TOTAL SYNTHESIS OF VERANAMINE

A Thesis

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Hugo C. Araujo Lino

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Major Professor: Jakob Magolan, Ph.D.

Authorization to Submit Thesis

This thesis of Hugo C. Araujo Lino, submitted for the degree of Master of Science with a Major in Chemistry and titled "Total Synthesis of Veranamine," has been reviewed in final form. Permission, as indicated by the signatures and dates below, is now granted to submit final copies to the College of Graduate Studies for approval.

Major Professor: _____ Date:_____
Dr. Jakob Magolan

Committee Members: _____ Date:_____
Dr. Patrick Hrdlicka

_____ Date:_____
Dr. Armando McDonald

Department Administrator: _____ Date:_____
Dr. Ray von Wandruszka

Discipline's College Dean: _____ Date:_____
Dr. Paul Joyce

Final Approval and Acceptance by the College of Graduate Studies:

_____ Date:_____
Dr. Jie Chen

Abstract

Clinical depression is the fourth leading cause of disability and death in the world.[1] Although a great number and diversity of antidepressant drugs are already on the market, there remain many problems and much room for improvement in this class of therapeutics. Given the problems of current treatments,[2] discovery and development of new and improved antidepressant drugs remains a pressing need. The subject of the first chapter is the recently-accomplished first total synthesis of a new and structurally unique antidepressant natural product called veranamine[3]. We have completed this synthesis in a total of 7 steps with overall yield of 21 % starting with readily available inexpensive starting materials. The key step is an unprecedented vinylogous Pictet-Gams reaction used to assemble the dihydronaphthyridine core scaffold of the natural product. This marine-derived heterocyclic compound is the first structurally new antidepressant lead of its kind in many years[3a]. Our synthesis is part of a collaborative effort to further develop this compound as a therapeutic lead.

The second chapter is devoted to an unrelated topic. One branch of research in Dr. Magolan's laboratory aims to develop unique synthetic methods that rely on the use of heterogeneous reagents in one-pot multi-step processes. An important benefit of these methods is the facile separation of catalysts and reagents from reaction products through filtration, generating inexpensive and easy product purification. Here we present our initial investigations on the use of clays as aerobic dehydroaromatization catalysts, including a clay-mediated one-pot Fischer indole synthesis and Povarov reaction.

Acknowledgements

First and foremost, I am thankful to my supervisor, Dr. Jakob Magolan, who has also served as my professor and advisor. I feel very fortunate to have started research with him at the same time he started his career as a professor, and more so, to be the first graduate student from his lab to leave the bench. Under his guidance I have learned so much about organic chemistry and research in general. He has become a great role model and good friend to me.

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I would like to acknowledge the support of all my family and friends. My brothers Jesus, Jorge, Javier, and Cruz, my sister Blanca, and my parents, Jesus and Audelia. My good friends Andres and Victor, and finally, the support and company of my best friend, Maricela, who helped me unconditionally throughout this journey. Thank you so much.

Para mis padres, hermanos y hermana…

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List of Schemes

List of Abbreviations

Acac- acetyl acetonate

Ar- Aryl

COSY- Correlation spectroscopy

DCM- Dichloromethane

DMSO- Dimethylsulfoxide

dppf- 1,1'-Bis(diphenylphosphino)ferrocene

equiv- Equivalents

ESI- Electrospray ionization

FTIR- Fourier Transform Infrared

HMBC- Heteronuclear multiple bond correlation

HSQC- Heteronuclear single quantum coherence

HPLC- High pressure liquid chromatography

hr- Hour

HRMS- High resolution mass spectrometry

LAH- Lithium aluminum hydride

MALDI- Matrix-assisted laser desorption/ionization

MAOI- Monoamine oxidase inhibitor

CH_3NO_2- Nitromethane

MHz- Megahertz

min- Minutes

Mont- Montorillonite

MP- Melting Point

MW- Microwave

NMR- Nuclear magnetic resonance

-OTf- Triflate

PCC- Pyridinium chlorochromate

p-TsOH- *para*-Toluene sulfonic acid

Q-TOF- Quadrupole time-of-flight

r.t.- Room temperature

Rf- Relative to front

SNRI- Serotonin and norepinephrine reuptake inhibitor

SSRI- Selective serotonin reuptake inhibitor

TCA- Tricyclic/tetracyclic

Temp- Temperature

TFA- Trifluoroacetic acid

THF- Tetrahydrofuran

TLC- Thin layer chromatography

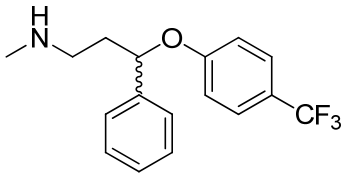
W- Watt

Chapter 1: Total Synthesis of Veranamine

1.1 Introduction

1.1.1 Antidepressant Drugs

Clinical depression or 'major depressive disorder' is the fourth leading cause of disability and death in the world.[1] This psychiatric syndrome has high socioeconomic impact and a lifetime prevalence of 10 % for men and 20 % for women.[1] Although many studies on the development of antidepressant drugs are continuously published, the increasing cost of depression and related disorders has not been paralleled by improvements in efficacy of drugs and other antidepressant treatments.[2] As reported by Lindsley, antidepressant drugs are the most prescribed class of drugs in the United States with 264 million prescriptions given in 2011.[3] In that year, of the $319.9 billion total prescription drug sales in the United States $11.9 billion was spent on antidepressants.[3] Since the time of its introduction to the market in the 1980s, Fluoxetine (Prozac®, Figure 1.1) has been the most prescribed antidepressant drug worldwide.[4]



Fluoxetine (Prozac®)

Figure 1.1 Chemical structure of Fluoxetine.

All currently available antidepressant drugs are believed to function via a common biochemical approach, i.e., they influence the levels of one or more of three neurotransmitters: dopamine, norepinephrine, and serotonin (Figure 1.2).

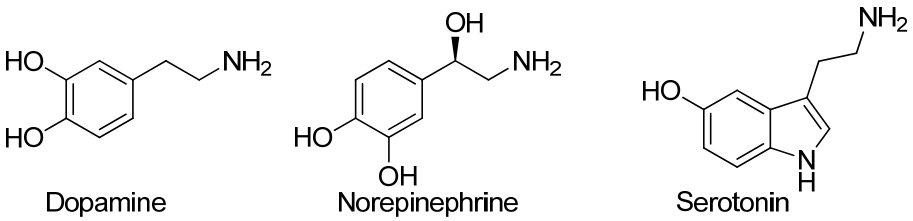


Figure 1.2 Structure of three different neurotransmitters.

Of these neurotransmitters, serotonin regulation is the most common target.[5] More specifically, antidepressants interact with a variety of pre- and post-synaptic receptors to increase the activity of one or these neurotransmitters.[6]

There are four major classes of antidepressants. These are: 1) tricyclic and tetracyclic antidepressants (TCAs), 2) selective serotonin reuptake inhibitors (SSRI), 3) serotonin and norepinephrine reuptake inhibitors (SNRIs), and 4) monoamine oxidase inhibitors (MAOIs).[3,4,7] The following sections will briefly describe some of the current drugs in each of these classes.

1.1.1.1 Tricyclic and Tetracyclic Antidepressants

Tricyclic and tetracyclic antidepressants (TCAs) share similar tricyclic, or tetracyclic, core structures with varying side chains. All of these drugs also have similar pharmacodynamic and pharmacokinetic properties.[6,7,8] Examples of drugs in this category include imipramine (Tofranil®), desipramine (Norpramin®), clomipramine (Anafranil®), doxepin (Sinequan®) Maprotiline (Ludiomil®), amoxapine (Amokisan®) and Mirtazapine (Remeron®, Figure 1.3).

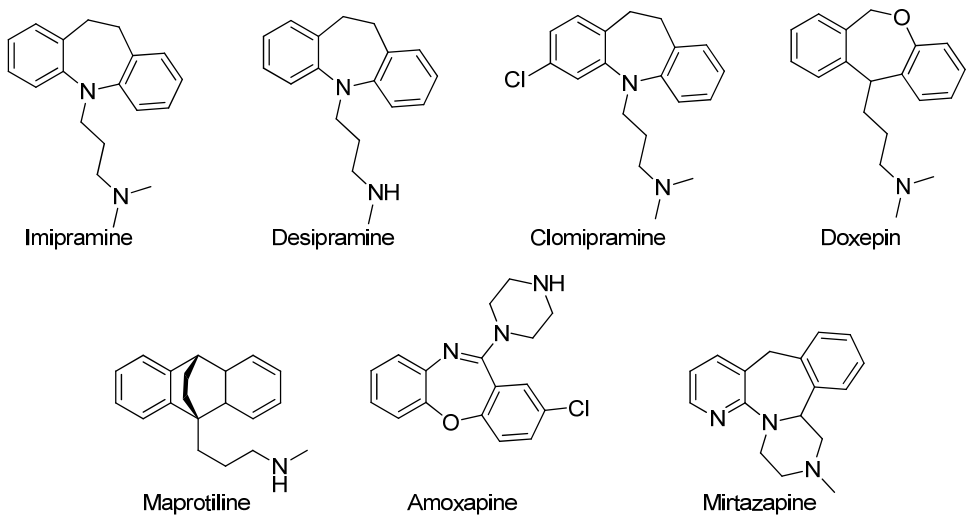


Figure 1.3 Chemical structures of tricyclic and tetracyclic antidepressants (TCAs).

Although this class of compounds was intended for the treatment of psychosis, they were found to have poor antipsychotic properties but powerful antidepressant effects.[4] They are also known as first generation antidepressants since they were among the first drugs used for the treatment of depression. Their mechanism of action consists of inhibiting the reuptake of norepinephrine and/or serotonin neurotransmitters by blocking their respective transport proteins. This in turn induces a blockade that leads to antidepressant effects by increasing synaptic neurotransmitter concentrations. Desipramine, for example, is a strong selective norepinephrine reuptake inhibitor, while imipramine has both norepinephrine and serotonin effects. Although TCAs were the standard first-line therapy for the treatment of depression, in the past three decades new antidepressant agents have been developed with equal potency to TCAs but improved tolerability and decrease risk in overdose.[9]

1.1.1.2 Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are named for their mechanism of action.[4] Just like TCAs, SSRIs are reuptake inhibitors, however the former have greater affinity for the serotonin reuptake transporter than any other receptor system.[3] Today, SSRIs are the most commonly prescribed drugs for the treatment of clinical depression. SSRIs include: fluvoxamine (Luvox®), sertraline (Zoloft®), citalopram (Celexa®), fluoxetine (Prozac®), and paroxetine (Pexeva®) among others (Figure 1.4).

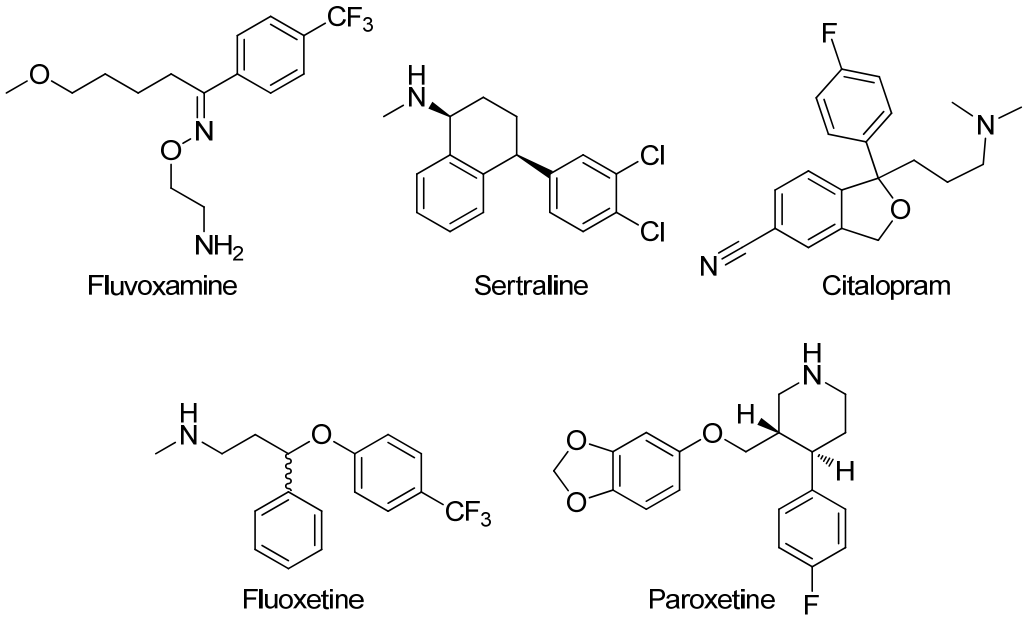


Figure 1.4 Chemical structures of various selective serotonin reuptake inhibitors (SSRIs).

1.1.1.3 Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) were a serendipitous discovery.[4] They were initially discovered when a precursor to this class of drugs was being evaluated as an antituberculosis agent. When patients with co-morbid depression were treated with this MAOI they experienced decreased depression symptoms. Monoamine oxidase is a presynaptic catabolic enzyme for the

neurotransmitters dopamine, norepinephrine, and serotonin. There are two subtypes of this enzyme: MAO-A and MAO-B. MAO-A metabolizes norepinephrine and serotonin and MAO-B metabolizes only serotonin. The mechanism of action for MAOIs consists of inhibition of these MAO enzymes leading to an increase of neurotransmitters in the synaptic space.[4,10] Isocarboxazid (Marplan®), Phenelzine (Nardil®), and tranylcypromine (Parnate®) are examples of nonselective and irreversible inhibitors of both subtypes of MAO (Figure 1.5).

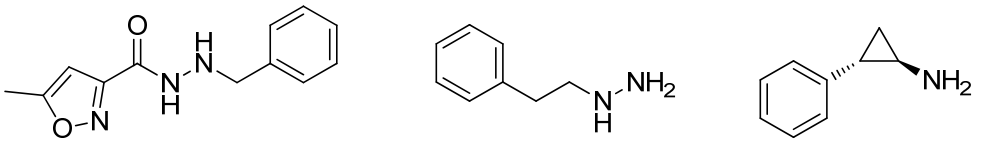


Figure 1.5 Chemical structures of different non-selective Monoamine Oxidase Inhibitors (MAOIs).

1.1.1.4 Serotonin and Norepinephrine Reuptake Inhibitors

Serotonin noradrenaline reuptake inhibitors (SNRIs) work by blocking serotonin and norepinephrine reuptake in the central nervous system. This dual blockade mechanism for down regulation of β-adrenergic receptors is thought to be the justification for the fact that this class of antidepressants has a shorter latency period than the other classes.[4, 11] Two examples of SNRIs are venlafaxine (Effexor®) and duloxetine (Cymbalta®, Figure 1.6).

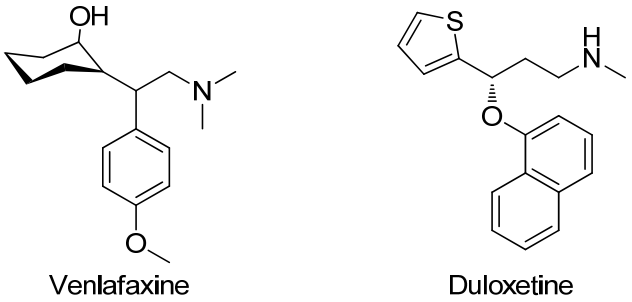


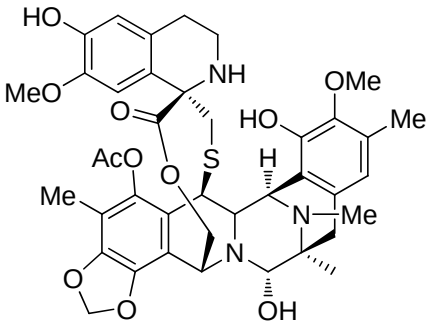
Figure 1.6 Chemical structures of SNRIs Venlafaxine and Duloxetine.

Although a great number and diversity of antidepressant drugs are on the market today there remain many problems and much room for improvement in this class of therapeutics. First and foremost, approximately 30 % of patients do not respond to current treatments. Secondly, it is typical for patients to experience a 6 weeks delay before full therapeutic effect occurs. Finally there are many problematic side effects experienced with all of these drugs including: sedation, cardiovascular, psychiatric, metabolic, and dependence.[12]

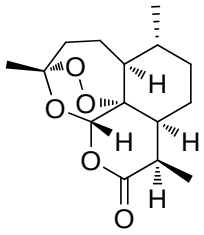
Given the problems of current treatments stated above, discovery and development of new and improved drugs in this field remains a pressing need. The subject of this chapter is the chemical synthesis of a structurally novel antidepressant natural product called veranamine. This marine-derived heterocyclic compound is the first structurally new antidepressant lead in many years.[13] The next section briefly introduces the subject of natural products as leads for the development of drugs.

1.1.2 Natural Products as Pharmaceutical Leads

Natural products have always played a substantial role in drug discovery in recent decades.[14] Detailed studies of the biological activity of natural products has led to the identification of new modes of action, biochemical pathways, and protein targets that have proven to be of high importance for the treatment of various human diseases.[15] Natural products themselves have been directly used as drugs and they have often served as lead compounds for drug discovery efforts.[16] About 20 % of all natural product-based drugs are used as drugs without further structural modifications. Two examples of these are: Trabectedin and Artemisinin (Figure 1.7).



Trabectedin



Artemisinin

Figure 1.7 Structures of Trabectedin and Artemisinin.

Trabectedin was discovered in 1969 from marine tunicate *Ecteinascidia turbinata.* In 2007 it became the first European anti-cancer drug derived from a marine source. Artemisinin is a valuable treatment for malaria. It was originally extracted from the shrub *Artemisia annua.* Due to the unsustainability of obtaining artemisinin in large quantities from its biological source, bulk production of this drug is now achieved via synthesis and semisynthesis.[15]

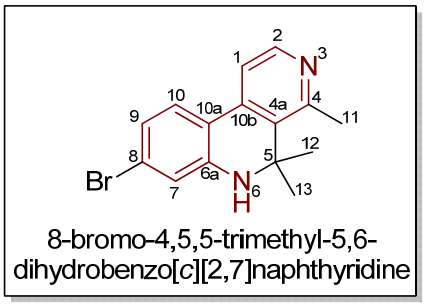
Effective synthetic access to a natural product leads is often critical for successful biological activity testing and medicinal chemistry optimization programs. The vast majority of commercial drugs derived from natural products required synthetic efforts to enable economical access to bulk material and/or optimize drug properties through structural modifications.[15]

1.1.3 Introduction to Veranamine

1.1.3.1 Isolation of Veranamine

In 2008, Prof. Mark Hamann from the University of Mississippi and co-workers isolated and characterized the marine alkaloid veranamine from the marine sponge *Verongida rigida* harvested in the Florida Keys (Figure 1.8).[17]

V. Rigida

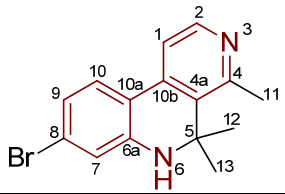


Veranamine

Figure 1.8 Image of sponge *V. Rigida* (left, image obtained with permission from coralpedia.com[18]) and structure of veranamine (right).

Veranamine was isolated using the following process: *V. rigida* was ground and extracted exhaustively with ethanol. The crude extract was reduced in volume and fractioned on silica gel column by vacuum liquid chromatography using a gradient of solvents from hexane to methanol. Polar fractions were further purified by reverse phase on a solid C18 phase extraction cartridge by flash chromatography, followed by HPLC on a C8 column. An initial 3 kg of sponge yielded 8 mg of the new alkaloid veranamine. The HRMS of the compound showed two peaks with close intensity at *m/z* 303.0494 and 305.0475 [M+H] indicating presence of one bromine atom and a molecular formula of $C_{15}H_{15}BrN_2$. NMR data obtained by Dr. Hamann is listed in Table 1.1.

Table 1.1 ^{1}H (400 MHz), ^{13}C (100 MHz) chemical shifts, COSY, HMBC correlations for veranamine in methanol-d_4.[13]



Carbon	δ C	δ H	COSY	HMBC
1	115.4	7.61 (d)	8.25	144.8; 134.0; 116.5
2	144.8	8.25 (d)	7.61	153.1; 115.4; 140.6
4	153.1	-	-	-
4a	134.0	-	-	-
5	53.5	-	-	-
6a	146.0	-	-	-
7	117.3	6.93 (d)	6.88	125.2; 116.5; 120.6
8	125.2	-	-	-
9	120.6	6.88 (dd)	7.55, 6.93	125.9; 125.2; 117.3
10	125.9	7.55 (d)	6.88	146.0; 140.6; 125.2
10a	116.5	-	-	-
10b	140.6	-	-	-
11	24.1	2.7 (s)	-	153.1; 134.0
12	27.9	1.62 (s)	-	134.0; 53.5
13	27.9	1.62 (s)	-	134.0; 53.5

Both carbon and proton NMR indicated the presence of aromatic rings. By ^{1}H NMR spectrum, 5 signals in the downfield region belong to these aromatic rings. The proton NMR contained signals in the upfield region which corresponded to the three methyl groups (δ 1.62 integrated for 6 protons and δ 2.69 for 3 protons). The structure assignment was completed using HMBC, and COSY correlations as shown in Table 1.1. Veranamine was isolated as dark yellow crystals making it possible to confirm the structure by X-ray analysis. Figure 1.9 shows the results of the X-ray analysis.

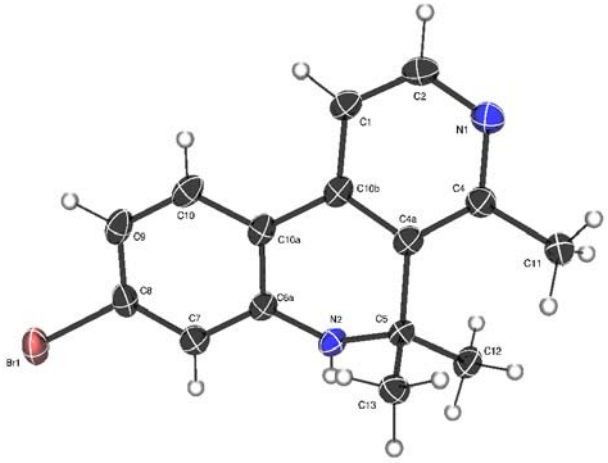


Figure 1.9 Crystal structure of veranamine (8-bromo-4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine) (image courtesy of M. Hamann[13]).

1.1.3.2 Antidepressant Activity of Veranamine

The structure of veranamine possesses some obvious similarities to other compounds that are known to be psychoactive including some indole alkaloids and cannabinoids (Figure 1.10).

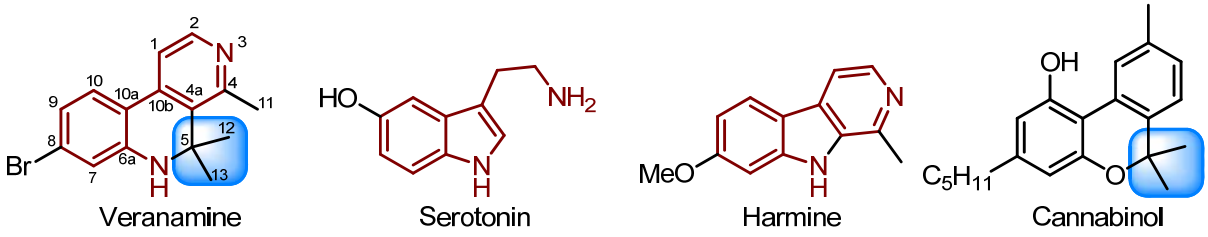


Figure 1.10 Structural similarities between veranamine and other psychoactive compounds.

The relative distance between the two nitrogen atoms on the naphthyridine ring of veranamine is analogous to the nitrogen atoms of the neurotransmitter serotonin (Figure 1.10). The indole alkaloid Harmine, a β-carboline monoamine oxidase inhibitor, has a very similar tricyclic core structure to veranamine. The geminal dimethyl moiety of veranamine can be mapped onto the psychoactive compound cannabinol. In the case of veranamine, this dimethyl moiety prevents

oxidation and complete aromatization of the tricyclic ring system. The fully aromatized benzo[c][2,7]naphthyridine ring system is known to occur in a number of natural products,[19] however no previous reports are known of the 5,6-dihydrobenzo[c][2,7]naphthyridine ring core of veranamine.

Because of the structural features described above, Dr. Hamann hypothesized that veranamine was likely to have psychoactive properties. Consequently he evaluated the compound by means of an in vivo assay known as a forced swim test. This assay consists of placing rodents (usually mice) in small enclosed cylinders where they are forced to swim. Typically, after an initial period of vigorous activity the rodents become immobile and float. This 'immobility' has been correlated with "behavioral despair". The total immobility time during a 15 minute period is measured and typically reduced by antidepressant drugs. As summarized in Figure 1.11, veranamine effectively decreased immobility time relative to the control treatment. Consequently, this assay showed that veranamine had potent antidepressant activity at 20 mg/kg. The results were comparable to commercially available antidepressant drug desipramine (Figure 1.11).

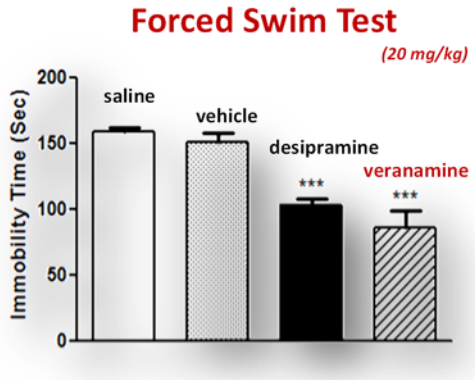


Figure 1.11 Veranamine forced swim test. *** $p < 0.001$ versus corresponding vehicle. (Image courtesy of Mark Hamann).[17]

A second test in vivo assay was also performed in order to discard any possibility of nonspecific stimulation, which can lead to false-positive result in forced swim test. This second test was the locomotor activity test. It provides a comprehensive assessment of the motor behavioral activity of the mice. These assessments are done in an open field Plexiglas chamber equipped with multiple photocell receptors and emitters which measure animal activity via a grid of invisible infrared light beams. Based on the results of the locomotor activity test (Figure 1.12), the possibility of nonspecific stimulant action, which would create false-positive in forced swim test, was ruled out.[17]

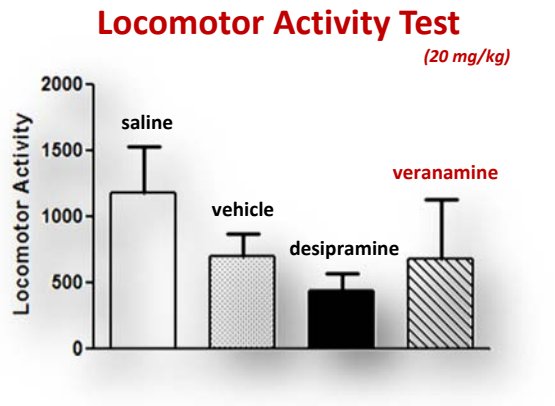
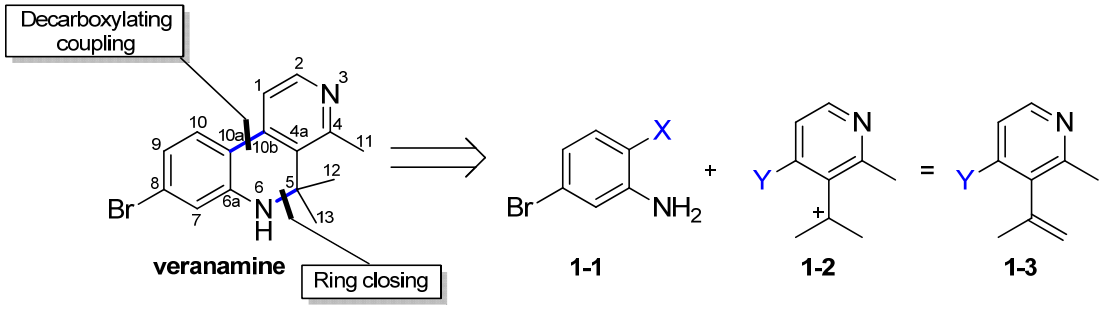


Figure 1.12 Veranamine locomotor activity test (image courtesy of Mark Hamann). [17]

In conclusion, results of the forced swim and locomotor activity tests have led Dr. Hamann to believe that veranamine represents a promising lead for the control of depression.[17] At this point, there are no additional biological results available and no indication of the mechanism of action of veranamine. Dr. Hamann's efforts to learn more about this compound have been stalled due to lack of availability of sufficient quantities of veranamine for further studies. The successful total synthesis described in the following sections has recently yielded enough synthetic veranamine to enable the resumption of further testing which is presently underway.

1.1.4 Previous Synthetic Studies toward Veranamine

Prior to our involvement in the project, Dr. Hamann and co-workers attempted to synthesize veranamine. They were ultimately unsuccessful and the details of their efforts remain unpublished.[13] Their approach is briefly summarized below (Scheme 1.1). They envisioned two obvious disconnections that essentially cleave the molecule in half. One of the disconnections is that between N6 and C5 and the other between C10a and C10b. The second of these, an aryl-aryl bond formation, seemed like an obvious choice because of the well-established utility of palladium in cross coupling for aryl-aryl bond formation.

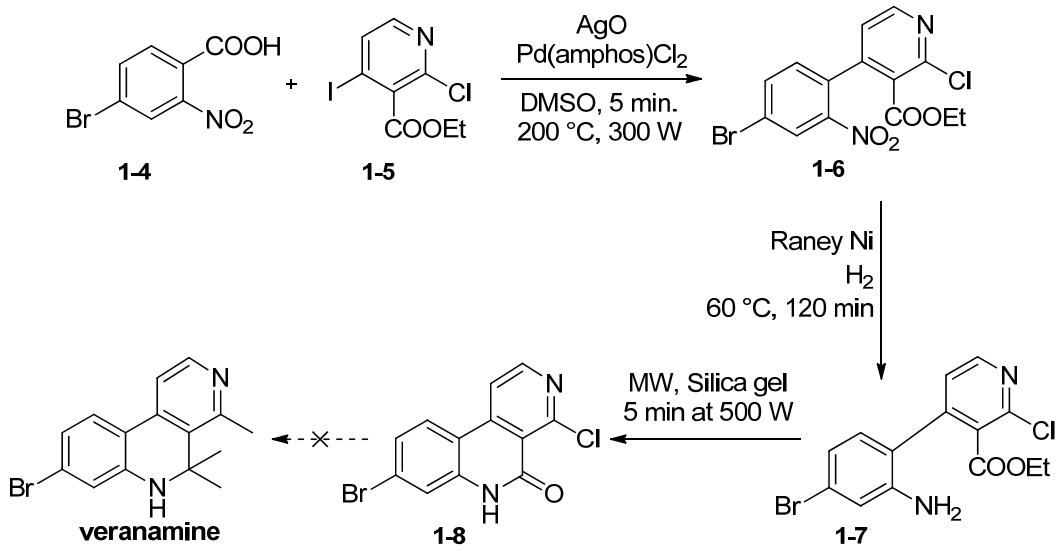


Scheme 1.1 Proposed retrosynthetic analysis by Hamann's research group.

Unfortunately, some of this retrosynthetic plan suffered from some limitations. First and foremost was the lack of availability of the pyridine substrate **1-3**. In general, 2,3,4-trisubstituted pyridines are not commercially available and not accessible using any of the most common published pyridine synthesis strategies. The second problem is the issue of selectivity in the proposed Pd-catalyzed cross coupling chemistry due to the presence of an aryl-Br in the natural product. Because of this second complication, Dr. Hamann decided to employ a unique cross-coupling approach termed 'decarboxylative coupling' that uses carboxylic acid (rather than an aryl halide) as a substrate. Decaboxylative Heck and Sonogashira reactions with Ar-COOH substrates have been reported.[20] In these cases, the coupling occurs regioselectively at the site of

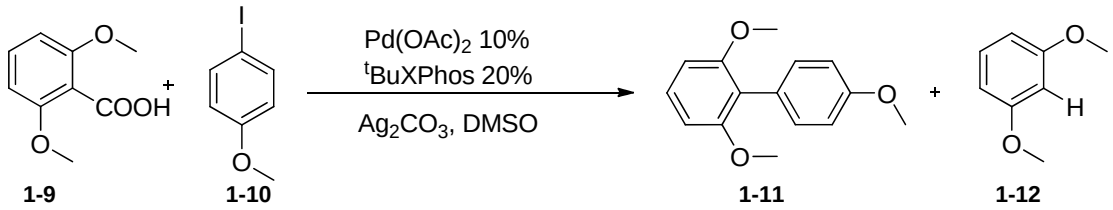
decarboxylation. Aryl carboxylic acids have also been coupled with aryl chlorides, bromides, and iodides.[21]

Dr. Hamann and co-workers investigated a model system for veranamine that began with one of the few commercially available 2,3,4 substituted pyridines, **1-5**, which is available from Sigma Aldrich® at a cost of $600 per gram. Their overall effort is summarized in Scheme 1.3.



Scheme 1.2 Summary of synthetic efforts in Dr. Hamann's research group.[13]

The first reaction is a Pd-catalyzed decarboxylative cross-coupling between an aryl-COOH and a heteroaryl iodide. This was closely related to work reported by Voutchkova *et al.* in 2006.[22] These authors developed a general procedure for Pd-catalyzed decarboxylative coupling of aromatic acids and aryl iodides as shown in Scheme 1.3.

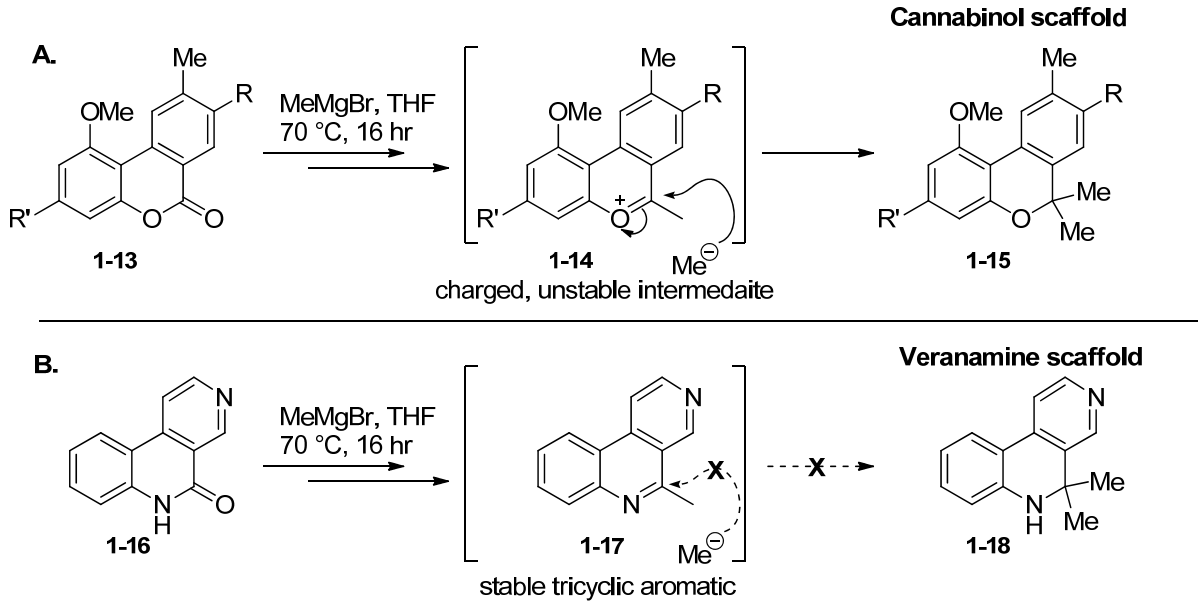


1-9 **1-10** **1-11** **1-12**

Scheme 1.3 Literature precedent for decarboxylating coupling of aromatic carboxylic acids and aryl iodides.[22]

In Dr. Hamann's reaction the reported conditions were modified slightly by using AgO instead of Ag_2CO_3. The reaction of **1-4** with **1-5** proceeded under Pd(amphos)Cl_2 catalysis to achieve a 70 % yield of compound **1-6** (Scheme 1.2). With **1-6** in hand the next step was a reduction of the aryl-nitro group to the corresponding aniline using hydrogen and Raney Ni. This successfully produced compound **1-7** in good yield. The third and final step was a silica gel mediated ring-closing reaction that assembled the tricyclic scaffold of veranamine. The procedure, using microwave irradiation on silica gel for 5 minutes, was adapted from a method reported by Pandey *et al.* from 2001.[23] Naphthyridinone **1-8** was successfully obtained.

At this stage the model studies arrived at a dead-end. The primary problem was installation of the geminal dimethyl group. An analogy can be drawn with previous syntheses of cannabinol as illustrated in Scheme 1.4 A.



Scheme 1.4 Comparison of cannabinol synthetic steps vs. veranamine model studies dead-end.

In the cannabinol system it was possible to introduce two methyl groups to a lactone using MeMgBr (Scheme 1.4A).[24] However, in the case of the analogous lactam (compound **1-16**) addition of a nucleophilic methyl (ie. MeMgBr) would yield a stable aromatic species after one methyl group was added (Scheme 1.4B). Compound **1-17** is unreactive towards a second methylation.

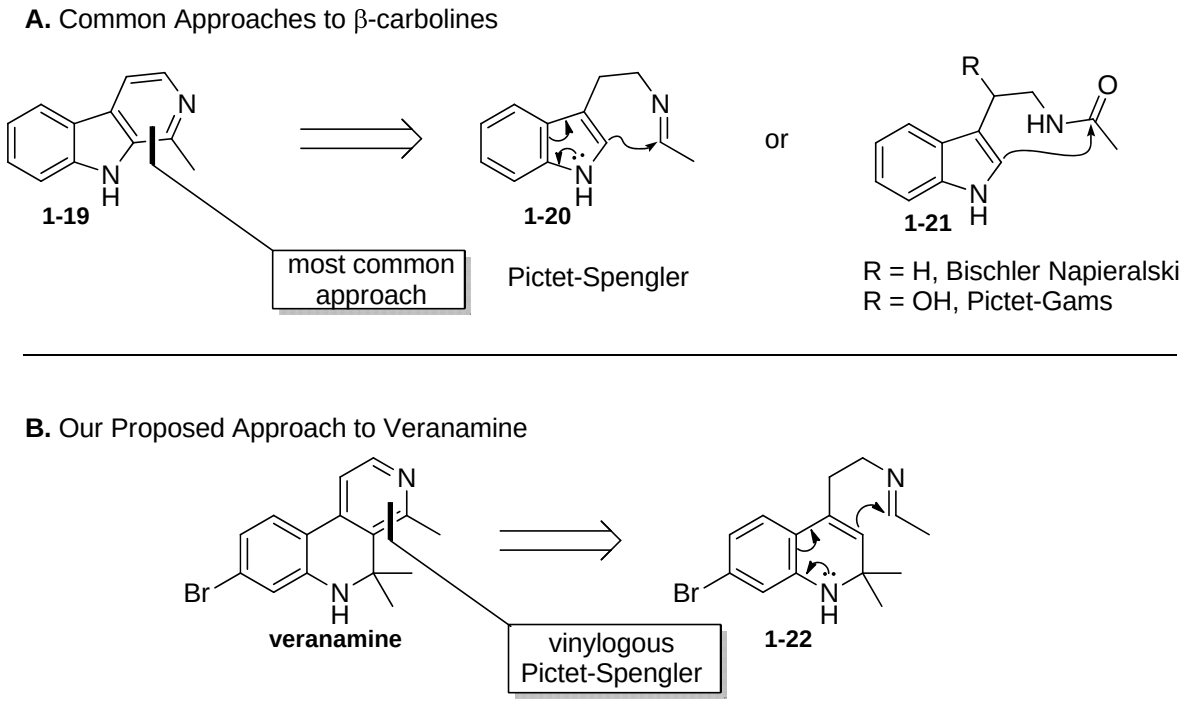
In 2012 Dr. Magolan was asked by Dr. Hamann to join the effort to prepare synthetic veranamine. Our subsequent work, culminating in a successful gram-scale synthesis, is detailed in the following sections.

1.2 Results and Discussion

1.2.1 Our Retrosynthetic Analysis of Veranamine

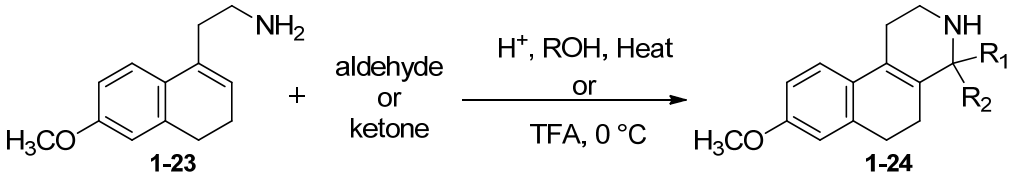
Due to the potent antidepressant activity demonstrated by veranamine and the challenges of obtaining bulk material from its natural source, this compound is a particularly interesting synthetic target. Multiple grams of synthetic veranamine were needed to continue its biological evaluation. In this work, we present the first total synthesis of the natural product veranamine. Several unsuccessful approaches will be described prior to our ultimately feasible synthetic route.

We initially employed an entirely different retrosynthetic strategy from that of Dr. Hamann described in the previous section. Our approach was based on the structural similarities between veranamine and β-carboline natural products. Both contain the synthetically daunting 2,3,4-trisubstituted pyridine moiety. Many β-carbolines have been previously synthesized by assembling this pyridine portion of the compound using a common disconnection that corresponds to Pictet-Spengler, Bischler Napieralski, or Pictet-Gams reactions (Scheme 1.5A).[25] We hypothesized that a vinylogous version of the Pictet-Spengler reaction could be employed to prepare the scaffold of veranamine (Scheme 1.5B).



Scheme 1.5 Retrosynthetic analysis inspired by β-carboline syntheses.

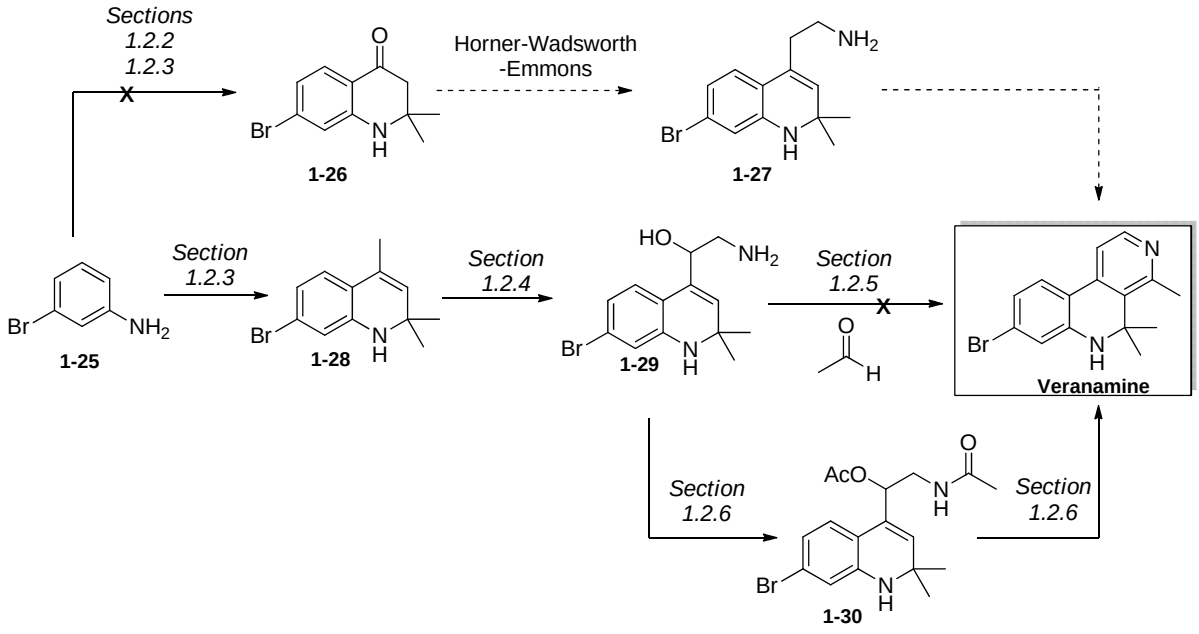
Our proposal was supported by one successful example of a previous vinylogous version of the Pictet-Spengler reaction reported in 2000 by Katzenellenbgen *et al.* (Scheme 1.6).[26] The authors prepared substituted hexahydrobenzo[*f*]isoquinolines **1-24** starting from amine **1-23** and various aldehydes and ketones.



Scheme 1.6 Literature report of a vinylogous Pictet-Spengler cyclization.[26]

Ultimately, the vinylogous Pictet-Spengler reaction would fail as an approach to veranamine (see Section 1.2.5) however it paved the way for a similar strategy that did prove successful. Scheme

1.7 can be thought of as a 'graphical table of contents' that summarizes the remainder of this chapter. This summary scheme of our overall efforts is intended to help the reader navigate through our synthetic efforts with a better sense of overall context.

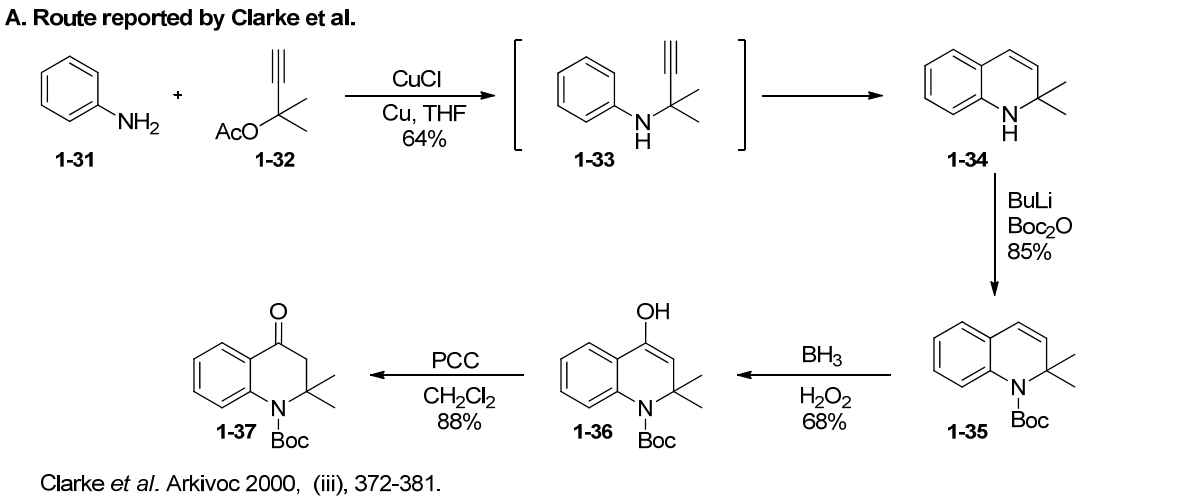


Scheme 1.7 Graphical summary of our overall synthetic efforts.

1.2.2 First Approach towards Dihydroquinolinone 1-26

Our ultimately untested initial proposal was the synthesis of amine **1-27** (Scheme 1.7) by elaboration of dihydroquinolinone **1-26** using Horner-Wadsworth-Emmons type chemistry. The first task thus became the preparation of the dihydroquinolinone **1-26**. This was done with the assistance of undergraduate student Sarah Vukelich. We attempted to follow a series of reactions previously reported by Clarke *et al.* in 2000 to generate tetrahydroquinolin-4-ones.[27] The work of Clarke *et al.* is summarized in Scheme 1.8A. Our analogous efforts are shown in Scheme 1.8B.

Clarke and co-workers started with commercially available aniline leading to the desired 1,2,3,4-tetrahydro-2,2-dimethylquinoli-4-one (**1-37**) in an overall yield of about 33 %. Our work, on the other hand, began using commercially available 3-bromoaniline with propargyl acetate (**1-40**) which was prepared from acetic anhydride (**1-38**) and propargyl alcohol (**1-39**) using catalytic amounts of $Mg(ClO_4)_2$.



Scheme 1.8 Synthesis of dihydroquinoline **1-37** by Clarke *et al.* (top) and our approach towards dihydroquinoline **1-41**.

In the presence of CuCl and refluxing THF, Clarke *et al.* obtained dihydroquinoline **1-34** in 64% yield. In our case we faced an unexpected regioselectivity problem. Upon ring closing, two isomers were formed, the desired product (**1-41**) and an undesired regioisomer (**1-42**). It was surprising and unfortunate that the sterically congested, and undesired, regioisomer was favored over the desired product. After considerable efforts to optimize this reaction (Table 1.2) the best ratio between **1-41** and **1-42** was an unfavorable 1 : 2.0. This ratio determined by ^{1}H NMR as illustrated in Figure 1.13.

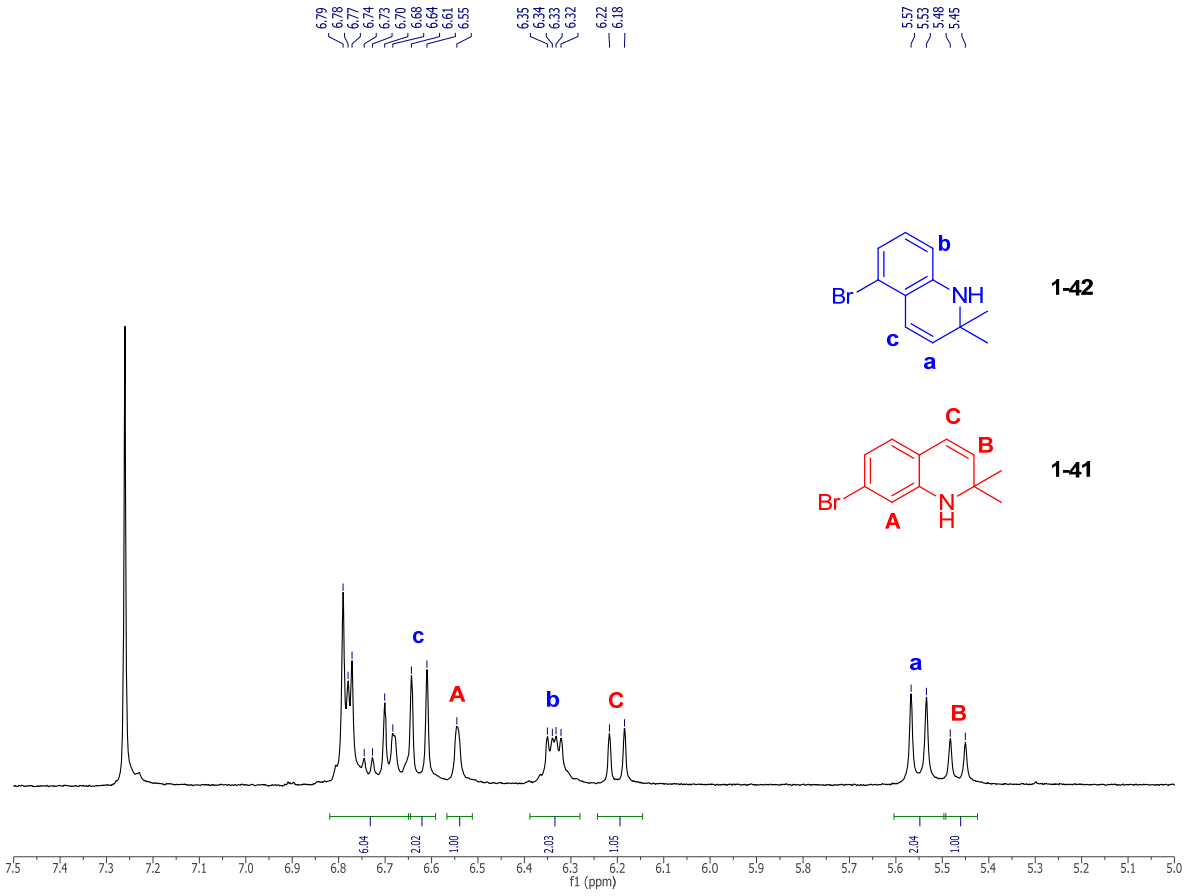
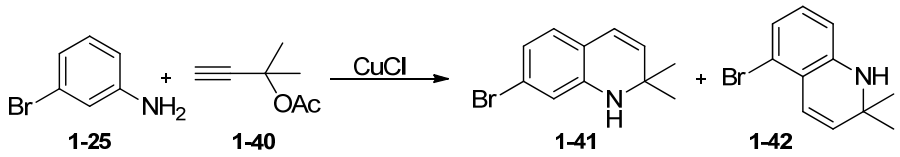


Figure 1.13 ^{1}H NMR spectrum of mixture of regioisomers **1-41** and **1-42**.

As observed by ^{1}H NMR, proton labeled **A** in the desired regioisomer **1-41** is expected to show up as the only singlet present in the spectrum found at 6.55 ppm and integrated to 1. With this assignment, integration of peaks **B** and **C** were assigned to the corresponding protons in the desired regioisomer **1-41**. Protons labeled **a** and **c** on the undesired regioisomer **1-42** are expected to be slightly more downfield due to the closer interaction with the electron withdrawing bromine atom. The doublet of doublets labeled **b** on the spectrum was assigned to the proton in the *para* position relative to the Br group in the undesired regioisomer **1-42** exhibiting both *ortho* and *meta* coupling to its neighboring protons giving the observed multiplicity.

Highlights from our optimization effort are reported in Table 1.2. The best conversion (based on ^{1}H NMR) was obtained by using refluxing THF for 4 hours (Entry 6, ratio of **1-41** : **1-42** = 1 : 2.04, 66 % combined yield of **1-41** and **1-42**).

Table 1.2 Optimization for the formation of **1-41**.



1-25 **1-40** **1-41** **1-42**

Entry	A (equiv)	B (equiv)	CuCl (equiv)	Solvent	Temp (°C)	Time (hr)	Ratio based on ^{1}H NMR (1-41 : 1-42)
1	1.2	1	1	THF	25	16	No rxn
2	2	1	1	THF	25	16	1 : 2.56
3	2	1	1	DCM	25	16	1 : 2.84
4	2	1	1	Ether	25	16	No rxn
5	2	1	1	THF	25	16	No rxn
6*	2	1	1	THF	Reflux	4	1 : 2.04
7*	10	1	0.2	THF	Reflux	4	1 : 2.09

Oddly the major regioisomer (compound **1-42**, Table 1.2) is the more sterically congested isomer of the two products formed. We hypothesize that the explanation for this selectivity is a

coordination between the aryl-Br and the copper catalyst which directs the alkyne to its preferred reactive site (Figure 1.14).

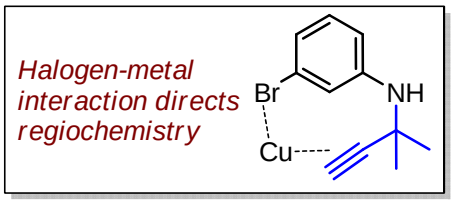
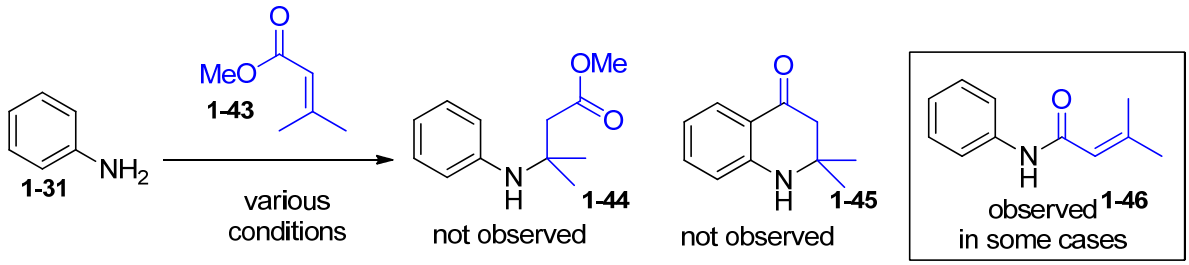


Figure 1.14 Proposed halogen-metal interaction.

The observation that the above reaction yielded an unfavorable ratio, along with the fact that the two regioisomeric products were inseparable by column chromatography in our hands caused us to reconsider this synthetic strategy. Ultimately the synthesis of **1-26** was not successful. However, before the effort was abandoned we attempted one other approach as described in the next section.

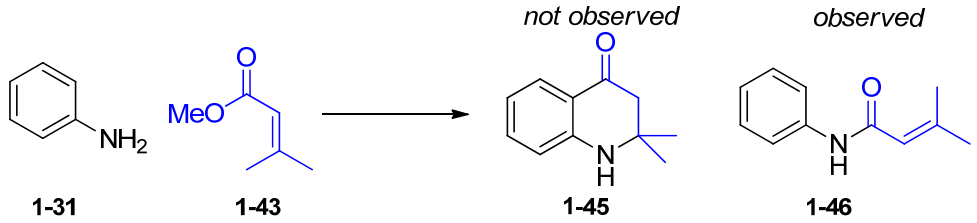
1.2.3 Second Approach towards Dihydroquinolinone 1-26

Inspired by the work of Azizi *et al.* in 2004,[28] we attempted an aza-Michael addition of aniline to dimethylacrylate **1-26** as illustrated in Scheme 1.9. Our goal was to produce either the ester **1-44** or the quinolinone **1-45** directly in one step. Table 1.3 lists the conditions used in our attempted reactions. In no case was formation of either of the desired products observed. In some cases formation of amide **1-46** was observed.



Scheme 1.9 Attempted approach to compound **1-46**.

Table 1.3 Ineffective conditions to obtain compound **1-46**.



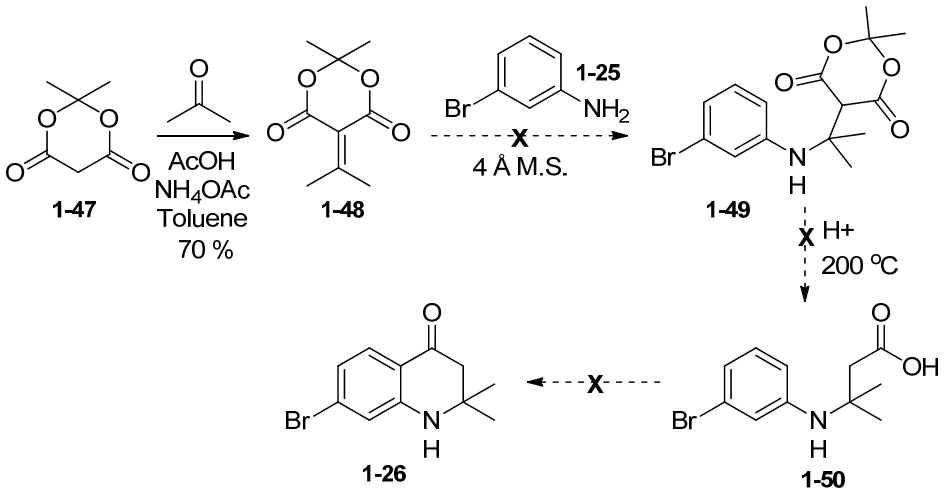
Entry	Catalyst	Solvent	Time (hr)	Temp (°C)	Results by ^{1}H NMR
1	----	AcOH	16	70	SM
2	$Yb(OTf)_3$	Toluene	16	120	SM
3	$BF_3 \cdot OEt_2$ (0.5 eq)	Toluene	8	r.t.	SM
4	$BF_3 \cdot OEt_2$ (0.5eq)	Toluene	2	120	SM
5	$BF_3 \cdot OEt_2$ (0.5 eq)	Toluene	6	120	Decomposition
6	NaH (1.5eq)	THF	16	160	Decomposition
7	HBr (excess)	1,4-dioxane	16	Reflux	SM + **1-46**
8	P_2O_5 (0.7eq)	$MeSO_3H$	16	90	**1-46**
9	Mont K-10	Solvent free	0.5	160	SM
10	Mont KSF	Solvent free	0.5	160	SM
11	Mont K-30	Solvent free	0.5	160	SM
12	Ti-Mont	Solvent free	0.5	160	SM + **1-46**
13	Ti-Mont	Solvent free	1	160	SM + **1-46**
14	Ti-Mont	Solvent free	0.5	200	SM + **1-46**
15	Ti-Mont	Solvent free	1	200	SM + **1-46**

*SM = starting material

First, we tried acetic acid to promote an acid catalyzed cycloaddition (Entry 1, Table 1.3). After 16 hours of heating the reaction at 70 °C only starting material was recovered. Lewis acids $Yb(OTf)_3$ and $BF_3 \cdot OEt_2$ (Entries 2-5), under various conditions, were applied but no formation of

desired product was achieved. The use of a strong base (NaH, Entry 6) and strong acid (HBr, Entry 7) were also not fruitful. The formation of amide **1-46** was observed under HBr conditions. This compound was also produced when P_2O_5 in methanesulfonic acid was employed (Entry 8). Montmorillonite clay catalysts K-10, KSF and K-30 were also employed under solvent-free microwave irradiation conditions. The use of acidic clays under these conditions has been recently found to promote various acid-catalyzed cycloadditions.[29] In all three cases (Entries 9-11) only the presence of starting material was observed. A different result was achieved with $TiCl_4$-doped montmorillonite (prepared from $TiCl_4$ and natural montmorillonite).[30] In this case, formation of amide **1-46** was observed and starting material was still present (Entries 12-15).

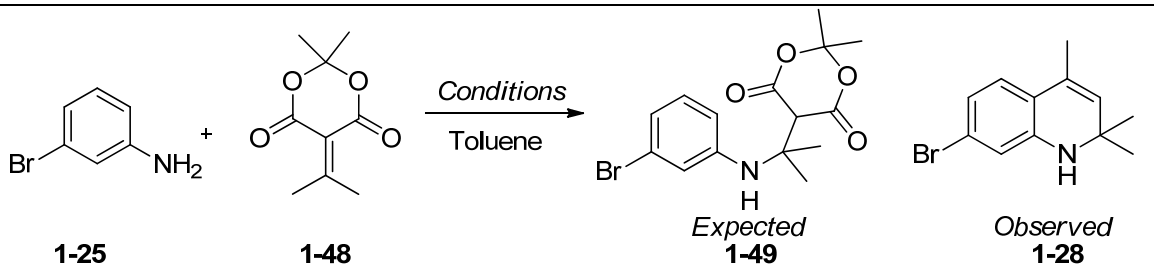
Formation of desired product was not observed in any of the previous attempts. We hypothesized that the steric hindrance created by the geminal dimethyl moiety made the alkene substrate (**1-43**, Table 1.3) unreactive towards nucleophilic 1,4-addition. At this point we attempted to prepare a more electronically reactive substrate (compound **1-48**, Scheme 1.10). To do this we made use of Meldrum's acid which was previously shown to make substituted dimethylindan-1-ones by Vogt *et al.* in 2001.[31] As shown in Scheme 1.10, our desired isopropylidene malonate **1-48** was made by condensation between Meldrum's acid **1-47** and acetone. We hoped that this compound would be more reactive to Michael addition yielding **1-49** which could undergo acid mediated hydrolysis and decarboxylation to yield compound **1-50** which would be a candidate for cyclization to dehydroquinolinone **1-26.**



Scheme 1.10 Proposed route towards dihydroquinolinone **1-26.**

The aldol condensation between Meldrum's acid and acetone went on to completion to obtain isopropylidene malonate **1-48** in 70% yield. In attempt to achieve compound **1-49**, compound **1-48** was treated with 3-bromoaniline **1-25** under varying conditions as highlighted on Table 1.4.

Table 1.4 Conditions for Michael addition of 3-bromoaniline to **1-25.**

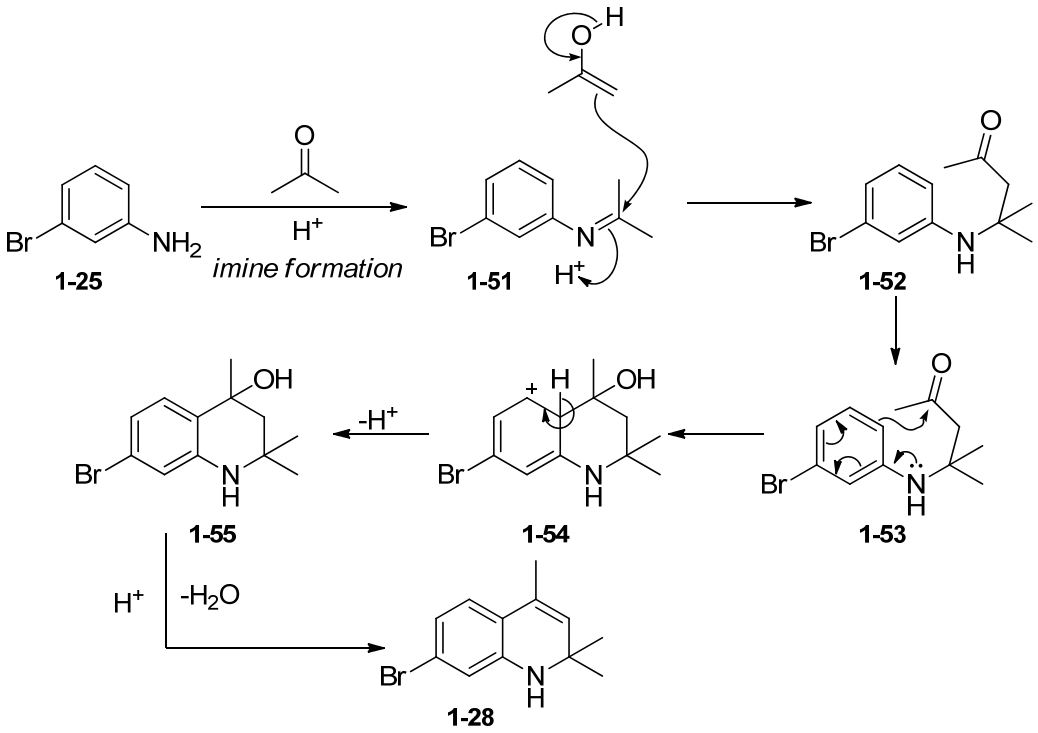


1-25 **1-48** **1-49** **1-28**

Entry	Catalyst	Temp (°C)	Time (hr)	Results
1	----	120	4	**1-25**
2	----	120	8	**1-25**
3	$Yb(OTf)_3$ (10 mol %)	120	8	**1-25** + **1-28**
4	$Yb(OTf)_3$ (10 mol %)	120	16	**1-25**
5	$BF_3 \cdot OEt_2$ (0.5 equiv)	120	8	**1-25** + **1-28**
6	$BF_3 \cdot OEt_2$ (1.0 equiv)	120	8	**1-28**
7*	Ti-Mont/SiO_2	180	30 mins	**1-28**

*****Solvent free conditions were used and irradiated in microwave.

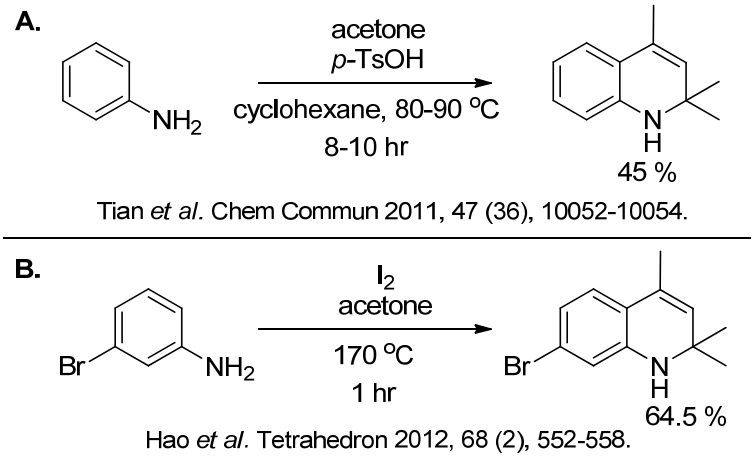
Under none of these conditions did we observe formation of our desired product **1-49**. Surprisingly, in a number of cases we observed the clean formation of dihydroquinoline **1-28** as the major product of the reaction. The formation of **1-28** can be explained by the decomposition of **1-48** into Meldrum's acid and acetone (via retro-aldol condensation) followed by a modified-Skraup reaction between acetone and 3-bromoaniline to yield dihydroquinoline **1-28**. Scheme 1.11 shows the proposed mechanism for this reaction which appears in the literature.[32] 3-bromoaniline and acetone undergo imine formation and the product (**1-51**) is attacked by the enol ether of acetone forming compound **1-52**. Intramolecular electrophilic aromatic substitution followed by dehydration leads to dihydroquinoline **1-28.** This unexpected product led us to redefine our path towards achieving a feasible route towards veranamine.



Scheme 1.11 Proposed mechanism for our modified-Skraup reaction.

1.2.4 Synthetic Efforts toward the Amino Alcohol Intermediate 1-29

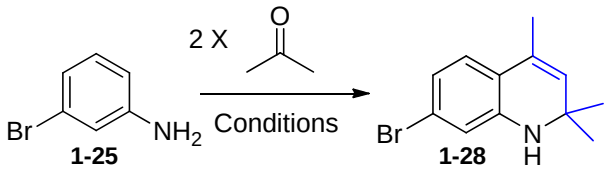
In 2011, Tian *et al.* published the use Iodine for catalyzing the modified Skraup reaction between aniline and acetone to prepare dihydroquinolines with a geminal dimethyl group located in analogous position to veranamine in a 45 % yield (Scheme 1.12A).[33] In 2012, Hao *et al.* reported the same reaction with a 3-bromo aniline substrate (Scheme 1.12B).[34]



Scheme 1.12 Previously reported conditions for the modified-Skraup reaction.

With the assistance of undergraduate student Stephen Holmbo we attempted this reaction and found that it required considerable optimization to achieve yields comparable to those reported in the literature. Table 1.5 lists the different conditions applied.

Table 1.5 Optimized conditions for modified Skraup reaction.



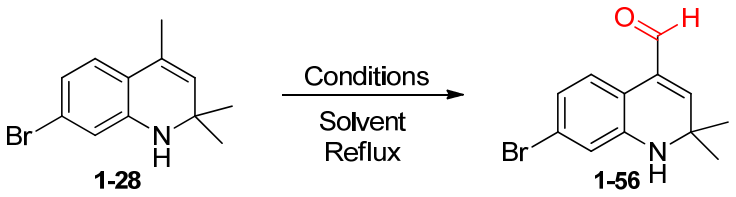
1-25 **1-28**

Entry	Solvent	Acetone (equiv)	Catalyst	Temp (°C)	Time	Yield (%)
1	Toluene	20	$Yb(OTf)_3$ (20 mol %)	120	4h	45
2	Toluene	20	$Yb(OTf)_3$ (5 mol %)	120	4 days	53
3	Toluene	20	I_2 (20 mol %)	120	4 days	56
4	Toluene	20	I_2 (10 mol %)	120	4 days	54
5	Acetone	----	I_2 (10 mol %)	70	5 days	78
6	Acetone	----	I_2 (10 mol %)	70	6 days	65
7	Acetone	----	I_2 (20 mol %)	70	5 days	63

As noted, the best conditions achieved were obtained when acetone (reagent and solvent) in the presence of I_2 was refluxed for 5 days. These conditions yielded 78 % of pure dihydroquinoline **1-28** after purification (Entry 5, Table 1.5). This reaction has been scaled up to >10 grams with comparable yields obtained.

Our next task toward the amino alcohol **1-29** (Scheme 1.7) was allylic oxidation of **1-28** with selenium dioxide. A screening of different solvents and conditions was undertaken as highlighted in Table 1.6.

Table 1.6 Optimization for the oxidation of allylic methyl group in dihydroquinoline **1-28.**



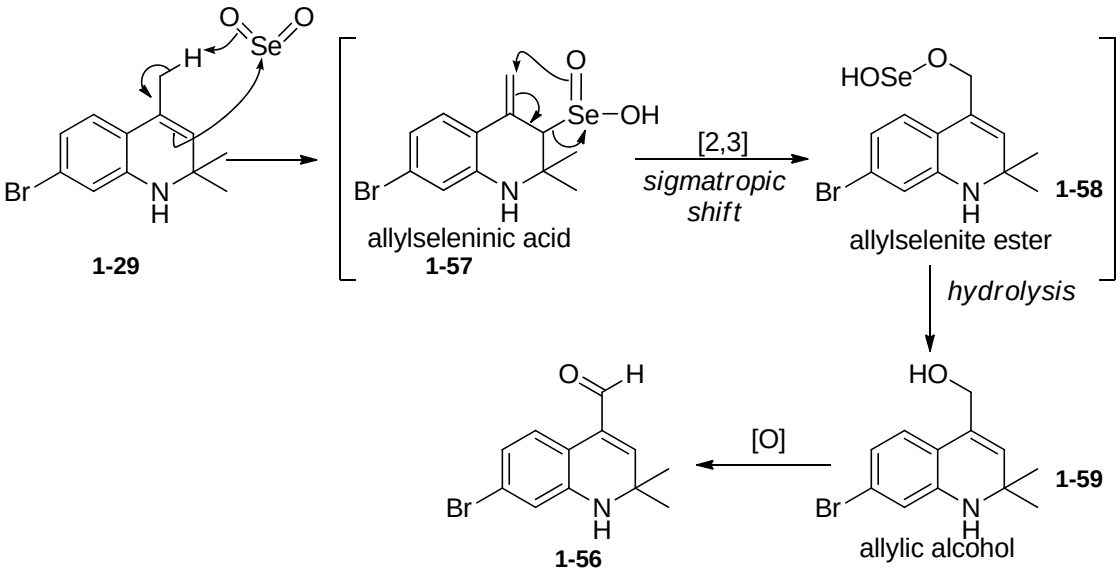
1-28 **1-56**

Entry	Catalyst (equiv)	Solvent	Time (hr)	Yield %
1	SeO_2 (1.0)	Benzene	16	20*
2	SeO_2 (2.0)	Benzene	4	49
3	SeO_2 (2.0)	1,4-dioxane	4	55
4	SeO_2 (2.0) H_2O (35 wt %)	1,4-dioxane	4	72
5	SeO_2 (2.0) H_2O (100 wt %)	1,4-dioxane	4	68
6	SeO_2 (2.0) H_2O (200 wt %)	1,4-dioxane	4	58
7	SeO_2 (2.0) H_2O (400 wt %)	1,4-dioxane	4	15

*Approximate yield estimated by analysis of ^{1}H NMR

A good yield was obtained by following the work of Batra *et al.*[35] (Entry 4, Table 1.6). Previous reports of this reaction often utilized benzene as their solvent[36] however in our case benzene was less effective than 1,4-dioxane. We also varied the amount of SeO_2 and found that 2.0 equiv was optimal. Following the precedent of Batra *et al.* we found that yields were improved by addition of H_2O. When 35 wt % of H_2O was used obtained a yield of 72 % of aldehyde **1-57** (Entry 4).

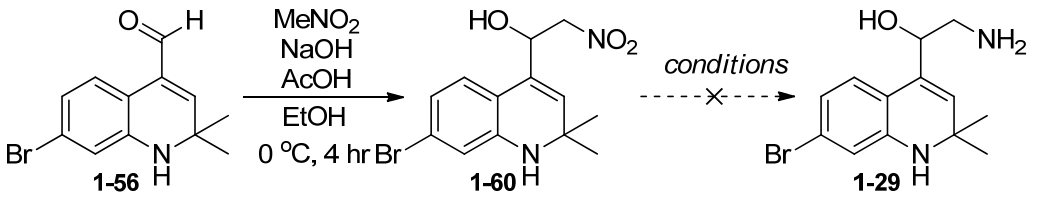
The accepted mechanism of selenium dioxide allylic oxidation is described in Scheme 1.13.[37] The formation of allylic seleninic acid is the first step followed by a [2,3]-sigmatropic shift. This in turn gives an allylselenite ester which is further hydrolyzed to the allylic alcohol. In-situ oxidation of the alcohol leads to the formation of aldehyde **1-56**.



Scheme 1.13 Allylic oxidation mechanism.

The next step in our synthetic route was to form the amino alcohol from aldehyde **1-56**. We began with a Henry nitro aldol strategy.[38] As illustrated in Table 1.7, the nitro aldol reaction between **1-56** and nitromethane proceeded successfully to yield nitro alcohol **1-60**. We attempted to reduce this compound under a variety of conditions to obtain the desired amino alcohol (**1-29**). Application of different reducing agents such as LAH, $NaBH_4$ as well as $Pd/C/NH_4HCO_2$ all yielded complex mixtures evident by ^1H NMR. A number of unproductive side reactions can be envisioned including eliminations and conjugate reductions. We did not further explore this reaction. Instead, we shifted our focus to an alternative approach involving a cyanohydrin intermediate.

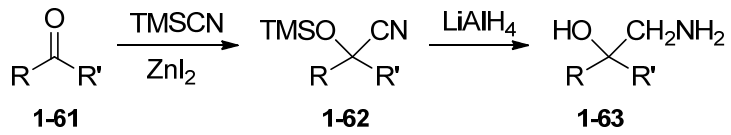
Table 1.7 Unsuccessful reduction of nitro group.



Entry	Reducing Agent	Solvent	Temp (°C)	Time (hr)	Results
1	LAH (1 equiv)	Ether	0	3	No product formed
2	$NaBH_4$ (25 equiv) $NiCl_2$ (3 equiv)	MeOH	0	1hr	No product formed
3	Pd/C (10 % by wt) NH_4HCO_2 (5 equiv)	THF:MeOH (1:1)	0	24 hr	No product formed

In 1974 Evans *et al.* reported the use of trimethylsilyl cyanide (TMSCN) as a reagent for the direct formation of trimethylsilyl cyanohydrin ethers from ketones with further reduction with lithium aluminum hydride to the corresponding β-aminomethyl alcohols (Scheme 1.14A).[39] Evans reported that to 1 equiv of ketone **(1-62)** and 1.1 equiv of TMSCN were applied along with catalytic amount of anhydrous ZnI_2 in a solvent free environment. The resulting cyanohydrin ether **(1-63**) was then added to a solution of $LiAlH_4$ in refluxing diethyl ether. In this manner, amino alcohols (**1-64**) were obtained in high yields. In 2008, Linn *et al.* reported the transformation of 2-fluorobenzaldehyde (**1-65**) to 2-amino-1-(2-fluorophenyl)ethanol (**1-66**) using a similar approach (Scheme 1.14B).[40]

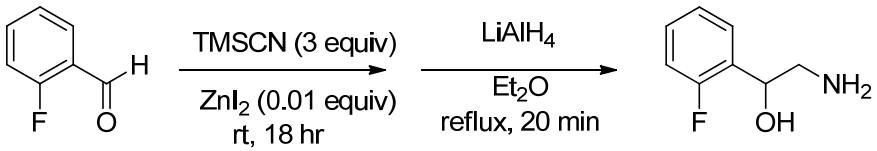
A.



1-61 **1-62** **1-63**

Evans *et al.* J Org Chem 1974, 39 (7), 914-917

B.



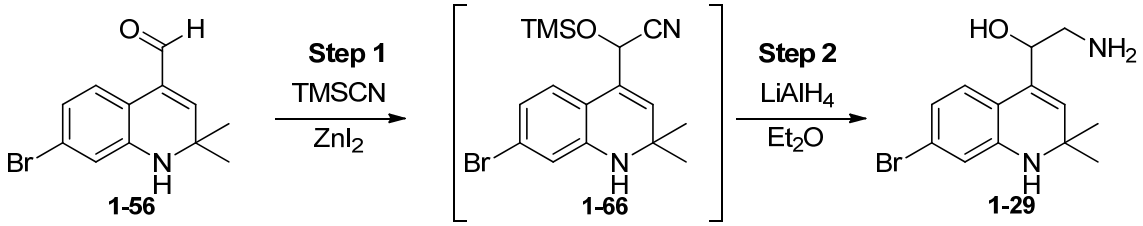
1-64 **1-65**

Linn, et al. WO 2008/024634 A1, 2008.

Scheme 1.14 Amino alcohol synthesis from ketones (top) or 2-amino-1-(2-fluorophenyl) ethanol (bottom).

Based on this literature, we investigated a series of reaction conditions to derive the amino alcohol **1-29** from aldehyde **1-56.** Table 1.8 highlights some of the conditions applied for the formation of TMS-protected cyanohydrin **1-66** as well as the reduction step of the -CN group to the corresponding amino-alcohol **1-29**.

Table 1.8 Optimization reactions for the preparation of amino-alcohol **1-29**.



Step 1.

Entry	TMSCN (equiv)	ZnI_2 (equiv)	Solvent	Temp (°C)	Time (hr)	Results
1	3	0.0125	Neat	r.t	12	Partial product formation (^{1}H NMR)
2	3	0.0125	Neat	r.t.	16	Substantial product formation (^{1}H NMR)
3	3	0.0125	Neat	r.t.	18	Complete reaction (with some impurities visible by ^{1}H NMR)
4	3	0.0125	$CHCl_3$	r.t.	18	Complete reaction (very clean crude ^{1}H NMR spectrum)

Step 2.

	$LiAlH_4$ (equiv)	Temp (°C)	Time (min)	Results
1	0.25	35	20	Complex mixture (^{1}H NMR)
2	1	0	30	Complex mixture (1H NMR)
3	2	0	30	Product + impurities; 72 % mass recovery.
4	1.5	0	60	Product + impurities; 80% mass recovery.
5	2	0	60	Product + impurities; 85% mass recovery.
6	2	0	90	Clean product (^{1}H NMR), 81% mass recovery
7	2	0	120	Clean product (^{1}H NMR), 97% mass recovery
8	2	0	180	Clean product (^{1}H NMR), 90% mass recovery

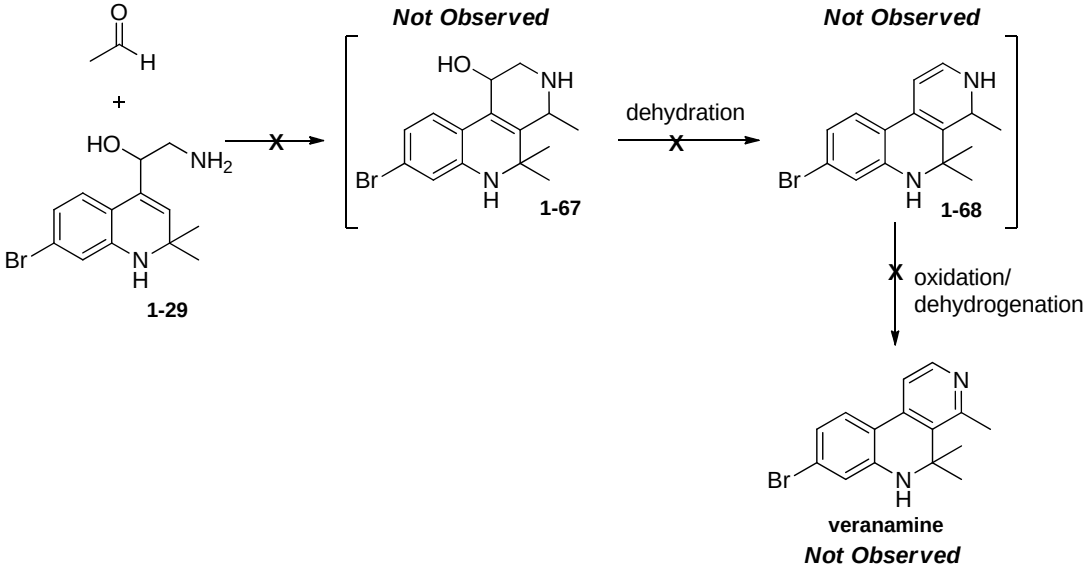
Starting with Step 1, formation of intermediate **1-66** was accomplished after 12 hours (Entry 1, Step 1) however small traces of starting material remained. Starting material was still present even after stirring for 16 hours (Entry 2, Step 1). After 18 hours, there was no sign of starting material present by TLC or ^{1}H NMR and the reaction was completed. Although no solvent was required, we found that the addition of small amount of solvent ($CHCl_3$, as employed by Evans)[39] helped for better stirring and product purity. Also, it was noted that even after leaving the reaction for 24 hours no decomposition of product or side reactions were observed. Without further purification, once the reaction was complete (after 18 hours), the product was warmed to 70 °C under the fumehood with flushing N_2 gas to facilitate the evaporation of excess TMSCN and solvent. The crude concentrate was then used for Step 2 in the reaction.

For step 2, employing the exact conditions reported by Evans' and Linn's groups yielded a complex mixture of products as judged by ^{1}H NMR analysis of our crude reaction (Entry 1, Step 2). After a thorough investigation our final conditions consisted of cooling the reaction to 0 °C followed by addition of 2 equiv of $LiAlH_4$ stirring for 2 hours in Et_2O. 97 % mass recovery of clean amino alcohol **1-29** was obtained (Entry 7).

Unfortunately attempts to purify amino-alcohol **1-29** via column chromatography (EtOAc/Hexanes or MeOH/DCM) and recrystallization were unsuccessful. The high polarity of this compound along with the apparent instability of the 1,2-amino-alcohol functionality appeared to make this compound prone to decomposition during chromatography. By ^{1}H NMR, the product even appeared to decompose within days upon storage in the freezer. Consequently we decided to continue onto the next steps with crude material **1-29** without further attempts to purify this compound. The end result of this investigation was a successful approach towards achieving high yields of amino-alcohol **1-29**.

1.2.5 Unsuccessful Vinylogous Pictet-Spengler Approach to Veranamine

Looking back to our proposed retrosynthetic analysis of veranamine (Scheme 1.5) a Pictet-Spengler condensation and cyclization of the previously synthesized amino-alcohol **1-29** and acetaldehyde would lead us to veranamine. From the original work of Pictet and Spengler in 1911,[41] this reaction has been extensively studied.[42] As previously mentioned, Katzenellenbogen *et al.* reported the first vinylogous Pictet-Spengler approach towards the preparation of hexahydrobenzo[f]isoquinolines (Scheme 1.6).[43] We envisioned a similar approach. Scheme 1.15 depicts the possible intermediates that we expected to see in this reaction. The Pictet-Spengler product **1-68** can undergo dehydration to **1-69** followed by dehydrogenation to yield veranamine. Due to the nature of the reactions (open to the air) we expected that under all conditions veranamine was likely to be formed.



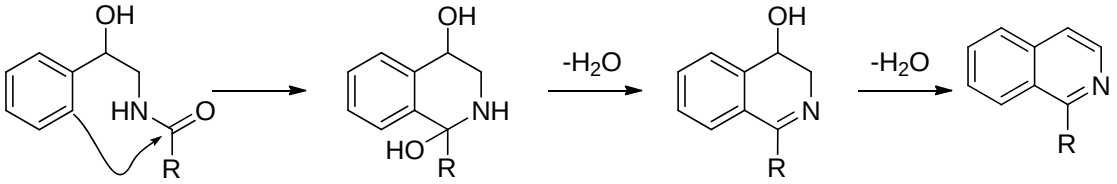
Scheme 1.15 Vinylogous Pictet-Spengler attempt towards veranamine.

We began by conducting a thorough screening of catalysts reported in literature for this cyclization.[42, 44] These were: TFA, P_2O_5, $POCl_3$, $BF_3 \bullet OEt_2$, HCl, H_2SO_4, PPA, Mont-KSF and Mont-K30.

Unfortunately, in no case were we able to observe intermediates **1-67**, **1-68**, or veranamine (via ^{1}H NMR analysis of crude reaction mixtures). In most cases, decomposition occurred. Interestingly, when our amino-alcohol compound **1-29** was treated with TFA, $POCl_3$, $BF_3{\cdot}OEt_2$ and P_2O_5 an unexpected product was observed which has not been fully characterized at this point. The compound was prone to decomposition on column chromatography and was not investigated further. At this point we were forced to abandon the Pictet-Spengler approach to veranamine.

1.2.6 Vinylogous Pictet-Gams Approach: Completion of Veranamine Synthesis

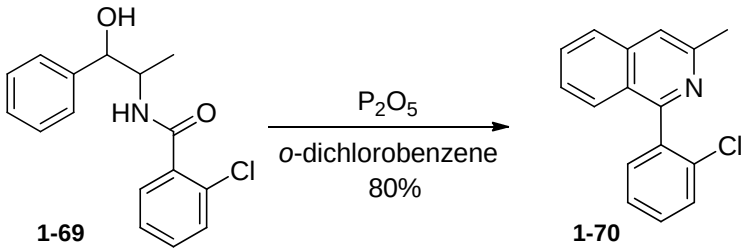
Looking back at Scheme 1.5, possible routes for the cyclization of β-carbolines were discussed. So far, with no success, we had explored the Pictet-Spengler approach. However, Bischler-Napieralski, and Pictet-Gams methods were also candidates for this reaction. In 1949, Hartung and Whaley reported the synthesis of isoquinoline derivatives by applying Pictet-Gams conditions.[45] The reaction proceeds by electrophilic aromatic substitution followed by two sequential dehydration reactions to yield isoquinoline (Scheme 1.16). Unlike the Pictet-Spengler reaction, this reaction yields a fully aromatic product without the need for an oxidation event.



Scheme 1.16 Literature studies on direct formation of isoquinoline intermediate styrylamide.[45]

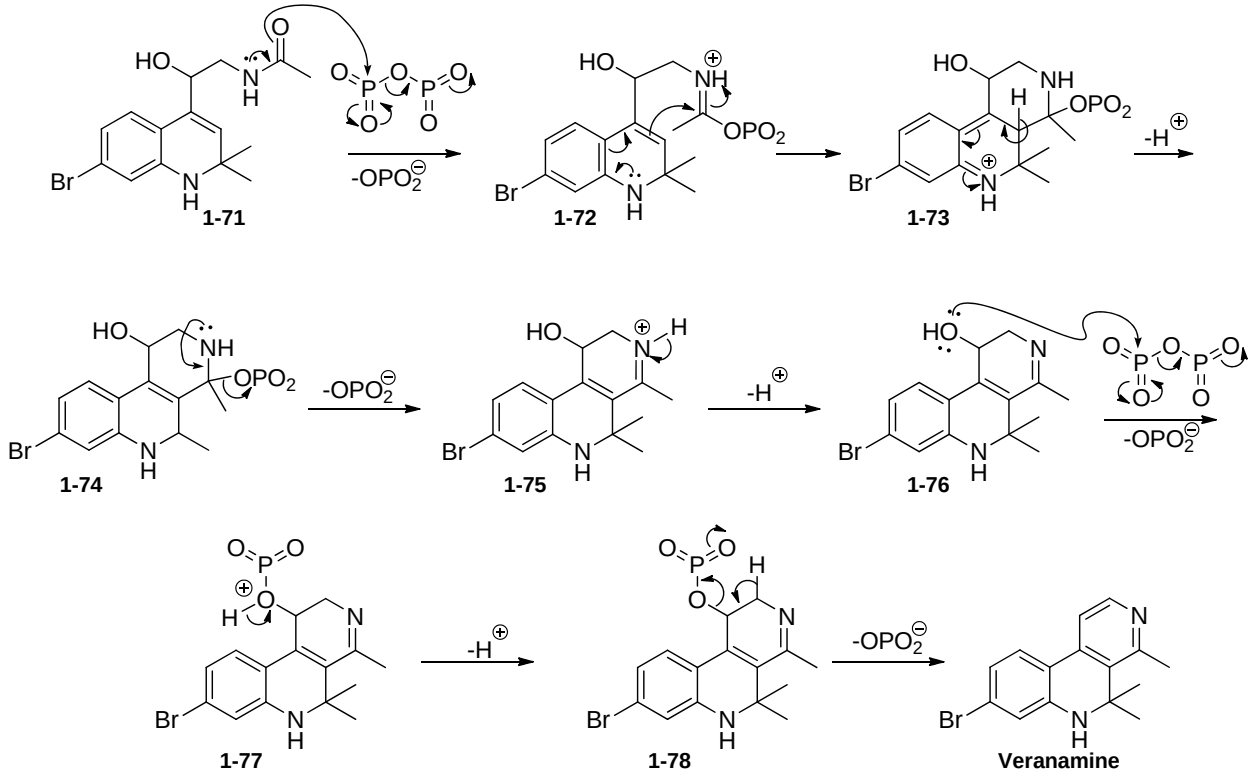
More recently, in 2002, Bornhop *et al.* applied this reaction in the preparation of isoquinoline **1-70** from compound **1-69** (Scheme 1.17). They achieved this by an overnight reflux of

compound **1-69** and P_2O_5 in *o*-dichlorobenzene with an 80 % yield after recrystallization.[46] Based on these examples, we decided to try this approach.



Scheme 1.17 Literature report on the formation of isoquinoline **1-70** via Pictet-Gams reaction.[46]

A potential mechanism for our proposed '*vinylogous'* Pictet-Gams reaction (based on the Pictet-Gams mechanism by Mundy *et al.)*[47] is presented in Scheme 1.18.

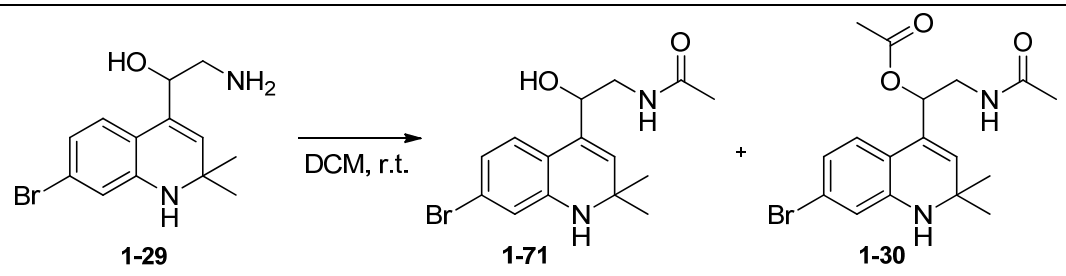


Scheme 1.18 Proposed vinylogous Pictet-Gams mechanism.

The acetyl group from the amide plays an important role in providing a strong electrophilic center upon reacting with P_2O_5 for the desired cyclization to take place. After dehydrogenation and aromatization veranamine is formed.

To prepare the Pictet-Gams substrate, we selectively acetylated the amine group in the presence of the secondary alcohol. Various conditions with Ac_2O allowed us to acetylate the amine with higher selectivity over the alcohol (Table 1.9). The best selectivity and yield was achieved by using 1.5 equiv of Ac_2O with 1.6 equiv of Et_3N (75% yield, Entry 5, Table 1.9).

Table 1.9. Conditions for mono-acetylation of amino-alcohol **1-29**.

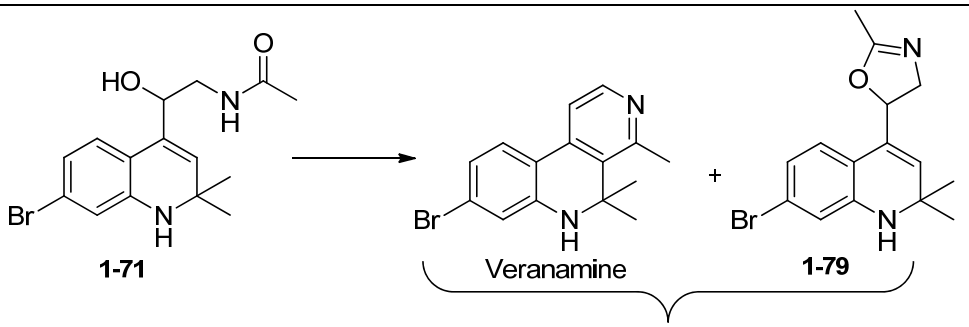


1-29 **1-71** **1-30**

Entry	Ac_2O (equiv)	Base (equiv)	Time	Ratio of 1-71 : 1-30 (by ^{1}H NMR)	% Yield of 1-71
1	2	Pyridine (2.0)	1 day	4:1	52
2	3	Pyridine (3.0)	1 day	3:1	48
3	2	Et3N (2.3)	2 hr	5:1	60
4	2	Et3N (2.3)	2.5 hr	6:1	64
5	1.5	Et3N (1.6)	2.5 hr	14:1	75

We explored the reactivity of common Pictet-Gams dehydrating agents $POCl_3$ and P_2O_5 towards mono-acetylated compound **1-71**. Table 1.10 illustrates the conditions applied. The use of $POCl_3$ failed to give the desired product (Entries 1 and 2). Only starting material was recovered in both cases. P_2O_5 was then applied under various conditions (Entries 3-6). *o*-Dichlorobenzene, nitrobenzene, toluene, and 1,4-dioxane were all used as solvents. Of these, only toluene exhibited formation of product veranamine.

Table 1.10 Conditions for Pictet-Gams reaction with mono-acetylated compound **1-71**.



Entry	Dehydrating Agent (equiv)	Solvent	Temp (°C)	Time (hr)	Results
1	$POCl_3$ (1)	DCM	0-r.t.	2	80 % mass recovery of **1-71**
2	$POCl_3$ (1)	Toluene	90	16	76 % mass recovery of **1-71**
3	P_2O_5 (5)	o-dichlorobenzene	Reflux	16	60 % mass recovery of **1-71**
4	P_2O_5 (5)	Nitrobenzene	Reflux	16	35 % mass recovery of **1-71**
5	P_2O_5 (5)	1,4-dioxane	Reflux	16	50 % mass recovery of **1-71**
6	P_2O_5 (5)	Toluene	Reflux	16	81 % mass recovery, veranamine : oxazoline **1-79** (1 : 4.5)
7	P_2O_5 (15)	Toluene	Reflux	16	59 % mass recovery, veranamine : oxazoline **1-79** (1 : 1.5)
8	P_2O_5 (15)	Toluene	Reflux	48	59 % mass recovery, veranamine : oxazoline **1-79** (1 : 8)
9	P_2O_5 (5)	Toluene	Reflux	48	65 % mass recovery, veranamine : oxazoline **1-79** (1 : 8)
10	P_2O_5 (5)	Toluene	Reflux	120	59 % mass recovery, veranamine : oxazoline **1-79** (1 : 3)

Veranamine was not the major product of this reaction. It was accompanied with unidentified minor impurities as well as one substantial oxazoline side product **1-79** with the same Rf as that of veranamine. We attempted to separate veranamine from oxazoline **1-79** using column

chromatography but we only achieved a mixture of both. In order to increase the ratio of veranamine to oxazoline **1-79**, we adjusted the equivalents of P_2O_5 used as well as the time. Instead of 5 equivalents we increased it up to 15. Among all of these conditions (Entries 7-10, Table 1.10) using 15 equivalents of P_2O_5 for 16 hours gave the best selectivity of veranamine to oxazoline **1-79** (1 : 1.5, Entry 7). We identified oxazoline **1-79** based on previous reports of oxalozine formation[42c, 48] as well as ^{1}H NMR data from our isolated mixture of veranamine and oxazoline **1-79** (Figure 1.15).

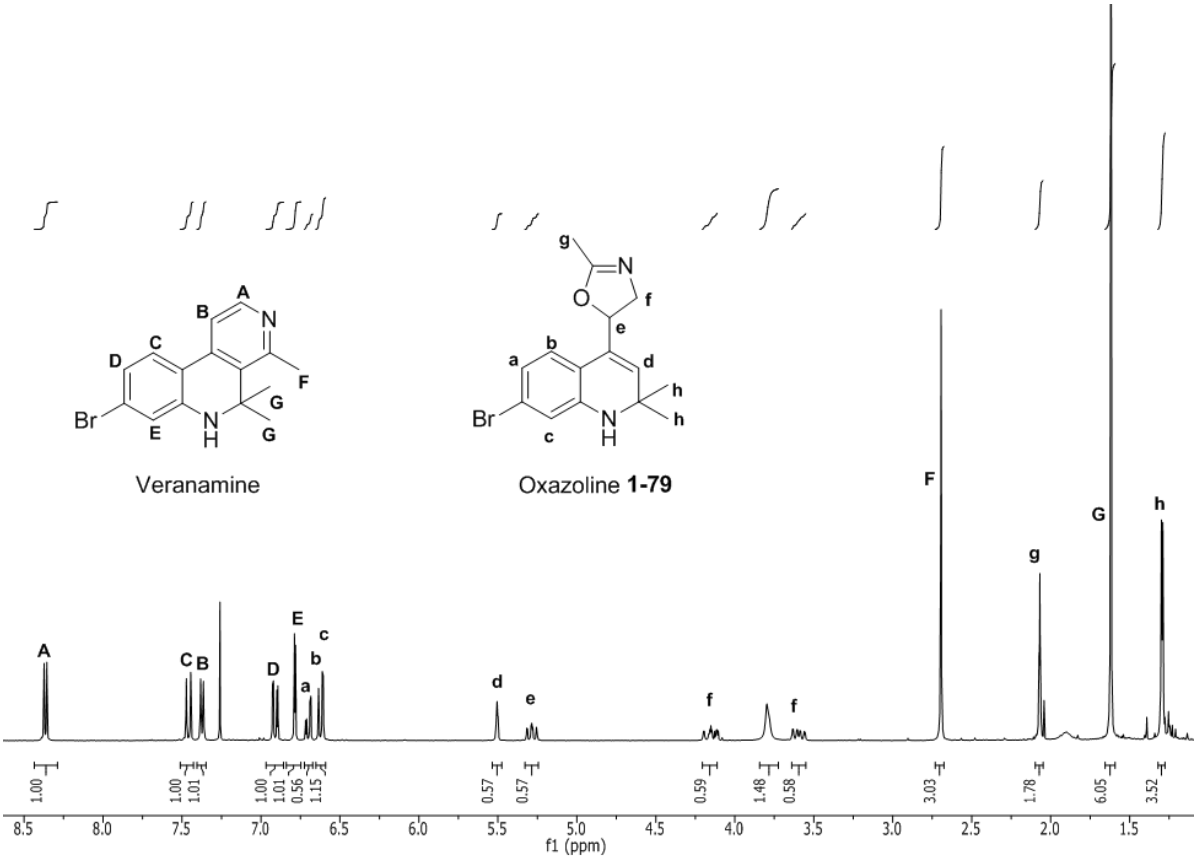
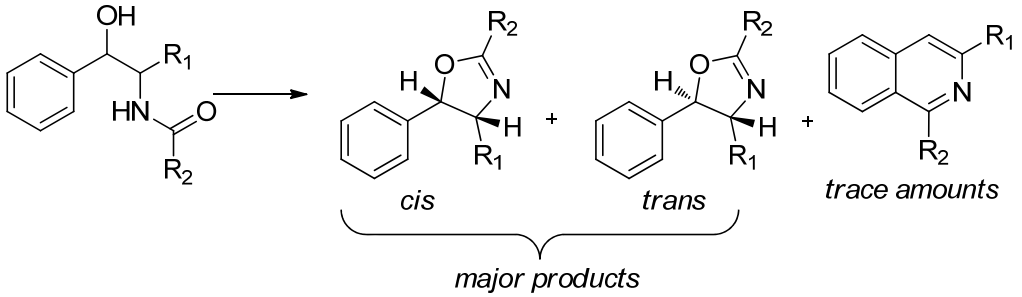


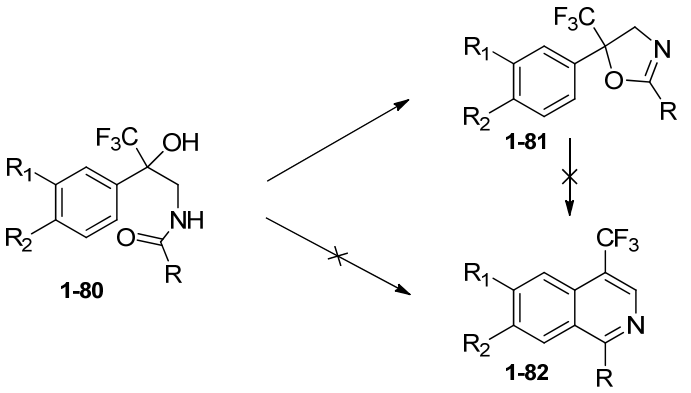
Figure 1.15 ^{1}H NMR of veranamine/oxazoline **1-79** mixture (in $CDCl_3$ at 300 MHz).

In 1979 Ardabilchi *et al.* characterized a similar oxazoline side product in Pictet-Gams reactions.[42c] In their work, a mixture of *–cis* and *–trans* oxazoline compounds with only trace amount of the desired isoquinoline (Scheme 1.19).



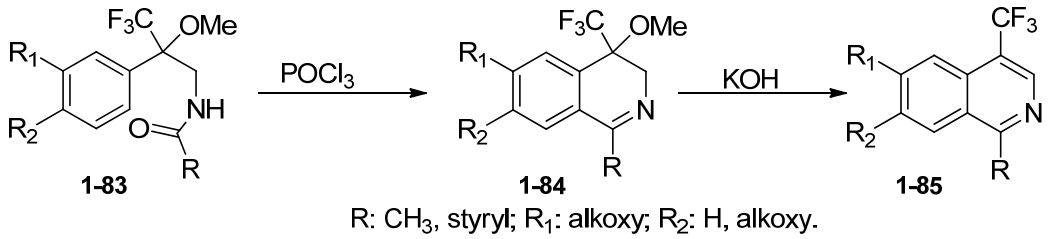
Scheme 1.19 Oxazoline as major product of Pictet-Gams reaction.

In 2000, Siming *et al.* also reported the formation of oxazolines when attempting to do a Pictet-Gams reaction.[48] In attempting to do a cyclization of arylethylamines (**1-80**) under Pictet-Gams conditions they afforded 2-oxazolines (**1-81**) instead of the expected isoquinolines (**1-82**, Scheme 1.20). Using spectroscopic and analytical data they proved that 2-oxazoline was the structure of the products. They attributed this unusual behavior to the presence of the trifluoromethyl group, which destabilizes the cationic transition state of the acid catalyzed elimination of the alcohol and instead leading to 2-oxazoline products.



Scheme 1.20 Literature report of cyclization of arylethylamine **1-80** affording 2-oxazolines **1-81** instead of isoquinoline **1-82**.[48]

Remarkably, a year after this observation in 2001, Siming reported the formation of isoquinolines **1-85** under the same conditions applied to previous approaches but using slightly different substrates.[49] Instead of the hydroxyl group present in arylehtylamines **1-80**, a methoxy group occupied this position (Scheme 1.21). Using Pictet-Gams conditions, formation of 3,4-dihydroisoquinolines **1-84** was achieved which were further aromatized to isoquinolines **1-85** by methanol elimination using a base-catalyzed approach.

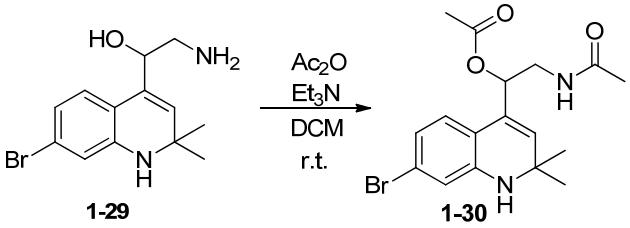


Scheme 1.21 Literature report of isoquinoline formation.[49]

Since we were not able to isolate veranamine from oxazoline, we did not focus on complete characterization of the oxazoline product at this time but instead on how to increase the ratio of veranamine to side-product by manipulating reaction conditions. Looking back at Table 1.9 where the conditions for mono-acetylation of amino alcohol **1-29** were discussed, we noticed that

di-acetylation of both the amine and alcohol was unavoidable. We therefore decided to try the Pictet-Gams reaction using the di-acetylated compound, which would be easier to achieve and perhaps provide better yields and selectivity for formation of veranamine over the oxazoline **1-79**. The conditions for getting the di-acetylated compound are highlighted on Table 1.11. 85 % yield was achieved when 2.7 equiv of Ac_2O and 3.5 equiv of Et_3N were added and remained stirring for 48 hours at room temperature (Entry 4, Table 1.11).

Table 1.11 Optimization for di-acetylation of amino alcohol **1-29**.



1-29 **1-30**

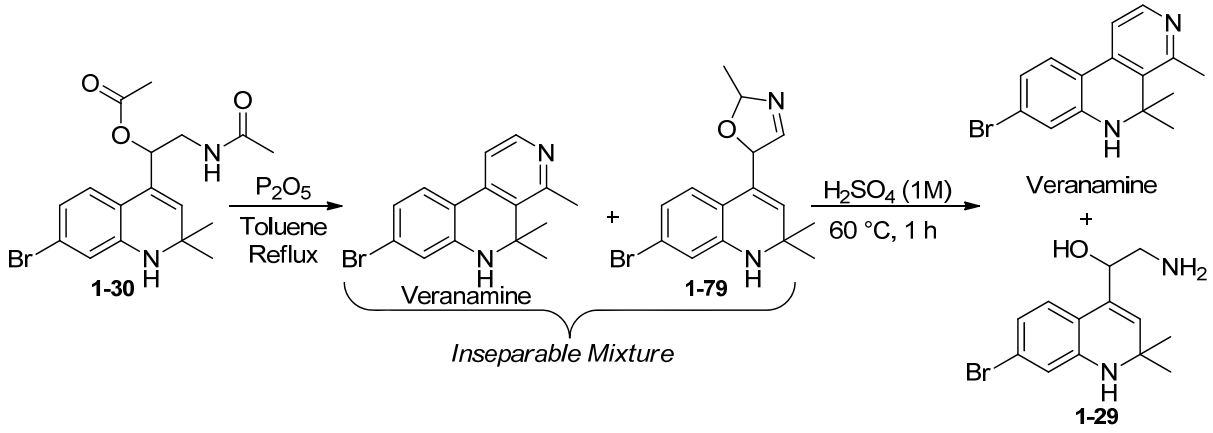
Entry	Ac_2O (equiv)	Et_3N (equiv)	Time (hr)	% Yield
1	2.5	3	3	43
2	2.7	3	24	52
3	2.7	3	48	80
4	2.7	3.5	48	85
5	5	5	24	73

With di-acetylated substrate **(1-30)** in hand, we attempted the vinylogous Pictet-Gams reaction again. This time, with just 5 equiv of P_2O_5, instead of 15 as previously used with mono-acetylated compound **1-71**, the selectivity increased in our favor from 1 : 1.5 to 1 : 0.7 of veranamine to oxazoline **1-79** (Entry 1, Table 1.12). The highest selectivity (1 : 0.17) was achieved when the reaction was left refluxing for four days, however the mass recovery decreased to 25 % (Entry 5).

As before, the oxazoline **1-79** byproduct could not be separated from veranamine by chromatography. Fortunately, oxazolines are labile to acid hydrolysis, which provided an avenue to

remove the unwanted byproduct. Treatment of the veranamine and oxazoline mixture with 1M H_2SO_4 for 1 hour at 60 °C, resulted in the appearance of two main spots on TLC; that of veranamine and a second spot below veranamine. After work-up, ^{1}H NMR indicated that oxazoline **1-79** hydrolyzed to amino alcohol **1-29**, while leaving veranamine intact. The amino alcohol **1-29** was easily separated from veranamine by chromatography although recovery of the amino alcohol was impractical because of the tendency of this compound to decompose on the column. Reducing the P_2O_5 equiv from 5 to 4 favored selectivity. Also, increasing the concentration of the reaction mixture (Entries 7-9) allowed for a maximum yield of 41% to be achieved (Entry 7).

Table 1.12 Pictet-Gams conditions for di-acetylated compound **1-30**.

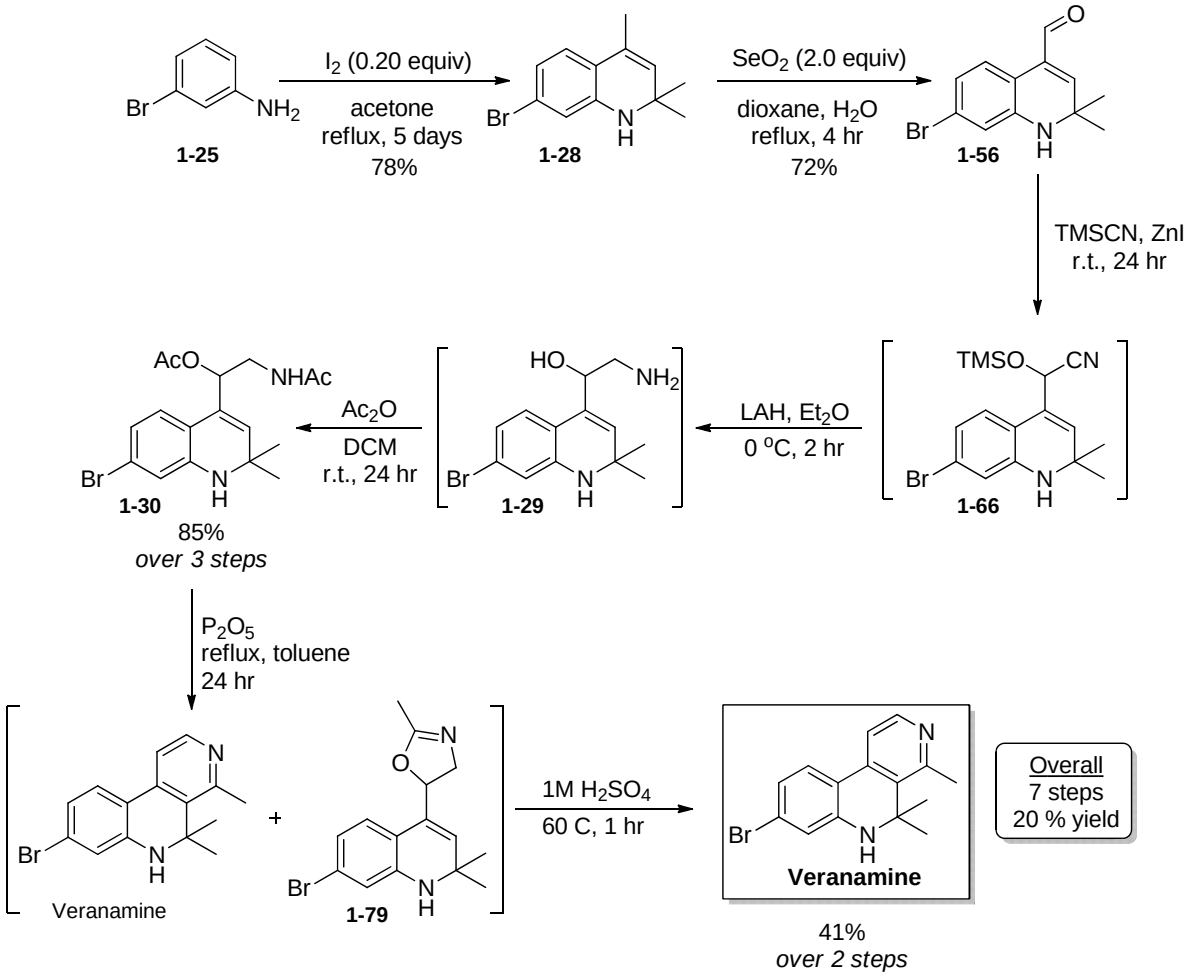


Entry	P_2O_5 (equiv)	Time (hr)	Mass Recovery (Veranamine : 1-79)	Veranamine Yield
1	5	16	75% (1 : 0.70)	34%
2	10	16	25% (1 : 0.71)	14%
3	5	24	83% (1 : 0.60)	38%
4	5	48	68% (1 : 2.14)	21%
5	5	96	25% (1 : 0.17)	18%
6	4	48	78% (1 : 1.8)	33%
7[a]	4	24	78% (1 : 0.35)	41%
8[b]	4	24	78% (1 : 0.35)	19 %
9[c]	4	24	56% (1 : 0.35)	16 %

[a]0.2 mL of toluene per mg of **1-37**. [b]0.4 mL of toluene per mg of **1-37**. [c]0.6 mL of toluene per mg of **1-37**.

1.2.7 Total Synthesis of Veranamine Summary

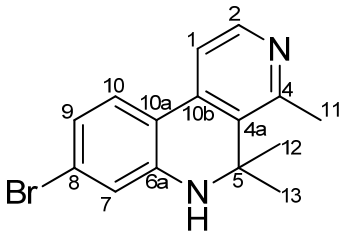
Overall we were able to complete the first synthesis of antidepressant marine alkaloid veranamine in a total of 7 steps and an overall yield of 20 % starting from commercially available 3-bromoaniline. The key step in our synthesis is a novel vinylogous Pictet-Gams reaction to assemble the dihydronaphthyridine scaffold of the natural product. The optimal method for the synthesis is highlighted in Scheme 1.22.



Scheme 1.22 Optimal method for the synthesis of veranamine.

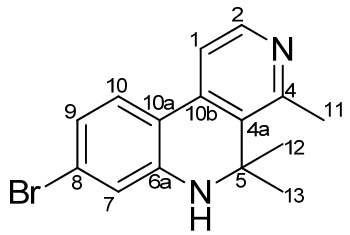
Both ^{13}C and ^{1}H NMR of synthetic veranamine were taken and compared to the natural spectra of veranamine (provided by Dr. Hamann). Tables 1.13 and 1.14 show the comparison of natural vs synthetic veranamine for ^{13}C and ^{1}H NMR data, respectively. In both cases minimal difference in ppm is observed.

Table 1.13 ^{13}C NMR comparison of natural vs synthetic veranamine.



Carbon #	Natural Veranamine [δ]	Synthetic Veranamine [δ]	Difference (ppm)
1	115.4	115.0	-0.4
2	144.8	145.9	1.1
4	153.1	153.7	0.6
4a	134.0	134.5	0.5
5	53.5	53.4	-0.1
6a	146.0	146.5	0.5
7	117.3	117.2	-0.1
8	125.2	124.6	-0.6
9	120.6	120.5	-0.1
10	125.9	125.6	-0.3
10a	116.5	116.9	0.4
10b	140.6	139.4	-1.2
11	24.1	24.7	0.6
12	27.9	28.0	0.1
13	27.9	28.0	0.1
^{13}C NMR in Methanol-d_4 (Ref: 47.600 ppm)			

Table 1.12 ^{1}H NMR comparison of natural vs synthetic veranamine.



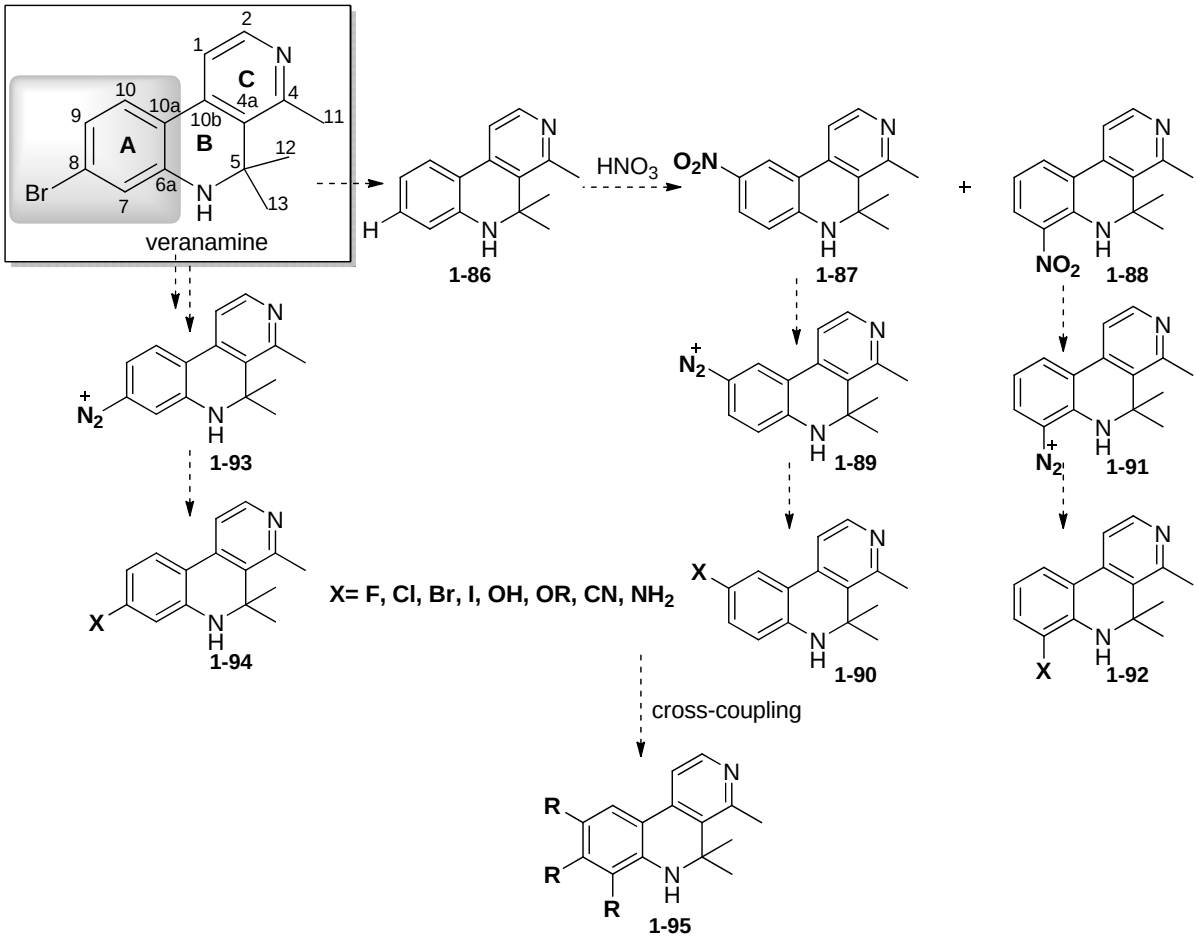
Proton #	Natural Veranamine [δ] (multi.)	Synthetic Veranamine [δ] (multi.)	Difference (ppm)
1	7.61 (d, J = 5.2 Hz)	7.53 (d, J = 5.3 Hz)	-0.08
2	8.25 (d, J = 5.2 Hz)	8.23 (d, J = 5.3 Hz)	-0.02
7	6.93 (d, J = 1.8 Hz)	6.91 (d, J = 1.9 Hz)	-0.02
9	6.88 (dd, J = 8.4, 1.8 Hz)	6.83 (dd, J = 8.4, 1.9 Hz)	-0.05
10	7.55 (d, J = 8.4 Hz)	7.51 (d, J = 8.4 Hz)	-0.04
11	2.7 (s)	2.67 (s)	-0.03
12	1.62 (s)	1.61 (s)	-0.01
13	1.62 (s)	1.61 (s)	-0.01
^{1}H NMR in Methanol-d_4 (Ref: 4.851 ppm)			

A total of 2 grams of veranamine has been synthesized and shipped to Hamann's Research Group for further biological studies. A mechanism of action of veranamine is still yet to be identified and a manuscript describing this work is forthcoming.

1.2.8 Synthesis of Veranamine Analogs

With veranamine in hand we begin to work on the synthetic development of analogues. Because of the potent bioactivity found in veranamine, we are interested in comprehensive SAR evaluation. Looking at the three rings that make up veranamine (Scheme 1.23) we began to investigate variation around ring A. Starting with veranamine itself, upon dehalogenation, nitration would allow us to obtain both nitrated compounds **1-87** and **1-88**. These can further be converted to the diazonium salts which can later be functionalized to achieve a library of compounds (**1-90**

and **1-92**) with different substituents at carbons 7 and 9. The same principle can be applied to veranamine itself. After formation of diazonium salts at carbon 8 of veranamine functionalization to the diazonium salt can take place and from here make a series compounds of general structure **1-94** which along with compounds **1-90** and **1-92** can be used for cross coupling reactions to make a library of compounds **1-95**.



Scheme 1.23 Overall scheme of variation around ring A of veranamine.

To date, we have worked on both halogen exchange and dehalogenation reactions of veranamine as shown on Figure 1.16 and described below.

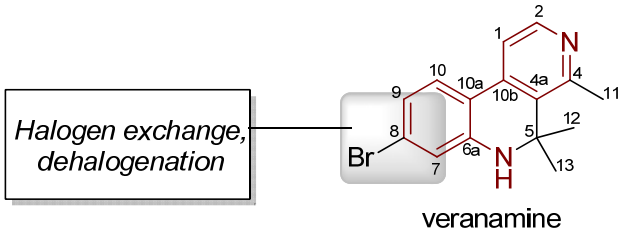
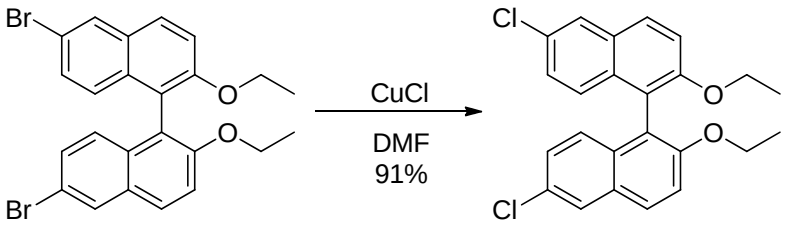


Figure 1.16 Veranamine sites of immediate functionalization.

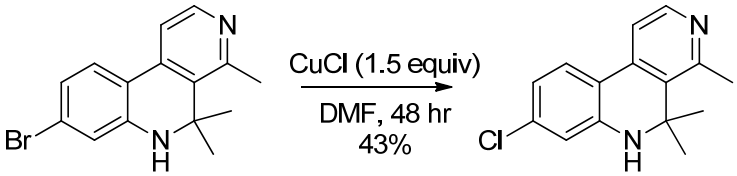
After trying several methods for halogen exchange reactions to obtain the chlorine analogue of veranamine, we arrived at the work by Lee *et al.*[50] In their work, the use of CuCl in DMF produced the desired product in 91 % yield (Scheme 1.24).



1-96 **1-97**

Scheme 1.24 Literature report of CuCl-catalyzed halogen exchange of substrate **1-96**.[50]

After treatment of veranamine with CuCl in DMF for 48 hours we achieved a 43 % yield of the chlorinated analogue becoming the first analogue of this natural compound (Scheme 1.25).

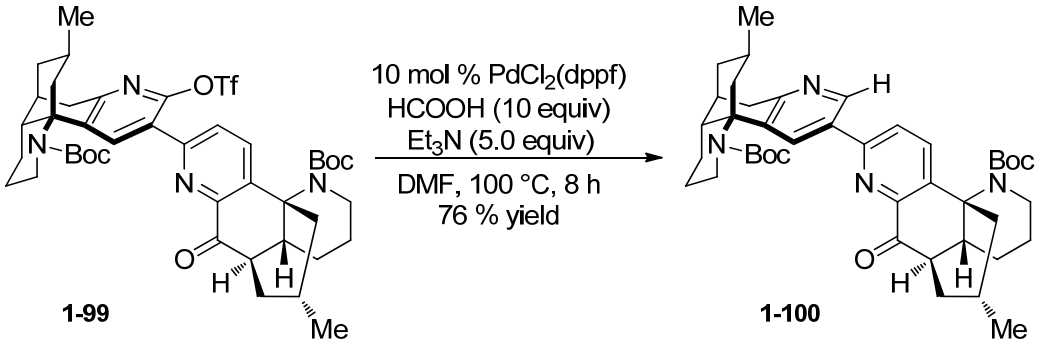


Veranamine **1-98**

Scheme 1.25 Halogen exchange reaction to achieve Cl-analogue **1-98**.

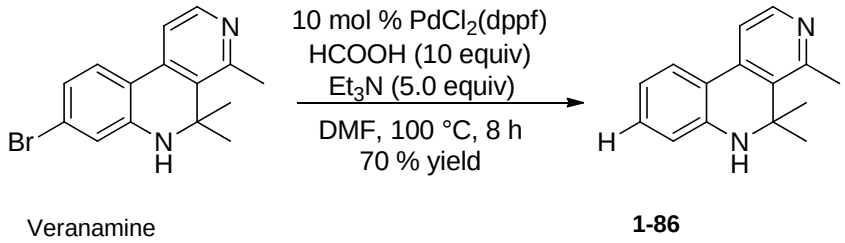
The dehalogenated analogue of veranamine was our next target. Several reagents that have previously been used for reductive dehalogenation of aromatic substrates were applied,[51]

including: Zn(s), Cu_2O, and Pd/C with $NaBH_4$. However none, of these provided the desired product. Instead we were inspired by the work done by Sarpong *et al.* in early 2013.[52] In their total synthesis of Complanadine B they employed Pd-catalyzed reductive conditions to an –OTf group from a pyridine ring in their substrate **1-99** (Scheme 1.26). They used 10 mol % of $PdCl_2$(dppf) along with 10 equivalents of formic acid and 5 equivalents of triethylamine. After heating for 8 hours in DMF at 100 °C they achieved a yield of 76 %.



Scheme 1.26 Literature report of Pd-catalyzed reduction conditions for removal of –OTf group.[52]

Using the same conditions as those applied by the Sarpong group, we were able to obtain dehalogenated analogue **1-86** in 85% yield (Scheme 1.27).



Veranamine **1-86**

Scheme 1.27 Dehalogenated analogue of veranamine.

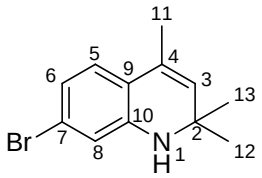
Overall, we have achieved two analogs of veranamine (**1-98** and **1-86**). Both analogues have been shipped to Dr. Hamann for further bioactivity analysis. This work will be continued on by other students to provide full analysis of veranamine's structural-activity relationships starting with ring A of veranamine, as discussed in Scheme 1.24, followed by rings B and C.

1.3 Chapter 1: Experimental Section

1.3.1 General Experimental

Melting points are uncorrected. Infrared spectra were obtained as thin films on ZnSe disks. NMR experiments were performed on 500 and 300 MHz instruments and samples were recorded in $CDCl_3$ (referenced to 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C) and Methanol-d_4 (referenced to 4.851 ppm for ^{1}H and 47.6 ppm for ^{13}C to match natural veranamine spectra). Coupling constants (J) are reported in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. All substrates, reagents, and solvents were obtained from commercial suppliers and used as purchased without further purification. Toluene, diethyl ether, *N,N*-dimethylformamide (DMF), and methylene chloride were dried over activated molecular sieves (4Å). All reactions were open to the atmosphere unless otherwise stated. Reaction progress was monitored by thin-layer chromatography on silica gel plates (60-F_{254}), visualized under UV light, and plates were developed using *p*-anisaldehyde or potassium permanganate stains. Flash chromatography was performed using silica gel (particle size 40-63 µm). MALDI-HRMS spectra of compounds were recorded on a Q-TOF mass spectrometer.

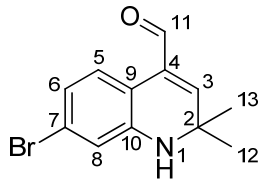
1.3.2 Experimental Section 1.2.2 - 1.2.6



1-28

7-bromo-2,2,4-trimethyl-1,2-dihydroquinoline (1-28): *m*-Bromoaniline **1-25** (10.0 g, 58.13 mmol), iodine (2.95 g, 11.63 mmol) and acetone (150 mL) were added into a 500 mL flask charged with stir

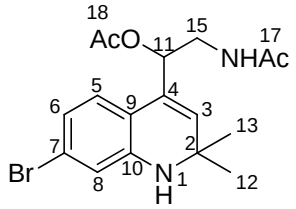
bar. The mixture was heated to reflux and stirred for 5 days. Addition of acetone was added to keep it at a constant volume throughout the reaction time period. The solvent removed *in vacuo* and the residue was subjected to flash column chromatography (EtOAc/Hexanes, gradient elution 5/95 to 30/70) to give 11.45 g of dihydroquinoline **1-28** as a yellow low-melting solid (45.41 mmol, 78 % yield). **R_f** (EtOAc/Hex 3:7) = 0.24; **MP** = 34-37 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 6.88-6.87 (d, *J* = 8.1 Hz, 1H, H^5), 6.73-6.71 (dd, *J* = 8.1, 1.9 Hz, 1H, H^6), 6.57 (d, *J* = 1.9 Hz, 1H, H^8), 5.31 (d, *J* = 1.5 Hz, 1H, H^3), 3.72 (s, 1H, NH), 1.95 (d, *J* = 1.5 Hz, 3H, H^{11}), 1.27 (s, 6H, $H^{12, 13}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 144.7, 128.7, 128.0, 125.1, 121.9, 120.5, 119.9, 115.4, 52.3, 31.3, 18.6; **FTIR** (ν_{max}, thin film, cm^{-1}): 3371, 3020, 2970, 2929, 1652, 737; **HRMS** (ESI) *m/z* calculated for $C_{12}H_{14}BrN$ ($[M+H]^+$) 252.0388, found 252.0382.



1-56

7-bromo-2,2-dimethyl-1,2-dihydroquinoline-4-carbaldehyde (1-56): To a solution of **1-28** (10.0 g, 39.66 mmol) in dioxane (250 mL), were added SeO_2 (4.39 g, 39.56 mmol, 2.0 equiv) and H_2O (3.5 mL). The mixture was heated to reflux and stirred for 4 hr. The reaction was cooled to room temp washed with H_2O (200mL) and extracted with EtOAc (2 x 200mL). The solvent was removed *in vacuo* and the resulting residue was subjected to flash column chromatography (EtOAc/Hexanes, gradient elution 5/95 to 30/70) to give **1-56** (7.64 g, 28.71 mmol, 72 % yield) as a dark orange solid. **R_f** (SiO_2, EtOAc/Hexanes 3:7) = 0.53; **MP** = 127 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 9.60 (s, 1H, H^{11}), 8.05 (d, *J* = 8.4 Hz, 1H, H^5), 6.80 (dd, *J* = 8.4, 2.0 Hz, 1H, H^6), 6.66 (d, *J* = 2.0 Hz, 1H, H^8), 6.28 (s, H^3), 3.74 (s, 1H, NH), 1.40 (s, 6H, $CH_3^{12, 13}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 191.9, 151.2, 144.4, 132.6, 127.5,

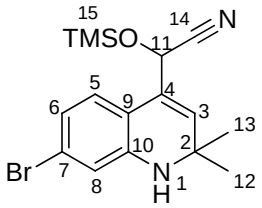
123.7, 120.9, 116.2, 114.3, 52.8, 29.9; **FTIR** (ν_{max}, thin film, cm^{-1}): 3308, 3060, 2962, 2918, 2848, 1680, 1630, 737; **HRMS** (ESI) *m/z* calculated for $C_{12}H_{12}BrNO$ ($[M+H]^+$) 266.0181, found 266.0173.



1-30

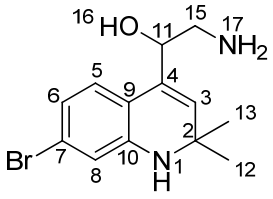
2-acetamido-1-(7-bromo-2,2-dimethyl-1,2-dihydroquinolin-4-yl)ethyl acetate (1-30): In an oven-dried 500 mL round-bottom flask, aldehyde **1-56** (1.00 g, 3.76 mmol) was dissolved in 20 mL of $CHCl_3$. TMSCN (1.41 mL, 11.28 mmol, 3 equiv) was added via syringe followed by addition of ZnI_2 (15.0 mg, 0.047 mmol, 0.0125 equiv). The reaction was left stirring under argon (balloon) for 24 hr at room temperature. Excess TMSCN and solvent were evaporated off by heating flask to 70 °C and flushing with N_2 (in fumehood) for approximately 30 minutes. [Caution: flammable liquid, highly toxic by inhalation and by skin absorption]. The crude product (**1-66**, R_f = 0.82, EtOAc/Hexanes 3:7) was then dissolved in 200 mL of anhydrous diethyl ether. The reaction was cooled to 0 °C and LAH (0.285 g, 7.52 mmol) was added in several portions over 5 minutes. The reaction was left stirring for 2 hr under argon. LAH was quenched by slow addition of H_2O (~ 10 mL). 2M NaOH (~100mL) was added followed by extraction with EtOAc (3 x 200 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo.* The crude amino alcohol **1-29** was obtained as a brown solid (1.11 g, Rf = baseline in 100% EtOAc) and was immediately dissolved in 50 mL of CH_2Cl_2 followed by addition of Ac_2O (1.48 mL, 15.62 mmol) and Et_3N (1.81 mL, 13.02 mmol) via syringe. The reaction was stirred for 24 hr at room temperature followed by aqueous workup (CH_2Cl_2, water, $NaHCO_3$, and brine). The organic layer was dried with Na_2SO_4 and solvent removed *in vacuo*. The residue was subjected to flash column chromatography (EtOAc/Hexanes, gradient

elution 20/80 to 90/10) to give **1-30** (1.23 g, 3.23 mmol, 85% yield over 3 steps) as an off-white solid. **R_f** (SiO_2, EtOAc) = 0.49; **MP** = 70-74 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.07 (d, *J* = 8.3 Hz, 1H, H^5), 6.70 (dd, *J* = 8.3, 2.0 Hz, 1H, H^6), 6.56 (d, *J* = 2.0 Hz, 1H, H^8), 5.94 (br, 1H, NH^1), 5.78 (ddd, *J* = 8.3, 3.8, 1.1 Hz, 1H, H^{11}), 5.52 (d, *J* = 1.1 Hz, 1H,H^3), 3.86 (J = 6.0 Hz, 1H, NH^{17}), 3.66 (ddd, *J* = 14.4, 6.2, 3.8 Hz, 1H, H^{15}), 3.35 (ddd, *J* = 14.4, 8.3, 6.0, 1H, H^{15}), 2.07 (s, 3H, $-CH_3^{18}$), 1.92 (s, 3H, $-CH_3^{17}$), 1.24 (s, 3H, $-CH_3^{12}$), 1.21 (s, 3H, $-CH_3^{13}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 170.4, 170.4, 145.0, 129.3, 129.2, 124.8, 122.5, 120.3, 116.9, 116.3, 71.4, 51.9, 43.1, 30.9, 30.6, 23.2, 21.3; **FTIR** (ν_{max}, thin film, cm^{-1}): 3295, 3080, 2964, 1730, 1651, 744; **HRMS** (ESI) *m/z* calculated for $C_{17}H_{21}BrN_2O_3$ ($[M+H]^+$) 381.0814, found 381.0810.



1-66

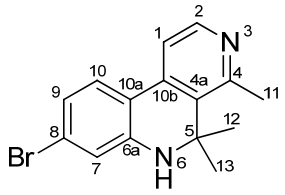
2-(7-bromo-2,2-dimethyl-1,2-dihydroquinolin-4-yl)-2-((trimethylsilyl)oxy)acetonitrile (1-67): R_f (SiO_2, EtOAc/Hex 3:7) = 0.82; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.3 Hz, 1H, H^5), 6.75 (dd, *J* = 8.3, 1.9 Hz, 1H, H^6), 6.62 (d, *J* = 1.9 Hz, 1H, H^8), 5.76 (d, *J* = 1.0 Hz, 1H, H^3), 5.26 (d, *J* = 1.0 Hz, 1H, H^{11}), 3.74 (s, 1H, NH^1), 1.33 (s, 3H, $-CH_3^{12}$), 1.32 (s, 3H, $-CH_3^{13}$), 0.22 (s, 9H, $-CH_3^{15}$).



1-29

2-amino-1-(7-bromo-2,2-dimethyl-1,2-dihydroquinolin-4-yl)ethanol: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8.3 Hz, 1H, H^5), 6.68 (dd, *J* = 8.3, 2.0 Hz, 1H, H^6), 6.59 (d, *J* = 2.0 Hz, 1H, H^8), 5.66 (d, *J* =

1.3 Hz, 1H, H^3), 4.58 (ddd, *J* = 6.8, 3.7, 1.3 Hz, 1H, H^{11}), 3.76 (s, 1H, NH^1), 2.97 (dd, *J* = 12.8, 3.7 Hz, 1H, H^{15}), 2.72 (dd, *J* = 12.8, 6.8 Hz, 1H, H^{15}), 2.33 (brs, 2H, NH_2), 1.29 (s, 3H, $-CH_3^{12}$), 1.25 (s, 3H, $-CH_3^{13}$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.2, 132.5, 128.0, 124.5, 122.1, 120.1, 117.9, 116.2, 70.2, 52.2, 46.4, 31.3, 30.8.

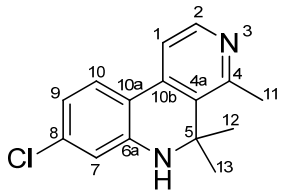


Veranamine

8-bromo-4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (Veranamine): In an oven dried 250 mL flask, **1-30** (0.652 g, 1.71 mmol) was added to 120 mL of anhydrous toluene. P_2O_5 (1.94 g, 6.84 mmol, 4.0 equiv) was added to this stirred solution and the resulting suspension was then heated to reflux for 24 hr under Ar (balloon). The reaction flask was cooled to 0 °C, ice-water was added slowly and all solids dissolved to yield a dark red mixture. The pH was slowly adjusted to pH > 7 using 2M NaOH. The reaction mixture extracted with EtOAc (4 X 300 mL). The combined organic layers were washed with brine solution and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield 0.50 g *(*76% mass recovery) of a dark yellow solid that contained mixture of **veranamine** and oxazoline **1-79** which could not be readily separated by column chromatography (ratio~1 : 0.35, identified by ^{1}H NMR). Without further purification, to the veranamine-oxazoline mixture, 1M H_2SO_4 (100 mL) was added and the reaction was stirred at 60 °C for 1 hr. [This process hydrolyses the oxazoline moiety of **1-79** to yield amino alcohol **1-29** which is readily separable from **veranamine**]. The reaction was then cooled down (ice bath) and the pH was adjusted to basic using 2M NaOH. The reaction was extracted with EtOAc (3 X 200 mL). The combined organic fractions

were washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo*. The resulting residue was subjected to column chromatography (EtOAc/Hexanes, gradient elution 20/80 to 90/10) to give **veranamine** (0.212 g, 0.701 mmol, 41% yield from **1-30**). **R_f** (SiO_2, EtOAc) = 0.49**; MP** = 191-193 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 8.37 (d, *J* = 5.3 Hz, 1H, H^2), 7.47 (d, *J* = 8.3 Hz, 1H, H^{10}), 7.38 (d, *J* = 5.3 Hz, 1H, H^1), 6.92 (dd, *J* = 8.3, 2.0 Hz, 1H, H^9), 6.79 (d, *J* = 2.0 Hz, 1H, H^9), 3.75 (s, 1H, NH^6), 2.70 (s, 3H, $-CH_3^{11}$), 1.63 (s, 6H, $-CH_3^{12, 13}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 154.3, 147.3, 145.5, 138.4, 133.9, 125.9, 124.7, 121.8, 118.1, 117.6, 115.1, 54.3, 29.8, 26.9; **^{1}H NMR** (500 MHz, Methanol-d_4, referenced to 4.851 ppm to match Dr. Hamann's natural spectrum) δ: 8.23 (d, *J* = 5.3 Hz, 1H, H^2), 7.53 (d, *J* = 6.4 Hz, 1H, H^1), 7.51 (d, *J* = 8.4 Hz, 1H, H^{10}), 6.91 (d, *J* = 2.0 Hz, 1H, H^7), 6.83 (dd, *J* = 8.4, 2.0 Hz, 1H, H^9), 2.67 (s, 3H, CH_3^{11}), 1.61 (s, 6H, $CH_3^{12, 13}$). **^{13}C NMR** (125 MHz, Methanol-d_4, referenced to 47.600 ppm to match Dr. Hamann's natural spectrum) δ: 153.7 , 146.5 , 145.9, 139.4, 134.5, 125.6, 124.6, 120.5, 117.2, 116.9, 115.0, 53.4, 28.0, 24.7; **FTIR** (ν_{max}, thin film, cm^{-1}): 3237, 3022, 2969, 1602, 790; **HRMS** (ESI) *m/z* calculated for $C_{15}H_{15}BrN_2$ ($[M+H]^+$) 303.0506, found 303.0497.

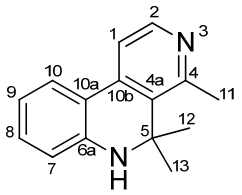
1.3.3 Experimental Section 1.2.8



1-98

8-chloro-4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (**1-98**): To a stirred solution of **veranamine** (0.150 g, 0.495 mmol) in dry DMF (3 mL), CuCl (73.5 mg, 0.713 mmol, 1.5 equiv) was added. The reaction mixture was heated at reflux under Ar for 48 hr. The solvent removed under pressure and the resulting residue was subjected to flash column chromatography (EtOAc/hexanes,

gradient elution 20/80 to 90/10) to give **1-98** (55.2 mg, 0.213 mmol, 43 % yield) as an amber-colored solid. **R_f** (SiO_2, EtOAc) = 0.50; **MP** = 189-192 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 8.37 (d, *J* = 5.3 Hz, 1H, H^2), 7.53 (d, *J* = 8.4 Hz, 1H, H^{10}), 7.37 (d, *J* = 5.3 Hz, 1H, H^1), 6.76 (dd, *J* = 8.4, 2.0 Hz, 1H, H^9), 6.62 (d, *J* = 2.0 Hz, 1H, H^7), 3.80 (s, 1H, NH^6), 2.70 (s, 3H, $-CH_3^{11}$), 1.62 (s, 6H, $-CH_3^{12, 13}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 154.3, 147.3, 145.3, 138.5, 136.5, 133.9, 125.8, 119.1, 117.7, 115.9, 114.7, 54.4, 29.9, 26.9; **FTIR** (ν_{max}, thin film, cm^{-1}): 3237, 2960, 2920, 1608, 799, 740; **HRMS** (ESI) *m/z* calculated for $C_{15}H_{15}ClN_2$ ($[M+H]^+$) 259.1002, found 259.0998.



1-86

4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (**1-86**): A 5 mL microwave vial was charged with $PdCl_2$(dppf) (29.93 mg, 0.0409 mmol, 0.10 equiv) sealed, and evacuated/backfilled with Ar (3X). Veranamine (124 mg, 0.409 mmol, 1 equiv) in DMF (3 mL) was added to the vial, followed by formic acid (10 equiv) and Et_3N (5 equiv). The stirred mixture was heated at 100 °C for 8 hr. The solvent was removed *in vacuo* and the crude mixture was purified by flash column chromatography (EtOAc/hexanes, gradient elution 20/80 to 90/10) to give **1-86** (78 mg, 0.348 mmol, 85 % yield) as a brown solid. **R_f** (SiO_2, EtOAc) = 0.391; MP: **143-144 °C; ^{1}H NMR** (500 MHz, $CDCl_3$) δ: 8.36 (d, *J* = 5.2 Hz, 1H, H^2), 7.61 (dd, *J* = 7.9, 1.2 Hz, 1H, H^{10}), 7.42 (d, *J* = 5.2 Hz, 1H, H^1), 7.16 (ddt, *J* = 7.9, 7.3, 1.2 Hz, 1H, H^8), 6.80 (tt, *J* = 7.9, 1.1 Hz, 1H, H^9), 6.61 (dd, *J* = 7.3, 1.1 Hz, 1H, H^7), 3.77 (s, 1H, NH^6), 2.70 (s, 3H, $-CH_3^{11}$), 1.61 (d, *J* = 1.0 Hz, 6H, $-CH_3^{12, 13}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 154.1, 147.2, 144.4, 139.3, 134.3, 130.9, 124.5, 119.2, 118.9, 115.3, 115.1, 54.1, 29.7, 26.9; **FTIR** (ν_{max}, thin film, cm^{-1}): 3248, 2961, 1612, 1597, 773; **HRMS** (ESI) *m/z* calculated for $C_{15}H_{16}N_2$ ($[M+H]^+$) 225.1392, found 225.1385.

Chapter 2: Aerobic Oxidation Using Clays

2.1 Introduction

2.1.1 Overall Goal of Our Project

Over the years, the fields of agrochemical and pharmaceutical research have been challenged by the restrains of time, expense, and waste production associated with multi-step synthesis of molecules. These challenges have led to the development of new methods to achieve structural complexity from simple substrates in fewer transformations.[53] Chemists have traditionally been concerned with increased selectivity and yield while variables such as cost, labor, and waste reduction have rarely been taken into account.[54] Traditionally, solution phase reactions are the method of choice for mechanistic elucidation, reactivity, selectivity, and yield but heterogeneous methods can often satisfy these criteria while reducing the environmental impact, expense, and workload.[55] One branch of research in Dr. Magolan's laboratory aims to target these overlooked issues by developing unique synthetic methods that rely on the use of heterogeneous reagents in a one-pot multi-step process. An important potential benefit of these methods is the facile separation of catalysts or reagents from reaction products by filtration.

2.1.2 Aerobic Dehydrogenation

Traditional methods for oxidation reactions require the use of expensive, corrosive, and toxic oxidants such as chromium (IV) and manganese complexes. Oxygen is among the cheapest and least polluting stoichiometric oxidants. It provides significant economic and environmental advantage as a green oxidant for chemical synthesis.[56] Besides being inexpensive and abundant, water is the only byproduct of oxidation with O_2. The implementation of catalysts in combination

with molecular oxygen represents an emerging alternative to traditional oxidation methods, which most commonly include stoichiometric amount of heavy metal reagents.[57] Despite the great benefits that molecular oxygen brings, little attention has been devoted to the development of heterogeneous catalysts for aerobic dehydrogenations to produce aromatic compounds. Some methodologies have been developed for catalytic aerobic dehydrogenation which use transition-metal catalysis and Pd chemistry.[58] Aromatic compounds are key components of numerous pharmaceuticals, commodity and electronic materials.[59] The development of new synthetic methods to access these scaffolds can offer great benefits to industry, medicinal chemistry, and drug discovery research. This chapter is focused on our recent to merge molecular oxygen with heterogeneous catalysts to access aromatic scaffolds via dehydrogenation chemistry.

2.1.3 Clays in Organic Chemistry

In the past decades, an increased awareness of the environmental impact of chemistry has led to an increasing focus on synthetic methods that are environmentally benign. Among these, clay catalysis has gained significant attraction.[60] Clays are inexpensive, easily available, recyclable, and non-toxic chemical substances with promising catalytic properties. Operational simplicity and time saved is often significant when compared to analogous homogeneous reactions. Due to their physical nature, clays absorb microwave radiation and can catalyze organic reactions on their surface under solvent-free conditions leading to reactions that are often faster and cleaner than homogenous solution-phase analogs.[60b]

Clays are naturally occurring, crystalline, layered silicates of fine particle size (<2 μm). Of the many known clay varieties, montmorillonite has been the most used in organic reactions.[61] This clay belongs to the family of 2:1 clays whose structure features an aluminosilicate layer formed by

sandwiching a single (Al, Mg, Fe) octahedral sheet between two tetrahedral sheets (Al, Si) leading to a repeating tetrahedral:octahedral:tetrahedral layers (Figure 2.1). The layers possess net negative charge which is neutralized by cations (Na^+, K^+, or Ca^{2+}) in the interlayer space. Clays exhibit both Brøsnted and Lewis acid properties. Brønsted acidity results from dissociation of protons from cation hydration spheres while the Lewis acidity are the result of exposed coordinated Al^{3+} ions substituting for Si^{4+} ions in the tetrahedral sheets.

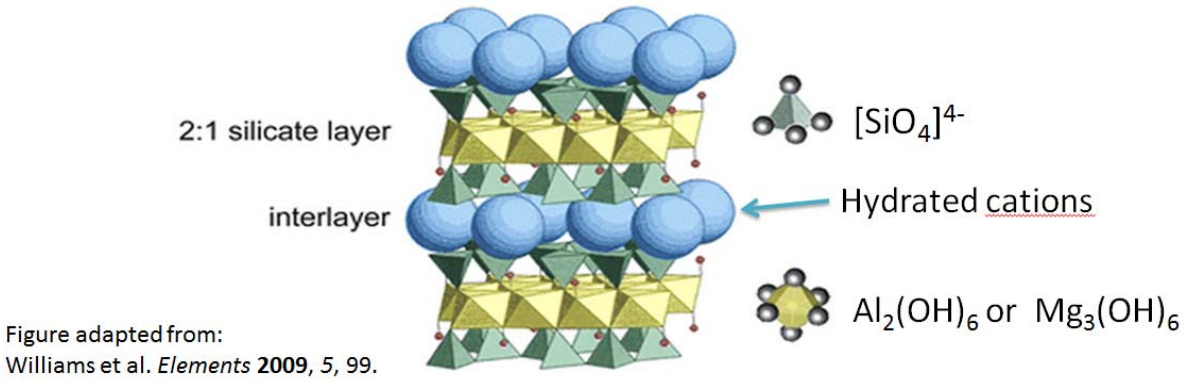


Figure 2.1 Schematic structure of montmorillonite clay.[61]

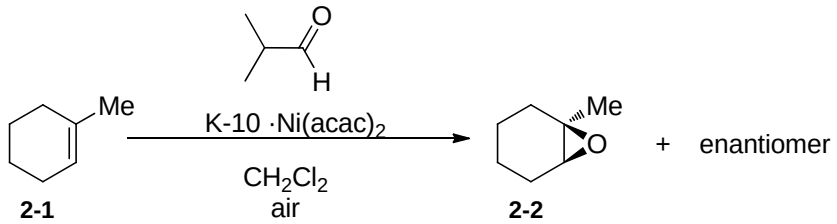
These interlayer cations can be easily replaced by other cations or other molecules leading to incredible amenability for modification of this clay. This composition and structure can vary and can be deliberately altered by acid treatment, cation exchange, hydration/dehydration, or calcination.[60c] These techniques can be used to fine-tune Brønsted and Lewis acidity and thus catalytic properties.

Industrial applications of clays as catalysts goes back to early 1900s when acid-treated clays were used as catalysts for oil cracking.[60a] Their applications have grown tremendously since then bringing promising catalytic applications to the field of organic chemistry.[60a] The two most

common clay catalysts used for synthetic applications are modified montmorillonites known as 'K-10' and 'KSF'. Both are commercially available from many sources and inexpensive. One of the differences between these two lies on their surface area. K-10 has a substantially higher surface area (250 mg^2/g) than KSF (10 mg^2/g) with comparable acidity.[60b] Basic clays are also known but have received less attention as potential catalysts.[60a] Several modifications of clays are found, many using inorganic supporters, catalysts, or reagents including Lewis acids (such as $ZnCl_2$, $AlCl_3$, or $FeCl_3$) and Fe(III) or Cu (II) nitrates.[60c]

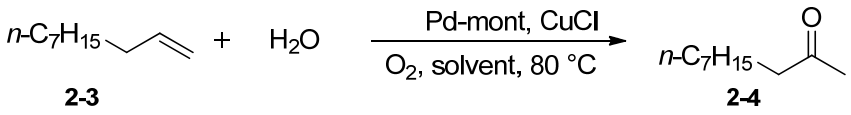
2.1.3.1 Aerobic Oxidation on Clays

Typically, methods that focus on the effective use of molecular oxygen as the prime oxidant in reactions utilize homogeneous transition metal catalysts of copper, palladium and ruthenium. Although clays and their use in organic chemistry have gained recognition over the past decades, use of clays in the context of aerobic oxidation has received little attention. One of the earlier reports that paired clay with molecular oxygen was that of by Bouhlel *et al.* in 1993.[62] Using a montmorillonite supported nickel catalyst and isobutyraldehyde as a reducing agent, olefins were epoxidized in good yields in the presence of compressed air at room temperature in a convenient procedure (Scheme 2.1).[62]



Scheme 2.1 Epoxidation of alkenes using montmorillonite supported Nickel catalyst and O_2.

Another example appears in the work by Kaneda *et al.* in 2005.[63] They reported the use of a Pd-montmorillonite complex and CuCl as a co-catalyst for an efficient and recyclable heterogeneous catalyst system for a liquid-phase Wacker oxidation of a broad range of terminal olefins to their respective methyl ketones. Molecular oxygen is used as the terminal oxidant in this work (Scheme 3.18).

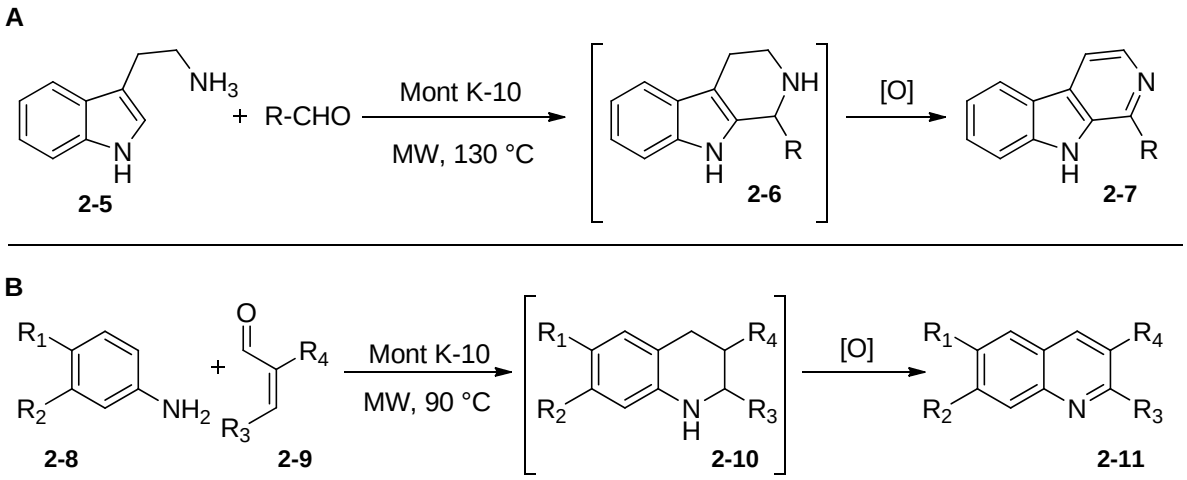


2-3 **2-4**

Scheme 2.2 Wacker oxidation using Pd-mont catalyst.

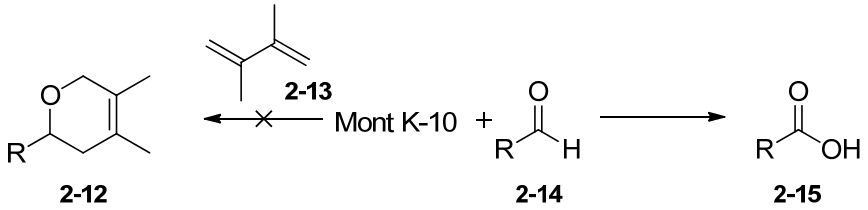
This Pd-mont catalyst provided high selectivity for the oxidation of various olefins with yields of 73-95 %. Not only was the catalyst recyclable, but it maintained high activity and selectivity after its reuse.

Torok *et al.* have shown several examples of montmorillonite K-10 used in combination with air for oxidative dehydrogenation reactions.[42a, 64] Formation of substituted β-carbolines via Pictet-Spengler reactions (Scheme 2.3 A), and quinolines (Scheme 2.3 B) have been reported. These reports focus on the efficient preparation of heterocycles rather than on the mechanistic aspect of oxidation. In fact, oddly, Torok *et al.* provide little acknowledgement of the fact that oxidations are taking place in their reactions. No mechanistic details are given (Scheme 2.3).



Scheme 2.3 Literature reports on the use of Montmorllonite K-10 and oxygen.[42a, 64]

In a recent report by Dintzner *et al.*, aliphatic aldehydes where shown to be oxidized to their respective carboxylic acids using only clay and atmospheric oxygen. The aim of their work was to obtain a hetero-Diels-Alder reaction between propanal (**2-14**) with 2,3-dimethyl-1,3-dimethyl-1,3-butadiene (**2-13**) in the presence of montmorillonite K-10. However, they found propanoic acid **2-15** to be the major product of the reaction (Scheme 2.4).[65]



Scheme 2.4 Oxidation of aliphatic aldehydes using montmorillonite K-10.

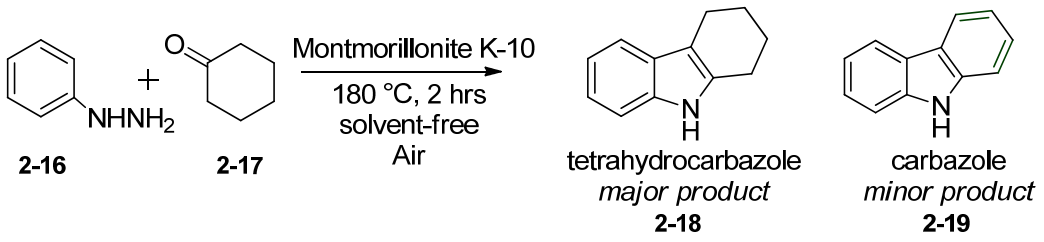
To confirm that atmospheric oxygen was a participant in the reaction, a control experiment was conducted in a nitrogen environment; no carboxylic acid was observed after 7 days. Although no insights about the mechanism were presented, this was found to be a much friendlier alternative to traditional methodology for the synthesis of aliphatic carboxylic acids.

The above examples are essentially a comprehensive review of all reported literature that involves aerobic oxidation with clays. This interesting field is in need of further development. The following chapters describe our work in the area.

2.2 Results and Discussion

2.2.1 Initial Observations from Fischer Indole Synthesis

In this chapter we report the use of aerobic oxidation on the surface of clays, particularly for the dehydroaromatization of heterocyclic compounds. Acid-treated montmorillonite clays have been used as heterogeneous alternatives to homogeneous acids such as TsOH, AcOH, and HCl in various transformations.[60b] This project began with an unusual observation during our attempt to perform a Fischer indole synthesis using montmorillonite K-10 under solvent-free conditions. In addition to the expected product, tetrahydrocarbazole **2.5.3**, we observed the formation of carbazole **2.5.4** as a minor byproduct. This suggested that some dehydrogenation of tetrahydrocarbzole to carbazole was taking place under our reaction conditions (Scheme 2.5).

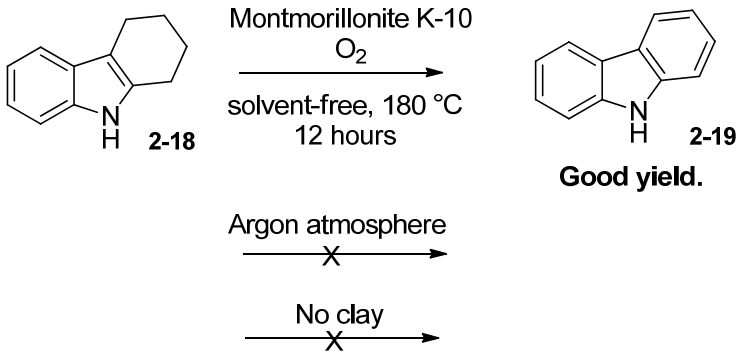


2-16 **2-17** tetrahydrocarbazole *major product* **2-18** carbazole *minor product* **2-19**

Scheme 2.5 Fischer Indole synthesis using montmorillonite K-10 in solvent-free conditions.

We found that the dehydrogenation of tetrahydrocarbazole to carbazole does indeed occur on the surface of montmorillonite K-10 under solvent free conditions and an oxygen atmosphere at high temperature. Control experiments revealed that no reaction took place in an Argon

atmosphere or in the absence of clay (Scheme 2.6). This proved that oxygen, along with the clay, work together to yield carbazole and both components are crucial for dehydrogenation to occur (Scheme 2.6).



Scheme 2.6 Oxidative dehydrogenation of tetrahydrocarbazole **2-18** in the presence of montmorillonite K-10 and O_2.

Due to the fact that montmorillonite clays contain small amounts of iron oxides and Fe^{3+} has been shown to catalyze benzylic oxidation,[66] we hypothesize that this dehydrogenation may occur via this mechanism catalyzed by exposed iron species in the clay matrix (Figure 2.2).

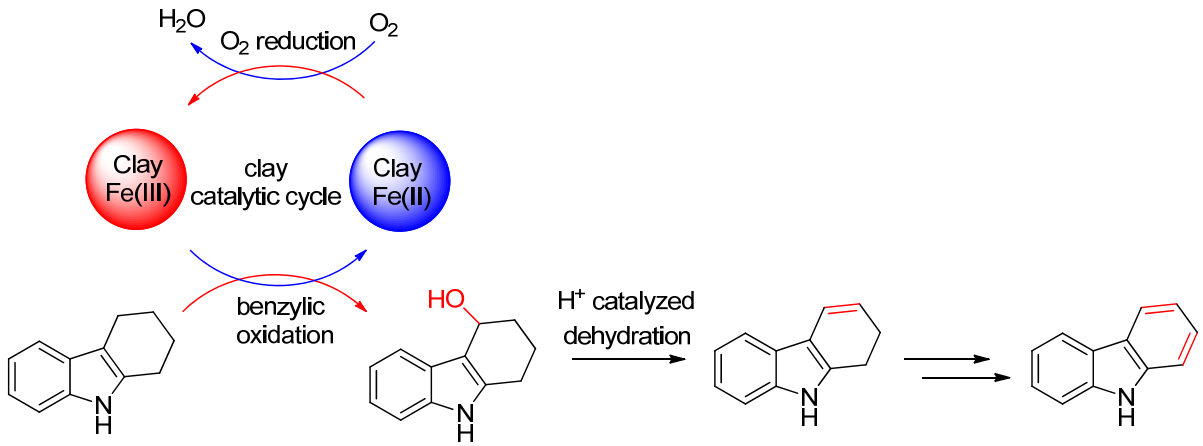


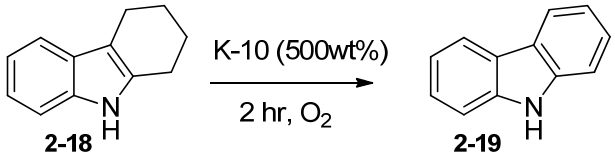
Figure 2.2 Proposed dehydroaromatization mechanism.

Based on this initial observation, our work towards the implementation of clays for aerobic dehydrogenation began. Most of our efforts have focused on the use of clays and air or molecular oxygen under solvent-free conditions using conventional heating.

2.2.2 Aerobic Dehydroaromatization of Tetrahydrocarbazole and One-pot Fischer Indole synthesis.

Using tetrahydrocarbazole **2-18** as our substrate, we began by optimizing temperature. A typical reaction was set up as follows. Our substrate was ground with the clay using a mortar and pestle and transferred to a vial. The vial was capped under oxygen atmosphere using an oxygen balloon. The reaction was then heated using an oil bath. Upon completion, the organic contents were extracted from the solid support by stirring with EtOAc. All organic solutions were combined and concentrated under reduced pressure. A crude ^{1}H NMR showed predominantly just two compounds starting material and product. We found that crude mass recovery was poor in many cases. In order to optimize this reaction, it was critical for us to determine mass recovery and record crude ^{1}H NMR to obtain a ratio of starting material to product. Table 2.1 shows the results of these reactions.

Table 2.1 Temperature optimization for aerobic dehydrogenation of tetrahydrocarbazole **2-18** using montmorillonite K-10.

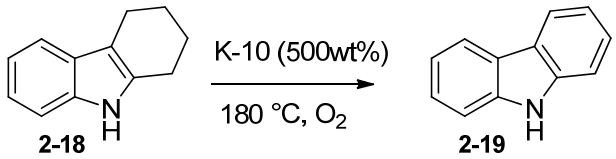


2-18 **2-19**

Entry	Temp (°C)	Mass recovery (%)	Conversion to 2-19 by ^{1}H NMR (%)
1	100	90	13
2	120	89	20
3	140	90	21
4	160	88	70
5	180	82	74
6	200	64	56

The highest mass recoveries were achieved when reactions were performed under 140 °C. Presumably at higher temperatures decomposition of starting material began to take place accounting for the loss of material. On the other hand, conversion to carbazole **2-19** significantly increased after this temperature, from 21 % at 140 °C to 70 % at 160 °C (Entries 3 and 4, Table 2.1). Entry 5 shows the best combination of mass recovery and conversion results achieved at 180 °C getting 74 % conversion to product. At higher temperature, a decrease in mass recovery and percent conversion to product was observed. With a set temperature in hand we then began to explore the time required for reaction completion and high mass recovery. The results are tabulated on Table 2.2.

Table 2.2 Time optimization for aerobic dehydrogenation of tetrahydrocarbazole **2-18** using montmorillonite K-10.



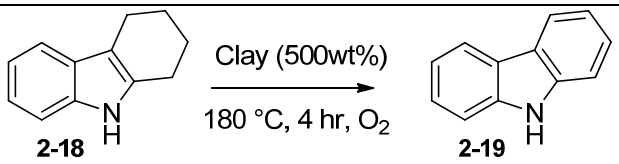
2-18 **2-19**

Entry	Time (hr)	Mass recovery (%)	Conversion to 2-19 by ^{1}H NMR (%)
1	2	82	74
2	4	73	78
3	8	68	94
4	16	40	99
5	24	30	99

Our results indicate that the longer the time spent heating, the less mass recovered, however conversion of up to 99 % was achieved if left longer than 16 hours. However, after 16 hours, significant decomposition of our substrate was observed (Entries 4-5). The best results were determined to be 8 hours at 180 °C which resulted in 68 % mass recovery and 94 % conversion (Entry 3).

Based on this, we decided to carry out a screen of **2-18**, while maintaining a reaction time and temperature of 4 hours and 180 °C respectively. We used the most common clays used in organic synthesis and explored various clays obtained from the Clays Mineral Society (Table 2.3). Montmorillonite clays K-10, KSF, K-30 and natural mont all gave different results (Entries 1-4). Highest mass recovery achieved was with natural mont, whereas K-30 gave the highest conversion to product. The use of bentonite and SYn-1 clays resulted in similar conversion to product, but higher mass recovery in particular with the case of bentonite (Entries 5 and 6). Entries 7-10 displays the results obtained when unusual clays obtained from Australian mining sources were applied. Although none gave a conversion greater than 50 %, product was formed.

Table 2.3 Clay comparison for aerobic dehydrogenation of tetrahydrocarbazole.

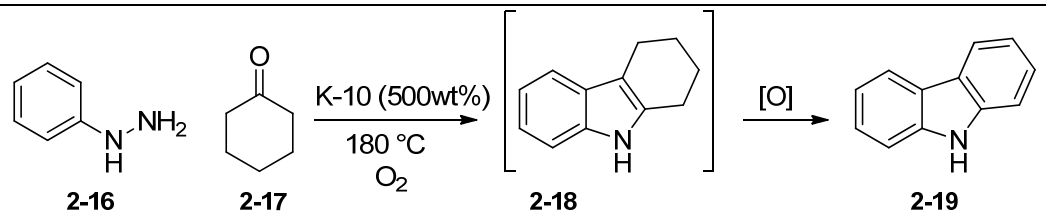


2-18 **2-19**

Entry	Clay (500 wt %)	Mass recovery (%)	Conversion to 2-19 by ^{1}H NMR (%)
1	Mont-K-10	73	74
2	Mont-KSF	71	10
3	Mont-K-30	57	91
4	Natural Mont	91	32
5	Bentonite	99	42
6	SYn-1	56	37
7	Rectrorite	99	5
8	Nontronite Brown	55	44
9	Nontronite Green	92	19
10	Illite	99	9

Since montmorillonite K-10 clay offered the best combination of conversion to product and mass recovery, we explored a one-pot Fischer indole synthesis using this clay. The temperature was set to 180 °C and reactions at different times were run. As expected product formation took place. However varying ratios of unoxidized tetrahydrocarbazole **2-18** and carbazole **2-19** were obtained. These results are illustrated in Table 2.4.

Table 2.4 Time optimization for the one-pot Fischer indole synthesis.



2-16 **2-17** **2-18** **2-19**

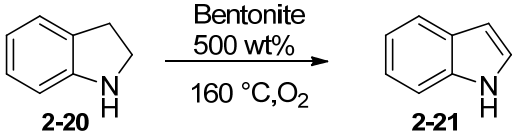
Entry	Time (hr)	Mass recovery (%)	Ratio of 2-18 : 2-19 by ^{1}H NMR
1	2	55	1:1.8
2	4	43	1:2.1
3	8	30	1:6.7

The best results were achieved with 8 hours of heating (Entry 3). A ratio of 1 : 6.7 (**2-18** : **2-19**) was obtained by crude ^{1}H NMR. However significant loss of material is observed. Less than 55 % of material is recovered in all cases. At this point we consider this reaction to be interesting however synthetically impractical due to low yields and the requirement for high temperatures. We have not expanded the substrate scope to include substituted carbazoles. The work remains unpublished to date.

2.2.3 Aerobic Dehydroaromatization of Indoline and Future Work on Other Heterocycles

Knowing that aerobic dehydroaromatization works readily for tetrahydrocarbazole, we began to explore the reactivity and conditions for other heterocyclic compounds with a series of clays. In the case of indoline it was found that bentonite work the best for mass recovery and conversion into indole. Also, after optimization with temperature, 160 °C seemed to give the best percent conversion and recovery after 4 hours. Table 2.5 shows the results obtained at different times with heating at 160 °C.

Table 2.5. Oxidative dehydrogenation of indoline to indole using bentonite clay.



2-20 **2-21**

Time (hr)	Mass recovery (%)	Conversion to 2-21 by ^{1}H NMR
4	71	88
8	65	89
16	57	92
24	45	92

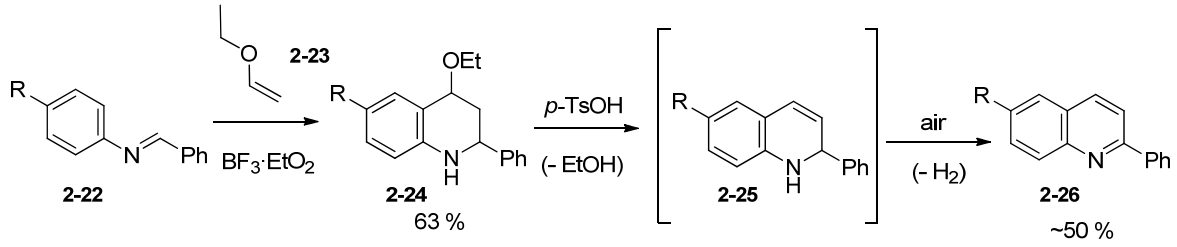
Results show that there was not a significant change in percent conversion after 4 hours. Also, mass recovery began to drop lower than 45 % after 24 hours (Entry 1).

One of the major problems that have risen in this project is mass recovery. We have observed that when nitrogen-containing heterocycles are used, low mass recovery ensues. We believe that many heterocyclic compounds are will likely be prone to decomposition at high temperatures on the acidic surface of clays. Nonetheless, our plan is to investigate different filtration methods and optimization conditions to achieve the highest possible mass recovery as well as to continue this work by optimizing the dehydroaromatization of different substrates including tetrahydroquinoline, tetrahydroisoquinoline, tetrahydronaphtalene, dihydronaphthalene, among others.

2.2.4 One-pot Inverse-electron Demand Hetero-Diels Alder (Povarov) Reaction.

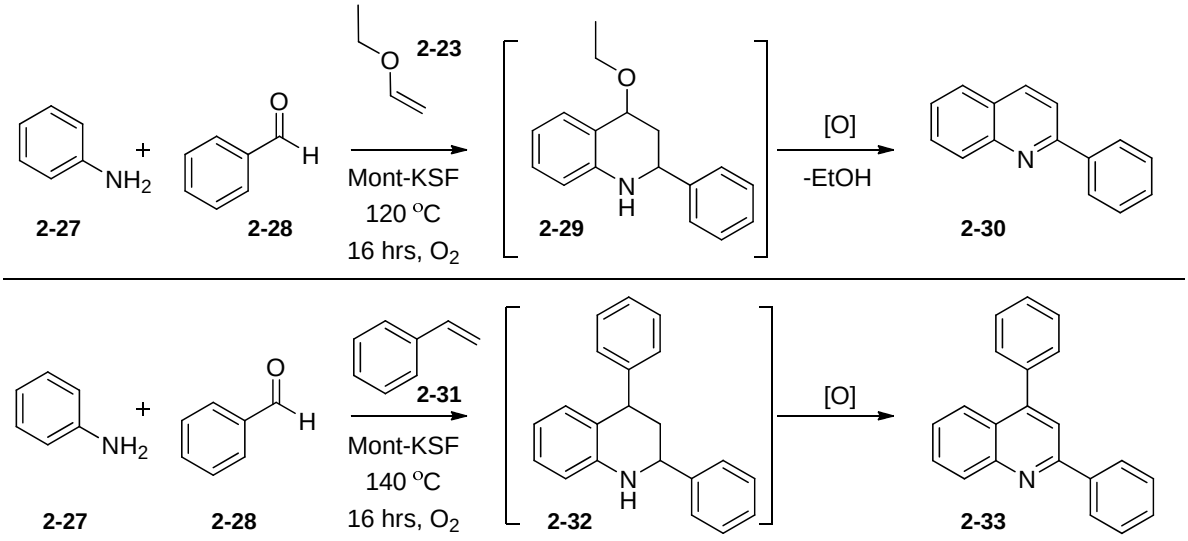
In 1963, Povarov reported the use of ethyl vinyl ether **2-23** and N-aryl aldimine **2-22** under acid catalysis to obtain substituted tetrahydroquinolines **2-24** which were converted into their

corresponding quinolines **2-26** (Scheme 2.7).[67] This inverse-electron demand Diels-Alder reaction has gained significant importance for the preparation of quinolines.[67]



Scheme 2.7 Literature report of the first works of Povarov.[68]

We set out to investigate the use of clays for the one-pot multistep synthesis of quinolines via the Povarov reaction. We found that the combination of clay (acid catalyst and redox catalyst) and molecular oxygen, yields fully aromatic quinolines via a three component coupling reaction. Illustrated in Scheme 2.8 are optimal conditions to generate the fully aromatized substituted quinoline.

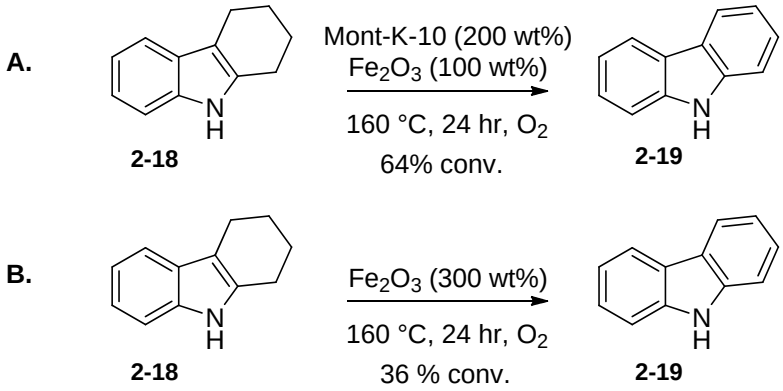


Scheme 2.8 Synthesis of substituted quinolines **2-30** and **2-33** through clay catalyzed aerobic dehydrogentation.

To date we have succeeded in making compounds **2-30** and **2-33**, using aniline **2-27**, benzaldehyde **2-28**, and two different alkenes (**2-23** and **2-31**, Scheme 2.8). In both, the reaction proceeds to completion at 140°C in 16 hours. Unfortunately, some minor impurities are formed (^{1}H NMR) and the yields to date are low and inconsistent (30-70 %). This is an ongoing effort that will be continued by other students. Our goal is to further optimize reaction conditions and evaluate our substrate scope.

2.2.5 Dehydroaromatization with V_2O_5

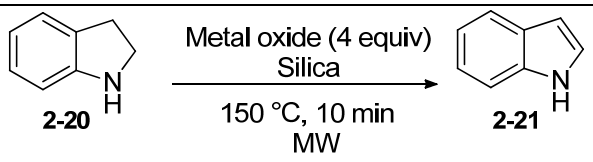
During initial investigations of iron-supported clays as strong oxidative catalysts, we used iron oxide (Fe_2O_3) as a co-catalyst with montmorillonite K-10 to dehydrogenate tetrahydrocarbazole (Scheme 2.9A). The reaction proceeded to 64% conversion after heating for 24 hours at 160 °C. A control reaction, using Fe_2O_3 alone, was found to result in less efficient conversion to the aromatized product (Scheme 2.9B). This strongly suggested that the combination of the clay and iron oxide is a stronger catalyst for aerobic dehydrogenation than the oxide alone.



Scheme 2.9 Dehydroaromatization using (**A**) a combination of Mont-K-10 and Fe_2O_3 and (**B**) only Fe_2O_3.

Next, we investigated other metal oxides for their activity. Metal oxides have been used extensively as catalysts for various transformations in industry such as catalytic photodegradation of organic compounds in waste water treatment.[69] We screened different metal oxides for the oxidative dehydrogenation of indoline to indole. Silica was used as a solid support. The reactions were carried out using microwave irradiation at 150 °C for only 10 minutes. The results of this screen are shown in Table 2.6.

Table 2.6. Metal oxides screened for the dehydroaromatization of indoline **2-21** (performed by graduate student Megha Karki).



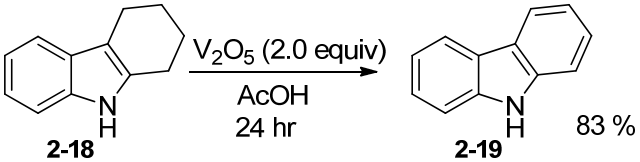
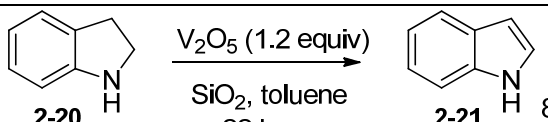
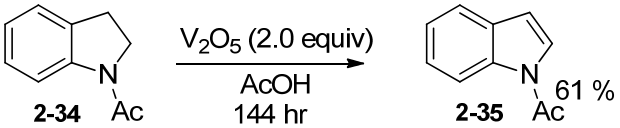
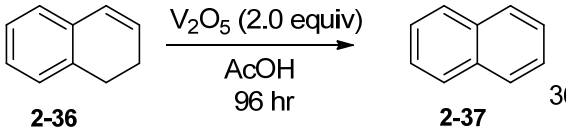
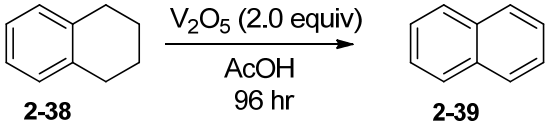
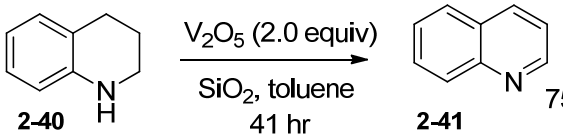
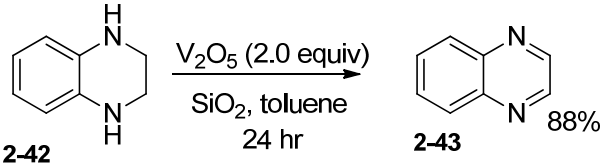
2-20 **2-21**

Entry	Metal oxide	% conversion (by 1H NMR)
1	Zinc (II) oxide	11
2	Lead oxide	12
3	Alumina	14
4	Nickel (II) oxide	16
5	Lead (IV) oxide	17
6	Copper (II) oxide	17
7	Manganese (III) oxide	18
8	Magnesium (II) oxide	19
9	Iron (III) oxide	28
10	Chromium (VI) oxide	39
11	Copper (I) oxide	43
12	Molybdenum (IV) oxide	57
13	Vanadium (V) oxide	100

Of the thirteen metal oxides that were screened, V_2O_5 (Vanadium (V) oxide, Entry 13) displayed remarkable reactivity compared to the other twelve. By ^{1}H NMR, all of the indoline present in the microwave vial was converted to indole. Given its prominence in this role, we chose to investigate the suitability of V_2O_5 for dehydroaromatization of more complex substrates.

The best conditions for the dehydroaromatization of different substrates were achieved after a thorough optimization of catalyst amount, temperature, solvent, and reaction time. Table 2.7 shows some of the substrates used with their respective yields after column chromatography.

Table 2.7 Substrate scope on the dehydroaromatization with V_2O_5.

Entry	Substrate and Reaction Conditions
1	 **2-18** **2-19**
2	 **2-20** **2-21**
3	 **2-34** **2-35**
4	 **2-36** **2-37**
5	 **2-38** **2-39**
6	 **2-40** **2-41**
7	 **2-42** **2-43**

As observed, the reactivity of V_2O_5 greatly depends on the substrates. The combination of AcOH (providing an acidic environment for the reaction) along with V_2O_5 in refluxing toluene, was found

to work favorably for tetrahydrocarbazole. This was also the case with substrates **2-34**, **2-36**, and **2-38** (Entries 3, 4, and 5) However, nitrogen containing heterocycles **2-20**, **2-40**, and **2-42** (Entries 2, 6, and 7) were found to be inert to V_2O_5 in AcOH but readily aromatized by V_2O_5/SiO_2 in refluxing toluene. Both dihydro- and tetrahydronaphthalenes (**2-36** and **2-38**) reacted poorly with these conditions. Further work on this concept (including a one-pot Fischer indole synthesis-dehydrogenation sequence) was implemented in collaboration with graduate student Megha Karki which led to an in-depth evaluation of V_2O_5 to mediate dehydroaromatization reactions. This work has been recently published in *Synlett*[70].

2.2.6 Conclusion and Future Work

Based on our preliminary results, clays show some promise as catalysts for aerobic oxidation. Complications have arisen from poor mass recovery presumed to be caused by decomposition of substrates and/or products at under the relatively harsh reaction conditions. This work will be continued by other graduate students. Dr. Magolan intends to further investigate the scope and limitations of clays as aerobic oxidation catalysts.

2.3 Chapter 2: Experimental Section

2.3.1 General Experimental:

All substrates, reagents, and solvents were obtained from commercial suppliers and used as purchased without further purification. NMR experiments were performed on 500 and 300 MHz instruments and samples were obtained in $CDCl_3$ (referenced to 7.26 ppm for ^1H and 77.0 ppm for ^{13}C). All reactions were performed under an oxygen atmosphere unless otherwise stated. Reaction progress was monitored by thin-layer chromatography on silica gel plates (60-F_{254}), which were visualized under UV light and developed using *p*-anisaldehyde or potassium permanganate stains. Flash chromatography was performed using silica gel (particle size 40-63 μm). Bentonite and montmorillonite clays (K-10, KSF, K-10, and Natural Mont) were purchased from Sigma Aldrich.® Syn-1, Rectrorite, Nontronite Brown, Nontronite Green, and Illite were obtained from The Clays Minerals Society. Reaction products in this chapter: carbazole, indole, 1-acetylindole, naphthalene, quinoline, and quinoxaline are all well characterized commercially available compounds. In all cases our products were characterized by comparison of ^1H NMR to authentic samples and the spectra matched perfectly.

2.3.2 Experimental Section 2.2.2 - 2.2.3

General procedure for the dehydroaromatization of heterocycles 2-18 and 2-20.

Tetrahydrocarbazole **2-18** (1.0 mmol) and clay (500 weight %) were ground using a mortar and pestle for 5 min. Contents were transferred into a glass reaction vial, capped under an oxygen atmosphere using an oxygen balloon and heated using a paraffin wax bath. During the optimization process, the progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate was added to the mixture, and the product was separated from the catalyst by filtration

through a silica plug. The combined filtrate was concentrated *in vacuo* to obtained carbazole **2-19**. ^{1}H and ^{13}C NMR spectra matched authentic samples.

2.3.2 Experimental Section 2.2.4

General procedure for the one-pot multistep synthesis of quinolines via Povarov reaction. Aniline **2-27** (1.0 mmol), benzaldehyde **2-31** (1.0 mmol), and clay (500 weight %) were ground using a mortar and pestle for 5 min and transferred to a microwave vial. The vial was capped under oxygen atmosphere using an oxygen balloon. The reaction was heated using a sand bath for 2 hours at 120 °C. After completion of imine formation by TLC, the respective alkene (**2-23** or **2-31**) was added via syringe. Upon completion the organic contents were extracted from the solid support by stirring with EtOAc and separated from the catalyst by filtration through a celite plug. The combined filtrate was concentrated *in vacuo* to obtaine quinolines **2-30** or **2-33**. ^{1}H NMR spectra matched literature values.[71]

2.3.4 Experimental Section 2.2.5

Representative experimental procedures:

Indoline to indole (V_2O_5, silica, toluene): Indoline (1.0 mmol), V_2O_5 (2.0 mmol), silica gel (800 mg), and toluene (6 mL) were added to a round bottomed flask equipped with a stir bar and reflux condenser. The reaction mixture was stirred at reflux temperature under an argon atmosphere and monitored by TLC. After 22 hours the reaction was cooled and filtered through a celite plug. The solids were washed repeatedly with chloroform. The combined filtrate was concentrated *in vacuo* and purified by silica gel chromatography (EtOAc/Hexanes) to offer indole in 82 % yield. ^{1}H and ^{13}C NMR spectra matched an authentic sample.

Tetrahydrocarbazole to carbazole (cat. V_2O_5, AcOH): Tetrahydrocarbazole (1.0 mmol), V_2O_5 (0.05 mmol), and acetic acid (6 mL) were added to a round bottom flask equipped with a stir bar and reflux condenser. The reaction mixture was stirred at reflux temperature under an Argon atmosphere for 5 days. The reaction mixture was cooled to RT, water was added and the aqueous layer was extracted three times with chloroform. The combined extracts were washed with brine and dried over Na_2SO_4, concentrated *in vacuo*, and the residue was purified by column chromatography (EtOAc/Hexanes) to offer carbazole in 68 % yield. ^{1}H and ^{13}C NMR spectra matched an authentic sample.

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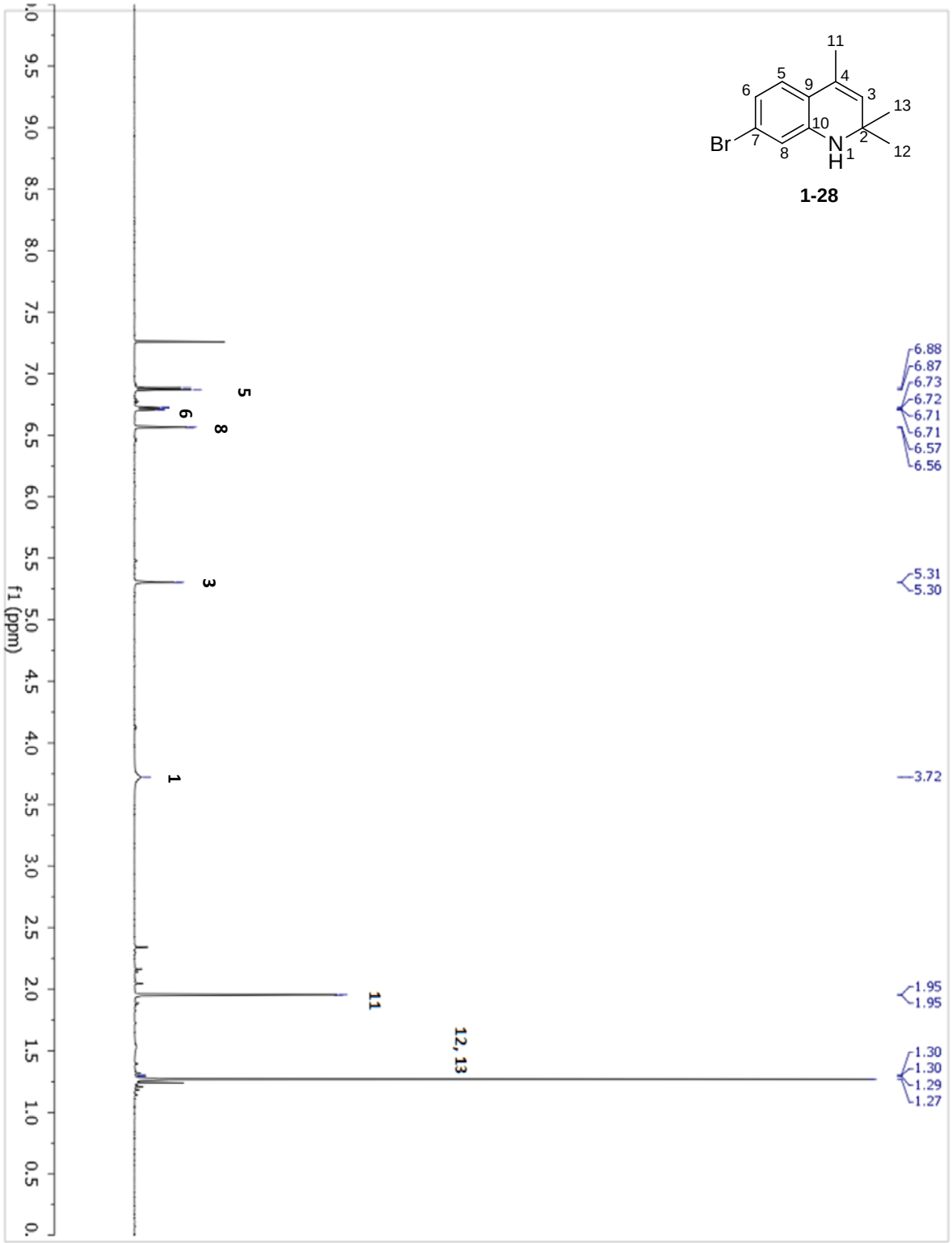
Appendix

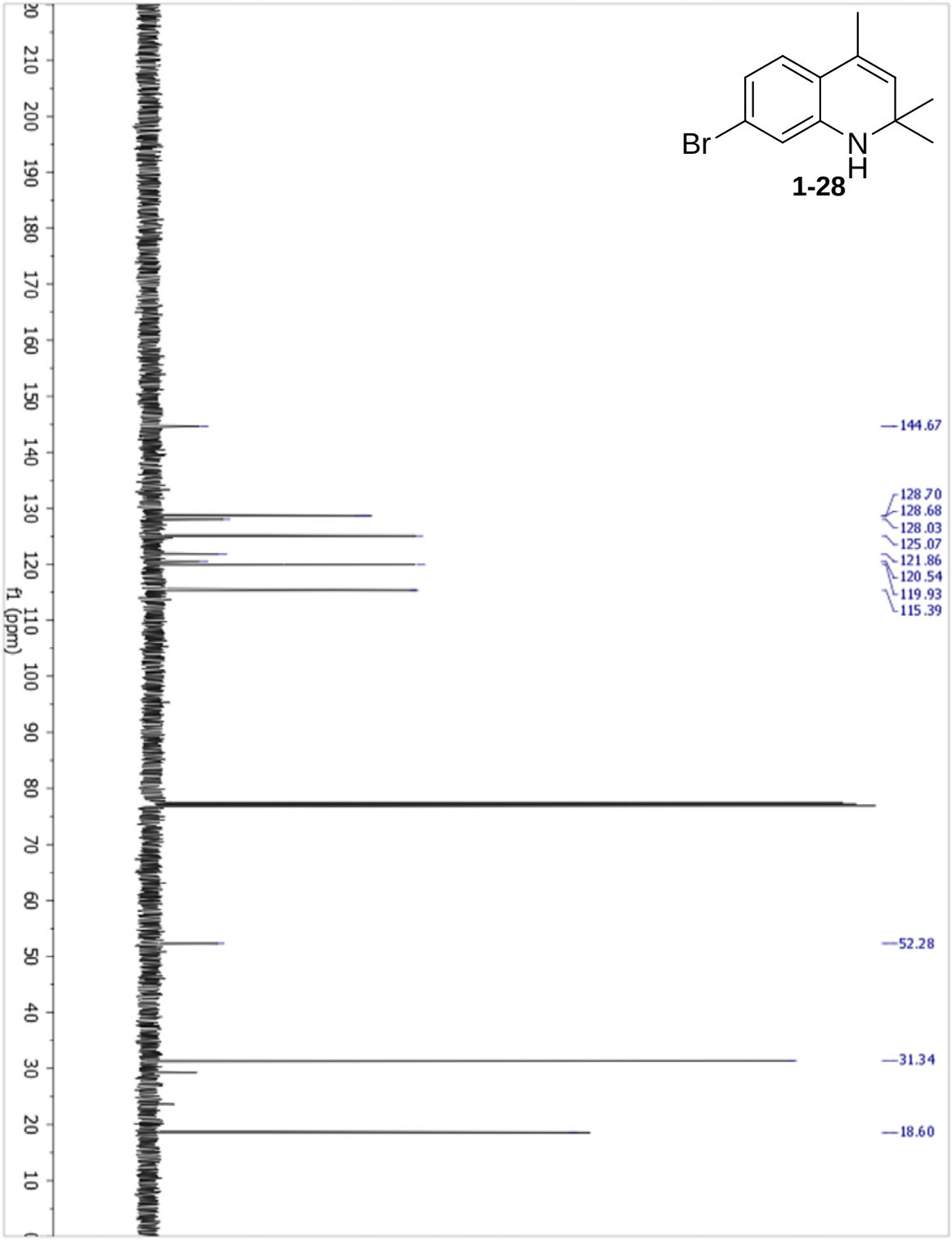
^{1}H and ^{13}C NMR spectra

Chapter 1

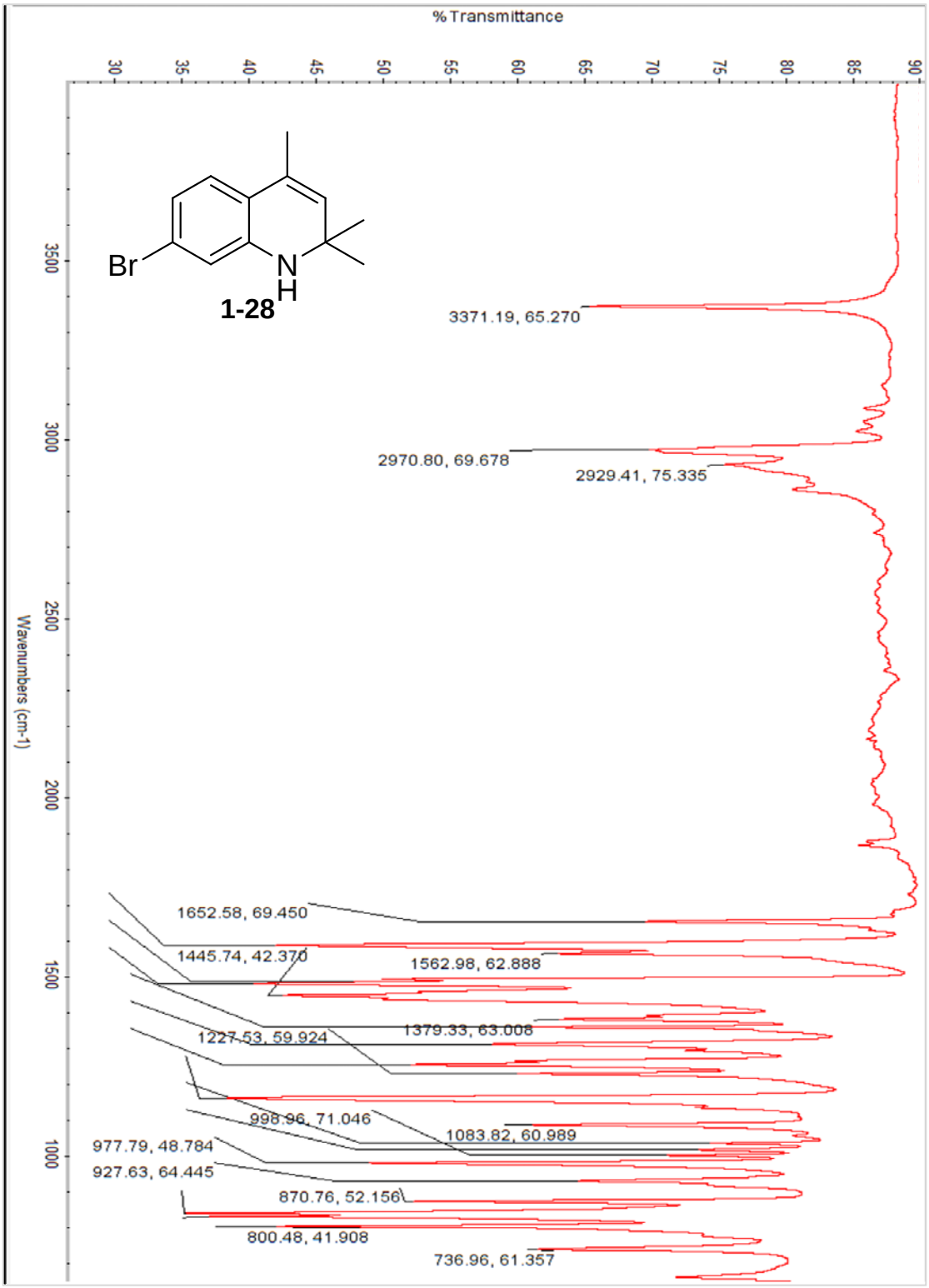
^{1}H NMR (500 MHz) in $CDCl_3$ of 7-bromo-2,2,4-trimethyl-1,2-dihydroquinoline (1-28).



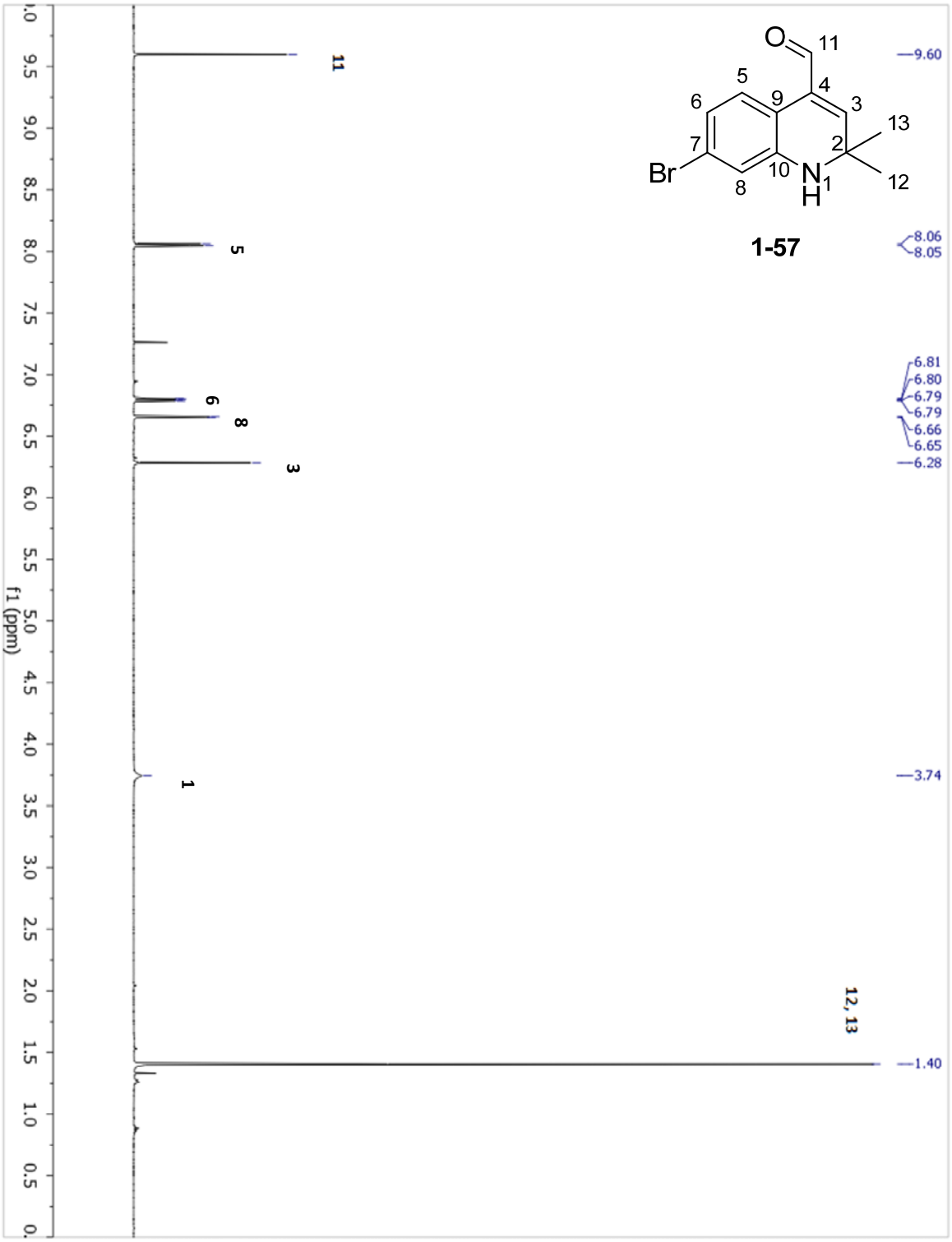
^{13}C NMR (125 MHz) in $CDCl_3$ of 7-bromo-2,2,4-trimethyl-1,2-dihydroquinoline (1-28).



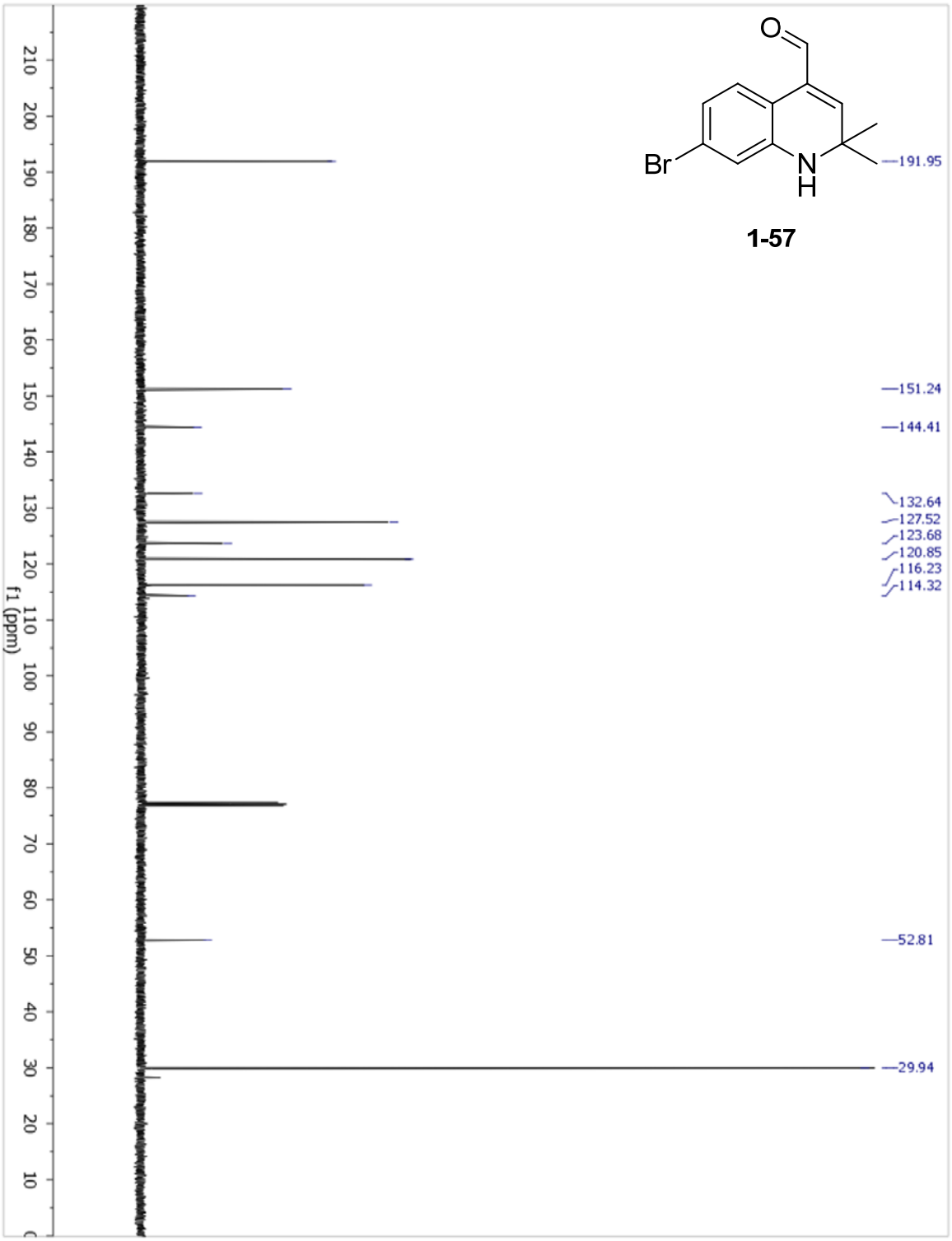
FTIR spectrum of 7-bromo-2,2,4-trimethyl-1,2-dihydroquinoline (1-28).



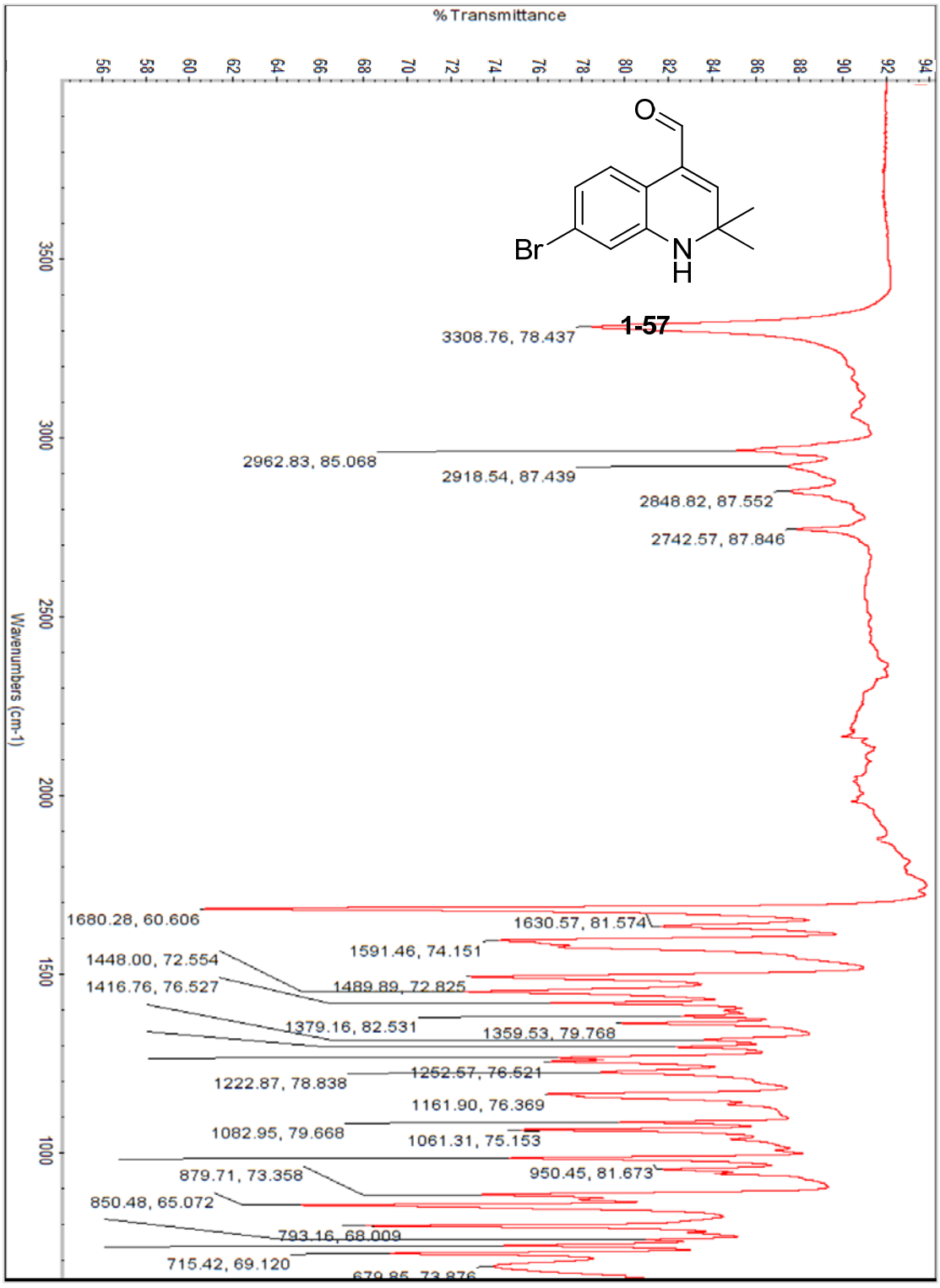
^{1}H NMR (500 MHz) in $CDCl_3$ of 7-bromo-2,2-dimethyl-1,2-dihydroquinoline-4-carbaldehyde (1-57).



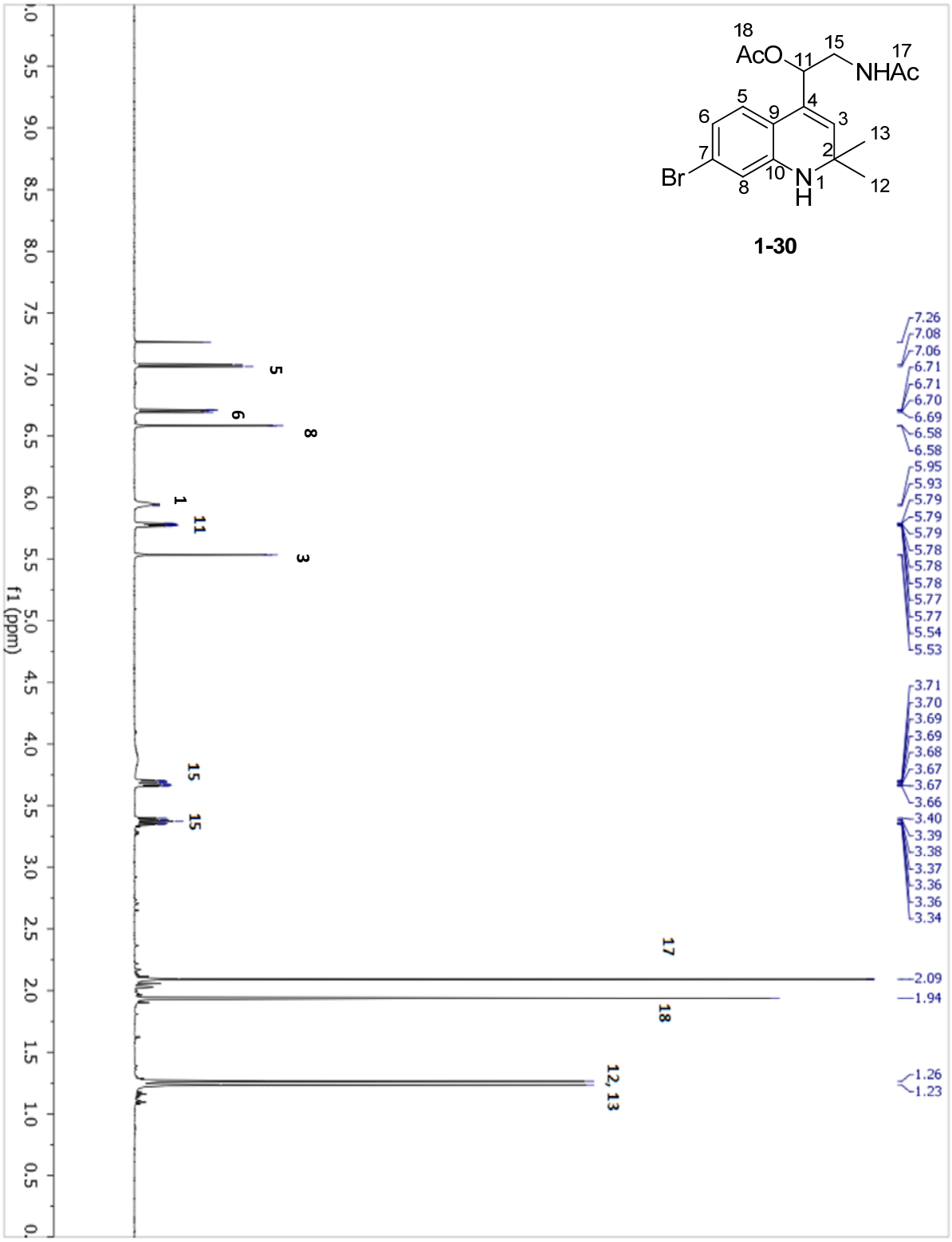
^{13}C NMR (125 MHz) in $CDCl_3$ of 7-bromo-2,2-dimethyl-1,2-dihydroquinoline-4-carbaldehyde (1-57).



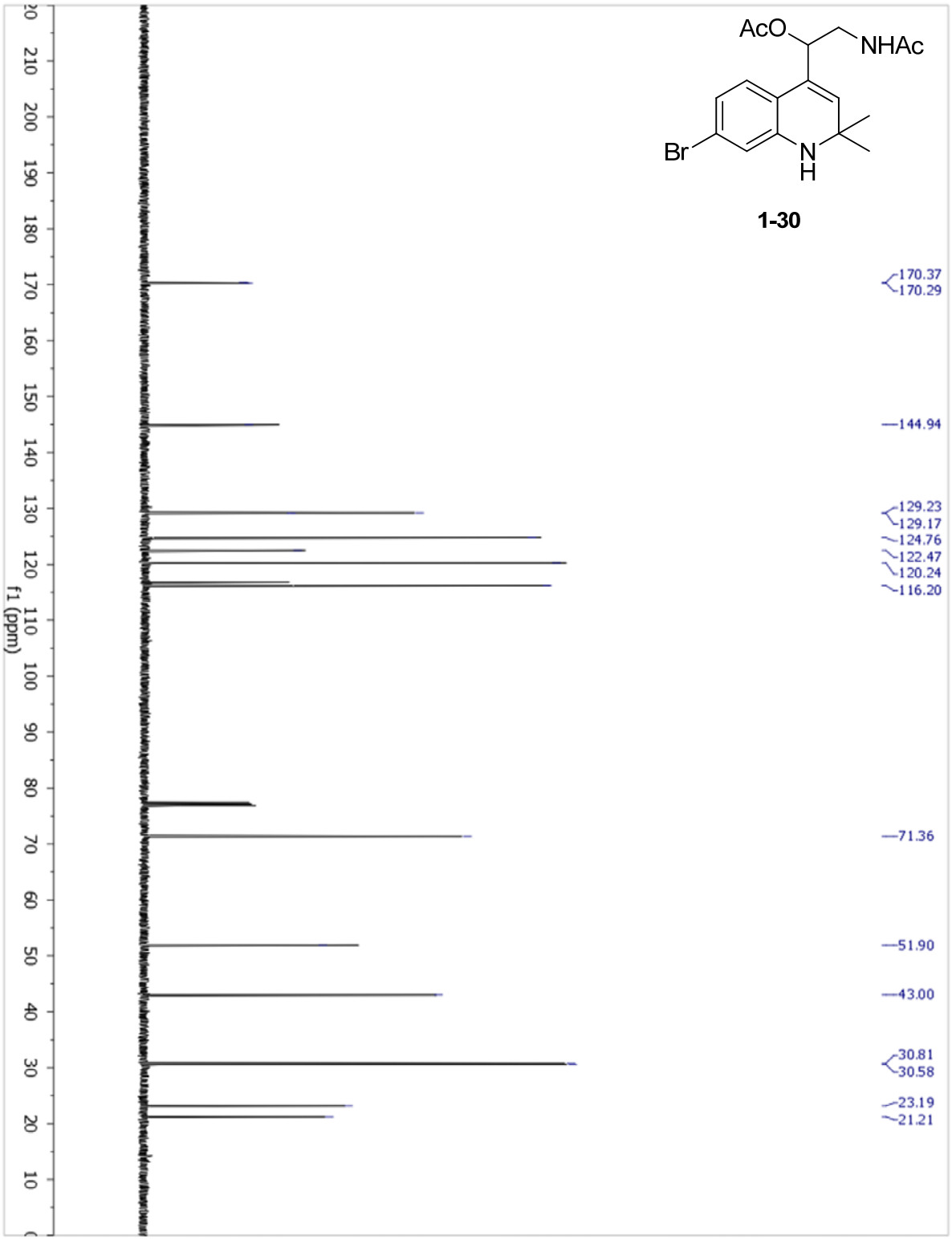
FTIR of 7-bromo-2,2-dimethyl-1,2-dihydroquinoline-4-carbaldehyde (1-57).



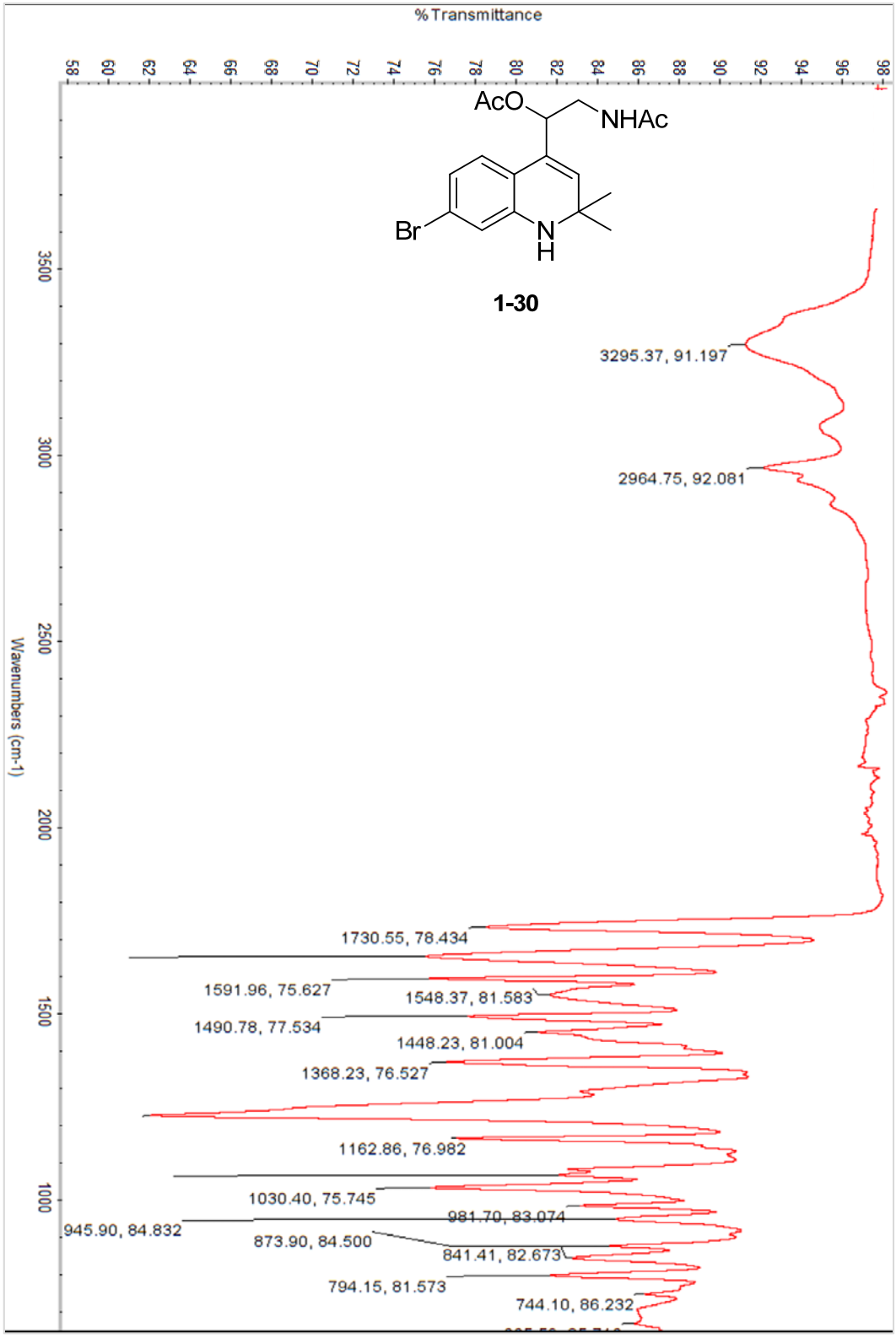
^{1}H NMR (500 MHz) in $CDCl_3$ of 2-acetamido-1-(7-bromo-2,2-dimethyl-1,2-dihydroquinolin-4-yl)ethyl acetate (1-30).



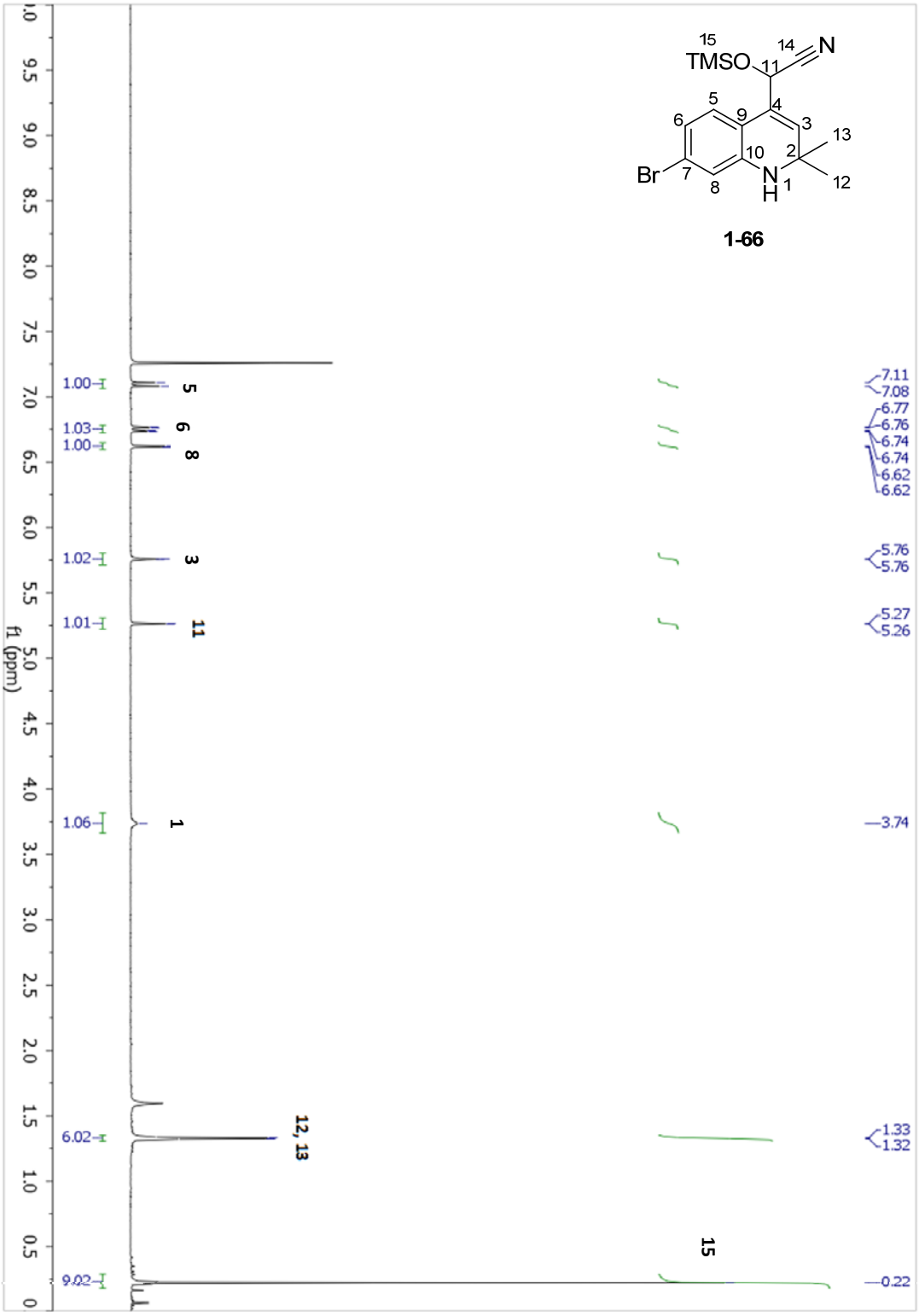
^{13}C NMR (125 MHz) in $CDCl_3$ of 2-acetamido-1-(7-bromo-2,2-dimethyl-1,2-dihydroquinolin-4-yl)ethyl acetate (1-30).



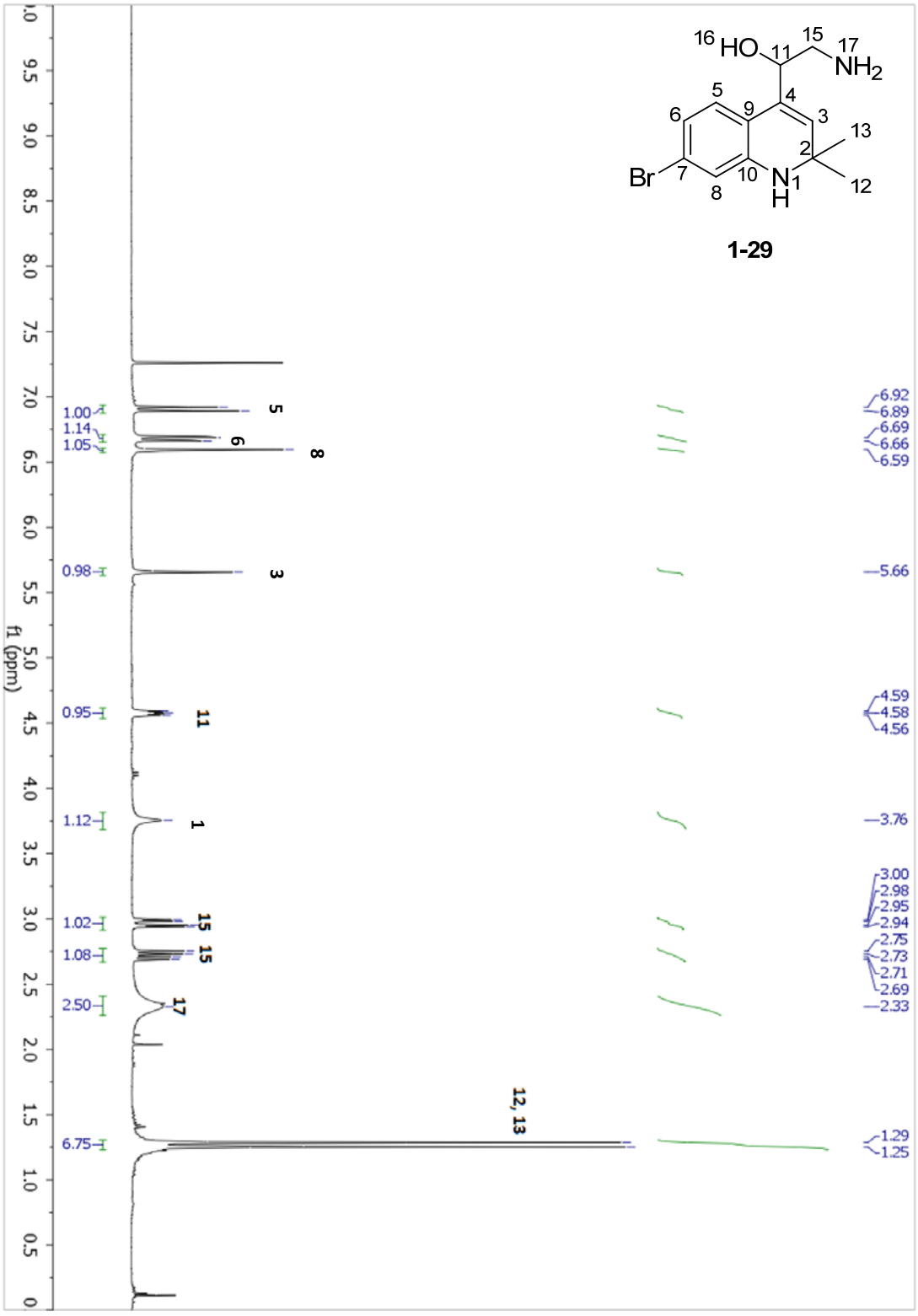
FTIR of 2-acetamido-1-(7-bromo-2,2-dimethyl-1,2-dihydroquinolin-4-yl)ethyl acetate (1-30).



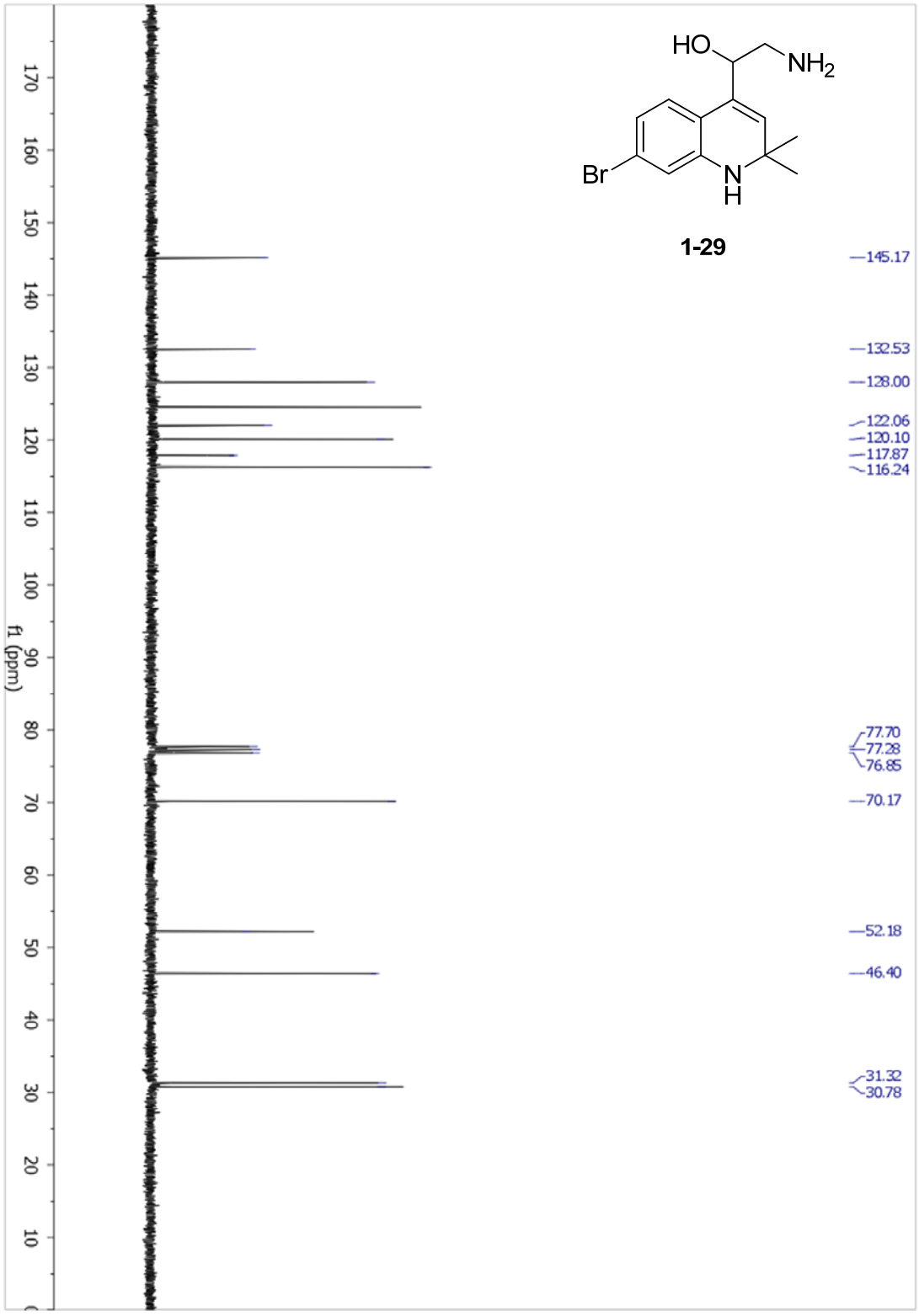
^{1}H NMR (500 MHz) in $CDCl_3$ of 2-(7-bromo-2,2-dimethyl-1,2-dihydroquinolin-4-yl)-2-((trimethylsilyl)oxy)acetonitrile (1-67).



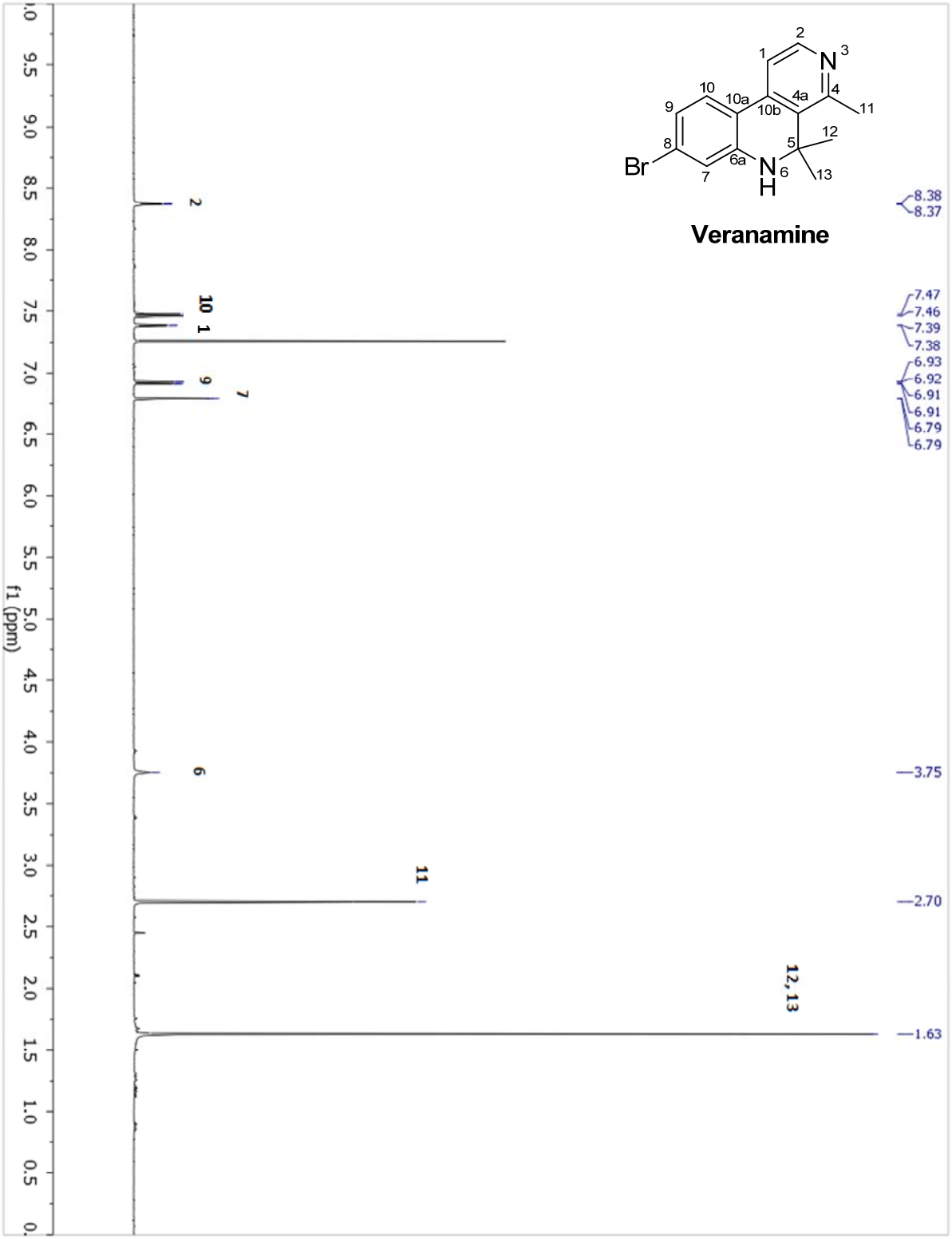
^{1}H NMR (500 MHz) in $CDCl_3$ of 2-amino-1-(7-bromo-2,2-dimethyl-1,2-dihydroquinolin-4-yl)ethanol (1-29).



^{13}C NMR (125 MHz) in $CDCl_3$ of 2-amino-1-(7-bromo-2,2-dimethyl-1,2-dihydroquinolin-4-yl)ethanol (1-29).



^{1}H NMR (500 MHz) in $CDCl_3$ of 8-bromo-4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (Veranamine).



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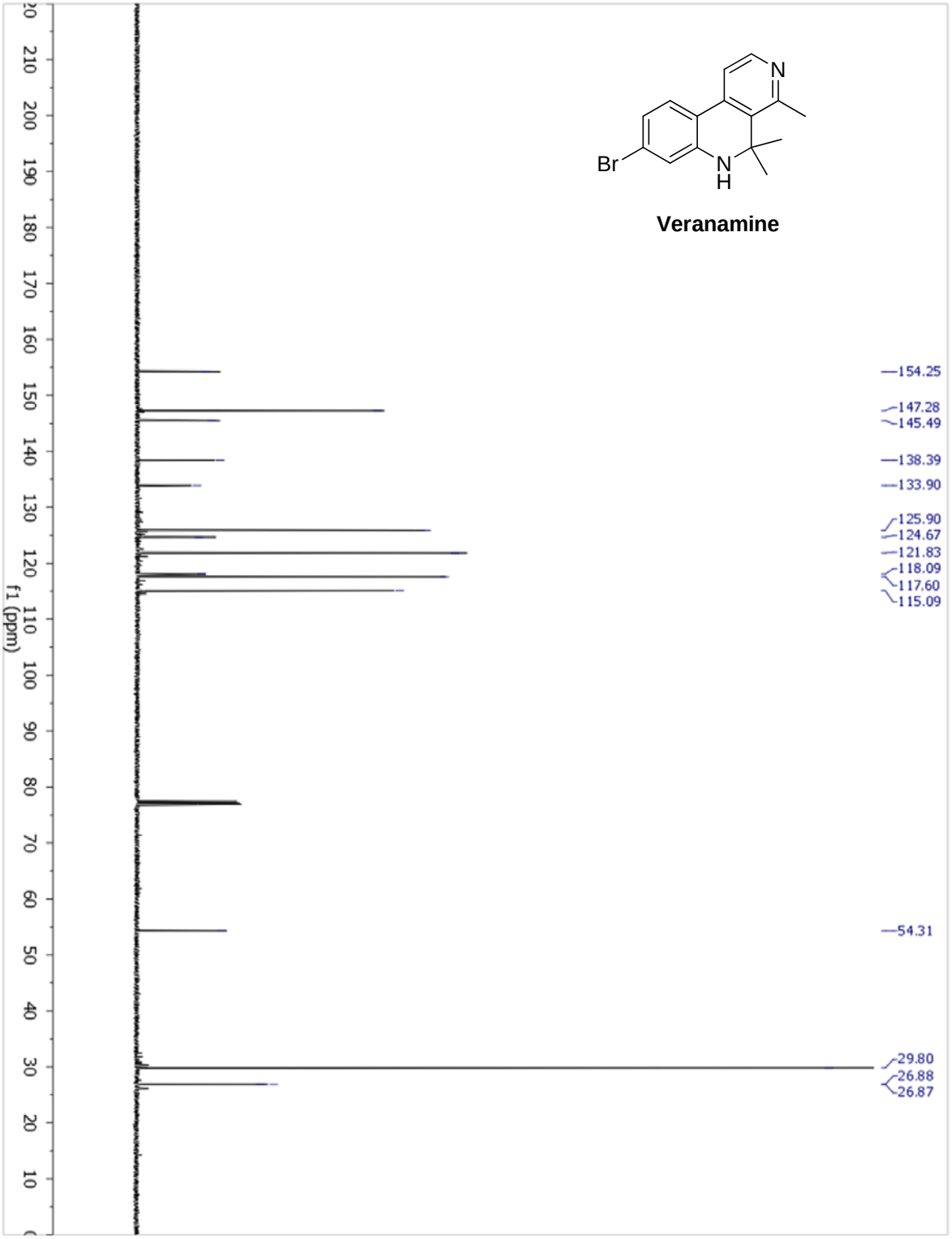
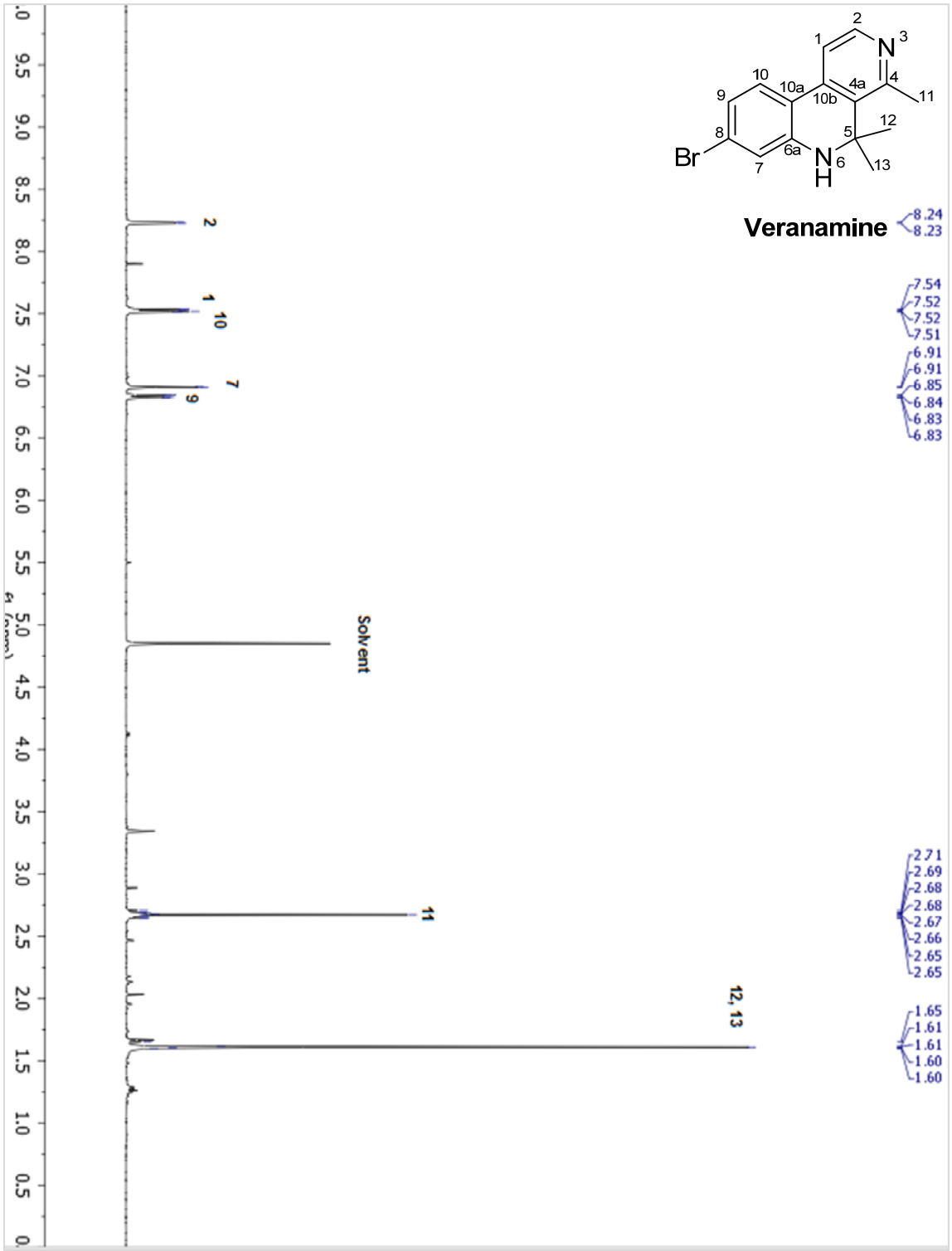
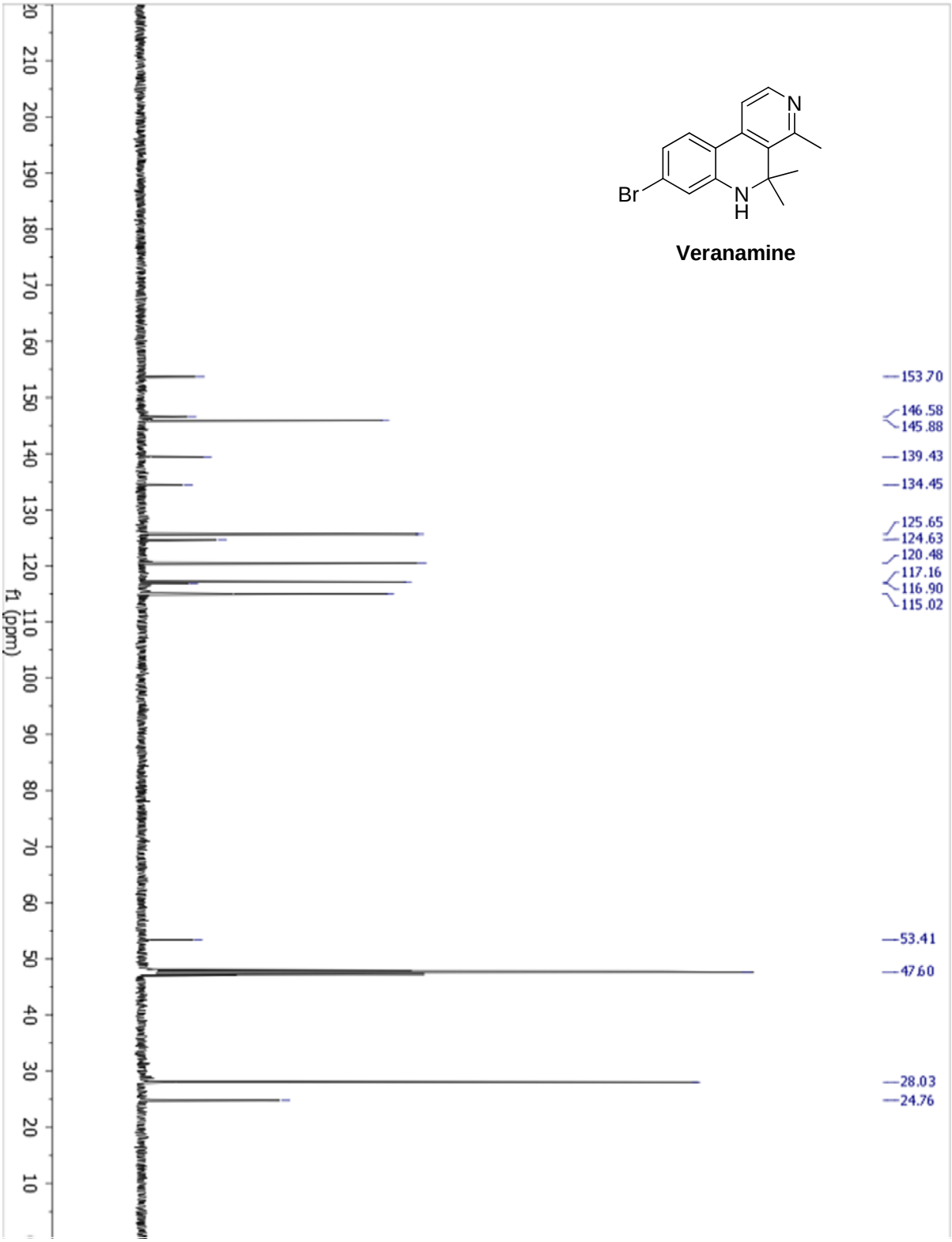


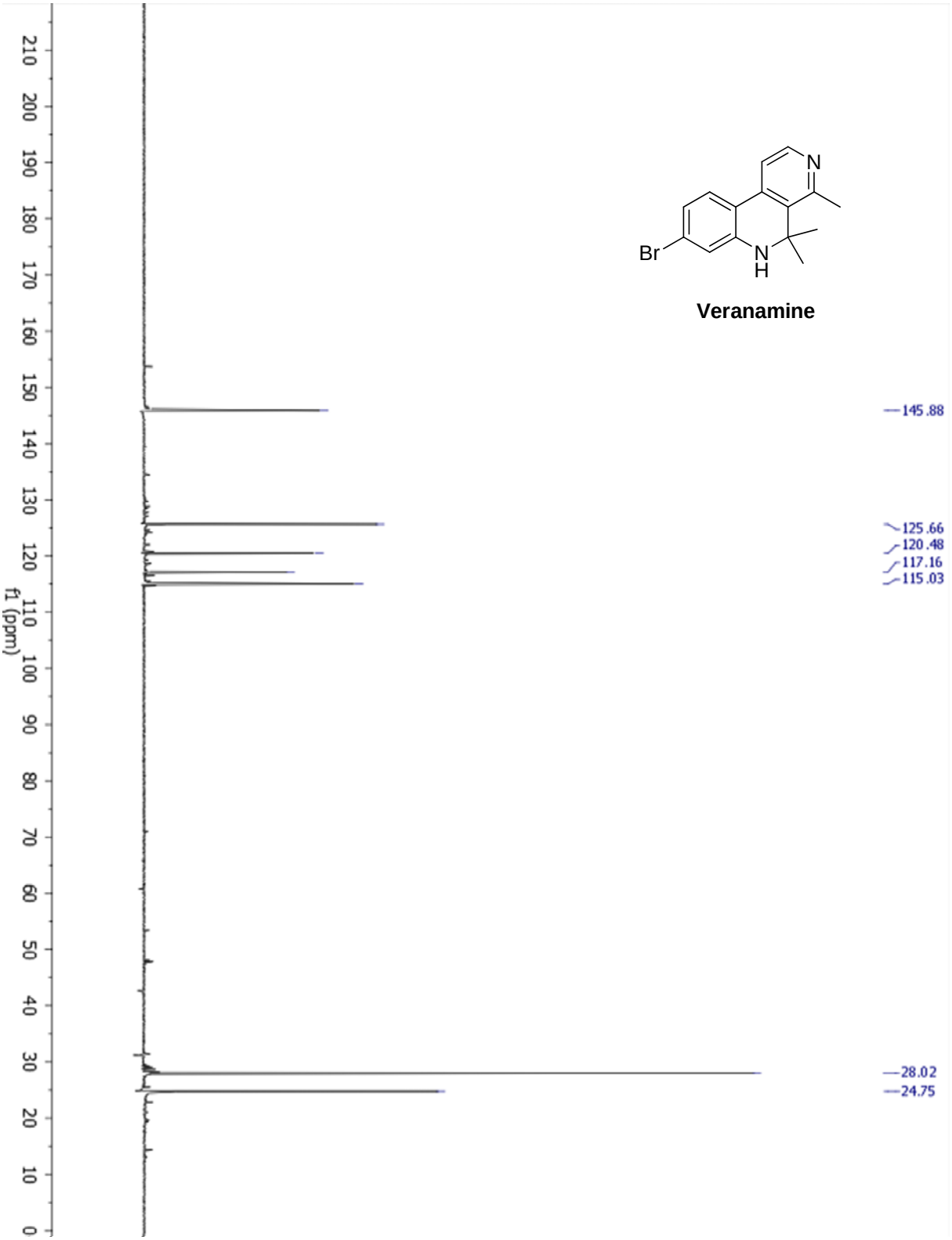
^{1}H NMR (500 MHz) in Methanol-d_4 of 8-bromo-4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (Veranamine).



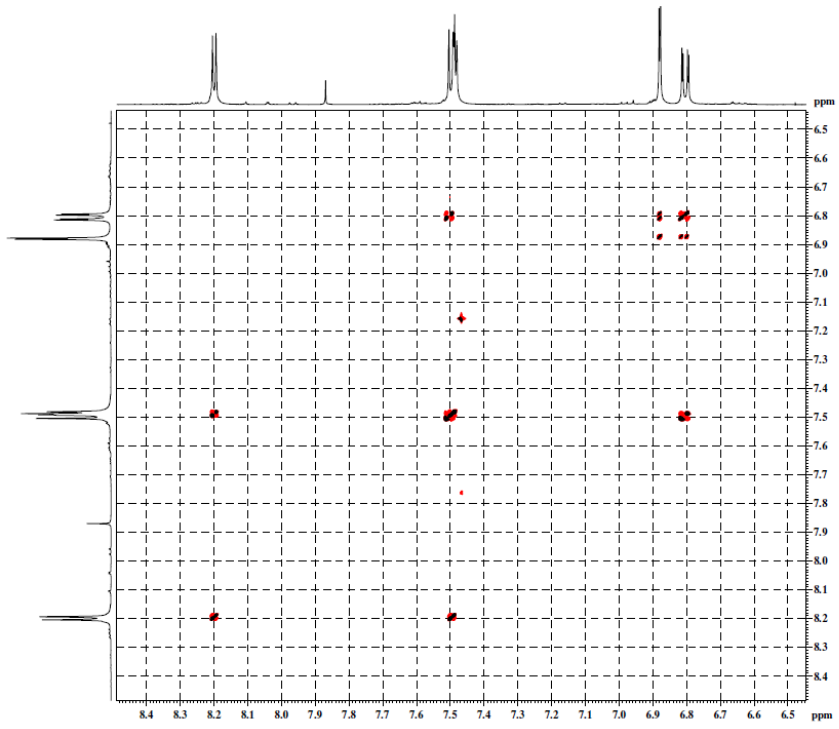
^{13}C NMR (125 MHz) in Methanol-d_4 of 8-bromo-4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (Veranamine).



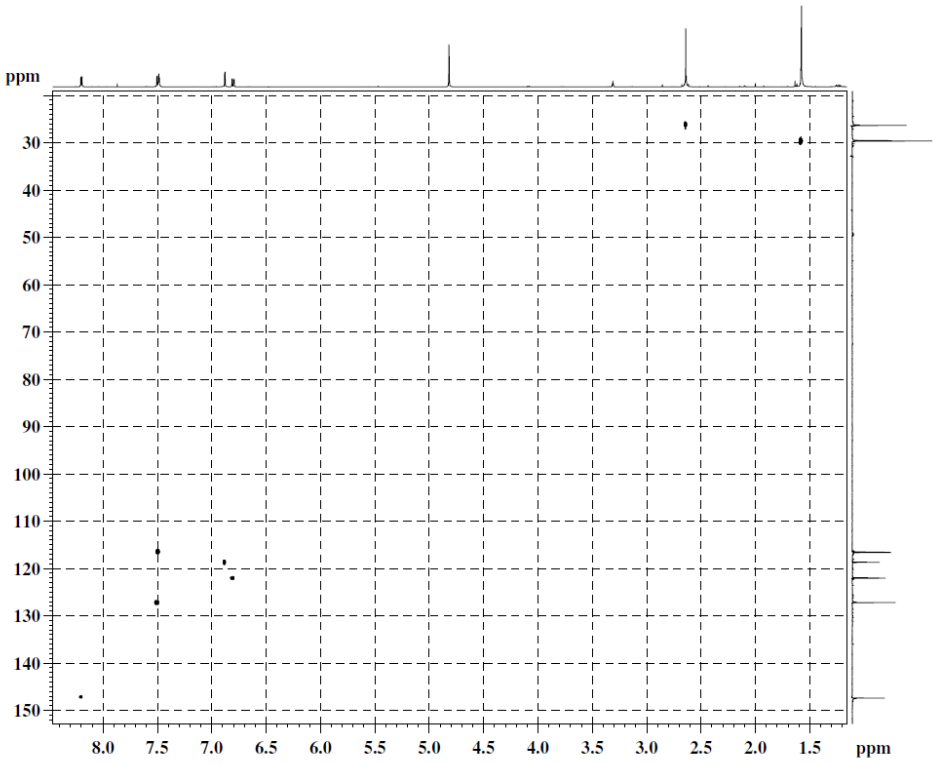
DEPT-135 for Veranamine in Methanol-d_4, 500 MHz



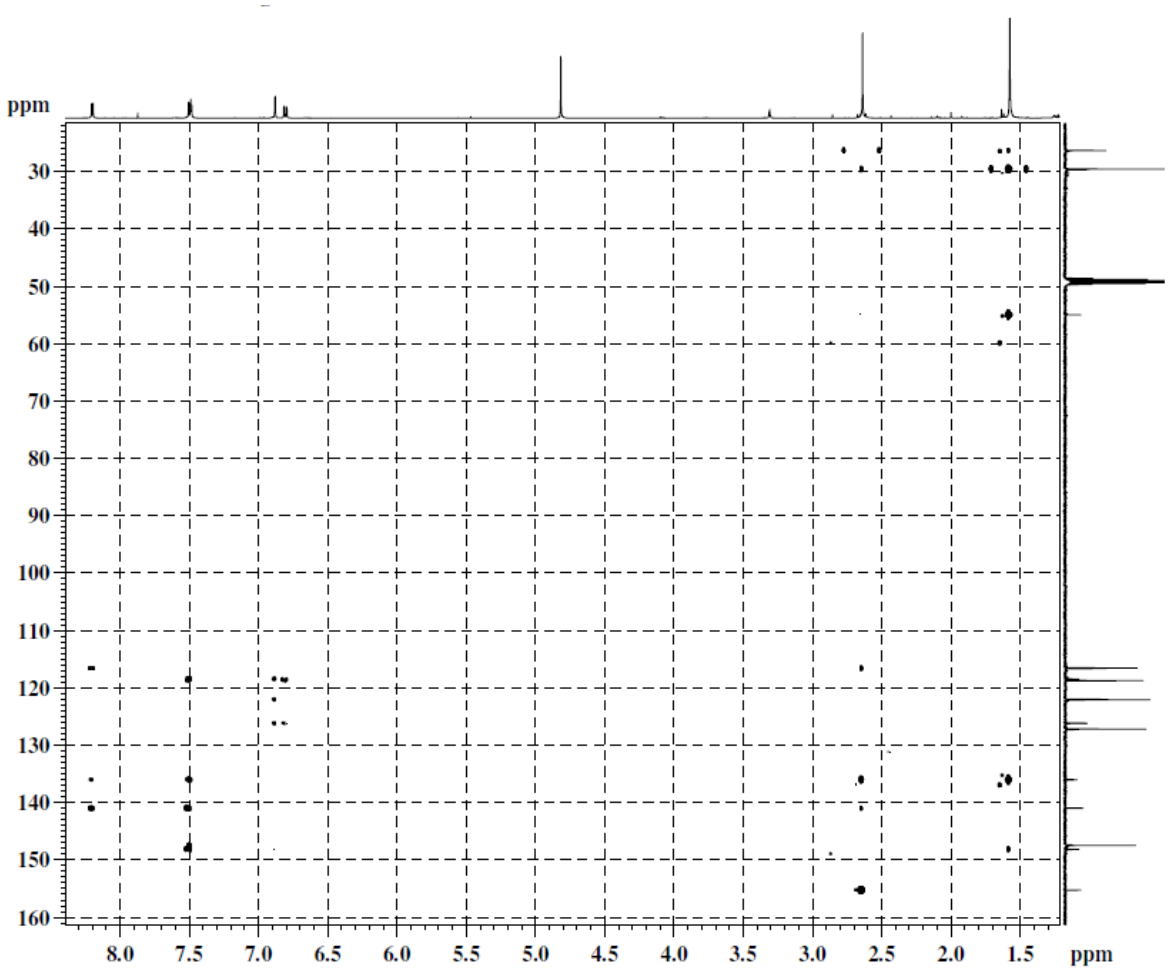
DQF-COSY for Veranamine in Methanol-d_4, 500 MHz



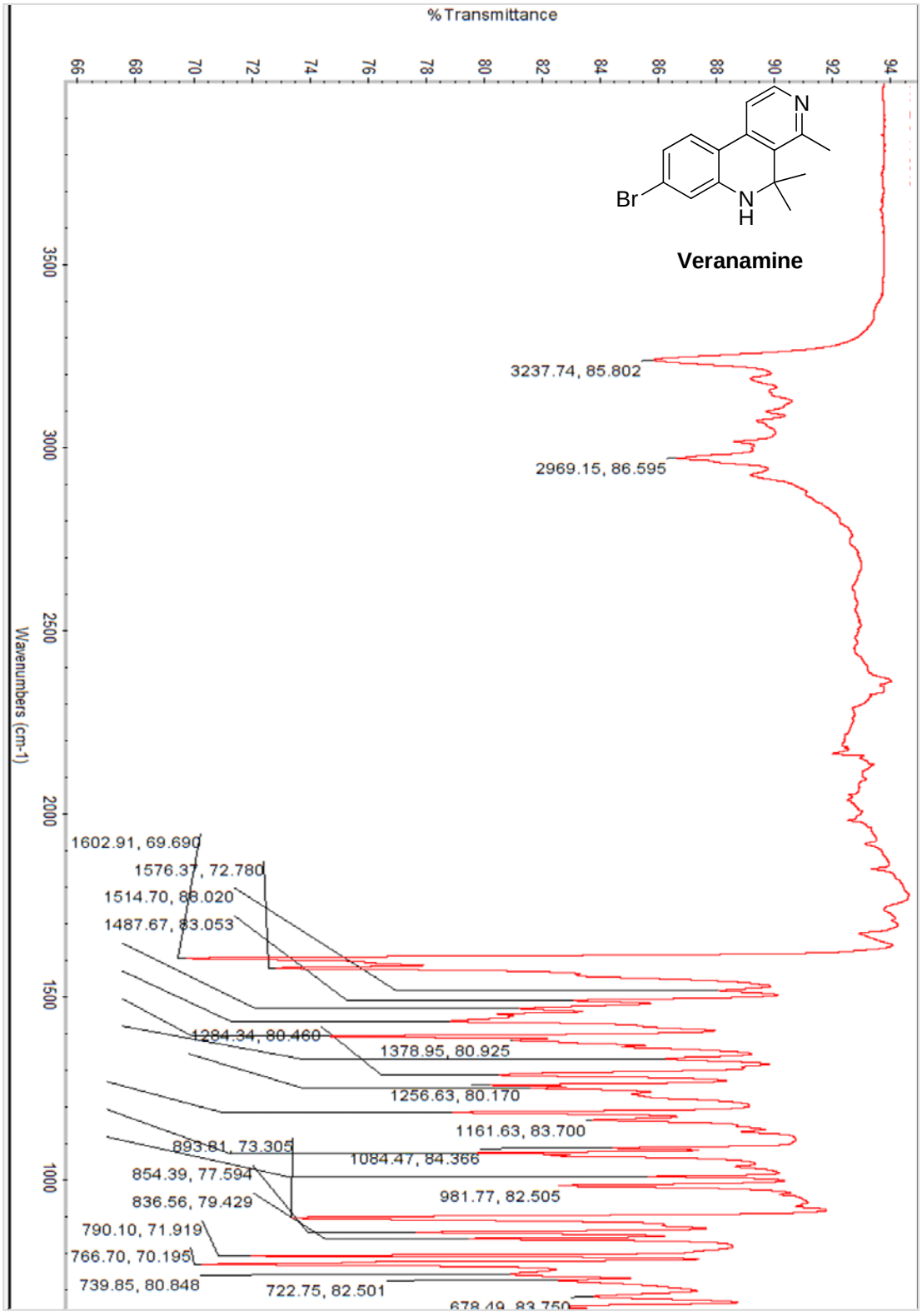
HSQC for Veranamine in Methanol-d_4, 500 MHz



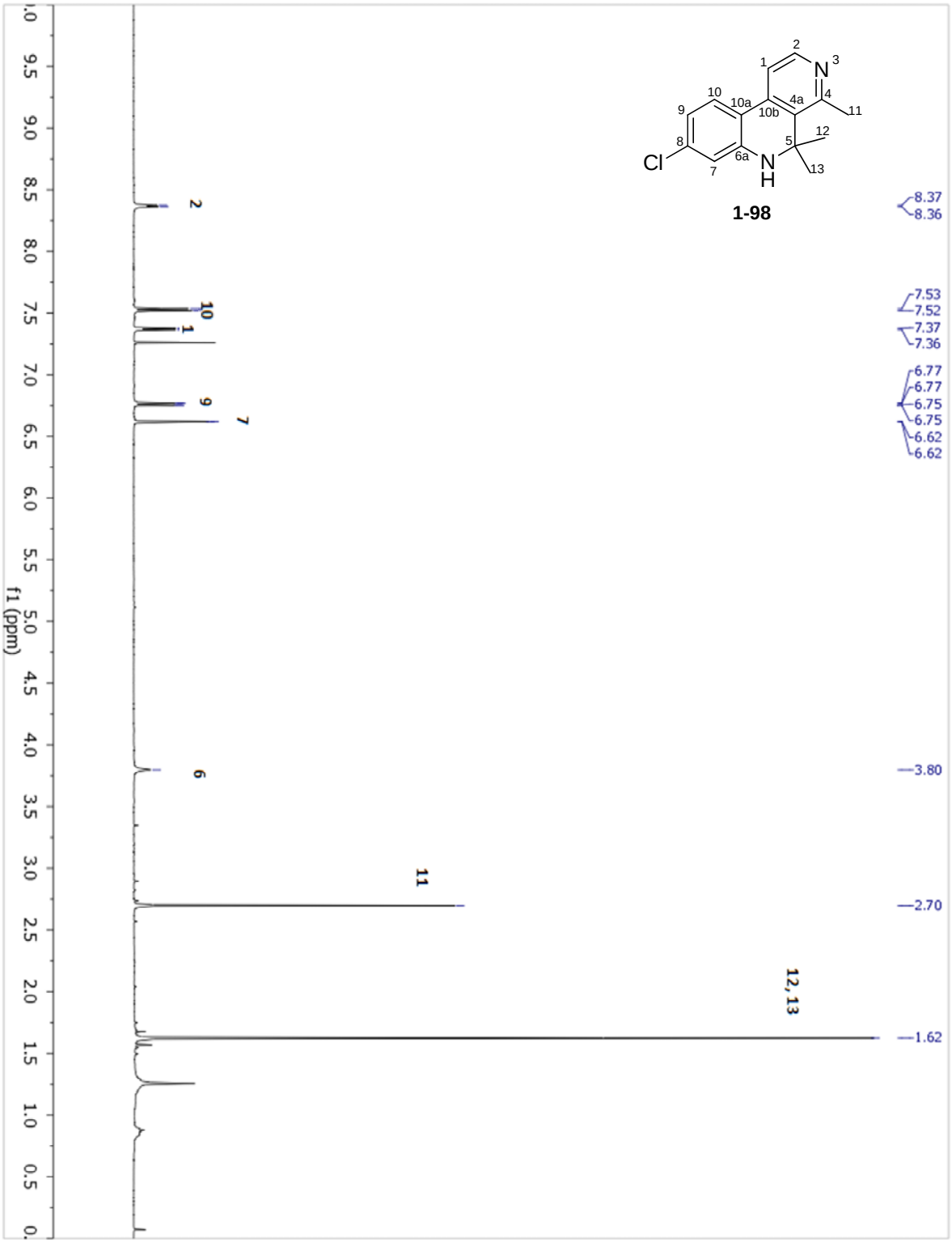
HMBC for Veranamine in Methanol-d_4, 500 MHz



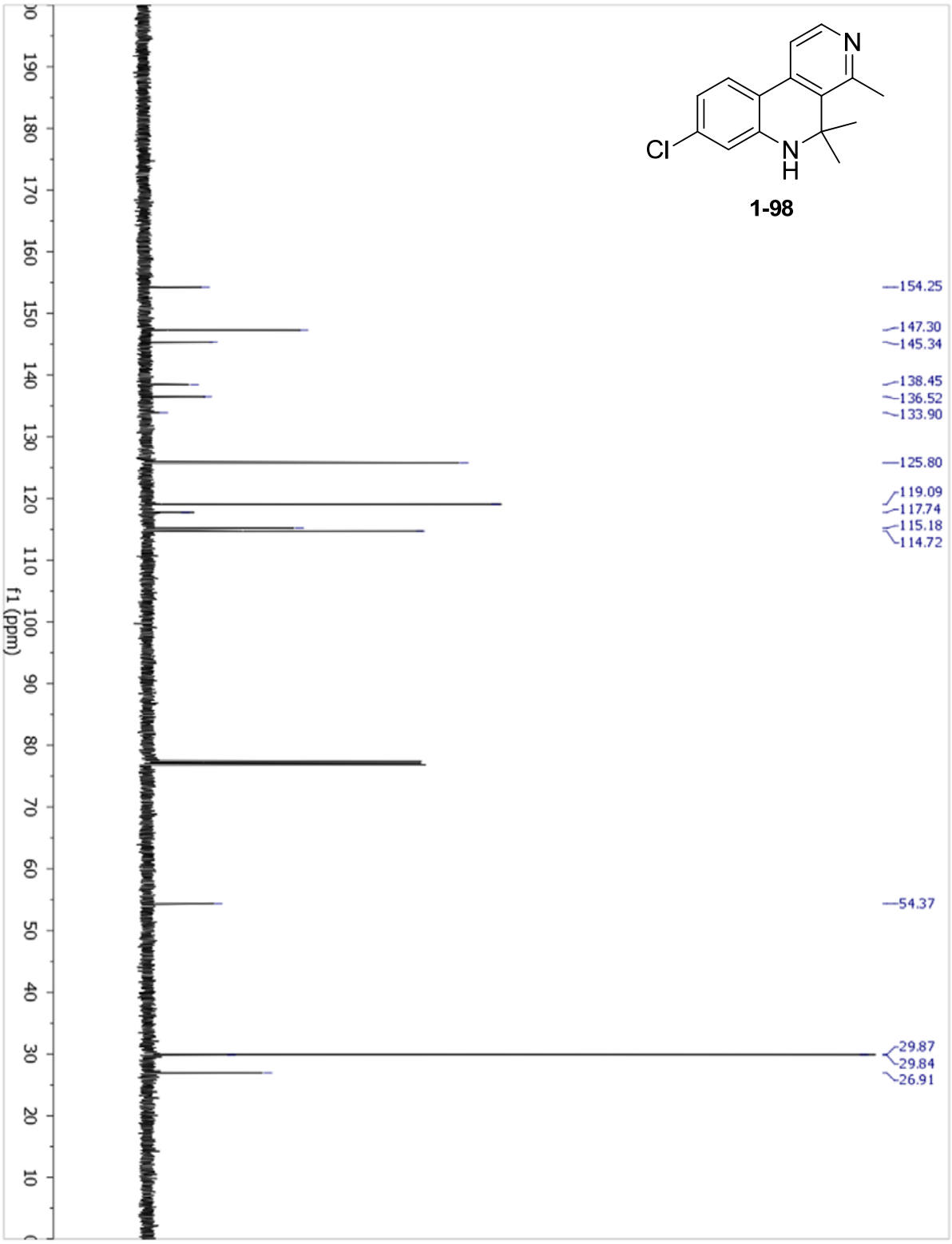
FTIR of 8-bromo-4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (Veranamine).



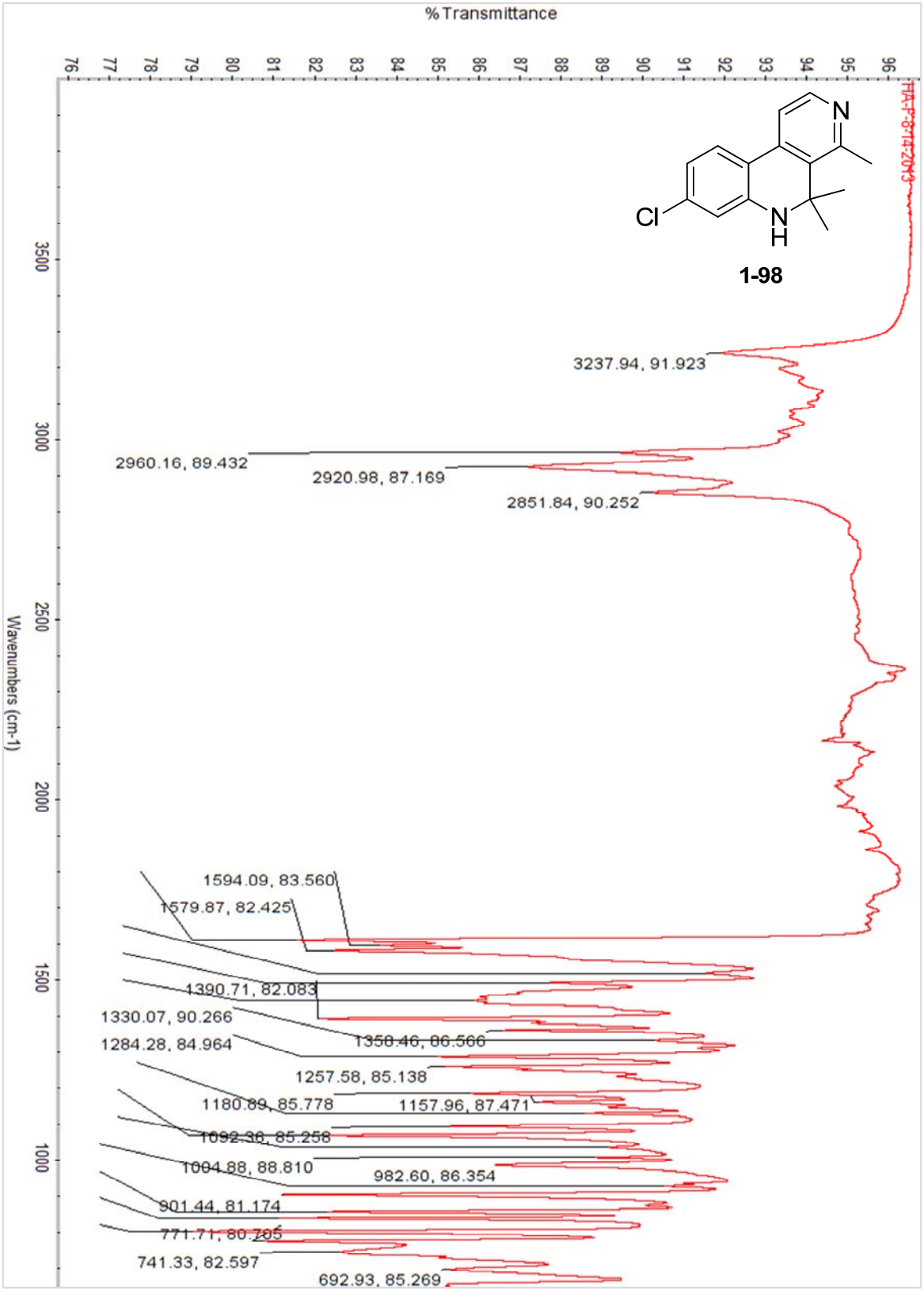
^{1}H NMR (500 MHz) in $CDCl_3$ of 8-chloro-4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (1-98).



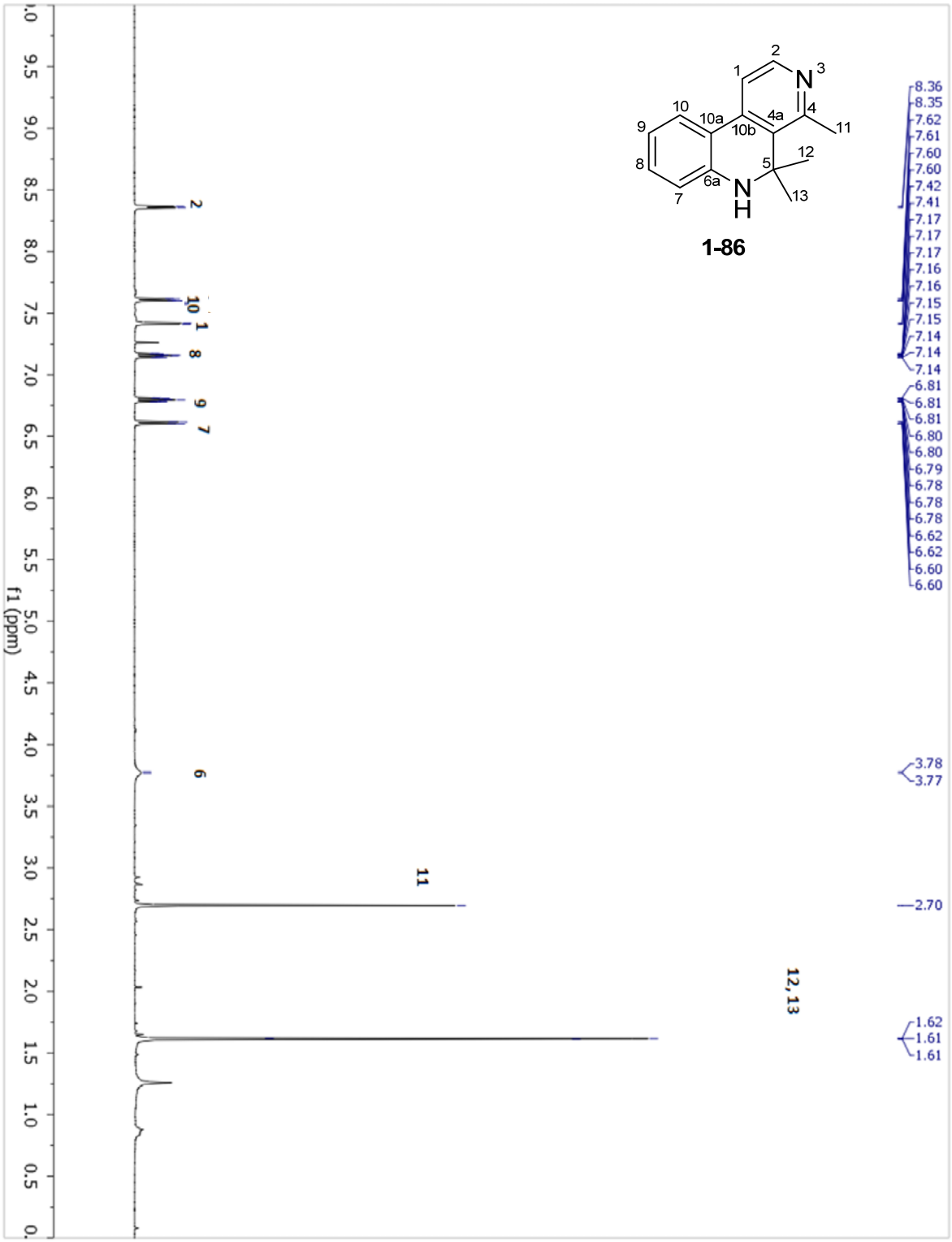
^{13}C NMR (125 MHz) in $CDCl_3$ of 8-chloro-4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (1-98).



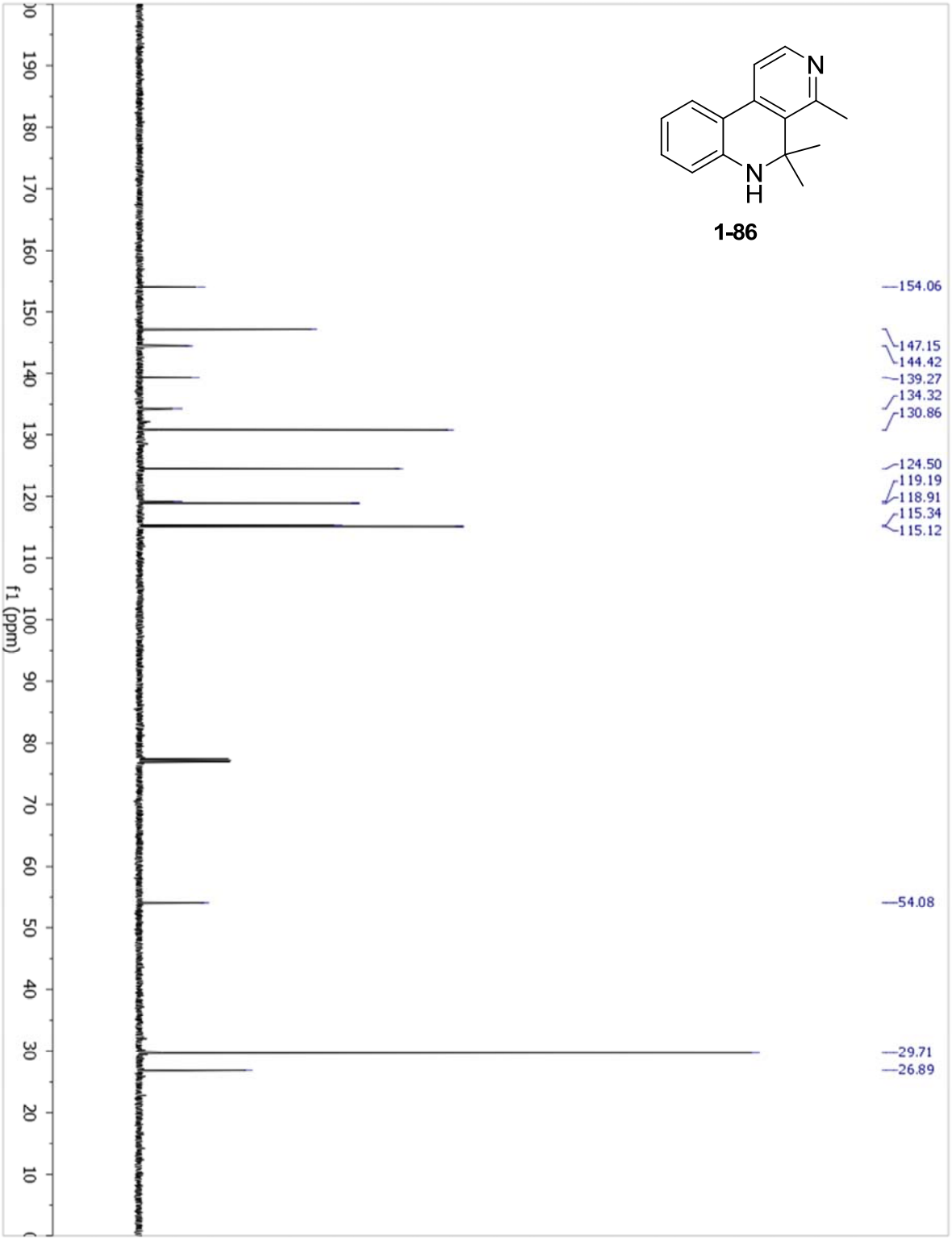
IR of 8-chloro-4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (1-98).



^{1}H NMR (500 MHz) in $CDCl_3$ of 4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (1-86).



^{13}C NMR (125 MHz) in $CDCl_3$ of 4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (1-86).



IR of 4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (1-86).