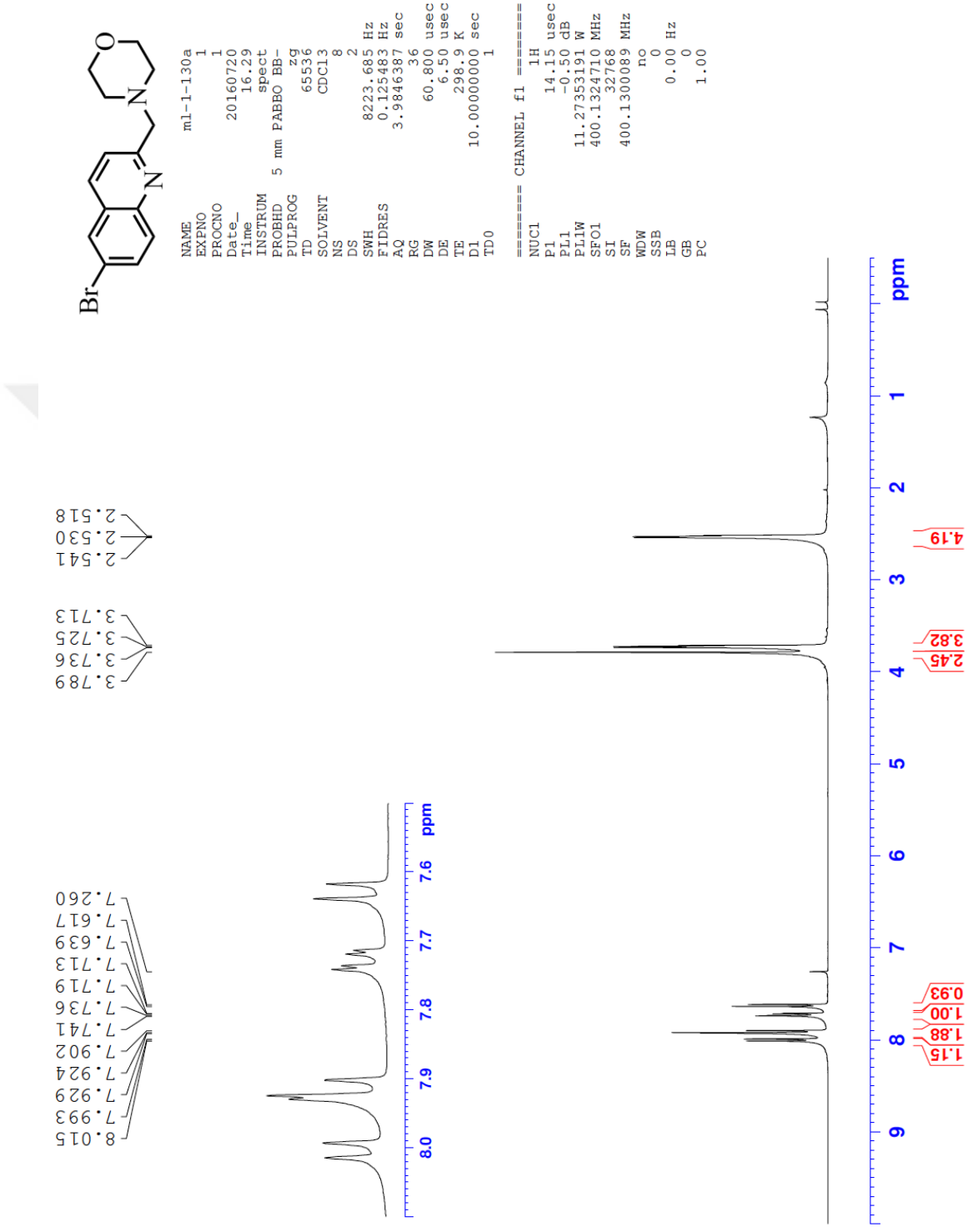

Figure 30. ^{1}H-NMR spectrum of Compound **9**

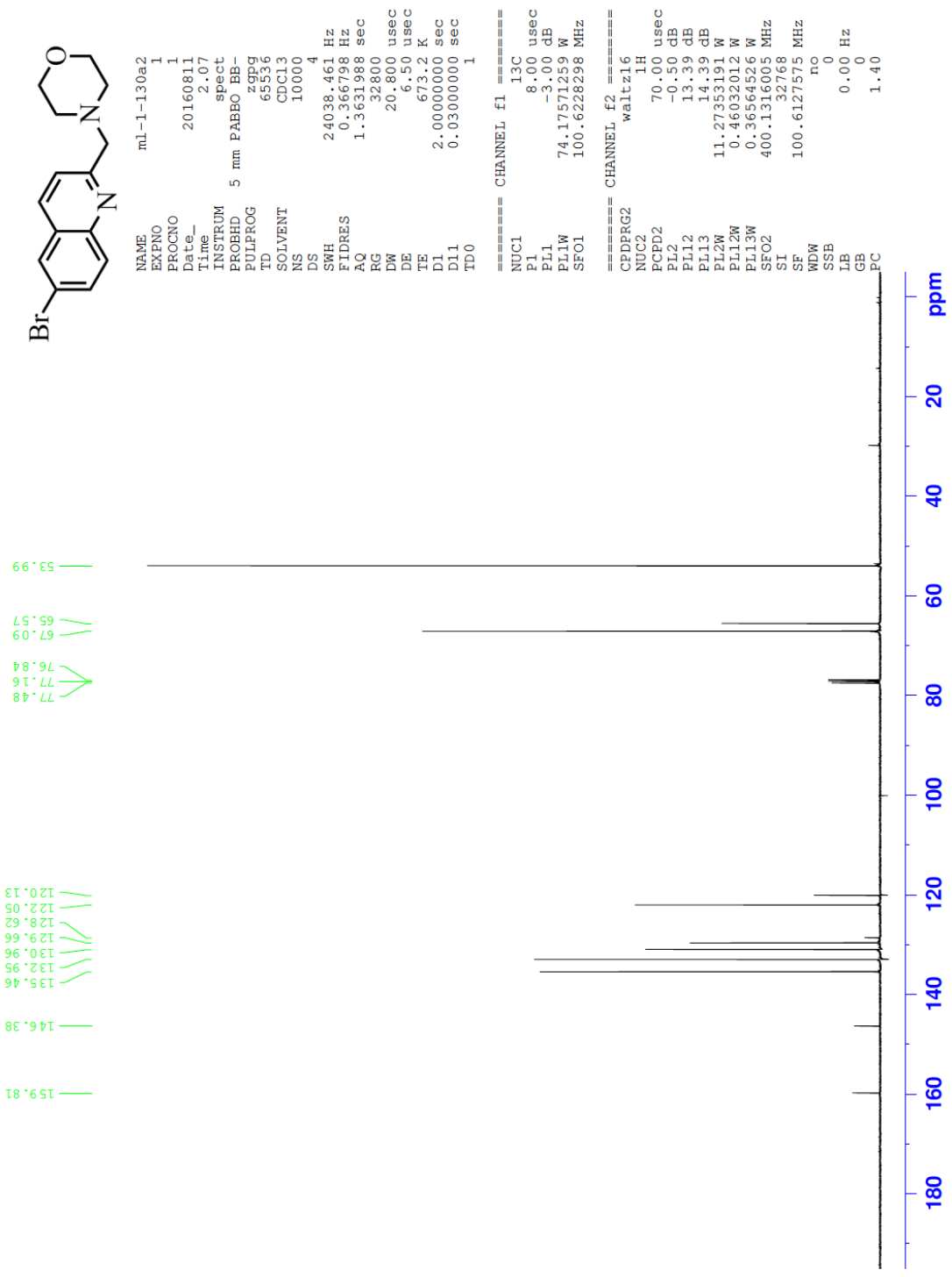

Figure 31. ^{13}C-NMR spectrum of Compound **9**

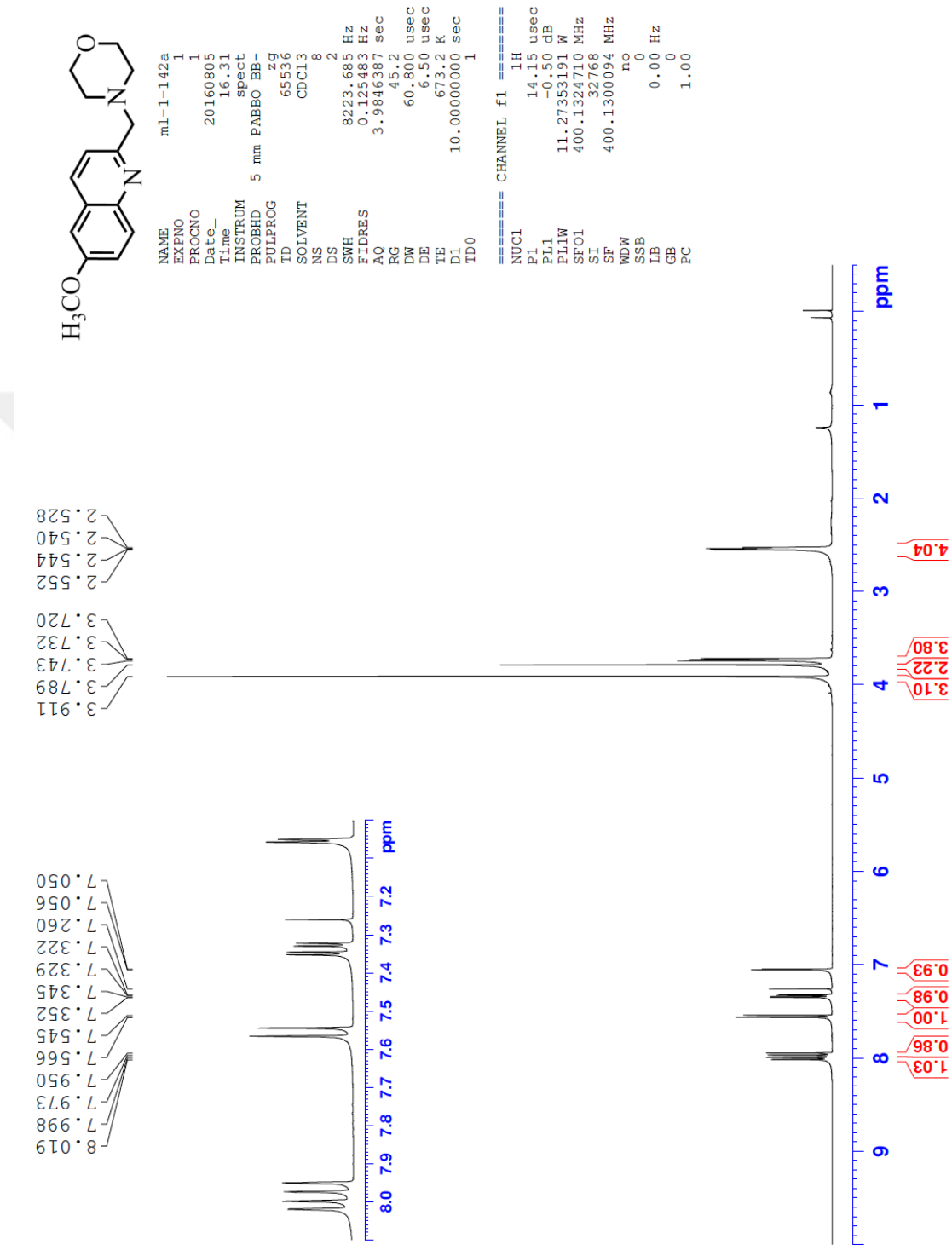

Figure 32. [1]H-NMR spectrum of Compound **10**

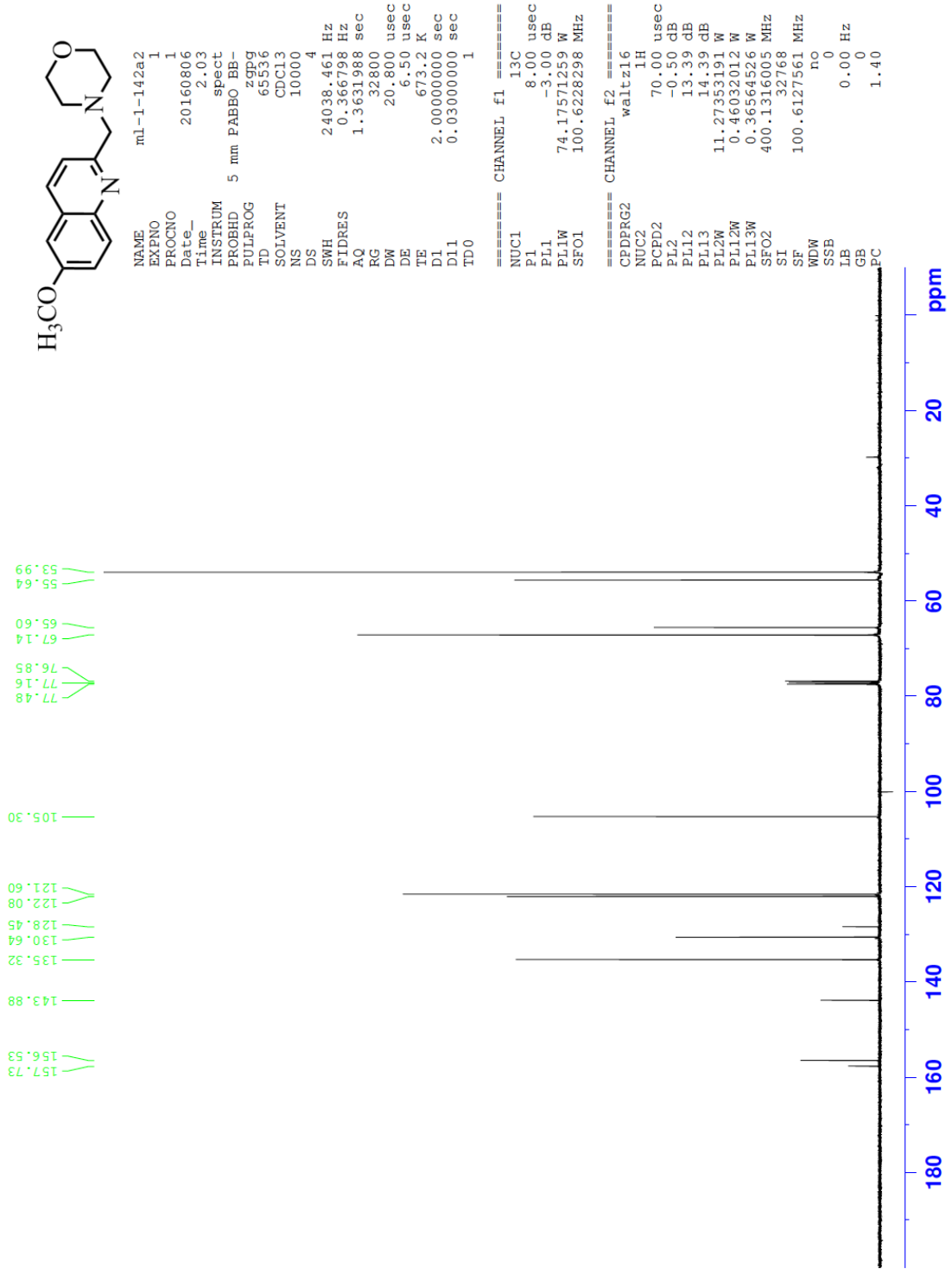

Figure 33. ^{13}C-NMR spectrum of Compound **10**

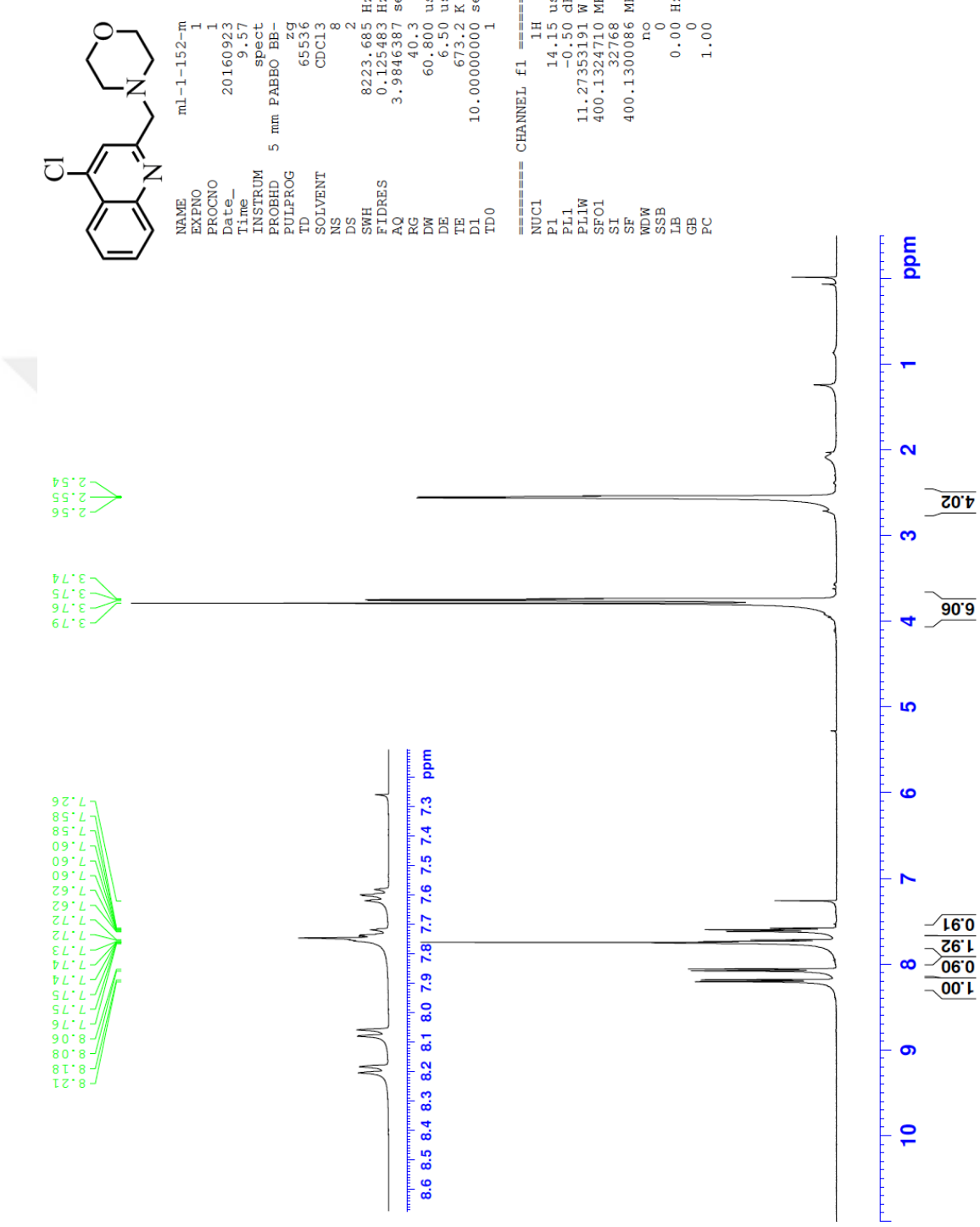

Figure 34. ^{1}H-NMR spectrum of Compound **11**

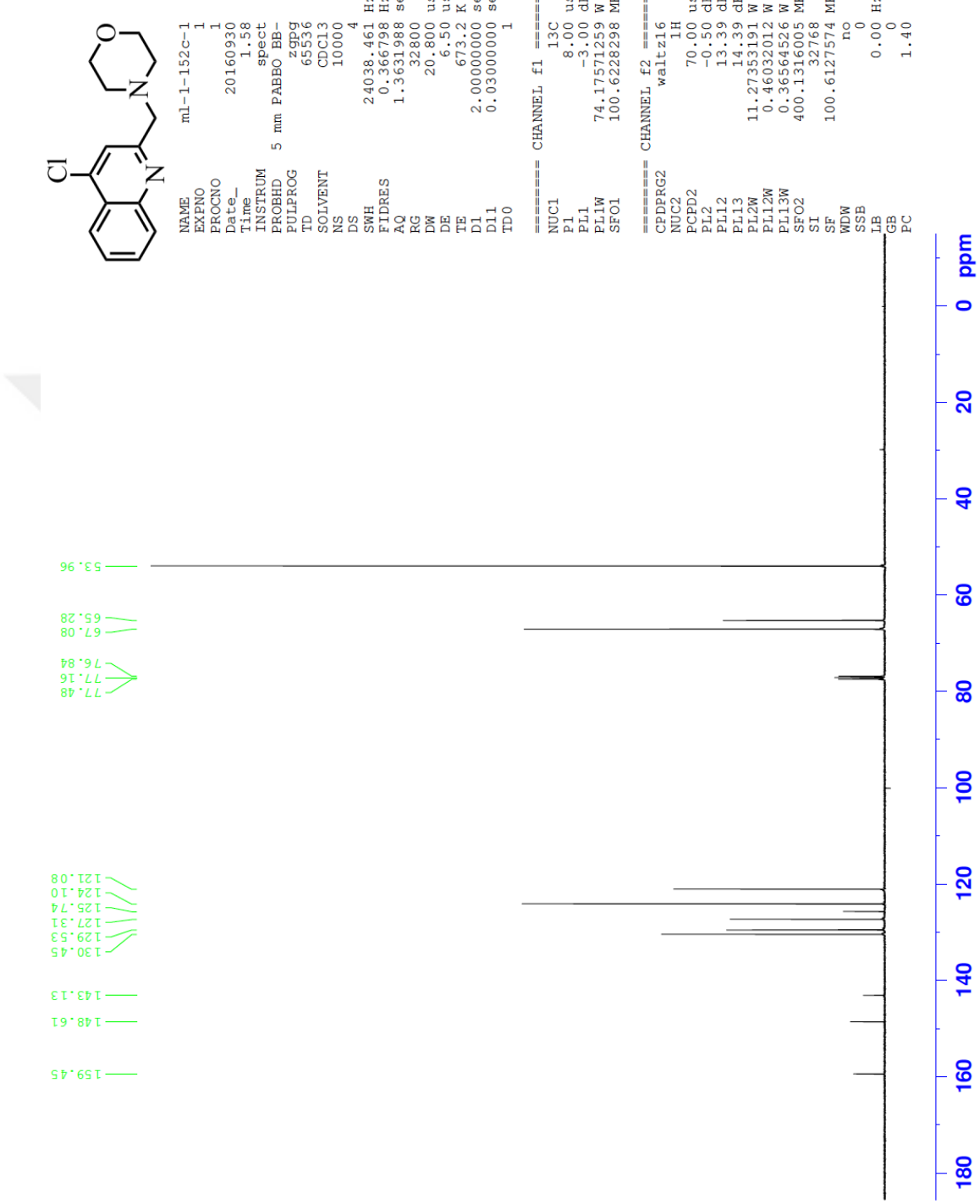

Figure 35. ^{13}C-NMR spectrum of Compound **11**

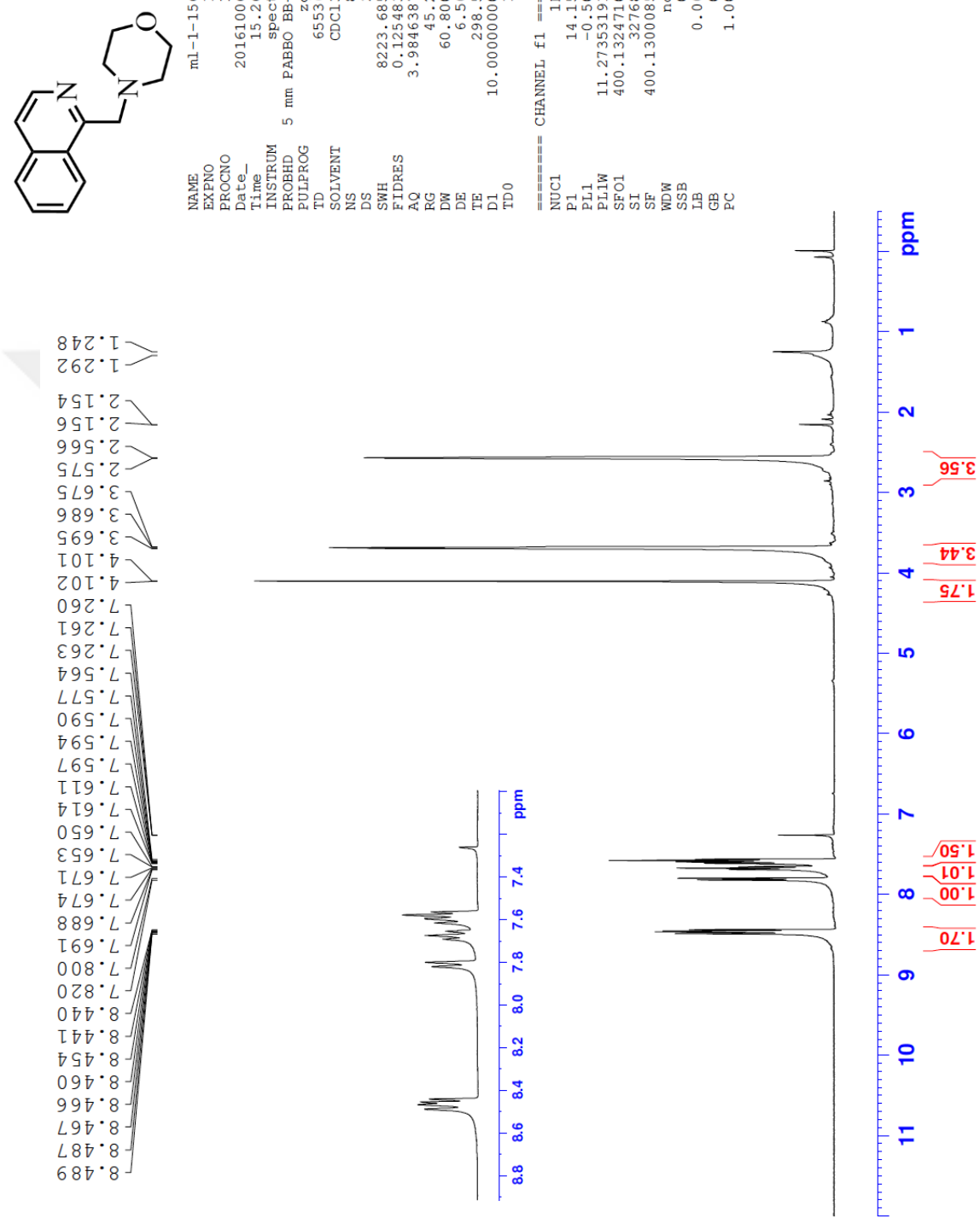

Figure 36. ^{1}H-NMR spectrum of Compound **12**

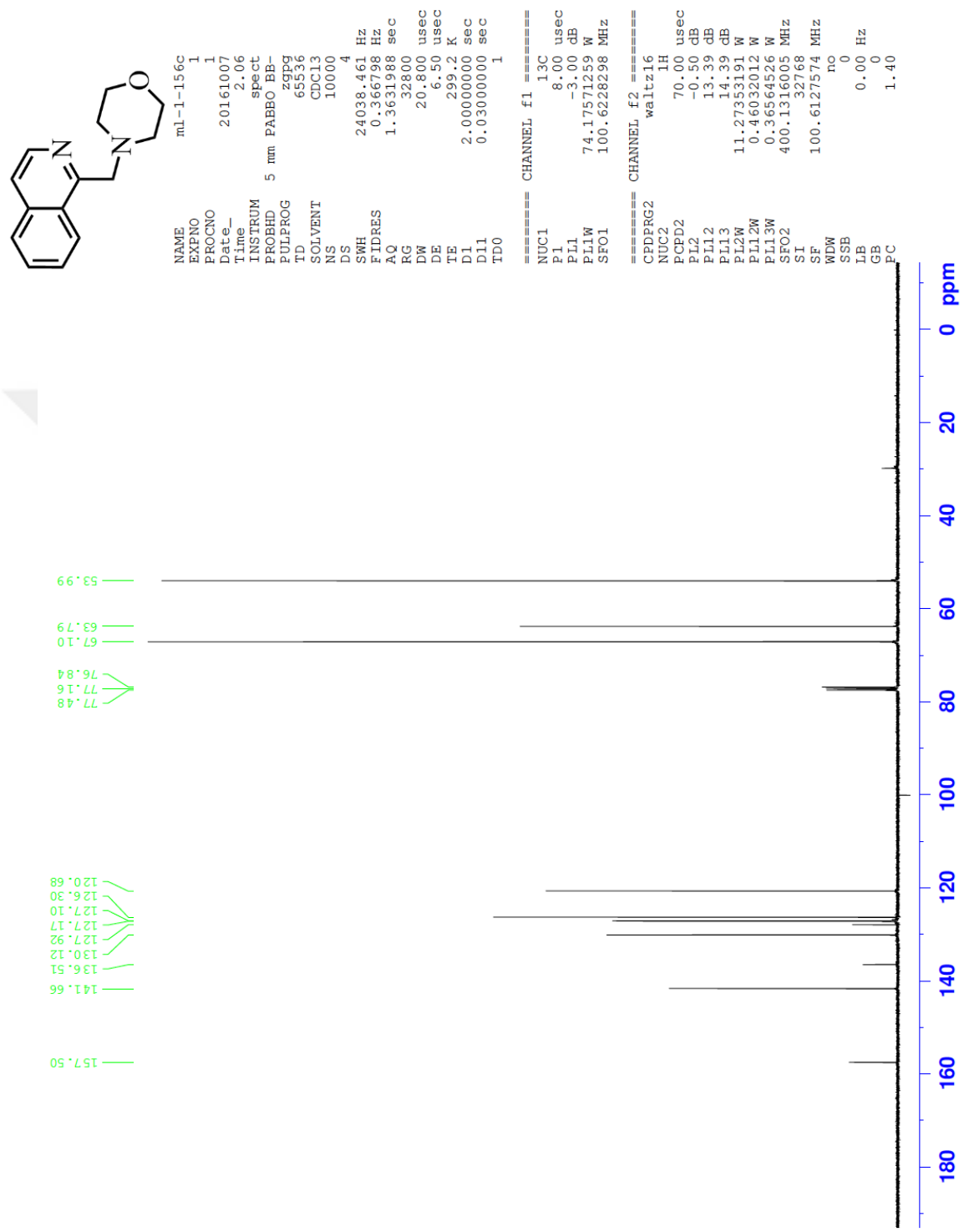

Figure 37. ^{13}C-NMR spectrum of Compound **12**

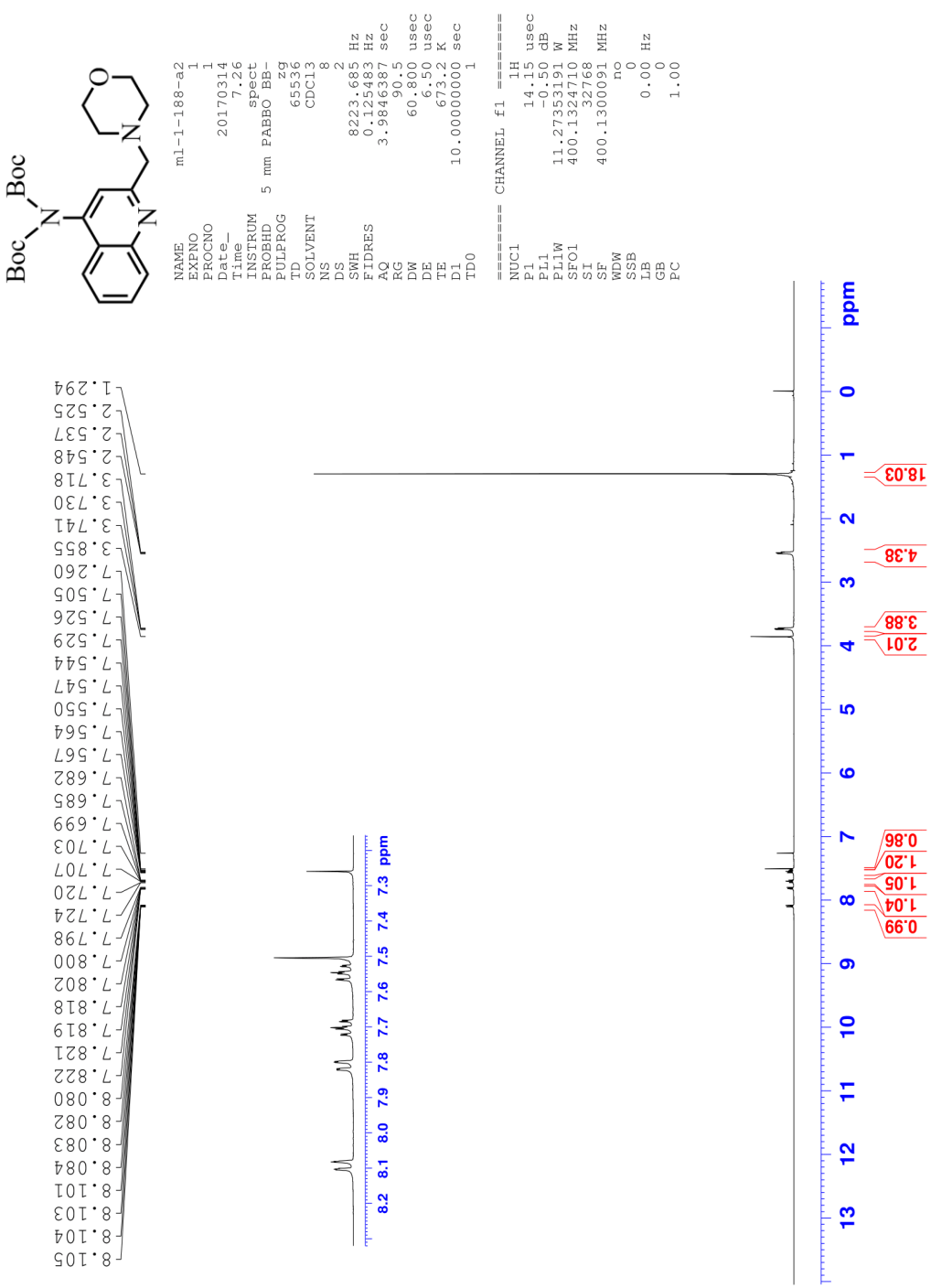

Figure 38. ^{1}H-NMR spectrum of Compound **13**

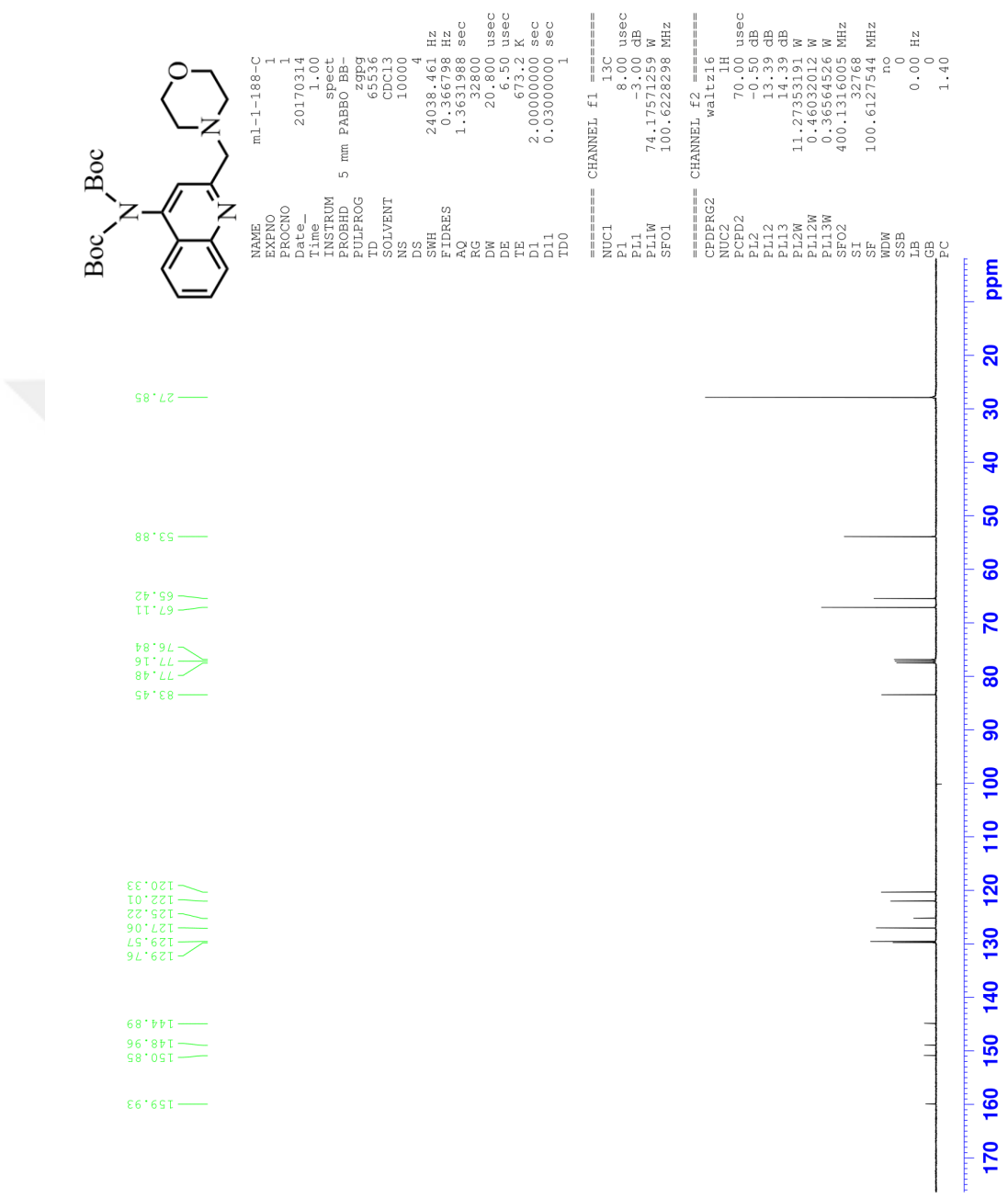

Figure 39. ^{13}C-NMR spectrum of Compound **13**

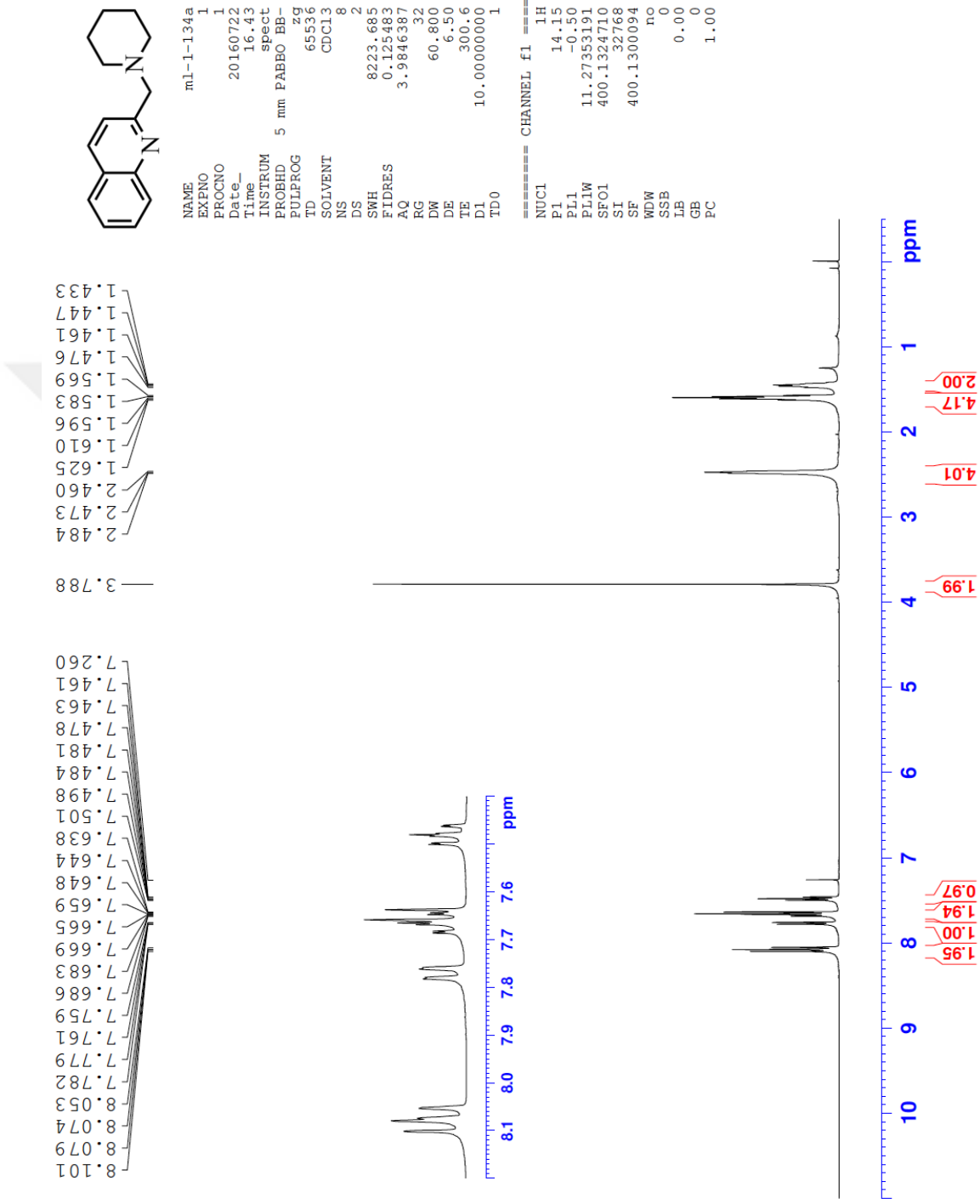

Figure 40. [1]H-NMR spectrum of Compound **14**

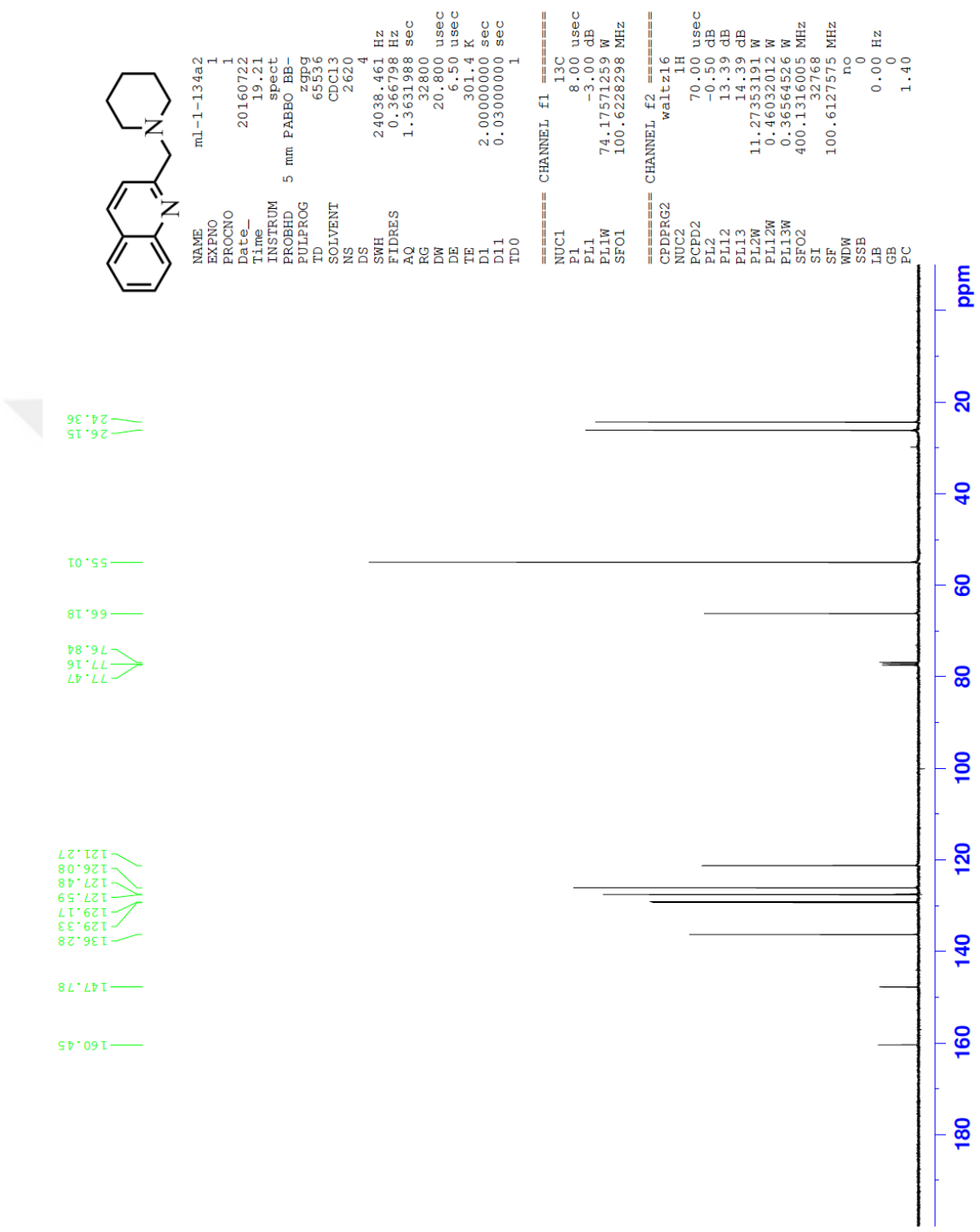

Figure 41. ^{13}C-NMR spectrum of Compound **14**

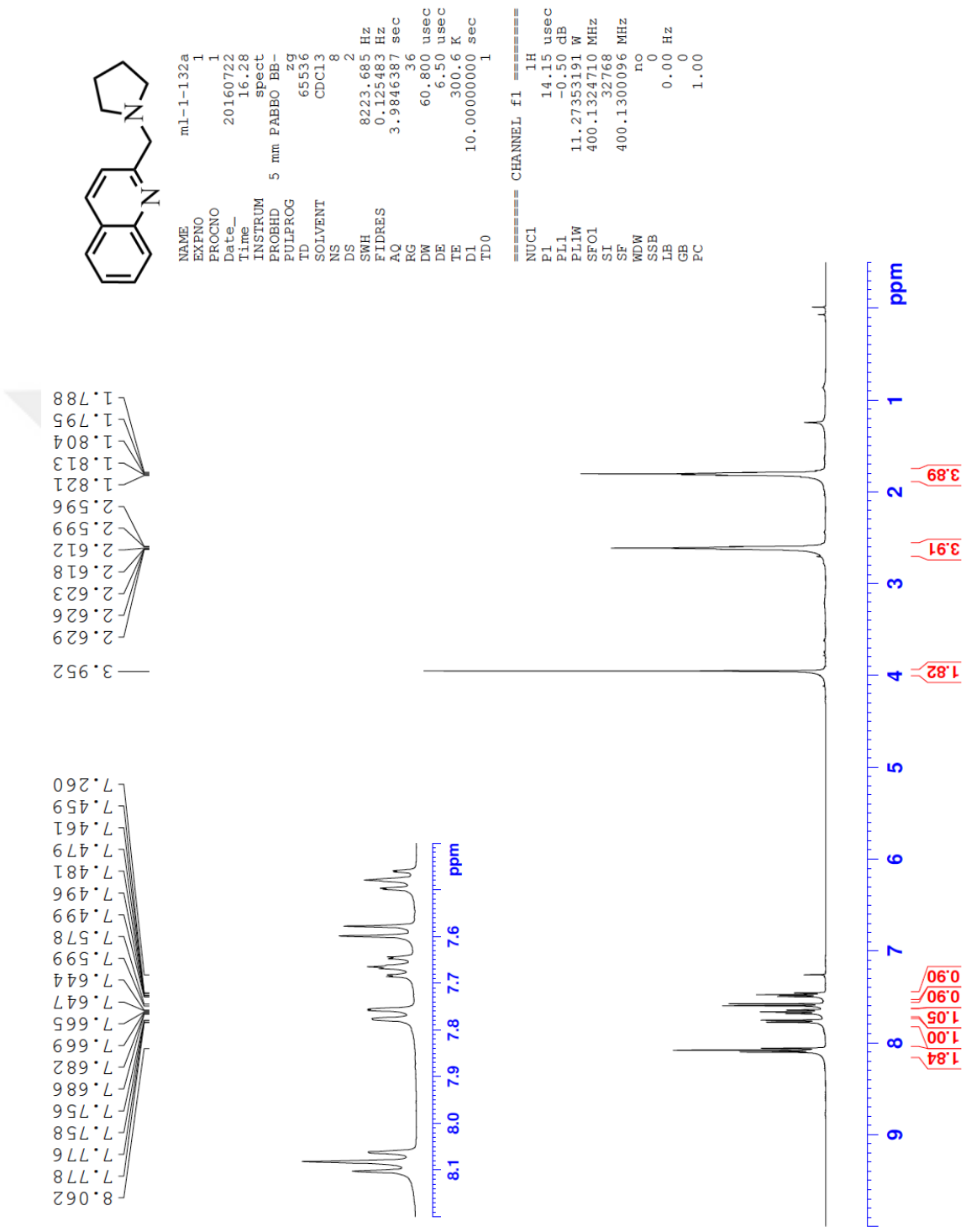

Figure 42. [1]H-NMR spectrum of Compound **15**

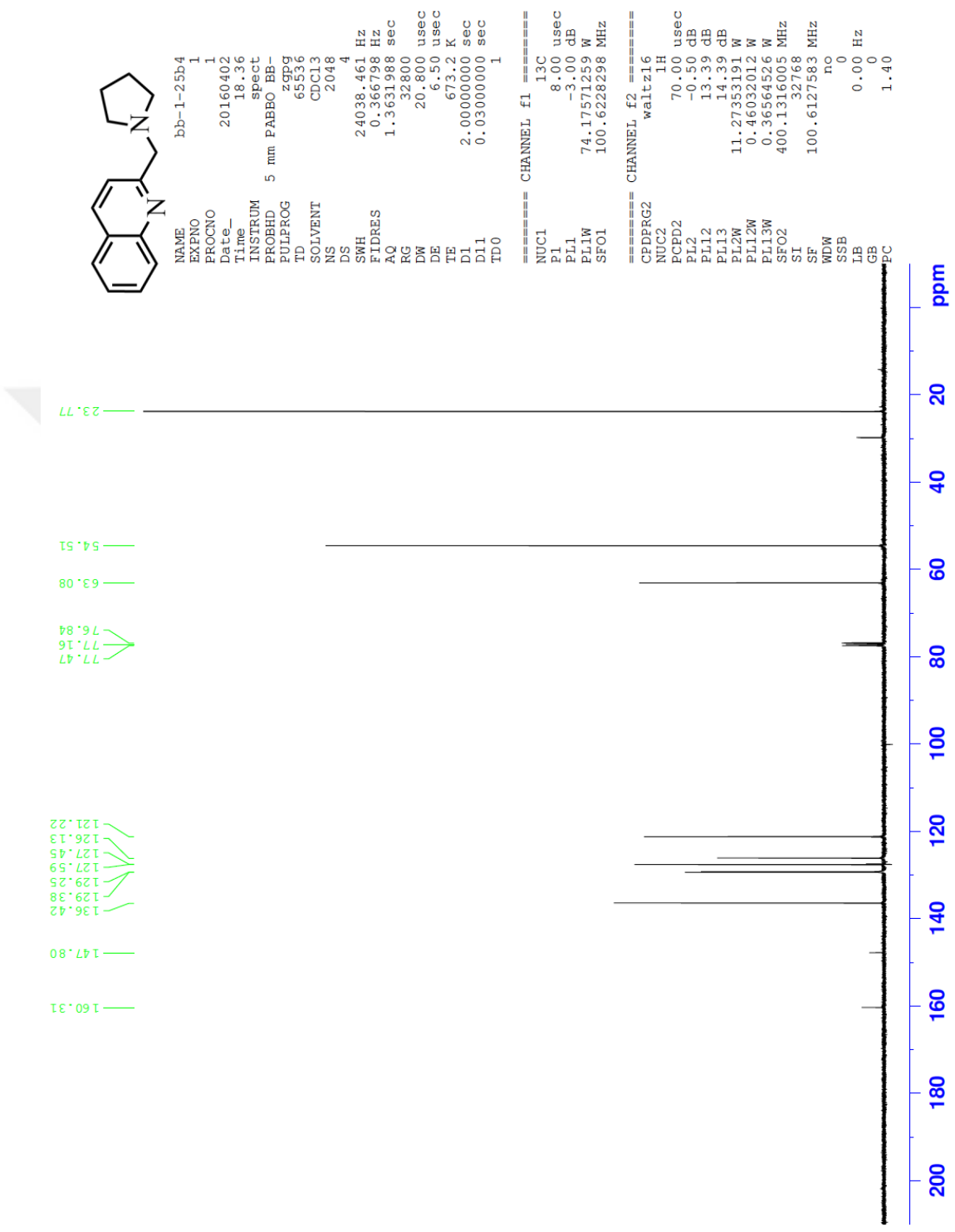

Figure 43. ^{13}C-NMR spectrum of Compound **15**

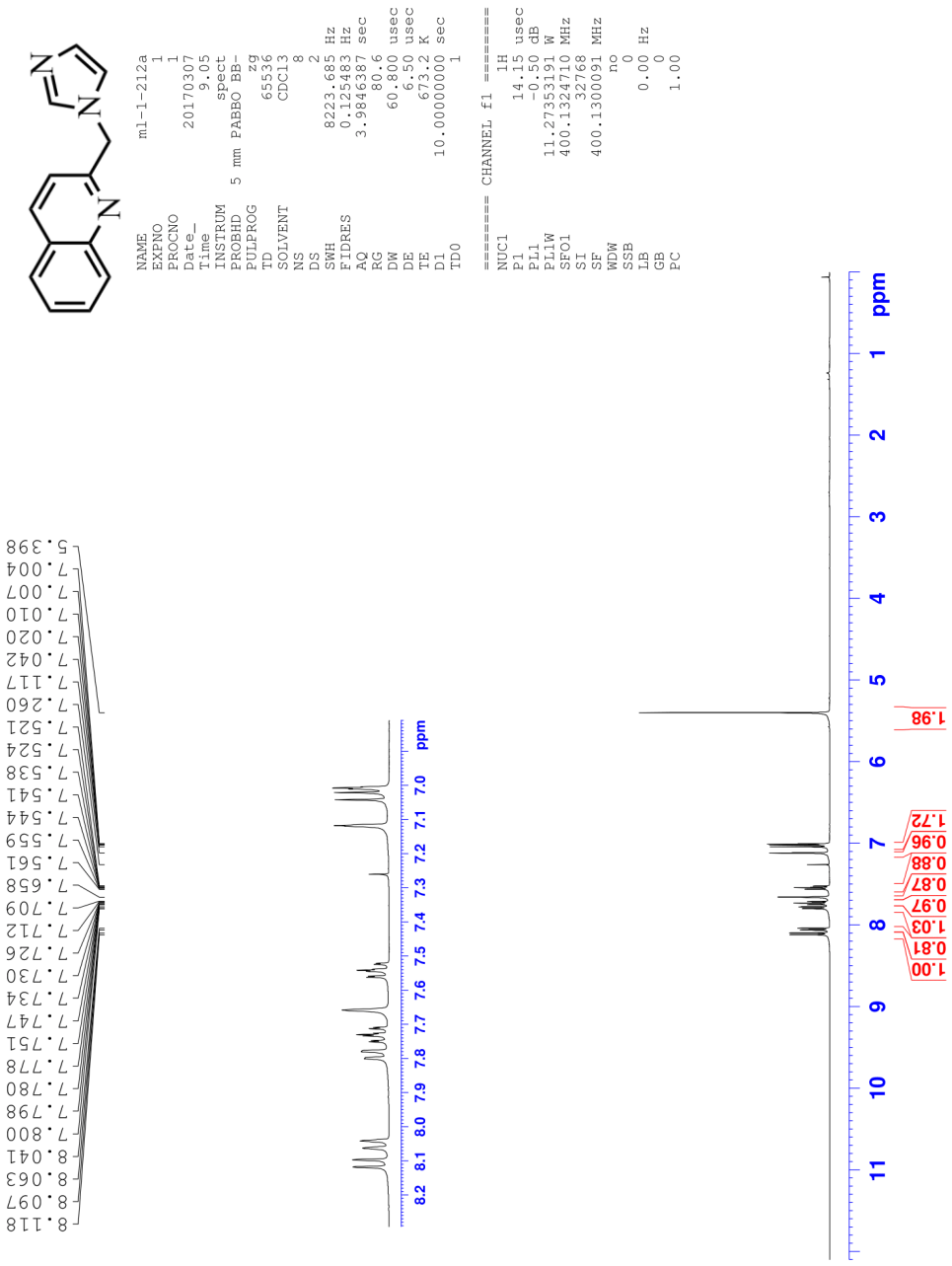

Figure 44. [1]H-NMR spectrum of Compound **16**

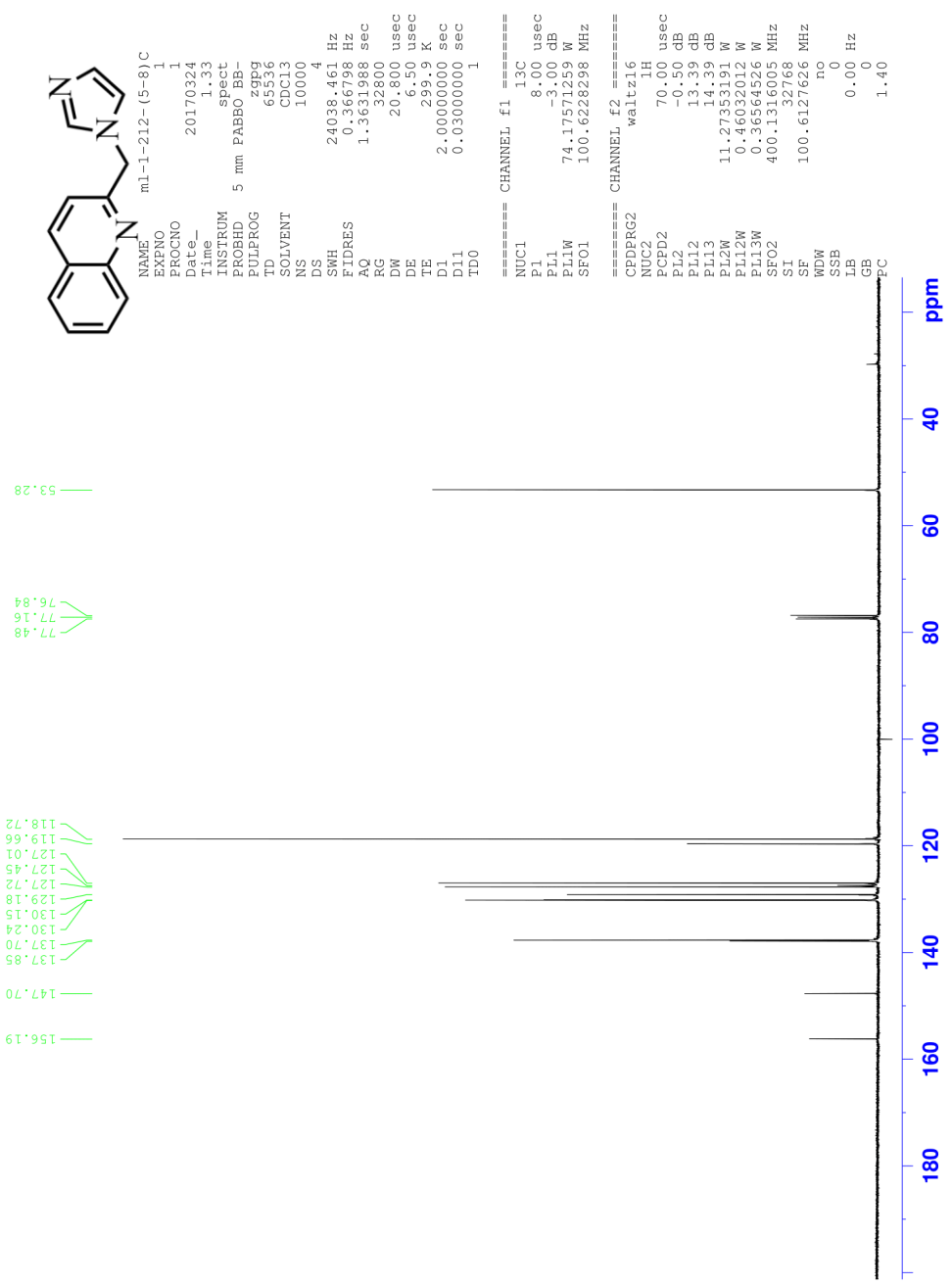

Figure 45. ^{13}C-NMR spectrum of Compound **16**

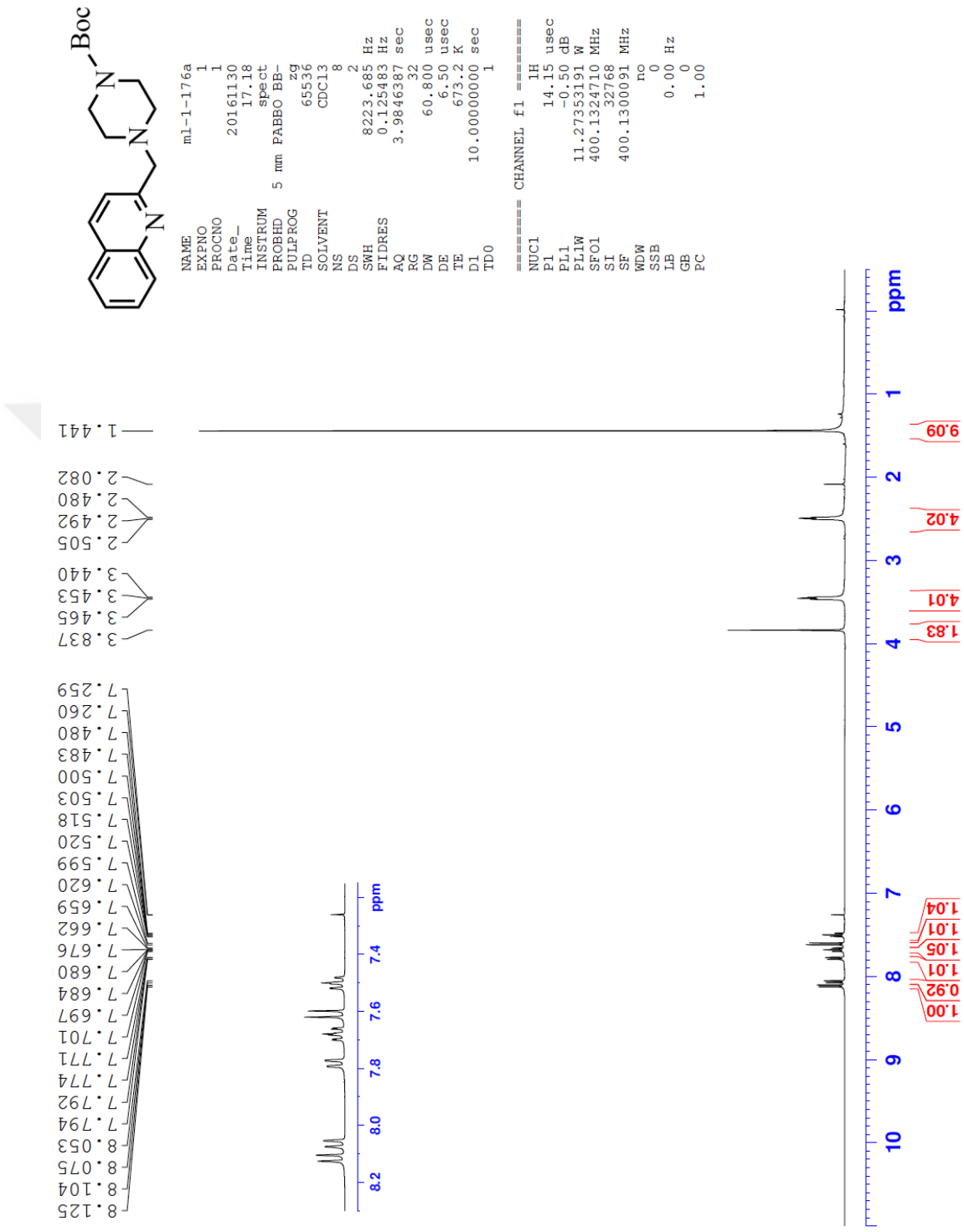

Figure 46. ^{1}H-NMR spectrum of Compound **17**

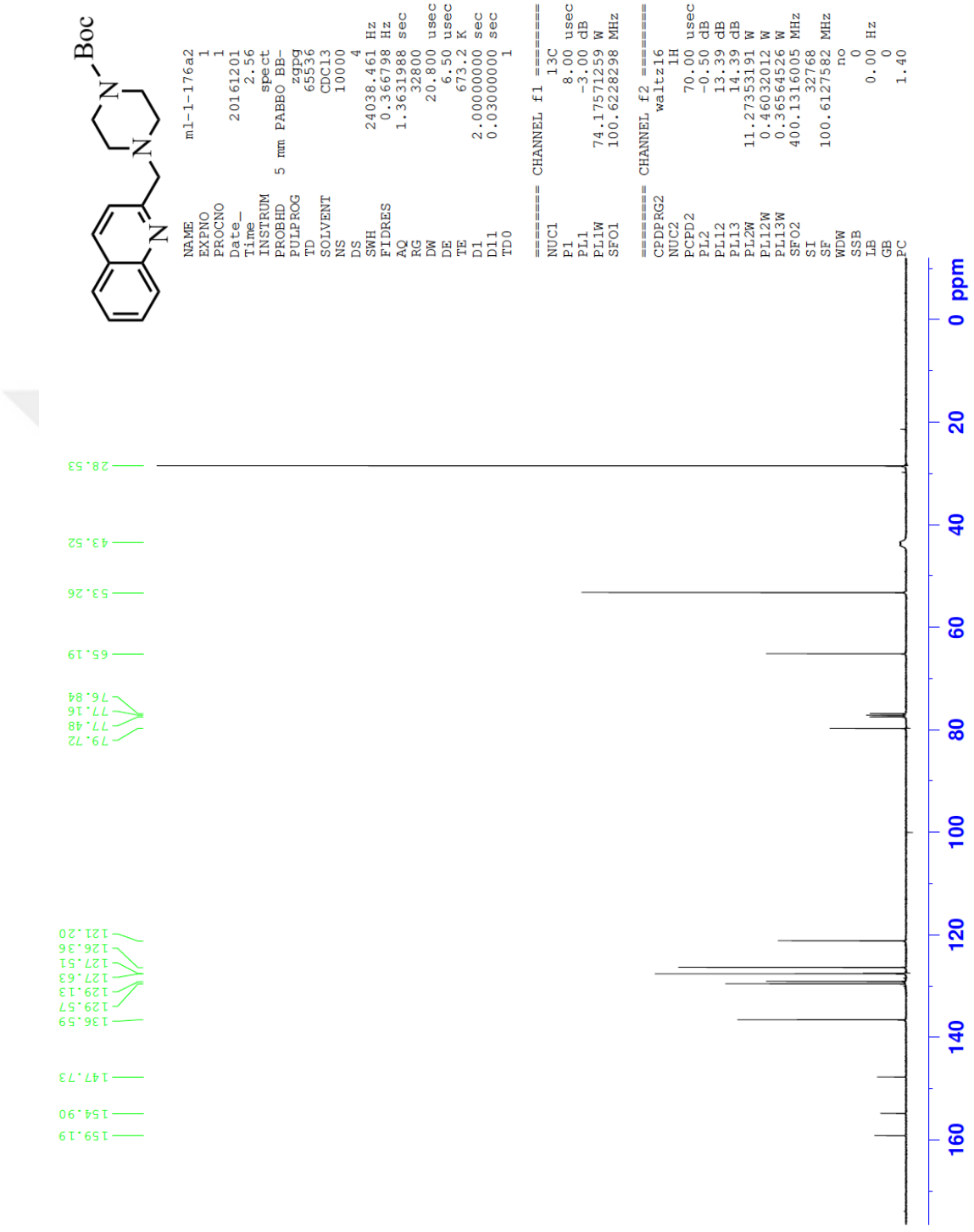

Figure 47. ^{13}C-NMR spectrum of Compound **17**

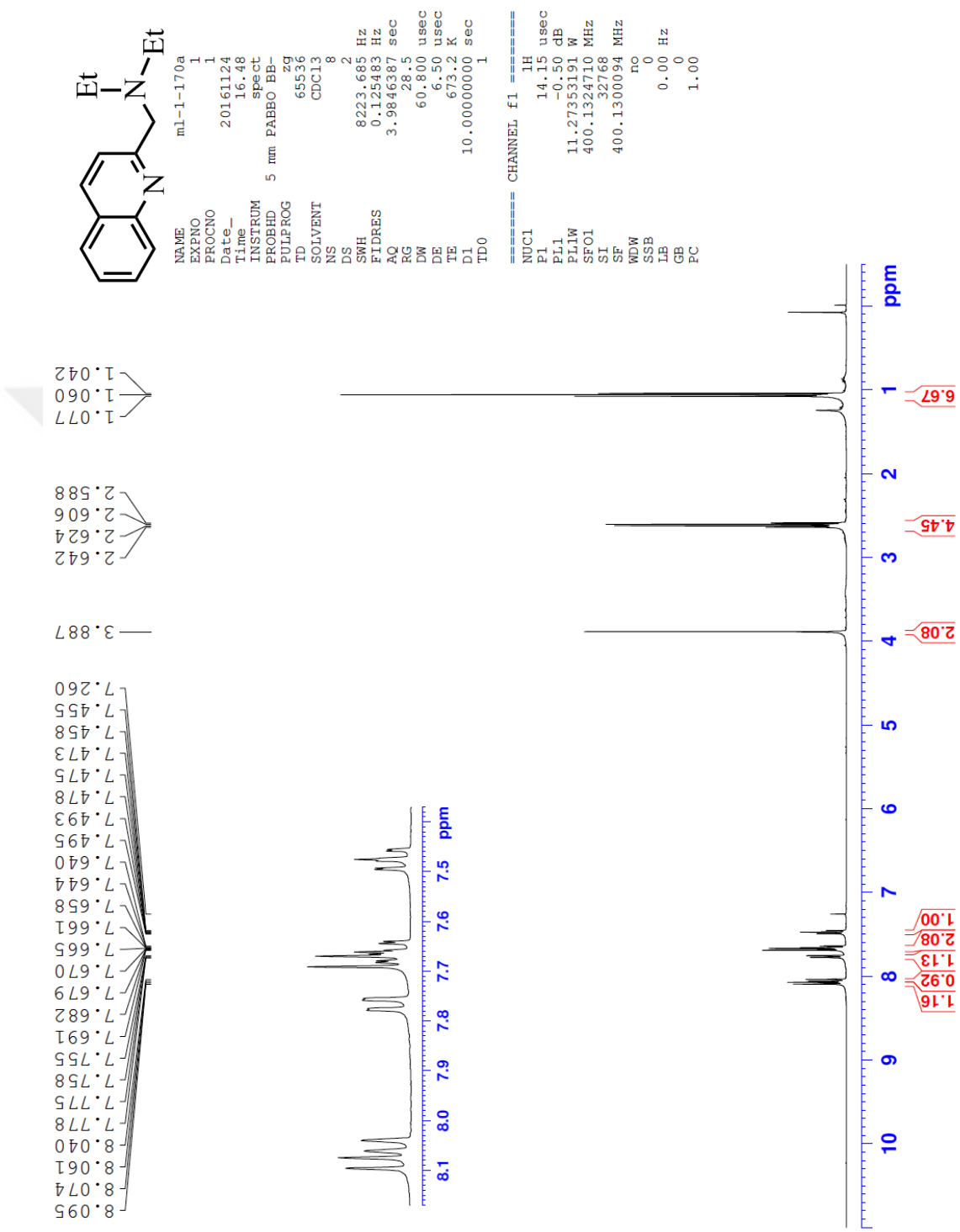

Figure 48. ^{1}H-NMR spectrum of Compound **18**

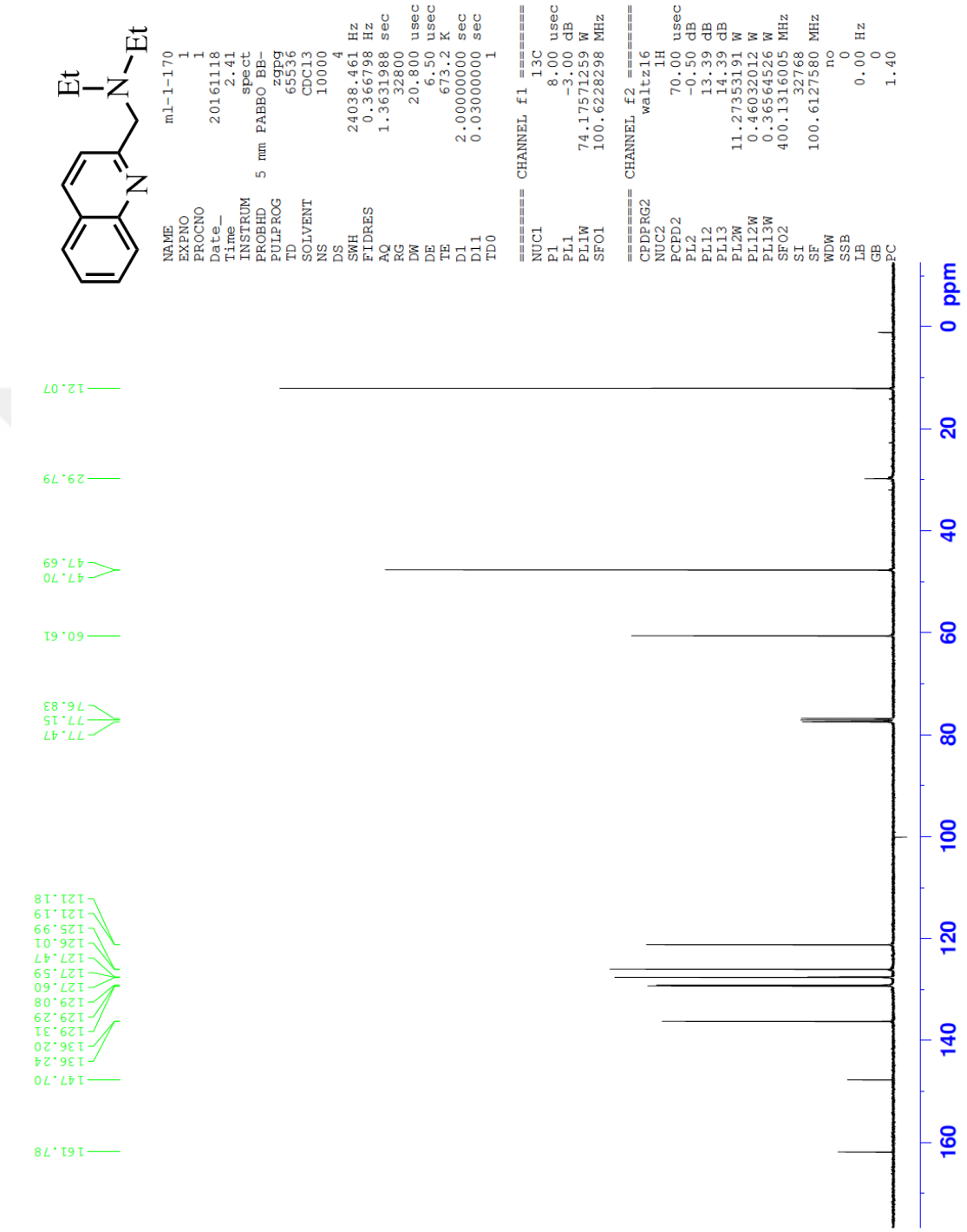

Figure 49. ^{13}C-NMR spectrum of Compound **18**

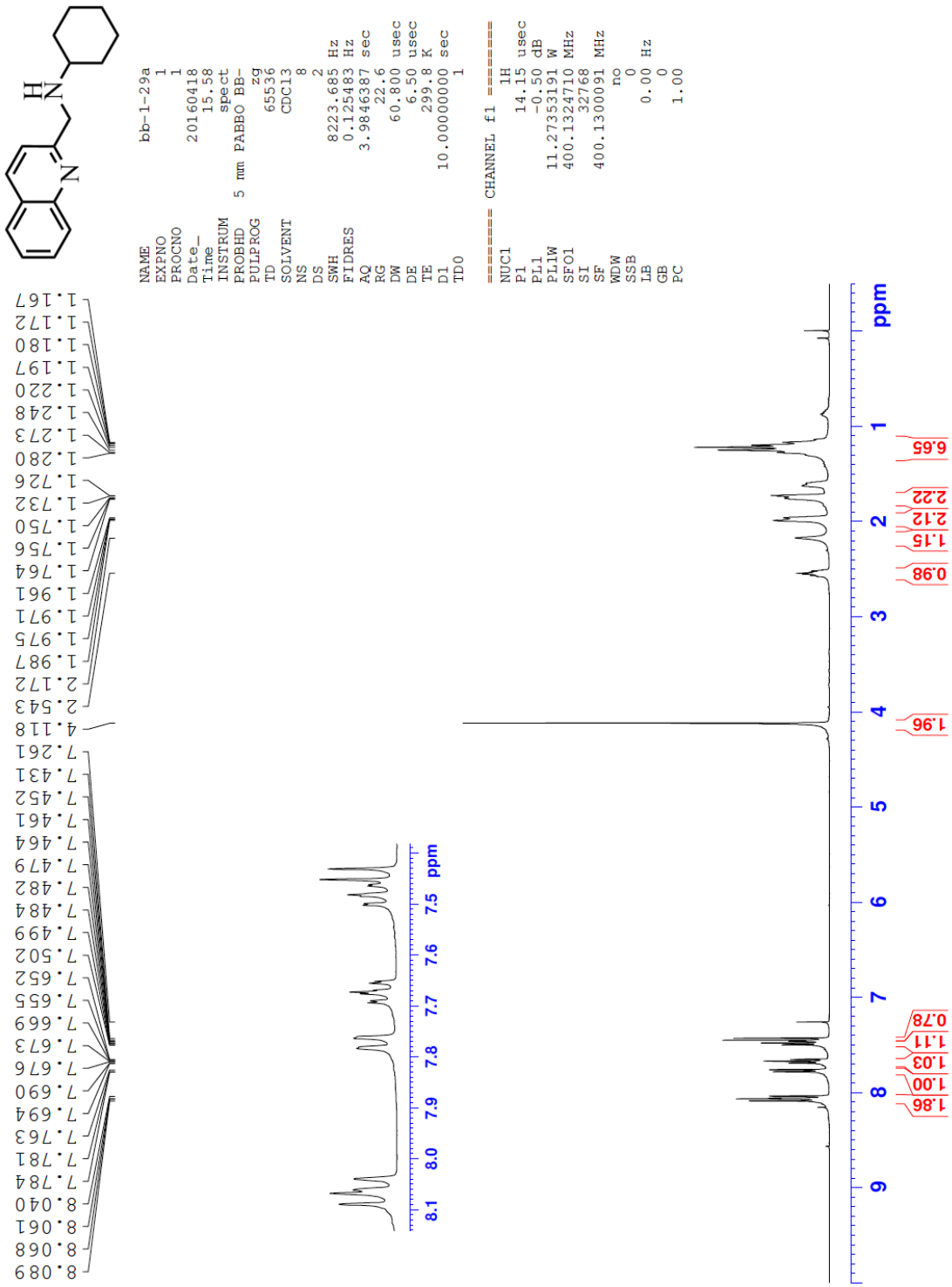

Figure 50. [1]H-NMR spectrum of Compound **19**

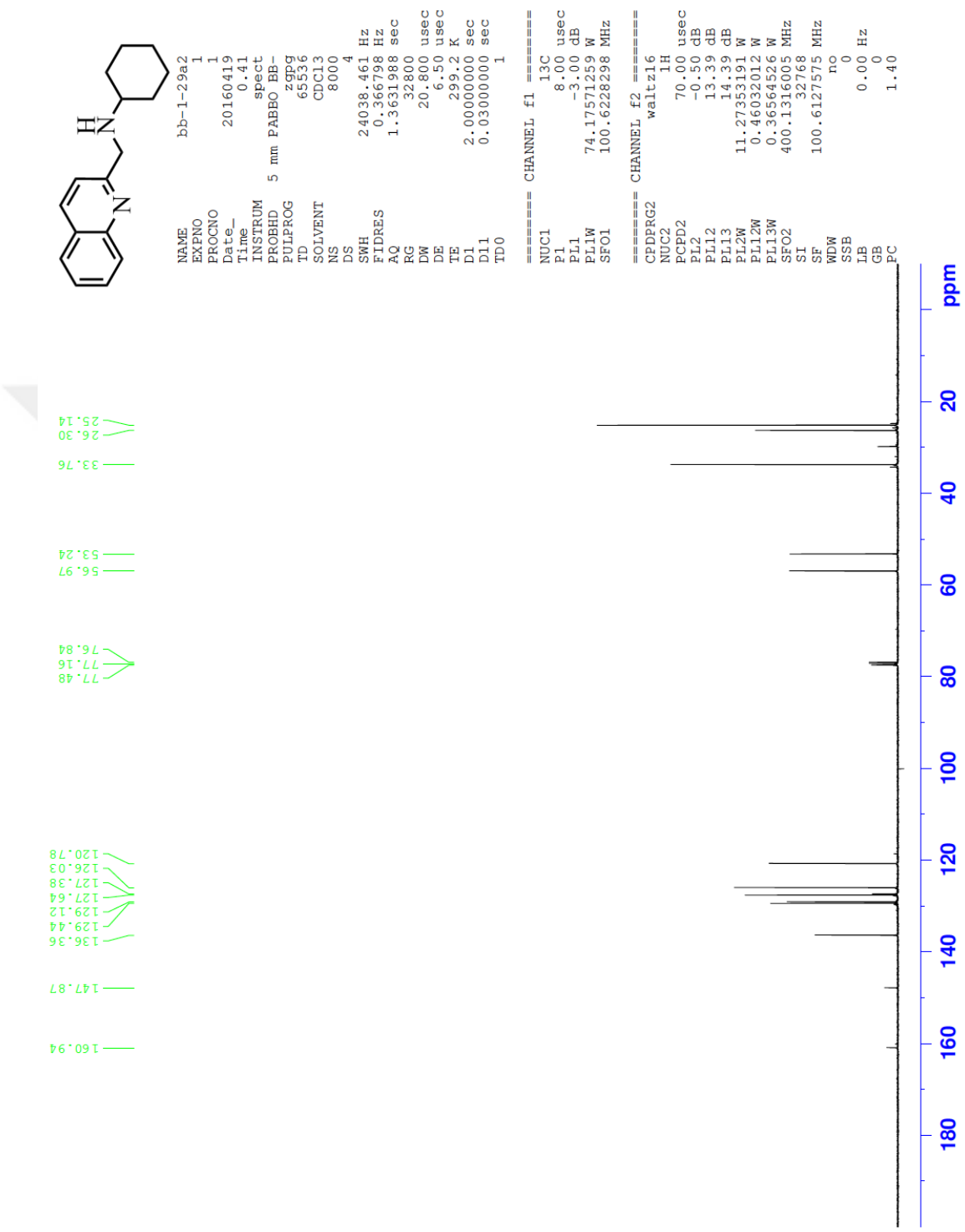

Figure 51. ^{13}C-NMR spectrum of Compound **19**

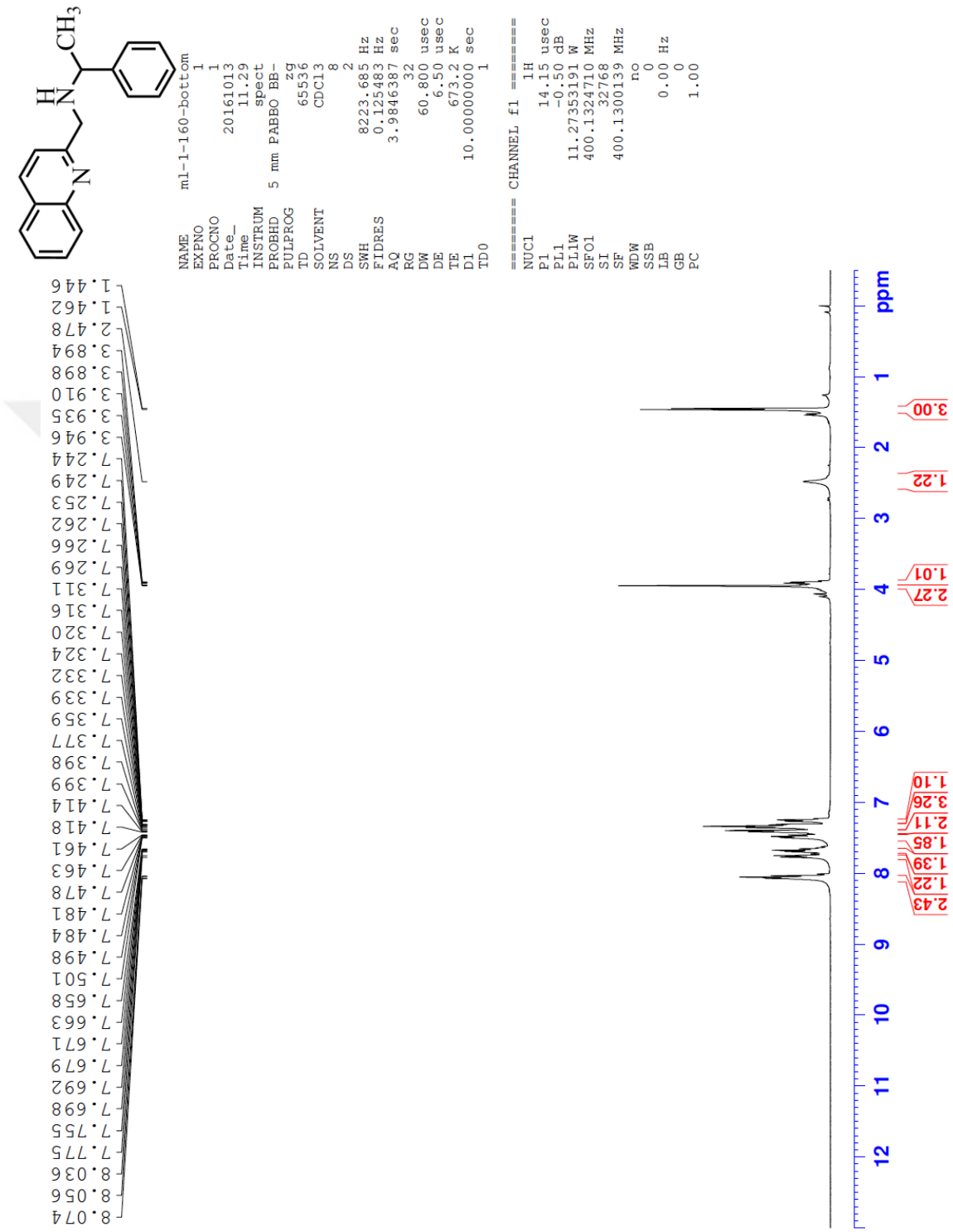

Figure 52. [1]H-NMR spectrum of Compound **20**